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Ferri's CLINICAL ADVISOR

5 BOOKS IN 1

- I Diseases and Disorders
- II Differential Diagnosis
- III Clinical Algorithms
- IV Laboratory Tests and Interpretation of Results
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PTG Patient Teaching Guides

EBM Evidence-Based Diagnosis

FRED F. FERRI

ELSEVIER

CLINICAL DISORDERS

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Respiratory syncytial virus (RSV)	I
Rheumatic fever	I
Rocky Mountain spotted fever	I
Roseola	I
Rubella (German measles)	I
Salmonellosis	I
Scabies	I
Scarlet fever	I
Schistosomiasis	I
Sepsis	I
Septic arthritis	I
Severe acute respiratory syndrome	I
Shigellosis	I
Sialadenitis	I
Sinus thrombosis	I
Sinusitis	I
Smallpox	I
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Spinal epidural abscess	I
Spontaneous bacterial peritonitis	I
Sporotrichosis	I
Stomatitis	I
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Tinea cruris	I
Tinea versicolor	I
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Trichinosis	I
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Tuberculosis, pulmonary	I
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Anorexia	II
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Mediastinitis	I
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Paraneoplastic syndromes	I
Pleurisy	I
Retroperitoneal fibrosis	I
Sarcoma	I
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Vitamin deficiency (hypovitaminosis)	I

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Acute tubular necrosis	I
Acute urinary retention (AUR)	I
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Bartter's syndrome	I
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Ferri's CLINICAL ADVISOR

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Preface

This book is intended to be a clear and concise reference for physicians and allied health professionals. Its user-friendly format was designed to provide a fast and efficient way to identify important clinical information and to offer practical guidance in patient management. The book is divided into five sections and an appendix, each with emphasis on clinical information.

The tremendous success of the previous editions and the enthusiastic comments from numerous colleagues have brought about several positive changes. Each section has been significantly expanded from prior editions, bringing the total number of medical topics covered in this book to more than 1000. Nearly 500 new illustrations and tables have been added to the edition to enhance recollection of clinically important facts. The expedited claims submission and reimbursement ICD-10CM codes have been added to all the topics, along with existing ICD-9CM codes. Please note that the implementation of the ICD-10CM codes has been delayed until at least 2016; therefore, for billing purposes please use the ICD-9CM codes until the ICD-10CM codes are officially implemented.

Section I describes in detail more than 800 medical disorders. Twenty-one new topics have been added to the 2016 edition. Each medical topic in this section is arranged alphabetically, and the material in each topic is presented in outline format for ease of retrieval. Topics with an accompanying algorithm in Section III are identified with an algorithm symbol (ALG). Similarly, if topics also have a Patient Teaching Guide (PTG) available online, this has been noted. Throughout the text, key quick-access information is consistently highlighted, clinical photographs are used to further illustrate selected medical conditions, and relevant ICD-9CM and ICD-10CM codes are listed. Most references focus on current peer-reviewed journal articles rather than outdated textbooks and old review articles. Evidence-based medicine data have been added to relevant topics.

Topics in Section I use the following structured approach:

1. Basic Information (Definition, Synonyms, ICD-9CM and ICD-10CM Codes, Epidemiology & Demographics, Physical Findings & Clinical Presentation, Etiology)
2. Diagnosis (Differential Diagnosis, Workup, Laboratory Tests, Imaging Studies)
3. Treatment (Nonpharmacologic Therapy, Acute General Rx, Chronic Rx, Disposition, Referral)
4. Pearls & Considerations (Comments, Suggested Readings)
5. Evidence-Based Data and References

Section II includes the differential diagnosis, etiology, and classification of signs and symptoms. This section has been significantly expanded for the 2016 edition with the addition of 22 new topics. It is a practical section that allows the user investigating a physical complaint or abnormal laboratory value to follow a "workup" leading to a diagnosis. The physician can then easily look up the presumptive diagnosis in Section I for the information specific to that illness.

Section III includes clinical algorithms to guide and expedite the patient's workup and therapy. Fifteen new algorithms have been added for the 2016 edition. Many physicians describe this section as particularly valuable in today's managed-care environment.

Section IV includes normal laboratory values and interpretation of results of commonly ordered laboratory tests. By providing interpretation of abnormal results, this section facilitates the diagnosis of medical disorders and further adds to the comprehensive, "one-stop" nature of our text.

Section V focuses on preventive medicine. Information in this section includes recommendations for the periodic health examination, screening for major diseases and disorders, patient counseling, and immunization and chemoprophylaxis recommendations.

The **Appendix** has been divided into six major sections. Section I contains extensive information on complementary and alternative medicine (CAM). With the material in this appendix, we hope to lessen the current scarcity of exposure of allopathic and osteopathic physicians to the diversity of CAM therapies. Section II focuses on nutrition, with an emphasis on dietary supplements, vitamins, and minerals. Section III deals with diagnosis and treatment of acute poisoning. Section IV is a guide on impairment and disability evaluation. Section V, available online, contains an extensive section on primary care procedures. Section VI contains several patient teaching guides not linked to Section I topics.

As clinicians, we all realize the importance of patient education and the need for clear communication with our patients. Toward that end, practical patient instruction sheets, organized alphabetically and covering the majority of the topics in this book, are available online and can be easily customized and printed from any computer. They represent a valuable addition to patient care and are useful for improving physician-patient communication, patient satisfaction, and quality of care.

I believe that we have produced a state-of-the-art information system with significant differences from existing texts. It contains five sections and patient education guides that could be sold separately based on their content, yet are available under a single cover, offering the reader a tremendous value. I hope that the *Clinical Advisor*'s user-friendly approach, numerous unique features, and yearly updates will make this book a valuable medical reference, not only to primary care physicians but also to physicians in other specialties, medical students, and allied health professionals.

Fred F. Ferri, M.D., F.A.C.P.

Note: Comments from readers are always appreciated and can be forwarded directly to Dr. Ferri at fred_ferri@brown.edu.

EVALUATION OF EVIDENCE

Ferri's Clinical Advisor evaluates all evidence based on a rating system published by the American Academy of Family Physicians. In order to indicate the strength of the supporting evidence, each summary statement is accorded one of three levels:

LEVEL A

- Systematic reviews of randomized controlled trials, including meta-analyses
- Good-quality randomized controlled trials

LEVEL B

- Good-quality nonrandomized clinical trials
- Systematic reviews not in Level A
- Lower-quality randomized controlled trials not in Level A
- Other types of study: case-control studies, clinical cohort studies, cross-sectional studies, retrospective studies, and uncontrolled studies

LEVEL C

- Evidence-based consensus statements and expert guidelines

SOURCES OF EVIDENCE

Evidence is summarized principally from three critically evaluated, very highly regarded sources:

- **Cochrane Systematic Reviews** are respected throughout the world as one of the most rigorous searches of medical journals for randomized controlled trials. They provide highly structured systematic reviews, with evidence included or excluded on the basis of explicit quality-related criteria, and they often use meta-analyses to increase the power of the findings of numerous studies.
- ***Clinical Evidence*** is produced by the BMJ Publishing Group. It provides synopses of the best currently available evidence on the treatment and prevention of many clinical conditions, based on searches and appraisals of the available literature.
- **The National Guideline Clearinghouse™** is a comprehensive database of evidence-based clinical practice guidelines and related documents produced by the Agency for Healthcare Research and Quality in partnership with the American Medical Association and the American Association of Health Plans.

In addition, where evidence exists that has not yet been critically reviewed in one of the three sites above, the evidence is summarized briefly, categorized, and fully referenced. Guidelines are also sourced from government and professional bodies.

Ferri's Clinical Advisor 2016 — How to Use This Book

Mouse icon – Indicates content with additional references, figures, or tables available at www.expertconsult.com

PTG

PTG icon – indicates an accompanying Patient Teaching Guide available at www.expertconsult.com There are also many additional PTGs online not linked to a topic in Section I.

ALG

ALG icon – indicates a topic with an accompanying Algorithm in Section III or additional Algorithms available at www.expertconsult.com

EBM icon – indicates evidence-based medicine data added to relevant topics available at www.expertconsult.com

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Cerebral palsy
Cerebral vasculitis
Cervical disk syndromes
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Chancroid
Cholera
Chorea
Churg-Strauss syndrome
Cogan's syndrome
Colorado tick fever
Congenital adrenal hyperplasia
Creutzfeldt-Jakob disease
Cryptorchidism
Cutaneous larva migrans
Dengue fever
Diabetes insipidus
Digoxin overdose
Diphtheria
Dumping syndrome
Ehlers-Danlos syndrome
Emergency contraception
Encopresis
Eosinophilic fasciitis
Eosinophilic pneumonias
Factitious disorder (including Munchausen's syndrome)
Felty's syndrome
Filariasis
Fungal meningitis
Gingivitis, necrotizing ulcerative (NUG)
Granuloma inguinale
Granulomatous arthritis
Hantavirus pulmonary syndrome
Hemoptysis
Herpangina
Histiocytosis X (Langerhans cell histiocytosis)
Histrionic personality disorder
Hypereosinophilic syndrome
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Korsakoff's psychosis
Lambert-Eaton myasthenic syndrome
Laryngitis
Leishmaniasis
Leprosy
Leptospirosis
Lymphogranuloma venereum
Measles (rubeola)
Meningomyelocele
Mesenteric adenitis
Metatarsalgia
Milk-Alkali syndrome
Myotonia
Narcissistic personality disorder
Nocardiosis
Oppositional defiant disorder (ODD)
Osler-Rendu-Webber syndrome
Otosclerosis (otospongiosis)
Paranoid personality disorder
Paroxysmal cold hemoglobinuria
Paroxysmal nocturnal hemoglobinuria
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Pediatric medication errors
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Piriformis syndrome
Poliomyelitis
Polypharmacy
Postpoliomyelitis syndrome
Premenstrual dysphoric disorder
Progressive multifocal leukoencephalopathy
Psittacosis
Pure red cell aplasia
Pyoderma gangrenosum
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Additional *PTGs* Available at www.expertconsult.com Not Linked to Topics in Section I

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Acne
Acquired Polyneuropathies
Alcohol Abuse
Anal Cancer
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Avascular Necrosis
Back Pain
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Bartholin Cyst
Blisters
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Brain Trauma
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Cardiac Pacemaker and Defibrillator
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Cervical Incompetence
Cervical Radiculopathy
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Elbow Dislocation
Endometriosis
Eosinophilic Esophagitis
Epilepsy
Exercise and Cardiovascular Health
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Femoral Hernia
Finger Sprain
Forgetfulness
Gastrointestinal System
Gastroparesis and Gastric Motility Disorders
Good Nutrition
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Hearing Loss
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Pneumoconiosis (Coal Workers' Pneumoconiosis)
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Prediabetes
Premature Ventricular Contractions
Probiotics
Puberty
Pulmonary Hypertension and Thromboembolic Disease
Radial Neuropathy
Rectal Cancer
Respiratory System
Sciatica
Shin Splints
Shoulder Dislocation
Sleep Disorder and Heart Disease
Slipped Disc
Small Intestinal Bacterial Overgrowth
Smoke Inhalation
Smoking
Spinal Cord Trauma
Stress Test Used to Predict Heart Attack Risk
Sudden Infant Death Syndrome (SIDS)
Sun Poisoning
Supraventricular Tachycardia
Tendinitis
Traveler's Diarrhea
Ulnar Neuropathy
Vaginal Dryness
Vertigo
Vomiting
Warfarin Therapy
Wrist Fracture

SECTION I

Diseases and Disorders

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BASIC INFORMATION

DEFINITION

An abdominal aortic aneurysm (AAA) is a focal full-thickness dilation of the abdominal aortic artery to at least 1.5 times the diameter measured at the level of the renal arteries, or exceeding the normal diameter of the abdominal aorta by 50%. The normal diameter at the renal arteries is 2 cm (range 1.4-3.0 cm), and a diameter 3 cm or larger is generally considered aneurysmal.

SYNONYMS

AAA

ICD-9CM CODES
441.4 Aneurysm, abdominal (aorta)
441.3 Ruptured abdominal aortic aneurysm
ICD-10CM CODES
I71.4 Abdominal aortic aneurysm, without rupture
I71.3 Abdominal aortic aneurysm, ruptured

EPIDEMIOLOGY & DEMOGRAPHICS

- Approximately 15,000 deaths/year in the United States are attributed to AAA.
- AAA is predominantly a disease of older adults, affecting men more than women (4:1).
- The prevalence rate ranges from 4% to 9% in men older than age 60.
- Clinically important AAAs ≥4 cm are present in 1% of men between age 55 and 64; and the prevalence rate increases by 2% to 4% per decade thereafter.
- The peak incidence is among men approximately 70 years old.
- The frequency is much higher in smokers than in nonsmokers (8:1); and the risk decreases with smoking cessation.
- Risk factors for AAA are similar to other atherosclerotic cardiovascular diseases. They include age, smoking, male gender, family history, hypertension, hyperlipidemia, peripheral vascular disease, and aneurysm of other large vessels.
- AAA is two to four times more common in first-degree male relatives of known AAA patients.
- Rupture of the AAA occurs in 1% to 3% of men age 65 or older.
  1. Rupture is the 10th leading cause of death in men older than age 55.
  2. Mortality from rupture is 70% to 95%.
  3. Risk factors for rupture include cardiac or renal transplants, severe obstructive lung disease, uncontrolled blood pressure, female sex, and ongoing tobacco use.
- A recent decline in incidence and prevalence of AAA and related mortality has been attributed to reductions in tobacco use.

ETIOLOGY

- Exact etiology is unknown and is likely multifactorial. AAA formation and rupture may result from elastin and collagen degradation by proteases such as plasmin, matrix metalloproteinases (MMPs), and cathepsin S and K. Degenerative:
  1. The most common association is atherosclerosis. It is uncertain if atherosclerosis causes or results from AAAs.
  2. Tobacco use: >90% of people who develop an AAA have smoked at some point in their life.
- Inherited: Familial clusters are common. High familial prevalence rate is notable in male individuals. The nature of the genetic disorder is unclear but may be linked to alpha-1-antitrypsin deficiency or X-linked mutation. Connective tissue disorders, such as Marfan's syndrome and Ehlers-Danlos syndrome, have also been strongly associated with AAA.
- Inflammatory, arteritis.
- Infection, mycotic: syphilis, *Salmonella.*

NATURAL HISTORY

- The risk of aneurysmal rupture is largely influenced by aneurysm size, rate of expansion, and sex. Other factors associated with increased risk for rupture include continued smoking, uncontrolled hypertension, and increased wall stress.
- AAAs tend to develop in the infrarenal aorta.
- Higher tension in the abdominal aorta (together with histopathologic changes such as accumulation of foam cells, cholesterol crystals, and matrix metalloproteinases) renders the abdominal aortic wall more susceptible to dilation and subsequent rupture.
- The 5-year rupture rate of asymptomatic AAAs is 25% to 40% for aneurysms >5.0 cm in diameter, 1% to 7% for AAAs 4.0 to 5.0 cm, and nearly 0% for AAAs <4.0 cm. The rate of rupture of aneurysms that were 4.0 to 5.5 cm in diameter is four times greater in women compared with men.
- Mortality rate after rupture can be as high as 90% because most patients do not reach the hospital in time for surgical repair. Of those who reach the hospital, the mortality rate is still 50%, compared with the 1% to 4% mortality rate for elective repair of a nonruptured AAA. The U.S. Preventive Services Task Force (USPSTF) also concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for AAA in women aged 65 to 75 who ever smoked and recommends against routine screening in women who never smoked (Lefevre).

SCREENING AND MONITORING

- The USPSTF recommends one-time screening for AAA by ultrasonography in men ages 65 to 75 who have a history of smoking, and in those 60 years of age or older with a history of AAA in a parent or sibling. These populations have been shown to have a higher prevalence of AAA, and selectively screening this group has been shown to decrease AAA-specific mortality.
- Monitoring by ultrasound or CT scan should be performed every 6 to 12 months for patients with AAAs measuring 4.0 to 5.4 cm in diameter and by ultrasound every 2 years for those with AAAs measuring <4 cm.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most aneurysms are asymptomatic and incidentally discovered on imaging studies; however, symptomatic aneurysms are at an increased risk for rupture.
- Physical examination has a sensitivity of 76% for detecting AAAs >5 cm and only 29% for AAAs 3.0-3.9 cm.
- Symptomatic patients may present with abdominal, back, flank, or groin pain.
- A pulsatile epigastric mass that may or may not be tender may be present.
- Abdominal pain radiating to the back, flank, and groin.
- Abdominal bruits can be present in case of renal or visceral arterial stenosis.
- Common iliac arteries can be aneurysmal and palpable in the lower abdominal quadrants. In addition, prominent femoral and popliteal pulses warrant an abdominal ultrasound and lower extremity ultrasound.
- Early satiety, nausea, and vomiting may be caused by compression of adjacent bowel.
- Venous thrombosis or insufficiency may occur from iliocaval venous compression.
- Thromboembolization can cause lower extremity pain and discoloration.
- Ureteral obstruction and hydronephrosis can cause flank and groin pain and lead to obstructive renal failure.
- Rupture classically presents as a triad of abdominal or back pain, hypotension, and a pulsatile abdominal mass in 50% of patients.
- Acute blood loss may lead to myocardial infarction; arteriovenous fistulas may present as heart failure; aortoenteric fistulas may present as hematemesis or melena associated with abdominal and back pain.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Almost 75% of patients with AAA are asymptomatic, and the condition is discovered on routine examination or serendipitously when ordering studies for other symptoms. Diagnosis of AAA should be considered in the differential of the following symptoms: abdominal pain, back pain, and/or pulsatile abdominal mass.

LABORATORY TESTS

Not routinely indicated. For suspected infected or inflammatory aneurysms, WBC, ESR/CRP, and blood cultures can be considered. An elevated D-dimer may indicate a thrombus within the aneurysm. Fig A1-1 describes an algorithm for the diagnosis and treatment of abdominal aortic aneurysms.

IMAGING STUDIES

- Abdominal ultrasound (Fig. A1-2) has nearly 100% sensitivity and specificity in identifying an aneurysm and estimating the size to within 0.3 to 0.4 cm. It is not accurate in estimating the extension to the renal arteries or the iliac arteries.

Abdominal Aortic Aneurysm ALG EBM PTG

- Computed tomography (CT) (Fig. A1-3) scan is recommended for preoperative aneurysm imaging and estimates the size of the AAA to within 0.3 mm. There are no false-negative results, and the scan can localize the extent to renal vessels with more precision than ultrasound. CT can also detect the integrity of the wall and exclude rupture.
- Magnetic resonance angiography (MRA) may also be used and is at least as accurate as CT.
- Plain radiographs may show the outline of an aneurysm in calcified aortas. This is an insensitive test for diagnosing AAA.
- Diagnostic aortography has essentially been replaced by other noninvasive imaging modalities such as CT or MR angiography. Intraoperative angiography is still used for determining treatment options and post-procedure efficacy.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Despite lack of data substantiating reduction in expansion rate through treatment of cardiac risk factors, nonpharmacologic treatment continues to focus on risk factor modification (most importantly smoking cessation, diet, and exercise).
- Serial studies have shown that expansion rates are faster in current smokers than in former smokers. Patients with known AAA or a family history of aneurysms should be advised to stop smoking and be offered smoking cessation interventions.
- Definitive treatment depends on the size of the aneurysm (see "Chronic Rx").

ACUTE GENERAL Rx

- Acute symptomatic or ruptured AAA can be treated with open surgical or endovascular aneurysm repair (EVAR). The choice is determined by anatomic considerations, operative risks, and availability of regular patient follow-up for EVAR.
- Emergent open repair has been the traditional method of treatment. However, trials have shown fewer perioperative deaths and shorter hospital stay with EVAR. More centers are increasingly using endovascular repair for patients who fit certain anatomic and physiologic criteria.
- The major limitations for EVAR include anatomical issues such as tortuosity or small caliber iliac arteries and inability to follow up of patients to exclude late failure of stents grafts and development of endoleaks.

CHRONIC Rx

- Blood pressure and fasting lipids should be monitored and controlled as recommended for patients with atherosclerotic disease. Statins are associated with decreased mortality after successful AAA repair, and are recommended for those with known AAA to reduce the progression of atherosclerosis.
- The most commonly used predictor of rupture is the maximum diameter of the AAA.
- Monitoring by ultrasound or CT scan should be performed every 6 to 12 months for patients with AAAs measuring 4.0 to 5.4 cm in diameter and by ultrasound every 2 years for those with AAAs measuring <4 cm.
- Long-term beta-blocker therapy has slowed the rate of aortic dilation and decreased the incidence of aortic complications in patients with Marfan's syndrome. Several studies have also suggested that beta-blocker therapy may reduce the rate of expansion and risk of rupture; however, conclusive evidence is lacking. In a Cochrane Database Systematic Review, propranolol was poorly tolerated in all beta-blocker trials and had only minimal, nonsignificant protective benefit.
- Antibiotics such as doxycycline and roxithromycin have shown to limit the expansion of small AAAs.
- Surgical repair to eliminate the risk for rupture should be performed for patients with infrarenal or juxtarenal AAA of approximately 5.5 cm or larger in diameter. All patients who are symptomatic should undergo repair, regardless of size.
- There is no clear advantage to early repair (open or endovascular) for small AAAs (less than 5.5 cm).
- Percutaneous, endovascular, stent-anchored grafts placed with the patient under local anesthesia have provided an alternative approach (Fig. A1-4) for patients with favorable anatomy. In patients who have undergone endovascular repair, long-term surveillance is required to assess for an endoleak, stent migration, change in aneurysm size, and need for re-intervention.
- Randomized trials have shown that endovascular repair of AAA is associated with a significantly lower operative mortality than open surgical repair but it has increased rates of graft-related complications and reintervention, and is more costly. EVAR leads to increased long-term survival among younger patients but not among older patients. There are no differences between endovascular repair and open surgical repair in total mortality or aneurysm-related mortality in the long term.
- Most recent meta-analysis concludes that EVAR has lower rates of 30-day mortality, 30-day MI, and length of hospital stay in both elective and ruptured AAA repair.
- Based on current data, less than 1% of endovascular repairs require open conversion and approximately half of all early endoleaks resolve spontaneously within a period of 30 days.
- Endovascular repair in patients who are poor candidates for open repair, as determined by comorbidities, is of uncertain effectiveness.
- In high-risk patients undergoing AAA repair, specifically those with coronary artery disease or those with more than one clinical risk factor based on the American Heart Association (AHA) guidelines, preoperative administration of beta-blockers titrated to a goal heart rate of 60 have been shown to decrease incidence of death from cardiac causes or nonfatal myocardial infarctions.
- Patients with chronic obstructive pulmonary disease (COPD) are at higher risk for major clinical complications, particularly if the COPD is suboptimally managed or if it is present in conjunction with cardiac or renal disease. Smoking cessation for 2 months before surgery has also been shown to decrease pulmonary morbidity.
- Renal dysfunction is a strong predictor of mortality, showing up to as high as 41% mortality in those with impaired renal function compared with 6% in those without renal dysfunction.

REFERRAL

- Vascular surgical referral should be made in asymptomatic patients with AAAs that are approximately 4.5 cm.
- In patients with an expansion rate of 0.6-0.8 cm/year, it is reasonable to offer repair, although small studies have shown that using expansion as a criterion for surgical referral is of unclear benefit.
- It is important to optimize any comorbid conditions before surgical referral.

PEARLS & CONSIDERATIONS

- Repairing asymptomatic AAAs smaller than 5.5 cm has not been shown to improve survival because the risk of rupture is lower than the risk of surgery.

COMMENTS

- Most AAAs are infrarenal.
- Surgical risk is increased in patients with coexisting coronary artery disease, pulmonary disease, or chronic renal failure. Evaluation for ischemia and aggressive perioperative hemodynamic monitoring help identify high-risk patients and decrease postoperative complications.
- It is estimated that AAA at <5 cm expand at a rate of 0.4 cm/year.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Abdominal Aortic Aneurysm (AAA) (Patient Information)

AUTHORS: **CHRIS W. PAN, M.D., M.B.A., M.S.,** and **PRANAV M. PATEL, M.D.**

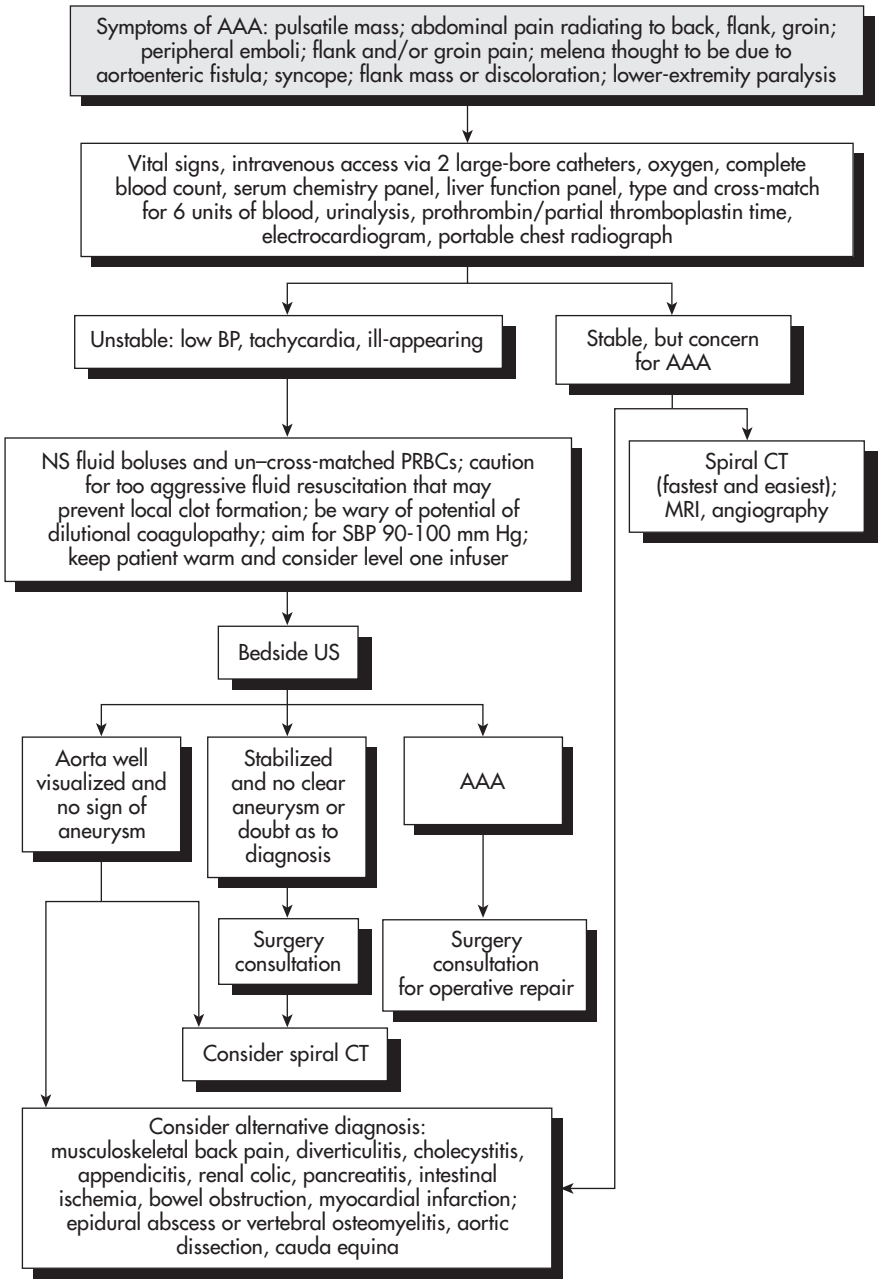


FIGURE A1-1 Algorithm for the diagnosis and treatment of abdominal aortic aneurysms (AAAs). *BP,* Blood pressure; *CT*, computed tomography; *MRI*, magnetic resonance imaging; *NS*, normal saline; *PRBCs*, packed red blood cells; *SBP*, systolic blood pressure; *US*, ultrasonography. (From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

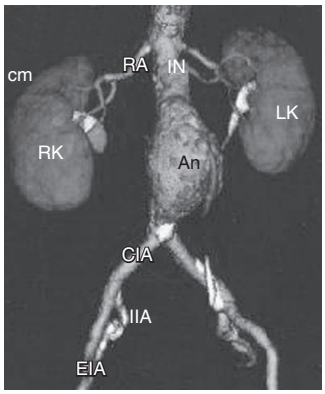


FIGURE A1-3 Three-dimensional CT image illustrates the presence of an infrarenal abdominal aortic aneurysm. *An,* Aneurysm; *CIA,* common iliac artery; *EIA,* external iliac artery; *IIA,* internal iliac artery; *IN,* infrarenal neck; *LK,* left kidney; *RA,* renal artery; *RK,* right kidney. (From Townsend CM et al [eds]: *Sabiston textbook of surgery*, ed 17, Philadelphia, 2004, Saunders.)

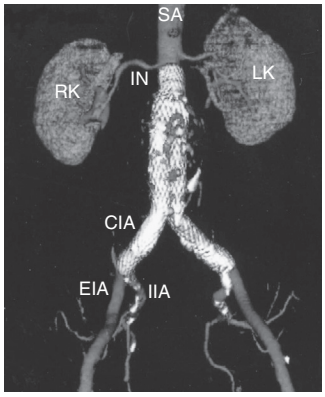


FIGURE A1-4 Endovascular abdominal aortic aneurysm repair involves aneurysm exclusion with an endoluminal aortic stent-graft introduced remotely, usually through the femoral artery. An endovascular graft extends from the infrarenal aorta to both common iliac arteries, preserving the flow to the internal iliac arteries. *CIA,* Common iliac artery; *IIA,* internal iliac artery; *IN,* infrarenal aortic neck; *LK,* left kidney; *RK,* right kidney; *SA,* suprarenal aorta. (From Townsend CM et al [eds]: *Sabiston textbook of surgery*, ed 17, Philadelphia, 2004, Saunders.)

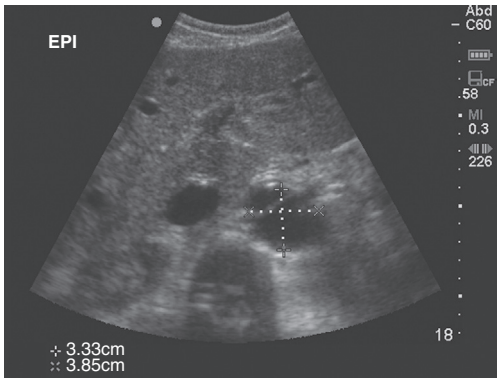


FIGURE A1-2 Transverse image of an abdominal aortic aneurysm. Note the measurements of 3.35 × 3.85 cm. The inferior vena cava is seen to the patient's right of the aorta, and the vertebral body is seen below the two vessels. Note also that there appears to be an echogenic flap within the aorta, possibly representing an aortic dissection. (From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

EVIDENCE

Abstract[1]

Background:
The long-term effects of abdominal aortic aneurysm (AAA) screening were investigated in extended follow-up from the UK Multicentre Aneurysm Screening Study (MASS) randomized trial.

Methods:
A population-based sample of men aged 65-74 years were randomized individually to invitation to ultrasound screening (invited group) or to a control group not offered screening. Patients with an AAA (3.0 cm or larger) detected at screening underwent surveillance and were offered surgery after predefined criteria had been met. Cause-specific mortality data were analyzed using Cox regression.

Results:
Some 67,770 men were enrolled in the study. Over 13 years, there were 224 AAA-related deaths in the invited group and 381 in the control group, a 42% (95% confidence interval 31 to 51) reduction. There was no evidence of effect on other causes of death, but there was an overall reduction in all-cause mortality of 3% (1 to 5). The degree of benefit seen in earlier years of follow-up was slightly diminished by the occurrence of AAA ruptures in those with an aorta originally screened normal. About half of these ruptures had a baseline aortic diameter in the range 2.5-2.9 cm. It was estimated that 216 men need to be invited to screening to save one death over the next 13 years.

Conclusion: Screening resulted in a reduction in all-cause mortality, and the benefit in AAA-related mortality continued to accumulate throughout follow-up. Ⓐ

Abstract[2]

Background:
Whether elective endovascular repair of abdominal aortic aneurysm reduces long-term morbidity and mortality, as compared with traditional open repair, remains uncertain.

Methods:
We randomly assigned 881 patients with asymptomatic abdominal aortic aneurysms who were candidates for both procedures to either endovascular repair (444) or open repair (437) and followed them for up to 9 years (mean, 5.2). Patients were selected from 42 Veterans Affairs medical centers and were 49 years of age or older at the time of registration.

Results:
More than 95% of the patients underwent the assigned repair. For the primary outcome of all-cause mortality, 146 deaths occurred in each group (hazard ratio with endovascular repair versus open repair, 0.97; 95% confidence interval [CI], 0.77 to 1.22; $P = 0.81$). The previously reported reduction in perioperative mortality with endovascular repair was sustained at 2 years (hazard ratio, 0.63;95%CI, 0.40 to 0.98; $P = 0.04$) and at 3 years (hazard ratio, 0.72; 95% CI, 0.51 to 1.00; $P = 0.05$) but not thereafter. There were 10 aneurysm-related deaths in the endovascular-repair group (2.3%) versus 16 in the open-repair group (3.7%) ($P = 0.22$). Six aneurysm ruptures were confirmed in the endovascular-repair group versus none in the open-repair group ($P = 0.03$). A significant interaction was observed between age and type of treatment ($P = 0.006$); survival was increased among patients under 70 years of age in the endovascular-repair group but tended to be better among those 70 years of age or older in the open repair group.

Conclusions:
Endovascular repair and open repair resulted in similar long-term survival. The perioperative survival advantage with endovascular repair was sustained for several years, but rupture after repair remained a concern. Endovascular repair led to increased long-term survival among younger patients but not among older patients, for whom a greater benefit from the endovascular approach had been expected. (Funded by the Department of Veterans Affairs Office of Research and Development; OVER ClinicalTrials.gov number, NCT00094575.) Ⓐ

Abstract[3]

Background:
Long-term clinical outcomes have been similar for endovascular and open repair of abdominal aortic aneurysm (AAA), increasing the importance of comparing cost effectiveness.

Methods:
We compared data to two years from a multicenter randomized trial of 881 patients. Quality-adjusted life years (QALYs) were calculated from EQ-5D questionnaires. Healthcare utilization data were obtained from patients and from national VA and Medicare sources. VA costs were obtained using methods previously developed by the VA Health Economics Resource Center. Costs for non-VA care were determined from Medicare or billing data.

Results:
Mean life-years were 1.78 in the endovascular and 1.74 in the open repair group ($P = 0.29$), and mean QALYs were 1.462 in the endovascular and 1.461 in the open group ($P = 0.78$). Although graft costs were higher in the endovascular group ($14,052 vs. $1363; $P < 0.001$), length of stay was shorter (5.0 vs. 10.5 days; $P < 0.001$), resulting in lower cost of AAA repair hospitalization in the endovascular group ($37,068 vs. $42,970; $P = 0.04$). Costs remained lower after 2 years in the endovascular group but the difference was no longer significant ($5019; 95%CI: $16,720 to $4928; $P = 0.35$). The probability that endovascular repair was both more effective and less costly was 70.9% for life-years and 51.4% for QALYs.

Interpretation:
Endovascular repair is a cost-effective alternative to open repair in the US VA healthcare system for at least the first two years. Ⓐ

Abstract[4]

A systematic review and meta-analysis of the association between markers of hemostasis and abdominal aortic aneurysm presence and size.

Objective:
The purpose of this study was to summarize the current evidence of the association between markers of hemostasis and both the presence and size of abdominal aortic aneurysms (AAAs).

Methods:
A systematic review and meta-analysis was performed according to Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines by use of the search terms “aneurysm AND abdominal AND aortic AND coagulation” NOT “thoracic.” Outcome data including concentration of hemostatic marker, number of patients, and significance level were recorded.

Results:
A total of 22 nonrandomized studies were included in the analysis, with a total of 9862 patients. Fibrinogen mean difference (MD) (0.43 g/L; 95% confidence interval [CI], 0.28-0.58 g/L; $P \leq 0.00001$), D-dimer MD (325.82 ng/mL; 95% CI, 199.74-451.89 ng/mL; $P \leq 0.00001$), and thrombin-antithrombin III complex MD (5.58 g/L; 95% CI, 3.34-7.83 g/L; $P \leq 0.0001$) were significantly elevated in the presence of AAAs. Tissue plasminogen activator, prothrombin fragments F1DF2, and platelet count were not shown to be significantly different between patients with and those without AAAs. Meta-regression of studies reporting plasma D-dimer concentration and aneurysm diameter suggests a strong and significant association ($r(2) = 0.94$; $P \leq 0.0001$).

Conclusions:
This study suggests that the presence of AAAs is associated with increased fibrin turnover, fibrinolysis, and thrombin generation, as shown by increased levels of fibrinogen, D-dimer, and thrombinantithrombin III complex. This is clinically relevant because markers of hemostasis are independent risk factors for cardiovascular events, highlighting the necessity of addressing all modifiable cardiovascular risk factors in patients with AAAs. Furthermore, the finding that plasma D-dimer concentration appears to have a linear relationship with aneurysm diameter may be useful as a future biomarker of AAAs (Figs 3 and 4). Ⓐ

Abstract[5]

Familial abdominal aortic aneurysm is associated with more complications after endovascular aneurysm repair.

Objective:
A familial predisposition to abdominal aortic aneurysms (AAAs) is present in approximately one-fifth of patients. Nevertheless, the clinical implications of a positive family history are not known. We investigated the risk of aneurysm-related complications after endovascular aneurysm repair (EVAR) for patients with and without a positive family history of AAA.

Methods:
Patients treated with EVAR for intact AAAs in the Erasmus University Medical Center between 2000 and 2012 were included in the study. Family history was obtained by written questionnaire. Familial AAA (fAAA) was defined as patients having at least one first-degree relative affected with aortic aneurysm. The remaining patients were considered sporadic AAA. Cardiovascular risk factors, aneurysm morphology (aneurysm neck, aneurysm sac, and iliac measurements), and follow-up were obtained prospectively. The primary end point was complications after EVAR, a composite of endoleaks, need for secondary interventions, aneurysm sac growth, acute limb ischemia, and postimplantation rupture. Secondary end points were specific components of the primary end point (presence of endoleak, need for secondary intervention, and aneurysm sac growth), aneurysm neck growth, and overall survival. Kaplan-Meier estimates for the primary end point were calculated and compared using log-rank (Mantel-Cox) test of equality. A Cox-regression model was used to calculate the independent risk of complications associated with fAAA.
Results:
A total of 255 patients were included in the study (88.6% men; age 72±7 years, median follow-up 3.3 years; interquartile range, 2.2-6.1). A total of 51 patients (20.0%) were classified as fAAA. Patients with fAAA were younger (69 vs 72 years; P = 0.015) and were less likely to have ever smoked (58.8% vs 73.5%; P = 0.039). Preoperative aneurysm morphology was similar in both groups. Patients with fAAA had significantly more complications after EVAR (35.3% vs 19.1%; P = 0.013), with a two-fold increased risk (adjusted hazard ratio, 2.1; 95% confidence interval, 1.2-3.7). Secondary interventions (39.2% vs 20.1%; P = 0.004) and aneurysm sac growth (20.8% vs 9.5%; P = 0.030) were the most important elements accounting for the difference. Furthermore, a trend toward more type I endoleaks during follow-up was observed (15.6% vs 7.4%; P = 0.063) and no difference in overall survival.
Conclusions:
The current study shows that patients with a familial form of AAA develop more aneurysm-related complications after EVAR, despite similar AAA morphology at baseline. These findings suggest that patients with fAAA form a specific subpopulation and create awareness for a possible increase in the risk of complications after EVAR. Ⓐ

Abstract[6]
Comparative effectiveness of endovascular versus open repair of ruptured abdominal aortic aneurysm in the Medicare population.
Objective:
Endovascular aortic repair (EVAR) for abdominal aortic aneurysm (AAA) is increasingly used for emergent treatment of ruptured AAA (rAAA).We sought to compare the perioperative and long-term mortality, procedure-related complications, and rates of reintervention of EVAR vs open aortic repair of rAAA in Medicare beneficiaries.
Methods:
We examined perioperative and long-term mortality and complications after EVAR or open aortic repair performed for rAAA in all traditional Medicare beneficiaries discharged from a United States hospital from 2001 to 2008. Patients were matched by propensity score on baseline demographics, coexisting conditions, admission source, and hospital volume of rAAA repair. Sensitivity analyses were performed to evaluate the effect of bias that might have resulted from unmeasured confounders.
Results:
Of 10,998 patients with repaired rAAA, 1126 underwent EVAR and 9872 underwent open repair. Propensity score matching yielded 1099 patient pairs. The average age was 78 years, and 72.4% were male. Perioperative mortality was 33.8% for EVAR and 47.7% for open repair (P < 0.001), and this difference persisted for >4 years. At 36 months, EVAR patients had higher rates of AAA-related reinterventions than open repair patients (endovascular reintervention, 10.9% vs 1.5%; P < 0.001), whereas open patients had more laparotomy-related complications (incisional hernia repair, 1.8% vs 6.2%; P < 0.001; all surgical complications, 4.4% vs 9.1%; P < 0.001). Use of EVAR for rAAA increased from 6% of cases in 2001 to 31% in 2008, whereas during the same interval, overall 30-day mortality for admission for rAAA, regardless of treatment, decreased from 55.8% to 50.9%.
Conclusions:
EVAR for rAAA is associated with lower perioperative and long-term mortality in Medicare beneficiaries. Increasing adoption of EVAR for rAAA is associated with an overall decrease in mortality of patients hospitalized for rAAA during the last decade (Figs 1 and 2, Tables 2 and 3). Ⓐ

Abstract[7]
Survival following ruptured abdominal aortic aneurysm before and during the IMPROVE trial: a single-centre series.
Objectives:
The first large-scale randomised trial (Immediate Management of the Patient with Rupture: Open Versus Endovascular repair [IMPROVE]) for endovascular repair of ruptured abdominal aortic aneurysm (rEVAR) has recently finished recruiting patients. The aim of this study was to examine the impact on survival after rEVAR when the IMPROVE protocol was initiated in a high volume abdominal aortic aneurysm (AAA) centre previously performing rEVAR.
Methods:
One hundred and sixty-nine patients requiring emergency infrarenal AAA repair from January 2006 to April 2013 were included. Eighty-four patients were treated before (38 rEVAR, 46 open) and 85 (31 rEVAR, 54 open) were treated during the trial period. A retrospective analysis was performed.
Results:
Before the trial, there was a significant survival benefit for rEVAR over open repair (90-day mortality 13% vs. 30%, p = 0.04, difference remained significant up to 2 years postoperatively). This survival benefit was lost after starting randomisation (90-day mortality 35% vs. 33%, p = 0.93). There was an increase in overall 30-day mortality from 15% to 31% (p = 0.02), while there was no change for open repair (p = 0.438). There was a significant decrease in general anaesthetic use (p = 0.002) for patients treated during the trial. Randomised patients had shorter hospital and intensive treatment unit stays (p = 0.006 and p = 0.03, respectively).
Conclusions:
The change in survival seen during the IMROVE trial highlights the need for randomised rather than cohort data to eliminate selection bias. These results from a single centre reinforce those recently reported in IMPROVE (Fig. 2). Ⓐ

Abstract[8]
Editor's choice:
Five-year outcomes in men screened for abdominal aortic aneurysm at 65 years of age: a population-based cohort study.
Objective:
Acquiring contemporary data on prevalence and natural history of abdominal aortic aneurysms (AAA) is essential in the effort to optimise modern screening programmes. The primary aim of this study was to determine the fate of a 65-year-old male population 5 years following an invitation to an aortic ultrasound (US) examination.
Methods:
In this population-based cohort-study, men were invited to US examination at age 65, and were re-invited at age 70. Mortality, AAA repair, and risk factors were recorded. An AAA was defined as a diameter ≥30 mm, and a sub-aneurysmal aorta as 25–29 mm.
Results:
In 2006–2007, 3,268 65-year-old men were invited, and 2,736 (83.7%) were examined. After 5 years, 24 had completed AAA repair (6 died within 0–4 years), an additional 239 had died, and 194 had moved. Thus, 2,811 70-year-old men were re-invited, and 2,247 (79.9%) were examined. The AAA prevalence increased from 1.5% at 65 to 2.4% (95% CI: 1.8 to 3.0) at 70, and of sub-aneurysmal aortas from 1.7% at 65 to 2.6% (2.0 to 3.3), at 70. Of 2,041 with <25 mm at 65, 0.7% had an AAA at 70. Of 40 with a sub-aneurysmal aorta at 65, 52.5% progressed to AAA at 70. In a Cox regression analysis, subaneurysmal aorta at 65 (hazard ratio [HR] 59.78) and smoking (HR 2.78) were independent risk factors for AAA formation. Among 44 with AAA at 65, 22 completed AAA repair with no 30-day mortality.

Conclusions:
AAA screening in a contemporary setting was safe at 5 years, with a single AAA rupture observed among non-attenders. Men with a screening detected AAA had a high repair rate and high non-AAA related mortality. AAA-formation was common among men with sub-aneurysmal dilatation, indicating a possible need for surveillance of this group. Ⓐ

Abstract[9]
A review of current reporting of abdominal aortic aneurysm mortality and prevalence in the literature.
Background:
It is common for authors to introduce a paper by demonstrating the importance of the clinical condition being addressed, usually by quoting data such as mortality and prevalence rates. Abdominal aortic aneurysm (AAA) epidemiology is changing, and therefore such figures for AAA are subject to error. The aim of this study was to analyse the accuracy of AAA prevalence and mortality citations in the contemporaneous literature.
Methods:
Two separate literature searches were performed using PubMed to identify studies reporting either aneurysm prevalence or mortality. The first 40 articles or those published over the last 2 years were included in each search to provide a snapshot of current trends. For a prevalence citation to be appropriate, a paper had to cite an original article publishing its own prevalence of AAA or a national report. In addition, the cited prevalence should match that published within the referenced article. These reported statistics were compared with the most recent data on aneurysm-related mortality.
Results:
The prevalence of AAA was reported to be as low as 1% and as high as 12.7% (mean 5.7%, median 5%). Only 47.5% of studies had referenced original articles, national reports or NICE, and only 32.4% of cited prevalences matched those from the referenced article. In total 5/40 studies were completely accurate. 80% of studies cited aneurysm mortality in the USA, with the majority stating 15,000 deaths per year (range 9,000 to 30,000). Current USA crude AAA mortality is 6,289 (2010).
Conclusion:
References for AAA mortality and prevalence reported in the current literature are often inaccurate. This study highlights the importance of accurately reporting mortality and prevalence data and using up-to-date citations.

Evidence-Based Reference

Thompson SG: Final follow-up of the Multicentre Aneurysm Screening Study (MASS) randomized trial of abdominal aortic aneurysm screening, *Br J Surg* 99:1649–1656, 2012.

Lederle FA: Long-term comparison of endovascular and open repair of abdominal aortic aneurysm, *N Engl J Med* 367:1988–1997, 2012.

Lederle FA: Cost effectiveness at two years in the VA open versus endovascular repair trial, *Eur J Vasc Endovasc Surg* 44:543–548, 2012.

Sidloff DA, Stather PW, Choke E, et al.: A systematic review and meta-analysis of the association betwenn markers of hemostasis and abdominal aortic aneurysm presence and size, *J Vasc Surg* 59:528, 2014. Ⓑ

van de Luijtgaarden KM, Bastos Gonçalves F, Hoeks SE, et al.: Familial abdominal aortic aneurysm is associated with more complications after endovascular aneurysm repair, *J Vasc Surg* 59:275–282, 2014. Ⓑ

Edwards ST, Schermerhorn ML, O'Malley AJ, et al.: Comparative effectiveness of endovascular versus open repair of ruptured abdominal aortic aneurysm in the Medicare population, *J Vasc Surg* 59:575–582, 2014. Ⓐ

Ambler GK, Twine CP, Shak J, et al.: Survival following ruptured abdominal aortic aneurysm before and during the IMPROVE Trial: a single-centre series, *Eur J Vasc Endovasc Surg* 47:388–393, 2014. Ⓐ

Svensjö S, Björck M, Wanhainen A, Five-year outcomes in men screened for abdominal aortic aneurysm at 65 years of age: a population-based cohort study, *Eur J Vasc Endovasc Surg* 47:37–44, 2014.

Stather PW, Sidloff DA, Rhema IA, et al.: A review of current reporting of abdominal aortic aneurysm mortality and prevalence in the literature, *Eur J Vasc Endovasc Surg* 47:240–242, 2014. Ⓑ

SUGGESTED READINGS

De Bruin JL et al.: Long-term outcome of open or endovascular repair of abdominal aortic aneurysm, *N Engl J Med* 362:1863–1871, 2010.

Fleming C et al.: Screening for abdominal aortic aneurysm: a best-evidence systematic review for the U.S. Preventive Services Task Force, *Ann Intern Med* 142(3):203, 2005.

Hirsch AT et al.:ACC/AHA 2005, Practice guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report, *Circulation* 113(11):e463–e465, 2006.

Jackson RS et al.: Comparison of long-term survival after open vs endovascular repair of intact abdominal aortic aneurysm among Medicare beneficiaries, *JAMA* 307(15):1621–1628, 2012.

Kent KC: Abdominal aortic aneurysms, *N Engl J Med* 371:2101–2108, 2014.

Lefevre ML: Screening for abdominal aortic aneurysm: US Preventive Services Task Force Recommendation Statement, *Ann Intern Med* 161:281–290, 2014.

Lederle FA et al.: Long-term comparison of endovascular and open repair of abdominal aortic aneurysm, *N Engl J Med* 367:1988–1997, 2012.

Mohan PP, Hamblin MH: Comparison of endovascular and open repair of ruptured abdominal aortic aneurysm in the United States in the past decade, *Cardiovasc Intervent Radiol* 37(2):337–342, 2013.

Norman PE et al.: Understanding the effects of tobacco smoke on the pathogenesis of aortic aneurysm, *Arterioscler Thromb Vasc Biol* 33:1473, 2013.

RESCAN Collaborators et al.: Surveillance intervals for small abdominal aortic aneurysms: a meta-analysis, *JAMA* 309(8):806–813, 2013.

Rooke TW et al.: 2011 ACCF/AHA Focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline), *J Am Coll Cardiol* 58(19):2020–2045, 2011.

Takayama T, Yamanouchi D: Aneurysmal disease: the abdominal aorta, *Surg Clin N Am* 93:877, 2013.

The United Kingdom EVAR Trial Investigators: Endovascular versus open repair of abdominal aortic aneurysm, *N Engl J Med* 362:1863–1871, 2010.

The United Kingdom EVAR Trial Investigators: Endovascular repair of aortic aneurysm in patients physically ineligible for open repair, *N Engl J Med* 362:1872–1880, 2010.

Thomas DM et al.: Open versus endovascular repair of abdominal aortic aneurysm in the elective and emergent setting in a pooled population of 37,781 patients: A systemic review and meta-analysis, *Vascular*, Aug 18 (Epub ahead of print) 2014.

Abdominal Compartment Syndrome

BASIC INFORMATION

DEFINITION

Abdominal compartment syndrome (ACS) is defined by the presence of organ dysfunction as a result of increased abdominal pressure or intraabdominal hypertension. The increased abdominal pressure reduces blood flow to internal organs, which can lead to multiple system failure and death if not promptly recognized and treated.

ICD-9CM CODES

729.73 Nontraumatic compartment syndrome of abdomen

958.93 Traumatic compartment syndrome of abdomen

ICD-10CM CODES

M79.A3 Nontraumatic compartment syndrome of abdomen

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Very few studies have examined the incidence of ACS outside of trauma patients, among whom it ranges from 1% to 14%, depending on the population and type of trauma studied. The incidence is the highest among critically ill patients.

RISK FACTORS: The biggest risk factor for developing ACS is critical illness stemming from a wide array of medical and surgical conditions (Table A1-1). In particular, any illness that requires a patient to undergo large volume intravenous fluid resuscitation can be associated with ACS; the third spacing of fluid can lead to increased intraabdominal pressures secondary to tissue edema. Due to large volume fluid resuscitation, ACS is commonly seen in severe burns, trauma, post-surgical patients, and sepsis. Other conditions associated with ACS include intraabdominal and retroperitoneal pathologies such as significant bowel distention, liver transplantation, massive ascites, ruptured abdominal aortic aneurysm with resulting hemoperitoneum, pancreatitis, and abdominal surgery (Table A1-2).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The most striking physical exam finding is often massive abdominal distention.
- Difficulty maintaining respiratory support and decreased urine output are also typical hallmarks.
- Other common findings include those associated with poor perfusion states and hypotension such as skin mottling, cool extremities, and obtundation. Patients will often have abdominal tenderness, signs of volume overload such as edema and elevated jugular venous pressures and may present with acute respiratory decompensation.

ETIOLOGY

- ACS can impact nearly every organ system. High intraabdominal pressures are associated with increased intracranial pressures, which can precipitate cerebral ischemia. Elevated abdominal pressures can cause cardiac compression by decreasing ventricular compliance and contractility as well as impairing inferior vena cava venous return, leading to increased central venous and pulmonary pressures. Due to elevation of the diaphragms, patients will often have reduced tidal volumes and lower chest wall compliance, which can lead to atelectasis, pneumonia, hypoxemia, and hypercarbia. Mechanically ventilated patients will also require increased airway pressures that can lead to barotrauma. In addition, renal vein compression and renal artery vasoconstriction lead to decreased urine output. Reduced mesenteric blood flow can lead to intestinal ischemia and lactic acidosis.

TABLE A1-1 Causes of Intraabdominal Hypertension and Abdominal Compartment Syndrome

Increased Abdominal Contents	Decreased Abdominal Volume
Ascites	Reduction of large long-standing hernia
Hemoperitoneum	Direct closure of large, long-standing abdominal wall defect
Visceral edema	Circumferential abdominal-wall burn
Abdominal packs	Continuous positive-pressure ventilation
Peritonitis	
Retroperitoneal edema (pancreatitis)	Retroperitoneal edema (pancreatitis)
Large pelvic, retroperitoneal hematoma	Large pelvic, retroperitoneal hematoma
Intestinal obstruction	
Ileus	
Gastric distention (esophageal ventilation)	
Abdominal aortic aneurysm	
Severe constipation	
Large abdominal tumor (chronic)	
Morbid obesity (chronic)	
Pregnancy (chronic)	

From Vincent JL, et al. *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Mesenteric ischemia.
- Sepsis.
- Shock.
- Acute kidney injury.
- Adult respiratory distress syndrome.

WORKUP

- Measurement of intraabdominal pressure is required to make a definitive diagnosis. Bladder pressure is the most common surrogate used to estimate intraabdominal pressures and is measured using a bladder catheter. The most accurate measurements can be obtained with the patient in supine position at end expiration in the absence of abdominal contractions. The threshold abdominal pressure often set for research purposes to define ACS is >20 mm Hg, but patients may have ACS with pressures of >10 mm Hg and above. Oliguria tends to develop at a pressure of 15 mm Hg, and anuria occurs around 30 mm Hg. Intraabdominal pressures can also be estimated using intragastric, intracolonic, and inferior vena cava approaches (Table A1-3).

LABORATORY TEST(S)

- Laboratory testing is generally not helpful for the diagnosis of ACS. The presence of lactic acidosis would suggest bowel ischemia that would portend a poorer prognosis.

IMAGING STUDIES

- Imaging alone has no diagnostic value in ACS, but chest imaging can be helpful to evaluate for diaphragmatic elevation and evidence of pulmonary complications (atelectasis, volume overload, pneumonia, etc.). Abdominal CT imaging will sometimes show renal displacement, inferior vena cava compression, abdominal wall thickening, or bowel injury related to ischemia, but should not be relied upon to make the diagnosis of ACS.

TREATMENT

Supportive care and, when appropriate, surgical abdominal decompression are the mainstays of ACS treatment.

NONPHARMACOLOGIC THERAPY

- Supportive care, often with hemodynamic and ventilatory support, as well as techniques to improve abdominal wall compliance are the foundations of ACS management.
- Severe burns to the abdomen leading to ACS will require surgical escharotomy to improve abdominal wall compliance.
- Patients with tense ascites leading to ACS will require large volume paracentesis to decrease intraabdominal pressures.
- Patients should be positioned supine if possible as any elevation of the head will increase abdominal pressures.

TABLE A1-2 Independent Predictors of Postinjury Primary and Secondary Abdominal Compartment Syndrome

	ED Model independent predictors	ICU Model independent predictors
Primary ACS	To OR <75 min	Temp ≤34°C
	Crystalloids ≥3 L	$GAPco_2$ ≥16
		Hb ≤8/dL
		BD ≥12 mEq/L
Secondary ACS	Crystalloids ≥3 L	$GAPco_2$ ≥16
	No urgent surgery	Crystalloids ≥7.5 L
	PRBC ≥3 units	UO ≤150 mL

ACS, Abdominal compartment syndrome; *BD*, arterial base deficit; *CI*, confidence interval; *ED*, emergency department; *$GAPco_2$*, carbon dioxide gap; *Hb*, hemoglobin concentration; *ICU*, intensive care unit; *OR*, operating room; *PRBC*, packed red blood cells; *Temp*, temperature; *UO*, urine output.
From Vincent JL, et al. *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

TABLE A1-3 Classification of Abdominal Compartment Syndrome

Basis of Classification	Subcategories
Time frame	Acute
	Chronic
Relation to peritoneal cavity	Primary
	Secondary
Etiology	Trauma
	Burn
	Postoperative
	Pancreatitis
	Bowel obstruction
	Ileus
	Abdominal aortic aneurysm
	Oncologic
	Gynecologic

From Vincent JL, et al. *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

- Rectal and nasogastric decompression is required if ACS is due to massive bowel distention.
- Proper sedation and pain control can decrease intraabdominal pressures, and some patients may require ventilatory support and chemical paralysis to maximize abdominal wall relaxation.
- Mechanical ventilation is often difficult due to the high pressures that need to be generated to overcome the increased intraabdominal pressures. Often a combination of low tidal volumes, permissive hypercapnia, chemical paralysis, and high PEEP are required to ensure adequate ventilatory support.
- Although there is little data to support its use, the administration of colloid may be superior to crystalloid if the patient requires further volume resuscitation. The administration of intravenous fluids will transiently increase renal blood flow, leading to increased urine output and improved organ perfusion and cardiac output. Pressors may also have a role to maintain perfusion pressures, but all of these measures are temporizing and supportive until definitive action through surgical decompression is performed.
- The threshold to perform surgical decompression for ACS has yet to be established; however, data suggest that early decompression prior to the development of ACS may lead to better outcomes. If appropriate, consensus dictates that surgical decompression should be performed on all patients with intraabdominal pressure >25 mm Hg; however, some surgeons are more aggressive and will consider decompression with pressures of 15-25 mm Hg in the right clinical setting. Surgical decompression by incising vertically through the linea alba can be performed at the bedside in emergent situations and most surgeons will then keep the abdomen open through the use of a temporary abdominal closure device that retains heat/fluid and prevents evisceration until the time is appropriate to attempt to close the abdomen again.

ACUTE GENERAL Rx

- There are no direct pharmacologic agents that treat ACS other than pressors, sedatives, pain medications, and paralytics required for supportive care as described above. Despite underlying volume overload, diuretics have no role in therapy. Definitive management is surgical decompression.

DISPOSITION

- Close inpatient monitoring, preferably in an intensive care setting, is indicated as mortality can be extremely high (>40%) with this condition.

REFERRAL

- Patients with ACS often require admission to an intensive care setting with surgical consultation in case decompression is required.

PEARLS & CONSIDERATIONS

COMMENTS

- ACS is seen in critically ill medical and surgical patients, and its diagnosis requires both the presence of intraabdominal hypertension and end organ dysfunction.
- ACS is truly a systemic illness that can lead to multisystem organ failure and is therefore associated with a high mortality.
- Definitive diagnosis of ACS requires measurement of intraabdominal pressure, which is most frequently estimated using bladder pressure as a surrogate.
- Supportive care, including hemodynamic support with colloids and pressors and ventilatory support, is often required, but surgical decompression is the only definitive treatment.
- Surgical decompression is indicated for intraabdominal pressures >25 mm Hg; however, precise thresholds have not been established and earlier decompression may lead to better outcomes.

AUTHORS: JASON FERREIRA, M.D., and **AMANDA PRESSMAN, M.D.**

SUGGESTED READINGS

Available at www.expertconsult.com

Abdominal Compartment Syndrome

SUGGESTED READINGS

Hunt L, Frost SA, Hillman K, Newton PJ, Davidson PM: Management of intra-abdominal hypertension and abdominal compartment syndrome: a review, *J Trauma Manag Outcomes* 8(2), 2014.

Kirkpatrick AW, Roberts DJ, De Waele J, et al.: Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome, *Intensive Care Med* 39:1190–1206, 2013.

Abruptio Placentae (PTG)

BASIC INFORMATION

DEFINITION

Abruptio placentae is the separation of placenta from the uterine wall before delivery of the fetus. The condition occurs in approximately 1% of pregnancies. There are three classes of abruption based on maternal and fetal status, including an assessment of uterine contractions, quantity of bleeding, fetal heart rate monitoring, and abnormal coagulation studies (fibrinogen, prothrombin time, partial thromboplastin time).

- Grade I: mild vaginal bleeding, uterine irritability, stable vital signs, reassuring fetal heart rate, normal coagulation profile (fibrinogen 450 mg%). Approximately half of abruptions are Grade I.
- Grade II: moderate vaginal bleeding, hypertonic uterine contractions, orthostatic blood pressure measurements, unfavorable fetal status, fibrinogen 150 to 250 mg%. Approximately a quarter of abruptions are Grade II.
- Grade III: severe bleeding (may be concealed), hypertonic uterine contractions, overt signs of hypovolemic shock, fetal death, thrombocytopenia, fibrinogen <150 mg%. Approximately a quarter of abruptions are Grade III.

SYNONYMS

Premature separation of placenta

ICD-9CM CODES

641.2 Premature separation of placenta
641.21 Premature separation of placenta, delivered, with or without mention of antepartum condition
641.23 Premature separation of placenta, antepartum condition or complication

ICD-10CM CODES

O45.8X9 Other premature separation of placenta, unspecified trimester
O45.8X1 Other premature separation of placenta, first trimester
O45.8X2 Other premature separation of placenta, second trimester
O45.8X3 Other premature separation of placenta, third trimester
O45.91 Premature separation of placenta, unspecified, first trimester
O45.92 Premature separation of placenta, unspecified, second trimester
O45.93 Premature separation of placenta, unspecified, third trimester

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): One in 86 to 206 births; 80% occur before the onset of labor

RISK FACTORS: Hypertension (greatest association), trauma, polyhydramnios, multifetal gestation, smoking, use of cocaine, chorioamnionitis, preterm premature rupture of membranes

RECURRENCE RATE: 5% to 17%, some studies showing a 5- to 10-fold increase in risk; with two prior episodes, 25%

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Triad of uterine bleeding (concealed or per vagina), hypertonic uterine contractions or signs of preterm labor, and evidence of fetal compromise exists.
- More than 80% of cases have external bleeding; 20% of cases have no bleeding but have indirect evidence of abruption, such as failed tocolysis for preterm labor.
- Tetanic uterine contractions are found in only 17%.

ETIOLOGY

- Primary etiology: unknown
- Hypertension: found in 40% to 50% of grade III abruptions
- Rapid decompression of uterine cavity, as can occur in polyhydramnios or multifetal gestation
- Blunt external trauma (motor vehicle accident, spousal abuse)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Placenta previa
- Cervical or vaginal trauma
- Labor
- Cervical cancer
- Rupture of membranes
- The differential diagnosis of vaginal bleeding in pregnancy is described in Section III

WORKUP

- Placental abruption is primarily a clinical diagnosis that is supported by laboratory, radiographic, and pathologic studies. Initial assessment should evaluate for the source of bleeding, ruling out placenta previa that may contraindicate any type of vaginal examination (e.g., pelvic speculum examination).
- Continuous fetal heart monitoring is indicated for all viable gestations (60% incidence of fetal distress in labor); may show early signs of maternal hypovolemia (late decelerations or fetal tachycardia) before overt maternal vital sign changes.
- Actual amount of blood loss is often greater than initially perceived because of the possibility of concealed retroplacental bleeding and apparent "normal" vital signs. The relative hypervolemia of pregnancy initially protects the patient until late in the course of bleeding, when abrupt and sudden cardiovascular collapse can occur.

LABORATORY TESTS

- Baseline hemoglobin helps quantify blood loss and establish baseline values for serial comparisons during expectant management.
- Coagulation profile: platelets, fibrinogen, prothrombin, and partial thromboplastin time. Diffuse intravascular coagulation can develop with severe abruption. If fibrinogen is <150 mg%, estimated blood loss is approximately 2000 ml; if fibrinogen is <100 mg%, consider fresh frozen plasma to prevent further bleeding.
- Type and antibody screen is important to identify Rh-negative patients who need Rh immune globulin.

IMAGING STUDIES

Ultrasound should include fetal presentation and status, amniotic fluid volume, placental location, as well as any evidence of hematoma (retroplacental, subchorionic, or preplacental) (Fig. A1-5).

TREATMENT

ACUTE GENERAL Rx

- Stabilization of the mother is the first priority.
- Treatment depends on gestational age of the fetus, severity of the abruption, and maternal status.
- Initial assessment for signs of maternal hemodynamic compromise or hemorrhagic shock; large-bore intravenous access, with crystalloid fluid resuscitation using a replacement of 3 ml lactated Ringer's solution for every 1 ml estimated blood loss.
- Indwelling Foley catheter to monitor urine output and maternal volume status, with a goal of 30 ml/hr urine output.

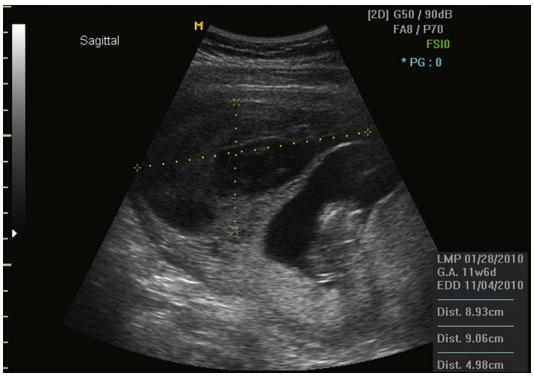


FIGURE A1-5 Ultrasonic image of a subchorionic abruption. (Courtesy K. Francois; from Gabbe SG: Obstetrics, 6th ed, Philadelphia, Saunders, 2012.)

- Assess fetal status and gestational age by sonogram and continuous fetal heart rate monitoring.
- Because of the unpredictable nature of abruptions, cross-matched blood should be made available during the initial resuscitation period.

CHRONIC Rx

- In the term fetus or when lung maturity has been documented, delivery is indicated.
- In the preterm fetus or a fetus with an immature lung profile, consider betamethasone 12.5 mg IM q24h for two doses and then delivery, depending on the severity of the abruption and the likelihood of fetal complications from preterm birth.
- Cesarean section should be reserved for cases of fetal distress or for standard obstetric indications. While cesarean delivery may be needed to stabilize the fetal and/or maternal status, the mother's coagulation status may complicate the procedure and availability of blood products may be critical.
- In select cases, such as severe prematurity with a stable mother and mild contractions, magnesium sulfate can be used for tocolysis, 6 g IV loading dose then 3 g/hr maintenance, to allow for a course of steroids.

DISPOSITION

Because of the unpredictable nature of abruptions, expectant management should occur only under controlled circumstances and is rarely practiced.

REFERRAL

Abruptio placentae places mother and fetus in a high-risk situation and should be managed by a qualified obstetrician in a facility with capability for neonatal and maternal resuscitation, for supporting a preterm infant if delivery is indicated at an early gestational age, and for performing emergency cesarean sections.

RELATED CONTENT

Premature Labor (Related Key Topic)
Vaginal Bleeding During Pregnancy (Related Key Topic)
Abruptio Placentae (Patient Information)

AUTHOR: **RUBEN ALVERO, M.D.**

Abscess, Breast PTG

BASIC INFORMATION

DEFINITION

Breast abscess is an acute inflammatory process resulting in the formation of a collection of purulent material in breast tissue. Typically there is painful erythematous mass formation in the breast, occasionally draining through the overlying skin or nipple duct.

SYNONYMS

Subareolar abscess
Lactational or puerperal abscess

ICD-9CM CODES
6.110 Abscess of the breast
675.0 Abscess of the nipple related to childbirth
675.1 Abscess of the breast related to childbirth
ICD-10CM CODES
O91.119 Abscess of breast associated with pregnancy, unspecified trimester

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 10% to 30% of all breast abscesses are lactational; acute mastitis occurs in 10% of nursing mothers, with one in 15 of these women developing abscess. A recent Cochrane review, however, found that as many as 30% of nursing mothers may have evidence of mastitis. Smoking and diabetes may be risk factors for non-puerperal mastitis with abscess. More recently, nipple piercing may also be associated with infection.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Painful erythematous induration involving breast and leading to fluctuant abscess

ETIOLOGY

- Lactational abscess: milk stasis and bacterial infection leading to mastitis and then abscess, with *Staphylococcus aureus* the most common causative agent
- Subareolar abscess:
  1. Central ducts involved, with obstructive nipple duct changes leading to bacterial infection
  2. Cultured organisms mixed, including anaerobes, staphylococci, streptococci, and others

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Inflammatory carcinoma
- Advanced carcinoma with erythema, edema, and/or ulceration
- Tuberculous abscess (rare in the United States)
- Hidradenitis of breast skin
- Sebaceous cyst with infection

WORKUP

- Clinical examination. Figure A1-6 illustrates the various areas where breast abscesses can develop
- If abscess suspected, referral to surgeon for incision, drainage, and biopsy

LABORATORY TESTS

- Perform culture and sensitivity test of abscess contents.
- If mammogram or ultrasound is required but prevented by discomfort, perform after treatment and subsequent resolution of abscess.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Established abscess: incision and drainage
- Biopsy of abscess cavity wall to exclude carcinoma

ACUTE GENERAL Rx

- Antibiotics: generally staphylococci in lactational abscess. Recommended initial antibiotic therapy is nafcillin or oxacillin 2 g q4h IV or cefazolin 1 g q8h IV for 10 to 14 days. Alternative includes vancomycin 1 g IV q12h.
- If acute mastitis is identified and treated early without the development of an abscess, resolution without drainage is possible.
- Subareolar abscess: broad-spectrum antibiotic treatment (e.g., cephalexin 500 mg PO qid or cefazolin 1 g q8h IV for 10 to 14 days for more severe infection) and drainage (Figure A1-6) are needed to control acute phase. If abscess is odoriferous, consider anaerobes as most likely etiology and add metronidazole 500 mg PO/IV tid.

CHRONIC Rx

Further surgical treatment for recurrences or fistula

DISPOSITION

- Lactational abscess: possible to continue breastfeeding without risk of infection to the infant
- Subareolar abscess:
  1. High risk for recurrence or complication of fistula formation
  2. Patient informed and referred to General Surgery for evaluation and treatment

REFERRAL

- If abscess drainage required
- If subareolar abscess involved, refer to surgery

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Breast Cancer (Related Key Topic)
Mastodynia (Related Key Topic)
Breast Abscess (Patient Information)

AUTHOR: **RUBEN ALVERO, M.D.**

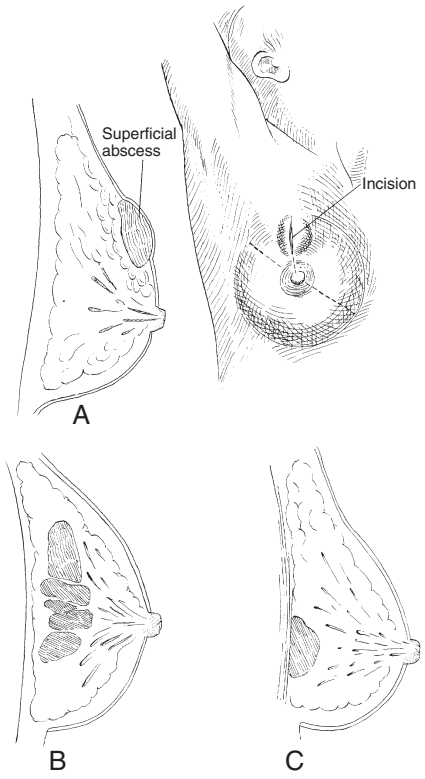


FIGURE A1-6 **A**, A superficial breast abscess may be drained with a linear incision that radiates from the nipple. **B** and **C**, Diagrams of intramammary abscess (B) and retromammary abscess (C). Both require drainage under general anesthesia. The abscess itself may not be fully appreciated if it is deep-seated, and the mistaken diagnosis of cellulitis may be made. (Redrawn from Wolcott MW: Ferguson's surgery of the ambulatory patient, 5th ed. Philadelphia, JB Lippincott, 1974. Reprinted with permission.)

SUGGESTED READINGS

Schwarz RJ, Shrestha R: Needle aspiration of breast abscesses, *Am J Surg* 182(2):117, 2001.

Tan YM et al.: Breast abscess as the initial presentation of squamous cell of the breast, *Eur J Surg Oncol* 28(1):91, 2002.

Dixon JM, Khan LR: Treatment of breast infection, *BMJ* 342:d396, 2011.

BASIC INFORMATION

DEFINITION

Epidural abscess is a suppurative infection of the central nervous system localized between the dura mater and the overlying skull or vertebral column. There are two types of epidural abscess: spinal epidural abscess (SEA) and intracranial epidural abscess (IEA), depending on the location within the central nervous system.

SYNONYMS

Spinal epidural abscess
Intraspinal abscess
Epidural abscess

ICD-9CM CODES
324.9 Epidural abscess
324.0 Intracranial abscess
ICD-10CM CODES
G06.2 Extradural and subdural abscess, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Spinal epidural abscess: 2 to 25 patients per 100,000 admissions; spinal epidural abscess is 9 times more common than intracranial abscess
PEAK INCIDENCE: Median age at onset of spinal epidural abscess: 50 years old
PREVALENCE: Greatest between 50 and 70 years of age
PREDOMINANT SEX: More common in men
RISK FACTORS: Bacteremia, secondary to distant infection; epidural catheter placement (0.5% to 3% risk), paraspinal injections of glucocorticoids or for pain management, contiguous bone or soft tissue infection, intravenous drug abuse, diabetes, immunosuppressive therapy, HIV

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Initially nonspecific, such as fever and malaise
- Classic triad: fever, spinal pain, and neurologic deficits are not common
- More commonly:
  1. Localized and significant back pain is present.
  2. Nerve root pain is present ("shooting" or "electrical" from involved nerve root).
  3. Motor weakness, sensory changes, and even paralysis can occur.
  4. Fever may not be a prominent sign.

ETIOLOGY

- Bacteria enter the epidural space most often secondary to hematogenous spread from foci elsewhere in the body (25% to 50% of cases) or by direct extension from nearby infected tissues such as vertebral body or psoas muscle. A local intervention such as injection can also cause infection.
- Hematogenous foci include furuncles, cellulitis, urinary tract infection, pharyngitis, and pneumonia.
- Microbiology:
  1. *Staphylococcus aureus*, including methicillin-resistant S. *aureus* (MRSA), accounts for 50% to 90% of cases.
  2. Aerobic and anaerobic streptococci account for 8% to 17% of cases.
  3. Aerobic gram-negative rods (*Escherichia coli* and *Pseudomonas*) account for 10% to 17% of cases.
  4. Coagulase-negative staphylococci can be seen with spinal procedures.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Disc and degenerative bone disease
- Metastatic tumors
- Vertebral discitis and osteomyelitis

WORKUP

Includes a combination of physical exam with neurologic evaluation, blood work, and radiographic studies

LABORATORY TESTS

- Blood cultures
- Culture of fluid or pus by CT-guided aspiration if possible
- Erythrocyte sedimentation rate and/or C-reactive protein
- CBC with differential

IMAGING STUDIES

- MRI with gadolinium is the diagnostic test of choice and imperative if diagnosis is considered.
- CT is an alternative but not as good as MRI for visualizing spinal cord and epidural space.
- CT myelography can be performed if MRI is not available.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Immediate surgery is required if neurologic deficits occur or the patient worsens with medical therapy.
- CT-guided aspiration of abscess with antimicrobial therapy is an alternative treatment to surgery for patients without neurologic deficits.

ACUTE GENERAL Rx

- Empiric antibiotic regimen should include antibiotics effective against staphylococci (including MRSA), streptococci, and gram-negative rods.
- Examples are vancomycin (30 to 60 mg/kg daily divided in q12h doses adjusted for creatinine clearance *plus* metronidazole (500 mg IV q8h) *plus* ceftriaxone (2 g IV q12h) or ceftazidime (2 g IV q8h) if *Pseudomonas* is suspected.
- If cultures reveal methicillin-sensitive S. *aureus*, use nafcillin 2 g IV q4h.

CHRONIC Rx

Antimicrobial therapy tailored to culture results may have to be continued for 4 to 6 weeks depending on whether or not there was surgical or CT-guided drainage. If osteomyelitis is suspected, treat for 6 to 8 weeks.

DISPOSITION

- Mortality rates vary from 5% to 32%. Irreversible paralysis can affect 4% to 22% of patients.
- Complete recovery is more likely if neurologic signs are present less than 24 hours before the start of treatment.
- Final functional capacity may continue to improve for up to 1 year after the end of treatment.

REFERRAL

- Neurosurgery should be involved early when this diagnosis is considered.
- Refer to an interventional radiologist for possible aspiration.
- An infectious diseases evaluation is needed for antimicrobial therapy.

PEARLS & CONSIDERATIONS

COMMENTS

It is important to think of spinal epidural abscess early to permit early treatment and prevent permanent neurologic deficits.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Abscess, Brain (Related Key Topic)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Darouiche RO: Spinal epidural abscess, *N Engl J Med* 355(19):2012–2020, 2006.
Tompkins M et al.: Spinal epidural abscess, *J Emerg Med* 39(3):384–390, 2010.

BASIC INFORMATION

DEFINITION

Liver abscess is a necrotic infection of the liver usually classified as pyogenic or amebic.

SYNONYMS

Pyogenic hepatic abscess
Amebic hepatic abscess

ICD-9CM CODES
572.0 Abscess of liver
ICD-10CM CODES
K75.0 Abscess of liver

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Incidence of pyogenic liver abscess is 2.3 cases per 100,000 population.
PREVALANCE (WORLDWIDE): Amebic liver abscess is more common than pyogenic liver abscess.
PREVALENCE (IN U.S.): Pyogenic liver abscess is more common than amebic liver abscess.
PREDOMINANT SEX AND AGE: More common in men than women; male/female ratio of 2:1; most common in fourth to sixth decades of life.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fever, chills, and sweats
- Weakness/malaise
- Anorexia with weight loss
- Nausea, vomiting, and diarrhea
- Cough with pleuritic chest pain
- Right upper quadrant abdominal pain
- Hepatomegaly
- Splenomegaly
- Jaundice
- Pleural effusions, rales, and friction rubs may be present
- Most abscesses occur on the right lobe of the liver

ETIOLOGY:

- Pyogenic liver abscess is usually polymicrobial (*Klebsiella pneumoniae* [43%], *Escherichia coli* [33%], *Streptococcus* spp. [37%], *Pseudomonas aeruginosa, Proteus* spp., *Bacteroides* spp. [24%], *Fusobacterium* spp., *Actinomyces* spp., gram-positive anaerobes, and *Staphylococcus aureus*).
- Pyogenic liver abscess occurs from:
  1. Biliary disease with cholangitis (accounts for approximately 40% to 60%).
  2. Gallbladder disease with contiguous spread to the liver.
  3. Diverticulitis or appendicitis with spread via the portal circulation.
  4. Hematogenous spread via the hepatic artery, though uncommon; if a solitary organism is isolated, a distant source of hematogenous seeding should be sought.
  5. Penetrating wounds.
  6. Cryptogenic.
  7. Infection by way of portal system (portal pyemia).
  8. No causes found in approximately half of cases.
  9. Incidence increased in patients with diabetes and metastatic cancer.
  10. Table A1-4 summarizes underlying etiology and bacteriology of liver abscesses.
- Amebic hepatic abscess is caused by the parasite *Entamoeba histolytica.* Amebiasis is usually due to fecal-oral contamination and invades the intestinal mucosa, gaining entry into the portal system to reach the liver.

Box A1-1 describes pearls for amebic liver abscesses.

DIAGNOSIS

The diagnosis of liver abscess requires a high index of suspicion after a detailed history and physical examination. Imaging studies and microbiologic, serologic, and percutaneous techniques (e.g., aspiration) confirm the presence of a liver abscess.

DIFFERENTIAL DIAGNOSIS

- Cholangitis
- Cholecystitis
- Diverticulitis
- Appendicitis
- Perforated viscus
- Mesentery ischemia
- Pulmonary embolism
- Pancreatitis

TABLE A1-4 Underlying Etiology and Bacteriology

Etiology	Bacteriology
Biliary, benign	*Escherichia coli* *Klebsiella* spp. *Enterococcus*
Biliary, malignant	*Pseudomonas* spp. Multiply resistant GN aerobes VRE Yeast
Diverticulitis/ appendicitis	GN aerobes *Bacteroides fragilis*
Severe cholecystitis	See Biliary, benign *Clostridium perfringens* *Bacteroides* spp.
Subcutaneous abscess	*Staphylococcus* spp. MRSA
Endocarditis	*Enterococcus* spp. *Staphyloccus* spp.
Cryptogenic	Anaerobes

GN, Gram-negative.
From Cameron, JL, Cameron AM: *Current surgical therapy*, ed 10, Philadelphia, 2011, Saunders.

WORKUP

- The workup of a liver abscess should focus on differentiating between amebic and pyogenic causes.
- Features suggesting an amebic cause include travel to an endemic area, single abscess rather than multiple abscesses, subacute onset of symptoms, and absence of conditions predisposing to pyogenic liver abscess, as highlighted under "Etiology."
- Laboratory studies are not specific but are useful as adjunctive tests.
- Imaging studies cannot differentiate between the two, and bacteriologic cultures may be sterile in 50% of the cases.

LABORATORY TESTS

- Complete blood count: leukocytosis
- Liver function tests: alkaline phosphatase is most commonly elevated (95% to 100%); aspartate transaminase (AST) and alanine transaminase (ALT) elevated in 50% of cases; elevated bilirubin (28% to 30%); decreased albumin
- Prothrombin time (INR): prolonged (70%)
- Blood cultures: positive in 50% of cases
- Aspiration (50% sterile)
- Stool samples for *E. histolytica* trophozoites (positive in 10% to 15% of amebic liver abscess cases)
- Serologic testing for *E. histolytica* should be done on all patients, but it is important to remember that it does not differentiate acute from old infections.

IMAGING STUDIES

- Ultrasound (80% to 100% sensitivity in detecting abscesses) shows round or oval hypoechogenic mass (Fig. A1-7, *A*).
- CT scan is more sensitive in detecting hepatic abscesses and contiguous organ extension and is the imaging study of choice (Fig. A1-7, *B*).
- Chest x-ray: abnormal in 50% of the cases, may reveal elevated right hemidiaphragm, subdiaphragmatic air-fluid levels, pleural effusions, and consolidating infiltrates.

BOX A1-1 Pearls for Amebic Liver Abscesses

- Only 10% to 20% of patients with amebic liver abscess have a history of diarrhea.
- Treat the intestinal infection to prevent relapse of amebic liver abscess. Failure to use luminal amebicidal agents after metronidazole in cases of amebic abscess results in a 10% relapse rate.
- Failure to show response to antiamebic medication requires evaluation for polymicrobial infection with bacteria.
- Amebic abscess usually responds clinically to antimicrobial therapy in 3 to 7 days, although imaging takes several months to show resolution.
- Percutaneous drainage is rarely required.

From Cameron, JL, Cameron AM: *Current surgical therapy*, ed 10, Philadelphia, 2011, Saunders.

- Most liver abscesses are single; however, multiple liver abscesses can occur with systemic bacteremia.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- The management of pyogenic liver abscess differs from that of amebic liver abscess.
- Medical management is the cornerstone of therapy in amebic liver abscess, whereas early intervention in the form of surgical therapy or catheter drainage and parenteral antibiotics is the rule in pyogenic liver abscess.

ACUTE GENERAL Rx

- Percutaneous drainage under CT or ultrasound guidance is essential in the treatment of pyogenic liver abscesses.
- Aspiration of hepatic amebic abscesses is not required unless there is no response to treatment or a pyogenic cause is being considered.
- Empiric broad-spectrum antibiotics are recommended initially until culture results are available. Common choices include:
  1. Metronidazole (500 mg IV q8h) plus ceftriaxone or levofloxacin.
  2. Monotherapy with a beta-lactam/beta-lactamase inhibitor, such as piperacillin/tazobactam (4.5 g q6h), ticarcillin-clavulanate (3.1 g q4h), or ampicillin-sulbactam (3 g q6h).
  3. Monotherapy with a carbapenem, such as imipenem (500 mg IV q6h), meropenem (1 g q8h), or ertapenem (1 g daily).
  4. Duration of antibiotic treatment is usually 4 to 6 wk with IV antibiotics used for the first 1 to 2 wk or until a favorable clinical response, followed thereafter with oral antibiotics (e.g., metronidazole 500 mg PO q8h plus ciprofloxacin 500 mg PO q12h).
  5. Third-generation cephalosporins should not be used as single agents for empiric therapy because of risk of the emergence of beta-lactamase-producing bacteria.
- Antibiotic coverage for amebic liver abscesses includes:
  1. Tissue agent: metronidazole 750 mg PO tid for 10 days
  2. Luminal agent: after therapy with tissue agent treatment with any luminal agent is required even if the stool is negative, such as paromomycin for 10 days or diiodohydroxyquin for 20 days.

CHRONIC Rx

- If fever persists for 2 wk despite percutaneous drainage and antibiotic therapy as outlined under "Acute General Rx," or if there is failure of aspiration or failure of percutaneous drainage, surgery is indicated.
- In patients not responding to intravenous antibiotics and percutaneous drainage, hepatic artery antibiotic infusion can be considered.
- In patients with evidence of metastatic disease that is causing biliary obstruction, a gastroenterology consultation for endoscopic retrograde cholangiopancreatography and stenting should be considered.

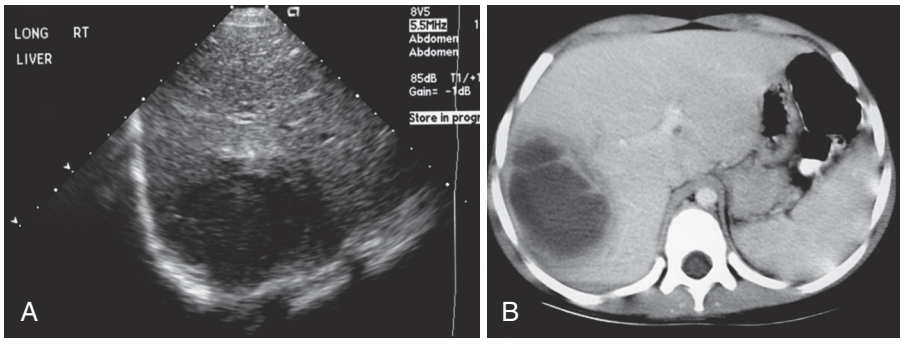


FIGURE A1-7 A, Amebic abscess. Sonogram demonstrates a hypoechogenic mass in the right lobe of the liver with a more hypoechoic surrounding rim. **B,** CT scan demonstrates a low-attenuation mass in the right lobe of the liver with a prominent halo. (From Kuhn JP et al: *Caffrey's pediatric diagnostic imaging*, vol 2, ed 10, Philadelphia, 2004, Mosby.)

DISPOSITION

- Most patients with pyogenic liver abscesses defervesce within 2 wk of treatment with antibiotics and drainage.
- No randomized controlled studies have evaluated the optimal duration of antibiotic therapy for pyogenic liver abscess. Typical duration of antibiotic therapy is at least 4 to 6 wk.
- Pyogenic liver abscess cure rates using percutaneous drainage and antibiotics have been reported to be between 88% and 100%.
- Mortality rate of untreated pyogenic liver abscess is nearly 100%.
- Most patients with amebic liver abscesses defervesce within 4 to 5 days of treatment.
- Amebic liver abscess mortality rate is <1% unless complications occur (see "Comments").
- Follow-up imaging should be used to monitor response to therapy; continue treatment until CT scan shows complete or near-complete resolution of cavity.

REFERRAL

Infectious disease, gastroenterology, interventional radiology, and general surgical consultations are recommended in any patient with hepatic abscess.

PEARLS AND CONSIDERATIONS

COMMENTS

- Complications of pyogenic and amebic liver abscesses include:
  1. Pleuropulmonary extension, resulting in empyema, abscess, and fistula formation
  2. Peritonitis
  3. Purulent pericarditis
  4. Sepsis
- Amebic liver abscesses complicate amebic colitis in nearly 10% of cases.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Liver Abscess (Patient Information)

AUTHOR: **TANYA ALI, M.D.**

SUGGESTED READINGS

Blessman J et al.: Treatment of amoebic liver abscess with metronidazole alone or in combination with ultrasound guided needle aspiration: a comparative, prospective and randomized study, *Trop Med Int Health* 8(11):1030, 2003.

Kaplan GG et al.: Population-based study of the epidemiology of and the risk factors for pyogenic liver abscess, *Clin Gastroenterol Hepatol* 2(11):1032, 2004.

Kurland JE et al.: Pyogenic and amebic liver abscess, *Curr Gastroenterol Rep* 6(4):273, 2004.

Lodhi S et al.: Features distinguishing amebic from pyogenic liver abscess: a review of 577 adult cases, *Trop Med Int Health* 9(6):718, 2004.

Yu SC et al.: Treatment of pyogenic liver abscess: prospective randomized comparison of catheter drainage and needle aspiration, *Hepatology* 39(9):932, 2004.

Abscess, Lung PTG

BASIC INFORMATION

DEFINITION

A lung abscess is an infection of the lung parenchyma resulting in a necrotic cavity containing pus.

SYNONYMS

Pulmonary abscess

ICD-9CM CODES
513.0 Abscess of the lung
ICD-10CM CODES
J85.1 Abscess of lung with pneumonia
J85.2 Abscess of lung without pneumonia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Has decreased over the last 30 years as a result of antibiotic therapy.

- Lung abscess in patients age 50 and over is associated with primary lung neoplasia in 30% of the cases.
- Lung abscesses commonly coexist with empyemas.

RISK FACTORS (see Table A1-5):

1. Alcohol-related problems
2. Seizure disorders
3. Cerebrovascular disorders with dysphagia
4. Drug abuse
5. Esophageal disorders (e.g., scleroderma, esophageal carcinoma, etc.)
6. Poor oral hygiene
7. Obstructive malignant lung disease
8. Bronchiectasis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms are generally insidious and prolonged, occurring for weeks to months
- Fever, chills, and sweats
- Cough
- Sputum production (purulent with foul odor)
- Pleuritic chest pain
- Hemoptysis
- Dyspnea
- Malaise, fatigue, and weakness
- Tachycardia and tachypnea
- Dullness to percussion, whispered pectoriloquy, and bronchophony
- Amphoric breath sounds (low-pitched sound of air moving across a large open cavity)

ETIOLOGY

- The most important factor predisposing to lung abscess is aspiration.
- Following aspiration as a major predisposing factor is periodontal disease.
- Lung abscess is rare in an edentulous person.
- Approximately 90% of lung abscesses are caused by anaerobic microorganisms (peptostreptococci, microaerophilic streptococci such as *Streptococcus milleri, Bacteroides* species, *Fusobacterium nucleatum, Prevotella*). Pulmonary actinomycosis will also generate lung abscess.
- In most cases anaerobic infection is mixed with aerobic or facultative anaerobic organisms *(S. aureus, E. coli, K. pneumoniae, P. aeruginosa).*
- Parasitic organisms including *Paragonimus westermani* and *Entamoeba histolytica.*
- Fungi including *Aspergillus, Cryptococcus, Histoplasma, Blastomyces,* and *Coccidioides* spp.
- Immunocompromised hosts may become infected with *Aspergillus,* mycobacteria, *Nocardia, Legionella micdadei,* and *Rhodococcus equi.*
- Lung necrosis caused by community strains of MRSA (USA 300 strain) in young adults or adolescents after acute influenza was initially reported in 2002 and can be quite fulminant.

DIAGNOSIS

Lung abscess may be primary or secondary.

- *Primary lung abscess* refers to infection from normal host organisms within the lung (e.g., aspiration, pneumonia).
- Secondary lung abscess results from other preexisting conditions (e.g., endocarditis, underlying lung cancer, pulmonary emboli).

Lung abscess may be acute or chronic.

- Acute lung abscess is present if symptoms are of less than 4 to 6 wk.
- Chronic lung abscess is present if symptoms last longer than 6 wk.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is similar to that for cavitary lung lesions:

- Bacterial (anaerobic, aerobic, infected bulla, empyema, actinomycosis, tuberculosis)
- Fungal (histoplasmosis, coccidioidomycosis, blastomycosis, aspergillosis, cryptococcosis, zygomycetes)
- Parasitic (amebiasis, echinococcosis)
- Malignancy (primary lung carcinoma, metastatic lung disease, lymphoma, Hodgkin's disease)
- Granulomatosis with polyangiitis, sarcoidosis, endocarditis, and septic pulmonary emboli

WORKUP

- The workup of a patient with lung abscess attempts to elicit a primary or a secondary cause.
- Blood tests are not specific in diagnosing lung abscesses.
- Most diagnoses are made from imaging studies; however, to diagnose a specific cause bacteriologic studies are needed.

LABORATORY TESTS

- CBC with leukocytosis
- Bacteriologic studies
  1. Sputum Gram stain and culture (commonly contaminated by oral flora)
  2. Percutaneous transtracheal aspiration
  3. Percutaneous transthoracic aspiration
  4. Fiberoptic bronchoscopy using bronchial brushings or bronchoalveolar lavage is the most widely used intervention when trying to obtain diagnostic bacteriologic cultures
- Blood cultures on some occasions (<30%) may be positive
- If an empyema is present, obtaining empyema fluid via thoracentesis may isolate the organism

IMAGING STUDIES

- Chest x-ray makes the diagnosis of lung abscess showing the cavitary lesion with an air-fluid level.
- Lung abscesses are most commonly found in the posterior segment of the right upper lobe.
- Chest CT scan can localize and size the lesion and assist in differentiating lung abscesses from other pathologic processes (e.g., tumor, empyema, infected bulla, etc.) (Fig. A1-8).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Oxygen therapy
- Postural drainage
- Respiratory therapy maneuvers

ACUTE GENERAL Rx

Piperacillin/tazobactam 3.375 g IV q6h in aspiration pneumonia with lung abscess

- Ceftriaxone 1 g IV q24h plus metronidazole 1 g IV q12h
- Clindamycin is more effective for anaerobic lung abscess than penicillin alone. Dose: 600 mg IV q8h until improved, then 300 to 600 mg PO q6h.

TABLE A1-5 Risk Factors for Aspiration Pneumonia and Lung Abscess

Increased bacterial inoculum	Periodontal disease, gingivitis, tonsillar or dental abscess, drugs that decrease gastric acidity
Impairment of consciousness	Drugs, alcohol, general anesthesia, metabolic encephalopathy, coma, shock, cerebrovascular accident, cardiopulmonary arrest, seizures, surgery, trauma
Impaired cough and gag reflexes	Vocal cord paralysis, intratracheal anesthesia, endotracheal tube, tracheostomy, myopathy, myelopathy, other neurologic disorders
Impairment of esophageal function	Diverticula, achalasia, strictures, disorders of gastrointestinal motility, neoplasm, tracheoesophageal fistula, pseudobulbar palsy
Emesis	Nasogastric tube, gastric dilation, ileus, intestinal obstruction

From Cohen J, Powderly WG: *Infectious diseases*, ed 2, St Louis, 2004, Mosby.

- Penicillin 1 to 2 million units IV q4h until improvement (afebrile, decreased phlegm production), followed by penicillin VK 500 mg PO q6h for 2 to 3 weeks but often up to 6 to 8 weeks) can be given with metronidazole doses of 7.5 mg/kg IV q6h followed by PO 500 mg bid to qid dosing as an alternative to clindamycin.
- Penicillin should not be used alone because many mouth flora anaerobes now produce penicillinase enzymes. Metronidazole should not be used alone because it is not active against microaerophilic streptococci and some anaerobic cocci.
- Other alternatives are ampicillin/sulbactam and carbapenems such as ertapenem and meropenem.

CHRONIC Rx

- Bronchoscopy to assist with drainage and/or diagnosis is indicated in patients who fail to respond to antibiotics or if there is suspected underlying malignancy.
- Surgery is indicated on rare occasions (<10%) in patients with complications of lung abscess (see "Comments").

DISPOSITION

- More than 95% of patients are cured with the use of antibiotics alone.
- Complications of lung abscesses include:
  1. Empyema
  2. Massive hemoptysis
  3. Pneumothorax
  4. Bronchopleural fistula
  5. Hepatobronchial fistula
  6. Brain abscess
  7. Bronchiectasis
- Mortality is low in community-acquired lung abscess (2.5%).
- Hospital-acquired lung abscess carries a high mortality rate (65%).

REFERRAL

If lung abscess is present, consultation with pulmonary and infectious disease specialist is recommended.

PEARLS & CONSIDERATIONS

COMMENTS

- Refractory cases are usually the result of:
  1. Large cavity size (>6 cm)
  2. Recurrent aspiration
  3. Thick-walled cavities
  4. Underlying lung carcinoma
  5. Empyema formation
- Necrotizing pneumonia is similar to a lung abscess but differs in size (<2 cm in diameter) and number (usually multiple suppurative cavitary lesions).

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Lung Abscess (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

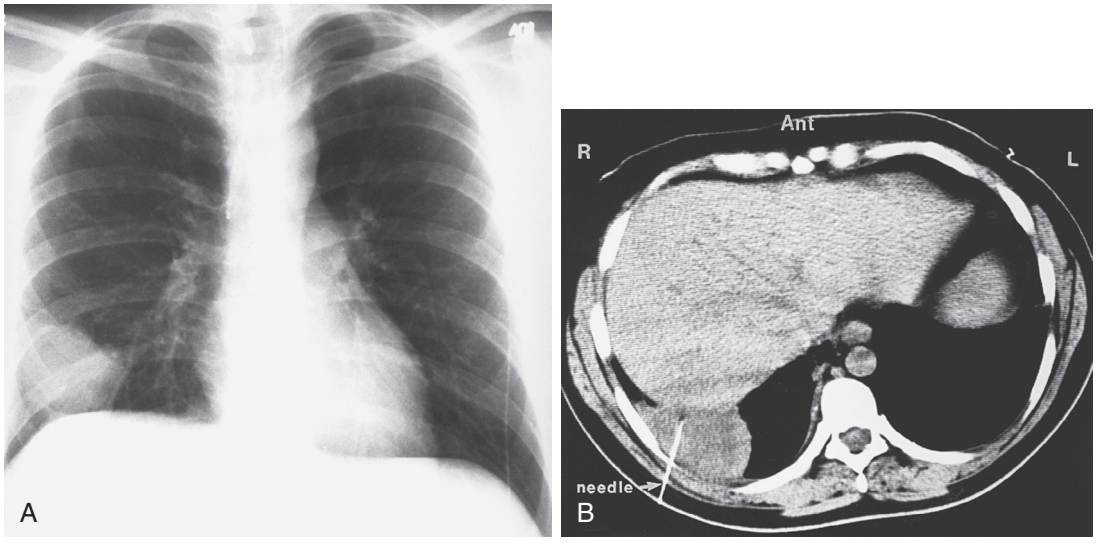


FIGURE A1-8 Lung abscess. On a chest radiograph, a lung abscess may look to be a solid rounded lesion **(A),** or, if it has a connection with the bronchus, there may be an air-fluid level in a thick-walled cavitary lesion. CT scanning **(B)** can be used to localize the lesion and to place a needle for drainage and aspiration of contents for culture. (From Mettler FA [ed]: *Primary care radiology,* Philadelphia, 2000, Saunders.)

SUGGESTED READINGS

Herth F et al.: Endoscopic drainage of lung abscesses: technique and outcome, *Chest* 127(4):1378, 2005.

Levison J et al.: The value of a CT-guided fine needle aspirate in infants with lung abscess, *J Paediatr Child Health* 40(8):474, 2004.

Lorber B: Lung abscess. In *Mandell, Douglas, and Bennett's principles and practice of infectious diseases.* ed 6, New York, Churchill Livingstone.

Mansharamani NG, Koziel H: Chronic lung sepsis: lung abscess, bronchiectasis, and empyema, *Curr Opin Pulm Med* 9(3):181, 2003.

Mansharamani N et al.: Lung abscess in adults: clinical comparison of immunocompromised to non-immunocompromised patients, *Respir Med* 96(3):178, 2002.

Schiza S, Siafakas NM: Clinical presentation and management of empyema, lung abscess and pleural effusion, *Curr Opin Pulm Med* 12(3):205, 2006.

Abscess, Pelvic PTG

BASIC INFORMATION

DEFINITION

Pelvic abscess is an acute or chronic infection, most commonly involving the pelvic viscera. Treatment and possible cure require directed therapy that will involve antibiotic therapy and, if medical therapy fails, subsequent surgical therapy. There are four categories based on etiologic factors:

- Ascending infection, spreading from cervix through endometrial cavity to adnexa, forming a tubo-ovarian complex
- Infection occurring in the puerperium, which spreads to the adnexa from the endometrium or myometrium by a hematogenous or lymphatic route
- Abscess complicating pelvic surgery
- Involvement of the pelvic viscera as a result of spread from contiguous organs, such as appendicitis or diverticulitis

SYNONYMS

Tubo-ovarian abscess (TOA)
Vaginal cuff abscess

ICD-9CM CODES
614.2 Salpingitis and oophoritis not specified as acute, subacute, or chronic

ICD-10CM CODES
N70.93 Salpingitis and oophoritis, unspecified
N70.0 Acute salpingitis and oophoritis
N70.1 Chronic salpingitis and oophoritis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- 34% of hospitalized patients with pelvic inflammatory disease
- 1% to 2% of patients undergoing hysterectomy, most with vaginal approach
- Peak incidence third to fourth decade

RISK FACTORS: Same risk factors as for pelvic inflammatory disease, although in 30% to 50% of patients there is no prior history of salpingitis before abscess forms.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Abdominal or pelvic pain (90%)
- Fever or chills (50%)
- Abnormal bleeding (21%)
- Vaginal discharge (28%)
- Nausea (26%)
- Up to 60% to 80% present in the absence of fever or leukocytosis; absence of these findings should not exclude diagnosis

ETIOLOGY

- Mixed flora of anaerobes, aerobes, and facultative anaerobes, such as *Escherichia coli, Bacteroides fragilis, Prevotella* spp., aerobic streptococci, and *Peptococcus* and *Peptostreptococcus* spp.
- *Neisseria gonorrhoeae* and *Chlamydia* are the major etiologic bacteria in cervicitis and salpingitis but are rarely found in abscess cavity cultures.
- In elderly patients consider diverticular disease.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Pelvic neoplasms, such as ovarian tumors and leiomyomas.
- Inflammatory masses involving adjacent bowel or omentum, such as ruptured appendicitis or diverticulitis.
- Pelvic hematomas, as may occur after cesarean section or hysterectomy.
- Section III describes the diagnostic approach to patients with a pelvic mass; the differential diagnosis of pelvic mass is described in Section II.
- The differential diagnosis of pelvic pain is described in Section II.
- Sonogram or CT scan: commonly used due to associated pain and guarding, resulting in a suboptimal abdominal or pelvic examination, and to characterize anatomic abnormalities such as an adnexal mass.
- Most common cause of preventable death: physician delay in diagnosis.

LABORATORY TESTS

- CBC with differential
- Aerobic as well as anaerobic cultures of cervix, blood, urine, sputum, peritoneal cavity (if entered), and abscess cavity before starting antibiotics
- Pregnancy test in patients of reproductive age

IMAGING STUDIES

- Sonogram: noninvasive, inexpensive study to confirm diagnosis, estimate size of abscess, and monitor response to therapy; sensitivity >90%
- CT scan: used for both diagnosis and therapy (CT-guided drainage) (Fig. EA1-9)
  1. Useful where sonogram provides insufficient information, as with intraabdominal abscesses
  2. Success rate with CT-guided abscess drainage: unilocular, 90%; multilocular, 40%

TREATMENT

Major concerns:
1. Desire for future fertility
2. Likelihood of rupture of abscess, with resulting peritonitis, septic shock, and morbid sequelae

ACUTE GENERAL Rx

- Clinical quandary is whether patient requires immediate surgery (uncertain diagnosis or suspicion of rupture) or management with IV antibiotics, reserving surgery for those with inadequate clinical response (e.g., 48 to 72 hr of therapy, with persistent fever or leukocytosis, increasing size of mass, or suspicion of rupture)
- Surgery indicated in poor response to medical therapy. Early surgery may be needed in those with large adnexal masses (>8 cm), or in immunocompromised patients
- Antibiotic combinations:
  1. Clindamycin 900 mg IV q8h or metronidazole 500 mg IV q6-8h plus gentamicin either 5 to 7 mg/kg q24h or 1.5 mg/kg q8h
  2. Alternatives: ampicillin-sulbactam 3 g IV q6h or cefoxitin 2 g IV q6h or cefotetan 2 g IV q12h plus doxycycline 100 mg IV q12h
- During medical management, high index of suspicion for acute rupture, such as acute worsening of abdominal pain or new-onset tachycardia and hypotension, mandating immediate surgical intervention after patient stabilization
- Surgical options:
  1. Laparoscopy with drainage and irrigation
  2. Transvaginal colpotomy (abscess must be midline, dissect rectovaginal septum, and be adherent to vaginal fornix)
  3. Laparotomy, including total abdominal hysterectomy with bilateral salpingo-oophorectomy or unilateral salpingo-oophorectomy
  4. Evidence of ruptured tubo-ovarian abscess is a surgical emergency

DISPOSITION

- Of patients treated with medical therapy, response in 75%, with a 50% pregnancy rate. Pregnancy rate decreases with recurrent episodes.
- No response in 30% to 40%; can be treated with either CT-guided drainage or surgical intervention, keeping in mind that unilateral adnexectomy may give equal chance of cure versus hysterectomy, yet preserve reproductive potential.

REFERRAL

If patient has a tubo-ovarian abscess, refer to gynecologist.

PEARLS & CONSIDERATIONS

COMMENTS

If *Actinomyces* species is isolated from culture, treatment with penicillin is required for an extended period (6 wk to 3 mo).

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pelvic Inflammatory Disease (Related Key Topic)
Pelvic Abscess (Patient Information)

AUTHORS: **SCOTT J. ZUCCALA, D.O.,** and **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Aimakhu CO et al.: Surgical management of pelvic abscess: laparotomy versus colpotomy, *J Obstet Gynaecol* 23(1):71, 2003.

Sudakoff GS et al.: Transrectal and transvaginal sonographic intervention of infected pelvic fluid collections: a complete approach, *Ultrasound Q* 21(3):175, 2005.

FIGURE EA1-9 CT with oral and intravenous contrast material in patient with large pelvic abscess. Abscess cavity demonstrates classic rim enhancement of abscess wall. Percutaneous drainage should be performed under image guidance. (From Vincent JL et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

A perirectal abscess is a localized inflammatory process that can be associated with infections of soft tissue and anal glands based on anatomic location. Perianal and perirectal abscesses may be simple or complex, causing suppuration. Infections in these spaces may be classified as superficial perianal or perirectal with involvement in the following anatomic spaces: ischiorectal, intersphincteric, perianal, and supralevator. The Parks classification of anorectal abscess is subdivided into intersphincteric, transsphincteric, suprasphincteric, and extrasphincteric abscess (Fig. A1-10).

SYNONYMS

Rectal abscess
Perianal abscess
Anorectal abscess

ICD-9CM CODES
566 Perirectal abscess
ICD-10CM CODES
K61.0 Anal abscess
K61.1 Rectal abscess

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Commonly encountered
PREDOMINANT SEX: Male > female
PREDOMINANT AGE: All ages
PEAK INCIDENCE: Not seasonal; common
GENETICS: None known

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Localized perirectal or anal pain—often worsened with movement or straining
- Perirectal erythema or cellulitis
- Perirectal mass by inspection or palpation
- Fever and signs of sepsis with deep abscess
- Urinary retention

ETIOLOGY

- Polymicrobial aerobic and anaerobic bacteria involving one of the anatomic spaces (see "Definition"), often associated with localized trauma
- Microbiology: most bacteria are polymicrobial, mixed enteric and skin flora
- Predominant anaerobic bacteria:
  1. *Bacteroides fragilis*
  2. *Peptostreptococcus* spp.
  3. *Prevotella* spp.
  4. *Porphyromonas* spp.
  5. *Clostridium* spp.
  6. *Fusobacterium* spp.
- Predominant aerobic bacteria:
  1. *Staphylococcus aureus*
  2. *Streptococcus* spp.
  3. *Escherichia coli*
  4. *Enterococcus* spp.

DIAGNOSIS

Many patients will have predisposing underlying conditions including:
- Malignancy or leukemia
- Immune deficiency
- Diabetes mellitus
- Recent surgery
- Steroid therapy

DIFFERENTIAL DIAGNOSIS

- Neutropenic enterocolitis
- Crohn's disease (inflammatory bowel disease)
- Pilonidal disease
- Hidradenitis suppurativa
- Tuberculosis or actinomycosis; Chagas' disease
- Cancerous lesions
- Chronic anal fistula
- Rectovaginal fistula
- Proctitis—often STD-associated, including: syphilis, gonococcal, chlamydia, chancroid, condylomata acuminata
- AIDS-associated: Kaposi's sarcoma, lymphoma, CMV

WORKUP

- Examination of rectal, perirectal/perineal areas
- Rule out necrotic process and crepitance suggesting deep tissue involvement
- Local aerobic and anaerobic culture
- Blood cultures if toxic, febrile, or compromised
- Possible sigmoidoscopy

IMAGING STUDIES

Usually not indicated unless extensive disease abscess but can include CT. One study showed that CT had only a sensitivity of 77% and was particularly poor in detecting a perirectal abscess in immunocompromised patients.

TREATMENT

ACUTE GENERAL Rx

- Incision and drainage of abscess
- Debridement if necrotic tissue
- Rule out need for fistulectomy
- Local wound care—packing
- Sitz baths
- Antibiotic treatment: directed toward coverage for mixed skin and enteric flora

OUTPATIENT—ORAL:
- Trimethoprim/sulfamethoxazole DS bid or ciprofloxacin 750 mg bid or levofloxacin 750 mg q24h plus metronidazole 500 mg q6h x 7-10 days
- Amoxicillin/clavulanic acid 875 to 1000 mg 2 tabs bid
- Clindamycin 150 to 300 mg PO q8h ± ciprofloxacin

INPATIENT—INTRAVENOUS:
- Piperacillin/tazobactam 3.375 g IV q6 to 8h
- Ampicillin/sulbactam 1.5 to 3 g IV q6h
- Cefotetan 1 to 2 g IV q8h
- Imipenem or meropenem 500 to 1000 mg IV q8h

DISPOSITION

Follow-up with a general surgeon or infectious disease physician is often warranted.

REFERRAL

- General surgeon or colorectal surgeon for drainage.
- AIDS specialist may be needed for perirectal complications of HIV infection.
- Gastroenterologist follow-up may be warranted in Crohn's disease with perirectal fistula and other complications.

PEARLS & CONSIDERATIONS

Perirectal abscess may be a presenting manifestation of type 2 diabetes mellitus in older adults. Check the blood sugar in patients to exclude the possibility of undiagnosed diabetes mellitus.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Perirectal Abscess (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

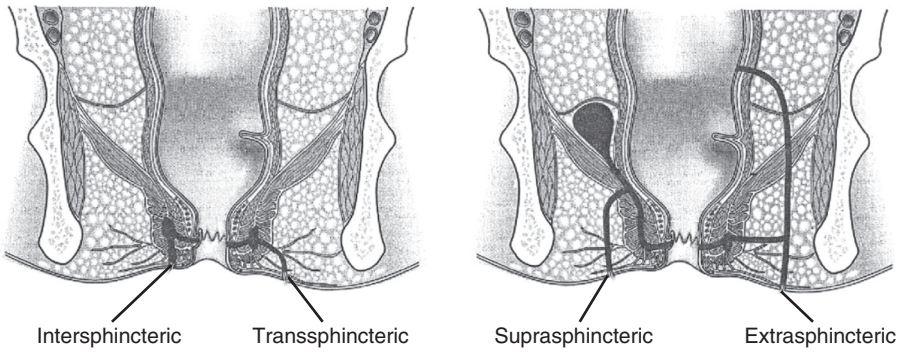


FIGURE A1-10 Parks classification of anorectal abscess. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 10, Philadelphia, 2011, Saunders.)

SUGGESTED READINGS

Caliste X et al.: Sensitivity of computed tomography in detection of perirectal abscess, *Am Surg* 77(2):166–168, 2011.

Marcus RH et al.: Perirectal abscess, *Ann Emerg Med* 25(5):597–603, 1995.

Abscess, Peritonsillar

BASIC INFORMATION

DEFINITION

Peritonsillar abscess is an acute infection located between the capsule of the palatine tonsil and the superior constrictor muscle of the pharynx.

SYNONYMS

Quinsy, PTA

ICD-9CM CODES
475.0 Peritonsillar abscess
ICD-10CM CODES
J36 Peritonsillar abscess

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 30:100,000/yr for ages 5-59. For adolescents, the incidence is 40:100,000/yr. It is the most common deep infection of the head and neck in children and adolescents, accounting for at least 50% of cases.
PEAK INCIDENCE: Bimodal frequency during the year, with highest occurrence from November to December and April to May.
PREVALENCE: 45,000 cases/yr in the United States
PREDOMINANT SEX: Male > female
PREDOMINANT AGE: Highest incidence is adults aged 20-40 yr.
RISK FACTORS: Smoking, periodontal disease, oropharyngeal or dental infection, male gender

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Sore throat, which may be severe and unilateral
- Dysphagia and odynophagia
- Otalgia on the side of abscess
- Foul-smelling breath
- Facial swelling
- Drooling
- Headache
- Fever
- Trismus
- Hoarseness, muffled voice (also called "hot potato voice")
- Tender submandibular and anterior cervical lymph nodes
- Tonsillar hypertrophy with likely peritonsillar edema
- Contralateral deflection of the uvula
- Stridor

ETIOLOGY

- Peritonsillar abscess is usually a complication of tonsillitis or acute bacterial pharyngitis caused by blockage of salivary ducts. Tonsillitis → peritonsillar cellulitis → peritonsillar abscess
- Group A β-hemolytic *Streptococcus* is the most common bacterial cause, accounting for 15% to 30% of cases in children and 5% to 10% of cases in adults.
- Less common aerobic causes are *Staphylococcus aureus, Haemophilus influenzae, Neisseria* species.
- The most common anaerobic organism is *Fusobacterium.*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Tonsillitis
- Infectious mononucleosis
- Peritonsillar cellulitis
- Retropharyngeal abscess
- Epiglottitis
- Dental abscess (retromolar)
- Lymphoma
- Ludwig's angina

WORKUP

- Based on history and physical exam
- Consider additional testing if presentation is less clear.

LABORATORY TESTS

- Consider rapid strep antigen testing and/or pharyngeal culture and sensitivity.
- Aspiration of the abscess for culture and sensitivity (see "Treatment" for role of aspiration in tx)

IMAGING STUDIES

- Consider ultrasound, CT scan (Fig. EA1-11), or MRI to help differentiate abscess from cellulitis or mass.
- Intraoral ultrasound may improve diagnosis and aspiration of PTA compared with visual inspection in adult patients.
- MRI provides better soft-tissue differentiation than CT.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Drainage of the abscess by needle aspiration or by surgical incision and drainage

ACUTE GENERAL Rx

- Aspiration or surgical drainage AND antibiotics for 10 to 14 days
- Initial antibiotics should cover group A *Streptococcus* and anaerobes
  Intravenous
  - Piperacillin/tazobactam or ticarcillin/clavulanate. If penicillin allergic, use IV clindamycin (600-900 mg IV q8h).
  - Ampicillin-sulbactam 3 g q6h
  - Penicillin G 10 million units q6h AND metronidazole 500 mg q6h (may use clindamycin 900 mg q8h if penicillin allergic)

  OR oral
  - Amoxicillin-clavulanic acid 875 mg twice daily
  - Penicillin VK 500 mg 4 times daily AND metronidazole 500 mg 4 times daily
  - Clindamycin 600 mg twice daily or 300 mg 4 times daily
- Selection of antibiotics should be guided by culture and sensitivity of the organism. Consulting local antimicrobial guidelines for resistance profiles is also advisable for empiric coverage before culture results are available.

CHRONIC Rx

- Tonsillectomy can be considered 3 to 6 mo after diagnosis of peritonsillar abscess with or without the diagnosis of recurrent tonsillitis.
- Though rare, in adults and children with an acute case of peritonsillar abscess and a history of recurrent pharyngitis or previous peritonsillar abscess, a specialist may recommend a *quinsy or hot tonsillectomy,* an immediate removal of the tonsils after starting IV antibiotics.

DISPOSITION

- Successful treatment is defined by symptomatic improvement in sore throat, fever, and/or tonsillar swelling within 24 hr of intervention.
- Treatment failure is defined by lack of symptomatic improvement or worsening despite 24 hr of antimicrobial therapy (with or without surgical drainage).

REFERRAL

- Consider ENT or diagnostic radiology for drainage of abscess.
- Consider ENT for tonsillectomy if criteria are met.

PEARLS & CONSIDERATIONS

COMMENTS

- Risk for a recurrence is immediate (within 4 days) and long term (2 to 3 yr).
- Most recurrences occur shortly after the initial presentation, suggesting continued infection rather than recurrence.
- Overall recurrence rate is 10% to 15%.
- Supportive treatment for pain control and hydration. Newer reports suggest a single dose of dexamethasone (10 mg) administered following needle aspiration will reduce pain at 24 hours as compared with placebo (see Suggested Readings).

PREVENTION

- Adequate treatment of peritonsillar abscess.
- Up to 30% of patients with peritonsillar abscess meet criteria for tonsillectomy.

PATIENT/FAMILY EDUCATION

Advise family members to call with any trouble breathing, swallowing, or talking.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **PETER J. SELL, D.O.**, and **AMITY RUBEOR, D.O.**

SUGGESTED READINGS

Al Yaghchi C et al.: Out-patient management of patients with a peritonsillar abscess, *Clin Otolaryngol* 33(1):52–55, 2008.

Chau JKM et al.: Corticosteroids in peritonsillar abscess treatment: a blinded placebo-controlled clinical trial, *Laryngoscope* 124:97–103, 2014.

Dunn N et al.: Use of antibiotics for sore throat and incidence of quinsy, *Br J Gen Pract* 57:45–49, 2007.

Galioto NJ: Peritonsillar abscess, *Am Fam Physician* 77:109–202, 2008.

Johnson RF et al.: An evidence-based review of the treatment of peritonsillar abscess, *Otolaryngol Head Neck Surg* 128(3):332–343, 2003.

Powell EL et al.: A review of the pathogenesis of adult peritonsillar abscess: time for a re-evaluation, *J Antimicrob Chemother* 68:1941–1950, 2013.

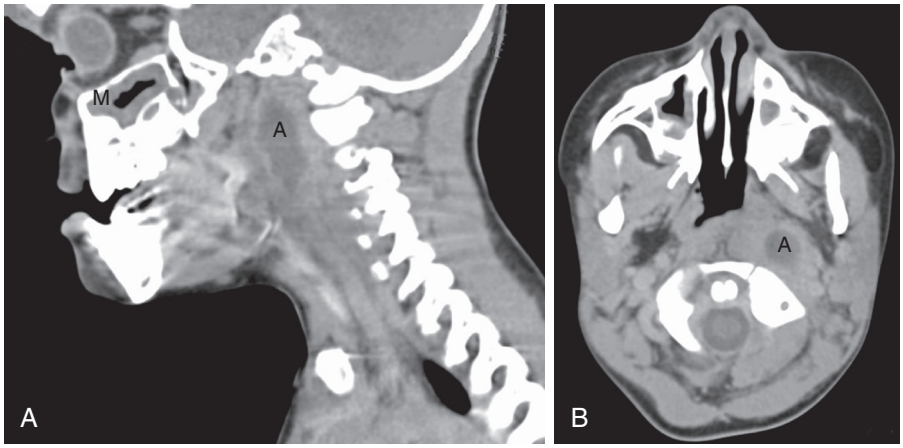


FIGURE EA1-11 CT of parapharyngeal abscess in a 3-yr-old child. A, Sagittal section demonstrating parapharyngeal abscess *(A)* and mucosal swelling *(M)* in the maxillary sinus. **B,** Coronal section of parapharyngeal abscess *(A)*. (From Kliegman RM et al: *Nelson textbook of pediatrics*, ed 19, Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Renal abscess and perinephric abscess are a purulent complication of an underlying urinary infection of the ascending tract with an obstructed pyelonephritis. Predisposing factors include diabetes and renal stones. There is lobar necrosis with renal abscess and perirenal fat necrosis in perinephric abscess.

SYNONYMS

Intrarenal abscess
Perinephric abscess

ICD-9CM CODES
590.2 Renal and perinephric abscess
ICD-10CM CODES
N15.1 Renal and perinephric abscess

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Ranges from 1 to 10 per 10,000 hospital admissions
PREDOMINANT SEX AND AGE: In one study median age was 59.8 years
RISK FACTORS: Diabetes and renal stones

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms include fever, flank pain, abdominal pain, and urinary frequency or dysuria.
- At times renal abscess can present insidiously in the elderly or persons with diabetes.

ETIOLOGY

These infections may be a complication of a urinary tract infection that ascends to the upper tract, usually due to gram-negative bacteria, or a complication of a bacteremia with hematogenous seeding to the kidney, usually secondary to a *Staphylococcus aureus* infection.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute pyelonephritis with papillary necrosis
- Acute lobar nephronia: acute nonsuppurative renal infection
- Renal cell carcinoma
- Malakoplakia: rare granulomatous inflammatory disease seen with *Escherichia coli* infection
- Emphysematous pyelonephritis: gas formation within the renal parenchyma caused by infection by facultative anaerobes or *Candida* spp.

WORKUP

Combination of laboratory tests and imaging

LABORATORY TESTS

- Blood cultures, urine cultures, urinalysis, and CBC are basic tests.
- Elevated ESR or C-reactive protein may be marker for a deep-seated infection.

IMAGING STUDIES

- Ultrasound may show thick-walled fluid-filled cavity in renal parenchyma. A perinephric abscess is confined to the perinephric space by Gerota's fascia.
- CT with contrast is preferred over ultrasound for the diagnosis (Fig. A1-12).
- MRI and nuclear scans are of limited value.

TREATMENT

Antibiotic therapy and, when necessary, interventional radiology or surgical drainage procedure

NONPHARMACOLOGIC THERAPY

- Therapy for a renal abscess greater than 5 cm in diameter should be percutaneous drainage by CT- or US-guided therapy along with intravenous antibiotics.
- A perinephric abscess should be drained percutaneously with CT or US guidance.
- At times a nephrectomy may be required for severe cases, usually in diabetic patients.

FIGURE A1-12 Renal abscess. Contrast-enhanced CT scan shows an abscess in the medulla of the kidney *(arrowhead)* with penetration and extension into the perinephric space *(arrows)*. (Courtesy L. Towner.)

ACUTE GENERAL Rx

A renal abscess less than 5 cm in diameter can be treated successfully with targeted intravenous therapy (92% success rate for abscess 3 to 5 cm in diameter). Antibiotic choices are based on culture results but initially should target gram-negative bacteria unless infection is secondary to staphylococcal bacteremia. Empiric antibiotic therapy in geographic areas where fluoroquinolone resistance rates are <10% consists of ciprofloxacin 400 mg IV loading dose. In areas with high fluoroquinolone resistance rates, ceftriaxone 1 g IV is appropriate. If perinephric abscess is associated with staphylococcal bacteremia, give IV nafcillin if methicillin-susceptible *Staphylococcus aureus* (MSSA) or vancomycin 1 g IV q12h if methicillin-resistant *S. aureus*.

CHRONIC Rx

Antibiotic therapy generally continues for 2 to 3 weeks, some of which can be completed with oral therapy.

DISPOSITION

Antibiotics such as trimethoprim-sulfamethoxazole and quinolone antibiotics penetrate well in the kidney and are ideal oral agents for therapy.

REFERRAL

Interventional radiology, urologic surgeon, and infectious diseases consult

PEARLS & CONSIDERATIONS

COMMENTS

This diagnosis should be considered in patients who are being treated for pyelonephritis with appropriate antibiotics and fail to respond clinically after 5 days.

PREVENTION

Early and targeted therapy for urinary tract infections, especially in diabetic patients

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pyelonephritis (Related Key Topic)
Urinary Tract Infection (Related Key Topic)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Vourganti S et al.: Ultrasonographic evaluation of renal infections, *Radiol Clin North Am* 44:763–775, 2006.

Yen DH et al.: Renal abscess: early diagnosis and treatment, *Am J Emerg Med* 17:192–197, 1999.

Abscess, Retropharyngeal

BASIC INFORMATION

DEFINITION

Retropharyngeal abscess is a soft tissue infection of the throat involving retropharyngeal space. The anatomic boundaries of the retropharyngeal space are the middle layer of the deep cervical fascia (abutting the posterior esophageal wall) anteriorly and the deep layer of the deep cervical fascia posteriorly (Fig. A1-13). These two fasciae fuse inferiorly at the level between the first and second thoracic vertebrae.

ICD-9CM CODES
478.79
ICD-10CM CODES
J39.0 Retropharyngeal and parapharyngeal abscess

EPIDEMIOLOGY & DEMOGRAPHICS

Retropharyngeal abscess occurs most commonly in children between the ages of 2 and 4 yr, analogous to suppurative cervical adenitis. This represents the peak age group for numerous viral upper respiratory tract infections and their attendant complications, acute otitis media and sinusitis. Retropharyngeal space infection is less common in older children and adults because the lymph nodes atrophy by the age of 3 to 4 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The onset of a retropharyngeal infection may be insidious, with little more than fever, irritability, drooling, a muffled voice (dysphonia), or possibly nuchal rigidity.
- The acute symptoms relate to pressure and inflammation produced by the abscess on either the airway or the upper digestive tract and pharynx. The patient may have intense dysphagia, drooling, and odynophagia, or there may be some element of respiratory distress from edema and inflammation of the airway (stridor, tachypnea, or both).
- Unwillingness to move the neck because of discomfort is often a prominent presenting feature and should lead to consideration of retropharyngeal abscess if the child is febrile and irritable.
- Extension of the neck is usually affected more than flexion. This causes the patient to hold his or her neck stiffly or to present with torticollis.
- Trismus is unusual.
- On physical examination it may be possible to appreciate midline or unilateral swelling of the posterior pharyngeal wall. The mass may be fluctuant to the examining finger, and care must be taken to avoid rupture of the abscess into the upper airway.

Complications are numerous and could be fatal; these include airway obstruction, septicemia, thrombosis of the internal jugular vein, carotid artery rupture, and acute necrotizing mediastinitis. Aspiration with resultant pneumonia may complicate retropharyngeal abscess if rupture of the abscess occurs and empties into the airway. Infection can spread from one space in the neck to another.

The most dreaded complication is jugular vein suppurative thrombophlebitis (Lemierre's syndrome), in which the vessels of the carotid sheath become infected, leading to bacteremia and metastatic spread of infection to the lungs, brain, and mediastinum.

ETIOLOGY

- The retropharyngeal space comprises two chains of lymph nodes that drain the nasopharynx, adenoids, posterior paranasal sinuses, middle ear, and eustachian tube. Accordingly, suppurative infections in these areas may provide the seeds for infection for retropharyngeal abscess.
- The predominant bacterial species are *Streptococcus pyogenes* (group A *Streptococcus*), *Staphylococcus aureus,* and respiratory anaerobes (including *Fusobacteria, Prevotella,* and *Veillonella* species). *Haemophilus* species are also occasionally found.
- In young children, infection usually reaches this space by lymphatic spread from a septic focus in the pharynx or sinuses.
- In adults, infection may reach the retropharyngeal space from either local or distant sites. Penetrating trauma (e.g., from chicken bones or iatrogenic) is the usual source of local spread. More distant sources of infection include odontogenic sepsis and peritonsillar abscess (now a rare cause).

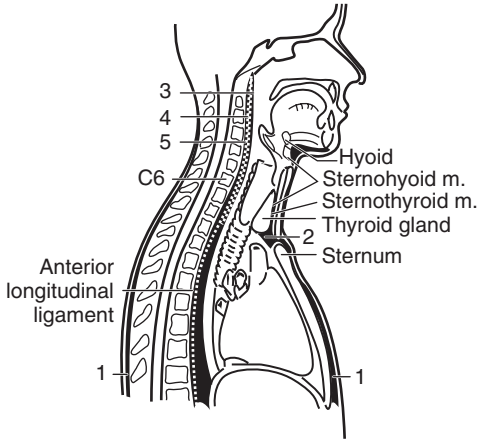
DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cervical osteomyelitis
- Pott's disease
- Meningitis
- Calcific tendonitis of the long muscle of the neck

IMAGING STUDIES

- A lateral neck film may be helpful in delineating the presence of a retropharyngeal abscess and may demonstrate cervical lordosis; the retropharyngeal space is considered widened and pathologic if it is greater than 7 mm at C2 or 14 mm at C6 (Fig. A1-14).
  1. There must be attention to technical issues when performing the study, especially in children. The film should be a perfect lateral, and the child must keep the neck in extension during inspiration to avoid a false thickening of the retropharyngeal space. Crying, particularly in infants, may also cause false thickening of the retropharyngeal space.
- A CT scan of the neck is the best tool to identify abscesses in the retropharyngeal area, but it is not perfect. Both the sensitivity and specificity of the CT scan in predicting the



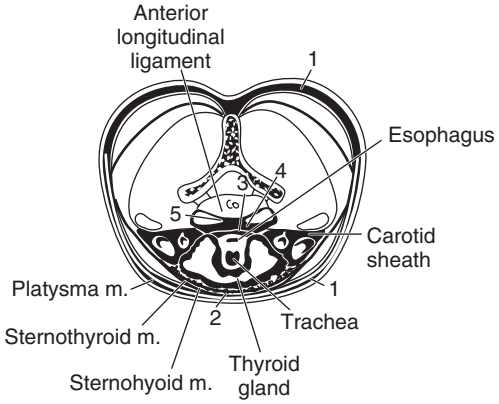


FIGURE A1-13 Relation of various cervical fascial spaces to the superficial and deep layers of the cervical fascia. A, Cross section of the neck at the level of the thyroid isthmus. **B,** Coronal section in the suprahyoid region of the neck. *1,* Superficial space; *2,* pretracheal space; *3,* retropharyngeal space; *4,* "danger" space; *5,* prevertebral space.

presence of drainable purulent material are quite variable from study to study, ranging between 68% and 100%.

1. The CT scan provides more information than the plain radiograph because it can generally differentiate between retropharyngeal cellulitis and retropharyngeal abscess and can demonstrate extension of the retropharyngeal abscess to contiguous spaces in the neck. Findings on CT common to both cellulitis and abscess are a low-density core, soft tissue swelling, obliterated fat planes, and mass effect. The best differential finding on CT scan is "complete rim enhancement," which is indicative of abscess (Fig. A1-15). The abscess may be seen as a mass impinging on the posterior pharyngeal wall.
- MRI of the neck is more sensitive than CT, and technetium scanning can be helpful in detecting bone involvement. T2-weighted images may identify and localize areas of pus for drainage or aspiration. Gadolinium enhancement is important to accurately define the soft tissue component. Finally, MRI is useful for imaging vascular lesions, such as jugular thrombophlebitis.

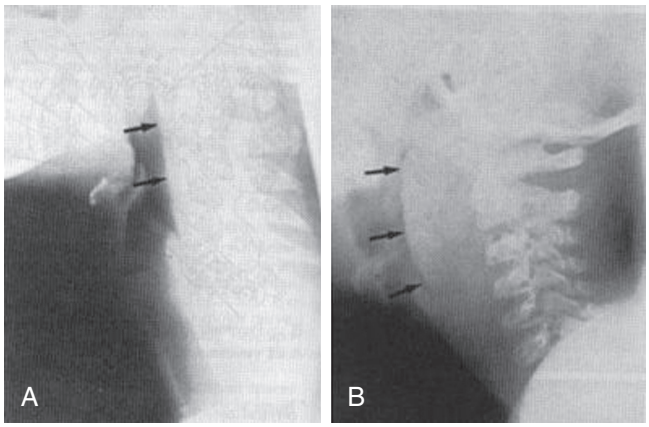


FIGURE A1-14 Lateral radiographs of the neck show normal lateral cervical view **(A)** and expansion of the prevertebral soft tissues by a retropharyngeal abscess **(B).**

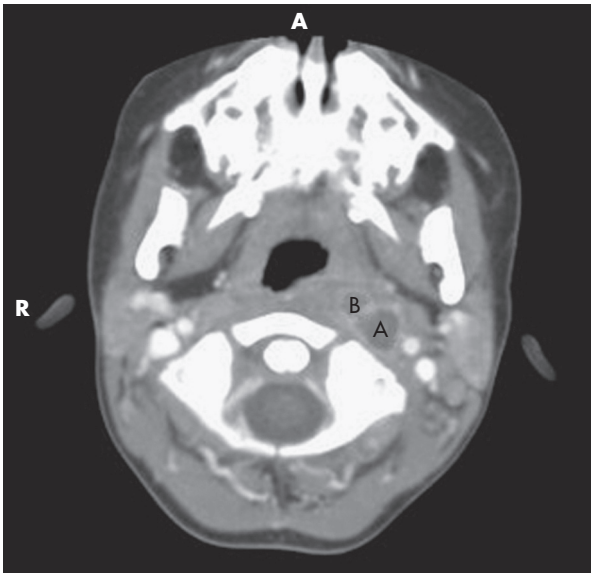


FIGURE A1-15 CT scan of a retropharyngeal abscess (*A* and *B*) demonstrates a low-density core, soft tissue swelling, obliterated fat planes, mass effect, and rim enhancement.

Rx TREATMENT

ACUTE GENERAL & CHRONIC Rx

- High-dose penicillin (2 million to 4 million units IV q4h) plus metronidazole (500 mg IV q8h) or ampicillin-sulbactam (50 mg/kg/dose IV q6h) or clindamycin (13 mg/kg/dose IV q8h) are effective antimicrobial selections. Parenteral treatment is maintained until the patient is afebrile and clinically improved. Antibiotics should be adjusted as culture data become available, and oral therapy is continued to complete at least a 14-day course.
- Surgical intervention has historically played a prominent role in the management of retropharyngeal abscess in conjunction with antibiotic therapy. Drainage is indicated when there is a large hypodense area or when a patient has not responded to parenteral therapy alone.
- When the CT does not demonstrate a large hypodense area, a trial of antibiotic therapy without drainage is appropriate. Some investigators also support a trial of IV antibiotic therapy alone when small abscesses are identified by CT scans as long as there is no compromise of the airway.

PEARLS & CONSIDERATIONS

PREVENTION

The complications of deep neck infection in any space are numerous and potentially fatal. Early diagnosis, with prompt and appropriate management, is key to avoiding these complications.

AUTHOR: **RUBY K. SATPATHY, M.D.**

Absence Seizures PTG

BASIC INFORMATION

DEFINITION

Absence seizures are a type of generalized seizure, characterized by brief episodes of staring with impairment of consciousness (absence). They usually last a few seconds, up to 20 to 30 sec. The onset and the end of the seizures are sudden. Usually the patients are not aware of them and resume the activity they were doing before the seizure. The electroencephalogram signature of absence seizures consists of a generalized 3-Hz spike and slow wave discharges.

SYNONYMS

Childhood absence epilepsy
Petit mal epilepsy

ICD-9CM CODES
345.0 Generalized nonconvulsive epilepsy
ICD-10CM CODES
G40.309 Generalized idiopathic epilepsy and epileptic syndromes, not intractable, without status epilepticus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1 to 10 cases per 100,000 population.
PEAK INCIDENCE: 6 to 7 yr.
PREVALENCE: Represents up to 18% of all pediatric epilepsy syndromes.
PREDOMINANT SEX AND AGE: More common in girls than in boys, absences typically begin between 4 and 8 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with absence seizures usually have normal physical and neurologic examinations.
- During the seizures, the patients are unresponsive and can have motor phenomena (automatisms, eye blinks, mouth and hand movements).
- Tonic clonic seizures are not usually a feature of this syndrome. If this is the case, other etiologies should be investigated, such as juvenile absence epilepsy, juvenile myoclonic epilepsy, complex partial seizures, etc.

ETIOLOGY

Genetic.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Juvenile absence epilepsy.
- Juvenile myoclonic epilepsy.
- Complex partial seizures.

WORKUP

- EEG with hyperventilation and photic stimulation is crucial in the diagnosis.
- Ambulatory EEG and video EEG are recommended for patients with diagnostic uncertainty.

LABORATORY TESTS

No specific studies needed.

IMAGING STUDIES

- MRI of the brain should be performed in all epilepsy patients, especially if the EEG does not show the typical characteristic of absence seizures (3-Hz spike and slow wave discharges).
- CT scans of the head should be avoided in children due to unnecessary exposure to radiation and low yield of the test except when MRI cannot be obtained.

TREATMENT

The medication of choice based on the best current data available is ethosuximide, followed by valproic acid and lamotrigine.

NONPHARMACOLOGIC THERAPY

Not applicable.

GENERAL Rx

- Ethosuximide: initial dose: 10 mg/kg/day; then after 7 days, 20 mg/kg.
- Valproic acid (Depakote): initial dose: 5-10 mg/kg/day (divided bid), maximum dose 60 mg/kg/day
- Lamotrigine: dose for patients on no other antiepileptic drugs. Wk 1 and 2: 0.3 mg/kg/day. Wk 3 and 4: 0.6 mg/kg/day. Wk 5 onward: increase every 1 to 2 wk by 0.6 mg/kg/day. Maintenance: 4.5 to 7.5 mg/kg/day. Warning: should be used with caution due to the potential for toxicity and Stevens-Johnson syndrome. Patients on other antiepileptic drugs can also have severe adverse reactions.

CHRONIC Rx

- Children with recurrent seizures require chronic treatment.
- If children are seizure free for a period of 1 to 2 yr, a trial on no medications should be considered; children, unlike adults, can "outgrow" seizures.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Not applicable.

DISPOSITION

- Response to treatment is excellent.
- Absence seizures tend to remit in teenage years.

REFERRAL

Patients with epilepsy and seizures should be referred for a consultation by a neurologist, preferably one specializing in epilepsy.

PEARLS & CONSIDERATIONS

COMMENTS

- Absence seizures can be present in other epilepsy syndromes.
- Valproic acid should be avoided in girls and women with childbearing potential due to the risk of teratogenicity.
- Carbamazepine and phenytoin should be avoided in the treatment of absence seizures, since these medications may worsen seizures and could provoke absence status epilepticus.
- All women of childbearing age taking antiepileptic drugs should take folic acid supplementation (1 to 4 mg/day) for the prevention of neural tube defects.

PREVENTION

Sleep deprivation and alcohol consumption should be avoided.

PATIENT & FAMILY EDUCATION

- Patients with epilepsy have normal lives.
- The goal of treatment is no seizures and no side effects to medications.
- Patient education and information can be obtained from the Epilepsy Foundation: www.epilepsyfoundation.org.
- Pregnant women with epilepsy should visit the Antiepileptic Drug Pregnancy Registry website for information and assistance: www2.massgeneral.org/aed.
- Patients with ongoing seizures are forbidden to drive; check state regulations and laws regarding driving and epilepsy.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Absence Seizures (Patient Information)

AUTHOR: **PATRICIO SEBASTIAN ESPINOSA, M.D., M.P.H.**

SUGGESTED READINGS

Glauser TA et al.: Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy, *N Engl J Med* 362(9):790–799, 2010.

Wyllie E et al.: *The treatment of epilepsy: principles & practice,* ed 5, Philadelphia, Lippincott Williams & Wilkins.

BASIC INFORMATION

DEFINITION

Definition from the Federal Child Abuse Prevention and Treatment Act (CAPTA): any recent act or failure to act on the part of a parent or caretaker that results in death, serious physical or emotional harm, sexual abuse or exploitation of a child; or an act or failure to act that presents an imminent risk of serious harm to a child.

- Neglect: failure to provide for the basic needs of a child
  1. Physical neglect: failure to provide necessary food, shelter, and supervision
  2. Medical neglect: failure to provide necessary medical or mental health care
  3. Educational neglect: failure to meet educational needs
  4. Emotional neglect: failure to attend to emotional needs, exposure to domestic violence
- Physical abuse: physical injury inflicted by a parent or caregiver intentionally or in the course of excessive discipline
- Sexual abuse: sexual act inflicted by parent or caretaker; includes exploitation and pornography
- Emotional/psychological abuse: pattern of behavior of caretaker toward a child that impairs emotional development. This includes verbal abuse, cruelty, and threats. Difficult to prove. Almost always present when other forms of abuse occur.
- Abandonment: child left and parents' whereabouts unknown.
- Substance abuse: includes: prenatal exposure to mother's use of illicit drugs; manufacture of drugs, e.g., methamphetamine in the presence of a child; selling or giving drugs to a child; use of mood-altering substance by caregivers that impairs their ability to provide care for their child.

SYNONYMS

Child maltreatment syndrome
Physical abuse
Sexual abuse
Battered child syndrome
Shaken baby syndrome
Shaken impact syndrome
Abusive head trauma

Complex coding categorized as physical, psychological, sexual
ICD-9-CM and DSM-5 CODES
995.51-995.54
ICD-10CM CODES

T74	Adult and child abuse, neglect or other maltreatment, confirmed
T74.02	Child neglect or abandonment, confirmed
T74.12	Child physical abuse, confirmed
T74.32	Child psychological abuse confirmed
T74.22	Child sexual abuse, confirmed

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Any reports of incidence are underestimates because many cases are not recognized or reported. The following data are based on Child Protective Services (CPS) state aggregate as reported in *Child Maltreatment 2012*. In 2012, roughly 686,000 unique children were determined to be victims of abuse or neglect. This is a rate of 9.2 unduplicated victims per 1000 children.

- Types of abuse by percentage (note the total is greater than 100% since children are often victims of more than one type of abuse).
  1. Neglect: 78.3%
  2. Physical abuse: 18.3%
  3. Sexual abuse: 9.3%
  4. Psychological abuse: 8.5%
  5. Medical neglect: 2.3%
  6. Other: 10.1% (e.g., abandonment, threats of harm, congenital drug addiction)
- For 2012, an estimated 1640 child deaths were caused by abuse or neglect.
  1. Overall annual death rate resulting from abuse or neglect is estimated to be 2.2 deaths/100,000 children.
  2. 69.9% of these deaths were due to neglect alone or in combination with other forms of abuse; 44% were due to physical abuse; alone or in combination.
  3. 70.3% of these children were younger than 3 yr of age with 44% less than 1 yr old.
  4. Most fatalities were directly caused by one or both parents (80%).
  5. Many child abuse fatalities are underreported because of misdiagnosis or variations in state definitions and coding.
- 80% of abused children were victimized by one or both of their parents.
- One fifth of adult women report history of molestation or sexual assault as a child or adolescent.

PREDOMINANT SEX: There is a slight predominance of girls as victims. However, boys have a higher child fatality rate than girls (2.54/100,000 for boys and 1.94/100,000 for girls).
PREDOMINANT AGE: Youngest children (0 to 3 yr old) have the highest rates of victimization with 27% being younger than the age of 3.
GENETICS: No known genetic factors.

ETIOLOGY

Multiple factors contribute to the incidence. No factor or combination of factors can definitively predict which children will be victimized. Factors contributing to risk of abuse or neglect include the following:

- Parent
  1. Substance abuse
  2. Mental illness
  3. Intellectual impairment
  4. Parental history of being abused as a child
- Child
  1. Low birth weight or prematurity
  2. Chronic physical disability
- Family
  1. Social isolation
  2. Poor parent-child bonding
  3. Stress: unemployment, chronic illness, eviction, arrest, poverty
  4. Domestic violence
- Community/society
  1. Limited transportation
  2. Limited day care
  3. Unsafe neighborhoods
  4. Poverty

DIAGNOSIS

Careful history and physical examination are the most important aspects of the evaluation. Careful documentation of any statements regarding origin of injuries or history of abuse is crucial. Chart and photographic documentation

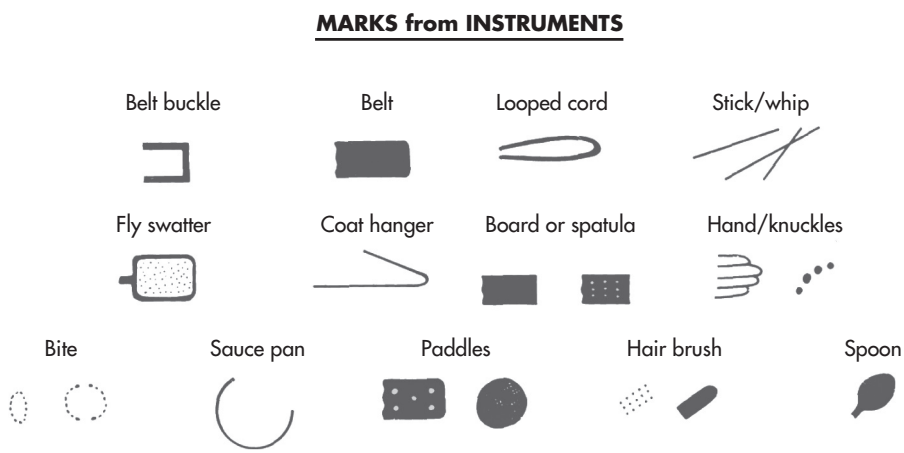


FIGURE A1-16 A variety of instruments may be used to inflict injury on a child. Often the choice of an instrument is a matter of convenience. Marks tend to silhouette or outline the shape of the instrument. The possibility of intentional trauma should prompt a high degree of suspicion when injuries to a child are geometric, paired, mirrored, of various ages or types, or on relatively protected parts of the body. Early recognition of intentional trauma is important to provide therapy and prevent escalation to more serious injury. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

of injuries is also essential. The following are keys to the final diagnosis:

- Patterned bruising (e.g., loop-shaped, square, oval) is indicative of being struck with an object (Fig. A1-16).
- Injury observed is incompatible with the history provided.
- History of injury provided is incompatible with the developmental capabilities of the child.
- Delay in seeking care for a significant injury (e.g., callus formation on a fracture, eschar formation on a burn).
- Bruising is rare in healthy preambulatory infants and warrants further investigation.
- Multiple significant injuries of different ages.
- Infant with clinically significant head trauma attributed to a trivial cause (e.g., a short fall). Often associated with retinal hemorrhages and skeletal fractures, which are indicative of shaken baby syndrome or abusive head trauma.
- Certain fractures in infants without a history of significant trauma (e.g., motor vehicle accident) are characteristic of abuse: metaphyseal, rib, sternum, scapula, vertebral body.
- Inflicted contact burns are indicated by an impression of the burning object: lighter, iron, cigarette (Fig. A1-17).
- Inflicted immersion burns are indicated by "stocking" burns of the feet or "glove" burns of the hands. Stocking burns are often associated with buttocks/perineal burns from immersion of a minor in a flexed position.
- Most sexual abuse victims will have a normal or nonspecific genital examination. A normal genital examination does not mean the child was not abused. History is the most important part of the diagnosis. Forensic interview by a trained professional is recommended, as is an examination by a health care provider experienced in child sexual abuse evaluations for child and adolescent victims of sexual abuse.
- The identification of a sexually transmitted disease in a prepubertal child who is beyond the neonatal period is suggestive of sexual abuse. Reporting and further careful investigation are warranted. Consult current CDC guidelines and a child sexual abuse expert for further guidance.

DIFFERENTIAL DIAGNOSIS

In all categories, accidental injury is the most common entity to be distinguished from abuse. Accidental injuries are most common over bony prominences: forehead, elbows, knees, shins; soft, fleshy areas are more common for inflicted injury: buttocks, thighs, upper arms. Table A1-6 describes patterns of injury.

BRUISING:

- Bleeding disorder (idiopathic thrombocytopenic purpura, hemophilia, leukemia, hemorrhagic disease of the newborn, von Willebrand's disease)
- Connective tissue disorder (Ehlers-Danlos syndrome, vasculitis)
- Pigments (Mongolian spots)
- Dermatitis (phytophotodermatitis, nickel allergy)
- Folk treatment (coining, cupping)

BURNS:

- Chemical burn
- Impetigo
- Folk treatment (moxibustion)
- Dermatitis (phytophotodermatitis)

INTRACRANIAL HEMORRHAGE:

- Bleeding disorder
- Perinatal trauma (should resolve by 4 wk)
- Arteriovenous malformation rupture
- Glutaric aciduria

FRACTURES:

- Osteogenesis imperfecta
- Rickets
- Congenital syphilis
- Very low birth weight (osteopenia of prematurity)

SEXUAL ABUSE:

- Normal variants
- Lichen sclerosis et atrophicus
- Congenital abnormalities
- Urethral prolapse
- Hemangioma
- Nonsexually acquired infection (group A *Streptococcus, Shigella*)

WORKUP (Fig. EA1-18)

History and physical examination:

- Careful history from all caretakers and child.
- Scene investigation may be necessary.
- Complete physical examination.
- Sexual abuse: forensic interview and magnified examinations by trained professionals are the standard for evaluation and evidence collection. This is especially important to avoid further psychological or physical trauma to the child.

Laboratory tests to assess for bleeding disorder in the case of children with suspicious bruising. These tests may not be necessary if the abuse was witnessed or if the child has clear patterned bruising or other indicators of physical abuse:

- CBC with differential and platelets.
- Prothrombin time, activated partial thromboplastin time.
- Von Willebrand factor antigen and activity
- Factor VIII and IX levels
- Alanine aminotransferase, amylase, urinalysis should be considered in infants or other children with abdominal bruising to look for evidence of internal injury to the liver, pancreas, or kidneys.

Laboratory tests to assess for bleeding disorder in the case of children with suspicious ICH. These tests may not be necessary if the abuse was witnessed or if the child has clear patterned bruising or other indicators of physical abuse:

- CBC with differential and platelets.
- Prothrombin time, activated partial thromboplastin time.
- Factor VIII and IX levels
- DIC Panel
- Consultation with a child abuse expert physician should be strongly considered to ensure that appropriate medical evaluation is carried out in children with suspicion of abusive head trauma.

Laboratory tests for sexual abuse:

- If within 72 hr of acute sexual assault/abuse, swabs are obtained from the oropharynx, areas of skin exposure (use an alternate light source to ID), genitalia, and rectum to send to the crime lab for DNA and other testing. Also collect samples of foreign hair, blood, saliva, or other tissue if present. A wet mount from cervical/vaginal specimen should be done to look for motile sperm.

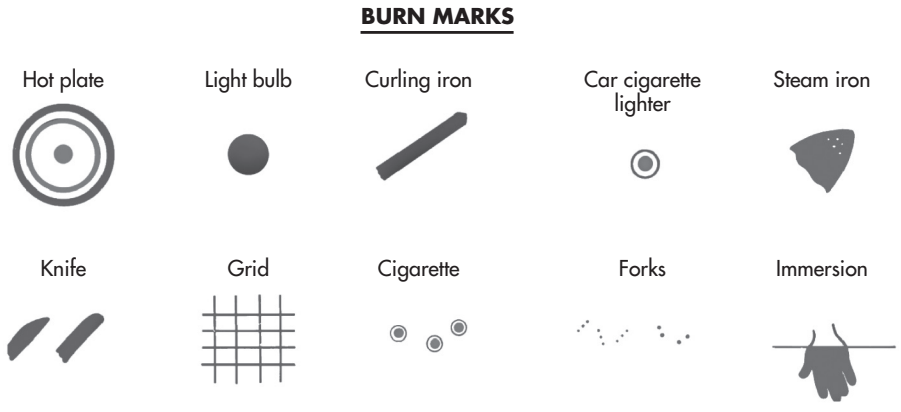


FIGURE A1-17 Marks from heated objects cause burns in a pattern that duplicates that of the object. Familiarity with the common heated objects that are used to traumatize children facilitates recognition of possible intentional injuries. The location of the burn is important in determining its cause. Children tend to explore surfaces with the palmar surface of the hand and rarely touch a heated object repeatedly or for a long time. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

TABLE A1-6 Patterns of Injury

Accidental	Nonaccidental
Unilateral	Bilateral/symmetrical
Isolated injury	Multiple injuries
Amorphous shape	Well-defined shape
Prominent bone areas	Soft tissue areas
Posterior aspect of body	Anterior aspect of body
One age of injury	Multiple ages of injury

From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.

- Per current CDC recommendations, adolescent victims of acute assault should have appropriate specimens collected from sites of penetration or attempted penetration for *Neisseria gonorrheae* and *Chlamydia.* Nucleic acid amplification tests (NAATs) may be used and are preferred. In females, wet mount and culture or POC testing of vaginal swab for *T. vaginalis* should also be done. If there is itching, vaginal discharge or malodor present, wet mount for bacterial vaginosis and *Candida* should also be done. Serum should be obtained for HIV, hepatitis B, and syphilis testing acutely. If negative, HIV and syphilis testing should be repeated 6, 12, and 24 wk after the assault.
- Child victims (i.e., prepubertal) should have specimens collected if considered high risk for a sexually transmitted infection (STI) per current CDC recommendations. Cervical specimens are not collected and vaginal specimens must be collected with care by an experienced provider to avoid further trauma to the child. Gonorrhea and *Chlamydia* culture is the gold standard for diagnosis and legal purposes. However, many providers now analyze specimens using urine or vaginal NAAT followed by culture confirmation or 2nd NAAT if any positive results are obtained. However, extragenital sites should have cultures obtained when assessing for gonorrhea and *Chlamydia*. Any culture testing positive for *N. gonorrheae* should be confirmed by at least two laboratory tests that are based on different principles. Specimens should be collected for gonorrhea and *Chlamydia,* wet mount, and blood for serologic testing (HIV, hepatitis B, syphilis) in the following cases:
  1. Child has a past or current symptom of an STI, such as vaginal discharge, genital ulcer, or vaginal pain or currently diagnosed STI
  2. Alleged assailant is known to have an STI or be at high risk for an STI
  3. A sibling or adult in the same household has a known STI
  4. Evidence of ejaculation or of oral, genital, and/or anal penetration is present on the examination
  5. Child or parent requests testing

IMAGING STUDIES

Physical abuse:

- Radiographic skeletal survey for all children up to 2 yr; for 2- to 5-yr-olds, done only for severe abuse. Consider repeat skeletal survey in 2 wk if severe physical injury is present. Adjunct imaging (MRI, ultrasound, bone scan) may be useful to further define suspicious lesions seen on plain films.
- Noncontrast head CT scan or MRI for all children <1 yr; for children over 1 yr, clinical judgment should be used.
- Head MRI for children with significant abusive head trauma. This is used as an adjunct a few days after initial head CT.
- Abdominal CT scan if indicated by clinical examination or laboratory evaluation.
- Box EA1-2 describes the specificity of radiologic findings for child abuse.

Rx TREATMENT

ACUTE GENERAL Rx

- Stabilize and treat acute medical injuries.
- Report to Child Protective Services. HIPAA allows reports for suspected child abuse without parental authorization.
- Early report to law enforcement for suspected physical abuse or sexual abuse to allow scene investigation.
- Disposition, once medically stable, is dependent on CPS. The child cannot be returned home if the environment is not safe.
- Physician should remain available to discuss with investigators. This is often critical to determining the outcome of the case and placement of the child.
- Because follow-up of adolescent sexual assault victims can be difficult, many experts recommend offering empiric treatment for STIs: gonorrhea, *Chlamydia, Trichomonas,* and bacterial vaginosis. Pregnancy prophylaxis should also be offered. Hepatitis B immunization should be offered if not previously given. HIV prophylaxis is offered in certain situations depending on local epidemiology and type of assault. Consult local infectious disease experts for current recommendations. Repeat examination should be done in 2 wk for all victims of sexual assault, especially if they declined empiric treatment. If empiric treatment was not done, STI testing should be repeated at the 2-week follow-up visit.
- Empiric treatment of child victims of sexual abuse is generally not recommended. This is especially important if NAATs are used for screening for STIs because confirmation is necessary for any positive results. Careful follow-up within 2 wk and treatment based on culture results are indicated. HIV prophylaxis is offered in certain circumstances according to local epidemiology and risk. Consult with a local infectious disease expert for further recommendations.

CHRONIC Rx

- Often depends on CPS and court-ordered interventions
- Treatment of parental mental illness
- Treatment of parental substance abuse, including requirements for random drug testing
- Instruction for parents in behavior management skills, including appropriate limit setting and discipline
- Anger management classes for parents
- Trauma-focused cognitive-behavioral therapy is an evidence-based practice for victims of sexual abuse and exposure to domestic violence; useful to include nonoffending parent/caregiver
- Ongoing individual and family therapy
  1. Parent-child interactive therapy is an evidence-based practice that is used with young children with behavioral problems and parent-child relationship problems
  2. Child-parent psychotherapy is an evidence-based practice that is for young children (<5 yr) who have experienced a trauma and their caregivers
- May need long-term placement in foster care before it is safe to return home. In extreme cases of abuse, parental rights may be terminated without offering services.

OUTCOMES

- Victims of chronic abuse and neglect:
  1. Have higher rates of mental illness (depression, suicide, posttraumatic stress disorder, eating disorders)
  2. Have more cognitive difficulties, often impaired academic performance
  3. Are more likely to become aggressive
  4. Are more likely as adults to have adverse physical health outcomes (cardiovascular disease, cancer, STDs)
- Victims of abusive head trauma:
  1. One third die, one third have severe disability, one third appear normal in the short term.

PEARLS & CONSIDERATIONS

PREVENTION

- Home visitation by a specially trained nurse to high-risk families during pregnancy and infancy has shown positive outcomes (Nurse-Family Partnership).
- Anticipatory guidance at health visits to teach normal developmental expectations and appropriate discipline.
- Screening to identify at-risk or abused children.
- Targeted education in the newborn nursery for shaken baby prevention has been shown to be effective.
- Substance abuse prevention and treatment.
- Identification and intervention for domestic violence before children are born.

SUGGESTED READINGS

available at www.expertconsult.com

RELATED CONTENT

Protecting Children from Abuse (Patient Information)

AUTHOR: **NANCY R. GRAFF, M.D.**

SUGGESTED READINGS

Adams JA: Medical evaluation of suspected child sexual abuse: 2011 update, *J Child Sex Abuse* 20(5):588–605, 2011.

American Academy of Pediatrics Section on Radiology: Diagnostic Imaging of Child Abuse, *Pediatrics* 123(5):1430–1435, 2009.

Anderst JD et al.: Evaluation for bleeding disorders in suspected child abuse, *Pediatrics* 131(4):e1314–e1322, 2013.

Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines 2010, *MMWR Morb Mortal Wkly Rep* 59(RR-12), 2010.

Dubowitz H: Tackling child neglect: a role for pediatricians, *Pediatr Clin North Am* 56(2):363–378, 2009.

Gilbert R et al.: Burden and consequences of child maltreatment in high-income countries, *Lancet* 373(9657):68–81, 2009.

Girardet RG et al.: Epidemiology of sexually transmitted infections in suspected child victims of sexual assault, *Pediatrics* 124(1):79–86, 2009.

Kodner C, Wetherton A: Diagnosis and management of physical abuse in children, *Am Fam Phys* 88(15):669–675, 2013.

Saperia J et al.: Guideline Development Group and Technical Team: When to suspect child maltreatment: summary of NICE guidelines, *BMJ* 339:b2689, 2009.

U.S. Department of Health and Human Services: Available at http://www.acf.hhs.gov/programs/cb/resource/child-maltreatment-2012. *Child Maltreatment*, 2011.

BOX EA1-2 Specificity of Radiologic Findings for Child Abuse

High Specificity
Classic metaphyseal lesions
Rib fractures, especially posterior
Scapular fractures
Spinous process fractures
Sternal fractures

Moderate Specificity
Multiple fractures, especially bilateral
Fractures of different ages
Epiphyseal separations
Vertebral body fractures and subluxations
Digital fractures
Complex skull fractures

Common but Low Specificity
Subperiosteal new bone formation
Clavicular fractures
Long bone shaft fractures
Linear skull fractures

From Manaster BJ: *Musculoskeletal imaging—the requisites,* ed 3, Philadelphia, Mosby, 2006.

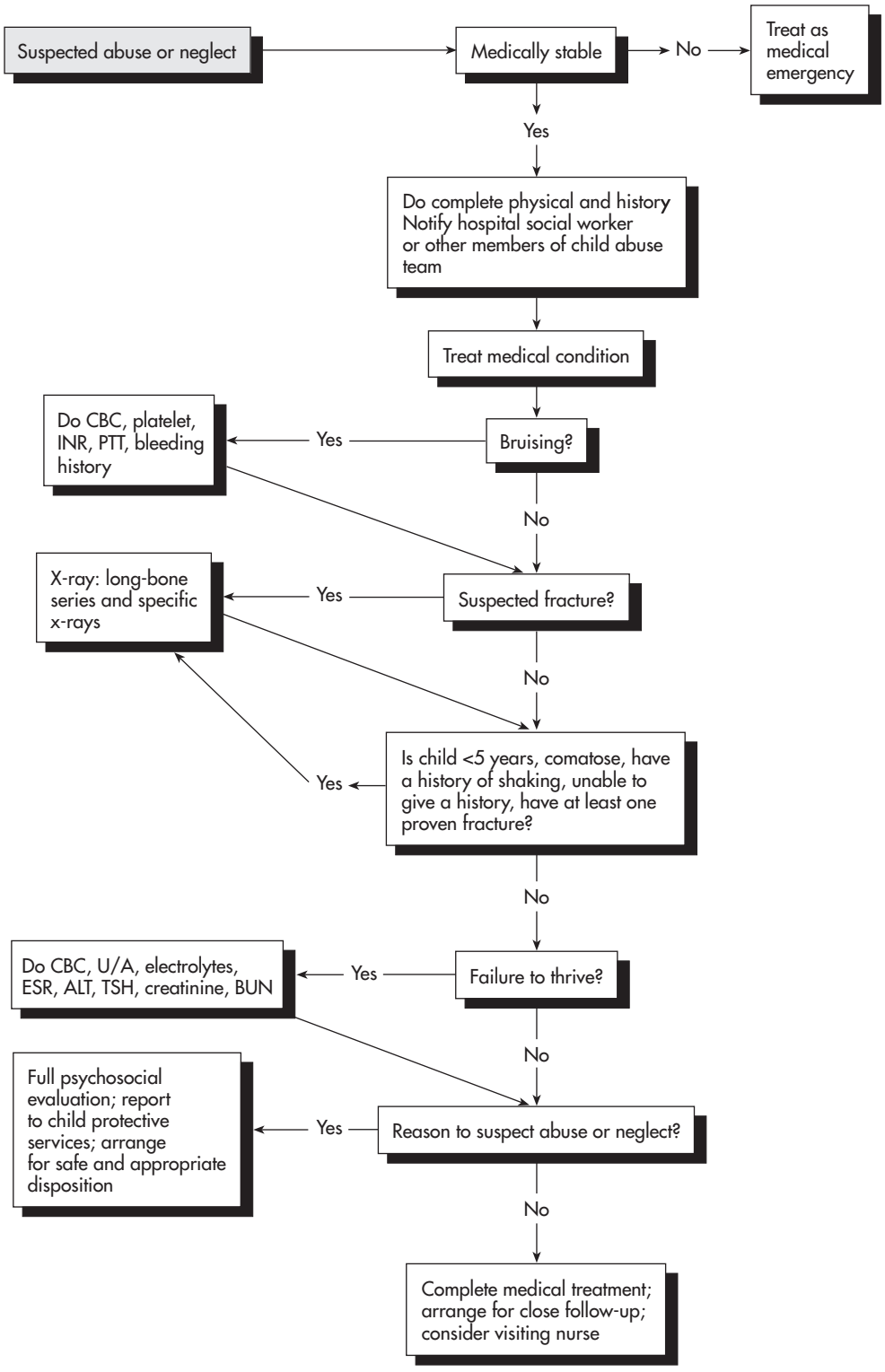


FIGURE EA1-18 Management of suspected child abuse. *ALT,* Alanine aminotransferase; *BUN,* blood urea nitrogen; *CBC,* complete blood count; *ESR,* erythrocyte sedimentation rate; *INR,* international normalized ratio; *PTT,* partial thromboplastin time; *U/A,* urinalysis.

BASIC INFORMATION

DEFINITION

Drug abuse is a recurring pattern of harmful use of a substance despite adverse consequences to work, school, relationships, the legal system, or physical health. This may occur concurrently with or independently from *substance dependence,* in which the impairment or distress is more pervasive and often (though not necessarily) includes physical dependence and withdrawal symptoms (Table A1-7).

SYNONYMS

Substance use disorder
Substance abuse
Addiction

ICD-9CM and DSM-5 codes are defined by specific substance.
ICD-10CM CODES
F19.129 Other psychoactive substance abuse, unspecified
F10-F19 Defined by specific substance
The new term *substance use disorder* in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) combines the categories of substance abuse and substance dependence into a single disorder measured on a continuum from mild to severe.

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Alcohol or drug dependence: 5% to 10% of population
PREVALENCE (IN U.S.): Approximately 15% of patients in primary care practice have an at-risk pattern of drug and/or alcohol use; lifetime prevalence of any alcohol use disorder: 30%; prescription drug misuse is on the rise with 5% past-year prevalence.
PREDOMINANT SEX: Males > females
PREDOMINANT AGE:
- Problematic use of substances may begin in early life (8 to 10 yr).
- Mean age of onset of problem drinking is approximately 25 yr for men and 30 yr for women.

PEAK INCIDENCE: For most substances: age 15 to 30 yr

DURATION OF CONDITION:
- Men: average >20 yr of heavy drinking
- Women: average 15 yr of heavy drinking
- In general, substance use disorders are chronic and relapsing and often progressive

GENETICS: There is evidence of nonspecific genetic factors. Addiction may result in part from underlying, inherited abnormalities in brain structure that impair behavior control and encourage impulsive behavior.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Polysubstance use and comorbidity with psychiatric disorders are common.
- History often reveals recurring behavioral problems, such as relationship, work, or legal problems; violence and traumatic injuries; and anxiety, depression, insomnia, and cognitive and memory dysfunction.
- Repeated requests for early refills of controlled substances and obtaining prescriptions from multiple providers should raise concern for prescription drug abuse (Table A1-8).
- Physical findings may include injection marks, nasal lesions or recurrent epistaxis, poor dentition, scars or bruises from falls or trauma, and poor nutritional status; signs/symptoms of intoxication or withdrawal are highly suggestive of substance use disorder.

ETIOLOGY

Several models of addiction have been proposed:
1. Disease model: Addiction is a mental illness, which occurs as a result of the impairment of healthy neurochemical or behavioral processes.
2. Genetic model: Genetic predisposition is often a factor in dependency and certain addictive behaviors.
3. Social model: Person–environment interactions (i.e., socialization, imitation of observable behavior, and the influence of modeling) shape addictive behavior.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Psychiatric disorders such as depression, mania, psychosis, and anxiety disorders may coexist or occur as a consequence of substance use.
- Rule out seizure disorder and underlying illness.

WORKUP

- A thorough history is crucial for diagnosis.
- The physician's history-taking style and techniques strongly affect patient's willingness to report use and participate in future treatment activities.
- A structured, nonjudgmental approach is generally preferable:
  1. Ask about quantity and frequency of alcohol or drug use. For example, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) declares that *problem drinking* is defined as more than 2 drinks per day for men and more than 1 drink per day for women or anyone older than 65 yr.
  2. Use a short screening instrument such as the CAGE questionnaire ("1. Have you ever felt you need to cut down on your alcohol or drug use? 2. Have people annoyed you by criticizing your alcohol or drug use? 3. Have you ever felt guilty about alcohol or drug use? 4. Have you ever felt you need to drink first thing in the morning [Eye opener] to stop shakiness?").

TABLE A1-7 Key Features of Substance Abuse

1. The substance is often taken in larger amounts over a longer period than intended
2. Unsuccessful efforts to cut down
3. A great deal of time spent obtaining the substance or recovering from its effects
4. Craving
5. Social, occupational, or recreational
6. Recurrent despite hazards
7. Tolerance or withdrawal

Reprinted from Goldman L, Bennett JC (eds): *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, Saunders.

TABLE A1-8 "Red Flags" for Abuse Behavior and Opioid Addiction

Potential Abuse/Addiction Behaviors*

1. Patient displays an overwhelming focus on opioid issues during clinic visits that occupies a significant proportion of the clinic visit and impedes progress with other pain issues or medical problems.
2. Patient has a pattern of early refills (three or more) or escalating drug use in the absence of acute change or progression of his or her medical condition.
3. Patient generates multiple telephone calls or unscheduled visits to request more opioids, early refills, or problems associated with the opioid prescription that often creates a disturbance of the clinic staff.
4. There is a pattern of prescription problems with reports of medications lost, spilled, or stolen.
5 Patient has supplemental sources of opioids from multiple providers, emergency departments, or illegal sources.

Additional "Red Flag" Abuse Behavior

1. Selling prescribed medications
2. Prescription forgery
3. Stealing another patient's medications
4. Injecting or snorting oral medication
5. Concurrent use of illicit drug(s)
6. Appears intoxicated or oversedated
7. Insists on obtaining a specific opioid medication

*Adapted from Chabal criteria for opioid abuse.
From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

- Problematic behavior during intoxication or withdrawal is diagnostic.
- Because self-report of substance use and its consequences can be unreliable, obtaining corroborating information, such as from family members, past detoxifications, or drug rehabilitations is often helpful.
- Adolescent drug abuse detection and treatment is extremely challenging. Stages of adolescent substance use are described in Table A1-9. An assessment for evaluating the seriousness of adolescent drug abuse is described in Table A1-10.

LABORATORY TESTS

- Blood alcohol content (BAC) measured on the breath is practical to define intoxication and provides a rough measure of impairment.
- Obtain toxicology screen in urine or blood samples.
- Biologic markers such as elevated mean corpuscular volume (MCV), γ-glutamyltransferase (GGT), liver function tests (AST and ALT), and carbohydrate deficient transferrin (CDT) may also be used to diagnose and monitor.

IMAGING STUDIES

Not helpful in routine diagnosis and management of substance abuse, but possibly useful in the management of sequelae of substance abuse (e.g., brain imaging to evaluate the alcohol abuse–associated increased risk of subdural hematomas or increased evidence of cerebral atrophy).

TABLE A1-9 Stages of Adolescent Substance Abuse

Stage	Description
1	Potential for abuse Decreased impulse control Need for immediate gratification Available drugs, alcohol, inhalants Need for peer acceptance
2	Experimentation: learning the euphoria Use of inhalants, tobacco, marijuana, and alcohol with friends Few, if any, consequences Use may increase to weekends regularly Little change in behavior
3	Regular use: seeking the euphoria Use of other drugs, e.g., stimulants, LSD, sedatives Behavioral changes and some consequences Increased frequency of use; use alone Buying or stealing drugs
4	Regular use: preoccupation with the "high" Daily use of drugs Loss of control Multiple consequences and risk-taking Estrangement from family and "straight" friends
5	Burnout: use of drugs to feel normal Polysubstance use/cross-addiction Guilt, withdrawal, shame, remorse, depression Physical and mental deterioration Increased risk-taking, self-destructive, suicidal

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- First assess readiness for change; if precontemplative or contemplative, counsel about risks of use and benefits of abstinence; a motivational interviewing approach has been shown to be effective.
- Nonpharmacologic strategies have the greatest documented efficacy: advice, feedback, goal setting, problem solving, and additional contacts for further assistance.
- Opiate contracts, prohibiting a patient from getting early refills or obtaining opiates from multiple prescribers, should be considered for all patients with chronic pain receiving opioid painkillers, especially for patients with a history of substance abuse or medication abuse.
- Relapse prevention facilitated by avoidance of trigger stimuli or by uncoupling trigger stimuli from substance ingestion.
- Self-help and support groups such as Alcoholics Anonymous and Narcotics Anonymous are helpful in achieving and maintaining sobriety.
- Residential or inpatient treatment programs should be a consideration for any individual with continued or escalating use despite outpatient treatment.

ACUTE GENERAL Rx

- Detoxification is an important first step in substance abuse treatment. Its goals are to facilitate withdrawal and reduce symptoms, initiate abstinence, and refer the patient to ongoing treatment.
- Benzodiazepines are effective in acute alcohol withdrawal for the management of symptoms as well as the prevention of seizures. One strategy is to give the patient a loading dose of a long-acting benzodiazepine (e.g., 20 mg of diazepam) and then continue the benzodiazepine as scheduled while tapering down the dose gradually. An alternative "symptom-driven" strategy is to follow the patient closely with serial assessments, such as the Clinical Institute Withdrawal Assessment for Alcohol (CIWA) scale, and to dose with 1 to 2 mg of lorazepam as needed to treat withdrawal symptoms.
- The prophylactic administration of thiamine and folic acid (first intravenously or intramuscularly followed by supplemental oral doses) in alcohol withdrawal is recommended before starting any carbohydrate-containing fluids or food to prevent Wernicke-Korsakaff syndrome (alcoholic encephalopathy and psychosis). Magnesium appears to be effective in the treatment of alcohol withdrawal–related cardiac arrhythmias, but not other symptoms of alcohol withdrawal.
- Beta-blockers and clonidine generally should be avoided in alcohol withdrawal; they may mask markers of the severity of the withdrawal (blood pressure and pulse rate).
- Unlike withdrawal from alcohol or benzodiazepines, opioid withdrawal is not life threatening.
- Clonidine alleviates the discomfort of opiate withdrawal. Clonidine tablets, 0.1 mg q4-6h as needed, can be used while monitoring patient's blood pressure. Clonidine transdermal patch, 0.1 mg/24 hr, can be used to treat autonomic hyperactivity symptoms; however, it has a very slow onset and may take 2-3 days to achieve therapeutic levels. Antidiarrheals, ibuprofen, and dicyclomine can be used as adjuncts to treat opiate withdrawal symptoms.
- Methadone taper is an effective approach for detoxification in opioid dependence.
- Buprenorphine is a partial μ-opioid receptor agonist that may be used for detoxification and maintenance in treatment of opioid dependence (see dosing in next section).

CHRONIC Rx

- Naltrexone helps reduce craving for alcohol. Naltrexone 50 mg once daily for 12 wk can be a useful adjunct to substance abuse counseling or rehabilitation programs. Randomized

TABLE A1-10 Assessing the Seriousness of Adolescent Drug Abuse

Variable	0	+1	+2
Age (yr)	>15	<15	
Sex	Male	Female	
Family history of drug abuse		Yes	
Setting of drug use	In group		Alone
Affect before drug use	Happy	Always poor	Sad
School performance	Good, improving		Recently poor
Use before driving	None		Yes
History of accidents	None		Yes
Time of week	Weekend	Weekdays	
Time of day		After school	Before or during school
Type of drug	Marijuana, beer, wine	Hallucinogens, amphetamines	Whiskey, opiates, cocaine, barbiturates

Total score: 0-3, less worrisome; 3-8, serious; 8-18, very serious.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

treatment studies are equivocal for long-term outcomes. Naltrexone reduces relapse and the intensity or frequency of any drinking that does occur. It can be hepatotoxic and is contraindicated in opiate users. Intramuscular naltrexone (380 mg monthly) may be considered if adherence is an issue.
- Acamprosate also helps reduce craving for alcohol. Acamprosate 666 mg three times daily may be an effective adjunct to counseling. A recent meta-analysis showed overall benefit with increase in the number of abstinent days.
- Disulfiram provokes acetaldehyde accumulation after alcohol ingestion, producing a toxic state manifested by nausea, headache, flushing, and respiratory distress. Studies have shown limited efficacy mostly due to noncompliance.
- Topiramate may be an alternative treatment for alcoholism. In a 12-wk randomized trial topiramate up to 300 mg daily significantly reduced the number of heavy drinking days.
- Methadone maintenance for opiate addiction is effective and involves once-daily dosing of methadone in a controlled setting via methadone clinics.
- Buprenorphine is as effective as low-dose methadone and may be prescribed by physicians who have completed approved training. For induction, initiate 12 to 24 hr after short-acting opioid use and 24 to 48 hr after long-acting opioid use. Use buprenorphine/naloxone tablets in most patients, since buprenorphine-only tablets have risk of abuse. Maximum first-day dosage is 4 to 8 mg of buprenorphine. Titrate buprenorphine dose up to 12 mg on day 2 for signs of withdrawal. Then adjust dosage in frequent outpatient visits (weekly) to minimum needed for maintenance (up to 32 mg daily).
- Naltrexone (oral or injectable) may also be used for maintenance in opioid dependence treatment, though evidence of effectiveness is limited.
- Always combine pharmacotherapy with counseling.
- Treatment of comorbid psychiatric disorders improves outcomes.
- Intervention may be used to break through **denial** of a person with a serious addictive disorder to help the person acknowledge that he or she suffers from a disorder and agree to treatment.

DISPOSITION

- Substance abuse is a chronic relapsing illness, so relapses are best approached as part of the course of the illness, as opposed to as treatment failure.
- The goal of treatment is always abstinence, but success of treatment is measured by return of function, increasing duration between relapses, and prevention of sequelae of use.

REFERRAL

Physicians should refer patients who do not make progress on changing substance use patterns to addiction specialists and/or specialized substance abuse programs. Patients with comorbid psychiatric illness should be referred for mental health care.

PEARLS & CONSIDERATIONS

- Acute withdrawal from alcohol can become life threatening.
- Withdrawal from opioids can resemble a severe case of the flu.
- A brief intervention (providing information and advising the patient to reduce consumption of alcohol) by the primary care doctor has been demonstrated in randomized trials to reduce drinking in at-risk patients.
- Treatment rates for alcohol use disorders remain low despite available effective treatments.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Drug Abuse (Patient Information)
Alcoholism (Related Key Topic)
Opioid Dependence (Related Key Topic)

AUTHORS: **TAHIR TELLIOGLU, M.D., OMRI BERGER, M.D.,** and **RADHIKA A. RAMANAN, M.D., M.P.H.**

EVIDENCE

Abstract[1]

Objectives:
To examine the influence of cannabis use on long-term outcome in patients with a first psychotic episode, comparing patients who have never used cannabis with (a) those who used cannabis before the first episode but stopped using it during follow-up and (b) those who used cannabis both before the first episode and during follow-up.

Methods:
Patients were studied following their first admission for psychosis. They were interviewed at years 1, 3, and 5. At follow-up after 8 years, functional outcome and alcohol and drug abuse were recorded. Patients were classified according to cannabis use: 25 had cannabis use before their first psychotic episode and continuous use during follow-up (CU), 27 had cannabis use before their first episode but stopped its use during follow-up (CUS), and 40 never used cannabis (NU).

Results:
The 3 groups did not differ significantly in symptoms or functional outcome at baseline or during short-term follow-up. The CUS group exhibited better long-term functional outcome compared with the other 2 groups and had fewer negative symptoms than the CU group, after adjusting for potential confounders. For the CUS group, the effect size was 1.26 (95% confidence interval [CI]=0.65 to 1.86) for functional outcome and −0.72 (95% CI=−1.27 to −0.14) for negative symptoms. All patients experienced improvements in positive symptoms during long-term follow-up.

Conclusions:
Cannabis has a deleterious effect, but stopping use after the first psychotic episode contributes to a clear improvement in outcome. The positive effects of stopping cannabis use can be seen more clearly in the long term. Ⓐ

Abstract[2]

Objective:
Naltrexone, an efficacious medication for alcohol dependence, does not work for everyone. Symptoms such as insomnia and mood instability that are most evident during early abstinence might respond better to a different pharmacotherapy. Gabapentin may reduce these symptoms and help prevent early relapse. This clinical trial evaluated whether the combination of naltrexone and gabapentin was better than naltrexone alone and/or placebo during the early drinking cessation phase (first 6 weeks), and if so, whether this effect persisted.

Method:
A total of 150 alcohol-dependent individuals were randomly assigned to a 16-week course of naltrexone alone (50 mg/day [N=50]), naltrexone (50 mg/day) with gabapentin (up to 1,200 mg/day [N=50]) added for the first 6 weeks, or double placebo (N=50). All participants received medical management.

Results:
During the first 6 weeks, the naltrexone-gabapentin group had a longer interval to heavy drinking than the naltrexone-alone group, which had an interval similar to that of the placebo group; had fewer heavy drinking days than the naltrexone-alone group, which in turn had more than the placebo group; and had fewer drinks per drinking day than the naltrexone-alone group and the placebo group. These differences faded over the remaining weeks of the study. Poor sleep was associated with more drinking in the naltrexone-alone group but not in the naltrexone-gabapentin group, while a history of alcohol withdrawal was associated with better response in the naltrexone-gabapentin group.

Conclusions:
The addition of gabapentin to naltrexone improved drinking outcomes over naltrexone alone during the first 6 weeks after cessation of drinking. This effect did not endure after gabapentin was discontinued. Ⓐ

Evidence-Based References

González-Pinto A et al.: Cannabis and first-episode psychosis: different long-term outcomes depending on continued or discontinued use, *Schizophr Bull* 37:631–639, 2011. Ⓐ

Anton RF et al.: Gabapentin combined with naltrexone for the treatment of alcohol dependence, *Am J Psychiatry* 168:709–717, 2011. Ⓐ

SUGGESTED READINGS

Center for Substance Abuse Treatment. U.S. Department of Health and Human Services. www.csat.samhsa.gov.

Ersche KD et al.: Abnormal brain structure implicated in stimulant drug addiction, *Science 335* 601, 2012.

Kleber HD et al.: Treatment of patients with substance use disorders, *Am J Psychiatry* 164(4 suppl):5–123, 2007.

Lucey MR et al.: Alcoholic hepatitis, *N Engl J Med* 360(26):2758–2759, 2009.

Willenbring ML et al.: Helping patients who drink too much: an evidence-based guide for primary care physicians, *Am Fam Physician* 80(1):44–50, 2009.

BASIC INFORMATION

DEFINITION

Elder abuse includes abuse committed by someone in a trust relationship whether in the community or institutional setting.

- Physical abuse: inflicting physical pain or injury
- Sexual abuse: inflicting nonconsensual sexual activity
- Psychological abuse: inflicting mental anguish, including intimidation, humiliation, or threats
- Financial abuse: improper use of resources, property, or assets without the person's consent
- Neglect: abandonment, failure to fulfill a care-taking obligation, including provision of food, safe shelter, physical health and mental health care, or basic custodial care

SYNONYMS

Battered elder syndrome
Elder mistreatment
Domestic violence in the elderly
Diogenes syndrome

Adult maltreatment and neglect problems cover a range of diagnostic codes depending on whether the issue is confirmed or suspected and whether the problem is physical, psychological, or sexual.

Core Codes:

ICD-9-CM and DSM-5 CODES

995.81/82/83

ICD-10CM CODES

T74 Maltreatment syndrome
T74.0 Neglect or abandonment
T74.1 Physical abuse
T74.2 Sexual abuse
T74.3 Psychological abuse
T74.8 Other maltreatment syndromes
T74.9 Maltreatment syndromes, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: According to the National Center on Elder Abuse, between 1 and 2 million Americans aged 65 yr and older have been injured, exploited, or mistreated by someone whom they depend on for care.

PEAK INCIDENCE: >75 yr; more recent studies now suggest <75 yr

PREVALENCE:

- About 10% of those 60 years or older
- Emotional followed by financial abuse are the most common forms.
- 12-month U.S. prevalence rates: emotional abuse 9.0% and 4.6%; physical abuse 0.2% and 1.6%; sexual abuse 0.6%; neglect 0.5%; and financial abuse 3.5% and 5.2%.
- Family members reported 21% of nursing home residents were neglected on one or more occasion in the past 12 months, and over 24% had been subjected to physical abuse during their entire stay.
- Among caregivers of patients with dementia in the U.K., one half reported behaving abusively at least some of the time, and one third reported "important" levels of abuse. Verbal abuse was common and physical abuse was rare.
- Elder abuse is associated with increased risk of mortality, functional impairment, and greater emotional distress, including depression, anxiety, and posttraumatic stress.
- Adult intimate partner violence perpetrators are significantly more likely to have witnessed intimate partner violence as a child than nonperpetrators.

RISK FACTORS (VICTIM):

- Impaired cognition
- Behavioral problems
- Psychiatric illness or psychological problems
- Mental or physical dependence
- Poor physical health or frailty
- Trauma or past abuse
- Shared living situation and premorbid relationship with abuser
- Social isolation and poor social support
- Low household income

RISK FACTORS (PERPETRATOR):

- Relationship conflict with the victim
- Substance abuse, mental illness, particularly depression
- Caregiver burden or stress, being an involuntary caregiver, overwhelmed or resentful

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical abuse with multiple injuries at various stages with implausible descriptions of their origins.
- Fear, hypervigilance, or withdrawal.
- Evidence of poor nutrition, dehydration, poor hygiene, multiple or neglected pressure ulcers, genital or anal pain, neglected medical conditions, or evidence of restraint use (bruises around wrists or ankles).
- Toxicologic evidence of unprescribed medications.
- Poor adherence, frequent no-shows, or little contact with health care system.
- Caregiver not allowing interviewing the patient alone.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Dementia
- Depression, substance misuse, or other psychiatric disorder
- Malnutrition from intrinsic causes
- Nonadherence to medical treatment
- Relationship distress
- Falling

WORKUP

1. Ask direct specific questions such as:
   - "Has anyone close to you called you names or put you down recently?"
   - "Are you afraid of anyone who lives with you or cares for you?"
   - "Has anyone at home ever hurt you?"
   - "Has anyone touched you without your consent?"
   - "Has anyone forced you to do things you didn't want to do?"
   - "Has anyone taken things or money that belong to you without your OK?"
   - "Have you signed any documents that you don't understand?"
   - "Are you often alone?"
   - "When you need help has anyone ever failed to help you take care of yourself?"
   - "If appropriate, ask, "Have you been abused?"
2. Interview patient separately from the suspected abuser.
3. Pelvic examination if sexual abuse suspected.
4. Take photographs of physical injuries as legal evidence.

LABORATORY TESTS & IMAGING STUDIES

- Toxicology screens and therapeutic drug monitoring are sometimes helpful.
- Other tests and radiology according to presentation.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Separate patient and abuser.
- Patient and caregiver may benefit from psychiatric evaluation and treatment for substance abuse, mental illness, or cognitive impairment.
- If appropriate, assess the patient's capacity.
- Fig. A1-19 describes a management algorithm for geriatric abuse.

ACUTE GENERAL Rx

- As indicated for injury or pain relief
- As indicated for mental disorders, dementia, or delirium

DISPOSITION

If the patient's level of disability does not allow independent living, institutionalization may be required. Guidelines vary at the state and county levels regarding guardianship and conservatorship requirements.

REFERRAL

- For outpatients, report to local adult protective services agency. Reporting is mandatory in most states.
- For nursing home patients, report to regional long-term care ombudsman. Reporting is mandatory under federal law.
- Mental health services may be needed.

PEARLS & CONSIDERATIONS

COMMENTS

Care should be taken in interacting with the alleged abuser so that access to the victim is not lost.

PREVENTION

- Offer social services (e.g., respite care or homecare) for stressed caregivers.
- Make financial arrangements and arrange durable power of attorney for health care and finances while patient is still cognitively intact.

PATIENT & FAMILY EDUCATION

In the U.S., the elder care help line is 1-800-677-1116.

National Center on Elder Abuse: http://www.ncea.aoa.gov

JAMA Patient Page: Hildreth CJ et al: JAMA patient page. Elder abuse, *JAMA* 302(5):588, 2009

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Elder Abuse (Patient Information)

AUTHOR: **ROBERT KOHN, M.D.**

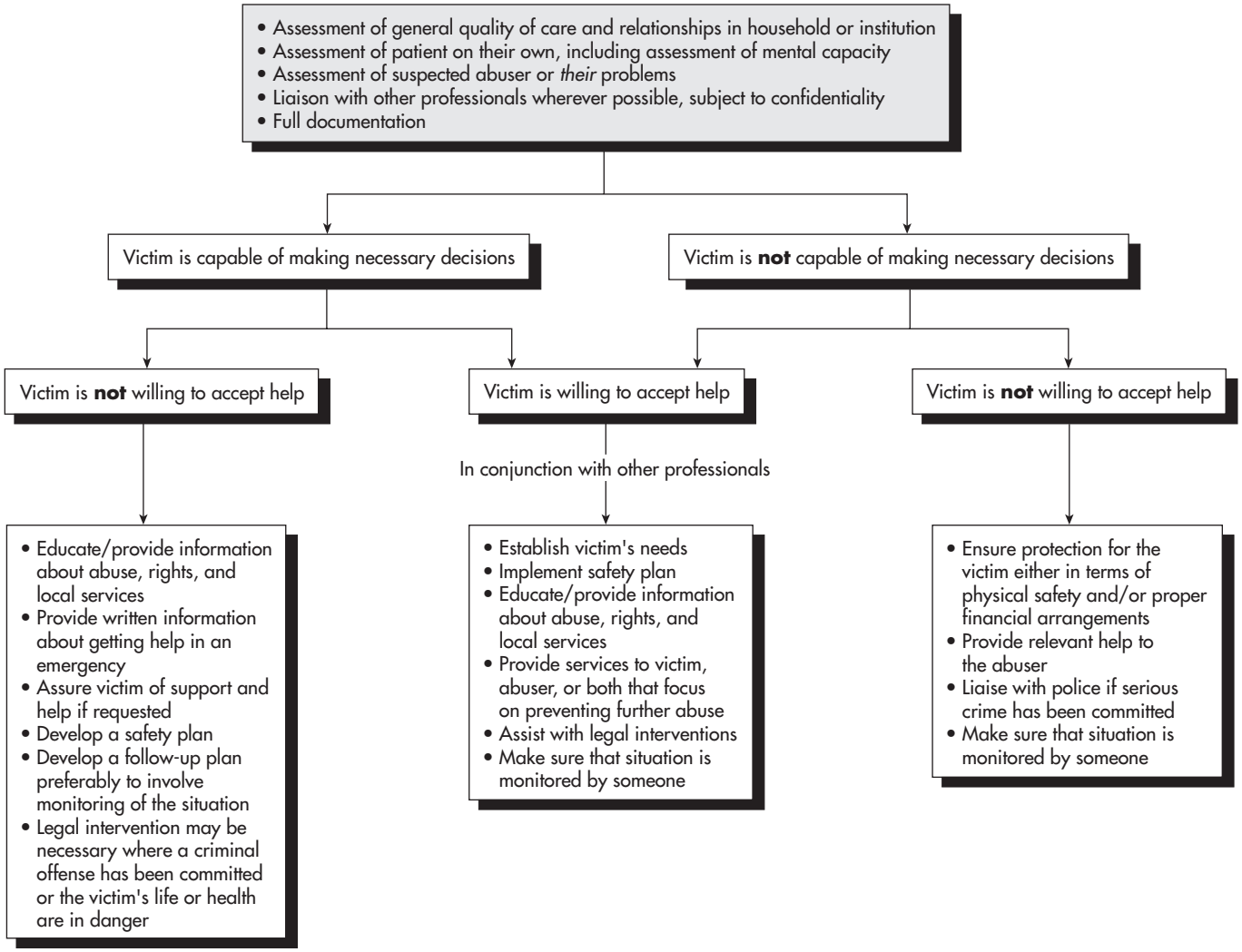


FIGURE A1-19 Management of geriatric abuse. (From Tallis RC, Fillit HM [eds]: *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 6, London, 2003, Churchill Livingstone.)

SUGGESTED READINGS

Acierno R et al.: Prevalence and correlates of emotional, physical, sexual and financial abuse and potential neglect in the United States: the National Elder Mistreatment Study, *Am J Public Health* 100(2):292–297, 2010.

Cohen M et al.: Elder abuse: disparities between older people's disclosure of abuse, evident signs of abuse, and high risk of abuse, *J Am Geriatr Soc* 55:1224, 2007.

Cooper C et al.: Abuse of people with dementia by family carers: representative cross sectional survey, *BMJ* 338:b155, 2009.

Dong X et al.: Elder abuse and psychological well-being: a systematic review and implications for research and policy—a mini review, *Gerontology* 59(2):132–142, 2013.

Johannesen M: L Giudice D. Elder abuse: a systematic review of risk factors in community-dwelling elders, *Age Aging* 42(3):292–298, 2013.

Laumann EO et al.: Elder mistreatment in the United States: prevalence estimates from a nationally representative study, *J Gerontol B Psychol Sci Soc Sci* 63(4):S248–S254, 2008.

Mosqueda L, Dong X: Elder abuse and self-neglect, *JAMA* 306(5):532–540, 2011.

BASIC INFORMATION

DEFINITION

Acetaminophen (APAP) poisoning is a disorder caused by excessive intake of APAP and is manifested by jaundice, nausea, vomiting, and potential death from hepatic necrosis if not treated appropriately.

SYNONYMS

Paracetamol poisoning

ICD-9CM CODES
965.4 Acetaminophen poisoning
ICD-10CM CODES
T39.1 Poisoning by 4-aminophenol derivatives, accidenta
X60 Intentional self-poisoning by 4-aminophenol derivatives

EPIDEMIOLOGY & DEMOGRAPHICS

- APAP is one of the most widely prescribed antipyretics and analgesics in the U.S. Potentially toxic ingestions, both intentional and unintentional, exceed 100,000 cases annually in the U.S.
- APAP toxicity has become the number one cause of acute liver failure in the U.S.
- Death rate is approximately one in 1000 persons. Nearly 50% of exposures occur in children ≤6 yr.
- Hepatic necrosis is most likely to occur in people who are chronically malnourished, who regularly abuse alcohol, and who are using other potentially hepatotoxic medications.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The physical examination may vary depending on the amount of time since ingestion.
- Phase I (0 to 24 hr): initial symptoms may be mild or absent and may consist of anorexia, diaphoresis, malaise, nausea, vomiting, and a subclinical rise in transaminase levels.
- Phase II (24 to 72 hr): right upper quadrant pain, vomiting, somnolence, tachycardia, hypotension, and continued increase in transaminases.
- Phase III (72 to 96 hr): hepatic necrosis with abdominal pain, jaundice, hepatic encephalopathy, coagulopathy, hypoglycemia, renal failure, fatality from multi-organ failure.
- Phase IV (4 days to 2 wk): complete resolution of symptoms and resolution of organ failure.
- Table EA1-11 summarizes the four phases/stages of acetaminophen poisoning.

ETIOLOGY

- The amount of APAP necessary for hepatic toxicity varies with the patient's body size and hepatic function. It is recommended that APAP intake should not exceed 4 g for adults and 90 mg/kg in children within a 24-hr period.
- A standardized nomogram is used to determine potential hepatic toxicity by knowing the APAP plasma level and the number of hours after ingestion. See the APAP ingestion algorithm (Fig. EA1-20).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Liver disease from alcohol abuse or viral hepatitis
- Ingestion of other hepatotoxic substances
- Bacterial/viral gastroenteritis

WORKUP

Initial workup is aimed at confirming APAP overdose with plasma APAP level and assessment of hepatic damage. A careful history should elicit the time of APAP ingestion, amount, preparation (e.g., extended release) and possible coingestants (see "Laboratory Tests").

LABORATORY TESTS

- Initial laboratory evaluation should include an initial plasma APAP level with a second level drawn approximately 4 hr after the initial ingestion. Subsequent levels can be obtained every 2 to 4 hr until the levels stabilize or decline. These levels should be plotted on the Rumack-Matthew nomogram (see acetaminophen ingestion algorithm [Fig. EA1-20] to calculate potential hepatic toxicity). The nomogram cannot be used with patients who present >24 hr after ingestion, took extended-release preparations, had chronic ingestions, or when the time of ingestion is unknown.
- Transaminases (AST, ALT), serum glucose, bilirubin level, lipase level, prothrombin time (INR), blood urea nitrogen, creatinine, EKG, and urinalysis should be initially obtained on all patients.
- Serum and urine toxicology screen for other potential toxic substances is also recommended on admission. Screening for infectious hepatitis should also be considered.
- Urine for β-hCG should be obtained from all women of childbearing age.

TREATMENT

NONPHARMACOLOGIC THERAPY

Consultation with a Poison Control Center is recommended for patients who have ingested a large amount of APAP and/or other toxic substances. A single toxic dose of APAP usually exceeds 7 g or 150 mg/kg in the adult.

ACUTE GENERAL Rx

- Hepatotoxicity is defined as any increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1000 IU/L, and hepatic failure manifests as hepatotoxicity with hepatic encephalopathy. For those who cannot be risk stratified using the nomogram, the American College of Emergency Physicians recommends that *N*-acetylcysteine be administered without delay to those >12 yr and >8 hr after ingestion at presentation.
- Administer activated charcoal 1g/kg PO if the patient is seen within 1 hr of ingestion or the clinician suspects polysubstance ingestion that delays gastric emptying.
- Determine blood levels 4 hr after ingestion; if in the toxic range based on the Rumack-Matthew nomogram, start *N*-acetylcysteine (NAC) either IV (Acetadote) or PO (Mucomyst). Acetylcysteine IV loading dose is 150 mg/kg ×1 diluted in 200 ml D5W over 15 to 60 min. Maintenance dose is 50 mg/kg diluted in 500 ml D5W over 4 hr, followed by 100 mg/kg diluted in 1000 ml D5W over 16 hr. The dose does not require adjustment for renal or hepatic impairment or for dialysis. Total administration time is 21 hours.
- Oral administration is 140 mg/kg PO as a loading dose, followed after 4 hr by 70 mg/kg PO q4h for a total of 17 doses. *N*-acetylcysteine therapy should be started within 24 hr of APAP overdose. Total administration time is 72 hours.
- Advantages of IV administration include more reliable absorption, fewer doses, and shorter duration of treatment. Disadvantages include cost and lower hepatic concentrations from first-pass flow as compared to oral acetylcysteine.
- Monitor APAP level; use Rumack-Matthew nomogram to trend hepatic toxicity. Repeat AST/ALT and APAP levels after 12 to 14 hr of IV acetylcysteine infusion and continue infusion longer than 16 hr if transaminases are elevated, if APAP concentration is still measurable, or if coagulopathy exists (INR >1.5-2.0).
- Provide adequate IV hydration (e.g., D_5½NS at 150 ml/hr).
- Patients on IV *N*-acetylcysteine with liver failure require frequent monitoring of vital signs, oxygen saturation by pulse oximetry, and frequent blood draws. Frequent re-assessment for hypoglycemia and infection is also essential.
- If APAP level is nontoxic, *N*-acetylcysteine therapy may be discontinued.

DISPOSITION

All patients with confirmed APAP poisoning will require admission, usually to an intensive care unit. Most patients (90%) will recover fully without persisting hepatic abnormalities. Hepatic failure is particularly unusual in children <6 yr.

REFERRAL

Psychiatric referral is recommended after intentional ingestions.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Acetaminophen Overdose (Patient Information)

AUTHOR: **STEVEN ROUGAS, M.D., M.S.**

EVIDENCE

Abstract[1]

Context:
Current treatment of paracetamol (acetaminophen) poisoning involves initiating a 3-phase *N*-acetylcysteine (NAC) infusion after comparing a plasma concentration, taken ≥ 4h post-overdose, to a nomogram. This may result in dosing errors, a delay in treatment, or possibly more adverse effects—due to the use of a high dose rate for the first infusion when treatment is initiated.

Objective:
Our aim was to investigate a novel dosing regimen for the immediate administration of NAC on admission at a lower infusion rate.

Methods:
We used a published population pharmacokinetic model of NAC to simulate a scenario where a patient presents to the hospital 2 h post-overdose. The conventional regimen is commenced 6 h post-overdose when the 4-h plasma paracetamol concentration is available. We investigated an NAC infusion using a lower dosing rate initiated immediately on presentation. We determined a dosing rate that gave an area under the curve (AUC) of the concentration-time curve that was the same or greater than that from the conventional regimen on 90% of occasions.

Results:
Lower dosing rates of NAC initiated immediately resulted in a similar exposure to NAC. An infusion of 110 mg/kg over the first 5 h (22 mg/kg/h) followed by the last two phases of the conventional regimen, or 200 mg/kg over 9 h (22.6 mg/kg/h) followed by the last phase of the conventional regimen could be used.

Conclusion:
The novel dosing regimen allowed immediate treatment of a patient using a lower dosing rate. This greatly simplifies the current dosing regimen and may reduce NAC adverse effects while ensuring the same amount of NAC is delivered. Ⓐ

Evidence-Based Reference

Shen F et al.: A dosing regimen for immediate N-acetylcysteine treatment for acute paracetamol overdose, *Clin Toxicol* 49:643–647, 2011. Ⓐ

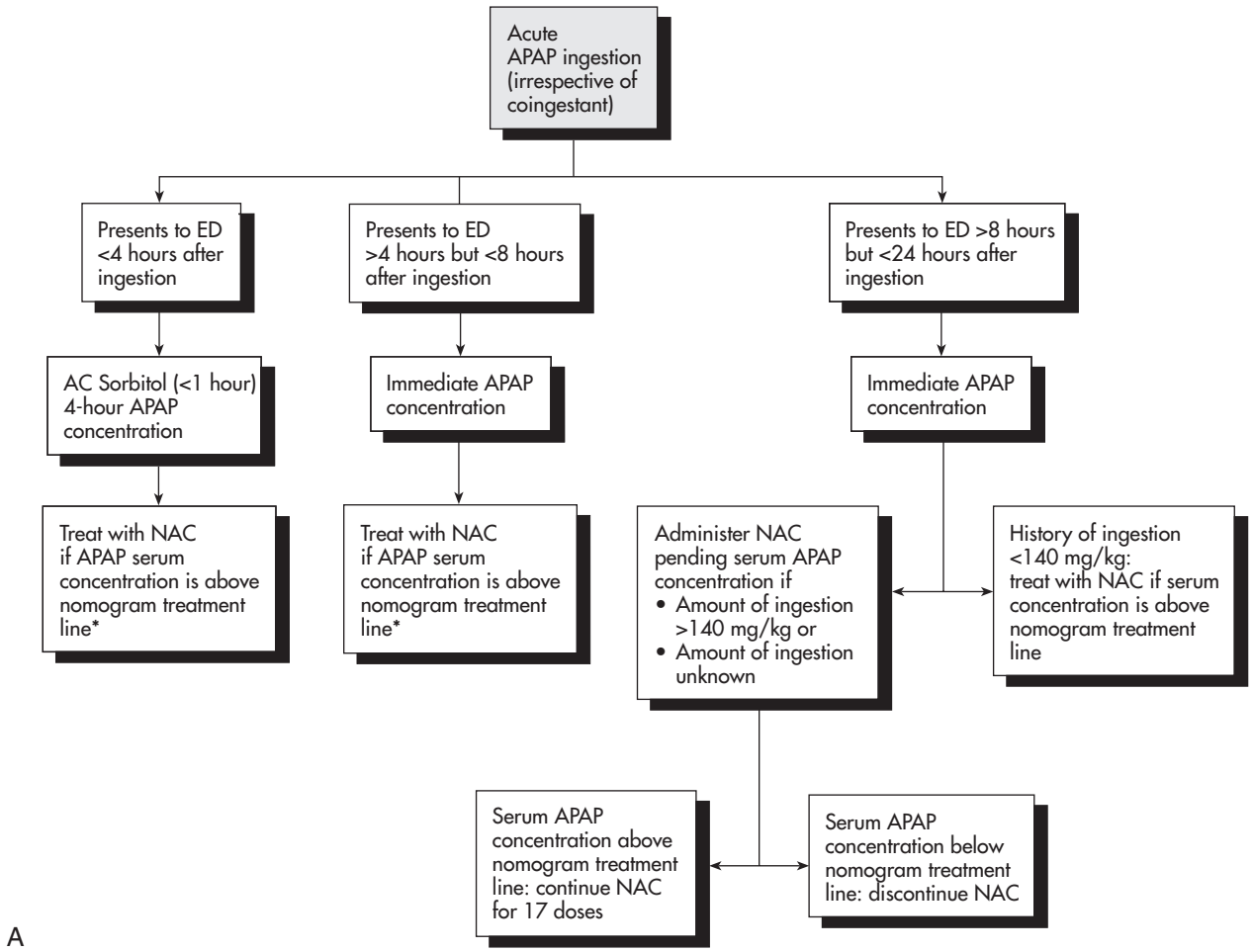
SUGGESTED READINGS

Heard KJ: Acetylcysteine for acetaminophen poisoning, *N Engl J Med* 359: 285–292, 2008.

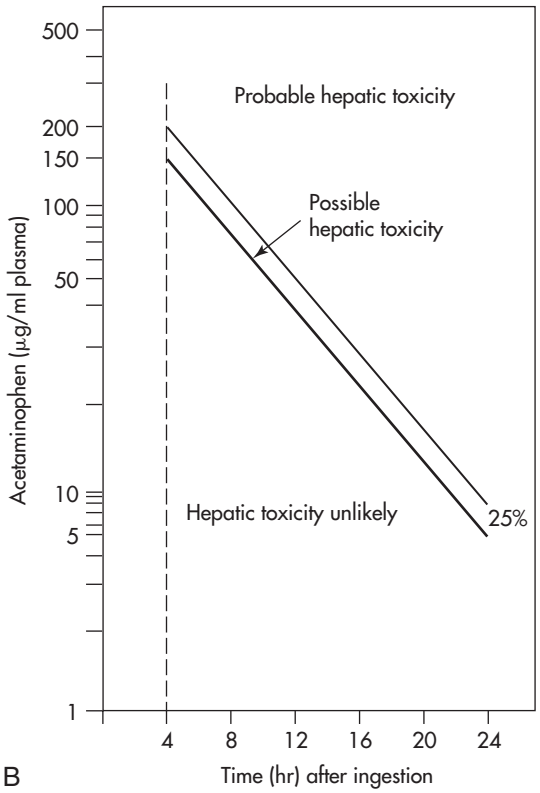
TABLE EA1-11 Four Stages of Acetaminophen Poisoning

Stage 1 (0-24 hr)	Asymptomatic	Patients are initially asymptomatic, with normal vital signs and no physical findings. Laboratory results are normal. Nonspecific complaints of nausea, vomiting, and malaise may start to develop near the end of this stage.
Stage 2 (24-72 hr)	Onset of hepatotoxicity	Right upper quadrant abdominal pain may develop. Levels of AST, the most sensitive indicator of hepatotoxicity, and ALT begin to rise. Later, INR values may begin to rise and renal function to deteriorate.
Stage 3 (72-96 hr)	Maximal hepatotoxicity	The patient exhibits clinical and laboratory manifestations of hepatic necrosis: varying degrees of hepatic encephalopathy, jaundice, renal failure, coagulation defects, and myocardial abnormalities. AST and ALT levels peak, the INR value rises, blood urea nitrogen and creatinine levels rise, and pH drops.
		Death may occur, typically 3-5 days after overdose. Death from fulminant hepatic failure may be characterized by cerebral edema, sepsis, multisystem organ failure, hemorrhage, and acute respiratory distress syndrome.
Stage 4 (4 days to 2 wk)	Recovery phase	Patients who survive stage 3 undergo complete regeneration of the liver. Laboratory abnormalities typically return to normal 5-7 days after overdose.

ALT, Alanine transaminase; *AST*, aspartate transaminase; *INR*, international normalized ratio.
From Adams J (ed), Barton E et al (associate eds): *Emergency medicine: clinical essentials,* ed 2, Philadelphia, 2013, Saunders.



A



B

FIGURE EA1-20 A, Treatment of acetaminophen ingestion. *APAP,* Acetaminophen; *ED,* emergency department; *NAC, N*-acetylcysteine. **B,** Rumack-Matthew nomogram for acetaminophen poisoning. *See Fig. EA1-20*B*. (**A** from Marx J [ed]: *Rosen's emergency medicine,* ed 5, St Louis, 2002, Mosby. **B** modified from Rumack BH, Matthew H: Pediatrics 55:871, 1975. In Marx J [ed]: *Rosen's emergency medicine,* ed 6, St Louis, 2006, Mosby.)

http://internalmedicinebook.com/

BASIC INFORMATION

DEFINITION

Achalasia is a motility disorder of the esophagus classically characterized by incomplete relaxation of the lower esophageal sphincter (LES) and aperistalsis of esophageal smooth muscle. The result is functional obstruction of the esophagus.

SYNONYMS

Achalasia and cardiospasm
Achalasia (of cardia)
Aperistalsis of esophagus
Megaesophagus
Esophageal achalasia
Esophageal cardiospasm

ICD-9CM CODES
530.0 Achalasia
ICD-10CM CODES
K22.0 Achalasia of cardia

EPIDEMIOLOGY & DEMOGRAPHICS

- Annual incidence is approximately 0.5-1.0 in 100,000 persons.
- Prevalence is <10 per 100,000 persons.
- Although the onset of symptoms may occur at any age, incidence is typically bimodal, 20 to 40 yr, then after 60 yr, with greater incidence in the older group.
- Men and women are affected equally.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms:
- Dysphagia (most commonly with both solids and liquids)
- Difficulty belching
- Regurgitation
- Chest pain and/or heartburn
- Globus
- Frequent hiccups
- Vomiting of undigested food
- Symptoms of aspiration such as nocturnal cough; possible dyspnea and pneumonia
- Weight loss

Physical findings:
- Focal lung examination abnormalities and wheezing also possible

ETIOLOGY

- Etiology is poorly understood.
- Loss of myenteric nerve fibers in the LES and smooth muscle portion of the esophagus. This has been associated with lymphocytic and eosinophilic infiltrates and fibrosis in later stages of disease.
- Loss of intrinsic inhibitory neurons in the myenteric plexus as well as depletion of networks of interstitial cells of Cajal of the LES, leads to incomplete relaxation secondary to loss of inhibitory neurotransmitters nitric oxide and vasoactive intestinal polypeptide.
- This disorder may be caused by autoimmune degeneration of the esophageal myenteric plexus because association with the HLA class II antigen DQw1 has been noted. Antimyenteric plexus and other antineural autoantibodies have also been described.
- Abnormal immune reactions to neurotropic viruses such as varicella zoster, herpes simplex type 1, and measles viruses have been implicated, but the association has not been confirmed. A host T cell–mediated response may lead to neuronal injury.
- Achalasia is also seen in the rare autosomal recessive disorder Allgrove syndrome (achalasia, alacrima, autonomic disturbance, and acetylcholine insensitivity), which has been linked to a gene mutation on chromosome 12q13. Neurons in this syndrome may be susceptible to oxidative injury.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Primary achalasia:
  1. Idiopathic
- Secondary achalasia:
  1. Chagas disease
  2. Vagal injury or surgery, including fundoplication
  3. Achalasia-like esophageal dilation has been described after laparoscopic gastric banding
- Pseudoachalasia:
  1. Esophageal cancer
  2. Infiltrating gastric cancer
  3. Oat cell and bronchogenic lung cancer
  4. Lymphoma
  5. Amyloidosis
  6. Paraneoplastic syndrome
- Angina
- Bulimia
- Anorexia nervosa
- Gastric bezoar
- Gastritis
- Peptic ulcer disease
- Postvagotomy dysmotility
- Esophageal disease (Table A1-12):
  1. Gastroesophageal reflux disease
  2. Sarcoidosis
  3. Amyloidosis
  4. Esophageal stricture
  5. Esophageal webs and rings
  6. Scleroderma
  7. Barrett's esophagus
  8. Esophagitis
  9. Diffuse esophageal spasm

WORKUP

- Physical examination and laboratory analyses to rule out other causes and assess complications
- Imaging studies, manometry, and endoscopy (may be complementary)

LABORATORY TESTS

- Assessment of nutritional status
- Complete blood count, ECG, stress test if diagnosis is in doubt
- Serologic assays for *Trypanosoma cruzi* (Chagas disease) in appropriate individuals

IMAGING STUDIES

Barium swallow with fluoroscopy may demonstrate:
- Uncoordinated or absent esophageal contractions (loss of peristalsis)
- An acutely tapered contrast column ("bird's beak"; Fig. A1-21)
- Dilation of the distal (smooth muscle portion) esophagus
- Esophageal air-fluid level with evidence of poor esophageal emptying

TABLE A1-12 Esophageal Motor Disorders

	Achalasia	Scleroderma	Diffuse Esophageal Spasm
Symptoms	Dysphagia Regurgitation of nonacidic material	Gastroesophageal reflux disease Dysphagia	Substernal chest pain (angina-like) Dysphagia with pain
Radiographic appearance	Dilated, fluid-filled esophagusDistal *bird-beak* stricture	Aperistaltic esophagus Free reflux Peptic stricture	Simultaneous noncoordinated contractions
Manometric findings			
Lower esophageal sphincter	High resting pressure Incomplete or abnormal relaxation with swallow	Low resting pressure	Normal pressure
Body	Low-amplitude, simultaneous contractions after swallowing	Low-amplitude peristaltic contractions or no peristalsis	Some peristalsis Diffuse and simultaneous nonperistaltic contractions, occasionally high amplitude

From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine*, ed 8, Philadelphia, 2010, Saunders.

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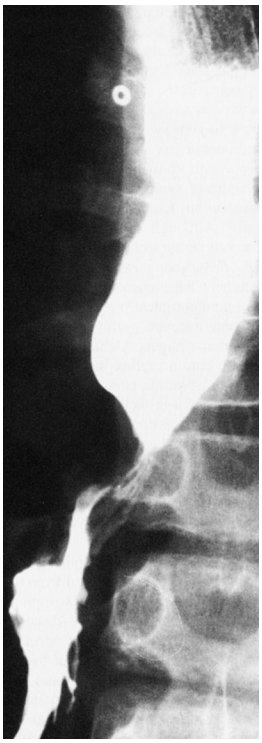

FIGURE A1-21 Classic appearance of achalasia of the esophagus. The dilated esophagus ends in a narrow segment. (From Hoekelman R [ed]: *Primary pediatric care*, ed 3, St Louis, 1997, Mosby.)

Manometry is generally considered to be the "gold standard" test to confirm the diagnosis. In classic achalasia, conventional manometric abnormalities are as follows:

- Low-amplitude disorganized contractions/aperistalsis
- Incomplete or absent LES relaxation (with residual pressure >10 mm Hg) after swallow
- High resting LES pressure
- A subset of patients with "vigorous achalasia" may have high-amplitude, long-duration, simultaneous esophageal contractions. This term is now felt to be imprecise because of a newer classification of the disease.
- High-resolution manometry (HRM), or high-resolution esophageal pressure topography (HREPT), has recently defined subsets of patients with achalasia who may have different responses to medical or surgical therapies. Unlike classic achalasia (type I), type II achalasia shows panesophageal pressurization to greater than 30 mm Hg with ≥20% of test swallows, and type III achalasia shows spastic lumen-obliterating contractions of the distal esophagus with ≥20% of swallows. This technique uses the Integrated Relaxation Pressure (IRP) to better define the adequacy of esophagogastric junction relaxation.
- HREPT has also defined an achalasia variant described as esophagogastric junction outflow obstruction.
- Direct visualization by endoscopy, including careful visualization of the esophagogastric junction and cardia, should be performed to exclude other causes of dysphagia, including "functional esophagogastric junction obstruction," strictures, secondary causes of achalasia (including infiltrating cancers), and pseudoachalasia.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- The goals of therapy are to decrease LES pressure, relieve symptoms, and prevent progression to a dilated or megaesophagus.
- Pneumatic dilation to disrupt the LES muscle fibers may benefit 65% to 90% of patients. Multiple sessions may be required, and most protocols use a graded dilation approach, starting with a 30-mm balloon, and repeating if required with a 35-mm or 40-mm balloon. Some studies suggest this may be more effective in women or older patients. Esophageal rupture or perforation is a rare complication (2% to 4%) that may be managed conservatively in some stable patients with a small perforation.
- Surgical: laparoscopic, or now less commonly open, (Heller's) esophagomyotomy is effective (90%). Approximately 35% of patients undergoing surgery will develop reflux disease. As a result, some surgeons will perform a "loose" antireflux repair (fundoplication) as part of the surgical procedure. Some studies suggest this may be more effective in men and younger patients. An observational study has suggested that those who have had prior endoscopic treatment before myotomy may not do as well as those who have a primary myotomy.
- Studies suggest that type I and type II patients have better treatment responses to these therapies compared with type III patients.
- A large European study suggested that in experienced hands, patients may expect similar medium-term outcomes from myotomy and balloon dilation. A meta-analysis suggests better long-term durability of myotomy. Balloon dilation may be the more cost-effective treatment. A small percentage (20 to 30%) of patients undergoing either therapy may require re-treatment within 5 to 7 years.
- Assessment of esophagogastric junction distensibility by an endoscopic functional luminal imaging probe may help to better evaluate the efficacy of treatment.
- Endoscopic submucosal myotomy (POEM [per oral endoscopic myotomy]) has been reported in several uncontrolled series, with a high success rate, and is being explored as another option for treatment.
- Esophagectomy has been performed in patients with end-stage achalasia with a sigmoid or mega-esophagus who have failed myotomy or pneumatic dilation.

GENERAL Rx

- Medications may be useful for short-term symptom relief and in patients with refractory chest pain. They should only be considered in patients unable to receive, or who are scheduled for, more definitive procedures. LES pressure may be lowered by 50% through sublingual use of long-acting nitrates (e.g., isosorbide dinitrate 5 to 20 mg) or calcium channel blockers (e.g., nifedipine 10 to 30 mg). Side effects are common and duration of relief tends to be short. Sildenafil was shown to be effective in a few small, short-term studies, but it is generally not recommended.
- Botulinum toxin injection will benefit up to 85% of patients by inhibiting acetylcholine release from cholinergic nerve endings, blocking the unopposed cholinergic stimulation of the LES, but having no impact on the myogenic tone; up to half of these patients will require repeat injections by 6 months. A few studies have suggested that repeated injections can lead to fibrosis, which may complicate subsequent attempts at surgical therapy.

PEARLS & CONSIDERATIONS

COMMENTS

- Medication has a limited role in treatment.
- Botulinum toxin is transiently effective in improving symptoms. Pneumatic dilation and surgical myotomy provide more durable long-term responses and are the treatment of choice for most patients. Botulinum toxin should be considered primarily in patients too elderly or ill to be considered for these other therapies.
- Patients with achalasia may be at long-term risk of squamous cell carcinoma of the esophagus and non–reflux-associated esophagitis. Treated patients may be at long-term risk for reflux esophagitis, Barrett's esophagus, and adenocarcinoma. Endoscopic surveillance is not routinely recommended in these patients.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Dysphagia (Related Key Topic)
Achalasia (Patient Information)

AUTHOR: **HARLAN G. RICH, M.D.**

http://internalmedicinebook.com/

EVIDENCE

Abstract[1]

Background:

Many experts consider laparoscopic Heller's myotomy (LHM) to be superior to pneumatic dilation for the treatment of achalasia, and LHM is increasingly considered to be the treatment of choice for this disorder.

Methods:

We randomly assigned patients with newly diagnosed achalasia to pneumatic dilation or LHM with Dor's fundoplication. Symptoms, including weight loss, dysphagia, retrosternal pain, and regurgitation, were assessed with the use of the Eckardt score (which ranges from 0 to 12, with higher scores indicating more pronounced symptoms). The primary outcome was therapeutic success (a drop in the Eckardt score to ≤3) at the yearly follow-up assessment. The secondary outcomes included the need for retreatment, pressure at the lower esophageal sphincter, esophageal emptying on a timed barium esophagogram, quality of life, and the rate of complications.

Results:

A total of 201 patients were randomly assigned to pneumatic dilation (95 patients) or LHM (106). The mean follow-up time was 43 months (95% confidence interval [CI], 40 to 47). In an intention-to-treat analysis, there was no significant difference between the two groups in the primary outcome; the rate of therapeutic success with pneumatic dilation was 90% after 1 year of follow-up and 86% after 2 years, as compared with a rate with LHM of 93% after 1 year and 90% after 2 years (P=0.46). After 2 years of follow-up, there was no significant between-group difference in the pressure at the lower esophageal sphincter (LHM, 10 mm Hg [95% CI, 8.7 to 12]; pneumatic dilation, 12 mm Hg [95% CI, 9.7 to 14]; P=0.27); esophageal emptying, as assessed by the height of barium-contrast column (LHM, 1.9 cm [95% CI, 0 to 6.8]; pneumatic dilation, 3.7 cm [95% CI, 0 to 8.8]; P=0.21); or quality of life. Similar results were obtained in the per-protocol analysis. Perforation of the esophagus occurred in 4% of the patients during pneumatic dilation, whereas mucosal tears occurred in 12% during LHM. Abnormal exposure to esophageal acid was observed in 15% and 23% of the patients in the pneumatic-dilation and LHM groups, respectively (P=0.28).

Conclusions:

After 2 years of follow-up, LHM, as compared with pneumatic dilation, was not associated with superior rates of therapeutic success. (European Achalasia Trial Netherlands Trial Register number, NTR37, and Current Controlled Trials number, ISRCTN56304564.) Ⓐ

Evidence-Based Reference

Boeckxstaens GE et al.: Pneumatic dilation versus laparoscopic Heller's myotomy for idiopathic achalasia, *N Engl J Med* 364:1807–1816, 2011. Ⓐ

SUGGESTED READINGS

Bansal A et al.: Has high resolution manometry changed the approach to esophageal motility disorders? *Curr Opin Gastroenterol* 26:344–351, 2010.

Boeckxstaens GE et al.: Pneumatic dilatation versus laparoscopic Heller's myotomy for idiopathic achalasia, *N Engl J Med* 364:1807–1816, 2011.

Bredenoord AJ et al.: Chicago classification criteria of esophageal motility disorders defined in high resolution esophageal pressure topography, *Neurogastroenterol Motil* 24(Suppl 1):57–65, 2012.

Campos GM et al.: Endoscopic and surgical treatments for achalasia: a systematic review and meta-analysis, *Ann Surg* 249:45–57, 2009.

Di Nardo G et al.: Review article: molecular, pathological and therapeutic features of human enteric neuropathies, *Aliment Pharmacol Ther* 28:25, 2008.

Kraichely RE et al.: Achalasia: physiology and etiopathogenesis, *Dis Esophagus* 19:213, 2006.

Leyden JE, et al.: Endoscopic pneumatic dilation versus botulinum toxin injection in the management of primary achalasia, *Cochrane Database Syst Rev* 4:CD005046, 2006.

Pandolfino JE et al.: Achalasia: a new clinically relevant classification by high-resolution manometry, *Gastroenterology* 135:1526, 2008.

Richter JE: Achalasia—an update, *J Neurogastroenterol Motil* 16:232–242, 2010.

Smith CD et al.: Endoscopic therapy for achalasia before Heller myotomy results in worse outcomes than Heller myotomy alone, *Ann Surg* 243(5):579, 2006.

Achilles Tendon Rupture EBM PTG

BASIC INFORMATION

DEFINITION

Achilles tendon rupture is a disruption of the continuity of the Achilles tendon that most often results from the combination of mechanical stress and intratendinous degeneration.

ICD-9CM CODES
727.67 Nontraumatic rupture of Achilles tendon
ICD-10CM CODES
M66.27 Spontaneous rupture of extensor tendons, ankle and foot

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1 in 10,000/year (third most frequent tendon disruption in the body)
PEAK INCIDENCE: 30 to 39 yr age group
PREDOMINANT AGE: 30 to 55 yr age group

RISK FACTORS

General risk factors include the recreational athlete, advancing age, previous tear or rupture, extreme change in training level, or participation in a new activity. Other risk factors can be categorized into intrinsic and extrinsic.

- **Intrinsic:** Achilles tendinitis/tendinosis, tight musculature, poor vascularity, tibial varum, overpronation, cavus foot, systemic lupus erythematosus, rheumatoid arthritis, gout
- **Extrinsic:** Inadequate training equipment/training techniques, recent steroid or fluoroquinolone therapy

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The typical patient is a middle-aged man who gives a history of recent physical activity with a sudden push-off, jump, or misstep that causes a snap sensation or audible pop in the back of the leg, followed by the onset of acute pain, swelling, and weakened plantarflexion power. Patients commonly relate feeling as though they were "hit in the back of the leg with a bat." Most often patients have sedentary occupations and indulge occasionally in strenuous activity.

- Depending on the severity of the rupture, initial pain may not be severe.
- Several hours after injury, diffuse pain, swelling, and ecchymosis are usually evident.
- The patient has difficulty walking, with a weakened plantarflexion power and inability to perform a single heel raise on the injured extremity.
- Referred stabbing pain in the posterior leg and ankle from muscle spasm is common.
- A palpable gap within the Achilles tendon, which increases with dorsiflexion of the ankle, is present.

ETIOLOGY

Although a history of direct trauma is uncommon, it may include blunt trauma to the posterior ankle, crushing injury, and laceration. Indirect injury as a cause of rupture is more common. Etiologic factors of indirect injury are of three types: mechanical, vascular, and related to poor tissue quality.

- Mechanical: involves variations of a rapid loading process on an already tensed tendon such as a sudden dorsiflexion of the ankle with the knee extended while an eccentric load is applied
  1. Tripping on a curb
  2. Lunging for a tennis shot
  3. Jumping from a height
- Vascular: factors include the known watershed area located 2 to 6 cm proximal to the insertion, an area of poor blood supply.
- Poor tissue quality: refers to the common notion that prior tendon degeneration is required to weaken the tendon before it is ruptured. This often occurs in the form of repetitive microtrauma from improper training techniques.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Achilles tendinopathy
- Retrocalcaneal bursitis
- Ankle sprain
- Calcaneal avulsion fracture
- Partial rupture of gastrocnemius
- Plantaris rupture
- Rupture of Baker's cyst
- Os trigonum syndrome
- Plantaris rupture

WORKUP

Approximately 25% of Achilles tendon ruptures are misdiagnosed initially. A thorough history and physical exam, coupled with high clinical suspicion, can prevent this from happening. The clinical history in most presentations is very specific, and the physical exam is usually diagnostic. Below is a list of specific clinical tests and imaging modalities. Please see section "Physical Findings & Clinical Presentation" for more information.

- **Thompson's test:** The patient is placed in a prone position with the knees flexed. The examiner squeezes the calf musculature, which should produce plantarflexion of the ankle. If no plantarflexion is obtained, this indicates an Achilles tendon rupture (a positive test). (See Fig. A1-22.)
- **Matles test:** The patient is placed in the prone position with the knees flexed to 90 degrees. If the injured foot falls to neutral or a dorsiflexed position, the Achilles tendon is ruptured (a positive test).
- MRI and ultrasound may be useful when clinical suspicion is high, but clinical tests are inconclusive.

TREATMENT

Controversy exists over conservative versus surgical repair of the ruptured Achilles tendon, but most evidence shows that early treatment has a far better prognosis than later repair. Conservative treatment is associated with a higher re-rupture rate. Surgical repair often facilitates earlier return to full activity. In general, older, more sedentary patients should be treated conservatively and younger athletic patients should receive surgical repair.

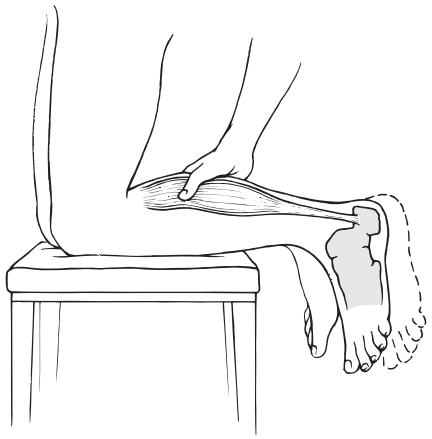

FIGURE A1-22 Thompson's test. Compression of the calf muscles normally produces plantarflexion of the ankle. If the Achilles tendon is ruptured, this reponse is greatly diminished or absent. (From Browner BD et al: *Skeletal trauma: basic science, management, and reconstruction,* ed 3, Philadelphia, 2003, Saunders.)

- *Conservative treatment:* A long leg cast is applied with the foot in approximately 20 degrees equinovarus, ensuring that the knee is bent during the casting process. The cast is removed at 8 weeks, with gradual reduction in equinovarus with a short leg cast. After removal of the cast, physical therapy should be instituted to regain dorsiflexion of the ankle. This gradual process may take up to 12 weeks. The total conservative rehabilitation period may last 6-9 months.
- *Surgical treatment:* Several surgical techniques exist to repair the ruptured Achilles tendon. Many involve lengthening and flap down methods to bridge the gap in the tendon. Multiple biologic grafts are available that may be used to augment and reinforce the rupture site. After surgery, 10 to 12 weeks of immobilization followed by rehabilitation is recommended.

DISPOSITION

- Conservative care carries a 20% to 30% chance of re-rupture.
- Re-rupture rates are very low with surgical repair
- A physical therapist should work closely with the patient in the rehabilitation period regardless of whether surgical or conservative care is used.
- Early treatment, whether conservative or surgical, has far better results than treatment of neglected cases

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Achilles Tendon Rupture (Patient Information)

AUTHOR: **DOMINIC RODA, D.P.M.**

EVIDENCE

Abstract[1]

Background:
Animal studies have shown that local application of platelet-rich plasma (PRP) stimulates tendon repair. Preliminary results from a retrospective case series have shown faster return to sports.

Hypothesis:
Autologous PRP stimulates healing of acute Achilles tendon ruptures.

Study Design:
Randomized controlled trial; level of evidence, 2.

Methods:
Thirty patients were recruited consecutively. During surgery, tantalum beads were implanted in the Achilles tendon proximal and distal to the rupture. Before skin suture, randomization was performed, and 16 patients were injected with 10 mL PRP (10 times higher platelet concentration than peripheral blood) whereas 14 were not. With 3-dimensional radiographs (roentgen stereophotogrammetric analysis; RSA), the distance between the beads was measured at 7, 19, and 52 weeks while the patient resisted different dorsal flexion moments over the ankle joint, thereby estimating tendon strain per load. An estimate of elasticity modulus was calculated using callus dimensions from computed tomography. At 1 year, functional outcome was evaluated, including the heel raise index and Achilles Tendon Total Rupture Score. The primary effect variables were elasticity modulus at 7 weeks and heel raise index at 1 year.

Results:
The mechanical variables showed a large degree of variation between patients that could not be explained by measuring error. No significant group differences in elasticity modulus could be shown. There was no significant difference in heel raise index. The Achilles Tendon Total Rupture Score was lower in the PRP group, suggesting a detrimental effect. There was a correlation between the elasticity modulus at 7 and 19 weeks and the heel raise index at 52 weeks.

Conclusion
The results suggest that PRP is not useful for treatment of Achilles tendon ruptures. The variation in elasticity modulus provides biologically relevant information, although it is unclear how early biomechanics is connected to late clinical results. B

Evidence-Based Reference

Schepull T, et al.: Autologous platelets have no effect on the healing of human Achilles tendon ruptures: a randomized single-blind study, *Am J Sports Med* 39:38–47, 2011. B

SUGGESTED READINGS

Bhandari M et al.: Treatment of acute Achilles tendon rupture: a systematic overview and metaanalysis, *Clin Orthop* 190(400), 2002.

Khan RJ et al.: Treatment of acute Achilles tendon ruptures: a meta-analysis of randomized controlled trials, *J Bone Joint Surg Am* 87A:2202, 2005.

Lawrence SJ, Grau GF: Management of acute Achilles tendon ruptures, *Orthopedics* 27:579, 2004.

Maffulli N et al.: Chronic rupture of tendo Achilles, *Foot Ankle Clin* 12:583, 2007.

Reddy SS et al.: Surgical treatment for chronic disease and disorders of the Achilles tendon, *J Am Acad Orthop Surg* 17:3, 2009.

Rettig AC et al.: Potential risk of rerupture in primary Achilles tendon repair in athletes younger than 30 years of age, *Am J Sports Med* 33:119, 2005.

Roberts C, Deliss L: Acute rupture of tendo Achilles, *J Bone Joint Surg Br* 84(4):620, 2002.

Smigielski R: Management of partial tears of the gastro-soleus complex, *Clin Sports Med* 27:219, 2008.

Wallace RG et al.: Combined conservative and orthotic management of acute ruptures of the Achilles tendon, *J Bone Joint Surg Am* 86A:1198, 2004.

Wick MC, Reiger M: Images in clinical medicine. Rupture of a calcified Achilles' tendon, *N Engl J Med* 358:2618, 2008.

Worth N et al.: Management of acute Achilles tendon ruptures in the United Kingdom, *J Orthop Surg (Hong Kong)* 15:311, 2007.

BASIC INFORMATION

DEFINITION

Acne vulgaris is a chronic disorder of the pilosebaceous apparatus caused by abnormal desquamation of follicular epithelium leading to obstruction of the pilosebaceous canal, resulting in inflammation and subsequent formation of papules, pustules, nodules, comedones, and scarring. Acne can be classified by the type of lesion (comedonal, papulopustular, and nodulocystic). The American Academy of Dermatology classification scheme for acne denotes the following three levels:

1. Mild acne: characterized by the presence of comedones (noninflammatory lesions), few papules and pustules (generally <10), but no nodules.
2. Moderate acne: presence of several to many papules and pustules (10 to 40) along with comedones (10 to 40). The presence of >40 papules and pustules along with larger, deeper nodular inflamed lesions (up to five) denotes moderately severe acne (Fig. A1-23).
3. Severe acne (Fig. A1-24): presence of numerous or extensive papules and pustules as well as many nodular lesions.

SYNONYMS

Acne

ICD-9CM CODES
706.1 Acne vulgaris
ICD-10CM CODES
L70.0 Acne vulgaris

EPIDEMIOLOGY & DEMOGRAPHICS

- Acne is the most common skin disease in the U.S.
- It is most common in teenagers (highest incidence between ages of 16 and 18 yr).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Open comedones (blackheads), closed comedones (whiteheads)
- Greasiness (oily skin)
- Presence of scars from prior acne cysts
- Various stages of development and severity may be present concomitantly
- Common distribution of acne: face, back, and upper chest
- Inflammatory papules, pustules, and ectatic pores

ETIOLOGY

- Overactivity of the sebaceous glands and blockage in the ducts. The obstruction leads to the formation of comedones, which can become inflamed because of overgrowth of *Propionibacterium acnes.*
- Exacerbated by environmental factors (hot, humid, tropical climate), medications (e.g., iodine in cough mixtures, hair greases), industrial exposure to halogenated hydrocarbons.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Gram-negative folliculitis
- Staphylococcal pyoderma
- Acne rosacea
- Drug eruption
- Sebaceous hyperplasia
- Angiofibromas, basal cell carcinomas, osteoma cutis
- Occupational exposures to oils or grease
- Steroid acne
- Hidradenitis suppurativa
- Perioral dermatitis
- Pseudofolliculitis barbae
- Miliaria
- Seborrheic dermatitis

WORKUP

History and physical examination:

- Inquire about previous treatment
- Careful drug history
- Family history, history of cyclic menstrual flares
- History of use of cosmetics and cleansers
- Oral contraceptive use

LABORATORY TESTS

- Laboratory evaluation is generally not helpful.
- Patients who are candidates for therapy with isotretinoin should have baseline liver enzymes, cholesterol, and triglycerides checked because this medication may result in elevation of lipids and liver enzymes.
- A negative serum pregnancy test or two negative urine pregnancy tests should also be obtained in females 1 wk before initiation of isotretinoin; it is also imperative to maintain effective contraception during and 1 mo after therapy with isotretinoin ends because of its teratogenic effects. Pregnancy status should be rechecked at monthly visits.
- If hyperandrogenism is suspected in female patients, levels of dehydroepiandrosterone sulfate, testosterone (total and free), and androstenedione should be measured. For women with regular menstrual cycles, serum androgen measurements generally are not necessary.

TREATMENT

NONPHARMACOLOGIC THERAPY

Blue light (ClearLight therapy system) can be used for treatment of moderate inflammatory acne vulgaris. Light in the violet/blue range can cause bacterial death by a photoreaction in which porphyrins react with oxygen to generate reactive oxygen species, which damage the cell membranes of *P. acnes.* Treatment usually consists of 15-min exposures twice weekly for 4 wk.

ACUTE GENERAL Rx

Treatment generally varies with the type of lesions (comedones, papules, pustules, cystic lesions) and the severity of acne.

- Comedones (noninflammatory acne) can be treated with retinoids or retinoid analogs. Topical retinoids are comedolytic and work by normalizing follicular keratinization. Commonly available agents are Adapalene (Differin, 0.1% gel or cream, applied once or twice daily), tazarotene (Tazorac 0.1% cream or gel applied daily), tretinoin (Retin-A 0.1% cream or 0.025 gel applied once daily), tretinoin microsphere (Retin-A Micro, 0.1% gel, applied at bedtime). Tretinoin is inactivated by ultraviolet light and oxidized by benzoyl peroxide; therefore it should only be applied at night and not used concomitantly with benzoyl peroxide.
- Tretinoin is pregnancy category C and tazarotene is pregnancy category X. Salicylic acid preparations (e.g., Neutrogena 2% wash) have keratolytic and anti-inflammatory properties and are also useful in the treatment of comedones. Large, open comedones (blackheads) should be expressed.

FIGURE A1-23 Acne on back and shoulders. This acne is typically inflammatory and usually needs oral antibiotics or possibly isotretinoin, but the patient may apply topical medication as well. Heat and sweat may aggravate the condition. (From White GM, Cox NH [eds]: *Diseases of the skin,* ed 2, St Louis, 2006, Mosby.)

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FIGURE A1-24 Severe acne. Acne this severe on presentation should prompt the consideration of early use of isotretinoin. The dose should be low initially to prevent a severe flare. An oral tetracycline or erythromycin may be helpful to calm the acne before isotretinoin. (From White GM, Cox NH [eds]: *Diseases of the skin,* ed 2, St Louis, 2006, Mosby.)

- Patients should be reevaluated after 4 to 6 wk. Benzoyl peroxide gel (2.5% or 5%) may be added if the comedones become inflamed or form pustules. The most common adverse effects are dryness, erythema, and peeling. Topical antibiotics (erythromycin, clindamycin lotions or pads) can also be used in patients with significant inflammation. They reduce *P. acnes* in the pilosebaceous follicle and have some anti-inflammatory effects. The combination of 5% benzoyl peroxide and 3% erythromycin (Benzamycin) or 1% clindamycin with 5% benzoyl peroxide (BenzaClin) is highly effective in patients who have a mixture of comedonal and inflammatory acne lesions.
- Fixed-dose combinations of clindamycin phosphate 1.2% and tretinoin 0.025% are available (Veltin gel, Ziana) and are more effective than either product used alone; however, they are much more expensive than the individual generic components.
- Pustular acne can be treated with tretinoin and benzoyl peroxide gel applied on alternate evenings; drying agents (sulfacetamide-sulfa lotions [Novacet, Sulfacet]) are also effective when used in combination with benzoyl peroxide; oral antibiotics (doxycycline 100 mg qd or erythromycin 1 g qd given in 2 to 3 divided doses) are effective in patients with moderate to severe pustular acne. Patients not responding well to these antibiotics can be switched to minocycline 50 to 100 mg bid; however, this medication is more expensive.
- Patients with nodular cystic acne can be treated with systemic agents: antibiotics (erythromycin, tetracycline, doxycycline, minocycline), isotretinoin (available on a restricted basis), or oral contraceptives. Periodic intralesional triamcinolone (Kenalog) injections by a dermatologist are also effective. The possibility of endocrinopathy should be considered in patients responding poorly to therapy.
- Isotretinoin is indicated for acne resistant to antibiotic therapy and severe acne. It is available only on a restricted basis. Dosage is 0.5 to 1 mg/kg/day in 2 divided doses (maximum of 2 mg/kg/day); duration of therapy is generally 20 wk for a cumulative dose ≥120 mg/kg for severe cystic acne. Before using this medication patients should undergo baseline laboratory evaluation (see "Laboratory Tests"). This drug is absolutely contraindicated during pregnancy because of its teratogenicity. It should be used with caution in patients with history of depression. Physicians, distributors, pharmacies, and patients must register in the iPLEDGE program (http://www.ipledgeprogram.com) before using isotretinoin.
- Azelaic acid is a bacteriostatic dicarboxylic acid used to normalize keratinization and reduce inflammation. It can be used in pregnant women.
- Oral contraceptives reduce androgen levels and therefore sebum production. They represent a useful adjunctive therapy for all types of acne in women and adolescent girls. Commonly used agents are norgestimate/ethinyl estradiol (Ortho Tri-Cyclen) and drosperinone/ethinyl estradiol (Yasmin).

REFERRAL

Referral for intralesional injection and dermabrasion should be considered in patients with severe acne unresponsive to conventional therapy.

PEARLS & CONSIDERATIONS

- Gram-negative folliculitis should be suspected if inflammatory acne worsens after several months of oral antibiotic therapy.
- Acne may worsen during the first 3 to 4 wk of retinoid therapy before improving.

COMMENTS

Indications for systemic therapy of acne are:
- Painful deep papules or nodules
- Extensive lesions
- Active acne with severe scarring or hyperpigmentation
- Patient's morale

Patients should be educated that in most cases acne can be controlled but not cured and that at least 4 to 6 wk of initial therapy should be required before significant improvement is noted.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Background:
Acne vulgaris is a chronic and frequently recurring disease. A fixed-dose adapalene-benzoyl peroxide (adapalene-BPO) gel is an efficacious and safe acne treatment.

Objectives:
To assess the long-term effect of adapalene-BPO on relapse prevention among patients with severe acne after successful initial treatments.

Methods:
This is a multicenter, double-blind, randomized and controlled study. In total, 243 subjects who had severe acne vulgaris and at least 50% global improvement after a previous 12-week treatment were randomized into the present study to receive adapalene-BPO gel or its vehicle once daily for 24 weeks.

Results:
At week 24, compared with vehicle, adapalene-BPO resulted in significantly higher lesion maintenance success rate (defined as having at least 50% improvement in lesion counts achieved in initial treatment) for all types of lesions (total lesions: 78.9% vs. 45.8%; inflammatory lesions: 78.0% vs. 48.3%; noninflammatory lesions: 78.0% vs. 43.3%; all $P<0.001$). Significantly more subjects with adapalene-BPO than with vehicle had the same or better Investigator's Global Assessment score at week 24 than at baseline (70.7% vs. 34.2%; $P<0.001$). The time when 25% of subjects relapsed was 175 days with adapalene-BPO and 56 days with vehicle (17 weeks earlier; $P<0.0001$). Adapalene-BPO led to further decrease of lesion counts during the study and 45.7% of subjects were "clear" or "almost clear" at week 24. It was also safe and well tolerated in the study.

Conclusions:
Adapalene-BPO not only prevents the occurrence of relapse among patients with severe acne, but also continues to reduce disease symptoms during 6 months. Ⓐ

Abstract[2]

Background:
There is no direct correlation between acne severity and lesion numbers and patients with moderate acne may present with varying lesion counts. The fixed-dose adapalene 0.1%-benzoyl peroxide (BPO) 2.5% combination gel is an efficacious and safe acne treatment.

Objectives:
We sought to evaluate whether the benefit of adapalene-BPO relative to vehicle varies with baseline lesion counts.

Methods:
Data were pooled from 3 randomized, double-blind, controlled studies, which compared efficacy in 4 treatment groups (adapalene-BPO, adapalene, BPO, and the gel vehicle). Three lesion count subgroups (Low, Mid, and High) were defined based on the number of total, inflammatory, or noninflammatory lesion at baseline. Efficacy of each treatment and benefit of each treatment relative to vehicle were evaluated on the entire population and in all lesion count subgroups. Safety was assessed by local tolerability score and adverse events.

Results:
Adapalene-BPO provided significant benefit relative to vehicle and monotherapies on the entire population and in all lesion count subgroups ($P<.05$). At study end point, the benefit of adapalene-BPO relative to vehicle was greatest in the High subgroup, suggesting that patients with the highest baseline lesion counts contributed the most to the treatment benefit observed in the entire population. This effect was only observed with adapalene-BPO and not with monotherapies. Higher baseline lesion counts did not lead to more related adverse event or worse tolerability score for adapalene-BPO.

Limitation:
These results were generated from clinical trials. Results in clinical practice could differ.

Conclusion:
The relative benefit of adapalene-BPO increases with higher lesion counts at baseline. Ⓐ

Evidence-Based References

Poulin Y et al.: A 6-month maintenance therapy with adapalene-benzoyl peroxide gel prevents relapse and continuously improves efficacy among patients with severe acne vulgaris: results of a randomized controlled trial, *Br J Dermatol* 164:1376–1382, 2011. Ⓐ

Feldman S et al.: The efficacy of adapalene-benzoyl peroxide combination increases with number of acne lesions, *J Am Acad Dermatol* 64:1085–1091, 2011. Ⓐ

SUGGESTED READINGS

Haider A, Shaw JC: Treatment of acne vulgaris, *JAMA* 292:726, 2004.

James WD: Acne, *N Engl J Med* 352:1463, 2005.

Titus S, Hodge J: Diagnosis and treatment of acne, *Am Fam Physician* 86:736–740, 2012.

BASIC INFORMATION

DEFINITION

Acoustic neuroma is a benign proliferation of the Schwann cells that cover the vestibular branch of the eighth cranial nerve (CN VIII). Symptoms are commonly a result of compression of the acoustic branch of CN VIII, the facial nerve (CN VII), and the trigeminal nerve (CN V). The glossopharyngeal nerve (CN IX) and vagus nerve (CN X) are less commonly involved. In extreme cases compression of the brain stem may lead to obstruction of cerebrospinal fluid (CSF) outflow and elevated intracranial pressure (ICP).

SYNONYMS

Vestibular schwannoma

ICD-9CM CODES
225.1 Acoustic neuroma
ICD-10CM CODES
D33.3 Benign neoplasm of cranial nerves

EPIDEMIOLOGY & DEMOGRAPHICS

Overall incidence is approximately one in 100,000 person-years, with a higher incidence in patients with neurofibromatosis type 2 (NF2). There may be a slight female predominance. The tumor most commonly presents in the fifth and sixth decades.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most frequently unilateral hearing loss and/or tinnitus. Also balance problems, vertigo, facial pain (trigeminal neuralgia) and weakness, difficulty swallowing, fullness or pain of the involved ear. Headache may occur.
- With elevated ICP, patients may also have vomiting, fever, and visual changes.
- Hearing loss is the most common presenting complaint and is usually high frequency.

ETIOLOGY

The etiology is incompletely understood, but long-term exposure to acoustic trauma has been implicated. Bilateral acoustic neuromas may be inherited in an autosomal-dominant manner as part of NF2. This disease is associated with a defect on chromosome 22q1. Childhood exposure to low-dose radiation for benign head and neck conditions may increase risk for acoustic neuromas. There is inconclusive evidence to link chronic exposure to radiofrequency radiation from cellular telephone use and the risk for developing brain tumors.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Benign positional vertigo
- Menière's disease
- Trigeminal neuralgia
- Cerebellar disease
- Normal-pressure hydrocephalus
- Presbycusis
- Glomus tumors
- Vertebrobasilar insufficiency
- Ototoxicity from medications
- Other tumors:
  1. Meningioma, glioma
  2. Facial nerve schwannoma
  3. Cavernous hemangioma
  4. Metastatic tumors

WORKUP

- A detailed neurologic examination with special attention to the cranial nerves is crucial.
- Otoscopic evaluation may help rule out other causes of hearing loss.

LABORATORY TESTS

- Audiometry is useful, often showing asymmetric, sensorineural, high-frequency hearing loss.
- CSF protein may be elevated.

IMAGING STUDIES

- MRI with gadolinium (Fig. A1-25) is the preferred test. It can detect tumors as small as 2 mm in diameter.
- High-resolution CT scan with and without contrast can detect tumors 1 cm in diameter or larger.
- Treatment decisions should be based on the size of the tumor, rate of growth (older patients tend to have slower-growing tumors), degree of neurologic deficit, desire to preserve hearing, life expectancy, age of the patient, and surgical risk. A combination of treatments can also be used.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Surgery is the definitive treatment. Choice of approach (middle cranial fossa, translabyrinthine, or retromastoid suboccipital) may vary depending on the size of the tumor, amount of residual hearing desired, and degree of surgical risk that can be tolerated. Partial resection is sometimes undertaken to minimize the risk of injury to nearby structures. Intraoperative facial nerve monitoring is recommended.
- Radiation therapy (stereotactic radiotherapy, stereotactic radiosurgery, or proton beam radiotherapy) is useful for tumors <3 cm in diameter or for those in whom surgery is not an option. Radiotherapy after partial resection has also been used to minimize complications.
- Age alone is not a contraindication to surgery.

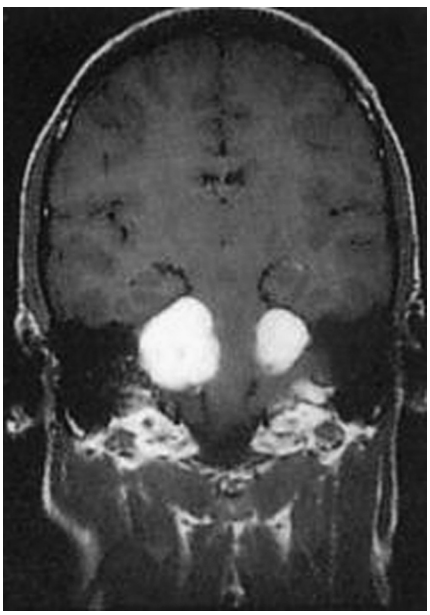

FIGURE A1-25 MR with enhancement shows bilateral acoustic neuromas. Coronal view. (From Kanski JJ, Bowling B: *Clinical ophthalmology, a systematic approach,* ed 7, Philadephia, 2011, Saunders.)

GENERAL Rx

- Bevacizumab, an antivascular endothelial growth factor (VEGF) monoclonal antibody, has been shown to improve hearing and reduce the volume of growing acoustic neuromas in some neurofibromatosis type 2 patients.
- Observation with MRI every 6 to 12 mo may be appropriate for frail patients with small tumors, but risk of unrecoverable hearing loss may increase if surgery is delayed. Also, progressive hearing loss may occur despite absence of growth on subsequent imaging.

DISPOSITION

Hearing can be preserved at near-preoperative levels in more than two thirds of patients with small- to medium-sized tumors. Occurrence of secondary radiation-related tumors following radiosurgery is rare. There are no standard posttreatment follow-up recommendations. Therefore, an individualized approach to follow-up imaging and audiometry is recommended.

REFERRAL

Prompt referral to an ear-nose-throat specialist or neurosurgeon who is facile with all three surgical approaches is recommended.

PEARLS & CONSIDERATIONS

COMMENTS

- Presents most commonly as unilateral, sensorineural hearing loss.
- Treatment outcomes are generally good, with cure rates approaching 90% at 5 years.
- Of those who are managed with observation only, approximately half have continued enlargement and approximately one fifth eventually have a surgical intervention.

PATIENT/FAMILY EDUCATION

Acoustic Neuroma Association: http://anausa.org.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Tinnitus (Related Key Topic)
Acoustic Neuroma (Patient Information)

AUTHOR: **COURTNEY CLARK BILODEAU, M.D.**

http://internalmedicinebook.com/

SUGGESTED READINGS

Evans DG et al.: Incidence of vestibular schwannoma and neurofibromatosis 2 in the North West of England over a 10-year period: higher incidence than previously thought, *Otol Neurotol* 26(1):93–97, 2005.

Kondziolka D et al.: The newly diagnosed vestibular schwannoma: radiosurgery, resection, or observation? *Neurosurg Focus* 33(3):E8, 2012 Sep.

Mendenhall WM et al.: Management of acoustic schwannoma, *Am J Otolaryngol* 25(1):38, 2004.

Pitts LH, Jackler RK: Treatment of acoustic neuromas, *N Engl J Med* 339:1471, 1998.

Régis J et al.: Radiosurgery for vestibular schwannomas. http://www.ncbi.nlm.nih.gov/pubmed/24093570, 24 (4):521–30, 2013.

Theodosopoulos PV et al.: Contemporary management of acoustic neuromas, *Laryngoscope* 121:1133–1137, 2011.

Yoshimoto Y: Systematic review of the natural history of vestibular schwannoma, *J Neurosurg* 103(1):59, 2005.

You Y-P, et al.: Vestibular Schwannoma Surgical Treatment, *CNS Neuroscience & Therapeutics* 19:289–293, 2013.

Acquired Immunodeficiency Syndrome PTG ALG

BASIC INFORMATION

DEFINITION

Acquired immunodeficiency syndrome (AIDS) is a disorder caused by infection with the human immunodeficiency virus (HIV) and marked by progressive deterioration of the cellular immune system, leading to secondary (opportunistic) infections or malignancies.

SYNONYMS

AIDS

ICD-9CM CODES
042 AIDS, unspecified
ICD-10CM CODES
B20 Human immunodeficiency virus [HIV] disease

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- The estimated number of persons diagnosed with AIDS exceeds 30,000/year.
- Over 40% of new AIDS cases are in black/African Americans, almost 20% in Hispanics, and over 25% in white Americans.
- Over 50% of AIDS cases are among gay, bisexual, or other men who have sex with men (MSM).

PREVALENCE (IN U.S.):

- The cumulative number of AIDS diagnoses in the U.S. exceeds 1.2 million.

PREDOMINANT SEX: Over 50% of AIDS diagnoses occur in men who have sex with men (MSM).

PREDOMINANT AGE: The predominant age group diagnosed with AIDS is 30-49 years of age.

PEAK INCIDENCE: Ages 45-49

GENETICS

- Familial disposition: Although there is no proven genetic predisposition, individuals with deletions in the *CCR5* gene are immune from infection with macrophage tropic virus (the predominant virus in sexual transmission).
- Congenital infection:
  1. Transmittable from an infected mother to the fetus in utero in as many as 30% of pregnancies.
  2. No specific congenital malformations associated with infection; low birth weight and spontaneous abortion are possible.
- Neonatal infection: transmission possible to the neonate intrapartum or postpartum through breastfeeding.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Nonspecific findings: fever, weight loss, anorexia.
- Specific syndromes:
  1. Seen in association with opportunistic infection and malignancies, so-called indicator diseases; these include:
     a. Opportunistic infections:
     Disseminated strongyloidiasis
     Disseminated toxoplasmosis, cryptococcosis, histoplasmosis, cytomegalovirus (CMV), herpes simplex, or mycobacterial disease
     Candida esophagitis or bronchopulmonary disease
     Chronic *Cryptosporidia* spp. diarrhea
     Pneumocystis jiroveci pneumonia (PJP)
     Extensive pulmonary and extrapulmonary tuberculosis
     Recurrent bacterial pneumonia
     Progressive multifocal leukoencephalopathy (PML)
     b. AIDS-related neoplasms:
     Kaposi's sarcoma
     Primary brain lymphoma
     Invasive cervical carcinoma
     High-grade B cell non-Hodgkin's lymphoma, Burkitt's lymphoma, undifferentiated non-Hodgkin's lymphoma, or immunoblastic lymphoma
  2. Most common:
     Respiratory infections (*Pneumocystis jiroveci* [formerly known as *Pneumocystis carinii*] pneumonia, TB, bacterial pneumonia, fungal infection)
     CNS infections (toxoplasmosis, cryptococcal meningitis, TB)
     GI (cryptosporidiosis, isosporiasis, CMV); Sections II and III describe organisms associated with diarrhea in patients with AIDS
     Eye infections (CMV, toxoplasmosis)
     Kaposi's sarcoma (cutaneous or visceral) or lymphoma (nodal or extranodal)
- Possibly asymptomatic.
- Diagnosis of AIDS if T-lymphocyte subset analysis demonstrating CD4 cell count <200 or <14% of total lymphocyte in the presence of proven HIV infection even in the absence of other infections.
- The various manifestations of HIV infection are described in Section II.

ETIOLOGY

- Caused by infection with HIV-1 or HIV-2.
- Transmitted by sexual contact, needle-sharing (during IV drug use), transfusion of contaminated blood or blood products, and from infected mother to fetus or neonate as described previously.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other wasting illnesses mimicking the nonspecific features of AIDS:
  1. TB
  2. Neoplasms
  3. Disseminated fungal infection
  4. Malabsorption syndromes
  5. Depression
- Other disorders associated with dementia or demyelination producing encephalopathy, myelopathy, or neuropathy.

WORKUP

Prompt evaluation of respiratory, CNS, and GI complaints

LABORATORY TESTS

- HIV antibody testing. See "Human Immunodeficiency Virus" topic for the 2014 revised surveillance case definition for HIV infection.
- T-lymphocyte subset analysis: performed to determine the degree of immunodeficiency (i.e., CD4 cell count).
- Viral load assay: to plan long-term antiviral therapy and to follow progression and success of treatment (i.e., HIV RNA PCR).
- CSF examination: for meningitis (if indicated).
- Serologic tests for syphilis, hepatitis B, hepatitis C, and toxoplasmosis.
- Genotypic resistance testing: used to assess for primary resistance in naïve patients and secondary resistance in patients failing a regimen.
- Eye exam: to evaluate for CMV retinitis in patients with CD4 counts <50 cells/mm^3.
- Cryptococcal antigen: part of the evaluation in AIDS patients with CD4 counts <100 cells/mm^3 who have fever, diffuse pneumonia, or symptoms of meningitis.
- Evaluation for infection with mycobacterium (TB or MAI) including PPD, sputum cultures, chest radiograph, and blood cultures for acid-fast bacteria, depending on clinical presentation.

IMAGING STUDIES

- MRI or CT of head for encephalopathy or focal CNS complications (e.g., toxoplasmosis, lymphoma).
- Pulmonary gallium scanning to aid in the diagnosis of *Pneumocystis jiroveci* (*P. carinii*) pneumonia.
- Baseline chest radiograph.

TREATMENT

The most important aspect in management of AIDS due to HIV infection is the timely initiation of antiretroviral therapy (see section on HIV treatment).

NONPHARMACOLOGIC THERAPY

- Maintain adequate caloric intake.
- Encourage good oral hygiene and regular dental care.
- Avoid high-risk behaviors that increase the risk of repeated exposure to HIV and other potential pathogens—safer sexual practices, avoid sharing needles, etc.
- Update vaccines—particularly the pneumococcal and hepatitis B vaccine along with annual influenza vaccines.
- Avoid administration of any live attenuated vaccines that may be a risk to these immunocompromised patients (i.e., MMR, varicella). (See Section V for immunization schedules for HIV-infected children.)

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- When feasible, avoid activities that might increase risk of exposure to opportunistic infections (i.e., cleaning out a cat litter box [toxoplasmosis], getting scratched by a cat [*Bartonella* infections], exposure to pet reptiles [salmonellosis], traveling to developing countries [cryptosporidiosis, tuberculosis], eating undercooked foods and drinking from unsafe water supplies, etc.).

ACUTE GENERAL Rx

Acute management of opportunistic infections and malignancies is reviewed elsewhere in this text under specific AIDS-related disorders.

CHRONIC Rx

For all HIV-infected patients, particularly those meeting the case definition of AIDS:

- Preventive therapy for *Pneumocystis jiroveci* pneumonia and TB (see specific chapters elsewhere in this text). With the advent of modern antiretroviral therapy many patients have experienced substantial restoration of cellular immune function. It has become clear that preventive therapy for *Pneumocystis jiroveci* and *Mycobacterium avium* complex as well as suppressive therapy for CMV and cryptococcal infection can often be safely withdrawn if the CD4 cell count rises above 200 for at least 6 months.
- Based on the Department of Health and Human Services (DHHS) Guidelines of 2013, active antiretroviral therapy (ART) should be started regardless of CD4 cell count. Individuals with CD4 cell counts <350 and especially CD4 cell counts <200 should be strongly encouraged to start ART in a timely fashion.
- ART usually includes three-drug combinations of:
  1. Nucleoside reverse transcriptase inhibitors (NRTI): tenofovir (TDF), zidovudine (AZT), didanosine (DDI), lamivudine (3TC), emtricitabine (FTC), stavudine (D4T), and abacavir (ABC).
  2. Protease inhibitors (PI): saquinavir, amprenavir, indinavir, nelfinavir, agenerase, lopinavir/ritonavir, atazanavir, and darunavir.
  3. Nonnucleoside reverse transcriptase inhibitors (NNRTI): nevirapine, delavirdine, efavirenz (EFV), etravirine, and rilpivirine.
  4. Integrase inhibitors: raltegravir, elvitegravir, and dolutegravir.
  5. Others: maraviroc and enfuvirtide.

The protease inhibitor ritonavir should be used in low dose (100 mg) in combination with other protease inhibitors to obtain more sustained drug levels. Usual initial dosing regimens include two NRTIs and an NNRTI (or a PI or raltegravir). Examples of initial regimens recommended by the guidelines:

1. Atripla (EFV/TDF/FTC) in a single combination pill taken once a day.
2. Truvada (TDF/FTC) plus either atazanavir (with ritonavir), darunavir (with ritonavir), or raltegravir.
3. Truvada (TDF/FTC) may be substituted with either epzicom (ABC/3TC) or combivir (AZT/3TC). Before using ABC, individuals should be tested for the presence of HLA-B*5701 to check for hypersensitivity to this drug.

All these drugs have unique and class-specific side effects and require careful and expert follow-up to achieve optimal antiviral effects, ensure compliance, and maintain efficacy. Antiviral response should be monitored by baseline HIV viral load and CD4 count and repeat measurement at 2 weeks and 4 weeks into treatment and then periodically (every 3 months) to ensure viral suppression.

- An approach to evaluating chronic diarrhea in patients with HIV infection is described in Fig. EA1-26, the approach to the acutely ill HIV-infected patient is outlined in Fig. EA1-27, and the evaluation of HIV-positive patients with respiratory complaints is described in Figs. EA1-28 and EA1-29. The approach to a patient with a suspected CNS lesion is described in Figs. EA1-30 and E1-31. Fig. EA1-32 presents an approach to cardiac dysfunction.
- Genotypic resistance testing is strongly encouraged for all patients initiating treatment and for any patient failing antiretroviral therapy. Poor adherence to therapy, however, often underlies virologic failure.

DISPOSITION

The outlook for AIDS has changed radically since the advent of ART therapy from an essentially fatal disease to a chronic medical illness compatible with long-term survival and remarkably good quality of life. Patients should be aggressively treated for severe illnesses as outcomes following ICU admissions remain good. This is accomplished through expert and continuous follow-up, use of ART, and careful detail to compliance to medications and lifestyle modification.

REFERRAL

All patients with AIDS: to a physician knowledgeable and experienced in the management of the disease and its complications

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Acquired Immunodeficiency Syndrome (AIDS) (Patient Information)
Candidiasis, Cutaneous (Related Key Topic)
Candidiasis, Invasive (Related Key Topic)
Cryptosporidium Infection (Related Key Topic)
Cytomegalovirus Infection (Related Key Topic)
Herpes Simplex (Related Key Topic)
Histoplasmosis (Related Key Topic)
HIV Cognitive Dysfunction (Related Key Topic)
Human Immunodeficiency Virus (Related Key Topic)
Kaposi Sarcoma (Related Key Topic)
Pneumocystis jirovecii Pneumonia (Related Key Topic)
Progressive Multifocal Leukoencelphalopathy (Related Key Topic)
Toxoplasmosis (Related Key Topic)
Tuberculosis (Related Key Topic)

AUTHOR: **PHILIP A. CHAN, M.D., M.S.**

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SUGGESTED READINGS

d'Arminio Monforte A et al.: The changing incidence of AIDS events in patients receiving highly active antiretroviral therapy, *Arch Intern Med* 165(4):416, 2005.

Hammer SM et al.: Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society—USA panel, *JAMA* 296(7):827, 2006.

Hermsen ED et al.: Discontinuation of prophylaxis for HIV-associated opportunistic infections in the era of highly active antiretroviral therapy, *Am J Health Syst Pharm* 61(3):245, 2004.

Huang L et al.: Intensive care of patients with HIV infection, *N Engl J Med* 355(2):173, 2006.

Kantor R et al.: Evolution of resistance to drugs in HIV-1-infected patients failing antiretroviral therapy, *AIDS* 18(11):1503, 2004.

Monier PL, Wilcox R: Metabolic complications associated with the use of highly active antiretroviral therapy in HIV-1-infected adults, *Am J Med Sci* 328(1):48, 2004.

Olsen CH et al.: Risk of AIDS and death at given HIV-RNA and CD4 cell count, in relation to specific antiretroviral drugs in regimen, *AIDS* 19(3):319, 2005.

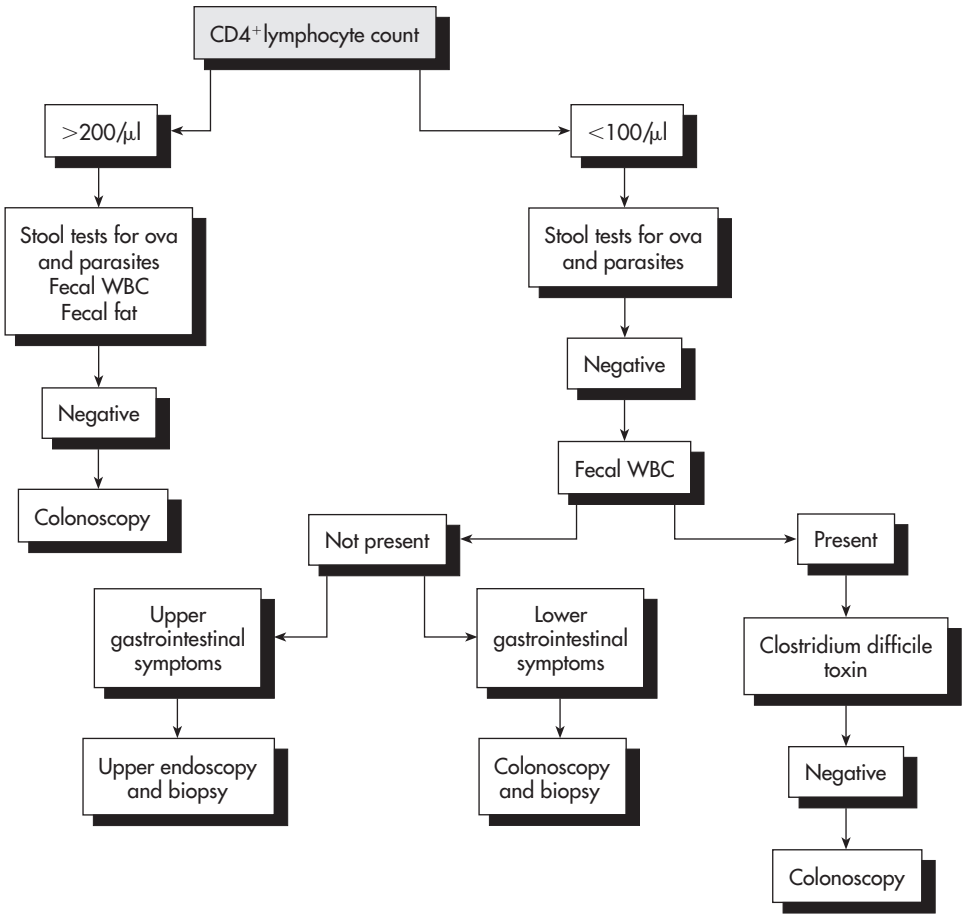

FIGURE EA1-26 Approach to evaluating chronic diarrhea in patients with HIV infection. *WBC,* White blood cell count. (Modified from Wilcox CM: *Gastrointest Dis Today* 5:9, 1996.)

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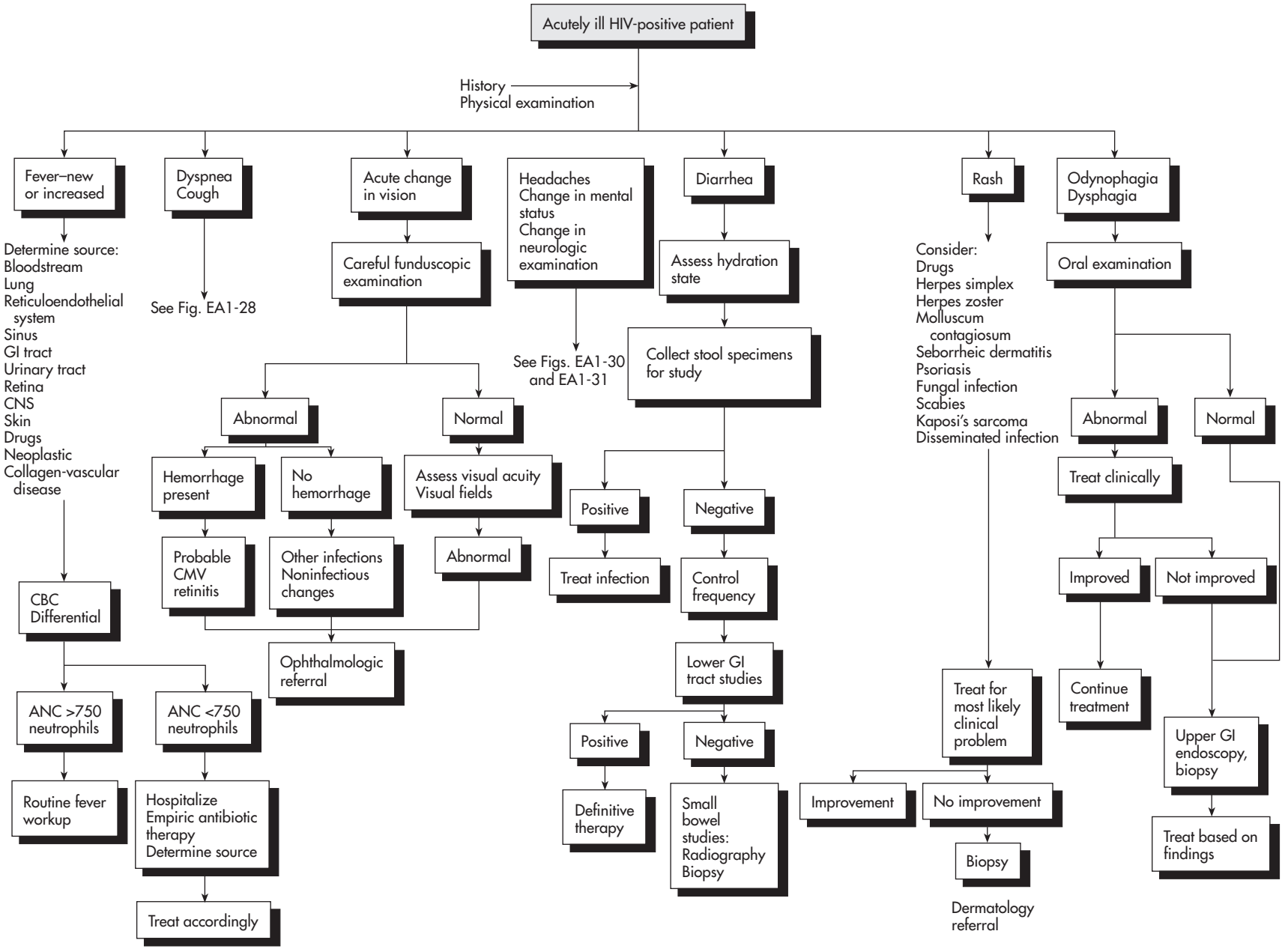

FIGURE EA1-27 Acutely ill HIV-positive patient. *ANC,* Absolute neutrophil count; *CBC,* complete blood count; *CMV,* cytomegalovirus; *CNS,* central nervous system; *GI,* gastrointestinal. (Modified from Greene HL et al [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

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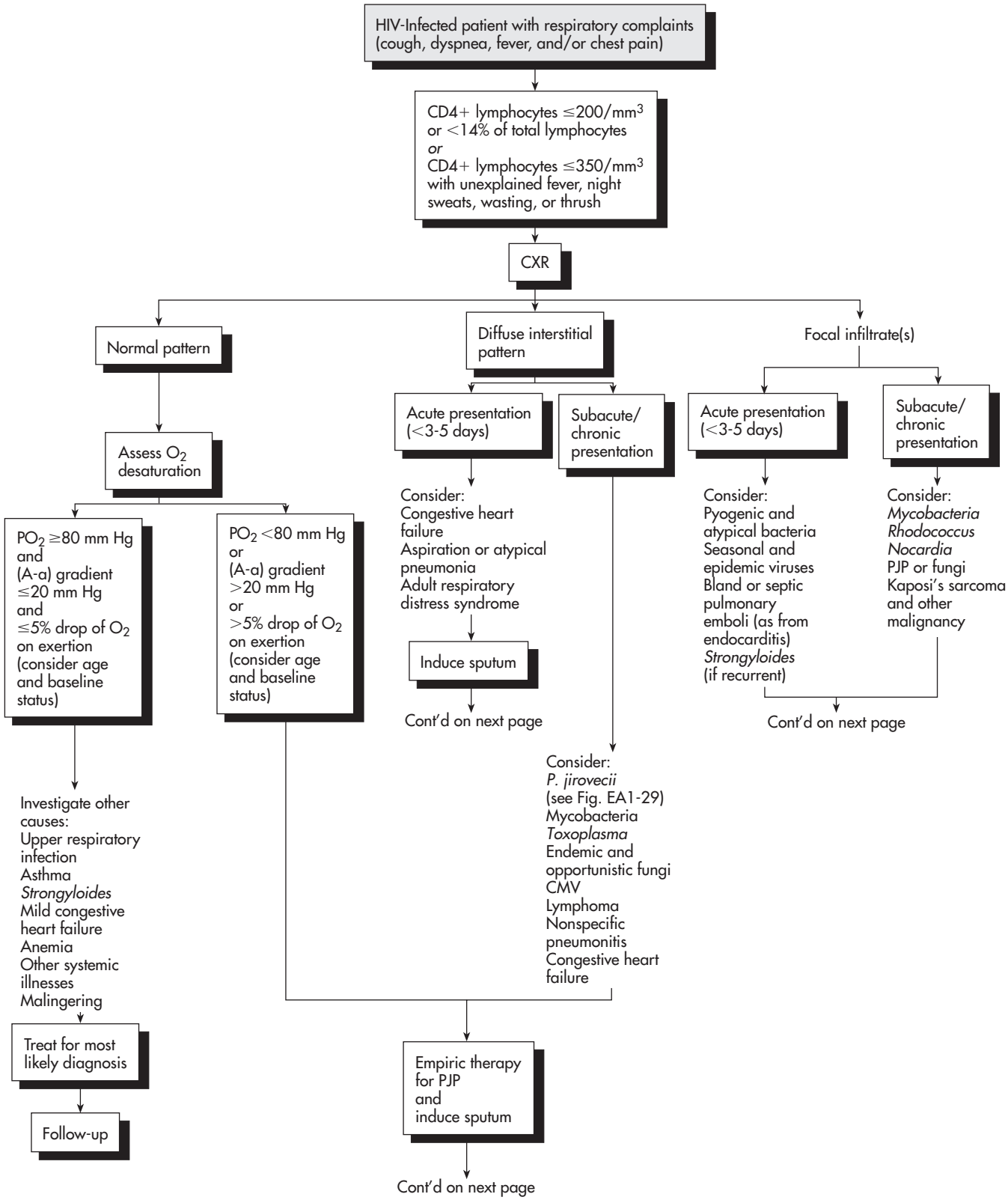

FIGURE EA1-28 HIV-infected patient with respiratory complaints. *BAL,* Bronchoalveolar lavage; *CMV,* cytomegalovirus; *CXR,* chest x-ray examination; *PJP,* Pneumocystis jirovecii pneumonia; *TBB,* transbronchial biopsy. (Modified from Greene HL et al [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

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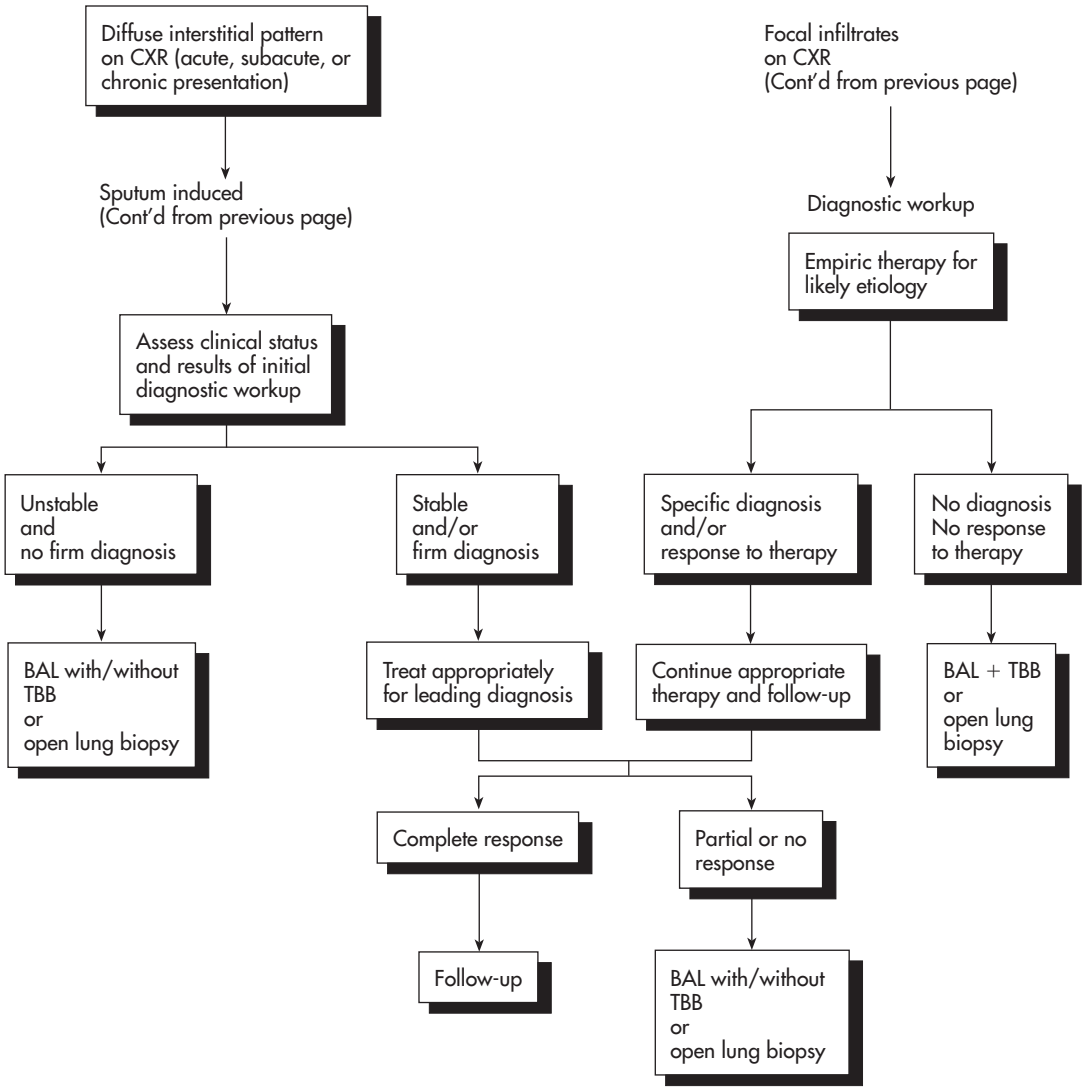

FIGURE EA1-28, cont'd

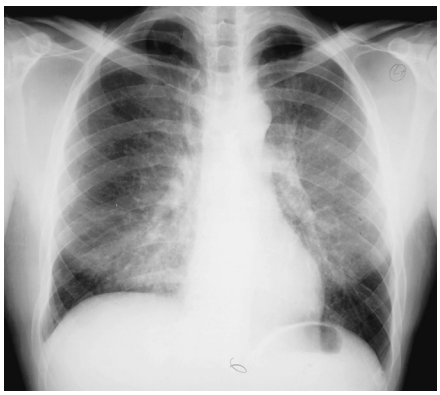

FIGURE EA1-29 Chest radiograph of patient with acquired immunodeficiency syndrome and pneumonia due to *Pneumocystis jirovecii.* Infiltrates representing alveolar filling are most prominent at the right base but also in the left midlung field as diffuse haziness. (From Weinberg SE et al: *Principles of pulmonary medicine,* ed 5, Philadelphia, 2008, Saunders.)

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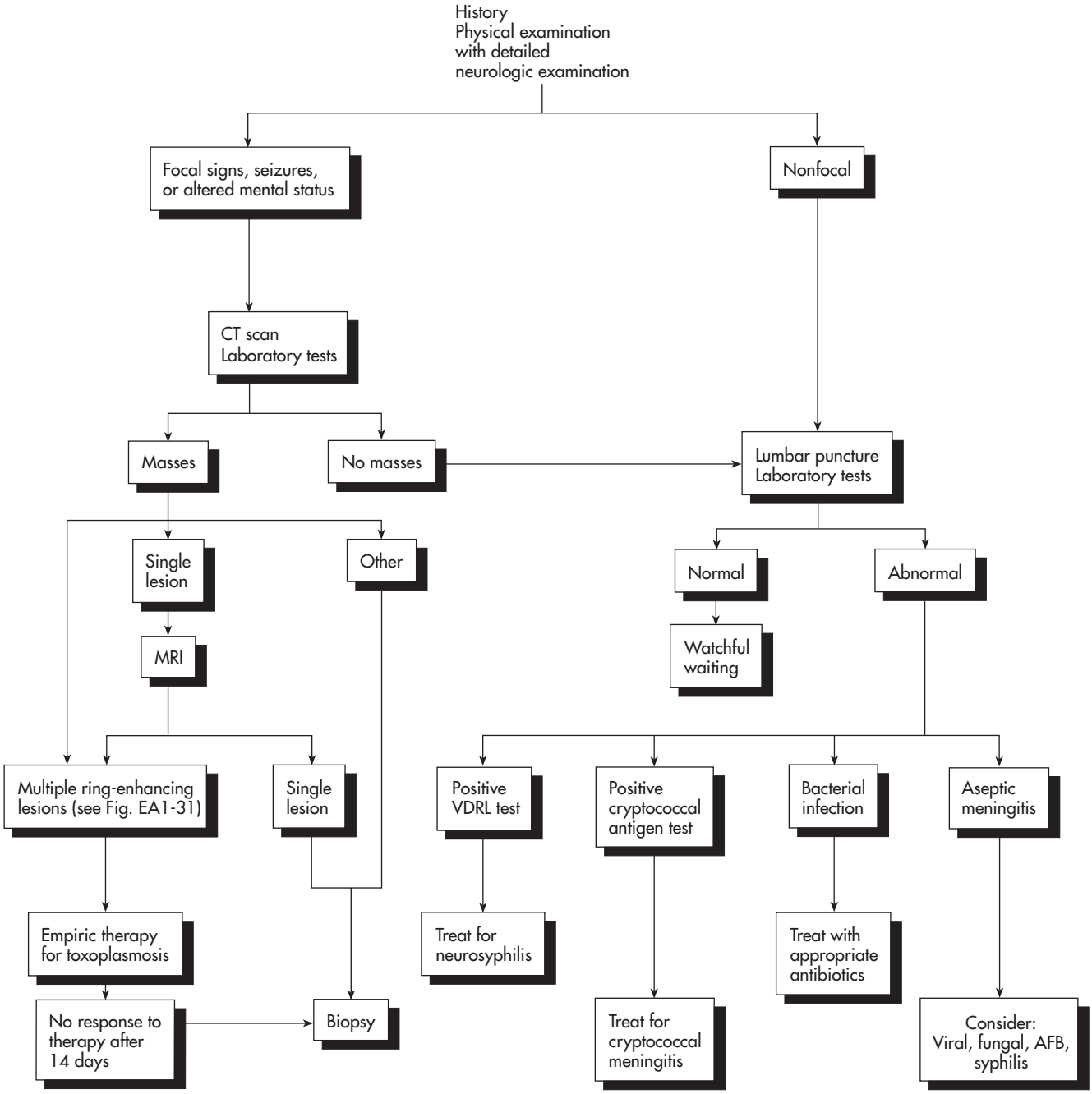

FIGURE EA1-30 HIV-positive patient with suspected central nervous system infection. *AFB,* Acid-fast bacilli; *CNS,* central nervous system; *CT,* computed tomography; *MRI,* magnetic resonance imaging; *VDRL,* Venereal Disease Research Laboratory. (Modified from Greene HL, Johnson WP, Lemcke D [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

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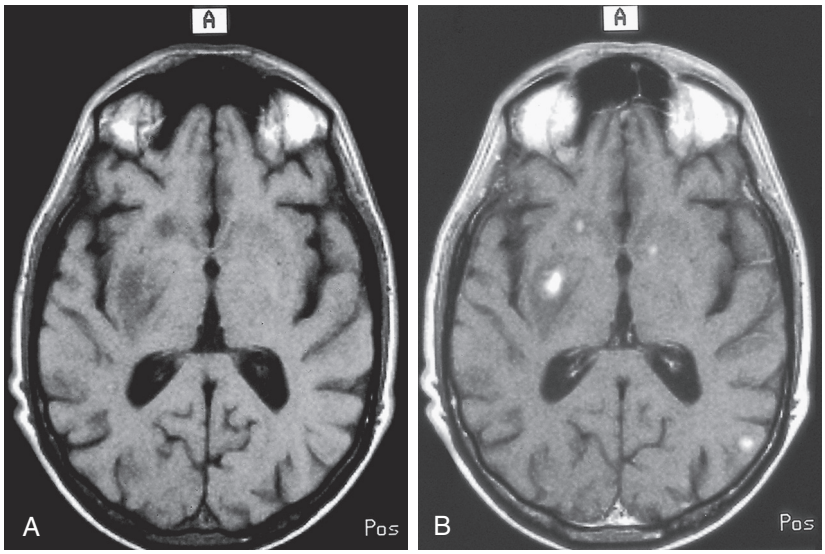

FIGURE EA1-31 Central nervous system lesion: toxoplasmosis. A 26-year-old female with multiple prior opportunistic infections developed left-sided motor and sensory deficits. MR scan revealed multiple focal defects on T1-weighted imaging **(A),** which enhanced with gadolinium **(B).** The patient failed to respond to empiric antitoxoplasma therapy, but on stereotactic biopsy had histologically confirmed toxoplasma abscess to which she rapidly succumbed. (From Skarin AT: *Atlas of diagnostic oncology,* ed 3, St Louis, 2003, Mosby.)

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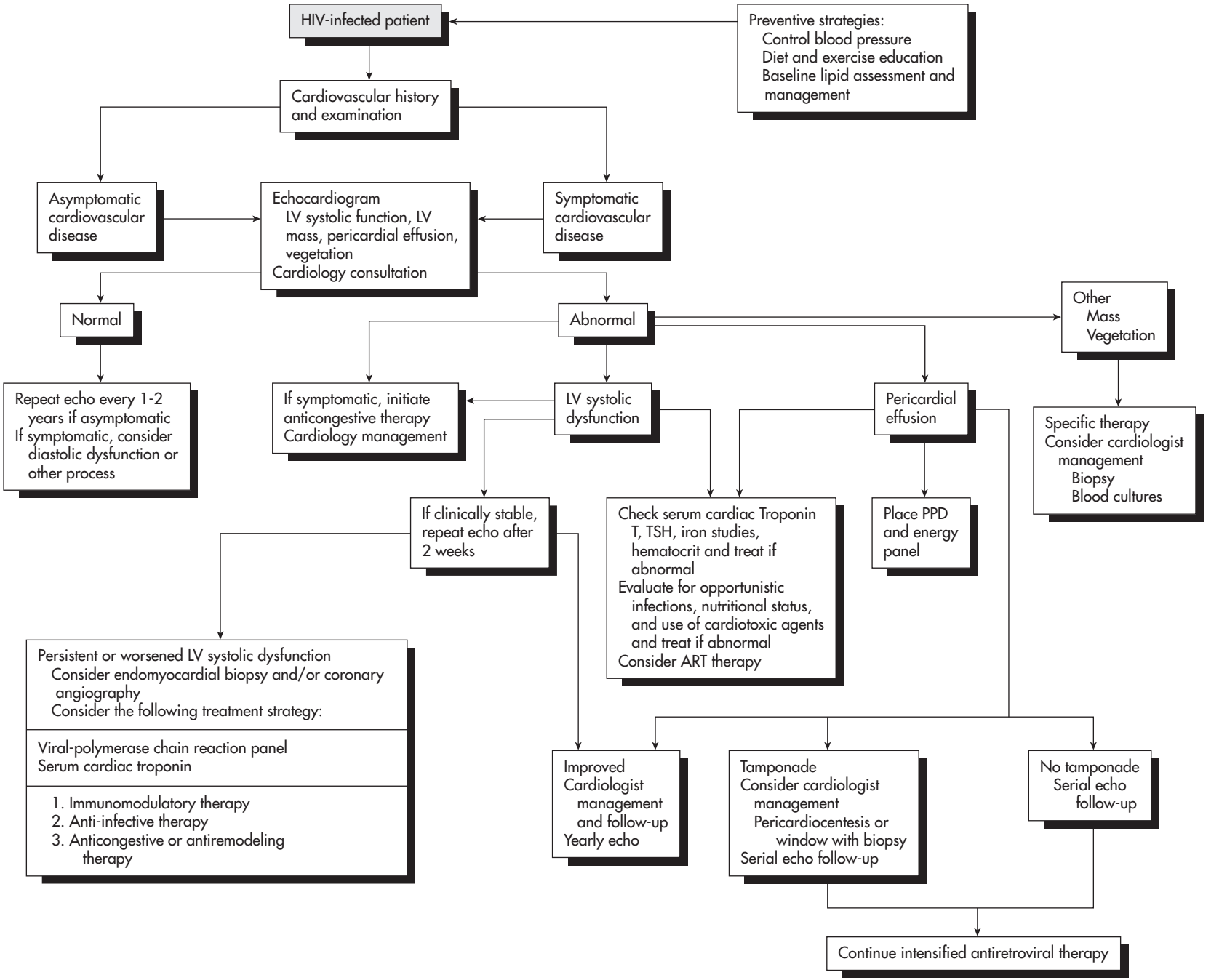

FIGURE EA1-32 Cardiac dysfunction in HIV-infected patients. *ART,* active antiretroviral therapy; *LV,* left ventricular; *PPD,* purified protein derivative; *TSH,* thyroid-stimulating hormone. (Modified from Dolin R et al [eds]: *AIDS therapy,* ed 2, New York, 2003, Churchill Livingstone.)

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Acromegaly

BASIC INFORMATION

DEFINITION

Acromegaly occurs due to hypersecretion of growth hormone (GH) or increased amounts of insulin-like growth factor I (IGF-I). It is a chronic debilitating disease with an insidious onset.

SYNONYMS

Marie's disease

ICD-9CM CODES
253.0 Acromegaly
ICD-10CM CODES
E22.0 Acromegaly and pituitary gigantism

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Three to four new cases per 1 million persons annually
PREVALENCE: 50 to 60 cases per 1 million persons, with some estimates as high as 90 cases per 1 million persons
PREDOMINANT SEX: No sexual predominance
MEAN AGE AT DIAGNOSIS: Males: 40 yr; females: 45 yr

RISK FACTORS

- Increased mortality rate, primarily from cardiovascular and respiratory causes
- Death in 50% of untreated patients by age 50 yr
- Increased prevalence of colon carcinoma and other malignancies

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Coarse features resulting from growth of soft tissue
- Coarse, oily skin
- Hands and feet that are spadelike, fleshy, and moist (Fig. EA1-33)
- Prognathism, which can give an underbite
- Carpal tunnel syndrome
- Excessive sweating
- Arthralgias and severe osteoarthritis
- History of increased hat, glove, and/or shoe size
- Hypertension
- Skin tags
- Muscle weakness and decreased exercise capacity
- Headache, often severe
- Diabetes mellitus
- Visual field defects

ETIOLOGY

Cause is usually a pituitary adenoma affecting the anterior lobe. In rare cases extrapituitary production of either GH or GH-releasing hormone (GHRH) can also lead to clinical manifestations.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Ectopic production of GHRH from a carcinoid or other neuroendocrine tumor

WORKUP

1. First screening test: measure serum IGF-I level.
   a. Direct measurement of the GH level is not as useful because it is secreted in a pulsatile fashion and a random level may be falsely normal.
   b. Upper limits of a normal IGF-I level, depending on the assay: >380 ng/ml or 2.5 U/ml.
2. Failure to suppress serum GH to less than 2 ng/ml after 100 g oral glucose is considered conclusive.
   a. Patients may show suppression of GH (paradoxic response).
   b. Patients will not suppress GH to 2 ng/ml or less (typical response in patients with acromegaly).
   c. GHRH level >300 ng/ml is indicative of an ectopic source of GHRH such as from carcinoid tumors of the pancreas or lung.

LABORATORY TESTS

- Elevated IGF-I level
- Elevated serum phosphate
- Elevated urine calcium

IMAGING STUDIES

- Imaging studies of choice: MRI of the pituitary and hypothalamus
- CT of the pituitary and hypothalamus sometimes used initially

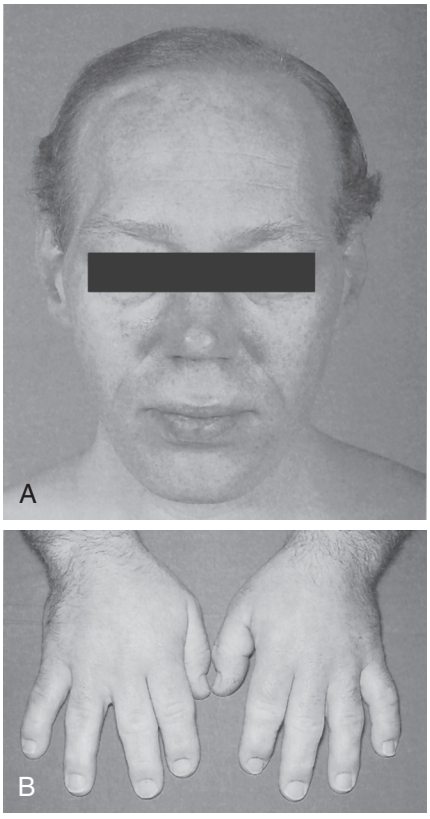

FIGURE EA1-33 Typical appearances of acromegaly. A, Face showing enlarged supraorbital ridges, nose, lips, and jaw. B, Spade-like hands. (From Souhami RL, Moxham J: *Textbook of medicine,* ed 4, London, 2002, Churchill Livingstone.)

TREATMENT

SURGERY

Treatment of choice: transsphenoidal microsurgical adenomectomy

- Surgical failure rate: approximately 13.3% for microadenomas (tumors <10 mm) and 11.1% for macroadenomas (tumors >10 mm confined to the sella)
- Preoperative IGF-I level: indicator of surgical outcome with higher levels associated with surgical failure

RADIOTHERAPY

- Radiotherapy is usually reserved for tumor recurrence or persistence after surgery in patients with resistance to or intolerance of medical treatment.
- Major complication: hypopituitarism, which may occur in up to 50% of patients; this complication is more likely in patients who had postoperative radiotherapy.

MEDICAL THERAPY

- Indicated when patients have not responded to surgical therapy, when surgery is contraindicated, and in patients waiting for the effects of radiotherapy to begin
- Somatostatin receptor ligands: octreotide, lanreotide:
  1. Important in the preoperative shrinkage of pituitary tumors and softening of adenomatous tissue.
  2. Pegvisomant is a GH receptor antagonist that has shown promising results in the treatment of acromegaly. It is generally used in patients with resistance to or intolerance of somatostatin analogs. It should be used in patients who do not have central compressive symptoms and those with resistant diabetes.
  3. Dopamine receptor agonists: Bromocriptine, cabergoline: can be used in addition to somatostatin receptor ligands.

CHRONIC Rx

Combination of bromocriptine and octreotide may be synergistic, allowing a lower combination dosage than either alone.

DISPOSITION

- Patients receiving radiotherapy need long-term follow-up to monitor the potential development of hypopituitarism.
- Continuation of medical therapy should be based on the normalization of IGF-I levels.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pituitary Adenoma (Related Key Topic)
Acromegaly (Patient Information)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Doga M et al.: Diagnostic and therapeutic consensus on acromegaly, *J Endocrinol Invest* 28(5 suppl):56, 2005.

Ezzat S: Pharmacological options in the treatment of acromegaly, *Curr Opin Investig Drugs* 6(10):1023, 2005.

Ketznelson L: Diagnosis and treatment of acromegaly, *Growth Horm IGF Res* 15(suppl A):S31, 2005.

Melmed S: Acromegaly, *N Engl J Med* 355:2558, 2006.

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Actinic Keratosis

BASIC INFORMATION

DEFINITION

Actinic keratoses (AKs) are common skin lesions usually presenting as multiple, erythematous or yellow-brown, dry, scaly lesions in the middle aged or elderly.

SYNONYMS

Solar keratosis
Senile keratosis
AK

ICD-9CM CODES
702.0 Actinic keratosis
ICD-10CM CODES
L57.0 Actinic keratosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: In regions of the northern hemisphere, 11%-25% of adults have a minimum of one AK. In regions closer to the equator, 40%-60% of adults have a minimum of one AK.
PEAK INCIDENCE: The risk of squamous cell carcinoma in patients with AK is 6%-10%. Incidence increases with age, and mortality from non-melanoma skin cancers increases significantly in the sixth decade. The rate of mortality is approximately 0.1% of the incidence rate (Table A1-13).
PREVALENCE

- In the United States, 58.08 million per year.
- Highest prevalence in those with fair complexions with high sun exposure.
- Approximately 60% of predisposed individuals older than 40 years will have one AK.
- Caucasians' risk increases with age: at age 20-29 prevalence is <10%; at age 80-89, prevalence is approximately 75%.

PREDOMINANT SEX AND AGE: Males > females, age 65-74. Occurs most in those with fair complexions who burn rather than tan following sun exposure.
GENETICS: There is increased frequency of non-melanoma skin cancers connected to squamous cell cancers with the genetic conditions xeroderma pigmentosum, oculocutaneous albinism, epidermodysplasia verruciformis, dystrophic epidermolysis bullosa, Ferguson-Smith syndrome, and Muir-Torre syndrome.
RISK FACTORS

- Immunosuppression, exposure to ultraviolet (UV) light, ionizing radiation, arsenic, human papillomavirus, cigarette smoke, chronic ulcers, thermal burns, chronic discoid lupus erythematosus, and nonhealing wounds.
- Lichen planus, lichen sclerosis, linear and classic porokeratosis, and disseminated superficial actinic porokeratosis.
- Age, gender, skin color, and mutations in p53 tumor suppressor gene.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Typical lesions occur on sun-damaged skin, usually on the face and neck and the dorsal aspects of hands (Fig. A1-34) and forearms.
- Advanced lesions are characterized by a hard, spiky scale (Fig. A1-35) and usually measure 1 cm in diameter or less. Early lesions manifest with redness and minimal scale. With progression, scales become thicker and yellow and may resemble a small squamous cell carcinoma. On examinations, lesions are rough and gritty (Fig. A1-36).
- The surrounding skin frequently shows additional features of sun damage, including atrophy (Fig. A1-37), pigment changes, and telangiectasia.
- Classifications
  1. Hypertrophic AK with a cutaneous horn: Biopsy is necessary to distinguish the cutaneous horn from squamous cell carcinoma, seborrheic keratosis, verruca, and trichilemmoma and basal cell carcinoma. Hypertrophic AK has appearance of thick, scaling skin elevations.
  2. Lichenoid AK: Most commonly found on the torso and upper extremities. Must be distinguished from BCC due to pink and pearly characteristics.
  3. Proliferative AK: Often reappear after treatment and are characterized by a diameter >1 cm. Often occurs in same differential as Bowen's disease or SCC.
  4. Spreading pigmented AK: Must be biopsied to distinguish from lentigo maligna–type melanoma in situ as well as solar lentigo.
  5. Actinic cheilitis: Characterized by red and sometimes abrasive lesions around the border of the lips and skin.

ETIOLOGY

- Sun exposure, ionizing radiation.
- Arsenic, polycyclic hydrocarbon exposure.

TABLE A1-13 Incidence Rates Per Year (Per 100,000) of BCC and SCC by Geographic Location

Geographic Location	BCC (Men/Women)	SCC (Men/Women)
Finland	49/45	9/5
Switzerland	52/38	16/8
The Netherlands	53/38	—
United Kingdom	112/54	32/6
New Hampshire	159/87	32/8
Rochester, Minnesota	175/124	63/23
United States	247/150	65/24
Hawaii	576/298	153/92
Nambour, Australia	2074/1579	1035/472

BCC, Basal cell carcinoma; *SCC,* squamous cell carcinoma.
From Bolognia JL et al (eds): *Dermatology,* ed 2, vol 2, St Louis, 2003, Mosby, p. 1678.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Heavily pigmented variants may be clinically mistaken for lentigo maligna.
- Basal cell or squamous cell carcinoma.
- Seborrheic keratosis.
- Eczema.
- Bowen disease (intraepithelial carcinoma).
- Wart.
- Lichenoid keratosis.
- Cutaneous lupus.

FIGURE A1-34 Several scaly, adherent, yellow-brown lesions on the sun-exposed dorsum of the hand. (From Ferri F et al: *Ferri's fast facts in dermatology,* Philadelphia, 2010, Saunders.)

FIGURE A1-35 Scaly, raised lesion on sun-exposed back. Pain was elicited when scraping this lesion. (From Ferri F et al: *Ferri's fast facts in dermatology,* Philadelphia, 2010, Saunders.)

FIGURE A1-36 Raised, rough, gritty actinic keratosis on the anterior thigh of an outdoorsman. (From Ferri F et al: *Ferri's fast facts in dermatology,* Philadelphia, 2010, Saunders.)

FIGURE A1-37 Actinic keratosis (shown here on a patient's forehead) is often best appreciated by its rough, tactile quality, similar to that of sandpaper. (From Ferri F et al: *Ferri's fast facts in dermatology,* Philadelphia, 2010, Saunders.)

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WORKUP

- History, physical, and lesion biopsy. Include risk assessment and family or personal history of skin cancers or previous skin lesions.

LABORATORY TESTS

- Skin biopsy in recurrent lesions or when diagnosis is unclear to rule out squamous cell or basal cell carcinoma.
- Microscopy reveals atypical keratinocytes in the lower epidermis basal layers. They are enlarged and often lack normal polarity. The thickness of the epidermis can be compromised with a distribution of atrophic to hyperplastic. Abnormal keratinocytes can cause parakeratosis of the overlying stratum corneum. Visible signs of an alternating orthohyperkeratosis can overlie the spared epithelium, causing the signature "flag sign." Additionally, there is a distinct margin between normal epidermis and the region of AK at lateral edges. Histologic subtypes are hypertrophic, acantholytic, lichenoid, and bowenoid, which are characterized by a thick stratum corneum, lack of intracellular cohesion, presence of lymphocytic infiltrate in papillary dermis, and either lack of association of adnexal epithelium or full epithelial thickness with pleomorphic kertinocytes, respectively.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Cryosurgery with liquid nitrogen.
- Carbon dioxide laser.
- Dermabrasion.
- Chemical peel.
- Curettage.
- Excision.
- Photodynamic therapy with 5-aminolevulinic acid and blue light (16 minutes) or methyl aminolevulinate and red light (7-10 minutes).

ACUTE GENERAL Rx

- Topical 5-fluorouracil bid for 4 weeks.
- Topical diclofenac sodium 3% gel bid for 60-90 days.
- Topical imiquimod 5% cream bid for 3-4 months.
- Oral retinoids.
- Topical Ingenol mebutate 0.05% gel applied for 2 days with exception of face—or 0.015% for 3 days. Combination medication therapy or nonpharmacologic therapy with pharmacologic therapy is common (especially in refractory AK).

REFERRAL

- To a dermatologist for biopsy of suspicious lesions, then follow up minimum annually or semiannually.

PEARLS & CONSIDERATIONS

COMMENTS

- AKs are of particular importance because they are a sensitive indicator of exposure to UV light and strongly predict the likelihood of developing cutaneous squamous cell carcinoma.
- The cumulative probability of development of invasive squamous cell carcinoma in patients with 10 or more AKs has been estimated at 14% in a 5-year period.
- It is estimated that up to 10% of AKs tend to progress to invasive carcinoma.

PREVENTION

- Avoidance of sun exposure or sunless tanning booths, use of sunscreens.
- Routine self-skin examinations.
- Pharmaceutical prevention:
  1. Mild to moderate reduction of AK formation has been documented with the use of topical tretinoin, isotretinoin, and arotinoid methysulfone.
  2. Nicotinamide as preventative rx has been documented to have a possible 30% relative reduction in AK.
  3. Decreased AK development has been documented with the use of high-SPF sunscreens.
  4. Decreased AK development has been seen in patients with xeroderma pigmentosum who used DNA repair enzymes.
  5. Decreased AK formation has been documented in high-risk patients (specifically those with xeroderma pigmentosum, nevoid basal cell carcinoma syndrome, and organ transplantation recipients) with the use of oral retinoids.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **FRED F. FERRI, M.D.,** and **HEATHER FERRI, D.O.**

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SUGGESTED READINGS

Horn TD et al.: *Dermatology*. vol. 2 Philadelphia: Elsevier.

McGovern TW, Leffell DJ: Actinic keratoses and non-melanoma skin cancer, *J Am Acad Dermatol* 35:1012–1013, 1996.

McIntyre WJ et al.: Treatment options for actinic keratoses, *Am Fam Physician* 76(5):667–671, 2007.

The Lewen Group: The Society for Investigative Dermatology and the American Academy of Dermatology Association (website), I*nc: The Burden of Skin Diseases,* 2005 www.lewin.com/content/publications/april2005skindisease.pdf (2005).

Uhlenhake E: Optimal treatment of actinic keratosis, *Clinical Interventions in Aging* 8:29–35, January 2013, Dove Medical Press Ltd.

BASIC INFORMATION

DEFINITION

Actinomycosis is an indolent, slowly progressive infection caused by anaerobic or microaerophilic bacteria, mostly from the genus *Actinomyces,* that normally colonize the mouth, vagina, and colon. Actinomycosis is characterized by the formation of painful abscesses, soft tissue infiltration, and draining sinuses.

SYNONYMS

Actinomyces infection
Lumpy jaw

ICD-9CM CODES
039.9 Actinomycosis
ICD-10CM CODES
A42.9 Actinomycosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

GEOGRAPHIC DISTRIBUTION:

- Actinomycosis is worldwide in distribution.
- Commonly found as normal flora of the oral cavity (within gingival crevices, tonsillar crypts, periodontal pockets, dental plaques, and carious teeth), pharynx, tracheobronchial tree, gastrointestinal tract, and female urogenital tract.
  Incidence and prevalence:

INCIDENCE:

- 1:300,000 in 1970s but now less with better oral hygiene and antibiotic use.
- Males infected more often than females 3:1.
- Can occur at any age but commonly seen in midlife.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Actinomycosis can affect any organ. Although not typically considered as opportunistic pathogens, *Actinomyces* species capitalize on tissue injury or mucosal breach to invade adjacent structures in the head and neck regions. As a result, dental infections and oromaxillofacial trauma are common antecedent events. Characteristic manifestations include:

- Cervicofacial disease (most common site):
  1. Occurs in the setting of poor dental hygiene, recent dental surgery, or minor oral trauma
  2. Painful soft tissue swelling (Fig. A1-38) commonly seen at the angle of the mandible
  3. Fever, chills, and weight loss
  4. Trismus
  5. Soft tissue facial infection with sinus tract or fistula formation
- Thoracic disease:
  1. Can involve the lungs, pleura, mediastinum, or chest wall.
  2. Presumed secondary to aspiration of *Actinomyces* organisms in patients with poor oral hygiene.
  3. Fever, cough, weight loss, and pleuritic chest pains are common symptoms.
  4. Signs of pneumonia or pleural effusion may be present.
  5. With extension beyond the lungs to mediastinal structures and the chest wall, signs and symptoms of pericarditis, empyema, chest wall sinus drainage, and tracheoesophageal fistula can all occur (Fig. A1-39).
- Abdominal disease:
  1. Occurs most commonly after appendectomy, perforated bowel, diverticulitis, or surgery to the gastrointestinal tract.
  2. Lesions develop most commonly in the ileocecal valve, causing abdominal pain, fever, weight loss, and a palpable mass.
  3. Extension may occur to the liver, causing jaundice and abscess formation.
  4. Sinus tracts to the abdominal wall can occur.

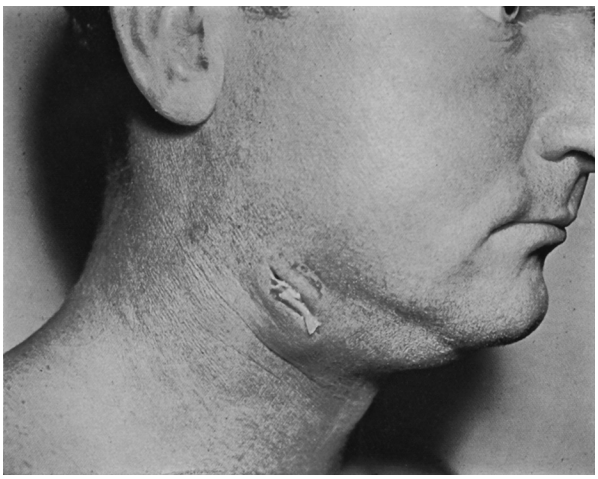

FIGURE A1-38 Actinomycosis of the jaw, observed at Letterman General Hospital, San Francisco, Calif., in a sergeant who had punctured the floor of his mouth while picking his teeth. (Office of Medical History, Office of the Surgeon General, U.S. Army; from Goldman L, Schaefer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

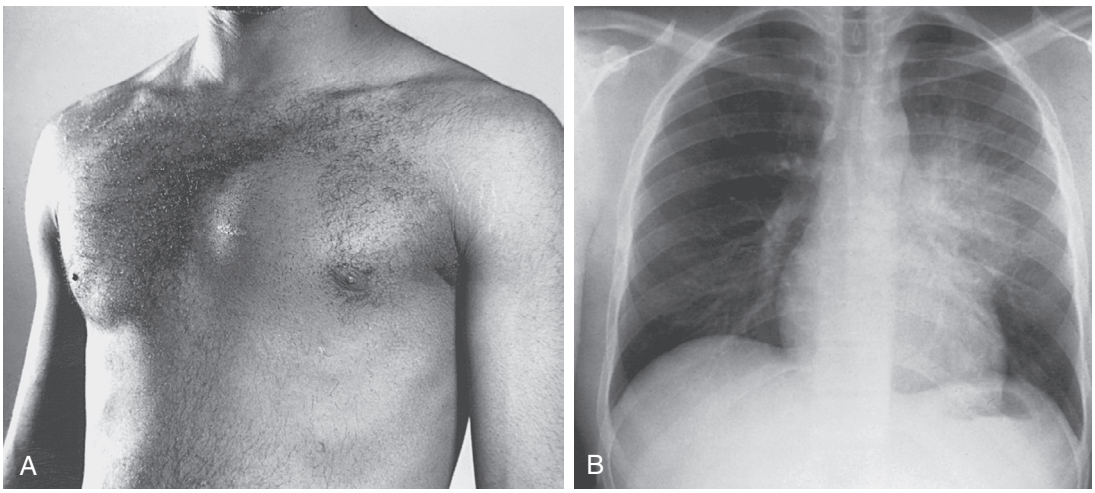

FIGURE A1-39 Thoracic actinomycosis. A, Initial presentation with a bulging mass lesion in the chest wall with a central sinus tract. **B,** The chest radiograph with the associated pulmonary infiltrate. (From Gorbach SL: *Infectious diseases,* ed 2, Philadelphia, 1998, Saunders.)

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- Pelvic disease:
  1. Commonly occurs by extension from abdominal disease of the ileocecal valve to the right adnexa (80% of cases).
  2. Endometritis.

ETIOLOGY

- Actinomycosis is most commonly caused by *Actinomyces israelii.* Other causes are *A. naeslundii, A. odontolyticus, A. viscosus,* and *A. meyeri.*
- *Actinomyces* are gram-positive, non–spore-forming, filamentous, anaerobic or microaerophilic rods.
- Actinomycosis infections are polymicrobial, usually associated with *Streptococcus, Bacteroides, Eikenella corrodens, Enterococcus,* and *Fusobacterium* spp.
- Infects individuals only after entry into disrupted mucosa or tissue injury.
- Predisposing conditions include diabetes mellitus, malnutrition, and immunosuppression.

Dx DIAGNOSIS

Isolating the bacteria in the proper clinical setting makes the diagnosis of actinomycosis.

DIFFERENTIAL DIAGNOSIS

- Cervicofacial disease: odontogenic abscesses, brachial cleft cyst
- Pulmonary disease: nocardiosis, botryomycosis, chromomycosis, fungal disease of the lung, tuberculosis
- Intestinal disease: intestinal tuberculosis, ameboma, Crohn's disease, colon cancer
- Pelvic disease: chronic pelvic inflammatory disease, Crohn's disease
- CNS disease: other forms of brain abscess, brain tumors, toxoplasmosis, intracranial hematoma

WORKUP

The workup includes obtaining specimens either by aspirating abscesses, excising sinus tracts, or tissue biopsies. All specimens should be set up to culture anaerobic bacteria and held at least 5 to 7 days.

LABORATORY TESTS

- Isolating "sulfur granules" from tissue specimens or draining sinuses confirms the diagnosis of actinomycosis. *Actinomyces* are noted for forming characteristic sulfur granules in infected tissue but not in vitro. The term *sulfur granule* is a misnomer, reflecting only the yellow color of the granule in pus, because the granules are not composed of any sulfur at all.
  1. Sulfur granules are nests of *Actinomyces* species. Sulfur granules may be macroscopic or microscopic.
  2. Sulfur granules are crushed and stained for identification of *Actinomyces* organisms and may take up to 3 wk to grow in culture media.

IMAGING STUDIES

Imaging studies are useful adjunctive tests in localizing the site and spread of infection.

1. Chest x-ray examination
2. CT scan of the head, chest, abdomen, and pelvic areas is useful

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Incision and drainage of abscesses
- Excision of sinus tract

ACUTE GENERAL Rx

- Ampicillin 50 mg/kg/day in 3-4 divided doses x 4-6 wk, then Pen VK 2-4 g/day PO x 4-6 wk. In place of ampicillin, can also use penicillin 3-4 million units IV q4h for 4-6 wk.
- In penicillin-allergic patients, erythromycin (500-1000 mg IV q6h), tetracycline or doxycycline (100 mg IV q12h), and clindamycin (900 mg IV q8h) are reasonable alternatives. Other alternatives include cetriaxone, imipenem, and piperacillin/tazobactam.
- Avoid use of metronidazole, aminoglycosides, oxacillin, and cephalexin.

CHRONIC Rx

- Following 4 to 6 wk IV amoxicillin or penicillin, oral penicillin V 500 mg PO qid for 4 to 6 wk. Longer treatment may be necessary in selected cases.
- Other available oral agents are erythromycin, doxycycline, and clindamycin.
- Treatment of associated microorganisms is not needed.

DISPOSITION

- Clinical actinomycosis, if not treated, spreads to contiguous tissues and structures ignoring tissue planes. Hematogenous spread, although possible, is rare.
- Actinomycosis is very sensitive to antibiotics but requires chronic long-term treatment to prevent relapse.

REFERRAL

If the diagnosis of actinomycosis is suspected, consultation with an infectious disease specialist is suggested. General surgical consultation for excision of sinus tracts and abscess incision and drainage is recommended.

PEARLS & CONSIDERATIONS

COMMENTS

- There is no person-to-person transmission of *Actinomyces.*
- Isolation of the organism in an asymptomatic individual does not mean the person has actinomycosis. Active symptoms must be present to make the diagnosis.
- Pelvic actinomycosis has been associated with use of an intrauterine device (IUD).
- Actinomycosis can also involve the CNS, causing multiple brain abscesses.

SUGGESTED READINGS

Available at www.expertconsult.com

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http://internalmedicinebook.com/

SUGGESTED READINGS

Choi J: Optimal duration of IV and oral antibiotics in the treatment of thoracic actinomycosis, *Chest* 128(4):2211, 2005.

Russo TA: Agents of actinomycosis. In: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*. ed 7, New York, Churchill Livingstone.

Sharkawy AA: Cervicofacial actinomycosis and mandibular osteomyelitis, *Infect Dis Clin North Am* 21:543–556, 2007.

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Acute Bronchitis PTG

BASIC INFORMATION

DEFINITION

Acute bronchitis is a self-limited inflammation of trachea and bronchi.

SYNONYMS

Chest cold

ICD-9CM CODES
466.0 Acute bronchitis
ICD-10CM CODES
J20.9 Acute bronchitis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Highest incidence in smokers, older adults, and young children and during winter months.
- In the U.S. there are nearly 30 million ambulatory visits annually for cough, leading to more than 12 million diagnoses of "bronchitis."
- Acute lower respiratory tract infection is the most common condition treated in primary care.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Cough, usually worse in the morning, often productive; mainly caused by transient bronchial hyperresponsiveness
- Low-grade fever
- Substernal discomfort worsened by coughing
- Postnasal drip, pharyngeal injection
- Rhonchi that may clear after cough, occasional wheezing

ETIOLOGY

- Viral infections are the leading cause of bronchitis (rhinovirus, influenza virus, adenovirus, respiratory syncytial virus)
- Atypical organisms *(Mycoplasma, Chlamydia pneumoniae)*
- Bacterial infections *(Bordetella pertussis, Haemophilus influenzae, Moraxella, Streptococcus pneumoniae)*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Pneumonia
- Asthma
- Sinusitis
- Bronchiolitis
- Aspiration
- Cystic fibrosis
- Pharyngitis
- Cough secondary to medications
- Neoplasm (elderly patients)
- Influenza
- Allergic aspergillosis
- Gastroesophageal reflux disease
- Congestive heart failure (in elderly patients)
- Bronchogenic neoplasm

WORKUP

Seldom necessary (e.g., to rule out pneumonia, neoplasm)

LABORATORY TESTS

Laboratory tests are generally not necessary.

IMAGING STUDIES

Chest x-ray examination is usually reserved for patients with suspected pneumonia, influenza, or underlying chronic obstructive pulmonary disease (COPD) and no improvement with therapy.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of tobacco and other pulmonary irritants
- Increased fluid intake
- Use of vaporizer to increase room humidity

ACUTE GENERAL Rx

- Inhaled bronchodilators (e.g., albuterol, metaproterenol) PRN for 1 to 2 wk in patients with wheezing or troublesome cough. Inhaled albuterol has been proven effective in reducing the duration of cough in adults with uncomplicated acute bronchitis.
- Cough suppression with dextromethorphan and guaifenesin is commonly recommended; addition of codeine for cough suppression if cough is severe and is significantly interrupting patient's sleep pattern.
- Use of antibiotics (TMP-SMX, amoxicillin, doxycycline, cefuroxime) for acute bronchitis is generally not indicated; should be considered only in patients with concomitant COPD and purulent sputum or in patients with suspected pertussis. In the few cases of acute bronchitis caused by *B. pertussis* or atypical bacteria such as *C. pneumoniae* or *Mycoplasma pneumoniae,* early use of macrolide antibiotics is reasonable.
- Antibiotics are overused in patients with acute bronchitis (70% to 90% of office visits for acute bronchitis result in treatment with antibiotics); this practice pattern is contributing to increases in resistant organisms.
- Trials have shown that there are no significant differences in patients receiving antibiotics compared with those receiving placebo in overall clinical improvements or limitations in work or other activities. There was a significant increase in adverse effects in the antibiotic group, particularly gastrointestinal symptoms.[1]

CHRONIC Rx

Avoidance of tobacco and other pulmonary irritants

DISPOSITION

- Complete recovery within 7 to 10 days in most patients.
- Patients should be informed to expect to have a cough for 10 to 14 days after the visit.

REFERRAL

For pulmonary function testing only in patients with recurrent bronchitis and suspected underlying pulmonary disease.

PEARLS & CONSIDERATIONS

COMMENTS

- Intervention studies reveal that patient and physician education are effective in reducing the use of antibiotic therapy. No offer or delayed offer of antibiotics for acute uncomplicated lower respiratory tract infection is acceptable, is associated with little difference in symptom resolution, and is likely to reduce antibiotic use and beliefs in the effectiveness of antibiotics.
- It is helpful to refer to acute bronchitis as a "chest cold." Patients should be informed that antibiotics are probably not going to be beneficial and may result in significant side effects.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Acute Bronchitis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

[1]Smith SM, Smucny J, Fahey T: Antibiotics for acute bronchitis, *JAMA* 312:2678, 2014.

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SUGGESTED READINGS

Aspinall SL et al.: Antibiotic prescribing for presumed nonbacterial acute respiratory tract infections, *Am J Emerg Med* 27:544–551, 2009.

Wenzel R, Fowler A: Acute bronchitis, *N Engl J Med* 355:2125, 2006.

Zoorob R et al.: Antibiotic use in upper respiratory tract infections, *Am Fam Physician* 86:817–822, 2012.

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BASIC INFORMATION

DEFINITION

Ogilvie's syndrome is characterized by acute massive dilation of the cecum and right colon, with occasional extension to the rectum, in the absence of any mechanical obstruction. Oftentimes, acute colonic pseudo-obstruction occurs after surgery, and it can also be seen in patients with significant underlying medical illnesses. Cecal diameter on abdominal radiographs greater than nine centimeters is considered to be the threshold where spontaneous perforation becomes more likely. Medications such as opiates and anti-cholinergics also contribute to the development of this condition.

SYNONYMS

Ogilvie's syndrome
ACPO
Acute megacolon

ICD-9CM CODES
560.89 Other specified intestinal obstruction
ICD-10CM CODES
K56.6 Other and unspecified intestinal obstruction

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Unknown
PEAK INCIDENCE: Unknown
PREVALENCE: Unknown
PREDOMINANT SEX AND AGE: Although recent data is lacking, data from a retrospective study in 1986 suggested a male predominance with average age of onset in the 6th decade. Affected females tended to be slightly younger because cases were described in association with obstetrical complications.
GENETICS: None
RISK FACTORS: Elderly patients seem to be at greatest risk. Other risk factors include significant underlying medical illness, electrolyte abnormalities, certain medications (opiates, anticholinergics, phenothiazines, benzodiazepines, calcium channel blockers, chemotherapeutic agents, and antiparkinsonian agents), and postoperative patients (Box A1-3).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute abdominal distention and crampy abdominal pain are the most common symptoms associated with Ogilvie's syndrome. The distention can be so severe that it may lead to labored breathing. Nausea, vomiting, obstipation, constipation, and, paradoxically, diarrhea, can also be seen but are not consistently present. It has been estimated that 40-50% of patients continue to pass flatus.
- Physical exam is significant for massive abdominal distention that is tympanic to percussion and varying degrees of abdominal pain or discomfort are also present. Hypoactive or hyperactive bowel sounds are often described. Peritoneal signs are often absent early on but their presence is concerning for imminent perforation.

ETIOLOGY

- Colonic motor and secretory functions are mediated by the autonomic nervous system with the ascending colon receiving parasympathetic innervation from the medulla oblongata via the vagus nerve, which increases gut motility, and sympathetic innervation from the spinal cord, which decreases motility. It is thought that parasympathetic dysfunction is the main driving force that leads to Ogilvie's syndrome but the exact mechanism is unknown.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Mechanical obstruction
- Volvulus
- Intussusception
- Ileus
- Toxic megacolon

WORK-UP

- History should be focused on the perceived progression of distention and timing of most recent flatus or bowel movement as well as determining any predisposing factors such as recent surgery, severe illness, and recent medication changes. Physical examination should focus on assessing the degree of abdominal distention and percussion to evaluate for tympanic sounds, which is a hallmark of Ogilvie's syndrome. Serial abdominal exams should be performed to ensure no peritoneal signs such a rebound, guarding, or rigidity that would suggest impending or frank perforation.
- Laboratory evaluation should center on metabolic abnormalities and leukocytosis that can both be used as a barometer of the degree of the patient's underlying illness as well as a marker for impending perforation.
- Imaging of the abdomen with plain radiograph is important for tracking degree of distention.

BOX A1-3 Clinical Factors Predisposing to Ogilvie's Syndrome or Acute Colonic Pseudo-Obstruction

Cardiovascular
- Heart failure, stroke
- Gut ischemia

Critical illness
- Severe sepsis
- Acute pancreatitis
- Shock or hypoxemia

Postoperative state or trauma
- Intestinal manipulation
- Peritonitis
- Immobility and dehydration
- Vertebral, pelvic or hip fracture/surgery
- Retroperitoneal hematoma

Metabolic factors
- Hypokalemia and hyperglycemia
- Hypothyroidism, diabetes mellitus
- Liver or renal failure
- Amyloidosis

Drugs
- α-Adrenergic agonists, dopamine
- Clonidine and dexmedetomidine
- Opioids
- Anticholinergics, calcium channel antagonists
- Antipsychotics
- Antidepressants
- High-dose phosphodiesterase inhibitors

Gastrointestinal infections
- Cytomegalovirus, herpes zoster
- Tuberculosis

Neurologic
- Transection of the spinal cord
- Low spinal cord disease
- Parkinson's disease

Obstetric
- Caesarean section
- Normal delivery

(From Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP: *Textbook of Critical Care*, ed 6, Philadelphia, 2011, Saunders.)

LABORATORY TESTS

- Metabolic abnormalities such as hypocalcemia, hypomagnesemia, and hypokalemia are commonly present and should be corrected accordingly.
- Leukocytosis as a marker of underlying disease and impending perforation.

IMAGING STUDIES

- Plain and upright abdominal radiographs (Figure A1-40) are important to establish degree of colonic distention, which often involves the cecum but can also extend to the splenic flexure or rectum. Haustral markings are usually normal.
- CT scan or enema enhanced radiograph is imperative to confirm the diagnosis and rule out underlying mechanical obstruction.

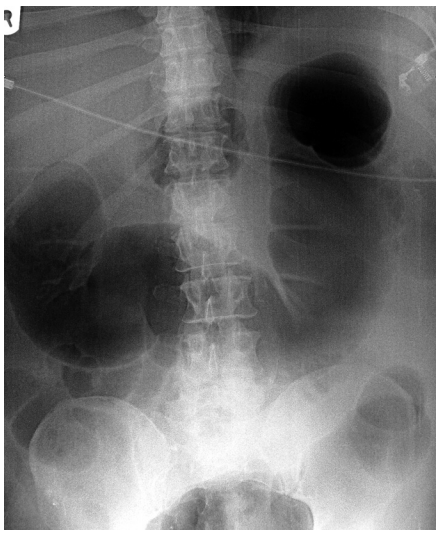

FIGURE A1-40 Plain abdominal radiograph of patient with Ogilvie's syndrome 11 days after surgery for ruptured aneurysm of abdominal aorta. Dilation (probably due to ischemia) is present in both right and left colon. Syndrome resolved with vasodilators and intravenous neostigmine. (From Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP: *Textbook of Critical Care*, ed 6, Philadelphia, 2011, Saunders.)

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Acute Colonic Pseudo-Obstruction (Ogilvie's Syndrome)

Rx TREATMENT

The goals of treatment are to decompress the colon in order to relieve the patient's abdominal discomfort and also mitigate the risk of developing intestinal ischemia or frank perforation.

NONPHARMACOLOGIC THERAPY

- Supportive care with plain radiographs every 12-24 hr, serial abdominal exams, elimination of potential precipitants (medications, treatment of underlying medical illness), correction of electrolyte abnormalities, restricting PO intake, gastric decompression with NG tube to intermittent suction, rectal decompression with rectal tube attached to gravity, IV fluids, encouraging ambulation if possible, and alternating the patient in bed between right and left lateral decubitus and prone positioning with hips elevated are all appropriate nonpharmacologic approaches that can be made initially in the absence of colonic distention >12 cm or significant abdominal pain.
- Colonoscopic decompression with or without placement of a decompression tube is often the next step in management although use of this technique remains controversial as some studies indicate that the majority of patients spontaneously resolve within 48 hr. The risk of complication with colonoscopy in this setting is 3%, with a quoted death rate of 1%. Other studies suggest a success rate of 69%-90% with colonoscopic decompression.
- Colonoscopic decompression is indicated when supportive measures fail, there is clinical deterioration, or colonic diameter is between 11-13 cm. Placement of a decompression tube at the time of colonoscopy is thought to reduce the need for repeat colonoscopic decompression, which is required in about 40% of cases, but no trials have been done to compare rates of repeat decompression with and without decompression tube placement.
- Alternative minimally invasive options which are usually reserved for failed colonoscopic decompression include percutaneous tube cecostomy performed under radiologic guidance and percutaneous endoscopic colostomy, which are both techniques that grant percutaneous access to the colon for both decompression and irrigation to promote transit.
- Surgical management is reserved for those who have failed minimally invasive approaches or for patients with peritonitis or perforation. Surgical cecostomy tube or right hemicolectomy can be performed in the absence of perforation whereas ileostomy, colectomy, and Hartmann procedure can be performed in patients who have perforated or who have significant ischemia.

BOX A1-4 Strategies to Prevent Ogilvie's Syndrome in the Critically Ill

- Early resuscitation of the circulation
- Minimizing prolonged infusion of high doses of α-adrenergic drugs
- Minimizing the use of dopamine
- Minimizing the prolonged use of opioids
- Use of thoracic epidural anesthesia
- Minimally invasive or laparoscopic surgery
- Selective decontamination of the digestive tract
- Avoiding antibiotics that disrupt growth of anaerobic fecal bacteria
- Early oral or enteral feeding
- Avoidance of proton pump inhibitors
- Early mobilization and ambulation
- Promoting timely defecation with
- Oral polyethylene glycol from day 3
- Intravenous neostigmine from day 5

(From Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP: *Textbook of Critical Care*, ed 6, Philadelphia, 2011, Saunders.)

ACUTE GENERAL Rx

- Neostigmine is an IV anticholinesterase inhibitor that induces rapid colonic decompression in 80%-100% of appropriate candidates with a median response rate of 4 minutes at a starting dose of 2 mg, but requires close cardiovascular monitoring at the time of its administration and has several contraindications. Dose adjustments are required in chronic kidney disease and caution should be used in patients who have bradyarrhythmias, recent myocardial infarction, beta-blocker use, and asthma. Atropine should be made available at bedside and administration of glycopyrrolate, an anticholinergic agent, should be considered to decrease the risk of bradycardia and bronchoconstriction.
- Methylnaltrexone, a peripherally acting opiate receptor antagonist, can also be considered for use in cases precipitated by opiate use but little data supports its usage at this time.

CHRONIC Rx

- None

COMPLEMENTARY AND ALTERNATIVE MEDICINE

- None

DISPOSITION

- Close inpatient monitoring is indicated until there is return of spontaneous bowel function and resolution of abdominal distention.

REFERRAL

- Ogilvie's syndrome is best managed in a team approach involving both surgeons and gastroenterologists. Administration of neostigmine in proper candidates or decompressive colonoscopy should be pursued in patients with absence of peritoneal signs. If there is evidence of perforation, surgical management is indicated.

PEARLS & CONSIDERATIONS

COMMENTS

- Maximal supportive care should be initiated for up to 48 hr barring any significant abdominal pain or massive distention greater than 12 cm on imaging.
- Administration of neostigmine is suggested in appropriate candidates.
- Colonic decompression should be attempted with or without decompression tube placement in patients who fail neostigmine or those who have contraindications to its use.
- Minimally invasive fluoroscopic, endoscopic, or surgical approaches are rarely needed. Surgery is reserved for patients who show signs of perforation.
- Oral laxatives should be discontinued with diagnosis but should be restarted once decompression is achieved.

PREVENTION

Box A1-4 describes some prevention strategies for Ogilvie's Syndrome in the critically ill.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **JASON FERREIRA, M.D.,** and **AMANDA PRESSMAN, M.D.**

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SUGGESTED READINGS

Harrison ME, Anderson MA, Appalaneni V, et al.: The role of endoscopy in the management of patients with known and suspected colonic obstruction and pseudo-obstruction, *Gastrointest Endosc* 71:669–679, 2010.

De Giorgio R, Knowles CH: Acute colonic pseudo-obstruction, *Br J Surg* 96:229–239, 2009.

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BASIC INFORMATION

DEFINITION

Acute coronary syndrome (ACS) represents a spectrum of clinical disorders that include unstable angina (UA), non–ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). Although the severity of disease will vary between the three subsets of ACS, they share a common clinical presentation and pathophysiology. This syndrome is typically caused by atherosclerotic coronary artery disease (CAD). In this spectrum, UA and NSTEMI are represented electrocardiographically by the absence of ST-segment elevation in the appropriate clinical setting (i.e., chest discomfort). NSTEMI is represented by the addition of positive cardiac biomarkers. STEMI is characterized by ST-segment elevation or presumed new left bundle branch block on electrocardiogram (ECG). ACS should be thought of as a continuous spectrum as UA will often progress to a myocardial infarction if left untreated (Table A1-14).

SYNONYMS

Unstable angina
NSTEMI
STEMI
Acute myocardial infarction

ICD-9CM CODES

410.0 Acute Myocardial Infarction
411.1 Intermediate Coronary Syndrome

ICD-10CM CODES

I20.0	Unstable angina
I21.0-I21.3	ST elevation (STEMI)
I21.4	non-ST elevation (NSTEMI) myocardial infarction
I24.9	Acute ischemic heart disease, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: In the United States there are 1.56 million hospitalizations for ACS yearly; 0.89 million are listed as myocardial infarction, and the remainder are UA. Approximately two thirds of myocardial infarctions are listed as NSTEMI, with the remainder being listed as STEMI. The underlying etiology, atherosclerotic CAD, is the number one cause of mortality.

PREDOMINANT SEX AND AGE: In evaluating chest pain, male gender and older age are important clinical factors that can identify ACS as a potential cause. The 2007 overall death rate from cardiovascular disease was 126 per 100,000. The rates were 165.6 per 100,000 for white males, 191.6 per 100,000 for African-American males, 94.2 per 100,000 for white females, and 121.5 per 100,000 for African-American females.

RISK FACTORS: Hypertension, diabetes mellitus, dyslipidemia, tobacco use, family history of premature CAD (CAD in a male first-degree relative younger than 55 years or a female younger than 65 years). Presence of these risk factors causes damage to the vascular endothelium and progression of atherosclerotic coronary artery plaques.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms often, but not always, include chest discomfort described as a pressure that may radiate to the shoulders, neck, jaw, or back. Typical angina is substernal in location, brought on by emotional or physical stress, and relieved with rest and/or nitroglycerin.
- Women, diabetics, and the elderly often have an atypical presentation for ACS.
- Angina is considered unstable if it is new onset (<2 months), increasing in frequency (crescendo pattern), or occurring at rest (typically lasting >20 minutes).
- "Anginal equivalents" may include dyspnea, nausea, vomiting, and fatigue.
- ECG for UA and NSTEMI may reveal ST-segment depression and/or T-wave inversion. ECG for definition of STEMI will reveal at least 1-mm ST-segment elevation in two contiguous leads or new left bundle branch block in the appropriate clinical setting.
- Physical exam findings alone are insufficient for the diagnosis of ACS. It is, however, important to assess the patient's hemodynamic stability and volume status. The patient may be diaphoretic and tachycardic. Signs of heart failure may be present, which include elevated jugular venous pressure (JVP), presence of an S3 gallop, and peripheral edema. The degree of heart failure with MI can be represented by the Killip classification: Killip Class 1 is no heart failure; Class 2 includes individuals with rales, elevated JVP, and S3 on exam; Class 3 includes individuals with frank pulmonary edema; Class 3 describes individuals in cardiogenic shock. The greater the Killip class, the worse the prognosis is. Another model that is now infrequently used is an invasive measurement of pulmonary capillary wedge pressure and stratification based on the Forrester classification system.

ETIOLOGY

Atherosclerotic CAD is the underlying etiology. The hallmark of ACS is the vulnerable atherosclerotic plaque, which typically has a thin fibrous cap and a large lipid core. This vulnerable plaque ultimately ruptures, which leads to platelet activation and aggregation, leading to thrombus formation. STEMI typically results from complete thrombotic occlusion of a coronary artery, whereas UA and NSTEMI often have partial occlusion. Angiographically, it is often the intermediate coronary artery lesions (30% to 50% diameter vessel stenosis) that lead to subtotal or total vessel occlusion in two thirds of STEMI cases.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Chest pain mimicking ACS may be the result of various underlying disorders, some of which are also accompanied by ECG changes and/or cardiac biomarker release. Examples include acute pulmonary embolism, acute aortic dissection, pericarditis, myocarditis, costochondritis, pneumonia, tension pneumothorax, perforating ulcer, or Boerhaave syndrome.

WORKUP

Focused history and physical exam, 12-lead ECG, cardiac biomarkers, and chest radiograph (CXR). Initial biomarkers may not be positive. Often serial biomarkers are drawn every 6 to 8 hours for a total of three sets for the purposes of ruling out myocardial infarction (MI), or until peak to determine the severity of an established MI. Echocardiogram may reveal new regional wall motion abnormalities. Figure A1-41 summarizes the evaluation of patients for acute coronary syndrome.

LABORATORY TESTS

- Cardiac biomarkers, which include creatine kinase (CK), its MB isoenzyme, myoglobin, and troponin I or T, will be positive in the setting of NSTEMI or STEMI. See Fig. A1-42*A* for timing of release of each biomarker. Troponin I is the most sensitive biomarker for cardiac myocyte damage and also predicts 42-day mortality in ACS and is considered to the gold standard biomarker for diagnosis of myocardial infarction. (Fig. A1-42*B*)
- Testing for B-type natriuretic peptide (BNP) levels may also be helpful in patients with heart failure.
- A complete fasting lipid panel should be obtained during the hospital admission.

TABLE A1-14 Acute Coronary Syndromes

SPECTRUM OF ACUTE CORONARY SYNDROME			
	Unstable Angina	**NSTEMI**	**STEMI**
Chest discomfort	1	1	1
Cardiac biomarkers	2	1	1
ECG changes	TWI and/or ST depression	TWI and/or ST depression	ST elevation or presumed new left bundle branch block
Pathophysiology	Partial/transient thrombotic occlusion	Partial/transient thrombotic occlusion	Complete thrombotic occlusion

NSTEMI, Non–ST-segment elevation myocardial infarction; *STEMI,* ST-segment myocardial infarction; *TWI,* T-wave inversion; *ECG,* electrocardiogram.

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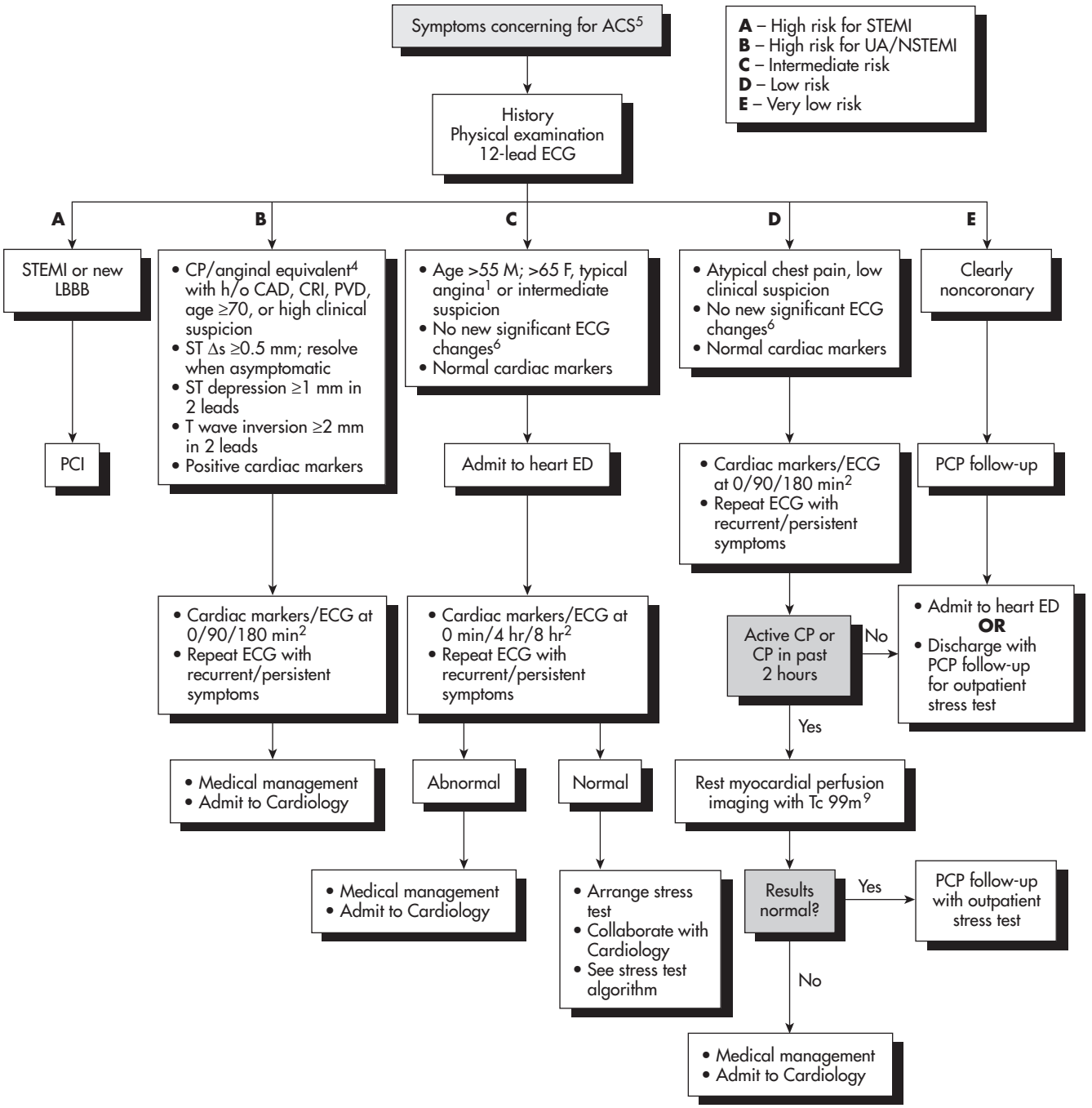

DEFINITIONS:

[1]Typical angina:
1) Substernal chest pain or discomfort that is 2) provoked by exertion or emotional stress and 3) relieved by rest and/or nitroglycerin

[2]Cardiac marker timing: based on symptom onset; in cases of uncertainty assume symptom onset at ED arrival

[3]ECG normal: no significant ST depression/T wave inversions, BBB, LVH with repolarization, conduction defect, digoxin effect

[4]Anginal equivalent:
- Any symptoms that the physician feels may represent ACS
- Exertional dyspnea—most common anginal equivalent symptom

[5]ACS:
- STE-ACS—1 mm ST elevation in 2 leads
- NSTE-ACS
  - NSTEMI—positive cardiac biomarkers
  - Unstable angina—ischemia with negative biomarkers

[6]New significant ECG changes:
- ST Δs ≥0.5 mm; resolve when asymptomatic
- ST depression ≥1 mm in 2 leads
- T wave inversion ≥2 mm in 2 leads

[7]Regadenoson is preferred agent for chemical nuclear stress test. Technetium Tc-99m tetrofosmin is the preferred tracer.

FIGURE A1-41 Evaluation of patients for acute coronary syndrome (ACS). *CAD,* Coronary artery disease; *CP,* chest pain; *CRI,* chronic renal insufficiency; *ECG,* electrocardiogram; *ED,* emergency department; *h/o,* history of; *LBBB,* left bundle branch block; *NSTE,* non–ST-segment elevation; *NSTEMI,* non–ST-segment elevation myocardial infarction; *PCP,* primary care physician; *PVD,* peripheral vascular disease; *STE,* ST-segment elevation; *STEMI,* ST-segment elevation myocardial infarction; *UA,* unstable angina. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

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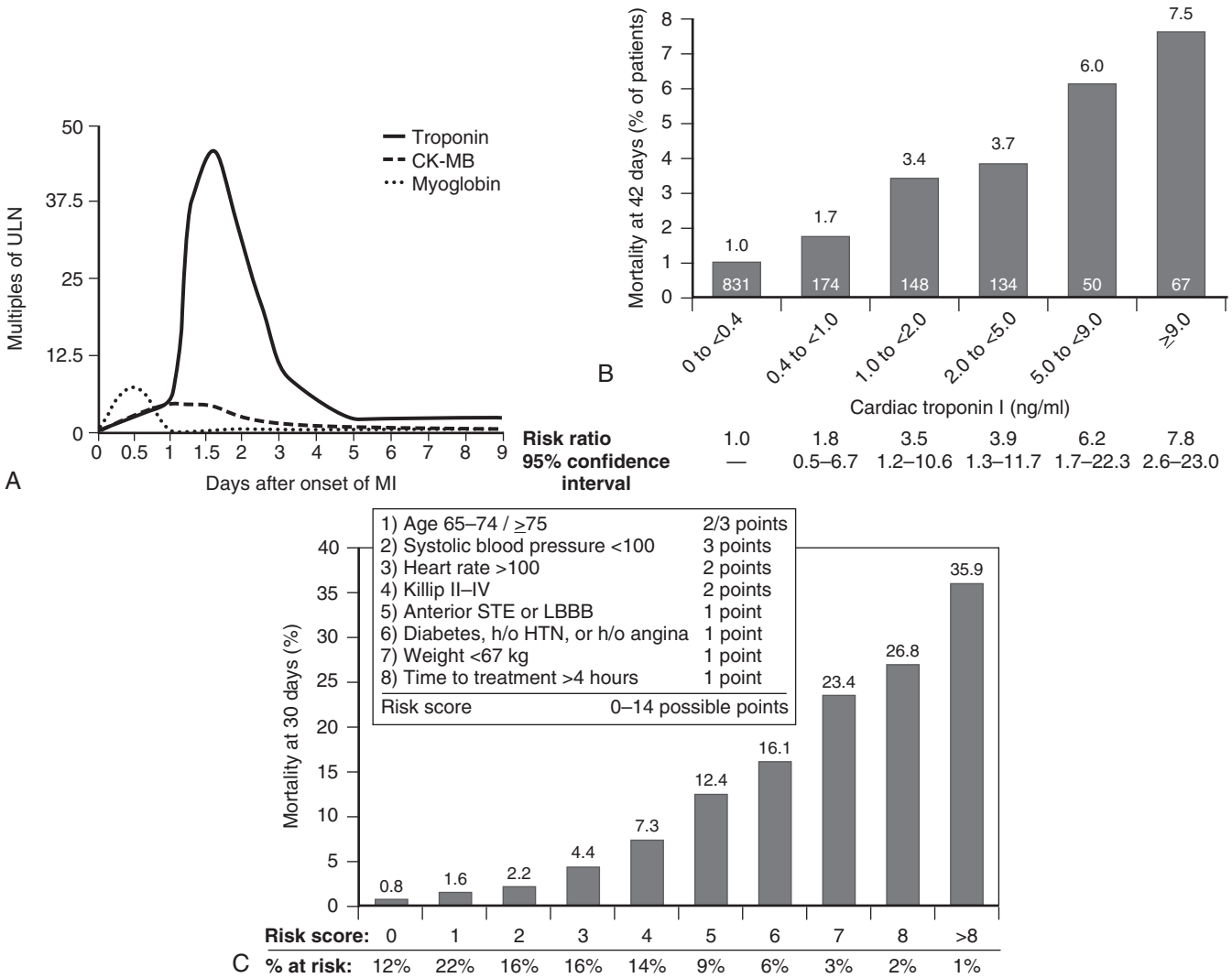

FIGURE A1-42 Timing of release of cardiac biomarkers in ACS. *ULN,* Upper limit of normal; *MI,* myocardial infarction. (Modified from Shapiro BP, Jaffe AS: Cardiac biomarkers. In: Murphy JG, Lloyd MA [eds]: *Mayo Clinic cardiology: concise textbook*, ed 3, Rochester, MN: Mayo Clinic Scientific Press and New York, 2007, Informa Healthcare USA, pp 773-780; and Anderson JL et al: *J Am Coll Cardiol* 50:e1-e157, 2007, Fig. 5.)

RISK MODELS AND RISK SCORES

Risk models and scores such as TIMI, PURSUIT, and GRACE based on clinical, ECG, and laboratory data at presentation help to discriminate patients at high risk versus low risk for short- and intermediate-term adverse outcomes (Fig.A1-42*C*).

IMAGING STUDIES

- CXR to assist in evaluating for volume status and for other possible causes of chest discomfort.
- In patients for whom ECG and cardiac biomarkers are nondiagnostic but the suspicion for ACS is high given the history, an echocardiogram may be helpful to assess left ventricular (LV) function and regional wall motion abnormalities.
- Cardiac stress testing (treadmill ECG, imaging stress studies using echocardiography or nuclear modalities) may further help to diagnose and risk stratify these patients. (See Coronary Artery Disease topic in Section I.)
- Coronary angiogram/cardiac catheterization will reveal coronary artery luminal irregularities/stenotic lesions. In patients with ACS who undergo coronary angiography, approximately 25% will have one vessel disease, 25% will have two vessel disease, 25% will have three vessel disease, 10% will have left main disease, and 15% will have coronary stenosis of <50% or normal coronaries.

Rx TREATMENT

The overall goal for patients with UA and NSTEMI is to relieve myocardial ischemia and to prevent recurrent cardiovascular events. Antithrombotic therapy is needed to reduce thrombus burden, prevent further thrombosis, and improve coronary artery flow. Revascularization is needed to prevent further events and improve flow within the coronary artery lumen. For patients with STEMI, the goal is immediate reperfusion therapy, whether it is chemical (i.e., thrombolysis) or mechanical (i.e., percutaneous coronary intervention [PCI]), and time from onset of ischemia to revascularization is an important prognostic factor. STEMI patients presenting to a hospital with PCI capability should be treated with primary PCI within 90 minutes of first medical contact (Figs. A1-43 and A1-44). Thrombolytic therapy should not be administered 24 hours after initial diagnosis of STEMI.

NONPHARMACOLOGIC THERAPY

- STEMI is a medical emergency and requires immediate reperfusion therapy; the best outcomes are seen with cardiac catheterization with primary PCI. Guidelines call for a goal door-to-balloon time of ≤90 minutes.
- Patients with UA or NSTEMI should be risk stratified in conjunction with the cardiology consult service. Risk scores such as the TIMI and GRACE scores can be used to decide between an early invasive strategy and an initial conservative management strategy. Overall, an early invasive strategy is associated with better outcomes in patients with higher risk (i.e., TIMI score >3) and involves

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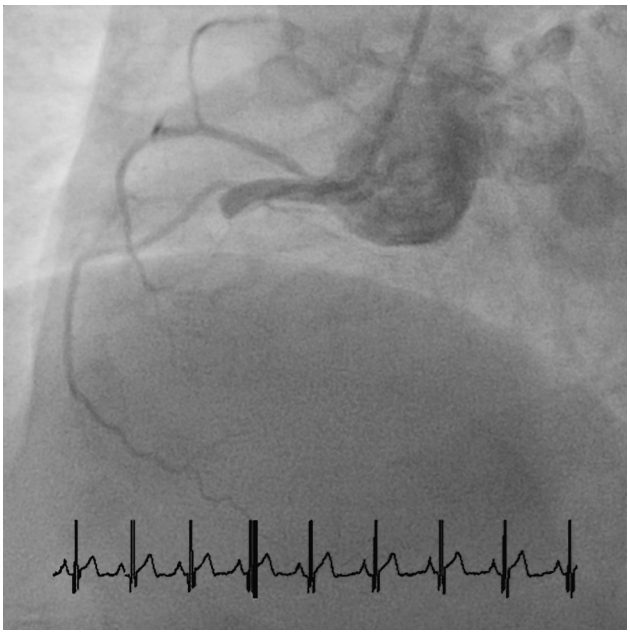

FIGURE A1-43 Right coronary artery totally occluded proximally during STEMI.

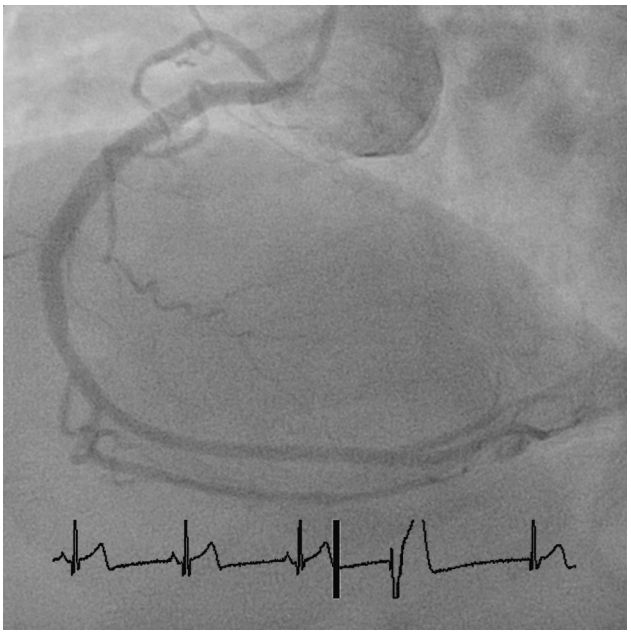

FIGURE A1-44 Right coronary artery after successful percutaneous coronary artery stenting during STEMI.

cardiac catheterization followed by revascularization with PCI or coronary artery bypass grafting (CABG) within 4 to 24 hours of presentation. An initial conservative strategy involves aggressive medical management and revascularization only if ischemia recurs or is documented on noninvasive testing. This should only be reserved for selected patients with low-risk scores (TIMI score 0-2).

- Bed rest and continuous ECG monitoring is recommended for all ACS patients. Supplemental oxygen should be administered to patients with signs of hypoxia or respiratory distress. Finger pulse oximetry should be utilized to assess arterial oxygen saturation.

ACUTE GENERAL Rx

- All patients with ACS should receive full-dose aspirin with the first dose chewed to establish a high blood level for its antiplatelet effects. Thereafter, daily dose of 75 to 325 mg are prescribed and continued indefinitely, with the lower dose of 81 mg showing lower bleeding risk with comparable efficacy.
- Antithrombotic therapy is critical in treating the underlying pathophysiology of ACS. This consists of administering antiplatelet and anticoagulant agents.
- Antiplatelet agents inhibit platelet activation and aggregation. Aspirin is a cyclooxygenase inhibitor that blocks platelet aggregation and should be administered to all ACS patients without contraindications at an initial dose of 162 to 325 mg. Clopidogrel is a thienopyridine agent that inhibits platelet activation and aggregation. It should be administered in all ACS patients, with the timing dependent on the clinical scenario and management strategy. It requires a loading dose of 300 to 600 mg followed by 75 mg daily. It should be discontinued at least 5 days before CABG. Other antiplatelet agents that can be substituted instead of clopidogrel include prasugrel, ticlopidine, and ticagrelor. However, maintenance doses of aspirin above 100 mg reduce the effectiveness of ticagrelor and should be avoided after any initial dose; use with aspirin 75 to 100 mg per day. Prasugrel is not recommended in STEMI patients with stroke or transient ischemic attack (TIA), or those patients managed with fibrinolysis. As a rule, all ACS patients should have two antiplatelet agents initiated and should be continued up to 12 months regardless of conservative vs invasive strategy.
- GP IIB/III a inhibitors may be considered as an intravenous antiplatelet therapy in addition to aspirin for
  1. Medium- or high-risk patients with UA/NSTEMI in whom an invasive strategy is planned (Class I). Eptifibatide or tirofiban may be used prior to PCI and any GP IIB/IIIa inhibitor, including abciximab, may be used during PCI.
  2. Patients in whom an initial conservative strategy is selected, if recurrent symptoms/ischemia, heart failure, or serious arrhythmias subsequently appear, then before diagnostic angiography an IV GP IIb/IIIa inhibitor (Eptifibatide or tirofiban) may be started (Class I).
- Anticoagulant agents should be administered to all ACS patients. Options include either unfractionated heparin (UFH), or low-molecular-weight heparin (enoxaparin), or factor Xa inhibitors such as fondaparinux, or direct thrombin inhibitors such as bivalirudin.
- In the most recent guidelines, enoxaparin and UFH have both received Class I recommendations for use among ACS patients managed conservatively or invasively, but enoxaparin is preferred for conservatively managed patients.
- For STEMI, fondaparinux can be used for anticoagulation. It has been shown to decrease bleeding complications as compared with either UFH or LMWH. However, it has a long half-life (15 hours), and thrombosis on catheters has been noted when using only fondaparinux in the cath lab.
- Bivalirudin is a reversible direct thrombin inhibitor and may be considered as an alternative to UFH and GP IIb/IIIa inhibitors in patients with STEMI (HORIZONS AMI trial) who are undergoing primary PCI (PPCI). When bivalirudin was compared to UFH plus a glycoprotein inhibitor in patients with STEMI and PPCI, less bleeding and a short- and long-term reduction in cardiac events and overall mortality was observed. With bivalirudin, there is no risk of heparin-induced thrombocytopenia, less bleeding is observed, and no anticoagulant monitoring is needed. Similar results were reported in the use of bivalirudin alone in patients with UA/NSTEMI in the ACUITY trial when compared to enoxaparin/UFH with GP IIb/IIIa arms.
- Beta-blocker therapy reduces ischemia by decreasing myocardial oxygen demand and should be initiated within 24 hours of onset of ACS unless signs or symptoms of heart failure are present or arrhythmias preclude its use. Oral administration, titrated to a heart rate of 50-60 beats/min, is preferred. Intravenous beta-blockers should not be administered to STEMI patients who have any of the following:
  1. Signs of heart failure,
  2. Evidence of a low output state,
  3. Increased risk for cardiogenic shock, or
  4. Other relative contraindications to beta-blockade (PR interval >0.24 second, second- or third-degree heart block, active asthma, or reactive airway disease).

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- Nitroglycerin is a vasodilator that should be administered to relieve chest discomfort in all ACS patients. It can be administered sublingually at first, up to 3 doses, followed by intravenous administration if symptoms persist. In the setting of an inferior STEMI, it is wise to rule out a right ventricular (RV) infarct with a right-sided ECG before the administration of nitroglycerin. This is because RV infarcts are preload dependent and nitroglycerin decreases preload through venodilation, which leads to hypotension in this setting. This can be corrected by discontinuing nitroglycerin and starting intravenous fluids. Nitroglycerin provides no mortality benefit in ACS patients.
- Oxygen should be administered to patients with shortness of breath, signs of acute heart failure, cardiogenic shock, or an arterial oxyhemoglobin saturation of less than 94%. The 2011 American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend against the routine usage of oxygen therapy beyond 6 hours without compelling evidence of benefit.
- The 2012 ACC/AHA Guidelines for unstable angina/NSTEMI has downgraded the recommendation for morphine use for uncontrolled ischemic chest discomfort from a Class I to a Class IIa recommendation due to reports linked to increased mortality.
- Calcium channel blockers (nondihydropyridine) may be used in patients with persisting or recurrent symptoms, despite treatment with beta-blockers and nitroglycerin. They work by causing coronary vasodilation and decreasing myocardial oxygen demand. They are useful when beta-blockers are contraindicated and in patients with Prinzmetal variant angina. Calcium channel blockers should not be used in cases of severe LV dysfunction or pulmonary edema.
- Patients routinely taking nonsteroidal antiinflammatory drugs (NSAIDs) (except for aspirin), both nonselective as well as COX-2 selective agents, before STEMI should discontinue those agents at the time of presentation with STEMI because of the increased risks of mortality, reinfarction, hypertension, heart failure, and myocardial rupture associated with their use.
- Angiotensin-converting enzyme (ACE) inhibitors may be added and should be used within 24 hours of onset of ACS in all patients with depressed LV function (ejection fraction [EF] <40%) or pulmonary vascular congestion. Angiotensin receptor blockers (ARBs) should be used in patients who are ACE inhibitor intolerant.

CHRONIC Rx

- Post-ACS medical therapy involves aspirin, statin, beta-blocker, and a second anti-platelet agent such as clopidogrel, ticagrelor, or prasugrel.
- Lipid lowering with statins has been evaluated in trials such as the MIRACL study, in which high-dose atorvastatin 80 mg reduced death, MI, and cardiac events at 16 weeks when administered early, within 24-96 hours after an ACS. The A-Z trial and PROVE IT trials demonstrated benefit of early high dose statin therapy with LDL targets <70 mg/dl in ACS.
- ACE inhibitors may be added to treat hypertension and should be used in all patients with depressed LV function (EF <40%) or pulmonary vascular congestion. ARBs should be used in patients who are ACE inhibitor intolerant.
- Eplerenone, an aldosterone receptor blocker, should be considered in post-MI patients with LV EF ≤40% and evidence of congestive heart failure.
- Cardiac rehabilitation and a monitored exercise program should be recommended.
- Aggressive risk factor management, including smoking cessation, weight loss, diet and exercise, diabetes control, and so on, for secondary prevention of future events is crucial.

REFERRAL

- All ACS patients should be cared for in conjunction with the cardiology consult service.
- When appropriate, referral to a cardiac surgeon may be necessary for CABG.

PEARLS & CONSIDERATIONS

COMMENTS

- ACS is common and a leading cause of mortality in the United States.
- The diagnosis hinges on the basics—history and physical, ECG, biomarkers, and CXR.
- Remember the potentially fatal non-ACS causes of chest discomfort, which include acute pulmonary embolism and acute ascending aortic dissection.
- STEMI patients presenting to a hospital with PCI capability should be treated with primary PCI within 90 minutes of first medical contact.
- STEMI patients presenting to a hospital without PCI capability and who cannot be transferred to a PCI center and undergo PCI within 90 minutes of first medical contact should be treated with fibrinolytic therapy within 30 minutes of hospital presentation unless fibrinolytic therapy is contraindicated.

PREVENTION

- Primary prevention of ACS is based on recognizing the major risk factors for CAD and treating them as appropriate.
- Patients with depressed LV function (ejection fraction <35%) at least 40 days after an acute MI benefit from an implantable cardioverter defibrillator (ICD) for the prevention of sudden cardiac death.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Acute Coronary Syndrome (Patient Information)
Angina (Related Key Topic)
Myocardial Infarction (Related Key Topic)

AUTHORS: **RAHUL BHARDWAJ, M.D.,** and **PRANAV M. PATEL, M.D.**

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EVIDENCE

Abstract[1]

Objectives:
Annually, almost 6 million U.S. citizens are evaluated for acute chest pain syndromes (ACPSs), and billions of dollars in resources are utilized. A large part of the resource utilization results from precautionary hospitalizations that occur because care providers are unable to exclude the presence of coronary artery disease (CAD) as the underlying cause of ACPSs. The purpose of this study was to examine whether the addition of coronary computerized tomography angiography (CCTA) to the concurrent standard care (SC) during an index emergency department (ED) visit could lower resource utilization when evaluating for the presence of CAD.
Methods:
Sixty participants were assigned randomly to SC or SC+CCTA groups. Participants were interviewed at the index ED visit and at 90 days. Data collected included demographics, perceptions of the value of accessing health care, and clinical outcomes. Resource utilization included services received from both the primary in-network and the primary out-of-network providers. The prospectively defined primary endpoint was the total amount of resources utilized over a 90-day follow-up period when adding CCTA to the SC risk stratification in ACPSs.
Results:
The mean (± standard deviation [SD]) for total resources utilized at 90 days for in-network plus out-of-network services was less for the participants in the SC+CCTA group ($10,134; SD±$14,239) versus the SC-only group ($16,579; SD±$19,148; p = 0.144), as was the median for the SC+CCTA ($4,288) versus SC only ($12,148; p = 0.652; median difference=–$1,291; 95% confidence interval [CI]=–$12,219 to $1,100; p = 0.652). Among the 60 total study patients, only 19 had an established diagnosis of CAD at 90 days. However, 18 (95%) of these diagnosed participants were in the SC+CCTA group. In addition, there were fewer hospital readmissions in the SC+CCTA group (6 of 30 [20%] vs. 16 of 30 [53%]; difference in proportions=–33%; 95% CI=–56% to –10%; p = 0.007).
Conclusions:
Adding CCTA to the current ED risk stratification of ACPSs resulted in no difference in the quantity of resources utilized, but an increased diagnosis of CAD, and significantly less recidivism and rehospitalization over a 90-day follow-up period. Ⓐ

Abstract[2]

Background:
Primary results of the HORIZONS-AMI trial have been previously reported. In this final report, we aimed to assess 3-year outcomes.
Methods:
HORIZONS-AMI was a prospective, open-label, randomised trial undertaken at 123 institutions in 11 countries. Patients aged 18 years or older were eligible for enrollment if they had ST-segment elevation myocardial infarction (STEMI), presented within 12 h after onset of symptoms, and were undergoing primary percutaneous coronary intervention. By use of a computerised interactive voice response system, we randomly allocated patients 1:1 to receive bivalirudin or heparin plus a glycoprotein IIb/IIIa inhibitor (GPI; pharmacological randomisation; stratified by previous and expected drug use and study site) and, if eligible, randomly allocated 3:1 to receive a paclitaxel-eluting stent or a bare metal stent (stent randomisation; stratified by pharmacological group assignment, diabetes mellitus status, lesion length, and study site). We produced Kaplan-Meier estimates of major adverse cardiovascular events at 3 years by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00433966.
Findings:
Compared with 1802 patients allocated to receive heparin plus a GPI, 1800 patients allocated to bivalirudin monotherapy had lower rates of all-cause mortality (5.9 vs 7.7, difference –1.9 [–3.5 to –0.2], HR 0.75 [0.58–0.97]; $p = 0.03$), cardiac mortality (2.9 vs 5.1, –2.2 [–3.5 to –0.9], 0.56 [0.40–0.80]; $p = 0.001$), reinfarction (6.2 vs 8.2, –1.9 [–3.7 to –0.2], 0.76 [0.59–0.99]; $p = 0.04$), and major bleeding not related to bypass graft surgery (6.9 vs 10.5, –3.6 [–5.5 to –1.7], 0.64 [0.51–0.80]; $p = 0.0001$) at 3 years, with no significant differences in ischaemia-driven target vessel revascularisation, stent thrombosis, or composite adverse events. Compared with 749 patients who received a bare-metal stent, 2257 patients who received a paclitaxel-eluting stent had lower rates of ischaemia-driven target lesion revascularisation (9.4 vs 15.1, –5.7 [–8.6 to –2.7], 0.60 [0.48–0.76]; p <0.0001) after 3 years, with no significant differences in the rates of death, reinfarction, stroke or stent thrombosis. Stent thrombosis was high (≥4.5) in both groups.
Interpretation:
The effectiveness and safety of bivalirudin monotherapy and paclitaxel-eluting stenting are sustained at 3 years for patients with STEMI undergoing primary percutaneous coronary intervention. Ⓐ

Evidence-Based References

Miller AH et al.: Is coronary computed tomography angiography a resource sparing strategy in the risk stratification and evaluation of acute chest pain? Results of a randomized controlled trial, *Acad Emerg Med* 18:458–467, 2011. Ⓐ

Stone GW, on behalf of the HORIZONS-AMI Trial Investigators: Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial, *Lancet* 377:2193–2204, 2011. Ⓐ

SUGGESTED READINGS

Anderson JL et al.: ACC/AHA 2007. guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction, *Circulation* 116:e148–e304, 2007.

Armstrong PW et al.: Fibrinolysis or primary PCI in ST-segment elevation myocardial infarction, *N Engl J Med* 368:1379–1387, 2013.

Kazi DS et al.: Cost-effectiveness of genotype-guided and dual antiplatelet therapies in acute coronary syndrome, *Ann Int Med* 160:221–232, 2014.

Kumar A, Cannon CP: Acute coronary syndromes: diagnosis and management, part 1, *Mayo Clin Proc* 84(10):917–938, 2009.

Kushner FG et al.: 2009 Focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction, *Circulation* 120:2271–2306, 2009.

Libby P: Mechanisms of acute coronary syndromes and their implications for therapy, *N Engl J Med* 368:2004–2013, 2013.

Menees DS et al.: Door-to-balloon time and mortality among patients undergoing primary PCI, *N Engl J Med* 369:901–909, 2013.

Acute Fatty Liver of Pregnancy

BASIC INFORMATION

DEFINITION

Acute fatty liver of pregnancy (AFLP) is characterized histologically by microvesicular fatty cytoplasmic infiltration of hepatocytes with minimal hepatocellular necrosis.

SYNONYMS

Acute fatty metamorphosis
Acute yellow atrophy
Fatty liver of pregnancy

ICD-9CM CODES
646.7 Liver disorders in pregnancy
ICD-10CM CODES
026.619 Liver and biliary tract disorders in pregnancy, unspecified trimester

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:
- Approximately one in 10,000 pregnancies.
- Equal frequencies in all races and at all maternal ages.

AVERAGE GESTATIONAL AGE: 37 wk (range 28 to 42 wk).

RISK FACTORS:
- Primiparity.
- Multiple gestation.
- Male fetus.

GENETICS: Some with a familial deficiency of long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Initial manifestations:
  1. Nausea and vomiting (70%).
  2. Pain in right upper quadrant or epigastrium (50% to 80%).
  3. Malaise and anorexia.
- Jaundice often in 1 to 2 wk.
- Late manifestations:
  1. Fulminant hepatic failure.
  2. Encephalopathy.
  3. Renal failure.
  4. Pancreatitis.
  5. Gastrointestinal and uterine bleeding.
  6. Disseminated intravascular coagulation.
  7. Seizures.
  8. Coma.
- Liver:
  1. Usually small.
  2. Normal or enlarged in preeclampsia, eclampsia, HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets), and acute hepatitis.
  3. Coexistent preeclampsia in up to 46% of patients.

ETIOLOGY

- Postulated that inhibition of mitochondrial oxidation of fatty acids may lead to microvesicular fatty infiltration of liver.
- Fatty metamorphosis of preeclamptic liver disease believed to be of different etiology.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute gastroenteritis.
- Preeclampsia or eclampsia with liver involvement.
- HELLP syndrome.
- Acute viral hepatitis.
- Fulminant hepatitis.
- Drug-induced hepatitis caused by halothane, phenytoin, methyldopa, isoniazid, hydrochlorothiazide, or tetracycline.
- Intrahepatic cholestasis of pregnancy
- Gallbladder disease.
- Reye's syndrome.
- Hemolytic-uremic syndrome.
- Budd-Chiari syndrome.
- Systemic lupus erythematosus.

WORKUP

- A clinical diagnosis is based predominantly on physical and laboratory findings.
- Most definitive diagnosis is through liver biopsy with oil red O staining and electron microscopy.
- Liver biopsy is reserved for atypical cases only and only after any existing coagulopathy is corrected with fresh frozen plasma due to concerns for excessive bleeding.

LABORATORY TESTS

Tests to determine the following:
- Hypoglycemia (often profound <60 mg/dl).
- Hyperammonemia.
- Elevated aminotransferases (usually <500 U/ml).
- Thrombocytopenia.
- Leukocytosis (white blood cell count >15,000).
- Hyperbilirubinemia (usually <10 mg/dl).
- Low albumin.
- Hypofibrinogenemia (<300 mg/dl).
- Disseminated intravascular coagulation (DIC) (in 75%).

IMAGING STUDIES

- Ultrasound: best used to rule out other diseases in the differential diagnosis such as gallbladder disease.
- CT scan: plays minimal role because of a high false-negative rate.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Patient is admitted to intensive care unit for stabilization.
- Fetus is delivered; spontaneous resolution usually follows delivery.
- Mode of delivery is based on obstetric indications and clinical assessment of disease severity.

ACUTE GENERAL Rx

- Decrease in endogenous ammonia through dietary protein restriction; neomycin 6 to 12 g/day PO to decrease presence of ammonia-producing bacteria; magnesium citrate 30 to 50 ml PO or enema to evacuate nitrogenous wastes from colon.
- Administration of IV fluids with glucose to keep glucose levels >60 mg/dl.
- Coagulopathy corrected with fresh frozen plasma.
- Avoidance of drugs metabolized by liver.
- Aggressive avoidance and treatment for nosocomial infections; consideration of prophylactic antibiotics.
- Monitor closely for development of complications such as hepatic encephalopathy, pulmonary edema, DIC, and respiratory arrest.

CHRONIC Rx

Orthotopic liver transplantation is the only treatment for irreversible liver failure.

DISPOSITION

- Before 1980, both maternal and fetal mortality rates were approximately 85%.
- Since 1980, both maternal and fetal mortality rates are less than 20%.
- Usually rapid return of liver function to normal after delivery.
- Minimal risk of recurrence with future pregnancies.

REFERRAL

- To tertiary health care facility as soon as diagnosis is suspected.
- Infants of mothers with AFLP should be evaluated for LCHAD deficiency.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Eclampsia (Related Key Topic).
Preeclampsia (Related Key Topic).

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Cunningham FG, et al. Gastrointestinal disorders. In: (editor: Cunningham F.G.; et al.) Williams' obstetrics. ed 20 Appleton & Lange: Stamford, CT.

Davidson KM: Acute fatty liver of pregnancy, *Postgrad Obstet Gynecol* 15(1), 1995.

Steingrub JS: Pregnancy-associated severe liver dysfunction, *Crit Care Clin* 20(4):763, 2004.

Toro Ortiz JC, et al.: Acute fatty liver of pregnancy, *J Matern Fetal Neonatl Med* 12(4):277, 2003.

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BASIC INFORMATION

DEFINITION

Acute kidney injury (AKI) is the rapid (<48 hr) impairment in renal function resulting in retention of products in the blood that are normally excreted by the kidneys and concurrent volume and acid-base dysregulation in the body. Criteria and classifications of AKI are described in Table A1-15.

SYNONYMS

ARF
Acute renal insufficiency syndrome
Acute renal failure
AKI

ICD-9CM CODES
584.9 Acute renal failure, unspecified
ICD-10CM CODES
N17.9 Acute kidney failure, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence of AKI is 3 cases/1000 persons. AKI requiring dialysis develops in five in 100,000 persons annually.
- >10% of intensive care unit patients develop AKI.
- >40% of hospital AKI is iatrogenic.
- The most common cause of AKI in hospitalized patients is intrinsic renal failure caused by acute tubular necrosis (ATN) and prerenal disease.
- AKI occurs in 20% of patients with moderate sepsis and more than 50% of patients with septic shock and positive blood cultures.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The physical examination should focus on volume status. The physical findings noted below vary with the duration and rapidity of onset of renal failure.
- Peripheral edema resulting from volume overload, heart failure, liver failure, or nephrotic syndrome
- Skin pallor, ecchymoses
- Arrhythmias due to electrolyte imbalances and acidosis
- Oliguria (i.e., <400 to 500 ml urine/24 hr; however, patients can have nonoliguric renal failure), anuria
- Change in mental status, delirium, lethargy, myoclonus, seizures
- Uremic odor, pruritus
- Flank pain, fasciculations, muscle cramps
- Tachypnea, tachycardia
- Weakness, anorexia, generalized malaise, nausea
- Pulmonary rales due to volume overload
- Flapping tremors
- Pericardial effusion
- Hypotension or hypertension can occur, suggesting volume depletion and overload, respectively

ETIOLOGY

- **Prerenal:** inadequate perfusion caused by hypovolemia, congestive heart failure, cirrhosis, sepsis. Sixty percent of community-acquired cases of AKI are from prerenal conditions.
- **Postrenal:** outlet obstruction from prostatic enlargement, fibrosis, ureteral obstruction (stones), bilateral renal vein occlusion. Postrenal causes account for 5% to 15% of community-acquired AKI.
- **Intrinsic renal:** glomerulonephritis, ATN, rhabdomyolysis, systemic hypotension, sepsis, drug toxicity, contrast nephropathy. Contrast-induced nephropathy (increase in serum creatinine >25% within 3 days of intravascular contrast administration in absence of an alternative cause) is the third most common cause of new AKI in hospitalized patients.
- Causes of AKI are described in Table A1-16.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Refer to "Etiology." Diagnostic tests to distinguish prerenal and renal AKI are described in Table A1-17. A diagnostic approach to patients with suspected AKI is described in Fig. A1-45.

LABORATORY TESTS

- Elevated serum creatinine: the rate of rise is approximately 1 mg/dl/day in complete renal failure.
- Elevated blood urea nitrogen (BUN): BUN/creatinine ratio is >20:1 in prerenal azotemia, postrenal azotemia, and acute glomerulonephritis; it is <20:1 in acute interstitial nephritis and ATN (Table A1-18).
- Electrolytes (potassium, phosphate) are elevated; bicarbonate level, sodium, and calcium are decreased; metabolic acidosis is noted.
- Complete blood count may reveal anemia because of decreased erythropoietin production, hemoconcentration, hemolysis, or leukocytosis, suggesting infection.
- Urinalysis may reveal the presence of hematuria (glomerulonephritis), proteinuria (nephrotic syndrome), casts (e.g., granular casts in ATN, red blood cell casts in acute glomerulonephritis, white blood cell casts in acute interstitial nephritis), eosinophiluria (acute interstitial nephritis). These findings may be absent in less severe disease.
- Urinary sodium and urinary creatinine should be obtained to calculate the fractional excretion of sodium (FENa) (FENa = Urine sodium/Plasma sodium × Plasma creatinine/Urine creatinine × 100). FENa is <1 in prerenal failure and >1 in intrinsic renal failure in patients with urine output <400 ml/day. The FENa can be falsely high in patients taking diuretics. It can also be falsely low in several intrinsic renal conditions such as acute glomerulonephritis, contrast-induced nephropathy, and rhabdomyolysis.
- Urinary osmolarity is 250 to 300 mOsm/kg in ATN, <400 mOsm/kg in postrenal azotemia, and >500 mOsm/kg in prerenal azotemia and acute glomerulonephritis (Table A1-19).
- Combined use of cystatin C, a protein that is freely filtered by the glomerulus, and serum creatinine has been shown to improve estimates of GFR in AKI.

TABLE A1-15 RIFLE and AKIN Criteria for Diagnosis of Acute Kidney Injury

	RIFLE CLASSIFICATION	
	GFR Criteria	**Urine Output Criteria**
Risk	S_{Cr} >1.5 × baseline or ΔGFR >25% reduction	UO <0.5 ml/kg/h × 6 h
Injury	S_{Cr} >2.0 × baseline or ΔGFR >50% reduction	UO <0.5 ml/kg/h × 12 h
Failure	S_{Cr} >3.0 × baseline or ΔGFR >75% reduction or S_{Cr} >4.0 mg/dl	UO <0.3 ml/kg/h × 24 h or anuria × 12 h
Loss	Persistent acute kidney injury = Complete loss of function for >4 wk	
ESRD	End-stage renal disease >3 mo	
	AKIN CLASSIFICATION	
Stage	**Serum Creatinine Criteria**	**Urine Output Criteria**
1	ΔS_{Cr} ≥0.3 mg/dl (30 μmol/L) or S_{Cr} ≥1.5, ≤2.0 × baseline	UO <0.5 ml/kg/h × 6 h
2	S_{Cr} >2.0, ≤3.0 × baseline	UO <0.5 ml/kg/h × 12 h
3	S_{Cr} >3.0 × baseline or	
	S_{Cr} ≥4.0 mg/dl with an acute rise ≥0.5 mg/dl (50 μmol/L) or on renal replacement therapy	UO <0.3 ml/kg/h × 24 h or anuria × 12 h

AKIN, Acute Kidney Injury Network; *GFR,* glomerular filtration rate; *RIFLE,* risk, injury, failure, loss, ESRD; *SCr,* serum creatinine; *UO,* urinary output.
From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

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TABLE A1-16 Etiologies of Acute Kidney Injury

Prerenal Causes (Decreased Renal Blood Flow)	Intrinsic Renal Causes	Postrenal Causes
Hypovolemia	**Vascular: Large and Small Vessels**	**Ureteral Obstruction**
Renal losses (diuretics, osmotic agents, polyuria)	Trauma	Calculus
Gastrointestinal losses (vomiting, diarrhea)	Renal vein obstruction (thrombosis, ventilation with high-level PEEP, abdominal compartment syndrome)	Tumor (intrinsic or extrinsic)
Cutaneous losses (burns, exfoliative syndromes)	Microangiopathy (thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome, disseminated intravascular coagulation, preeclampsia)	Fibrosis
Hemorrhage	Malignant hypertension	Ligation during pelvic surgery
Pancreatitis	Scleroderma renal crisis	**Bladder Neck Obstruction**
Decreased Cardiac Output	Transplant rejection	Benign prostatic hypertrophy
Congestive heart failure	Atheroembolic disease	Prostate cancer
Pulmonary embolism	**Glomerular**	Neurogenic bladder
Acute myocardial infarction	Antiglomerular basement membrane disease (Goodpasture syndrome)	Tricyclic antidepressants
Severe valvular heart disease	Antineutrophil cytoplasmic antibody-associated glomerulonephritis (Wegener granulomatosis)	Ganglionic blockers
Abdominal compartment syndrome	Immune complex glomerulonephritis, systemic lupus erythematosus, postinfectious cryoglobulinemia, primary membranoproliferative glomerulonephritis	Bladder tumor
Renal artery obstruction (stenosis, embolism, thrombosis, dissection)	**Tubular**	Calculus
Systemic Vasodilation	Ischemic	Hemorrhage/clot
Sepsis	Cytotoxic	**Urethral Obstruction**
Anaphylaxis	Heme pigment (rhabdomyolysis, intravascular hemolysis)	Strictures
Anesthetics	Crystals (tumor lysis syndrome, seizures, ethylene glycol poisoning, vitamin C megadose, acyclovir, indinavir, methotrexate)	Tumor
Drug overdose	Drugs (aminoglycosides, lithium, amphotericin B, pentamidine, cisplatin, ifosfamide, radiocontrast agents), synthetic cannabinoid use	Phimosis
Afferent Arteriolar Vasoconstriction	**Interstitial**	Renal calcinosis
Hypercalcemia	Drugs (penicillins, cephalosporins, NSAIDs, proton pump inhibitors, allopurinol, rifampin, indinavir, mesalamine, sulfonamides)	Obstructed urinary catheter, ureteral stent, or ileal conduit
Drugs (NSAIDs, amphotericin B, calcineurin inhibitors, norepinephrine, radiocontrast agents, aminoglycosides)	Infection (pyelonephritis, viral infection)	Pelvic trauma, retroperitoneal hematoma
Hepatorenal syndrome	**Systemic Disease**	
Efferent arteriolar vasodilation (angiotensin converting enzyme inhibitors, aldosterone receptor blockers)	Sjögren syndrome, sarcoidosis, systemic lupus erythematosus, lymphoma, leukemia, tubulonephritis, uveitis	

NSAIDs, Nonsteroidal anti-inflammatory drugs; *PEEP,* positive end-expiratory pressure.
Modified from Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

TABLE A1-17 Diagnostic Tests to Distinguish Between Prerenal and Renal Acute Kidney Injury

Index	Prerenal Causes	Renal Causes
FENa	<1%	>2%
Urine sodium	<10 mmol/L	>40 mmol/L
Urine/plasma osmolality	>1.5	1 to 1.5
Renal failure index	<1	>2
BUN/creatinine ratio	>20	<10

BUN, Blood urea nitrogen; *FENa,* fractional excretion of sodium. Calculation of FENa: (Urine sodium × Plasma creatinine)/(Plasma sodium × Serum creatinine) × 100. Renal failure index: (Urine sodium × Urine creatinine)/Plasma creatinine.
From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

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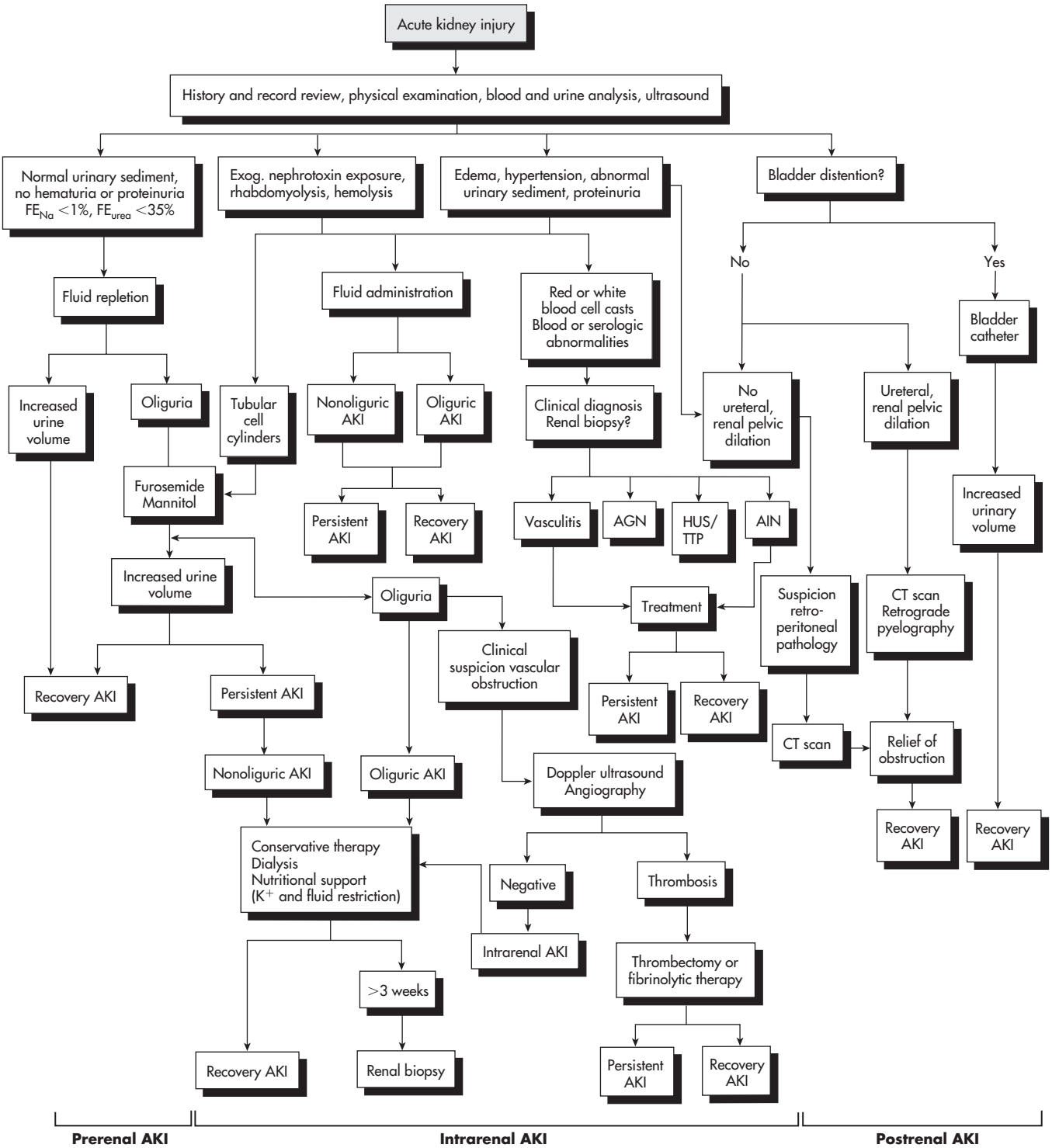

FIGURE A1-45 Diagnostic approach to patients with suspected AKI. *AGN,* Acute glomerulonephritis; *AIN,* acute interstitial nephritis; *CT,* computed tomography; *Exog.,* exogenous; *HUS/TTP,* hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

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TABLE A1-18 Serum and Radiographic Abnormalities in Renal Failure

	Prerenal	Postrenal (Acute)	Intrinsic Renal (Acute)	Intrinsic Renal (Chronic)
BUN	↑ 10:1 > Cr	↑ 20-40/day	↑ 20-40/day	Stable; ↑ varies with protein intake
Serum creatinine	N/moderate ↑	↑ 2-4/day	↑ 2-4/day	Stable ↑ (production equals excretion)
Serum potassium	N/moderate ↑	↑ varies with urinary volume	↑↑ (particularly when patient is oliguric) ↑↑↑ with rhabdomyolysis	Normal until end stage, unless tubular dysfunction (type 4 RTA)
Serum phosphate	N/moderate ↑	Moderate ↑	↑	Becomes significantly elevated when serum creatinine surpasses 3 mg/dl
		↑↑ with rhabdomyolysis	Poor correlation with duration of renal disease	
Serum calcium	N	N/↓ with PO_4^{-3} retention	↓ (poor correlation with duration of renal failure)	Usually ↓
Renal size				
By ultrasonography	N/↑	↑ and dilated calyces	N/↑	↓ and with ↑ echogenicity
FE_{Na}*	<1	<1 → >1	>1†	1

↑, Increase; ↓, decrease; ↑↑, large increase; ↑↑↑, very high increase; *BUN,* blood urea nitrogen; *Cr,* creatinine; *N,* normal; *Na,* sodium; *P,* plasma; *RTA,* renal tubular acidosis; *U,* urine.

*$FE_{Na}\left[\frac{U/P_{Na}+}{U/P_{Cr}} \times 100\right]$ (useful only in oliguric patient).

†May be ≤1 in radiocontrast-induced myoglobinuric acute tubular necrosis and in early sepsis.
From Ferri FF (ed): *Practical guide to the care of the medical patient,* ed 8, St Louis, 2011, Mosby.

TABLE A1-19 Urinary Abnormalities in Renal Failure

	Prerenal	Postrenal (Acute)	Intrinsic Renal (Acute)	Intrinsic Renal (Chronic)
Urinary volume	↓	Absent-to-wide fluctuation	Oliguric or nonoliguric	1000 ml + until end stage
Urinary creatinine	↑ (U/P Cr 640)	↓ (U/P Cr 620)	↓ (U/P Cr <20)	↓ (U/P Cr <20)
Osmolarity	↑ (6400 mOsm/kg)	(<350 mOsm/kg)	(<350 mOsm/kg)	(<350 mOsm/kg)
Degree of proteinuria	Minimum	Absent	Varies with cause of renal failure: Modest with ATN Nephrotic range common with acute glomerulopathies, usually <2 g/24 hr with interstitial disease*	Varies with cause of renal disease (from 1-2 g/day to nephrotic range)
Urinary sediment	Negative, or occasional hyaline cast	Negative or hematuria with stones or papillary necrosis Pyuria with infectious prostatic disease Nephrosis: oval fat bodies	ATN: muddy brown casts Interstitial nephritis: lymphocytes, eosinophils (in stained preparations), and WBC casts RPGN: RBC casts	Broad casts with variable renal "residual" acute findings

↑, Increased; ↓, decreased; *ATN,* acute tubular necrosis; clearance = $\frac{\text{urinary concentration} \times \text{urinary volume}}{\text{plasma concentration}}$; *Cr,* creatinine; *RBC,* red blood cell; *RPGN,* rapidly progressive glomerulonephritis; *U/P,* urine/plasma; *WBC,* white blood cell.
*Except nonsteroidal anti-inflammatory drug-induced allergic interstitial nephritis with concomitant "nil disease."
From Ferri FF (ed): *Practical guide to the care of the medical patient,* ed 8, St Louis, 2011, Mosby.

- The fractional excretion of urea (FEU) is a useful measure for assessing renal dysfunction in acute kidney injury. FEU is calculated as:

  $$\frac{\text{serum creatinine} \times \text{urinary urea}}{\text{serum urea} \times \text{urinary creatinine}}$$

  An FEU of less than 35% suggests a prerenal cause of acute kidney injury, whereas a value over 50% indicates an intrinsic cause. FEU is more useful than FENa in patients on diuretics.
- Blood cultures for patients suspected of sepsis.
- Abnormal liver function tests, decreased complement levels, elevated anti–glomerular basement membrane antibody titers, antineutrophil cytoplasmic antibodies, antinuclear antibodies, cryoglobulins, and circulating immune complexes are useful diagnostic tools for diagnosing glomerulonephritis or vasculitis.
- Creatinine kinase level in patients with suspected rhabdomyolysis.
- Serum and urine protein electrophoresis in patients suspected of myeloma.
- Renal biopsy may be indicated in patients with intrinsic renal failure when considering specific therapy; major uses of renal biopsy are differential diagnosis of nephrotic syndrome, separation of lupus vasculitis from other vasculitis and lupus membranous from idiopathic membranous, confirmation of hereditary nephropathies on the basis of the ultrastructure, diagnosis of rapidly progressing glomerulonephritis, separation of allergic interstitial nephritis from ATN, separation of primary glomerulonephritis syndromes.
- Tubular enzymes can be used biomarkers for renal failure. Among them are proximal renal tubular epithelial antigen (HRTE-1), *N*-acetyl-beta-glucosaminidase (NAG), alpha-glutathione S-transferase (alpha-GST), gamma-glutamyltranspeptidase (gamma-GT), and lactate dehydrogenase (LDH). The majority of them are released before an increase in serum creatinine; however, they do not provide any clear parameters to differentiate ATN from prerenal failure.

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- Alpha1-microglobulin (alpha1-M), beta2-microglobulin (beta2-M), adenosine deaminase binding protein (ABP), retinol binding protein (RBP), urinary cystatin C, and neutrophil gelatinase–associated lipocalin (NGAL) are being further studied for diagnostic evaluation.

IMAGING STUDIES

- ECG is done to evaluate changes especially in hyperkalemia.
- Chest x-ray is useful to evaluate for congestive heart failure and for pulmonary renal syndromes (Goodpasture's syndrome, Wegener's granulomatosis).
- Ultrasound of kidneys is used to evaluate kidney size (useful to distinguish acute from chronic renal failure), evaluate for the presence of obstruction, and evaluate renal vascular status (with Doppler evaluation).
- Computed tomography (CT) with radiocontrast agent administration is usually avoided in AKI; however, unenhanced CT scans are useful for the identification of obstructing ureteral stones.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Stop all nephrotoxic medications.
- Dietary modification to supply adequate calories while minimizing accumulation of toxins; appropriate control of fluid balance. Physicians should recommend a nutrition program with an energy prescription of 120 to 150 KJ/kg/day and restriction of potassium (60 mEq/day), sodium (90 mEq/day), and phosphorus (800 mg/day). Ideal protein supplementation ranges from 0.6 to 1.4 g/kg depending on whether dialysis is required.
- Daily weight.
- Modifications of dosage of renally excreted drugs.

ACUTE GENERAL Rx

- Correction of electrolyte abnormalities and metabolic acidosis
- Loop diuretics in patients with volume overload and, if needed, pressors or vasodilators in patients with congestive heart failure

Specific treatment is variable with etiology of AKI:

- Prerenal: IV volume expansion in hypovolemic patients.
- Intrinsic renal: discontinuation of any potential toxins and treatment of condition causing the renal failure. In severe cases of acute interstitial nephritis, a trial of steroids is also given to improve clinical course.
- Postrenal: removal of obstruction. Immediate insertion of catheter for lower urinary tract obstruction and nephrostomy or ureteral stents are required in patients with upper urinary tract obstruction.
- IV insulin and glucose for patients with hyperkalemia-related ECG changes.

CHRONIC Rx

- Monitoring of renal function and electrolytes.
- Doses of medications that are renally excreted should be adjusted according to creatinine clearance to prevent further damage to the kidneys.
- Prevention of further insults to the kidneys with proper hydration, especially before contrast studies, and avoidance of nephrotoxic agents. Hydration with sodium bicarbonate (addition of 154 ml of 1000 mEq/L sodium bicarbonate to 846 ml of 5% dextrose in water) before contrast exposure is more effective than hydration with sodium chloride for prophylaxis of contrast-induced renal failure. Administration of *N*-acetylcysteine prophylaxis has shown conflicting results regarding its ability to reduce the risk of contrast-induced nephropathy. In high-risk patients having angiography or angioplasty, the RenalGuard System using saline plus *N*-acetylcysteine and furosemide has been shown to be better than sodium bicarbonate plus *N*-acetylcysteine for preventing contrast-induced AKI.
- See "Chronic Kidney Disease" entry for indications for initiation of dialysis. Daily hemodialysis is superior to every-other-day hemodialysis in patients with ATN and ARF.

DISPOSITION

- General indications for initiation of dialysis are:
  1. Florid symptoms of uremia (encephalopathy, pericarditis)
  2. Severe volume overload
  3. Severe acid-base imbalance
  4. Significant derangement in electrolyte concentrations (e.g., hyperkalemia, hyponatremia)
- Intermittent hemodialysis and continuous renal replacement therapy have similar outcomes for patients with AKI.
- Renal function recovery (ability to discontinue dialysis) varies from 50% to 75% in survivors of AKI.
- Overall mortality rate in AKI is nearly 50%, varying from 60% in patients with ATN to 35% in patients with prerenal or postrenal AKI.
- The combination of AKI and sepsis is associated with a 70% mortality rate.

PEARLS & CONSIDERATIONS

- Patients with AKI are susceptible to infections and sepsis.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Acute Renal Failure (Patient Information)
Chronic Renal Failure (Patient Information)

AUTHORS: **SYEDA M. SAYEED, M.D.,** and **FRED F. FERRI, M.D.**

http://internalmedicinebook.com/

EVIDENCE

Abstract[1]

Objective:
Biomarkers for detection of acute kidney injury and prediction of mortality will be useful to improve the outcomes of critically ill patients. Although several promising acute kidney injury biomarkers have been reported, evaluation in heterogeneous disease-oriented populations is necessary to confirm their reliability before their translation to clinical use. This study was undertaken to evaluate the reliability of new acute kidney injury biomarkers including urinary L-type fatty acid-binding protein with heterogeneous intensive care unit populations.

Design:
Prospective observational cohort study.

Setting:
Single-center study, 15-bed medical–surgical mixed intensive care unit at a university hospital.

Patients:
Three hundred thirty-nine adult critically ill patients who had been admitted to the intensive care unit were studied prospectively.

Interventions:
None.

Measurements and Main Results:
Five urinary biomarkers (L-type fatty acid-binding protein, neutrophil gelatinase-associated lipocalin, interleukin-18, *N*-acetyl-β-D-glucosaminidase, and albumin) were measured at intensive care unit admission. By the RIFLE (Risk, Injury, Failure, Loss, End-stage kidney disease) criteria, 131 patients (39%) were diagnosed as acute kidney injury. Urinary L-type fatty acid-binding protein detected acute kidney injury better than the other biomarkers did (the area under the receiver operating characteristic curves for L-type fatty acid-binding protein 0.75, neutrophil gelatinase-associated lipocalin 0.70, interleukin-18 0.69, *N*-acetyl-β-D-glucosaminidase 0.62, albumin 0.69). Urinary L-type fatty acid-binding protein predicted later-onset acute kidney injury after intensive care unit admission with the highest area under the receiver operating characteristic curve value of 0.70. Furthermore, L-type fatty acid-binding protein, neutrophil gelatinase-associated lipocalin, and interleukin-18 were able to predict 14-day mortality with higher area under the receiver operating characteristic curves than acute kidney injury detection (area under the receiver operating characteristic curve for L-type fatty acid-binding protein 0.90, neutrophil gelatinase-associated lipocalin 0.83, interleukin-18 0.83). The combination of L-type fatty acid-binding protein and neutrophil gelatinase-associated lipocalin improved mortality prediction (area under the receiver operating characteristic curve 0.93).

Conclusion:
This prospective observational study with a cohort of heterogeneous patients treated in a mixed intensive care unit revealed that new acute kidney injury biomarkers have a significantly and moderately predictive use for acute kidney injury diagnosis and that urinary L-type fatty acid-binding protein and neutrophil gelatinase-associated lipocalin can serve as new biomarkers of mortality prediction in critical care. Ⓐ

Evidence-Based Reference

Doi K et al.: Evaluation of new acute kidney injury biomarkers in a mixed intensive care unit, *Crit Care Med* 39:2464–2469, 2011. Ⓐ.

SUGGESTED READINGS

Abdel-Kader K, Palersky PM: Acute kidney injury in the elderly, *Clin Geriatr Med* 25:331–358, 2009.

Briguori C et al.: Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II): RenalGuard System in high-risk patients for contrast-induced acute kidney injury, *Circulation* 124:1260, 2011.

Chawla LS et al.: Acute kidney injury and chronic kidney disease as interconnected syndromes, *N Engl J Med* 371:58–66, 2014.

Gotfried J et al.: Finding the cause of acute kidney injury: which index of fractional excretion is better? *Clev Clin J Med* 79:121, 2012.

Grams ME, Estrella MM, Coresh J et al.: Fluid balance, diuretic use, and mortality in acute kidney injury, *Clin J Am Soc Nephrol* 6:966, 2011.

Hwang YJ et al.: Atypical antipsychotic drugs and the risk for acute kidney injury and other adverse outcomes in older adults, *Ann Intern Med* 161:242–248, 2014.

Inker LA et al.: Estimating GFR from serum creatinine and cystatin C, *N Engl J Med* 367:20, 2012.

Kelly A et al.: Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy, *Ann Intern Med* 148:284–294, 2008.

Lameire N et al.: Acute renal failure, *Lancet* 365:417–430, 2005.

Li Y et al.: Nutritional support for acute kidney injury, *Cochrane Database Syst Rev* (1):CD005426, 2010.

Pannu N et al.: Renal replacement therapy in patients with acute renal failure, *JAMA* 299(7):793–805, 2008.

Rahman M et al.: Acute kidney injury: a guide to diagnosis and management, *Am Fam Physician* 86(7):631–639, 2012.

Ralib AM et al.: Test characteristics of urinary biomarkers depend on quantitation method in acute kidney injury, *J Am Soc Nephrol* 23(2):322, 2012.

BASIC INFORMATION

DEFINITION

Acute liver failure (ALF) is defined as rapid development (<26 wk) of severe hepatic injury, coagulation abnormalities (international normalized ratio [INR] >1.5), and encephalopathy in a patient without preexisting liver disease, in the absence of acute alcoholic hepatitis.

SYNONYMS

Fulminant hepatic failure
Fulminant hepatitis
Fulminant hepatic necrosis
Acute hepatic necrosis
Acute and subacute necrosis of liver

ICD-9CM CODES
070.9 Unspecified viral hepatitis without mention of hepatic coma
573.3 Hepatitis, unspecified
ICD-10CM CODES
72.00 Acute liver failure w/o coma
72.01 Acute liver failure w/ coma

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Affects approximately 2000 people/yr
PREDOMINANT SEX AND AGE: Seen more in women than men (73% vs. 27%)
RISK FACTORS: Intentional drug overdose, intravenous drug use, alcohol use, occupational exposure to blood or body fluids, taking hepatotoxic medications

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms of ALF include mental status changes, nausea, vomiting, easy bleeding or bruising. Abdominal pain and jaundice are often present.
- Physical findings include some degree of encephalopathy (see Table A1-20) and may include icteric sclera, jaundice, asterixis, hepatomegaly, decreased hepatic mass on percussion, and ascites. Multisystem organ failure can ensue. In rare cases, cerebral edema and increased intracranial pressure can occur, with abnormal pupillary exam, hypertension, bradycardia, seizures, and loss of brainstem reflexes.

TABLE A1-20 Grades of Encephalopathy

Grade	Description
I	Changes in behavior with minimal change in level of consciousness
II	Gross disorientation, drowsiness, possibly asterixis, inappropriate behavior
III	Marked confusion, incoherent speech, sleeping most of the time but arousable to vocal stimuli
IV	Comatose, unresponsiveness to pain, decorticate or decerebrate posturing

- Vesicular skin lesions are suggestive of herpes simplex virus (HSV).
- Family history of unexplained liver disease/cirrhosis should prompt ocular exam to look for Kayser-Fleischer rings (copper rings around the iris seen in Wilson disease).

ETIOLOGY

- Common causes include:
  1. Acetaminophen toxicity (46%)
  2. Indeterminate (14%)
  3. Idiosyncratic drug reaction (12%)
  4. Viral hepatitis (A, B) (10%)

  Rarer causes include alcoholic hepatitis, autoimmune hepatitis, Wilson disease, ischemic hepatopathy, Budd-Chiari syndrome, acute fatty liver of pregnancy, venoocclusive disease, toxin ingestion (e.g., mushroom poisoning *[Amanita phalloides]*), sepsis, infiltrative malignancy (breast cancer, lymphoma, myeloma, melanoma, small cell lung cancer), and other viruses (adenovirus, hepatitis E, HSV).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Severe acute hepatitis (including alcoholic hepatitis) —jaundice and coagulopathy without encephalopathy
- Cirrhosis (includes decompensated cirrhosis)
- Hepatocellular carcinoma

WORKUP (Box A1-5)

- Fig. A1-46 describes an algorithm for evaluation of acute liver failure.
- Clinical history is critical and should include medication use (prescriptions, over-the-counter medications, herbal supplements), alcohol use, recreational drug use, prior symptoms of jaundice, onset of symptoms, history of suicide attempts, recent travel to endemic areas of viral hepatitis, and family history of liver failure/disease.
- Laboratory evaluation: complete blood count, liver function tests (LFTs) (AST, ALT, alkaline phosphatase, GGT, total and direct bilirubin, PT/INR, albumin), chemistry panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, magnesium, phosphate, calcium), arterial blood gas, arterial lactate, blood type and screen, acetaminophen level, ethanol level, toxicology screen, viral hepatitis serologies (anti–hepatitis A IgM, hepatitis B surface antigen, anti–hepatitis B core IgM, anti–hepatitis C antibody, hepatitis C viral load, anti–hepatitis E Ab, HSV-1 IgM, varicella zoster virus, ceruloplasmin level, pregnancy test, arterial ammonia level, autoimmune markers (ANA, ASMA, total IgG levels), HIV-1, HIV-2, amylase, lipase, ceruloplasmin.
- Abdominal ultrasound with Dopplers, CT/MRI of the head
- Prompt liver biopsy (via transjugular approach to decrease risk of bleeding) should be performed in cases where:
  1. the etiology remains unknown after initial workup or
  2. it is thought to be secondary to autoimmune hepatitis or malignancy.

LABORATORY TESTS

- Patients with ALF typically have a prolonged prothrombin time (INR >1.5), elevated transaminases, elevated bilirubin, and low platelet count (<150,000).
- Other possible lab findings can include an elevated BUN/creatinine (studies show 30%-50% also have acute kidney injury), hypoglycemia (impairment of gluconeogenesis), hypophosphatemia, hypomagnesemia, hypokalemia, acidosis or alkalosis, elevated LDH, and elevated ammonia.

IMAGING STUDIES

- Abdominal ultrasound with Dopplers should be ordered to evaluate for Budd-Chiari syndrome, cirrhosis, portal hypertension, hepatic congestion, and hepatic steatosis.
- CT or MRI scan of the head should be obtained to ensure no other causes for altered mental status.

BOX A1-5 Investigations in Fulminant Hepatic Failure

Baseline essential investigations
Biochemistry
- Bilirubin, transaminases
- Alkaline phosphatase
- Albumin
- Urea and electrolytes
- Creatinine
- Calcium, phosphate
- Ammonia
- Acid-base, lactate
- Glucose

Hematology
- Full blood count, platelets
- PT, PTT
- Factors V or VII
- Blood group cross-match

Septic screen
Omitting lumbar puncture
- Radiology
- Chest radiograph
- Abdominal ultrasound
- Head CT scan or MRI

Neurophysiology
- Electroencephalogram

Diagnostic investigations
Serum
- Acetaminophen levels
- Cu, ceruloplasmin (>3 yr)
- Autoantibodies
- Immunoglobulins
- Amino acids
- Lactate
- Pyruvate
- Hepatitis A, B, C, E
- EBV, CMV, HSV
- Other viruses

Urine
- Toxic metabolites
- Amino acids, succinylacetone
- Organic acids
- Reducing sugars

CMV, Cytomegalovirus; *EBV,* Epstein-Barr virus; *HSV,* herpes simplex virus; *PT,* prothrombin time; *PTT,* partial thromboplastin time.
From Fuhrman BP, Zimmerman JJ: *Fuhrman and Zimmerman's pediatric critical care,* ed 4, Philadelphia, 2011, Mosby.

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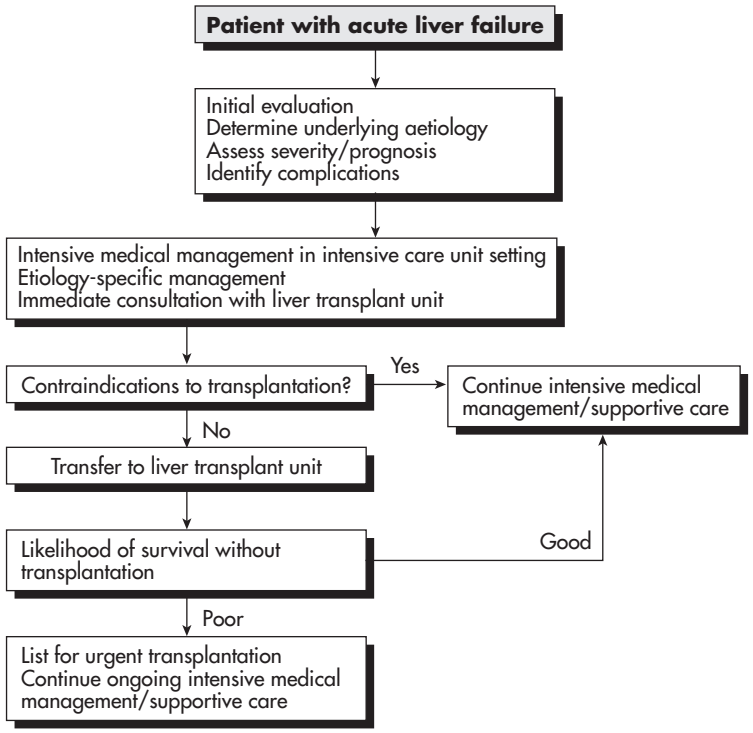

FIGURE A1-46 Management of acute liver failure. (From Tally, NJ; *Gastroenterology and Hepatology,* Philadelphia, 2008, Churchill Livingston.)

Rx TREATMENT (Boxes A1-6 and A1-7)

NONPHARMACOLOGIC THERAPY

- Initial treatment should focus on the patient's mental status.
- A liver specialist should be notified urgently, and arrangements should be made for imminent transfer to a transplant center.
- Patients with suspected acetaminophen toxicity should have LFTs monitored every 12 hr. Otherwise, LFTs can be monitored daily.
- Chemistry panels and PT/INR should be monitored every 8-12 hr.
- Glucose finger sticks should be checked every 6 hr initially to evaluate for hypoglycemia.
- Because of the increased risk of infection, daily urine, sputum, and blood cultures should be checked in the absence of signs or symptoms of infection.
- Patients with Grade I encephalopathy or greater should be admitted to a monitored setting (e.g., intensive care unit [ICU]) given rapidity of mental status deterioration and need for close neurologic monitoring. Sedating medications should be avoided as they may worsen hepatic encephalopathy. If necessary, short-acting medications should be used given decreased hepatic clearance.
- Patients with grade III/IV encephalopathy should be intubated for airway protection, and transfer to a transplant center should be made a priority once the patient is stabilized. Placement of ICP monitoring devices should be considered to evaluate for ICH.
- Hypotension can occur due to decreased oral intake as well as extravasation of fluid into extravascular space. Care must taken to maintain cerebral perfusion pressures (MAP goal is >70 mm Hg and CPP 60-80 mm Hg) in order to optimize neurologic recovery from ALF. Patients can be resuscitated with normal saline; acidotic patients can be resuscitated with ½ normal saline with 75 meq/L sodium bicarbonate.
- Norepinephrine is the initial vasopressor of choice; vasopressin can be added as a second pressor. Persistent hypotension despite fluid resuscitation and pressor support should prompt concern for adrenal insufficiency.
- Nutritional support should be initiated early. A daily intake goal of 60 g of protein is recommended to prevent catabolism of protein stores.
- For acetaminophen ingestions (known or suspected), refer to Acute General Rx.

ACUTE GENERAL Rx

- Correction of coagulopathy should be avoided because it can interfere with assessment of liver function.
- In the setting of life-threatening bleeding, FFP and recombinant factor VIIa can be considered.
- Patient should be placed on stress ulcer prophylaxis given risk of gastrointestinal bleeding.
- Antibiotics should be started immediately if infection is suspected. Sources usually include respiratory, urinary, and blood; there is no evidence for empiric antibiotic treatment.

BOX A1-6 Management of Fulminant Hepatic Failure

No sedation except for procedures
Minimal handling
Enteric precautions until infection ruled out
Monitor:
- Heart and respiratory rate
- Arterial BP, CVP
- Core/toe temperature
- Neurologic observations
- Gastric pH (>5.0)
- Blood glucose (>4 mmol/L)
- Acid-base
- Electrolytes
- PT, PTT

Fluid balance
- 75% maintenance
- Dextrose 10%-50% (provide 6-10 mg/kg/min)
- Sodium (0.5-1 mmol/L)
- Potassium (2-4 mmol/L)

Maintain circulating volume with colloid/FFP
Coagulation support only if required
Drugs
- Vitamin K
- H_2 antagonist
- Antacids
- Lactulose
- *N*-acetylcysteine for acetaminophen toxicity
- Broad-spectrum antibiotics
- Antifungals

Nutrition
- Enteral feeding (1-2 g protein/kg/day)
- PN if ventilated

BP, Blood pressure; *CVP,* central venous pressure; *FFP,* fresh frozen plasma; *PN,* parenteral nutrition; *PT,* prothrombin time; *PTT,* partial thromboplastin time.
From Fuhrman BP, Zimmerman JJ: *Fuhrman and Zimmerman's pediatric critical care,* ed 4, Philadelphia, 2011, Mosby.

- If acetaminophen is the known or suspected cause, an IV acetylcysteine protocol must be initiated (there are few studies on oral *N*-acetylcysteine [NAC] treatment). NAC is not harmful and dramatically alters the course in acetaminophen toxicity, so there should be a low threshold to start it, particularly in young patients or those with no known cause of ALF.

The 20-hr protocol is:

1. Initial loading dose of 150 mg/kg IV given over 60 min followed by
2. 12.5 mg/kg IV/hr over 4 hr followed by
3. 6.25 mg/kg IV/hr for 16 hr

A repeat acetaminophen level and ALT should be checked at hour 18 of treatment. If either acetaminophen level or ALT is elevated, the 16-hour portion of treatment (6.25 mg/kg) should be extended and another ALT, INR, or acetaminophen level should be checked every 12 hr. The acetylcysteine can be stopped once the acetaminophen level is undetectable, INR <2, or ALT is shown to be either normal or decreasing.

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BOX A1-7 Hepatic Replacement Therapeutic Options Available to Patients with Fulminant Hepatic Failure

Liver Transplantation
Cadaveric transplantation
Whole liver
Reduced-size liver
Split liver
Auxiliary partial liver
Orthotopic position
Heterotopic position
Auxiliary whole liver
Heterotopic position
Living-related transplantation
Left lateral segment
Left lobe
Extended left lobe
Right lobe

Artificial Liver Assist Devices
Non–cell-based systems
Charcoal hemoperfusion
High-volume plasmapheresis
Continuous high-frequency hemodiafiltration
Molecular adsorbent recirculating system (MARS)
Cell-based systems (bioartificial liver assist devices)
Primary porcine hepatocytes
Human hepatoblastoma cells
Extracorporeal liver assist device (ELAD)

Hepatocyte Transplantation

From Vincent JL, Abraham E, Moore FA, et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

TABLE A1-21 King's College Hospital Criteria for Liver Transplantation in Acute Liver Failure

Acetaminophen-Induced Acute Liver Failure	Non–Acetaminophen Induced Acute Liver Failure
Arterial pH <7.3 (irrespective of grade of encephalopathy) *OR* Grade III or IV encephalopathy *and* Prothrombin time >100 sec *and* Serum creatinine >3.4 mg/dL	Prothrombin time >100 seconds (irrespective of grade of encephalopathy *OR* Any of three of the following variables (irrespective of grade of encephalopathy): 1. Age <10 yr or >40 yr 2. Etiology: non–A hepatitis, non–B hepatitis, halothane hepatitis, idiosyncratic drug reactions 3. Duration of jaundice before onset of encephalopathy >7 days 4. Prothrombin time >50 sec 5. Serum bilirubin >18 mg/dL

DISPOSITION

- Because of the potential for rapid deterioration of mental status and progression to multiorgan dysfunction, these patients should be managed in an ICU.
- Given the tenuous state, potential for rapid deterioration, and overall poor prognosis of these patients, they should be transferred to a liver transplant center once stabilized. A liver specialist should be consulted upon presentation. The King's College Criteria remains the most useful assessment tool to assess need for liver transplantation (see Table A1-21).
- Overall mortality from ALF is 30%-40%.
- Transplant-free survival in ALF in the setting of acetaminophen, hepatitis A, shock liver, and pregnancy-related disease is >50%; for all other causes of ALF, transplant-free survival is <25%.

PEARLS & CONSIDERATIONS

- ALF is severe hepatic injury with INR >1.5 and hepatic encephalopathy from a disease process that started <26 wk before presentation in a patient with no prior history of liver disease.
- Close to ½ of acute liver is due to drug ingestion, usually acetaminophen.
- Rapidity of deterioration referral must be made as soon as possible to a liver transplant center.
- There should be a low threshold to start NAC.
- Do not correct coagulopathy unless life-threatening bleeding occurs or it is recommended by the liver transplant hepatologist.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Acetaminophen Poisoning (Related Key Topic)
Ascites (Related Key Topic)
Encephalopathy (Related Key Topic)
Hepatopulmonary Syndrome (Related Key Topic)
Hepatorenal Syndrome (Related Key Topic)

AUTHORS: **PRANITH PERERA, M.D.**, and **TALIA ZENLEA, M.D.**

SUGGESTED READINGS

American Association for the Study of Liver Diseases. Practice Guidelines for Acute Liver Failure. Available at http://www.aasld.org/practiceguidelines/Documents/AcuteLiverFailureUpdate2011.pdf.

Bernal W, Auzinger G, Dhawan A, et al.: Acute liver failure, *Lancet* 376:190–201, 2010.

Fontana R.. Acute liver failure. In: Feldman M, Friedman L, Brandt L, editors: Sleisenger and Fordtran's gastrointestinal and liver disease, ed 8, Saunders: Philadelphia, pp. 1993–2006.

Larson AM, Polson J, Fontana RJ, et al.: Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study, *Hepatology* 42:1364–1372, 2005.

Lee WM: Etiologies of acute liver failure, *Semin Liver Dis* 28:142–152, 2008.

Lee WM, Squires Jr RH, Nyberg SL, et al.: Acute liver failure: summary of a workshop, *Hepatology* 47:1401–1415, 2008.

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BASIC INFORMATION

DEFINITION

Acute lymphoblastic leukemia (ALL) is a malignancy of B or T lymphoblasts characterized by uncontrolled proliferation of abnormal, immature lymphocytes and their progenitors, ultimately replacing normal bone marrow elements.

SYNONYMS

Lymphoid leukemia
ALL

ICD-9CM CODES
204.0 Acute lymphoblastic leukemia
ICD-10CM CODES
C91.00 Acute lymphoblastic leukemia not having achieved remission

EPIDEMIOLOGY & DEMOGRAPHICS

- ALL is primarily a disease of children (peak incidence from ages 2 to 10 yr).
- It is diagnosed in 3000 to 4000 persons in the United States each year; two thirds are children. It is the most common malignancy of childhood.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Skin pallor, purpura, or easy bruising.
- Lymphadenopathy or hepatosplenomegaly.
- Fever, bone pain, oliguria, weakness, weight loss, mental status changes.
- Table A1-22 summarizes the clinical presentation of acute lymphoblastic leukemia.

ETIOLOGY

- Unknown; increased risk in patients with a previous use of antineoplastic agents (e.g., chemotherapy of non-Hodgkin's lymphoma, Hodgkin's disease, ovarian cancer, myeloma).
- Environmental factors (e.g., ionizing radiation), toxins (e.g., benzene).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute myeloid leukemia (AML): the morphologic, cytochemical, and biochemical characteristics helpful in distinguishing ALL from AML are described in Table A1-23.
- Lymphoblastic lymphoma.
- Aplastic anemia.
- Infectious mononucleosis.
- Leukemoid reaction to infection.
- Multiple myeloma.

WORKUP

- Laboratory evaluation.
- Bone marrow examination (with biopsy, cytochemistry, immunophenotyping, and cytogenetics) (Fig. EA1-47).
- Lumbar puncture and imaging studies.

LABORATORY TESTS

- Complete blood count reveals normochromic, normocytic anemia, thrombocytopenia.
- Peripheral smear will reveal lymphoblasts.
- Initial blood work should also include blood urea nitrogen, creatinine, serum electrolytes, uric acid, and lactate dehydrogenase.
- Special diagnostic tests include immunophenotyping, cytogenetics, and cytochemistry.

IMAGING STUDIES

- Chest x-ray to evaluate for the presence of mediastinal mass.
- CT scan or ultrasound of abdomen/pelvis to assess splenomegaly or leukemic infiltration of abdominal organs.

TREATMENT

ACUTE GENERAL Rx

Table A1-24 summarizes the preferred approach to the treatment of adult ALL patients. For younger adults, induction therapy usually consists of an anthracycline, vincristine, L-asparaginase, and a corticosteroid.

DISPOSITION

- Prognosis is generally poorer in adult disease compared with childhood disease (40% adult cure rate versus 80% cure rate in children).

TABLE A1-22 Clinical Presentation of Acute Lymphoblastic Leukemia

Symptoms and Signs	Etiology	Management
Fever	Disease or infection	Always conduct fever workup and provide broad antimicrobial coverage until infectious etiology is ruled out
Fatigue, pallor	Anemia (ALL infiltrating BM)	RBC transfusion (slow if anemia is severe; avoid in hyperleukocytosis)
Petechiae, bruising, bleeding	Thrombocytopenia (ALL infiltrating BM)	Transfuse with platelets
Pain	Leukemia infiltrating bones or joints or expanding BM cavity	Establish diagnosis and start chemotherapy
Respiratory distress, superior vena cava syndrome	Mediastinal mass	Avoid sedation in the presence of tracheal compression; establish diagnosis as soon as possible and start chemotherapy

ALL, Acute lymphoblastic leukemia; *BM,* bone marrow; *RBC,* red blood cell. From Hoffman R: *Hematology, basic principles and practice*, 6th ed, Philadelphia, 2013, Saunders.

TABLE A1-23 Morphologic, Cytochemical, and Biochemical Characteristics Helpful in Distinguishing Acute Lymphoblastic Leukemia from Acute Myelocytic Leukemia

Morphologic Features	ALL	AML
Nuclear/cytoplasmic ratio	High	Low
Nuclear chromatin	Clumped	Spongy
Nucleoli	0-2	2-5
Granules	–	+
Auer rods	–	+/–
Cytoplasm	Blue	Blue-gray
Cytochemical Reaction		
Peroxidase	–	+
Sudan black B	–	+
Periodic acid–Schiff	+/–	–
Naphthyl AS-D chloroacetate esterase	–	+/–
α-Naphthyl acetate esterase	–	+/–
α-Naphthyl butyrate esterase	–	–
Terminal deoxynucleotidyl transferase	+*	–

The table provides information on characteristics that may be useful in differentiating acute lymphoblastic leukemia (ALL) from acute myelocytic leukemia (AML) (see text for details). Wide variation in morphology is encountered in both disease categories. Diagnostic evaluation should include more refined classification of disease according to FAB subtype.
*Terminal deoxynucleotidyl transferase is usually negative in FAB L3 ALL.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

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- Five-year leukemia-free survival is <40%.
- Prognostic factors in acute lymphoblastic leukemia are described in Tables A1-25 and A1-26.

REFERRAL

Referral to a hematologist is indicated in all cases of ALL.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Acute Lymphocytic Leukemia (ALL) (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

TABLE A1-24 Preferred Approach to the Treatment of Adult Acute Lymphocytic Leukemia Patients

	Low-Risk ALL	High-Risk ALL	Very High-Risk ALL	Mature B-ALL
Definition	*B-lineage* WBC <30,000/mL Time to CR <4 wk No Pro-B/ t(4;11) *T-lineage* Thy ALL Molecular CR	*B-lineage* WBC >30,000/mL Time to CR >4 wk Pro-B/ t(4;11) *T-lineage* Early T, mature T No molecular CR	Ph/BCR-ABL positive	
Multidrug-induction	Yes	Yes	Yes + imatinib	Short intensive cycles including HDM, fractionated C, HDAC, and other drugs Rituximab
CNS prophylaxis*	Yes	Yes	Yes	Yes
Consolidation (also other combinations)	Alternating cycles, e.g., HDM, HDAC, asparaginase reinduction	One cycle	One cycle + imatinib	6 cycles
SCT in CR1	None	Allogeneic SCT (if matched related or unrelated donor) Autologous SCT After additional (if no donor and negative MRD, consolidation)		None
Maintenance	6-MP/M + intensification for 2-2½ yr		Imatinib	None

AC, Cytosine arabinoside; *ALL,* acute lymphocytic leukemia; *CR,* complete remission; *HDM,* high-dose methotrexate; *MRD,* minimal residual disease; *SCT,* stem cell transplantation; *Thy ALL,* thymic ALL.
*Intrathecal therapy with M or triple combination (M, AC, steroid) continued during maintenance therapy; additional CNS irradiation and/or high-dose chemotherapy according to subgroup.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

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TABLE A1-25 Prognostic Factors in Acute Lymphoblastic Leukemia

Factor	Prognosis	Clinical Application
Age		
<1 yr	MLL+ (70%-80% infants): Poor outcome	MLL−: Do well on standard ALL therapy
	MLL−: Same outcome as for older children	Potential role for FLT3 inhibitor for MLL+
1–9 yr	Standard risk	ALL biology may change risk
>9 yr	Higher risk	ALL biology may change risk
White Blood Cell Count		
$<50 \times 10^9$/L	Standard risk	ALL biology may change risk
$\geq 50 \times 10^9$/Lww	Higher risk	ALL biology may change risk
Central Nervous System		
CNS3	Higher risk	Therapy intensification
CNS2	Higher risk of CNS relapse	CNS-directed therapy intensification Traumatic lumbar puncture with blasts
Testicular	Higher risk	Therapy intensification
Immunophenotype		
T cell	Higher risk	Poor outcome abolished with current therapy
Pre–B cell (clgM+)	Higher risk	Poor outcome abolished with current therapy
Early pre–B cell	Standard risk	Genetics may change risk
ETP	Dismal prognosis	Ongoing studies exploring effective therapies
Ploidy		
>50 (DI >1.16)	Low risk	Good response to antimetabolites
<44	Higher risk	Therapy intensification
Genetic Alterations		
t(9;22)/*BCR-ABL1*	Higher risk	BCR-ABL inhibitors
t(4;11)/*MLL-AF4*	Higher risk	Potential role for FLT3 inhibitors and hypomethylating agents
t(1;19)/*E2A-PBX1*	Higher risk	Poor outcome cancelled on current therapy
t(12;21)/*ETV6-RUNX1*	Low risk	
IKZF1	Poor prognosis. Present in 80% BCR-ABL1+ and also in BCR-ABL1 like	Potential role for TKI, JAK inhibitors
NUP214-ABL1	High risk	Potential benefits from TKI
CRLF2	In 1/3 BCR-ABL1–like, associated with Hispanic or Latino ethnicity and poor outcome	Potential role for JAK inhibitors
CREBBP	Associated with drug resistance and relapse	Potential benefit from histone deacetylase inhibitors
Minimal Residual Disease		
Day 15 <0.01%	Excellent outcome	No benefit from second delayed intensification
Slow early responders	Higher MRD = Higher risk of relapse	Benefit from augmented delayed intensification
EOI >1%	Dismal prognosis	HSCT in first CR
4 mo >0.1%	Dismal outcome	HSCT in first CR

CNS, Central nervous system; *CR,* complete remission; *DI,* DNA index; *EOI,* end of induction; *HSCT,* hematopoietic stem cell transplantation; *MRD,* minimal residual disease; *JAK,* Janus kinase; *TKI,* tyrosine kinase inhibitor.
From Hoffman R: *Hematology, basic principles and practice*, 6th ed, Philadelphia, 2013, Saunders.

TABLE A1-26 Markers for Poor Prognosis in Adult Acute Lymphoblastic Leukemia

Established Risk Factors	
Age	>60 years
Presenting WBC count	>30,000/μL (B-cell ALL); >100,000/μL (T-cell AL)
Immunophenotype	Pro–B cell; early T-cell
Cytogenetics	t(4;11)(q21;q23) and other *MLL* rearrangements
	t(9;22)(q34;q11.2)—Philadelphia chromosome
	Hypodiploidy (<44 chromosomes)
	Complex (>five abnormalities)
Therapy response	Time to complete remission >4 weeks
MRD	≥0.01% at 3-6 months after initiation of therapy*
Emerging Risk Factors	
Immunophenotype	CD20
Molecular	*BAALC*
	IKAROS
	FUS
	ERG
	JAK
	CRLF2

ALL, Acute lymphoblastic leukemia; *MRD,* minimal residual disease; *WBC,* white blood cell.
*Different studies have used different time points for MRD assessment.
From Hoffman R: *Hematology, basic principles and practice*, 6th ed, Philadelphia, 2013, Saunders.

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SUGGESTED READINGS

Mullighan CG et al.: Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia, *N Engl J Med* 360:470–480, 2009.

Pui CH et al.: Treating childhood acute lymphoblastic leukemia without cranial irradiation, *N Engl J Med* 360:2730–2741, 2009.

Schrappe M et al.: Outcomes after induction failure in childhood acute lymphoblastic leukemia, *N Engl J Med* 366:1371–1381, 2012.

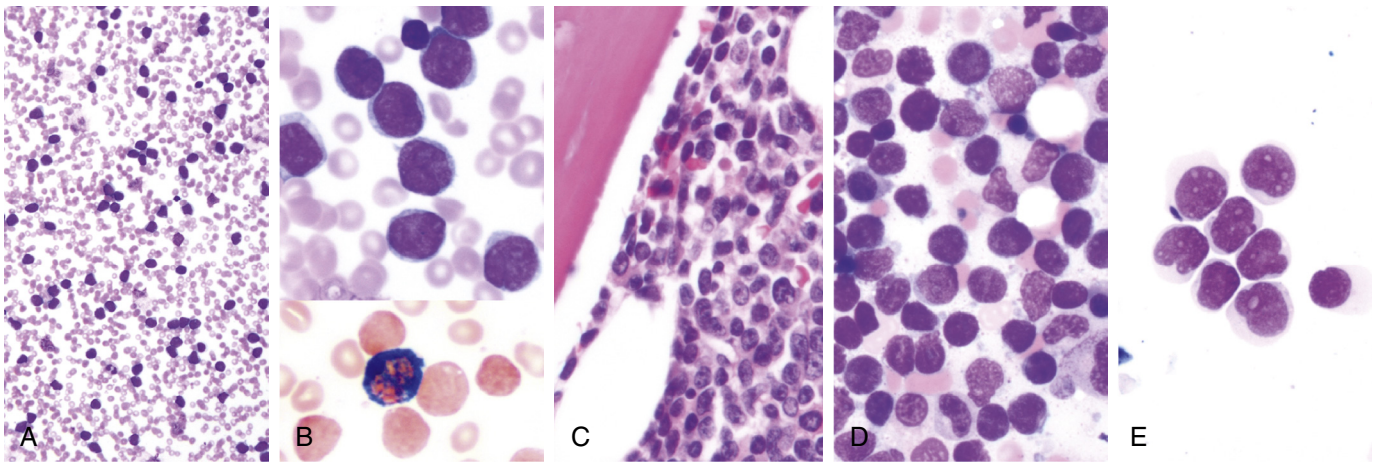

FIGURE EA1-47 Acute lymphoblastic leukemia: peripheral blood, bone marrow biopsy and aspirate, and cerebral spinal fluid. The illustration is from a 37-year-old male who presented with a WBC of 170,000/L and over 90% blasts with lymphoid morphology (**A** and **B,** *top*). An initial myeloperoxidase reaction (**B,** bottom) showed the blasts to be negative (positive cell is a segmented neutrophil that serves as an internal control). The bone marrow was packed with blasts as seen on the biopsy and aspirated material (**C** and **D**). The blasts were immunophenotyped by flow cytometry and were shown to be precursor-B lymphoblasts with the following phenotype: CD34+, HLA–DR+, TdT+, CD19+, CDl0+, cyCD79A+, cyIgM–, and slg–. Cytogenetic studies illustrated the t(9;22), and molecular analysis revealed the p190 *BCR/ABL*. A spinal tap showed a WBC count of 120/L with an RBC count of 37/L. The differential showed 80% blasts. The morphology of the blasts on the cytospin of the cerebrospinal fluid (**E**) is somewhat altered by the preparation. Note the absence of significant red blood cells in the specimen. Given the high number of blasts in the peripheral blood, a more traumatic tap would have made it difficult to distinguish between central nervous system disease and contamination of the cerebrospinal fluid specimen by blood. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

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Acute Myelogenous Leukemia PTG

BASIC INFORMATION

DEFINITION

Acute myelogenous leukemia (AML) is a malignancy of myeloid progenitor cells. It is characterized by uncontrolled proliferation of primitive myeloid cells (blasts), ultimately replacing normal bone marrow elements and frequently resulting in hematopoietic insufficiency (granulocytopenia, thrombocytopenia, or anemia) with or without leukocytosis.

SYNONYMS

Acute nonlymphoblastic leukemia (ANLL)
Acute nonlymphocytic leukemia
Acute myeloid leukemia
AML

ICD-9CM CODES
205.0 Acute myelogenous leukemia
ICD-10CM CODES
C92.00 Acute myeloblastic leukemia, not having achieved remission

EPIDEMIOLOGY & DEMOGRAPHICS

- AML usually affects adults (most patients are 30 to 60 yr; median age at presentation is 50 yr).
- Annual incidence is 2 to 4 cases/100,000 persons.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Patients generally come to medical attention because of the effects of the cytopenias:

- Anemia manifests with weakness or fatigue.
- Thrombocytopenia can manifest with bleeding, petechiae, and ecchymosis.
- Neutropenia can result in infections and fever.
- Physical examination may reveal skin pallor, bruises, petechiae; abdominal examination may reveal hepatosplenomegaly; peripheral lymphadenopathy may also be present.
- Hyperleukocytosis can lead to symptoms of leukostasis, such as ocular and cerebrovascular dysfunction or bleeding.

TABLE A1-27 Congenital Disorders or Acquired Factors Predisposing to Acute Myeloid Leukemia

Genetic Factors
Down syndrome
Fanconi anemia
Bloom syndrome
Neurofibromatosis type I
Klinefelter syndrome
Turner syndrome
Congenital Bone Marrow Failure Syndromes
Kostmann syndrome
Diamond-Blackfan anemia
Drugs
Benzene
Alkylating agents
Epipodophyllotoxins
Ionizing radiation
Myelodysplastic syndromes

From Hoffman R et al: *Hematology: basic principles and practice*, ed 6, Philadelphia, 2013, Elsevier.

ETIOLOGY

Risk factors are previous use of antineoplastic agents, chromosomal abnormalities, ionizing radiation, toxins, immunodeficiency states, and chronic myeloproliferative disorders. Congenital disorders or acquired factors predisposing to AML are described in Table A1-27.

DIAGNOSIS

A diagnostic algorithm for acute myeloid leukemia is illustrated in Box A1-8 and Fig. A1-48.

DIFFERENTIAL DIAGNOSIS

- Acute lymphocytic leukemia
- Leukemoid reaction
- Myelodysplastic syndrome
- Infiltrative diseases of the bone marrow
- Epstein-Barr virus, other viral infection

LABORATORY TESTS

- Complete blood count reveals anemia and thrombocytopenia. Peripheral white blood cell count varies from <5000/mm^3 to >100,000/mm^3.
- Additional laboratory findings may include elevated lactate dehydrogenase and uric acid levels, decreased fibrinogen, and increased fibrin degradation product as a result of disseminated intravascular coagulation (DIC).
- Cytogenetic abnormalities are common (chromosome 8 is most frequently involved in AML). Table A1-28 describes gene mutations in patients with AML. DNMT3A mutations are highly recurrent in patients with de novo AML with an intermediate-risk cytogenetic profile

BOX A1-8 Stepwise Algorithm for Diagnosis and Classification of Acute Myelogenous Leukemia Using Cytomorphology, Cytochemistry, Immunophenotyping, Cytogenetics, and Molecular Cytogenetics

The criteria are based on Wright-Giemsa–stained blood and marrow smears and biopsy. The percentage of blast cells separates acute myeloid leukemia (AML) from myelodysplastic syndrome (MDS). The World Health Organization (WHO) classification defines AML as greater than 20% blasts in the marrow or blood. The next step is to define the blast population by immunophenotyping and/or immunohistochemistry. The initial evaluation separates AML from ALL. A history of exposure to prior cytotoxic chemotherapy or agents associated with AML defines the leukemia as *therapy-related acute myeloid leukemia* (t-AML). The WHO recognizes the unique clinical and biologic features of the therapy-related leukemias (t-AML). This subtype results from prior exposure to cytotoxic chemotherapy and/or radiation therapy. A majority of patients will have clonal cytogenetic abnormalities and now account for more than 40% of all patients with AML. The WHO recognizes two types of t-AML based on the type of prior exposure or treatment: alkylating agent–related AML and topoisomerase II inhibitor–related AML. The WHO classification defines major subgroups of AML that manifest recurring cytogenetic abnormalities. As a group, these AMLs have chromosomal translocations that result in the production of chimeric proteins, which are pivotal in the leukemogenic process. The genetic abnormalities define a specific biology, clinical course, and prognosis and therefore it is important to classify them separately. In this group of patients, the diagnosis is defined by the cytogenetic abnormality independent of the percentage of blasts. There are four recurrent translocations in this group. The diagnosis is defined by the cytogenetic abnormalities and is not dependent on the number of blasts: (a) AML with t(8;21)(q22;q22), (AML1/ETO) (RUNX/CBFA2T1); (b) AML with abnormal bone marrow eosinophils and inv^{16}(p13;q22) or t(16;16)(p13;q22), (CBFB/MYH11); (c) acute promyelocytic leukemia: AML with t(15;17)(q22;q21)(PML/RARA) or t(11;17)(q23;q12) (PLZF/RARA) or t(5;17)(q23;q12)(NPM/RARA), or t(11;17)(q13;q12) (NuMA/RARA); and (d) AML with 11q23 (MLL) abnormalities. If multilineage dysplasia is present, then the leukemia is classified as *acute leukemia with multilineage dysplasia*.

AML with multilineage dysplasia is characterized by the presence of 20% or more blasts in the marrow and dysplasia in at least 50% of the cells of at least two of the three main hemopoietic lines. The leukemia may occur de novo or after a preceding myelodysplastic, myeloproliferative, or overlap myelodysplastic/myeloproliferative syndrome unrelated to prior exposure to chemotherapy. If such a syndrome preceded the development of acute leukemia, the AML is best designated as AML "evolving from a myelodysplastic syndrome." When a leukemia fails to satisfy the cytogenetic, morphologic, or clinical criteria for the newly defined subgroups, it is classified as AML not otherwise categorized. The *not otherwise categorized* designation essentially applies the original FAB classification with some modifications, namely, acute promyelocytic leukemia (M3) is no longer included; a pure erythroleukemia has been distinguished from erythroleukemia, acute erythroid/myeloid type; and acute basophilic leukemia (very rare) has been added, as is a rare entity termed acute panmyelosis with myelofibrosis and the solid tumor myeloid sarcoma.

CD, Cluster designation; *MPO,* myeloperoxidase; *NEC,* nonerythroid cells; *NSE,* nonspecific esterase; *PAS,* periodic acid–Schiff; *SBB,* Sudan black B; *TdT,* terminal deoxynucleotidyl transferase; *TNC,* total nucleated cells.

From Hoffman R et al: *Hematology, basic principles and practice*, ed 5, Philadelphia, 2009, Churchill Livingstone.

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and are independently associated with a poor outcome.

- The distinction between acute lymphoblastic leukemia (ALL) and AML and the classification of the various subtypes are partly based on the following factors:
  1. Cell morphology: myeloblasts reveal abundant cytoplasm; cytoplasmic granules are often present (Auer rods).
  2. Histochemical stains:
     1. Peroxidase and Sudan black stains are negative in ALL.
     2. Chloroacetate esterase: a pink cytoplasmic reaction identifies granulocytes; useful to distinguish granulocytes from monocytes in patients with AML.
- AML is diagnosed by the presence of at least 30% blast cells and positive peroxidase or Sudan black histochemical stain in the bone marrow aspirate.
- The French, American, British (FAB) Cooperative Study Group has classified AML into seven categories (M1 to M7) based on the type and percentage of immature cells. The classification of acute myeloid leukemia according to the revised World Health Organization classification (2008) is described in Table A1-29. A summary of diagnostic features of AML in the FAB classification is outlined in Table A1-30.
- Cytogenetic risk categories in AML are described in Table A1-31. Bone marrow findings are described in Fig. EA1-49.

TABLE A1-28 Gene Mutations in Patients with Acute Myelogenous Leukemia, and Normal Karyotype

Gene Mutation	Frequency (%)	Prognosis
NPM	45-63	Favorable
FLT3	23-33	Adverse
MLL	5-30	Adverse
C/EBP	8-19	Favorable

From Hoffman R et al: *Hematology: basic principles and practice*, ed 6, Philadelphia, 2013, Elsevier.

IMAGING STUDIES

- Chest x-ray is useful to evaluate for the presence of mediastinal masses.
- CT scan of the abdomen may reveal hepatosplenomegaly or leukemic involvement of other organs.

Rx TREATMENT

ACUTE GENERAL Rx

- Intensive induction chemotherapy to destroy a significant number of leukemic cells and achieve remission usually consists of cytarabine and daunorubicin. It is a 7 + 3 regimen consisting of 7 days of continuous IV infusion of cytarabine and 3 days of daunorubicin. With this regimen, the chance of obtaining a complete remission is 65% to 70% with significantly lower rates in older patients (.56 yr old). All-trans retinoic acid is effective for the induction of remission of AML M3 subtype (acute promyelocytic leukemia).

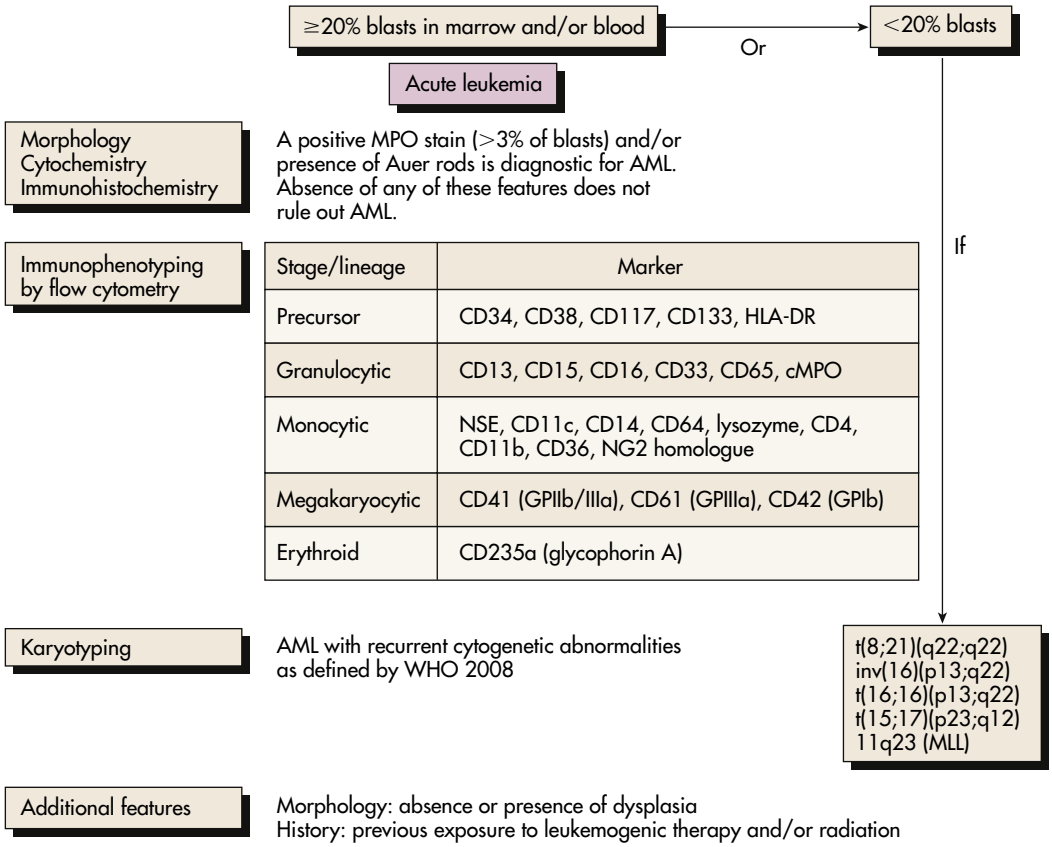

FIGURE A1-48 Diagnostic algorithm of acute myeloid leukemia (AML). The diagnostic workup consists of a morphologic assessment (including application of stains), immunophenotyping by flow cytometry, and assessment of the karyotype. Whereas morphologic assessment by itself is often not specific enough (including use of special stains), flow cytometry is nowadays always required to confirm the lineage assignment (myeloid versus lymphoid) and stage of differentiation. In more than 95% of cases, a lineage can thus be assigned to the blast phenotype. In only a few cases, no lineage-specific antigens are expressed (acute undifferentiated leukemia) or antigens of more than one lineage are present (mixed-phenotype acute leukemia). In the latter scenario, antigens of several lineages can be found on one blast population (biphenotypic) or several types of blasts, each expressing a more or less lineage-specific set of antigens (bilineal), can be detected. Karyotyping may add additional diagnostic information in some of those morphologically ambiguous situations but is far more useful prognostically in most other patients. The combined assessment applying the aforementioned methods, including information from the patient's prior history (exposure to previous chemotherapy agents and/or radiation therapy), forms the basis for the classification of AML, according to the World Health Organization system as per its most recent revision in 2008. *MPO,* Myeloperoxidase; *WHO,* World Health Organization. (From Hoffman R: *Hematology, basic principles and practice*, 6th ed, Philadelphia, 2013, Saunders, 2013.)

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TABLE A1-29 Classification of Acute Myeloid Leukemia According to the Revised World Health Organization Classification (2008)

Category	Subtype/Definition
AML with recurrent cytogenetic abnormalities	t(8;21)(q22;q22); RUNX1-RUNX1T1*
	inv(16)(p13.1q22); CBFB-MYH11*
	t(16;16)(p13.1q22); CBFB-MYH11*
	t(15;17)(q22;q12); PML-RARA*
	t(9;11)(p22;q23); MLLT3-MLL
	t(6;9)(p23;q34); DEK-Nup214
	inv(3)(q21q26.2); RPN1-EVI1
	t(3;3)(q21;q26.2); RPN1-EVI1
	t(1;22)(p13q13); RBM15-MKL1
AML with MDS-related changes	Morphologic features of MDS, or
	Prior history of MDS or MDS/MPN, or
	MDS-related karyotype, and
	None of the recurrent genetic abnormalities above
Therapy-related myeloid neoplasms	Late complications of cytotoxic chemotherapy (alkylating agents, topoisomerase II inhibitors) and/or ionizing radiation therapy†
AML, not otherwise specified	AML with minimal differentiation
	AML without maturation
	AML with maturation
	Acute myelomonocytic leukemia
	Acute monoblastic/monocytic leukemia
	Acute erythroid leukemia
	Acute megakaryoblastic leukemia
	Acute basophilic leukemia
	Acute panmyelosis with myelofibrosis
Myeloid sarcoma	
Myeloid proliferations related to Down syndrome	Transient abnormal myelopoiesis
	Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm	
Acute leukemia of ambiguous lineage	Acute undifferentiated leukemia
	Mixed-phenotype acute leukemia with t(9;22)(q34;q11.2); BCR-ABL1
	t(v;11q23); MLL rearranged
	Mixed-phenotype acute leukemia, B/myeloid, NOS
	Mixed-phenotype acute leukemia, T/myeloid, NOS
Provisional entities	AML with mutated NPM1
	AML with mutated CEBPA
	NK-cell lymphoblastic leukemia/lymphoma

AML, Acute myeloid leukemia; *MDS,* myelodysplastic syndrome; *MPN,* myeloproliferative neoplasm; *NK,* natural killer.
*Diagnosis of AML regardless of percentage of blasts.
†Excluded are patients with AML who have transformed from MPN.
From Hoffman R: *Hematology, basic principles and practice*, 6th ed, Philadelphia, 2013, Saunders, 2013.

- High-dose cytarabine (ARA-C) (HiDAC) can be used in patients with refractory or relapsed AML. It usually takes 28 to 32 days from the start of therapy to achieve remission. The duration of remission is variable; the median duration of remission in an adult with AML is 1 yr.
- Emergency treatment consisting of one or more of the following is indicated in patients with intracerebral leukostasis:
  1. Cranial irradiation
  2. Leukapheresis
  3. Oral hydroxyurea
- Urate nephropathy can be prevented by vigorous hydration and lowering uric acid level with allopurinol and urine alkalinization with acetazolamide.
- Infections must be aggressively treated with broad-spectrum antibiotics.
- Correct significant thrombocytopenia with platelet transfusions.
- Bleeding from DIC is treated with heparin and replacement of clotting factors.
- Postremission therapy following complete remission with induction chemotherapy may include either allogeneic bone marrow transplant (younger patients with donor match) or consolidation chemotherapy.
- Consolidation therapy consists of an aggressive course of chemotherapy with or without radiation shortly after complete remission has been obtained; its purpose is to prolong the remission period or cure. Complications of consolidation therapy are usually attributable to severe bone marrow suppression (anemia, thrombocytopenia, granulocytopenia).
- Goal of therapy is to maintain a state of remission. A postinduction course of high-dose cytarabine can provide equivalent disease-free survival and somewhat better overall survival than autologous marrow transplantation in adults.
- Autologous bone marrow transplantation is indicated in patients <55 yr without a sibling donor. Allogeneic bone marrow transplantation is generally available to <20% of patients; it is usually performed only in patients <40 yr because of higher incidence of graft-versus-host disease with advancing age.

DISPOSITION

- Remission can be achieved in nearly 80% of patients <55 yr. Remission rates are highest in children. Patient characteristics relating to duration of remission are described in Table A1-32.
- Allogeneic stem cell transplantation (SCT) after myoablative conditioning is a curative option in younger patients with AML in first complete remission (CR1). However, concerns related to toxicity limit its use. Cure for allogeneic bone marrow transplantation approaches 60%; cure rates with autologous transplantation are lower. Compared with nonallogeneic SCT therapies, allogeneic SCT has significant relapse-free survival (RFS) and overall survival benefit for intermediate- and poor-risk AML but not for good-risk AML in first complete remission.
- Favorable cytogenics are inv (16) (p13;q22) and t(8;21), t(15;17). Prognostic models in older patients with acute myeloid leukemia are described in Table A1-33.
- High expression of an LSC (leukemic stem cell) gene signature is independently associated with adverse outcomes with AML.

PEARLS & CONSIDERATIONS

- The major complication of chemotherapy is profound marrow depression with pancytopenia lasting 3 to 4 wk. Treatment is aimed at red blood cell and platelet replacement and aggressive monitoring and treatment of suspected infections.
- Low doses of arsenic trioxide can induce complete remission in patients with acute promyelocytic leukemia.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Acute Myelogenous Leukemia (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

http://internalmedicinebook.com/

TABLE A1-30 Summary of Diagnostic Features of Acute Myeloid Leukemia in the FAB Classification

FAB Subtype (%)	Diagnostic Features
AML-M0 (3%-5%)	≥30% blasts; >3% blasts reactive to MPO, SBB, or NSE; immunophenotyping $CD33^+$, $CD13^+$, may be $CD34^+$, TdT^+
AML-M1 (15%-20%)	≥30% blasts; ≥3% blasts reactive to MPO or SBB; <10% of marrow nucleated cells are promyelocytes or more mature neutrophils
AML-M2 (25%-30%)	≥30% blasts; ≥3% blasts reactive for MPO or SBB; ≥10% of marrow nucleated cells are promyelocytes or more mature neutrophils; t(8:21) chromosome abnormality
AML-M3 (10%-15%)	≥30% blasts and abnormal promyelocytes; intense MPO and SBB reactivity; promyelocytes and blasts with multiple Auer rods (faggot cells); t(15:17) cytogenetic abnormality
AML-M4 (20%-30%)	≥30% myeloblasts, monoblasts, and promonocytes; ≥20% monocytic cells in marrow; $\leq 5 \times 10^9$/L monocytic cells in blood: ≥20% neutrophils and precursors in marrow; monocytic cells reactive for NSE; abnormal eosinophils in M4 with associated inv(16) chromosome abnormality
AML-M5a (2%-7%)	≥80% monocytic cells; monoblasts ≥80% of monocytic cells; monoblasts and promonocytes NSE positive; monoblasts usually MPO and SBB negative
AML-M5b (2%-5%)	≥80% monocytic cells; monoblasts ≥80% of monocytic cells; promonocytes predominate; monoblasts and promonocytes NSE positive; promonocytes may have scattered MPO- and SBB-positive granules
AML-M6 (3%-5%)	≥50% erythroid precursors: ≥30% of nonerythroid precursors are myeloblasts; Auer rods may be present in myeloblasts; dysplastic erythroid precursors frequently are PAS positive
AML-M7 (3%-5%)	≥30% blasts; ≥50% cells megakaryoblasts by morphology or electron microscopy; immunophenotyping $CD41^+$, $CD61^+$

AML, Acute myeloid leukemia; *CD,* cluster designation; *FAB,* French-American-British; *MPO,* myeloperoxidase; *NSE,* nonspecific esterase; *PAS,* periodic acid–Schiff; *SBB,* Sudan black B; *TdT,* terminal deoxynucleotidyl transferase.
% of all AML.
From Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

TABLE A1-31 Cytogenetic Risk Categories in Acute Myelogenous Leukemia

Category	Abnormality
Favorable	t(8;21),* t(15;17), inv(16) with or without other abnormalities
Intermediate	Normal, +6, +8, +21, +22 –Y, del(9q)
Unfavorable	–5/del(5q), –7/del(7q), abn(3q) t(9;22),t(6;9), abn(11q), 20q or 21q, abn(17p), complex karyotype

*Without deletion 9q or complex karyotype.
From Hoffman R et al: *Hematology: basic principles and practice*, ed 5, Philadelphia, 2009, Churchill Livingstone.

TABLE A1-32 Patient Characteristics Relating to Duration of Remission

Characteristics	Favorable Value
Cytogenetics	t(15;17), t(8;21), inv(16)
Leukocyte count	$<100{,}000/mL^{-1}$
Secondary acute myeloid leukemia	Not present
FAB subtype	M1 or M2 with Auer rods, M3 and M4eo
FLT3	Wild-type
Courses to complete remission	1

From Hoffman R et al: *Hematology: basic principles and practice*, ed 5, Philadelphia, 2009, Churchill Livingstone.

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TABLE A1-33 Prognostic Models in Older Patients With Acute Myeloid Leukemia

Model	Predicted Factor	Negative Prognostic Scores
Study Alliance Leukemia	Survival Disease-free survival	CD34 expression >10% WBC >20 $\times 10^9$/L Age >65 yr LDH >700 units/L NPM1 status wild-type*
UK Medical Research Council (UKMRC)	Survival	Adverse cytogenetic group Elevated WBC† Poor performance status† Older age† Secondary AML
Acute Leukemia French Association (ALFA)	Survival	High-risk cytogenetics ± Age ≥75 yr Performance status ≥2 WBC ≥50 × 10^9/L
M.D. Anderson (MDACC)	Remission rate Induction mortality Survival	Age ≥75 yr Secondary AML‡ AHD duration ≥6‡ (12) mo Treatment outside LAFR Unfavorable cytogenetics WBC ≥25 × 10^9/L‡ Hemoglobin ≤8 g/dL‡ Creatinine >1.3 mg/dL Performance status >2 LDH >600 units/L§
Hematopoietic cell transplantation comorbidity index	Early mortality Survival	Dyspnea Coronary artery disease, CHF, MI, or EF <50% Chronic hepatitis, elevation of bilirubin and/or transaminases Cirrhosis Elevations of creatinine, dialysis, renal transplant Secondary AML Depression/anxiety requiring therapy Continued use of antimicrobial therapy after day 0 BMI >35 kg/m^2

AHD, Antecedent hematologic disorder; *AML,* acute myeloid leukemia; *BMI,* body mass index; *CHF,* congestive heart failure; *EF,* ejection fraction; *LAFR,* laminar air flow room (isolation floor); *LDH,* lactic dehydrogenase; *MI,* myocardial infarction; *WBC,* white blood cell count.

*Favorable and high-risk groups were defined solely by cytogenetic aberrations. Above factors served to further divide the intermediate-risk group into good intermediate versus adverse intermediate.

†As continuous variables.

‡Only significant for prediction of remission.

§Only significant for prediction of survival.

From Hoffman R: *Hematology, basic principles and practice*, 6th ed, Philadelphia, 2013, Saunders.

http://internalmedicinebook.com/

SUGGESTED READINGS

Gentles AJ et al.: Association of a leukemic stem cell gene expression signature with clinical outcomes in acute myeloid leukemia, *JAMA* 304(24):2706–2715, 2010.

Ho C, Butera JN: Acute myeloid leukemia in the elderly, *Medicine & Health Rhode Island* 94:71, 2011.

Koreth J et al.: Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission, *JAMA* 301(22):2349–2361, 2009.

Ley TJ et al.: DNMT3A mutations in acute myeloid leukemia, *N Engl J Med* 363:2424, 2010.

Lowenberg B et al.: Cytarabine dose for acute myeloid leukemia, *N Engl J Med* 364:1027–1036, 2011.

Patel JP et al.: Prognostic relevance of integrated genetic profiling in acute myeloid leukemia, *N Engl J Med* 366:1079–1089, 2012.

Walter MJ et al.: Clonal architecture of secondary acute myeloid leukemia, *N Engl J Med* 366:1090–1098, 2012.

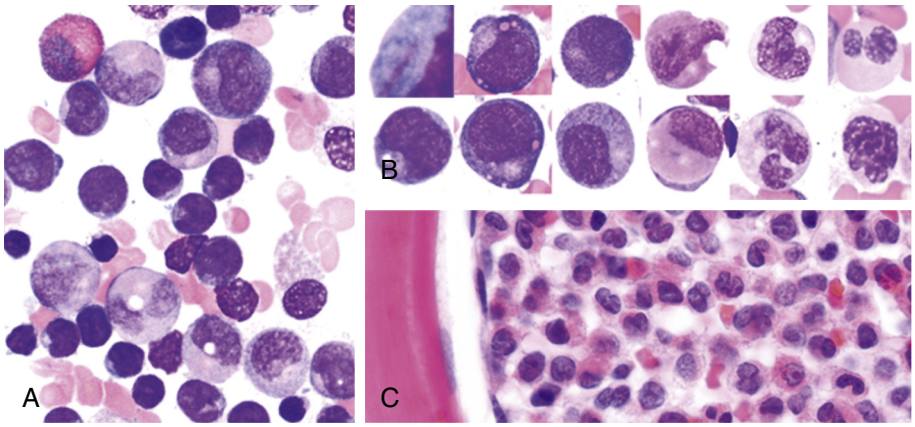

FIGURE EA1-49 Acute myeloid leukemia with t(8;21)(q22;q22), (AML/ETO). A, Low-power, Wright-stained bone marrow aspirate smear showing increased blasts associated with differentiating myeloid cells. **B,** Details illustrating some of the features associated with the leukemia. They include blasts with long thin Auer rods *(top left),* immature cells with abnormal eosinophilic globules *(top and bottom, second from left),* abnormal salmon-colored granulation in the maturing cells, sometimes associated with a basophilic periphery *(top and bottom, fourth from left),* and slightly abnormal features in the mature neutrophils *(far right).* Pseudo–Chédiak-Higashi granules were not seen in this case. **C,** Biopsy shows the significant degree of maturation that is sometimes seen. In some cases the blast count is less than 20%, but the diagnosis of acute myeloid leukemia still can be made with the cytogenetic finding of t(8;21). (From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

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BASIC INFORMATION

DEFINITION

- Acute pancreatitis is an inflammatory process of the pancreas with intrapancreatic activation of enzymes that may also involve peripancreatic tissue and/or remote organ systems.
- Commonly used scoring systems for acute pancreatitis are described in Table A1-34.

The **Revised Atlanta Criteria**[1] use early prognostic signs, organ failure, and local complications to define disease severity:

1. Mild pancreatitis: no organ failure, no local or systemic complications, pancreatitis typically resolves in first week
2. Moderate pancreatitis: transient organ failure (≤48 hours) *or* local complications (e.g., pancreatic necrosis, peripancreatic fluid collections, peripancreatic necrosis) *or* exacerbation of comorbid disease
3. Severe pancreatitis: persistent organ failure (>48 hours)

The **BALI Score**[2] evaluates only four variables:

1. BUN ≥25 mg/dL
2. Age ≥65 years
3. LDH ≥300 U/L
4. Interleukin-6 level ≥300 pg/mL

These measurements are taken at admission and at 48 hours. Mortality is >25% for a score of 3 and exceeds 50% with a score of 4.

Severe acute pancreatitis (SAP) is diagnosed by the presence of any of the following four criteria:

1. Organ failure with one or more of the following: shock (systolic blood pressure <90 mm Hg), pulmonary insufficiency (Pa_{O_2} ≤60 mm Hg), renal failure (serum creatinine >2 mg/dl after rehydration), and gastrointestinal bleeding (>500 ml/24 hr)
2. Local complications such as necrosis, pseudocyst, or abscess
3. At least three of Ranson's criteria (see below) *or*
4. At least eight of the Acute Physiology and Chronic Health Evaluation II (APACHE II) criteria

EPIDEMIOLOGY & DEMOGRAPHICS

- There are >240,000 cases of acute pancreatitis reported annually in the United States, with nearly 50% due to gallstone disease.
- Acute pancreatitis is most often secondary to biliary tract disease and alcohol. The rate of pancreatitis continues to rise and ranges from 10 to 45 cases/100,000 in Western countries.
- Incidence in urban areas is twice that of rural areas (20/100,000 persons in urban areas).
- 20% of patients have necrotizing pancreatitis; the remainder have interstitial, or edematous, pancreatitis.
- Acute pancreatitis accounts for >220,000 hospital admissions in the United States each year.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Epigastric tenderness and guarding, often radiating to the back; pain usually developing suddenly, reaching peak intensity within 10 to 30 min, severe and lasting several hours without relief
- Hypoactive bowel sounds (from ileus)
- Tachycardia, shock (from decreased intravascular volume)
- Confusion (from metabolic disturbances)
- Fever
- Tachycardia, decreased breath sounds (atelectasis, pleural effusions, acute respiratory distress syndrome [ARDS])
- Jaundice (from obstruction or compression of biliary tract)
- Ascites (from tear in pancreatic duct, leaking pseudocyst)
- Palpable abdominal mass (pseudocyst, phlegmon, abscess, carcinoma)
- Evidence of hypocalcemia (Chvostek's sign, Trousseau's sign)
- Evidence of intraabdominal bleeding (hemorrhagic pancreatitis):
  1. Gray-blue discoloration around the umbilicus ***(Cullen's sign)***
  2. Bluish discoloration involving the flanks ***(Grey Turner's sign)***
- Tender subcutaneous nodules (caused by subcutaneous fat necrosis)

ETIOLOGY

- In >90% of cases: biliary tract disease (calculi or sludge) or alcohol, most common after 5 to 10 yr of heavy drinking
- Drugs (e.g., thiazides, furosemide, corticosteroids, tetracycline, estrogens, valproic acid, metronidazole, azathioprine, methyldopa, pentamidine, ethacrynic acid, procainamide, amiodarone, sulindac, nitrofurantoin, angiotensin-converting enzyme inhibitors, danazol, cimetidine, piroxicam, gold, ranitidine, sulfasalazine, isoniazid, acetaminophen, cisplatin, didanosine, opiates, erythromycin, metformin, GLP-1 receptor agonists, incretin mimetics)
- Abdominal trauma
- Surgery
- Endoscopic retrograde cholangiopancreatography (ERCP)
- Infections (predominantly viral infections)
- Peptic ulcer (penetrating duodenal ulcer)

TABLE A1-34 Commonly Used Scoring Systems: Advantages and Disadvantages

System	Scoring	Advantages	Disadvantages
Ranson's criteria on admission: 1. Age >55 yr 2. WBC >16 × 10^9/L 3. LDH >350 U/L 4. AST >250 U/L 5. Glucose >200 mg/dl During initial 48 hr: 1. Hgb falls below 10 mg/dl 2. BUN rises by >5 mg/dl 3. Ca <8 mg/dl 4. Pa_{O_2} <60 mm Hg 5. Base deficit >4 mEq/L 6. Fluid sequestration >6 L	1 point for each factor listed; score >3 indicates SAP	Well known, relatively easy to calculate	Requires 48 hr to complete evaluation
APACHE II*	Score >8 predicts SAP	Can be calculated within 24 hr of admission	Requires large dataset for processing
BISAP 1. BUN >25 mg/dl 2. Altered mental status 3. Presence of SIRS 4. Age >60 yr 5. Pleural effusions	1 point for each factor listed; score >3 indicates SAP	Ease of use, available within 24 hr of admission	Significantly lower sensitivity than either Ranson's or APACHE II; results in greater likelihood of missing severe AP
CTSI	Based on radiographic data	Excellent predictor of local complications; can show infected pancreatic necrosis	Requires 72 to 96 hr, making it a poor test for guiding decisions at admission

APACHE, Acute Physiology and Chronic Health Evaluation; *AST,* aspartate aminotransferase; *BISAP,* Bedside Index for Severity in Acute Pancreatitis; *BUN,* blood urea nitrogen; *Ca,* serum calcium; *CTSI,* Computed Tomography Severity Index; *Hgb,* hemoglobin; *LDH,* lactate dehydrogenase; *SAP,* severe acute pancreatitis; *SIRS,* systemic inflammatory response syndrome; *WBC,* white blood cell count.

*Based on diverse variables, including age, physiology, and long-term health; equation available at www.sfar.org/scores2/apache22.html#calcul. Adding body mass index (BMI) to APACHE II (the APACHE 0 score) increases discrimination (1 point added for BMI 26-30; 2 points for BMI >30).

Modified from Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

[1]Banks PA et al.; Acute Pancreatitis Classification Working Group: Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus, *Gut* 62(1):102-111, 2013.

[2]Spitzer AL et al.: Applying Ockham's razor to pancreatitis prognostication: a four-variable predictive model, *Ann Surg* 243(3):380-388, 2006.

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- Pancreas divisum (congenital failure to fuse of dorsal or ventral pancreas)
- Idiopathic
- Pregnancy
- Vascular (vasculitis, ischemic)
- Hypolipoproteinemia (types I, IV, and V)
- Hypercalcemia
- Pancreatic carcinoma (primary or metastatic)
- Renal failure
- Hereditary pancreatitis
- Occupational exposure to chemicals: methanol, cobalt, zinc, mercuric chloride, creosol, lead, organophosphates, chlorinated naphthalenes
- Others: scorpion bite, obstruction at ampulla region (neoplasm, duodenal diverticula, Crohn's disease), hypotensive shock, autoimmune pancreatitis

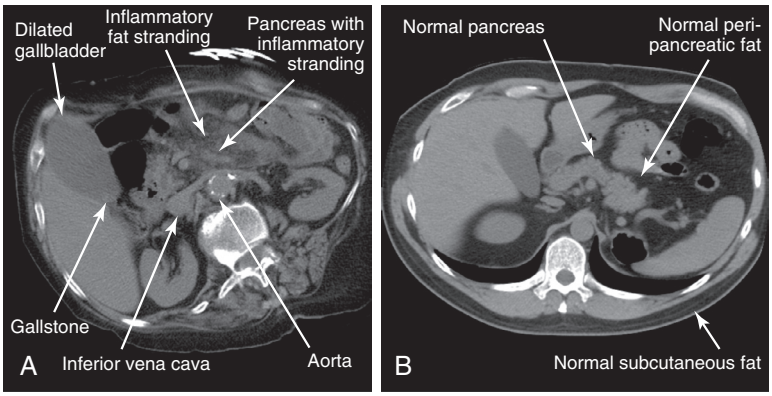

FIGURE A1-50 Gallstone pancreatitis and normal pancreas for comparison, axial CT without contrast. A, Gallstone pancreatitis CT. A dilated gallbladder is visible with a hyperdense dependent lesion consistent with a gallstone. The region of the pancreas shows significant inflammatory stranding. In this patient, the pancreas lies just anterior to the left renal vein, which can be seen crossing anterior to the aorta and entering the inferior vena cava. **B,** A normal pancreas is visible. This pancreas is surrounded by uninflamed fat, which is dark (nearly black). Compare this normal fat with normal subcutaneous fat. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- PUD
- Acute cholangitis, biliary colic
- High intestinal obstruction
- Early acute appendicitis
- Mesenteric vascular obstruction
- DKA
- Pneumonia (basilar)
- Myocardial infarction (inferior wall)
- Renal colic
- Ruptured or dissecting aortic aneurysm
- Mesenteric ischemia

LABORATORY TESTS

Pancreatic enzymes:

Amylase is increased, usually elevated in the initial 3 to 5 days of acute pancreatitis. Isoamylase determinations (separation of pancreatic cell isoenzyme components of amylase) are useful in excluding occasional cases of salivary hyperamylasemia. The use of isoamylase rather than total serum amylase reduces the risk of erroneously diagnosing pancreatitis and is preferred by some as initial biochemical test in patients suspected of having acute pancreatitis.

Urinary amylase determinations are useful to diagnose acute pancreatitis in patients with lipemic serum, to rule out elevated serum amylase caused by macroamylasemia, and to diagnose acute pancreatitis in patients whose serum amylase is normal.

Serum lipase levels are elevated in acute pancreatitis; the elevation is less transient than serum amylase; concomitant evaluation of serum amylase and lipase increases diagnostic accuracy of acute pancreatitis. An elevated lipase/amylase ratio is suggestive of alcoholic pancreatitis.

Elevated serum trypsin levels are diagnostic of pancreatitis (in absence of renal failure).

Serum C-reactive protein at 48 hr is an excellent laboratory marker of severity.

Rapid measurement of urinary trypsinogen-2 (if available) is useful in the emergency department as a screening test for acute pancreatitis in patients with abdominal pain; a negative dipstick test for urinary trypsinogen-2 rules out acute pancreatitis with a high degree of probability, whereas a positive test indicates need for further evaluation.

Interleukin-6 level: worse prognosis with level ≥300 pg/mL.

ADDITIONAL TESTS

- Complete blood count: reveals leukocytosis; hematocrit (Hct) may be initially increased as a result of hemoconcentration; decreased Hct may indicate hemorrhage or hemolysis.
- Blood urea nitrogen (BUN) is increased because of dehydration. Serial BUN measurements are the most valuable lab test for predicting mortality during the initial 48 hr.
- Elevation of serum glucose in a previously normal patient correlates with the degree of pancreatic malfunction and may be related to increased release of glycogen, catecholamines, and glucocorticoid release and decreased insulin release.
- Liver profile: aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) are increased as a result of tissue necrosis; bilirubin and alkaline phosphatase may be increased from common bile duct obstruction. A threefold or greater rise in serum alanine aminotransferase concentrations is an excellent indicator (95% probability) of biliary pancreatitis.
- Serum calcium is decreased as a result of saponification, precipitation, and decreased parathyroid hormone response.
- Arterial blood gases: Pa_{O_2} may be decreased as a result of ARDS, pleural effusion(s); pH may be decreased as a result of lactic acidosis, respiratory acidosis, and renal insufficiency.
- Serum electrolytes: potassium may be increased from acidosis or renal insufficiency; sodium may be increased from dehydration.

IMAGING STUDIES

- Abdominal plain films are useful initially to distinguish other conditions that may mimic pancreatitis (perforated viscus). They may reveal localized ileus (sentinel loop), pancreatic calcifications (chronic pancreatitis), blurring of left psoas shadow, dilation of transverse colon, calcified gallstones.
- Chest x-ray may reveal elevation of one or both diaphragms, pleural effusions, basilar infiltrates, or platelike atelectasis.
- Abdominal ultrasonography is useful in detecting gallstones (sensitivity of 60% to 70% for detecting stones associated with pancreatitis). It is also useful for detecting pancreatic pseudocysts. Its availability and noninvasive nature make it the initial imaging study of choice; its major limitation is the presence of distended bowel loops overlying the pancreas.
- CT scan (Fig. A1-50) is superior to ultrasonography in identifying pancreatitis and defining its extent, and it also plays a role in diagnosing pseudocysts (they appear as a well-defined area surrounded by a high-density capsule); gastrointestinal fistulation or infection of a pseudocyst can also be identified by the presence of gas within the pseudocyst. Sequential contrast-enhanced CT is useful for detection of pancreatic necrosis. The severity of pancreatitis can also be graded by CT scan (Table A1-35). (A = normal pancreas, B = enlarged pancreas [1 point], C = pancreatic and/or peripancreatic inflammation [2 points], D = single peripancreatic collection [3 points], E = at least two peripancreatic collections and/or retroperitoneal air [4 points]. Percentage of pancreatic necrosis <30% [2 points], 30% to 50% [4 points], >50% [6 points]. The CT severity index is calculated by adding grade points to points assigned for percentage of necrosis.)
- Magnetic resonance cholangiopancreatography (MRCP) has >90% sensitivity for choledocholithiasis and can identify other anatomic abnormalities.
- Endoscopic ultrasonography (EUS) is a minimally invasive test that provides high-resolution imaging of the pancreas. It is useful to identify anatomic abnormalities of the pancreas and has good sensitivity and specificity for small gallstones (≤5 mm).

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TABLE A1-35 Computed Tomography Severity Index Score for Pancreatitis*

Grade†	CT Findings	Score
A	Normal pancreas	0
B	Focal or diffuse enlargement of the pancreas, contour irregularities, heterogeneous attenuation, no peripancreatic inflammation	1
C	Grade B plus peripancreatic inflammation	2
D	Grade C plus a single fluid collection	3
E	Grade C plus multiple fluid collections or gas	4
Percent Necrosis Present on Ct		**Score**
0		0
<33		2
33-50		4
>50		6

*Severity Index Score = Grade score + Percent necrosis score. Maximum score = 10; severe disease = 6 or higher.
†Severity of the acute inflammatory process.
From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

- ERCP indications: useful to perform biliary sphincterotomy and stone removal in the presence of a retained bile duct stone seen on imaging. The role and timing of ERCP in patients with acute biliary pancreatitis has been controversial. Guidelines from the American College of Gastroenterology suggest that urgent ERCP (within 24 hr of admission) is indicated in patients with biliary pancreatitis who have concurrent acute cholangitis, but it is not needed in most patients who do not have evidence of ongoing biliary obstruction.[3,4]

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Bowel rest with avoidance of liquids or solids during the acute illness
- Avoidance of alcohol and any drugs associated with pancreatitis

ACUTE GENERAL Rx

GENERAL MEASURES:

- Assess severity of pancreatitis (see Table A1-34).
- Maintain adequate intravascular volume with vigorous IV hydration. Aggressive fluid resuscitation is critical in managing acute pancreatitis.
- Patient should remain NPO until clinically improved, stable, and hungry. Enteral feedings are preferred over total parenteral nutrition. Enteral nutrition reduces mortality, multiple organ failure, systemic infections, and operative interventions more than total parenteral nutrition does in patients with acute pancreatitis. Parenteral nutrition may be necessary in patients who do not tolerate enteral feeding or in whom an adequate infusion rate cannot be reached within 2 to 4 days. Early enteral feeding through a nasogastric (NG) feeding tube is often used instead of an oral diet, but evidence to support this strategy is limited. A recent trial did not show superiority of early NG tube feeding, as compared to oral diet after 72 hours, in reducing the rate of infection or death in patients with acute pancreatitis at high risk for complications.[5]
- Nasogastric suction is useful only in severe pancreatitis to decompress the abdomen in patients with ileus.
- Control pain: IV morphine or fentanyl. Meperidine and hydromorphone are also commonly used narcotics for pain control.
- Correct metabolic abnormalities (e.g., replace calcium and magnesium as necessary).

SPECIFIC MEASURES:

- Pancreatic or peripancreatic infection develops in 40% to 70% of patients with pancreatic necrosis. However, IV antibiotics should not be used prophylactically for all cases of pancreatitis; their use is justified if the patient has evidence of septicemia, pancreatic abscess, or pancreatitis caused by biliary calculi. Their use should generally be limited to 5 to 7 days to prevent development of fungal superinfection. Appropriate empiric antibiotic therapy should cover:
  1. *Bacteroides fragilis* and other anaerobes (cefotetan, cefoxitin, metronidazole, or clindamycin plus aminoglycoside)
  2. *Enterococcus* (ampicillin)
- Surgical therapy has a limited role in acute pancreatitis; it is indicated in the following:
  1. Gallstone-induced pancreatitis: cholecystectomy when acute pancreatitis subsides. However, randomized trials have shown that patients with mild gallstone pancreatitis can undergo cholecystectomy safely during the first 48 hr of hospitalization.
  2. Perforated peptic ulcer.
  3. Necrotizing pancreatitis with infected necrotic tissue is associated with an elevated rate of complications and increased risk of death. Traditional treatment has been open necrosectomy; surgical necrosectomy induces a proinflammatory response and is associated with a high complication rate. Recent trials have shown that a step-up approach consisting of percutaneous drainage followed, if necessary, by minimally invasive retroperitoneal necrosectomy may have a lower rate of complications and death. Endoscopic transgastric necrosectomy, a form of natural orifice transluminal endoscopic surgery, has been shown in recent trials to be effective in reducing the proinflammatory response as well as reducing complications.
- Identification and treatment of complications:
  1. **Pseudocyst:** round or spheroid collection of fluid, tissue, pancreatic enzymes, and blood.
     1. Diagnosed by CT scan or sonography.
     2. Treatment: Pancreatic pseudocysts can be drained surgically or endoscopically. The endoscopic approach is preferable when the patient's anatomy is suitable and an experienced endoscopist is available. CT scan or ultrasound-guided percutaneous drainage (with a pigtail catheter left in place for continuous drainage) can be used, but the recurrence rate is high; the conservative approach is to reevaluate the pseudocyst (with CT scan or sonography) after 6 to 7 wk and surgically drain it if the pseudocyst has not decreased in size.
     3. Generally, pseudocysts <5 cm in diameter are reabsorbed without intervention, whereas those >5 cm require surgical intervention after the wall has matured.
  2. **Phlegmon:** represents pancreatic edema. It can be diagnosed by CT scan or sonography. Treatment is supportive because it usually resolves spontaneously.
  3. **Pancreatic abscess:** diagnosed by CT scan (presence of bubbles in the retroperitoneum); Gram staining and cultures of fluid obtained from guided percutaneous aspiration usually identify bacterial organism. Therapy is surgical (or catheter) drainage and IV antibiotics (imipenem-cilastatin is the drug of choice).
  4. **Pancreatic ascites:** usually caused by leaking of pseudocyst or tear in pancreatic duct. Paracentesis reveals very high amylase and lipase levels in the pancreatic fluid; ERCP may demonstrate the lesion. Treatment is surgical correction if exudative ascites from severe pancreatitis does not resolve spontaneously.
  5. Gastrointestinal bleeding: caused by alcoholic gastritis, bleeding varices, stress ulceration, or disseminated intravascular coagulation (DIC).
  6. Renal failure: caused by hypovolemia, resulting in oliguria or anuria, cortical or tubular necrosis (shock, DIC), or thrombosis of renal artery or vein.
  7. Hypoxia: caused by ARDS, pleural effusion, or atelectasis.

[3]Fogel EL, Sherman S: ERCP for gallstone pancreatitis, *N Engl J Med* 370:150-157, 2014.
[4]Tenner S et al: American College of Gastroenterology guidelines: management of acute pancreatitis, *Am J Gastroenterol* 108:1400-1415, 2013.
[5]Bakker OJ et al.: Early versus on-demand nasogastric tube feeding in acute pancreatitis, *N Engl J Med* 371:1983-1993, 2014.

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TABLE A1-36 Prognostic Criteria for Acute Pancreatitis

Ranson Criteria*	Simplified Glasgow Criteria†	Computed Tomography Criteria‡
On admission: Age >55 yr	*Within 48 hr of admission:* Age	Normal
WBC >16,000/μL	>55 yr	Enlargement
AST >250 U/L LDH >350 U/L	WBC >15,000/μL	Pancreatic inflammation
Glucose >200 mg/dl	LDH >600 U/L	Single fluid collection
48 hr after admission:	Glucose >180 mg/dl	Multiple fluid collection
Hematocrit decrease by >10	Albumin <3.2 g/dl	
BUN increase by >5 mg/dl	Ca^{2+} <8 mg/dl	
Ca^{2+} <8 mg/dl	Arterial Po_2 <60 mm Hg	
Arterial Po_2 <60 mm Hg	BUN >45 mg/dl	
Base deficit >4 mEq/L		
Fluid sequestration >6 L		

AST, Aspartate aminotransferase; *BUN,* blood urea nitrogen; *LDH,* lactate dehydrogenase; *WBC,* white blood cells.

*Three or more Ranson's criteria predict a complicated clinical course. Data from Ranson JH et al: Prognostic signs and nonoperative peritoneal lavage in acute pancreatitis, *Surg Gynecol Obstet* 143:209-219, 1976.

†Data from Blamey SL et al: Prognostic factors in acute pancreatitis, *Gut* 25:1340, 1984.

‡Grades A and B represent mild disease with no risk of infection or death. Grade C represents moderately severe disease with a minimal likelihood of infection and essentially no risk of mortality. Grades D and E represent severe pancreatitis with an infection rate of 30% to 50% and mortality rate of 15%. Data from Balthazar EJ et al: Acute pancreatitis value of CT in establishing prognosis, *Radiology* 174:331, 1990.

From Goldman L, Ausiello D (eds): *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.

THERAPY OF UNCOMMON FORMS OF PANCREATITIS

1. **Autoimmune pancreatitis (AIP):** Fibroinflammatory disease characterized by an IgG4 lymphoplasmacytic infiltrate. It has been associated with other autoimmune disorders (e.g., primary sclerosing cholangitis, Sjögren syndrome). The inflammatory process is generally responsive to corticosteroid therapy. Type II autoimmune hepatitis (idiopathic duct-centric chronic pancreatitis) is associated with inflammatory bowel disease and not related to IgG4 cell deposition.
2. **Hypertriglyceridemic pancreatitis (HTGP):** Beneficial results have been reported with early (within 48 hr) initiation of apheresis with IV heparin and insulin in addition to conventional treatment modalities for acute pancreatitis when there is concomitant hyperglycemia with severe acute pancreatitis.

DISPOSITION

Prognosis varies with the severity of pancreatitis; overall mortality rate in acute pancreatitis is 5% to 10%. Prognostic criteria for acute pancreatitis are described in Table A1-36.

REFERRAL

- Hospitalization is indicated in moderate to severe cases of pancreatitis.
- Surgical consultation is needed in suspected gallstone pancreatitis, perforated peptic ulcer, or presence of necrotic or infected foci. Acute pancreatitis can generally be attributed to gallstones when patients have both abnormal liver enzymes and gallstones (or sludge) on imaging. Such patients should consider cholecystectomy to prevent recurrent pancreatitis.
- Gastroenterology consultation in severe or recurrent pancreatitis, when ERCP is needed for gallstone pancreatitis, or when the cause of pancreatitis is unclear.

PEARLS & CONSIDERATIONS

- Acute pancreatitis is the most common major complication of ERCP. NSAIDs are potent inhibitors of phospholipase A_2, cyclooxygenase, and neutrophil-endothelial interactions, which play an important role in the pathogenesis of acute pancreatitis. Preliminary trials show that among patients at high risk for post-ERCP pancreatitis, rectal indomethacin (given as two 50 mg indomethacin suppositories administered immediately after ERCP) significantly reduced the incidence of post-ERCP pancreatitis.
- Pancreatic stent placement decreases the risk of post-ERCP pancreatitis.
- Statins reduce risk for pancreatitis in adults. Fibrates do not affect risk for pancreatitis.

EVIDENCE

available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Acute Pancreatitis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Background:
Acute pancreatitis is a common complication of ERCP. Several randomized, controlled trials (RCTs) have evaluated the use of pancreatic stents in the prevention of post-ERCP pancreatitis with varying results.

Objective:
We conducted a meta-analysis and systematic review to assess the role of prophylactic pancreatic stents for prevention of post-ERCP pancreatitis.

Design:
MEDLINE, Cochrane Central Register of Controlled Trials and Database of Systematic Reviews, PubMed, and recent abstracts from major conference proceedings were searched. RCTs and retrospective or prospective, nonrandomized studies comparing prophylactic stent with placebo or no stent for post-ERCP pancreatitis were included for the meta-analysis and systematic review. Standard forms were used to extract data by 2 independent reviewers. The effect of stents (for RCTs) was analyzed by calculating pooled estimates of post-ERCP pancreatitis, hyperamylasemia, and grade of pancreatitis. Separate analyses were performed for each outcome by using the odds ratio (OR) or weighted mean difference. Random- or fixed-effects models were used. Publication bias was assessed by funnel plots. Heterogeneity among studies was assessed by calculating I^2 measure of inconsistency.

Setting:
Systematic review and meta-analysis of patients undergoing pancreatic stent placement for prophylaxis against post-ERCP pancreatitis.

Patients:
Adult patients undergoing ERCP.

Intervention:
Pancreatic stent placement for the prevention of post-ERCP pancreatitis.

Main Outcome Measurements:
Post-ERCP pancreatitis, hyperamylasemia, and complications after pancreatic stent placement.

Results:
Eight RCTs (656 subjects) and 10 nonrandomized studies met the inclusion criteria (4904 subjects). Meta-analysis of the RCTs showed that prophylactic pancreatic stents decreased the odds of post-ERCP pancreatitis (odds ratio, 0.22; 95% CI, 0.12-0.38; $P<.01$). The absolute risk difference was 13.3% (95% CI, 8.8%-17.8%). The number needed to treat was 8 (95% CI, 6-11). Stents also decreased the level of hyperamylasemia (WMD, −309.22; 95% CI, −350.95 to −267.49; P≤.01). Similar findings were also noted from the nonrandomized studies.

Limitations:
Small sample size of some trials, different types of stents used, inclusion of low-risk patients in some studies, and lack of adequate study of long-term complications of pancreatic stent placement.

Conclusions:
Pancreatic stent placement decreases the risk of post-ERCP pancreatitis and hyperamylasemia in high-risk patients. Ⓐ

Evidence-Based Reference

Choudhary A et al.: Pancreatic stents for prophylaxis against post-ERCP pancreatitis: a meta-analysis and systematic review, *Gastrointest Endosc* 73:275–282, 2011. Ⓐ

SUGGESTED READINGS

Al-Omran M et al.: Enteral versus parenteral nutrition for acute pancreatitis, *Cochrane Database Syst Rev* 1:CD002837, 2010.

Bakker OJ: Endoscopic transgastric vs. surgical necrosectomy for infected necrotizing pancreatitis, *JAMA* 307(10):1053–1061, 2012.

Balthazar EJ: Acute pancreatitis: assessment of severity with clinical and CT evaluation, *Radiology* 223:603, 2002.

Bechien W et al.: Blood urea nitrogen in the early assessment of acute pancreatitis, *Arch Intern Med* 171(7):669–676, 2011.

Bosmann M et al.: Coexistence of Cullen's and Grey Turner's signs in acute pancreatitis, *Am J Med* 122:333–334, 2009.

Elmunzer BJ et al.: A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis, *N Engl J Med* 366:1414–1422, 2012.

Falor AE et al.: Early laparoscopic cholecystectomy for mild gallstone pancreatitis: time for a paradigm shift, *Arch Surg* 147:1031–1035, 2012.

Finkelberg D et al.: Autoimmune pancreatitis, *N Engl J Med* 355:2670, 2006.

Jain P et al.: Insulin and heparin in treatment of hypertriglyceridemia-induced pancreatitis, *World J Gastroenterol* 13:2642–2643, 2007.

Knaus WA et al.: APACHE II: a severity of disease classification system, *Crit Care Med* 13:818, 1984.

Quinlan JD: Acute pancreatitis, *Am Fam Physician* 90(9):632–639, 2014.

Swaroop VS et al.: Severe acute pancreatitis, *JAMA* 291:2865, 2004.

Trna J et al.: Lack of significant liver enzyme elevations and gallstones and/or sludge on ultrasound on day 1 of acute pancreatitis is associated with recurrence after cholecystectomy: a population-based study, *Surgery* 151:199–205, 2012.

Van Santvoort HC et al.: A step-up approach or open necrosectomy for necrotizing pancreatitis, *N Engl J Med* 362:1491–1502, 2010.

Vitale GC: Early management of acute gallstone pancreatitis, *Ann Surg* 245(1):18, 2007.

Whitcomb DC: Acute pancreatitis, *N Engl J Med* 354:2142, 2006.

Wu BU et al.: Early changes in BUN predict mortality in acute pancreatitis, *Gastroenterology* 137:129–135, 2009.

BASIC INFORMATION

DEFINITION

Acute respiratory distress syndrome (ARDS) is a form of noncardiogenic pulmonary edema that results from acute damage to the alveoli. It is characterized by acute diffuse infiltrative lung lesions with resulting interstitial and alveolar edema, severe hypoxemia, and respiratory failure. The cardinal feature of ARDS, refractory hypoxemia, is caused by formation of protein-rich alveolar edema after damage to the integrity of the lung's alveolar-capillary barrier.

The definition of ARDS based on the American–European Consensus Conference (AECC) from 1994 included the following components:

1. The syndrome must present acutely
2. A ratio of Pa_{O_2} to F_{IO_2} ≤200 regardless of the level of positive end expiratory pressure (PEEP)
3. The detection of bilateral pulmonary infiltrates on frontal chest radiograph
4. Absence of congestive heart failure (pulmonary artery wedge pressure [PAWP] ≤18 mm Hg or no clinical evidence of elevated left atrial pressure on the basis of chest radiograph or other clinical data)

The Berlin definition of ARDS adopted in 2011 addresses some of the limitations of the AECC definition and establishes the following criteria for ARDS:

- Timing: Within 1 week of a known clinical insult or new or worsening respiratory symptoms
- Chest imaging (chest x-ray or CT scan): Bilateral opacities, not fully explained by effusions, lobar/lung collapse, or nodules
- Origin of edema: Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
- Oxygenation (if altitude is higher than 1000 m, the correction factor should be calculated as follows: [Pa_{O_2}/F_{IO_2} × {barometric pressure/760}]
- Mild: 200 mm Hg <Pa_{O_2}/F_{IO_2} ≤300 mm Hg with PEEP or CPAP ≥5 cm H_2O (this may be delivered noninvasively in the mild ARDS group)
- Moderate: 100 mm Hg <Pa_{O_2}/F_{IO_2} ≤200 mm Hg with PEEP or CPAP ≥5 cm H_2O
- Severe; Pa_{O_2}/F_{IO_2} ≤100 mm Hg with PEEP or CPAP ≥5 cm H_2O

SYNONYMS

ARDS
Adult respiratory distress syndrome

ICD-9CM CODES
518.82 Acute respiratory distress syndrome
ICD-10CM CODES
J80 Acute respiratory distress syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- More than 150,000 ARDS cases per year in the U.S. 7.1% of all patients admitted to an ICU and 16.1% of all patients on mechanical ventilation develop ARDS.
- Incidence is 1.5 to 8.3 cases per 100,000 per year.
- Approximately 50% of patients who develop ARDS do so within 24 hours of the inciting event. Mortality rate is 40% to 50%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Signs and symptoms
  1. Dyspnea
  2. Chest discomfort
  3. Cough
  4. Anxiety
- Physical examination
  1. Tachypnea
  2. Tachycardia
  3. Hypertension
  4. Coarse crepitations of both lungs
  5. Fever may be present if infection is the underlying etiology

ETIOLOGY

- Sepsis (>40% of cases)
- Aspiration: near-drowning, aspiration of gastric contents (>30% of cases)
- Trauma (>20% of cases)
- Multiple transfusions, blood products
- Drugs (e.g., overdose of morphine, methadone, heroin; reaction to nitrofurantoin)
- Noxious inhalation (e.g., chlorine gas, high O_2 concentration)
- Postresuscitation
- Cardiopulmonary bypass
- Pneumonia
- Burns
- Pancreatitis
- A history of chronic alcohol abuse significantly increases the risk of developing ARDS in critically ill patients.
- Table A1-37 describes risk factors associated with development of ARDS.

TABLE A1-37 Risk Factors Associated with Development of Acute Lung Injury and Acute Respiratory Distress Syndrome

Direct Lung Injury	Indirect Lung Injury
Pneumonia	Sepsis
Aspiration of gastric contents	Multiple trauma
Pulmonary contusion	Cardiopulmonary bypass
Fat, amniotic fluid, or air emboli	Drug overdose
Near-drowning	Acute pancreatitis
Inhalational injury	Transfusion of blood products
Reperfusion pulmonary edema	

From Vincent JL et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, Saunders.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cardiogenic pulmonary edema
- Viral pneumonitis
- Lymphangitic carcinomatosis

WORKUP

The search for an underlying cause should focus on treatable causes (e.g., infections such as sepsis or pneumonia)

- Arterial blood gases (ABGs)
- Hemodynamic monitoring
- Bronchoalveolar lavage (selected patients)

LABORATORY TESTS

- ABGs:
  1. Initially: varying degrees of hypoxemia, generally resistant to supplemental oxygen
  2. Respiratory alkalosis, decreased P_{CO_2}
  3. Widened alveolar-arterial gradient
  4. Hypercapnia as the disease progresses
- Bronchoalveolar lavage:
  1. The most prominent finding is an increased number of polymorphonucleocytes.
  2. The presence of eosinophilia has therapeutic implications because these patients respond to corticosteroids.
- Blood and urine cultures

IMAGING STUDIES

Chest radiograph (Fig. A1-51).

- The initial chest radiograph might be normal in the initial hours after the precipitating event.
- Bilateral interstitial infiltrates are usually seen within 24 hr; they often are more prominent in the bases and periphery.
- "White out" of both lung fields can be seen in advanced stages.
- CT scan of chest: diffuse consolidation with air bronchograms, bullae, pleural effusions. Pneumomediastinum and pneumothoraces may also be present.

TREATMENT

NONPHARMACOLOGIC THERAPY

Treatment of ARDS is supportive.

Hemodynamic monitoring:

- Can be used for the initial evaluation of ARDS (in ruling out cardiogenic pulmonary edema) and its subsequent management. However, a pulmonary catheter is not indicated in the routine management of ARDS and trials have shown that clinical management involving the early use of pulmonary artery catheters in patients with ARDS did not significantly affect mortality and morbidity rates and may result

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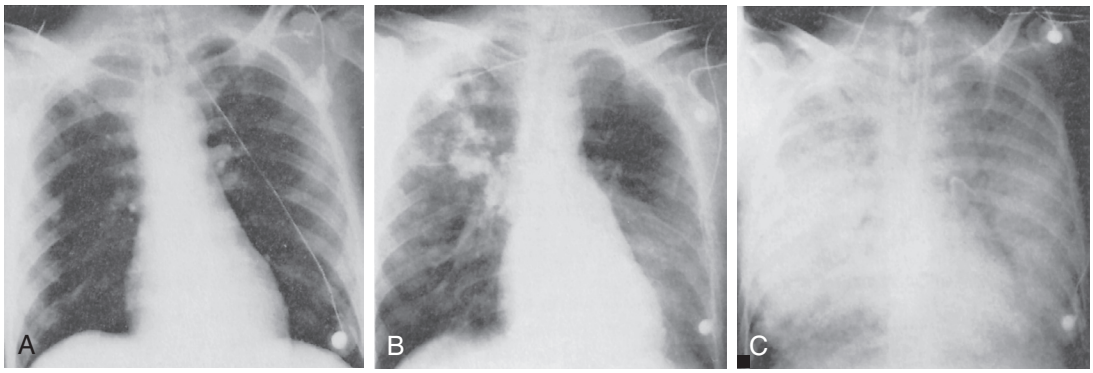

FIGURE A1-51 Acute respiratory distress syndrome. X-ray of a young man who had sustained severe trauma and blood loss in a road traffic accident; the limbs cover a period of 5 days from a relatively normal x-ray **(A)**, to bilateral inflitrates **(B)**, to bilateral "white out"' **(C)**, accompanied by severe hypoxemia. A Swan-Ganz catheter for measurement of pulmonary artery "wedge" pressure (as a reflection of left atrial pressure) can be seen *in situ* on the x-ray in **C**. The patient died shortly after the last film. (From Souhami RL, Moxham J: *Textbook of medicine*, ed 4, London, 2002, Churchill Livingstone.)

in more complications as compared with a central venous catheter.

- Although no dynamic profile is diagnostic of ARDS, the presence of pulmonary edema, a high cardiac output, and a low pulmonary capillary wedge pressure (PCWP) is characteristic of ARDS.
- It is important to remember that partially treated intravascular volume overload and flash pulmonary edema can have the hemodynamic features of ARDS; filling pressures can also be elevated by increased intrathoracic pressures or with fluid administration; cardiac function can be depressed by acidosis, hypoxemia, or other factors associated with sepsis.

Ventilatory support: mechanical ventilation is generally necessary to maintain adequate gas exchange (Table A1-38). General recommendations for ventilator settings in ARDS are described in Table A1-39. A low tidal volume and low plateau pressure ventilator strategy are recommended to avoid ventilator-induced injury. Assist-control is generally preferred initially with the following ventilator settings:

- Fio_2 1.0 (until a lower value can be used to achieve adequate oxygenation). When possible, minimize oxygen toxicity by maintaining Fio_2 at <60%.
- Tidal volume: Set initial tidal volume at 6 ml/kg of predicted body weight (PBW 5 50.0 1 0.91 [height: 152.4 cm] for men, PBW 5 45.5 1 0.91 [height: 152.4 cm] for women). The concept of using PBW is based on the fact that lung size depends most strongly on height and sex; PBW normalizes the tidal volume to lung size. Aim to maintain plateau pressure (Pplat) at <30 mm Hg.
- PEEP 5 cm H_2O or greater (to increase lung volume and keep alveoli open). PEEP should be applied in small increments of 3 to 5 cm H_2O (see Table A1-38) to achieve acceptable arterial saturation (>0.9) with nontoxic Fio_2 values (<0.6) and acceptable airway plateau pressures (>30 to 35 cm H_2O). It is important to remember that an increase in PEEP may lower cardiac output and, despite improvement in Pao_2, may actually have a negative effect on tissue oxygenation (the major determinants of tissue oxygenation are hemoglobin, percent saturation, and cardiac output). The optimal level of PEEP remains unestablished. Although higher levels of PEEP may help prevent life-threatening hypoxemia and be associated with lower hospital mortality in patients meeting criteria for ARDS, such benefit is unlikely in patients with less severe lung injury and a strategy of treating such patients with high PEEP levels may be harmful.
- Inspiratory flow: 60 L/min.
- Ventilatory rate: high ventilatory rates of 18 to 24 breaths/min are often necessary in patients with ARDS because of their increased physiologic dead space and smaller lung volumes. Patients must be monitored for excessive intrathoracic gas trapping (auto-PEEP or intrinsic PEEP) that can depress cardiac output.
- Sedation: GABA receptor agonists (including propofol and benzodiazepines such as midazolam) have traditionally been the most commonly administered sedative drugs for ICU patients. Recent trials indicate that the alpha-2 agonist dexmedetomidine (Precedex) may have distinct advantages. At comparable sedation levels, dexmedetomidine-treated patients spent less time on ventilator, experienced less delirium, and developed less tachycardia and hypertension. The most notable adverse effect of dexmedetomidine was bradycardia. Preliminary trials involving early administration of the neuromuscular blocking agent cisatracurium in patients with severe ARDS have shown improvement in the adjusted 90-day survival and increase in the time off the ventilator without increase in muscle weakness. However, patients who receive continuous infusions of sedatives generally need to be on mechanical ventilation longer than those who receive intermittent dosing. Paralysis of patients with neuromuscular blockade (NMB) to facilitate controlled ventilation is associated with protracted mechanical ventilation and postparalysis weakness. It should ideally be conducted for a brief period, and limited to patients with severe ARDS. Daily interruption of sedation (daily awakening) in mechanically ventilated patients is safe and is associated with a shorter length of mechanical ventilation.
- The management of sedation and delirium can have important effects on the outcomes of patients in ICUs. The best outcomes are achieved with the use of a protocol in which the depth of sedation and the presence of pain and delirium are routinely monitored, pain is treated promptly and effectively, sedation is kept to the necessary minimum for the comfort and safety of the patient, and early mobilization is achieved whenever possible (Reade, Finfer, 2014).

ACUTE GENERAL Rx

Identify and treat precipitating conditions:

- Blood and urine cultures and trial of antibiotics in presumed sepsis (routine administration of antibiotics in all cases of ARDS is not recommended).
- Prompt repair of bone fractures in patients with major trauma.
- Bowel rest and crystalloid resuscitation in pancreatitis.
- Fluid management: In most patients with ARDS, fluid restriction is associated with better outcomes than a liberal fluid policy. Optimal fluid and hemodynamic management of patients with ARDS should be patient specific; in general, administration of crystalloids is recommended if a downward trend in PCWP is associated with diminished cardiac index, resulting in prerenal azotemia, oliguria, and relative tachycardia. On the other hand, if PCWP increases with little or no change in cardiac index, one should consider diuretic therapy and use of low-dose dopamine (2 to 4 mg/kg/min) to maintain natriuresis and support adequate renal flow.
- Positioning the patient: changes in position can improve oxygenation by improving the distribution of perfusion to ventilated lung regions; repositioning (lateral decubitus

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TABLE A1-38 Management of Patients with ARDS

Calculate Predicted Body Weight (PBW)	• Males: PBW (kg) = 50 + 2.3[(height in inches) – 60] or 50 + 0.91[(height in cm) – 152.4]. • Females: PBW (kg) = 45.5 + 2.3[(height in inches) – 60] or 45.5 + 0.91[(height in cm) – 152.4].
Ventilator Mode	• Volume assist/control until weaning.
Tidal Volume (V_T)	• Initial V_T: 6 ml/kg predicted body weight. • Measure inspiratory plateau pressure (Pplat, 0.5 sec inspiratory pause) every 4 hours AND after each change in PEEP or V_T. • If Pplat >30 cm H_2O, decrease V_T to 5 or to ml/kg. • If Pplat <25 cm H_2O and V_T <6 ml/kg PBW, increase V_T by 1 ml/kg PBW.
Respiratory Rate (RR)	• With initial change in V_T, adjust RR to maintain minute ventilation. • Make subsequent adjustments to RR to maintain pH of 7.30-7.45, but do not exceed RR = 35/min, and do not increase set rate if $Paco_2$ <25 mm Hg.
I:E Ratio	• Acceptable range = 1:1 to 1:3 (no inverse ratio).
Fio_2, Positive End-Expiratory Pressure (PEEP), and Arterial Oxygenation	• Maintain Pao_2 = 55-80 mm Hg or Spo_2 = 88%-95% using the following PEEP/Fio_2 combinations:

Fio_2	0.3-0.4	0.4	0.5	0.6	0.7	0.8	0.9	1
PEEP	5-8	8-14	8-16	10-20	10-20	14-22	16-22	18-25

Acidosis Management	1. If pH <7.30, increase RR until pH ≥7.30 or RR = 35/min. 2. If pH remains <7.30 with RR = 35, consider bicarbonate infusion. 3. If pH <7.15, V_T may be increased (Pplat may exceed 30 cm H_2O).
Alkalosis Management	• If pH >7.45 and patient not triggering ventilator, decrease set RR but not below 6/min.
Fluid Management	• Once patients are out of shock, adopt a conservative fluid management strategy. • Use diuretics or fluids to target a central venous pressure (CVP) of <4 or a pulmonary artery occlusion pressure (PAOP) of <8.
Liberation from Mechanical Ventilation	• Daily interruption of sedation. • Daily screen for spontaneous breathing trial (SBT). • SBT when all of the following criteria are present: (a) Fio_2 <0.40 and PEEP <8 cm H_2O. (b) Not receiving neuromuscular blocking agents. (c) Patient awake and following commands. (d) Systolic arterial pressure >90 mm Hg without vasopressor support. (e) Tracheal secretions are minimal, and the patient has a good cough and gag reflex.
Spontaneous Breathing Trial	• Place patient on 5 mm Hg pressure support with 5 mm Hg PEEP *or* T-piece. • Monitor HR, RR, oxygen saturation for 30-90 minutes. • Extubate if there are no signs of distress (tachycardia, tachypnea, agitation, hypoxia, diaphoresis).

From Vincent JL, Abraham E, Moore FA, et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, Elsevier Saunders.

TABLE A1-39 Recommendations for Ventilator Settings in ARDS

Conventional Mechanical Ventilation		
Mode		Volume- or pressure-controlled "Airway pressure release ventilation" preferred when preservation of spontaneous ventilation is desired
Tidal volume	6-10 ml/kg	Permissive hypercapnia (increase <5 mm Hg/h) $PaCO_2$ 65-85 mm Hg well tolerated unless increased ICP Arterial pH >7.15
End-inspiratory plateau pressure	<30 cm H_2O	Above this limit, increased risks of barotrauma and air leaks
Positive end-expiratory pressure	10-15 cm H_2O	Lower PEEP levels, if heterogeneous lung injury Higher PEEP levels, if diffuse lung injury Consider early prone positioning (6-12 h)
Respiratory rate	20-60 beats/min	Adjusted to age; higher than normal may limit hypercapnia
Inspiratory/expiratory ratio	1:2 to 1:1	Check for inadvertent PEEP
FiO_2	<60%-80%	Depends on how the diseased lung may be recruited PaO_2 40-60 mm Hg, SpO_2 85%-95%
High-Frequency Oscillatory Ventilation		
Amplitude pressure	30-50 cm H_2O	To achieve visible chest vibrations
Mean airway pressure	15-30 cm H_2O	To achieve adequate chest recruitment (7 to 9 ribs)
Respiratory rate	3-10 Hz	Decrease to increase tidal volume (usually not measured)
Inspiratory/expiratory ratio	1:3 to 1:1	1:1 more appropriate in diffuse lung injury
FiO_2	<60%-80%	Depends on whether the lung may be recruited

ICP, Intracranial pressure.
From Fuhrman BP et al: *Pediatric critical care*, ed 4, Philadelphia, 2011, Saunders.

positioning) should be attempted in patients with hypoxemia that is not responsive to other medical interventions. Placing patients with moderate and severe hypoxemia in a prone position may improve their oxygenation. Recent trials (Guerin et al) have shown that in patients with severe ARDS, early application of prolonged prone-positioning sessions significantly decreases 28-day and 90-day mortality.

- Corticosteroids: routine use of corticosteroids in ARDS is not recommended; corticosteroids may be beneficial in patients with many eosinophils in the bronchoalveolar lavage fluid. Systemic infections should be ruled out or adequately treated before administration of corticosteroids. Use of methylprednisolone has not been shown to increase the rate of infectious complications but is associated with a higher rate of neuromuscular weakness. In addition, starting methylprednisolone therapy more than 2 wk after the onset of ARDS may increase the risk of death.
- Nutritional support: nutritional support, preferably administered by the enteral route, is necessary to maintain adequate colloid oncotic pressure and intravascular volume. The inclusion of eicosapentaenoic acid from fish oil may be beneficial in improving ventilation requirements and length of stay in patients with ARDS.

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- Tracheostomy: tracheostomy is warranted in patients requiring >2 wk of mechanical ventilation; discussion regarding tracheostomy should begin with patient (if alert and oriented) and family members/legal guardian after 5 to 7 days of ventilatory support. Early tracheostomy (within 4 days of admission to critical care) does not limit mortality and results in many unneeded procedures (Young et al, 2013).
- Some form of deep vein thrombosis prophylaxis is indicated in all patients with ARDS.
- Stress ulcer prophylaxis with sucralfate suspension (by nasogastric tube), or IV proton pump inhibitors or H_2 blockers.
- The use of surfactant remains controversial. Patients who receive surfactant have a greater improvement in gas exchange in the initial 24-hour period than patients who receive standard therapy alone; however, the use of exogenous surfactant does not improve survival.

DISPOSITION

- Patients who survive ARDS are at risk of diminished functional capacity, mental illness, and decreased quality of life. Prognosis for ARDS varies with the underlying cause. Prognosis is worse in patients with chronic liver disease, nonpulmonary organ dysfunction, sepsis, and advanced age.
- Elevated values of dead space fraction ([$Paco_2$ 2 $Peco_2$]/$Paco_2$; normal is <0.3) is associated with an increased risk of death.
- In ARDS, the percentage of potentially recruitable lung is variable and associated with the response to PEEP.
- Overall mortality rate varies between 32% and 45%. Most deaths are attributable to sepsis or multiorgan dysfunction rather than primary respiratory causes.
- Recent trials have shown that as compared with the current standard of care, a ventilator strategy using esophageal measures to estimate the transpulmonary pressure significantly improves oxygenation and compliance. Further trials will determine if this approach should be widely adapted.
- Strategies for treatment of life-threatening refractory hypoxemia (prone positioning, inhaled nitric acid, extracorporeal membrane oxygenation (ECMO), high-frequency oscillatory ventilation, recruitment maneuvers) may improve oxygenation, but their impact on mortality remains unproven. Use of ECMO in combination with lung protective ventilation was found to be beneficial as a treatment strategy early in the course of ARDS related to H1N1 infection. Extracorporeal gas exchange may allow the use of low tidal volumes and lower levels of inspired oxygen and use of higher PEEP if desired. ECMO is costly and labor-intensive. The role and proper use of ECMO for patients with ARDS have not been clearly defined. General indications for venovenous ECMO in severe cases of ARDS are:
  1. Severe hypoxemia (e.g., ratio of PaO_2 to FiO_2 <80 despite the application of high levels of PEEP [typically 15 to 20 cm H_2O]) for at least 6 hr in patients with potentially reversible respiratory failure
  2. Uncompensated hypercapnia with acidemia (pH <7.15) despite the best accepted standard of care for management with a ventilator
  3. Excessively high end-inspiratory plateau pressure (>35 to 45 cm H_2O, according to the patient's body size) despite the best accepted standard of care for management with a ventilator

REFERRAL

Surgical referral for tracheostomy (see "Acute General Rx").

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Acute Respiratory Distress Syndrome (ARDS) (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

http://internalmedicinebook.com/

EVIDENCE

Abstract[1]

Background:
The acute respiratory distress syndrome (ARDS) is a proinflammatory condition that often complicates trauma and critical illness. Animal studies have shown that both gender and sex hormones play an important role in inflammatory regulation. Human data are scant regarding the role of gender and sex hormones in developing ARDS. Our objective was to describe gender and hormonal differences in patients who develop ARDS in a large cohort of critically injured adults.

Methods:
A prospective cohort study of adult trauma patients requiring intensive care unit admission for at least 48 hours was performed. Demographic and clinical data were collected prospectively, and sex hormones were assayed at study entry (48 hours). The primary outcome was the development of ARDS. Multivariate logistic regression was used to determine the adjusted odds of death associated with differences in gender.

Results:
Six hundred forty-eight patients met entry criteria, and 180 patients developed ARDS (31%). Women were more likely to develop ARDS (35% vs. 25%, $p = 0.02$). This association remained after adjusting for age, mechanism of injury, injury severity, and blood product transfusion (odds ratio, 1.6; 95% confidence interval: 1.1–2.4; $p = 0.02$). Of patients with ARDS, there was no difference in mortality related to gender (22% mortality in women with ARDS vs. 20% in men; $p =$ not significant). A proinflammatory sex hormone profile (low testosterone and high estradiol) was associated with ARDS in both men and women.

Conclusion:
Women are more likely than men to develop ARDS after critical injury. Despite the increased incidence in ARDS, the mortality in patients with ARDS does not differ according to gender. The inflammatory properties of sex hormones may contribute to ARDS, but they do not fully explain observed gender differences. Ⓐ

Abstract[2]

Rationale:
Despite recent advances in critical care and ventilator management, acute lung injury and acute respiratory distress syndrome continue to cause significant morbidity and mortality. Granulocyte-macrophage colony stimulating factor may be beneficial for patients with acute respiratory distress syndrome.

Objectives:
To determine whether intravenous infusion of granulocyte-macrophage colony stimulating factor would improve clinical outcomes for patients with acute lung injury/acute respiratory distress syndrome.

Design:
A randomized, double-blind, placebo-controlled clinical trial of human recombinant granulocyte-macrophage colony stimulating factor vs. placebo. The primary outcome was days alive and breathing without mechanical ventilatory support within the first 28 days after randomization. Secondary outcomes included mortality and organ failure-free days.

Setting:
Medical and surgical intensive care units at three academic medical centers.

Patients:
One hundred thirty individuals with acute lung injury of at least 3 days duration were enrolled, out of a planned cohort of 200 subjects.

Interventions:
Patients were randomized to receive human recombinant granulocyte-macrophage colony stimulating factor (64 subjects, 250 $\mu g/M^2$) or placebo (66 subjects) by intravenous infusion daily for 14 days. Patients received mechanical ventilation using a lung-protective protocol.

Measurements and Main Results:
There was no difference in ventilator-free days between groups (10.7±10.3 days placebo vs. 10.8±10.5 days granulocyte-macrophage colony stimulating factor, $p = <82$). Differences in 28-day mortality (23% in placebo vs. 17% in patients receiving granulocyte-macrophage colony stimulating factor ($p = <31$) and organ failure-free days (12.8±11.3 days placebo vs. 15.7±11.9 days granulocyte-macrophage colony stimulating factor, $p = <16$) were not statistically significant. There were similar numbers of serious adverse events in each group.

Conclusions:
In a randomized phase II trial, granulocyte-macrophage colony stimulating factor treatment did not increase the number of ventilator-free days in patients with acute lung injury/acute respiratory distress syndrome. A larger trial would be required to determine whether treatment with granulocyte-macrophage colony stimulating factor might alter important clinical outcomes, such as mortality or multiorgan failure. (ClinicalTrials.gov number, NCT00201409 [ClinicalTrials.gov]). Ⓐ

Abstract[3]

Rationale:
β_2-Adrenergic receptor agonists accelerate resolution of pulmonary edema in experimental and clinical studies.

Objectives:
This clinical trial was designed to test the hypothesis that an aerosolized β_2-agonist, albuterol, would improve clinical outcomes in patients with acute lung injury (ALI).

Methods:
We conducted a multicenter, randomized, placebo-controlled clinical trial in which 282 patients with ALI receiving mechanical ventilation were randomized to receive aerosolized albuterol (5 mg) or saline placebo every 4 hours for up to 10 days. The primary outcome variable for the trial was ventilator-free days.

Measurements and Main Results:
Ventilator-free days were not significantly different between the albuterol and placebo groups (means of 14.4 and 16.6 d, respectively; 95% confidence interval for the difference, −4.7 to 0.3 d; $P = 0.087$). Rates of death before hospital discharge were not significantly different between the albuterol and placebo groups (23.0 and 17.7%, respectively; 95% confidence interval for the difference, −4.0 to 14.7%; $P = 0.30$). In the subset of patients with shock before randomization, the number of ventilator-free days was lower with albuterol, although mortality was not different. Overall, heart rates were significantly higher in the albuterol group by approximately 4 beats/minute in the first 2 days after randomization, but rates of new atrial fibrillation (10% in both groups) and other cardiac dysrhythmias were not significantly different.

Conclusions:
These results suggest that aerosolized albuterol does not improve clinical outcomes in patients with ALI. Routine use of β_2-agonist therapy in mechanically ventilated patients with ALI cannot be recommended.Clinical trial registered with www.clinicaltrials.gov (NCT 00434993). Ⓐ

Abstract[4]

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) represent a continuum of a clinical syndrome of respiratory failure due to refractory hypoxia. ARDS is differentiated from ALI by a greater degree of hypoxemia and is associated with higher morbidity and mortality. The mortality for ARDS ranges from 10% to 41%, with survivors usually requiring long-term rehabilitation to regain normal physiologic function. Numerous pharmacologic therapies have been studied for prevention and treatment of ARDS; however, studies demonstrating clear clinical benefit for ARDS-related mortality and morbidity are limited. In this focused review, controversial pharmacologic therapies that have demonstrated, at minimum, a modest clinical benefit are discussed. Three pharmacologic treatment strategies are reviewed in detail: corticosteroids, fluid management, and neuromuscular blocking agents. Use of corticosteroids to attenuate inflammation remains controversial. Available evidence does not support early administration of corticosteroids. Additionally, administration after 14 days of disease onset is strongly discouraged. A liberal fluid strategy during the early phase of comorbid septic shock, balanced with a conservative fluid strategy in patients with ALI or ARDS during the postresuscitation phase, is the optimum approach for fluid management. Available evidence supports an early, short course of continuous-infusion cisatracurium in patients presenting with severe ARDS. Evidence of safe

and effective pharmacologic therapies for ARDS is limited, and clinicians must be knowledgeable about the areas of controversies to determine application to patient care. Ⓐ

This is a useful review of medications and medication studies in acute respiratory distress syndrome (ARDS) studies. The new frontier, in my opinion, will be a retro approach: How can we block progression to ARDS and/or systemic inflammatory response syndrome in high-risk patients? Much effort was put into this in the 1970s and 1980s. However, care strategies appear to have plateaued after the ARDS Clinical Trials Network trial.

J. A. Barker, MD, CPE, FACP, FCCP, FAASM

Evidence-Based References

Heffernan DS et al.: Gender and acute respiratory distress syndrome in critically injured adults: a prospective study, *J Trauma* 71:878–885, 2011. Ⓐ

Paine R et al.: A randomized trial of recombinant human granulocyte-macrophage colony stimulating factor for patients with acute lung injury, *Crit Care Med* 40:90–97, 2012. Ⓐ

The National Heart: Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network: Randomized, placebo-controlled clinical trial of an aerosolized β-agonist for treatment of acute lung injury, *Am J Respir Crit Care Med* 184:561–568, 2011. Ⓐ

Shafeeq H, Lat I: Pharmacotherapy for acute respiratory distress syndrome, *Pharmacotherapy* 32:943–957, 2012. Ⓐ

SUGGESTED READINGS

ARDS Definition Task Force: Acute respiratory distress syndrome, the Berlin definition, *JAMA* 307(23):2526–2533, 2012.

Briel M et al.: Higher vs lower PEEP in patients with acute lung injury and SRDS, *JAMA* 303(9):865–873, 2010.

Brodie D, Bacchetta M: Extracorporeal membrane oxygenation for ARDS in adults, *N Engl J Med* 365:1905–1914, 2011.

Checkley W: Extracorporeal membrane oxygenation as a first-line treatment strategy for ARDS: is the evidence sufficiently strong? *JAMA* 306:1703–1704, 2011.

Guerin C et al.: Prone positioning in severe acute respiratory distress syndrome, *N Engl J Med* 368:2159–2168, 2013.

Malhotra A: Low tidal volume ventilation in the acute respiratory distress syndrome, *N Engl J Med* 357:1113, 2007.

Mercat A et al.: Positive end-respiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome, *JAMA* 299(6):646–655, 2008.

Papazian L et al.: Neuromuscular blockers in early ARDS, *N Engl J Med* 363:1107–1116, 2010.

Pipeling MR, Fan E: Therapies for refractory hypoxemia in ARDS, *JAMA* 304(22):2521–2527, 2010.

Putensen C et al.: Meta-analysis: ventilation strategies and outcomes of the ARDS and acute lung injury, *Ann Intern Med* 151:566–576, 2009.

Reade MC, Finfer S: Sedation and delirium in the intensive care unit, *N Engl J Med* 370:444–454, 2014.

Riker RR et al.: Dexmedetomidine vs. midazolam for sedation of critically ill patients, *JAMA* 301(5):489–499, 2009.

Saguil A, Fargo M: Acute respiratory distress syndrome: diagnosis and management, *Am Fam Physician* 86:352–358, 2012.

Serpa Neto A et al.: Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without ARDS, *JAMA* 308:1651–1658, 2012.

Taccone P et al.: Prone positioning in patients with moderate and severe ARDS, *JAMA* 302(18):1977–1984, 2009.

Talmor D et al.: Mechanical ventilation by esophageal pressure in acute lung injury, *N Engl J Med* 359:2095–2104, 2008.

Wheeler AP: Acute lung injury and the acute respiratory distress syndrome, *Lancet* 369:1553, 2007.

Young D: Effect of early vs late tracheostomy on survival in patients receiving mechanical ventilation: the Trachman Randomized Trial, *JAMA* 309:2121, 2013.

BASIC INFORMATION

DEFINITION

Acute stress disorder (ASD) includes severe acute stress reactions (ASRs) that occur between 3 days to one month after exposure to a traumatic event.

SYNONYMS

ASD, ASR

ICD-9CM and DSM-5 CODES
308.3 Other acute reactions to stress
ICD-10CM CODES
F43.0 Acute stress reaction

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Prevalence varies according to the nature of the traumatic event. Prevalence is estimated at less than 20% in cases that do not involve assault and at 20% to 50% in cases of interpersonal trauma (e.g., rape, witnessing a mass shooting)
PREDOMINANT AGE: Diagnosed among individuals of all ages. Children may manifest symptoms differently (e.g., may report frightening dreams that do not directly reflect the trauma). Young children may also not report fear at the time of the trauma or when re-experiencing the trauma
PREDOMINANT SEX: Females more than males
GENETICS: Differential function of the serotonin transporter may mediate differential responses to trauma. The 5-HTTLPR may constitute a genetic candidate region. Higher rates of ASD among women may be attributable to higher rates of violence against women and sex-linked neurobiological differences in the stress response.
RISK FACTORS:

- Greater perceived severity of the trauma (i.e., catastrophic interpretations of the event, exaggerated appraisals of future harm, hopelessness), high levels of negative affect, avoidant coping style, history of prior trauma, lack of social support, premorbid mental disorder (e.g., preexisting anxiety or depressive disorders)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

DSM-5 criteria are met when the following criteria are satisfied:

A. Exposure to actual or threatened serious injury, death, or sexual violation in one or more of the following ways:
- Directly experiencing a traumatic event
- Witnessing a traumatic event as it occurred
- Learning that a traumatic event occurred to a family member or close friend
- Repeated or extreme exposure to traumatic details of an event

B. Presence of nine or more of the following symptoms from any of the following five categories: 1) Intrusion; 2) negative mood; 3) dissociation; 4) avoidance; and 5) arousal
- Recurrent, distressing, involuntary memories of the trauma (intrusion)
- Recurrent distressing dreams relating to the trauma (intrusion)
- Flashbacks to the event, in which the individual feels/acts as if the event is recurring (intrusion)
- Intense or prolonged psychological distress or physiological reaction in response to cues that are reminiscent of the trauma (intrusion)
- Continual inability to experience positive emotions (negative mood)
- Altered sense of reality (dissociation)
- Inability to remember components of the trauma (dissociation)
- Avoidance of memories, thoughts, or feelings associated with the event (avoidance)
- Avoidance of external reminders of the event (avoidance)
- Sleep disturbance (arousal)
- Irritability and anger outbursts (arousal)
- Hypervigilance (arousal)
- Difficulties concentrating (arousal)
- Exaggerated startle response (arousal)

Symptoms typically begin immediately after the trauma and must persist for at least 3 days (up to one month) and result in clinically significant impairment in functioning. If symptoms persist for greater than 1 month, a diagnosis of post-traumatic stress disorder (PTSD) may be considered. Symptoms must not be attributable to a medical condition or substance use.

ETIOLOGY

Factors predicting the development of ASD have not been established; however, multiple theoretical models have been proposed. Dissociative models propose that individuals minimize the emotional consequences of trauma by restricting awareness of the event to reduce fear. Cognitive perspectives propose that intentional cognitive processes (e.g., avoidance, distraction, dysfunctional appraisals, attribution of responsibility) result in pathological reactions to trauma. Biological theories focus on the immediate effects of trauma on neuronal function, including cortisol, catecholamines, glucocorticoids, serotonin, and endogenous opioids as mediating factors of the trauma response.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Adjustment disorder
- Panic disorder
- Dissociative disorders
- PTSD
- Obsessive-compulsive disorder
- Psychotic disorders
- Traumatic brain injury

WORKUP

- Diagnosis is made based on individual interviews, including a history of past trauma, age at the time of the trauma, and duration of the trauma. Structured clinical interviews may be used and may be supplemented with standardized self-report measures. It should be noted that dissociative symptoms may prevent individuals from remembering components of the trauma, as well as remembering feelings of fear, helplessness, or horror. Collateral data from other sources (family members, close friends, medical providers, therapists, etc.) may be useful.

LABORATORY TESTS

- None indicated

IMAGING STUDIES

- None indicated

TREATMENT

Early treatment should focus on establishing a therapeutic alliance and acknowledging fears about reexposure. Resilience-focused psychosocial interventions may focus on better tolerating the distress of trauma-related memories, reducing re-experiencing and reactivity to reminders of the trauma, reducing trauma-related avoidance and sleep disturbances and nightmares, increasing social support, decreasing behaviors that interfere with daily life, limiting generalization of the danger experienced, and altering maladaptive attributions and appraisals. Early behavioral and educational interventions also show small to moderate effects for reducing symptoms of psychological trauma. In cases of interpersonal trauma, safety planning is necessary for individuals who remain in unsafe situations or relationships. Pharmacological treatment is typically reserved for individuals who have already received psychotherapy. There are few controlled pharmacological treatment trials for ASD. There are currently no medications approved by the FDA for treatment of ASD. Clinicians may consider FDA-approved medications for PTSD, such as paroxetine and sertraline.

NONPHARMACOLOGIC THERAPY

- Cognitive behavioral therapy
- Prolonged exposure
- Cognitive processing therapy
- Relaxation and mindfulness

ACUTE GENERAL Rx

- Acute medication may be necessary when the individual is dangerous, agitated, or psychotic. In emergencies, short-acting benzodiazepines or neuroleptics with minimal side effects may be effective.
- Antiadrenergic agents may be useful for treatment of arousal.
- Brief, time-limited treatment using benzodiazepines may be useful for treating arousal, insomnia, and anxiety. It should be noted that prolonged use of benzodiazepines has been associated with higher rates of PTSD.
- Prazosin is recommended for treatment of nightmares.
- SSRIs and other antidepressants may be useful for re-experiencing symptoms, avoidance, and hyperarousal.

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COMPLEMENTARY & ALTERNATIVE MEDICINE

Patients may find activities that increase relaxation (i.e., yoga, mindfulness, meditation) useful.

DISPOSITION

Treatment should be delivered in the least restrictive environment that can ensure patient safety. Most patients with ASD can be managed in an outpatient setting. Partial or inpatient hospitalization may be necessary for crisis management and may be considered for patients who have comorbid psychiatric/medical diagnoses; who are experiencing suicidal or homicidal ideation, plans, or intention; or who are severely ill.

REFERRAL

Patients are treated by a mental health clinician.

PEARLS & CONSIDERATIONS

COMMENTS

- Although many individuals with ASD go on to develop PTSD, many with ASD do not go on to develop PTSD. Available data at this time suggest that ASD criteria are not adequate for identifying individuals at risk for developing PTSD.
- Standardized assessment tools, such as the Structured Clinical Interview for DSM-5 Dissociative Disorders (SCID-D), the Acute Stress Disorder Interview (ASDI), the Stanford Acute Stress Reaction Questionnaire (SASRQ), and the Acute Stress Disorder Scale (ASDS), may be helpful in the diagnosis of ASD and/or treatment monitoring.

PREVENTION

- Critical incident stress debriefing (CISD) following a trauma is typically administered in one two to three-hour group session within 72 hours of the trauma, with the goals of allowing survivors to "vent." There is some evidence that CISD does not prevent PTSD and may contribute to poor recovery. Psychological first aid (PFA) is designed to improve outcomes following trauma by fostering safety, calmness, social connectedness, and optimism. Although PFA has received some empirical support, questions remain regarding the optimal format of administration.

PATIENT & FAMILY EDUCATION

- National Center for PTSD, Public Section, Information on Trauma and PTSD for Veterans, the General Public and Families: Acute Stress Disorder. (http://www.ptsd.va.gov/public/pages/acute-stress-disorder.asp)

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Post-traumatic Stress Disorder (Related Key Topic)

AUTHOR: **LINDSAY M. ORCHOWSKI, PH.D.**

SUGGESTED READINGS

Armour C, Elkit A, Shevlin M: The latent structure of acute stress disorder: A post-traumatic stress disorder approach, *Psychological Trauma: Theory, Research, Practice, and Policy* 5:18–25, 2013.

Bryant RA, Friedman MJ, Speigel D, Ursano R, Strain J: A review of acute stress disorder in DSM-5, *Depression and Anxiety* 28:802–817, 2011.

Kouchy EM, Galovski TE, Nixon RDV: Acute stress disorder: Conceptual issues and treatment outcomes, *Cognitive Behavioral Practice* 19:437–450, 2012.

Tol WA, Barbui C, van Ommeren M: Management of acute stress, PTSD, and bereavement: WHO recommendations, *JAMA: Journal of the American Medical Association* 310:477–478, 2013.

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BASIC INFORMATION

DEFINITION

Acute tubular necrosis (ATN), the most common form of acute renal failure (ARF), is a potentially reversible abrupt decline in renal function occurring over minutes to days. ATN may be secondary to ischemia or toxic insult or may be multifactorial.

SYNONYMS

ATN
Acute tubular injury
Ischemic or nephrotoxic acute renal failure (ARF)
Tubular necrosis, acute

ICD-9CM CODES
584.5 Acute renal failure with lesion of tubular necrosis
586 Renal failure, unspecified

ICD-10CM CODES
N17.0 Acute kidney failure with tubular necrosis
N19 Unspecified kidney failure

EPIDEMIOLOGY & DEMOGRAPHICS

- Most common cause of ARF among hospitalized patients.
- Patients with impaired afferent arteriolar autoregulation are most vulnerable.
- Elderly patients and patients with atherosclerotic disease, hypertension, and chronic renal failure are at an increased risk.
- Early identification of ATN is paramount as many etiologies are reversible.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- No apparent physical findings.
- Suspect ischemic ATN in the setting of hemorrhage, hypotension, recent surgery, sepsis
- Suspect nephrotoxic ATN in the setting of contrast imaging, nephrotoxic medications, rhabdomyolysis, hemolysis, or myeloma
- The classic progression of ATN includes three phases, but can be highly variable:
  1. Initiation phase (hours to days): Renal hypoperfusion, evolving ischemia. Acute decrease in glomerular filtration rate (GFR), sudden rise in BUN and serum creatinine, and decrease in urine output.
  2. Maintenance phase (1 to 2 wk): Renal cell injury established, GFR stabilizes at its nadir (5 to 10 ml/min), urine output at its lowest (usually 40 to 400 ml/day). May be complicated by hyperkalemia, metabolic acidosis, uremia, salt and water overload. Patients are at an increased risk of infection, with approximately 25% of deaths from ATN occurring during the maintenance phase.
  3. Recovery phase (>2 wk): Renal parenchymal cell repair and regeneration, gradual return of GFR to premorbid levels; may be complicated by a marked diuresis.

PATHOLOGIC FINDINGS

- Ischemic ATN: Characterized by focal necrosis of the tubular epithelium, often with associated basement membrane disruption and occlusion of the tubular lumen by casts. Eosinophilic hyaline casts and pigmented granular casts are common. Interstitial edema and leukocytic accumulation within the vasa recta may also be observed.
- Nephrotoxic ATN: Necrosis is most prominent in the proximal tubule and the basement membrane is commonly spared.

ETIOLOGY

- Diagnosis of exclusion. Pre-renal, post-renal, and other intrinsic renal causes of ARF must be ruled out.
- Ischemic processes that may contribute to ATN include hypotension, shock, prolonged prerenal azotemia, and surgery.
- Renal hypoperfusion may occur without clinically apparent hypotension.
- Medications: NSAIDs, COX-2 inhibitors, antimicrobial drugs (acyclovir, foscarnet, aminoglycosides, amphotericin B, pentamidine, cephalosporins), calcineurin inhibitors, cisplatin, ifosfamide, thiazides, anesthetics, ACE inhibitors
- Radiocontrast (contrast nephropathy)
- Hemoglobin and myoglobin (rhabdomyolysis, transfusion reactions)
- Heavy metals
- Crystals (urate, oxalate, acute phosphate nephropathy)
- Hypercalcemia
- Immunoglobulin light chain disease (amyloidosis, multiple myeloma, MGUS)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Rapidly progressive glomerular nephritis (RPGN), diffuse vasculitic processes such as microscopic polyangiitis, acute papillary necrosis secondary to pyelonephritis, interstitial nephritis, diffuse cortical necrosis

LABORATORY TESTS

- Urinalysis for specific gravity, U_{Na}, P_{Cr}, P_{Na}, U_{Cr}.
- Urine analysis with microscopic inspection.
- Calculate fractional excretion of sodium: $FE_{Na} = [(U_{Na} \times P_{Cr}) / (P_{Na} \times U_{Cr})] \times 100$.
- Potential biomarkers for early diagnosis of ATN are currently under investigation.

LABORATORY FINDINGS

- FE_{Na} >1%
- U_{Na} >40 mmol/L
- Urinalysis: "muddy brown" granular and epithelial cell casts
- SG <1.015

IMAGING STUDIES

Not indicated

TREATMENT

ACUTE GENERAL Rx

Treatment is etiology-specific. Hemodynamic abnormalities should be corrected and potentially nephrotoxic agents discontinued. Peritoneal or hemodialysis may be required until renal function is restored. Diuretic use is not recommended.

DISPOSITION

Renal function typically recovers within 1 to 2 wk of insult. Outcomes are variable and depend upon premorbid renal function as well as the mechanism of injury. Ischemic ATN in the setting of severe multiorgan failure may carry a mortality rate exceeding 50%. However, in patients who survive the inciting incident, up to 95% will recover, with GFR approaching premorbid levels. The absence of oliguria (referred to as nonoliguric ATN) imparts a benign prognosis.

REFERRAL

Renal consultation for severe cases of ATN requiring dialysis

PEARLS & CONSIDERATIONS

COMMENTS

Prevention is paramount.

PREVENTION

- Aggressive restoration of intravascular volume in surgical/trauma patients to prevent ischemic ATN.
- Appropriate dosing of nephrotoxic agents in regards to body weight and GFR.
- Low-volume contrast, pre- and post-study intravenous fluids, and acetylcysteine (600 mg PO bid × 2 days or 600 to 1200 mg IV bid) to reduce the risk of contrast nephropathy.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Acute Kidney Injury (Related Key Topic)

AUTHOR: **BRIAN SAVOIE, M.D.**

http://internalmedicinebook.com/

SUGGESTED READINGS

Abuelo JG: Normotensive ischemic acute renal failure, *N Engl J Med* 357(8):797–805, 2007.

Gill N et al.: Renal failure secondary to acute tubular necrosis: epidemiology, diagnosis, and management, *Chest* 128:2847–2863, 2005.

Schmitt R et al.: Recovery of kidney function after acute kidney injury in the elderly: a systematic review and meta-analysis, *Am J Kidney Dis* 52(2):262–271, 2008.

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Acute Urinary Retention (AUR)

BASIC INFORMATION

DEFINITION

The acute cessation of urinary flow; inability to void.

SYNONYMS

Inability to urinate

ICD-9CM CODES
788.20 Retention of urine, unspecified
ICD-10CM CODES
R33.9 Retention of urine, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Can occur in any age group and both sexes. It is the most common urologic emergency.
PEAK INCIDENCE: Males older than age 60. Over a 5-year period, AUR will occur in 10% of men older than 70 and one third of men older than 80.
PREVALENCE: Increased longevity has caused an increase in prevalence.
PREDOMINANT SEX AND AGE: Men older than 60 years.
GENETICS: None known.
RISK FACTORS: Obstructive risk factors include benign prostatic hypertrophy (BPH) and bladder, pelvic, and urethral masses. Acute trauma, surgery, medications (especially over-the-counter [OTC] antihistamines), neurologic disease, and infection can be contributing or precipitating factors, particularly when superimposed on obstructive risk factors.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients will present with the acute inability to pass urine.
- Pain in the lower abdomen and suprapubic region is typical (this is not typically present with chronic urinary retention due to the more gradual onset).
- The bladder may be palpable on abdominal or rectal exam. There may be tenderness with deep palpation.
- Patients with cognitive deficits may present with restlessness, discomfort, worsened confusion, or delirium but may not be able to give the history of urinary retention.

ETIOLOGY

- Most commonly the result of obstruction from various causes, including BPH and bladder and pelvic masses.
- Nonobstructive causes include medications, surgery, trauma, neurologic disease, and infection.
- In older patients, cause is frequently multifactorial, with an underlying obstructive risk factor and an acute precipitant.
- In women, AUR may be caused by benign tumors (especially fibroids); malignant tumors of pelvic, urethral, or vaginal origin; postpartum vulvar edema; or labial fusion.
- Infection such as prostatitis, urethritis, and genital herpes and herpes zoster can also cause AUR.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- AUR is typically self-evident to the cognitively intact patient, and to the physician. Differential diagnosis focuses on the underlying cause of the problem.

WORKUP

- History should focus on urologic symptoms, including dysuria, hematuria, history of retention, and urologic cancer.
- Review of symptoms (ROS) should include fever, back pain, neurologic symptoms, and rash.
- History should include a complete list of prescribed and OTC medications.
- Rectal exam for masses, fecal impaction, perineal sensation, and sphincter tone.
- Pelvic exam for female patients.
- Neurologic exam to rule out an underlying neurologic cause.

LABORATORY TESTS

- Creatinine level. Note that in acute retention this may not be elevated above baseline.
- Urinalysis and culture (which will be obtained via catheterization).
- BUN, electrolytes
- Prostate-specific antigen (PSA) testing is not helpful in the acute situation, as it is expected to be elevated during an episode of retention.

IMAGING STUDIES

- Imaging may not be necessary when AUR is felt to be due to reversible causes.
- Ultrasound may be valuable, particularly if there is suspicion of a pelvic mass.
- Pelvic computed tomography (CT) scan is done if, on physical exam or ultrasound, masses are found requiring further evaluation.
- Magnetic resonance imaging (MRI) is used when symptoms suggest spinal cord problems.
- Evaluation of bladder function may be considered after initial management, particularly in women with no evidence of anatomic obstruction.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Given that AUR recurs 68% of the time when caused by BPH, consider surgical treatment for this issue. Transurethral resection of the prostate (TURP) should be delayed until at least 30 days after the episode of AUR, to minimize surgical complications.

ACUTE GENERAL Rx

- Prompt bladder decompression and drainage is the initial management of AUR.
- Urethral catheterization should be promptly initiated if the patient has no history of recent genitourinary (GU) surgery.
- If there is a history of recent surgery, suprapubic catheterization is indicated.
- Partial drainage and clamping of catheter is not necessary and may increase the risk of urinary tract infection (UTI).
- Clean intermittent catheterization (CIC) may be considered, although in the acute setting it may be limited by patient acceptance and the time required for teaching this technique. Use of CIC may improve the rate of spontaneous voiding.

CHRONIC Rx

- Consider catheter removal in 2 to 3 days, particularly in patients younger than 65 years old, when the catheterized volume is less than 1 L, and when a precipitating event can be identified.
- Otherwise 1 to 2 weeks of catheterization should be considered before voiding trial.
- Alpha blockers are effective in treatment of the symptoms of BPH and may increase the success of trials of early removal of catheter.
- 5-Alpha reductase inhibitors are not effective for acute management when AUR is caused by BPH, due to slow onset of the decrease of prostate volume.

COMPLEMENTARY & ALTERNATIVE MEDICINE

- None noted.

DISPOSITION

- Patients may be sent home if close follow-up can be assured.
- Hospital admission may be needed, particularly in patients with urosepsis or when retention is due to malignancy or spinal cord compression.

REFERRAL

- To urology, particularly in cases where the underlying cause cannot be addressed acutely or is not self-limited.
- To gynecology when gynecologic masses are the underlying cause of AUR.

PEARLS & CONSIDERATIONS

PREVENTION

Patients with BPH should avoid the use of antihistamines, sedatives, and other medications that can precipitate acute retention. Inhaled anticholinergic agents may increase the risk of AUR and should be used cautiously in patients with risk factors, especially BPH.

PATIENT/FAMILY EDUCATION

Education regarding catheter use and care is helpful in patients who are discharged to home.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **MARGARET TRYFOROS, M.D.**

SUGGESTED READINGS

Curtis LA et al.: Acute urinary retention and urinary incontinence, *Emerg Med Clin North Am* 19:591, 2001.

Fitzpatrick JM, Kirby RS: Management of acute urinary retention, *BJU Int* 97 (Suppl 2):16, 2006.

Mevcha A, Drake MJ: Etiology and management of urinary retention in women, *Indian J Urol* 26(2):230–235, 2010.

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BASIC INFORMATION

DEFINITION

Adrenal insufficiency is characterized by inadequate secretion of corticosteroids resulting from partial or complete destruction of the adrenal glands.

SYNONYMS

Primary adrenocortical insufficiency
Addison disease

ICD-9CM CODES
255.4 Addison disease
ICD-10CM CODES
E27.1 Primary adrenocortical insufficiency
E27.2 Addisonian crisis
E27.3 Drug-induced adrenocortical insufficiency
E23.3 Hypopituitarism

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 1 in 20,000 persons
PREDOMINANT SEX: Female/male ratio of 2:1

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Adrenal insufficiency may present insidiously with nonspecific symptoms. A high index of suspicion is required for diagnosis. About half of patients may present acutely with adrenal crises. Table A1-40 summarizes the clinical features of primary adrenal insufficiency.
- Hyperpigmentation of skin (Figs. EA1-52 and EA1-53) and mucous membranes is a cardinal sign of adrenal insufficiency: more prominent in palmar creases, buccal mucosa, pressure points (elbows, knees, knuckles), perianal mucosa, and around areolas of nipples
- Hypotension, postural dizziness
- Generalized weakness, chronic fatigue, malaise, anorexia
- Amenorrhea and loss of axillary hair in females

ETIOLOGY

- Autoimmune destruction of the adrenal glands (80% of cases)
- Tuberculosis (TB) (15% of cases)
- Carcinomatous destruction of the adrenal glands, lymphoma
- Adrenal hemorrhage (anticoagulants, trauma, coagulopathies, pregnancy, sepsis)
- Adrenal infarction (antiphospholipid syndrome, arteritis, thrombosis)
- AIDS (adrenal insufficiency develops in 30% of patients with AIDS, often cytomegalovirus [CMV] adrenalitis)
- Other: sarcoidosis, amyloidosis, hemochromatosis, Wegener's granulomatosis, postoperative, fungal infections (candidiasis, histoplasmosis)

TABLE A1-40 Clinical Features of Primary Adrenal Insufficiency

Feature	Frequency (%)
Symptoms	
Weakness, tiredness, fatigue	100
Anorexia	100
Gastrointestinal symptoms	92
Nausea	86
Vomiting	75
Constipation	33
Abdominal pain	31
Diarrhea	16
Salt craving	16
Postural dizziness	12
Muscle or joint pains	13
Signs	
Weight loss	100
Hyperpigmentation	94
Hypotension (<110 mm Hg systolic)	88-94
Vitiligo	10-20
Auricular calcification	5
Laboratory Findings	
Electrolyte disturbances	92
Hyponatremia	88
Hyperkalemia	64
Hypercalcemia	6
Azotemia	55
Anemia	40
Eosinophilia	17

From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Sepsis, hypovolemic shock, acute abdomen, apathetic hyperthyroidism in the elderly, myopathies, gastrointestinal malignancy, major depression, anorexia nervosa, hemochromatosis, salt-losing nephritis, chronic infection

WORKUP

- If the clinical picture is highly suggestive of adrenocortical insufficiency, the diagnosis can be made with the rapid adrenocorticotropic hormone (ACTH) test:
  1. Give 250 mcg ACTH (Sinachten, tetracosatrin) by IV push and measure cortisol levels at 0, 30, and 60 min.
  2. An increase in serum cortisol level to peak concentration >500 nmol/L (18 mcg/dl) indicates a normal response. Cortisol level <18 mcg/dl at 30 or 60 min is suggestive of adrenal insufficiency.
  3. Measure plasma ACTH. A high ACTH level confirms primary adrenal insufficiency.
- Critical illness-related corticosteroid insufficiency (e.g., in sepsis) is best established with the 1-mcg ACTH stimulation test in which cortisol levels are measured at baseline and 30 min after administration of ACTH. A level <25 mcg/dl (690 nmol/L) or an increment over baseline of <9 mcg (250 nmol/L) represents an inadequate adrenal response.
- Secondary adrenocortical insufficiency (caused by pituitary dysfunction) can be distinguished from primary adrenal insufficiency by the following:
  1. Normal or low plasma ACTH level after rapid ACTH
  2. Absence of hyperpigmentation
  3. No significant impairment of aldosterone secretion (because aldosterone secretion is under control of the renin-angiotensin system)
  4. Additional evidence of hypopituitarism (e.g., hypogonadism, hypothyroidism)

LABORATORY TESTS

- Hyponatremia, hyperkalemia
- Decreased glucose
- Increased BUN/creatinine ratio (prerenal azotemia)
- Mild normocytic, normochromic anemia, neutropenia, lymphocytosis, eosinophilia (significant dehydration may mask hyponatremia and anemia), hypercalcemia, metabolic acidosis
- A morning cortisol level >500 mmol/L (18 mcg/dl) generally excludes the diagnosis whereas a level <165 mmol/L (6 mcg/dl) is suggestive of Addison disease and requires further evaluation (see "Workup")
- Useful tests in evaluating the cause of adrenal insufficiency are: PPD (rule out TB), adrenal cortex antibodies and 21-hydroxylase antibodies (rule out autoimmune Addison disease), plasma very-long-chain fatty acids (rule out adrenoleukodystrophy)

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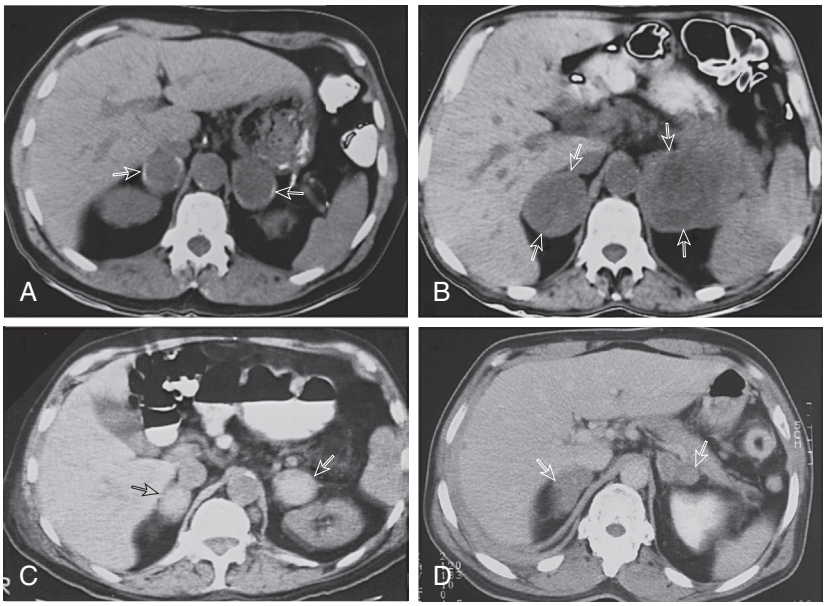

FIGURE A1-54 Computed tomographic (CT) scans of patients with primary adrenal insufficiency. The affected adrenal glands are indicated by arrows. **A,** CT scan of a 59-year-old man with histoplasmosis. Notice the subcapsular calcium in both glands. **B,** CT scan of a 59-year-old man with metastatic melanoma. **C,** CT scan of an 80-year-old man with bilateral adrenal hemorrhage resulting from anticoagulation for pulmonary emboli. **D,** Bilateral adrenal tuberculomas in a 79-year-old man with tuberculosis affecting the urogenital tract. (**A** and **B** courtesy of Dr. William D. Salmon, Jr.; **C,** courtesy of Dr. Craig R. Sussman.) (From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

IMAGING STUDIES

- Abdominal CT scan (Fig. A1-54): small adrenal glands generally indicate either idiopathic atrophy or longstanding TB, whereas enlarged glands are suggestive of early TB or potentially treatable diseases.
- Chest radiograph may reveal a small heart (Fig. EA1-55).
- Abdominal radiograph: adrenal calcifications may be noted if the adrenocortical insufficiency is secondary to TB or fungal infection.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Perform periodic monitoring of serum electrolytes, vital signs, and body weight; liberal sodium intake is suggested.
- Periodic measurement of bone density may be helpful in identifying patients at risk for the development of osteoporosis.
- Patients should carry a MedicAlert bracelet and an emergency pack containing hydrocortisone 100-mg ampule, syringe, and needle.
- Patients and partners should be educated on how to give IM injection in case of vomiting or coma.

ACUTE GENERAL Rx

- Addisonian crisis is an acute complication of adrenal insufficiency characterized by circulatory collapse, dehydration, nausea, vomiting, hypoglycemia, and hyperkalemia.
  1. Draw plasma cortisol level; do not delay therapy while waiting for confirming laboratory results.
  2. Administer hydrocortisone 100 mg IV immediately, followed by 100 to 200 mg of hydrocortisone every 24 hours divided into 3 or 4 doses; if patient shows good clinical response, gradually taper dosage and change to oral maintenance dose (usually prednisone 7.5 mg/day).
  3. Provide adequate volume replacement with D_5NS solution until hypotension, dehydration, and hypoglycemia are completely corrected. Large volumes (2 to 3 L) under continuous cardiac monitoring may be necessary in the first 2 to 3 hr to correct the volume deficit and hypoglycemia and to avoid further hyponatremia.
- Identify and correct any precipitating factor (e.g., sepsis, hemorrhage).

CHRONIC Rx

- Give hydrocortisone 15 to 20 mg PO every morning and 5 to 10 mg in late afternoon or prednisone 5 mg in morning and 2.5 mg hs.
- Give oral fludrocortisone 0.05 mg/day to 0.20 mg/day: this mineralocorticoid is necessary if the patient has primary adrenocortical insufficiency. The dose is adjusted based on the serum sodium level and the presence of postural hypotension or marked orthostasis.
- Instruct patients to increase glucocorticoid replacement in times of stress and to receive parenteral glucocorticoids if diarrhea or vomiting occurs. Typical supplementation varies from 25 mg PO qd of hydrocortisone for minor medical and surgical stress to 50 to 100 mg IV hydrocortisone q8h for sepsis-induced hypotension or shock.
- The administration of dehydroepiandrosterone 50 mg PO qd improves well-being and sexuality in women with adrenal insufficiency.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Addison's Disease (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

http://internalmedicinebook.com/

SUGGESTED READINGS

Bornstein SR: Predisposing factors for adrenal insufficiency, *N Engl J Med* 360:2328–2339, 2009.

Chakera AJ, Vaidya B: Addison disease in adults: diagnosis and management, *Am J Med* 123:409–413, 2010.

Charmandari E et al.: Adrenal insufficiency, *Lancet* 383:2152–2167, 2014.

Michels A, Michels N: Addison disease: early detection and treatment principles, *Am Fam Physician* 89(7):563–568, 2014.

FIGURE EA1-52 Pigmentation in Addison disease. A, Hands of an 18-year-old woman with autoimmune polyendocrine syndrome and Addison disease. Pigmentation in a patient with Addison disease before **(B)** and after **(C)** treatment with hydrocortisone and fludrocortisone. Notice the additional presence of vitiligo. **D,** Similar changes in a 60-year-old man with tuberculous Addison disease before *(left)* and after *(right)* corticosteroid therapy. **E,** Buccal pigmentation in the same patient as in **D.** (**B** and **C** courtesy of Professor CRW Edwards.) (From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders)

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FIGURE EA1-53 Pigmentation of scars is a particular feature of Addison disease resulting from adrenal failure or surgery. (From White GM, Cox NH [eds]: *Diseases of the skin,* ed 2, St Louis, 2006, Mosby.)

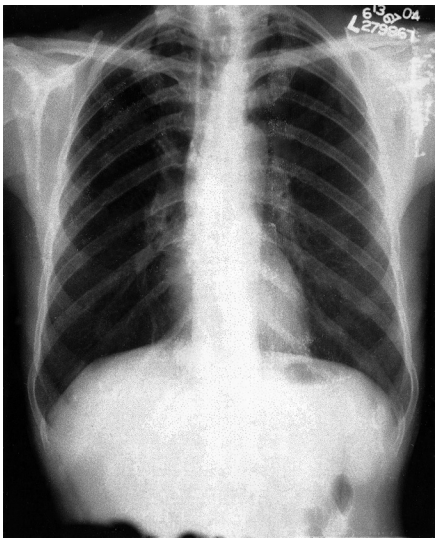

FIGURE EA1-55 Routine chest radiograph of a patient with Addison disease related to tuberculosis. In addition to the small cardiac silhouette, there are calcified lymph nodes in the hilum of the right lung. (Courtesy of Dr. J.B. Naldlch.)

BASIC INFORMATION

DEFINITION

Adult-onset Still's disease (AOSD) is a rare systemic autoinflammatory disorder of unknown etiology characterized by high spiking quotidian fever >102 °F, arthralgia or arthritis, evanescent skin rash, and leukocytosis with neutrophilic predominance. Temperature often returns to normal between fever spikes. Articular symptoms may be absent or mild initially, but most patients develop a persistent destructive arthropathy.

SYNONYMS

Adult Still's disease
Wissler's syndrome
Wissler-Fanconi syndrome

ICD-9CM CODES
714.2 Other rheumatoid arthritis with visceral or systemic involvement
ICD-10CM CODES
M06.1 Adult-onset Still disease

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 0.22/100,000 in men, 0.34/100,000 in women
PEAK INCIDENCE: Age 16 to 35
PREVALENCE: Unknown
PREDOMINANT SEX AND AGE: Slightly women > men, bimodal 15 to 25 and 36 to 46
GENETICS: Relative risk ranging from 2.1 to 2.9 associated with HLA B17, B18, B35, and DR2. Cytokine production also implicated in the pathogenesis: IL6, IL2, interferon gamma, and tumor necrosis factor alpha (TNF-α)
RISK FACTORS: Stress has been proved to be the only known risk factor.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Triad: High spiking fevers, characteristic rash, and arthritis/arthralgias
- Fever is >102 °F, transient, quotidian in pattern, usually in the late afternoon or early evening
- Nonspecific symptoms: myalgias, serositis including pleuritis and pericarditis, sore throat
- Rash is typically an evanescent, salmon pink, and maculopapular located on the trunk and proximal extremities and accompanies the fever. Often resolves when patient is afebrile.
- Arthritis is symmetric and destructive, involving the wrists, knees, and ankles. Extensive carpal involvement distinguishes this from rheumatoid arthritis (Figs. EA1-56 and EA1-57).

ETIOLOGY

- None identified

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infection, malignancy, or autoimmune disorders
  1. Infection: Rubella, CMV, EBV, mumps, coxsackievirus, adenovirus
  2. Neoplasms: Leukemia, lymphoma, angioblastic lymphadenopathy
  3. Autoimmune: Reactive arthritis, spondyloarthropathies, dermatomyositis, vasculitis
  4. Periodic fever syndromes: Familial Mediterranean fever (FMF), TNF receptor–associated periodic syndrome (TRAPS)

DIAGNOSTIC CRITERIA

Multiple potential diagnostic criteria have been proposed in the evaluation of patients suspected of having adult-onset Still's disease.

1. Yamaguchi et al. (93.5% sensitivity)

MAJOR CRITERIA:
- Arthralgia >2 weeks
- Fever > 102 °F; intermittent >1 week
- Typical rash
- WBC >10,000

MINOR CRITERIA:
- Sore throat
- Lymphadenopathy and/or splenomegaly
- LFT abnormalities
- Negative ANA and RF

Exclusion criteria: infections, malignancies, and rheumatic diseases

Diagnosis: 4 criteria with at least 2 major criteria

1. Cush (80.6% sensitivity)

MAJOR CRITERIA:
- Quotidian fever >102 °F
- Evanescent rash
- WBC >12 + ESR >40
- Negative ANA and RF
- Carpal ankylosis

MINOR CRITERIA:
- Onset age <35 years
- Arthritis
- Prodromal sore throat
- Reticuloendothelial system involvement
- Abnormal LFTs
- Serositis
- Cervical or tarsal ankylosis

Probable AOSD: 10 points with 12 weeks of observation

Definite AOSD: 10 points with 6 months observation

1. Fautrel et al. (80.6% sensitivity, 98.5% specificity)

MAJOR:
- Spiking fever >102 °F
- Arthralgia
- Transient erythema
- Pharyngitis
- PMN >80%
- Glycosylated ferritin <20%

MINOR:
- Maculopapular rash
- Leukocytosis >10

Diagnosis: 4 major criteria or 3 major + 2 minor criteria

FIGURE EA1-56 Typical salmon-colored rash. (From Fautrel B: Adult-onset still disease, *Best Pract Res Clin Rheumatol* 22;5:773-92, 2008.)

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FIGURE EA1-57 Ankylosing carpal arthritis. (From Fautrel B: Adult-onset Still disease, *Best Pract Res Clin Rheumatol* 22;5:773-92, 2008.)

WORKUP
- According to differential diagnosis

LABORATORY TESTS
- CBC generally demonstrates leukocytosis with a predominance of polymorphonuclear leukocytes.
- ANA and RF are generally negative in AOSD, whereas inflammatory markers are generally markedly elevated.
- Liver transaminases are often elevated.
- Ferritin can be markedly elevated beyond the level expected for a typical inflammatory process.
- Glycosylated ferritin (if available)

IMAGING STUDIES
- Radiographs are not helpful at early onset of symptoms; helpful if chronic.
- Radionuclide bone scan and MRI with gadolinium may be used for early diagnosis.

Rx TREATMENT

NSAIDs, corticosteroids, and disease-modifying antirheumatic drugs are generally used to control symptoms.

NONPHARMACOLOGIC THERAPY
- Control of stress factors

ACUTE GENERAL Rx
- NSAIDs at full doses
- Systemic glucocorticoids are often required to control systemic inflammation.

CHRONIC Rx
- In patients with persistent symptoms, steroid-sparing immunomodulatory disease–modifying agents are often required.
- Oral or injectable methotrexate is often added to control chronic disease.
- TNF-inhibitors including etanercept and infliximab can be effective at controlling symptoms.
- Anti-IL6 and IL1 blockade may also be effective in controlling disease activity.

DISPOSITION
- Three distinct patterns of its clinical course
  1. Self-limited/monocyclic pattern: systemic symptoms of fever, rash, serositis, organomegaly; remission in 1 year
  2. Intermittent/polycyclic pattern: recurrent fevers with or without articular symptoms; may have complete remission between flares that could be years apart
  3. Chronic articular pattern: severe articular presentation leading to joint destruction; more disability, worst prognosis

REFERRAL
- Rheumatology for diagnosis and treatment
- Dermatology for evaluation and possible biopsy of rash

PEARLS & CONSIDERATIONS

COMMENTS
- Evanescent rash often dissipates when the patient is afebrile; it is therefore important to do a skin exam while the patient is febrile.
- Fever may present before arthritis, complicating accurate diagnosis.

PREVENTION
None

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SUGGESTED READINGS

Cush JJ et al.: Adult-onset Still's disease. Clinical course and outcome, *Arthritis Rheum* 30:186–194, 1987.

Efthimiou P, Paik PK, Bielory L: Diagnosis and management of adult onset Still's disease, *Ann Rheum Dis* 65:564–572, 2006.

Fautrel B: Adult-onset Still disease, *Best Pract Res Clin Rheumatol* 22(5):773–792, 2008.

Fautrel B et al.: Proposal for a new set of classification criteria for adult-onset Still's disease, *Medicine (Baltimore)* 81:194–200, 2002.

Kadar J, Petrovicz E: Adult-onset Still's disease, *Best Pract Res Clin Rheumatol* 18:663–676, 2004.

Magadur-Joly G, Billaud E, et al.: Epidemiology of adult Still's disease: estimate of the incidence by a retrospective study in west France, *Ann Rheum Dis* 54:587–590, 1995.

Ohta A, Yamaguchi M, Kaneoka H, Nagayoshi T, et al.: Adult Still's disease: review of 228 cases from the literature, *J Rheumatol* 61:1055–1065, 1987.

Pouchot J, Sampalis JS, et al.: Adult Still's disease: manifestations, disease course and outcome in 62 patients, *Medicine (Baltimore)* 70:118–136, 1991.

Sampalis JS, Medsger TA Jr, et al.: Risk factors for adult Still's disease, *J Rheumatol* 23:2049–2054, 1996.

Wakai K, Ohta A, Tamakoshi A, et al.: Estimated prevalence and incidence of adult Still's disease: findings by a nationwide epidemiological survey in Japan, *J Epidemiol* 7:221–225, 1997.

Yamaguchi M et al.: Preliminary criteria for classification of adult Still's disease, *J Rheumatol* 19:424–430, 1992.

BASIC INFORMATION

DEFINITION

Alcoholic hepatitis is a severe, progressive, inflammatory, and cholestatic liver disease occurring in patients with long-term ethanol abuse.

ICD-9CM CODES
571.1 Acute alcoholic hepatitis
ICD-10CM CODES
K70.10 Alcoholic hepatitis without ascites
K70.9 Alcoholic liver disease, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Approximately 2 million people in the U.S. (about 1% of the population) are affected by alcoholic liver disease.
- Typical presentation age: 40 to 50 yr. Majority occurs before age 60.

PREVALENCE: Approximately 25% to 30%
PREDOMINANT SEX AND AGE: The majority of patients are males. Males are two times as likely as women to abuse alcohol. However, women develop alcoholic hepatitis after a shorter time and smaller amount of alcoholic exposure than men.
GENETICS: No genetic predilection for any one race. In the U.S., however, there is increased incidence in minority groups.
RISK FACTORS: Drinking multiple alcohol types, drinking alcohol between meal times, poor nutrition, female gender, obesity, Hispanic ethnicity, long-term ingestion of >10 to 20 g/day of alcohol in women and >20 to 40 g/day in men

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Common presenting symptoms include:
- Nausea /vomiting
- Malaise
- Low-grade fever
- Anorexia
- Abdominal distention/pain
- Weight loss
- Complications of liver impairment (GI bleed; confusion, lethargy, ascites)

Findings on physical examination include:
- Fever
- Tachycardia
- Hepatomegaly
- Jaundice
- Splenomegaly
- Asterixis (a flapping tremor)
- Peripheral edema
- Abdominal distention with shifting dullness (ascites)
- Hepatic bruit
- With coexistent cirrhosis look for:
  1. Gynecomastia
  2. Proximal muscles wasting
  3. Spider angiomata
  4. Altered hair distribution

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hepatitis B
- Hepatitis C
- Nonalcoholic steatohepatitis (NASH)
- Chronic pancreatitis
- Drug-induced liver injury
- Hemochromatosis
- Cholangitis

WORK-UP

- A thorough and detailed history is needed.
- Relevant questions may include:
  1. When patients started drinking
  2. Number of times patient drinks per day
  3. How many years of regular/daily drinking
  4. Types of alcohol
  5. Home or bar drinking?
  6. Rehabilitation for drinking?
  7. Social problems (e.g., arrest for public intoxication or driving under the influence, marital discord due to alcoholism)

LABORATORY TESTS

- Elevated C-reactive protein
- Electrolyte disorder
- Hypophosphatemia
- Hypomagnesemia
- CBC (may reveal leukocytosis with bandemia or anemia)
- Elevated transaminase (AST >45 U/L but <300 U/L; AST:ALT ratio >2.0)
- S-bilirubin >2 mg/dl
- Increased prothrombin time (PT)
- Decreased gamma glutamyltransferase (GGT)
- Carbohydrate-deficient transferrin (CDT) is a reliable marker for chronic alcoholism
- Screening tests to rule out other conditions include checking:
  1. Hepatitis B surface antigen (HBsAg)
  2. Anti–hepatic C
  3. Ferritin-transferrin saturation
  4. Alpha-fetoprotein
  5. Alkaline phosphatase

IMAGING STUDIES

Ultrasonography is the preferred imaging study.

LIVER BIOPSY

- Liver biopsy is rarely needed.
- Useful to:
  1. Confirm the diagnosis.
  2. Evaluate the effect of coexisting disease.
  3. Rule out cirrhosis.
  4. Exclude other diagnosis (especially other causes of liver diseases).
- Typical finding include:
  1. Macrovascular steatosis
  2. Hepatocyte injury (ballooning and necrosis)
  3. Mallory's bodies (characteristic of alcoholic hepatitis)
  4. Perivenular fibrosis
  5. Portal and lobular inflammation

TREATMENT

Treatment can be divided into three main components:
1 Lifestyle modifications
2 Nutritional support
3 Pharmacologic therapy

LIFESTYLE MODIFICATIONS

- Abstinence from alcohol (this improves both short- and long-term survival). Fig. A1-58 describes the effect of subsequent alcohol intake on 5-year survival in patients with alcoholic hepatitis
- Smoking cessation (to decrease oxidative stress)
- Treatment of substance abuse

NUTRITIONAL SUPPORT

- Good nutrition is an essential part of treatment because many patients with alcoholic hepatitis are usually in a catabolic state.
- Nutritional support includes:
  1. Liberal vitamin supplementation (especially thiamine, folic acid, vitamin K)
  2. Minerals supplementation (**but not iron**)

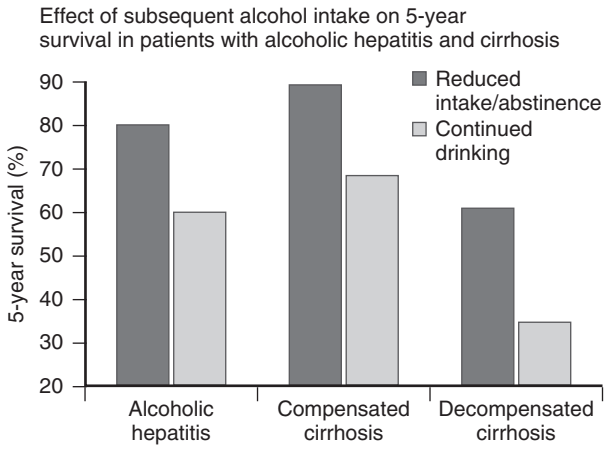

FIGURE A1-58 Effect of subsequent alcohol intake on 5-year survival in patients with alcoholic hepatitis and cirrhosis. (From Day CP, Liver Disorder Part 1 of 2, *Medicine* 35(1), 2007, p 22–25.)

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3. Calorie counting is essential. A high calorie intake (1.2 to 1.4 times the normal resting intake) may be required.
4. Protein intake of 1.2 to 1.5 g/kg of ideal body weight per day will provide adequate support. **Exception: in patients with severe encephalopathy, protein restriction may be required.**

PHARMACOLOGIC THERAPY

Severe alcoholic hepatitis may require treatment. Severity can be assessed by calculating the Model for End-Stage Liver Disease (MELD) score or Maddrey's Discriminant Function (DF) or the Glasgow score.

- Maddrey's DF = 4.6 × PT in sec prolonged + serum bilirubin (mg/dl)
  1. DF >32 indicates significant or severe alcoholic hepatitis (30-day mortality of 50%).
- MELD score can easily be calculated (visit http://www.unos.org/resources/meldpeldcalculator.asp?index=98). This score predicts short-term survival in patients with cirrhosis. A score ≥20 predicts increased short-term mortality.
- Glasgow score: contains four variables (BUN, PT, WBC count, and bilirubin). A score ≥9 indicates increased mortality.

Indications for initiating therapy include:

- DF >30
- MELD >20
- Glasgow score >8
- Hepatic encephalopathy

Patients with severe alcoholic hepatitis may be treated with glucocorticosteroids (prednisolone 40 mg/day for 28 days with a 2-wk taper). Glucocorticosteroids reduce hepatic injury, suppress inflammation, and promote liver regeneration. An alternative first-line agent (especially for patients with contraindications to corticosteroids) in patients with severe alcoholic hepatitis is pentoxifylline. There are various other treatments, but these are mainly experimental.

LIVER TRANSPLANTATION

- Usually reserved for patients with end-stage liver disease. Patients whose hepatitis is not responding to medical therapy have a 6-month survival rate of approximately 30%. Since most hepatitis deaths occur within 2 months, early liver transplantation is attractive but controversial.
- Patients with alcoholic hepatitis must be sober for at least 6 mo before they can be eligible for consideration for liver transplantation.

REFERRAL

Severe acute alcoholic hepatitis may require ICU care and referral to different subspecialists:

- GI/hepatology (for patients with evidence of GI hemorrhage)
- Nutritional services
- Nephrology (for acute renal failure, hepatorenal syndrome)
- Neurology (for change in mental status, seizures)
- Infectious disease (for fever/leukocytosis)

PEARLS & CONSIDERATIONS

COMMENTS

- Referral to substance abuse treatment programs may be helpful.
  - Stress to patients that there are limited long-term drug treatments for alcoholic hepatitis.
  - Maintaining good general nutrition is important.
  - Advise patient about the risk of taking certain medications, especially acetaminophen.
- Periodic follow-up to monitor patient's response to check BMP and LFTs.
- Encourage alcohol abstinence. Abstinence improves long-term survival.
- If patient develops liver cirrhosis, check serum alpha-fetoprotein every 6 mo and liver ultrasound annually to rule out hepatocellular carcinoma.
- Vaccinate patient against hepatitis A and B viruses, pneumococci, influenza A virus, and routine adult vaccinations, if appropriate.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Alcoholic Hepatitis (Patient Information)

AUTHOR: **DANIEL K. ASIEDU, M.D., PH.D.**

SUGGESTED READINGS

Lucey MR et al.: Alcoholic hepatitis, *N Engl J Med* 360:2758–2769, 2009.

Mathurin P et al.: Early liver transplantation for severe alcoholic hepatitis, *N Engl J Med* 365:1790–1800, 2011.

Maziya A, Runyon BA: Alcoholic hepatitis 2010: a clinician's guide to diagnosis and therapy, *World J Gastroenterol* 16(39):4905, 2010.

Sass DA, Shaikh OS: Alcoholic hepatitis, *Clin Liver Dis 1s0* 219, 2006.

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BASIC INFORMATION

DEFINITION

Moderate drinking has been defined as two standard drinks (e.g., 12 oz of beer) per day and one drink per day for women and persons older than 65 yr. Although not generally included under the alcoholism topic, hazardous or at-risk drinking should also be considered. For men, *at-risk drinking* is defined as more than 14 drinks/wk or more than 4 drinks/occasion. For women, at-risk drinking is defined as approximately half that given for men.

The American Psychiatric Association defines diagnostic criteria for *alcohol withdrawal* as follows:

A. Cessation of (or reduction in) alcohol use that has been heavy and prolonged.
B. Two (or more) of the following, developing within several hours to a few days after criterion A:
   1. Autonomic hyperactivity (e.g., sweating or pulse rate >100 beats/min)
   2. Increased hand tremor
   3. Insomnia
   4. Nausea and vomiting
   5. Transient visual, tactile, or auditory hallucinations or illusions
   6. Psychomotor agitation
   7. Anxiety
   8. Grand mal seizures
C. The symptoms in criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

The symptoms are not attributable to a general medical condition and are not better accounted for by another mental disorder.

SYNONYMS

Alcohol abuse
Substance abuse

ICD-9CM CODES
303.9 Alcoholism
ICD-10CM CODES
F10 Mental and behavioral disorders due to use of alcohol
F10.1 Mental and behavioral disorders due to use of alcohol: harmful use
F10.2 Mental and behavioral disorders due to use of alcohol: dependence syndrome
F10.3 Mental and behavioral disorders due to use of alcohol: withdrawal state
F10.4 Mental and behavioral disorders due to use of alcohol: withdrawal state with delirium
F10.5 Mental and behavioral disorders due to use of alcohol: psychotic disorder
F10.6 Mental and behavioral disorders due to use of alcohol: amnesic syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.)

- The clinical history suggests alcohol problems in 15% to 20% of patients in primary care and hospitalized patients. In the U.S., alcohol abuse generates nearly $223 billion in annual economic costs. An estimated 9% of adults in the U.S. have alcohol dependence.
- 20% achieve abstinence without help; 70% achieve sobriety for 1 yr.

PREVALENCE (IN U.S.): 7% of population ≥18 yr

PREDOMINANT SEX:

- Lifetime risk for males 8% to 10%
- Lifetime risk for females 3% to 5%

PEAK INCIDENCE: 20 to 40 yr. The most common age range for initial treatment of alcohol dependence is 35 to 45 yr. However, the peak period for meeting alcohol dependence criteria is ≥10 years earlier.

GENETICS: More common with a family history of alcoholism and in patients of Irish, Scandinavian, and Native American descent

PHYSICAL FINDINGS & CLINICAL PRESENTATION:

- Recurring minor trauma
- Gastrointestinal bleeding from gastritis and/or varices
- Pancreatitis (acute and chronic)
- Liver disease
- Odor of alcohol on breath
- Tremulousness
- Tachycardia
- Peripheral neuropathy
- Recent memory loss

ETIOLOGY

- Social and genetic factors important
- Risk factors:
  1. Broken homes
  2. Unemployment
  3. Divorce
  4. Recurrent depression
  5. Addiction to another substance, including tobacco
  6. Working long hours (≥55 hours/week)

DIAGNOSIS

WORKUP

- The USPSTF recommends that clinicians screen adults 18 years and older for alcohol misuse and provide persons engaged in risky or hazardous drinking with brief behavioral counseling interventions to reduce alcohol misuse. Several screening tests (CAGE, TWEAK, CRAFFT, AUDIT-C) are available. The four-item CAGE (feeling need to Cut down, Annoyed by criticism, Guilty about drinking, and need for an Eye-opener in the morning) is the most popular screening test in primary care (Fig. EA1-59). A positive response should lead to further questioning. The sensitivity of the CAGE ranges from 43% to 94% and its specificity ranges from 70% to 97%. The five-item TWEAK scale (**T**olerance, **W**orry, **E**ye-openers, **A**mnesia, [**K**] cut down) and the TACE questionnaire (**T**olerance, **A**nnoyance, **C**ut down, **E**ye-opener) are designed to screen pregnant women for alcohol misuse. They detect lower levels of alcohol consumption that may pose risks during pregnancy. The CRAFFT questionnaire (riding in **C**ar with someone who was drinking, using alcohol to **R**elax, using alcohol while **A**lone, **F**orgetfulness, criticism from **F**riends and **F**amily, **T**rouble) is useful as a screening tool for adolescents. Its sensitivity is 92% and specificity 64% for alcohol abuse. Single-question screening about alcohol consumption in a day ("When was the last time you had more than X drinks in a day?" [where X is 5 for men and 4 for women]) with the threshold set at "in the past 3 months" is 85% sensitive and 70% specific in men and 82% and 70% in women for unhealthy alcohol use. The 3-question AUDIT-C is a shorter form of the 10-item AUDIT, and the questions center on the quantity and frequency of alcohol use. It asks how often someone has had a drink containing alcohol, how many standard drinks containing alcohol one consumes on a typical day when one is drinking, and how often one has six or more drinks on one occasion. Scoring ranges from 0 to 4 on each question with a total score range of 0 to 12. A total score of 3 or higher for women and 4 or higher for men indicates alcohol use disorder and need for further assessment. Its sensitivity ranges from 85% in Hispanic women to 95% in white men.
- Laboratory evaluation (see below).

LABORATORY TESTS:

- Lab tests alone do not accurately detect alcohol problems but can help identify medical complications related to alcohol use, such as pancreatitis or cirrhosis.
- Gamma-glutamyltransferase (GGTP), generally elevated
- Liver transaminases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), often elevated, may be normal or low in advanced liver disease.
- Low albumin level, hypophosphatemia, hypomagnesemia from malnutrition
- Complete blood count (CBC) reveals elevated mean corpuscular volume from toxic effect of alcohol on erythrocyte development in nutritional deficiencies.
- Stool for occult blood may be positive as a result of gastritis or variceal bleeding
- RBC folate, vitamin B_{12} level, vitamin B_6, vitamin B_1 level

IMAGING STUDIES

Indicated only with a history of trauma. CT or ultrasound of abdomen may reveal fatty liver or cirrhosis in advanced stages.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Twelve-step facilitation, cognitive behavioral therapy, and motivational enhancement therapy improve the chances of recovery in patients with alcohol abuse and dependence.

- Depression, if present, should be treated at same time alcohol is withdrawn.

ACUTE GENERAL Rx

Alcohol withdrawal syndrome (AWS) occurs when a person stops ingesting alcohol after prolonged consumption. It can result in four possible clinical patterns depending on the severity of the patient's alcohol abuse and the time from the patient's previous alcohol ingestion. Fig. A1-60 illustrates typical symptoms depending on time course of alcohol withdrawal. Blood ethanol level decreases by ~20 mg/dl/hr (Fig. EA1-61) in a normal person.

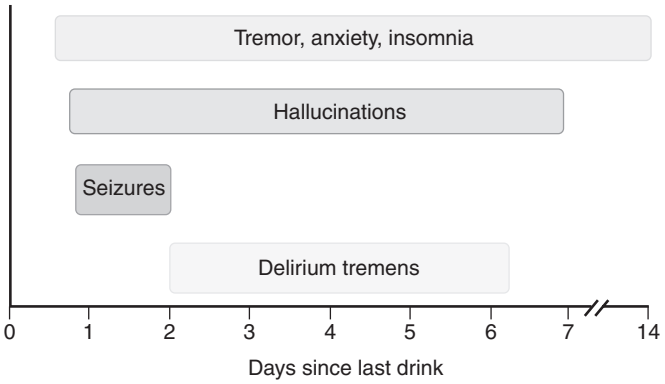

FIGURE A1-60 Time course of alcohol withdrawal. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

Although discussed separately, these withdrawal states blend together in real life. Table A1-41 summarizes medications for the treatment of alcohol dependence.

1. **Tremulous state** (early alcohol withdrawal, "impending DTs," "shakes," "jitters").
   a. Time interval: usually occurs 6 to 8 hr after the last drink or 12 to 48 hr after reduction of alcohol intake; becomes most pronounced at 24 to 36 hr.
   b. Manifestation: tremors, mild agitation, insomnia, tachycardia; symptoms are relieved by alcohol.
   c. Detoxification can be in the outpatient (ambulatory) or inpatient setting. Candidates for outpatient detoxification should have a reasonable support system (e.g., reliable contact person) who can monitor progress and lack of any significant comorbid conditions (e.g., suicide risk, seizure disorder, coexisting benzodiazepine dependence, prior unsuccessful outpatient detoxification, pregnancy, cirrhosis) or risk factors for severe withdrawal (age >40 yr, drinking >100 g of ethanol daily [e.g., 1 pint of liquor or eight 12-oz cans of beer, random blood alcohol concentration >200 mg/dl]).
   d. Inpatient treatment:
      (1) Admit to medical floor (private room); monitor vital signs q4h; institute seizure precautions; maintain adequate sedation.
      (2) Administer lorazepam as follows:
         (a) Day 1: 2 mg PO q4h while awake and not lethargic.
         (b) Day 2: 1 mg PO q4h while awake and not lethargic.
         (c) Day 3: 0.5 mg PO q4h while awake and not lethargic.
         (d) NOTE: Hold sedation for lethargy or abnormal vital or neurologic signs. The preceding doses are only guidelines; it is best to titrate the dose case by case.

TABLE A1-41 Medications for the Treatment of Alcohol Dependence*

Medication	Dose and Route	Frequency	Effects	Major Common Adverse Effects
Alcohol Withdrawal				
			Benzodiazepines†	
Chlordiazepoxide*	25-100 mg, PO/IV/IM†	Every 4-6 hr	Decreased severity of withdrawal; stabilization of vital signs; prevention of seizures and delirium tremens	Confusion, oversedation, respiratory depression
Diazepam‡	5-10 mg, PO/IV/IM†	Every 6-8 hr		
Oxazepam‡	15-30 mg, PO†	Every 6-8 hr		
Lorazepam‡	1-4 mg, PO/IV/IM†	Every 4-8 hr		
			β-Blockers	
Atenolol	25-50 mg, PO	Once a day	Improvement in vital signs	Bradycardia, hypotension
Propranolol	10-40 mg, PO	Every 6-8 hr	Reduction in craving	
			α-Agonists	
Clonidine	0.1-0.2 mg, PO	Every 6 hr	Decreased withdrawal symptoms	Hypotension, fatigue
			Antiepileptics	
Carbamazepine	200 mg, PO	Every 6-8 hr	Decreased severity of withdrawal; prevention of seizures	Dizziness, fatigue, red blood cell abnormalities
			Prevention of Relapse	
Disulfiram‡	125-500 mg, PO	Daily	Decreased alcohol use among those who relapse	Disulfiram-alcohol reaction, rash, drowsiness, peripheral neuropathy
Naltrexone‡	50 mg, PO	Daily	Increased abstinence, decreased drinking days	Nausea, abdominal pain, myalgias-arthralgias
	380 mg, IM	Every 4 wk		
Acamprosate‡	666 mg, PO	Three times a day	Increased abstinence	Diarrhea

*Most commonly used medications listed.
†Currently approved by U.S. Food and Drug Administration for the indication noted.
‡Dose and routes given for standard fixed-dose regimens, which include dose tapers over time.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

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(3) In patients with mild to moderate withdrawal and without history of seizures, individualized benzodiazepine administration (rather than a fixed-dose regimen) results in lower benzodiazepine administration and avoids unnecessary sedation. The Clinical Institute Withdrawal Assessment Scale for Alcohol, Revised (CIWA-Ar) scale (Box A1-9) can be used to measure the severity of alcohol withdrawal. It consists of 10 items: nausea; tremor; autonomic hyperactivity; anxiety; agitation; tactile, visual, and auditory disturbances; headache; and disorientation. Each item is assigned a score from 0 to 7. For example, in the "agitation" category 0 indicates normal activity, and 7 indicates that the patient constantly thrashes about. For the category of "tremor," 0 indicates that tremor is not present and 7 that tremor is severe, even with arms not extended. The maximum total score is 67. Patients with mild AWS symptoms (CIWA-Ar score <8 to 10 can be monitored on an outpatient basis. Benzodiazepines are recommended in patients with substantial withdrawal symptoms (CIWA-Ar score >12). Patients with CIWA-Ar score of ≥15 should be admitted to detox unit. In-patient treatment is also recommended for patients with history of withdrawal seizures and for those with suicidal ideation and significant comorbidities.

(4) Beta-adrenergic blockers: beta-blockers are useful for controlling blood pressure and tachyarrhythmias. However, they do not prevent progression to more serious symptoms of withdrawal and, if used, should not be administered alone but in conjunction with benzodiazepines. Beta-blockers should be avoided in patients with contraindications to their use (e.g., bronchospasm, bradycardia, or severe congestive heart failure). Centrally acting alpha-adrenergic agonists such as clonidine ameliorate symptoms in patients with mild to moderate withdrawal but do not reduce delirium or seizures.

(5) Vitamin replacement: thiamine 100 mg IV or IM for at least 5 days plus oral multivitamins. The IV administration of glucose can precipitate Wernicke's encephalopathy in alcoholics with thiamine deficiency; therefore thiamine administration should precede IV dextrose.

(6) Hydration PO or IV (high-caloric solution): if IV, glucose with Na^+, K^+, Mg^{2+}, and phosphate replacement prn.

(7) Laboratory studies.
- (a) CBC, platelet count, INR.
- (b) Electrolytes, glucose, blood urea nitrogen, creatinine.
- (c) GGTP, ALT, AST.
- (d) Phosphorus and magnesium.
- (e) Serum vitamin B_{12} and folic acid (if megaloblastic features in blood smear).

(8) Diagnostic imaging: generally not necessary; if subdural hematoma is suspected (evidence of trauma, persistent lethargy), a CT scan should be ordered.

(9) Social rehabilitation: group therapy such as Alcoholics Anonymous; identification and treatment of social and family problems should be initiated during the patient's hospital stay.

2. **Alcoholic hallucinosis:**
   a. Manifestations: hallucinations usually are auditory, but hallucinations occasionally are visual, tactile, or olfactory; usually there is no clouding of sensorium as in delirium (clinical presentation may be mistaken for an acute schizophrenic episode). Disordered perceptions become most pronounced after 24 to 36 hr of abstinence.
   b. Treatment: same as for DTs (see "withdrawal seizures").
3. **Withdrawal seizures ("rum fits"):**
   a. Time interval: usually occurs 7 to 30 hr after cessation of drinking, with a peak incidence between 13 and 24 hr.
   b. Manifestations: generalized convulsions with loss of consciousness; focal signs are usually absent; consider further investigation with CT scan of head and electroencephalography if clearly indicated (e.g.,

BOX A1-9 Alcohol Withdrawal Assessment Scoring Guidelines (Revised Clinical Institute Withdrawal Assessment for Alcohol Scale)

Nausea and Vomiting (0-7)
0, none; 1, mild nausea with no vomiting; 4, intermittent nausea; 7, constant nausea, frequent dry heaves and vomiting

Tremor (0-7)
0, no tremor; 1, not visible, but can be felt fingertip to fingertip; 4, moderate, with patient's arms extended; 7, severe, even with arms not extended

Paroxysmal Sweats (0-7)
0, no sweats; 1, barely perceptible sweating, palms moist; 4, beads of sweat obvious on forehead; 7, drenching sweats

Anxiety (0-7)
0, no anxiety, patient at ease; 1, mildly anxious; 4, moderately anxious or guarded, so anxiety is inferred; 7, equivalent to acute panic states seen in severe delirium or acute schizophrenic reactions

Agitation (0-7)
0, normal activity; 1, somewhat more than normal activity; 4, moderately fidgety and restless; 7, pacing back and forth during, or constantly thrashing about

Tactile Disturbances (0-7)
Ask, "Have you experienced any itching, pins and needles sensation, burning or numbness, or a feeling of bugs crawling on or under your skin?"
0, none; 1, very mild itching, pins and needles, burning, or numbness; 2, mild itching, pins and needles, burning, or numbness; 3, moderate itching, pins and needles, burning, or numbness; 4, moderately severe tactile hallucinations; 5, severe hallucinations; 6, extremely severe hallucinations; 7, continuous hallucinations

Auditory Disturbances (0-7)
Ask, "Are you more aware of sounds around you? Are they harsh? Do they startle you? Do you hear anything that disturbs you or that you know isn't there?"
0, not present; 1, very mild harshness or ability to startle; 2, mild harshness or ability to startle; 3, moderate harshness or ability to startle; 4, moderate hallucinations; 5, severe hallucinations; 6, extremely severe hallucinations; 7, continuous hallucinations

Visual Disturbances (0-7)
Ask, "Does the light appear to be too bright? Is its color different than normal? Does it hurt your eyes? Are you seeing anything that disturbs you?"
0, not present; 1, very mild sensitivity to light; 2, mild sensitivity; 3, moderate sensitivity; 4, moderate hallucinations; 5, severe hallucinations; 6, extremely severe hallucinations; 7, continuous hallucinations

Headache (0-7)
0, not present; 1, very mild; 2, mild; 3, moderate; 4, moderately severe; 5, severe; 6, very severe; 7, extremely severe

Orientation and Clouding of Sensorium (0-4)
Ask, "What day is this? Where are you? Who am I?"
0, oriented; 1, cannot do serial additions or is uncertain about date; 2, disoriented to date by no more than 2 calendar days; 3, disoriented to date by more than 2 calendar days; 4, disoriented to place and/or person

Total Score
0 to 9: absent or minimal withdrawal
10 to 19: mild to moderate withdrawal
More than 20: severe withdrawal

From Sullivan JT, Sykora K, Schneiderman J, et al: Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *Br J Addict* 84:1353–1357, 1989.

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presence of focal neurologic deficits, prolonged postictal confusion state). In addition, in a febrile patient who is having a seizure or altered mental state, a lumbar puncture is necessary.

c. Treatment:
   (1) Diazepam 2.5 mg/min IV until seizure is controlled (check for respiratory depression or hypotension) may be beneficial for prolonged seizure activity; IV lorazepam 1 to 2 mg q2h can be used in place of diazepam. Withdrawal seizures generally are self-limited and treatment is not required; the use of phenytoin or other anticonvulsants for short-term treatment of alcohol withdrawal seizures is not recommended.
   (2) Thiamine 100 mg IV, followed by IV dextrose, should also be administered.
   (3) Electrolyte imbalances (increased Mg^{2+}, decreased K^+, increased or decreased Na^+, decreased PO_4^{3-}) that may exacerbate seizures should be corrected.

4. **DTs:**
   a. Time interval: variable; usually occurs within 1 wk after reduction or cessation of heavy alcohol intake and persists for 1 to 3 days. Peak incidence is 72 hr and 96 hr after the cessation of alcohol consumption.
   b. Manifestations: profound confusion, tremors, vivid visual and tactile hallucinations, autonomic hyperactivity; this is the most serious clinical presentation of alcohol withdrawal (mortality rate is approximately 15% in untreated patients).
   c. Treatment
      (1) Admission to a detoxification unit where patient can be observed closely.
      (2) Vital signs q30min (neurologic signs, if necessary).
      (3) Use of lateral decubitus or prone position if restraints are necessary
      (4) NPO: nasogastric tube for abdominal distention may be necessary but should not be routinely used.
      (5) Laboratory studies: same as for early alcohol withdrawal.
      (6) Vigorous hydration (4 to 6 L/day): IV with glucose (Na^+, K^+, PO_4^{3-} and Mg^{2+} replacement).
      (7) Vitamins: thiamine 100 mg IV qd. The initial dose of thiamine should precede the administration of IV dextrose; multivitamins (may be added to the hydrating solution).
      (8) Sedation: control of agitation should be achieved with rapid-acting sedative-hypnotic agents in adequate doses to maintain light somnolence for the duration of delirium.
         (a) Initially: lorazepam 2 to 5 mg IM/IV repeated prn.
         (b) Maintenance (individualized dosage): chlordiazepoxide, 50 to 100 mg PO q4-6h, lorazepam 2 mg PO q4h, or diazepam 5 to 10 mg PO tid; withhold doses or decrease subsequent doses if signs of oversedation are apparent.
         (c) Midazolam is also effective for managing DTs. Its rapid onset (sedation within 2 to 4 min of IV injection) and short duration of action (approximately 30 min) make it an ideal agent for titration in continuous infusion.
      (9) Treatment of seizures (as previously described).
      (10) Diagnosis and treatment of concomitant medical, surgical, or psychiatric conditions.

CHRONIC Rx

- See "Referral."
- Pharmacotherapies for alcoholism include:
  1. Acamprosate is a synthetic compound with a chemical structure similar to the neurotransmitter gamma-aminobutyric acid and the amino acid neuromodulator taurine. Its mechanism of action is not completely understood. It is indicated for the maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation. It should be used only as part of a comprehensive psychosocial treatment program. It does not cause a disulfiram-like reaction as a result of ethanol ingestion. Dose is two 333-mg tablets tid. Treatment should be initiated as soon as possible after the period of alcohol withdrawal, when the patient has achieved abstinence, and should be maintained if the patient relapses.
  2. The long-acting opiate antagonist naltrexone inhibits the rewarding effects of alcohol. The starting dose is 25 mg/day, increased to 50 mg PO qd after 1 wk. An extended-release, once-monthly injection of naltrexone is also available and can be used along with psychosocial support to maintain alcohol abstinence. In patients with opioid dependence, naltrexone can precipitate acute withdrawal syndrome and should not be used at least 7 days from last opioid use. There are no established guidelines on the appropriate length of naltrexone treatment for alcohol dependence. One study recommends at least 3 mo of treatment.
  3. In a recent study, gabapentin showed a significant dose-response effect, and estimates of effect sizes were larger than those seen for naltrexone and acamprosate.[1]
  4. Disulfiram (Antabuse). Dosage is 500 mg max qd for 1 to 2 wk, then 125 to 500 mg qd. It interferes with the metabolism of alcohol by inhibiting aldehyde dehydrogenase, causing an accumulation of acetaldehyde. It produces unpleasant symptoms (nausea, flushing, elevated blood pressure, headache, weakness) when alcohol is ingested. It is an older drug that is now rarely used.

DISPOSITION

See "Referral."

REFERRAL

- To Alcoholics Anonymous or Adult Children of Alcoholics
- Family members to Al-Anon or Al-A-Teen
- Many cities have Salvation Army Adult Rehabilitation centers; all patients accepted, regardless of ability to pay

PEARLS & CONSIDERATIONS

COMMENTS

- Relative indications for inpatient alcohol detoxification are as follows: history of DTs or withdrawal seizures, severe withdrawal symptoms, concomitant psychiatric or medical illness, pregnancy, multiple previous detoxifications, recent high levels of alcohol consumption, and lack of reliable support network.
- Detoxification is not a stand-alone treatment but should serve as a bridge to a formal treatment program for alcohol dependence.
- The cure rate for alcoholism is highly disappointing, regardless of the modality. Only those who want to be helped will be helped. An effective strategy for the primary care physician is a prominently displayed sign in the office that states, "If you think you consume too many alcoholic beverages, please discuss it with me." Those who do open up the discussion can be given the facts in a nonjudgmental way and often can be helped. All too often problem drinkers lie on the questionnaire until they face a life-threatening health issue—and even then denial often reigns supreme.
- In a recent clinical trial, patients receiving medical management with naltrexone (100 mg/day), combined behavioral intervention (CBI), or both fared better on drinking outcomes, whereas acamprosate showed no evidence of efficacy, with or without CBI. No combination produced better efficacy than naltrexone or CBI alone in the presence of medical management.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Alcohol Addiction (Patient Information)
Abuse, Drug (Related Key Topic)
Alcoholic Hepatitis (Related Key Topic)
Wernicke Syndrome (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

[1]Mason BJ et al: Gabapentin treatment for alcohol dependence: a randomized clinical trial, *JAMA Intern Med* 174:70-77, 2014.

http://internalmedicinebook.com/

EVIDENCE

Abstract[1]

Objective:

Naltrexone, an efficacious medication for alcohol dependence, does not work for everyone. Symptoms such as insomnia and mood instability that are most evident during early abstinence might respond better to a different pharmacotherapy. Gabapentin may reduce these symptoms and help prevent early relapse. This clinical trial evaluated whether the combination of naltrexone and gabapentin was better than naltrexone alone and/or placebo during the early drinking cessation phase (first 6 weeks), and if so, whether this effect persisted.

Method:

A total of 150 alcohol-dependent individuals were randomly assigned to a 16-week course of naltrexone alone (50 mg/day [N=50]), naltrexone (50 mg/day) with gabapentin (up to 1,200 mg/day [N=50]) added for the first 6 weeks, or double placebo (N=50). All participants received medical management.

Results:

During the first 6 weeks, the naltrexone-gabapentin group had a longer interval to heavy drinking than the naltrexone-alone group, which had an interval similar to that of the placebo group; had fewer heavy drinking days than the naltrexone-alone group, which in turn had more than the placebo group; and had fewer drinks per drinking day than the naltrexone-alone group and the placebo group. These differences faded over the remaining weeks of the study. Poor sleep was associated with more drinking in the naltrexone-alone group but not in the naltrexone-gabapentin group, while a history of alcohol withdrawal was associated with better response in the naltrexone-gabapentin group.

Conclusions:

The addition of gabapentin to naltrexone improved drinking outcomes over naltrexone alone during the first 6 weeks after cessation of drinking. This effect did not endure after gabapentin was discontinued. Ⓐ

Evidence-Based Reference

Anton RF et al.: Gabapentin combined with naltrexone for the treatment of alcohol dependence, *Am J Psychiatry* 168:709–717, 2011. Ⓐ

SUGGESTED READINGS

American College of Physicians: Alcohol use, *Ann Intern Med* 3–11, 2009.

Anton RF: Naltrexone for the management of alcohol dependence, *N Engl J Med* 359:715, 2008.

Anton RF et al.: Combined pharmacotherapies and behavioral interventions for alcohol dependence, the COMBINE study: a randomized clinical trial, *JAMA* 295:2006, 2003.

Fagbemi K: What is the best questionnaire to screen for alcohol use disorder in an office practice? *Clev Clinic J Med* 78:649–651, 2011.

Friedmann PD: Alcohol use in adults, *N Engl J Med* 368:365–373, 2013.

Johnson B et al.: Topiramate for treating alcohol dependence, a randomized controlled trial, *JAMA* 298(14):1641–1651, 2007.

Jonas DE et al.: Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis, *JAMA* 311:1889–1900, 2014.

Moss M, Burnham EL: Alcohol abuse in the critically ill patient, *Lancet* 368:2231, 2006.

Moyer VA: Screening and behavioral counseling interventions in primary care to reduce alcohol misuse: US Preventive Services Task Force Recommendations Statement, *Ann Intern Med* 159:210–218, 2013.

Muncie HL: Outpatient management of alcohol withdrawal syndrome, *Am Fam Phys* 88(9):589–595, 2013.

Saitz R: Chronic care management for dependence on alcohol and other drugs, the AHEAD randomized trial, *JAMA* 310(11):1156–1167, 2013.

Willenbring ML et al.: Helping patients who drink too much: an evidence-based guide for primary care physicians, *Am Fam Physician* 80(1):44–50, 2009.

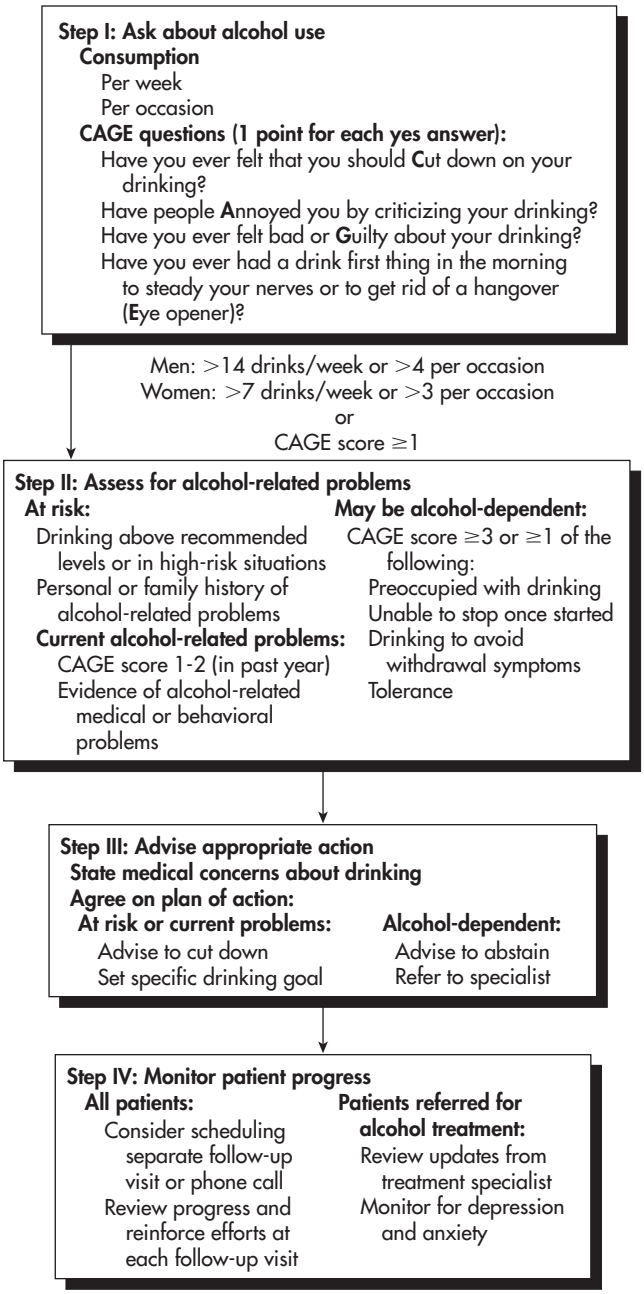

FIGURE EA1-59 Screening and brief intervention for alcohol problems in clinical practice. (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 23, Philadelphia, 2008, Saunders.)

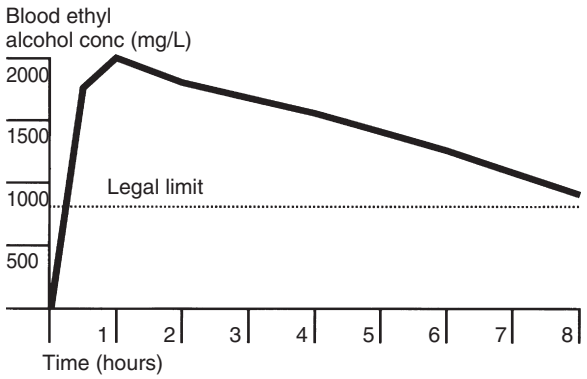

FIGURE EA1-61 Blood concentrations after oral administration of ethyl alcohol (2 ml/kg). The concentration declines in a zero-order fashion at an average rate of 190 mg/L each hour. (From Souhami RL, Moxham J: Textbook of medicine, ed 4, London, 2002, Churchill Livingstone.)

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BASIC INFORMATION

DEFINITION

Primary hyperaldosteronism is a clinical syndrome characterized by hypokalemia, hypertension, low plasma renin activity (PRA), and excessive aldosterone secretion.

SYNONYMS

Hyperaldosteronism
Primary aldosteronism
Conn's syndrome

ICD-9CM CODES
255.1 Primary aldosteronism
ICD-10CM CODES
E26.0 Primary hyperaldosteronism
E26.1 Secondary hyperaldosteronism
E26.8 Other hyperaldosteronism
E26.9 Hyperaldosteronism, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1% to 2% of patients with hypertension
PREVALENCE: More common in females

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Generally asymptomatic
- If significant hypokalemia is present, possible muscle cramping, weakness, paresthesias
- Hypertension
- Polyuria, polydipsia

ETIOLOGY

- Aldosterone-producing adenoma (>60%)
- Idiopathic hyperaldosteronism (>30%)
- Glucocorticoid-suppressible hyperaldosteronism (<1%)
- Aldosterone-producing carcinoma (<1%)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Diuretic use
- Hypokalemia from vomiting, diarrhea
- Renovascular hypertension
- Other endocrine neoplasm (pheochromocytoma, deoxycorticosterone-producing tumor, renin-secreting tumor)

WORKUP

Fig. EA1-62 provides guidance on when to consider testing for primary aldosteronism. Fig. A1-63 describes a diagnostic approach to patients with suspected primary aldosteronism. CT, MRI, and adrenal vein sampling (AVS) are used to distinguish unilateral from bilateral increased aldosterone secretion. This distinction will dictate treatment options since unilateral primary aldosteronism is treated surgically rather than medically. In patients with hypokalemia and a low PRA, confirming tests for primary hyperaldosteronism include the following:

- 24-hr urine test for aldosterone and potassium levels (potassium >40 mEq and aldosterone >15 mcg).
- Captopril test: administer 25 to 50 mg of captopril (an angiotensin-converting enzyme [ACE] inhibitor) and measure plasma renin and aldosterone levels 1 to 2 hr later. A plasma aldosterone level >15 ng/dl confirms the diagnosis of primary aldosteronism. This test is more expensive and is best reserved for situations in which the 24-hr urine test for aldosterone is ambiguous.
- 24-hr urinary tetrahydroaldosterone (<65 mcg/24 hr) and saline infusion test (plasma aldosterone >10 ng/dl) can also be used in ambiguous cases.
- The renin-aldosterone stimulation test (posture test) is helpful in differentiating idiopathic hyperaldosteronism (IHA) from aldosterone-producing adenoma (APA). Patients with APA have a decrease in aldosterone levels at 4 hr, whereas patients with IHA have an increase in aldosterone levels.
- As a screening test for primary aldosteronism, an elevated plasma aldosterone-renin ratio (ARR), drawn randomly from patients taking hypertensive drugs, is predictive of primary aldosteronism (positive predictive value 100% in a recent study). ARR is calculated by dividing plasma aldosterone (mg/dl) by PRA (mg/ml/hr). ARR >100 is considered elevated.
- Bilateral AVS may be done to localize APA when adrenal CT scan is equivocal. In APA, ipsilateral/contralateral aldosterone level is >10:1, and ipsilateral venous aldosterone concentration is very high (>1000 ng/dl).

LABORATORY TESTS

Routine laboratory tests can be suggestive but are not diagnostic of primary aldosteronism. Common abnormalities are:

- Spontaneous hypokalemia or moderately severe hypokalemia while receiving conventional doses of diuretics
- Possible alkalosis and hypernatremia

IMAGING STUDIES

- Adrenal CT scans (with 3-mm cuts) or MRI may be used to localize neoplasm.
- Adrenal scanning with iodocholesterol (NP-59) or 6-beta-iodomethyl-19-norcholesterol after dexamethasone suppression. The uptake of tracer is increased in those with aldosteronoma and absent in those with IHA and adrenal carcinoma.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Regular monitoring and control of blood pressure
- Low-sodium diet, tobacco avoidance, maintenance of ideal body weight, and regular exercise

ACUTE GENERAL Rx

- Control of blood pressure and hypokalemia with spironolactone, amiloride, or ACE inhibitors
- Surgery (unilateral adrenalectomy) for APA

CHRONIC Rx

Chronic medical therapy with spironolactone, eplerenone, amiloride, or ACE inhibitors to control blood pressure and hypokalemia is necessary in all patients with bilateral IHA.

DISPOSITION

- Unilateral adrenalectomy normalizes hypertension and hypokalemia in 70% of patients with APA after 1 yr. After 5 yr, 50% of patients remain normotensive.
- Experimental animal studies have suggested that long-term exposure to increased aldosterone levels in untreated aldosteronism may result in renal structural damage. However, clinical trials have shown that primary aldosteronism is characterized by partially reversible renal dysfunction in which elevated albuminuria is a marker of a dynamic rather than structural renal defect.

REFERRAL

Surgical referral for unilateral adrenalectomy after confirmation of unilateral APA or carcinoma

PEARLS & CONSIDERATIONS

- Frequent monitoring of blood pressure and electrolytes postoperatively is necessary because normotension after unilateral adrenalectomy may take up to 4 mo.
- Recent investigations regarding serum aldosterone and the incidence of hypertension in nonhypertensive persons indicate that increased aldosterone levels within the physiologic range predispose to the development of hypertension.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Aldosteronism (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

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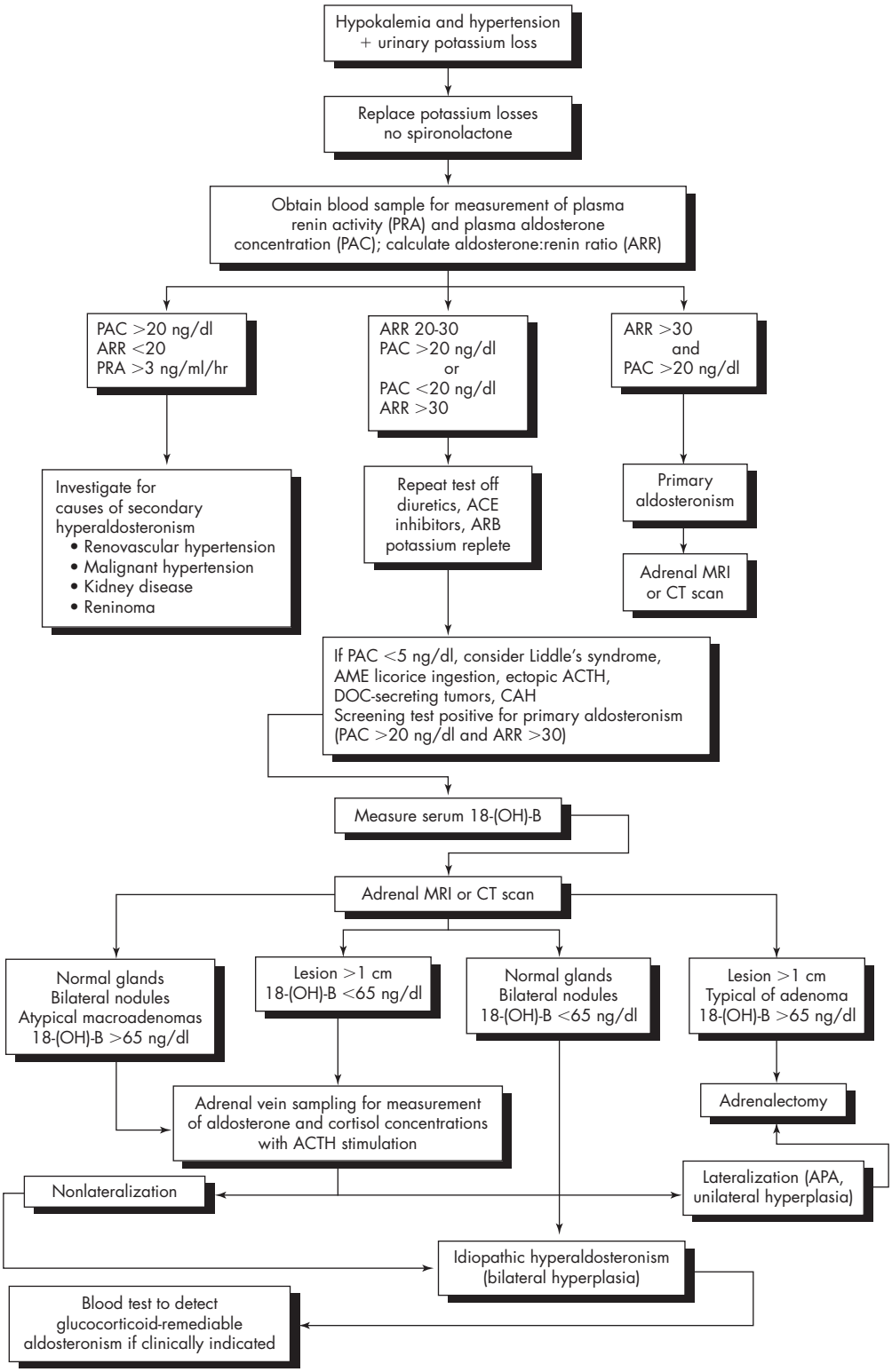

FIGURE A1-63 Diagnostic approach to patients with suspected primary aldosteronism. Cortisol concentration ratio in an adrenal vein four times greater than that in the other adrenal vein and/or an aldosterone/cortisol concentration ratio from the vein of the unaffected adrenal that is less than the ratio in the vena cava. Urinary loss of potassium can be documented by measuring potassium excretion in a 24-hour collection of urine; excretion of more than 30 mEq per day in the presence of hypokalemia indicates potassium wasting. An alternative and simpler approach is to obtain a random sample of urine to calculate fractional excretion of potassium. A fractional excretion greater than 10% when hypokalemia is present indicates potassium wasting. *AME,* Syndrome of apparent mineralocorticoid excess; *APA,* aldosterone-producing adenoma; *CAH,* congenital adrenal hyperplasia; *CT,* computed tomography; *DOC,* deoxycorticosterone; *ectopic ACTH,* production of corticotrophin by a tumor outside the pituitary gland; *serum 18-(OH)-B,* serum concentration of 18-hydroxycorticosterone. (From Runge MS, Greganti MA: *Netter's internal medicine,* Philadelphia, 2008, Saunders.)

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EVIDENCE

Abstract[1]

Background:

Eplerenone is claimed to be a more selective blocker of the mineralocorticoid receptor than spironolactone being associated with fewer antiandrogenic side-effects. We compared the efficacy, safety, and tolerability of eplerenone versus spironolactone in patients with hypertension associated with primary aldosteronism.

Methods:

The study was multicentre, randomized, double-blind, active-controlled, and parallel group design. Following a single-blind, placebo run-in period, patients were randomized 1:1 to a 16-week double-blind, treatment period of spironolactone (75–225 mg once daily) or eplerenone (100–300 mg once daily) using a titration-to-effect design. To be randomized, patients had to meet biochemical criteria for primary aldosteronism and have a seated DBP at least 90 mmHg and less than 120 mmHg and SBP less than 200 mmHg. The primary efficacy endpoint was the antihypertensive effect of eplerenone versus spironolactone to establish noninferiority of eplerenone in the mean change from baseline in seated DBP.

Results:

Changes from baseline in DBP were less on eplerenone (–5.6±1.3 SE mmHg) than spironolactone (–12.5±1.3 SE mmHg) [difference, –6.9 mmHg (–10.6, –3.3); $P<0.001$]. Although there were no significant differences between eplerenone and spironolactone in the overall incidence of adverse events, more patients randomized to spironolactone developed male gynaecomastia (21.2 versus 4.5%; $P = 0.033$) and female mastodynia (21.1 versus 0.0%; $P = 0.026$).

Conclusion:

The antihypertensive effect of spironolactone was significantly greater than that of eplerenone in hypertension associated with primary aldosteronism. Ⓐ

Evidence-Based Reference

Parthasarathy HK et al.: A double-blind, randomized study comparing the antihypertensive effect of eplerenone and spironolactone in patients with hypertension and evidence of primary aldosteronism, *J Hypertens* 29:980–990, 2011. Ⓐ

SUGGESTED READINGS

Douma S et al.: Prevalence of primary hyperaldosteronism in resistant hypertension: a retrospective observational study, *Lancet* 371:1921, 2008.

Kempers MJ et al.: Systematic review: diagnostic procedures to differentiate unilateral from bilateral adrenal abnormality in primary aldosteronism, *Ann Intern Med* 151:329–337, 2009.

Sechi L et al.: Long-term renal outcomes in patients with primary aldosteronism, *JAMA* 295:2638, 2006.

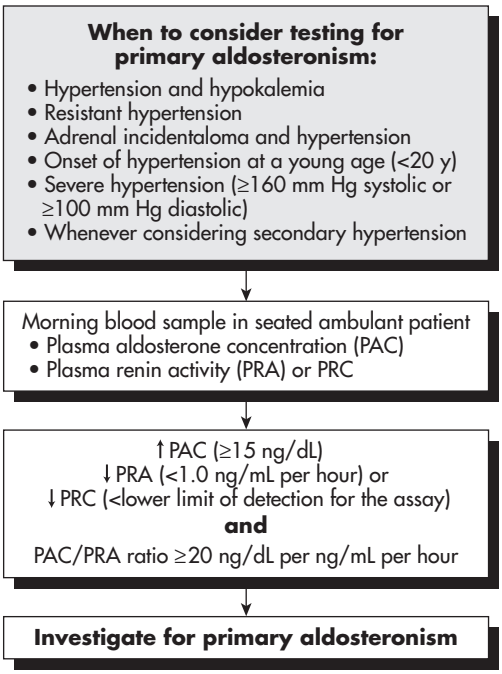

FIGURE EA1-62 Algorithm provides guidance on when to consider testing for primary aldosteronism and use of the ratio of plasma aldosterone concentration (PAC) to plasma renin activity (PRA) as a case-detection tool. *PRC,* Plasma renin concentration. (Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

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BASIC INFORMATION

DEFINITION

Allergic rhinitis is an IgE-mediated hypersensitivity response to nasally inhaled allergens that causes sneezing, rhinorrhea, nasal pruritus, and congestion. It may be seasonal or perennial.

SYNONYMS

Hay fever
IgE-mediated rhinitis
Seasonal allergic rhinitis
SAR

ICD-9CM CODES
477.9 Allergic rhinitis
ICD-10CM CODES
J30.1 Allergic rhinitis due to pollen
J30.2 Other seasonal allergic rhinitis
J30.3 Other allergic rhinitis
J30.4 Allergic rhinitis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Allergic rhinitis affects approximately 10% to 20% of the U.S. population and 40% of children.
- Mean age of onset is 8 to 12 yr.
- The prevalence of allergic rhinitis in patients presenting to their primary care provider with nasal symptoms is estimated to be 30% to 60%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pale or violaceous mucosa of the turbinates caused by venous engorgement (this can distinguish it from erythema present in viral rhinitis)
- Nasal polyps
- Lymphoid hyperplasia in the posterior oropharynx with cobblestone appearance
- Erythema of the throat, conjunctival and scleral injection
- Clear nasal discharge
- Clinical presentation: usually consists of sneezing, nasal congestion, cough, postnasal drip, loss of or alteration of smell, and sensation of plugged ears

ETIOLOGY

- Pollens in the springtime, ragweed in fall, grasses in the summer
- Dust, mites, animal allergens
- Smoke or any irritants
- Perfumes, detergents, soaps
- Emotion, changes in atmospheric pressure or temperature

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infections (sinusitis; viral, bacterial, or fungal rhinitis)
- Rhinitis medicamentosa (cocaine, sympathomimetic nasal drops)
- Vasomotor rhinitis (e.g., secondary to air pollutants)
- Septal obstruction (e.g., deviated septum), nasal polyps, nasal neoplasms
- Systemic diseases (e.g., Wegener's granulomatosis, hypothyroidism [rare])

WORKUP

- The initial strategy should be to determine whether patients should undergo diagnostic testing or receive empirical treatment.
- Workup is often unnecessary if the diagnosis is apparent. A detailed medical history is useful in identifying the culprit allergen.
- Selected patients with allergic rhinitis that is not controlled with standard therapy may benefit from allergy testing to target allergen avoidance measures or guide immunotherapy. Allergy testing can be performed using skin testing or radioallergosorbent (RAST) testing. Immunoglobulin E (IgE) testing using newest generation assays is also an excellent tool for diagnosing the cause of symptoms related to rhinitis. Allergy testing with skin or blood testing is most useful as confirmatory tests when the patient's history is compatible with an IgE-mediated reaction and should generally be reserved for ambiguous or complicated cases.
- Examination of nasal smears for the presence of neutrophils to rule out infectious causes and the presence of eosinophils (suggestive of allergy) may be useful in selected patients.
- Peripheral blood eosinophil counts are not useful in allergy diagnosis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Maintain allergen-free environment by covering mattresses and pillows with allergen-proof casings, eliminating carpeting, eliminating animal products, and removing dust-collecting fixtures.
- Use of air purifiers and dust filters is helpful.
- Maintain humidity in the environment below 50% to prevent dust mites and mold.
- Use air conditioners, especially in the bedroom.
- Remove pets from homes of patients with suspected sensitivity to animal allergens.
- Use of acupuncture to treat seasonal allergic rhinitis is controversial. A recent trial showed that acupuncture led to statistically significant improvement in disease-specific quality of life and antihistamine use measures after 8 weeks of treatment compared with sham acupuncture and with rescue medication alone.

ACUTE GENERAL Rx

- Determine if the patient is troubled by swollen turbinates (best treated with decongestants) or blockages secondary to mucus (effectively treated by antihistamines).
- Topical nasal steroids are very effective and are preferred by many as first-line treatment for allergic rhinitis in adults. Patients should be instructed on proper use and informed that improvement might not occur for at least 1 wk after initiation of therapy. Commonly available inhalers follow.
- Beclomethasone dipropionate: one to two sprays in each nostril bid
- Fluticasone: initially two sprays in each nostril qd or one spray in each nostril bid, decreasing to one spray in each nostril qd based on response
- Flunisolide: initially two sprays in each nostril bid
- Budesonide: two sprays in each nostril bid or four sprays in each nostril qam
- Most first-generation antihistamines can cause considerable sedation and anticholinergic symptoms. The second-generation antihistamines (loratadine, fexofenadine, cetirizine, levocetirizine, desloratadine) are preferred because they do not have any significant anticholinergic or sedative effects.
- Montelukast, a leukotriene receptor antagonist commonly used for asthma, is also effective for allergic rhinitis. Usual adult dose is 10 mg qd.
- Azelastine is an antihistamine nasal spray effective for seasonal allergic rhinitis. Olopatadine is an intranasal H_1-antihistamine alternative to azestaline in mild to moderate seasonal allergic rhinitis.

CHRONIC Rx

- Cromolyn sodium: one spray to each nostril three to four times daily can be used for prophylaxis (mast cell stabilizer).
- Immunotherapy is generally reserved for patients responding poorly to the above treatments. Traditionally, immunotherapy consisted of subcutaneous injections of gradually increased doses of allergens. Recently, the FDA has approved 3 allergen extracts for sublingual administration as immunotherapy.

DISPOSITION

Most patients experience significant relief with avoidance of allergens and proper use of medications.

REFERRAL

Allergy testing in patients with severe symptoms who are unresponsive to therapy or when the diagnosis is uncertain

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Allergic Rhinitis (Patient Information)

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http://internalmedicinebook.com/

EVIDENCE

Abstract[1]

Background:
Allergen-specific subcutaneous immunotherapy (SCIT) of seasonal allergic rhinitis (SAR) is usually considered a "second-line," slow-acting, disease-modifying treatment.

Objective:
We sought to test whether SCIT is as effective as antisymptomatic treatment in the control of symptoms in patients with SAR in the first year of treatment.

Methods:
We reviewed meta-analyses with 5 or more randomized, double-blind, placebo-controlled trials of SCIT or antisymptomatic treatment in patients with SAR. We then selected trials measuring the total nasal symptom score (TNSS), the total symptom score (TSS), or both during the first pollen season after treatment initiation. Efficacy was determined as the percentage reduction in TSSs and TNSSs obtained with active treatment compared with placebo (relative clinical impact [RCI]) and the standardized mean difference (SMD) of treatment versus placebo (effect size [ES]).

Results:
The weighted mean RCI of SCIT on TNSSs (–34.7% ± 6.8%) was higher than those of mometasone (–31.7% ± 16.7%, $P < .00001$) and montelukast (–6.3% ± 3.0%, $P < .00001$). The weighted mean RCI of SCIT on TSSs (–32.9% ± 12.7%) was higher than that of desloratadine (–12.0% ± 5.1%, $P < .00001$). The overall ES of SCIT in terms of TNSSs (SMD, –0.94; 95% CI, –1.45 to –0.43) was similar to that of mometasone (SMD, –0.47; 95% CI, –0.63 to –0.32; $P > .05$) and higher than that of montelukast (SMD, –0.24; 95% CI, –0.33 to –0.16; $P < .05$). The overall ES of SCIT in terms of TSSs (SMD, –0.86; 95% CI, –1.17 to –0.55) was comparable with that of desloratadine (SMD, –1.00; 95% CI, –1.68 to –0.32; $P > .05$).

Conclusions:
Our data provide indirect but consistent evidence that SCIT is at least as potent as pharmacotherapy in controlling the symptoms of SAR as early as the first season of treatment. Ⓐ

Abstract[2]

Background:
Subcutaneous (SCIT) and sublingual (SLIT) immunotherapy are the 2 most prescribed routes for administering allergen-specific immunotherapy. They were shown to be effective in control of symptoms and in reducing rescue medication use in patients with allergic diseases, but their effectiveness has to be balanced against side effects. In recent years, SLIT has been increasingly prescribed, instead of SCIT, because of improved safety and easy administration.

Objective:
We assessed which route is the most effective in the treatment of patients with seasonal allergic rhinitis to grass pollen.

Methods:
An indirect meta-analysis–based comparison between SCIT and SLIT was performed. Treatment efficacy was determined as the standardized mean difference (SMD) in symptom and medication scores obtained with active treatment, SCIT, or SLIT, compared with placebo. Studies were included if they were double-blind randomized controlled trials comparing SCIT or SLIT with placebo. Thirty-six randomized controlled trials (3014 patients; 2768 controls) were analyzed.

Results:
The overall effect size of SCIT for symptom score (SMD, –0.92; 95% CI, –1.26 to –0.58) was significantly higher than SLIT, both administered via drops (SMD, –0.25; 95% CI, –0.45 to –0.05) and tablets (SMD, –0.40; 95% CI, –0.54 to –0.27). Similar results were reported for medication score (SCIT: SMD, –0.58; 95% CI, –0.86 to –0.30. SLIT drops: SMD, –0.37; 95% CI, –0.74 to –0.00. SLIT tablets SMD, –0.30; 95% CI, –0.44 to –0.16).

Conclusions:
Our results provide indirect but solid evidence that SCIT is more effective than SLIT in controlling symptoms and in reducing the use of antiallergic medications in seasonal allergic rhinoconjunctivitis to grass pollen. Ⓐ

Evidence-Based Reference

Matricardi PM et al.: Subcutaneous immunotherapy and pharmacotherapy in seasonal allergic rhinitis: a comparison based on meta-analyses, *J Allergy Clin Immunol* 128:791–799, 2011. Ⓐ

Di Bona D et al.: Efficacy of subcutaneous and sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: a meta-analysis–based comparison, *J Allergy Clin Immunol* 30:1097–1107e2, 2012. Ⓐ

SUGGESTED READINGS

Brinkhaus B et al.: Acupuncture in patients with seasonal allergic rhinitis, *Ann Intern Med* 158(225):234, 2013.

Quillen DM, Feller DB: Diagnosing rhinitis: allergic vs. nonallergic, *Am Fam Physician* 73:1583, 2006.

Sur DK, Scandale S: Treatment of allergic rhinitis, *Am Fam Physician* 81(12):1440–1446, 2010.

Wallace DV et al.: The diagnosis and management of rhinitis: an updated practice parameter, *J Allergy Clin Immunol* 122(2 suppl):S21, 2008.

Wheatley LM, Togias A: Allergic rhinitis, *N Engl J Med* 372:456–463, 2015.

BASIC INFORMATION

DEFINITION

Alopecia is the term used to describe involuntary hair loss, typically on the scalp but can occur anywhere over the body. *Nonscarring alopecia* is hair loss without clinically apparent scarring, inflammation, or skin atrophy. *Scarring alopecia* is characterized by permanent hair loss accompanied by tissue destruction in the form of scarring, inflammation, and/or skin atrophy.

SYNONYMS

Hair loss
Balding

ICD-9CM CODES
704.0 Alopecia
704.01 Alopecia Areata
704.02 Telogen Effluvium
ICD-10CM CODES
L63 Alopecia aerata
L63.0 Alopecia (capitis) totalis
L64 Androgenic alopecia
L64.0 Drug-induced androgenic alopecia
L64.8 Other androgenic alopecia
L64.9 Androgenic alopecia, unspecified
L65 Other nonscarring hair loss
L66 Cicatricial alopecia
L65.9 Nonscarring hair loss, unspecified
L63.8 Other alopecia areata
L65.0 Telogen effluvium

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Depends on etiology, for example:
- Alopecia areata affects 1% of the U.S. population by age 50 yr. There is a higher incidence at a younger age and both sexes are affected equally.
- Androgenetic alopecia affects males > females with 50% of Caucasian men affected by age 50 yr. Less common in Asians and African-American men, and often has later onset. By age 70, 40% of females are affected with incidence increasing after menopause.

GENETICS: Depends on etiology, for example:
- Androgenetic alopecia is polygenic with variable penetrance and can be inherited from one or both parents.
- Certain scarring alopecias are more predominant in people with coarser hair.

ETIOLOGY

NONSCARRING
- Failure of follicle production
- Hair shaft abnormality
- Pattern hair loss, i.e., androgenetic alopecia
- Hair breakage, i.e., trichotillomania, traction alopecia, cosmetic overprocessing
- Problem with cycling (excess shedding), i.e., telogen effluvium, anagen effluvium, loose anagen syndrome, alopecia areata, syphilis

SCARRING
- Infectious: tinea capitis with inflammation (kerion), bacterial folliculitis as in dissecting folliculitis and folliculitis decalvans
- Neoplasm: alopecia mucinosa in cutaneous T-cell lymphoma or alopecia neoplastica due to metastatic carcinoma (breast cancer)
- Autoimmune: chronic cutaneous lupus erythematosus
- Congenital

CLINICAL FEATURES

HISTORY: A careful history must be taken and should include time course for hair loss, the pattern of hair loss, any recent change in life situation/stresses, any associated medical conditions, new medications, any family history of hair loss, diet, hair care practices, and other skin/nail symptoms.

PHYSICAL EXAMINATION:
- General: patient's emotional response to hair loss
- Hair/skin:
  1. Hair thinning/loss
  2. May have fine downy hairs also referred to as vellous hairs
  3. Skin may show changes consistent with inflammation, infection, and/or atrophy
  4. Women may show virilization (e.g., hirsutism)
  5. Exclamation point hairs can be seen in alopecia areata
  6. Broken hairs of different length may be seen in traumatic alopecia
  7. Hairs that crack or crumble with palpation most often signify shaft damage due to overprocessing

DIAGNOSIS

WORKUP

- Pull test—no shower for 24 hr, 60 hairs are gently pulled from the scalp, removal of 6 or more hairs is considered positive result and indicated telogen effluvium (active shedding). Look for telogen bulbs on recovered hairs to differentiate from breaking (blunt ends).
- Punch biopsy—Mandatory when suspecting scarring alopecia. Send two punches: one for vertical and one for horizontal sectioning for histopathologic analysis preferably by a dermatopathologist.
- Trichogram—quantifies hair loss. Pull 25-50 hairs and measure proportion of anagen to catagen and telogen hairs under light microscopy. Ten to twenty percent telogen hairs is normal, >35% is highly suspicious for telogen effluvium.
- Fig. EA1-64 describes the evaluation and treatment of alopecia in females.

LABORATORY TESTS

Initiate laboratory studies if not clear based on clinical presentation:
- CBC—rule out Fe deficiency
- Total Fe/ferritin—rule out subclinical Fe deficiency
- TSH—rule out underlying thyroid disease
- ANA—screen for autoimmune disease
- RPR—rule out cutaneous syphilis if history suggestive of increased risk

DIFFERENTIAL DIAGNOSIS

NONSCARRING:
- *Telogen effluvium:* This type of alopecia is usually diffuse thinning that follows significant life stress (death of loved one, high fever, severe infection, crash dieting) or change in hormones (postpartum, change in or cessation of oral contraceptives). Patient often presents with a bag of hair that has fallen out. This is caused by a large number of anagen (growing) hairs entering telogen (dying phase) simultaneously. Telogen effluvium is more common in women.
- *Androgenetic alopecia:* Gradual thinning of hair and a trend toward finer hair, which in men has a typical pattern of receding anterior bitemporal hairline resulting in an M-shaped pattern and hair loss at the vertex and in women has a typical pattern of thinning along vertex with or without frontotemporal thinning. This type of thinning is due to a combination of genetic predisposition and androgenic conversion of hair follicles into vellus-like follicles.
- *Alopecia areata:* Patches of acute hair loss (Fig. A1-65*A*), typically 2 to 5 cm in diameter, with

FIGURE A1-65 A Alopecia areata: patchy hair loss. The alopecic area is devoid of hairs, and the scalp does not present inflammatory changes. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

normal-appearing skin, black dots (cadaver hairs, point noir) from hair that breaks before reaching the skin's surface, and occasional "exclamation point hairs," which are evidence of hair breaking off as they are pushed from the follicle. Fingernails may show fine pitting. On biopsy, lymphocytes surround the hair bulb and resemble a "swarm of bees," evidence of the autoimmune etiology. Patients often have positive family history.

AA Universalis (AAU)—generalized loss of body hair

AA Totalis (AAT)—complete loss of scalp hair

- *Tinea:* This type of hair loss is evident in round patches, possibly with scarring, erythema, and lymphadenopathy. This is the most common type of hair loss in children. Diagnosis can be made by scraping the erythematous edge and placing the scraping with KOH under a microscope to check for hyphae. Wood's lamp only fluoresces if tinea is caused by *Microsporum* spp.; however, the most common (in the U.S.) *Trichophyton* spp. does not fluoresce. If a kerion (severe alopecia associated with bogginess) is present, it may cause scarring.
- *Traumatic alopecia:* This type of hair loss is in a pattern consistent with breaking off of hairs due to traction (hair pulling) or chemical or heating agents (hair straightening or permanent). Etiology usually becomes apparent with careful history taking and visualizing the pattern of hair loss. In trichotillomania (Fig. A1-65*B*) the alopecia area has an irregular shape, scalp excoriations may present, and hairs are broken at different lengths.

SCARRING

- *Lichen planus:* The hair loss associated with LP is typically associated with scaling and atrophy of pruritic, painful skin underlying the hair loss. This hair loss is more common in middle-aged women. While there are numerous variations in clinical presentation, the general clinical picture is one of a chronic inflammatory condition of the skin, nails, mucous membranes, and/or hair. The typical skin lesions are flat topped, violaceous lesions with white lines (Wickham's striae), while the typical oral lesions are milky white.
- *Chronic cutaneous (discoid) lupus erthematosus:* This type of hair loss frequently is evident in well-demarcated, erythematous plaques in chronically sun-exposed areas of skin. Lesions exhibit hypopigmentations or hyperpigmentations, atrophy, erythema, and scaling. It may be present concurrently with SLE or be the first presenting symptom of SLE, but in most cases it is a purely cutaneous condition.
- *Tinea with kerion:* A kerion represents an exuberant delayed-type hypersensitivity reaction to the tinea capitis, resulting in one (or many) inflamed boggy plaque(s) on the scalp depending on the severity of the infection.

Rx TREATMENT

- *Telogen effluvium:* Stop insulting stress/medication and in 3 to 4 months anagen recurs. Hair density should be normalized by 12 months. Multiple medications have been shown to be an inciting factor and one should consider stopping them (these include, but are not limited to, enalapril, colchicine, levodopa, metoprolol, propranolol, oral contraceptives, and lithium). Full regrowth is expected in most cases.
- *Androgenetic alopecia:* For men, the most likely first-line treatment is oral finasteride (type II 5α-reductase inhibitor) which leads to lower levels of dihydrotestosterone. This leads to hair regrowth in about 6 months, but with cessation, hair returns to pattern of loss within 6 to 9 months. Topical minoxidil has shown similar results to finasteride and can be useful in partially restoring lost hair in both men and women. Dutasteride (off-label) has been shown to be superior to finasteride in a randomized trial but requires higher doses than that used for BPH. Discontinuation of minoxidil will result in loss of regrown hair often over several months. Other options include surgical intervention with hair transplantation or hair flaps, camouflaging agents, the use of a hairpiece, or low-level light therapy. In women with elevated androgens, antiandrogens such as spironolactone, flutamide, and cimetidine may be considered.
- *Alopecia areata:* Spontaneous remission occurs in patchy AA, but less commonly in AAT or AAU. Glucocorticoids (GCs) are the mainstay of treatment but have little effect on the long-term outcome of hair loss—topical GC for small patches, intralesional injection of high-potency GC, and even systemic steroids can all be temporarily effective but at the cost of glucocorticoid exposure. Induction of allergic contact dermatitis using short-contact anthralin therapy or squaric acid sensitization can be effective but tends to have significant local discomfort, thereby limiting its use. Photochemotherapy has shown some beneficial outcomes, although there is a high relapse rate after discontinuation.
- *Tinea capitis:* To effectively treat tinea capitis, oral antifungal agents must be used. Griseofulvin is considered the drug of choice in the U.S., and the recommended time course is 6 weeks to several months. Other oral agents to consider include terbinafine, itraconazole, fluconazole, and ketaconazole. If there is a kerion (area of boggy, purulent inflammation underlying the area of hair loss), the patient is at increased risk for scarring alopecia due to bacterial superinfection and a short course of oral steroids and oral antibiotic must be considered.
- *Traumatic alopecia:* First priority is stopping inciting activity/agent, ideally leading to gradual resolution of hair loss and hair regrowth.
- *Lichen planus:* Associated hair loss is often permanent; however, for symptomatic control of itching and pain, topical or oral glucocorticoids may be considered.
- *Chronic cutaneous discoid erythematosus:* The best prevention is sun protection, with SPF lotion. Treatment options center around the cautious use of topical or intralesional glucocorticoids. Hydroxychloroquinone and retinoids are also used with caution.

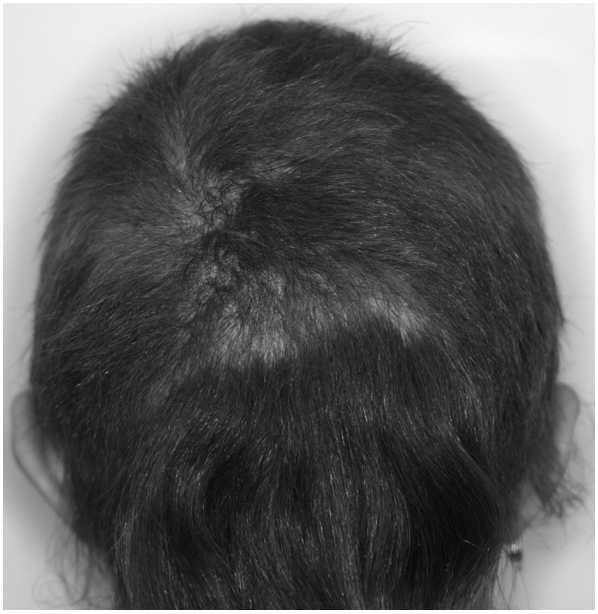


FIGURE A1-65 B Trichotillomania: patchy hair loss. The alopecic area has an irregular shape and present hairs are broken at different lengths. Also note scalp excoriations. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

REFERRAL

Dermatology

PATIENT/FAMILY EDUCATION

Alopecia areata: www.naaf.org

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Alopecia (Patient Information)

AUTHOR: **JON SKALECKI, M.D.**

SUGGESTED READINGS

Gilhar A et al.: Alopecia areata, *N Engl J Med* 366:1515–1525, 2012.

Habif T: Hair diseases. In: *Clinical Dermatology*. St Louis: Mosby.

Mounse A Reed S: Diagnosing and treating hair loss, *Am Fam Physician* 80(4):356, 2009.

Olsen EA et al.: The importance of dual 5alpha-reductase inhibition in the treatment of male pattern hair loss: results of a randomized placebo-controlled study of dutasteride versus finasteride, *J Am Acad Dermatol* 55(6):1014, 2006.

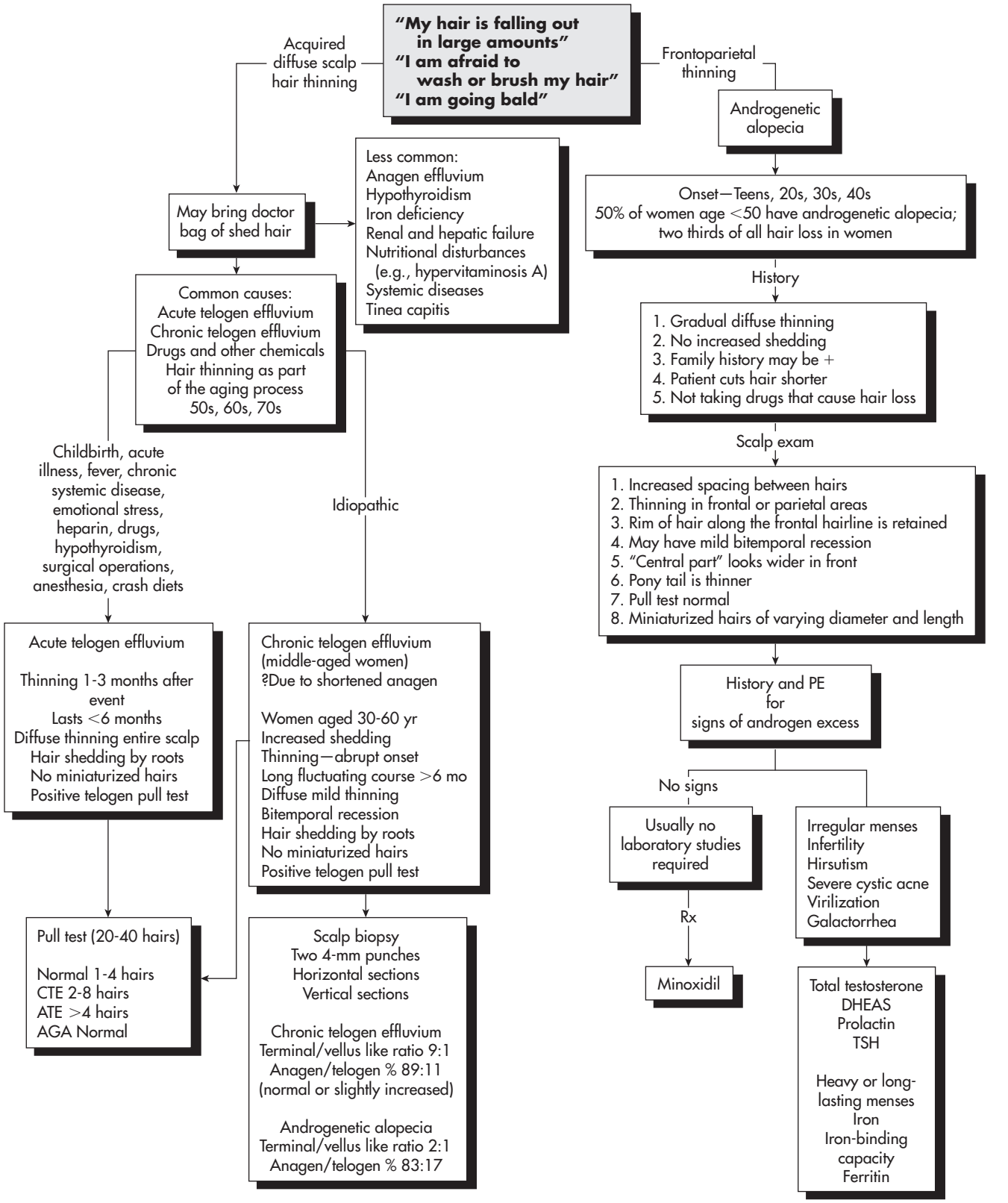


FIGURE EA1-64 Evaluation and treatment of alopecia in females. *AGA,* Androgenetic alopecia; *ATE,* acute telogen effluvium; *CTE,* chronic telogen effluvium; *DHEAS,* dehydroepiandrosterone-sulfate; *PE,* physical examination; *TSH,* thyroid-stimulating hormone. (Modified from Habif TA: *Clinical dermatology,* ed 4, St Louis, 2004, Mosby.)

Alpha-1-Antitrypsin Deficiency PTG

BASIC INFORMATION

DEFINITION

Alpha-1-antitrypsin deficiency is a genetic deficiency of the protease inhibitor alpha-1-antitrypsin that results in a predisposition to pulmonary emphysema and hepatic cirrhosis.

SYNONYMS

AATD

ICD-9CM CODES
277.6 Alpha-1-antitrypsin deficiency
ICD-10CM CODES
E88.01 Alpha-1-antitrypsin deficiency

EPIDEMIOLOGY & DEMOGRAPHICS

- Underrecognized by clinicians, but accounts for approximately 2% to 5% of chronic obstructive pulmonary disease (COPD) cases in Americans
- Prevalence is about 1 per 2000 to 5000 people in the United States
- Inherited as an autosomal codominant disorder
- Most frequent mutation is in the *SERPINA 1* gene (previously known as *PI* gene)
- Most common alleles are:
  1. normal "M" allele (95% frequency in the U.S.)
  2. deficient variant "Z" allele (1% to 2%)
  3. deficient variant "S" allele (2% to 3%)
- Severe deficiency is most commonly due to homozygotes ZZ
- Risk of lung disease is uncertain with MZ genotype, but increased with SZ genotype (especially in smokers)
- One in 10 individuals of European descent carries one of two mutations that may result in partial alpha-1-antitrypsin deficiency

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical findings and clinical presentation are varied and depend on phenotype (see "Etiology")
- Most often affects the lungs but can also involve liver and skin
- Classically associated with early-onset, severe, lower-lobe predominant panacinar emphysema; bronchiectasis may also be seen
- Symptoms are similar to "typical" COPD presentation (dyspnea, cough, sputum production)
- Liver involvement includes neonatal cholestasis, cirrhosis in children and adults, and primary carcinoma of the liver
- Panniculitis is the major dermatologic manifestation (Rare: 1 in 1000 AATD individuals)

ETIOLOGY

- Degree of alpha-1-antitrypsin deficiency depends on phenotype.
- "MM" represents the normal genotype and is associated with alpha-1-antitrypsin levels in the normal range.
- Mutation most commonly associated with emphysema is Z, with homozygote (ZZ) resulting in approximately 85% deficit in plasma alpha-1-antitrypsin concentrations.
- Development of emphysema is believed to result from an imbalance between the proteolytic enzyme elastase, produced by neutrophils, and alpha-1-antitrypsin, which normally protects lung elastin by inhibiting elastase.
- Deficiency of alpha-1-antitrypsin increases risk of early-onset emphysema, but not all alpha-1-antitrypsin deficient individuals will develop lung disease.
- Smoking increases risk and accelerates onset of COPD.
- Liver disease is caused by pathologic accumulation of alpha-1-antitrypsin in hepatocytes.
- Similar to lung disease, skin involvement is thought to be attributable to unopposed proteolysis in skin.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

See "Chronic Obstructive Pulmonary Disease."
See "Cirrhosis."

WORKUP

- Suspicion for alpha-1-antitrypsin deficiency usually results from emphysema developing at an early age and with basilar predominance of disease.

LABORATORY TESTS

- Serum level of alpha-1-antitrypsin can confirm or reject suspicion of deficiency.
- Investigate possibility of abnormal alleles with genotyping.
- Pulmonary function testing is generally consistent with "typical" COPD.

IMAGING STUDIES

- Chest x-ray shows characteristic emphysematous changes at lung bases.
- High-resolution chest CT usually confirms the basal-predominant emphysema (64%) and may also show significant bronchiectasis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of smoking is paramount.
- Avoidance of other environmental and occupational exposures that may increase risk of COPD. Routine vaccinations are also recommended.

ACUTE GENERAL Rx

Acute exacerbations of COPD from alpha-1-antitrypsin deficiency are treated in a similar fashion to "typical" COPD exacerbations.

CHRONIC Rx

- The goal of treatment in alpha-1-antitrypsin deficiency is to increase serum alpha-1-antitrypsin levels above a minimum, "protective" threshold of 50 mg/dL.
- Although several therapeutic options are under investigation, IV administration of pooled human alpha-1-antitrypsin is currently the only approved method to raise serum alpha-1-antitrypsin levels. AAT augmentation therapy has been approved by the FDA for patients with AAT deficiency who have COPD. Augmentation therapy is expensive ($93,000 to $120,000/year) and requires lifelong treatment. However, given the cost and a lack of evidence of clinical benefit, a 2010 Cochrane Collaboration review noted that augmentation therapy with alpha-1-antitrypsin cannot be recommended.
- Organ transplantation for patients with end-stage lung or liver disease is also an option.

DISPOSITION

- Prognosis of patients with alpha-1-antitrypsin deficiency will depend on phenotype and level of deficiency.
- Among patients with severe alpha-1-antitrypsin deficiency, the most common underlying causes of death are respiratory failure (45% to 72%) and cirrhosis (10% to 13%).

REFERRAL

- Referral to specialists with experience in AAT deficiency is preferred
- Pulmonary and hepatology referrals for advanced lung and liver disease, or if replacement therapy is contemplated (e.g., moderate-severe lung disease)
- Lung and liver transplantation in suitable cases

PEARLS & CONSIDERATIONS

- The liver damage arising from the mutation is not from a deficiency in alpha-1-antitrypsin but from a pathologic accumulation of alpha-1-antitrypsin in hepatocytes.
- Strong association between PI*ZZ phenotypes and liver disease has prompted recommendations for AATD testing in individuals with unexplained liver disease.
- Consider alpha-1-antitrypsin deficiency in patients presenting with lower-lobe predominant emphysema; in most smokers without alpha-1-antitrypsin deficiency, emphysema predominates in the upper lobes.
- Alpha-1-antitrypsin deficiency is believed to be under-recognized.
- The American Thoracic Society and the European Respiratory Society recommend testing for AAT deficiency in all symptomatic patients with COPD, emphysema, or asthma with irreversible obstruction, whereas the Global Initiative for Chronic Obstructive Lung Disease only recommends testing for those with early-onset COPD (age <45 yr) or a strong family history of COPD.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Alpha-1-Antitrypsin Deficiency (Patient Information)
Chronic Obstructive Pulmonary Disease (Related Key Topic)
Cirrhosis (Related Key Topic)

AUTHORS: **JOSEPH A. DIAZ, M.D., M.P.H.,** and **TARO MINAMI, M.D.**

SUGGESTED READINGS

American Thoracic Society/European Respiratory Society Statement: Standards for the diagnosis and management of individuals with alpha-1 antitrypsin deficiency, *Am J Respir Crit Care Med* 168:818, 2003.

Brode SK et al.: Alpha-1 antitrypsin deficiency: a commonly overlooked cause of lung disease, *CMAJ* 184(12), 2012.

Gøtzsche PC, Johansen HK: Intravenous alpha-1 antitrypsin augmentation therapy for treating patients with alpha-1 antitrypsin deficiency and lung disease, *Cochrane Database Syst Rev 7* 7:CD007851, 2010.

Kelly E et al.: Alpha-1 antitrypsin deficiency, *Respir Med* 104(6):763–772, 2010.

Marciniuk DD et al.: Alpha-1 antitrypsin deficiency targeted testing and augmentation therapy: a Canadian Thoracic Society clinical practice guideline, *Can Respir J* 19(2):109–116, 2012.

Stroller J, Aboussouan LS: A review of α1-antitrypsin deficiency, *Am J Respir Crit Care Med* 185(3):246–259, 2012.

BASIC INFORMATION

DEFINITION

Dementia is a syndrome characterized by progressive loss of previously acquired cognitive skills including memory, language, insight, and judgment. Alzheimer's disease (AD) is believed to account for the majority (50% to 75%) of all cases of dementia.

ICD-9CM CODES
331.0 Alzheimer's disease
290.0 Senile dementia, uncomplicated
ICD-10CM CODES
G30.9 Alzheimer's disease, unspecified
F03.90 Unspecified dementia without behavioral disturbance

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Risk doubles every 5 yr after the age of 65; above the age of 85 the incidence is about 8%.
PREVALENCE: Currently an estimated 5.2 million Americans have AD; 6% between the ages of 65 and 74, 44% between 75 and 84, and 46% at 85 years and older.
PREDOMINANT SEX: Female

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Spouse or other family member, usually not the patient, notes insidious memory impairment.
- Patients have difficulties learning and retaining new information and handling complex tasks (e.g., balancing the checkbook) and have impairments in reasoning, judgment, spatial ability, and orientation (e.g., difficulty driving, getting lost away from home).
- Behavioral changes, such as mood changes and apathy, may accompany memory impairment. In later stages patients may develop agitation and psychosis.
- Atypical presentations include early and severe behavioral changes, focal findings on examination, parkinsonism, hallucinations, falls, or onset of symptoms younger than the age of 65.

DIAGNOSIS

There is no definitive imaging or laboratory test for the diagnosis of AD. Diagnosis is commonly made based on clinical history, a thorough physical and neurologic examination, and use of reliable and valid diagnostic criteria (i.e., DSM-IV or NINDCS-ADRDA) such as the following:

- Loss of memory and one or more additional cognitive abilities (aphasia, apraxia, agnosia, or other disturbance in executive functioning)
- Impairment in social or occupational functioning that represents a decline from a previous level of functioning and results in significant disability
- Deficits that do not occur exclusively during the course of delirium
- Insidious onset and gradual progression of symptoms
- Cognitive loss documented by neuropsychologic tests
- No physical signs, neuroimaging, or laboratory evidence of other diseases that can cause dementia (i.e., metabolic abnormalities, medication or toxin effects, infection, stroke, Parkinson's disease, subdural hematoma, or tumors)

The National Institute on Aging (NIA) and the Alzheimer's Association recommended new diagnostic criteria and guidelines for AD in 2011. These differ from prior DSM-IV or NINDCS-ADRDA criteria in that they now recommend that AD be considered a disease well before the onset of symptoms, they incorporate the use of biomarkers in diagnosis, and they define three distinct stages of AD: (1) *preclinical* AD, in which there is measurable biologic evidence of AD pathology but no symptoms; (2) *mild cognitive impairment* (MCI) due to AD, in which there is mild memory loss but no functional impairment at home or work; and (3) *dementia due to AD.*

DIFFERENTIAL DIAGNOSIS

- Cancer (brain tumor, meningeal neoplasia)
- Infection (AIDS, neurosyphilis, PML)
- Toxic/metabolic (EtOH, hypothyroidism, vitamin B_{12} deficiency, mercury exposure, drug effects)
- Organ failure (dialysis dementia, Wilson's disease)
- Vascular disorder (multiple strokes, severe small vessel changes, chronic vasculitides, or chronic subdural hematoma)
- Depression (pseudodementia)

WORKUP

HISTORY & GENERAL PHYSICAL EXAMINATION:

- Medication lists should always be reviewed for drugs or home remedies that may cause mental status changes.
- Patients should be screened for depression, because it can sometimes mimic dementia but also often occurs as a coexisting condition and should be treated.
- On examination, look for signs of metabolic disturbance, presence of psychiatric features, or focal neurologic deficits.

MENTAL STATUS TESTING: Brief mental status testing can be done easily and quickly in the office. For detecting mild cognitive impairment and dementia, the Montreal Cognitive Assessment (MoCA, http://www.mocatest.org/) is a highly sensitive 30-point test that takes approximately 10 minutes to administer. Cognitive domains tested include visual-spatial, attention, verbal recall, language, abstraction, and orientation. A score of 25 points or less (26 points if the patient has less than 12 years of education) indicates cognitive impairment. The test is available in over 35 languages and dialects, and multiple forms in English allow for repeated assessments over time.

Mental status testing should include tests that assess the following cognitive functions:

- Orientation: ask the patient to give the day, date, month, year, and place and to name the current president.
- Attention: ask the patient to recite the months of the year forward and in reverse.
- Verbal recall: ask the patient to remember three items; test for recall after a 1- and 5-min delay.
- Language: ask the patient to write and then read a sentence; have the patient name both common and less common objects.
- Visual-spatial: ask the patient to draw a clock and to set the hands of the clock at 11:10.

Patients with AD typically have trouble with verbal recall, plus visual-spatial or language deficits. Attention is usually preserved until the late stages of AD, so consider alternate diagnoses in patients who perform poorly on tests of attention.

LABORATORY TESTS

- CBC
- Serum electrolytes
- Glucose
- BUN/creatinine
- Liver and thyroid function tests
- Serum vitamin B_{12}
- Syphilis serology (RPR), if supported by clinical history
- HIV screening as appropriate
- Lumbar puncture if history or signs of cancer, infectious process, or when the clinical presentation is unusual (i.e., rapid progression of symptoms)
- EEG if there is history of seizures, episodic confusion, rapid clinical decline, or suspicion of Creutzfeldt-Jakob disease
- Measurement of apolipoprotein E genotyping, CSF tau and amyloid, and functional imaging including positron emission tomography (PET) or single proton emission computed tomography (SPECT) are not yet routinely indicated
- Brain biopsy (usually reserved for diagnoses such as prion disease, certain vasculitides). Generally performed post mortem.

IMAGING STUDIES

- CT scan or MRI to rule out hydrocephalus and mass lesions, including subdural hematoma
- Florbetapir-PET imaging of the brain correlates with the presence and density of beta-amyloid

TREATMENT

NONPHARMACOLOGIC THERAPY

- Patient safety, including risks associated with impaired driving, wandering behavior, leaving stoves unattended, and accidents, must be addressed with the patient and family early and appropriate measures implemented.
- Wandering, hoarding or hiding objects, repetitive questioning, withdrawal, and social inappropriateness often respond to behavioral therapies.

Alzheimer's Disease EBM ALG PTG

ACUTE GENERAL Rx

None

CHRONIC Rx

1. Symptomatic treatment of memory disturbance (Table A1-42):
   a. Cholinesterase inhibitors (ChEIs):
      FDA approved for the treatment of mild to moderate AD. Common side effects include nausea, diarrhea, and anorexia and may be bothersome enough to require a slower escalation of dosage or switching to another agent.
   b. NMDA receptor antagonist: memantine (Namenda)
      FDA approved for the treatment of moderate to severe AD. Common side effects include constipation, dizziness, or headache. Memantine is contraindicated in patients with renal insufficiency or history of seizures.
2. Symptomatic treatment of neuropsychiatric and behavioral disturbances (Table A1-43).

Depression, agitation, delusions, or hallucinations may respond to medications.

DISPOSITION & REFERRAL

- Patients with complex or atypical presentations or challenging management issues should be referred to a neurologist or another specialist with expertise in dementia.
- Approximately 1 in 8 hospitalized patients with AD who develop delirium will have at least one adverse outcome (e.g., institutionalization, cognitive decline, death) associated with delirium.
- Family education and support may help reduce need for skilled nursing facility and reduce caregiver stress, depression, and burnout.

PEARLS & CONSIDERATIONS:

The physician should make a thorough search for the treatable causes of dementia. Current American Academy of Neurology practice parameters recommend:

- Treat cognitive symptoms of AD with ChEIs.
- Treat agitation, psychosis, and depression.
- Encourage caregivers to participate in educational programs and support groups.

COMMENTS

- Ginkgo biloba is marketed widely as effective in delaying cognitive impairment; however, trials have shown that it is not effective in reducing the incidence of Alzheimer dementia or dementia overall.
- Higher midlife fitness levels seem to be associated with lower hazards of developing all-cause dementia later in life independent of cerebrovascular disease.
- Lower plasma beta-amyloid 42/40 is associated with greater cognitive decline among elderly persons without dementia over 9 yr, and this association is stronger among those with low measures of cognitive reserve.
- The *APOE* genotype provides information on the risk for AD, but the genotyping of patients raises ethical and emotional concerns. Because the benefits of genetic testing are often modest, and the tests themselves often imprecise in identifying risk, the test is generally discouraged. Recent trials, however, reveal that the disclosure of *APOE* genotyping results to adult children of patients with AD did not result in significant short-term psychological risks. Test-related distress was reduced among those who learned that they were *APOE4* negative. Persons with high levels of emotional distress before undergoing genetic testing are more likely to have emotional difficulties after disclosure.

For additional information for patients, families, and clinicians, contact the following organizations:

- Alzheimer's Association (www.alz.org; 800-272-3900)
- Alzheimer's Disease Education and Referral Center (http://www.nia.nih.gov/Alzheimers; 800-438-4380)

TABLE A1-42 Symptomatic Treatment of Memory Disturbance

	Initial Dose	Target Dose
Donepezil	5 mg qd for 4-6 weeks	10 mg qd
Rivastigmine	1.5 mg bid with food, increase by 1.5 mg bid weekly	3-6 mg bid
Galantamine	4 mg bid with food, increase by 4 mg bid every 4 weeks	8-12 mg bid
Memantine	5 mg qd, increase by 5 mg weekly	10 mg bid

TABLE A1-43 Treatment of Behavioral and Neuropsychiatric Symptoms

	Initial Dose	Maximum Dose
Atypical Antipsychotics		
Olanzapine	2.5 mg qd to bid, may increase by 2.5 mg as needed	7.5 mg bid
Quetiapine	25 mg bid, may increase by 25 mg every 2 days	250 mg tid
Antidepressants		
Sertraline	25-50 mg qd, may increase by 25 mg every week	200 mg qd
Citalopram	10 mg qd, may increase after 1 week	20 mg qd

EVIDENCE

available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Alzheimer's Disease (Patient Information)
Dementia with Lewy Bodies (Related Key Topic)
Mild Cognitive Impairment (Related Key Topic)

AUTHOR: **TAMARA G. FONG, M.D., PH.D.**

EVIDENCE

Abstract[1]

Objective:

The impact of the atypical antipsychotics olanzapine, quetiapine, and risperidone on cognition in patients with Alzheimer's disease is unclear. The authors assessed the effects of time and treatment on neuropsychological functioning during the Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's Disease study (CATIE-AD).

Method:

CATIE-AD included 421 outpatients with Alzheimer's disease and psychosis or agitated/aggressive behavior who were randomly assigned to receive masked, flexible-dose olanzapine, quetiapine, risperidone, or placebo. Based on their clinicians' judgment, patients could discontinue the originally assigned medication and receive another randomly assigned medication. Patients were followed for 36 weeks, and cognitive assessments were obtained at baseline and at 12, 24, and 36 weeks. Outcomes were compared for 357 patients for whom data were available for at least one cognitive measure at baseline and one follow-up assessment that took place after they had been on their prescribed medication or placebo for at least 2 weeks.

Results:

Overall, patients showed steady, significant declines over time in most cognitive areas, including in scores on the Mini-Mental State Examination (MMSE; −2.4 points over 36 weeks) and the cognitive subscale of the Alzheimer's Disease Assessment Scale (−4.4 points). Cognitive function declined more in patients receiving antipsychotics than in those given placebo on multiple cognitive measures, including the MMSE, the cognitive subscale of the Brief Psychiatric Rating Scale, and a cognitive summary score summarizing change on 18 cognitive tests.

Conclusions:

In CATIE-AD, atypical antipsychotics were associated with worsening cognitive function at a magnitude consistent with 1 year's deterioration compared with placebo. Further cognitive impairment is an additional risk of treatment with atypical antipsychotics that should be considered when treating patients with Alzheimer's disease. Ⓐ

Abstract[2]

Evidence of reduced blood-brain barrier (BBB) integrity preceding other Alzheimer's disease (AD) pathology provides a strong link between cerebrovascular angiopathy and AD. However, the "Vascular hypothesis" holds that BBB leakiness in AD is likely due to hypoxia and neuroinflammation leading to vascular deterioration and apoptosis. We propose an alternative hypothesis: amyloidogenesis promotes extensive neoangiogenesis leading to increased vascular permeability and subsequent hypervascularization in AD. Cerebrovascular integrity was characterized in Tg2576 AD model mice that overexpress the human amyloid precursor protein (APP) containing the double missense mutations, APPsw, found in a Swedish family, that causes early-onset AD. The expression of tight junction (TJ) proteins, occludin and ZO-1, were examined in conjunction with markers of apoptosis and angiogenesis. In aged Tg2576 AD mice, a significant increase in the incidence of disrupted TJs, compared to age-matched wild-type littermates and young mice of both genotypes, was directly linked to an increased microvascular density but not apoptosis, which strongly supports amyloidogenic triggered hypervascularity as the basis for BBB disruption. Hypervascularity in human patients was corroborated in a comparison of postmortem brain tissues from AD and controls. Our results demonstrate that amyloidogenesis mediates BBB disruption and leakiness through promoting neoangiogenesis and hypervascularity, resulting in the redistribution of TJs that maintain the barrier and thus, provides a new paradigm for integrating vascular remodeling with the pathophysiology observed in AD. Thus the extensive angiogenesis identified in AD brain exhibits parallels to the neovascularity evident in the pathophysiology of other diseases such as age-related macular degeneration. Ⓐ

Evidence-Based References

Vigen CL et al.: Cognitive effects of atypical antipsychotic medications in patients with Alzheimer's disease: outcomes from CATIE-AD, *Am J Psychiatry* 168:1–9, 2011. Ⓐ

Biron KE et al.: Amyloid triggers extensive cerebral angiogenesis causing blood brain barrier permeability and hypervascularity in Alzheimer's disease, *PLoS One* 6:e23789, 2011. Ⓐ

SUGGESTED READINGS

Bateman RJ et al.: Clinical and biomarker changes in dominantly inherited Alzheimer's disease, *N Engl J Med* 367:795–804, 2012.

Clark CM et al.: Use of florbetapir-PET for imaging β-amyloid pathology, *JAMA* 305(3):275–283, 2011.

Cummings JL: Alzheimer's disease, *N Engl J Med* 351:56, 2004.

DeFina LF et al.: The association between midlife cardiorespiratory fitness levels and later-life dementia, *Ann Intern Med* 158:162–168, 2013.

DeKosky ST et al.: Ginkgo-biloba for prevention of dementia, *JAMA* 300(19): 2253–2262, 2009.

Doody RS et al.: Management of dementia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology, *Neurology* 56:1154, 2001.

DSM-V. Diagnostic and Statistical Manual of Mental Disorders. ed 5 American Psychiatric Association: Washington, DC.

Folstein MF et al.: "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician, *J Psychiatr Res* 12:189, 1975.

Fong T et al.: Adverse outcomes after hospitalization and delirium in persons with Alzheimer disease, *Ann Intern Med* 156:848–856, 2012.

Green RC et al.: Disclosure of APOE genotype for risk of Alzheimer's disease, *N Engl J Med* 361:245–254, 2009.

Kawas CH: Early Alzheimer's disease, *N Engl J Med* 349(11):1056, 2003.

Mattsson N et al.: CSF biomarkers and incipient Alzheimer's disease in patients with mild cognitive impairment, *JAMA* 302(4):385–393, 2009.

Mayeux R: Early Alzheimer's disease, *N Engl J Med* 362:2194–2201, 2010.

McKhann GM et al.: The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease, *Alzheimer's & Dementia* 7(3):263–269, 2011.

Mitchell SL et al.: Advanced dementia: state of the art and priorities for the next decade, *Ann Intern Med* 156:45–51, 2012.

Querfurth H, LaFerla FM: Alzheimer's disease, *N Engl J Med* 362:329–344, 2010.

Snitz B et al.: Ginkgo biloba for preventing cognitive decline in older adults, *JAMA* 302(24):2663–2670, 2009.

Yaffe K et al.: Association of plasma β-amyloid level and cognitive reserve with subsequent cognitive decline, *JAMA* 305(3):261–266, 2011.

BASIC INFORMATION

DEFINITION

Amaurosis fugax is a temporary loss of monocular vision caused by transient retinal ischemia.

ICD-9CM CODES
362.34 Amaurosis fugax
ICD-10CM CODES
G45.3 Amaurosis fugax

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): An uncommon but important presentation of carotid artery disease
PEAK INCIDENCE: Approximately 55 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Onset is sudden, typically lasting seconds to minutes, and often accompanied by scotomas such as a shade or curtain being pulled over the front of the eye (usually downward).
- Vision loss can be complete, hemianopic, or quadrantic.
- Acute stage: cholesterol emboli may be seen in retinal artery (*Hollenhorst plaque*); carotid bruits or other evidence of generalized atherosclerosis.
- If embolus is cardiac in origin, atrial fibrillation is often present.

ETIOLOGY

- Usually embolic from the internal carotid artery or the heart
- Giant cell arteritis causing inflammation of retinal arteries
- Hyperviscosity syndromes, such as sickle cell disease, which causes ischemia in the vascular territory of the ophthalmic artery
- Hypercoagulability states
- Transient vasospasm often associated with exercise

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Retinal migraine: in contrast to amaurosis, the onset of visual loss develops more slowly, usually over 15 to 20 min.
- Transient visual obscurations occur in the setting of papilledema; intermittent rises in intracranial pressure briefly compromise optic disc perfusion and cause transient visual loss lasting 1 to 2 seconds. The episodes may be binocular. If the visual loss persists at the time of evaluation (i.e., vision has not yet recovered), then the differential diagnosis should be broadened to include:
  1. Anterior ischemic optic neuropathy: arteritic (classically GCA) or nonarteritic
  2. Central retinal vein occlusion

WORKUP

- Workup should focus on embolic sources, but GCA should always be considered.
- Careful examination of retina; embolus may be visible and confirm the diagnosis (Fig. A1-66).
- Auscultation of arteries for carotid bruits.
- Examination of all pulses and for temporal artery tenderness.
- Inquire about symptoms of GCA (scalp tenderness, headache, fever, jaw claudication).
- Examine for signs of hemispheric stroke resulting from intracranial aneurysm (contralateral limb and facial weakness or sensory loss, aphasia, etc.).

LABORATORY TESTS

- Complete blood count with erythrocyte sedimentation rate and C-reactive protein.
- Serum chemistries, including lipid profile.
- Cardiac enzymes and ECG.
- Hypercoagulable workup is discretionary based on younger age and history.

IMAGING STUDIES

- Carotid Doppler imaging followed by MR or CT angiography as indicated.
- Transthoracic echocardiography is indicated to screen for sources of emboli in patients with evidence of heart disease and in patients without an evident source for transient neurologic deficit. Transesophageal echocardiography is more sensitive for detecting cardiac sources of emboli (ventricular mural thrombus, atrial appendage, patent foramen ovale, aortic arch).
- MRI of the brain with diffusion-weighted imaging to look for infarcts, especially those presenting with focal neurologic disturbances.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Diet (decrease saturated fatty acids and high-cholesterol foods)
- Exercise
- Cessation of tobacco use

FIGURE A1-66 A cholesterol crystal embolus lodged at an arterial bifurcation. (From Stein JH [ed]: *Internal medicine,* ed 5, St Louis, 1998, Mosby.)

ACUTE GENERAL Rx

- Investigate as an emergency.
- Aspirin if etiology is presumed embolic.
- If GCA is suspected, start prednisone and refer for temporal artery biopsy within 48 hr (see "Giant Cell Arteritis" in Section I).

CHRONIC Rx

- Reduce risks by carotid endarterectomy or carotid stenting if stenosis >70%. Stenting may be performed in high-risk surgical candidates.
- Control hypertension and manage vascular risk factors.
- Antiplatelet therapy.
- Consider starting statin medication.

DISPOSITION

Among patients with >50% carotid stenosis who do not undergo carotid endarterectomy, those who present with transient monocular blindness have an approximate 10% risk of stroke in 3 yr compared with an approximate 20% risk in patients who present with a hemispheric transient ischemic attack (TIA).

REFERRAL

- Recommend referral to a neurologist for evaluation and workup.
- If significant carotid stenosis, consider carotid endarterectomy or carotid stenting for the following:
  1. High-grade (≥70%) stenosis
  2. Multiple TIAs despite medical therapy in the setting of high-grade or ulcerative disease

PEARLS & CONSIDERATIONS

- Cholesterol emboli in retinal arteries on funduscopy confirm the diagnosis.
- Recognize that transient visual loss has multiple other causes.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Carotid Stenosis (Related Key Topic)
Giant Cell Arteritis (Related Key Topic)
Transient Ischemic Attack (Related Key Topic)
Amaurosis Fugax (Patient Information)

AUTHOR: **TZU-CHING (TEDDY) WU, M.D., M.P.H.**

SUGGESTED READING

Murtha T, Stasheff SF: Visual dysfunction in retinal and optic nerve disease, *Neurol Clin* 21:445, 2003.

Amblyopia

BASIC INFORMATION

DEFINITION

Amblyopia refers to a decrease in vision in one or both eyes in the presence of an otherwise normal ophthalmologic examination. The major types of amblyopia are strabismic, anisometropic (refractive), and combined strabismic and refractive. Less common types are ametropic and deprivation (rare).

SYNONYMS

Deprivation amblyopia
Occlusion amblyopia
Strabismus amblyopia
Refractive amblyopia
Organic or toxic amblyopias
Lazy eye

ICD-9CM CODES
368.00 Amblyopia
ICD-10CM CODES
H53.00 Unspecified amblyopia, unspecified eye

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 1% to 5% of the general population. Amblyopia is the leading cause of vision loss in children. It is also the cause of permanent vision loss in 2.9% of adults.
PREVALENCE (IN U.S.): High incidence in premature infants with drug-dependent mothers and in neurologically impaired children. Children with a family history of strabismus or amblyopia are at increased risk.
PREDOMINANT SEX: None
PREDOMINANT AGE: Childhood
PEAK INCIDENCE: Childhood

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Decreased vision using best refraction in the presence of normal corneal, lens, retinal, and optic nerve appearance (Fig. A1-67).

ETIOLOGY

- Visual deprivation
- Strabismus
- Occlusion with patching
- Refractive error organic lesions in the nervous system
- Toxins

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Central nervous system (CNS) disease (brainstem)
- Optic nerve disorders
- Corneal or other eye diseases
- Retinal disorders

WORKUP

- Complete eye examination to find cause of amblyopia or deprivation of vision. Referral to an ophthalmologist is recommended for any child with a visual acuity in either eye of ≤20/40 at age 3 to 5 yr or worse at age ≥6 yr or a two-line difference in acuity between eyes.
- Motility evaluation.

LABORATORY TESTS

Usually none

IMAGING STUDIES

Usually not necessary unless central nervous system (CNS) lesion suspected

TREATMENT

NONPHARMACOLOGIC THERAPY

- Treatment depends on the age of the patient, severity of amblyopia, and compliance with patching or atropine.
- Glasses or prisms to align eyes with minor deviations and improve vision.
- Patching and atropine are both effective. Atropine 1% is used daily for 6 mo; patching is used 2 to 6 hr/day for 6 mo. Patching may be more effective; 50% get best vision improvement by 16 wk.
- Removal of the cause of the amblyopia if possible.
- Surgery to align the eyes or remove obstruction to vision.

CHRONIC Rx

- Patching or optics, including prisms and atropine, most effective in 3- to 7-yr-olds; although treatment ideally should begin before age 5, a recent trial demonstrated that children may benefit even at an older age.
- Tapering the amount of time a patch is worn each day at the end of treatment reduces the risk of recurrence.

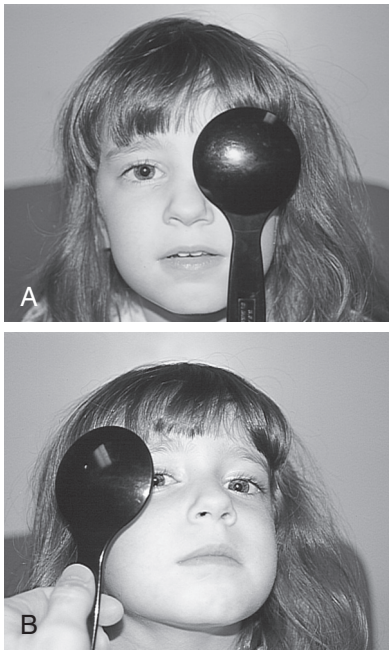


FIGURE A1-67 A, This child happily fixes with her right eye and does not object if the left eye is covered. **B,** When the right eye is covered she moves her head away and tries to remove the cover, demonstrating a fixation preference for the right eye and amblyopia of the left eye. (From Hoekelman R [ed]: *Primary pediatric care,* ed 3, St Louis, 1997, Mosby.)

DISPOSITION

Immediate patching, alternating eyes daily

REFERRAL

To ophthalmologist if vision is compromised

PEARLS & CONSIDERATIONS

COMMENTS

- The earlier the referral, the better the outcome. Amblyopia is more responsive to treatment among children younger than 7 years of age. Although the average treatment response is smaller in children 7 to less than 13 years of age, some children show a marked response to treatment.
- The success of therapy is highly dependent on treatment compliance.
- Amblyopia recurs in 25% of children after patching is discontinued.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **MELVYN KOBY, M.D.,** and **R. SCOTT HOFFMAN, M.D.**

SUGGESTED READINGS

Bradfield YS: Identification and treatment of amblyopia, *Am Fam Physician* 87:348–352, 2013.

Doshi NR, Rodriguez ML: Amblyopia, *Am Fam Physician* 75:361, 2007.

BASIC INFORMATION

DEFINITION

Amebiasis is an infection caused by the protozoal parasite *Entamoeba histolytica.* Although primarily an infection of the colon, amebiasis may cause extraintestinal disease, particularly liver abscess.

SYNONYMS

Amebic dysentery (when severe intestinal infection)

ICD-9CM CODES
006.9 Amebiasis
ICD-10CM CODES
A06.9 Amebiasis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 1.2 cases per 100,000 U.S. population. Highest in institutionalized patients, and travelers to/immigrants from developing nations.
PREVALENCE (IN U.S.): 4% (80% of infections asymptomatic)
PREDOMINANT SEX:
- Equal sex distribution in general
- Striking male predominance of liver abscess

PREDOMINANT AGE: 2nd through 6th decades
PEAK INCIDENCE: Peaks at age 2 to 3 yr and >40 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Often nonspecific
- Approximately 20% of cases symptomatic
  1. Diarrhea, which may be bloody
  2. Abdominal and back pain
- Abdominal tenderness in 83% of severe cases
- Fever in 38% of severe cases
- Hepatomegaly, right upper quadrant tenderness, and fever in almost all patients with liver abscess (may be absent in fulminant cases)

ETIOLOGY

- Caused by the protozoal parasite *E. histolytica. E. dispar* and *E. moshkovskii* are 10 times more common but nonpathogenic and difficult to distinguish from *E. histolytica.*
- Transmission by the fecal-oral route
- Infection usually localized to the large bowel, particularly the cecum where a localized mass lesion (ameboma) may form
- Extraintestinal infection in which the organism invades the bowel mucosa and gains access to the portal circulation

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Severe intestinal infection possibly confused with ulcerative colitis or other infectious enterocolitis syndromes, such as those caused by *Shigella, Salmonella, Campylobacter,* or invasive *Escherichia coli*
- In elderly patients: ischemic bowel possibly producing a similar picture

WORKUP

- Three stool specimens over a period of 7 to 10 days to search for cysts or trophozoites has a sensitivity of 85% to 95%, but microscopy cannot differentiate between the species
- Concentration and staining the specimen with Lugol's iodine or methylene blue to increase the diagnostic yield
- Fecal leukocytes not always present

LABORATORY TESTS

- Fecal ELISA antigen detection is specific for *E. histolytica* (87% percent sensitive) and also useful for diagnosis of liver abscess.
- Mucosal biopsy is occasionally necessary to look for cysts or trophozoites.
- Serum antibody assays specific for *E. histolytica* are available and are particularly sensitive and specific for extraintestinal infection or severe intestinal disease.
- Aspiration of abscess fluid is used to distinguish amebic from bacterial abscesses.

IMAGING STUDIES

Abdominal imaging studies (sonography or CT scan) to diagnose liver abscess

TREATMENT

ACUTE GENERAL Rx

- Table A1-44 summarizes drug treatment options for amebiasis in adults and children.
- Liver abscess is generally responsive to medical management but surgical intervention indicated for extension of liver abscess into pericardium or for toxic megacolon.

DISPOSITION

Host immunity incomplete and reinfection rate high for patients remaining at risk

REFERRAL

- For consultation with infectious diseases specialist for extraintestinal infection or persistent or relapsing intestinal infection
- For surgical consultation:
  1. For toxic megacolon
  2. For impending rupture of or extension of liver abscess into adjacent structures

PEARLS & CONSIDERATIONS

COMMENTS

- Infection with other intestinal parasites, particularly *Giardia lamblia,* may coexist with amebiasis.
- There is a high prevalence of *E. dispar* in homosexual males, which is nonpathogenic but may be difficult to distinguish from the pathogen *E. histolytica.*

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Amebiasis (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

TABLE A1-44 Drug Treatment for Amebiasis

Medication	Adult Dosage (Oral)	Pediatric Dosage (Oral)*
Invasive Disease		
Metronidazole	Colitis or liver abscess: 750 mg tid for 7-10 days	Colitis or liver abscess: 35-50 mg/kg/day in 3 divided doses for 7-10 days
or		
Tinidazole	Colitis: 2 g once daily for 3 days Liver abscess: 2 g once daily for 3-5 days	Colitis: 50 mg/kg/day once daily for 3 days Liver abscess: 50 mg/kg/day once daily for 3-5 days
Followed by:		
Paromomycin (preferred)	500 mg tid for 7 days	25-35 mg/kg/day in 3 divided doses for 7 days
or		
Diloxanide furoate† or	500 mg tid for 10 days	20 mg/kg/day in 3 divided doses for 7 days
Iodoquinol	650 mg tid for 20 days	30-40 mg/kg/day in 3 divided doses for 20 days
Asymptomatic Intestinal Colonization		
Paromomycin (preferred)	As for invasive disease	As for invasive disease
or		
Diloxanide furoate†		
or		
Iodoquinol		

*All pediatric dosages are up to a maximum of the adult dose.
†Not available in the United States.
From Kliegman RM et al: *Nelson textbook of pediatrics*, ed 19, Philadelphia, 2011, Saunders.

SUGGESTED READINGS

DuPont HL: Acute infectious diarrhea in immunocompetent adults, *N Engl J Med* 370:1532–1540, 2014.

Haque R et al.: Entamoeba histolytica infection in children and protection from subsequent amebiasis, *Infect Immun* 74(2):904, 2006.

Pritt BS, Clark CG: Amebiasis, *Mayo Clin Proc* 83(10):1159–1160, 2008.

BASIC INFORMATION

DESCRIPTION

Amenorrhea means absence of menstruation. It is classified as either primary or secondary depending on whether the patient has had previous menstrual cycles.

- Primary amenorrhea is defined as the absence of menses by age 16 in the presence of secondary sexual characteristics. However, in the absence of these secondary sexual features by the age of 14 years, one should begin the workup for primary amenorrhea.
- Secondary amenorrhea is the absence of menses for more than six months in a patient who has had previous normal progesterone withdrawal cycles. The duration of amenorrhea required for the diagnosis of secondary amenorrhea varies somewhat depending on the source.

ICD-9CM CODES
626.0 Absence of menstruation
ICD-10CM CODES
N91.2 Amenorrhea, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence of primary amenorrhea and secondary amenorrhea in the U.S. is <1% and 5% to 7%, respectively.
- There is no racial or ethnic predilection.

ETIOLOGY

- Physiologic amenorrhea
  1. Pregnancy
  2. Lactation
  3. Menopause
- Pathologic amenorrhea
  A. Primary amenorrhea
     1. Hypergonadotropic hypogonadism
        a. Turner's syndrome
        b. Pure gonadal dysgenesis
        c. Autoimmune oophoritis
        d. 17,20-desmolase deficiency or 17-hydroxylase deficiency
        e. Galactosemia
     2. Eugonadism (Table A1-45)
        a. Müllerian agenesis
        b. Transverse vaginal septum
        c. Imperforate hymen
        d. Androgen insensitivity syndrome (AIS) (1%)
        e. 5-alpha reductase deficiency
        f. Polycystic ovarian syndrome (PCOS)
        g. Adult-onset congenital adrenal hyperplasia (CAH)
        h. Cushing's syndrome
        i. Hypothyroidism
     3. Hypogonadotropic hypogonadism
        a. Constitutional delay
        b. Hypothalamic disorders
        c. Pituitary diseases
        d. Other CNS diseases
  - Secondary amenorrhea
    1. Ovarian diseases
       a. PCOS
       b. Iatrogenic (oophorectomy, S/P radiation, chemotherapy)
       c. Primary ovarian insufficiency (previously premature ovarian failure [POF])
       d. Ovarian tumors
    2. Hypothalamic dysfunction
       a. Functional (eating disorders, exercise, stress)
       b. Congenital GnRH deficiency
       c. Infiltrative diseases (sarcoidosis, histiocytosis, lymphoma)
    3. Pituitary diseases
       a. Hyperprolactinemia (drug induced, hypothyroidism, prolactinoma)
       b. Craniopharyngiomas
       c. Empty sella syndrome
       d. Sheehan's syndrome
       e. S/P radiation
       f. Infiltrative diseases
    4. Asherman's syndrome
    5. Others

Hypothyroidism, Cushing's syndrome, adult-onset congenital adrenal hyperplasia, drug induced (Lupron Depot, Depo-Provera, levonorgestrel IUD, Danazol, etc.), chronic illnesses

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Turner's syndrome
  1. Usually presents with primary amenorrhea unless mosaic
  2. Short stature
  3. Epicanthic folds
  4. Low-set ears
  5. High-arched palate
  6. Micrognathia
  7. Sensorineural hearing loss
  8. Otitis media
  9. Webbing of the neck
  10. Pigmented nevi
  11. Square/shield chest
  12. Widely spaced nipples
  13. Absent breast development
  14. Bicuspid aortic valve
  15. Coarctation of aorta
  16. Cubit valgus
  17. Short fourth metacarpal
  18. Hyperconvex nails
  19. Leg edema
  20. Renal abnormalities
  21. Autoimmune disorders including thyroiditis
  22. Diabetes mellitus
- Pure gonadal dysgenesis
  1. Unlike Turner's syndrome has no dysmorphic features
- Müllerian agenesis
  1. Sporadic inheritance
  2. Primary amenorrhea
  3. Normal breast development
  4. Normal pubic and axillary hair
  5. Normal female external genitalia
  6. Absent uterus and upper part of vagina
  7. Ovaries present
  8. Renal and vertebral anomalies in some patients; renal agenesis should be evaluated
- Transverse vaginal septum and imperforate hymen
  1. Primary amenorrhea
  2. Progressive cyclic lower abdominal pain
  3. Imperforate hymen or transverse vaginal septum on pelvic examination
  4. Perirectal fullness from hematocolpos
  5. Imaging with MRI identifies level of obstruction
- Androgen insensitivity syndrome
  1. Primary amenorrhea
  2. X-linked recessive inheritance in some patients
  3. Normal breast development
  4. Absent pubic and axillary hair
  5. Testis may be present in the groin or inguinal canal
  6. Uterus and vagina absent
  7. No associated renal or vertebral anomalies
- Adult-onset congenital adrenal hyperplasia
  1. Commonly seen in Ashkenazi Jewish, Inuit Native American, French Canadian, Mexican population
  2. Mimics the presentation of PCOS
  3. Features of hyperandrogenism (virilization, hirsutism, acne)
  4. Hypertension
- 5-alpha reductase deficiency
  1. Primary amenorrhea
  2. Undergo striking virilization at puberty
- PCOS
  1. Usually presents with secondary amenorrhea and oligomenorrhea
  2. Features of hyperandrogenism
  3. Obesity (60% to 80% of PCOS patients)
  4. Infertility
  5. Insulin resistance, predisposition to type II diabetes mellitus
  6. Association with the metabolic syndrome
- Cushing's syndrome (rare disorder, prevalence 1/1,000,000)
  1. Secondary amenorrhea
  2. Features of hyperandrogenism
  3. Abnormal fat distribution (dorsocervical fat pad [buffalo hump], spider legs, significant central obesity)
  4. Abdominal striae due to weakening of skin integument
  5. Easy bruising
  6. Hypertension
  7. Proximal muscle weakness
- Hypothyroidism
  1. Secondary amenorrhea
  2. Lethargy
  3. Constipation
  4. Decreased appetite
  5. Weight gain
  6. Cold intolerance
  7. Hair loss
  8. Dry skin
  9. Hypotension
  10. Bradycardia
- Primary ovarian insufficiency (previously premature ovarian failure)
  1. Secondary amenorrhea prior to the age of 40
  2. History of oophorectomy or pelvic radiation or chemotherapy

TABLE A1-45 Congenital Anatomic Causes of Primary Amenorrhea with Normal Breast Development*

Diagnosis	Müllerian Agenesis	Androgen Insensitivity (AI)	Transverse Vaginal Septum	Imperforate Hymen
Patients with primary amenorrhea†	15%	1%	3%	1%
Patients with primary amenorrhea and apparent obstruction or absence of vagina†	75%	5%	15%	5%
Chromosomes‡	46,XX	46,XY	46,XX	46,XX
Gonads	Ovaries	Testes	Ovaries	Ovaries
Serum testosterone‡	Normal female level	Normal male level (high)	Normal female level	Normal female level
Vagina	Absent or shallow	Absent or shallow	Obstructed by septum which may be thick or thin, high or low	Obstructed by thin membrane, which may look blue from hematocolpos
Axillary/pubic hair	+	Absent unless AI is incomplete	+	+
Cyclic pain	±	–	+	+
Uterus	Absent or rudimentary	–	+	+
Mass	–	–	+ Can present with acute urinary retention as hematocolpos mass obstructs urethra	+ Can present with acute urinary retention
Introitus bulges with Valsalva maneuver	–	–	–	+
Associated anomalies	Urinary tract and skeletal	Inguinal hernias; gonadal malignancy in adulthood	Major urinary tract abnormalities in 15%	Possibly some increase in urinary tract abnormalities
Treatment	Vaginal dilation or surgical neovagina	Gonadectomy after age 16-18 yr Vaginal dilation or surgical neovagina	Surgical approach depends on extent and location of septum; may be extensive; should be done as soon as possible	Excision of hymen as soon as possible; diagnostic needle aspiration contraindicated because of risk of infection
Fertility	Advanced reproductive technology required; in vitro fertilization surrogate with uterus to gestate pregnancy	Not fertile	Variable, low septa have a better prognosis than do high septa	Usually fertile

+, Present; –, absent; ±, may be present or absent.
*Cervix not visible on pelvic examination. Short vagina; may be absent or obstructed.
†Data from Reindollar RH, Byrd JR, McDonough PG: Delayed sexual development: a study of 252 patients, *Am J Obstet Gynecol* 140:371, 1981.
‡Sometimes useful in differentiating Müllerian agenesis from androgen insensitivity.
From Kliegman RM et al: *Practical strategies in pediatric diagnosis and therapy,* ed 2, Philadelphia, 2004, Elsevier.

3. Vasomotor symptoms
4. Dry, thin vaginal mucosa without rugosity
5. Associated autoimmune or karyotypic abnormalities possible

- Hyperprolactinemia
  1. Usually presents with secondary amenorrhea
  2. History of use of drugs such as antipsychotics, oral contraceptive (OC) pills, antidepressants, antihypertensives, H_2 blockers, opioids, etc.
  3. Pituitary adenomas may be associated with headache, vomiting, vision changes
  4. Galactorrhea
- Sheehan's syndrome
  1. History of secondary amenorrhea following postpartum hemorrhage
  2. Failure of lactation
  3. Other features of hypopituitarism
- Asherman's syndrome
  1. History of D&C
  2. Secondary amenorrhea
  3. Recurrent miscarriage/infertility
- Functional hypothalamic disorders
  1. Usually presents with secondary amenorrhea
  2. History of eating disorders, severe exercise or stress
  3. Use of street drugs
- Kallmann's syndrome
  1. Usually presents with anosmia, congenital defect of development of both the GnRH neurons and olfactory placode

Dx DIAGNOSIS

- First step in the workup of amenorrhea is to rule out pregnancy by serum/urine pregnancy test.
- Diagnostic workup depends on history and physical.
- Physical examination, determining the presence or absence of advanced breast Tanner stage and presence or absence of uterus can help guide evaluation (e.g., presence of breasts but absence of uterus can only be Müllerian agenesis or androgen insensitivity syndrome).Primary amenorrhea (Fig. EA1-68 and Box EA1-10):

1. Pelvic ultrasonography or MRI to detect any anatomic abnormalities of uterus, cervix, ovaries, or vagina. At times examination under anesthesia is needed to assess the pelvic organs.
2. Karyotyping (46,XX in Müllerian agenesis; 46,XY in AIS; 45,XO in Turner's syndrome) is done when uterus is absent or Turner's syndrome is suspected.
3. Serum FSH, TSH/FT4, prolactin, estradiol:
   FSH 40 mIU/ml along with estradiol <20 pg/ml is indicative of primary ovarian insufficiency.
   Prolactin >200 ng/ml is suggestive of prolactinoma. Lower levels may also be associated with prolactinoma. Threshold levels may vary by laboratory, and providers are advised to become familiar with their institution's normal range.

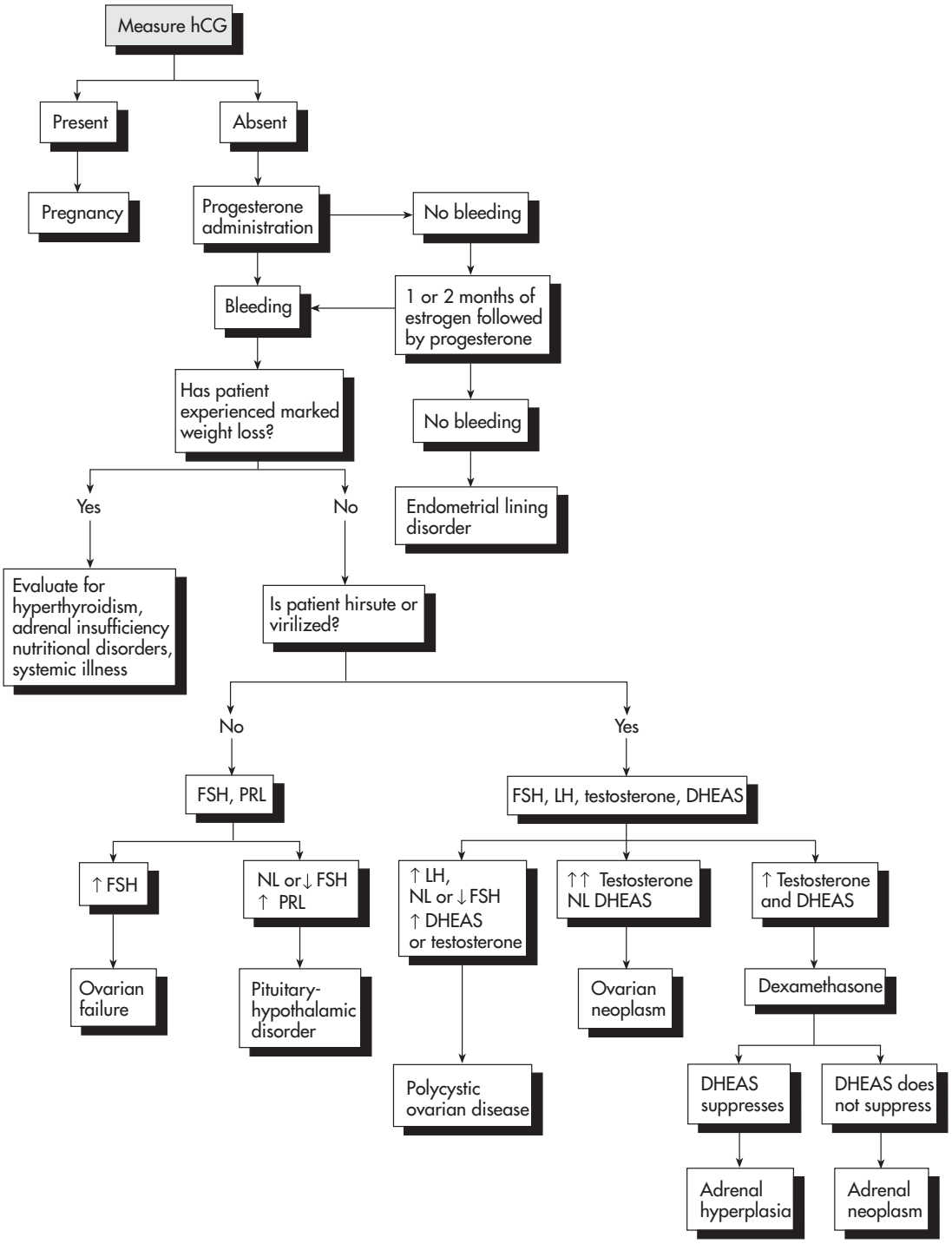


FIGURE A1-69 Evaluation of secondary amenorrhea. *DHEAS* Dehydroepiandrosterone-sulfate; *FSH*, follicle-stimulating hormone; *hCG*, human chorionic gonadotropin; *LH*, luteinizing hormone; *NL*, normal; *PRL*, prolactin; ↑, increased; ↑↑, markedly increased; ↓, decreased. (From Andreoli TE [ed]: *Cecil essentials of medicine*, ed 7, Philadelphia, 2008, Saunders.)

4. Check serum testosterone (male range in AIS; female range in Müllerian agenesis) when uterus is absent or in presence of features of hyperandrogenism.
5. 17-alpha hydroxyprogesterone level in presence of features of hyperandrogenism to rule out CAH. In addition to high level of 17 alpha hydroxyprogesterone due to compromised 21-hydroxylase activity, these patients have elevated level of serum progesterone and deoxycorticosterone, hypernatremia, and hypokalemia.
6. MRI of head in presence of:

- Primary hypogonadotrophic hypogonadism.
  1. Hyperprolactinemia.
  2. Visual field defects.
  3. Headaches.
  4. Signs of hypothalamic-pituitary dysfunction.
- Secondary amenorrhea (Fig. A1-69):
  1. Serum FSH, TSH/FT4, prolactin, estradiol:
     Low serum FSH with low estradiol indicates hypogonadotropic hypogonadism.
     High serum FSH with low estradiol suggests hypergonadotropic hypogonadism.
     Progesterone withdrawal bleeding.

10 mg medroxyprogesterone is given for 10 days.
Withdrawal bleeding suggests euestrogenic anovulation in presence of normal end organ (outflow tract) and ovarian function.

- Estrogen-progesterone withdrawal bleeding:
  In the absence of progesterone withdrawal bleeding, the patients are exposed to 25 to 35 days of estrogen (0.625 to 2.5 mg Premarin daily) followed by 10 days of medroxyprogesterone.
  Withdrawal bleeding indicates hypogonadism.
  Absence of bleeding suggests defects with end organ (e.g., Asherman's syndrome).
- Serum LH, testosterone and DHEA-S:
  When features of hyperandrogenism seen these tests are ordered.
  Serum testosterone >200 ng/ml suggests androgen-producing adrenal or ovarian tumors (high index of suspicion with moderate elevation; threshold value not required in cases of ovarian or adrenal tumors). This level may be mildly elevated in patients with PCOS.
  DHEA-S >700 mcg/dl suggests adrenal origin over ovarian (high index of suspicion with moderate elevation; threshold value not required in cases of ovarian or adrenal tumors).
  LH/FSH ratio >2 may be present in patients with PCOS, although this is not part of diagnostic criteria according to the Rotterdam consensus conference.
- Pelvic ultrasound when PCOS or ovarian tumor suspected.
- Abdominal CT when adrenal tumor suspected.
- MRI of head when indicated.
- HSG, sonohysterography, or diagnostic hysteroscopy in patients with suspected Asherman's syndrome.
- Karyotyping is indicated when primary ovarian insufficiency occurs before the age of 40.
- Other tests which are rarely needed:
  Serum transferrin when hemochromatosis is suspected.
  Serum ACE when sarcoidosis is suspected.

Rx TREATMENT

- The treatment of amenorrhea depends on the etiology, as well as the aims of the patient, such as a desire to treat hirsutism or to become pregnant.
- In the absence of pregnancy, withdrawal bleeding may be induced in the majority of patients with amenorrhea using 5 to 10 mg of medroxyprogesterone for 10 days.
- Estrogen replacement along with calcium and vitamin D should be instituted in essentially every patient with hypogonadism to avoid osteoporosis. Women with a uterus require continuous or intermittent progesterone administration to protect against endometrial hyperplasia or cancer. Frequently, it is easiest to prescribe combination OC pills. For most patients, continuation until ~50 years, the usual age of menopause, seems reasonable.
  Young women in whom secondary sex characteristics have failed to develop fully should be exposed initially to very low dose estrogen (0.3 mg of conjugated equine estrogen or equivalent) given unopposed daily for 6 mo with incremental dose increases at 6-mo intervals until the required maintenance dose is achieved. Cyclic progesterone therapy, 12 to 14 days per month, should be instituted once vaginal bleeding ensues.
- Most patients with anatomic abnormalities will require surgical correction. Creation of a new vagina for patients with Müllerian agenesis is usually delayed until the woman is emotionally mature and ready to participate in the serial dilation or postoperative care required to maintain vaginal patency. However, if adequate correction is impossible, pregnancy will often require a surrogate to carry a gestation. One should not forget to look for the associated urogenital anomalies, such as renal agenesis, in these patients and, when present, treat them appropriately.
- In patients with androgen insensitivity syndrome, the incidence of gonadal malignancy is 22%. However, it rarely occurs before the age of 20. Gonadectomy is performed by laparoscopy following breast development and the attainment of adult stature. In the absence of a uterus these individuals only need estrogen replacement without progesterone.
- Women with adult-onset CAH may be treated with low-dose corticosteroids in addition to sex steroids to partially block ACTH stimulation of adrenal function and thereby decrease overproduction of adrenal androgens.
  Universal treatment of adult-onset CAH with corticosteroids is controversial.
- Patients with primary ovarian insufficiency (POI) will need estrogen and progesterone replacement. These patients will require in vitro fertilization using donor oocytes to conceive. These patients have an increased risk of osteoporosis and heart disease. It can also be associated with autoimmune disorders such as hypothyroidism, Addison's disease, and diabetes mellitus. Therefore, fasting blood glucose, TSH, and, if clinically appropriate, morning cortisol should be measured. In the presence of a Y chromosome, removal of gonadal tissue is recommended at the time of diagnosis to avoid gonadal tumors.
- Hypothyroidism should be treated with thyroid replacement.
- Hyperprolactinemia is treated by avoiding the culprit drugs or by giving dopamine agonists, such as bromocriptine or cabergoline. Pituitary adenomas rarely require surgery but surgery may be performed if secondary deficits such as visual changes are observed, when they are resistant to medical therapy, or the lesion is rapidly growing.
- Treatment of hypothalamic amenorrhea depends on the etiology. Patients with eating disorders or who exercise excessively will require behavioral modification and nutritional counseling. Elite athletes may choose not to alter their exercise regimens and will therefore require estrogen treatment and prevention of osteoporosis. When associated with infertility, ovulation induction with clomiphene citrate, exogenous gonadotropins, or pulsatile GnRH therapy should be offered.
- The primary treatment of PCOS is weight loss through diet and exercise. Other treatment options include:
  1. Use of OC pills or cyclic progestational agents to help maintain a normal endometrium.
  2. Insulin-sensitizing agents such as metformin to reduce insulin resistance and improve ovulatory function. Recent studies suggest that insulin-sensitizing agents may not be as effective in improving ovulatory effort.
  3. Oral contraceptives and/or spironolactone to treat hyperandrogenism.
  4. Clomiphene citrate or an aromatase inhibitor such as letrozole to induce ovulation.
- In patients with Asherman's syndrome, hysteroscopic lysis of intrauterine adhesions is followed by administration of long-term exogenous estrogen to stimulate regrowth of endometrial tissue.
- Geneticist consult is given in patients with hereditary causes of amenorrhea.
- Psychiatrist consult is needed in patients with major depression, anorexia nervosa, bulimia nervosa, or other major psychiatric disorders.

COMPLICATIONS

- Osteoporosis
- Endometrial hyperplasia and uterine cancer
- Infertility

PROGNOSIS

Depends on the primary cause of amenorrhea

PATIENT EDUCATION

- Patients with amenorrhea should be reassured that this is, in and of itself, not a concern.
- All women with an intact endometrium should understand the risks of unopposed estrogen action, whether the estrogen is exogenous such as through hormone therapy, or endogenous such as PCOS.
- Hypoestrogenic women should be counseled about the importance of estrogen replacement to protect against bone loss.
- Potential for future childbearing should be discussed.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Infertility (Related Key Topic)
Pituitary Adenoma (Related Key Topic)
Polycystic Ovary Syndrome (Related Key Topic)
Sheehan's Syndrome (Related Key Topic)
Amenorrhea (Patient Information)

AUTHOR: **HEMANT K. SATPATHY, M.D.**

EVIDENCE

Abstract[1]

Context:

In the general population, about 30% of asymptomatic women have polycystic ovary-like abnormalities (PCO-L), i.e., polycystic ovarian morphology (PCOM) at ultrasound and/or increased anti-Müllerian hormone (AMH) serum level. PCOM has also been reported in 30%-50% of women with functional hypothalamic amenorrhea (FHA).

Objective:

The aim of this study was to verify whether both PCOM and excessive AMH level indicate PCO-L in FHA and to elucidate its significance.

Design:

We conducted a retrospective analysis using a database and comparison with a control population.

Setting:

Subjects received ambulatory care in an academic hospital.

Patients:

Fifty-eight patients with FHA were compared to 217 control women with nonendocrine infertility and body mass index of less than 25 kg/m^2.

Interventions:

There were no interventions.

Main Outcome Measures:

We measured serum testosterone, androstenedione, FSH, LH, AMH, and ovarian area values. The antral follicle count (AFC) was used as a binary variable (i.e., negative or positive) because of the evolution of its sensitivity over the time of this study. The ability of these variables (except AFC) to detect PCO-L in both populations was tested by cluster analysis.

Results:

One cluster (cluster 2) suggesting PCO-L was detected in the control population (n = 52; 24%), whereas two such clusters were observed in the FHA population (n = 22 and n = 6; 38 and 10%; clusters 2 and 3, respectively). Cluster 2 in FHA had similar features of PCO-L as cluster 2 in controls, with higher prevalence of positive AFC (70%) and PCOM (70%), higher values of ovarian area and higher serum AMH (P <0.0001 for all), and testosterone levels (P < 0.01) than in cluster 1. Cluster 3 in FHA was peculiar, with frankly elevated AMH levels. In the whole population (controls + FHA), PCO-L was significantly associated with lower FSH values (P <0.0001).

Conclusion:

PCO-L in FHA is a frequent and usually incidental finding of unclear significance, as in controls. The association of PCO-L with hypothalamic amenorrhea should not lead to a mistaken diagnosis of PCOS. Ⓐ

Polycystic ovary syndrome (PCOS) is a common disorder affecting women of reproductive age and is associated with androgenization, anovulation, and the metabolic syndrome. Robin et al make a link between functional hypothalamic amenorrhea (FHA), which is a frequent cause of anovulation, hypoestrogenism, and negative energy balance from excessive exercise leading to hypoinsulinism (in contrast to insulin resistance in PCOS). In FHA, luteinizing hormone levels tend to be higher than follicle-stimulating hormone levels as observed in PCOS.

This also results in polycystic ovarian morphology (PCOM), which is observed in 30% to 50% of women with FHA. The presence of PCOM in women with FHA might lead to the mistaken diagnosis of PCOS. Another confounding finding in both disorders is that anti-Müllerian hormone (AMH) might be elevated in both, because AMH is the most common endocrine abnormality associated with PCOM. PCO-like disorder is also common in the general population. The authors observed the occurrence of PCOM in about 70% of women with FHA.

Based on their study, they do not think that the association of PCO-like disorder with hypothalamic amenorrhea should be mistakenly diagnosed with PCOS.[1-5]

AW Meikle, MD

Evidence-Based References

Scheid JL, De Souza MJ: Menstrual irregularities and energy deficiency in physically active women: the role of ghrelin, PYY and adipocytokines, *Med Sport Sci* 55:82–102, 2010. Ⓐ

Robin G, Gallo C, Catteau-Jonard S, et al.: Polycystic ovary-like abnormalities (PCO-L) in women with functional hypothalamic amenorrhea, *J Clin Endocrinol Metab* 97:4236–4243, 2012. Ⓐ

Dumesic DA, Abbott DH, Padmanabhan V: Polycystic ovary syndrome and its developmental origins, *Rev Endocr Metab Disord* 8:127–141, 2007. Ⓐ

Meczekalski B, Czyzyk A, Podfigurna-Stopa A, et al.: Hypothalamic amenorrhea in a Camurati-Engelmann disease—a case report, *Gynecol Endocrinol* 29:511–514, 2013. Ⓐ

Santoro N: Update in hyper- and hypogonadotropic amenorrhea, *J Clin Endocrinol Metab* 96:3281–3288, 2011. Ⓐ

Caronia LM, Martin C, Welt CK, et al.: A genetic basis for functional hypothalamic amenorrhea, *N Engl J Med* 364:215–225, 2011. Ⓐ

SUGGESTED READINGS

Gordon CM: Functional hypothalamic amenorrhea, *N Engl J Med* 363:365–371, 2010.

Klein DA, Path MA: Amenorrhea: an approach to diagnosis and management, *Am Fam Physician* 87(11):781–788, 2013.

Master-Hunter T, Heiman DL: Amenorrhea: evaluation and treatment, *Am Fam Physician* 73(8):1374–1382, 2006.

Practice Committee of the American Society for Reproductive Medicine: Current evaluation of amenorrhea, *Fertil Steril* 82(suppl 1):S33–39, 2004.

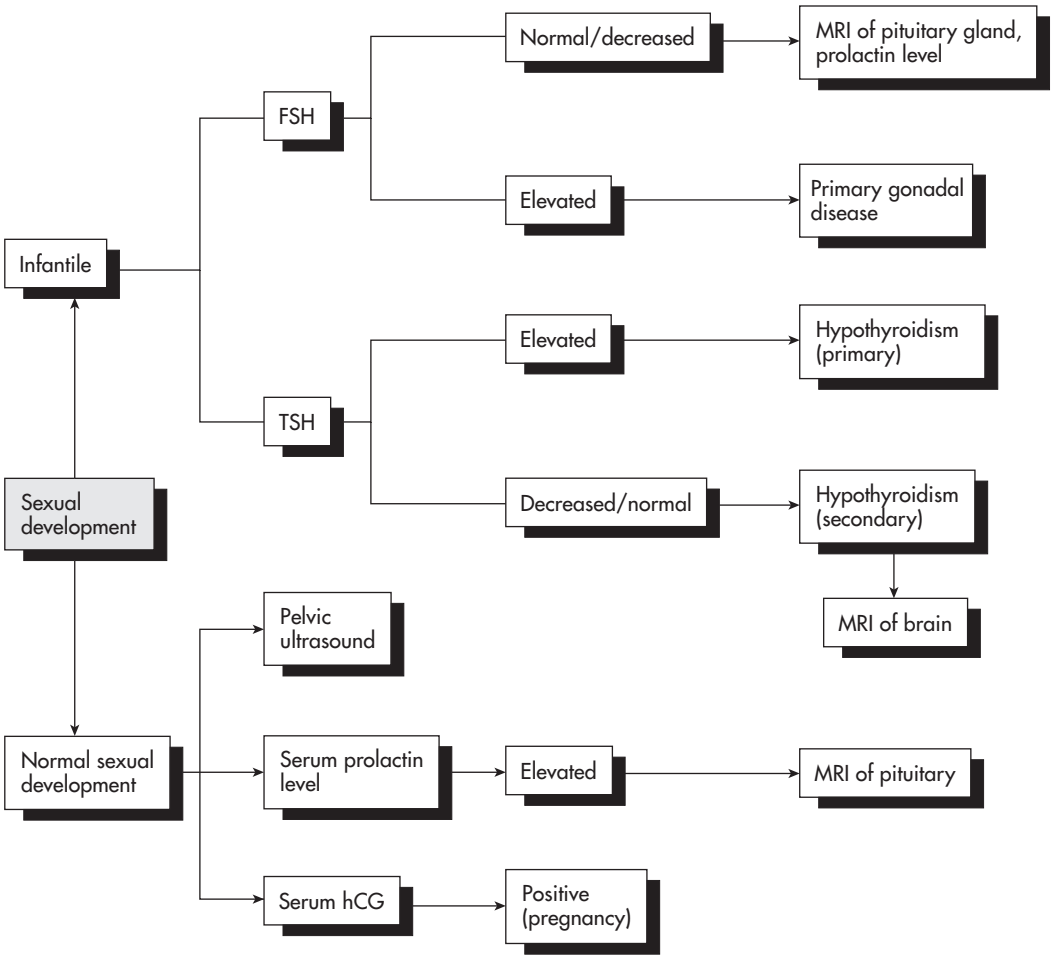


FIGURE EA1-68 Evaluation of primary amenorrhea. *FSH,* Follicle-stimulating hormone; *hCG,* human chorionic gonadotropin; *MRI,* magnetic resonance imaging; *TSH,* thyroid-stimulating hormone. (From Ferri FF: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 2, Philadelphia, 2009, Mosby.)

BOX EA1-10 Primary Amenorrhea

Diagnostic Imaging	Laboratory Evaluation
Best Test	***Best Tests***
MRI of pituitary/hypothalamus with gadolinium when hypothalamic/pituitary lesion is suspected	FSH Prolactin TSH
Ancillary Tests	***Ancillary Tests***
Pelvic ultrasound	Serum hCG

FSH, Follicle-stimulating hormone; *hCG*, human chorionic gonadotropin; *MRI*, magnetic resonance imaging; *TSH*, thyroid-stimulating hormone.

From Ferri F: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging*, ed 3, Philadelphia, 2014, Mosby.

Amnestic Disorders

BASIC INFORMATION

The word "amnesia" is derived from the Greek word *amnéstia* meaning "forgetfulness."

DEFINITION

The acquired inability to learn new, or recall previously learned, information. The impairment compromises social and occupational functioning. It is caused by an identifiable medical condition or by persisting effects of a substance. Disorder is not caused by delirium or dementia. It may be transient or chronic.

SOME WELL-KNOWN AMNESTIC DISORDERS

Korsakoff syndrome
Transient global amnesia

Dementia, delirium, and amnestic disorders have been subsumed under the category "Neurocognitive Disorders" in DSM-5.

With behavioral disturbance:
ICD-9CM and DSM-5 CODES
294.11
ICD-10CM CODES
F02.81
Without behavioral disturbance:
ICD-9CM and DSM-5 CODES
294.10
ICD-10CM CODES
F02.80

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Data not available on true incidence or lifetime risk of most amnestic disorders. Transient global amnesia has an incidence in the general population of 23 to 50 per 100,000 population over age 50.
PREDOMINANT AGE: Variable, depending on causative pathology. Transient global amnesia onset usually after age 50 years. Korsakoff syndrome usually presents in patients after the age of 40.
GENETICS: Genetic defect for thiamine metabolism has been described in Korsakoff syndrome.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

HISTORY:

- Diagnosis depends on history.
- The inability to learn new or recall previously learned information is the key feature of this disorder.
- The Mini-Mental State Examination is useful. Patients unable to recall events that transpire during the interview but may have a normal digit span and be able to attend to the conversation.
- Neuropsychiatric testing demonstrates specific memory impairments in absence of other cognitive deficits
- Patients are unable to recall events subsequent to the onset of the amnesia.
- Individuals may learn new motor tasks but are unable to recall those learning experiences.
- Amnesia generally is both anterograde and retrograde.
- Commonly, patients are disoriented to time and place. Most lack insight while others may have insight but appear indifferent. Some present with personality change or confabulation.
- Table A1-46 describes memory systems. Clinico-anatomic correlations of memory disorders are described in Table A1-47.

ETIOLOGY (MEDICAL CONDITIONS AND PERSISTENT EFFECTS OF DRUGS)

The etiology can be either medical or due to the persistent effects of a substance/chemical.

- Traumatic brain injury
- Focal tumors or infarction
- Herpes simplex encephalitis
- Cerebral anoxia
- Korsakoff syndrome (thiamine deficiency)
- Carbon monoxide poisoning
- Transient amnesia may arise from concussion, acute intoxication, anesthesia, medications, seizures, transient global amnesia, and electroconvulsive therapy
- Persistent effects of drugs (note that this must not be because of acute effects of intoxication or withdrawal)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Dementia
- Delirium
- Major depression
- Minimal cognitive impairment
- Dissociative amnesia
- Memory impairment in substance intoxication or withdrawal
- Malingering
- Factitious disorder

WORKUP

- Complete medical history and mental status testing, with emphasis on identifying underlying medical condition and/or history of drug use
- Neuropsychological testing

TABLE A1-46 Description of Memory Systems

Type of Memory Function	Regional Localization	Learning Efficiency	Time Span until Effective Retrieval	Capacity	Clinical Testing Techniques	Examples in Daily Life
Declarative episodic memory	Hippocampus, medial thalamus	Single exposure	Decades	Very large, with rehearsal and elaboration	Recall of 3-4 words after 5 min	Recall of recent events and conversations
Declarative semantic memory	Temporal-parietal association cortices	Capable of single exposure; enhanced with repetition	Decades	Very large, perhaps limitless	Confrontation naming, general knowledge	Vocabulary, knowledge of life events from remote past
Attention span, "immediate memory"	Primary auditory or visual cortex	Single exposure only	Seconds	Very small: 7 ± 2 digits (auditory)	Digit span	Dialing a telephone number after hearing it or reading it
Working memory	Lateral frontal cortex	Single exposure only	Seconds	Small	Digits backward	Supporting many mental activities, such as mental arithmetic, abstract reasoning
Procedural memory	Basal ganglia, probably association neocortices	Requires extensive training	Decades	Moderate	Experimental laboratory methods only	Retention of motor skills, e.g., riding a bicycle or typing

From Goldman L, Schafer AI: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Saunders.

TABLE A1-47 Clinico-Anatomic Correlations of Memory Disorders

Anatomic Site of Damage	Memory Finding	Other Neurologic and Medical Findings
Frontal lobe	Lateralized deficits in working memory—right: spatial defects, left: verbal defects, impaired recall with spared recognition	Personality change Perseveration Chorea, dystonia Bradykinesia, tremor, rigidity
Basal forebrain	Domain-independent declarative memory deficits	
Ventromedial cortex	Frontal lobe-type declarative memory deficits	Upper visual field defects
Hippocampus and parahippocampal cortex	Bilateral lesions yield global amnesia, unilateral lesions show lateralization of deficits—left: verbal deficits; right: spatial deficits	Myoclonus Depressed level of consciousness Cortical blindness Autonomations
Fornix	Global amnesia	
Mammillary bodies	Declarative memory deficits	Confabulation, ataxia, nystagmus, signs of alcohol withdrawal
Dorsal and medial dorsal nucleus thalamus	Declarative memory deficits	Confabulation
Anterior thalamus	Declarative memory deficits	
Lateral temporal cortex	Deficits in autobiographical memory	

From Goetz CG, Pappert EJ: *Textbook of clinical neurology*, Philadelphia, 1999, Saunders.

LABORATORY TESTS

Tests to determine potential underlying medical condition (e.g., B_{12} levels, TSH, brain imaging).

IMAGING STUDIES

- No specific or diagnostic features of amnestic disorder are detectable on imaging.
- Brain MRI indicates specific atrophy in diencephalic structures in Korsakoff syndrome and in the hippocampus in hypoxic amnesia.
- Neuroradiologic examination with MRI is valuable in the diagnosis of acute Wernicke's encephalopathy.
- Brain MR diffusion-weighted imaging may show hippocampal lesions in transient global amnesia.

Rx TREATMENT

Treatment is as diverse as the medical conditions causing it.

NONPHARMACOLOGIC THERAPY

- Cognitive rehabilitation to promote recovery from brain injury may be helpful.
- Supervised living to ensure appropriate long-term care.

ACUTE GENERAL Rx

Initial treatment directed to the underlying etiology. Generally, transient global amnesia has full remission of symptoms. Korsakoff, on the other hand, is not usually improved significantly, even after administration of thiamine.

CHRONIC Rx

No known effective treatments to reverse or ameliorate memory deficits.

DISPOSITION

Amnesias may be chronic or transient depending upon etiology.

REFERRAL

Refer for neuropsychological testing.

PEARLS & CONSIDERATIONS

COMMENTS

In Korsakoff syndrome, anterograde amnesia (disturbance in acquisition of new information) is more prominent than retrograde amnesia (problems remembering old information).

PREVENTION

Cases of amnestic disorder due to trauma are usually not preventable. Refraining from abuse of alcohol and other drugs prevents substance-induced amnestic disorder, and high-dose thiamine has been shown to prevent Korsakoff syndrome.

PATIENT & FAMILY EDUCATION

Respite care and in-home services for family caregivers

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Korsakoff's Psychosis (Related Key Topic)

AUTHOR: **WASIM RASHID, M.D.**

SUGGESTED READINGS

Butler CR et al.: Recent insights into the impairment of memory in epilepsy: transient epileptic amnesia, accelerated long-term forgetting and remote memory impairment, *Brain* 131(9):2243–2263, 2008.

Kopelman MD et al.: The Korsakoff syndrome: clinical aspects, psychology and treatment, *Alcohol and Alcoholism* 44(2):148–154, 2009.

BASIC INFORMATION

DEFINITION

The term *amyloidosis* refers to a heterogeneous group of disorders that are all characterized by the deposition of an amorphous, extracellular fibrillar protein in various organs and tissues of the body. It has the following subtypes:

- Primary amyloidosis (AL)
- Secondary amyloidosis (AA)
- Hereditary amyloidosis
- Localized amyloidosis

ICD-9CM CODES
277.3 Amyloidosis
ICD-10CM CODES
E85.9 Amyloidosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Between 1500 and 3500 new cases are diagnosed annually. The most common type is AL.

PREVALENCE

Amyloidosis primarily affects men between the ages of 60 and 70 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The most common presenting symptoms of amyloidosis are fatigue, dyspnea, edema, paresthesias, and weight loss. Other findings depend on organ system involvement.
- Signs and symptoms of nephrotic syndrome may be present with renal involvement.
- Fatigue and dyspnea may occur with pulmonary involvement.
- GI involvement is uncommon but presents with diarrhea, nausea, abdominal pain, and macroglossia (Fig. EA1-70).
- Patients with cardiac involvement have an infiltrative cardiomyopathy and present with a preserved ejection fraction (EF) and diastolic dysfunction.
- Patients may present with bleeding problems caused by either factor X deficiency or fragile blood vessels caused by infiltration by amyloid. Bleeding around the eyes (raccoon eyes) is a characteristic finding.
- Involvement of the nervous system presents with peripheral neuropathy, tendinopathy (Fig. EA1-71), muscle weakness, numbness, syncope, or dizziness. Associated autonomic neuropathy can also cause severe disabling symptoms.

ETIOLOGY

The deposition of an amorphous, extracellular fibrillar protein in various tissues that stains with Congo red is the common underlying mechanism, but there are important differences among various subtypes:

- AL is associated with an underlying clonal plasma cell disorder making an abnormal light chain protein with possible deposition in multiple organ systems.
- AA has no underlying plasma cell disorder and is a consequence of longstanding systemic inflammation (e.g., tuberculosis, leprosy, malaria, untreated syphilis).
- Localized amyloidosis results from localized synthesis of fibrillar material with no underlying plasma cell disorder.
- Familial amyloidosis is another subtype, with the most common form resulting from mutation of transthretin gene (TTR). Transthyretin amyloidosis is caused by the deposition of hepatocyte-derived transthyretin amyloid in peripheral nerves and the heart.
- A classification of amyloidosis is described in Table EA1-48.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Differential diagnosis varies depending on the organ involvement:

- Renal involvement (toxin- or drug-induced necrosis, glomerulonephritis, renal vein thrombosis)
- Interstitial lung disease (sarcoidosis, connective tissue disease, infectious causative factors)
- Restrictive cardiomyopathy (endomyocardial fibrosis, viral myocarditis)
- Carpal tunnel (rheumatoid arthritis, hypothyroidism, overuse)
- Peripheral neuropathy (alcohol abuse, vitamin deficiencies, diabetes mellitus)

WORKUP

Workup consists of performing blood and urine tests to look for abnormal light chain in urine or blood, performing various tests to look for target organ damage, and getting histologic confirmation by doing a fat pad and bone marrow biopsy and then performing Congo red staining on that. Fig. EA1-72 describes an algorithm for diagnosis of amyloidosis and determination of type.

LABORATORY TESTS

- Immunofixation of serum and urine (SPEP, UPEP) to look for immunoglobulin light chain is a sensitive screening test
- CBC, blood urea nitrogen (BUN)/creatinine, liver function tests, thyroid functions, and urine for albumin
- Histologic confirmation is necessary with a fat pad and bone marrow biopsy with Congo red staining to establish a diagnosis
- If a noninvasive fat pad biopsy does not establish a diagnosis, then a biopsy of the affected organ may be needed

IMAGING STUDIES

- Two-dimensional Doppler echocardiography to study diagnostic filling is useful to evaluate for cardiac involvement.
- Nuclear imaging with technetium-labeled aprotinin may detect cardiac amyloidosis. Serum amyloid P component (SAP) scintigraphy has high sensitivity for the detection of amyloid deposits in liver, spleen, kidneys, adrenal glands, and bones.

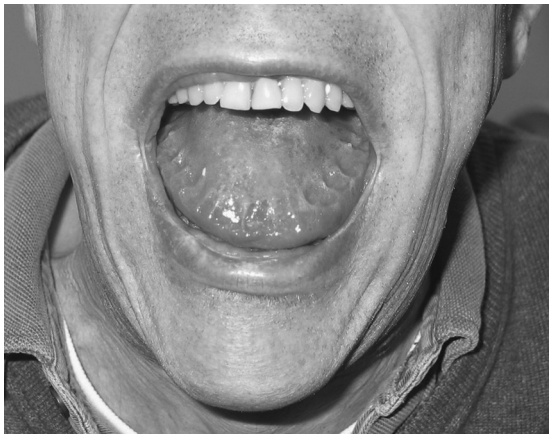


FIGURE EA1-70 Macroglossia in a patient with AL amyloidosis, demonstrating peripheral ridging due to teeth indentation. (From Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.)

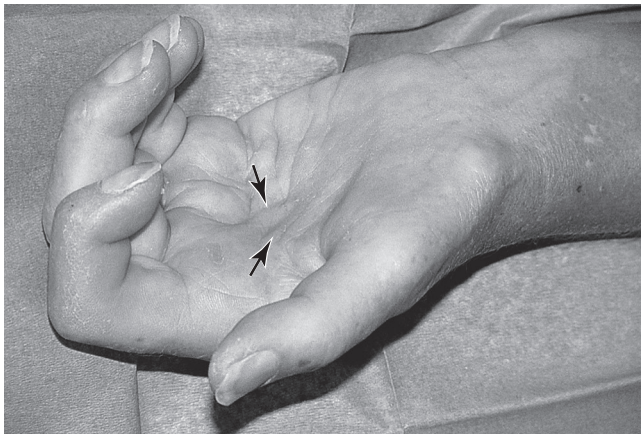


FIGURE EA1-71 Hand involvement in Aβ_2M amyloidosis. Hand of a long-term hemodialysis patient showing maximal extension. Note the prominence of shrunken flexor tendons (arrows). This is also known as the "guitar string" sign. (From Floege J et al: *Comprehensive clinical nephrology*, ed 4, Philadelphia, 2010, Saunders.)

Rx TREATMENT

ACUTE GENERAL Rx

- The goal of therapy is to decrease the production of the amyloidogenic light chain with therapy directed at the clonal plasma cells.
- All agents used to treat multiple myeloma are effective against AL including melphalan, prednisone, oral dexamethasone, systemic chemotherapy like cyclophosphamide, doxorubicin (Adriamycin), and more recently immunomodulatory compounds (IMiDs) like thalidomide or lenalidomide, or proteosome inhibitors but none has shown to be superior to melphalan and prednisone, which remain the treatment of choice Table EA1-49 summarizes major treatment options for amyloidosis.
- Anti–tumor necrosis factor drugs may be useful to treat kidney amyloid A amyloidosis but may increase the risk and severity of infection.
- Diflusinal, an NSAID, stabilized transthyretin tetramers and prevents amyloid formation in vitro. Recent trials[1] have shown that diflusinal reduces the rate of progression of neurologic impairment and preserves quality of life.

[1]Berk JL et al: Repurposing diflusinal for familial amyloid polyneuropathy. A randomized clinical trial, *JAMA* 310(24): 262-267, 2013.

- The use of high-dose chemotherapy and stem cell transplantation (SCT) for patients with amyloidosis remains controversial due to high treatment-related mortality. In highly selected patients with preserved organ function, autologous bone marrow transplant can have good results.
- Patients who experience development of renal failure can be supported with hemodialysis or renal transplant.
- Liver transplantation has been used successfully in patients with familial amyloidosis.
- Recognition and treatment of the underlying disorder is needed for secondary amyloidosis.
- Table EA1-50 summarizes supportive treatment options for all types of amyloidosis.

DISPOSITION

Prognosis is determined primarily by the presence or absence of cardiac involvement and the form of amyloidosis:

- In patients with endomyocardial biopsy-documented cardiac amyloidosis, longer-term survival is more strongly associated with New York Heart Association functional class compared with ECG or echocardiography variables.
- In AA, eradication of the predisposing disease slows and can occasionally reverse the progression of amyloid disease. Median survival after diagnosis is 133 mo.
- Patients with familial amyloidotic polyneuropathy generally have a prolonged course lasting 10 to 15 yr.
- The progression of amyloidosis associated with renal hemodialysis can be improved with newer dialysis membranes that can pass beta-2-microglobulin.
- Median survival in patients with overt CHF is ~6 mo; it is 30 mo without CHF.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **BILAL H. NAQVI, M.D.,** and **FRED F. FERRI, M.D.**

TABLE EA1-48 Classification of Amyloidosis*

Type	Fibril Precursor Protein	Clinical Syndrome
AA	Serum amyloid A protein	Systemic amyloidosis usually with predominant renal involvement associated with acquired or hereditary chronic inflammatory diseases. Formerly known as *secondary* or *reactive amyloidosis.*
AL	Monoclonal immunoglobulin light chains	Systemic amyloidosis potentially involving many organ systems associated with myeloma, monoclonal gammopathy, and occult B-cell dyscrasias. Formerly known as *primary amyloidosis.*
ATTR	Normal plasma transthyretin	Senile systemic amyloidosis with predominant cardiac involvement (senile cardiac amyloidosis).
ATTR	Genetic variants of transthyretin (e.g., ATTR Met30, Ala60, Ile122)	Familial amyloid polyneuropathy (FAP), often with prominent amyloid cardiomyopathy. Predominant cardiac involvement without neuropathy with certain mutations (e.g., TTR Ile122).
Ab2M	β2-Microglobulin	Dialysis-related amyloidosis (DRA) associated with renal failure and long-term dialysis. Predominant articular and periarticular involvement.
Ab	β-Protein precursor (and rare genetic variants)	Cerebrovascular and intracerebral plaque amyloid in Alzheimer's disease. Occasionally familial.
AApoAI AApoAII	Genetic variants of apolipoprotein AI (e.g., AApoAI Arg26, Arg60) Genetic variants of apolipoprotein AII	Autosomal-dominant systemic amyloidosis. Predominantly non-neuropathic with prominent visceral involvement, especially nephropathy. Minor wild-type ApoAI amyloid deposits may occur in the aorta in aging individuals. Autosomal-dominant systemic amyloidosis with predominant renal involvement.
AFib	Genetic variants of fibrinogen A α-chain (e.g., AFib Val526)	Autosomal-dominant systemic amyloidosis. Non-neuropathic with predominant nephropathy.
ALys	Genetic variants of lysozyme (e.g., ALys His67)	Autosomal-dominant systemic amyloidosis. Non-neuropathic with predominant renal and gastrointestinal involvement. Rarely presents with hepatic rupture.
ACys	Genetic variant of cystatin C (ACys Gln68)	Hereditary cerebral hemorrhage with cerebral and systemic amyloidosis in Icelandic subjects.
AGel	Genetic variants of gelsolin (e.g., AGel Asn187)	Autosomal-dominant systemic amyloidosis. Predominant cranial nerve involvement plus lattice corneal dystrophy. Described and most common in Finland.

*Not exhaustive, and amyloid composed of peptide hormones, prion protein, and unknown proteins not included.
Modified from Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.

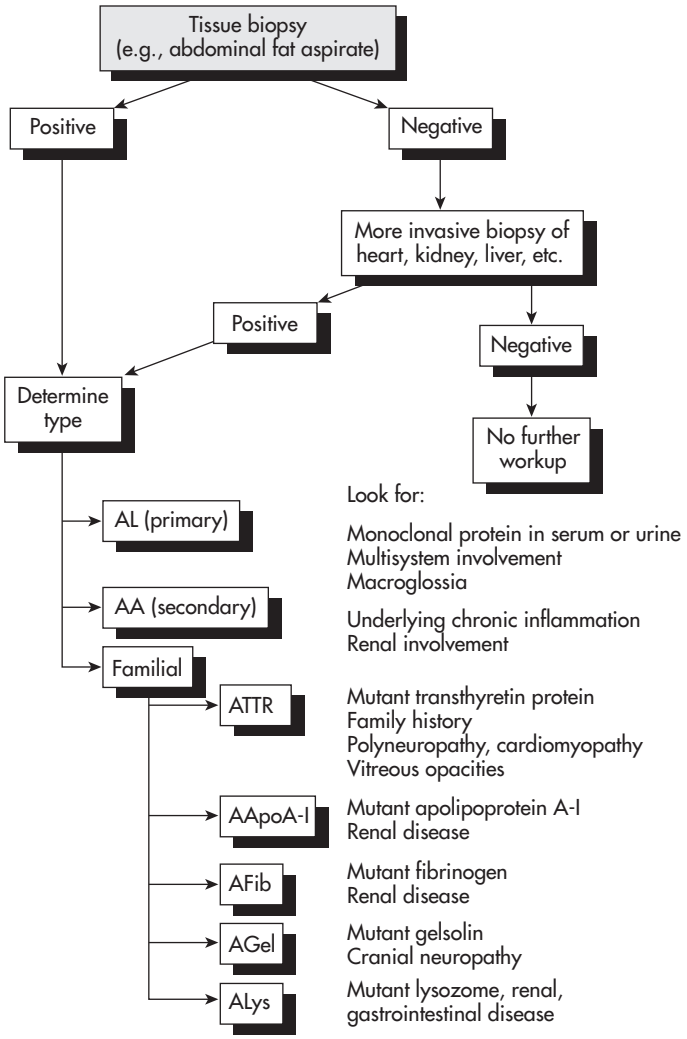


FIGURE EA1-72 Algorithm for the diagnosis of amyloidosis and determination of type. (From Firestein GS, Budd RC, Gabriel SE, et al: *Kelly's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.)

TABLE EA1-49 Major Treatment Options for Amyloidosis

AL Amyloidosis

Intravenous melphalan with autologous stem cell rescue

- Granulocyte colony-stimulating factor–mobilized peripheral blood stem cell collection
- Intravenous melphalan 140-200 mg/m^2
- Autologous stem cell reinfusion

Cyclic oral melphalan and dexamethasone

- Melphalan 0.22 mg/kg/day × 4 days
- Dexamethasone 20-40 mg/day × 4 days, or weekly
- Repeat administration every 4 weeks

Immunomodulators

- Lenalidomide 5-15 mg/day × 21 days
- Dexamethasone 20-40 mg/day weekly
- Repeat administration every 4 weeks

Proteasome inhibitors

- Intravenous bortezomib, 0.7-1.6 mg/m^2 1-2 times per week
- Repeat every 3-5 weeks

AA Amyloidosis

- Aggressive treatment of underlying inflammatory disease
- Medical or surgical treatment of underlying infection
- Colchicine 1.2-1.8 mg/day for AA amyloidosis secondary to familial Mediterranean fever
- Antifibril drug, eprosidate (investigational)

ATTR Amyloidosis

- Orthotopic liver transplantation
- Transthyretin stabilizers: tafamadis, diflunisal (investigational)

From Firestein GS, Budd RC, Gabriel SE, et al: *Kelly's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.

TABLE EA1-50 Supportive Treatment for All Types of Amyloidosis

Organ System	Symptom	Treatment Options
Cardiac	Congestive failure	Salt restriction of 1-2 g/day
		Diuretics: furosemide, spironolactone, metolazone
	Arrhythmia	Pacemaker
		Automatic implantable cardiac defibrillator
		Antiarrhythmics
Renal	Nephrotic syndrome	Salt restriction of 1-2 g/day
		Elastic stockings, leg elevation
		Maintaining dietary protein
		Angiotensin-converting enzyme inhibitor, if blood pressure tolerates
	Renal failure	Dialysis (long-term ambulatory peritoneal dialysis or hemodialysis)
Autonomic nervous	Orthostatic hypotension	Midodrine
		Increased dietary salt or added fludrocortisone, depending on edema
		Elastic stockings
	Gastric atony or ileus	Small frequent feedings (6/day) low in fat
		Oral nutritional supplements
		Jejunostomy tube feeding
		Parenteral nutrition
Gastrointestinal	Diarrhea	Low-fat diet (≤40 g)
		Psyllium hydrophilic mucilloid (Metamucil)
		Loperamide hydrochloride (Imodium)
		Tincture of opium
		Parenteral nutrition
	Macroglossia	Soft solid diet
		Partial glossectomy (rarely effective)
Peripheral nervous	Sensory neuropathy	Avoiding trauma
		Gabapentin (Neurontin) 100-300 mg 3 times daily
		Amitriptyline 25-50 mg at bedtime
		Pregabalin (Lyrica) 50-100 mg 3 times daily
	Motor neuropathy	Ankle-foot orthotics for footdrop
		Physical therapy
Hematologic	Intracutaneous bleeding	Avoiding trauma, antiplatelet agents
	Factor X deficiency	Factor replacement (recombinant factor VIIa, prothrombin complex concentrates)
		Splenectomy for splenomegaly

From Firestein GS, Budd RC, Gabriel SE, et al: *Kelly's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.

SUGGESTED READINGS

Austin BA, et al.: Comparison of functional status, ECG and echocardiography parameters to mortality in endomyocardial-biopsy proven cardiac amyloidosis, *Am J Cardiol* 103:1429–1433, 2009.

Coelho T, et al.: Safety and efficacy of RNA: therapy for transthyretin amyloidosis, *N Eng J Med* 369:819–829, 2013.

Fernandes-Nebro A, et al.: Long-term TNF-alpha blockade in patients with amyloid A amyloidosis complicating rheumatic diseases, *Am J Med* 123:454–461, 2010.

Kumar SK, et al.: Recent improvements in survival in primary systemic amyloidosis and the importance of an early mortality risk score, *Mayo Clin Proc* 86(1):12–18, 2011.

Kyle RA, et al.: A trial of three regimens for primary amyloidosis: colchicine alone, melphalan and prednisone, and melphalan, prednisone, and colchicine, *N Engl J Med* 336(17):1202–1207, 1997.

Sideras K, et al.: Amyloidosis, *Adv Clin Chem* 47:1–44, 2009.

Wang AK, et al.: Patterns of neuropathy and autonomic failure in patients with amyloidosis, *Mayo Clin Proc* 83(11):1226–1230, 2008.

Amyotrophic Lateral Sclerosis EBM PTG

BASIC INFORMATION

DEFINITION

Amyotrophic lateral sclerosis (ALS) is a progressive, degenerative neuromuscular condition of undetermined etiology affecting corticospinal tracts and anterior horn cells, resulting in dysfunction of both upper motor neurons (UMN) and lower motor neurons (LMN), respectively.

SYNONYMS

Lou Gehrig's disease

ICD-9CM CODES
335.20 Amyotrophic lateral sclerosis
ICD-10CM CODES
G12.21 Amyotrophic lateral sclerosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:
- 0.5 to 2 cases per 100,000 persons.
- Onset is usually between the ages of 50 and 70 yr.
- Male/female ratio is 2:1.

PREVALENCE: Five in 100,000 persons

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- LMN signs (weakness, hypotonia, wasting, fasciculations, hypoflexia or areflexia).
- UMN signs (loss of fine motor dexterity, spasticity, extensor plantar responses, hyperreflexia, clonus).
- Preservation of extraocular movements, sensation, bowel and bladder function.
- Dysarthria, dysphagia, pseudobulbar affect, frontal lobe dysfunction.
- Respiratory insufficiency typically occurs late in the disease.
- ALS comprises approximately 90% of adult-onset motor neuron diseases. Other presentations of motor neuron disease include progressive muscular atrophy, primary lateral sclerosis, progressive bulbar palsy, progressive pseudobulbar palsy, and ALS-parkinsonism-dementia complex.

ETIOLOGY

- 90% to 95% of all cases are sporadic; of the familial cases, 10% to 20% are associated with a genetic defect in the copper-zinc superoxide dismutase enzyme.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Multifocal motor neuropathy with conduction block
- Cervical spondylotic myelopathy with polyradiculopathy
- Spinal stenosis with compression of lumbosacral nerve roots
- Chronic inflammatory demyelinating polyneuropathy with central nervous system lesions
- Syringomyelia
- Syringobulbia
- Foramen magnum tumor
- Meningeal carcinomatosis
- Spinal muscular atrophy
- Polyglucosan body disease
- Bulbospinal muscular atrophy (Kennedy disease)
- Monomelic amyotrophy
- ALS-like syndromes have been reported in the setting of lead intoxication, HIV, hyperparathyroidism, hyperthyroidism, lymphoma, and vitamin B_{12} deficiency.

WORKUP

- Electromyography and nerve conduction studies (El Escorial criteria; see Table EA1-51)
- Assessment of respiratory function (forced vital capacity [FVC], negative inspiratory force)

LABORATORY TESTS

- Vitamin B_{12}, thyroid function, parathyroid hormone, HIV may be considered.
- Serum protein and immunofixation electrophoresis.
- DNA studies for SMA or bulbospinal atrophy, hexosaminidase levels in pure LMN syndrome.
- 24-hour urine for heavy metals if indicated.

IMAGING STUDIES

- Craniospinal neuroimaging contingent on clinical scenario
- Modified barium swallow to evaluate aspiration risk

TREATMENT

NONPHARMACOLOGIC THERAPY

- Noninvasive positive-pressure ventilation may improve quality of life and may increase tracheostomy-free survival in patients with respiratory difficulty (defined by orthopnea or FVC 50% of predicted).
- Percutaneous endoscopic gastrostomy (PEG) tube placement improves nutritional intake, promotes weight stabilization, and eases medication administration. Some studies suggest PEG placement may prolong life 1 to 4 mo, particularly when placed before FVC falls to ≤50% of predicted value.
- Nutrition, speech therapy, physical and occupational therapy services.
- Suction device for sialorrhea.
- Communication may be eased with computerized assistive devices.
- Early discussion of living will, resuscitation orders, desire for PEG and tracheostomy, potential long-term care options.
- Encourage contact with local support groups.

ACUTE GENERAL Rx

Riluzole (Rilutek), a glutamate antagonist, is the only FDA-approved medication known to extend tracheostomy-free survival in patients with ALS. Dosage is 50 mg q12h, at least 1 hr before or 2 hr after meals. It is shown to prolong survival by 2 to 3 months. Manufacturer recommends checking alanine aminotransferase (ALT) once a month for 3 months initially, followed by once every 3 months until the first year of therapy is completed. ALT should be checked periodically thereafter.

CHRONIC Rx

- Sialorrhea may respond to either glycopyrrolate or amitriptyline (consider either propranolol or metoprolol if secretions are thick). Botulinum toxin may be effective in medically refractory cases.
- Spasticity may be treated pharmacologically with baclofen, tizanidine, clonazepam.
- Pseudobulbar affect may improve with amitriptyline, sertraline (Zoloft), or dextromethorphan/quinine.

DISPOSITION

- Mean duration of symptoms is 3 to 5 yr.
- Approximately 20% of patients survive >5 yr.

REFERRAL

- Referral to a neurologist experienced in neuromuscular disease is recommended to confirm the diagnosis. One prospective, population-based study suggested improved survival in subjects treated in a multidisciplinary clinic.
- Gastrointestinal referral for PEG placement is recommended while FVC remains >50% to minimize morbidity attributable to risks inherent to the procedure.

PEARLS & CONSIDERATIONS

- Patient-physician communication is an integral and essential part in both the initial diagnosis and subsequent treatment of ALS.
- A multidisciplinary approach to supportive care may lead to an improved level of daily functioning and foster an increased sense of independence.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Amyotrophic Lateral Sclerosis (Patient Information)

AUTHOR: **TAYLOR HARRISON, M.D.**

EVIDENCE

Abstract[1]

Objective:
To estimate the potential diagnostic added value of the Awaji criteria for diagnosis of amyotrophic lateral sclerosis (ALS), which have been compared with the previously accepted gold standard, the revised El Escorial criteria, in several studies.

Data Sources:
MEDLINE and Web of Science (until October 2011).

Study Selection:
We searched for studies testing the diagnostic accuracy of the Awaji criteria vs the revised El Escorial criteria in patients referred with suspected ALS.

Data Extraction:
Evaluation and data extraction of identified studies were done independently. The Quality Assessment of Diagnostic Accuracy Studies list was used to assess study quality. We determined the proportion of patients classified as having probable/definite ALS and derived indices of diagnostic performance (sensitivity, specificity, and diagnostic odds ratio). Quantitative data synthesis was accomplished through random-effects meta-analysis, and heterogeneity was assessed with the I2 test.

Data Synthesis:
Eight studies were included (3 prospective and 5 retrospective) enrolling 1187 patients. Application of Awaji criteria led to a 23% (95% CI, 12% to 33%; I2 = 84%) increase in the proportion of patients classified as having probable/definite ALS. Diagnostic performance of the Awaji criteria was higher than the revised El Escorial criteria (pooled sensitivity: 81.1% [95% CI, 72.2% to 90.0%; I2 = 91%] vs 62.2% [95% CI, 49.4% to 75.1%; I2 = 93%]; pooled diagnostic odds ratio, 35.8 [95% CI, 15.2 to 84.7; I2 = 3%] vs 8.7 [95% CI, 2.2 to 35.6; I2 = 50%]). Diagnostic accuracy of Awaji criteria was higher in bulbar- than in limb-onset cases.

Conclusion:
The Awaji criteria have a significant clinical impact allowing earlier diagnosis and clinical trial entry in ALS. Ⓐ

Evidence-Based Reference

Costa J, Swash M, de Carvalho M: *Arch Neurol* 69:1410–1416, 2012. Ⓐ

SUGGESTED READINGS

Miller RG et al.: Practice parameter update: The care of the patient with amyotrophic lateral stenosis: Drug, nutritional, and respiratory therapies (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology, *Neurology* 73:1218–1226, 2009.

Mitchell JD, Borasio GD: Amyotrophic lateral sclerosis, *Lancet* 369:2031–2041, 2007.

TABLE EA1-51 Revised EL Escorial Diagnostic Criteria for Amyotrophic Lateral Sclerosis

The diagnosis of ALS requires:

- [A:1] Evidence of LMN degeneration by clinical, electrophysiologic, or neuropathologic examination
- [A:2] Evidence of UMN degeneration by clinical examination and
- [A:3] Progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination

Together with the absence of:

- [B:1] Electrophysiologic and pathologic evidence of another disease that might explain the signs of LMN and/or UMN degeneration and
- [B:2] Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiologic signs

Levels of diagnostic certainty:

Definite ALS

- UMN signs and LMN signs in 3 regions

Probable ALS

- UMN signs and LMN signs in 2 regions with UMN signs rostral to LMN signs

Probable ALS—laboratory supported

- UMN signs in 1 or more regions *and* LMN signs defined by EMG in at least 2 regions

Possible ALS

- UMN signs and LMN signs in 1 region (together) or
- UMN signs in 2 or more regions
- UMN and LMN signs in 2 regions with *no* UMN signs rostral to LMN signs

From Goldman L, Schafer AI: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Saunders.

BASIC INFORMATION

DEFINITION

An anaerobic infection is caused by one of a group of bacteria that requires a reduced oxygen tension for growth.

ICD-9CM CODES
See specific condition
ICD-10CM CODES
A41.4 Sepsis, anaerobic
A48 Cellulitis, anaerobic

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- May occur at any site, but most are anatomically related to mucosal surfaces
- Should be suspected when there is foul-smelling tissue, soft tissue gas, necrotic tissue, or abscesses
- Head and neck
  1. Odontogenic infections from dental or soft tissue possibly progressing to periapical abscesses, at times extending to bone
  2. Both anaerobic and aerobic pathogens in chronic sinusitis, chronic mastoiditis, peritonsillar abscess, and chronic otitis media
  3. Complications: deep neck space infections, brain abscesses, mediastinitis
  4. Specific examples of anaerobic infections in head and neck:
     a. Ludwig's angina: bilateral infection of sublingual and submandibular spaces that causes swelling of the base of the tongue with potential airway compromise. Usually mixed aerobic and anaerobic flora
     b. Lemierre's syndrome: jugular vein suppurative thrombophlebitis caused by anaerobic bacteria: *Fusobacterium necrophorum*
- Pleuropulmonary
  1. May involve anaerobes present in the oropharynx
  2. Aspiration more common in persons with altered mental status or seizures
  3. Anaerobic bacteria more likely in those with gingivitis or periodontitis
  4. Manifestations: necrotizing pneumonia, empyema, lung abscess
- Intraabdominal
  1. Disruption of intestinal integrity leading to infection involving anaerobic bacteria
  2. Bacteria from colonic neoplasm, perforated appendicitis, diverticulitis, or bowel surgery, causing bacteremia, peritonitis, at times intraabdominal abscesses
  3. Resulting infections usually mixed, containing both anaerobes and aerobes
- Female genital tract
  1. Anaerobes in bacterial vaginosis, salpingitis, endometritis, pelvic abscesses, septic abortion; infections tend to be mixed
  2. Possible pelvic thrombophlebitis when resolving pelvic infection is accompanied by new or persistent fever
- Other anaerobic infections
  1. Skin and soft tissue infection at any site
  2. More commonly associated infections: synergistic gangrene, bite wound infections, infected decubitus ulcers
  3. Clinical significance of anaerobes in diabetic foot infections unclear
  4. Anaerobic bacteremia uncommon with source usually intraabdominal, followed by female genital tract, pleuropulmonary, and head and neck infections
  5. Osteomyelitis especially when associated with decubitus ulcers or vascular insufficiency
  6. Facial bone osteomyelitis from adjacent infections of the teeth or sinuses

ETIOLOGY

- Most commonly endogenous, arising from bacteria that normally line mucosal surfaces
- Disruption of mucosal barriers resulting from various conditions (trauma, ischemia, surgery, perforation), with infection occurring when organisms gain access to normally sterile sites, causing tissue destruction and abscess formation
- Synergy between different anaerobes or between anaerobes and aerobes important
- Examples of anaerobic bacteria include gram-negative bacteria such as *Bacteroides* species, *Fusobacterium* and *Prevotella* species; and gram-positive bacteria such as *Peptostreptococcus, Clostridium* species, and *Actinomyces* species

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Primary differential possibility is an aerobic bacterial infection without the presence of anaerobic bacteria.
- Ischemic necrosis without accompanying anaerobic infection (or "dry" gangrene [non-infected necrosis] vs. "wet" gangrene [infected tissue with anaerobic infection]).

WORKUP

- Specimens submitted for anaerobic culture should be processed within 30 min and may take up to 5 to 7 days to grow
- Large volume of material more likely to have significant growth; swabs less efficient for transporting infected material
- Blood cultures—preferably before antibiotic administration

LABORATORY TESTS

- Elevated WBC count, with extremely high WBC counts sometimes seen with pseudomembranous colitis
- Positive stool *C. difficile* toxin A and B assay
- Increased lactate levels in ischemia or perforation
- Possible positive blood or wound cultures, but failure to grow anaerobes in culture may be common, attributed to inadequate culturing techniques or fastidious organisms

IMAGING STUDIES

- Plain film of an affected area to show gas in tissues, free air resulting from a perforated viscus, or an air/fluid level inside an abscess
- Ultrasound, CT scan, or MRI to reveal abscesses or tissue destruction

TREATMENT

NONPHARMACOLOGIC THERAPY

- Removal of necrotic tissue
- Drainage of abscesses (accomplished by CT scan–guided percutaneous drainage)

ACUTE GENERAL Rx

Oral antibiotics with anaerobic activity: clindamycin, metronidazole, and chloramphenicol

- Broader spectrum of activity with amoxicillin/clavulanate
- Penicillin VK in odontogenic infections
- Oral metronidazole for *C. difficile*–associated diarrhea, with oral vancomycin used for severe, recurrent, or recalcitrant infections

Parenteral antibiotics for more serious illness

- IV clindamycin, metronidazole, and chloramphenicol
- Cephalosporins (anaerobic or mixed infections): cefoxitin and cefotetan
- Extended-spectrum penicillins (e.g., piperacillin) and combination beta-lactamase plus beta-lactamase inhibitor drugs (e.g., clavulanic acid, sulbactam, tazobactam)
  1. Significant anaerobic activity, plus various degrees of broad-spectrum coverage
  2. Include ampicillin/sulbactam, ticarcillin/clavulanate, and piperacillin/tazobactam
- Imipenem or other carbapenems, such as meropenem, doripenem, or ertapenem, which are broad-spectrum agents with extensive anaerobic activity
- Actinomycosis treated with penicillin for 6 to 12 mo
- SMX/TMP and fluoroquinolones are generally ineffective, but some newer quinolones (e.g., moxifloxacin) have inhibitory activity against anaerobes

DISPOSITION

It is essential that all necrotic debris be removed when treating an anaerobic infection or it will recur; follow-up is critically important to ensure resolution of the process.

REFERRAL

Refer to a surgeon if drainage is required; infectious disease consultation may be useful in complicated patients or if treatment regimen is failing or slow to respond.

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Available at www.expertconsult.com

SUGGESTED READINGS

Nagy E: Anaerobic infections: update on treatment considerations, *Drugs* 70(7):841–858, 2010.

Stein GE, Goldstein EJ: Fluoroquinolones and anaerobes, *Clin Infect Dis* 42(11):1598, 2006.

Wexler HM: Bacteroides: the good, the bad, and the nitty-gritty, *Clin Microbiol Rev* 20:593, 2007.

BASIC INFORMATION

DEFINITION

A fissure is a tear in the epithelial lining of the anal canal (i.e., from the dentate line to the anal verge).

SYNONYMS

Anorectal fissure
Anal ulcer

ICD-9CM CODES
565.0 Anal fissure
ICD-10CM CODES
K60.2 Anal fissure, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT SEX: Occurs in men more than women. Women are more likely to have anterior fissure than men (10% vs. 1%, respectively). Common in women before and after childbirth.
PREDOMINANT AGE: Can occur at any age. Most common in young and middle-aged adults. Most common cause of rectal bleeding in infants.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

With separation of the buttocks will see a tear in the posterior midline or, less frequently, in the anterior midline (Fig. A1-73)

- Acute anal fissure:
  1. Sharp burning or tearing pain exacerbated by bowel movements
  2. Bright-red blood on toilet paper, a streak of blood on the stool or in the water

FIGURE A1-73 Lateral anal fissure. (From Seidel HM et al: *Mosby's guide to physical examination,* ed 3, St Louis, 1995, Mosby. Courtesy Gershon Efron, MD, Sinai Hospital of Baltimore.)

- Chronic anal fissure:
  1. Pruritus ani
  2. Pain seldom present
  3. Intermittent bleeding
  4. Sentinel tag at the caudal aspect of the fissure, hypertrophied anal papilla at the proximal end
- Underlying disease possible if the fissure:
  1. Is ectopically located
  2. Extends proximal to the dentate line
  3. Is broad-based or deep
  4. Is especially purulent

ETIOLOGY

- Most initiated after passage of a large, hard stool
- May result from frequent defecation and diarrhea
- Bacterial infections: tuberculosis (TB), syphilis, gonorrhea, chancroid, lymphogranuloma venereum
- Viral infections: herpes simplex virus, cytomegalovirus, human immunodeficiency virus
- Inflammatory bowel disease (IBD): Crohn's disease, ulcerative colitis
- Trauma: surgery (hemorrhoidectomy), foreign bodies, anal intercourse
- Malignancy: carcinoma, lymphoma, Kaposi sarcoma

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Proctalgia fugax
- Thrombosed hemorrhoid
- Carcinoma

WORKUP

- Digital rectal examination after lubricating the entire anus with anesthetic jelly (i.e., 2% lidocaine) and waiting 5 to 10 min
- Anoscopy
- Proctosigmoidoscopy to exclude inflammatory or neoplastic disease
- Biopsy if doubt exists about the etiology of the condition
- All studies done under adequate anesthesia

IMAGING STUDIES

- Colonoscopy if diagnosis of IBD or malignancy is suspected
- Small-bowel series occasionally obtained for similar reasons

TREATMENT

NONPHARMACOLOGIC THERAPY

- Sitz baths
- High-fiber diet
- Increased oral fluid intake

ACUTE GENERAL Rx

- Bulk-producing agent (e.g., Metamucil) or stool softener
- Local anesthetic jelly (may exacerbate pruritus ani)
- Nitroglycerin ointment (0.4%): apply 1 inch of ointment (equivalent to 1.5 mg of nitroglycerin) intraanally every 12 hours for up to 3 weeks. This medication (Reactiv) is expensive (over $400 for 30-g tube) and can cause headaches. Topical Diltiazem (compounded by pharmacist) is also effective and much less expensive.
- Suppositories *not* recommended
- Surgery

CHRONIC Rx

- Surgery: lateral internal anal sphincterotomy. It is a more durable treatment for chronic anal fissure compared with topical nitroglycerin therapy and does not compromise long-term fecal continence
- Topical glyceryl trinitrate ointment
- Injection of botulinum toxin (an injection into each side of the internal anal sphincter) is effective in healing chronic anal fissures in more than 90% of patients

DISPOSITION

Outpatient surgery

REFERRAL

- If fissure does not resolve with conservative therapy in 4 to 6 wk
- If patient prefers surgery for acute fissure
- If patient has chronic fissure

PEARLS & CONSIDERATIONS

COMMENTS

HIV-positive patients should be referred to clinicians who are well versed in the myriad infectious and neoplastic conditions that masquerade as anal ulcers in these patients.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Anorectal Fistula (Related Key Topic)
Hemorrhoids (Related Key Topic)
Anal Fissure (Patient Information)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Brisinda G et al.: A comparison of injection of botulinum toxin and topical nitroglycerin ointment for the treatment of chronic anal fissure, *N Engl J Med* 341:65, 1999.

Brisinda G et al.: Treating chronic anal fissure with botulinum neurotoxin, *Nat Clin Pract Gastroenterol Hepatol* 1(2):82, 2004.

Dwarkasing S et al.: Magnetic resonance imaging of perianal fistulas, *Semin Ultrasound CT MR* 26(4):247, 2005.

Pfenninger JL, Zainea GG: Common anorectal conditions, *Am Fam Physician* 64:77, 2001.

BASIC INFORMATION

DEFINITION

Anaphylaxis is a severe allergic reaction that is rapid in onset and life-threatening. It is characterized by respiratory, cardiovascular, gastrointestinal, and cutaneous manifestations, as well as vasodilatory hemodynamic changes in response to a particular allergen. Anaphylactoid reaction is an entity closely related to anaphylaxis and is caused by release of mast cells and basophil mediators triggered by non–IgE-mediated events.

SYNONYMS

Anaphylactoid reaction.

ICD-9CM CODES

995.0	Anaphylactic shock
995.60	Anaphylaxis due to food
999.4	Anaphylaxis due to immunization
977.9	Anaphylaxis due to drugs
989.5	Anaphylaxis following stings

ICD-10CM CODES

T78.2	Anaphylactic shock, unspecified, initial encounter
T78.00XA	Anaphylactic reaction due to unspecified food, initial encounter
T80.52XA	Anaphylactic reaction due to vaccination, initial encounter
T50.904A	Poisoning by unspecified drugs, medicaments, and biologic substances, undetermined, initial encounter
T63.94XA	Toxic effect of contact with unspecified venomous animal, undetermined, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The incidence of anaphylaxis in the U.S. is 50 to 2000 episodes per 100,000 persons. Lifetime prevalence is 0.05% to 2%, with a mortality rate of 1%. Anaphylaxis rates are 0.0004% for food, 0.7% to 10% for penicillin, 0.22% to 1% for contrast media, and 0.5% to 5% after insect stings. Annual mortality is 500 to 1000 persons per year in the U.S.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Urticaria, pruritus, skin flushing, angioedema
- Dyspnea, cough, wheezing, shortness of breath
- Nausea, vomiting, diarrhea, difficulty swallowing
- Hypotension, tachycardia, weakness, dizziness, malaise, vascular collapse

ETIOLOGY

Anaphylaxis results from a sudden systematic release of histamine and other inflammatory mediators from basophils and mast cells. This causes swelling of the mucus membranes and the urticarial rash on the skin. Virtually any substance may induce anaphylaxis.

- Foods and food additives: peanuts, tree nuts, eggs, shellfish, fish, cow's milk, fruits, soy
- Medications: antibiotics (especially penicillins), insulin, allergen extracts, opiates, vaccines, NSAIDs, contrast media, streptokinase
- Environmental exposures: bee or wasp sting, snake venom, fire ant venom
- Blood products: plasma, immunoglobulin, cryoprecipitate, whole blood
- Latex

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Endocrine disorders (carcinoid, pheochromocytoma)
- Globus hystericus, anxiety disorder
- Systemic mastocytosis
- Pulmonary embolism, serum sickness, vasovagal reactions
- Severe asthma (the key clinical difference is the abrupt onset of symptoms in anaphylaxis versus a history of progressive worsening of symptoms)
- Septic shock or other form of vasodilatory shock
- Airway foreign body

WORKUP

Workup is aimed at ruling out other conditions that may mimic anaphylaxis.

LABORATORY TESTS

- Laboratory evaluation is generally not helpful because anaphylaxis is typically diagnosed clinically.
- ABG analysis may be useful to help differentiate between pulmonary embolism, status asthmaticus, and foreign body aspiration.
- Elevated serum and urine histamine levels and serum tryptase levels can be useful for diagnosis of anaphylaxis, but these tests are not commonly available in the emergency setting.

IMAGING STUDIES

Generally not helpful.

- Chest radiography for evaluation of foreign body aspiration or pulmonary pathology is indicated in patients with acute respiratory compromise.
- Consider ECG in all patients with sudden loss of consciousness or reports of chest pains or dyspnea and in any elderly patient. ECG in anaphylaxis usually reveals sinus tachycardia.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Establish and protect airway. Provide supplemental O_2 if indicated.
- IV access should be rapidly established, and IV fluids (i.e., normal saline) should be administered.
- Cardiac monitoring is recommended.

ACUTE GENERAL Rx

- Epinephrine should be rapidly administered as an IM injection at a dose of 0.3 mg of aqueous epinephrine for adults and children >30 kg. Epinephrine 0.15 mg should be given for children <30 kg (1:1000 concentration). Intramuscular administration is preferred because it provides more reliable and quicker rise to effective plasma levels. The dose may be repeated after approximately 5 to 15 min if symptoms persist.
- Adjunct therapies include H_1 and H_2 receptor antagonists such as diphenhydramine 25 to 50 mg IV or IM (or PO in mild cases) and famotidine 20 to 40 mg IV (or PO in mild cases). Although useful to improve cutaneous erythema and pruritus, H_1 antagonists are not as effective as epinephrine, since onset of action is 1 to 2 hours and they are not effective in reversing upper airway obstruction or improving hypotension.
- Corticosteroids are not useful in the acute episode because of their slow onset of action; however, they should be administered in most cases to prevent prolonged or recurrent anaphylaxis. Commonly used agents are prednisone, methylprednisolone 40 to 250 mg IV in adults (1 to 2 mg/kg in children), or dexamethasone.
- Aerosolized β-agonists (e.g., albuterol, 2.5 mg, repeat prn 20 min) are useful to control bronchospasm.
- Vasopressor therapy with epinephrine (1:10,000), or dopamine is indicated in patients with refractory hypotension/cardiovascular collapse after crystalloid resuscitation.

PEARLS & CONSIDERATIONS

COMMENTS

- Patient education regarding the nature of the illness and preventive measures is recommended. A documented history of previous anaphylactic episodes or known triggers is the most reliable method of identifying individuals at risk.
- Prescription for prefilled epinephrine syringe (EpiPen or EpiPen Jr.) should be given, and the patient should be instructed on the use of this emergency kit, and to carry it on his/her person at all times. School-aged children should keep an additional EpiPen at school with the appropriate staff.
- Patients should also be advised to carry or wear a MedicAlert ID describing substances that have caused anaphylaxis.
- Avoidance of radiologic contrast is also recommended in those who have had a prior reaction. However, pretreatment regimens with methylprednisolone diphenhydramine, or n-acetylcysteine exist for those who have had contrast reactions in the past.
- Venom immunotherapy immediately after a sting is effective and recommended for up to 5 yr after the anaphylactic incident.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **STEVEN ROUGAS, M.D., M.S.**

SUGGESTED READINGS

Lieberman PL: Recognition and first-line treatment of anaphylaxis, *Am J Med* 127:S6–S11, 2011.

Mustafa SS: *Anaphylaxis* (website). Available at: http://emedicine.medscape.com/article/135065-overview#a0101. Accessed February 15, 2013.

Nowak RM et al.: Anaphylaxis on the other front line: Perspectives from the emergency department, *Am J Med* 127:S34–S44, 2014.

Sclarda et al.: Anaphylaxis: underdiagnosed, underreported, and undertreated, *Am J Med* 127:S1–S5, 2014.

Williams PM, Arnold JJ: Anaphylaxis: recognition and management, *Am Fam Physician* 84(10):1111–1118, 2011.

BASIC INFORMATION

DEFINITION

Angina pectoris is a term used to describe a clinical syndrome, typically characterized by chest, jaw, shoulder, back or arm discomfort, that is caused by myocardial ischemia. This is most commonly related to atheromatous plaque in one or more than one large epicardial coronary artery; however, myocardial ischemia may occur in the absence of obstructive coronary artery disease (CAD), such as uncontrolled hypertension, valvular heart disease, hypertrophic cardiomyopathy, coronary spasm, or endothelial dysfunction. Any situation that causes an imbalance in myocardial oxygen supply and demand can cause an angina syndrome. Angina can be classified as follows:

1. Chronic stable ischemic heart disease (ISHD):
   - Predictable. Usually follows a precipitating event (e.g., climbing stairs, sexual intercourse, a heavy meal, emotional stress, cold weather).
   - Generally same severity as previous attacks; relieved by rest or by the customary dose of nitroglycerin.
   - Caused by a fixed coronary artery obstruction secondary to atherosclerosis. The presence of one or more obstructions in major coronary arteries is likely; the severity of stenosis is usually >70%.
2. Unstable (rest or crescendo, acute coronary syndrome; will be reviewed under Acute Coronary Syndrome):
   - Recent onset. Less than 2 months after the onset of the symptoms.
   - Increasing severity, duration, or frequency of chronic angina.
   - Occurs at rest or with minimal exertion.
3. Prinzmetal's variant:
   - Occurs at rest.
   - Manifests electrocardiographically as episodic ST-segment elevations.
   - Caused by coronary artery spasms with or without superimposed CAD.
   - Patients also more likely to develop ventricular arrhythmias.
4. Microvascular angina (syndrome X):
   - Refers to patients with angina symptoms, positive exercise test, normal coronary angiograms and no coronary spasm. Defective endothelium-dependent dilation in the coronary microcirculation contributes to the altered regulation of myocardial perfusion and the ischemic manifestations in these patients.
   - Patients with chest pain and normal or nonobstructive coronary angiograms are predominantly women, and many have a prognosis that is not as benign as commonly thought (2% risk of death or myocardial infarction [MI] at 30 days of follow-up).
5. Refractory angina:
   - Refers to patients who, despite optimal medical therapy, have both angina and objective evidence of ischemia and are not considered candidates for revascularization.
6. Other:
   - Angina due to aortic stenosis and idiopathic hypertrophic subaortic stenosis, cocaine-induced coronary vasoconstriction.

FUNCTIONAL CLASSIFICATION

Stable angina should be classified using a grading system. The most commonly adopted is that of the Canadian Cardiovascular Society:

- Class I: Ordinary physical activity, such as walking or climbing stairs, does not cause angina. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.
- Class II: Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals, in cold, in wind, or under emotional stress; or only during the few hours after awakening. Angina occurs on walking more than two level blocks and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
- Class III: Marked limitations of ordinary physical activity. Angina occurs on walking one to two level blocks and climbing one flight of stairs in normal conditions and at a normal pace.
- Class IV: Inability to carry on any physical activity without discomfort; anginal symptoms may be present at rest.

ICD-9CM CODES

411.1 Angina, stable
413 Angina pectoris
413.1 Prinzmetal's angina
413.9 Angina, unspecified

ICD-10CM CODES

I20.8 Other forms of angina pectoris
I20.9 Angina pectoris, unspecified
I20.1 Angina pectoris with documented spasm

EPIDEMIOLOGY & DEMOGRAPHICS

- Based on the NHANES survey 2007-2010, an estimated of 15.4 million have coronary heart disease of which 7.8 million have angina.
- Angina is most common in middle-aged and elderly men.
- Women are usually affected after menopause.
- The initial manifestation of ischemic heart disease is angina pectoris in 50%, and about 50% of patients presenting to the hospital with acute coronary syndrome have preceding angina.
- Two older population-based studies from Olmstead County, MN, and Framingham, MA, showed annual rated of myocardial infarction in patients with symptomatic angina of 3 to 3.5%/year.
- Within 12 months of initial diagnosis, 10% to 20% of patients with diagnosis of stable angina progress to MI or unstable angina.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Although there is significant individual variation, most patients report substernal chest pain (pressure, tightness, heaviness, sharp pain, sensation similar to intestinal gas or dysphagia).
- Pain is of short duration (typically <10 minutes); nonpleuritic; and often accompanied by shortness of breath, nausea, diaphoresis, and numbness or pain in the left arm, jaw, or shoulder. Ischemic pain of more than 30 minutes' duration should raise concern for possible MI.
- Women are more likely than men to report atypical chest pain or discomfort (65% reported on Women's Ischemic Syndrome Evaluation [WISE] study).
- Elderly and diabetics may report symptoms other than chest pain, such as dyspnea, fatigue, or diaphoresis.

ETIOLOGY

RISK FACTORS

- Advanced age
- Male sex
- Genetic predisposition, family history of premature coronary artery disease (CAD) in first degree relatives (men younger than 55 years of age, and women younger than 65 years of age).
- Smoking (risk is almost double)
- Hypertension (risk is double if systolic blood pressure is >180 mm Hg)
- Hyperlipidemia
- Impaired glucose tolerance or diabetes mellitus
- History of stroke or peripheral arterial disease
- Chronic kidney disease (CKD)
- Metabolic syndrome
- Physical inactivity
- Obesity (weight >30% over ideal). A higher body mass index during childhood is also associated with an increased risk of coronary heart disease (CHD) in adulthood
- Hypothyroidism
- Left ventricular hypertrophy
- Aortic stenosis or idiopathic subaortic stenosis
- Oral contraceptive and HRT use
- Cocaine use (used by >5 million Americans regularly and is responsible for >64,000 emergency department [ED] evaluations yearly to rule out myocardial ischemia)
- Coronary artery calcium is associated with an increased risk of MI
- Long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs)
- Exposure to air pollution from traffic (dilute diesel exhaust) promotes myocardial ischemia and is associated with adverse cardiovascular events
- Low serum folate levels required for conversion of homocysteine to methionine are associated with an increased risk of fatal CHD. Hyperhomocysteinemia has a toxic effect on vascular endothelium and interferes with proliferation of arterial wall smooth muscle cells.

- Elevated plasma homocysteine level is a strong and independent risk factor for CHD events, especially in patients with type 2 diabetes mellitus.
- Elevated levels of highly sensitive C-reactive protein (hs-CRP, cardio CRP), suggesting that diseases associated with systemic inflammation can lead to accelerated atherosclerosis
- Depression
- Vasculitis
- Elevated levels of lipoprotein-associated phospholipase A_2
- Elevated fibrinogen levels
- Low level of red blood cell glutathione peroxidase-1 activity
- Radiation therapy

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Nonischemic Cardiovascular: Aortic dissection, pericarditis

Pulmonary: Pulmonary embolism, pneumothorax, pneumonia, pleuritis

Gastrointestinal: Esophageal, esophagitis, spasm, reflux, biliary colic, cholecystitis, choledocholithiasis, cholangitis, peptic ulcer, pancreatitis

Chest Wall: Costochondritis, fibrositis, rib fracture, sternoclavicular arthritis, Herpes zoster (before the rash)

Psychiatric: Anxiety disorders, hyperventilation, panic disorder, primary anxiety, affective disorders (i.e., depression), somatiform disorders, thought disorders (i.e., fixed delusions)

WORKUP

- In patients with chest pain, the probability of CAD should be estimated on the basis of patient age, sex, cardiovascular risk factors, and pain characteristics.
- The most important diagnostic factor is the history. Chest pain or left arm pain or discomfort occurring with exertion and relieved by rest in a patient with cardiovascular risk factors is consistent with a high likelihood of CAD.
- In assessing the likelihood of underlying ISHD it is helpful to classify the chest pain as typical angina, atypical angina, and/or noncardiac chest pain.
- Typical angina, (definite) will have the following three features: (1) substernal chest discomfort with a characteristic quality and duration, (2) provoked by exertion or emotional stress, and (3) relieved by rest and/or sublingual nitroglycerin (NTG).
- Atypical angina, (probable) will have two of the above listed three features.
- Noncardiac chest pain will have one of the above listed features.
- Physical examination may be completely normal in many patients; however, certain findings may be helpful in the assessment of the patient with suspected ISHD. Some findings may identify consequences of ischemia or possible causes of the anginal syndrome other than CAD. The presence of hypertension, arcus senilis, xanthelasma, carotid or peripheral bruits, and a prominent S4 are all physical signs that could raise concern for the presence of CAD. A murmur of mitral regurgitation may be a marker of an ischemic cardiomyopathy or transient ischemia. A murmur suggestive of hypertrophic cardiomyopathy or aortic stenosis may suggest a cause of angina other than CAD.

LABORATORY TESTS

- Initial laboratory tests in patients with chronic ISHD should include a hemoglobin, fasting glucose, and fasting lipid panel.
- Cardiovascular screening: Measurement of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and fasting serum triglycerides. Also, measurement of Non–HDL-C, the ratio of total cholesterol to HDL-C, and apolipoprotein fractions (e.g., apolipoprotein B100, apolipoprotein A1).
- Electrocardiogram should be obtained during pain and when the patient is free of any discomfort. A normal resting electrocardiogram is not unusual in patients with ISHD; in patients who present with chest pain, 1% to 6% who have an acute MI will have a normal or nondiagnostic electrocardiogram. Chest x-ray PA and lateral, to rule out heart failure, valvular disease, pericardial disease, aortic aneurysm/dissection.
- Cardio-CRP (hs-CRP): Its elevation is a relatively moderate predictor of CHD, and it adds prognostic information to that conveyed by the Framingham risk score.

EXERCISE TESTING AND IMAGING STUDIES

- The value of further testing is greatest in patients who have an intermediate risk of CAD. Exercise testing is used for the purpose of diagnosis as well as prognosis. If the patient is physically capable to perform at least moderate physical exercise, exercise stress testing (Fig. EA1-74) is useful because of the important prognostic information obtained from exercise performance and the hemodynamic response. Patients who have an intermediate risk of CAD, as patients in a low-risk or high-risk category are more likely to have a false-positive or false-negative result, respectively. Risk assessment is also indicated in patients with ISHD who are being considered for revascularization of known coronary stenosis of unclear physiological significance. Stress echocardiography or stress testing with myocardial perfusion imaging may be employed when baseline electrocardiographic abnormalities are present that render the electrocardiographic response to exercise uninterpretable, such as >1 mm ST segment depression, LBBB, WPW, paced ventricular rhythm, digoxin treatment with ST segment changes. Stress echocardiography has the advantage of higher specificity and a lower cost. Stress radionuclide perfusion imaging has a higher sensitivity, particularly for single-vessel coronary disease, and has a higher technical success rate. When the patient is unable to exercise adequately, pharmacological testing (i.e., dobutamine, adenosine, regadenoson) may be used with these imaging modalities
- A very good predictor of risk for a patient with stable angina is the Duke treadmill score, which incorporates the patient's functional status (METS or time in minutes during the Bruce protocol), ST-segment depression, and an angina index. Patients with favorable Duke scores have a 5-year survival rate of >97%; this is independent of other factors such as coronary anatomy and LV function.
- Echocardiography is indicated in patients with murmurs suggestive of aortic stenosis, hypertrophic cardiomyopathy, mitral regurgitation, mitral valve prolapse, previous MI, pathological Q waves, complex ventricular arrhythmias, heart failure, hypertension, diabetes, and abnormal EKG.
- Cardiac computed tomography (CCTA; Fig A1-75) is useful for the detection of subclinical CAD in asymptomatic patients with an intermediate Framingham 10-year risk estimate of 10% to 20%. Detects and quantifies coronary calcium and evaluates the lumen and wall of the coronary artery. CCTA can be useful as a first-line test for risk assessment in patients with ISHD who are unable to exercise to an adequate workload regardless of interpretability of ECG. Also can be used when a functional test has an indeterminate result. CCTA CT cost and radiation exposure are limiting factors to recommending widespread routine use of this marker.
- Coronary artery calcium (CAC) score is a strong predictor of incidence of CAD and provides predictive information beyond that provided by standard risk factors. A below 100 indicates low risk, and a score above 300 high risk.
- Cardiac magnetic resonance imaging (CMRA), in addition to its use for diagnosis of arrhythmogenic right ventricular dysplasia, can also be used to assess myocardial perfusion and viability as well as function. Additional studies are needed to determine the cost effectiveness of these studies in patients with ischemic cardiomyopathy.
- Invasive coronary angiography remains the gold standard for the identification of clinically significant CAD. Angiography is performed to define the location and extent of coronary disease; indicated in selected patients who are candidates for coronary revascularization (either coronary artery bypass graft [CABG] surgery or angioplasty).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Aggressive modification of preventable risk factors through patient education on smoking cessation, weight reduction in obese patients, regular aerobic exercise program (at least 30 to 60 min/day), correction of

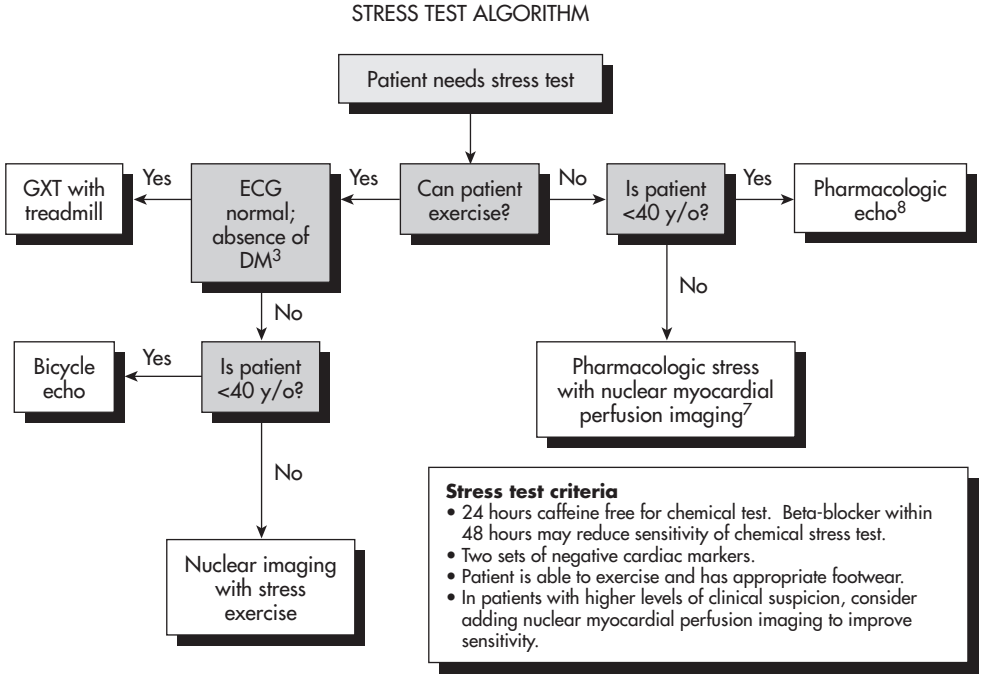
folate deficiency, reduced intake of saturated fats (to <7% of total calories), trans fatty acids (to <1% of total calories), cholesterol (to <200 mg/day), low-sodium diet (<2 g/day), and teaching importance of medication adherence). Whole grains as the main form of carbohydrates, an abundance of fruits and vegetables, and adequate omega-3 fatty acids are optimal for prevention of ISHD.

- Correction of possible aggravating factors (e.g., anemia, hypertension, diabetes mellitus, hyperlipidemia, thyrotoxicosis). Use caution regarding the routine use of blood transfusions to maintain arbitrary hematocrit levels in stable patients with IHD.

PHARMACOLOGIC THERAPY

Treatment can be classified based on medications that prevent MI and death.

- Aspirin reduces cardiovascular mortality and morbidity rates by 20% to 25% among patients with CAD. Initial dose is at least 160 mg/day followed by 75 to 162 mg/day. It inhibits the enzyme cyclooxygenase and synthesis of thromboxane A2 and reduces the risk of adverse cardiovascular events by 33% in patients with unstable angina. Patients intolerant to aspirin can be treated with the other antiplatelet agents (see below).
- Clopidogrel is a thienopyridine, which acts by irreversibly blocking the P2Y12 adenosine diphosphate receptor on the platelet surface, thereby interrupting platelet activation and aggregation. Patients are now commonly being tested to see if clopidogrel is effectively



DEFINITIONS:

[1]Typical angina:
1) Substernal chest pain or discomfort that is 2) provoked by exertion or emotional stress and 3) relieved by rest and/or nitroglycerin

[2]Cardiac marker timing: based on symptom onset; in cases of uncertainty assume symptom onset at ED arrival

[3]ECG normal: no significant ST depression/T wave inversions, BBB, LVH with repolarization, conduction defect, digoxin effect

[4]Anginal equivalent:
- Any symptoms that the physician feels may represent ACS
- Exertional dyspnea—most common anginal equivalent symptom

[5]ACS:
- STE-ACS—1 mm ST elevation in 2 leads
- NSTE-ACS
  - NSTEMI—positive cardiac biomarkers
  - Unstable angina—ischemia with negative biomarkers

[6]New significant ECG changes:
- ST $\Delta s \geq 0.5$ mm; resolve when asymptomatic
- ST depression ≥ 1 mm in 2 leads
- T wave inversion ≥ 2 mm in 2 leads

[7]Regadenoson is preferred agent for chemical nuclear stress test. Technitium Tc 99m tetrofosmin is the preferred tarcer.

FIGURE A1-75 Stress test algorithm. *ACS*, Acute coronary syndrome; *BBB*, bundle branch block; *DM*, diabetes mellitus; *ECG*, electrocardiogram; echo, echocardiography; *ED*, emergency department; *GTX*, graded exercise test; *LVH*, left ventricular hypertrophy; *NSTE*, non–ST-segment elevation; *NSTEMI*, NSTE myocardial infarction; *STE*, ST-segment elevation; *y/o*, years old. (From Adams JG et al: *Emergency medicine: clinical essentials,* ed 2, Philadelphia, 2013, Saunders.)

inhibiting platelets, although the usefulness of these tests in vivo has not yet demonstrated clinical utility. The hepatic enzyme CYP2C19 is competitively inhibited by most proton pump inhibitors (PPIs), and earlier studies had suggested an increased risk of clopidogrel failure, leading to concerns of stent thrombosis. Recent studies have not demonstrated clinically significant increased risk of adverse cardiovascular events due to interference with clopidogrel's efficacy. Clopidogrel can be combined with ASA in high-risk patients with ISHD.

- Prasugrel, a newer P2Y12 receptor inhibitor, and ticagrelor, the newest CTPT inhibitor are faster, more potent, more predictable, and have less patient intervariability antiplatelet agents than clopidogrel. These have been studied in patients with acute coronary syndromes (ACSs). Studies in patients with ISHD are undergoing. However, they are associated with a slight increased risk of bleeding when compared with clopidogrel.
- Beta-adrenergic blockers, which prevent MI and death, are first-line therapy in the management of angina pectoris. They achieve their major antianginal effect by decreasing myocardial oxygen demand in reducing heart rate and systolic blood pressure product, AV nodal conduction, and myocardial contractility, in this manner contributing to a reduction in angina onset, with improvement in the ischemic threshold during exercise and during the usual daily activities. Absent contraindications, they should be regarded as initial therapy for stable angina for all patients. Their dose should generally be adjusted to reduce the resting heart rate to 55 to 60 beats/min.
- Nitrates cause venodilation and relaxation of vascular smooth muscle; the decreased venous return from venodilation decreases diastolic ventricular wall tension (preload) and thereby reduces mechanical activity (and myocardial oxygen consumption) during systole. Relaxation of vascular smooth muscle increases coronary blood flow and reduces systemic pressure. Dilatation of the artery wall will not be affected by plaque, but independent of an intact endothelium, leads to reduced resistance across the obstructed lumen. Nitroglycerin contributes to coronary blood flow redistribution by augmenting collateral flow and lowering ventricular diastolic pressure from areas of normal perfusion to ischemic zones. Nitroglycerin also has demonstrated antithrombotic and antiplatelet effects. Sublingual nitroglycerin should be prescribed to all patients with ISHD for angina relief. Tolerance to nitrates can be minimized by avoiding sustained blood levels with a daily nitrate-free period (e.g., omission of bedtime dose of oral isosorbide dinitrate or 12 hr on/12 hr off transdermal nitroglycerin therapy). Nitrates are relatively contraindicated in patients with hypertrophic obstructive cardiomyopathy, and should also be avoided in patients with severe aortic stenosis. Nitrates should not be used within 24 hr of sildenafil (Viagra) or vardenafil (Levitra) or within 48 hr of tadalafil (Cialis) because of the potential for hypotension.
- Calcium channel blockers are antiischemic medications that have no proven mortality benefit in ISHD. They improve myocardial oxygen supply by decreasing coronary vascular resistance and augmenting epicardial conduit vessel and systemic arterial blood flow. Myocardial demand is decreased by a reduction in myocardial contractility, systemic vascular resistance, and arterial pressure. They are first-line treatment when beta-blockers are contraindicated. They play a major role in preventing and terminating myocardial ischemia induced by coronary artery spasm. They are particularly effective in treating microvascular angina. All classes of calcium channel blockers reduce anginal episodes, increase exercise duration, and reduce use of sublingual nitroglycerin in patients with effort-induced angina. Short-acting calcium channel blockers should be avoided. Calcium channel blockers (particularly non-dihydropyridine) should generally also be avoided in patients with CHF secondary to systolic dysfunction due to its negative inotropic effect.
- Ranolazine inhibits the late inward sodium current, indirectly reducing the sodium-dependent calcium current during ischemic conditions and leading to improvement in ventricular diastolic tension and oxygen consumption. It seems to increase the efficiency of energy production in the heart, maintaining cardiac function. Its antianginal and antiischemic effects do not depend on reductions in heart rate or blood pressure. It is indicated for treatment of chronic angina that is inadequately controlled with other antianginals. It represents a new class of drugs known as metabolic modulators and is labeled for use in combination with beta-blockers, amlodipine, or nitrates in patients without an adequate antianginal response to those agents. Side effects include prolongation of QT interval. Low doses of diltiazem and verapamil should be used with ranolazine. The extended-release preparation reduces the frequency of angina, improves exercise performance, and delays the development of exercise-induced angina and ST-segment depression.
- Angiotensin-converting enzyme (ACE) inhibition through changes in the physiological balance between angiotensin II and bradykinin could contribute to the reductions in LV and vascular hypertrophy, atherosclerosis progression, plaque rupture, and thrombosis; the favorable changes in cardiac hemodynamics; and the improved myocardial oxygen supply/demand. It has been shown to be effective in reducing cardiovascular death, MI, and stroke in patients who are at risk for or who had vascular disease. They are indicated in patients with hypertension, diabetes, LVEF <40%, and CKD.
- Use of lipid-lowering drugs is recommended in patients with CAD and in patients with hyperlipidemia refractory to diet and exercise. Among patients who have recently had an acute coronary syndrome, an intensive lipid-lowering statin regimen to reduce LDL cholesterol to <70 mg/dl is a reasonable treatment objective. Statins also decrease the level of the inflammatory marker hs-CRP independently of the magnitude of change in lipid parameters.

REFERRAL

Revascularization (see Table A1-52):

- Revascularization methods should be formulated taking into consideration improved survival or improved symptoms. Revascularization includes either percutaneous coronary intervention (balloon angioplasty and stenting) or CABG. However, note that although the role of PCI is unquestionable in the presence of an acute myocardial infarction, its role is not so clear in stable CAD. The utilization of PCI for stable CAD was reduced by 51.7% from 2007 to 2011, and hospitals with higher volumes of PCI had the largest reduction of these procedures.
- **To improve survival:**
  1. Perform CABG for patients with significant (>50% diameter stenosis) left main coronary artery stenosis. More than 70% diameter stenosis in three main epicardial vessels, >70% diameter stenosis in two major coronary arteries with severe or extensive myocardial ischemia, and in patients with mild to moderate LV systolic dysfunction (EF 35% to 50%) and significant multivessel CAD. Left internal mammary artery (LIMA) graft improves survival when used to bypass a proximal left anterior descending (LAD) artery stenosis.
  2. Percutaneous coronary intervention (PCI) is reasonable as an alternative to CABG in selected stable patients with unprotected left main CAD, low risk of PCI procedural complications, and a high likelihood of good long-term outcome *and* clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (e.g., STS-predicted risk of operative mortality >5).
- **To improve symptoms:**
  1. CABG or PCI to improve symptoms is beneficial in patients with one or more significant (>70% diameter) coronary artery stenoses amenable to revascularization and unacceptable angina despite maximal medical treatment, or in whom increasing medical therapy cannot be implemented because of medication contraindications, adverse effects, or patient preferences.
  2. Hybrid coronary revascularization: LIMA-to-LAD artery grafting and of >1 non-LAD coronary artery can be used in patients who have an unfavorable aorta, have poor target vessels for CABG, are unsuitable graft conduits, or have unfavorable LAD for PCI.

TABLE A1-52 Current Recommendations for Myocardial Revascularization in Patients with Chronic Stable Angina

CABG Surgery versus Medical Therapy

Among patients with medically refractory angina pectoris, CABG surgery is indicated for symptom improvement.

Among patients with medically stable angina pectoris, CABG surgery is indicated to prolong life in left main coronary artery disease or three-vessel disease (regardless of left ventricular function) and, possibly, to help symptoms.

CABG surgery may be indicated for prolongation of life if the proximal left anterior descending coronary artery is involved (regardless of the number of diseased vessels).

CABG surgery may reduce the composite end point of death, myocardial infarction, or stroke in diabetic patients with extensive multivessel (two- to three-vessel) coronary artery disease compared with medical therapy.

PCI versus Medical Therapy

For the initial management of patients with stable ischemic heart disease, PCI does not reduce the risk of death, myocardial infarction, or other major cardiovascular events when added to optimal medical therapy.

Among patients with medically refractory angina pectoris, PCI is indicated for symptom improvement.

PCI may be indicated in the presence of severe myocardial ischemia, regardless of symptoms. PCI does not appear to improve survival compared with medical treatment among patients with one- or two-vessel disease.

In the absence of symptoms or myocardial ischemia, PCI is not indicated (merely for the presence of an anatomic stenosis).

PCI versus CABG Surgery

For single-vessel disease, PCI and CABG surgery provide excellent symptom relief, but repeated revascularization procedures are required more frequently after PCI. Intracoronary stenting is preferred to regular PCI, but direct comparison with CABG surgery is limited.

For treated diabetic patients with two- or three-vessel disease, CABG surgery is the treatment of choice.

For nondiabetic patients, multivessel PCI and CABG surgery are acceptable alternatives. The choice of PCI or CABG surgery for initial treatment depends primarily on local expertise and the patient's and physician's preferences.

In general, PCI is preferred for patients at low risk and CABG surgery for patients at high risk.

CABG, Coronary artery bypass graft; *PCI*, percutaneous coronary intervention.
From Goldman L, Schafer AI: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Saunders.

- Surgical therapy improves prognosis, particularly in diabetic patients with multivessel disease. Compared with percutaneous coronary intervention (PCI), CABG is more effective in relieving angina and leads to fewer repeated revascularizations but has a higher risk for procedural stroke. Survival to 10 years is similar for both procedures.

Angioplasty and coronary stents (Fig. EA1-76):

- PCI has an established place in treating angina but is not superior to intensive medical therapy to prevent MI and death in symptomatic or asymptomatic patients. Patients selected for PCI should also be candidates for CABG. Approximately 80% of patients show immediate benefit after PCI. The development of coronary stents has increased the number of patients who can be treated in the cardiac laboratory. Cardiac stents (Fig. EA1-77) are currently used in nearly 95% of all patients with PCI lesions. The rate of restenosis is reduced by placing a stent electively in primary atheromatous lesions. The major limitations of stenting are subacute thrombosis, restenosis within the stent, bleeding complications when anticoagulants are used after stenting, and higher cost. The combination of aspirin and thienopyrimidines (P2Y12 antagonists) is effective in preventing coronary stent thrombosis and the duration of therapy depends on whether bare metal stents (BMS) or drug-eluting stents (DES) are used. Duration of dual antiplatelet therapy can be as short as 4 weeks for BMS, but 12 months of therapy is generally required for DES. This difference in duration is due to the lack of endothelium proliferation in DES initially, which confers a higher risk of stent thrombosis than with BMS. New drug-eluting stents with thin struts releasing Limus-family analogs from durable polymers have lowered the risk of stent thrombosis compared with early-generation stents releasing sirolimus or pallitaxel. Current evidence supports the use of drug-eluting stents in most clinical settings without safety concerns (unless there are contraindications to use of dual antiplatelet therapy). Recent data has shown that extending clopidogrel therapy beyond 6 months after stent placement does not reduce death or ischemic events, and it increases the risk of bleeding complications.
- Provide alternative therapies for relief of symptoms in patients with refractory angina. Although some of these therapies may improve symptoms and quality of life, they have not been shown to improve mortality rate.

1. Enhanced external counterpulsation (EECP)
2. Spinal cord stimulation
3. Transmyocardial revascularization (TMR)
4. Implantation of coronary-sinus reducing device: a small clinical trial showed significant improvement in symptoms and quality of life in patients with refractory angina who are not candidates for revascularization.[1]

The following treatments have not shown to be beneficial in reducing cardiovascular risk or improve clinical outcomes: estrogen therapy, vitamin C, vitamin E, and beta-carotene supplementation; treatment of elevated homocysteine with folate or vitamins B_6 and B_{12}; chelation therapy; garlic; coenzyme Q10; selenium; or chromium.

PEARLS & CONSIDERATIONS

COMMENTS

- Although nitrate responsiveness is usually an integral part of a diagnostic strategy for ISHD, recent reports question its value and conclude that in a general population admitted for chest pain, relief of pain after nitroglycerin treatment does not predict active CAD and should not be used to guide diagnosis in the acute care setting.
- CABG is associated with higher long-term survival rates and lower rates of repeat revascularization than PCI and stenting; however, patients often prefer stenting because it is less invasive, involves a shorter hospital stay, and has a lower in-hospital mortality rate.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Angina (Patient Information)
Acute Coronary Syndrome (Related Key Topic)

AUTHORS: **CLAUDIA SERRANO-GOMEZ, M.D.,** and **JUAN A. ESCARFULLER, M.D.**

[1] Verheye S et al: Efficacy of a device to narrow the coronary sinus in refractory angina, *N Engl J Med* 372:519-527, 2015.

EVIDENCE

Abstract[1]

Background:
In patients with suspected coronary heart disease, single-photon emission computed tomography (SPECT) is the most widely used test for the assessment of myocardial ischaemia, but its diagnostic accuracy is reported to be variable and it exposes patients to ionising radiation. The aim of this study was to establish the diagnostic accuracy of a multiparametric cardiovascular magnetic resonance (CMR) protocol with x-ray coronary angiography as the reference standard, and to compare CMR with SPECT, in patients with suspected coronary heart disease.

Methods:
In this prospective trial patients with suspected angina pectoris and at least one cardiovascular risk factor were scheduled for CMR, SPECT, and invasive x-ray coronary angiography. CMR consisted of rest and adenosine stress perfusion, cine imaging, late gadolinium enhancement, and MR coronary angiography. Gated adenosine stress and rest SPECT used 99mTc tetrofosmin. The primary outcome was diagnostic accuracy of CMR. This trial is registered at controlled-trials.com, number ISRCTN77246133.

Findings:
In the 752 recruited patients, 39% had significant CHD as identified by x-ray angiography. For multiparametric CMR the sensitivity was 86.5% (95% CI 81.8 to 90.1), specificity 83.4% (79.5 to 86.7), positive predictive value 77.2%, (72.1 to 81.6) and negative predictive value 90.5% (87.1 to 93.0). The sensitivity of SPECT was 66.5% (95% CI 60.4 to 72.1), specificity 82.6% (78.5 to 86.1), positive predictive value 71.4% (65.3 to 76.9), and negative predictive value 79.1% (74.8 to 82.8). The sensitivity and negative predictive value of CMR and SPECT differed significantly ($p<0.0001$ for both) but specificity and positive predictive value did not ($p=0.916$ and $p=0.061$, respectively).

Interpretation:
CE-MARC is the largest, prospective, real world evaluation of CMR and has established CMR's high diagnostic accuracy in coronary heart disease and CMR's superiority over SPECT. It should be adopted more widely than at present for the investigation of coronary heart disease. Ⓐ

Abstract[2]

Background:
Hypercholesterolemia is a risk factor for coronary artery disease and closely linked to unstable plaque. Hypoadiponectinemia is frequently observed in patients with metabolic syndrome complicated with macroangiopathy and predicts poor clinical outcome. Spectral analysis of intravascular ultrasonography radiofrequency (IVUS-Virtual Histology [VH]) allows quantitative analysis of plaque composition. The purpose of this study was to verify the effects of low-density lipoprotein (LDL) cholesterol level on plaque morphology, and test the hypothesis that adiponectin influences coronary plaque volume and composition.

Methods:
Preintervention IVUS-VH using a continuous pullback was performed in 92 coronary vessels in 92 patients with coronary artery disease. The morphological distribution of plaque was evaluated prospectively in a 60 mm segment of coronary vessels containing the culprit lesion.

Results:
Serum LDL cholesterol levels correlated positively with necrotic core volume ($r = 0.217$, $P = 0.037$) and percent necrotic core tissue ($r = 0.308$, $P = 0.003$), while plasma adiponectin levels correlated negatively with plaque volume ($r = -0.297$, $P = 0.004$) and necrotic core volume ($r = -0.306$, $P = 0.003$). Multiple regression analyses showed close association between necrotic core volume and statin-use ($\beta = -21.68$, $P = 0.004$) and adiponectin levels ($\beta = -31.25$, $P=0.038$), and that percent necrotic core tissue was influenced by statin-use ($\beta = -4.595$, $P = 0.026$) and LDL cholesterol levels ($\beta = 0.092$, $P = 0.031$).

Conclusion:
Adiponectin is closely linked to coronary plaque volume. Hypercholesterolemia and hypoadiponectinemia correlate with necrotic core lesions and may contribute to increased risk of coronary plaque vulnerability. Statins can effectively prevent necrotic core plaque formation associated with hypercholesterolemia and hypoadiponectinemia. Ⓐ

Abstract[1]

Background:
Endothelial dysfunction and injury are thought to play an important role in the progression of coronary artery disease (CAD). High density lipoprotein from healthy subjects (HDLHealthy) has been proposed to exert endothelial antiapoptotic effects that may represent an important antiatherogenic property of the lipoprotein. The present study therefore aimed to compare effects of HDLCAD and HDLHealthy on the activation of endothelial anti- and proapoptotic pathways and to determine which changes of the lipoprotein are relevant for these processes.

Methods and Results:
HDL was isolated from patients with stable CAD (HDLsCAD), an acute coronary syndrome (HDLACS), and healthy subjects. HDLHealthy induced expression of the endothelial antiapoptotic Bcl-2 protein Bcl-xL and reduced endothelial cell apoptosis in vitro and in apolipoprotein E–deficient mice in vivo. In contrast, HDLsCAD and HDLACS did not inhibit endothelial apoptosis, failed to activate endothelial Bcl-xL, and stimulated endothelial proapoptotic pathways, in particular, p38-mitogenactivated protein kinase–mediated activation of the proapoptotic Bcl-2 protein tBid. Endothelial antiapoptotic effects of HDLHealthy were observed after inhibition of endothelial nitric oxide synthase and after delipidation, but not completely mimicked by apolipoprotein A-I or reconstituted HDL, suggesting an important role of the HDL proteome. HDL proteomics analyses and subsequent validations and functional characterizations suggested a reduced clusterin and increased apolipoprotein C-III content of HDLsCAD and HDLACS as mechanisms leading to altered effects on endothelial apoptosis.

Conclusions:
The present study demonstrates for the first time that HDLCAD does not activate endothelial antiapoptotic pathways, but rather stimulates potential endothelial proapoptotic pathways. HDL-proteome remodeling plays an important role for these altered functional properties of HDL. These findings provide novel insights into mechanisms leading to altered vascular effects of HDL in coronary disease. Ⓐ

Evidence-Based References

Greenwood JP, et al.: Cardiovascular magnetic resonance and single-photon emission computed tomography for diagnosis of coronary heart disease (CE-MARC): a prospective trial, *Lancet* 379:453–460, 2012. Ⓐ

Kojima S, et al.: Hypercholesterolemia and hypoadiponectinemia are associated with necrotic core-rich coronary plaque, *Int J Cardiol* 147:371–376, 2011. Ⓐ.

SUGGESTED READINGS

Abraham NS et al.: ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of PPIs and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the GI risks of antiplatelet therapy and NSAID use, *J Am Coll Cardiol* 56:2051, 2010.

Criqui HM et al.: Calcium density of coronary artery plaque and risk of incident cardiovascular events, *JAMA* 311(3):271–278, 2013.

C.U.R.R.E.N.T.-O.A.S.I.S. 7 investigators: Dose comparisons of clopidogrel and aspirin in acute coronary syndromes, *N Engl J Med* 363:930–942, 2010.

Fox K et al.: Guidelines on the management of stable angina pectoris: Executive summary, The Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology, *Eur Heart J* 27:1341–1381, 2006.

Go AS, Mozaffarian D, Roger VL, et al.: Heart disease and stroke statistics–2013 update: a report from the American Heart Association, *Circulation* 127:e6–e245, 2013.

Gibbons RJ et al.: ACC/AHA guideline update for the management of patients with chronic stable angina, *J Am Coll Cardiol* 107:149–158, 2003.

Greenland P et al.: ACCF/AHA 2007. Clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain, *J Am Coll Cardiol* 49:378–402, 2007.

Hilas O: Ranolazine for chronic angina, *Am Fam Physician* 75:544, 2007.

Hlatky MA et al.: Comparative effectiveness of multivessel coronary bypass surgery and multivessel percutaneous coronary intervention, *Ann Int Med* 158:727–736, 2013.

Kim LK et al.: Rate of percutaneous coronary intervention for the management of acute coronary syndromes and stable coronary artery disease in the United States (2007 to 2011), *Am J Cardiol* 114:1003–1010, 2014.

Polonsky T et al.: Coronary artery calcium score and risk classification for coronary heart disease prediction, *JAMA* 303(160):1610–1616, 2010.
Serruys PW et al.: Percutaneous coronary interventions versus coronary-artery bypass for severe coronary artery disease, *N Engl J Med* 360:961–972, 2009.
Sipahi I et al.: Coronary artery bypass grafting vs percutaneous coronary intervention and long-term mortality and morbidity in multivessel disease, *JAMA* 174(2):223–230, 2014.
Smith SC et al.: AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update, *Circulation* 113:2363, 2006.
Snow V et al.: Evaluation of primary care patients with chronic stable angina: guidelines from the American College of Physicians, *Ann Intern Med* 141: 57–64, 2004.
Stefanini GG, Holmes DR Jr: Drug-eluting coronary-artery stents, *N Engl J Med* 368:254–265, 2013.
Stone GW, Aronow HD: Long-term care after percutaneous coronary intervention: focus on the role of antiplatelet therapy, *Mayo Clin Proc* 81(5):641, 2006.
Valgimigli M et al.: Short- versus long-term duration of dual anti-platelet therapy after coronary stenting: a randomized multicenter trial, *Circulation* 125:2015–2026, 2012.

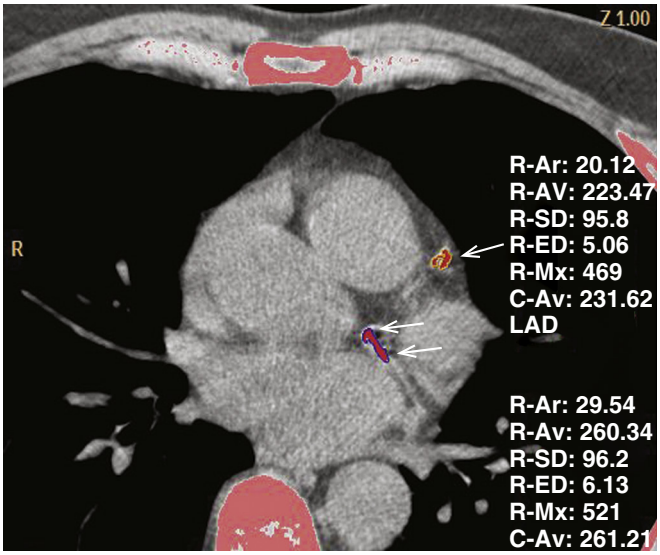


FIGURE EA1-74 Example of coronary artery calcium scoring in which calcified foci are identified within the left anterior descending (orange; single arrow) and left circumflex (pink outlined in blue; double arrow) coronary arteries. The region's area (R-Ar) and its average density in Hounsfield units (R-Av) are displayed and used in the area-density calcium scoring calculation. (From Bonow RO et al: *Heart disease,* ed 9, Philadelphia, 2012, Saunders.)

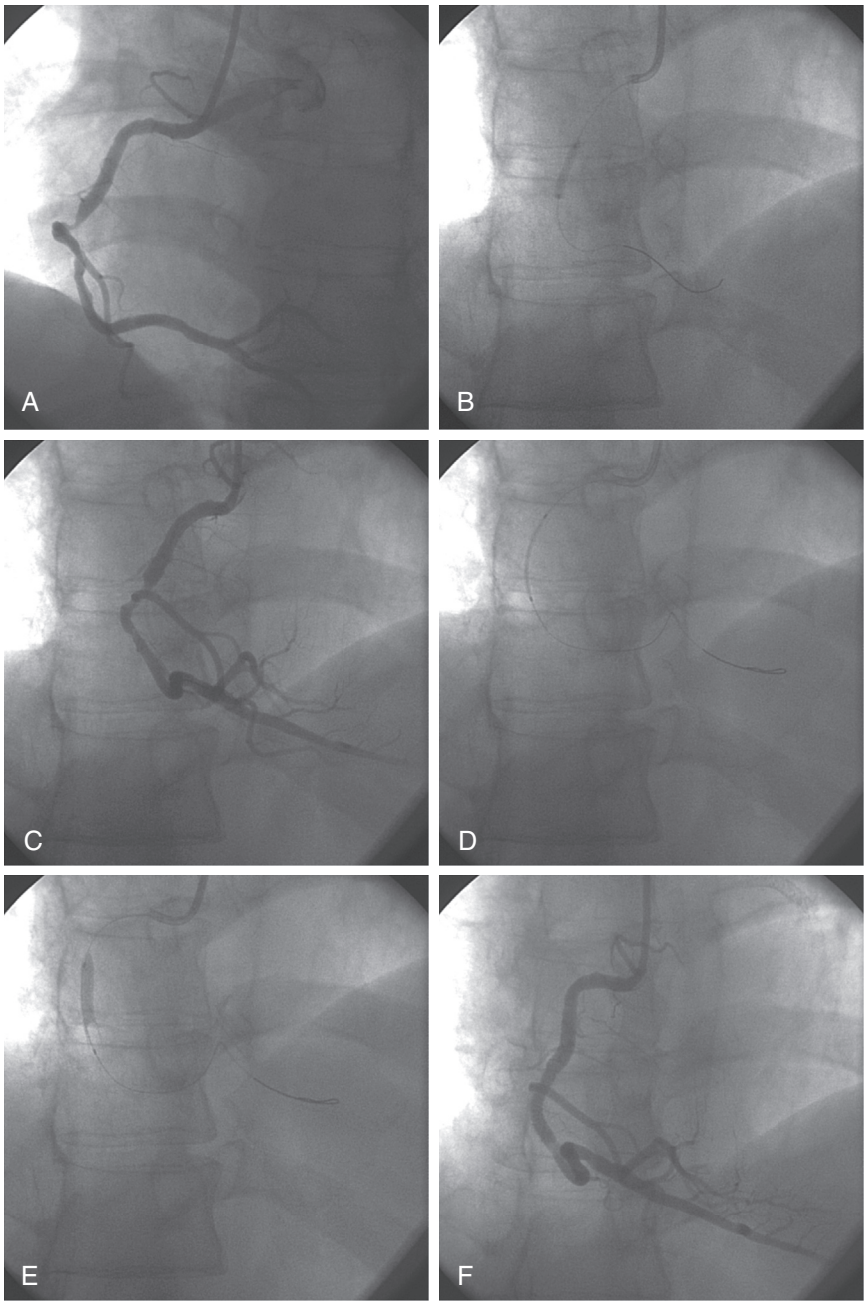


FIGURE EA1-76 Coronary angioplasty procedure. **A,** Critical stenosis in midsegment of a right coronary artery. **B,** Inflation of a 3.5-mm-diameter angioplasty balloon. **C,** Anglographic control after balloon inflation. **D,** Placement of a 3.5-mm-diameter, 18-mm-long metal stent. **E,** Inflation of the balloon. **F,** Final result. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

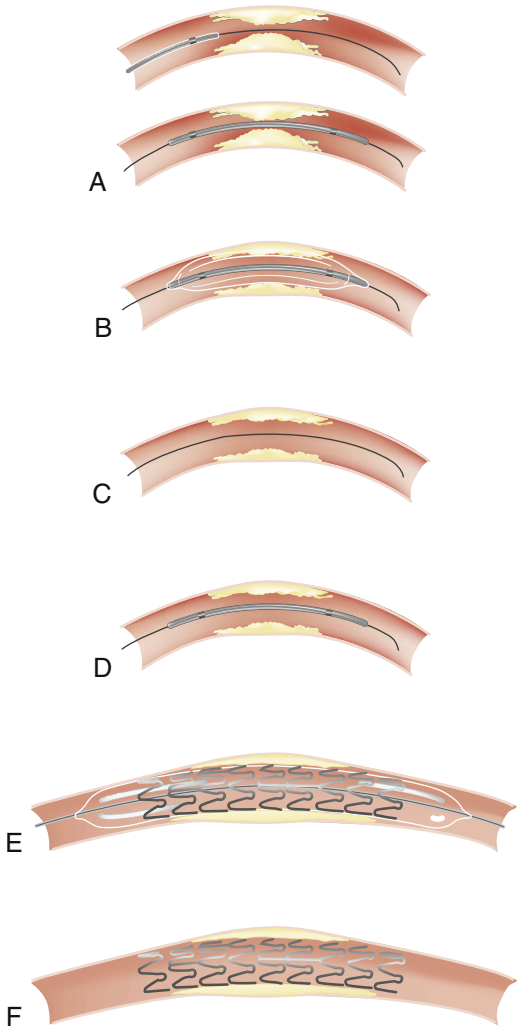


FIGURE EA1-77 Implantation of a coronary stent. **A,** Placement of balloon catheter. **B,** Predilation with balloon catheter. **C,** Balloon is withdrawn. **D,** Placement of coronary stent, which has been crimped on a balloon catheter. **E,** Inflation of balloon and expansion of stent. **F,** Withdrawal of balloon catheter and final result. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

- The mucocutaneous swelling caused by the release of vasoactive mediators is called urticaria and angioedema.
- Urticaria causes edema of the superficial dermis.
- Angioedema involves the deep layers of the dermis and the subcutaneous tissue.

SYNONYMS

Angioneurotic edema
HAE (hereditary angioedema)

ICD-9CM CODES
995.1 Angioedema (allergic)
277.6 Angioedema (hereditary)
ICD-10CM CODES
T78.3 Angioedema
D84.1 Angioedema, hereditary

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 100 to 3000/100,000 persons (for urticaria and angioedema)
LIFETIME PREVALENCE: Approximately 20% of the population experiences urticaria and/or angioedema at some time during life. The prevalence of hereditary angioedema is 1 case per 50,000 persons.
DEMOGRAPHICS:
Race: Slightly more common among African Americans.
Sex: More occurrences in women than men.
Angioedema commonly occurs after adolescence in the third decade of life.
Angioedema can occur together with urticaria (40%) or alone (20%); the remaining 40% have urticaria alone.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Angioedema may be acute or chronic.
  1. Acute angioedema is defined as symptoms lasting 6 wk.
  2. Chronic angioedema is defined as symptoms lasting >6 wk.
- Urticaria is commonly known as "hives" and is:
  1. Pruritic
  2. Palpable and well demarcated
  3. Erythematous
  4. Millimeters to centimeters in size
  5. Multiple in number
  6. Fades within 12 to 24 hr
  7. Reappears at other sites
- Angioedema is characterized by the following:
  1. Nonpruritic
  2. Burning
  3. Not well demarcated
  4. Involves eyelids (Fig. A1-78), lips, tongue, and extremities
  5. Can involve the upper airway, causing respiratory distress
  6. Can involve the gastrointestinal tract, leading to cyclic abdominal pain, nausea, vomiting, and diarrhea
  7. Resolves slowly

ETIOLOGY

- Angioedema, with or without urticaria, is classified as acquired (allergic or idiopathic) or hereditary.
- Angioedema is primarily caused by mast cell activation and degranulation with release of vasoactive mediators (e.g., histamine, serotonin, bradykinins), resulting in postcapillary venule inflammation, vascular leakage, and edema in the deep layers of the dermis and subcutaneous tissue.
- Pathologically, angioedema has both immunologic- and nonimmunologic-mediated mechanisms.
  1. Immunoglobulin E–mediated angioedema may result from antigen exposure (e.g., foods [milk, eggs, peanuts, shellfish, tomatoes, chocolate, sulfites] or drugs [penicillin, aspirin, nonsteroidal anti-inflammatory drugs, phenytoin, sulfonamides, recombinant tissue plasminogen activator]).
  2. Complement-mediated angioedema involving immune complex mechanisms can also lead to mast cell activation that manifests as serum sickness.
  3. Hereditary angioedema is an autosomal-dominant disease caused by a deficiency of or mutation in C1 esterase inhibitor (C1-INH). C1-INH is a protease inhibitor normally present in high concentrations in the plasma. C1-INH serves many functions, one of which is to inhibit plasma kallikrein, a protease that cleaves kininogen and releases bradykinin. Deficient C1-INH activity results in excess concentration of kininogen and the subsequent release of kinin mediators.
  4. Acquired angioedema is usually associated with other diseases, most commonly B-cell lymphoproliferative disorders, but may also result from the formation of autoantibodies directed against C1 inhibitor protein.
  5. Other causes of angioedema include infection (e.g., herpes simplex, hepatitis B, Coxsackie A and B, *Streptococcus, Candida, Ascaris,* and *Strongyloides*), insect bites and stings, stress, physical factors (e.g., cold, exercise, pressure, and vibration), connective tissue diseases (e.g., systemic lupus erythematosus, Henoch-Schönlein purpura), and idiopathic causes. Angiotensin-converting enzyme (ACE) inhibitors can increase kinin activity and lead to angioedema.

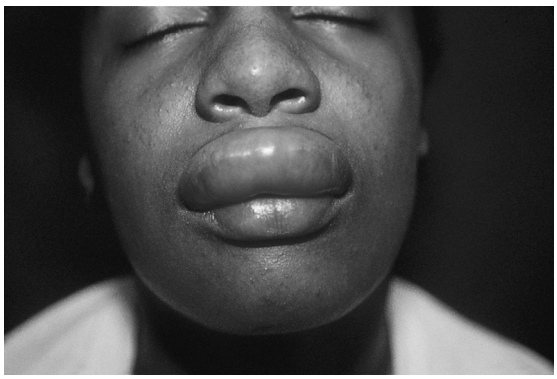


FIGURE A1-78 Angioedema of the upper lip, with severe swelling of deeper tissues. (From Goldstein BG, Goldstein AO: *Practical dermatology,* ed 2, St Louis, 1997, Mosby.)

DIAGNOSIS

A detailed history and physical examination usually establish the diagnosis of angioedema. Extensive laboratory testing is of limited value.

DIFFERENTIAL DIAGNOSIS

- Cellulitis
- Arthropod bite
- Hypothyroidism
- Contact dermatitis
- Atopic dermatitis
- Mastocytosis
- Granulomatous cheilitis
- Bullous pemphigoid
- Urticaria pigmentosa
- Anaphylaxis
- Erythema multiforme
- Epiglottitis
- Peritonsillar abscess

WORKUP

- An extensive workup searching for the cause of angioedema is often unrevealing (90%).
- Workup, including diagnostic blood tests and allergy testing, is performed according to results of the history and physical examination.

LABORATORY TESTS

- Complete blood count, erythrocyte sedimentation rate, and urinalysis are sometimes helpful as part of the initial evaluation.
- Stools for ova and parasites.
- Serology testing.
- C4 levels are usually reduced in acquired and hereditary angioedema (occurring without urticaria). If C4 levels are low, C1-INH levels and activity should be obtained. There are isolated reports of hereditary angioedema with normal C4 levels but reduced C1-INH levels.

- Skin and radioallergosorbent testing may be done if food allergies are suspected.
- Skin biopsy is usually done in patients with chronic angioedema refractory to corticosteroid treatment.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Eliminate the offending agent
- Avoid triggering factors (e.g., cold, stress)
- Cold compresses to affected areas

ACUTE GENERAL Rx

- Acute life-threatening angioedema involving the larynx is treated with:
  1. Epinephrine 0.3 mg in a solution of 1:1000 given SC
  2. Diphenhydramine 25 to 50 mg IV or IM
  3. Cimetidine 300 mg IV or ranitidine 50 mg IV
  4. Methylprednisolone 125 mg IV
- Mainstay therapy in nonhereditary angioedema is H_1 antihistamines
  1. Diphenhydramine 25 to 50 mg q6h
  2. Chlorpheniramine 4 mg q6h
  3. Hydroxyzine 10 to 25 mg q6h
  4. Cetirizine 5 to 10 mg qd
  5. Loratadine 10 mg qd
  6. Fexofenadine 60 mg qd
- H_2 antihistamines can be added to H_1 antihistamines
  1. Ranitidine 150 mg bid
  2. Cimetidine 400 mg bid
  3. Famotidine 20 mg bid
- Tricyclic antidepressants
  1. Doxepin 25 to 50 mg qd
- Corticosteroids are rarely required for symptomatic relief of acute angioedema.
- Antihistamines are probably ineffective in acute hereditary angioedema.
- Purified plasma-derived C1-INH replacement therapy is effective and safe in treating acute attacks of hereditary angioedema caused by C1 inhibitor deficiency. Cost is a limiting factor. Acute attacks can be managed with plasma-derived or recombinant preparations of C1 inhibitor, with ecallantide, a specific plasma kallikrein inhibitor, or with the use of the B2 bradykinin-receptor antagonist icatibant.

CHRONIC Rx

- Chronic angioedema is treated as described under "Acute General Rx." Fig. A1-79 describes a therapeutic algorithm for chronic angioedema
- Corticosteroids are used more often in chronic nonhereditary angioedema.
- Prednisone 1 mg/kg/day for 5 days and then tapered over a period of weeks.
- Androgens (danazol, stanozolol, oxandrolone, methyltestosterone) and antifibrinolytic agents can be used for the treatment of chronic hereditary angioedema, which does not respond to antihistamines or corticosteroids but are associated with many adverse effects. Long-term prophylaxis with plasma-derived C1 inhibitor is safe and effective and may be used in patients who have frequent or severe attacks. Cost is a limiting factor. C1-INH replacement therapy was approved by the FDA in 2008. Available agents are Cinryze and Berinert. Icatibant is a new bradykinin-receptor antagonist in hereditary angioedema currently undergoing trials. A recent phase 2 study among patients with ACE-inhibitor–induced angioedema revealed that the time to complete resolution of edema was significantly shorter with icatibant than with combination therapy with a glucocorticoid and an antihistamine.[1]

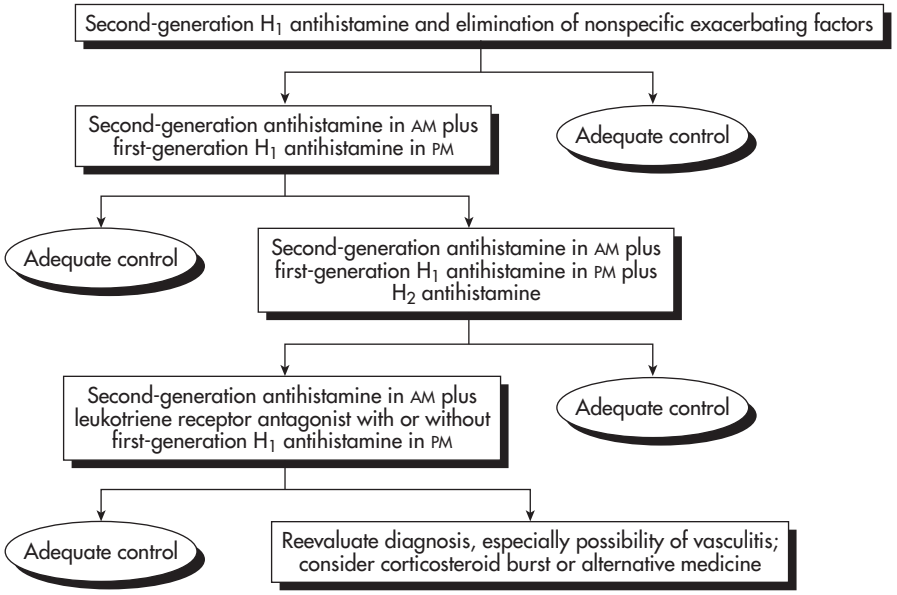


FIGURE A1-79 Therapeutic algorithm for chronic urticaria/angioedema. (From Leung D, Sampson H, Geha R, Szefler S: Pediatric Allergy: Principles and Practice, Chapter 55, 2010, Saunders, p 575-584.)

DISPOSITION

- Antihistamines achieve symptomatic relief in more than 80% of patients with nonhereditary acute angioedema.
- In chronic nonhereditary angioedema, corticosteroids are given in addition to antihistamines.
- A small percentage of people will have recurrence of symptoms after steroid treatment.
- Chronic angioedema can last for months and even years.

REFERRAL

Dermatology consultation is recommended in patients with chronic angioedema, hereditary angioedema, and recurring angioedema.

PEARLS & CONSIDERATIONS

ACE inhibitors can cause angioedema up to many months after initiation. There are multiple case reports and case series of angiotensin receptor blocker (ARB)–induced angioedema, although the risk is substantially less than that of ACE inhibitors. (Incidence rates per 1000 person-years are 4.38 cases for ACE inhibitors, 1.66 cases for ARBs.) The incidence rate is also very high for the direct renin inhibitor aliskiren (4.67).

COMMENTS

- Identifying a cause for angioedema in patients is often difficult and met with frustration.
- Chronic angioedema, unlike acute angioedema, is rarely caused by an allergic reaction.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Angioedema (Patient Information)

AUTHOR: **MEL L. ANDERSON, M.D.**

[1] Bas M et al.: A randomized trial of icatibant in ACE-inhibitor–induced angioedema, *N Engl J Med* 372: 418-425, 2015.

SUGGESTED READINGS

Baxi S, Dinakar C: Urticaria and angioedema, *Immunol Allergy Clin North Am* 25(2):353, 2005.

Bork K, Hardt J: Hereditary angioedema: increased number of attacks after frequent treatments with C1 inhibitor concentrate, *Am J Med* 122:780–783, 2009.

Bowen T et al.: Hereditary angioedema: a current state-of-the-art review, VII: Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema, *Ann Allergy Asthma Immunol* 100(1 suppl 2):S30–40, 2008.

Cicardi M et al.: Ecallantide for the treatment of acute attacks in hereditary angioedema, *N Engl J Med* 363:523–531, 2010.

Cicardi M et al.: Icatibant, a new bradykinin-receptor antagonist in hereditary angioedema, *N Engl J Med* 363:532–541, 2010.

Frigas E, Park M: Idiopathic recurrent angioedema, *Immunol Allergy Clin North Am* 26(4):739, 2006.

Morgan BP: Hereditary angioedema: therapies old and new, *N Engl J Med* 363:581–583, 2010.

Temiño VM, Peebles Jr RS: The spectrum and treatment of angioedema, *Am J Med* 121:282–286, 2008.

Toh S et al.: Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system, *Arch Intern Med* 172:1582–1588, 2012.

Tse K, Zuraw BL: Recognizing and managing hereditary angioedema, *Cleve Clin J Med* 80:297–308, 2013.

Zuraw BL et al.: Hereditary angioedema, *N Engl J Med* 359:1027–1036, 2008.

BASIC INFORMATION

DEFINITION

Ankle fractures involve the lateral, medial, or posterior malleolus of the ankle and may occur either alone or in some combination. Associated ligamentous injuries are included.

CLASSIFICATION

The Danis-Weber (Fig. A1-80) and Lauge-Hensen classifications of ankle fractures are described in Table A1-53.

ICD-9CM CODES

824.8 Ankle fracture (malleolus) (closed)
824.2 Lateral malleolus fracture (fibular)
824.0 Medial malleolus fracture (tibial)

ICD-10CM CODES

S82.899A Other fracture of unspecified lower leg, initial encounter for closed fracture
S82.63XA Displaced fracture of lateral malleolus of unspecified fibula, initial encounter for closed fracture
S82.53XA Displaced fracture of medial malleolus of unspecified tibia, initial encounter for closed fracture

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Deformity usually depends on extent of displacement
- Pain, tenderness, and hemorrhage at the site of injury

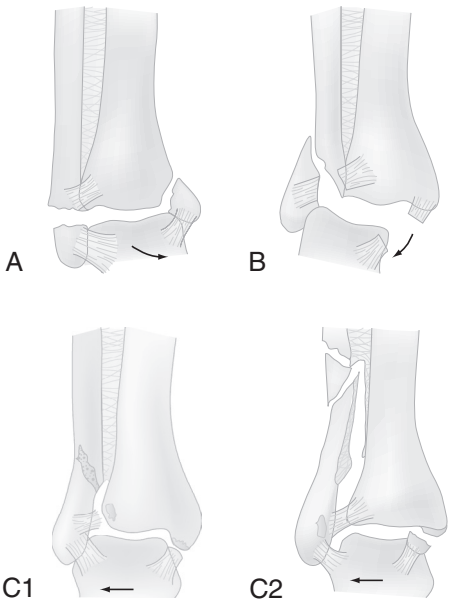


FIGURE A1-80 The Danis-Weber classification of ankle fractures focuses on the location of the fibular fracture in relation to the tibiotalar joint. (From Wilson FC: The pathogenesis and treatment of ankle fractures: classification. In Green WB [ed]: *Instructional course lectures,* ed 39, Easton, PA, 1990, American Academy of Orthopedic Surgeons.)

- Gentle palpation of ligamentous structures (especially deltoid ligament) to determine the extent of soft tissue injury
- Evaluation of distal neurovascular status; results recorded

ETIOLOGY

- The ankle depends on its ligamentous and bony support for stability. The joint, or *mortise,* is an inverted U with the dome of the talus fitting into the medial and lateral malleoli. The posterior margin of the tibia is often called the *third* or *posterior malleolus.*
- Most common ankle fractures are the result of eversion or lateral rotation forces on the talus (in contrast with common sprains, which are usually caused by inversion).

DIAGNOSIS

The diagnosis is usually established on the basis of the nature of the injury, the presence of typical findings of bony tenderness with swelling, and abnormal imaging studies.

DIFFERENTIAL DIAGNOSIS

- Ankle sprain
- Avulsion fracture of hindfoot or metatarsal

IMAGING STUDIES

Standard AP and lateral views (Fig. A1-81) accompanied by an AP taken 15 degrees internally rotated. The last view is taken to properly visualize the mortise.

TREATMENT

All fractures: elevation and ice to control swelling for 48 to 72 hr.

ACUTE GENERAL Rx

- Clinical and roentgenographic assessment of the status of the ankle mortise and stability of the injury is mandatory to determine treatment.
- There is potential for displacement if both sides of the joint are significantly injured (e.g., fracture of the lateral malleolus with deltoid ligament injury).

TABLE A1-53 Classifications and Treatment of Ankle Fractures

	Normal	Abnormal
Talocrural angle—angle formed by parallel line to distal tibial articular surface and line connecting malleolar tips	**8-15 degrees** (or 83 degrees ± 4 degrees if perpendicular used)	> 2-3 degrees difference from contralateral = **fibular shortening**
Medial clear space—distance between lateral border of medial malleolus and lateral border of talus	< **4 mm** and equal to superior clear space	> 4 mm = lateral talar shift and **instability**
Tibiofibular clear space—distance between medial wall of fibula and tibial incisura	< **6 mm** on AP and mortise views	> 6 mm = **syndesmotic disruption (instability)**
Talar tilt—difference between medial and lateral superior clear space measurements	< **2 mm**	> 2 mm = **instability**

Classification:

1. **Danis-Weber**—based on location of fibular fracture
   A. Below syndesmosis
   B. At level of syndesmosis
   C. Above syndesmosis

1. **Lauge-Hansen**—based on position of foot and deforming force
   Supination external rotation—most common
   Supination adduction
   Pronation external rotation
   Pronation abduction

Treatment: Surgical decisions mostly based on stability.

Stable	Unstable
Isolated lateral malleolar fractions if:	**Lateral malleolus fractures** if:
Below syndesmosis	Medial injury/tenderness (bimalleolar equivalent)
No medial ligament injury or talar shift	Talar shift
Displacement < 5 mm	Above syndesmosis
No shortening	Shortened or displaced > 5 mm
Isolated medial malleolus fractures (although 5%-15% nonunion rates have been reported)	**Bimalleolar fractures** **Trimalleolar fractures** (fix posterior if > 25% of articular surface)
	Maisonneuve fractures

From Parvizi J: *High-yield orthopedics,* Philadelphia, 2010, Saunders.

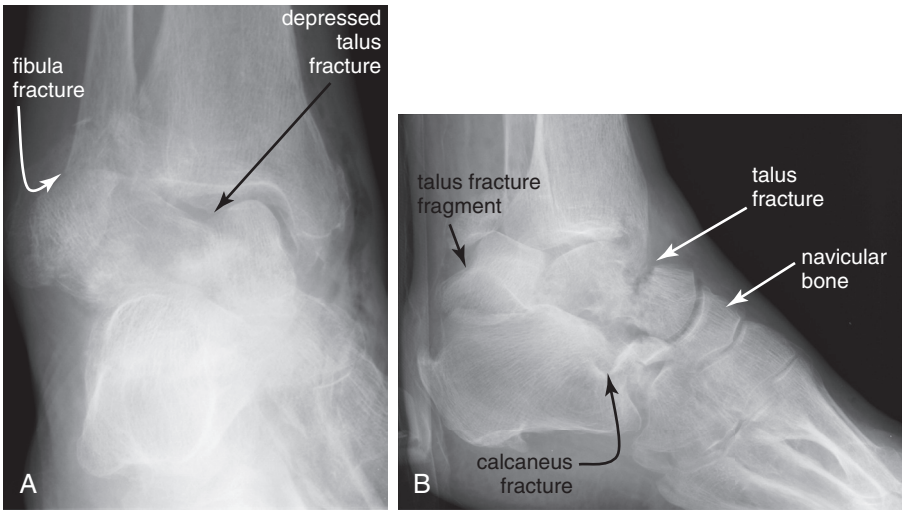


FIGURE A1-81 **A**, Anterior-posterior view. **B,** Lateral view. A depressed talus fracture is visible. In **B,** this fracture is seen to run through the midbody of the talus. **A** also demonstrates a distal fibula fracture, whereas in **B,** a calcaneal fracture is seen. The patient underwent CT to characterize these fractures further. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

- Deviation of the position of the talus in the mortise could lead to traumatic arthritis.
- If there is no widening of the ankle mortise, many injuries can be safely treated with simple casting without reduction:
  1. Undisplaced or avulsion fractures of either malleolus below the ankle joint line:
     a. Stability of the joint is not compromised and a short leg walking cast or ankle support is sufficient.
     b. Weight bearing is allowed as tolerated.
     c. In 4 to 6 wk, protection may be discontinued.
  2. Isolated undisplaced fractures of the medial, lateral, or posterior malleolus:
     a. Usually stable and require only the application of a short leg walking cast with the ankle in the neutral position or fracture cast boot.
     b. Immobilization should be continued for 8 wk.
     c. Fracture line of lateral malleolus may persist roentgenographically for several months, but immobilization beyond 8 wk is usually unnecessary.
     d. Undisplaced bimalleolar fractures are treated with a long leg cast flexed 30 degrees at the knee to prevent motion and displacement of the fracture fragments. In 4 wk, a short leg walking cast may be applied for an additional 4 wk.
  3. Isolated fractures of the lateral malleolus that are slightly displaced:
     a. May be treated with casting if no medial injury is present.
     b. A below-knee walking cast is applied with ankle in the neutral position; weight bearing is allowed as tolerated.
     c. Six wk of immobilization is sufficient.
     d. If medial tenderness is present, suggesting deltoid ligament rupture, a carefully molded cast may suffice if weight bearing is not allowed and the patient is followed up closely for signs of instability, especially after swelling recedes. If significant widening of the medial ankle mortise (increase in the "medial clear space") develops as a result of lateral displacement of the talus, referral for possible reduction is indicated.
     e. If signs of instability are already present at initial examination (widening of the medial clear space with medial tenderness), referral is indicated.
  4. Undisplaced fracture of the distal fibular epiphysis:
     a. Often diagnosed clinically.
     b. There is tenderness over the epiphyseal plate.
     c. Roentgenographic findings are often negative.
     d. A short leg walking cast or fracture boot is applied for 4 wk.
     e. Growth disturbance is rare.
  5. Isolated posterior malleolar fractures involving less than 25% of the joint surface on the lateral roentgenogram:

Safely treated by applying a short leg walking cast or fracture brace. (Fractures involving >25% of the weight-bearing surface should be referred because of the potential for instability and subsequent traumatic arthritis.)

CHRONIC Rx

- Early motion is encouraged through a home exercise program.
- Protection from reinjury is appropriate for 4 to 6 wk after cast or brace removal.
- Temporary increase in lower extremity swelling that frequently occurs after short leg cast removal may benefit from the use of support hose.

DISPOSITION

Significant factors involved in the development of traumatic arthritis:

- Amount of joint trauma at the time of injury
- Eventual position of the talus in the mortise

Fracture nonunion is uncommon unless displacement is significant.

REFERRAL

Orthopedic consultation for:

- Unstable ankle joint
- Widened ankle mortise
- Posterior malleolar fracture over 25% of joint with incongruity
- Marked displacement of fracture fragment

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Ankle Fracture (Patient Information)
Ankle Sprain (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

The aim of this literature review is to systematically gather the highest level of available evidence on the long-term outcome after operatively treated ankle fractures in the English, German and Dutch literature. A search term with Boolean operators was constructed. The search was limited to humans and adults and the major databases were searched from 1966 to 2008 to identify studies relating to functional outcome, subjective outcome and radiographic evaluation at least 4 years after an operatively treated ankle fracture. Of the 42 initially relevant papers, 18 met our inclusion criteria. A total of 1822 fractures were identified. The mean sample-size weighted follow-up was 5.1 years. The initial number of patients that were included in the studies was 2724, which results in a long-term follow-up success rate of 66.9%. Regarding the fracture reduction we found 4 papers reporting on 106 fractures. Of the fractures that were classified according to Danis–Weber, 736 were eligible for correlation with the long-term outcome. In 442 fractures a comparison was possible between supination-external rotation stage 2 and 4 of the Lauge-Hansen classification. Only one study reported on the influence of initial cartilage lesions on the outcome. Regarding the involvement of the posterior malleolus, two studies reported on the long-term outcome. None of the studies addressed the influence of hindfoot varus or valgus on the long-term outcome after ankle fracture. Only 79.3% of the optimally reduced fractures show good to excellent long-term outcome. The Weber A type fractures do not show a better long-term outcome than Weber B type fractures. Recommendations for future research were formulated. Ⓐ

Abstract[2]

Background:

Biodegradable implants for internal fixation of ankle fractures may overcome some disadvantages of metallic implants, such as imaging interference and the potential need for additional surgery to remove the implants. The purpose of this study was to evaluate the outcomes after fixation of ankle fractures with biodegradable implants compared with metallic implants.

Methods:

In this prospectively randomized study, 109 subjects with an ankle fracture underwent surgery with metallic (Group I) or biodegradable implants (Group II). Radiographic results were assessed by the criteria of the Klossner classification system and time to bone union. Clinical results were assessed with use of the American Orthopaedic Foot & Ankle Society (AOFAS) ankle-hindfoot scale, Short Musculoskeletal Function Assessment (SMFA) dysfunction index, and the SMFA bother index at three, six, and twelve months after surgery.

Results:

One hundred and two subjects completed the study. At a mean of 19.7 months, there were no differences in reduction quality between the groups. The mean operative time was 30.2 minutes in Group I and 56.4 minutes in Group II ($P < .001$). The mean time to bone union was 15.8 weeks in Group I and 17.6 weeks in Group II ($P = .002$). The mean AOFAS score was 87.5 points in Group I and 84.3 points in Group II at twelve months after surgery ($P = .004$). The mean SMFA dysfunction index was 8.7 points in Group I and 10.5 points in Group II at twelve months after surgery ($P = .060$). The mean SMFA bother index averaged 3.3 points in Group I and 4.6 points in Group II at twelve months after surgery ($P = .052$). No difference existed between the groups with regard to clinical outcomes for the subjects with an isolated lateral malleolar fracture.

Conclusions:

The outcomes after fixation of bimalleolar ankle fractures with biodegradable implants were inferior to those after fixation with metallic implants in terms of the score on the AOFAS scale and time to bone union. However, the difference in the final AOFAS score between the groups may not be clinically important. The outcomes associated with the use of biodegradable implants for the fixation of isolated lateral malleolar fractures were comparable with those for metallic implants. Ⓐ

Abstract[3]

Foot and ankle

Risk factors for posttraumatic synostosis and outcomes following operative treatment of ankle fractures.

Background:

Distal tibiofibular synostosis is a known but poorly described complication of ankle fractures. The objective of this study was to evaluate the relationship between ankle fracture fixation method and other risk factors in the development of synostosis in posttraumatic operative ankle fractures. Outcomes of patients with no synostosis, incomplete bony bridging, or complete synostosis also were compared.

Methods:

All operative ankle fractures from a single surgeon's prospectively collected clinical database were evaluated for the presence of distal tibiofibular synostosis not earlier than 3 months postoperatively. All fractures were treated in a fracture-specific and ligament-specific fashion. Syndesmotic screws, when used, were routinely removed no sooner than 4 months after operation. Patient demographic and medical history data as well as injury and fixation profile were evaluated. Incidence of complications was also reviewed. Foot and ankle outcome score (FOAS) and a range of motion (ROM) were compared between the groups.

Results:

Of the 564 ankle fractures included in the study, 91 demonstrated complete synostosis and 46 demonstrated incomplete bony bridging. Multivariate analysis revealed male sex (odds ratio [OR] = 2.82, $P<0.001$). Syndesmotic screw fixation (OR = 2.46, $P<0.001$), and tibiotalar dislocation (OR = 1.74, $P < 0.032$) to remain significant independent risk factors for the development of incomplete bony bridging or complete synostosis while adjusting for confounding risk factors. Ankles with synostosis also demonstrated significant reduction in dorsiflexion ($P < 0.017$), plantarflexion ($P < 0.024$), and inversion ($P < 0.001$), though patient-reported outcome measures were equivalent with patients without synostosis.

Conclusion:

Syndesmotic screw fixation, male sex, and tibiotalar dislocation were significant risk factors in the formation of postoperative distal tibiofibular synostosis, though patient-reported outcome measures seemed equivalent among patients with and without synostosis. This large cohort study focuses on the issue of synostosis as a complication of ankle fracture treated with open reduction and internal fixation. Treating surgeons have wondered about the functional significance of this complication, and it appears that it is negligible. The association with screw fixation may simply be related to the fact that screws were used for the most significant disruptions of the syndesmosis. The association with dislocation seems self-explanatory, and the association with male sex likely relates to higher energy injuries in this population. The fact that there is no functional significance is reassuring to the orthopedic community. Ⓐ

Evidence-Based Reference

Stufkens SAS, et al.: Long-term outcome after 1822 operatively treated ankle fractures: a systematic review of the literature, *Injury* 42:119–127, 2011. Ⓐ

Noh JH, et al.: Outcomes of operative treatment of unstable ankle fractures: a comparison of metallic and biodegradable implants, *J Bone Joint Surg Am* 94:e166.1–e166.7, 2012. Ⓐ

Hinds RM, Lazaro LE, Burket JC, et al.: Risk factors for posttraumatic synostosis and outcomes following operative treatment of ankle fractures, *Foot Ankle Int* 35:141–147, 2014. Ⓐ

SUGGESTED READINGS

Chaudhary SB, et al.: Complications of ankle fracture in patients with diabetes, *J Am Acad Orthop Surg* 16:159, 2008.

Egol KA, et al.: Predictors of short-term functional outcome following ankle fracture surgery, *J Bone Joint Surg Am* 88A:974, 2006.

Haraguchi N, et al.: Pathoanatomy of posterior malleolar fractures of the ankle, *J Bone Joint Surg Am* 88A:1085, 2006.

Leontaritis N, et al.: Arthroscopically deleted intraarticular lesions associated with acute ankle fractures, *J Bone Joint Surg Am* 9:333, 2009.

Park JC, Laurin TM: Acute syndesmosis injuries associated with ankle fractures: current perspectives in management, *Bull NYU Hosp Jt Dis* 67:39, 2009.

Schnetzler KA, Hoernschemeyer D: The pediatric triplane fracture, *J Am Acad Orthop Surg* 15:738, 2007.

Tejwani NC, et al.: Are outcomes of bimalleolar fractures poorer than those of lateral malleolar fractures with medial ligamentous injury? *J Bone Joint Surg Am* 89:1438, 2007.

BASIC INFORMATION

DEFINITION

An ankle sprain is an injury to the ligamentous support of the ankle. Most (85%) involve the lateral ligament complex (Fig. A1-82). The anterior inferior tibiofibular (AITF) ligament, deltoid ligament, and interosseous membrane may also be injured. Damage to the tibiofibular syndesmosis is sometimes called a *high sprain* because of pain above the ankle. Lateral ankle sprains classically are graded I, II, or III, representing no, partial, or complete rupture of the lateral ligaments, respectively. Table A1-54 describes a classification of ankle sprains.

ICD-9CM CODES
845.00 Sprain, ankle or foot
ICD-10CM CODES
S93.409A Sprain of unspecified ligament of unspecified ankle, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: One case/10,000 people each day
PREDOMINANT SEX: Varies according to age and level of physical activity

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Often a history of a "pop"
- Variable amounts of tenderness and hemorrhage
- Possible abnormal anterior drawer test (pulling the plantar flexed foot forward to determine if there is any abnormal increase in forward movement of the talus in the ankle mortise) (Fig. A1-83)
- Inversion sprains: tender laterally; syndesmotic injuries: area of tenderness is more anterior and proximal
- Evaluation of motor function (Fig. A1-84)

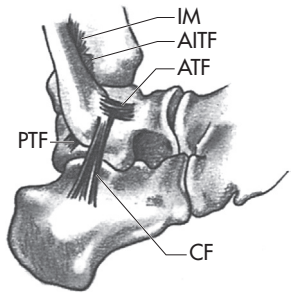


FIGURE A1-82 The lateral ankle ligaments, anterior and posterior talofibular *(ATF, PTF)* and calcaneofibular *(CF).* Also shown are the anterior inferior tibiofibular ligament *(AITF)* and the beginning of the interosseous membrane *(IM).* (From Mercier LR [ed]: *Practical orthopaedics,* ed 4, St Louis, 1995, Mosby.)

ETIOLOGY

- Lateral injuries usually result from inversion and plantar flexion injuries.
- Eversion and rotational forces may injure the deltoid or AITF ligament or the interosseous membrane.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Fracture of the ankle or foot, particularly involving the distal fibular growth plate in the immature patient
- Avulsion fracture of the fifth metatarsal base

WORKUP

- History and clinical examination are usually sufficient to establish the diagnosis.
- Plain radiographs are always needed.

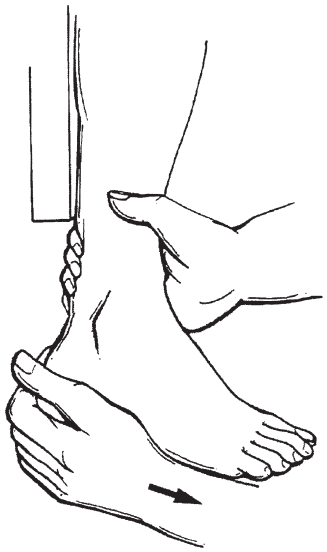


FIGURE A1-83 Anterior drawer test of the ankle (tests the integrity of the anterior talofibular ligament). (From Brinker MR, Miller MD: *Fundamentals of orthopaedics,* Philadelphia, 1999, Saunders.)

IMAGING STUDIES

Roentgenographic evaluation (Fig. A1-85): According to the Ottawa criteria, radiography is indicated if there is pain in the malleolar or midfoot zone and either bone tenderness over an area of potential fracture or an inability to bear weight for four steps immediately after the injury and in the physician's office.

TREATMENT

ACUTE GENERAL Rx

- The first line of treatment is described by the mnemonic *RICE:*
  1. ***R***est
  2. ***I***ce (3 to 7 days)
  3. ***C***ompression
  4. ***E***levation
- Pain control with NSAIDs, acetaminophen, mild opioids
- In 48 to 72 hr, active range of motion and weight bearing as tolerated
- Compression, support, and bracing is best achieved with an Air-Stirrup brace combined with an elastic compression wrap, or lace-up support alone.
- In 4 to 5 days, exercise against resistance added
- Possible cast immobilization for some patients who require early independent walking; short leg orthoses also available for the same purpose
- Surgery is rarely recommended, even for grade III sprains; reports of equally satisfactory outcomes with nonsurgical treatment

CHRONIC Rx

- Lateral heel and sole wedge to prevent inversion
- Protective taping or bracing during vigorous activities (Fig. A1-86)
- Strengthening exercises

FIGURE A1-84 Talar tilt test (inversion stress) of the ankle (tests the integrity of the anterior talofibular ligament and the calcaneofibular ligament). (From Brinker MR, Miller MD: *Fundamentals of orthopaedics,* Philadelphia, 1999, Saunders.)

TABLE A1-54 Classification of Ankle Sprains

Type of Injury	Extent of Injury	Physical Findings
Grade I	Stretch of the ligament with microscopic but not macroscopic tearing	Minor swelling but no joint instability
Grade II	Involves partial tearing of the particular ligament	Minor to moderate swelling and some instability of the affected ankle
Grade III	Involves complete rupture of the ligament	Significant swelling, tenderness, and ecchymosis; instability of the joint and inability to bear weight

From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

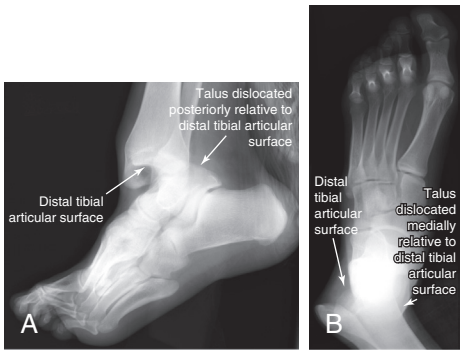


FIGURE A1-85 Tibiotalar dislocation. This 17-year-old male landed on his left ankle after dunking a basketball, sustaining a deformity. His tibiotalar joint is dislocated, with the talus dislocated posteriorly (visible on the lateral view, **A**) and medially (visible on the anterior-posterior view, **B**). No fractures are present in this case, although fractures are commonly associated with this injury because of the amount of force required to dislocate the ankle. This was an open injury, and the patient underwent exploration, irrigation, and debridement with primary closure. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

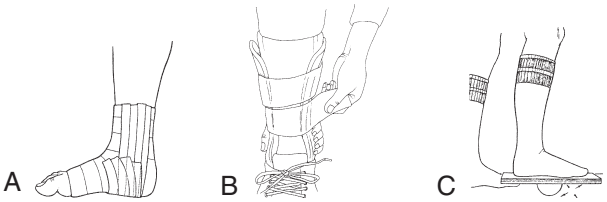


FIGURE A1-86 A, The most effective method of supporting most acute ankle sprains is by using an ACE wrap (BD, Franklin Lakes, NJ) reinforced with 1-inch medial and lateral tape strips. The anterior and posterior aspects of the ankle are left free to allow the patient to flex and extend the ankle. The patient is encouraged to bear weight with crutches. **B,** Diagram of an air splint. Straps are adjusted to heel size, the lower straps are wrapped about the ankle, and the side extensions are centered. The splint is then pressurized and straps adjusted until comfortable support and pressure are attained. **C,** As the ankle pain subsides, about the third to fifth day, balancing exercises can begin to allow the patient to regain ankle proprioception and avoid recurrent instability problems. (From Jardon OM, Mathews MS: Orthopedics. In Rakel RE [ed]: *Textbook of family practice,* ed 5, Philadelphia, 1995, Saunders.)

DISPOSITION

- Lateral sprains of any severity may cause lingering symptoms for weeks and months.
  1. Some syndesmotic sprains take even longer to heal.
  2. Heterotopic ossification may even develop in the interosseous membrane, but long-term results do not seem to be affected by such ossification.
- Continuing lateral symptoms may require surgical reconstruction, although late traumatic arthritis or long-term instability is rare regardless of treatment.

REFERRAL

For orthopedic consultation for patients who do not respond to conservative treatment. Most ankle sprains resolve in 2 to 6 wk.

PEARLS & CONSIDERATIONS

COMMENTS

If healing seems delayed (more than 6 wk), the following conditions should be considered:

1. Talar dome fracture
2. Reflex sympathetic dystrophy
3. Chronic tendinitis
4. Peroneal tendon subluxation
5. Other occult fracture
6. Peroneal weakness (poor rehabilitation)
7. A "high" (syndesmotic) sprain

Repeat plain roentgenograms, bone scan, or MRI may be indicated.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Ankle Sprain (Patient Information)
Ankle Fracture (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Ankle injuries, especially ankle sprains, are a common problem in sports and medical care. Ankle sprains result in pain and absenteeism from work and/or sports participation, and can lead to physical restrictions such as ankle instability. Nowadays, treatment of ankle injury basically consists of taping the ankle. The purpose of this review is to evaluate the effectiveness of ankle braces as a treatment for acute ankle sprains compared with other types of functional treatments such as ankle tape and elastic bandages. A computerized literature search was conducted using PubMed, EMBASE, CINAHL and the Cochrane Clinical Trial Register. This review includes randomized controlled trials in English, German and Dutch, published between 1990 and April 2009 that compared ankle braces as a treatment for lateral ankle sprains with other functional treatments. The inclusion criteria for this systematic review were (i) individuals (sports participants as well as non-sports participants) with an acute injury of the ankle (acute ankle sprains); (ii) use of an ankle brace as primary treatment for acute ankle sprains; (iii) control interventions including any other type of functional treatment (e.g. Tubigrip™, elastic wrap or ankle tape); and (iv) one of the following reported outcome measures: re-injuries, symptoms (pain, swelling, instability), functional outcomes and/or time to resumption of sports, daily activities and/or work. Eight studies met all inclusion criteria. Differences in outcome measures, intervention types and patient characteristics precluded pooling of the results, so best evidence syntheses were conducted. A few individual studies reported positive outcomes after treatment with an ankle brace compared with other functional methods, but our best evidence syntheses only demonstrated a better treatment result in terms of functional outcome. Other studies have suggested that ankle brace treatment is a more cost-effective method, so the use of braces after acute ankle sprains should be considered. Further research should focus on economic evaluation and on different types of ankle brace, to examine the strengths and weaknesses of ankle braces for the treatment of acute ankle sprains. Ⓐ

Abstract[2]

Ankle injury manipulation before or after X-ray, does it influence success?

Many acute, deformed ankle injuries are manipulated in the emergency department (ED) before X-rays are taken to confirm the nature of the injury. This often occurs in the absence of neurovascular or skin compromise without consideration of other possible injuries such as talar, subtalar or calcaneal injuries. We believe that an inappropriate manipulation of an unknown injury pattern may place the patient at increased risk. A balance needs to be struck between making the correct diagnosis and preventing any further neurovascular or skin compromise.

We prospectively reviewed 197 patients admitted to the Royal Blackburn hospital with acute ankle injuries. Their ED notes were reviewed, specifically assessing whether a manipulation was performed; if so, was it performed before X-rays and the documented reasons. A total of 90 ankle fractures were manipulated and 31 of these were performed before X-ray. One manipulation was performed for vascular compromise, one for nerve symptoms, three for critical skin, and 25 for undocumented reasons.

Outcomes (re-manipulation, delay to surgery, and need for open reduction and internal fixation (ORIF)) were compared between injuries manipulated before or after X-ray. Re-manipulation was found to be significant (44% before X-ray vs. 18% after X-ray; chi-squared test: $P < 0.03$; relative risk (RR) <2.72; 95% confidence interval (CI):). Delay to surgery and need for ORIF were not statistically different.

We conclude that performing ankle injury X-rays before an attempt at manipulation, in the absence of neurovascular deficit or critical skin, may constitute best practice as it provides a better assessment of fracture configuration, guides initial reduction and significantly lowers the risk of re-manipulation and the potential; risks associated with sedation without delaying surgery.

I like studies that attempt to address questions we may all have asked ourselves. Especially those that have the potential to change practice. As the ED becomes dominated by the ED physician, this issue is even more relevant. So, why and when should an ankle be manipulated (reduced?) in the ED before an X-ray? Logic and current practice would say that when there is marked, obvious displacement with neurovascular compromise, immediate reduction is appropriate. This was the case in this study. Lacking these features, this study found no value in a blind manipulation before a plane radiograph. This would seem to offer a scientific basis for our clinical practice. Ⓐ

B. F. MORREY, M.D.

Evidence-Based References

Kemler E et al.: A systematic review on the treatment of acute ankle sprain: brace versus other functional treatment types, *Sports Med* 41:185–197, 2011. Ⓐ.

Hastie GR et al.: Ankle injury manipulation before or after X-ray—does it influence success?, *Injury* 45:583–585, 2014. Ⓐ.

SUGGESTED READINGS

Dahners LE, Mullis BH: Effects of nonsteroidal anti-inflammatory drugs on bone formation and soft tissue healing, *J Am Acad Orthop Surg* 12:139, 2004.

Hale SA et al.: The effect of a 4-week comprehensive rehabilitation program on postural control and lower extremity function in individuals with chronic ankle instability, *J Orthop Sports Phys Ther* 37:303, 2007.

Ivins D: Acute ankle sprain: an update, *Am Fam Physician* 74:1714, 2006.

Le Gall F et al.: Injuries in young elite female soccer players: an 8-season prospective study, *Am J Sports Med* 36:276, 2008.

Maffulli N, Ferran N: Management of acute and chronic ankle instability, *J Am Acad Orthop Surg* 16:608, 2008.

Mizel MS et al.: Evaluation and treatment of chronic ankle pain, *J Bone Joint Surg Am* 86A:622, 2004.

O'Neill PJ et al.: Excursion and strain of the superficial peroneal nerve during inversion ankle sprain, *J Bone Joint Surg Am* 89A:979, 2007.

Pedowtiz DI et al.: Prophylactic bracing decreases ankle injuries in collegiate female volleyball players, *Am J Sports Med* 36:324, 2008.

Tiemstra JD: Update on acute ankle sprains, *Am Fam Physician* 85:1170–1176, 2012.

Van Rijin RG et al.: What is the clinical course of acute ankle sprains? A systematic literature review, *Am J Med* 121:324, 2008.

Zalavras C, Thordarson D: Ankle syndesmotic injury, *J Am Acad Orthop Surg* 15:330, 2007.

BASIC INFORMATION

DEFINITION

Ankylosing spondylitis is a type of inflammatory arthritis involving the sacroiliac joints and axial skeleton characterized by ankylosis and enthesitis (inflammation at tendon insertions). It is one of a family of overlapping syndromes called seronegative spondyloarthropathies that includes reactive arthritis (Reiter syndrome), psoriatic spondylitis, and enteropathic arthritis.

SYNONYMS

Marie-Strümpell disease

ICD-9CM CODES
720.0 Ankylosing spondylitis
ICD-10CM CODES
M45.9 Ankylosing spondylitis of unspecified sites in spine

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Between 0.1% and 1% of the population
PREDOMINANT AGE AT ONSET: 15 to 35 yr
PREDOMINANT SEX: Male/female ratio 2 to 3:1

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Prolonged morning back stiffness of insidious onset lasting more than 3 mo
- Bilateral sacroiliac tenderness (sacroiliitis)
- Limited lumbar spine motion (Fig. A1-87)
- Tenderness at tendon insertion sites, especially the Achilles tendons and plantar fascia
- Loss of chest expansion reflecting rib cage involvement
- Occasionally, peripheral joint arthritis, usually involving the large joints of the lower extremities
- In advanced cases the typical posture consists of compensatory hyperextension of neck, fixed flexion of hips, and compensatory flexion of knees (Fig. A1-88)
- Extraskeletal manifestations may affect the cardiovascular system (aortic insufficiency), lungs (pulmonary fibrosis), and eye (uveitis), but are not usually severe.

ETIOLOGY

Genetic factors, particularly *HLA-B27*, play an important role in susceptibility to the spondyloarthropathies. Infectious triggers have been implicated in some cases. Tumor necrosis factor is important in the inflammatory response.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Diffuse idiopathic skeletal hyperostosis (Forestier disease)
- Noninflammatory back pain (A clinical algorithm for the evaluation of back pain is described in Section III.)
- Table A1-55 compares ankylosing spondylitis and related disorders.

LABORATORY TESTS

- Elevated sedimentation rate, C-reactive protein
- Mild hyperchromic anemia
- Demonstration of inflammatory sacroiliitis by radiography or MRI is essential for diagnosis
- HLA/B27 antigen is not useful in the evaluation of noninflammatory back pain because it is present in up to 8% to 10% of the normal population.

IMAGING STUDIES

- Classic features are those of bilateral sacroiliitis on radiographs of the pelvis
- Vertebral bodies lose anterior concave shape and become square
- With progression, calcification of the annulus fibrosus and paravertebral ligaments develop, giving rise to the so-called *bamboo spine* and a "trolley track" appearance (Fig. A1-89).
- MRI (Fig A1-90) may be useful in detecting early inflammatory lesions and is especially helpful when the history is suggestive but radiographs are equivocal.

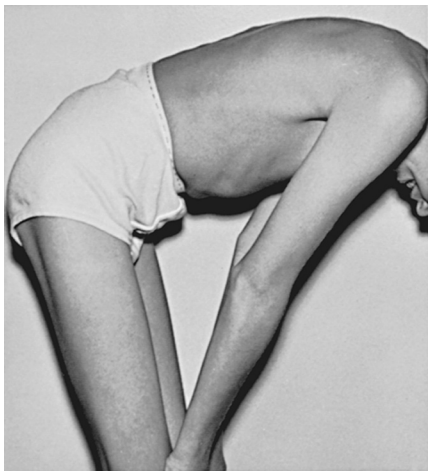


FIGURE A1-87 Loss of lumbodorsal spine mobility in a boy with ankylosing spondylitis. The lower spine remains straight when the patient bends forward. (From Behrman RE: *Nelson textbook of pediatrics,* ed 17, Philadelphia, 2005, Saunders.)

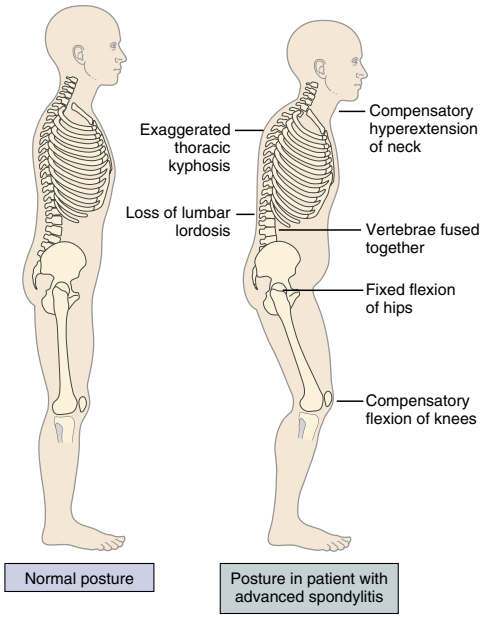


FIGURE A1-88 Ankylosing spondylitis. Typical posture in advanced cases compared with normal posture. (From Ballinger A: *Kumar & Clark's essentials of clinical medicine,* ed 6, Edinburgh, 2012, Saunders.)

TABLE A1-55 Comparison of Ankylosing Spondylitis and Related Disorders

Feature	Ankylosing Spondylitis	Psoriatic Arthritis	Reactive Arthritis	Enteropathic Arthropathy
Gender (M:F)	2-3:1	1:1	8:1 (GU) [1:1 (GI)]	1:1
Age at onset	<40	35-55	20-40	Young adult
Sacroiliitis or spondylitis	100%	~20%	~40%	<20%
Symmetry of sacroiliitis	Symmetric	Asymmetric	Asymmetric	Symmetric
Peripheral arthritis	~25%	95%	90%	15%-20%
Distribution	Axial and lower limbs	Any joint	Lower limbs	Variable
HLA-B27	85%-95%	25%	30%-80%	7%
Uveitis	25%-40%	25%	25%	10%-36%

From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

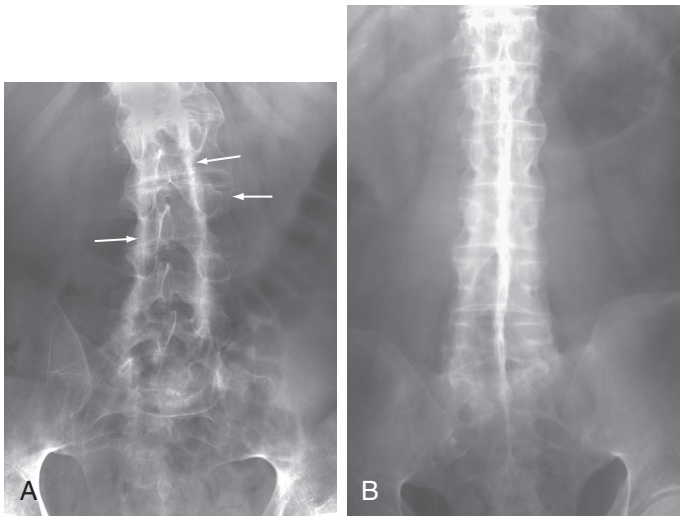


FIGURE A1-89 Ankylosing spondylitis. A, Fusion of the facet joints and ossification of the adjacent soft tissue have produced a "trolley track" appearance *(arrows)*. The sacroiliac joints are fused. Syndesmophytes are present. **B,** In another patient, there is a prominent fusion of the interspinous ligaments producing a "saber sheath" appearance. (From Harris ED: *Kelley's textbook of rheumatology,* ed 7, Philadelphia, 2005, Saunders.)

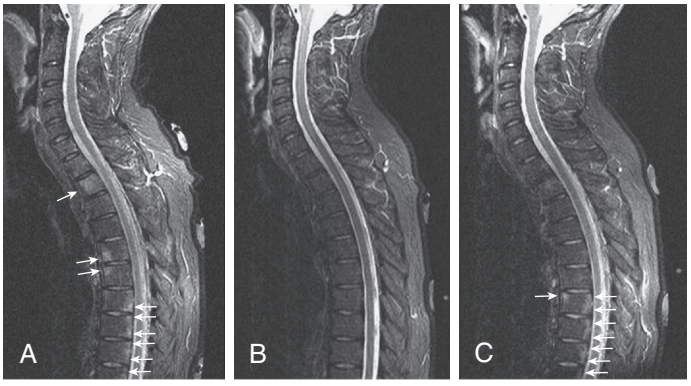


FIGURE A1-90 Spine inflammation in ankylosing spondylitis (magnetic resonance imaging [MRI]). A 43-year-old man with HLA-B27–positive ankylosing spondylitis with deteriorating symptoms, including inflammatory back pain, had an MRI scan before starting biologic therapy. Baseline sagittal short tau inversion recovery (STIR) MRI **(A)** shows diffuse increased signal (edema) in the T2 vertebral body and multiple foci of corner inflammation anteriorly at T5 and T6, and posteriorly at T7, T8, T9, and T10 *(arrows).* Other images confirmed extensive active inflammation in the spine. The patient responded very well, and after 6 months of therapy, a repeat STIR MRI **(B)** showed complete resolution of bone marrow inflammation. Subsequently, the patient experienced recurrence of symptoms, and a third MRI **(C)** was performed (2 months after anti-TNF therapy was stopped). This MRI shows no edema at T5-T6, a conspicuous new lesion anteriorly at T7, and recurrent inflammation posteriorly in the lower thoracic spine *(arrows).* (From Firestein GS, et al: *Kelley's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Exercises primarily to maintain on flexibility and aerobic activity are important
- Postural training
  1. Patients must be instructed on spinal extension exercises to avoid fusion in a flexed position
  2. Sleeping should be in the supine position on a firm mattress; pillows should not be placed under the head or knees.

CHRONIC Rx

- NSAIDs: Patients with ankylosing spondylitis should be prescribed full-dose continuous NSAID therapy. There is anecdotal evidence suggesting that indomethacin may be more effective than other NSAIDs, but other NSAIDs are efficacious and may be better tolerated. One study suggested that continuous NSAID therapy may retard the radiographic progression of ankylosing spondylitis.
- Sulfasalazine may be efficacious in some patients, especially for peripheral arthritis
- Tumor necrosis factor (TNF) antagonists such as etanercept, infliximab, and adalimumab have been shown to be very effective for relieving symptoms of spinal inflammatory arthritis in numerous controlled studies. Anti-TNF therapy should be recommended for patients whose symptoms are not completely controlled with NSAIDs, and it sometimes results in dramatic improvement in symptoms, range of motion of the spine, and quality of life for these patients. There is evidence suggesting that anti-TNF therapy slows the radiographic progression of the disease.

DISPOSITION

Most patients have a normal life span but many suffer significant disability from loss of spinal mobility.

REFERRAL

All patients with seronegative spondyloarthropathy should be referred to a rheumatologist for consideration of anti-TNF therapy.

PEARLS & CONSIDERATIONS

A family history of seronegative spondyloarthropathy increases the specificity of testing for *HLA-B27.*

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fig. 3-194 Spondyloarthropathy, diagnosis (Algorithm)
Fig. 3-195 Spondyloarthropathy, treatment (Algorithm)
Ankylosing Spondylitis (Patient Information)

AUTHOR: **BERNARD ZIMMERMANN, M.D.**

SUGGESTED READINGS

Brown J: Ankylosing spondylitis, *Lancet* 369:1379–1390, 2007.

Davis JC Jr et al.: Health-related quality of life outcomes in patients with active ankylosing spondylitis treated with adalimumab: results from a randomized controlled study, *Arthritis Rheum* 57(6):1050, 2007.

Haroon N et al.: The impact of tumor necrosis factor inhibitors on radiographic progression in ankylosing spondylitis, *Arthritis Rheum* 65:2645, 2013.

Heiberg MS et al.: The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study, *Arthritis Rheum* 59:234, 2008.

Oosttveen J et al.: Early detection of sacroiliitis on magnetic resonance imaging and subsequent development of sacroiliitis on plain radiography: a prospective, longitudinal study, *J Rheumatol* 26:19523–19528, 1999.

Wanders A et al.: Nonsteroidal antiinflammatory drugs reduce radiographic progression in patients with ankylosing spondylitis: a randomized clinical trial, *Arthritis Rheum* 52(6):1756, 2005.

BASIC INFORMATION

DEFINITION

A fistula is an inflammatory tract with a secondary (external) opening in the perianal skin and a primary (internal) opening in the anal canal at the dentate line. It originates in an abscess in the intersphincteric space of the anal canal. Fistulas can be classified as follows:

1. Intersphincteric: fistula track passes within the intersphincteric plane to the perianal skin (most common)
2. Transsphincteric: fistula track passes from the internal opening, through the internal and external sphincter, and into the ischiorectal fossa to the perianal skin (frequent)
3. Suprasphincteric: after passing through the internal sphincter, fistula tract passes above the puborectalis and then tracts downward, lateral to the external sphincter, into the ischiorectal space to the perianal skin (uncommon); if abscess cavity extends cephalad, a supralevator abscess possibly palpable on rectal examination
4. Extrasphincteric: fistula tract passes from the rectum, above the levators, through the levator muscles to the ischiorectal space and perianal skin (rare)

With a horseshoe fistula, the tract passes from one ischiorectal fossa to the other behind the rectum.

SYNONYMS

Fistula-in-ano

ICD-9CM CODES
565.1 Anal fistula
ICD-10CM CODES
K60.3 Anal fistula

EPIDEMIOLOGY & DEMOGRAPHICS

- Common in all ages
- Occurs equally in men and women
- Associated with constipation
- Pediatric age group: more common in infants; boys more than girls

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute stage: perianal swelling, pain, and fever
- Chronic stage: history of rectal drainage or bleeding; previous abscess with drainage
- Tender external fistulous opening, within 2 to 3 cm of the anal verge, with purulent or serosanguineous drainage on compression; the greater the distance from the anal margin, the greater the probability of a complicated upward extension
- Goodsall's rule:
  1. Location of the internal opening related to the location of the external opening.
  2. With external opening anterior to an imaginary line drawn horizontally across the midpoint of the anus: fistulous tract runs radially into the anal canal.
  3. With opening posterior to the transanal line: tract is usually curvilinear, entering the anal canal in the posterior midline.
  4. Exception to this rule: an external, anterior opening that is >3 cm from the anus. In this case the tract may curve posteriorly and end in the posterior midline.
- If perianal abscess recurs, presence of a fistula is suggested.

ETIOLOGY

- Most common: nonspecific cryptoglandular infection (skin or intestinal flora)
- Fistulas more common when intestinal microorganisms are cultured from the anorectal abscess
- Tuberculosis
- Lymphogranuloma venereum
- Actinomycosis
- Inflammatory bowel disease (IBD): Crohn's disease, ulcerative colitis
- Trauma: surgery (episiotomy, prostatectomy), foreign bodies, anal intercourse
- Malignancy: carcinoma, leukemia, lymphoma
- Treatment of malignancy: surgery, radiation

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hidradenitis suppurativa
- Pilonidal sinus
- Bartholin's gland abscess or sinus
- Infected perianal sebaceous cysts

WORKUP

- Digital rectal examination:
  1. Assess sphincter tone and voluntary squeeze pressure
  2. Determine the presence of an extraluminal mass
  3. Identify an indurated track
  4. Palpate an internal opening or pit
- Gentle probing of external orifice to avoid creating a false tract; 50% do not have clinically detectable opening
- Anoscopy
- Proctosigmoidoscopy to exclude inflammatory or neoplastic disease
- All studies done under adequate anesthesia

LABORATORY TESTS

- Complete blood count
- Rectal biopsy if diagnosis of IBD or malignancy suspected; biopsy of external orifice is useless

IMAGING STUDIES

- Colonoscopy or barium enema if:
  1. Diagnosis of IBD or malignancy is suspected
  2. History of recurrent or multiple fistulas
  3. Patient <25 yr
- Small bowel series: occasionally obtained for reasons similar to above
- Fistulography: unreliable but may be helpful in complicated fistulas

TREATMENT

NONPHARMACOLOGIC THERAPY

Sitz baths

ACUTE GENERAL Rx

- Treatment of choice: surgery
- Broad-spectrum antibiotic given if:
  1. Cellulitis present
  2. Patient is immunocompromised
  3. Valvular heart disease present
  4. Prosthetic devices present
- Stool softener/laxative

CHRONIC Rx

- Surgery
- Surgical goals are as follows:
  1. Cure the fistula
  2. Prevent recurrence
  3. Preserve sphincter function
  4. Minimize healing time
- Methods for the management of anal fistulas: fistulotomy, setons (maintains fistula patent for drainage while spontaneous healing occurs), rectal advancement flaps, colostomy

DISPOSITION

Outpatient surgery

REFERRAL

Refer to a surgeon with expertise in this area.

PEARLS & CONSIDERATIONS

COMMENTS

- HIV-positive and diabetic patients with perirectal abscesses/fistulas are true surgical emergencies.
- Risk of septicemia, Fournier's gangrene, and other septic complications make immediate drainage imperative.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Anal Fissure (Related Key Topic)
Hemorrhoids (Related Key Topic)

AUTHORS: **RUBEN ALVERO, M.D.,** and **GEORGE T. DANAKAS, M.D.**

SUGGESTED READINGS

Pfenninger JL, Zainea GG: Common anorectal condition, *Am Fam Physician* 64:22, 2001.

Rickard MJ: Anal abscesses and fistulas, *ANZ J Surg* 75(1–2):64, 2005.

Schwartz DA, Herdman CR: The medical treatment of Crohn's perianal fistulas, *Aliment Pharmacol Ther* 19(9):953, 2004.

Anorexia Nervosa (ALG) (PTG)

BASIC INFORMATION

DEFINITION

Anorexia nervosa is a psychiatric disorder characterized by abnormal eating behavior, severe self-induced weight loss, and a specific psychopathology (see "Workup").

ICD-9CM CODES
307.1 Anorexia nervosa
ICD-10CM CODES
F50.00 Anorexia nervosa, unspecified
F50.01 Restricting type
F50.02 Binge-eating/purging type

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE/PREVALENCE (IN U.S.):

- Anorexia nervosa occurs in 0.2% to 1.3% of the general population, with an annual incidence of 5 to 10 cases per 100,000 persons.
- Participation in activities that promote thinness (athletics, modeling) is associated with a higher incidence of anorexia nervosa.

PREDOMINANT SEX: Female/male ratio is 9:1. Approximately 0.5% to 1% of women between the ages of 15 and 30 yr have anorexia nervosa.
PREDOMINANT AGE: Adolescence to young adulthood is the predominant age. Mean age of onset is 17 yr. Approximately 0.5% to 1% of college-aged women have anorexia nervosa.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Eating disorders can affect every organ system. Primary care physicians must be skilled at recognizing this disorder because patients with mild cases usually present with nonspecific symptoms such as asthenia, cold intolerance, lack of energy, or dizziness. Children and adolescents are at particular risk due to their active phase of growth and development. The physical examination may be normal in the early stages or in mild cases. Patients with moderate to severe anorexia have the following physical characteristics:

- Patient is emaciated and bundled in clothing.
- Skin is dry and has excessive growth of lanugo. Skin may also be yellow-tinged from carotenodermia.
- Brittle nails, thinning scalp hair are present.
- Bradycardia, hypotension, hypothermia, and bradypnea are common.
- Female fat distribution pattern is no longer evident.
- Axillary and pubic hair is preserved.
- Peripheral edema may be present.

ETIOLOGY

- Etiology is unknown, but probably multifactorial (sociocultural, psychological, familial, and genetic factors).
- A history of sexual abuse has been reported in as many as 50% of patients with anorexia nervosa.
- Psychological factors: anorexics often have an incompletely developed personal identity. They struggle to maintain a sense of control over their environment, they usually have a low self-esteem, and they lack the sense that they are valued and loved for themselves.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other eating disorders (bulimia nervosa, binge eating disorder [see Table A1-56])
- Substance abuse
- Depression with loss of appetite
- Obsessive compulsive disorder
- Schizophrenia
- Conversion disorder
- Occult carcinoma, lymphoma
- Endocrine disorders: Addison disease, diabetes mellitus, hypothyroidism or hyperthyroidism, panhypopituitarism
- Gastrointestinal disorders: celiac disease, Crohn's disease, intestinal parasitosis
- Infectious disorders: AIDS, tuberculosis
- A clinical algorithm for the evaluation of anorexia is described in Section III

WORKUP

- A diagnosis can be made by using the following DSM-5 diagnostic criteria for anorexia nervosa.
  A. Restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children or adolescents, less than that minimally expected.
  B. Intense fear of gaining weight or becoming fat, or persistent behavior that interferes with weight gain, even though at a significantly low weight.
  C. Disturbance in the way in which one's body or shape is experience, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight.

TABLE A1-56 Diagnostic Features of Eating Disorders

Anorexia nervosa	Body weight willfully maintained below normal level Abnormal perception of body morphology Intense fear of weight gain Amenorrhea
Bulimia nervosa	Large uncontrolled eating binges at least twice weekly Inappropriate compensatory behavior (e.g., vomiting, purging)
Binge eating disorder	Large uncontrolled eating binges at least twice weekly No regular inappropriate compensatory disorders Marked distress about binges

From Besser CM, Thorner MO: *Comprehensive clinical endocrinology,* ed 3, St Louis, 2002, Mosby.

Specify type:
Restricting type: During the last 3 mo, the individual has not engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas). This subtype describes presentations in which weight loss is accomplished primarily through dieting, fasting, and/or excessive exercise.
Binge-eating/purging type: During the last 3 mo, the individual has engaged in recurrent episodes of binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas).

Severity level: see "Acute General Rx" section

The SCOFF questionnaire is a screening tool for eating disorders used in England. It consists of the following five questions:
1. Do you make yourself ***s***ick because you feel full?
2. Have you lost ***c***ontrol over how much you eat?
3. Have you lost more than ***o***ne stone (approximately 6 kg) recently?
4. Do you believe yourself to be ***f***at when others say you are thin?
5. Does ***f***ood dominate your life?

A positive response to two or more questions has a reported sensitivity of 100% for anorexia and bulimia and an overall specificity of 87.5%.

In college-aged women a positive response to any of the following screening questions also warrants further evaluation:
1. How many diets have you been on in the past year?
2. Do you think you should be dieting?
3. Are you dissatisfied with your body size?
4. Does your weight affect the way you think about yourself?

Baseline ECG should be performed on all patients with anorexia nervosa. Routine monitoring of patients with prolonged QT interval is necessary; sudden death in these patients is often caused by ventricular arrhythmias related to QT interval prolongation.

A dual-energy x-ray absorptiometry (DEXA) scan to screen for osteopenia should be considered after 6 mo of amenorrhea in patients suspected of anorexia nervosa.

LABORATORY TESTS

- In mild cases, laboratory findings may be completely normal.
- Endocrine abnormalities:
  1. Decreased follicle-stimulating hormone, luteinizing hormone, T_4, T_3, estrogens, urinary 17-OH steroids, estrone, and estradiol
  2. Normal free T_4, thyroid-stimulating hormone
  3. Increased cortisol, growth hormone, rT_3, T_3RU
  4. Absence of cyclic surge of luteinizing hormone
- Leukopenia, thrombocytopenia, anemia, reduced erythrocyte sedimentation rate, reduced complement levels, and reduced CD4 and CD8 cells may be present.

- Metabolic alkalosis, hypocalcemia, hypokalemia, hypomagnesemia, hypercholesterolemia, and hypophosphatemia may be present.
- Increased plasma b-carotene levels are useful to distinguish these patients from others on starvation diets.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- A multidisciplinary approach with psychological, medical, and nutritional support is necessary.
- A goal weight should be set and the patient should be initially monitored at least once a week in the office setting. The target weight is 100% of ideal BW for teenagers and 90% to 100% for older patients.
- Weight gain should be gradual (1 to 3 lb/wk) to prevent gastric dilation. Begin with 800 to 1200 kcal in frequent small meals (to avoid bloating sensation), then increase calories to 1500 to 3000 depending on height and age.
- Add, as necessary, vitamin and mineral supplements.
- In severe cases, total parenteral nutrition must be used (starting at 800 to 1200 kcal/day).
- Electrolyte levels should be strictly monitored.
- Mealtime should be a time for social interaction, not confrontation.
- Postprandially, sedentary activities are recommended. The patient's access to a bathroom should be monitored to prevent purging.

ACUTE GENERAL Rx

- Criteria to decide on the appropriate initial course of treatment for patients with anorexia nervosa are usually based on the presence of complications, percentage of ideal BW, and severity of body image distortion. According to DSM-5,[1] the minimum level of severity is based, for adults, on current body mass index (BMI; see below) or, for children and adolescents, on BMI percentile. The level of severity may be increased to reflect clinical symptoms, the degree of functional disability, and need for supervision.
  - Mild: BMI ≥17 kg/m^2
  - Moderate: BMI 16-16.99 kg/m^2
  - Severe: BMI 15-15.99 kg/m^2
  - Extreme: BMI <15 kg/m^2

[1]American Psychiatric Association: Desk Reference to the Diagnostic Criteria from DSM-5, Arlington, VA, 2013, American Psychiatric Association.

- Outpatient treatment is adequate for most patients.
- Indications for hospitalization are described under "Referral" section and summarized in Table A1-57.
- Medically stable patients who are within 85% of ideal BW can be followed up by the primary care physician at 3- or 4-wk intervals, which can be lengthened as the patient improves.
- Pharmacologic treatment generally has no role in anorexia nervosa unless major depression or another psychiatric disorder is present. SSRIs can be used to alleviate the depressed mood and moderate obsessive-compulsive behavior in some individuals.

CHRONIC Rx

- Psychotherapy continued for years and focused specifically on self-image, family and peer interactions, and relapse prevention is an integral part of a successful recovery.
- Family therapy is also recommended, especially in younger patients.

TABLE A1-57 Indications for In-Patient Medical Hospitalization of Patients with Anorexia Nervosa

Physical and Laboratory
Heart rate <45 beats/min
Other cardiac rhythm disturbances
Blood pressure <80/50 mm Hg
Postural hypotension resulting in a >10 mm Hg drop or a >20 beats/min increase
Hypokalemia
Hypophosphatemia
Hypoglycemia
Dehydration
Body temperature <97°F
<80% healthy body weight
Hepatic, cardiac, or renal compromise
Psychiatric
Suicidal intent and plan
Very poor motivation to recover (in family and patient)
Preoccupation with ego-syntonic thoughts
Coexisting psychiatric disorders
Miscellaneous
Requires supervision after meals and while using the restroom
Failed day treatment

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

DISPOSITION

- The long-term prognosis is generally poor and marked by recurrent exacerbations. The percentage of patients with anorexia nervosa who fully recover is modest. Most patients continue to have a distorted body image, disordered eating habits, and psychic difficulties.
- Most patients with anorexia nervosa will recover menses within 6 mo of reaching 90% of their ideal BW. It is important to note that patients with anorexia nervosa can become pregnant despite amenorrhea.
- Mortality rates vary from 5% to 20% and are six times that of peers without anorexia. Frequent causes of death are electrolyte abnormalities, starvation, or suicide.
- Factors that predict improved outcome in patients with eating disorders include early age at diagnosis, brief interval before initiation of treatment, good parent-child relationships, and having other healthy relationships with friends or therapists.
- A prolonged QT interval is a marker for risk of sudden death.

REFERRAL

Hospitalization should be considered in the following situations:

1. Severe dehydration or electrolyte imbalance
2. ECG abnormalities (prolonged QT interval, arrhythmias)
3. Significant physiologic instability (hypotension, orthostatic changes)
4. Intractable vomiting, purging, or bingeing
5. Suicidal thoughts
6. Weight loss exceeding 30% of ideal BW and unresponsiveness to outpatient treatment
7. Rapidly progressing weight loss (>2 lb in a week)
8. Failure to progress in nutritional rehabilitation in outpatient treatment

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fig. 3-20 Evaluation of anorexia (Algorithm)
Anorexia Nervosa (Patient Information)
Bulimia Nervosa (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

American Psychiatric Association: Practice guideline for the treatment of patients with eating disorders, *Am J Psychiatry* 157(suppl):4, 2000.

Anstine D, Grinenko D: Rapid screening for disordered eating in college-aged females in the primary care setting, *J Adolesc Health* 26:338, 2000.

Attia E, Walsh BT: Behavioral management for anorexia nervosa, *N Engl J Med* 360:500–506, 2009.

DerMarderosian D, Hall A: Early identification of eating disorders in primary care pediatrics, *Med Health R I* 94(7):197, 2011.

Mehler PS: Diagnosis and care of patients with anorexia nervosa in primary care setting, *Ann Intern Med* 134:1048, 2001.

Miller KK et al.: Medical findings in outpatients with anorexia nervosa, *Arch Intern Med* 165:561, 2005.

Morgan JF et al.: The SCOFF questionnaire: assessment of a new screening tool for eating disorders, *BMJ* 319:1467, 1999.

Pritts SD, Susman J: Diagnosis of eating disorders in primary care, *Am Fam Physician* 67:297, 2003.

Williams PM et al.: Treating eating disorders in primary care, *Am Fam Physician* 77(2):187–195, 2008.

Yager J, Andersen AE: Anorexia nervosa, *N Engl J Med* 353:1481, 2005.

Anoxic Brain Injury

BASIC INFORMATION

DEFINITION

Anoxic brain injury is cerebral ischemic injury due to decreased blood flow or oxygen to the brain typically caused by interruption of cardiac circulation or respiratory failure, respectively

SYNONYMS

Hypoxic-ischemic injury
Anoxic encephalopathy
Cerebral hypoxia
Hypoxia of brain

ICD-9CM CODES
348.1 Anoxic brain damage
ICD-10CM CODES
G93.1 Anoxic brain damage, not elsewhere classified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:
- Variable based on diagnostic criteria
- 492,000 out-of-hospital cardiac arrests per year in the U.S.

PREVALENCE:
- Vegetative state varies from 40 to 168 per 1 million population, depending on definition used.
- Recovery is rare after 3 months with life expectancy lasting 2 to 5 years.

RISK FACTORS: Same as risk factors for cardiorespiratory arrest: age, race, HTN, hyperlipidemia, tobacco use, drug or alcohol abuse, and physical inactivity.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Variable depending on degree of insult
- Minimally conscious state: altered consciousness with normal sleep-wake cycles and intermittent interaction with the environment: intermittently follows simple commands, and maintains visual tracking
- Vegetative state: able to maintain normal sleep-wake cycles; there is loss of cognitive awareness and ability to interact with environment
- Coma: pathologic loss of awareness and ability to interact with the environment; loss of sleep-wake cycles
- Brain death: irreversible loss of cortical and brainstem function manifesting as loss of awareness, cranial reflexes, and motor response, isoelectric EEG

ETIOLOGY

- Ischemia (decreased cerebral perfusion): myocardial infarction, hemorrhage, shock
- Hypoxia (decreased oxygenation): drowning, strangulation, aspiration, carbon monoxide poisoning
- Figure A1-91 shows categories of mechanisms proposed to be involved in the evolution of secondary damage after severe traumatic brain injury in infants and children.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other causes of encephalopathy, including toxic, metabolic, infectious, or neoplastic causes; nonconvulsive status epilepticus; hypothermia

WORKUP

- Neurologic examination (coma examination) to ascertain level of encephalopathy
- Systemic evaluation for causes of cardiorespiratory failure
- Laboratory studies (listed below) to evaluate alternate causes of encephalopathy
- Imaging studies: MRI of brain or CT of head (if MRI cannot be obtained)

LABORATORY TESTS

Urine drug screen, serum metabolic profile, ammonia, complete blood count, coagulation panel, finger stick glucose, arterial blood gas, blood alcohol panel, serum neuron-specific enolase (if available)

IMAGING STUDIES

- Imaging is usually not revealing within first 24 hr of an anoxic event.
- Head CT without contrast (Fig. A1-92): obtain 24 hr after anoxic event to evaluate for stroke, trauma, or hemorrhage
- MRI of brain (Fig. A1-93): obtain if head CT scan unrevealing; may show cortical necrosis and infarcts of the basal ganglia

OTHER STUDIES

- EEG: to assess for nonconvulsive status epilepticus
- Somatosensory evoked potentials (SSEP; aka, N20 response): obtain 24-72 hr after anoxic event

TREATMENT

NONPHARMACOLOGIC THERAPY

- Hypothermia: evidence suggests that inducing hypothermia 32°-34° C for 24 hr following anoxic brain injury reduces metabolic need and may improve prognosis for recovery.
- Complications from hypothermia include bradycardia, hemodynamic instability, coagulopathy, infection, hyperglycemia, and hypokalemia.
- Contraindications for hypothermia: active hemorrhage, hemodynamic instability, sepsis, or trauma
- Indication for hypothermia: patients who have been resuscitated from a cardiac arrest with VF/VT as the presenting rhythm
- Hyperbaric oxygen is used in carbon monoxide poisoning.

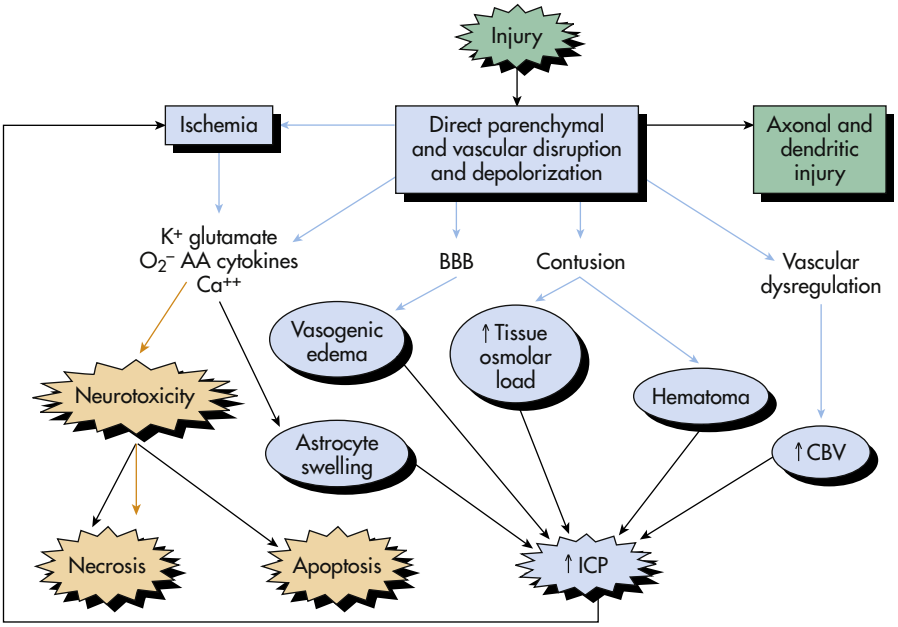


FIGURE A1-91 Categories of mechanisms proposed to be involved in the evolution of secondary damage after severe traumatic brain injury in infants and children. Three major categories for these secondary mechanisms are (1) ischemia, excitotoxicity, energy failure, and cell death cascades; (2) cerebral swelling; and (3) axonal injury. (From Fuhrman BP: *Pediatric critical care*, ed 4 St. Louis, 2011, Mosby.)

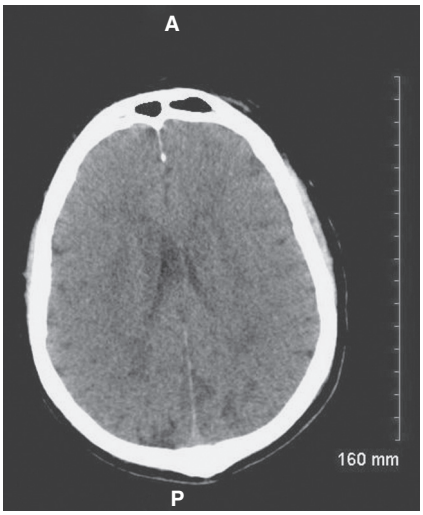


FIGURE A1-92 CT without contrast of a patient 1 day after pulseless electrical activity showing diffuse sulci effacement and loss of gray-white matter differentiation indicating cerebral edema. Diffuse white and gray matter hypodensities are also present. The patient remained comatose and life support was eventually withdrawn.

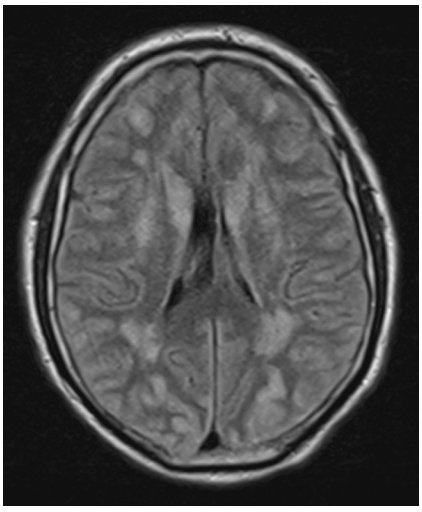


FIGURE A1-93 MRI FLAIR (fluid attenuated inversion recovery) of a patient 1 day after pulseless electrical activity showing bilateral multiple cortical, subcortical, gray and white hyperintensities. The patient remained comatose and life support was eventually withdrawn.

ACUTE GENERAL Rx

- Supportive care: ABCs, secure airway, cardiopulmonary support in the critical care unit
- Control seizures with antiepileptic medications (may need midazolam or propofol drip if severe uncontrolled seizures).
- Treat myoclonus with clonazepam 8-12 mg daily in divided doses; levetiracetam and divalproate may be used for myoclonic status epilepticus.

CHRONIC Rx

- Maintain adequate nutrition, infection precautions; provide DVT and gastric ulceration prophylaxis.
- Physical, occupational, and speech therapy as indicated per prognosis and patient ability
- May consider withdrawal of treatment per prognosis, family consultation, and respect for autonomy and dignity of the patient

PROGNOSIS

- Out-of-hospital cardiopulmonary resuscitation (CPR) for cardiac arrest has a success rate of <10%.
- There is no standardized battery of testing to quantify anoxic injury and reliably predict outcomes.
- Anoxia time, duration of CPR, and cause of cardiac arrest are related to poor outcome after CPR but not sufficient for prognosis.
- Strong predictors of poor outcome (evidence level A or B) are:
  - Presentation with myoclonus status epilepticus within the first 24 hours following injury
  - Absence of bilateral cortical SSEPs (N20 response) anytime
  - Absent papillary or corneal reflexes, or absent or extensor motor responses after 72 hours following injury
  - Serum NSE levels >33 μg/L 24-72 hours following injury
- Neuroimaging or EEG are sensitive but not specific predictors of outcome.
- Burst-suppression pattern or flat-line EEG carries bad prognosis, while reactive EEG to noxious stimuli predicts favorable outcome. Refer to Table A1-58 for predictors of good prognosis.

DISPOSITION

Varies per extent of insult from acute rehabilitation to long-term care facility to return to home

REFERRAL

Referral to a neurologist is appropriate for definitive prognostication.

PEARLS & CONSIDERATIONS

COMMENTS

When assessing prognosis, use caution if patient is being treated with anesthetic agents or depressants including anticonvulsants. Thus serial neurologic exams are substantial.

PREVENTION

CPR, risk factor modification, induced hypothermia

PATIENT/FAMILY EDUCATION

Consult with family members regularly and provide accurate assessment of prognosis.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **ABDULLAH AL-SAWAF, M.D., M.B.B.S.,** and **SIDDHARTH KAPOOR, M.D.**

TABLE A1-58 Predictors of Good Prognosis

Time from Onset of Anoxic Event	Clinical Exam
Initial exam	Pupils react to light (reflex present), motor response flexor or extensor, and eye movements spontaneous roving conjugate or orienting
24 hr	Motor response withdrawal or better, and eye opening improved at least 2 grades
72 hr	Motor response withdrawal or better and normal spontaneous eye movements present
1 wk	Follows commands
2 wk	Normal oculocephalic response

Composed from data presented in Levy DE et al: Predicting outcome from hypoxic-ischemic coma, *JAMA* 253(10):1420-1426, 1985.

SUGGESTED READINGS

American Academy of Neurology: *AAN summary of evidence-based guideline for clinicians: prediction of outcome in comatose survivors after cardiopulmonary resuscitation.* http://aan.com/professionals/practice/guidelines/coma_clinician.pdf. Accessed February 19, 2013

American Academy of Neurology: *AAN summary of evidence-based guideline for patients and their families: prediction of recovery from coma after CPR.* http://aan.com/professionals/practice/guidelines/coma_patient.pdf. Accessed February 19, 2013.

Hypothermia after Cardiac Arrest Study Group: Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest, *N Engl J Med* 346(8):549–556, 2002.

Laureys S et al.: Brain function in coma, vegetative state, and related disorders, *Lancet Neurol* 3(9):537–546, 2004.

Levy DE et al.: Predicting outcome from hypoxic-ischemic coma, *JAMA* 253(10):1420–1426, 1998.

Posner J et al. Plum and Posner's diagnosis of stupor and coma. Oxford University Press: New York.

Wijdicks EF, Hijdra A, Young GB et al.: Practice parameter: Prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology, *Neurology* 67:203–210, 2006.

Young GB: Clinical practice: neurologic prognosis after cardiac arrest, *N Engl J Med* 361(6):605–611, 2009.

BASIC INFORMATION

DEFINITION

Anthrax is an acute infectious disease caused by the spore-forming bacterium *Bacillus anthracis.*

ICD-9CM CODES
022.0 Cutaneous anthrax
022.1 Inhalation anthrax
022.2 Gastrointestinal anthrax
022.3 Sepsis from anthrax
ICD-10CM CODES
A22.0 Cutaneous anthrax
A22.1 Pulmonary anthrax
A22.2 Gastrointestinal anthrax
A22.7 Anthrax sepsis

EPIDEMIOLOGY & DEMOGRAPHICS

- Anthrax most commonly occurs in hoofed animals and can only incidentally infect human beings who come in contact with infected animals or animal products. Between 20,000 and 100,000 cases of cutaneous anthrax occur worldwide annually. In the United States the annual incidence was about 130 cases before 2001.
- Until the bioterrorism attack in 2001, most cases of anthrax occurred in industrial environments (contaminated raw materials used in manufacturing process) or in agriculture.
- In 2001 there were more than 20 confirmed cases of anthrax resulting from bioterrorism, most of which were associated with handling of contaminated mail (Fig. EA1-94). Inhalation anthrax is the most lethal form of anthrax and results from inspiration of 8000 to 50,000 spores of *B. anthracis.* Before 2001 there had not been a case of inhalation anthrax in the United States for 20 years.
- Direct person-to-person spread of anthrax is extremely unlikely, if it occurs at all; therefore there is no need to immunize or treat contacts of persons ill with anthrax, such as household contacts, friends, or co-workers, unless they also were exposed to the same source of infection.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms of disease vary depending on how the disease was contracted but usually occur within 7 days after exposure. The serious forms of human anthrax are inhalation anthrax, cutaneous anthrax, and gastrointestinal anthrax.

- **Inhalation anthrax** begins with a brief prodrome resembling a viral respiratory illness followed by development of hypoxia and dyspnea, with radiographic evidence of mediastinal widening. Host factors, dose of exposure, and chemoprophylaxis may affect the duration of the incubation period. Initial symptoms include mild fever, muscle aches, and malaise and may progress to respiratory failure and shock; meningitis often develops.
- **Cutaneous anthrax** (Fig. EA1-95) is characterized by a skin lesion evolving from a papule, through a vesicular stage, to a depressed black eschar. The incubation period ranges from 1 to 12 days. The lesion is usually painless, but patients also may have fever, malaise, headache, and regional lymphadenopathy. The eschar dries and falls off in 1 to 2 wk with little scarring.
- **Gastrointestinal anthrax** is characterized by severe abdominal pain followed by fever and signs of septicemia. Bloody diarrhea and signs of acute abdomen may occur. This form of anthrax usually follows after eating raw or undercooked contaminated meat and can have an incubation period of 1 to 7 days. Gastric ulcers may occur and may be associated with hematemesis. Oropharyngeal and abdominal forms of the disease have been described. Involvement of the pharynx is usually characterized by lesions at the base of the tongue, dysphagia, fever, and regional lymphadenopathy. Lower bowel inflammation typically causes nausea, loss of appetite, and fever followed by abdominal pain, hematemesis, and bloody diarrhea.

ETIOLOGY

The disease is caused by *B. anthracis,* a gram-positive, spore-forming bacillus. It is aerobic, nonmotile, nonhemolytic on sheep's blood agar, and grows readily at a temperature of 37° C, forming large colonies with irregularly tapered outgrowths (a Medusa's head appearance). In the host it appears as single organisms or chains of two or three bacilli (Fig. EA1-96).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Inhalation anthrax must be distinguished from influenza-like illness (ILI) and tularemia. Most cases of ILI are associated with nasal congestion and rhinorrhea, which are unusual in inhalation anthrax. Additional distinguishing factors are the usual absence of abnormal chest radiograph in ILI (see below).
- Cutaneous anthrax should be distinguished from staphylococcal disease, ecthyma,

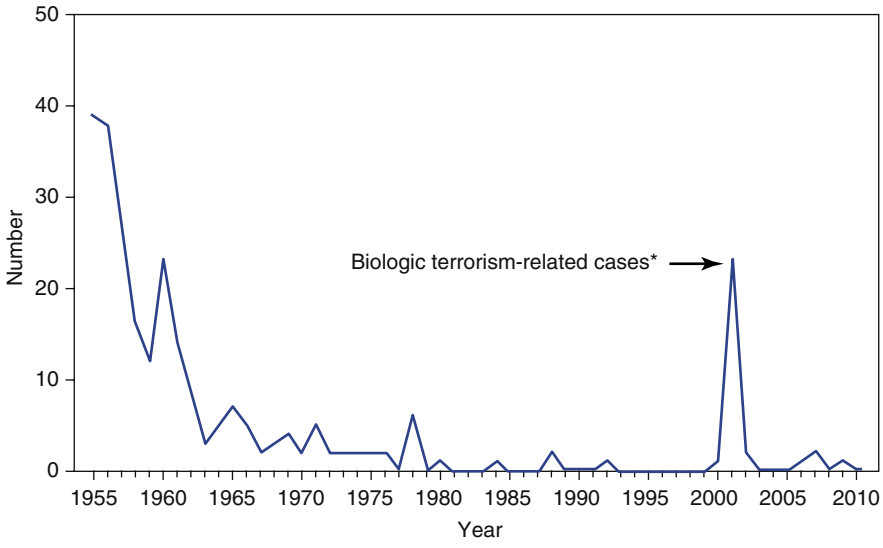


FIGURE EA1-94 Anthrax. Number of reported cases, by year—United States, 1955-2010. (From Centers for Disease Control and Prevention: Summary of notifiable diseases—United States, 2010, *MMWR Morb Mortal Wkly Rep* 59:1-111, 2012.)

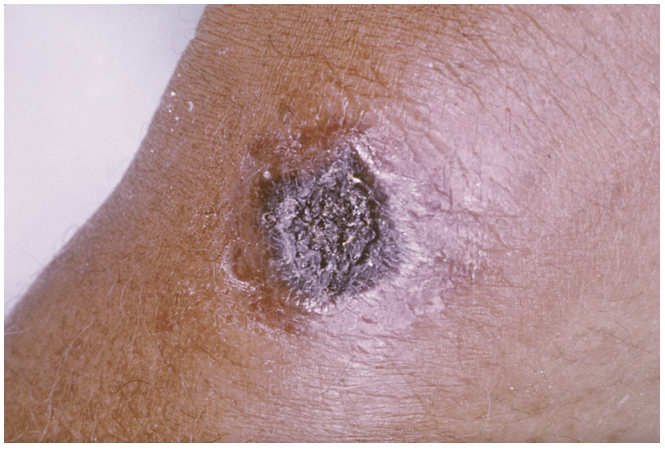


FIGURE EA1-95 Cutaneous anthrax lesion on the skin of the forearm caused by the bacterium *Bacillus anthracis.* (From the Centers for Disease Control and Prevention Public Health Image Library. http://phil.cdc.gov/Phil/home.asp.)

ecthyma gangrenosum, plague, brown recluse spider bite, and tularemia.
- The differential diagnosis of gastrointestinal anthrax includes viral gastroenteritis, shigellosis, and yersiniosis.

LABORATORY TESTS

- Presumptive identification is based on Gram stain of material from skin lesion, CSF, or blood showing encapsulated gram-positive bacilli.
- Confirmatory tests are performed at specialized laboratories. Virulent strains grow on nutrient agar in the presence of 5% CO_2. Susceptibility to lysis by gamma phage and DFA staining of cell-wall polysaccharide antigen are also useful confirmatory tests.
- Nasal swab culture to determine inhalation exposure is of limited diagnostic value. A negative result does not exclude the possibility of exposure. It may be used by public health officials to assist in epidemiologic investigations of exposed persons to evaluate the dispersion of spores.
- Serologic testing by enzyme-linked immunosorbent assay (ELISA) can confirm the diagnosis.
- A skin test (Anthracin test) that detects anthrax cell-mediated immunity is also available in specialized laboratories.

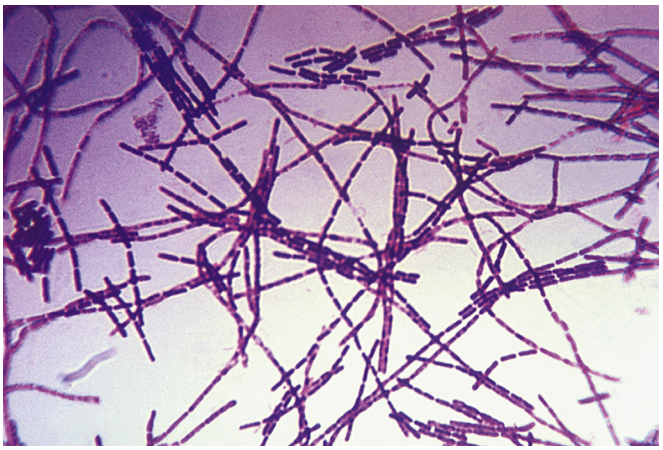


FIGURE EA1-96 A photomicrograph of *Bacillus anthracis* bacteria using Gram stain technique. Anthrax is diagnosed by isolating *B. anthracis* from the blood, skin lesions, or respiratory secretions or by measuring specific antibodies in the blood of persons with suspected cases. (From the Centers for Disease Control and Prevention Public Health Image Library. http://phil.cdc.gov/Phil/home.asp.)

IMAGING STUDIES

Chest radiographs usually reveal mediastinal widening. Additional findings include infiltrates and pleural effusion.

Rx TREATMENT

NONPHARMACOLOGIC Rx

IV hydration and ventilator support may be necessary with inhalation anthrax.

ACUTE GENERAL Rx

- Most naturally occurring *B. anthracis* strains are sensitive to penicillin. Ciprofloxacin, levofloxacin, and doxycycline are effective antibiotics for the treatment of inhalational anthrax infection. Antibiotics are used in combination with IV raxibacumab, a fully human monoclonal antibody. The recommended adult dose of raxibacumab is 40 mg/kg administered IV over 2 hr and 15 min.
- Table EA1-59 describes a treatment protocol for inhalation anthrax.

TABLE EA1-59 Inhalation Anthrax Treatment Protocol[a,b]

Category	Initial Therapy (IV)[c,d]	Duration
Adults	Ciprofloxacin 400 mg q12h[a] **or** Doxycycline 100 mg q12h[f] **and** One or two additional antimicrobials[d] plus raxibacumab	IV treatment initially.[e] Switch to oral antimicrobial therapy when clinically appropriate: Ciprofloxacin 500 mg PO bid **or** Doxycycline 100 mg PO bid Continue for 60 days (IV and PO combined)[g]
Children	Ciprofloxacin 10-15 mg/kg q12h[h,i] **or** Doxycycline:[f,j] >8 yr and >45 kg: 100 mg q12h >8 yr and ≤45 kg: 2.2 mg/kg q12h ≤8 yr: 2.2 mg/kg q12h **and** One or two additional antimicrobials[d]	IV treatment initially.[e] Switch to oral antimicrobial therapy when clinically appropriate: Ciprofloxacin 10-15 mg/kg PO q12h[i] **or** Doxycycline[j]: >8 yr and >45 kg: 100 mg PO bid >8 yr and ≤45 kg: 2.2 mg/kg PO bid ≤8 yr: 2.2 mg/kg PO bid Continue for 60 days (IV and PO combined)[g]
Pregnant women[k]	Same for nonpregnant adults (the high death rate from the infection outweighs the risk posed by the antimicrobial agent)	IV treatment initially. Switch to oral antimicrobial therapy when clinically appropriate.[b] Oral therapy regimens same for nonpregnant adults.
Immunocompromised persons	Same for nonimmunocompromised persons and children	Same for nonimmunocompromised persons and children

[a]For gastrointestinal and oropharyngeal anthrax, use regimens recommended for inhalational anthrax.
[b]Ciprofloxacin or doxycycline should be considered an essential part of first-line therapy for inhalational anthrax.
[c]Steroids may be considered as an adjunct therapy for patients with severe edema and for meningitis based on experience with bacterial meningitis of other etiologies.
[d]Other agents with in vitro activity include rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and clarithromycin. Because of concerns of constitutive and inducible beta-lactamases in *Bacillus anthracis,* penicillin and ampicillin should not be used alone. Consultation with an infectious disease specialist is advised.
[e]Initial therapy may be altered based on clinical course of the patient; one or two antimicrobial agents (e.g., ciprofloxacin or doxycycline) may be adequate as the patient improves.
[f]If meningitis is suspected, doxycycline may be less optimal because of poor central nervous system penetration.
[g]Because of the potential persistence of spores after an aerosol exposure, antimicrobial therapy should be continued for 60 days.
[h]If IV ciprofloxacin is not available, oral ciprofloxacin may be acceptable because it is rapidly and well absorbed from the gastrointestinal tract with no substantial loss by first-pass metabolism. Maximum serum concentrations are attained 1 to 2 hr after oral dosing but may not be achieved if vomiting or ileus is present.
[i]In children, ciprofloxacin dosage should not exceed 1 g/day.
[j]The American Academy of Pediatrics recommends treatment of young children with tetracyclines for serious infections (e.g., Rocky Mountain spotted fever).
[k]Although tetracyclines are not recommended during pregnancy, their use may be indicated for life-threatening illness. Adverse effects on developing teeth and bones are dose related; therefore doxycycline might be used for a short time (7 to 14 days) before 6 mo of gestation.
Modified from *MMWR Morb Mortal Wkly Rep* 5:987, 2001.

- Initial postexposure prophylaxis therapy in adults is with ciprofloxacin, 500 mg PO bid, or doxycycline 100 mg bid, or levofloxacin 500 mg daily. The total duration of treatment is 60 days. Adminstration of anthrax vaccine adsorbed (AVA), an inactivated cell-free filtrate of an avirulent strain available from the CDC in a series of three SC injections at 2-wk intervals, is also recommended for known or suspected inhalation exposure to anthrax in adults.
- A single dose of raxibacumab, a human monoclonal antibody directed against protective antigen, a component of the anthrax toxin, has been reported effective in improving survival in rabbits and monkeys with symptomatic inhalational anthrax. Based on this research, the FDA has approved raxibacumab for treatment of inhalational anthrax in combination with antibiotics.

DISPOSITION

- Case fatality estimates for inhalation anthrax are extremely high (>90%).
- The case fatality rate for cutaneous anthrax is 20% without and <1% with antibiotic treatment.
- The case fatality rate for gastrointestinal anthrax is estimated to be 25% to 60%.

REFERRAL

Consultation with an infectious disease specialist is recommended in all cases of anthrax. Local and state authorities should also be notified of suspected cases of anthrax.

PEARLS & CONSIDERATIONS

COMMENTS

- Postexposure prophylaxis: If the exposure to *B. anthracis* is confirmed and anthrax vaccine is available, 3 doses of the vaccine should be given at 0, 2, and 4 wk, and antibiotics should be continued throughout the 4-wk period. If vaccine is not available, antibiotics should be continued for 60 days.
- Preexposure vaccination is limited to groups at risk for repeated exposures to *B. anthracis* spores, such as bioterrorism level-B laboratories and workers who will be making repeated entries into known *B. anthracis* spore-contaminated areas.
- The U.S. anthrax vaccine is an inactivated cell-free product licensed to be given in a 6-dose series.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Holty JE et al.: Systematic review: a century of inhalational anthrax cases from 1900 to 2005, *Ann Intern Med* 144:270, 2006.

Hupert N et al.: Accuracy of screening for inhalational anthrax after a bioterrorist attack, *Ann Intern Med* 139:337, 2003.

Inglesby TV et al.: Anthrax as a biological weapon, *JAMA* 287:2236, 2002.

Interim guidelines for investigation of and response to Bacillus anthracis exposures, *MMWR Morb Mortal Wkly Rep* 50:987, 2001.

Migone TS et al.: Raxibacumab for the treatment of inhalational anthrax, *N Engl J Med* 361:135–144, 2009.

Post-exposure anthrax prophylaxis, *Med Lett Drugs Ther* 43:91, 2001.

Swartz MN: Recognition and management of anthrax: an update, *N Engl J Med* 345:1621, 2001.

Use of anthrax vaccine for pre-exposure vaccination, *MMWR Morb Mortal Wkly Rep* 51:1024, 2002.

BASIC INFORMATION

DEFINITION

Antiphospholipid antibody syndrome (APS), the most common acquired thrombophilia, is characterized by clinical features of arterial or venous thrombosis and/or pregnancy morbidity *and* the presence of at least one type of antiphospholipid autoantibody (aPL). aPLs are antibodies directed against serum proteins bound to anionic phospholipids. Autoantibodies inhibit the fibrinolytic system and bind to antigenic anticoagulants, which activate endothelial cells, monocytes, and trophoblasts, resulting in complement-mediated thrombosis.

Three types of aPL have been characterized:

- Anticardiolipin antibodies—the most common
- Lupus anticoagulants
- Anti-β2-glycoprotein-1 antibodies

APS can occur with or without associated rheumatic disease, the most common being systemic lupus erythematosus (SLE). APS can affect all organ systems and includes venous and arterial thrombosis, recurrent fetal losses, and thrombocytopenia.

ICD-9CM CODES
795.79 Antiphospholipid antibody syndrome
ICD-10CM CODES
D68.61 Antiphospholipid syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- Up to 5% of healthy individuals have positive aPLs
- Approximately 10% of patients with a deep venous thrombosis have aPLs
- Nearly 20% of women under 50 who have a cerebrovascular accident (CVA) test positive for aPLs
- 10% to 15% of women with recurrent miscarriages have aPLs
- Rule of 40s with systemic lupus erythematosus; 40% of patients with SLE have aPLs but only 40% of patients with antibodies will have thrombosis
- aPL without APS can be seen in patients with certain medications, infections, malignancies, and autoimmune conditions

PREDOMINANT AGE: Young to middle-age adults

RISK FACTORS:

- Underlying SLE and collagen-vascular diseases; other autoimmune disorders, including rheumatoid arthritis, Sjögren's syndrome, Behçet's syndrome, primary immune thrombocytopenia (also known as idiopathic thrombocytopenic purpura); AIDS; hypertension (HTN).
- Most individuals are otherwise healthy and have no underlying medical condition.

GENETICS: Some APS-positive families exist, and human leukocyte antigen (HLA) studies have suggested associations with HLA DR7, DR4, and Dqw7+Drw53.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

No pathognomonic findings on examination; Table A1-60 summarizes other features suggesting the presence of antiphospholipid antibodies; abnormal findings consistent with ischemia or infarction.

- Thrombosis:
  1. Patients with APS are at risk for both venous and arterial thromboses. Venous thromboses are more common, occurring as the initial manifestation of APS in approximately ~30% of APS patients. Of all patients with deep venous thrombosis, approximately 10% have aPL. The most common site for deep vein thrombosis is the calf, but thromboses may also occur in the renal, hepatic, axillary, subclavian, vena cava, and retinal veins. The most common site of arterial thrombosis is the cerebral vessels, followed by the coronary, renal, mesenteric, and bypass arteries. Recurrent thrombosis is common with APS.
- Commonly involved organ systems include:
  1. Central nervous system: stroke, transient ischemic attack, migraine, multi-infarct dementia, epilepsy, movement disorders, transverse myelopathy, depression, Guillain-Barré syndrome, and migraine.
  2. Pulmonary: pulmonary embolism and infarction; pulmonary hypertension; acute respiratory distress syndrome; intraalveolar pulmonary hemorrhage; a postpartum syndrome characterized by fever, pleuritic chest pain, dyspnea, and patchy infiltrates with pleural effusion on chest radiograph.
  3. Cardiology: Libman-Sacks endocarditis, intracardiac thrombosis, coronary artery disease, myocardial infarction.
  4. Gastrointestinal: abdominal pain, gastrointestinal bleed secondary to ischemia, splenic or pancreatic infarction, hepatic vein thrombosis, Budd-Chiari syndrome (second most common cause of syndrome).
  5. Renal: proteinuria, acute renal failure, hypertension, renal infarct, renal artery or vein thrombosis, postpartum hemolytic uremic syndrome.
  6. Hematology: thrombocytopenia, hemolytic anemia.
  7. Endocrine: Addison's disease secondary to adrenal hemorrhage and, less frequently, thrombosis.
  8. Cutaneous: livedo reticularis, cutaneous necrosis, skin ulcerations, gangrene of digits (Fig. A1-97).
  9. Obstetrics: recurrent spontaneous abortion, premature delivery or fetal growth retardation.
- Catastrophic APS (CAPS) (Table A1-61): CAPS is a rapidly progressive multiorgan thrombotic disease. Approximately 1% of APS is CAPS; approximately 45% of CAPS do not present as APS initially. A 50% mortality rate is seen in patients with CAPS. To make the diagnosis of catastrophic APS, four criteria must be satisfied:
  1. Evidence of involvement of three or more organs, systems, and/or tissues. The most common symptoms are abdominal pain, dyspnea, neurologic symptoms, chest pain, and skin rash.

TABLE A1-60 Other Features Suggesting the Presence of Antiphospholipid Antibodies

Clinical
Livedo reticularis
Thrombocytopenia (usually 50,000-100,000 platelets/mm^3)
Autoimmune hemolytic anemia
Cardiac valve disease (vegetations or thickening)
Multiple sclerosis–like syndrome, chorea, or other myelopathy
Laboratory
IgA anticardiolipin antibody
IgA anti–β_2-glycoprotein I

From Firestein GS, et al: Kelly's *textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.

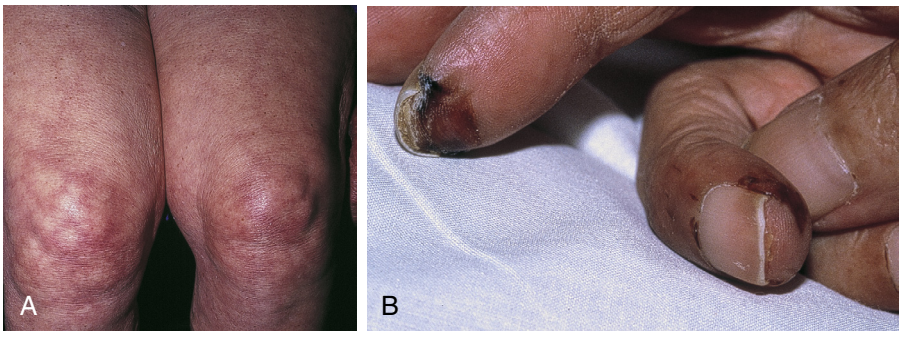


FIGURE A1-97 Antiphospholipid syndrome. The clinical presentations of this disorder are protean and include those shown here. **A,** Broad bands of livedo around the knees in a patient with anticardiolipin antibodies. Physiologic livedo has a finer patterning and less obvious lesions. **B,** Digital infarcts, a nonspecific feature of several vascular occlusion disorders. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

2. Development of manifestations simultaneously or in ≤1 week.
3. Confirmation by histopathology of small-vessel occlusion in at least one organ or tissue.
4. Laboratory confirmation of the presence of aPL.

ETIOLOGY

- aPLs react with negatively charged phospholipids.
- Possible mechanisms of thrombosis include effects of aPL on platelet membranes, endothelial cells, and clotting components such as prothrombin, protein C, or protein S. The mammalian target of rapamycin complex (mTORC) has been shown to be involved in the vascular lesions associated with the antiphospholipid syndrome.
- Studies have recently shown that prephospholipids are not immunogenic and that a binding protein (β_2-glycoprotein I) may be the key immunogen in the APS.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Other hypercoagulable states (inherited or acquired):

- Inherited: ATIII, protein C and protein, S deficiencies, factor V Leiden, prothrombin gene mutation.
- Acquired: heparin-induced thrombocytopenia, myeloproliferative syndromes, cancer
- Nephrotic syndrome.

WORKUP

Diagnostic criteria of APS include at least one clinical criterion and at least one laboratory criterion. A single clot may not be sufficient, especially with other thrombotic risk factors.

- Clinical:
  1. Venous, arterial, or small vessel thrombosis *or*
  2. Morbidity with pregnancy, defined as:
     1. Fetal death at ≥10 weeks' gestation *or*
     2. ≥1 premature births before 34 weeks' gestation secondary to eclampsia, preeclampsia, or severe placental insufficiency *or*
     3. ≥3 unexplained spontaneous abortions at 10 weeks' gestation.
- Laboratory (see Table A1-62):
- Screening tests
  1. Partial thromboplastin time (PTT): Elevated, indicating either the presence of a clotting factor deficiency, or the presence of an inhibitor such as a lupus anticoagulant.
  2. Mixing study: Elevated. Normal plasma is incubated with the patient's plasma. In cases of clotting factor deficiencies the PTT will correct. If an inhibitor is present the PTT WILL NOT correct.
  3. Dilute Russell viper venom time: Elevated. Laboratory clotting requires the addition of phospholipids and calcium to plasma samples. Anti-phospholipid antibodies bind the phospholipids in the test tube, thereby preventing clot formation. The addition of Russell viper venom to plasma results in immediate activation of Factor X (common pathway). It, therefore, will not be prolonged in intrinsic or extrinsic factor deficiencies but will be prolonged in the presence of an antiphospholipid antibody. The Lupus Anticoagulant screen is the addition of Russell viper venom to plasma. In the Lupus Anticoagulant confirmatory testing massive doses of phospholipids are added to saturate the antiphospholipid antibody thereby correcting the prolonged PTT.
- Initial testing for presence of aPL:
  1. ELISA anticardiolpin antibody aCL antibody in medium or high titers *or*
  2. Lupus anticoagulant activity found *or*
  3. Anti-beta$_2$-glycoprotein (anti-b2GPI)-ELISA antibodies no more than 5 years from the clinical event.
- Confirmatory aPL testing: repeat after 12 weeks to confirm persistence of aCL, anti-β2GPI or LA test. Transient elevations of aCL can occur. Traditional aPL tests include aCL and B2GPI. Newer aPL tests include aps/PT and β2GPI.

TABLE A1-61 Differential Diagnosis of Catastrophic Antiphospholipid Syndrome (CAPS)

Laboratory Abnormalities	CAPS	TTP	DIC
Microangiopathic hemolytic anemia	–	+	+
Thrombocytopenia	+	+	+
Fibrinogen/FDP	Normal/Normal	Normal/Increased	Decreased/Increased
Anticardiolipin antibody	+	–	–
Lupus anticoagulant	+	–	–

TABLE A1-62 Assays Used to Confirm Diagnosis of Antiphospholipid Syndrome

Assay	Methodology
"Criteria" aPL Assays	
aCL	ELISA
Anti-β_2-GPI	ELISA
LAC	Clotting/functional assays
"Noncriteria" aPL Assays	
Assays to detect antibodies to other phospholipids (i.e., phosphatidylserine, phosphatidylinositol, phosphatidic acid, phosphatidylglycerol, phosphatidylethanolamine, phosphatidylcholine)	ELISA
Annexin A5 resistance assay	Clotting/mechanistic assay
Assays to detect antibodies to prothrombin or prothrombin/phosphatidylserine	ELISA
Assays to detect antibodies to clotting proteins (i.e., protein C, protein S)	ELISA

aCL, Anticardiolipin; *aPL,* antiphospholipid antibody; *ELISA,* enzyme-linked immunosorbent assay; *LAC,* lupus anticoagulant.
From Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.

LABORATORY TESTS

Diagnostic evaluation of aCL and LA antibodies is indicated in:

- Patient with underlying SLE or collagen-vascular disease with thrombosis.
- Patient with recurrent, familial, or juvenile deep vein thrombosis (DVT) or thrombosis in an unusual location (mesenteric or cerebral).
- One or more unexplained thrombotic events. Do not test in those at low risk, e.g., the elderly with clot and other risk factors.
- One or more specific pregnancy events.
- Unexplained thrombocytopenia.
- Patients with an elevated PTT.

Abnormal tests include:

- False-positive test for syphilis (RPR/VDRL).
- Lupus anticoagulant activity.
- Presence of anticardiolipin antibodies (ELISA for anticardiolipin is the most sensitive and specific test [>80%]).
- Presence of anti-b$_2$-glycoprotein I antibody.

Rx TREATMENT

ACUTE Rx

Treatment includes use of heparin, low-molecular-weight heparin (LMWH), warfarin, novel oral anticoagulants, antiplatelet agents, acetylsalicylic acid (aspirin), clopidogrel, hydroxychloroquine.

- For a patient with positive aPL and venous or arterial thrombosis: Treat as would any other thrombosis.
  1. Anticoagulation with heparin or LMWH, then followed by indefinite warfarin treatment, with a target international normalized ratio (INR) of 2.0 to 3.0.
  2. There is some evidence to support a higher INR target or the addition of other agents in patients with arterial clots, especially if they have recurrent events while taking warfarin.
- Length of treatment needed is unknown, but likely indefinite barring no contraindication to anticoagulation, as the lifelong recurrence rate is 11% to 29%.
- Unfractionated heparin (UFH) is preferred if quick reversibility is needed.

PRIMARY PREVENTION

- Aspirin is of no benefit for prevention in patients with a prior clot.
- Aspirin may help patients without a history of clot.
- Patients with a previous history of venothromboembolism and antiphospholipid antibodies are typically placed on an indefinite course of anticoagulation.
- Hydroxychloroquine may be useful in those patients with SLE and aPL.
- Avoid oral contraceptive pills; modifiable risk factors for thrombosis such as smoking and immobility should be addressed.
- For pregnant women with a positive test for aPL antibodies without a history of DVT or pregnancy loss, consider low-dose subcutaneous UFH or LMWH SC, aspirin 81 mg, or surveillance.

SECONDARY PREVENTION

- For pregnant women with previously diagnosed APS:
  1. Warfarin should be discontinued in early pregnancy secondary to its teratogenic effects.
  2. Aspirin 81 mg, and subcutaneous UFH or LMWH to therapeutic partial thromboplastin time (PTT) or factor Xa levels, respectively.
  3. Pregnant patients taking LMWH should be transitioned to unfractionated heparin before delivery due to reversibility.
  4. Intravenous immunoglobulin (IVIG), plasmapheresis, hydroxychloroquine, statins, clopidogrel, dipyridamole, and rituximab have been used when other treatments have failed.
- For pregnant women with a positive test for aPL antibodies and a history of fewer than three spontaneous abortions:
  1. Low-dose aspirin at conception, followed by UFH, prophylactically or an intermediate dose at 7 weeks, continuing until 6 weeks' postpartum.
  2. A mid-interval PTT should be checked and should be normal or similar to baseline before therapy.
  3. LMWH can be used in place of unfractionated heparin and should be titrated to factor Xa levels in the recommended prophylactic range. The combination aspirin (75 mg daily) plus LMWH has been associated with a higher live birth rate when compared with IVIG.

FOR CATASTROPHIC ANTIPHOSPHOLIPID ANTIBODY SYNDROME

- Highest survival rates are achieved with the combination of anticoagulation, corticosteroids, and IVIG or plasma exchange.
- Case reports have shown rituximab to be a successful therapy for patients with life-threatening thrombosis refractory to anticoagulation.

CHRONIC Rx

- Anticoagulation with warfarin therapy.
- Immunosuppressive agents such as corticosteroids and cyclophosphamide have not been shown to be effective.
- Limited data suggest that hydroxychloroquine may be effective in patients with APS and SLE.

DISPOSITION

- APS patients have a 20% to 70% risk for recurrent thrombosis.
- Initial arterial thrombosis tends to be followed by arterial events, and initial venous thrombosis tends to be followed by venous events.
- Catastrophic APS is associated with a high mortality rate, approaching 50%.
- Incidence of developing catastrophic APS is approximately 0.8% among APS patients.

REFERRAL

To hematology or rheumatology and/or obstetric medicine when diagnosis is made.

PEARLS & CONSIDERATIONS

COMMENTS

Cerebral features of SLE may be more related to thrombosis than inflammation and may respond better to anticoagulants than immunosuppression.

PREVENTION

Prophylaxis for asymptomatic patients with positive aPL tests without previous thrombosis:

- No routine prophylaxis is recommended.
- Questionable whether low-dose aspirin is effective.
- Antithrombotic prophylaxis for major surgery, prolonged immobilization, and pregnancy.
- Avoid oral contraceptive pills in women with positive aPL test.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hypercoagulable States (Related Key Topic)
Deep Vein Thrombosis (Related Key Topic)
Pulmonary Embolism (Related Key Topic)
Antiphospholipid Antibody Syndrome (Patient Information)

AUTHORS: **KALYAN C. MANTRIPRAGADA, M.D., M.P.H.,** and **JOHN L. REAGAN, MD**

SUGGESTED READINGS

Ahn ER et al.: Long-term remission from life-threatening hypercoagulable state associated with lupus anticoagulant (LA) following rituximab therapy, *Am J Hematol* 78(2):127, 2005.

Ansell J et al.: Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, (8th Edition) *Chest* 133(6 Suppl):160S–198S, 2008.

Asherson RA et al.: Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines, *Lupus* 12:530, 2003.

Barbhaiya M, Erkan D: Primary thrombosis prophylaxis in antiphospholipid antibody positive patients. Where do we stand? *Curr Rheumatol Rep* 13(1):59–69, 2011.

Canaud G et al.: Inhibition of the mTORC pathway in the antiphospholipid syndrome, *N Engl J Med* 371:303–312, 2014.

Charakida M et al.: Vascular abnormalities, paraoxonase activity, and dysfunctional HDL in primary antiphospholipid syndrome, *JAMA* 302(11):1210–1217, 2006.

Donadini MP et al.: antiphospholipid syndrome: a challenging hypercoagulable state with systemic manifestations, *Hematol Oncol Clin North Am* 24(4): 667–676, 2010.

Erkan D, Lockshin MD: New treatments for antiphospholipid syndrome, *Rheum Dis Clin North Am* 32:129, 2006.

Espinosa G, Cervera R: Thromboprophylaxis and obstetric management of the antiphospholipid syndrome, *Expert Opin Pharmacother* 10(4):601, 2009.

Giannakopoulos MB, Krilis SA: The pathogenesis of the antiphospholipid syndrome, *N Engl J Med* 368:1033–1044, 2013.

Hoppe B et al.: Heparin or aspirin or both in the treatment of recurrent abortions in women with antiphospholipid antibody syndrome, *Curr Opin Rheumatol* 23(3):299–304, 2011.

Lim W et al.: Management of antiphospholipid antibody syndrome: a systematic review, *JAMA* 295(9):1050, 2006.

Miyakis S et al.: International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome, *J Thromb Haemost* 4:295, 2006.

Mullen MT et al.: Antiphosphatidylserine-prothrombin antibodies are associated with outcome in TIA cohort, *Frot Neurol* 3:137, 2012.

Rubenstein E et al.: Rituximab treatment for resistant antiphospholipid syndrome, *J Rheumatol* 33(2):355, 2006.

Ruiz-Irastorza G et al.: Antiphospholipid syndrome, *Lancet* 376:1498–1509, 2010.

Ruiz-Irastorza G et al.: Evidence based recommendations for the prevention and long term management of thrombosis in antiphospholipid antibody positive patients, *Lupus* 20:206, 2011.

Van den Boogaard E et al.: Number and sequence of preceding miscarriages and maternal age for the prediction of antiphospholipid syndrome in women with recurrent miscarriage, *Fertil Steril* 99:188–192, 2013.

BASIC INFORMATION

DEFINITION

Generalized anxiety disorder (GAD) is most likely to present in combination with other psychiatric and medical conditions. Individuals with GAD commonly present with excessive and disproportionately high levels of anxiety, fear, or worry for most days over at least a 6-mo period. The worrying must be greater than would be expected given the situation, and it must cause significant interference in functioning. The subjective anxiety must be accompanied by at least three somatic symptoms in adults, and one in children (e.g., restlessness, irritability, sleep disturbance, muscle tension, difficulty concentrating, or fatigue). GAD cannot be diagnosed if it occurs only in the context of an active mood disorder, such as depression, or if the anxiety is better explained by another active anxiety disorder, such as PTSD or panic disorder.

SYNONYMS

Anxiety neurosis (former name for a subset of anxiety disorders)
Chronic anxiety
GAD

ICD-9CM CODE
300.02
ICD-10CM CODES
F41.1 Generalized anxiety disorder
DSM-IV CODE
300.02

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 6% to 9% per year in adult primary care clinics; 1-yr incident rate per 100 person-yr of 1.12
PEAK INCIDENCE: Peak incidence tends to occur later relative to other anxiety disorders, such as phobias; cumulative incidence of 4.3% by age 34 in a German community sample
PREVALENCE (IN U.S.):
- In general population: lifetime morbid risk of 9%; 12-month prevalence of 2%
- In primary care setting: 3% (the most common anxiety disorder in this setting)

PREDOMINANT SEX: Women are more frequently affected (2:1 ratio) but may present for treatment less often (3:2 female/male).
PREDOMINANT AGE:
- 30% report onset before age 11
- 50% have onset before age 18
- Median age of onset: 30 years

GENETICS: Concordance rates in dizygotic twins and monozygotic twins are not different (0% to 5%)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Report of being "anxious" all of their lives.
- Excessive worry, usually regarding family, finances, work, or health.
- Sleep disturbance, particularly early insomnia.
- Muscle tension (typically in the muscles of neck and shoulders) or headache.
- Difficulty concentrating.
- Daytime fatigue.
- GI symptoms compatible with IBS (one third of patients).
- Physical symptoms are the usual reason for seeking medical attention.
- Comorbid psychiatric illness (e.g., dysthymia or major depression) and substance abuse (e.g., alcohol abuse) are frequent.

ETIOLOGY

- Hypotheses include models based on neurotransmitters (catecholamines, indolamines) and developmental psychology (e.g., behavioral inhibition, neuroticism, and harm avoidance).
- Prevalence increased with a family history, increase in stress, history of physical or emotional trauma, and medical illness.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Wide range of psychiatric and medical conditions:
  1. Cardiovascular and pulmonary disease, such as cardiac arrhythmias or COPD
  2. Hyperthyroidism, hypoglycemia
  3. Substance abuse (e.g., cocaine, amphetamines, and PCP) or withdrawal (e.g., alcohol or benzodiazepines)
  4. Other anxiety disorders (e.g., social anxiety disorder), mood disorder

WORKUP

- Screening tests may enhance detection. A screening tool often used in primary care is the GAD-2. It asks, "During the past month, have you been bothered a lot by: (1) Nerves or feeling anxious or on edge? (2) Worrying about a lot of different things?" The response to each question is given a score of 0 (not at all), 1 (several days), 2 (more than half of the days), 3 (nearly every day). A score of ≥3 has a sensitivity of 86% and a specificity of 83% for detecting GAD. A simple 7-item in-office case finding instrument, the GAD-7, includes additional questions to assess symptom severity and can be used to monitor symptoms.
- Physical examination: additional laboratory and radiologic workup depend on presenting symptoms.
- Iatrogenic cause should be suspected if anxiety follows recent changes in medication.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cognitive-behavioral therapy
- Acceptance and commitment therapy
- Relaxation training
- Biofeedback
- Psychodynamic psychotherapy

PHARMACOLOGIC THERAPY

- SSRIs/SNRIs
- Azapirones (e.g., buspirone)
- Benzodiazepines (less favored)

ACUTE GENERAL Rx

- Acute treatment is rarely indicated because GAD is a chronic condition.
- If patients are in acute distress, the possibility of another cause, including another anxiety disorder such as panic disorder, should be considered.
- Caution in prescribing benzodiazepines because of the propensity for misuse and dependence. If used, the patient should be educated about the options and the risks.

CHRONIC Rx

- SSRIs and SNRIs (e.g., venlafaxine and duloxetine) are effective typical first-line treatment. Particularly useful if comorbid depression present.
- Buspirone can be effective with minimal potential for tolerance or abuse. May be less effective in patients with previous benzodiazepine exposure and may require a high-dose titration.
- Benzodiazepines can be effective under close supervision; however, they have fallen out of favor as a first-line treatment given their potential for functional impairment, abuse, and dependence.
- Sedating antidepressants, such as mirtazapine, may also be useful for initial insomnia secondary to anxious ruminations.

DISPOSITION

- GAD is chronic with periodic exacerbations.
- Treatment is given to reduce level of symptoms and improve functioning. Suicide risk is higher than in the general population.

REFERRAL

- For refractory symptoms.
- For comorbid psychiatric conditions.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Anxiety (Patient Information)
Panic Disorder (Related Key Topic)
Social Anxiety Disorder (Related Key Topic)

AUTHOR: **KRISTY L. DALRYMPLE, PH.D.**

SUGGESTED READINGS

Beesdo K et al.: Incidence and risk patterns of anxiety and depressive disorders and categorization of generalized anxiety disorder, *Arch Gen Psychiatry* 67(1):47–57, 2010.

Davidson JR: First-line pharmacotherapy approaches for generalized anxiety disorder, *J Clin Psychiatry* 70(suppl 2):25–31, 2009.

Fricchione G: Clinical practice. Generalized anxiety disorder, *N Engl J Med* 351(7):675, 2004.

Hayes-Skelton SA et al.: A randomized clinical trial comparing an acceptance-based behavior therapy to applied relaxation for generalized anxiety disorder, *J Consult Clin Psychol*, 2013.

Kroenke K et al.: Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection, *Ann Intern Med* 146(5):317–325, 2007.

Patel G, Fancher TL: In the clinic: generalized anxiety disorder, *Annals of Internal Medicine ITC* 6(10), Dec 3, 2013.

Stanley MA et al.: Cognitive behavior therapy for generalized anxiety disorder among older adults in primary care, *JAMA* 301(14):1460–1467, 2009.

Stewart RE, Chambless DL: Cognitive-behavioral therapy for adult anxiety disorders in clinical practice: a meta-analysis of effectiveness studies, *J Consult Clin Psychol* 77(4):595–606, 2009.

Weisberg RB: Overview of generalized anxiety disorder: epidemiology, presentation, and course, *J Clin Psychiatry* 70(suppl 2):4–9, 2009.

Aortic Dissection EBM PTG

BASIC INFORMATION

DEFINITION

Aortic dissection is part of a spectrum of aortic pathologies (acute aortic syndromes) that include intramural hematomas and penetrating atherosclerotic ulcers. Aortic dissection occurs when blood passes through an intimal tear, separating the intima from the medial layers and creating a false lumen. Intramural hematoma (IMH) occurs when the vasa vasorum ruptures within the medial wall. IMH does not involve an intimal tearing unless a dissection develops. Seventeen percent of IMH will transform into aortic dissection. Penetrating atherosclerotic ulcers, which occur in the setting of extensive aortic atherosclerosis and hypertension, destroy the aortic intima and dissect into the aortic media. Rupture of atherosclerotic plaques with subsequent blood entry into the median wall forms a pseudoaneurysm. Fig. A1-98 illustrates acute aortic syndromes.

SYNONYMS

Dissecting aortic aneurysm

ICD-9CM CODES
441.00 Aortic dissection
444.01 Aortic dissection, thoracic
ICD-10CM CODES
I71.00 Dissection of unspecified site of aorta

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT SEX AND AGE: Males (65%) females (35%), ages 60 to 80 yr; mean, 63 yr
INCIDENCE: 2.6-3.5 per 100,000 person-years

RISK FACTORS:
- Hypertension (found in up to 72% of patients with aortic dissection).
- Atherosclerosis (found in up to 31% of patients with aortic dissection)
- Age (60 to 80 years)
- Family history of aortic aneurysms/dissection
- History of cardiac surgery, aortic valve replacement, intraaortic catheterization
- Disorders of collagen (Marfan's syndrome, Ehlers-Danlos syndrome)
- Vascular inflammation (giant cell arteritis, Takayasu arteritis, rheumatoid arthritis, syphilitic aortitis)
- Aortic coarctation, bicuspid aortic valve
- Turner's syndrome
- Cocaine abuse (usually within 12 hours of last use of cocaine)
- Trauma

CLASSIFICATION

Aortic dissection is generally classified according to anatomic location (Fig. A1-99):
- Stanford (more commonly used classification system): type A ascending aorta (proximal), type B descending aorta (distal) (Fig. A1-100)
- DeBakey: type I ascending and descending aorta, type II ascending aorta, type III descending aorta
- Aortic dissection can also be classified by acuity of presentation (acute or chronic), based on the time of onset.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Sudden onset of severe sharp, tearing, or ripping chest pain
- Anterior chest pain (ascending dissection)
- Back pain, abdominal pain (descending dissection)
- Syncope (secondary to cardiac tamponade or stroke), congestive heart failure (CHF)
- May present with hypertension (70% in type B dissection, 36% for type A), 25% with hypotension (systolic blood pressure <100 mm Hg), which can indicate bleeding, cardiac tamponade, or severe aortic regurgitation
- Pulse and blood pressure differentials (>20 mm Hg between arms) in 9% to 30% of cases, caused by partial compression of subclavian arteries
- Aortic regurgitation in 18% to 50% of cases of proximal dissection, often with diastolic decrescendo murmur
- Myocardial ischemia caused by coronary artery occlusion, most commonly involving the right coronary artery
- Stroke in 5% to 10% of patients (secondary to dissection into or decreased blood flow to the carotids)
- Horner syndrome (ptosis, miosis, anhidrosis)
- Vocal cord paralysis/hoarse voice (due to compression of the left recurrent laryngeal nerve)

ETIOLOGY

Genetics, in addition to other risk factors listed above, contribute to the development of aortic dissection.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Known as the great imitator: Pulmonary embolism, acute coronary syndrome, aortic stenosis/insufficiency, nondissecting aneurysm, pericarditis, cholecystitis, peptic ulcer disease, pancreatitis, musculoskeletal pain
- Consider aortic dissection in patients with unexplained stroke, chest pain, syncope, acute-onset CHF, abdominal pain, back pain, and malperfusion of extremities or internal organs.

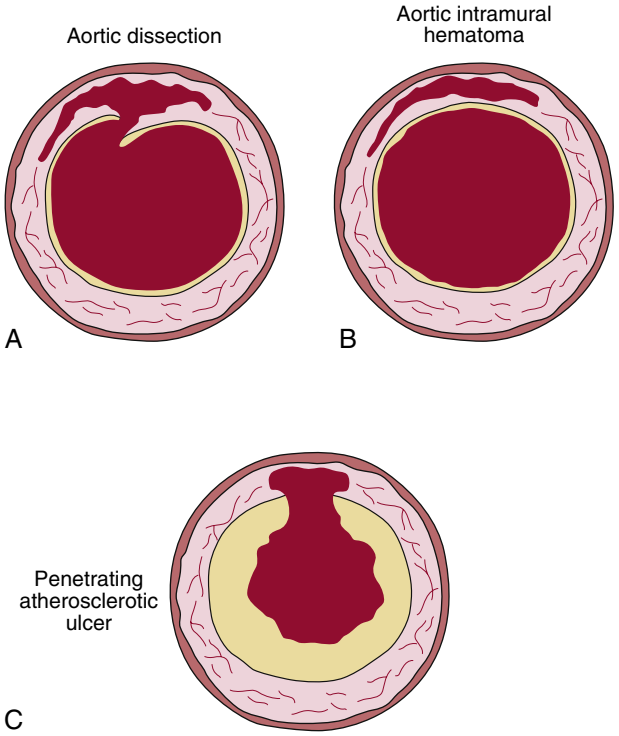


FIGURE A1-98 Acute aortic syndromes. A, Classic aortic dissection. **B,** Aortic intramural hematoma. **C,** Penetrating atherosclerotic aortic ulcer. (From Bonow RO, et al: *Heart disease*, ed 9, 2012, Saunders.)

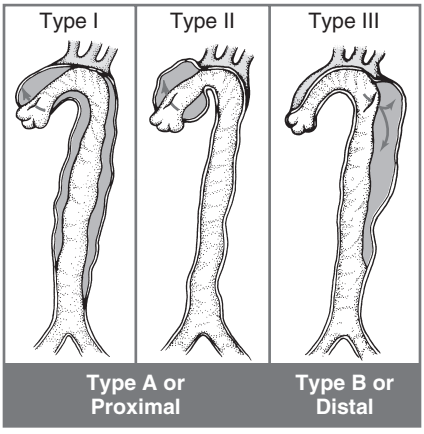


FIGURE A1-99 Classification systems for aortic dissection. (From Isselbacher EM et al: Disease of the aorta. In Braunwald E [ed]: *Heart disease: a textbook of cardiovascular medicine,* ed 5, Philadelphia, 1997, Saunders.)

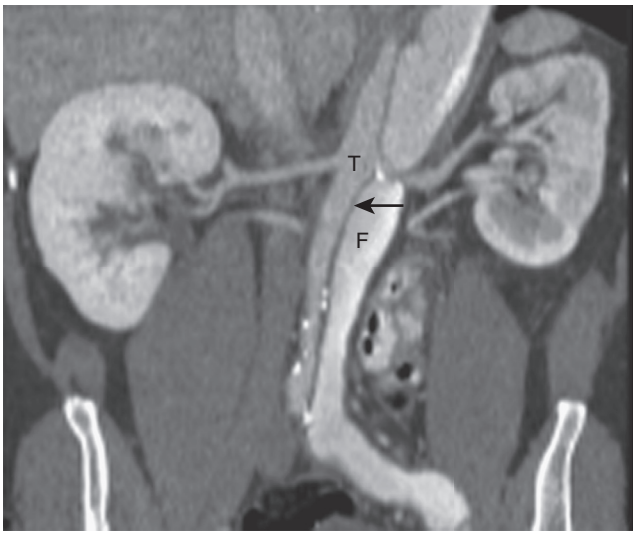


FIGURE A1-100 Computed tomographic angiogram of the aorta shows type B aortic dissection. The intimal flap *(arrow)* separates the two lumen *(T)* from the false lumen *(F)* and compromises blood flow to the right kidney, causing renal atrophy and cortical thinning. (Image courtesy of Bart Domatch, M.D., Radiology Department, University of Texas Southwestern Medical Center, Dallas, TX; from Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.)

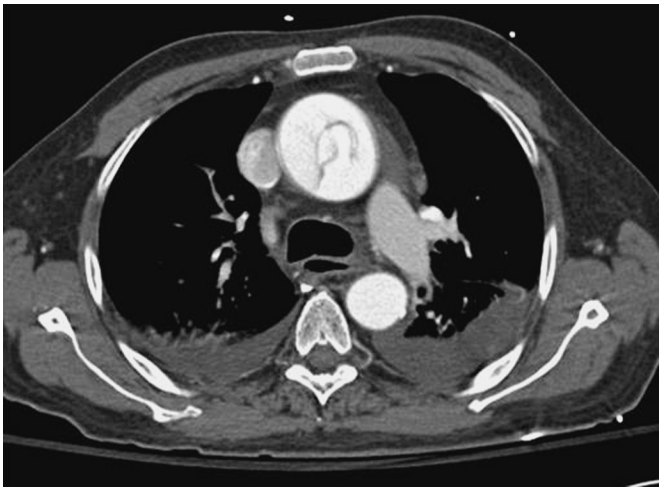


FIGURE A1-101 Thin-slice CT image of a classic ascending dissection with aneurysmal dilation. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

LABORATORY TESTS

- ECG: helpful to rule out MI, although dissection can lead to coronary ischemia
- D-dimer has a 100% negative predictive value but lacks specificity in the setting of acute aortic dissection.
- Three biomarkers with different diagnostic windows can be used in the diagnosis of aortic dissection.
- Smooth muscle myosin heavy chain protein (released from damaged medial smooth muscle) can be used to detect proximal aortic dissections (91% sensitivity and 93% specificity). Myosin heavy chains will peak within 3 hr of dissection and clear within 24 hr of aortic injury.
- CK-BB isoenzyme also peaks within 6 hr of dissection.
- Calponin, a smooth muscle troponin counterpart, increases in aortic dissection with a wider diagnostic window when compared to smooth muscle myosin heavy chain and CK-BB.
- C-reactive protein, fibrinogen, and elastin fragments are under investigation

IMAGING STUDIES

- Multidetector CT is considered the gold standard; but its use may be limited in patients with renal failure as it involves the use of IV contrast. Fig. A1-101 shows a thin-slice CT image of a classic ascending dissection with aneurysmal dilation.
- TEE, multidetector CT, and MRI are all highly sensitive (98% to 100%) and specific (95% to 98%). Test of choice depends on clinical circumstances and hospital availability.
- Transesophageal echocardiography (TEE) is study of choice in unstable patients with type A dissection but is operator dependent.
- MRI has high sensitivity and specificity but limited availability; not suitable for unstable patients; contraindicated with pacemakers, metal devices.
- With medium or high pretest probability, a second diagnostic test should be done if the first is negative.
- Coronary computed tomographic angiography (CTA) may be an alternative and useful diagnostic study when evaluating for pulmonary embolism, acute coronary syndrome, and aortic dissection.
- Aortography rarely done, as less sensitive than TEE, CT, or MRI.
- Chest radiograph may show widened mediastinum (62%) and displacement of aortic intimal calcium. It is negative in 11% to 16% of patients with aortic dissection.
- Although the diagnostic sensitivity of transthoracic echocardiography is suboptimal, it is useful in assessing potential high-risk features or complications, such as pericardial effusion, and making other potential diagnoses. A negative transthoracic echocardiography, however, does not exclude aortic dissection.

Rx TREATMENT

- Proximal dissections (acute type A) require emergent surgery to prevent rupture or pericardial effusion.
- Distal dissections (Stanford type B) are usually treated medically unless distal organ involvement or impending rupture occurs.
  1. Surgical intervention for distal dissections is reserved for patients who have a complicated course, including occlusion of a major aortic branch, propagation of the dissection, presence within an aortic aneurysm, and evidence of aortic rupture.
  2. Fig. A1-102 describes an algorithm for the diagnosis and treatment of aortic dissection.

ACUTE GENERAL Rx

- Admit to ICU for monitoring.
- Target SBP 100 to 120 mm Hg or as low as tolerated; heart rate <60 beats/min to reduce aortic wall stress.
- IV beta-blockers are cornerstones of treatment, but multiple medications may be needed.
  1. Propranolol 1 mg every 3 to 5 min; metoprolol 5 mg IV every 5 min; or labetalol 20 mg IV, then 20 to 80 mg every 10 min, followed by nitroprusside 0.3 to 10 mcg/kg/min.
  2. Nitroprusside should not be used without beta-blockade because vasodilation can induce reflex sympathetic stimulation and increased aortic sheer stress.
  3. IV calcium channel blockers with negative inotropy (i.e., verapamil, diltiazem) may be used if beta-blockers are contraindicated.
- Pain control, often with morphine.

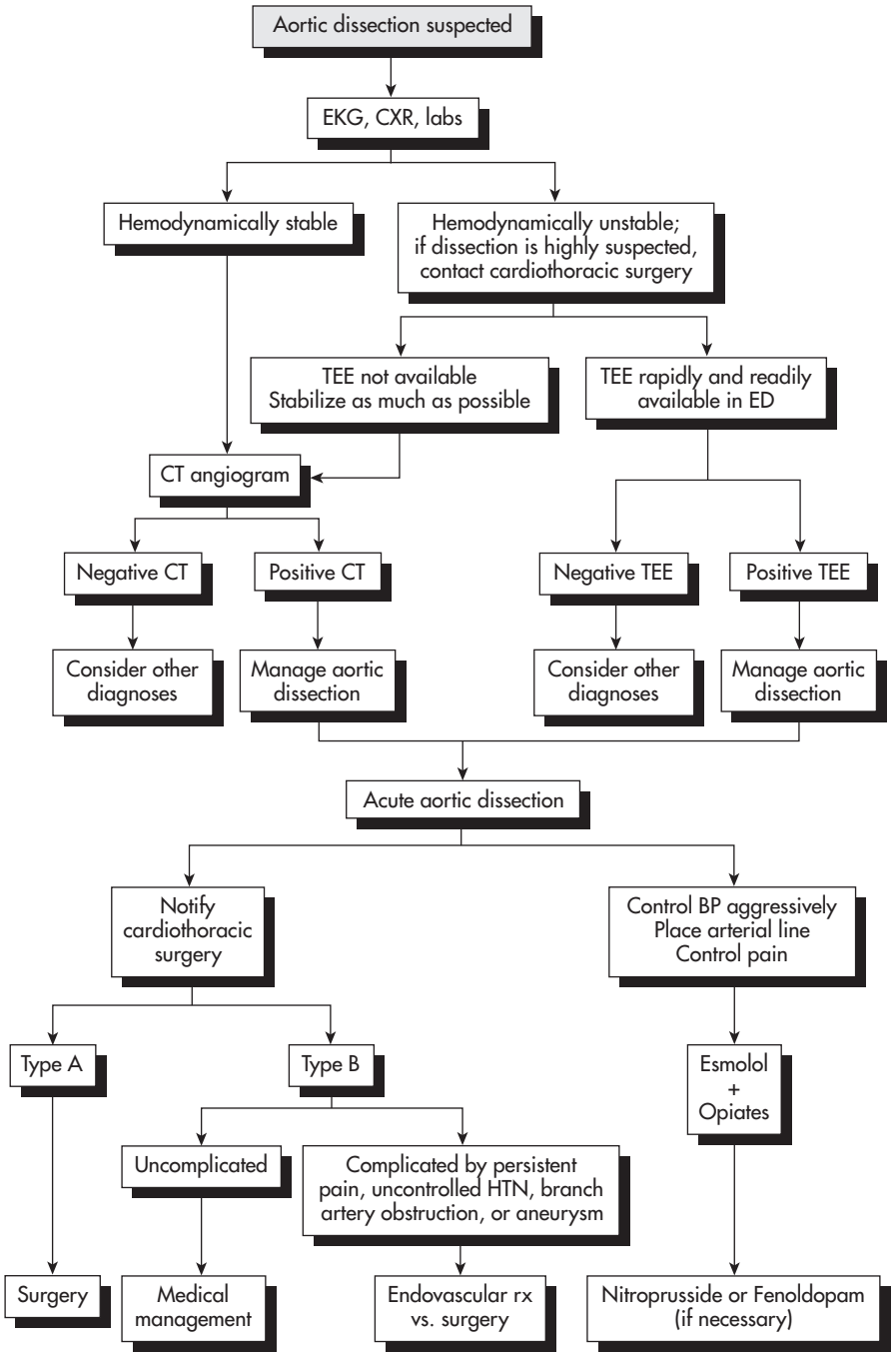


FIGURE A1-102 Algorithm for the diagnosis and treatment of aortic dissection. *BP*, Blood pressure; *CT*, computed tomography; *CXR*, chest radiograph; *ECG*, electrocardiography; *ED*, emergency department; *HTN*, hypertension; *labs*, laboratory tests; *TEE*, transesophageal echocardiography. (Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

- Thoracic endovascular repair (TEVAR) is a less invasive option for complicated type B aortic dissections. Literature has shown significant decrease in short- and mid-term morbidity and mortality with stent grafting when compared to surgery in chronic type B dissections. A meta-analysis found that morbidity and mortality was significantly higher with acute compared to chronic dissections. However, current expert consensus supports TEVAR for first-line treatment in both complicated acute and chronic type B dissection. Long-term outcome data are still under investigation.

CHRONIC Rx

- Chronic aortic dissection (>2 wk) managed with aggressive blood pressure control: target <120/80 mm Hg in most patients.
- Target low-density lipoprotein <70 mg/dl.
- Minimize strenuous physical activity such as heavy lifting.
- Serial imaging of the aorta, with multidetector CT or MRI should be performed at presentation, at 1 wk, and at 6 wks given the higher risk of instability early on, followed by yearly clinical and imaging follow-up.
- As stated above, endovascular repair should be considered in complicated chronic type B dissections, i.e., when the aortic diameter exceeds 5.5 cm, when there is uncontrolled pain or blood pressure, or when there is rapid growth of the dissecting aneurysm (>4 mm per year).

DISPOSITION

- 85% mortality rate within 2 weeks for an untreated type A dissection.
- Proximal dissection is a surgical emergency. Time is critical; mortality rate is 1% to 3% per hour.
- Overall, in-hospital mortality rate is 30% with proximal dissections and 10% with distal dissections.

REFERRAL

For ICU management and surgical intervention

PEARLS & CONSIDERATIONS

- Blood pressure control is essential; beta-blocker is first-line medication.
- Proximal dissection is a surgical emergency.
- Cardiac tamponade is not uncommon in patients with acute type A aortic dissection. Syncope, altered mental status, and a widened mediastinum on chest radiograph on presentation suggest tamponade which warrants urgent operative therapy.
- Surgery for acute type A aortic dissection in patients ≥70 years old can be performed with acceptable outcomes.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Aortic Dissection (Patient Information)
Abdominal Aortic Aneurysm (Related Key Topic)

AUTHORS: **SUNIT-PREET CHAUDHRY, M.D., PHILIP STOCKWELL, M.D.,** and **MEGHANA RAO, M.A., M.D.**

EVIDENCE

Abstract[1]

Objective:

This prospective multicenter comparative study examined early and mid-term results of medication and stent-graft therapies on chronic type B aortic dissection in China.

Methods:

The study consisted of 303 consecutive patients with chronic type B aortic dissection from four centers in China from January 2007 to December 2010 who were prospectively enrolled and treated by either optimal medical therapy (OMT) or thoracic endovascular aorta repair (TEVAR). Of the patients, 219 were male and 84 were female (average age, 53.6±20.3 years; range, 29-81 years). Baseline diameter of the thoracic aorta was 41.2 (19.1) mm (mean [standard deviation]), and dissection extended beyond the celiac axis in 87.1% of cases.

Results:

In total, there were 208 patients in the TEVAR group and 95 patients in the OMT group. Procedural success was 100%, and no deaths occurred during index hospitalization in the two groups. In the TEVAR group, two patients (0.9%) suffered from retrograde type A dissection, and two (0.9%) suffered from paraplegia or paraparesis. For in-hospital outcome, multivariate analysis revealed that age >75 years and American Society of Anesthesiologists class greater than III were independent predictors of major early adverse events. Average follow-up time for hospital survivors was 28.5±16.3 months (range, 1.0-58 months). In the OMT group, five patients died from rupture of an enlarged false lumen, and six patients died suddenly of unknown reasons. Fourteen cases required crossover to TEVAR (n = 12) or surgical conversion (n = 2). In the TEVAR group, nine patients required reintervention or surgical conversion, and one died of postoperative multi-organ failure. One patient died of delayed retrograde type A dissection, and four died suddenly of unknown reasons. The Kaplan-Meier analysis of survival probability at 2 and 4 years was 87.5% and 82.7% with TEVAR, respectively, and 77.5% and 69.1% with OMT, respectively (P = .0678, log-rank test). The estimated cumulative freedom from aorta-related death at 2 and 4 years was 91.6% and 88.1% with TEVAR, respectively, and 82.8% and 73.8% with OMT, respectively (P = .0392, log-rank test). The thoracic aorta diameter decreased from 42.4 (23.1) mm to 37.3 (12.8) mm in the TEVAR group and increased from 40.7 (18.6) mm to 48.1 (17.3) mm in the OMT group.

Conclusions:

This was the first prospective multicenter comparative study on the treatment of type B aortic dissection in China. TEVAR had a significantly lower aorta-related mortality compared with OMT but failed to improve overall survival rate or lower the aorta-related adverse event rate. Ⓐ

Evidence-Based Reference

Riwanto M, et al.: Altered activation of endothelial anti- and proapoptotic pathways by high-density lipoprotein from patients with coronary artery disease: role of high-density lipoproteine proteome remodeling, *Circulation* 127:891–904, 2013. Ⓐ

SUGGESTED READINGS

Akin I, Kische S: Indication, timing, and results of endovascular treatment of type B dissection, *Eur J Vasc Endovasc Surg* 37(3):289–296, 2009.

Fattori R et al.: Interdisciplinary expert consensus document on management of type B aortic dissection, *J Am Coll Cardiol* 61(16):1661–1678, 2013.

Gilon D et al.: Characteristics and in-hospital outcomes of patients with cardiac tamponade complicating type A acute aortic dissection, *Am J Cardiol* 103:1029–1031, 2009.

Golledge J, Eagle KA: Acute aortic dissection, *Lancet* 372(9632):55, 2008.

Himanshu P, Deeb M: Ascending and arch aorta pathology, natural history, and treatment, *Circulation* 118:188, 2008.

Kische SE, Ehrlich MP: Endovascular treatment of acute and chronic aortic dissection: midterm results from the Talent Thoracic Retrospective Registry, *J Thorac Cardiovasc Surg* 138(1):115–124, 2009.

Ramanath VS et al.: Acute aortic syndromes and thoracic aortic aneurysm, *Mayo Clin Proc* 84(5):465–481, 2009.

Shiga T et al.: Diagnostic accuracy of TEE, helical CT, and MRI for suspected thoracic aortic dissection, *Arch Intern Med* 166:1350–1356, 2006.

BASIC INFORMATION

DEFINITION

Aortic regurgitation (AR) is retrograde blood flow into the left ventricle from the aorta as a result of an incompetent aortic valve.

SYNONYMS

Aortic insufficiency
AI
AR

ICD-9CM CODES
424.1 Aortic valve disorders
ICD-10CM CODES
I35.1 Aortic valve insufficiency
I35.2 Aortic value stenosis with insufficiency
I35.9 Aortic valve disorder, unspecified
I35.8 Other nonrheumatic aortic valve disorders

EPIDEMIOLOGY & DEMOGRAPHICS

- Prevalence ranges from 4.9% to 10% and increases with age.
- The most common cause of isolated severe AR is aortic root dilation.
- Infectious endocarditis is the most frequent cause of acute AR.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The pathophysiology of AR is described in Fig. A1-103. The clinical presentation varies depending on whether aortic insufficiency is acute or chronic. Chronic aortic insufficiency is well tolerated (except when secondary to infective endocarditis), and the patients remain asymptomatic for years. Common manifestations after significant deterioration of left ventricular function are dyspnea on exertion, syncope, chest pain, and congestive heart failure (CHF). Acute aortic insufficiency manifests primarily with hypotension caused by a sudden fall in cardiac output and resultant cardiogenic shock. In addition, a rapid rise in left ventricular diastolic pressure results in a further decrease in coronary blood flow.

Physical findings in chronic aortic insufficiency include the following:

- Widened pulse pressure (markedly increased systolic blood pressure, decreased diastolic blood pressure). Fig. A1-104 illustrates characteristics of AR murmur.
- Findings associated with the widened pulse pressure:
  1. Bounding pulses, "water hammer" or collapsing pulse (***Corrigan's pulse***), can be palpated at the wrist or on the femoral artery and is caused by rapid rise and sudden collapse of the arterial pressure during late systole.
  2. Head "bobbing" with each systole (***de Musset's sign***).
  3. "Pistol shot femorals" (***Traube's sign***) is a term used to describe a loud sound over the femoral artery
  4. Capillary pulsations (***Quincke's sign***) may occur at the base of the nail beds.
- A to-and-fro Duroziez murmur may be heard over femoral arteries with slight compression.
- Popliteal systolic pressure is increased more than 20 mm Hg over brachial systolic pressure (***Hill's sign***), with a 40 to 60 mm difference representing moderate AR and >60 mm difference severe AR.
- Other findings associated with AR, which are more of historical than practical interest, include:
  1. ***Mueller's sign***—Systolic pulsations of the uvula.
  2. ***Becker's sign***—Visible pulsations of the retinal arteries and pupils.
  3. ***Mayne's sign***—More than a 15 mm Hg decrease in diastolic blood pressure with arm elevation from the value obtained with the arm in the standard position.
  4. ***Rosenbach's sign***—Systolic pulsations of the liver.
  5. ***Gerhard's sign***—Systolic pulsations of the spleen.
- Cardiac auscultation reveals:
  1. Displacement of cardiac impulse downward and to the patient's left
  2. S_3 heard over the apex
  3. Decrescendo, blowing diastolic murmur heard along left sternal border
  4. Low-pitched apical diastolic rumble (***Austin-Flint murmur***)—the precise etiology of the murmur is uncertain, but it is generally believed to be related to increased velocity of mitral inflow consequent to the AR.
  5. Early systolic ejection sound and systolic ejection murmur.

In patients with acute aortic insufficiency both the wide pulse pressure and the large stroke volume are absent. A short, blowing diastolic murmur may be the only finding on physical examination.

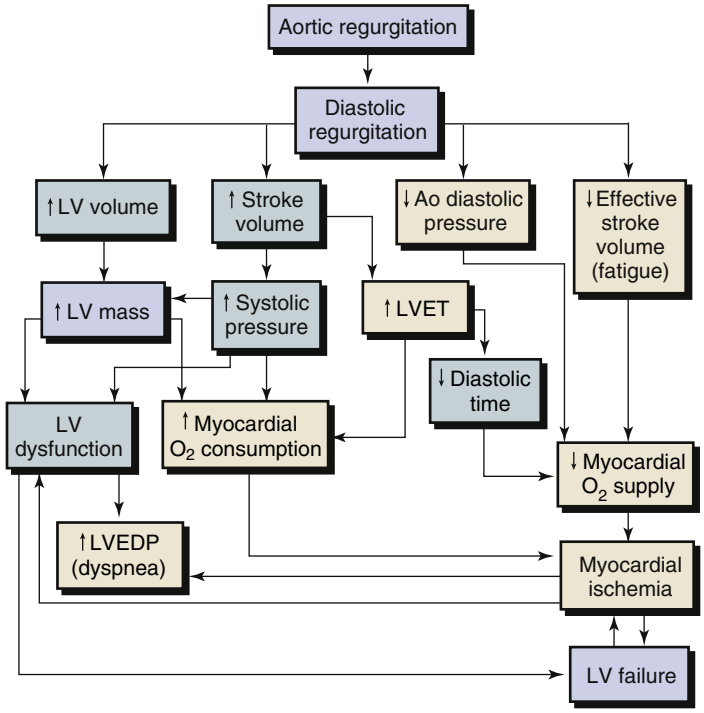


FIGURE A1-103 Pathophysiology of aortic regurgitation. Aortic regurgitation results in an increased left ventricular *(LV)* volume, increased stroke volume, increased aortic *(Ao)* systolic pressure, and decreased effective stroke volume. Increased LV volume results in an increased LV mass, which may lead to LV dysfunction and failure. Increased LV stroke volume increases systolic pressure and prolongation of LV ejection time *(LVET)*. Increased LV systolic pressure results in a decrease in diastolic time. Decreased diastolic time (myocardial perfusion time), diastolic aortic pressure, and effective stroke volume reduce myocardial O_1 supply. Increased myocardial O_2 consumption and decreased myocardial O_2 supply produce myocardial ischemia, which further deteriorates LV function. *LVEDP,* LV end-diastolic pressure. (From Boudoulas H, Gravanis MB: Valvular heart disease. In Gravanis MB [ed]: *Cardiovascular disorders: pathogenesis and pathophysiology,* St Louis, 1993, Mosby.)

ETIOLOGY

- Leaflet abnormalities:
  1. Infective endocarditis
  2. Rheumatic fibrosis (most common cause in developing countries)
  3. Trauma with valvular rupture
  4. Congenital bicuspid aortic valve (most common cause in the United States)
  5. Myxomatous degeneration
  6. Fenfluramine, dexfenfluramine, pergolide, cabergoline
  7. Ankylosing spondylitis
- Aortic root or ascending aorta abnormalities:
  1. Annuloaortic ectasia
  2. Ehlers-Danlos syndrome
  3. Marfan's syndrome
  4. Trauma: ankylosing spondylitis

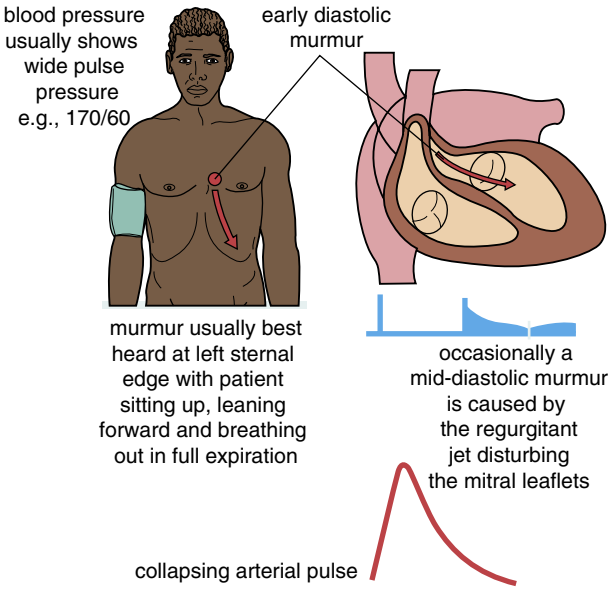


FIGURE A1-104 Aortic regurgitation as an example of an early diastolic murmur. (From Epstein O: *Pocket Guide to Clinical Examination,* ed 4, 2009.)

5. Syphilitic aortitis
6. Systemic hypertension
7. Aortic dissection

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Patent ductus arteriosus, pulmonary regurgitation, and other valvular abnormalities.
- The differential diagnosis of cardiac murmurs is described in Section II.

WORKUP

- Echocardiogram, chest radiograph, electrocardiogram (ECG), and cardiac catheterization (selected patients).
- Medical history and physical examination focused on the following clinical manifestations:
  1. Dyspnea on exertion.
  2. Syncope.
  3. Chest pain.
  4. CHF.

IMAGING STUDIES

- Chest radiography:
  1. Left ventricular hypertrophy (LVH) (chronic AR).
  2. Aortic dilation.
  3. Normal cardiac silhouette with pulmonary edema: possible in patients with acute AR.
- ECG: LVH.
- Echocardiography (Fig. EA1-105) is the main imaging modality to diagnose AR and assess left ventricular size and function. Quantification of the severity of regurgitation can be made either qualitatively by Doppler vena contracta width (severe if >0.6 cm) or quantitatively by effective regurgitant orifice area (severe if >0.30 cm^2) and/or regurgitant volume (severe if >60 mL per/beat).
- Cardiac catheterization is indicated in selected patients to assess the degree of left ventricular dysfunction, to assess the degree of AR when echocardiographic parameters are inconclusive, and to determine if there is coexistent coronary artery disease.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of competitive sports and heavy weight lifting if the AR is severe and associated with aortic root dilatation.
- Salt restriction.
- In 2007, the American Heart Association (AHA) guidelines for prevention of infectious endocarditis were revised; and routine antibiotic prophylaxis to undergo dental or other invasive procedures is no longer recommended, unless the patient has a prior history of endocarditis.

MEDICAL

ACUTE GENERAL RX

- Afterload reduction: angiotensin-converting enzyme (ACE) inhibitors and vasodilators (i.e., nitroprusside) in acute AR; diuretics for pulmonary edema.
- Avoid beta-blockers that can prolong diastole.
- Emergent surgical referral for cardiogenic shock.

CHRONIC RX

- Long-term vasodilator therapy with ACE inhibitors or nifedipine in patients who have concomitant hypertension. In one 1994 study [Scognamiglio et al, NEJM 1994] nifedipine delayed the need for aortic valve surgery compared to digoxin, but in a second randomized trial [Evangelista et al, NEJM 2005] comparing placebo to nifedipine and enalapril, there was no reduction in need for aortic valve surgery when followed up to 7 years. Therefore there is no current definitive indication of medical therapy with afterload reduction for aortic regurgitation other than hypertension control.
- Diuretics and sodium restriction for CHF.
- Comparable efficacy of losartan and atenolol was shown in curbing aortic root dilatation growth in children and young adults (6 mo-25 yr) with Marfan's syndrome, with similar outcomes of aortic regurgitation severity, surgery, aortic dissection, and death at 3 years.

SURGICAL RESERVED FOR: REFERRAL

Reserved for:

- Patients with acute severe AR (i.e., infective endocarditis) and cardiogenic shock.
- Patients with hemodynamically stable severe AR undergoing CABG or surgery on the aorta or other heart valves.
- Symptomatic patients with chronic, severe AR.
- Evidence of systolic dysfunction with left ventricular ejection fraction of less than 50%.
- Asymptomatic patients with severe AR and left ventricular ejection fraction >50%, but with left ventricular dilation:
  1. Echocardiographic end-systolic dimension >50 mm (Class IIa level of evidence) *or*
  2. Echocardiographic end-diastolic dimension >65 mm with low surgical risk (Class IIb).

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Aortic Insufficiency (Patient Information)

AUTHOR: **NEELESH LALJI CHUDASAMA, M.D.**

SUGGESTED READINGS

Evangelista A et al.: Long-term vasodilator therapy in patients with severe aortic regurgitation, *N Engl J Med* 353(13):1342–1349, 2005.

Lacro RV et al.: Atenolol versus Losartan in Children and Young Adults with Marfan's Syndrome, *N Engl J Med*, 2014 Nov 18. [Epub ahead of print].

Nishimura RA et al.: 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 63(22):2438–2488, 2014.

Scognamiglio R et al.: Nifedipine in asymptomatic patients with severe aortic regurgitation and normal left ventricular function, *N Engl J Med* 331(11):689–694, 1994.

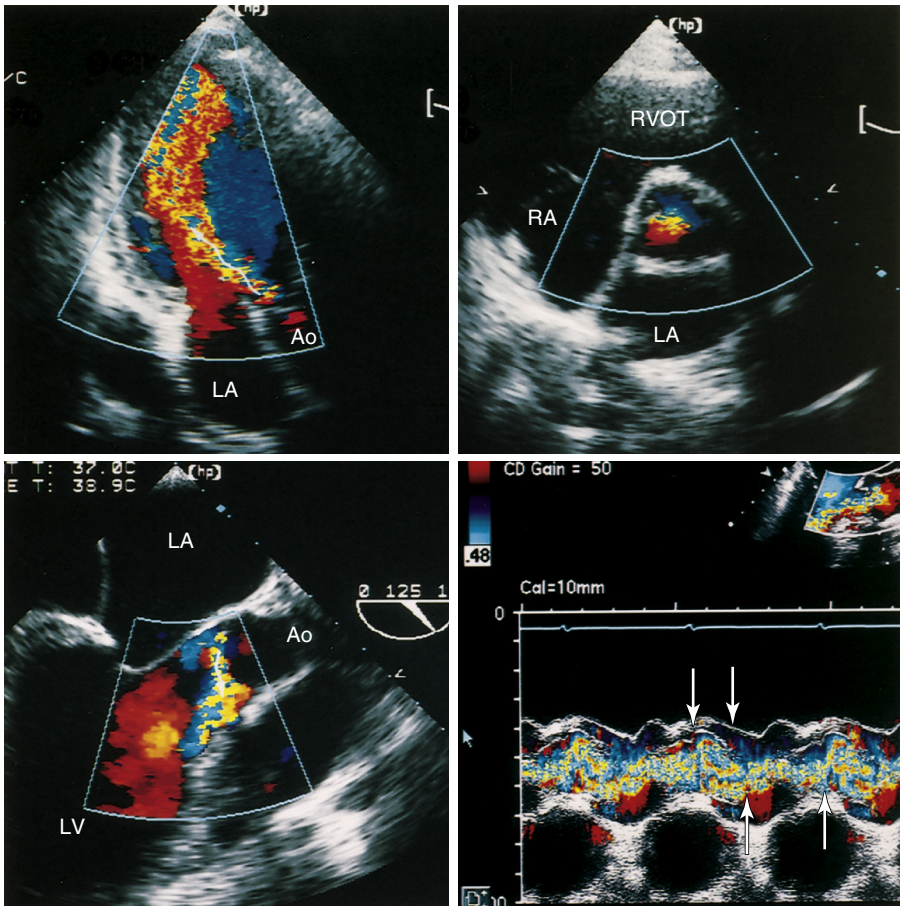


FIGURE EA1-105 Composite of echocardiograms recorded in patients with aortic regurgitation. The two top panels were recorded in the same patient and show, on the left, an apical long-axis view and, on the right, a parasternal short-axis view. In the apical long-axis view, note the fairly extensive confetti-like aortic regurgitation jet arising from the proximal aorta and traversing to the left ventricular apex. Note also that the aortic regurgitation jet velocities merge with the mitral inflow velocities, rendering quantitation problematic. The top right panel is recorded in the same patient and shows a central aortic regurgitation jet. The bottom left panel is a transesophageal echocardiogram recorded in a longitudinal view. Note the highly eccentric aortic regurgitation jet that appears to fill the entire width of the left ventricular outflow tract. This apparent filling of the left ventricular outflow tract is due to the posterior to anterior jet direction *(white arrow)* rather than to a substantial true width of the jet. The bottom right panel is a color M-mode echocardiogram recorded in a patient with aortic insufficiency in which the normal systolic flow can be appreciated as well as a continuous diastolic flow in the lumen of the aorta that represents aortic insufficiency. The two downward-pointing arrows denote the duration of systole, and the two upward-pointing arrows indicate the duration of diastole. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle; *RA,* right atrium; *RVOT,* right ventricular outflow tract. (From Zipes DP et al [eds]: *Braunwauld's heart disease,* ed 7, Philadelphia, 2005, Saunders.)

BASIC INFORMATION

DEFINITION

Aortic stenosis (AS) is obstruction to left ventricular systolic outflow across the aortic valve. Symptoms typically appear when the valve orifice decreases to <1 cm^2 (normal orifice is 3 to 4 cm^2). Criteria for severe AS include a valve area <1.0 cm^2, a mean gradient > 40 mm Hg, or a peak gradient > 4 m/s.

SYNONYMS

Aortic valvular stenosis
AS

ICD-9CM CODES
424.1 Aortic valvular stenosis
ICD-10CM CODES
I35.0 Nonrheumatic aortic (valve) stenosis
I35.2 Aortic valve stenosis with insufficiency
I35.8 Other aortic valve disorders
I35.9 Aortic valve disorder, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Aortic stenosis is the most common valve lesion in adults in Western countries.
- Calcific stenosis (most common cause in patients >70 yr) occurs in 75% of patients.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Harsh midsystolic, crescendo-decrescendo murmur (Fig. A1-106) best heard at base of heart and radiating into neck vessels; often associated with a thrill or ejection click; may also be heard well at the apex.
- Signs of severe AS include absent or diminished intensity of the second heart sound and/or late rising carotid upstroke with delayed amplitude (pulsus parvus et tardus), presence of S4, and a reverse splitting of the second heart sound.
- Classic symptoms include angina, syncope, and heart failure.
- Acquired von Willebrand disease is seen in approximately 20% of severe AS, which can lead to GI bleeding from angiodysplasia (Heyde's syndrome) that resolves after aortic valve replacement.

ETIOLOGY

- Idiopathic calcification of the aortic valve (most common cause, presents at ages 60 to 80)
- Progressive stenosis of congenital bicuspid valve (found in 1% to 2% of the population, presents at ages 40 to 60)
- Rheumatic heart disease
- Less common causes include congenital (major cause of AS in patients < 30 yr), radiation, and obstructive vegetations (endocarditis)
- Genetic variation in the LPA locus, mediated by Lp(2) levels, is associated with aortic valve calcification across multiple ethnic groups and with incidental clinical aortic stenosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hypertrophic cardiomyopathy
- Mitral regurgitation
- Ventricular septal defect
- Aortic sclerosis. Aortic stenosis is distinguished from aortic sclerosis by the degree of valve impairment. In aortic sclerosis, the valve leaflets are abnormally thickened but obstruction to outflow is absent or minimal.
- Subvalvular membrane or supravalvular AS

WORKUP

- ECG: may demonstrate left ventricular hypertrophy and/or left atrial abnormality (Fig. A1-107).
- Chest radiograph: may demonstrate cardiomegaly. Poststenotic dilation of the ascending aorta may also be evident.
- Echocardiography (see "Imaging Studies")
- Cardiac catheterization in selected patients (see "Imaging Studies")
- Dobutamine challenge (for low-gradient, low-flow AS)
- Fig. EA1-108 describes an algorithm for evaluation of AS.

IMAGING STUDIES

- Chest x-ray:
  1. Poststenotic dilation of the ascending aorta
  2. Calcification of aortic cusps
  3. Rounding of left ventricle (LV) apex
- ECG:
  1. Left ventricular hypertrophy (found in 80% of patients)
  2. Left atrial enlargement
  3. Atrial fibrillation (in late disease)

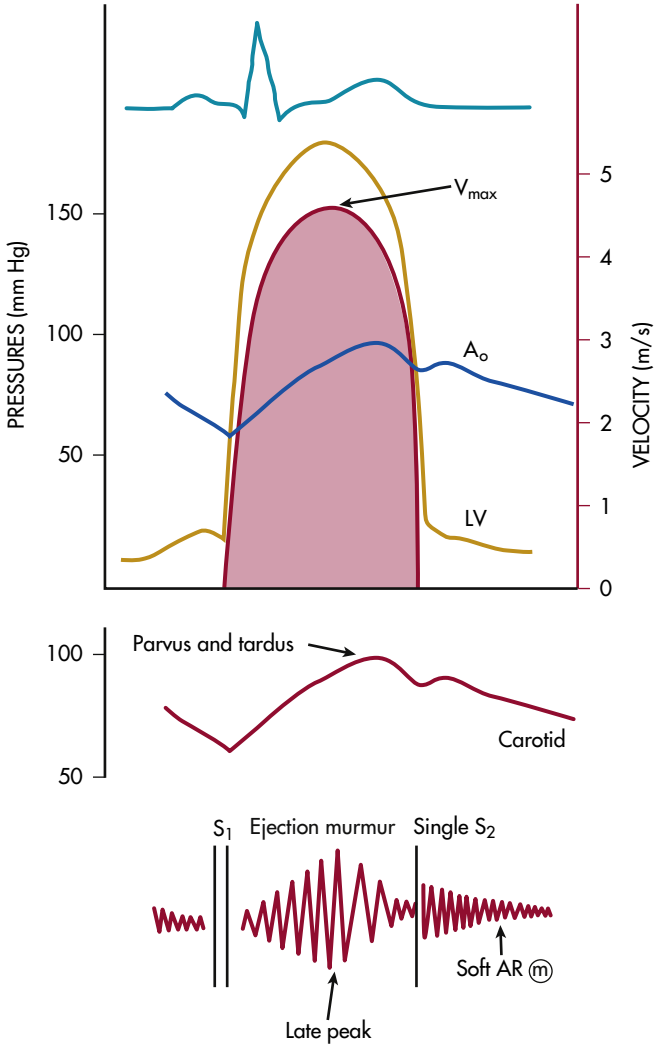


FIGURE A1-106 Relationship between left ventricle (LV) and aortic (Ao) pressures and the Doppler aortic stenosis velocity curve (in red). The pressure difference between the LV and aorta in systole is four times the velocity squared (the Bernoulli equation). Thus, a maximum velocity (Vmax) of 4.3 m/sec corresponds to a maximum LV to Ao pressure difference of 74 mm Hg and a mean systolic gradient of 44 mm Hg. On physical examination, the slow rate of rise and delayed peak in the carotid pulse (or parvus and tardus) matches the contour of the aortic pressure waveform. The murmur corresponds to the Doppler velocity curve with a harsh crescendo-decrescendo late-peaking systolic murmur, best heard at the aortic region (upper right sternal border). Often, a soft, high-pitched diastolic decrescendo murmur of aortic regurgitation also is appreciated. (From Bonow et al [eds]: *Braunwald's heart disease,* ed 9, Philadelphia, 2012, Saunders.)

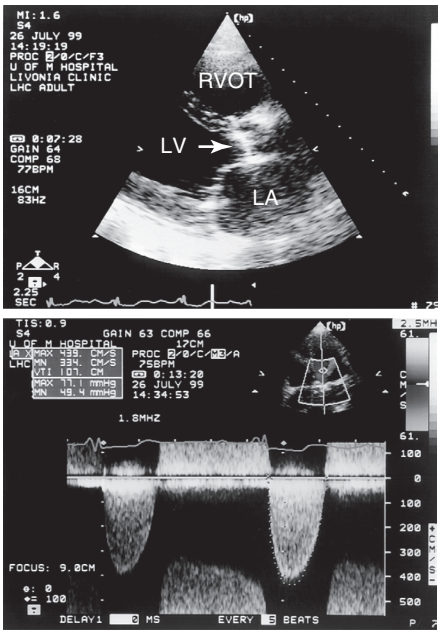


FIGURE A1-107 Echocardiogram recorded in a patient with severe aortic stenosis. The *top panel* is a parasternal long-axis view recorded in systole. Left ventricular function is diminished. The aortic valve is markedly thickened and partially calcified. Its motion is markedly reduced, and in systole it appears that the valve occludes the orifice *(arrow).* The *lower panel* is a continuous-wave Doppler recorded from the apex of the left ventricle along a line aimed through the stenotic aortic valve. Note the aortic stenosis signal below the zero crossing line. The peak velocity is 430 cm/sec, which corresponds to a maximum gradient of 77 mm Hg and a mean gradient of 49.4 mm Hg. *LA,* Left atrium; *LV,* left ventricle; *RVOT,* right ventricular outflow tract. (From Zipes DP et al [eds]: *Braunwauld's heart disease,* ed 7, Philadelphia, 2005, Saunders.)

- Doppler echocardiography: thickening of the left ventricular wall; allows calculation of both aortic valve area and estimation of pressure gradients to determine severity of AS.
- Cardiac catheterization: indicated in symptomatic patients awaiting aortic valve replacement (AVR) in order to detect coexisting coronary artery stenosis that may need bypass at the same time as aortic valve replacement; also indicated in symptomatic patients when noninvasive tests are inconclusive or when there is a discrepancy between noninvasive tests and clinical findings regarding severity of AS as it confirms the diagnosis and the estimates of the severity of the valvular stenosis by directly measuring the gradient across the valve, allowing calculation of the valve area.
- A CT with contrast for imaging the aorta may be needed for annular sizing, aortic measurements, etc., if a transcatheter aortic-valve replacement (TAVR) is planned.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Strenuous activity should be avoided in patients with moderate to severe AS
- Sodium restriction if CHF is present

GENERAL Rx

MEDICAL:

- Once symptomatic, AS is a surgical disease.
- Gentle diuresis for volume overload as preload dependent; control hypertension (HTN) but avoid vasodilators (nitrates), maintain sinus rhythm
- In 2007, the AHA guidelines for prevention of infectious endocarditis were revised and routine antibiotic prophylaxis to undergo dental or other invasive procedures is no longer recommended, unless the patient has prior endocarditis.

SURGICAL:

- Surgical valve replacement is the treatment of choice in symptomatic patients because there is a 50% mortality rate at 2 years with medical therapy alone. Valve replacement is a Class I indication for patients with (a) severe AS, (b) asymptomatic severe AS with LV ejection fraction (EF) <50%, and (c) asymptomatic severe AS undergoing CABG or surgery on the aorta or other heart valves. Valve replacement is a class 2a indication for patients with (a) severe AS and abnormal blood pressure response (decrease in systolic blood pressure) during exercise (b) patients with rapidly asymptomatic and very severe AS (peak velocity > 5 m/s) with low surgical risk, and (c) low flow-low gradient (with low ejection fraction) with a positive low dose dobutamine stress echo.
- Percutaneous aortic balloon valvuloplasty serves best as palliative therapy in severely symptomatic patients who are not surgical candidates and as a bridge to surgery in hemodynamically unstable adult patients. It is not an option in patients who are good candidates for surgical valve replacement because restenosis occurs in most adult patients at 6 mo.
- Percutaneous heart valve replacement is an emerging catheter-based technology that allows for implantation of a prosthetic valve without open heart surgery. Transcatheter aortic-valve replacement (TAVR) has been shown to reduce mortality by 20% in patients with severe AS and coexisting conditions that exclude them as candidates for surgical replacement of the aortic valve. In another randomized trial involving high-risk patients with severe AS who were candidates for surgery, TAVR was found to be noninferior to surgical valve replacement for short-term efficacy with similar all-cause mortality at 2 yr. The surgical group had double the incidence of new-onset atrial fibrillation and major bleeding, but the TAVR group had a higher rate of paravalvular regurgitation, major stroke, and vascular complications. Clinical trials have shown that among patients with high-risk aortic stenosis undergoing TAVR, the use of a balloon-expandable valve results in a greater rate of device success than use of a self-expandable valve.

DISPOSITION

- The presence of even mild symptoms is an indicator of poor survival for patients with AS. With the average duration of symptoms before death is angina, 5 yr; syncope, 3 yr; CHF, 2 yr.
- Approximately 75% of patients with symptomatic AS will die within 3 yr of symptom onset unless the aortic valve is replaced.

REFERRAL

- Surgical referral for valve replacement in all symptomatic AS patients. There are studies that are examining the presence of moderate or severe valvular calcification, together with a rapid increase in aortic jet velocity and elevated BNP, to identify patients with a very poor prognosis who should be considered for early valve replacement rather than have surgery delayed until symptoms develop. Additionally, patients with severe AS who are asymptomatic should be considered for exercise stress test to see if they are truly without symptoms (low exercise tolerance) or if the BP drops with exercise, both which would be indications for surgical referral. Surgical mortality rate for valve replacement is 3% to 5%; however, it varies with patient's age (>8% in patients >75 yr).
- Referral to cardiology should be considered if patient with low-flow, low-gradient (low ejection fraction) symptomatic aortic stenosis for further work-up (dobutamine stress echo).
- Balloon valvuloplasty is useful in infants and children or poor surgical candidates who do not have calcified valve apparatus; it can be done as an intermediate procedure to stabilize high-risk patients before surgery.
- Patients who are considered high risk for cardiac surgery or have contraindications (porcelain aorta) should be referred to a center with a transcatheter program for TAVR evaluation.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Aortic Stenosis (Patient Information)

AUTHORS: **DEEPA KUMARAIAH, M.D., M.B.A**

EVIDENCE

Abstract[1]

Objectives:

The goal of this study was to assess the prognostic significance of midwall and infarct patterns of late gadolinium enhancement (LGE) in aortic stenosis.

Background:

Myocardial fibrosis occurs in aortic stenosis as part of the hypertrophic response. It can be detected by LGE, which is associated with an adverse prognosis in a range of other cardiac conditions.

Methods:

Between January 2003 and October 2008, consecutive patients with moderate or severe aortic stenosis undergoing cardiovascular magnetic resonance with administration of gadolinium contrast were enrolled into a registry. Patients were categorized into absent, midwall, or infarct patterns of LGE by blinded independent observers. Patient follow-up was completed using patient questionnaires, source record data, and the National Strategic Tracing Service.

Results:

A total of 143 patients (age 68±14 years; 97 male) were followed up for 2.0±1.4 years. Seventy-two underwent aortic valve replacement, and 27 died (24 cardiac, 3 sudden cardiac deaths). Compared with those with no LGE (n=49), univariate analysis revealed that patients with midwall fibrosis (n=54) had an 8-fold increase in all-cause mortality despite similar aortic stenosis severity and coronary artery disease burden. Patients with an infarct pattern (n=40) had a 6-fold increase. Midwall fibrosis (hazard ratio: 5.35; 95% confidence interval: 1.16 to 24.56; p=0.03) and ejection fraction (hazard ratio: 0.96; 95% confidence interval: 0.94 to 0.99; p=0.01) were independent predictors of all-cause mortality by multivariate analysis.

Conclusions:

Midwall fibrosis was an independent predictor of mortality in patients with moderate and severe aortic stenosis. It has incremental prognostic value to ejection fraction and may provide a useful method of risk stratification. Ⓐ

Evidence-Based Reference

D1weck MR et al.: Midwall fibrosis is an independent predictor of mortality in patients with aortic stenosis, *J Am Coll Cardiol* 58:1271–1279, 2011. Ⓐ

SUGGESTED READINGS

Abdel-Wahab M et al.: Comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement, the CHOICE randomized clinical trial, *JAMA* 311(15):1503–1514, 2014.

Nishimura RA et al.: AHA/ACC Guideline for the Management of Patients WithValvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. http://circ.ahajournals.org/content/early/2014/02/27/CIR.0000000000000029.citation, 2014.

Coeytaux RR et al.: Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery, *N Engl J Med* 363:1597–1607, 2010.

Kapadia SR et al.: Percutaneous treatment of aortic valve stenosis, *Clev Clin J Med* 75(11):805–812, 2008.

Kodali SK et al.: Two-year outcomes after transcatheter or surgical aortic-valve replacement, *N Engl J Med* 366:1686, 2012.

Leon M et al.: Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery, *N Engl J Med* 363:1597–1607, 2010.

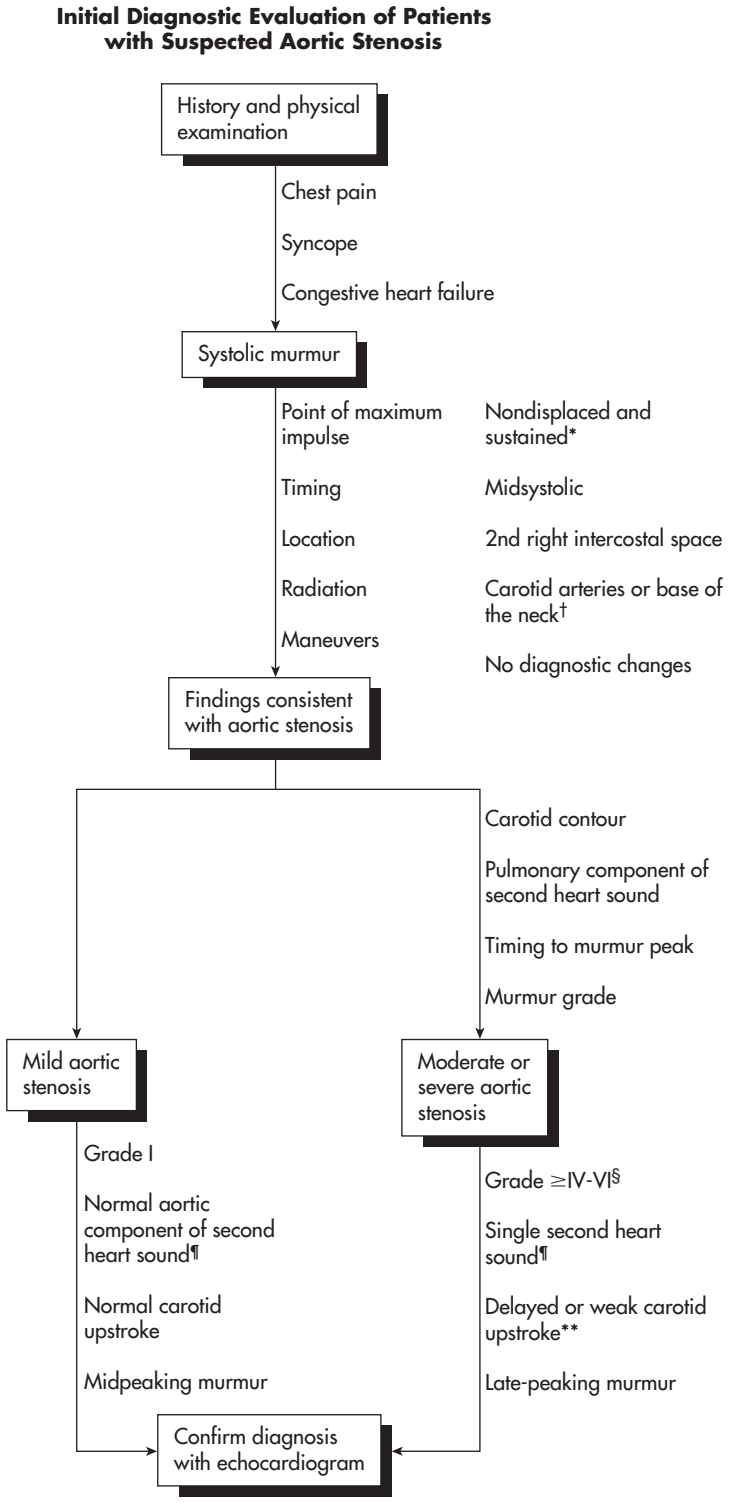
Leon MB et al.: Transcatheter aortic-valve replacement for aortic stenosis: state of the evidence, *Ann Intern Med* 153:314–324, 2010.

Otto CM et al.: Aortic-valve stenosis — from patients at risk to severe valve obstruction, *N Engl J Med* 371:744–756, 2014.

Singh I et al.: Percutaneous treatment of aortic valve stenosis, *Cleve Clin J Med* 75:805–812, 2008.

Smith CR et al.: Transcatheter versus surgical aortic-valve replacement in high-risk patients, *N Engl J Med* 364:2187, 2011.

Thanassoulis G et al.: Genetic associations with valvular calcifications and aortic stenosis, *N Engl J Med* 368:503–512, 2013.



*May be displaced in the setting of left ventricular systolic dysfunction.
†Radiation to apex with Gallavardin phenomenon.
§Grade I: severe stenosis unlikely; grade IV: highly specific for severe stenosis.
¶Normal aortic component of second heart sound implies normal valve closure and absence of severe stenosis.
**Carotid upstroke may be normal in severe aortic stenosis in those patients with longstanding hypertension secondary to decreased arterial wall compliance.

FIGURE EA1-108 Aortic stenosis, diagnostic approach. Initial diagnostic evaluation of patients with suspected aortic stenosis. (From Crawford MH et al [eds]: *Cardiology*, ed 2, St Louis, 2004, Mosby.)

BASIC INFORMATION

DEFINITION

Aplastic anemia is a bone marrow failure syndrome defined by peripheral blood pancytopenia and hypocellular bone marrow aplasia.

SYNONYMS

Refractory anemia
Hypoplastic anemia

ICD-9CM CODES
284.9 Aplastic anemia
284.8 Acquired aplastic anemia
284.0 Congenital aplastic anemia

ICD-10CM CODES
D61.9 Aplastic anemia, unspecified
D60.9 Acquired pure red cell aplasia, unspecified
D60.8 Other acquired pure red cell aplasias

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The annual incidence of aplastic anemia is 2 cases per million.
PREDOMINANT SEX AND AGE: The incidence has two peaks, with most patients presenting between ages 15 and 25 or after 60 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Mucosal bleeding, easy bruising, petechiae or heavy menstrual bleeding is seen secondary to thrombocytopenia.
- Fatigue, lassitude, skin pallor, exertional dyspnea, or palpitations are seen secondary to anemia.
- Infection is an uncommon presentation, but neutropenia may lead to fever and sore throat.
- Various physical manifestations like short stature, skeletal or nail changes may be seen in congenital forms of aplastic anemia.

TABLE A1-63 Classification of Drugs and Chemicals Associated With Aplastic Anemia

I. Agents That Regularly Produce Bone Marrow Depression as a Major Toxic Effect When Used in Commonly Used Doses or Normal Exposures

Cytotoxic drugs used in cancer chemotherapy
Alkylating agents (busulfan, melphalan, cyclophosphamide)
Antimetabolites (antifolic compounds, nucleotide analogs) antimitotics (vincristine, vinblastine, colchicine)
Some antibiotics (daunorubicin, doxorubicin [Adriamycin])
Benzene (and less often benzene-containing chemicals: kerosene, carbon tetrachloride, Stoddard solvent, chlorophenols)

II. Agents Probably Associated With Aplastic Anemia but With a Relatively Low Probability Relative to Their Use

Chloramphenicol
Insecticides
Antiprotozoals (quinacrine and chloroquine)
Nonsteroidal antiinflammatory drugs (including phenylbutazone, indomethacin, ibuprofen, sulindac, diclofenac, naproxen, piroxicam, fenoprofen, fenbufen, aspirin)
Anticonvulsants (hydantoins, carbamazepine, phenacemide, ethosuximide)
Gold, arsenic, and other heavy metals such as bismuth and mercury
Sulfonamides as a class
Antithyroid medications (methimazole, methylthiouracil, propylthiouracil)
Antidiabetes drugs (tolbutamide, carbutamide, chlorpropamide)
Carbonic anhydrase inhibitors (acetazolamide, methazolamide, mesalazine)
D-Penicillamine
2-Chlorodeoxyadenosine

III. Agents More Rarely Associated With Aplastic Anemia

Antibiotics (streptomycin, tetracycline, methicillin, ampicillin, mebendazole and albendazole, sulfonamides, flucytosine, mefloquine, dapsone)
Antihistamines (cimetidine, ranitidine, chlorpheniramine)
Sedatives and tranquilizers (chlorpromazine, prochlorperazine, piperacetazine, chlordiazepoxide, meprobamate, methyprylon, remoxipride)
Antiarrhythmics (tocainide, amiodarone)
Allopurinol (can potentiate marrow suppression by cytotoxic drugs)
Ticlopidine
Methyldopa
Quinidine
Lithium
Guanidine
Canthaxanthin
Thiocyanate
Carbimazole
Cyanamide
Deferoxamine
Amphetamines

From Hoffman R: *Hematology, basic principles and practice,* 6th ed, Philadelphia, Saunders, 2013.

ETIOLOGY

- In most patients with idiopathic aplastic anemia, bone marrow failure results from immunologically mediated, active destruction of blood-forming cells by lymphocytes.
- Mutations in *TERT,* the gene for the RNA component of telomerase, cause short telomerases in congenital aplastic anemia and in some cases of apparently acquired hematopoietic failure. In patients with severe aplastic anemia receiving immunosuppressive therapy, telomere length is unrelated to response but is associated with risk of relapse, clonal evolution, and overall survival.
- Common etiologic factors in acquired aplastic anemia include:
  1. Toxins (e.g., benzene, insecticides)
  2. Drugs (e.g., felbamate [Felbatol], cimetidine, NSAIDs, antiepileptics, gold salts, chloramphenicol, sulfonamides, trimethadione, quinacrine, phenylbutazone). Table A1-63 describes a classification of drugs and chemicals associated with aplastic anemia.
  3. Ionizing irradiation
  4. Infections (e.g., hepatitis C, HIV, Epstein-Barr virus, parvovirus B19)
- Inherited aplastic anemia
  1. Fanconi's anemia
  2. Reticular dysgenesis
  3. Dyskeratosis congenita
  4. Nonhematologic syndromes (Down syndrome, etc.)
  5. Shwachman-Diamond syndrome
- Pregnancy
- Idiopathic

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bone marrow infiltration from lymphoma, carcinoma, myelofibrosis
- Severe infection
- Hypoplastic myelodysplastic syndrome or hypoplastic acute myeloid leukemia in adults
- Hypersplenism
- Hairy cell leukemia

WORKUP

- Diagnostic workup (Fig. EA1-109) consists primarily of bone marrow aspiration and biopsy, and laboratory evaluation (CBC and examination of blood film).
- Bone marrow examination generally shows paucity or absence of erythropoietic and myelopoietic precursor cells (Fig. EA1-110, *B* and *C*); patients with pure red cell aplasia demonstrate only absence of red blood cell (RBC) precursors in the marrow.

LABORATORY TESTS

- CBC reveals pancytopenia (Fig. EA1-111, *A*). Macrocytosis and toxic granulation of neutrophils may also be present. Isolated cytopenias may occur in the early stages.
- Reticulocyte count reveals reticulocytopenia.

- Additional initial laboratory evaluation should include Ham test and/or peripheral blood flow cytometry to exclude paroxysmal nocturnal hemoglobinuria and testing for hepatitis C.

IMAGING STUDIES

MRI with spin-echo sequence is helpful in the study of bone marrow disease, and the high fat content of an aplastic marrow can be easily seen on MRI.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Discontinue any offending drugs or agents.

ACUTE GENERAL Rx

- Aggressive treatment of neutropenic fevers with parenteral broad-spectrum antibiotics.
- Administer platelet and RBC transfusions as needed; however, it is important to avoid transfusions in patients who are candidates for bone marrow transplantation.
- Fig. A1-112 describes a treatment algorithm for aplastic anemia.

CHRONIC Rx

- Allogenic bone marrow transplantation (ABMT) from a human leukocyte antigen (HLA)–matched sibling donor is curative.
- Patients who do not have a matched sibling can be treated with a matched unrelated transplant, but the mortality rate is higher. Studies have shown an association between leukocyte telomere length and outcomes in matched unrelated allogeneic hematopoietic stem cell transplant (HSCT). Longer donor leukocyte telomere length was associated with increased 5-year survival.[1]
- Immunosuppressive therapy with anti-thymocyte globulin (ATG) is an effective alternate treatment for patients who are not candidates for ABMT.
- Other immunosuppressive agents such as cyclosporin, cyclophosphamide, or corticosteroids also have a role in the treatment of aplastic anemia.
- Androgens such as danazol are effective second-line agents.
- The oral thrombopoietin mimetic eltrombopag can improve hematopoiesis in refractory severe aplastic anemia.

[1]Gadalla SM et al: Association between donor leukocyte telomere length and survival after unrelated allogeneic hematopoietic cell transplantation for severe aplastic anemia, *JAMA* 313(6):594-602, 2015.

DISPOSITION

- The most recent update of the European Group for Bone Marrow Transplantation long-term survival rate has been reported to be 80%.
- Graft rejection and graft-versus-host disease are the major complications of ABMT.

REFERRAL

Hematology referral is indicated in all patients with aplastic anemia.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fig. 3-12 Algorithm for Diagnosis of Anemias

AUTHORS: **BILAL H. NAQVI, M.D.,** and **FRED F. FERRI, M.D.**

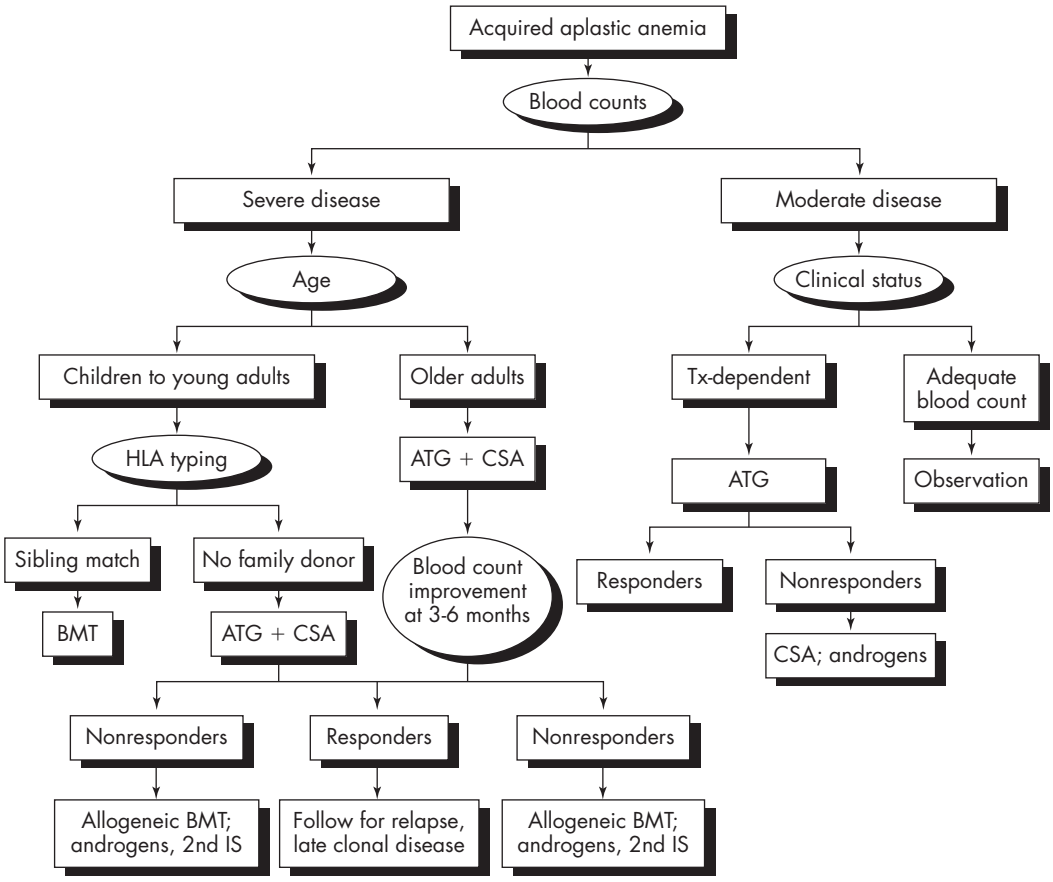


FIGURE A1-112 Treatment algorithm in aplastic anemia. Algorithm-based selection of treatment for patients with aplastic anemia. *ATG,* Antithymocyte globulin; *BMT,* bone marrow transplantation; *CSA,* cyclosporine A; *HLA,* human leukocyte antigen; *IS,* immunosuppression; *Tx,* treatment. (From Hoffmann R et al: *Hematology, basic principles and practice,* ed 6, Philadelphia, 2013, Elsevier.)

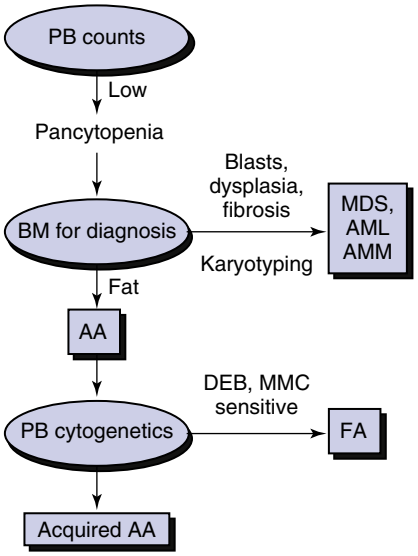


FIGURE EA1-109 Diagnostic algorithm in aplastic anemia *(AA).* *AML,* Acute myeloid leukemia; *AMM,* agnogenic myeloid metaplasia; *BM,* bone marrow; *DEB,* diepoxybutane; *FA,* Fanconi's anemia; *MDS,* myelodysplastic syndrome; *MMC,* mitomycin C; *PB,* peripheral blood. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 6, Philadelphia, 2013, Elsevier.)

SUGGESTED READINGS

Bacigalupo A: Diagnosis and treatment of aplastic anemia, *Hematol Oncol Clin North Am* 23(2):159–170, 2009.

Gafter-Gavili A, et al.: ATG plus cyclosporine reduces all cause mortality in patients with aplastic anemia: systemic review and meta analysis, *Acta Hematol* 120(4):237–243, 2008.

Olnes MJ, et al.: Eltrombopag and improved hematopoiesis in refractory aplastic anemia, *N Engl J Med* 367:11–19, 2012.

Scheinberg P, et al.: Association of telomere length of peripheral blood leukocytes with hematopoietic relapse, malignant transformation, and survival in severe aplastic anemia, *JAMA* 304(12):1358–1364, 2010.

Sloand EM, et al.: Successful treatment of pure red-cell aplasia with an anti-interleukin-2 receptor antibody (Daclizumab), *Ann Intern Med* 144:181, 2006.

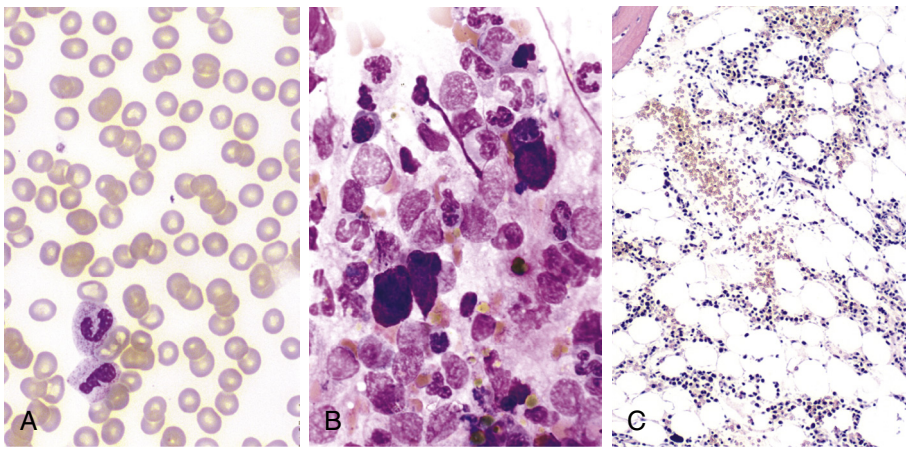


FIGURE EA1-110 Pancytopenia in measles-associated aplastic anemia **(A).** Note the toxic granulation in the neutrophils. The hypocellular bone marrow smear contains numerous mast cells **(B),** and the trephine biopsy reflects subtotal aplasia **(C).** (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

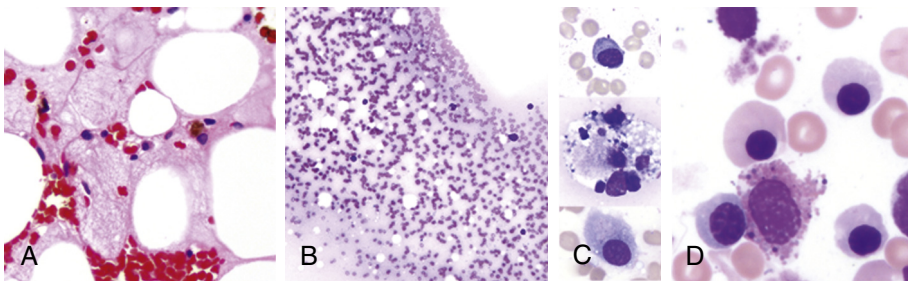


FIGURE EA1-111 Some morphologic features occasionally observed in patients with aplastic anemia. Empty marrow with eosinophilic ground substance consistent with serous atrophy or stromal injury **(A),** possibly indicative of marrow damage. Scanty marrow aspirate in severe disease **(B)** showing only rare nucleated elements many of which are from blood. Presence of plasma cells, histiocytes, and osteoblasts **(C)** confirms marrow nature of aspirate. Note: sometimes the histiocytes can show hemophagocytosis. Megaloblastoid erythropoiesis **(D)** is sometimes seen in aplastic anemia and in recovery. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 6, Philadelphia, 2013, Elsevier.)

BASIC INFORMATION

DEFINITION

Appendicitis is the acute inflammation of the appendix.

ICD-9CM CODES
540.9 Appendicitis
540.0 Appendicitis with generalized peritonitis
ICD-10CM CODES
K35.80 Unspecified acute appendicitis
K35.89 Other acute appendicitis
K35.2 Acute appendicitis with generalized peritonitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Appendicitis occurs in 10% of the population, most commonly between the ages of 10 and 30 yr. Median age is 22 years. Lifetime risk is 7%.
- More than 250,000 appendectomies are performed in the U.S. each year.
- It is the most common abdominal surgical emergency.
- Incidence of appendicitis has declined over the past 30 yr.
- Male/female ratio is 3:2 until mid-20s; it equalizes after age 30 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- In children with abdominal pain, fever is the single most useful sign associated with appendicitis. Vomiting, rectal tenderness, and rebound tenderness along with fever are more indicative of appendicitis in children than in adults.
- Abdominal pain: initially the pain may be epigastric or periumbilical in nearly 50% of patients; it subsequently localizes to the right lower quadrant within 12 to 18 hr. Pain can be found in back or right flank if appendix is retrocecal or in other abdominal locations if there is malrotation of the appendix.
- Pain with right thigh extension *(psoas sign),* low-grade fever: temperature may be >38° C if there is appendiceal perforation.
- Pain with internal rotation of the flexed right thigh *(obturator sign)* is present.
- Right lower quadrant (RLQ) pain on palpation of the left lower quadrant (LLQ) *(Rovsing's sign):* physical examination may reveal right-sided tenderness in patients with pelvic appendix.
- Point of maximum tenderness is in the RLQ *(McBurney's point).*
- Nausea, vomiting, tachycardia, cutaneous hyperesthesias at the level of T12 can be present.

ETIOLOGY

Obstruction of the appendiceal lumen with subsequent vascular congestion, inflammation, and edema; common causes of obstruction are:

- Fecaliths: 30% to 35% of cases (most common in adults)
- Foreign body: 4% (fruit seeds, pinworms, tapeworms, roundworms, calculi)
- Inflammation: 50% to 60% of cases (submucosal lymphoid hyperplasia [most common etiology in children, teens])
- Neoplasms: 1% (carcinoids, metastatic disease, carcinoma)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Intestinal: regional cecal enteritis, incarcerated hernia, cecal diverticulitis, intestinal obstruction, perforated ulcer, perforated cecum, Meckel's diverticulitis
- Reproductive: ectopic pregnancy, ovarian cyst, torsion of ovarian cyst, salpingitis, tuboovarian abscess, mittelschmerz, endometriosis, seminal vesiculitis
- Renal: renal and ureteral calculi, neoplasms, pyelonephritis
- Vascular: leaking aortic aneurysm
- Psoas abscess
- Trauma
- Cholecystitis
- Mesenteric adenitis

WORKUP

Patients with RLQ pain, nausea, vomiting, anorexia, and RLQ rebound tenderness should undergo prompt clinical and laboratory evaluation. Imaging studies are generally not necessary in typical appendicitis and generally reserved for patients with an equivocal likelihood of appendicitis. They are useful when the diagnosis is uncertain. Laparoscopy may be useful as both a diagnostic and a therapeutic modality.

LABORATORY TESTS

- Complete blood count with differential reveals leukocytosis with a left shift in 90% of patients with appendicitis. Total white blood cell (WBC) count is generally lower than 20,000/mm^3. Higher counts may be indicative of perforation. Less than 4% have a normal WBC and differential. A WBC count <10,000/mm^3 decreases the likelihood of appendicitis. Low hemoglobin and hematocrit levels in an older patient should raise suspicion for GI tract carcinoma.
- Microscopic hematuria and pyuria may occur in <20% of patients.
- HCG to rule out pregnancy in females of reproductive age.

IMAGING STUDIES

- Multidetector computed tomography (Fig. A1-113) is a useful test for routine evaluation of suspected appendicitis in adults. CT of the abdomen/pelvis without contrast has a sensitivity of >90% and an accuracy >94% for acute appendicitis. A distended appendix, periappendiceal inflammation, and a thickened appendiceal wall are indicative of appendicitis. Table A1-64 describes CT findings of appendicitis. In children and young adults, exposure to CT radiation is of particular concern. Trials with low-dose CT

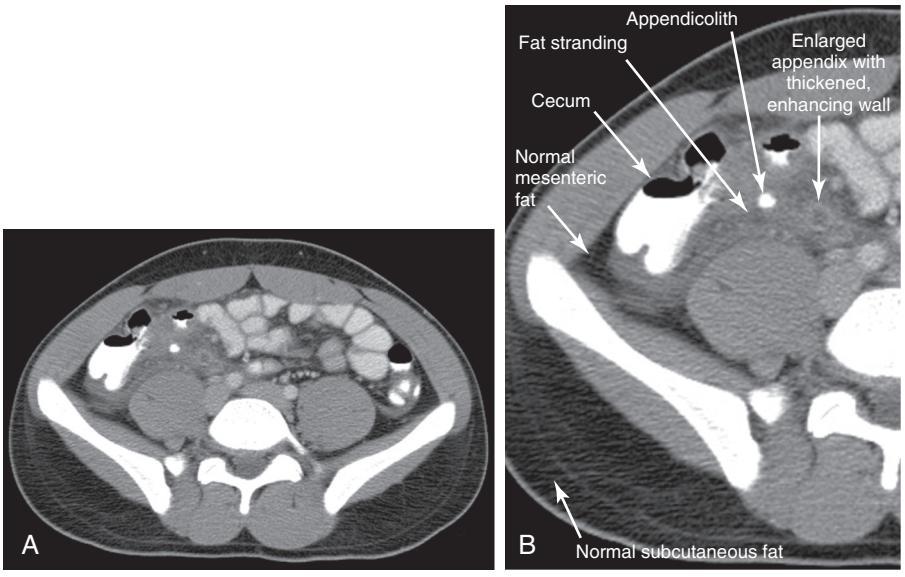


FIGURE A1-113 Appendicitis, CT with IV and oral contrast. This CT demonstrates classic findings of appendicitis in an 18-year-old male with right lower quadrant pain, as seen with CT with IV and oral contrast. Studies suggest that CT without contrast has similar sensitivity and specificity. An enlarged appendix is seen near the cecum as a right lower quadrant tubular structure in short-axis cross section, giving it a circular appearance. The surrounding fat shows stranding, a smoky appearance indicating inflammation (compare with normal mesenteric and subcutaneous fat, which is nearly black). The appendiceal wall shows enhancement, a brightening after administration of IV contrast. This slice also shows an appendicolith, an occasional finding of appendicitis. It does not appear to be within the appendix in this slice, because the appendix bends in and out of the plane of this slice. An appendicolith usually appears as a calcified (white) rounded structure, visible without any contrast. **A,** Axial CT image. **B,** Close-up. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

TABLE A1-64 CT Findings of Appendicitis: SCALPEL Mnemonic

Term	Description
Stranding	Fat stranding suggests regional inflammation, possibly because of appendicitis.
Cecum	The appendix originates from the cecum, which should be identified first to help localize the appendix. The cecum may show wall thickening, suggesting appendicitis.
Air	Air outside of the lumen of the appendix is pathologic and suggests perforation. Air within the appendiceal wall is also abnormal.
Large	The normal appendix is <6 mm; an enlarged appendix >6 mm suggests appendicitis. Wall thickening >1 mm also suggests appendicitis.
Phlegmon	Inflammatory changes surrounding the appendix suggest a perforated appendix. A heterogeneous collection called a phlegmon may be seen. If the appendix has ruptured, a pericecal phlegmon may be the only remaining evidence, because the appendix itself may not be seen.
Enhancement	The wall of an abnormal appendix enhances with IV contrast and appears brighter than the normal bowel or the normal psoas muscle.
Lith	An appendicolith is a calcified stone sometimes found in the lumen of an inflamed appendix.

From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.

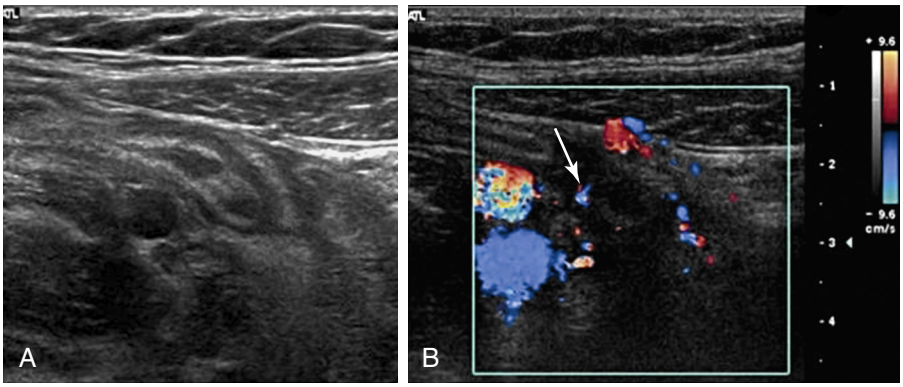


FIGURE A1-114 Appendicitis. A, Transabdominal ultrasound using a linear transducer demonstrates a thick, tubular, noncompressible structure. **B,** Same imaging method with addition of color Doppler ultrasound shows increased vascularity within the luminal wall consistent with inflammation *(arrow).* (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.)

(116 mGy cm) have shown that low-dose CT is not inferior to standard-dose CT (521 mGy cm) with respect to negative (unnecessary) appendectomy rates in young adults with suspected appendicitis.

- Ultrasonography (Fig. A1-114) has a sensitivity of 75% to 90% for the diagnosis of acute appendicitis, although it is highly operator dependent and difficult in patients with large body habitus. Ultrasound is useful, especially in pregnancy and in younger women when diagnosis is unclear. Normal ultrasonographic findings should not deter surgery if the history and physical examination are indicative of appendicitis.
- MRI of the abdomen and pelvis can also be used to accurately diagnose acute appendicitis in pregnant patients (100% sensitivity, 93.6% specificity) without exposure to ionizing radiation.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Nothing by mouth
- Do not administer analgesics until the diagnosis is made

ACUTE GENERAL Rx

- Urgent appendectomy (laparoscopic or open), correction of fluid and electrolyte imbalance with vigorous IV hydration and electrolyte replacement
- IV antibiotic prophylaxis to cover gram-negative bacilli and anaerobes (ampicillin/sulbactam 3 g IV q6h or piperacillin/tazobactam 4.5 g IV q8h in adults)

PEARLS & CONSIDERATIONS

COMMENTS

- Perforation is common (20% in adult patients). Indicators of perforation are pain lasting >24 hr, leukocytosis >20,000/mm^3, temperature >102° F, palpable abdominal mass, and peritoneal findings.
- In general, prognosis is excellent. Mortality rate is <1% in young adults without complications; however, it exceeds 10% in elderly patients with ruptured appendix.
- In approximately 20% of patients who undergo exploratory laparotomy because of suspected appendicitis, the appendix is normal.
- Trials comparing antibiotic treatment with emergency appendectomy have shown that amoxicillin plus clavulanic acid is not inferior to emergency appendectomy for acute appendicitis. Researchers have shown that over 60% of patients with uncomplicated appendicitis assigned to the antibiotic group do not need appendectomy. A recent trial assessing the feasibility of nonoperative management for uncomplicated acute appendicitis in children using either IV piperacillin-tazobactam or ciprofloxacin metronidazole therapy for at least 24 hours followed by oral antibiotics for 10 days revealed that 90% of children managed nonoperatively had no progression within 30 days.[1] However, the need to remove the appendix in patients with acute appendicitis is so entrenched in the minds of physicians that nonsurgical options are only rarely considered.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Appendicitis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

[1]Minneci PC et al: Feasibility of a nonoperative management strategy for uncomplicated acute appendicitis in children, *J Am Coll Surg* 219:272-279, 2014.

EVIDENCE

Abstract[1]

Background:
Researchers have suggested that antibiotics could cure acute appendicitis. We assessed the efficacy of amoxicillin plus clavulanic acid by comparison with emergency appendectomy for treatment of patients with uncomplicated acute appendicitis.
Methods:
In this open-label, non-inferiority, randomized trial, adult patients (aged 18–68 years) with uncomplicated acute appendicitis, as assessed by CT scan, were enrolled at six university hospitals in France. A computer-generated randomization sequence was used to allocate patients randomly in a 1:1 ratio to receive amoxicillin plus clavulanic acid (3 g per day) for 8–15 days or emergency appendectomy. The primary endpoint was occurrence of postintervention peritonitis within 30 days of treatment initiation. Non-inferiority was shown if the upper limit of the two-sided 95% CI for the difference in rates was lower than 10 percentage points. Both intention-to-treat and per-protocol analyses were done. This trial is registered with ClinicalTrials.gov, number NCT00135603.
Findings:
Of 243 patients randomized, 123 were allocated to the antibiotic group and 120 to the appendectomy group. Four were excluded from analysis because of early dropout before receiving the intervention, leaving 239 (antibiotic group, 120; appendectomy group, 119) patients for intention-to-treat analysis. 30-day postintervention peritonitis was significantly more frequent in the antibiotic group (8%, n=9) than in the appendectomy group (2%, n=2; treatment difference 5·8; 95% CI 0·3-12·1). In the appendectomy group, despite CT-scan assessment, 21 (18%) of 119 patients were unexpectedly identified at surgery to have complicated appendicitis with peritonitis. In the antibiotic group, 14 (12% [7·1-18·6]) of 120 underwent an appendectomy during the first 30 days and 30 (29% [21.4–38.9]) of 102 underwent appendectomy between 1 month and 1 year, 26 of whom had acute appendicitis (recurrence rate 26%; 18.0–34.7).
Interpretation:
Amoxicillin plus clavulanic acid was not non-inferior to emergency appendectomy for treatment of acute appendicitis. Identification of predictive markers on CT scans might enable improved targeting of antibiotic treatment. Ⓐ

Abstract[2]

Background:
The skin is closed in open appendectomy traditionally with few interrupted nonabsorbable sutures. The use of this old method is based on a suggestion that this technique decreases wound infections. In pediatric surgery, skin closure with running intradermal absorbable sutures has been found to be as safe as nonabsorbable sutures, even in complicated cases. Our purpose was to compare the safety of classic interrupted nonabsorbable skin closure to continuous intradermal absorbable sutures in appendectomy wounds in adult patients.
Methods:
A total of 206 adult patients with clinically suspected appendicitis were allocated to the study and prospectively randomized into two groups of wound closure: the interrupted nonabsorbable (NA) suture and the intradermal continuous absorbable (A) suture group. Primary wound healing was controlled on the first postoperative day, at 1 week clinically and after 2 weeks by means of a telephone interview. Follow-up data were obtained from 185 patients (90 in group NA and 95 in group A).
Results:
Continuous absorbable intradermal suturing was as safe as nonabsorbable sutures in regard to wound infections.
Conclusion:
Continuous, absorbable sutures can be used safely even in complicated appendectomies without increasing the risk of wound infection. Considering the benefits of absorbable suturing, we recommend this method in all open appendectomies. Ⓐ

Appendectomy for acute appendicitis results in a clean contaminated or contaminated wound. Thus, many forms of wound closure have been used to obviate the risk of postoperative wound infection. This prospective, randomized trial evaluated continuous absorbable suture closure vs interrupted nonabsorbable suture as a technique of skin/wound closure. Evaluation of wound complications was done at 1 week clinically (nurse, resident, attending physician) and by telephone interview. It is presumed that all wound infectious complications would present themselves by at least 2 weeks, although some declare themselves after this period. No significant differences in wound infectious and other complications were noted comparing the 2 groups. As the authors noted, the use of continuous absorbable suture technique is easier on the patient. Given the results of this trial, continuous nonabsorbable suture technique should become the gold standard after uncomplicated appendectomy.
JM Daly, MD Ⓐ

Abstract[3]

Objective:
The aim of the current study was to perform a multicentered prospective double-blinded randomized controlled trial comparing laparoendoscopic single-site access (LESS) versus conventional three-port laparoscopic appendectomy (TPLA).
Background:
The clinical benefits and disadvantages of LESS appendectomy are uncertain.
Methods:
Between October 2009 and March 2011, consecutive patients admitted with clinical or radiologic evidence of appendicitis were randomly assigned to receive either LESS or TPLA. The main outcome measurement was overall pain score. Secondary outcome measurements included operative time, conversion rates, morbidity rates, activity pain scores, activity scores, patient satisfaction, and cosmesis scores.
Results:
During the study period, 200 patients were recruited to the study. There were no significant differences in the morbidity rates, operative time, conversion rates, and postoperative recovery. There were also no differences in the overall pain score and pain score at rest. However, patients in the LESS group experienced significantly more pain upon coughing or standing and required more intravenous analgesics ($P = 0.001$, 0.038, and 0.035, respectively).Wound cosmesis and satisfaction scores on the contrary were better in the LESS group ($P = 0.002$ and $P = 0.052$). No differences in the quality-of-life assessments were present at 2 weeks after operation.
Conclusions:
LESS and conventional appendectomy resulted in similar perioperative outcomes. However, LESS appendectomy resulted in worst pain scores upon exertion and required a higher dosage of intravenous analgesics when compared with TPLA. On the contrary, wound cosmesis and satisfaction scores were better in the LESS group. Hence, adoption of the technique for appendectomy will depend on patient preferences and the presence of local expertise. Ⓐ

This group from Hong Kong presents a double-blinded, randomized, controlled trial of laparoendoscopic single-site access (LESS) compared with conventional 3-port appendectomy (TPLA). Adult patients (200) with a diagnosis of appendicitis with 5 days or less of symptoms and without a palpable right lower quadrant mass were randomized to 1 of either procedure. Reasons for exclusion from the study included previous surgery, peritonitis, extended symptoms, coagulopathy, previous pregnancy, palpable mass, shock, myocardial infarction, or refusal to enter the study. LESS was performed by making a 13-mm transumbilical incision with insertion of a 10-mm and two 5-mm trocars through separate fascial incisions. The TPLA approach included a 10-mm subumbilical port and a 5-mm port in each of the right and left lower quadrants. The mesoappendix was divided with ultrasonic dissection and the appendix ligated with 2 endoloop sutures. The fascial defects of the 10-mm ports were closed along with the skin, and 3 wound dressings were left in place simulating the wound coverage for the TPLA. This clever approach, therefore, blinded the patient and the data collection staff to the surgical technique.

Evaluation of the efficacy of either procedure revealed no advantage to either approach with regard to morbidity, operative time (63 vs 60 minutes), conversion rate (8 vs 3%), or hospital stay. Overall, LESS patients reported improved cosmesis with the single-site approach and overall satisfaction with the operation. Although total pain scores were equal, patients undergoing LESS had more pain with standing and extended coughing, which correlated with higher pain medication usage.

This also correlated with less activity in the LESS group early in the postoperative period. The authors surmise that the difference in pain may be explained by the fact that the total fascial incision distance is the same with each procedure, and that the pelvic peritoneum where the 5-mm TPLA trocars were introduced is less sensitive to pain triggers than the peritoneum in the rest of the abdominal cavity. However, most surgeons performing laparoscopic procedures recognize that patients complain most commonly about the umbilical trocar site, and in the LESS group all 3 ports were placed through the umbilicus. Whether single-site appendectomy ultimately becomes the newest standard is unknown. This well-executed study does demonstrate, though, that single-site appendectomy can be safely performed with little additional time over that of a traditional laparoscopic approach. Also, supply cost-savings may be realized with the described procedures in this study. The appendiceal stump can be safely controlled with an endoloop rather than an endoGIA, and a single-port approach does not require special access devices. The same trocars used for a laparoscopic appendectomy can be used for a LESS procedure.

J Hines, MD

Evidence-Based Reference

Vons C et al.: Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial, *Lancet* 377:1573–1579, 2011. Ⓐ

Kotaluoto S, Pauniaho SL, Helminen M, et al.: Wound healing after open appendectomies in adult patients: a prospective, randomised trial comparing two methods of wound closure, *World J Surg* 36:2305–2310, 2012. Ⓐ

Teoh AYB, Vons PWY, Vons TCL, et al.: A double-blinded randomized controlled trial of laparoendoscopic single-site access versus conventional 3-port appendectomy, *Ann Surg* 256:909–914, 2012. Ⓐ

SUGGESTED READINGS

Bundy DG et al.: Does this child have appendicitis? *JAMA* 298(4):438, 2007.

Ebell MH: Diagnosis of appendicitis: laboratory and imaging tests, *Am Fam Physician* 77(1153), 2008.

Freeland M et al.: Diagnosis of appendicitis in pregnancy, *Am J Surg* 198:753–758, 2009.

Kim K et al.: Low-dose abdominal CT for evaluating suspected appendicitis, *N Engl J Med* 366:1596–1605, 2012.

Pedrosa I et al.: MR imaging evaluation of acute appendicitis in pregnancy, *Radiology* 238(3):891–899, 2006.

Pickhardt P et al.: Diagnostic performance of multidetector computed tomography for suspected acute appendicitis, *Ann Intern Med* 154:789–796, 2011.

Teresawa T et al.: Systematic review: computed tomography and ultrasonography to detect acute appendicitis in adults and adolescents, *Ann Intern Med* 141(537), 2004.

Vons C et al.: Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomized controlled trial, *Lancet* 377:1573–1579, 2011.

BASIC INFORMATION

DEFINITION

Arrhythmogenic right ventricular dysplasia (ARVD) is a disorder characterized by replacement of the normal myocardium by fibrofatty tissue, RV myocyte loss, and RV wall thinning, and represents a kind of cardiomyopathy. It is defined clinically by life-threatening ventricular arrhythmias in otherwise healthy young people.

SYNONYMS

Arrhythmogenic right ventricular cardiomyopathy

ICD-9CM CODES
427.1 Paroxysmal ventricular tachycardia
425.4 Other primary cardiomyopathies
427.89 Other specified cardiac dysrhythmias
ICD-10CM CODES
I42.8 Arrhythmogenic ventricular dysplasia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: ARVD comprises 2% of sudden cardiac arrest cases.
PREVALENCE: 1:5000 persons
PREDOMINANT SEX AND AGE: Men <35 yr old
RISK FACTORS: Family history of ARVD
GENETICS:

- Autosomal dominant with variable penetrance, and polymorphic phenotypic expression
- Desmosomal dysfunction (desmosome gene mutations)
- 11 subtypes of ARVD are identified based on the involved genes.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Suspect when young males present with syncope, sudden cardiac arrest, ventricular tachycardia, premature ventricular beats originating from the right ventricle, or, less commonly, signs and symptoms of right heart failure. Symptoms vary and range from palpitations, dizziness, and syncope to atypical chest pain, dyspnea, and fatigue.
- Cardiac arrest after physical exertion may be the initial presentation.
- Physical examination will be normal in most patients. Widely split S2 is an important diagnostic clue.

ETIOLOGY

ARVD is characterized by progressive replacement of the right ventricular myocardium with fibrofatty tissue after apoptotic myocardial cell death

DIAGNOSIS

- Diagnosis is made when two major criteria, one major and two minor, or four minor criteria are met.
- See Table A1-65 for diagnostic criteria.

TABLE A1-65 Criteria for the Diagnosis of Arrhythmogenic Right Ventricular Dysplasia

Global and/or Regional Dysfunction and Structural Alterations
Major
Severe dilation and reduction of right ventricular ejection fraction with no (or only mild) left ventricular impairment
Localized right ventricular aneurysms
Severe segmental dilation of the right ventricle
Minor
Mild global right ventricular dilation and/or ejection fraction with a normal left ventricle
Mild segmental dilation of the right ventricle
Regional right ventricular hypokinesis
Tissue Characterization of the Walls
Major
Fibrofatty replacement of myocardium on endomyocardial biopsy
ECG Repolarization Abnormalities
Minor
Inverted T waves in the right precordial leads (V_2 and V_3) in patients older than 12 yr and in the absence of right bundle branch block
ECG Depolarization/Conduction Abnormalities
Major
Epsilon waves or localized prolongation (greater than 110 ms) of the QRS complex in right precordial leads (V_1 through V_3)
Minor
Late potentials visible on signal-averaged ECG
Arrhythmias
Minor
Sustained or nonsustained left bundle branch block type VT documented on ECG, Holter monitoring, or during exercise stress testing
Frequent ventricular extrasystoles (more than 1000 per 24 hr on Holter monitoring)
Family History
Major
Familial disease confirmed at autopsy or surgery
Minor
Family history of premature sudden death (younger than 35 yr) caused by suspected ARVD/C
Family history (clinical diagnosis based on present criteria)

The diagnosis of arrhythmogenic right ventricular dysplasia is made if one of the following is met: two major criteria, one major and two minor criteria, or four minor criteria.
ARVD/C, Arrhythmogenic right ventricular dysplasia/cardiomyopathy; *ECG,* electrocardiography; *VT,* ventricular tachycardia.
From Anderson EL: Arrhythmogenic right ventricular dysplasia, *Am Fam Physician* 73[8]:1391-1398, 2006.

DIFFERENTIAL DIAGNOSIS

- Cardiomyopathy with involvement of the right ventricle
- Uhl's anomaly: rare anomaly that presents mainly in childhood with signs and symptoms of right heart failure and characterized by a paper-thin right ventricle resulting from death of the myocytes throughout the right ventricle
- Idiopathic RV tachycardia
- Left dominant arrhythmogenic cardiomyopathy

WORKUP

- Resting ECG will have diagnostic findings in 50% to 90% of patients with ARVD. These changes include T-wave inversions in anterior precordial leads V_1-V_6, epsilon waves (Fig. A1-115*A*), and *ventricular tachycardia* (VT) with left bundle branch block pattern.
- Endomyocardial biopsy is the preferred method for diagnosis of ARVD. It has specificity of 92%, but it lacks sensitivity (<20%).
- Electrophysiologic study is important to identify delayed potentials that can lead to tachycardiac events.
- Routine immunohistochemical analysis of a conventional endomyocardial-biopsy sample appears to be a highly sensitive and specific diagnostic test for arrhythmogenic right ventricular cardiomyopathy.

IMAGING STUDIES

- MRI is a noninvasive method to detect structural changes and regional dysfunction. Cardiac MRI (CMR) is the most sensitive method to detect ARVD, but has high false-positive rates. Cardiac CT angiogram (Fig. A1-115*B*) will reveal thinning and aneurysmal dilation of the RV anterior wall and outflow tract.
- Echocardiography will show right ventricular dilation with regional wall motion abnormalities that varied with the severity of the disease.
- Other diagnostic modalities used for evaluation of suspected ARVD include signal averaged ECG, Holter monitor, stress test, and radionuclide ventriculography.

Arrhythmogenic Right Ventricular Dysplasia

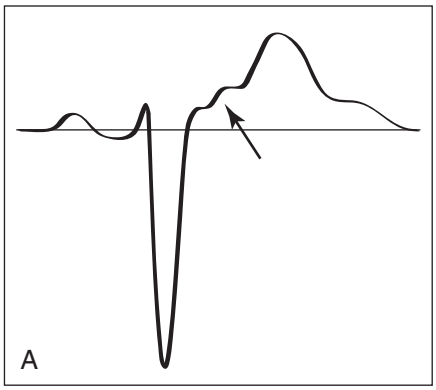


FIGURE A1-115 A Epsilon waves are small deflections just beyond the QRS complex. Best visualized in leads V_1-V_3. Any potential in leads V_1-V_3 that exceeds the QRS in leads V6 by more than 25 millisecond should be considered epsilon wave. (From Anderson EL: Arrhythmogenic right ventricular dysplasia, *Am Fam Physician* 73(8):1391-1398, 2006.)

Rx TREATMENT

No definitive therapy is available. Treatment goal is to prevent sudden cardiac death. Placement of an automatic implantable cardioverter defibrillator (AICD) may be used to avoid sudden cardiac death in patients with severe symptoms. It is worth noting that complications related to AICD can make this treatment option undesirable in some patients, but with an experienced cardiologist/cardiac center, this can be a great option.

NONPHARMACOLOGIC THERAPY

- Avoidance of activity that may trigger tachycardia
- Right ventriculotomy
- Cardiac transplantation

ACUTE GENERAL Rx

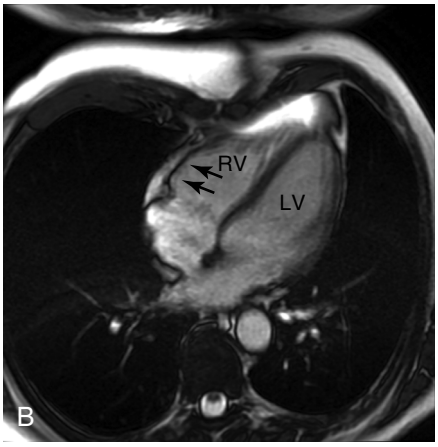
Intravenous amiodarone has been proved to be effective in terminating VT.

CHRONIC Rx

- Antiarrhythmic therapy with sotalol, amiodarone, propafenone, beta-blocker alone or in combination can be used
- Radiofrequency ablation is used in cases of refractory VT, frequent tachycardia after defibrillator placement, or localized arrhythmia sites
- Implantable cardioverted defibrillators hold promise

REFERRAL

- Early cardiology and electrophysiology referral
- Consider referring for genetic counseling



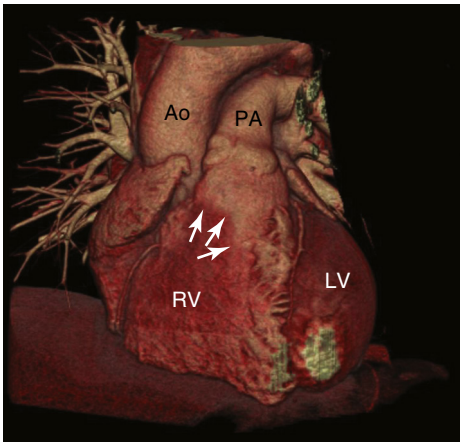


FIGURE A1-115 B Right ventricular aneurysm. This cardiac computed tomography angiogram shows thinning and aneurysmal dilation of the RV anterior wall and outflow tract *(arrows)* in a patient with arrhythmogenic right ventricular dysplasia, cardiomyopathy, and ventricular tachycardia. *Ao,* Aorta; *LV,* left ventricle; *PA,* pulmonary artery. (Courtesy of Dr. Nasar Nallamothu, Prairie Cardiovascular Consultants, Springfield, Ill. From Issa Z et al: *Clinical arrhythmology and electrophysiology,* ed 2, Philadelphia, 2012, Saunders.)

PEARLS & CONSIDERATIONS

PREVENTION

Test first-degree relatives if there is a positive history of sudden cardiac death or death at an early age.

EDUCATION

Patient handout can be found in *American Family Physician* (American Academy of Family Physicians: Information from your family doctor. Arrhythmogenic right ventricular dysplasia: what you should know. *Am Fam Physician* 73(8):1401, 2006).

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **ABDULRAHMAN ABDULBAKI, M.D., NADIA MUJAHID, M.D.,** and **PATRICK NSEREKO, M.D.**

SUGGESTED READINGS

Anderson EL: Arrhythmogenic right ventricular dysplasia, *Am Fam Physician* 73(8):1391–1398, 2006. Review.

Asimaki A et al.: A new diagnostic test for arrhythmogenic right ventricular cardiomyopathy, *N Engl J Med* 360:1075–1084, 2009.

Bhonsale A et al.: Incidence and predictors of implantable cardioverter-defibrillator therapy in patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy undergoing implantable cardioverter-defibrillator implantation for primary prevention, *J Am Coll Cardiol* 58:1485–1496, 2011.

Calkins H et al.: Arrhythmogenic right ventricular cardiomyopathy/dysplasia: an update, *Curr Cardiol Rep* 10(5):367–375, 2008.

Jain A et al.: Role of cardiovascular magnetic resonance imaging in arrhythmogenic right ventricular dysplasia, *J Cardiovasc Magn Reson* 10(1):32, 2008. 10.1186/1532-429X-10-32.

Kies P et al.: Arrhythmogenic right ventricular dysplasia/cardiomyopathy: screening, diagnosis, and treatment, *Heart Rhythm* 3(2):225–234, 2006.

Kim C et al.: Studying arrhythmogenic right ventricular dysplasia with patient-specific iPSCs, *Nature* 6(494):105–110, 2013.

Peters S: QRS fragmentation and epsilon waves in Fontaine leads in arrhythmogenic right ventricular cardiomyopathy, *Int J Cardiol*, 2014.

Schinkel AF: Implantable cardioverter defibrillators in arrhythmogenic right ventricular dysplasia/cardiomyopathy: patient outcomes, incidence of appropriate and inappropriate interventions, and complications, *Circ Arrhythm Eletrophysiol* 562–568, 2013.

Sequeira IB et al.: Utility of exercise testing in children and teenagers with arrhythmogenic right ventricular cardiomyopathy, *Am J Cardiol* 104:411–413, 2009.

BASIC INFORMATION

DEFINITION

Asbestosis is a slowly progressive diffuse interstitial fibrosis resulting from dose-related inhalation exposure to fibers of asbestos.

ICD-9CM CODES
501 Asbestosis
ICD-10CM CODES
J61 Pneumoconiosis due to asbestos and other mineral fibers

EPIDEMIOLOGY & DEMOGRAPHICS

- Five to 10 new cases per 100,000 persons per year in the United States.
- Prolonged interval (20 to 30 yr) between exposures to inhaled fibers and clinical manifestations of disease
- Most common in workers involved in the primary extraction of asbestos from rock deposits and in those involved in the fabrication and installation of products containing asbestos (e.g., naval shipyards in World War II; installation of floor tiles, ceiling tiles, acoustic ceiling coverings, wall insulation, and pipe coverings in public buildings)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Insidious onset of shortness of breath with exertion is usually the first sign of asbestosis.
- Dyspnea becomes more severe as the disease advances; with time, progressively less exertion is tolerated.
- Cough is frequent and usually paroxysmal, dry, and nonproductive.
- Scant mucoid sputum may accompany the cough in the later stages of the disease.
- Fine end-respiratory crackles (rales, crepitations) are heard more predominantly in the lung bases.
- Digital clubbing, edema, jugular venous distention are present.

ETIOLOGY

Inhalation of asbestos fibers

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Silicosis
- Siderosis, other pneumonoconioses
- Lung cancer
- Atelectasis

WORKUP

Documentation of exposure history, diagnostic imaging, pulmonary function testing

LABORATORY TESTS

- Generally not helpful
- Possible mild elevation of erythrocyte sedimentation rate (ESR), positive antinuclear antibody (ANA), and rheumatoid factor (RF) (these tests are nonspecific and do not correlate with disease severity or activity)
- Pulmonary function testing: decreased vital capacity, decreased total lung capacity, decreased carbon monoxide gas transfer
- Arterial blood gases: hypoxemia, hypercarbia in advanced stages

IMAGING STUDIES

Chest radiograph (Fig. A1-116):
- Small, irregular shadows in lower lung zones.
- Thickened pleura, calcified plaques (present under diaphragm and lateral chest wall).
- CT scan of chest confirms diagnosis. Typical findings on high-resolution CT of the chest include increased interstitial markings found mainly at the bases. As the disease progresses, honeycombing is noted.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Smoking cessation, proper nutrition, exercise program to maximize available lung function
- Home oxygen therapy PRN
- Removal of patient from further asbestos fiber exposure

GENERAL Rx

- Prompt identification and treatment of respiratory infections
- Supplemental oxygen on a PRN basis
- Annual influenza vaccination, pneumococcal vaccination

DISPOSITION

- There is no specific treatment for asbestosis.
- Death is usually from respiratory failure from cor pulmonale.
- Patients with asbestosis have increased risk for mesotheliomas, lung cancer, and tuberculosis. Recent reports indicate that the risk of asbestos-induced lung cancer may be overestimated.
- Survival in patients after development of mesothelioma is 4 to 6 yr.

REFERRAL

To pulmonologist initially

PEARLS & CONSIDERATIONS

COMMENTS

Patient information on asbestosis can be obtained from the American Lung Association, 1740 Broadway, New York, NY 10019.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Asbestosis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

FIGURE A1-116 Asbestosis. Posteroanterior radiograph shows coarse linear opacities at both lung bases obscuring the cardiac borders. (From McLoud TC: *Thoracic radiology: the requisites,* St Louis, 1998, Mosby.)

SUGGESTED READINGS

American Thoracic Society: Diagnosis and initial management of nonmalignant diseases related to asbestos, *Am J Respir Crit Care Med* 170(691), 2004.

O'Reilly K et al.: Asbestos-related lung disease, *Am Fam Physician* 75(683), 2007.

BASIC INFORMATION

DEFINITION

Ascariasis is a parasitic infection caused by the nematode *Ascaris lumbricoides.* The majority of those infected are asymptomatic; however, clinical disease may arise from pulmonary hypersensitivity, intestinal obstruction, and secondary complications.

SYNONYMS

Round worms
Worms

ICD-9CM CODES
127.0 Ascariasis
ICD-10CM CODES
B77.9 Ascariasis, unspecified
B77.81 Ascariasis pneumonia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN THE UNITED STATES):
- Unknown
- Three times the infection rates found in blacks as in whites

PEAK INCIDENCE: Unknown
PREVALENCE (IN THE UNITED STATES): Estimated at 4 million, the majority of which live in the rural southeastern part of the country; ascariasis is associated with poor sanitation
PREDOMINANT SEX: Both sexes probably equally affected, with a possible slight female preponderance
PREDOMINANT AGE: Most common in children from ages 2 to 10 years old and decreases after age 15; infections tend to cluster in families
NEONATAL INFECTION: Probable transmission, though not specifically studied

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Occurs approximately 9 to 12 days after ingestion of eggs (corresponding to the larval migration through the lungs)
- Nonproductive cough
- Substernal chest discomfort
- Fever
- In patients with large worm burdens, especially children, intestinal obstruction associated with perforation, volvulus, and intussusception
- Migration of worms into the biliary tree giving clinical appearance of biliary colic and pancreatitis as well as acute appendicitis with movement into that appendage
- Rarely, infection with *A. lumbricoides* producing interstitial nephritis and acute renal failure
- In endemic areas in Asia and Africa, malabsorption of dietary proteins and vitamins as a consequence of chronic worm intestinal carriage; 1 billion people worldwide are infected with this nematode

ETIOLOGY

- Transmission is usually hand to mouth, but eggs may be ingested via transported vegetables grown in contaminated soil.
- Eggs are hatched in the small intestine, with larvae penetrating intestinal mucosa and migrating via the circulation to the lungs.
- Larval forms proceed through the alveoli, ascend the bronchial tree, and return to the intestines after swallowing, where they mature into adult worms.
- Estimated time until the female adult worm begins producing eggs is 2 to 3 mo.
- Eggs are passed out of the intestines with feces and can survive for years in warm, moist, shaded soil.
- Within human host, adult worm life span is 1 to 2 yr.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Radiologic manifestations and eosinophilia to be distinguished from drug hypersensitivity and Löffler's syndrome

LABORATORY TESTS

- Examination of the stool for *Ascaris* ova (Fig. EA1-117)
- Expectoration or fecal passage of adult worm
- Adult male worms: 10 to 30 cm long; adult female worms: larger than male, up to 40 cm
- Eosinophilia: most prominent early in the infection and subsides as the adult worm infestation established in the intestines; usually in 5% to 12% range but can be up to 50%
- Serology: patients develop IgG antibodies, but they cross react with antigens from other helminths and are not protective; thus serology is used more for epidemiologic purposes than for individual diagnosis

IMAGING STUDIES

- Chest x-ray to reveal bilateral oval or round infiltrates of varying size (Löffler's syndrome); NOTE: infiltrates are transient and eventually resolve.
- Plain films of the abdomen and contrast studies to reveal worm masses in loops of bowel.
- Ultrasonography and endoscopic retrograde cholangiopancreatography (ERCP) to identify worms in the pancreaticobiliary tract.
- CT scan with oral contrast can also assist in the detection of GI foreign bodies such as parasites.

TREATMENT

NONPHARMACOLOGIC THERAPY

Aggressive IV hydration, especially in children with fever, severe vomiting, and resultant dehydration

ACUTE GENERAL Rx

- All infected patients, including asymptomatic ones, should be treated
  1. Albendazole: 400 mg PO × 3 days is the first-line agent for intestinal infection with *A. lumbricoides*
  2. Mebendazole 100 mg daily × 3 days
- Cure rate with these agents is 95% to 100%, but they are contraindicated in pregnancy.
- Side effects: GI discomfort, headache, and rarely leukopenia
- Alternative agent or for use in pregnancy: pyrantel pamoate (Antiminth)
  1. Given at a dose of 11 mg/kg PO (maximum dose of 1 g/day)
  2. Considered safe for use in pregnant women
- Other alternative agents:
  1. Ivermectin: 150 to 200 mcg/kg orally once
  2. Nitazoxanide: cure rates in heavy worm burden are only 50% to 80%
  3. Piperazine citrate: no longer first-line agent due to toxicity but still used in cases of intestinal or biliary obstruction, as drug paralyzes the worm, helping its expulsion. Dose: 50 to 75 mg/kg once daily up to maximum of 3.5 g for 2 days.
  4. Levamisole: 2.5 mg/kg once orally is recommended by the WHO as alternative therapy, but not available in the United States.
- Complete obstruction should be managed surgically.

DISPOSITION

Overall prognosis is good. Patients should be reevaluated in 2 to 3 months. Reinfection is common.

REFERRAL

- To gastroenterologist in cases of visualized pancreaticobiliary tract or appendiceal obstruction
- To surgeon in cases of complete obstruction or suspected secondary complication (e.g., perforation or volvulus)

PEARLS & CONSIDERATIONS

COMMENTS

- Hepatic abscess, containing both viable and dead worms, complicating *Ascaris*-induced biliary duct disease has been documented.
- Given the known transmission of the parasite, routine hand washing with soap and proper disposal of human waste would significantly decrease the prevalence of this disease.
- Other protective measures to avoid ingestion of worm eggs:
  1. Peel or cook food.
  2. Boil drinking water.
  3. Do not place small children directly on soil.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Ascariasis (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Bethony J et al.: Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm, *Lancet* 367(9521):1521–1532, 2006.

Keiser J, Utzinger J et al.: Efficacy of current drugs against soil-transmitted helminth infections: systematic review and meta-analysis, *JAMA* 299(16):1937–1948, 2008.

Legesse M et al.: Comparative efficacy of albendazole and three brands of mebendazole in the treatment of ascariasis and trichuriasis, *East Afr Med J* 81(3):134, 2004.

Sangkhathat S et al.: Massive gastrointestinal bleeding in infants with ascariasis, *J Pediatr Surg* 38(11):1696, 2003.

Shah OJ et al.: Biliary ascariasis: a review, *World J Surg* 30(8):1500, 2006.

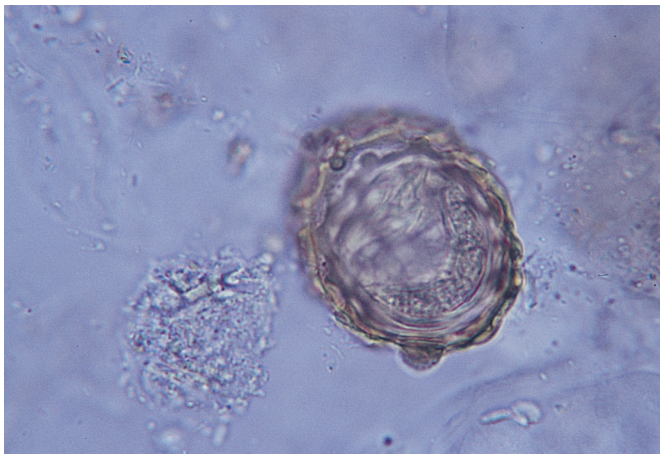


FIGURE EA1-117 *Ascaris lumbricoides* ovum in feces. The ovum measures 50 to 70 mm × 40 to 50 mm and is elliptical. The rough albuminous coat gives it a mammillated appearance. (From Cohen J, Powderly WG: *Infectious diseases*, ed 2, St. Louis, 2004, Mosby.)

BASIC INFORMATION

DEFINITION

Ascites is the accumulation of excess fluid in the peritoneal cavity, most commonly caused by liver cirrhosis.

SYNONYMS

Fluid in peritoneal cavity
Hydroperitoneum
Hydroperitonia
Hydrops abdominis

ICD-9CM CODES
789.5 Ascites
568.82 Peritoneal effusion (chronic)
ICD-10CM CODES
R18 Ascites
C78.6 Malignant ascites

EPIDEMIOLOGY & DEMOGRAPHICS

Ascites is the most common complication of cirrhosis. Ascites occurs in 50% of individuals with cirrhosis within 10 years of diagnosis. Cirrhosis is the cause of 75% of cases of ascites. Other causes include malignancy, heart failure, tuberculosis, pancreatitis, nephrotic syndrome, and Budd-Chiari syndrome.

CLINICAL PRESENTATION

- Important information to elicit within history:
  1. History of viral hepatitis
  2. Alcoholism
  3. Increasing abdominal girth
  4. Increasing lower extremity edema
  5. Intravenous drug use
  6. Sexual history (i.e., men who have sex with men)
  7. History of transfusions

FIGURE A1-118 Ascites in a patient with alcoholic cirrhosis showing distended abdomen; dilated superficial collateral veins; hemorrhagic scratch marks due to pruritus and coagulopathy; umbilical varices; and plaster in left iliac fossa indicating diagnostic paracentesis. (From Forbes A et al [eds]: *Atlas of clinical gastroenterology,* ed 3, Oxford, 2005, Mosby.)

- Important physical exam findings:
  1. Bulging flanks
  2. Flank dullness to percussion
  3. Fluid wave on abdominal exam
  4. Lower extremity edema
  5. Shifting dullness on abdominal exam
  6. Physical signs associated with liver cirrhosis: spider angiomas, jaundice, loss of body hair, Dupuytren's contracture, muscle wasting, bruising, palmar erythema, gynecomastia, testicular atrophy, hemorrhoids, and caput medusae (Fig. A1-118)

ETIOLOGY

Pathophysiology of ascites (Fig. EA1-119): increased hepatic resistance to portal flow leads to portal hypertension. The splanchnic vessels respond by increased secretion of nitric oxide, causing splanchnic artery vasodilation. Early in the disease increased plasma volume and increased cardiac output compensate for this vasodilation. However, as disease progresses the effective arterial blood volume decreases, causing sodium and fluid retention through activation of the renin-angiotensin system. The change in capillary pressure causes increased permeability and retention of fluid in the abdomen.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Chronic parenchymal liver disease, leading to portal hypertension
- Peritoneal carcinomatosis
- Congestive heart failure
- Peritoneal tuberculosis
- Nephrotic syndrome
- Pancreatitis

LABORATORY TESTS

- Initial evaluation should always include:
  1. Diagnostic paracentesis (Fig. EA1-120). Laboratory tests on this fluid should include a CBC with differential, albumin, total protein, culture, and Gram stain. A serum-ascites albumin gradient (SAAG) should be calculated in all patients. If the SAAG is greater than 1.1, the cause of ascites can be attributed to portal hypertension. If SAAG is less than 1.1, a nonportal hypertension etiology of ascites must be sought (see Table A1-66). Optional tests on paracentesis fluid include amylase, LDH, acid-fast bacilli, and glucose levels.
  2. AST, ALT, total and direct bilirubin, albumin, alkaline phosphatase, GGTP
  3. CBC, coagulation studies
  4. Electrolytes, BUN, creatinine

IMAGING STUDIES

- Abdominal ultrasound (Fig. A1-121) is the most sensitive measure for detecting ascitic fluid; a CT or MRI scan is a viable alternative.
- Endoscopy of the upper GI tract to evaluate for esophageal varices if ascites is secondary to portal hypertension.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Sodium-restricted diet (<2 g/day).
- Fluid restriction to 1 L/day in patients with hyponatremia (sodium <130 mEq/L).

ACUTE GENERAL Rx

- Patients with moderate-volume ascites causing only moderate discomfort may be treated on an outpatient basis with the following diuretic regimen: spironolactone 50 to 200 mg daily or amiloride 5 to 10 mg daily. Add furosemide 20 to 40 mg/day in the first several days of treatment, monitoring renal function carefully for signs of prerenal azotemia (in patients without edema, goal weight loss is 300 to 500 g/day; in patients with edema it is 800 to 1000 g/day).
- Patients with large-volume ascites causing marked discomfort or decrease in activities of daily living may also be treated as outpatients if there are no complications. There are two options for treatment in these patients: (1) large-volume paracentesis or (2) diuretic therapy until loss of fluid is noted (maximum spironolactone 400 mg daily and furosemide 160 mg daily). No difference in long-term mortality rate was found; however, paracentesis is faster, more effective, and associated with fewer adverse effects.
- Table A1-67 summarizes primary medical therapy and adjunctive medications used to increase the efficacy of primary therapy in the treatment of ascites.

CHRONIC Rx

5% to 10% of patients with large-volume ascites will be refractory to high-dose diuretic

TABLE A1-66 Using the Serum-Ascites Albumin Gradient and the Ascites Total Protein Level to Diagnose the Cause of Ascites

Condition	Serum-Ascites Albumin Gradient*	Ascites Total Protein Level†
Cirrhosis	High	Low
Malignant ascites	Low	High
Cardiac ascites	High	High

*High is greater than 1.1 g/dL; low is less than 1.1 g/dL.
†High is greater than 2.5 g/dL; low is less than 2.5 g/dL.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

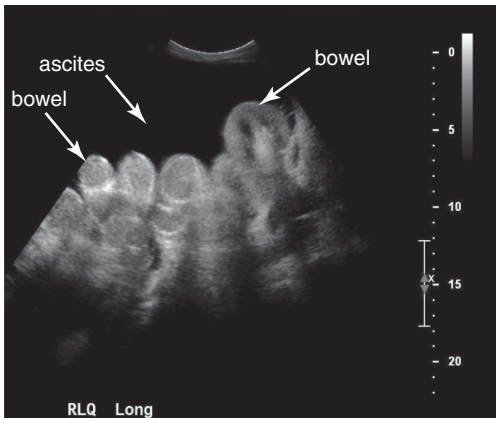


FIGURE A1-121 Ascites, ultrasound. Ultrasound is useful for detection of ascites. Simple fluids such as ascites are excellent sound transmission media, reflecting almost no sound waves. As a consequence, they appear quite hypoechoic *(black)* on ultrasound. This view of the right lower quadrant shows loops of bowel surrounded by fluid. During the ultrasound, the bowel loops would be seen to undergo peristalsis and drift back and forth in the ascitic fluid with patient movement. Ultrasound cannot distinguish the composition of the fluid; ascites, liquid blood, liquid bile, urine, and infectious fluids have a similar appearance, with a few exceptions. Blood may coagulate and form septations within the fluid collection. Infectious fluids also frequently form loculated fluid collections that may be recognized on ultrasound, although the exact composition cannot be determined. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

TABLE A1-67 Primary Medical Therapy and Adjunctive Medications Used to Increase the Efficacy of Primary Therapy in the Treatment of Ascites

Class	Medication	Dosing	Relevant Action	Notes
Diuretics	Spironolactone	400 mg + daily*	Aldosterone receptor antagonist	Primary therapy
	Furosemide	160 mg + daily*	Inhibits Na-K-2Cl symporter	Primary therapy
	Mannitol	20%*	Osmotic diuresis	Give dose just prior to furosemide and spironolactone
Vasoconstrictors	Octreotide	300 mcg bid*	Splanchnic vasoconstriction, inhibits RAAS	Also used in combination with midodrine to treat hepatorenal syndrome; given for first 5 days following variceal bleeding to decrease recurrence
	Midodrine	7.5 mg tid*	Inhibits RAAS	Also used in combination with octreotide and albumin to treat hepatorenal syndrome
α2-Agonist	Clonidine	0.075 mg bid*	Inhibits sympathetic outflow, inhibits RAAS	Increases sensitivity to spironolactone
Colloid	Albumin	25 g*	Increased oncotic pressure	Also utilized with LVP and in the treatment of hepatorenal syndrome
Aquaretics	None are FDA approved	N/A	Vasopressin receptor antagonist	May also treat hyponatremia

*The above doses have been derived from various studies and may not be suitable for all patients. Titration is always recommended.
From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

treatment. Treatment strategies include repeated large-volume paracentesis with infusion of albumin every 2 to 4 weeks or placement of a transjugular intrahepatic portosystemic shunt (TIPS). A treatment approach to patients with malignant ascites is described in Fig. EA1-122.

DISPOSITION

Monitor closely for worsening liver function, development of spontaneous bacterial peritonitis (SBP).

REFERRAL

Referral to gastroenterology with ascites

PEARLS & CONSIDERATIONS

COMMENTS

Prevalence of SBP in patients with ascites ranges between 10% and 30%. Presence of at least 250 neutrophils per cubic millimeter of ascitic fluid is diagnostic. Gram negative bacteria such as *E. coli* are the most common isolates. Third-generation cephalosporins are the treatment of choice. By 1 year, 70% of patients have recurrence of SBP and may be prophylaxed with trimethoprim/sulfamethoxazole DS 1 tab PO bid 5 days/wk or ciprofloxacin 750 mg PO once/wk.

PREVENTION

Prevention of liver cirrhosis through avoidance of long-term use of alcohol, immunization against hepatitis A and B, and treatment of hepatitis C

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Ascites (Patient Information)
Cirrhosis (Related Key Topic)

AUTHORS: **JOANNE M. SILVIA, M.D.,** and **PAUL F. GEORGE, M.D.**

SUGGESTED READINGS

Cardenas A et al.: Management of patients awaiting liver transplant, *Gut* 60:412–421, 2011.

Salerno F et al.: Refractory ascites: pathogenesis, definition and therapy of a severe complication in patients with cirrhosis, *Liver Int* 30(7):937–947, 2010.

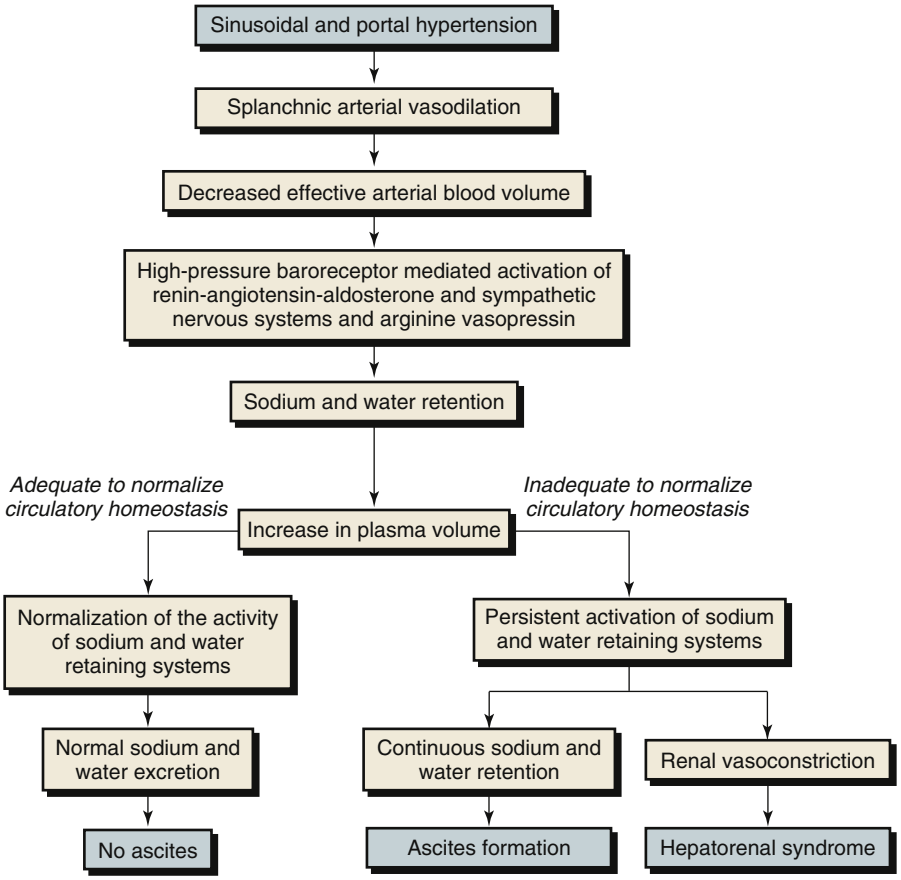


FIGURE EA1-119 Pathogenesis of functional renal abnormalities and ascites formation in liver cirrhosis. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

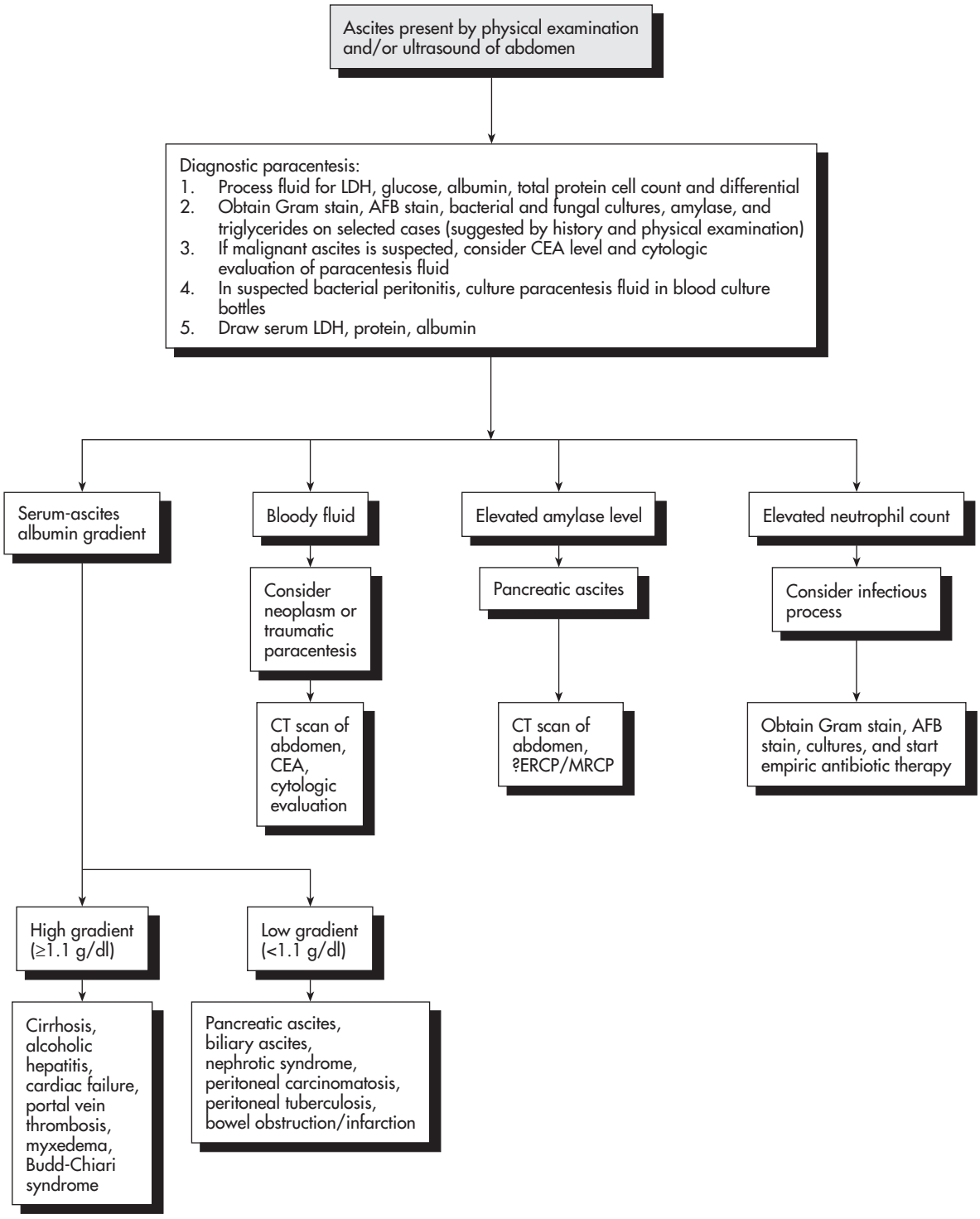


FIGURE EA1-120 Evaluation of ascites. *AFB,* Acid-fast bacillus; *CEA,* carcinoembryonic antigen; *CT,* computed tomography; *ERCP,* endoscopic retrograde cholangiopancreatography; *LDH,* lactate dehydrogenase; *MRCP,* magnetic resonance cholangiopancreatography.

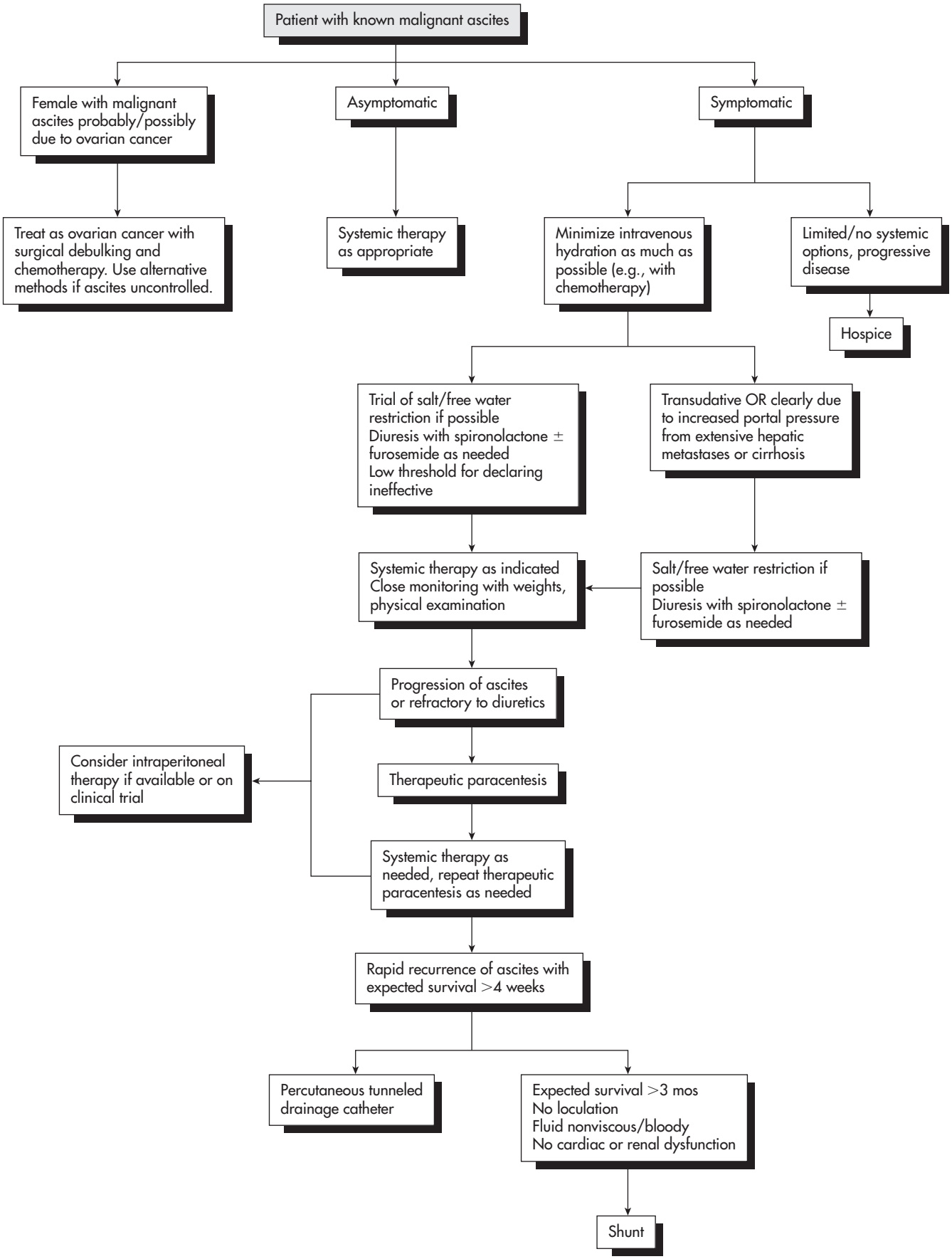


FIGURE EA1-122 Malignant ascites, treatment approach. (From Abeloff MD: *Clinical oncology,* ed 3, Philadelphia, 2004, Churchill Livingstone.)

BASIC INFORMATION

DEFINITION

Aspergillosis refers to several forms of a broad range of illnesses caused by infection with *Aspergillus* species.

ICD-9CM CODES
117.3 Aspergillosis
117.3 Aspergillosis with pneumonia
117.3 *Aspergillus* infection (*A. flavus, fumigatus, terreus*)
ICD-10CM CODES
B44.9 Aspergillosis, unspecified
B44.89 Other forms of aspergillosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE & PREVALENCE

- *Aspergillus* species are ubiquitous in the environment internationally and occur as a mold found in soil.
- Cause a variety of illness from hypersensitivity pneumonitis to disseminated overwhelming infection in immunosuppressed patients.
- Frequently cultured from hospital wards from unfiltered outside air circulating through open windows as well as water sources.
- Reach the patient by airborne conidia (spores) that are small enough (2.5 to 3 μm) to reach the alveoli on inhalation.
- Can invade the nose, paranasal sinuses, external ear, or traumatized skin.

RISK FACTORS

- The clinical syndrome depends on the underlying lung architecture, the host's immune response, and the degree of inoculum.
- Incidence of invasive aspergillosis is increasing with advances in the treatment of life-threatening diseases, such as aggressive chemotherapy or bone marrow and organ transplantation. It also can rarely occur in normal hosts, especially associated with influenza A. Liver and lung transplant recipients are at highest risk for pulmonary disease. Genetic deficiency of the soluble-pattern-recognition receptor known as long pentraxin 3 (PTX3) affects the antifungal capacity of neutrophils and may contribute to the risk of invasive aspergillosis in patients treated with hematopoietic stem-cell transplantation (HSCT).
- Patients with AIDS and a CD4 count <50/mm^3 have an increased susceptibility to invasive aspergillosis.
- Pandemic influenza A (H1N1) infection may predispose immunocompromised patients to invasive aspergillosis.

ETIOLOGY

- *A. fumigatus* is the usual cause.
- *A. flavus* is the second most important species, particularly in invasive disease of immunosuppressed patients and in lesions beginning in the nose and paranasal sinuses. *A. niger* can also cause invasive human infection.

ALLERGIC ASPERGILLOSIS

- Is a hypersensitivity pneumonitis.
- Presents as cough, dyspnea, fever, chills, and malaise typically 4 to 8 hr after exposure.
- Repeated attacks can lead to granulomatous disease and pulmonary fibrosis.

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA)

- Symptoms occur most commonly in atopic individuals during the third and fourth decades of life.
- Hypersensitivity reaction to *Aspergillus* fungal antigens present in the bronchial tree.
- Results from an initial type I (immediate hypersensitivity) and type III reactions (immune complexes).
- Underdiagnosed pulmonary disorder in patients with asthma and cystic fibrosis (reported prevalence in asthmatic patients varies from 6% to 28% and in cystic fibrosis 6% to 25%).

ASPERGILLOMAS ("FUNGUS BALLS")

- In the absence of invasion or significant immune response, *Aspergillus* can colonize a preexisting cavity, causing pulmonary aspergilloma.
- Forms masses of tangled hyphal elements, fibrin, and mucus.
- Patients typically have a history of chronic lung disease, tuberculosis, sarcoidosis, or emphysema.
- Manifests commonly as hemoptysis.
- Many are asymptomatic.

INVASIVE ASPERGILLOSIS

- Patients with prolonged and profound granulocytopenia or impaired phagocytic function are predisposed to rapidly progressive *Aspergillus* pneumonia.
- Typically a necrotizing bronchopneumonia, ranging from small areas of infiltrate to intensive bilateral hemorrhagic infarction.
- Most common presentation: unremitting fever and a new pulmonary infiltrate despite broad-spectrum antibiotic therapy in an immunosuppressed patient.
- Dyspnea and nonproductive cough are common; sudden pleuritic pain and tachycardia, sometimes with a pleural rub, may mimic pulmonary embolism; hemoptysis is uncommon.
- Chest radiograph (CXR) may reveal patchy bronchopneumonic, nodular densities, consolidation, or cavitation. High-resolution CT scan is more sensitive and specific than CXR in neutropenic patients.
- Immunocompromised patients: invasive pulmonary *Aspergillus* (IPA) generally is acute and evolves over days to weeks; less commonly, patients with normal or only mild abnormalities of the immune system may develop a more chronic, slowly progressive form of IPA.

EXTRAPULMONARY DISSEMINATION

- Cerebral infarction from hematogenous dissemination may occur in immunosuppressed individuals.
- Abscess formation from direct extension or invasive disease in the sinuses.
- Esophageal or gastrointestinal ulcerations may occur in the immunosuppressed host.
- Fatal perforation of the viscus or bowel infarction may occur.
- Necrotizing skin ulcers involving the extremities (Fig. A1-123).
- Osteomyelitis.
- Endocarditis in patients who have recently undergone open heart surgery.
- Infection of an implantable cardioverter-defibrillator has been reported.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Tuberculosis
- Cystic fibrosis
- Carcinoma of the lung
- Eosinophilic pneumonia
- Bronchiectasis
- Sarcoidosis
- Lung abscess

WORKUP

Physical examination and laboratory data

LABORATORY TESTS

ABPA

- Peripheral blood eosinophilia and an elevated total serum immunoglobulin E (IgE) level.
- Skin test with *Aspergillus* antigenic extract is usually positive but nonspecific.
- *Aspergillus* serum precipitating antibody is present in 70% to 100% of cases.

FIGURE A1-123 Cutaneous aspergillosis in a patient with acute leukemia and marked neutropenia. The lesion developed at the site where a steel needle had been left for several days of intravenous infusion. (From Mandell GL [ed]: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 6, New York, 2005, Churchill Livingstone.)

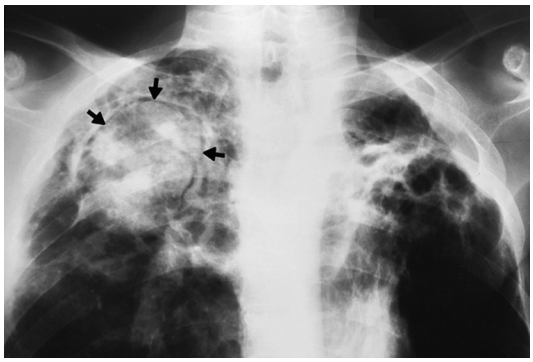


FIGURE A1-124 Fungus ball or mycetoma caused by *Aspergillus.* Coned-down posteroanterior view of the chest of a patient with biapical fibrocavitary tuberculosis accompanied by volume loss. There is a mass in a large right upper-lobe cavity with air dissecting into the cavity producing "air crescents" *(arrows).* (From McLoud TC: *Thoracic radiology: the requisites,* St Louis, 1998, Mosby.)

- Sputum cultures may be positive for *Aspergillus* spp. but are nonspecific.

ASPERGILLOMAS

- Sputum culture
- Serum precipitating antibody

Invasive aspergillosis: definitive diagnosis requires the demonstration of tissue invasion (i.e., septate, acute angle branching hyphae) or a positive culture from the tissue obtained by an invasive procedure such as transbronchial biopsy.

- Sputum and nasal cultures: in high-risk patients a positive culture is strongly suggestive of invasive aspergillosis.
- Serology: the *Platelia Aspergillus* ELISA assay detects a circulating fungal antigen, galactomannan, and is used in some centers in neutropenic patients and for those undergoing stem cell transplantation.
- Blood cultures: usually negative.
- Lung biopsy is necessary for definitive diagnosis.
- Biopsy and culture of extrapulmonary lesions.
- Real-time polymerase chain reaction tests are investigational.

IMAGING STUDIES

ABPA

- CXRs show a variety of abnormalities, from small, patchy, fleeting infiltrates (commonly in the upper lobes) to lobar consolidation or cavitation.
- A majority of patients eventually develop central bronchiectasis.

ASPERGILLOMAS: CXR or CT scans usually show the characteristic intracavity mass partially surrounded by a crescent of air (Fig. A1-124).

INVASIVE ASPERGILLOSIS: CXR and CT scanning may reveal cavity formation.

Rx TREATMENT

ACUTE GENERAL Rx

ABPA

- Prednisone (0.5 to 1 mg/kg PO) until the CXR has cleared, followed by alternate-day therapy at 0.5 mg/kg PO (3 to 6 mo).
- If a patient is corticosteroid dependent, prophylaxis for the prevention of *Pneumocystis jiroveci* infection and maintenance of bone mineralization should be considered.
- Bronchodilators and physiotherapy.
- Serial CXR and serum IgE is useful in guiding treatment.
- Itraconazole 200 mg PO bid for 4 to 6 mo, then taper over 4 to 6 mo may be considered as a steroid-sparing agent or if steroids are ineffective.

ASPERGILLOMAS

- Controversial and problematic; the optimal treatment strategy is unknown.
- Up to 10% of aspergillomas may resolve clinically without overt pharmacologic or surgical intervention.
- Observation for asymptomatic patients.
- Surgical resection/arterial embolization for those patients with severe hemoptysis or life-threatening hemorrhage.
- For those patients at risk for marked hemoptysis with inadequate pulmonary reserve, consider itraconazole 200 to 400 mg/day PO.

INVASIVE ASPERGILLOSIS (IA)

- The guidelines of the Infectious Diseases Society of America recommend the use of voriconazole as the primary therapy for invasive aspergillosis Voriconazole reduces death compared with amphotericin when used for invasive *Aspergillus* infection. Voriconazole dose is 6 mg/kg IV bid followed by 4 mg/kg IV q12h or 200 mg PO q12h for body weight >40 kg but 100 mg PO q12h for body weight <40 kg.
- Amphotericin B 0.8 to 1.2 mg/kg IV daily to total dose of 2 to 2.5 g; itraconazole 200 to 400 mg/d PO × 1 yr.
- Amphotericin B lipid complex (ABLC) 5 mg/kg IV daily in those intolerant of or refractory to amphotericin B.
- Amphotericin B colloidal dispersion (ABCD) 3 to 6 mg/kg IV daily; stepwise approach in those who have not responded to amphotericin B.
- Liposomal amphotericin B (L-AMB) 3 to 5 mg/kg IV daily; stepwise approach is indicated as empiric therapy for presumed fungal infection in febrile neutropenic patients who are refractory to or intolerant of amphotericin B.
- Itraconazole 200 mg IV bid × 4 doses followed by 200 mg IV daily or 200 mg tid for 4 days, then 200 mg PO bid—first-line therapy if not taking p450 inducers. Levels may be obtained to ensure compliance and adequate absorption. Approved only for salvage therapy in the United States at this time.
- Posaconazole 200 mg PO 4x/day followed by 400 mg PO bid after stabilization of disease with food or liquid nutritional supplement to enhance absorption is approved in the European Union, but in the United States is approved only for prophylaxis in leukemic neutropenic patients, those with myelodysplasia, or those who have undergone allogeneic hematopoietic stem cell transplantation; ravuconazole is currently under investigation.
- Caspofungin (Candigas) is the first of a new class of antifungals, the echinocandins, approved for the treatment of invasive aspergillosis in patients who do not respond to or are unable to tolerate other antifungal drugs. Starting dose 70 mg IV over 1 hr on day 1, then 50 mg IV daily thereafter (reduce to 35 mg IV daily in cases with moderate hepatic insufficiency). Can switch to oral voriconazole after 2 to 3 wk if the response is favorable. Micafungin 150 mg IV daily is another alternative.
- Because azoles and echinocandins target different cellular sites, combination therapy may have additive activity against *Aspergillus* species. Although still under investigation, some bone marrow transplant units use caspofungin and voriconazole as the preferred initial treatment, especially in patients receiving high-dose corticosteroids. Recent trials (Marr et al., 2015) have shown that compared with voriconazole monotherapy, combination therapy with anidulafungin, and echinocandin antifungal drug that blocks the synthesis of (13)β-D glucan led to higher survival in subgroups of patients with IA.
- Cytokine therapy may offer future treatment options in conjunction with the currently available antifungals.

REFERRAL

To an infectious diseases specialist

PEARLS & CONSIDERATIONS

- Unlike fluconazole, the potential for drug-drug interactions with voriconazole is high. Azoles may interact with drugs used for chemotherapy by increasing toxicity and/or by reducing efficacy.
- Agitation of hospital buildings by renovations or repairs may increase the incidence of *Aspergillus* infections in immunosuppressed individuals.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Aspergillosis (Patient Information)

AUTHOR: **SAJEEV HANDA, M.D.**

SUGGESTED READINGS

Cook RJ et al.: Aspergillus infection of implantable cardioverter defibrillator, *Mayo Clin Proc* 79(4):549–552, 2005.

Cunha C et al.: Genetic PTX3 deficiency and aspergillosis in stem-cell transplantation, *N Engl J Med* 370:421–432, 2014.

Garcia-Vidal C et al.: Invasive aspergillosis complicating pandemic Influenza A (H1N1) infection in severely immunocompromised patients, *Clin Infect Dis* 53(6):e16–e19, 2011.

Hasejima N et al.: Invasive pulmonary aspergillosis associated with influenza B, *Respirology* 10(1):116–119, 2005.

Marr KA et al.: Combination antifungal therapy for invasive aspergillosis, *Clin Infect Dis* 39:797, 2004.

Marr KA et al.: Combination antifungal therapy for invasive aspergillosis, a randomized trial, *Ann Intern Med* 162:81-89, 2015.

Pfaller MA: Anidulafungin: an echinocandin antifungal, *Expert Opin Invest Drugs* 13(9):1183–1197, 2004.

Segal BH: Aspergillosis, *N Engl J Med* 360:1870–1884, 2009.

Steinbach WJ, Stevens DA: Review of newer antifungal and immunomodulatory strategies for invasive aspergillosis, *Clin Infect Dis* 37(suppl 3):S157, 2003.

Tillie-Leblond I, Tonnel AB: Allergic bronchopulmonary aspergillosis, *Allergy* 60:1004–1013, 2005.

Walsh JW et al.: Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America, *Clin Infect Dis* 46:327, 2008.

BASIC INFORMATION

DEFINITION

Aspiration pneumonia is a vague term that refers to pulmonary abnormalities following abnormal entry of endogenous or exogenous substances in the lower airways. It is generally classified as:

- Aspiration (chemical pneumonitis)
- Primary bacterial aspiration pneumonia
- Secondary bacterial infection of chemical pneumonitis

ICD-9CM CODES
507.0 Aspiration pneumonia
ICD-10CM CODES
J69.0 Pneumonitis due to inhalation of food and vomit

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.)

- Few reliable data.
- 20% to 35% of all pneumonias.
- 5% to 15% of all community-acquired pneumonias.

PEAK INCIDENCE: Elderly patients in hospitals or nursing homes.
PREVALENCE (IN U.S.): Unknown (unreliable data).
PREDOMINANT SEX: Males and females affected equally.
PREDOMINANT AGE: Elderly.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Shortness of breath, tachypnea, cough, sputum, fever after vomiting, or difficulty swallowing.
- Rales, rhonchi, often diffusely throughout lung.

ETIOLOGY

Complex interaction of etiologies, ranging from chemical (often acid) pneumonitis after aspiration of sterile gastric contents (generally not requiring antibiotic treatment) to bacterial aspiration.

COMMUNITY-ACQUIRED ASPIRATION PNEUMONIA

- Generally results from predominantly anaerobic mouth bacteria (anaerobic and microaerophilic streptococci, fusobacteria, gram-positive anaerobic nonspore-forming rods), *Bacteroides* species (*melaninogenicus*, *intermedius*, *oralis*, *ureolyticus*), *Haemophilus influenzae,* and *Streptococcus pneumoniae*
- Rarely caused by *Bacteroides fragilis* (of uncertain validity in published studies) or *Eikenella corrodens*
- High-risk groups: the elderly; alcoholics; IV drug users; patients who are obtunded; stroke victims; and those with esophageal disorders, seizures, poor dentition, or recent dental manipulations.

HOSPITAL-ACQUIRED ASPIRATION PNEUMONIA

- Often occurs among elderly patients and others with diminished gag reflex; those with nasogastric tubes, intestinal obstruction, or ventilator support; and especially those exposed to contaminated nebulizers or unsterile suctioning.
- High-risk groups: seriously ill hospitalized patients (especially patients with coma, acidosis, alcoholism, uremia, diabetes mellitus, nasogastric intubation, or recent antimicrobial therapy, who are frequently colonized with aerobic gram-negative rods); patients undergoing anesthesia; those with strokes, dementia, or swallowing disorders; the elderly; and those receiving antacids or H_2 blockers (but not sucralfate).
- Hypoxic patients receiving concentrated O_2 have diminished ciliary activity, encouraging aspiration.
- Causative organisms:
  1. Anaerobes listed above, although in many studies gram-negative aerobes (60%) and gram-positive aerobes (20%) predominate.
  2. *E. coli, P. aeruginosa, S. aureus* including MRSA, *Klebsiella, Enterobacter, Serratia, Proteus* spp., *H. influenzae, S. pneumoniae, Legionella,* and *Acinetobacter* spp. (sporadic pneumonias) in two thirds of cases.
  3. Fungi, including *Candida albicans,* in <1%.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other necrotizing or cavitary pneumonias (especially tuberculosis, gram-negative pneumonias).
- See "Pulmonary Tuberculosis."

WORKUP

- Chest x-ray.
- Complete blood count (CBC), blood cultures.
- Sputum Gram stain and culture.
- Consideration of tracheal aspirate.

LABORATORY TESTS

- CBC: leukocytosis often present.
- Sputum Gram stain.
  1. Often useful when carefully prepared immediately after obtaining suctioned or expectorated specimen, examined by experienced observer.
  2. Only specimens with multiple white blood cells and rare or absent epithelial cells should be examined.
  3. Unlike nonaspiration pneumonias (e.g., pneumococcal), multiple organisms may be present.
  4. Long, slender rods suggest anaerobes.
  5. Sputum from pneumonia caused by acid aspiration may be devoid of organisms.
  6. Cultures should be interpreted in light of morphology of visualized organisms.

IMAGING STUDIES

- Chest x-ray often reveals bilateral, diffuse, patchy infiltrates and posterior segment upper lobes. Chemical pneumonitis typically affects the most dependent regions of the lungs.
- Aspiration pneumonia of several days' or longer duration may reveal necrosis (especially community-acquired anaerobic pneumonias) and even cavitation with air-fluid levels, indicating lung abscess.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Airway management to prevent repeated aspiration.
- Ventilatory support if necessary.

ACUTE GENERAL Rx

Acute aspiration of acidic gastric contents without bacteria may not require antibiotic therapy; consult infectious disease or pulmonary expert.

- Community-acquired anaerobic aspiration pneumonia: clindamycin (600 mg IV twice daily followed by 300 mg q6h orally). Intravenous penicillin G (1 to 2 million U q4 to 6h) can also still be used. Alternative oral agents include: amoxicillin-clavulanate (875 mg orally twice daily), amoxicillin plus metronidazole or oral moxifloxacin (400 mg orally once daily). Do not use metronidazole alone, as this is associated with high failure rates.
- Nursing home aspirations: levofloxacin 500 to 750 mg qd or piperacillin-tazobactam 3.375 g q6h or ceftazidime 2 g q8h ± vancomycin if MRSA suspected or known.
- Hospital-acquired aspiration pneumonia:
  1. Piperacillin-tazobactam 3.375 g IV q6h, or cefoxitin 2 g IV q8h ± vancomycin IV to cover MRSA. Alternative agents are ceftriaxone 1 g IV q24h plus metronidazole 500 mg IV q6h or 1 g IV q12h.
  2. Knowledge of resident flora in the microenvironment of the aspiration within the hospital is crucial to intelligent antibiotic selection; consult infection control nurses or hospital epidemiologist.
  3. Confirmed *Pseudomonas* pneumonia should be treated with antipseudomonal beta-lactam agent plus an aminoglycoside until antimicrobial sensitivities confirm that less toxic agents may replace the aminoglycoside.
  4. Do not use metronidazole alone for anaerobes.

DISPOSITION

Repeat chest x-ray in 6 to 8 wk.

REFERRAL

For consultation with infectious disease and/or pulmonary experts for patients with respiratory distress, hypoxia, ventilatory support, pneumonia in more than one lobe, or necrosis or cavitation on x-ray examination or for those not responding to antibiotic therapy within 2 to 3 days.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Aspiration Pneumonia (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Daoud E, Guzman J: Are antibiotics indicated for the treatment of aspiration pneumonia? *Cleve Clin J Med* 77(9):573, 2010.

Ott SR et al.: Moxifloxacin vs. ampicillin/sulbactam in aspiration pneumonia and primary lung abscess, *Infection* 36:23, 2008.

Shigemitsu H, Afshar K: Aspiration pneumonias: under-diagnosed and under-treated, *Curr Opin Pulm Med* 13(3):192–198, 2007.

BASIC INFORMATION

DEFINITION

The National Asthma Education and Prevention Program (NAEPP) guidelines define asthma as "a chronic inflammatory disease of the airways in which many cells and cellular elements play a role: in particular mast cells, neutrophils, eosinophils, T lymphocytes, macrophages, and epithelial cells. In susceptible individuals, this inflammation causes recurrent episodes of coughing (particularly at night or early in the morning), wheezing, breathlessness, and chest tightness. The episodes are usually associated with widespread but variable airflow obstruction that is reversible either spontaneously or as a result of treatment." Status asthmaticus can be defined as a severe continuous bronchospasm.

SYNONYMS

Bronchospasm
Reactive airway disease
Bronchial asthma

ICD-9CM CODES

493.9 Asthma, unspecified
493.1 Intrinsic asthma
493.0 Extrinsic asthma

ICD-10CM CODES

J45	Asthma
J46	Status asthmaticus
J45.0	Predominantly allergic asthma
J45.1	Non-allergic asthma
J45.8	Mixed asthma
J45.9	Asthma, unspecified
J45.909	Unspecified asthma, uncomplicated
J45.20	Mild intermittent asthma, uncomplicated

EPIDEMIOLOGY & DEMOGRAPHICS

- Asthma affects 5% to 12% of the population and accounts for more than 450,000 hospitalizations and nearly 2 million emergency department visits yearly in the United States.
- It is more common in children (10% of children, 5% of adults).
- 50% to 80% of children with asthma develop symptoms before 5 yr of age. Early childhood risk factors for asthma are described in Table A1-68.
- Overall asthma mortality rate in the United States is 20 per 1 million persons.
- The population of seniors with asthma is increasing rapidly in the United States. These patients have a high level of morbidity and mortality from their asthma.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Physical examination varies with the stage and severity of asthma and may reveal only increased inspiratory and expiratory phases of respiration. Physical examination during status asthmaticus may reveal:

- Tachycardia and tachypnea
- Use of accessory respiratory muscles
- Pulsus paradoxus (inspiratory decline in systolic blood pressure >10 mm Hg)
- Wheezing: absence of wheezing (silent chest) or decreased wheezing can indicate worsening obstruction
- Mental status changes: generally secondary to hypoxia and hypercapnia and constitute an indication for urgent intubation
- Paradoxic abdominal and diaphragmatic movement on inspiration (detected by palpation over the upper part of the abdomen in a semirecumbent position): important sign of impending respiratory crisis, indicates diaphragmatic fatigue
- The following abnormalities in vital signs are indicative of severe asthma:
  1. Pulsus paradoxus >18 mm Hg
  2. Respiratory rate >30 breaths/min
  3. Tachycardia with heart rate >120 beats/min

ETIOLOGY

- Symptoms are more commonly due to specific (aeroallergens) or nonspecific (dust, cigarette smoke, fumes, cold air, exercise, etc.) exposures.
- Traditionally, intrinsic asthma was described as occurring in patients who have no history of allergies possibly triggered by upper respiratory infections or psychological stress and extrinsic asthma (allergic asthma) as brought on by exposure to allergens (e.g., dust mites, cat allergen, industrial chemicals).
- Exercise-induced asthma: seen most frequently in adolescents; manifests with bronchospasm after beginning exercise and improves with discontinuation of exercise.
- Drug-induced asthma: often associated with use of NSAIDs, β-blockers, sulfites, and certain foods and beverages.
- There is a strong association of the *ADAM 33* gene with asthma and bronchial hyperresponsiveness.
- Experimental, genetic, and clinical studies support an important role for Th2 immune pathways in the pathogenesis of severe asthma.

TABLE A1-68 Early Childhood Risk Factors for Persistent Asthma

Parental asthma
Allergy:
Atopic dermatitis (eczema)
Allergic rhinitis
Food allergy
Inhalant allergen sensitization
Food allergen sensitization
Severe lower respiratory tract infection:
Pneumonia
Bronchiolitis requiring hospitalization
Wheezing apart from colds
Male gender
Low birthweight
Environmental tobacco smoke exposure
Possible use of acetaminophen (paracetamol)
Exposure to chlorinated swimming pools
Reduced lung function at birth

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- CHF
- COPD
- Pulmonary embolism (in adult and elderly patients)
- Foreign body aspiration (most frequent in younger patients)
- Pneumonia and other upper respiratory infections
- Rhinitis with postnasal drip
- TB
- Hypersensitivity pneumonitis
- Anxiety disorder
- Wegener's granulomatosis
- Diffuse interstitial lung disease

WORKUP

- The clinician should evaluate for environmental causes (e.g., house dust mites, indoor pets) and exposure to other allergens such as tobacco smoke. For symptomatic adults and children aged >5 yr who can perform spirometry, asthma can be diagnosed after a medical history and physical examination documenting an episodic pattern of respiratory symptoms and from spirometry that indicates partially reversible airflow obstruction (>12% increase and 200 ml in forced expiratory volume in 1 sec [FEV_1] after inhaling a short bronchodilator or receiving a short [2 to 3 wk] course of oral corticosteroids). For children aged <5 yr, spirometry is generally not feasible. Young children with asthma symptoms should be treated as having suspected asthma once alternative diagnoses are ruled out.
- The degree of reversibility measured by spirometry correlates with airway obstruction, and patients with a high degree of reversibility have a greater risk of irreversible airflow obstruction in subsequent years.
- Fig. EA1-125 describes an algorithm for diagnosing asthma.
- After diagnosis, severity of asthma should be classified during the initial assessment before initiating therapy. The following questions from Asthma Control and endorsed by the American Lung Association are important in assessing patients with asthma:
  1. Has your asthma prevented normal activities at home or work?
  2. Have you had shortness of breath in the past 4 wk?
  3. Has your asthma kept you awake at night?
  4. How often have you used your asthma inhaler in the last 4 weeks?
  5. Overall, how have you kept your asthma in control in the last 4 weeks?
- Once therapy is initiated, the emphasis for clinical management is changed to the assessment of asthma control. The level of asthma control should be used to guide decisions either to maintain or adjust therapy.
- Schedule visits at 2- to 6-wk intervals for patients who are just starting therapy or who require a step up in therapy to achieve or regain asthma control. Schedule visits at

1- to 6-mo intervals, after asthma control is achieved, to monitor whether asthma control is maintained. The interval will depend on factors such as the duration of asthma control or the level of treatment required. Consider scheduling visits at 3-mo intervals if step-down therapy is anticipated.

TABLE A1-69 Relative Severity of an Asthmatic Attack as Indicated by PEFR, FEV_1, and MMEFR

Test	Predicted Value (%)	Severity of Asthma
PEFR	>80	
FEV_1	>80	No spirometric abnormalities
MMEFR	>80	
PEFR	>80	
FEV_1	>70	Mild asthma
MMEFR	55-75	
PEFR	>60	
FEV_1	45-70	Moderate asthma
MMEFR	30-50	
PEFR	<50	
FEV_1	<50	Severe asthma
MMEFR	10-30	

FEV_1, Forced expiratory volume in the first second; *MMEFR,* maximal mid-expiratory flow rate; *PEFR,* peak expiratory flow rate.

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

LABORATORY TESTS

Laboratory tests are usually not necessary and the results can be normal if obtained during a stable period.

- Arterial blood gases (ABGs) can be used during acute bronchospasm in staging the severity of an asthmatic attack:
  1. Mild: decreased Pa_{O_2} and Pa_{CO_2}, increased pH
  2. Moderate: decreased Pa_{O_2}, normal Pa_{CO_2}, normal pH
  3. Severe: marked decreased Pa_{O_2}, increased Pa_{CO_2}, and decreased pH
- Complete blood count: leukocytosis with left shift may indicate the existence of bacterial infection.
- Spirometry is recommended at the initial assessment and at least every 1 to 2 yr after treatment is initiated and when the symptoms and peak expiratory flow have stabilized. Spirometry as a monitoring measure may be performed more frequently, if indicated, based on severity of symptoms and the disease's lack of response to treatment.
- Pulmonary function studies: during acute severe bronchospasm, FEV_1 is <1 L and peak expiratory flow rate (PEFR) <80 L/min. Table A1-69 describes the relative severity of an asthma attack as indicated by PEFR, FEV_1 and MMEFR.

IMAGING STUDIES

- Chest x-ray: usually normal, may show evidence of thoracic hyperinflation (e.g., flattening of the diaphragm, increased volume over the retrosternal air space).
- ECG: tachycardia, nonspecific ST-T wave changes are common during an asthma attack; may also show cor pulmonale, right bundle branch block, right axial deviation, counterclockwise rotation.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of triggering factors (e.g., salicylates, sulfites), environmental or occupational triggers
- Encouragement of regular exercise (e.g., swimming)
- Patient education regarding warning signs of an attack and proper use of medications (e.g., correct use of inhalers)

GENERAL Rx

- The 2007 NAEPP guidelines (see Tables A1-70 to A1-78) broadly classify treatment options by age: 0 to 4 yr, 5 to 11 yr, and >12 yr. An approach to home management of acute

TABLE A1-70 Classifying Asthma Severity and Initiating Treatment in Youths ≥12 Yr and Adults (Assessing severity and initiating treatment for patients who are not currently taking long-term control medications)

		CLASSIFICATION OF ASTHMA SEVERITY (≥12 yr)			
			PERSISTENT		
Components of Severity		**Intermittent**	**Mild**	**Moderate**	**Severe**
Impairment	Symptoms	≤2 days/wk	>2 days/wk but not daily	Daily	Throughout the day
Normal FEV_1/FVC:	Nighttime awakenings	≤2x/mo	3-4x/mo	>1x/wk but not nightly	Often 7x/wk
8-19 yr 85%	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/wk	>2 days/wk but not daily, and not more than 1x on any day	Daily	Several times per day
20-39 yr 80%	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
40-59 yr 75%	Lung function	Normal FEV_1 between exacerbations			
60-80 yr 70%		FEV_1>80% predicted	FEV_1>80% predicted	FEV_1>60% but <80% predicted	FEV_1<60% predicted
		FEV_1/FVC normal	FEV_1/FVC normal	FEV_1/FVC reduced 5%	FEV_1/FVC reduced>5%
Risk	Exacerbations requiring oral systemic corticosteroids	0-1 per yr	≥2 per yr		
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.			
Recommended Step for Initiating Therapy		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	Step 4 or 5
		In 2-6 wk, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.

Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2-4 wk and spirometry. Assign severity to the most severe category in which any feature occurs.

At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.

To access the complete *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma,* go to www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.

EIB, Exercise-induced bronchospasm; *FEV_1,* forced expiratory volume in 1 second; *FVC,* forced vital capacity; *ICU,* intensive care unit.

From National Asthma Education and Prevention Program: *Expert panel report 3: Guidelines for diagnosis and management of asthma*, National Institutes of Health, National Heart, Lung, and Blood Institute, August 2007, NIH publication 08-4051.

asthma is described in Fig. EA1-126. When asthma symptoms are mild, short-lived, or infrequent, use of short-acting beta-selective adrenergic agonists (SABAs) administered by inhalation is the most effective therapy for quick relief of asthmatic symptoms. They are recommended for use only as needed for relief of symptoms or before anticipated exposure to known triggers such as exercise. When symptoms become more frequent or more severe, step-up treatment includes use of an inhaled steroid or leukotriene receptor antagonist (LTRA). If symptoms persist, recommendations include use of long-acting beta-agonist (LABA) or LTRA plus inhaled steroid. There are currently several corticosteroid/LABA combination inhalers available (fluticasone/salmeterol [Advair], budesonide/formoterol [Symbicort], mometasone/formoterol [Dulera]). None of these combinations is indicated for the initial treatment of asthma or for acute therapy of asthma symptoms. There is no evidence that one product is more effective than the others. If asthma control remains inadequate, additional treatment consists of inhaled steroid plus LABA plus long-term medication. The addition of omalizumab, an anti-IgE monoclonal antibody, is indicated for the treatment of moderate and severe persistent asthma refractory to other treatment noted earlier. It is administered subcutaneously every 2 or 4 wk. This medicine is expensive ($10,000 to $30,000/yr). Patients should be closely monitored in the first month because omalizumab can result in allergic reactions (anaphylaxis) in 1 to 2 patients/1000. The NIH guidelines recommend considering omalizumab only after consultation with an asthma specialist. Recent trials (Wenzel et al) have also shown that in patients with persistent, moderate to severe asthma and elevated eosinophil levels who used inhaled glucocorticoids and LABAs, therapy with the human monoclonal antibody dupilumab, as compared with placebo, was associated with fewer asthma exacerbations when LABAs and inhaled glucocorticoids were withdrawn, with improved lung function and reduced levels of Th2-associated inflammatory markers. The human monoclonal antibody mepolizumab has also been shown to significantly reduce asthma exacerbations in patients with persistent eosinophilic inflammation despite continuous treatment with high-dose glucocorticoids.

Treatment of status asthmaticus is as follows:

- Oxygen generally started at 2 to 4 L/min by nasal cannula or Venti-Mask at 40% Fio_2; further adjustments are made according to the ABGs.
- Bronchodilators: Initiate treatment with high-dose SABA plus ipratropium bromide administered by means of a nebulizer every 20 min. Use of a metered-dose inhaler with valved holding chamber may be acceptable for patients with mild-to-moderate exacerbations.
- Albuterol nebulizer solution (0.63 mg/3 ml, 1.25 mg/3 ml, 2.5 mg/3 ml, or 5.0 mg/ml): 2.5 to 5 mg every 20 min over the first hr, then 2.5-10 mg every 1-4 hr as needed or 10-15 mg/hr continuously. Other useful

TABLE A1-71 Assessing Asthma Control and Adjusting Therapy in Youths ≥12 Yr and Adults

Components of Control		CLASSIFICATION OF ASTHMA CONTROL (≥12 yr)		
		Well Controlled	**Not Well Controlled**	**Very Poorly Controlled**
Impairment	Symptoms	≤2 days/wk	>2 days/wk	Throughout the day
	Nighttime awakenings	≤2×/mo	1-3x/wk	≥4/wk
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/wk	>2 days/wk	Several times per day
	FEV_1 or peak flow	>80% predicted/personal best	60%-80% predicted/personal best	<60% predicted/personal best
	Validated questionnaires			
	ATAQ	0	1-2	3-4
	ACQ	≤0.75*	≥1.5	N/A
	ACT™	≥20	16-19	≤15
Risk	Exacerbations requiring oral systemic corticosteroids	0-1 per yr	≥2 per yr	
		Consider severity and interval since last exacerbation		
	Progressive loss of lung function	Evaluation requires long-term follow-up care		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment		Maintain current step. Regular follow-up every 1-6 mo to maintain control. Consider step down if well controlled for at least 3 mo.	Step up 1 step and reevaluate in 2-6 wk. For side effects, consider alternative treatment options.	Consider short course of oral systemic corticosteroids. Step up 1-2 steps. Reevaluate in 2 wk. For side effects, consider alternative treatment options.

The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.

The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient's recall of previous 2-4 wk and by spirometry or peak flow measures. Symptom assessment for longer periods should reflect a global assessment, such as inquiring whether the patient's asthma is better or worse since the last visit.

At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.

Validated questionnaires for the impairment domain (the questionnaires do not assess lung function or the risk domain)

- ATAQ = Asthma Therapy Assessment Questionnaire
- ACQ = Asthma Control Questionnaire (user package may be obtained at www.qoltech.co.uk or juniper@qoltech.co.uk)
- ACT = Asthma Control Test™
- Minimal Important Difference: 1.0 for the ATAQ; 0.5 for the ACQ; not determined for the ACT

Before step up in therapy:

- Review adherence to medication, inhaler technique, environmental control, and comorbid conditions
- If an alternative treatment option was used in a step, discontinue and use the preferred treatment for that step

*ACQ values of 0.76-1.4 are indeterminate regarding well-controlled asthma.

EIB, Exercise-induced bronchospasm; *FEV_1,* forced expiratory volume in 1 second; *ICU,* intensive care unit.

The Asthma Control Test is a trademark of QualityMetric Incorporated.

From National Asthma Education and Prevention Program: *Expert panel report 3: Guidelines for diagnosis and management of asthma*, National Institutes of Health, National Heart, Lung, and Blood Institute, August 2007, NIH publication 08-4051.

TABLE A1-72 Stepwise Approach for Managing Asthma in Youths ≥12 Yr and Adults

Intermittent Asthma	Persistent Asthma: Daily Medication Consult with asthma specialist if step 4 care or higher is required. Consider consultation at step 3.					
Step 1 *Preferred:* SABA prn	**Step 2** *Preferred:* Low-dose ICS *Alternative:* Cromolyn, LTRA, nedocromil, or theophylline	**Step 3** *Preferred:* Low-dose ICS + LABA OR Medium-dose ICS *Alternative:* Low-dose ICS + either LTRA, theophylline, or zileuton	**Step 4** *Preferred:* Medium-dose ICS + LABA *Alternative:* Medium-dose ICS + either LTRA, theophylline, or zileuton	**Step 5** *Preferred:* High-dose ICS + LABA AND Consider omalizumab for patients who have allergies	**Step 6** *Preferred:* High-dose ICS + LABA + oral corticosteroid AND Consider omalizumab for patients who have allergies	Step up if needed (first, check adherence, environmental control, and comorbid conditions) **Assess control** Step down if possible (and asthma is well controlled at least 3 months)
Each step: Patient education, environmental control, and management of comorbidities Steps 2-4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma						
Quick-Relief Medication for All Patients • SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed. • Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.						

The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
Zileuton is a less desirable alternative due to limited studies as adjunctive therapy and the need to monitor liver function. Theophylline requires monitoring of serum concentration levels.
In step 6, before oral systemic corticosteroids are introduced, a trial of high-dose ICS + LABA + either LTRA, theophylline, or zileuton may be considered, although this approach has not been studied in clinical trials.
Steps 1, 2, and 3 preferred therapies are based on Evidence A; step 3 alternative therapy is based on Evidence A for LTRA, Evidence B for theophylline, and Evidence D for zileuton. Step 5 preferred therapy is based on Evidence B. Step 6 preferred therapy is based on (EPR-2 1997) and Evidence B for omalizumab.
Immunotherapy for steps 2-4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults.
Clinicians who administer immunotherapy or omalizumab should be prepared and equipped to identify and treat anaphylaxis that may occur.
This information is directly abstracted from the 2007 NAEPP *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* and is not intended to promote or endorse any of the listed products.
To access the complete *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma,* go to www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.
EIB, Exercise-induced bronchospasm; *ICS,* inhaled corticosteroid; *LABA,* inhaled long-acting beta$_2$-agonist; *LTRA,* leukotriene receptor antagonist; *SABA,* inhaled short-acting beta$_2$-agonist.
From National Asthma Education and Prevention Program: *Expert panel report 3: Guidelines for diagnosis and management of asthma*, National Institutes of Health, National Heart, Lung, and Blood Institute, August 2007, NIH publication 08-4051.

medications are levalbuterol nebulizer solution (0.31 mg/3 ml, 0.63 mg/3 ml, 1.25 mg/3 ml) and ipratropium nebulizer solution (0.25/ml [0.025%]).

- Corticosteroids:
  1. Early administration is advised, particularly in patients using steroids at home.
  2. Patients may be started on systemic corticosteroids: methylprednisolone, prednisone, or prednisolone may be used. Dose range is from 40-80 mg/day in one or two divided doses, generally given until peak expiratory flow reaches 70% of predicted value.
  3. Generally for corticosteroid courses <1 week there is no need to taper the dose
- IV hydration: judicious use is necessary to avoid congestive heart failure in elderly patients. Aggressive IV hydration is not recommended
- IV antibiotics are indicated when there is suspicion of bacterial infection (e.g., infiltrate on chest radiograph, fever, or leukocytosis).
- Intubation and mechanical ventilation are indicated when previous measures fail to produce significant improvement (Fig. A1-127).
- Discharge home from the emergency department is appropriate if the FEV_1 or PEF after treatment is 70% or greater of the personal best or predicted value and if there is sustained improvement in lung function and symptoms for at least 1 hr.

REFERRAL

Box A1-11 describes indications for referral to an asthma specialist.

PEARLS & CONSIDERATIONS

COMMENTS

- The differentiation of asthma from COPD can be challenging. A history of atopy and intermittent, reactive symptoms points toward a diagnosis of asthma, whereas smoking and advanced age are more indicative of COPD. Spirometry is useful in distinguishing asthma from COPD.
- In all asthma patients it is important to treat or prevent comorbid conditions (e.g., rhinosinusitis, vocal cord dysfunction, gastroesophageal reflux disease). However, despite the presumed association between asthma and GERD, trials of PPIs in patients with poorly controlled asthma did not reveal any beneficial effects.
- Inhaled low-dose corticosteroids are the single most effective therapy for adult patients with asthma who require more than an occasional use of SABAs to control their asthma.
- Leukotriene modifiers/receptor agonists represent a reasonable alternative in adults unable or unwilling to use corticosteroids; however, these agents are less effective than monotherapy with inhaled corticosteroids.

TABLE A1-73 Classifying Asthma Severity and Initiating Treatment in Children 5-11 Yr
(Assessing severity and initiating treatment in children who are not currently taking long-term control medications)

Components of Severity		CLASSIFICATION OF ASTHMA SEVERITY (5-11 yr of age)			
			PERSISTENT		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/wk	>2 days/wk but not daily	Daily	Throughout the day
	Nighttime awakenings	≤23/mo	3-4×/mo	>1×/wk but not nightly	Often 7×/wk
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/wk	>2 days/wk but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	Normal FEV_1 between exacerbations			
		FEV_1>80% predicted	FEV_1 = >80% predicted	FEV_1 60%-80% predicted	FEV_1 <60% predicted
		FEV_1/FVC>85%	FEV_1/FVC>80%	FEV_1/FVC 75%-80%	FEV_1/FVC <75%
Risk	Exacerbations requiring oral systemic corticosteroids	0-1 per yr	≥2 per yr		
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV_1.			
Recommended Step for Initiating Therapy		Step 1	Step 2	Step 3, medium-dose ICS option	Step 3, medium-dose ICS option, or Step 4
				and consider short course of oral systemic corticosteroids	
		In 2-6 wk, evaluate level of asthma control that is achieved and adjust therapy accordingly.			

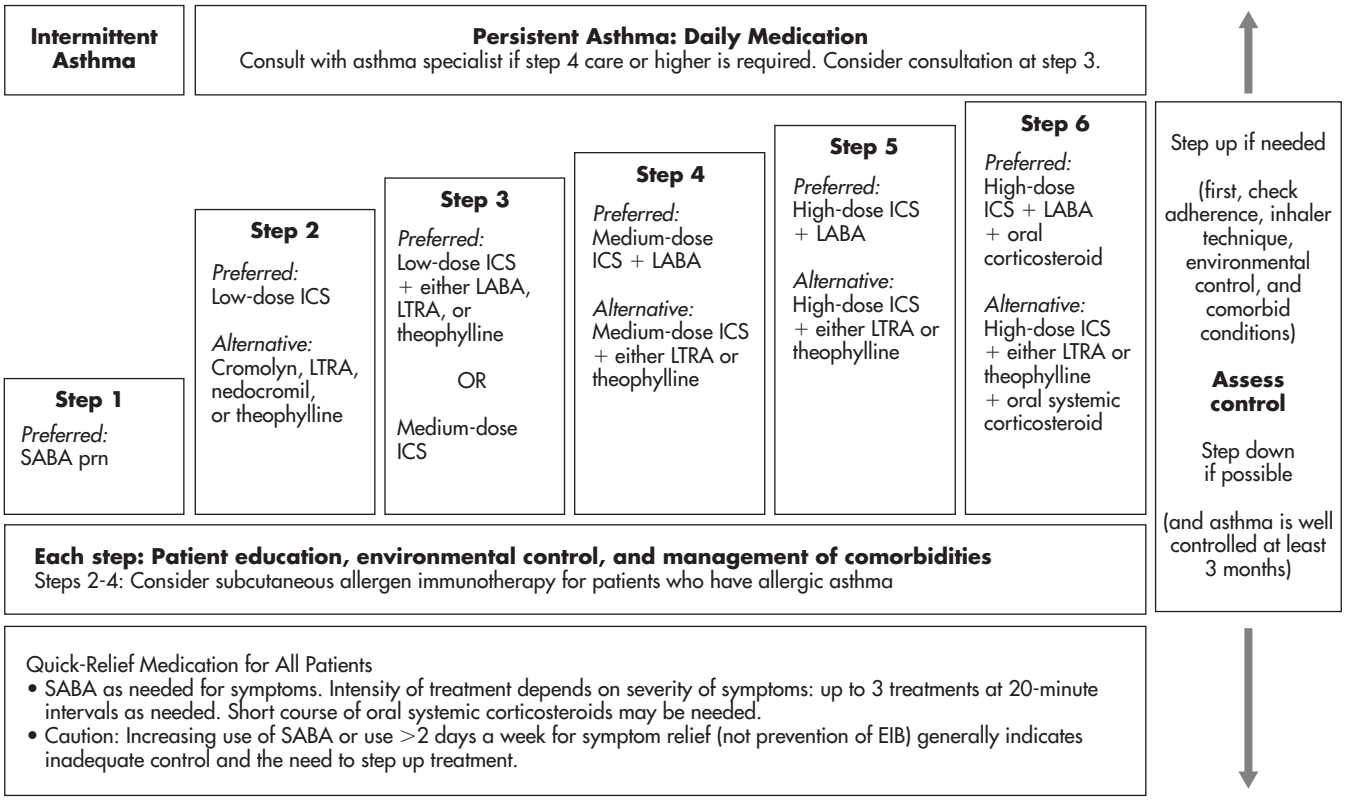
The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
Level of severity is determined by both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2-4 wk and spirometry. Assign severity to the most severe category in which any feature occurs.
At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate greater underlying disease severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.
EIB, Exercise-induced bronchospasm; *FEV_1,* forced expiratory volume in 1 second; *FVC,* forced vital capacity; *ICU,* intensive care unit.
From National Asthma Education and Prevention Program: *Expert panel report 3: Guidelines for diagnosis and management of asthma,* National Institutes of Health, National Heart, Lung, and Blood Institute, August 2007, NIH publication 08-4051.

TABLE A1-74 Assessing Asthma Control and Adjusting Therapy in Children 5-11 Yr

Components of Control		CLASSIFICATION OF ASTHMA CONTROL (5-11 yr of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/wk but not more than once on each day	>2 days/wk or multiple times on ≤2 days/wk	Throughout the day
	Nighttime awakenings	≤1×/mo	≥2×/mo	≥2×/wk
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting $beta_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/wk	>2 days/wk	Several times per day
	Lung function			
	FEV_1 or peak flow	>80% predicted/personal best	60%-80% predicted/personal best	<60% predicted/personal best
	FEV_1/FVC	>80% predicted	75%-80%	<75% predicted
Risk	Exacerbations requiring oral systemic corticosteroids	0-1 per yr	≥2 per yr	
		Consider severity and interval since last exacerbation		
	Reduction in lung growth	Evaluation requires long-term follow-up care		
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment		Maintain current step. Regular follow-up every 1-6 mo. Consider step down if well controlled for at least 3 mo.	Step up 1 step and reevaluate in 2-6 wk. For side effects, consider alternative treatment options.	Consider short course of oral systemic corticosteroids. Step up 1-2 steps. Reevaluate in 2 wk. For side effects, consider alternative treatment options.

The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
The level of control is based on the most severe impairment or risk category. Assess impairment domain by patient's/caregiver's recall of previous 2-4 wk and by spirometry or peak flow measures. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit.
At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.
Before step up in therapy:
– Review adherence to medications, inhaler technique, environmental control, and comorbid conditions.
– If an alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.
EIB, Exercise-induced bronchospasm; *FEV_1,* forced expiratory volume in 1 second; *ICU,* intensive care unit.
From National Asthma Education and Prevention Program: *Expert panel report 3: Guidelines for diagnosis and management of asthma,* National Institutes of Health, National Heart, Lung, and Blood Institute, August 2007, NIH publication 08-4051.

TABLE A1-75 Stepwise Approach for Managing Asthma in Children 5-11 Yr



The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
Theophylline is a less desirable alternative due to the need to monitor serum concentration levels.
Step 1 and step 2 medications are based on Evidence A. Step 3 ICS 1 adjunctive therapy and ICS are based on Evidence B for efficacy of each treatment and extrapolation from comparator trials in older children and adults—comparator trials are not available for this age group; steps 4-6 are based on expert opinion and extrapolation from studies in older children and adults.
Immunotherapy for steps 2-4 is based on Evidence B for house-dust mites, animal danders, and pollens; evidence is weak or lacking for molds and cockroaches. Evidence is strongest for immunotherapy with single allergens. The role of allergy in asthma is greater in children than in adults. Clinicians who administer immunotherapy should be prepared and equipped to identify and treat anaphylaxis that may occur.
This information is directly abstracted from the 2007 NAEPP *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* and is not intended to promote or endorse any of the listed products.
ICS, Inhaled corticosteroid; *LABA,* inhaled long-acting beta$_2$-agonist; *LTRA,* leukotriene receptor antagonist; *SABA,* inhaled short-acting beta$_2$-agonist.
From National Asthma Education and Prevention Program: *Expert panel report 3: Guidelines for diagnosis and management of asthma*, National Institutes of Health, National Heart, Lung, and Blood Institute, August 2007, NIH publication 08-4051.

- Use of LABAs alone without use of a long-term asthma medication, such as an inhaled corticosteroid, is contraindicated. LABAs should also not be used in patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids. Continued use of LABAs may cause down-regulation of the beta-2 receptor with loss of the bronchoprotective effect from rescue therapy with a SABA.
- Patients who remain symptomatic despite inhaled corticosteroids benefit from the addition of LABAs. Trials in patients with poorly controlled asthma despite the use of inhaled glucocorticoids and LABAs have shown that the addition of tiotropium, a long-acting anticholinergic bronchodilator approved for treatment of COPD, increased the time to the first severe exacerbation and provided modest sustained bronchodilation.
- Therapy with systemic corticosteroids accelerates the resolution of acute asthma and reduces the risk of relapse. There is no evidence that doses >50-100 mg prednisone equivalent are beneficial.
- In patients with allergies and elevated serum immunoglobulin (Ig) E levels, use of anti-IgE therapy is beneficial.
- Bronchial thermoplasty (Alair System) may be used to reduce airway smooth muscle mass and widen the airway in adult patients with severe persistent asthma not well controlled with inhaled corticosteroids and LABAs. It requires the insertion of a catheter via bronchoscopy and use of a radiofrequency controller.
- Biologic modifiers of the Th2 immune pathways (neutralizing monoclonal antibodies, receptor antagonists, soluble receptors) are potential options for the development of new treatments of severe asthma.
- The response to treatment for asthma is characterized by wide individual variability. A functional glucocorticoid-induced transcript 1 gene (GLCCI1) variant is associated with substantial decrements in the response to inhaled glucocorticoids in patients with asthma. Another potential cause of the variability in response to treatment is heterogeneity in the role of interleukin-13 expression in the clinical asthma phenotype. Patients with asthma who have a certain biochemical signature are more likely to respond to an anti–interleukin-13 monoclonal antibody than those without such a signature. Identification of genetic variants can eventually lead to personalized asthma treatment.

EVIDENCE

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SUGGESTED READINGS

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RELATED CONTENT

Asthma (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

TABLE A1-76 Classifying Asthma Severity and Initiating Treatment in Children 0-4 Yr (Assessing severity and initiating treatment in children who are not currently taking long-term control medications)

Components of Severity		CLASSIFICATION OF ASTHMA SEVERITY (0-4 yr of age)			
			PERSISTENT		
		Intermittent	Mild	Moderate	Severe
Impairment	Symptoms	≤2 days/wk	>2 days/wk but not daily	Daily	Throughout the day
	Nighttime awakenings	0	1-2×/mo	3-4×/mo	>1×/wk
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/wk	>2 days/wk but not daily	Daily	Several times per day
	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
Risk	Exacerbations requiring oral systemic corticosteroids	0-1 per yr	≥2 exacerbations in 6 mo requiring oral systemic corticosteroids, or ≥4 wheezing episodes/1 yr lasting >1 day AND risk factors for persistent asthma.		
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time.			
		Exacerbations of any severity may occur in patients in any severity category.			
Recommended Step for Initiating Therapy		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	
		In 2-6 wk, depending on severity, evaluate level of asthma control that is achieved. If no clear benefit is observed in 4-6 wk, consider adjusting therapy or alternative diagnoses.			

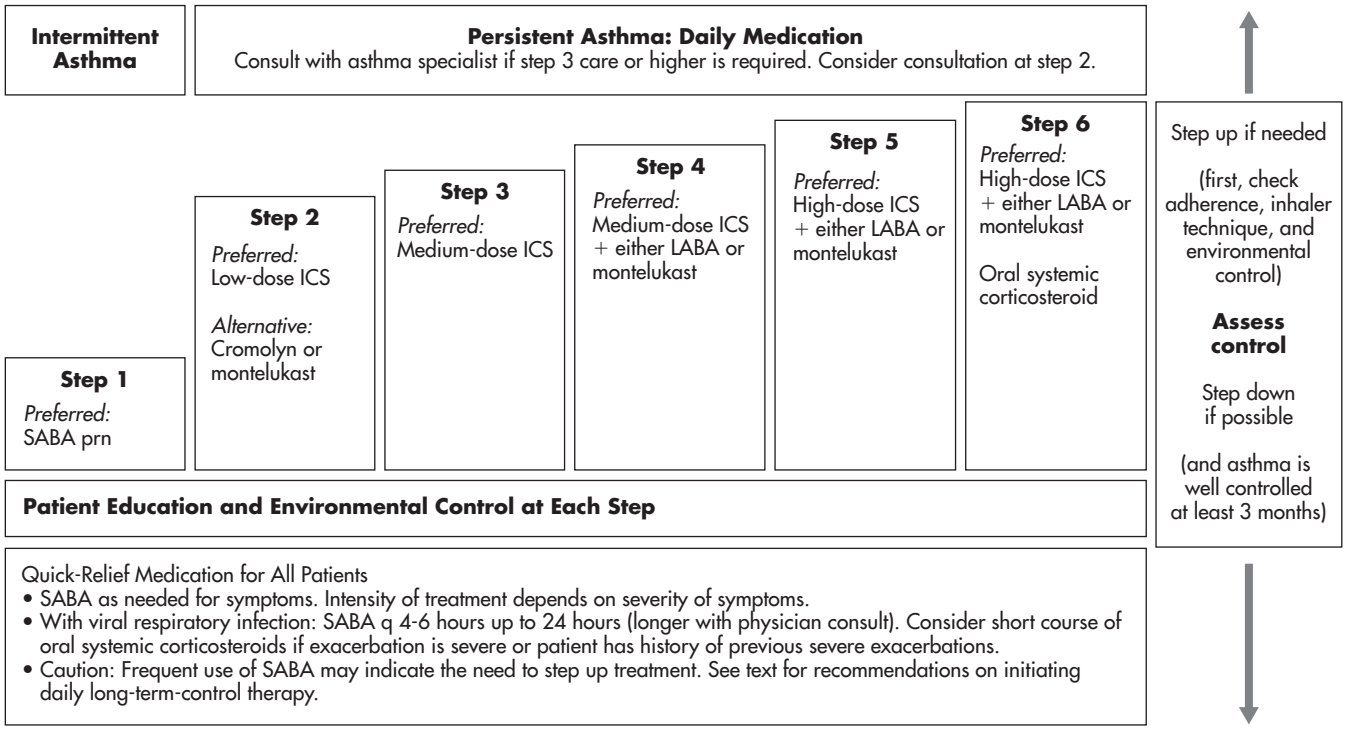
The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
Level of severity is determined by assessment of both impairment and risk. Assess impairment domain by patient's/caregiver's recall of previous 2-4 wk. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit. Assign severity to the most severe category in which any feature occurs.
At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma severity. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past six months, or ≥4 wheezing episodes in the past year, and who have risk factors for persistent asthma may be considered the same as patients who have persistent asthma, even in the absence of impairment levels consistent with persistent asthma.
To access the complete Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, go to www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf.
EIB, Exercise-induced bronchospasm.
From National Asthma Education and Prevention Program: *Expert panel report 3: Guidelines for diagnosis and management of asthma,* National Institutes of Health, National Heart, Lung, and Blood Institute, August 2007, NIH publication 08-4051.

TABLE A1-77 Assessing Asthma Control and Adjusting Therapy in Children 0-4 Yr of Age

Components of Control		CLASSIFICATION OF ASTHMA CONTROL (0-4 yr of age)		
		Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	Symptoms	≤2 days/wk	>2 days/wk	Throughout the day
	Nighttime awakenings	≤13/mo	>1×/mo	>1×/wk
	Interference with normal activity	None	Some limitation	Extremely limited
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/wk	>2 days/wk	Several times per day
Risk	Exacerbations requiring oral systemic corticosteroids	0-1 per yr	2-3 per yr	>3 per yr
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.		
Recommended Action for Treatment		Maintain current step. Regular follow-up every 1-6 mo. Consider step down if well controlled for at least 3 mo.	Step up 1 step. Reevaluate in 2-6 wk. If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy. For side effects, consider alternative treatment options.	Consider short course of oral systemic corticosteroids. Step up 1-2 steps. Reevaluate in 2 wk. If no clear benefit in 4-6 wk, consider alternative diagnoses or adjusting therapy. For side effects, consider alternative treatment options.

The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
The level of control is based on the most severe impairment or risk category. Assess impairment domain by caregiver's recall of previous 2-4 wk. Symptom assessment for longer periods should reflect a global assessment such as inquiring whether the patient's asthma is better or worse since the last visit.
At present, there are inadequate data to correspond frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (e.g., requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer disease control. For treatment purposes, patients who had ≥2 exacerbations requiring oral systemic corticosteroids in the past year may be considered the same as patients who have not-well-controlled asthma, even in the absence of impairment levels consistent with not-well-controlled asthma.
Before step up in therapy:
– Review adherence to medications, inhaler technique, and environmental control.
– If an alternative treatment option was used in a step, discontinue it and use preferred treatment for that step.
EIB, Exercise-induced bronchospasm; *ICU,* intensive care unit.
From National Asthma Education and Prevention Program: *Expert panel report 3: Guidelines for diagnosis and management of asthma,* National Institutes of Health, National Heart, Lung, and Blood Institute, August 2007, NIH publication 08-4051.

TABLE A1-78 Stepwise Approach for Managing Asthma in Children 0-4 Yr



The stepwise approach is meant to assist, not replace, the clinical decision-making required to meet individual patient needs.
If alternative treatment is used and response is inadequate, discontinue it and use the preferred treatment before stepping up.
If clear benefit is not observed within 4-6 wk and patient/family medication technique and adherence are satisfactory, consider adjusting therapy or alternative diagnosis.
Studies on children 0-4 yr are limited. Step 2 preferred therapy is based on Evidence A. All other recommendations are based on expert opinion and extrapolation from studies in other children.
This information is directly abstracted from the 2007 NAEPP *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* and is not intended to promote or endorse any of the listed products.
ICS, Inhaled corticosteroid; *LABA,* inhaled long-acting beta$_2$-agonist; *SABA,* inhaled short-acting beta$_2$-agonist.
From National Asthma Education and Prevention Program: *Expert panel report 3: Guidelines for diagnosis and management of asthma*, National Institutes of Health, National Heart, Lung, and Blood Institute, August 2007, NIH publication 08-4051.

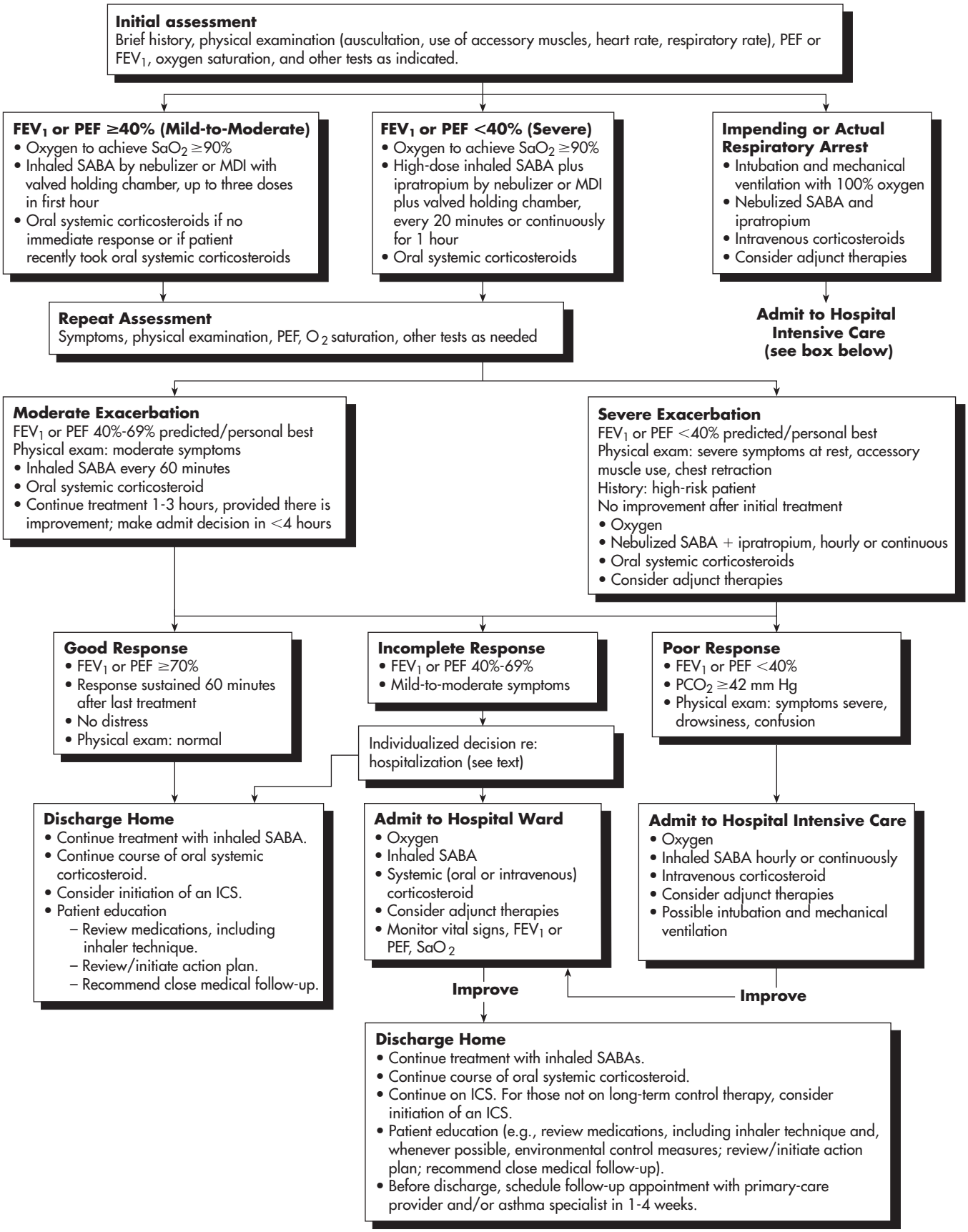


FIGURE A1-127 Management of asthma exacerbations: emergency department and hospital-based care. *FEV_1*, Forced expiratory volume in 1 second; *ICS*, inhaled corticosteroid; *MDI*, metered-dose inhaler; *PCO_2*, partial pressure carbon dioxide; *PEF*, peak expiratory flow; *SABA*, short-acting beta$_2$-agonist; *SaO_2*, oxygen saturation. (From National Asthma Education and Prevention Program: *Guidelines for the diagnosis and management of asthma*, 2007, National Institutes of Health, National Heart, Lung, and Blood Institute.)

BOX A1-11 Possible Indications for Referral to an Asthma Specialist

- Severe, acute asthma that has caused loss of consciousness, hypoxia, respiratory failure, convulsions, or near death
- Poorly controlled asthma as indicated by admission to a hospital, frequent need for emergency care, need for oral corticosteroids, absence from school or work, disruption of sleep, interference with quality of life
- Severe, persistent asthma requiring step 4 care (consider for patients who require step 3 care)
- Patient <3 yr who requires step 3 or 4 care (consider for patient <3 yr who requires step 2 care)
- Requirement for continuous oral corticosteroids or high-dose inhaled corticosteroids or more than two short courses of oral corticosteroids within 1 yr
- Need for additional diagnostic testing such as allergy skin testing, rhinoscopy, provocative challenge, complete pulmonary function testing, bronchoscopy
- Consideration for immunotherapy
- Need for additional education regarding asthma, complications of asthma and treatment of asthma, problems with adherence to management recommendations, or allergen avoidance
- Uncertainty of diagnosis
- Complications of asthma, including sinusitis, nasal polyposis, aspergillosis, severe rhinitis, vocal cord dysfunction, gastroesophageal reflux

Modified from National Asthma Education and Prevention Program, National Heart, Lung, and Blood Institute: *Expert Panel Report 2: guidelines for the diagnosis and management of asthma,* Bethesda, MD, 1997, National Institutes of Health, NIH publication No 97-4051.

EVIDENCE

Abstract[1]

Background:
Fluticasone furoate (FF) is a novel inhaled corticosteroid with 24 h activity. FF is being developed as a once-daily treatment in combination with the long-acting β_2 agonist vilanterol trifenatate for asthma and chronic obstructive pulmonary disease.

Objectives:
To determine the optimal dose(s) of FF for treating patients with asthma.

Methods:
An 8-week multicentre, randomised, double-blind study. 627 patients with persistent moderate-to-severe asthma, symptomatic on medium-dose inhaled corticosteroid therapy, were randomised to placebo, FF 200, 400, 600 or 800 μg (once daily in the evening using a novel dry powder inhaler), or fluticasone propionate 500 μg twice daily (via Diskus™/Accuhaler™). The primary efficacy measure was mean change from baseline in pre-dose evening forced expiratory volume in one second (FEV_1). Other endpoints included morning and evening peak expiratory flow, and rescue/symptom-free 24 h periods.

Results:
Each dose was significantly superior to placebo for the primary endpoint ($p<0.001$) with efficacy at least similar to that reported with fluticasone propionate. There was no dose–response relationship across the FF doses studied. Peak expiratory flow improved in all groups ($p<0.001$ vs placebo), and there were significant treatment effects on rescue/symptom-free 24 h periods with all active treatments. FF was generally well tolerated. The incidence of oral candidiasis was higher with FF 800 μg than placebo; pharmacokinetic and 24 h urinary cortisol analyses confirmed a higher systemic exposure of FF at this highest dose level.

Conclusions:
FF doses <800 μg have a favourable therapeutic index. The absence of an efficacy dose response suggests that 200 μg is an appropriate dose in patients with moderate persistent asthma.
ClinicalTrials.gov identifier: NCT00603746. Ⓐ

Abstract[2]

Objective:
The goal was to determine if adding inhaled budesonide to standard asthma therapy improves outcomes of pediatric patients presenting to the emergency department (ED) with acute asthma.

Methods:
The authors conducted a randomized, double-blind, placebo-controlled trial in a tertiary care, urban pediatric ED. Patients 2 to 18 years of age with moderate to severe acute asthma were randomized to receive either a single 2-mg dose of budesonide inhalation suspension (BUD) or normal sterile saline (NSS) placebo, added to albuterol, ipratropium bromide (IB), and systemic corticosteroids (SCS). The primary outcome was the difference in median asthma scores between treatment groups at 2 hours. Secondary outcomes included differences in vital signs and hospitalization rates.

Results:
A total of 180 patients were enrolled. Treatment groups had similar baseline demographics, asthma scores, and vital signs. A total of 169 patients (88 BUD, 81 NSS) were assessed for the primary outcome. No significant difference was found between groups in the change in median asthma score at 2 hours (BUD −3, NSS −3, p=0.64). Vital signs at 2 hours were also similar between groups. Fifty-six children (62%) were admitted to the hospital in the BUD group and 55 (62%) in the NSS group (difference 0%, 95% confidence interval [CI]=−14% to 14%). Neither multivariate adjustment nor planned subgroup analysis by inhaled corticosteroids (ICS) use prior to the ED significantly altered the results.

Conclusions:
For children 2 to 18 years of age treated in the ED for acute asthma, a single 2-mg dose of budesonide added to standard therapy did not improve asthma severity scores or other short-term ED-based outcomes. Ⓐ

Abstract[3]

Background:
Fluticasone furoate (FF) is an inhaled corticosteroid (ICS) with 24-hour activity in development as a once-daily treatment for the long-term management of asthma.

Objective:
To assess the efficacy and safety of 4 doses of once-daily FF administered using a dry powder inhaler in patients (≥12 years) with moderate asthma, uncontrolled on low-dose ICS (fluticasone propionate [FP] 200 mg/day or equivalent).

Methods:
This double-blind, placebo-controlled, dose-ranging study randomized 622 patients to 1 of 6 treatments: FF (100, 200, 300, or 400 mg) once daily in the evening, FP 250 mg twice daily (active control), or placebo for 8 weeks. The primary endpoint was the change from baseline in predose evening forced expiratory volume in 1 second (FEV1) at week 8.

Results:
At week 8, relative to placebo, all doses of FF once daily and FP twice daily demonstrated significantly ($P<.001$) greater increases from baseline and greater than 200-mL increases in predose FEV1. There was no evidence of a dose-response relationship between FF doses. Improvement with once-daily FF was similar to or greater than that for twice-daily FP.
Secondary efficacy endpoint findings generally supported the efficacy of FF 100 to 400 mg once daily, although statistically significant improvements versus placebo in symptom-free 24-hour periods were only reported for FF 400 mg. There were few withdrawals due to lack of efficacy. Oral candidiasis was reported in 0% to 4% of patients; 24-hour urinary cortisol excretion ratios were similar across active treatment groups and not significantly different from placebo.

Conclusion:
FF 100 to 400 mg once daily in the evening is effective and well tolerated in patients with asthma uncontrolled on low-dose ICS, with 100 mg and 200 mg, considered the most applicable doses in this asthma population.
Trial Registration: clinicaltrials.gov Identifier: NCT00603278. Ⓐ

Abstract[4]

Background:
The inhaled corticosteroid, fluticasone propionate, and the long-acting β_2-adrenergic agonist, formoterol fumarate, are both highly effective treatments for bronchial asthma. This study (NCT00393952/EudraCT number: 2006-005989-39) compared the efficacy and safety of fluticasone/formoterol combination therapy (flutiform; 250/10 mg) administered twice daily (b.i.d.) via a single aerosol inhaler, with the individual components (fluticasone 250 mg b.i.d.; formoterol 10 mg b.i.d.), in adult and adolescent patients with moderate-to-severe asthma.

Methods:
This was a 12-week, double-blind, randomized, parallel-group, multicenter, placebo-controlled phase 3 study. The co-primary efficacy endpoints were: i) the mean change in the forced expiratory volume in the first second (FEV1) from morning pre-dose at baseline to pre-dose at week 12 (fluticasone/formoterol 250/10 mg vs. formoterol), ii) the mean change in FEV1 from morning pre-dose at baseline to 2 h post-dose at week 12 (fluticasone/formoterol 250/10 mg vs. fluticasone), and iii) the number of patients who discontinued prematurely due to lack of treatment efficacy (fluticasone/formoterol 250/10 mg vs. placebo). The secondary endpoints included measures of lung function, disease control, and asthma symptoms. Safety was assessed based on adverse events, vital signs, and clinical laboratory evaluations.

Results:
Overall, 395 (70.9%) patients completed the study. Fluticasone/formoterol 250/10 mg b.i.d. was superior to the individual components and placebo for all three co-primary endpoints and demonstrated numerically greater improvements for multiple secondary efficacy analyses. Fluticasone/formoterol combination therapy had a good safety profile over the 12 weeks.

Conclusion:
Fluticasone/formoterol combination therapy will provide clinicians with an efficacious alternative treatment option for patients with moderate-to-severe asthma. Ⓐ

Evidence-Based References

Busse WW, et al.: Fluticasone furoate demonstrates efficacy in patients with asthma symptomatic on medium doses of inhaled corticosteroid therapy: an 8-week, randomised, placebo-controlled trial, *Thorax* 67:35–41, 2012. Ⓐ

Upham BD et al.: Nebulized budesonide added to standard pediatric emergency department treatment of acute asthma: a randomized, double-blind trial, *Acad Emerg Med* 18:665–673, 2011. Ⓐ

Bleecker ER, Bateman ED, Busse WW et al.: Once-daily fluticasone furoate is efficacious in patients with symptomatic asthma on low-dose inhaled corticosteroids, *Ann Allergy Asthma Immunol* 109:353–358.e4, 2012. Ⓐ

Corren J, Mansfield LE, Pertseva T et al.: Efficacy and safety of fluticasone/formoterol combination therapy in patients with moderate-to-severe asthma, *Respir Med* 107:180–195, 2013. Ⓐ

SUGGESTED READINGS

American Lung Association Asthma Clinical Research Centers: Randomized comparison of strategies for reducing treatment in mild persistent asthma, *N Engl J Med* 356:2027, 2007.

Bel EH et al.: Mild asthma, *N Engl J Med* 369:549–557, 2013.

Boulet LP, O'Byrne PM: Asthma and exercise-induced bronchoconstriction in athletes, *N Engl J Med* 372:641–648, 2015.

Braman SS, Vigg A: The National Asthma Education and Prevention Program (NAEPP) Guidelines: will they improve the quality of care in America? *Med Health R I* 91:166, 2008.

Busse WW: Randomized trial of omalizumab (Anti-IgE) for asthma in inner-city children, *N Engl J Med* 364:1005–1015, 2011.

Corren J et al.: Lebrikizumab treatment in adults with asthma, *N Engl J Med* 365:1088–1098, 2011.

DiMango E et al.: Effect of asymptomatic proximal and distal esophageal reflux on asthma severity, *Am J Respir Crit Care Med* 180:809, 2009.

Fanta CH: Asthma, *N Engl J Med* 360:10, 2009.

Hanania NA et al.: Omalizumab in severe allergic asthma inadequately controlled with standard therapy, *Ann Intern Med* 154:573–582, 2011.

Kerstjens H et al.: Tiotropium in asthma poorly controlled with standard combination therapy, *N Engl J Med* 367:1198–1207, 2012.

Krishan JA et al.: An umbrella review: corticosteroid therapy for adults with acute asthma, *Am J Med* 122:977–991, 2009.

Kurtis SE, Pollart SM: Medical therapy for asthma: updates from the NAEPP guidelines, *Am Fam Physician* 82(10):1242–1251, 2010.

Lazarus SC: Emergency treatment of asthma, *N Engl J Med* 363:755–764, 2010.

Levine SJ, Wenzel SE: Narrative review: the role of the Th2 immune pathway modulation in the treatment of severe asthma and its phenotypes, *Ann Intern Med* 152:232–237, 2010.

National Asthma Education and Prevention Program. Expert panel report 3: guidelines for diagnosis and management of asthma. National Institutes of Health: Bethesda, MD.

Ortega HG et al.: Mepolizumab treatment in patients with severe eosinophilic asthma, *N Engl J Med* 371:1198–1207, 2014.

Schatz M, Dombrowski MP: Asthma in pregnancy, *N Engl J Med* 360:1862–1869, 2009.

Stupka E, deShazo R: Asthma in seniors: Part 1. Evidence for underdiagnosis, undertreatment, and increasing morbidity and mortality, *Am J Med* 122:6–11, 2009.

Tantisira KG et al.: Genomewide association between GLCCI1 and response to glucocorticoid therapy in asthma, *N Engl J Med* 365:1173–1183, 2011.

Wenzel S et al.: Dupilimab in persistent asthma with elevated eosinophil levels, *N Engl J Med* 368:2455–2466, 2013.

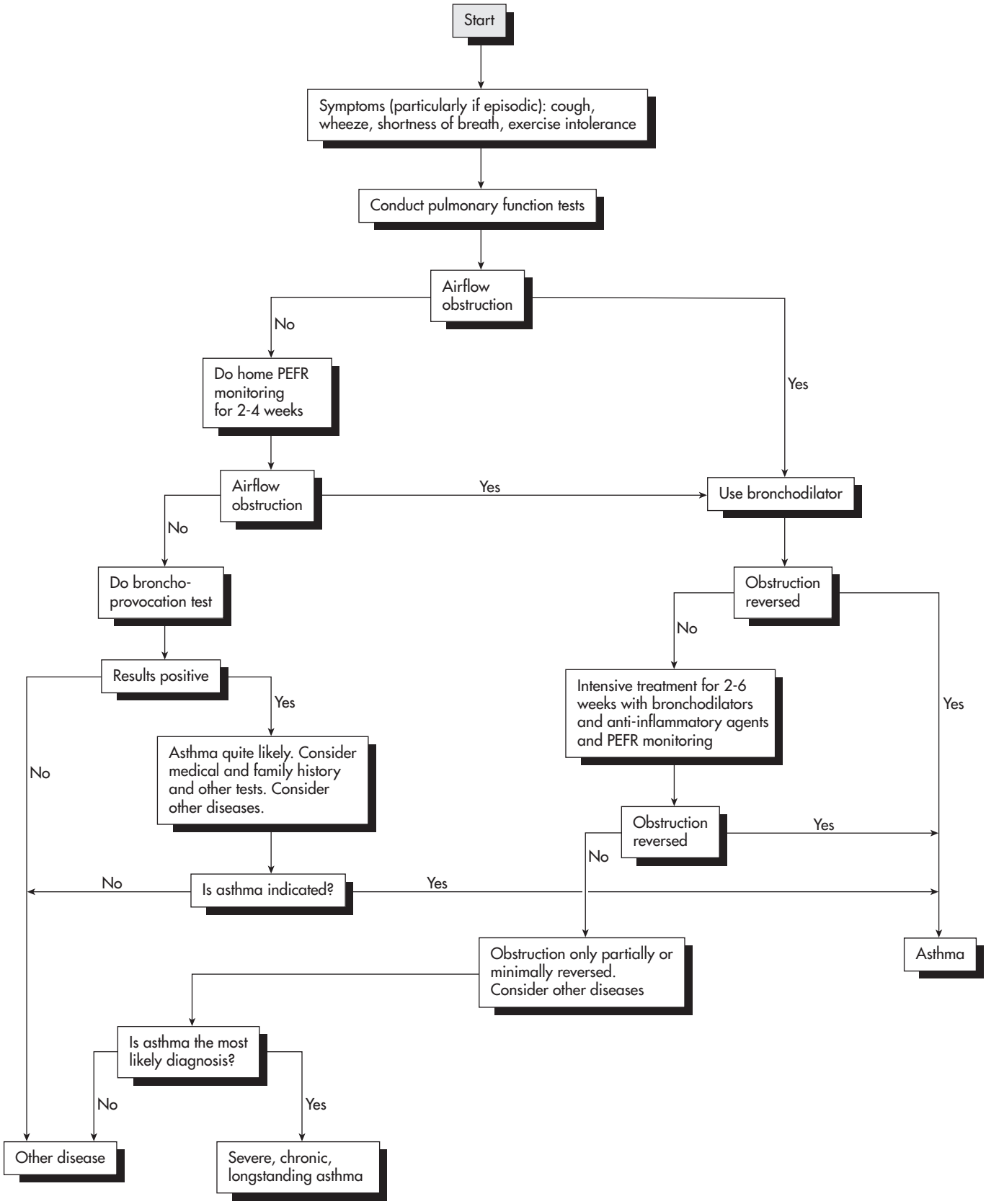


FIGURE EA1-125 Algorithm for diagnosing asthma. *PEFR,* Peak expiratory flow rates. (From Fireman P: *Atlas of allergies and immunology*, ed 3, St Louis, 2006, Mosby.)

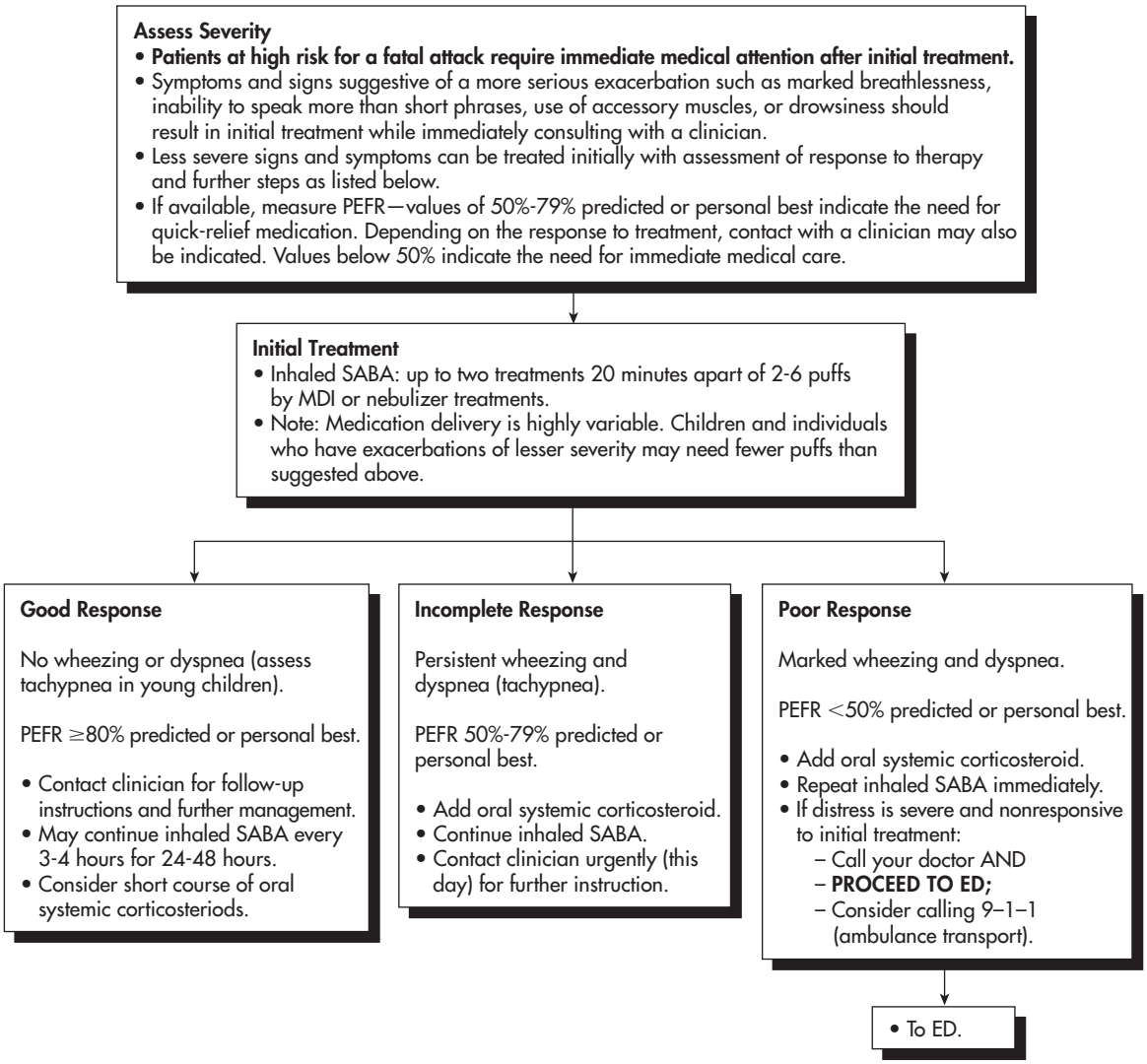


FIGURE EA1-126 Home management of acute asthma. *ED,* Emergency department; *MDI,* metered-dose inhaler; *PEFR,* peak expiratory flow rate; *SABA,* short-acting beta$_2$-agonist (quick-relief inhaler). (Modified from National Asthma Education and Prevention Program, National Heart, Lung, and Blood Institute, *Expert Panel Report 3: Guidelines for the diagnosis and management of asthma,* 2007.)

BASIC INFORMATION

DEFINITION

Astrocytoma is a type of neuroepithelial tumor that arises from glial precursor cells (astrocytes, oligodendrocytes, ependymal cells, epithelial cells of the choroid plexus, and others). Astrocytoma arises from astrocytes within the central nervous system (CNS). They are commonly graded by the World Health Organization (WHO) or the Saint Anne–Mayo grading system.

The WHO grades astrocytomas as follows:

- Grade I: pilocytic astrocytoma
- Grade II: low-grade astrocytoma (LGA), fibrillary infiltrating astrocytoma
- Grade III: anaplastic astrocytoma
- Grade IV: glioblastoma multiforme (GBM)
- Grades III and IV are considered high-grade astrocytomas (HGAs) or malignant.

Kernohan system grades astrocytomas based on histologic features: cellularity, mitoses, pleomorphism, vascularity, and necrosis. It has proved to be of prognostic value.

- Grade I: increased cellularity
- Grade II: greater cellularity than grade I plus pleomorphism
- Grade III: greater cellularity and pleomorphism than grade II plus vascular proliferation
- Grade IV: all the above, plus necrosis and pseudopalisading

SYNONYMS

Astroglial neoplasms

ICD-9CM CODES
191.9 Astrocytoma, unspecified site
ICD-10CM CODES
C71.9 Malignant neoplasm of brain, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- According to SEER registry, the incidence of primary CNS tumor is 2.2 to 8.3/100,000 persons and about 30% of these tumors are astrocytomas.
- Astrocytomas can be found at all ages, with an early peak from birth to 4 yr, followed by a trough between the ages of 15 and 24 yr, and then a steady increase in incidence.
- Male/female ratio is 2:1.
- In adults, glioblastoma is the most common brain tumor.
- In children, astrocytomas are the second most common primary brain tumor and medulloblastoma is the most common.
- Low-grade astrocytomas represent approximately 25% of all CNS gliomas in children.
- Peak age of incidence for juvenile pilocytic astrocytomas is 5 to 14 yr.
- Peak age of incidence for glioblastoma is 45 to 70 yr.

GENETICS:

- Alteration of *p53,* a tumor-suppressor gene encoded by the *TP53* gene on chromosome 17, plays a key role in the development of a large number of adult astrocytomas.
- Genetic abnormalities occur in a stepwise manner with accumulation of multiple abnormalities leading to dedifferentiation and transformation into higher grade.
- Abnormalities of the cell cycle regulatory complex that includes p16, cdk6/cyclinD1, cdk4/cyclinD1, and loss of chromosome 9P that targets the CDKN2A locus is thought to play an important role in progression to grade III astrocytoma.
- Transformation to GBM is the result of multiple mitogenic effects, with deregulation of p16-CDK4D1-pRb pathway being an important component. Loss of chromosome 10, which targets the PTEN tumor-suppressor gene, is also a frequent finding.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The presenting symptoms of astrocytoma depend, in part, on the location of the lesion and its rate of growth. Astrocytomas classically present with any one or more of the following features:

- Headache (less frequent)
- New-onset partial or generalized seizures (>50%)
- Nausea and vomiting
- Focal neurologic deficit (cranial nerve palsy, hemiplegia, ataxia)
- Change in mental status
- Papilledema (rare)

ETIOLOGY

- The specific etiology of astrocytoma is unknown.
- The only proven risk factor for development of astrocytoma has been significant exposure to ionizing radiation.
- Other risk factors, such as increased exposure to certain chemicals (petroleum, solvents, lead, pesticides and herbicides), have been proposed but not proved.

DIAGNOSIS

A provisional diagnosis of astrocytoma is made on clinical grounds and radiographic imaging studies. Tissue pathology is needed to establish the diagnosis and to grade the astrocytoma.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is vast and includes any cause of headache, seizures, change in mental status, and focal neurologic deficits.

WORKUP

- A CT scan or MRI of the head makes the diagnosis of an intracranial brain tumor. However, tissue is needed to establish a diagnosis of astrocytoma.
- Stereotactic biopsy under CT or MRI guidance has been shown to be a relatively safe and accurate method for diagnosis of LGA.
- In the presence of mass effect, either clinically or radiologically, craniotomy with open biopsy and tumor debulking is more appropriate than stereotactic biopsy to establish a tissue diagnosis.

LABORATORY TESTS

There are no diagnostic or supportive blood tests for astrocytoma.

IMAGING STUDIES

- MRI (Fig. A1-128) is the diagnostic imaging study of choice. MRI with contrast and magnetic resonance angiography are used to locate the margins of the tumor, distinguish vascular masses from tumors, detect LGAs not seen by CT scan, and provide clear views of the posterior fossa.
- Newer imaging modalities like magnetic resonance spectroscopy, dynamic enhanced MRI, diffusion perfusion MRI, and functional MRI may lead to improved tumor delineation and functional mapping, and provide information to facilitate resection.

TREATMENT

ACUTE GENERAL Rx

- Once a clinical diagnosis is made on imaging and there is evidence of edema, patients

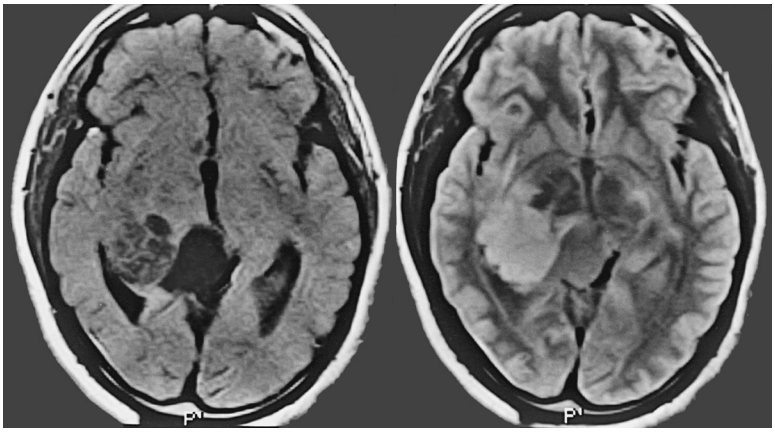


FIGURE A1-128 MR image of a low-grade astrocytoma, demonstrating a hypointense right temporal lesion without contrast enhancement on T1 and hyperintense signal on T2. (From Goetz CG, Pappert EJ: *Textbook of clinical neurology,* Philadelphia, 1999, Saunders.)

should be started on dexamethasone 10 mg intravenously (IV) followed by 4 mg IV q6h.
- If there is increased intracranial pressure and impending herniation, patient should be started on IV mannitol, and mechanical ventilation with hyperventilation should be considered if there is depressed consciousness.
- Surgery remains the initial treatment of almost all astrocytomas, particularly if the tumor is in an anatomically accessible location. Surgery helps in the following ways:
  1. Establishing a pathologic diagnosis and providing information on grade
  2. Debulking the tumor
  3. Alleviating intracranial pressure
- Grade I astrocytomas are usually circumscribed, and complete resection is possible with a high likelihood of long-term remission.
- In grade II astrocytomas, the extent of surgical resection and amount of postoperative residual disease is an important variable for time to first relapse. Randomized trials have shown that postoperative radiotherapy in grade II astrocytoma increases progression-free survival (PFS), but no increase in median survival occurs.
- In grade III and grade IV astrocytomas, gross total resection is the initial treatment of choice. Patients with no residual enhancing tumor have a longer median survival (17.9 vs 12.9 mo; P <0.001) than patients with residual tumor.
- Use of radiation after surgery in high-grade astrocytomas has shown a clear benefit in overall survival.
- In a randomized trial of patients with GBM, radiation with concurrent temozolomide versus radiation alone followed by six cycles of adjuvant temozolomide increases median and overall survival, and this is considered the standard of care for patients with GBM.

CHRONIC Rx

- Attempt at reresection again should be considered in all types of astrocytomas on relapse if possible and in grade I astrocytomas can lead to long-term remissions.
- Radiation therapy can be considered in the relapsed setting in grade II astrocytomas if not given in the adjuvant setting. Chemotherapy has been tried but has no proven role in these tumors.
- Chemotherapy in anaplastic astrocytomas that have relapsed after radiation (Fig. A1-129) does have a role, and the active agents are nitrosourea-based regimen and temozolomide. Grade III anaplastic astrocytomas that have 1p and 19q deletions are especially sensitive to chemotherapy.
- Bevacizumab alone or more commonly in combination with irinotecan is an effective regimen in relapsed GBM, with a response rate of 30% to 50% on the basis of at least two prospective phase II trials.
- Patients presenting with seizures should be treated with anticonvulsants.

DISPOSITION

- Approximately 10% to 35% of astrocytomas (usually grade I pilocytic astrocytomas) are amenable to complete surgical excision and cure. WHO grade I astrocytomas usually do not progress to higher grade tumors.
- Grade II astrocytomas have a median survival of 7.7 yr if they are low risk and 3.2 yr if they are high risk.
- Grade III astrocytomas have a 3-yr survival rate of 55%.
- Median survival for patients with GBM is about 1 yr. Median survival of patients with GBM treated with supportive care is approximately 14 wk. This increases to 20 wk with surgical resection alone, 36 wk with surgery plus x-ray therapy, and 40 to 50 wk with the addition of adjuvant chemotherapy.

REFERRAL

A team of specialty consultations is indicated in patients diagnosed with astrocytoma. A neurosurgeon, radiation oncologist, and neurooncologist are all needed to assist in establishing the diagnosis and to provide immediate and follow-up treatment.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Brain Cancer (Patient Information)

AUTHOR: **BILAL H. NAQVI, M.D.**

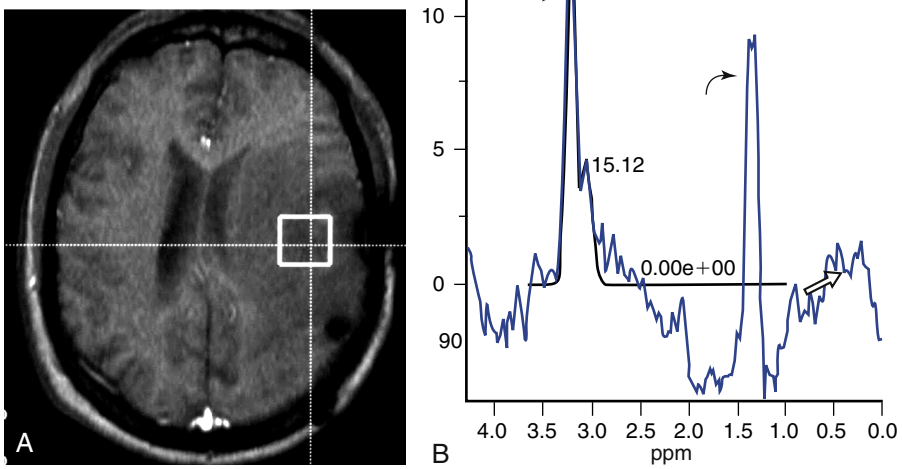


FIGURE A1-129 Recurrent high-grade astrocytoma. Study performed after radiation therapy (not shown) showed increased edema and mass effect; differential diagnosis included recurrent tumor and radiation necrosis. **A,** Axial MRI scan shows volume of tissue *(box)* selected for spectroscopy. **B,** Proton spectroscopy reveals increase in choline peak *(arrow),* decrease in *N*-acetyl aspartate peak *(curved arrow),* and appearance of a lactate peak *(open arrow).* This appearance is consistent with recurrent tumor, which was verified with repeat surgery and biopsy. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

SUGGESTED READINGS

Batchelor T et al: Management of malignant gliomas. Available at http://www.uptodate.com. Accessed Sep 28, 2008.

Grossman SA, Batara JF: Current management of glioblastoma multiforme, *Semin Oncol* 31(5):635, 2004.

Olson JJ, et al.: Management of newly diagnosed glioblastoma: guidelines development, value and application, *J Neurooncol* 93(1):1–23, 2009.

Reardon DA, et al.: Recent advances in the treatment of malignant astrocytoma, *J Clin Oncol* 24:8, 2006.

BASIC INFORMATION

DEFINITION

Ataxia refers to a general incoordination of movement and a disturbance of speech; it is a dysfunction of coordination, force, and tone. It can affect the limbs, structures involved in swallowing, and vision.

SYNONYMS

Gait instability
Loss of balance
Functional impairment

ICD-9CM CODES
334.3 Other cerebral ataxia
334.4 Cerebellar ataxia in diseases classified elsewhere
438.84 Effects of cerebrovascular disease ataxia
334.0 Friedreich's ataxia
ICD-10CM CODES
R27.0 Ataxia, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Hereditary ataxia can affect 1 in 50,000 people in the United States.
PEAK INCIDENCE: Can affect all age groups. Hereditary ataxias peak in young adulthood.
PREVALENCE: 13.9 per 10,000.
PREDOMINANT SEX AND AGE: Ataxia can affect both sexes in equal proportions.
GENETICS: The most common type of inherited ataxia in the United States is Friedreich's ataxia (FA), which is autosomal recessive. The second most inherited ataxia is autosomal dominant spinocerebellar ataxia (SCA) type 3.
RISK FACTORS:
- A positive family history of ataxia
- Excessive alcohol use
- Hypothyroidism
- Anticonvulsant use
- A history of celiac disease
- A history of cerebrovascular disease

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most individuals will complain of double vision or a sense of the environment moving and then a sense of unsteadiness and eventually frequent falls. Speech may become unintelligible, and they are frequently asked to repeat themselves. A history of difficulty cycling or performing physical activities may be present.
- Physical exam findings include slurred speech, nystagmus, square wave jerks, dysconjugate gaze, and ocular bobbing. Dysmetria and past pointing may be noted in the finger to nose and heel to shin testing. Finger chase may be abnormal. Dysdiadochokinesia may be noted on exam.
- Gait is notable for wide-based and difficulty turning and possible easy falling to one side. Tandem gait is abnormal.

ETIOLOGY

- Ataxia can be caused by hereditary, structural, and metabolic factors.
- Hereditary factors include mitochondrial diseases such as MELAS (mitochondrial encephalopathy, lactic acidosis, stroke-like episodes) and MIRAS (mitochondrial recessive ataxic syndrome).
- Structural causes may be due to lesions of the cerebellum such as stroke, masses, Arnold-Chiari malformation, and multiple sclerosis.
- Metabolic causes include hypothyroidism and vitamin E, B1, and B12 deficiency, alcohol, and celiac disease.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Ataxia
- Vitamin (B_{12}, B_1, B_6, or E) deficiency
- Alcoholism
- Anticonvulsant use, such as phenytoin.
- Inherited metabolic disorder, such as Alexander's disease
- Severe neuropathy
- Epilepsy
- Celiac sprue disease
- Wilson's disease
- Cerebral anoxia
- Cerebral tumors
- Stroke
- Cerebellitis
- Conversion disorder

WORKUP

- The workup for ataxia should be systematic and should always look for easily reversible disorders.
- Always start with a family history and investigate for any family members that were affected. This may guide genetic testing.
- Head imaging, preferably magnetic resonance imaging (MRI), is highly recommended.
- A lumbar puncture may be necessary if infection is suspected.

LABORATORY TESTS

- Complete metabolic panel including liver function tests
- Complete blood count and a manual differential
- Thyroid function tests
- HIV and RPR
- Vitamin B_{12}, B_1, B_6, and E
- Anti-endomysial antibodies
- Anti-tissue transglutaminase
- Deaminated gliadin peptide
- Serum copper and ceruloplasmin

IMAGING STUDIES

- MRI with contrast is preferable.
- Computed tomography (CT) scan of the head if MRI is not feasible.
- Cardiac echocardiogram is recommended for the inherited ataxias.

TREATMENT

Treatment of ataxia is highly variable. The best way to treat ataxia is to investigate the cause and, if treatable, then treat the underlying condition. For example, if there is a vitamin deficiency, then vitamin replacement is recommended.

However, sometimes the cause is genetic or unknown, and treatment is directed at minimizing complications, such as neuropathy or cardiac disease, and rehabilitative therapy for the ataxia and motor complications.

NONPHARMACOLOGIC THERAPY

- Rehabilitative services such as physical, occupational, and speech therapy are a necessary part of the treatment of all ataxias, and evidence suggests it does improve functional status for individuals affected by ataxia.

ACUTE GENERAL Rx

- Abrupt and sudden ataxia should always be subjected to a stroke workup, which includes a CT of the head within minutes of presenting.

CHRONIC Rx

- Search for the underlying cause and focus on symptomatic management to prevent future disabilities. Rehabilitative services are integral to long-term care. Always evaluate cardiac and renal function and check for signs of developing neuropathy.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

- There is currently no widely accepted or evidence-based form of complementary medicine for ataxia.

DISPOSITION

- Reversible causes of ataxia may see rapid improvement in symptoms. Genetic ataxias tend to be progressive.

REFERRAL

- Always refer to a neurologist

PEARLS & CONSIDERATIONS

COMMENTS

Look for reversible causes.

PREVENTION

A gluten-free diet would be preferable for people with celiac sprue disease.

PATIENT/FAMILY EDUCATION

Educate families on the need to be supportive and make the home environment safe.

RELATED TOPICS

Friedreich's Ataxia (Related Key Topic)

AUTHOR: **NAWAZ K.A. HACK, M.D.**

EVIDENCE

- Long physical therapy has been shown to improve mood, function, and ability to regain some lost abilities in individuals suffering from ataxia secondary to traumatic brain injury and also inherited ataxias. Ⓐ

Evidence-Based References

Sartor-Glittenberg C et al.: A multidimensional physical therapy program for individuals with cerebellar ataxia secondary to traumatic brain injury: a case series, *Physiother Theory Pract*, Jul 25 2013. [Epub ahead of print] Ⓐ

SUGGESTED READINGS

Brent LF: Childhood cerebellar ataxia, *J Child Neurol* 27(9):1138–1145, 2012.

Shneyder N et al.: Cerebellar ataxia from multiple potential causes: hypothyroidism, Hashimoto's thyroiditis, thalamic stimulation, and essential tremor, *Tremor Other Hyperkinet Mov* 2, 2012.

BASIC INFORMATION

DEFINITION

Ataxia telangiectasia (AT) is a rare autosomal recessive disorder of childhood that results from defective DNA repair mechanisms. AT is a multisystemic disease characterized by progressive cerebellar ataxia, choreoathetosis, oculocutaneous telangiectasias (Fig. EA1-130), frequent infections, increased sensitivity to ionizing radiation, and predisposition to malignancies.

ICD-9CM CODES
334.8 Ataxia telangiectasia
ICD-10CM CODES
G11.3 Cerebellar ataxia with defective DNA repair

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1/40,000 live births; it is estimated that 1.4% to 2% of whites in the United States carry one defective AT gene.
PEAK INCIDENCE: Childhood
PREDOMINANT SEX: Males and females are equally affected.
GENETICS: Condition is autosomal recessive and progressive. The defective gene, designated *ATM* (for AT Mutated), has been mapped to chromosome 11q22.3. The gene product, which is expressed in all tissues, encodes a large protein that is a member of the phosphatidylinositol-3 kinases and another region similar to DNA repair genes.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Children show normal early development until they start to walk, when gait and truncal ataxia become apparent. This is followed by the development of polyneuropathy, progressive apraxia of eye movements and slurred speech, choreoathetosis, mild diabetes mellitus, delayed physical and sexual development, and signs of premature aging (graying of the hair).
- Children with AT experience deterioration of motor skills; by the second decade of life, most patients rely on wheelchairs for at least part of the day. Progressive oromotor difficulties also develop over time, placing patients at risk for aspiration.
- Telangiectasias appear when the child reaches 3 to 5 yr of life, occur primarily in the bulbar conjunctivae, over the surface of the ears and cheeks, in the corners of the eyes, on exposed parts of the neck, on the bridge of the nose, and in the flexor creases of the forearms. Sometimes a delay or absence of the appearance of telangiectasias results in a delayed diagnosis. Children with AT may also have café-au-lait macules, hypopigmented macules, or melanocytic nevi.
- Immunodeficiencies occur in 60% to 80% of individuals with AT. Impaired humoral and cellular immunity lead to recurrent sinopulmonary infections.
- Malignancy: Beyond 10 yr of age, incidence rate is 1% per yr; overall risk rate is approximately 10% to 20%, of which 85% of cases are leukemia and lymphoma. Predisposition to other cancers (such as breast cancer) may also exist, which is thought to be due to the phosphorylation of the tumor-suppressor/breast cancer susceptibility gene *BRCA1* by *ATM.*
- Typically, individuals with AT have normal intelligence. Deterioration of speech is typically noted after the age of 5 to 8 yr. Slow motor and verbal responses may make traditional timed assessments inaccurate.
- Up to 2% of the U.S. population may be carriers of AT. Heterozygote/carriers of the *ATM* gene are thought to have none of the classic manifestations of AT; however, they may have a greater incidence of malignancy at a younger age.

FIGURE EA1-130 Ataxia telangiectasia. (From Callen JP [ed]: *Color atlas of dermatology,* ed 2, Philadelphia, 2000, Saunders.)

ETIOLOGY

- Cytogenetics show a 7;14 translocation in 5% to 15% of individuals with AT. Cloning and sequencing has identified the *ATM* gene (for ataxia telangiectasia, mutated, mapped to chromosome 11q22.3), which is a protein kinase that is missing or defective. This delays accumulation of the tumor-suppressor p53 in response to DNA damage, thereby increasing the risk for cancer. Cells are susceptible to damage by ionizing radiation or chemotherapeutic agents that cause double-stranded DNA breakages (also see genetics section).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Early-onset ataxia:
- Friedreich's ataxia
- Abetalipoproteinemia (Bassen-Kornzweig syndrome)
- Acquired vitamin E deficiency
- Early-onset cerebellar ataxia with retained reflexes (EOCA)
- Ataxia-ocular apraxia type 1 (AOA1)
- Ataxia-ocular apraxia type 2 (AOA2)
- Ataxia telangiectasia-like disorder (ATLD)

WORKUP

Diagnosis relies on the constellation of clinical findings, including ataxia and speech changes, as well as family history and neuroimaging studies.

LABORATORY TESTS

- Serum immunoglobulin levels (IgA, IgG, IgE, and IgG subclasses) should be measured to evaluate for immunoglobulin deficiency and oligoclonal gammopathy.
- Serum α-fetoprotein is increased in more than 95% of patients with AT over the age of 8 mo.
- Prenatal testing is available. Fibroblasts can be screened for abnormal sensitivity to ionizing radiation.
- Immunoblotting for ATM protein can be done. This determines whether ATM protein is present in cells; approximately 90% of individuals will have no detectable ATM protein.

IMAGING STUDIES

CT or MRI scans will show cerebellar atrophy but may not be obvious in very young children.

TREATMENT

- No proven disease-specific treatment is currently available. Treatment is focused on amelioration of disease manifestations.
- Surveillance for infections and neoplasms is necessary. Individuals with frequent and severe infections may benefit from intravenous immunoglobulin. Children should be immunized with pneumococcal and influenza vaccines.
- The cloning and sequencing of the gene for AT have opened several avenues for intervention, including gene therapy, targeted pharmacologic intervention to correct the function of the altered protein, and direct replacement of the functional protein.

NONPHARMACOLOGIC THERAPY

- Minimize radiation as it may induce further chromosomal damage and lead to neoplasms. Even diagnostic x-rays should be limited because of the theoretical risk that radiation may lead to chromosomal breakages.
- Monitor swallowing as needed to evaluate for aspiration.
- Physical and occupational therapy to maintain flexibility and minimize contractures.

COMPLEMENTARY & ALTERNATIVE MEDICINE

- Antioxidant treatment with vitamin E is often given empirically, though it has not been formally tested. α-Lipoic acid crosses the blood-brain barrier and may, therefore, have some advantage.

DISPOSITION

- AT has a poor prognosis given the multisystem involvement; however, the expected life span has increased considerably. Most individuals now live beyond 25 yr of age and some into the fourth and fifth decades of life.

REFERRAL

- Immunology
- Neurology
- Gastroenterology and nutrition
- Physical and occupational therapy
- Genetic counselor

PEARLS & CONSIDERATIONS

COMMENTS

- Most common cause of hereditary ataxia
- Defect in DNA repair
- Predisposition to frequent infections, malignancies, and sensitivity to ionizing radiation

PATIENT/FAMILY EDUCATION

Ataxia Telangiectasia Children's Project: www.atcp.org
National Ataxia Foundation (NAF): www.ataxia.org

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fig. 3-25 Ataxia, progressive (Algorithm)

AUTHOR: **NICOLE J. ULLRICH, M.D., PH.D.**

SUGGESTED READINGS

Butch AW et al.: Immunoassay to measure ataxia-telangiectasia mutated protein in cellular lysates, *Clin Chem* 50:2302–2308, 2004.
Crawford TO et al.: Survival probability in ataxia telangiectasia, *Arch Dis Child* 91:610, 2006.
Gatti RA et al.: Localization of an ataxia-telangiectasia gene to chromosome 11q22-23, *Nature* 336:577, 1988.
McKinnon PJ: ATM and ataxia telangiectasia, *EMBO. Rep* 5(8):772–776, 2004.
Nowak-Wegrzyn A: Immunodeficiency and infections in ataxia-telangiectasia, *J Pediatr* 144:505, 2004.
Renwick A, Thompson D, Seal S et al.: ATM mutations that cause ataxia-telangiectasia are breast cancer susceptibility alleles, *Nat Genet* 38:873, 2006.
Sun X et al.: Early diagnosis of ataxia-telangiectasia using radiosensitivity testing, *J Pediatr* 140:724–731, 2002.
Swift M et al.: The incidence and gene frequency of ataxia-telangiectasia in the United States, *Am J Hum Genet* 39:573–583, 1986.
Taylor AMR, Byrd PJ: Molecular pathology of ataxia telangiectasia, *J Clin Pathol* 58(10):1009–1015, 2005.

BASIC INFORMATION

DEFINITION

Atelectasis is the collapse of lung volume.

ICD-9CM CODES
518.0 Atelectasis
ICD-10CM CODES
J98.11 Atelectasis

EPIDEMIOLOGY & DEMOGRAPHICS

- Occurs frequently in patients receiving mechanical ventilation with higher Fio_2
- Dependent regions of the lung are more prone to atelectasis: they are partially compressed, they are not as well ventilated, and there is no spontaneous drainage of secretions with gravity

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Decreased or absent breath sounds
- Abnormal chest percussion
- Cough, dyspnea, decreased vocal fremitus and vocal resonance
- Diminished chest expansion, tachypnea, tachycardia

ETIOLOGY

- Mechanical ventilation with higher Fio_2
- Chronic bronchitis
- Cystic fibrosis
- Endobronchial neoplasms
- Foreign bodies
- Infections (e.g., TB, histoplasmosis)
- Extrinsic bronchial compression from neoplasms, aneurysms of ascending aorta, enlarged left atrium
- Sarcoidosis
- Silicosis
- Anterior chest wall injury, pneumothorax
- Alveolar injury (e.g., toxic fumes, aspiration of gastric contents)
- Pleural effusion, expanding bullae
- Chest wall deformity (e.g., scoliosis)
- Muscular weaknesses or abnormalities (e.g., neuromuscular disease)
- Mucus plugs from asthma, allergic bronchopulmonary aspergillosis, postoperative state

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Neoplasm
- Pneumonia
- Encapsulated pleural effusion
- Abnormalities of brachiocephalic vein and the left pulmonary ligament

WORKUP

- Chest x-ray (Fig. A1-131)
- CT scan and fiberoptic bronchoscopy (selected patients)

IMAGING STUDIES

- Chest radiograph will confirm diagnosis.
- CT scan is useful in patients with suspected endobronchial neoplasm or extrinsic bronchial compression.
- Fiberoptic bronchoscopy (selected patients) is useful for removal of foreign body or evaluation of endobronchial and peribronchial lesions.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Deep breathing, mobilization of the patient
- Incentive spirometry
- Tracheal suctioning
- Humidification
- Chest physiotherapy with percussion and postural drainage

ACUTE GENERAL Rx

- Positive-pressure breathing (continuous positive airway pressure by face mask, positive end-expiratory pressure for patients on mechanical ventilation)
- Use of mucolytic agents (e.g., acetylcysteine [Mucomyst])
- Recombinant human DNase (dornase alpha) in patients with cystic fibrosis
- Bronchodilator therapy in selected patients

CHRONIC Rx

- Chest physiotherapy
- Humidification of inspired air
- Frequent nasotracheal suctioning

DISPOSITION

Prognosis varies with the underlying etiology

REFERRAL

- Bronchoscopy for removal of foreign body or plugs unresponsive to conservative treatment
- Surgical referral for removal of obstructing neoplasms

PEARLS & CONSIDERATIONS

COMMENTS

Patients should be educated that frequent changes of position are helpful in clearing secretions. Sitting the patient upright in a chair is recommended to increase both volume and vital capacity relative to the supine position.

RELATED CONTENT

Atelectasis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

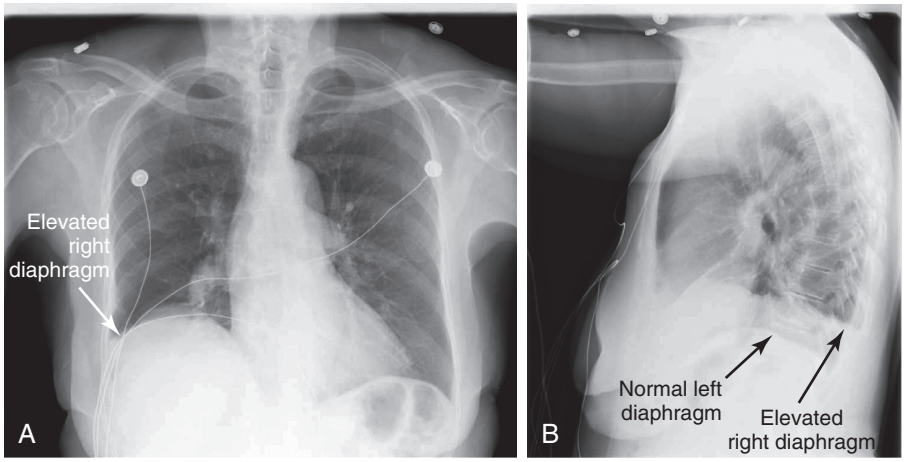


FIGURE A1-131 Atelectasis with elevated diaphragm: an example of volume loss. The right hemidiaphragm in this patient appears elevated on both the posterior-anterior **(A)** and the lateral **(B)** views. Is this the correct interpretation of the x-ray, and if so, what is the cause? Consider the alternative interpretations. A subpulmonic pleural effusion would appear similar, as it would have the same density as liver, heart, and diaphragm and would layer over the diaphragm with the patient upright. This appears less likely in that a meniscus might be seen along the lateral chest wall with a pleural effusion but is not present here. In addition, a pleural effusion occupies space and might be expected to push the heart to the left, whereas in this case the heart may be slightly deviated to the right. Atelectasis of the lower right lung would result in volume loss, pulling the heart and hemidiaphragm into the space normally occupied by lung. This is consistent with the observed features. An infiltrate in this location could explain the x-ray findings but appears less likely for similar reasons to those cited for effusion. Some simple maneuvers could narrow the differential diagnosis. Chest ultrasound, decubitus x-ray views, or CT could identify an effusion. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

Atopic Dermatitis PTG

BASIC INFORMATION

DEFINITION

Atopic dermatitis is a genetically determined eczematous eruption that is pruritic, symmetric, and associated with personal family history of allergic manifestations (atopy).

SYNONYMS

Eczema
Atopic neurodermatitis
Atopic eczema

ICD-9CM CODES
691.8 Atopic dermatitis
ICD-10CM CODES
L20.89 Other atopic dermatitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence is between 5 and 25 cases/1000 persons.
- Highest incidence is among children (10% to 20%). It accounts for 4% of acute care pediatric visits. It affects 1% to 3% of the adult population.
- Onset of disease before age 5 yr in 85% of patients.
- More than 50% of children with generalized atopic dermatitis develop asthma and allergic rhinitis by age 13 yr.
- Concordance in monozygotic twins is 77%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Atopic dermatitis presentation can be subdivided into three phases:
  1. Acute: vesicular, crusting, weeping eruption
  2. Subacute: dry, scaly, erythematous papules and plaques
  3. Chronic: lichenification from repeated scratching
- The lesions are typically on the neck, face, upper trunk, and bends of elbows and knees (symmetric on flexural surfaces of extremities) (Fig. EA1-132). Atopic dermatitis lesions are usually discrete but vaguely delineated, scaly, and erythematous.
- There is dryness, thickening of the involved areas, discoloration, blistering, and oozing.
- Papular lesions are frequently found in the antecubital and popliteal fossae.
- In children, red scaling plaques are often confined to the cheeks and the perioral and perinasal areas.
- Inflammation in the flexural areas and lichenified skin is a very common presentation in children.
- Constant scratching may result in areas of hypopigmentation or hyperpigmentation (more common in blacks).
- In adults, redness and scaling in the dorsal aspect of the hands or about the fingers are the most common expression of atopic dermatitis; oozing and crusting may be present.
- Secondary skin infections may be present (*Staphylococcus aureus,* dermatophytosis, herpes simplex).

ETIOLOGY

Unknown; elevated T-lymphocyte activation, defective cell immunity, and B-cell IgE overproduction may play a significant role.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Scabies
- Psoriasis
- Dermatitis herpetiform
- Contact dermatitis
- Photosensitivity
- Seborrheic dermatitis
- Candidiasis, tinea
- Lichen simplex chronicus
- Other: xerosis, impetigo, Wiskott-Aldrich syndrome, PKU, ichthyosis, HIV dermatitis, nonnummular eczema, histiocytosis X, malignancies (T-cell lymphoma/Mycosis fungoides, Letterer-Siwe disease), graft-versus-host disease, metabolic and nutritional deficiencies (zinc, niacin, pyridoxine deficiencies)

WORKUP

Diagnosis is based on the presence of three of the following major features and three minor features.

MAJOR FEATURES
- Pruritus
- Personal or family history of atopy: asthma, allergic rhinitis, atopic dermatitis
- Facial and extensor involvement in infants and children
- Flexural lichenification in adults

MINOR FEATURES
- Elevated IgE
- Eczema-perifollicular accentuation
- Recurrent conjunctivitis
- Ichthyosis
- Nipple dermatitis
- Wool intolerance
- Cutaneous *S. aureus* infections or herpes simplex infections
- Food intolerance
- Hand dermatitis (nonallergic irritant)
- Facial pallor, facial erythema
- Cheilitis
- White dermographism
- Early age of onset (after 2 mo of age)

LABORATORY TESTS

- Lab tests are generally not helpful.
- Elevated IgE levels are found in 80% to 90% of atopic dermatitis.
- Consider skin biopsy only in cases unresponsive to treatment.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Clip nails to decrease abrasion of skin
  Avoidance of triggering factors:
- Sudden temperature changes, sweating, low humidity in the winter
- Contact with irritating substance (e.g., wool, cosmetics, some soaps and detergents, tobacco)
- Foods that provoke exacerbations (e.g., eggs, peanuts, fish, soy, wheat, milk)
- Stressful situations
- Allergens and dust
- Excessive hand washing

GENERAL Rx

- Emollients can be used to prevent dryness. Severely affected skin can be optimally hydrated by occlusion in addition to application of emollients.
- Low-potency topical corticosteroids (e.g., 1% to 2.5% hydrocortisone) may be helpful and are generally considered first-line therapy. Use intermediate-potency steroids (e.g., triamcinolone, fluocinolone) for more severe cases and limit potent corticosteroids (e.g., betamethasone, desoximetasone, clobetasol) to severe cases.
- Oral antihistamines (e.g., hydroxyzine, diphenhydramine) are effective in controlling pruritus and inducing sedation, restful sleep, and prevention of scratching during sleep. Doxepin and other tricyclic antidepressants also have antihistamine effect, induce sleep, and reduce pruritus.
- The topical immunomodulators pimecrolimus and tacrolimus are especially useful for treatment of the face and intertriginous sites, where steroid-induced atrophy may occur. However, due to concerns about carcinogenic potential, the FDA recommends limiting their use for short periods in patients who are intolerant or unresponsive to other treatments. Pimecrolimus cream 1% is applied bid and has antiinflammatory effects secondary to blockage of activated T-cell cytokine production. Tacrolimus ointment (0.03% or 0.1%) applied bid is a macrolide that suppresses humoral and cell-mediated immune responses.
- Oral prednisone, IM triamcinolone, Goeckerman regimen, PUVA are generally reserved for severe cases.
- Cyclosporine, azathioprine, mycophenolate, and interferon gamma are sometimes tried for recalcitrant disease in adults by physicians who specialize in severe inflammatory skin conditions.

Clinical trials have shown that the human monoclonal antibody dupilumab is effective in adults with moderate to severe atopic dermatitis.

DISPOSITION

- Resolution occurs in approximately 70% of patients by adulthood.
- Most patients have a course characterized by remissions and intermittent flares.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Dermatitis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Beck LA et al.: Dupilumab treatment in adults with moderate to severe atopic dermatitis, *N Engl J Med* 371:130–139, 2014.
Berke R et al.: Atopic dermatitis: an overview, *Am Fam Physician* 86:35–42, 2012.
Bershad SV: In the clinic: atopic dermatitis (eczema), *Ann Intern Med* 155, 2011. ITC 5–1.
Bieber T: Atopic dermatitis, *N Engl J Med* 358:1483–1494, 2008.
Buys LM: Treatment options for atopic dermatitis, *Am Fam Physician* 75:523–528, 2007.
Wasserbauer N, Ballow M: Atopic dermatitis, *Am J Med* 122(2):120–125, 2009.

FIGURE EA1-132 A, Flexural atopic dermatitis with lichenification. Many of the skin changes are secondary to scratching. Linear lichenification, as shown here, and excoriations are typical. **B,** Hertoghe sign: loss of the outer eyebrow may occur in the atopic patient as a result of chronic rubbing. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

BASIC INFORMATION

DEFINITION

Atrial fibrillation (AF) is a supraventricular tachyarrhythmia characterized by disorganized and rapid atrial activation and uncoordinated atrial contraction. AF occurs when structural and/or electrophysiologic abnormalities alter atrial tissue to promote abnormal impulse formation and/or propagation. The ventricular rate is dependent on the conduction properties of the atrioventricular node, which can be influenced by vagal/sympathetic tone, medications, or disease of the atrioventricular node.

Multiple classification schemes have been used in the past to characterize AF. The current classification scheme (divided into three major types) used by the ACC/AHA guideline committee is as follows:

- Paroxysmal AF—more than one episode of AF that terminate spontaneously within 7 days (most episodes last less than 24 hr)
- Persistent AF—episodes of AF that last longer than 7 days and may require either pharmacologic or electrical intervention to terminate
- Permanent AF—AF that has persisted for longer than 1 yr, either because cardioversion has failed or because cardioversion has not been attempted
- In addition to the previous AF categories, which are mainly defined by episode timing and termination, the ACC/AHA/ESC guidelines describe additional AF categories in terms of other characteristics of the patient:
- Lone atrial fibrillation (LAF)—generally refers to AF in younger patients (<60 yr old) who have normal echocardiographic findings
- Nonvalvular AF—absence of rheumatic mitral valve disease, a prosthetic heart valve, or mitral valve repair
- Secondary AF—occurs in the setting of a primary condition that may be the cause of the AF, such as acute myocardial infarction, cardiac surgery, pericarditis, myocarditis, hyperthyroidism, pulmonary embolism, pneumonia, or other acute disease. It is considered separately because AF is less likely to recur once the precipitating condition has resolved.

SYNONYMS

AF
PAF

ICD-9CM CODES
427.31 Atrial fibrillation
ICD-10CM CODES
I48 Atrial fibrillation and flutter

EPIDEMIOLOGY & DEMOGRAPHICS

- The prevalence of AF increases with age, from 0.1% in adults >55 yr to 9% of those >80 yr.
- AF affects 2.7 million people in the United States. AF is uncommon in infants and children and, when present, almost always occurs in association with structural heart disease.
- The incidence of AF is significantly higher in men than in women in all age groups (1.1% versus 0.8%). AF appears to be more common in whites than in blacks, who may have lower awareness of the disease.
- Stroke due to thromboembolism is the most common and dreaded complication of AF. The rate of ischemic stroke in patients with non-rheumatic AF averages 5% a year, which is somewhere between two and seven times the rate of stroke in patients without AF. The risk of stroke is not due solely to AF; it increases substantially in the presence of other cardiovascular diseases. The attributable risk of stroke from AF is estimated to be 1.5% for those aged 50 to 59 yr, and it approaches 36% for those aged 80 to 89 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Clinical presentation is variable:

- Palpitations, dizziness, or lightheadedness
- Fatigue, weakness, or impaired exercise tolerance
- Angina
- Dyspnea
- Some patients are asymptomatic
- Cardiac auscultation revealing irregularly irregular rhythm
- Thromboembolic phenomenon such as stroke

ETIOLOGY

- The most frequent change in AF is the loss of atrial muscle mass and atrial fibrosis.
- Fibrillation is caused by multiple wandering wavelets, usually originating from the pulmonary veins. Both reentrant and focal mechanisms have been proposed.
- Vascular causes: hypertensive heart disease
- Valvular heart disease
- Pulmonary causes: pulmonary embolism, chronic obstructive pulmonary disease, obstructive sleep apnea, carbon monoxide poisoning
- Structural cardiac disease: hypertrophic cardiomyopathy, congestive heart failure, coronary artery disease, myocardial infarction, congenital heart disease (especially those that lead to atrial enlargement such as atrial septal defect)
- Pericarditis and myocarditis
- Arrhythmias: atrial tachycardias and atrial flutters have been associated with atrial fibrillation, as has Wolff-Parkinson-White syndrome
- Endocrine: thyrotoxicosis, hyperthyroidism or subclinical hyperthyroidism, pheochromocytoma, obesity
- Surgery: both cardiac and noncardiac
- Electrolytes: hypokalemia, hypomagnesemia
- Systemic stress: fever, anemia, hypoxia, sepsis, infections (e.g., pneumonia)
- Medications/toxins: digitalis, adenosine, theophylline, amphetamines, cocaine, antihistamines, alcohol abuse and/or withdrawal, caffeine, steroidal anti-inflammatory drugs (SAIDs), nonsteroidal anti-inflammatory drugs (NSAIDs)
- Frequency of vigorous exercise is associated with an increased risk of developing AF in young men and joggers
- Porphyrias have been associated with autonomic dysfunction and increased risk of AF
- Patients with metabolic syndrome, excessive vitamin D intake, or excessive niacin intake have a higher risk of AF

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Multifocal atrial tachycardia
- Atrial flutter
- Frequent atrial premature beats
- Atrial tachycardia
- Atrioventricular nodal reentry tachycardia (AVNRT)
- Wolff-Parkinson-White syndrome

WORKUP

The evaluation of atrial fibrillation involves diagnosis, determination of the etiology, and classification of the arrhythmia. A minimal evaluation includes a history and physical examination, ECG, transthoracic echocardiogram, and case-specific laboratory work to rule out secondary AF.

LABORATORY TESTS

- Thyroid-stimulating hormone, free T_4
- Serum electrolytes
- Toxicity screen
- CBC count (looking for anemia, infection)
- Cardiac enzymes—CK and/or troponin level (to investigate cardiomyopathies or myocarditis and myocardial infarction)
- BNP (to evaluate for CHF)
- D-dimer/CT scan of chest PE protocol (if the patient has risk factors to merit a pulmonary embolism workup)

IMAGING STUDIES

- ECG (Fig. A1-133)
- Absence of P waves
- Fibrillatory or f waves at the isoelectric baseline with varying amplitude, morphology, and intervals
- Irregular ventricular rate
- Echocardiography to rule out structural heart disease (evaluate ventricular size, thickness, and function, atrial size, pericardial disease, and valve function)
- Transesophageal echocardiography (TEE): helpful to evaluate for left atrial thrombus (particularly in the LA appendage) to guide cardioversion or ablation (if thrombus is seen, cardioversion should be delayed)
- CT and MRI: in patients with a positive D-dimer result, chest CT angiogram may be necessary to rule out pulmonary embolus. Three-dimensional imaging technologies (CT scan or MRI) are often helpful to evaluate atrial anatomy if AF ablation is planned

- Six-minute walk test or exercise test: six-minute walk or exercise testing can help assess the adequacy of rate control. Exercise testing can also exclude ischemia prior to treatment of patients with class Ic antiarrhythmic drugs and can be used to reproduce exercise-induced AF
- Holter monitor or event recorder if the diagnosis of AF is in question, such as in paroxysmal cases
- Electrophysiologic study to clarify the mechanism of wide QRS tachycardia with AF, such as in suspected Wolff-Parkinson-White syndrome

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of alcohol in patients with suspected excessive alcohol use
- Avoidance of caffeine and nicotine
- Treatment of underlying source/cause, if any found
- The Cox-Maze III surgical procedure, with its recent modifications creating electrical barriers to the macroreentrant circuits that are believed to underlie AF, is being performed with good results in several medical centers (preservation of sinus rhythm in 70% to 95% of patients without the use of long-term antiarrhythmic medication). Success rates are higher in paroxysmal than in persistent or permanent atrial fibrillation. It is important to understand that ablation therapy will not eliminate the need to take anticoagulant drugs. Even after ablation, patients with AF face increased risk of thromboembolic events and most electrophysiologists suggest lifelong anticoagulation. Due the increasing success rate of ablation, catheter based therapy is now considered an acceptable first line alternative to cardioversion and pharmacologic management to *paroxysmal* atrial fibrillation in the most recent ACC/AHA Guidelines in 2014. It remains second line therapy for patients in persistent and permanent atrial fibrillation.
- Pulmonary vein ablation for chronic AF: Sinus rhythm can be maintained long term in the majority of patients with chronic AF by circumferential pulmonary vein ablation performed in experienced centers. Established centers have reported success rates of 70% to 85% in patients with paroxysmal AF, but most patients may require more than one ablation to achieve success. Success with persistent AF is much lower.
- Pulmonary vein isolation is being increasingly used to treat AF in patients with heart failure. Trials have shown that pulmonary vein isolation is superior to AV node ablation with biventricular pacing in patients with heart failure who have drug-refractory AF.

ACUTE GENERAL Rx

New-onset AF:

- If the patient is hemodynamically unstable (hypotension, congestive heart failure or angina), perform synchronized cardioversion after immediate conscious sedation with a rapid short-acting sedative (e.g., midazolam). The likelihood of cardioversion-related clinical thromboembolism is low in patients with AF lasting <48 hr. Patients with AF lasting >2 days have a 5% to 7% risk for clinical thromboembolism if cardioversion is not preceded by several weeks of anticoagulation therapy. However, if transesophageal echocardiography reveals no atrial thrombus, cardioversion may be performed safely once therapeutic anticoagulation has been achieved. Alternatively, patients can be safely anticoagulated for approximately 1 mo and then undergo cardioversion without transesophageal echocardiogram. Anticoagulant therapy should be continued for at least 1 mo after cardioversion to minimize the incidence of adverse thromboembolic events. It can be stopped after 1 mo as long as AF has not recurred.
- If the patient is hemodynamically stable, a rate-control strategy is typically pursued initially.
- Treatment options for rate control include the following:
  1. Diltiazem 0.25 mg/kg (maximum of 25 mg) given intravenously (IV) over 2 min followed by a second dose of 0.35 mg/kg (maximum of 25 mg) 15 min later if the rate is not slowed to <100 beats/min. May then follow with IV infusion 10 mg/hr (range, 5 to 15 mg/hr) to achieve a resting heart rate of <100 beats/min. Onset of action after IV administration is usually within 3 min, with peak effect most often occurring within 10 min. After the ventricular rate is slowed, the patient can be changed to oral diltiazem 60 to 90 mg q4 to 6h. High doses of calcium channel blockers can exacerbate heart failure and thus should be used with caution in patients presenting with symptoms of heart failure and/or depressed ejection fraction.
  2. Verapamil 2.5 to 5 mg IV initially, then 5 to 10 mg IV 10 min later if the rate is still not slowed to <100 beats/min. After the ventricular rate is slowed, the patient can be changed to oral verapamil 80 to 120 mg q6 to 8h. Main concern is hypotension and heart failure with this medication. Due to its poor safety profile, it is infrequently used.
  3. Esmolol, metoprolol, and atenolol are beta-blockers available in IV preparations that can be used in AF. High doses of β-blockers can have negative inotropic effects in heart failure and should be used with caution.
  4. Digoxin is not a potent atrioventricular nodal blocking agent, has a potential for toxicity and, therefore, cannot be relied on for acute control of the ventricular response but may be used in conjunction with β-blockers and calcium channel blockers. However, it is very useful in

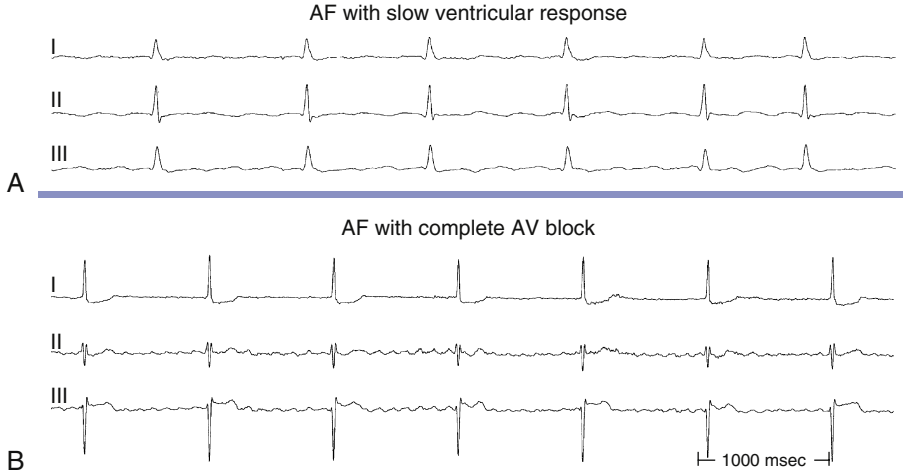


FIGURE A1-133 Atrial fibrillation (AF) with slow ventricular rate. A, The ventricular rhythm is irregular, indicating that it is the result of conducted atrial beats. **B,** The ventricular rhythm is regular, consistent with the presence of complete atrioventricular *(AV)* block and a regular junctional escape rhythm. (From Issa Z et al: *Clinical arrhythmology and electrophysiology,* ed 2, Philadelphia.)

the hypotensive or heart failure patient, which is not infrequent. When used, give 0.5 mg IV loading dose (slow), then 0.25 mg IV 6 hr later. A third dose may be needed after 6 to 8 hr; daily dose varies from 0.125 to 0.25 mg (decrease dosage in patients with renal insufficiency and elderly patients) depending on the heart rate and signs/symptoms of digoxin toxicity. Toxicity is manifested by GI and visual complaints, atrial tachyarrhythmias, heart block, and ventricular tachycardia.

5. Amiodarone has a class IIa recommendation from the ACC/AHA/ESC for use as a rate-controlling agent for patients who are intolerant of or unresponsive to other agents, such as patients with heart failure who may otherwise not tolerate diltiazem or metoprolol. Caution should be exercised in those who are not receiving anticoagulation because amiodarone can promote cardioversion, thereby posing a thromboembolic risk.

- All atrioventricular nodal blocking agents should be avoided in patients with Wolff-Parkinson-White syndrome and AF because, by blocking the AV node, AF impulses may be transmitted exclusively down the accessory pathway, which can result in ventricular fibrillation. If this happens, the patient will require immediate defibrillation. Procainamide, flecainide, or amiodarone can be used instead if Wolff-Parkinson-White syndrome is suspected.
- In the acute setting, pharmacologic cardioversion (e.g., ibutilide, dofetilide) is less commonly used than electrical cardioversion. A major disadvantage with pharmacologic cardioversion is the risk of development of ventricular tachycardia and other serious arrhythmias, especially due to acute prolongation of the QT interval.

CHRONIC Rx

- Per the AFFIRM and RACE trials, either rate control or rhythm control strategies show no difference in composite cardiovascular end points of death, CHF, bleeding, drug side effects, or thromboembolism. Both approaches have similar outcomes as long as appropriate anticoagulation is maintained based on the individual's stroke risk.
- For patients without symptomatic AF, rate-control strategy with calcium channel blockers, beta-blockers, or digoxin is a reasonable option. RACE 2 trial indicates that a lenient rate control strategy, with a target resting heart rate of <110 beats/min is noninferior for a composite primary end point that included CV death, heart-failure hospitalization, stroke, and other major events over a median 3-yr follow-up as compared to a strict control strategy, with a target resting heart rate of <80 beats/min and an exercise heart rate of <110 beats/min. Most recent ACC/AHA guidelines however, recommend targeting a HR <80 bpm over a target of <110 bpm.
- AV nodal ablation with permanent pacemaker implantation may become necessary in some patients in whom rate is difficult to control despite drugs and cardioversion, though it is generally used as a therapy of last resort.
- In patients with symptomatic AF, younger patients, or those with difficult to control heart rate, attempt should be made to maintain sinus rhythm with antiarrhythmic agents. Options of antiarrhythmic agents include amiodarone, dronedarone, (paroxysmal atrial fibrillation only without heart failure), dofetilide, flecainide, propafenone (contraindicated with structural heart disease), procainamide, or sotalol. The decision of which strategy to follow should be best made in consultation with cardiology. Use of dronedarone should be avoided in patients with persistent and/or permanent atrial fibrillation due to worsened cardiovascular outcomes, especially in those with concomitant symptomatic heart failure (See Fig. A1-134 for proposed algorithm to guide maintenance of sinus rhythm).
- The decision whether to pursue long-term anticoagulation must be made in light of the patient's risk for a cardioembolic event versus risk for a bleeding event. The CHA2DS2-VASc has superseded the CHADS2 scoring system (C = congestive heart failure; H = hypertension; A = age (>75 years is 2 points); D = diabetes; S = stroke, transient ischemic attack, or thromboembolic disease (2 points); V = vascular disease, A = age 65-74 years; and Sc = sex category, with females getting 1 extra point). Patients with

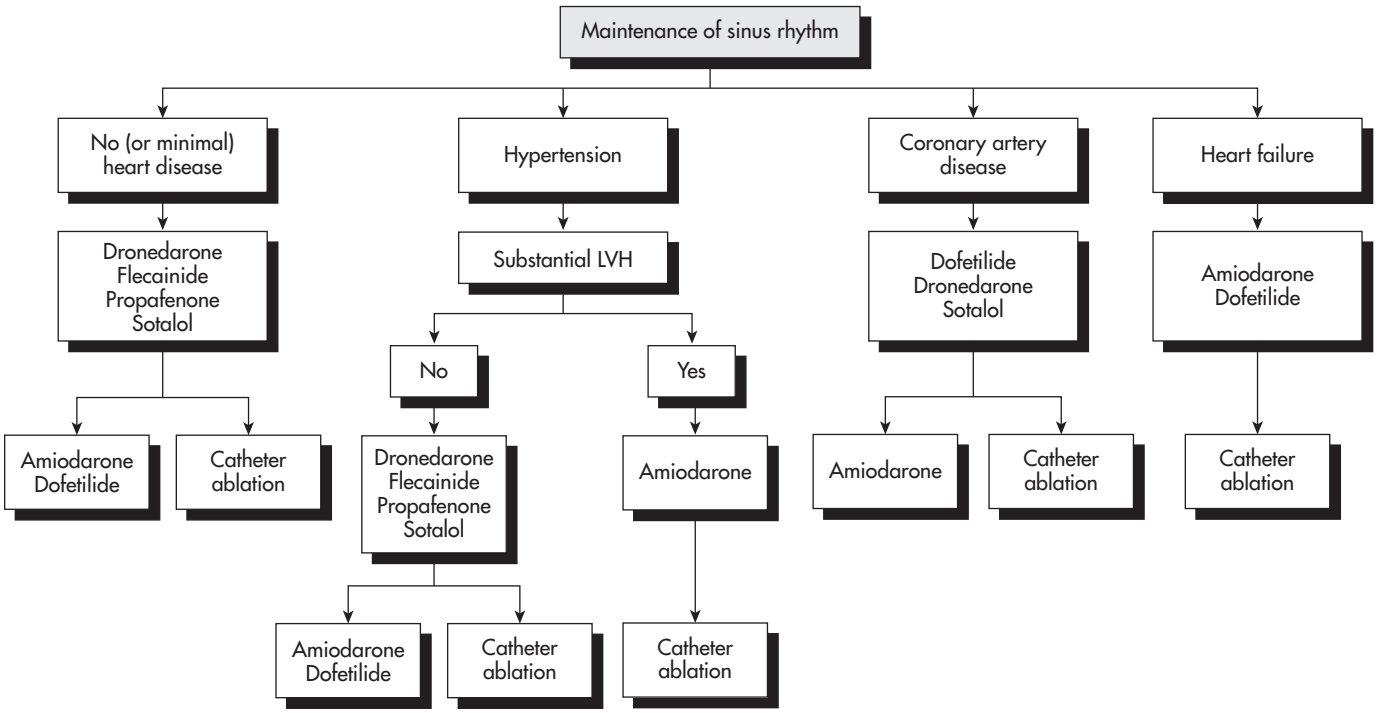


FIGURE A1-134 Therapy to maintain sinus rhythm in patients with recurrent paroxysmal or persistent atrial fibrillation. Drugs are listed alphabetically and not in order of suggested use. The seriousness of heart disease progresses from left to right, and selection of therapy in patients with multiple conditions depends on the most serious condition present. *LVH,* Left ventricular hypertrophy. (From 2011 ACCF/AHA/HRS Focused Update on the Management of Patients With Atrial Fibrillation [Updating the 2006 Guideline]: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 57[2]:223-242, 2011.)

a CHA2DS2-VASc score of 0 are considered low risk, 1 to 2 are considered moderate risk, and >2 are considered high risk. Per guidelines, patients with a score of 0 do not merit anticoagulation. Patients with a score of 1 can be treated at the discretion of the physician with either aspirin or an oral anticoagulant (warfarin versus a novel oral anticoagulant), Anticoagulation with either warfarin or a novel oral anticoagulant is recommended for all patients with a CHADS2VASC score of 2 or above.

- Increasing amounts of evidence now show that aspirin likely does not protect a person from stroke in AF and has recently been dropped from most of the ACC/AHA and European Atrial Fibrillation guidelines. Target INR for patients with a CHADS-VASc score of >1 is 2 to 3 and should be diligently monitored to avoid risk of stroke versus bleeding. Patients with hypertrophic cardiomyopathy or thyrotoxicosis with AF also have a high risk of stroke and should be anticoagulated irrespective of their CHADS-VASc score.
- Alternatives to warfarin now include several factor Xa inhibitors and a direct thrombin inhibitor.
  1. Dabigatran is an FDA-approved direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. In the RE-LY trial, 18,113 patients with nonvalvular AF and at least one risk factor for stroke (mean CHADS2 score 2.1) were randomly assigned to receive oral dabigatran at one of two doses (110 or 150 mg) twice daily, or adjusted-dose warfarin. After a median follow-up of 2 yr, the rate of the primary efficacy outcome of stroke (including hemorrhagic stroke) or systemic embolism was 1.54%, 1.11%, and 1.71% per year in the dabigatran 110 mg, dabigatran 150 mg, and warfarin groups, respectively. Dabigatran 110 mg was noninferior compared to adjusted-dose warfarin, whereas dabigatran 150 mg was significantly more effective than warfarin. In patients <75 yr, lower risks of both intracranial and extracranial bleeding were found in both doses of dabigatran compared with warfarin. In patients >75 yr, intracranial bleeding risk is lower, but extracranial bleeding risk is similar or higher with both doses of dabigatran when compared with warfarin. No monitoring is generally required for dabigatran unless risk of renal insufficiency exists where dose adjustment is needed. Disadvantages include twice-daily dosing, the need for consistent timing of doses because of its 10-12 hour half-life and lack of an antidote.
- Factor Xa inhibitors (apixaban, rivaroxaban) are also effective in reducing stroke and systemic embolism in patients with atrial fibrillation. The ARISTOTLE trial in patients at high risk for stroke (mean CHADS2 score 2.1) using apixaban and the ROCKET AF trial using rivaroxaban in patients with CHADS2 score 3.5 showed that these anticoagulants reduce the risk of stroke, systemic embolism, and serious bleeding compared with warfarin. Rivaroxaban showed noninferior efficacy to warfarin and apixaban showed superior stroke reduction and an overall mortality benefit. Rivaroxaban is dosed once a day and apixaban is dosed twice a day. Edoxaban is a fourth agent that has not been approved yet, although clinical trials appear promising for its higher daily dosed regimen.
- The decision to anticoagulate should be made irrespective of whether the atrial fibrillation is paroxysmal, persistent or permanent.
- For patients in whom anticoagulation with warfarin or other anticoagulants is contraindicated due to high bleeding risk, left atrial appendage exclusion either by Watchman device or Lariat device is a promising solution that is still being studied and not yet available in the United States.

PROGNOSIS

- AF is associated with a 1.5- to 1.9-fold higher risk of death, which is in part due to the strong association between AF and thromboembolic events.
- AF is also independently associated with an increased risk of incident MI, especially in women and blacks.[1]
- Development of AF predicts heart failure and is associated with a worse New York Heart Association Heart Failure classification. AF may also worsen heart failure in individuals who are dependent on the atrial component of the cardiac output.
- AF in the setting of acute myocardial infarction was associated with a 40% increase in mortality compared to patients in sinus rhythm.

DISPOSITION

Factors associated with maintenance of sinus rhythm after cardioversion include:

- Left atrium diameter <60 mm
- Absence of mitral valve disease
- Short duration of AF

REFERRAL

Refer to a cardiologist those patients in whom antiarrhythmic therapy or catheter-based/surgical intervention is being considered.

PEARLS & CONSIDERATIONS

COMMENTS

The number of patients anticoagulated in the United States is approximately half the amount that should be anticoagulated for AF, resulting in a large burden of stroke. The exact burden of AF needed to trigger the need for anticoagulation is not known, though recent pacemaker trials have suggested that as little as 6 min confers significant stroke risk. Reversal agents for the new class of anticoagulation are in development.

The American Academy of Family Physicians and the American College of Physicians provide the following recommendations for the management of newly detected AF:

- Rate control with chronic anticoagulation is the recommended strategy for the majority of asymptomatic patients with chronic AF. Rhythm control has not been shown to be superior to rate control (with chronic anticoagulation) in reducing morbidity and mortality, and may be inferior in some patient subgroups to rate control. Rhythm control is appropriate when based on other special considerations, such as patient symptoms, exercise tolerance, and patient preference.
- Patients with AF should receive chronic anticoagulation, unless they are at low risk for stroke as stated earlier or have specific contraindications.
- For patients with AF, the following drugs are recommended for their demonstrated efficacy in rate control during exercise and while at rest: atenolol, metoprolol, diltiazem, and verapamil (drugs listed alphabetically by class). Digoxin is effective only for rate control at rest and, therefore, should be used only as a second-line agent for rate control in AF.
- For patients who elect to undergo acute cardioversion to achieve sinus rhythm in AF, both direct-current cardioversion and pharmacologic conversion are appropriate options in an otherwise healthy patient.
- Both transesophageal echocardiography with short-term prior anticoagulation followed by early acute cardioversion (in absence of intracardiac thrombus) with postcardioversion anticoagulation vs. delayed cardioversion with preanticoagulation and postanticoagulation are appropriate management strategies for patients who elect to undergo cardioversion.
- Among patients with paroxysmal AF without previous antiarrhythmic drug treatment, ablation compared with antiarrhythmic drugs resulted in a lower rate of recurrent atrial tachyarrhythmias at 2 years. However, recurrence was frequent in both groups.[2]

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Atrial Fibrillation (Patient Information)

AUTHOR: **BARRY FINE, M.D., Ph.D.**

[1]Soliman EZ et al: Atrial fibrillation and the risk of myocardial infarction, *JAMA Int Med* 174(1):107-113, 2014.

[2]Morillo CA et al: Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2), a randomized trial, *JAMA* 311(7):692-699, 2014.

EVIDENCE

Abstract[1]

Background:
Vitamin K antagonists have been shown to prevent stroke in patients with atrial fibrillation. However, many patients are not suitable candidates for or are unwilling to receive vitamin K antagonist therapy, and these patients have a high risk of stroke. Apixaban, a novel factor Xa inhibitor, may be an alternative treatment for such patients.
Methods:
In a double-blind study, we randomly assigned 5599 patients with atrial fibrillation who were at increased risk for stroke and for whom vitamin K antagonist therapy was unsuitable to receive apixaban (at a dose of 5 mg twice daily) or aspirin (81 to 324 mg per day), to determine whether apixaban was superior. The mean follow up period was 1.1 years. The primary outcome was the occurrence of stroke or systemic embolism.
Results:
Before enrollment, 40% of the patients had used a vitamin K antagonist. The data and safety monitoring board recommended early termination of the study because of a clear benefit in favor of apixaban. There were 51 primary outcome events (1.6% per year) among patients assigned to apixaban and 113 (3.7% per year) among those assigned to aspirin (hazard ratio with apixaban, 0.45; 95% confidence interval [CI], 0.32 to 0.62; P<0.001). The rates of death were 3.5% per year in the apixaban group and 4.4% per year in the aspirin group (hazard ratio, 0.79; 95% CI, 0.62 to 1.02; P=0.07). There were 44 cases of major bleeding (1.4% per year) in the apixaban group and 39 (1.2% per year) in the aspirin group (hazard ratio with apixaban, 1.13; 95% CI, 0.74 to 1.75; P=0.57); there were 11 cases of intracranial bleeding with apixaban and 13 with aspirin. The risk of a first hospitalization for cardiovascular causes was reduced with apixaban as compared with aspirin (12.6% per year vs. 15.9% per year, P<0.001). The treatment effects were consistent among important subgroups.
Conclusions:
In patients with atrial fibrillation for whom vitamin K antagonist therapy was unsuitable, apixaban reduced the risk of stroke or systemic embolism without significantly increasing the risk of major bleeding or intracranial hemorrhage. (Funded by Bristol-Myers Squibb and Pfizer; ClinicalTrials.gov number, NCT00496769.)Ⓐ

Abstract[2]

Background:
The use of warfarin reduces the rate of ischemic stroke in patients with atrial fibrillation but requires frequent monitoring and dose adjustment. Rivaroxaban, an oral factor Xa inhibitor, may provide more consistent and predictable anticoagulation than warfarin.
Methods:
In a double-blind trial, we randomly assigned 14,264 patients with nonvalvular atrial fibrillation who were at increased risk for stroke to receive either rivaroxaban (at a daily dose of 20 mg) or dose-adjusted warfarin. The per-protocol, as-treated primary analysis was designed to determine whether rivaroxaban was noninferior to warfarin for the primary end point of stroke or systemic embolism.
Results:
In the primary analysis, the primary end point occurred in 188 patients in the rivaroxaban group (1.7% per year) and in 241 in the warfarin group (2.2% per year) (hazard ratio in the rivaroxaban group, 0.79; 95% confidence interval [CI], 0.66 to 0.96; P<0.001 for noninferiority). In the intention-to-treat analysis, the primary end point occurred in 269 patients in the rivaroxaban group (2.1% per year) and in 306 patients in the warfarin group (2.4% per year) (hazard ratio, 0.88; 95% CI, 0.74 to 1.03; P<0.001 for noninferiority; P=0.12 for superiority). Major and nonmajor clinically relevant bleeding occurred in 1475 patients in the rivaroxaban group (14.9% per year) and in 1449 in the warfarin group (14.5% per year) (hazard ratio, 1.03; 95% CI, 0.96 to 1.11; P=0.44), with significant reductions in intracranial hemorrhage (0.5% vs. 0.7%, P=0.02) and fatal bleeding (0.2% vs. 0.5%, P=0.003) in the rivaroxaban group.
Conclusions:
In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group. (Funded by Johnson & Johnson and Bayer; ROCKET AF ClinicalTrials.gov number, NCT00403767.)Ⓐ

Abstract[3]

Background:
The postoperative risks for patients with coronary artery disease (CAD) undergoing noncardiac surgery are well described. However, the risks of noncardiac surgery in patients with heart failure (HF) and atrial fibrillation (AF) are less well known. The purpose of this study is to compare the postoperative mortality of patients with HF, AF, or CAD undergoing major and minor noncardiac surgery.
Methods and Results:
Population-based data were used to create 4 cohorts of consecutive patients with either nonischemic HF (NIHF; n=7700), ischemic HF (IHF; n=12249), CAD (n=13786), or AF (n=4312) who underwent noncardiac surgery between April 1, 1999, and September 30, 2006, in Alberta, Canada. The main outcome was 30-day postoperative mortality. The unadjusted 30-day postoperative mortality was 9.3% in NIHF, 9.2% in IHF, 2.9% in CAD, and 6.4% in AF (each versus CAD, *P*<0.0001). Among patients undergoing minor surgical procedures, the 30-day postoperative mortality was 8.5% in NIHF, 8.1% in IHF, 2.3% in CAD, and 5.7% in AF (*P*<0.0001). After multivariable adjustment, postoperative mortality remained higher in NIHF, IHF, and AF patients than in those with CAD (NIHF versus CAD: odds ratio 2.92; 95% confidence interval 2.44 to 3.48; IHF versus CAD: odds ratio 1.98; 95% confidence interval 1.70 to 2.31; AF versus CAD: odds ratio 1.69; 95% confidence interval 1.34 to 2.14).
Conclusions:
Although current perioperative risk prediction models place greater emphasis on CAD than HF or AF, patients with HF or AF have a significantly higher risk of postoperative mortality than patients with CAD, and even minor procedures carry a risk higher than previously appreciated.Ⓐ

Abstract[4]

Aims:
On the basis of the current knowledge, cardiac resynchronization therapy (CRT) cannot be recommended as a first-line treatment for patients with severely symptomatic permanent atrial fibrillation undergoing atrioventricular (AV) junction ablation. We examined whether CRT was superior to conventional right ventricular (RV) pacing in reducing heart failure (HF) events.
Methods and Results:
In this prospective, multi-centre study, we randomly assigned 186 patients, in whom AV junction ablation and CRT device implantation had been successfully performed, to receive optimized echo-guided CRT (97 patients) or RV apical pacing (89 patients). The data were analysed according to the intention-to-treat principle. During a median follow-up of 20 months (interquartile range 11–24), the primary composite endpoint of death from HF, hospitalization due to HF, or worsening HF occurred in 11 (11) patients in the CRT group and 23 (26) patients in the RV group [CRT vs. RV group: sub-hazard ratio (SHR) 0.37 (95 CI 0.18–0.73),*P*=0.005]. In the CRT group, compared with the RV group, fewer patients had worsening HF [SHR 0.27 (95 CI 0.12–0.58), *P*=0.001] and hospitalizations for HF [SHR 0.20 (95 CI 0.06–0.72), *P*=0.013]. Total mortality was similar in both groups [hazard ratio (HR) 1.57 (95 CI 0.58–4.27), *P*=0.372]. The beneficial effects of CRT were consistent in patients who had ejection fraction ≤35, New York Heart Association Class ≥III and QRS width ≥120 and in those who did not. At multi-variable Cox regression, only CRT mode remained an independent predictor of absence of clinical failure during the follow-up [HR=0.23 (95 CI 0.08–0.66), *P*=0.007].
Conclusions:
In patients undergoing 'Ablate and Pace' therapy for severely symptomatic permanent atrial fibrillation, CRT is superior to RV apical pacing in reducing the clinical manifestations of HF. (ClinicalTrials.gov number: NCT00111527.) Ⓐ

Evidence-Based References

Connolly: SJ for the AVERROES Steering Committee and Investigator. Apixaban in patients with atrial fibrillation, *N Engl J Med* 364:806–817, 2011. Ⓐ

Patel MR: Rivaroxaban versus warfarin in nonvalvular atrial fibrillation, *N Engl J Med* 365:883–891, 2011. Ⓐ

Van Diepen S et al.: Mortality and readmission of patients with heart failure, atrial fibrillation, or coronary artery disease undergoing noncardiac surgery: an analysis of 38047 patients, *Circulation* 124:289–296, 2011. Ⓐ

Brignole M et al.: Cardiac resynchronization therapy in patients undergoing atrioventricular junction ablation for permanent atrial fibrillation: a randomized trial, *Eur Heart J* 32:2420–2429, 2011. Ⓐ

SUGGESTED READINGS

2014AHA/ACC/HRS: Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society, *Am Coll Cardiol*, 2014. http://dx.doi.org/10.1016/j.jacc.2014.03.021.

Adam SS et al.: Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism, *Ann Intern Med* 157:796–807, 2012.

Aizer A et al.: Relation of vigorous exercise to risk of atrial fibrillation, *Am J Cardiol* 103:1572–1577, 2009.

Badheka AO et al.: Influence of obesity on outcomes in atrial fibrillation: yet another obesity paradox, *Am J Med* 123:646–651, 2010.

Calkins H et al.: HRS/EHRA/ECAS expert Consensus Statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on catheter and surgical ablation of atrial fibrillation, *Heart Rhythm* 4(6):816–861, 2007. 2007 Epub, Apr 30.

Camm AJ, et al.: Focused update of the ESC Guidelines for the Management of Atrial Fibrillation, *Eur Heart J* 33:2719–2747, 2012.

Connolly SJ et al.: Dabigatran versus warfarin in patients with atrial fibrillation, *N Engl J Med* 361:1139–1151, 2009.

Connolly SJ et al.: Dronedarone in high-risk permanent atrial fibrillation, *N Engl J Med* 365:2268–2276, 2011.

De Caterina RD et al.: Long-term use of anti-inflammatory drugs and risk of atrial fibrillation, *Arch Intern Med* 170(16):1450–1455, 2010.

Dhoble A et al.: Relation of porphyria to atrial fibrillation, *Am J Cardiol* 104:373–376, 2009.

Eagle KA et al.: Management of atrial fibrillation: translating clinical trial data into clinical practice, *Am J Med* 124:4–14, 2011.

European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery, Camm AJ et al.: Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC), *Eur Heart J* 31:2369–2429, 2010.

Freeman JV et al.: Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation, *Ann Intern Med* 154:1–11, 2011.

Granger CB et al.: for the ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation, *N Engl J Med* 365:981–992, 2011.

Gutierrez C, Blanchard DG: Atrial fibrillation: diagnosis and treatment, *Am Fam Physician* 83(1):61–68, 2011.

Hart RG et al.: Meta-analysis: antithrombotic therapy to prevent stroke in patients who have non-valvular atrial fibrillation, *Ann Intern Med* 146:857, 2007.

Khan M et al.: Pulmonary-vein isolation for atrial fibrillation in patients with heart failure, *N Engl J Med* 359:1778–1785, 2008.

Lip G, Halperin J: Improving stroke risk stratification in atrial fibrillation, *Am J Med* 123:484–488, 2010.

Lip G, Tse H: Management of atrial fibrillation, *Lancet* 370:604, 2007.

Morillo CA et al.: Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial, *JAMA* 311:692–700, 2014.

Patel MR et al.: Rivaroxaban versus warfarin in nonvalvular atrial fibrillation, *N Engl J Med* 365:883–891, 2011.

Uchino K et al.: Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials, *Arch Intern Med* 172(5):397–402, 2012.

Van Gelder IC et al.: Lenient versus strict rate control in patients with atrial fibrillation, *N Engl J Med* 362:1363–1373, 2010.

BASIC INFORMATION

DEFINITION

Atrial flutter is characterized by an atrial macroreentrant circuit (usually in the right atrium) leading to regular atrial depolarizations, typically at a rate of 250 to 350 beats/min. There are varying levels of conduction block through the atrioventricular node resulting in heart rates usually close to 150 beats/min. Higher degrees of atrioventricular (AV) block can occur in patients with AV nodal disease, with increased vagal tone, or when certain drugs such as AV-blocking agents are used. The atrial impulses may be conducted at a constant rate through the atrioventricular node, resulting in a regular rhythm, or the atrial impulses may be conducted at a variable rate, resulting in an irregular rhythm.

ICD-9CM CODES
427.32 Atrial flutter
ICD-10CM CODES
I48.92 Unspecified atrial flutter

EPIDEMIOLOGY & DEMOGRAPHICS

- Atrial flutter is the second most common atrial tachyarrhythmia after atrial fibrillation, with an estimated 200,000 new cases annually in the United States.
- Atrial flutter is common during the first week after open-heart surgery.
- Atrial flutter occurs 2.5 times more frequently in men than in women.
- Patients taking antiarrhythmics for chronic suppression of atrial fibrillation may convert to atrial flutter.
- Atrial flutter is typically seen in patients with underlying structural heart disease and is uncommon in children or young adults.

CLASSIFICATION

The Wells classification remains the most commonly used. There are two types of atrial flutter, the common type I and rarer type II. They can only manifest as one type at a time.

TYPE I: Type I atrial flutter, also known as common atrial flutter or typical atrial flutter, has an atrial rate of 240 to 350 beats/min. The reentrant loop circles the right atrium, passing through the cavo-tricuspid isthmus—a body of fibrous tissue in the lower atrium between the inferior vena cava, and the tricuspid valve.

Type I flutter is further divided into two subtypes, known as counterclockwise atrial flutter and clockwise atrial flutter, depending on the direction of the current passing through the loop.

- Counterclockwise atrial flutter (also known as cephalad-directed atrial flutter or typical atrial flutter) is the most common type. The flutter waves are inverted in electrocardiogram (ECG) leads II, III, and aVF.
- Clockwise atrial flutter (atypical): The reentry loop cycles in the opposite direction; thus, the flutter waves are upright in leads II, III, and aVF.

TYPE II: Type II atrial flutter is considered to result from an intraatrial reentrant circuit that is much shorter than type I, at an atrial rate of usually 340 to 440 beats/min. Left atrial flutter type II is common after incomplete left atrial ablation procedures.

Type I is distinguished from type II by:

1. The flutter rate (240-340 beats/min compared to 340-440 beats/min in type II).
2. The observation that type II can change in a "stepwise" manner to type I.
3. The existence of an excitable gap in type I, defined as a period after the wave of depolarization that has recovered its excitability and can be reactivated. After a depolarizing stimulus excites an area of the atrium in type I atrial flutter, it travels slowly in a long pathway with sufficient time for an "excitable gap." In contrast, type II lacks excitable gaps, likely due to short intraatrial reentrant circuits.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Palpitations
- Dizziness, lightheadedness, syncope, or near syncope
- Angina
- Congestive heart failure
- Embolic phenomena from intracardiac thrombus

ETIOLOGY

- Rheumatic heart disease
- Congenital heart disease
- Left ventricular dysfunction
- Acute myocardial infarction (rarely)
- Thyrotoxicosis
- Pulmonary embolism
- Mitral valve disease
- Cardiac surgery
- Chronic obstructive pulmonary disease
- Obesity
- Pericarditis
- Pulmonary hypertension
- Atrial flutter can also occur spontaneously or as a result of organization of atrial fibrillation from antiarrhythmic therapy

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Atrial fibrillation
- Paroxysmal atrial tachycardia:
  Supraventricular tachycardia, atrioventricular node reentry
  Supraventricular tachycardia, junctional ectopic tachycardia
  Supraventricular tachycardia, atrioventricular reentrant tachycardia or Wolf-Parkinson-White syndrome

WORKUP

- ECG
- Laboratory evaluation

LABORATORY TESTS

- Thyroid function studies
- Serum electrolytes

IMAGING STUDIES

- ECG (Fig. A1-135):
  1. Absence of P waves.

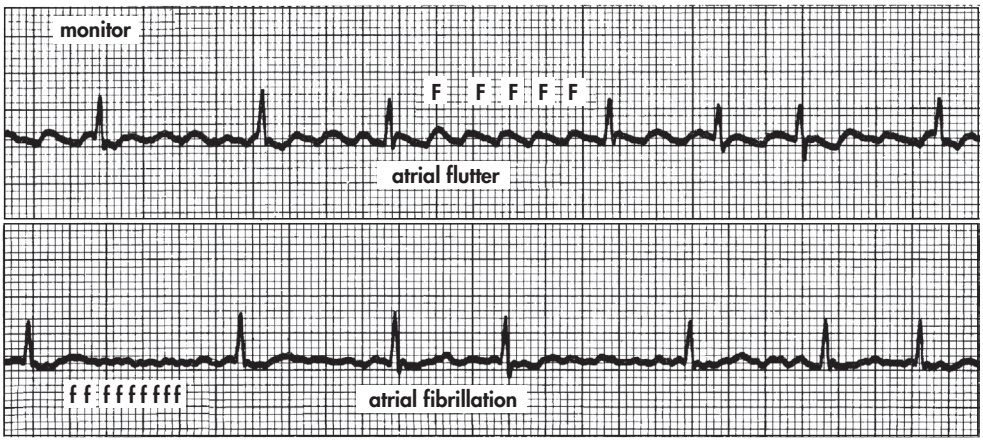


FIGURE A1-135 Atrial flutter and fibrillation. Notice the sawtooth waves with atrial flutter *(F)* and the irregular fibrillatory waves with atrial fibrillation *(f).* (From Goldberger AL [ed]: *Clinical electrocardiography,* ed 5, St Louis, 1994, Mosby.)

2. Regular, "sawtooth," or "F" (flutter)" wave pattern in the isoelectric baseline, best seen in leads II, III, and AVF (seen most commonly with typical Type I flutter)
3. There is rarely 1:1 atrioventricular (AV) conduction in atrial flutter (unless preexcitation is present). Rather, AV conduction is usually in a 2:1, 3:1, or 4:1 fashion, with corresponding usual ventricular rates of 150, 100, or 75 beats/min, respectively (assuming an atrial rate of 300 beats/min).

- Echocardiography to evaluate for structural heart disease (ventricular size, thickness, and function; atrial size, and valve function).
- Transesophageal echocardiography: consider in patients with associated structural or functional heart disease to ascertain the presence of intracardiac thrombi, in the absence of an appropriate duration of anticoagulation.
- Holter monitoring or event recorder to assess for paroxysmal atrial flutter or rate control or to identify the arrhythmia if symptoms are nonspecific or to identify triggering events.
- Electrophysiologic studies: required for a precise diagnosis, for mapping pathway, and for ablation.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Valsalva maneuver or carotid sinus massage usually slows the ventricular rate (increases grade of AV block) and may make flutter waves more evident. Adenosine may be similarly helpful for diagnostic purposes, allowing the unmasking of the atrial rhythm in the absence of ventricular activity.
- Direct current cardioversion is the treatment of choice for acute management of atrial flutter associated with hemodynamic instability or debilitating symptoms such as angina, congestive heart failure, or poor perfusion. Electrical cardioversion may be successful with energies as low as 25 joules, but since 100 joules is virtually always successful, this may be a reasonable initial shock strength. If the electrical shock results in atrial fibrillation, a second shock at a higher energy level is used to restore normal sinus rhythm. Sedation of a conscious patient is highly recommended before cardioversion is performed. The use of external defibrillators with biphasic waveforms decreases the amount of energy required for cardioversion and improves cardioversion success rate. Due to atrial stunning, patients should be therapeutically anticoagulated for at least a month or longer depending on their stroke risk.
- Overdrive pacing in the atrium may also terminate atrial flutter. This method is especially useful in patients who have recently undergone cardiac surgery and still have temporary atrial pacing wires.
- Radiofrequency ablation to interrupt the atrial flutter is highly effective for patients with chronic or recurring atrial flutter and is generally considered first-line therapy in those with recurrent episodes of atrial flutter. It has been shown to improve health-related quality of life. However, there remains an increased risk of subsequent atrial fibrillation and stroke.

ACUTE Rx

- Treatment choices are based on clinical circumstances. If the patient is unstable, proceed directly to electrical cardioversion.
- In the hemodynamically stable patient, proceed with rate control or rhythm control strategy.
- AV blocking agents such as calcium channel blockers, beta-blockers, and digitalis may all be used for rate control. Atrial flutter may spontaneously convert to normal sinus rhythm with this strategy.
- In general, atrial flutter is more difficult to rate-control than atrial fibrillation.
- The rate of recurrence of atrial flutter is difficult to determine because most published data combine atrial flutter with atrial fibrillation. However, the recurrence rate is substantial, perhaps 50% at 1 yr.
- Ibutilide is the first-line medication for chemical cardioversion of atrial flutter in patients with normal systolic function and QT intervals. Success rate is approximately 60% to revert atrial flutter to a sinus mechanism and it is more effective than procainamide, sotalol, or amiodarone.

CHRONIC Rx

- Fewer data exist to decide on the choice of rate control versus rhythm control in patients with atrial flutter. There are several options to help maintain sinus rhythm after cardioversion of atrial flutter, such as dofetilide, amiodarone, flecainide, propafenone, or sotalol. The choice of antiarrhythmic therapy is, in part, dictated by the presence or absence of underlying structural heart disease. In patients who have chronic atrial flutter, rate control (to rates as physiologic as possible) can be achieved using AV blocking agents, to prevent occurrence of tachycardia-mediated cardiomyopathy.
- Elective outpatient cardioversion can be performed either immediately preceded by TEE to evaluate the left atrium and the left atrial appendage for thrombus or after a period of at least 3 weeks of documented therapeutic anticoagulation before cardioversion. At least 4 weeks of anticoagulation should be performed after cardioversion, if not longer, depending on the overall thromboembolic risk of the patient as determined by the CHADS2-VASC2 score.
- Although data are much less convincing than in atrial fibrillation, current consensus is to treat atrial flutter similar to atrial fibrillation in terms of the risk for thromboembolic events and the need for anticoagulation. In this case, the CHADS2-VASC scoring system (see "Atrial Fibrillation" entry) can be used to risk-stratify patients for their need to stay on long-term anticoagulation.

DISPOSITION

More than 85% of patients convert to regular sinus rhythm after cardioversion with as little as 25 to 50 joules.

REFERRAL

Refer patients who are considered for rhythm control of atrial flutter to cardiologists, especially patients who are candidates for radiofrequency ablation.

PEARLS & CONSIDERATIONS

COMMENTS

- Patients with atrial flutter have a stroke risk at least as high as those with atrial fibrillation and carry a greater risk for subsequent development of atrial fibrillation than in the general population.
- Anticoagulation should be considered for all patients whose CHA2DS2-VASc score is ≥2.
- Anticoagulation with warfarin is generally not recommended in patients with a CHA2DS2-VASc score of zero. For patients with a CHA2DS2-VASc score of 1 low-dose aspirin or oral anticoagulants (warfarin, dabigatran, rivaroxaban, or apixaban) are appropriate options.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fig. 3-152 Palpitations, dizziness, and/or syncope (Algorithm)
Fig. 3-199 Tachycardia, diagnostic approach (Algorithm)
Fig. 3-200 Tachycardia, narrow complex (Algorithm)
Atrial Flutter (Patient Information)
Atrial Fibrillation (Related Key Topic)

AUTHOR: **BARRY FINE, M.D., Ph.D.**

SUGGESTED READINGS

Ghali WA et al.: Atrial flutter and the risk of thromboembolism: a systematic review and meta-analysis, *Am J Med* 118(2):101–107, 2005.

Natale A et al.: Prospective randomized comparison of antiarrhythmic therapy versus first-line radiofrequency ablation in patients with atrial flutter, *J Am Coll Cardiol* 35(7):1898–1904, 2007.

BASIC INFORMATION

DEFINITION

Atrial myxoma is a benign neoplasm of mesenchymal origin and is the most common primary tumor of the heart.

SYNONYMS

Cardiac myxoma

ICD-9CM CODES
212.7 Benign neoplasm, heart
ICD-10CM CODES
D15.1 Benign neoplasm of heart

EPIDEMIOLOGY & DEMOGRAPHICS

- Primary cardiac tumors are extremely rare, with an autopsy frequency of 0.001% to 0.03%. The most frequent cardiac tumors are metastases, occurring 30 times more frequently than primary tumors.
- Myxomas account for 30% to 50% of all primary tumors of the heart.
- 65% of cardiac myxomas occur in females. 4.5% to 10% of cardiac myxomas are familial (Carney syndrome).
- Average age of incidence of sporadic cases is 30 to 50 yr but can occur at any age.
- Average age of incidence of familial cases is 25 yr.
- Most arise in the left atrium (75%), but myxomas can also be found in the right atrium (18%), right ventricle (4%), and left ventricle (3%). They are usually pedunculated and attached to the intra-atrial septum.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Patients with atrial myxomas, when symptomatic, characteristically present in one of three ways:

1. Atrioventricular valve obstruction (e.g., mitral or tricuspid valve): may present with dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, dizziness, syncope, chest pain, atrial fibrillation, and sudden death (rare). A marked change in the severity of any symptom caused by a change in position of the patient, especially if recumbency relieves dyspnea, is suggestive of myxoma
2. Systemic embolization: leading to cerebrovascular accidents, pulmonary embolism, paradoxical embolism
3. Constitutional symptoms: fever, weight loss, arthralgias, Raynaud's phenomenon

On exam there may be widely split loud S1, secondary pulmonary hypertension, murmurs of regurgitation (holosystolic) or stenosis (rumbles), an early diastolic sound 80-120 milliseconds after A2 called "tumor plop" which may resemble an opening snap,

ETIOLOGY

- Most cases (90%) of atrial myxomas are sporadic with no known cause
- Carney complex, transmitted in an autosomal dominant pattern, accounts for the majority of familial myxomas and as much as 7% of cardiac myxomas. Carney syndrome manifests as cardiac and extracardiac myxomas, pigmented skin discoloration, endocrine hyperactivity, and other tumors, such as schwannomas. There at least three different genetic loci with two identified genes for this complex

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Primary valvular diseases: mitral stenosis, mitral regurgitation, tricuspid stenosis, tricuspid regurgitation
- Pulmonary hypertension
- Endocarditis
- Vasculitis
- Atrial thrombus
- Pulmonary embolism
- Cerebrovascular accidents
- Collagen-vascular disease
- Carcinoid heart disease
- Benign tumors of the heart (papillary fibroelastoma, rhabdomyoma, fibroma, teratoma, and lipoma)
- Malignant tumors of the heart (angiosarcoma, rhabdosarcoma, fibrosarcoma, and leiomyosarcoma)
- Metastatic tumors to the heart (melanoma, lung, breast, renal, esophageal, and sarcomas)

WORKUP

A high index of suspicion is needed because the clinical manifestations are nonspecific and similar to many common cardiovascular and pulmonary diseases.

LABORATORY TESTS

Although not very specific, the following laboratory findings may be abnormal in patients with atrial myxomas:

- Complete blood count: anemia, polycythemia, thrombocytopenia may occur
- Erythrocyte sedimentation rate, C-reactive protein, and serum immunoglobulins are commonly elevated
- Electrocardiogram: left or right atrial enlargement, atrial fibrillation, premature ventricular depolarizations, or ventricular tachycardia

IMAGING STUDIES

- Echocardiography: initial test of choice in suspected cases of atrial myxoma
- Chest radiograph: about one third of patients have normal findings. Evidence of altered cardiac contour, pulmonary edema, and chamber enlargement may be present
- Transesophageal echocardiography: is the recommended measure for initial assessment and may better define cardiac masses not clearly visualized by transthoracic echocardiography
- CT: often used for diagnosis; defines tumor extension and evaluates adjacent cardiac structures
- MRI (Fig. EA1-136): delineates size, shape, and tissue characteristics, helping distinguish thrombus from tumor
- Cardiac catheterization: will show neovascularization in 50% of the cases and may be required to rule out concomitant coronary artery disease in anticipation of surgical excision

TREATMENT

ACUTE GENERAL THERAPY

- Surgical excision is the treatment of choice
- Surgery should be done promptly because systemic embolization and/or sudden death can occur while waiting for the procedure

CHRONIC Rx

Postoperative arrhythmias and conduction abnormalities were present in 26% of patients and can be treated accordingly.

DISPOSITION

- Surgical results have reported a 95% survival rate after a follow-up of 3 yr.
- Careful follow-up is necessary because up to 5% of sporadic cases and 20% of familial cases of atrial myxoma may recur within the first 6 yr after surgery.
- Sudden death in untreated patients may occur in up to 15%, resulting from coronary or systemic embolization or obstruction of the mitral or tricuspid valve.

REFERRAL

- Consultation with a cardiologist is recommended.
- Once the presence of cardiac tumor is confirmed, consultation with a cardiovascular surgeon is needed for prompt surgical excision.

PEARLS & CONSIDERATIONS

- Approximately two thirds of patients present with cardiovascular symptoms, specifically dyspnea, often suggestive of valvular obstruction.
- Nearly one third of patients have evidence of systemic embolization.

COMMENTS

Annual echocardiograms should be performed to monitor for recurrence of atrial myxomas after surgical excision.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Atrial Myxoma (Patient Information)

AUTHOR: **BARRY FINE, M.D., Ph.D**

SUGGESTED READINGS

Ipek G et al.: Surgical management of cardiac myxoma, *J Card Surg* 20(3):300, 2005.

Swartz MF et al.: Atrial myxomas: pathologic types, tumor location, and presenting symptoms, *J Card Surg* 21(4):435, 2006.

Vasquez A et al.: Atrial myxomas in the elderly: a case report and review of the literature, *Am J Geriatr Cardiol* 13(1):39–44, 2004.

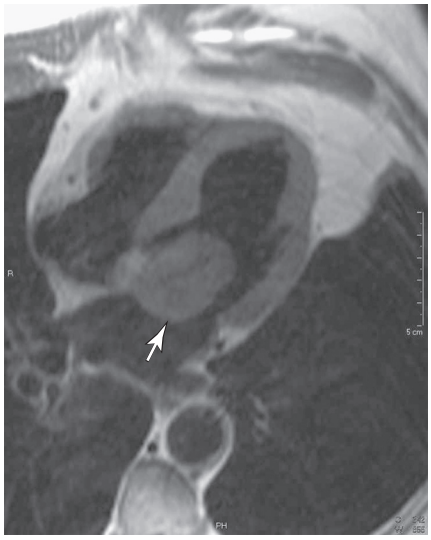


FIGURE EA1-136 Diastolic magnetic resonance image of a large left atrial myxoma (arrow) showing that it is attached to the atrial septum and is prolapsing across the mitral valve. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

Atrial Septal Defect PTG

BASIC INFORMATION

DEFINITION

An atrial septal defect (ASD) is a true deficiency in the interatrial septum that allows blood flow between the atria. It should be distinguished from patent foramen ovale (PFO), which is a is a probe-patent defect caused by a failure of the septum primum to fuse to the superior limb of the septum secundum at the edge of the fossa ovalis in postnatal life, leaving a flaplike communication between the two atria. PFO occurs in approximately 20%-25% of the normal adult population. Fig. A1-137 illustrates the physiology of ASD. There are several forms of ASD (Fig. A1-138):

- Primum: This type of ASD occurs when there is failure of normal fusion of anterior and posterior endocardial cushions with the septum primum, with resultant deficiency in the inferior portion of the septum primum. The defect frequently coexists with abnormalities of the atrioventricular valves, commonly resulting in a cleft anterior mitral leaflet.
- Secundum: The most common form of ASD; it represents a true deficiency—a hole in the septum primum or a septum secundum, or both. This defect most often occurs in the region of the fossa ovalis.
- Sinus venosus defect: This defect is located at the junction of the right atrium and either the superior vena cava or inferior vena cava. In a sinus venosus defect, the wall separating the pulmonary veins and the right atrium is deficient, causing a left-to-right shunt. Most commonly this defect involves the right upper pulmonary vein, which is still anatomically connected to the left atrium but is deficient anteriorly and thus drains anomalously into the right atrium. Less commonly, the right lower pulmonary vein is involved.
- Coronary sinus septal defect (unroofed coronary sinus): This defect results when the wall separating the coronary sinus from the left atrium is deficient, causing a left-to-right shunt. This defect is often associated with a persistent left superior vena cava.

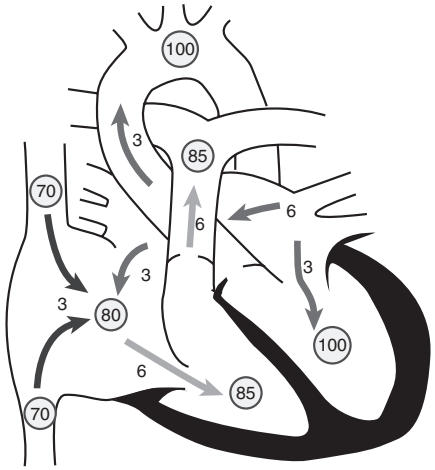


FIGURE A1-137 Physiology of atrial septal defect (ASD). Circled numbers represent oxygen saturation values. The numbers next to the arrows represent volumes of blood flow (in L/min/m^2). This illustration shows a hypothetical patient with a pulmonary-to-systemic blood flow ratio (Qp/Qs) of 2:1. Desaturated blood enters the right atrium from the venae cavae at a volume of 3 L/min/m^2 and mixes with an additional 3 L of fully saturated blood shunting left to right across the ASD; the result is an increase in oxygen saturation in the right atrium. Six liters of blood flow through the tricuspid valve and cause a mid-diastolic flow rumble. Oxygen saturation may be slightly higher in the RV because of incomplete mixing at the atrial level. The full 6 L flows across the RV outflow tract and causes a systolic ejection flow murmur. Six liters return to the left atrium, with 3 L shunting left to right across the defect and 3 L crossing the mitral valve to be ejected by the left ventricle into the ascending aorta (normal cardiac output). (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

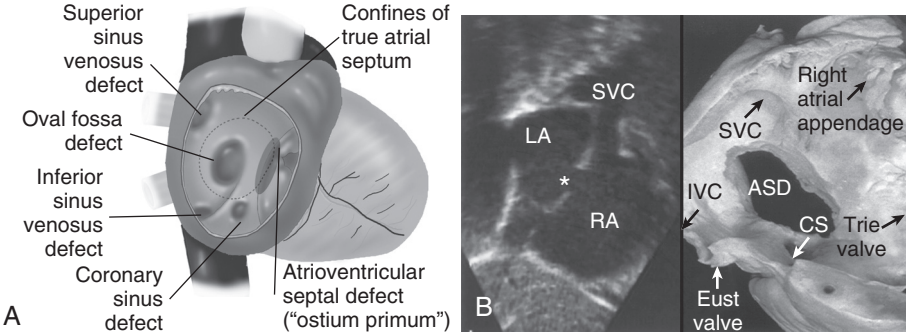


FIGURE A1-138 A, Schematic diagram outlining the different types of interatrial shunting that can be encountered. Note that only the central defect is suitable for device closure. **B,** Subcostal right anterior oblique view of a secundum atrial septal defect *(ASD) (asterisk)* that is suitable for device closure. The right panel is a specimen as seen in a similar view, outlining the landmarks of defect. *CS,* Coronary sinus; *IVC,* inferior vena cava; *LA,* left atrium; *RA,* right atrium; *SVC,* superior vena cava. (From Zipes DP et al [eds]: *Braunwauld's heart disease,* ed 7, Philadelphia, 2005, Saunders.)

SYNONYMS

ASD
Interatrial septal defect

ICD-9CM CODES
429.71 Atrial septal defect
745.60 Endocardial cushion defect, unspecified type
745.61 Ostium primum defect
745.5 Ostium secundum type atrial septal defect
745.6 Endocardial cushion defects

ICD-10CM CODES
Q21.1 Atrial septal defect

EPIDEMIOLOGY & DEMOGRAPHICS

- Secundum, 75%; primum, 15%-20%; sinus venosus, 5%-10%; coronary sinus, <1%
- Incidence is greater in females and in patients with Down syndrome
- Accounts for 8% to 10% of congenital heart abnormalities
- Prevalence is 1.6 per 1000 live births
- Holt-Oram syndrome is an autosomal dominant disorder that involves skeletal anomalies, such as absent radial bones in both arms, as well as ASD and cardiac conduction disease, such as AV blocks.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Exertional dyspnea and fatigue
- Recurrent respiratory infections, heart failure, and failure to thrive in infants with large ASDs
- Cyanosis and clubbing (when abnormal right ventricular [RV] compliance has led to right-to-left shunting)
- Increased jugular venous pressure (with RV failure)
- Prominent RV impulse
- Visible and palpable pulmonary artery pulsations
- Wide fixed splitting of S_2
- Pansystolic murmur best heard at apex secondary to mitral regurgitation (ostium primum defect)
- Ejection systolic flow murmur (pulmonary valve flow murmur) (Figure A1-139)
- Diastolic rumble (atrioventricular valve flow murmur)
- Patients with small defects: generally asymptomatic

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

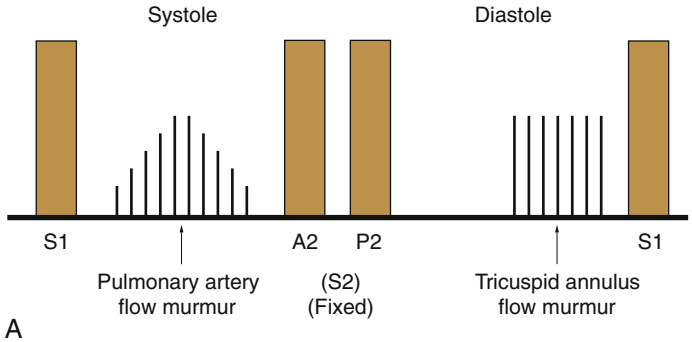
- Primary pulmonary hypertension
- Pulmonary stenosis
- Rheumatic heart disease
- Mitral valve prolapse
- Cor pulmonale
- Anomalous pulmonary venous connection

WORKUP

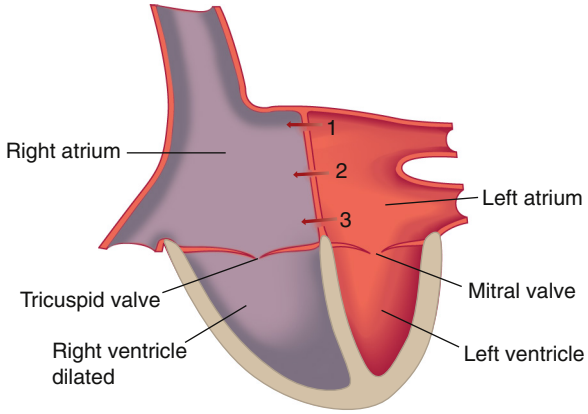
- ECG:
  1. Ostium primum defect: left axis deviation, incomplete or total right bundle branch block, prolongation of PR interval
  2. Sinus venosus defect: right axis deviation, abnormal P axis
  3. Ostium secundum defect: right axis deviation, incomplete or total right bundle branch block, right atrial enlargement
- Chest x-ray examination
- Echocardiography (Fig. A1-140)
- Cardiac catheterization
- Cardiac magnetic resonance imaging (MRI), CT, or both

IMAGING STUDIES

- Chest x-ray: cardiomegaly, right heart enlargement, increased pulmonary vascular pattern
- Echocardiography with saline bubble contrast and Doppler flow studies: may demonstrate the size of the defect, the direction of shunting, presence of anomalous pulmonary return (in sinus venosus ASD), right heart volume overload, and elevated pulmonary artery pressures
- Transesophageal echocardiography is much more sensitive than transthoracic echocardiography in identifying sinus venosus defects and can be helpful for all forms of ASD when the transthoracic echo is nondiagnostic. It is also useful to determine defect size, proximity to other cardiac structures, and sizes of rims when determining suitability for device closure and is therefore used in the cath lab to assist with these issues.
- Cardiac catheterization: Left heart catheterization is not usually a diagnostic necessity; it is only useful when the coronary arteries need to be assessed before surgery. Right heart catheterization may be necessary to assess shunt severity and severity of pulmonary hypertension and to determine pulmonary vascular resistance (PVR), and to assess pulmonary artery vasoreactivity in response to vasodilators.
- Cardiac MRI and CT: may be useful if echo is not diagnostic; MRI is gold standard for assessing RV size and function, and it can determine whether the right-sided chambers are, in fact, enlarged. MRI is also useful to assess anomalous pulmonary venous return and persistent left superior vena cava. Cardiac CT can offer similar information.



A



B

FIGURE A1-139 Atrial septal defect. **A,** Murmur at the left sternal edge. **B,** Anatomy. (From The patient with a murmur. In Baker T, Nikolic G, O'Connor S [eds]: *Practical cardiology,* Philadelphi, 2008, Elsevier.)

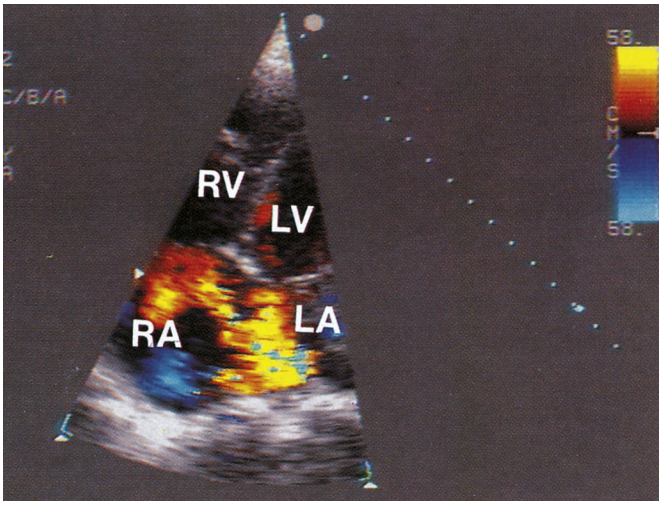


FIGURE A1-140 Color flow Doppler apical four-chamber view showing blood flow from the left atrium (LA) to the right atrium (RA) through a moderately sized atrial septal defect. *LV,* Left ventricle; *RV,* right ventricle. (From Forbes CD, Jackson WF: *Color atlas and text of clinical medicine,* ed 3, London, 2003, Mosby.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Symptomatic patients should avoid strenuous activity.
- Asymptomatic patients with small defects with shunts with a pulmonary to systemic flow ratio (Qp/Qs) of <1.5:1 without pulmonary artery hypertension (PAH) and normal RV size require no medical therapy and may be observed. Routine assessment of these patients includes assessment of symptoms, arrhythmias, and embolic events and serial echocardiography.
- A repeat echocardiogram should be obtained every 2 to 3 yr to assess RV size and function and pulmonary pressure; with increasing age, the degree of left-to-right shunting may increase due to progressive noncompliance of the left ventricle with age-related acquired heart disease.

GENERAL Rx

- Children and infants: Closure of ASD before age 10 yr is indicated if Qp/Qs is >1.5:1, ASD size is significantly >5 mm, or if there is evidence of RV dilation.
  1. Small ASDs with a diameter of <5 mm and no evidence of RV volume overload do not impact the natural history of the individual and thus may not require closure unless associated with paradoxic embolism.
  2. Closure of an ASD either percutaneously or surgically is indicated for right atrial and RV enlargement with or without symptoms.
  3. A sinus venosus, coronary sinus, or primum ASD should be repaired surgically rather than by percutaneous closure.
  4. Surgical closure of secundum ASD is appropriate when concomitant surgical repair/replacement of associated defects is needed or when the anatomy of the defect precludes the use of a percutaneous device.
- Adults: Closure of an ASD, either percutaneously or surgically, may be considered in the presence of net left-to-right shunting with Qp/Qs >1.5:1, right-sided chamber enlargement, symptoms, pulmonary hypertension with pulmonary artery pressure less than two-thirds systemic levels, PVR less than two-thirds systemic vascular resistance, or when pulmonary hypertension is responsive to either acute or chronic pulmonary vasodilator therapy. These patients must be treated in conjunction with providers who have expertise in the management of adult congenital heart disease and pulmonary hypertension.
- Patients with severe irreversible PAH and no evidence of a left-to-right shunt should not undergo ASD closure.
- Closure of an ASD, either percutaneously or surgically, is reasonable in the presence of:
  1. Paradoxic embolism (Class 2a indication)
  2. Documented orthodeoxia-platypnea (Class 2a indication)
- Percutaneous catheter device closure is possible in many patients with secundum ASDs (if stretched diameter is <41 mm with adequate rims), with >95% success rate in appropriate candidates. A combination of low-dose aspirin and clopidogrel is usually prescribed for 3-6 mo after the procedure to prevent thrombus formation. Early complications include device thrombus formation, atrial arrhythmias, erosion, and device dislodgement. Potential mid- and long-term complications include late device erosion into the aortic root or pericardium, atrial dysrhythmias, and infective endocarditis. In one study the long-term outcomes of device closure using the Amplatzer septal occluder were excellent as evidenced by no deaths and minimal complication in 151 patients followed for 6.5 years after ASD closure. In October 2013 the Food and Drug Administration (FDA) began alerting health care providers and patients that in very rare instances, tissue surrounding the Amplatzer ASO can erode and result in life-threatening emergencies that require immediate surgery, especially when the rim adjacent to the aortic root is <5 mm. Based on published estimates, these events occur in approximately 1 to 3 of every 1,000 patients implanted with the Amplatzer device. Close clinical follow up and an echocardiogram is recommended predischarge, at 1 wk, at 6 mo, and at 12 mo after implant.
- Percutaneous closure is contraindicated in those with sinus venosus, primum, or unroofed coronary sinus defects. In addition, it is not suitable for secundum defects with unsuitable anatomy (too large; too close to coronary sinus, AV valves, or pulmonary veins; or inadequate rims), presence of sepsis, bleeding disorder, or intracardiac thrombi.
- In adult patients undergoing surgical closure, the surgical mortality should be <1%. Surgical closure of ASD improves function status, exercise capacity, and patient survival; however, it does not prevent atrial fibrillation or stroke, especially if patients are operated on after age 40. Concomitant maze procedure may be considered for intermittent or chronic atrial tachyarrhythmias in adults with ASDs who are undergoing surgical repair.

DISPOSITION

- Mortality rate is elevated in patients with large ASDs if left untreated, with complications such as RV failure, arrhythmias, paradoxic embolism, and PAH leading to right-to-left shunting (Eisenmenger syndrome).
- Patients with small shunts (<1.5:1) have a normal life expectancy.
- Basic assessment for adult congenital heart disease patients should include systemic arterial oximetry, an ECG, chest radiograph, transthoracic echocardiography, and blood tests for full blood count and coagulation screen.
- Intracardiac shunts are considered moderate risk for preoperative evaluation for noncardiac procedure. High-risk features include severe systolic dysfunction (ejection fraction <35%), severe pulmonary hypertension whether primary or secondary, cyanotic heart disease, or severe left-side outlet obstruction.
- Annual clinical follow-up is recommended for patients postoperatively if their ASD was repaired as an adult to monitor for PAH, atrial arrhythmias, RV or left ventricular dysfunction, and coexisting valvular lesions.
- Preoperative atrial fibrillation is a risk factor for immediate postoperative and long-term atrial fibrillation. Patients with a repaired ASD still have an increased risk for development of atrial fibrillation that directly correlates with the age at which the defect is corrected (later correction poses greater risk).
  1. After closure, anticipated benefits include improved functional status and exercise capacity, improved survival after closure as a child, improved quality of life, prevention of right heart failure, and prevention of PAH.
  2. Potential mid- to long-term complications after ASD closure in adulthood include tachyarrhythmias (atrial fibrillation or atrial flutter), bradyarrhythmias (sinus node dysfunction or heart block), stroke (greater risk in older patients), residual ASDs (because of patch dehiscence or incomplete closure by device), right heart failure or PAH (risk is correlated with the size of the original defect and inversely related to age at time of closure), mitral valve regurgitation or subaortic stenosis (in patients with primum ASDs), device migration/erosion, and pulmonary venous congestion (uncommon).
  3. Pregnancy is usually well tolerated in women with ASDs. Follow-up during pregnancy is recommended because of small risk for paradoxic embolus, stroke, arrhythmia, and heart failure. If known, ASDs should be closed before pregnancy is indicated. The sole contraindication to pregnancy in women with an ASD is severe PAH.
  4. Scuba diving is generally contraindicated in patients with unrepaired ASDs because of the risk of paradoxic emboli. In addition, high-altitude climbing should be avoided because it can cause oxygen desaturation from right-to-left shunting in these patients.
- In regard to infective endocarditis prophylaxis for dental procedures:
  1. Prophylaxis is not indicated for an unrepaired ASD.
  2. Prophylaxis is indicated for a repaired ASD or any congenital heart disease with prosthetic material as part of the repair during the first 6 mo after the repair.
  3. Prophylaxis is indicated for a repaired ASD or any congenital heart defect in the presence of residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (both of which inhibit endothelialization).

The estrogen-containing oral contraceptive pill is not recommended in acute coronary heart disease patients at risk of thromboembolism, such as those with cyanosis related to an intracardiac shunt, atrial fibrillation, severe PAH, or Fontan repair.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Atrial Septal Defect (ASD) (Patient Information)

AUTHOR: **JONATHAN GINNS, M.D.**

SUGGESTED READINGS

Krasuski RA: When and how to fix a "hole in the heart": approach to ASD and PFO, *Cleve Clin J Med* 74:137, 2007.

Moake L: Transcatheter device closure for atrial septal defects: safety, efficacy, complications, and costs, *Crit Care Nurs Clin North Am* 23(2):339–348, 2011.

Warnes CA et al.: ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Adults With Congenital Heart Disease), *J Am Coll Cardiol* 52:e143–e263, 2008.

Webb G, Gatzoulis MA: Atrial septal defects in the adult: recent progress and overview, *Circulation* 114:1645–1653, 2006.

BASIC INFORMATION

DEFINITION

Attention deficit hyperactivity disorder (ADHD) is a chronic disorder of attention and/or hyperactivity-impulsivity. Symptoms must be present before 12 yr of age, last at least 6 mo, and cause functional impairment in multiple settings. The diagnostic keys for ADHD are described in Table A1-79.

SYNONYMS

Hyperactivity
Hyperkinetic disorder
Attention deficit disorder (ADD)

ICD-9CM CODES
314.00 Attention deficit hyperactivity disorder, predominantly inattentive
314.01 unspecified, predominantly hyperactive/impulsive, or combined hyperactive/inattentive
ICD-10CM CODES
F90.0 predominantly inattention
F90.1 predominantly hyperactivity
F90.2 combined
DSM-V CODES
314.00, 314.01

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Diagnosis is usually first made in school-aged children (6 to 9 yr).
PREVALENCE: Five percent to 10% of school-aged children (most prevalent neurodevelopmental disorder among children) and 2% to 5% of adults. The prevalence increased by an estimated 3% annually between 1997 and 2006.
PREDOMINANT SEX: Among children, male predominance with ratio of 2:1 to 4:1. Among adults, ratio is closer to 1:1 (sex difference may reflect referral bias).
PREDOMINANT AGE: Some symptoms must occur before age 12 yr. Symptoms (especially motoric hyperactivity) tend to diminish with age. Up to 70% continue to meet criteria in adolescence, and an estimated 40% to 65% have some symptoms in adulthood.
GENETICS: Strong polygenetic component. First-degree relatives of ADHD patients have 5 times greater risk of ADHD relative to controls. Studies suggest potential involvement of several genes, including those associated with serotonin and glutamate transporters as well as dopamine metabolism.
RISK FACTORS: Possible environmental and epidemiologic risk factors include in utero tobacco/drug exposure or hypoxia, low birth weight, prematurity, pregnancy, lead exposure (though most children with elevated lead levels do not develop ADHD), head trauma in young children, family dysfunction, low socioeconomic status. Evidence supports possible association between dietary factors (e.g., refined sugar, food additives) and ADHD in a small percentage of patients. A causal link between environmental toxins and ADHD has not been clearly established.

TABLE A1-79 Diagnostic Keys for Attention Deficit Hyperactivity Disorder

1. Inattention
   a. Careless mistakes in schoolwork, work, or other activities
   b. Seems not to listen when spoken to directly
   c. Poor follow through on schoolwork or chores
   d. Difficulty organizing
   e. Easily distracted by extraneous stimuli and is forgetful
2. Hyperactivity
   a. Trouble sitting still
   b. May act as if "driven by a motor"
   c. May talk excessively
3. Impulsivity
   a. Trouble holding back in class
   b. Trouble taking turns
   c. Interrupts

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Three types:
  1. Predominantly inattentive: difficulty organizing, planning, remembering, concentrating, starting/completing tasks; symptoms may not be present during preferred activities.
  2. Predominantly hyperactive-impulsive: edgy/restless, talkative, disruptive/intrusive, disinhibited, impatient.
  3. Combined.
- Usually diagnosed in elementary school when achievement is compromised and behavioral problems are not tolerated. Children with academic underproductivity, problems with peer and family relations, or discipline issues are often referred for evaluation. Of the more than 4 million children in the U.S. who have ADHD, most have comorbid conditions (see below) and nearly half use special education and mental health services.
- Up to 50% may have associated disorders such as psychiatric diagnoses (oppositional defiant disorder, conduct disorder, depression, anxiety), learning disabilities, or substance abuse.
- In adults, motoric hyperactivity is less common, but restlessness, edginess, and difficulty relaxing are often seen. Disorganization and difficulty completing tasks are other common complaints.

ETIOLOGY

Strongest evidence exists for genetic inheritance. Other theories include abnormal metabolism of brain catecholamines, structural brain abnormalities, reduced activation in the basal ganglia and anterior frontal lobe, as well as environmental factors (see earlier).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Medical: visual/hearing impairment, seizure disorder, head injury, sleep disorder, medication interactions, mental retardation intellectual disability, specific learning disorder, autism spectrum disorder/development delay, thyroid abnormalities, lead toxicity, movement disorders.
- Psychiatric: depression, bipolar disorder, disruptive mood, dysregulation disorder, anxiety, obsessive-compulsive disorder, oppositional defiant disorder, intermittent explosive disorder, conduct disorder, posttraumatic stress disorder, reactive attachment disorder, and substance abuse.
- Psychosocial: mismatch of learning environment with ability, family dysfunction, abuse/neglect.

WORKUP

- Clinical interview should include assessment of symptoms and impact on work/school and relationships; developmental history; personal and family psychiatric history, including substance abuse; social history, including family dysfunction; medical history.
- Physical examination should be performed to investigate medical causes for symptoms, coexisting conditions, and contraindications to treatment. Special focus should be paid to evaluation of dysmorphic features; neurologic examination, including assessment for neurocutaneous findings; and assessment of hearing and vision.
- Information from collateral sources (parents, partners, teachers) is crucial to diagnosis. Many patients will not display symptoms during an office visit and may underreport or overreport symptoms.
- Self-rating scales and standardized symptom-specific questionnaires from collateral sources can help diagnose and assess response to treatment. The use of ADHD-specific rating scales over broadband behavioral scale is associated with improved sensitivity and specificity.
- Laboratory or imaging studies should be undertaken only if indicated by history or physical examination.
- Ancillary testing (e.g., IQ/achievement testing, language evaluation, and mental health assessment) may be indicated based on clinical findings and may require referral.

TREATMENT

NONPHARMACOLOGIC THERAPY

- The majority of studies comparing the efficacy of pharmacologic vs nonpharmacologic interventions demonstrate the superiority of pharmacologic treatments.
- Studies on combined treatments have not shown significant improvements in core ADHD symptoms when behavioral treatments are added to stimulant medications. However, improvements in related areas of concern such as parent-child relations, aggressiveness, teacher-rated social skills, and reaching achievement have been seen in combined treatment groups.

- Prevailing opinion favors a multimodal approach in which nonpharmacologic behavioral therapies including parent-child behavioral therapy and social skills training can be used to target comorbid conditions or behaviors that have not responded to medication.
- Behavioral therapy alone is often considered when children are under 6 yr, symptoms and impairment are mild, if parents are opposed to or patients cannot tolerate medications, or if there is uncertainty or disagreement about the diagnosis (e.g., between parents and teachers).
- Educational interventions are recommended, particularly in the setting of learning disabilities. Children with ADHD are entitled to reasonable educational accommodations under a 504 Plan or the Individuals with Disabilities Education Act.
- Behavioral interventions (e.g., goal setting and rewards systems) show short-term efficacy and are endorsed by most national organizations (e.g., American Academy of Pediatrics, American Medical Association). Time management and organizational skills appear useful. Social skills training may also be useful.
- Psychotherapy such as cognitive therapy, play therapy, or insight-oriented therapy are unlikely to be useful in addressing the core symptoms of ADHD. However, it may be beneficial in treating comorbid psychiatric conditions.
- Elimination diets are not routinely recommended.
- Many support and advocacy groups provide education and other resources (e.g., Children and Adolescents with ADHD, National ADD Association, American Academy of Child and Adolescent Psychiatry).

ACUTE GENERAL Rx

- Most studies on treatment of ADHD are performed in children; limited data available on adults.
- Mainstay of treatment is stimulant medications. Second-line therapies include antidepressants and alpha-agonists.
- Stimulants:
  1. Release or block uptake of dopamine and norepinephrine.
  2. Include short- and long-acting methylphenidate, dextroamphetamine, and dextroamphetamine/amphetamine combinations (mixed amphetamine salts). A methylphenidate patch (Daytrana) is available, as is a pro-drug form of dextroamphetamine, lisdexamfetamine (Vyvanse), which is designed to limit the abuse potential, and a long-acting oral suspension of methylphenidate (Quillivant XR).
  3. All stimulants equally effective; however, not all patients improve with stimulants. Patients who do not respond well to one stimulant may respond to another.
  4. Do not cause euphoria or lead to addiction when taken as directed.
  5. Improve cognition, inattention, impulsiveness/hyperactivity, and driving skills. Limited impact on academic performance, learning, and emotional problems.
  6. Side effects are usually mild, reversible, and dose dependent, including anorexia, weight loss, sleep disturbances, increased heart rate and blood pressure, irritability, moodiness, headache, onset or worsening of motor tics, reduction of growth velocity (but not adult height). Do not worsen seizures in patients on adequate anticonvulsant therapy. Rebound of symptoms can occur with withdrawal of medication.
  7. Stimulants have generally been associated with cardiovascular events and death. Patients should be carefully evaluated for cardiovascular disease before beginning therapy and be periodically monitored, including blood pressure checks, while they are treated. However, despite concerns regarding cardiovascular risk, these medications are generally safe. Recent studies have shown that among young and middle-aged adults, current or new use of ADHD medications, compared with nonuse or remote use, is not associated with an increased risk of serious cardiovascular events. Routine, pre-treatment screening with ECGs is not currently recommended by the American Academy of Pediatrics or the American Academy of Child and Adolescent Psychiatry.
- Atomoxetine (Strattera):
  1. Selective norepinephrine reuptake inhibitor.
  2. Generally felt to be less effective than stimulants, but a useful alternative in patients who have not tolerated or responded to stimulants or in the setting of patient or family substance abuse.
  3. Efficacy and safety of use beyond 2 years of treatment have not been studied. There have been reports of behavioral abnormalities and increased suicidality in children and adolescents.
  4. Side effects: gastrointestinal upset, sleep disturbance, decreased appetite, dizziness, sexual side effects in men. Cardiovascular side effects have also been reported.
  5. There have been rare reports of severe liver injury in adults and children.
- Antidepressants (bupropion, imipramine, desipramine, nortriptyline):
  1. May be useful in patients with coexisting psychiatric disorders.
  2. Studies comparing efficacy versus stimulants are inconclusive.
  3. Side effects: arrhythmias, anticholinergic effects, lowering of seizure threshold.
- Alpha-2-adrenergic agonists (clonidine, guanfacine)
  1. Appear to be less effective than stimulants, but may be particularly useful as an adjunctive treatment to stimulants, particularly in patients with a partial stimulant response or who experience side effects such as sleep disturbance or concurrent symptoms of overarousal, irritability, or aggression.
  2. Extended-release formulations of guanfacine (Intuniv) and clonidine (Kapray) have been approved by the FDA for treatment of ADHD in children ages 6 to 17 yr. A transdermal clonidine patch is also available.
  3. Potential side effects include sedation, fatigue, headache, bradycardia, hypotension, and depression.
- Use of medications, particularly stimulants (which are monitored under the Controlled Substance Act), requires frequent monitoring.

DISPOSITION

- Although symptoms may change over time, for many patients ADHD represents a chronic condition that requires lifelong management.
- Patients are at higher risk for academic underachievement, lower socioeconomic status, work and relationship difficulties, high-risk behavior, and psychiatric comorbidities.

REFERRAL

- Diagnosis complicated by difficult-to-treat comorbid psychiatric conditions, developmental disorders, or mental retardation
- Lack of adequate response to stimulants/atomoxetine/alpha-adrenergic agents.

PEARLS & CONSIDERATIONS

- The World Health Organization's Adult Self-Report Scale (ASRS) v1.1 has good sensitivity and adaptability to the primary care setting.
- Among adults with persistent ADHD symptoms treated with medication, trials have shown that the use of cognitive behavioral therapy compared with relaxation with educational support resulted in improved ADHD symptoms, which were maintained at 12 mo.
- ADHD has been associated with criminal behavior in some studies. Data analysis has shown that among patients with ADHD, rates of criminality are lower during periods when they receive ADHD medication.
- Recommendations for the diagnosis and management of ADHD have been published by the Centers for Disease Control and Prevention (www.cdc.gov/ncbddd/adhd/treatment/treatment.html).

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Attention Deficit Hyperactivity Disorder (ADHD) (Patient Information)

AUTHOR: **EMILY R. KATZ, M.D.**

EVIDENCE

Abstract[1]

Objective:

There is considerable epidemiologic and neuropsychological evidence that attention deficit hyperactivity disorder (ADHD) is best considered dimensionally, lying at the extreme end of a continuous distribution of symptoms and underlying cognitive impairments. The authors investigated whether cortical brain development in typically developing children with symptoms of hyperactivity and impulsivity resembles that found in the syndrome of ADHD. Specifically, they examined whether a slower rate of cortical thinning during late childhood and adolescence, which they previously found in ADHD, is also linked to the severity of symptoms of hyperactivity and impulsivity in typically developing children.

Method:

In a longitudinal analysis, a total of 193 typically developing children with 389 neuroanatomic magnetic resonance images and varying levels of symptoms of hyperactivity and impulsivity (measured with the Conners' Parent Rating Scale) were contrasted with 197 children with ADHD with 337 imaging scans. The relationship between the rates of regional cortical thinning and severity of symptoms of hyperactivity/impulsivity was determined.

Results:

Youth with higher levels of hyperactivity/impulsivity had a slower rate of cortical thinning, predominantly in prefrontal cortical regions, bilaterally in the middle frontal/premotor gyri, extending down the medial prefrontal wall to the anterior cingulate; the orbitofrontal cortex; and the right inferior frontal gyrus. For each increase of one point in the hyperactivity/impulsivity score, there was a decrease in the rate of regional cortical thinning of 0.0054 mm/year (SE=0.0019 mm/year). Children with ADHD had the slowest rate of cortical thinning.

Conclusions:

Slower cortical thinning during adolescence characterizes the presence of both the symptoms and syndrome of ADHD, providing neurobiologic evidence for dimensionality of the disorder. Ⓐ

Evidence-Based Reference

Shaw P et al.: Cortical development in typically developing children with symptoms of hyperactivity and impulsivity: support for a dimensional view of attention deficit hyperactivity disorder, *Am J Psychiatry* 168:143–151, 2011. Ⓐ

SUGGESTED READINGS

American Academy of Pediatrics/American Heart Association clarification of statement on cardiovascular evaluation and monitoring of children and adolescents with heart disease receiving medications for ADHD: *J Dev Behav Pediatr* 29(4):335, 2008.

Babcock T, Ornstein CS: Comorbidity and its impact in adult patients with attention-deficit/hyperactivity disorder; a primary care perspective, *Postgrad Med* 121(3):73–82, 2009.

Dopheide JA, Pliszka SR: Attention-deficit/hyperactivity disorder: an update, *Pharmacotherapy* 29(6):656–679, 2009.

Feldman HM, Reiff MI: Attention deficit-hyperactivity disorder in children and adolescents, *N Engl J Med* 370:838–846, 2014.

Felt BT et al.: Diagnosis and management of ADHD in children, *Am Fam Physician* 90(7):456–464, 2014.

Habel LA et al.: ADHD medications and risk of serious cardiovascular events in young and middle-aged adults, *JAMA* 306(24):2673–2683, 2011.

Larson K et al.: Patterns of comorbidity, functioning, and service use for U.S. children with ADHD, 2007, *Pediatrics* 127:462, 2011.

Lichtenstein P et al.: Medication for attention deficit-hyperactivity disorder and criminality, *N Engl J Med* 367:2006–2014, 2012.

Rader R et al.: Current strategies in the diagnosis and treatment of childhood attention-deficit/hyperactivity disorder, *Am Fam Physician* 79(8):657–665, 2009.

Safren SA et al.: Cognitive behavioral therapy vs relaxation with educational support for medication-treated adults with ADHD and persistent symptoms, *JAMA* 304(8):875–880, 2010.

Volkow ND, Swanson JM et al.: Adult attention deficit-hyperactivity disorder, *N Engl J Med* 369:1935–1944, 2013.

BASIC INFORMATION

DEFINITION

Autism spectrum disorders encompass a continuum of developmental disorders characterized by marked social impairment. Table A1-80 describes the diagnostic keys for autism spectrum disorder. There is usually impairment in several additional domains, integral to social functioning, including language and communication. Stereotypic behavior and sensory issues (i.e., hypersensitivity, hyposensitivity) also are prominent. Comorbid intellectual disability and an increased risk of psychiatric disorder are frequently associated with autism spectrum disorder. Onset is typically before age 3 yr and may be diagnosed as early as 12 mo of age if developmental delays are severe. In rare cases, a child may be observed to develop normally to 12 to 24 mo and be diagnosed with autism spectrum disorder at 30 to 36 mo following gradual (or rapid) loss of social and language skills. The diagnosis of autism spectrum disorder without accompanying intellectual and language impairment (aka Asperger's syndrome) is typically made at a later age with 50% of affected children first diagnosed in kindergarten or 1st grade. DSM-5 criteria no longer differentiate autism and Asperger's as separate disorders. Instead, an overarching diagnosis of autism spectrum disorder is applied to both syndromes using severity levels (1, 2, or 3) to identify the magnitude of social and behavioral impairment and the support required to ensure the safety and well-being of the individual.

SYNONYMS

ASD
Autism
Autistic disorder
Early infantile autism
Childhood autism
Kanner's autism
Asperger's disorder
Pervasive developmental disorder PDD NOS

ICD-9CM CODES
299.00 Autism spectrum disorder
ICD-10CM CODES
F84.0 Autism spectrum disorder
DSM-5 CODE
299.00 Autism spectrum disorder

TABLE A1-80 Diagnostic Keys for Autism Spectrum Disorder

1. Impairment in social interaction
   a. Uses nonverbal behaviors
   b. Poor peer relationships
   c. Lack of interest in shared activities
   d. Lack of social or emotional reciprocity
2. Impairments in communication
   a. Delay in language
   b. Stereotyped or repetitive language
   c. Lack of age-appropriate social play
3. Repetitive behaviors
   a. Inflexibility
   b. Preoccupation with parts of objects

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Autism spectrum disorder afflicts approximately 1% of children in the United States.
PREVALENCE: 1:88 (1:54 for boys). It is unclear whether the increase in prevalence reflects an expansion of the diagnosis to include subthreshold cases, increased awareness of the disorder, and changes in public policy related to special education eligibility or a true increase in the frequency of autism spectrum disorder.
PREDOMINANT SEX: Male/female ratio of 4:1
PREDOMINANT AGE: Lifelong
PEAK INCIDENCE: Before age 3 yr
GENETICS:

- Autism spectrum disorder is highly heritable with a heritability index of 82% to 90%.
- De novo mutations account for 15% to 20% of autism spectrum disorder cases. In the remaining cases, the risk appears to be polygenic. Active research into common biologic mechanisms underlying autism spectrum disorder (including defective synaptic function) has identified chromosomal abnormalities in 6 major genes with as many as 20 to 30 additional genes in contributory roles, including glutamate-related genes.
- 5% risk rate for siblings of an affected individual, unless fragile X syndrome is determined as the pathway, increasing the risk rate to 50%.
- 70% to 95% concordance for autism spectrum disorder in monozygotic twins and 5% for dizygotic pairs.
- Clinical signs of autism spectrum disorder correlate with abnormal brain development. Overgrowth and neural dysfunction are evident at young ages and involve an abnormal excess number of neurons in the prefrontal cortex (PFC). This entirely neurobiologic signal of abnormal development has been reported to begin at 9 to 18 months of age.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Common triad of marked impairment in social interactions (poor social-emotional reciprocity), impaired and atypical verbal and nonverbal communication, and repetitive and unusual behavior or play.
- Marked impairment in the understanding and use of both verbal and nonverbal communication, including unchanging facial expression and lack of gestures during interactions.
- Stereotypic behavior (i.e., hand flapping, body rocking), or language (i.e., echolalia, palilalia).
- Perceptual hypersensitivity (i.e., auditory, tactile, olfactory, gustatory) and avoidance of novel stimuli; or perceptual hyposensitivity (e.g., abnormally high threshold for pain).

ETIOLOGY

- Majority of cases are not associated with a comorbid medical condition. However, two thirds of cases have a comorbid psychiatric feature (ADHD 29%, anxiety 22%, bipolar 20%, depression 20%).
- Significant increase in comorbid seizure disorder (25%) and intellectual disability (75%).
- Autism spectrum disorder is sometimes associated with other neurologic conditions (e.g., encephalitis, cytomegalovirus, toxoplasmosis, tuberous sclerosis, phenylketonuria [PKU], fragile X syndrome), suggesting that it also may result from nonspecific neuronal injury.
- Several studies have shown that there is no association between immunizations (specifically MMR vaccine) or thimerosal-containing vaccines (i.e., DPT) and autism spectrum disorder.
- Maternal use of valproate during pregnancy has been associated with increased risk for autism spectrum disorder and childhood autism in offspring.[1]
- Studies have raised concern about an association between the use of selective serotonin uptake inhibitors (SSRIs) during pregnancy and an increased risk of autism spectrum disorder. A recent study,[2] however, did not detect a significant association between maternal use of SSRIs during pregnancy and autism spectrum disorder in the offspring.
- Current research on the Shank family of proteins (SHANK3 [SH3 and multiple ankyrin repeat domains]) suggest that the systematic effects of alterations in Shank3 might contribute to the systematic features of autism spectrum disorders found in many patients.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rett's syndrome: occurs in females; follows a brief period of normal development (i.e., 12 to 15 mo; characterized by severe neurodevelopmental regression including head growth deceleration, loss of purposeful use of hands, hyperventilation (risk of aerophagia), and motor incoordination
- Childhood disintegration disorder: normal development until age 4 yr, followed by marked neurodevelopmental and behavioral regression beginning with loss of bladder and bowel control
- Childhood-onset schizophrenia: follows period of normal development
- Asperger's syndrome: lacks the language and cognitive deficits characteristic of autism
- Isolated symptoms of autism spectrum disorder: when occurring in isolation, defined as disorders (i.e., Phelan-Mcdermid syndrome, Aciardi syndrome, selective mutism, expressive language disorder, mixed

[1]Christensen J et al: Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism, *JAMA* 309:1696-1703, 2013.
[2]Hviid A et al: Use of selective serotonin reuptake inhibitors during pregnancy and risk of autism, *N Engl J Med* 369:2406-2415, 2013.

receptive-expressive language disorder, stereotypic movement disorder, severe-to-profound intellectual disability)

WORKUP

- Rule out underlying medical condition including genetic intellectual disability syndromes.
- Administer age-appropriate diagnostic instruments based on questionnaires and observation noting scales. Validated autism spectrum disorder–specific screening tools are available for children age ≥18 mo (e.g., Modified Checklist for Autism in Toddlers, Childhood Autism Rating Scale; Autism Diagnostic Observation Scale; Autism Diagnostic Interview-Revised; PDDST-III; Asperger's Syndrome Diagnostic Scale; Gilliam Asperger's Diagnostic Scale) and are being developed for younger children. General developmental screening tools are currently used in children <18 mo.

LABORATORY TESTS

- PKU screen (usually done at birth in the United States)
- Lead exposure screening
- Audiology testing for young children with autism spectrum disorder; school-based hearing screening may be sufficient in older children with autism spectrum disorders and without significant language or learning deficits
- Karyotype, microarray analysis, and DNA testing for fragile X syndrome in both boys and girls, as well as for different de novo copy number variants or de novo mutations in specific genes associated with the disorder.

IMAGING STUDIES

- EEG to diagnose coexisting seizure disorder if seizure is suspected or if language regression is present (i.e., Landau-Kleffner syndrome)
- Brain MRI if tuberous sclerosis or Aicardi syndrome (callosal agenesis) is suspected

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Consistent behavioral training program in both the home and school environments
- A number of programs are currently used; many are based on applied behavioral analysis (ABA), others include Pivotal Response Training (PRT), Floortime, and the Early Start Denver Model for Young Children with Autism.
- Special educational program focused on language and communication skills, social and life skills development
- Highly structured home environment
- Education for families and teachers; the Autism Speaks™ website may be helpful in this regard: http://www.autismspeaks.org/about_us.php

ACUTE GENERAL Rx

- Obsessive or ritualistic behaviors: selective serotonin reuptake inhibitors (SSRIs), atypical antipsychotics, valproic acid.
- Aggression, irritability, self-injury: atypical antipsychotic agents (e.g., risperidone), α-agonists, anticonvulsant mood stabilizers, SSRIs, beta-blockers, opiate antagonist (self-injury only).
- Hyperactivity, impulsivity, inattention: stimulants, alpha-agonists, atypical antipsychotics.
- Anxiety: SSRIs, buspirone, mirtazapine.
- Bipolar, mood lability: valproic acid, carbamazepine, lithium, aripiprazole.
- Depression: SSRIs, mirtazapine.

CHRONIC Rx

- Extended use of medications for acute management of comorbid psychiatric disorder.
- Pharmacotherapy is palliative, not curative of autism spectrum disorder.

DISPOSITION

- Most children will require some degree of assistance as adults.
- DSM-5 identifies 3 severity levels based on social communication and restricted, repetitive behaviors: Level 1 (requiring support), Level 2 (requiring substantial support), and Level 3 (requiring very substantial support).
- With early diagnosis and proper treatment/support, the prognosis for children without language and intellectual impairment (aka Asperger's syndrome) is fair to very good despite ongoing symptoms.
- Poorer outcomes include a lack of joint attention by age 4 yr, a lack of functional speech by age 5 yr, intellectual disability, seizures, comorbid medical or psychiatric syndromes, and a pervasive lack of social relatedness.
- Best outcomes are associated with early identification and treatment, the development of oral communication skills, and the cognitive and behavioral capacity for inclusion in regular education settings with typically developing peers.

REFERRAL

Assistance may be needed in diagnosis (child psychiatrist, clinical psychologist, geneticist, pediatric neurologist, developmental pediatrician), management (speech language pathologist, occupational therapist, clinical psychologist), parental teaching (psychiatric social worker), or intervention with the school system (educational advocate, attorney).

PEARLS & CONSIDERATIONS

- There is no scientific evidence of a relation between childhood vaccination and the development of autism spectrum disorder.
- Preliminary evidence suggests that a disproportionate number of children with autism spectrum disorder suffer from sleep difficulties, including obstructive sleep apnea, with sequelae mimicking ADHD.
- The Center for Autism & Developmental Disabilities at Bradley Hospital, an affiliate of the Brown Medical School, is the largest and most comprehensive treatment program in the U.S. for children with autism spectrum disorder and comorbid psychiatric illness (www.bradleyhospital.org).
- University of California Davis M.I.N.D. Institute is devoted to the study of autism (http://www.ucdmc.ucdavis.edu/mindinstitute).

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Autism (Patient Information)

AUTHOR: **ROWLAND P. BARRETT, PH.D.**

EVIDENCE

Abstract[1]

Context:

As many as 1 in every 110 children in the United States has an autism spectrum disorder (ASD). Secretin is one of many medical treatments studied for treating the symptoms of ASDs, but there is currently no consensus regarding which interventions are most effective.

Objective:

To systematically review evidence regarding the use of secretin in children with ASDs who are aged 12 years and younger.

Methods:

We searched the Medline, PsycINFO, and ERIC (Education Resources Information Center) databases from 2000 to May 2010 and reference lists of included articles. Two reviewers independently assessed each study against predetermined inclusion/exclusion criteria. Two reviewers independently extracted data regarding participant and intervention characteristics, assessment techniques, and outcomes and assigned overall quality and strength-of-evidence ratings on the basis of predetermined criteria.

Results:

Evidence from seven randomized controlled trials supports a lack of effectiveness of secretin for the treatment of ASD symptoms including language and communication impairment, symptom severity, and cognitive and social skill deficits. No studies have resulted in significantly greater improvements in measures of language, cognition, or autistic symptoms when compared with placebo; study authors who reported improvement over time did so equally for both the intervention and placebo groups.

Conclusions:

Secretin has been studied extensively in multiple randomized controlled trials, and there is clear evidence that it lacks benefit. The studies of secretin included in this review uniformly point to a lack of significant impact of secretin in the treatment of ASD symptoms. Given the high strength of evidence for a lack of effectiveness, secretin as a treatment approach for ASDs warrants no further study. Ⓐ

Evidence-Based Reference

Krishnaswami S et al.: A systematic review of secretin for children with autism spectrum disorders, *Pediatrics* 127:e1322–e1325, 2011. Ⓐ

SUGGESTED READINGS

Attwood T. The complete guide to Asperger's syndrome. Jessica Kingsley Publishers: London.

Autism and Developmental Disabilities Monitoring Network Surveillance Year 2006 Principal Investigators: Centers for Disease Control and Prevention (CDC): Prevalence of autism spectrum disorders—Autism and Developmental Disabilities Monitoring Network, United States, 2006, *MMWR Surveill Summ* 58:1–20, 2009.

Courchesne E et al.: Preliminary communication: neuron number and size in prefrontal cortex of children with autism, *JAMA* 306(18):2001–2010, 2011.

Dawson G et al.: Randomized, controlled trial of an intervention for toddlers with autism: The Early Start Denver Model, *Pediatrics* 125:e17, 2010.

Gerber JS, Offit PA: Vaccines and autism: a tale of shifting hypotheses, *Clin Infect Dis* 48(4):456–461, 2009.

Herbert MR: SHANK3, the synapse, and autism, *N Engl J Med* 365(2):173–175, 2011.

Johnson CP et al.: For the Council on Children with Disabilities Identification and evaluation of children with autism spectrum disorders, *Pediatrics* 120(5):1183–1215, 2007.

Mefforrd HC et al.: Genomics, intellectual disability, and autism, *N Engl J Med* 366:733–743, 2012.

Price CS et al.: Prenatal and infant exposure to thimerosal from vaccines and immunoglobulins and risk of autism, *Pediatrics* 126:656, 2010.

Ramachandran VS, Oberman LM: Broken mirrors: a theory of autism, *Sci Am* 63–69, 2006.

Rapin I, Tuchman RF: Autism: definition, neurobiology, screening, diagnosis, *Pediatr Clin North Am* 55(5):1129–1146, 2008. viii, Review.

Zwaigenbaum L et al.: Clinical assessment and management of toddlers with suspected autism spectrum disorder: insights from studies of high-risk infants, *Pediatrics* 123(5):1383–1391, 2009. Review.

BASIC INFORMATION

DEFINITION

Autoimmune hemolytic anemia (AIHA) is anemia secondary to premature destruction of red blood cells (RBCs) caused by the binding of autoantibodies and/or complement to RBCs. A classification of the hemolytic anemias is described in Table A1-81.

ICD-9CM CODES
283.0 Autoimmune hemolytic anemia
ICD-10CM CODES
D58.9 Drug-induced autoimmune hemolytic anemia

EPIDEMIOLOGY & DEMOGRAPHICS

Predominant sex and age: most common in women <50 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pallor, jaundice.
- Tachycardia with a flow murmur may be present if anemia is pronounced.
- Most common presentation is dyspnea and fatigue.
- Patients with intravascular hemolysis may present with dark urine and back pain.
- The presence of hepatomegaly and/or lymphadenopathy suggests an underlying lymphoproliferative disorder or malignancy; splenomegaly may indicate hypersplenism as a cause of hemolysis.

ETIOLOGY

- Warm antibody mediated: immunoglobulin (Ig) G (often idiopathic or associated with leukemia, lymphoma, thymoma, myeloma, viral infections, and collagen-vascular disease)
- Cold antibody mediated: IgM and complement in majority of cases (often idiopathic; at times associated with infections, lymphoma, or cold agglutinin disease)
- Drug induced (Table A1-82): three major mechanisms:
  1. Antibody directed against Rh complex (e.g., methyldopa)
  2. Antibody directed against RBC-drug complex (hapten induced; e.g., penicillin)
  3. Antibody directed against complex formed by drug and plasma proteins; the drug-plasma protein-antibody complex causes destruction of RBCs (innocent bystander; e.g., quinidine)

TABLE A1-81 Classification of the Hemolytic Anemias

Acquired
Environmental factors
- Antibody: immunohemolytic anemias
- Mechanical trauma: TTP, HUS, heart valve
- Toxins, infectious agents: malaria, etc.

Membrane defects
- Paroxysmal nocturnal hemoglobinuria
- Spur cell anemia

Hereditary spherocytosis, etc.

Congenital
Defects of cell interior
- Hemoglobinopathies: sickle cell, thalassemia
- Enzymopathies: G6PD deficiency, etc.

G6PD, Glucose-6-phosphate dehydrogenase; *HUS,* hemolytic-uremic syndrome; *TTP,* thrombotic thrombocytopenic purpura.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hemolytic anemia caused by membrane defects (paroxysmal nocturnal hemoglobinuria, spur cell anemia, Wilson disease)
- Non–immune mediated (microangiopathic hemolytic anemia, hypersplenism, cardiac valve prosthesis, giant cavernous hemangiomas, march hemoglobinuria, physical agents, infections, heavy metals, certain drugs [nitrofurantoin, sulfonamides, ribavirin])

WORKUP

Evaluation consists primarily of laboratory evaluation to confirm hemolysis and exclude other causes of the anemia. Although most cases of AIHA are idiopathic, potential causes should always be sought.

LABORATORY TESTS

- The basic features of hemolytic anemia are reticulocytosis, low haptoglobin levels, elevated indirect bilirubin, and elevated LDH.
- Initial laboratory tests: complete blood count (anemia), reticulocyte count (elevated; Fig. EA1-141 describes the evaluation of anemia with elevated reticulocyte count), liver function studies (elevated indirect bilirubin, lactate dehydrogenase), evaluation of peripheral smear (Fig. EA1-142).
- A direct antiglobulin test (DAT, Coombs test) is initially performed with a polyspecific antibody to detect IgG or complement C3d bound to RBCs. If the DAT is positive the diagnosis of autoimmune hemolytic anemia (AIHA) is confirmed. A positive direct Coombs test indicates presence of antibodies or complement on the surface of RBCs (Fig. A1-143); positive indirect Coombs test implies presence of anti-RBC antibodies freely circulating in the patient's serum (Fig. A1-144).
- If the DAT is positive with IgG alone or with IgG + C3d, the AIHA is most likely due to warm antibody (WAIAHA), whereas if the DAT is positive with C3d only it is most likely caused by a cold antibody (CAIHA).
- Hepatitis serology, antinuclear antibody.
- Urinary tests may reveal hemosiderinuria or hemoglobinuria.

IMAGING STUDIES

- Chest x-ray
- CT scan of chest and abdomen to rule out lymphoma should be considered

TABLE A1-82 Drug-Induced Autoimmune Hemolytic Anemia

Drug	Risk Factors	AIHA Onset	Type of AIHA	Response to Treatment	Diseases Treated
Methyldopa	Not known	Delayed	WAIHA	Resolution after withdrawal	Hypertension
INF-α	Pretherapeutic positive DAT	Delayed (8-11 mo)	WAIHA	Resolution spontaneous or after steroids	Hepatitis C Hematologic malignancies
Efazulimab	Not known	Many months	WAIHA	Resolution after withdrawal	Arthritis (rare)
Etanercept	Not known	Delayed	CAIHA	Resolution after rituximab	Rheumatoid arthritis (rare)
Fludarabine Cladribine Pentostatin	CLL Pretherapeutic positive DAT result	Early (median, 3-4 cycle) or delayed	WAIHA Mixed AIHA	Half of AIHA resolve after steroids	CLL Lymphomas* AML*
Bendamustine	CLL	No or only very low risk of AIHA			CLL Lymphomas
Chlorambucil	CLL	Delayed onset	WAIHA		CLL
Eculizumab	Patients with incomplete response	After treatment	CAIHA		PNH
Lenalidomide		During treatment	WAIHA	Resolution after withdrawal	One case treated for lymphoma

*No or very low risk.
AML, Acute myeloid leukemia; *CAIHA,* cold autoimmune hemolytic anemia; *CLL,* chronic lymphocytic leukemia; *INF,* interferon; *PNH,* paroxysmal nocturnal hemoglobinuria; *WAIHA,* warm autoimmune hemolytic anemia.
From Hoffman R: *Hematology, basic principles and practice,* 6th ed, Philadelphia, 2013, Saunders.

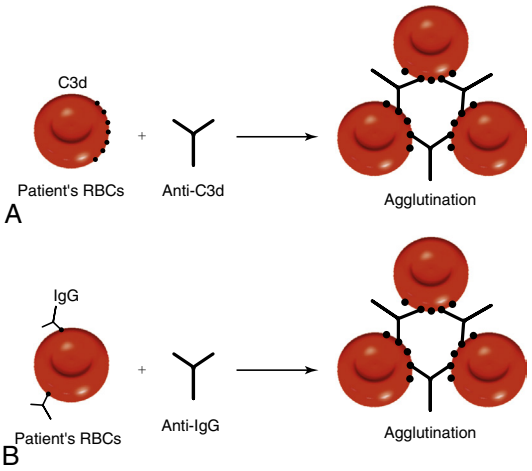


FIGURE A1-143 Direct antiglobulin test for detection of **(A)** erythrocyte bound C3d or **(B)** IgG. Hemagglutination occurs when anti-C3d or anti-IgG can create a lattice structure by bridging sensitized red blood cells *(RBCs).* (From Hoffman R et al: *Hematology, basic principles and practice,* ed 6, Philadelphia, 2013, Saunders.)

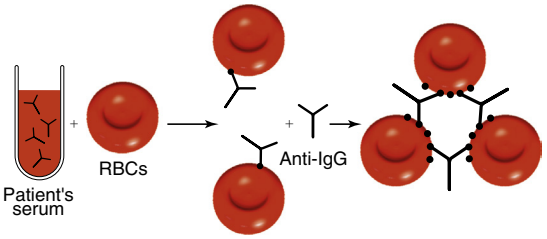


FIGURE A1-144 Indirect antiglobulin test for detection of antierythrocyte antibodies in serum. The patient's serum is mixed with a panel of normal red blood cells *(RBCs),* some (or all) of which express the antigen(s) recognized by the serum antibodies. Afrer the antibody-coated erythrocytes are washed, an anti-IgG reagent is added and hemagglutination occurs. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 6, Philadelphia, 2013, Elsevier.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Discontinuation of any potentially offensive drugs
- Plasmapheresis exchange transfusion for severe life-threatening cases only
- Avoid cold exposure in patients with cold antibody

ACUTE GENERAL Rx

- Prednisone 1 to 2 mg/kg/day in divided doses initially in warm antibody AIHA. Corticosteroids are generally ineffective in cold antibody AIHA.
- Splenectomy in patients responding inadequately to corticosteroids when RBC sequestration studies indicate splenic sequestration.
- Immunosuppressive drugs and/or immunoglobulins only after both corticosteroids and splenectomy (unless surgery is contraindicated) have failed to produce an adequate remission.
- Danazol, typically used in conjunction with corticosteroids (may be useful in warm antibody AIHA).
- Immunosuppressive drugs (azathioprine, cyclophosphamide) may be useful in warm antibody AIHA but are indicated only after both corticosteroids and splenectomy (unless surgery is contraindicated) have failed to produce an adequate remission.
- Table A1-83 summarizes treatment options for primary and secondary warm autoimmune hemolytic anemia and cold autoimmune hemolytic anemia. Second-line treatment options after steroids are described in Table A1-84.

DISPOSITION

Prognosis is generally good unless anemia is associated with underlying disorder with a poor prognosis (e.g., leukemia, myeloma).

REFERRAL

- Hematology referral in all cases of AIHA
- Surgical referral for splenectomy in refractory cases

PEARLS & CONSIDERATIONS

COMMENTS

- The direct antiglobulin test demonstrates the presence of antibodies or complement on the surface of RBCs and is the hallmark of autoimmune hemolysis.
- Warm AIHA is often associated with autoimmune diseases, whereas cold AIHA often follows viral infections (e.g., mononucleosis) and *Mycoplasma pneumoniae* infections.
- HIV can induce both warm and cold AIHA.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **FRED F. FERRI, M.D.**

TABLE A1-83 Treatment Options for Primary and Secondary Warm Autoimmune Hemolytic Anemia and Cold Autoimmune Hemolytic Anemia

Disease or Condition	First Line	Second Line	Beyond Second Line	Last Resort
Primary AIHA	Steroids	Splenectomy Rituximab	Azathioprine, MMF, cyclosporine, cyclophosphamide	High-dose cyclophosphamide, alemtuzumab
B- and T-cell NHL	Steroids	Chemotherapy +/– rituximab (splenectomy in SMZL)		
Hodgkin's lymphoma	Steroids	Chemotherapy		
Solid tumors	Steroids Surgery			
Ovarian dermoid cyst	Ovariectomy			
SLE	Steroids	Azathioprine	MMF	Rituximab Autologous SCT
Ulcerative colitis	Steroids	Azathioprine		Total colectomy
CVID	Steroids + IgG replacement			
ALPD	Steroids	MMF	Sirolimus	
Wiskott Aldrich syndrome	Steroids	Allogeneic SCT		
Allogeneic SCT	Steroids	Rituximab*	Splenectomy T-cells infusion	
Organ transplantation	Reduction of immune suppression, steroids			
Drug induced	Withdrawal	Steroids		
Primary CAD	Protection from cold exposure	Rituximab Chlorambucil	Fludarabine + rituximab	Eculizumab,† bortezomid†
PCH	Supportive treatment (postinfectious)	Rituximab* (chronic)		

AIHA, Autoimmune hemolytic anemia; *ALPD,* autoimmune lymphoproliferative disorders; *CAD,* cold agglutinin disease; *CVID,* common variable immune deficiency; *IgG,* immunoglobulin G; *MMF,* mycophenolate mofetil; *NHL,* non-Hodgkin lymphoma; *PCH,* paroxysmal cold hemoglobinuria; *SCT,* stem cell transplantation; *SLE,* systemic lupus erythematosus; *SMZL,* splenic marginal zone lymphoma.

*Early second-line treatment because of known poor response to steroids.

†Off-label use in single cases.

From Hoffman R: *Hematology, basic principles and practice,* 6th ed, Philadelphia, 2013, Saunders.

TABLE A1-84 Second-Line Treatment Options After Steroids

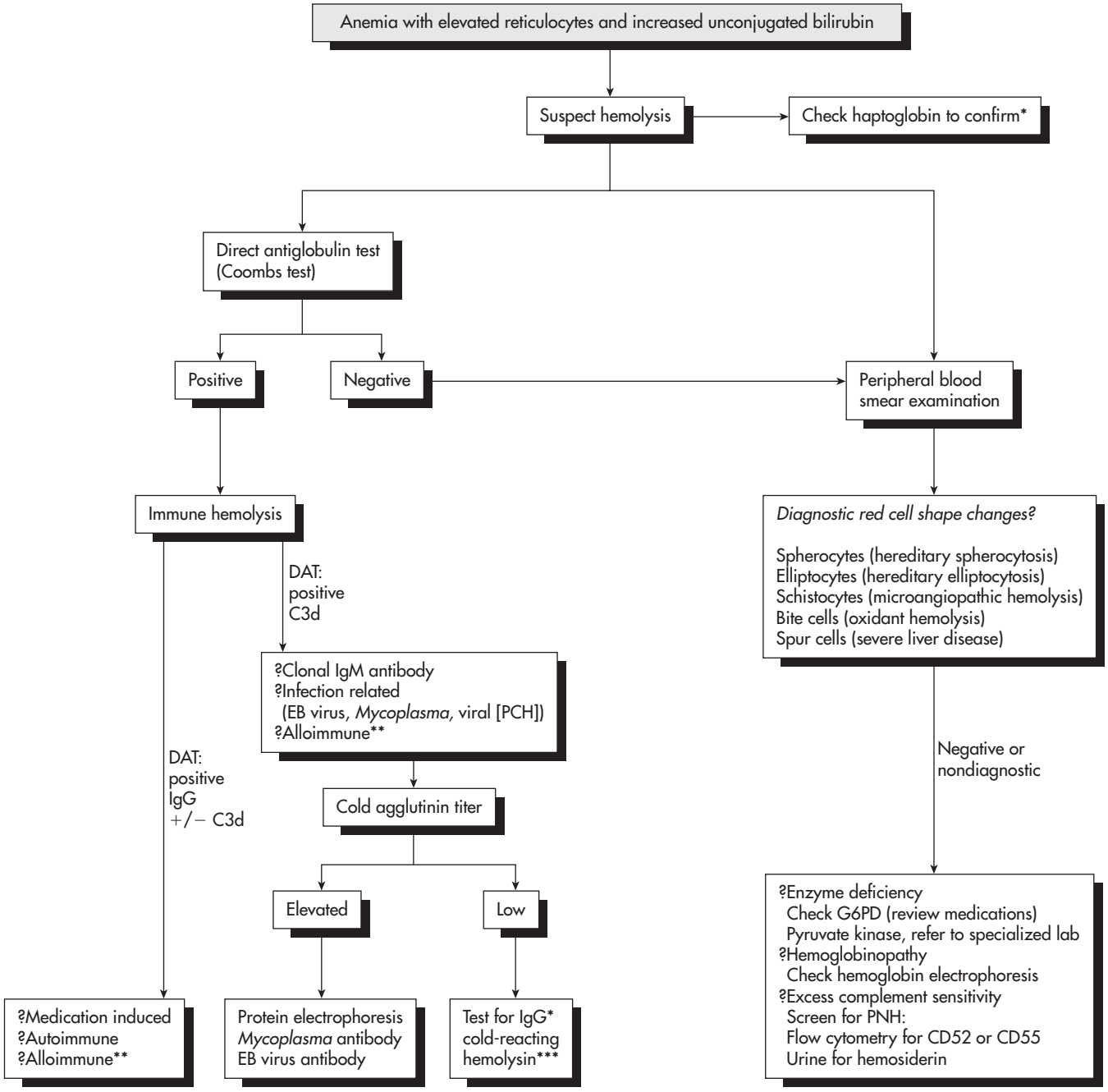
Treatment	Dosing and Application	Side Effects	Precautions
Splenectomy (acute)	Preferentially laparoscopic	Infections, thrombosis	Postoperative thromboprophylaxis
Splenectomy (long term)	—	Infections Venous thrombosis	Vaccination, patient information
Rituximab	375 mg/m^2 on days 1, 8, 15, and 22 IV	Infusional reactions Infections	Premedication with antihistamines (and steroids)
Danazol	200-400/day PO	Hepatotoxicity	None
Cyclophosphamide	PO or IV Dose adjusted to neutrophil count	Neutropenia Mutagenesis	Neutrophil count monitoring, bladder protection after high doses
Azathioprine	2.0-3.mg/kg/day PO Dose adjusted to neutrophil count	Neutropenia	Neutrophil count monitoring; avoid interaction with other drugs (e.g., allopurinol)
Mycophenolate mofetil	1-2 × 1 g/d PO	Gastrointestinal	
Cyclosporine	PO Dose adjusted to blood levels of CyA Target level, 200-400 ng/mL	Nephrotoxicity Gum hyperplasia	Monitoring of CyA levels and creatinine
Alemtuzumab	SC (variable doses)	Neutropenia	Anti-infectious prophylaxis

CyA, Cyclosporine A; *IV,* intravenous; *PO,* oral; *SC,* subcutaneous.

From Hoffman R: *Hematology, basic principles and practice,* 6th ed, Philadelphia, 2013, Saunders.

SUGGESTED READINGS

Dhaliwal G, et al.: Hemolytic anemia, *Am Fam Physician* 69:2599, 2004.
Gehrs BC, Friedberg RC: Autoimmune hemolytic anemia, *Am J Hematol* 69:258, 2002.



*Other parameters that may be useful: serum lactic dehydrogenase, which is markedly increased in intravascular hemolysis, and plasma hemoglobin, which is elevated in severe hemolysis.
**Hemolytic transfusion reactions, mismatched red blood cell transplants.
***Donath-Landsteiner test.

FIGURE EA1-141 Anemia with elevated reticulocytes and increased unconjugated bilirubin. *DAT,* Direct antiglobulin test; *EB,* Epstein-Barr; *G6PD,* glucose-6-phosphate dehydrogenase; *PCH,* paroxysmal cold hemoglobinuria; *PNH,* paroxysmal nocturnal hemoglobinuria. (From Young NS et al [eds]: *Clinical hematology,* St Louis, 2006, Mosby.)

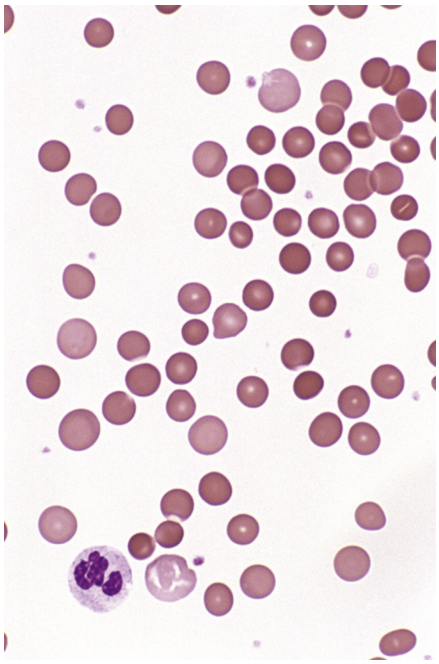


FIGURE EA1-142 In warm antibody hemolytic anemia, numerous spherocytes are seen. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

Autoimmune Hepatitis PTG EBM

BASIC INFORMATION

DEFINITION

Autoimmune hepatitis is a chronic inflammatory condition of the liver characterized by elevated serum globulin levels (IgG), presence of circulating autoantibodies, interface hepatitis on histology, and plasma cell rich infiltrate. Two types have been described:

- Type 1, or "classic," autoimmune hepatitis is the most predominant form in the United States and worldwide (80%); has a bimodal age distribution with peaks between 10 to 20 and 45 to 70 years of age; patients are positive for antinuclear antibodies (ANA) and/or antismooth muscle antibodies (SMA) and have specific associated HLA haplotypes: B8, DR3, DR4.
- Type 2 is rare in the United States and primarily affects young children between 2 and 14 years of age; characterized by the presence of antibodies to liver/kidney microsomes (anti-LKM-1) or liver cytosol 1; patients have associated HLA haplotypes: B14, DR. This form is generally more advanced at presentation and more difficult to treat.

SYNONYMS

Autoimmune chronic active hepatitis
Chronic active hepatitis
Lupoid hepatitis
Plasma cell hepatitis

ICD-9CM CODES
571.49 Chronic hepatitis
ICD-10CM CODES
K75.4 Autoimmune hepatitis
K73.2 Chronic active hepatitis, not elsewhere classified

EPIDEMIOLOGY & DEMOGRAPHICS

- Annual incidence (estimated): 0.2 to 2.0 cases per 100,000, similar to PBC, more common than PSC.
- Point prevalence (estimated): 16.9 per 100,000
- Type 1: age of onset has a bimodal distribution with peaks between 10 to 20 and 45 to 70 years; type 2: more common in young children 2 to 14 years of age.
- Female/male ratio is 3.6:1, type 1 has 80% female predominance whereas type 2 has 90% female predominance.
- Approximately 100,000 to 200,000 persons affected in the United States.
- Accounts for 4% to 6% of liver transplants in United States.
- Associated with HLA-DRB1*0301 and HLA-DRB1*0401 alleles.

CLINICAL PRESENTATION

- Varies from intermittent asymptomatic elevations of liver enzymes to advanced cirrhosis. Cirrhosis is often the presenting stage. AIH can also present initially as a fulminant hepatitis.
- Symptoms may include fatigue, anorexia, nausea, abdominal pain, pruritus, and arthralgia.
- Autoimmune findings may include arthritis, xerostomia, keratoconjunctivitis, cutaneous vasculitis, and erythema nodosum.
- Patients with advanced disease can show hepatosplenomegaly, ascites, peripheral edema, abnormal bleeding, and jaundice.

ETIOLOGY

- Exact etiology is unknown; liver histology demonstrates cell-mediated immune attack against hepatocytes.
- Presence of a variety of autoantibodies suggests an autoimmune mechanism.
- There are likely two components involved: genetic predisposition and an inciting environmental trigger.
- Potential triggering agents such as viruses (hepatitis A, B, C) or drugs (minocycline, nitrofurantoin) likely possess some homology similar to liver-specific antigens.

Dx DIAGNOSIS

- A simplified diagnostic criteria for routine clinical practice has been developed by the International Autoimmune Hepatitis Group (see Table A1-85).
- Histology: lymphoplasmacytic infiltrate invading the hepatocyte boundary surrounding the portal triad (limiting plate). Also a periportal infiltrate may be seen (interface hepatitis).

DIFFERENTIAL DIAGNOSIS

- Acute viral hepatitis (A, B, C, D, E, cytomegalovirus, Epstein-Barr, herpes).
- Chronic viral hepatitis (B, C).
- Toxic hepatitis (alcohol, drugs).
- Primary biliary cirrhosis.
- Primary sclerosing cholangitis.
- Hemochromatosis.
- Nonalcoholic steatohepatitis.
- SLE.
- Wilson's disease.
- Alpha-1 antitrypsin deficiency.

WORKUP

- History and physical examination with attention to the presence of autoimmune abnormalities such as autoimmune thyroiditis, Graves' disease, inflammatory bowel disease, celiac sprue, and rheumatoid arthritis.
- Liver function tests and serum gammaglobulins.
- Tests for autoantibodies: ANA, SMA, anti-LKM.
- Liver biopsy for establishing diagnosis and disease severity.

LABORATORY TESTS

- Aminotransferases generally elevated, may fluctuate.
- Bilirubin and alkaline phosphatase moderately elevated or normal.
- Elevation of gamma globulin (>2.0 g/dl [20 g/L]) and immunoglobulin G.
- Circulating autoantibodies often present:
  1. Rheumatoid factor.
  2. ANAs.
     a. Present in two thirds of patients.
     b. Typical pattern is homogeneous or speckled.
     c. Titer does not correlate with the stage, activity, or prognosis.
  3. SMAs
     a. Present in 87% of patients.
     b. Titer does not correlate with course or prognosis.
  4. Anti-LKM antibodies.
     a. Typically found in patients who are ANA negative and SMA negative.
     b. Characterizes type 2 AIH.
     c. Present in pediatric population and up to 20% of adults in Europe; also present in patients with drug-induced hepatitis.
  5. Autoantibodies against soluble liver antigen and liver-pancreas antigen (anti-SLA/LP).
     a. Present in 10% to 30% of patients.
     b. Associated with higher rate of relapse after corticosteroid therapy.
     c. Several studies suggest that patients with anti-SLA/LP have a more severe course.
  6. Serum p-ANCA levels are useful for diagnosis of the 10% to 15% of patients with negative SMA, ANA, and low gamma globulin levels.
- Hypoalbuminemia and prolonged prothrombin time with advanced disease.
- There is a well-described overlap syndrome with primary biliary cirrhosis (7%), primary sclerosing cholangitis (6%), and autoimmune cholangitis (11%). In patients who do not respond to therapy after 3 mo, consider cholangiographic studies to evaluate for primary sclerosing cholangitis.

TABLE A1-85 Simplified Diagnostic Criteria for Autoimmune Hepatitis

Variable	Cutoff	Points	Cutoff	Points
ANA or SMA	≥1:40	1	≥1:80	2
LKM			≥1:40	2
SLA			Positive	2
IgG	≥ULN	1	≥1.1 × ULN	2
Histology	Compatible with AIH	1	Typical of AIH	2
Absence of viral hepatitis			Yes	2

Maximum number of points for all antibodies = 2, total = 8.
Probable AIH ≥6 points, definite AIH ≥7 points. 88% sensitivity and 97% specificity.
AIH, Autoimmune hepatitis; *ANA,* antinuclear antibody; *IgG,* immunoglobulin G; *LKM,* liver/kidney microsomes; *SLA,* soluble liver antigen; *SMA,* smooth muscle antibody; *ULN,* upper limit of normal.

IMAGING STUDIES

- Ultrasound of liver and biliary tree to rule out obstruction or hepatic mass.
- Cirrhosis secondary to AIH is a risk factor for development of hepatocellular carcinoma (although less so than viral hepatitis). Cirrhotics should get ultrasonography and AFP every 6 months.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoid alcohol and hepatotoxic medications.
- Liver transplantation is an option for end-stage disease or fulminant hepatic failure.

PHARMACOLOGIC THERAPY

- Initial treatment:
  1. Prednisone or prednisolone 40 to 60 mg/day PO or combination treatment with prednisone 30 mg/day PO plus azathioprine 50 mg/day PO, with a gradual taper to prednisone 10 mg PO daily over 2 to 3 mo as liver function test (LFT) results normalize. A combination of oral budesonide (6 to 9 mg/day) and azathioprine (1 to 2 mg/kg/day) can be used to induce and maintain remission in patients with noncirrhotic AIH, with a lower rate of steroid-specific side effects.
  2. Combination therapy allows lower prednisone doses, fewer steroid side effects, and faster normalization of LFTs.
  3. Goal of therapy is remission (normalization of gamma-globulin and bilirubin, reduction of aminotransferases to less than twice the upper limit of normal, resolution of symptoms, and improvement in liver histology).
- Indications for treatment:
  1. Serum aminotransferase more than 10 times greater than the upper limit of normal.
  2. Serum aminotransferase more than five times the upper limit of normal, with serum gamma-globulin level twice the upper limit of normal.
  3. Histologic features of bridging necrosis.
  4. Symptomatic disease: incapacitating symptoms such as fatigue and arthralgia.
- Relative indications:
  Asymptomatic patients with elevated liver enzymes or limited histological activity.
- Treatment not indicated.
  Inactive cirrhosis.
- Evaluation of treatment response:
  1. Goal is the absence of symptoms, resolution of liver function test abnormalities, and histologic improvement. Generally, this is a steroid-responsive condition, but up to 20% do not respond.
  2. Patients whose transaminase levels normalize may continue to have ongoing active hepatitis involving inflammation and fibrosis.
  3. Histologic improvement may lag behind clinical and laboratory improvement by as much as 6 mo. Because of this, repeat liver biopsy should be considered after normalization of transaminase levels. A review of AIH studies between 1972 and 2013 shows that hepatic fibrosis improves in 53% to 57% of cases and progressive fibrosis slows or is prevented in 79% of patients.
  4. After initial remission is achieved, one may consider tapering medications. Steroid withdrawal should be done only if liver function tests normalize and histologic quiescence is achieved. About 50% to 86% of patients will relapse after this and require long-term maintenance medications.
  5. Complete normalization on biopsy is associated with a 15% to 20% risk of relapse, whereas persistent interface hepatitis is associated with a 90% risk of relapse.
  6. Do not attempt multiple treatment withdrawals. The risk of developing cirrhosis with single relapse is 9.5%, whereas multiple relapses are associated with 37.5% risk of developing cirrhosis. The patient with sustained remission has a risk of cirrhosis of 4.5%.

DISPOSITION

- Follow up as outpatient.
- Long-term treatment may be necessary for sustained remission in individuals who continuously relapse and in partial responders.
- Sixty-five percent of patients achieve remission by 18 mo; 80% achieve remission by 3 yr.
- Approximately 10% to 15% of patients do not respond to conventional therapy. The risk factors for nonresponse include presence of underlying cirrhosis, younger age or longer duration of disease, HLA-B8 or DR3. High dose therapy can achieve remission in 70%: prednisone 60 mg or dual therapy with prednisone 30 mg and AZA 150 mg. Other alternatives: mycophenolate or tacrolimus have been used successfully.
- Patients in whom end-stage liver disease develops are candidates for liver transplantation. AIH can recur in transplanted livers (25% in first 5 years; 50% in 10 years, probability).

REFERRAL

Patients with advanced cirrhosis or who progress to end-stage liver disease are candidates for liver transplantation and should be referred to appropriate medical centers that provide liver transplantation services.

PEARLS & CONSIDERATIONS

COMMENTS

- ANA and SMA are observed together in 60% of cases. Serum titers >1:40 suggest autoimmune hepatitis.
- A variety of autoimmune conditions can be seen in association with autoimmune hepatitis, including thyroiditis, Graves' disease, ulcerative colitis, rheumatoid arthritis, uveitis, pernicious anemia, Sjögren's syndrome, mixed connective tissue disease, CREST syndrome, and vitiligo.
- Variant forms of autoimmune hepatitis (overlap syndrome) have clinical and serologic findings of autoimmune hepatitis plus features of other forms of chronic liver disease such as primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC).

PREVENTION

None

PATIENT & FAMILY EDUCATION

- American Liver Foundation (ALF): Phone: 800-GO-LIVER (465-4837); Internet: www.liverfoundation.org
- National Digestive Diseases Information clearinghouse: http://digestive.niddk.nih.gov/ddiseases/pubs/autoimmunehep

EBM EVIDENCE

Available at www.expertconsult.com.

SUGGESTED READINGS

Available at www.expertconsult.com.

RELATED CONTENT

Autoimmune Hepatitis (Patient Information).

AUTHORS: **MARIA ANDREA CATANA, M.D.,** and **KITTICHAI PROMRAT, M.D.**

EVIDENCE

Abstract[1]

Background & Aims:

The long-term outcomes of patients treated for autoimmune hepatitis (AIH) are considered to be good. However, follow-up data beyond 10 years are limited and confined to tertiary referral centers. We assessed long-term outcomes and determinants of outcome in patients with AIH from a nontransplant center.

Methods:

We studied 245 patients (204 women; median age, 56 years; range, 2.5 to 87 years) with AIH (167 definite by International AIH Group criteria) managed at a single nontransplant center from 1971 to 2007.

Results:

A group of 229 patients (93%) achieved normal serum levels of alanine aminotransferase within 12 months after treatment. After a median follow-up period of 9.4 years (range, 0.01 to 36 years), 11 patients received liver transplants (2 subsequently died). Seventy other patients died (30 from liver disease), 15 were censored (moved away, defaulted, or developed primary biliary cirrhosis), and 149 were still being followed up on December 31, 2007. Survival rates from all-cause death or transplantation were 82% ± 3% and 48% ± 5% after 10 and 20 years, respectively, and from liver-related death or transplantation were 91% ± 2% and 70% ± 5%, respectively. The standardized mortality ratio was 1.63 for all-cause death (95% confidence interval [CI], 1.25 to 2.02), 1.86 also considering liver transplant as "death" (95% CI, 1.49 to 2.26), and 0.91 for non–liver-related death (95% CI, 0.62 to 1.19). By Cox regression analysis, liver decompensation, cirrhosis at any time, failure to normalize levels of alanine aminotransferase within 12 months, and >4 relapses per decade were significantly associated with liver-related death or transplant.

Conclusions:

Despite a good initial response to immunosuppression, long-term mortality of patients with AIH is greater than that of the general population. Ⓐ

Evidence-Based Reference

Hoeroldt B, et al.: Long-term outcomes of patients with autoimmune hepatitis managed at a nontransplant center, *Gastroenterology* 140:1980–1989, 2011. Ⓐ

SUGGESTED READINGS

Björnsson E et al.: Drug-induced autoimmune hepatitis: clinical characteristics and prognosis, *Hepatology* 51(6):2040–2048, 2010.

Boberg KM, Aadland E, Jahnsen J, Raknerud N, Stiris M, Bell H: Incidence and prevalence of primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis in a Norwegian population, *Scand J Gastroenterol* 33(1):99–103, 1998.

Czaja AJ: Review article: the prevention and reversal of hepatic fibrosis in autoimmune hepatitis, *Aliment Pharmacol Ther* 39(4):385–406, 2014.

Czaja AJ, Manns MP: Advances in the diagnosis, pathogenesis, and management of autoimmune hepatitis, *Gastroenterology* 139(1):58–72, 2010.

Duclos-Vallee JC, Sebagh M: Recurrence of autoimmune disease, primary sclerosing cholangitis, primary biliary cirrhosis, and autoimmune hepatitis after liver transplantation, *Liver Transplant* 15(Suppl 2):S25–S34, 2009.

Gossard AA, Lindor KD: Autoimmune hepatitis: a review, *J Gastroenterol* 47(5):498–503, 2012.

Heneghan MA et al.: Autoimmune hepatitis, *Lancet* S0140–6736(12), June 2013.

Heneghan MA, McFarlane IG: Current and novel immunosuppressive therapy for autoimmune hepatitis, *Hepatology (Baltimore, Md)* 35(1):7–13, 2002.

Manns MP et al.: American Association for the Study of Liver Diseases: Diagnosis and management of autoimmune hepatitis, *Hepatology* 51(6):2193–2213, 2010a.

Manns MP et al.: European AIH-BUC-Study Group. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis, *Gastroenterology* 139(4):1198–1206, 2010b.

Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, et al.: Diagnosis and management of autoimmune hepatitis, *Hepatology (Baltimore, Md)* 51(6):2193–2213, 2010c.

Montano-Loza AJ, Carpenter HA, Czaja AJ: Consequences of treatment withdrawal in type 1 autoimmune hepatitis, *Liver Int* 27(4):507–515, 2007.

BASIC INFORMATION

DEFINITION

Cerebral arteriovenous malformations (AVMs) are congenital vascular lesions that are characterized by blood flow from high-pressure arterial vessels directly into thin-walled veins without passing through an intervening capillary/venule system (Fig. A1-145*A*).

SYNONYMS

AVM
Brain AVM

ICD-9CM CODES
Q28.2 Arteriovenous malformation of cerebral vessels
I60.8 Ruptured cerebral arteriovenous malformation
ICD-10CM CODES
Q28.2 Arteriovenous malformations of cerebral vessels

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:
- Detection rates in large prospective studies range from 1.1 to 1.4 per 100,000 person-years.
- Incidence of hemorrhage, the most common and often most clinically dangerous presentation, is estimated to be 2% to 4% per year.

PREVALENCE: Estimated about 1.3 per 100,000.
PREDOMINANT SEX AND AGE:
- There is a slight male preponderance; studies of varying populations show 1.04:1 to 1.2:1 M:F ratio.
- Peak age at time of hemorrhage occurrence is about 20 years, but it can occur in younger and older patients.

GENETICS:
- Cerebral AVMs are sporadic in most cases.
- AVMs are present in about 20% of cases of Osler-Weber-Rendu syndrome (also known as hereditary hemorrhagic telangiectasia [HHT]), an autosomal dominant disorder that results in abnormal blood vessel formation in the skin, lungs, liver, brain, and other organs.

RISK FACTORS:
- Male sex and presence of HHT are risk factors for AVM.
- The risk of hemorrhage is increased with prior hemorrhage, presence of a single draining vein, and diffuse nidus morphology.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The most common presentation is hemorrhage; symptoms vary based on location and magnitude of hemorrhage.
- Patients may present with seizures or neurologic deficits related to mass effect of the AVM nidus.
- Headache and pulsatile tinnitus may be present.
- In infants, AVM may present as cyanotic heart failure, macrocephaly, or hydrocephalus.
- A bruit may be auscultated through the scalp or orbit.
- AVMs may also present with associated intracranial aneurysms that occur on distant, unrelated vessels, on a proximal artery that feeds the aneurysm (flow-related aneurysm), or within the AVM nidus itself (intranidal aneurysm). Patients may present with a subarachnoid hemorrhage related to the aneurysm rather than to the AVM.

ETIOLOGY

AVMs are congenital abnormalities caused by failure of formation of a capillary bed between embryonic arterial and venous vascular plexuses during the first trimester of gestation.

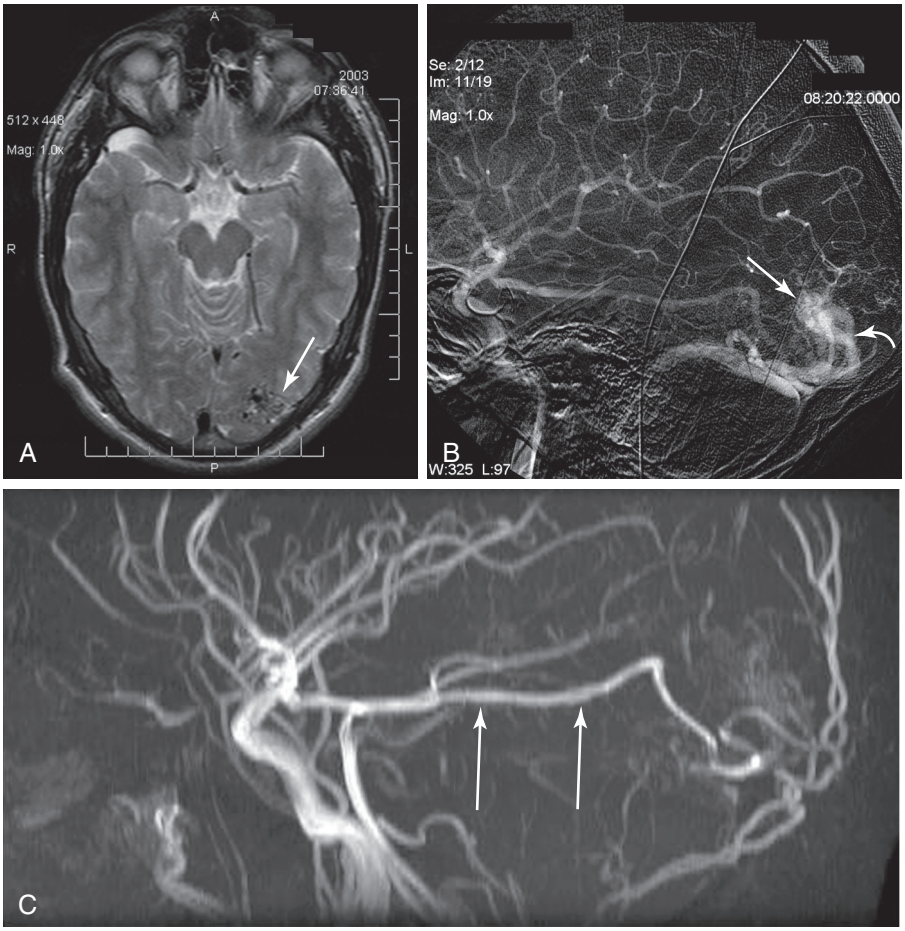


FIGURE A1-145A A 14-year-old child with a left occipital arteriovenous malformation (AVM). **A,** MRI shows multiple flow voids in the left occipital lobe *(arrow).* **B,** Lateral view from catheter angiogram confirms the presence of an AVM *(arrow)* and early draining veins *(curved arrow).* **C,** Lateral maximum intensity projection image from an MR angiogram shows an enlarged posterior cerebral artery branch *(arrows),* which feeds the tangle of abnormal vessels. (From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of cerebral AVMs includes other vascular lesions such as cavernous malformations, dural arteriovenous fistulas, and intracranial aneurysms. Table EA1-86 compares vascular malformations, and Table EA1-87 describes major differences between hemangiomas and vascular malformations.

LABORATORY TESTS

- CBC and BMP with renal function panel prior to contrast dye administration with CT angiography/cerebral angiogram.
- PT/INR/PTT should be drawn and corrected in the case of bleeding diathesis.

IMAGING STUDIES

- In the acute setting, a CT scan of the head to check for hemorrhage and a CT angiogram of the head for characterization of the lesion may be helpful (although calcification may be present and potentially pose as small acute blood).
- MRI of the brain delineates the nidus and its relationship to surrounding soft tissue structures better than a CT scan; however, in the setting of an acute hemorrhage these details will be obscured.
- Four-vessel cerebral angiogram (arteriogram) is the best study to evaluate AVM. Angiography in multiple projections helps identify the number and location of feeding and draining vessels for treatment planning (Fig. A1-145*B*). High-resolution images of the nidus may also reveal other irregularities such as aneurysms that often arise given the abnormal histology of the vessel walls and the high-pressure blood flow traversing them.

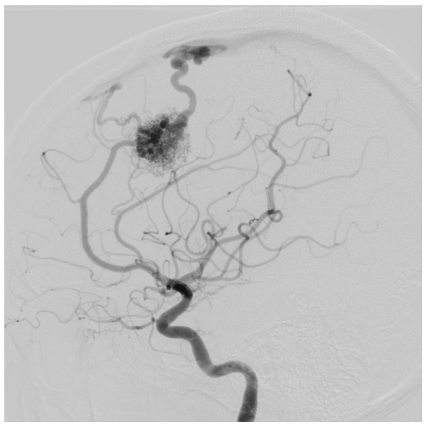


FIGURE A1-145B Arteriovenous malformation of the frontal lobe. The anterior cerebral artery provides primary arterial supply with venous drainage superficially into the superior sagittal sinus.

Rx TREATMENT

Pharmacologic management of seizures with antiepilepsy drugs and of headaches with oral analgesics can provide symptomatic relief.

NONPHARMACOLOGIC THERAPY

- Nonemergent outpatient setting: cerebral angiogram provides characterization of the lesion. Based on angiographic characteristics, the Spetzler-Martin AVM grading system may be used to help guide treatment. In general, grade 5 AVMs are considered unresectable; they are not treated because the risks of treatment likely outweigh the risk of hemorrhage. Current tools for the treatment of AVMs include surgical resection, radiosurgery, and endovascular embolization (with liquid glues or embolic agents).
- Surgical resection: in low-grade lesions by an experienced neurosurgeon yields a high cure rate (~95% in published studies). Resection should include removal of all of the nidus of the AVM; failure to remove the complete nidus may increase the risk of recurrence. An increasing Spetzler-Martin grading scale increases risk of neurologic complications. Intraoperative imaging techniques such as indocyanine-green in-field angiography and conventional digital subtraction angiography are used to verify complete resection.
- Radiosurgery: alternative definitive treatment for AVMs. Traditionally employed to treat AVMs in eloquent areas (e.g., brainstem); sterotactic radiosurgery is increasingly used for higher Spetzler-Martin grade AVM. Reported rates of confirmed radiographic obliteration after AVM radiosurgery range from 47%-90%.
- Endovascular embolization involves transarterial superselective blockage of the AVM. It has become an important adjunctive tool. Currently recommended and approved for use before resection, preoperative embolization can reduce arterial flow and pressure within the AVM, assisting in speed and safety of surgical resection. In addition, embolization may often be used to treat intranidal or flow-related aneurysms in coordination with either resection or radiosurgery. Embolization alone in obliterating an AVM is not routinely recommended.
- Treatment decisions should take into consideration the morbidity associated with the treatment modality versus the risk of future hemorrhage or neurologic deterioration. Disability stemming from intractable seizures or severe headaches may make invasive definitive treatment a more attractive option.
- Acute cerebral hemorrhage: in the case of an acute hemorrhage, airway and breathing must be maintained, with intubation if necessary. Acute neurosurgical intervention for clot evacuation may be warranted. Microsurgical resection of the AVM may or may not be feasible in the acute setting and is controversial.

DISPOSITION

Whether the patient is receiving elective treatment of a known lesion or presenting with an acute hemorrhage, the patient should receive care in a progressive or intensive care unit with experience dealing with cerebrovascular disease. Once the patient is stabilized, appropriate rehabilitation should be arranged.

REFERRAL

- Cerebral AVMs should be managed by a qualified neurosurgeon.
- Referral to radiation medicine for adjuvant radiosurgery should be made when indicated.
- Referral to an interventional radiologist for endovascular treatment may be warranted.
- Treatment in a primary stroke center or other specialized center that offers all treatment modalities is recommended.

PEARLS & CONSIDERATIONS

COMMENTS

No two AVMs are exactly the same; individualization of treatment decisions is the mainstay. Additionally, many AVMs could be effectively treated through one of several modalities or a combination thereof. Factors such as patient age, overall health status, radiographic characteristics, route of surgical access, and potential morbidities of each treatment modality are vital variables in consideration for treatment. The advisability of intervention for unruptured AVMs remains controversial. In a recent randomized trial comparing medical management with specific interventions to obliterate AVMs (neurosurgery, embolization, radiotherapy, or a combination) the rates of neurological disability were much higher in the intervention group than with conservative treatment.[1]

PATIENT/FAMILY EDUCATION

If a patient with a known AVM suffers from acute-onset neurologic deficits or strokelike symptoms, emergency medical attention is warranted for potential hemorrhage. Presence of AVMs, cerebral or otherwise, in family members should be disclosed to the patient's primary care physician because the presence of a genetic condition predisposing to cerebral AVMs should be considered.

SUGGESTED READINGS

Available at www.expertconsult.com

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[1]Mohr JP et al: Medical management with or without interventional therapy for unruptured brain arteriovenous malformations (ARUBA): a multicentre non-blinded, randomized trial, *Lancet* 383:614-621, 2014.

SUGGESTED READINGS

Al-Shahi Salman R et al.: Outcome after conservative management or intervention for unruptured brain arteriovenous malformations, *JAMA* 311:1661–1669, 2014.

Başkaya MD et al.: Cerebral arteriovenous malformations, *Clin Neurosurg* 53:114–144, 2006.

Maruyama K et al.: The risk of hemorrhage after radiosurgery for cerebral arteriovenous malformations, *N Engl J Med* 352:146–153, 2005.

Natarajan SK et al.: Multimodality treatment of brain arteriovenous malformations with microsurgery after embolization with onyx: single-center experience and technical nuances, *Neurosurgery* 62:1213–1226, 2008.

Stieg PE: Intracranial arteriovenous malformations. Informa Healthcare: New York.

TABLE EA1-86 Vascular Malformations

Type	Example(s)
Capillary	Port-wine stain
Venous	Venous malformation Angiokeratoma circumscriptum (hyperkeratotic venule) Cutis marmorata telangiectasia congenita (congenital phlebectasia)
Arterial	Arteriovenous malformation
Lymphatic	Superficial lymphatic malformation (lymphangioma circumscriptum) Deep lymphatic malformation with macrocysts and/or microcysts (cystic hygroma)

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

TABLE EA1-87 Major Differences Between Hemangiomas and Vascular Malformations

	Hemangiomas	Vascular Malformations (Capillary, Venous, Lymphatic, Arterial, and Arteriovenous, Pure, or Complex-Combined)
Clinical	Variably visible at birth	Usually visible at birth (AVMs may be quiescent)
	Subsequent rapid growth	Growth proportionate to the skin's growth (or slow progression); present lifelong
	Slow, spontaneous involution	
Sex ratio F:M	3:1-5:1; 7:1 in severe cases	1:1
Pathology	Proliferating stage: hyperplasia of endothelial cells and smooth muscle cell actin–positive cells	Flat endothelium
	Multilaminated basement membrane	Thin basement membrane
	Higher mast cell content in involution	Often irregularly attenuated walls (VM, LM)
Radiology	Fast-flow lesion on Doppler sonography	Slow-flow (CM, LM, VM) or fast-flow (AVM) on Doppler ultrasonography
	Tumoral mass with low voids on MRI	MRI: hyperintense signal on T2-weighted images when slow-flow (LM, VM); flow voids on T1- and T2-weighted images when fast-flow (AVM)
	Lobular tumor on arteriogram	Arteriography of AVM demonstrates AV shunting
Bone changes	Rarely mass effect with distortion but no invasion	*Slow-flow VM:* distortion of bones, thinning, underdevelopment
		Slow-flow CM: hypertrophy
		Slow-flow LM: distortion, hypertrophy, and invasion of bones
		High-flow AVM: destruction, rarely extensive lytic lesions
		Combined malformations (e.g., slow-flow [capillary lymphatic venous malformation, Klippel-Trenaunay syndrome] or fast-flow [capillary arteriovenous malformation, Parkes Weber syndrome]): overgrowth of limb bones, gigantism
Immunohistochemistry on tissue samples	*Proliferating hemangioma:* high expression of PCNA, type IV collagenase, VEGF, urokinase, and bFGF, glucose transporter-1	Lack expression of PCNA, type IV collagenase, urokinase, VEGF, and bFGF One familial (rare) form of VM linked to a mutated gene on 9p *(VMCM1)*
	Involuting hemangioma: high levels of tissue inhibitor of metalloproteinase-1, bFGF	
Hematology	No coagulopathy (Kasabach-Merritt syndrome is a complication of other vascular tumors of infancy, e.g., kaposiform hemangioendothelioma and tufted angioma)	Slow-flow VM, LM, or LVM may have an associated localized intravascular coagulopathy with risk of bleeding (disseminated intravascular coagulation)

AVM, Arteriovenous malformation; *bFGF,* basic fibroblast growth factor; *CM,* capillary malformation/port-wine stain; *LM,* lymphatic malformation; *LVM,* lymphovenous malformation; *PCNA,* proliferating cell nuclear antigen; *VEFG,* vascular endothelial growth factor; *VM,* venous malformation.
From Eichenfeld LF et al: *Textbook of neonatal dermatology,* Philadelphia, 2001, Saunders.

BASIC INFORMATION

DEFINITION

Avascular necrosis (AVN) is ischemic death of bone due to insufficient blood supply. Osteonecrosis is not a specific disease entity but a final common pathway to several disorders that impair blood supply to the femoral head and other locations.

SYNONYMS

AVN
Osteonecrosis
Aseptic necrosis

ICD-9CM CODES
733.40 Aseptic necrosis
733.43 Aseptic necrosis of femoral condyle
733.42 Aseptic necrosis of femoral head
733.41 Aseptic necrosis of humeral head
733.44 Aseptic necrosis of talus

ICD-10CM CODES
M87 Idiopathic aseptic necrosis of bone
M87.1 Osteonecrosis due to drugs
M87.2 Osteonecrosis due to previous trauma
M87.3 Other secondary osteonecrosis
M87.9 Osteonecrosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- 15,000 new cases per year in the United States. It is most commonly associated with the hip and accounts for 10% of total hip replacements in the United States.
- Usually occurs in middle age and is more frequent in males than females
- Associated conditions:
  1. Corticosteroid treatment: 35%
  2. Alcohol abuse: 22%
  3. Idiopathic and other: 43%
  4. Hemoglobinopathies, pancreatitis, chronic renal failure, SLE, chemotherapy, decompression sickness
- Common sites involved
  1. Femoral head
  2. Femoral condyle
  3. Humeral head
  4. Navicular and lunate wrist bones
  5. Talus

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- May be asymptomatic in early stages
- Pain in the involved area exacerbated by movement or weight bearing in later stages
- Decreased range of motion as the disease progresses
- Functional limitation

ETIOLOGY

Final common pathway of conditions that lead to impairment of the blood supply to the involved bone. Trauma disrupting the blood supply is the most common cause of AVN. Arterial factors are considered the most common cause of AVN. Table A1-88 describes proposed mechanism of disease of common conditions associated with osteonecrosis.

TABLE A1-89 Modified Steinberg Staging System for Osteonecrosis

Stage	Radiographic Appearance	Reversible
I	Normal radiographs, but abnormal bone scan or magnetic resonance image	Yes
II	Lucent and sclerotic changes	Yes
III	Subchondral fracture without flattening	No
IV	Subchondral fracture with flattening or segmental depression of femoral head	No
V	Joint space narrowing or acetabular changes	No
VI	Advanced degenerative changes	No

From Firestein GS, Budd RC, Gabriel SE, et al: *Kelly's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.

STAGING

Table A1-89 describes the Modified Steinberg Staging System for osteonecrosis.

Stages:
- Stage 0
  1. Asymptomatic
  2. Normal imaging
  3. Histologic findings only (i.e., silent osteonecrosis)
- Stage 1
  1. Asymptomatic or symptomatic
  2. Normal radiographs and CT scan
  3. Abnormal bone scan or MRI
- Stage 2
  1. Abnormal radiographs or CT scan, including linear sclerosis, focal bead mineralization, cysts; however, the overall architecture of the involved bone is normal
- Stage 3
  1. Early evidence of mechanical bone failure (subchondral fracture), but the overall shape of the bone is still intact
- Stage 4
  1. Flattening or collapse of the bone
- Stage 5
  1. Joint space narrowing
- Stage 6
  1. Extensive joint destruction

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- None in late stages
- Early: any condition causing focal musculoskeletal pain, including arthritis, bursitis, tendinitis, myopathy, neoplastic bone and joint diseases, traumatic injuries, pathologic fractures

WORKUP

Fig. A1-146 describes a diagnostic algorithm for osteonecrosis.

IMAGING STUDIES (Fig. A1-147)

1. MRI: the most sensitive technology to diagnose early aseptic necrosis. The first sign is a margin of low signal. An inner border of high signal associated with a low-signal line

TABLE A1-88 Proposed Mechanism of Disease of Common Conditions Associated with Osteonecrosis

	MECHANISM OF OSTEONECROSIS							
Associated Condition	Apoptosis	Osteoblast/ Osteoclast Homeostasis	Lipid Abnormalities	Coagulation Abnormalities	Oxidative Stress	Parathyroid/ Calcium Imbalance	Vascular Plugging	Vasoactive Substances
Corticosteroids	X	X	X	X	X			X
Bisphosphonates	X	X	X					
Alcohol abuse	X	X	X	X	X			
Trauma	X	X						X
Renal transplantation	X	X		X		X		
Dialysis						X		
Sickle cell disease							X	

From Firestein GS, Budd RC, Gabriel SE, et al: *Kelly's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.

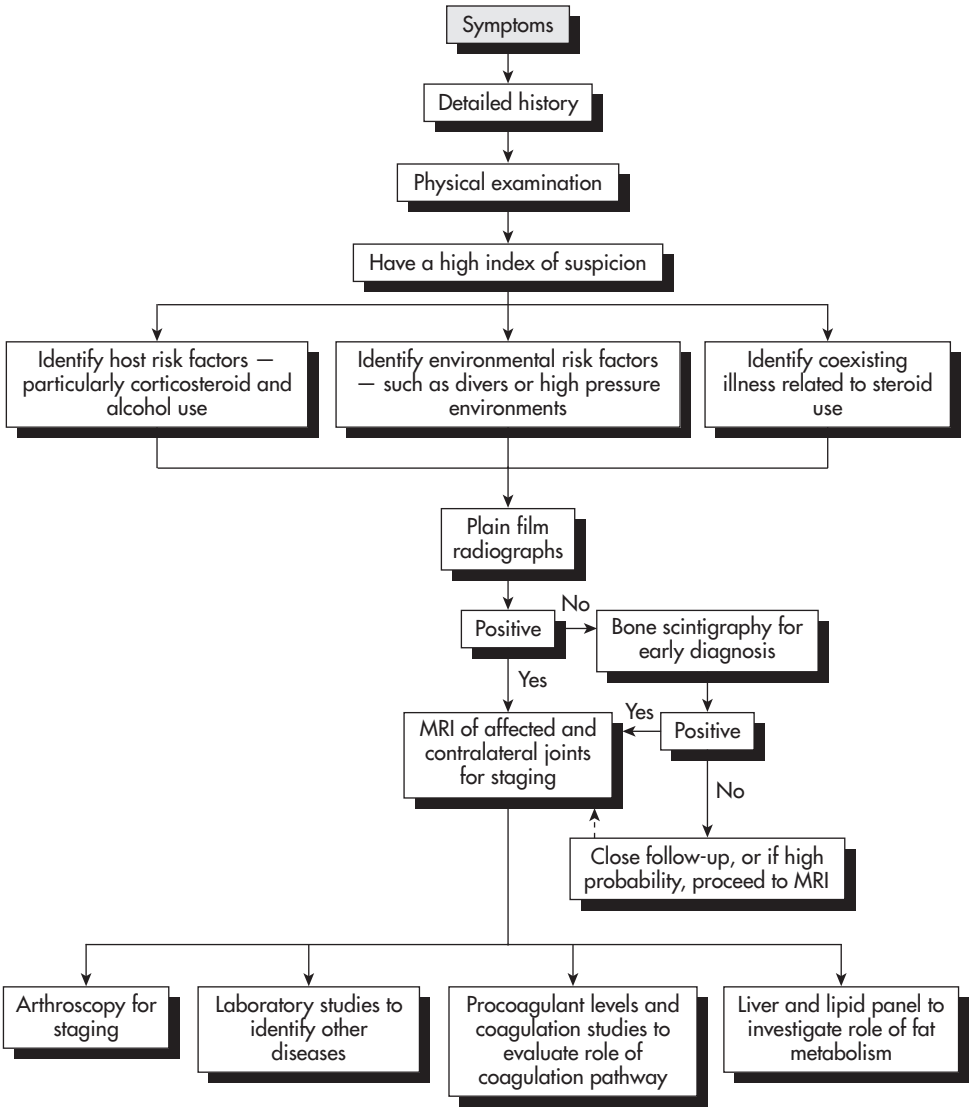

FIGURE A1-146 Diagnostic algorithm for osteonecrosis. *MRI*, Magnetic resonance image. (From Firestein GS, Budd RC, Gabriel SE, et al: *Kelly's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.)

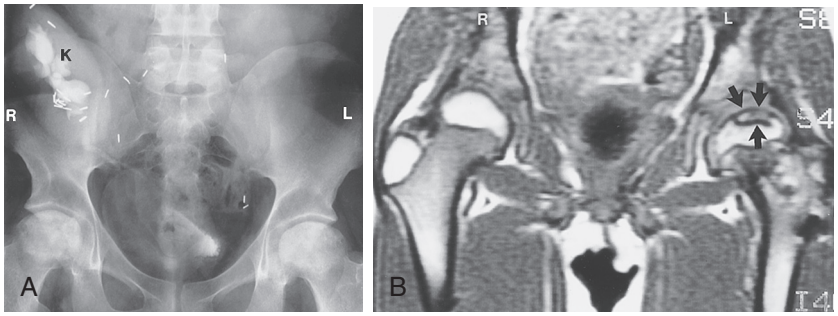

FIGURE A1-147 Aseptic necrosis of the hips. A, Aseptic necrosis can occur from a number of causes, including trauma and steroid use. In this patient, an anteroposterior view of the pelvis shows a transplanted kidney *(K)* in the right iliac fossa. Use of steroids has caused this patient to have bilateral aseptic necrosis. The femoral heads are somewhat flattened, irregular, and increased in density. **B,** Aseptic necrosis in a different patient is demonstrated on an MRI scan as an area of decreased signal *(arrows)* in the left femoral head. This is the most sensitive method for detection of early aseptic necrosis. (From Mettler FA [ed]: *Primary care radiology,* Philadelphia, 2000, Saunders.)

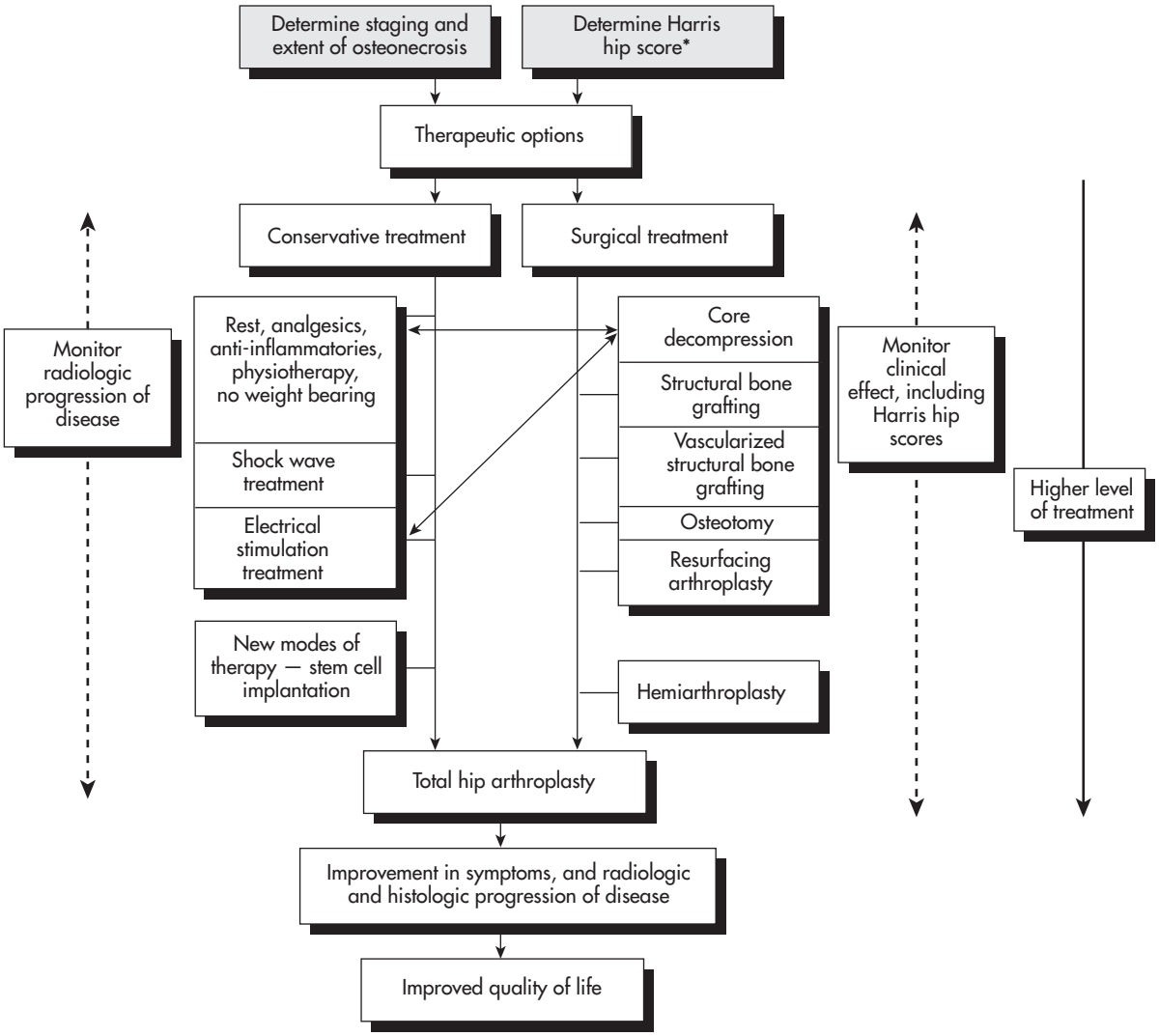

FIGURE A1-148 Treatment algorithm for osteonecrosis. *www.ncbi.nlm.nih.gov/pubmed/22588745.
(From Firestein GS, Budd RC, Gabriel SE, et al: *Kelly's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.)

is specific for aseptic necrosis ("double line sign"). Sensitivity is 75% to 100%.

2. Radiography: insensitive early in the course. The earliest changes include diffuse osteopenia, areas of radiolucency with sclerotic border, and linear sclerosis. Later, a subchondral lucency (crescent sign) indicates subchondral fracture. More advanced cases reveal flattening, collapsed bone, and abnormal bone contour. In late disease, osteoarthritic changes are seen.
3. Bone scan:
   - Early: "cold" area.
   - Later: increased radionuclide uptake as a result of remodeling.
   - Sensitivity in early disease is only 70% and specificity is poor.
4. CT scan: may reveal central necrosis and area of collapse before those are visible on radiographs.

Rx TREATMENT

PREVENTION

- Manage etiologic conditions
- Minimize corticosteroid use

NONPHARMACOLOGIC THERAPY

- Core decompression: effectiveness 35% to 95% in early phases
- Bone grafting
- Osteotomies
- Joint replacement

ACUTE GENERAL Rx

- Decrease weight bearing of affected area.
- Pulsing electromagnetic fields applied externally (still experimental).
- Peripheral vasodilators (e.g., dihydroergotamine) (unproven).
- Late-stage AVN is most often treated by total joint arthroplasty.
- A treatment algorithm for osteonecrosis is described in Fig. A1-148.

PROGNOSIS

- When diagnosed at an early stage treatment is appropriate in all cases because 85% to 90% can be expected to progress to a more advanced stage.
- Contralateral joint involvement is common (30% to 70%).

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Avascular Necrosis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Glesby MJ et al.: Osteonecrosis in patients infected with HIV, *J Infect Dis* 184: 519–523, 2001.

Mont MA et al.: Atraumatic osteonecrosis of the knee, *J Bone Joint Surg Am* 82A:1279–1290, 2000.

BASIC INFORMATION

DEFINITION

Babesiosis is a tick-transmitted protozoan disease of animals, caused by intraerythrocytic parasites of the genus *Babesia.* Humans are incidentally infected, resulting in a nonspecific febrile illness. The disease can be severe in immunocompromised hosts.

ICD-9CM CODES
088.82 Babesiosis
ICD-10CM CODES
B60.0 Babesiosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Unknown
PREVALENCE (IN U.S.)
- In areas of high endemicity, seropositivity ranging from 9% (Rhode Island) to 21% (Connecticut)
- Highest number of reported cases in New York

PREDOMINANT SEX: Males (most likely through increased exposure to vectors during recreational or occupational activities)
PREDOMINANT AGE: Severity apparently increasing with age greater than 60 yr
PEAK INCIDENCE: Spring and summer months, May through September
GENETICS: None known
CONGENITAL INFECTION: At least one case of probable vertical transmission
NEONATAL INFECTION: At least two cases of perinatal transmission
BLOOD TRANSFUSION: Many instances

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Incubation period 1 to 4 wk, or 6 to 9 wk in transfusion-associated disease
- Gradual onset of irregular fever, chills, diaphoresis, headache, myalgia, arthralgia, fatigue, and dark urine
- On physical examination: petechiae, frank or mild hepatosplenomegaly, and jaundice. Most patients have a normal physical exam.
- Infection with *B. divergens* (Europe) producing a more severe illness with a rapid onset of symptoms and increasing parasitemia progressing to massive intravascular hemolysis and renal failure

ETIOLOGY

- Vector: Deer tick, *Ixodes scapularis* (also known as *I. dammini*)
  1. Feeds on rodents during the spring and summer while in its larval and nymphal stages and on deer as an adult
  2. Requires a blood meal to mature to each stage, hence human infection
  3. During the warmer months in endemic areas, humans are readily infected while engaging in outdoor activities
- *B. microti* and *B. divergens* account for most human infections.
- In the U.S., cases caused by *B. microti* are acquired on offshore islands of the northeastern coast, including Nantucket Island, Cape Cod, and Martha's Vineyard in Massachusetts; Block Island in Rhode Island; and Long Island, Fire Island, and Shelter Island in New York; as well as the nearby mainland including Connecticut and New Jersey.
- Sporadic cases reported from California, Georgia, Maryland, Minnesota, Virginia, Wisconsin, and most recently the WA-1 strain from Washington State and the MO-1 strain from Missouri.
- *B. divergens* is implicated in human disease in Europe, where the disease remains rare and predominantly associated with asplenia.
- Majority of cases are asymptomatic.
- May be transmissible by transfusion, through platelets and erythrocytes.
- Mixed infections (*B. microti* and *Borrelia burgdorferi,* the causative agent of Lyme disease) are estimated to occur in 10% (Rhode Island and Connecticut) to 60% (New York) of cases.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Amebiasis
- Ehrlichiosis
- Hepatic abscess
- Leptospirosis
- Malaria
- Salmonellosis, including typhoid fever
- Acute viral hepatitis
- Hemorrhagic fevers
- Subacute bacterial endocarditis

WORKUP

Should be suspected in any febrile patient living or traveling in an endemic area, irrespective of exposure history to ticks or tick bites, especially if asplenic

LABORATORY TESTS

- The preferred method for diagnosing babesiosis is PCR using whole blood specimens.
- Babesial DNA by polymerase chain reaction (PCR) has comparable sensitivity and specificity to microscopic analysis of thin blood smears. PCR is more sensitive than smears at the onset of infection when parasite load may be minimal.
- Diagnosis achieved serologically by indirect immunofluorescence assay (IFA) is specific for *B. microti.*
  1. Assay is hampered by the inability to distinguish between exposed patients and those who are actively infected.
  2. IGG titer of ≥1:64 is indicative of seropositivity, whereas one ≥1:1024 is considered diagnostic of acute infection. IGM titer of 1:64 is considered indicative of acute infection.
  3. Immunoglobulin M indirect immunofluorescent-antibody test may be highly sensitive and specific for diagnosis. IGM titer of 1:64 is considered indicative of acute infection.
- CBC to reveal mild to moderate pancytopenia
- Abnormally elevated serum chemistries, including creatinine, liver function profile, lactate dehydrogenase, and indirect and total bilirubin levels; heptoglobin is low.
- Urinalysis to reveal proteinuria and hemoglobinuria
- Examination of Giemsa- or Wright-stained thin blood films for intraerythrocytic parasites
  1. In its classic, though infrequently seen, form a "tetrad" or "Maltese cross" composed of four daughter cells attached by cytoplasmic strands is observed (Fig. B1-1).
  2. More commonly, smaller forms composed of a single chromatin dot are eccentrically located within bluish cytoplasm.
  3. Parasitized erythrocytes may be multiply infected but not enlarged.
  4. Extra-erythrocytic forms may be seen.

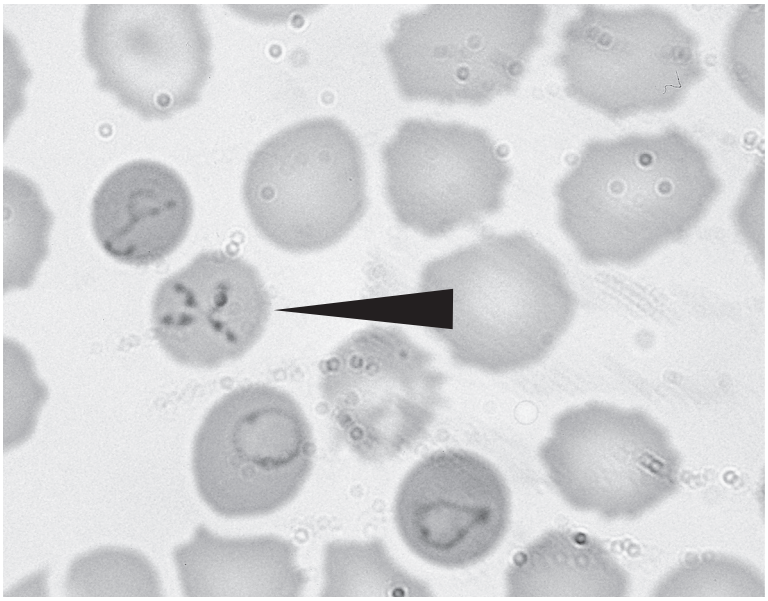

FIGURE B1-1 Babesia spp. Single and multiple intraerythrocytic parasites can be seen. The *arrow* marks a typical Maltese cross. (From Cohen J, Powderly WG: *Infectious diseases,* ed 2, St Louis, 2004, Mosby.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Supportive care with adequate hydration

ACUTE GENERAL Rx

- In patients with intact spleens: predominantly asymptomatic or if symptomatic, generally self-limited
- Therapy reserved for the severely ill patient, especially if asplenic, elderly, or immunosuppressed. Therapy may be offered to any symptomatic patient.
- Combination of atovaquone 750 mg q12h and azithromycin 500 mg on day 1 and 250 mg per day thereafter for 7 to 10 days appears to be as effective as a regimen of clindamycin and quinine with fewer adverse reactions. This is the preferred regimen for mild disease.
- Combination of quinine sulfate 650 mg PO tid plus clindamycin 600 mg PO tid (600 mg parenterally qid) taken for 7 to 10 days: effective but may not eliminate parasites
- Severely ill patients are hospitalized and treated with clindamycin and quinine
- Exchange transfusions in addition to antimicrobial therapy: successful treatment for severe infections in asplenic patients associated with high levels of *B. microti* or *B. divergens* parasitemia. Exchange transfusion is recommended for patients with >10% parasitemia, but may be considered for any severely ill patient.
- Relapsed and immunocompromised patients may require a longer duration of therapy.

DISPOSITION

Prognosis is usually good and fatal outcomes are rare.

REFERRAL

- For prompt consultation with an infectious disease specialist if the diagnosis is acutely suspected, especially in the asplenic, elderly, or immunocompromised patient
- For hospitalization for the severely ill patient who may require exchange transfusions in addition to antibiotic therapy

PEARLS & CONSIDERATIONS

COMMENTS

- Prevention of babesiosis in asplenic or immunocompromised hosts is best achieved by avoidance of areas where the vector is endemic, especially May through September.
- If residence or travel in endemic areas is unavoidable, advise patients to perform daily cutaneous self-examination, wear light-colored clothing (to facilitate removal of ticks), tuck pants into socks, and apply tick repellent (diethyltoluamide and dimethylphthalate) to skin or clothing.
- Advise a daily inspection for ticks in family pets (e.g., cats and dogs).
- Infection with *B. divergens,* especially in the asplenic patient, is often fatal.
- Concurrent cases of babesiosis and Lyme disease have been documented—check for combined infection in severely ill patients.
- A combination of clindamycin and quinine has been successfully used to treat babesiosis during the third trimester of pregnancy without incurring apparent adverse effect on the fetus.
- In 2011 the CDC added babesiosis to the list of nationally notifiable diseases.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Babesiosis (Patient Information)

AUTHOR: **PATRICIA CRISTOFARO, M.D.**

SUGGESTED READINGS

Centers for Disease Control and Prevention: Babesiosis surveillance—18 states, *MMWR Morb Mortal Wkly Rep* 61:505, 2012.

Gubernot DM et al.: Babesia infection through blood transfusions: reports received by the US FDA, *1997-2007. Clin Infect Dis* 48:25, 2009.

Hunfeld KP et al.: Babesiosis: recent insights into an ancient disease, *Int J Parasitol* 38(11):1219–1237, 2008.

Joseph JT et al.: Vertical transmission of Babesia microti, US, *Emerg Infect Dis* 18:1318, 2012.

Krause PJ et al.: Persistent and relapsing babesiosis in immunocompromised patients, *Clin Infect Dis* 46:370, 2008.

Vannier E et al.: Human babesiosis, *Infect Dis Clin North Am* 22:469, 2008.

Vannier E, Krause PJ: Human babesiosis, *N Engl J Med* 366:2397, 2012.

Wormser GP et al.: The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the IDSA, *Clin Infect Dis* 43:1089, 2006.

Wormser GP et al.: Emergence of resistance to azithromycin-atovaquone in immunocompromised patients with Babesia microti infection, *Clin Infect Dis* 50:381, 2010.

Young C et al.: Preventing transfusion-transmitted babesiosis: preliminary experience of the first laboratory-based blood donor screening program, *Transfusion* 52:1523, 2012.

BASIC INFORMATION

DEFINITION

Bacterial meningitis is an inflammation of meninges with increased intracranial pressure, and pleocytosis or increased WBCs in cerebrospinal fluid (CSF) secondary to bacteria in the pia-subarachnoid space and ventricles, leading to neurologic sequelae and abnormalities.

SYNONYMS

Spinal meningitis

ICD-9CM CODES
320 Bacterial meningitis
ICD-10CM CODES
G00.9 Bacterial meningitis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 1.3 to 2.0 cases/100,000 persons; 1.2 million cases per year in the world; 135,000 deaths annually worldwide. The rate of bacterial meningitis declined dramatically in the U.S. starting in the early 1990s with the introduction of the *Haemophilus influenzae* type b (Hib) vaccine and in 2000 with the introduction of the conjugate pneumococcal vaccine.
PREDOMINANT SEX: Male = female
PREDOMINANT AGE: All ages, neonate to geriatric

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fever
- Headache
- Neck stiffness, nuchal rigidity, meningismus
- Altered mental state, lethargy
- Vomiting, nausea
- Photophobia
- Seizures
- Coma; lethargy, stupor
- Rash: petechial associated with meningococcal infection (Fig. B1-2), purpura fulminans (Fig. B1-3)
- Myalgia
- Cranial nerve abnormality (unilateral)
- Papilledema
- Dilated, nonreactive pupil(s)
- Posturing: decorticate/decerebrate
- Physical examination findings of Kernig's sign and Brudzinski's sign in adults with meningitis are often not helpful in determining meningeal inflammation

ETIOLOGY

The bacterial etiology of meningitis depends on the age of the patient. *Neisseria meningitidis* is now more common than *Haemophilus influenzae* as a cause of bacterial meningitis in children as well as adults, and streptococci are still common causes of bacterial meningitis. *H. influenzae* is the cause of >30% of cases of meningitis (usually in infants and children <6 yr of age). It is associated with sinusitis, otitis media.

- Neonates: group B streptococcus, gram-negative rods such as *E. coli, Listeria monocytogenes*
- Infants ≥1 mo and <3 mo: group B streptococci (40%), gram-negative rods (30%), *Streptococcus pneumoniae* (14%), and *Neisseria meningitidis* (12%)
- Infants ≥3 mo and <3 yr:
  1. *S. pneumoniae* (45%)
  2. *N. meningitidis* (34%)
  3. *S. agalactiae* (group B streptococci) (11%)
  4. *H. influenzae*
  5. *E. coli*
- Ages ≥3 yr and <10 yr:
  1. *S. pneumoniae* (47%)
  2. *N. meningitidis* (32%)
- Ages ≥10 yr and <19 yr
  1. *N. meningitidis* (55%)
  2. *S. pneumoniae*
- Adults: *S. pneumoniae, N. meningitidis,* and *L. monocytogenes* (especially over age 50-60 or with cell-mediated immune deficiencies)
- People with HIV/AIDS are at increased risk for invasive meningococcal disease (IMD).

DIAGNOSIS

Diagnostic approach is based on patient presentation and physical examination (Fig. B1-4). Lumbar puncture should be performed as soon as possible. Key elements to diagnosis are CSF evaluation and CT scan or MRI if the patient is in a coma or has focal neurologic deficits, pupillary abnormalities, or papilledema.

DIFFERENTIAL DIAGNOSIS

- Endocarditis, bacteremia
- Intracranial tumor
- Lyme disease
- Brain abscess
- Partially treated bacterial meningitis
- Medications
- SLE
- Seizures
- Acute mononucleosis
- Other infectious meningitides

FIGURE B1-2 Fully developed, almost pathognomonic hemorrhagic rash of meningococcal sepsis. (From Cohen J, Powderly WG: *Infectious diseases,* ed 2, St Louis, 2004, Mosby.)

FIGURE B1-3 Meningococcal purpura fulminans in overwhelming meningococcal meningitis. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

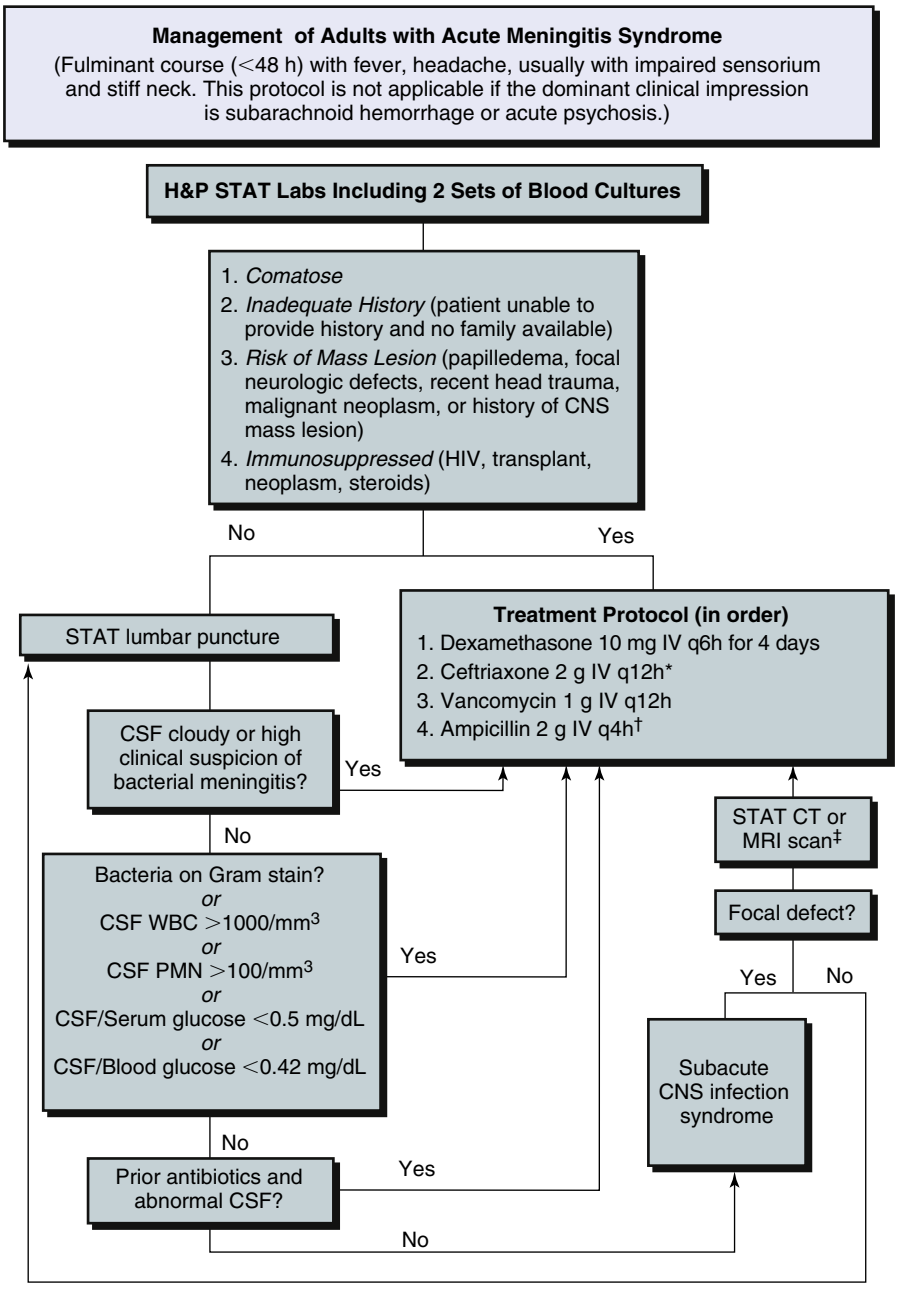

FIGURE B1-4 Algorithm for management of adult patients with acute meningitis syndrome. *For severe cephalosporin allergy, consider meropenem or moxifloxacin. †Ampicillin is indicated if there is a history of alcoholism, organ transplant, malignancy, pregnancy, or age older than 50 years. For penicillin-allergic patients, an alternative is trimethoprim-sulfamethoxazole. ‡Consider magnetic resonance imaging *(MRI)* if the patient is known or suspected to have human immunodeficiency virus *(HIV),* if it can be obtained rapidly. *CNS,* Central nervous system; *CSF,* cerebrospinal fluid; *CT,* computed tomography; *H&P,* history and physical examination; *PMN,* polymorphonuclear leukocyte; *WBC,* white blood cell. (From Vincent JL et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, Saunders.)

- Neuroleptic malignant syndrome
- Subdural empyema
- Rocky Mountain spotted fever

WORKUP

CSF examination:
- Opening pressure >100 to 200 mm Hg
- WBC usually >1000 WBC/mm^3
- Neutrophilic predominance: >80%
- Gram stain of CSF: positive in 60% to 90% of patients
- CSF protein: >50 mg/dl
- CSF glucose: <40 mg/dl
- Culture: positive in 65% to 90% of cases
- CSF bacterial antigen: 50% to 100% sensitivity
- E-test for susceptibility of pneumococcal isolates

LABORATORY TESTS

Blood culturing, WBC with differential, and CSF examination (see "Workup")

IMAGING STUDIES

- CT scan or MRI of head: necessary with increased intracranial pressure, coma, neurologic deficits
- Sinus CT: if sinusitis suspected

Rx TREATMENT

Empiric therapy is necessary with IV antibiotic treatment if patient has purulent CSF fluid at time of lumbar puncture, is asplenic, or has signs of DIC/sepsis pending Gram stain and culture results. Try to obtain blood and CSF cultures before starting antimicrobial therapy, but do not delay therapy if obtaining them is not possible. Therapy after Gram stain pending cultures is recommended for the following:

1. Neonates: ampicillin: 200-400 mg/kg per day divided q6 to 8 hr plus gentamicin: 7.5 mg/kg

IV in 3 divided doses plus a third-generation cephalosporin: cefotaxime or ceftriaxone
2. 1-23 months: vancomycin: 60 mg/kg per day IV (maximum up to 4 g/day) divided in 4 doses plus third-generation cephalosporin: ceftriaxone: 100 mg/kg (maximum dose 4 g/day) in 1 or 2 divided doses or cefotaxime: 300 mg/kg per day IV (maximum dose of 12 g/day) in 3 or 4 divided doses
3. Children: vancomycin: 60 mg/kg per day IV (maximum dose 4 g/day) in 4 divided doses plus third-generation cephalosporin: ceftriaxone 100 mg/kg per day IV (maximum 4 g/day) or cefotaxime: 300 mg/kg IV (maximum dose of 12 g/day) in 3 or 4 divided doses
4. Adults: vancomycin: 15-20 mg/kg IV every 8 to 12 hours plus third-generation cephalosporin: ceftriaxone: 2 g IV q12 hours or cefotaxime: 2 g IV q4 to 6 hr. For adults over 50 yr of age also add ampicillin 2 g IV every 4 hr to cover *Listeria*
5. Immunocompromised patients: vancomycin *plus* ampicillin *plus* either cefepime 2 g IV every 8 hr to cover *Pseudomonas* or meropenem 2 g IV q8 hr for adults, which also covers *Pseudomonas*
    1. Use of corticosteroids in adults: dexamethasone 0.15 mg/kg q6h for first 4 days of therapy should be used for adults in developed countries with known or suspected bacterial meningitis. Decreased mortality and neurologic sequelae are seen with adjunct therapy. The benefit of dexamethasone is less clear in developing countries with high HIV prevalence and malnutrition or with delayed clinical presentations.
    2. Dexamethasone also benefits children with Hib meningitis if given at the same time or before the first dose of the antibiotic: 0.15 mg/kg per dose q6 hr for 2 to 4 d. The use and benefit of corticosteroids in suspected or pneumococcal or meningococcal meningitis to prevent neurologic sequelae is not as clear and should be individualized after analysis of risk and benefits.

DISPOSITION

Bacterial meningitis is a reportable disease that needs to be reported to local health authorities. Droplet precautions should be used for first 24 hr of therapy for suspected or confirmed *N. meningitidis* infection.

REFERRAL

- To a neurologist if persistent neurologic sequelae develop after bacterial meningitis
- To an infectious disease consultant if a patient has recurrent bacterial meningitis; such patients deserve a workup for an anatomic (CSF dural leak) or immunologic defect (complement defect, hyposplenism, immunoglobulin deficiency)

PEARLS & CONSIDERATIONS

COMMENTS

- Nosocomial bacterial meningitis may result from invasive procedures (e.g., placement of ventricular catheters, lumbar puncture, craniotomy, spinal anesthesia). Treatment of this different spectrum of microorganisms requires empirical antimicrobial therapy with vancomycin plus either cefepime, ceftazidime, or meropenem. In cases of basilar skull fracture, effective empirical antimicrobial therapy consists of vancomycin plus a third-generation cephalosporin.
- Prevention of meningitis can be achieved through chemoprophylaxis of close contacts (household members and anyone exposed to oral secretions).
- Effective medications are rifampin 10 mg/kg PO bid for 2 days or ceftriaxone 250 mg IM single dose in patients older than age 12; 125 mg IM if age 12 or younger.
- Ciprofloxacin 500 mg for prevention of *Neisseria* meningitis can be given to patients older than 18 yr who cannot tolerate rifampin to eradicate pharyngeal colonization.
- Menactra: a protein-conjugate vaccine against serogroup A, C, Y, W-135 capsular polysaccharides is available for adults (up to 55 yr) and children older than 2 yr.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Meningitis (Patient Information)
Viral Meningitis (Related Key Topic)
Fungal Meningitis (Related Key Topic)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

EVIDENCE

Abstract[1]

Background:
Southern Africa has a high incidence of bacterial meningitis in adults, often associated with HIV co-infection. Mortality exceeds 50%, even with appropriate antibiotic therapy, and is not improved with corticosteroids. Glycerol adjuvant therapy reduces long-term morbidity in bacterial meningitis in children, and its use is being promoted. We aimed to assess the effectiveness of glycerol as an adjuvant therapy for adults with bacterial meningitis in Africa.

Methods:
The study was done in two phases. First, in an open-label dose-finding study, 45 adult patients with symptoms, signs, and cerebrospinal fluid findings consistent with bacterial meningitis received either 50 mL, 75 mL, or 100 mL of glycerol four times a day for 4 days. We then did a randomized, double-blind, placebo-controlled trial of oral glycerol in adults with bacterial meningitis. Patients with clinical and cerebrospinal fluid findings suggestive of bacterial meningitis were randomly assigned in blocks of 12 by use of a random number list produced by an independent statistician to receive either glycerol or an equivalent volume of sugar solution. Glycerol and placebo were indistinguishable by color or taste. The primary outcome was mortality at 40 days, with secondary outcomes including disability and mortality restricted to pneumococcal disease. All patients were analyzed for the primary outcome excluding those who were lost to follow-up. This trial is registered at controlled-trials.com, number ISRCTN70121840.

Findings:
75 mL glycerol four times a day was the highest tolerated dose, and was used for the main study. 265 patients were assigned treatment: 137 glycerol and 128 placebo. The trial was stopped early on the advice of the data and safety monitoring board after a planned interim analysis. By day 40, 61 (49%) of 125 patients in the placebo group and 86 (63%) of 136 in the glycerol group had died (adjusted odds ratio 2.4, 95% CI 1.3-4.2, p=0.003). There was no benefit from glycerol for death and disability by day 40, and glycerol did not improve death and disability by day 40 or death at day 40 in patients with proven bacterial disease or pneumococcal disease. Two serious adverse events occurred that were possibly due to the study drug.

Interpretation:
Oral glycerol therapy cannot be recommended as an adjuvant therapy in adults with bacterial meningitis in resource-poor settings with a high HIV prevalence. A

Abstract[2]

Objective:
To examine the occurrence, disease course, prognosis, and vaccination status of patients with community-acquired bacterial meningitis with a history of splenectomy or functional hyposplenia.

Patients and Methods:
Patients with bacterial meningitis proven by cerebrospinal fluid culture were prospectively included in a nationwide cohort study between March 1, 2006, and September 1, 2011. Splenectomy or diseases associated with functional hyposplenia were scored for all patients. Vaccination status, clinical features, and outcome of patients with a history of splenectomy or functional hyposplenia were analyzed and compared with patients with normal spleen function.

Results:
Twenty-four of 965 patients (2.5%) had an abnormal splenic function: 16 had a history of splenectomy and 8 had functional hyposplenia. All patients had pneumococcal meningitis. Pre-illness vaccination status could be retrieved for 19 of 21 patients (90%), and only 6 patients (32%) were adequately vaccinated against pneumococci. Pneumococcal serotype was known in 21 patients; 52% of pneumococcal isolates had a serotype included in the 23-valent vaccine. Vaccine failure occurred in 3 patients. Splenectomized patients more often presented with signs of septic shock compared with patients with a normal spleen (63% vs 24%; P ¼.02). Outcome was unfavorable in 14 patients (58%), and 6 patients died (25%).

Conclusion:
Splenectomy or functional hyposplenia is an uncommon risk factor for bacterial meningitis but results in a high rate of mortality and unfavorable outcome. Most patients were not adequately vaccinated against Streptococcus pneumoniae. A

Evidence-Based References

Ajdukiewicz KM et al.: Glycerol adjuvant therapy in adults with bacterial meningitis in a high HIV seroprevalence setting in Malawi: a double-blind, randomized controlled trial, *Lancet Infect Dis* 11:293–300, 2011. A

Adriani KS, Brouwer MC, van der Ende A et al.: Bacterial Meningitis in Adults After Splenectomy and Hyposplenic States, *Mayo Clin Proc* 88:571–578, 2013. A

Brouwer MC, Tunkel AR, van de Beek D: Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis, *Clin Microbiol Rev* 23:467–492, 2010. A

van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M: Clinical features and prognostic factors in adults with bacterial meningitis, *N Engl J Med* 351:1849–1859, 2004. A

SUGGESTED READINGS

Bamberger DM: Diagnosis, initial management, and prevention of meningitis, *Am Fam Physician* 82(12):1491–1498, 2010.

Bhimraj A: Acute community-acquired bacterial meningitis in adults: an evidence-based review, *Cleve Clin J Med* 79:393, 2012.

Greenwood BM: Corticosteroids for acute bacterial meningitis, *N Engl J Med* 357:2507, 2007.

Heyderman RS: Early management of suspected bacterial meningitis and meningococcal septicaemia in immunocompetent adults—second edition, *J Infect* 50(5):373, 2005.

Kim KS: Acute bacterial meningitis in infants and children, *Lancet Infect Dis* 10:32–42, 2010.

Kutz JW et al.: Clinical predictors for hearing loss in children with bacterial meningitis, *Arch Otolaryngol Head Neck Surg* 132(9):941, 2006.

Miller L et al.: Elevated risk for invasive meningococcal disease among persons with HIV, *Ann Intern Med* 160:30–37, 2014.

Mongelluzzo J et al.: Corticosteroids and mortality in children with bacterial meningitis, *JAMA* 299:2048, 2008.

Stephens DS et al.: Epidemic meningitis, meningococcemia, and Neisseria meningitidis, *Lancet* 369:2196, 2007.

Thigpen M et al.: Bacterial meningitis in the United States, 1998-2007, *N Engl J Med* 351:1849, 2004.

van de Beek D et al.: Clinical features and prognostic factors in adults with bacterial meningitis, *N Engl J Med* 351:1849, 2004.

van de Beek D et al.: Nosocomial bacterial meningitis, *N Engl J Med* 362: 146–154, 2010.

Weisfelt M et al.: Pneumococcal meningitis in adults: new approaches to management and prevention, *Lancet Neurol* 5(4):332, 2006.

Bacterial Pneumonia EBM PTG

BASIC INFORMATION

DEFINITION

Bacterial pneumonia is an infection involving the lung parenchyma.

ICD-9CM CODES

486.0 Pneumonia, acute
507.0 Pneumonia, aspiration
482.9 Pneumonia, bacterial
481 Pneumonia, pneumococcal
482.1 Pneumonia, *Pseudomonas*
482.4 Pneumonia, staphylococcal
482.0 Pneumonia, *Klebsiella*
482.2 Pneumonia, *Haemophilus influenzae*

ICD-10CM CODES

J15.9 Unspecified bacterial pneumonia
J69.0 Pneumonitis due to inhalation of food and vomit
J15.9 Unspecified bacterial pneumonia
J13 Pneumonia due to *Streptococcus pneumoniae*
J15.1 Pneumonia due to *Pseudomonas*
J15.20 Pneumonia due to staphylococcus, unspecified
J15.0 Pneumonia due to *Klebsiella pneumoniae*
J14 Pneumonia due to *Haemophilus influenzae*

EPIDEMIOLOGY & DEMOGRAPHICS

- The incidence of community-acquired pneumonia (CAP) is 1 in 100 persons. CAP is the most common infectious cause of death in the U.S.
- The incidence of health care facility–acquired pneumonia (HCAP) is 8 cases per 1000 persons annually.
- Primary care physicians see an average of 10 cases of pneumonia annually.
- Hospitalization rate for pneumonia is 15% to 20%.
- Most cases of pneumonia occur in the winter and in elderly patients.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fever, tachypnea, chills, tachycardia, cough
- Presentation varies with the cause of pneumonia, the patient's age, and the clinical situation:
  1. Patients with streptococcal pneumonia usually present with high fever, shaking chills, pleuritic chest pain, cough, and copious production of rusty-appearing purulent sputum. Pleurisy and parapneumonic effusions are also common. Potential complications include bacteremia, empyema, and distant infections (e.g., meningitis).
  2. *Mycoplasma pneumoniae:* insidious onset; headache; dry, paroxysmal cough that is worse at night; myalgias; malaise; sore throat; extrapulmonary manifestations (e.g., erythema multiforme, aseptic meningitis, urticaria, erythema nodosum) may be present.
  3. *Chlamydia pneumoniae:* persistent, nonproductive cough, low-grade fever, headache, sore throat.
  4. *Legionella pneumophila:* high fever, mild cough, mental status change, myalgias, diarrhea, respiratory failure.
  5. MRSA pneumonia: often preceded by influenza, may present with shock and respiratory failure.
  6. Elderly or immunocompromised hosts with pneumonia may initially present with only minimal symptoms (e.g., low-grade fever, confusion); respiratory and nonrespiratory symptoms are less commonly reported by older patients with pneumonia.
  7. In general, auscultation of patients with pneumonia reveals crackles and diminished breath sounds.
  8. Percussion dullness is present if the patient has pleural effusion.
  9. The clinical impression of pneumonia has an overall sensitivity of 70% to 90%; specificity ranges from 40% to 70%.

ETIOLOGY

- *Streptococcus pneumoniae* (20% to 60% of CAP cases): incidence has been declining due to widespread use of pneumococcal vaccination
- *Haemophilus influenzae* (3% to 10% of CAP cases)
- *L. pneumophila* (1% to 5% of adult pneumonias) (2% to 8% of CAP cases)
- *Klebsiella, Pseudomonas, Escherichia coli*
- *Staphylococcus aureus* (3% to 5% of CAP cases)
- Atypical organisms such as *M. pneumoniae, C. pneumoniae,* and *L. pneumophila* implicated in up to 40% of cases of CAP
- Pneumococcal infection responsible for 50% to 75% of CAPs. Influenza infection is one of the important predisposing factors to *S. pneumoniae* and *S. aureus* pneumonia; gram-negative organisms cause >80% of nosocomial pneumonias
- Predisposing factors:
  1. Chronic obstructive pulmonary disease: *H. influenzae, S. pneumoniae, Legionella, Moraxella catarrhalis*
  2. Seizures: aspiration pneumonia
  3. Compromised hosts: *Legionella,* gram-negative organisms
  4. Alcoholism: *Klebsiella, S. pneumoniae, H. influenzae*
  5. HIV: *S. pneumoniae*
  6. IV drug addicts with right-sided bacterial endocarditis: *S. aureus*
  7. Older patient with comorbid diseases: *C. pneumoniae*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Exacerbation of chronic bronchitis
- Pulmonary embolism or infarction
- Lung neoplasm
- Bronchiolitis
- Sarcoidosis
- Hypersensitivity pneumonitis
- Pulmonary edema
- Drug-induced lung injury
- Viral pneumonias
- Fungal pneumonias
- Parasitic pneumonias
- Atypical pneumonia
- Tuberculosis

WORKUP

Laboratory evaluation and chest x-ray. Table B1-1 summarizes diagnostic testing for CAP. Useful tools for assessing severity of illness are the *CURB-65* (see Disposition section) and *Pneumonia Severity Index.* Poor prognostic indicators are hypotension (SBP <90 or DBP <60), respiratory rate >30/min, hyperpyrexia (>40° C), or hypothermia (<35° C). None of these indices is as valuable as clinical judgment of the physician.

LABORATORY TESTS

- Complete blood count with differential; white blood cell count is elevated, usually with left shift
- Blood cultures (hospitalized patients only): positive in approximately 20% of cases of pneumococcal pneumonia
- Pneumococcal urinary antigen test can be used to detect the C-polysaccharide antigen of *S. pneumoniae.* It is a useful tool in the treatment of hospitalized adult patients with CAP.
- Direct immunofluorescent examination of sputum when suspecting *Legionella* (e.g., direct fluorescent antibody stain is a highly specific and rapid test for detecting legionellae in clinical specimen) or urine *Legionella* antigen test
- Serologic testing for HIV in selected patients
- Serum electrolytes (hyponatremia in suspected *Legionella* pneumonia), BUN, creatinine
- Pulse oximetry or arterial blood gases: hypoxemia with partial pressure of oxygen <60 mm Hg while the patient is breathing room air, a standard criterion for hospital admission

IMAGING STUDIES

Chest x-ray (Fig. B1-5): findings vary with the stage and type of pneumonia and the hydration of the patient:

- Classically, pneumococcal pneumonia presents with a segmental lobe infiltrate.
- Diffuse infiltrates on chest x-ray can be seen with *L. pneumophila* (Fig. B1-6), *M. pneumoniae,* viral pneumonias, *P. jirovecii (carinii),* miliary tuberculosis, aspiration, aspergillosis.
- An initial chest x-ray is also useful to rule out the presence of any complications (pneumothorax, empyema, abscesses).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of tobacco use
- Oxygen to maintain partial oxygen pressure in arterial blood >60 mm Hg
- IV hydration, correction of dehydration
- Assisted ventilation in patients with significant respiratory failure

TABLE B1-1 Diagnostic Testing for Community-Acquired Pneumonia (CAP)

Test	Sensitivity	Specificity	Comment
Chest radiograph	65%-85%	85%-95%	CT is more sensitive to infiltrates. Recommended for all patients.
Computed tomography	Gold standard	Not infection specific	Should not be done routinely but helpful to identify cavitation and loculated pleural fluid. Recommended in the evaluation of nonresponding patients.
Blood cultures	10%-20%	High when positive	Usually shows pneumococcus (in 50%-80% of positive samples) and defines antibiotic susceptibility. Recommended in patients with severe CAP, particularly if not on antibiotic therapy at the time of testing.
Sputum Gram stain	40%-100% depending on criteria	0%-100% depending on criteria	Can correlate with sputum culture to define predominant organism and can be used to identify unsuspected pathogens. Recommended if sputum culture is obtained. May not be able to narrow empirical therapy choices.
Sputum culture			Use if suspect drug-resistant or unusual pathogen, but positive result cannot separate colonization from infection. Obtain via tracheal aspirate in all intubated patients.
Oximetry or arterial blood gas			Both define severity of infection, need for oxygen; if hypercarbia is suspected, a blood gas sample is needed. Recommended in severe CAP.
Serologic testing for *Legionella, Chlamydia pneumoniae, Mycobacterium pneumoniae,* viruses			Accurate, but usually requires acute and convalescent titers collected 4-6 wk apart. Not routinely recommended.
Legionella urinary antigen	50%-80%		Specific to serogroup 1, but the best acute diagnostic test for *Legionella.*
Pneumococcal urinary antigen	70%-100%	80%	False positives if recent pneumococcal infection. Can increase sensitivity with concentrated urine.
Serum procalcitonin			Not a routine test, but if done, should be measured with the highly sensitive Kryptor assay. May help guide duration of therapy and need for ICU admission.

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders

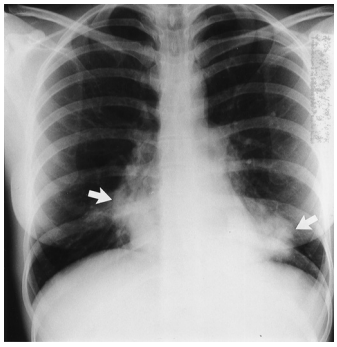

FIGURE B1-5 *Streptococcus pneumoniae* pneumonia, bilateral lower zone consolidation (*arrows*). Although pneumococcal pneumonia is typically unifocal, multifocal involvement is not uncommon. (From Grainger RG et al: *Grainger and Allison's diagnostic radiology*, ed 4, London, 2001, Harcourt.)

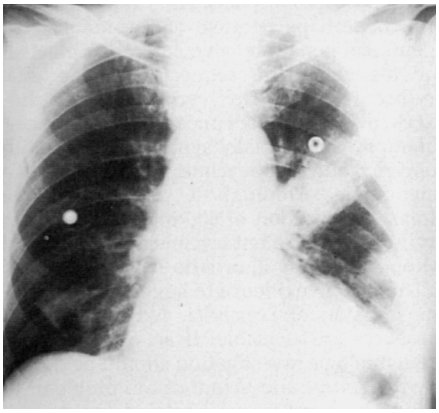

FIGURE B1-6 Multilobar involvement occurring with *Legionella pneumophila* pneumonia. (From Mason ,RJ: *Murray & Nadel's textbook of respiratory medicine*, 5th ed, Philadelphia, 2010, Saunders.)

ACUTE GENERAL Rx

- Initial antibiotic therapy should be based on clinical, radiographic, and laboratory evaluation.
- Macrolides (azithromycin or clarithromycin) or levofloxacin is recommended for empiric outpatient treatment of CAP. Box EB1-1 summarizes empirical therapy regimens for severe CAP. Cefotaxime or a beta-lactam/beta-lactamase inhibitor can be added in patients with more severe presentation who insist on outpatient therapy. Duration of treatment ranges from 7 to 14 days. The treatment of choice in suspected *Legionella* pneumonia is either a quinolone (e.g., moxifloxacin) or a macrolide (e.g., azithromycin) antibiotic.
- In the hospital setting, patients admitted to the general ward can be treated empirically with a second- or third-generation cephalosporin (ceftriaxone, ceftizoxime, cefotaxime, or cefuroxime) plus a macrolide (azithromycin or clarithromycin) or doxycycline. An antipseudomonal quinolone (levofloxacin or moxifloxacin) can be substituted in place of the macrolide or doxycycline.
- Empiric therapy in ICU patients: IV beta-lactam (ceftriaxone, cefotaxime, ampicillin-sulbactam) plus an IV quinolone (levofloxacin, moxifloxacin) or IV azithromycin.
- In hospitalized patients at risk for *P. aeruginosa* infection, empiric treatment should consist of an antipseudomonal beta-lactam (meropenem, doripenem, imipenem, or piperacillin-tazobactam) plus an aminoglycoside plus an antipseudomonal quinolone.
- In patients with suspected methicillin-resistant *S. aureus,* vancomycin or linezolid is effective.

CHRONIC Rx

Parapneumonic effusion empyema can be managed with chest tube placement for drainage. Instillation of fibrinolytic agents (streptokinase, urokinase) by chest tube may be necessary in resistant cases.

DISPOSITION

- Most patients respond well to antibiotic therapy. Risk factors for a poor outcome from CAP are summarized in Box B1-2.
- Indications for hospital admission are:
  1. Hypoxemia (oxygen saturation <90% while patient is breathing room air)
  2. Hemodynamic instability
  3. Inability to tolerate medications
  4. Active coexisting condition requiring hospitalization. A criterion often used to determine hospital admission is known as the "CURB-65": **C**onfusion, B**U**N >19.6 mg/dl, **R**espiratory rate >30 breaths/min, systolic **B**P <90 mg Hg, and diastolic BP ≤60 mm Hg, age ≥**65.** Patients are generally admitted to the hospital if they fulfill 2

or more criteria and to the ICU if they have 3 or more criteria

PEARLS & CONSIDERATIONS

COMMENTS

- Use of gastric acid suppressive therapy (H_2 receptor antagonists, proton pump inhibitors [PPIs]) has been associated with an increased risk of CAP. It appears that PPI therapy started within the previous 30 days is associated with an increased risk for CAP, whereas longer-term current use is not.
- Causes of slowly resolving or nonresolving pneumonia:
  1. Difficult to treat infections: viral pneumonia, *Legionella,* pneumococci or staphylococci with impaired host response, tuberculosis, fungi
  2. Neoplasm: lung, lymphoma, metastasis
  3. Congestive heart failure
  4. Pulmonary embolism
  5. Immunologic or idiopathic: Wegener granulomatosis, pulmonary eosinophilic syndromes, systemic lupus erythematosus
  6. Drug toxicity (e.g., amiodarone)
- If patients with pneumonia are not doing well, repeat films should be taken promptly. In those with complete clinical recovery, it is reasonable to wait 6 to 8 wk before repeating the radiograph to document clearing of the infiltrate. The benefit of routine radiography after pneumonia has been questioned due to the low 1 yr incidence of lung cancer. Opponents propose a selective approach limiting follow-up chest x-ray to middle-aged and older adults.
- Prevention: Older adults should receive the 23-valent pneumococcal polysaccharides vaccine (PPSV23)

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Bacterial Pneumonia (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

BOX B1-2 Risk Factors for a Poor Outcome from Community-Acquired Pneumonia

Patient-Related Factors
- Male sex
- Absence of pleuritic chest pain
- Nonclassic clinical presentation
- Neoplastic illness
- Neurologic illness
- Age >65 years
- Family history of severe pneumonia or death from sepsis

Abnormal Physical Findings
- Respiratory rate >30 breaths/min on admission
- Systolic (<90 mm Hg) or diastolic (<60 mm Hg) hypotension
- Tachycardia (>125 beats/min)
- High fever (>40° C) or afebrile
- Confusion

Laboratory Abnormalities
- Blood urea nitrogen >19.6 mg/dl
- Leukocytosis or leukopenia (<4000/mm^3)
- Multilobar radiographic abnormalities
- Rapidly progressive radiographic abnormalities during therapy
- Bacteremia
- Hyponatremia (<130 mmol/L)
- Multiple organ failure
- Respiratory failure
- Hypoalbuminemia
- Thrombocytopenia (<100,000/mm^3)
- Arterial pH <7.35
- Pleural effusion

Pathogen-Related Factors
- High-risk organisms:
  - Type III pneumococcus, *Staphylococcus aureus,* gram-negative bacilli (including *Pseudomonas aeruginosa*), aspiration organisms, severe acute respiratory syndrome
- Possibly high levels of penicillin resistance (minimal inhibitory concentration of at least 4 mg/L) in pneumococcus

Therapy-Related Factors
- Delay in initial antibiotic therapy (more than 4-6 hours)
- Initial therapy with inappropriate antibiotic therapy
- Failure to have a clinical response to empirical therapy within 72 hours

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

EVIDENCE

Abstract[1]

Background:

Telavancin is a lipoglycopeptide bactericidal against gram-positive pathogens.

Methods:

Two methodologically identical, double-blind studies (0015 and 0019) were conducted involving patients with hospital-acquired pneumonia (HAP) due to gram-positive pathogens, particularly methicillin-resistant *Staphylococcus aureus* (MRSA). Patients were randomized 1:1 to telavancin (10 mg/kg every 24 h) or vancomycin (1 g every 12 h) for 7–21 days. The primary end point was clinical response at follow-up/test-of-cure visit.

Results:

A total of 1503 patients were randomized and received study medication (the all-treated population). In the pooled all-treated population, cure rates with telavancin versus vancomycin were 58.9% versus 59.5% (95% confidence interval [CI] for the difference, −5.6% to 4.3%). In the pooled clinically evaluable population (*n*=654), cure rates were 82.4% with telavancin and 80.7% with vancomycin (95% CI for the difference, −4.3% to 7.7%). Treatment with telavancin achieved higher cure rates in patients with monomicrobial *S. aureus* infection and comparable cure rates in patients with MRSA infection; in patients with mixed gram-positive/gram-negative infections, cure rates were higher in the vancomycin group. Incidence and types of adverse events were comparable between the treatment groups. Mortality rates for telavancin-treated versus vancomycin-treated patients were 21.5% versus 16.6% (95% CI for the difference, −0.7% to 10.6%) for study 0015 and 18.5% versus 20.6% (95% CI for the difference, −7.8% to 3.5%) for study 0019. Increases in serum creatinine level were more common in the telavancin group (16% vs 10%).

Conclusions:

The primary end point of the studies was met, indicating that telavancin is noninferior to vancomycin on the basis of clinical response in the treatment of HAP due to gram-positive pathogens. Ⓐ

Evidence-Based Reference

Rubinstein E, for the ATTAIN Study Group, et al.: Telavancin versus vancomycin for hospital-acquired pneumonia due to Gram-positive pathogens, *Clin Infect Dis* 52:31–40, 2011. Ⓐ

SUGGESTED READINGS

Aujesky D et al.: Prospective comparison of three validated prediction rules for prognosis in community-acquired pneumonia, *Am J Med* 118:384–392, 2005.

Bruns AHW et al.: Patterns of resolution of chest radiograph abnormalities in adults hospitalized with severe community-acquired pneumonia, *Clin Infect Dis* 45:983, 2007.

Carratala J et al.: Outpatient care compared with hospitalization for community-acquired pneumonia, *Ann Intern Med* 142:165, 2005.

Davidson R et al.: Resistance to levofloxacin and failure of treatment of pneumococcal pneumonia, *N Engl J Med* 346:747, 2002.

Halm EA, Teirstein AS: Management of community-acquired pneumonia, *N Engl J Med* 347:2039, 2002.

Musher DM, Thorner AR: Community-acquired pneumonia, *N Engl J Med* 371:1619-1628, 2014.

Sarkar M et al.: Proton-pump inhibitor use and the risk for community-acquired pneumonia, *Ann Intern Med* 149:391–398, 2008.

Sordé R et al.: Current and potential usefulness of pneumococcal urinary antigen detection in hospitalized patients with community-acquired pneumonia to guide antimicrobial therapy, *Arch Intern Med* 171(2):166–172, 2011.

Tang KL et al.: Incidence, correlates, and chest radiographic yield of new lung cancer diagnosis in 3398 patients with pneumonia, *Arch Intern Med* 171:1193, 2011.

Thibodeau K, Viera AJ: Atypical pathogens and challenges in community-acquired pneumonia, *Am Fam Physician* 69:1699, 2004.

Watkins RR, Lemonovich TL: Diagnosis and management of community-acquired pneumonia in adults, *Am Fam Physician* 83(11):1299–1306, 2011.

Wunderink RG, Waterer GW et al.: Community-acquired penumonia, *N Engl J Med* 370:551–573, 2014.

BOX EB1-1 Empirical Therapy Regimens for Severe Community-Acquired Pneumonia

No Pseudomonal Risk Factors

Selected β-lactam (cefotaxime, ceftriaxone)
plus
Intravenously administered macrolide *or* quinolone (moxifloxacin or levofloxacin*)

Pseudomonal Risk Factors Present

Selected antipseudomonal β-lactam (cefepime, piperacillin/tazobactam, imipenem, meropenem)
plus
Ciprofloxacin or levofloxacin*
or
Selected antipseudomonal β-lactam
plus
Aminoglycoside
plus
Intravenously administered macrolide or antipneumococcal quinolone (moxifloxacin or levofloxacin*)

*For patients with normal renal function, the recommended dose of levofloxacin is 750 mg daily. Note: Although routine MRSA coverage is not recommended for all severe community-acquired pneumonia, consider CA-MRSA, especially after influenza and with bilateral necrotizing pneumonia, and if suspected, treat by adding either linezolid or the combination of vancomycin and clindamycin.

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

BASIC INFORMATION

DEFINITION

Bacterial vaginosis (BV) is a thin, gray, homogeneous, malodorous vaginal discharge that results from a shift in the vaginal flora from a predominance of lactobacilli to high concentrations of anaerobic bacteria.

SYNONYMS

BV
Nonspecific vaginitis
Haemophilus vaginalis vaginitis
Corynebacterium vaginalis vaginitis
Gardnerella vaginalis vaginitis
Vaginosis, bacterial

ICD-9CM CODES
616.10 Vaginitis, bacterial
ICD-10 CODES
A59.01 Trichomonal vulvovaginitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Most common vaginal infection
- *Gardnerella, Mycoplasma,* and *Mobiluncus* are harbored in the urethra of male partners; however:
  1. Male partners are asymptomatic.
  2. There is no improved cure rate or lower reinfection rate if the infected patient's male partner is treated.
  3. Abstinence from intercourse or condom use while the patient completes her treatment regimen may improve cure rates and lessen recurrences.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- 50% of patients are asymptomatic
- A thin, dark, or dull gray homogeneous discharge that adheres to the vaginal walls
- An offensive, "fishy" odor that is accentuated after intercourse or menses
- Pruritus (only in 13%)

ETIOLOGY

- *Gardnerella vaginalis* is detected in 40% to 50% of vaginal secretions.
  1. Increase in vaginal pH caused by decrease in hydrogen peroxide–producing lactobacilli
  2. Anaerobes predominate and produce amines
- Amines, when alkalinized by semen, menstrual blood, the use of alkaline douches, or the addition of 10% potassium hydroxide, volatilize and cause the unpleasant "fishy" odor. This amine-whiff test is one of the diagnostic approaches used for BV.
- In BV:
  1. *Bacteroides* (anaerobes) species are increased 1000× the usual concentration.
  2. *G. vaginalis* are 100× normal.
  3. *Peptostreptococcus* are 10× normal.
  4. *Mycoplasma hominis* and Enterobacteriaceae members are present in increased concentrations.

DIAGNOSIS

WORKUP

Seattle Group criteria:
- The presence of three of the four following signs will diagnose 90% correctly, with <10% false-positive results:
  1. Thin, gray, homogeneous, malodorous discharge that adheres to the vaginal walls
  2. Elevated pH >4.5
  3. Positive potassium hydroxide whiff test
  4. Clue cells present on wet mount
- Cultures are unnecessary.
- Pap smear will not identify *G. vaginalis.*
- Gram stain of vaginal secretions will reveal clue cells and abnormal mixed bacteria (Fig. B1-7).

TREATMENT

ACUTE GENERAL Rx

- Recommended regimens (equal efficacy):
  1. Metronidazole 500 mg PO bid for 7 days
  2. 0.75% metronidazole gel in vagina bid for 5 days
  3. 2% clindamycin cream qd for 7 days
- Alternate regimens (lower efficacy for BV):
  1. Clindamycin ovules 100 g intravaginally qhs for 3 days
  2. Clindamycin 300 mg PO bid for 7 days (increased incidence of diarrhea)
  3. Metronidazole ER 750 mg PO qd for 7 days
  4. Metronidazole 2 g PO single dose (higher relapse rate)
- Patients should be advised to avoid alcohol while taking metronidazole and for 24 hr thereafter due to disulfiram-type (antabuse) reaction when taken concurrently with alcohol.
- Treatment in pregnancy:
  1. All pregnant patients proved to have BV should be treated because of its association with preterm labor, chorioamnionitis, and premature rupture of membranes (PROM).
- Recommended regimens:
  1. Metronidazole 250 mg PO tid for 7 days
  2. Clindamycin 300 mg PO bid for 7 days
- Existing data do not support the use of topical agents during pregnancy.
- Multiple studies and meta-analyses have not demonstrated associations between metronidazole use during pregnancy and teratogenic effects in newborns.
  1. Tinidazole, an oral antiprotozoal drug, is now FDA approved for treatment of BV. Dosage is 2 g once/day for 2 days or 1 g qd × 5 days
- Recurrent BV:
  1. Condom use may help reduce the risk of recurrence.
  2. Concurrent treatment of male partner is controversial. Consider treating the male partner if there is recurrent vaginitis or any suspicion of associated upper genital tract infection.

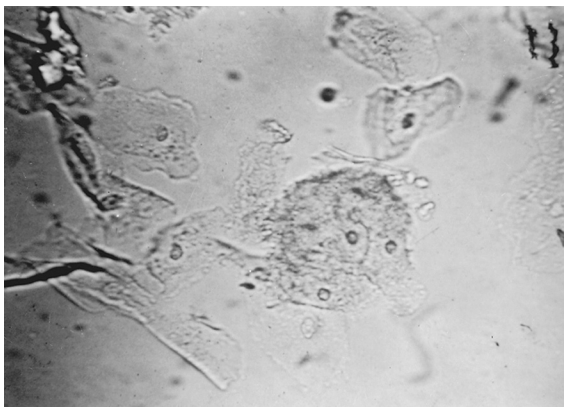

FIGURE B1-7 Clue cells characteristic of bacterial vaginosis, squamous epithelial cells whose borders are obscured by bacteria. (From Carlson K [ed]: *Primary care of women,* St Louis, 1995, Mosby.)

PEARLS & CONSIDERATIONS

- BV has been associated with pelvic inflammatory disease, cystitis, posthysterectomy vaginal cuff cellulitis, postabortal infection, preterm delivery, PROM, amnionitis, chorioamnionitis, and postpartum endometritis. New evidence also shows BV increases women's risk of acquiring HIV.
- Higher cumulative cure rates have been found at 3 to 4 wk for a 7-day regimen of metronidazole (500 mg twice daily) than with a single dose (2 g).
- Persistent BV is associated with several bacteria in the Clostridiales order, *Megasphaera* phylotype 2, and *P. lacrimalis.*

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Bacterial Vaginal Infections (Patient Information)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Marrazzo JM et al.: Relationship of specific vaginal bacteria and bacterial vaginosis treatment failure in women who have sex with women, *Ann Intern Med* 149:130, 2008.

Mitchell H: Vaginal discharge: causes, diagnosis, and treatment, *BMJ* 328(7451):1306, 2004.

Baker's Cyst PTG

BASIC INFORMATION

DEFINITION

Baker's cyst is a fluid-filled popliteal bursa located along the medial border of the popliteal fossa. It is an extension of the semimembranosus bursa posteriorly (see Fig. B1-8).

SYNONYMS

Popliteal synovial cyst

ICD-9CM CODES
727.51 Baker's cyst (knee)
ICD-10CM CODES
M71.2 Synovial cyst of popliteal space [Baker], unspecified knee

EPIDEMIOLOGY & DEMOGRAPHICS

- Most are asymptomatic and incidentally found on imaging exams.
- Occurs at all ages, most commonly between age 35 to 70, increasing with age.
- The prevalence of popliteal cysts varies based on the imaging technique used and the age of the patient population.
- Between 2% and 6% of all patients believed to have clinical deep venous thrombosis (DVT) have symptomatic Baker's cysts.
- Approximately 5% to 40% of MRIs performed for osteoarthritis or internal derangement reveal popliteal cysts.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms associated with associated joint pathology (knee swelling or stiffness)
- Pain in the popliteal space
- Leg edema
- Prominence of the popliteal fossa
- Decreased range of motion of the knee
- Locking of the knee
- ***Foucher's sign:*** the cyst becomes hard with knee extension and soft with knee flexion.
- Neuropathic lancinating pains radiating from the knee down the back of the leg
- Pain/discomfort with prolonged standing and hyperflexion of the knee
- Presence of associated DVT

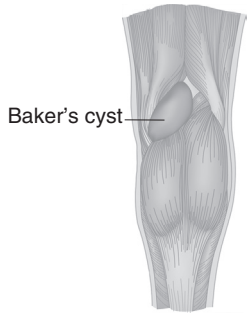

FIGURE B1-8 Baker's cyst is an extension of the semimembranosus bursa posteriorly. This bursa is often connected with a joint cavity. (From Marx J: *Rosen's emergency medicine: concepts and clinical practice,* ed 6, Philadelphia, 2006, Saunders.)

ETIOLOGY

- Believed to be fluid distention of bursal sac separating semimembranous tendon from medial head of gastrocnemius.
- May represent a true cyst but more often a degenerative or inflammatory joint disease or injury; they usually communicate with adjacent knee joint space. Thus a Baker's cyst usually denotes increased intraarticular pressure from underlying joint disease. Sequestration of synovial fluid in the popliteal fossa can result from a valve-like effect between joint space and cyst controlled by gastrocnemius-semimembranosus muscle changes with knee flexion and extension.
- In children, popliteal cysts are usually a primary process arising from the gastrocnemius-semimembranosus bursa without direct communication with the joint space.
- In adults, Baker's cysts are usually associated with pathologic changes of the knee joint, such as the following:
  1. Rheumatoid arthritis (RA)
  2. Osteoarthritis of the knee
  3. Meniscal tears
  4. Patellofemoral chondromalacia
  5. Fracture
  6. Gout
  7. Pseudogout
  8. Infection (tuberculosis)

DIAGNOSIS

Baker's cyst frequently mimics DVT and is sometimes referred to as *pseudothrombophlebitis syndrome.*

DIFFERENTIAL DIAGNOSIS

- Deep venous thrombosis
- Popliteal artery aneurysm
- Abscess
- Tumor (sarcomas/lymphomas)
- Lymphadenopathy
- Varicosity
- Synovial or ganglion cysts

WORKUP

The diagnosis can be made by physical examination alone. However, anyone suspected of having a popliteal cyst should undergo imaging studies to exclude other causes.

LABORATORY TESTS

Blood tests are not specific.

IMAGING STUDIES

- Plain radiographs (AP and lateral views) may show calcification in a solid tumor or in the posterior meniscal area.
- Ultrasound (Fig. B1-9) is safe, portable, cost effective, and excludes other clinically important causes of popliteal fossa pathology, including DVT.
- MRI if internal derangement is suspected, surgery being considered, or diagnosis unclear after ultrasound.

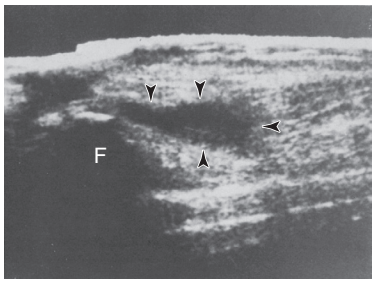

FIGURE B1-9 Sonography of a popliteal cyst. Sagittal sonographic section through the popliteal space in this patient demonstrates a sonolucent fluid collection *(arrowheads)* posterior and inferior to the medial femoral condyle *(F).* (From DeLee D, Drez D [eds]: *DeLee and Drez's orthopaedic sports medicine,* ed 2, Philadelphia, 2003, Saunders.)

TREATMENT

Asymptomatic cysts found incidentally do not require treatment.

NONPHARMACOLOGIC THERAPY

- Rest
- Strenuous activity avoidance
- Knee immobilization sometimes necessary

ACUTE GENERAL Rx

- NSAIDs can be used to treat underlying joint pathology (RA, gout, and pseudogout).
- Arthrocentesis with intraarticular injection or injection of the cyst with corticosteroids (triamcinolone acetonide 40 mg).

CHRONIC Rx

- The majority of Baker's cysts are successfully treated conservatively.
- If refractory symptoms, surgical procedures addressing the underlying cause include:
  1. Arthroscopic surgery to remove loose cartilaginous fragment
  2. Partial or total meniscectomy
  3. Open excision of the cyst

DISPOSITION

- Baker's cyst may spontaneously resolve without treatment.
- Complications of Baker's cysts include:
  1. Rupture
  2. DVT
  3. Nerve impingement resulting in posterior tibial nerve entrapment, anterior compartment syndrome, or posterior compartment syndrome
  4. Popliteal artery occlusion

REFERRAL

Orthopedic surgeon if surgery is contemplated

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Baker's Cyst (Patient Information)

AUTHORS: **JOHANNES STEINER, M.D.,** and **RICHARD REGNANTE, M.D.**

SUGGESTED READINGS

Handy JR: Popliteal cysts in adults: a review, *Semin Arthritis Rheum* 31(2):108, 2001.

Torreggiani WC et al.: The imaging spectrum of Baker's (popliteal) cysts, *Clin Radiol* 57(8):681, 2002.

BASIC INFORMATION

DEFINITION

Balanitis is an inflammation of the superficial tissues of the penile head (glans penis). If the foreskin (prepuce) is involved, it is called *balanoposthitis*.

ICD-9CM CODES
112.2 Balanitis
ICD-10CM CODES
B37.42 Candidal balanitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): More common in uncircumcised males and in diabetic patients
PREVALENCE (IN U.S.): One study reports that 11% of adult men seen in a urology clinic and 3% of male children (mostly uncircumcised) have balanitis.
PREDOMINANT SEX: Almost exclusive to males but can affect clitoris
PEAK INCIDENCE: All ages, especially in sexually active men. It occurs in ¼ of male sex partners of women infected with *Candida.*

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Itching and tenderness
- Pain, dysuria, and local edema and erythema (Fig. B1-10)
- Rarely, ulceration and lymph node enlargement
- Severe ulcerations leading to superimposed bacterial infections
- Inability to void: unusual, but a more distressing and serious complication

FIGURE B1-10 Candidal balanitis. (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

ETIOLOGY

- Causes include infectious agents, skin disorders, or miscellaneous.
- Infectious diseases: *Candida species (40%), Neisseria gonorrhoeae,* HPV, herpes simplex, *Gardnerella vaginalis, Treponema pallidum* (syphilis), HIV, *Trichomonas, Staphylococcus aureus,* anaerobic bacteria
- Skin disorders: circinate balanitis of **Reiter's syndrome,** lichen sclerosis
- Miscellaneous: poor hygiene, causing erosion of tissue with erythema and promoting growth of *Candida albicans* (Fig. EB1-11), trauma (zippers, urinary catheters), allergic reactions to condoms or medications

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Leukoplakia
- Nummular eczema
- Balanitis xerotica obliterans
- Psoriasis
- Carcinoma of the penis
- Plasma cell balanitis (noninfectious)
- Erythroplasia of Queyrat
- Nodular scabies
- Circinate balanitis (Reiter's syndrome)

WORKUP

- Sexually active males: assessment for evidence of other sexually transmitted diseases
- Biopsy if lesions do not heal

LABORATORY TESTS

- VDRL for syphilis
- Serum glucose to rule out diabetes
- Wet mount for *Trichomonas*
- KOH prep for yeast
- Microbial culture to rule out STD

TREATMENT

NONPHARMACOLOGIC THERAPY

- Maintenance of meticulous hygiene
- Retraction and bathing of prepuce several times a day
- Warm sitz baths to ease edema and erythema
- Consideration of circumcision, especially when symptoms are severe or recurrent
- With Foley catheters, strict catheter care strongly advised

ACUTE GENERAL Rx

- Metronidazole 2 g PO as a single dose or fluconazole 150 mg PO × 1 or itraconazole 200 mg PO bid × 1 day
- Clotrimazole 1% cream applied topically twice daily to affected areas
- Bacitracin or Neosporin ointment applied topically 4 times daily
- With more severe bacterial superinfection: cephalexin 500 mg PO qid
- Topical corticosteroids added 4 times daily if dermatitis severe
- Patients with suspected urinary tract infections: trimethoprim-sulfa DS twice daily or ciprofloxacin 500 mg PO bid after obtaining appropriate cultures

DISPOSITION

Balanitis is often self-limited and usually responds to conservative therapy; if it does not improve, consider circinate balanitis of Reiter's syndrome, nodular scabies, and primary skin lesions including skin carcinoma.

PEARLS & CONSIDERATIONS

Don't forget about nodular scabies involving the prepubic area—examine the region carefully for burrows and tracks of *Sarcoptes scabiei.*

REFERRAL

- For surgical evaluation for circumcision if symptoms are recurrent, especially if phimosis or meatitis occurs (note: Severe phimosis with an inability to void may require prompt slit drainage.)
- For biopsy to rule out other diagnoses such as premalignant or malignant lesions if lesions are not healing

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Balanitis (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Buechner SA: Common skin disorders of the penis, *BJU Int* 90(5):498, 2002.
Bunker CB: Topics in penile dermatology, *Clin Exp Dermatol* 26(6):469, 2001.
Lisboa C et al.: Noninfectious balanitis in patients attending a sexually transmitted disease clinic, *Int J Dermatol* 48(4):445–446, 2009.
Pandher BS et al.: Treatment of balanitis xerotica obliterans with topical tacrolimus, *J Urol* 170(3):923, 2003.
Thiruchelvan M et al.: Emergency dorsal slit for balanitis with retention, *J R Soc Med* 97(4):206, 2004.

FIGURE EB1-11 Candidal balanitis. (From Swartz MH: Male genitalia and hernias. In Swartz MH [ed]: *Textbook of physical diagnosis: history and examination,* Philadelphia, 2014, Elsevier.)

Barrett Esophagus PTG

BASIC INFORMATION

DEFINITION

Barrett esophagus occurs when the squamocolumnar junction is displaced proximal to the gastroesophageal junction and the squamous lining of the lower esophagus is replaced by metaplastic columnar epithelium, which predisposes to the development of esophageal adenocarcinoma. While cardia-type epithelium has been shown to predispose to esophageal cancer, the presence of intestinalized epithelium is still considered essential for the diagnosis. Recent data show that the absolute annual risk for esophageal carcinoma in Barrett esophagus is 0.12%, which is much lower than the assumed risk of 0.5% that is the basis for current surveillance guidelines.

SYNONYMS

Barrett's esophagus
Esophagus, Barrett
Esophagus, columnar-lined
Ulcer, Barrett's

ICD-9CM CODES
530.85 Barrett esophagus
ICD-10CM CODES
K22.70 Barrett esophagus without dysplasia

EPIDEMIOLOGY & DEMOGRAPHICS

- Male/female ratio of 4:1.
- Mean age of onset is 40 yr, with a mean age range of diagnosis of 55 to 60 yr.
- Occurs more frequently in white and Hispanic individuals than in African American individuals, with a ratio of 10 to 20:1.
- Mean prevalence of 5% to 15% in patients undergoing endoscopy (EGD) for symptoms of gastroesophageal reflux disease (GERD).
- Independent risk factors include chronic reflux (>5 years), hiatal hernia, age >50 years, male gender, white ethnicity, smoking history, and intra-abdominal obesity. A family history with at least one first-degree relative with Barrett esophagus or adenocarcinoma of the esophagus may also be a risk factor.
- It is estimated that 5.6% of adults in the United States have Barrett esophagus. Prevalence rate in asymptomatic cohorts ranges from 5% to 25%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

SYMPTOMS:
- Chronic heartburn
- Dysphagia with solid food
- May be an incidental finding on EGD in patients without reflux symptoms
- Less frequent: chest pain, hematemesis, melena
- Patients may be asymptomatic.

PHYSICAL FINDINGS:
- Nonspecific; can be completely normal
- Epigastric tenderness on palpation

ETIOLOGY

- Metaplasia is thought to result from reepithelialization of esophageal tissue injured as a result of chronic GERD.
- Patients with Barrett esophagus tend to have more severe esophageal motility disturbances (decreased lower esophageal sphincter pressure, ineffective peristalsis) and greater esophageal acid exposure on 24-hour pH monitoring.
- Intraesophageal bile reflux may also play a role in the pathogenesis.
- Familial clustering of GERD and Barrett esophagus suggests a genetic predisposition, but no gene has yet been identified. Early data suggest that patients who develop Barrett are genetically predisposed to a severe inflammatory response to GERD.
- Progression from metaplasia to carcinoma is associated with changes in gene structure and expression, including the caudal-related homeobox family of transcription factors (CDX1 and CDX2) and the tumor suppressors p16 (CDKN2A) and TP53.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- GERD, uncomplicated
- Erosive esophagitis
- Gastritis
- Peptic ulcer disease
- Angina
- Malignancy
- Stricture or Schatzki's ring

WORKUP

- The Practice Parameters Committee of the American College of Gastroenterology (ACG) has suggested that the highest yield for Barrett esophagus screening is in older (age >50 yr) white men with longstanding heartburn. The American Gastroenterological Association Medical Position Panel gave a weak recommendation for screening patients with multiple risk factors, including age over 50, male sex, white race, chronic GERD, hiatal hernia, elevated body mass index, and intraabdominal distribution of body fat. General population screening is not currently recommended. The benefit of screening in high-risk populations is not established. Although screening has become standard of practice in some communities, the effectiveness of screening using current techniques is controversial because it may not improve mortality rates from adenocarcinoma or be cost-effective.
- EGD with biopsy is necessary for diagnosis.
- Wireless esophageal capsule endoscopy may detect Barrett, but with a lower sensitivity and specificity than EGD. Imaging studies are nonspecific and insensitive for the diagnosis. Other modalities under investigation include unsedated transnasal endoscopy and an esophageal cytology device called a *cytosponge.*
- Diagnosis requires the presence of metaplastic columnar epithelium proximal to the gastroesophageal junction (Fig. B1-12). Longer-segment (≥3 cm) Barrett esophagus is more readily diagnosed (Fig. B1-13). At least two expert gastrointestinal pathologists should concur if dysplasia is diagnosed.
- Intestinal metaplasia of the gastric cardia is not Barrett esophagus and does not have the same risk for malignancy.
- Biomarkers and advanced imaging techniques such as chromoendoscopy, narrow band imaging, and confocal laser endomicroscopy are being evaluated to assist with diagnosis and to better understand progression of disease, prediction of response to therapy, or prognosis.
- Screening for *Helicobacter pylori* infection in patients with GERD and Barrett esophagus is not recommended.

TREATMENT

The goal is to control GERD symptoms and maintain healed mucosa.

NONPHARMACOLOGIC THERAPY

Nonpharmacologic therapy includes lifestyle modifications; elevating head of bed; and avoiding chocolate, tobacco, caffeine, mints, and certain drugs (see "Gastroesophageal Reflux Disease").

ACUTE GENERAL Rx

- Proton pump inhibitors are the most effective treatment for GERD. Therapy should be dosed to control symptoms and/or to promote healing of endoscopic signs of disease.
- If patient is asymptomatic and incidentally found to have Barrett esophagus, proton pump inhibitors may still be considered, as they may reduce the risk of neoplastic progression.

CHRONIC Rx

- Chronic acid suppression is often necessary to control symptoms and maintain healing.
- Antireflux surgery may be considered for management of GERD and associated sequelae, but it has not been proven to be superior to medical therapy. Patients continue to require endoscopic surveillance of their esophagus.
- When GERD is controlled by either medical or surgical therapy, ablation of metaplastic epithelium usually leads to replacement by normal squamous epithelium. Because only a minority of patients with Barrett esophagus progress to high-grade dysplasia or carcinoma, endoscopic eradication therapy is not recommended for the general population of patients with nondysplastic Barrett esophagus.
- While endoscopic eradication therapy has been shown to reduce the progression of Barrett esophagus with low-grade dysplasia to high-grade dysplasia and adenocarcinoma in selected patients, a long-term benefit has not been clearly established.

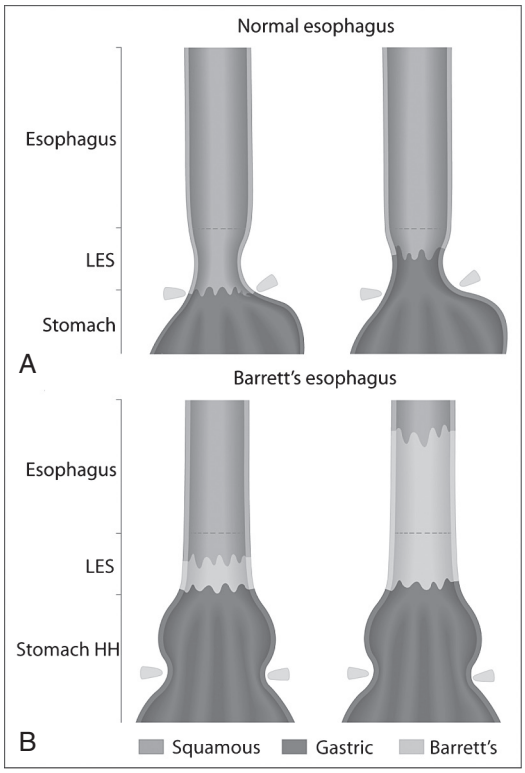

FIGURE B1-12 Anatomic landmarks of the normal LES region (A) and of Barrett esophagus (B). Note that gastric mucosa is very common and normal in the LES region and that in Barrett esophagus, the squamocolumnar junction is not only proximally displaced within the tubular esophagus, but that the intervening mucosa is composed of intestinalized Barrett's metaplastic epithelium. *HH,* Hiatial hernia. (From Silverburg SG: *Principles of practice of surgical pathology and cytopathology,* ed 4, New York, 2006, Churchill Livingstone.)

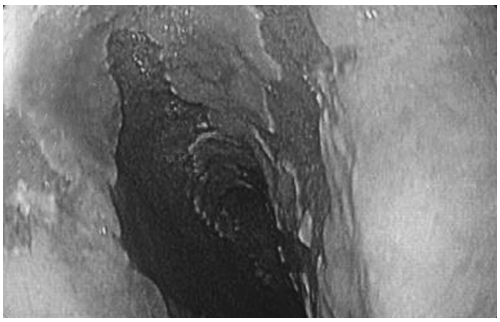

FIGURE B1-13 Long-segment Barrett esophagus. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

- Endoscopic eradication therapy is the treatment of choice for high-grade dysplasia. Radiofrequency ablation, thermal ablation techniques, or photodynamic therapy, combined with endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) of visible mucosal irregularities, are accepted approaches to the treatment of patients with Barrett esophagus and high-grade dysplasia, in conjunction with aggressive surveillance and eradication of all remaining Barrett's epithelium. Endoscopic therapy is preferred over surgical treatment in properly staged individuals. These therapies may even be considered for patients with focal intramucosal carcinoma, if properly staged (T1SM1 or lower). Cryotherapy is being evaluated for the complete eradication of both dysplasia and intestinal metaplasia and reduced risk for disease progression. All these options run the risk for residual or buried metaplasia.
- Surgical resection is definitive therapy and may be offered for multifocal high-grade dysplasia or carcinoma that has extended into the submucosa. Mortality appears to be lower with experienced surgeons operating in high-volume centers.
- Patients with cardiovascular risk factors may be considered for low-dose aspirin therapy for chemoprevention of esophageal adenocarcinoma.

DISPOSITION

- The relative risk of developing esophageal adenocarcinoma for a patient with Barrett esophagus, as compared with the general population, is 11.3, a substantial drop from the increase by a factor of 30 or 40 estimated in early reports.
- The risk of progression from untreated Barrett with high-grade dysplasia to esophageal adenocarcinoma ranges from 6% to 19% per year.
- Frequency of monitoring is controversial. No studies have proved that endoscopic surveillance is cost effective or increases life expectancy. Although some studies have suggested that close adherence to surveillance protocols is associated with higher rates of detection of dysplasia and cancer, a recent case-control study showed no reduction in mortality.
- Patients with Barrett esophagus currently undergo surveillance EGD and systematic four-quadrant biopsy at intervals determined by the presence and grade of dysplasia. All mucosal abnormalities should undergo biopsy. Patients who have had two consecutive EGDs showing no dysplasia should have follow-up every 3 to 5 yr. Patients with low-grade dysplasia should have extensive mucosal sampling within 6 mo and follow-up every 6 to 12 mo. Patients with high-grade dysplasia should have expert confirmation and extensive mucosal sampling. High-grade dysplasia with visible mucosal irregularities should be removed by EMR or ESD. Consider intensive surveillance every 3 mo. Endoscopic treatment is preferred over intensive surveillance in patients with high-grade dysplasia.
- Patients should be treated aggressively for GERD before surveillance.

REFERRAL

- Consider EGD with biopsy in patients (particularly white men ≥50 yr old) with multiple risk factors who have not had previous EGD.
- Refer patients with GERD for evaluation if "red flag" symptoms are present (dysphagia, odynophagia, weight loss, vomiting, early satiety, GI bleeding, iron deficiency).
- Refer patients with biopsy-proved Barrett esophagus for surveillance.
- For those with high-grade dysplasia, refer for ablative therapy with EMR or ESD if appropriate, followed by intensive surveillance. Esophageal resection may be considered.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Barrett Esophagus (Patient Information)
Esophageal Tumors (Related Key Topic)

AUTHOR: **HARLAN G. RICH, M.D.**

SUGGESTED READINGS

American Gastroenterological Association, et al.: American Gastroenterological Association medical position statement on the management of Barrett's esophagus, *Gastroenterology* 140:1084, 2011.

Bennett C et al.: Consensus statements for management of Barrett's dysplasia and early-stage esophageal adenocarcinoma, based on a Delphi process, *Gastroenterology* 143:336–346, 2012.

Bonino JA, Sharma P: Barrett's esophagus, *Curr Opin Gastroenterol* 22:406, 2006.

Dellon ES, Shaheen NJ: Does screening for Barrett's esophagus and adenocarcinoma of the esophagus prolong survival? *J Clin Oncol* 23:4478, 2005.

Hvid-Jensen F et al.: Incidence of adenocarcinoma among patients with Barrett's esophagus, *N Engl J Med* 365:1375–1383, 2011.

Kahrilas PJ: The problem with surveillance of Barrett's esophagus, *N Engl J Med* 365:1437–1438, 2011.

Shaheen NJ: Advances in Barrett's esophagus and esophageal adenocarcinoma, *Gastroenterology* 128:1554, 2005.

Shaheen NJ, Richter JE: Barrett's esophagus, *Lancet* 373:850–861, 2009.

Shaheen NJ et al.: Radiofrequency ablation in Barrett's esophagus with dysplasia, *N Engl J Med* 360:2277–2288, 2009.

Shaheen NJ et al.: Garlic, silver bullets, and surveillance upper endoscopy for Barrett's esophagus, *Gastroenterology* 145:273–275, 2013.

Sharma P: Barrett's esophagus, *N Engl J Med* 361:26, 2009.

Sharma P et al.: A critical review of the diagnosis and management of Barrett's esophagus: the AGA Chicago workshop, *Gastroenterology* 127:310, 2004.

Spechler SJ, Barr B: Review article: screening and surveillance of Barrett's esophagus: what is a cost-effective framework? *Aliment Pharmacol Ther* 1(Suppl 1):49, 2004.

Spechler SJ, Souza RF: Barrett's esophagus, *N Engl J Med* 371:836–845, 2014.

Spechler SJ et al.: History, molecular mechanisms, and endoscopic treatment of Barrett's esophagus, *Gastroenterology* 138:854, 2010.

Spechler SJ et al.: American Gastroenterological Association technical review on the management of Barrett's esophagus, *Gastroenterology* 140:e18, 2011.

Wang KK, Sampliner RE: Updated guidelines 2008 for the diagnosis, surveillance, and therapy of Barrett's esophagus, *Am J Gastroenterol* 103:788, 2008.

BASIC INFORMATION

DEFINITION

Bartter's syndrome refers to a group of rare autosomal recessive conditions involving the renal tubules that is characterized by metabolic alkalosis, hypokalemia, hyperreninemia, hyperplasia of the juxtaglomerular apparatus (the source of renin in the kidney), and in some patients, hypomagnesemia.

SYNONYMS

Hypokalemic alkalosis with hypercalciuria, Bartter's syndrome, juxtaglomerular hyperplasia.

ICD-9CM Codes
255.13 Bartter's syndrome
ICD-10CM CODES
E26.8 Other hyperaldosteronism

EPIDEMIOLOGY & DEMOGRAPHICS

Classic Bartter's syndrome can present with symptoms at 2 yr of age or younger. Neonatal Bartter's syndrome can be diagnosed at birth or even prenatally. The prevalence of Bartter's syndrome is 1:1,000,000 with similar incidence in males and females and among racial and ethnic groups.

CLINICAL PRESENTATION

- Neonatal Bartter's syndrome is mostly seen between 24-30 weeks with maternal polyhydramnios. Frequent preterm delivery, fetal polyuria, and failure to thrive (FTT) are common.
- Classic Bartter's syndrome also may include a history of maternal polyhydramnios and premature delivery. The following features are characteristic:
  1. Polyuria and polydipsia due to decreased urinary concentrating ability with a tendency to dehydrate.
  2. Hypokalemia.
  3. Vomiting.
  4. Metabolic alkalosis.
  5. Hypercalciuria with development of kidney stones.
  6. Plasma magnesium can be normal or mildly reduced.
  7. Patients have normal to low blood pressure.
  8. Elevated renin and aldosterone levels.
  9. Patients do not have edema.
  10. Elevated renal prostaglandins.
  11. Growth and mental retardation remain a major complication in children with primary tubular disorders, despite treatment.
- Other complications may include hearing loss, renal disease, cardiac arrhythmias, and sudden death.

ETIOLOGY

- The primary defect is impairment of the transporter involved in sodium chloride reabsorption in the thick ascending loop of Henle.
- Bartter's syndrome is caused by genetic mutations that manifest in a similar phenotype. The multiple and complex functions of the renal tubule in regulating water, electrolyte, and mineral homeostasis make it prone to numerous genetic abnormalities resulting in malfunction (Table EB1-2).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Diuretic or laxative abuse.
- Surreptitious vomiting, which can be seen in conditions such as factitious disorder and eating disorder.
- Gitelman's syndrome (Table EB1-2).
- Autosomal dominant hypocalcemia.
- Hyperprostaglandin E syndrome.

WORKUP

- Classic Bartter's syndrome is usually a diagnosis of exclusion.
- Vomiting can be distinguished from Bartter's by a low urine chloride concentration. Scarring of the dorsum of the hand and dental erosions may suggest bulimia nervosa.
- Diuretic abuse can only be excluded by a urinary assay for diuretics.

LABORATORY TESTS

- Serum sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, plasma renin, plasma aldosterone.
- Urine calcium, chloride, urine prostaglandin E, and assay for diuretics.
- Serum pH can be confirmed by performing ABG.
- Genetic diagnosis is possible, but not widely available.

IMAGING STUDIES

- Renal ultrasonography may show nephrocalcinosis, hydronephrosis, and hydroureter in neonatal Bartter's syndrome.
- Signs of hypokalemia may be seen on ECG or prenatal ultrasound scanning and amniocentesis.

TREATMENT

ACUTE GENERAL Rx

Neonatal Bartter's syndrome requires correction of electrolyte imbalances and volume depletion.

CHRONIC Rx

- Bartter's syndrome is caused by a genetic mutation, and currently there is no cure. The tubular defects cannot be corrected, and as a result, treatment is lifelong. Patients are generally treated with oral potassium and magnesium supplementation, though achievement of normal serum potassium and magnesium levels is often difficult.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) in combination with a potassium-sparing diuretic (such as spironolactone) have been used effectively in the treatment of Bartter's. Proton-pump inhibitors and H-2 antagonists have been used to reduce gastritis and GI bleeding with chronic NSAID use.
- Angiotensin-converting enzyme (ACE) inhibitors may be used to reduce production of angiotensin II and aldosterone.
- Growth hormone (GH) may be used to treat short stature.
- Calcium or magnesium supplements may be needed.
- Renal transplantation should correct the transporter abnormalities seen in Bartter's, and recurrence of disease in the transplant has not been reported. However, this aggressive approach has been performed in isolated cases.

REFERRAL

Consultation with nephrology facilitates diagnosis and management of this condition.

PEARLS & CONSIDERATIONS

COMMENTS

- Bartter's syndrome resembles loop diuretic use in laboratory testing, whereas Gitelman's syndrome appears identical to thiazide diuretic use.
- High urine calcium is the best way to distinguish Bartter's from Gitelman's syndrome.
- Serum magnesium differences have been described but are likely to be low in both syndromes and are probably not useful in distinguishing these syndromes.

PATIENT/FAMILY EDUCATION

- Foods with high potassium content should be emphasized in dietary education.
- Patients with Bartter's syndrome are more vulnerable to volume depletion due to potassium derangement during exercise and exposure.
- Genetic counseling may be indicated in some cases.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **JONATHAN BURNS, M.A., M.D.,** and **ANDREW CARAGANIS, M.D.**

SUGGESTED READINGS

Bhat YR, Vinayaka G, Sreelakshmi K: Antenatal Bartter syndrome: a review, *Int J Pediatr* 2012:857136, 2012.

Chadha V, Alon US: Hereditary renal tubular disorders, *Semin Nephrol* 29(4):399–411, 2009.

Gil-Peña H et al.: Longitudinal growth in chronic hypokalemic disorders, *Pediatr Nephrol* 25(4):733–737, 2010.

Hebert SC: Bartter syndrome, *Curr Opin Nephrol Hypertens* 12(5):527, 2003.

Kurtz I: Molecular pathogenesis of Bartter's and Gitelman's syndromes, *Kidney Int* 54:1396, 1998.

Online Mendelian Inheritance in Man: www.omim.org.

TABLE EB1-2 Bartter and Gitelman Syndromes

	Type I Bartter Syndrome	Type II Bartter Syndrome	Type III Bartter Syndrome	Type IV Bartter Syndrome	Type V Bartter Syndrome	Gitelman Syndrome
Inheritance	AR	AR	AR	AR	AD	AR
Affected tubular region	TAL	TAL + CCD	TAL + DCT	TAL + DCT	TAL	DCT
Gene	*SLC12A1*	*KCNJ1*	*CLCBRK*	*BSND*	*CASR*	*SLC12A3*
Onset	Prenatal, postnatal	Prenatal, postnatal	Variable	Prenatal, postnatal	Variable	Adolescent, adult
Urine PGE_2	Very high	Very high	Slightly elevated	Elevated	Elevated	Normal
Hypokalemic metabolic alkalosis	Present	Present	Present	Present	Present	Present
Features	Polyhydramnios, prematurity, nephrocalcinosis, dehydration, hyposthenuria, polyuria, failure to thrive	Same as type 1	Failure to thrive, dehydration, low serum magnesium in 20%, mildest form	Same as type I, with sensorineural hearing loss and no nephrocalcinosis	Hypocalcemia, low parathyroid hormone levels, hypercalciuria, uncommon cause of Bartter syndrome	Hypomagnesemia in 100%, mild dehydration, occasional growth retardation, tetany

AR, Autosomal recessive; *AD,* autosomal dominant; *CCD,* cortical collecting duct; *DCT,* descending convoluted tubule; *PGE_2,* prostaglandin E2; *TAL,* thick ascending loop of Henle.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

Basal Cell Carcinoma PTG

BASIC INFORMATION

DEFINITION

Basal cell carcinoma (BCC) is a malignant tumor of the skin arising from basal cells of the lower epidermis and adnexal structures. It may be classified as one of six types: nodular, superficial, pigmented, cystic, sclerosing or morpheaform, and nevoid. The most common type is nodular (21%); the least common is morpheaform (1%). A mixed pattern is present in approximately 40% of cases. BCC advances by direct expansion and destroys normal tissue.

SYNONYMS

BCC

ICD-9CM CODES	
179.9	Basal cell carcinoma, site unspecified
173.3	Basal cell carcinoma, face
173.4	Basal cell carcinoma, neck, scalp
173.5	Basal cell carcinoma, trunk
173.6	Basal cell carcinoma of the limb
173.7	Basal cell carcinoma, lower limb
ICD-10CM CODES	
C44.90	Unspecified malignant neoplasm of skin, unspecified
C44.300	Unspecified malignant neoplasm of skin of unspecified part of face
C44.40	Unspecified malignant neoplasm of skin of scalp and neck
C44.509	Unspecified malignant neoplasm of skin of other part of trunk
C44.601	Unspecified malignant neoplasm of skin of unspecified upper limb, including shoulder
C44.701	Unspecified malignant neoplasm of skin of unspecified lower limb, including hip

EPIDEMIOLOGY & DEMOGRAPHICS

- Most common cutaneous neoplasm
- 85% of cases appear on the head and neck region
- Most common site: nose (30%)
- Increased incidence with age >40 yr
- Increased incidence in men
- Risk factors: fair skin, increased sun exposure, use of tanning salons with ultraviolet A or B radiation, history of irradiation (e.g., Hodgkin's disease), personal or family history of skin cancer, impaired immune system

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Variable with the histologic type:

- Nodular: dome-shaped, painless lesion that may become multilobular and frequently ulcerates (rodent ulcer); prominent telangiectatic vessels are noted on the surface. Border is translucent, elevated, pearly white (Fig. B1-14). Some nodular BCCs may contain pigmentation, giving an appearance similar to a melanoma.
- Superficial: circumscribed, scaling, black appearance with a thin, raised, pearly-white border (Fig. B1-15); a crust and erosions may be present. Occurs most frequently on the trunk and extremities.
- Morpheaform: flat or slightly raised yellowish or white appearance (similar to localized scleroderma); appearance similar to scars; surface has a waxy consistency.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Keratoacanthoma
- Melanoma (pigmented BCC)
- Xeroderma pigmentosa
- Basal cell nevus syndrome
- Molluscum contagiosum
- Sebaceous hyperplasia
- Psoriasis

WORKUP

Biopsy to confirm diagnosis

TREATMENT

Variable with tumor size, location, and cell type:

- Excision surgery: preferred method for large tumors with well-defined borders on the legs, cheeks, forehead, and trunk.
- Mohs' micrographic surgery: preferred for lesions in high-risk areas (e.g., nose, eyelid), very large primary tumors, recurrent BCCs, and tumors with poorly defined clinical margins.
- Electrodesiccation and curettage: useful for small (>6 mm) nodular BCCs.
- Cryosurgery with liquid nitrogen: useful in BCCs of the superficial and nodular types with clearly definable margins; no clear advantages over the other forms of therapy; generally reserved for uncomplicated tumors.
- Radiation therapy: generally used for BCCs in areas requiring preservation of normal surrounding tissues for cosmetic reasons (e.g., around lips); also useful in patients who cannot tolerate surgical procedures or for large lesions and surgical failures.
- Imiquimod 5% cream can be used for treatment of small, superficial BCCs of the trunk and extremities. Efficacy rate is approximately 80%. Its main advantage is lack of scarring, which must be weighed against higher cure rates with surgical intervention.
- Vismodegib, an orally active hedgehog pathway inhibitor, has been FDA approved for metastatic BCC, recurrent basal cell carcinoma post-surgery, and locally advanced BCC in patients who are not candidates for surgery or radiation. Dose is 150 mg PO qd. Cost of 1-month supply may exceed $7000.

DISPOSITION

- More than 90% of patients are cured; however, periodic evaluation for at least 5 yr is necessary because of increased risk of recurrence of another BCC (<40% risk within 5 yr of treatment).
- A lesion is considered low risk if it is >1.5 cm in diameter, is nodular or cystic, is not in a difficult-to-treat area (H zone of face), and has not been previously treated.
- Nodular and superficial BCCs are the least aggressive.
- Morpheaform lesions have the highest incidence of positive tumor margins (<30%) and the greatest recurrence rate.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Basal Cell Skin Cancer (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

FIGURE B1-14 Basal cell carcinoma. Note rolled translucent border and central ulceration in typical facial location. (From Noble J et al: *Textbook of primary care medicine,* ed 3, St Louis, 2001, Mosby.)

FIGURE B1-15 Superficial variant of basal cell carcinoma. Multiple lesions are common with this variant, often on the trunk. Closer examination shows the typical raised pearly edge. (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

SUGGESTED READING

Von Hoff DD et al.: Inhibition of the hedgehog pathway in advanced basal cell carcinoma, *N Engl J Med* 361:1164–1172, 2009.

BASIC INFORMATION

DEFINITION

A bedbug's bite is a wound caused by the penetration of the bedbug mouthpiece into the skin as the insect feeds on blood from vessels or extravasated blood from the damaged surrounding tissue. The saliva of the bedbug contains pharmacologically active substances responsible for a spectrum of undesirable skin reactions depending on the individual. The bugs typically feed during times when an individual is at rest and may feed without being detected. Typically feedings take 5 to 10 minutes.

SYNONYMS

Insect bite
Bedbug *Cimex lectularius* bite

ICD-9CM Codes
919.4 Insect bite w/o infection (may also code based on bite location)
ICD-10CM CODES
T00.9 Multiple superficial (insect bite) injuries, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Traditionally, bedbugs were considered more common in poorer areas, but they are now increasingly found in areas of frequent travel.
- Bedbug infestations may spread among multifamily and institutional facilities with shared walls and are consequently difficult to eradicate.
- Reports of bedbug infestations have increased dramatically in the U.S., as well as worldwide, likely because of the decreased use of pesticides and increased international travel.
- Bedbugs are attracted to carbon dioxide gas and warm bodies.
- Bedbugs do not have a preference for specific age groups, ethnicity, or sex.
- Persons at higher risk include those that have recently stayed overnight in a hotel, dorm room, hospital, or new home.
- Studies have shown increased sensitivity of cutaneous reaction in previous bite victims.

PHYSICAL FINDINGS AND CLINICAL PRESENTATION

- Bites typically occur at night on exposed areas of skin, most often the face, neck, arms, and legs.
- The bites are painless and so do not awaken the individual.
- Onset of signs and symptoms of bites can be immediately on awakening or up to 10 days after the bite.
- Firm, purpuric or erythematous macules, urticaria, papules (Fig. B1-16), or bullae may be present. Bites are often inflammatory and pruritic, although bedbug-naive individuals may be asymptomatic to their first bites.
- Bite may have a central hemorrhagic punctum.
- Victim may observe a linear series of three bites ("breakfast, lunch, and dinner").
- Bites are typically pruritic.
- The size, degree of itching, and propensity toward vesiculation all increase with repeated bedbug bites.
- Figure B1-17 illustrates symptoms and behaviors resulting from bed bug bites.

ETIOLOGY

- The *Cimex lectularius* species, also known as the common bedbug, feeds on mammals and birds. *Cimex hemipterus* is a tropical species that bites mostly humans, and hybrid species of the two insects exist. Both generally feed nocturnally on the blood of sleeping humans. The adult bedbug is wingless and about 5 to 7 mm in length. It has a modified mouthpart for piercing and sucking that usually leaves a bite mark of papular urticarial presentation to exposed areas of skin. Bedbugs have weak appendages for latching on to their hosts and are not usually transported from person to person.
- The saliva of the bedbug contains nitrophorin that enables vasodilation, an anticoagulant that interferes with production of coagulation factor Xa, a salivary apyrase that inhibits platelet aggregation, and an anesthetic. Consequently, the host often does not feel the bite until the effects have worn off.

FIGURE B1-16 Pruritic papules after bedbug bites. (From Kliegman RM et al: Nelson textbook of pediatrics, ed 19, Philadelphia, 2011, Saunders.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Scabies, flea and mite bites, vesicular disorders, delusional parasitosis, dermatitis herpetiformis, pemphigus herpetiformis, ecthyma, drug eruptions

WORKUP

- Workup begins with history and physical for clinical symptoms and environmental findings.
- Victims should carefully scrutinize the bedroom for signs of bedbug infestation. One may encounter fecal smears or flecks of blood on bed linens, inside furniture cracks and crevices, and behind peeling wallpaper. Bedbugs may travel as far as 20 feet for a meal. Densely infested rooms may also have a distinctive, pungent, soda syrup–like odor.

LABORATORY TESTS

- No specific tests recommended except for identification of the insect.
- The histology of bedbug bites is similar to other insect bites. Perivascular infiltrate of lymphocytes, histiocytes, eosinophils, and mast cells is seen within the upper dermis. One may also observe collagen bundles with interstitial eosinophils, dermal edema, and extravasated erythrocytes.
- Hypersensitivity to bedbug salivary proteins may be tested via intradermal allergy skin testing.

IMAGING STUDIES

None

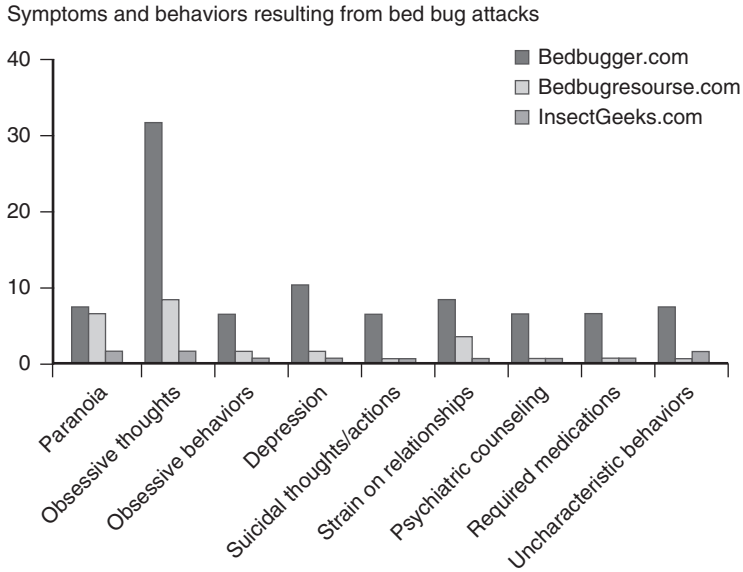

FIGURE B1-17 Distribution of symptoms in 135 Internet reports describing effects of bed bug bites. (From Goddard J, de Shazo R: Psychological effects of bed bug attacks *(Cimex lectularius L.), Am J Med* 125:101-103, 2012.)

Rx TREATMENT

- Specific treatment of bedbug bites is often not necessary. Bites may self-resolve within a week for milder cases and a few weeks for more severe cases. Treatment regimens are based on resolving symptoms of the bites, mainly pruritus.
- To prevent infection, avoid scratching the area.
- Topical glucocorticoids or systemic antihistamines are appropriate in patients with severe pruritus from the bedbug bite.
  1. Triamcinolone cream 0.1%; apply thin film to affected areas bid
  2. Chlorpheniramine 4 mg PO at bedtime (adults), 2 mg PO at bedtime (children)
- Insecticides may be effective in eradicating the bedbug, but growing resistance has been seen and multi-insecticide therapy is recommended.
  1. Use permethrin spray for clothing and bedsheets or bednets
  2. Diethyltoluamide (DEET): Be wary of toxic levels in children when used at high concentrations.
  3. Deltamethrin and chlorfenapyr are two common insecticides used.
  4. Please consult a pest control professional for safe eradication.

NONPHARMACOLOGIC THERAPY

Vacuuming is effective in removing bedbugs but does not remove the eggs. Wash bedsheets and clothing in hot water with detergent with at least 20 minutes in a dryer. Bedbugs have a high thermal death point of 45° C and also may survive at temperatures as low as 7° C. Some companies perform a treatment in which the room is heated above 50° C, which is a lethal temperature for all stages of a bedbug's life cycle. Coating bedposts with antifriction or adhesive substances such as petrolatum or duct tape may hinder bedbugs from gaining access to the bed.

ACUTE GENERAL Rx

Immunologic response is dependent on immunocompetence and individual sensitivity to the salivary components of the bedbug bite. Often, patients with papular urticaria have IgG antibodies to specific bedbug proteins. IgE antibodies may also mediate bullae formation. Anaphylaxis and death from bites is rare but documented in literature.

DISPOSITION

Patient may resume normal activity and lifestyle. Travelers should inspect their clothing and suitcases before returning home.

BEDBUGS AS POTENTIAL VECTORS

The bedbug has been studied extensively as a potential vector for human pathogens such as HIV, hepatitis B, hepatitis C, and Chagas' disease. To date, there is no evidence of transmission from an infected bedbug to a human.

PEARLS & CONSIDERATIONS

COMMENTS

- Bedbugs are an increasing source of anguish and frustration for humans, and clinicians should evaluate for signs of stress and depression.
- A combination of chemical and physical intervention is often necessary for complete eradication. All hiding areas must be carefully inspected and cleaned. Treatment may include pesticides, laundering, heat, freezing, vacuuming, and hiring a professional service to eradicate bedbugs.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Bedbugs (Patient Information)

AUTHOR: **SCOTT M. SOUTHER, M.D.**

SUGGESTED READINGS

Goddard J, deShazo R. Bedbugs *(Cimex lectularius)* and clinical consequences of their bites, *JAMA* 301(13):1358–1366, 2009.

Kolb A et al.: Bedbugs, *Dermatol Ther* 22(4):347–352, 2009.

Markova A, Kam SA, Miller DD, Lichtman MK: In the clinic: common cutaneous parasites, *Ann Intern Med*, Sept 2, 2014.

Studdiford JS et al.: Bedbug infestation, *Am Fam Physician* 86(7):653–658, 2012.

Vaidyanathan R et al.: Bed bug detection: current technologies and future directions, *Am J Trop Med Hyg* 88:619–625, 2013.

BASIC INFORMATION

DEFINITION

Behçet's disease is a chronic, relapsing, inflammatory disorder characterized by the presence of recurrent oral aphthous ulcers, genital ulcers, uveitis, and skin lesions (Fig. B1-18).

SYNONYMS

Behçet's syndrome

ICD-9CM CODES
136.1 Behçet's syndrome
ICD-10CM CODES
M35.2 Behçet's disease

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE

- Behçet's disease is observed in two different geographic locations.
  1. One region consists of Eastern Asia, Turkey, and the Mediterranean basin.
     1. Prevalence ranges from 18 to 30 cases per 100,000 persons.
     2. Turkey has the highest prevalence at 80 to 370 cases per 100,000 persons.
  2. The second region consists of North America and Northern Europe.
     1. Prevalence ranges from 0.5 to 17 cases per 100,000 persons. Germany has the greatest prevalence.
     2. Prevalence of Behçet's disease in the U.S. is 0.12 to 0.33 cases per 100,000 persons.
- In these regions, the prevalence of HLA-B51 is greater in patients with Behçet's disease.

PREDOMINANT SEX: Equal sex distribution
GENETICS: No clear pattern of inheritance can be determined. Familial disease was noted in 15% of affected children.
AGE: Peak age of onset is between 20 and 40 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Behçet's disease typically affects individuals in the third to fourth decade of life and primarily presents with painful aphthous oral ulcers. The ulcers occur in crops measuring 2 to 12 mm and are found on the mucous membrane of the cheek, gingiva, tongue, pharynx, and soft palate.
- Genital and perianal ulcers are similar to the oral ulcers. They may result in scarring.
- Decreased vision secondary to uveitis, keratitis, and retinal artery occlusion with ischemia may be followed by neovascularization, vitreous hemorrhage and contraction, glaucoma, and retinal detachment. Younger male individuals are at greater risk for ocular involvement.
- Skin findings (41% to 97%) include nodular lesions, which are histologically divided into erythema nodosum-like lesions, pseudofolliculitis, papulopustular lesions, acneiform nodules, or pyoderma gangrenosum-like lesions (cutaneous aphthosis).
- Intermittent, symmetric oligoarthritis (40% to 70%) is the most common; ankylosing spondylitis or arthralgias may occur.
- Central nervous system (CNS; 30% in U.S. and 5% in Turkey) meningeal findings including headache, fever, and stiff neck can occur. Cerebellar ataxia, pseudobulbar palsy, and dementia occur with involvement of the brainstem. Fig. B1-19 illustrates the different age distributions at neurologic presentation.
- Vascular involvement (25% to 30%), arterial and venous, of all sizes may cause systemic arterial vasculitis (aneurysms and occlusions), pulmonary artery vasculitis, venous occlusions (including superficial, deep, cerebral, portal, and mesenterial veins), pulmonary embolus, right ventricle thrombosis, and Budd-Chiari syndrome.
- GI involvement is more common in Japanese individuals; ulcerative lesions primarily involve distal ileum and cecum, but any region can be affected. GI lesions tend to perforate or bleed and may recur after surgery.

ETIOLOGY

The etiology of Behçet's disease is unknown. An immune-related vasculitis, a perivascular inflammation, or both are thought to lead to many of the manifestations of Behçet's disease. Multiple triggers for this process have been investigated, including herpes simplex virus infection, streptococcal antigen, and others.

DIAGNOSIS

According to the International Study Group for Behçet's Disease, the diagnosis of Behçet's disease is established when oral ulcerations recur at least three times in one 12-mo period plus at least two of the following conditions in the absence of other systemic diseases:

- Recurrent genital ulceration
- Eye lesions
- Skin lesions
- Positive pathergy test (erythematous papules or pustules [>2 mm in diameter] at sterile needle injection sites after 24 to 48 hours)

DIFFERENTIAL DIAGNOSIS

- Inflammatory bowel disease (ulcerative colitis and Crohn's disease)
- Sprue disease
- Herpes simplex infection

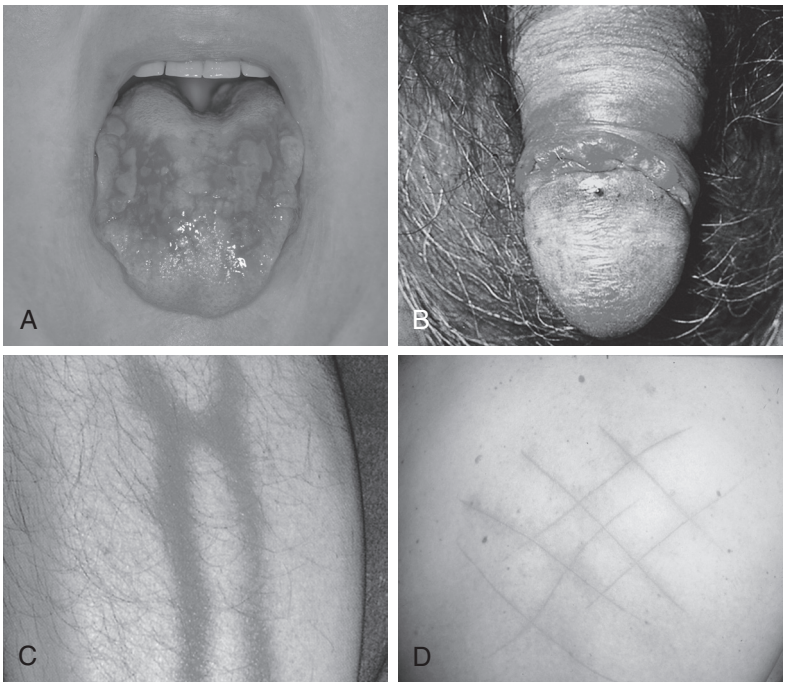

FIGURE B1-18 Behçet's syndrome. A, Major aphthous ulceration; **B,** genital ulceration; **C,** superficial thrombophlebitis; **D,** dermatographia. (**C** courtesy Mir MA: *Atlas of clinical diagnosis,* Philadelphia, 2003, Saunders.) (From Kanski JJ, Bowling B: *Clinical ophthalmology, a systemic approach,* ed 7, Philadelphia, 2010, Saunders.)

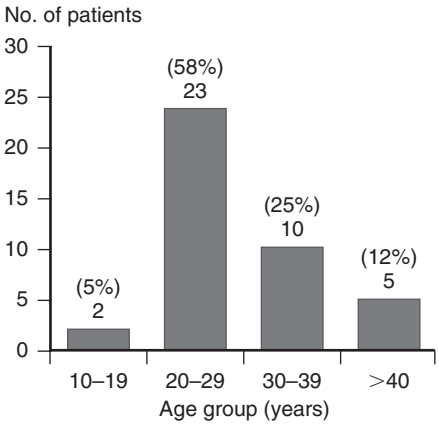

FIGURE B1-19 Distribution of 40 patients with Behçet's disease over different age groups at neurologic presentation. (From Al-Fahad SA, Al-Araji AH; Neuro-Behçet's disease in Iraq: a study of 40 patients, *J Neurol Sci* 170:105–111, 1999.)

- Benign aphthous stomatitis
- Cyclic neutropenia
- Acquired immune deficiency syndrome (AIDS)
- Systemic lupus erythematosus
- Reiter's syndrome
- Ankylosing spondylitis
- Hypereosinophilic syndrome
- Sweet's syndrome
- Lichen planus
- Pemphigoid

WORKUP

The diagnosis of Behçet's disease is a clinical diagnosis. Laboratory tests and x-ray imaging may be helpful in working up the complications of Behçet's disease or excluding other diseases in the differential.

LABORATORY TESTS

No diagnostic laboratory tests for Behçet's disease exist. The measurements of T-cell proliferative response to heat shock protein (HSP) and impaired fibrinolytic activity have been proposed for the diagnosis of Behçet's disease, but the value of testing has not been confirmed.

IMAGING STUDIES

CT scan, MRI, and angiography are useful for detecting CNS and vascular lesions.

Rx TREATMENT

Treatment is directed at the patient's clinical presentation and complications (e.g., mucocutaneous lesions, ocular lesions, arthritis, GI, CNS, or vascular lesions).

NONPHARMACOLOGIC THERAPY

Supportive care and rest during flares, and moderate exercises such as swimming or walking when symptoms improve or disappear

ACUTE GENERAL Rx

- Oral and genital ulcers:
  1. Topical and intralesional corticosteroids (e.g., triamcinolone acetonide ointment applied tid)
  2. Tetracycline tablets 250 mg dissolved in 5 cc water and applied to the ulcer for 2 to 3 min
  3. Colchicine 0.5 to 1.5 mg/day PO
  4. Thalidomide 100 to 300 mg PO daily
  5. Dapsone 100 mg PO daily
  6. Pentoxifylline 300 mg/day PO
  7. Azathioprine 1 to 2.5 mg/kg/day PO
  8. Methotrexate 7.5 to 25 mg/wk PO or intravenously
  9. Interferon alfa-2a and interferon alfa-2b (generally given 3 to 19 million units three times weekly)
- Ocular lesions:
  1. Anterior uveitis is treated by an ophthalmologist with topical corticosteroids (e.g., betamethasone drops 1 to 2 drops tid); topical injection with dexamethasone 1 to 1.5 mg has also been tried
  2. Infliximab 5 mg/kg single dose
  3. Cyclosporine A (5 mg/kg/day) with or without prednisone or azathioprine 1 to 2.5 mg/kg/day PO
- CNS disease:
  1. Chlorambucil 0.1 mg/kg/day is used in the treatment of posterior uveitis, retinal vasculitis, or CNS disease; patients not responding to chlorambucil can be tried on cyclosporine 5 to 7 mg/kg/day.
  2. In CNS vasculitis, cyclophosphamide 2 to 3 mg/kg/day is used. Prednisone can be used as an alternative.
- Arthritis:
  1. NSAIDs (e.g., ibuprofen 400 to 800 mg tid PO or indomethacin 50 to 75 mg/day PO)
  2. Sulfasalazine 1 to 3 g/day PO is an alternative treatment
- GI lesions:
  1. Sulfasalazine 1 to 3 g/day PO
  2. Prednisone 40 to 60 mg/day PO
- Vascular lesions:
  1. Prednisone 40 to 60 mg/day PO
  2. Cytotoxic agents as mentioned previously
  3. Heparin 5000 to 20,000 U/day followed by oral warfarin

CHRONIC Rx

- Chronic therapy is usually continued for approximately 1 yr after remission.
- Surgery may be indicated in patients with complications of bowel perforation, vascular occlusive disease, and aneurysm formation.
- Mortality is associated with early age of onset, arterial involvement, male gender, frequent disease flares.

DISPOSITION

- The aphthous oral ulcers last 1 to 2 wk, recurring more frequently than genital ulcers.
- 25% of Japanese patients with ocular lesions become blind.
- The disease course is unpredictable.
- The morbidity of Behçet's disease comes primarily from ocular and cutaneous involvement; however, mortality relates primarily to large-size vessel involvement and CNS diseases.

REFERRAL

If the diagnosis of Behçet's disease is suspected, a referral to dermatology, rheumatology, and ophthalmology is indicated because the disease is so rare.

PEARLS & CONSIDERATIONS

COMMENTS

- The pathergy test refers to the formation of an erythematous papule or pustule of ≥2 mm after oblique insertion of a sterile 20- or 25-gauge needle into the skin after 24 to 48 hours.
- Because of the rarity of this disease, data from controlled, prospective, randomized clinical trials are lacking.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Behçet's Syndrome (Patient Information)

AUTHOR: **MONZR M. AL MALKI, M.D.**

SUGGESTED READINGS

Al-Otaibi LM et al.: Behçet's disease: a review, *J Dent Res* 84(3):209, 2005.
Bonfioli AA, Orefice F: Behcet's disease, *Semin Ophthalmol* 20(3):199, 2005.
Evereklioglu C: Managing the symptoms of Behcet's disease, *Expert Opin Pharmacother* 5(2):317, 2004.
Kurokawa MS et al.: Behcet's disease, *Semin Respir Crit Care Med* 25(5):557, 2004.
Yazici H: Behçet's syndrome: an update, *Curr Rheumatol Rep* (5):195, 2003.

BASIC INFORMATION

DEFINITION

Acute peripheral facial (seventh) nerve palsy

SYNONYMS

Idiopathic facial paralysis
Facial nerve palsy

ICD-9CM CODES
351.0
ICD-10CM CODES
G51.0 Bell's palsy

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 20-30 cases per 100,000
PEAK INCIDENCE: People <70 yr and pregnant females, especially during the third trimester and/or 1 wk postpartum
PREDOMINANT SEX AND AGE: Sexes are equally affected. Median age is 40 yr.
RISK FACTORS: Diabetes, older age, pregnancy.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Dependent on location of facial nerve injury. Onset is usually acute to subacute over hours of unilateral facial paralysis with maximal weakness at 3 wk. One third of patients demonstrate incomplete paralysis, and the remaining two thirds have complete paralysis. Recovery is present within the first 6 mo.
- Based on the following criteria: diffuse facial nerve involvement depicted by paralysis of the facial muscles (Fig. B1-20), along with variable involvement of taste over the anterior two thirds of the tongue or altered secretion of the lacrimal and salivary glands.
  1. The degree of involvement is dependent on proximity of facial nerve involvement and involvement of associated branches.

ETIOLOGY

Most cases of Bell's palsy are thought to be secondary to a viral inflammatory/immune mechanism of injury. Herpes simplex virus is thought to be the most common viral pathogen, followed by herpes zoster. Other infectious causes include EBV, CMV, adenovirus, rubella, and mumps.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Lyme disease: facial nerve palsy is the most common cranial neuropathy associated with Lyme meningitis; may be unilateral or bilateral.
- HIV
- Ramsay Hunt syndrome: facial nerve paralysis associated with ipsilateral zoster oticus
- Parotid gland tumors
- Trauma/temporal bone fracture
- Meningeal processes
  1. Infectious: Lyme (mentioned earlier), HIV, syphilis, leprosy, tuberculosis
  2. Inflammatory: sarcoid, Sjögren's, Guillain-Barré syndrome
  3. Carcinomatous: breast, lung, lymphoma
- Congenital: Möbius syndrome
- Melkersson-Rosenthal syndrome
- Brainstem stroke: Affecting the nucleus or fascicle of the seventh nerve

WORKUP

- Bell's palsy is a clinical diagnosis.
- Additional workup may be necessary in those patients with complete injury or lack of any recovery or in whom the diagnosis of Bell's palsy is uncertain.

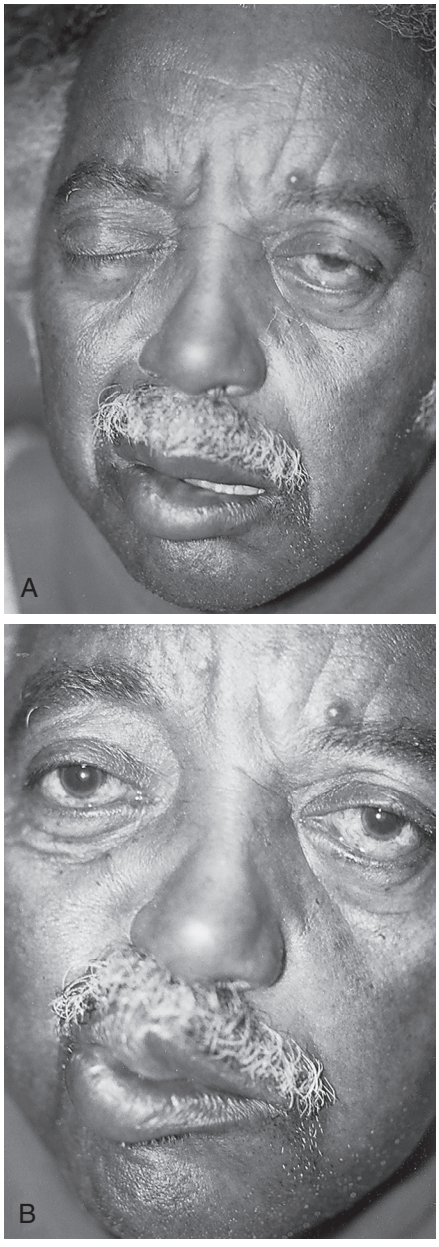

FIGURE B1-20 A patient with a lesion of the facial nerve. A, The patient has difficulty in closing his left eye, and the left corner of his mouth droops. **B,** The latter defect is especially evident when the patient attempts to purse his lips. (From Haines DE: *Fundamental neuroscience for basic and clinical applications,* ed 3, Philadelphia, 2006, Churchill Livingstone.)

LABORATORY TESTS

Not typically recommended. However, if the diagnosis of Bell's palsy versus facial nerve paralysis from secondary causes is in question (especially if the facial paralysis is bilateral), the following are reasonable:

- Lyme antibody followed by Western blot for positive cases
- ACE level
- Glycosylated hemoglobin
- HIV
- VDRL
- ESR

ELECTRODIAGNOSTIC TESTING

May be performed 2 wk after onset to assess prognosis. Facial motor response remains normal for the first 3 days following injury and then rapidly decreases depending on severity of lesion. Facial motor study may be performed at 10 days and compared to contralateral side. A motor response that is 10% the amplitude of the unaffected side has been defined as a critical value in one study in which recovery was poor when associated with 90% degeneration. EMG can be used to visualize any motor units in the affected muscles that would assess the integrity of the facial nerve.

IMAGING STUDIES

Not usually indicated.

- Brain MRI is indicated in certain cases, such as an upper motor neuron pattern (able to wrinkle forehead) where the temporalis branch of the facial nerve is spared.
- Brain MRI with gadolinium is indicated when other cranial nerve palsies are present or when a meningeal process is suspected.
- CT temporal bone: is indicated in cases of trauma or cases with complete facial paralysis in which the surgeon is considering decompression.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Reassurance that most patients have a full recovery and that the patient did not sustain a stroke.
- Eye patch: To prevent corneal drying/abrasion and subsequent ulceration.
  1. Lacri-Lube to eye at night and artificial tears during the day.
- A recent study involving acupuncture revealed that in patients with Bell's palsy, strong stimulation acupuncture with needle manipulation improved recovery more than acupuncture without needle manipulation.[1]

[1]Xu SB et al: Effectiveness of strengthened stimulation during acupuncture for the treatment of Bell palsy: a randomized controlled trial, *CMAJ* 185:473-479, 2013.

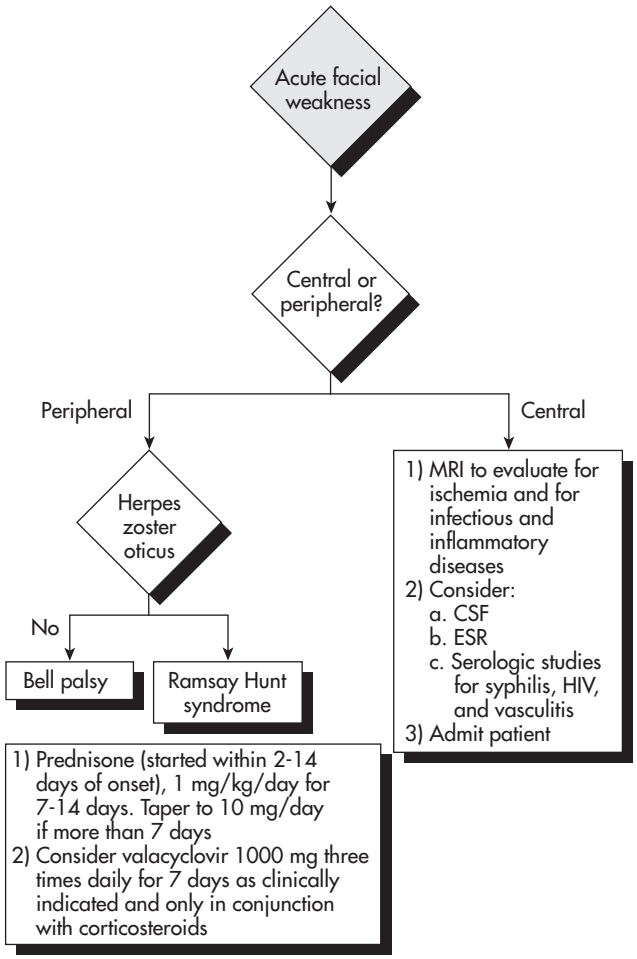

FIGURE B1-21 Algorithm outlining the treatment of patients with Bell's palsy. *CSF,* Cerebrospinal fluid; *ESR,* erythrocyte sedimentation rate; *HIV,* human immunodeficiency virus; *MRI,* magnetic resonance imaging. (Modified from Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, St Louis, 2013, Elsevier.)

ACUTE GENERAL Rx

- Corticosteroids (based on early findings of inflammation and swelling during decompression studies) and antiviral therapy (predicated on findings of herpes simplex virus in the endoneural fluid)
  1. Two high-quality randomized trials assessed efficacy of early (<72 hr) treatment with glucocorticoids alone, antiviral treatment alone, and combination therapy of Bell's palsy. Glucocorticoid treatment alone was effective, while antiviral therapy showed no benefit when given either alone or with concomitant glucocorticoid therapy.
  2. Largest study compared prednisolone (60 mg daily) versus valacyclovir (1000 mg 3 times daily × 7 days) versus combination therapy versus placebo within 72 hr of presentation.
  3. At 1-year follow-up, time to recovery was shorter in prednisolone-treated group, while valacyclovir therapy efficacy did not differ from placebo. No added benefit was seen with combination therapy.
- Treatment guidelines, in lieu of above, recommend prednisone 60 to 80 mg/day for 1 wk.
  1. Some authors still recommend treatment with valacyclovir (1000 mg 3 times daily for 1 wk) in severe cases (i.e., level IV or greater on the House-Brackmann grading system) despite lack of strong clinical evidence.
- Surgical decompression: Not currently recommended.
  1. AAN Practice Parameter (2001) concluded there was insufficient evidence to make any recommendation regarding surgical decompression for Bell's palsy.
  2. AAN Practice Parameter conclusion was further substantiated by Cochrane systematic review in 2011 that looked at two additional studies again citing insufficient evidence regarding surgical decompression for Bell's palsy.
- Fig. B1-21 describes an algorithm for the treatment of patients with Bell's palsy.

FIGURE B1-22 Bell's palsy. The patient with Bell's palsy (facial nerve palsy) will demonstrate an unwrinkled forehead, widely opened eyes (with weakness of eyelid color), flattening of the nasolabial fold, and a droop of the corner of the mouth. (From Remmel KS et al: *Handbook of symptom-oriented neurology,* ed 3, St Louis, 2002, Mosby.)

CHRONIC Rx

Botulinum toxin may be used in cases of hemifacial spasm.

DISPOSITION

- 71% of patients had complete recovery.
- 85% show recovery at 3 wk.
- 13% had slight sequelae.
- 16% had residual weakness, synkinesis, or contracture.
- Prognosis is favorable if recovery is seen within the first 3 wk.
- Recurrence rate is 7%. Average time to recurrence was 10 yr.

REFERRAL

- Neurologist if clinical diagnosis is in question
- Ophthalmologist if concern for corneal abrasion or ulceration

PEARLS & CONSIDERATIONS

COMMENTS

- Assess wrinkling of forehead (Fig. B1-22). If present on affected side, need to ensure that the facial weakness is not central.
- Assess for other cranial nerve deficits or long-tract signs because brainstem fascicular lesions of the seventh nerve can show peripheral facial pattern of weakness.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Bell's Palsy (Facial Palsy) (Patient Information)

AUTHOR: **JOHN SLADKY, M.D.**

SUGGESTED READING

Albers JR, Tamang S: Common questions about Bell palsy, *Am Fam Phys* 89(3):209–212, 2014.

Gilden DH, Tyler KL: Bell's palsy: is glucocorticoid treatment enough? *N Engl J Med* 357:1653–1655, 2007.

Lee HY et al.: Steroid antiviral treatment improves the recovery rate in patients with severe Bell's palsy, *Am J Med* 126:336–341, 2013.

BASIC INFORMATION

DEFINITION

Benign paroxysmal positional vertigo (BPPV) is a labyrinthine disorder and is the most common cause of vertigo. It is characterized by paroxysms of brief spinning sensation accompanied by nystagmus that usually lasts less than a minute. These paroxysms are generally induced by changes in head position with respect to gravity.

SYNONYMS

BPPV

ICD-9 CM CODES
386.11 Benign paroxysmal positional vertigo
CD-10 CM CODES
H81.1 Benign paroxysmal vertigo

EPIDEMIOLOGY & DEMOGRAPHICS

Higher prevalence seen in elderly and women.
INCIDENCE: Not reported
PREVALENCE: Lifetime prevalence is 2.4%. Reported prevalence is 10.7 and 64 cases per 100,000 population.
PREDOMINANT SEX AND AGE: Female (2:1 to 3:1 ratio); peak onset: 50-60 years.
GENETICS: unknown
RISK FACTORS: Head trauma, inner ear surgery, viral labyrinthitis, Meniere's disease, migraine.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Brief paroxysms of vertigo and nystagmus with certain head positions are seen in 70%
- Episodes are typically triggered by head position changes such as while getting in or out of bed, rolling over in bed, forward head tilt or bending forward.
- Episodes are brief usually lasting 30 to 40 seconds but can recur for several days or months.
- Usually no hearing abnormalities are present.
- Direction of nystagmus depends on the canal affected with reversal of direction being seen while sitting up, and fatigability with repeated testing.
- Rarely persistent vertigo and disequilibrium may be seen.

POSTERIOR SEMICIRCULAR CANAL (PCC)

While posterior, horizontal or superior semicircular canal can be affected as isolated or in different combinations, PCC involvement is commonest (60-90%) and will be discussed in the following sections. Nystagmus is up-beating and torsional and can be elicited by the Dix Hallpike maneuver.
DIX-HALLPIKE MANEUVER: With head turned to one side at an angle of 45 degrees, patient is moved from sitting to supine position with head hanging below the end of the table at an angle of 20 deg. The posterior semicircular canal comes into the sagittal plane and the free floating otolith debris moves down and away from the ampulla. An up-beating and torsional nystagmus will be seen with the top poles of the eye beating towards the lower ear.

HORIZONTAL SEMICIRCULAR CANAL

Involvement may be underestimated as it may remit spontaneously. It produces either geotropic nystagmus beating towards the ground or apogeotropic nystagmus beating towards the ceiling when the head is turned to either side in the supine position. The nystagmus beats stronger towards the affected ear.
HEAD ROLL TEST FOR THE RIGHT HORIZONTAL SEMICIRCULAR CANAL (INDUCING GEOTROPIC NYSTAGMUS): Patient is moved from sitting to supine position, then head is rolled 90 degrees to the left. The otolithic debris moves away from the cupula of horizontal semicircular canal, a left beating geotropic nystagmus (towards the ground) is seen. Next the head is turned 90 degrees to the right—a right-beating stronger geotropic nystagmus is seen as otolithic debris moves towards the cupula of the right horizontal semicircular canal.
SUPINE HEAD ROLL TEST FOR THE RIGHT HORIZONTAL SEMICIRCULAR CANAL (INDUCING APOGEOTROPIC NYSTAGMUS): Patient is moved from sitting to supine position, then head is rolled 90 degrees to the left. This induces deflection of the cupula of the right horizontal semicircular canal due to otolithic debris near or attached to the cupula. A strong, right-beating apogeotropic nystagmus (towards the ceiling) is induced. Next, the head is turned 90 degrees in the opposite direction. Now the right horizontal semicircular canal cupula is deflected in the opposite direction and a weak, left-beating apogeotropic nystagmus results.

ANTERIOR SEMICIRCULAR CANAL

Involvement is rare as it is located uppermost in the labyrinth and so otolithic debris is unlikely to become trapped. A downbeat and torsional nystagmus where the top poles of the eye beat towards the lower ear is seen. Evaluating for central lesions is a must in these cases.

ETIOLOGY

The fundamental pathologic process is believed to be the movement of otolithic debris in the endolymph of the inner ear. The debris may be present in the cupula (cupulolithiasis) or free floating within the semicircular canal near the cupula (canalithiasis). Static head position changes with respect to gravity, causing the debris to move within the semicircular canal and creating a false sense of rotation.

DIAGNOSIS

Elicitation of a typical nystagmus with Dix-Hall pike is the standard for diagnosing posterior canal BPPV. However, 25% of symptomatic patients may not exhibit nystagmus. Appropriate referral to a neurologist or neuro-otologist should be considered in these cases.

Figure B1-23 shows a diagnostic algorithm for vertigo and dizziness.

BOX B1-3 Causes of Vertigo With and Without Hearing Loss

Hearing Loss
Conductive
- Otitis media with effusion
- Chronic suppurative otitis media or cholesteatoma should be considered

Sensorineural
- Perilymphatic fistula
- Tumor
- Ménière's disease
- Migraine headache
- Genetic syndromes
- Temporal bone fracture
- Vestibular concussion

No Hearing Loss
Acute Vertigo
- Perilymphatic fistula
- Benign positional vertigo
- Seizure
- Labyrinthitis

Recurrent or Chronic Vertigo
- Acoustic neuroma
- Multiple sclerosis

(From Marx JA et al: *Rosen's emergency medicine: concepts and clinical practice*, 7th ed, Philadelphia, 2010, Elsevier.)

DIFFERENTIAL DIAGNOSIS

- Vestibular neuritis
- Vestibular migraine
- Meniere's disease
- Stroke
- Box B1-3 lists causes of vertigo with and without hearing loss.
- Table B1-3 describes the differential diagnosis of true vertigo

WORK-UP

None; BPPV is a clinical diagnosis

IMAGING STUDIES

- To be obtained only when stroke remains high in the differential diagnosis.

TREATMENT

- BPPV usually resolves without treatment in 2-4 weeks.
- Nausea and vomiting may be treated symptomatically with medications.
- Canalith repositioning maneuvers (Epley's and Semont's maneuvers for the posterior canal) are effective. They are designed to "flush" otolithic debris out of the semicircular canals into the vestibule where they are resorbed. Epley's maneuver for BPPV of the posterior canal is recommended as standard of care by the American Academy of Neurology and American Academy of Otolaryngology-Head and Neck Surgery. Other maneuvers such as Barbecue, Vannucchis and Gufoni's maneuver are used to reposition debris in the horizontal semicircular canal and will not be discussed here.

Benign Paroxysmal Positional Vertigo

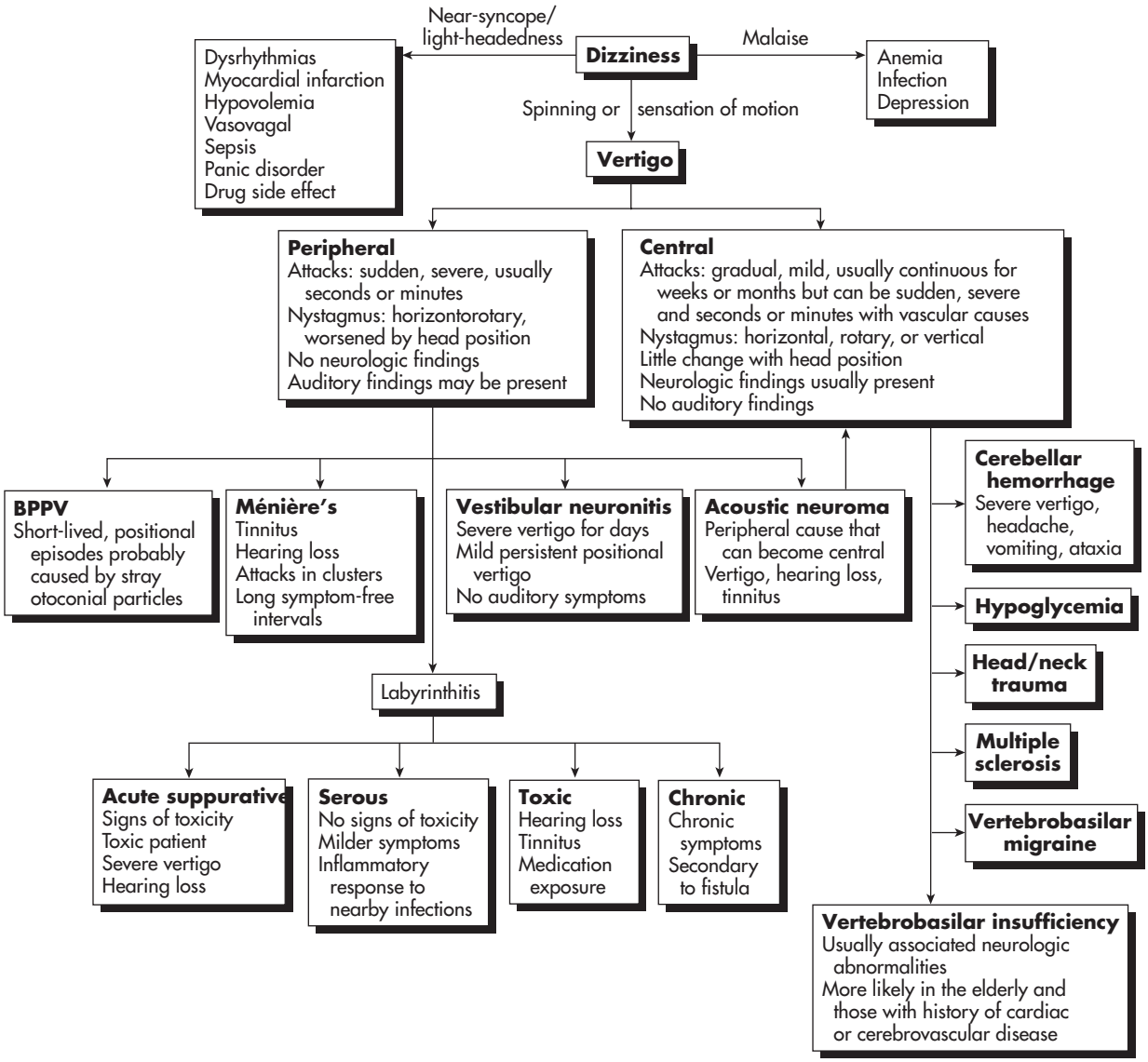

FIGURE B1-23 Diagnostic algorithm for dizziness and vertigo. *BPPV*, benign paroxysmal positional vertigo. (From Marx JA et al: *Rosen's emergency medicine: concepts and clinical practice*, 7th ed, Philadelphia, 2010, Elsevier.)

EPLEY'S MANEUVER:

- Head is turned 90 degrees towards unaffected side. The head and trunk are then turned an additional 90 degrees in the same direction, so that the patient lies on the unaffected side with head pointing towards the floor. The otolithic debris moves in the same direction, producing a brief nystagmus. The patient is then moved to a sitting position which allows the debris to fall out of the canal into the utricle through the common crus.
- Each position should be maintained for 30 seconds or until the nystagmus or vertigo resolves. Sometimes nystagmus in the opposite direction is seen. It is prudent for patients to sit still in the upright position for about 15 minutes and then to walk cautiously.

NONPHARMACOLOGIC THERAPY

Transection of the ampullary nerve (singular nerve) and plugging of the involved canal are rarely performed for intractable and treatment resistant cases.

ACUTE GENERAL Rx

Canalith repositioning

CHRONIC Rx

If multiple treatments are needed, patients should be instructed to perform the maneuvers at home.

REFERRAL

To a neuro-otologist, otolaryngologist, neurologist

PEARLS & CONSIDERATIONS

BPPV is a benign and self-limiting condition but can be disabling

Diagnosis is clinical and canalith repositioning maneuvers are effective.

PATIENT/FAMILY EDUCATION

- Reassurance
- Fall precautions

RELATED CONTENT

Meniere's Disease (Related Key Topic)
Vestibular Neuritis (Related Key Topic)

SUGGESTED READINGS

Available online at www.expertconsult.com

AUTHORS: **PADMAJA SUDHAKAR, M.B.B.S.,** and **SACHIN KEDAR, M.B.B.S., M.D.**

TABLE B1-3 Differential Diagnosis of Patients with True Vertigo

Cause	History	Associated Symptoms	Physical
Peripheral			
1. Benign paroxysmal positional vertigo	Short-lived, positional, fatigable episodes	Nausea, vomiting	Single position can precipitate vertigo. Horizontorotary nystagmus often can be induced at bedside.
2. Labyrinthitis			
A. Serous	Mild to severe positional symptoms. Usually coexisting or antecedent infection of ear, nose, throat, or meninges	Mild to severe hearing loss can occur	Usually nontoxic patient with minimal fever elevation
B. Acute suppurative	Coexisting acute exudative infection of the inner ear. Severe symptoms	Usually severe hearing loss, nausea, vomiting	Febrile patient showing signs of toxicity. Acute otitis media
C. Toxic	Gradually progressive symptoms: Patients on medication causing toxicity	Hearing loss that may become rapid and severe, nausea and vomiting	Hearing loss. Ataxia common feature in chronic phase
3. Ménière's disease	Recurrent episodes of severe rotational vertigo usually lasting hours. Onset usually abrupt. Attacks may occur in clusters. Long symptom-free remissions	Nausea, vomiting, tinnitus, hearing loss	Positional nystagmus not present
4. Vestibular neuronitis	Sudden onset of severe vertigo, increasing in intensity for hours, then gradually subsiding over several days. Mild positional vertigo often lasts weeks to months. Sometimes history of infection or toxic exposure that precedes initial attack. Highest incidence is found in third and fifth decades	Nausea, vomiting. Auditory symptoms do not occur	Spontaneous nystagmus toward the involved ear may be present.
5. Acoustic neuroma	Gradual onset and increase in symptoms. Neurologic signs in later stages. Most occur in women between 30 and 60	Hearing loss, tinnitus. True ataxia and neurologic signs as tumor enlarges	Unilateral decreased hearing. True truncal ataxia and other neurologic signs when tumor enlarges. May have diminution or absence of corneal reflex. Eighth cranial nerve deficit may be present.
Central			
1. Vascular disorders			
A. Vertebrobasilar insufficiency	Should be considered in any patient of advanced age with isolated new-onset vertigo without an obvious cause. More likely with history of atherosclerosis. Initial episode usually seconds to minutes	Often headache. Usually neurologic symptoms including dysarthria, ataxia, weakness, numbness, double vision. Tinnitus and deafness uncommon	Neurologic deficits usually present, but initially neurologic examination can be normal.
B. Cerebellar hemorrhage	Sudden onset of severe symptoms	Headache, vomiting, ataxia	Signs of toxicity. Dysmetria, true ataxia. Ipsilateral sixth cranial nerve palsy may be present.
C. Occlusion of posterior inferior cerebellar artery (Wallenberg's syndrome)	Vertigo associated with significant neurologic complaints	Nausea, vomiting, loss of pain and temperature sensation, ataxia, hoarseness	Loss of pain and temperature sensation on the side of the face ipsilateral to the lesion and on the opposite side of the body, paralysis of the palate, pharynx, and larynx. Horner's syndrome (ipsilateral ptosis, miosis, and decreased facial sweating)
D. Subclavian steal syndrome	Classic picture is syncopal attacks during exercise, but most cases present with more subtle symptoms.	Arm fatigue, cramps, mild lightheadedness may be only other symptoms than vertigo	Diminished or absent radial pulses in affected side or systolic blood pressure differentials between the two areas occur in most patients.
2. Head trauma	Symptoms begin with or shortly after head trauma. Positional symptoms most common type after trauma. Self-limited symptoms that can persist weeks to months	Usually mild nausea	Occasionally, basilar skull fracture
3. Neck trauma	Usual onset 7–10 days after whiplash injury. Symptoms may last weeks to months. Episodes seconds to minutes when turning head	Neck pain	Neck tenderness, pain on movement, and positional nystagmus and vertigo when head is turned to side of the whiplash
4. Vertebrobasilar migraine	Vertigo almost always followed by headache. Patient has usually had similar episodes in past. Most patients have a family history of migraine. Syndrome usually begins in adolescence	Dysarthria, ataxia, visual disturbances, or paresthesias usually precede headache	No residual neurologic or otologic signs are present after attack.
5. Multiple sclerosis	Vertigo presenting symptoms in 7–10% and appears in the course of the disease in a third. Onset may be severe and suggest labyrinth disease. Disease onset usually between ages 20 and 40. Often history of other attacks with varying neurologic signs or symptoms	Nausea and vomiting, which may be severe	May have horizontal, rotary, or vertical nystagmus. Nystagmus may persist after the vertiginous symptoms have subsided. Bilateral internuclear ophthalmoplegia and ataxic eye movements suggest multiple sclerosis.
6. Temporal lobe epilepsy	Can be initial or prominent symptom in some patients with the disorder	Memory impairment, hallucinations, trancelike states, seizures	May have aphasia or convulsions
7. Hypoglycemia	Should be considered in diabetics and any other patient with unexplained symptoms	Sweating, anxiety	Tachycardia, mental status change may be present.

From Marx JA et al: *Rosen's emergency medicine: concepts and clinical practice*, 7th ed, Philadelphia, 2010, Elsevier.

SUGGESTED READINGS

Kim JS, Zee DS: Clinical practice. Benign paroxysmal positional vertigo, *N Engl J Med* 370(12):1138–1147, 2014 Mar 20. http://dx.doi.org/10.1056/NEJMcp1309481. Review.

Imai T, Ito M, Takeda N, Uno A, Matsunaga T, Sekine K, Kubo T: Natural course of the remission of vertigo in patients with benign paroxysmal positional vertigo, *Neurology* 64(5):920–921, 2005 Mar 8.

Benign Prostatic Hyperplasia EBM ALG PTG

BASIC INFORMATION

DEFINITION

Benign prostatic hyperplasia (BPH) is the benign growth of the prostate, generally originating in the periureteral and transition zones, with subsequent obstructive and irritative voiding symptoms.

SYNONYMS

BPH
Prostatic hypertrophy

ICD-9CM CODES
600 Benign prostatic hyperplasia
ICD-10CM CODES
N40 Hyperplasia of prostate
N40.0 Enlarged prostate without lower urinary tract symptoms

EPIDEMIOLOGY & DEMOGRAPHICS

- 80% of men have evidence of BPH by age 80 yr.
- Medical and surgical intervention for problems caused by BPH is required in <20% of males by age 75 yr.
- Transurethral resection of the prostate (TURP) is the tenth most common operative procedure (~400,000/yr in the United States).
- 10% to 30% of men with BPH have occult prostate cancer.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Digital rectal examination (DRE) reveals enlargement of the prostate.
- Focal enlargement may be indicative of malignancy.
- There is poor correlation between size of prostate and symptoms (BPH may be asymptomatic if it does not encroach on the urethral lumen).
- Most patients with BPH report difficulty in initiating urination (hesitancy), decrease in caliber and force of stream, incomplete emptying of bladder often resulting in double voiding (need to urinate again a few minutes after voiding), postvoid "dribbling," and nocturia.

ETIOLOGY

Multifactorial; a functioning testicle is necessary for development of BPH (as evidenced by the absence in males who were castrated before puberty).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Prostatitis.
- Prostate cancer.
- Strictures (urethral).
- Medications interfering with the muscle fibers in the prostate and also with bladder function.
  1. Opiates: impaired autonomic function.
  2. Decongestants: increased sphincter tone.
  3. Antihistamines: decreased parasympathetic tone.
  4. Tricyclic antidepressants: anticholinergic effects.
- Neurogenic bladder.
- Bladder cancer.

WORKUP

Symptom assessment (use of American Urological Association [AUA] Symptom Index for BPH [Table B1-4]), laboratory tests, and imaging studies Fig. B1-24 describes a diagnostic approach to patients with BPH.

LABORATORY TESTS

- Prostate-specific antigen (PSA): protease secreted by epithelial cells of the prostate; elevated in 30% to 50% of patients with BPH. Testing for PSA increases detection rate for prostate cancer and tends to detect cancer at an earlier stage. However, the PSA test does not discriminate well between patients with symptomatic BPH and those with prostate cancer, particularly if the cancer is pathologically localized and curable. The test may also trigger additional evaluation, including ultrasound biopsy of the prostate. Asymptomatic men with PSA levels >2 ng/ml do not need annual testing. According to the AUA, PSA testing and DRE should be offered to any asymptomatic man <50 yr with a life expectancy of 10 yr. PSA testing can also be offered at an earlier age in men at higher risk of prostatic cancer (e.g., first-degree relatives with prostate cancer; African American race).
- Measurement of "free" PSA is useful to assess the probability of prostate cancer in patients with normal DRE and total PSA between 4 and 10 ng/ml. In these patients the global risk of prostate cancer is 25%. However, if the free PSA is >25%, the risk of prostate cancer decreases to 8%, whereas if the free PSA is <10%, the risk of cancer increases to 56%. Free PSA is also useful to evaluate the aggressiveness of prostate cancer. A low free PSA percentage generally indicates a high-grade cancer, whereas a high free PSA percentage is generally associated with a slower growing tumor.
- Elevated measurement of prostate cancer gene 3 *(PCA3)* in urine specimens collected after digital exam is helpful in deciding about prostate biopsy in men with elevated PSA (increased *PCA3* = increased likelihood of prostate cancer).

TABLE B1-4 American Urological Association (AUA) Symptom Score*

Symptom	SCORE						Total Score
	Not at All	Less Than 1 Time in 5	≤50% of the Time	± 50% of the Time	≥50% of the Time	Almost Always	
Incomplete emptying: Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5	
Frequency: Over the past month, how often have you had to urinate again <2 hr after you finished urinating?	0	1	2	3	4	5	
Intermittency: Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
Urgency: Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5	
Weak stream: Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
Straining: Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	1 Time	2 Times	3 Times	4 Times	5 or More Times	
Nocturia: Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5	
Total AUA symptom score =							

*Interpretation: 0-7 mild symptoms; 8-19 moderate symptoms; 20-35 severe symptoms.

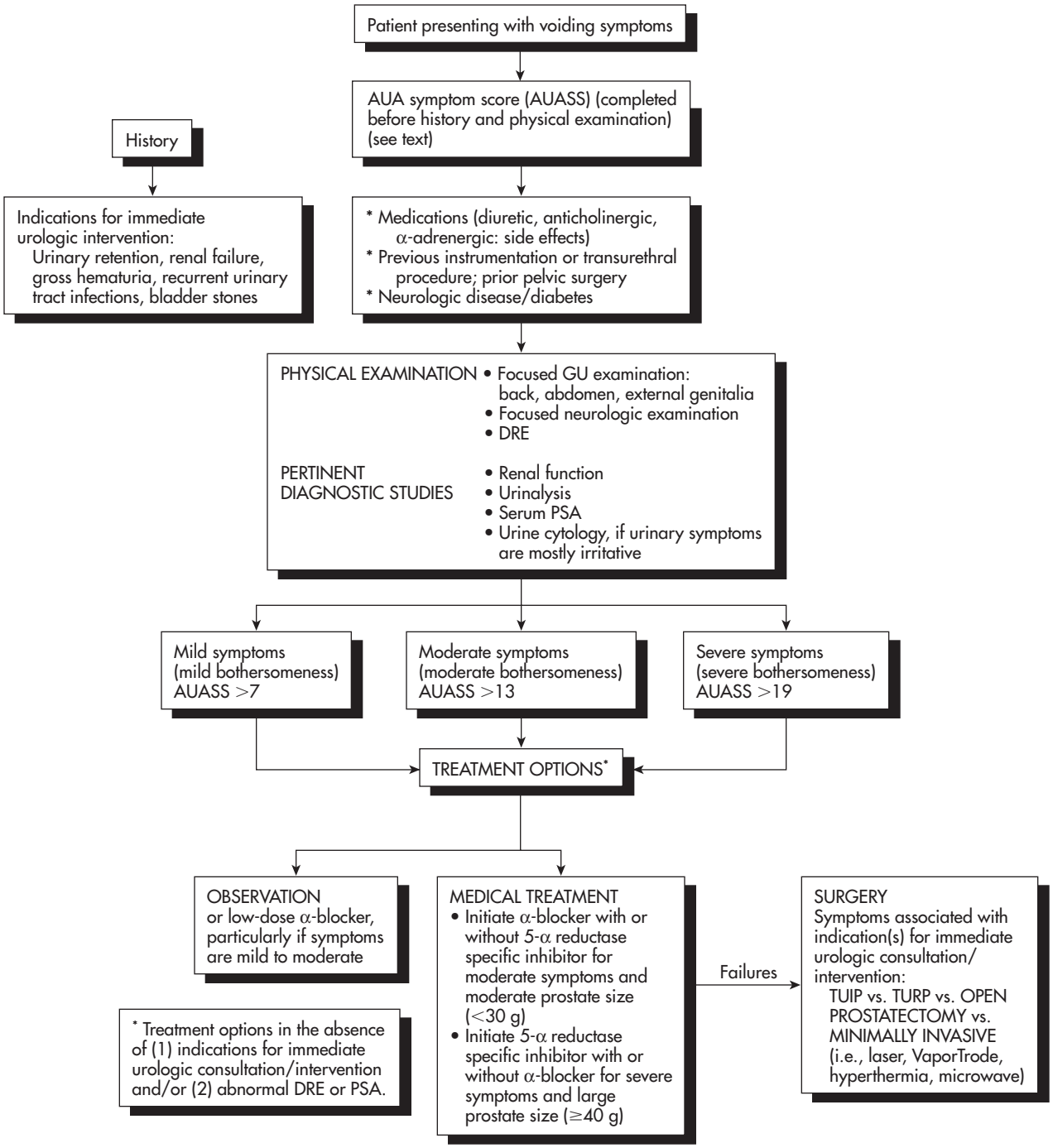

FIGURE B1-24 Critical pathway for patients with benign prostatic hypertrophy. *AUA,* American Urological Association; *DRE,* digital rectal examination; *GU,* genitourinary; *PSA,* prostate-specific antigen; *TUIP,* transurethral incision of the prostate; *TURP,* transurethral resection of the prostate. (From Nseyo UO [ed]: *Urology for primary care physicians,* Philadelphia, 1999, Saunders.)

- Urinalysis, urine culture, and sensitivity to rule out infection (if suspected).
- Blood urea nitrogen and creatinine to rule out postrenal insufficiency.

IMAGING STUDIES

- Transrectal ultrasound may be indicated in patients with palpable nodules or significant elevation of PSA. It is also useful to estimate prostate size. BPH may also be evident in suprapubic ultrasound and MRI.
- Uroflowmetry may be used to determine relative impact of obstruction on urine flow. Urethral pressure profile is useful to predict prostatic hypertrophy within the urethral lumen.
- Pressure flow studies, although invasive, are particularly helpful in patients whose history and/or examination suggests primary bladder dysfunction as a cause of symptoms of prostatism. They are also useful in patients for whom a distinction between prostatic obstruction and impaired detrusor contractility may affect the choice of therapy. However, pressure flow studies may not be useful in the workup of the usual patient with symptoms of prostatism.
- Postvoid residual urine measurement has not been proved useful in predicting the need for or response to treatment; it may be useful in monitoring the course of the disease in patients who elect nonsurgical treatment.
- Urethral cystoscopy is an option during later evaluation if invasive treatment is being planned.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of caffeine or any other foods that may exacerbate symptoms.
- Avoidance of medications that may exacerbate symptoms (e.g., most cold and allergy remedies).

GENERAL Rx

- Asymptomatic patients with prostate enlargement caused by BPH generally do not require treatment. Patients with mild to moderate symptoms are candidates for pharmacologic treatment (see below). For patients who have specific complications from BPH, prostate surgery is usually the most appropriate form of treatment. However, surgery may result in significant complications (e.g., incontinence, infection).
- Alpha-blockers (e.g., tamsulosin, alfuzosin, doxazosin, prazosin, terazosin) relax smooth muscle of the bladder neck and prostate and can increase peak urinary flow rate. They have no effect on the size of the prostate. Alpha-1 blockers are useful in symptomatic patients to relieve symptoms of obstruction by causing relaxation of smooth muscle tone in the prostatic capsule, urethra, and bladder neck.
- Hormonal manipulation with finasteride, a 5-alpha-reductase inhibitor that blocks conversion of testosterone to dihydrotestosterone, can reduce the size of the prostate. Usual dose is 5 mg qd. Treatment requires ≥6 mo for maximal effect.
- Dutasteride is also a 5-alpha-reductase inhibitor useful to decrease prostate size and improve urinary flow. In addition to inhibiting the isoform of 5-alpha-reductase located in the prostate, the medication inhibits a second isoform and reduces dihydrotestosterone formation in the skin and liver. Usual dose is 0.5 mg qd.
- Combined drug therapy for BPH with an alpha-blocker and a 5-alpha-reductase inhibitor is superior to monotherapy with either agent.
- Tadalafil 5 mg qd has been FDA-approved to treat patients with signs and symptoms of BPH and patients with both ED and signs and symptoms of BPH. Tadalafil can potentiate the hypotensive effect of alpha-blockers and should not be used in combination with alpha-blockers.
- The dietary supplement saw palmetto is commonly used for relief of symptoms of BPH. Recent trials using 160 mg of saw palmetto bid did not improve symptoms of BPH. This contrasts with the positive findings of many previous studies. Trials with higher dose-ranging protocols are currently in progress.
- TURP is the most commonly used surgical procedure for BPH. It is recommended for patients unresponsive to medical therapy who have renal insufficiency, recurrent UTIs, bladder stones, or gross hematuria. Transurethral incision of the prostate (TUIP), a procedure almost equivalent in efficacy, is limited to patients whose estimated resection tissue weight would be 30 g or less. TUIP can be performed in an ambulatory setting or during a 1-day hospitalization. Open prostatectomy is typically performed on patients with very large prostates. A prostatic urethral lift implant (Urolift) is now available for BPH. It is placed transurethrally at the site of obstruction to open the urethra by compressing the obstructing prostatic lobes and holding them permanently retracted with suture-based implants.
- Laser therapy for BPH is a less invasive alternative to TURP; YAG laser enucleation has minimal effect on potency, libido, or patient satisfaction with his sex life and is associated with retrograde ejaculation. However, recent studies indicate that at least in the initial 7 mo after surgery, TURP is moderately more effective than laser therapy in relieving symptoms of BPH.
- Transurethral needle ablation with radiofrequency to remove periurethral prostate tissue is being increasingly used in patients with prostate volume >60 mL and moderate symptoms. It has a low morbidity rate, but treatment failure is approximately 25% at 5 yr and >80% at 10 yr.
- Balloon dilation of the prostatic urethra is less effective than surgery for relieving symptoms but is associated with fewer complications. It is a reasonable treatment option for patients with smaller prostates and no middle lobe enlargement.
- Surgery need not be the treatment of last resort for most patients; that is, patients need not undergo other treatments for BPH before they can have surgery. However, recommending surgery on the grounds that a patient's surgical risk will "only increase with age" is generally inappropriate.

DISPOSITION

With appropriate therapy, symptoms improve or stabilize in >70% of patients with BPH.

REFERRAL

Urology referral for patients with severe or intolerable symptoms and for any patient suspected of having prostate cancer (10% to 30% of men with BPH).

PEARLS & CONSIDERATIONS

COMMENTS

- Emerging technologies for treating BPH, including transurethral holmium laser enucleation, transurethral electrovaporization, and transurethral microwave thermotherapy of the prostate, appear promising; however, long-term effectiveness has not yet been demonstrated.
- The increase in the use of pharmacologic management has resulted in >30% reduction in the total number of TURP procedures.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Enlarged Prostate (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Purpose:
We evaluated the long-term efficacy and safety of low-dose oral desmopressin in elderly patients with benign prostatic hyperplasia with more than two nocturnal voids and nocturnal polyuria (more than 30% of total daily urine volume).

Materials and Methods:
Eligible patients with benign prostatic hyperplasia older than 65 years with nocturia, nocturnal polyuria, and International Prostate Symptom Score 14 or greater were included in the study. All patients received placebo or 0.1 mg desmopressin orally at bedtime. Patients were required to visit the outpatient clinic from the first visit, and after 1, 3, 6, and 12 months of treatment. Patients maintained flow volume charts and used diaries to record voiding data throughout the study. During follow-up urinalysis, urine sodium, urine osmolality, serum electrolytes, prostate specific antigen, International Prostate Symptom Score, quality of life, transrectal ultrasonography of prostate, uroflowmetry, and post-void residual urine volume were performed at each visit.

Results:
A total of 115 patients were enrolled in the study and randomized as 58 in the placebo group and 57 in the desmopressin group. Desmopressin significantly decreased nocturnal urine output and the number of nocturia episodes and prolonged the first sleep period ($p < 0.01$). Compared with before treatment, desmopressin gradually decreased serum sodium and induced statistically but not clinically significant hyponatremia after 12 months of treatment. No serious systemic complications were found during medication.

Conclusions:
Low-dose oral desmopressin is an effective and well-tolerated treatment for nocturnal polyuria in the lower urinary tract symptoms of patients with benign prostatic hyperplasia. Long-term desmopressin therapy gradually decreases serum sodium and it might induce hyponatremia even in patients without initial hyponatremia. For long-term desmopressin administration serum sodium should be assessed carefully, at least at 1 week after treatment. Ⓐ

Abstract[2]

Purpose:
To evaluate whether prostatic arterial embolization (PAE) might be a feasible procedure to treat lower urinary tract symptoms associated with benign prostatic hyperplasia (BPH).

Materials and Methods:
Fifteen patients (age range, 62 to 82 yr; mean age, 74.1 yr) with symptomatic BPH after failure of medical treatment were selected for PAE with nonspherical 200-μm polyvinyl alcohol particles. The procedure was performed by a single femoral approach. Technical success was considered when selective prostatic arterial catheterization and embolization was achieved on at least one pelvic side.

Results:
PAE was technically successful in 14 of the 15 patients (93.3%). There was a mean follow-up of 7.9 months (range, 3 to 12 months). International Prostate Symptom Score decreased a mean of 6.5 points ($P = 0.005$), quality of life improved 1.14 points ($P = 0.065$), International Index of Erectile Function increased 1.7 points ($P = 0.063$), and peak urinary flow increased 3.85 mL/sec ($P = 0.015$). There was a mean prostate-specific antigen reduction of 2.27 ng/mL ($P = 0.072$) and a mean prostate volume decrease of 26.5 mL ($P = 0.0001$) by ultrasound and 28.9 mL ($P = 0.008$) by magnetic resonance imaging. There was one major complication (a 1.5-cm^2 ischemic area of the bladder wall) and four clinical failures (28.6%).

Conclusions:
In this small group of patients, PAE was a feasible procedure, with preliminary results and short-term follow-up suggesting good symptom control without sexual dysfunction in suitable candidates, associated with a reduction in prostate volume. Ⓐ

Abstract[3]

Medical Treatment

Purpose:
Tadalafil has regulatory approval for the treatment of men with signs/symptoms of benign prostatic hyperplasia with and without erectile dysfunction. We assessed whether the effects of treatment with tadalafil for lower urinary tract symptoms/benign prostatic hyperplasia are independent of improvements in erectile dysfunction.

Materials and Methods:
Four separate analyses used integrated data from 4 randomized, double-blind, placebo controlled studies in men with lower urinary tract symptoms/benign prostatic hyperplasia with and without erectile dysfunction to test whether total I-PSS (International Prostate Symptom Score) improvement was due to improvement in IIEFEF (International Index of Erectile Function-Erectile Function domain score). Unidirectional and bidirectional path analysis models determined direct and indirect treatment effects mediated by improvements in lower urinary tract symptoms/benign prostatic hyperplasia and erectile dysfunction symptoms.

Results:
A total of 1,496 men, of whom 77% had erectile dysfunction, received at least 1 dose of tadalafil 5 mg once daily or placebo. The placebo adjusted treatment effect for men with erectile dysfunction was represented by a mean decrease of –2.3 ($p < 0.0001$) in total I-PSS versus_2.2 ($p = 0.0007$) for men without erectile dysfunction. The correlation between change from baseline in total I-PSS and IIEF-EF was weak ($r(2) = 0.08$, $p < 0.0001$). The unidirectional path analysis model suggested that the total treatment effect on total I-PSS score improvement (2.25) was derived from a direct treatment effect of 1.57 (70%, $p < 0.001$) and an indirect treatment effect of 0.67 (30% via IIEF-EF improvement, $p < 0.001$). Bidirectional path analysis showed that total I-PSS improvement was largely attributed to direct (92.5%, $p < 0.001$) versus indirect (7.5%, $p = 0.32$) treatment effects via IIEF-EF improvement.

Conclusions:
Regardless of the analytical approach, self-reported erectile dysfunction status did not appreciably influence tadalafil treatment response in men with lower urinary tract symptoms/benign prostatic hyperplasia, supporting the dual action of tadalafil on lower urinary tract symptoms/benign prostatic hyperplasia and erectile dysfunction. Ⓐ

Evidence-Based References

Wang CJ et al.: Low-dose oral desmopressin for nocturnal polyuria in patients with benign prostatic hyperplasia: a double-blind, placebo controlled, randomized study, *J Urol* 185:219–223, 2011. Ⓐ

Pisco JM: Prostatic arterial embolization to treat benign prostatic hyperplasia, *J Vasc Interv Radiol* 22:11–19, 2011. Ⓐ

Brock GB, McVary KT, Roehrborn C, et al.: Direct effects of tadalafil on lower urinary tract symptoms versus indirect effects mediated through erectile dysfunction symptom improvement: integrated data analyses from 4 placebo controlled clinical studies, *J Urol* 191:405–411, 2014. Ⓐ

SUGGESTED READINGS

AUA Practice Guidelines Committee: AUA guideline on management of benign prostatic hyperplasia, *J Urol* 170, 2003.

Barry MJ et al.: Effect of increasing saw palmetto extract on lower urinary tract symptoms: a randomized trial, *JAMA* 306(12):1344–1351, 2012.

Crawford ED et al.: Diagnostic performance of *PCA3* to detect prostate cancer in men with increased prostate specific antigen: a prospective study of 1,962 cases, *J Urol* 188:1726–1731, 2012.

Edwards JL: Diagnosis and management of benign prostatic hyperplasia, *Am Fam Physician* 77(10):1403–1410, 2008.

Fullhase J: Systematic review of combination drug therapy for non-neurogenic male lower urinary tract symptoms, *Eur Urol* 64:228–243, 2013.

Larcher A et al.: Urethral lift for benign prostatic hyperplasia: a comprehensive review of the literature, *Curr Urol Rep* 14:620, 2013.

Lepor H: Insights into the natural history and treatment of benign prostatic hyperplasia, *J Urol* 175:815, 2006.

Sarma AV, Wei JT: Benign prostatic hyperplasia and lower urinary tract symptoms, *N Engl J Med* 367:248–257, 2012.

BASIC INFORMATION

DEFINITION

Biceps tendonitis is a common cause of anterior shoulder pain characterized by an inflammatory process that involves the long head of the biceps tendon as well as its sheath within the bicipital groove. The tendon involvement can be intraarticular from its attachment to the superior glenoid labrum as it runs across the glenohumeral joint and extraarticular as it runs in the bicipital or intertubercular groove (Fig. B1-25).

SYNONYMS

Bicipital tendonitis
Bicipital tenosynovitis
Biceps tendinosis

ICD-9CM CODES
726.12 Bicipital tenosynovitis
ICD-10CM CODES
M75.20 Bicipital tendinitis, unspecified shoulder

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 41% of complete rotator cuff tears have concomitant biceps tendonitis
PREVALENCE: Common but prevalence uncertain
PREDOMINANT AGE: 18 to 35 yr old
RISK FACTORS: Athletes involved in throwing sports, swimming, contact sports, weight lifting, gymnastics, martial arts; repetitive overhead movements among carpenters, electricians, mechanical wheelchair users

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pain referred to the anterior shoulder
- Pain that worsens at night
- A history of trauma may or may not be present
- Pain on lifting, pulling, and repetitive overhead reaching
- Most common physical exam finding is tenderness over bicipital groove by palpating the biceps tendon 3 to 6 cm below the anterior acromion and felt most easily in 10 degrees of internal rotation
- Yergason's test—pain on biceps tendon area on resisted supination of pronated forearm with elbow at 90 degrees
- Speed's test—pain on the biceps tendon area on resisted forward flexion of the shoulder with elbows and arms fully supinated and extended

ETIOLOGY

- Primary—of unknown cause and the inflammation is specific to the intertubercular groove without any associated shoulder pathology
- Secondary—associated with other pathologic conditions such as rotator cuff disease, impingement syndrome, SLAP (Superior Labrum from Anterior to Posterior) injuries, presence of spurs, or any systemic inflammatory disease involving the shoulders

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Impingement syndrome
- Rotator cuff tendonitis
- Subacromial bursitis
- Rotator cuff tears
- SLAP injuries
- Adhesive capsulitis
- Acromioclavicular joint arthritis
- Glenohumeral joint arthritis
- Cervical radiculopathy
- Coracoid impingement
- Brachial plexus neuritis

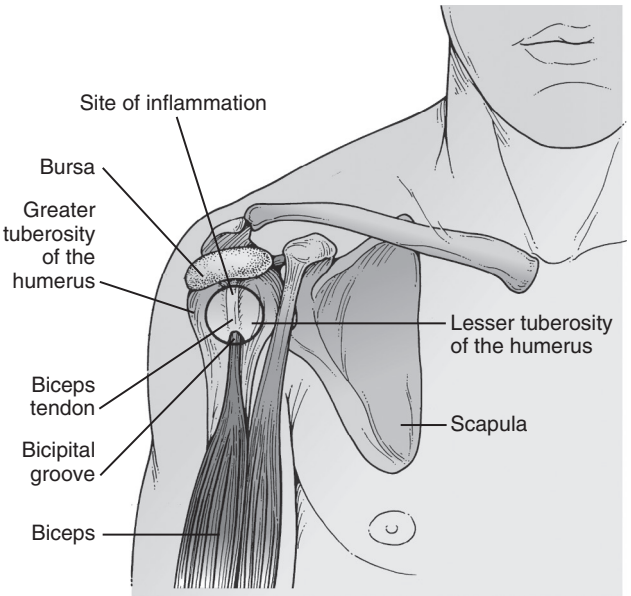

FIGURE B1-25 Anatomic location of the long head of the biceps tendon with surrounding structures of the shoulder. (From Roberts JR et al: *Clinical procedures in emergency medicine,* ed 5, Philadelphia, 2009, Saunders.)

WORKUP

May proceed to imaging modalities

IMAGING STUDIES

- X-ray plain films are usually normal in primary tendinopathy; special views of the bicipital groove may demonstrate presence of spurs
- Musculoskeletal ultrasound evaluates dynamic movements of the biceps tendon; it is 49% sensitive but 91% to 97% specific; use in both diagnosis and treatment
- Ultrasound may reveal the presence of effusion in the long head of the biceps tendon sheath (Fig. B1-26)
- CT/MRI arthrography are early techniques used to reliably identify shoulder pathology
- MRI is a non-invasive way of getting detailed images of the biceps tendon and other shoulder structures such as the superior labrum and rotator cuff structures and identifying pathologies that may or may not coexist
- Arthroscopy is the gold standard technique for diagnosis and treatment

TREATMENT

It is often necessary to establish whether the tendonitis is primary or secondary to address certain aspects of the treatment. Initial conservative treatment is usually very successful.

NONPHARMACOLOGIC THERAPY

Ice, rest from overhead physical activities, physical therapy after acute phase

ACUTE GENERAL Rx

Nonsteroidal anti-inflammatory drugs (NSAIDs) are good adjuncts to treatment that expedites the recovery process by decreasing edema, inflammation, and pain.

CHRONIC Rx

- If with persistent pain or severe night symptoms that fail to resolve after 6 to 8 wk of conservative treatment, corticosteroid injections may be considered
- Injection into the tendon sheath (Fig. B1-27), with care not to inject into the biceps tendon, may have good to excellent results; best done under ultrasound guidance
- Subacromial steroid injections can address tendonitis secondary to impingement
- Glenohumeral joint injection delivers the steroids directly to the intraarticular portion of the biceps that is often irritated
- Gradual biceps and rotator cuff strengthening with physical therapy if symptoms have decreased
- Low-power laser therapy has reported beneficial effects but disputes exist

DISPOSITION

- Usually self-limited with conservative measures
- If pain persists after 3 mo, referral to orthopedic surgery
- Surgical options are tendon debridement, release of constricted synovial sheath, tenodesis, or tenotomy.

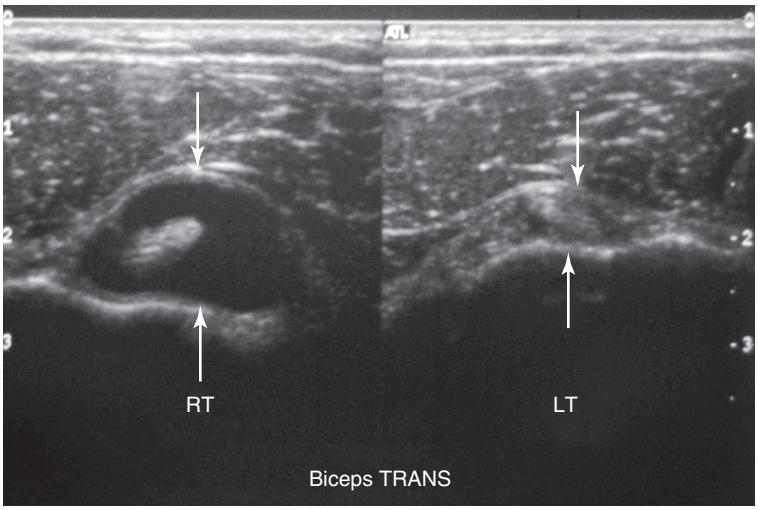

FIGURE B1-26 Ultrasound image of bicipital tendonitis. Transverse image shows large effusion in the long head of biceps tendon sheath. (From Hoechberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

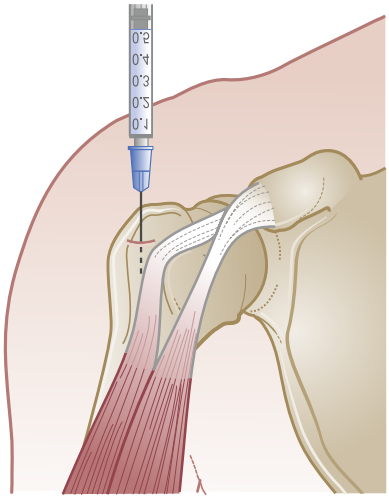

FIGURE B1-27 Injection of the long head of the biceps tendon in the bicipital groove. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, St Louis, 2013, Elsevier.)

- Tenodesis is done by moving the attachment to relieve pressure of the irritated tendon; results in better strength and cosmesis but requires longer rehab; consider for younger, active patients
- Tenotomy consists of cutting the long head of the biceps tendon prior to its intraarticular superior labral insertion; technically simple procedure with short rehabilitation but deformity, weakness, and cramping may occur; consider for older patients
- Can progress to tendon rupture resulting in a "Popeye deformity" (Fig. B1-28)

REFERRAL

- Refer to physical therapy early in the phase of conservative treatment
- Refer to orthopedics if symptoms persist beyond 3 to 4 mo

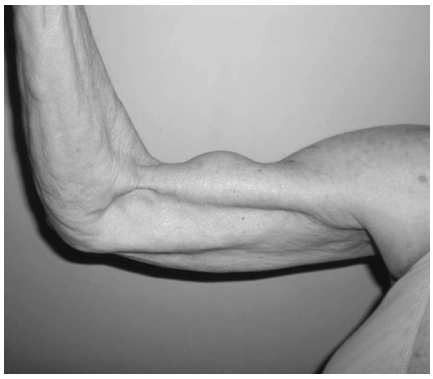

FIGURE B1-28 Popeye deformity after a biceps tendon rupture. (Illustration borrowed from Fernandez et al FIGURE 4, PAGE 7. Seminarios de la Fundación Española de Reumatologia Maniobras exploratorias del hombro doloros martes, 13 jul 2010, Elsevier.)

PEARLS & CONSIDERATIONS

COMMENTS

A complete rotator cuff tear almost always involves the biceps tendon as its intraarticular portion gets exposed to the overlying acromion, which causes further impingement and pain.

PREVENTION

After corticosteroid injection, patient should not return immediately to vigorous physical activities that could potentially progress into a biceps tendon complete tear.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **CRISOSTOMO R. BALIOG, JR., M.D.**

SUGGESTED READINGS

Ahrens PM et al.: Aspects of current management: the long head of biceps and associated tendinopathy, *J Bone Joint Surg* 89B:1001–1009, 2007.

Bicos J: Biomechanics and anatomy of the proximal biceps tendon, *Sports Med Arthrosc* 16:111–117, 2008.

Busconi BB et al.: The proximal biceps tendon: tricks and pearls, *Sports Med Arthrosc Rev* 16:187–194, 2008.

Chen C-H et al.: Incidence and severity of biceps long head tendon lesion in patients with complete rotator cuff tears, *J Trauma* 58:1189–1193, 2005.

Churgay CA et al.: Diagnosis and treatment of biceps tendinitis and tendinosis, *Am Fam Physician* 80:470–476, 2009.

Ejnisman B et al.: Disorder of the long head of the biceps tendon, *Br J Sports Med* 44:347–354, 2009.

Finley MA et al.: Prevalence and identification of shoulder pathology in athletic and nonathletic wheelchair users with shoulder pain: a pilot study, *J Rehabil Res Dev* 41:395–402, 2004.

Krupp JR et al.: Long head of the biceps tendon pain: differential diagnosis and treatment, *J Orthop Sports Phys Ther* 39:55–70, 2009.

Murthi AM et al.: The incidence of pathologic changes of the long head of the biceps tendon, *J Shoulder Elbow Surg* 9:382–385, 2000.

BASIC INFORMATION

DEFINITION

Bipolar disorder is an episodic, recurrent, and frequently progressive condition in which the afflicted individual experiences at least one episode of mania, characterized by at least 1 wk of continuous symptoms of elevated, expansive, or irritable mood, in association with three or more of the following symptoms (four if irritability is the presenting mood):

- Decreased need for sleep
- Grandiosity or inflated self-esteem
- Pressured speech
- Flight of ideas or subjective sense of racing thoughts
- Distractibility
- Increased level of goal-directed activity
- Problematic behavior with a high potential for painful consequences

Most individuals with bipolar disorder also experience one or more episodes of major depression over their lifetimes or have symptoms of a depressive episode commingled with those of mania (mixed episode). Hypomanic episodes may also occur.

SYNONYMS

Manic-depression
Cycloid psychosis

ICD-9CM and DSM-5 CODES
296.4-296.7 Depression symptoms
ICD-10CM CODES
F42.0 Bipolar affective disorder, current episode hypomanic
F31.1 Bipolar affective disorder, current episode manic without psychotic symptoms
F31.2 Bipolar affective disorder, current episode manic with psychotic symptoms
F31.3 Bipolar affective disorder, current episode mild or moderate depression
F31.4 Bipolar affective disorder, current episode severe depression without psychotic symptoms
F31.5 Bipolar affective disorder, current episode severe depression with psychotic symptoms
F31.6 Bipolar affective disorder, current episode mixed
F31.8 Bipolar II disorder

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 0.016% to 0.021%
PREVALENCE (IN U.S.): 0.4% to 1.6% (lifetime); bipolar spectrum disorders: 2.8%
PREDOMINANT SEX: Equal distribution among male and female
PREDOMINANT AGE: Lifelong condition with age of onset 14 to 30 yr
PEAK INCIDENCE: Onset in 20s
GENETICS:

- Concordance rates for monozygotic twins: 0.7 to 0.8; for dizygotic twins: 0.2
- Risk of affective disorder in offspring with one affected parent with bipolar disorder: 27% to 29%; with two affected parents: 50% to 74%
- Heritability estimate of 0.85
- No specific causal mutations have been identified. Genome-wide association analyses have suggested a role for *CACNA1C, ODZ4, ZNF 804A,* and *NCAN,* among others, and implicated ion channelopathies in pathogenesis of bipolar disorder. It remains unclear whether the high heritability is the result of the additive effect of many common risk variants or a fewer higher-risk rare variants.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Mania associated with:
  1. Psychomotor activation that is usually goal directed but not necessarily productive
  2. Increase in goal-directed activity and excessive involvement in activities leading to unexpected adverse outcomes
  3. Elevated, euphoric, and frequently labile mood
  4. Decreased need for sleep
  5. Flight of ideas with rapid, loud, pressured speech
- Psychosis may occur, with delusions, hallucinations, and formal thought disorder
- Depressive episodes resembling major depressive disorder (see "Depression, Major"); however, atypical features (hypersomnia, weight gain) may be present
- Mixed states, characterized by activation, irritability, and dysphoria, also possible

KEY DIAGNOSTIC CRITERIA DISTINGUISHING BIPOLAR I DISORDER FROM BIPOLAR II DISORDER:*

Manic episode (Bipolar I Disorder)

- Distinct period during which there is an abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy lasting at least 1 wk (or less if hospitalization is required)
- Must be accompanied by at least three of the following symptoms (four if mood is only irritable): inflated self-esteem or grandiosity, decreased need for sleep, pressured speech, racing thoughts, distractibility, increased involvement in goal-directed activity or psychomotor agitation, excessive involvement in pleasurable activities with a high potential for painful consequences
- Symptoms do not meet criteria for a mixed episode
- Disturbance must be sufficiently severe to cause marked impairment in social or occupational functioning or to require hospitalization, or it is characterized by the presence of psychotic features
- Symptoms not due to direct physiologic effect of medication, general medication condition, or substance abuse

Hypomanic episode (Bipolar II Disorder)

- Distinct period during which there is an abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently elevated activity or energy lasting at least 4 consecutive days
- Must be accompanied by at least three of the following symptoms (four if mood is only irritable): inflated self-esteem or grandiosity, decreased need for sleep, pressured speech, racing thoughts, distractibility, increased involvement in goal-directed activity or psychomotor agitation, excessive involvement in pleasurable activities with a high potential for painful consequences
- Hypomanic episodes must be clearly different from the person's usual nondepressed mood, and there must be a clear change in functioning that is not characteristic of the person's usual functioning
- Changes in mood and functioning must be observable by others. In contrast to a manic episode, a hypomanic episode is not severe enough to cause marked impairment in social or occupational functioning or to require hospitalization, and there are no psychotic features
- Symptoms not due to direct physiologic effect of medication, general medication condition, or substance abuse

ETIOLOGY

Hypotheses:

1. Abnormalities of receptor and membrane function, calcium dysregulation
2. Alteration of cAMP, MAP kinase, protein kinase C, arachidonic acid cascade, and glycogen synthase kinase-3 signal transduction pathways; mitochondrial dysfunction
3. Alteration in cell survival pathways, glial and neuronal death and loss of neuroplasticity; proposed biomarkers include BDNF and measures of inflammation, oxidative stress, and endothelial function.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Secondary manias caused by medical disorders (e.g., hyperthyroidism, AIDS, stroke, Cushing syndrome) or pharmacologic treatment (e.g., steroids, stimulants).
- First onset of mania after age 50 yr suggestive of secondary mania.
- Less severe, and possibly distinct, conditions of bipolar type II and cyclothymia
- Comorbid substance abuse or dependency may confound diagnosis and treatment.
- Presentation can be confused with schizophrenia or paranoid psychosis.

WORKUP

- History
- Physical examination
- Mental status examination
- Mood Disorder Questionnaire (MDQ)

*Criteria are from the American Psychiatric Association: *Diagnostic and statistic manual of mental disorders, fifth edition,* Washington, DC, 2013, American Psychiatric Association.

LABORATORY TESTS

Because of high rate of secondary manias, initial evaluation to confirm health of all major organ systems (routine chemistries, complete blood count, urinalysis, sedimentation rate)

IMAGING STUDIES

- Consider brain imaging if late onset or if neurologic examination is abnormal.
- Neuroimaging may show evidence of ventricular enlargement or increased white matter hyperintensities; decrements in prefrontal and temporal lobe cortical thickness also reported.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Cognitive-behavioral and family-focused psychoeducational psychotherapy to help patients cope with consequences of the disease, improve adherence with medications, and identify possible environmental triggers
- Bright light therapy in the northern latitudes in individuals exhibiting a seasonal pattern of winter depression
- Lifestyle "regularization"; interpersonal and social rhythm therapy

ACUTE GENERAL Rx

- First-line agents for acute mania and mixed states: lithium 1500 to 1800 mg/day (0.8 to 1.2 mEq/L), valproate 1000 to 1500 mg/day (50 to 125 ng/ml), carbamazepine 600 to 800 mg/day (4 to 12 micrograms/ml), oxcarbazepine 900 to 2400 mg/day, olanzapine 10 to 20 mg/day, risperidone 2 to 4 mg/day, quetiapine 350 to 800 mg/day, ziprasidone 80 to 120 mg/day, asenapine 10 to 20 mg/day, or aripiprazole 10 to 30 mg/day.
- Useful adjuncts to acute treatment of mania: benzodiazepines: lorazepam 1 to 2 mg q4h, clonazepam 1 to 2 mg q4h.
- Traditional antidepressants can induce manic episodes and exacerbate mania in mixed episodes.
- Lamotrigine can have acute antidepressant benefit, but appears more effective in prophylaxis of future episodes.
- Although best evidence data are limited, first-line options for bipolar depression include lithium, quetiapine, lamotrigine, lurasidone, and olanzapine/fluoxetine combination. Bupropion may have a lower risk for triggering mania, and MAOIs or ECT may be efficacious in treatment-resistant cases.

CHRONIC Rx

- Goal of long-term treatment: prevention of relapse or episode recurrence
- Best agents for prophylaxis of mania: lithium, valproate, and olanzapine (carbamazepine/oxcarbazepine possibly beneficial)
- Best agents for prophylaxis of depression: lamotrigine and lithium
- Risk/benefit of atypical antipsychotics versus traditional mood stabilizers in maintenance unclear
- Long-term use of antidepressants: frequently destabilizes patient and leads to more frequent relapses; depression outweighs mania as the most debilitating dimension over the life span; bipolar disorder accounts for 7% of all disease-related disability-adjusted life years.

DISPOSITION

- Course is variable.
- More than 90% of patients having a single manic episode are likely to experience others.
- Uncontrolled manic or depressive episodes can lead to additional episodes.
- Lithium shown to specifically decrease suicidal risk.
- Psychosocioeconomic consequences of both mania and depression can be severe and disabling.

REFERRAL

- If use of antidepressant contemplated
- If patient is severely manic, rapid cycling, or suicidal or is in a bipolar, mixed episode

PEARLS & CONSIDERATIONS

COMMENTS

- All patients presenting with depression should be asked about past personal and family history of mania and hypomania; 70% of bipolar patients have previously been misdiagnosed.
- Prompt recognition of the earliest signs of mania in a given individual (e.g., decreased need for sleep, increased rate of speech) allows earlier intervention and a better likelihood of preventing a full episode.
- Bipolar disorder in children frequently manifests as behavioral disinhibition and temper dysregulation, but current consensus indicates that the condition is overdiagnosed in this age group. Disruptive mood dysregulation disorder (DMDD) describes children who exhibit persistent irritability and severe temper outbursts on a frequent basis (at least three times/week for a year or more.
- Rapid cycling (greater than three episodes/year) is associated with a poorer prognosis, including a longer course, more treatment resistance, more substance use comorbidity, and increased suicidal risk.
- Patients treated with atypical antipsychotic agents should be carefully monitored for development of metabolic syndrome.
- Despite some variation in prevalence, the severity, impact, and patterns of comorbidity of bipolar disorder are similar in different countries in world health surveys.
- Bipolar disorder often co-occurs with anxiety disorders and attention deficit hyperactivity disorder (ADHD), making attribution of specific symptoms difficult.
- Patients receiving anticonvulsants or antidepressants should be monitored for a possible increase in suicidal thoughts or behavior.
- There is preliminary evidence that nutraceutical agents like omega-3 fatty acids and *N*-acetyl cysteine (NAC) may have efficacy in the treatment of bipolar disorder.

PATIENT/FAMILY EDUCATION

Information available at www.NMHA.org/ and www.dbsalliance.org/.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Depression, Major (Related Key Topic)
Bipolar Disorder (Patient Information)

AUTHOR: **VICTOR I. REUS, M.D.**

SUGGESTED READINGS

Brenner CJ, Shyn SI: Diagnosis and management of bipolar disorder in primary care, *Med Clin North Am* 98(5):1025–1048, 2014.

Brooks JO, Vizueta N: Diagnostic and clinical implications of functional neuroimaging in bipolar disorder, *J Psychiatr Res* 57c:12–25, 2014.

Cerimele JM et al.: The prevalence of bipolar disorder in general primary care samples: a systematic review, *Gen Hosp Psychiatry* 36(1):19–25, 2014.

Connolly KR, Thase ME: The clinical management of bipolar disorder: a review of evidence-based guidelines, *Prim Care Companion CNS Disord* 13(4), 2011.

Craddock N, Sklar P: Genetics of bipolar disorder, *Lancet* 381(9678):1654–1662, 2013.

Faedda GL et al.: Clinical risk factors in bipolar disorders: a systematic review of prospective studies, *J Affec Disord* 168c:314–321, 2014.

Geddes JR, Miklowitz DJ: Treatment of bipolar disorder, *Lancet* 381(9678):1672–1682, 2013.

Goodwin FK, Redfield JK. Manic-depressive illness: bipolar disorders and recurrent depression. Ed 2 Oxford University Press: New York.

McIntyre RS et al.: A review of FDA-approved treatment options in bipolar depression, *CNS Spectr Suppl* 1:4–20, 2013.

Nivoli AM et al.: New treatment guidelines for acute bipolar mania: a critical review, *J Affect Disord* 140(2):125–141, 2012.

Pompili M et al.: Impact of living with bipolar patients: making sense of caregivers' burden, *World J Psychiatry* 4(1):1–12, 2014.

Price AL, Marzani-Nissen GR: Bipolar disorder: a review, *Am Fam Physician* 85(5):483–493, 2012.

Reinares M et al.: Psychosocial interventions in bipolar disorder: what, for whom, when, *J Affect Disord* 156:46–55, 2014.

Renk K et al.: Bipolar disorder in children, *Psychiatry J Epub*, 2014 Feb 24.

BASIC INFORMATION

DEFINITION

Bone cell death in the jaw observed with therapeutic dosages of bisphosphonates (BPs). Osteoclast apoptosis may occur due to the antiresorptive effects of BPs preventing the release of bone regenerative proteins and thus preventing bone renewal and remodeling. This results in tissue loss and exposed bone. BPs are not believed to be toxic to osteoblasts, although evidence suggests some antiangiogenic effects.

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) primarily involves the jawbone due to its higher risk for complications from minor injury and infection when the healing potential or vascular supply is compromised. Recent evidence suggests that high turnover rates of bones may or may not be associated with BRONJ; higher rates have been reported in the mandible of the jaw versus the maxilla, despite its lower rate of bone turnover.

Cases of ONJ have also been reported in patients with malignancy treated with high doses of denosumab as well as antiangiogenic agents, such as bevacizumab and sunitinib. Product labeling for each of these agents includes an ONJ warning. The American Association of Oral and Maxillofacial Surgeons (AAOMS) therefore now uses the term "medication-related osteonecrosis of the jaw" (MRONJ).

SYNONYMS

Bisphosphonate-induced osteonecrosis of the jaw (BIONJ)

ICD-9CM CODES
Not applicable
ICD-10CM CODES
M87.180 Osteonecrosis due to drugs, jaw

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- The incidence with alendronate has been estimated to be 0.7 per 100,000 persons per year by the original manufacturer.
- A 2014 study of 7332 patients in Taiwan estimated the incidence of ONJ from alendronate to be greater than 200 per 100,000 persons per year. Potential contributing factors included advanced age, longer drug duration, and concomitant diabetes and rheumatoid arthritis.
- The incidence after tooth extraction has ranged from 8.3% to 40% in the medical literature.
  1. Incidence at 42 months after tooth extraction has been estimated at 3.9% with oral BPs and 14.8% with IV BPs.

PEAK INCIDENCE:

- ONJ has been identified as early as 7 months after the use of IV BPs in patients with cancer and as early as 13 months in patients with osteoporosis only. Incidence may depend on when dentoalveolar surgery occurs.

PREVALENCE:

- Prevalence in 2008 estimated at 13.3% of patients with cancer who received an IV BP
- Most prevalent in patients with multiple myeloma or breast cancer versus other cancers or osteoporosis

PREDOMINANT SEX AND AGE:

- Sex not statistically associated with BRONJ
- Age greater than or equal to 65

GENETICS:

- Single nucleotide polymorphisms (SNPs) have been identified in the *CYP2C8* gene among patients with multiple myeloma and exposure to IV BPs.

RISK FACTORS:

- The 2014 AAOMS position paper estimates that the risk of ONJ is about 100 times greater for patients with cancer who receive antiresorptive agents versus patients without cancer who are treated for osteoporosis.
- Patients with cancer exposed to IV BPs who undergo dentoalveolar surgery have an estimated 5- to 21-fold increased risk for BRONJ than similar patients who do not undergo this surgery.
- IV formulations such as zoledronic acid: risk ratio for developing BRONJ is 14.6 with IV versus oral products.
- Patients with cancer who are exposed to IV zoledronate have an estimated ONJ risk of 1%, or 100 cases per 10,000 patients. The risk of ONJ for patients with cancer exposed to denosumab is similar; an estimated 0.7%, or 70 cases per 10,000 patients.
- Patients with cancer who are exposed to bevacizumab may have a risk of 0.2%, or 20 cases per 10,000 patients.
- Longer duration of BP therapy
- Age greater than or equal to 65 with risk ratio estimated to be 200.2 in those exposed to IV BPs vs. similar patients not exposed
- Malignancy
- Chemotherapeutic agents and corticosteroids
- History of periodontal and dental abscesses
- Bacterial infection

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Exposed bone in the maxilla or mandible, with 65% of cases involving the mandible. Multifocal or bilateral involvement may be present.
- Pain in the maxillofacial region, although one third of lesions may be painless
- Tooth mobility/spontaneous tooth loss
- Mucosal swelling, erythema, ulceration, altered sensation
- Infection

ETIOLOGY

- Exposure to BPs as well as other antiresorptive and antiangiogenic agents

DIAGNOSIS

The AAOMS considers a diagnosis of BRONJ if the following three characteristics are present:

1. Current or previous treatment with a BP
2. Exposed bone or bone that can be probed through intraoral or extraoral fistulae in the maxillofacial region persisting for more than 8 weeks
3. No history of radiation therapy to the maxillofacial region or evident metastatic disease to the jaw

DIFFERENTIAL DIAGNOSIS

- Suppurative osteomyelitis of the jaw (SOJ)
- Osteoradionecrosis of the jaw (ORNJ)
- Alveolar osteitis, gingivitis, sinusitis, fibro-osseous lesion, sarcoma, sclerosing osteomyelitis, periodontitis, dental caries, and temporomandibular joint disorders

WORKUP

- Treatment history, including medications and radiation therapy
- Past medical history, including malignancy

LABORATORY TESTS

A validated diagnostic test is not available to identify patients at an increased risk of BRONJ. Tissue biopsy should only be performed if metastatic disease is strongly suspected and its detection would change the management of BRONJ. Histopathology of BRONJ shows empty osteocytic lacunae, empty Haversian and Volkmann canals, an absence of inflammatory cells or blood vessels in the marrow space, and absence of extracellular collagenase.

IMAGING STUDIES

Panoramic and periapical radiographs

TREATMENT

Goals of treatment for BRONJ include:

- Control and/or reduce pain.
- Control secondary infection.
- Minimize progression or occurrence of bone necrosis, as well as extension of lesion.

NONPHARMACOLOGIC THERAPY

Surgery for BRONJ should be deferred if possible as a surgical margin with viable bone is difficult to obtain. The entire jawbone likely has been exposed to accumulation of BPs, and therefore successful eradication of necrotic bone is often not possible. Those areas of necrosis that consistently irritate soft tissues should undergo debridement as necessary. Limited evidence supports the use of hyperbaric oxygen as adjunct to surgery and antibiotics to slow progression and improve pain. Small case reports have documented the use of platelet-rich plasma, low-level laser irradiation, parathyroid hormone, and bone morphogenic protein; however, the efficacy of these methods has not been established through controlled studies.

The AAOMS recommends the following surgical strategies based on BRONJ staging:

- Stage 0 (no clinical evidence of necrotic bone, nonexposed bone variant): no surgery
- Stage I (exposed and necrotic bone, or fistulae that probe to bone, asymptomatic): no surgery
- Stage II (exposed and necrotic bone, or fistulae that probe to bone, with pain and/or infection): superficial debridement
- Stage III (exposed and necrotic bone with pain, infection, **and** one of the following

features: necrosis extending beyond alveolar bone, pathologic fracture, extraoral fistula, oral antral or nasal communication, osteolysis extending to mandible of sinus floor): surgical debridement or resection for palliation of infection and pain

ACUTE GENERAL Rx

Both chlorhexidine mouth rinse and antibiotics for 1 to 3 weeks have been found useful for stage reduction.

- Chlorhexidine 0.12% antibacterial mouth rinse daily for Stages I to III
- Oral antibiotics for symptomatic Stage II and oral or IV antibiotics for Stage III
- Analgesics for Stages II or III

CHRONIC Rx

- Determine whether discontinuation of BPs (or other agents associated with MRONJ) is appropriate.
  1. Evaluate potential benefit of continuing BP, such as relief of bone pain in malignancy or prevention of fractures with high morbidity and mortality.
  2. BPs have a prolonged half-life, so return to normal osteoclast function and bone turnover may be too gradual.
  3. Consider other risks of BPs such as spontaneous atypical fractures.
- If discontinuing BP therapy, consider other alternative treatments for osteoporosis or bone pain.
- Anecdotal case reports exist for using teriparatide or pentoxifylline with tocopherol to heal BRONJ.

DISPOSITION

- Patients with involvement of the maxilla appear to have a greater likelihood of repeat surgery.
- Patients on oral BPs may have less severe complications and may have a better response.
- Treatment with antibiotics and chlorhexidine mouth rinse, withdrawal of BPs, and surgical removal of loose sequestra may possibly reduce pain and lesions of osteonecrosis.

REFERRAL

Oral and maxillofacial surgeon

PEARLS & CONSIDERATIONS

COMMENTS

- Patients may be asymptomatic for weeks to years before BRONJ is apparent. Radiographic changes may not be observed until significant disease has developed.
- Tooth extraction may be difficult to avoid in patients at high risk of BRONJ if an underlying bacterial infection is present.
- Patients with cancer are at highest risk as the dosage of BPs are much greater for osteoporosis.
- Product labeling for BPs states that there is no evidence that discontinuation of therapy reduces the risk of ONJ; therefore, the optimal duration of therapy is unknown.
  1. Results from the FLEX trial suggest that women with postmenopausal osteoporosis who have taken alendronate for 5 years and are at low risk of vertebral fractures may discontinue the drug for up to 5 years.
- Results from the HORIZON-PFT extension trial suggest that women with postmenopausal osteoporosis who have taken IV zoledronic acid for 3 years and are at low risk of vertebral fractures may discontinue for up to 3 years.
- Use of BPs in pediatric patients has increased without identified cases of BRONJ to date. Further evaluation of long-term use of BPs in these patients is warranted.

PREVENTION

- Regular dental hygiene and routine dental examinations
- Assessment of patients for other risk factors of BRONJ
- Completion of any anticipated dental procedures before beginning BP therapy
- Consideration of appropriateness of oral BP instead of IV formulations
- After dentoalveolar surgery, initiation of BPs delayed by 2 to 3 weeks to allow for osseous healing
- Careful monitoring of patients after dentoalveolar surgery
- Examination of mucosa in patients with full or partial dentures
- In asymptomatic patients receiving IV BPs, limiting dental surgery to removal of nonrestorable teeth and avoiding dental implants in patients who also have cancer
- Currently, the FDA reports a lack of substantial evidence to make recommendations related to drug holidays with BPs
- The 2014 AAOMS position paper supports a two-month drug holiday before oral surgery for patients who have received BPs for greater than 4 years or for patients exposed to less than 4 years of BPs and taking concomitant corticosteroids or antiangiogenics. Osseous healing should be complete before restarting BPs.

Evidence suggests a three-fold reduction in the incidence of ONJ when preventive measures are practiced.

PATIENT/FAMILY EDUCATION

- All health care providers should be aware of past and current BP use
- Contact a health care provider if any of the following are noticed:
  1. Presence of exposed bone in the maxillofacial area
  2. Persisting pain in the maxillofacial area
  3. Signs of infection such as fever, pus, and swelling
- Practice good dental hygiene and keep regular dental appointments

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **CHRISTINE EISENHOWER, PHARM.D.** and **MELISSA C. STRIGLIO, PHARM.D. CANDIDATE**

SUGGESTED READINGS

American Association of Oral and Maxillofacial Surgeons: *Medication-Related Osteonecrosis of the Jaw*, 2014. Retrieved from http://www.aaoms.org/docs/position_papers/mronj_position_paper.pdf?pdf=MRONJ-Position-Paper.

Compston J et al.: Diagnosis and management of osteoporosis in postmenopausal women and older men in the UK: National Osteoporosis Guideline Group (NOGG) update 2013, *Maturitas* 75:392–396, 2013.

Ruggiero SL et al.: Bisphosphonate-related osteonecrosis of the jaw: background and guidelines for diagnosis, staging and management, *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 102:433–441, 2006.

Yamakazi T et al.: Increased incidence of osteonecrosis of the jaw after tooth extraction in patients treated with bisphosphonates: a cohort study, *Int J Oral Maxillofac Surg* 41:1397–1403, 2012.

BASIC INFORMATION

DEFINITION

A bite wound can be animal or human, accidental, or intentional.

ICD-9CM Codes
879.8 Bite wound, unspecified site
ICD-10CM CODES
T14.1 Open wound of unspecified body region
T01.9 Multiple open wounds, unspecified
S31.000A Unspecified open wound of lower back and pelvis without penetration into retroperitoneum, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

- Bite wounds account for 1% of emergency department visits, and about 2% of patients need hospitalization.
- More than 1 million bites occur in human beings annually in the U.S.
- Dog bites account for 85% to 90% of all bites and result in 10 to 20 fatalities yearly in the U.S.; most dog bite victims are children. Cat bites account for 10% to 20%. The animal typically is owned by the victim.
- Infection rates are highest for cat bites (30% to 50%), followed by human bites (15% to 30%) and dog bites (5%).
- The extremities are involved in 75% of bites.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The appearance of the bite wound is variable (e.g., puncture wound, tear, avulsion).
- Cellulitis, lymphangitis, and focal adenopathy may be present in infected bite wounds.
- Patient may have fever and chills.

ETIOLOGY

- Increased risk of infection: human and cat bites, closed-fist injuries, wounds involving joints, puncture wounds, face and lip bites, bites with skull penetration, bites in immunocompromised hosts
- Most frequent infecting organisms:
  1. *Pasteurella* spp.: responsible for majority of infections within 24 hr of dog *(P. canis)* and cat *(P. multocida, P. septica)* bites
  2. *Capnocytophaga canimorsus* (formerly DF-2 bacillus): a gram-negative organism responsible for late infection, usually after dog bites
  3. Gram-negative organisms *(Pseudomonas, Haemophilus)*: often found in human bites
  4. *Streptococcus* spp., *Staphylococcus aureus*
  5. *Eikenella corrodens* in human bites

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bite from a rabid animal (often the attack is unprovoked)
- Factitious injury

WORKUP

- Determination of the time elapsed since the patient was bitten, status of rabies immunization of the animal, and underlying medical conditions that might predispose the patient to infection (e.g., DM, immunodeficiency)
- Documentation of bite site, notification of appropriate authorities (e.g., police department, animal officer)

LABORATORY TESTS

- Generally not necessary
- Hct if there has been significant blood loss
- Wound cultures (aerobic and anaerobic) if there is evidence of sepsis or victim is immunocompromised; cultures should be obtained before irrigation of the wound but after superficial cleaning

IMAGING STUDIES

Radiographs are indicated when bony penetration is suspected or if there is suspicion of fracture or significant trauma; they are also useful for detecting foreign bodies (when suspected).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Local care with debridement, vigorous cleansing, and saline irrigation of the wound; debridement of devitalized tissue
- High-pressure irrigation to clean bite wound and ensure removal of contaminants (e.g., use saline solution with a 30- to 35-ml syringe equipped with a 20-gauge needle or catheter with tip of syringe placed 2 to 3 cm above the wound)
- Avoid blunt probing of wounds (increased risk of infection)
- If the animal is suspected to be rabid: infiltrate wound edges with 1% procaine hydrochloride, swab wound surface vigorously with cotton swabs and 1% benzalconium solution or other soap, and rinse wound with normal saline

ACUTE GENERAL Rx

- Avoid suturing of hand wounds and any wounds that appear infected
- Puncture wounds should be left open
- Give antirabies therapy and tetanus immune globulin (250 to 500 units IM in limb contralateral to toxoid) and toxoid (adult or child older than 5 yr: 0.5 ml DT given IM, child <5 yr 0.5 ml DPT IM) as needed
- Use empiric antibiotic therapy in high-risk wounds (e.g., cat bite, hand bites, face bites, genital area bites, bites with joint or bone penetration, human bites, immunocompromised host): amoxicillin-clavulanate 875 to 1000 mg bid for 7 days or cefuroxime 500 mg bid for 7 days
- In hospitalized patients, IV antibiotics of choice are cefoxitin 1 to 2 g q6h, ampicillin-sulbactam 1.5 to 3 g q6h, ticarcillin-clavulanate 3 g q6h, cefoxitin 2 g IV q8h, or ceftriaxone 1 to 2 g q24h
- Penicillin allergy: animal bite (doxycycline or moxifloxacin or trimethoprim/sulfamethoxazole with either clindamycin or metronidazole); human bite (moxifloxacin plus clindamycin, trimethoprim/sulfamethoxazole plus metronidazole)
- Prophylactic therapy for persons bitten by others with HIV and hepatitis B (see Section V)
- Table B1-5 summarizes the treatment of mammalian bites

DISPOSITION

- Prognosis is favorable with proper treatment.
- Important prognostic factors are type and depth of wound, which compartments are entered, and pathogenicity of inoculated bacteria.
- Punctures that are difficult to irrigate adequately, carnivore bites over vital structures (arteries, nerves, joints), and tissue crushing that cannot be debrided have a worse prognosis.
- In general, human bites have a higher complication and infection rate than do animal bites.
- Nearly 50% of the anaerobic gram-negative bacilli isolated from human bite wounds may be penicillin resistant and beta-lactamase positive.

PREVENTION

- Box B1-4 provides advice for avoiding the bites and attacks of common pets.

REFERRAL

- Hospitalization and IV antibiotic therapy for infected human bites; bites with injury to joints, nerves, or tendons; or any animal bites unresponsive to oral therapy.
- Human bites with tendon involvement should go to operating room for washout.
- In the outpatient setting, bite wounds should be reevaluated within 48 hr to assess for signs of infection.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Animal and Human Bites (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

TABLE B1-5 Treatment of Mammalian Bites

Type	Wound Care	Antibiotic PR	Tetanus PR	Rabies PR	HIV PR	Hepatitis PR
Human	High-pressure irrigation of the wound with normal saline or dilute (<1%) povidone-iodine solution; débride devitalized tissue or ragged edges	Amoxicillin-clavulanate, second-generation cephalosporin with anaerobic activity, penicillin plus dicloxacillin, clindamycin plus ciprofloxacin or trimethoprim-sulfamethoxazole	Tetanus immunoglobulin (250 units IM) and tetanus toxoid (0.5 mg IM) if never had a tetanus vaccine or have not had 3 doses of tetanus toxoid; tetanus toxoid (0.5 mg IM) if >5 yr since previous tetanus booster	None	ART therapy started within the first 48-72 hr and continued for 28 days or bite source tested HIV negative; refer to the hospital for the specific drugs used in ART therapy	HBIG (0.06 ml/kg IM); HBV given at separate site from HBIG
Cat	High-pressure irrigation of the wound with normal saline or dilute (<1%) povidone-iodine solution; débride devitalized tissue or ragged edges	Amoxicillin-clavulanate, second-generation cephalosporin with anaerobic activity, penicillin plus a first-generation cephalosporin, clindamycin plus a fluoroquinolone or trimethoprim-sulfamethoxazole	Tetanus immune globulin (250 units IM) and tetanus toxoid (0.5 mg IM) if never had a tetanus vaccine or have not had 3 doses of tetanus toxoid; tetanus toxoid (0.5 mg IM) if >5 yr since previous tetanus booster	HRIG (20 IU/kg) injected IM and/or around the bite site; rabies vaccine (1 ml IM) given in the deltoid in adults and in the thigh in children, on days 0, 3, 7, 14, and 28	None	None
Dog	High-pressure irrigation of the wound with normal saline or dilute (<1%) povidone-iodine solution; débride devitalized tissue or ragged edges	Amoxicillin-clavulanate, second-generation cephalosporin with anaerobic activity, penicillin plus a first-generation cephalosporin, clindamycin plus a fluoroquinolone or trimethoprim-sulfamethoxazole	Tetanus immune globulin (250 units IM) and tetanus toxoid (0.5 mg IM) if never had a tetanus vaccine or have not had 3 doses of tetanus toxoid; tetanus toxoid (0.5 mg IM) if >5 yr since previous tetanus booster	HRIG (20 IU/kg) injected IM and/or around the bite site; rabies vaccine (1 ml IM) given in the deltoid in adults and in the thigh in children, on days 0, 3, 7, 14, and 28	None	None

ART, Antiretroviral therapy; *HBIG*, hepatitis B immune globulin; *HBV*, hepatitis B vaccine; *HIV*, human immunodeficiency virus; *HRIG*, human rabies immune globulin; *IM*, intramuscularly; *PR.*, prophylaxis.
From Adams JG et al: *Emergency medicine: clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

BOX B1-4 Advice for Avoiding the Bites and Attacks of Common Pets*

Dogs
- Do not leave a young child alone with a dog.
- Never approach or try to pet an unfamiliar dog, especially if it is tied up or confined.
- Always ask the dog's owners if you can pet the dog.
- Do not lean over a dog or pet it directly on the head.
- Do not kiss a dog.
- Avoid quick or sudden movements that may startle a dog.
- Never pet or step over a sleeping dog.
- Never try to take a bone or toy away from a dog (other than your own dog).
- Know the appearance of an angry dog: barking, growling, snarling with teeth showing, ears laid flat, legs stiff, tail up, and hair on the back standing up.
- Never step between two fighting dogs; if you need to separate them, use a bucket of water or a hose.
- Do not approach a female dog that is nursing her pups.
- Teach injury prevention advice to children from an early age.

Cats
- Be aware that some cats do not like prolonged petting.
- Know warning signs of an impending bite: twitching of the tail, restlessness, and "intention" bites (i.e., the cat moves to bite but does not bite).

Ferrets
- Do not sell or adopt a ferret that is known to bite.
- Do not push your fingers through the wires of a ferret cage.
- Reach for a ferret from the side with the palm upward rather than from above.
- Do not handle food and then handle young ferrets without washing your hands first.
- Do not poke a ferret or pull on its tail or ears.
- Never leave a ferret alone with a child or infant.
- If a ferret bites and locks on very tightly, pour cold and fast-running water over its face.

From Auerbach P: *Wilderness medicine, expert consult,* premium edition—Enhanced online features and print, Philadelphia, 2012, Elsevier.

SUGGESTED READINGS

Broder J et al.: Human bites, *Am J Med 22* 10, 2004.
Ellis R, Ellis C: Dog and cat bites, *Am Fam Physician* 90(4):239–243, 2014.

BASIC INFORMATION

DEFINITION

There are two major classes of arthropods: insects and arachnida. This chapter focuses on the class arachnida. Arachnid bites consist of bites caused by:

- Spiders
- Scorpions
- Ticks

ICD-9CM CODES

E905.1	Venomous spiders (black widow spider, brown spider, tarantula)
E905.2	Scorpion
989.5	Bites of venomous snakes, lizards, and spiders; tick paralysis
E906.4	Bite of nonvenomous arthropod; insect bite NOS

ICD-10CM CODES

T63.301A	Toxic effect of unspecified spider venom, accidental (unintentional), initial encounter
T63.2X1A	Toxic effect of venom of scorpion, accidental (unintentional), initial encounter
E906	Bite of nonvenomous arthropod; insect bite NOS

EPIDEMIOLOGY & DEMOGRAPHICS

- Spiders—ubiquitous; only three types potentially significantly harmful:
  1. Sydney funnel web spider—Australia
  2. Black widow (Fig. EB1-29)—worldwide (excluding Alaska)
  3. Brown recluse (Fig. EB1-30)—most common (South Central U.S.)
- Scorpions—various warm climates: Africa, Central South America, Middle East, India; Texas, New Mexico, California, and Nevada in the U.S.
- Ticks—woodlands

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Spiders:

- Sydney funnel web—atracotoxin toxin
  1. Piloerection, muscle spasms leading to tachycardia, hypertension, increased intracranial pressure, coma
- Black widow—females toxic
  1. Initial reaction: local swelling, redness (two fang marks) leading to local piloerection, edema, urticaria, diaphoresis, lymphangitis
  2. Pain in limb leading to rest of body (chest pain, abdominal pain), compartment syndrome
- Brown recluse
  1. Minor sting or burn.
  2. Wound may become pruritic and red with a blanched center with vesicle (Fig. EB1-31). Can necrose, especially in fatty areas (Fig. EB1-32). Leaves eschar, which sloughs and leaves ulcer; can take months to heal.
  3. Systemic symptoms: headache, fever, chills, gastrointestinal upset, hemolysis, renal tubular necrosis, disseminated intravascular coagulation possible.

Scorpions:

- Sting leading to sympathetic and parasympathetic stimulation: hypertension, bradycardia, vasoconstriction, pulmonary edema, reduced coronary blood flow, priapism, inhibition of insulin.
- Also possible: tachycardia, arrhythmia, vasodilation, bronchial relaxation, excessive salivation, vomiting, sweating, bronchoconstriction, pancreatitis.
- Clinically significant scorpion envenomation by *Centruroides sculpturatus* produces a severe neuromotor syndrome and respiratory insufficiency that often requires ICU admission.

Ticks: U.S., Europe, Asia

- Very small (<1 mm). Must be attached >36 hr to transmit disease.
- Lyme disease—most common
  1. Early: erythema migrans in 60% to 80% of cases
  2. 7 to 10 days: mild to moderate constitutional symptoms—disseminated—secondary skin lesions, fever, adenopathy, constitutional symptoms, facial palsy, peripheral neuropathy, lymphocytic meningitis, meningoencephalitis, cardiac manifestations (heart block)
  3. Late: chronic arthritis, dermatitis, neuropathy, keratitis
- Babesiosis (see "Babesiosis")
- Ehrlichiosis/anaplasmosis (see "Ehrlichosis and Anaplasmosis")

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cellulitis
- Urticaria

Other tick-borne illnesses:

- Babesiosis
- Tick-borne relapsing fever/*Borrelia miyamotoi*
- Tularemia
- Rocky Mountain spotted fever
- Ehrlichiosis/anaplasmosis
- Colorado tick fever
- Tick paralysis
- Community-acquired cutaneous methicillin-resistant *Staphylococcus aureus*

WORKUP

Physical examination: thorough skin examination may reveal fang marks, attached ticks, black eschar.

TREATMENT

ACUTE GENERAL Rx

Spiders:

- Sydney funnel web
  1. Pressure, immediate immobilization, supportive care, antivenin.
- Black widow
  1. Treatment based on severity of symptoms; bite is rarely fatal.
  2. All should receive oxygen, IV, cardiac monitor, tetanus prophylaxis.
  3. Symptomatic/supportive therapy.
  4. 10% calcium gluconate for muscle cramps (controversial).
  5. Antivenin only for more severe reactions; it carries a risk of anaphylaxis.
     1. Dose: one vial in 100 ml 0.9% saline over 20 to 30 min.
     2. Skin test before use.
     3. Give antihistamines with use.
- Brown recluse
  1. Pain management, tetanus, supportive treatment.
  2. No consensus regarding best treatment; some evidence for hyperbaric oxygen.

Scorpions:

- Fluids, supportive care, species-specific antivenin (equine based, risk of serum sickness) is controversial.
- IV administration of scorpion-specific F(ab')2 antivenin has been reported effective in resolving the clinical syndrome within 4 hours and reducing the need for concomitant sedation with midazolam and reducing the levels of circulating unbound venom.

Ticks:

- Prophylactic: tick >36 hr: single dose of doxycycline 200 mg
- Early localized disease
  1. Treatment of choice in children: amoxicillin for 14 days.
  2. Doxycycline preferred in patients with possible concurrent ehrlichiosis.
  3. Early disseminated: treatment depends on manifestation.
  4. Late disease: may require longer term or IV therapy; controversial for neurologic disease (see "Lyme Disease").

DISPOSITION

- For patients with systemic reactions, send home with emergency epinephrine kit.
- If severe or anaphylactic reaction, admit and observe for 48 hr for cardiac, renal, or neurologic problems.

REFERRAL

For patients with systemic reactions, refer to allergist for immunotherapy; 95% to 98% effective in preventing anaphylaxis.

PEARLS & CONSIDERATIONS

Actual spider bites rare, need witnessed bite, patient should bring spider if possible for confirmation. Bites usually occur in settings of unusually close contact with spider. Bedbugs becoming more prevalent, repeated exposure increases severity of reaction.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Bites and Stings, Insect (Related Key Topic)
Bites and Stings (Patient Information)

AUTHOR: **GAIL M. O'BRIEN, M.D.**

SUGGESTED READINGS

Gugliotta JL et al.: Meningoencephalitis from Borrelia miyamotoi in an Immunocompromised Patient, *N Engl J Med* 368:240–245, 2013.

Boyer LV et al.: Antivenom for critically ill children with neurotoxicity from scorpion stings, *N Engl J Med* 360:2090–2098, 2009.

Diaz JH, LeBlanc KE: Common spider bites, *Am Fam Physician* 75:869–873, 2007.

Isbister GK, Bawaskar HS: Scorpion envenomation, *N Engl J Med* 371:457–463, 2014.

FIGURE EB1-29 Black widow spider *(Latrodectus hesperus).* (Courtesy Sean Bush, MD.)

FIGURE EB1-31 Brown recluse spider bite after 24 hours, with central ischemia and rapidly advancing cellulitis. (From Ignatavicius DD, Workman LM: *Medical surgical nursing,* ed 6, Philadelphia, 2010, Elsevier, pp 147.)

FIGURE EB1-30 *Loxosceles* sp. (brown recluse spider). (Courtesy Katia C. Barbaro, Sao Paulo, Brazil.)

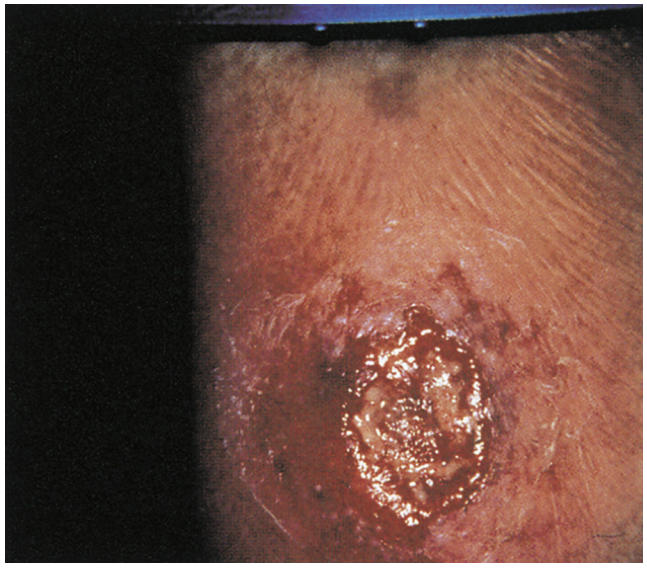

FIGURE EB1-32 Brown recluse spider bite after 48 hours of treatment. (From Hill MJ: *Skin disorders-Mosby's clinical nursing series,* St. Louis, 1994, Mosby. Courtesy Dr. William N. New, Dallas.)

BASIC INFORMATION

DEFINITION

Most stinging insects belong to the Hymenoptera order and include yellow jackets, hornets, bumblebees, sweat bees, wasps, harvester ants, fire ants, and the Africanized honey bee ("killer bee"). Wasps cause 70% of all reactions. Spiders, which are arachnids, not insects, are another cause of bites (Fig. B1-33) (see "Bites and Stings, Arachnids"). The usual effect of a sting is intense local pain, some immediate erythema, and often a small area of edema from the injecting venom. Allergic reactions can be either local or generalized, leading to anaphylactic shock. The majority of reactions occur within the first 6 hr after the sting or bite, but a delayed presentation may occur up to 24 hr.

SYNONYMS

Venom allergy

ICD-9CM Codes
989.5 Stings (bees, wasps)
989.5 Bites (fire ant, brown recluse spider)
ICD-10CM CODES
T63.444A Toxic effect of venom of bees, undetermined, initial encounter
T63.464A Toxic effect of venom of wasps, undetermined, initial encounter
T63.424A Toxic effect of venom of ants, undetermined, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE (OF BEE STINGS AND INSECT BITES)

- Unknown.
- Account for 2.3% of ED visits.
- 5%-7.5% of the population is hypersensitive, with systemic or excessive local reaction, to the venom of one or more stinging insects.
- Insect bites are the most common cause of anaphylaxis reactions.
- Most anaphylactic reactions occur during summer months in those most likely to be exposed, including children, males, outdoor workers. There are no tests to accurately predict reaction; the reaction to a prior sting is still the best predictor.
- Approximately half of fatal reactions occur without prior allergic response.
- Bites by fire ants and spiders are less likely to cause systemic disease.
- Spider bites are rare; only a few of the thousands of spider species cause a reaction in humans. Observation and collection of the spider inflicting the bite is necessary.

INCIDENCE (IN U.S.): Forty to 100 people die each year from insect sting anaphylaxis; anaphylaxis occurs most often within 10 to 30 min of a sting. Delayed reactions are rare, occurring only in <0.3% of stings.

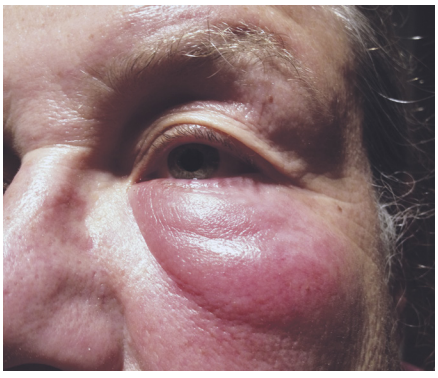

FIGURE B1-33 Spider bite to lower eyelid. (From Swartz MH: *Textbook of physical diagnosis*, ed 7, Philadelphia, 2014, Elsevier.)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Stings:

- Cutaneous: the skin is the most common site of a local allergic reaction. Manifestations include flushing, urticaria, pruritus, and angioedema. Local reactions may last several days.
- Respiratory: Symptoms of upper and lower airway obstruction including hoarseness, choking, throat tightness or tingling may progress to stridor, laryngeal edema, laryngospasm, and bronchoconstriction. This is the leading cause of anaphylactic death.
- Cardiovascular: most common reaction is hypotension which can progress to profound hypovolemic shock. Tachycardia and arrhythmia may occur. Myocardial infarction is rare. Cardiac manifestations are the second leading cause of death from anaphylaxis.
- Other symptoms: abdominal pain, nausea, vomiting, and diarrhea.

Fire ant bites:

- Initial wheal and flare response.
- Subsequent development of circularly arrayed blisters within 24 hr (Fig. B1-34).
- Blisters may develop appearance of pustules, but they are not infected.

ETIOLOGY

Stings:

- Most systemic reactions to insect stings are classic immunoglobulin E (IgE)–mediated reactions. Anaphylaxis can be the presenting sign of indolent mastocytosis.
- Reactions occur in previously sensitized patients who have produced high titers of IgE antibody to insect venom antigens.
- Sensitization to wasp venom requires only a few stings and can occur after a single sting.
- Sensitization to bee venom occurs mainly in people who have been stung frequently by bees.
- Fig. EB1-35 illustrates representative venomous hymenoptera

Bites:

- Fire ant venom contains proteins toxic to the skin.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Stings: cellulitis, bites
- Bites: stings, cellulitis

WORKUP

History is essential for accurate diagnosis including timing of sting or bite and type of insect (bee, wasp, spider, or ant) if known.

LABORATORY TESTS

- Skin test: either skin prick test or intradermal method with fire ant or hymenoptera venom.
- Venom skin tests and occasionally radioallergosorbent tests (RAST) to provide additional information, only for those with history of a systemic reaction.
- Venom-specific IgE tests are of limited use.
- Basophil activation tests and mast cell mediator testing are being developed to identify those with allergy and predict those who will have more severe reactions.

TREATMENT

ACUTE GENERAL Rx

Sting:

- Local Poison Control Center can be contacted
- Removal of the stinger most easily performed with a flat tool such as a credit card, followed by cleansing and application of ice.
- Avoid squeezing, which may push venom out of the venom sac and into the tissue.
- Oral antihistamines and nonsteroidal antiinflammatory medications and topical corticosteroids for limited reactions.
- Patients with previous reactions or multiple stings to the mouth or neck should be evaluated in an emergency department.
- Local reactions (>10 cm) may benefit from oral steroids.
- Systemic reactions should be treated with intramuscular epinephrine (no contraindication for use). Antihistamines, oxygen, IV corticosteroids, beta-agonists, pressors, and IV fluids may also be beneficial for anaphylaxis.

Bite:

- Supportive care—wash with soap and water
- Application of ice or cooling. Calamine lotion may be helpful.
- Surveillance for secondary infection

DISPOSITION

Sting:

- Prognosis for a limited reaction is excellent.
- Subsequent anaphylaxis may occur in 35% to 65% of patients stung again with history of prior systemic reaction. Large local reaction does not predict a systemic reaction.
- There is no evidence that the next sting will necessarily cause a more severe reaction. Variable outcome is due to the patient's age, comorbidities, time elapsed since prior exposure, dose of venom injected, and site of sting.
- Watch for secondary cellulitis.
- Patients who have a history of a severe allergic reaction or a systemic reaction:
  1. Should be educated to avoid stinging insects
  2. Carry syringes preloaded with epinephrine for self-administration

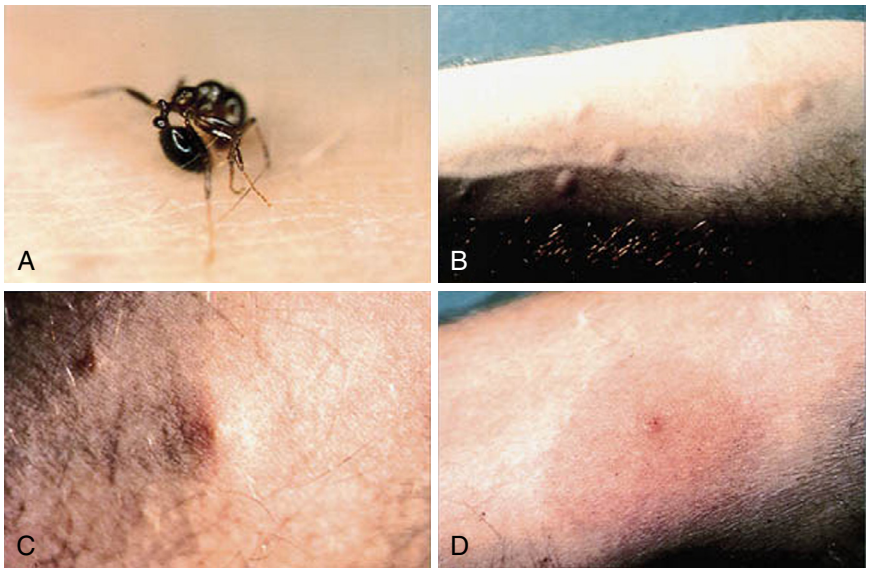

FIGURE B1-34 A, Stinging fire ant (*S. invicta*). **B,** Wheal-and-flare reactions 5 minutes after multiple fire ant stings. **C,** Sterile pustule 24 hours after fire ant sting. **D,** Cutaneous late-phase allergic reaction 24 hours after fire ant sting. Excoriated sterile pustule in center of lesion. (From Kemp SF et al: Expanding habitat of the imported fire ant (*Solenopsis invicta*): a public health concern, *J Allergy Clin Immunol* 105(4):683-691, 2000.)

3. Undergo testing for IgE antibodies to stinging insects
4. Refer to allergist for venom immunotherapy (VIT), which reduces chance of serious allergic reaction by 90%
5. Carry medical identification for stinging insect hypersensitivity

Bite:

- Prognosis for fire ant bite is excellent.
- Large lesions from brown recluse spider bites may take months to heal.
- Watch for secondary cellulitis.

REFERRAL

- Consider a referral to an allergist for venom immunotherapy (VIT).
- Risk of subsequent anaphylaxis with immunotherapy falls to <3%.
- VIT for 3 to 5 yr induces long-term protection in most patients.

PEARLS & CONSIDERATIONS

Hypersensitivity to stings is common. Reactions range from local nonallergic reaction to venom to life-threatening anaphylaxis. Venom-specific immunotherapy is highly effective in decreasing subsequent anaphylaxis. Although venom immunotherapy is currently indicated only for systemic reactions, investigation is under way to assess efficacy for prevention of large local reactions, which can result in significant morbidity.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Bites and Stings, Arachnids (Related Key Topic)
Bites and Stings (Patient Information)

AUTHOR: **LYNN BOWLBY, M.D.**

SUGGESTED READINGS

Antolin-Amerigo D, et al.: Venom immunotherapy: an updated review, *Curr Allergy Asthma Rep* 14(7):449, 2014.

Bilo B: Epidemiology of insect-venom anaphylaxis, *Curr Opin Allergy Clin Immunol* 8:330–337, 2008.

Casale TB, Wesley Burks A: Hymenoptera-sting hypersensitivity, *N Engl J Med* 370:1432–1439, 2014.

Freeman TM: Hypersensitivity to hymenoptera stings, *N Engl J Med* 351(19):1978, 2004.

Golden D, et al.: Stinging insect hypersensitivity: a practice parameter update 2011, *J Allergy Clin Immunol* 127(4):854e1–854e23, 2011.

Graft D: Insect sting allergy, *Med Clin North Am* 1(90):211, 2006.

Weinstein SA, et al.: Envenomations: an overview of clinical toxicology for the primary care physician, *Am Fam Physician* 80(8):793–802, 2009.

Clin Cosmet Investig Dermatol 4:191–196, 2011.

Venom Immunotherapy for preventing allergic reactions to insect stings, *Cochran Database Systemic Review*, 17 October 2012.

Worm M, et al.: Triggers and treatment of anaphylaxis: an analysis of 4,000 cases from Germany, Austria, and Switzerland, *Dtsch Arztebl Int* 111(21):367–375, 2014.

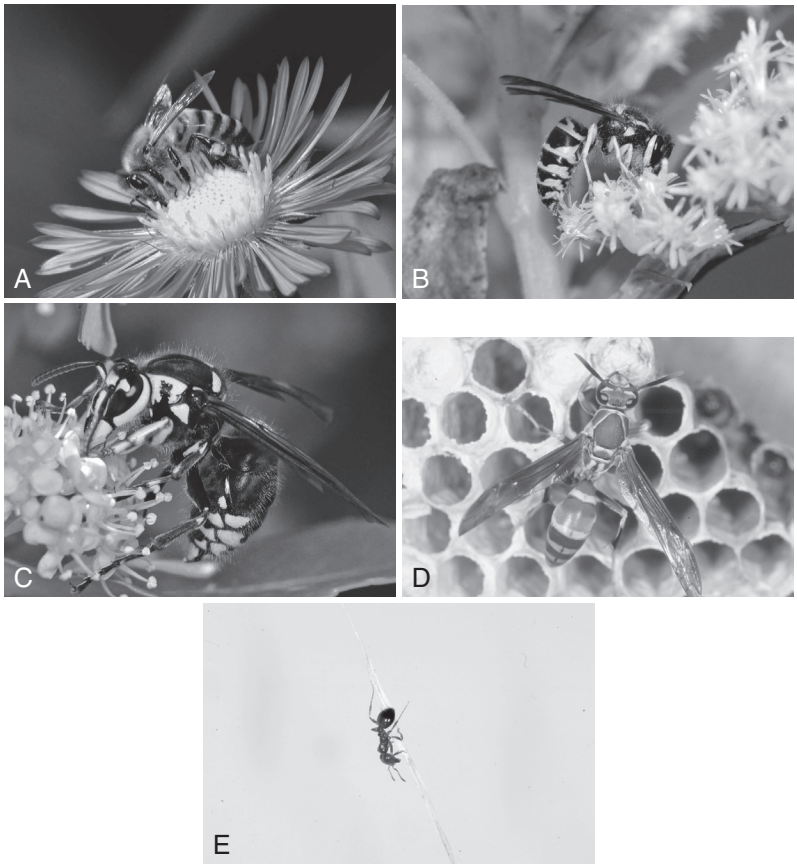

FIGURE EB1-35 Stinging insects of the order Hymenoptera: A, Honeybee (*Apis mellifera*). **B,** Yellow jacket (*Vespula maculifrons*). **C,** White-faced hornet (*Dolichorespula maculata*). **D,** Paper wasp (*Polistes exclamans*). **E,** Imported fire ant (*Solenopsis invicta*). (Reproduced by permission of ALK-Abelló A/S, Hørsholm, Denmark.)

BASIC INFORMATION

DEFINITION

Injury resulting from snake biting a human.

ICD-9CM CODES

989.5 Venomous poisoning

ICD-10CM CODES

T63.001A Toxic effect of unspecified snake venom, accidental (unintentional), initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

- 45,000 snakebites occur annually in the U.S. Of the 5000 to 7000 caused by poisonous snakes, approximately 5 to 12 result in fatality (i.e., <1%-2%). Children, the elderly, and those in whom treatment has been delayed are at highest risk.
- In the U.S., at least one species of poisonous snake (Fig. B1-36) has been identified in every state except Alaska, Hawaii, and Maine. Table B1-6 summarizes medically important snake families. The Crotalidae family, which includes rattlesnakes, copperheads, and cottonmouths, is responsible for the vast majority of venomous snakebites. The Elapidae family includes the mambas and cobras internationally, but in the U.S. includes only the coral snake. Coral snakes are not only much less common in the U.S. than crotalids, but they also tend to be less aggressive and account for only 1% of venomous snakebites in the U.S.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

In addition to local tissue injury, envenomation may affect the renal, neurologic, gastrointestinal, vascular, and coagulation systems. Symptoms vary widely depending on type of envenomation. Not all snakebites are poisonous, and not all bites lead to envenomation. Species-specific signs and symptoms following envenomation are discussed.

CROTALIDAE (PIT VIPERS): Local signs and symptoms

- Pain within 5 min
- Edema within 30 min
- Erythema of site and adjacent tissues/serous or hemorrhagic bullae, ecchymosis, and/or lymphangitis over the ensuing hours (Fig. B1-37)

If no edema or erythema is manifested within 8 hr after a confirmed crotalid snakebite, it is safe to assume envenomation did not occur. (Roughly 25% of cases do not involve envenomation.) In general, rattlesnake bites are more severe than those of the other snakes in the Crotalidae family.

Systemic manifestations may include:

- Mild to moderate nausea/vomiting, perioral paresthesias, metallic taste, tingling of fingers or toes (especially with rattlesnake bites), and/or fasciculations (local or generalized)
- Severe hypotension (due to increased vascular permeability), mental status change, respiratory distress, tachycardia, acute renal failure, rhabdomyolysis, and coagulopathies including intravascular hemolysis and disseminated intravascular coagulation

ELAPIDAE (CORAL SNAKES): Signs and symptoms:

- Local symptoms are far less pronounced (little or no pain/swelling immediately after the bite).
- Neurologic symptoms are more common due to neurotoxins in *elapid* venom.
- Systemic symptoms predominate, but onset may be delayed for up to 12 hr. Examples include:
  1. Altered mental status and cranial nerve palsies featuring ptosis, dysphagia, or dysarthria
  2. Tremors

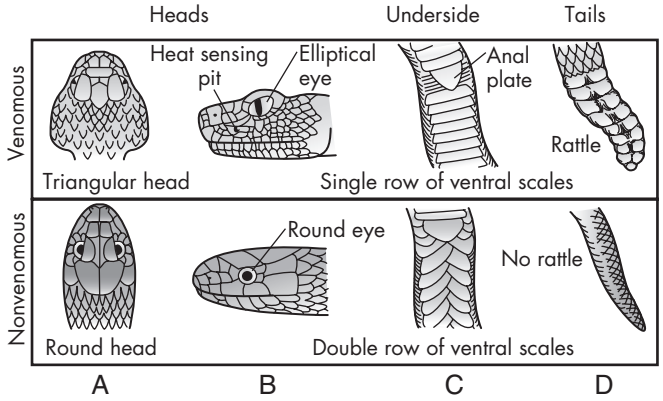

FIGURE B1-36 Comparison of pit vipers and nonvenomous snakes. Rattle in **D** *(top)* applies to rattlesnakes only. (**A** to **D**, From Sullivan JB et al: North American venomous reptile bites. In Auerbach PS [ed]: *Wilderness medicine: management of wilderness and environmental emergencies,* ed 3, p. 684, St Louis, 1995, Mosby.)

TABLE B1-6 Medically Important Snake Families

Family	Venomous?	Location	Examples	Toxin Effects/Other Comments
Colubridae	Some species	Most parts of the world	Garter snakes (*Thamnophis* spp), king snakes and milk snakes (*Lampropeltis* spp)	Largest family of snakes; most are considered harmless to humans; a few species are dangerously toxic (e.g., African boomslang [*Dispholidus typus*])
Boidae	None	Most parts of the world	*Boa* sp, *Python* sp	Constrictors; unsupervised children should not be allowed access to large constrictors
Viperidae				
Subfamily Crotalinae (pit vipers)	All	Americas, Asia	Rattlesnakes (*Crotalus* spp), cottonmouths and copperheads (*Agkistrodon* spp), Lancehead pit vipers (*Bothrops* spp)	Heat-sensing "pit" between each eye and nostril
Subfamily Viperinae (true vipers)	All	Europe, Africa, Middle East, Asia	Puff adder (*Bitis arietans*), Gaboon viper (*Bitis gabonica*)	No heat-sensing pits
Elapidae	All	Americas, Africa, Middle East, Asia	Cobras (*Naja* spp), mambas (*Dendroaspis* spp), kraits (*Bungarus* spp), coral snakes (*Micrurus* spp), and the venomous snakes of Australia	Highly variable venom effects—some largely neurotoxic, others causing severe local tissue damage
Hydrophiidae	All	Warm waters of the Pacific Ocean, Indian Ocean, and Oceania (none in the Atlantic Ocean)	Sea snakes including the pelagic sea snake (*Pelamis platurus*)	Neurotoxins and myotoxins; rarely bite humans unless provoked

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

3. Intense salivation, nausea, vomiting, or abdominal pain
4. Loss of DTRs and respiratory depression (late manifestations)

ETIOLOGY

- Farm workers and other people working or doing recreational activities in the outdoors are the most common victims of snake bites, because they are in the snakes' natural habitat.
- Intoxication and intentional provocation also contribute to many of the cases of snake bites in the U.S.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Harmless snakebite
- Scorpion bite
- "Dry bite"
- Insect bite
- Cellulitis
- Laceration or puncture wound
- Necrotizing fasciitis

NOTE: Harmless snakebites are usually characterized by four rows of small scratches (teeth in upper jaw) separated from two rows of scratches (teeth in lower jaw). This is in distinction to venomous snakebites, which should have paired puncture wounds produced by the snake's fangs, whether other teeth marks are noted. A "dry bite" is a bite with puncture wounds but no evidence of swelling, erythema, or lab abnormalities.

WORKUP

An estimated 25% of venomous snakebites do not result in envenomation, but all cases of suspected envenomation should be observed for 8 hr or longer:

FIGURE B1-37 Southern Pacific rattlesnake *(Crotalus helleri)* bite wounds. (Courtesy Sean Bush, M.D.)

- Check for signs of envenomation.
  1. Swelling, tenderness, redness, ecchymosis, or blebs at the bite site
  2. Elevated protime, decreased fibrinogen or platelets
  3. Systemic signs such as hypotension, bleeding complications, vomiting, diarrhea, angioedema, or neurotoxicity
- Determine if patient has indications for antivenom (Table B1-7). Continual reassessment is indicated throughout the observation period because severity of symptoms may change.

LABORATORY TESTS

- For all suspected envenomations, obtain CBC (with peripheral smear and platelet count), DIC screen (PT/INR, PTT, fibrinogen, fibrin degradation products, d-dimer), ECG, serum electrolytes, BUN, Cr, and urinalysis. Serial measurements of hemoglobin, platelets, protime, and fibrinogen are needed to monitor for acute and delayed hematologic complications.
- For more severe bites, consider LFTs, sedimentation rate, creatine kinase (rule out rhabdomyolysis), ABG, and type and crossmatch.
- Other: consider chest radiograph in cases with severe envenomation or in patients over 40 years old with underlying cardiopulmonary disease; radiograph of bite site for retained fangs (poor sensitivity); head CT if concern is raised for intracranial hemorrhage

Rx TREATMENT

ACUTE GENERAL Rx

IN THE FIELD: For a suspected snakebite:

- Transport immediately to nearest medical facility. No treatments in the field should delay travel to the nearest facility where an antivenom agent can be given if necessary.
- Immobilize affected part.
- Remove any constricting items. Applying tourniquets, incising, and applying suction to the wound is discouraged. Tourniquets cause more local tissue damage due to tissue necrosing venom seen in crotalid bites and should not delay transport to a medical facility.
- Do not apply ice; keep victim warm.
- Avoid alcohol, stimulants (caffeine), or agents that can suppress mental status.

IN THE HOSPITAL:

- Record vital signs: BP, HR, T, RR, and O_2 sat.
- Establish intravenous access and initiate IV hydration with crystalloid if the patient is hypotensive.
- Obtain time of bite and description of snake if possible. Crotalids have a triangle-shaped head, nostril holes (pits), and elliptical pupils. The most dangerous of the crotalids is the rattlesnake, distinguished by its telltale rattle. Elapids, like the western and eastern coral snakes of the U.S., have brightly colored red, black, and yellow stripes.
- Obtain and initiate reconstitution of appropriate antivenom. (Antivenoms are typically supplied in powder form and must be reconstituted before administration. If using older antivenoms, this process can take up to 1 hr, so it is recommended that it be initiated as soon as the patient arrives in the ED.)
  1. Inspect site of bite for fang marks and local symptoms.
  2. Delineate margins of erythema/edema with a marker.
  3. Measure circumference of bitten part at two or more proximal sites and compare with unaffected limb; repeat every 15 to 20 min; assess for extension of erythema/edema.
  4. Conduct a complete neurologic examination.
  5. Obtain past medical history; ask about allergies to horse serum in those previously treated for snakebite.
- If no signs of envenomation:
  1. Clean and immobilize affected part.
  2. Immunize against tetanus.
  3. For crotalid bites, observe patient for at least 8 hr. If, at the end of this interval, local and systemic sequelae are absent and lab values remain normal, the likelihood of significant envenomation is low, and the patient can be discharged from the acute setting. Some sources recommend observing patients with crotalid bites to the lower extremities for at least 24 hours because swelling in the larger compartments of the legs could be slower and less easily recognizable. All definitive elapid bites should be treated. If elapid bite is only suspected, the patient must be monitored for up to 18 hr as symptoms can be delayed.
- Patients who have progressive local symptoms or any systemic symptoms should be considered for antivenom. Crotalid envenomations without any progressive local or any systemic symptoms can be monitored for 12 to 24 hours, with repeat labs obtained 4 to 6 hours before discharge. If they have no new symptoms during that period of observation, they may be safely discharged. Specifically, copperhead bites often need no further interventions.
- Contact Poison Control: 1-800-222-1222; they can provide guidance and track snake bite incidence.

Once the decision is made to use antivenom:

- Prepare epinephrine 0.5 to 1.0 mg (0.5 to 1 ml of a 1:1000 solution) to be administered subcutaneously (SQ) in case of a hypersensitivity reaction to the antivenom. The incidence of hypersensitivity reaction with sheep-based antivenom, now standard for crotalid envenomations, is estimated to be

TABLE B1-7 Indications for Snake Antivenom Administration

Evidence of systemic toxicity:	
Hemodynamic or respiratory instability	Hypotension, respiratory distress
Hemotoxicity	Clinically significant bleeding or abnormal coagulation studies
Neurotoxicity	Any evidence of toxicity: usually beginning with cranial nerve abnormalities and progressing to descending paralysis including the diaphragm
Evidence of local toxicity	*Progressive* soft tissue swelling

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

less than 1 in 7. This is much lower than that with horse serum antivenom previously used for crotalid and currently the standard for elapid envenomations. Empiric prophylactic antihistamines or epinephrine have not been proved to prevent reactions.

ANTIVENOM TREATMENT OF CROTALID (RATTLESNAKE, PIT VIPER, COPPERHEAD, COTTONMOUTH) ENVENOMATIONS

- For patients with mild to moderate symptoms:
  1. An initial IV loading dose of 4 to 6 vials (depending on the size and age of the patient and the severity of the bite) is infused over 60 min. The infusion should be given very slowly for the first 10 min to watch for allergic reaction. For patients with shock or serious active bleeding, use an initial dose of 8 to 12 vials.
  2. If the patient has not responded after 1 hr, repeat the initial dose.
- Relapse is seen in up to two thirds of patients after an initial response. Consequently, it is recommended that three maintenance doses—each consisting of 2 vials—be given at 6, 12, and 18 hr following the patient's initial response to the loading dose.
- The manufacturer of CroFab maintains a 24/7 hotline: 877-377-3784
- Antivenin Crotalidae polyvalent horse serum is no longer produced but may still be available at some pharmacies. It should be given as follows:
  1. Progressive local or any systemic symptoms: 5 to 10 vials
  2. Severe symptoms: 15 vials
  3. Shock: 20 vials

ANTIVENOM TREATMENT OF ELAPID (CORAL SNAKE) ENVENOMATIONS

- Production of horse serum–based coral snake antivenom was discontinued in 2006 (horse serum–based antivenoms are being phased out due to much higher risk of hypersensitivity). All stock is expired as of October 31, 2008, except for lot 4030026, which received a 3-yr extension until October 31, 2013, and there has been no update at the time of this submission. After that date, one option will be to seek compassionate release of expired stock in conjunction with your local Poison Control Center. A potent, safe, sheep-based antivenom for elapid bites exists and is being used internationally but is not yet approved in the U.S. Another option is to contact a zoo that cares for exotic snakes and obtain Mexican coral snake or Australian Tiger snake antivenom, although efficacy for North American coral snake envenomation is unproved.
- For confirmed coral snake bites, antivenom should be administered immediately if available.
- If there are no systemic symptoms at the time of administration, start with 3 vials. If symptoms progress, repeat with 5 vials.
- If systemic symptoms are already present, an initial dose of 6 to 10 vials is recommended.

TREATMENT OF NONNATIVE (EXOTIC) SNAKEBITES

- For bites by exotic or nonnative snakes, contact a Poison Control Center or your local zoo. (Zoos with exotic snakes are required to maintain a supply of snake-specific antivenom on their premises.)

DISPOSITION

Prognosis is good with prompt evaluation and treatment. All patients who receive antivenom should be monitored in an ICU setting. Patients should be monitored for 18 to 24 hours after initial control of progression of symptoms. If at that time they have no progression of symptoms and labs prior to discharge are normal, patients can be safely discharged home. Give instructions to return for worsening nondependent swelling, abnormal bleeding, or signs of serum sickness and to follow bleeding precautions (no contact sports, elective surgery, etc.) for 2 weeks. Patients who received antivenom need follow-up in 2 to 3 days and in 5 to 7 days to evaluate for delayed hematologic complications and serum sickness.

REFERRAL

Refer to a medical facility with ICU for administration of antivenom. The approach to snakebites should be multidisciplinary and should include medical toxicology or other physician snakebite specialist, as well as hematology or nephrology consultations if needed. All cases of snake bites should also be reported to Poison Control and the local health department as data are limited.

PEARLS & CONSIDERATIONS

OTHER CONSIDERATIONS

- Dosage of antivenom is based on typical envenomation rather than age or weight, so dose is the same for children and adults.
- Pregnancy is not a contraindication to antivenom. The rate of miscarriage is significantly lower in pregnant patients treated with antivenom.
- Immunize against tetanus if no booster within past 5 yr; if never immunized, give immunoglobulin as well as toxoid.
- Manage pain as needed (narcotic preferred to NSAIDs due to theoretical bleeding complications).
- Avoid sedation in Mojave rattlesnake, Eastern diamondback rattlesnake, and coral snake bites as all can have more systemic and neurologic than local effects.
- Antibiotics rarely needed; reserve for moderate to severe contamination or definite infection; broad-spectrum coverage to include gram negatives preferred (i.e., ampicillin-sulbactam or quinolone derivatives).
- Antivenom is most effective when given within 4 hr of the bite and least effective if delayed beyond 12 hr. Systemic symptoms (coagulopathy, CNS effects, etc.) respond better to treatment than do local symptoms (erythema/edema, bullae, etc.).
- Although local wound effects can be severe, wound management should not take precedence over antivenom administration. Some studies suggest that even in the case of compartment syndrome, antivenom may be more effective than fasciotomy, although both may be necessary.

COMPLICATIONS

- Allergic reactions were very frequent with horse serum antivenoms. CroFab from sheep serum should be preferentially used over equine serum if available.
- Anaphylaxis occurs within 30 min and should be treated by immediately stopping the infusion to managing the symptoms of anaphylaxis, including epinephrine SQ or IM initially and IV if needed, diphenhydramine IV, and hydrocortisone IV. If the anaphylactic symptoms can be managed and the envenomation is severe, the infusion can then be resumed.
- Delayed hematologic complications are common and can manifest up to 4 days post treatment. Most bleeding is self-limited but can rarely be severe, necessitating close follow-up.
- Serum sickness occurs 7 to 14 days after antivenom administration and is characterized by fever, rash, arthralgias, and lymphadenopathy. It can be treated with prednisone 60 mg/d PO, tapered over 7 to 10 days.
- Injuries also result from:
  1. Tourniquet placement on the field, which should be avoided
  2. Ice application (cryotherapy), which can worsen tissue damage
- National Poison Control hotline: 800-222-1222

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Snake Bites (Patient Information)

AUTHORS: **ROBERT BUTLER, M.D.** and **NEHA P. RAUKAR, M.D., M.S.**

SUGGESTED READINGS

Dart RC: Efficacy, safety and use of snake antivenoms in the United States, *Ann Emerg Med* 37:181–188, 2001.

Gold BS et al.: Bites of venomous snakes, *N Engl J Med* 347:347, 2002.

Juckett G, Honcox JG: Venomous snakebites in the United States: management review and update, *Am Fam Physician* 65:1367, 2002.

LoVecchio F et al.: Antibiotics after rattlesnake envenomation, *J Emerg Med* 23:327–328, 2002.

Lovonas E et al.: Unified treatment algorithm for the management of crotaline snakebite in the United States: results of an evidence-informed consensus workshop, *BMC Emergency Medicine* 11:2, 2011.

The Medical Letter: a new snake antivenom, *Med Lett Drugs Ther* 43:55, 2001.

Offerman SR et al.: Crotaline Fab antivenom for the treatment of children with rattlesnake envenomation, *Pediatrics* 110:968–971, 2002.

Quan D: North American poisonous bites and stings, *Crit Care Clin* 28(4):633–659, 2012.

Ries NL, Dart RC: New developments in antidotes, *Med Clin North Am* 89(6):1379, 2005.

Seifert SA et al.: Recurrent, persistent, or late, new-onset hematologic abnormalities in crotaline snakebite, *Clin Toxicol* 49(4):324–329, 2011.

Warrell DA: Snake bite, *Lancet* 375:77–88, 2010.

Weinstein SA et al.: Envenomations: an overview of clinical toxicology for the primary care physician, *Am Fam Physician* 80(8):793–802, 2009.

BASIC INFORMATION

DEFINITION

Bladder cancer is a heterogeneous spectrum of neoplasms ranging from non–life-threatening, low-grade, superficial papillary lesions to high-grade invasive tumors, which often have metastasized at the time of presentation. It is a field change disease in which the entire urothelium from the renal pelvis to the urethra may be susceptible to malignant transformation. The three types of bladder cancer are transitional cell carcinoma (TCCa), squamous cell carcinoma, and adenocarcinoma.

ICD-9CM Codes

Primary:	188.9
Secondary:	198.1
CIS:	233.7
Benign:	223.3
Uncertain behavior:	236.7
Unspecified:	239.4

ICD-10CM CODES

C67.9	Malignant neoplasm of bladder, unspecified
C79.11	Secondary malignant neoplasm of bladder
D09.0	Carcinoma in situ of bladder
D30.3	Benign neoplasm of bladder
D41.4	Neoplasm of uncertain behavior of bladder
D49.4	Neoplasm of unspecified behavior of bladder

EPIDEMIOLOGY & DEMOGRAPHICS

Each year over 70,000 new cases are diagnosed and more than 14,000 deaths are attributed to bladder cancer. Overall, bladder cancer is the sixth most prevalent malignancy in the U.S. and the seventh leading cause of solid-cancer–related death.

Until 1990, the incidence of bladder cancer in the U.S. was rising. Since 1990, the incidence of bladder cancer is decreasing at a rate of 0.8% per year (1.2% among men and 0.4% among women).

PREDOMINANT SEX: In males, it is the fourth most common cancer, accounting for 10% of all cancers. In females, it is the eighth most common cancer, accounting for 4% of all cancers.

RISK: The lifetime risk of developing bladder cancer is 2.8% in white males, 0.9% in black males, 1% in white females, and 0.6% in black females.

Smoking:

- Users of "black" tobacco in place of "blond" tobacco have a twofold to threefold increase in developing bladder cancer.
- Smoking risk is based on consumption:
  1. A twofold to threefold increase for subjects smoking at least 10 cigarettes per day
  2. The risk increases again when the daily consumption rises above 40 to 60 cigarettes per day
- Smokers of low-tar and nicotine cigarettes have a lower risk when compared with higher tar and nicotine cigarettes.
- Those who smoke unfiltered cigarettes have a 50% increased risk of bladder cancer compared with those who smoke filtered cigarettes.
- Pipe smokers have a lower risk of bladder cancer compared with cigarette smokers.
- Cigars, snuff, and chewing tobacco, although implicated in nonurologic cancers, are not believed to influence bladder cancer risk.

Diet:

- Diets rich in beef, pork, and animal fat increase risk of bladder cancer.
- There is no indication that consumption of non-beer alcoholic drinks contributes to bladder cancer development.
- Beer consumption has been linked to bladder cancer development as a result of the presence of nitrosamines in the beer. Nitrosamines have also been implicated in the development of rectal cancer.
- Drinking coffee is not believed to contribute to bladder cancer risk. There is additional evidence that coffee consumption is protective for colorectal cancers, possibly by diminishing fecal transit time.

Medications: Long-term (>1 yr) use of pioglitazone and rosiglitazone

PEAK INCIDENCE: Incidence increases with age: higher after age 60 yr, uncommon younger than 40 yr.

GENETICS: It is thought to be multifactorial in etiology, involving both genetic and environmental interactions. Overall, approximately 20% to 25% of the male population in the U.S. with bladder cancer is estimated to have the disease as a result of occupational exposure.

DISTRIBUTION: In North America, transitional cell carcinomas comprise 93%, squamous cell carcinomas comprise 6%, and adenocarcinomas account for 1% of bladder cancers.

PATHOGENESIS: Two pathways exist for bladder cancer (TCCa):

1. Papillary superficial disease occasionally leading to invasive cancer (75%)
2. Carcinoma in situ (CIS) and solid invasive cancer with high risk of disease progression (25%)

Two distinct forms of "superficial cancer" exist:

1. T_a: Papillary low-grade tumor with a high rate of recurrence; disease progression occurs in 5%.
2. T_1: Higher grade papillary tumor that infiltrates the lamina propria; often associated with flat CIS that may involve the urothelium diffusely. Disease progression occurs in 30% to 50%.

Subdivided into:

- T_{1a}: Penetration of tumor up to the muscularis mucosa; disease progression in 5.3%
- T_{1b}: Penetration of tumor through the muscularis mucosa; disease progression 53%

Flat CIS:

- Entirely different and separate pathway of cancer development whose mechanism is manifested by dysplasia, which leads to the occurrence of poorly differentiated malignant cells that replace or undermine the normal urothelium and extend along the plane of the bladder wall. It penetrates the basement membrane and lamina propria in 20% to 30% of cases and is associated with the development of solid tumor growth. A defect in chromosome 17p53 occurs in 50% of the cases.

At presentation, 72% of cancers are localized to the bladder, 20% of the cancers extend to the regional lymph nodes, and 3% present with distant metastases. Eighty percent of superficial TCCa recur, with up to 30% progressing to a higher stage or grade. Younger patients most commonly develop low-grade papillary noninvasive TCCa and are less likely to have recurrences when compared with older patients with similar lesions. Involvement of the upper tracts with tumor occurs in 25% to 50% of the cases.

STAGING (BASED ON THE TNM SYSTEM):

T_0	No tumor in specimen
T_{is}	CIS
T_a	Papillary TCCa noninvasive
T_1	Papillary TCCa into lamina propria
T_2	TCCa invasive of superficial muscle
T_{3a}	Invasive of deep muscle
T_{3b}	Invasive of perivesical fat
T_{4a}	Invasive of adjacent pelvic organ
T_{4b}	Invasive of pelvic wall with fixation
Invasive of nodal status	
N_0	No nodal involvement
N_{1-3}	Pelvic nodes
N_4	Nodes above bifurcation
N_x	Unknown
Invasive of metastatic status	
M_0	No distant metastases
M_1	Distant metastases
M_x	Unknown

MOLECULAR EPIDEMIOLOGY:

TCCa is usually a field change disease with tumors arising at different times and sites in the urothelium, suggesting a polyclonal etiology of bladder cancer. Bladder cancers have been associated with abnormalities on chromosomes 1, 4, 11, 5, 7, 3, 9, 21, 18, 13, 8; with alterations in suppressor genes *P53,* retinoblastoma gene, and *P16;* and with alterations in oncogenes H-ras and epidermal growth factor receptor.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Gross, painless hematuria
- Microhematuria
- Frequency, urgency, occasional dysuria
- With locally invasive to distant metastatic disease, the presentation can include:
  1. Abdominal pain
  2. Flank pain
  3. Lymphedema
  4. Renal failure
  5. Anorexia
  6. Bone pain

ETIOLOGY

Bladder cancer is a potentially preventable disease associated with specific etiologic factors:

- Cigarette smoking is associated with 25% to 65% of cases. The risk of developing a TCCa is two to four times higher in smokers

than in nonsmokers, and that risk persists for many years, being equal to nonsmokers only after 12 to 15 yr of smoking abstinence. Smoking tobacco is associated with tumors that are characterized by higher histologic grade, increased tumor stage, increase in the numbers of tumor present, and increased tumor size.
- Occupational exposures: dye workers, textile workers, tire and rubber workers, petroleum workers.
- Chemical exposure: O-toluidine, 2-naphthylamine, benzidine, 4-amino-biphenyl, and nitrosamines.
- Exposure to herpes papilloma virus type 16.

Squamous carcinomas are associated with:
- Schistosomiasis
- Urinary calculi
- Indwelling catheters
- Bladder diverticula

Miscellaneous causes:
- Phenacetin abuse
- Cyclophosphamide
- Pelvic irradiation
- Tuberculosis

Adenocarcinomas are associated with:
- Exstrophy
- Endometriosis
- Neurogenic bladder
- Urachal abnormalities
- As a secondary site for distant metastases from other organs (e.g., colon cancer)

Dx DIAGNOSIS

- History and physical examination.
- Urinalysis.
- Cystoscopy with bladder barbotage and biopsy. Fluorescence cystoscopy offers improvement in the detection of flat neoplastic lesions such as carcinoma in situ.
- Transurethral resection of bladder tumor(s).
- There is insufficient evidence to determine whether a decrease in mortality rate from bladder cancer occurs with hematuria testing, urinary cytology, or a variety of other tests on exfoliated urinary cells or other substances.
- In addition to urinary cytology and bladder barbotage, BTA, NMP22, and fibrin degradation products have been approved by the FDA as bladder cancer tumor markers. No marker has general, widespread acceptance because the results are affected by the presence of stents, recent urologic manipulation, stones, infection, bowel interposition, and prostatitis, creating false-positive results.

DIFFERENTIAL DIAGNOSIS

- Urinary tract infection
- Frequency-urgency syndrome
- Interstitial cystitis
- Stone disease
- Endometriosis
- Neurogenic bladder

LABORATORY TESTS

- Urine cytology.
- Urine telomerase: telomerase activity in voided urine or bladder washings determined by the telomeric repeat amplification protocol (TRAP) assay. This test has been reported to accurately detect the presence of bladder tumors in men. It represents a potentially useful noninvasive diagnostic innovation for bladder cancer detection in high-risk groups such as habitual smokers or in symptomatic patients.

RADIOLOGIC TESTS

- IVP, renal ultrasound, retrograde pyelography, CT scan, and MRI.
- One or a combination of studies can be used. In the absence of skeletal symptoms, bone scan is not recommended.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Initially, transurethral resection of bladder tumor (TURBT) (Fig. B1-38)
- Loop biopsy of the prostatic urethra if high-grade TCCa is suspected

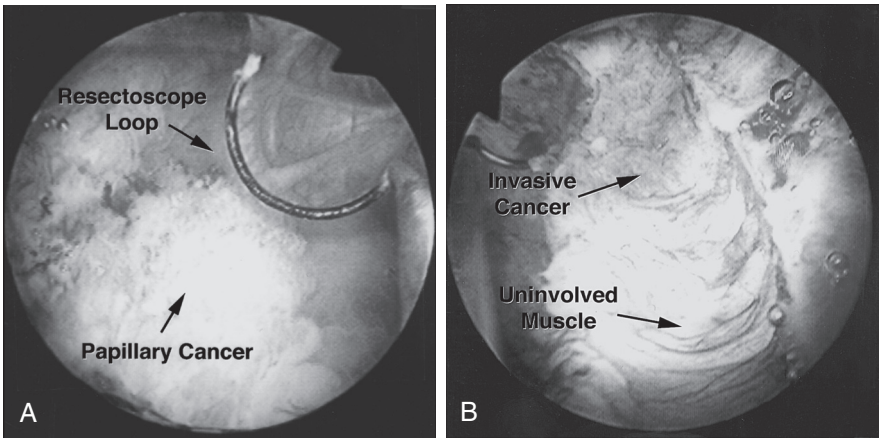

FIGURE B1-38 A, Papillary bladder cancer in right lower aspect of photo with resection loop poised to begin transurethral resection. **B,** Demonstration of grossly uninvolved muscularis propria *(bottom)* and cancer grossly invading the bladder wall *(top).* (From Abeloff MD: *Clinical oncology*, ed 3, Philadelphia, 2004, Churchill Livingstone.)

- If superficial disease, follow-up protocol with repeat TURBT and/or the use of intravesical agents is recommended
- For advanced bladder cancer, radical cystectomy with urethrectomy (unless orthotopic diversion is planned), and either ileal loop conduit or orthotopic diversion

BLADDER PRESERVATION APPROACHES: After cystectomy for muscle-invasive disease, 50% or more of the patients will develop metastases. Most patients develop metastases at distant sites; a third relapse locally. Bladder preservation management is offered in individuals who refuse surgery or who might not be suitable radical cystectomy patients. Bladder-sparing protocols include extensive TURBT or partial cystectomy with external-beam or interstitial radiotherapy and systemic chemotherapy. Radiotherapy as a single treatment modality is not effective. The best predictor of successful bladder preservation is a complete response after the combination of initial TURBT and two cycles of CMV (cisplatin, methotrexate, vinblastine) chemotherapy used with stages T_2 to T_{3a}.

INDICATIONS FOR PARTIAL CYSTECTOMY:
- Tumor within a bladder diverticulum
- Solitary, primary, and muscle-invasive or high-grade lesion of a region of the bladder that allows complete excision with adequate surgical margins
- Inability to adequately resect tumor by TURBT alone because of size or location
- Tumor overlying a ureteral orifice requiring ureteral reimplantation
- Biopsy of a radiation-induced ulceration
- Palliation of severe local symptoms
- Patient refusal of urinary diversion
- Poor-risk patient who is not a diversion candidate

CONTRAINDICATIONS:
- Multiple tumors
- CIS
- Cellular atypia on biopsy
- Prostatic invasion
- Invasion of the trigone
- Inability to achieve adequate surgical margins
- Prior radiotherapy
- Inability to maintain adequate bladder volume after resection
- Evidence of extravesical tumor extension
- Poor surgical risk

ACUTE GENERAL Rx

INDICATIONS FOR INTRAVESICAL CHEMOTHERAPY:
- High-grade tumor
- Tumor size >5 cm
- Tumor multiplicity
- Presence of CIS
- Positive urinary cytologic findings after a resection
- Incomplete tumor resection

Intravesical agents: thiotepa, Adriamycin, mitomycin C, AD-32, BCG, interferon, bropirimine, Epodyl, interleukin-2, and keyhole-limpet hemocyanin. Photodynamic therapy with hematoporphyrin derivatives has also been used.

INDICATIONS FOR CYSTECTOMY:
- Large tumors not amenable to complete TURBT
- High-grade tumor
- Multiple tumors with frequent recurrences
- Diffuse CIS not responsive to intravesical chemotherapy
- Prostatic urethra involvement
- Irritative bladder symptoms with upper tract deterioration
- Muscle-invasive disease
- Disease outside the bladder

SYSTEMIC CHEMOTHERAPY: Used as neoadjuvant and adjuvant therapy for systemic disease. The most effective agents are cisplatin, methotrexate, vinblastine, Adriamycin (MVAC). Other agents include mitoxantrone, vincristine, etoposide (VP16), 5-fluorouracil, ifosfamide, Taxol, gemcitabine, Piritrexim, mitomycin C, and gallium nitrate. Chemotherapy in combination can provide palliation and modest survival benefit.

RADIOTHERAPY: Conflicting reports suggest that superficial bladder cancer is more sensitive to radiotherapy. Squamous changes within the tumor and secretion of human chorionic gonadotropin by the lesion are associated with poor response to radiotherapy. Only 20% to 30% of patients with invasive bladder cancer can be cured by external-beam radiation therapy alone. It is used in combination with surgery or with systemic agents to treat bladder cancer primarily in patients who are not surgical candidates or who refuse surgery. Trials with synchronous chemotherapy with fluorouracil and mitomycin C combined with radiotherapy have shown significant improved locoregional control of bladder cancer, as compared with radiotherapy alone in patients with muscle-invasive bladder cancer.

CHRONIC Rx

FOLLOW-UP RECOMMENDATIONS FOR SUPERFICIAL BLADDER CANCER:
- Cystoscopy, bladder barbotage, and bimanual examination every 3 mo for 2 yr, then every 6 mo for 2 yr, and annually thereafter.
- Upper tract studies are based on the risk of upper tract tumor development, generally every 2 to 5 yr.

FOLLOW-UP RECOMMENDATIONS FOR ADVANCED DISEASE: Bladder preservation:
- Cystoscopy, barbotage, bimanual examination, biopsy (when indicated), every 3 mo for 2 yr, then every 6 mo for 2 yr, yearly thereafter
- CT scan of abdomen and pelvis every 6 mo for 2 yr in addition to chest x-ray examination, liver function testing, and serum creatinine

Cystectomy with ileal loop/orthotopic bladder:
- Neobladder endoscopy and IVP yearly
- CT scan of abdomen and pelvis every 6 mo for 2 yr in addition to chest x-ray examination, liver function tests, and serum creatinine
- Loopogram every 6 mo for 2 yr, then annually

PEARLS & CONSIDERATIONS

COMMENTS
- The most useful prognostic parameters for bladder tumor recurrence and subsequent cancer progression are tumor grade, depth of tumor penetration, multifocal tumors, frequency of recurrence, tumor size, CIS, lymphatic invasion, papillary or solid tumor configuration.
- Box B1-5 describes the American Urological Association Guideline Recommendations for bladder cancer.

BOX B1-5 American Urological Association Guideline Recommendations

For all index patients:
- Standard: Physicians should discuss with the patient the treatment options and the benefits and harms, including side effects, of intravesical treatment.

For a patient who presents with an abnormal growth on the urothelium but who has not yet been diagnosed with bladder cancer:
- Standard: If the patient does not have an established histologic diagnosis, a biopsy should be obtained for pathologic analysis.
- Standard: Under most circumstances, complete eradication of all visible tumors should be performed.
- Standard: If bladder cancer is confirmed, periodic surveillance cystoscopy should be performed.
- Option: An initial single dose of intravesical chemotherapy may be administered immediately postoperatively.

For a patient with small volume, low-grade Ta bladder cancer:
- Recommendation: An initial single dose of intravesical chemotherapy may be administered immediately postoperatively.

For a patient with multifocal and/or large volume, histologically confirmed, low-grade Ta or a patient with recurrent low-grade Ta bladder cancer:
- Recommendation: An induction course of intravesical therapy with bacillus Calmette-Guérin or mitomycin C is recommended for the treatment of these patients with the goal of preventing or delaying recurrence.
- Option: Maintenance bacillus Calmette-Guérin or mitomycin C may be considered.

For a patient with initial histologically confirmed high-grade Ta, T1, and/or carcinoma in situ bladder cancer:
- Standard: For patients with lamina propria invasion (T1) but without muscularis propria in the specimen, repeat resection should be performed prior to additional intravesical therapy.
- Recommendation: An induction course of bacillus Calmette-Guérin followed by maintenance therapy is recommended for treatment of these patients.
- Option: Cystectomy should be considered for initial therapy in select patients.

For a patient with high-grade Ta, T1, and/or carcinoma in situ bladder cancer that has recurred after prior intravesical therapy:
- Standard: For patients with lamina propria invasion (T1) but without muscularis propria in the specimen, repeat resection should be performed prior to additional intravesical therapy.
- Recommendation: Cystectomy should be considered as a therapeutic alternative for these patients.
- Option: Further intravesical therapy may be considered for these patients.

From the American Urological Association, Guideline Division, http://www.auanet.org.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Bladder Cancer (Patient Information)

AUTHORS: **PHILIP J. ALIOTTA, M.D., M.S.H.A.** and **RUBEN ALVERO, M.D.**

EVIDENCE

Abstract[1]

Background:
The medical community lacks results from prospective controlled multicenter studies of the diagnostic efficacy of 5-aminolevulinic acid (5-ALA) cystoscopy on tumor recurrence in patients with superficial bladder tumors.
Methods:
A prospective randomized, double-blind, placebo-controlled study was conducted in 370 patients with nonmuscle-invasive urinary bladder carcinoma who received either 5-ALA (n=187) or a placebo (n=183) intravesically before cystoscopy. Each group underwent cystoscopy under visible white light and under fluorescent light followed by transurethral tumor resection. The primary study objective was to evaluate the 12-month recurrence-free survival.
Results:
Slightly more patients with tumors were detected by using 5-ALA than by using the placebo (88.5% vs 84.7%). The mean numbers of tumor specimens per patient were 1.8 (5-ALA) and 1.6 (placebo). Intrapatient comparison of fluorescent light versus white light cystoscopy in patients randomized to receive 5-ALA showed a higher tumor detection rate with fluorescent light than with white light cystoscopy. In patients receiving 5-ALA cystoscopy, the percentage of lesions that would not have been detected in these patients by white light cystoscopy ranged between 10.9% (pT1) and 55.9% (atypia). Progression-free survival was 89.4% (5-ALA) and 89.0% (placebo) (P=0.9101), and recurrence-free survival 12 months after tumor resection was 64.0% (5-ALA) and 72.8% (placebo) (P=0.2216).
Conclusions:
In comparison to the placebo, 5-ALA cystoscopy did not increase the rates of recurrence-free or progression-free survival 12 months after tumor resection. Although more tumors per patient were detected in the 5-ALA group, the higher detection rate did not translate into differences in long-term outcome. Ⓐ

Abstract[2]

Purpose:
This article presents the long-term results of the international multicenter randomized trial that investigated the use of neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) chemotherapy in patients with muscle-invasive urothelial cancer of the bladder treated by cystectomy and/or radiotherapy. Nine hundred seventy-six patients were recruited between 1989 and 1995, and median follow-up is now 8.0 years.
Patients and Methods:
This was a randomized phase III trial of either no neoadjuvant chemotherapy or three cycles of CMV.
Results:
The previously reported possible survival advantage of CMV is now statistically significant at the 5% level. Results show a statistically significant 16% reduction in the risk of death (hazard ratio, 0.84; 95% CI, 0.72 to 0.99; P=.037, corresponding to an increase in 10-year survival from 30% to 36%) after CMV.
Conclusion:
We conclude that CMV chemotherapy improves outcome as first-line adjunctive treatment for invasive bladder cancer. Two large randomized trials (by the Medical Research Council/European Organisation for Research and Treatment of Cancer and Southwest Oncology Group) have confirmed a statistically significant and clinically relevant survival benefit, and neoadjuvant chemotherapy followed by definitive local therapy should be viewed as state of the art, as compared with cystectomy or radiotherapy alone, for deeply invasive bladder cancer. Ⓐ

Abstract[3]

Background:
After radical cystectomy, patients are in a catabolic state because of postoperative stress response, extensive wound healing, and ileus.
Objective:
To evaluate whether recovery can be improved with total parenteral nutrition (TPN) in patients following extended pelvic lymph node dissection (ePLND), cystectomy, and urinary diversion (UD).
Design, Setting, and Participants:
We conducted a prospective, randomized, single-center study of 157 consecutive cystectomy patients.
Intervention:
Seventy-four patients (group A) received TPN during the first 5 postoperative days, with additional oral intake ad libitum. Eighty-three patients (group B) received oral nutrition alone.
Outcome Measurements and Statistical Analysis:
The primary outcome was the occurrence of postoperative complications. Secondary outcomes were time to recovery of bowel function, biochemical nutritional (serum albumin, serum prealbumin, serum total protein) and inflammatory (C-reactive protein) parameters, length of hospital stay, and costs attributed to the TPN. The Pearson $c\chi 2$ test was used for dichotomous variables; the Wilcoxon rank sum test was used for continuous variables.
Results and Limitations:
Postoperative complications occurred in 51 patients (69%) in group A and in 41 patients (49%) in group B (P = 0.013), a difference resulting from group A having more infectious complications than group B (32% vs 11%; p = 0.001). Serum prealbumin and serum total protein were significantly lower in group B on postoperative day 7 but not on postoperative day 12. Time to gastrointestinal recovery and length of hospital stay did not differ between the two groups. The costs for TPN were VO614 per patient. A potential limitation is the use of a glucose-based parenteral nutrition without lipids.
Conclusions:
Postoperative TPN is associated with a higher incidence of complications, mainly infections, and higher costs following ePLND, cystectomy, and UD versus oral nutrition alone. Ⓐ

Evidence-Based References

Stenzl A, et al.: Detection and clinical outcome of urinary bladder cancer with 5-aminolevulinic acid-induced fluorescence cystoscopy: a multicenter randomized, double-blind, placebo-controlled trial, *Cancer* 117:938–947, 2011. Ⓐ

International Collaboration of Trialists on behalf of the Medical Research Council Advanced Bladder Cancer Working Party (now the National Cancer Research Institute Bladder Cancer Clinical Studies Group), the European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group, the Australian Bladder Cancer Study Group, the National Cancer Institute of Canada Clinical Trials Group, Finnbladder, Norwegian Bladder Cancer Study Group, and Club Urologico Espanol de Tratamiento Oncologico Group. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial, *J Clin Oncol* 29:2171–2177, 2011. Ⓐ

Roth B, Birkhaüser FD, Zehnder P et al.: Parenteral nutrition does not improve postoperative recovery from radical cystectomy: results of a prospective randomised trial, *Eur Urol* 63:475–482, 2013. Ⓐ

SUGGESTED READINGS

James ND et al.: Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer, *N Engl J Med* 366:1477–1488, 2012.

Sanchini MA et al.: Relevance of urine telomerase in the diagnosis of bladder cancer, *JAMA* 294:2052, 2005.

Sharma S et al.: Diagnosis and treatment of bladder cancer, *Am Fam Physician* 80(7):717–723, 2009.

BASIC INFORMATION

DEFINITION

Blastomycosis is a systemic pyogranulomatous disease caused by a dimorphic fungus, *Blastomyces dermatitidis.*

ICD-9CM CODES
116.0 Blastomycosis
ICD-10CM CODES
B40.9 Blastomycosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE & PREVALENCE:
- Most patients reside in the southeastern and south central states, especially those bordering the Mississippi and Ohio River valleys, the Midwestern states, and Canadian provinces bordering the Great Lakes.
- Rare cases reported outside the U.S.

RISK FACTORS:
- Widely disseminated disease is most common in immunocompromised hosts, especially those with acquired immunodeficiency syndrome (AIDS).
- Initial infections result from inhalation of conidia into the lungs, although primary cutaneous blastomycosis has been reported after dog bites.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute infection: <50% symptomatic, median incubation 30 to 45 days. Symptoms are nonspecific: mimic influenza or bacterial infection with abrupt onset of myalgias, arthralgias, chills, and fever; transient pleuritic pain, cough that is initially nonproductive. Resolution within 4 wk is usual.
- Chronic or recurrent infection: indolent, progressive; includes pulmonary or extrapulmonary disease.

PULMONARY MANIFESTATIONS: Symptoms and signs of chronic pneumonia: productive cough, hemoptysis, pleuritic chest pain, weight loss, low-grade pyrexia

EXTRAPULMONARY MANIFESTATIONS:

1. Cutaneous: most common; may occur with or without pulmonary disease (Fig. EB1-39). Two different lesions:
   - *Verrucous:* beginning as a small papulopustular lesion on exposed body areas that may develop into an eschar with peripheral microabscesses (Fig. EB1-40)
   - *Ulcerative:* Subcutaneous nodules (cold abscesses) and rarely cutaneous inoculation blastomycosis may occur
2. Bone and joint: 10% to 50% have osteolytic lesions (Fig. EB1-41); affects long bones, vertebrae, and ribs; lesions may present with contiguous soft tissue abscess or draining sinus that spreads to a joint, resulting in pyarthrosis
3. Genitourinary: 10% to 30%; prostatic involvement is most common and may present as obstruction; epididymis and testes may also be affected
4. Central nervous system: 5% normal host; 40% AIDS patients; meningitis and abscess formation

ETIOLOGY

Blastomyces dermatitidis exists in warm, moist soil that is rich in organic material. When these microfoci are disturbed, the aerosolized spores or conidia are inhaled into the lungs. Disease at other sites is a result of dissemination from the initial pulmonary infection; the latter may be acute or chronic.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

PULMONARY INFECTION:
- Tuberculosis
- Bronchogenic carcinoma
- Histoplasmosis
- Bacterial pneumonia

CUTANEOUS INFECTION:
- Bromoderma
- Pyoderma gangrenosum
- *Mycobacterium marinum* infection
- Squamous cell carcinoma
- Giant keratoacanthoma

WORKUP

- Physical examination and laboratory data
- Definitive diagnosis established by culture

LABORATORY TESTS

- Presumptive diagnosis can be made by visualizing the distinctive yeast forms in clinical specimens
- Culture: on Sabouraud medium or more enriched media
  1. Aspirated material from abscesses
  2. Skin scrapings
  3. Prostatic secretions (urine culture with prostatic massage)

FIGURE EB1-40 The typical verrucous skin lesion of blastomycosis on the cheek. Note the circumscribed edges. (From Mandell GL et al: *Principles and practice of infectious diseases,* ed 6, Philadelphia, 2005, Churchill Livingstone.)

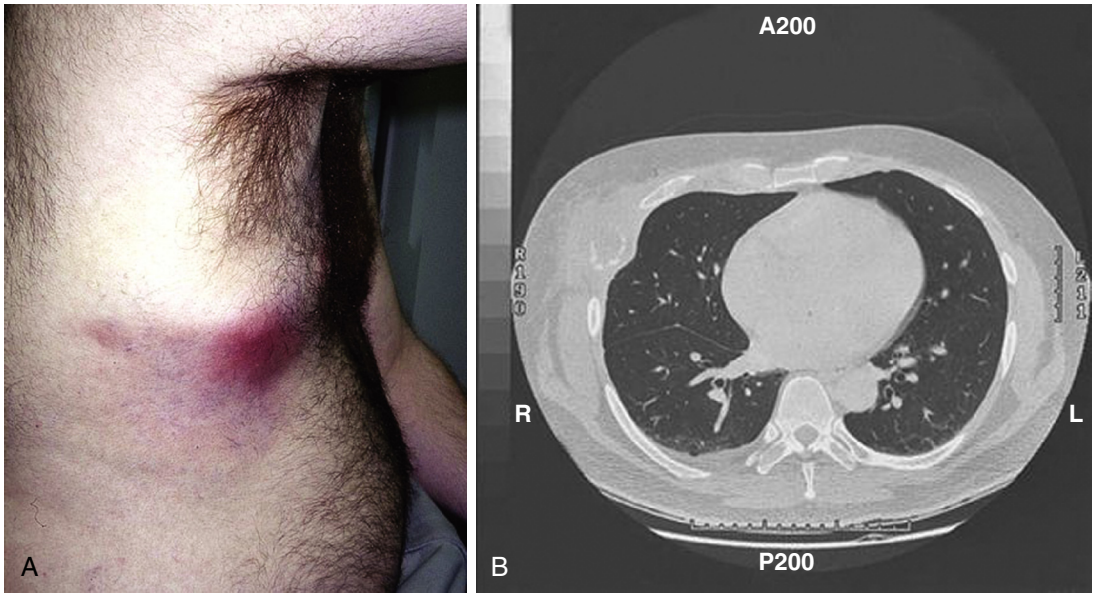

FIGURE EB1-39 A, Blastomycosis osteomyelitis of a rib and chest wall. **B,** Computed tomography scan appearance. Primary infection in the blood may spread to the skeleton. (From Firestein GS et al: *Kelly's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders, Elsevier.)

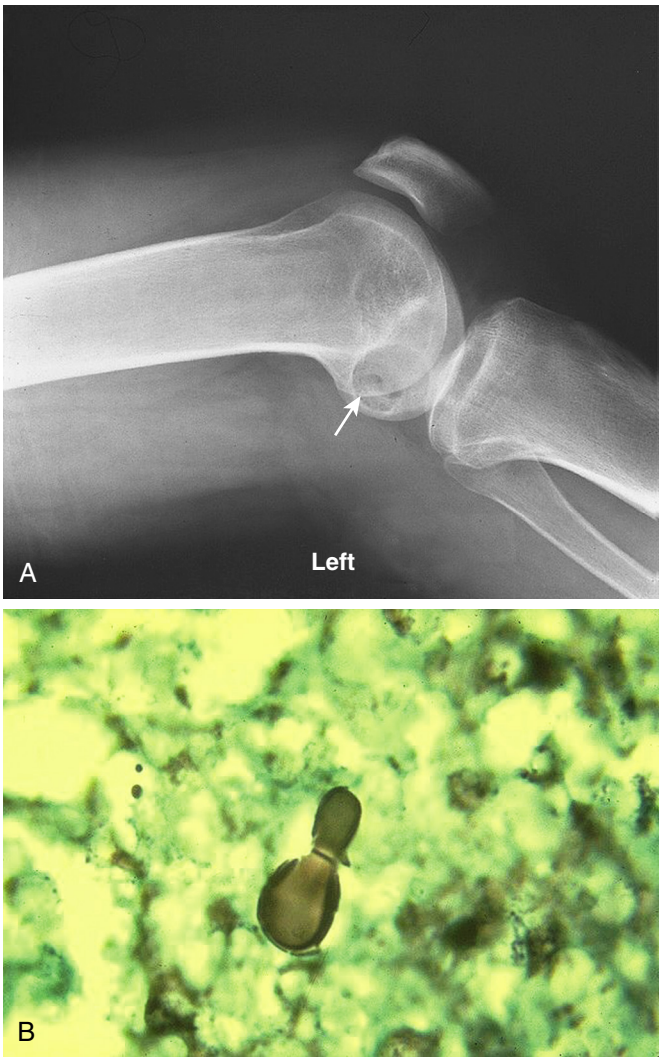

FIGURE EB1-41 Blastomycosis joint infection. A, Radiographs commonly show punched-out bone lesions. **B,** Synovial histology shows epithelioid granulomas with budding yeast forms. (From Firestein GS et al: *Kelly's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders, Elsevier.)

- Direct examination of specimens
  1. Wet preparation with 10% KOH (Fig. EB1-42)
  2. Histopathology: typically demonstrates pyogranulomas; yeast identification requires special stains
- A commercial test for *Blastomyces* antigen in specimens of urine, blood, and other fluids is available
- Serologic tests: a negative test cannot exclude blastomycosis, and a positive titer should not be an indication to start treatment

IMAGING STUDIES

In chronic disease, chest radiographic findings are nonspecific, but lobar or segmental alveolar infiltrates, especially of the upper lobes, are most common and may progress to cavitation.

Rx TREATMENT

ACUTE BLASTOMYCOSIS GENERAL Rx

- Treatment remains controversial for acute pulmonary blastomycosis.
- Because the acute form may be benign and self-limited, patients may be closely observed.
- Some patients progress to chronic infection with significant morbidity and therefore may require treatment.
- Patients who are immunocompromised or who have extrapulmonary disease or progressive pulmonary disease should be treated.

PULMONARY BLASTOMYCOSIS

- Amphotericin B (AmB) lipid formulation 3 to 5 mg/kg/day or AmB deoxycholate at 0.7 to 1 mg/kg/day for 1 to 2 wk or until improvement is noted, followed by oral itraconazole 200 mg PO tid for 3 days and then 200 mg PO bid for a total of 6 to 12 mo.
- Itraconazole 200 mg PO tid for 3 days and then once or bid for 6 to 12 mo for mild to moderate diseases.
- Fluconazole 400 to 800 mg PO once a day for those intolerant to itraconazole.

DISSEMINATED EXTRAPULMONARY BLASTOMYCOSIS

- Lipid formulation AmB 3 to 5 mg/kg/day or AmB deoxycholate 0.7 to 1 mg/kg/day for 1 to 2 wk or until improvement is noted followed by oral itraconazole 200 mg PO tid for 3 days and then 200 mg PO bid for a total of at least 12 mo for moderately severe to severe disease.
- Itraconazole 200 mg PO tid for 3 days and then once or bid for 6 to 12 mo for mild to moderate diseases.

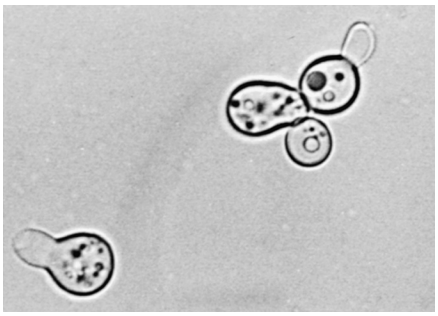

FIGURE EB1-42 Yeast cells of *Blastomyces dermatitidis in wet smear (×1000).* (From Mandell GL et al: *Principles and practice of infectious diseases,* ed 6, Philadelphia, 2005, Churchill Livingstone.)

CENTRAL NERVOUS SYSTEM BLASTOMYCOSIS

AmB lipid formulation at a dosage of 5 mg/kg/day over 4 to 6 wk followed by either fluconazole 800 mg/day or itraconazole 200 mg PO two to three times per day or voriconazole 200 to 400 mg PO twice a day for at least 12 mo and until resolution of CSF abnormalities.

BLASTOMYCOSIS IN IMMUNOSUPPRESSED INDIVIDUALS

- AmB as a lipid formulation 3 to 5 mg/kg/day or AmB deoxycholate 0.7 to 1 mg/kg/day for 1 to 2 wk or until improvement is noted followed by itraconazole 200 mg PO tid for 3 days and then bid as step-down therapy for at least 12 mo. Lifelong suppressive therapy with oral itraconazole 200 mg/day may be required.
- Serum itraconazole levels should be determined in all patients after they have received treatment with this agent for 2 wk.
- Surgery may be indicated for drainage of large abscesses.

DISPOSITION

- Before antifungal therapy, the disease had a progressive course with eventual extrapulmonary disease and a mortality rate <60%.
- Relapse rate for patients treated with AmB is 5%; relapse is more common in AIDS patients.

PEARLS & CONSIDERATIONS

- *Blastomyces dermatitidis* may mimic other diseases.
- Colonization does not occur as with *Candida* and *Aspergillus* species.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **SAJEEV HANDA, M.D.**

SUGGESTED READINGS

Bradsher RW et al.: Blastomycosis, *Infect Dis Clin North Am* 17:21, 2003.

Martynowicz MA et al.: Pulmonary blastomycosis: an appraisal of diagnostic techniques, *Chest* 121(3):768, 2002.

Stanley WC et al.: Clinical practice guidelines for the management of blastomycosis: 2008 update by the Infectious Diseases Society of America, *Clin Infect Dis* 46:1801–1812, 2008.

BASIC INFORMATION

DEFINITION

Blepharitis is a chronic inflammation of the eyelid margins that is often refractory to treatment with infectious and noninfectious etiologies.

SYNONYMS

Eyelid infection or inflammation
Eczema of the eyelids
Dermatoblepharitis
Angular blepharitis

ICD-9CM CODES
373.0 Blepharitis
ICD-10CM CODES
H01.009 Unspecified blepharitis unspecified eye, unspecified eyelid

EPIDEMIOLOGY & DEMOGRAPHICS

- Common in children, particularly those with atopic dermatitis and eczema.
- Adults with seborrhea involving the eyelids.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Common symptoms: red eyes, burning sensation, excessive tearing, blurred vision, pruritic eyelids.
- Chronically infected lids are usually diffusely erythematous, with collarettes (fibrin exudate) at the base of the lashes (Fig. B1-43).
- Lid margins thicken over time, with associated loss of eyelashes (madarosis), misdirected growth of lashes (trichiasis), and overflow or inspissation of the meibomian glands.

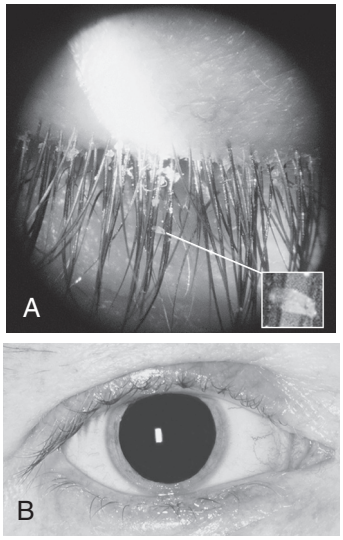

FIGURE B1-43 A, Seborrheic blepharitis. The typical scales (scurf) are translucent and easily removed. **B,** Staphylococcal blepharitis showing the typical lid margin erythema and discharge. (From Palay D [ed]: *Ophthalmology for the primary care physician,* St Louis, 1997, Mosby.)

- Associated conjunctivitis with erythema, edema but no discharge.
- Chalazion: chronic sterile inflammation of an oil gland of the eyelid.
- Superficial punctate erosions of the inferior corneal epithelium are common.
- More severe findings, such as corneal pannus, ulcerative keratitis, or lid ectropion, are less common.

ETIOLOGY

Multiple: bacterial and nonbacterial causes

- Staphylococcal infection most common but streptococcal, Moraxella, and other bacterial infections; viral infections (e.g., herpes simplex, herpes zoster, *Molluscum contagiosum*); and a number of ecoparasites, including pediculosis, may cause blepharitis
- Seborrheic dermatitis
- Rosacea
- Dry eye (keratoconjunctivitis sicca): decrease in tear volume
- Meibomian gland dysfunction
- Contact lens intolerance
- Two categories of blepharitis:
  1. Anterior blepharitis, most often associated with staphylococcal infection
  2. Posterior blepharitis, associated with meibomian gland dysfunction and seborrheic dermatitis or rosacea

NOTE: Blepharitis patients have normal skin microflora in greater amounts (mostly *S. epidermidis* and *Propionibacterium acnes*). (*S. aureus* and *S. epidermidis* can be cultured in 10% to 35% and 90% to 95% of healthy persons, respectively.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Keratoconjunctivitis sicca
- Eyelid malignancies
- Herpes simplex blepharitis
- Molluscum contagiosum
- Phthiriasis palpebrarum
- *Phthirus pubis* (pubic lice)
- *Demodex folliculorum* (transparent mites)
- Allergic blepharitis

WORKUP

Scrapings of the eyelids to show polymorphonuclear leukocytes and gram-positive cocci

LABORATORY TESTS

Eyelid cultures and antibiotic sensitivity testing (usually not done unless patient fails to respond to initial treatment regimen)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Alkaline soaps may be beneficial; alcohol and some detergents remove surface lipids and microflora.
- Hot compresses applied to closed lids for 5 to 10 min: heat loosens debris from lid margins and increases meibomian gland fluidity.
- Firm massage of the lid margins to enhance the flow of secretions from glands, followed by cleansing of the lids with cotton-tipped applicators dipped in a 50:50 mixture of baby shampoo and water.
- Lashes and lid margins scrubbed vigorously while the eyelids are closed, followed by thorough rinsing.
- Following local massage and cleansing, the mainstay of treatment is application of topical antibiotic ointment to the eyelid margins.
  1. Most effective topical antibiotics include bacitracin, erythromycin or 1% azithromycin solution, aminoglycoside and fluoroquinolone ophthalmic ointments.
  2. Ointment is applied 1 to 4 times daily, depending on the severity, for 1 to 2 wk, followed by once daily, at bedtime, for another 4 to 8 wk until all signs of inflammation have disappeared.
- Oral antibiotics: long-term use of doxycycline or tetracycline in a tapering dose may be helpful in severe cases for patients older than 8 years of age.
- Topical glucocorticoids: short-term use in acute exacerbations of blepharitis.
- For patients with rosacea:
- Tetracycline 250 mg orally 4 times daily or doxycycline 100 mg orally bid along with local treatment for several months.

Recalcitrant cases with antibiotic resistance:
1. Vancomycin eye drops 1%
2. Ciprofloxacin or ofloxacin eye drops

CHRONIC Rx

By definition, this is a chronic condition for which there is frequently no cure.

Some newer agents being evaluated are topical cyclosporine 0.05% eye drops, thermal pulsation systems to break up material in meibomian glands, topical metronidazole and topical tacrolimus, and tear lipid substitutes.

DISPOSITION

This condition may be refractory to treatment.

REFERRAL

To an ophthalmologist if patient fails to respond to local therapy.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Lindsley K et al.: Interventions for chronic blepharitis, *Cochrane Database Syst Rev* 5:CD005556, 2012.

Mathers WD, Choi D: Cluster analysis of patients with ocular surface disease, blepharitis and dry eye, *Arch Ophthalmol* 122:1700, 2004.

McCann LC et al.: Tear and meibomian gland function in blepharitis and normals, *Eye Contact Lens* 35(4):203–208, 2009.

BASIC INFORMATION

DEFINITION

Body dysmorphic disorder (BDD) is classified as an obsessive-compulsive and related disorder. It is characterized by preoccupation with one or more perceived defects or flaws in physical appearance that are not observable or appear slight to others, as well as repetitive behaviors (e.g., excessive grooming, mirror checking) in response to the appearance concerns. The preoccupations cause clinically significant distress or impairment in social, occupational, or other important areas of functioning. The appearance preoccupations are not better explained by concerns with body fat or weight in a person whose symptoms meet diagnostic criteria for an eating disorder.

SYNONYMS

Dysmorphophobia
BDD

ICD-9CM and DSM-5 CODES
300.7
ICD-10CM CODES
F45.22 Body dysmorphic disorder

EPIDEMIOLOGY & DEMOGRAPHICS

- Affects 1.7% to 2.4% of the general population (in nationwide epidemiologic studies)
- Prevalence among cosmetic surgery patients (in most studies) is 7% to 15%.
- Prevalence among dermatology patients is 9% to 14%.
- Slightly higher prevalence among females
- Onset most commonly in adolescence

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Excessive preoccupation (obsession) with one or more perceived defects in appearance that are not observable or appear slight to others. Patients believe they look abnormal, ugly, or deformed, whereas in reality they look normal. Any part of the body may be a focus of concern; skin, hair, and nose concerns are most common. Most patients are preoccupied with multiple body areas.
- The body areas with which the patient is concerned appear physically normal; if a physical defect is present, it is slight, and the patient's reaction to it is excessive.
- Most patients have poor insight (i.e., mostly convinced) or are delusional (i.e., completely convinced) regarding the accuracy of their belief about the appearance of the perceived defects.
- Over the course of the disorder, all patients engage in repetitive behaviors such as frequent mirror checking, excessive grooming, camouflaging (trying to hide the perceived flaws—e.g., with makeup, a hat, hair), skin picking to try to fix perceived skin flaws, reassurance seeking, and repeatedly measuring or feeling the perceived defect. The intent of these behaviors is to check, try to improve, or be reassured about the appearance of the perceived flaws.
- Nearly all experience impairment in psychosocial functioning and quality of life; impairment is usually substantial.
- Suicidal ideation, suicide attempts, and completed suicide appear common.
- Commonly co-occurring mental disorders are major depressive disorder, substance use disorders, social anxiety disorder, obsessive-compulsive disorder (OCD), and personality disorder.

ETIOLOGY

Likely multifactorial, with both genetic and environmental risk factors (e.g., teasing). Neuropsychological and fMRI studies indicate abnormalities in visual processing consisting of excessive focus on details rather than larger configural elements of visual stimuli.

DIAGNOSIS

Psychiatric interview
Ask:

1. Are you very worried about your appearance in any way? *OR:* Are you unhappy with how you look?
2. Does this concern with your appearance preoccupy you?
3. How much distress does this concern cause you?
4. What effect does this concern have on your life?
5. Is there anything you feel an urge to do over and over again in response to your appearance concerns? (Give examples, such as mirror checking, comparing with others, skin picking to remove perceived skin flaws)
   - Determine that the perceived appearance defects are actually nonexistent or only slight

DIFFERENTIAL DIAGNOSIS

- Often undiagnosed because of patient's reluctance to divulge symptoms due to shame and fear of being misunderstood (e.g., considered vain)
- OCD
- Eating disorder
- Social anxiety disorder
- Major depressive disorder

WORKUP

Clinical evaluation focused on BDD symptoms and associated impairment in functioning.

TREATMENT

NONPHARMACOLOGIC THERAPY

- CBT, with a focus on cognitive restructuring, exposure, and response prevention; CBT must be specifically tailored to BDD's unique symptoms.
- Do not try to talk patients out of their concern; it is ineffective.
- Avoid cosmetic procedures; a majority of patients with BDD receive them, but such treatments do not appear effective for BDD. Dissatisfied patients may sue or even become violent toward the treating clinician.

ACUTE GENERAL Rx

Precautions/hospitalization if actively suicidal

CHRONIC Rx

- SRIs are medication of choice; relatively high doses often needed.
- Other agents (e.g., neuroleptics, tricyclic antidepressants other than clomipramine) do not appear as beneficial.
- CBT tailored specifically to BDD is recommended, with an SRI if BDD symptoms are more severe, the patient is suicidal because of BDD symptoms, or comorbidity is present that may benefit from an SRI.
- Support groups if available.

DISPOSITION

- Untreated BDD tends to be chronic and can lead to social isolation; school dropout; major depression; unnecessary surgery, dermatologic treatment, or other cosmetic treatment; and even suicide.
- With correct diagnosis and treatment, a majority improve.

REFERRAL

Refer for psychiatric evaluation and treatment if diagnosis is suspected.

PEARLS & CONSIDERATIONS

- In clinical settings, more than 60% have co-occurring major depressive disorder.
- Reassurance that the patient looks normal is rarely helpful.
- Patients often have an unrealistic expectation of improvement with plastic surgery, dermatologic treatment, and other cosmetic procedures; these treatments do not appear to be effective.
- All patients should be screened for suicidality.

PATIENT/FAMILY EDUCATION

- Patients and family members usually benefit from psychoeducation.
- Family support and encouragement of appropriate treatment is important.
- Phillips KA: *Understanding Body Dysmorphic Disorder: An Essential Guide.* Oxford University Press, 2009
- http://www.bodyimageprogram.com (http://www.rhodeislandhospital.org/RIH/Services/MentalHealth/BodyImage/default.htm)

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Obsessive Compulsive Disorder (Related Key Topic)
Body Dysmorphic Disorder (Patient Information)

AUTHOR: **KATHARINE A. PHILLIPS, M.D.**

SUGGESTED READINGS

Cerand CE et al.: Body dysmorphic disorder: diagnosis and approach, *Plast Reconstr Surg* 119(6):1924, 2007.

National Institute for Health and Clinical Excellence (National Health Service) Obsessive Compulsive Disorder (OCD) and body dysmorphic disorder (BDD) Practice Guideline (website) www.nice.org.uk/CG31

Phillips KA. Understanding body dysmorphic disorder: an essential guide. Oxford University Press: New York.

Phillips KA et al.: Body dysmorphic disorder: treating an underrecognized disorder, *Am J Psychiatry* 165(9):1111–1118, 2008.

Wilhelm S et al. Cognitive-behavioral therapy for body dysmorphic disorder. Guilford Press: New York.

Bone Tumor, Primary Malignant ALG PTG

BASIC INFORMATION

DEFINITION

Primary malignant bone tumors are invasive and anaplastic and have the ability to metastasize. Most arise from the marrow (myeloma), but tumors may develop from bone, cartilage, fat, and fibrous tissues. Leukemia and lymphoma are excluded from this discussion.

FIBROSARCOMA AND LIPOSARCOMA: Extremely rare. They are similar to tumors arising in soft tissue.

OSTEOSARCOMA: A rare primary malignant tumor of bone characterized by malignant tumor cells that produce osteoid or bone. Several variants have been described: parosteal sarcoma, periosteal sarcoma, multicentric, and telangiectatic forms.

CHONDROSARCOMA: A malignant cartilage tumor that may develop primarily or secondarily from transformation of a benign osteocartilaginous exostosis or enchondroma.

EWING'S SARCOMA: A malignant tumor of unknown histogenesis.

MULTIPLE MYELOMA: A neoplastic proliferation of plasma cells.

SYNONYMS

Multiple myeloma:
1. Plasma cell myeloma
2. Plasmacytoma

ICD-9CM CODES	
203.0	Multiple myeloma
170.9	Neoplasm, bone (periosteum), primary malignant
M9180/3	Osteosarcoma
N9220/3	Chondrosarcoma
M9260/3	Ewing's sarcoma
ICD-10CM CODES	
C90.00	Multiple myeloma not having achieved remission
C41.9	Malignant neoplasm of bone and articular cartilage, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

MULTIPLE MYELOMA:
- The most common tumor in bone
- Age at onset: usually >40 yr
- Male/female ratio of 2:1

OSTEOGENIC SARCOMA:
- Average age at onset: 10 to 20 yr
- Males afflicted more often than females
- Parosteal sarcoma in older patients

CHONDROSARCOMA:
- Age at onset: 40 to 60 yr
- Male/female ratio of 2:1

EWING'S SARCOMA: Age at onset: 10 to 15 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

MULTIPLE MYELOMA:
- May present as a systemic process or, less commonly, as a "solitary" lesion
- Early manifestations: anorexia, weight loss, and bone pain; majority of cases present initially with back pain that often leads to the detection of a destructive skeletal lesion
- Other organ systems eventually become involved, resulting in more bone pain, anemia, renal insufficiency, and/or bacterial infections, usually as a result of the dysproteinemia typical of this disorder
- Possible secondary amyloidosis, leading to cardiac failure or nephrotic syndrome

OSTEOSARCOMA:
- Most originating in the metaphysis
- 50% to 60% around the knee
- Possible pain and swelling, but otherwise healthy patient
- Osteosarcoma in conjunction with Paget's disease, manifested primarily as a sudden increase in bone pain

CHONDROSARCOMA:
- Tumor most commonly involving the pelvis, upper femur, and shoulder girdle
- Painful swelling

EWING'S SARCOMA:
- Painful soft tissue mass often present
- Possibly increased local heat
- Midshaft of a long bone usually affected (in contrast to other tumors)
- Weight loss, fever, and lethargy

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Osteomyelitis
- Metastatic bone disease

LABORATORY TESTS

- Slightly elevated alkaline phosphatase in osteosarcoma
- In Ewing's sarcoma: reflective of systemic reaction; includes anemia, an increase in white blood cell count, and an elevated sedimentation rate
- In multiple myeloma:
  1. Bence Jones protein in the urine
  2. Anemia and elevated sedimentation rate
  3. Characteristic dysproteinemia on serum protein electrophoresis
  4. Diagnostic feature: peak in the electrophoretic pattern suggestive of a monoclonal gammopathy
  5. Rouleaux formation in the peripheral blood smear
  6. Often presence of hypercalcemia, but alkaline phosphatase levels usually normal

IMAGING STUDIES

- Classic osteogenic sarcoma penetrates the cortex early in many cases.
  1. A blastic (dense), lytic (lucent), or mixed response may be seen in the affected bone (Fig. EB1-44).
  2. An aggressive perpendicular sunburst pattern may be present as a result of periosteal reaction, and peripheral Codman's triangles are often noted.
  3. Margins of the tumor are poorly defined.
- Speckled calcifications in a destructive radiolucent lesion are usually suggestive of chondrosarcoma.
- Ewing's sarcoma is characterized radiographically by mottled, irregular destructive changes with periosteal new bone formation. The latter may be multilayered, producing the typical "onion skin" appearance.
- Typical roentgenographic finding in multiple myeloma is the "punched out" lesion with sharply demarcated edges.
  1. Multiple lesions are usual.
  2. Diffuse osteoporosis may be the only finding in many cases.
  3. Pathologic fractures are common.

TREATMENT

The evaluation and treatment of malignant bone tumors are complicated. Diagnostic studies and treatment should be supervised by an orthopedic cancer specialist and oncologist.

DISPOSITION

- In the past 20 yr, dramatic improvements have been made in the treatment protocols for osteosarcoma with the use of adjuvant multidrug regimens and limb-sparing surgery.
- Prognosis of multiple myeloma remains poor despite new therapies.
- Prognosis for Ewing's sarcoma has improved with a combination of chemotherapy, local resection, and radiation therapy.
- Chondrosarcomas are not sensitive to chemotherapy or radiation, and prognosis depends on the grade of the tumor and the ability to obtain an adequate resection.

PEARLS & CONSIDERATIONS

Early diagnosis is important because most tumors have not metastasized at the time of initial presentation.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Multiple Myeloma (Related Key Topic)
Sarcoma (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Dormans JP, Moroz L: Infection and tumors of the spine in children, *J Bone Joint Surg Am* 89A:79, 2007.

Futani H et al.: Long-term follow-up after limb salvage in skeletally immature children with a primary malignant tumor of the distal end of the femur, *J Bone Joint Surg Am* 88A:595, 2006.

Hoffmann C et al.: Functional results and quality of life after treatment of pelvic sarcomas involving the acetabulum, *J Bone Joint Surg Am* 88A:575, 2006.

Lewis VO: What's new in musculoskeletal oncology? *J Bone Joint Surg Am* 89:1399, 2007.

Messerschmitt PJ et al.: Osteosarcoma, *J Am Acad Orthop Surg* 17:515, 2009.

Plate AM et al.: Malignant tumors of the hand and wrist, *J Am Acad Orthop Surg* 14:680, 2006.

Staals EL et al.: Dedifferentiated chondrosarcomas arising in preexisting osteochondromas, *J Bone Joint Surg Am* 89A:987, 2007.

van Kampen M et al.: Replacement of the hip in children with a tumor in the proximal part of the femur, *J Bone Joint Surg Am* 90:785–795, 2008.

Worch J et al.: Ethnic and racial differences in patients with Ewing sarcoma, *Cancer* 116:983, 2010.

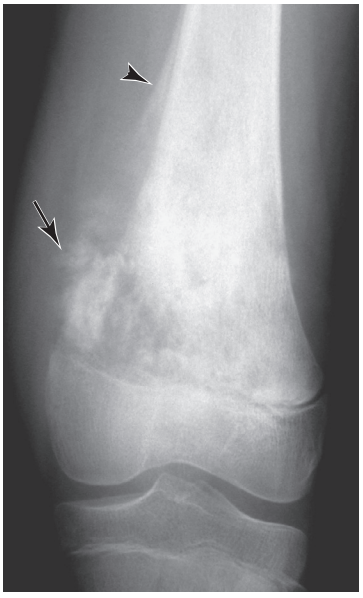

FIGURE EB1-44 Conventional central osteosarcoma. AP radiograph of the distal femur showing a classic osteosarcoma with mixed lytic and sclerotic areas, tumor bone formation in the extraosseous mass *(arrow),* and a proximal Codman's triangle *(arrowhead).* (From Adam A et al: *Grainger & Allison's diagnostic radiology,* ed 5, Philadelphia, 2008, Churchill Livingstone.)

BASIC INFORMATION

DEFINITION

Borderline personality disorder (BPD) is characterized by a pervasive pattern of instability in interpersonal relationships, self-image, affect regulation, and impulse control that causes significant subjective distress or impairment of functioning. The individual must meet five or more of the following criteria:

1. Frantic efforts to avoid real or imagined abandonment
2. Unstable and intense personal relationships characterized by alternating between extremes of idealization and devaluation
3. Identity disturbance characterized by an unstable self-image
4. Impulsivity in at least two areas that are potentially self-damaging (e.g., overspending, sex, substance abuse, binge eating, reckless driving)
5. Recurrent suicidal behavior, gestures, threats, or self-mutilating behavior
6. Affective instability due to a marked reactivity of mood
7. Chronic feelings of emptiness
8. Inappropriate, intense anger or difficulty controlling anger
9. Transient, stress-related paranoid ideation or severe dissociative symptoms

ICD-9CM and DSM-5 CODES
301.83
ICD-10CM CODES
F60.3 Emotionally unstable personality disorder

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Affects approximately 1% to 2% of the general population and up to 10% of psychiatric outpatients
PREDOMINANT SEX: Female (3:1)
PREDOMINANT AGE: 20s
GENETICS: BPD is five times as likely if disorder is present in a first-degree relative. Increased prevalence of mood disorders and substance abuse disorders also found in first-degree relatives.
RISK FACTORS: Association with childhood physical, sexual, or emotional abuse and/or neglect

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- No specific associated physical findings.
- Mental status examination may reveal affective lability.
- Clinical presentation may reveal the following:
  1. A pervasive sense of loneliness and emptiness.
  2. Underlying negative affect with dysphoria.
  3. High frequency of multiple psychiatric disorders, especially posttraumatic stress disorder (PTSD), mood disorders, attention-deficit/hyperactivity disorder, and substance use disorders. Intense emotions with difficulty returning to emotional baseline.
  4. All-or-nothing, either/or cognitive style that is represented by a phenomenon known as "splitting," in which patient sees situations or people as all good or all bad.
  5. Difficulty in maintaining commitment to long-term goals; history of numerous stormy relationships and multiple jobs.
  6. Reports a high number of sexual partners due to either/both impulsivity and victimization.
  7. Reacts with rage, panic, despair to actual or perceived abandonment; may present with suicidality or self-mutilating behavior in response to recent stressor.
  8. Attempts to block the experience of pain, which may induce feelings of derealization, depersonalization, changes in consciousness, and/or brief psychotic reactions with delusions and hallucinations.
  9. Substance use, gambling, overspending, eating binges, and/or self-mutilation as a way to escape intensely painful affect.
- Some patients may display psychotic symptoms.

ETIOLOGY

- Interaction of psychosocial adversity plus genetic factors
- Hypotheses:
  1. Genetic: increased risk if first-degree relative with BPD.
  2. Biologic: abnormalities in limbic system and other areas of the brain cause emotional dysregulation. Serotonergic functioning appears to be disturbed.
  3. Environmental: history of childhood abuse (most commonly sexual) or neglect.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Histrionic, antisocial, and narcissistic personality disorders share some common features.
- Dysthymia and other depressive disorders: requires a stability of affective symptoms not seen in BPD.
- Bipolar disorder: mood changes in BPD often triggered by stressors and less sustained than in bipolar disorder. Many patients with BPD are incorrectly diagnosed with bipolar disorder.
- Substance abuse or dependence: often induces impulsive, emotionally labile behavior.
- Posttraumatic stress disorder (PTSD): individuals with BPD often have history of trauma but do not avoid the feared stimulus or reexperience the trauma, as with PTSD.
- Mild cases of schizophrenia may superficially resemble BPD.

WORKUP

- History (helpful to gather collateral information from family and friends)
- Physical examination
- Mental status examination

LABORATORY TESTS

- Toxicology screen; substance use is common and can mimic features of personality disorders.
- Screen for HIV and other sexually transmitted illnesses.

IMAGING STUDIES

Structural and functional MRI demonstrate amygdala hyperactivity (Fig. B1-45), reduced hippocampus and amygdala volume, greater activation within the insula and posterior cingulate cortex, and less activation in regions extending from the amygdala to the cingulate and prefrontal cortex. PET scans reveal reduced metabolism in prefrontal cortex. Recent PET research reveals dysregulation of endogenous opioid function. Imaging is not recommended as part of routine evaluation.

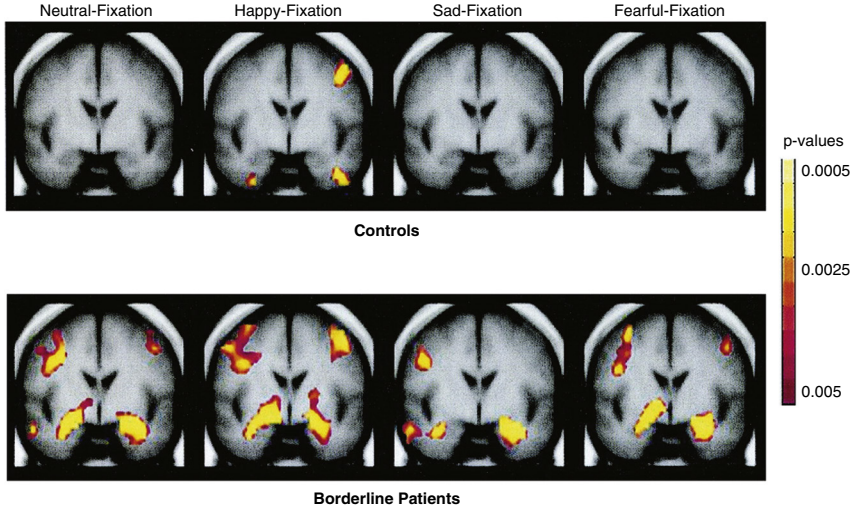

FIGURE B1-45 Activation map showing regions in an amygdala slice in which activation exceeded the criterion threshold level of $P < .005$ for the normal control and borderline personality disorder groups for each of the four facial expressions. (From Donegan NH et al: Amygdala hyperreactivity in borderline personality disorder: implications for emotional dysregulation, *Biol Psychiatr* 54:1284–1293, 2003.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Psychotherapy is the recommended primary treatment for BPD. Dialectical behavior therapy (DBT), mentalization-based therapy, variations of cognitive behavior therapy (CBT), and transference-focused psychotherapy, a type of psychodynamic therapy, have the most empirical support from randomized trials. The goal of DBT and most CBT variations is to help patients improve mindful awareness of emotions, control impulsive behaviors and angry outbursts, and develop social skills. The emphasis of mentalization treatment is to teach patients to stand outside of their feelings and observe emotions in oneself and others. The focus of transference-focused psychotherapy is on examining the affect-laden themes that emerge in the relationship between patient and therapist. Effective therapeutic treatments typically combine weekly group and individual therapy meetings. Treatment may also include inpatient and partial hospitalization in more severe cases.

ACUTE GENERAL Rx

Low-dose antipsychotics to control impulsivity, brief psychotic episodes.

CHRONIC Rx

- Medications have low to moderate effectiveness and are most effective in improving symptoms of impulsivity, mood instability, and self-destructive behavior. Effectiveness only studied for the first 3 mo of treatment.
- SSRIs if concurrent mood disorder. Higher doses may be required than for major depression.
- Low-dose antipsychotics.
- Mood stabilizers (lithium, valproate, carbamazepine, topiramate).
- In preliminary studies, omega-3 fatty acids improve irritability.

DISPOSITION

- Course is variable. The most unstable period is typically in early adulthood; the majority achieve greater stability in social/occupational functioning later in life but often continue with difficulty maintaining intimate relationships.
- Clinically salient features such as alcohol/substance use and self-injury may be less common in older adults.
- No evidence of progression to schizophrenia, but there is a high incidence of concurrent major depression and other psychiatric disorders.
- Patients with high pre-treatment symptom severity who report a strong therapeutic alliance with their providers report highest treatment benefits.
- Drop-out rates are variable in research studies and may be high for individual patients.

REFERRAL

- Referral to mental health specialist:
  1. For diagnosis and management.
  2. Use of pharmacotherapy
  3. Patient is severely impaired or suicidal

PEARLS & CONSIDERATIONS

COMMENTS

- Consider frequent, brief, scheduled visits for needy, demanding, or somaticizing patients with BPD.
- Validate the patient's feelings while stating the expectation of behavior control.
- Be matter-of-fact; avoid expressing extreme emotions.
- Be alert to the risk of suicide and assess suicide risk often.
- Be alert to the risk of nonsuicidal self-harm, such as cutting
- Convey a demeanor of competence but openly acknowledge minor errors.
- Have a low threshold for seeking psychiatric consultation.
- An alternative model of diagnosing borderline personality disorder exists in the DSM-5 section III, consisting of: (1) impairment in personality functioning (identity, self-direction, empathy, or intimacy) and (2) four or more of seven maladaptive personality traits (emotional lability, anxiousness, separation insecurity, depressivity, impulsivity, risk-taking, and hostility).

PREVENTION

- There are no known ways to prevent BPD (or other personality disorders).
- Suicidality should be actively and consistently monitored.
- Benzodiazepines, narcotic analgesics, and other drugs with potential for dependency should be used rarely and with great caution, due to impaired impulse control and risk of addictive behavior.
- Patients should be asked frequently and in detail about parenting practices. Low frustration tolerance, externalization of blame for psychological distress, and impaired impulse control put children at risk for neglect or abuse.

PATIENT & FAMILY EDUCATION

National Alliance for the Mentally Ill (NAMI; http://www.nami.org) provides patient information, online chat groups, and information on support groups throughout the U.S. for people with BPD and their families.

National Education Alliance for Borderline Personality Disorder (NEA, BPD) (http://www.borderlinepersonalitydisorder.com) provides patient, family, and professional information on BPD.

Additional, local and/or online support groups for BPD are common and should be investigated.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Borderline Personality Disorder (Patient Information)

AUTHORS: **MARK ZIMMERMAN, M.D.,** and **THERESA A. MORGAN, PH.D, M. PHIL**

SUGGESTED READINGS

American Psychiatric Association. Practice guidelines for the treatment of patients with BPD. Available at http://www.psychiatryonline.com/pracGuide/pracGuideTopic_13.aspx.

Gunderson JG: Borderline personality disorder, *N Engl J Med* 364:2037–2042, 2011.

Gunderson JG, Links P: *Handbook of good psychiatric management for borderline personality disorders*, Arlington, VA, 2014, American Psychiatric Publishing.

Kendall T et al.: Borderline and antisocial personality disorders: summary of NICE guidance, *BMJ* 338:B93, 2009.

Skodol AE: Personality disorders in DSM-5, *Annu Rev Clin Psychol* 8:17–44, 2012.

BASIC INFORMATION

DEFINITION

Botulism is an illness caused by a neurotoxin produced primarily by *Clostridium botulinum.* Five types of disease can occur: foodborne botulism, wound botulism, infant intestinal botulism, adult enteric botulism (similar to infant botulism), and inhalational botulism. Of note, inhalational botulism is exceedingly rare, but could occur as a result of bioterrorism.

SYNONYMS

Clostridium botulinum food poisoning
Botulinum toxin food poisoning
Wound botulism
Infantile botulism

ICD-9CM CODES
005.1 Botulism
ICD-10CM CODES
A05.1 Botulism food poisoning

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Approximately 24 cases/yr of foodborne illness, 29 cases/yr of wound botulism, and 94 cases/yr of infant botulism

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms usually begin 12 to 36 hr following ingestion.
- Severity of illness is related to the quantity of toxin ingested.
- Significant findings:
  1. Acute, bilateral cranial nerve palsies, with ocular and bulbar manifestations being most frequent (diplopia, ophthalmoplegia, ptosis, dysphagia, dysarthria, fixed and dilated pupils, and dry mouth)
  2. Usually bilateral nerve involvement that may progress to a descending flaccid paralysis
  3. No sensory deficits, aside from possible blurred vision
  4. GI symptoms (dry mouth, nausea, vomiting, diarrhea, or cramps)
  5. Generally an absence of fever
  6. Normal heart rate to mild bradycardia with patient remaining normotensive
- Wound botulism
  1. Occurs primarily in injecting drug users (subcutaneous "black tar" heroin injection—"skin popping") or with traumatic injury.
  2. Presentation is similar to that of foodborne disease, except for a longer incubation period (4-14 days) and absence of GI symptoms.
  3. Fever is uncommon and if present may be due to wound infection, which is not always apparent.

ETIOLOGY

- Cause is one of several types of neurotoxins (usually A, B, E, or F) produced by *C. botulinum,* an anaerobic, gram-positive bacillus. Spore production guarantees survival of the organism in extreme conditions, and they are found in the environment worldwide. Botulinum toxin is the most powerful neurotoxin known.
- Disease results from absorption of toxin into the circulation from a mucosal surface or wound. Botulinum toxin does not penetrate intact skin.
- In foodborne variety, disease is caused by ingestion of preformed toxin. Although rapidly inactivated by heat, the toxin can survive the proteolytic environment of the stomach.
- In wound botulism, toxin is elaborated by organisms that contaminate a wound.
- In infant botulism (and probably adult botulism of unknown etiology), toxin is produced by organisms in the GI tract. Antibiotic use and achlorhydria can predispose to colonization by *C. botulinum* and elaboration of toxin.
- Inhalational botulism has been demonstrated experimentally in primates. Rare case reports of inhalational botulism from snorting contaminated cocaine have been reported, and there is concern for the potential use of manufactured aerosolized toxin as a bioterrorism agent.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Myasthenia gravis, Lambert-Eaton myasthenic syndrome
- Guillain-Barré syndrome or other acute inflammatory demyelinating polyneuropathy
- Tick paralysis
- CVA
- Other: polio, heavy metal intoxication, and shellfish poisoning

LABORATORY TESTS

- Anaerobic cultures of serum, of food, and/or stool
- Food, serum, and stool are sent for toxin assay.
- Public health laboratories may perform mouse bioassay testing, which confirms toxin type in 75% of cases.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive care with intubation if respiratory failure occurs
- Debridement of the wound in wound botulism

ACUTE GENERAL Rx

- **For non-infants:** Give equine heptavalent botulinum antitoxin (HBAT), which contains antibodies for seven known botulism types (A through G), as early as possible. Once a clinical diagnosis is made, antitoxin should be administered before laboratory confirmation.
  1. The antitoxin (BAT, Cangene Corporation) is available from the Centers for Disease Control and Prevention (1-404-639-2206 Monday-Friday or 1-404-639-2888 evenings/weekends); it is derived from horse serum, so there is a significant incidence of serum sickness.
  2. Skin testing (conjunctival instillation and observation for 15 min), and possible desensitization, is recommended before treatment. Reported hypersensitivity rates range from 9% to 20%.
- Give wound botulism patients penicillin 2 million U IV q4h after antitoxin has been given. Use metronidazole 500 million U IV q8h as alternative for penicillin allergic patients. Avoid aminoglycosides and tetracyclines, as they are ineffective and can worsen neuromuscular blockade.
- **For infants:** Give human botulinum immunoglobulin (BabyBIG) IV, single dose. Call 1-510-540-2646. Do not use equine antitoxin. Babies with infantile intestinal botulism may benefit from a cathartic to mechanically clear the number of *C. botulinum* vegetative forms and spores residing in the gastrointestinal tract. Avoid antibiotics in infant botulism because antimicrobials may lyse *C. botulinum* in the gut and increase toxin load.

DISPOSITION

- Highest mortality in the first cases in an outbreak, with subsequent cases receiving rapid treatment
- Complete recovery for most individuals (may take up to 1 year)

REFERRAL

Immediate for all cases to an ER and an infectious disease consultant

PEARLS & CONSIDERATIONS

COMMENTS

- Routine cooking inactivates the toxin, but spores are resistant to environmental factors. At room temperature, spores can germinate and produce toxin. Pressure cooking can kill spores as well, however.
- Most outbreaks are associated with home-canned foods, including fruits, vegetables, and fish.
- Patients must be closely monitored for progression to respiratory paralysis.
- Notify public health authorities immediately to alert other health care services of possible additional cases and to initiate investigation into cause and scope of outbreak.
- Immunity to botulism does not occur after toxin exposure/infection, and repeated botulism can occur.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Botulism (Patient Information)

AUTHORS: **CHRISTELLE ILBOUDO, M.D.,** and **RUSSELL J. MCCULLOH, M.D.**

SUGGESTED READINGS

Arnon SS et al.: Botulinum toxin as a biological weapon, *JAMA* 285(8):1059, 2001.

Arnon SS et al.: Human botulism immune globulin for the treatment of infant botulism, *N Engl J Med* 354(5):462, 2006.

California Department of Public Health: Infant botulism treatment and prevention program. Accessed January 26, 2015 www.infantbotulism.org.

Cherington M: Botulism: update and review, *Semin Neurol* 24:155, 2004.

Francisco AM, Arnon SS: Clinical mimics of infant botulism, *Pediatrics* 119(4):826–828, 2007.

Reddy P, Bleck TP: Clostridium botulinum (botulism). In: (editors: Mandell G.L.; Bennett J.E.; Dolin R.) Principles and practice of infectious diseases. ed 7 Churchill Livingstone: New York.

Sobel J: Botulism, *Clin Infect Dis* 41(8):1167, 2005.

BASIC INFORMATION

DEFINITION

A brain abscess is a focal intracerebral infection that can arise as a complication from a bacterial, mycobacterial, fungal, or parasitic (protozoa or helminths) infection, surgery, or trauma.

ICD-9CM CODES
324.0 Brain abscess
ICD-10CM CODES
G06.0 Intracranial abscess and granuloma

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Reported 0.4 to 0.9 cases per 100,000 population; occurs about 2% as commonly as brain tumors. Rates are higher in immunosuppressed patients.
PEAK INCIDENCE: Preadolescence and middle age (and depends on predisposing condition); increased rates in the immunocompromised host.
PREDOMINANT AGE: Occurs at any age
PREDOMINANT SEX:
- Men affected more than women (ratio 2:1 to 3:1)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Classic triad: fever, headache, and focal neurologic deficit (present in less than 50% of cases).
- Clinical presentation is often due to the manifestations of the space-occupying lesion rather than to signs of systemic infection.
- Fever is present in only 32% to 79% of patients.
- Headache is usually localized to the side of the abscess; onset can be gradual or severe; present in an average of 70% to 75% of cases.
- Focal neurologic findings (e.g., seizures, hemiparesis, aphasia, ataxia) depend on the location of the abscess and are seen in 23% to 66% of cases.
- Papilledema is present in 9% to 51% of cases.
- Presence of adjacent infections (dental abscess, otitis media, and sinusitis) may be a clue to the underlying diagnosis and should be sought in any suspected case.
- Time course from symptom onset to presentation ranges from hours in fulminant cases to more than 1 month; 75% present in the first 2 weeks.
- The nonspecific presentation of a brain abscess warrants that clinicians maintain a high index of suspicion. Table B1-8 describes common initial features of brain abscess.

TABLE B1-8 Brain Abscess: Initial Features in 123 Cases

Headache	55%
Disturbed consciousness	48%
Fever	58%
Nuchal rigidity	29%
Nausea, vomiting	32%
Seizures	19%
Visual disturbance	15%
Dysarthria	20%
Hemiparesis	48%
Sepsis	17%

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

ETIOLOGY

- Brain abscesses are classified based on the likely portal of entry and can arise from:
  Contiguous infection
  Hematogenous spread from a remote site
- Likely source of abscess and common organisms involved:
  A. Contiguous focus or primary infection (55% of all brain abscesses):
     1. Paranasal sinus: occur in frontal lobe; streptococci (especially microaerophilic and anaerobic streptococci), *Bacteroides, Haemophilus,* and *Fusobacterium* spp.
     2. Otitis media/mastoiditis: occur in temporal lobe and cerebellum; aerobic and anaerobic streptococci, Enterobacteriaceae, *Bacteroides,* and *Pseudomonas* spp.
     3. Dental sepsis: occur in frontal lobe; mixed *Fusobacterium, Bacteroides*, and Streptococcus spp. (especially *S. viridans* and anaerobic streptococci)
     4. Penetrating head injury: site of abscess depends on site of wound; *Staphylococcus aureus,* aerobic streptococci, *Clostridium* spp., Enterobacteriaceae
     5. Postoperative: *Staphylococcus epidermidis* and *S. aureus*, Enterobacteriaceae, and *Pseudomonas aeruginosa*
  B. Hematogenous spread from a distant site of infection (25% of all brain abscesses): abscesses most commonly multiple, especially in middle cerebral artery distribution; infecting organism(s) depend on source.
     1. Congenital heart disease: streptococci, *Haemophilus* spp.
     2. Endocarditis: *S. aureus,* viridans streptococci
     3. Urinary tract: Enterobacteriaceae, Pseudomonadaceae
     4. Intraabdominal: streptococci, Enterobacteriaceae, anaerobes
     5. Lung: streptococci, *Actinomyces* spp., *Fusobacterium* spp.
     6. Immunocompromised host: *Toxoplasma* species, fungi, Enterobacteriaceae, *Nocardia* spp., tuberculosis, listeriosis
  C. Cryptogenic (unknown source): 20% of all brain abscesses

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other parameningeal infections: subdural empyema, epidural abscess, thrombophlebitis of the major dural venous sinuses and cortical veins
- Embolic strokes in patients with bacterial endocarditis
- Mycotic aneurysms with leakage
- Acute hemorrhagic leukoencephalitis
- Parasitic infections: toxoplasmosis, echinococcosis, cysticercosis
- Metastatic or primary brain tumors
- Cerebral infarction
- CNS vasculitis
- Chronic subdural hematoma
- Table EB1-9 summarizes the differential diagnosis of central nervous system infection and tumor

WORKUP

Physical examination, laboratory tests, and imaging studies

LABORATORY TESTS

- White blood cell counts are elevated in 60% of patients.
- Erythrocyte sedimentation rate is usually elevated but may be normal.
- Blood cultures are most often negative (10% positive).
- Lumbar puncture may be helpful in those with suspicion of meningitis or abscess rupture into the ventricular system; however, the risk of herniation must be considered. Lumbar puncture is contraindicated in patients with brain shift on imaging or coagulation disorder.
- The yield of Gram stain and culture of material aspirated at time of surgical drainage is very high.

IMAGING STUDIES

- MRI with and without gadolinium is the diagnostic procedure of choice; provides superior detail compared with CT scan (higher sensitivity and specificity than CT scan, but not always immediately available).
- CT scan (Fig. B1-46) with intravenous contrast is still an excellent test (sensitivity 95%-99%).
- Serial CT or MRI scanning is recommended to follow the response to therapy.

TREATMENT

ACUTE GENERAL Rx

- Effective treatment involves a combination of empiric antibiotic therapy and timely excision or aspiration of the abscess.
- If evidence of edema or mass effect, treatment of elevated intracranial pressure is paramount.
  1. Hyperventilation of mechanically ventilated patient.
  2. Dexamethasone initially in a dosage of 10 mg IV followed by 4 mg IV q6h until symptoms of cerebral edema subside. Steroids should be discontinued as soon as possible.
  3. Mannitol 0.25 to 1 g/kg IV over 20 to 30 min q6 to 8h; maximum of 6 g/kg in 24 hr.

- Medical therapy is never a substitute for surgical intervention to relieve increased intracranial pressure. Neurologic deterioration usually mandates surgery.
- Steroids should be limited to patients with severe cerebral edema or midline shift.

MEDICAL Rx

If abscess <2.5 cm and patient is neurologically stable and conscious, may start antibiotics and observe. Empiric antibiotic therapy guided by:

- Abscess location
- Suspicion of primary source
- Presence of single or multiple abscesses
- Patient's underlying medical conditions (e.g., HIV, immunocompromised)

Selection of empiric antibiotic therapy:

- Primary infection or contiguous source:
  1. Otitis media/mastoiditis, sinusitis, dental infection: third-generation cephalosporin (cefotaxime 2 g q4h IV or ceftriaxone 2 g q12h IV) plus metronidazole 15 mg/kg IV as a loading dose, then 7.5 mg/kg q8h IV, not to exceed 4 g per day
  2. Dental infection: penicillin G (20 million to 24 million units per day IV in six divided doses) plus metronidazole (dose as above)
  3. Head trauma: third or fourth-generation cephalosporin (cefotaxime 2 g IV q4h or ceftriaxone 2 g IV q12h or cefepime 2 g IV q8h) plus vancomycin (30 mg/kg IV in two divided doses adjusted for renal function) plus metronidazole 500mg IV q8h
  4. Postoperative neurosurgery: vancomycin (dose as above) plus ceftazidime (2 g IV q8h) or cefepime (2 g IV q8h), or meropenem (1 g IV q8h). Replace vancomycin with nafcillin (2g IV q4h) if susceptibility testing reveals methicillin-sensitive *Staphylococcus aureus.*
- Hematogenous spread (congenital heart disease, endocarditis, urinary tract, lung, intraabdominal): vancomycin (empiric therapy, dose as above) or nafcillin (if susceptibility testing reveals methicillin-sensitive *S. aureus,* dose as above) plus metronidazole plus third-generation cephalosporin (cefotaxime 2 g IV q4h or ceftriaxone 2 g IV q12h)
- HIV infection: cefotaxime or ceftriaxone plus metronidazole, pyrimethamine, and sulfadiazine; consider isoniazid, rifampin, pyrazinamide, and ethambutol to cover possible tuberculosis infection
- Transplant recipients: cefotaxime or ceftriaxone plus metronidazole, voriconazole, and trimethoprim-sulfamethoxazole or sulfadiazine

Duration of antibiotic therapy is guided by the clinical course and whether or not the abscess was surgically aspirated or excised. It is usually prolonged. Most recommend parenteral treatment for at least 4 to 8 weeks, with serial neuroimaging to ensure adequate resolution. (Imaging weekly could be considered for first 2 weeks of therapy, then every 2 weeks until resolution.) Surgical therapy may be required for clinical failure (i.e., increasing size of abscess on imaging despite antibiotic therapy).

SURGICAL Rx

- Three indications for surgical intervention:
  1. Collect specimens for culture and sensitivity
  2. Reduce mass effect
  3. Clinical failure with antibiotic therapy alone
- Stereotactic biopsy or aspirate of the abscess if surgically feasible
- Essential to selection of targeted antimicrobial coverage
- Timing and choice of surgery depends on:
  1. Primary infection source
  2. Number and location of the abscesses
  3. Whether the procedure is diagnostic or therapeutic
  4. Neurologic status of the patient

DISPOSITION

- Prompt diagnostic consideration, early institution of appropriate antimicrobial therapy, and advanced neuroradiologic imaging have reduced the mortality rate from brain abscesses from 40% to 80% in the preantibiotic era to 10% to 20% at present.
- Morbidity is usually manifest as persistent neurologic sequelae (seizures, intellectual or behavioral impairment, motor deficits).

REFERRAL

Consultation with a neurosurgeon is mandatory.

PEARLS & CONSIDERATIONS

COMMENTS

- It is important to maintain a high index of suspicion because a brain abscess often presents with nonspecific symptoms.
- Rapid imaging and early institution of appropriate antimicrobial therapy improve patient morbidity and mortality.
- Neurosurgical consultation is mandatory.

PREVENTION

Because brain abscesses arise from either contiguous infections or hematogenously from a remote site, early and appropriate treatment of predisposing infections is paramount to prevent brain abscess.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Brain Abscess (Patient Information)

AUTHOR: **ERICA HARDY, M.D., M.M.S**

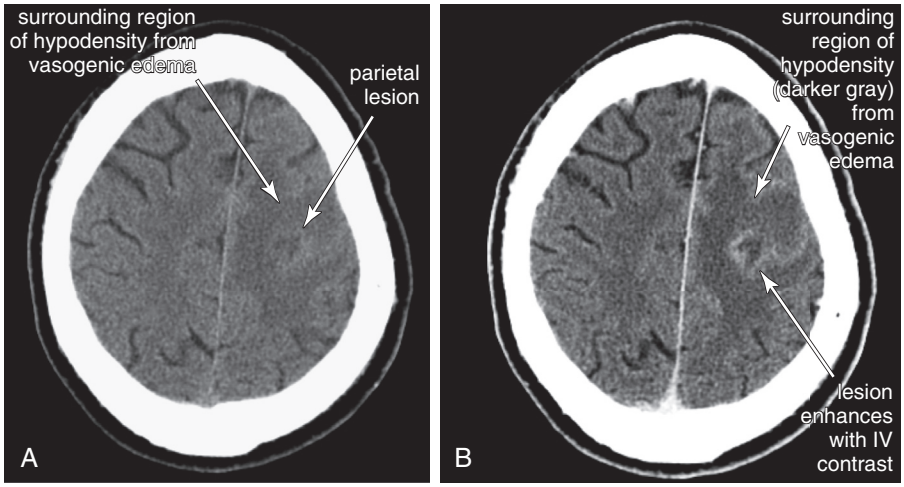

FIGURE B1-46 Brain abscess. This 48-year-old male presented with status epilepticus. Computed tomography (CT) showed a parietal mass, which at brain biopsy was found to be an abscess. Cultures grew mixed gram-positive and gram-negative organisms and anaerobes. The patient was subsequently found to be human immunodeficiency virus positive. **A,** Noncontrast head CT, brain windows. **B,** CT with intravenous (IV) contrast moments later, brain windows. Abscesses and other infectious, inflammatory, or neoplastic lesions typically have surrounding hypodense regions representing vasogenic edema. When IV contrast is administered **(B),** the lesion may enhance peripherally, often referred to as ring enhancement. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

EVIDENCE

Although antimicrobial therapy and surgical drainage are the mainstays of the clinical management of brain abscess, evidence for these therapies is limited.

SUGGESTED READINGS

Bhand AA: Brain abscess—diagnosis and management, *J Coll Physicians Surg Pak* 14:7, 2004.

Brouwer MC, Tunkel AR, McKhann GM, van de Beek D: Brain Abscess, *NEJM* 371:447–456, 2014.

Carpenter J et al.: Retrospective analysis of 49 cases of brain abscess and review of the literature, *Eur J Clin Microbiol Infect Dis* 26:1, 2007.

Gomes JA et al.: Glucocorticoid therapy in neurologic critical care, *Crit Care Med* 33(6):1214, 2005.

Helweg-Larsen et al.: Pyogenic brain abscess–a 15 year survey, *BMC Infectious Diseases* 12:332, 2012.

Kao PT et al.: Brain abscess: clinical analysis of 53 cases, *J Microbiol Immunol Infect* 36:2, 2003.

McClelland S 3rd et al.: Postoperative central nervous system infections: incidence and associated factors in 2111 neurosurgical procedures, *Clin Infect Dis* 45:1, 2007.

Tattevin P et al.: Bacterial brain abscesses: a retrospective study of 94 patients admitted to an intensive care unit (1980–1999), *Am J Med* 115:143, 2003.

The rational use of antibiotics in the treatment of brain abscess. Report by the "Infection in Neurosurgery" Working Party of the British Society for Antimicrobial Chemotherapy, *Br J Neurosurg* 14(6):525, 2000.

TABLE EB1-9 Differential Diagnosis of Central Nervous System Infection and Tumor

	Brain Abscess	Bacterial Meningitis	Herpetic Encephalitis	Brain Tumor
History				
Headache	Severe, often focal	Severe, generalized	Mild to severe	Absent to severe
Focal defect	Often	Occasional	Occasional	Often
Progression	Days to weeks	Hours to days	Days	Days to months
Physical Examination				
Fever/degree	Variable	>90%	>90%	Rare
Early focal signs	Often	Occasional	Occasional	Often
Pressure signs	Often	Rare	Occasional	Often
Extra-CNS infection	Often	Often	No	No
CT or MRI Scan				
Focal	Always*	No	Often	Always
Ring effect/onset	Often/late†	No	No	Often/early

CT, computed tomography; *MRI*, magnetic resonance imaging.
*May be negative or nonspecific during first 48 hours of illness.
†Development of abscess wall may be delayed by steroid therapy.
From Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP: *Textbook of Critical Care*, ed 6, Philadelphia, 2011, Saunders.

BASIC INFORMATION

DEFINITION

Brain metastases result from a spread of cancers originating in other organs to the brain. Brain metastases are the most common intracranial tumors in adults and account for more than one half of brain tumors.

SYNONYMS

ICD-9CM CODES

198 Secondary neoplasm of other specified sites

ICD-10CM CODES

C80.0 Malignant neoplasm, primary site unknown

C80.9 Malignant neoplasm, unspecified

C79.89 Secondary malignant neoplasm of other specified sites

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE

- In the United States, an estimated 98,000 to 170,000 new cases occur each year, which represents 24% to 45% of all cancer patients. The increased incidence is likely due to improved detection and better control of extracerebral disease. The incidence is higher in autopsy series, where 20% of patients with systemic disease have brain metastases.
- The prevalence is thought to be 120,000 to 140,000/yr.

PREDOMINANT SEX AND AGE

- In patients with systemic malignancies, brain metastases occur in 10% to 30% of adults and 6% to 10% of children. Of these, about 60% of patients are between the ages of 50 to 70.
- There is no gender predilection.

RISK FACTORS

- In adults, the most common primary tumors accounting for brain metastases are carcinomas, including lung (16% to 20%), breast (5%), kidney (7% to 10%), and colorectal cancers (1% to 2%), and melanoma (7%).
- In children, the most common primary tumors are sarcomas, neuroblastoma, and germ cell tumors.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Brain metastases should be suspected in any cancer patient who develops acute neurologic signs or symptoms. Neurologic symptoms, however, are common in patients with systemic cancer. In an analysis of more than 800 patients with neurologic symptoms, brain metastases were found in only 16%.
- Symptoms:
  1. Headache occurs in 40% to 50% of patients with brain metastases. Frequency is higher with metastases located in the posterior fossa, which may result in obstructive hydrocephalus. The headache is often accompanied by nausea, vomiting, focal neurologic signs, and postural variation.
  2. Focal neurologic signs/symptoms are the presenting symptom in 20% to 40% of patients. Hemiparesis is the most frequent complaint.
  3. Cognitive dysfunction, including memory problems and/or mood/personality changes, is the presenting problem in 30% to 45% of patients.
  4. The frequency of seizures in patients with metastatic brain tumor is 30% to 40%.
  5. Acute stroke secondary to hemorrhage into a metastasis, hypercoagulability, or local vascular invasion accounts for 5% to 10% of patients.

ETIOLOGY

The most common mechanism of metastasis to the brain is by hematogenous spread. The most common location is at the junction of the gray and white matter. The blood vessels decrease in diameter in these regions, which is thought to act like a trap for clumps of tumor cells. Different tumor types have a tendency to metastasize to different regions of the brain. For example, metastases of small cell lung carcinoma are equally distributed in all regions, whereas pelvic (prostate and uterine) and gastrointestinal tumors more commonly metastasize to the posterior fossa.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Primary brain tumor
- Infection: abscess/fungal disease
- Progressive multifocal leukoencephalopathy
- Demyelinating disease: multiple sclerosis, postinfectious encephalomyelitis
- Cerebral infarction/bleeding
- Effects of treatment, such as radiation necrosis

LABORATORY TESTS

- Routine laboratory studies are not typically helpful.
- Lumbar puncture is generally contraindicated due to increased intracranial pressure and risk of herniation.
- Brain biopsy is necessary in some cases for a definitive diagnosis, particularly in the case of unknown primary tumor.

IMAGING STUDIES

- MRI (Fig. B1-47) with and without contrast is the imaging study of choice. Important features on MRI that suggest brain metastases include: presence of multiple lesions, localization at the junction of the gray and white matter, circumscribed margins, large amounts of vasogenic edema. CT of head with contrast (Fig. B1-48) can be used when MRI is contraindicated.
- MR spectroscopy and PET are useful to delineate tumor from other space-occupying lesions or from radiation necrosis.
- Newer experimental imaging studies, such as receptor-targeted and ligand-based molecular imaging, are on the horizon.
- Patients without a known primary tumor. In about 80% of patients, brain metastases develop after the diagnosis of systemic cancer. In the remaining patients, brain metastases are diagnosed simultaneously or before the primary tumor is found. In patients without a known primary tumor, the lung should be the primary focus of evaluation. Other frequent sites include melanoma, colon cancer, and breast cancer. PET scan may be useful in these patients to help identify the primary tumor or to identify other sites of metastatic disease—these latter sites might also be more amenable to biopsy.

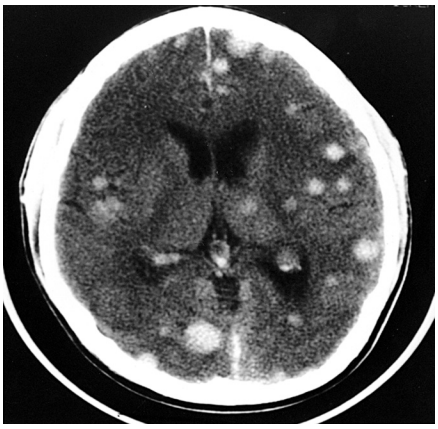

FIGURE B1-48 Intracranial metastatic disease. Axial contrast-enhanced CT scan of head reveals multiple enhancing nodules throughout gray and white matter structures consistent with metastatic disease. (From Vincent JL et al [eds]: *Textbook of critical care*, ed 6, Philadelphia, 2011, Saunders.)

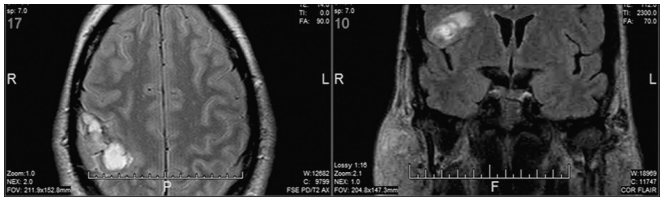

FIGURE B1-47 Brain magnetic resonance imaging (axial and coronal fluid-attenuated inversion recovery sequences) showing hemorrhagic metastatic deposition in the inferior right frontoparietal lobe (lobulated high signal focus) in a 40-year-old woman with metastatic choriocarcinoma to the brain. (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.)

Rx TREATMENT

- Management of patients with brain metastases is influenced by the overall prognosis and may include treatments targeted at the metastases, management and prevention of complications (seizures, edema), and treatment of systemic malignancy, where appropriate. Fig. B1-49 illustrates a decision tree for treatment of patients with brain metastases.
- In patients considered to have a favorable prognosis, treatment focuses on eradication or control of the brain metastases. Approaches include surgical resection and radiation therapy.
- In patients with poor prognosis, treatment focuses on symptom control.

ACUTE GENERAL Rx

- Steroids are used to reduce peritumoral edema and intracranial pressure.
- Antiepileptics are started for patients who present with seizures. Prophylactic treatment for seizure is not necessary in patients with no prior history of seizure.
- Anticoagulants are sometimes used to prevent venous thromboembolic disease.

CHRONIC Rx

- Radiation therapy has become the mainstay of treatment for brain metastases, including whole brain radiation therapy and stereotactic radiosurgery (SRS).
- For highly chemosensitive tumors, chemotherapy has been integrated into the primary management of patients with disseminated disease.
- For other tumors (e.g., small cell and non-small cell lung cancers, breast cancer, melanoma) systemic chemotherapy or molecularly targeted agents may be of palliative value when surgery, whole brain radiation therapy, and SRS have failed or are inappropriate. In most cases, two to three agents in combination and in conjunction with whole brain radiation therapy are used.

DISPOSITION

- The median survival of patients who receive supportive care and are treated with corticosteroids only is approximately 1 to 2 months.
- Key prognostic factors are performance status, extent of systemic disease, and age. Most favorable outcome is found in patients with Karnofsky performance score ≥70, age younger than 70 years, no systemic disease or local control of primary tumor without extracranial metastases, and female gender. In this group, median survival is estimated at 7.1 months.

REFERRAL

Treatment involves a multispecialty team. Consultations from oncology, neurosurgery, neurology, radiation oncology, psychiatry, and physical therapy are all warranted.

PEARLS & CONSIDERATIONS

COMMENTS

- Brain metastases are the most common intracranial tumors in adults, accounting for more than half of all brain tumors.
- Lung cancer, melanoma, renal cell carcinoma, and breast cancer are the most common primary tumors that metastasize to the brain.
- MRI is the most reliable imaging modality.
- Patient treatment depends upon the overall prognosis.

PATIENT/FAMILY EDUCATION

American Brain Tumor Association (http://www.abta.org)

National Brain Tumor Society (http://www.braintumor.org)

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Brain Cancer (Patient Information)

AUTHOR: **NICOLE J. ULLRICH, M.D., PH.D.**

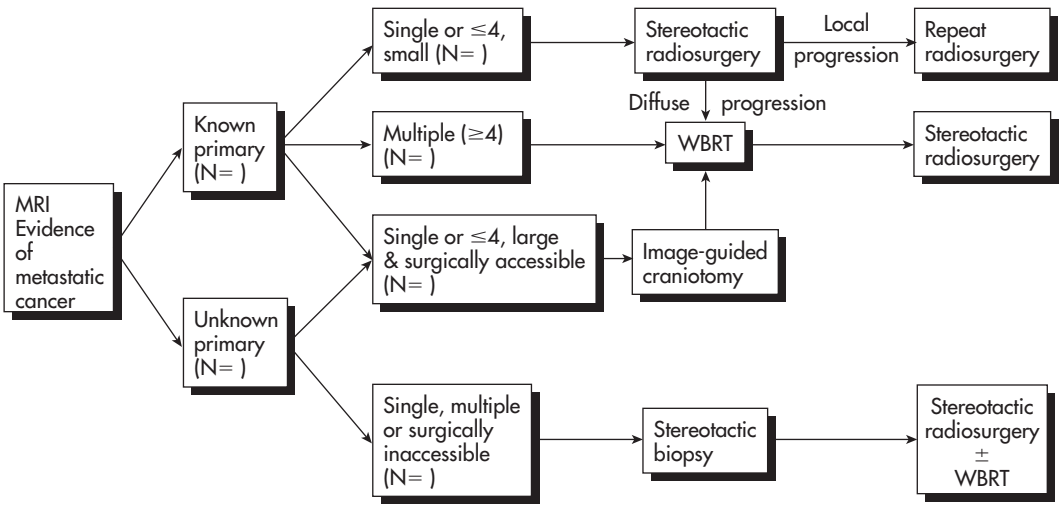

FIGURE B1-49 Decision tree for treatment of patients with brain metastases. (From Sheehan J et al: The expanding role of neurosurgeons in the management of brain metastases. *Surgical Neurology* 62(1), 32–40, 2004.)

SUGGESTED READINGS

Bradley KA, Mehta MP: Management of brain metastases, *Semin Oncol* 31(5):693–701, 2004.

Drappatz J, Wen PY: Chemotherapy and targeted molecular therapies for brain metastases, *Expert Rev Neurother* 6(10):1465–1479, 2006.

Gaspar L et al.: Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials, *Int J Radiat Oncol Biol Phys* 37(4):745–751, 1997.

Kalkanis SN et al.: The role of surgical resection in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline, *J Neurooncol* 96(1):33–43, 2010.

Linskey ME et al.: The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline, *J Neurooncol* 96(1):45–68, 2010.

Mikkelsen T et al.: The role of prophylactic anticonvulsants in the management of brain metastases: a systematic review and evidence-based clinical practice guideline, *J Neurooncol* 96(1):97–102, 2010.

Norden AD et al.: Brain metastases, *Curr Opin Neurol* 18(6):654–661, 2005.

Schouten LJ et al.: Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma, *Cancer* 94:2698–2705, 2002.

Brain Neoplasm, Benign EBM PTG

BASIC INFORMATION

DEFINITION

Brain neoplasms are a diverse group of primary (nonmetastatic) tumors arising from one of many different cell types within the central nervous system (CNS). Specific tumor subtypes and prognosis depend on the tumor cell of origin and pattern of growth. The diffuse low-grade gliomas (LGGs) include World Health Organization Grade II astrocytomas, oligodendrogliomas, and oligoastrocytomas.

SYNONYMS

Low-grade glioma (LGG)
Glioneuronal tumor
Meningioma
Primary brain tumor

ICD-9CM CODES
225.0 Brain neoplasm (benign)
239.2 Brain neoplasm (unspecified)
ICD 10-CM CODES
D33.2 Benign neoplasm of brain, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: U.S. incidence rate is approximately 24.6 cases/100,000 persons per yr for all primary brain tumors (Table B1-10). One third of these are considered malignant and the remainder benign or borderline malignant. The incidence rate in children aged 0 to 19 years is lower (48.6/1,000,000 children). Primary brain neoplasms account for ~2% of all cancers, with a disproportionate share of cancer morbidity and mortality. It is the most common cause of cancer death in children up to 15 yr.
PEAK INCIDENCE: Depends on histology, though highest peak at ~age 50 yr
PREDOMINANT SEX AND AGE: Slight male preponderance (8.0 vs. 5.5/100,000 person/yr)

GENETICS: Most primary CNS neoplasms are sporadic; 5% is associated with hereditary syndromes that predispose to neoplasia. The most common of these include:

- Li-Fraumeni syndrome: *p53* mutation on chromosome 17q13, gliomas
- Von Hippel-Lindau: VHL, chromosome 3p25, hemangioblastoma
- Tuberous sclerosis: TSC1/TSC2 (chromosome 9q34/16p13), subependymal giant cell astrocytoma
- Neurofibromatosis type 1: NF1, chromosome 17q11, neurofibroma, optic nerve glioma, low-grade glioma
- Neurofibromatosis type 2: NF2, chromosome 22q12, schwannoma, meningioma, ependymoma
- Retinoblastoma: pRB, chromosome 13q, retinoblastoma
- Gorlin's syndrome: chromosome 9q31, desmoplastic medulloblastoma

RISK FACTORS: Exposure to ionizing radiation has been implicated in meningiomas, gliomas, and nerve sheath tumors. No convincing evidence has shown a link with trauma, occupation, cellular phone use, diet, or electromagnetic fields.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- In general, the location, size, and rate of growth will determine the symptoms and signs of a brain tumor.
- Headache is common and is the worst symptom in nearly half of all patients. Symptoms of intracranial pressure may also be present, including nausea and vomiting. Headache may be localizing. Papilledema is suggestive of obstructive hydrocephalus.
- Seizures occur in 33% of patients and are among the most common symptoms, particularly with brain metastases and low-grade gliomas. The type of seizure and clinical presentation depends on location. Seizures are more common in low-grade compared with high-grade gliomas. It is thought that patients with seizures typically have smaller tumors at time of diagnosis compared with those with other symptoms, because the onset of seizures prompts an imaging study, leading to an earlier diagnosis.
- Focal neurologic signs and symptoms, including muscle weakness, sensory changes, or visual disturbances are also quite frequent. In addition, cognitive dysfunction, accompanied by changes in memory or personality change, may be recounted, often in retrospect.

TABLE B1-10 Frequency of Primary CNS Tumors

CHILDREN (0-14 YEARS)		ADULTS (≥15 YEARS)	
Type	**Percentage**	**Type**	**Percentage**
Glioblastoma	20	Glioblastoma	50
Astrocytoma	21	Astrocytoma	10
Ependymoma	7	Ependymoma	2
Oligodendroglioma	1	Oligodendroglioma	3
Medulloblastoma	24	Medulloblastoma	2
Neuroblastoma	3	Neurilemmoma	2
Neurilemmoma	1	Pituitary adenoma	4
Craniopharyngioma	5	Craniopharyngioma	1
Meningioma	5	Meningioma	17
Teratoma	2	Pinealoma	1
Pinealoma	2	Hemangioma	2
Hemangioma	3	Sarcoma	1
Sarcoma	1	Others	5
Others	5	TOTAL	100
TOTAL	100		

From Goetz CG, Pappert EJ: *Textbook of clinical neurology,* Philadelphia, 1999, Saunders.

DIAGNOSIS

- Diagnosis is typically based on clinical presentation and imaging characteristics.
- Tumors are best seen on MRI; calcifications are sometimes present.
- Benign and low-grade tumors, typically in the glioma family, are heterogeneous. Recent results have implicated molecular pathway alterations in a subset of patients.

LABORATORY

- Ultimately, only histologic examination can provide the exact diagnosis. Information may also be gleaned from additional features such as proliferative index, immunohistochemical stains, and electron microscopy.
- The current classification schema for gliomas is based on pathologic and microscopic criteria. Tumor histology/histologic diagnosis (World Health Organization [WHO] grading system), includes number of mitoses, capillary endothelial proliferation, and necrosis (*Note:* There can be a high degree of morbidity based on tumor location, even with more benign histology.)
- Genetic analysis of tumors is rapidly becoming important for genetic classification, stratification of treatments, and predicting outcome. Different subtypes of gliomas have distinct gene-expression profiles, which can be distinguished from one another and from normal tissue; these differences typically involve pathways of cell proliferation, energy metabolism, and signal transduction. In adults, global expression profiling identified differences in 360 genes between low-grade and high-grade tumors.

DIFFERENTIAL DIAGNOSIS

- Stroke/cerebral hemorrhage
- Abscess/parasitic cyst
- Demyelinating disease: multiple sclerosis, postinfectious encephalomyelitis
- Metastatic tumors
- Primary CNS lymphoma

WORKUP

- Neuroimaging studies and pathologic sampling are the most important diagnostic modalities in

ETIOLOGY

Most cases are idiopathic, though specific chromosomal abnormalities have been implicated in some tumor types.

evaluation of brain tumors and may be critical for preoperative planning.

IMAGING STUDIES

- MRI with gadolinium enhancement is highly sensitive, though CT scanning is useful if calcification or hemorrhage is suspected. MRI permits visualization of the tumor, as well as the relation to the surrounding tissue. Enhancing tumor can be distinguished from surrounding edema. Low-grade tumors often present as an infiltrating lesion without mass effect. MRI is superior to CT scanning to evaluate the meninges, subarachnoid space, and posterior fossa, and for defining relation to major intracranial vessels. Figure EB1-50 shows the appearance of astrocytoma in imaging studies.
- Magnetic resonance spectroscopy is increasingly being used as a diagnostic tool to define metabolic composition of an area of interest and may be useful to contrast areas of tumor progression from radiation necrosis. N-acetylaspartate is often decreased in brain tumors, whereas choline, a component of cell membranes, is increased because of high cellular turnover.
- PET scan is helpful to distinguish neoplastic lesions (with high rate of metabolism) from other lesions such as demyelination or radiation necrosis (with a much lower metabolic rate). Such lesions take up greater amounts of glucose than surrounding tissues or tumors with slower metabolic rates. May be useful to help map functional areas of the brain before surgery or radiation.
- Functional MRI is now used as an adjunct in perioperative planning for patients whose lesion is in vital regions, such as those responsible for speech, language, and motor control.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Maximal surgical removal or debulking is the initial treatment of choice and provides tissue for diagnosis and molecular characterization. Maximal safe resection is often favored with a trend toward improved survival with this approach.
- Biopsy alone is performed if the tumor is located in eloquent regions of brain or is inaccessible; this is essential for histopathologic diagnosis. Biopsy can be performed under CT or MRI guidance using stereotactic localization.
- If the tumor is benign (e.g., meningioma, acoustic neuroma), often no further therapy is required.

ACUTE GENERAL Rx

Antiseizure medications have been used perioperatively and to control seizures resulting from focal lesions. Prophylactic use of anticonvulsants is not typically recommended without clear history of seizures.

CHRONIC Rx

- Chemotherapy (combination or single agent) may be used before, during, or after surgery and radiation therapy. (In children, chemotherapy is often used to delay radiation therapy.) Radiosensitizers may help increase the therapeutic effect of radiation therapy.
- Radiation is useful for certain types of tumors and is often used if there is residual tumor after surgery; conventional radiation uses external beams over a period of weeks, whereas stereotactic radiosurgery delivers a single, high dose of radiation to a well-defined area (usually <1 cm). Long-term effects of radiation therapy include radiation necrosis (particularly of white matter), blood vessel hyalinization, and secondary tumors (usually meningiomas, sarcomas, and malignant astrocytomas).
- Experimental therapies are continually in development and are typically based on molecular characterization of tumors and small molecule blockers of signal transduction cascades. Some of these therapies involve antisense molecules, biologic agents, immunotherapies, or angiogenesis inhibitors. Intratumoral drug infusions and convection-enhanced delivery of novel agents are currently under study.

DISPOSITION: In general, younger age, high performance status, and lower pathologic grade have more favorable prognosis. For all histologic subtypes of brain tumors, pediatric and young adult patients have a better survival rate.

REFERRAL

- All cases warrant evaluation by an oncologist and neurosurgeon.
- Patients should be evaluated for physical and occupational therapy.
- Children should undergo neuropsychologic evaluations and screening for learning disabilities.

PEARLS & CONSIDERATIONS

COMMENTS

In general, younger age, high performance status, and lower pathologic grade have more favorable prognosis. For all histologic subtypes of brain tumors, pediatric and young adult patients have a better survival.

PATIENT/FAMILY EDUCATION

American Brain Tumor Association (http://www.abta.org)

National Brain Tumor Society (http://www.braintumor.org)

Pediatric Low Grade Astrocytoma (PLGA) (http://fightplga.org)

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Brain Cancer (Patient Information)

AUTHOR: **NICOLE J. ULLRICH, M.D., PH.D.**

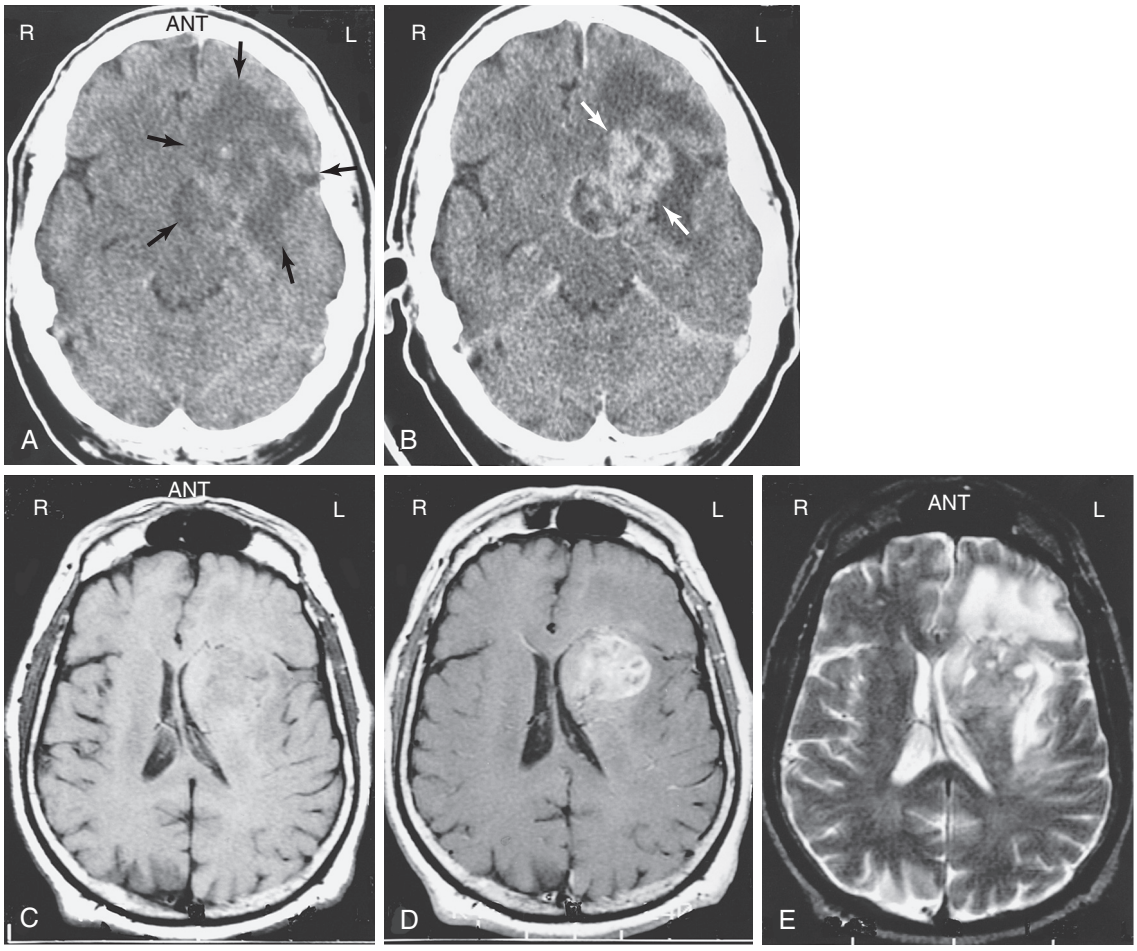

FIGURE EB1-50 Astrocytoma. These contrasted and noncontrasted computed tomography (CT) and magnetic resonance (MR) images were obtained from the same patient and demonstrate a left astrocytoma with a large amount of surrounding edema. The noncontrasted CT scan (**A**) shows only a large area of low density that represents the tumor and edema *(arrows)*. A contrasted CT scan (**B**) shows enhancement of the tumor *(arrows)* surrounded by the dark or low-density area of edema. A noncontrasted T1 MR image (**C**) clearly shows a mass effect due to impression of the tumor on the left lateral ventricle and some midline shift. A gadolinium-enhanced T1 MR image (**D**) clearly outlines the tumor, but the edema is difficult to see. A T2 MR image (**E**) shows the tumor rather poorly, but the surrounding edema is easily seen as an area of increased signal *(white)*. (From Mettler FA Jr: *Essentials of radiology,* ed 3, Philadelphia, 2014, Elsevier.)

EVIDENCE

Abstract[1]

Objective:
The IDH1(R132H) mutation is both a strong prognostic predictor and a diagnostic hallmark of gliomas and therefore has major clinical relevance. Here, we developed a new technique to detect the IDH1(R132H) mutation in the plasma of patients with glioma.

Methods:
Small-size DNA (150-250 base pairs) was extracted from the plasma of 31 controls and 80 patients with glioma with known IDH1(R132H) status and correlated with MRI data. The IDH1(R132H) mutation was detected by a combination of coamplification at lower denaturation temperature and digital PCR.

Results:
The small-size DNA concentration was 1.2 ng/ml (range, 0.1-6.6) in controls vs. 1.2 ng/ml (range, 0.1-50.3) in patients with glioma (P = not significant) and 0.9 ng/ml (0.0-3.0) in low-grade gliomas vs. 1.5 ng/ml in high-grade gliomas (P <0.01). The small-size DNA concentration correlated with enhancing tumor volume (1.6 ng/ml [0.4-24.9] when <10 cm^3 and 14.0 ng/ml[0.6-50.3] when ≥10 cm^3). The IDH1(R132H) mutation was detected in 15 out of 25 plasma DNA mixtures (60%) from patients with mutated tumors and in none of the 14 patients with a nonmutated tumor. The sensitivity increased with enhancing tumor volume (3/9 in nonenhancing tumors, 6/10 for enhancing volume <10 cm^3, and 6/6 for enhancing volume ≥10 cm^3).

Conclusion:
With a specificity of 100% and a sensitivity related to the tumor volume and contrast enhancement, IDH1(R132H) identification has a valuable diagnostic accuracy in patients not amenable to biopsy. Ⓐ

Abstract[2]

Object:
Patients with gliomas frequently have cognitive deficits, and surgery can exacerbate these deficits. Preoperative assessment is therefore crucial in patients undergoing surgery for glioma in eloquent areas because the proximity of functional areas increases the risk of permanent postoperative cognitive disturbances. Although preoperative and postoperative language and motor function in patients with glioma have been investigated frequently, data on good cognition studies are scarce. Most studies have focused on clinical neurologic functioning or have only used brief neurologic instruments. The authors investigated whether surgery for glioma in eloquent areas influences cognition early after surgery, by using an elaborate test protocol.

Methods:
Twenty-eight patients with gliomas of the left hemisphere in language and nonlanguage areas were assessed before and 3 months after surgery with a comprehensive neuropsychologic test protocol. The authors performed a correlation analysis between change in cognitive performance and tumor characteristics (that is, location, volume, pathologic features, and histologic grade) and between cognitive change and treatment-related factors (the extent of the resection and postoperative treatment with chemotherapy and radiotherapy).

Results:
Both preoperatively and postoperatively, the mean performance of the patients was worse than the performance of the normal population in the language domain, the memory domain, and the executive functions (P <0.05). Postoperatively, a decline was found in the language domain (t = 2.34, P = 0.027) and in the executive functions (t = 2.45, P = 0.022). However, cognitive change postsurgery was influenced by the location of the tumor; the decrease of cognitive score in the language domain was only observed in patients with tumors in or close to language areas (t = 2.33, P = 0.029). No effect on cognitive change was found for the other tumor characteristics and treatment-related factors.

Conclusions:
This study underlines the importance of the use of a neuropsychologic test protocol before and after surgery in patients with glioma because several tasks in the domains of language, memory, and executive functions appeared to deteriorate after surgery. Tumor resection in language areas increases the risk of cognitive deficits in the language domain postoperatively. Ⓐ

Evidence-Based References

Boisselier B et al.: Detection of IDH1 mutation in the plasma of patients with glioma, *Neurology* 79:1693–1698, 2012. Ⓐ

Satoer D et al.: Cognitive functioning early after surgery of gliomas in eloquent areas, *J Neurosurg* 117:831–838, 2012. Ⓐ

SUGGESTED READINGS

Bogomolny DL et al.: Functional MRI in the brain tumor patient, *Top Magn Reson Imaging* 15(5):325–335, 2004.

Drappatz J et al.: Medical management of brain tumor patients, *Neurol Clin* 25(4):1035–1071, ix, 2007.

Glantz MJ et al.: Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors, *Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology* 54:1886, 2000.

Inskip PD et al.: Cellular-telephone use and brain tumors, *N Engl J Med* 344(2):79–86, 2001.

Jakola AS et al.: Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in low-grade gliomas, *JAMA* 308(18):1881–1888, 2012.

Jemel A et al.: Cancer statistics, 2007, *CA Cancer J Clin* 57(43), 2007.

Louis DN et al. (editor): *WHO classification of tumors of the central nervous system.* Lyon, IARC Press.

Kleihues P: Pathology and genetics of tumors of the nervous system. In Kleihues P, Cavenee WK, (eds): *International agency for research on cancer,* Lyon, Harcourt, p 22.

Mischel PS et al.: DNA-microarray analysis of brain cancer: molecular classification for therapy, *Nat Rev Neurosci* 5(10):782–792, 2004.

Purow B, Fine HA: Progress report on the potential of angiogenesis inhibitors for neuro-oncology, *Cancer Invest* 22(4):577–587, 2004.

Riva M: Brain tumoral epilepsy: a review, *Neurol Sci* 26(Suppl 1):S40–S42, 2005.

Wen PY, DeAngelis LM: Chemotherapy for low-grade gliomas: emerging consensus on its benefits, *Neurology* 68(21):1762–1763, 2007.

Wrensch M: Epidemiology of primary brain tumors: current concepts and review of the literature, *Neuro Oncol* 4:278, 2002.

Brain Neoplasm, Glioblastoma EBM PTG

BASIC INFORMATION

DEFINITION

Brain neoplasms are a diverse group of primary (nonmetastatic) tumors arising from one of the many different cell types within the central nervous system. Malignant brain tumors are defined by histopathologic features and a rapidly progressive pattern of growth. Glioblastoma is the most common primary brain tumor in adults, accounting for 50% to 60% of primary brain tumors.

SYNONYMS

Glioblastoma
GBM

ICD-9CM CODES
191.9
ICD-10CM CODES
C71.9 Malignant neoplasm of brain, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Annual incidence rate of glioblastoma is approximately 2 to 3 cases/100,000 persons in Europe and North America. High-grade/malignant astrocytomas are slightly more common in whites than in blacks, Latinos, and Asians.
PREDOMINANT SEX AND AGE: Glioblastoma is slightly more common in men than women with a male/female ratio of 3:2. Peak incidence is between 45 and 70 yr. Approximately 10% of glioblastomas occur in children.
PEAK INCIDENCE: High-grade gliomas, such as anaplastic astrocytoma and glioblastoma, tend to originate in the fourth to fifth decade of life and beyond.
RISK FACTORS: Prior radiation may increase risk for primary brain tumor. Glioblastomas are more common in individuals who have a heritable cancer predisposition syndrome, such as Li-Fraumeni syndrome and Turcot syndrome. Prior history of a low-grade astrocytoma, which may progress into a higher grade tumor.
GENETICS: Malignant progression is associated with inactivation of *PTEN* tumor-suppressor gene and amplification of epidermal growth factor receptor *(EGFR)* gene. Overexpression of *EGFR* gene occurs in 40% to 50% of primary glioblastoma cases. Loss of heterozygosity on chromosome 10q occurs in 60% to 90% of both primary and secondary glioblastoma cases and is associated with poor prognosis. The pathway involving mutations of the tumor-suppressor gene *p53* is typically associated with secondary glioblastoma. Other genetic mutations have also been recognized as potential contributors in the pathogenesis of glioblastoma, including *PTEN* and *MDM2*. Deletion of *NFKBIA* has an effect that is similar to the effect of *EGFR* amplification in the pathogenesis of glioblastoma and is associated with comparatively short survival.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- In general, the location, size, and rate of growth will determine the symptoms and signs. Clinical history of patients with glioblastoma is typically brief, <3 mo in the majority of patients with primary glioblastoma.
- Most frequent symptoms include:
  1. Headache occurs in the majority of cases. The headache can be localizing or may result from increased intracranial pressure.
  2. Seizures occur in 30% to 60% depending on tumor location and grade.
  3. Symptoms and signs of hydrocephalus and raised intracranial pressure (headache, vomiting, clouding of consciousness, papilledema).
  4. Other symptoms seen in 20% or more of patients include memory loss, focal motor weakness, visual changes, language deficits, and cognitive disturbances or memory changes due to involvement of the temporal and frontal lobes.

ETIOLOGY

- Glioblastomas are classified as primary or secondary. Primary glioblastoma constitutes the majority of cases (60%) in adults older than 50 yr and are considered de novo tumors. Secondary glioblastoma typically involves malignant progression from a lower grade (grade II or III) glioma.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Stroke
- Arteriovenous malformations
- Abscess/parasitic cyst (neurocysticercosis)
- Demyelinating disease: tumefactive multiple sclerosis, postinfectious encephalomyelitis
- Metastases
- Primary central nervous system lymphoma

LABORATORY TESTS

- Routine laboratory studies are not typically helpful.
- Lumbar puncture is generally contraindicated; cerebrospinal fluid studies do not add much specific additional information for the diagnosis for glioblastoma.
- Ultimately, only a histologic examination can provide the exact diagnosis. Information may also be gleaned from additional features such as proliferative index, immunohistochemical stains, and electron microscopy, as well as molecular markers.

IMAGING STUDIES (Fig. B1-51)

- MRI with and without contrast is the imaging study of choice, though CT scanning is useful if calcification or hemorrhage is suspected. MRI permits visualization of the tumor, as well as the relation to the surrounding tissue. Enhancing tumor can be distinguished from surrounding edema. MRI is superior to CT scanning to evaluate the meninges, subarachnoid space, and posterior fossa, and for defining relation to major intracranial vessels.
- Magnetic resonance spectroscopy (MRS) is increasingly being used as a diagnostic tool to define metabolic composition of an area of interest and may be useful to contrast areas of tumor progression from radiation necrosis. *N*-acetylaspartate, a marker of neurons, is often decreased in brain tumors, whereas choline, a component of cell membranes, is increased because of high cellular turnover.
- PET scan is helpful to distinguish neoplastic lesions (with high rate of metabolism) from other lesions such as demyelination or radiation necrosis (with a much lower metabolic rate). Such lesions take up greater amounts of glucose than surrounding tissues or tumors with slower metabolic rates. PET imaging also aids in preoperative planning to increase diagnostic yield and to help map functional areas of the brain before surgery.
- Functional MRI is now used as an adjunct modality in perioperative planning for patients whose lesion is in vital regions (eloquent regions), such as those responsible for speech, language, and motor control.

TREATMENT

- Current standard-of-care therapies include surgery, radiation, and palliative chemotherapy,

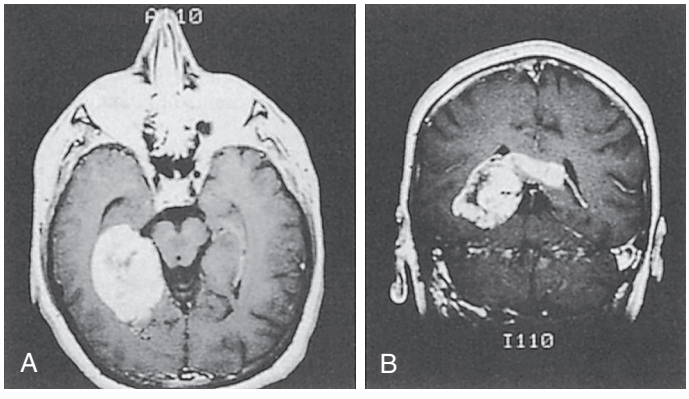

FIGURE B1-51 Glioblastoma multiforme. Axial **(A)** and coronal **(B)** postcontrast enhanced T1-weighted image showing a large homogeneously contrast-enhancing mass in the right medial temporal lobe with extension across the midline. (From Specht N [ed]: *Practical guide to diagnostic imaging,* St Louis, 1998, Mosby.)

all of which have significant adverse effects and limited efficacy. Median time to recurrence after standard therapy is 6.9 mo.

PHARMACOLOGIC AND NONPHARMACOLOGIC THERAPY

- Maximal surgical removal or debulking is the initial treatment of choice and is the first stage in treatment. Removal of 98% or more of the tumor is associated with a significantly longer event-free survival.
- Biopsy alone is performed if the tumor is located in eloquent regions of brain or is inaccessible; this is essential for histopathologic diagnosis. Biopsy can be performed with CT or MRI guidance using stereotactic localization.
- Radiation therapy is the mainstay of treatment for individuals with glioblastoma and improves local control and overall survival after surgery. Even patients with a gross total resection of tumor have a high recurrence rate.
- Chemotherapy (combination or single agent) may be used before, during, or after surgery and radiation therapy. (In children, chemotherapy is often used to delay radiation therapy.) Radiosensitizers may help increase the therapeutic effect of radiation therapy. Conventional treatment includes radiation in combination with temozolomide. Bevacizumab is used to treat patients with glioblastoma at progression after standard therapy.
- Experimental therapies in development are typically based on molecular characterization of tumors and small molecule blockers of signal transduction cascades. Some of these therapies involve antisense molecules, biologic agents, immunotherapies, or angiogenesis inhibitors. Intratumoral drug infusions and convection-enhanced delivery of novel agents are currently under study. In addition, delivery systems such as the use of a vector to permit gene transfer with the goal to selectively kill cancer cells are being investigated.

ACUTE GENERAL Rx

- Corticosteroids are used to reduce edema and may also be used perioperatively or during radiation therapy.
- Antiepileptic medications have been used perioperatively and to control seizures resulting from focal lesions. Prophylactic use of anticonvulsants is not typically recommended without clear history of seizures.

DISPOSITION

- Glioblastoma multiforme is the most aggressive form of primary brain tumor. The important prognostic factors include the extent of resection, patient age, tumor grade/histology, and performance status. In general, younger age, high performance status, and lower pathologic grade have more favorable prognosis. For all histologic subtypes of brain tumors, pediatric and young adult patients have a better survival.
- Terminal events typically result from increased intracranial pressure.

REFERRAL

Treatment should involve a multispecialty team with consultations from oncology, neurosurgery, neurology, radiation oncology, psychiatry, and physical therapy.

PEARLS & CONSIDERATIONS

COMMENTS

Glioblastoma is distinguished pathologically by the presence of vascular proliferation and necrosis.

PATIENT/FAMILY EDUCATION

American Brain Tumor Association
National Brain Tumor Society (http://www.braintumor.org)

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Brain Cancer (Patient Information)

AUTHOR: **NICOLE J. ULLRICH, M.D., PH.D.**

EVIDENCE

Abstract[1]

Introduction:

Reliable differentiation between glioblastoma and primary CNS lymphoma (PCNSL) using conventional MR imaging is challenging since both entities may show similar appearance on structural MR imaging. Here we analyzed if the appearance of intratumoral susceptibility signals (ITSS) on susceptibility weighted imaging (SWI) may differentiate between both entities.

Methods and Materials:

SWI and contrast-enhanced T1-weighted images were acquired from 15 patients with newly diagnosed PCNSL (14 B-cell PCNSL, 1 T-cell PCNSL) and 117 patients with newly diagnosed glioblastoma with a 3-tesla MR. Additional phase images were available in 8 patients with PCNSL and 88 patients with glioblastoma. Appearance of ITSS was assessed by two readers on SWI, and the size of the enhancing lesions on contrast-enhanced T1-weighted images was measured. Furthermore it was assessed if ITSS displayed more clearly on SWI or on phase images.

Results:

ITSS were detected in 106 (reader 1) and 109 (reader 2) glioblastoma, respectively. Both readers identified ITSS within the T-cell PCNSL, while both readers did not identify any ITSS within the 14 B-cell PCNSL. Inter-reader variability as determined by Cohen κ was excellent for glioblastoma ($\kappa = 0.938$) and for PCNSL ($\kappa = 1$). The medium size of the enhancing lesion of the glioblastoma that did not harbor ITSS was significantly smaller than the size of the glioblastoma exhibiting ITSS ($P < 0.008$). All identified ITSS displayed more clearly on SWI than on phase images.

Conclusion:

Presence of ITSS differentiates reliably between glioblastoma and B-cell PCNSL and provides a fast basis for the clinical decision without causing any postprocessing work. Ⓐ

Evidence-Based Reference

Radbruch A, et al.: Differentiation of glioblastoma and primary CNS lymphomas using susceptibility weighted imaging, *Eur J Radiol* 82:552–556, 2013. Ⓐ

SUGGESTED READINGS

Bogomolny DL et al.: Functional MRI in the brain tumor patient, *Top Magn Reson Imaging* 15(5):325–335, 2004.

Bredel M et al.: NFKBIA deletion in glioblastomas, *N Engl J Med* 364:627–637, 2011.

Chao ST: The sensitivity and specificity of FDG PET in distinguishing recurrent brain tumor from radionecrosis in patients treated with stereotactic radiosurgery, *Int J Cancer* 96:191, 2001.

Glantz MJ et al.: Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors, Report of the Quality Standards Subcommittee of the American Academy of Neurology, *Neurology* 54:1886, 2000.

Inskip PD et al.: Cellular-telephone use and brain tumors, *N Engl J Med* 344(2):79–86, 2001.

Jemel A et al.: Cancer statistics, 2007, *CA Cancer J Clin* 57:43, 2007.

In: (editors: Kleihues P.; Cavenee W.K.) Pathology and genetics of tumors of the nervous system. International Agency for Research on Cancer: Lyon, p. 22.

Mischel PS et al.: DNA-microarray analysis of brain cancer: molecular classification for therapy, *Nat Rev Neurosci* (10):782–792, 2004.

Norden AD, Drappatz J, Wen PY: Antiangiogenic therapies for high-grade glioma, *Nat Rev Neurol* (11):610–620, 2009.

Riva M: Brain tumoral epilepsy: a review, *Neurol Sci* 26(Suppl 1):S40–S42, 2005.

Stupp R et al.: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma, *N Engl J Med* 352(10):987–996, 2005.

Wrensch M: Epidemiology of primary brain tumors: current concepts and review of the literature, *Neuro Oncol 4* 278, 2002.

BASIC INFORMATION

DEFINITION

The term *breast cancer* refers to invasive carcinoma of the breast, whether ductal or lobular.

SYNONYMS

Carcinoma of the breast

ICD-9CM CODES
174.9 Malignant neoplasm female breast
ICD-10CM CODES
C50.919 Malignant neoplasm of unspecified site of unspecified female breast

EPIDEMIOLOGY & DEMOGRAPHICS

- Nearly exclusively the disease of women, with only 1% of breast cancers in males
- Steady increase in its incidence in the U.S., with approximately 210,000 new patients annually; more than 50,000 are Stage 0 ductal carcinoma in situ (DCIS). The most common form of breast cancer is hormone-receptor positive; its incidence has increased in the past decade, particularly among young women.
- Annual mortality of approximately 40,000
- 21% of breast cancers are diagnosed in women <50 yr. Risk steadily increases with age. Table B1-11 describes risk factors for breast cancer.
- Genetically defined group of women with *BRCA-1* or *BRCA-2* genes identified to carry lifetime risk as high as 85%

TABLE B1-11 Risk Factors for Breast Cancer

Risk Factor	Relative Risk
Any benign breast disease	1.5
Postmenopausal hormone replacement (estrogen with or without progestin)	1.5
Menarche at <12 yr	1.1-1.9
Moderate alcohol intake (two to three drinks/day)	1.1-1.9
Menopause at >55 yr	1.1-1.9
Increased bone density	1.1-1.9
Sedentary lifestyle and lack of exercise	1.1-1.9
Proliferative breast disease without atypia	2
Age at first birth >30 yr or nulliparous	2-4
First-degree relative with breast cancer	2-4
Postmenopausal obesity	2-4
Upper socioeconomic class	2-4
Personal history of endometrial or ovarian cancer	2-4
Significant radiation to chest	2-4
Increased breast density on mammogram	2-4
Older age	> 4
Personal history of breast cancer (in situ or invasive)	> 4
Proliferative breast disease with atypia	> 4
Two first-degree relatives with breast cancer	5
Atypical hyperplasia and first-degree relative with breast cancer	10

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Increasing number of small breast cancers found by mammograms
- Patients usually completely free of physical findings
- Palpable tumors possibly as small as 1 cm or even smaller
- Size of the mass and its location measured and documented
- Skin and/or nipple retraction and skin edema, erythema, ulcer, satellite nodule
- Nodal enlargement in axilla and supraclavicular areas
- Advanced disease: clinical signs of pleural effusion and/or hepatomegaly
- Rare instances: clear, serous, or bloody discharge only symptom
- Nipple evaluation (see "Paget's Disease of the Breast")

ETIOLOGY

- Precise mechanism of carcinogenesis not understood. Gene expression analysis has altered the way breast cancer is perceived in that it is no longer regarded as a single disease. Estrogen receptor (ER)-positive and ER-negative cancers are clinically distinct diseases. So-called triple negative breast cancers constitute approximately 20% of all breast cancers but have different behavior than non-triple negative. The term refers to absence of the estrogen, progesterone, and HER2/neu receptors. Absence of these receptors removes an important target for non-surgical treatment. Stage for stage, long-term prognosis is similar when compared to receptor-positive tumors, but the overall treatment approach will need to be more aggressive. Relapse rates are also different, with an initially elevated rate up to five years but subsequently with substantial decrease in the rate of cancer relapse.
- Approximately 10% of all women with breast cancer have a germline mutation of *BRCA-1, BRCA-2, P53,* or other mutations.
- Possibly interaction of ovarian estrogen, non-ovarian estrogen, estrogens of exogenous origin with breast tissue of varied carcinogenic susceptibility to develop cancer
- Other known or suspected variables: childbearing, breastfeeding practice, diet, physical activities, body mass, alcohol intake
- *BRCA-1* and *BRCA-2* genes are responsible for 90% of hereditary breast cancer

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

The following nonmalignant breast lesions can simulate breast cancer on both physical and mammogram examinations:
- Fibrocystic changes
- Fibroadenoma
- Hamartoma

WORKUP

- Physical examination:
  1. Mass detected by patient or medical professional: workup required
  2. Negative mammogram: breast cancer not ruled out
  3. Sonogram: to demonstrate mass to be cyst, usually eliminating need for further workup
  4. Screening with both MRI and mammography might rule out cancerous lesions better than mammography alone in women who are known or likely to have an inherited predisposition to breast cancer
- To establish diagnosis:
  1. Positive aspiration cytology on a clinically and mammographically malignant mass—highly accurate but still requires open biopsy confirmation
  2. Stereotactic core needle biopsy diagnosis: Stereotactic- and ultrasonography-guided core-needle biopsy procedures seem to be almost as accurate as open surgical biopsy with lower complication rates. They are reliable with invasive carcinoma identified, but negative or equivocal results require careful evaluation
  3. Atypical hyperplasia or in situ carcinoma found by core needle biopsy: open surgical biopsy confirmation still required
  4. Excisional or incisional biopsy: establishes diagnosis

  NOTE: Do not rely on negative mammogram or negative aspiration cytology findings to exclude malignancy. Make appropriate referral. Obtain imaging studies such as bone scan, chest x-ray, CT scan of abdomen, or CT scan of liver.
- Breast radiologic evaluation and an algorithm for breast cancer screening and evaluation are described in Section III. The differential diagnosis of breast lumps is described in Section II.

IMAGING STUDIES

Mammograms (Figs. B1-52 and B1-53): 30% to 50% of breast cancers detected by screening mammograms only as a spiculated mass, a mass with or without microcalcifications, or a cluster of microcalcifications. MRI is an excellent modality that is particularly useful in patients with breast implants and when there is a strong family history of breast cancer. MRI is also better than other methods of assessing the response to neoadjuvant chemotherapy and is useful in identifying the primary tumor in patients who present with axillary adenopathy.

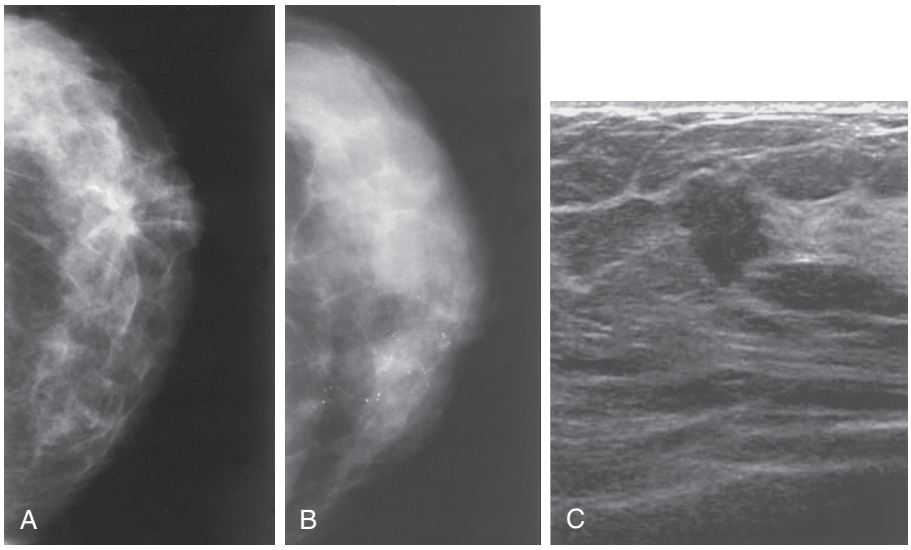

FIGURE B1-52 Mammogram and ultrasound findings of breast disease. A, A stellate mass in the breast. The combination of a density with spiculated borders and distortion of surrounding breast architecture suggests a malignancy. **B,** Clustered microcalcification. Fine, pleomorphic, and linear calcifications that cluster together suggest the diagnosis of ductal carcinoma in situ (DCIS). **C,** An ultrasound image of breast cancer. The mass is solid, containing internal echoes, and displaying an irregular border. Most malignant lesions are taller than they are wide. (From Townsend CM et al [eds]: *Sabiston textbook of surgery*, ed 17, Philadelphia, 2004, Saunders.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Early breast cancer: primarily surgical or surgical and radiotherapeutic. Table B1-12 compares ductal versus lobular carcinoma in situ. Adjuvant treatment guidelines for patients with early-stage invasive breast cancer are described in Table B1-13.
- Choice in 60% to 70% of women between modified mastectomy and breast-conserving treatment, which consists of lumpectomy, axillary staging with sentinel node biopsy or axillary dissection, and breast irradiation
- Recent trials reveal that among patients with limited sentinel lymph nodes (SNL), metastatic breast cancer treated with breast conservation and systemic therapy, the use of sentinel lymph node dissection (SNLD) alone compared with axillary lymph node dissection (ALND) did not result in inferior survival

ACUTE GENERAL Rx

DCIS: Local breast-conserving therapy (lumpectomy plus radiation therapy) or mastectomy followed by tamoxifen therapy in estrogen receptor-positive cases

- Invasive breast cancer: Mastectomy and sentinel lymph node evaluation *or* lumpectomy and sentinel lymph node evaluation plus whole breast radiation therapy
- Invasive breast cancer may require adjuvant chemotherapy or endocrine therapy. Standard chemotherapy consists of either cyclophosphamide, methotrexate, and fluorouracil or cyclophosphamide plus doxorubicin. Endocrine therapy is recommended after chemotherapy in patients with hormone-receptor positive tumors. Adjuvant hormone therapy with anti-estrogen drugs reduces disease recurrence and mortality in these postmenopausal women with breast cancer. Aromatase inhibitors decrease the agonist effect of estrogen by inhibiting estrogen synthesis and have become preferred first-line hormonal treatment agents over the selective estrogen receptor modulator tamoxifen.
- Table B1-14 describes intrinsic molecular subtypes of breast cancer. Molecular targets in clinical breast cancer management are described in Table B1-15. Clinicopathologic considerations for patients with ER-positive and human epidermal growth factor receptor 2 (HER2)-negative disease are summarized in Table B1-16.
- Weekly paclitaxel after standard adjuvant chemotherapy with doxorubicin and cyclophosphamide improves disease-free and overall survival in women with breast cancer. However, patients with *HER2*-negative, estrogen-receptor–positive, node-positive breast cancer may gain little benefit from administration of paclitaxel after adjuvant chemotherapy with doxorubicin plus cyclophosphamide.
- Fig. B1-54 illustrates considerations for adjuvant chemotherapy in the management of recurrent and metastatic breast cancer.
- The combination of the aromatase inhibitor anastrozole and fulvestrant is superior to anastrozole alone or sequential anastrozole and fulvestrant for the treatment of HR-positive metastatic breast cancer.
- Trastuzumab emtansine (T-DM1), an antibody-drug conjugate incorporating HER2-targeted antitumor properties of trastuzumab with the cytotoxic activity of the microtubule inhibitor agent DM1, has been shown to significantly prolong progression-free and overall survival with less toxicity than lapatinib plus capecitabine in patients with HER2-positive advanced breast cancer.
- Recent trials in patients with HER2-positive metastatic breast cancer have shown that the addition of pertuzumab to trastuzumab and docetaxel, as compared with the addition of placebo, significantly improved the median overall survival to 56.6 months and extended the results of precious analyses showing the efficacy of the drug combination.[1]

CHRONIC Rx

Follow-up required after proper treatment of primary breast cancer includes:

- Periodic clinical evaluations as delineated by medical oncologist or surgeon
- Annual mammograms/MRI
- Other tests as indicated
- Patient instruction in monthly breast self-examination technique

DISPOSITION

- Prognosis after curative therapy: depends on size of tumor, extent of nodal metastasis, and pathologic grade of tumor
  1. Patient with 1-cm tumor with no axillary node metastasis: 10-yr disease-free survival rate of 90%
  2. Patient with 3-cm tumor with metastasis in four nodes: 10-yr disease-free survival rate of 15% if no systemic adjuvant therapy given
  3. Outlook for most patients is between these extremes
- Systemic adjuvant therapy: improves prognosis significantly. Women who take tamoxifen for 10 yr lower their risk of recurrence by 25% and dying of breast cancer by 27% compared with those who took the pills for just 5 yr. Adjuvant therapy with an aromatase inhibitor improves outcomes, compared with tamoxifen, in postmenopausal women with hormone receptor–positive breast cancer. Recent trials have shown that in premenopausal women with hormone receptor–positive early breast cancer, adjuvant treatment with the aromatase inhibitor exemestane plus ovarian suppression, compared with tamoxifen plus ovarian suppression, significantly reduced recurrence.
- Isolated tumor cells or micrometastases in regional lymph nodes is associated with a reduced 5-yr rate of disease-free survival among women with favorable early-stage breast cancer who do not receive adjuvant therapy. Survival is improved in patients with isolated tumor cells or micrometastases who received adjuvant therapy.
- Retrospective analyses suggest that occult lymph-node metastases are an important prognostic factor for disease recurrence or survival among patients with breast cancer; however, recent trials indicate that the mag-

[1]Swain SM, Baselga J et al: Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer, *N Engl J Med 372:724-34,* 2015.

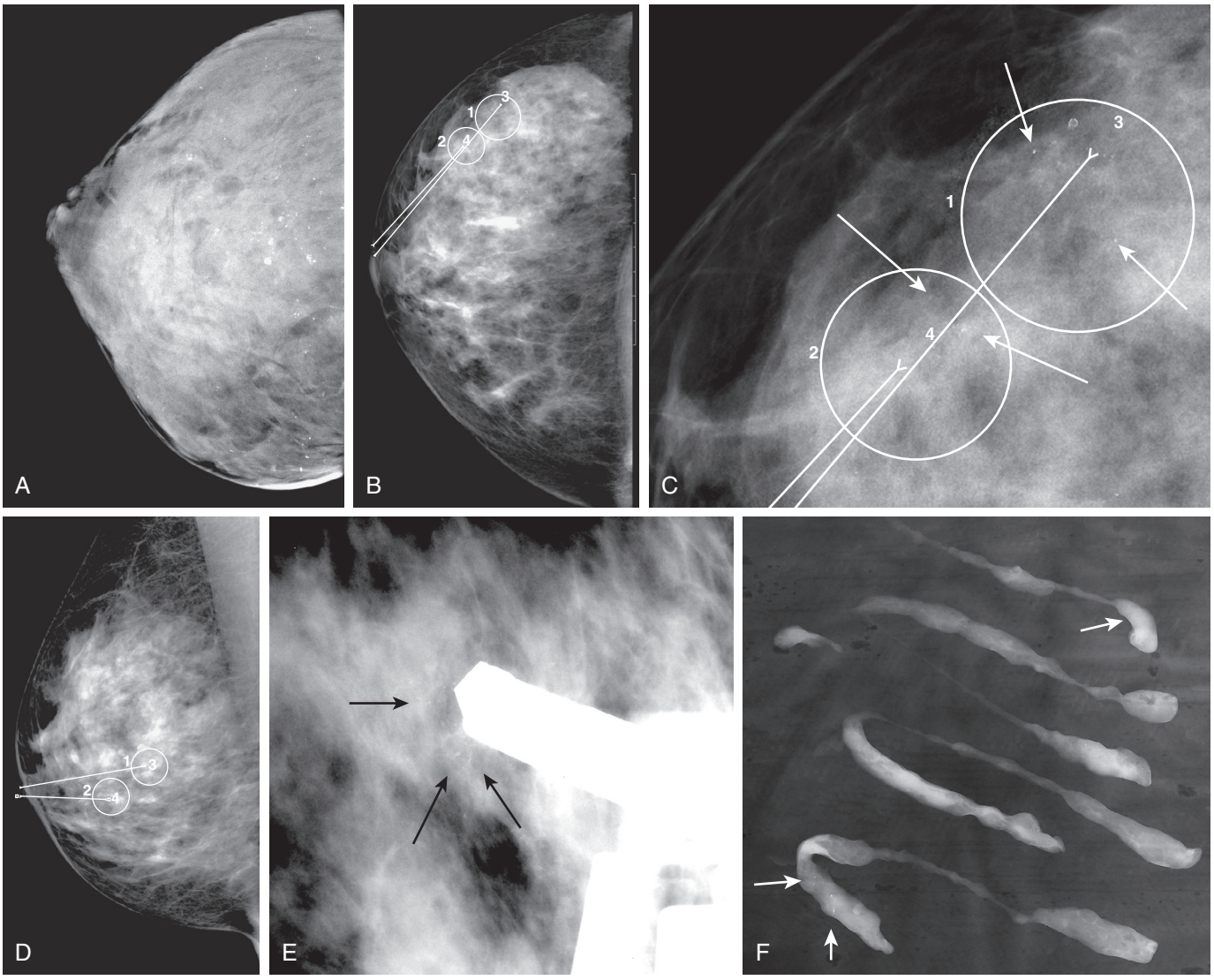

FIGURE B1-53 Digital mammography and workup of breast calcifications. **A,** Craniocaudal (CC) view in a routine screening of a 43-year-old woman. Digital mammography penetrates dense breast tissue better than film-screen mammography, clearly showing diffuse benign pattern of large and small calcifications throughout the breast. **B,** CC view in a routine screening of a 46-year-old woman. Digital mammography shows two areas of very faint calcification in the outer breast that require further workup. **C,** Close-up view of **B,** showing the calcifications (*arrows*) to be variable in size and shape, which is worrisome for malignancy, particularly ductal carcinoma in situ. Such tiny calcifications in a background of dense breast stroma are easier to see on digital mammography than on film-screen mammography. Computer-assisted diagnosis programs also help the radiologist to locate even tiny groups of faint calcifications such as these. **D,** Mediolateral view in the same patient as in **B,** showing that the calcifications are in the lower breast. **E,** Image from stereo core biopsy procedure in the same patient as in **B,** showing the core needle immediately proximal to one of the groups of calcifications. Stereo core biopsy allows histologic sampling of tiny groups of calcifications, which can be very helpful in planning surgical approach. This interventional procedure can decrease the total number of surgeries that a patient must undergo to achieve definitive treatment. **F,** Radiograph of specimen from stereo core biopsy procedure on the same patient as in **B,** showing that there are several tiny calcifications (*arrows*) within some of the core samples. Pathologic analysis of the core biopsy revealed ductal carcinoma in situ, high grade, with comedo features. (From Skarin AT: *Atlas of diagnostic oncology*, ed 4, Philadelphia, 2010, Elsevier.)

nitude of the difference in outcome at 5 yr is small (1.2 percentage points). These data do not favor a clinical benefit of additional evaluation (including immunohistochemical analysis) of initially negative sentinel nodes in patients with breast cancer.
- The addition of zoledronic acid to adjuvant endocrine therapy improves disease-free survival in premenopausal patients with estrogen-responsive early breast cancer.

REFERRAL

Referral is necessary as soon as breast cancer is suspected.

PEARLS & CONSIDERATIONS

Breast cancer in pregnancy and lactation

1. Frequency in women 40 yr or younger reported to be 15%
2. May carry worse prognosis because disease discovery delayed by engorged and nodular breast changes and/or because disease progression more rapid in pregnancy
3. Survival rates similar to those for nonpregnant early-stage breast cancer patients in same age group
4. Mass usually found by patient or obstetrician
5. Expedient workup recommended, including mammography and sonography
6. Diagnosis to be made without delay
7. Choice of mastectomy or lumpectomy with axillary dissection for treatment
8. Adjuvant chemotherapy delayed until third trimester or after delivery
9. Irradiation to breast after lumpectomy delayed until after delivery

Ductal carcinoma in situ (DCIS, intraductal carcinoma) (see Table B1-12)

1. Discovered by mammogram as cluster of microcalcifications and/or density
2. Presents less often as a palpable mass or nipple discharge

TABLE B1-12 Carcinoma in Situ: Lobular Versus Ductal

Feature	Lobular Carcinoma in Situ	Ductal Carcinoma in Situ
Age	Younger	Older
Palpable mass	No	Uncommon
Mammographic appearance	Not detected on mammography	Microcalcifications, mass
Immunophenotype	E-cadherin negative	E-cadherin positive
Usual manifestation	Incidental finding on breast biopsy	Microcalcifications on mammography or breast mass
Bilateral involvement	Common	Uncertain
Risk and site of subsequent breast cancer	25% risk for invasive breast cancer in either breast over remaining lifespan	At site of initial lesion; 0.5% risk/yr of invasive breast cancer in opposite breast
Prevention	Consider tamoxifen or raloxifene	Consider tamoxifen or raloxifene if estrogen-receptor positive
Treatment	Yearly mammography and breast examination	Lumpectomy ± radiation; mastectomy for large or multifocal lesions

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

TABLE B1-13 Adjuvant Treatment Guidelines for Patients with Early-Stage Invasive Breast Cancer*

Patient Group*	Treatment
Favorable Histology (Tubular or Colloid)	
ER- and/or PR-Positive Breast Cancer	
<1 cm	No adjuvant therapy
1-2.9 cm	Consider adjuvant hormonal therapy†
≥3 cm or node-positive	Adjuvant hormonal therapy ± adjuvant chemotherapy†
ER- and PR-Negative Breast Cancer	
<1 cm	No adjuvant therapy
1-2.9 cm	Consider adjuvant chemotherapy
≥3 cm or node-positive	Adjuvant chemotherapy
Hormone Receptor-Positive (ER- and/or PR-Positive) Breast Cancer	
Lymph Nodes Negative	
≤0.5 cm	No adjuvant therapy
0.6-1.0 cm well differentiated and no unfavorable features‡	Consider adjuvant hormonal therapy
0.6-1.0 cm moderate or poorly differentiated or unfavorable features	Adjuvant hormonal therapy ± adjuvant chemotherapy
>1 cm	Adjuvant hormonal therapy ± adjuvant chemotherapy
Lymph Nodes Positive	
	Adjuvant hormonal therapy + adjuvant chemotherapy
Hormone Receptor-Negative (ER- and PR-Negative) Breast Cancer	
≤0.5 cm	No adjuvant therapy
0.6-1.0 cm	Consider chemotherapy
>1 cm or lymph-node positive	Adjuvant chemotherapy
HER2 Positive	
	Trastuzumab should be added to the suggested treatment above for all node-positive patients; trastuzumab not recommended for tumors ≤1 cm for most node-negative patients; for tumors >1 cm, trastuzumab should be considered for most patients

ER, Estrogen receptor; *HER2,* human epidermal growth factor receptor 2; *PR,* progesterone receptor.
*Data are insufficient to make chemotherapy recommendations for patients ≥70 yr. Treatment should be individualized for these patients based on life expectancy and comorbidity.
†In ER-positive or PR-positive patients, decisions regarding the added value of chemotherapy in addition to hormonal therapy alone can be aided by accurately assessing the added value of chemotherapy in individual patients using a web-based model: www.adjuvantonline.com or Oncotype Dx assay.
‡Unfavorable characteristics include high-grade tumor, blood vessel or lymphatic invasion by tumor, and high tumor proliferation rate (high S phase by flow cytometry or high Ki-67 value by immunohistochemistry) or HER2-positive status.
Modified from National Comprehensive Cancer Network Guidelines. Available at www.nccn.org.

3. Before mammogram screening, DCIS accounted for 1% of all breast cancers
4. Now 15% to 20% or even higher proportion have DCIS
5. Formerly treated with mastectomy, now lumpectomy
6. Cure rates 98% to 99%
7. No axillary dissection required
8. With radiation, breast recurrences reduced
9. Mastectomy possibly required with extensive and/or high-grade DCIS
10. Systemic adjuvant treatment is not indicated

Inflammatory carcinoma:

1. Rare but rapidly progressive and often lethal form of breast cancer
2. Presents as erythematous and edematous breast resembling mastitis
3. Biopsy required, including skin
4. Treatment with combination chemotherapy followed by surgery and radiation therapy
5. Prognosis once dismal, now 5-yr disease-free survival in 50% of patients

COMMENTS

- The U.S. Preventive Services Task Force (USPSTF) now recommends against automatic "routine" screening of younger women (age range 40 to 49). The task force recommends biennial screening mammography for all middle-aged women (age range 50 to 74). It also states that current evidence is insufficient to assess the benefits and harms of screening mammography in older women (aged 75 and older). The task force also discourages women from performing breast self-examination. Several other U.S. organizations, such as the American Congress of Obstetricians and Gynecologists, however, still recommend annual screening beginning at age 40. This has created confusion among both physicians and the general public. Physicians should be familiar with the risks and benefits of various competing recommendations in order to better counsel patients.
- Breast radiologic evaluation, evaluation of nipple discharge, and evaluation of palpable mass are described in Section III.
- Exposure of the heart to ionizing radiation during breast cancer radiotherapy increases risk of ischemic heart disease. The increased rate of ischemic heart disease begins within a few years of exposure and continues for at least 20 yr. The increase is proportional to the mean radiation dose to the heart.

RISK REDUCTION STRATEGIES

- Prophylactic bilateral mastectomy reduces the risk for invasive breast cancer by >90%.
- Selective estrogen receptor modulators (SERM) reduce the incidence of hormone receptor-positive invasive breast cancer by 50%.
- Ovarian failure is a common toxic effect of chemotherapy. Administration of the gonadotropin-releasing hormone (GnRH) agonist Goserelin appears to protect against ovarian failure,

TABLE B1-14 Intrinsic Molecular Subtypes of Breast Cancer

Type	Characteristics	Markers
Luminal A	Low grade, high ER, 50% of breast cancer	ER+, PR+, HER2–, CK8+, CK18+
Luminal B	Higher grade, lower ER, 10% of breast cancer	ER+, PR+/–, HER2+/–
HER2	High grade, p53 mutations, 5% to 10% of breast cancer	ER–, PR–, HER2+
Basal	High proliferation CK5+, CK14+, CK17+, EGFR+,30% of breast cancer	ER–, PR–, HER2–

CK, Cytokeratin.
From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

TABLE B1-15 Molecular Targets in Clinical Breast Cancer Management

Target	Drug	Status
ER	Tamoxifen	Survival benefit, adjuvant treatment, and metastatic disease, premenopausal and postmenopausal women
	Aromatase inhibitors (anastrozole, letrozole, exemestane)	Survival benefit, adjuvant and metastatic disease, postmenopausal women
	Fulvestrant	Second-line therapy, metastatic disease in postmenopausal women
HER2	Trastuzumab	Survival benefit, adjuvant and metastatic disease
HER1+ HER2	Lapatinib	Second-line therapy, metastatic disease; phase II adjuvant trials ongoing
HER1 (EGFR)	Gefitinib, erlotinib	Benefit unclear after phase II trials
	Cetuximab	In trial
VEGF	Bevacizumab	Progression-free survival benefit, metastatic disease; phase III adjuvant trials ongoing
PARP1/PARP2	PARP1 inhibitor	Improved PFS, OS in phase II trial, phase III initiated

OS, Overall survival; *PFS,* progression-free survival.
From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

TABLE B1-16 Clinicopathologic Considerations for Patients with ER-Positive, HER2-Negative Disease

Clinicopathologic Features	Consider Adding Chemotherapy	Factors Not Useful for Decision	Consider Endocrine Therapy Only
ER and PR	Lower ER/PR levels		Higher ER/PR levels
Grade	Grade 3	Grade 2	Grade 1
Proliferation	Ki-67 >30%	Ki-67 16% to 30%	Ki-67 ≤15%
Nodes	Node positive (four or more nodes)	Node positive (one to three nodes)	Node negative
Peritumoral vascular invasion	Extensive PVI		Absence of PVI
Tumor size	>5 cm	2.1-5 cm	≤2cm
Patient preference	Favors using all possible treatments		Favors avoiding side effects of chemotherapy

Adapted from highlights of the St. Gallen consensus panel. From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

reducing the risk of early menopause and improving prospects for fertility.[2]

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Breast Cancer (Patient Information)
Breast Cancer: For Men (Patient Information)
Abscess, Breast (Related Key Topic)
Fibrocystic Breast Disease (Related Key Topic)

AUTHORS: **TAKUMA NEMOTO, M.D.,** and **RUBEN ALVERO, M.D.**

[2]Moore HC, Unger JM et al: Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy, *N Engl J Med* 372:923-32, 2015.

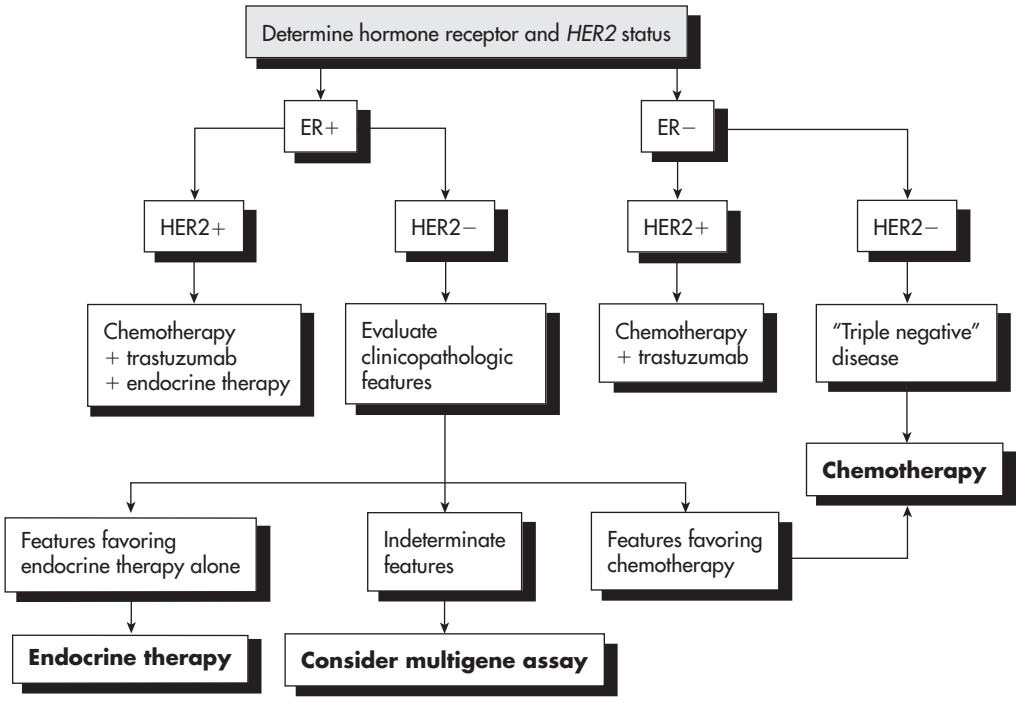

FIGURE B1-54 Management of recurrent and metastatic breast cancer. Considerations for adjuvant chemotherapy. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

EVIDENCE

Abstract[1]

Targeted exercise training could reduce risk factors for fracture and obesity-related diseases that increase from breast cancer treatment, but has not been sufficiently tested. We hypothesized that progressive, moderate-intensity resistance+impact training would increase or maintain hip and spine bone mass, lean mass and fat mass and reduce bone turnover compared to controls who participated in a low-intensity, non-weight bearing stretching program. We conducted a randomized, controlled trial in 106 women with early stage breast cancer who were >1 year post-radiation and/or chemotherapy, ≥50 years of age at diagnosis and postmenopausal, free from osteoporosis and medications for bone loss, resistance and impact exercise naïve, and cleared to exercise by a physician. Women were randomly assigned to participate in 1 year of thrice-weekly progressive, moderate-intensity resistance+impact (jump) exercise or in a similar frequency and length control program of progressive, low-intensity stretching. Primary endpoints were bone mineral density (BMD; g/cm^2) of the hip and spine and whole body bone-free lean and fat mass (kg) determined by DXA and biomarkers of bone turnover—serum osteocalcin (ng/ml) and urinary deoxypyridinoline cross-links (nmol/mmolCr). Women in the resistance + impact training program preserved BMD at the lumbar spine (0.47 vs. −2.13%; *P*=0.001) compared to controls. The resistance+impact group had a smaller increase in osteocalcin (7.0 vs. 27%, *P*=0.03) and a larger decrease in deoxypyridinoline (−49.9 vs. −32.6%, *P*=0.06) than controls. Increases in lean mass from resistance+impact training were greatest among women currently taking aromatase inhibitors compared to controls not on this therapy (*P*=0.01). Our combined program of resistance+impact exercise reduced risk factors for fracture among postmenopausal breast cancer survivors (BCS) and may be particularly relevant for BCS on aromatase inhibitors (AIs) because of the additional benefit of exercise on muscle mass that could reduce falls. Ⓐ

Abstract[2]

Purpose:

We recently reported that the mRNA-based, 21-gene Genomic Health recurrence score (GHI-RS) provided additional prognostic information regarding distant recurrence beyond that obtained from classical clinicopathologic factors (age, nodal status, tumor size, grade, endocrine treatment) in women with early breast cancer, confirming earlier reports. The aim of this article is to determine how much of this information is contained in standard immunohistochemical (IHC) markers.

Patients and Methods:

The primary cohort comprised 1,125 estrogen receptor–positive (ER-positive) patients from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial who did not receive adjuvant chemotherapy, had the GHI-RS computed, and had adequate tissue for the four IHC measurements: ER, progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2), and Ki-67. Distant recurrence was the primary end point, and proportional hazards models were used with sample splitting to control for overfitting. A prognostic model that used classical variables and the four IHC markers (IHC4 score) was created and assessed in a separate cohort of 786 patients.

Results:

All four IHC markers provided independent prognostic information in the presence of classical variables. In sample-splitting analyses, the information in the IHC4 score was found to be similar to that in the GHI-RS, and little additional prognostic value was seen in the combined use of both scores. The prognostic value of the IHC4 score was further validated in the second separate cohort.

Conclusions:

This study suggests that the amount of prognostic information contained in four widely performed IHC assays is similar to that in the GHI-RS. Additional studies are needed to determine the general applicability of the IHC4 score. Ⓐ

Abstract[3]

Aims:

A meta-analysis was performed to identify the clinicopathological variables most predictive of non-sentinel node (NSN) metastases when the sentinel node is positive.

Methods:

A Medline search was conducted that ultimately identified 56 candidate studies. Original data were abstracted from each study and used to calculate odds ratios. The random-effects model was used to combine odds ratios to determine the strength of the associations.

Findings:

The 8 individual characteristics found to be significantly associated with the highest likelihood (odds ratio >2) of NSN metastases are SLN metastases >2mm in size, extracapsular extension in the SLN, >1 positive SLN, ≤1 negative SLN, tumour size >2cm, ratio of positive sentinel nodes >50% and lymphovascular invasion in the primary tumor. The histological method of detection, which is associated with the size of metastases, had a correspondingly high odds ratio.

Conclusions:

We identified 8 factors predictive of NSN metastases that should be recorded and evaluated routinely in SLN databases. These factors should be included in a predictive model that is generally applicable among different populations. Ⓐ

Abstract[4]

Background:

Ipsilateral breast tumor recurrence (IBTR) is the most common failure event after lumpectomy for ductal carcinoma in situ (DCIS). We evaluated invasive IBTR (I-IBTR) and its influence on survival among participants in two National Surgical Adjuvant Breast and Bowel Project (NSABP) randomized trials for DCIS.

Methods:

In the NSABP B-17 trial (accrual period: October 1, 1985, to December 31, 1990), patients with localized DCIS were randomly assigned to the lumpectomy only (LO, n=403) group or to the lumpectomy followed by radiotherapy (LRT, n=410) group. In the NSABP B-24 double-blinded, placebo-controlled trial (accrual period: May 9, 1991, to April 13, 1994), all accrued patients were randomly assigned to LRT+placebo, (n=900) or LRT+tamoxifen (LRT+TAM, n=899). Endpoints included I-IBTR, DCIS-IBTR, contralateral breast cancers (CBC), overall and breast cancer-specific survival, and survival after I-IBTR. Median follow-up was 207 months for the B-17 trial (N=813 patients) and 163 months for the B-24 trial (N=1799 patients).

Results:

Of 490 IBTR events, 263 (53.7%) were invasive. Radiation reduced I-IBTR by 52% in the LRT group compared with LO (B-17, hazard ratio [HR] of risk of I-IBTR=0.48, 95% confidence interval [CI]=0.33 to 0.69,*P*<.001). LRT+TAM reduced I-IBTR by 32% compared with LRT+placebo (B-24, HR of risk of I-IBTR=0.68, 95% CI=0.49 to 0.95, *P*=.025). The 15-year cumulative incidence of I-IBTR was 19.4% for LO, 8.9% for LRT (B-17), 10.0% for LRT+placebo (B-24), and 8.5% for LRT+TAM. The 15-year cumulative incidence of all contralateral breast cancers was 10.3% for LO, 10.2% for LRT (B-17), 10.8% for LRT+placebo (B-24), and 7.3% for LRT+TAM. I-IBTR was associated with increased mortality risk (HR of death=1.75, 95% CI=1.45 to 2.96, *P*<.001), whereas recurrence of DCIS was not. Twenty-two of 39 deaths after I-IBTR were attributed to breast cancer. Among all patients (with or without I-IBTR), the 15-year cumulative incidence of breast cancer death was 3.1% for LO, 4.7% for LRT (B-17), 2.7% for LRT+placebo (B-24), and 2.3% for LRT+TAM.

Conclusions:

Although I-IBTR increased the risk for breast cancer–related death, radiation therapy and tamoxifen reduced I-IBTR, and long-term prognosis remained excellent after breast-conserving surgery for DCIS. Ⓐ

Abstract[5]
Background:
Quality-of-life (QOL) measurement is often incorporated into randomized clinical trials in breast cancer. The objectives of this systematic review were to assess the incremental effect of QOL measurement in addition to traditional endpoints (such as disease-free survival or toxic effects) on clinical decision making and to describe the extent of QOL reporting in randomized clinical trials of breast cancer.
Methods:
We conducted a search of MEDLINE for English-language articles published between May–June 2001 and October 2009 that reported: 1) a randomized clinical trial of breast cancer treatment (excluding prevention trials), including surgery, chemotherapy, hormone therapy, symptom control, follow-up, and psychosocial intervention; 2) the use of a patient self-report measure that examined general QOL, cancer-specific or breast cancer-specific QOL or psychosocial variables; and 3) documentation of QOL outcomes. All selected trials were evaluated by two reviewers, and data were extracted using a standardized form for each variable. Data are presented in descriptive table formats.
Results:
A total of 190 randomized clinical trials were included in this review. The two most commonly used questionnaires were the European Organization for Research and Treatment of Cancer QOL Questionnaire and the Functional Assessment of Cancer Therapy/Functional Assessment of Chronic Illness Therapy. More than 80% of the included trials reported the name(s) of the instrument(s), trial and QOL sample sizes, the timing of QOL assessment, and the statistical method. Statistical power for QOL was reported in 19.4% of the biomedical intervention trials and in 29.9% of the nonbiomedical intervention trials. The percentage of trials in which QOL findings influenced clinical decision making increased from 15.2% in the previous review to 30.1% in this updated review for trials of biomedical interventions but decreased from 95.0% to 63.2% for trials of nonbiomedical interventions. Discordance between reviewers ranged from 1.1% for description of the statistical method (yes vs no) to 19.9% for the sample size for QOL.
Conclusion:
Reporting of QOL methodology could be improved. Ⓐ

Abstract[6]
Background:
It has been suggested that selective sentinel node (SN) biopsy alone can be used to manage early breast cancer, but definite evidence to support this notion is lacking. The aim of this study was to investigate whether refraining from completion axillary lymph node dissection (ALND) suffices to produce the same prognostic information and disease control as proceeding with completion ALND in early breast cancer patients showing micrometastasis at SN biopsy.
Methods:
This prospective, randomized clinical trial included patients with newly diagnosed early-stage breast cancer (T <3.5 cm, clinical N0, M0) who underwent surgical excision as primary treatment. All had micrometastatic SN. Patients were randomly assigned to one of the two study arms: complete ALND (control arm) or clinical follow-up (experimental arm). Median follow-up was 5 years, recurrence was assessed, and the primary end point was disease-free survival.
Results:
From a total sample of 247 patients, 14 withdrew, leaving 112 in the control arm and 121 in the experimental arm. In 15 control subjects (13%), completion ALND was positive, with a low tumor burden. Four patients experienced disease recurrence: 1 (1%) of 108 control subjects and 3 (2.5%) of 119 experimental patients. There were no differences in disease-free survival ($P = 0.325$) between arms and no cancer-related deaths.
Conclusions:
Our results strongly suggest that in early breast cancer patients with SN micrometastasis, selective SN lymphadenectomy suffices to control locoregional and distant disease, with no significant effects on survival. Ⓐ

Abstract[7]
Objective:
To assess the role of axillary dissection in older breast cancer patients with a clinically clear axilla.
Background:
Axillary dissection, once standard treatment for breast cancer, is associated with considerable morbidity. It has been substituted by sentinel node biopsy with dissection only if the sentinel node is positive. We aimed to determine whether axillary surgery can be omitted in older women, thereby sparing them morbidity, without compromising long-term disease control.
Methods:
We carried out a randomized clinical trial on 238 older (65-80 years) breast cancer patients, with clinically N0 disease of radiographic diameter 2 cm or less. Patients were randomized to quadrantectomy with or without axillary dissection. All received radiotherapy to the residual breast but not the axilla; all were prescribed tamoxifen for 5 years. Main outcome measures were overall survival and breast cancer mortality. We also assessed overt axillary disease in those who did not receive axillary dissection.
Results:
After 15 years of follow-up, distant metastasis rate, overall survival, and breast cancer mortality in the axillary dissection and no axillary dissection arms were indistinguishable. The 15-year cumulative incidence of overt axillary disease in the no axillary dissection arm was only 6%.
Conclusions:
Older patients with early breast cancer and a clinically clear axilla treated by conservative surgery, postoperative radiotherapy, and adjuvant tamoxifen do not benefit from axillary dissection. This study was registered atclinicaltrials.gov (ID NCT00002720). Ⓐ

Evidence-Based References

Winters-Stone KM et al.: Strength training stops bone loss and builds muscle in postmenopausal breast cancer survivors: a randomized, controlled trial, *Breast Cancer Res Treat* 127:447–456, 2011. Ⓐ

Cuzick J et al.: Prognostic value of a combined estrogen receptor, progesterone receptor, Ki-67, and human epidermal growth factor receptor 2 immunohistochemical score and comparison with the genomic health recurrence score in early breast cancer, *J Clin Oncol* 29:4273–4278, 2011. Ⓐ

van la Parra RFD et al.: Meta-analysis of predictive factors for non-sentinel lymph node metastases in breast cancer patients with a positive SLN, *Eur J Surg Oncol* 37:290–299, 2011. Ⓐ

Wapnir IL et al.: Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS, *J Natl Cancer Inst* 103:478–488, 2011. Ⓐ

Lemieux J et al.: Quality-of-life measurement in randomized clinical trials in breast cancer: an updated systematic review (2001-2009), *J Natl Cancer Inst* 103:178–231, 2011. Ⓐ

Solá M, Alberro JA, Fraile M, et al.: Complete axillary lymph node dissection versus clinical follow-up in breast cancer patients with sentinel node micrometastasis: final results from the Multicenter Clinical Trial AATRM 048/13/2000, *Ann Surg Oncol* 20:120–127, 2013. Ⓐ

Martelli G, Boracchi P, Ardoino I, et al.: Axillary dissection versus no axillary dissection in older patients with T1N0 breast cancer: 15-year results of a randomized controlled trial, *Ann Surg* 256:920–924, 2012. Ⓐ

SUGGESTED READINGS

Baselga J et al.: Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer, *N Engl J Med* 366:520–529, 2012.

Baselga J et al.: Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer, *N Engl J Med* 366:109–119, 2012.

Berry DA et al.: Estrogen-receptor status and outcomes of modern chemotherapy for patients with node-positive breast cancer, *JAMA* 295:1658–1667, 2006.

Bruening W et al.: Systematic review: comparative effectiveness of core-needle and open surgical biopsy to diagnose breast lesions, *Ann Intern Med* 152:238–246, 2010.

Buchholz T: Radiation therapy for early-stage breast cancer after breast conserving surgery, *N Engl J Med* 360:63–70, 2009.

Darby SC et al.: Risk of ischemic heart disease in women after radiotherapy for breast cancer, *N Engl J Med* 368:987–998, 2013.

De Boer M et al.: Micrometastases or isolated tumor cells and the outcome of breast cancer, *N Engl J Med* 361:653–663, 2009.

Giuliano AE et al.: Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis, *JAMA* 305(6):569–575, 2011.

Gnant M et al.: Endocrine therapy plus zoledronic acid in premenopausal breast cancer, *N Engl J Med* 360:679–691, 2009.

Hayes DF et al.: HER2 and response to paclitaxel in node-positive breast cancer, *N Engl J Med* 357:1496–1506, 2007.

Knutson D, Steiner E: Screening for breast cancer: current recommendations and future directions, *Am Fam Physician* 5:1660–1666, 2007.

Marchionni L et al.: Systematic review: gene expression profiling assays in early stage breast cancer, *Ann Intern Med* 148:358–368, 2008.

Mehta RS et al.: Combination anastrozole and fulvestrant in metastatic breast cancer, *N Engl J Med* 367:435–444, 2012.

Miller K et al.: Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer, *N Engl J Med* 357:2666–2676, 2007.

Morrow M et al.: MRI for breast cancer screening, diagnosis, and treatment, *Lancet* 378:1804–1811, 2011.

Moyer VA: Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer in women: U.S. Preventive Services Task Force recommendation statement, *Ann Intern Med* 160:271–281, 2014.

Muss HB et al.: Adjuvant chemotherapy in older women with early-stage breast cancer, *N Engl J Med* 360:2055–2065, 2009.

Pagani O et al.: Adjuvant exemestane with ovarian suppression in premenopausal breast cancer, *N Engl J Med* 371:107–118, 2014.

Punglia RS et al.: Local therapy and survival in breast cancer, *N Engl J Med* 356:2399–2405, 2007.

Reis-Filho J, Pusztai L: Gene expression profiling in breast cancer: classification, prognostication, and prediction, *Lancet* 378:1820–1823, 2011.

Robson M, Offit K: Management of an inherited predisposition to breast cancer, *N Engl J Med* 357:154–162, 2007.

Smith RA: The evolving role of MRI in the detection and evaluation of breast cancer, *N Engl J Med* 256(13), 2007.

Sparano JA et al.: Weekly paclitaxel in the adjuvant treatment of breast cancer, *N Engl J Med* 358:1663–1671, 2008.

Verma S et al.: Trastuzumab emtansine for HER-2 positive advanced breast cancer, *N Engl J Med* 367:1783–1791, 2012.

von Minckwitz G et al.: Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer, *N Engl J Med* 366:299–309, 2012.

Warner E et al.: Systematic review: using magnetic resonance imaging to screen women at risk for breast cancer, *Ann Intern Med* 148:671–679, 2008.

Weaver DL et al.: Effect of occult metastases on survival in node-negative breast cancer, *N Engl J Med* 364:412–421, 2011.

Whelan TJ et al.: Long-term results of hypofractionated radiation therapy for breast cancer, *N Engl J Med* 362:513–520, 2010.

Woolf SH: The 2009 breast cancer screening recommendations of the US Preventive Services Task Force, *JAMA* 303:162, 2010.

BASIC INFORMATION

DEFINITION

Breech presentation occurs when fetal longitudinal axis is such that the cephalic pole occupies the uterine fundus (Fig. B1-55). Three types exist: frank (48% to 73%, flexed hips, extended knees), complete (4.6% to 11.5%, flexed hips and knees), and footling (12% to 38%, hips extended).

ICD-9CM CODES

652.2 Breech presentation without mention of version
763.0 Breech delivery and extraction affecting fetus or newborn

ICD-10CM CODES

083 Breech extraction
032.1 Maternal care for breech extraction

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Gestational age dependent: 3% to 4% overall, 14% at 29 to 32 wk, 33% at 21 to 24 wk

PERINATAL MORTALITY: 3 to 5 times increase over vertex presentation at term, regardless of delivery route. When corrected for associated increase in congenital anomalies and complications of prematurity, morbidity and mortality rates approach those of vertex presentation at term regardless of delivery route.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Lack of presenting part on vaginal examination
- Fetal heart tones heard above the umbilicus
- Leopold maneuvers revealing mobile fetal part in the uterine fundus

ETIOLOGY

- Abnormal placentation (fundal), uterine anomalies (fibroids, septa), pelvic or adnexal masses, alterations in fetal muscular tone, or fetal malformations
- Associated conditions: trisomy 13, 18, 21; Potter syndrome; myotonic dystrophy; prematurity

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Vertex, oblique, or transverse lie

WORKUP

- Determine reason for breech presentation, history of uterine anomalies, gestational age, or associated fetal congenital anomalies
- Assess fetal status by continuous FHR monitoring or ultrasound
- Assess pelvis to determine feasibility of vaginal delivery
- Assess risk for safety of vaginal versus abdominal delivery

IMAGING STUDIES

Ultrasound to evaluate for:

- Fetal anomalies, such as hydrocephalus
- Placental location
- Position of fetal head relative to spine (check for hyperextension)
- Estimated fetal weight (2500 to 3800 g for attempt of vaginal delivery)
- Type of breech (frank, complete, footling)

TREATMENT

ACUTE GENERAL Rx

- Vaginal delivery in selected patients (see "Comments" section): allow maternal expulsive forces to deliver fetus until scapula visible (avoiding traction); with flexion and/or Piper forceps, deliver fetal head
- Perform cesarean section (see "Comments")
- External cephalic version: success 60% to 75% after 37 wk, contraindicated with placental abruption, low-lying placenta, maternal hypertension, previous uterine incision, multiple gestation, non-reassuring fetal status
- Adequate pelvic/cervical relaxation essential (i.e., anesthesia in-room during delivery with uterine relaxants on hand [terbutaline])

COMPLICATIONS

- Head entrapment: leading cause of death (with the exception of anomalous fetuses), 88 cases per 1000 deliveries; avoid by maintaining flexion of fetal head (Mauriceau Smellie Veit maneuver), use of Piper forceps or Dührssen's incisions. Avoid hyperextension of head during delivery.
- Cord prolapse: usually occurs late in labor. Incidence depends on type of breech: frank (0.5%), complete (4% to 5%), footling (10%).
- Nuchal arm: arm extended above fetal head, occurs when there is undue traction before delivery of fetal scapulas. Treatment: bring trapped arm across infant's face (Lovset's maneuver).

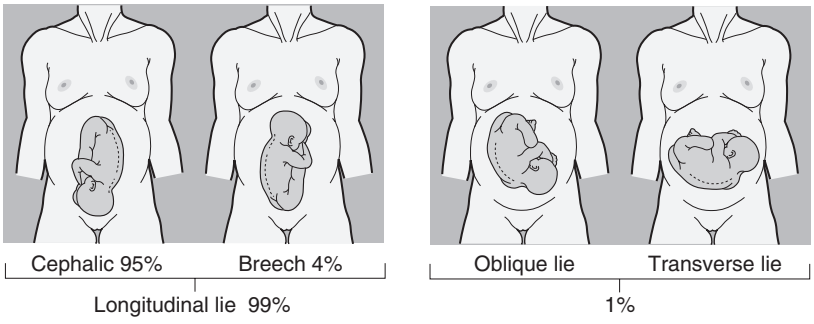

FIGURE B1-55 Fetal lie at term. (From Drife J, Magowan B: *Clinical obstetrics and gynecology,* Philadelphia, 2004, Saunders.)

DISPOSITION

If confounding variables are corrected for (prematurity, associated congenital anomalies [6.3% of breeches vs. 2.4% in general population]), route of delivery plays less important role in fetal outcome than previously believed, if the obstetrician performing the delivery is experienced in breech delivery. As fewer providers perform breech deliveries and seasoned obstetricians retire, fewer new physicians learn the technique of breech delivery.

REFERRAL

An obstetrician trained in vaginal breech delivery is prerequisite for attempt; explain to the patient that with cesarean section certain risks (i.e., hyperextension of the fetal head with resultant spinal cord injury) may be minimized but not eliminated.

PEARLS & CONSIDERATIONS

COMMENTS

For breech presentation, mortality rate increased 13-fold and morbidity 7-fold, mainly due to an increase in congenital anomalies, perinatal hypoxia, birth injury, prematurity.

No contraindication to induction of labor in breech presentation; labor not prohibited in primigravida.

CRITERIA FOR TRIAL OF LABOR

- Estimated fetal weight 2500 to 3800 g (recognizing inherent error in estimated fetal weight approximations: actual fetal weight may be substantially smaller)
- Frank breech
- Adequate pelvis
- Flexed fetal head
- Continuous fetal monitoring
- Normal progress of labor
- Bedside availability of anesthesia and capability for immediate cesarean section
- Informed consent
- Obstetrician trained in vaginal breech delivery

CRITERIA FOR CESAREAN SECTION

- Estimated fetal weight <1500 g or >4000 g
- Footling presentation (20% risk of cord prolapse, usually late in course of labor)
- Inadequate pelvis
- Hyperextended fetal head (21% risk of spinal cord injury)
- Nonreassuring fetal status
- Abnormal progress of labor
- Lack of trained obstetrician

EVIDENCE

Available at www.expertconsult.com

RELATED CONTENT

Breech Birth (Patient Information)
Premature Labor (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

EVIDENCE

Abstract[1]

Vaginal delivery versus caesarean section in preterm breech delivery: a systematic review

Bergenhenegouwen LA, Meertens LJE, Schaaf J, et al (Ziekenhuis Groep Twente, The Netherlands; Maastricht Univ, The Netherlands; Amsterdam Med Centre, The Netherlands; et al)

Eur J Obstet Gynecol Reprod Biol 172:1-6, 2014

There is controversy on the preferred mode of delivery (vaginal delivery (VD) versus caesarean section (CS)) in preterm breech delivery in relation to neonatal outcome. While CS is supposed to be safer for the fetus, arguments against CS can be the increased risk of maternal morbidity, risks for future pregnancies, and costs. Moreover, neonatal respiratory distress syndrome occurs more frequently after CS compared to VD. In the past, several RCTs have been started on this subject, but they were all preliminary and stopped due to recruitment difficulties. As the Cochrane review of these RCTs reported on 116 women only, knowledge on the effectiveness of CS and VD can at present only be obtained from non-randomized studies.

We performed a systematic review and meta-analysis of nonrandomized studies that assessed the association between mode of delivery and neonatal mortality in women with preterm breech presentation. We searched Pubmed, Embase and the Cochrane library for articles comparing neonatal mortality after VD versus CS in preterm breech presentation (gestational age 25+0 till 36+6 weeks). Seven studies, involving a total of 3557 women, met the eligibility criteria and were included in this systematic review. The weighted risk of neonatal mortality was 3.8% in the CS group and 11.5% in the VD group (pooled RR 0.63 (95% CI 0.48-0.81)). We conclude that cohort studies indicate that CS reduces neonatal mortality as compared to VD.

AUTHOR: **A. A. Fanaroff, MBBCh, FRCPE** Ⓑ

Evidence-Based Reference

1. Hannah ME, et al.: Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomised multicentre trial. Term Breech Trial Collaborative Group, *Lancet* 356:1375–1383, 2000. Ⓑ

BASIC INFORMATION

DEFINITION

Bronchiectasis is the abnormal dilation and destruction of bronchial walls, which may be congenital or acquired.

ICD-9CM CODES
494.0 Bronchiectasis
ICD-10CM CODES
J47.9 Bronchiectasis, uncomplicated

EPIDEMIOLOGY & DEMOGRAPHICS

- Cystic fibrosis is responsible for nearly 50% of all cases of bronchiectasis.
- Acquired primary bronchiectasis is uncommon because of rapid diagnosis of pulmonary infections and frequent use of antibiotics.
- Effective childhood immunizations have led to a significant decrease in the incidence of bronchiectasis resulting from pertussis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Moist crackles at lung bases
- Cough with expectoration of large amount of purulent sputum
- Fever, night sweats, generalized malaise, weight loss
- Hemoptysis
- Halitosis, skin pallor
- Clubbing (infrequent)

ETIOLOGY

- Cystic fibrosis
- Lung infections (pneumonia, lung abscess, TB, fungal infections, viral infections)
- Abnormal host defense (panhypogammaglobulinemia, Kartagener's syndrome, AIDS, chemotherapy)
- Localized airway obstruction (congenital structural defects, foreign bodies, neoplasms)
- Inflammation (inflammatory pneumonitis, granulomatous lung disease, allergic aspergillosis)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- TB
- Asthma
- Chronic bronchitis or chronic sinusitis
- Interstitial fibrosis
- Chronic lung abscess
- Foreign body aspiration
- Cystic fibrosis
- Lung carcinoma

LABORATORY TESTS

- Sputum for Gram stain, culture and sensitivity, and acid-fast bacteria
- Complete blood count with differential (leukocytosis with left shift, anemia)
- Serum protein electrophoresis to evaluate for hypogammaglobulinemia
- Antibody test for aspergillosis
- Sweat test in patients with suspected cystic fibrosis

IMAGING STUDIES

- Chest radiograph: hyperinflation, crowded lung markings, small cystic spaces at the base of the lungs.
- High-resolution CT scan of the chest (Fig. B1-56) has become the best tool to detect cystic lesions and exclude underlying obstruction from neoplasm. The CT study should be a noncontrast study with the use of 1- to 1.5-mm window every 1 cm with acquisition time of 1 sec. Typical findings on CT include dilation of airway lumen, lack of tapering of an airway toward periphery, ballooned cysts at the end of bronchus, and varicose constrictions along airways.
- Bronchoscopy may be helpful to evaluate hemoptysis, rule out obstructive lesions, and remove mucus plugs.
- Table B1-17 summarizes diagnostic studies for the classification and management of patients with bronchiectasis.

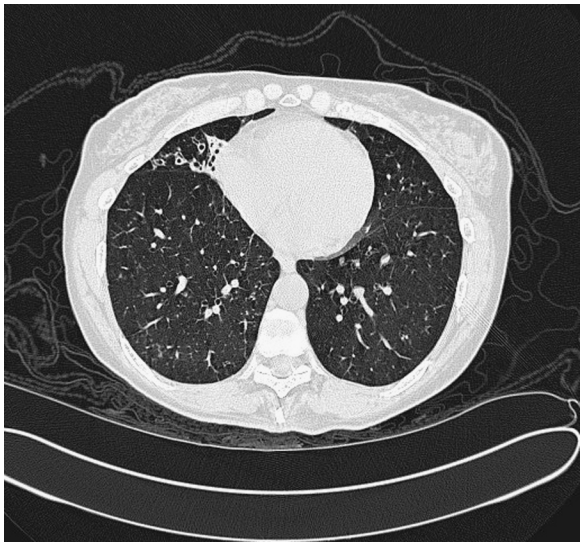

FIGURE B1-56 High-resolution computed tomographic image of nodular bronchiectasis due to nontuberculous mycobacterium infection. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Postural drainage (reclining prone on a bed with the head down on the side) and chest percussion with use of inflatable vests or mechanical vibrators applied to the chest may enhance removal of respiratory secretions.
- Adequate hydration.
- Supplemental oxygen for hypoxemia.

ACUTE GENERAL Rx

- Antibiotic therapy is based on the results of sputum, Gram stain, and culture and sensitivity; in patients with inadequate or inconclusive results, empiric therapy with amoxicillin/clavulanate 500 to 875 mg q12h, TMP-SMX q12h, doxycycline 100 mg bid, or cefuroxime 250 mg bid for 10 to 14 days is recommended.
- Bronchodilators are useful in patients with demonstrable airflow obstruction.

CHRONIC Rx

- Avoidance of tobacco
- Maintenance of proper nutrition and hydration
- Prompt identification and treatment of infections
- Pneumococcal vaccination and annual influenza vaccination

DISPOSITION

Prognosis is variable with severity of the disease and underlying etiology of bronchiectasis.

REFERRAL

Surgical referral for partial lung resection in patients with localized severe disease unresponsive to medical therapy or in patients with massive hemoptysis

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Bronchiectasis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

TABLE B1-17 Diagnostic Studies for the Classification and Management of Patients with Bronchiectasis

Test	Comments
ROUTINE, UNIVERSAL STUDIES	
Computed tomography lung scan (CTLS)	If bronchiectasis (BXSIS) is suspected, CTLS is the definitive test. Thin-section, high-resolution images may help detect subtle airway dilation before bronchial walls are grossly thickened. Contrast is generally not helpful and may, in fact, compromise the overall resolution of the study. CTLS may also identify esophageal abnormalities.
Pulmonary function tests (PFTs)	For patients with significant BXSIS, comprehensive PFTs, including spirometry, bronchodilator responsiveness, lung volumes, and diffusion capacity, are important studies that aid in management and prognosis. PFTs may also provide useful hints regarding predisposing conditions.
Complete blood count	Anemia may reflect effects of chronic infection or blood loss (consider inflammatory bowel disorders). Leukocytosis may mark severity of infection. Eosinophilia may suggest ABPA/M.
ESR, C-reactive protein	Nonspecific markers of inflammation; very high levels may suggest underlying connective tissue disease or vasculitis.
Routine sputum culture	Antibiotic therapy in BXSIS should generally be directed against specific pathogens and guided by in vitro susceptibility. The presence of mucoid strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus* may raise suspicions for CF. *Stenotrophomonas maltophilia*, *Alcaligenes xylosoxidans*, and *Burkholderia cepacia* are gram-negative bacilli that may prove problematic pathogens in patients with long-standing BXSIS. Isolation of *B. cepacia* and *Helicobacter pylori* requires special laboratory techniques.
Mycobacterial sputum culture	Environmental mycobacteria such as *Mycobacterium avium* complex, *M. chelonae*, and *M. abscessus* appear to be increasingly common in contemporary BXSIS. May be commensal but often are pathogenic.
Fungal sputum culture	Especially in patients with an asthmatic component, the presence of *Aspergillus* species (or other molds including Pseudallescheria or penicillium) may suggest etiology.
CT scan of sinuses	Many BXSIS patients also suffer chronic rhinosinusitis. The presence of extensive sinus involvement suggests possible CF, immunoglobulin deficiencies, or ciliary disorders. Also, optimal management often entails aggressive sinus care.
SPECIFIC, DIRECTED STUDIES	
Sweat chloride, CF genotyping, and nasal potential differences	For BXSIS patients with bilateral disease, sinusitis, and no other identified risk factor, mild variants of CF appear to be relatively common. Sweat chloride is regarded as the primary screening test for CF, but a considerable portion of adults with CF have borderline or normal results. Nasal potential difference may be useful for identifying CF in equivocal cases.
$Alpha_1$-antitrypsin (AAT) levels and phenotype	AAT anomalies appear to be a substantial risk factor for BXSIS, especially with white females. Abnormal proteinase inhibitor (Pi) phenotypes, even heterozygous patterns such as MS, appear to confer risk even with normal levels of AAT. Repletion of AAT may enhance resistance to lower respiratory tract infections.
Immunoglobulin (Ig) levels	Deficiencies of IgG or IgA may promote BXSIS; IgG subclass deficiencies may also be a factor. Elevated levels of IgE may suggest ABPA/M or Job's syndrome. Hyper-IgM may be associated, as well, with chronic infections.
Ciliary morphology or function	For individuals with suggestive stories, a nasal ciliated epithelium biopsy with transmission electron microscopy may identify primary ciliary dyskinesia. Other studies including ex vivo ciliary activity, the saccharine test, or spermatozoa analysis may aid in this diagnosis.
Nasal nitric oxide (NNO) levels	Patients with documented PCD have significantly lower levels of NNO than normal or patients with CF. Although not universally available, such testing may prove highly useful in identifying PCD. Paradoxically, exhaled NO levels have been elevated in BXSIS of diverse etiologies except CF.
Barium swallow (BaS)	The BaS may detect disturbed deglutition, esophageal diverticula, obstructing lesions (tumors or strictures), hypomotility, achalasia, hiatal hernias, or lower esophageal sphincter (LES) incompetence with reflux. Note that the absence of reflux on a BaS does not exclude this problem (see pH probe).
pH probe	For patients suspected of gastroesophageal reflux, an 18- to 24-hour study with a transnasal pH probe may identify, quantitate, and characterize reflux. Obviously, medications that inhibit acid production must be stopped before such tests.
Esophageal manometry	For patients being considered for surgical repair of the LES, manometry should be performed to determine that the esophagus generates sufficient pressure to propel food and liquids through the tightened sphincter.
Tailored hypopharyngography (TH)	TH is useful in detecting abnormalities of the initial phase of swallowing, deglutition. Persons particularly prone to problems include those with prior strokes, Parkinson's disease, bulbar disorders including postpolio syndrome, and those with prior laryngeal or pharyngeal surgery. Note that some patients have gross aspiration without clinical manifestations (choking, coughing); this may occur in individuals with none of the above risk factors.
LESS COMMON, EXOTIC STUDIES	
Collagen vascular disease (CVD) serologies	Various CVDs may contribute to the risk for BXSIS, including RA, ankylosing spondylitis, and systemic lupus erythematosus. Thus, for patients with compatible histories or physical findings, assays for rheumatoid factor, HLA-B27, and ANA may provide insight into predisposing conditions. CVD serologies may also suggest the diagnosis of Sjögren syndrome, particularly SSA/Ro and/or SSB/La.
Schirmer's test	For patients with histories suggestive of "sicca syndrome" (dry eyes, dry mouth, oral ulcers), a positive Schirmer test may indicate the presence of either primary or secondary (associated with a CVD) Sjögren's syndrome.

ABPA/M, Allergic bronchopulmonary aspergillosis/other mycoses; *ANA*, antinuclear antibody; *CF*, cystic fibrosis; *ESR*, erythrocyte sedimentation rate; *HLA*, human leukocyte antigen; *PCD*, primary ciliary dyskinesia; *RA*, rheumatoid arthritis.

From Mason, RJ: *Murray & Nadel's textbook of respiratory medicine*, 5th ed, Philadelphia, 2010, Saunders.

SUGGESTED READING

Barker AF: Bronchiectasis, *N Engl J Med* 346:1383, 2002.

BASIC INFORMATION

DEFINITION

Brucellosis is a zoonotic infection caused by one of four species of *Brucella.* It commonly presents as a nondescript febrile illness.

SYNONYMS

Malta fever, undulant fever
Bang's disease

ICD-9CM CODES
023.9 Brucellosis
ICD-10CM CODES
A23.9 Brucellosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): About 100 to 200 cases/yr (may be underreported) (Fig. EB1-57), predominantly *B. melitensis*

PREDOMINANT SEX: Male
PREDOMINANT AGE: Adult
CONGENITAL INFECTION: Recent evidence suggests a high rate of spontaneous abortions in untreated pregnant women during the first and second trimesters.
NEONATAL INFECTION: Can occur if mother is infected during pregnancy.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Incubation period is 1 wk to 3 mo.
- Patients may be asymptomatic or have nonspecific symptoms such as fever, sweats, malaise, weight loss, depression, arthralgia, and arthritis.
- Fever is the most common finding.
- Hepatomegaly, splenomegaly, or lymphadenopathy is possible.
- Localized disease includes endocarditis, meningitis, spondylitis, sacroiliitis, and osteomyelitis (especially vertebral).
- Chronic hepatosplenic suppurative brucellosis (CHSB) presents with hepatic or splenic abscesses. This form is thought to be a reactivation and can occur years after the acute infection.
- Table EB1-18 describes a clinical classification of human brucellosis

ETIOLOGY

- Caused by infection with *Brucella* species:
  1. Most commonly *B. melitensis,* but also *suis, abortus,* or *canis*
  2. A small, gram-negative coccobacillus (Fig. EB1-58)
- Acquired through ingestion of organisms (unpasteurized goat or cow's milk) or breaks in the skin, or by inhalation.
- Most cases occur after exposure to animals (sheep, goats, swine, cattle, or dogs), or animal products (i.e., milk, cheese, hides, tissue).
- Most cases (in the U.S.) occur in men with occupational exposure to animals (e.g., farmers, ranchers, laboratory workers, veterinarians, abattoir workers). Accidental animal vaccine exposure warrants evaluation for a full therapeutic antibiotic regimen.
- Laboratory workers, especially those in microbiology, are also at increased risk. Guidelines for postexposure prophylaxis are available from *MMWR Surveill Summ* 57:39, 2009.

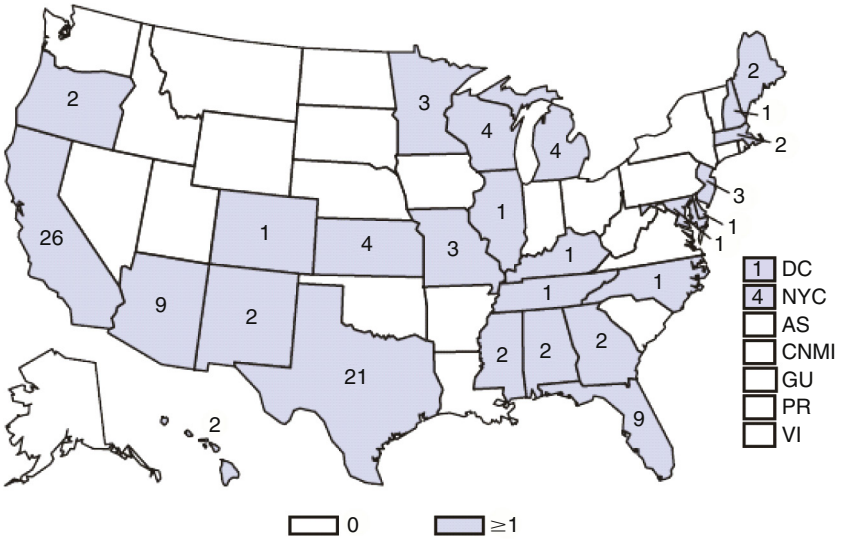

FIGURE EB1-57 Brucellosis. Number of reported cases—United States and U.S. territories, 2010. (From Centers for Disease Control and Prevention: Summary of notifiable diseases—United States, 2010, *MMWR Morb Mortal Wkly Rep* 59:1-111, 2012.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Many febrile conditions without localizing manifestations (i.e., TB, endocarditis, typhoid fever, malaria, autoimmune diseases)

WORKUP

- Cultures of blood, bone marrow, or other tissue (e.g., lymph node, liver) should be sent and held for 4 wk because *Brucella* spp. grow slowly in vitro.

TABLE EB1-18 Clinical Classification of Human Brucellosis

Classification	Duration of Symptoms Before Diagnosis	Major Symptoms and Signs	Diagnosis	Comments
Subclinical	—	Asymptomatic	Positive (low titer) serology, negative cultures	Occurs in abattoir workers, farmers, and veterinarians
Acute and subacute	Up to 2-3 mo and 3 mo-1 yr	Malaise, chills, sweats, fatigue, headache, anorexia, arthralgias, fever, splenomegaly, lymphadenopathy, hepatomegaly	Positive serology, positive blood or bone marrow cultures	Presentation can be mild, self-limited *(B. abortus)* or fulminant with severe complications *(B. melitensis)*
Localized	Occurs with acute or chronic untreated disease	Related to involved organs	Positive serology, positive cultures in specific tissues	Bone or joint, genitourinary, hepatosplenic involvement most common
Relapsing	2-3 mo after initial episode	Same as acute illness but may have higher fever and more fatigue, weakness, chills, and sweats	Positive serology, positive cultures	May be extremely difficult to distinguish relapse from reinfection
Chronic	>1 yr	Nonspecific presentation but neuropsychiatric symptoms and low-grade fever most common	Low titer or negative serology, negative cultures	Most controversial classification; localized disease may be associated

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

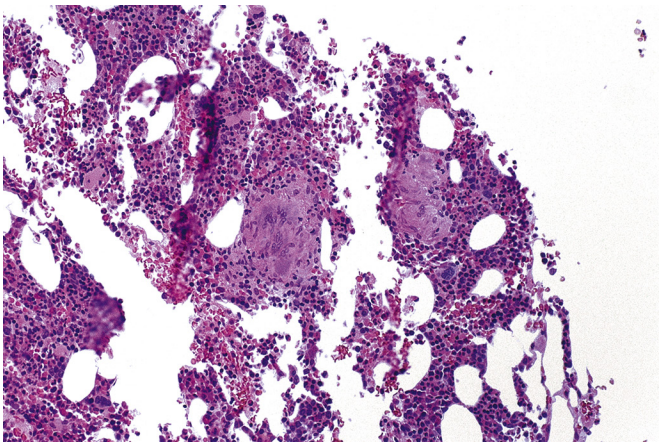

FIGURE EB1-58 Brucellosis. Several small noncaseating granulomas are present in the bone marrow of a patient with an unexplained febrile disease. He was not aware of exposure to *Brucella* in over 30 years (HANDE, x40, *Brucella suis* isolated from blood cultures). (From Scott MA et al: Infectious disease pathology. Silverberg SG, ed.: *Principles and practice of surgical pathology and cytopathology,* ed 4, Philadelphia, 2006, Churchill Livingstone, p 101.)

- Granulomas on biopsy are suggestive of diagnosis.

LABORATORY TESTS

- WBC count: normal or low
- Serology:
  1. Serum agglutination test (SAT) to detect antibodies to *B. abortus, melitensis,* and *suis.* Positive tests warrant confirmatory testing with specific *Brucella* agglutination tests.
  2. Specific antibody test to identify antibodies to *B. canis.*
  3. False-negative SAT possibly resulting from a prozone effect.
  4. PCR (polymerase chain reaction) for *Brucella* spp. specific 16S rRNA or DNA sequences are increasingly used for the diagnosis of brucellosis from blood, tissue samples, and bone marrow.

IMAGING STUDIES

- Radiographs to show splenic or hepatic calcifications in chronic disease
- Bone scan, MRI, and radiographs of the spine to suggest osteomyelitis
- Ultrasound or CT scan of the abdomen to show an enlarged liver or spleen
- Echocardiogram to reveal vegetations in endocarditis

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Drainage of abscesses
- Valve replacement for endocarditis

ACUTE GENERAL Rx

Combination antibiotics required:

- Major options:
  - Doxycycline 100 mg PO bid for 6 wk plus gentamycin of 5 mg/kg qd for 7 days.
- Alternative therapies:
  - Doxycycline 100 mg PO bid plus rifampin 600 to 900 mg PO qd for 6 wk
  - Sulfamethoxazole 800 mg/trimethoprim 160 mg one DS tablet PO qid, ciprofloxacin 500 mg bid for 6 wk along with doxycycline or rifampin as an alternative regimen
- Courses <6 wk are associated with higher relapse rates; longer courses are recommended for complicated disease (e.g., osteomyelitis, endocarditis, and neurobrucellosis).

DISPOSITION

- Relapse is possible weeks to months after the completion of therapy.
- Reactivation with CHSB has been reported up to 35 yr after initial illness.

REFERRAL

For all cases to an infectious disease specialist

PEARLS & CONSIDERATIONS

COMMENTS

- Alert the microbiology laboratory to the possibility of *Brucella* spp. (prolonged incubation needed and biohazard for laboratory personnel).
- Do not use doxycycline in children or pregnant women.
- Avoid aminoglycosides in pregnant women.
- Fluoroquinolones have good in vitro activity against *Brucella* spp. and are under study as components of complex regimens. Monotherapy is not effective.

SUGGESTED READINGS

Available at www.expertconsult.com

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SUGGESTED READINGS

Bosilkovski M et al.: Human brucellosis in Macedonia–10 years of clinical experience in endemic region, *Croat Med J* 51:327, 2010.

Colmenero JD: Clinical findings, therapeutic approach, and outcome of brucellar vertebral osteomyelitis, *Clin Infect Dis* 46:426, 2008.

Erdem H et al.: Efficacy and tolerability of antibiotic combinations in neurobrucellosis: results of the Istanbul study, *Antimicrob Agents Chemother* 50:1523, 2012.

Franco MP: Human brucellosis, *Lancet Infect Dis* 7(12):775–786, 2007.

Gomez M et al.: Evaluation of seven tests for diagnosis of human brucellosis in an area where the disease is endemic, *Clin Vaccine Immunol* 15(6):1031, 2008.

Koruk ST et al.: Management of Brucella endocarditis: results of the Gulhane study, *Int J Antimicrob Agents* 40:145, 2012.

Mantor BG et al.: *Brucella melitensis*—a sexually transmissible agent? *Lancet* 347(9017):1763, 1996.

Navarro E et al.: Use of real-time quantitative PCR to monitor the evolution of *Brucella melitensis* DNA load during therapy and post-therapy follow-up in patients with brucellosis, *Clin Infect Dis* 42:1266, 2006.

Pappas G et al.: Brucellosis, *N Engl J Med* 352:2335, 2005.

Pappas G et al.: The new global map of human brucellosis, *Lancet* 6:91, 2006.

Ramin B: Human brucellosis, *BMJ* 10:341–c4545, Sept 2010.

Shen MW: Diagnostic and therapeutic challenges of childhood brucellosis in a nonendemic country, *Pediatrics* 121:e1178, 2008.

Storakis I: Unusual manifestations of brucellosis, *East Mediter Health J* 16(4):365–370, 2010.

BASIC INFORMATION

DEFINITION

Brugada syndrome (BRS) is a genetically determined channelopathy characterized by typical electrocardiographic abnormalities. No other features are needed for diagnosis. BRS predisposes one to sudden cardiac death (SCD) secondary to polymorphic ventricular tachycardia (PVT)/ventricular fibrillation (VF) in the absence of structural heart disease.

SYNONYMS

BRS

ICD-9CM CODES
746.89 Other specified congenital anomalies of heart
ICD-10CM CODES
I49.9 Cardiac arrhythmia, unspecified
I47.2 Ventricular tachycardia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The incidence ranges from 1 to 5:10,000 people in Europe and 12:10,000 in Southeast Asia.
PREVALENCE: It comprises 4% of SCD and 20% of SCD in structurally normal hearts. Although found in every population, the prevalence is much higher in Asian and Southeast Asian countries; in fact in some Southeast Asian countries, such as Laos and Thailand, it may be the most common form of natural death in younger males.
PREDOMINANT SEX AND AGE: BRS is more common in males (80% of patients). Mean age at presentation is 40 to 45.
GENETICS: The disease is autosomal dominant with variable expression.

- Twelve culprit genes have been identified so far.
- *SCN5A,* the gene that encodes for the alpha subunit of the cardiac sodium channel, accounts for about 20% to 25% of cases of BRS.
- Genetic abnormalities are only found in one third of patients; thus the impact of genetic testing is limited. When available, it may be useful in identifying silent carriers.
- In all genotypes, the basic abnormality is either a decrease in the inward sodium or calcium current or an increase in the outward potassium current.

RISK FACTORS

- First-degree relatives with the disease

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical exam is usually benign.
- Classic ECG finding is a pattern of right bundle branch block (RBBB) with persistent ST elevation of cove-like morphology and T-wave inversion in the anterior leads (V_1-V_3)
- Often an incidental finding diagnosed from a typical ECG pattern
- Palpitations
- Nocturnal agonal respirations
- Syncope
- Sudden cardiac arrest (SCA)/SCD secondary to rapid PVT that frequently degenerates into VF more often at night
- Three ECG patterns were described. Type 1 is the most common and characteristic (Fig. B1-59*A*).
- Type 1 ECG pattern can be transient and may be provoked (sodium channel blockers, vagal maneuvers, increased alpha-adrenergic tone, beta-blockers, tricyclic or tetracyclic antidepressants, fever, hypokalemia, hyperkalemia, hypercalcemia, and alcohol and cocaine toxicity). Types 2 and 3 can change to type 1 pattern with these triggers as well. Table B1-19 describes drugs used to unmask Brugada ECG pattern.

ETIOLOGY

- Autosomal dominant inheritance with variable penetration.
- Mutations in SCN5A16 gene leading to a loss of function of the cardiac sodium (Na^+) channel by different mechanisms is the most common genotype found among BS patients. Table B1-20 describes the molecular basis of BS.

DIAGNOSIS

Diagnosis is made by ECG alone.

- ST segment elevation with type 1 morphology ≥2 mm in one or more right-sided leads (V_1-V_2), occurring either spontaneously or after provocative drug testing
- Type II or III ECG that converts into type 1 following sodium channel blocker (procainamide/flecainide/ajmaline) challenge (Fig. B1-59*A*)

DIFFERENTIAL DIAGNOSIS

A number of diseases can lead to a BRS-like abnormality on the surface ECG, including the following:

- Atypical RBBB
- Early repolarization
- Acute pericarditis
- Acute myocardial infarction or ischemia
- Pulmonary embolism
- Various central and autonomic system abnormalities
- Duchenne's muscular dystrophy
- Electrolyte abnormalities such as hyperkalemia and hypercalcemia
- Arrhythmogenic right ventricular cardiomyopathy
- Pectus excavatum

WORKUP

- Cardiology consult is strongly recommended if BRS is suspected.
- Clinical history with special emphasis on syncope, palpitations, nocturnal agonal respirations, and family history.
- Echocardiography to rule out structural heart disease. While no structural heart disease is usually apparent, there are some recent reports indicating mild abnormalities in the right ventricle (RV) and left ventricle (LV).
- MRI, especially to rule out ARVC (arrhythmogenic right ventricular cardiomyopathy).
- Electrophysiology study. No consensus exists on the value of arrhythmia induction in predicting future clinical events in individual patients. However, findings such as HV (His ventricular) conduction interval >60 ms and VERP (ventricular effective refractory period) <200 ms during electrophysiology study can help in confirming a diagnosis.

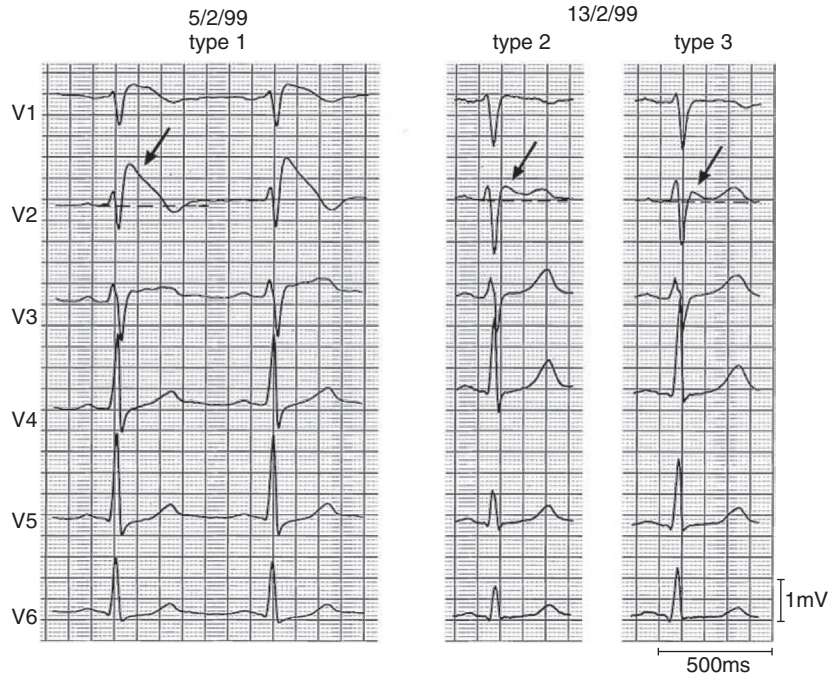

FIGURE B1-59 A ECG changes in Brugada syndrome. ST elevation occurs in the anterior precordial leads, leads V1 and V2. Type 1 (coved) ECGs with 1 mV of ST elevation have the most prognostic significance. (From Strickberger SA et al: AHA/ACCF scientific statement on the evaluation of syncope, *J Am Coll Cardiol* 47:473-484, 2006.)

TABLE B1-19 Drugs Used to Unmask Brugada ECG Pattern

Drug	Dose
Ajmaline	1-mg/kg IV infusion over 5 min
Flecainide	2-mg/kg IV infusion over 10 min, maximum 150 mg; or 400 mg PO
Procainamide	10-mg/kg IV infusion over 10 min
Pilsicainide	1-mg/kg IV infusion over 10 min

From Issa Z et al: *Clinical arrhythmology and electrophysiology,* ed 2, Philadelphia, 2012, Saunders.

TABLE B1-20 Molecular Basis of the Brugada Syndrome

Disease	Gene	Protein	Ionic Current	Function	Inheritance
BrS type 1	*SCN5A*	$Na_v1.5$	Subunit alpha I_{Na}	Loss	Autosomal dominant
BrS type 2	*GPD1L*	G3PD1L	Interaction subunit alpha I_{Na}	Loss	Autosomal dominant
BrS type 3	*CACNA1C*	$Ca_v1.2$	Subunit alpha I_{CaL}	Loss	Autosomal dominant
BrS type 4	*CACNB2B*	$Ca_v\beta_2$	Subunit beta IC_{aL}	Loss	Autosomal dominant
BrS type 5	*SCN1B*	$Na_v\beta_1/\beta_{1b}$	Subunit beta I_{Na}	Loss	Autosomal dominant
BrS type 6	*KCNE3*	MiRP2	Subunit beta I_{Ks}/I_{to}	Gain	Autosomal dominant
BrS type 7	*SCN3B*	$Na_v\beta_3$	Subunit beta I_{Na}	Loss	Autosomal dominant

From Issa Z et al: *Clinical arrhythmology and electrophysiology,* ed 2, Philadelphia, 2012, Saunders.

- Laboratory tests are unhelpful. Genetic testing may be helpful but not necessary for diagnostic purposes.
- First-degree relatives should obtain ECG and be evaluated for symptoms.
- Risk stratification in the asymptomatic patient
- The following are considered indicators of high risk
  - Spontaneous type 1 ECG at baseline
  - Presence of fragmented QRS on ECG
  - RVERP (right ventricular effective refractory period) <200 ms on EPS
  - Male sex
  - Spontaneous atrial fibrillation

Note that family history of sudden death is not considered a high risk feature in BRS.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- The only effective strategy that prevents sudden cardiac death in BRS is implantable cardioverter-defibrillator (ICD). Currently there are no class I recommendations for primary prevention because clinical events are extremely rare, even in high-risk patients. Fig. B1-59*B* depicts the algorithm for clinical decision making regarding recommendation of an ICD.
- Definitive candidates for ICD (class I) are patients who survived SCD or have had sustained VT (secondary prevention).
- ICD can be useful (class IIa) for patients who have type 1 ECG pattern in the absence of class IC drug test associated with history of syncope.
- ICD may be considered (class IIb) if there is inducible VF on electrophysiologic (EP) study.
- Patients with spontaneous type 1 ECG without syncope or inducible VF on EP study or asymptomatic patients with drug-induced type 1 ECG pattern are considered a lower risk group for SCD, and ICD is not indicated in these patients.

ACUTE GENERAL Rx

- Isoproterenol (class IIa) is also used for electrical storm.
- Quinidine, which blocks both Ito and IKr currents in the RV epicardium, is used in patients with a history of multiple appropriate ICD shocks, as well as for electrical storms and treatment of supraventricular tachycardia (SVT) in these patients. It is also useful in cases where the patient refuses an ICD implant or when an ICD implant is contraindicated.
- Radiofrequency ablation: There are a few published case reports of radiofrequency ablation of premature ventricular contractions (PVCs) leading to reduced clinical events. These have been performed in patients already implanted with an ICD. In addition, epicardial substrate ablation in the right ventricular outflow tract (RVOT) has been shown to prevent VF inducibility.

REFERRAL

Consultation with cardiology is strongly recommended if BRS is suspected.

PEARLS & CONSIDERATIONS

COMMENTS

- The clinical manifestations, such as syncope and SCD, are rare in the pediatric group, but fever can acutely predispose to cardiac arrest. Mean age of presentation is 40 to 45 years.
- Cardiac events may occur during sleep, at rest, or after a large meal.
- BRS patients should be advised to avoid all drugs that may induce a type 1 ECG pattern and/or be known to trigger ventricular arrhythmias and avoid unnecessary use of drugs (a drug that is not yet identified as potentially dangerous for these patients does not make its use safe). For up-to-date information on this matter, the following website has been developed: www.brugadadrugs.org.
- Fever may induce the appearance of a type 1 BRS ECG pattern and may trigger episodes of PVT/VF in BRS patients. In the case of fever, close ECG monitoring is appropriate in combination with lowering of the body temperature.
- The classic ECG changes in BRS can be transient with patients having normal ECGs in between highly abnormal ones.
- The appearance of syncope, seizures, or nocturnal agonal respiration must lead to prompt medical evaluation.
- Family screening of BS in first-degree relatives is strongly recommended.
- Although participation in sports is not strictly prohibited, competitive training can lead to development of strong vagal tone and subsequent higher risk of clinical events. Hence, participation in sports at a competitive or professional level is not advised.
- Once diagnosed initially by an ECG pattern, all patients must be followed up on a regular basis by an electrophysiologist.

PREVENTION

Identification of patients with BRS, risk stratification, and appropriate screening of family members are paramount to the prevention of SCD.

PATIENT/FAMILY EDUCATION

Immediate family members should be notified and be screened for BRS.

SUGGESTED READINGS

Available at www.expertconsult.com

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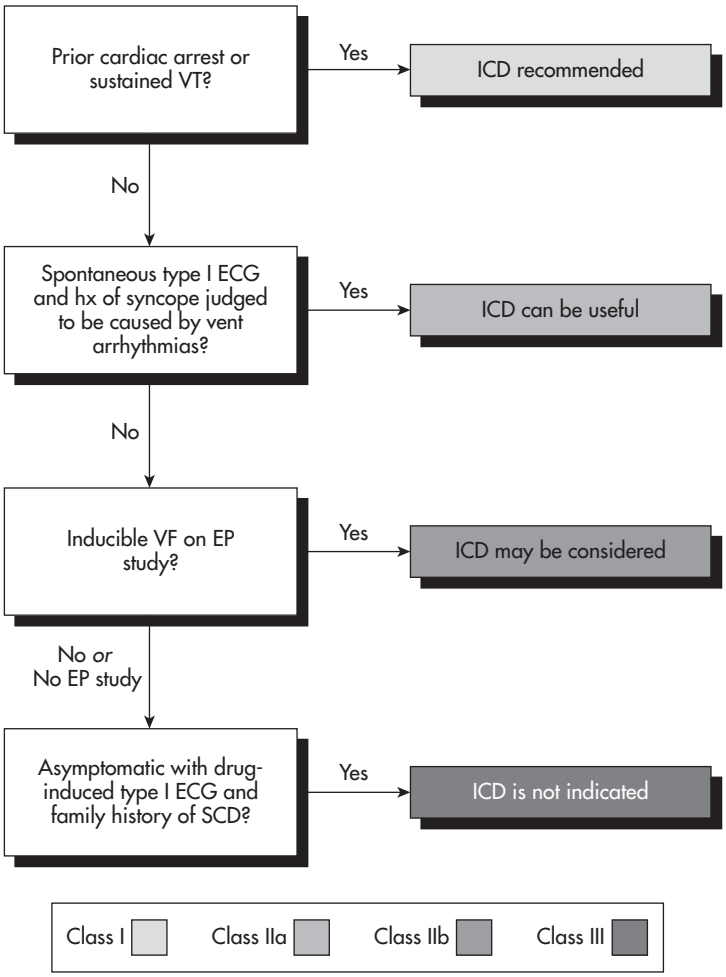


FIGURE B1-59 B Consensus recommendations for ICDs in patients diagnosed with Brugada syndrome. (Priori SG et al: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes, *Heart Rhythm* 10:1932-1963, 2013.)

SUGGESTED READINGS

Berne P, Brugada J: Brugada syndrome 2012, *Circ J* 76:1563–1571, 2012.

Bonow RO et al. *Braunwald's heart disease: a textbook of cardiovascular medicine.* Ed 9 Saunders: Philadelphia.

Chen PS et al.: The Brugada syndrome, *J Am Coll Cardiol* 51:12, 2008.

Epstein AE et al.: ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons, *Circulation* 117:e350, 2008.

Priori SG et al.: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes, *Heart Rhythm* 10:1932–1963, 2013.

Zipes DP et al.: ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death-Executive Summary A Report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death), *J Am Coll Cardiol* 48:1064, 2006.

BASIC INFORMATION

DEFINITION

Forcible clenching or grinding of the teeth during sleep or wakefulness, often leading to damage of the teeth.

ICD-9CM CODES
306.8 Bruxism
ICD-10CM CODES
F45.8 Other somatoform disorders

EPIDEMIOLOGY & DEMOGRAPHICS

- Occurs in 15% of children and 75% of adults
- Familial cases have occasionally been described.
- Bruxism often presents between age 10 and 20 yr but may persist throughout life.
- Nocturnal bruxism is noted most often during stages I and II NREM sleep and REM sleep.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Complaints of grinding of teeth from a sleep partner or members of the family are common. In many cases the masticatory system will adapt to the phenomenon, but in severe cases nearly every part of the masticatory system may be damaged. Excessive wearing of dentition is the most common physical finding. Tender or hypoatrophied masticatory muscles may also be observed.

ETIOLOGY

- Cause is controversial. Fig. B1-60 illustrates the cascade of physiologic events in the genesis of sleep bruxism and rhythmic masticatory muscle activity and course of action for management.
- Possible causes include occlusal discrepancies, anatomy of the bony structures of the orofacial region, part of the sleep arousal response, disturbances of the central dopaminergic system, smoking, alcohol, drugs, stress, and personality.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Dental compression syndrome
- Temporomandibular joint disorders
- Chronic orofacial pain disorders
- Oral motor disorders
- Malocclusion

WORKUP

- History should have an emphasis on sleep habits, including excessive snoring, pain in the temporal mandibular region, interview with close family members, health habits, personality quirks.
- Physical examination of the teeth and masticatory muscles is mandatory.
- Sleep studies in selected cases may be helpful.

LABORATORY TESTS

None indicated unless a systemic disease is suspected (e.g., infection, autoimmune disorder)

IMAGING STUDIES

X-ray studies of teeth and temporomandibular joints

TREATMENT

NONPHARMACOLOGIC THERAPY

Biofeedback, psychological counseling, and elimination of harmful health habits have been used with limited success.

GENERAL Rx

- Oral splints (Fig. B1-61); night guard to protect teeth may be useful
- Correction of malocclusion
- Pain management (e.g., gabapentin, ibuprofen)
- Medication to relieve anxiety and improve sleep (e.g., benzodiazepine or trazodone at bedtime)
- Local injections of botulinum toxin into masseter muscles to prevent dental and temporomandibular joint complications

DISPOSITION

Referral to dentist mandatory if damage to teeth evident

PEARLS & CONSIDERATIONS

- Like any poorly understood disease, treatment is often unsatisfactory and subject to quackery.
- Both diurnal and nocturnal bruxism may be associated with various movement and degenerative disorders (e.g., Huntington disease, oromandibular dystonia) and are quite common in children with cerebral palsy and mental retardation.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Bruxism (Tooth Grinding) (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

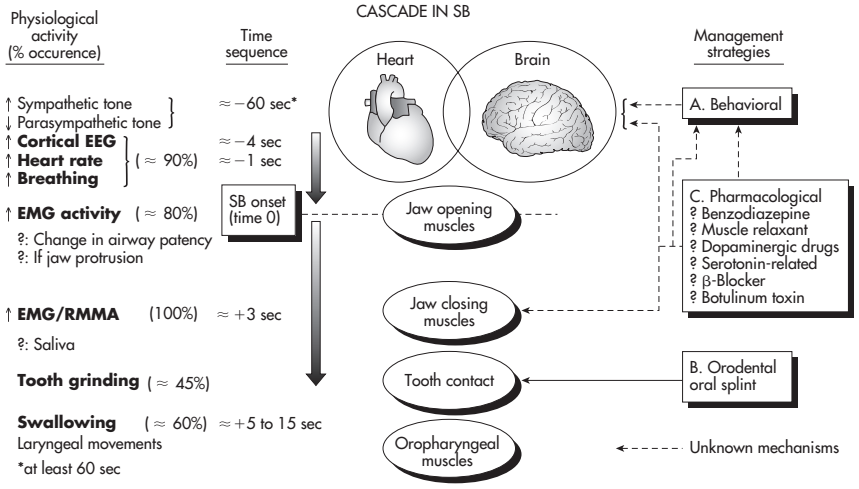


FIGURE B1-60 Cascade of physiologic events in genesis of sleep bruxism and rhythmic masticatory muscle activity
(*left*) and courses of action for management (*right*). (From Lavigne G et al: Sleep bruxism. In Kryger MH, Roth T, Dement WC [eds]: *Principles and practice of sleep medicine*, ed 5, Philadelphia, 2011, Elsevier, pp 1128–1139.)

FIGURE B1-61 Occlusal splint. (From Hochberg MC et al [eds]: *Rheumatology,* ed 3, St Louis, 2003, Mosby.)

SUGGESTED READINGS

Attansio R: An overview of bruxism and its management, *Dent Clin North Am* 41(2):229, 1997.

Dae TT, Lavigne EJ: Oral splints: the crutches for temporomandibular disorders and bruxism, *Crit Rev Oral Biol Med* 9(3):345, 1998.

Lopbezoo F, Naeije M: Bruxism is mainly regulated centrally, not peripherally, *J Oral Rehabil* 28(12):1085, 2001.

Tan EK, Jankovic J: Treating severe bruxism with botulinum toxin, *J Am Dent Assoc* 131:211, 2000.

BASIC INFORMATION

DEFINITION

Budd-Chiari syndrome (BCS) is a rare disease defined by the obstruction of hepatic venous outflow anywhere from the small hepatic veins to the junction of the inferior vena cava (IVC) and the right atrium. Primary BCS is defined by endoluminal obstruction as seen in thromboses or webs. Secondary BCS occurs when the obstruction is caused by compression or invasion by a lesion originating outside the veins (tumor, abscess, cyst, etc.). It can also be a postoperative complication of orthotopic liver transplantation.

SYNONYMS

Hepatic vein thrombosis
Obliterative endophlebitis of the hepatic veins
IVC thrombosis (obliterative hepatocavopathy)

ICD-9CM CODES
453.0 Budd-Chiari syndrome
ICD-10CM CODES
I82.0 Budd-Chiari syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1/2.5 million persons per yr
PREDOMINANT SEX: In Western countries, women are more commonly affected (approximately 2/3 of cases)
PREDOMINANT AGE: Presentation is usually in the third and fourth decades of life, with the median age being 35

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Clinical presentation and characteristics vary with geography. In Africa and South Asia, intravascular webs are more often associated with IVC thrombosis with a stronger association with subsequent hepatocellular carcinoma. In the U.S., BCS is more commonly associated with primary myeloproliferative disorders and underlying hypercoagulable states. Underlying factors that contribute to BCS can be identified in ~85% of cases; multiple causative factors are identified in 50% of cases.

- Clinical manifestations can be caused by complete or partial occlusion of any or all of the three major hepatic veins, or inferior vena cava.
- Presentation is variable according to the degree, location, acuity of obstruction, and presence of collateral circulation:
  1. Fulminant/acute (20%): severe right upper quadrant abdominal pain, fever, nausea, vomiting, jaundice, hepatomegaly, transudative ascites, marked elevation in serum aminotransferases (ALT >5 times the upper limit of normal), elevation of alkaline phosphatase to 300 to 400 IU/L, decrease in coagulation factors, variceal bleeding, encephalopathy within 8 wk of onset of jaundice; biopsy, if performed, would reveal liver cell loss; early recognition and treatment are essential for survival; a slow decrease in ALT is associated with poor survival.
  2. Subacute/chronic (60%): vague abdominal discomfort, gradual progression to caudate lobe hypertrophy with atrophy of the rest of the liver, portal hypertension with or without cirrhosis and its sequelae, transudative ascites, lower-extremity edema, esophageal varices, splenomegaly, coagulopathy, hepatorenal syndrome in up to half of patients, hepatopulmonary syndrome in up to 28% of patients, and rarely, encephalopathy
  3. Asymptomatic (5% to 20%): usually discovered incidentally by abnormal liver function tests

ETIOLOGY

- Primary myeloproliferative diseases: 20% to 53%
  1. Polycythemia vera, responsible for 10% to 40% of cases
  2. Essential thrombocythemia and idiopathic myelofibrosis are less common causes
  3. *JAK2* mutations are implicated in cases of idiopathic BCS (identified in 26% to 59% of cases)
  4. Rare but recently reported: idiopathic hypereosinophilia syndrome
- Hypercoagulable states (inherited and acquired): often coexist with other causes, 30% to 65%
  1. Factor V Leiden (25%)
  2. Factor II gene mutation (5%)
  3. Anticardiolipin antibodies (25%)
  4. Hyperhomocysteinemia (22%)
  5. Paroxysmal nocturnal hemoglobinuria (19%)
- Protein C, protein S, and antithrombin III deficiency are difficult to interpret because the presence of liver disease may confound results.
- Heterozygosity for G20210A prothrombin gene mutation or methylene-tetrahydrofolate reductase (MTHFR) mutation may be seen in BCS
- Pregnancy and oral contraceptive pills (cases reported after <2 wk of use)
- Malignancy (up to 10% of cases, causing external compression or invasions of vascular structures)
  1. Most commonly due to hepatocellular carcinoma but also can be due to neoplasms of the kidney, adrenal gland, pancreas, stomach, and sarcomas of the right atrium, inferior vena cava, and hepatic veins
- Rare but reported: sickle cell anemia, infections with liver abscess, hydatid cyst (echinococcosis), schistosomiasis, sarcoidosis, Behçet's disease (<5%), membranous webs of IVC or hepatic veins (more common in Africa and South Asia, can be congenital or acquired secondary to underlying myeloproliferative disorder), abdominal trauma, liver torsion, ulcerative colitis, celiac disease, idiopathic (10% to 20%)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hepatitis from ischemia, viral infection, toxin, alcohol
- Cholecystitis
- Hepatic venoocclusive disease (sinusoidal obstruction syndrome)
- Congestive hepatopathy, also known as *cardiac cirrhosis,* from tricuspid regurgitation, right atrial myxoma, constrictive pericarditis
- Cirrhosis from any etiology

LABORATORY TESTS

- Assessment of liver injury and function: serum aminotransferases, alkaline phosphatase, prothrombin time (PT), albumin, bilirubin
- Exclusion of another form of liver disease: viral hepatitis panel, autoantibodies (antinuclear antibody, anti–smooth muscle antibody, anti-mitochondrial antibody), serum iron, transferrin saturation, ferritin, ceruloplasmin, and α-1 antitrypsin
- Ascites protein content >3.0 g/dl and serum ascites albumin gradient ≥1.1 g/dl are suggestive of transudative ascites from BCS, cardiac or pericardial disease
- Evaluation for underlying myeloproliferative disorder and hypercoagulable state: CBC, bone marrow biopsy, tests for hypercoagulable states (Factor V Leiden, prothrombin gene G20210A mutation, protein C, protein S, and antithrombin deficiencies, antiphospholipid antibodies, hyperhomocysteinemia, paroxysmal nocturnal hemoglobinuria, and MTHFR C677T mutation); protein C, protein S, and antithrombin deficiencies may be difficult to interpret in the setting of liver dysfunction, but levels <20% of normal are suggestive of a true deficiency; thrombophilia screening for the JAK2 V617F mutation may be useful if no other cause for myeloproliferative disorders/hypercoagulable states identified

IMAGING STUDIES

- Diagnosis of BCS is made by radiographic imaging.
- Ultrasound and color and pulsed Doppler are the first-line tests. Diagnostic sensitivity and specificity are 85% to 90%. Findings include large hepatic vein with an absent flow signal, or with reversed or turbulent flow; large intrahepatic collateral vessels; enlarged, stenotic, thickened, or tortuous hepatic veins; and caudate lobe hypertrophy (as the caudate lobe has an alternate blood supply through anastomoses).
- MRI with gadolinium contrast—better than contrast-enhanced CT (Fig. B1-62), with a sensitivity and specificity of approximately 90%—is the second-line test. Findings include obstructed hepatic veins or IVC; large, intrahepatic or subcapsular collaterals; and caudate lobe hypertrophy. Three-dimensional

FIGURE B1-62 CT scan of Budd-Chiari syndrome.The appearances are not immediately diagnostic for the nonexpert, and infiltrative disease is sometimes suspected. (From Forbes A et al [eds]: *Atlas of clinical gastroenterology*, ed 3, 2005, Mosby.)

contrast-enhanced magnetic resonance angiography (MRA, see Fig. EB1-63) rivals hepatic venography in sensitivity.
- Contrast-enhanced CT may reveal similar findings as Doppler ultrasound, as well as delayed or absent filling of the hepatic veins, parenchymal opacification of the liver, and narrowing of the inferior vena cava.
- CT image reconstruction of vasculature is becoming available.
- Venography: This is not essential for diagnosis; it should be performed when other noninvasive imaging tests are nondiagnostic in the setting of strong clinical suspicion for BCS; measurement of pressure gradients can help predict success of percutaneous or surgical shunt intervention and plan surgical intervention. Confirms the pathognomonic web pattern caused by collateral venous flow.
- Liver biopsy: This is not necessary to diagnose BCS but may be helpful in patients with cirrhosis in whom the diagnosis remains uncertain and critical for differentiating from hepatic venoocclusive disease. Findings include hepatic congestion, hepatocyte necrosis and fibrosis in centrilobular areas, and compensatory nodular regenerative hyperplasia with progression to fibrosis and cirrhosis. In advanced BCS, may also see infarction caused by concomitant thrombosis of the intrahepatic, extrahepatic, and portal veins. There are conflicting studies regarding the association of histologic findings and prognosis.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY
- Goal of therapy is decompression of hepatic congestion.
- In general, therapeutic procedures should be introduced by order of increasing invasiveness based on response/failure to therapy rather than disease severity.
- Hypercoagulable states should be investigated in all patients.

ACUTE GENERAL Rx
- Anticoagulation, first with low-molecular-weight heparin (LMWH), followed by warfarin, even in the absence of an underlying hypercoagulable disorder
- In situ thrombolysis: can be successful when performed in recently thrombosed veins (clot less than 3 to 4 wk old) that are well defined on venography and do not involve the inferior vena cava; mature clots are nonresponsive to thrombolysis, and bleeding risk is high if portal hypertension has developed
- Balloon angioplasty: complicated by 50% restenosis rate; effective when membranous webs are the etiology
- Stenting: may improve long-term patency rates to 90%, but if placed above the intrahepatic IVC, may complicate future liver transplantation
- Transjugular intrahepatic portosystemic shunt (TIPS) has been increasingly used in recent years; usually performed in patients with no improvement on anticoagulation therapy or when a dilatable lesion cannot be found; TIPS has replaced surgical shunting as the most common invasive therapeutic procedure; recently polytetrafluoroethylene (ePTFE)-coated stents have improved TIPS-patency rates, especially in patients with underlying hypercoagulable defects.
- Surgical portal systemic shunts: feasibility depends on technical factors, long-term patency of the stent, the extent of liver damage before surgery, as well as on locating a center with well-trained surgeons
- Liver transplant may be indicated in patients with fulminant hepatic failure and in patients who fail to respond to TIPS; 10-year survival reported to range between 69% and 84%.
- Supportive measures

CHRONIC Rx
- Lifelong anticoagulation: Warfarin therapy with a target international normalized ratio (INR) of 2 to 3 lessens, but does not completely prevent, recurrence. This should be continued permanently unless the patient has an adverse event to anticoagulation.
- In patients with an underlying myeloproliferative disorder, treatment with hydroxyurea and aspirin, or anagrelide, may be given instead of traditional anticoagulation.
- Treat liver dysfunction and complications related to portal hypertension, such as ascites (diuretics and low-sodium diet).
- Invasive interventions should be reserved for symptomatic patients who do not improve with medical therapy.
- Manage shunt thrombosis, which is a common complication.
- Liver transplantation is another treatment option; up to 10% recurrence of BCS after transplant has been recognized
- Monitor for development of hepatocellular carcinoma and transformation of myeloproliferative disease in patients with longstanding, well-controlled BCS.

DISPOSITION
Prognosis is variable and depends on multiple factors, including time to recognition and treatment, etiology, acuity, the type of intervention, and the condition of the patient at the time of treatment. Overall mortality rates are decreasing with the use of anticoagulation and early diagnosis of asymptomatic cases. Survival rates have been reported as 77%, 65%, and 57% at 1, 5, and 10 yr from diagnosis. A prognostic index called the *Rotterdam BCS Index* has been described: 1.27 × Encephalopathy + 1.04 × Ascites + 0.72 × PT + 0.004 × Bilirubin. Encephalopathy and ascites are scored as 1 for present or 0 as absent, and PT is scored as greater (1) or less than (0) an INR of 2.3. An index of >1.1 correlates to low risk (5-yr survival rate, 89%), 1.1 to 1.5 with intermediate risk (5-yr survival rate, 74%), and <1.5 with high risk (5-yr survival rate, 42%).

REFERRAL
Fulminant presentations should immediately be referred to a center capable of liver transplantation. All cases benefit from referral to a hepatologist, a hematologist, an interventional radiologist, and a surgeon specializing in hepatobiliary disease.

! PEARLS & CONSIDERATIONS

COMMENTS
- Look for one or more underlying causes, especially hypercoagulable or hematologic disorders, and malignancies or space-occupying lesions that may compress or invade the hepatic outflow tract.
- Myeloproliferative disorders are most common.
- Diagnosis relies on imaging, beginning with Doppler ultrasound.
- Treatment with anticoagulation comes first, followed by invasive interventions as needed. Prophylaxis of portal hypertension can reduce the risk of major bleeding associated with anticoagulation therapy.
- Referral for liver transplantation may be necessary.
- Prognosis depends on presence of ascites, encephalopathy, PT, and serum bilirubin levels.

PREVENTION
In the setting of known risk factors, such as a hypercoagulable state or myeloproliferative disorder, any additional risks, such as smoking or oral contraceptive therapy, should be avoided.

SUGGESTED READINGS
Available at www.expertconsult.com

RELATED CONTENT
Hypercoagulable States (Related Key Topic)
Budd-Chiari Syndrome (Patient Information)

AUTHORS: **MICHAEL PRODROMOU, M.D.** and **JEANETTE G. SMITH, M.D.**

SUGGESTED READINGS

Darwish Murad S et al.: EN-Vie (European Network for Vascular Disorders of the Liver): Etiology, management, and outcome of the Budd-Chiari syndrome, *Ann Intern Med* 151:167–175, 2009.

DeLeve LD et al.: American Association for the Study of Liver Diseases: Vascular disorders of the liver, *Hepatology* 49(5):1729–1764, 2009.

Fox MA et al.: Budd-Chiari syndrome—a review of the diagnosis and management, *Acute Medicine* 10(1):5–9, 2011.

Garcia-Pagán JC et al.: Budd-Chiari Syndrome-Transjugular Intrahepatic Portosystemic Shunt Group: TIPS for Budd-Chiari syndrome: long-term results and prognostics factors in 124 patients, *Gastroenterology* 135(3):808–815, 2008.

Hoekstra J et al.: Impaired fibrinolysis as a risk factor for Budd-Chiari syndrome, *Blood* 115:388, 2010.

Menon KV et al.: The Budd-Chiari syndrome, *N Engl J Med* 350(6):578, 2004.

Mishchenko E, et al.: Hypereosinophilia, JAK2V617F, and Budd-Chiari syndrome: who is responsible for what? *Am J Hematol* 86:223, 2011.

Plessier A, Valla DC: Budd-Chiari syndrome, *Semin Liver Dis* 28(3):259–269, 2008.

Qi X et al.: Meta-analysis: the significance of screening for JAK2V617F mutation in Budd-Chiari syndrome and portal venous system thrombosis, *Aliment Pharmacol Ther* 33:1087, 2011.

Ren W, Qi X, Yang Z et al.: Prevalence and risk factors of hepatocellular carcinoma in Budd-Chiari syndrome: a systematic review, *Eur J Gastroenterol Hepatol* 25(7):830–841, 2013.

Xue H et al.: The role of intravascular intervention in the management of Budd-Chiari syndrome, *Dig Dis Sci* 55:2659, 2010.

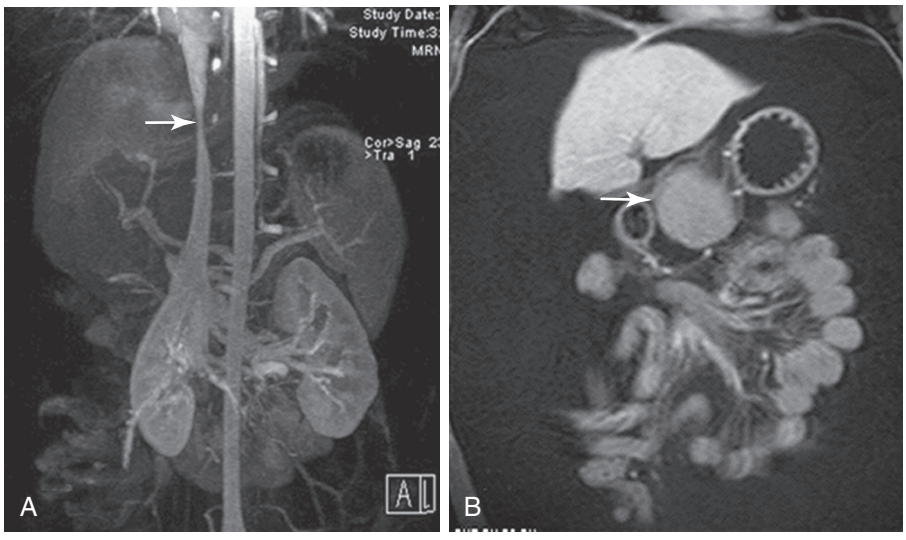


FIGURE EB1-63 Magnetic resonance venogram. A, IVC obstruction *(arrow)* at the level of the caudate. B, Hypertrophic caudate lobe. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Bulimia nervosa is a prolonged illness characterized by a specific psychopathology. According to the *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition, bulimia nervosa can be diagnosed by: (A) recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:

1. Eating, in a discrete period of time, an amount of food that is definitely larger than what most individuals would eat in a similar period of time under similar circumstances.
2. A sense of lack of control over gating during the episode.

(B) Recurrent inappropriate compensators/behaviors in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise. (C) The binge eating and inappropriate compensatory behaviors both occur, on average, at least once a week for 3 mo. (D) Self-evaluation is unduly influenced by body shape and weight. (E) The disturbance does not occur exclusively during episodes of anorexia nervosa.

ICD-9CM CODES
783.6 Bulimia
ICD-10CM CODES
F50.2 Polyphagia, bulimia nervosa

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE/PREVALENCE: Affects 1% to 3% of female adolescents and young adults
PREDOMINANT SEX: Female/male ratio of 10:1
PREDOMINANT AGE: Adolescence to young adulthood; mean age of onset: 17 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Parotid and salivary gland swelling
- Scars on the back of the hand and knuckles (Russell sign) from rubbing against the upper incisors when inducing vomiting
- Eroded enamel, particularly on the lingual surface of the upper teeth; pyorrhea and other gum disorders possible
- Petechial hemorrhages of the cornea, soft palate, or face possibly noted after vomiting
- Loss of gag reflex, well-developed abdominal musculature
- Often no emaciation; normal physical examination possible

ETIOLOGY

- Etiology is unknown but likely multifactorial (sociocultural, psychological, familial factors).
- Bulimia is much more common in Western societies, where there is a strong cultural pressure to be slender.
- According to the American Psychiatric Association, patients with eating disorders display a broad range of symptoms that occur along a continuum between those of anorexia nervosa and bulimia.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Schizophrenia
- Gastrointestinal disorders
- Neurologic disorders (seizures, Kleine-Levin syndrome, Klüver-Bucy syndrome)
- Brain neoplasms
- Psychogenic vomiting

WORKUP

- The following questions are useful to screen patients for bulimia:
  1. "Are you satisfied with your eating habits?"
  2. "Do you ever eat in secret?"
- Answering "no" to the first question and/or "yes" to the second question has 100% sensitivity and 90% specificity for bulimia. The SCOFF questionnaire can also be used as a screening tool for eating disorders (see "Anorexia Nervosa").
- According to DSM-5, the level of severity is based on the frequency of inappropriate compensatory behaviors and may be increased to reflect other symptoms and degree of functional disability, as noted below:
  - Mild: An average of 1 to 3 episodes of inappropriate compensatory behaviors per week.
  - Moderate: An average of 4 to 7 episodes of inappropriate compensatory behaviors per week
  - Severe: An average of 8 to 13 episodes of inappropriate compensatory behaviors per week
  - Extreme: An average of ≥14 inappropriate compensatory behaviors per week
- Table B1-21 describes eating and weight control habits commonly found in children and adolescents with an eating disorder.

LABORATORY TESTS

- Electrolyte abnormalities from vomiting (hypokalemia and metabolic alkalosis) or diarrhea from laxative abuse (hypokalemia and hyperchloremic metabolic acidosis)
- Hyponatremia, hypocalcemia, hypomagnesemia (caused by laxative abuse)
- Elevated cortisol, decreased luteinizing hormone, decreased follicle-stimulating hormone

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cognitive behavioral therapy, particularly interpersonal therapy to control abnormal behaviors
- Use of food diaries, nutritional counseling, and planning meals at least 1 day in advance are useful measures to counter abnormal eating behaviors
- Correction of electrolyte abnormalities

ACUTE GENERAL Rx

- Selective serotonin reuptake inhibitors are generally considered to be the safest medication option in these patients. They are useful in severely depressed patients and in those who do not benefit from cognitive behavioral therapy.
- Prompt recognition and treatment of complications:
  1. Ipecac cardiotoxicity from laxative abuse
  2. Electrolyte abnormalities (see "Laboratory Tests")
  3. Esophagitis and Mallory-Weiss tears; esophageal rupture from repeated vomiting
  4. Aspiration pneumonia and pneumomediastinum
  5. Menstrual irregularities (including amenorrhea)
  6. Gastrointestinal abnormalities: acute gastric dilation, pancreatitis, abdominal pain, constipation

CHRONIC Rx

- Psychotherapy continued for years and focused specifically on self-image and family and peer interactions is an integral part of successful recovery.
- Family therapy is also recommended, especially in younger patients.

DISPOSITION

Course is variable and marked by frequent recurrence of exacerbations.

REFERRAL

- In addition to the primary care physician, the multidisciplinary team should include a dietician, a psychiatrist, and a family therapist.
- Hospitalization should be considered for patients with severe electrolyte abnormalities or those with suicidal thoughts.

PEARLS & CONSIDERATIONS

COMMENTS

- Bulimia has a close association with depression, bipolar disorder, obsessive-compulsive disorder, alcoholism, and substance abuse.
- Bulimia should be considered in all patients (especially adolescents) with unexplained hypokalemia and metabolic alkalosis.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Bulimia (Patient Information)
Anorexia Nervosa (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

TABLE B1-21 Eating and Weight Control Habits Commonly Found in Children and Adolescents with an Eating Disorder

	PROMINENT FEATURES		CLINICAL COMMENTS REGARDING EATING DISORDER HABITS	
Habit	**Anorexia Nervosa**	**Bulimia Nervosa**	**Anorexia Nervosa**	**Bulimia Nervosa**
Overall intake	Inadequate energy (calories), although volume of food and beverages may be high due to very low caloric density of intake due to "diet" and nonfat choices	Variable, but calories normal to high; intake in binges often "forbidden" food or drink that differs from intake at meals	Consistent inadequate caloric intake leading to wasting of the body	Inconsistent balance of intake, exercise and vomiting, but severe caloric restriction is short-lived
Food	Counts and limits calories, especially from fat; emphasis on "healthy food choices" with reduced caloric density Monotonous, limited "good" food choices, often leading to vegetarian or vegan diet Strong feelings of guilt after eating more than planned leads to exercise and renewed dieting	Aware of calories and fat, but less regimented in avoidance than AN Frequent dieting interspersed with overeating, often triggered by depression, isolation, or anger	Obsessive-compulsive attention to nutritional data on food labels and may have "logical" reasons for food choices in highly regimented pattern, such as sports participation or family history of lipid disorder	Choices less structured, with more frequent diets
Beverages	Water or other low- or no-calorie drinks; nonfat milk	Variable, diet soda common; may drink alcohol to excess	Fluids often restricted to avoid weight gain	Fluids ingested to aid vomiting or replace losses
Meals	Consistent schedule and structure to meal plan Reduced or eliminated caloric content, often starting with breakfast, then lunch, then dinner Volume can increase with fresh fruits, vegetables, and salads as primary food sources	Meals less regimented and planned than in AN; more likely impulsive and unregulated, often eliminated following a binge-purge episode	Rigid adherence to "rules" governing eating leads to sense of control, confidence, and mastery	Elimination of a meal following a binge-purge only reinforces the drive for binge later in the day
Snacks	Reduced or eliminated from meal plan	Often avoided in meal plans, but then impulsively eaten	Snack foods removed early because "unhealthy"	Snack "comfort foods" can trigger a binge
Dieting	Initial habit that becomes progressively restrictive, although often appearing superficially "healthy" Beliefs and "rules" about the patient's idiosyncratic nutritional requirements and response to foods are strongly held	Initial dieting gives way to chaotic eating, often interpreted by the patient as evidence of being "weak" or "lazy"	Distinguishing between healthy meal planning with reduced calories and dieting in ED may be difficult	Dieting tends to be impulsive and short-lived, with "diets" often resulting in unintended weight gain
Binge eating	None in restrictive subtype, but an essential feature in binge-purge subtype	Essential feature, often secretive Shame and guilt prominent afterward	Often "subjective" (more than planned but not large)	Relieves emotional distress, may be planned
Exercise	Characteristically obsessive-compulsive, ritualistic, and progressive May excel in dance, long-distance running	Less predictable May be athletic, or may avoid exercise entirely	May be difficult to distinguish active thin vs. ED	Males often use exercise as means of "purging"
Vomiting	Characteristic of binge-purge subtype May chew then spit out, rather than swallow, food as a variant	Most common habit intended to reduce effects of overeating Can occur after meal as well as a binge	Physiologic and emotional instability prominent	Strongly "addictive" and self-punishing, but does not eliminate calories ingested—many still absorbed
Laxatives	If used, generally to relieve constipation in restrictive subtype, but as a cathartic in binge-purge subtype	Second most common habit used to reduce or avoid weight gain, often used in increasing doses for cathartic effect	Physiologic and emotional instability prominent	Strongly "addictive," self-punishing, but ineffective means to reduce weight (calories are absorbed in the small intestine, but laxatives work in the colon)
Diet pills	Very rare, if used; more common in binge-purge subtype	Used to either reduce appetite or increase metabolism	Use of diet pills implies inability to control eating	Control over eating may be sought by any means

AN, Anorexia nervosa; *BN,* bulimia nervosa; *ED,* eating disorder.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

SUGGESTED READINGS

American Psychiatric Association. Desk reference to the diagnostic criteria from DSM-5. American Psychiatric Association: Arlington, VA.

American Psychiatric Association: Practice guideline for the treatment of patients with eating disorders, *Am J Psychiatry* 157(suppl):4, 2000.

Mehler PS: Bulimia nervosa, *N Engl J Med* 349:875, 2003.

Williams PM et al.: Treating eating disorders in primary care, *Am Fam Physician* 77(2):187, 2007.

BASIC INFORMATION

DEFINITION

Bullous pemphigoid is an autoimmune, subepidermal blistering disease commonly seen in the elderly. A related entity is cicatricial pemphigoid, which predominantly affects the mucous membranes.

SYNONYMS

Pemphigoid

ICD-9CM CODES
694.5 Pemphigoid
ICD-10CM CODES
L12.0 Bullous pemphigoid

EPIDEMIOLOGY & DEMOGRAPHICS

- Occurs most commonly in people older than 60 yr, with peak incidence in those aged ≥80 yr
- Incidence is approximately 10 cases per 1 million persons
- No gender or racial predilection
- Most common of the autoimmune bullous dermatoses

PHYSICAL FINDINGS & CLINICAL PRESENTATION

HISTORY:
- Skin lesions typically start as eczematous or urticarial plaques on the extremities and are often very pruritic
- Taut blisters can form within 1 wk to several months

PHYSICAL FINDINGS:
- Anatomic distribution
  1. Flexor surfaces of the arms and legs, groin, axilla, chest, and abdomen; generally spares the head and neck
  2. Rare involvement of mucous membranes
- Lesion configuration
  1. May be localized to the extremities or generalized
  2. Lesions irregularly grouped but may sometimes be serpiginous (Fig. B1-64)
- Lesion morphology
  1. Taut blisters (bullae) measuring 5 mm to 2 cm in diameter filled with clear or bloody fluid on either normal or erythematous skin are characteristic
  2. Heal without scarring but may leave postinflammatory hyperpigmentation

ETIOLOGY

- Autoimmune disease with immunoglobulin (Ig) G and/or C3 complement targeting hemidesmosomal antigens located in the epidermal basement membrane zone
- Drug-induced pemphigoid, although rare, can occur in patients taking penicillamine, furosemide, captopril, penicillin, or sulfasalazine

DIAGNOSIS

Skin biopsy aids in the diagnosis, and specimens should be sent for routine histochemical staining and direct immunofluorescence.

DIFFERENTIAL DIAGNOSIS

- Cicatricial pemphigoid
- Epidermolysis bullosa acquisita
- Pemphigus
- Linear IgA disease

LABORATORY TESTS

- Histology of lesional skin shows a subepidermal blister with a superficial inflammatory infiltrate, often with numerous eosinophils.
- Indirect immunofluorescence detects anti–basement membrane antibodies in 70% of patients with bullous pemphigoid.
- Direct immunofluorescence of perilesional skin shows C3 and IgG linearly arranged along the epidermal basement membrane.
- Approximately half of patients will have a peripheral blood eosinophilia.

TREATMENT

Bullous pemphigoid may be a self-limited disease, but its course may last from months to years. Treatment is based on the degree of disease involvement and the rate of disease progression.

NONPHARMACOLOGIC THERAPY

- Mild soaps with emollients to wet skin after bathing
- Topical antipruritic creams

FIGURE B1-64 Bullous pemphigoid. Note intact bullae with erosions in a flexural distribution. (From Goldstein BG, Goldstein AO: *Practical dermatology,* ed 2, St Louis, 1997, Mosby.)

ACUTE GENERAL Rx

Localized disease:
- Potent topical steroids (e.g., clobetasol) until blistering ceases with gradual tapering over several weeks
- Oral antihistamines to control pruritus

Generalized disease:
- Mainstay of therapy is prednisone, usually beginning with a minimal dose of 1 mg/kg/day
- Steroid-sparing agents, such as azathioprine or mycophenolate mofetil, may be started with prednisone or shortly after prednisone therapy is initiated and may be continued once prednisone is discontinued
- Tetracyclines
- Low-dose methotrexate has recently been suggested to be an optimal therapy in the elderly
- Rituximab, a monoclonal antibody to CD20, has been used for treatment-refractory bullous pemphigoid

CHRONIC Rx

- Prednisone combined with steroid-sparing agents with the goal of limiting oral corticosteroid intake
- Other immunosuppressive agents, such as cyclophosphamide or cyclosporine, are occasionally used

DISPOSITION

Mortality rates are estimated at between 10% and 40% after 1 yr. Patients with widespread disease requiring immunosuppressive therapy and with other comorbidities are at highest risk for complications from the disease. Approximately 50% of treated patients experience remission within 2 to 6 yr.

REFERRAL

Dermatology

PEARLS & CONSIDERATIONS

COMMENTS

- Bullous pemphigoid is mainly a disease of elderly persons and should be suspected in older persons with chronic pruritic eruptions and in those patients who have new-onset taut vesicles and bullae
- Not believed to represent a paraneoplastic process.

RELATED CONTENT

Bullous Pemphigoid (Patient Information)

AUTHORS: **JESSICA CORWIN, M.D., M.P.H.** and **KACHIU LEE, B.A.**

Burning Mouth Syndrome

BASIC INFORMATION

DEFINITION

Burning mouth syndrome (BMS) is characterized by continuous burning pain in the tongue or oral mucous membranes where no underlying dental or medical cause can be identified and no oral signs are found. BMS may be accompanied by subjective xerostomia (dry mouth sensation in which no cause can be found), dysgeusia (altered taste), dysosmia (altered smell), and oral paresthesia (e.g., tingling).

CLASSIFICATION

- Type 1: Symptoms not present upon waking, then increase throughout the day
- Type 2: Symptoms upon waking and throughout the day (most common type)
- Type 3: No regular pattern of symptoms

SYNONYMS

Glossodynia
Oral dysesthesia
Glossopyrosis
BMS

ICD-9CM CODES
529.6 Glossodynia
ICD-10CM CODES
K14.6 Glossodynia

EPIDEMIOLOGY & DEMOGRAPHICS

- 5 per 100,000 general population
- Women 3 to 7 times more likely than men of a similar age; most prevalent in postmenopausal women
- Typically occurs in middle-aged or older adults. The prevalence may increase from 3- to 12-fold with increasing age.
- Asian and Native Americans have considerably higher risk

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Sensation is usually bilaterally located on the tongue, most frequently on the anterior two thirds of the tongue, the anterior hard palate, and the lower lip mucosa.
- Sensation most typically described as burning, scalded, or tingling. Sometimes described as "discomfort," "tender," or "annoying" rather that pain or burning.
- The oropharyngeal exam may show atrophy, erythema, leukoplakia, erosion, or ulceration.
- May present with oral parafunctional habits such as bruxism, jaw clenching, and tongue thrusting, which are increased with anxiety.
- Pain is chronic and often lasts at least 4 to 6 mo.
- Up to two thirds of patients report a spontaneous partial recovery within 6 to 7 years from onset, with the pain changing from constant to intermittent.

ETIOLOGY

More than 50% of cases have no identifiable cause (primary BMS). Many of the currently proposed etiologies of secondary BMS include:

- Psychological dysfunction: many patients concomitantly have personality or mood changes, report more adverse life events, somatization, anxiety, and depression. A proportion of patients have anxiety centered around concerns of cancer (cancerphobia).
- Endocrine: Hormonal alterations in oral mucosa have been suggested as a cause, especially in menopause.
- Immunologic: Observational studies have shown elevation of serum erythrocyte sedimentation rate and salivary immunoglobulin A compared with control patients.
- Infectious: Fusospirochetes, *Candida, Enterobacter, Helicobacter pylori,* and *Klebsiella* infection. *Candida* may not always produce visible lesions.
- Local irritants, such as smoking, and dental materials, such as mercury.
- Medications: e.g., angiotensin-converting enzyme (ACE) inhibitors and protease inhibitors.
- Nerve damage.
- Nutritional deficiencies: iron, zinc, folate, and vitamin B.

There may be an association between supertasters (those with enhanced ability to taste) and those with BMS due to their increased density of taste buds that are surrounded by bundles of trigeminal nerve neurons.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Mucosal disease such as lichen planus or candidiasis
- Nutritional deficiency in zinc, iron, folate, or vitamins B_1, B_2, B_6, B_9, B_{12}
- Dry mouth from Sjögren's syndrome or after chemo/radiation therapy
- Cranial nerve injury
- Medication effect

WORKUP

- Clinical history is the most important in diagnosing BMS.
- Very important to rule out other pathologic conditions first.

LABORATORY TESTS

There is no diagnostic test for BMS, but consider testing for vitamin B, folate, ferritin, or zinc deficiency as well as CBC, luteinizing hormone, follicle-stimulating hormone, and erythrocyte sedimentation rate.

TREATMENT

NONPHARMACOLOGIC THERAPY

Consider discontinuation of medications that may cause xerostomia (e.g., anticholinergics, psychotropics) and substitution for medications that may cause oral burning (e.g., ACE inhibitors, angiotensin-receptor blockers, antiretrovirals). Formal psychotherapy and cognitive behavioral therapy have been helpful for some patients.

Capsaicin (hot pepper powder) can be used as a topical desensitizing agent.

- Rinse mouth with 1 tsp of a 1:2 solution of hot pepper and water; increase strength of capsaicin as tolerated to a maximum 1:1 dilution.

ACUTE GENERAL Rx

No definitive cure exists. Attempting combinations of therapies may be appropriate. Interestingly, cognitive therapy may be synergistic with other agents.

Treatment options currently include:

- Low-dose benzodiazepines:
  1. Clonazepam 0.25 to 2 mg/day; start with 0.25 mg at bedtime and increase dose q 4 to 7 days until oral burning is relieved or side effects.
- Low-dose tricyclic antidepressants:
  1. Amitriptyline or nortriptyline 10 to 150 mg/day; start with 10 mg at bedtime and increase dose by 10 mg q 4 to 7 days.
- Low-dose gabapentin 300 to 1600 mg/day; start with 100 mg at bedtime and increase dose by 100 mg q 4 to 7 days (take in divided doses).
  1. Oral nystatin
- Capsaicin (topical oral)

COMPLEMENTARY & ALTERNATIVE MEDICINE

- Antioxidant alpha lipoic acid
- Acupuncture may be effective
- Relaxation programs and massage

REFERRAL

Consider referral to a subspecialist in this area, such as a dentist or ENT, if initial therapy fails to resolve symptoms. Surgery is not recommended.

PEARLS & CONSIDERATIONS

COMMENTS

BMS is a rare but possibly debilitating disease which can be highly frustrating to the patient and the practitioner: the patient often experiences an unremitting burning pain in the mouth without any apparent clinical signs, while the practitioner is unable to definitively diagnose symptoms, even with the use of laboratory testing or imaging. Other diseases should be ruled out.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **PATAN GULTAWATVICHAI, M.D.**

SUGGESTED READINGS

de Moraes M et al.: Randomized trials for the treatment of burning mouth syndrome: an evidence-based review of the literature, *J Oral Pathol Med* 41(4):281–287, 2012.

Gao J et al.: A case-control study on etiological factors involved in patients with burning mouth syndrome, *J Oral Pathol Med* 38(1):24–28, 2009.

Heckmann SM et al.: A double-blind study on clonazepam in patients with burning mouth syndrome, *Laryngoscope* 122(4):813–816, 2012.

Klasser GD et al.: Burning mouth syndrome: recognition, understanding, and management, *Oral Maxillofac Surg Clin North Am* 20(2):255–271, 2008.

MayoClinic.com: http://www.mayoclinic.com/health/burning-mouth-syndrome/DS00462/DSECTION=treatments-and-drugs. Accessed October 26, 2012.

Yan Z et al.: A systematic review of acupuncture or acupoint injection for management of burning mouth syndrome, *Quintessence Int* 43(8):695–701, 2012.

Zakrzewska JM et al.: Interventions for the treatment of burning mouth syndrome, *Cochrane Database Syst Rev* 1:CD002779, 2005.

BASIC INFORMATION

DEFINITION

- Cutaneous burns can be classified by type of injury (e.g., thermal vs. chemical), burn depth (e.g., 1st, 2nd, 3rd degree), extent of burn (total burn surface area [TBSA]), and burn severity (e.g., minor vs. major). Types of burn injury include thermal (flames, scalds, hot contactants), chemical, electrical, and radiation burns. This chapter will focus on thermal and electrical burns.
- Burns can affect skin and respiratory, ocular, oral, and genital mucosa.

SYNONYMS

Thermal injury
Chemical injury
Electrical injury
Radiation injury

ICD-9CM CODES
942-949 (by region, % burn)
ICD-10CM CODES
T29.0 Burns of multiple regions, unspecified degree
T30.0 Burn of unspecified body region, unspecified degree
T30.1 Burn of first degree, body region unspecified
T30.2 Burn of second degree, body region unspecified
T30.3 Burn of third degree, body region unspecified
T31.0 Burns involving less than 10% of body surface
T31.1 Burns involving 10-19% of body surface
T31.2 Burns involving 20-29% of body surface
T31.3 Burns involving 30-39% of body surface
T31.4 Burns involving 40-49% of body surface
T31.5 Burns involving 50-59% of body surface

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE (IN U.S.):

- More than 1.2 million individuals experience burns in the U.S., and burn injuries account for approximately 500,000 emergency department visits, with 9% (45,000) requiring hospitalization and 0.8% (4000) resulting in death annually.
- Of thermal injury, scald burn from liquid is most common—followed by flame, flash burn, then contact burn.

PREDOMINANT AGE & SEX:

- Children ages 2-4 years have the greatest frequency of burns (most commonly scald burns), with male adolescent and young adults ages 17 to 25 with second greatest frequency (most commonly from flammable liquids).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- It is important to note that burns occur unevenly—often with various depths (Table B1-22).
- 1st-degree (superficial) burns—penetrate epidermis only (minimal barrier loss)
  1. Very painful, intact, erythematous skin with minimal to no edema and no blistering.
- 2nd-degree (partial-thickness) burns—epidermis and part of dermis is affected.
  1. Moist, very painful skin with edema and blistering/blebs
  2. Superficial partial-thickness burns—cherry red with two-point discrimination intact, incredibly painful
  3. Deep partial-thickness burns—mottled white and cherry red; only the sensation of pressure is intact in these areas
- 3rd-degree (full-thickness) burns—entire epidermis and dermis are affected, with destruction of hair follicles and sweat glands.
  1. The skin is dry, charred, pale, painless, and leathery. Charred vessels may be visible beneath, little or no pain, and hair pulls out easily.

DIAGNOSIS

CLASSIFICATION

- Burns are classified by (1) depth of injury, (2) extent of injury, and (3) severity, according to the American Burn Association.
- Depth of injury (see Table B1-22)
  1. Indicates how the wound will heal and whether grafting will be needed
- Extent of TBSA
  1. The TBSA is best classified by using age-specific burn charts and the "rule of nines" (Fig. B1-65).
  2. For scattered burns, utilizing patient's palm including fingers to equate 1% body surface area can be helpful.
  3. TBSA indicates how aggressively the patient will need to be resuscitated.
- Severity—determined by burn depth, TBSA, age, location, type of injury, and presence/absence of coexisting conditions. Severity classification helps triage patients to outpatient, inpatient, or burn unit care (see Table B1-23).
  1. Minor burns—outpatient management.
  2. Moderate burns—admission to hospital with experience managing burns or burn center referral.
  3. Major burns—referral to burn center.

LABORATORY STUDIES (MODERATE OR MAJOR BURNS)

- CBC, electrolytes, BUN, creatinine, glucose, liver function tests, venous blood gas, blood coagulation, and type and screen in anticipation of blood transfusion
- *If smoke inhalation expected:* serial ABG carboxyhemoglobin and continuous ECG
- *If electrical burn or if concern for rhabdomyolysis:* urinalysis, urine myoglobin, and CPK levels
- *If severe lactic acidosis:* consider checking cyanide level

IMAGING STUDIES

- If smoke inhalation suspected: chest radiograph and bronchoscopy
- If high-voltage electrical burn: cardiac monitoring first 24 hours

TABLE B1-22 Categorization of Burn by Depth

Burn Type	Histologic Depth	Clinical Presentation	Treatment	Healing Time/ Prognosis
1st degree	Epidermis	Erythematous but intact skin, no blisters, pain may range in severity	Topical salves, cold compresses, NSAIDs for pain control	2-5 days with no scarring
Superficial 2nd degree (partial thickness)	Papillary dermis	Erythematous with superficial blisters, intense pain	Topical antimicrobials with gauze dressing or biosynthetic dressing (if widespread), pain control	5-21 days with no grafting
Deep 2nd degree (partial thickness)	Reticular dermis	Erythematous with superficial/deep blisters, range of pain depending on nerve involvement	Same	21-35 days with no infection; if infected, converts to full-thickness burn
3rd degree (full thickness)	Through dermis to subcutaneous tissue. Can involve fascia, muscle and bone.	White or black, possible eschar, may or may not be painful depending on nerve damage	Usually requires grafting, may require resuscitation depending on TBSA affected, pain control	Large areas require grafting, but small areas may heal from the edges after weeks

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders; and Kessides MC, Skelsey MK: Management of acute partial-thickness burns, *Cutis* 86:249-257, 2010.

Rx TREATMENT

DIFFERENTIAL DIAGNOSIS

Cultural practices leading to burnlike lesions in distinctive patterns (e.g., cupping, coining, moxibustion), cellulitis, Stevens-Johnson syndrome/toxic epidermolytic necrolysis

ACUTE GENERAL Rx

MINOR BURNS (1ST DEGREE BURNS AND 2ND/3RD DEGREE BURNS OF LIMITED TBSA):

- Outpatient management—"6 Cs"
  1. Clothing: Remove hot or burned clothing
  2. Cooling: Cool (approximately 54 °F) for 10 to 30 minutes (under faucet or compress) to reduce edema/pain by conducting heat away from skin. Not recommended with extensive burns due to theoretical risk of hypothermia and shock. No ice packs.
  3. Cleaning: Wash gently with mild alcohol-free soap, then normal saline daily. Remove all old ointment and any loose skin. Blot dry. No evidence supports vigorous cleansing with antiseptic solutions. Embedded materials should be removed by copious irrigation using a large-gauge syringe.
  4. Chemoprophylaxis: Tetanus immunization (all deep 2nd and 3rd degree burns). Routine skin cultures are NOT recommended except when wound infection suspected, and prophylactic systemic antibiotics are NOT recommended. All 2nd and 3rd degree burns are treated with topical antimicrobial agent. This may include silver sulfadiazine, bacitracin, bismuth-impregnated Vaseline gauze, or silver-impregnated synthetic dressings.
  5. Covering: All 2nd and 3rd degree burns should be covered with sterile dressing. If financial resources are limited, instead of gauze can purchase cotton gloves, T-shirts, or similar at discount stores, wash, and reuse.
  6. Comfort: Analgesics around the clock are recommended. Tylenol and NSAIDs—alone or in combination with opioids. Additional "rescue" analgesics before dressing changes and physical activity recommended.

MODERATE AND MAJOR BURNS (2ND/3RD DEGREE BURNS OF EXTENSIVE TBSA):

- Patients with moderate/major burns should be admitted to the hospital or referred to a burn center. Indications for hospitalization for burns are described in Table B1-23.
- Resuscitation (in addition to above)
  1. Assessment of ABCs: Establish airway and assess breathing (inspect for inhalation injury and intubate for suspected airway edema, often seen 12 to 24 hr later); O_2; establish circulation (place two large-bore peripheral IV lines, ECG).
  2. IV fluid resuscitation—Parkland formula (Ringer's lactate at 2 to 4 ml/kg per % TBSA per 24 hr with half the calculated fluid given in the first 8 hr is an effective modality in severe burns)
  3. Baseline neurologic and vascular assessment
  4. Foley catheter and NG tube (20% of patients develop an ileus)—urine output 30 ml/hr
  5. Optimize nutritional support: Mayes equations to calculate energy requirements after burn (Box B1-6)
- Frequent reassessment in the first 24 to 72 hours, as wound depth can change significantly
- The four phases of burn care, with physiologic changes and objectives, are described in Table EB1-24. Box B1-7 describes the modified Brooke resuscitation formula.

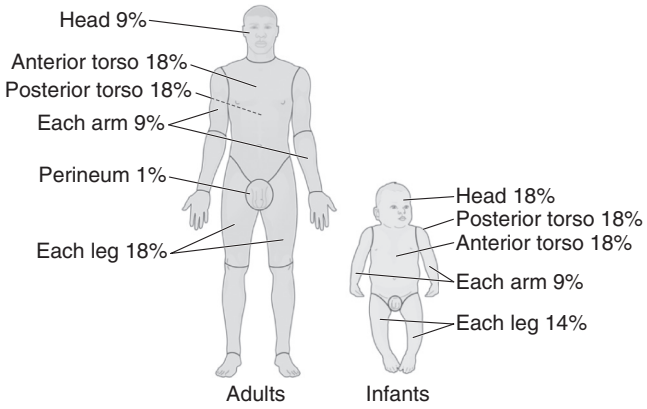


FIGURE B1-65 The "rule of nines" for estimating second-degree and third-degree burns. Because infants have significantly larger heads and smaller legs than do adults, different rules must be used in evaluating these patients. A simple, practical rule is that the palm of the patient's hand, with fingers, equals 1% of the total body area. (From Ferri F: *Practical guide to the care of the medical patient,* ed 9, St Louis, 2014, Elsevier.)

BURN WOUND CARE BY BURN DEPTH Rx

GENERAL:

- Vigilant wound care with dressings to prevent evaporation and minimize threat of wound colonization and infection of nonintact skin
- Daily activity necessary to maintain function of burned extremity, decrease pain and swelling, and promote healing
- 1st-degree burns (skin intact):
  - *Dressing:* None required (except to protect from injury); topical antibacterial agents not recommended
  - *Other:* Emollients, cool compresses (avoid ice), if pruritic, trial of antihistamines
  - *Prognosis:* Heals within 1 week without scarring. May heal with pigmentary changes (limit by sunscreen and sun avoidance of area for 1 year).

TABLE B1-23 Classification of Burns by Severity and Indications for Hospitalization or Burn Center Referral

Criteria	Minor Burn	Moderate Burn	Major Burn
Total body surface area (%)	• All 1st degree burns <10% adults <5% children or elderly • <2% for 3rd degree	• 2nd degree burns 10-20% adults 5-10% in children or elderly • 2-5% 3rd degree	• All 1st degree burns >20% adults >10% children and elderly • >5% 3rd degree
Type of burn injury		• Low-voltage burn • Suspected inhalation injury	• High-voltage burn • Chemical burn • Known
Location		Circumferential burn	• Clinically significant burn to face, eyes, ears, genitalia, over joints
Coexisting conditions		• Concomitant medical problem predisposing to infection (e.g., diabetes, sickle cell anemia)	• Significant associated injuries (e.g., fracture, other major trauma)
	Outpatient management	Inpatient management—consider referral to burn center*	Referral to burn center

*Per the American Burn Association (ABA), any partial-thickness burn >10% total body surface area or any factors listed in moderate or major burn category warrant referral to burn center. Additional factors per the ABA include burned children in a hospital without qualified personnel or equipment for the care of children and burn injury in a patient who will require special social, emotional, or rehabilitative intervention (including suspected child abuse).

Modified from Singer AJ, Dagum AB: Current management of acute cutaneous wounds, *N Engl J Med 359* (10):1037-1046, 2008; www.ameriburn.org.

BOX B1-6 Mayes Equations to Calculate Energy Requirement After a Burn

Mayes equation for a 5- to 10-year-old burn patient with injury < 50% TBSA:

$$818 + 37.4\,(\text{weight in kilograms}) + 9.3 \times \%\ \text{TBSA burn}$$

Mayes equation for a 5.5-year-old patient with a 45% TBSA scald burn weighing 20 kg:

$$818 + 37.4\,(20\ \text{kg}) + 9.3 \times 45\%\ \text{TBSA scald}$$
$$818 + 748 + 481.5 = 2047.5\ \text{calories/day}$$

From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.

BOX B1-7 Modified Brooke Resuscitation Formula

0-24 Hours
Adults and Children >10 kg
Lactated Ringer's: 2 to 4 mL/kg/% burn/24 hr (first half in first 8 hr)
Colloid: none*
Children <10 kg
Lactated Ringer's: 2 to 3 mL/kg/% burn/24 hr (first half in first 8 hr)
Lactated Ringer's with 5% dextrose: 4 mL/kg/hr
Colloid: none
24-48 Hours
All Patients
Crystalloid: to maintain urine output. If silver nitrate is used, sodium leaching will mandate continued isotonic crystalloid. If other topical is used, free water requirement is significant. Serum sodium should be monitored closely. Nutritional support should begin, ideally by the enteral route.
Colloid: (5% albumin in lactated Ringer's):
0% to 30% burn: none
30% to 50% burn: 0.3 mL/kg/% burn/24 hr
50% to 70% burn: 0.4 mL/kg/% burn/24 hr
>70% burn: 0.5 mL/kg/% burn/24 hr. *Note:* The Modified Brooke formula is a common consensus formula that is only useful in individual patients if adjusted to physiologic endpoints. Like all resuscitative formulas, it is a helpful starting point, but optimum-quality resuscitation requires the bedside presence of a physician capable of regularly evaluating resuscitation endpoints.

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

- 2nd degree (superficial partial-thickness) burns without adherent exudate or eschar:
  - *Blisters:* Sharp debridement of ruptured blisters; leave intact blisters. Quicker healing and reduced infections when intact blisters are not disturbed. Consider unroofing blisters that show no sign of resorption over several weeks or contain cloudy fluid.
  - *Dressing:* Topical antimicrobial ointment (bacitracin) or A&D ointment with nonadherent dressing twice a day. Alternate: biosynthetic dressing (alginates, hydrofibers, or foam dressings)—many with silver as antimicrobial (absorb exudates, maintain moist environment, require fewer dressing changes, which reduces pain/anxiety)
  - *Prognosis:* heal with minimal scarring in 10 to 14 days. May heal with pigmentary changes (reduced with sunscreen and sun avoidance of area × 1 year)
- 2nd degree (deep partial-thickness) burns with adherent exudates; localized 3rd degree burns; cellulitic wounds:
  - *Dressing:* silver sulfadiazine 1%: broader spectrum, better penetration of necrotic tissue than bacitracin, but inhibits epithelialization. Must stop use once exudates and eschar have separated from wound. Alternative: enzymatic debrider (e.g., Santyl or Accuzyme)—chemically debrides devitalized tissue without harming healthy tissue.
  - *Referral:* Burn specialist for consultation regarding need for excision and grafting.
  - *Prognosis:* Deep 2nd degree burns heal with significant scarring, often take 3 to 4 weeks to heal. If infected, convert to 3rd degree burns. 3rd degree burns typically require skin graft, but small areas may heal from edges after weeks.

DISPOSITION/FOLLOW-UP CARE

- Outpatient: Evaluate next day to assess level of injury, level of pain, and ability to manage dressing changes on own. If insufficient, daily evaluation until complete wound epithelialization recommended. Epithelialization = tiny islands of epithelialization throughout wound. If no epithelialization after 2 weeks, or subsequent evaluation reveals 3rd degree burn, referral to burn surgeon recommended. Box EB1-8 describes common complications in burn patients.
- Following re-epithelialization, visits every 4 to 6 weeks to monitor for hypertrophic scar formation (early referral to burn/scar specialist if occurs).
- Mortality rates higher in patients >60 yr of age, with burns >40% TBSA, or with inhalation injury. Long-term risk of developing squamous cell carcinoma of the skin within burn injury. Long-term monitoring necessary.

REFERRAL

Consultation of burn specialist or burn center referral per Table B1-23.

PEARLS & CONSIDERATIONS

COMMENTS

- In circumferential skin burns, look for compartment syndrome of limbs (e.g., tightening, progressive deterioration of peripheral motor and sensory exam findings, severe pain, and loss of arterial Doppler signals). Escharotomy may be necessary.
- If child abuse is suspected, social services at the hospital or child protective services must be contacted.
- Fig. EB1-66 describes an algorithm for the treatment of chemical burns.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Burns (Patient Information)

AUTHOR: **LISA PAPPAS-TAFFER, M.D.**

EVIDENCE

Abstract[1]

Objective:

Several formulas have been developed to guide resuscitation in severely burned patients during the initial 48 hrs after injury. These approaches require manual titration of fluid that may result in human error during this process and lead to suboptimal outcomes. The goal of this study was to analyze the efficacy of a computerized open-loop decision support system for burn resuscitation compared to historical controls.

Design:

Fluid infusion rates and urinary output from 39 severely burned patients with >20% total body surface area burns were recorded upon admission (Model group). A fluid-response model based on these data was developed and incorporated into a computerized open-loop algorithm and computer decision support system. The computer decision support system was used to resuscitate 32 subsequent patients with severe burns (computer decision support system group) and compared with the Model group.

Setting:

Burn intensive care unit of a metropolitan Level 1 Trauma center.

Patients:

Acute burn patients with >20% total body surface area requiring active fluid resuscitation during the initial 24 to 48 hours after burn.

Measurements and Main Results:

We found no significant difference between the Model and computer decision support system groups in age, total body surface area, or injury mechanism. Total crystalloid volume during the first 48 hrs post burn, total crystalloid intensive care unit volume, and initial 24-hr crystalloid intensive care unit volume were all lower in the computer decision support system group. Infused volume per kilogram body weight (mL/kg) and per percentage burn (mL/kg/total body surface area) were also lower for the computer decision support system group. The number of patients who met hourly urinary output goals was higher in the computer decision support system group.

Conclusions:

Implementation of a computer decision support system for burn resuscitation in the intensive care unit resulted in improved fluid management of severely burned patients. All measures of crystalloid fluid volume were reduced while patients were maintained within urinary output targets a higher percentage of the time. The addition of computer decision support system technology improved patient care. Ⓐ

Abstract[2]

Previous research has shown clinical effectiveness of dermal substitution; however, in burn wounds, only limited effect has been shown. A problem in burn wounds is the reduced take of the autograft, when the substitute and graft are applied in one procedure. Recently, application of topical negative pressure (TNP) was shown to improve graft take. The aim of this study was to investigate if application of a dermal substitute in combination with TNP improves scar quality after burns. In a four-armed multicenter randomized controlled trial, a split-skin graft with or without a dermal substitute and with or without TNP was compared in patients with deep dermal or full-thickness burns requiring skin transplantation. Graft take and rate of wound epithelialization were evaluated. Three and 12 months postoperatively, scar parameters were measured. The results of 86 patients showed that graft take and epithelialization did not reveal significant differences. Significantly fewer wounds in the TNP group showed postoperative contamination compared with other groups. Highest elasticity was measured in scars treated with the substitute and TNP, which was significantly better compared to scars treated with the substitute alone. Concluding, this randomized controlled trial shows the effectiveness of dermal substitution combined with TNP in burns, based on extensive wound and scar measurements. Ⓐ

Abstract[3]

Burns

Cost study of dermal substitutes and topical negative pressure in the surgical treatment of burns

Hop MJ, TOPSKIN Study Group (Maasstad Hosp, Rotterdam, The Netherlands; et al)

Burns 40:388-396, 2014

Background:

A recently performed randomised controlled trial investigated the clinical effectiveness of dermal substitutes (DS) and split skin grafts (SSG) in combination with topical negative pressure (TNP) in the surgical treatment of burn wounds. In the current study, medical and non-medical costs were investigated, to comprehensively assess the benefits of this new treatment.

Methods:

The primary outcome was mean total costs of the four treatment strategies: SSG with or without DS, and with or without TNP. Costs were studied from a societal perspective. Findings were evaluated in light of the clinical effects on scar elasticity.

Results:

Eighty-six patients were included. Twelve months postoperatively, highest elasticity was measured in scars treated with DS and TNP ($p = 0.027$). The initial cost price of treatment with DS and TNP was €2912 compared to treatment with SSG alone €1703 ($p < 0.001$). However, mean total costs per patient did not differ significantly between groups (range €29,097 to €43,774).

Discussion:

Costs of the interventional treatment contributed maximal 7% to the total costs and total costs varied widely within and between groups, but were not significantly different. Therefore, in the selection of the most optimal type of surgical intervention, cost considerations should not play an important role.

AUTHOR: **S. H. Miller, MD** Ⓐ

Evidence-Based References

Salinas J et al.: Computerized decision support system improves fluid resuscitation following severe burns: an original study, *Crit Care Med* 39:2031–2038, 2011. Ⓐ

Bloemen MCT, van der Wal MBA, Verhaegen PDHM, et al.: Clinical effectiveness of dermal substitution in burns by topical negative pressure: A multicenter randomized controlled trial, *Wound Repair Regen* 20:797–805, 2012. Ⓐ

Hop MJ, TOPSKIN Study Group: Cost study of dermal substitutes and topical negative pressure in the surgical treatment of burns, *Burns* 40:388–396, 2014. Ⓐ

SUGGESTED READINGS

Kessides MC, Skelsey MK: Management of acute partial-thickness burns, *Cutis* 86:249–257, 2010.

Latenser B: Critical care of the burn patient: the first 48 hours, *Crit Care Med* 37(10):2819–2826, 2009.

Morgan ED et al.: Ambulatory management of burns, *Am Fam Physician* 62(9):2015–2026, 2000.

Moss L: Treatment of the burn patient in primary care, *Adv Skin Wound Care* 23(11):517–524, 2010.

Orgill DP: Excision and skin grafting of thermal burns, *N Engl J Med* 360:893–901, 2009.

Singer AJ: Management of local burn wounds in the ED, *Am J Emerg Med* 25(6):666, 2007.

TABLE EB1-24 The Four Phases of Burn Care, with Physiologic Changes and Objectives

Phase and Timing	Physiologic Changes	Objectives
1: Initial evaluation and resuscitation, 0 to 72 hr	Massive capillary leak and burn shock	Accurate fluid resuscitation and thorough evaluation
2: Initial wound excision and biologic closure, days 1-7	Hyperdynamic and catabolic state with high risk of infection	Accurately identify and remove all full-thickness wounds and achieve biologic closure
3: Definitive wound closure, day 7 to week 6	Continued catabolic state and risk of nonwound septic events	Replace temporary with definitive covers and close small complex wounds
4: Rehabilitation, reconstruction, and reintegration, day 1 through discharge	Waning catabolic state and recovering strength	Initially to maintain range of motion and reduce edema; subsequently to strengthen and facilitate return to home, work, school

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

BOX EB1-8 Common Complications in Burn Patients

Cardiovascular
- Cardiovascular
- Endocarditis and suppurative thrombophlebitis are intravascular infections that typically present as fever and bacteremia without signs of local infection.
- Hypertension occurs in up to 20% of children and is best managed with β-adrenergic blockers.
- Venous thromboembolic complications are so infrequent in patients with large burns that routine prophylaxis is not routine in all programs. Iatrogenic catheter insertion complications are minimized by meticulous technique.

Pulmonary
- Carbon monoxide intoxication, best managed acutely with effective ventilation with pure oxygen, can be associated with delayed neurologic sequelae.
- Pneumonia may occur with or without antecedent inhalation injury and is treated with pulmonary toilet and antibiotics.
- Respiratory failure may occur early post injury secondary to inhalation of noxious chemicals or later in the course secondary to sepsis or pneumonia.

Neurologic
- Transient delirium occurs in up to 30% of patients and generally resolves with supportive therapy when the possibility of anoxia, metabolic disturbance, and structural lesions is eliminated by appropriate studies.
- Seizures most commonly result from hyponatremia or abrupt benzodiazepine withdrawal.
- Peripheral nerve injuries occur from direct thermal injury, compression from compartment syndrome or overlying inelastic eschar, major metabolic disturbances, or improper splinting techniques.
- Delayed peripheral nerve and spinal cord deficits develop weeks or months after high-voltage injury secondary to small vessel injury and demyelinization.

Hematologic
- Neutropenia and thrombocytopenia, as well as disseminated intravascular coagulation, are common indicators of impending sepsis and should prompt appropriate investigations.
- Global immunologic deficits associated with burn injury contribute to a high rate of infectious complications.

Renal
- Early acute renal failure follows inadequate perfusion during resuscitation or myoglobinuria.
- Late renal failure complicates sepsis and multiorgan failure or the use of nephrotoxic agents.

Adrenal
- Acute adrenal insufficiency secondary to hemorrhage into the gland presents as hypotension, fever, hyponatremia, and hyperkalemia.

Otolaryngologic
- Auricular chondritis secondary to bacterial invasion of cartilage results in rapid loss of viable tissue and is prevented by routine use of topical mafenide acetate on burned ears.
- Sinusitis and otitis media can be caused by transnasal instrumentation and are treated by relocation of tubes, antibiotics, and judicious surgical drainage.
- Complications of endotracheal intubation include nasal alar and septal necrosis, vocal cord erosions and ulcerations, tracheal stenosis, and tracheoesophageal and tracheoinnominate artery fistulas. The occurrence of such complications is minimized by compulsive attention to tube position, avoidance of oversized tubes, and attention to cuff pressures.

Gastrointestinal
- Hepatic dysfunction secondary to transient hepatic blood flow deficits and manifested as transaminase elevations is common during resuscitation from large burns and resolves with volume restitution. Late hepatic failure, beginning with elevations of cholestatic chemistries and progressing through coagulopathy and frank failure, complicates sepsis and multiorgan failure.
- Pancreatitis, beginning with amylase and lipase elevations and ileus and progressing through hemorrhagic pancreatitis, is generally coincident with splanchnic flow deficits early and sepsis-induced organ failures later in the hospital course.
- Acalculous cholecystitis can present as sepsis without localized symptoms or signs accompanied by rising cholestatic chemistries. A standard radiographic evaluation can be followed by bedside percutaneous cholecystostomy in unstable patients.
- Gastroduodenal ulceration secondary to splanchnic flow deficits that degrade mucosal defenses is extremely common and often life threatening if routine histamine-receptor blockers and antacids are not administered.
- Intestinal ischemia, which can progress to infarction, is secondary to inadequate resuscitation and splanchnic flow deficits.

Ophthalmologic
- Ectropia from progressive contraction of burned ocular adnexa results in exposure of the globe. This requires acute eyelid release. Tarsorrhaphy is rarely helpful, more often resulting in injury to the tarsal plate as contraction forces pull out tarsorrhaphy sutures.
- Corneal ulceration, which develops after initial epithelial injury or later exposure due to ectropion, can progress to full-thickness corneal destruction if secondary infection occurs. This is prevented by careful globe lubrication with topical antibiotics in the former case and acute lid release in the later.
- Symblepharon, or scarring of the lid to the denuded conjunctiva after chemical burns or corneal epithelial defects complicating toxic epidermal necrolysis, is prevented by daily examination and adhesion disruption with a fine glass rod.

Genitourinary
- Urinary tract infections are minimized by maintaining bladder catheters only when absolutely required and are treated with appropriate antibiotics. Neither catheterization nor colonic diversion is usually required for management of perineal and genital burns.
- Candida cystitis occurs in those patients treated with bladder catheters and broad-spectrum antibiotics. Catheter change and amphotericin irrigation for 5 days is generally successful. If infections are recurrent, the upper tracts should be screened ultrasonographically.

Musculoskeletal
- Burned exposed bone is generally débrided with a dental drill until viable cortical bone is reached, which is then allowed to granulate and is autografted. Patients whose overall condition and wounds are appropriate are managed with local or distant flaps.
- Fractured and burned extremities are best immobilized with external fixators while overlying burns are grafted. Burn patients with coincident fractures in unburned extremities benefit from prompt internal fixation.
- Heterotopic ossification develops weeks after injury, is seen most commonly around deeply burned major joints such as the triceps tendon, and presents as pain and decreased range of motion. Most patients respond to physical therapy, but some require excision of heterotopic bone to achieve full function.

Soft Tissue
- Hypertrophic scar formation is a major cause of long-term functional and cosmetic deformities seen in burn patients. This poorly understood process is heralded by a secondary increase in neovascularity between 9 and 13 weeks after epithelialization. Management options include grafting of deep dermal and full-thickness wounds, compression garments, judicious steroid injections, topical silicone products, and scar release and resurfacing procedures. Note: Systematic reassessment of seriously ill burn patients facilitates timely detection of complications. It is the very rare burn patient who does not experience complications during their care, particularly while in the intensive care unit. Unfortunately, many common burn complications are obscured by the fevers and hyperdynamic physiology that accompany a large burn.

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

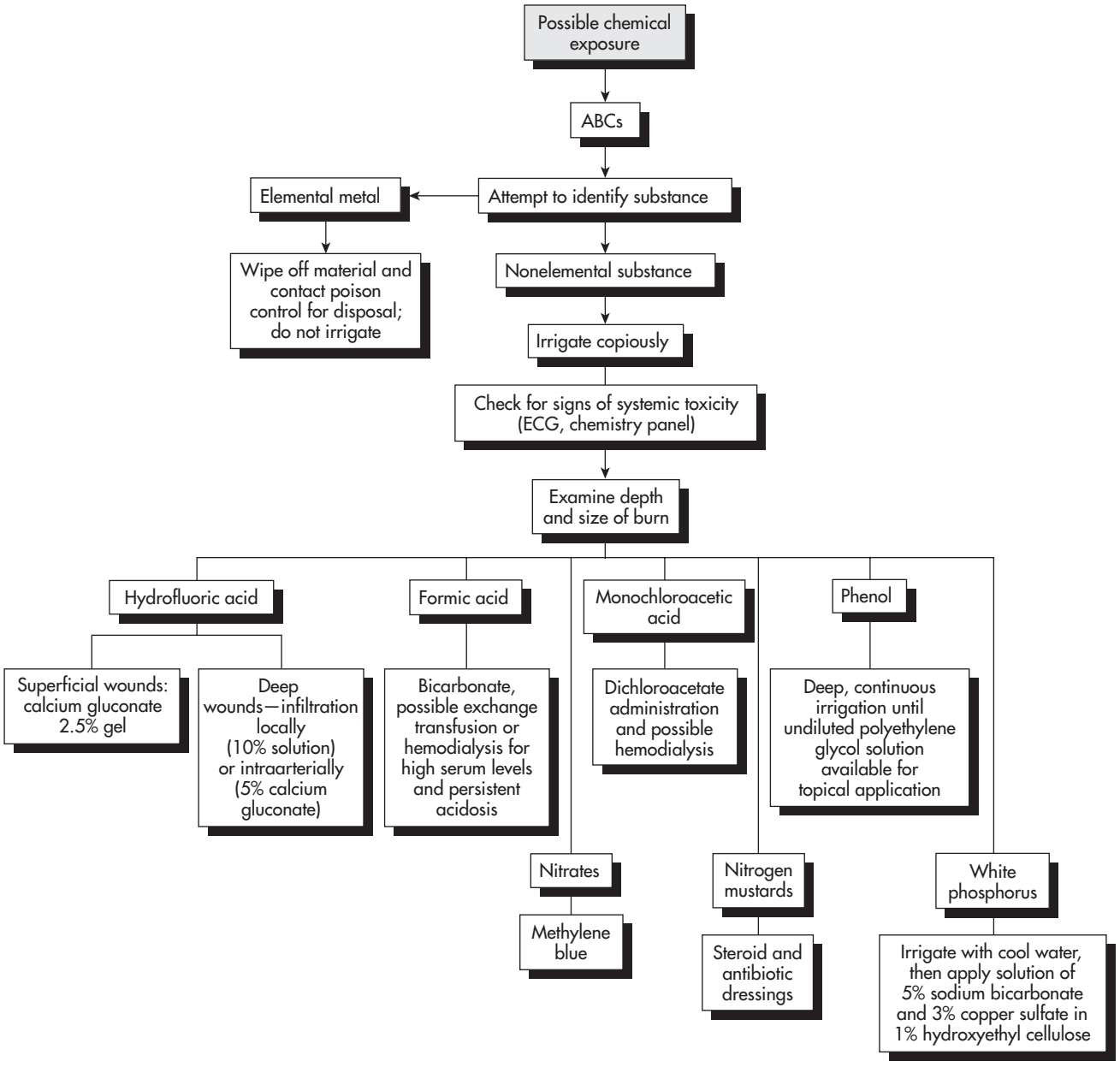


FIGURE EB1-66 Algorithm for the treatment of chemical burns. (From Adams JG et al: *Emergency medicine: clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

BASIC INFORMATION

DEFINITION

Bursitis is an inflammation of bursa, which is a thin-walled sac lined with synovial tissue. Bursae facilitate movement of tendons and muscles over bony prominences.

SYNONYMS

Student's elbow (olecranon bursitis)
Housemaid's knee (prepatellar bursitis)
Weaver's bottom (ischial gluteal bursitis)
Baker's cyst (gastrocnemius-semimembranosus bursa)

ICD-9CM CODES

726.19	Subacromial bursitis
726.33	Olecranon bursitis
726.5	Ischiogluteal bursitis (hip)
726.5	Iliopsoas bursitis (hip)
726.61	Anserine bursitis
726.5	Trochanteric bursitis
726.65	Prepatellar bursitis
727.51	Baker's cyst
726.79	Retrocalcaneal bursitis

ICD-10CM CODES

M75.80	Other shoulder lesions, unspecified shoulder
M70.20	Olecranon bursitis, unspecified elbow
M70.60	Trochanteric bursitis, unspecified hip
M70.70	Other bursitis of hip, unspecified hip
M76.899	Other specified enthesopathies of unspecified lower limb, excluding foot
M70.40	Prepatellar bursitis, unspecified knee
M71.20	Synovial cyst of popliteal space [Baker], unspecified knee
M77.50	Other enthesopathy of unspecified foot

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Local swelling, tenderness, erythema, warmth over the site of bursa
- Pain with active joint movement greater than passive range of motion or at rest
- Range of motion less painful and less restricted in septic bursitis than in septic arthritis
- Referred pain

ETIOLOGY

- Direct trauma or repetitive injury
- Infection (septic bursitis)—from hematogenous seeding or spread from contiguous infection (*Staphylococcus aureus* >80%)
- Crystal diseases (e.g., gout, pseudogout)
- Systemic inflammatory arthritis, such as rheumatoid arthritis (RA)
- Bleeding

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute monoarthritis due to septic arthritis or crystal arthritis (gout, pseudogout)
- Tendinitis, tenosynovitis
- Cellulitis

WORKUP

- Bursal fluid aspiration: send for Gram stain; culture and sensitivity; cell count; and crystal analysis

IMAGING STUDIES

- Plain radiography can rule out foreign body penetration and other bone or joint problems such as fracture (Fig. B1-67)
- MRI to define soft tissue involvement
- Musculoskeletal ultrasound for visualizing superficial and deep bursae can guide aspiration/injection

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoid direct pressure or repetitive irritation
- Joint protection (e.g., kneeling pads)
- Rest, ice, elevation for acute phase
- Physical therapy

ACUTE GENERAL Rx

- Septic:
  1. Appropriate antibiotic coverage and drainage. If MSSA, use nafcillin or oxacillin 2 g IV q4h or dicloxacillin 500 mg PO qid. If MRSA, use vancomycin 15 to 20 mg/kg IV q8-12h or linezolid 600 mg PO bid.
  2. Serial aspirations of purulent fluid or surgical drainage may be indicated.
- Nonseptic:
  1. Aspiration of bursal fluid or blood from acute trauma
  2. Nonpharmacologic therapy
  3. Traumatic bursitis may respond well to aspiration and corticosteroid injection.
  4. Crystal-related bursitis: systemic anti-inflammatories or injection of corticosteroid

CHRONIC Rx

- Aspiration of fluid, followed by compression dressing to prevent fluid reaccumulation (repeat aspiration may be required)
- Steroid injection into bursa (40 mg triamcinolone mixed with 1 to 3 ml lidocaine, depending on size of bursa)
- Oral NSAIDs, although steroid injection may be more effective in certain types of bursitis

DISPOSITION

- Nonsurgical treatment is effective in most cases. Surgical drainage may be indicated for loculated bursitis. Recurrent bursitis may require open bursectomy.

REFERRAL

Orthopedic consultation may be needed to assist in treatment of septic bursitis or for excision of chronic enlarged bursa when indicated.

PEARLS & CONSIDERATIONS

- Bursae in patients with RA are not usually the sole site of active flare. Therefore, in patients with RA, acute bursitis should be considered septic bursitis until proven otherwise.

COMMENTS

- Scapulothoracic bursitis is under-recognized and undertreated. It results from friction between superomedial angle of scapula and adjacent second and third ribs. Crepitus, snapping, and tenderness are suggestive findings; it can also cause chest wall pain.
- Do not incise and drain sterile bursae because chronic draining sinus tract may develop.
- In bursitis caused by infectious or systemic inflammatory disorders, the leukocytosis in bursal fluid may be substantially less intense than the elevations in the joint fluid.
- Investigate crystal-induced bursitis for underlying metabolic or hematologic diseases (hemochromatosis, hyperparathyroidism [calcium pyrophosphate deposition disease]), and for hyperuricemia (gout).

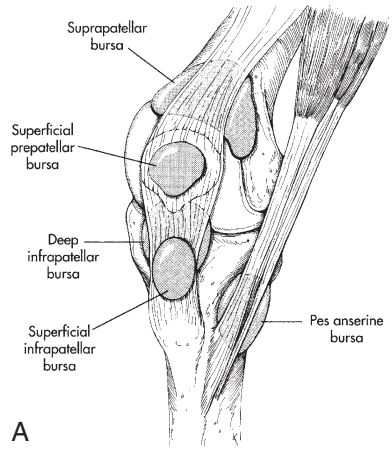
SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Bursitis (Patient Information)

AUTHOR: **CANDICE YUVIENCO, M.D.**



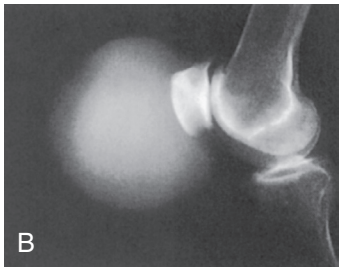


FIGURE B1-67 A, Bursae around the knee. **B,** Markedly swollen prepatellar bursa. (From Scudieri G [ed]: *Sports medicine principles of primary care,* St Louis, 1997, Mosby.)

SUGGESTED READINGS

Boneti C et al.: Scapulothoracic bursitis as a significant cause of breast and chest wall pain: Underrecognized and undertreated, *Ann Surg Oncol* 217(Suppl 3):321–324, 2010. Epub Sep 19, 2010.

Canoso JJ, Yood RA: Reaction of superficial bursae in response to specific disease stimuli, *Arthritis Rheum* 22(12):1361–1364, 1979.

Dawn B et al.: Prepatellar bursitis: a unique presentation of tophaceous gout in a normouricemic patient, *J Rheumatol* 24(5):976–978, 1997.

Del Cura JL: Ultrasound-guided therapeutic procedures in the musculoskeletal system, *Curr Probl Diagn Radiol* 37(5):203–218, 2008.

Metz JP: Helpful tips for perfoming musculoskeletal injections, *Am Fam Physician* 78:971, 2008.

Molloy ES et al.: Calcium crystal deposition diseases: Update on pathogenesis and manifestations, *Rheum Dis Clin North Am* 32:383, 2006.

Sheon R: Bursitis: an overview of clinical manifestations, diagnosis, and management, *UpToDate,* version 19.2: May 2011.

Silvan M et al.: A one-stop approach to the management of soft tissue and degenerative musculoskeletal conditions using clinic-based ultrasonography, *Musculoskeletal Care* 9(2):63–68, 2011.

BASIC INFORMATION

DEFINITION

Calcium pyrophosphate dihydrate crystal deposition disease, commonly known as pseudogout, refers to an acute synovitis caused by calcium pyrophosphate dihydrate (CPPD) crystals. CPPD deposition diseases comprise a spectrum of clinical syndromes including pseudogout, chondrocalcinosis, and pyrophosphate arthropathy. *Chondrocalcinosis* (CC) refers to the presence of calcification in cartilage by radiograph and does not confirm the diagnosis of pseudogout as it can be present in other types of crystal deposition diseases or asymptomatic. Pyrophosphate arthropathy is the term used for a chronic structural arthropathy related to CPPD deposition.

SYNONYMS

Pseudogout
CPPD crystal deposition disease
Chondrocalcinosis
Pyrophosphate arthropathy

ICD-9CM CODES
275.4 Chondrocalcinosis
ICD-10CM CODES
M11.2 Other chondrocalcinosis
M11.9 Crystal arthropathy, unspecified
M11.8 Other specified crystal arthropathies
M11.1 Familial chondrocalcinosis

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- The epidemiology of CPPD crystal deposition is described in Table C1-1.
- Most linked with advancing age (average age of 70)

GENETICS: Associated with *ANKH* (ankylosis human) gene, which functions to transport inorganic pyrophosphate (PPi) out of cells. Familial mutations can increase extracellular PPi and lead to onset of CPPD disease in third or fourth decade of life.

TABLE C1-1 Epidemiology of Calcium Pyrophosphate Dihydrate Crystal Deposition

Age association	Rises with age
Sex distribution	(F:M) 1:1
Chondrocalcinosis prevalence	8.1% (age range 63 to 93)
Pyrophosphate arthropathy prevalence	3.4% (age range 40 to 89)
Geography	Appears ubiquitous
Genetic associations	Mutations of *ANKH* gene on chromosome 5p (CCAL2) and unknown genes on chromosome 8q (CCAL1)

From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute pseudogout: monoarticular attacks most commonly involve the knee but can be polyarticular. Patients, especially the elderly, can have systemic manifestations such as fever and altered mental status. Situations that may trigger acute CPPD crystal arthritis are described in Box C1-1.
- Asymptomatic CC
- Pyrophosphate arthropathy: chronic arthritis with osteoarthritic features
- "Pseudo–polymyalgia rheumatica (pseudo-PMR)": pain and stiffness in the neck and shoulder girdle mimicking PMR
- "Pseudo–rheumatoid arthritis (pseudo-RA)": symmetric polyarthritis
- Crowned-dens syndrome caused by crystal deposition in the ligamentum flavum of the cervical spine either asymptomatic or causing acute neck pain

ETIOLOGY

- Idiopathic
- Metabolic: hyperparathyroidism, hypophosphatasia, hypomagnesemia, hemochromatosis, ochronosis, familial hypocalciuric hypercalcemia, X-linked hypophosphatemic rickets

BOX C1-1 Situations That May Trigger Acute Calcium Pyrophosphate Dihydrate Crystal Arthritis

Definite
Direct trauma to joint
Intercurrent medical illness (e.g., chest infection, myocardial infarction)
Surgery (especially parathyroidectomy)
Blood transfusion, parenteral fluid administration
Joint lavage

Possible
Institution of thyroxine replacement therapy
Intraarticular injection of hyaluronan
Bisphosphonate treatment

Note: Most cases of pseudogout develop spontaneously.
From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Gouty arthritis
- Septic arthritis
- RA
- PMR

Table C1-2 describes metabolic diseases predisposing to CPPD disposition. Section II describes the differential diagnosis of acute monoarticular and oligoarticular arthritis and crystal-induced arthritides. An algorithm for evaluation and treatment of CPPD is shown in Fig. C1-1.

LABORATORY TESTS

- Arthrocentesis with presence of weakly positive birefringent rhomboid-shaped crystals (yellow perpendicular and blue parallel to polarizer axis) (Fig. EC1-2)
- Synovial fluid should always be analyzed for cell count with differential, crystals, Gram stain, and culture because gout and septic arthritis can coexist with pseudogout.
- Evaluate for possible metabolic cause, especially in younger patients aged <55 yr or patients with florid polyarticular disease. Box C1-2 describes screening blood tests for metabolic diseases associated with CPPD crystal deposition.

IMAGING STUDIES

Plain radiographs often reveal CC located parallel to subchondral bone.

- Classic locations for CC include knee menisci (Fig. EC1-3), wrist triangular fibrocartilage, and symphysis pubis (Fig. C1-4).

TREATMENT

NONPHARMACOLOGIC THERAPY

General measures such as immobilization of inflamed joint

ACUTE GENERAL Rx

- Monoarticular pseudogout:
  - Aspiration with corticosteroid injection (often superior to systemic treatment in the elderly)

TABLE C1-2 Metabolic Diseases Predisposing to Calcium Pyrophosphate Dihydrate Deposition

	CC	Pseudogout	Chronic PA
Hemochromatosis	Yes	Yes	Yes
Hyperparathyroidism	Yes	Yes	No
Hypophosphatasia	Yes	Yes	No
Hypomagnesemia	Yes	Yes	No
Hypothyroidism	No	No	No
Gout	Possibly	Possibly	No
Acromegaly	Possibly	No	No
Ochronosis	Yes	Yes	No
Familial hypocalciuric hypercalcemia	Possibly	No	No
X-linked hypophosphatemic rickets	Possibly	Possibly	Possibly

CC, Chondrocalcinosis; *PA,* pyrophosphate arthropathy.

Calcium Pyrophosphate Dihydrate Crystal Deposition Disease PTG ALG

- Polyarticular pseudogout:
  - ○ Oral corticosteroids or NSAIDs if not contraindicated

CHRONIC GENERAL Rx

Prophylaxis: daily low-dose colchicine 0.6 mg twice daily or once daily as tolerated

- Pseudo-RA or refractory disease: hydroxychloroquine or methotrexate
- Treat underlying metabolic disease

DISPOSITION

Structural joint damage may occasionally occur, requiring arthroplasty in rare cases.

REFERRAL

Rheumatology

PEARLS & CONSIDERATIONS

COMMENTS

Acute pseudogout attacks have been reported to occur in the setting of surgical procedures, diuresis, bisphosphonate administration, and hyaluronate joint injections.

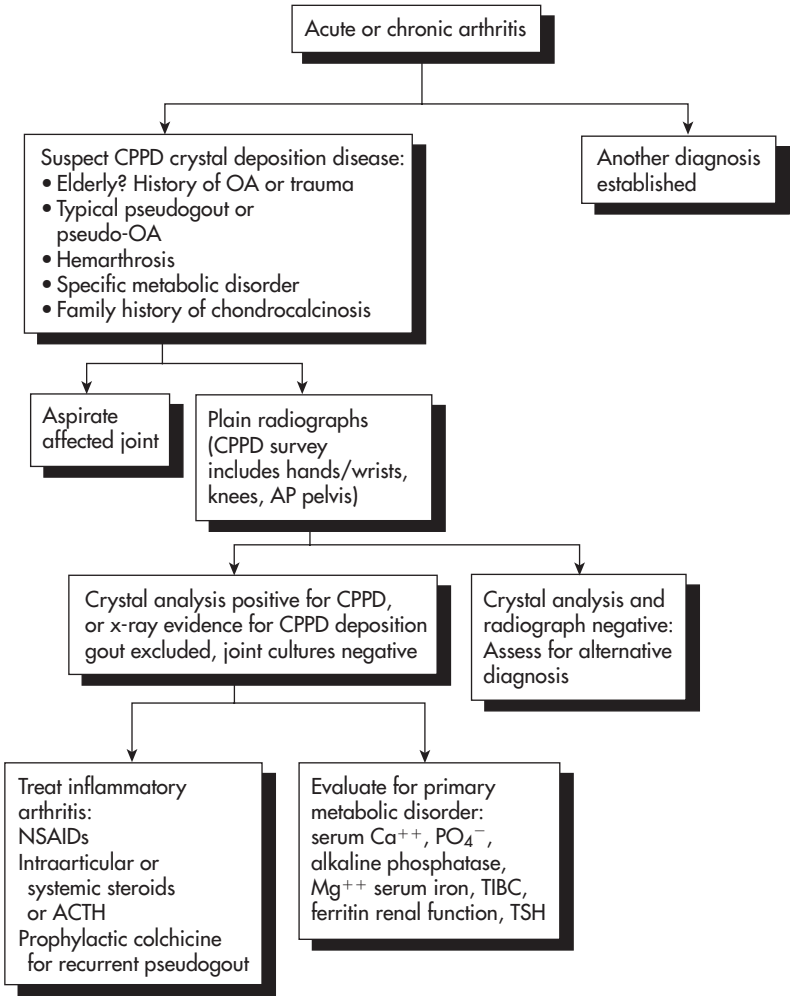


FIGURE C1-1 Algorithm for evaluation and treatment of calcium pyrophosphate dihydrate disease. *ACTH,* Adrenocorticotropic hormone; *AP,* anteroposterior; *CPPD,* calcium pyrophosphate deposition; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *OA,* osteoarthritis; *TIBC,* total iron-binding capacity; *TSH,* thyroid-stimulating hormone. (From Harris ED et al: *Kelley's textbook of rheumatology,* ed 7, Philadelphia, 2005, Saunders.)

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pseudogout (Patient Information)
Gout (Related Key Topic)

AUTHOR: **ELISABETH B. MATSON, D.O.**

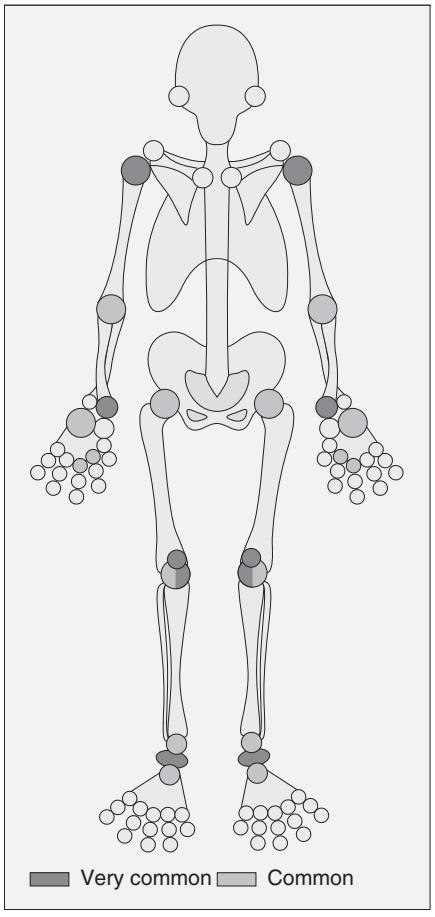


FIGURE C1-4 Chronic arthropathy. Common sites of involvement of chronic pyrophosphate. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

BOX C1-2 Screening Blood Tests for Metabolic Diseases Associated with Calcium Pyrophosphate Dihydrate Crystal Deposition

Calcium
Alkaline phosphatase
Magnesium
Ferritin
Liver function
Thyroid-stimulating hormone

From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

SUGGESTED READINGS

Andres M et al.: Methotrexate is an option for patients with refractory calcium pyrophosphate crystal arthritis, *J Clin Rheumatol* 18(5):234–236, 2012.

Announ N, Guerne PA: Treating difficult crystal pyrophosphate dihydrate deposition disease, *Curr Rheumatol Rep 10* 228, 2008.

Ea HK, Liote F: Advances in understanding calcium-containing crystal disease, *Curr Opin Rheumatol* 21(2):150, 2009.

Liote F, Ea HK: Recent developments in crystal-induced inflammation pathogenesis and management, *Curr Rheumatol Rep* 9(3):243, 2007.

Richette P et al.: *An update on the epidemiology of calcium pyrophosphate dihydrate crystal deposition disease*, 48. Oxford, 2009, Rheumatology. 711–715.

Wise CM: Crystal-associated arthritis in the elderly, *Rheum Dis Clin North Am* 33(1):33, 2007.

Young-Min S et al.: Weekly alendronate-induced acute pseudogout, *Rheumatology 44* 131, 2005.

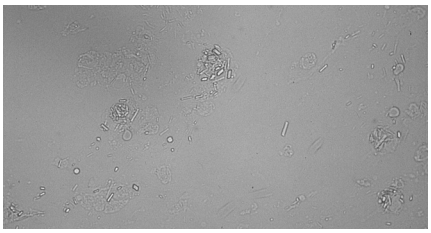


FIGURE EC1-2 Synovial fluid calcium pyrophosphate crystals. (From Hochberg M et al: *Rheumatology,* Philadelphia, 2011, Mosby.)

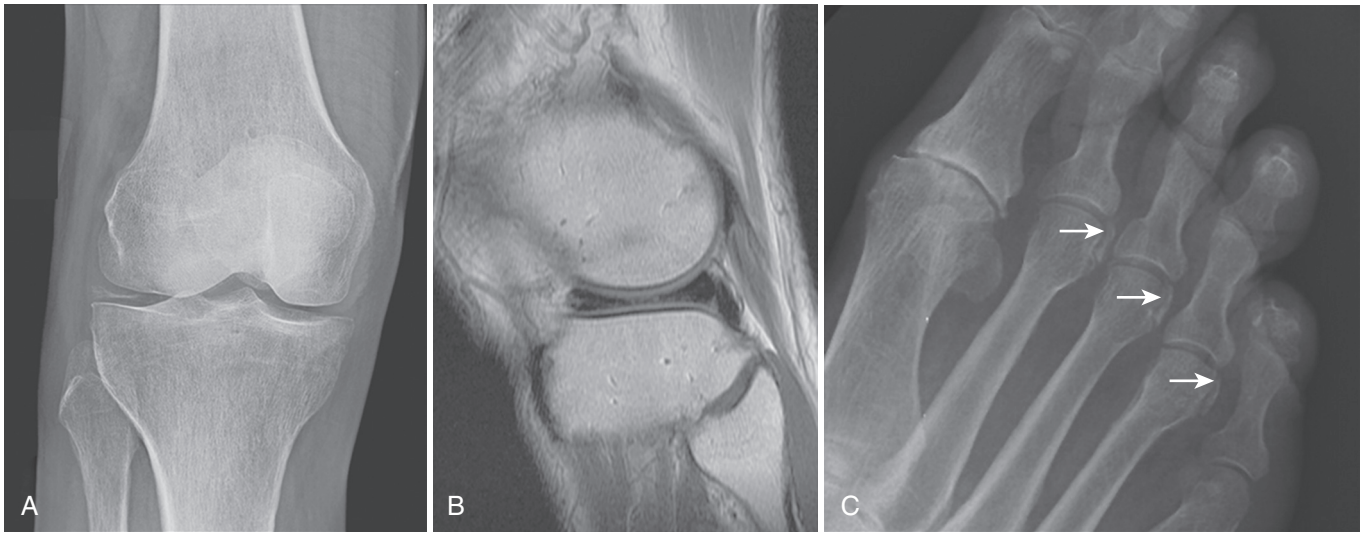


FIGURE EC1-3 Calcium pyrophosphate dihydrate crystal deposition disease (x-ray and magnetic resonance imaging [MRI]). X-ray of the knee **(A)** shows linear calcification within the lateral meniscus, whereas sagittal proton density MRI **(B)** of the same patient shows increased signal within the lateral meniscus, corresponding to chondrocalcinosis. **C,** X-ray of forefoot shows cartilaginous and capsular calcifications *(arrows)* within the second through fourth metatarsophalangeal joints. A nondisplaced fracture of the fourth metatarsal neck is noted. (From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

BASIC INFORMATION

DEFINITION

Infection caused by the species of the genus *Candida,* mainly *Candida albicans. Candida* species are ubiquitous. They are the most common fungal pathogens affecting mankind. Cutaneous candidiasis comprises superficial *Candida* infections of the skin and mucosal membranes.

Cutaneous candidiasis can be classified into two subgroups: cutaneous candidiasis syndromes and chronic mucocutaneous syndromes. Cutaneous candidiasis syndromes include:

- Generalized cutaneous candidias
- Intertrigo
- *Candida* folliculitis
- Paronychia/onychomycosis
- Perianal candidiasis
- Erosio interdigitalis blastomycetica
- Balanitis

Chronic mucocutaneous syndromes include:

- Oropharyngeal candidiasis
- Esophageal candidiasis
- Vulvovaginal candidiasis
- GI candidiasis (gastric/intestines/perianal)
- *Candida* cystitis

SYNONYMS

Yeast infection
Candidosis
Moniliasis
Oidiomycosis

ICD-9CM CODES
112 Candidiasis
ICD-10CM CODES
B37.2 Candidiasis of skin and nail
B37.8 Candidiasis, unspecified
B37.89 Other sites of candidiasis

EPIDEMIOLOGY & DEMOGRAPHICS

- *Candida* species: it is the most common fungal infection in immunocompromised people.
- Most females (75%) experience an episode of vulvovaginal candidiasis in their lifetime.

INCIDENCE: Estimated to be 50 cases per 100,000 persons

PREVALENCE: Colonizes more than 50% of U.S. population

PREDOMINANT SEX AND AGE

- Female >male
- No predominant age, but neonates and the elderly (adults >65 yr) are susceptible to *Candida* colonization and to getting mucocutaneous candidiasis.

RISK FACTORS: Risk factors that allow *Candida* infection include:

- Age >65 yr
- Females in the third trimester
- Defects in the mucocutaneous barrier (e.g., wounds, burns, ulcerations)
- Decreased/defective granulocytes/monocytes
- Diseases of white blood cells (e.g., chronic granulomatous disease)
- Complement deficiency
- Certain diseases associated with cell-mediated immunity (e.g., HIV, DM)
- Use of certain medications (e.g., broad-spectrum antibiotics, high doses of corticosteroids)
- Increased skin pH due to panty liners and occlusive attire
- **Chronic mucocutaneous candidiasis** (CMC) is characterized by susceptibility to *Candida* infection of skin, nails, and mucous membranes. Patients with recessive CMC and autoimmunity have mutations in the autoimmune regulator *AIRE.* Mutations in the CC domain of *STAT1* underlie autosomal dominant CMC and lead to defective Th1 and Th17 responses which may explain the increased susceptibility to fungal infections (van de Veerdonk et al).

Anatomical sites predisposed to *Candida* infection include:

- Axilla
- Beneath the breast, abdominal fold, intertriginous areas
- Periungual creases
- Inguinal creases
- Back and buttocks of bedridden persons

PHYSICAL FINDINGS & CLINICAL PRESENTATION

There are several clinical presentations of cutaneous candidiasis. A few are presented here.

A. Cutaneous candidiasis
1. Presents as erythematous, sometimes shiny with flakes and fluid lesions at the edge of the redness (satellite pustules). It is itchy and the skin becomes inflamed. Pustules may be present in candidiasis of the scrotal and perineal skin.

B. Gastrointestinal tract candidiasis
1. Oropharyngeal candidiasis
   - Usually seen in diabetics, after exposure to inhaled steroids or broad-spectrum antibiotics and in immunosuppressed individuals (e.g., patients with a history of HIV infection). Symptoms include:
     1. White thick patches on the oral mucosa (Fig. C1-5)
     2. Dysphagia, mouth soreness, and pain
     3. Tongue burning
   - Physical examination shows:
     1. Erythema of the buccal mucosa
     2. White patches on buccal cavity surfaces
     3. Transverse fissuring
2. Esophageal candidiasis:
   - History of oropharyngeal candidiasis
   - Symptoms include:
     1. Dysphagia
     2. Odynophagia
     3. Epigastric pain
     4. Retrosternal pain
   - Physical examination shows:
     1. Affects mainly the distal one third of the esophagus
     2. Endoscopy shows areas of the erythema and edema; scattered white patches or ulcers
3. Perianal candidiasis
   - Skin maceration
   - Itching
   - Frequently extends to the perineum

C. Paronychia/onychomycosis
- Fungal infection of the nail and surrounding tissues
- Associated with diabetes mellitus and immersion of hands or feet in water
- History: pain and redness around and beneath the nail and nail bed
- Physical exam: inflammation around the toe nail. There may also be nail thickening and discoloration (dystrophic nails). Nail loss may also occur.

D. Respiratory tract candidiasis
1. Usually seen in hospitalized patients
2. About 25% of outpatients have their respiratory tract colonized by *Candida* species
   - Genitourinary tract candidiasis
   - Vulvovaginal candidiasis
     1. It causes itching, curdy white discharge, and occasionally dysuria and dyspareunia.
     2. On examination the mucosa may be inflamed.
     3. Painful erythema or itchy penile inflammation may occur in male sexual partners of affected females.
   - *Candida* balanitis
     1. Usually acquired through sexual contact with a partner who has vulvovaginal candidiasis.
     2. Symptoms include penile pruritus and white patches on penis.
     3. Physical exam: dry, erythematous, and scaly patches on penis.

E. Others
1. Erosio interdigitalis blastomycetica: Denudating/macerating area commonly seen in third web space
2. *Candida* folliculitis: Pustulous nodules in hairy areas
3. Intertrigo: This occurs in folds of the skin and creases (Fig. C1-6). It is characterized by erosions, exudation, oozing, and maceration.

FIGURE C1-5 Oral candidiasis. (From Swartz, MH: *Textbook of physical diagnosis,* ed 7, Philadelphia, 2014, Elsevier.)

ETIOLOGY

The most common cause of cutaneous candidiasis is *Candida albicans.*

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Intertrigo

WORKUP

Mucocutaneous and cutaneous candidiasis
- Obtain scrapings from the skin, oral, and vaginal mucosa or nails.
- The presence of hyphae/pseudohyphae or budding yeast cells on wet smear, as well as confirmation by culture, is the recommended procedure to diagnose cutaneous candidiasis.
- KOH smears are helpful.

Respiratory candidiasis
- Sputum Gram stain: shows yeast cells
- Sputum cultures
- Lung biopsy: establishes the diagnosis (Fig. C1-6)

Gastrointestinal candidiasis
- Upper endoscopy with or without biopsy (Fig. C1-7)

FIGURE C1-6 Intertriginous candidosis of the neck. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

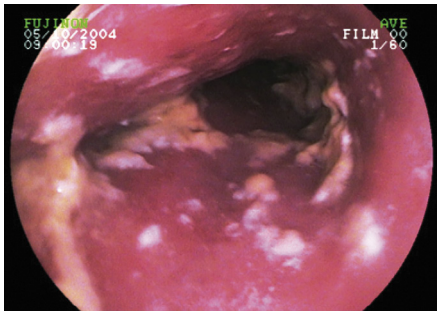


FIGURE C1-7 Endoscopic appearance of esophageal candidiasis. (Courtesy Dr. B. Rembacken, Leeds, U.K.)

Rx TREATMENT

PHARMACOLOGIC THERAPY

A. Cutaneous candidiasis
1. Decrease/prevent moisture in area
2. Apply antifungal agents (nystatin powder or cream with an azole or ciclopirox [e.g., clotrimazole, econazole, miconazole])

B. Gastrointestinal candidiasis
1. Oropharyngeal candidiasis
   - Treat with either
     1. Oral topical antifungal agent (e.g., nystatin swish and swallow) OR
     2. Systemic oral azoles (e.g., fluconazole)
2. In HIV-positive patients, use high doses of fluconazole (100-200 mg PO qd for 7-14 days), itraconazole, or posaconazole.

C. *Candida* esophagitis
- Treat with systemic fluconazole for 2 to 3 wk.
- Treat with IV fluconazole if patient is unable to take oral medication.

D. Genitourinary tract candidiasis
- Vulvovaginal candidiasis: Treatment options for acute cases include:
  1. A single dose of oral fluconazole (fluconazole 150 mg PO × 1 dose) OR
  2. Topical antifungal agent
- For chronic or recurrent cases, treat with fluconazole 150 mg qod × 3 doses and then 150 mg/wk for 6 mo.

E. Chronic mucocutaneous candidiasis
- Treatment with azoles is effective (e.g., fluconazole 100-400 mg daily).
- When patient improves, follow with maintenance treatment with same azole for life.

FOLLOW-UP CARE

Mucocutaneous candidiasis
- Patient should be instructed to call or follow up if symptoms persist, recur, or worsen.
- For recurrent infections:
  1. Check HIV antibodies.
  2. Check FBS, HbA_{1c}.
  3. Rule out hematologic malignancy or solid organ malignancy.
  4. Refer to infectious disease specialist if no etiology is found.

PREVENTION

- Maintaining dry environment (e.g., by wearing cotton underwear)
- Decreased use of antibiotic
- No douching

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Candidiasis (Patient Information)

AUTHOR: **DANIEL K. ASIEDU, M.D., Ph.D.**

SUGGESTED READINGS

Pappas PG, et al: Guidelines for treatment of candidiasis, *Clin Infect Dis* 38:161–189, 2004.

Veerdonk Van de, et al: STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis, *N Engl J Med* 365:54–61, 2011.

BASIC INFORMATION

DEFINITION

Severe and invasive diseases are caused by *Candida* infection. Invasive candidiasis embodies a variety of diseases including candidemia, disseminated candidiasis, meningitis, and endophthalmitis. Invasive candidiasis is a significant cause of morbidity and mortality for certain groups of patients.

SYNONYMS

Systemic candidiasis

ICD-9CM CODES
112.5 Disseminated candidiasis
ICD-10CM CODES
B37.89 Other sites of candidiasis
B37.1 Pulmonary candidiasis
B37.2 Candidiasis of skin and nail
B37.5 Candidal meningitis
B37.6 Candidal endocarditis
B37.7 Candidal sepsis
B37.9 Candidiasis unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Estimated to be 22 to 24 cases per 100,000 persons per year
PREVALENCE: No data available
PREDOMINANT SEX AND AGE: Equal between males and females; all ages are susceptible.
RISK FACTORS: Prolonged hospitalization and ICU stay, use of broad-spectrum antibiotics, prolonged indwelling of catheters (especially central venous catheters), acute and chronic renal failure, surgery requiring general anesthesia, cancer (e.g., solid neoplasms), transplantation (bone marrow or solid organ), recent chemotherapy/radiation therapy, use of immunosuppressive drugs, parenteral alimentation, use of internal prosthetic devices

PHYSICAL FINDINGS & CLINICAL PRESENTATION

1. History
   - Fever unresponsive to broad-spectrum antibiotics
   - History of prolonged indwelling IV catheter
   - A personal history of any of the risk factors listed earlier
2. Physical findings (general)
   - Fever
   - Hypotension
   - Generalized malaise
   - Tachycardia
   - Change in mental status
3. Specific diseases
   - Candidemia
     1. *Candida* species are isolated from at least one blood culture.
     2. Most common form of invasive candidiasis
     3. Physical exam may include fever, macronodular skin lesions, septic shock, *Candida* endophthalmitis.
   - Disseminated candidiasis
     1. Seen in patients with neutropenia
     2. Associated with multiple deep-organ infections or failure
     3. Blood culture negative
     4. Fever not responding to broad-spectrum antibiotics
     5. Physical exam: discrete erythematous or palpable rash, sepsis/septic shock
   - Endophthalmitis
     1. Iatrogenic/accidental fungal infection of the eye (exogenous) or hematogenous seeding of the eye (endogenous)
     2. Starts as choroidal lesion, progresses to vitreitis and endophthalmitis and eventually blindness
     3. Physical exam shows fever. Funduscopic examination shows large and off-white cottonball-like lesions with indistinct borders.
   - *Candida* infection of the CNS
     1. Exogenous and endogenous forms
     2. Commonly found in long-term ICU patients
     3. May present as meningitis, mycotic aneurysms, change in mental status
     4. Physical examination reveals fever, neck rigidity, confusion, and coma.
   - Candidal musculoskeletal infections
     1. Previously uncommon; now relatively common probably due to increased frequency of candidemia and disseminated candidiasis
     2. Knee and vertebral column (especially lumbosacral vertebral disks and vertebral bodies) are involved.
     3. Physical exam is usually unremarkable but may show tenderness over involved area, fever, erythema, bone deformity, weight loss, and sometimes a draining fistulous tract.
   - Candidal infections of the heart
     1. May present as infective endocarditis, myocarditis, or pericarditis.
     2. Physical examination reveals fever, hypotension, tachycardia, new or changing murmur.
   - Hepatosplenic candidiasis (chronic systemic candidiasis)
     1. Seen in patients with hematologic malignancy and neutropenia; usually develops during recovery from a neutropenic state (normally after undergoing myeloablative chemotherapy)
     2. On examination, patients have low-grade fever, right upper quadrant pain, palpable/tender liver, splenomegaly, and rarely jaundice.
   - *Candida* peritonitis
     1. Associated with GI surgery, peritoneal dialysis
     2. Clinical manifestations include fever, chills, abdominal pain; nausea, vomiting, constipation.
     3. Physical examination reveals abdominal distention, abdominal pain, absent bowel sounds.
   - Other forms of invasive candidiasis
     1. *Candida* splenic abscess
     2. *Candida* cholecystitis
     3. Renal candidiasis

ETIOLOGY

- Several species of *Candida* exist in nature
- Medically significant include:
  1. *C. albicans:* together with *C. glabrata,* they account for 70% to 80% of *Candida* in invasive candidiasis.
  2. *C. glabrata:* together with *C. albicans,* they account for 70% to 80% of *Candida* in invasive candidiasis.
  3. *C. parapsilosis:* associated with indwelling vascular catheters and prosthetic devices
  4. *C. tropicalis:* especially in leukemic patients
  5. *C. krusei:* resistant to fluconazole and ketoconazole

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Sepsis (bacterial)
- Septic shock
- Cryptococcosis
- Aspergillosis

WORKUP

LABORATORY TESTS

- Laboratory studies are nonspecific.
- High index of suspicion is needed.
- Candidemia/disseminated candidiasis: Candidemia represents the tip of the iceberg (Fig. C1-8) with respect to the more invasive forms of candidiasis. Central lines often contribute to the propagation of candidemia. From the blood, infection can spread to almost any organ.
  1. Blood cultures are the mainstay of diagnosis. They are helpful but have low positive yield.
  2. Diagnosis can also be made from normally sterile sites.
  3. Serum (1,3) beta-D-glucan detection assay: high specificity and high positive predictive value but it is relatively difficult to perform.
- Hepatosplenic candidiasis (focal)
  1. Elevated serum alkaline phosphatase

IMAGING STUDIES

- Imaging studies are generally not required or useful.
- Ultrasound is useful for diagnosing hepatosplenic abscess. "Bull's eye or target lesions" are observed in the liver and spleen.
- CT scanning may be used to diagnose hepatosplenic candidiasis, as well as intraabdominal/renal abscesses.
- ECHO is useful to rule in or rule out *Candida* endocarditis.

TREATMENT

- To successfully treat invasive *Candida* infection, it is important to start antifungal medication as early as possible. A small delay (approximately 12-24 hr) in starting treatment

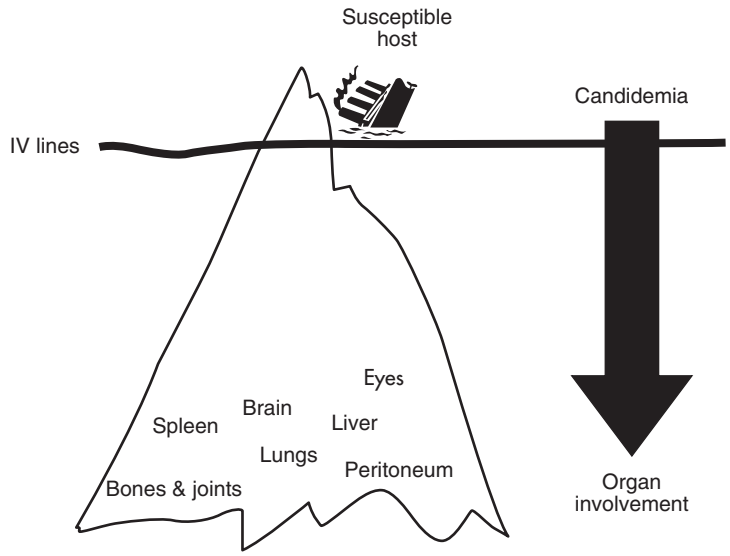


FIGURE C1-8 Spectrum of disease of invasive candidiasis. Candidemia represents the tip of the iceberg with respect to the more invasive forms of candidiasis. Central lines often contribute to the propagation of candidemia. From the blood, infection can spread to almost any organ. (From Ostrosky-Zeichner L et al: Deeply invasive candidiasis, *Infect Dis Clin North Am* 16:821-835, 2002.)

may result in a significantly excessive mortality rate.
  - ○ Do not dismiss Candida spp as a contaminant when it is isolated in blood cultures or other sterile sites.
  - ○ Before treatment, also consider removal of an intravenous catheter.
- Antifungals available include:
  1. Azoles (e.g., fluconazole, posaconazole, itraconazole, voriconazole). They inhibit the synthesis of ergosterol, a fungal cell component.
  2. Echinocandins (e.g., caspofungin, micafungin, anidulafungin). These are glucan synthesis inhibitors. Glucan is an important component of fungal cell walls.
  3. Polyenes (e.g., amphotericin B, lipid formulation of amphotericin, nystatin). Broad spectrum. Their mechanism of action is to increase cytoplasmic permeability.
  4. Antimetabolites (e.g., flucytosine). Flucytosine is deaminated to 5-fluorouracil in fungal cell. 5-Fluorouracil inhibits RNA and protein synthesis.

TREATMENT PLANS

CANDIDEMIA

- Treatment depends on whether the patient is neutropenic or not.
  1. Nonneutropenic adult patients: drug of choice is fluconazole; 800 mg as loading dose then 400 mg/day for at least 2 wk after clinical improvement or negative blood culture. Amphotericin B is equally efficacious.
  2. Neutropenic adult patients: an echinocandin is the drug of choice (e.g., caspofungin 70 mg IV loading dose then 50 mg/day IV or micafungin 100 mg/day IV or anidulafungin 200 mg IV loading dose then 100 mg IV all for at least 2 wk after clear blood culture and after clinical improvement.

DISSEMINATED CANDIDIASIS: Fluconazole is the drug of choice.

DISSEMINATED CANDIDIASIS WITH END-ORGAN INFECTION

- Treatment is the same as for candidemia of nonneutropenic patients. In most cases, therapy is prolonged for at least 4 to 6 wk.
- The echinocandins are the first-line therapy.

OSTEOMYELITIS OR SEPTIC ARTHRITIS

- Fluconazole 400 mg IV or PO *or*
- Lipid-based amphotericin B 3-5 mg/kg qd

ENDOCARDITIS

- Caspofungin 50-150 mg/day or
- Micafungin 100-150 mg/day or
- Anidulafungin 100-200 mg/day

MYOCARDITIS

- Lipid-based amphotericin B 3-5 mg/kg daily

or

- Fluconazole 400-800 mg daily IV or PO

ESOPHAGITIS:

- Fluconazole 200-400 mg/day or
- Caspofungin 50 mg IV daily

PERICARDITIS:

- Lipid-based amphotericin B 3-5 mg/kg daily

or

- Fluconazole 400-800 mg PO qd IV or PO

SURGICAL CARE: Include:

- Drainage
- Removal of any foreign bodies
- Surgical debridement
- Organ-specific care (e.g., valve replacement for endocarditis, splenectomy for splenic abscess, or vitrectomy for fungal endophthalmitis)

DISPOSITION

- Several factors affect prognosis: infection site, degree of immune suppression, and how quickly diagnosis and therapy is initiated
- Overall mortality rate: 30% to 40%

REFERRAL

- Always involve an infectious disease specialist.
- Referral to specialist will depend on the organ involved. For example:
  1. Endocarditis will require a cardiothoracic surgeon.
  2. Endophthalmitis will require an ophthalmologist.

FOLLOW-UP CARE

- Prolonged periods, mainly in the hospital, of antifungal treatment may be necessary.
- Closely monitor patients on amphotericin B because of the high incidence of side effects. Check basic metabolic panel, magnesium, and CBC at least twice a week.

PEARLS & CONSIDERATIONS

PREVENTION

Basic preventive measures are similar to those used for nosocomial infections. This includes:

- Maximizing hand hygiene recommendations:
  1. Hand washing
  2. Using alcohol/chlorhexidine solution
- Adhering strictly to recommendations for placement and care of central lines and catheters.
- Judicious use of antimicrobials

PROPHYLAXIS

Antifungal prophylaxis recommended for:
Solid organ transplant recipients
Stem cell transplant recipients

PATIENT/FAMILY EDUCATION

- Inform them about the risk factors for invasive candidiasis.
- Inform them of the seriousness of the disease and the associated high morbidity/mortality rates, thus requiring aggressive treatment.
- Side effects and toxicities associated with treatment

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Candidiasis (Patient Information)
Candidiasis, Cutaneous (Related Key Topic)

AUTHOR: **DANIEL K. ASIEDU, M.D., PH.D.**

EVIDENCE

Abstract[1]

Objectives:

To provide a global, up-to-date picture of the prevalence, treatment, and outcomes of *Candida* bloodstream infections in intensive care unit (ICU) patients and compare *Candida* with bacterial bloodstream infection.

Design:

A retrospective analysis of the Extended Prevalence of Infection in the ICU Study (EPIC II). Demographic, physiologic, infection-related, and therapeutic data were collected. Patients were grouped as having *Candida,* gram-positive, gram-negative, and combined *Candida*/bacterial bloodstream infection. Outcome data were assessed at ICU and hospital discharge.

Setting:

EPIC II included 1265 ICUs in 76 countries.

Patients:

Patients in participating ICUs on study day

Interventions:

None

Measurement and Main Results:

Of the 14,414 patients in EPIC II, 99 patients had *Candida* bloodstream infections for a prevalence of 6.9 per 1000 patients. Sixty-one patients had candidemia alone and 38 patients had combined bloodstream infections. *Candida albicans* (n = 70) was the predominant species. Primary therapy included monotherapy with fluconazole (n = 39), caspofungin (n = 16), and a polyene-based product (n = 12). Combination therapy was infrequently used (n = 10). Compared with patients with gram-positive (n = 420) and gram-negative (n = 264) bloodstream infections, patients with candidemia were more likely to have solid tumors ($p < .05$) and appeared to have been in an ICU longer (14 days [range, 5-25 days], 8 days [range, 3-20 days], and 10 days [range, 2-23 days], respectively), but this difference was not statistically significant. Severity of illness and organ dysfunction scores were similar among groups. Patients with *Candida* bloodstream infections, compared with patients with gram-positive and gram-negative bloodstream infections, had the greatest crude ICU mortality rates (42.6%, 25.3%, and 29.1%, respectively) and longer ICU lengths of stay (median [interquartile range] 33 days [18-44], 20 days [9-43], and 21 days [8-46], respectively); however, these differences were not statistically significant.

Conclusion:

Candidemia remains a significant problem in ICU patients. In the EPIC II population, *C. albicans* was the most common organism and fluconazole remained the predominant antifungal agent used. *Candida* bloodstream infections are associated with high ICU and hospital mortality rates and resource use. Ⓐ

Evidence-Based Reference

Kett DH et al.: Extended Prevalence of Infection in the ICU Study (EPIC II) Group of Investigators. *Candida* bloodstream infections in intensive care units: analysis of the extended prevalence of infection in intensive care unit study, *Crit Care Med* 39:665–670, 2011. Ⓐ

SUGGESTED READINGS

Pappas PG: Invasive candidiasis, *Infect Dis Clin North Am* 20:485, 2006.

Pappas PG et al.: Guidelines for treatment of candidiasis, *Clin Infect Dis* 38:161–189, 2004.

BASIC INFORMATION

DEFINITION

Carbon monoxide (CO) is a colorless, odorless, tasteless, nonirritating gas. When inhaled it produces toxicity by causing cellular hypoxia and damage.

ICD-9CM CODES
986 Carbon monoxide poisoning
ICD-10CM CODES
T68 Toxic effect of carbon monoxide
T58.01 Toxic effect of carbon monoxide from motor vehicle exhaust, accidental (unintentional), initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

- A leading cause of accidental and intentional poisoning in the U.S.
- CO poisoning is seen more frequently during the fall and winter months in cold climates. Frequently seen after storm-related power outages, mostly due to the use of portable gasoline-powered electrical generators.
- In adults, 20% of CO poisonings occur in occupational settings.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Depends on the severity and duration of exposure. The brain and heart are most sensitive to CO poisoning.
- Presentation is often nonspecific and may be mistaken for a flulike illness.
- Severity of poisoning does not correlate with carboxyhemoglobin (COHb) levels.
- Mild to moderate poisoning may present with headache, malaise, dizziness, nausea, dyspnea, difficulty concentrating, confusion, and blurred vision. Patients may have tachypnea and tachycardia.
- Severe poisoning may present with hypotension, arrhythmias, myocardial ischemia, pulmonary edema, lethargy, ataxia, loss of consciousness, seizure, coma, or rarely, cherry-red skin.
- Delayed neurologic sequelae may develop days to weeks after apparent recovery from acute poisoning. Patients may present with neurologic or psychiatric symptoms (cognitive deficits, memory loss, personality changes, movement disorders, Parkinson's, psychosis, neurologic deficits).

ETIOLOGY

- CO results from the incomplete combustion of carbon-containing compounds. CO poisoning occurs from inhaling smoke from fires, motor vehicle exhaust, or the burning of fuel (oil, wood, coal, gasoline, natural gas) in poorly functioning or improperly ventilated devices (heating systems, stoves/grills, portable generators, etc.). Methylene chloride (paint stripper) fumes are converted to CO by the liver.
- CO toxicity results from tissue hypoxia and direct CO-mediated damage at the cellular level. This may explain why COHb levels alone are not predictive of clinical toxicity. The mechanisms of CO toxicity are not completely understood.
- CO impairs oxygen delivery. CO reversibly binds hemoglobin with an affinity 250 times greater than oxygen, displacing oxygen from hemoglobin and decreasing the oxygen-carrying capacity of blood. By binding to hemoglobin, CO changes the structure of the hemoglobin molecule and decreases oxygen release to tissue.
- CO also interferes with peripheral oxygen utilization. It binds to other heme-containing proteins including cytochromes and myoglobin. Cellular respiration is depressed by inhibition of the mitochondrial cytochrome oxidase system. By binding to myoglobin, CO decreases its ability to use and store oxygen.
- Neurologic toxicity is not explained by hypoxia alone and is related to the complex intracellular actions of CO. CO precipitates an inflammatory cascade that results in oxidative damage and brain lipid peroxidation.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Viral syndromes
- Cyanide, hydrogen sulfide
- Methemoglobinemia
- Amphetamines and derivatives
- Cocaine, phencyclidine (PCP)
- Cyclic antidepressants
- Phenothiazines
- Theophylline

WORKUP

History (duration and source of CO exposure, loss of consciousness), physical examination (detailed neurologic examination), laboratory and imaging tests

LABORATORY TESTS

- COHb level (measured by CO-oximetry on arterial blood; venous blood may be used to screen large populations exposed to CO or monitor change in COHb with treatment). COHb level >3% in nonsmokers confirms exposure. Heavy smokers may have baseline levels of up to 10%. Levels may be low if the patient has already received supplemental oxygen or if delay occurs between exposure and testing.
- Direct measurement of arterial carboxyhemoglobin (by CO-oximetry): Pulse oximetry and arterial blood gas (ABG) may be falsely normal because neither measures oxygen saturation of hemoglobin directly. Pulse oximetry is inaccurate because of the similar absorption characteristics of oxyhemoglobin and COHb. An ABG is inaccurate because it measures oxygen dissolved in plasma (which is not affected by CO) and then calculates oxygen saturation of hemoglobin.
- Electrolytes, glucose, BUN, creatinine, cardiac biomarkers, ABG (lactic acidosis and rhabdomyolysis may develop), CBC (polycythemia from hypoxia in chronic CO poisoning).
- ECG (ischemia, arrhythmia).
- Pregnancy test (fetus at high risk).
- Consider toxicology screen.

IMAGING STUDIES

- Chest x-ray (noncardiogenic edema)
- Brain CT, MRI if neurologic abnormalities are present

TREATMENT

ACUTE GENERAL Rx

- Remove from site of CO exposure.
- Ensure adequate airway.
- Continuous ECG monitor.
- Fetal monitoring if pregnant.
- 100% oxygen by nonrebreather mask or endotracheal tube (decreases half-life of COHb from 4 to 6 hr to 60 to 90 min) until COHb level is <10% and patient is asymptomatic. Table C1-3 describes the half-life of COHb.
- Hyperbaric oxygen (2.5 to 3 atm).
  1. Questionable beneficial effect over normobaric oxygen. Disparate findings in various studies: some suggest hyperbaric oxygen treatment reduces the incidence of neurologic sequelae, and others have found it worsens neurologic outcomes compared to normobaric oxygen treatment.
  2. Decreases half-life of COHb to 20 to 30 min; increases amount of oxygen dissolved in plasma. It also reduces CO binding to other heme-containing proteins.
  3. Consider for:
     1. Severe intoxication (COHb >25%, history of loss of consciousness, neurologic symptoms or signs, cardiovascular compromise, severe metabolic acidosis)
     2. Pregnant women with COHb >20% or signs of fetal distress. CO elimination is slower in fetus than mother, fetal Hgb has greater affinity for CO than adult Hgb
  4. Should be instituted quickly if deemed necessary
- Consider concomitant poisoning with other toxic/irritant gases that may be present in smoke (e.g., cyanide) or thermal injury to airway. Toxic effects of CO and cyanide are synergistic.

TABLE C1-3 Half-Life of COHb

Oxygen Concentration	Half-Life
21% (room air)	4-5 hr
100% (mask or endotracheal)	60-90 min
100% (hyperbaric molecular oxygen)	20-30 min

From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.

- Identify source of exposure and determine if poisoning was accidental. Fig C1-9 illustrates a suggested management algorithm for carbon monoxide poisoning.

DISPOSITION

- Patients with mild accidental poisoning can be treated in an ambulatory setting. Those with moderate/severe poisoning or coexisting illness require hospitalization.
- Survivors of severe poisoning are at 14% to 40% risk for neurologic sequelae.
  1. Deficits are usually apparent within 3 wk of poisoning but may present months later.
  2. Risk of developing sequelae is greater if patient lost consciousness during acute poisoning and with older age.
  3. Brain MRI and functional CT may reveal changes; damage is seen most often in the globus pallidus and deep white matter.
  4. Recovery may occur over months to years.
- CO-mediated cardiac damage is associated with increased long-term mortality.
- High risk of fetal demise

REFERRAL

- American Association of Poison Control Centers: 1-800-222-1222
- Hyperbaric unit; accredited facilities are listed on the Undersea & Hyperbaric Medical Society website (www.uhms.org)
- Psychiatric evaluation if intentional poisoning

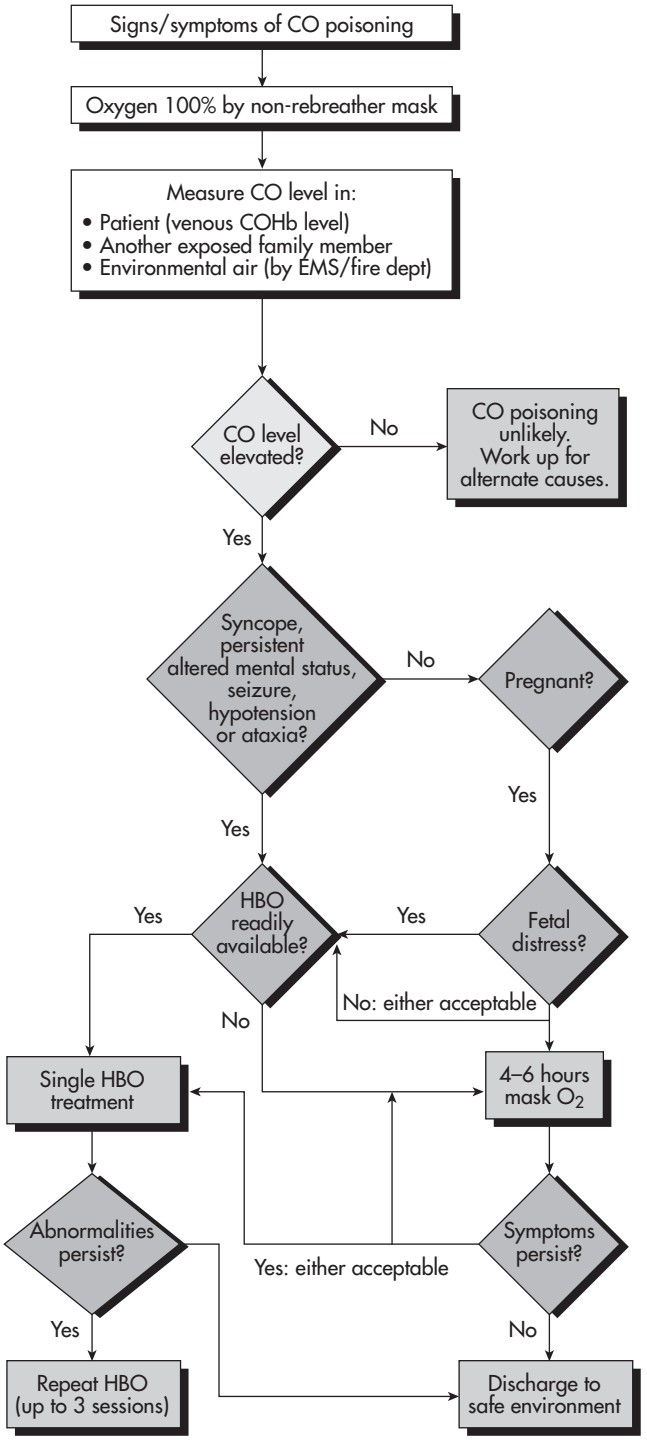


FIGURE C1-9 Suggested management algorithm for carbon monoxide poisoning. (From Lavonas EJ: Carbon monoxide poisoning. In Shannon M.W., Borron S.W., Burns M. (eds): *Haddad and Winchester's clinical management of poisoning and drug overdose,* Philadelphia, 2007, Elsevier.)

PEARLS & CONSIDERATIONS

- Severity of poisoning and prognosis do not correlate with COHb levels.
- Neuropsychometric testing is an objective measure of cognitive function but is not universally used.
- Imaging techniques and biomarkers to allow for early prediction of CNS damage are being studied but are not ready for application.
- Pulse oximeter measurement of CO saturation has limited clinical use.
- Treatment with hydroxocobalamin (for cyanide toxicity) may make subsequent COHb testing unreliable.
- Contact local Fire Department to assess environment and identify source of CO.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Carbon Monoxide Poisoning (Patient Information)

AUTHOR: **SUDEEP KAUR AULAKH, M.D.**

EVIDENCE

Abstract[1]

Rationale:

Clinical reports describe life-threatening cardiac arrhythmias after environmental exposure to carbon monoxide (CO) or accidental CO poisoning. Numerous case studies describe disruption of repolarization and prolongation of the QT interval, yet the mechanisms underlying CO-induced arrhythmias are unknown.

Objectives:

To understand the cellular basis of CO-induced arrhythmias and to identify an effective therapeutic approach.

Methods:

Patch-clamp electrophysiology and confocal Ca_2+ and nitric oxide (NO) imaging in isolated ventricular myocytes was performed together with protein S-nitrosylation to investigate the effects of CO at the cellular and molecular levels, whereas telemetry was used to investigate effects of CO on electrocardiogram recordings in vivo.

Measurements and Main Results:

CO increased the sustained (late) component of the inward Na+ current, resulting in prolongation of the action potential and the associated intracellular Ca_2+ transient. In more than 50% of myocytes these changes progressed to early after-depolarization–like arrhythmias. CO elevated NO levels in myocytes and caused S-nitrosylation of the Na+ channel, Nav1.5. All proarrhythmic effects of CO were abolished by the NO synthase inhibitor L-NAME, and reversed by ranolazine, an inhibitor of the late Na+ current. Ranolazine also corrected QT variability and arrhythmias induced by CO in vivo, as monitored by telemetry.

Conclusions:

Our data indicate that the proarrhythmic effects of CO arise from activation of NO synthase, leading to NO-mediated nitrosylation of NaV1.5 and to induction of the late Na+ current. We also show that the antianginal drug ranolazine can abolish CO-induced early afterdepolarizations, highlighting a novel approach to the treatment of CO-induced arrhythmias.

This is very interesting research on arrhythmogenic effects of carbon monoxide (CO). From a clinical perspective, I can't recall the last time I had a serious arrhythmia to deal with in a CO case. However, one of the essential theories of CO poisoning is that cardiac depression leads to syncope and begins a cascade of injurious central nervous system events. I wonder if this mechanism contributes to that as well. Still, it is very helpful to understand the arrhythmia mechanism and to have a readily available drug identified that will treat it. Ⓐ

Evidence-Based Reference

Dallas ML et al.: Carbon monoxide induces cardiac arrhythmia via induction of the late Na+ current, *Am J Respir Crit Care Med* 186:648–656, 2012. Ⓐ

SUGGESTED READINGS

Annane D et al.: Hyperbaric oxygen therapy for acute domestic carbon monoxide poisoning: two randomized controlled trials, *Intensive Care Med* 37:486, 2011.

Beppu T et al.: 1H-magnetic resonance spectroscopy indicates damage to cerebral white matter in the subacute phase after CO poisoning, *J Neurol Neurosurg Psychiatry* 82:869, 2011.

Buckley NA et al.: Hyperbaric oxygen for carbon monoxide poisoning, *Cochrane Database Syst Rev* 4:CD002041, 2011.

Domachevsky L et al.: Hyperbaric oxygen in the treatment of carbon monoxide poisoning, *Clin Toxicol* 43:181–188, 2005.

Graber J et al.: Results from a state-based surveillance system for carbon monoxide poisoning, *Public Health Reports* 122(2):145, 2007.

Hampson N: Storm-related carbon monoxide poisoning: lessons learned from recent epidemics, *Undersea Hyperb Med* 33(4):257, 2006.

Henry CR et al.: Myocardial injury and long-term mortality following moderate to severe carbon monoxide poisoning, *JAMA* 295(4):398, 2006.

Kao LW, Nanagas KA: Toxicity associated with carbon monoxide, *Clin Lab Med* 26:99–125, 2006.

Livshits Z et al.: Falsely low carboxyhemoglobin level after hydroxocobalamin therapy, *N Engl J Med* 367:1270–1271, 2012.

Toshimitsu I et al.: Elevated S100B level in cerebrospinal fluid could predict poor outcome of carbon monoxide poisoning, *Am J Emerg Med* 30:222, 2012.

Weaver LK: Carbon monoxide poisoning, *N Engl J Med* 360:1217–1225, 2009.

Weaver LK et al.: False positive rate of carbon monoxide saturation by pulse oximetry of emergency department patients, *Respir Care* 58:232–240, 2013.

Weaver LK et al.: Hyperbaric oxygen for acute carbon monoxide poisoning, *N Engl J Med* 347:1057–1067, 2002.

BASIC INFORMATION

DEFINITION

Carcinoid syndrome is a symptom complex characterized by paroxysmal vasomotor disturbances, diarrhea, and bronchospasm. It is caused by the action of amines and peptides (serotonin, bradykinin, histamine) produced by tumors arising from neuroendocrine cells.

SYNONYMS

Flush syndrome
Argentaffinoma syndrome

ICD-9CM CODES
259.2 Carcinoid syndrome
ICD-10CM CODES
E34.0 Carcinoid syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- Carcinoid tumors are found incidentally in 0.5% to 0.75% of autopsies.
- Carcinoid tumors are principally found in the following organs: appendix (40%); small bowel (20%; 15% in the ileum); rectum (15%); bronchi (12%); esophagus, stomach, and colon (10%); and ovary, biliary tract, and pancreas (3%).
- The incidence of carcinoids is 2.47 to 4.48/100,000, depending on race and sex, and is highest in black men. The overall incidence has increased over the last 30 years due in part to improved diagnostic modalities.
- Carcinoid tumors can be classified using the WHO classification as follows:
  1. WHO I: Well-differentiated, <2 cm diameter, low proliferation index (<2%), confined to mucosa and submucosa
  2. WHO II: Differentiated, >2 cm diameter, invasive growth, high proliferation index (2% to 15%)
  3. WHO III: Poorly differentiated carcinomas with metastases and proliferation index >15%

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Cutaneous flushing (75% to 90%)
  1. The patient usually has red-purple flushes starting in the face, then spreading to the neck and upper trunk (Fig. EC1-10).
  2. The flushing episodes last from a few minutes to hours (longer-lasting flushes may be associated with bronchial carcinoids).
  3. Flushing may be triggered by emotion, alcohol, or foods or may occur spontaneously.
  4. Dizziness, tachycardia, and hypotension may be associated with the cutaneous flushing.
- Diarrhea (>70%): often associated with abdominal bloating and audible peristaltic rushes
- Intermittent bronchospasm (25%): characterized by severe dyspnea and wheezing
- Facial telangiectasia
- Tricuspid insufficiency, pulmonic stenosis from carcinoid heart lesions

ETIOLOGY

- Carcinoid syndrome is caused by neoplasms originating from neuroendocrine cells.
- Carcinoid tumors do not usually produce the syndrome unless liver metastases are present or the primary tumor does not involve the gastrointestinal tract.

DIAGNOSIS (Fig. C1-11)

DIFFERENTIAL DIAGNOSIS

- Flushing: Carcinoid syndrome must be distinguished from idiopathic flushing (IF); patients with IF more often are female, are younger, and have a longer duration of symptoms; palpitations, syncope, and hypotension occur primarily in patients with IF. Additional causes of flushing that need to be ruled out are menopause, medications (niacin, nitrates), alcohol, renal cell carcinoma, medullary cancer of thyroid, VIPoma, mastocytosis, and chronic use of food additives (nitrites, sulfites)
- Diarrhea: IBD, IBS, laxative abuse, infectious colitis
- Bronchospasm: asthma, foreign body, GERD, lung neoplasm

LABORATORY TESTS

- The biochemical marker for carcinoid syndrome is increased 24-hr urinary 5-hydroxyindoleacetic acid, a metabolite of serotonin (5-hydroxytryptamine).
- False elevations can be seen with ingestion of certain foods (bananas, pineapples, eggplant, avocados, walnuts) and certain medications (acetaminophen, caffeine, guaifenesin, reserpine); therefore patients should be on a restricted diet and avoid these medications when the test is ordered.
- Falsely low results can occur with use of alcohol, aspirin, MAO inhibitors, and St. John's wort.
- Liver function studies are an unreliable indicator of liver involvement.

IMAGING STUDIES

- CT scan of chest is useful to detect bronchial carcinoids.
- CT scan or MRI of abdomen or a liver and spleen radionuclide scan is useful to detect liver metastases (palpable in >50% of cases).
- Iodine-123–labeled somatostatin can detect carcinoid endocrine tumors with somatostatin receptors.
- Scanning with radiolabeled octreotide (Fig. C1-12) can visualize previously undetected or metastatic lesions.
- PET scan.

TREATMENT

NONPHARMACOLOGIC THERAPY

Avoidance of ethanol ingestion (may precipitate flushing)

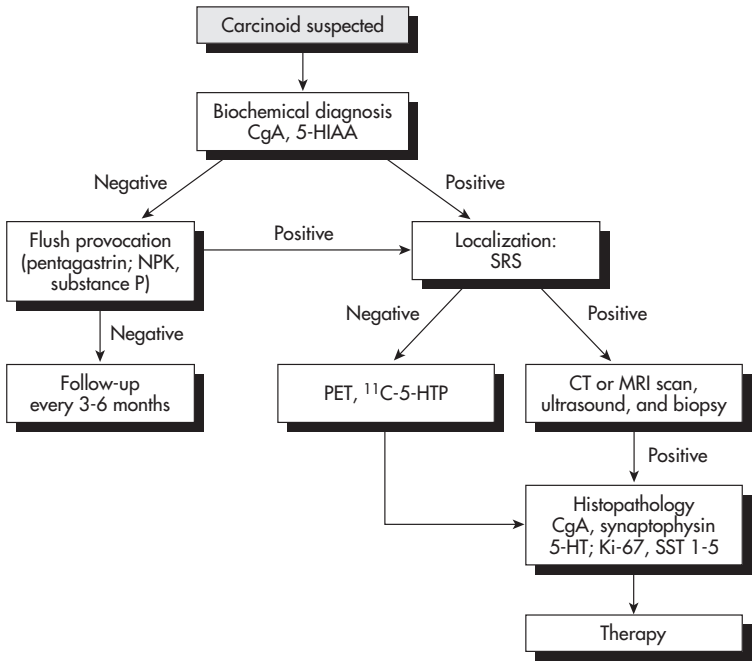


FIGURE C1-11 Diagnostic algorithm for patients with carcinoid tumors. *CgA,* Chromogranin A; *C-5-HTP,* C-5-hydroxytryptophan; *CT,* computed tomography; *5-HIAA,* 5-hydroxyindoleacetic acid; *5-HT,* 5-hydroxytryptamine; *MRI,* magnetic resonance imaging; *NPK,* neuropeptide K; *PET,* positron emission tomography; *SRS,* somatostatin receptor scintigraphy; *SST 1-5,* somatostatin receptor subtypes 1 through 5. (From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

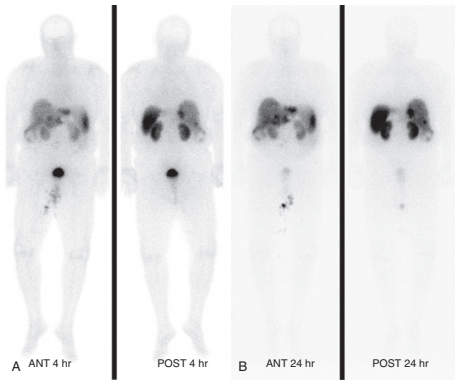


FIGURE C1-12 A and B, Octreoscan illustrating uptake pattern in liver metastases from a small bowel carcinoid. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

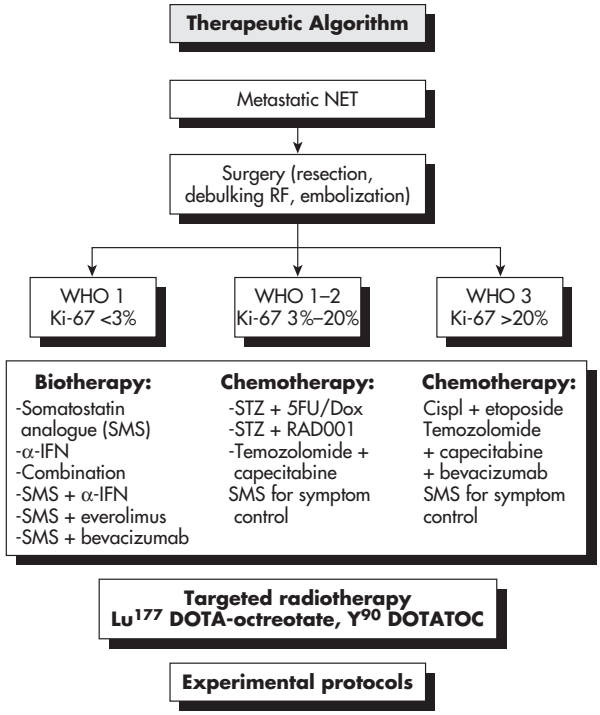


FIGURE C1-13 Therapeutic algorithm for treatment of metastatic carcinoid tumor. *DOTATOC,* DOTA-octreotide; *Dox,* doxorubicin; *5FU,* 5-fluorouracil; *IFN,* interferon; *NET,* neuroendocrine tumor; *RAD001,* everolimus; *STZ,* streptozotocin; *WHO,* World Health Organization classification. (From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders)

GENERAL Rx

- Surgical resection of the tumor can be curative if the tumor is localized or palliative and results in prolonged asymptomatic periods if metastases are present. Surgical manipulation of the tumor can, however, cause severe vasomotor abnormalities and bronchospasm (carcinoid crisis).
- Percutaneous embolization and ligation of the hepatic artery can decrease the bulk of the tumor in the liver and provide palliative treatment of tumors with hepatic metastases.
- Cytotoxic chemotherapy: combination chemotherapy with 5-fluorouracil and streptozocin can be used in patients with unresectable or recurrent carcinoid tumors; however, it has only limited success. Fig. C1-13 describes a therapeutic algorithm for treatment of metastatic carcinoid tumor.
- Control of clinical manifestations:
  1. Somatostatin analogues (octreotide and lanreotide) are effective for both flushing and diarrhea in most patients. Interferon alfa may be useful as an additive therapy for persistent symptoms despite use of somatostatin analogues; however, data remain inconclusive.
  2. Flushing may be controlled by the combination of H_1- and H_2-receptor antagonists (e.g., diphenhydramine 25 to 50 mg PO q6h and ranitidine 150 mg bid).
  3. Diarrhea may respond to diphenoxylate with atropine (Lomotil).
  4. Bronchospasm can be treated with aminophylline and/or albuterol.
- Nutritional support: supplemental niacin therapy may be useful to prevent pellagra because the tumor uses dietary tryptophan for serotonin synthesis, resulting in a nutritional deficiency in some patients.
- Interferon alfa may be useful as an additive to control symptoms unresponsive to somatostatin analogues.
- Echocardiography and monitoring for right-sided congestive heart failure are recommended for patients with unresectable disease because endocardial fibrosis, involving predominantly the endocardium, chordae, and valves of the right side of the heart, can occur.

DISPOSITION

Carcinoids of the appendix and rectum have a low malignancy potential and rarely produce the clinical syndrome; metastases are also uncommon if the size of the primary lesion is <2 cm in diameter.

RELATED CONTENT

Carcinoid Syndrome (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

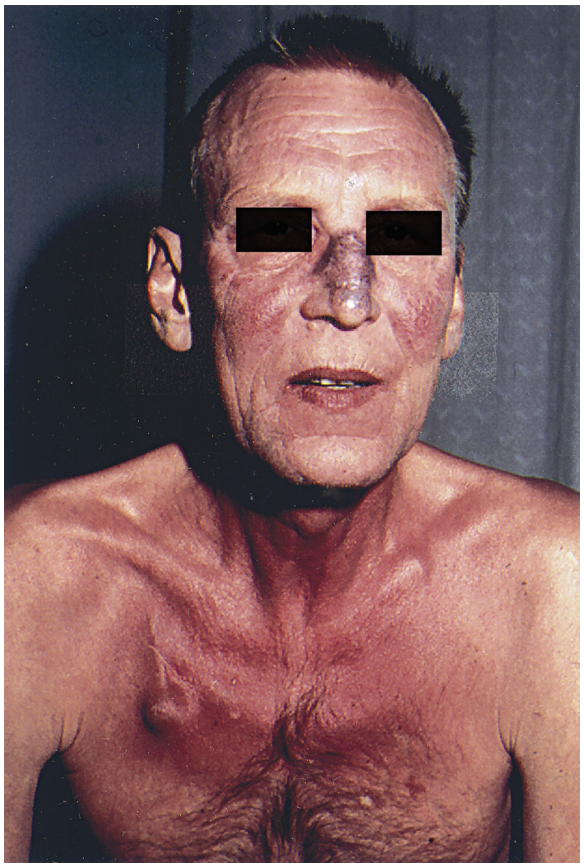


FIGURE EC1-10 Long-lasting, chronic flushing in a patient with long-standing carcinoid disease. Note the telangiectases. (From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Cardiac tamponade is a life-threatening condition where an accumulation of fluid within the pericardial sac causes equal elevation of atrial, end diastolic pressures in the ventricles, and pericardial pressures, as well as an exaggerated inspiratory decrease in arterial systolic pressure (pulsus paradoxus) along with arterial hypotension.

ICD-9CM CODES
423.3 Cardiac tamponade
ICD-10CM CODES
I31.9 Disease of pericardium, unspecified

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Chest pain
- Tachypnea/dyspnea
- Beck's triad
  1. Absolute or relative hypotension
  2. Elevated jugular venous pressure (with prominent *x* descent and blunted *y* descent)
  3. Muffled heart sounds
- Tachycardia (except in uremia or hypothyroid patients)
- Pulsus paradoxus (decrease in systolic arterial pressure of 10 mm Hg or more during normal inspiration while in normal sinus rhythm)
- Pericardial friction rub may or may not be present
- Reduced or absent apical cardiac impulse

ETIOLOGY

Acute (rapidly accumulating pericardial effusion leading to cardiac tamponade): does not need a large amount of effusion to cause tamponade, rather it is the rapidity of fluid accumulation that leads to tamponade.

- Penetrating trauma
- Aortic dissection
- Post-infarction myocardial rupture and/or hemorrhagic pericarditis
- Iatrogenic (central line and pacemaker insertions, post–coronary bypass surgery or post–percutaneous coronary intervention)
- Subacute or chronic (effusion is usually large)
- Malignancy (e.g., lung, breast, lymphoma)
- Viral pericarditis (e.g., Coxsackie, human immunodeficiency virus, enterovirus, HSV 6, parvovirus, etc.)
- Bacterial, fungal, or tuberculous pericarditis
- Uremia
- Hypothyroidism/myxedema (rare)
- Collagen vascular disease (e.g., lupus, rheumatoid arthritis, scleroderma)
- Radiation
- Idiopathic

DIAGNOSIS

Cardiac tamponade is a clinical diagnosis made at the bedside from history and physical examination. The echocardiogram will help confirm or reject the clinical diagnosis. Tamponade can be confirmed invasively by the measurement of elevated intrapericardial pressures with an intrapericardial catheter and right-sided heart catheterization. Typical findings are diastolic equalization of pressures, usually ranging from 10 to 30 mm Hg (diastolic pulmonary artery pressure = right ventricular diastolic pressure = right atrial pressure = intrapericardial pressure), and lowering of the intrapericardial pressure with fluid drainage. Thereafter, the underlying etiology must be determined with specific laboratory work (see "Laboratory Tests").

DIFFERENTIAL DIAGNOSIS

Other conditions that can also lead to elevated jugular venous pressure, decreased systemic pressure, and pulsus paradoxus include:

- Chronic obstructive pulmonary disease and asthma exacerbations
- Constrictive pericarditis (Table C1-4)
- Restrictive cardiomyopathy
- Right ventricular infarction
- Pulmonary embolism
- Chronic biventricular heart failure

LABORATORY TESTS

- Electrolytes, blood urea nitrogen, creatinine, erythrocyte sedimentation rate, thyroid function tests, antinuclear antibody, rheumatoid factor, PPD, blood cultures, viral titers, and pericardial fluid analysis including cytology and cultures
- Possible 12-lead ECG findings:
  1. Sinus tachycardia
  2. PR depression and/or diffuse ST elevations if acute pericarditis is present
  3. Electrical alternans (beat to beat alternations in the QRS complex heights) (Fig. EC1-14)
  4. Low voltage if massive effusion is present. (QRS complex <0.5 mV in the limb leads and <1.0 mV in precordial leads)

IMAGING STUDIES

- Chest radiograph (enlarged cardiac silhouette with clear lung fields) (Fig. C1-15)
- Chest CT (may overestimate size of the effusion) (Fig. C1-16)
- Echocardiogram findings (Fig. C1-17):
  1. Pericardial effusion
  2. Diastolic collapse of the right atrium (late diastole) is virtually 100% sensitive but has low specificity.
  3. Diastolic collapse of the right ventricle (early diastole) is pathognomic and very specific.
  4. >25% mitral and >50% tricuspid valve inflow variation with respiration
  5. Plethoric inferior vena cava (IVC dilation and <50% decrease in the diameter of the IVC during inspiration)
  6. Left atrial collapse (high specificity)
- Cardiac catheterization as discussed earlier will see equalization of intracardiac diastolic pressures and increase of right-sided pressures and reduction of left-sided pressures, which subsequently causes pulsus paradoxus (the pathognomonic finding on physical examination)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cardiac tamponade should be treated emergently.
- Avoid drugs that reduce preload (e.g., nitrates, diuretics).

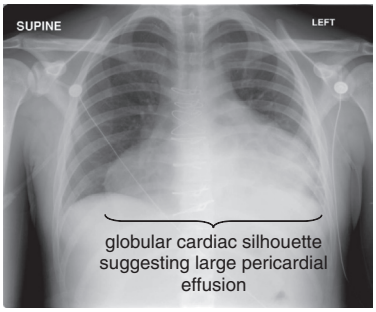


FIGURE C1-15 Massive pericardial effusion and tamponade. This 23-year-old male has a history of aortic valve replacement for infective endocarditis. He presented with increased chest pain and dyspnea. His chest x-ray shows a globular cardiac silhouette, suggesting a large pericardial effusion. The lung fields and right costophrenic angle appear clear, although the left costophrenic angle is hidden behind the heart and cannot be assessed. The patient underwent chest computed tomography to evaluate his aorta, as he complained of severe interscapular pain as well (see Fig. C1-16). (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

TABLE C1-4 Hemodynamics in Cardiac Tamponade and Constrictive Pericarditis

	Tamponade	Constriction
Paradoxical pulse	Usually present	Present in ~1/3
Equal left- and right-sided filling pressures	Present	Present
Systemic venous wave morphology	Absent *y* descent	Prominent *y* descent (M or W shape)
Inspiratory change in systemic venous pressure	Decrease (normal)	Increase or no change (Kussmaul sign)
"Square root" sign in ventricular pressure	Absent	Present

From Bonow RO: *Heart disease,* ed 9, Philadelphia, 2012, Saunders.

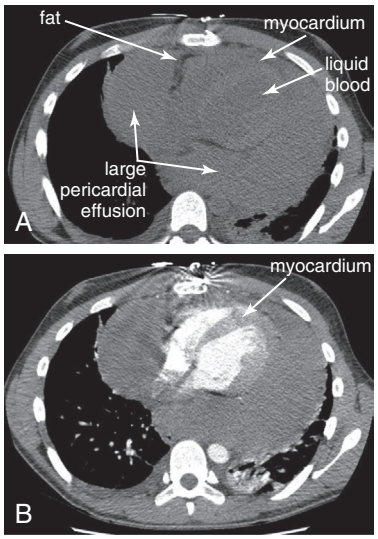


FIGURE C1-16 Massive pericardial effusion. Same patient as Fig. C1-15. The patient underwent chest computed tomography (CT) without **(A)** and then with **(B)** intravenous contrast to evaluate his aorta, which was normal. However, the CT confirmed a massive pericardial effusion surrounding a normal-appearing heart. Without contrast, note that fluid blood within the chambers of the heart has a slightly lower density than the pericardial effusion, which has a density more similar to that of myocardium. When contrast is administered, the ventricular chambers fill completely, and the myocardium enhances and becomes somewhat brighter than the surrounding pericardial effusion. The heart itself is outlined by a thin stripe of fat, which appears nearly black on soft tissue windows. The patient developed hypotension, suggesting cardiac tamponade, and pericardial window was performed for drainage of the effusion. In the operating room, the effusion was found to be coagulated blood. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

- Large pericardial effusions without hemodynamic compromise (tamponade) can be managed conservatively with careful monitoring, IV fluids, treatment of the underlying cause, clinical follow-up, and frequent serial surveillance echocardiography.

ACUTE GENERAL Rx

- Aggressive intravascular volume expansion (saline or blood)
- Emergency pericardial fluid removal by pericardiocentesis or surgical pericardiotomy by way of the subxiphoid pericardial window
- Pericardiocentesis should be performed under fluoroscopic or echocardiographic guidance when available.

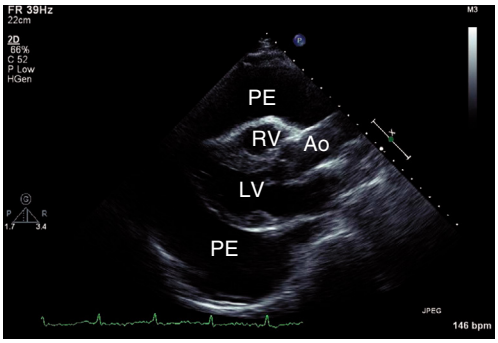


FIGURE C1-17 Two-dimensional echocardiogram of a large, circumferential pericardial effusion (PE). *Ao,* Aorta; *LV,* left ventricle; *RV,* right ventricle. (From Kabbani SS, LeWinter M: Cardiac constriction and restriction. In Crawford MH, DiMarco JP [eds]: *Cardiology*, St Louis, 2001, Mosby.)

- Pericardiocentesis is an absolute contraindication if the etiology of the pericardial effusion is aortic dissection.
- Inotropic or vasopressor support if above measures cannot be performed immediately

CHRONIC Rx

- Depends on etiology.
- Pericardiocentesis with draining catheter: the catheter can be left inside the pericardium to allow continued drainage for 24 to 48 hr. If residual fluid still persists with hemodynamic compromise, surgical drainage should be considered. In the absence of hemodynamic compromise or significant residual fluid, discontinuation of the draining catheter can be done with periodic postprocedure echocardiographic monitoring for re-accumulation (e.g., 24 hr, 7 days, 30 days, 3 mo, 6 mo, 12 mo) depending on the etiology and the rate of reaccumulation.
- Other surgical drainage procedures include:
  1. Subxiphoid pericardiotomy drainage
  2. Limited pericardiectomy draining the pericardial fluid into the left hemithorax
  3. Pericardial window
  4. Complete pericardiectomy, especially in patients with effusive-constrictive pericarditis, bacterial pericarditis, or tuberculous pericarditis. (see "Pearls & Considerations").

DISPOSITION

The prognosis of cardiac tamponade depends on the underlying cause.

REFERRAL

- Emergent cardiology consultation along with thorough echocardiographic exam should be made if cardiac tamponade is suspected.
- Cardiothoracic surgery or interventional cardiology consultation should also be considered if pericardial drainage is indicated.

PEARLS & CONSIDERATIONS

- Cardiac tamponade should always be considered during pulseless electrical activity arrest and may require emergent pericardiocentesis at the bedside.
- Evaluation for pulsus paradoxus should always be performed during normal respiration because deep inspiration may render a false-positive finding.
- Strong consideration should be given to performing early pericardiocentesis in patients who have pericardial effusion associated with bacterial pneumonia or empyema because the incidence of bacterial pericarditis is especially high in this clinical situation and the subsequent development of cardiac tamponade and severe chronic constrictive pericarditis are ominous complications.
- Pericardiocentesis is an absolute contraindication if the etiology of the pericardial effusion is due to aortic dissection extending into the pericardial sac.
- As little as 100 ml of fluid can lead to acute cardiac tamponade if the rate of accumulation is rapid, whereas with gradual accumulation, the pericardial sac can hold up to 5 L of fluid before tamponade occurs.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Cardiac Tamponade (Patient Information)
Pericarditis (Related Key Topic)

AUTHORS: **PHILLIP RUISI, D.O.** and **ARAVIND RAO KOKKIRALA, M.D.**

SUGGESTED READINGS

Weaver LK et al.: False positive rate of carbon monoxide saturation by pulse oximetry of emergency department patients, *Respir Care*, Jul 10, 2012. [Epub ahead of print].

Holmes DR et al.: Iatrogenic pericardial effusion and tamponade in the percutaneous intracardiac intervention era, *JACC Cardiovasc Interv* 2(8):705, 2009.

Meltser H, Kalaria VG: Cardiac tamponade, *Catheter Cardiovasc Interv* 64(2):245, 2005.

Roy CL et al.: Does this patient with pericardial effusion have cardiac tamponade? *JAMA* 297(16):1810, 2007.

Sagristà-Sauleda J et al.: Hemodynamic effects of volume expansion in patients with cardiac tamponade, *Circulation* 117(12):1545, 2008.

Spodick DH: Acute cardiac tamponade, *N Engl J Med* 349(7):684, 2003.

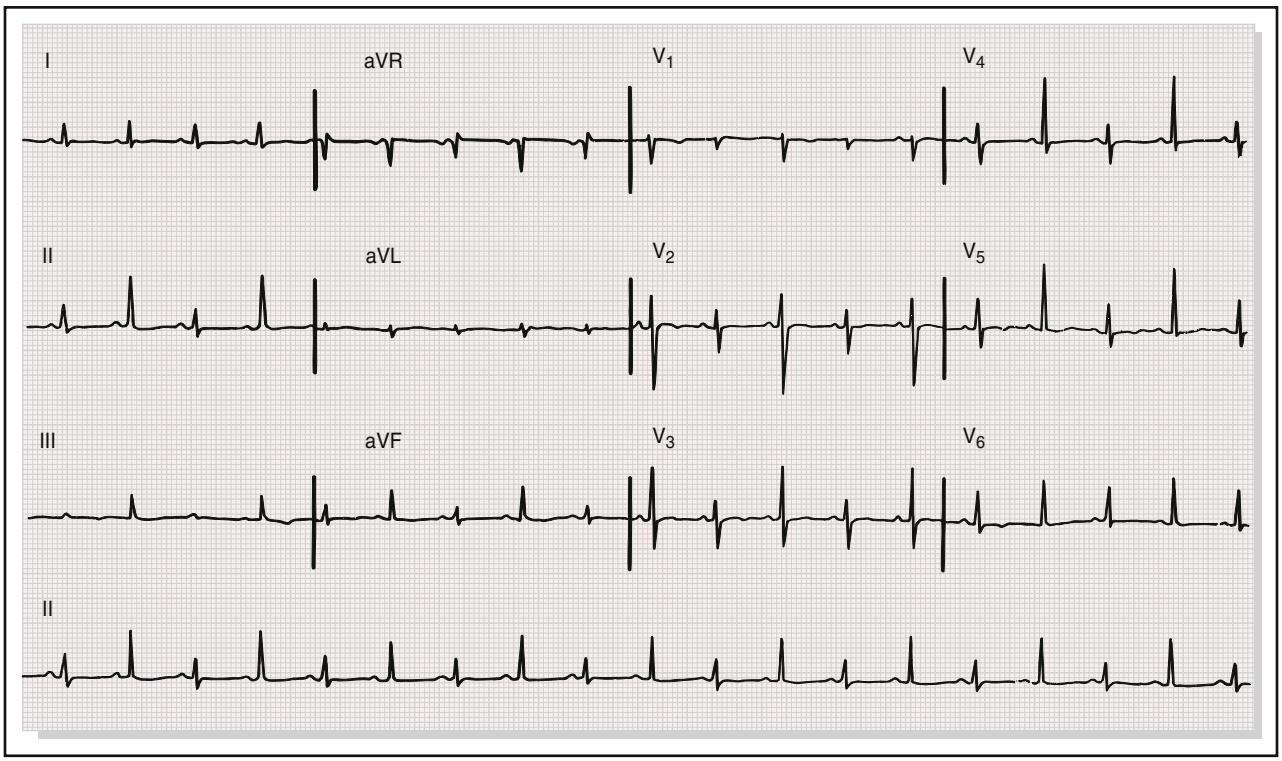


FIGURE EC1-14 Total electrical alternans (P-QRS-T) caused by pericardial effusion with tamponade. This finding, particularly in concert with sinus tachycardia and relatively low voltage, is a highly specific, although not sensitive, marker of cardiac tamponade. (From Bonow RO: *Heart disease*, ed 9, Philadelphia, 2012, Saunders.)

DEFINITION

Cardiomyopathy, chemical-induced (CMc), is the changes of cardiac structure and function caused by chemical compounds, either medically prescribed or not medically prescribed. The common chemicals available in the U.S. include alcohol, cocaine, amphetamine, doxorubicin, 5-fluorouracil (5-FU), zidovudine, and trastuzumab.

SYNONYMS

Alcoholic cardiomyopathy (ACM)
Cocaine-induced CM
Anabolic steroid–induced CM
Anthracycline-induced CM

ICD-10CM CODES
I42.7 Cardiomyopathy due to drug and external agent

EPIDEMIOLOGY & DEMOGRAPHICS

- ACM occurs in about 10% of alcoholics. The prevalence ranges from 23% to 40% of non-ischemic cardiomyopathy.
- Doxorubicin-induced cardiomyopathy is dose dependent based on cumulative doses. The incidence is reported as 0.14% at doses less than 300 mg/m^2, 5% at doses less than 450 mg/m^2, 7% at 550 mg/m^2, and as great as 18% at 700 mg/m^2.
- Significant cardiotoxicity is also caused by the chemotherapeutic agent trastuzumab, used commonly in breast cancer, which can cause cardiomyopathy in >8% cases, but it is a reversible cardiomyopathy. However, the incidence of cardiomyopathy can be as high as 27% when given in conjunction or following anthracycline therapy.
- Other chemotherapeutic agents known to cause cardiomyopathy include epirubicin, docetaxel, mitomycin, cyclophosphamide, bortezomib, sunitinib, 5-fluorouracil [5-FU], and emerging reports of carfilzomib.

PREDOMINANT SEX AND AGE: Among ACM cases, men represent more than 80% and have higher mortality compared with women. In all races, blacks have higher death rates compared to whites. Anthracycline- and trastuzumab-induced cardiomyopathy is predominantly more common in those age >60 years.

GENETICS:

- In patients with ACM, deletion (DD) genotype of ACE is more common than insertion (II) and deletion insertion (DI) genotypes. The underlying mechanism involves direct toxicity of ethanol to the myocardium through uncoupling of ATP.
- Anthracycline-induced cardiomyopathy is linked to an increase in cardiac oxidative stress via the pathways of mitochondria, nitric oxide synthesis, and nicotinamide adenine dinucleotide phosphate reduction.
- One study suggests that polymorphisms in the carbonyl reductase genes could be related to anthracycline-induced CM.

RISK FACTORS

- Consumption of more than 90 gm/day of alcohol for more than 5 years is necessary to develop ACM.
- The occurrence of chronic anthracycline-induced CM is correlated to cumulative dose (ranging from 7% to 26% of patients who received >550 mg/m^2), age, preexisting heart disease, concomitant chemotherapy, and history of mediastinal radiation therapy. Children are more susceptible to anthracycline-induced CM.
- Continuous infusions of chemotherapy pose a higher risk for cardiotoxicity, compared to bolus regimens.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The majority of clinical characteristics of CMc are similar to the dilated cardiomyopathy of other etiologies. Symptoms may develop either insidiously or acute in onset.

- The acute anthracycline-induced cardiotoxicity can start at anytime after the first dose and presents with arrhythmias, most commonly supraventricular tachycardia, ventricular dysfunction, and pericardial diseases. Typically the first manifestation of anthracycline-induced cardiotoxicity is subtle diastolic dysfunction noted on tissue Doppler. The sub-acute and chronic symptoms occur from 3 months after the last dose to 10 years later. Patients usually present with congestive heart failure (CHF). More recently, mortality has improved as a result of medical treatment with ACE inhibitors and beta-blockers. In fact, some recent trials including the Overcome Trial have demonstrated a possible benefit in preemptively treating patients with beta-blockers and ACE-inhibitors undergoing anthracycline therapy before the development of any CM.
- Cardiac symptoms after 5-FU treatment include angina (most common), myocardial infarction, arrhythmia, acute pulmonary edema, cardiac arrest, and pericarditis. The mortality of 5-FU–induced cardiotoxicity is 2% to 13%.
- The presentation of CHF may occur over 15 years of heavy drinking. In the presentation of arrhythmia, atrial fibrillation is most common with chronic ETOH abuse and can also be seen acutely with intoxication.
- Patients with cocaine CM may present with adrenergic symptoms (palpitations, pallor, diaphoresis, and anxiety), hypertension, angina, atrial and ventricular arrhythmia, and heart failure.
- Anabolic steroids can cause left ventricular hypertrophy and dilation, and can lead to heart failure, arrhythmia, myocardial infarction, hypertension, and sudden death.

ETIOLOGY

The underlying mechanism of chemotherapy is not well established. Several pathways have been proposed, including an increase in oxidative stress, free radical production, apoptosis, disturbance of DNA, RNA and protein synthesis, and vasospasm. Nutritional deficiency, such as thiamine deficiency, also plays a role in ACM.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Ischemic cardiomyopathy
- Dilated cardiomyopathy, related to valvular disease, hypertension, and causes other than chemicals
- Cirrhotic cardiomyopathy

WORKUP

- The diagnosis is based on the history of chemical exposure and the clinical presentation of heart failure, arrhythmia, and angina pectoris.
- Electrocardiogram (ECG) and serum electrolytes, renal function, and hepatic function
- Serum troponin and brain natriuretic peptide (BNP) levels
- Transthoracic echocardiogram for the evaluation of heart structure and function
- Rule out the diagnosis of coronary artery disease by coronary angiography.

LABORATORY TESTS

- There are no specific diagnostic tests to help differentiate CMc from other forms of CM, but the following laboratory tests are generally helpful.
- Serum electrolytes, renal function, hepatic function, thyroid-stimulating hormone, iron profile, and inflammatory factors
- Recent studies have suggested that early elevation of troponin I levels and BNP (brain natriuretic peptide) following chemotherapy may be an early predictor of future development of cardiomyopathy.

IMAGING STUDIES

- ECG
  1. ST deviation and atrial and ventricular arrhythmia in 5-FU toxicity
     1. Sinus tachycardia
     2. Nonspecific ST-T change
     3. Decreased QRS voltage
     4. Prolonged QT interval
- Echocardiogram
  1. Asymptomatic alcoholics may present with mild left ventricular (LV) hypertrophy, diastolic dysfunction, LV dilation, and decrease in left ventricular ejection fraction (LVEF).
  2. Baseline LVEF should be performed before initiation of doxorubicin-based chemotherapy with either serial echocardiograms or MUGA (multigated acquisition) scan.
     1. If baseline LVEF is >55%, then subsequent evaluation should be at the end of treatment if anthracycline dose is <200 mg/m^2 or serially at 200, 300, 350, and 400 mg/m^2 dose completion. Doxorubicin therapy should be discontinued if there is a >15% absolute drop or >10% drop below normal or symptomatic congestive heart failure develops.
     2. Global longitudinal strain imaging (GSLI) is an emerging echocardiographic measurement that may predict early cardiotoxicity before an actual drop in LVEF occurs.

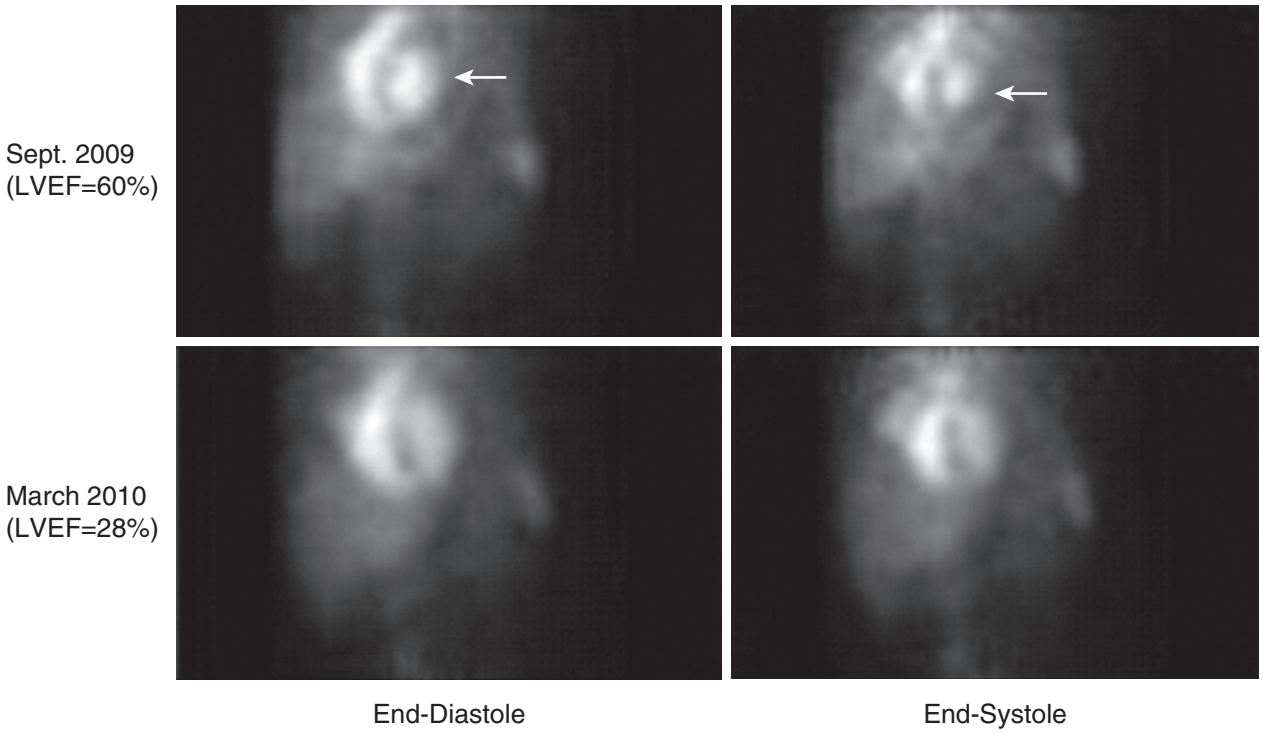


FIGURE C1-18 Technetium-99m-pertechnetate multigated acquisition scans in a 47-year-old woman with breast cancer treated with doxorubicin. The top scan was taken before initiation of doxorubicin and cyclophosphamide therapy in September 2009. The left ventricular ejection fraction (left ventricular end-diastolic counts minus left ventricular end-systolic counts/left ventricular end-diastolic counts 100) was calculated at 60%. The bottom scan was taken in March 2010 after treatment with a total doxorubicin dose of 451 mg/m^2. Left ventricular ejection fraction was calculated at 28%. Left ventricle (*white arrows*) during end-diastole and end-systole. (From Figuerado VM: Chemical cardiomyopathies: the negative effects of medications and nonprescribed drugs on the heart, *Am J Med* 124:480-488, 2011.)

- Radionuclide imaging (Figure C1-18).
  1. If baseline LVEF ≤55%, the cardiac risks vs. oncological benefits should be discussed with the patient, cardiologist, and oncologist before initiating therapy. Cardioprotective agents such as ACE inhibitors and beta-blockers should be initiated and serial LVEF measurements done after each dose.
  2. Even after chemotherapy is completed, annual LVEF measurements with echocardiograms or MUGA scans should be done for 5 years to detect late anthracycline cardiotoxicity.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- The noninvasive assessment of LV function before, during, and after anthracycline-containing chemotherapy by means of echocardiograms and MUGA scan.
- To reduce the risk of anthracycline-induced cardiotoxicity, the lifetime cumulative dosage should be limited to <350 mg/m^2 in adults.
- Other approaches include the use of infusion other than bolus, liposomal encapsulated doxorubicin, less cardiotoxic analogs of doxorubicin such as epirubicin, and coadministration of protective agents such as dexrazoxane.
- Termination of 5-FU treatment if cardiac symptoms manifest and re-administration is not recommended

ACUTE GENERAL Rx

- Treat decompensated CHF with diuresis and vasopressors if low cardiac output.
- For angina in acute cocaine intoxication, benzodiazepines, nitrites, and calcium channel blockers are the first line of therapy. Once myocardial infarction is indicated by ECG and serum troponin, patients should be evaluated by cardiac catheterization.

CHRONIC Rx

- Nitrates, beta-blockers, and calcium channel blockers for angina caused by 5-FU.
- Dexrazoxane is an ethylenediaminetetraacetic acid–like chelator that acts by binding to iron, which prevents anthracycline cardiotoxicity. Cardio-Oncology experts suggest a 10:1 ratio of dexrazoxane to anthracycline, administered 15 to 30 minutes before doxorubicin administration. However, the routine use of the drug is currently not approved in adults except in cases of cumulative dose of doxorubicin of 300 mg/m^2 or greater.
- Those developing anthracycline cardiomyopathy should never be re-challenged with the drug as the cardiac damage is usually irreversible due to cell death (Type I cardiotoxicity). The cardiotoxicity from trastuzumab, however, is reversible (Type II cardiotoxicity).
- Beta-blocker: In one study, carvedilol preserved LV diastolic function and chamber size after doxorubicin treatment, compared to placebo.
- ACE inhibitor: Enalapril and ramipril can improve myocardial contractility after doxorubicin or epirubicin treatment.
- Thiamine, folic acid, and multivitamins are adjunctive treatment for alcoholic cardiomyopathy. Abstinence can usually reverse the cardiomyopathy.

DISPOSITION

Prognosis depends on the dosage of chemicals and the severity of LV dysfunction.

REFERRAL

Close follow-up with cardiologist.

PEARLS & CONSIDERATIONS

The presentation of chemotherapy-induced cardiac toxicity ranges from asymptomatic decline in LVEF to heart failure. The incidence is dose-dependent in the case of anthracyclines and may manifest itself up to 10 years after initial exposure. Therefore, a regular clinical follow-up of such patients is advised and echocardiographic surveillance is possibly indicated to detect late cardiotoxicity.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **PHILLIP RUISI, D.O.** and **ARAVIND RAO KOKKIRALA, M.D.**

SUGGESTED READINGS

Curry LA, Wagman DF: Qualitative description of the prevalence and use of anabolic androgen steroids by United States power lifters, *Precept Mot Skills* 88:224–233, 1999.

Ewer MS, Von Hoff DD, Benjamin RS: A historical perspective of anthracycline cardiotoxicity, *Heart Fail Clin* 7:363–372, 2011.

Figueredo VM: Chemical cardiomyopathies: the negative effects of medications and nonprescribed drugs on the heart, *Am J Med* 124:480–488, 2011.

George A, Figueredo VM: Alcoholic cardiomyopathy: a review, *J Card Fail* 10:844–889, 2011.

Panjrath GS, Jain D: Monitoring chemotherapy-induced cardiotoxicity: role of cardiac nuclear imaging, *J Nucl Cardiol* 13:415–426, 2006.

Piano MR: Alcoholic cardiomyopathy: incidence, clinical characteristics, and pathophysiology, *Chest* 121:1638–1650, 2002.

BASIC INFORMATION

DEFINITION

Dilated cardiomyopathy describes a group of diseases involving the myocardium and characterized by myocardial dysfunction that is not wholly the result of hypertension, coronary atherosclerosis, valvular dysfunction, or congenital or other structural heart disease. As a result, the heart is enlarged and the ventricles are dilated with impaired systolic function.

SYNONYMS

Congestive cardiomyopathy

ICD-9CM CODES
425.4 Other primary cardiomyopathies
425.5 Alcoholic cardiomyopathy
425.8 Cardiomyopathy in other diseases classified elsewhere
425.9 Secondary cardiomyopathy, unspecified

ICD-10CM CODES
I42.5 Other restrictive cardiomyopathy
I42.6 Alcoholic cardiomyopathy
I43 Cardiomyopathy in diseases classified elsewhere
I42.7 Cardiomyopathy due to drug and external agent

EPIDEMIOLOGY & DEMOGRAPHICS

- The estimated prevalence of dilated cardiomyopathy in the general adult population is approximately 1:2500. The incidence is approximately 4 to 8 per 100,000 persons per yr.
- The incidence of dilated cardiomyopathy is greatest in middle age and among men.
- It is the most common cardiomyopathy and accounts for 25% of cases of congestive heart failure.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The patient will present the common symptoms of congestive heart failure, which may be of insidious or more sudden onset. The patient may also be asymptomatic and the diagnosis made by the unexpected finding of cardiomegaly on a chest x-ray. The history should focus also on information that could help determine the etiology. Classical signs of heart failure may be absent. When present, findings are indistinguishable from other heart failure syndromes, including:

- Increased jugular venous pressure
- Narrow pulse pressure
- Pulmonary rales, hepatomegaly, peripheral edema
- S3, S4
- Mitral regurgitation, tricuspid regurgitation (less common)

ETIOLOGY

In approximate order of occurrence:

- Idiopathic (often a viral infection that cannot be confirmed)
- Infections (viral [Coxsackie B, adenovirus, parvovirus, HIV], rickettsial, mycobacterial, toxoplasmosis, trichinosis, Chagas' disease)
- Alcoholism (15% to 40% of all cases in Western countries)
- Uncontrolled tachyarrhythmia ("tachycardia-mediated")
- Peripartum (greatest risk from last trimester of pregnancy to 6 mo postpartum)
- Chemotherapeutic (anthracycline, doxorubicin, daunorubicin) or pharmacologic agents (antiretrovirals, phenothiazines)
- Substance abuse (cocaine, heroin, organic solvents "glue-sniffer's heart")
- Postmyocarditis
- Toxins (cobalt, lead, phosphorus, carbon monoxide, mercury)
- Collagen-vascular disease (systemic lupus, rheumatoid arthritis, polyarteritis, dermatomyositis, sarcoidosis)
- Heredofamilial neuromuscular disease (e.g., muscular dystrophy)
- Excess hormones (acromegaly, osteogenesis imperfecta, myxedema, thyrotoxicosis, diabetes)
- Hematologic (e.g., sickle cell anemia, hemochromatosis, hypereosinophilia)
- Stress-induced (i.e., takotsubo or broken heart syndrome)
- LV noncompaction
- TTN truncating mutations (mutations in TTN, the gene encoding the sarcomere protein titin) are a common cause of dilated cardiomyopathy, occurring in approximately 25% of familial cases of idiopathic dilated cardiomyopathy and in 18% of sporadic cases.

DIAGNOSIS

Dilated cardiomyopathy is a diagnosis of exclusion, made after ruling out other potential causes of myocardial dysfunction.

DIFFERENTIAL DIAGNOSIS

- Coronary atherosclerosis, that is, left ventricular dysfunction secondary to ischemia and/or myocardial infarction
- Valvular dysfunction (especially aortic and mitral regurgitation)
- Other cardiomyopathies (restrictive, hypertrophic)
- Pulmonary disease (embolism, obstructive, restrictive)
- Pericardial abnormalities (constrictive pericarditis, tamponade)
- Hypothyroidism/myxedema
- Athlete heart

WORKUP

- Medical history: emphasis on symptoms of dyspnea, orthopnea, paroxysmal nocturnal dyspnea, weight gain, palpitations, or signs of systemic and pulmonary embolism
- Physical exam (see "Physical Findings & Clinical Presentation")
- Testing (see "Laboratory Tests" and "Imaging Studies" for more detail): laboratory, chest x-ray, ECG, echocardiogram, cardiac catheterization; myocardial biopsy is not routinely recommended, unless acute myocarditis requiring immunosuppressive therapy is considered (e.g., giant cell myocarditis)

LABORATORY TESTS

- Chemistries/metabolites (deficiencies), renal function tests (renal dysfunction)
- Cardiac biomarkers (elevation of cardiac troponin or BNP)
  1. Persistently increased cardiac troponin T levels are a marker of poor outcome in cardiomyopathy patients
- Endocrine (particularly thyroid)
- Iron studies (hemochromatosis, deficiency)
- Rheumatologic and inflammatory (ANA, ESR, CRP)
- Others as indicated (HIV, Lyme, neurohormonal)

IMAGING STUDIES

Chest x-ray:

- Cardiac silhouette enlargement (particularly left ventricle)
- Pulmonary vascular redistribution and congestion (Kerley B lines, cephalization of vasculature), pleural effusion (may appear as unilateral, most often on the right side)

ECG:

- ECG findings are typically nonspecific, and sinus tachycardia is usually a reflection of underlying heart failure
- Intraventricular conduction defects and left bundle branch block
- Arrhythmias (atrial fibrillation, premature ventricular or atrial contractions, ventricular tachycardia)

Echocardiogram (Fig. EC1-19):

- Low ejection fraction with global hypokinesis
- Four-chamber enlargement (LV enlargement usually predominates)
- Mitral or tricuspid regurgitation (tethering due to incomplete leaflet closure caused by ventricular dilation)

Cardiac catheterization:

- On initial presentation to exclude obstructive epicardial coronary artery disease

Cardiac magnetic resonance imaging (CMRI):

- Particularly if infiltrative or inflammatory etiology suspected

TREATMENT

NONPHARMACOLOGIC THERAPY

- Treatment of underlying disease (systemic lupus, alcoholism)
- Dietary sodium restriction (<2 g/day).
- Exercise training has been shown to be associated with reduced risk for hospitalization and death in patients with history of heart failure in limited trials; enrollment in a formal cardiac rehabilitation program may be beneficial in improving patient's functional status

ACUTE GENERAL Rx

- Diuretics are indicated for all patients with current symptoms or history of heart failure and reduced left ventricular ejection fraction

(LVEF) with evidence of volume overload (pulmonary edema, peripheral edema, orthopnea, paroxysmal nocturnal dyspnea).
- ACE inhibitors (and angiotensin receptor blockers) have been shown to have favorable effects on ventricular remodeling in patients with cardiomyopathy and a demonstrable mortality benefit in these patients. They also reduce afterload and improve cardiac output. Therefore they are recommended in all patients with reduced LV systolic function, regardless of symptoms, unless specific contraindications exist.
- Beta-blockers (in particular, carvedilol, long-acting metoprolol, and bisoprolol) work by inhibiting the adverse effects of the sympathetic nervous system in patients with ventricular systolic dysfunction and have likewise shown a mortality benefit in patients with LV systolic dysfunction; unless specifically contraindicated, they should be started once the acute exacerbation has resolved and titrated to the maximum tolerated dose.
- Aldosterone antagonists have shown mortality benefit along with decreased rate of hospitalization for heart failure in patients with symptomatic heart failure and reduced LV systolic function. They should be used following label guidelines and with close monitoring of renal function and potassium.
- Additional medical therapies (hydralazine/nitrates, digitalis) can be considered in certain patient subpopulations with persistent symptoms on otherwise optimal medical management.
- Patients with associated coronary atherosclerosis (angina, ECG changes, reversible defects on myocardial perfusion imaging) may benefit from percutaneous or surgical revascularization.
- In a phase III clinical trial, neprilysin inhibition on top of optimal medical therapy was recently found to significantly reduce multiple heart failure endpoints including death, hospitalizations, and CV death in a large randomized control trial (Paradigm – Hf).

CHRONIC Rx

- As above in "Acute General Rx."

DISPOSITION

- Annual mortality rate is 20% in patients with moderate heart failure, and it exceeds 50% in patients with severe heart failure. Once symptomatic, hospitalizations are frequent and readmission rates are high (>50% at 3 mo). A multispecialty treatment approach (e.g., primary care, cardiology, nutrition, cardiac rehabilitation) is recommended.
- Factors associated with an adverse outcome in dilated cardiomyopathy are described in Table C1-5.

REFERRAL

- Patients with dilated cardiomyopathy are at increased risk for ventricular arrhythmias and sudden cardiac death. Implantation of a cardiac defibrillator for primary prevention of sudden cardiac death can be considered for patients with LVEF <35% on optimal medical therapy regardless of symptom status.
- Patients with LVEF <35%, bundle branch block on ECG (QRS ≥0.12 sec), and persistent heart failure symptoms may benefit from cardiac resynchronization therapy via a biventricular pacemaker.
- Consider heart transplantation for relatively young patients (there is no precise age threshold) free of other significant comorbid conditions who are unresponsive to medical therapy. Dilated cardiomyopathy is the reason for 45% of all heart transplantations in the U.S.

TABLE C1-5 Factors Associated with an Adverse Outcome in Dilated Cardiomyopathy

Clinical	Noninvasive	Invasive
NYHA Class III/IV	Low LV ejection fraction	High LV filling pressures
Increasing age	Marked LV dilation	
Low exercise peak oxygen consumption	Low LV mass	
Marked intraventricular conduction delay	≥Moderate mitral regurgitation	
Complex ventricular arrhythmias	Abnormal diastolic function	
Abnormal signal-averaged ECG	Abnormal contractile reserve	
Evidence of excessive sympathetic stimulation	Right ventricular dilation or dysfunction	
Protodiastolic gallop (S_3)		
Elevated serum BNP		
Elevated uric acid		
Decreased serum sodium		

BNP, Brain natriuretic peptide; *ECG,* electrocardiogram; *LV,* left ventricular; *NYHA,* New York Heart Association.
From Hare JM: The dilated, restrictive, and infiltrative cardiomyopathies. In Bonow RO et al (eds): *Braunwald's heart disease—a textbook of cardiovascular medicine,* ed 9, St Louis, 2011, Saunders.

PEARLS & CONSIDERATIONS

COMMENTS

- Patients should be encouraged to restrict or eliminate alcohol and reduce sodium intake (<2 g daily).
- Patients may benefit from daily weight checks as a means of early detection of volume overload and decompensated heart failure.
- Vulnerability to cardiomyopathy among chronic alcohol abusers is partially genetic and related to the presence of the ACE DD genotype.
- Idiopathic dilated cardiomyopathy is often familial, and apparently healthy relatives may have latent, early, or undiagnosed disease. Echocardiographic evaluation of family members is recommended.
- Incorporation of sequencing approaches that detect TTN truncations into genetic testing for dilated cardiomyopathy may substantially increase test sensitivity and allow earlier diagnosis of dilated cardiomyopathy.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fig. 3-44 Initial approach to classification of cardiomyopathy (Algorithm)
Dilated Cardiomyopathy (Patient Information)

AUTHOR: **BARRY FINE, M.D., PhD.**

SUGGESTED READINGS

Abraham W et al.: Pharmacologic therapies across the continuum of left ventricular dysfunction, *Am J Cardiol* 102(5A):21G–28G, 2008.

Adams KF et al.: Executive summary: 2006. Comprehensive Heart Failure Practice Guidelines, *J Cardiac Failure* 12:10–38, 2006.

Arbustini E, Narula N, Dec GW et al.: The MOGE(S) Classification for a Phenotype–Genotype Nomenclature of Cardiomyopathy: Endorsed by the World Heart Federation, *Am Coll Cardiol* 62(22):2046–2072, 2013, http://dx.doi.org/10.1016/j.jacc.2013.08.1644.

Harmon WG et al.: Treating children with idiopathic dilated cardiomyopathy (from the pediatric cardiomyopathy registry), *Am J Cardiol* 104:281–286, 2009.

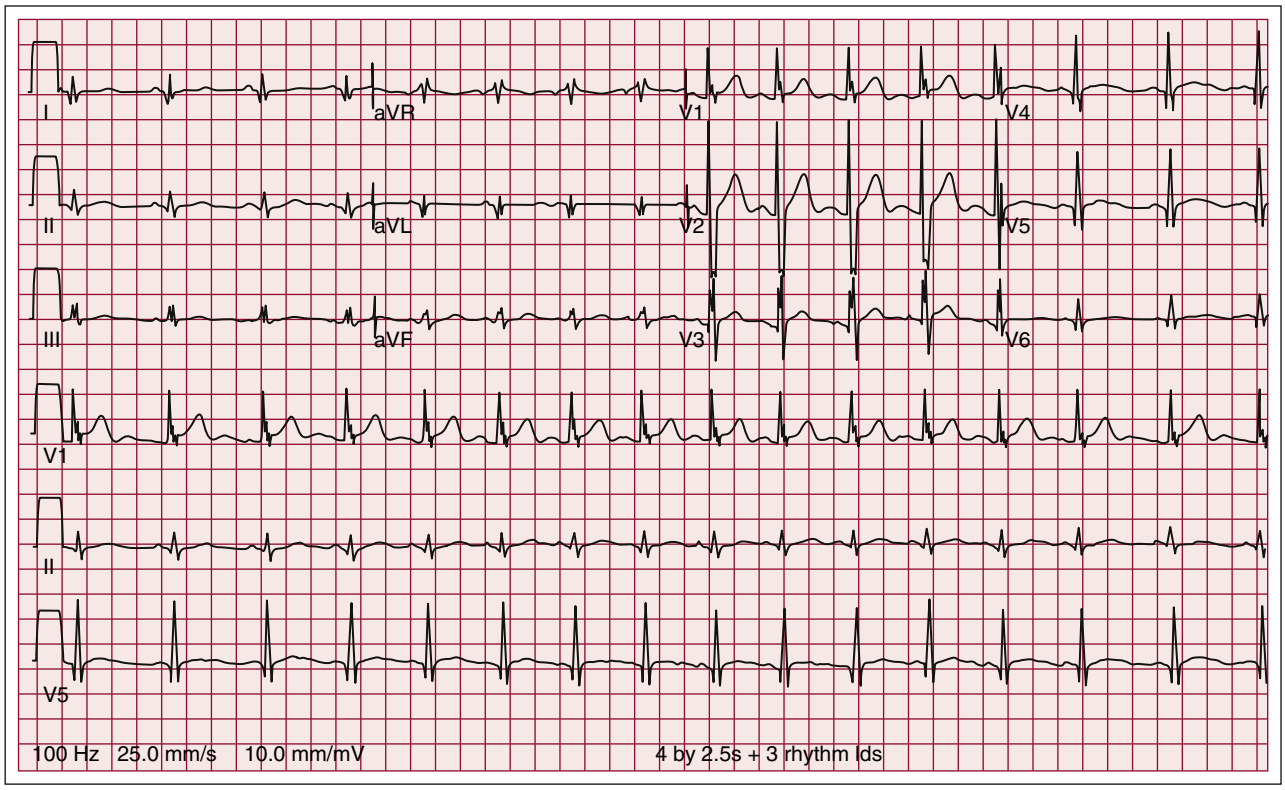
Herman DS et al.: Truncations of titin causing dilated cardiomyopathy, *N Engl J Med* 366:619–628, 2012.

Hunt SA et al.: 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults, *Circulation* 119:e391, 2009.

Kadish A et al.: Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy, *N Engl J Med* 350:2151, 2004.

Mahon NG et al.: Echocardiographic evaluation in asymptomatic relatives of patients with dilated cardiomyopathy reveals preclinical disease, *Ann Intern Med* 143:108, 2005.

Maron BJ et al.: Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention, *Circulation* 113:2006, 1807.



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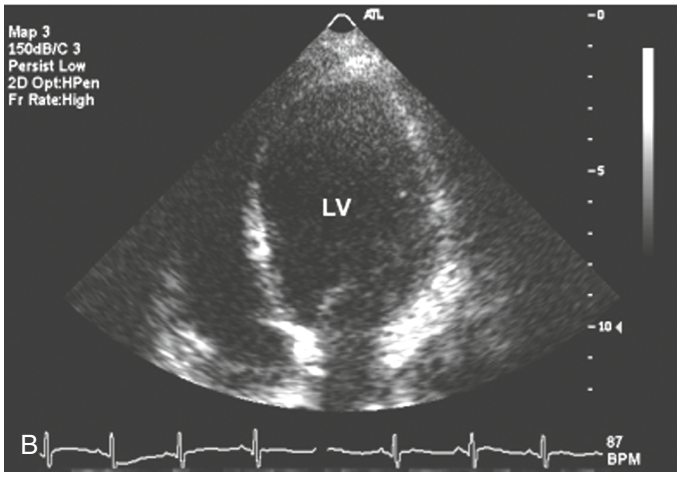

FIGURE EC1-19 Dilated cardiomyopathy in a 19-year-old man with Duchenne muscular dystrophy. **A,** ECG showing a QRS complex that is typical of Duchenne dystrophy, with tall R waves in V1 and deep, narrow Q waves in leads I and aVL. **B,** Two-dimensional echocardiogram (parasternal four chamber) showing a dilated, thinned left ventricle (LV). (From Bonow RO et al: *Braunwald's heart disease—a textbook of cardiovascular medicine,* ed 9, St Louis, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Hypertrophic cardiomyopathy (HCM) is an autosomal dominant myocardial disorder characterized by disorganized myocyte architecture and marked thickening (hypertrophy) of the left ventricular wall (>15 mm), without dilation, not explained by another cardiac or systemic disorder. The interventricular septum is the most common site of enlargement, though hypertrophy may involve other focal regions or may be concentric. HCM may result in hemodynamically significant obstruction within the left ventricular outflow tract (LVOT) and/or impairment of the diastolic function of the left ventricle.

SYNONYMS

HCM
Hypertrophic cardiomyopathy
Idiopathic hypertrophic subaortic stenosis (IHSS)
Hypertrophic obstructive cardiomyopathy (HOCM)
Asymmetric septal hypertrophy (ASH)

ICD-9CM CODES

425.1 Hypertrophic obstructive cardiomyopathy
425.4 Other primary cardiomyopathies
746.84 Congenital obstructive anomalies of the heart not elsewhere classified

ICD-10CM CODES

I42.1 Obstructive hypertrophic cardiomyopathy

EPIDEMIOLOGY & DEMOGRAPHICS

- Prevalence in the general population is 1 in 500 (the most common genetically transmitted cardiovascular disease).
- HCM is the most common cause of sudden cardiac death in young athletes (more commonly among blacks).
- There is equal prevalence in men and women (probably underdiagnosed in women).
- It occurs across ethnicities, perhaps underdiagnosed among blacks.
- Mortality rate is approximately 1%/yr, as high as to 2%/yr in children.
- The most common form of the disease is familial (60% to 70% of cases), and it follows an autosomal dominant inheritance pattern with variable expression.
- Spontaneous mutations can also occur, accounting for approximately 20% of cases. It is otherwise indistinguishable from the familial form.
- A variant form seen in the elderly (5% to 10% of cases) has a better prognosis, and it is not typically associated with sudden cardiac death.
- The familial form is usually diagnosed in young patients. It is most often caused by a mutation in one of the contractile protein genes of the cardiac sarcomere. More than 1400 mutations with variable phenotype, expressivity, and penetrance have been identified thus far. The most vigorous evidence indicates that 8 genes are known to definitively cause HCM: beta myosin heavy chain, myosin binding protein C, troponin T, troponin I, alpha tropomyosin, actin, regulatory light chain, and essential light chain.
- Nonsarcomeric genetic mutations that cause storage disease (e.g., Fabry disease) have a very similar clinical presentation.
- Apical HCM is a variant more common among Asians: as many as 41% of Chinese HCM and 15% of Japanese HCM patients. Clinically there is no LVOT obstruction.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Patients may have subtle symptoms of progressive congestive heart failure (CHF). At time of diagnosis, most patients are asymptomatic, referred and diagnosed based on family history. HCM may be suspected on the basis of abnormalities found on physical examination. Classic findings include:

- Harsh, systolic, crescendo–decrescendo murmur at the left sternal border or apex. The murmur increases with maneuvers that decrease venous return or LV size (Valsalva, standing), and decreases with those that increase venous return or afterload (squatting, hand grip, post-Valsalva release).
- Paradoxical splitting of S2 (if left ventricular obstruction is present).
- S4 may be present.
- Double or triple LV apical impulse ("triple ripple": atrial contraction, early rapid ejection, and late slow ejection).
- Pulsus bisferiens (double pulsation on palpation of the carotid pulse).

Increased obstruction can occur with:

- Drugs: digitalis, β-adrenergic stimulators (isoproterenol, dopamine, epinephrine), nitroglycerin, vasodilators, diuretics, alcohol
- Hypovolemia
- Tachycardia
- Valsalva maneuver
- Standing position

Decreased obstruction is seen with:

- Drugs: β-adrenergic blockers, calcium channel blockers, disopyramide, α-adrenergic stimulators
- Volume expansion
- Bradycardia
- Hand-grip exercise
- Squatting position
- Release phase of the Valsalva maneuver

Clinical manifestations are as follows:

- Dyspnea
- Syncope (usually seen with exercise)
- Angina
- Palpitations
- Sudden cardiac death

ETIOLOGY

- Genetic: Autosomal dominant trait with variable penetrance caused by mutations in multiple genes encoding proteins of the cardiac sarcomere and calcium regulation. To date, >1400 mutations have been identified among at least 13 genes. The most vigorous evidence indicates that 8 genes are known to definitively cause HCM: beta myosin heavy chain, myosin binding protein C, troponin T, troponin I, alpha tropomyosin, actin, regulatory light chain, and essential light chain.
- Sporadic occurrence.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hypertensive heart disease
- Valvular disease, especially aortic stenosis
- Cardiac amyloidosis
- Fabry disease
- Non–sarcomeric protein mutations: gamma 2 regulatory subunit of AMP-activated protein kinase (PRKAG2) mutation
- Lysosome-associated membrane protein 2 (LAMP2) mutation: Danon disease
- Athlete's heart

WORKUP

- Medical history: focus on signs and symptoms of CHF (dyspnea, orthopnea, paroxysmal nocturnal dyspnea), palpitations, any history of syncope or presyncope, chest pain, and family history of sudden death.
- Physical exam: see "Physical Findings & Clinical Presentation."
- Genetic counseling with or without testing.
- ECG is abnormal in 75% to 95% of patients, although there are no pathognomonic findings. Typical findings include:
  1. LV hypertrophy (abnormally tall R waves in the precordial leads) in up to 80% of patients
  2. Abnormal Q waves in lateral and inferior leads (Fig. C1-20)
  3. T wave inversions (associated with the apical hypertrophy predominant variant)
- Echocardiography (Fig. C1-21) is usually diagnostic as the majority of patients have significant LV hypertrophy (See "Imaging Studies" for details) and should be repeated every 12 to 24 months or as clinically needed.
- 24-hour Holter monitor to screen for potentially lethal ventricular arrhythmias (principal cause of syncope or sudden death in obstructive cardiomyopathy) should be performed initially at diagnosis to detect ventricular tachycardia and to identify patients who are candidates for ICD therapy and in patients that subsequently develop palpitations, lightheadedness, or syncope.
- In the absence of significant LVOT obstruction, exercise testing is indicated at diagnosis and annually afterward to evaluate for symptoms and response to exercise. A drop in systolic blood pressure or failure to augment with exercise is a marker of poor prognosis and it is one of the indicators for referral for myotomy/myomectomy. Cardiopulmonary exercise testing can provide objective evidence for worsening diseases, but need only be performed every 2 to 3 years.
- Biomarkers of myocardial fibrosis in HCM include BNP and high-sensitivity cardiac troponin T and I. Other labs include CBC, BMP, LFTs, TSH, SPEP, UPEP, Kappa/Lambda.
- Screening for sarcomere protein gene mutations in family members of patients with HCM can identify a broad subgroup of patients with increased propensity toward long-term impairment of left ventricular function and adverse outcome, irrespective of the myofilament (thick, intermediate, or thin) involvement.

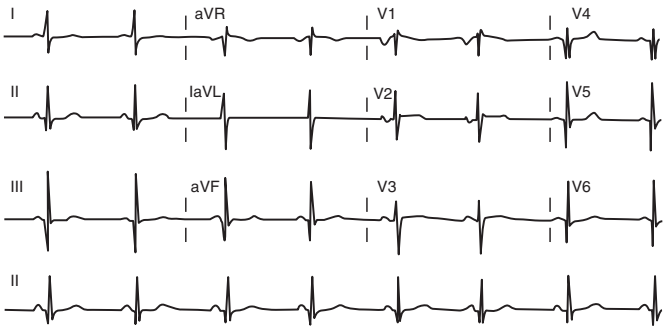

FIGURE C1-20 Surface ECG in a patient with hypertrophic cardiomyopathy. Note the deep narrow Q waves in the inferolateral leads. (From Issa Z et al: *Clinical arrhythmology and electrophysiology,* ed 2, Philadelphia, 2012, Saunders.)

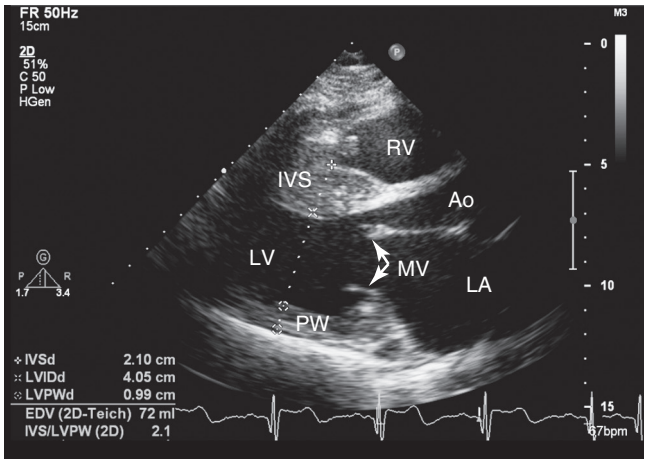

FIGURE C1-21 Echocardiographic appearance of hypertrophic cardiomyopathy. Parasternal long-axis view from a patient with hypertrophic cardiomyopathy demonstrating asymmetrical septal hypertrophy. The interventricular septum (marked by *arrow*) measures 2.1 cm; the posterior wall measures 0.99 cm. *Ao*, Aorta; *IVS*, interventricular septum; *LA*, left atrium; *LV*, left ventricle; *MV*, mitral valve; *PW*, posterior wall; *RV*, right ventricle. (From Issa Z et al: *Clinical arrhythmology and electrophysiology*, ed 2, Philadelphia, 2012, Saunders.)

- In individuals with pathogenic mutations who do not express the HCM phenotype, it is recommended to perform serial electrocardiogram (ECG), transthoracic echocardiogram (TTE), and clinical assessment at periodic intervals (12 to 18 months in children and adolescents and about every 5 years in adults), based on the patient's age and change in clinical status.

IMAGING STUDIES

- Chest x-ray may be normal or show cardiomegaly.
- Two-dimensional echocardiography is used to establish the diagnosis and assess the severity of obstruction when present. LV wall thickness will usually be >15 mm (although some may be genetically positive but phenotype negative), and most patients (up to 95%) will have asymmetric (ratio of septum thickness to left ventricular wall thickness >1.3:1) LV wall hypertrophy. Symmetric LV hypertrophy is less common. The septum is most often affected, followed by the left ventricular mid-cavity and apex. In addition, 25% to 30% of patients will manifest systolic anterior motion of the anterior leaflet of the mitral valve, causing obstruction of the LVOT and mitral regurgitation. Two-dimensional strain imaging echocardiography is useful for differentiation of HCM and cardiac amyloidosis from other causes of ventricular wall thickening. Up to 80% of HCM patients will also have diastolic dysfunction as evidenced by pulsed mitral valve inflow pattern and tissue Doppler.
- Cardiac MRI or cardiac CT may be of diagnostic value when echocardiographic studies are technically inadequate. MRI is also useful in identifying unusual segmental hypertrophy undetectable by standard echocardiography and can detect myocardial replacement fibrosis (an independent predictor of adverse cardiac outcomes and ventricular arrhythmias) using late gadolinium enhancement. CMR evaluation may be considered every 5 years or every 2 to 3 years in patients with progressive disease.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoid volume depletion: HCM patients experience decrease in stroke volume and consequent increase in left ventricular outflow gradient with exercise. This may lead to hypotension, dizziness, and syncope.
- Exercise restriction: the risk of sudden cardiac death is increased by exercise in HCM patients. Participation in competitive sports and intense physical activity should be avoided. As a part of a healthy lifestyle, low-intensity aerobic exercise is reasonable.
- Advise avoidance of alcohol: alcohol use (even in small amounts) may result in increased obstruction of the left ventricular outflow tract. Other stimulants such as cocaine and other sympathomimetic recreational drugs should also be avoided.

GENERAL Rx

- Therapy for HCM is directed at blocking the effect of catecholamines that can exacerbate the dynamic left ventricular outflow tract obstruction and avoiding vasodilator or diuretic agents that can also worsen the obstruction.
- Beta-blockers: the beneficial effects of beta-blockers on symptoms (principally dyspnea and chest pain) and exercise tolerance appear to be largely a result of a decrease in the heart rate with consequent prolongation of diastole and increased passive ventricular filling. By reducing the inotropic response, beta-blockers may also reduce myocardial oxygen demand and decrease the outflow gradient during exercise, when sympathetic tone is increased.
- The nondihydropyridine calcium channel blockers (verapamil, diltiazem) can also decrease left ventricular outflow obstruction through a mechanism similar to beta-blockers. However, they are mainly second-line agents used in patients who cannot tolerate beta-blockers as they have theoretic vasodilatory properties as well that may worsen severe outflow tract gradients.
- Disopyramide is an antiarrhythmic that is also a negative inotrope, resulting in further decrease in outflow gradient. It is sometimes used in combination with beta-blockers.
- Prophylactic antibiotics before dental, GI, and genitourinary procedures are no longer recommended according to the 2007 American Heart Association (AHA) guidelines.
- Avoid use of digitalis, intravenous inotropes, dihydropyridine calcium channel blockers, nitrates, and vasodilators.
- Diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers should be used with caution.
- Intravenous phenylephrine (or another pure vasoconstricting agent) is recommended for the treatment of acute hypotension in patients with obstructive HCM who do not respond to fluid administration.
- Implantable cardiac defibrillators (ICDs) are a safe and effective therapy in HCM patients prone to ventricular arrhythmias. In their practice guidelines, the major cardiology societies (AHA/ACC/HRS) give a strong recommendation (Class I) for ICD implantation in all patients with HCM who have had an episode of sustained ventricular tachycardia or fibrillation. In addition, they endorse the prophylactic placement of an ICD (Class IIa recommendation) for patients with one or

more of the major risk factors for sudden cardiac death (outlined in "Disposition").
- Dual-chamber pacing may provide symptomatic relief of symptoms attributable to LVOT obstruction and refractory to medical therapy.
- HCM patients are at an increased risk of atrial fibrillation (AF) as well as systemic thromboembolization. AF occurs in over 20% of the HCM population. AF is an important source of symptoms, morbidity, and mortality and correlates to a worse prognosis. AF therapy should aim for thromboembolic risk mitigation with a vitamin K antagonist (unless contraindicated) and symptom alleviation via rate or rhythm control.
- Fig EC1-22 describes management strategies for subgroups of patients within the broad HCM clinical spectrum.

DISPOSITION

HCM is not a static disease. Some adults may experience subtle regression in wall thickness, whereas others (~5% to 10%) paradoxically evolve into an end-stage cardiomyopathy resembling dilated cardiomyopathy, characterized by cavity enlargement, left ventricular wall thinning, and systolic dysfunction. Patients with HCM are at increased risk for sudden death, especially if onset of symptoms began during childhood. Severe left ventricular outflow obstruction at rest is also a strong, independent predictor of severe symptoms of heart failure and death. ICD implantation for primary prevention should be considered if patients (particularly the young) have any of the following high risk features:
- Personal history of sudden cardiac death or out of hospital cardiac arrest (major risk factor)
- Spontaneous sustained ventricular tachycardia or ventricular fibrillation (major risk factor)
- Family history of premature death in a first degree relative possibly caused by HCM
- Unexplained syncope
- Nonsustained ventricular tachycardia during Holter monitoring
- Substantial septal hypertrophy (>30 mm)
- Abnormal blood pressure response during exercise
- Increased delayed gadolinium enhancement on cardiac magnetic resonance imaging is suggested in some recent studies as a marker of increased SCD risk

REFERRAL

- Surgical treatment (septal myectomy involving resection of the basal septum) is now the gold standard for relieving outflow tract obstruction in patients with large outflow gradient (≥50 mm Hg) and moderate-severe symptoms unresponsive to medical therapy. The risk for sudden death from arrhythmias is not altered by surgery. When this operation is performed by experienced surgeons in tertiary referral centers, the operative mortality rate is <1%, and many patients are able to achieve near-normal exercise capacity after surgery. Mitral valvuloplasty or plication in combination with myectomy may be necessary in <5% of patients. Risks of surgery include AV nodal block, ventricular septal defect, and aortic regurgitation (AR).
- Septal ablation: as an alternative, nonsurgical reduction of the interventricular septum via alcohol septal ablation can be done in patients with HCM refractory to pharmacologic treatment, particularly in those who are not candidates for myectomy due to high surgical risk. This technique involves the injection of ethanol in a septal perforator branch of the left anterior descending coronary artery (Fig. C1-23), producing a controlled myocardial infarction of the interventricular septum, and thereby reducing septal mass and consequently the left ventricular outflow tract gradient. This method may lead to improvement in both subjective and objective measures of exercise capacity, but results are not as effective as surgery and are associated with a high incidence of heart block, requiring permanent pacing in approximately one fourth of patients and/or recurrence of obstruction and symptoms. This should be done only at centers with experienced operators.
- Refractory end-stage HF symptoms can be treated with LVAD, BiVAD, or heart transplant.

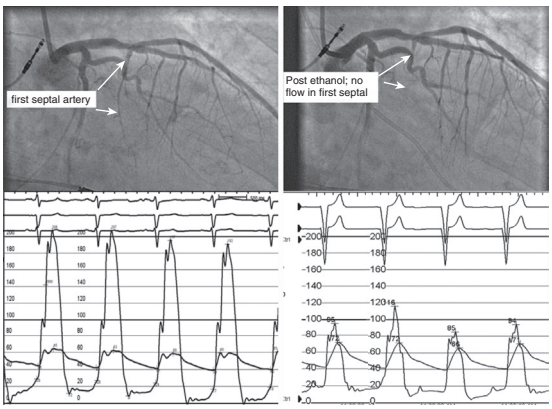

FIGURE C1-23 Septal ablation for obstructive hypertrophic cardiomyopathy. *Left*, Large pressure gradient between the left ventricle and aorta. A large proximal septal perforating artery is identified. *Right*, Following selective injection of ethanol, there is no flow within the septal artery and the gradient is dramatically reduced. (From Bonow RO et al: *Braunwald's heart disease—a textbook of cardiovascular medicine,* ed 9, St Louis, 2011, Saunders.)

PEARLS & CONSIDERATIONS

COMMENTS

- Clinical screening of first-degree relatives with two-dimensional echocardiography and ECG is indicated. Starting at the age of 12, periodic screening at 12- to 18-month intervals is recommended for children of patients with HCM and in competitive athletes. Periodic screening of first-degree adult family members not in competitive athletics is recommended at 5-yr intervals because hypertrophy may not be detected until the sixth decade of life. Genetic testing is not indicated in relatives of index patients who do not have a definite pathogenic mutation.
- Genetic counseling and screening is recommended in first-degree relatives of patients with HCM. Genetic screening of first-degree relatives can refine or eliminate the need for periodic clinical screening. At least 13 genes are known to cause HCM, among them: cardiac myosin binding protein-C, beta-myosin heavy chain, troponin T, troponin I, alpha tropomyosin, actin regulatory light chain, and essential light chain. Clinical predictors of positive genotype, such as the presence of ventricular arrhythmias, age at diagnosis, degree of left ventricular wall hypertrophy, and family history of HCM, may aid in patient selection for genetic testing and increase the yield of cardiac sarcomere gene screening. Currently a mutation can be identified in 40% to 60% of all cases, sporadic or familial.
- All HCM patients who wish to become pregnant should be given prenatal counseling about the risk of transmission (about 50%) to their offspring and should be followed at a tertiary care center that specializes in high-risk pregnancies. Most patients with HCM tolerate pregnancy well due to the higher circulating blood volume.
- The mortality rate in HCM is approximately 1% to 2% per yr.
- About one third of HCM patients will not have a resting or labile outflow gradient (i.e., nonobstructive form of HCM), and lethal ventricular arrhythmias can occur in the absence of obstruction or symptoms.
- Myocardial fibrosis is a hallmark of hypertrophic cardiomyopathy. Biomarkers of collagen metabolism such as serum C-terminal propeptide of type I procollagen (PICP) are significantly higher in mutation carriers without left ventricular hypertrophy and in subjects with overt hypertrophic cardiomyopathy than in controls, indicating that a probiotic state precedes the development of hypertrophy of fibrosis identifiable with cardiac MRI.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **MARC PAUL WAASE, M.D., Ph.D**

EVIDENCE

Abstract[1]

Impaired left ventricular systolic function (ILVSF) in hypertrophic cardiomyopathy (HC) is a risk factor for sudden death and a determinant of high mortality. We determined its prevalence, clinical parameters, long-term outcome, and pathologic findings of explanted hearts. We retrospectively analyzed 382 patients with HC; ILVSF was characterized by LV ejection fraction <50% at rest and was identified in 24 patients (6.3%). Patients with ILVSF were younger than patients with normal SF (43.5±14.1 vs 55.3±20.4 years, p = 0.001) and had larger LV end-diastolic cavity diameter (53.2±12.2 vs 43.8±6.2mm, p = 0.001), larger left atrium (51.2±6.5 vs 44.3±8mm, p <0.001), and lower fractional shortening (30.7±11.1% vs 45.5%±10.3%, p <0.001). A combined end point (heart failure, death, or heart transplantation) was considered. Median follow-up was 3 years (1.2 to 6.3). Fourteen patients with ILVSF (58.3%) had the end point compared to 3 (0.8%) with normal SF (p <0.001). In explanted hearts, fibrosis represented 30.5±12.5% of the left ventricle; we observed a direct correlation between fibrosis and ventricular dilation (r = 0.794, p = 0.001) and an inverse correlation between fibrosis and ejection fraction (r = –0.623, p = 0.023). Number and length density of small arterioles (<50 μm in diameter) were significantly decreased. In conclusion, ILVSF in HC has a poor prognosis and is associated with fibrosis and selective decreased development of small arterioles. Ⓐ

Evidence-Based Reference

Fernández A, et al.: Comparison of prevalence, clinical course, and pathological findings of left ventricular systolic impairment versus normal systolic function in patients with hypertrophic cardiomyopathy, *Am J Cardiol* 108:548–555, 2011. Ⓐ

SUGGESTED READINGS

Epstein AE et al.: ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: executive summary, *Heart Rhythm* 5(6):934, 2008.

Fifer MA, Vlahakes GJ: Management of symptoms in hypertrophic cardiomyopathy, *Circulation* 117:429, 2008.

Gersh BJ et al.: 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation/American Health Association Task Force on practice guidelines, *Circulation* 124:e783–e831, 2011.

Ho CY et al.: Myocardial fibrosis as an early manifestation of hypertrophic cardiomyopathy, *N Eng J Med* 363:552–563, 2010.

Maron BJ: Hypertrophic cardiomyopathy, a systematic review, *JAMA* 287:1308, 2002.

Maron BJ et al.: Genetics of hypertrophic cardiomyopathy after 20 years: clinical perspectives, *J Am Coll Cardiol* 60(8):705–715, 2012.

Maron BJ et al.: Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy, *JAMA* 298(4):405, 2007.

Maron MS et al.: Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy, *N Engl J Med* 348:295, 2003.

Montgomery JV, et al.: Relation of electrocardiographic pattern to phenotypic expression and clinical outcome in hypertrophic cardiomyopathy, *Am J Cardiol* 96:270, 2005.

Nagueh SF, Mahmarian JJ: Noninvasive cardiac imaging in patients with hypertropic cardiomyopathy, *J Am Coll Cardiol* 48:2410, 2006.

Nishimura RA, Holmes DR: Hypertrophic obstructive cardiomyopathy, *N Engl J Med* 350:1320, 2004.

Olivotto I et al.: Myofilament protein gene mutation screening and outcome of patients with hypertrophic cardiomyopathy, *Mayo Clin Proc* 83(60):630–638, 2008.

Sun JP et al.: Differentiation of hypertrophic cardiomyopathy and cardiac amyloidosis from other causes of ventricular wall thickening by two-dimensional strain imaging echocardiography, *Am J Cardiol* 103:411, 2009.

Wang L et al.: Narrative review: harnessing molecular genetics for the diagnosis and management of hypertrophic cardiomyopathy, *Ann Intern Med* 152:13, 2010.

Watkins H et al.: Inherited cardiomyopathies, *N Engl J Med* 364:1643–1656, 2011.

Wilson W et al.: Prevention of infectious endocarditis: guidelines from the American Heart Association, *Circulation* 116:1736, 2007.

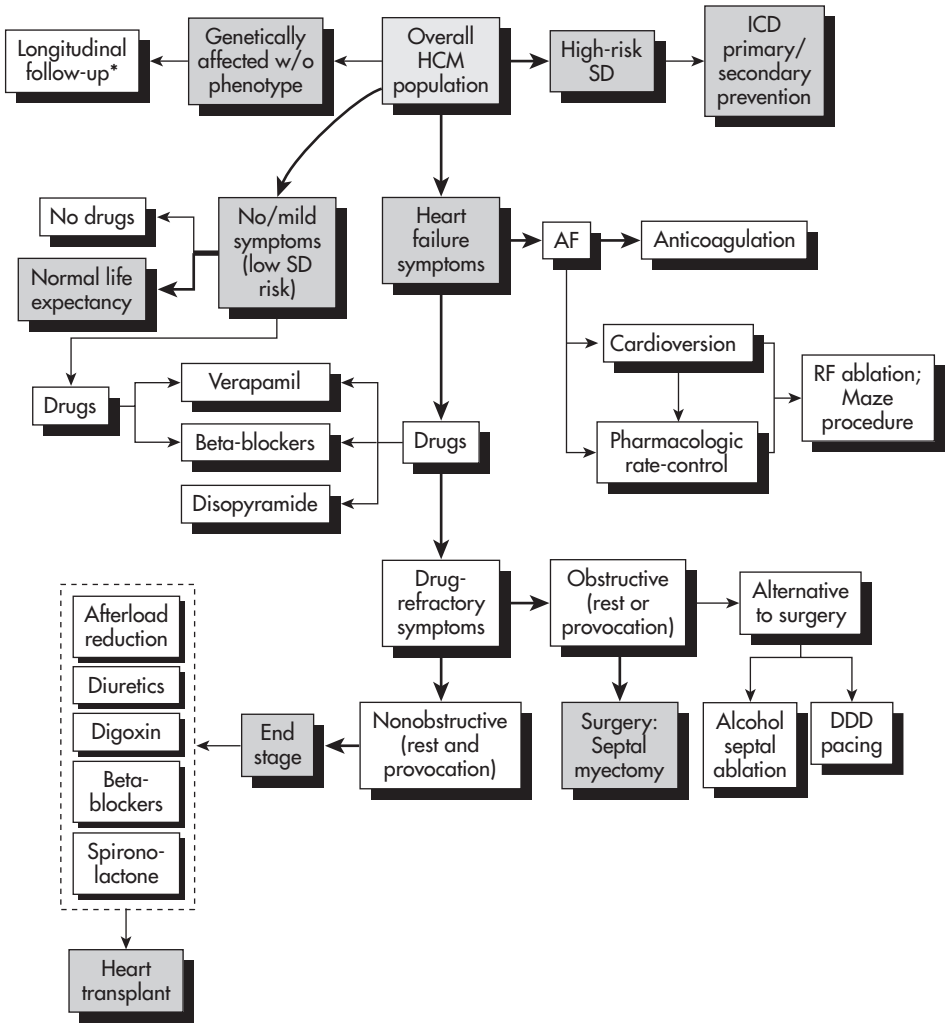

FIGURE EC1-22 Management strategies for subgroups of patients within the broad HCM clinical spectrum. *Generally no specific treatment or intervention indicated. *AF*, Atrial fibrillation; *DDD*, dual-chamber; *ICD*, implanted cardioverter-defibrillator; *RF*, radiofrequency; *SD*, sudden death. (From Bonow RO et al: *Braunwald's heart disease—a textbook of cardiovascular medicine*, ed 9, St Louis, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Restrictive cardiomyopathy refers to either an idiopathic or a systemic myocardial disorder (in the absence of ischemic, hypertensive, valvular, and congenital heart disease) characterized by restrictive filling (Fig. C1-24), normal or reduced left ventricular (LV) and right ventricular (RV) volumes, and normal or near normal systolic LV and RV function. Pathophysiologically, the heart muscle is abnormally stiff, resulting in decreased compliance, abnormal relaxation in diastole, and increased filling pressures. Except for primary nonhypertrophic cardiomyopathy and a few infiltrative diseases, restrictive cardiomyopathies are secondary.

ICD-9CM CODES

425.4 Other primary cardiomyopathies
425.9 Secondary cardiomyopathy, unspecified
277.39 Restrictive cardiomyopathy secondary to amyloidosis

ICD-10CM CODES

I42.5 Other restrictive cardiomyopathy
I42.8 Other cardiomyopathies
I43.1 Cardiomyopathy in metabolic diseases
I42.9 Cardiomyopathy, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Relatively uncommon cardiomyopathy, accounting for 5% of all primary myocardial diseases
- Most frequently caused by amyloidosis, myocardial fibrosis (following open heart surgery, transplantation or radiation).
- Patients classified as having "idiopathic" restrictive cardiomyopathy may have mutations in the gene for cardiac troponin I, and restrictive cardiomyopathy may represent an overlap with hypertrophic cardiomyopathy in many familial cases.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Restrictive cardiomyopathy presents with symptoms of progressive left-sided and right-sided heart failure:

- Fatigue, weakness (caused by low output as patients are unable to augment cardiac output by increasing heart rate without compromising ventricular filling).
- Progressively worsening exercise intolerance and dyspnea.
- Anginal chest pain can be seen (particularly in patients with amyloidosis) from myocardial compression of small coronaries.
- Palpitations (atrial fibrillation is common), dizziness or syncope (from orthostasis, heart block, or malignant arrhythmia).
- Edema, ascites, hepatomegaly, distended neck veins (from elevated heart pressures).
- Kussmaul's sign may be present (rise, or failure to fall, of the jugular venous on inspiration).
- On auscultation: murmurs of mitral or tricuspid regurgitation may be heard; an S3 may be present.
- Apical impulse may be palpable (can help distinguish it from constrictive pericarditis) and nondisplaced.

ETIOLOGY

Disease may be classified according to pathophysiologic processes:

Infiltrative:
1. Amyloidosis (most common overall)
2. Sarcoidosis (usually results in a dilated cardiomyopathy with regional wall motion abnormalities)

Noninfiltrative:
1. Idiopathic (familial subtypes may have genetic overlap with hypertrophic cardiomyopathy)
2. Scleroderma
3. Diabetic cardiomyopathy
4. Pseudoxanthoma elasticum

Storage diseases:
1. Hemochromatosis (unusual as it is commonly associated with a dilated cardiomyopathy)
2. Glycogen or other storage diseases (Gaucher, Hurler, Fabry—all rare)

Endomyocardial:
1. Endomyocardial fibrosis
2. Hypereosinophilic syndrome (Loeffler's)

1. Carcinoid heart disease
2. Radiation
3. Metastatic cancers
4. Drug related (anthracyclines, serotonin, ergotamine, busulfan, methysergide)

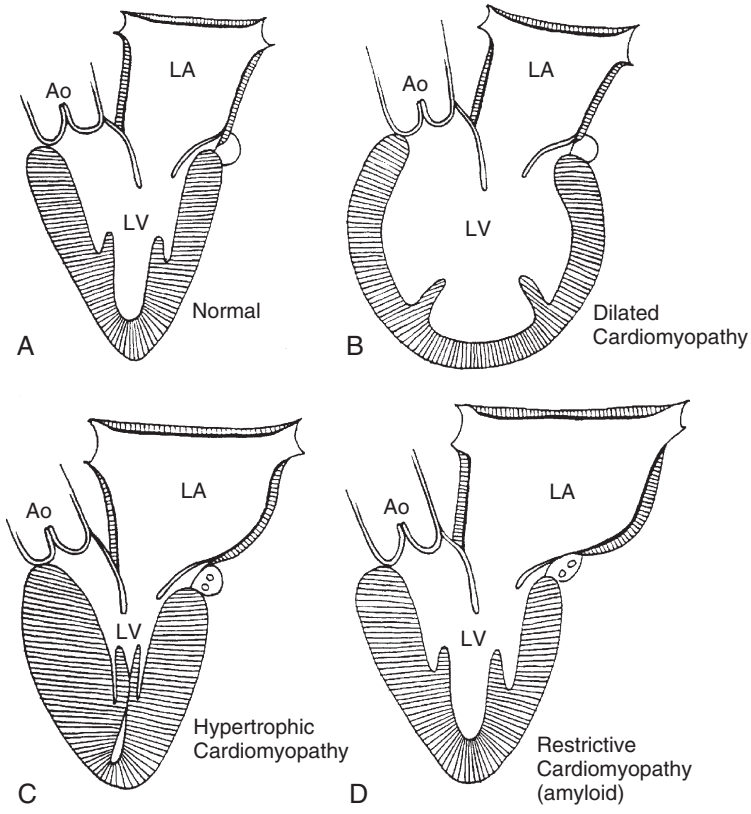

FIGURE C1-24 Cardiomyopathies. **A,** Normal. **B,** Dilated. **C,** Hypertrophic. **D,** Restrictive. *Ao*, Aorta; *LA*, left atrium; *LV*, left ventricle. (Modified from Roberts WC, Ferrans VJ: Pathologic anatomy of the cardiomyopathies. *Hum Pathol* 6:289–342, 1975.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Constrictive pericarditis (see Table EC1-6)
- Valvular dysfunction (especially aortic stenosis)
- Hypertrophic cardiomyopathy
- Hypertensive heart disease

WORKUP

- Blood count (to identify eosinophilia), iron studies, serum renal function studies, chest x-ray, ECG, echocardiogram.
- Cardiac catheterization, magnetic resonance imaging, and computed tomography (selected cases)
- Aspiration biopsy of subcutaneous fat to detect amyloidosis.
- Endomyocardial biopsy if diagnostic confirmation needed.
- Brain natriuretic peptide (BNP) serum levels: there is data suggesting that BNP levels are markedly elevated in restrictive cardiomyopathy but near normal in patients with constrictive pericarditis, despite nearly identical clinical and hemodynamic features, most likely resulting from the lack of myocardial stretching in constriction that is required for BNP release.

IMAGING STUDIES

- Chest x-ray:
  1. Ranges from normal cardiomediastinal silhouette to moderate cardiomegaly (primarily because of biatrial enlargement).
  2. Evidence of heart failure may be present.
  3. Presence of pericardial calcification favors alternate diagnosis of constrictive pericarditis.
- ECG:
  1. Nonspecific ST-T wave abnormalities are the most common finding. Voltage may be low in infiltrative etiologies such as amyloidosis.
  2. Frequent atrial and ventricular ectopy are often present. Atrial fibrillation may be present.
  3. High-degree atrioventricular block, intraventricular conduction delay may be seen in advanced cases.
- Echocardiogram (Fig. C1-25):
  1. Biatrial enlargement almost always present.
  2. Wall thickness depends on etiology; often thickened in infiltrative disease such as amyloidosis.
  3. Myocardial appearance may be altered (speckled pattern suggestive of infiltration).
  4. Ventricular chamber sizes and systolic function are often normal or reduced.
  5. Echo Doppler shows evidence of diastolic dysfunction. Tissue Doppler demonstrates low mitral annular velocities.
- Cardiac catheterization:
  1. Characteristic hemodynamic finding is a dip and plateau, or square-root sign in the left ventricular tracing, where deep and rapid decline in ventricular pressure at the onset of diastole is immediately followed by rapid rise and plateau in early diastolic phase. To distinguish restrictive cardiomyopathy from constrictive processes (Fig. C1-26):

     Constrictive: Usually involves both ventricles and leads to equalization of diastolic pressures between all four cardiac chambers to within 5 mm Hg. There is a discordance in RV and LV pressures generated during inspiration, which is due to increased ventricular interdependence and decreased left atrial filling (caused by a decreased gradient in inspiration between the pulmonary veins, which are outside the constrictive process and the left atrium).

     Restrictive cardiomyopathy: Impairs the left ventricle more than the right, often with left-sided end-diastolic pressures of 5 mm Hg greater than the right. The presence of increased pulmonary arterial systolic pressures is also suggestive of restrictive disease. Simultaneous RV and LV pressure tracings demonstrate concordant patterns during the respiratory cycle.
- Cardiac computed tomographic scan may be helpful to identify a thickened and calcified pericardium, consistent with constrictive pericarditis.
- Cardiac magnetic resonance imaging (CMRI) may also be useful to distinguish restrictive cardiomyopathy from constrictive pericarditis (thickness of the pericardium greater than 4 mm in the latter). CMRI is particularly helpful in the diagnosis of the amyloid or sarcoid variants and may have value in other variants as well. Late gadolinium enhancement can be seen with infiltrative diseases.

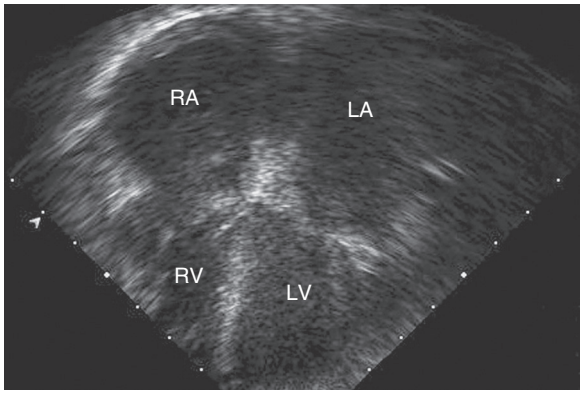

FIGURE C1-25 Echocardiogram of a patient with restrictive cardiomyopathy. The optical four-chamber view shows the markedly enlarged right and left atria, compared to the normal-sized left and right ventricular chambers. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Congestive symptoms may respond to dietary sodium restriction (<2 g/day).

ACUTE GENERAL Rx

Treatment of volume overload and heart failure symptoms with diuretic therapy.

CHRONIC Rx

- Treatment involves management of the underlying disease if it exists:
  1. Hemochromatosis may respond to repeated phlebotomy and iron chelators to decrease iron deposition in the heart.
  2. Sarcoidosis may respond to corticosteroid therapy.
  3. Primary amyloidosis may respond to antiplasma cell therapy with chemotherapeutics (usually melphalan) and steroids. Autologous bone marrow biopsy, if EF is >40%, may also be indicated.
  4. Eosinophilic cardiomyopathy may respond to corticosteroid and cytotoxic drugs.
  5. There is no effective therapy for other causes of restrictive cardiomyopathy.
- Overall, the goal of treatment is to reduce symptoms by decreasing filling pressures while preserving cardiac output. Since there is currently no drug available to specifically act on myocardial relaxation, therapy centers on low-dose diuretics to lower the preload.
- Beta-blockers or calcium channel blockers have not been demonstrated to improve symptoms or alter the course of disease.
- ACE inhibitors (or angiotensin receptor blockers [ARBs]) and vasodilators should be avoided in patients with amyloidosis as they are poorly tolerated. Even small doses can trigger profound hypotension (probably due to associated autonomic neuropathy).
- Atrial fibrillation is common and patients with it or with a history of embolization should be anticoagulated. Tachycardia (of any cause) is poorly tolerated and a common cause of decompensation. Rate control is of paramount importance. Cardioversion in case of rapid atrial fibrillation should be considered. Of note, digoxin should be used with caution as it is potentially arrhythmogenic (particularly in patients with amyloidosis).
- Fibrosis of the cardiac conduction system may result in complete heart block presenting as dizziness or syncope (especially in amyloidosis) and pacemaker implantation may be required. The course of restrictive cardiomyopathy is variable and depends on the underlying etiology. Death usually results from heart failure or arrhythmias, and interventions aimed at addressing these are recommended.
  1. For the amyloid variant, an implantable cardiac defibrillator offers little prophylactic benefit beyond the ability to pace as the cause of sudden cardiac death is usually electromechanical disassociation.

DISPOSITION

Prognosis varies with the etiology of the cardiomyopathy but is poor overall as disease is rarely detected before advanced stages.

REFERRAL

Cardiac transplantation can be considered in patients with refractory symptoms and idiopathic or familial restrictive cardiomyopathies.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Restrictive Cardiomyopathy (Patient Information)

AUTHOR: **BARRY FINE, M.D., Ph.D**

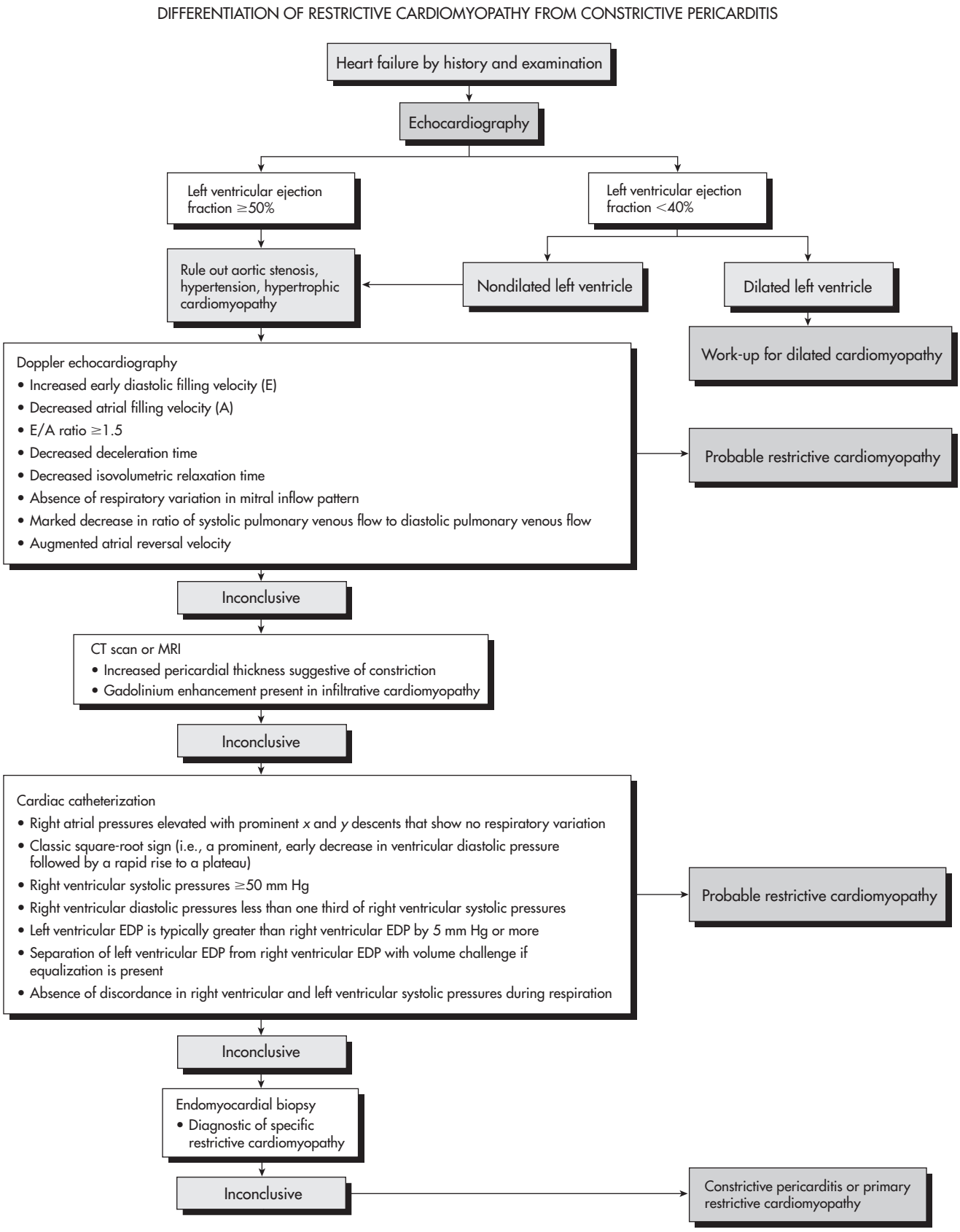

FIGURE C1-26 Differentiation of restrictive cardiomyopathy from constrictive pericarditis. *CT*, Computed tomography; *MRI*, magnetic resonance imaging; *EDP*, end-diastolic pressure. (From Pereira NL, Dec GW: Restrictive and infiltrative cardiomyopathies. In Crawford MH et al: *Cardiology,* Philadelphia, 2010, Elsevier.)

SUGGESTED READINGS

Falk RH: Diagnosis and management of the cardiac amyloidosis, *Circulation* 112:2047, 2005.

Katritsis D et al.: Primary restrictive cardiomyopathy: clinical and pathologic characteristics, *J Am Coll Cardiol* 18(5):1230, 1991.

Kushwaha SS et al.: Restrictive cardiomyopathy, *N Engl J Med* 336:267, 1997.

Leya FS et al.: The efficacy of brain natriuretic peptide levels in differentiating constrictive pericarditis from restrictive cardiomyopathy, *J Am Coll Cardiol* 45(11):2005, 1900.

Maron BJ et al.: Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention, *Circulation* 113:2006, 1807.

TABLE EC1-6 Differentiation between Restrictive Cardiomyopathy and Constrictive Pericarditis

Type of Evaluation	Restrictive Cardiomyopathy	Constrictive Pericarditis
Physical examination	Kussmaul sign present Apical impulse may be prominent Regurgitant murmurs are common	Kussmaul sign may be present Apical impulse usually not palpable Pericardial knock may be present Pulsus paradoxus may be present
Electrocardiography	Low QRS voltage (especially in amyloidosis) Pseudoinfarction pattern Bundle branch blocks AV conduction disturbances Atrial fibrillation	Low QRS voltage Repolarization abnormalities
Chest radiography		Calcification of the pericardium may be present
Echocardiography	Marked enlargement of the atria Increased wall thickness (especially in amyloidosis) Valvular thickening (especially in hypereosinophilia)	Atria usually of normal size Normal wall thickness Pericardial thickening may be seen
Doppler echocardiography	Restrictive mitral inflow (dominant E wave with short deceleration time) No significant variation of transvalvular velocities with respiration (<10%) Reversal of forward flow in hepatic veins during inspiration Low tissue Doppler velocities	Restrictive mitral inflow (dominant E wave with short deceleration time) Increased velocity of RV filling and decreased velocity of LV filling with inspiration; opposite with expiration; variation in velocity exceeds 15% Reversal of forward flow in hepatic veins during expiration High tissue Doppler velocities
Cardiac catheterization	Prominent atrial x and y descents (w sign) Dip-and-plateau appearance of ventricular diastolic pressure Diastolic pressures increased but not equalized (LV diastolic pressure higher than RV diastolic pressure)	Prominent atrial x and y descents (w sign) Dip-and-plateau appearance of ventricular diastolic pressure Increase and equalization of diastolic pressures Discordance of RV and LV peak systolic pressures (with inspiration, RV systolic pressure increases and LV systolic pressure decreases)
Endomyocardial biopsy	May reveal specific cause of restrictive cardiomyopathy	No specific findings on endomyocardial biopsy Pericardial biopsy may reveal abnormality
Computed tomography, magnetic resonance imaging	Late gadolinium myocardial enhancement in certain conditions	Pericardial thickening >4 mm
Laboratory testing	BNP is elevated	BNP may be normal to slightly elevated

AV, Atrioventricular; *BNP*, brain natriuretic peptide; *LV,* left ventricular; *RV,* right ventricular.
From Andreoli TE et al [eds]: *Andreoli and Carpenter's Cecil essentials of medicine*, ed 8, Philadelphia, 2010, Saunders.

BASIC INFORMATION

DEFINITION

Cardiorenal syndrome (CRS) is a pathophysiologic disorder in which acute or chronic dysfunction of the heart or kidneys can induce acute or chronic dysfunction of the other organ. Another definition proposed by the National Heart, Lung, and Blood Institute (NHLBI) is one in which therapy to relieve congestive symptoms of heart failure is limited by progressive renal insufficiency. There are five types of CRS:

Type 1: Acute cardiac dysfunction leading to acute kidney injury

Type 2: Chronic heart failure leading to renal dysfunction

Type 3: Acute kidney injury leading to or resulting in acute cardiac dysfunction

Type 4: Chronic kidney disease (CKD) leading to cardiac dysfunction

Type 5: Systemic conditions that cause both cardiac and renal dysfunction

This section will focus on CRS types 1 and 2.

ICD-9CM CODES

404 Cardiorenal syndrome

ICD-10CM CODES

I13 Hypertensive heart and renal disease

I13.0 Hypertensive heart and renal disease with (congestive) heart failure

I13.2 Hypertensive heart and renal disease with both (congestive) heart failure and renal failure

I17.8 Other renal failure

EPIDEMIOLOGY & DEMOGRAPHICS

- CKD is present in 20% to 67% of patients with congestive heart failure (CHF).
  1. Women, the elderly, whites, and patients with diabetes or systolic blood pressure >160 mm Hg have an increased incidence.
  2. In general terms, mortality is increased in patients with heart failure who have a reduced glomerular filtration rate (GFR)
  3. Patients with chronic kidney disease have an increased risk of both atherosclerotic heart disease and heart failure.
  4. Cardiovascular disease is responsible for about 50% of deaths in patients with CKD
- 20%-30% of patients who are treated for acute or chronic CHF will develop acute kidney injury.
  1. In patients with acute CHF, the severity of acute kidney injury is increased with decreased left ventricular systolic function and baseline CKD.
  2. Only 9% of patients with acute heart failure in the ADHERE trial had normal renal function with GFR >90 ml/min/1.73 m^2.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute/subacute decompensated heart failure (ADHF)
  1. Clinical symptoms:
     1. Dyspnea with exertion or at rest
     2. Orthopnea
     3. Paroxysmal nocturnal dyspnea
     4. Right upper quadrant pain
  2. Vital signs:
     1. Sinus tachycardia
     2. Hypertension or hypotension in the setting of a low cardiac output state
     3. Elevated respiratory rate
     4. Narrow pulse pressure
     5. Pulsus alternans: poor prognostic indicator
  3. Physical exam findings:
     1. Elevated jugular venous pressures in the neck
     2. Peripheral edema
     3. Third heart sound (S3)
     4. Respiratory crackles
     5. Abdominal ascites
     6. Hepatomegaly and splenomegaly
     7. Scrotal edema
- Chronic heart failure
  1. Clinical symptoms:
     1. Dyspnea
     2. Fatigue
     3. Anorexia: poor prognostic indicator
  2. Vital signs:
     1. Similar to ADHF, but may not have sinus tachycardia, and may have hypotension associated with a low cardiac output state.
  3. Physical exam findings:
     1. Similar to ADHF, but may lack respiratory crackles reflecting the rapidity of the collection of fluid. In addition, in chronic heart failure, the pulmonary vasculature becomes adept at storing large fluid volumes within the alveoli rather than the total volume of fluid
- These findings of heart failure will be associated with laboratory findings of kidney disease (discussed later) or in extreme cases physical exam findings of severe kidney disease such as asterixis, uremic frost, uremic smell, and uremic pericarditis, etc.

ETIOLOGY

The etiology of CRS can be divided into four mechanisms (Figs. EC1-27 and C1-28):

- Reduced renal perfusion
  1. Is a common cause of CRS type 1 (acute CHF resulting in acute kidney injury)
  2. Loop diuretic therapy can lead to reduced ventricular preload, which can result in as much as 20% reduction in cardiac output.
- Increased renal venous pressure
  1. Can occur secondary to elevated central venous pressure or elevated intraabdominal pressure
  2. The frequency of worsening kidney function is lowest in patients who have a CVP less than 8 mm Hg.
  3. An increase in GFR can occur following diuretic therapy, which is most likely mediated by a reduction in renal venous pressure and/or a reduction in right ventricular dilation.
- Right ventricular dilation and dysfunction
  1. May result in increased central venous pressures, which results in increased renal venous pressures and therefore a reduced GFR.
  2. Right ventricular dilation and dysfunction begets reduced left ventricular filling and therefore poor forward flow to the kidneys.
  3. Therefore right ventricular dilation and dysfunction can lead to renal dysfunction via both increased renal venous pressure and decreased renal perfusion pressure.
- Neurohormonal
  1. Caused by activation of the renin-angiotensin-aldosterone system, sympathetic nervous system, antidiuretic hormone, and endothelin-1, which results in both increased salt and water retention and systemic vasoconstriction leading to decreased renal perfusion
  2. The activation of the above systems overrides the vasodilatory effects of natriuretic peptides, nitric oxide, prostaglandins, and bradykinin.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Before making the diagnosis of CRS, it is necessary to rule out other causes of renal failure such as:
  1. Prerenal causes
     1. Volume depletion (overdiuresis, gastrointestinal losses, or vomiting)
     2. Fluid overload states besides CHF (cirrhosis, nephrotic syndrome)
  2. Intrinsic renal disease
     1. Acute tubular necrosis
     2. Glomerular disease
        - Nephrotic and nephritic syndromes
  3. Postrenal causes
     1. Obstruction

WORKUP

- The medical history will be consistent with symptoms of CHF and may include dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, increasing abdominal girth, or weight gain. Additionally, laboratory results will show signs of kidney injury.
- Diagnostic workup includes chest radiograph, echocardiogram, renal ultrasound, and laboratory tests (see next section)

LABORATORY TESTS

- Serum creatinine
  1. Patients with CRS whose creatinine levels were elevated at least 0.3 to 0.5 mg/dl had an odds ratio of 1.48 for mortality compared with those whose creatinine levels were elevated less than 0.3 mg/dl.
     1. If creatinine levels increased by >0.5 mg/dl, the odds ratio for mortality increased to 3.22.
- Estimated glomerular filtration rate (eGFR)
  1. Similar results to that of creatinine, but is more accurate for diagnosing elderly patients with less muscle mass
- Blood urea nitrogen

INTERACTIONS BETWEEN THE HEART AND THE KIDNEY IN CARDIORENAL SYNDROME

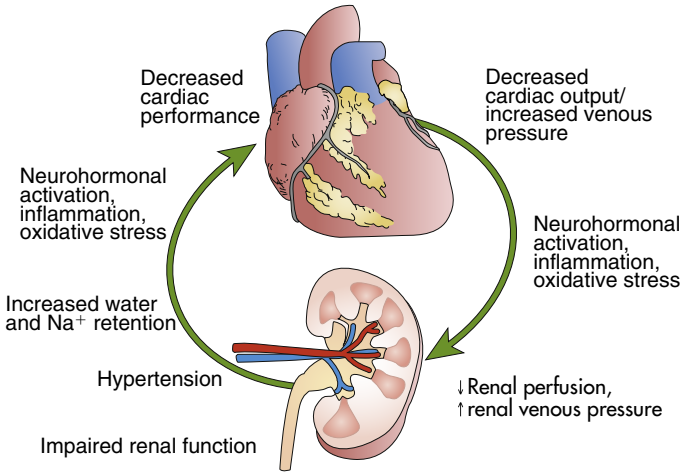

FIGURE C1-28 Interactions between the heart and the kidney in cardiorenal syndrome. (From Pereira NL, Dec GW: Special problems in chronic heart failure. In Crawford MH et al [eds]: *Cardiology,* Philadelphia, 2010, Elsevier.)

1. Admission levels >43 mg/dl are associated with a higher in-hospital mortality rate in patients with CRS

- Cystatin C
  1. Better correlation to GFR than serum creatinine
- Beta natriuretic peptide (BNP)
  1. Patients with initial admission values exceeding 480 pg/ml had a 51% chance of death, hospital readmission, or emergency room visit within 6 months compared with patients whose levels were <230 pg/ml.
- It can be difficult to distinguish between CKD and impaired kidney function due to cardiorenal syndrome. Some patients have both underlying CKD and CRS. Findings that support underlying CKD include significant proteinuria (>1000 mg/day), urine sediment with hematuria and/or pyuria and cellular casts, and/or small kidneys on ultrasound.

IMAGING STUDIES

- Chest radiograph
  1. May show signs of fluid overload, such as pulmonary edema, pulmonary effusions, or fluid in the fissure
- Echocardiogram
  1. Will help to determine if there is underlying systolic or diastolic dysfunction and/or significant valvular disease
- Renal ultrasound
  1. Can help to distinguish between acute and chronic kidney disease, and can help rule out obstruction as a cause of worsening renal function

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Fluid restriction
- Hemodialysis/ultrafiltration
  1. Can be used if there is no response to pharmacologic treatment or if the use of pharmacologic agents is limited secondary to hemodynamics or worsening laboratory values
- Left ventricular assist device/cardiac resynchronization therapy (CRT)
  1. Can be used to improve forward flow/cardiac output and cardiac dyssynchrony. Use of CRT has been shown to improve ejection fraction by 7% and improve CHF symptoms in patients who have NYHA class II heart failure and above with ejection fractions ≤35% with a left bundle branch block morphology QRS duration greater than 150 ms.

ACUTE GENERAL Rx

There is no treatment that directly improves eGFR/serum creatinine level, but an increase in cardiac output can reduce the incidence of the four mechanisms of CRS listed previously.

- Diuretics
  1. Fluid off-loading helps patients return to their ideal position on the Frank-Starling curve.
  2. Removal of fluid will improve renal perfusion pressure by decreasing central venous pressure, therefore decreasing renal venous pressure and reducing right ventricular dilation along with improvement in right ventricular systolic function that will then lead to improved left ventricular performance.
  3. May need high doses to achieve success because of decreased diuretic responsiveness as eGFR decreases
- Inhibitors of the renin-angiotensin-aldosterone system
  1. Includes angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and aldosterone antagonists, along with newer renin inhibitors
     1. Use is limited by worsening renal function, especially when serum creatinine is above 2.5
     2. Allows for decreasing use of diuretic therapy
- Vasodilators
  1. Includes nitroglycerin, nitroprusside, and nesiritide
     1. Work by increasing renal perfusion pressure by placing patients more favorably on the Starling curve and improving forward flow/cardiac output
- Inotropic agents
  1. Includes dobutamine, dopamine, and milrinone
  2. Are used in treatment of cardiogenic shock as well as in low cardiac output states with normal blood pressures, and work by improving cardiac output, resulting in better renal perfusion pressures via their vasodilatory properties
  3. Caution: dobutamine and milrinone can lower blood pressures.
- The use of mechanical methods of fluid removal such as extracorporeal ultrafiltration (UF) may be needed to achieve control of fluid retention, particularly in patients who become resistant and/or refractory to diuretic therapy. UF removes salt and water isotonically by driving the patient's blood through a highly permeable filter via an extracorporeal circuit in an arteriovenous or venovenous mode. With slow continuous UF, the patient's intravascular fluid volume remains stable as fluid shifts from the extravascular to intravascular space without affecting cardiac hemodynamics.

DISPOSITION

Is based upon improvement of patient's volume status as creatinine levels return to baseline

REFERRAL

Consultation by a cardiologist and nephrologist are recommended.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Acute Kidney Injury (Related Key Topic)
Heart Failure (Related Key Topic)

AUTHORS: **PHILLIP RUISI, D.O.,** and **ARAVIND RAO KOKKIRALA, M.D.**

SUGGESTED READINGS

Bart BA et al.: Ultrafiltration in decompensated heart failure with cardiorenal syndrome, *N Engl J Med* 367:2296–2304, 2012.

Bock JS, Gottlieb SS: Cardiorenal syndrome: new perspectives, *Circulation* 121:2592–2600, 2010.

Heywood JT et al.: High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database, *J Card Fail* 13:422–430, 2007.

Ronco C et al.: Cardiorenal syndrome, *J Am Coll Cardiol* 52:1527, 2008.

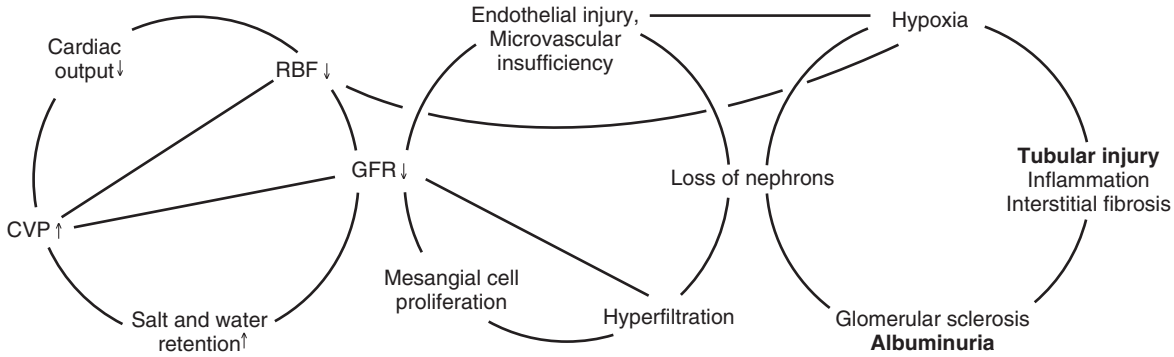

FIGURE EC1-27 Integrated pathways of the cardiorenal syndrome in HF. (From Damman K et al: The cardiorenal syndrome in heart failure, *Prog Cardiovasc Dis* 54:144–153, 2011.)

BASIC INFORMATION

DEFINITION

Light-headedness, dizziness, presyncope, or syncope in a patient with carotid sinus hypersensitivity is defined as carotid sinus syndrome (CSS). Carotid sinus hypersensitivity is the exaggerated response to carotid stimulation resulting in bradycardia, hypotension, or both. CSS is often considered a variant of neurocardiogenic syncope. The 2013 European Guidelines (ESC) define CSS as syncope with reproduction of symptoms during carotid sinus massage of 10-second duration. There are two components of CSS: cardioinhibitory and vasodepressor.

SYNONYMS

Carotid sinus syncope
CSS
Carotid sinus hypersensitivity

ICD-9CM CODES

337.0	Idiopathic peripheral autonomic neuropathy
780.2	Syncope or collapse

ICD-10CM CODES

G90.01	Carotid sinus syncope
R55	Syncope and collapse

EPIDEMIOLOGY & DEMOGRAPHICS

- Carotid sinus hypersensitivity accounts for 1% of syncopal episodes.
- Carotid sinus hypersensitivity is frequently associated with atherosclerosis and diabetes mellitus.
- Incidence increases with age, with an average age of onset at 61 to 74 yr. Fig. C1-29 illustrates age distribution of the patients with carotid sinus syndrome.
- Men are affected more often than women (2:1).
- CSS is rarely found in patients younger than 50 yr.

MECHANISM

- The carotid sinus is located in the internal carotid artery.
- There is a reflex loop between the mechanoreceptors of the carotid sinus and the vagal nucleus in the midbrain.
- There is an exaggerated cardioinhibitory and vasodepressor reaction caused by decreased sympathetic and increased parasympathetic outflow to the heart and vasculature, respectively.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Usually associated with sudden neck movements, neck palpation, shaving, or tight-fitting collars
- Usually associated with prodrome of nausea, warmth, pallor, or diaphoresis
- Light-headedness or presyncopal symptoms
- Syncope

Properly performed carotid sinus massage (CSM) at the bedside is diagnostic. European Society of Cardiology recommends carotid sinus massage as part of the exam in patients with syncope of unknown etiology and age over 40. This maneuver can elicit three types of responses in patients with carotid sinus hypersensitivity (see "Diagnosis").

1. CSM should be performed with the patient in the supine and upright position while monitoring the patient's blood pressure by cuff and heart rate by ECG.
2. CSM should be performed on only one carotid artery at a time.
3. Vigorous circular pressure is applied over one carotid artery at the level of the cricoid cartilage for 10 seconds and repeated on the opposite side if no effect is produced.
4. Contraindications to CSM include the presence of carotid artery bruits, documented carotid artery stenosis >70%, history of stroke or transient ischemic attack <3 mo, history of myocardial infarction <6 mo, history of serious ventricular arrhythmia, or prior carotid endarterectomy.
5. Complications of transient visual disturbance or transient paresis occur in <1% of patients.
6. False-positive results with carotid sinus massage may be relatively common in the elderly population. Thus alternative explanations for syncope should be investigated prior to attribution of symptoms to carotid sinus hypersensitivity.

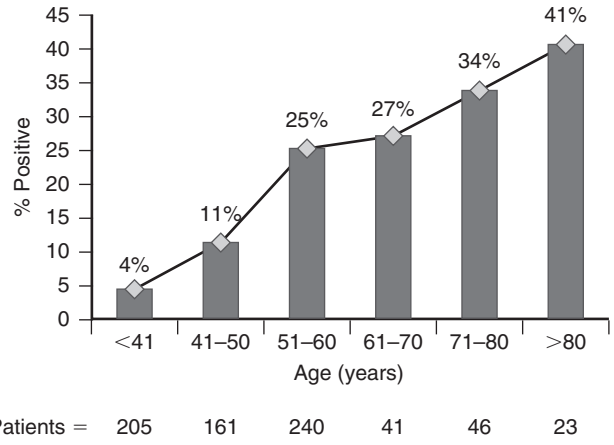

FIGURE C1-29 Age distribution of patients with carotid sinus syndrome. (From Puggioni E et al: Results and complications of the carotid sinus massage performed according to the "method of symptoms," *Am J Cardiol* 89:599–601, 2002.)

ETIOLOGY

- Idiopathic
- Head and neck tumors (e.g., thyroid)
- Significant lymphadenopathy
- Carotid body tumors
- Prior neck surgery

DIAGNOSIS

- The diagnosis of CSS is made when carotid sinus hypersensitivity is demonstrated by CSM and no other cause of syncope is identified.
- CSM can elicit three types of responses diagnostic of carotid sinus hypersensitivity:
  1. Cardioinhibitory type: CSM producing (1) asystole for at least 3 sec in the absence of symptoms or (2) reproduction of symptoms occurring with a decline in heart rate of 30% to 40% or asystole of up to 2 sec in duration. Symptoms should not recur when CSM is repeated after atropine infusion.
  2. Vasodepressor type: CSM producing (1) a decrease in systolic blood pressure of 50 mm Hg in the absence of symptoms or 30 mm Hg in the presence of neurologic symptoms; (2) no evidence of asystole; or (3) neurologic symptoms that persist after infusion of atropine.
  3. Mixed type: CSM producing both types of responses.

DIFFERENTIAL DIAGNOSIS

All causes of syncope

WORKUP

- CSS is a diagnosis of exclusion.
- Exclude other causes of syncope or presyncope: detailed history, physical examination including orthostatic vital signs, ECG. Other tests should be considered depending on the clinical setting.

TREATMENT

NONPHARMACOLOGIC THERAPY

Reassurance and education are important. Avoid applying neck pressure from tight collars, shaving, or rapid head turning.

ACUTE GENERAL Rx

Treatment will vary according to the type of carotid hypersensitivity response and symptoms present (see "Chronic Rx").

CHRONIC Rx

Therapy is divided into three classes: medical, surgical (carotid denervation), and cardiac pacing.

- Surgical therapy has been largely abandoned except in cases of compressing tumors or masses responsible for CSS.
- For infrequent and mildly symptomatic carotid sinus hypersensitivity of either the cardioinhibitory or vasodepressor type, treatment is generally not necessary.
- Cardiac pacing: 2008 ACC/AHA/HRS device guidelines recommend pacing in patients with recurrent syncope in spontaneous occurring carotid sinus stimulation, in whom carotid sinus pressure induces ventricular asystole of more than 3 seconds.

Permanent pacing may be considered in patients with recurrent syncope of unexplained origin, and a hypersensitive cardioinhibitory response of 3 seconds or more.

Permanent pacing is not indicated for carotid sinus hypersensitivity with no, or only vague, symptoms.

For symptomatic patients with a vasodepressor response to CSM:

- No medical treatment is proven to be effective
- Drugs, such as vasodilators, that would worsen the response should be discontinued or reduced if feasible
- Permissive hypertension
- Increased fluids (≥2 L) and salt intake (>6 g/day)
- Sympathomimetics: midodrine 2.5 to 10 mg tid (major side effect in urinary retention in elderly males)
- Serotonin-specific reuptake inhibitors
- Fludrocortisone
- Elastic knee-high or thigh-high stockings
- Carotid sinus denervation

For symptomatic patients with CSS with a mixed response to CSM:

- Combination of dual-chamber permanent pacemaker and agents used to treat vasodepressor response

DISPOSITION

- Up to 50% of the patients have recurrent symptoms.
- No increased mortality rate in patients with idiopathic CSS compared with the general population.

REFERRAL

Cardiology referral is indicated if cardiac testing, such as tilt-table test, or pacemaker placement is being considered.

Neurology referral is indicated if neurologic causes of syncope are suggested by history or physical examination findings.

PEARLS & CONSIDERATIONS

The most common type of CSS is cardioinhibitory, followed by mixed and vasodepressor responses.

Driving restrictions in the 2009 ESC syncope update and 2006 AHA/ACCF consensus document on syncope are stratified according to whether patients have mild or severe syncope.

Mild syncope is defined as infrequent mild symptoms (usually without syncope), clear precipitating causes (usually standing), warning signs, and infrequent occurrence. For patients with mild sinus hypersensitivity, no driving restrictions are recommended for private or commercial driving.

Severe syncope is classified as severe symptoms (with syncope), without warning and in any position, no clear precipitating causes, and/or frequent occurrence. For patients with severe hypersensitivity, all driving is prohibited. If symptoms are controlled, driving is permitted 1 to 6 months after, based on the modality of treatment.

COMMENTS

Prognosis depends on the underlying cause.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Syncope (Patient Information)
Orthostatic Hypotension (Related Key Topic)
Syncope (Related Key Topic)

AUTHOR: **BARRY FINE, M.D., Ph.D.**

SUGGESTED READINGS

AHA/ACCF: Scientific statement on the evaluation of syncope, *J Am Coll Cardiol* 47(2):473, 2006.

Grubb BP: Clinical practice: neurocardiogenic syncope, *N Engl J Med* 352:1004, 2005.

Kerr SR et al.: Carotid sinus hypersensitivity in asymptomatic older persons: implications for diagnosis of syncope and falls, *Arch Intern Med* 166(5):515, 2006.

Moya A et al.: Guidelines for the diagnosis of syncope (version 2009): the task force for the diagnosis and management of syncope of the European Society of Cardiology (ESC), *Eur Heart J* 30:2631, 2009.

BASIC INFORMATION

DEFINITION

Carotid stenosis is narrowing of the arterial lumen within the carotid artery that is typically a result of atherosclerosis.

SYNONYMS

Atherosclerotic disease of the carotid artery

ICD-9CM CODES
433.1 Carotid stenosis
ICD-10CM CODES
I65.29 Occlusion and stenosis of unspecified carotid artery

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 2.2 to 8/1000 persons per yr
PREVALENCE: 1. 1 to 77/100,000 persons; it is estimated that 5/1000 persons aged 50 to 60 yr and 100/1000 persons >80 yr have carotid stenosis >50%. (*Note:* The incidence of carotid stenosis is unknown as screening is not routine. However, the incidence of transient ischemic attack [TIA], a common presenting symptom of carotid stenosis, is well known.)
PREDOMINANT SEX AND AGE: Male/female ratio of 2:1; more common in whites than African Americans and Asians
PEAK INCIDENCE: Peak incidence is between 50 and 60 yr.
GENETICS: Multifactorial; twin studies (monozygous versus dizygous) suggest a familial influence
RISK FACTORS: Hypertension, dyslipidemia, diabetes mellitus, and smoking are the four major risk factors.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Patients with carotid stenosis are often asymptomatic, but many have the presence of a carotid bruit or TIA.

- Carotid bruit: In general, the presence of a carotid bruit is a better indicator of generalized atherosclerosis and as such, is a better predictor of ischemic heart disease than future stroke.
- TIA: Carotid stenosis is classically heralded by ipsilateral transient monocular blindness (amaurosis fugax), contralateral numbness or weakness, contralateral homonymous hemianopsia, aphasia, or syncope (if bilateral disease is present).

ETIOLOGY

- Atherosclerosis (most common by far).
- Aneurysm.
- Arteritis.
- Carotid dissection.
- Fibromuscular dysplasia.
- Postradiation necrosis.
- Vasospasm.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Aneurysm, arteritis, and carotid dissection.

WORKUP

Systematic history, examination, and diagnostic studies to assess for carotid stenosis and other risk factors of TIA.

LABORATORY TESTS

CBC, basic metabolic panel, fasting lipid profile, PT/international normalized ratio, APTT, CRP.

IMAGING STUDIES

- Four imaging modalities are available for the evaluation of carotid stenosis (Table C1-7).
- Patients who have neurologic sequelae suggestive of carotid stenosis should be screened via carotid duplex. If carotid stenosis is suspected on carotid duplex, but inconclusive, magnetic resonance angiography, computed tomography angiography, or conventional angiography should be obtained to confirm the degree of stenosis (Fig. C1-30).
- Screening of asymptomatic patients without any risk factors for atherosclerosis is not routinely recommended.
- When required, carotid duplex is considered the imaging modality of choice for screening.
- Screening with carotid duplex may be considered in asymptomatic patients with carotid bruit and in those with multiple risk factors for atherosclerosis or those with known atherosclerotic disease at other sites such as coronary artery disease, peripheral arterial disease, or abdominal aortic aneurysms.
- Patients identified to have >50% stenosis on carotid duplex may be re-imaged annually to assess progression.

TABLE C1-7 Imaging Modalities for Carotid Stenosis

Imaging Modality	Benefit	Drawback
Cerebral angiography	• Gold standard • Assesses plaque morphology • Assesses presence of collaterals	• Invasive • High cost • 4% incidence rate of complications • 1% incidence rate of serious complications or death
Carotid duplex	• Sensitive in detecting high-grade stenosis (>70%) • Less invasive • Lower cost	• Can be limited by body habitus • Technician dependent • Overestimates degree of stenosis
Magnetic resonance angiography (MRA)	• Sensitive in detecting high-grade stenosis (>70%) • Less operator dependent	• Overestimates degree of stenosis • Cannot be performed in patients who are critically ill, unable to tolerate supine positioning, have pacemaker or other ferromagnetic hardware, or are claustrophobic* • Expensive • Takes much longer to obtain compared with other modalities
Computed tomography angiography (CTA)	• Sensitive for high-grade stenosis	• Contraindicated in patients with serum creatinine concentration >1.5 mg/dl

*One study revealed that ~17% of patients are unable to tolerate MRA secondary to claustrophobia or are unable to lie still for procedure.

TREATMENT

ACUTE GENERAL Rx

- General medical therapy should be aimed at risk factor reduction. As stated earlier, the major risk factors for carotid stenosis are hypertension, diabetes mellitus, dyslipidemia, and smoking (see "Stroke, Secondary Prevention").
- Antiplatelet therapy: Three antiplatelet options are available for patients with carotid stenosis: ASA, ASA plus dipyridamole, and clopidogrel.

NONPHARMACOLOGIC THERAPY

Carotid endarterectomy (CEA) and carotid angioplasty and stenting (CAS) are the options available. The decision favoring revascularization procedures is dependent upon the presence or absence of symptoms, degree of stenosis, and medical co-morbidities.

ASYMPTOMATIC CAROTID STENOSIS

With significant improvements in medical therapy, the benefit of surgical revascularization of the carotids in asymptomatic patients with either CEA or CAS is not well established.

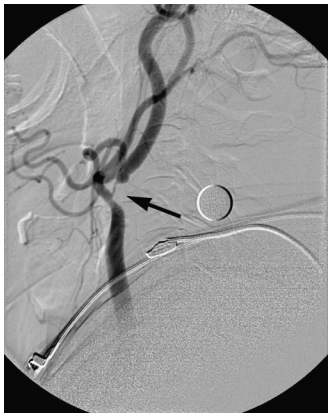

FIGURE C1-30 Conventional angiography demonstrating severe stenosis of the internal carotid artery at the bifurcation.

According to the most recent guidelines, revascularization procedures may be considered in asymptomatic patients with >70% stenosis if the anticipated perioperative risk is low, but this should be done only after considering their medical comorbidities, life expectancy, and after discussing the risks and benefits in detail with the patients.

SYMPTOMATIC CAROTID STENOSIS

In patients who have suffered a nondisabling ischemic stroke or TIA in the preceding 6 months, surgical revascularization by CEA is recommended if the degree of stenosis is >70% by noninvasive imaging or >50% by catheter angiogram and if the anticipated rate of perioperative stroke or mortality is <6%.

All patients undergoing CEA should be started on aspirin (ASA; 81 or 325 mg daily) before surgery and this should be continued indefinitely.

CAS can be an alternative to CEA in select patients considered to be at high surgical risk or with unfavorable neck anatomy for surgery.

CEA is preferred over CAS in older patients.

For patients undergoing CAS, dual antiplatelet therapy is recommended for a minimum of 30 days.

When feasible, early revascularization within 14 days might be undertaken unless there are definite contraindications.

Surgical revascularization is not recommended in <50% stenosis, total occlusion or in patients with major disabling strokes.

In patients who are considered high surgical risk for either CEA or CAS, the role of medical therapy alone compared with surgical revascularization is not well established.

DISPOSITION

Disposition and prognosis depend on several variables (Table C1-8): the degree of stenosis, the presence of symptoms, medication compliance, and the type of intervention (if any).

PEARLS & CONSIDERATIONS

There are ongoing studies concerning the best treatment of patients with carotid artery stenosis. Based on the results of these studies, guidelines may change rapidly.

SPECIAL CONSIDERATION

Some studies have shown that in patients with bilateral hemodynamically significant stenosis (>70%), reduction of blood pressure resulted in worse outcome in terms of stroke. These patients would likely be candidates for CEA.

Carotid artery occlusion (100% blockage), for which there is no routine treatment, is being reexamined in the national Carotid Occlusion Surgery Study (http://www.cosstrial.org). Consider referring symptomatic carotid occlusion patients for consideration of this study.

PREVENTION

Prevention of carotid stenosis should be guided at pursuing a healthy lifestyle and management of risk factors for development of atherosclerosis.

PATIENT/FAMILY EDUCATION

Patients should be counseled on pursuing a healthy lifestyle to include exercise and smoking cessation. In addition, patients should take an active role in controlling blood pressure and blood glucose. Further educational materials can be found online at: http://www.strokecenter.org/education.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Carotid Stenosis (Patient Information)
Transient Ischemic Attack (Related Key Topic)

AUTHOR: **PRASHANTH KRISHNAMOHAN, M.B.B.S., M.D.**

TABLE C1-8 Carotid Stenosis Management

Degree of Carotid Stenosis	<50%	50%-69%	70%-99%
Asymptomatic	• Medical management	• Medical management • Inconclusive evidence base to favor surgical treatment. May be considered in select patients with >60% stenosis.*	• Medical management • CEA in highly selected patients*
Symptomatic	• Medical management	• CEA • CAS can be an alternative	• CEA • CAS can be an alternative

CAS, Carotid artery stenting; *CEA,* carotid endarterectomy.
*CEA can be considered in asymptomatic patients with >70% stenosis if the anticipated rate of perioperative complications (Stroke, MI, and death) is low, after considering their life expectancy (minimum 5 years), medical co-morbidities and after a thorough discussion of the risks and benefits involved with the patients and their families.

EVIDENCE

Abstract[1]

Background:
The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have jointly developed guidelines for the diagnosis and management of cardiovascular disease since 1980. Their current recommendations for managing patients with extracranial carotid and vertebral artery disease are designed to help health care providers make clinical decisions, covering a range of generally acceptable practices in diagnosis, management, and prevention.

Diagnostic Recommendations:
Duplex ultrasonography is suitable for screening most asymptomatic patients with known or suspected carotid stenosis. Patients with symptoms or signs of extracranial carotid artery disease may be better screened using magnetic resonance angiography (MRA) or computed tomography angiography (CTA), with echocardiography used to search for the source of cardiogenic embolism. Vertebral artery disease can generally be detected using serial noninvasive CTA or MRA imaging. Cervical artery dissection is best diagnosed using contrast-enhanced CTA, MRA, and catheter-based contrast angiography.

Management Recommendations:
The management of patients with and without symptoms of extracranial carotid or vertebral atherosclerosis includes treating conditions such as hypertension, hyperlipidemia, and diabetes mellitus as needed, plus smoking cessation. Revascularization can be achieved via carotid endarterectomy (CEA) or carotid artery stenting (CAS). Patients who have extracranial carotid atherosclerotic disease but are not undergoing revascularization and patients with vertebral artery disease can reduce their risks through antithrombotic therapy with aspirin alone, clopidogrel alone, or a combination of aspirin and extended-release dipyridamole. A vitamin K antagonist may prevent thromboembolic ischemic events, with clopidogrel or ticlopidine substituted for patients who cannot take aspirin. Should restenosis develop after CEA or CAS, the procedure can be repeated. Patients with occlusive disease of the subclavian and brachiocephalic arteries may require extra anatomic carotid-subclavian bypass, percutaneous endovascular angioplasty and stenting, direct arterial reconstruction, or subclavian bypass and stenting, depending on the specific presentation. Carotid duplex ultrasound screening is performed before elective coronary artery bypass graft (CABG) procedures in older patients and those at particular risk. CEA or CAS with embolic protection can precede or accompany myocardial revascularization surgery in selected patients. Patients with fibromuscular dysplasia (FMD) of the extracranial carotid arteries should be initially followed annually via noninvasive imaging of the carotid arteries to detect changes. Once the condition appears stable, images can be obtained less often. Platelet-inhibitor medication may benefit some patients, but the best drug and optimal dosing regimen remain to be determined. Patients may also undergo carotid angioplasty with or without stenting. Cervical artery dissection associated with ischemic stroke or transient ischemic attacks may be managed using antithrombotic treatment for at least 3 to 6 months. Carotid angioplasty and stenting can be considered if no response occurs.

Conclusion:
The evidence supporting the recommendations guiding the diagnosis and management of extracranial carotid and vertebral artery disease varies in quality. Many opportunities remain for future research in these areas. Ⓐ

Abstract[2]

Background and Purpose:
The safety of carotid artery stenting (CAS) and carotid endarterectomy (CEA) has varied by symptomatic status in previous trials. The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) data were analyzed to determine safety in symptomatic and asymptomatic patients.

Methods:
CREST is a randomized trial comparing safety and efficacy of CAS versus CEA in patients with high-grade carotid stenoses. Patients were defined as symptomatic if they had relevant symptoms within 180 days of randomization. The primary end point was stroke, myocardial infarction, or death within the periprocedural period or ipsilateral stroke up to 4 years.

Results:
For 1321 symptomatic and 1181 asymptomatic patients, the periprocedural aggregate of stroke, myocardial infarction, and death did not differ between CAS and CEA (5.2% versus 4.5%; hazard ratio, 1.18; 95% CI, 0.82 to 1.68; P=0.38). The stroke and death rate was higher for CAS versus CEA (4.4% versus 2.3%; hazard ratio, 1.90; 95% CI, 1.21 to 2.98; P=0.005). For symptomatic patients, the periprocedural stroke and death rates were 6.0% ± 0.9% for CAS and 3.2% ± 0.7% for CEA (hazard ratio, 1.89; 95% CI, 1.11 to 3.21; P = 0.02). For asymptomatic patients, the stroke and death rates were 2.5% ± 0.6% for CAS and 1.4% ± 0.5% for CEA (hazard ratio, 1.88; 95% CI, 0.79 to 4.42; P = 0.15). Rates were lower for those aged <80 years.

Conclusion:
There were no significant differences between CAS versus CEA by symptomatic status for the primary CREST end point. Periprocedural stroke and death rates were significantly lower for CEA in symptomatic patients. However, for both CAS and CEA, stroke and death rates were below or comparable to those of previous randomized trials and were within the complication thresholds suggested in current guidelines for both symptomatic and asymptomatic patients. Ⓐ

Abstract[3]

Background:
Stroke occurs more commonly after carotid artery stenting than after carotid endarterectomy. Details regarding stroke type, severity, and characteristics have not been reported previously. We describe the strokes that have occurred in the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST).

Methods and Results:
CREST is a randomized, open-allocation, controlled trial with blinded end-point adjudication. Stroke was a component of the primary composite outcome. Patients who received their assigned treatment within 30 days of randomization were included. Stroke was adjudicated by a panel of board-certified vascular neurologists with secondary central review of clinically obtained brain images. Stroke type, laterality, timing, and outcome were reported. A periprocedural stroke occurred among 81 of the 2502 patients randomized and among 69 of the 2272 in the present analysis. Strokes were predominantly minor (81%, n = 56), ischemic (90%, n = 62), in the anterior circulation (94%, n = 65), and ipsilateral to the treated artery (88%, n = 61). There were 7 hemorrhages, which occurred 3 to 21 days after the procedure, and 5 were fatal. Major stroke occurred in 13 (0.6%) of the 2272 patients. The estimated 4-year mortality after stroke was 21.1% compared with 11.6% for those without stroke. The adjusted risk of death at 4 years was higher after periprocedural stroke (hazard ratio, 2.78; 95% confidence interval, 1.63 to 4.76).

Conclusion:
Stroke, particularly severe stroke, was uncommon after carotid intervention in CREST, but stroke was associated with significant morbidity and was independently associated with a nearly 3-fold increased future mortality. The delayed timing of major and hemorrhagic stroke after revascularization suggests that these strokes may be preventable. Ⓐ

Abstract[4]

Objective:
In patients with recently symptomatic carotid artery stenosis, guidelines recommend carotid revascularization within 2 weeks of the index event. The "index event" may be defined as either the first or the most recent event. The delay between the index event and carotid endarterectomy (CEA) over a period of 6 years in a single center was evaluated and the effect of defining the index event as either the first or the most recent event was assessed.

Design:
Observational study.

Methods:
A total of 555 consecutive patients with symptomatic carotid stenosis,

≥50% treated with CEA between 2007 and 2012 were assessed. In 2010, changes to the in-hospital process of care to reduce delays in referral and CEA were introduced. These changes included, for example, improving access to physicians, imaging, and operating rooms. The delay from symptoms to surgery was expressed in days.

Results:

The median time between the first event and surgery was reduced from 53 days (interquartile range [IQR] 30-78) in 2007 to 21 days (IQR 12-45) in 2012, and between the most recent event and CEA from 45 days (IQR 28-67) to 17 days (IQR 9-28). Patients referred directly by their general practitioner more often underwent CEA within 2 weeks than patients referred by specialists from other hospitals. Compared with patients with transient ischaemic attack or ocular symptoms, patients with ischemic stroke more often underwent CEA within 2 weeks.

Conclusions:

A small change in the process of care significantly reduced the delay from the index event to CEA, but in 2012 it still exceeded 14 days in the majority of patients. The definition of the "index event" has a large impact on the total duration of delay, and should therefore be uniform across studies. Ⓐ

Evidence-Based References

Brott TG et al.: 2011 SA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS Guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery, *Circulation* 124:489–532, 2011. Ⓐ

Silver FL: for the CREST Investigators: Safety of stenting and endarterectomy by symptomatic status in the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST), *Stroke* 42:675–680, 2011. Ⓐ

Den Hartog AG, Moll FL, Van der Worp HB, et al.: Delay to carotid endarterectomy in patients with symptomatic carotid artery stenosis, *Eur J Vasc Endovasc Surg* 47:233–239, 2014. Ⓑ

SUGGESTED READINGS

Caplan LR: Large artery occlusive disease of the anterior circulation. In Caplan LR, editor: *Caplan's stroke: a clinical approach*. Saunders: Philadelphia, pp. 221–257.

Carotid Stenting Trialists' Collaboration, Bonati LH, Dobson J, et al.: Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data, *Lancet* 376:1062–1073, 2010.

Grotta JC: Carotid stenosis, *N Engl J Med* 369:1143–1150, 2013.

Marquardt L, Barnett HJM: Carotid stenosis: To revascularize or not to revascularize, That is the question, *Neurology* 77:710, 2011.

Perkins W et al.: Carotid stenting versus endarterectomy: new results in perspective, *Mayo Clin Proc* 85(12):1101–1108, 2010.

Raman G et al.: Management strategies for asymptomatic carotid stenosis, *Ann Int Med* 158:676–685, 2013.

Sacco RL et al.: Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline, *Stroke* 37(2), 2006.

BASIC INFORMATION

DEFINITION

Carpal tunnel syndrome (CTS) is a compressive neuropathy of the median nerve as it passes under the transverse carpal ligament at the wrist (Fig. EC1-31). It is the most common entrapment neuropathy.

SYNONYMS

CTS

ICD-9CM CODES
354.0 Carpal tunnel syndrome
ICD-10CM CODES
G56.0 Carpal tunnel syndrome, unspecified upper limb

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENT AGE: 30 to 60 yr
PREVALENT SEX: Females are affected two to five times as often as males.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pain, paresthesia in 1st, 2nd, 3rd, and lateral ½ of 4th fingers, worse at night
- Tinel's sign at wrist (Fig. C1-32): tapping lightly over the median nerve on the volar surface of the wrist produces a tingling sensation radiating from the wrist to the hand
- Phalen's sign (Fig. C1-33): reproduction of symptoms after 1 min of gentle, unforced wrist flexion
- Carpal compression test: direct pressure over the patient's carpal tunnel for 30 sec elicits symptoms
- Findings may be bilateral in up to 65% of patients
- Thenar atrophy in longstanding cases with weakness of thumb abduction and opposition

ETIOLOGY

- Idiopathic in most cases
  1. Increased intracarpal tunnel pressure
  2. Ischemia, friction, or angulation of median nerve
- Space-occupying lesions in carpal tunnel (tenosynovitis, ganglia, aberrant muscles)
- Can be associated with diabetes, hypothyroidism, pregnancy, connective tissue diseases, acromegaly, amyloidosis
- Repetitive strain or job-related mechanical overuse may be a risk factor

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cervical radiculopathy
- Chronic tendinitis
- Other arthritides
- Complex regional pain syndrome
- Brachial plexopathy, thoracic outlet syndrome
- Polyneuropathy
- Other entrapment neuropathies
- Traumatic wrist injuries

IMAGING STUDIES

Carpal tunnel syndrome is a clinical diagnosis but imaging may assist workup in uncertain situations. Musculoskeletal ultrasound has been very effective in supporting the diagnosis and may help identify the structural cause of nerve compression. Roentgenograms or MRI may be helpful in ruling out other conditions.

ELECTRODIAGNOSTIC STUDIES

Nerve conduction velocity tests demonstrate impaired sensory conduction across the carpal tunnel. Electromyography may show active denervation muscle potentials.

TREATMENT

ACUTE GENERAL Rx

- Activity modification
- Nocturnal wrist splint
- No evidence for effectiveness of NSAIDs
- Corticosteroid injection of carpal canal on ulnar side of palmaris longus tendon proximal to wrist crease (Figs. EC1-34 and EC1-35): can be done with palpation guidance or under ultrasound guidance. A recent trial[1] has shown that methylprednisolone injections for CTS have significant benefits in relieving symptoms at 10 wk and reducing the rate of surgery 1 yr after treatment, but 3 out of 4 patients had surgery within 1 yr.
- Low-dose oral corticosteroids can be considered.
- Short-term benefit from ultrasound therapy (physical therapy modality)
- Ergonomic keyboards

DISPOSITION

Clinical course may have remissions and exacerbations. Some may progress from intermittent to persistent sensory complaints (numbness, tingling, paresthesias), then later to develop motor symptoms. In pregnancy, symptoms usually resolve spontaneously weeks after delivery.

REFERRAL

Surgical referral is needed if conservative treatment fails. It is usually reserved for severe symptoms or presence of weakness/thenar atrophy. Surgery (sectioning of transverse carpal ligament) to release pressure on the median nerve is done by open or endoscopic approach, with good long-term results.

PEARLS & CONSIDERATIONS

- The sensory changes of carpal tunnel syndrome spare the thenar eminence. This distinctive pattern occurs because the palmar sensory cutaneous branch of the median nerve arises proximal to the wrist, passing over, rather than through, the tunnel.
- Role of repetitive hand or wrist use and workplace factors in the development of carpal tunnel syndrome remains controversial.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Carpal Tunnel Syndrome (Patient Information)

AUTHOR: **CANDICE YUVIENCO, M.D.**

FIGURE C1-32 Tinel's sign. The wrist is held in extension while gentle percussion is performed over and just proximal to the transverse carpal ligament. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

FIGURE C1-33 Phalen's (wrist flexion) test. With the wrists held in unforced flexion for 30 to 60 seconds, a positive test reproduces or worsens the patient's symptoms. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

[1]Methylprednisolone injections for the carpal tunnel syndrome: a randomized, placebo-controlled trials, *Ann Int Med* 159:309-317, 2013.

EVIDENCE

Abstract[1]

Nerve

Preoperative corticosteroid injections are associated with worse long-term outcomes of surgical carpal tunnel release.

Background and purpose:

Failed closed treatment of carpal tunnel syndrome (CTS) is often followed by surgery. We investigated whether preoperative steroid injections could have a negative effect on the long-term outcome of the operation.

Patients and methods:

174 hands (164 patients) were operated on by a single surgeon at Tartu University Hospital in 2005. The patients were interviewed by telephone 5 to 6 years after the operation. Self-reported data were gathered retrospectively concerning the number of steroid injections received before the surgery and the perceived regression of symptoms (on a 100-point numeric rating scale) at the time of interview. The patients were also asked about the presence of specific symptoms of CTS if regression of their symptoms had not been complete.

Results:

93 of the 174 hands had complete regression of symptoms. Each additional injection was associated with an increased risk of occurrence of pain (RR=1.1, 95% CI: 1.02 to 1-2), paresthesiae (RR=1.1, CI: 1.1 to 1.2), and nocturnal awakenings (RR=1.2, CI: 1.1 to 1.3). There was a weak association between the number of injections and the score given to regression of symptoms.

Interpretation:

This is the first study to indicate that patients who received a greater number of local steroid injections preoperatively were more likely to have postoperative complaints associated with CTS.

The most commonly recommended nonoperative treatment for CTS includes bracing, brief periods of activity modification, and corticosteroid injections. There is conflicting evidence of the efficacy of these treatments in resolving CTS, particularly in those patients whose symptoms are chronic and associated with sensory and motor abnormalities. Carpal tunnel corticosteroid injections have been found to lessen the symptoms of CTS in many patients, but reports of duration of symptom relief are variable. Corticosteroid carpal tunnel injections have also been advocated as a method for predicting the outcome from carpal tunnel release surgery. It has not been established how many corticosteroid injections are safe or effective in attempts to resolve CTS before abandoning nonoperative treatment. Moreover, the interval between subsequent injections has not been established. This is the first study to investigate the effect of preoperative corticosteroid injections on the longer-term outcomes after carpal tunnel release. The study suffers from its retrospective design and patient-reported parameters but breaks new ground for further investigation.

S.D. TRIGG, M.D.

Abstract[2]

Nerve

Purpose:

To compare clinical outcomes 5 years after carpal tunnel release among patients with and without diabetes.

Methods:

In a prospective consecutive series, 35 patients with diabetes (median age, 54 y; 15 type 1 and 20 type 2 diabetes) with carpal tunnel syndrome were age- and sex-matched with 31 control patients without diabetes (median age, 51 y) with idiopathic carpal tunnel syndrome. Exclusion criteria were other nerve entrapment, cervical radiculopathy, inflammatory joint disease, thyroid disorder, previous wrist fracture, and long-term exposure to vibrating tools. Participants were examined independently at baseline, 1 year, and 5 years after surgery for sensory function (Semmes-Weinstein), motor function (abductor pollicis brevis muscle strength and grip strength), cold intolerance, and completion of the Boston Carpal Tunnel Questionnaire symptom severity and functional status score.

Results:

Five years after surgery, the overall attendance rate for clinical examinations and completion of the Boston Carpal Tunnel Questionnaire were 86% and 95%, respectively. Between 1 and 5 years after surgery, there was a tendency toward a decrease in sensory function but an increase in motor function, with no statistically significant difference between groups. Cold intolerance demonstrated long-term significant improvement for patients with diabetes. The improvement in symptom severity and functional status score, as well as the large effect size, were maintained at 5 years in both patient groups.

Conclusions:

Long-term improvement in patients with diabetes remained after carpal tunnel release to the same extent as for patients without diabetes. Furthermore, improvement in cold intolerance in patients with diabetes suggests the potential for the long-term regeneration of small nerve fibers.

Type of Study/ Level of Evidence:

Prognostic I.

This group previously published short-term results from a prospective study on carpal tunnel release among age- and sex-matched patients with and without diabetes. This investigation was to extend their clinical trial to compare outcomes 5 years after open carpal tunnel release in patients with and without diabetes. They found long-term improvement in patients after carpal tunnel release to the same extent as for patients without diabetes. There was also improvement in cold intolerance in the diabetes group. This is a very well done study. By publishing the original results and now following up with 5-year results, the authors certainly provide support for operative treatment of patients with carpal tunnel syndrome.

D.J. SMITH, Jr, M.D.

Evidence-Based References

1. Vahi P-S, Kals M, Kõiv L et al.: Operatsiooni eel tehtud kortikosteroidsüsted on seotud karpaalkanali sündroomi kirurgilise ravi halvema kaugtulemusega, *Acta Orthop* 85:102–106, 2014. B
2. Thomsen NOB, Cederlund RI, Andersson GS et al.: Carpal tunnel release in patients with diabetes: a 5-year follow-up with matched controls, *J Hand Surg Am* 39:713–720, 2014. B

SUGGESTED READINGS

Ahn DS: Hand elevation: a new test for carpal tunnel syndrome, *Ann Plast Surg* 46:120, 2001.

Atroshi I et al.: Carpal tunnel syndrome and keyboard use at work: a population-based study, *Arthritis Rheum* 56:3620, 2007.

Bland JD et al.: Clinical surveillance of carpal tunnel syndrome in two areas of the United Kingdom, *J Neurol Neurosurg Psychiatry* 74:1674, 2003.

Fowler JR et al.: Comparison of ultrasound and electrodiagnostic testing for diagnosis of carpal tunnel syndrome: study using a validated clinical tool as the reference standard, *J Bone Joint Surg Am* 96(17):e148, 2014.

Ghasemi-Esfe AR et al.: Combination of high-resolution and color Doppler ultrasound in diagnosis of carpal tunnel syndrome, *Acta Radiol* 52(2):191–197, 2011.

Huisstede BM et al.: Carpal tunnel syndrome. Part I: Effectiveness of nonsurgical treatments—a systematic review, *Arch Phys Med Rehabil* 91(7):981, 2010.

Huisstede BM et al.: Carpal tunnel syndrome. Part II: Effectiveness of surgical treatments—a systematic review, *Arch Phys Med Rehabil* 91(7):1005, 2010.

Jarvik JG et al.: Surgery versus non-surgical therapy for carpal tunnel syndrome: a randomised parallel-group trial, *Lancet* 374:1074, 2009.

Ly-Pen D et al.: Surgical decompression versus local steroid injection in carpal tunnel syndrome: a one-year, prospective, randomized, open, controlled clinical trial, *Arthritis Rheum* 52:612, 2005.

Nakamichi K et al.: Percutaneous carpal tunnel release compared with mini-open release using ultrasonographic guidance for both techniques, *J Hand Surg Am* 35(3):437, 2010.

Nashel D.J. Entrapment neuropathies. In: Hochberg MC et al (eds): *Rheumatology.* Mosby: St Louis.

Sucher BM: Ultrasound imaging of the carpal tunnel during median nerve compression, *Curr Rev Musculoskelet Med* 2:134, 2009.

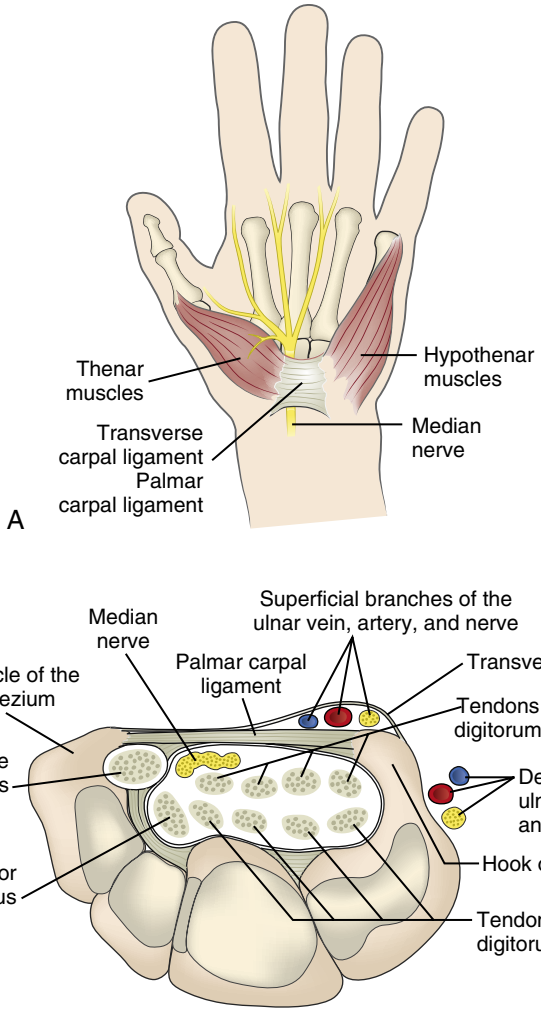

FIGURE EC1-31 Anatomic basis of carpal tunnel syndrome. A, General view of the relationship between the median nerve and the flexor retinaculum. **B,** Cross section at the distal carpal row showing the structures in the carpal tunnel. (Redrawing based on an illustration by Li-Guo Liang, in Yu HL et al: *Atlas of hand anatomy and clinical implications,* Philadelphia, 2004, Mosby. From Auerbach P: *Wilderness medicine,* ed 5, Philadelphia, 2007, Mosby.)

FIGURE EC1-34 Palmaris longus tendon. The pencil point identifies the tendon of the palmaris longus muscle, an important landmark in determining the site of injection for carpal tunnel syndrome. The tendon of the flexor carpi radialis can be seen just to the radial side of the palmaris longus tendon. (From Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.)

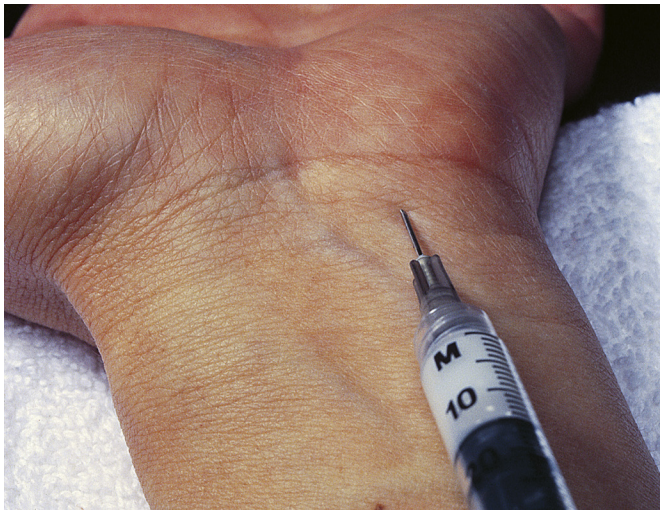

FIGURE EC1-35 Carpal tunnel injection. The needle is inserted just proximal to the wrist crease and to the ulnar side of the palmaris longus tendon. (From Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.)

BASIC INFORMATION

DEFINITION

Cataracts are the clouding and opacification of the normally clear crystalline lens of the eye. The opacity may occur in the cortex, the nucleus of the lens, or the posterior subcapsular region, but it is usually in a combination of areas.

SYNONYMS

Congenital cataracts (e.g., from rubella)
Metabolic cataracts (e.g., caused by diabetes)
Hereditary cataracts
Age-related senile cataracts (nuclear sclerotic and cortical cataracts)
Traumatic cataracts
Toxic or drug-induced cataracts (e.g., caused by steroids)
Lenticular opacities

ICD-9CM CODES
366 Cataract
ICD-10CM CODES
H26.9 Cataract, unspecified
H25.0 Senile incipient cataract
H25.1 Senile nuclear cataract
H26.0 Infantile, juvenile and presenile cataract

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Most common cause of treatable blindness; cataract removal is the most frequent surgical procedure in patients >65 yr (1.3 million operations per year, with an annual cost of approximately $3 billion). By year 2020 more than 30 million Americans will have cataracts. Of Americans >40 yr, 20.5 million (17.2%) have cataracts. Of these, 5% have had surgery.

PEAK INCIDENCE:
- In early life: congenital and hereditary causes predominant; consider drug related, diabetes, and trauma
- In older age group: senile cataracts (after 40 yr)

PREDOMINANT AGE: Elderly; some stage of cataract development is present in >50% of persons 65 to 74 yr and in 65% of those >75 yr. Lens opacification and sclerosis begins around age 40 yr and then usually progresses either slowly or rapidly depending on individual and health.

GENETICS: Hereditary with syndromes such as galactosemia, homocystinuria, diabetes

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Cloudiness and opacification of the crystalline lens of the eye (Figs. C1-36 and EC1-37)
- Decrease or absence of the red reflex (important in pediatric ages, since visual acuity is more difficult to assess)
- Painless decreased visual acuity
- Glare and decreased night vision (early symptom: difficulty with night driving)

ETIOLOGY

- Heredity
- Trauma
- Age related
- Drug related (e.g., corticosteroids)
- Congenital
- Inflammatory (e.g., history of uveitis)
- Diabetes
- Collagen vascular disease

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Corneal lesions
- Retinal lesions, detached retina, tumors
- Vitreous disease, chronic inflammation

WORKUP

- Complete eye examination, including visual acuity and measurement of refractive error, slit lamp examination, dilated funduscopic examination, and brightness acuity testing
- Complete physical examination for other underlying causes

LABORATORY TESTS

- Rarely, urinary amino acid screening and central nervous system imaging studies with congenital cataracts
- Fasting glucose in young adults with cataracts
- Diabetes, collagen vascular disease, other metabolic diseases in younger patients
- Genetic and hereditary evaluation

TREATMENT

There is no evidence that antioxidants or drugs will slow or treat cataracts.

NONPHARMACOLOGIC THERAPY

- Wait until vision is compromised before doing surgery.
- Plan cataract removal with intraocular lens implantation when vision is compromised and limiting activities of daily living, such as driving at night or reading. Removal of the cataract should be expected to improve the ability of the patient to perform these activities. Another indication to remove cataracts might be to improve the examination view for treatment and assessment of retinal diseases.
- Decision for timing of surgery depends upon patient complaints, best corrected visual acuity (e.g., 20/50), and glare measurements (brightness acuity test decreases vision significantly).

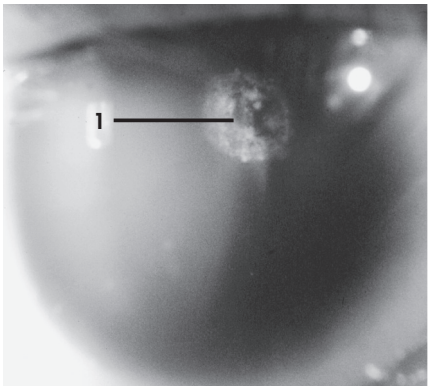

FIGURE C1-36 The central location of a posterior subcapsular cataract *(1)*. (From Palay D [ed]: *Ophthalmology for the primary care physician*, St Louis, 1997, Mosby.)

ACUTE GENERAL Rx

None necessary except when acute glaucoma or inflammation occurs

CHRONIC Rx

- Change glasses as cataracts develop.
- Myopia is common, and glasses can be adjusted until surgery is contemplated.

DISPOSITION

Refer if sight is compromised or the eye is red or inflamed.

REFERRAL

Refer to ophthalmologist for evaluation for extraction when vision is compromised (see "Nonpharmacologic Therapy").

PEARLS & CONSIDERATIONS

- Patients want to know five things about cataracts:
  1. Chance for vision improvement
  2. When vision will improve
  3. Risk from surgery (such as infection, hemorrhage, retinal detachment, corneal problems)
  4. Effect of surgery, including reduction of refractive errors
  5. Types of complications
- Men planning cataract surgery should, if feasible, delay the use of alpha blockers until after surgery has been completed. The risk of intraoperative floppy iris syndrome is substantial among men taking tamsulosin. This is often unavoidable, and discontinuation of alpha blockers does not help, although intraoperative techniques have improved to make floppy iris syndrome less complicated.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Cataracts (Patient Information)

AUTHOR: **R. SCOTT HOFFMAN, M.D.**

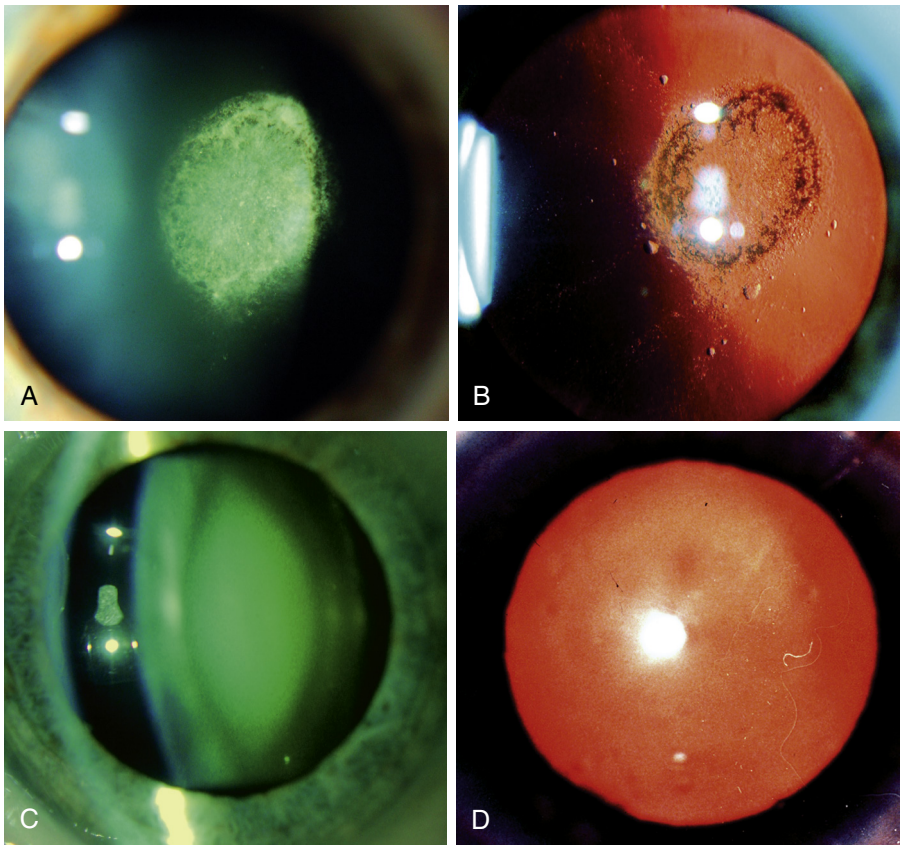

FIGURE EC1-37 Age-related cataract. A, Posterior subcapsular. **B,** On retroillumination. **C,** Nuclear. **D,** On retroillumination. (Courtesy Schuman V et al; from Lens and glaucoma. In *Rapid diagnosis in ophthalmology,* St Louis, 2008, Mosby.)

EVIDENCE

Abstract[1]

Purpose:
To evaluate the difference between target and actual refraction after phacoemulsification and intraocular lens implantation at an academic teaching institution's Comprehensive Ophthalmology Service.

Design:
Retrospective study.

Participants:
We examined 1275 eye surgeries for this study.

Methods:
All consecutive cataract surgeries were included if they were performed by an attending or resident surgeon from January through December 2010. Postoperative refractions were compared with preoperative target refractions. Patients were excluded if they did not have a preoperative target refraction documented or if they did not have a recorded postoperative manifest refraction within 90 days.

Main outcome measures:
The main outcome measure was percentage of cases achieving a postoperative spherical equivalent±1.0 diopter (D) of target spherical equivalent.

Results:
We performed 1368 cataract surgeries from January through December of 2010. Of these, 1275 (93%) had sufficient information for analysis. Of the included cases, 94% (1196 of 1275) achieved ±1.0 D of target refraction by 90 days after cataract surgery.

Conclusions:
This paper establishes a new benchmark for a teaching hospital, where 94% of patients achieved within 1.0 D of target refraction after cataract surgery. The refractive outcomes after cataract surgery at this academic teaching institution were higher than average international benchmarks.

This article establishes a new benchmark in refractive accuracy for a teaching hospital after cataract surgery. This was achieved by careful preoperative biometry using optical coherence interferometry for axial length whenever possible and optimizing intraocular lens power calculations. It is a retrospective study and eliminates patients who were not refracted at 3 months or who had no target refraction identified in the chart. This may introduce bias in the results. However, it is significant that the analysis included both resident and attending surgeons' cases. Other studies have examined mainly a single attending surgeon, and most achieved less than 94% within 1 diopter of target.

Although this type of refractive accuracy is laudable, more work needs to be done to achieve LASIK-like refractive predictability in cataract surgery. New instrumentation, such as intraoperative aberrometry, may help to reach this goal in the future.

M.F. PYFER, M.D.

Evidence-Based Reference

1. Simon SS, Chee YE, Haddadin RI, et al.: Achieving target refraction after cataract surgery, *Ophthalmology* 121:440–444, 2014. Ⓐ.

SUGGESTED READINGS

Congdon N et al.: Prevalence of cataract and pseudophakia/aphakia among adults in the US, *Arch Ophthalmol* 122(4):487, 2004.

Solomon R, Donninfeld ED: Recent advances and future frontiers in treating age-related cataracts, *JAMA* 290:248, 2003.

BASIC INFORMATION

DEFINITION

Cat-scratch disease (CSD) is an infectious disease consisting of gradually enlarging regional lymphadenopathy occurring after contact with a feline. Atypical presentations are characterized by a variety of neurologic manifestations as well as granulomatous involvement of the eye, liver, spleen, and bone. The disease is usually self-limiting, and recovery is complete; however, patients with atypical presentations, especially if immunocompromised, may suffer significant morbidity and mortality.

SYNONYMS

Cat-scratch fever
Benign inoculation lymphoreticulosis
Nonbacterial regional lymphadenitis

ICD-9CM CODES
078.3 Cat-scratch disease
ICD-10CM CODES
A28.1 Cat-scratch disease

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Unknown
INCIDENCE (IN U.S.):
- 9 to 10 cases per 100,000 persons per year (22,000 cases per year)
- Majority of reported cases occur in persons <21 yrs

PEAK INCIDENCE: August through January

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Classic, most common finding: regional lymphadenopathy occurring within 2 wk of a scratch or contact with felines; usually a new kitten in the household
- Tender, swollen lymph nodes most commonly found in the head and neck (Fig. EC1-38), followed by the axilla and the epitrochlear, inguinal, and femoral areas
- Erythematous overlying skin, showing signs of suppuration from involved lymph nodes
- On careful examination, evidence of cutaneous inoculation in the form of a nonpruritic, slightly tender pustule or papule
- Fever in most patients
- Malaise and headache in fewer than a third of patients
- Atypical presentations in fewer than 15% of cases
  1. Usually in association with lymphadenopathy and a low-grade or frank fever (>101 °F, >38.3 °C)
  2. Include granulomatous involvement of the conjunctiva (Parinaud's oculoglandular syndrome) and focal masses in the liver, spleen, and mesenteric nodes
- CNS involvement: neuroretinitis, encephalopathy, encephalitis, transverse myelitis, seizure activity, and coma
- Osteomyelitis in adults and children
- Can be a cause of culture-negative endocarditis
- In HIV-infected and other immunocompromised patients, *Bartonella henselae* is the cause of bacillary angiomatous and peliosis hepatis

ETIOLOGY

- Major cause: *Bartonella henselae,* possibly *Afipia felis* and *Bartonella clarridgeiae*
- Mode of transmission: predominantly by direct inoculation through the scratch, bite, or lick of a cat, especially a kitten
- Also can be transmitted by flea bite (with the flea obtaining the bacteria from a bacteremic cat); rarely after exposure to a dog, probably secondary to flea bites
- Approximately 2 wk after introduction of the bacteria into the host, regional lymphatic tissues displaying granulomatous infiltration associated with gradual hypertrophy
- Possible dissemination to distant sites (e.g., liver, spleen, and bone), usually characterized by focal masses or discrete parenchymal lesions

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Granulomas of this syndrome must be differentiated from those associated with:
- Tularemia
- Tuberculosis or other mycobacterial infections
- Brucellosis
- Sarcoidosis
- Sporotrichosis or other fungal diseases
- Toxoplasmosis
- Lymphogranuloma venereum
- Benign and malignant tumors such as lymphoma

WORKUP

Diagnosis should be considered in patients who present with a predominant complaint of gradually enlarging regional (focal) lymphadenopathy, often with fever and a recent history of having contact with a cat. A primary ulcer at the site of the cat scratch may or may not be present at the time lymphadenopathy becomes manifest.

LABORATORY TESTS

- Serologies: An IFA or EIA *Bartonella* serology (titer ≥1:64) is diagnostic. A PCR assay on tissue or blood is also available.
- Lymph node biopsy: granulomatous inflammation consistent with CSD.
- Warthin-Starry silver stain on biopsy can identify the bacteria.
- Histopathologically, Warthin-Starry silver stain has been used to identify the bacillus.
- Culture: *B. henselae* is a fastidious, slow-growing, gram-negative rod that requires specific culture techniques for tissue or blood.
- Routine laboratory findings:
  1. Mild leukocytosis or leukopenia
  2. Infrequent eosinophilia
  3. Elevated ESR or CRP
- Abnormalities of bilirubin excretion and elevated hepatic transaminases are usually secondary to hepatic obstruction by granuloma, mass, or lymph node.
- In patients with neurologic manifestations, lumbar puncture usually reveals normal CSF, although there may be a mild pleocytosis and modest elevation in protein.
- CSD skin test is no longer used for clinical purposes.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Warm compresses to the affected nodes
- In cases of encephalitis or coma: supportive care

ACUTE GENERAL Rx

- This disease is typically self-limited and generally resolves within 2 to 6 months. Most studies show no additional benefit from antibiotic therapy.
- It would be prudent to treat severely ill patients, especially if immunocompromised, with antibiotic therapy, because these patients tend to suffer dissemination of infection and increased morbidity.
- *Bartonella* is usually sensitive to a 5-day course of azithromycin, or alternatively tetracycline, sulfa, and the quinolones can be used for 7 to 10 days.
- When the isolate is proven by culture, the patient should receive antibiotic therapy as directed by the obtained susceptibilities.
- Antipyretics and NSAIDs may also be used.

DISPOSITION

Overall prognosis is good.

REFERRAL

- To an appropriate subspecialist to evaluate specific lesions
- For diagnostic aspiration or excision in presence of regional lymphadenopathy, bone lesions, and mesenteric lymph nodes and organs
- To ophthalmologist for ocular granulomas
  1. Usually diagnosed clinically
  2. Rarely require excision

PEARLS & CONSIDERATIONS

COMMENTS

- A presentation of this syndrome, especially in patients with HIV infection or impaired cellular immunity, may be fever of unknown origin.
- Hepatic and splenic granulomas, coronary valve infections may offer few physical clues to diagnosis, emphasizing the need for a complete history.
- CSD should be considered in the differential diagnosis of school-aged children presenting with status epilepticus.
- Chronically immunocompromised patients considering the acquisition of a young feline should be made aware of the possible risk of infection.
- No signs of illness may be apparent in bacteremic kittens.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Cat-Scratch Disease (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Batts S, Demers DM: Spectrum and treatment of cat-scratch disease, *Pediatr Infect Dis J* 23(12):1161, 2004.

Florin TA et al.: Beyond cat scratch disease: widening spectrum of *Bartonella henselae* infection, *Pediatrics* 121(5):e1413–e1425, 2008.

Klotz SA et al.: Cat-scratch disease, *Am Fam Physician* 83(2):152–155, 2011.

Koehler JE et al.: Prevalence of Bartonella infection among human immunodeficiency virus-infected patients with fever, *Clin Infect Dis* 37(4):559, 2003.

Massel F et al.: The expanded spectrum of bartonellosis in children, *Infec Dis Clin North Am* 19(3):691–711, 2005.

FIGURE EC1-38 Cat-scratch disease. A, Ulcerated papule on the cheek caused by a cat scratch 2 weeks previously and enlargement of submandibular lymph nodes. **B,** Line of papules on the forearm of another patient at the site of a cat scratch. **C,** Marked enlargement of the ipsilateral axillary lymph nodes. (Courtesy B.J. Zitelli and H.W. Davis. From Zitelli BJ: *Atlas of pediatric physical diagnosis,* St Louis, 2002, Mosby.)

BASIC INFORMATION

DEFINITION

Celiac disease is a chronic autoimmune disease characterized by malabsorption and diarrhea precipitated by ingestion of food products containing gluten. Gluten is a protein complex found in wheat, rye, and barley.

SYNONYMS

Gluten-sensitive enteropathy
Celiac sprue
Nontropical sprue

ICD-9CM CODES
579.0 Celiac disease
ICD-10CM CODES
K90.0 Celiac disease

EPIDEMIOLOGY & DEMOGRAPHICS

- The prevalence of celiac disease is 1% in the general population in North America and Western Europe and 5% in high-risk groups such as first-degree relatives of persons with the disease. The prevalence of celiac disease in the U.S. has increased fourfold over the past three decades. Worldwide celiac disease affects 0.6% to 1% of the population. Celiac disease is significantly more common in persons with type 1 DM and is associated with greater risk of retinopathy and nephropathy in this population.
- Incidence is highest during infancy and the first 36 mo of life (after introduction of foods containing gluten), in the third decade (frequently associated with pregnancy and severe anemia during pregnancy), and in the seventh decade.
- There is a slight female predominance.
- The average age of diagnosis is in the fifth decade of life.
- The risk for celiac disease is 5% to 10% in newborn children of parents with the disease and nearly 20% in siblings.
- It is estimated that only 10% to 15% of persons with celiac disease in the U.S. have been diagnosed.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination may be entirely within normal limits.
- Weight loss, dyspepsia, short stature, and failure to thrive may be noted in children and infants (Fig. C1-39).
- Weight loss, fatigue, and diarrhea are common in adults.
- Abdominal pain, nausea, and vomiting are unusual.
- Pallor as a result of iron-deficiency anemia is common.
- Atypical forms of the disease are being increasingly recognized and include osteoporosis, short stature, anemia, infertility, and neurologic problems. Manifestations of calcium deficiency, such as tetany and seizures, are rare and can be exacerbated by coexistent magnesium deficiency.
- Angular cheilitis, aphthous ulcers, atopic dermatitis, and dermatitis herpetiformis are frequently associated with celiac disease.
- Table C1-9 summarizes the clinical spectrum of celiac disease.

ETIOLOGY

- Celiac sprue is considered an autoimmune-type disease, with tissue transglutaminase (tTG) suggested as a major autoantigen. It results from an inappropriate T-cell–mediated immune response against ingested gluten in genetically predisposed individuals who carry either *HLA-DQ2* or *HLA-DQ8* genes. There is sensitivity to gliadin, a protein fraction of gluten found in wheat, rye, and barley. In patients with celiac disease, immune responses to gliadin fractions promote an inflammatory reaction, mainly in the upper small intestine, manifested by infiltration of the lamina propria and the epithelium with chronic inflammatory cells and villous atrophy.
- Seroconversion to celiac autoimmunity may occur at any time.
- Timing of introduction of gluten into the infant diet is associated with the appearance of celiac disease in children at risk. Children initially exposed to gluten in the first 3 mo of life have a fivefold increased risk. Current recommendations are to delay introduction of gluten into the diet of a genetically susceptible infant until 4 to 6 mo of age while the mother continues to breastfeed.

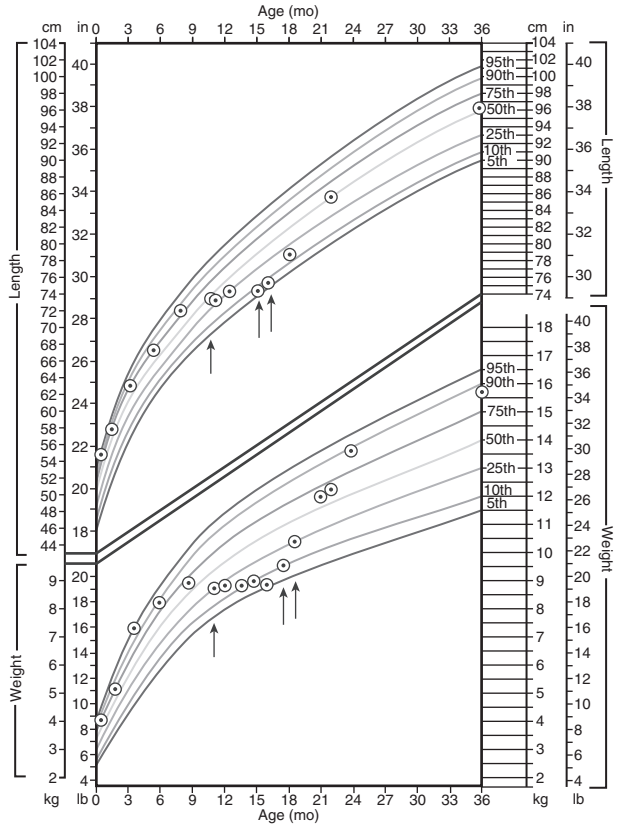

FIGURE C1-39 Gluten-sensitive enteropathy. Growth curve demonstrates initial normal growth from 0 to 9 mo, followed by onset of poor appetite with intermittent vomiting and diarrhea after initiation of gluten-containing diet *(single arrow).* After biopsy-confirmed diagnosis and treatment with gluten-free diet *(double arrow),* growth improves. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

TABLE C1-9 Clinical Spectrum of Celiac Disease

Symptomatic
Frank malabsorption symptoms: chronic diarrhea, failure to thrive, weight loss
Extraintestinal manifestations: anemia, fatigue, hypertransaminasemia, neurologic disorders, short stature, dental enamel defects, arthralgia, aphthous stomatitis
Silent
No apparent symptoms in spite of histologic evidence of villous atrophy
In most cases identified by serologic screening in at-risk groups (see laboratory tests)
Latent
Subjects who have a normal histology, but at some other time, before or after, have shown a gluten-dependent enteropathy
Potential
Subjects with positive celiac disease serology but without evidence of altered jejunal histology
It might or might not be symptomatic

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

Dx DIAGNOSIS

Diagnostic criteria for celiac disease require at least four out of five or three out of four if the *HLA* genotype is not performed:

1. Typical symptoms of celiac disease
2. Positivity of serum celiac disease Ig A class autoantibodies at high titer
3. *HLA-DQ2* or *HLA-DQ8* genotypes
4. Celiac enteropathy at the small intestinal biopsy
5. Response to gluten-free diet

DIFFERENTIAL DIAGNOSIS

- Inflammatory bowel disease
- Laxative abuse
- Intestinal parasitic infestations
- Lactose intolerance
- Other: irritable bowel syndrome, tropical sprue, chronic pancreatitis, Zollinger-Ellison syndrome, cystic fibrosis (children), lymphoma, eosinophilic gastroenteritis, short bowel syndrome, Whipple's disease
- Intestinal lymphoma, tuberculosis, radiation enteritis, HIV enteropathy

LABORATORY TESTS

- IgA anti-tTG antibody by enzyme-linked immunosorbent assay (tissue transglutaminase [tTG] test) is the best screening serologic test for celiac disease. IgA antiendomysial antibodies (EMA) test is also a good screening test for celiac disease but is best used as a confirmatory test in cases of borderline positive results. In patients with IgA deficiency, the IgG DPG test (deamidated gliadin peptides) can be used for diagnosis. Screening of close relatives is initially done with PCR testing for *HLA DQ2* or *HLA DQ8*. Those that are positive should then have serum tTG IgA screening. All diagnostic serologic testing for celiac disease should be performed before a gluten-free diet is initiated.
- CBC, ferritin level: Iron-deficiency anemia (microcytic anemia, low ferritin level) may be present.
- Celiac disease can lead to malabsorption: Screen for vitamin B_{12} level, folate level, vitamin D level, serum calcium, albumin, magnesium; vitamin B_{12} deficiency, vitamin D deficiency, hypomagnesemia, and hypocalcemia are not uncommon in celiac disease.
- Biopsy of the small bowel, considered the gold standard, has been questioned as a reliable and conclusive test in all cases. It may be reasonable in children with significant elevations of tTG levels (>100 U) to first try a gluten-free diet and consider biopsy in those who do not improve with diet.
- The HLA-DQ2 allele is identified in >90% of patients with celiac disease, and HLA-DQ8 is identified in most of the remaining patients. These genes occur in only 30% to 40% of the general population. Their greatest diagnostic value is in their negative predictive value, making them useful when negative in ruling out the disease.

IMAGING STUDIES

- Consider bone density in newly diagnosed adult patients.
- Capsule endoscopy can be used to evaluate mucosa of the small intestine, especially if future innovations will allow mucosal biopsy.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Patients should be instructed on a gluten-free diet (avoidance of wheat, rye, and barley). Safe grains (gluten-free) include rice, corn, oats, buckwheat, millet, amaranth, quinoa, sorghum, and teff (an Ethiopian cereal grain). The lowest amount of daily gluten that causes damage to the celiac intestinal mucosa is 10-15 mg/day. One slice of bread contains 1.6 g of gluten.

GENERAL Rx

- Correct nutritional deficiencies with iron, folic acid, calcium, vitamin D, and vitamin B_{12} as needed.
- Prednisone 20 to 60 mg qd gradually tapered is useful in refractory cases.
- Lifelong gluten-free diet is necessary. A referral to a nutritionist experienced in celiac disease and gluten-free diet is recommended at initial diagnosis.

DISPOSITION

- Prognosis is good with adherence to a gluten-free diet. Rapid improvement is usually seen within a few days of treatment. Healing of the intestinal damage typically occurs within 6 to 24 mo after initiation of the diet. Lack of response to gluten-free diet occurs in 5% of patients and is due to unintentional ingestion of gluten or presence of coexisting GI disorders such as IBD, lactose or other carbohydrate intolerance, and pancreatic insufficiency.
- Serial antigliadin or antiendomysial antibody tests can be used to monitor the patient's adherence to a gluten-free diet.
- Repeat small-bowel biopsy after treatment generally reveals significant improvement. It is also useful to evaluate for increased risk of small-bowel T-cell lymphoma in these patients, especially untreated patients. Some experts recommend a repeat biopsy only in selected patients who have an unsatisfactory response to a strict gluten-free diet; however, recent data (Lebwohl et al) show that the risk for lymphoproliferative malignancy (LPM) is affected by the results of follow-up intestinal biopsy performed to document mucosal healing. Increased risk for LPM in CD is associated with the follow-up biopsy results, with a higher risk among patients with persistent villous atrophy. Follow-up biopsy may effectively stratify patients with CD by risk for subsequent LPM.

PEARLS & CONSIDERATIONS

COMMENTS

- The presence of dermatitis herpetiformis is pathognomonic for celiac disease.
- In close relatives, repeated serum tTG IgA testing may be useful in those with positive *HLA-DQ2* or *HLA-DQ8* tests because celiac disease may not manifest until later in life, and initial negative results do not preclude the possibility of future onset of celiac disease.
- Celiac disease should be considered in patients with unexplained metabolic bone disease, osteoporosis, transaminasemia, or hypocalcemia, because gastrointestinal symptoms are absent or mild. Clinicians should also consider testing children and young adults for celiac disease if unexplained weight loss, abdominal pain or distention, or chronic diarrhea is present.
- Screening for celiac disease is recommended in first-degree relatives. It should also be considered in patients with type 1 diabetes mellitus and in those with certain autoimmune disorders such as primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis, IBD, thyroid disease (hypothyroidism occurs in up to 15% of patients with celiac disease), SLE, RA, and Sjögren's syndrome due to increased risk of celiac disease in these populations. Screening persons with Down syndrome or Turner syndrome has also been recommended.
- The prevalence of celiac disease in patients with dyspepsia is twice that of the general population. Screening for celiac disease should be considered in all patients with persistent dyspepsia.
- Patients with celiac disease have an overall risk of cancer that is almost twice that of the general population. The risk of adenocarcinoma of the small intestine is increased manifold compared with the risk in the general population. Celiac disease is also associated with an increased risk for non-Hodgkin's lymphoma, especially of T-cell type and primarily localized in the gut. Lymphoma is 4 to 40 times more common, and death from lymphoma is 11 to 70 times more common in patients with celiac disease.
- Patients with celiac disease who have followed a gluten-free diet for prolonged periods may not experience relapse of symptoms for several months after gluten is reintroduced.

Trials involving randomized feeding intervention in infants at high risk for celiac disease have shown that as compared to placebo, the introduction of small quantities of gluten at 16 to 24 weeks of age did not reduce the risk of celiac disease by 3 years of age.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Celiac Disease (Patient Information)
Dermatitis Herpetiformis (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Objectives:

Despite increased prescription of a gluten-free diet for gastrointestinal symptoms in individuals who do not have celiac disease, there is minimal evidence that suggests that gluten is a trigger. The aims of this study were to determine whether gluten ingestion can induce symptoms in non-celiac individuals and to examine the mechanism.

Methods:

A double-blind, randomized, placebo-controlled rechallenge trial was undertaken in patients with irritable bowel syndrome in whom celiac disease was excluded and who were symptomatically controlled on a gluten-free diet. Participants received either gluten or placebo in the form of two bread slices plus one muffin per day with a gluten-free diet for up to 6 weeks. Symptoms were evaluated using a visual analog scale and markers of intestinal inflammation, injury, and immune activation were monitored.

Results:

A total of 34 patients (aged 29 to 59 years, 4 men) completed the study as per protocol. Overall, 56% had human leukocyte antigen (HLA)-DQ2 and/or HLA-DQ8. Adherence to diet and supplements was very high. Of 19 patients (68%) in the gluten group, 13 reported that symptoms were not adequately controlled compared with 6 of 15 (40%) on placebo (P=0.0001; generalized estimating equation). On a visual analog scale, patients were significantly worse with gluten within 1 week for overall symptoms (P=0.047), pain (P=0.016), bloating (P=0.031), satisfaction with stool consistency (P=0.024), and tiredness (P=0.001). Anti-gliadin antibodies were not induced. There were no significant changes in fecal lactoferrin, levels of celiac antibodies, highly sensitive C-reactive protein, or intestinal permeability. There were no differences in any end point in individuals with or without DQ2/DQ8.

Conclusion:

"Non-celiac gluten intolerance" may exist, but no clues to the mechanism were elucidated. Ⓐ

Evidence-Based Reference

Biesiekierski JR et al.: Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial, *Am J Gastroenterol* 106:508–514, 2011. Ⓐ

SUGGESTED READINGS

Catassi C, Fasano A: Celiac disease diagnosis: simple rules are better than complicated algorithms, *Am J Med* 123:691–693, 2010.

Collins D et al.: Celiac disease and hypothyroidism, *Am J Med* 125:278–282, 2012.

Crowe SE: In the clinic: celiac disease, *Ann Intern Med ITC* 1–14, 2011.

Fasano A, Catassi C: Clinical practice. Celiac disease, *N Engl J Med* 367:2419–2426, 2012.

Godfrey JD et al.: Morbidity and mortality among older individuals with undiagnosed celiac disease, *Gastroenterology* 139:763, 2010.

Green PH, Cellier C: Celiac disease, *N Engl J Med* 357:1731–1743, 2007.

Hill ID: Diagnosing disease: how important is the biopsy? *J Pediatr 157* 353, 2010.

Kurppa K et al.: Celiac disease without villous atrophy in children: a prospective study, *J Pediatr* 157:353, 2010.

Lebwohl B et al.: Mucosal healing and risk for lymphoproliferative malignancy in celiac disease, *Ann Intern Med* 159:169–175, 2013.

Ludvigsson JF et al.: Small intestinal histopathology and mortality risk in celiac disease, *JAMA* 302(11):1171–1178, 2009.

Pelkowski TD, Viera AJ, et al.: Celiac disease: diagnosis and management, *Am Fam Physician* 89(2):99–105, 2014.

Van der Windt D et al.: Diagnostic testing for celiac disease among patients with abdominal symptoms, *JAMA* 303(17):1738–1746, 2010.

Vriezinga SL et al.: Randomized feeding intervention in infants at high risk for celiac disease, *N Engl J Med* 371:1304–1315, 2014.

BASIC INFORMATION

DEFINITION

Cellulitis is a superficial inflammatory condition of the skin and underlying tissues characterized by erythema, warmth, and tenderness of the involved area.

SYNONYMS

Erysipelas (cellulitis generally caused by group A β-hemolytic streptococci)
SSSIs (skin and skin structure infections)
ABSSSIs (acute bacterial skin and skin structure infections)

ICD-9CM CODES
682.9 Cellulitis
ICD-10CM CODES
L03.90 Cellulitis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Occurs most frequently in diabetics, immunocompromised hosts, and patients with venous and lymphatic compromise.
- Frequently found near skin breaks (trauma, surgical wounds [surgical site infections develop in 2% to 5% of all surgical procedures], ulcerations, tinea infections). Edema, animal or human bites, subadjacent osteomyelitis, and bacteremia are potential sources of cellulitis.
- Skin and soft-tissue infections account for >14 million outpatient visits in the U.S./yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Variable with the causative organism:

- Erysipelas (Fig. C1-40): superficial-spreading, warm, erythematous lesion distinguished by indurated, elevated margin; lymphatic involvement, vesicle formation common.
- Staphylococcal cellulitis: area involved is erythematous, hot, and swollen; differentiated from erysipelas by nonelevated, poorly demarcated margin; local tenderness and regional adenopathy are common; up to 85% of cases occur on the legs and feet.
- *Haemophilus influenzae* cellulitis: area involved is a blue-red/purple-red color; occurs mainly in children; generally involves the face in children and the neck or upper chest in adults.
- *Vibrio vulnificus:* larger hemorrhagic bullae, cellulitis, lymphadenitis, myositis; often found in critically ill patients in septic shock.

ETIOLOGY

- Group A β-hemolytic streptococci (may follow a streptococcal infection of the upper respiratory tract). β-hemolytic streptococci are implicated in most cases of non-traumatic cellulitis.
- Staphylococcal cellulitis: Diabetics, athletes, men who have sex with men, people living in public housing, and incarcerated men are at greater risk for methicillin-resistant *Staphylococcus aureus* (MRSA) infection. A community-acquired MRSA strain, USA 300, is replacing nosocomial strains of MRSA in hospitals.
- IV drug use: MRSA, *Pseudomonas aeruginosa.*
- *V. vulnificus:* higher incidence in patients with liver disease (75%) and in immunocompromised hosts. *V. vulnificus* infection is the leading cause of death related to seafood consumption in the U.S.
- *Erysipelothrix rhusiopathiae:* common in people handling poultry, fish, or meat.
- *Aeromonas hydrophila:* generally occurs in contaminated open wounds in fresh water.
- Fungi *(Cryptococcus neoformans):* in immunocompromised granulopenic patients.
- Gram-negative rods *(Serratia, Enterobacter, Proteus, Pseudomonas):* may be present in immunocompromised or granulopenic patients.
- Hot tub exposure: *P. aeruginosa*; fish tank exposure: *Mycobacterium marinum.*
- Bites: human *(Eikenella corrodens),* dog *(Pasteurella multocida, C. canimorsus),* cat *(P. multocida),* rat *(Streptobacillus moniliformis).*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Necrotizing fasciitis (reddish-purple discoloration of skin, rapid increase in size, woody induration and pale appearance rather than erythema, violaceous bullae, pain out of proportion to appearance, sepsis)
- Deep vein thrombosis
- Peripheral vascular insufficiency
- Paget disease of the breast
- Thrombophlebitis
- Acute gout
- Psoriasis
- *Candida* intertrigo
- Pseudogout
- Osteomyelitis
- Insect bite
- Fixed drug eruption
- Lymphedema
- Contact dermatitis
- Olecranon bursa infection
- Herpetic whitlow, early herpes zoster (before blisters)
- Erythema migrans (Lyme disease)
- Rare: *Vaccinia* vaccination, Kawasaki disease, pyoderma gangrenosum, Sweet syndrome, carcinoma erysipeloides, anaerobic myonecrosis, erythromelalgia, eosinophilic cellulitis (Well's syndrome), familial Mediterranean fever

LABORATORY TESTS

- Gram stain, culture (aerobic and anaerobic):
  1. Aspirated material from:
     a. Advancing edge of cellulitis
     b. Any vesicles
  2. Swab of any drainage material
  3. Punch biopsy (in selected patients)
- Blood cultures in hospitalized patients, patients with cellulitis superimposed on lymphedema, patients with buccal or periorbital cellulitis, and patients suspected of having a salt- or fresh-water source of infection. Bacteremia uncommon in cellulitis (positive blood cultures in 4% of patients).
- Anti-streptolysin O (ASLO) titer (in suspected streptococcal disease)

The cause of cellulitis remains unidentified in most patients. Patients with recurrent lower-extremity cellulitis should be inspected for tinea pedis. If found it should be treated.

IMAGING STUDIES

CT or MRI in patients with suspected necrotizing fasciitis (deep-seated infection of the subcutaneous tissue that results in the progressive destruction of fascia and fat).

TREATMENT

NONPHARMACOLOGIC THERAPY

Immobilization and elevation of the involved limb. Cool sterile saline dressings to remove purulence from any open lesion. Support stockings in patients with peripheral edema.

ACUTE GENERAL Rx

Erysipelas:

- PO: dicloxacillin 500 mg PO q6h
- IV: cefazolin 1 g q6 to 8h or nafcillin 1.0 or 1.5 g IV q4 to 6h

NOTE: Use vancomycin 1 g IV q12h in patients allergic to penicillin.

Staphylococcal cellulitis:

- PO: dicloxacillin 250 to 500 mg qid
- IV: nafcillin 1 to 2 g q4 to 6h
- Cephalosporins (cephalothin, cephalexin, cephradine) also provide adequate antistaphylococcal coverage, except for MRSA.
- Trimethoprim-sulfamethoxazole (160 mg/800 mg 1 PO bid) may be appropriate in mild MRSA infections. Use vancomycin 1.0 to 2.0 g IV qd or linezolid 0.6 g IV q12h in patients allergic to penicillin or cephalosporins and in patients with moderate/severe MRSA. Daptomycin (Cubicin), a cyclic lipopeptide, can be used as an alternative to vancomycin for complicated skin and skin structure infections. Usual dose is 4 mg/kg IV given over 30 min every 24 hr. Telavancin is a new glycopeptide derivative of vancomycin effective for gram-positive skin and skin structure infections, including those caused by MRSA. Tedizolid is an oxazolidinone effective in ABSSSI as an alternative to linezolid. Ceftaroline fosamil (Teflaro) is a new IV cephalosporin also effective against MRSA. Dalbavancin and tedizolid are two new drugs recently FDA-approved for skin and skin structure infections, including those caused by MRSA.

H. influenzae cellulitis:

- PO: cefixime or cefuroxime
- IV: cefuroxime or ceftriaxone

Vibrio vulnificus:

- Doxycycline 100 mg IV bid + ceftazidime 2 g IV q8h or IV ciprofloxacin 400 mg bid. Mild cases treated with oral antibiotics (doxycycline 100 mg bid + ciprofloxacin 750 mg bid).
- IV support and admission into intensive care unit (mortality rate >50% in septic shock).

E. rhusiopathiae:
- Penicillin

A. hydrophila:
- Aminoglycosides
- Chloramphenicol
- Complicated skin and skin structure infections in hospitalized patients can be treated with daptomycin (Cubicin) 4 mg/kg IV q24h

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Cellulitis (Patient Information)
Erysipelas (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

FIGURE C1-40 Erysipelas of the leg. A, Note the open wound on the proximal thigh, which gave rise to this infection. The patient should be monitored closely for more severe skin changes (e.g., purpura, bulla, postbullous ulceration, necrosis, hypoesthesia, fluctuance), which may suggest necrotizing fasciitis or pyomyositis. **B,** Chronic lymphedema has predisposed to cellulitis in this elderly patient. (From White GM, Cox NH, eds: *Diseases of the skin,* ed 2, St Louis, 2006, Mosby.)

SUGGESTED READINGS

Daum RS: Skin and soft-tissue infections caused by methicillin-resistant Staphylococcus aureus, *N Engl J Med* 357:380–390, 2007.

Khawcharoenporn T, Tice A: Empiric outpatient therapy with trimethoprim-sulfamethoxazole, cephalexin, or clindamycin for cellulitis, *Am J Med* 123: 942–950, 2010.

Prokocimer P et al.: Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: the ESTABLISH-1 randomized trial, *JAMA* 309(6):559–569, 2013.

Swartz MN: Cellulitis, *N Engl J Med* 350:904, 2004.

BASIC INFORMATION

DEFINITION

Cerebral palsy (CP) is a group of disorders of the central nervous system characterized by aberrant control of movement or posture, present since early in life and not the result of a progressive or degenerative disease. Fig. C1-41 provides a classification of CP.

SYNONYMS

Little's disease
Congenital static encephalopathy
Congenital spastic paralysis
CP

ICD-9CM CODES
343 Infantile cerebral palsy
342 Hemiplegia and hemiparesis
344 Quadriplegia and quadriparesis
ICD-10CM CODES
M41.40 Neuromuscular scoliosis, site unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 2 to 2.5 persons per 1000 live births
PREDOMINANT SEX: Males and females affected equally
PREDOMINANT AGE: Diagnosis typically made at 3 to 5 years of age

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Monoplegia, diplegia, quadriplegia, hemiplegia
- Often hypotonic in newborn period, followed by development of hypertonia
- Spasticity
- Athetosis
- Delay in motor milestones
- Hyperreflexia
- Seizures
- Mental retardation in many individuals

ETIOLOGY

Multifactorial, including low birth weight, congenital malformation, asphyxia, multiple gestation, intrauterine exposure to infection, neonatal stroke, hyperbilirubinemia, and maternal thyroid malfunction

DIAGNOSIS

A motor deficit is always present. The usual presenting complaint is that child is not reaching motor milestones at the appropriate age. Medical history establishes that the child is not losing function (i.e., that deficit is static and not progressive). This history, combined with a neurologic examination establishing that motor deficit is due to a cerebral abnormality, establishes the diagnosis of CP. Serial examinations may be necessary.

DIFFERENTIAL DIAGNOSIS

Other causes of neonatal hypotonia include muscular dystrophies, spinal muscular atrophy, Down syndrome, and spinal cord injuries. Causes of progressive spasticity in children include metabolic diseases involving white matter (e.g., leukodystrophy).

WORKUP

- Laboratory tests are not necessary to establish the diagnosis.
- Workup is helpful for assessment of recurrence risk, implementation of prevention programs, and medicolegal purposes.

LABORATORY TESTS

- Metabolic and genetic testing should be considered if on follow-up the child has (1) evidence of deterioration or episodes of metabolic decompensation, (2) no etiology determined by neuroimaging, (3) family history of childhood neurologic disorder associated with CP, or (4) developmental malformation on neuroimaging. Hypercoagulability workup should be considered if neuroimaging is suggestive of a remote stroke.
- EEG should be obtained when a child with CP has a history suggestive of seizures.
- Children with CP should be screened for ophthalmologic and hearing impairments, as well as speech and language disorders. Nutrition, growth, and swallowing function should be monitored.

IMAGING STUDIES

- Neuroimaging is recommended if the etiology has not been established previously, for example by perinatal imaging.
- MRI, when available, is preferred to CT scanning because of higher yield in determining an etiology and timing of the insult leading to CP.

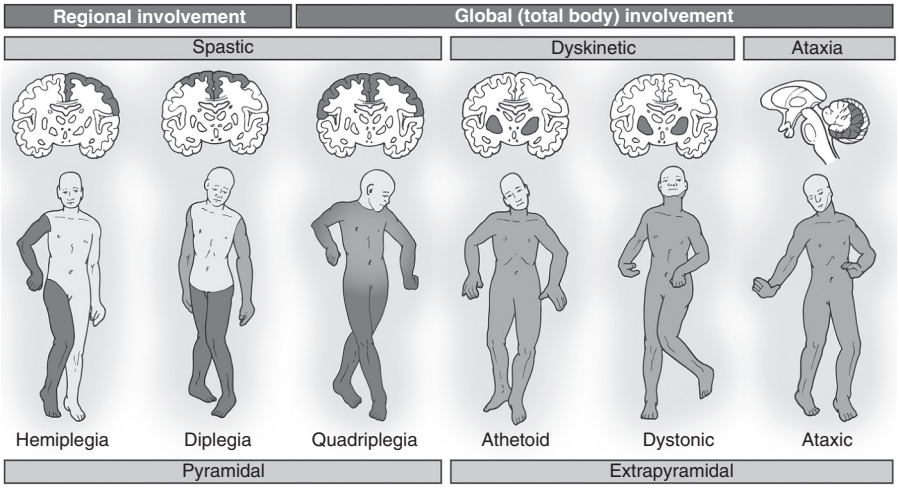

FIGURE C1-41 Classification of cerebral palsy. Although overlaps in terminology exist, cerebral palsy can be classified according to distribution (regional versus global involvement, hemiplegic, diplegic, quadriplegic), physiologic type (spastic, dyskinetic/dystonic, dyskinetic/athetoid, ataxic), or presumed neurologic substrate (pyramidal, extrapyramidal). (From Canale ST, Beaty JH: *Campbell's operative orthopaedics,* ed 11, Philadelphia, 2007, Mosby.)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Physical therapy, occupational therapy, and speech therapy.
- Orthotics and casting are used to increase musculotendinous length.

ACUTE GENERAL Rx

If present, treatment of seizures

CHRONIC Rx

- Treatment of seizures, as directed by seizure type.
- Medical treatment of spasticity includes baclofen (oral and intrathecal), as well as botulinum toxin A.
- Surgical treatments of spasticity include dorsal rhizotomy, tendon lengthening, and osteotomy.

DISPOSITION

Most children with CP live at home. Those children with severely impaired mobility or other disabilities may live in chronic-care nursing facilities.

REFERRAL

If the child has difficulty with spasticity, physical medicine and rehabilitation referrals are especially helpful.

PEARLS & CONSIDERATIONS

- In full-term infants, there is usually no history of traumatic delivery.
- Compared with delivery at 40 wks' gestation, delivery at 37 or 38 wks or at 42 wks or later was associated with an increased risk of CP.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Cerebral Palsy (Patient Information)

AUTHOR: **MAITREYI MAZUMDAR, M.D., M.P.H., M.SC.**

SUGGESTED READINGS

Ashwal S et al.: Practice parameter: diagnostic assessment of the child with cerebral palsy: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society, *Neurology* 62(6):851, 2004.

Moster D et al.: Cerebral palsy among term and post-term births, *JAMA* 304(9):976–982, 2010.

Nelson KB: The epidemiology of cerebral palsy in term infants, *Ment Retard Dev Disabil Res Rev* 8(3):146, 2002.

BASIC INFORMATION

DEFINITION

Cerebral vasculitis refers to a group of heterogeneous disorders characterized by pathologic inflammation and leukocytoclastic changes in the blood vessel walls.

SYNONYMS

Central nervous system angiitis
Cerebral arteritis

ICD-9CM CODES
437.4 Cerebral arteritis
ICD-10CM CODES
I67.7 Cerebral arteritis, not elsewhere classified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Average annual incidence rate is 2.4 cases per 1,000,000 person-yr.
PEAK INCIDENCE: Fourth decade of life
PREDOMINANT SEX: Males are affected twice as often as females.
PREDOMINANT AGE: Usual age of presentation is in the third and fourth decades of life, but can present in age ranging from 17 to 70 yr.
GENETICS: Multifactorial
RISK FACTORS: Infections, connective tissue disorders, systemic vasculitis, and substance abuse are the prominent risk factors for secondary cerebral vasculitis.
CLASSIFICATION:

- Primary cerebral vasculitis or primary angiitis of the central nervous system (CNS): involvement of the blood vessels in brain or spinal cord without involvement of blood vessels or organs beyond the CNS.
- Secondary CNS vasculitis (Table EC1-10): involvement of the brain or spinal cord blood vessels by a systemic disorder such as systemic vasculitis, connective tissue disorders, infections, malignancy, or substance abuse.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Presentation of cerebral vasculitis is diverse and includes the following:
  1. Nonspecific symptoms such as weight loss, lethargy, vomiting, headache, and confusion in the early course of the disease.
  2. Neurologic manifestations: seen in 80% of patients during course of illness; may mimic multiple sclerosis, with a relapsing and remitting course.
  3. Stroke can occur in 40% of the patients; transient ischemic attacks have been reported in 30%-50% of patients.
  4. Seizures occur in 25% of patients.
  5. Other common presentations include intracerebral hemorrhage (11%) and intracranial space-occupying lesions (15%).
- Secondary vasculitis often presents with stroke-like symptoms. Sjögren's syndrome and Behçet's disease can have varied presentations that mimic multiple sclerosis, seizures, movement disorders, encephalopathy, dementia, and aseptic meningitis.

ETIOLOGY

The exact etiology of primary cerebral vasculitis is unknown. It has been associated with various infectious agents such as herpes zoster, mycoplasma, HIV, and unknown viruses. Amyloid angiopathy has been described with primary cerebral vasculitis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Reversible cerebral vasoconstriction syndromes
- Intracranial vessels atherosclerosis
- Cerebral emboli
- Intravascular lymphoma
- Sarcoidosis
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)

TABLE EC1-10 Common Causes of Secondary Cerebral Vasculitis and Associated Features

Giant Cell Arteritis/Takayasu's Arteritis	"Pulseless Disease," Fever, Weight loss, Syncope, Visual Field Defects
Polyarteritis nodosa	Fever, weight loss, arthralgia, renal failure, myocardial infarction
Churg-Strauss syndrome	Asthma-like features followed by multiple-organ system involvement including GI, skin, kidneys, CNS, heart
Wegener's granulomatosis	Rhinitis, epistaxis, hemoptysis, hematuria, chronic renal failure
Behçet's disease	Oral ulcers, genital ulcers, skin lesions, uveitis, iritis
Systemic lupus erythematosus	Malar rash, oral ulcers, photosensitivity, arthralgia, renal failure, anemia, ANA positive
Rheumatoid arthritis	Arthritis involving hand joints, radiologic evidence of joint erosion, rheumatoid factor positive
Sjögren's syndrome	Dry mouth, dry eyes, involvement of lung, liver, pancreas, joints
Lymphoma	Fever, weight loss, night sweats, lymph node enlargement, hepatosplenomegaly

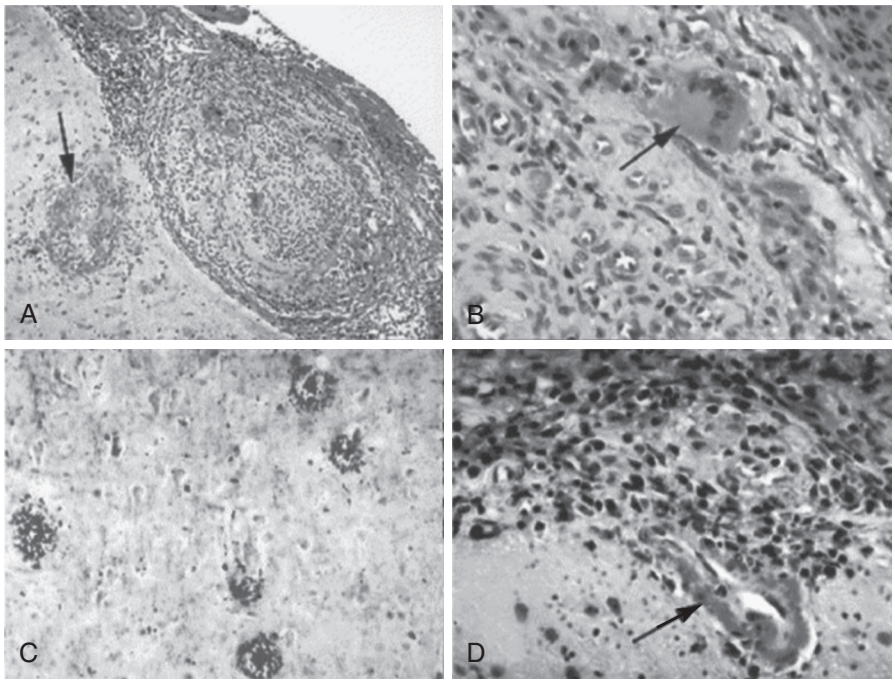

FIGURE EC1-42 A, Low-power hematoxylin and eosin stain (10×) demonstrates diffuse inflammation in the leptomeninges with infiltration of lymphocytes, eosinophils, and macrophages with destruction of the vessel wall. **B,** A multinucleated giant cell *(arrow).* **C,** Multiple neuritic plaques are seen on this silver stain. **D,** Congo red stain demonstrating the presence of amyloid within a vessel wall *(arrow).* (From Jacobs DA et al: Primary central nervous system angiitis, amyloid angiopathy and Alzheimer's pathology presenting with Balint's syndrome, *Surv Ophthalmol* 49[4]:454-459, 2004.)

WORKUP

- Brain biopsy (usually nondominant temporal lobe tip along with overlying leptomeninges) is the gold standard for diagnosis of cerebral vasculitis.
- Cerebral angiography supports the diagnosis of CNS vasculitis but has low sensitivity and specificity (Fig. EC1-42).

LABORATORY TESTS

- Lumbar puncture: may show elevated cerebrospinal fluid opening pressure, elevated protein, lymphocytic pleocytosis, and negative microbial cultures.
- Basic laboratory testing: should include CBC with differential, blood urea nitrogen and serum creatinine, hepatic functions and enzymes, erythrocyte sedimentation rate, RPR (for syphilis), C-reactive protein, and urine analysis.
- Specific serologic tests to evaluate autoimmune causes: ANA, rheumatoid factor, anti–double-stranded DNA, anti SS-A, anti SS-B, anti–neutrophil cytoplasmic antibody (ANCA), complement 3 and 4, cryoglobulins, serum immunoglobulins, and HIV testing.

IMAGING STUDIES

Magnetic resonance imaging (MRI) is the neuroimaging of choice. Abnormal findings are seen in 90% to 100% of the patients. Cerebral cortex, deep white and gray matter changes are commonly reported (Fig. EC1-43).

Rx TREATMENT

There are no randomized controlled trials evaluating treatment of cerebral vasculitis. Treatment strategies are similar to those for other systemic vasculitis.

NONPHARMACOLOGIC THERAPY

Patients with permanent deficits are provided with physical and occupational therapy.

ACUTE GENERAL Rx

- Steroids: For suspected cases, empiric therapy with glucocorticoids is started after exclusion of infectious causes. Intravenous methylprednisolone 1 g daily for 3 days is preferred for patients with severe disease; otherwise, oral prednisone is started at 1 mg/kg/day.

CHRONIC Rx

- Steroids: Oral prednisone is continued at high dose (1 mg/kg/day) for 4 to 6 wk and then tapered over 12 mo.
- Immunosuppressive treatment: cyclophosphamide orally for 3 to 6 months for remission induction. Once stable, milder and relatively safer immunosuppressants such as azathioprine, methotrexate, or mycophenolate are used for 2 to 3 years.

DISPOSITION

Course and prognosis of the disease is variable. It depends on the extent of neurologic involvement, severity of deficits, and response to treatment. Neurologic deficits may resolve acutely, slowly, or not at all. Some patients have symptomatic improvement with resolution of headache or altered mental status. Some have improvement in laboratory values, and others have improved MRI scans.

REFERRAL

- Neurology: referral to neurology is indicated in patients with neurologic deficits of uncertain etiology, younger age, intractable headaches, or uncertain diagnosis.
- Neurosurgical consult for brain biopsy.

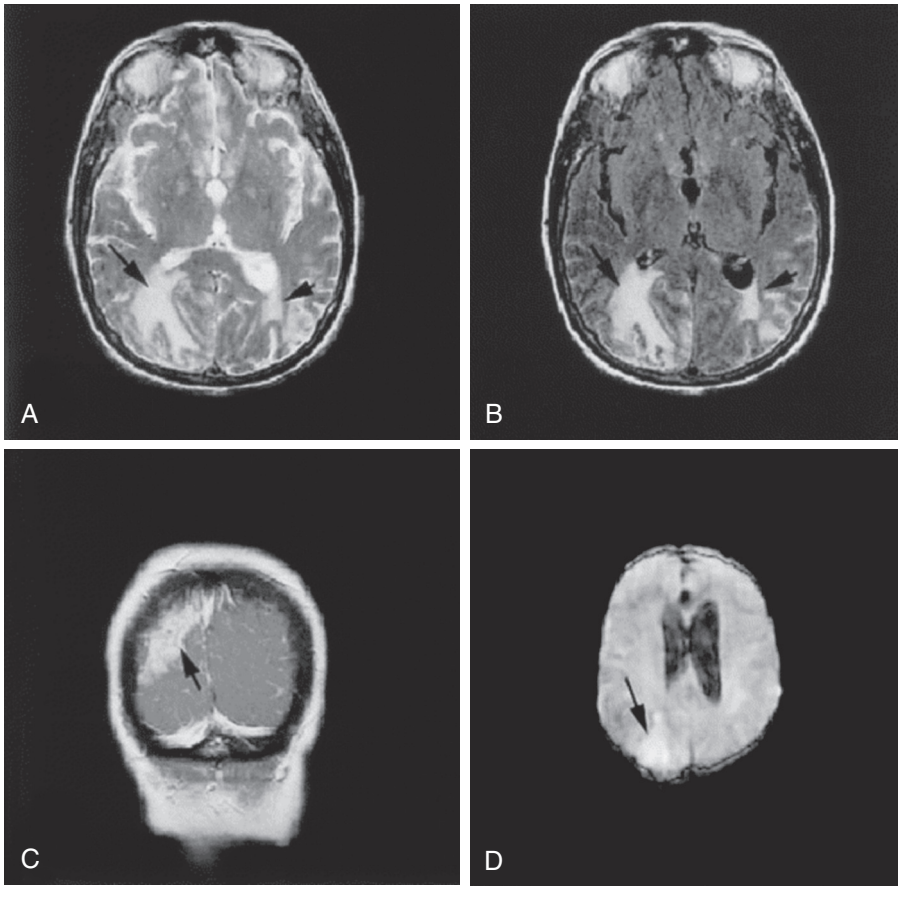

FIGURE EC1-43 A, Axial T2-weighted image shows abnormal signal in bilateral parietooccipital lobes, greater on the right than left *(arrows).* **B,** Axial fluid attenuated inversion recovery image further delineating the extent of bilateral parietooccipital lesions *(arrow).* **C,** Coronal T1-gadolinium study demonstrating nodular leptomeningeal enhancement in the lesion *(arrow).* **D,** Diffusion-weighted magnetic resonance imaging shows bright signal in the right parietooccipital region, suggesting ischemic changes *(arrow).* (From Jacobs DA et al: Primary central nervous system angiitis, amyloid angiopathy and Alzheimer's pathology presenting with Balint's syndrome, *Surv Ophthalmol* 49[4]:454-459, 2004.)

PEARLS & CONSIDERATIONS

COMMENTS

- Cerebral vasculitis is a rare disorder that is difficult to diagnose because of variable presentation.
- Early recognition of the clinical symptoms and signs is important to prevent long-term morbidity and mortality.
- Systemic causes should be excluded.
- Patients may need chronic immunosuppressive treatment.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Vasculitis (Related Key Topic)

AUTHOR: **FARIHA ZAHEER, M.D.**

SUGGESTED READINGS

Birnbaum J, Hellmann DB: Primary angiitis of the central nervous system, *Arch Neurol* 66(6):704–709, 2009.

de Boysson H et al.: Primary angiitis of the central nervous system: description of the first fifty-two adults enrolled in the French cohort of patients with primary vasculitis of the central nervous system, *Arthritis Rheumatol* 66:1315–1326, 2014.

Salvarani C et al.: Primary central nervous system vasculitis: analysis of 101 patients, *Ann Neurol* 62(5):442–451, 2007.

BASIC INFORMATION

DEFINITION

Cervical cancer is the penetration of the basement membrane and infiltration of the stroma of the uterine cervix by malignant cells.

ICD-9CM CODES
180 Malignant neoplasm of cervix uteri
ICD-10CM CODES
C53.9 Malignant neoplasm of cervix uteri, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Approximately 15,000 new cases annually, with 4000 to 5000 associated deaths. U.S. has age-adjusted mortality rate of 2.6 per 100,000 persons.
PREDOMINANCE: Higher incidence rates occur in developing countries. Among the U.S. population, Hispanics have a higher incidence than African Americans, who likewise have a higher incidence than whites. Worldwide, cervical cancer is the third most common cancer in women.
RISK FACTORS: Smoking, early age at first intercourse, multiple sexual partners, immunocompromised state, nonbarrier methods of birth control, infection with high-risk human papillomavirus (HPV; types 16 and 18), and multiparity.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Unusual vaginal bleeding, particularly postcoital
- Vaginal discharge and/or odor
- Advanced cases may present with lower-extremity edema or renal failure
- In early stages, there may be little or no obvious cervical lesion; more advanced cases may have large, bulky, friable lesions encompassing majority of vagina

ETIOLOGY

- Infection with high-risk HPV types is a necessary, although not sufficient, cause of almost all cases of cervical cancer. Persistent HPV infection leads to precancerous changes of cervix (cervical intraepithelial neoplasia [CIN]). CIN can progress to invasive cervical cancer.
- More than 40 HPV types can infect cervix. Most cases are believed to be linked to presence of HPV 16, 18, 45, and 56 by interaction of E6 oncoprotein on p53 gene product.
- There may be an association with past infection with *Chlamydia trachomatis.*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cervical polyp or prolapsed uterine fibroid
- Preinvasive cervical lesions
- Neoplasia metastatic from a separate primary neoplasia

WORKUP

- Thorough history and physical examination.
- Pelvic examination with careful rectovaginal examination.
- Compared with Pap testing, HPV testing has greater sensitivity for detection of CIN. Addition of HPV test for high-risk types to Pap test to screen women in mid-30s for cervical cancer reduces incidence of grade 2 or 3 CIN or cancer detected by subsequent screening examinations.
- Colposcopy with directed biopsy and endocervical curettage.
- FIGO staging described in Table C1-11.

LABORATORY TESTS

- Complete blood count, chemistry profile
- SCC antigen in research setting
- Carcinoembryonic antigen

IMAGING STUDIES

- Chest x-ray
- Depending on stage, may need cystoscopy, sigmoidoscopy or barium enema, CT scan or MRI (Fig. EC1-44), lymphangiography
- Intravenous pyelogram

TREATMENT

NONPHARMACOLOGIC THERAPY

- FIGO stage IA: cone biopsy or simple hysterectomy
- FIGO stage IB or IIA: type III radical hysterectomy and pelvic lymphadenectomy or pelvic radiation therapy
- Advanced or bulky disease: multimodality therapy (radiation, chemotherapy, and/or surgery); platinum use before radiation therapy

ACUTE GENERAL Rx

Table C1-11 summarizes treatment according to tumor stage. Chemotherapy is cisplatin-based. In advanced cases, cervical cancer may present with massive and acute vaginal bleeding requiring volume and blood replacement, vaginal packing or other hemostatic modalities, and/or high-dose local radiotherapy.

CHRONIC Rx

- Physical examination with Pap smear every 3 mo for 2 yr, every 6 mo for 3 to 5 yr, annually thereafter
- Chest x-ray examination annually

DISPOSITION

Five-year survival varies by stage:
- Stage I: 60% to 90%
- Stage II: 40% to 80%
- Stage III: <60%
- Stage IV: <15%

Early detection by Pap smear is imperative for long-term improvements in survival.

REFERRAL

Gynecologic oncologist for all invasive disease

TABLE C1-11 FIGO Staging of Cervical Cancer

Stage	Invasion	Prognosis 5-yr Survival	Treatment
1_{A1}	Depth of invasion up to 3 mm and width up to 7 mm (includes early stromal invasion of up to 1 mm)	84% to 90% if tumor <3 cm; 85% will have negative pelvic nodes and 95% of these patients will be "cured"	Local excision; if margins of cone clear (i.e., no residual tumor or CIN) then conization is adequate, with no need for pelvic lymphadenectomy
1_{A2}	Depth of invasion between 3 and 5 mm (i.e., 3.1-5 mm) and width up to 7 mm		Simple hysterectomy and pelvic lymphadenectomy
1_{B1}	Tumor confined to cervix and diameter less than 4 cm	66% if tumor >3 cm	Radical hysterectomy or radiotherapy
1_{B2}	Tumor confined to cervix and diameter more than 4 cm		Radical hysterectomy or radiotherapy
II_A	Upper 1/3 vagina	62%	Radical hysterectomy or radiotherapy
II_B	Upper 2/3 of vagina plus parametrial disease		Radiotherapy ± chemotherapy
III_A	Lower 1/3 vagina	40%	Radiotherapy ± chemotherapy
III_B	Pelvic sidewall and/or hydronephrosis		Radiotherapy ± chemotherapy
IV_A	Bladder, rectum	15%	Radiotherapy ± chemotherapy
IV_B	Beyond pelvis		Radiotherapy ± chemotherapy

From Drife J, Magowan B: *Clinical obstetrics and gynecology*, Philadelphia, 2004, Saunders.

PEARLS & CONSIDERATIONS

- Gardasil is a vaccine indicated in males and females age 9 to 26 yr for the prevention of cervical cancer caused by HPV types 6, 11, 16, and 18.
- Available evidence supports discontinuation of cervical cancer screening among women aged 65 yrs or older who have had adequate screening and are not otherwise at high risk.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Cervical Dysplasia (Related Key Topic)
Cervical Cancer (Patient Information)

AUTHOR: **RUBEN ALVERO, M.D.**

EVIDENCE

Abstract[1]

Purpose:
To determine whether addition of gemcitabine to concurrent cisplatin chemoradiotherapy and as adjuvant chemotherapy with cisplatin improves progression-free survival (PFS) at 3 years compared with current standard of care in locally advanced cervical cancer.

Patients and Methods:
Eligible chemotherapy- and radiotherapy-naive patients with stage IIB to IVA disease and Karnofsky performance score ≥70 were randomly assigned to arm A (cisplatin 40 mg/m^2 and gemcitabine 125 mg/m^2 weekly for 6 weeks with concurrent external-beam radiotherapy [XRT] 50.4 Gy in 28 fractions, followed by brachytherapy [BCT] 30 to 35 Gy in 96 hours, and then two adjuvant 21-day cycles of cisplatin, 50 mg/m^2 on day 1, plus gemcitabine, 1000 mg/m^2 on days 1 and 8) or to arm B (cisplatin and concurrent XRT followed by BCT only; dosing same as for arm A).

Results:
Between May 2002 and March 2004, 515 patients were enrolled (arm A, n=259; arm B, n=256). PFS at 3 years was significantly improved in arm A versus arm B (74.4% v 65.0%, respectively; *P*=.029), as were overall PFS (log-rank *P*=.0227; hazard ratio [HR], 0.68; 95% CI, 0.49 to 0.95), overall survival (log-rank *P*=.0224; HR, 0.68; 95% CI, 0.49 to 0.95), and time to progressive disease (log-rank *P*=.0012; HR, 0.54; 95% CI, 0.37 to 0.79). Grade 3 and 4 toxicities were more frequent in arm A than in arm B (86.5% v 46.3%, respectively; *P*<.001), including two deaths possibly related to treatment toxicity in arm A.

Conclusion:
Gemcitabine plus cisplatin chemoradiotherapy followed by BCT and adjuvant gemcitabine/cisplatin chemotherapy improved survival outcomes with increased but clinically manageable toxicity when compared with standard treatment. Ⓐ

Abstract[2]

Human papillomavirus (HPV)-based management of women with borderline atypical squamous cells of undetermined significance (ASCUS) or mildly abnormal cervical intraepithelial neoplasia (CINI) cervical cytology has been extensively studied in the research setting. We wished to assess safety and health care resource use of a real-life health care policy using HPV triaging. All 15 outpatient clinics involved in the organized population-based screening program in Stockholm, Sweden screening program were randomized to either continue with prior policy (colposcopy of all women with ASCUS/CINI) or to implement a policy with HPV triaging and colposcopy only of HPV-positive women. The trial enrolled the 3319 women who were diagnosed with ASCUS (*n*=1,335) or CINI (*n*=1,984) in Stockholm during 17th March 2003 to 16th January 2006. Detection of high-grade cervical lesions (CINII+) and health care cost consumption was studied by registry linkages. The proportion of histopathology-verified CINII+ was similar for the two policies (395 of 1752 women (22.5%; 95% Confidence interval [CI]: 20.6% to 24.6%) had CINII+ diagnosed with HPV triaging policy, 318 of 1567 women (20.3%; 95% CI: 18.3% to 22.4%) had CINII+ with colposcopy policy). Sixty-four percent of women with ASCUS and 77% of women with CINI were HPV positive. HPV-positivity was age-dependent, with 81% of women below 35 years of age and 44% of women above 45 years of age testing HPV-positive. HPV triaging was cost-effective only above 35 years of age. In conclusion, a real-life randomized health services study of HPV triaging of women with ASCUS/CINI demonstrated similar detection of CINII+ as colposcopy of all women. Ⓐ

Evidence-Based References

Dueñas-González A, et al.: Phase III, open label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix, *J Clin Oncol* 29:1678–1685, 2011. Ⓐ

Dillner L, et al.: Randomized healthservices study of human papillomavirus-based management of low-grade cytological abnormalities, *Int J Cancer* 129:151–159, 2011. Ⓐ

SUGGESTED READINGS

Kahn JA: HPV vaccination for the prevention of cervical intraepithelial neoplasia, *N Engl J Med* 361:271–278, 2009.

Long HJ, et al.: Prevention, diagnosis, and treatment of cervical cancer, *Mayo Clin Proc* 82(12):1566–1574, 2007.

Mayrand MH, et al.: Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer, *N Engl J Med* 357:1579–1588, 2007.

McCreath S: Cervical cancer: current management of early/late disease, *Surg Oncol Clin North Am* 14(2):249, 2005.

Naucler P, et al.: Human papillomavirus and Papanicolaou tests to screen for cervical cancer, *N Engl J Med* 357:1589–1597, 2007.

Vesco U, et al.: Risk factors and other epidemiologic considerations for cervical cancer screening: a narrative review for the U.S. Preventive Services Task Force, *Ann Intern Med* 155:698–705, 2011.

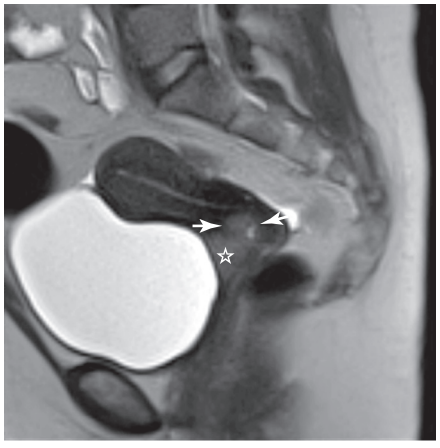

FIGURE EC1-44 Cervical carcinoma. T2-weighted sagittal image through the cervix shows an intermediate signal mass *(arrows)* disrupting the normally intense low signal ring of the cervical stroma with areas of high signal. The mass infiltrates the upper vagina *(star)*. (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Cervical disk syndromes refer to diseases of the cervical spine resulting from disk disorder, either herniation or degenerative change (spondylosis). When posterior osteophytes compress the anterior spinal cord, lower extremity symptoms may result, a condition called cervical spondylotic myelopathy.

ICD-9CM CODES

722.4 Degenerative intervertebral cervical disk

722.71 Degenerative cervical disk with myelopathy

ICD-10CM CODES

M50.00 Cervical disk disorder with myelopathy, unspecified cervical region

M50.30 Other cervical disk degeneration, unspecified cervical region

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 10% of general adult population (symptoms in 50% of population at some time in their life)

PREDOMINANT SEX: Males and females affected equally

PREDOMINANT AGE: 30 to 60 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Neck pain, radicular symptoms, or myelopathy, either alone or in combination
- Limited neck movement
- Pain with neck motion, especially extension
- Referred unilateral interscapular pain, resulting in a local trigger point
- Radicular arm pain (usually unilateral), numbness, and tingling possible, most commonly involving the C6 (C5 to C6 disk) or C7 (C6 to C7 disk) nerve root
- Weakness and reflex changes (C6, biceps; C7, triceps)
- Myelopathy, possibly resulting in gait disturbance, weakness, and even spasticity
- Sensory examination usually not helpful

ETIOLOGY

Unknown

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rotator cuff tendinitis
- Carpal tunnel syndrome
- Thoracic outlet syndrome
- Brachial neuritis

A differential diagnosis for evaluation of neck pain is described in Section II.

WORKUP

- In most cases, the diagnosis can be established on a clinical basis alone.
- Fig. EC1-45 describes an algorithm for a workup of suspected cases.

IMAGING STUDIES

- Plain roentgenograms within the first few weeks
  1. Usually normal in soft disk herniation
  2. With chronic degenerative disk disease, usually loss of height of the disk space, anterior and posterior osteophyte formation, and encroachment on the intervertebral foramen by osteophytes
- Myelography, CT scanning, and MRI indicated in patients whose symptoms do not resolve or when other spinal pathology suspected
- Electrodiagnostic studies to confirm the diagnosis or rule out peripheral nerve disorders

TREATMENT

NONPHARMACOLOGIC THERAPY

- Rest and cervical collar if needed
- Local modalities such as heat
- Physical therapy (Fig. EC1-46)
- Avoid extreme range-of-motion exercises in degenerative disk disease

ACUTE GENERAL Rx

- Nonsteroidal anti-inflammatory drugs
- "Muscle relaxants" for their sedative effect
- Analgesics as needed
- Epidural steroid injection for radicular pain

DISPOSITION

- Usually improves with time
- Surgical intervention in >5%

REFERRAL

Orthopedic or neurosurgical consultation for intractable pain or neurologic deficit

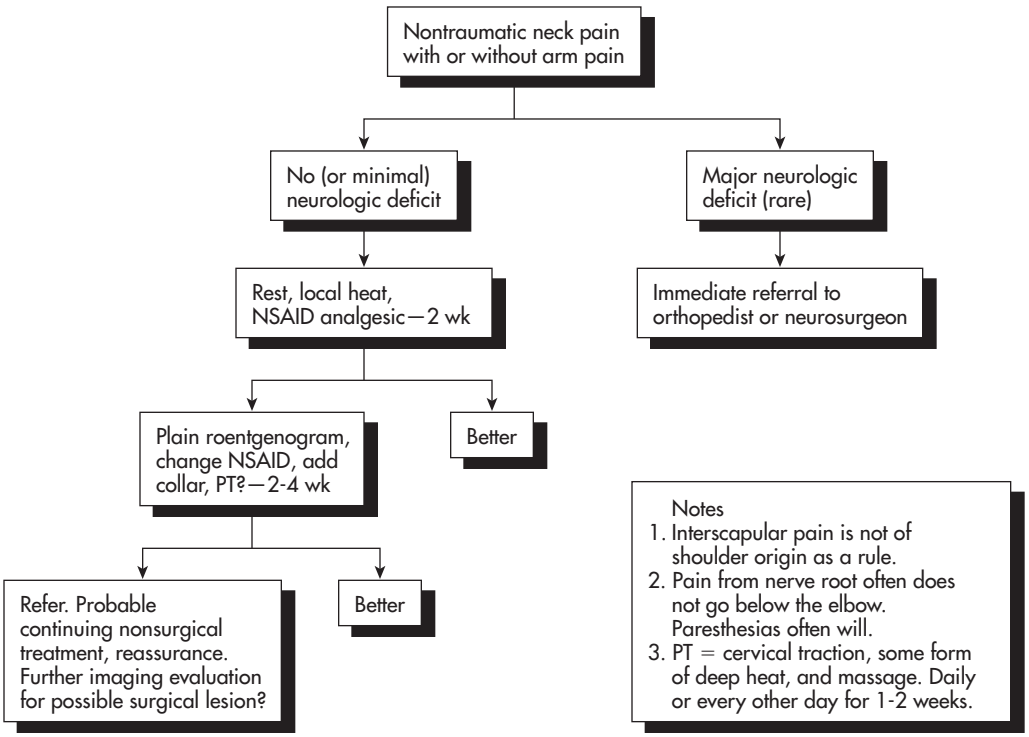

FIGURE EC1-45 Algorithm for suspected cervical disk syndrome. *NSAID,* Nonsteroidal anti-inflammatory drug; *PT,* physical therapy. (From Mercier LR [ed]: *Practical orthopedics,* ed 6, St Louis, 2004, Mosby.)

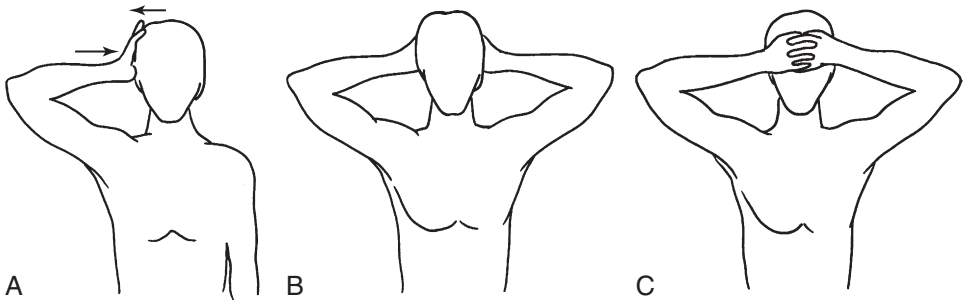

FIGURE EC1-46 Isometric neck exercises. A, The hand is placed against the side of the head slightly above the ear, and pressure is gradually increased while resisting with the neck muscles and keeping the head in the same position. The position is held 5 sec, relaxed, and repeated five times. **B,** The exercise is performed on the other side and then from the back and front **(C).** The exercise should be performed three to four times daily. (From Mercier LR [ed]: *Practical orthopedics,* ed 4, St Louis, 1995, Mosby.)

PEARLS & CONSIDERATIONS

Myelopathy from cervical spondylosis is the most common cause of acquired spastic paralysis in the adult and is usually progressive. Whether to intervene surgically is a complicated decision in these patients.

COMMENTS

- Pain relief with physical therapy seems anecdotal and short lived; any overall improvement usually parallels what would have probably occurred naturally.
- Sometimes carpal tunnel syndrome and cervical radiculopathy occur together; this is called *double-crush syndrome* and results from nerve compression at two separate levels. Proximal compression may decrease the ability of the nerve to tolerate a second, more distal compression.
- Surgical intervention is indicated primarily for relief of radicular pain caused by nerve root compression or for the treatment of myelopathy; it is generally not helpful when the chief complaint is neck pain alone.
- In many cases of cervical spondylosis with myelopathy, the lower-extremity symptoms are much more disabling than the neck symptoms, a situation that can cause some difficulty in determining their etiology.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Cervical Disc Syndrome (Patient Information)

AUTHORS: **LONNIE R. MERCIER, M.D., and FRED F. FERRI, M.D.**

SUGGESTED READINGS

Gorski JM, Schwartz LH: Shoulder impingement presenting as neck pain, *J Bone Joint Surg Am* 85A:635, 2003.

King JT et al.: Preference-based quality of life measurement in patients with cervical spondylotic myelopathy, *Spine* 29:1271, 2004.

Nasca RJ: Cervical radiculopathy: current diagnostic and treatment options, *J Surg Orthop Adv* 18:13, 2009.

Nowak DD et al.: Central cord syndrome, *J Am Acad Orthop Surg* 17:756, 2009.

Rao RD et al.: Operative treatment of cervical spondylotic myelopathy, *J Bone Joint Surg Am* 88A:1619, 2006.

Rao RD et al.: Degenerative cervical spondylosis: clinical syndromes, pathogenesis, and management, *J Bone Joint Surg Am* 89A:1360, 2007.

Rhee JM et al.: Cervical radiculopathy, *J Am Acad Orthop Surg* 15:486, 2007.

Seo M, Choi D: Adjacent segment disease after fusion for cervical spondylosis: myth or reality? *Br J Neurosurg* 22:195, 2008.

BASIC INFORMATION

DEFINITION

Cervical dysplasia refers to atypical development of immature squamous epithelium that does not penetrate the basement epithelial membrane. Characteristics include increased cellularity, nuclear abnormalities, and increased nuclear/cytoplasmic ratio. A progressive loss of squamous differentiation exists beginning adjacent to the basement membrane and progressing to the most advanced stage (severe dysplasia), which encompasses the complete squamous epithelial layer thickness. The revised 2001 Bethesda System terminology was used in a National Institutes of Health consensus conference, sponsored by the American Society for Colposcopy and Cervical Pathology (ASCCP) and its partner professional organizations in 2006. The conference updated therapeutic options for women based on studies such as the **A**SC-US (atypical squamous cells of undetermined significance)/**L**SIL (low-grade squamous intraepithelial lesions) **T**riage **S**tudy (ALTS) that appeared after revision of the Bethesda classification. Fig. C1-47 describes a comparison of grading systems for cervical squamous dysplasia.

In 2012, the American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology (ASCP) published a new set of recommendations for lifetime assessment and early diagnosis of cervical dysplasia and cancer. The recommendations attempted to reduce the number of lifetime assessments, thereby reducing the possible morbidity associated with excess testing and also optimizing the co-evaluation with Pap smear and HPV testing. In brief, women younger than 21 years of age should not have any screening. Women 21-29 years of age should have testing every three years with only cytology. With negative cytology or HPV-negative ASC-US, patients can repeat every three years. For HPV-positive ASC-US or cytology with LG-SIL, follow-up is as per the 2006 guidelines (essentially a colposcopic examination as the initial step with follow-up steps depending on the findings). Women between the ages of 30-65 should have co-testing every 5 years with both Pap cytology and HPV testing. Alternatively, it is also acceptable to perform cytology alone, but then the testing interval should be every three years. With negative cytology or HPV-negative ASC-US, patients can repeat with co-testing every five years. For HPV-positive ASC-US or cytology with LG-SIL, follow-up is as per the 2006 guidelines, as previously documented. For patients with positive HPV but negative cytology, the patient can repeat testing 12 months later with co-testing; patients can also specifically test for HPV 16 or HPV 16/18 genotypes and, if positive, should be referred for colposcopy. Patients with positive HPV but negative 16 and/or 18 should be retested in 12 months with co-testing.

Women over the age of 65 and those with a history of hysterectomy (including removal of cervix) should no longer be tested unless they had previous diagnosis of CIN 2 or more severe; these women should be tested for at least 20 years. Women who have been vaccinated for HPV should still use age-specific recommendations for screening.

BETHESDA 2001 UPDATED CLASSIFICATION: The Bethesda 2001 System was the result of a year-long iterative process held to update the original 1991 system and to broaden participation in the consensus process, clarify reporting of abnormalities, and incorporate data that had been collected since the initial system was created.

The reporting system includes the following areas:

Specimen adequacy: The system defines the specimen as either satisfactory for evaluation or unsatisfactory and then specifies the reason for inadequacy if necessary.

General categorization (optional): This serves to triage the specimen into normal finding (negative for intraepithelial lesion or malignancy) or identifies it as an "epithelial abnormality." The descriptions are meant to be mutually exclusive.

Interpretation/result: Makes a distinction between "interpretation" and "diagnosis" of the specimen so that the interpretation may be incorporated into the overall clinical context for the particular patient being evaluated.

Negative for intraepithelial lesion or malignancy: In this screening test, no intraepithelial lesion or malignancy is identified. Non-neoplastic findings such as organisms or reactive cellular findings may be specified but are still considered to be a negative result.

Epithelial cell abnormalities:

- Squamous cell:
  - Atypical squamous cell (ASC) of undetermined significance (ASC-US) emphasizing the unusual but still possible association with underlying cervical intraepithelial neoplasia (CIN) II/III and extremely rare possibility of squamous cell carcinoma
  - ASC cannot exclude high-grade squamous intraepithelial lesion (HSIL) (ASC-H), suggesting a risk for CIN II/III that is intermediate between ASC-US and HSIL
  - Low-grade squamous intraepithelial lesion (LSIL) suggests a transient viral infection with a greater likelihood for regression, more likely to encompass human papillomavirus (HPV) infection and CIN I histologically
  - HSIL suggestive of a more persistent viral infection and with a greater risk for progressive disease, more likely to encompass CIN II/III and carcinoma in situ (CIS) histologically
  - Squamous cell carcinoma
- Glandular cell
  - Atypical glandular cells (should specify endocervical, endometrial, or not otherwise specified)

Histological features	Traditional system	WHO system	British Society for Cervical Cytology	Bethesda system
Atypical squamous cells not meeting the criteria for dysplasia	Mild atypia	Mild atypia	Borderline nuclear abnormality	Atypical squamous cells (ASC)
Koilocytes plus mild atypia	HPV infection	HPV infection	HPV plus borderline change	Low-grade squamous intraepithelial lesion (SIL)
Dysplasia limited to lower third of epithelium	Mild dysplasia	CIN 1	Mild dyskaryosis (low-grade dyskaryosis)	Low-grade SIL
Dysplasia limited to lower two-thirds of epithelium	Moderate dysplasia	CIN 2	Moderate dyskaryosis (high-grade dyskaryosis)	High-grade SIL
Dysplasia extending into upper third of epithelium	Severe dysplasia	CIN 3	Severe dyskaryosis (high-grade dyskaryosis)	High-grade SIL
Dysplasia of full thickness of epithelium	Carcinoma in situ	CIN 3	Severe dyskaryosis (high-grade dyskaryosis)	High-grade SIL

FIGURE C1-47 Comparison of grading systems for cervical squamous dysplasia. (From Young B et al: Female reproductive system. In *Wheater's basic pathology,* Philadelphia, 2011, Elsevier, pp 216-315.)

Atypical glandular cell, favor neoplasia (should specify endocervical or not otherwise specified)
Endocervical adenocarcinoma in situ (AIS)
Adenocarcinoma

Other: Endometrial cells in a woman ≥40 yr of age. Because menopausal status is sometimes uncertain, age was chosen to discriminate women who might, with the findings of endometrial cells on cytology, warrant further evaluation with endometrial sampling

KEY POINTS

1. The cytologic distinctions of low grade (LSIL) and high grade (HSIL) do not necessarily equate to the histologic classifications CIN I and CIN II/III.
2. The 2006 conference notes that one cytologic abnormality can have different histologic risk in different women and highlights "special populations" such as adolescent and young women, and those women who are pregnant. In young women, spontaneous HPV clearance rates are exceptionally high. The new testing recommendations essentially remove the possibility of testing women younger than 21 years of age.
3. DNA testing for high-risk HPV types is incorporated into the evaluation and treatment algorithms for women with cytologic cervical abnormalities.

Histologically, a two-tiered system is developed in this guideline that distinguishes between the lower-risk CIN I and higher-risk CIN II/III diagnoses.

ICD-9CM CODES
622.1 Dysplasia of cervix (uteri)
ICD-10CM CODES
N87.9 Dysplasia of cervix uteri, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT AGE

- Dysplasia: peak age, 26 yr (3600 cases/100,000 persons)
- CIS: peak age, 32 yr (1100 cases/100,000 persons)
- Invasive cancer: peak age <60 yr (800 cases/100,000 persons)

PEAK INCIDENCE

- Age 35 yr
- Abnormal Pap smear rate revealing dysplasia approximates 2% to 5% depending on population risk factors and false-negative rate variance
- False-negative rate approaching 40%
- Average age-adjusted incidence of severe dysplasia is 35 cases/100,000 persons
- Approximately half of the cases of new cervical cancer had never been screened, and another 10% had not been screened in over 5 years. Many of these women come from underserved or underresourced communities. The single biggest impact in reducing the morbidity and mortality from cervical cancer would come from appropriately addressing these health disparities.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Cervical lesions associated with dysplasia often are not visible to the naked eye; therefore, physical findings are best viewed by colposcopy of a 3% acetic acid–prepared cervix.
- Patients evaluated by colposcopy are identified by abnormal cervical cytology screening from Pap smear screening.
- Colposcopic findings:
  1. Leukoplakia (white lesion seen by the unaided eye that may represent condyloma, dysplasia, or cancer)
  2. Acetowhite epithelium with or without associated punctation, mosaicism, abnormal vessels
  3. Abnormal transformation zone (abnormal iodine uptake, "cuffed" gland openings)

ETIOLOGY

- Strongly associated and initiated by oncogenic HPV infection (high-risk HPV types are 16, 18, 31, 33, 35, 45, 51, 52, 56, and 58; low-risk HPV types are 6, 11, 42, 43, and 44)
- Risk factors:
  1. HPV
  2. Any heterosexual coitus
  3. Coitus during puberty (transformation-zone metaplasia peak)
  4. Diethylstilbestrol exposure
  5. Multiple sexual partners
  6. Lack of prior Pap smear screening
  7. History of STD
  8. Other genital tract neoplasia
  9. HIV
  10. Tuberculosis
  11. Substance abuse
  12. "High-risk" male partner (HPV)
  13. Low socioeconomic status
  14. Early first pregnancy
  15. Tobacco use

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Metaplasia
- Hyperkeratosis
- Condyloma
- Microinvasive carcinoma
- Glandular epithelial abnormalities
- Vulvar intraepithelial neoplasm
- Vaginal intraepithelial neoplasm
- Metastatic tumor involvement of the cervix

WORKUP

- Periodic history and physical examination (including cytologic screening) depending on age, risk factors, and history of preinvasive cervical lesions
- Consider screening for sexually transmitted disease (gonorrhea, *Chlamydia,* herpes, HIV, HPV)
- Abnormal cytology (HSIL/LSIL, initial ASC/ASC-US/ASC-H in high-risk patients, recurrent in low-risk/postmenopausal patients) and grossly evident suspicious lesions; refer for colposcopy and possible directed biopsy/endocervical curettage (ECC; examination should include cervix, vagina, vulva, and anus)
- For glandular cell abnormalities (AGCs): refer for colposcopy and possible directed biopsy/ECC, and consider endometrial sampling
- In pregnancy: abnormal cytology followed by colposcopy in the first trimester and at 28 to 32 wk; only high-grade lesions suspicious for carcinoma biopsied; ECC is contraindicated

LABORATORY TESTS

- Gonorrhea, chlamydia to rule out STD
- Pap cytology screening (requires appropriate sampling, preparation, cytologist interpretation, and reporting)
- Colposcopy and directed biopsy, ECC for indications (see "Workup")
- HPV DNA typing if identified abnormal cytology
- As compared with Pap testing, HPV testing has greater sensitivity for the detection of intraepithelial neoplasia

IMAGING STUDIES

- Cervicography
- Computer-enhanced Pap cytology screening (e.g., PAPNET)

MANAGEMENT

Refer to the literature for a more comprehensive approach. The following treatment paradigms in Table C1-12 give a general outline for care.

DISPOSITION

- Because of the large number of women in high-risk groups, the prevalence of HPV, and the high false-negative Pap smear rate, routine Pap smear screening should be strongly encouraged for all women, especially those with a history of cervical dysplasia. The addition of an HPV test to the Pap test reduces the incidence of CIN II or III, or cancer detected by subsequent screening.
- Success rates for treatment approach 80% to 90%.
- Detection of persistence of recurrence requires careful follow-up.
- Cervical treatment possibly results in infertility (cervical stenosis or incompetence), which requires careful consideration and discretion for use of LEEP and cone biopsy.
- Appropriate counseling and informed consent are needed when considering any form of management of cervical dysplasia.

REFERRAL

- Patients with abnormal Pap cytology should be referred to a provider, likely a trained obstetrician/gynecologist, who can appropriately treat the patient in an age-specific manner and also perform a colposcopy if indicated as part of the new recommendations. Given the morbidity associated with both underevaluating and treating as well as reacting excessively to cytologic find-

TABLE C1-12 Summary of Recommendations

Population	Recommended Screening Method	Management of Screen Results	Comments
<21 yr	No screening		
21-29 yr	Cytology alone every 3 yr	HPV-positive ASC-US or cytology of LSIL or more severe: Refer to ASCCP Guidelines Cytology Negative or HPV-Negative ASC-USRe-screen with cytology in 3 yr	
30-65 yr	HPV and cytology "cotesting" every 5 yr (preferred)	HPV-positive ASC-US or cytology of LSIL or more severe: Refer to ASCCP guidelines HPV positive, cytology negative:Option 1 Y 12-month follow-up with cotesting Option 2 Y test for HPV16 or HPV16/18 genotypes If HPV16 or HPV16/18 positive, refer to colposcopy If HPV16 or HPV16/18 negative, 12-mo follow-up with cotesting Cotest negative or HPV-negative ASC-US: Rescreen with cotesting in 5 yr	Screening by HPV testing alone is not recommended for most clinical settings.
	Cytology alone every 3 yr (acceptable)	HPV-positive ASC-US or cytology of LSIL or more severe: Refer to ASCCP guidelines Cytology negative or HPV-negative ASC-US:Rescreen with cytology in 3 yr	
>65 yr	No screening following adequate negative prior screening		Women with a history of CIN2 or a more severe diagnosis should continue routine screening for at least 20 yr
After hysterectomy	No screening		Applies to women without a cervix and without a history of CIN2 or a more severe diagnosis in the past 20 yr or cervical cancer ever.
HPV vaccinated	Follow age-specific recommendations (same as unvaccinated women)		

Modified from Saslow D et al: American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer, *J Low Gen Tract Dis* 16(3):175-204, 2012.

ings, a provider who is intimately familiar with American Society for Colposcopy and Cervical Pathology guidelines should be sought.

- Patients with identified abnormal cytology should be evaluated by a skilled colposcopist (defined as documented didactic and preceptorship training, including 50 cases of identified pathology, ongoing colposcopy activity with a minimum of 2 cases/wk, quality-assurance log, and periodic continuing medical education).
- If treatment is required, patient should be referred to a gynecologist or gynecologic oncologist skilled in the diagnosis and treatment of preinvasive cervical disease.

PEARLS & CONSIDERATIONS

COMMENTS

- Testing for human papillomavirus by Hybrid capture 2 DNA test will identify 91% of the small proportion of women with post-treatment residual or recurrent disease, but 30% of all women who are tested will test positive and need colposcopy.
- Gardasil is a vaccine indicated in girls and women aged 9 to 26 yr for the prevention of CIN caused by HPV types 6, 11, 16, and 18. Food and Drug Administration approval for boys and men 9 to 26 yr was given in 2009.
- Cervarix is a vaccine that only protects against infection from types 16 and 18.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Cervical Dysplasia (Patient Information)
Cervical Cancer (Related Key Topic)
Cervical Polyps (Related Key Topic)

AUTHORS: **DENNIS M. WEPPNER, M.D.,** and **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

ACOG Committee on Practice Bulletins—Gynecology: ACOG Practice Bulletin no. 109: cervical cytology screening, *Obstet Gynecol* 114:1409–1420, 2009.

Apgar BS et al.: Update on ASCCP Consensus Guidelines for abnormal cervical screening tests and cervical histology, *Am Fam Physician* 80(2):147–155, 2009.

Chan B et al.: Posttreatment human papillomavirus testing for recurrent cervical intraepithelial neoplasia: a systematic review, *Am J Obstet Gynecol* 200:422, 2009.

Feldman S: Making sense of the new cervical cancer screening guidelines, *N Engl J Med* 365(23):2148, 2011.

Kahn JA: HPV vaccination for the prevention of cervical intraepithelial neoplasia, *N Engl J Med* 361:271–278, 2009.

Kizer N, Peipert JF: Cervical cancer screening: primum non nocere, *Ann Intern Med* 156:896–897, 2012.

Mayrand M et al.: Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer, *N Engl J Med* 357:1579, 2007.

Naucler P et al.: Human papillomavirus and Papanicolaou tests to screen for cervical cancer, *N Engl J Med* 357:1589–1597, 2007.

Saslow D et al.: American Cancer Society, American Society for Colposcopy and Lower Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and detection of early cervical cancer, *J Low Genit Tract Dis* 16(3):1–29, 2012.

Solomon D et al.: The 2001 Bethesda system terminology for reporting results of cervical cytology, *JAMA* 287:2114, 2002.

Stoler MH: New Bethesda terminology and evidence-based management guidelines for cervical cytology findings, *JAMA* 287:2140, 2002.

Vesco U et al.: Risk factors and other epidemiologic considerations for cervical cancer screening: a narrative review for the U.S. Preventive Services Task Force, *Ann Intern Med* 155:698–705, 2011.

Wright TC et al.: 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests, *Am J Obstet Gynecol* 197:346, 2007.

Wright TC et al.: 2006 consensus guidelines for the management of women with cervical intraepithelial neoplasia or adenocarcinoma in situ, *Am J Obstet Gynecol* 197:340, 2007.

BASIC INFORMATION

DEFINITION

Gradual, painless dilation of the cervix during pregnancy, leading to recurrent inability to maintain pregnancy beyond the second trimester. Cervical dilation occurs in the absence of clinical contractions and/or labor. Diagnosis is clinical.

SYNONYMS

Incompetent cervix
Shortened cervix
Preterm birth syndrome

ICD-9CM CODES
654.5 Cervical incompetency in pregnancy
ICD-10CM CODES
N88.3 Incompetence of cervix uteri

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:
1 in 1000 among general obstetrical population

RISK FACTORS: Prior cervical surgery (e.g. cone biopsy, loop electrosurgical excision procedure [LEEP]), *in utero* diethylstilbestrol (DES) exposure, prior first- or second-trimester abortions, uterine anomalies, multiple gestations, prior spontaneous preterm births not meeting the criteria for cervical insufficiency

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Painless cervical dilation during the second trimester
- Nonspecific presentation: backache, pelvic pressure, contractions, vaginal spotting, vaginal discharge

ETIOLOGY

- Most cases are either idiopathic or iatrogenic as a result of prior cervical surgery. The cause is thought to be a loss of elastic fibers in the cervices of affected women.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Preterm labor
- Shortened cervix

WORK-UP

- Prior obstetrical history, particularly with regard to previous preterm deliveries or spontaneous abortions
- Prior history of any gynecological procedures, especially those involving the cervix
- Serial digital cervical exams
- Transvaginal ultrasound

LABORATORY TEST(S)

- Amniocentesis with analysis for lactate dehydrogenase (LDH), glucose, Gram stain, and culture: abnormal results for any of these markers may indicate a subclinical infection, which increases risk for preterm birth. Abnormalities may help to select patients who would benefit from emergent cerclage, though this benefit should be weighed against the inherent risks of amniocentesis.

IMAGING STUDIES

- Transvaginal ultrasound: cervical shortening on ultrasound may be a diagnostic marker for cervical insufficiency; however, it is known to be a risk factor for preterm labor but is not sufficient for diagnosis of cervical insufficiency. Ultrasound may also help to avoid prophylactic cerclage in patients with history-indicated cerclage.

TREATMENT

NONPHARMACOLOGIC THERAPY

Cerclage has long been the mainstay of treatment for cervical insufficiency (Figs. C1-48 to C1-50). However, randomized controlled trials comparing the rates of preterm birth in patients receiving cervical cerclage versus those without cerclage have produced conflicting results, with many studies showing little or no improvement in preterm birth rates. A meta-analysis by Berghella et al (2005) showed that the greatest benefit of cerclage was in women with singleton pregnancies who had experienced a previous preterm birth, while cerclage was actually detrimental to women carrying multiple gestations. The most common risk associated with cerclage is cervical laceration during delivery (1%-13%). Bed rest is often used when there is a threat of preterm birth, though its benefit is not proven. It is thought to improve outcomes by putting less pressure on the cervix while the patient is in the supine position. Vaginal pessary placement has been used as a non-surgical alternative to cerclage, with promising results. Randomized controlled clinical trials are ongoing.

ACUTE GENERAL Rx

Physical examination-indicated cerclage should be initiated in women with physical exam or ultrasonographic evidence of cervical shortening before 24 weeks' gestation. Bed rest may be helpful, but does not have a proven benefit.

CHRONIC Rx

Prophylactic cerclage has been shown by several studies and meta-analyses to be most heavily indicated in women with prior history of

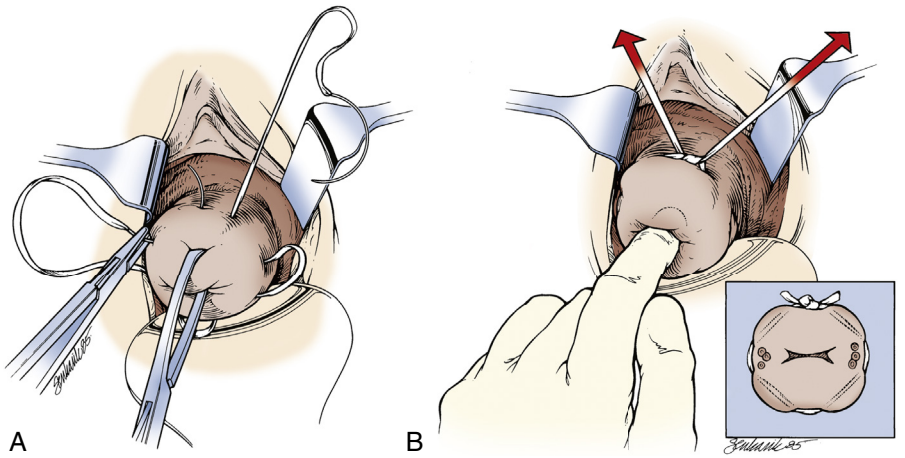

FIGURE C1-48 Placement of sutures for McDonald cerclage. A, We use a double-headed Mersilene band with four bites in the cervix, avoiding the vessels. **B,** The suture is placed high up in the cervix, close to the cervicovaginal junction, approximately at the level of the internal os. (From Gabbe SG: *Obstetrics*, 6th ed, Philadelphia, 2012, Saunders.)

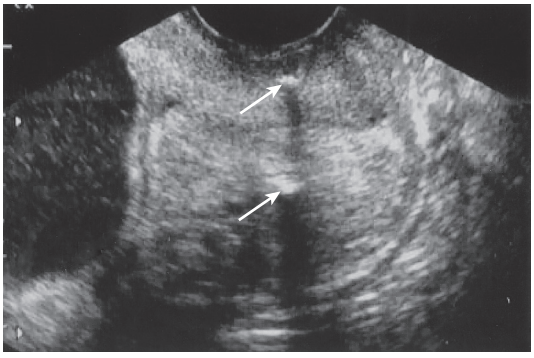

FIGURE C1-49 Transvaginal sonogram of the cervix after cerclage placement. The internal os is closed, and there is no funneling. Echogenic spots in the cervix correspond to cerclage *(arrows).* (From Gabbe SG: *Obstetrics*, 6th ed, Philadelphia, 2012, Saunders.)

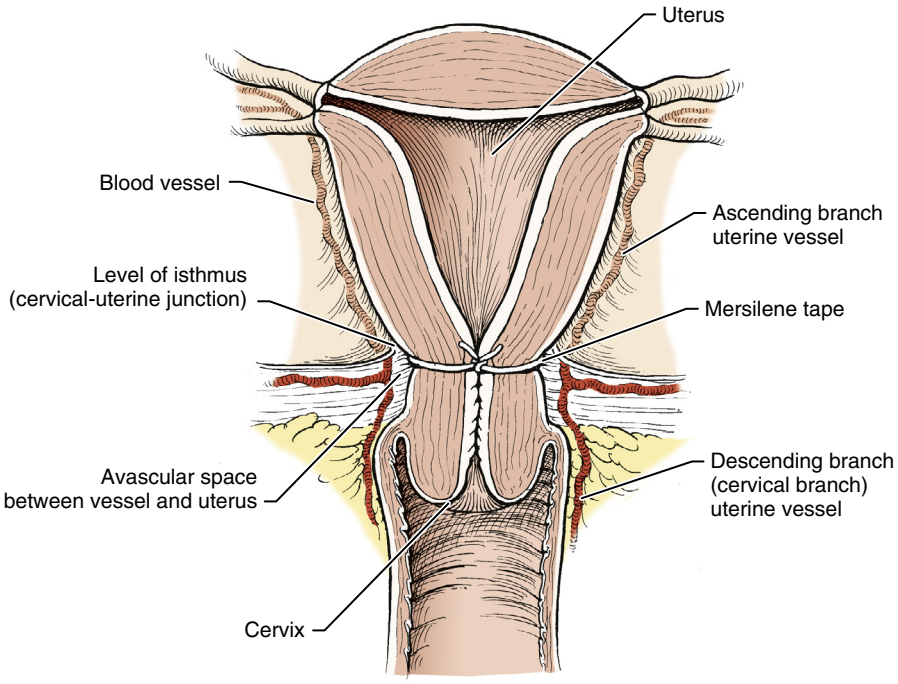

FIGURE C1-50 Abdominal cerclage. Surgical placement of circumferential Mersilene tape around uterine isthmus and median to uterine vessels. Knot is tied anteriorly. (From Gabbe SG: *Obstetrics*, 6th ed, Philadelphia, 2012, Saunders.)

multiple preterm births. Bed rest may be initiated. 17α-hydroxyprogesterone injections or vaginal progesterone have been shown in some studies to reduce preterm birth rates in women with a history of preterm birth; however, more evidence is required from randomized controlled clinical trials.

DISPOSITION

Patients with a singleton pregnancy, prior history of preterm birth, and shortened cervix (<25 mm) on transvaginal ultrasound should be counseled regarding amniocentesis, cerclage placement.

REFERRAL

Patients at risk of preterm labor should be referred to maternal-fetal medicine.

SUGGESTED READINGS

Available online at www.expertconsult.com

RELATED CONTENT

Premature Labor (Related Key Topic)
Premature Rupture of the Membranes (Related Key Topic)

AUTHOR: **SUSAN READ, M.D.**

SUGGESTED READINGS

Berghella V et al.: Cerclage for short cervix on ultrasonography, meta-analysis of trials using individual patient-level data, *Obstet Gynecol* 106:181, 2005.

Cerclage for the management of cervical insufficiency: Practice Bulletin No. 142. American College of Obstetricians and Gynecologists, *Obstet Gynecol* 123:372–379, 2014.

Gabbe SG et al.: Cervical Insufficiency. In Gabbe, SG et al: *Obstetrics: Normal and Problem Pregnancies,* Philadelphia, Elsevier Saunders, 2012. 609–626.

Cervical Polyps PTG

BASIC INFORMATION

DEFINITION

A cervical polyp is a growth protruding from the cervix or endocervical canal. Polyps that arise from the endocervical canal are called endocervical polyps. If they arise from the ectocervix, they are called cervical polyps.

ICD-9CM CODES
622.7 Mucous polyp of cervix
ICD-10CM CODES
N84.1 Polyp of cervix uteri

EPIDEMIOLOGY & DEMOGRAPHICS

Cervical polyps are found in approximately 4% of all gynecologic patients. They most commonly present in perimenopausal and multigravida women between the ages of 30 and 50 yr. Endocervical polyps are more common than cervical polyps and are almost always benign (Fig. C1-51). Malignant degeneration is extremely rare.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Polyps may be single or multiple and vary in size from being extremely small (a few mm) to large (4 cm). They are soft, smooth, and reddish-purple to cherry-red in color. They bleed easily when touched. Very large polyps can cause some cervical dilation. There may be vaginal discharge associated with cervical polyps if the polyp has become infected.

ETIOLOGY

- Most unknown
- Inflammatory
- Traumatic
- Pregnancy

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Endometrial polyp
- Prolapsed myoma
- Retained products of conception
- Squamous papilloma
- Sarcoma
- Cervical malignancy

WORKUP

Polyps are most commonly asymptomatic and are usually found at the time of annual gynecologic pelvic examination. Polyps are also found in women who present for evaluation of intermenstrual or postcoital bleeding and for profuse vaginal discharge. Polyps are generally painless. Unless a patient has a bleeding abnormality that necessitates evaluation by a physician, polyps would go undiagnosed until the next Pap smear was obtained.

TREATMENT

NONPHARMACOLOGIC THERAPY

Simple surgical excision can be done in the office. The physician should be prepared for bleeding, which can easily be controlled with silver nitrate or Monsel's solution. Most commonly a polyp is excised by grasping it at the stalk with a sponge forceps or similar device and twisting it off. Polyps can also be excised by electrocautery or, in the case of very large polyps, in an outpatient surgical suite. Sexual intercourse and tampon use are to be avoided until the patient's follow-up visit. Douching is not to be performed. Although cervical polyps are overwhelmingly benign, they should be sent to pathology for definitive histologic diagnosis.

ACUTE GENERAL Rx

Generally no medication is needed.

CHRONIC Rx

Patient is followed up in 2 wk for recheck of the surgical excision site unless there is active bleeding, in which case she would be seen immediately. The cervix should be checked at the patient's routine gynecologic visits.

DISPOSITION

Because these are almost always benign, no further treatment is usually needed. Annual gynecologic examinations should be performed to check for any regrowths.

REFERRAL

To a gynecologist for removal of polyps

PEARLS & CONSIDERATIONS

COMMENTS

A Pap smear should be obtained before removing the polyp. If an abnormal Pap smear is obtained, it is possible that the cause will be the polyp. If a colposcopic evaluation is needed, this should also be performed. During pregnancy the cervix is highly vascularized. If the polyps are stable and benign appearing, they should be observed during the pregnancy and removed only if they cause bleeding.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Cervical Dysplasia (Related Key Topic)
Cervical Polyps (Patient Information)

AUTHOR: **RUBEN ALVERO, M.D., and GEORGE T. DANAKAS, M.D.**

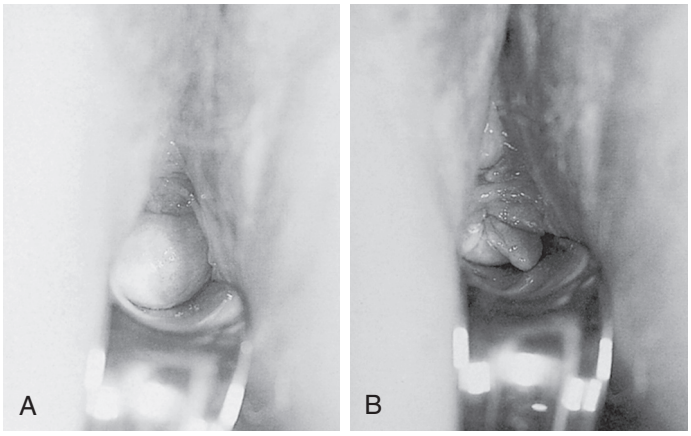

FIGURE C1-51 A, Fibroid polyp protruding through the external cervical os. **B,** Small endocervical polyp. (From Symonds EM, Macpherson MBA: *Color atlas of obstetrics and gynecology,* St Louis, 1994, Mosby.)

SUGGESTED READINGS

Endo H et al.: Cervical polyp with eccrine syringofibroadenoma-like features, *Histopathology* 42(3):301, 2003.

Rupke S: Family practice forum: clinical medicine. Evaluation and management of cervical polyps, *Hosp Pract* 33(6):81, 1998.

Scott PM: Procedures in family practice. Performing cervical polypectomy, *JAAPA* 12(6):81, 1999.

Spiewankiewicz B: Hysteroscopy in cases of cervical polyps, *Eur J Gynaecol Oncol* 24(1):67, 2003.

BASIC INFORMATION

DEFINITION

Cervicitis is an infection of the cervix. It may result from direct infection of the cervix, or it may be secondary to uterine or vaginal infection.

SYNONYMS

Endocervicitis
Ectocervicitis
Mucopurulent cervicitis

ICD-9CM CODES
616.0 Cervicitis
098.15 Acute gonococcal cervicitis
079.8 *Chlamydia* infection
ICD-10CM CODES
N72 Inflammatory disease of cervix uteri
A54.03 Gonococcal cervicitis, unspecified
A74.89 Other chlamydial diseases

EPIDEMIOLOGY & DEMOGRAPHICS

Cervicitis accounts for 20% to 25% of patients with abnormal vaginal discharge. It is most common in adolescents, but it can be found in any sexually active woman. Practicing unsafe sex with multiple partners increases the risk of developing cervicitis as well as other sexually transmitted diseases.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Cervicitis is usually asymptomatic or associated with mild symptoms. Copious purulent or mucopurulent vaginal discharge (Fig. C1-52), pelvic pain, and dyspareunia may be present if cervicitis is severe. The cervix can be erythematous and tender on palpation during bimanual examination. The cervix may also bleed easily when obtaining cultures or a Pap smear. Patients may have postcoital bleeding.

ETIOLOGY

- *Chlamydia trachomatis*
- *Trichomonas*
- *Neisseria gonorrhoeae*
- Herpes simplex
- *T. vaginalis*
- Human papillomavirus

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Carcinoma of the cervix
- Cervical erosion
- Cervical metaplasia
- Cervical ectropion

WORKUP

The patient usually presents with a vaginal discharge or history of postcoital bleeding. Otherwise the patient is asymptomatic and diagnosed during routine examination. On examination there is gross visualization of yellow, mucopurulent material on the cotton swab.

LABORATORY TESTS

A finding of leucorrhea (>10 WBC per high-power field on microscopic examination of vaginal fluid) has been associated with chlamydial and gonococcal infection of the cervix. Positive Gram stain is found. Nucleic acid amplification tests (NAAT) should be used for diagnosing *C. trachomatis* and *N. gonorrhoeae* in women with cervicitis; this testing can be performed in vaginal, cervical, or uterine samples. Use a wet mount to look for trichomonads, but because the sensitivity of microscopy to detect *T. vaginalis* is relatively low (~50%), symptomatic women with cervicitis and negative microscopy for trichomonads should receive further testing with culture. Obtain a Pap smear. HIV testing is recommended in all patients with supposed cervicitis. Although HSV-2 infection has been associated with cervicitis, the utility of specific testing (i.e., culture or serologic testing) for HSV-2 in this setting is unknown.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cervicitis is treated in an outpatient setting. Safe sex should be practiced with the use of condoms.
- Partners should be treated in all cases of infection proven by culture.

ACUTE GENERAL Rx

Because *Chlamydia* and *N. gonorrhoeae* cause 50% of cases of infectious cervicitis, if it is suspected treat without waiting for test results. Administer ceftriaxone 125 mg IM single dose followed by azithromycin 1 g single dose or doxycycline 100 mg PO bid for 7 days. If the patient is pregnant, treat with azithromycin 1 g single dose instead of using doxycycline, which is contraindicated in pregnant or nursing mothers. If *Trichomonas* is the etiologic agent, treat with metronidazole 2 g single dose. For herpes, treat with acyclovir 200 mg PO five times daily for 7 days.

DISPOSITION

Bacterial cervicitis responds well to antibiotics. Possible complications to watch for are a subsequent pelvic inflammatory disease (PID) and infertility (found in 5% to 10% of patients with increasing rates with repeat episodes of PID). Repeat cultures should be performed after treatment. Sexual relations can be resumed after negative cultures.

REFERRAL

If subsequent PID develops, consider hospital admission for IV antibiotics.

PEARLS & CONSIDERATIONS

COMMENTS

- Management of sex partners of women tested for cervicitis should be appropriate for the identified or suspected STD.
- Repeat testing 3 to 6 mo after treatment is recommended for all women diagnosed with chlamydia or gonorrhea,[1] and all sex partners in the preceding 60 days should be evaluated and treated for the STDs for which the index patient received treatment.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Cervicitis (Patient Information)
Chlamydia Genital Infections (Related Key Topic)
Gonorrhea (Related Key Topic)
Nongonococcal Urethritis (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

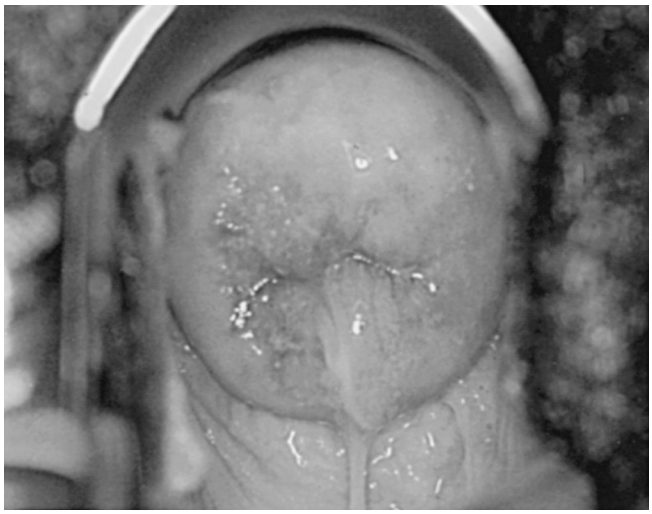

FIGURE C1-52 Colposcopy of a woman with mucopurulent cervicitis and purulent discharge from endocervical os. (Courtesy Dr. David Soper, Richmond, VA. From Mandell GL [ed]: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 6, New York, 2005, Churchill Livingstone.)

[1]Hosenfeld CB et al: Repeat infection with chlamydia and gonorrhea among females: a symptomatic review of the literature, *Sex Transm Dis* 36:478-488, 2009.

SUGGESTED READINGS

Centers for Disease Control and Prevention: 2010 sexually transmitted diseases treatment guidelines, *MMWR* 59:(RR-12), 2010.

Marrazzo JM: Mucopurulent cervicitis: no longer ignored, but still misunderstood, *Infect Dis Clin North Am* 19(2):333, 2005.

Simpson T: Urethritis and cervicitis in adolescents, *Adolesc Med Clin* 15(2):253, 2004.

BASIC INFORMATION

DEFINITION

Chagas' disease is an infection caused by the protozoan parasite *Trypanosoma cruzi.* This is a vector-borne disease transmitted by reduviid bugs from multiple wild and domesticated animal reservoirs. The disease is characterized by an acute nonspecific febrile illness that may be followed, after a variable latency period, by chronic cardiac, GI, and neurologic sequelae. Globally, Chagas' disease affects 8 to 11 million persons; vector-borne disease (as opposed to congenital infection) occurs only in the Americas.

SYNONYMS

American trypanosomiasis

ICD-9CM CODES
086.2 Chagas' disease
ICD-10CM CODES
B57.0 Acute Chagas' disease with heart involvement
B57.2 Chagas' disease (chronic) with heart involvement

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- Seven cases of autochthonous transmission in California, Texas, Tennessee, Louisiana
- In the last 2 decades, six cases of laboratory-acquired infection, three cases of transfusion-associated transmission, and nine cases of imported disease reported to the Centers for Disease Control and Prevention (none of the imported cases involved returning tourists)
- Infection has been transmitted by organ transplantation
- Infection has been transmitted congenitally from mother to fetus over more than one generation

PREVALENCE (IN U.S.): Based on regional seroprevalence studies in Hispanic blood donors, it is estimated that between 300,000 and 300,500 persons infected with *T. cruzi* are currently residing in the U.S.

In the Americas, 8 to 10 million people are believed to be infected.

PREDOMINANT SEX: Male = female

PREDOMINANT AGE:

- In highly endemic areas, mean age of acute infection: approximately 4 yr
- Variable age distribution for both types of chronic disease, depending on geography
- Mean age of onset of chronic disease: usually between 35 and 45 yr

PEAK INCIDENCE: Unknown

GENETICS: Congenital infection: Congenital transmission has been documented with attendant high fetal mortality and morbidity in surviving infants.

Neonatal infection: In rural areas, within substandard housing, transmission is likely to occur.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Inflammatory lesion that develops about 1 wk after contamination of a break in the skin with infected insect feces (chagoma)
  1. Area of induration and erythema
  2. Usually accompanied by local lymphadenopathy
- Presence of Romaña's sign, which consists of unilateral painless palpebral and periocular edema, when conjunctiva is portal of entry
- Constitutional symptoms of fever, fatigue, and anorexia, along with edema of the face and lower extremities, generalized lymphadenopathy, and mild hepatosplenomegaly after the appearance of local signs of disease
- Myocarditis in a small portion of patients, sometimes with resultant CHF
- Uncommonly, CNS disease, such as meningoencephalitis, which carries a poor prognosis
- Symptoms and signs of disease persisting for weeks to months, followed by spontaneous resolution of the acute illness; patient then in the indeterminate phase of the disease (asymptomatic with attendant subpatent parasitemia and reactive antibodies to *T. cruzi* antigens)
- Chronic disease may become manifest years to decades after the initial infection:
  1. Most common organ involved: heart, followed by GI tract, and to a much lesser extent the CNS
     a. Cardiac involvement takes the form of arrhythmias or cardiomyopathy, but rarely both.
     b. Cardiomyopathy is bilateral but predominantly affects the right ventricle and is often accompanied by apical aneurysms and mural thrombi.
     c. Arrhythmias are a consequence of involvement of the bundle of His and have been implicated as the leading cause of sudden death in adults in highly endemic areas.
     d. Right-sided heart failure, thromboembolization, and rhythm disturbances associated with symptoms of dizziness and syncope are characteristic.
  2. Patients with megaesophagus: dysphagia, odynophagia, chronic cough, and regurgitation, frequently resulting in aspiration pneumonitis
  3. Megacolon: abdominal pain and chronic constipation, which, when severe, may lead to obstruction and perforation
  4. CNS symptoms: most often secondary to embolization from the heart
  5. Varying degrees of peripheral neuropathy

ETIOLOGY

- *T. cruzi*
  1. Found only in the Americas, ranging from the southern U.S. to southern Argentina (Fig. EC1-53)
  2. Transmitted to humans by various species of bloodsucking reduviid ("kissing") insects, primarily those of the genera *Triatoma, Panstrongylus,* and *Rhodnius*
  3. Usually found in burrows and trees where infected insects transmit the parasite to natural reservoirs (e.g., opossums and armadillos)
  4. Intrusion into enzootic areas for farmland, allowing insects to take up residence in rural dwellings, thus including humans and domestic animals in the cycle of transmission
  5. Initial infection of insects by ingesting blood from animals or humans that have circulating flagellated trypanosomes (trypomastigotes)
  6. Multiplication in the insect midgut as epimastigotes, then differentiation into metacyclic trypomastigotes discharged with the feces during subsequent blood meals (Fig. EC1-54)
  7. Transmission to the second mammalian host through contamination of mucous membranes, conjunctivae, or wounds with insect feces containing infected forms
- In the vertebrate host
  1. Movement of parasites into various cell types, intracellular transformation into amastigotes, and thereafter differentiation into trypomastigotes
  2. Following rupture of the cell membrane, parasitic invasion of local tissues or hematogenous spread to distant sites, maintaining a parasitemia infective for vectors
- In addition to insect vectors, *T. cruzi* is transmitted through blood transfusions, transplacentally, and, occasionally, secondary to laboratory accidents or ingestion, including breast milk
- In 2007, voluntary screening was initiated in the U.S. blood supply; it is estimated to cover 75% to 90% of the blood supply.
- Platelet transfusions appear to be more infective than packed red blood cells.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Acute disease

- Early African trypanosomiasis
- New World cutaneous and mucocutaneous leishmaniasis

Chronic disease

- Idiopathic cardiomyopathy
- Idiopathic achalasia
- Congenital or acquired megacolon

WORKUP

Principal considerations in diagnosis:

- A history of residence where transmission is known to occur
- Recent receipt of a blood product while in an endemic area
- Occupational exposure in a laboratory

LABORATORY TESTS

For acute diagnosis:

- Demonstration of *T. cruzi* in wet preparations of blood (Fig. EC1-55), buffy coat, or Giemsa-stained smears

FIGURE EC1-53 Distribution of Chagas' disease. Human infection is endemic in parts of Central and South America from the Andes to the Atlantic coast and as far south as the latitude of the River Plate (Río de la Plata, shown in *green*). Two major intergovernmental programs were started in 1991 to eliminate domestic vectors by a combination of spraying residual insecticides in houses, the use of insecticidal paints, and the deployment of fumigant canisters. The countries covered in the two initiatives, the second of which started in 1997, are shown. The latter program instituted universal blood screening to avoid transmission from infected blood donors. In less than a decade, remarkable progress has been made. Transmission by the major vector *Triatoma infestans* was eliminated in Uruguay by 1997 and in Chile by 1999. Major reductions in transmission have also been reported from other endemic countries but, to date, not complete control. (From Hoffman R: *Hematology, basic principles and practice,* ed 6, Philadelphia, 2013, Elsevier.)

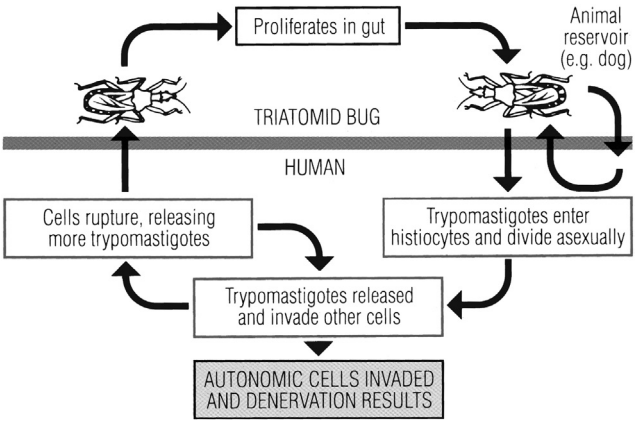

FIGURE EC1-54 Lifecycle of *Trypanosoma* cruzi. (From Souhami RL, Mozham J: *Textbook of medicine,* ed 4, London, 2002, Churchill Livingstone.)

- Xenodiagnosis, a technique involving laboratory-reared insect vectors fed on subjects with suspected infection thereafter examined for parasites, and culture of body fluids in liquid media to establish diagnosis
  1. Hampered by the length of time required for completion
  2. Of limited use in clinical decision making with regard to drug therapy
  3. Although xenodiagnosis and broth culture are considered to be more sensitive than microscopic examination of body fluids, sensitivities may not exceed 50%
- Recent advances in serologic testing include immunoblot assay, in situ indirect fluorescent antibody, PCR-based techniques, and an immunochromatographic assay (Chagas Stat Pak)

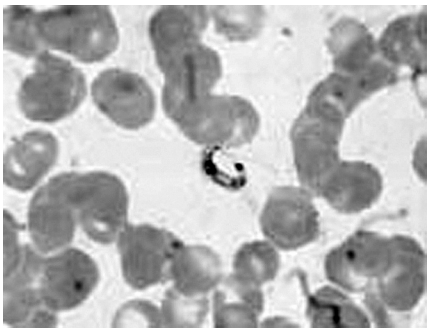

FIGURE EC1-55 *T. cruzi* in human blood film. The causative agent occurs in blood films characteristically as short C-shaped or S-shaped trypomastigotes with a prominent kinetoplast. It is otherwise monomorphic *(Giemsa × 950).* (From Hoffmann R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

- Response to treatment in acute, reactivated, or congenital infection can be assessed by quantitative PCR.
  For chronic *T. cruzi* infection:
- Traditional serologic tests including: complement fixation (CF), indirect immunofluorescence (IIF), indirect hemagglutination, and enzyme-linked immunosorbent assay (ELISA)
- Serologic tests have variable sensitivity and specificity and frequent false-positive results
- Saliva ELISA may be useful as a screening diagnostic test in epidemiologic studies of chronic trypanosomiasis infection in endemic areas
- Confirmation requires at least two different tests, and if discordant, three tests.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Chronic chagasic heart disease: mainly supportive
- Megaesophagus: symptoms usually amenable to dietary measures or pneumonic dilation of the esophagogastric junction
- Chagasic megacolon: in its early stages responsive to a high-fiber diet, laxatives, and enemas

ACUTE GENERAL Rx

It is now recommended that all patients—acute, indeterminant, and chronic—be treated with antiparasitic therapy. Treatment for individuals older than 50 years requires consideration of risk/benefit as the treatment appears to be more toxic at this age.

A single course of each of the medications below is thought to offer an approximately 50% cure rate. Neither drug is approved by the FDA but both can be obtained free of charge from the CDC and used under investigational protocol. Consultations and requests for drugs can be made to: Parasitic Diseases Public Inquiries Line (770-448-7775), parasites.cdc.gov, www.cdc.gov/parasites/chagas, CDC Drug Service (404-639-3670).

Benznidazole, a nitroimidazole derivative:

1. Has demonstrated similar efficacy as nifurtimox in limited trials, is usually better tolerated and is viewed by most experts as first-line treatment
2. Recommended oral dosage: 5 to 7 mg/kg/day for 30 to 90 days

Nifurtimox:

1. Recommended oral dosage for adults: 8 to 10 mg/kg/day given in 3 to 4 divided daily doses and continued for 90 to 120 days
2. Parasitologic cure in approximately 50% of those treated; should be begun as early as possible

Neither drug can be used during pregnancy.

Do not use in cases of severe renal or hepatic dysfunction.

Triazoles offer a new class of therapy. Case reports have had success with posaconazole. . Trials have shown that posaconazole has antitrypanosomal activity in patients with chronic Chagas' disease. However, significantly more patients in the posaconazole groups than in the benznidazole group had treatment failure during follow-up.

CHRONIC Rx

- In patients with indeterminate phase or chronic disease: Some evidence of benefit in a recent uncontrolled trial with benznidazole in patients with chagasic cardiomyopathy
- In patients exhibiting bradyarrhythmias: pacemakers
- In individuals with congestive heart failure:
  1. Treat with standard modalities for dilated, right-sided, cardiomyopathic disease.
  2. Cardiac transplant is an option for end-stage cardiomyopathy; moreover, reactivation rate found to be low and amenable to therapy without subsequent infection of the allograft.
  3. Myotomy or esophageal resection is reserved for patients with advanced disease.
- In advanced chagasic megacolon associated with chronic fecal impaction, perforation, or, less commonly, volvulus: surgical resection

DISPOSITION

Based on a few prospective studies, most patients infected with *T. cruzi* will not develop symptomatic Chagas' disease.

REFERRAL

- For consultation with an infectious disease specialist or communication with the Centers for Disease Control and Prevention when the disease is acutely suspected
- To a cardiologist for pacemaker implantation for patients with bradyarrhythmias
- To a surgeon for symptomatic disease with chagasic megaesophagus or megacolon

PEARLS & CONSIDERATIONS

COMMENTS

- All children of an infected mother should be screened for Chagas; household members should also be screened.
- In recipients of solid organ or bone marrow transplants, patients with AIDS, or those receiving chemotherapy, there may be reactivation of indeterminate phase disease.
- Mortality predictors associated with chagasic cardiomyopathy include CHF, QT-interval dispersion, left ventricular (LV) end-systolic dimension, the presence of pathologic Q waves, frequent PVCs, and isolated LAFB on ECG.
- Chagasic esophageal disease has an increased incidence of esophageal malignancy.
- The use of pyrethroid-impregnated curtains may represent an option for the reduction or elimination of Chagas' disease transmission in certain endemic areas.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **PATRICIA CRISTOFARO, M.D.**

SUGGESTED READINGS

Benchimol Barbosa PR: The oral transmission of Chagas' disease: an acute form of infection responsible for regional outbreaks, *Int J Cardiol* 112(1):132–133, 2006.

Bern C: Antitrypanosomal therapy for chronic Chagas' disease, *N Engl J Med* 364:2527–2534, 2011.

Bern C et al.: An estimate of the burden of Chagas' disease in the United States, *Clin Infect Dis* 49:e52, 2009.

Bern C et al.: Evaluation and treatment of Chagas disease in the United States, *JAMA* 298:2171–2181, 2007.

Bern C et al.: *Trypanosoma cruzi* and Chagas' disease in the United States, *Clin Microbiol Rev* 24:655, 2011.

Centers for Disease Control and Prevention: Congenital transmission of Chagas' disease—Virginia 2010, *MMWR Morb Mortal Wkly Rep* 61:477, 2012.

Centers for Disease Control and Prevention: Blood donor screening for Chagas disease—United States, 2006-7, *MMWR Morb Mortal Wkly Rep* 56:141, 2007.

Diniz Lde F et al.: Effects of ravuconazole treatment on parasite load and immune response in dogs infected with T cruzi, *Antimicrob Agents Chemother* 54:2979, 2010.

Duffy T et al.: Accurate real-time PCR strategy for monitoring bloodstream parasitic loads in Chagas disease patients, *PLoS Negl Trop Dis* 3:e419, 2009.

Garcia S et al.: Treatment with benznidazole during the chronic phase of experimental Chagas' disease decreases cardiac alterations, *Antimicrob Agents Chemother* 49(4):1521, 2005.

Golgher D, Gazzinelli RT: Innate and acquired immunity in the pathogenesis of Chagas disease, *Autoimmunity* 37(5):399, 2004.

Kirchhoff LV et al.: Transfusion-associated Chagas disease (American trypanosomiasis) in Mexico: implications for transfusion medicine in the United States, *Transfusion* 46(2):298, 2006.

Jackson Y et al.: Congenital transmission of Chagas disease in Latin American immigrants in Switzerland, *Emerg Infect Dis* 15:601, 2009.

Leiby DA et al.: Trypanosoma cruzi parasitemia in US blood donors with serologic evidence of infection, *J Infect Dis* 198:609, 2008.

Lescure FX et al.: Chagas disease: changes in knowledge and management, *Lancet Inf Dis* 10(8):556–570, August 2010.

Molina I et al.: Randomized trial of posaconazole and benznidazole for chronic Chagas' disease, *N Engl J Med* 370:1899–1908, 2014.

Murcia L et al.: Risk factors and primary prevention of congenital Chagas disease in a nonendemic country, *Clin Infect Dis* 56:496, 2013.

Pinazo MJ et al.: Successful treatment with posaconazole of a patient with chronic Chagas disease and SLE, *Am J Trop Med Hyg* 82:583, 2010.

Rassi A et al.: Chagas disease, *Lancet* 375:1388, 2010.

Rassi A et al. Clinical phases and forms of Chagas disease. In: Telleria J, Tibayrenc M, editors: *American trypanosomiasis: Chagas disease: one hundred years of research*. Elsevier: Burlington, Mass.

Reisenman CE et al.: Infection of kissing bugs with Trypanosoma cruzi, Tucson, Arizona, USA, *Emerg Infect Dis* 16:400, 2010.

Reyes P et al.: Trypanocidal drugs for late stage, symptomatic Chagas disease (Trypanosoma cruzi infection), *Cochrane Database Syst Rev* (4)CD004102, 2005.

Shikanai-Yasuda MA, Carvalho NB: Oral transmission of Chagas disease, *Clin Infect Dis* 54:845, 2012.

Urbina JA: Specific chemotherapy in Chagas disease: relevance, current limitations and new approaches, *Acta Trop* 115:55, 2010.

Villar R et al.: Trypanocidal drugs for chronic asymptomatic Trypanosoma cruzi infection, *Cochrane Database Sys Rev* (1)CD003463, 2002.

Viotti R et al.: Long-term cardiac outcomes of treating chronic Chagas disease with benznidazole versus no treatment: a nonrandomized trial, *Ann Intern Med* 144(10):724, 2006.

BASIC INFORMATION

DEFINITION

Chancroid is a sexually transmitted disease characterized by painful genital ulceration and inflammatory inguinal adenopathy.

SYNONYMS

Soft chancre
Ulcus molle

ICD-9CM CODES
099.0 Chancroid
ICD-10CM CODES
A57 Chancroid

EPIDEMIOLOGY & DEMOGRAPHICS

- Most frequent cause of genital ulcer disease worldwide.
- Exact incidence in U.S. is unknown. The prevalence of chancroid has declined in the United States and is currently rare (1 per 2 million in the developed world). When infection occurs, it is usually associated with sporadic outbreaks and in association with trading sex for drugs, particularly crack cocaine.
- Occurs more frequently in men (male/female ratio of 5:1 to 10:1).
- Clinical infection is rare in women.
- There is a higher incidence in uncircumcised men and in tropical and subtropical regions.
- Incubation period is 4 to 7 days but may take up to 3 wk.
- High incidence of HIV infection associated with chancroid.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- One to three extremely painful ulcers (Fig. EC1-56) accompanied by tender inguinal lymphadenopathy (especially if fluctuant). The chancre is typically soft in comparison with the hard, painless chancre of syphilis
- May present with inguinal bubo and several ulcers
- In women: initial lesion in the fourchette, labia minora, urethra, cervix, or anus; inflammatory pustule or papule that ruptures, leaving a shallow, nonindurated ulceration, usually 1- to 2-cm diameter with ragged, undermined edges
- Unilateral lymphadenopathy develops 1 wk later in 50% of patients

ETIOLOGY

Haemophilus ducreyi, a bacillus

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other genitoulcerative diseases such as syphilis, herpes, lymphogranuloma venereum (LGV), granuloma inguinale.
- A clinical algorithm for the initial management of genital ulcer disease is described in Section III.

WORKUP

Diagnosis based on history and physical examination is often inadequate. Must rule out syphilis in women because of the consequences of inappropriate therapy in those pregnant. Practitioner can base initial diagnosis and treatment recommendations on clinical impression of appearance of ulcer and most likely diagnosis for population. Definitive diagnosis is made by isolation of organism from ulcers by culture or Gram stain. Special culture media for *H. ducreyi*; is not widely available commercially, and even when these media are used, sensitivity is <80%.

The CDC criteria for clinical diagnosis include all of the following:

1. Single or multiple painful genital ulcers
2. No evidence to support a diagnosis of syphilis
3. A typical clinical presentation and appearance of the ulcer
4. A negative test for the presence of HSV in the ulcer exudate

LABORATORY TESTS

Darkfield microscopy, RPR, HSV cultures, *H. ducreyi* culture, HIV testing recommended

TREATMENT

NONPHARMACOLOGIC THERAPY

Fluctuant nodes should be aspirated through healthy adjacent skin to prevent formation of draining sinus. Incision and drainage not recommended because it delays healing. Use warm compresses to remove necrotic material.

ACUTE GENERAL Rx

- Ceftriaxone 250 mg IM (single dose) *or*
- Azithromycin 1 g PO (single dose) *or*
- Ciprofloxacin 500 mg PO bid for 3 days *or*
- Erythromycin 500 mg PO qid for 7 days

NOTE: Ciprofloxacin is contraindicated in patients who are pregnant, lactating, or <18 yr.

- HIV-infected patients may need more prolonged therapy.
- In HIV-positive patients, failures have been reported with single-dose azithromycin.

DISPOSITION

- All sexual partners should be treated with a 10-day course of one of the regimens (see "Acute General Rx").
- Patients should be reexamined 3 to 7 days after initiation of therapy. Ulcers should improve symptomatically within 3 days and objectively within 7 days after initiation of successful therapy.

PEARLS & CONSIDERATIONS

COMMENTS

- In the U.S. herpes simplex-1 and syphilis are the most common causes of genital ulcers, followed by chancroid, LGV, and granuloma inguinale.
- The combination of a painful genital ulcer and tender suppurative inguinal adenopathy suggests the diagnosis of chancroid.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Chancroid (Patient Information)
Condyloma Acuminatum (Related Key Topic)
Granuloma Inguinale (Related Key Topic)
Urethritis, Gonococcal (Related Key Topic)
Lymphogranuloma Venereum (Related Key Topic)
Syphilis (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

FIGURE EC1-56 Chancroid. Note shaggy, ragged-edged ulcer with edema and exudative base. (Courtesy Beverly Sanders. From Goldstein B [ed]: *Practical dermatology,* ed 2, St Louis, 1997, Mosby.)

SUGGESTED READINGS

Lewis DA: Chancroid: clinical manifestations, diagnosis and management, *Sex Transm Infect* 79(1):68, 2003.

Sehgal VN, Srivastave G: Chancroid: contemporary appraisal, *Int J Dermatol* 42(3):182, 2003.

Workowski KA, et al.: Sexually transmitted diseases treatment guidelines, 2010, *MMWR Morb Mortal Wkly Rep* 59(RR-12), 2010.

Charcot-Marie-Tooth Disease PTG EBM

BASIC INFORMATION

DEFINITION

Charcot-Marie-Tooth disease (CMT) is a heterogeneous group of noninflammatory inherited peripheral neuropathies characterized by chronic motor and sensory polyneuropathy. It is the most common inherited neuromuscular disorder (see also "Neuropathy, Hereditary").

SYNONYMS

Peroneal muscular atrophy
Hereditary motor and sensory neuropathy (HMSN)
CMT

ICD-9CM CODES
356.1 Charcot-Marie-Tooth disease, paralysis, or syndrome
ICD-10CM CODES
G60.0 Hereditary motor and sensory neuropathy

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 1:2500; CMT type 1 and type 2 are the major divisions with an estimated prevalence of 40 per 100,000
PREDOMINANT AGE: Onset usually 10 to 20 yr, and infants may be symptomatic
GENETICS: Transmission may be autosomal dominant, autosomal recessive, or X-linked, with some sporadic cases reported. Duplication of *peripheral myelin protein 22* (PMP22) is the most common cause of CMT. CMT is classified into types 1 through 7 and is genetically heterogeneous with at least 43 CMT genes known.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Wide variation in clinical presentation, but affected individuals in a family tend to have similar symptoms.
- Symmetric, slowly progressive distal motor neuropathy resulting in weakness and atrophy in legs, often progresses to involve hands.
- High-arched feet (pes cavus), claw toe deformities (Fig. C1-57), and hammer toes.
- Atrophy of the lower legs producing a stork-like appearance (muscle wasting does not involve the upper legs) (Fig. C1-58).
- Nerve enlargement.
- Mild to moderate distal sensory loss; uncommonly can have painful paresthesias.
- Decreased proprioception and weakness of ankle dorsiflexors often interfere with balance and gait (steppage gait).
- Depressed or absent deep tendon reflexes in many cases.
- Hearing loss and hip dysplasia are underrecognized manifestations.
- Ambulation usually maintained throughout life.
- CMT has been reported to be associated with renal diseases, mostly focal segmental glomerulosclerosis (FSGS).

ETIOLOGY

Genetic abnormalities cause defects in either peripheral nerve myelination, or result in axonal degeneration. Mutations in one of several myelin genes result in defects in myelin structure, maintenance, and formation. Duplication of the PMP22 gene causes CMT1A, the most common type of hereditary motor sensory neuropathy (~40% overall). INF_2 mutations appear to cause many cases of FSGS-associated CMT.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other inherited neuropathies.
- Acquired peripheral neuropathies such as toxic, metabolic, infectious, endocrine, inflammatory, immune-mediated, and nutritional polyneuropathies.

WORKUP

- Clinical diagnosis is based on family history, characteristic presentation, and findings on detailed physical and neurologic examination.
- Electrophysiologic studies are often diagnostic and may help define various subtypes of CMT.
- Occasionally, sural nerve biopsy is helpful in establishing diagnosis.

TREATMENT

ACUTE GENERAL Rx

- Symptomatic and supportive, managed by multidisciplinary team including physical and occupational therapy.
- Special shoes with good ankle support, ankle/foot orthoses.
- Some require crutches/cane for gait stability; <5% need wheelchair.
- Daily heel cord stretching exercises and hand grip exercises.
- Musculoskeletal pain may respond to acetaminophen or NSAIDs; neuropathic pain may respond to tricyclic antidepressants or drugs such as carbamazepine or gabapentin.

CHRONIC Rx

Occasionally, orthopedic surgery is required to correct severe pes cavus deformity or hip dysplasia. Avoiding obesity is essential as this makes walking difficult; avoiding potentially neurotoxic medications is also important, particularly *Vinca* alkaloids.

DISPOSITION

- Disability is usually compatible with a long life.
- 10% to 20% of patients are asymptomatic.

REFERRAL

- Orthopedic consultation for bracing and surgical treatment of deformity.
- Genetic counseling and family planning.

PEARLS & CONSIDERATIONS

COMMENTS

Patient information on CMT disease is available from the Muscular Dystrophy Association, 3300 East Sunrise Drive, Tucson, AZ 85718; (520) 529-2000.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Charcot-Marie-Tooth Disease (Patient Information)

AUTHOR: **CANDICE YUVIENCO, M.D.**

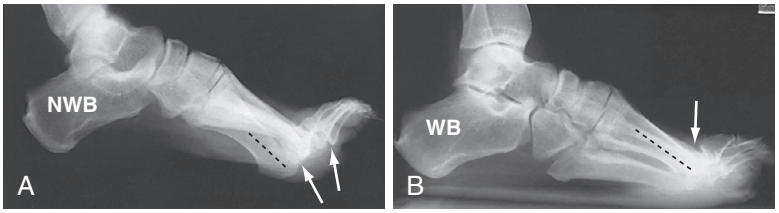

FIGURE C1-57 A, Non–weight-bearing view of cavus and claw toe deformities in a patient with Charcot-Marie-Tooth disease. **B,** On weight-bearing view, plantar flexion of first ray is less noticeable, but clawed hallux remains, indicating fixed extension contracture at first metatarsophalangeal joint. (From Canale ST, Beaty JH: *Campbell's operative orthopedics,* ed 11, Philadelphia, 2007, Mosby.)

FIGURE C1-58 Patient with Charcot-Marie-Tooth disease showing marked wasting of calf muscles and intrinsic foot muscles. (From Dubowitz V: *Muscle disorders in childhood,* London, 1995, Saunders.)

EVIDENCE

Abstract[1]

Objective:

To improve understanding of TRPV4-associated axonal Charcot-Marie-Tooth (CMT) neuropathy phenotypes and their debated pathologic mechanism.

Methods:

A total of 17 CMT2C phenotypic families with vocal cord and diaphragmatic involvement and 36 clinically undifferentiated CMT2 subjects underwent sequencing analysis of the coding region of *TRPV4*. Functional studies of mutant proteins were performed using transiently transfected cells for TRPV4 subcellular localization, basal and stimulated Ca^{2+} channel analysis, and cell viability assay with or without channel blockade.

Results:

Two *TRPV4* mutations, R232C and R316H, from 17 CMT2C families were identified in the ankyrin repeat domains. The R316H is a novel de novo mutation found in a patient with CMT2C phenotype. The family with R232C mutation had individuals with and without vocal cord and diaphragm involvement. Both mutant TRPV4 proteins had normal subcellular localization in HEK293 and HeLa cells. Cells transfected with R232C and R316H displayed increased intracellular Ca^{2+} levels and reversible cell death by the TRPV channel antagonist, ruthenium red.

Conclusion:

TRPV4 ankyrin domain alterations including a novel de novo mutation cause axonal CMT2. Individuals with the same mutation may have nondistinct CMT2 or have phenotypic CMT2C with vocal cord paresis. Reversible hypercalcemic gain-of-function of mutant TRPV4 instead of loss-of-function appears to be pathologically important. The reversibility of cell death by channel blockade provides an attractive area of investigation in consideration of treatable axonal degeneration. Ⓐ

Evidence-Based Reference

Klein CJ et al.: Mutations and cytotoxic hypercalcemia in axonal Charcot-Marie-Tooth neuropathies, *Neurology* 76:887–894, 2011. Ⓐ

SUGGESTED READINGS

Bird T.D. Charcot-Marie-Tooth hereditary neuropathy overview. In Pagon RA, et al editor: *GeneReviews* [Internet], University of Washington, Seattle. (Initial posting September 28, 1998, Last revision June 1, 2010.)

Braathen GJ et al.: Genetic epidemiology of Charcot-Marie-Tooth in the general population, *Eur J Neurol* 18:39–48, 2011.

Chance PF, Bird TD: Charcot-Marie-Tooth disease and other inherited neuropathies. In Kasper DL, et al, editor: Harrison's principles of internal medicine. McGraw-Hill: New York.

Lupski JR et al.: Whole-genome sequencing in a patient with Charcot-Marie-Tooth neuropathy, *N Engl J Med* 362(13):1181, 2010.

Pareyson D, Marchesi C: Diagnosis, natural history, and management of Charcot-Marie-Tooth disease, *Lancet Neurol* 8(7):654–657, 2009.

Roy EP 3d et al.: Longitudinal conduction studies in hereditary motor and sensory neuropathy type 1, *Muscle Nerve* 12:52, 1989.

BASIC INFORMATION

DEFINITION

Charcot's joint was first described by Jean Martin Charcot in reports of patients with tabes dorsalis. The term now describes a chronic progressive arthropathy that is associated with peripheral neuropathy and commonly results in destruction of the bone and soft tissues at peripheral weight-bearing joints. It is characterized early on by acute inflammation that often leads to joint degeneration, instability from joint dislocation and pathologic fractures, and gross deformities.

SYNONYMS

Neuropathic arthropathy
Charcot osteoarthropathy
Charcot neuroosteoarthropathy

ICD-9CM CODES
094.0 Charcot's arthropathy
ICD-10CM CODES
A52.16 Charcot's arthropathy

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- Estimated as 0.08% to 13% in patients with diabetes mellitus.
- 5 cases per 100 of those with peripheral neuropathy, primarily affecting the foot.
- 20% to 40% of patients with syringomyelia (shoulder, elbow, and wrist are most commonly involved).
- 5% to 10% of patients with tabes dorsalis (spine, hip, knee, and ankle are most commonly involved).
- Average age of onset is 50 to 60 years.
- No definite sex predilection, and ethnic variance is unknown.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Initial presentation is with a diffusely warm, erythematous, and swollen joint with or without associated pain. Continual attacks may occur, or there could be progressive arthropathy and insidious swelling over months to years.
- Pain is typically less than expected based on the severity of clinical and radiographic findings.
- It commonly affects the mid-foot (tarsus and tarsometatarsal joints), but the forefoot and hind foot can also be involved.
- Joint instability, osseous debris around the joint, and crepitus may be seen with progressive disease.
- Frank dislocation, fracture, and subsequent bony deformity may occur over time. Additionally, plantar ulcers may affect neuropathic foot joints.

ETIOLOGY

The most common identifiable risk factors for Charcot osteoarthropathy include any condition that causes a peripheral or autonomic neuropathy. Diabetes mellitus with peripheral neuropathy is the most common cause (Fig. C1-59). Less common associations include renal dialysis, syringomyelia, tabes dorsalis, Charcot-Marie-Tooth disease, congenital indifference to pain, chronic alcoholism, poliomyelitis, tertiary syphilis, leprosy, familial amyloid neuropathy, spinal or peripheral nerve surgery, and spinal dysraphism. Two theories contribute to the underlying processes involved in the disease:

1. Neurotraumatic theory:
   1. Impairment or loss of protective joint sensation with continued weight bearing and repetitive stress.
   2. Rapid and extensive bone destruction leads to joint subluxation, dislocation, and possible deformity.
   3. Chronic inflammation eventually contributes to joint instability and incongruity.
2. Neurovascular theory:
   1. Autonomic neuropathy leads to increased blood flow to the affected joints.
   2. Enhanced osteoclastic bone resorption contributes to osteopenia and further susceptibility to bone destruction.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Osteomyelitis
- Cellulitis
- Inflammatory arthritides, particularly gout or pseudogout
- Deep vein thrombosis
- Infectious arthritis/septic joint
- Osteoarthritis
- Complex regional pain syndrome

WORKUP

History and physical examination findings are important to establishing the diagnosis.

Early diagnosis, before radiographic changes are evident, requires a high index of suspicion because the acute phase is characterized by the classical signs of edema, increased warmth, and erythema as seen in an acute inflammatory process.

- Patients should be tested for an underlying peripheral neuropathy.
- It may be helpful to diagnose or rule out a previously unrecognized contributing condition or risk factor for the above.

LABORATORY TESTS

There are no specific lab criteria for diagnosis. Labs can help to exclude infection and identify underlying risk factors.

FIGURE C1-59 Diabetes mellitus and neuropathic arthritis. Note lateral displacement of metatarsals *(left)* and fragmentation and osseous debris *(right).* (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, Saunders.)

- Complete blood count and metabolic panel, and additional testing may include vitamin B_{12}, folate, RPR, ALP, and PTH
- In questionable cases, aspiration, sometimes including biopsy, to rule out soft tissue or bone infection and a septic joint

IMAGING STUDIES

Plain x-rays

- May reveal variable degrees of destruction and joint disruption. This is usually sufficient to establish the diagnosis in most cases.
- Three radiographic stages correspond to clinical progression of the disease: fragmentation, coalescence, and reconstruction.
- MRI can detect changes early on and has the highest diagnostic accuracy. Features include the center of signal enhancement within the joints and subchondral bone, disrupted ligaments, and joint deformity.
- PET-CT hybrid useful to rule out osteomyelitis in extremely difficult cases and is reported to have a sensitivity of nearly 100%.

TREATMENT

ACUTE GENERAL Rx

The cornerstone of therapy involves offloading, which is best achieved with cessation of weight-bearing activities and use of total contact casts, typically for a period of 8-12 weeks. This is followed by the use of a removal brace or Charcot restraint orthotic walker for 4-6 mo.
SURGERY: In severe cases, surgical correction of a joint might be necessary, but this should be avoided in most instances because it is associated with a relatively high failure rate.

PHARMACOLOGIC THERAPY

Antiresorptives such as bisphosphonates and calcitonin have shown improved symptom control and decreased bone turnover markers in controlled trials.

DISPOSITION

Early diagnosis of Charcot's joint is imperative to avoid compromise of bone and joint integrity. In general, it typically takes 1 to 2 yr for complete healing of a Charcot's joint. Once bony changes set in they are very difficult if not impossible to reverse. Timely, appropriate treatment can greatly reduce the risk of irreversible damage and enhance future ability to walk.

REFERRAL

Patient should be referred to a high-risk foot clinic with foot and ankle specialists.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Charcot Joint (Patient Information)

AUTHOR: **ANISHKA S. ROLLE, M.D.**

SUGGESTED READINGS

Botek G et al.: Charcot neuroarthropathy: An often overlooked complication of diabetes, *Clev Clin J Med* 77(9):593–599, 2010.

Desouza LJ: Charcot arthropathy and immobilization in a weight-bearing total contact cast, *J Bone Joint Surg Am* 90:754, 2008.

Frykberg RG, Belczyk R: Epidemiology of the Charcot foot, *Clin Podiatr Med Surg* 25:17–28, 2008.

Guyton GP, Saltzman CL: The diabetic foot: basic mechanisms of disease, *Instr Course Lect* 51:169, 2002.

Herbst SA et al.: Pattern of diabetic neuropathic arthropathy associated with peripheral bone mineral density, *J Bone Joint Surg Br* 86:378, 2004.

Jostel A et al.: Medical treatment of Charcot neuroosteoarthropathy, *Clin Podiatr Med Surg* 25:63–69, 2008.

Jude EB et al.: Medical treatment of Charcot's arthropathy, *J Am Podiatr Med Assoc* 92(7):381–383, 2002.

Neves FS et al.: Syringomyelia, neuropathic arthropathy and rheumatoid arthritis as diagnostic dilemmas in two different cases: confounding factor and true coexistence, *Clin Rheumatol* 26:98, 2007.

Pakarinen TK et al.: Charcot arthropathy of the diabetic foot: current concepts and review of 36 cases, *Scand J Surg* 91:195, 2002.

Perrin BM et al.: Charcot osteoarthropathy of the foot, *Austral Fam Phys* 39(3):117–119, 2010.

Petrov N et al.: Charcot neuro-osteoarthropathy—current standards, *Diabetes Metab Res Rev* 24:558–561, 2008.

Pinzur MS: Current concepts review: Charcot arthropathy of the foot and ankle, *Foot Ankle Int* 28:952, 2007.

Rogers LC et al.: The diagnosis of Charcot foot, *Clin Podiatr Med Surg* 25:43–51, 2008.

Slater RA et al.: The diabetic Charcot foot, *1st Med Assoc J* 6:280, 2004.

van der Ven A: Charcot neuropathy of the foot and ankle, *J Am Acad Orthop Surg* 17:562, 2009.

Chemotherapy-Induced Nausea and Vomiting

BASIC INFORMATION

DEFINITION

Chemotherapy-induced nausea and vomiting (CINV) refers to adverse effects of drugs used to treat cancer. There are three recognized subtypes: acute-phase CINV, where nausea and vomiting begin minutes to hours after initiation of chemotherapy; delayed-phase CINV, where symptoms begin or return 24 hours or more after administration of therapy(s); and anticipatory CINV, where nausea and vomiting begin before receiving therapy.

SYNONYMS

Drug-induced nausea and vomiting
Chemotherapy-induced emesis
CINV

ICD-9CM CODES
787.01 Nausea with vomiting
787.02 Nausea alone
787.03 Vomiting alone
E933.1 Adverse effect of antineoplastic and immunosuppressive drugs
V58.11-V58.12 Encounter for antineoplastic-chemotherapy and immunotherapy

ICD-10CM CODES
R11.2 Nausea with vomiting, unspecified
R11.0 Nausea
R11.10 Vomiting, unspecified
V58.11-V58.12 Encounter for antineoplastic chemotherapy and immunotherapy

EPIDEMIOLOGY & DEMOGRAPHICS

- The patient's risk for development of nausea and vomiting is most strongly dependent on the chemotherapy agent used.
- With certain chemotherapy regimens, nausea and vomiting will occur in almost 100% of patients. However, patients' tolerance may vary, and symptoms can be as low as 10%.
- Symptoms may be dose dependent (the higher the dose, the greater the risk for symptoms).
- CINV is more likely to affect female and younger patients.
- Patients expecting CINV before receiving therapy are at greater risk of experiencing symptoms (anticipatory emesis).
- Patients with a history of alcohol consumption are at lower risk.
- Patients with a history of motion sickness are at greater risk.

INCIDENCE: Highest incidence before or during the first cycle of chemotherapy.
PREVALENCE: More prevalent in younger patients and in female population.
GENETICS: Some rapid metabolizers of certain 5-HT3 receptor antagonists and polymorphisms in the 5-HT3 receptor confer greater risk for CINV.
RISK FACTORS: Previous history of CINV, history of motion sickness or vestibular dysfunction, and higher levels of anxiety. History of alcohol use decreases risk.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- For acute-phase CINV, nausea and vomiting start within minutes to hours after receiving chemotherapy.
- For delayed-phase CINV, nausea and vomiting begin or return 24 hours or more after receiving chemotherapy.
- With anticipatory CINV, symptoms begin before receiving therapy.
- Other symptoms may include anxiety and lightheadedness.
- The most common physical findings are elevated pulse and abnormal blood pressure (elevated if the person is highly anxious, reduced if the patient is dehydrated).
- Symptoms such as diarrhea, fever, headache, and abdominal pain may suggest an alternative diagnosis; physical examination findings such as increased blood pressure, abdominal tenderness, or focal neurologic deficits may suggest symptoms caused by cancer progression or other acute illness such as infection.

ETIOLOGY

CINV is probably the result of chemotherapy drugs acting in two places: in the gastrointestinal tract directly and in the vomiting center of the brain. In both areas, nausea and vomiting are mediated by the actions of certain neurotransmitters, with serotonin, dopamine, and neurokinin being the most important.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- The two main considerations are progression of cancer and infection
- Intestinal/gastric: obstruction or partial obstruction of the digestive tract from tumor
- Neurologic: metastases to the brain causing vomiting; metastatic infiltration of nerves affecting the digestive tract
- Infectious: acute bacterial, viral, or parasitic infections of the digestive tract causing symptoms (usually diarrhea will be present)
- Renal: dehydration leading to acute kidney injury and failure, causing a worsening of nausea and vomiting

WORKUP

No workup is indicated if patient's symptoms and onset of nausea and vomiting fit the usual presentation for CINV. If other symptoms or unexpected physical examination findings are present, then other causes need to be ruled out. A combination of blood work and imaging may be helpful.

LABORATORY TESTS

- If the onset of symptoms is not typical for CINV, then blood tests such as a CBC, liver function tests, and kidney function tests may be indicated.
- Stool studies looking for infections from bacteria or parasites may be ordered if diarrhea is also present.

IMAGING STUDIES

- Abdominal radiographs may be ordered to look for obstruction of the digestive tract but will not provide any information about tumor progression.
- Abdominal CT scan will provide more detailed information about local cancer progression/invasion in the proximity of the digestive tract and whether obstruction of the digestive tract is present.
- Brain CT scan or magnetic resonance imaging (MRI) will provide information about possible metastases to the brain.

TREATMENT

- Treatment depends on the likelihood of a given drug or drug regimen to cause CINV and is preventive in nature.
- For chemotherapy agents with a high probability of causing CINV, adding antinausea medications has proven to be highly effective in symptom prevention.
- Drug of choice and its duration of use is highly dependent on the chemotherapy regimen used.
- The most common treatment combination includes a serotonin-receptor antagonist (ondansetron, granisetron, dolasetron, tropisetron, or palonosetron), a corticosteroid (methylprednisolone or dexamethasone), and a neurokinin-1 receptor antagonist (aprepitant).
- Many other drugs are available, such as prochlorperazine, metochlopramide, haloperidol, and marinol, but they are less effective and have greater potential for adverse effects.
- Benzodiazepines (usually lorazepam) may help in patients with significant anxiety levels that lead to anticipatory CINV.
- Patients with uncontrolled symptoms may require hospitalization for supportive care including intravenous fluids.

NONPHARMACOLOGIC THERAPY

For those patients with a significant anxiety component to their CINV, cognitive behavioral therapy may help.

DISPOSITION

Although CINV is one of the most feared complications of cancer therapy, its treatment has been revolutionized in the last 20 years, with most patients achieving adequate symptom control.

PEARLS & CONSIDERATIONS

COMMENTS

- Aggressive symptom control in the acute phase of CINV is the key initial therapeutic approach. Prevention of the acute phase has led to much improved control of the delayed phase, which, in turn, has greatly decreased the incidence of anticipatory CINV.
- Prevention of symptoms is much easier to achieve than controlling or treating symptoms once they have begun.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Serotonin Syndrome (Related Key Topic)

AUTHOR: **BYUNG KIM, M.D**.

SUGGESTED READINGS

Hesketh P: Chemotherapy-induced nausea and vomiting, *N Engl J Med* 358:2482–2494, 2008.

Markman M: Progress in preventing chemotherapy-induced nausea and vomiting, *Cleve Clin J Med* 69:609–617, 2002.

BASIC INFORMATION

DEFINITION

Genital infection with *Chlamydia trachomatis* may result in urethritis, epididymitis, cervicitis, and acute salpingitis, but often it is asymptomatic in women (see "Pelvic Inflammatory Disease"). In men, urethritis, mucopurulent discharge, dysuria, and urethral pruritus are noted.

ICD-9CM CODES
597.80 Urethritis
604.0 Epididymitis
616.0 Cervicitis
381.51 Acute salpingitis
ICD-10CM CODES
N34.1 Nonspecific urethritis
N45.4 Abscess of epididymis or testis
N72 Inflammatory disease of cervix uteri

EPIDEMIOLOGY & DEMOGRAPHICS

- *C. trachomatis* is the most common sexually transmitted disease in the U.S. More than 4 million infections occur annually, although the exact number is unknown because reporting is not required in all states. Occurrence is common worldwide and has been increasing steadily over the last 2 decades in the U.S., Canada, Australia, and Europe.
- Most women with endocervical or urethral infections are asymptomatic.
- Up to 45% of cases of gonococcal infection may have concomitant chlamydial infection.
- Infertility or ectopic pregnancy can result as a complication from symptomatic or asymptomatic chronic infections of the endometrium and fallopian tubes.
- Conjunctival and pneumonic infection of the newborn may result from infection in pregnancy.
- In men 15% to 55% of cases are caused by *C. trachomatis.* Complications of nongonococcal urethritis in men infected with *C. trachomatis* include epididymitis and Reiter's syndrome.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Clinical manifestations may be similar to those of gonorrhea: mucopurulent endocervical discharge, with edema, erythema, and easily induced endocervical bleeding caused by inflammation of endocervical columnar epithelium. Less-frequent manifestations may include bartholinitis, urethral syndrome with dysuria and pyuria, and perihepatitis (Fitz-Hugh–Curtis syndrome).

ETIOLOGY

- *C. trachomatis,* serotypes D through K
- Obligate, intracellular bacteria

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Gonorrhea, nongonococcal urethritis (nonchlamydial etiologies)

WORKUP

Diagnosis based on laboratory demonstration of evidence of infection in intraurethral or endocervical swab by various tests. The intracellular organism is less readily recovered from the discharge.

LABORATORY TESTS

- Cell culture is the reference method for diagnosis (single culture sensitivity 80% to 90%), but it is labor intensive and takes 48 to 96 hr; it is not suited for large screening programs.
- Nonculture methods:
  1. NAATs are very sensitive tests for cervical and male urethral specimens and are FDA-approved for use with urine.
  2. Direct fluorescent antibody tests
  3. Enzyme immunoassay
  4. DNA probes
  5. Polymerase chain reaction (PCR)
- With the exception of PCR, the other tests are probably less specific than cell culture and may yield false-positive results.
- Because this is an intracellular organism, purulent discharge is not an appropriate specimen. An adequate sample of infected cells must be obtained.
- Ten white blood cells per high-power field.

TREATMENT

ACUTE GENERAL Rx

Nongonococcal urethritis, urethritis, cervicitis, conjunctivitis (except for lymphogranuloma venereum):

- Azithromycin 1 g PO × 1 *or*
- Doxycycline 100 mg PO bid for 7 days
- Alternatives
  1. Erythromycin base 500 mg PO qid for 7 days *or*
  2. Erythromycin ethylsuccinate 800 mg PO qid for 7 days *or*
  3. Ofloxacin 300 mg PO bid for 7 days *or*
  4. Levofloxacin 500 mg PO qd for 7 days

Infection in pregnancy:

- Erythromycin base 500 mg PO qid for 7 days *or*
- Amoxicillin 500 mg PO tid for 7 days

Alternatives:

1. Erythromycin base 250 mg PO qid for 7 days *or*
2. Erythromycin ethylsuccinate 800 mg PO qid for 7 days *or*
3. Erythromycin ethylsuccinate 400 mg PO qid for 14 days *or*
4. Azithromycin 1 g PO (single dose)

NOTE: Doxycycline and ofloxacin are contraindicated in pregnancy. Safety and efficacy of azithromycin are not established in pregnancy and lactation, although preliminary data indicate that it may be safe and effective. Erythromycin estolate is contraindicated in pregnancy because of drug-related hepatotoxicity.

FOLLOW-UP: Reculture after therapy completion and refer partners for evaluation and treatment.

RECURRENT AND PERSISTENT URETHRITIS: Retreat noncompliant patients with the above regimens. If patient was initially compliant, recommended regimens: metronidazole 2 g PO in single dose plus erythromycin base 500 mg PO qid for 7 days or erythromycin ethylsuccinate 800 mg PO qid for 7 days.

CLINICAL PEARL

When treating *Chlamydia,* it is best to assume concomitant gonorrhea because co-infection is common. Combination of ceftriaxone 125 mg IM single dose plus azithromycin 1 g PO single dose will treat both.

REFERRAL

Refer to infectious disease specialist if persistent infection or gynecologist if salpingitis is suspected.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Cervicitis (Related Key Topic)
Gonococcal Urethritis (Related Key Topic)
Gonorrhea (Related Key Topic)
Nongonococcal Urethritis (Related Key Topic)
Pelvic Inflammatory Disease (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Centers for Disease Control and Prevention: 2010 sexually transmitted diseases treatment guidelines, *MMWR Morb Mortal Wkly Rep* 59(RR-12), 2010.

Spiliopoulou A et al.: Chlamydia trachomatis: time for screening? *Clin Microbiol Infect* 11(9):687, 2005.

BASIC INFORMATION

DEFINITION

Cholangitis refers to an inflammation and/or infection of the hepatic and common bile ducts associated with obstruction of the common bile duct.

SYNONYMS

Biliary sepsis
Ascending cholangitis
Suppurative cholangitis

ICD-9CM CODES
576.1 Cholangitis
ICD-10CM CODES
K83.0 Cholangitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Complicates approximately 1% of cases of cholelithiasis
PEAK INCIDENCE: Seventh decade
PREVALENCE (IN U.S.): 2 cases/1000 hospital admissions
PREDOMINANT SEX:
- Females, for cholangitis secondary to gallstones
- Males, for cholangitis secondary to malignant obstruction and HIV infection

PREDOMINANT AGE: Seventh decade and older; unusual <50 yr of age

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Usually acute onset of fever, abdominal pain (RUQ), and jaundice (Charcot's triad)
- All signs and symptoms in only 50% to 85% of patients
- Often, dark coloration of the urine resulting from bilirubinuria
- Complications:
  1. Bacteremia (50%) and septic shock
  2. Hepatic abscess and pancreatitis

ETIOLOGY

Obstruction of the common bile duct causing rapid proliferation of bacteria in the biliary tree
- Most common cause of common bile duct obstruction: stones, usually migrated from the gallbladder
- Other causes: prior biliary tract surgery with secondary stenosis, tumor (usually arising from the pancreas or biliary tree), and parasitic infections from *Ascaris lumbricoides* or *Fasciola hepatica*
- Iatrogenic after contamination of an obstructed biliary tree by endoscopic retrograde cholangiopancreatoscopy (ERCP) or percutaneous transhepatic cholangiography (PTC)
- Primary sclerosing cholangitis (PSC)
- HIV-associated sclerosing cholangitis: associated with infection by CMV, *Cryptosporidium,* Microsporida, and *Mycobacterium avium* complex

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Biliary colic
- Acute cholecystitis
- Liver abscess
- Peptic ulcer disease (PUD)
- Pancreatitis
- Intestinal obstruction
- Right kidney stone
- Hepatitis
- Pyelonephritis

WORKUP

- Blood cultures
- CBC
- Liver function tests

LABORATORY TESTS

- Usually, elevated WBC count with a predominance of polymorphonuclear forms
- Elevated alkaline phosphatase and bilirubin in chronic obstruction
- Elevated transaminases in acute obstruction
- Positive blood cultures in 50% of cases, typically with enteric gram-negative aerobes (e.g., *Escherichia coli, Klebsiella pneumoniae*), enterococci, or anaerobes

IMAGING STUDIES

- Ultrasound:
  1. Allows visualization of the gallbladder and bile ducts to differentiate extrahepatic obstruction from intrahepatic cholestasis
  2. Insensitive but specific for visualization of common duct stones
- CT scan:
  1. Less accurate for gallstones
  2. More sensitive than ultrasound for visualization of the distal part of the common bile duct
  3. Also allows better definition of neoplasm
- ERCP:
  1. Confirms obstruction and its level
  2. Allows collection of specimens for culture and cytology
  3. Indicated for diagnosis if ultrasound and CT scan are inconclusive
  4. May be indicated in therapy (see "Treatment")

TREATMENT

NONPHARMACOLOGIC THERAPY

Biliary decompression
- May be urgent in severely ill patients or those unresponsive to medical therapy within 12 to 24 hr
- May also be performed semielectively in patients who respond
- Options:
  1. ERCP with or without sphincterotomy or placement of a draining stent
  2. Percutaneous transhepatic biliary drainage for the acutely ill patient who is a poor surgical candidate
  3. Surgical exploration of the common bile duct

ACUTE GENERAL Rx

- Nothing by mouth
- Intravenous hydration
- Broad-spectrum antibiotics directed at gram-negative enteric organisms, anaerobes, and enterococcus such as carbapenems (meropenem: 1 g q8h or imipenem: 500 mg IV q6h if life threatening), piperacillin/tazobactam: 3.375 or 4.5 g IV q6h, or ampicillin-sulbactam, or ticarcillin-clavulanate; if infection is nosocomial, post-ERCP, or the patient is in shock, broaden antibiotic coverage.

CHRONIC Rx

Repeated decompression may be necessary, particularly when obstruction is related to neoplasm.

DISPOSITION

Excellent prognosis if obstruction is amenable to definitive surgical therapy; otherwise relapses are common.

REFERRAL

- To biliary endoscopist if obstruction is from stones or a stent needs to be placed
- To interventional radiologist if external drainage is necessary
- To a general surgeon in all other cases
- To an infectious disease specialist if blood cultures are positive or the patient is in shock or otherwise severely ill

PEARLS & CONSIDERATIONS

- Cholangitis is a life-threatening form of intra-abdominal sepsis, though it may appear to be rather innocuous at its onset.
- Antibiotics alone will not resolve cholangitis in the presence of biliary obstruction because high intrabiliary pressures prevent antibiotic delivery. Decompression and drainage of the biliary tract to alleviate the obstruction with antimicrobial therapy is the therapy of choice.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Kumar R et al.: Endoscopic biliary drainage for severe acute cholangitis in biliary obstruction as a result of malignant and benign diseases, *J Gastroenterol Hepatol* 19(9):994, 2004.

Lee JG: Diagnosis and management of acute cholangitis, *Nat Rev Gastroenterol Hepatol* 6(9):533–541, 2009.

Ozden I et al.: Endoscopic and radiologic interventions as the leading causes of severe cholangitis in a tertiary referral center, *Am J Surg* 189(6):702, 2005.

BASIC INFORMATION

DEFINITION

Cholecystitis is acute or chronic inflammation of the gallbladder generally caused by gallstones (>95% of cases).

SYNONYMS

Gallbladder attack

ICD-9CM CODES

575.0 Acute cholecystitis
574.0 Calculus of the gallbladder with acute cholecystitis
575.1 Cholecystitis without mention of calculus

ICD-10CM CODES

K81.9 Acute cholecystitis
K80.00 Calculus of gallbladder with acute cholecystitis without obstruction
K81.9 Cholecystitis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Acute cholecystitis occurs most commonly in women during the fifth and sixth decades. Approximately 120,000 cholecystectomies are performed for acute cholecystitis annually in the U.S.
- The incidence of gallstones is 0.6% in the general population and much higher in certain ethnic groups (>75% of Native Americans by age 60 yr). Most patients with gallstones are asymptomatic. Of such patients, biliary colic develops in 1% to 4% annually.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pain and tenderness in the right hypochondrium or epigastrium; pain possibly radiating to the infrascapular region
- Palpation of the right upper quadrant (RUQ) eliciting marked tenderness and stoppage of inspired breath (***Murphy's sign***)
- Guarding
- Fever (33%)
- Jaundice (25% to 50% of patients)
- Palpable gallbladder (20% of cases)
- Nausea and vomiting (>70% of patients)
- Fever and chills (>25% of patients)
- Medical history often revealing ingestion of large, fatty meals before onset of pain in the epigastrium and RUQ

ETIOLOGY

- Gallstones (>95% of cases)
- Ischemic damage to the gallbladder, critically ill patient (acalculous cholecystitis)
- Infectious agents, especially in patients with AIDS (cytomegalovirus, *Cryptosporidium*)
- Strictures of the bile duct
- Neoplasms, primary or metastatic
- Risk factors for cholelithiasis include age, obesity, female sex, rapid weight loss, ethnicity/race (Native American), use of contraceptives, pregnancy, diabetes mellitus, hemolysis, total parenteral nutrition, biliary parasites

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hepatic: hepatitis, abscess, hepatic congestion, neoplasm, trauma
- Biliary: neoplasm, stricture, sphincter of Oddi dysfunction
- Gastric: pelvic ulcer disease, neoplasm, alcoholic gastritis, hiatal hernia, non-ulcer dyspepsia
- Pancreatic: pancreatitis, neoplasm, stone in the pancreatic duct or ampulla
- Renal: calculi, infection, inflammation, neoplasm, ruptured kidney
- Pulmonary: pneumonia, pulmonary infarction, right-sided pleurisy
- Intestinal: retrocecal appendicitis, intestinal obstruction, high fecal impaction, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD)
- Cardiac: myocardial ischemia (particularly involving the inferior wall), pericarditis
- Cutaneous: herpes zoster
- Trauma
- Fitz-Hugh-Curtis syndrome (perihepatitis), ruptured ectopic pregnancy
- Subphrenic abscess
- Dissecting aneurysm
- Nerve root irritation caused by osteoarthritis of the spine

WORKUP

Workup consists of detailed history and physical examination coupled with laboratory evaluation and imaging studies. No single clinical finding or laboratory test is sufficient to establish or exclude cholecystitis without further testing.

LABORATORY TESTS

- Leukocytosis (12,000 to 20,000) is present in >70% of patients.
- Elevated alkaline phosphatase, ALT, AST, bilirubin; bilirubin elevation >4 mg/dl is unusual and suggests presence of choledocholithiasis.
- Elevated amylase may be present (consider pancreatitis if serum amylase elevation exceeds 500 U).

IMAGING STUDIES

- Ultrasound of the gallbladder (Fig. EC1-60) is the preferred initial test; it will demonstrate the presence of stones and also dilated gallbladder with thickened wall and surrounding edema in patients with acute cholecystitis.
- Nuclear imaging (HIDA scan) (Fig. EC1-61) is useful for diagnosis of cholecystitis when sonogram is inconclusive: sensitivity and specificity exceed 90% for acute cholecystitis. This test is only reliable when bilirubin is <5 mg/dl. A positive test result (absence of gallbladder filling within 60 min after the administration of tracer) will demonstrate obstruction of the cystic or common hepatic duct; the test will not demonstrate the presence of stones.
- CT scan of abdomen is useful in cases of suspected abscess, neoplasm, or pancreatitis.
- Plain radiograph of the abdomen generally is not useful because <25% of stones are radiopaque.

TREATMENT

NONPHARMACOLOGIC THERAPY

Provide IV hydration; withhold oral feedings.

ACUTE GENERAL Rx

- Laparoscopic (percutaneous) cholecystectomy (PC) is considered the treatment of choice for most patients. The rate of conversion to open cholecystectomy is higher when laparoscopic cholecystectomy (CCY) is performed for acute cholecystitis rather than for uncomplicated cholelithiasis; conservative management with IV fluids and antibiotics (ampicillin-sulbactam 3 g IV q6h or piperacillin-tazobactam 4.5 g IV q8h) may be justified in some high-risk patients to convert an emergency procedure into an elective one with a lower mortality rate.
- Endoscopic retrograde cholangiopancreatography with sphincterectomy and stone extraction can be performed in conjunction with laparoscopic cholecystectomy for patients with choledochal lithiasis; approximately 7% to 15% of patients with cholelithiasis also have stones in the common bile duct.

DISPOSITION

- Prognosis is good; elective laparoscopic cholecystectomy can be performed as outpatient procedure.
- Hospital stay (when necessary) varies from overnight with laparoscopic cholecystectomy to 4 to 7 days with open cholecystectomy.
- Complication rate is approximately 1% (hemorrhage and bile leak) for laparoscopic cholecystectomy and <0.5% (infection) with open cholecystectomy.

REFERRAL

Surgical referral in all patients with acute cholecystitis

PEARLS & CONSIDERATIONS

COMMENTS

- Patients should be instructed that stones may recur in bile ducts.
- Gallbladder aspiration, in which all fluid visualized by ultrasound is aspirated, represents a nonsurgical treatment when patients who are at high operative risk develop acute cholecystitis. Salvage cholecystectomy is reserved for nonresponders.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Gallbladder Attack (Cholecystitis) (Patient Information)
Cholelithiasis (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Abi-Haidar Y et al.: Revisiting percutaneous cholecystectomy for acute cholecystitis based on a 10 year experience, *Arch Surg* 147(416), 2012.
Strasberg SM: Acute calculous cholecystitis, *N Engl J Med* 358(2804), 2008.

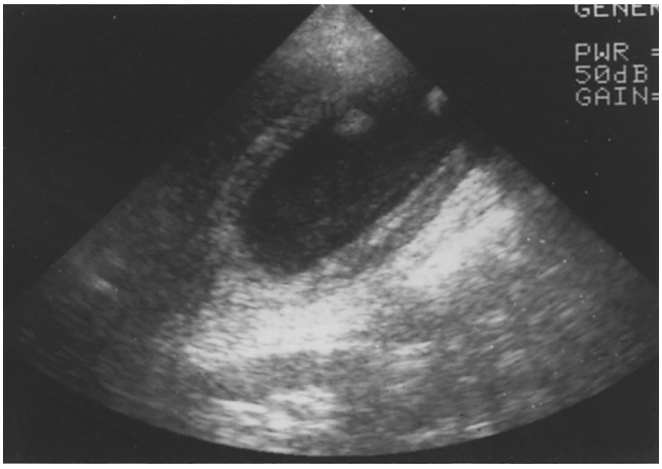

FIGURE EC1-60 Thickened gallbladder wall in acute cholecystitis. The gallbladder contains echogenic calculi. (From Grainger RG et al [eds]: *Grainger and Allison's diagnostic radiology,* ed 4, Philadelphia, 2001, Churchill Livingstone.)

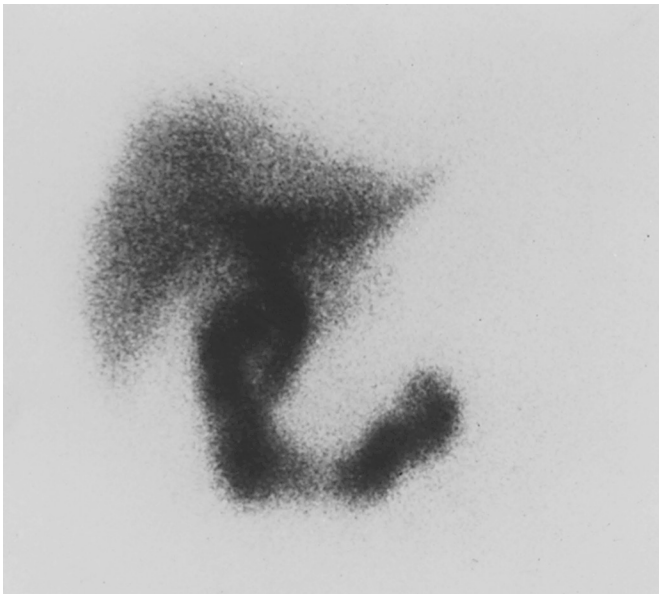

FIGURE EC1-61 Acute cholecystitis. Following the intravenous administration of 200 MBq (5 mCi) of 99mTc-HIDA and a stimulus of CCK, the region of the liver and gallbladder is imaged. Intrahepatic bile ducts are visualized, as is excretion through the common duct into the small bowel. The gallbladder is not seen. This patient had gallstones demonstrated by ultrasound and confirmed at surgery. The pathologic diagnosis was acute cholecystitis. (From Grainger RG et al [eds]: *Grainger and Allison's diagnostic radiology,* ed 4, Philadelphia, 2001, Churchill Livingstone.)

BASIC INFORMATION

DEFINITION

Cholelithiasis is the presence of stones in the gallbladder

SYNONYMS

Gallstones

ICD-9CM CODES

574.2 Calculus of the gallbladder without mention of cholecystitis
574.0 Calculus of the gallbladder with acute cholecystitis

ICD-10CM CODES

K80.2 Calculus of gallbladder without cholecystitis
K80.5 Calculus of bile duct without cholangitis or cholecystitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Gallstone disease can be found in 12% of the U.S. population. Of these, 2% to 3% (500,000 to 600,000) are treated with cholecystectomies each year.
- Annual medical expenditures for gallbladder surgeries in the U.S. exceed $5 billion.
- Incidence of gallbladder disease increases with age. Highest incidence is in the fifth and sixth decades. Predisposing factors for gallstones are female sex, pregnancy, age >40 yr, family history of gallstones, obesity, ileal disease, oral contraceptives, diabetes mellitus, rapid weight loss, estrogen replacement therapy. Risk factors for the development of cholelithiasis are described in Table EC1-13.
- Patients with gallstones have a 20% chance of developing biliary colic or its complications at the end of a 20-yr period.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination is entirely normal unless patient is having biliary colic; 80% of gallstones are asymptomatic.
- Typical symptoms of obstruction of the cystic duct include intermittent, severe, cramping pain affecting the right upper quadrant.
- Pain occurs mostly at night and may radiate to the back or right shoulder. It can last from a few minutes to several hours.

ETIOLOGY

- 75% of gallstones contain cholesterol and are usually associated with obesity, female sex, and diabetes mellitus; mixed stones are most common (80%); pure cholesterol stones account for only 10% of stones.
- 25% of gallstones are pigment stones (bilirubin, calcium, and variable organic material) associated with hemolysis and cirrhosis. These tend to be black-pigmented stones that are refractory to medical therapy.
- 50% of mixed-type stones are radiopaque.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Peptic ulcer disease
- Gastroesophageal reflux disease
- Irritable bowel disease
- Pancreatitis
- Neoplasms
- Nonnuclear dyspepsia
- Inferior wall myocardial infarction
- Hepatic abscess

LABORATORY TESTS

Generally normal unless patient has biliary obstruction (elevated alkaline phosphatase, bilirubin).

IMAGING STUDIES

- Ultrasound of the gallbladder (Fig. EC1-62) will detect small stones and biliary sludge (sensitivity, 95%; specificity, 90%); the presence of dilated gallbladder with thickened wall is suggestive of acute cholecystitis.
- Nuclear imaging (HIDA scan) can confirm acute cholecystitis (>90% accuracy) if gallbladder does not visualize within 4 hr of injection and the radioisotope is excreted in the common bile duct.
- Common bile duct stones can be detected noninvasively by magnetic resonance cholangiopancreatography or invasively by endoscopic retrograde cholangiopancreatography (ERCP) and intraoperative cholangiography.

TREATMENT

NONPHARMACOLOGIC THERAPY

Lifestyle changes (avoidance of diets high in polyunsaturated fats, weight loss in obese patients; however, avoid rapid weight loss)

ACUTE GENERAL Rx

- The management of gallstones is affected by the clinical presentation.
- Asymptomatic patients do not require therapeutic intervention. Proposed criteria for prophylactic cholecystectomy are described in Table C1-14.

TABLE C1-14 Proposed Criteria for Prophylactic Cholecystectomy

Life expectancy >20 years
Calculi >2 cm in diameter
Calculi >3 mm and patent cystic duct
Radiopaque calculi
Gallbladder polyps >15 mm
Nonfunctioning or calcified gallbladder ("porcelain" gallbladder)
Women <60 years
Patients in areas with high prevalence of gallbladder cancer

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

- Surgical intervention is generally the ideal approach for symptomatic patients. Laparoscopic cholecystectomy is preferred over open cholecystectomy because of the shorter recovery period and lower mortality rate. Between 5% and 26% of patients undergoing elective laparoscopic cholecystectomy will require conversion to an open procedure. Most common reason is the inability to clearly identify the biliary anatomy.
- Laparoscopic cholecystectomy after endoscopic sphincterectomy is recommended for patients with common bile duct stones and residual gallbladder stones. Where possible, single-stage laparoscopic treatments with removal of duct stones and cholecystectomy during the same procedure are preferable. Percutaneous cholecystectomy is an alternative for patients who are critically ill with gallbladder empyema and sepsis.
- Patients who are not appropriate candidates for surgery because of coexisting illness or patients who refuse surgery can be treated with oral bile salts: ursodiol or chenodiol. Candidates for oral bile salts are patients with cholesterol stones (radiolucent, noncalcified stones), with a diameter of ≤15 mm and having three or fewer stones. Candidates for medical therapy must have a functioning gallbladder and must have absence of calcifications on CT scans.
- Extracorporeal shock wave lithotripsy (ESWL) is another form of medical therapy. It can be used in patients with stone diameter of ≤3 cm and having three or fewer stones.

DISPOSITION

- Recurrence rate after bile acid treatment is approximately 50% in 5 yr. Periodic ultrasound is necessary to assess the effectiveness of treatment.
- After ESWL, stones recur in approximately 20% of patients after 4 yr.
- Patients with at least one gallstone <5 mm in diameter have a greater than fourfold increased risk of presenting with acute biliary pancreatitis. A policy of watchful waiting in such cases is generally warranted.
- A potential serious complication of gallstones is acute cholangitis. ERCP and endoscopic sphincterectomy followed by interval laparoscopic cholecystectomy are effective in acute cholangitis.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Gallstones (Patient Information)
Cholecystitis (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Abraham S, et al.: Surgical and nonsurgical management of gallstones, *Am Fam Physician* 89(10):795–802, 2014.
Bellows CF, et al.: Management of gallstones, *Am Fam Physician* 72(637), 2005.
Moon JH, et al.: The detection of bile duct stones in suspected biliary pancreatitis: comparison of MRCP, ERCP, and intraductal US, *Am J Gastroenterol* 100(1051), 2005.

TABLE EC1-13 Symptoms of Gallstone Disease and Its Complications

Disease	Pathophysiology	Symptoms
Biliary colic	Transient gallstone impaction at the cystic duct or ampulla of Vater	Intermittent RUQ pain associated with nausea or vomiting. Pain in the epigastrium or radiating to the right scapular tip. Episodes last 30 min to several hours with days or months between episodes.
Acute cholecystitis	Inflammation of the gallbladder caused by obstruction of the cystic duct May occur in the presence or absence of bacterial superinfection	Patients appear ill and cannot take deep breaths. They have constant pain that lasts 30-60 min and worsens with movement. Persistent common bile duct impaction usually promotes vomiting. Physical examination demonstrates RUQ tenderness with voluntary guarding and a positive Murphy sign (arrest of inspiration during deep palpation over the gallbladder).
Emphysematous cholecystitis	Infection with gas-producing bacteria such as *Escherichia coli, Clostridium perfringens*, and anaerobic streptococci	Symptoms are similar to those with acute cholecystitis.Gas may be seen on abdominal plain films or CT. Male diabetics are most commonly affected.
Chronic cholecystitis	Persistent inflammation and fibrosis of the gallbladder with poor motor and absorptive function	Patients are usually asymptomatic but may report multiple previous attacks of colic. Porcelain gallbladder develops from chronic inflammation and may progress to carcinoma.
Acalculous cholecystitis	Probably related to biliary stasis in the setting of critical illness and altered gastrointestinal motility	Seen in patients with traumatic injuries, burns, and critical illness, as well as in those receiving total parenteral nutrition. The mortality for this disorder is twice as high as that for acute calculous cholecystitis.
Gallbladder perforation	Stones erode through an inflamed and necrotic gallbladder wall Stones may travel into the peritoneal cavity or cause adhesions between nearby structures Bile peritonitis may develop	More than half of patients with gallbladder perforation have fever and a palpable RUQ mass. Mortality in these patients is 30%.

CT, Computed tomography; *RUQ*, right upper quadrant.
From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

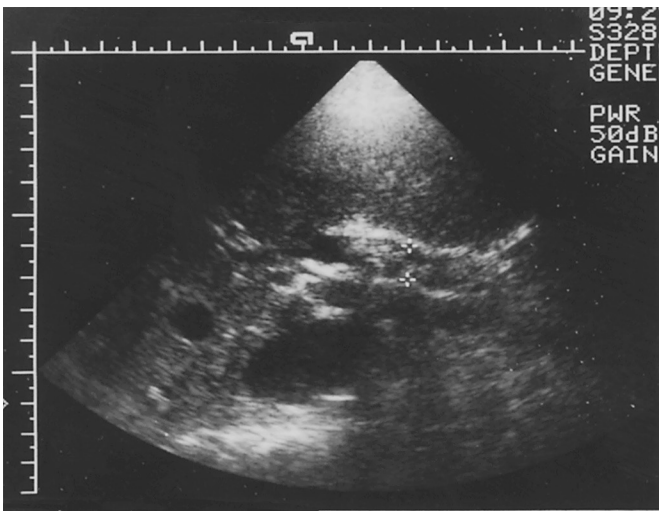

FIGURE EC1-62 Calculi in the common bile duct, casting an acoustic shadow. (From Grainger RG et al [eds]: *Grainger and Allison's diagnostic radiology,* ed 4, Philadelphia, 2001, Churchill Livingstone.)

BASIC INFORMATION

DEFINITION

Cholera is an acute diarrheal illness caused by *Vibrio cholerae.*

ICD-9CM CODES
001.0 Cholera
ICD-10CM CODES
A00.9 Cholera due to *Vibrio cholerae* 01, biovar cholerae

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Extremely rare. In 2010, all cholera infections in the U.S. were acquired during foreign travel (Fig. EC1-63).
PEAK INCIDENCE:
- None in the U.S.
- Summer and fall in endemic areas

PREDOMINANT SEX: None
PREDOMINANT AGE: In nonendemic areas, attack rates are equal in all age groups. In epidemic areas, children over the age of 2 yr are most commonly infected. Neonatal infection: illness is uncommon before the age of 2 yr, likely because of passive immunity.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Infection may result in asymptomatic illness or a mild diarrhea. The classic illness is described as the abrupt onset of voluminous watery diarrhea, which may lead to severe dehydration, acidosis, shock, and death. Vomiting may occur early in the illness, but fever and abdominal pain are usually absent. The typical "rice water" stools are pale with flecks of mucus and contain no blood. Muscle cramps may be prominent and are the result of loss of fluid and electrolytes. Untreated illness results in hypovolemic shock, and death may occur in hours to days. With adequate fluid and electrolyte repletion, cholera is a self-limited illness that resolves in a few days. The use of antimicrobials can shorten the course of illness.

ETIOLOGY

The organism responsible for this illness is one of several strains of *V. cholerae.* Most infections result from the O1 serotype, the El Tor biotype. In the U.S., one outbreak occurred from the ingestion of illegally imported crab, and sporadic infection has been associated with the consumption of contaminated shellfish in Gulf Coast states. Most cases are seen in returning travelers. Transmission during epidemics is the result of the ingestion of contaminated water and, in some instances, contaminated food.

An important outbreak of cholera followed the 2010 earthquake in Haiti, with many cases also in the Dominican Republic (which shares the island of Hispaniola with Haiti). Subsequently, cholera was detected in Cuba, Venezuela, and Florida in travelers from Hispaniola. Interestingly, the strain of cholera was related to the strains of Southeast Asia rather than South America and was possibly introduced by UN peacekeepers from Nepal.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Mild illness may mimic gastroenteritis resulting from a variety of etiologies.
- Sudden, voluminous diarrhea causing marked dehydration is uncommon in other illnesses.

WORKUP

Stool should be sent for culture and microscopy. Treatment should not be delayed while awaiting culture results.

LABORATORY TESTS

- WBC may be elevated, and hemoglobin may be increased as a result of hemoconcentration.
- Elevated BUN and creatinine suggests prerenal azotemia. Hypoglycemia may occur. Stool cultures on appropriate media may grow the organism. Wet mount of stool under dark field or phase contrast microscopy shows organisms with characteristic darting motility.

TREATMENT

NONPHARMACOLOGIC THERAPY

The mainstay of therapy is adequate fluid and electrolyte replacement (see Table EC1-15). This can usually be achieved using oral rehydration solutions containing salts and glucose. Some patients may require intravenous fluid and electrolyte replacement.

ACUTE GENERAL Rx

- Antimicrobial therapy can decrease shedding of fluid and organisms and can shorten the course of illness:
  1. Doxycycline 300 mg PO single dose *or*
  2. Azithromycin two 500-mg tablets PO as a single dose *or*
  3. Tetracycline 500 mg PO qid × 3 days *or*
  4. Erythromycin 500 mg qid × 3 days
- For pregnant women: azithromycin 1 g PO single dose
- For children: azithromycin 20 mg/kg PO as a single dose
- Resistance to SMX-TMP is increasing in travel-associated infections and is no longer recommended.
- Zinc supplementation may be helpful in children.

CHRONIC Rx

It is likely that asymptomatic chronic carriers exist; however, because they are difficult to identify, and their role in transmission of disease appears to be rather limited, there is no recommendation for treatment of these individuals.

DISPOSITION

The mortality of adequately hydrated patients is less than 1%.

REFERRAL

If more than mild illness occurs

REPORTING

In the U.S., all cases of cholera must be reported to the local and state health departments. Bacterial isolates must be sent to the state health department and the CDC.

PEARLS & CONSIDERATIONS

COMMENTS

- There is currently no indication for vaccination of travelers to endemic areas. The risk of infection is small, protection from available vaccines is limited, and side effects are prominent and frequent.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **PATRICIA CRISTOFARO, M.D.,** and **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Centers for Disease Control and Prevention: Two cases of *Vibrio cholerae* O1 infection after Hurricanes Katrina and Rita–Louisiana, October 2005, *MMWR Morb Mortal Wkly Rep* 55(2):31–32, 2006.

Centers for Disease Control and Prevention: Update on cholera—Haiti, Dominican Republic, and Florida, 2010, *MMWR Morb Mortal Wkly Rep* 59(50):1637–1641, 2010.

Chin CS et al.: The origin of the Haitian cholera outbreak strain, *N Engl J Med* 364:33, 2011.

Devault AM et al.: Second-pandemic strain of *Vibrio cholerae* from the Philadelphia cholera outbreak of 1849, *N Engl J Med* 370:334–340, 2014.

DuPont HL: Acute infectious diarrhea in immunocompetent adults, *N Engl J Med* 370:1532–1540, 2014.

Hill DR et al.: Oral cholera vaccines: use in clinical practice, *Lancet Infect Dis* 6(6):361, 2006.

Islam MS et al.: Susceptibility to fluoroquinolones of *Vibrio cholerae* O1 isolated from diarrheal patients in Zimbabwe, *JAMA* 302:2321, 2009.

Kitaoka M et al.: Antibiotic resistance mechanisms of *Vibrio cholerae, J Med Microbiol* 60:397, 2011.

Musekiwa A et al.: Oral rehydration salt solution for treating cholera: < or = 270 mOsm/L solutions vs > or = 310mOsm/L solutions, *Cochrane Database Syst Rev* CD003754, 2011.

Rabbani GH et al.: Antidiarrheal effects of 1-histidine-supplemented rice-based oral rehydration solution in the treatment of male adults with severe cholera in Bangladesh: a double blind, randomized trial, *J Infect Dis* 191:1507, 2005.

Roy SK et al.: Zinc supplementation in children with cholera in Bangladesh: randomized controlled trial, *BMJ* 336:266, 2008.

Sack PD et al.: Cholera, *Lancet* 363:223, 2004.

Saha D et al.: Single dose azithromycin for the treatment of cholera in adults, *N Engl J Med* 354(23):2452, 2006.

Tobin-D'Angelo M, et al.: Severe diarrhea caused by cholera toxin-producing *Vibrio cholerae* serogroup O75 infections acquired in the southeastern United States, *Clin Infect Dis* 47(8):1035–1040, 2008.

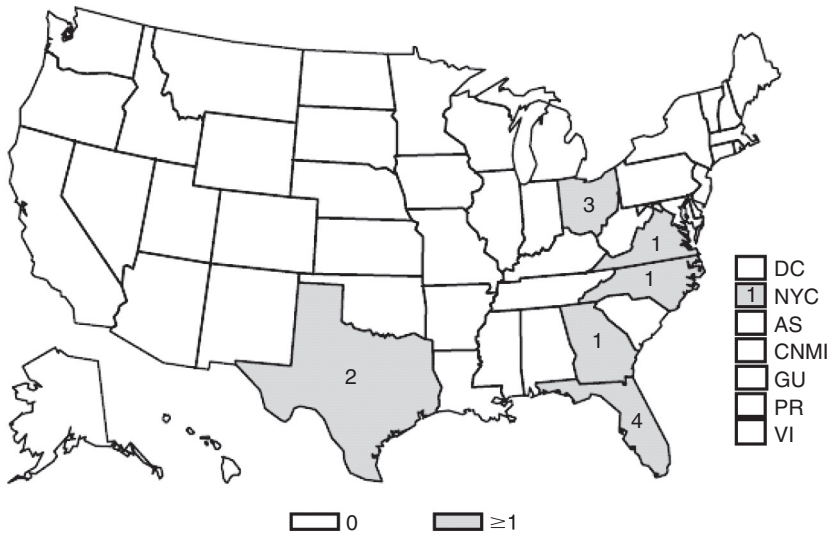

FIGURE EC1-63 Cholera. Number of reported cases in the United States and U.S. territories, 2010. (From Centers for Disease Control and Prevention: Summary of notifiable diseases—United States, 2010, *MMWR Morb Mortal Wkly Rep* 59[53]:12, 2012.)

TABLE EC1-15 Electrolyte Concentration of Cholera Stools and Common Solutions Used for Treatment

	ELECTROLYTE AND GLUCOSE CONCENTRATION (mmol/L)				
	Na^+	Cl^-	K^+	HCO_3^-	Glucose
Cholera stool					
Adults	130	100	20	44	
Children	100	90	33	30	
Intravenous solutions					
Ringer's lactate	130	109	4	28*	0
Dhaka	133	98	13	48	0
Normal saline	154	154	0	0	0
Peru polyelectrolyte	90	80	20	30	111
WHO ORS	90	80	20	30†	111

*Ringer's lactate does not contain HCO_3-; it has lactate instead.
†Bicarbonate is replaced by trisodium citrate, which persists longer than bicarbonate in sachets.
WHO ORS, World Health Organization oral rehydration solution.
From Mandell GL et al: *Principles and practice of infectious diseases,* ed 6, Philadelphia, 2005, Churchill Livingstone.

BASIC INFORMATION

DEFINITION

Chorea is the term used to describe brief movements that involve contiguous muscle groups. It comes from the Greek word meaning "dance."

SYNONYMS

Sydenham's chorea
Saint Vitus dance

ICD-9CM CODES
333.4 Huntington's chorea
333.5 Other choreas
392 Rheumatic chorea
ICD-10CM CODES
G25.4 Drug-induced chorea
G25.5 Other chorea

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: No published data exist on the incidence of chorea in the United States.
PREDOMINANT SEX AND AGE: Can affect any age and sex depending on the cause.
RISK FACTORS: The most important risk factors are a family history of Huntington's disease, exposure to rheumatic fever as a child, or being pregnant with a history of rheumatic fever.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Presentation depends on the underlying cause. Huntington's disease typically presents with neuropsychiatric symptoms that predate choreiform movements. In the case of Sydenham's and drug-induced chorea or chorea gravidarum, the hyperkinetic movements involving the hands and face may be noticed first. Brief contiguous movement that is not rhythmic and facial grimacing can be clues.

ETIOLOGY

- Genetic causes include Huntington's disease, neuroacanthocytosis, and Wilson's disease.
- Infectious causes include rheumatic fever causing Sydenham's chorea, chorea gravidarum during pregnancy, and spongiform encephalopathy (e.g., prion disease).
- Drug-induced causes include oral contraceptives, tricyclic antidepressants, cimetidine, digoxin, verapamil, baclofen, steroids, and antiepileptics.
- Strokes in the thalamic area of the brain can also cause choreiform movements.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Huntington's disease
- Stroke
- Prion disease
- Rheumatic fever
- Conversion disorder

LABORATORY TESTS

- Complete metabolic panel
- CBC with manual smear looking for acanthocytes
- Serum copper and ceruloplasmin levels
- Thyroid function tests
- Streptolysin O antibodies
- Erythrocyte sedimentation rate

IMAGING STUDIES

- MRI of the brain
- Echocardiogram if rheumatic fever is suspected

TREATMENT

- Depending on the cause, treatment must be tailored.
- Huntington's disease can be treated with tetrabenazine.
- Drug-induced chorea can be treated by withdrawing the offending drug.

NONPHARMACOLOGIC THERAPY

Rehabilitative services such as physical therapy, occupational therapy, and speech therapy are important for genetic forms of chorea.

ACUTE GENERAL Rx

Sudden-onset chorea warrants head imaging.

CHRONIC Rx

Tetrabenazine as medical therapy for the chorea and a multidisciplinary approach are useful for Huntington's chorea.

COMPLEMENTARY MEDICINE

There are case reports showing some efficacy in acupuncture for the treatment of temporomandibular chorea in a patient with Sydenham's chorea.

DISPOSITION

Sydenham's chorea and chorea gravidarum tend to resolve in a few weeks.

Huntington's disease is a progressive neurodegenerative disorder.

REFERRAL

Refer to a neurologist.

PEARLS & CONSIDERATIONS

COMMENTS

Chorea is a symptom of an underlying disorder. Investigations are targeted toward identifying reversible causes.

PREVENTION

Treat streptococcal throat infection early to prevent future complications.

PATIENT/FAMILY EDUCATION

For Huntington's disease or other genetic forms of chorea, it is important to provide support and refer to support groups.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Huntington's Disease (Related Key Topic)
Rheumatic Fever (Related Key Topic)
Wilson's Disease (Related Key Topic)

AUTHOR: **NAWAZ K.A. HACK, M.D.**

EVIDENCE

Neurorehabilitation has been proven effective in improving functional motor scores and functional independence in patients with Huntington's disease.

Evidence-Based Reference

Ciancarelli I et al.: Effectiveness of intensive neurorehabilitation in patients with Huntington's disease, *Eur J Phys Rehabil Med* 49(2):189–195, 2013. Ⓐ

SUGGESTED READING

Waln O et al.: An update on tardive dyskinesia: from phenomenology to treatment, *Tremor Other Hyperkinet Mov* 12:3, 2013.

BASIC INFORMATION

DEFINITION

Chronic fatigue syndrome (CFS) is characterized by four or more of the following symptoms, present concurrently for at least 6 mo:

- Impaired memory or concentration
- Sore throat
- Tender cervical or axillary lymph nodes
- Muscle pain
- Multijoint pain
- New headaches
- Unrefreshing sleep
- Postexertion malaise for longer than 24 hr

SYNONYMS

Yuppie flu
CFS
Chronic Epstein-Barr syndrome

ICD-9CM CODES
780.7 Chronic fatigue syndrome
300.8 Neurasthenia
ICD-10CM CODES
R53.82 Chronic fatigue, unspecified
F45.8 Other somatoform disorders

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE IN U.S: 10 to 300 cases per 100,000 persons
PREDOMINANT AGE: Young adulthood and middle age
PREDOMINANT SEX: Females affected more often than males
ECONOMICS: The estimated annual cost of lost productivity exceeds $10 billion.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- There are no physical findings specific for CFS.
- The physical examination may be useful to identify fibromyalgia and other rheumatologic conditions that may coexist with CFS.

ETIOLOGY

- The etiology of CFS is unknown.
- Some theorize that a viral illness may trigger certain immune responses that lead to the various symptoms. Most patients often report the onset of their symptoms with a flulike illness.
- The presence of numerous psychiatric comorbidities in CFS have led some experts to question the existence of any organic etiology.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Psychosocial depression, dysthymia, anxiety-related disorders, and other psychiatric diseases
- Sleep apnea
- Infectious diseases (subacute bacterial endocarditis, Lyme disease, fungal diseases, mononucleosis, HIV, chronic hepatitis B or C, tuberculosis (TB), chronic parasitic infections)
- Autoimmune diseases: systemic lupus erythematosus, myasthenia gravis, multiple sclerosis, thyroiditis, rheumatoid arthritis
- Endocrine abnormalities: hypothyroidism, hypopituitarism, adrenal insufficiency, Cushing's syndrome, diabetes mellitus, hyperparathyroidism, pregnancy, reactive hypoglycemia
- Occult malignant disease
- Substance abuse
- Systemic disorders: chronic renal failure, chronic obstructive pulmonary disease, cardiovascular disease, anemia, electrolyte abnormalities, liver disease
- Other: inadequate rest, sleep apnea, narcolepsy, fibromyalgia, sarcoidosis, medications, toxic agent exposure, Wegener's granulomatosis, vitamin deficiency

LABORATORY TESTS

- No specific laboratory tests exist for diagnosing CFS. Initial laboratory tests are useful to exclude other conditions that may mimic or may be associated with CFS.
  1. Screening laboratory tests: CBC, ESR, ALT, total protein, albumin, globulin, alkaline phosphatase, calcium, phosphorus, glucose, BUN, creatinine, electrolytes, TSH, and urinalysis are useful.
  2. Serologic tests for Epstein-Barr virus, *Candida albicans,* human herpesvirus 6, and other studies for immune cellular abnormalities are not useful; these tests are expensive and generally not recommended.
- Other tests may be indicated depending on the history and physical examination (e.g., ANA, RF in patients presenting with joint complaints or abnormalities on physical examination, Lyme titer in areas where Lyme disease is endemic).

IMAGING STUDIES

Generally not recommended unless history and physical examination indicate specific abnormalities (e.g., chest radiography in any patient suspected of TB or sarcoidosis)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Patients should be reassured that the illness is not fatal and that most patients improve over time.
- An initially supervised exercise program to preserve and increase strength is beneficial for most patients and can improve symptoms.
- Cognitive behavioral therapy trials have shown positive effects on fatigue levels, work, depression/anxiety, and social adjustment.

GENERAL Rx

Therapy is generally palliative. The following medications may be helpful; however, evidence is conflicting:

- Antidepressants: The choice of antidepressant varies with the desired side effects. Patients with difficulty sleeping or fibromyalgia-like symptoms may benefit from low-dose tricyclics (doxepin 10 mg hs or amitriptyline 25 mg qhs). When sedation is not desirable, low-dose SSRIs (paroxetine 20 mg qd) often help alleviate fatigue and associated symptoms.
- NSAIDs can be used to relieve muscle and joint pain and headaches.

"Alternative" medications (herbs, multivitamins, nutritional supplements) are very popular with many CFS patients but are generally not very helpful.

PEARLS & CONSIDERATIONS

COMMENTS

- In CFS the symptoms are serious enough to reduce daily activities by >50% in the absence of any other medically identifiable disorders.
- Moderate to complete recovery at 1 yr occurs in 22% to 60% of patients with CFS.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fig. 3-75 Evaluation of Fatigue (Algorithm)
Chronic Fatigue Syndrome (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Background:
Trial findings show cognitive behaviour therapy (CBT) and graded exercise therapy (GET) can be effective treatments for chronic fatigue syndrome, but patients' organisations have reported that these treatments can be harmful and favour pacing and specialist health care. We aimed to assess effectiveness and safety of all four treatments.

Methods:
In our parallel-group randomised trial, patients meeting Oxford criteria for chronic fatigue syndrome were recruited from six secondary-care clinics in the UK and randomly allocated by computer-generated sequence to receive specialist medical care (SMC) alone or with adaptive pacing therapy (APT), CBT, or GET. Primary outcomes were fatigue (measured by Chalder fatigue questionnaire score) and physical function (measured by short form-36 subscale score) up to 52 weeks after randomisation, and safety was assessed primarily by recording all serious adverse events, including serious adverse reactions to trial treatments. Primary outcomes were rated by participants, who were necessarily unmasked to treatment assignment; the statistician was masked to treatment assignment for the analysis of primary outcomes. We used longitudinal regression models to compare SMC alone with other treatments, APT with CBT, and APT with GET. The final analysis included all participants for whom we had data for primary outcomes. This trial is registered at http://isrctn.org, number ISRCTN54285094.

Findings:
We recruited 641 eligible patients, of whom 160 were assigned to the APT group, 161 to the CBT group, 160 to the GET group, and 160 to the SMC-alone group. Compared with SMC alone, mean fatigue scores at 52 weeks were 3.4 (95% CI 1.8 to 5.0) points lower for CBT ($p = 0.0001$) and 3.2 (1.7 to 4.8) points lower for GET ($p = 0.0003$), but did not differ for APT (0.7 [−0.9 to 2.3] points lower; $p = 0.38$). Compared with SMC alone, mean physical function scores were 7.1 (2.0 to 12.1) points higher for CBT ($p = 0.0068$) and 9.4 (4.4 to 14.4) points higher for GET ($p = 0.0005$), but did not differ for APT (3.4 [−1.6 to 8.4] points lower; p = 0.18). Compared with APT, CBT and GET were associated with less fatigue (CBT $p = 0.0027$; GET $p = 0.0059$) and better physical function (CBT $p = 0.0002$; GET $p<0.0001$). Subgroup analysis of 427 participants meeting international criteria for chronic fatigue syndrome and 329 participants meeting London criteria for myalgic encephalomyelitis yielded equivalent results. Serious adverse reactions were recorded in two (1%) of 159 participants in the APT group, three (2%) of 161 in the CBT group, two (1%) of 160 in the GET group, and two (1%) of 160 in the SMC-alone group.

Interpretation:
CBT and GET can safely be added to SMC to moderately improve outcomes for chronic fatigue syndrome, but APT is not an effective addition. Ⓐ

Evidence-Based Reference

White PD: On behalf of the PACE trial management group: Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial, *Lancet* 377:823–836, 2011. Ⓐ

SUGGESTED READINGS

Hickie I, et al.: Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study, *BMJ* 333:575, 2006.

Yancey JR, Thomas SM: Chronic fatigue syndrome: diagnosis and treatment, *Am Fam Physician* 86(8):741–746, 2012.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

BASIC INFORMATION

DEFINITION

Symmetric proximal and distal weakness with associated sensory loss along with reduced or absent reflexes for >2 mo

SYNONYMS

Chronic inflammatory demyelinating polyneuropathy
Chronic inflammatory demyelinating polyradiculoneuropathy

ICD-9CM CODES
357.81 Chronic inflammatory demyelinating polyneuritis
ICD-10CM CODES
G61.81 Chronic inflammatory demyelinating polyneuritis

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 0.5/100,000 children; 1 to 2/100,000 adults
PREDOMINANT SEX AND AGE: Slightly higher in males
RISK FACTORS: Association with certain systemic medical conditions (see under "Differential Diagnosis" below), but association is unclear

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Occurrence of symmetrical weakness in both proximal and distal muscles that progressively increases over 2 mo
- Associated with impaired sensation, postural instability, reduced or absent deep tendon reflexes, and variable craniofacial-bulbar involvement

ETIOLOGY

Immune-mediated disorder emerging from interplay of both cell-mediated and humoral immune responses directed against incompletely characterized peripheral nerve antigens. May also be associated with various concurrent illnesses (Table C1-16), although the pathogenetic significance is unclear.

DIAGNOSIS

There is no universal consensus regarding diagnostic criteria for CIDP. The three most widely used are the American Academy of Neurology (AAN), Saperstein, and Inflammatory Neuropathy Cause and Treatment (INCAT) criteria.

- The AAN and INCAT criteria are the least stringent regarding clinical criteria and require motor and sensory function in one limb, whereas the Saperstein criteria are more stringent, requiring both symmetrical proximal and distal weakness.
  1. Therefore, a patient with DADS (distal acquired demyelinating symmetric neuropathy) could fulfill AAN and INCAT criteria for CIDP.
- All require cerebral spinal fluid analysis to assess for albuminocytologic dissociation.
- Nerve conduction study (NCS): All require some features of demyelination including prolonged distal latencies and F-waves, slowed velocities, and at least one nerve demonstrating partial conduction block (feature of acquired demyelination).
- INCAT criteria do not require a nerve biopsy.
- See Table C1-16 for complete review of differences.

DIFFERENTIAL DIAGNOSIS

- Other demyelinating neuropathies such as:
  1. Distal acquired demyelinating symmetric neuropathy (DADS)
  2. Multifocal motor neuropathy (MMN)
  3. Multifocal acquired demyelinating sensory and motor neuropathy (MADSAM; Lewis-Sumner syndrome)
- Inherited neuropathies: family history, genetic testing, and lack of acquired demyelinating features on NCS will help differentiate it from CIDP
- Metabolic neuropathies: diabetes, uremia
- Paraneoplastic neuropathy: associated with lymphoma or carcinoma
- Neuropathy associated with monoclonal gammopathy: associated with osteosclerotic myeloma, MGUS, and Waldenström's macroglobulinemia
- Neuropathy associated with infectious diseases: HIV and leprosy
- Neuropathy associated with systemic inflammatory or immune-mediated diseases:
  1. Sarcoidosis
  2. Amyloidosis
  3. Vasculitis: PAN, Behçet's, Sjögren's, cryoglobulinemia, lupus, Castleman's disease, granulomatosis with polyangiitis, Churg-Strauss
- Toxic neuropathies: ETOH, acrylamide, drugs (platinum-based agents, amiodarone, tacrolimus, perhexiline)

WORKUP

Nerve conduction studies and EMG to assess for demyelinating polyneuropathy with features of acquired demyelination (temporal dispersion) and conduction block (Fig. C1-64)

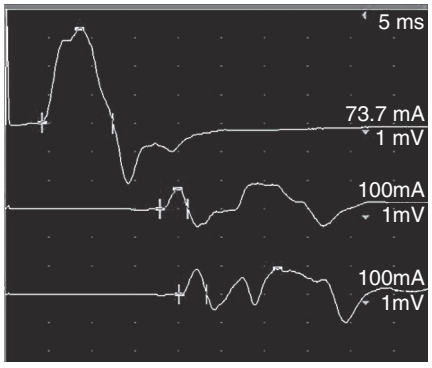

FIGURE C1-64 Conduction block.

TABLE C1-16 Diagnostic Criteria

Feature	American Academy of Neurology (AAN) Criteria	Saperstein Criteria	Inflammatory Neuropathy Cause and Treatment Criteria
Clinical involvement	Motor dysfunction, sensory dysfunction of >1 limb or both	Major: Symmetric proximal and distal weakness; minor: exclusively symmetrical distal weakness or sensory loss	Progressive or relapsing motor and sensory dysfunction of >1 limb
Time course	≥2 mo	≥2 mo	≥2 mo
Reflexes	Reduced or absent	Reduced or absent	Reduced or absent
Electrodiagnostics	Any 3 of the following 4 criteria: partial conduction block of ≥1 motor nerve, reduced velocity of ≥2 motor nerves, prolonged distal latency of ≥2 motor nerves, or prolonged F-waves of ≥2 motor nerves	2 of the 4 AAN electrodiagnostic criteria	Partial conduction block of ≥2 motor nerves and abnormal conduction velocity or distal latency or F-wave latency in 1 other nerve; or, in the absence of partial conduction block, abnormal conduction velocity, distal latency, or F-wave latency in 3 motor nerves; or electrodiagnostic abnormalities indicating demyelination in 2 nerves and histologic evidence of demyelination
CSF analysis	WBC count <10, negative CSF VDRL, and elevated protein (supportive)	Protein >45, WBC <10 (supportive)	CSF recommended but not mandatory
Biopsy findings	Evidence of demyelination and remyelination	Predominant features of demyelination; inflammation (not required)	Not mandatory (except in cases with electrodiagnostic abnormalities in only 2 motor nerves)

LABORATORY TESTS

- CSF analysis to assess for albumin-cytologic dissociation (i.e., elevated protein with normal cell count), along with appropriate laboratory studies to exclude associated conditions.
- Nerve biopsy specimens (rarely done now) also reveal signs of demyelination with variable degrees of inflammation and secondary axonal loss.

IMAGING STUDIES

MRI with/without gadolinium may show enlargement and enhancement of the proximal nerve root segments, respectively (Figs. C1-65 and C1-66)

Rx TREATMENT

Therapies are directed at blocking the underlying immune processes to arrest demyelination and inflammation and to prevent secondary axonal degeneration. The most widely used forms of immunomodulatory therapy are IV immunoglobulin (IVIg), plasmapheresis/plasma exchange (PE), and corticosteroids. There is no difference in efficacy between these three modalities of treatment. Azathioprine, mycophenolate mofetil, cyclophosphamide, rituximab, and cyclosporine may be used as secondary agents.

NONPHARMACOLOGIC THERAPY

Orthotics/braces for significant distal weakness

ACUTE GENERAL Rx

IVIg 2 g/kg divided over 2 to 5 days; plasmapheresis (5 to 6 exchanges)

CHRONIC Rx

- Oral prednisone (1 mg/kg daily starting dose). Typically changed to every other day after 1 mo or when strength plateaus. Reduce by 10 mg every month until 20 mg every other day. Then reduce by 5 mg/mo. Get tuberculin skin test prior to administration. Treat with calcium and vitamin D; low-sodium/high-protein diet, routine ophthalmologic evaluation for cataract and glaucoma screening, and surveillance for diabetes and GERD symptoms/signs.
- PREDICT study: compared dexamethasone (Decadron) 40 mg daily x4 days per month with prednisone 60 mg daily x2 months and then tapered over 27 wk. No difference in efficacy was found between the two groups. Less weight gain and cushingoid features occurred with pulsed steroids but possibly more sleep and psychological disturbances.
- Pulsed Solu-Medrol: no standard regimen. However, 1000 mg x3 days can be used, followed by 1000 mg wk with the goal of reduced frequency to every 2 to 12 wk.
- IVIg: 0.4 to 1 g/kg administered monthly. Check baseline IgA level. Check renal function panel and survey for hypercoagulable states and development of headache.
- Mycophenolate mofetil: Start 500 mg bid and increase in 2 to 4 wk to 1 g bid (check CBC, LFTs, and CBC monthly for first 3 mo, then every 3 mo thereafter). May cause GI upset.
- Imuran: Start 25 to 50 mg bid and increase in 4 wk to 100 mg bid (check baseline LFTs and CBC for first 3 mo, then every 3 mo thereafter). Watch for idiosyncratic reaction of fever, GI upset. If occurs, cannot re-challenge patient.
- Cytoxan: used for severe cases. 1000 mg/m^2 monthly for 6 months (moderate dose) or 50 mg/kg daily × 4 days (high dose).
- Other treatments used (case reports/anecdotal evidence): etanercept, rituximab, tacrolimus, interferon beta-1a.

DISPOSITION

- In one series, 90% of patients with CIDP improved. However, relapse rate was approximately 50%. In Mayo Clinic series, 64% of the patients were either improved or in remission and able to work, 8% were ambulatory but unable to work, 11% were bedridden or wheelchair bound, and 11% died from the disease.
- Patients with CIDP associated with IgM monoclonal gammopathy often respond poorly to treatment.
- Younger age, female gender, and relapsing-remitting course may portend a more favorable prognosis.

REFERRAL

- Neurologist, physical therapy/occupational therapy, orthotics

PEARLS & CONSIDERATIONS

- Patients are compliant with Imuran treatment if MCV >100.
- Always place PPD prior to initiation of steroid treatment.
- Consider Bactrim 3 times weekly in patients concomitant with steroids and other immunosuppressant agent for *Pneumocystis* pneumonia prophylaxis (especially in patients with coexisting lung disease).
- NCS: Look for acquired features of demyelination
  1. Conduction block
  2. Temporal dispersion
- CSF: albuminocytologic dissociation; high CSF protein with normal cell count.

PATIENT/FAMILY EDUCATION

CIDP is a chronic illness usually characterized by a relapsing-remitting course that typically responds well to treatment. Early referral to a neurologist is important, and education on steroid side effects and mitigating factors is paramount.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **JOHN SLADKY, M.D.**

FIGURE C1-65 Contrast-enhanced MRI shows enhancement of nerve roots.

FIGURE C1-66 T2-weighted axial MRI shows enlarged nerve roots.

SUGGESTED READINGS

Amato AA, Russell JA: Neuromuscular disorders. McGraw-Hill: New York.

Dyck PJ et al.: A plasma exchange versus immune globulin infusion trial in chronic inflammatory demyelinating polyradiculoneuropathy, *Ann Neurol* 36:838–845, 1994.

Gorson KC et al.: Chronic inflammatory demyelinating polyneuropathy: clinical features and response to treatment in 67 consecutive patients with and without a monoclonal gammopathy, *Neurology* 48:321–328, 1997.

Koller H et al.: Chronic inflammatory demyelinating polyneuropathy, *N Engl J Med* 352:1343–1356, 2005.

Saperstein D: Chronic acquired demyelinating polyneuropathies, *Semin Neurol* 28:168–184, 2008.

BASIC INFORMATION

DEFINITION

Chronic kidney disease (CKD) is a progressive decrease in renal function (glomerular filtration rate [GFR] <60 ml/min for >3 mo) with subsequent accumulation of waste products in the blood, electrolyte abnormalities, and anemia. The mechanisms and manifestations of CKD are summarized in Table C1-17. The National Kidney Foundation Disease Outcomes Quality Initiative defines CKD as follows, regardless of clinical diagnosis (Table C1-18): kidney damage (usually defined as an albumin-creatinine ratio [ACR] ≥30 mg/g) or a glomerular filtration rate (GFR) <60 ml/min per 1.73 m^2 (usually estimated from the serum creatinine level) for at least 3 mo.

Table EC1-19 describes the risk, injury, failure, and end-stage kidney disease (RIFLE) classification.

SYNONYMS

CKD
CRF
Chronic kidney disease
Chronic renal failure
End-stage renal disease

ICD-9CM CODES
585 Chronic renal failure
IC-10CM CODES
N18.9 Chronic kidney disease, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- The prevalence of patients with CKD in the U.S. is approximately 11%.
- The number of patients with end-stage renal disease (ESRD) is increasing at the rate of 7% to 9% per year in the U.S. The increases are partially explained by the increasing prevalence of diabetes mellitus and hypertension, the leading risk factors for CKD. Each year two in 10,000 persons develop end-stage CKD.
- In the U.S., >250,000 people per year receive dialysis treatment for ESRD.
- Although kidney transplantation is considered the best choice for renal replacement therapy, many patients are not eligible for transplantation and more than 100,000 patients start dialysis each year.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Skin pallor, ecchymoses.
- Edema, leg cramps, restless legs, peripheral neuropathy.
- Hypertension.
- Emotional lability and depression, decreased mental acuity.
- The clinical presentation varies with the degree of renal failure and its underlying etiology. Common symptoms are generalized fatigue, nausea, anorexia, pruritus (Fig. EC1-67), sleep disturbances, smell and taste disturbances, hiccups, and seizures.
- Clinical manifestations of uremic encephalopathy are described in Table C1-17.

ETIOLOGY

- Diabetes (37%), hypertension (30%), chronic glomerulonephritis (12%)
- Polycystic kidney disease
- Tubular interstitial nephritis (e.g., drug hypersensitivity, analgesic nephropathy), obstructive nephropathies (e.g., nephrolithiasis, prostatic disease)
- Vascular diseases (renal artery stenosis, hypertensive nephrosclerosis)
- Autoimmune diseases

DIAGNOSIS

- CKD is primarily distinguished from acute RF by the duration (progression over several months).

TABLE C1-17 Pathophysiology of Chronic Kidney Disease

Manifestation	Mechanisms
Accumulation of nitrogenous waste products	Decrease in glomerular filtration rate
Acidosis	Decreased ammonia synthesis Impaired bicarbonate reabsorption Decreased net acid excretion
Sodium retention	Excessive renin production Oliguria
Sodium wasting	Solute diuresis Tubular damage
Urinary concentrating defect	Solute diuresis Tubular damage
Hyperkalemia	Decrease in glomerular filtration rate Metabolic acidosis Excessive potassium intake Hyporeninemic hypoaldosteronism
Renal osteodystrophy	Impaired renal production of 1,25-dihydroxycholecalciferol Hyperphosphatemia Hypocalcemia Secondary hyperparathyroidism
Growth retardation	Inadequate caloric intake Renal osteodystrophy Metabolic acidosis Anemia Growth hormone resistance
Anemia	Decreased erythropoietin production Iron deficiency Folate deficiency Vitamin B_{12} deficiency Decreased erythrocyte survival
Bleeding tendency	Defective platelet function
Infection	Defective granulocyte function Impaired cellular immune functions Indwelling dialysis catheters
Neurologic symptoms (fatigue, poor concentration, headache, drowsiness, memory loss, seizures, peripheral neuropathy)	Uremic factor(s) Aluminum toxicity Hypertension
Gastrointestinal symptoms (feeding intolerance, abdominal pain)	Gastroesophageal reflux Decreased gastrointestinal motility
Hypertension	Volume overload Excessive renin production
Hyperlipidemia	Decreased plasma lipoprotein lipase activity
Pericarditis, cardiomyopathy	Uremic factor(s) Hypertension Fluid overload
Glucose intolerance	Tissue insulin resistance

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

TABLE C1-18 Criteria for Definition of Chronic Kidney Disease

Kidney damage for ≥3 months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, that can lead to decreased GFR, manifest by either:
- Pathologic abnormalities
- Markers of kidney damage, including abnormalities in the composition of blood or urine, or abnormalities in imaging tests
- GFR <60 ml/min/1.73 m^2 for ≥3 months, with or without kidney damage

GFR, Glomerular filtration rate.
From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

WORKUP

- Laboratory evaluation and imaging studies should be aimed at identifying reversible causes of acute decrements in GFR (e.g., volume depletion, urinary tract obstruction, heart failure) superimposed on chronic renal disease.
- Sonographic evaluation of the kidneys generally reveals smaller kidneys with increased echogenicity in CKD.
- Kidney biopsy: generally not performed in patients with small kidneys or with advanced disease.

LABORATORY TESTS

- Elevated blood urea nitrogen (BUN), creatinine, creatinine clearance. GFR is the best overall indicator of kidney function. It can be estimated by using prediction equations that take into account the serum creatinine level and some or all specific variables (body size, age, sex, race). GFR calculators are available on the National Kidney Foundation website (http://www.kidney.org/kls/professionals/gfr_calculator.cfm).
- Urinalysis: may reveal proteinuria, red blood cell casts.
- Serum chemistry: elevated BUN and creatinine, hyperkalemia, hyperuricemia, hypocalcemia, hyperphosphatemia, hyperglycemia, decreased bicarbonate. Measure urinary protein excretion. The finding of a protein/creatinine ratio of >1000 mg/g suggests the presence of glomerular disease.
- Special studies: serum and urine immunoelectrophoresis (in suspected multiple myeloma), antinuclear antibody (in suspected systemic lupus erythematosus).
- Cystatin C is a cysteine proteinase inhibitor produced by all nucleated cells, freely filtered at the glomerulus but not secreted by tubular cells. Given these characteristics, it may be superior to creatinine concentration both in kidney disease and as a marker of acute kidney injury. It is a better index of kidney function in elderly patients and a better predictor of outcomes than creatinine. The association of cystatin C is stronger than the association of measured GFR with all-cause and cardiovascular mortality in patients with advanced CKD.

IMAGING STUDIES

- Ultrasound of kidneys to measure kidney size and rule out obstruction
- Plain x-rays done for other reasons may reveal extraskeletal calcifications (Fig. EC1-68).

CLASSIFICATION

A classification of CKD based on GFR is described in Table C1-20.

Rx TREATMENT

The management plan for patients with CKD varies according to stage (Table C1-21).

NONPHARMACOLOGIC THERAPY

- Provide adequate nutrition and calories (147 to 168 kJ/kg/day in energy intake, chiefly from carbohydrate and polyunsaturated fats). Table C1-22 describes nutritional recommendations in renal disease. Referral to a dietitian for nutritional therapy for patients with GFR <50 ml/1.73 m^2 is recommended and is now a covered service by Medicare.
- Restrict sodium (approximately 100 mmol/day), potassium (≤60 mmol/day), and phosphate (<800 mg/day).
- Blood pressure: The optimal blood pressure target in patients with CKD is unclear. Available evidence is inconclusive but does not prove that a blood pressure target of <130/80 mm Hg improves clinical outcomes more than a target of <140/90 mm Hg in adults with CKD. Whether a lower target benefits patients with proteinuria >300 to 1000 mg/dl requires further evaluation.
- Adjust drug doses to correct for prolonged half-lives.
- Restrict fluid if significant edema is present.
- Resistance exercise training can preserve lean body mass, nutritional status, and muscle function in patients with moderate CKD.
- Avoid radiocontrast agents. Hydration with sodium bicarbonate before contrast exposure is more effective than hydration with sodium chloride for prophylaxis of contrast-induced renal failure.
- Smoking cessation.
- Initiate hemodialysis, usually performed in center three times per week, or peritoneal dialysis, usually done by the patient at home (see "General Rx"). Prompt referral to nephrologist is helpful. Late evaluation of patients with chronic renal disease is associated with greater burden and severity of comorbid disease and shorter survival. Suggested criteria for referral to a nephrologist is described in Table C1-23.
- Kidney transplantation in selected patients.

GENERAL Rx

- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are useful in reducing proteinuria and slowing the progression of chronic renal disease, especially in hypertensive diabetic patients. The combination of ACEi and ARBs is not recommended and should be used only with great caution in patients with CKD due to increased risk of hyperkalemia, hypotension, and worsening renal failure. A systolic blood pressure between 110 and 129 mm Hg may be beneficial in patients with urine protein excretion >1.0 g/day. Systolic blood pressure <110 mm Hg may be associated with a higher risk for kidney disease progression.
- Initiation of dialysis:
  1. Urgent indications: uremic pericarditis, neuropathy, neuromuscular abnormalities, CHF, hyperkalemia, seizures.
  2. Judgmental indications: creatinine clearance 10 to 15 ml/min; progressive anorexia, weight loss, reversal of sleep pattern, pruritus, uncontrolled fluid gain with hypertension and signs of CHF.
  3. General indications for initiation of dialysis are summarized in Table C1-24. Suggested steps for resolving conflict in the shared decision about starting dialysis are described in Fig. EC1-69. Recent trials have shown that early initiation of dialysis in patients with stage 5 CKD is not associated with increased survival. Initiation of dialysis when the GFR is 10 to 14 ml/min per 1.73 m^2 does not enhance survival compared with a strategy of symptom-driven initiation or initiation of dialysis at eGFR <7 ml/min per 173 m^2.
- Erythropoiesis-stimulating agents epoetin-alpha and darbepoetin-alpha can be used to reduce the need for transfusions in patients with anemia. Anemia should not be fully corrected in patients with CKD. Maintaining a target hemoglobin of 10 g/dl or hematocrit 30% to 33% is satisfactory. Targeting higher hemoglobin levels in CKD may increase risks for stroke, hypertension, and serious cardiovascular events.

TABLE C1-20 Classification of Chronic Kidney Disease Based on GFR

CKD Stage	Definition
1	Normal or increased GFR; some evidence of kidney damage reflected by microalbuminuria, proteinuria, and hematuria as well as radiologic or histologic changes
2	Mild decrease in GFR (89 to 60 ml/min per 1.73 m^2) with some evidence of kidney damage reflected by microalbuminuria, proteinuria, and hematuria as well as radiologic or histologic changes
3	GFR 59 to 30 ml/min per 1.73 m^2
3A	GFR 59 to 45 ml/min per 1.73 m^2
3B	GFR 44 to 30 ml/min per 1.73 m^2
4	GFR 29 to 15 ml/min per 1.73 m^2
5	GFR <15 ml/min per 1.73 m^2; when renal replacement therapy in the form of dialysis or transplantation has to be considered to sustain life

GFR, Glomerular filtration rate.
The suffix p to be added to the stage in proteinuric patients (proteinuria 0.5 g/24 h)
Classification of CKD based on GFR as proposed by the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines and modified by NICE in 2008.
From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

- Diuretics for significant fluid overload (loop diuretics are preferred).
- Correction of hypertension to at least 130/85 mm Hg with ACE inhibitors (avoid in patients with significant hyperkalemia); ARBs, and/or nondihydropyridine calcium channel blockers (verapamil, diltiazem) can be used in patients intolerant to ACE inhibitors or when other agents are needed to control blood pressure.
- Correction of electrolyte abnormalities (e.g., calcium chloride, glucose, sodium polystyrene sulfonate for hyperkalemia), sodium bicarbonate in patients with severe metabolic acidosis.
- Lipid management:[1] The Kidney Disease Improving Global Outcomes (KDIGO) 2013 guidelines for lipid management in CKD does not use LDL cholesterol to identify patients with CKD who should receive lipid lowering therapy and suggests focusing on the absolute risk for coronary events and evidence that such treatment is beneficial. They recommend treatment with a statin or statin/ezetimibe combination in adults aged ≥50 yr with eGFR <60 ml/min/1.73 m^2 but not treated with chronic dialysis or kidney transplantation.
- Control of renal osteodystrophy with calcium supplementation and vitamin D. Starting dose of calcium carbonate is 0.5 g with each meal, increased until the serum phosphorus concentration is normalized (most patients require 5 to 10 g/day). Calcitriol 0.125 to 0.25 mcg/day PO is effective in increasing serum calcium concentration. Paricalcitol, a new vitamin D analogue, has been reported to be more effective than calcitriol in lessening the elevations in serum calcium and phosphorus levels.

[1]Tonelli M et al: Lipid management in chronic kidney disease: synopsis of the kidney disease: improving global outcomes 2013 clinical practice guideline, *Ann Int Med* 160:182-189, 2014.

TABLE C1-21 Management Plan for Patients with Chronic Kidney Disease, According to Stage

KDOQI Classification	GFR (ml/min)	Typical Serum Creatinine in 65-kg Subject	Consequences	Actions to Consider
3	30-59	2 mg/dl (170 μmol/L)	Hypertension, secondary hyperparathyroidism	6 monthly eGFR initially 12 monthly eGFR if stable Annual Hb, K^+, Ca, P Treat hypertension Immunize against hepatitis B
4	15-29	4 mg/dl (350 μmol/L)	*Plus* anemia, hyperphosphatemia	3 monthly eGFR initially 6 monthly eGFR if stable 6 monthly Hb, K^+, Ca, P, and PTH Start phosphate-restricted diet and phosphate binders Correct vitamin D deficiency Start vitamin D analogue Plan renal replacement therapy, including vascular access
5	<15	8 mg/dl (700 μmol/L)	*Plus* sodium and water retention, anorexia, vomiting, reduced higher mental function	Plan elective start of dialysis or preemptive renal transplant
5	<5	17 mg/dl (1500 μmol/L)	*Plus* pulmonary edema, coma, fits, metabolic acidosis, hyperkalemia, death	Start dialysis or provide palliative care

The table gives a rough guide to the level of serum creatinine corresponding to each stage of CKD in a typical 65-kg subject and shows the approximate timing of the anticipated clinical problems and interventions required as CKD progresses. At each stage, the action plan for the previous CKD stage should be followed if it has not already been initiated.
eGFR, Estimated glomerular filtration rate; *PTH*, parathyroid hormone.
From Floege J et al: *Comprehensive clinical nephrology*, ed 4, Philadelphia, 2010, Saunders.

TABLE C1-22 Nutritional Recommendations in Renal Disease

Daily Intake	Predialysis CRF	Hemodialysis	Peritoneal Dialysis
Protein (g/kg ideal BW) (see KDOQI for estimation of adjusted edema-free body weight)	0.6-1.0 Level depends on the view of the nephrologist 1.0 for nephrotic syndrome	1.1-1.2 This is a broad recommendation as protein intake would be individualized for the patient's nutritional status, serum phosphate levels, and dialysis adequacy	1.0-1.3
Energy (kcal/kg BW)	35 (<60 yr) 30-35 (>60 yr)	35 (<60 yr) 30-35 (>60 yr)	35 including dialysate calories (<60 yr) 30-35 including dialysate calories (<60 yr)
Sodium (mmol)	<100 (more if salt wasting)	<100	<100
Potassium	Reduce if hyperkalemic	Reduce if hyperkalemic	Reduce if hyperkalemic; potassium restriction is generally not required
	If hyperkalemic, advice will take the form of decreasing certain foods (e.g., some fruits and vegetables) and giving information about cooking methods		
Phosphorus	Reduce; level dependent on protein intake Advice will take the form of reducing certain foods (e.g., dairy, offal, some shellfish) and giving information about the timing of binders with high-phosphorus meals and snacks		
Calcium	In CKD stages 3-5, total intake of elemental calcium (including dietary calcium) should not exceed 2000 mg/day	Total intake of elemental calcium (including dietary calcium) should not exceed 2000 mg/day	Total intake of elemental calcium (including dietary calcium) should not exceed 2000 mg/day

Recommendations are for typical patients but should always be individualized on the basis of clinical, biochemical, and anthropometric indices.
BW, Body weight; *CKD,* chronic kidney disease; *CRF,* chronic renal failure; *KDOQI,* Kidney Disease Outcomes Quality Initiative.
From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

TABLE C1-23 Suggested Criteria for Referral of Patients with Chronic Kidney Disease to a Nephrologist

New Diagnosis	Stage 3	Stage 4
eGFR <30 ml/min/per 173 m^2	eGFR falling by >4 ml/min per year	eGFR <20 ml/min per 173 m^2
Hemoglobin <11 g/dl	eGFR <50 ml/min in patient younger than 50 years	eGFR falling by >4 ml/min per year
K^+ >6 mmol/L	Hemoglobin <11 g/dl	Hemoglobin <11 g/dl
Ca <2.1 mmol/L	K^+ >6 mmol/L	K^+ >6 mmol/L
Pi >1.5 mmol/L	Ca <2.1 mmol/L	Ca <2.1 mmol/L
PTH >3× upper limit normal	Pi >1.5 mmol/L	Pi >1.5 mmol/L
Hematuria		PTH >3× upper limit normal
Urine ACR >30 mg/mmol		
Suspected renovascular disease		

ACR, Albumin to creatinine ratio; *eGFR,* estimated glomerular filtration rate; *PTH,* parathyroid hormone.
Modified from NICE CKD guideline. From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

TABLE C1-24 When to Initiate Dialysis

Indications for early start on dialysis
- Intractable fluid overload
- Intractable hyperkalemia
- Malnutrition due to uremia
- Uremic neurologic dysfunction
- Uremic serositis
- Functional deterioration otherwise unexplained

Uremic cognitive dysfunction can affect learning
Therefore, home-based self-dialysis may need to start earlier than center-assisted dialysis.

Start of dialysis may be delayed if patient is
asymptomatic, awaiting imminent kidney transplant, awaiting imminent placement of permanent HD or PD access, or, after appropriate education, has chosen conservative therapy.

If start of dialysis is delayed,
patient should be re-evaluated regularly to see if dialysis has become necessary.

Patients who choose PD
should not be required to have HD access placed, but venous sites for possible future HD access in arms should be preserved since HD may be required in the future.
Incremental start on PD may be considered if there is significant residual renal function.

Nephrologists should consider conservative (nondialysis) treatment of kidney failure an integral part of their clinical practice.

HD, Hemodialysis; *PD,* peritoneal dialysis.
Modified from NKF KDOQI Clinical Practice Guideline for initiation of dialysis. http://www.kidney.org/professional/Kdoqi/guideline_upHD_PD_VA/pd_rec1.htm. From Floege J et al: *Comprehensive clinical nephrology*, ed 4, Philadelphia, 2010, Saunders.

- Dietary phosphate restriction effectively reduces serum phosphate levels and is recommended in all patients with ESRD. For additional management of hyperphosphatemia, calcium-based agents are inexpensive, well tolerated, and should be the first-line phosphate binders for patients undergoing dialysis. Sevelamer and lanthanum are also effective as phosphate binders, but are much more expensive.
- General considerations in the continuing assessment of the CKD patient are described in Table C1-25.
- A sequential approach to the uremic patient with pruritus is described in Fig. EC1-70.

DISPOSITION

- Prognosis is influenced by comorbidity of multisystem diseases. Late referral of patients to a nephrologist is associated with higher mortality and morbidity rates and higher costs. Despite recommendations for early referral, up to 64% of patients with CKD are still referred late.
- Lower predialysis serum sodium concentration is associated with an increased risk of death.
- Apolipoprotein E variation predicts CKD progression, independent of diabetes, race, lipid, and nonlipid factors. The e2 allele moderately increases risk of kidney disease progression, whereas allele e4 decreases the risk.
- The use of cystatin C alone or in combination with creatinine strengthens the association between the eGFR and the risks of death and end-stage renal disease across diverse populations (Shlipak et al).
- Kidney transplantation in selected patients improves survival. The 2-yr kidney graft survival rate for living related donor transplantations is >80%, whereas the 2-yr graft survival rate for cadaveric donor transplantation is approximately 70%.
- Principles underlying withdrawal of dialysis are described in Table C1-26.

TABLE C1-25 Continuing Assessment of the Chronic Kidney Disease Patient

Kidney Function

Has kidney function declined?

Has kidney function declined at the predicted rate?

If not, are there exacerbating factors?

Should dialysis be started?

Are there life-threatening complications?
- Pericarditis
- Fluid overload
- Resistant hypertension
- Hyperkalemia
- Uncompensated metabolic acidosis

Should access be created or transplantation planned?

Supportive Treatment

Can salt, potassium, and fluid balance be improved by diet or diuretics?

Is the phosphate controlled?

Is the dose of vitamin D compound appropriate?

Should erythropoietin (EPO) be prescribed?

Are nutritional supplements needed?

Does the patient need counseling?

Questions to be posed in evaluation of the patient.
From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

TABLE C1-26 Principles Underlying Withdrawal of Dialysis

The ultimate responsibility for the decision rests with the physician, not the relative.

The patient's interests and dignity should be protected at all times.

The process should not be rushed. If there is any doubt about the correctness of the decision, treatment should continue.

There should be an open discussion among the multidisciplinary team to avoid any damaging disagreements.

The psychological needs of the health care team should not be overlooked.

Palliative care must be given in the most appropriate environment, e.g., a hospice or, ideally, the patient's own home.

From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Background:
The optimal blood pressure target in patients with chronic kidney disease (CKD) is unclear.

Purpose:
To summarize trials comparing lower versus higher blood pressure targets in adult patients with CKD and focus on proteinuria as an effect modifier.

Data Sources:
MEDLINE and the Cochrane Central Register of Controlled Trials (July 2001 through January 2011) were searched for reports from randomized, controlled trials with no language restriction.

Study Selection:
Authors screened abstracts to identify reports from trials comparing blood pressure targets in adults with CKD that had more than 50 participants per group; at least 1-year follow-up; and outcomes of death, kidney failure, cardiovascular events, change in kidney function, number of antihypertensive agents, and adverse events.

Data Extraction:
Reviewers extracted data on study design, methods, sample characteristics, interventions, comparators, outcomes, number of medications, and adverse events and rated study quality and quality of analyses for proteinuria subgroups.

Data Synthesis:
Three trials with a total of 2272 participants were included. Overall, trials did not show that a blood pressure target of less than 125/75 to 130/80 mm Hg is more beneficial than a target of less than 140/90 mm Hg. Lower-quality evidence suggests that a low target may be beneficial in subgroups with proteinuria greater than 300 to 1000 mg/d. Participants in the low target groups needed more antihypertensive medications and had a slightly higher rate of adverse events.

Limitations:
No study included patients with diabetes. Trial duration may have been too short to detect differences in clinically important outcomes, such as death and kidney failure. Ascertainment and reporting of adverse events was not uniform.

Conclusion:
Available evidence is inconclusive but does not prove that a blood pressure target of less than 130/80 mm Hg improves clinical outcomes more than a target of less than 140/90 mm Hg in adults with CKD. Whether a lower target benefits patients with proteinuria greater than 300 to 1000 mg/d requires further study. Ⓐ

Abstract[2]

Allopurinol ameliorates endothelial dysfunction and arterial stiffness among patients without chronic kidney disease (CKD), but it is unknown if it has similar effects among patients with CKD. Furthermore, because arterial stiffness increases left ventricular afterload, any allopurinol-induced improvement in arterial compliance might also regress left ventricular hypertrophy (LVH). We conducted a randomized, double-blind, placebo-controlled, parallel-group study in patients with stage 3 CKD and LVH. We randomly assigned 67 subjects to allopurinol at 300 mg/d or placebo for 9 months; 53 patients completed the study. We measured left ventricular mass index (LVMI) with cardiac magnetic resonance imaging (MRI), assessed endothelial function by flow-mediated dilation (FMD) of the brachial artery, and evaluated central arterial stiffness by pulse-wave analysis. Allopurinol significantly reduced LVH (P=0.036), improved endothelial function (P=0.009), and improved the central augmentation index (P=0.015). This study demonstrates that allopurinol can regress left ventricular mass and improve endothelial function among patients with CKD. Because LVH and endothelial dysfunction associate with prognosis, these results call for further trials to examine whether allopurinol reduces cardiovascular events in patients with CKD and LVH. Ⓐ

Abstract[3]

Objectives:
This study examined the functionality of high-density lipoprotein (HDL) in individuals with end-stage renal disease on dialysis (ESRD-HD).

Background:
The high rate of cardiovascular disease (CVD) in chronic kidney disease is not explained by standard risk factors, especially in patients with ESRD-HD who appear resistant to benefits of statin therapy. HDL is antiatherogenic because it extracts tissue cholesterol and reduces inflammation.

Methods:
Cellular cholesterol efflux and inflammatory response were assessed in macrophages exposed to HDL of patients with ESRD-HD or controls.

Results:
HDL from patients with ESRD-HD was dramatically less effective than normal HDL in accepting cholesterol from macrophages (median 6.9%; interquartile range [IQR]: 1.4% to 10.2%) versus control (median 14.9%; IQR: 9.8% to 17.8%; p <0.001). The profound efflux impairment was also seen in patients with ESRD-HD and diabetes compared with patients with diabetes without renal disease (median 8.1%; IQR: 3.3% to 12.9%) versus control (median 13.6%; IQR: 11.0% to 15.9%; P = 0.009). In vitro activation of cellular cholesterol transporters increased cholesterol efflux to both normal and uremic HDL. HDL of patients with ESRD-HD had reduced antichemotactic ability and increased macrophage cytokine response (tumor necrosis factor-alpha, interleukin-6, and interleukin-1-beta). HDL of patients with ESRD-HD on statin therapy had reduced inflammatory response while maintaining impaired cholesterol acceptor function. Interestingly, impaired HDL-mediated efflux did not correlate with circulating C-reactive protein levels or cellular inflammatory response.

Conclusions:
These findings suggest that abnormal HDL capacity to mediate cholesterol efflux is a key driver of excess CVD in patients on chronic hemodialysis and may explain why statins have limited effect to decrease CV events. The findings also suggest cellular cholesterol transporters as potential therapeutic targets to decrease CV risk in this population. Ⓐ

Abstract[4]

Background:
Disorders of mineral metabolism, including secondary hyperparathyroidism, are thought to contribute to extraskeletal (including vascular) calcification among patients with chronic kidney disease. It has been hypothesized that treatment with the calcimimetic agent cinacalcet might reduce the risk of death or nonfatal cardiovascular events in such patients.

Methods:
In this clinical trial we randomly assigned 3883 patients with moderate-to-severe secondary hyperparathyroidism (median level of intact parathyroid hormone, 693 pg per milliliter [10th to 90th percentile, 363 to 1694]) who were undergoing hemodialysis to receive either cinacalcet or placebo. All patients were eligible to receive conventional therapy, including phosphate binders, vitamin D sterols, or both. The patients were followed for up to 64 months. The primary composite end point was the time until death, myocardial infarction, hospitalization for unstable angina, heart failure, or a peripheral vascular event. The primary analysis was performed on the basis of the intention-to-treat principle.

Results:
The median duration of study-drug exposure was 21.2 months in the cinacalcet group, versus 17.5 months in the placebo group. The primary composite end point was reached in 938 of 1948 patients (48.2%) in the cinacalcet group and 952 of 1935 patients (49.2%) in the placebo group (relative hazard in the cinacalcet group vs. the placebo group, 0.93; 95% confidence interval, 0.85 to 1.02; P = 0.11). Hypocalcemia and gastrointestinal adverse events were significantly more frequent in patients receiving cinacalcet.

Conclusions:
In an unadjusted intention-to-treat analysis, cinacalcet did not significantly reduce the risk of death or major cardiovascular events in patients with moderate-to-severe secondary hyperparathyroidism who were undergoing dialysis. (Funded by Amgen; EVOLVE ClinicalTrials.gov number, NCT00345839.) Ⓐ

Evidence-Based References

Upadhyay A et al.: Systematic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier, *Ann Intern Med* 154:541–548, 2011. Ⓐ

Kao MP et al.: Allopurinol benefits left ventricular mass and endothelial dysfunction in chronic kidney disease, *J Am Soc Nephrol* 22:1382–1389, 2011. Ⓐ

Yamamoto S, Yancey PG, Ikizler TA et al.: Dysfunctional high-density lipoprotein in patients on chronic hemodialysis, *J Am Coll Cardiol* 60:2372–2379, 2012. Ⓐ

The EVOLVE Trial Investigators: Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis, *N Engl J Med* 367:2482–2494, 2012. Ⓐ

SUGGESTED READINGS

Abboud H, Henrich WL: Stage IV chronic kidney disease, *N Engl J Med* 362:56–65, 2010.

Appel L et al.: Intensive blood-pressure control in hypertensive chronic kidney disease, *N Engl J Med* 363:918–929, 2010.

Baumgarten M, Gehr T: Chronic kidney disease: detection and evaluation, *Am Fam Physician* 84(10):1138–1148, 2011.

Chawla LS et al.: Acute kidney injury and chronic kidney disease as interconnected syndromes, *N Engl J Med* 371:58–66, 2014.

Cooper BA et al.: Early initiation of dialysis inpatients with stage 5 chronic kidney disease is not associated with increased survival, *N Engl J Med* 363:609–619, 2010.

Herget-Rosenthal S et al.: Early detection of acute renal failure by serum cystatin C, *Kidney Int* 66:1115, 2004.

Hsu CC et al.: Apolipoprotein E and progression of chronic kidney disease, *JAMA* 293:2892, 2005.

Jafar TH et al.: Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition, *Ann Intern Med* 139:244, 2003.

Johnson CA et al.: Clinical practice guidelines for chronic kidney disease in adults, *Am Fam Physician* 70:869, 2004.

Kinchen KS et al.: The timing of specialist evaluation in chronic kidney disease and mortality, *Ann Intern Med* 137:479, 2003.

Ku E et al.: The hazards of dual renin-angiotensin blockade in chronic kidney disease, *Arch Intern Med* 169(11):1015–1018, 2009.

Kunz R et al.: Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin-angiotensin system on proteinuria in renal disease, *Ann Intern Med* 148:30–48, 2008.

Levey AS et al.: National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification, *Ann Intern Med* 139:137, 2003.

Levey AS: A new equation to estimate glomerular filtration rate, *Ann Intern Med* 150:604–612, 2009.

Levey AS et al.: Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults. A systematic review, *JAMA* 313(8):837–846, 2015.

Mann JFE et al.: Effect of telmisartan on renal outcomes, *Ann Intern Med* 151:1–10, 2009.

Menon V et al.: Cystatin C as a risk factor for outcomes in chronic kidney disease, *Ann Intern Med* 147:19, 2007.

Merten GJ et al.: Prevention of contrast-induced nephropathy with sodium bicarbonate, *JAMA* 291:2328, 2004.

Meyer TW, Hostetter TH: Uremia, *N Engl J Med* 357:1316–1325, 2007.

Palmer SC et al.: Meta-analysis: erythropoiesis-stimulating agents in patients with chronic kidney disease, *Ann Intern Med* 153:23–33, 2010.

Peralta CA et al.: Detection of chronic kidney disease with creatinine, cystatin C, and urine albumin-to-creatinine ratio and association with progression to end-stage renal disease and mortality, *JAMA* 305(15):1545–1552, 2011.

Shlipak MG et al.: Cystatin C versus creatinine in determining risk based on kidney function, *N Engl J Med* 369:932–943, 2013.

Singh AK et al.: Correction of anemia with epoetin alfa in chronic kidney disease, *N Engl J Med* 355:2085, 2006.

Snively C, Gutierrez C: Chronic kidney disease: prevention and treatment of common complications, *Am Fam Physician* 70:1921, 2004.

Sprangers B et al.: Late referral of patients with chronic kidney disease: no time to waste, *Mayo Clin Proc* 81:1487, 2006.

Stevens PE et al.: Evaluation and management of chronic kidney disease: synopsis of kidney disease: improving global outcomes 2012 Clinical Practice Guideline, *Ann Intern Med* 158:825–830, 2013.

Tonelli M et al.: Oral phosphate binders in patients with kidney failure, *N Engl J Med* 362:1312–1324, 2010.

Upadhyay A et al.: Systematic review: Blood pressure target in chronic kidney disease and proteinuria as an effect modifier, *Ann Intern Med* 154:541–548, 2011.

Upadhyay A et al.: Systematic review and meta-analysis: lipid-lowering therapy in persons with chronic kidney disease, *Ann Intern Med* 157:251–262, 2012.

Waikar SS: Mortality associated with low serum sodium concentration in maintenance hemodialysis, *Am J Med* 124:77–84, 2011.

Zoungas S et al.: Systematic review: sodium bicarbonate treatment regimens for the prevention of contrast-induced nephropathy, *Ann Intern Med* 151:631–638, 2009.

TABLE EC1-19 Chronic Kidney Disease

Class	Glomerular Filtration Rate Criteria	Urine Output Criteria
Risk	Serum creatinine ×1.5 over baseline	<0.5 ml/kg/hr × 6 hr
Injury	Serum creatinine ×2 over baseline	<0.5 ml/kg/hr × 12 hr
Failure	Serum creatinine ×3, or serum creatinine ≥4 mg/dl with an acute rise >0.5 mg/dl	<0.3 ml/kg/hr × 24 hr, or anuria × 12 hr
Loss	Persistent acute renal failure = complete loss of kidney function for >4 weeks	
End-stage kidney disease	End-stage kidney disease for >3 months	

For conversion of creatinine expressed in conventional units to SI units, multiply by 88.4. RIFLE class is determined based on the worst of either glomerular filtration criteria or urine output criteria. Glomerular filtration criteria are calculated as an increase of serum creatinine above the baseline serum creatinine level. Acute kidney injury should be both abrupt (within 1 to 7 days) and sustained (more than 24 hours). When the baseline serum creatinine is not known, and patients are without a history of chronic kidney insufficiency, it is recommended to calculate a baseline serum creatinine using the Modification of Diet in Renal Disease equation for assessment of kidney function, assuming a glomerular filtration rate of 75 ml/min/1.73 m^2. When the baseline serum creatinine is elevated, an abrupt rise of at least 0.5 mg/dl to more than 4 mg/dl is all that is required to achieve the Failure class.

From Risk, injury, failure, loss, and end-stage kidney disease (RIFLE) classification. In Cameron JL et al: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

FIGURE EC1-67 Prurigo nodularis. (Courtesy I. Macdougall, London. From Floege J et al: *Comprehensive clinical nephrology*, ed 4, Philadelphia, 2010, Saunders.)

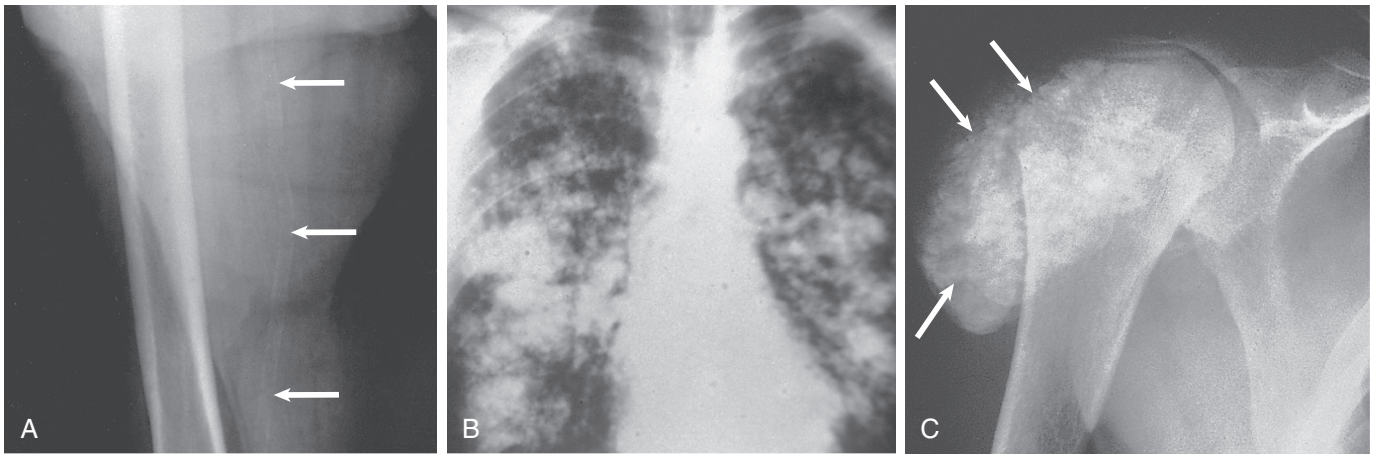

FIGURE EC1-68 Extraskeletal calcification in chronic renal failure. A, Arterial calcification *(arrows)*. **B,** Pulmonary calcification. **C,** Periarticular calcification *(arrows)*. (From Floege J et al: *Comprehensive clinical nephrology*, ed 4, Philadelphia, 2010, Saunders.)

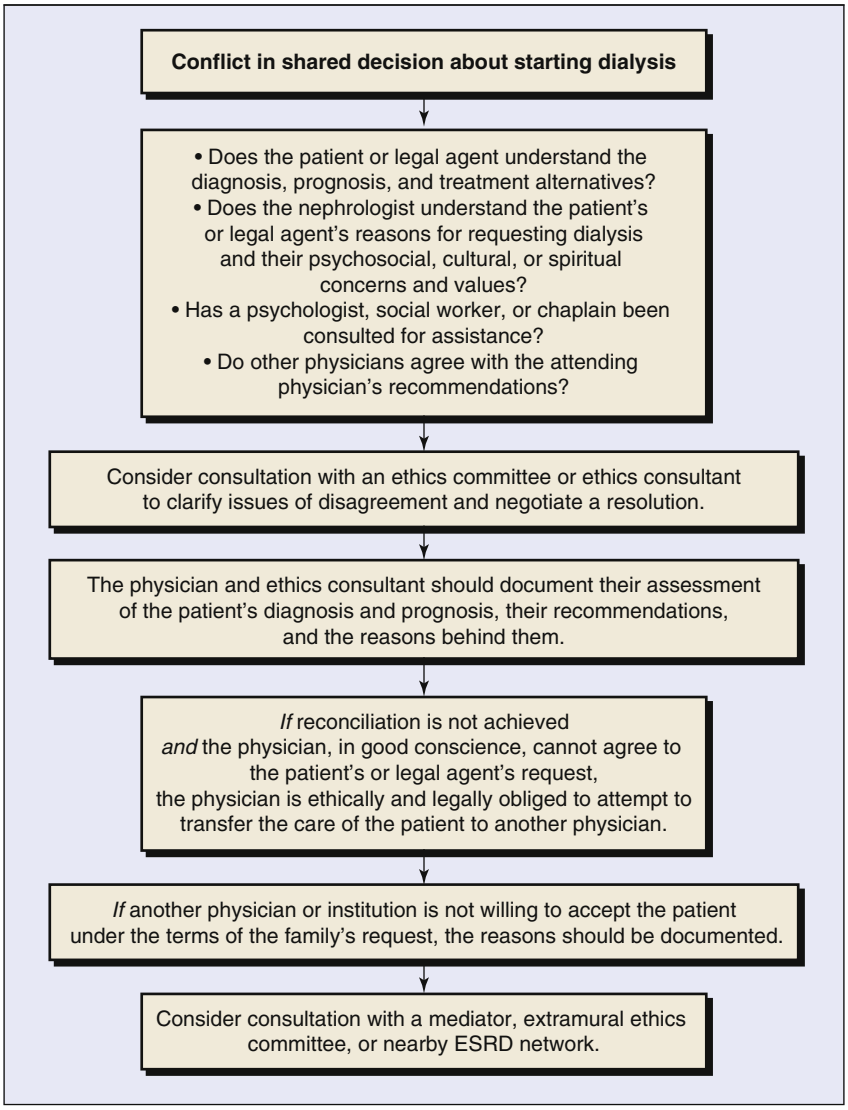

FIGURE EC1-69 Suggested steps for resolving conflict in the shared decision about starting dialysis. (From Floege J et al: *Comprehensive clinical nephrology*, ed 4, Philadelphia, 2010, Saunders.)

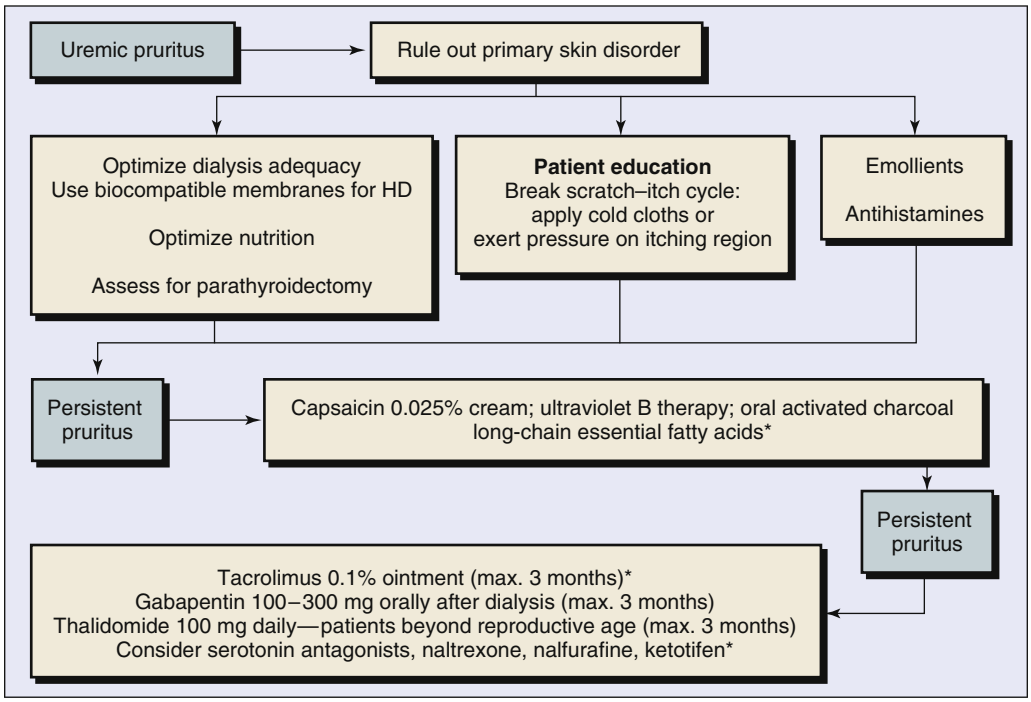

FIGURE EC1-70 Sequential approach to the uremic patient with pruritus. *Therapeutic benefit in studies has been described variably; see text for details. *HD*, Hemodialysis. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

Chronic Lymphocytic Leukemia PTG ALG

BASIC INFORMATION

DEFINITION

Chronic lymphocytic leukemia (CLL) is a lymphoproliferative disorder characterized by proliferation and accumulation of mature-appearing neoplastic lymphocytes.

SYNONYMS

CLL

ICD-9CM CODES
204.1 Leukemia, chronic lymphocytic
ICD-10CM CODES
C91.10 Chronic lymphocytic leukemia of B-cell type not having achieved remission

EPIDEMIOLOGY & DEMOGRAPHICS

- Most frequent form of leukemia in Western countries (15,000 new cases annually in the United States). Incidence rate is 2-6 cases per 100,000 per year, and increases to 13 cases per 100,000 at age 65. It is more common in Caucasians and in those with a family history of CLL or other lymphoid malignancy.
- Generally occurs in elderly patients (70% of diagnoses are made in patients >65 yr of age). Mean age at diagnosis is 65 yr.
- Male/female ratio of 2:1.
- CLL accounts for 11% of all hematologic neoplasms.
- There are over 5000 CLL deaths yearly in the United States.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- At presentation most patients are asymptomatic. Many cases are diagnosed on the basis of laboratory results obtained after routine physical examination.
- Lymphadenopathy (>50%), splenomegaly, and hepatomegaly 20% to 50%.
- Variable clinical presentation according to stage of the disease.
- B symptoms (fever, weight loss, and sweats) in 10% of patients at initial presentation.
- Some patients come to medical attention because of weakness and fatigue (as a result of anemia).

ETIOLOGY

CLL is a disease derived from antigen-experienced B lymphocytes that differ in the level of immunoglobulin V-gene mutations.

DIAGNOSIS

- The National Cancer Institute (NCI)-sponsored Working Group Guidelines for the Diagnosis of CLL require an absolute clinical lymphocyte count of 5000 cells/mm^3 or more and a characteristic phenotype combining the presence of CD19, the T-cell antigen CD5, and CD23.[1]

[1]Hallek M et al: Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: A report from the International Workshop on Chronic Lymphocytic Leukemia updating The National Cancer Institute Working Group 1996 Guidelines. *Blood* 111(12):5446-5456, 2010.

TABLE C1-27 Evaluation of Chronic Lymphocytic Leukemia (CLL) Patients at Diagnosis

History

B-symptom and fatigue assessment
Infectious history assessment
Occupational assessment for chemical exposure
Familial history of CLL and lymphoproliferative disorders
Preventive interventions for infections and secondary cancers

Physical Exam

Laboratory Assessment

Complete blood count with differential
Morphology assessment of lymphocytes
Chemistry, LFT enzymes, LDH
Flow cytometry assessment to confirm immunophenotype of CLL
Serum immunoglobulins
Serum b_2M levels
Interphase cytogenetics for del(17p13.1), del(11q22.3), del(13q14), del(6q21), and trisomy 12
IgV_H mutational analysis
Stimulated metaphase karyotype (if available)

Selected Tests Under Certain Circumstances

Direct antiglobulin test (DAT), haptoglobin, reticulocyte count if anemia present
CT scan if unexplained abdominal pain or enlargement present
PET scan and/or biopsy if large nodal mass present
Bone marrow aspirate and biopsy if cytopenias present
Familial counseling if first-degree relative with CLL

Teaching

Varicella zoster identification instruction
Skin cancer identification
Disease education (Leukemia and Lymphoma Society, CLL Topics, ACOR)

From Hoffmann R et al: *Hematology: basic principles and practice*, ed 6, Philadelphia, 2013, Elsevier.

- Table C1-27 describes the evaluation of CLL patients at diagnosis.

DIFFERENTIAL DIAGNOSIS

- Hairy cell leukemia.
- Adult T-cell lymphoma. Table C1-28 describes major diagnostic features of CLL and small lymphocytic lymphoma (SLL).
- Prolymphocytic leukemia.
- Viral infections.
- Waldenström's macroglobulinemia.

LABORATORY TESTS (FIG. EC1-71)

- Proliferative lymphocytosis of well-differentiated lymphocytes.
- Bone marrow exam (when done).
- Hypogammaglobulinemia and elevated lactate dehydrogenase may be present at the time of diagnosis.
- Anemia or thrombocytopenia, if present, indicates poor prognosis.
- Trisomy-12 is the most common chromosomal abnormality, followed by 14 q+, 13 q, and 11 q; these all indicate a poor prognosis.
- New laboratory techniques (CD 38, fluorescence in situ hybridization) can identify patients with early-stage CLL at higher risk of rapid disease progression. Staining of mononuclear cells by a two-color (fluorescein isothiocyanate/phycoerythrin) flow cytometric assay using antibodies to the chemokine receptors (CXCR1, CXCR2, etc.) can help in the staging and prognosis of patients. Increase in expression of chemokine receptors CXCR4 and CCR7 correlates with advanced Rai stage (stage IV). The presence of V-gene mutations, CD38+, or ZAP-70+ cells also has prognostic relevance. Patients with clones having few or no V-gene mutations or many CD38+ or ZAP-70+ B cells are associated with an aggressive, usually fatal course.
- There is monotonous replacement of the bone marrow by small lymphocytes (marrow contains ≥30% of well-differentiated lymphocytes). With the use of cell surface markers

TABLE C1-28 Major Diagnostic Features of Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL)

CLL
- Absolute mature lymphocytosis of ≥5 × 10^9/L sustained for at least 3 months
- Monoclonal B cell with mature phenotype, CD5 coexpression, weak CD20, weak surface immunoglobulin, CD23, weak CD22, weak CD11c
- Antigens typically *not* expressed include CD10, FMC7, and CD79b

SLL
- Extramedullary sites of disease predominate
- Diffuse infiltrate of small lymphocytes, proliferation foci
- Monoclonal B cell with mature phenotype similar to CLL

From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.

for clonality determination, the use of bone marrow aspirate and biopsy has become unnecessary for diagnosis or prognosis.
- The percentage of smudge cells (CLL cells ruptured during smear preparation) is associated with mutated IgVH gene status, a favorable prognostic factor. A high percentage of smudge cells on peripheral smear indicates a longer time to treatment from initial diagnosis and better overall survival in patients with early stage CLL.

STAGING: The Rai and Binet systems for staging CLL were established in 1975 and 1977, respectively. However, they do not account for new disease categories such as monoclonic B-cell lymphocytosis (peripheral blood clonal lymphocytosis that does not meet other criteria for CLL. Two subsets of CLL are now recognized based on risk stratification involving molecular and cytogenetic analysis.[2] Rai staging divided CLL into five clinical stages:
- Stage 0: Characterized by lymphocytosis only (>15,000/mm^3 on peripheral smear, bone marrow aspirate ≥40% lymphocytes). The coexistence of lymphocytosis and other factors increases the clinical stage.
- Stage 1: Lymphadenopathy.
- Stage 2: Lymphadenopathy/hepatomegaly.
- Stage 3: Anemia (hemoglobin [Hgb] <11 g/mm^3).
- Stage 4: Thrombocytopenia (platelets <100,000/mm^3).

Binet staging divides CLL into three stages:
- Stage A: Hgb >10 g/dl, platelets >100,000/mm^3, and fewer than three areas involved (the cervical, axillary, and inguinal lymph nodes [whether unilaterally or bilaterally]; the spleen; and the liver).
- Stage B: Hgb >10 g/dl, platelets >100,000/mm^3, and three or more areas involved.
- Stage C: Hgb <10 g/dl, low platelets (<100,000/mm^3), or both (independent of the areas involved).

[2]Nablan C, Rosen ST: Chronic lymphocytic leukemia: A clinical review. *JAMA* 312(21): 2265-2276, 2014.

IMAGING STUDIES

CT scans at diagnosis for assessment of end-organ involvement are not recommended in diagnostic guidelines. However, CT scan of abdomen may be done to evaluate for hepatomegaly and splenomegaly in patients with poor prognostic features.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Treatment goals are relief of symptoms and prolongation of life.
- Observation is appropriate for patients in Rai stage 0 or Binet stage A.
- There are no survival benefits and a slight trend toward worse survival for patients who have early intervention versus deferred chemotherapy.

ACUTE GENERAL Rx

- Symptomatic patients in Rai stage I or II or Binet stage B: fludarabine-based combination immunochemotherapy: local irradiation for isolated symptomatic lymphadenopathy and lymph nodes that interfere with vital organs.
- Best response rates are seen when combination chemotherapy and rituximab are used (>70% complete response, median time to disease progression >4 years).
- Rai stages III or IV, Binet stage C: chlorambucil chemotherapy with or without prednisone:
  1. Fludarabine, CAP (***c***yclophosphamide, ***A***driamycin, ***p***rednisone), or cyclophosphamide, doxorubicin, vincristine, and prednisone (mini-CHOP) can be used in patients who respond poorly to chlorambucil.
  2. Monoclonal antibodies: rituximab, ofatumumab, or alemtuzumab is useful for treatment of patients with CLL refractory to fludarabine.
  3. Splenic irradiation can be used in selected patients with advanced disease.
  4. Bendamustine, an alkylator in the nitrogen mustard family, is well tolerated and can also be used in some patients with CLL.
  5. Combination therapy with fludarabine (F), cyclophosphamide (C), rituximab (R) [FCR] provides additional benefits beyond single-agent therapy. It has shown to improve progression-free and overall survival in patients with CLL who do not have deletion of chromosome 17p and who are considered fit enough for fludarabine-based chemotherapy.
  6. Ibrutinib, an oral kinase inhibitor, is associated with a high frequency of durable remissions in patients with relapsed or refractory CLL. It was recently FDA approved for second-line treatment of CLL.
  7. A recent trial has also shown that the combination of idelalisib and rituximab, as compared with placebo and rituximab, significantly improved progression-free survival, response rate, and overall survival among patients with relapsed CLL who were less able to undergo chemotherapy.
- An algorithm to treatment approach to first relapsed CLL is described in Fig. C1-72.

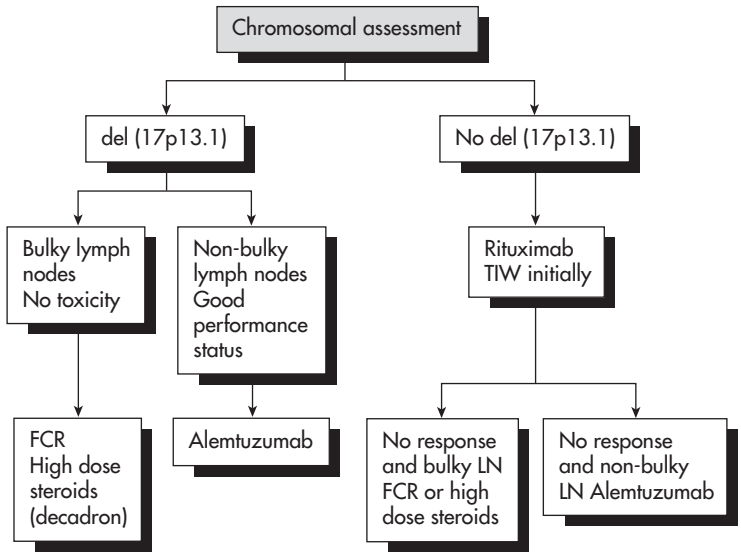

FIGURE C1-72 Algorithm to treatment approach to first relapsed chronic lymphocytic leukemia. (Modified from Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

CHRONIC Rx

Treatment of systemic complications:
- Hypogammaglobulinemia is frequent in CLL and is the chief cause of infections. Immune globulin (250 mg/kg IV every 4 wk) may prevent infections but has no effect on survival rate. Infections should be treated with broad-spectrum antibiotics. Patients should be monitored for opportunistic infections.
- Recombinant hematopoietic cofactors (e.g., granulocyte-macrophage colony stimulating factor and granulocyte colony stimulating factor) may be useful to overcome neutropenia related to treatment.
- Erythropoietin may be useful to treat anemia that is unresponsive to other measures.

DISPOSITION

The patient's prognosis is generally directly related to the clinical stage (e.g., the average survival in patients in Rai stage 0 or Binet stage A is >120 mo, whereas for Rai stage 4 or Binet stage C it is approximately 30 mo). Overall 5-yr survival has increased to 66% from 60% in the past 10 years by the addition of immunotherapy to combination chemotherapy. Measurement of ZAP-70 intracellular protein (where available) is also a useful indicator of prognosis.

SUGGESTED READINGS

Available at www.expertconsult.com.

RELATED CONTENT

Chronic Lymphocytic Leukemia (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Furman RR et al.: Idelalisib and rituximab in relapsed chronic lymphocytic leukemia, *N Engl J Med* 370:997–1007, 2014.

Hallek M et al.: Addition of rituximab to fludarabine and cyclophosphamide improved progression-free and overall survival in patients with chronic lymphocytic leukemia, *Lancet* 376:1164–1174, 2010.

Landgren O et al.: B-cell clones as early markers for chronic lymphocytic leukemia, *N Engl J Med* 360:659–667, 2009.

Perez K, Winer E: Chronic lymphocyte leukemia: something old, something new and something borrowed, *Medicine & Health Rhode Island* 94:15–19, 2011.

Wang L et al.: SF3B1 and other novel cancer genes in chronic lymphocytic leukemia, *N Engl J Med* 365:2497–2506, 2011.

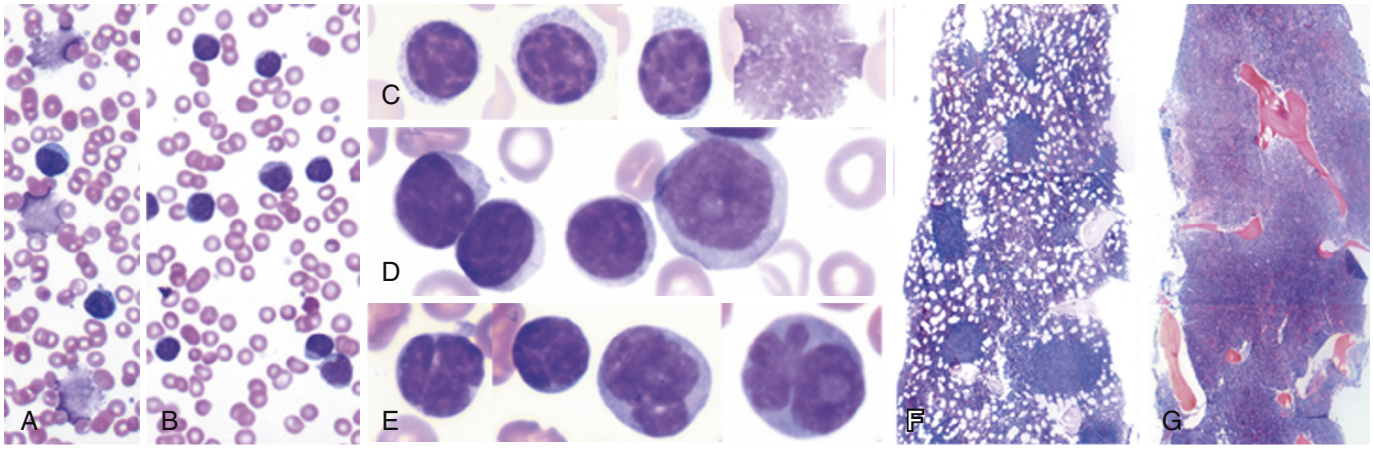

FIGURE EC1-71 Chronic lymphocytic leukemia. Peripheral blood smear **(A)** typically shows lymphocytosis and increased smudge cells as a result of the fragility of the CLL cells (see also smudge cell in C, *right side*). These can be avoided by making a preparation of blood and bovine serum albumin (22%) at a ratio of 11 drops of blood and 1 drop of albumin before preparing the slide **(B).** Cytologic features of CLL cells differ. Classic cells have a small nucleus with a "soccer ball" chromatin pattern **(C).** Some patients have increased large cells, or prolymphocytes, with more open chromatin and prominent "punched-out" nucleoli (**D;** prolymphocyte, *right side*). In other cases, sometimes referred to as "atypical," clefted cells and large cells may be present **(E).** The bone marrow can show nodular infiltrates of CLL cells **(F),** an interstitial infiltrate, or a diffuse infiltrate **(G)**. (From Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

BASIC INFORMATION

DEFINITION

Chronic myelogenous leukemia (CML) is a malignant clonal stem disease caused by an acquired somatic mutation that fuses, through chromosomal translocation, the *ABL* and *BCR* genes on chromosomes 9 and 22 and is characterized by abnormal proliferation and accumulation of immature granulocytes. CML manifests with a chronic phase (CP-CML) lasting months to years, followed by an advanced phase (AP-CML) characterized by poor response to therapy, worsening anemia, or decreased platelet count; the second phase then evolves into a terminal phase (acute transformation) that degenerates into acute leukemia (mostly myeloid and approximately 20% lymphoid subtype), characterized by elevated number of blast cells and numerous complications (e.g., sepsis, bleeding). The WHO criteria for accelerated and blast phases of CML are described in Table C1-29.

SYNONYMS

CML
Chronic granulocytic leukemia
Chronic myeloid leukemia

ICD-9CM CODES
201.1 Chronic myelogenous leukemia
ICD-10CM CODES
C92.10 Chronic myeloid leukemia, BCR/ABL-positive, not having achieved remission

EPIDEMIOLOGY & DEMOGRAPHICS

- CML usually affects elderly patients (median age at presentation is 65 yr) and accounts for 15% of adult cases of leukemia.
- Incidence is one to two cases per 100,000 people annually.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The chronic phase usually reveals splenomegaly; hepatomegaly is not infrequent, but lymphadenopathy is highly unusual and generally indicates the accelerated proliferative phase of the disease.
- Common symptoms at the time of diagnosis are weakness or discomfort from an enlarged spleen (abdominal discomfort or pain). Splenomegaly is present in up to 40% of patients at time of diagnosis.
- 40% of patients are asymptomatic, and diagnosis is based solely on an abnormal blood count.

ETIOLOGY

Current evidence strongly implicates the chromosome translocation t(9;22) (q34;q11.2) as the cause of chronic granulocytic leukemia. This translocation is present in >95% of patients. The remaining patients have a complex or variant translocation involving additional chromosomes that have the same end result (fusion of the *BCR* [break point cluster region] gene on chromosome 22 to *ABL* [Ableson leukemia virus] gene on chromosome 9).

TABLE C1-29 WHO Criteria for Accelerated and Blast Phases of CML

Accelerated phase	Diagnosis can be made if one or more of the following is present: Blasts 10% to 19% of peripheral blood white cells or bone marrow cells Peripheral blood basophils at least 20% Persistent thrombocytopenia ($<100 \times 10^9$/L) unrelated to therapy, or persistent thrombocytosis ($>1000 \times 10^9$/L) unresponsive to therapy Increasing spleen size and increasing WBC count unresponsive to therapy Cytogenetic evidence of clonal evolution (i.e., the appearance of an additional genetic abnormality that was not present in the initial specimen at the time of diagnosis of chronic phase CML) Megakaryocytic proliferation in sizable sheets and clusters, associated with marked reticulin or collagen fibrosis, and/or severe granulocytic dysplasia, should be considered as suggestive of CML-AP. (These findings have not yet been analyzed in large clinical studies; thus it is not clear whether they are independent criteria for accelerated phase. They often occur simultaneously with one or more of the other features listed.)
Blast crisis	Diagnosis can be made if one or more of following is present: Blasts 20% or more of peripheral blood white cells or bone marrow cells Extramedullary blast proliferation Large foci or clusters of blasts in bone marrow biopsy

From Hoffman R: *Hematology, basic principles and practice,* 6th ed, Philadelphia, 2013 Saunders.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Splenic lymphoma.
- Chronic lymphocytic leukemia.
- Myelodysplastic syndrome.

LABORATORY TESTS

- Elevated white blood cell count (generally >100,000/mm^3) with broad spectrum of granulocytic forms.
- Quantitative cytogenetic analysis of bone marrow aspirate is necessary for proper diagnosis. Bone marrow demonstrates hypercellularity with granulocytic hyperplasia, increased ratio of myeloid cells to erythroid cells, and increased number of megakaryocytes (Fig. C1-73). Blasts and promyelocytes constitute <10% of all cells. If the bone marrow aspirate is a "dry tap," perform interphase FISH using either a BCR-ABL extrasensitive or BCR-ABL dual fusion color probe.
- The Philadelphia chromosome results from the reciprocal translocation between the long arms of chromosomes 9 and 22 [Fig. C1-74] and is present in >95% of patients with CML; its presence (Ph1) is a major prognostic factor because survival rate of patients with Philadelphia chromosome is approximately eight times better than that of those without it. Some believe that Ph1(+) defines CML and that those who are Ph1(–) have another disease.
- Leukocyte alkaline phosphatase is markedly decreased (used to distinguish CML from other myeloproliferative disorders).
- Anemia and thrombocytosis are often present.
- Additional laboratory results are elevated vitamin B_{12} levels (caused by increased transcobalamin 1 from granulocytes) and elevated blood histamine levels (because of increased basophils).
- To monitor patients with CML during therapy, use FISH to study blood or bone marrow to track changes in the percentage of cells with BCR-ABL fusion at 3-month intervals.

IMAGING STUDIES

Chest radiograph and CT scan of abdomen/pelvis

TREATMENT

ACUTE GENERAL Rx

Treatment with a potential to either cure CML or prolong survival should be used during the chronic phase of the disease because it is often futile when administered during the advanced phase. Imatinib mesylate, an oral tyrosine kinase inhibitor, is effective and indicated as first-line treatment for CML myeloid blast crisis, accelerated phase, or CML in its chronic phase. More than 75% of patients have major cytogenetic response (<35% Philadelphia chromosome-positive cells in the marrow), and >80% have progression-free survival after 24 mo. Complete hematologic response usually occurs in <1 mo. Nilotinib and dasatinib are newer, more effective agents that also inhibit the activity of the BCR-ABL fusion protein by binding to a particular site and can be used after failure of imatinib and eventually may become first-line agents. Ponatinib is a newer oral tyrosine kinase inhibitor that blocks native and mutated BCR-ABL and has been shown to be highly active in pretreated patients with Ph-positive leukemias with resistance to other tyrosine kinase inhibitors.

- Symptomatic hyperleukocytosis (e.g., central nervous system symptoms) can be treated with leukapheresis and hydroxyurea; allopurinol should be started to prevent urate nephropathy after the rapid lysis of the leukemia cells.
- Allogeneic stem-cell transplantation (SCT) is the only curative treatment for CML in the chronic phase unresponsive to imatinib. In general only 20% of patients are candidates for SCT given the limitations of age or lack of HLA-matched related donors.

1. It should be considered in "young" patients (increased survival in patients <55 yr) with compatible siblings.
2. Early transplantation is also important for patient's survival.

- Interferon-alfa is an acceptable alternative in the early chronic phase for patients who do not tolerate tyrosine kinase inhibitors.
- Recent trials have shown that as compared with other treatments, the addition of peginterferon alfa-2a to imatinib therapy resulted in significantly higher rates of molecular response in patients with chronic-phase CML.
- Transplantation of marrow from an HLA-matched, unrelated donor is also now recognized as safe and effective therapy for selected patients with CML.

SUGGESTED READINGS

Available at www.expertconsult.com.

RELATED CONTENT

Chronic Myelogenous Leukemia (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

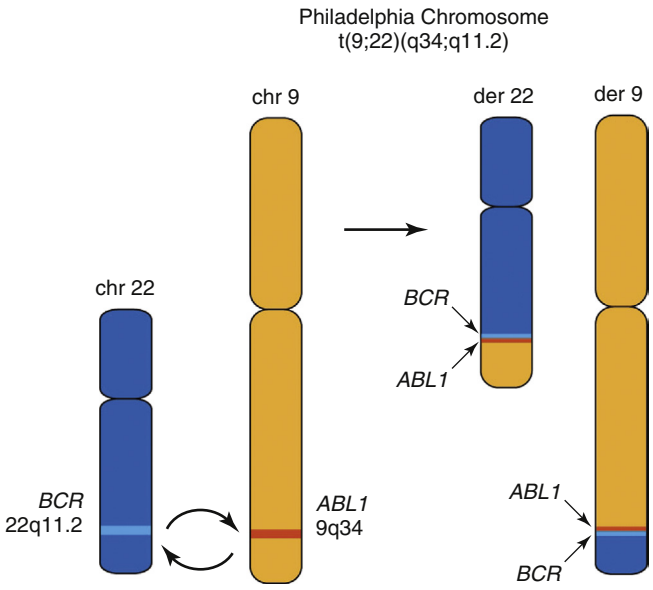

FIGURE C1-74 The Philadelphia chromosome, der(22q), results from the reciprocal translocation of a portion of the *ABL*1 gene on chromosome 9 at band q34 to the region of the *BCR* gene on chromosome 22 at band q11.2. In turn, a portion of *BCR* is translocated to chromosome 9 to the region of *ABL1*. In 5% to 10% of patients with chronic myelogenous leukemia, cryptic or complex rearrangements result in a *BCR-ABL1* fusion gene, even though no Philadelphia chromosome is detected cytogenetically. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

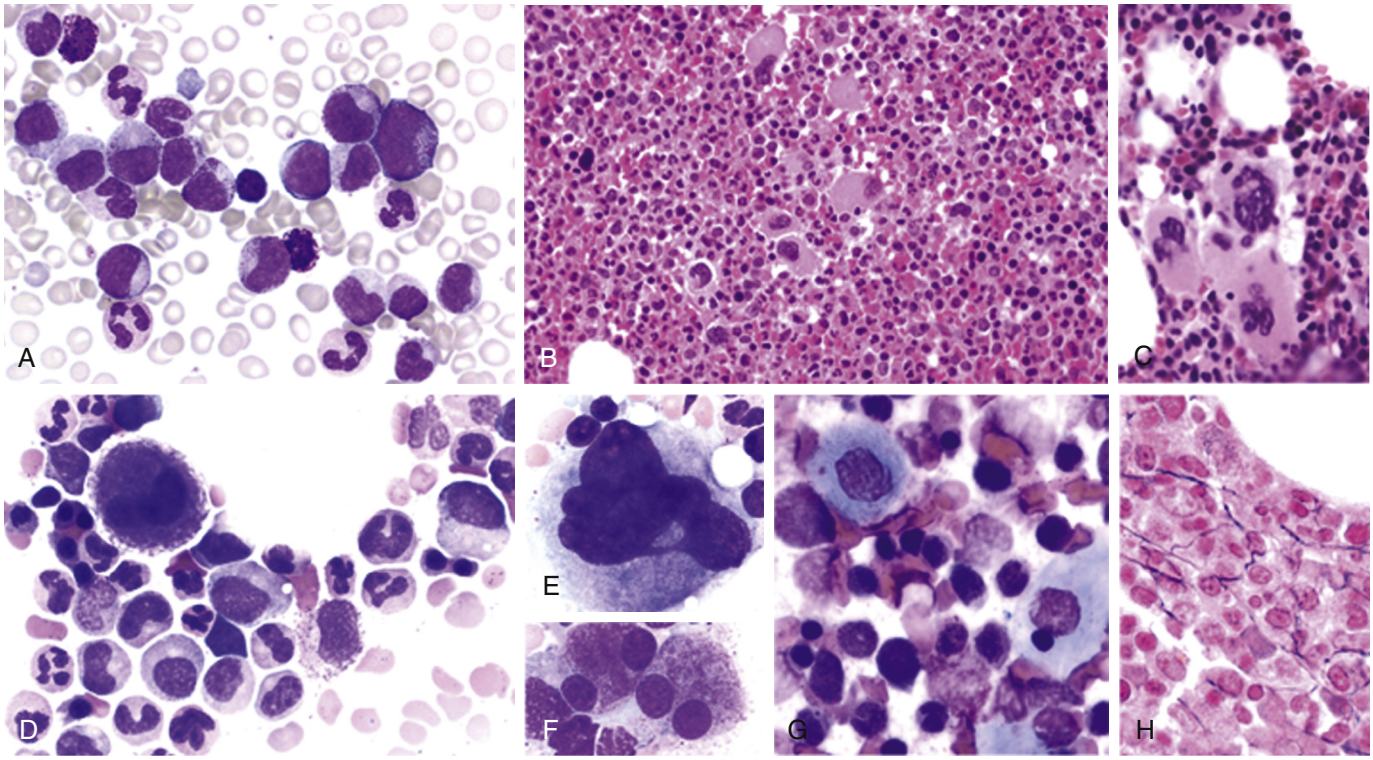

FIGURE C1-73 Chronic myelogenous leukemia, chronic phase. Peripheral smear **(A)** showing marked leukocytosis due to a granulocytic proliferation of all stages with particularly increased myelocytes and absolute basophilia. Bone core biopsy **(B)** illustrating markedly hypercellular marrow due to granulocytic proliferation and increased small hypolobated megakaryocytes. Compare with large megakaryocytes **(C)** from a myeloproliferative disorder other than CML. Bone marrow aspirate **(D)** showing granulocytic proliferation and small, "dwarf" megakaryocyte, compared with large-sized megakaryocyte **(E)** and micro-megakaryocytes **(F)** typical of MDS. Pseudo-Gaucher cells **(G)** and mild fibrosis **(H)** as seen on reticulin stain. (From Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

SUGGESTED READINGS

Cortes JE et al.: Ponatinib in refractory Philadelphia chromosome–positive leukemias, *N Engl J Med* 367:2075–2088, 2012.

Hehlmann R et al.: Chronic myeloid leukemia, *Lancet* 370:342, 2007.

Kantarjian H et al.: Dasatinib versus imatinib in newly diagnosed chronic-phase myeloid leukemia, *N Engl J Med* 362:2260–2270, 2010.

Kantarjian H et al.: Nilotinib in imatinib-resistant CML and Philadelphia chromosome-positive ALL, *N Engl J Med* 354:2542, 2006.

Preudhomme C et al.: Imatinib plus peginterferon alfa-2a in chronic myeloid leukemia, *N Engl J Med* 363:26, 2010.

Quintas-Cardam A, Cortes J: Chronic myeloid leukemia: diagnosis and treatment, *Mayo Clin Proc* 81(7):973, 2006.

Saglio G et al.: Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia, *N Engl J Med* 362:2251–2259, 2010.

Schiffer CA: BCR-ABL tyrosine kinase inhibitors for chronic myelogenous leukemia, *N Engl J Med* 357:258, 2007.

Talpaz M et al.: Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias, *N Engl J Med* 354:2531, 2006.

Chronic Obstructive Pulmonary Disease PTG EBM ALG

BASIC INFORMATION

DEFINITION

Chronic obstructive pulmonary disease (COPD) is an inflammatory respiratory disease usually caused by exposure to tobacco smoke. It is characterized by the presence of airflow limitation that is not fully reversible. The pathophysiology of COPD is related to chronic airway irritation, mucus production, and pulmonary scarring. Traditionally, COPD was described as encompassing *emphysema*, characterized by loss of lung elasticity and destruction of lung parenchyma with enlargement of air spaces, and *chronic bronchitis*, characterized by obstruction of small airways and productive cough >3 mo for more than 2 successive yr. These terms are no longer included in the formal definition of COPD, although they are still used clinically. Although emphysema and chronic bronchitis are commonly associated with COPD, neither is required to make the diagnosis.

SYNONYMS

COPD
Emphysema
Chronic bronchitis

ICD-9CM CODES
496 COPD
492.8 Emphysema
ICD-10CM CODES
J44.9 Chronic obstructive pulmonary disease, unspecified
J43.9 Emphysema, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- COPD affects more than 5% of adults in the U.S.
- Between 10% and 20% of COPD in the U.S. is due to occupational or other exposure to chemical vapors, irritants, and fumes; 80% to 90% is due to cigarette smoking.
- COPD is the third leading cause of death in the U.S.
- Highest incidence is in males >40 yr.
- 16 million office visits, 500,000 hospitalizations, 120,000 deaths annually, and >$18 billion in direct health care costs annually can be attributed to COPD.
- Patients with COPD living in isolated rural areas of the U.S. are at greater risk for COPD exacerbation-related mortality than those living in urban areas, independent of hospital rurality and volume.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with COPD have historically been classically subdivided in two major groups based on their appearance:
  1. *Blue bloaters* are patients with chronic bronchitis; the name is derived from the bluish tinge of the skin (as a result of chronic hypoxemia and hypercapnia) and from the frequent presence of peripheral edema (from cor pulmonale); chronic cough with production of large amounts of sputum is characteristic.
  2. *Pink puffers* are patients with emphysema; they have a cachectic appearance but pink skin color (adequate oxygen saturation); shortness of breath is manifested by pursed-lip breathing and use of accessory muscles of respiration.
- COPD may present with combinations of the following manifestations:
  1. Cyanosis, chronic cough (usually productive but may be intermittent and may be unproductive), tachypnea, tachycardia.
  2. Dyspnea (persistent, progressive), pursed-lip breathing with use of accessory muscles for respiration, decreased breath sounds, wheezing.
  3. Chronic sputum production.
  4. Chest wall abnormalities (hyperinflation, "barrel chest," protruding abdomen).
  5. Flattening of diaphragm.
     - Systemic manifestations and comorbidities of COPD are described in Table C1-30.
- Acute exacerbation of COPD is mainly a clinical diagnosis and generally manifests with worsening dyspnea, increase in sputum purulence, and increase in sputum volume. However, respiratory symptom status is not a reliable indicator of the presence of airflow obstruction. Individuals with normal spirometric values may report respiratory symptoms, whereas individuals who have severe to very severe airflow obstruction by spirometry may report no symptoms.

ETIOLOGY

- Tobacco exposure
- Occupational exposure to pulmonary toxins (e.g., dust, noxious gases, vapors, fumes, cadmium, coal, silica). The industries with the highest exposure risk are plastics, leather, rubber, and textiles.
- Atmospheric pollution.
- Alpha-1-antitrypsin deficiency (rare; <1% of COPD patients).

TABLE C1-30 Systemic Manifestations and Comorbidities of COPD

Cardiovascular	Infarction Arrhythmia Congestive heart failure Aortic aneurysm
Hypercoagulability	Stroke Pulmonary embolism Deep vein thrombosis Atrophy
Systemic	Weight loss Osteoporosis Skin wrinkling Anemia Fluid retention
Lung cancer	Depression

From Mason,RJ: *Murray & Nadel's textbook of respiratory medicine*, 5th ed, Philadelphia, 2010, Saunders.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Heart failure (HF)
- Asthma
- Tuberculosis, other respiratory infections
- Bronchiectasis
- Cystic fibrosis
- Neoplasm
- Pulmonary embolism
- Obliterative bronchiolitis
- Diffuse panbronchiolitis
- Sleep apnea, obstructive
- Hypothyroidism <50% predicted

WORKUP

Chest x-ray (seldom diagnostic but useful to exclude alternative diagnosis [CHF, TB]), pulmonary function testing (spirometry), oxygen saturation, blood gases (useful in selected patients with FEV_1 <50% predicted or with acute exacerbation). Alpha-1-antitrypsin deficiency screening may be useful in Caucasians with suspected COPD and no clear risk factors.

LABORATORY TESTS

- CBC: generally not helpful, may reveal leukocytosis with left shift during acute exacerbation. Recent trials have shown that eosinophilia in COPD patients predicts response to corticosteroids.
- Sputum may be purulent with bacterial respiratory tract infections. Sputum staining and cultures are usually reserved for cases refractory to antibiotic therapy.
- Arterial blood gases: normocapnia, mild to moderate hypoxemia may be present. ABGs and pulse oximetry are usually used to determine if a patient is a candidate for long-term oxygen therapy or if hypercapnia is present (ABGs).
- Spirometry pulmonary function testing (PFT) with measurement of forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1). Spirometry should be obtained to diagnose airflow obstruction in clinically stable patients with respiratory symptoms. It should not be used to screen for airflow obstruction in individuals without respiratory symptoms. Spirometry reveals that the primary physiologic abnormality in COPD is an accelerated decline in FEV_1 from the normal rate in adults >30 yr of approximately 30 ml/yr to nearly 60 ml/yr. PFT results in COPD reveal abnormal diffusing capacity, increased total lung capacity and/or residual volume, and fixed reduction in FEV_1 in patients with emphysema; normal diffusing capacity and reduced FEV_1 are found in patients with chronic bronchitis. Stage and severity of COPD according to postbronchodilator spirometry are described in Table C1-31. It is important to note that FEV_1 does not correlate well with individual patients' severity of dyspnea, exercise limitations, or health status. Evaluation of patients should also focus on symptom control and risk for adverse events in addition to FEV_1.

TABLE C1-31 Stage and Severity of COPD According to Postbronchodilator Spirometry

Stage and Severity	Definition
I: Mild	FEV_1/FVC <0.70, FEV_1 ≥80% of predicted
II: Moderate	FEV_1/FVC <0.70, 50%≤FEV_1 <80% of predicted
III: Severe	FEV_1/FVC <0.70, 30%≤FEV_1 <50% of predicted
IV: Very severe	FEV_1/FVC <0.70, FEV_1 <30% of predicted or FEV_1 <50% of predicted plus chronic respiratory failure

Data from the Global Initiative for Chronic Obstructive Lung Disease. Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

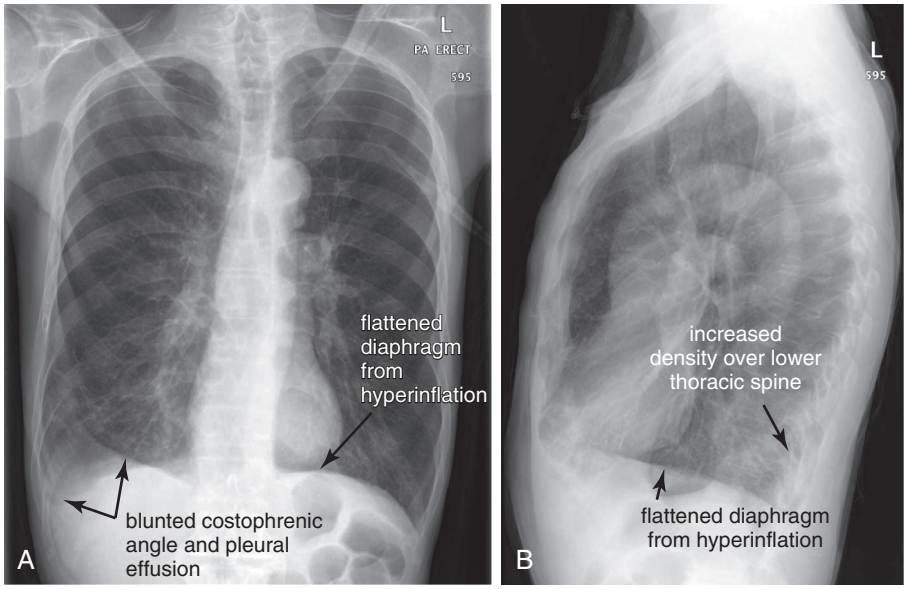

FIGURE C1-75 Chronic obstructive pulmonary disease (COPD). A, Posterior-anterior (PA) upright chest x-ray. **B,** Lateral upright chest x-ray. This 63-year-old man with a history of COPD presented with 2 weeks of worsening cough with yellow sputum and dyspnea. His oxygen saturation was 87% in the emergency room. He has evidence of hyperinflation with flat diaphragms (particularly evident on the lateral x-ray, **B)**. The patient also has a blunted right costophrenic angle with an apparent effusion and increased densities in both the right and the left lung base **(A).** The lateral x-ray also shows increased density overlying the inferior thoracic spine, an abnormal spine sign. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

- Patients with COPD can generally be distinguished from asthmatics by their incomplete response to albuterol (change in FEV_1 <200 ml and 12%) and absence of an abnormal bronchoconstrictor response to methacholine or other stimuli. However, nearly 40% of patients with COPD respond to bronchodilators.

ASSESSMENT

- The global initiative for chronic obstructive lung disease (COLD) assigns patients with COPD into four groups (A, B, C, D) based on on (1) the degree of airflow restriction (Table C1-31), (2) a patient symptom score using one of two symptom questionnaires (CAT or mMRC), or (3) the number of COPD exacerbations in one year.[1]

[1]Lee H, Kim J, Tagmazyan K: Treatment of stable chronic obstructive pulmonary disease: the GOLD guidelines, *Am Fam Physician* 88(10):655-663, 2013.

IMAGING STUDIES

Chest x-ray:

- Hyperinflation with flattened diaphragm, tenting of the diaphragm at the rib, and increased retrosternal chest space (Fig. C1-75)
- Decreased vascular markings and bullae in patients with emphysema
- Thickened bronchial markings and enlarged right side of the heart in patients with chronic bronchitis

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of tobacco and elimination of air pollutants.
- Supplemental oxygen, usually through a face mask, to ensure oxygen saturation >90% as measured by pulse oximetry. Continuous oxygen therapy should be prescribed for patients with COPD who have arterial partial pressure of oxygen 55 mm Hg or less, or oxygen saturation 88% or less as measured by pulse oximetry.
- Pulmonary clearing: careful nasotracheal suction is indicated only in patients with excessive secretions and an inability to expectorate. Mechanical percussion of the chest as applied by a physical or respiratory therapist is ineffective with acute exacerbations of COPD.
- Pulmonary rehabilitation should be considered in COPD patients who remain symptomatic despite optimal medical management. Medicare will cover up to 36 sessions of pulmonary rehabilitation in COPD patients.
- Weight loss in obese patients.

GENERAL Rx

- Pharmacologic treatment should be administered in a stepwise approach according to the severity of disease and patient's tolerance for specific drugs. Fig. C1-76 describes general management approaches for COPD. When using the COLD assessment criteria, pulmonary rehabilitation is recommended for patients in groups B, C, and D. Those in group A should receive a short-acting anticholinergic or short-acting β_2-agonist for mild intermittent symptoms. For patients in group B, long-acting anticholinergics or long-acting β_2-agonists should be added. Patients in group C or D are at high risk of exacerbations and should receive a long-acting anticholinergic or a combination of an inhaled corticosteroid and a long-acting β_2-agonist.
  1. Bronchodilators improve symptoms, quality of life, and exercise tolerance and decrease incidence of exacerbations. Inhaled bronchodilators *may be used* for stable COPD patients with respiratory symptoms and FEV_1 between 60% and 80% of predicted. They are *recommended* for stable COPD patients with respiratory symptoms and FEV_1 <60% of predicted. Recent guidelines from ACP, ACCP, ATS, and ERS recommend that clinicians prescribe monotherapy using either long-acting inhaled anticholinergics or long-acting inhaled β-agonists for symptomatic patients with COPD and FEV_1 <60% of predicted. Clinicians should base the choice of specific monotherapy on patient preference, cost, and adverse effect profile.
  2. Short-acting β_2-agonists (e.g., albuterol metered-dose inhaler 1 to 2 puffs q4 to 6h prn) or short-acting anticholinergic agents (e.g., ipratropium inhaler 2 puffs qid) are acceptable in patients with mild, variable symptoms. Anticholinergics are also effective and are available in combination with albuterol (Combivent). Long-acting inhaled agents are preferred in patients with mild to moderate or continuous symptoms. Tiotropium is an excellent long-acting bronchodilator. It is very effective for long-term, once-a-day use. It has been shown to be superior to salmeterol, an inhaled long-acting β-agonist

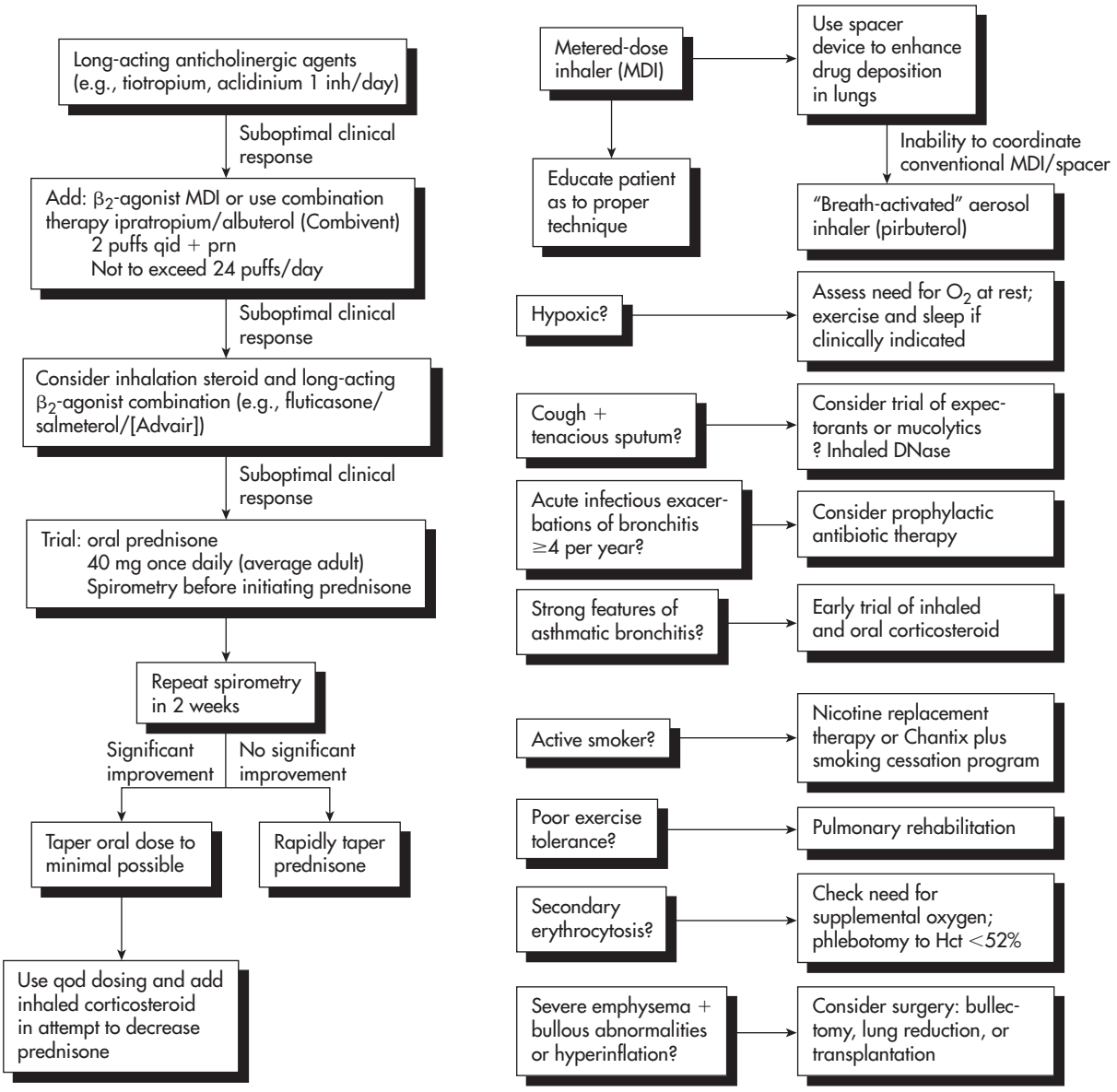

FIGURE C1-76 Managed care guide: pharmacotherapy and general management approaches for chronic obstructive pulmonary disease (COPD). *DNase*, Deoxyribonuclease; *Hct*, hematocrit; *prn*, as needed; *qid,* four times a day; *qod*, every other day. (Modified from Noble J: *Primary care medicine*, ed 3, St Louis, 2001, Mosby.)

(LABA) in patients with moderate to severe COPD; however, recent trials have shown higher hospitalization rates and mortality with tiotropium compared to LABAs. Indacaterol, aclidinium, and olodaterol are other available LABAs for long-term maintenance treatment of bronchospasm associated with COPD. Indacaterol provides the convenience of once-daily dosing. Aclidinium, unlike tiotropium, which is predominantly renally excreted, can be used safely in renal impairment. Olodaterol is also for once a day use. As with other LABAs, these medications should not be used with other sympathomimetic drugs, medications that can prolong the QT interval, or beta-blockers.

3. Addition of inhaled steroids (fluticasone, budesonide, triamcinolone) is used to reduce exacerbations in patients with moderate to severe COPD. Inhaled steroids are reserved for patients with either ≥2 exacerbations annually or FEV_1 <50% of predicted. The role of inhaled corticosteroids (ICS) in COPD is controversial. Although some trials have demonstrated mild improvement in patients' symptoms and decreased frequency of exacerbations, most pulmonologists believe that these drugs are ineffective in most patients with COPD but should be considered for patients with moderate to severe airflow limitation who have persistent symptoms despite optimal bronchodilator therapy. ICS therapy does not affect 1-yr all-cause mortality among patients with COPD and is associated with a higher risk of pneumonia.
4. Roflumilast is a selective oral PDE4 inhibitor useful to reduce the risk of COPD exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. It is not a bronchodilator and is not indicated for the relief of acute bronchospasm.
5. Recent guidelines from ACP (American College of Physicians), ACCP (American College of Chest Physicians), ATS (American Thoracic Society), and ERS (European Respiratory Society) suggest that clinicians may administer combination inhaled therapies for symptomatic patients with stable COPD and FEV_1 <60% predicted. They also recommend that clinicians should prescribe pulmonary rehabilitation for symptomatic patients with an FEV_1 <50% predicted and continuous

oxygen therapy in patients with COPD who have resting hypoxemia (Pa_{O_2} <55 mm Hg or Sp_{O_2} <88%).

- Acute exacerbation of COPD (increase in sputum volume and purulence, worsening dyspnea) can be treated with:
  1. Aerosolized β_2-agonists (e.g., metaproterenol nebulizer solution 5% 0.3 ml or albuterol nebulized 5% solution 2.5 to 5 mg).
  2. Anticholinergic agents, which have equivalent efficacy to inhaled beta-adrenergic agonists. Inhalant solution of ipratropium bromide 0.5 mg can be administered every 4 to 8 hr.
  3. Short courses of systemic corticosteroids have been shown to improve spirometric and clinical outcomes. Treatment failure occurs less often in patients who receive low-dose steroids than in those receiving high-dose parenteral steroids. Oral prednisone 40 mg/day for 5 to 14 days is generally effective. Courses of treatment that are extended for >14 days confer no added benefit and increase the risk of adverse events. Recent trials[2] have shown that in patients with acute COPD exacerbations, systemic glucocorticoid treatment for 5 days is not inferior to treatment for 14 days.
  4. Use of noninvasive positive pressure ventilation (NIPPV) decreases the risk of endotracheal intubation and decreases intensive care unit admission rates. Contraindications to its use are uncooperative patient, decreased level of consciousness, hemodynamic instability, inadequate mask fit, and severe respiratory acidosis. Increased airway pressure can be delivered by using inspiratory positive airway pressure, continuous positive airway pressure, or bilevel positive airway pressure, which combines the other modalities. When using NIPPV, the nasal mask is usually tolerated the best; however, patients must be instructed to keep their mouths closed while breathing with the nasal apparatus. Oxygen can be delivered at 10 to 15 L/min and started in spontaneous ventilation mode with an initial expiratory positive airway pressure setting of 3 to 5 cm H_2O and an inspiratory positive airway pressure setting of up to 10 cm H_2O. Adjustments in these settings should be made in 2-cm H_2O increments. It is important to monitor patients with frequent vital signs measurements, arterial blood gases, or pulse oximetry. Intubation and mechanical ventilation may be necessary if previous measures fail to provide improvement.
  5. IV aminophylline administration is controversial and generally not recommended. When used in patients with refractory symptoms, serum levels should be closely monitored (keep level 8 to 12 mcg/ml) to minimize risks of tachyarrhythmias.

[2]Leuppi JD et al: Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pumonary disease: the REDUCE randomized clinical trial, *JAMA* 309:2223-2231, 2013.

- Approximately 50% of COPD exacerbations are caused by bacterial infection. Antibiotics are indicated in suspected bacterial respiratory infection (e.g., increased purulence and volume of phlegm).
  1. *Haemophilus influenzae* and *Streptococcus pneumoniae* are frequent causes of acute bronchitis.
  2. Oral antibiotics of choice are azithromycin, levofloxacin, amoxicillin-clavulanate, trimethoprim-sulfamethoxazole, doxycycline, and cefuroxime.
  3. The two best predictors of potential benefit from antibiotics are purulent sputum and C-reactive protein (CRP) level >40 mg/L.[3]
- Guaifenesin may improve cough symptoms and mucus clearance; however, mucolytic medications are generally ineffective. Their benefits may be greatest in patients with more advanced disease.
- Guideline recommendations for hospital management of COPD exacerbations are described in Table C1-32. Indications for invasive mechanical ventilation are described in Box C1-3.
- Lung volume reduction surgery has been proposed as a palliative treatment for severe emphysema. Overall it increases the chance of improved exercise capacity but does not confer a survival advantage over medical therapy. It is most beneficial in patients with both predominantly upper-lobe emphysema and low baseline exercise capacity.
- In patients with end-stage emphysema who have an FEV_1 <25% of predicted normal value after administration of bronchodilator and additional complications such as severe hypoxemia, hypercapnia, and pulmonary hypertension, single-lung transplantation should be considered a surgical option.
- Trials involving endobronchial valves that allow air to escape from a pulmonary lobe but not to enter it have been done to improve lung function by reducing lobar volume in patients with advanced heterogeneous emphysema. Results have shown modest improvements in lung function, symptoms, and exercise tolerance, but more frequent exacerbations of COPD. Other complications included pneumonia and hemoptysis postimplantation.

DISPOSITION

- After the initial episode of respiratory failure, 5-yr survival is approximately 25%.
- Development of cor pulmonale or hypercapnia and persistent tachycardia are poor prognostic indicators.

PEARLS & CONSIDERATIONS

COMMENTS

- All patients with COPD should receive pneumococcal vaccine and yearly influenza vaccine.

[3]Miravilles M et al: Is it possible to identify exacerbations of mild to moderate COPD that do not require antibiotic treament? *Chest* 144:1571, 2013.

- Early antibiotic administration is associated with improved outcomes among patients hospitalized for acute exacerbations of COPD regardless of the risk of treatment failure.
- In assessing the severity of COPD, the FEV_1 is limited by the fact that it does not take into account the systemic manifestations of COPD. The BODE index (body mass index, degree of obstruction, dyspnea, and exercise capacity) has been proposed as a multidimensional scale to better assess the morbidity and mortality associated with COPD. It is better than the FEV_1 alone at predicting the risk of death from any cause and from respiratory causes among patients with COPD. In the BODE index, obstruction is measured by FEV_1 and dyspnea is measured by the modified Medical Research Council (MMRC) dyspnea questionnaire in a 6-minute walk test. A score of 0 on the MMRC indicates that the individual is not troubled with breathlessness except with strenuous exercise, 1 indicates shortness of breath when hurrying or walking up a slight hill, and 2 means the individual walks slower than people of the same age due to breathlessness or has to stop for breath when walking at own pace on level ground. A score of 3 means severe dyspnea because the person has to stop for breath after walking approximately 100 meters or after a few minutes on level ground, and a score of 4 indicates very severe dyspnea and is given when the individual is too breathless to leave the house or is breathless when dressing or undressing.
- Pulmonary artery enlargement as determined by a ratio of the diameter of the pulmonary artery to the diameter of the aorta [PA:A ratio] of >1 detected by CT is associated with severe exacerbations of COPD.
- The average person with COPD has one or two acute exacerbations each year. Prophylactic use of macrolide antibiotics (azithromycin 250 mg/day) has been shown to decrease the frequency of exacerbations and improve quality of life among selected patients with COPD; however, it leads to hearing decrements in a small percentage of patients and increased prevalence of macrolide-resistant bacteria colonizing the airway and is therefore not recommended.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Chronic Obstructive Pulmonary Disease (Patient Information)

Emphysema (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

TABLE C1-32 Guideline Recommendations for Hospital Management of COPD Exacerbations

	Global Initiative for Chronic Obstructive Lung Disease*	American Thoracic Society/European Respiratory Society†	National Institute for Clinical Excellence‡
Date of statement	2010	2004	2010
Diagnostic testing	Chest radiograph, oximetry, ABGs, and ECG. Other testing as warranted by clinical indication.	Chest radiograph, oxygen saturation, ABGs, ECG, sputum Gram stain and culture.	Chest radiograph, ABG, ECG, complete blood count, sputum smear and culture, blood cultures if febrile.
Bronchodilator therapy	Inhaled short-acting β_2-agonist is recommended. Consider ipratropium if inadequate clinical response. Consider theophylline or aminophylline as second-line intravenous therapy.	Inhaled short-acting β_2-agonist and/or ipratropium with spacer or nebulizer, as needed.	Administer inhaled drugs by nebulizer or handheld inhaler. Specific agents and dosing regimens not specified. Consider theophylline if inadequate response to inhaled bronchodilators.
Antibiotics	Recommended if (1) increases in dyspnea, sputum volume, and sputum purulence all are present; (2) increase in sputum purulence along with increase in either dyspnea or sputum volume; or (3) need for assisted ventilation. See original document for complex treatment algorithm.	Base choice on local bacterial resistance patterns. Consider amoxicillin/clavulanate or respiratory fluoroquinolones. If *Pseudomonas* species and/or other Enterobacteriaceae are suspected, consider combination therapy.	Administer only if history of purulent sputum. Initiate with an aminopenicillin, a macrolide, or a tetracycline, taking into account local bacterial resistance patterns. Adjust therapy according to sputum and blood cultures.
Systemic corticosteroids	Daily prednisolone 30-40 mg (or its equivalent) orally for 7-10 days.	Daily prednisone 30-40 mg orally for 10-14 days. Equivalent dose intravenously if unable to tolerate oral intake. Consider inhaled corticosteroids.	Daily prednisolone 30 mg (or its equivalent) orally for 7-14 days.
Supplemental oxygen	Maintain oxygen saturation >90%. Monitor ABGs for hypercapnia and acidosis.	Maintain oxygen saturation >90%. Monitor ABGs for hypercapnia and acidosis.	Maintain oxygen saturation within the individualized target range. Monitor ABGs.
Assisted ventilation	Indications for NPPV include severe dyspnea, acidosis (pH ≤7.35) and/or hypercapnia (PCO_2 >45 mm Hg), and respiratory rate >25 breaths/min. Contraindications to NPPV include respiratory arrest, hemodynamic instability, impaired mental status, copious bronchial secretions, and extreme obesity. Intubate if contraindication to NPPV or failure of NPPV (worsening ABGs or clinical status). Consider likelihood of recovery and patient's wishes and expectations before intubation.	Consider with pH <7.35 and PCO_2 >45-60 mm Hg and respiratory rate >24 breaths/min. Institute NPPV in a controlled environment, unless there are contraindications (e.g., respiratory arrest, hemodynamic instability, impaired mental status, copious bronchial secretions, and extreme obesity). Intubate if contraindication to NPPV or failure of NPPV (worsening ABGs or clinical status).	NPPV treatment of choice for persistent hypercapnic respiratory failure. Consider functional status, body mass index, home oxygen, comorbidities, prior ICU admissions, age, and FEV_1 when assessing suitability for intubation and ventilation.

ABGs, Arterial blood gases; *ECG*, electrocardiogram; *ICU,* intensive care unit; *NPPV*, noninvasive positive pressure ventilation.
*Data from http://www.goldcopd.com.
†Data from MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 23:932-946, 2004.
‡Data from http://www.nice.org.uk.
From Goldman L, Schafer AI: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Saunders.

BOX C1-3 Indications for Invasive Mechanical Ventilation

Severe dyspnea, with use of accessory muscles and paradoxical abdominal motion
Respiratory frequency >35 breaths/min
Life-threatening hypoxemia (Pao_2 <40 mm Hg or Pao_2/Fio_2 <200 mm Hg)
Severe acidosis (pH <7.25) and hypercapnia ($Paco_2$ >60 mm Hg)
Respiratory arrest
Somnolence, impaired mental status
Cardiovascular complications (hypotension, shock, heart failure)
Other complications: metabolic abnormalities, sepsis, pneumonia, pulmonary embolism, barotrauma, massive pleural effusion
Noninvasive positive-pressure ventilation failure (or exclusion criteria)

Fio_2, Inspired oxygen fraction; *Pao_2*, partial pressure of carbon dioxide in arterial blood; *Pao_2*, partial pressure of oxygen in arterial blood.
From Vincent JL et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, Saunders.

EVIDENCE

Abstract[1]

Background:

An individualized action plan (AP) is a potentially effective method of helping patients with chronic obstructive pulmonary disease (COPD) to recognise and anticipate early exacerbation symptoms. This multicentre randomised controlled trial evaluates the hypothesis that individualised APs reduce exacerbation recovery time.

Methods:

Two hundred and thirty-three patients with COPD (age 65±10 years, forced expiratory volume in 1 s 56±21% predicted) were randomised to receive either an individualised AP (n=111) or care as usual (n=122). The AP provides individualised treatment prescriptions (pharmaceutical and non-pharmaceutical) related to a colour-coded symptom status to enhance an adequate response to periods of symptom deterioration (reinforced at 1 and 4 months). Exacerbation onset was defined using the Anthonisen symptom diary card algorithm. Every 3 days the Clinical COPD Questionnaire (CCQ) was assessed to evaluate the longitudinal course of health status. The primary outcome was health status recovery in the event of an exacerbation.

Results:

During the 6-month follow-up period there was no difference in exacerbation rates and healthcare utilisation between the two groups. Cox-adjusted survival analysis including frailty showed enhanced health status recovery (HR 1.58; 95% CI 0.96 to 2.60) and reduced length of the exacerbation (HR 1.30; 95% CI 0.92 to 1.84). The mean difference in symptom recovery time was −3.68 days (95% CI −7.32 to −0.04). Mixed model repeated measure analysis showed that an AP decreased the impact of exacerbations on health status both in the prodromal and early post-onset periods. Between-group differences in CCQ scores were above the minimal clinically relevant difference of 0.4 points (3.0±0.7 vs 3.4±0.9; p≤0.01).

Conclusion:

This study shows that an individualised AP, including ongoing support by a case manager, decreases the impact of exacerbations on health status and tends to accelerate recovery. APs can be considered a key component of self-management programmes in patients with COPD. Ⓐ

Abstract[2]

Background:

Acute exacerbations adversely affect patients with chronic obstructive pulmonary disease (COPD). Macrolide antibiotics benefit patients with a variety of inflammatory airway diseases.

Methods:

We performed a randomized trial to determine whether azithromycin decreased the frequency of exacerbations in participants with COPD who had an increased risk of exacerbations but no hearing impairment, resting tachycardia, or apparent risk of prolongation of the corrected QT interval.

Results:

A total of 1577 subjects were screened; 1142 (72%) were randomly assigned to receive azithromycin, at a dose of 250 mg daily (570 participants), or placebo (572 participants) for 1 year in addition to their usual care. The rate of 1-year follow-up was 89% in the azithromycin group and 90% in the placebo group. The median time to the first exacerbation was 266 days (95% confidence interval [CI], 227 to 313) among participants receiving azithromycin, as compared with 174 days (95% CI, 143 to 215) among participants receiving placebo (P<0.001). The frequency of exacerbations was 1.48 exacerbations per patient-year in the azithromycin group, as compared with 1.83 per patient-year in the placebo group (P=0.01), and the hazard ratio for having an acute exacerbation of COPD per patient-year in the azithromycin group was 0.73 (95% CI, 0.63 to 0.84; P<0.001). The scores on the St. George's Respiratory Questionnaire (on a scale of 0 to 100, with lower scores indicating better functioning) improved more in the azithromycin group than in the placebo group (a mean [±SD] decrease of 2.8±12.8 vs. 0.6±11.4, P=0.004); the percentage of participants with more than the minimal clinically important difference of −4 units was 43% in the azithromycin group, as compared with 36% in the placebo group (P=0.03). Hearing decrements were more common in the azithromycin group than in the placebo group (25% vs. 20%, P=0.04).

Conclusions:

Among selected subjects with COPD, azithromycin taken daily for 1 year, when added to usual treatment, decreased the frequency of exacerbations and improved quality of life but caused hearing decrements in a small percentage of subjects. Although this intervention could change microbial resistance patterns, the effect of this change is not known. (Funded by the National Institutes of Health; ClinicalTrials.gov number, NCT00325897.) Ⓐ

Abstract[3]

Background:

The effect of inhaled corticosteroids (ICS) on fracture risk in patients with chronic obstructive pulmonary disease (COPD) remains uncertain. The aim of this study was to evaluate the association between ICS and fractures in COPD.

Methods:

MEDLINE, EMBASE, regulatory documents and company registries were searched up to August 2010. Randomised controlled trials (RCTs) of budesonide or fluticasone versus control treatment for COPD (≥24weeks duration) and controlled observational studies reporting on fracture risk with ICS exposure vs no exposure in COPD were included. Peto OR meta-analysis was used for fracture risk from RCTs while ORs from observational studies were pooled using the fixed effect inverse variance method. Dose–response analysis was conducted using variance-weighted least squares regression in the observational studies. Heterogeneity was assessed using the I^2 statistic.

Results:

Sixteen RCTs (14 fluticasone, 2 budesonide) with 17,513 participants, and seven observational studies (n=69,000 participants) were included in the meta-analysis. ICSs were associated with a significantly increased risk of fractures (Peto OR 1.27; 95% CI 1.01 to 1.58; p=0.04; I^2=0%) in the RCTs. In the observational studies, ICS exposure was associated with a significantly increased risk of fractures (OR 1.21; 95% CI 1.12 to 1.32; p<0.001; I^2=37%), with each 500 μg increase in beclomethasone dose equivalents associated with a 9% increased risk of fractures, OR 1.09 (95% CI 1.06 to 1.12; p<0.001).

Conclusion:

Among patients with COPD, long-term exposure to fluticasone and budesonide is consistently associated with a modest but statistically significant increased likelihood of fractures. Ⓐ

Evidence-Based References

Trappenburg JCA et al.: Effect of an action plan with ongoing support by a case manager on exacerbation-related outcome in patients with COPD: a multicentre randomised controlled trial, *Thorax* 66:977–984, 2011. Ⓐ

Albert RK et al for the COPD Clinical Research Network: Azithromycin for prevention of exacerbations of COPD, *N Engl J Med* 365:689–698, 2011. Ⓐ

Loke YK et al.: Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies, *Thorax* 66:699–708, 2011. Ⓐ

SUGGESTED READINGS

Abrams TE et al.: Geographic isolation and the risk for COPD-related mortality, *Ann Intern Med* 155:80–86, 2011.

Albert RK et al.: Azithromycin for prevention of exacerbation of COPD, *N Engl J Med* 365:689–698, 2011.

Bafadhel M et al.: Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial, *Am J Respir Crit Care Med* 186:48, 2012.

Cosio MG et al.: Immunologic aspects of chronic obstructive pulmonary disease, *N Engl J Med* 360:2445–2454, 2009.

Drummond MB et al.: Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease, *JAMA* 300(20):2407–2416, 2008.

Eisner MD et al.: COPD as a systemic disease: impact on physical functional limitations, *Am J Med* 121:789, 2008.

Gershon A et al.: Comparison of inhaled long-acting beta agonists and anticholinergic effectiveness in older patients with COPD: a cohort study, *Ann Intern Med* 154:583, 2011.

Gross NJ: Chronic obstructive pulmonary disease: an evidence-based approach to treatment with a focus on anticholinergic bronchodilation, *Mayo Clin Proc* 83(11):1241–1250, 2008.

Lindenauer PK et al.: Association of corticosteroid dose and route of administration with risk of treatment failure in acute exacerbation of chronic obstructive pulmonary disease, *JAMA* 303:2359, 2010.

Littner MR: In the clinic: chronic obstructive pulmonary disease, *Ann Intern Med* 154(7):ITC4-1-ITC4-15. 2011.

Nici L et al.: Pulmonary rehabilitation in the treatment of COPD, *Am Fam Physician* 82(6):655–660, 2010.

Niewoehner DE: Outpatient management of severe COPD, *N Engl J Med* 362:1407–1416, 2010.

Qaseem A et al.: Diagnosis and management of stable COPD: a clinical practice guideline update from ACP, ACCP, ATS, and ERS, *Ann Intern Med* 155:179–191, 2011.

Rodriguez J et al.: The association of pipe and cigar use with cotinine levels, lung function, and airflow obstruction, *Ann Intern Med* 152:201–210, 2010.

Rothberg MB: Antibiotic therapy and treatment failure in patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease, *JAMA* 303(20):2035–2042, 2010.

Sciurba FC et al.: A randomized study of endobronchial valves for advanced emphysema, *N Engl J Med* 363:1233–1244, 2010.

Sethi S, Murphy TF: Infection in the pathogenesis and course of chronic obstructive pulmonary disease, *N Engl J Med* 359:2355–2365, 2008.

Stephens MB, Yew KS: Diagnosis of chronic obstructive pulmonary disease, *Am Fam Physician* 78(1):87, 2008.

Tashkin DP et al.: Comparing COPD treatment: nebulizer, metered dose inhaler, and concomitant therapy, *Am J Med* 120:435, 2007.

U.S. Preventive Services Task Force: Screening for chronic obstructive pulmonary disease using spirometry: U.S. Preventive Services Task Force recommendation statement, *Ann Intern Med* 148:529, 2008.

Wedzicha J, Seemungal TA: COPD exacerbation: defining their cause and prevention, *Lancet* 370:786, 2007.

Wells JM et al.: Pulmonary arterial enlargement and acute exacerbations of COPD, *N Engl J Med* 367:913–921, 2012.

Wenzel RP et al.: Antibiotic prevention of acute exacerbations of COPD, *N Engl J Med* 367:340–347, 2012.

BASIC INFORMATION

DEFINITION

Chronic pain is pain that persists for longer than the expected time frame or that is associated with progressive, nonmalignant disease. Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. The perception of pain is influenced by physiologic, psychological, and social factors.

SYNONYMS

Nonmalignant chronic pain
Pain management

ICD-9CM CODES
338.29 Chronic pain
338.4 Chronic pain syndrome
780.96 Generalized pain
ICD-10CM CODES
G89.4 Chronic pain syndrome
R52 Pain, unspecified
G89.29 Other chronic pain

EPIDEMIOLOGY & DEMOGRAPHICS

Estimates of the prevalence of chronic pain in the United States vary widely. Data from one national survey (1999-2002 National Health and Nutrition Examination Survey [NHANES]) reported a prevalence of chronic regional and widespread pain of 11% and 3.6%, respectively, while the National Center for Health Statistics estimates that 32.8% of the U.S. population suffers from some form of chronic pain. Chronic pain is the third leading cause of physical impairment in the United States, and related costs are estimated to be tens of billions annually. Patients with chronic pain may also experience changes in mood, depression, sleep disturbances, fatigue, and decreased overall physical functioning.

CLINICAL PRESENTATION

- History: comprehensive patient assessment, including history of present illness (cause of pain, location, timing, characteristics, exacerbating/relieving factors, triggers), past therapies (pharmacologic and nonpharmacologic and outcomes of these therapies), medical history, family and social history, psychiatric history (including history of depression, anxiety, abuse, and/or other psychological disorders), substance use history, allergies, sleep patterns and disturbances, and current medications. Social supports, coping mechanisms, and spirituality can also help guide development of a treatment plan.
- Pain assessment should be performed at each visit; includes pain intensity (1 to 10), response to medication, and attributes of pain. Standardized templates for both initial and follow-up pain assessment have been developed by various organizations. The Brief Pain Inventory is an example of a widely used assessment tool. In addition, a functional assessment should be performed. Tools such as the Functional Ability Questionnaire (FAQ5) can guide the clinician in determining a patient's functional status. Lastly, consider assessment of a patient's risk for substance abuse.
- Physical examination: directed at systems affected by pain (often musculoskeletal) and neurologic examination.
- Look for contributing factors (e.g., co-morbidities, lifestyle factors) and barriers to effective care (e.g., behavioral, social, insurance)

ETIOLOGY

Chronic pain can generally be categorized as originating from one of five etiologies: musculoskeletal, neuropathic, inflammatory, mechanical, or mixed. Chronic pain may include such diagnoses as headache, low back pain, previous trauma, arthritis, neurogenic (e.g., trigeminal neuralgia), psychogenic (related to depression or anxiety), fibromyalgia, reflex sympathetic dystrophy, myofascial pain syndrome, phantom limb pain, idiopathic, or unknown.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Depends on etiology (musculoskeletal, neuropathic, inflammatory, mechanical, or mixed)
- Depression and anxiety disorders can be both a cause and a result of chronic pain, so temporal association of these disorders is important.

WORKUP

- Workup should be directed at identifying the source of pain
- Laboratory testing, imaging studies, and/or electromyographic studies should be used when etiology of chronic pain is unknown or unclear, when comorbidities are suspected, and as the history and physical examination direct.
- Consider use of random urine drug screens or other tests to screen for presence of illegal drugs, unreported prescribed medications, or alcohol use.

TREATMENT

- Studies increasingly support the application of a multidisciplinary, biopsychosocial approach that addresses the multiple facets of pain and includes the patient's perspective and goals.
- Therapeutic goal is the reduction of pain (elimination of chronic pain is generally unlikely and providers need to discuss these limitations with patients at outset).
- A written care plan that includes methods to address the patient's personal goals, improve sleep, increase physical activity, manage stress, and reduce pain.
- Fig. EC1-77 describes an algorithm for the treatment of pain.

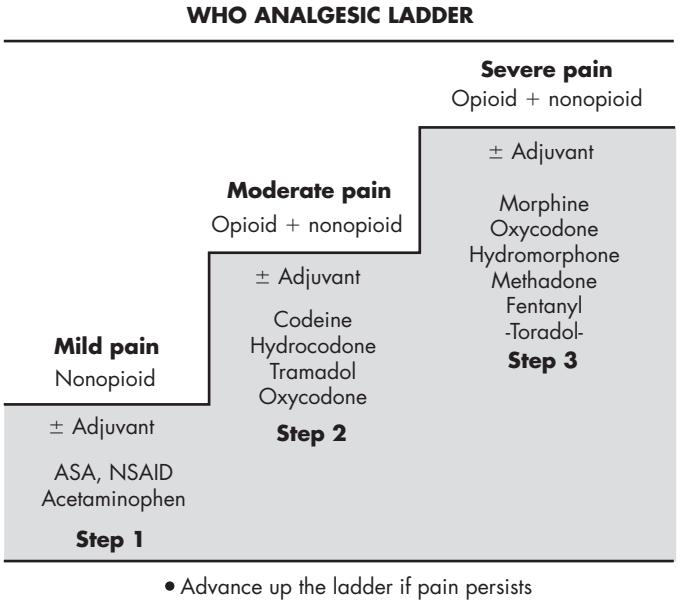

FIGURE C1-78 Strategy for pharmacologic management of pain using the World Health Organization *(WHO)* analgesic ladder. Multiagent therapy is usually required for optimal pain management. Patients with mild pain should be started on a nonopioid analgesic, and those with moderate pain on a step 2 opioid. Many patients can benefit from the addition of a nonopioid to the opioid (e.g., for bone pain) or an adjuvant agent to the opioid (e.g., for neuropathic pain). If this combination does not produce adequate relief or the patient has severe pain, step 3 opioids should be started initially. Toradol (ketorolac) is a nonsteroidal anti-inflammatory drug (NSAID) with the pain-relieving potency of a step 3 opioid. Many patients can benefit from the addition of nonopioid analgesics or adjuvants, if indicated. *ASA,* Aspirin. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

TABLE C1-33 Adjuvant Analgesic Drugs for Chronic Pain

Drug	Dosage	Indications	Adverse Effects	Comments
Tricyclic Antidepressants				
Amitriptyline, imipramine, desipramine, nortriptyline	10-150 mg/day	Peripheral neuropathy, postherpetic neuralgia, other types of peripheral neuropathic pain, central pain, facial pain, fibromyalgia, headache prophylaxis, irritable bowel syndrome, and chronic low back pain with or without radiculopathy	Sedation, dry mouth, confusion, weight gain, constipation, urinary retention, ataxia, cardiac conduction delay (QTc prolongation)	First-line agents for neuropathic pain and headache prophylaxis Secondary amine drugs (e.g., nortriptyline) have fewer side effects than tertiary amines (e.g., amitriptyline) Contraindicated in glaucoma
Serotonin-Norepinephrine Reuptake Inhibitors				
Venlafaxine	75-225 mg/day	Peripheral neuropathy, headache prophylaxis	Sedation, dry mouth, constipation, ataxia, hypertension, hyperhidrosis	Dose adjustment in patients with renal dysfunction
Duloxetine	60-120 mg/day	Peripheral neuropathy, fibromyalgia, chronic back pain	Sedation, dry mouth, constipation, hyperhidrosis	U.S. Food and Drug Administration (FDA)-approved for fibromyalgia and diabetic neuropathy Contraindicated in glaucoma
Anticonvulsants				
Gabapentin	600-3600 mg/day	Peripheral neuropathy, postherpetic neuralgia, other types of peripheral neuropathic pain, central pain, pelvic pain, headache prophylaxis, radiculopathy, chronic postsurgical pain	Sedation, weight gain, dry mouth, ataxia, edema	First-line agent for neuropathic pain FDA-approved for postherpetic neuralgia Effective preemptively for postoperative pain
Pregabalin	150-600 mg/day	Peripheral neuropathy, postherpetic neuralgia, central pain, fibromyalgia	Sedation, weight gain, dry mouth, ataxia, edema	First-line agent for neuropathic pain FDA-approved for diabetic neuropathy, postherpetic neuralgia, fibromyalgia Effective preemptively for postoperative pain Same mechanism of action as gabapentin
Carbamazepine	200-1600 mg/day	Facial neuralgias, diabetic neuropathy	Sedation, ataxia, diplopia, hyponatremia, agranulocytosis, diarrhea, aplastic anemia, hepatotoxicity, Stevens-Johnson syndrome	First-line agent and FDA-approved for trigeminal and glossopharyngeal neuralgia Contraindicated in patients with porphyria and atrioventricular conduction block
Topiramate	50-400 mg/day	Headache prophylaxis, chronic low back pain with or without radiculopathy	Sedation, ataxia, diplopia, weight loss, diarrhea, metabolic acidosis, kidney stones	First-line agent and FDA-approved for migraine prophylaxis Often used as appetite suppressant
Corticosteroids (Systemic)				
Prednisone	5-60 mg/day	Inflammatory arthritis, other inflammatory pain conditions (e.g., inflammatory bowel disease), traumatic nerve injury, complex regional pain syndrome	Myriad psychiatric, gastrointestinal, neurologic, and cardiac side effects; immunosuppression, weakness, edema, weight gain, elevated glucose, poor wound healing, others	Stronger evidence supports local (i.e., injection) administration More effective for acute pain Strong anti-inflammatory effects
Miscellaneous				
Muscle relaxants	Variable depending on drug	Skeletal muscle spasm, acute spinal pain, temporomandibular disorder Baclofen effective for spasticity, dystonia, and trigeminal neuralgia	Sedation, ataxia, blurred vision, confusion, asthenia, xerostomia and other gastrointestinal effects, palpitations	First-line agents for acute back pain and skeletal muscle spasm
Lidocaine patch	1-3 patches every 12 hr	Postherpetic neuropathy, peripheral neuropathy, other types of neuropathic and possibly myofascial pain associated with allodynia	Minimal systemic side effects when applied appropriately	Second-line agent and FDA-approved for postherpetic neuralgia
Capsaicin cream	0.025% applied three or four times per day	Postherpetic neuralgia, peripheral neuropathy and other types of neuropathic pain, chronic postsurgical pain, arthritis, and other musculoskeletal conditions	Burning on application Minimal systemic side effects when applied appropriately	FDA-approved for arthritis Second-line agent for postherpetic neuralgia and third-line agent for peripheral neuropathy Single application 8% patch providing up to 3 mo of pain relief was recently approved for postherpetic neuralgia
Cannabinoids	Variable depending on drug and delivery route	Strongest evidence is for multiple sclerosis May be effective for peripheral neuropathy and other types of neuropathic pain spasticity	Myriad psychiatric, neurologic, and cardiac effects; xerostomia, abdominal pain, and other gastrointestinal effects	Fourth-line agent with narrow therapeutic index Modest analgesic effect comparable to codeine

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

TABLE C1-34 Guidelines for Opioid Dose Selection, Conservative Initial Starting Doses for Opioid-Naïve Individuals, and Conversion Ratios for Opioid Rotation in Patients on Chronic Opioids

Opioid Naïve	Morphine SR	Codeine	Oxycodone	Hydrocodone	Hydromorphone	Methadone	Fentanyl	Oxymorphone
Initial dose and range in opioid-naive patient (starting dose range for repeated dosing)*	15 mg (15-30 mg q 8-12h)	30 mg (15-60 mg q 4-6h)	5 mg (5-15 mg q 4-6h)	5 mg (5-10 mg q 4-6h)	2 mg (2-4 mg q 4-6h)	2.5 mg q 6-12h	NA	5 mg q 4-6h
Opioid Tolerant Converting from:	**Morphine PO**	**Codeine**	**Oxycodone**	**Hydrocodone**	**Hydromorphone**	**Methadone**	**Fentanyl**	**Oxymorphone**
Morphine IM 10 mg (the gold standard for opioid comparisons)	20-30 mg	60-90 mg†	5 mg	5-10 mg q 4-6h	2 mg	2.5 mg	25-μg patch/72 hr	5 mg (the gold standard for opioid comparisons)
Morphine SR 30 mg PO q 8-12h, 60-90 mg/24h		30-90 mg q 4h	3-45 mg/24 hroxycodone, approx 50% of morphine dose	30-45 mg/24 hr	12-18 mg/24 hr	24-hr dose morphine 30-90 mg 4:1 conversion 90-300 mg 8:1 conversion >300 mg 12:1	25-mcg patch/72 hr	5 mg q 12h ER
Codeine 30-60 mg q 4h	15-30 mg q 3-4h		5-7.5 mg q 4h	5-10 mg q 4h	12 mg/24 hr	2.5 mg q 8-12h	12.5-μg patch/72 hr	2.5-5 mg q 4-6h IR
Oxycodone 5 mg q 3-4h	10 mg	30-60 mg q 3-4h		5-10 mg q 4h	12 mg/24 hr	2.5 mg q 8-12h	25-μg patch/72 hr	5 mg q 4-6h IR
Hydrocodone 10 mg q 3-4h	15 mg	30-60 mg q 3-4h	5 mg q 3-4h		12 mg/24 hr		12.5-μg patch/72 hr	2.5-5 mg q 4-6h IR
Hydromorphone 2 mg q 4h	10 mg		5 mg	5-10 mg q 4h		2.5 mg q 8-12h	25-μg patch/72 hr	5 mg q 4-6h IR
Methadone 5 mg q 8h	20 mg SR q 8h		10 mg q 3-4h		4 mg q 4-6h		25-μg patch/72 hr	5 mg q 12h ER
Fentanyl 25 μg/hr patch	90 mg morphine per 24 hr (1 μg to 4 mg morphine)					5 mg q 8-12h		5 mg q12h ER
Oxymorphone ER 5 mg q 12h	15 mg SR q 12h		5 mg q 8-12h	10 mg q 4-6h	12 mg/24 hr	5 mg q 8-12h	25-μg patch/72 hr	

Note: Recommended starting doses are low and should be titrated upward slowly to minimize adverse effects. Limitations of equianalgesic tables exist because they are based on single-dose studies in opioid-naïve individuals. Convert opioid 1 to morphine equivalents and calculate dose of opioid 2 according to conversion ratio then reduce the calculated dose for opioid 2 by 1/3 to 1/2 to ensure safety of the 24-hr total daily dose. Rescue dose is 10% to 20% of daily opioid dose given every 3 to 4 hr as needed. Titration upward for unrelieved pain should be by 25% to 30% of the current 24-hr dose, adjusted by daily amount of rescue medications needed over a several-week period. Equivalent or equianalgesic doses for the different opioid preparations vary in different publications. *ER,* Extended release; *IR,* immediate release.

*Conservative low equianalgesic starting doses for opioid-naïve individuals adapted from published recommendations.

†Doses above 1.5 mg/kg not recommended because of increase in side effects.

From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

NONPHARMACOLOGIC THERAPY

- Exercise (recommended for all patients and tailored to individual abilities and needs)
- Modalities: heat therapy, cold therapy, transcutaneous electrical nerve stimulation (TENS) units, manipulative therapy, cognitive behavioral therapy, psychological counseling, and physical therapy
- Electrostimulation therapy: TENS units
- Behavioral therapies: cognitive behavioral therapy, hypnosis, biofeedback, relaxation therapy
- Music therapy (in conjunction with other types of therapy)
- Surgery

ACUTE GENERAL Rx

- Short-acting anti-inflammatory and analgesic medications (e.g., acetaminophen/NSAIDs/opioids). Avoid use of NSAIDs in patients with hypertension, CHF, or any type of CKD.
- Topical analgesics (lidocaine, NSAIDs, capsaicin)
- Trigger point or joint injections (immediate anesthetic plus long-acting corticosteroids)
- Epidural steroid injections
- Nerve blocks

CHRONIC Rx

- Pain management with long-acting pharmacologic agents is considered a key aspect of therapy but is often underused. Fig. C1-78 illustrates a strategy for pharmacologic management of pain using the World Health Organization (WHO) analgesic ladder.
- Long-acting NSAIDs. Table C1-33 describes adjuvant analgesic drugs for chronic pain.
- Sustained-release opioids (used for moderate to severe pain that has failed other therapeutic interventions): oxycodone, morphine SR, methadone (use with caution), or fentanyl patch; short-acting opioids can be used in conjunction with these agents for management of breakthrough pain. Conversion to a long-acting opioid should be based on an equianalgesic conversion. Opioids are rarely beneficial in the treatment of inflammatory or mechanical pain and are not indicated for treatment of headaches (http://www.acpinternist.org/archives/2008/01/extra/pain_charts.pdf).
- Table C1-34 provides guidelines for opioid dose selection, conservative initial starting doses for opioid-naïve individuals, and conversion ratios for opioid rotation in patients on chronic opioids. Titration of these medications should not exceed the equivalent of 100 mg morphine/day to avoid risk of overdose.
- Antidepressants (tricyclic and selective serotonin reuptake inhibitor)
- Anticonvulsant medications particularly helpful for neuropathic conditions (e.g., carbamazepine, valproic acid, gabapentin, pregabalin)
- Implantable methods, epidural and intrathecal drug delivery systems, dorsal column stimulators
- Treatment of insomnia and sleep disorders to reduce pain with standard sleep-inducing agents (trazodone, antihistamines)

COMPLEMENTARY & ALTERNATIVE MEDICINE

Acupuncture and massage (evidence-based for some indications). Acupuncture is most likely to benefit patients with low back pain, neck pain, chronic idiopathic or tension headache, migraine, and knee osteoarthritis.

REFERRAL

- Pain medicine specialist or multidisciplinary pain clinic: useful when primary therapies fail, in patients with complex pain conditions, or for invasive therapies
- Consider referral to an addiction specialist if patient has a history of substance abuse or addiction
- Psychiatry/psychological services for counseling, if needed

PEARLS & CONSIDERATIONS

- Patient consent should be obtained in the form of a written treatment agreement before initiating treatment. This agreement should outline the goals of therapy, use of a single provider or treatment team and a single pharmacy, limitations on dose and number of prescribed medications, prohibition on use with alcohol or sedating medications, keeping medication safe and secure, prohibition on selling or sharing medication, limitations on refills, compliance with all components of the treatment plan, the role of drug screening, and consequences of nonadherence.
- Follow-up assessment should occur every 1 to 6 mo and include a complete pain assessment (see earlier), review of the type of long-acting analgesic used and dosage, use of breakthrough analgesics, side effects and their management, use of nonpharmacologic therapies, and adjunct medication use.

COMMENTS

- Medication dependence and addiction should not be confused. Most patients receiving chronic opioid therapy can become dependent on these medications for pain relief but opioid addiction does not occur. Patients exhibiting signs of addiction often will seek escalating doses of medication, request refills of prescriptions earlier than planned, and engage in drug-seeking activities (e.g., emergency department visits between prescriptions, seeking multiple prescriptions).
- Side effects need not preclude use of opioid medications and should be anticipated. Antiemetics can aid in controlling nausea. Constipation can be managed with stool softeners and laxatives.
- The emphasis of comprehensive pain management for non–cancer-related chronic pain has led to a fourfold increase in prescribing of opioid medications in the United States. This increase in opiate use has also led to a rise in the misuse and abuse of these medications. Providers should proceed with caution before initiating pain management with opiate medications and should familiarize themselves with processes and tools for pain assessment and medication management. Forty-two states have developed prescription drug monitoring programs (PDMPs) to assist providers in identifying issues of abuse, polypharmacy, and misuse of controlled substances.

PATIENT & FAMILY EDUCATION

National Pain Foundation (http://www.painconnection.org)
American Pain Foundation (http://www.painfoundation.org)
National Institutes of Health (http://www.nih.gov)

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **ANNGENE G. ANTHONY, M.D., M.P.H.**

SUGGESTED READINGS

American Academy of Pain Medicine: Homepage. www.painmed.org. Accessed April 25, 2013.

American College of Physicians: *ACP internist supplements, internist extra, chronic pain management: an appropriate use of opioid analgesics* (January 2008) http://www.acpinternist.org/supplements. Accessed October 2011.

Berland D, Rodgers P: Rational use of opioids for management of chronic nonterminal pain, *Am Fam Physician* 86(3):252–258, 2012.

Chang G et al.: Opioid tolerance and hyperalgesia, *Med Clin North Am* 91(2): 199–211, 2007.

Hardt JJ et al.: Prevalence of chronic pain in a representative sample in the United States, *Pain Med* 9(7):803–812, 2008.

Hooten WM et al.: *Institute for Clinical Systems Improvement. Assessment and management of chronic pain* Updated November, (2013).

Jackman RP et al.: Chronic non-malignant pain in primary care, *Am Fam Physician* 78(10):1155–1162, 2008.

Kelly RB: Acupuncture for pain, *Am Fam Physician* 80(5):481–484, 2009.

Makris UE et al.: Management of persistent pain in the older patient, *JAMA* 312(8):825–836, 2014.

Nuckols TK et al.: Opioid prescribing: a systematic review and critical appraisal of guidelines for chronic pain, *Ann Intern Med* 160:38–47, 2014.

Perrone J et al.: Medication reconciliation for controlled substances—an 'ideal' prescription drug monitoring program, *N Engl J Med* 366(25):2341–2343, 2012.

SBL Ltd: Pain treatment topics http://pain-topics.org Accessed October 2011.

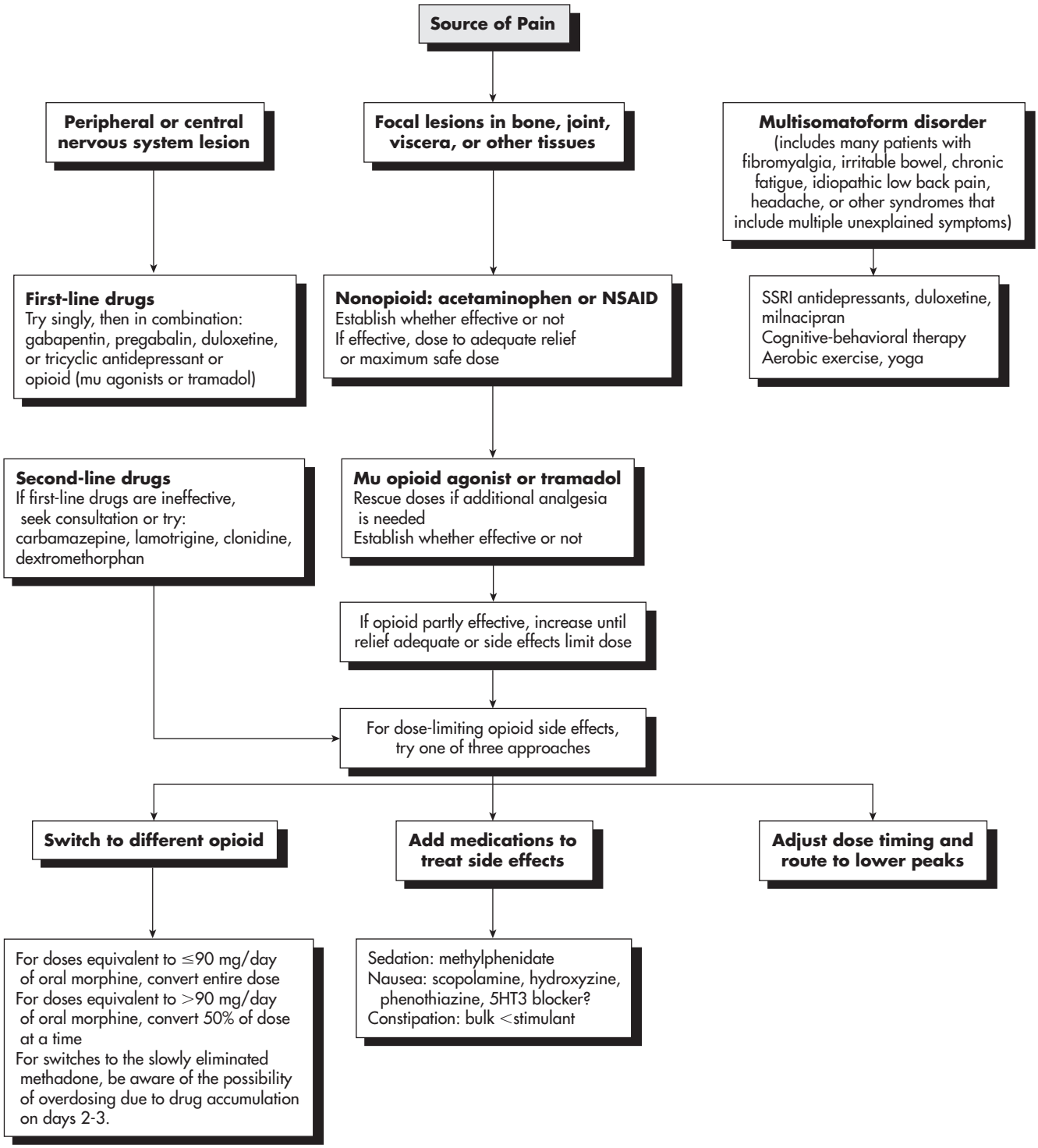

FIGURE EC1-77 Algorithm for the treatment of pain. *COX,* Cyclooxygenase; *NSAID,* nonsteroidal antiinflammatory drug; *SSRI,* selective serotonin reuptake inhibitor. (Modified from Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 23, Philadelphia, 2008, Saunders.)

BASIC INFORMATION

DEFINITION

Chronic pancreatitis is a recurrent or persistent inflammatory process of the pancreas characterized by chronic pain and by pancreatic exocrine and/or endocrine insufficiency.

ICD-9CM CODES
577.1 Chronic pancreatitis
ICD-10CM CODES
K86.1 Other chronic pancreatitis
K86.0 Alcohol-induced chronic pancreatitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Chronic pancreatitis occurs in approximately five to 10 per 100,000 persons in industrialized countries.
- Average age at diagnosis is 35 to 55 yr; male/female ratio is 5:1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Persistent or recurrent epigastric and left upper quadrant pain that may radiate to the back
- Tenderness over the pancreas, muscle guarding
- Significant weight loss
- Bulky, foul-smelling stools, greasy in appearance
- Epigastric mass (10% of patients)
- Jaundice (5% to 10% of patients)

ETIOLOGY

- Chronic alcoholism
- Obstruction (ampullary stenosis, tumor, trauma, pancreas divisum, annular pancreas)
- Hereditary pancreatitis
- Severe malnutrition
- Idiopathic
- Untreated hyperparathyroidism (hypercalcemia)
- Mutations of the cystic fibrosis transmembrane conductance regulator *(CFTR)* gene and the TF genotype
- ***Autoimmune pancreatitis (AIP):*** (5% of chronic pancreatitis cases): presents clinically with jaundice (63% of patients) and abdominal pain (35%). CT may reveal diffusely enlarged pancreas, enhanced peripheral rim of hypoattenuation "halo," and low-attenuation mass in head of pancreas. Laboratory values reveal elevated serum immunoglobulin (Ig) G4, elevated serum Ig or gamma-globulin level, presence of antilactoferrin antibody (ALA), anticarbonic anhydrase (ACA) II level, anti-smooth-muscle antibody (ASMA), or antinuclear antibody (ANA).
- ***Sclerosing pancreatitis:*** a form of chronic pancreatitis characterized by infrequent attacks of abdominal pain, irregular narrowing of the pancreatic duct, and swelling of the pancreatic parenchyma; patients have high levels of serum immunoglobulins (IgG4). Chronic sclerosing pancreatitis is also known as *autoimmune pancreatitis.*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Pancreatic cancer
- Peptic ulcer disease
- Cholelithiasis with biliary obstruction
- Malabsorption from other etiologies
- Recurrent acute pancreatitis
- Renal insufficiency
- Intestinal ischemia or infarction
- Other: Crohn's disease, gastroparesis, inflammatory bowel disease

WORKUP

Medical history with focus on alcohol use, laboratory tests, diagnostic imaging

LABORATORY TESTS

- Serum amylase and lipase may be elevated (normal amylase levels, however, do not exclude the diagnosis).
- Hyperglycemia, glycosuria, hyperbilirubinemia, and elevated serum alkaline phosphatase may also be present.
- 72-hr fecal fat determination (rarely performed) reveals excess fecal fat. Fecal elastase test requires only 20 g of stool.
- Secretin stimulation test is the best test for diagnosing pancreatic exocrine insufficiency.
- Lipid panel: significantly elevated triglycerides can cause pancreatitis.
- Serum calcium: hyperparathyroidism is a rare cause of chronic pancreatitis.
- Elevated levels of serum IgG4 are found in sclerosing pancreatitis and AIP.
- Elevated serum Ig or gamma-globulin level, presence of ALA, ACA II level, ASMA, or ANA in AIP.

IMAGING STUDIES

- Plain abdominal radiographs (Fig. EC1-79) may reveal pancreatic calcifications (95% specific for chronic pancreatitis).
- Ultrasound of abdomen may reveal duct dilation, pseudocyst, calcification, and presence of ascites.
- Contrast-enhanced CT scan of abdomen is the initial modality of choice. It is useful to detect calcifications, evaluate for ductal dilation, and rule out pancreatic cancer.
- Endoscopic retrograde cholangiopancreatography (ERCP) had been traditionally used to evaluate for the presence of dilated ducts, strictures, pseudocysts, and intraductal stones. However, for the evaluation of pancreatic parenchyma and duct system newer, less invasive modalities such as magnetic resonance cholangiopancreatography and endoscopic ultrasonography (EUS) are preferred. EUS (Fig. EC1-80) has a sensitivity of 97% and a specificity of 60% for chronic pancreatitis and a very low complication rate. Fine-needle aspiration biopsy combined with EUS is the preferred modality for evaluation of cystic or mass lesions to determine malignancy.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of alcohol and tobacco
- Frequent, small-volume, low-fat meals

ACUTE GENERAL Rx

- Avoidance of narcotics if possible (simple analgesics or NSAIDs can be used). Fig. EC1-81 describes an approach to the patient with painful chronic pancreatitis.
- Treatment of steatorrhea with pancreatic supplements (e.g., Pancrease, Creon, pancrelipase titrated prn based on the amount of steatorrhea and patient's weight loss). All non–enteric-coated enzymes should be used with acid-suppressing medications. Proton pump inhibitors and H_2 blockers reduce inactivation of the enzymes from gastric acid.
- Antioxidants (vitamin A, selenium, vitamin E) may be helpful for pain control in chronic pancreatitis.
- Percutaneous or via EUS celiac plexus blockade with corticosteroids or neurolysis with ethanol may provide temporary pain relief.
- Treatment of complications (e.g., type 1 diabetes mellitus).
- Glucocorticoid therapy in patients with AIP and sclerosing pancreatitis can induce clinical remission and significantly decrease serum concentrations of IgG4, immune complexes, and the IgG4 subclass of immune complexes.

CHRONIC Rx

- Surgical intervention may be necessary to eliminate biliary tract disease and improve flow of bile into the duodenum by eliminating obstruction of pancreatic duct.
- ERCP with endoscopic sphincterectomy and stone extraction is useful in selected patients.
- Transduodenal sphincteroplasty or pancreaticojejunostomy in selected patients. Surgery should also be considered in patients with intractable pain.

DISPOSITION

- Long-term survival is poor (50% of patients die within 10 yr from chronic pancreatitis or malignancy).
- Prognosis is best in patients with recurrent acute pancreatitis resulting from cholelithiasis, hyperparathyroidism, or stenosis of the sphincter of Oddi.

REFERRAL

Gastrointestinal referral for ERCP, surgical referral in selected patients (see "Chronic Rx")

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Chronic Pancreatitis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Finkelberg DL et al.: Autoimmune pancreatitis, *N Engl J Med* 355:2670, 2006.

Hamano H et al.: High serum IgG4 concentrations in patients with sclerosing pancreatitis, *N Engl J Med* 344:732, 2001.

Hollerbach S et al.: Endoscopic ultrasonography and fine needle aspiration cytology for diagnosis of chronic pancreatitis, *Endoscopy* 33:824, 2001.

Nair R et al.: Chronic pancreatitis, *Am Fam Physician* 76:1679–1688, 2007.

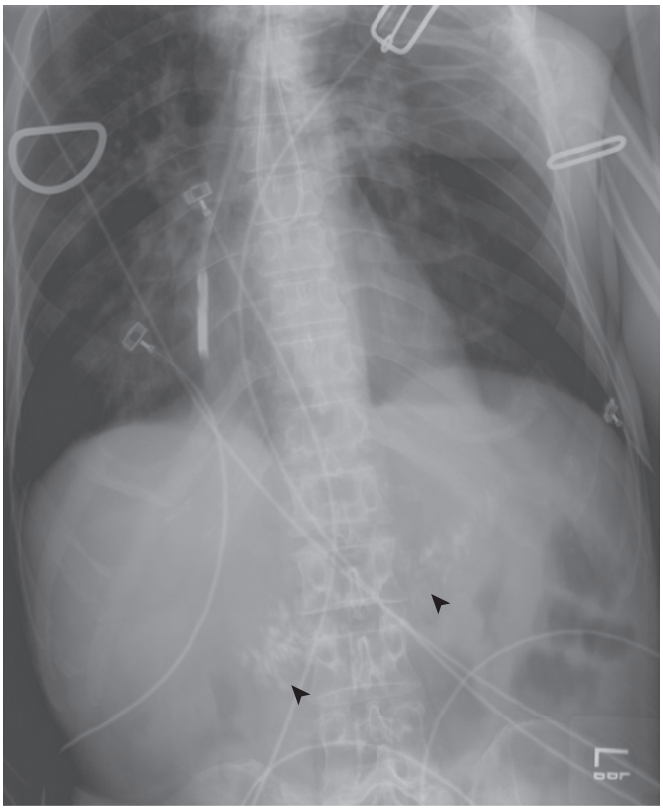

FIGURE EC1-79 Pancreatic calcifications *(arrowheads)* throughout the pancreas as seen in chronic pancreatitis. (Incidental finding of feeding tube in main bronchus.) (Image courtesy of Ronald Arildsen.) (From Marx JA et al [eds]: *Rosen's emergency medicine: concepts and clinical practice*, ed 7, Philadelphia, 2010, Elsevier.)

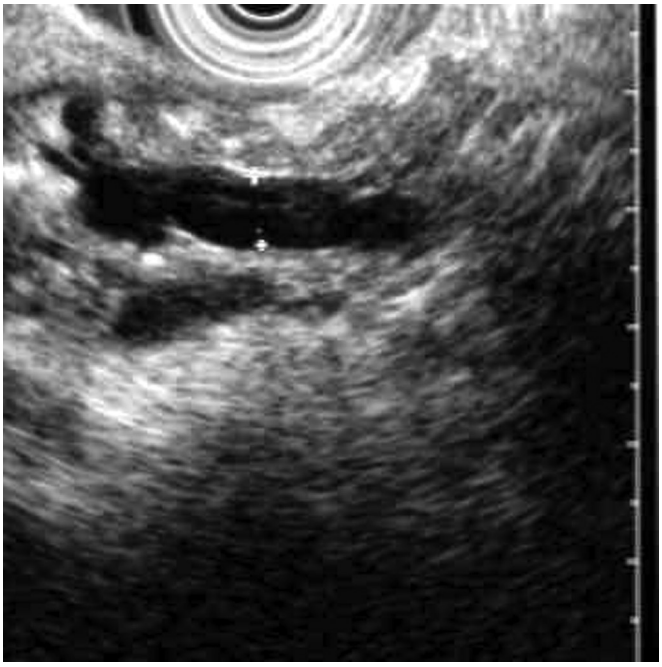

FIGURE EC1-80 Endoscopic ultrasound in a patient with chronic pancreatitis, demonstrating a dilated pancreatic duct (*marks* on margin of main duct). (From Goldman L, Schafer AI: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Saunders.)

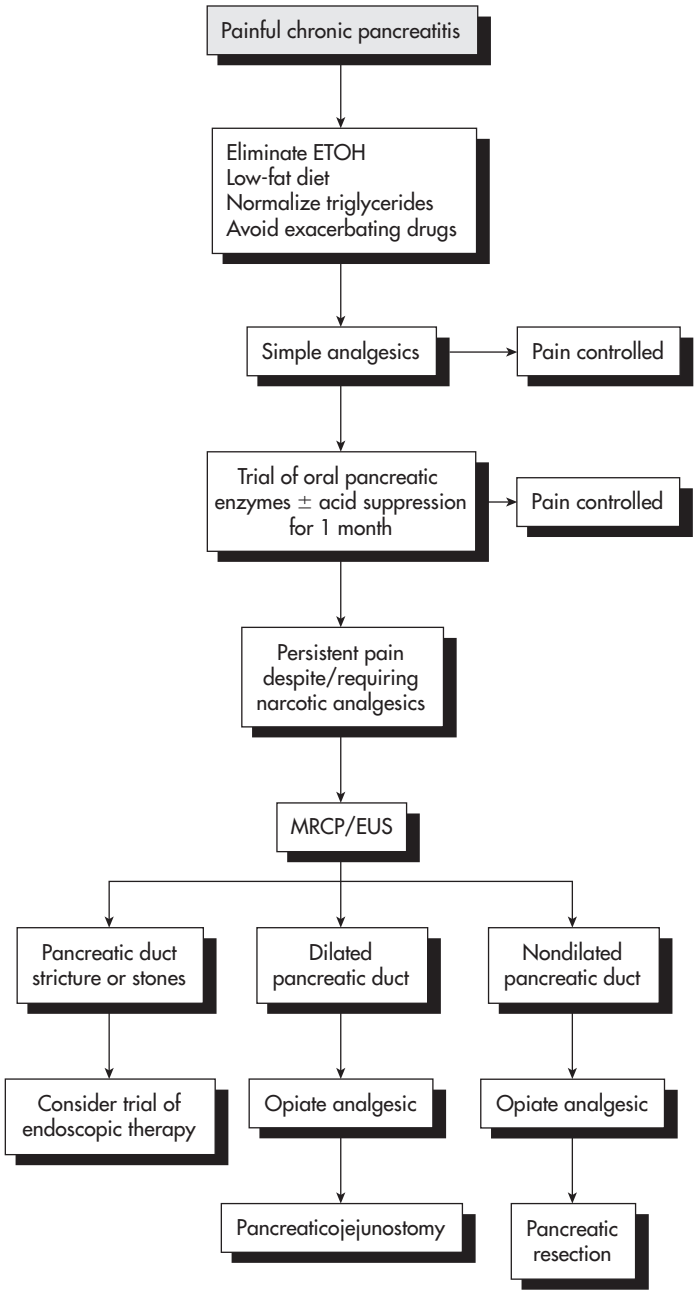

FIGURE EC1-81 Approach to the patient with painful chronic pancreatitis. *ETOH,* Alcohol; *EUS,* endoscopic ultrasound; *MRCP,* magnetic resonance cholangiopancreatography. (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

BASIC INFORMATION

DEFINITION

Churg-Strauss syndrome (CSS) refers to a systemic granulomatous vasculitis accompanied by severe asthma (core clinical feature) and hypereosinophilia. Classification criteria and definition for CSS are described in Table EC1-35.

SYNONYMS

Allergic angiitis
Allergic granulomatosis

ICD-9CM CODES
446.4 Angiitis, allergic granulomatous
ICD-10CM CODES
M31.30 Wegener's granulomatosis without renal involvement

EPIDEMIOLOGY & DEMOGRAPHICS

- Overall incidence of 2.4 cases per 1 million persons in the U.S. Among asthma patients, the annual incidence of CSS is estimated to average 34.6 per 1 million patients.
- Usually occurs at a mean age of 50 yr but may present as young as 4 yr or in the elderly
- Slight male/female predominance (1.3:1).
- With treatment, 1-year survival is approximately 90% and 5-year survival is 62%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The clinical picture of CSS typically consists of three partially overlapping phases, which may or may not be sequential:

1. Prodromal phase:
   - Severe adult-onset asthma, with or without allergic rhinitis, sinusitis, headache, cough, and wheezing
   - Precedes development of systemic vasculitis by several years
2. Eosinophilic/tissue infiltration phase:
   - Peripheral eosinophilia and eosinophilic infiltration of the lungs, myocardium, and gastrointestinal (GI) tract, with or without granulomas
   - Signs and symptoms of cough, fever, anorexia, weight loss, sweats, malaise, nausea, vomiting, abdominal pain, and diarrhea
3. Systemic vasculitic phase:
   - Development of necrotizing vasculitis that is clinically apparent primarily in peripheral nerves, skin, and kidneys
   - Any organ can be affected, with skin involvement present in 50% to 67% of patients

Skin involvement is divided into three categories:

1. Erythematous maculopapules (can resemble erythema multiforme)
2. Hemorrhagic lesions (associated with wheals)
3. Cutaneous and subcutaneous nodules

ETIOLOGY

- Etiology unknown, but believed to be an autoimmune-mediated process
- Triggering factors implicated in CSS include inhaled allergens, vaccinations, infections, and drugs such as macrolides (see "Comments").

DIAGNOSIS

- Clinical findings and biopsy showing eosinophilic vasculitis
- The American College of Rheumatology (ACR) has established the criteria for CSS diagnosis in patients without vasculitis:
  1. Asthma
  2. Eosinophilia >10% of white blood cell count
  3. Mononeuropathy or polyneuropathy
  4. Migratory pulmonary infiltrates
  5. Paranasal sinus abnormalities
  6. Extravascular eosinophils on biopsy

The presence of any four or more of the six criteria yields a sensitivity of 85% and a specificity of 99.7%. For patients with vasculitis, the presence of asthma and eosinophilia was 90% sensitive and 99% specific for CSS.

DIFFERENTIAL DIAGNOSIS

- Polyarteritis nodosa (PAN)
- Wegener's granulomatosis (WG)
- Goodpasture syndrome
- Loeffler syndrome
- Hypereosinophilia syndrome
- Rheumatoid arthritis
- Leukocytoclastic vasculitis

Although similar and at times grouped with patients with PAN or WG, CSS differs in that:

- CSS vasculitis involves small-sized arteries, veins, and venules
- CSS, unlike PAN, predominantly involves the lung. Other organs affected include heart, GI system, central nervous system, kidney, and skin
- Kidney involvement is much less common in CSS than in WG. Pulmonary lesions in WG usually involve the upper respiratory tract rather than the peripheral lung parenchyma in CSS
- CSS shows necrotizing vasculitis along with eosinophilic granulomas

LABORATORY TESTS

- Complete blood count with differential: eosinophilia >10% is an American College of Rheumatology (ACR) diagnostic criterion
- Blood urea nitrogen and creatinine may be mildly elevated, suggesting renal involvement
- Urinalysis may show mild hematuria and proteinuria
- 24-hour urine for protein; greater than 1 g/day is a poor prognostic factor
- Perinuclear antineutrophilic cytoplasmic antibody (P-ANCA) is found in 13% to 70% of patients. Negative ANCA does not rule out CSS
- Stools may be positive for occult blood (enteric involvement during eosinophilic phase)
- Elevation of aspartate aminotransferase, alanine aminotransferase, and creatine phosphokinase may indicate liver or muscle (skeletal or cardiac) involvement
- Rheumatoid factor and antinuclear antibody may be positive. Erythrocyte sedimentation rate is usually elevated
- Biopsy helps confirm the diagnosis. Surgical lung biopsy is the gold standard. Transbronchial biopsy is rarely helpful. Necrotizing vasculitis and extravascular necrotizing granulomas, usually with eosinophilic infiltrates, are suggestive of CSS. The presence of eosinophils in extravascular tissues is most specific for CSS

IMAGING STUDIES

- Chest radiograph is abnormal in eosinophilic and vasculitic phases: asymmetrical bilateral patchy migratory infiltrates, interstitial lung disease, or nodular infiltrates (Fig. EC1-82). Small pleural effusions are found in 29% of cases
- Lung lesions in CSS are noncavitating, as opposed to those in WG
- Paranasal sinus films may reveal sinus opacification, which is an ACR diagnostic criterion
- Angiography is sometimes done in patients with mesenteric ischemia or renal involvement

TABLE EC1-35 Classification Criteria and Definition for Churg-Strauss Syndrome

CLASSIFICATION CRITERIA		DEFINITION
Lanham (Requires 2 of 3)	**American College of Rheumatology (Requires 4 of 6)**	**Chapel Hill Consensus Conference**
Asthma Eosinophilia (>10% WBC count or >1.5 · 10^9) Systemic vasculitis affecting at least two extrapulmonary sites	Asthma Eosinophilia (>10% total WBC count) Neuropathy (mono or polyneuropathy) Pulmonary infiltrates (migratory or transitory) Paranasal sinus abnormality (pain, tenderness or radiologic abnormality) Extravascular eosinophils (in a biopsy including an artery, arteriole, or venule)	Eosinophil-rich and granulomatous inflammation involving the respiratory tract, necrotizing vasculitis affecting small to medium-sized vessels, and associated with asthma and eosinophilia

WBC, White blood cell.
From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

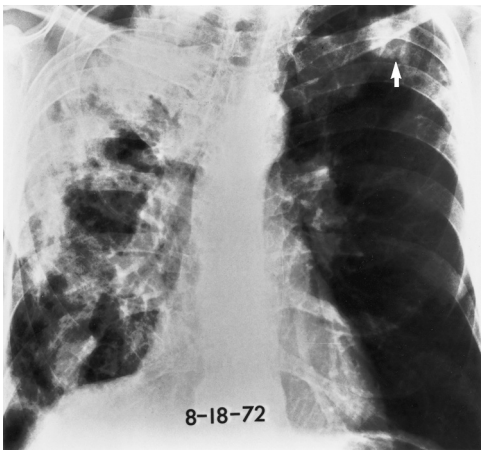

FIGURE EC1-82 Allergic angiitis and granulomatosis. Posteroanterior chest radiograph demonstrates peripheral air space consolidation in the right lung and a nodule *(arrow)* in the left upper lobe in this asthmatic patient. (From McLoud TC [ed]: *Thoracic radiology: the requisites,* St Louis, 1998, Mosby.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Oxygen therapy in severe asthmatic exacerbations

PHARMACOLOGIC THERAPY

The following five factors suggest poor prognosis (five-factor score) and determine the aggressiveness of the immune suppressive therapy:

1. Proteinuria >1 g/day
2. Creatinine >1.58 mg/dl
3. Cardiomyopathy
4. GI tract involvement
5. Central nervous system involvement

ACUTE GENERAL Rx

- Corticosteroids are the treatment of choice if no poor prognostic factors are present. Prednisone 1 mg/kg/day is the starting dose and is continued for 6 to 12 wk and then tapered to 10 mg/day at 1 yr as clinical disease resolves. Response to steroids may be dramatic. Patients with extensive disease may require IV corticosteroids.
- A drop in the patient's eosinophil count and the erythrocyte sedimentation rate indicates a response to treatment. ANCA does not reliably correspond with disease activity.

CHRONIC Rx

- In patients with one or more poor prognostic factors, immunosuppressant agents (cyclophosphamide 1 to 2 mg/kg/day) are used with corticosteroids as first-line therapy. Limit duration of cyclophosphamide to a maximum of 6 mo.
- In patients who do not respond to corticosteroid treatment or in CSS relapse, cyclophosphamide therapy is indicated as a second-line therapy.
- Azathioprine (2 mg/kg/day) or high-dose intravenous immunoglobulin has shown benefit in patients with severe disease and in patients unresponsive to corticosteroids.
- Corticosteroids, in combination with interferon-alpha, have also been used in refractory cases but may be difficult to tolerate.
- Patients with persistent symptoms of asthma will require long-term corticosteroids even if vasculitis is no longer present.
- Maintenance therapy using methotrexate (15 to 25 mg/wk) or azathioprine (2 mg/kg/day) is an alternative to cyclophosphamide.

DISPOSITION

- Clinical remission is obtained in more than 90% of patients after treatment. Relapse is common on cessation of therapy (approximately 26%).
- 5-yr survival rate with treatment is between 60% and 90% and decreases to 50% at 7 yr. Asthma generally remains persistent, and ischemic damage to peripheral nerves can be permanent.
- The 5-yr survival rate of untreated CSS is 25%.
- Death usually occurs from progressive refractory vasculitis, myocardial involvement (approximately 50% of deaths), or severe GI involvement (mesenteric ischemia, pancreatitis).

REFERRAL

- A pulmonary referral for diagnosis and management is appropriate.
- Patients should be followed up closely by rheumatology. Patients usually need long-term immunosuppressive medications.

PEARLS & CONSIDERATIONS

COMMENTS

- CSS is a rare disease that is less common than other ANCA-associated vasculitides
- CSS is distinguished from other vasculitides by the nearly universal presence of adult-onset asthma that typically precedes all other symptoms. Family history is often negative for allergies or asthma
- Up to 77% of patients in the prodromal phase of CSS require oral steroids for asthma control
- Patients often have constitutional symptoms of weight loss, fever, and malaise before specific organ involvement is clinically evident
- Peripheral nerve involvement from vasculitis of the vasa vasorum commonly manifests as mononeuritis multiplex. Patients may present with sudden foot or wrist drop, along with sensory deficits in the distribution of one or more distal nerves
- Most patients with GI involvement are symptomatic. Gastroenteritis, acute abdomen, cholecystitis, hemorrhage, bowel perforation, and mesenteric ischemia have all been reported in patients with CSS
- Most patients with CSS respond to corticosteroid treatment and do not require cytotoxic therapy
- Symptoms of CSS typically appear as oral corticosteroids are being decreased or discontinued for the treatment of asthma and not triggered by leukotriene receptor-1 antagonists, as previously reported
- Compared to WG, patients more often present with history of atopy, asthma, or allergic rhinitis. When present, eosinophilia in CSS is often >1000 eosinophils/mm^3 compared with WG, where eosinophilia is much milder (<500 eosinophils/mm^3)
- The heart is involved in up to 60% of patients with CSS and represents a major cause of mortality

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **KACHIU LEE, B.A.,** and **JESSICA CORWIN, M.D., M.P.H.**

SUGGESTED READINGS

Kallenberg CG: Churg-Strauss syndrome: just one disease entity? *Arthritis Rheum* 52(9):2589–2593, 2005.

Masi A et al.: American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome, *Arthritis Rheum* 33:1094, 1990.

Pagnoux C et al.: Churg-Strauss syndrome, *Curr Opin Rheumatol* 19(1):25–32, 2007.

Seo P et al.: Small-vessel and medium-vessel vasculitis, *Arthritis Rheum* 57(8):1552–1559, 2007.

BASIC INFORMATION

DEFINITION

Cirrhosis is defined histologically as the presence of fibrosis and regenerative nodules in the liver. It can be classified as micronodular, macronodular, or mixed; however, each form may be seen in the same patient at different stages of the disease. Cirrhosis manifests clinically with portal hypertension, hepatic encephalopathy, and variceal bleeding.

ICD-9CM CODES
571.5 Cirrhosis of the liver
571.2 Cirrhosis of the liver secondary to alcohol
ICD-10CM CODES
K74.60 Hepatic fibrosis and cirrhosis
K70.30 Alcoholic cirrhosis of liver without ascites
K74.6 Other and unspecified cirrhosis of liver

EPIDEMIOLOGY & DEMOGRAPHICS

- Cirrhosis is the eleventh leading cause of death in the U.S. (9 per 100,000 persons annually).
- Alcohol abuse and viral hepatitis are the major causes of cirrhosis in the U.S.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

SKIN: Jaundice, palmar erythema (alcohol abuse), spider angiomata, ecchymosis (thrombocytopenia or coagulation factor deficiency), dilated superficial periumbilical vein (caput medusae), increased pigmentation (hemochromatosis), xanthomas (primary biliary cirrhosis), and needle tracks (viral hepatitis). Cutaneous lesions often accompany cirrhosis and can be found in >40% of people with chronic alcoholism.
EYES: Kayser-Fleischer rings (corneal copper deposition seen in Wilson's disease; best diagnosed with slit lamp examination), scleral icterus
BREATH: Fetor hepaticus (musty odor of breath and urine found in cirrhosis with hepatic failure)
CHEST: Possible gynecomastia in men
ABDOMEN: Tender hepatomegaly (congestive hepatomegaly), small, nodular liver (cirrhosis), palpable, nontender gallbladder (neoplastic extrahepatic biliary obstruction), palpable spleen (portal hypertension), venous hum auscultated over periumbilical veins (portal hypertension), ascites (portal hypertension, hypoalbuminemia)
RECTAL EXAMINATION: Hemorrhoids (portal hypertension), guaiac-positive stools (alcoholic gastritis, bleeding esophageal varices, peptic ulcer disease, bleeding hemorrhoids)
GENITALIA: Testicular atrophy in males (chronic liver disease, hemochromatosis)
EXTREMITIES: Pedal edema (hypoalbuminemia, failure of right side of the heart), arthropathy (hemochromatosis)
NEUROLOGIC: Flapping tremor, asterixis (hepatic encephalopathy), choreoathetosis, dysarthria (Wilson's disease)

ETIOLOGY

- Alcohol abuse
- Secondary biliary cirrhosis, obstruction of the common bile duct (stone, stricture, pancreatitis, neoplasm, sclerosing cholangitis)
- Drugs (e.g., acetaminophen, isoniazid, methotrexate, methyldopa)
- Hepatic congestion (e.g., CHF, constrictive pericarditis, tricuspid insufficiency, thrombosis of the hepatic vein, obstruction of the vena cava)
- Primary biliary cirrhosis
- Hemochromatosis
- Chronic hepatitis B or C
- Wilson's disease
- Alpha-1-antitrypsin deficiency
- Infiltrative diseases (amyloidosis, glycogen storage diseases, hemochromatosis)
- Nutritional: jejunoileal bypass
- Others: parasitic infections (schistosomiasis), idiopathic portal hypertension, congenital hepatic fibrosis, systemic mastocytosis, autoimmune hepatitis, hepatic steatosis, inflammatory bowel disease (IBD)

DIAGNOSIS

WORKUP

In addition to an assessment of liver function, the evaluation of patients with cirrhosis should also include an assessment of renal and circulatory function. Diagnostic workup is aimed primarily at identifying the most likely cause of cirrhosis. The history is extremely important:

- Alcohol abuse: alcoholic liver disease
- History of hepatitis B (chronic active hepatitis, primary hepatic neoplasm, or hepatitis C)
- History of IBD (primary sclerosing cholangitis)
- History of pruritus, hyperlipoproteinemia, and xanthomas in a middle-aged or elderly woman (primary biliary cirrhosis)
- Impotence, diabetes mellitus, hyperpigmentation, arthritis (hemochromatosis)
- Neurologic disturbances (Wilson's disease, hepatolenticular degeneration)
- Family history of "liver disease" (hemochromatosis [positive family history in 25% of patients], alpha-1-antitrypsin deficiency)
- History of recurrent episodes of right upper quadrant pain (biliary tract disease)
- History of blood transfusions, IV drug abuse (hepatitis C)
- History of hepatotoxic drug exposure
- Coexistence of other diseases with immune or autoimmune features (immune thrombocytopenic purpura, myasthenia gravis, thyroiditis, autoimmune hepatitis)

LABORATORY TESTS

- Decreased hemoglobin and hematocrit, elevated mean corpuscular volume, increased blood urea nitrogen (BUN) and creatinine (the BUN may also be "normal" or low if the patient has severely diminished liver function), decreased sodium (dilutional hyponatremia), and decreased potassium (as a result of secondary aldosteronism or urinary losses). Evaluation of renal function should also include measurement of urinary sodium and urinary protein from 24-hr urine collection.
- Decreased glucose in a patient with liver disease, indicating severe liver damage.
- Other laboratory abnormalities:
  1. Alcoholic hepatitis and cirrhosis: possible mild elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), usually <500 IU; AST >ALT (ratio >2:3).
  2. Extrahepatic obstruction: possible moderate elevations of ALT and AST to levels <500 IU.
  3. Viral, toxic, or ischemic hepatitis: extreme elevations (>500 IU) of ALT and AST.
  4. Transaminases may be normal despite significant liver disease in patients with jejunoileal bypass operations or hemochromatosis or after methotrexate administration.
  5. Alkaline phosphatase elevation can occur with extrahepatic obstruction, primary biliary cirrhosis, and primary sclerosing cholangitis.
  6. Serum lactate dehydrogenase is significantly elevated in metastatic disease of the liver; lesser elevations are seen with hepatitis, cirrhosis, extrahepatic obstruction, and congestive hepatomegaly.
  7. Serum gamma-glutamyl transpeptidase is elevated in alcoholic liver disease and may also be elevated with cholestatic disease (primary biliary cirrhosis, primary sclerosing cholangitis).
  8. Serum bilirubin may be elevated; urinary bilirubin can be present in hepatitis, hepatocellular jaundice, and biliary obstruction.
  9. Serum albumin: significant liver disease results in hypoalbuminemia.
  10. Prothrombin time/INR: elevation in patients with liver disease indicates severe liver damage and poor prognosis.
  11. Presence of hepatitis B surface antigen implies acute or chronic hepatitis B.
  12. Presence of antimitochondrial antibody suggests primary biliary cirrhosis, chronic hepatitis.
  13. Elevated serum copper, decreased serum ceruloplasmin, and elevated 24-hr urine may be diagnostic of Wilson's disease.
  14. Protein immunoelectrophoresis may reveal decreased α-1 globulins (alpha-1-antitrypsin deficiency), increased IgA (alcoholic cirrhosis), increased IgM (primary biliary cirrhosis), increased IgG (chronic hepatitis, cryptogenic cirrhosis).
  15. An elevated serum ferritin and increased transferrin saturation are suggestive of hemochromatosis.
  16. An elevated blood ammonia suggests hepatocellular dysfunction; serial values, however, are generally not useful in monitoring patients with hepatic encephalopathy because there is poor correlation between blood ammonia level and degree of hepatic encephalopathy.
  17. Serum cholesterol is elevated in cholestatic disorders.

18. Antinuclear antibodies (ANA) may be found in autoimmune hepatitis.
19. Alpha fetoprotein: levels >1000 pg/ml are highly suggestive of primary liver cell carcinoma.
20. Hepatitis C viral testing identifies patients with chronic hepatitis C infection.
21. Elevated level of serum globulin (especially gamma-globulins) and positive ANA test may occur with autoimmune hepatitis.
22. End-stage liver disease is characterized by decreased levels of most procoagulant factors with the notable exceptions of factor VIII and von Willebrand factor, which are elevated.

IMAGING STUDIES

- Ultrasonography is the procedure of choice for detecting gallstones and dilation of common bile ducts. The use of sonography on a periodic basis to screen for hepatocellular carcinoma in patients with cirrhosis has been questioned and should be avoided until additional data are available.
- CT scan is useful for detecting mass lesions in liver and pancreas, assessing hepatic fat content, identifying idiopathic hemochromatosis, diagnosing Budd-Chiari syndrome early, assessing dilation of intrahepatic bile ducts, and detecting varices and splenomegaly.
- MRI can be used to identify hemangiomas.
- Technetium-99m sulfur colloid scanning is rarely used but can be useful for diagnosing cirrhosis (there is a shift of colloid uptake to the spleen and bone marrow), identifying hepatic adenomas (cold defect is noted), and diagnosing Budd-Chiari syndrome (there is increased uptake by the caudate lobe).
- Endoscopic retrograde cholangiopancreatography can be used for diagnosing periampullary carcinoma and common duct stones; it is also useful in diagnosing primary sclerosing cholangitis.
- Percutaneous transhepatic cholangiography is useful when evaluating patients with cholestatic jaundice and dilated intrahepatic ducts by ultrasonography; presence of intrahepatic strictures and focal dilation is suggestive of primary sclerosing cholangitis.
- Percutaneous liver biopsy is useful in evaluating hepatic filling defects; diagnosing hepatocellular disease or hepatomegaly; evaluating persistently abnormal liver function tests; and diagnosing hemachromatosis, primary biliary cirrhosis, Wilson's disease, glycogen storage diseases, chronic hepatitis, autoimmune hepatitis, infiltrative diseases, alcoholic liver disease, drug-induced liver disease, and primary or secondary carcinoma.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoid any hepatotoxins (e.g., ethanol, acetaminophen), improve nutritional status
- Transjugular intrahepatic portosystemic shunt (TIPS) in patients with recurrent variceal hemorrhage despite optical medical therapy (Fig. EC1-83). Early use of TIPS is associated with significant reductions in treatment failure and in mortality in patients with cirrhosis who are hospitalized for acute variceal bleeding and are at high risk for treatment failure.

GENERAL Rx

- Beta-blockers with or without nitrates in patients with cirrhosis and variceal hemorrhage.
- Pruritus due to liver disease may be treated with cholestyramine 4 g/day initially. Dose can be increased to 24 g/day as needed.
- Remove excess body iron with phlebotomy and deferoxamine in patients with hemochromatosis.
- Remove copper deposits with D-penicillamine in patients with Wilson's disease.
- Long-term ursodiol therapy will slow the progression of primary biliary cirrhosis. It is, however, ineffective in primary sclerosing cholangitis.
- Glucocorticoids (prednisone 20 to 30 mg/day initially or combination therapy or prednisone and azathioprine) are useful in autoimmune hepatitis.
- Liver transplantation may be indicated in otherwise healthy patients (age <65 yr) with sclerosing cholangitis, chronic hepatitis cirrhosis, or primary biliary cirrhosis with prognostic information suggesting <20% chance of survival without transplantation. Contraindications to liver transplantation are AIDS, most metastatic malignancies, active substance abuse, uncontrolled sepsis, and uncontrolled cardiac or pulmonary disease.
- Treatment of complications of portal hypertension (ascites, esophagogastric varices, hepatic encephalopathy, and hepatorenal syndrome; refer to these individual topics in Section I).

DISPOSITION

- Prognosis varies with the etiology of the patient's cirrhosis and whether there is ongoing hepatic injury. Regression of cirrhosis has been demonstrated after antiviral therapy in some patients with chronic hepatitis C. Regression is associated with decreased disease-related morbidity and improved survival. Mortality rate exceeds 80% in patients with hepatorenal syndrome.
- If advanced cirrhosis is present and transplantation is not feasible, survival is 1 to 2 yr.
- Cirrhosis is associated with an increased risk for hepatocellular carcinoma. However, the risk is low (1% 5-year cumulative risk in alcoholic cirrhosis).

TABLE C1-36 Child-Pugh Staging Criteria

CHILD-PUGH SCORE			
Criteria	**1 Point**	**2 Points**	**3 Points**
Total serum bilirubin (mg/dl)	<2	2-3	>3
Serum albumin (g/dl)	>3.5	2.8-3.5	<2.8
INR	<1.70	1.71-2.20	>2.20
Ascites	No ascites	Ascites controlled	Ascites not controlled
Encephalopathy	No encephalopathy	Encephalopathy controlled	Encephalopathy not controlled

INTERPRETATION OF CHILD-PUGH SCORES			
	Points	**Life Expectancy**	**Perioperative Mortality**
Child Class A	5-6	15-20 yr	10%
Child Class B	7-9	Candidate for liver transplant	30%
Child Class C	10-15	1-3 yr	82%

PEARLS & CONSIDERATIONS

COMMENTS

- Thrombocytopenia and advanced Child-Pugh cases (Table C1-36) are associated with the presence of varices. These factors are useful to identify cirrhotic patients who benefit most from referral for endoscopic screening for varices.
- A combination of endoscopic and drug therapy reduces overall and variceal rebleeding in cirrhosis more than either therapy alone.
- PPI use, but not H_2RA use, is associated with risk for serious infections in patients with decompensated cirrhosis.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Cirrhosis (Patient Information)
Ascites (Related Key Topic)
Encephalopathy (Related Key Topic)
Esophageal Varices (Related Key Topic)
Hepatorenal Syndrome (Related Key Topic)
Primary Biliary Cirrhosis (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Background & Aims:
Patients with cirrhosis and minimal hepatic encephalopathy (MHE) have driving difficulties but the effects of therapy on driving performance is unclear. We evaluated whether performance on a driving simulator improves in patients with MHE after treatment with rifaximin.

Methods:
Patients with MHE who were current drivers were randomly assigned to placebo or rifaximin groups and followed up for 8 weeks (n=42). Patients underwent driving simulation (driving and navigation tasks) at the start (baseline) and end of the study. We evaluated patients' cognitive abilities, quality of life (using the Sickness Impact Profile), serum levels of ammonia, levels of inflammatory cytokines, and model for end-stage-liver disease scores. The primary outcome was the percentage of patients who improved in driving performance, calculated as follows: total driving errors = speeding + illegal turns + collisions.

Results:
Over the 8-week study period, patients given rifaximin made significantly greater improvements than those given placebo in avoiding total driving errors (76% vs 31%; *P*=.013), speeding (81% vs 33%; *P*=.005), and illegal turns (62% vs 19%; *P*=.01). Of patients given rifaximin, 91% improved their cognitive performance, compared with 61% of patients given placebo (*P*=.01); they also made improvements in the psychosocial dimension of the Sickness Impact Profile compared with the placebo group (*P*=.04). Adherence to the assigned drug averaged 92%. Neither group had changes in ammonia levels or model for end-stage-liver disease scores, but patients in the rifaximin group had increased levels of the anti-inflammatory cytokine interleukin-10.

Conclusion:
Patients with MHE significantly improve driving simulator performance after treatment with rifaximin, compared with placebo. Ⓐ

Abstract[2]

Background and Aims:
The risk of exacerbating sub-clinical hepatic encephalopathy (HE) by propofol has not been established. The aim of this study is to determine whether the use of propofol, for upper endoscopy in patients with cirrhosis, precipitates subclinical HE.

Methods:
Sixty-one patients with compensated HCV and HBV cirrhosis (CP score 5 to 6) were randomly selected and divided into two groups (intent-to-treat population) matched for age, gender, and BMI. The first group received a single propofol sedation (*N*=31, age 57±12, dose range 70 to 100mg/procedure) and the second group (*N*=30, age 56±12, dose 3 to 6mg/procedure) received a single midazolam sedation, all done by an anesthesiologist. All patients completed number connection test (NCT), cognitive function score, time to recovery, time to discharge sheets, and hemodynamic parameters before sedation, and at discharge from the endoscopy unit, 1h post-procedure. Thirty control subjects without cirrhosis were matched to the cirrhotic patients who received sedation with regard to age, gender, BMI, and education level.

Results:
A total of 58/61 cirrhotic patients (95%) had sub-clinical encephalopathy before the endoscopy (mean NCT 84.7±77s, normal <30s). No patient developed overt HE after sedation. There were no differences between groups in the incidence of adverse effects, cognitive function, MELD score, CP score, oxygen saturation, or respiratory and heart rates before and after sedation. Propofol did not exacerbate minimal HE when compared to midazolam (NCT changed from 87.5±62s prior to sedation to 74.2±58s after sedation in the propofol group versus 72.8±62s before to 85.6±72s after sedation in the midazolam group; $p<0.01$). Time to recovery (4.1±1.9min vs. 11.5±5.0min, $p<0.001$), and time to discharge (38.0±9min vs. 110±42min, $p<0.001$) were significantly shorter with propofol than midazolam. Pre- and post-procedure NCT (from 25±20s to 24±20s), cognitive function score (from 25 to 26), time to recovery (3.5±1.0min), and time to discharge (35±10min) did not change in the healthy controls.

Conclusions:
Sedation with propofol has a shorter time recovery and a shorter time to discharge than midazolam and does not exacerbate sub-clinical hepatic encephalopathy in patients with compensated liver cirrhosis. Ⓐ

Evidence-Based References

Bajaj JS et al.: Rifaximin improves driving simulator performance in a randomized trial of patients with minimal hepatic encephalopathy, *Gastroenterology* 140:478–487, 2011. Ⓐ

Khamaysi I et al.: Sub-clinical hepatic encephalopathy in cirrhotic patients is not aggravated by sedation with propofol compared to midazolam: a randomized controlled study, *J Hepatol* 54:72–77, 2011. Ⓐ

SUGGESTED READINGS

Bajaj JS et al.: Proton pump inhibitors are associated with a high rate of serious infections in veterans with decompensated cirrhosis, *Aliment Pharmacol Ther* 36:866–874, 2012.

Garcia-Pagan JC et al.: Early use of TIPS in patients with cirrhosis and variceal bleeding, *N Engl J Med* 362:2370–2379, 2010.

Garcia-Tsao G, Bosch J: Management of varices and variceal hemorrhage in cirrhosis, *N Engl J Med* 362:823–832, 2010.

Gines P, Schrier RW: Renal failure in cirrhosis, *N Engl J Med* 361:1279–1290, 2009.

Gonzalez R et al.: Meta-analysis: combination endoscopic and drug therapy to prevent variceal rebleeding in cirrhosis, *Ann Intern Med* 149:109, 2008.

Heidelbaugh JJ, Bruderly M: Cirrhosis and chronic liver failure, *Am Fam Physician* 74:756, 2006.

Jepsen P et al.: Risk for hepatocellular carcinoma in patients with alcoholic cirrhosis: a Danish nation-wide cohort study, *Ann Intern Med* 156:841, 2012.

Lederle FA, Pocha C: Screening for liver cancer: the rush to judgement, *Ann Intern Med* 156:387–389, 2012.

Tripodi A, Mannucci PM: The coagulopathy of chronic liver disease, *N Engl J Med* 365:147–156, 2011.

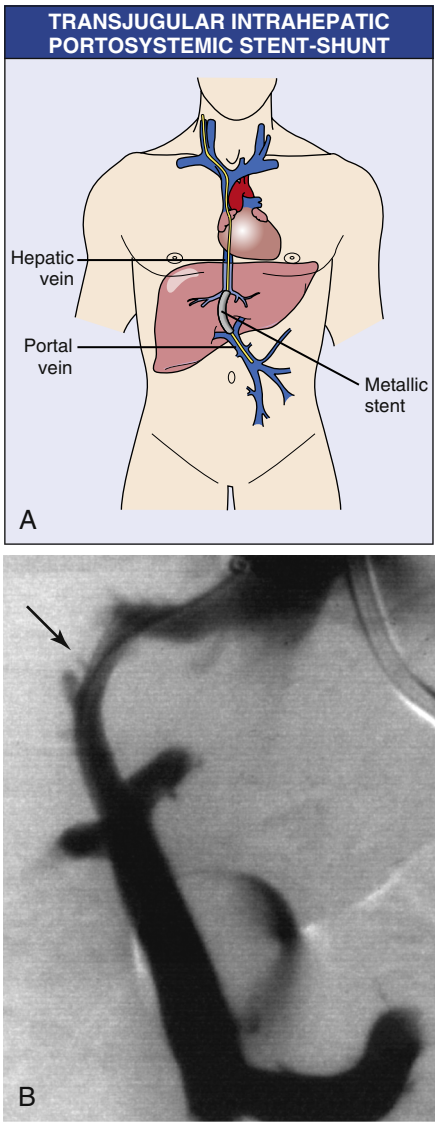

FIGURE EC1-83 Transjugular intrahepatic portosystemic stent shunt. A, An intrahepatic track has been created between the right hepatic vein and the right portal vein. **B,** The track is dilated *(arrow)* and stented, creating a shunt as demonstrated on shuntogram. (Courtesy Dr. W. K. Tso, Queen Mary Hospital, Hong Kong.)

BASIC INFORMATION

DEFINITION

Claudication refers to reproducible discomfort of muscles brought on by exertion and relieved with rest. This disorder results from a supply and demand imbalance in blood flow that is due to peripheral arterial disease (PAD). Intermittent vascular claudication is most common in the muscle groups of the lower extremities but it can also affect the upper extremities.

SYNONYMS

Intermittent claudication

ICD-9CM CODES

443.9 Peripheral vascular disease, unspecified
440.21 Intermittent claudication due to atherosclerosis

ICD-10CM CODES

I74 Arterial embolism and thrombosis
I74.5 Embolism and thrombosis of iliac artery
I73.9 Peripheral vascular disease, unspecified
I73.89 Other specified peripheral vascular diseases

EPIDEMIOLOGY & DEMOGRAPHICS

- The prevalence of PAD in the United States is approximately 12% to 21% of individuals 65 yrs or older and affects about 10 million Americans.
- Risk factors associated with development of PAD are similar to coronary atherosclerosis (CAD) and include increasing age, cigarette smoking, hypertension, diabetes mellitus, and dyslipidemia. In addition, chronic kidney disease, metabolic syndrome, and patients with elevated levels of C-reactive protein, lipoprotein(a), and homocysteine are at increased risk. Nontraditional risk factors include race/ethnicity, with African American patients being at higher risk.
- A strong correlation exists between PAD, CAD, carotid artery stenosis, and generalized cerebrovascular disease.
- The American College of Cardiology/American Heart Association (ACC/AHA) guidelines suggested the following distribution of clinical presentation of PAD in patients 50 yrs of age:
  1. Asymptomatic: 20% to 50%
  2. Atypical leg pain: 40% to 50%
  3. Classic claudication: 10% to 35%
  4. Critical limb ischemia: 1% to 2%

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The severity of symptoms varies with degree of PAD, collateral blood supply, and exertional demands.
- Classic symptoms include exertional calf pain, which causes the patient to cease exertion and the pain generally resolves within 10 minutes. Claudication can also classically present in the buttock and hip, thigh, calf, or foot, with one or more of the following signs or symptoms, depending on the level and degree of peripheral stenosis:
  1. Diminished or absent pedal pulses
  2. Bruit over the distal aorta, iliac, or femoral arteries
  3. Pallor of the distal extremities on elevation with cooling to the touch
  4. Rubor with prolonged capillary refill on dependency
  5. Trophic changes, including hair/nail loss and muscle atrophy
  6. Non-healing ulcers, necrotic tissue, and gangrene
  7. Weakness, numbness, or heaviness in the lower extremities
- True vascular claudication must be distinguished from "pseudoclaudication," which can be caused by severe venous obstruction or insufficiency, chronic compartment syndrome, spinal stenosis, osteoarthritis, and inflammatory muscle diseases. The characteristic features of pseudoclaudication that distinguish it from claudication are summarized in Table C1-37. Table C1-38 illustrates the differential diagnosis of intermittent claudication.
- Location of pain usually corresponds to analogous anatomy:
  1. Buttock and hip: aortic or iliac disease
  2. Thigh: aorta, iliac, or common femoral artery
  3. Upper two thirds of calf: superficial femoral artery
  4. Lower one third of calf: popliteal artery
  5. Foot: tibial or peroneal artery
- Asymptomatic PAD is typically diagnosed by screening studies (exercise ankle brachial index, lower extremity ultrasound) or incidentally on physical exam. Symptoms of intermittent claudication classically start distally within a muscle group (below the stenosis) and then ascend with continued activity. Rest pain that occurs with leg elevation and is relieved paradoxically by walking may suggest severe PAD. Critical limb ischemia may present as tissue ulceration and gangrene, which require prompt intervention.

ETIOLOGY

The primary cause of claudication is peripheral atherosclerosis, resulting in inability to supply enough blood to meet the metabolic demand of limb muscles first with activity then ultimately at rest.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Spinal stenosis (neurogenic or pseudoclaudication)
- Musculoskeletal disorders: arthritis or myositis
- Degenerative osteoarthritic joint disease, predominantly of the lumbar spine and hips
- Compartment or popliteal artery entrapment syndrome
- Peripheral neuropathy
- Atheromatous embolization and deep venous thrombosis
- Vasculitis: thromboangiitis obliterans, Takayasu, or giant cell arteritis

WORKUP

History and physical findings suggest the diagnosis of claudication and noninvasive studies help confirm the diagnosis.

- Measurement of resting ankle–brachial index (ABI) should be performed in all patients at risk for PAD and repeated at least once every 5 yrs. At-risk patients include:
  1. Patients with exertional leg symptoms.
  2. Non-healing lower-extremity wounds.
  3. Asymptomatic patients 50 years or older with a history of smoking or diabetes.
  4. All patients 65 yrs or older.
- An ABI is the ratio of highest ankle systolic pressure to the highest brachial systolic pressure of either arm. A normal ABI is 1.00 to 1.40. A low ABI has been shown to be an independent predictor of mortality.
- The severity of PAD is based on the resting ABI. The value of the ABI correlates with the severity of the perfusion mismatch but does not define the level of obstructive disease.
  1. Borderline disease: ABI at rest 0.91 to 0.99
  2. Mild disease: ABI at rest 0.71 to 0.90
  3. Moderate disease: ABI at rest 0.41 to 0.70
  4. Severe disease: ABI at rest <0.40
- Segmental systolic pressures are measured at the level of the thigh, calf, ankle, metatarsal, and toes. Normally, there should be <20 mm Hg difference in pressures between adjacent segments. If the gradient is >20 mm

TABLE C1-37 Characteristic Features of Pseudoclaudication That Distinguish It from Claudication

	Claudication	Pseudoclaudication
Characteristics	Limb cramping, tightness, fatigue	Similar to claudication with numbness
Location of discomfort	Lower extremity involving buttock, hip, thigh, calf, foot	Similar to claudication
Induced by exercise	Yes	Variable
Reproducible with distance walked	Consistent	Variable
Occurs with standing	No	Yes
Actions which provide relief	Stand	Sit
Time to relief	<5 min	≥30 min

Table C1-38 Differential Diagnosis of Intermittent Claudication

	Intermittent Claudication	Venous Claudication	Neurogenic Claudication
Quality of pain	Cramping	Aching, heaviness, tightness	"Pins and needles" sensation going down the leg, weakness
Onset	Gradual, consistent	Gradual; can, however, be immediate	Can be immediate
Relieved by	Stopping walking	Activity, elevation of leg	Sitting down, stooping, flexion at the waist
Location	Muscle groups (e.g., buttocks, thigh, calf)	Whole leg	Poorly localized, but can affect whole leg
Legs affected	Usually one	Usually one	Often both

From Swartz, MH: *Textbook of physical diagnosis,* 7th ed, Philadelphia, 2014, Saunders.

Hg, a significant stenosis is suspected in the interval vascular segment.
- ABI >1.3 may represent significant PAD. In such cases, measuring a toe–brachial index can increase the sensitivity of testing, as highly calcified arteries are incompressible and may have a normal or increased ABI. A toe–brachial index <0.7 is considered abnormal.
- Patients with symptoms of intermittent claudication with resting normal study should have ABI with exercise for further evaluation.
- Both ABI and segmental pressures can be taken before and after exercise by walking 1 to 2 mi/hr (5 min, or symptom-limited) to quantify severity of symptoms objectively. An ABI that decreases by at least 15% following exercise indicates significant PAD.

IMAGING STUDIES

- Duplex ultrasound can be used to assess occlusion location, length, and patency of the distal arterial system or prior grafts. Ultrasound is an excellent noninvasive modality for surveillance monitoring after revascularization.
- Continuous-wave Doppler ultrasound blood flow measurements can be used to assess location, severity, and progression of lower extremity PAD.
- In patients with prior infrainguinal bypass grafts, the long-term patency should be evaluated at regular intervals using a duplex ultrasound. The 2011 ACC guidelines recommend routine surveillance using a duplex ultrasound at approximately 3, 6, and 12 mo after graft placement and then yearly.
- Magnetic resonance angiography (MRA) and CT angiography (CTA) are effective for imaging of the aorta and peripheral lower-extremity arteries above the knee. MRA has almost replaced catheter-based angiography, with 90% sensitivity and 97% specificity in identification of hemodynamically significant stenosis in the lower extremities.
- MRA and CTA are useful to delineate the anatomy and help plan percutaneous and surgical revascularization.
- Angiography (Fig. C1-84) remains the gold standard for diagnosing PAD, especially below the knee, and is needed before revascularization.

FIGURE C1-84 Angiogram of the distal abdominal aorta and iliac arteries demonstrates an occluded left common iliac artery with extensive collateral circulation from contralateral internal iliac artery *(left panel),* which resolved after successful stent implantation *(right panel).* (Images courtesy of Bart Domatch, MD, Radiology Department, University of Texas Southwestern Medical Center, Dallas, Texas. From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Smoking cessation is vital. Smokers or former smokers should be asked about tobacco use status on each visit. Assistance and counseling for smoking cessation should be addressed.
- Aggressive risk factor modification for hypertension, dyslipidemia, and diabetes mellitus, including diet and weight loss counseling, is recommended.
- Supervised exercise training should be performed for a minimum of 30 to 45 minutes, in sessions performed at least 3 times per week for a minimum of 12 weeks.
- Home-based walking exercise program combined with group-mediated cognitive behavioral intervention significantly improved walking endurance, physical activity for patients unable or unwilling to participate in supervised exercise training.
- Lifestyle therapy in conjunction with exercise can be as or more effective than pharmacologic therapy and in some cases even better than stent revascularization, as shown by the CLEVER Study.
- New prospective data point to intermittent pneumatic compression as a promising adjunctive therapy.

ACUTE GENERAL Rx

Revascularization by an endovascular or surgical approach is usually reserved for patients with symptoms refractory to medical therapy or impending critical limb ischemia.

CHRONIC Rx

- Aspirin 81 to 325 mg daily is standard therapy. Thienopyridines (clopidogrel and ticlopidine) can be considered as alternatives, especially for those intolerant of aspirin. There are no current data to support combination treatment (CHARISMA trial).
- Hydroxymethyl glutaryl (HMG) coenzyme-A reductase inhibitor (statin) medication is indicated for all patients with PAD.
  1. LDL cholesterol level of less than 100 mg/dl is recommended.
  2. Patients with concomitant high risk for ischemic events should be treated to a goal LDL cholesterol level of less than 70 mg/dl.
- Antihypertensive therapy with beta-adrenergic blocking drugs and/or ACE inhibitors

should be administered to all hypertensive patients with PAD to reduce the risk of MI, stroke, congestive heart failure, and cardiovascular death.
   1. In non-diabetics, the target blood pressure is <140 mm Hg systolic over 90 mm Hg diastolic.
   2. In diabetics or patients with chronic renal disease, the target blood pressure is <130 mm Hg systolic over 80 mm Hg diastolic.
- Cilostazol 100 mg bid may be used in conjunction with aspirin or clopidogrel. It has been shown to increase walking distance by 50% to 67% in symptomatic patients.
- Among patients with intermittent claudication, a single randomized controlled trial has shown a 24-week treatment with ramipril resulted in significant increases in pain-free and maximum treadmill walking times compared with placebo.
- Pentoxifylline 400 mg three times per day may be considered as second-line alternative therapy to cilostazol to improve walking. However, the clinical effectiveness of pen toxifylline as therapy for claudication is not well established.
- In those patients with type II diabetes, a recent secondary analysis of the BARI 2D trial showed that an insulin-sensitizing approach (metformin, glitizones) reduces the risk of developing PAD when compared to insulin-providing therapy (glipizide, insulin). These patients also have lower rates of revascularization and amputation.
- Individuals with intermittent claudication who are offered the option of endovascular or surgical intervention should:
   1. Be provided information regarding supervised claudication exercise therapy and pharmacotherapy
   2. Receive comprehensive risk factor modification and antiplatelet therapy
   3. Have a significant disability, either being unable to perform normal work or having serious impairment of other activities important to the patient
   4. Have lower-extremity PAD lesion anatomy such that the revascularization procedure would have a low risk and a high probability of initial and long-term success
- Revascularization is indicated in patients with refractory rest pain or claudication that limits their lifestyle. It is also indicated in those with non-healing ulcers or gangrene, and in a select group of patients with functional disability. Common procedures include:
   1. Aorto-iliofemoral reconstruction or bypass or infrainguinal bypass (e.g., femoropop liteal, femorotibial).
   2. Angioplasty, often with stenting, is used primarily on short, discrete stenotic lesions in the iliac or femoropopliteal arteries.
   3. Endovascular intervention is recommended as the preferred revascularization for iliac and femoropopliteal arterial lesions.
   4. Stenting is effective primary therapy for common iliac artery and external iliac artery stenosis and occlusions. However, it is not recommended in the femoral, popliteal, or tibial arteries due to a low success rate.

COMPLEMENTARY & ALTERNATIVE MEDICINE

- A meta-analysis found that over 12 to 24 wk, *Ginkgo biloba* increased pain-free walking distance by 34 m compared with placebo, although the benefit is not well established according to ACC/AHA guidelines.
- Naftidrofuryl, a serotonin receptor inhibitor, available in Europe, has shown some efficacy in improving claudication symptoms.
- Estrogen replacement therapy, propionyl-L-carnitine, L-arginine, oral vasodilators, prostaglandins, and chelation therapy are ineffective in the treatment of intermittent claudication.

DISPOSITION

- Intermittent claudication progressing to an ischemic leg or limb loss is unusual, especially with aggressive use of conservative treatments, risk factor modification, exercise, and smoking cessation.
- The 5-yr risk for development of ischemic ulceration in patients treated for diabetes and with ABI <0.5 was 30% compared with only 5% in patients with neither characteristic.

REFERRAL

Consultation with physicians specializing in vascular medicine is recommended for the patient with threatened limb loss, rest pain, non-healing ulcers, functional disability from pain, and gangrene.

PEARLS & CONSIDERATIONS

- Approximately 70% of patients with peripheral vascular disease will have concomitant coronary artery disease.
- Beta-blockers may worsen claudication symptoms in some patients, although their underuse is associated with excess cardiovascular death. Patients with intermittent claudication are less likely to receive beta-blocker therapy after an initial myocardial infarction. Those who do not receive post-MI beta-blockers have at least a threefold higher mortality.
- Patients with peripheral vascular disease may benefit from secondary cardiovascular prevention with clopidogrel versus aspirin more so than other high-risk patients (CAPRIE trial).

COMMENTS

- Claudication is a marker for generalized atherosclerosis. This group of patients has a higher risk of death from cardiovascular events than from limb loss. Patients with claudication experience diminished overall quality of life similar to patients with diagnosed coronary artery or cerebrovascular disease.
- The ABI is more closely associated with exercise tolerance and severity of disease in persons with peripheral arterial disease than intermittent claudication or other leg symptoms.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Poor Circulation (Claudication) (Patient Information)
Peripheral Arterial Disease [PAD] (Related Key Topic)

AUTHORS: **AARON F JOLLY, M.D.,** and **PRANAV M. PATEL, M.D.**

SUGGESTED READINGS

Aboyans V et al.: Risk factors for progression of peripheral arterial disease in large and small vessels, *Circulation* 113:2623, 2006.

Abramson B et al.: Canadian Cardiovascular Society Consensus Conference: peripheral arterial disease—executive summary, *Can J Cardiol* 21(12): 997–1006, 2005.

Ahimastos AA et al.: Effect of ramipril on walking times and quality of life among patients with peripheral artery disease and intermittent claudication: a randomized controlled trial, *JAMA* 309(5):453–460, 2013.

Anderson JL et al.: Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, *Journal of the American College of Cardiology* 61(14):1555–1570, 2013.

Kakkos S et al.: Improvement of the walking ability in intermittent claudication due to superficial femoral artery occlusion with supervised exercise and pneumatic foot and calf compression: a randomized controlled trial, *Eur J Endovasc Surg* 302(2):164, 2005.

McDermott MM et al.: Leg symptoms in peripheral arterial disease: associated clinical characteristics and functional impairment, *JAMA* 286:1599, 2001.

McDermott MM et al.: Home-based walking exercise intervention in peripheral artery disease: a randomized clinical trial, *JAMA* 310(1):57–65, 2013.

McDermott MM et al.: Treadmill exercise and resistance training in patients with peripheral arterial disease with and without intermittent claudication: a randomized controlled trial, *JAMA* 301:165, 2009.

Met R et al.: Diagnostic performance of computed tomography angiography in peripheral arterial disease, *JAMA* 301(4):415–424, 2009.

Murphy et al.: Supervised exercise versus primary stenting for claudication resulting from aortoiliac peripheral artery disease six-month outcomes from the claudication: exercise versus endoluminal revascularization (CLEVER) study, *Circulation* 125:130–139, 2012.

Olin JW et al.: Peripheral artery disease: current insight into the disease and its diagnosis and management, *Mayo Clin Proc* 85(7):678–692, 2010.

Simon RW et al.: Intermittent claudication, *BMJ* 334:746, 2007.

Sobel M et al.: Antithrombotic therapy for peripheral arterial occlusive disease: American College of Chest Physicians Evidence-Based Clinical Practice guidelines (8th Edition), *Chest* 133(Suppl 6):815S–843S, 2008.

White C: Clinical practice: intermittent claudication, *N Engl J Med* 356: 1241–1250, 2007.

BASIC INFORMATION

DEFINITION

Clostridium difficile infection (CDI) is the occurrence of diarrhea and bowel inflammation associated with antibiotic use. CDI can manifest clinically in several forms ranging from fulminant diarrhea and leukocytosis associated with pseudomembranous colitis, mild to severe acute diarrhea, short-term colonization seen typically in health care facilities, and recurrent CDI with in 60 days after initial treatment occurring in 20% to 30% of cases.

SYNONYMS

Antibiotic-induced colitis
Pseudomembranous colitis
CDI

ICD-9CM CODES
008.45 *Clostridium difficile,* pseudomembranous colitis
ICD-10CM CODES
A04.7 Enterocolitis due to *Clostridium difficile*

EPIDEMIOLOGY & DEMOGRAPHICS

- Cephalosporins are the most frequent offending agent in CDI because of their high rates of use.
- The antibiotic with the highest incidence is clindamycin (10% incidence of CDI with its use).
- Since 1996, the incidence of CDI has more than doubled. Severity of CDI has also increased due to the emergence of an epidemic virulent strain (NAP1/BI/027). CDI is the most common infectious cause of healthcare-associated diarrhea in adults. In 2011, *C. difficile* was responsible for nearly half a million infections and was associated with approximately 29,000 deaths.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Abdominal tenderness (generalized or lower abdominal)
- Fever
- In patients with prolonged diarrhea, poor skin turgor, dry mucous membranes, and other signs of dehydration may be present

ETIOLOGY

The NAP1 strain is predominant among patients with *C. difficile* infection, whereas asymptomatic patients are more likely to be colonized with other strains. Risk factors for *C. difficile* (the major identifiable agent of antibiotic-induced diarrhea and colitis):

- Administration of antibiotics: can occur with any antibiotic, but occurs most frequently with clindamycin, ampicillin, cephalosporins, and fluoroquinolone
- Prolonged hospitalization
- Advanced age
- Abdominal surgery
- Underlying disease (malignancy, renal failure, debilitated status)
- Hospitalized, tube-fed patients are at risk for *C. difficile*–associated diarrhea. Clinicians should consider testing for *C. difficile* in tube-fed patients with diarrhea unrelated to the feeding solution.
- PPI and H_2 blocker therapy increases risk of CDI and recurrent CDI. Risk is 1.7-fold higher with PPIs.

DIAGNOSIS

The clinical signs of CDI generally include diarrhea, fever, and abdominal cramps after use of antibiotics.

DIFFERENTIAL DIAGNOSIS

- Gastrointestinal bacterial infections (e.g., *Salmonella, Shigella, Campylobacter, Yersinia*)
- Enteric parasites (e.g., *Cryptosporidium, Entamoeba histolytica*)
- Inflammatory bowel disease
- Celiac sprue
- Irritable bowel syndrome
- Ischemic colitis
- Antibiotic intolerance

WORKUP

- Fig. C1-85 illustrates recommendations for the diagnosis and management of diarrheal illnesses. All patients with diarrhea accompanied by current or recent antibiotic use should be tested for *C. difficile* (see later discussion). Testing and treatment for CDI is not recommended in asymptomatic individuals.
- Sigmoidoscopy (without cleansing enema) may be necessary when the clinical and laboratory diagnosis is inconclusive and the diarrhea persists.
- In antibiotic-induced pseudomembranous colitis, the sigmoidoscopy often reveals raised white-yellow exudative plaques adherent to the colonic mucosa (Fig. C1-86).

LABORATORY TESTS

- Stool test for *C. difficile* toxin: enzyme-linked immunosorbent assay for *C. difficile* toxins A and B. The latter is used most widely in the clinical setting. It has a sensitivity of 85% and a specificity of 100%.
- *C. difficile* toxin can be detected by cytotoxin tissue-culture assay (cytotoxin assay, gold standard for identifying *C. difficile* toxin in stool specimen). This test is difficult to perform and results are not available for 24 to 48 hr.
- Fecal leukocytes (assessed by microscopy or lactoferrin assay) are generally present in stool samples.
- Complete blood count usually reveals leukocytosis. A sudden increase in white blood cells to >30,000/mm^3 may be indicative of fulminant colitis.

IMAGING STUDIES

Abdominal film (flat plate and upright) is useful in patients with abdominal pain or evidence of obstruction on physical examination.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Discontinue offending antibiotic.
- Fluid hydration and correction of electrolyte abnormalities
- Probiotics to restore natural defense mechanisms may be useful as adjuvant therapy; however, evidence is limited. Probiotic trials have failed to show benefit in preventing *C. difficile*–associated diarrhea
- Fecal microbiota transplantation is an excellent treatment modality for recurrent CDI. It replaces the altered gut flora to allow colonization resistance. Trials have shown that it is more effective than vancomycin and may become standard treatment for recurrent CDI.

ACUTE GENERAL Rx

- Metronidazole 500 mg PO qid for 10 to 14 days.
- Vancomycin 125 mg PO qid for 10 to 14 days in cases resistant to metronidazole. However, vancomycin may be considered as first-line therapy in hospitalized patients who are seriously ill.
- When parenteral therapy is necessary (e.g., patient with paralytic ileus), IV metronidazole 500 mg qid can be used. It can also be supplemented with vancomycin 500 mg by nasogastric tube with intermittent clamping or retention enema.
- IV tigecycline (a broad-spectrum antibiotic used for skin or soft-tissue infection) can be used as adjunctive or alternative therapy for severe refractory *C. difficile* toxin infection.
- The addition of monoclonal antibodies against *C. difficile* toxins to antibiotic agents has been shown to reduce the recurrence of *C. difficile* infection.
- Fidaxomicin, a newer antibiotic, has shown non-inferiority to vancomycin and a lower rate of CDI recurrence.
- Fecal transplantation: When standard treatment has failed, intestinal microbiota transplantation (IMT) is an effective alternative therapy (eradication rate is 94%). It involves infusing intestinal microorganisms (in a suspension of healthy donor stool) into the intestine of a sick patient via enema, gastroscope/colonoscope, or nasojejunal tube to restore the microbiota.

SURGICAL MANAGEMENT OF CDI

- Indications: CDI unresponsive to medical therapy, fulminant colitis
- Clinical features: colonic distention, severe abdominal pain/tenderness, systemic inflammatory response syndrome. Diarrhea may be absent because of ileus.
- Surgical approaches:
  1. Traditional (subtotal or total colectomy), high mortality (50%)
  2. Colon-sparing (loop ileostomy with intraoperative colonic lavage using warmed polyethylene glycol solution via the ileostomy and instillations of postoperative vancomycin flushes via the ileostomy); lower mortality compared to traditional approach

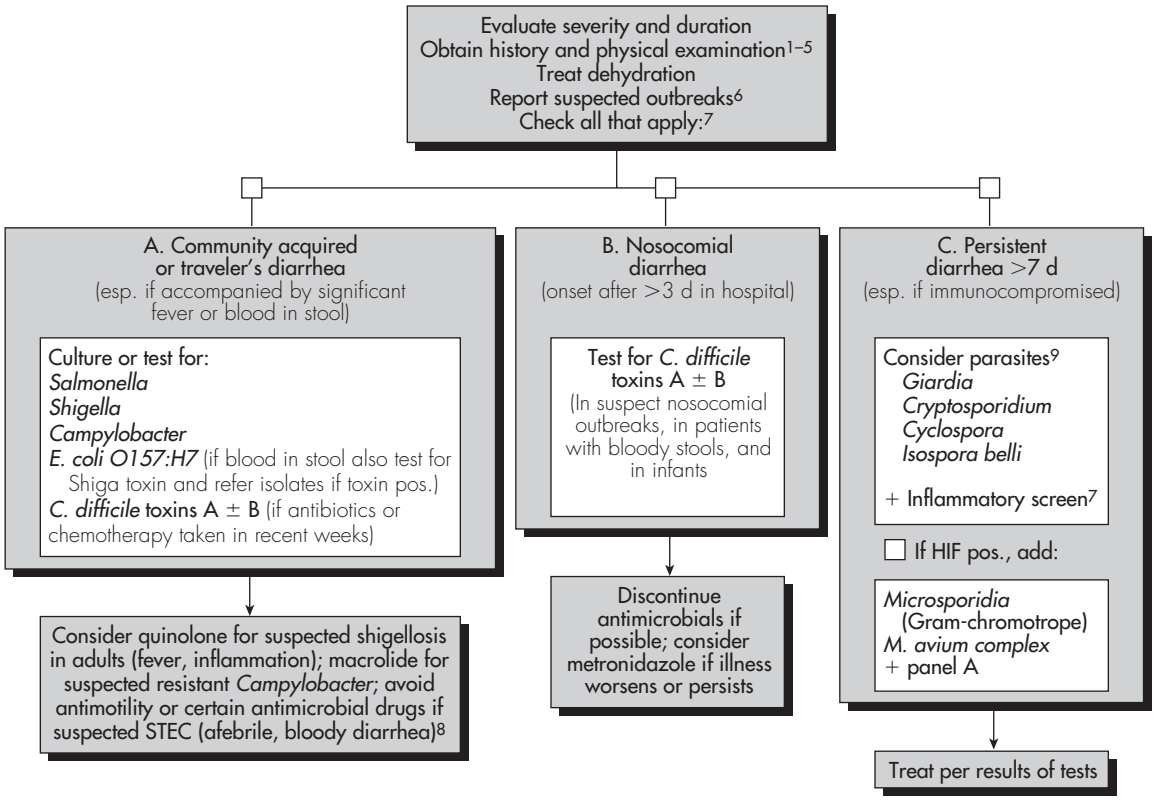

FIGURE C1-85 Recommendations for the diagnosis and management of diarrheal illnesses. 1, Seafood or seacoast exposure should prompt culture for *Vibrio* species. **2,** Traveler's diarrheal illnesses that have not responded to empirical therapy with a quinolone or TMP-SMX should be managed with the above approach. **3,** Persistent abdominal pain and fever should prompt culture for *Yersinia enterocolitic*a and cold enrichment. Right-side abdominal pain without high fever but with bloody or nonbloody diarrhea should prompt culture for Shiga toxin producing *E. coli* (STEC) O157. **4,** Proctitis in symptomatic homosexual men can be diagnosed with sigmoidoscopy. Involvement in only the distal 15 cm suggests herpesvirus, gonococcal, chlamydial, or syphilitic infection; colitis extending more proximally suggests *Campylobacter, Shigella, Clostridium difficile,* or chlamydial (LGV serotype) infection, and noninflammatory diarrhea suggests giardiasis. **5,** Postdiarrheal hemolytic uremic syndrome (HUS) should prompt testing of stools for STEC O157 and for Shiga toxin (send isolates to reference laboratory if toxin-positive but STEC-negative). **6,** Outbreaks should prompt reporting to the health department. Consider saving culture plates and isolates and freeze whole stools or swabs at –70° C. **7,** Fecal lactoferrin testing or microscopy for leukocytes can help document inflammation, which is often present in invasive colitis with *Salmonella, Shigella,* or *Campylobacter,* with more severe *C. difficile* colitis, and with inflammatory bowel disease. **8,** Some experts recommend avoiding administration of antimicrobial agents to persons in the United States who have bloody diarrhea. **9,** Commonly used tests for parasitic causes of diarrhea include fluorescence and EIA for *Giardia* and *Cryptosporidium*; acid-fast stains for *Cryptosporidium, Cyclospora, Isospora,* or *Mycobacterium* species (as well as culture for *Mycobacterium avium* complex); and special chromotrope or other stains for microsporidia. (From Guerrant RL, Van Gilder T, Steiner TS, et al: Practice guidelines for the management of infectious diarrhea. *Clin Infect Dis* 32:331-350, 2001.)

FIGURE C1-86 Pseudomembranous plaques seen with colonoscopy in a patient with *Clostridium difficile*–associated pseudomembranous colitis. (From Gorbach SL: *Infectious diseases,* ed 2, Philadelphia, 1998, Saunders.)

CHRONIC Rx

Judicious future use of antibiotics to prevent recurrences (e.g., avoid prolonged antibiotic therapy)

DISPOSITION

- Most patients recover completely with appropriate therapy. Fever resolves within 48 hr and diarrhea within 4 to 5 days. Overall mortality rate is 1% to 2.5% but exceeds 10% in untreated patients. CDI recurrence after an initial episode is 20% to 25% regardless of initial treatment with metronidazole or vancomycin. Each recurrence increases risk of repeat episodes (65% chance of recurrence after 3 CDI episodes). Recurrent CDI usually represents relapse rather than reinfection, no matter how long between episodes. Recurrent episodes are best treated with a prolonged course of oral vancomycin tapered off over several weeks to months.
- Hospital-acquired CDI is independently associated with an increased risk of in-hospital death.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pseudomembranous Colitis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Background:

Clostridium difficile is a major cause of nosocomial antibiotic-associated infectious diarrhea and pseudomembranous colitis. Detection of *C. difficile* by anaerobic bacterial culture and/or cytotoxicity assays has been largely replaced by rapid enzyme immunoassays (EIA). However, due to the lack of sensitivity of stool EIA, we developed a multiplex real-time PCR assay targeting the *C. difficile* toxin genes *tcdA* and *tcdB.* Stool samples from hospitalized pediatric patients suspected of having *C. difficile*-associated disease were prospectively cultured on cycloserine-cefoxitin-fructose agar following alcohol shock. Six testing modalities were evaluated, including stool EIA, culture EIA, and real-time PCR (*tcdA* and *tcdB*) of cultured isolates and stool samples. Real-time PCR detection was performed with *tcdA* and *tcdB* gene-specific primers and hydrolysis probes using the LightCycler platforms (Roche Diagnostics, Indianapolis, IN). A total of 157 samples from 96 pediatric patients were analyzed. The sensitivities of stool real-time PCR and stool EIA were 95% and 35%, respectively, with a specificity of 100% for both methods. The lower limit of detection of the stool real-time PCR was 30 CFU/ml of stool sample per reaction for *tcdA* and *tcdB*. This study highlights the poor performance of stool toxin EIAs in pediatric settings. Direct detection of *C. difficile* toxin genes in stool samples by real-time PCR showed sensitivity superior to that of stool and culture EIAs and performance comparable to that of real-time PCR assay of cultured isolates. Real-time PCR of DNA from stool samples is a rapid and cost-effective diagnostic modality for children that should facilitate appropriate patient management and halt the practice of serial testing by EIA. Ⓐ

Abstract[2]

Background:

Clostridium difficile infection is a serious diarrheal illness associated with substantial morbidity and mortality. Patients generally have a response to oral vancomycin or metronidazole; however, the rate of recurrence is high. This phase 3 clinical trial compared the efficacy and safety of fidaxomicin with those of vancomycin in treating *C. difficile* infection.

Methods:

Adults with acute symptoms of *C. difficile* infection and a positive result on a stool toxin test were eligible for study entry. We randomly assigned patients to receive fidaxomicin (200 mg twice daily) or vancomycin (125 mg four times daily) orally for 10 days. The primary end point was clinical cure (resolution of symptoms and no need for further therapy for *C. difficile* infection as of the second day after the end of the course of therapy). The secondary end points were recurrence of *C. difficile* infection (diarrhea and a positive result on a stool toxin test within 4 weeks after treatment) and global cure (i.e., cure with no recurrence).

Results:

A total of 629 patients were enrolled, of whom 548 (87.1%) could be evaluated for the per-protocol analysis. The rates of clinical cure with fidaxomicin were noninferior to those with vancomycin in both the modified intention-to-treat analysis (88.2% with fidaxomicin and 85.8% with vancomycin) and the per-protocol analysis (92.1% and 89.8%, respectively). Significantly fewer patients in the fidaxomicin group than in the vancomycin group had a recurrence of the infection, in both the modified intention-to-treat analysis (15.4% vs. 25.3%, P=0.005) and the per-protocol analysis (13.3% vs. 24.0%, P=0.004). The lower rate of recurrence was seen in patients with non–North American Pulsed Field type 1 strains. The adverse-event profile was similar for the two therapies.

Conclusions:

The rates of clinical cure after treatment with fidaxomicin were noninferior to those after treatment with vancomycin. Fidaxomicin was associated with a significantly lower rate of recurrence of *C. difficile* infection associated with non–North American Pulsed Field type 1 strains. (Funded by Optimer Pharmaceuticals;ClinicalTrials.gov number, NCT00314951.) Ⓐ

Abstract[3]

Background:

The epidemiology of community-associated *Clostridium difficile* infection is not well known. We performed a multicenter, case-control study to further describe community-associated *C. difficile* infection and assess novel risk factors.

Methods:

We conducted this study at 5 sites from October 2006 through November 2007. Community-associated *C. difficile* infection included individuals with diarrhea, a positive *C. difficile* toxin, and no recent (12 weeks) discharge from a health care facility. We selected controls from the same clinics attended by cases. We collected clinical and exposure data at the time of illness and cultured residual stool samples and performed ribotyping.

Results:

Of 1041 adult *C. difficile* infections, 162 (15.5%) met criteria for community-associated: 66 case and 114 control patients were enrolled. Case patients were relatively young (median 64 years), female (56%), and frequently required hospitalization (38%). Antimicrobials, malignancy, exposure to high-risk persons, and remote health care exposure were independently associated with community-associated *C. difficile* infection. In 40% of cases, we could not confirm recent antibiotic exposure. Stomach-acid suppressants were not associated with community-associated infection, and 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors appeared protective. Prevalence of the hypervirulent NAP-1/027 strain was infrequent (17%).

Conclusions:

Community-associated *C. difficile* infection resulted in a substantial health care burden. Antimicrobials are a significant risk factor for community-associated infection. However, other unique factors also may contribute, including person-to-person transmission, remote health care exposures, and 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors. A role for stomach-acid suppressants in community-associated *C. difficile* infection is not supported. Ⓐ

Evidence-Based References

Luna RA et al.: Rapid stool-based diagnosis of Clostridium difficile infection by real-time PCR in a children's hospital, *J Clin Microbiol* 49:851–857, 2011. Ⓐ

Louie TJ et al.: OPT-80-003 Clinical Study Group: Fidaxomicin versus vancomycin for Clostridium difficile infection, *N Engl J Med* 364:422–431, 2011. Ⓐ

Naggie S et al.: A case-control study of community-associated Clostridium difficile infection: no role for proton pump inhibitors, *Am J Med* 124:276.e1–276.e7, 2011. Ⓐ

SUGGESTED READINGS

Allen SJ et al.: Lactobacilli and bifidobacteria in the prevention of antibiotic –associated diarrhea and Clostridium difficile diarrhea in older inpatients (PLACIDE): a randomized, double-blind, placebo-controlled, multicenter trial, *Lancet* 382: 1249–1257, 2013.

Austin M et al.: Fecal microbiota transplantation in the treatment of Clostridium difficile infections, *Am J Med* 127:479–483, 2014.

Drekonja D et al.: Comparative effectiveness of *Clostridium difficile* treatments, a systematic review, *Ann Int Med* 155:839–847, 2011.

Grough E et al.: Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent *Clostridium difficile* infection, *Clin Infect Dis* 53(10):53, 2011.

Herpers BL et al.: IV tigecycline as adjunctive or alternative therapy for severe refractory *C. difficile infection. Clin Infect Dis* 48:1732, 2009.

Johnston B et al.: Probiotics for the prevention of *Clostridium difficile*-associated diarrhea, *Ann Intern Med* 157:878–888, 2012.

Kamboj M et al.: Relapse versus re-infection: surveillance of *Clostridium difficile* infection, *Clin Infect Dis* 53:1003, 2011.

Kelly CP, La Mont JT: *Clostridium difficile,* more difficult than ever, *N Engl J Med* 359:1932–1940, 2008.

Khanna S, Pardi DS: *Clostridium difficile* infection: new insights into management, *Mayo Clin Proc* 87(11):1106–1117, 2012.

Kwok CS et al.: Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics: meta-analysis, *Am J Gastroenterol* 107:1011–1019, 2012.

Lessa FC et al.: Burden of *Clostridium difficile* infection in the United States, *N Engl J Med* 372:825–834, 2015.

Linsky A et al.: Proton pump inhibitors and risk for recurrent *Clostridium difficile* infection, *Arch Intern Med* 170(9):772–778, 2010.

Loo VE et al.: Host and pathogen factors for *Clostridium difficile* infection and colonization, *N Engl J Med* 365:1693–1703, 2011.

Louie TJ et al.: Fidaxomicin versus vancomycin for Clostridium difficile infection, *N Engl J Med* 364:422–431, 2011.

Lowry I et al.: Treatment with monoclonal antibodies against *C. difficile* toxins, *N Engl J Med* 362:197–205, 2010.

Mattila E et al.: Fecal transplantation, through colonoscopy, is effective therapy for recurrent Clostridium difficile infection, *Gastroenterology* 142:490, 2012.

Oake N et al.: The effect of hospital-acquired *Clostridium difficile* infection on in-hospital mortality, *Arch Intern Med* 170(20):1804–1810, 2010.

van Nood E et al.: Duodenal infusion of donor feces for recurrent *Clostridium difficile, N Engl J Med* 368:407–415, 2013.

Younster I et al.: Oral, capsulized, frozen fecal microbiota transplantation for relapsing *Clostridium difficile* infection, *JAMA* 312:1772–1778, 2014.

BASIC INFORMATION

DEFINITION

The term *cluster headache* refers to attacks of severe, unilateral pain that is orbital, supraorbital, temporal, or any combination of these sites, lasting 15 to 180 minutes, and occurring from once every other day to eight times a day. The attacks are associated with one or more of the following, all of which are ipsilateral: conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, and eyelid edema. Most patients are restless or agitated during an attack.

SYNONYMS

Ciliary neuralgia
Erythromelalgia of the head
Erythroprosopalgia of Bing
Horton's headache

ICD-9CM CODES
339.00-339.02 Cluster headache
ICD-10CM CODES
G44.009 Cluster headache syndrome, unspecified, not intractable

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Estimated to occur in 0.05% to 1% of the population
PREDOMINANT SEX: Occurs in males at least five times more commonly than in females
PREDOMINANT AGE: Peak age of onset between 20 and 40 yr
GENETICS: May be inherited (autosomal dominant) in approximately 5% of cases

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- During attack: ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, facial sweating, Horner's syndrome.
- In contrast to migraine sufferers, patients are agitated and active during an attack.
- Permanent partial Horner's syndrome in 5% of patients; otherwise examination is normal.

ETIOLOGY

Activation of the posterior hypothalamic gray matter resulting in trigeminal activation coupled with parasympathetic activation. The pathophysiology remains controversial.

DIAGNOSIS

- Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15 to 180 minutes.
- Frequency of every other day to eight per day; they may cluster seasonally or at a certain time in a patient's life.
- Headache is accompanied by at least one of the following (ipsilateral):
  1. Conjunctival injection and/or lacrimation
  2. Nasal congestion and/or rhinorrhea
  3. Eyelid edema
  4. Forehead and facial sweating
  5. Miosis and/or ptosis
  6. Restlessness or agitation

DIFFERENTIAL DIAGNOSIS

- Migraine
- Trigeminal neuralgia
- Temporal arteritis
- Post-herpetic neuralgia
- Venous sinus thrombosis
- Carotid-cavernous fistula or other cavernous sinus lesions
- Other trigeminal autonomic cephalalgias
- Section II describes the differential diagnosis of headaches

WORKUP

Diagnosis is usually established by characteristic history.

IMAGING STUDIES

- None, unless history or examination suggests focal neurologic deficit or headaches change in character or are of new onset.
- MRI of the brain along with vascular imaging may be necessary to exclude secondary headaches at the time of initial diagnosis.

TREATMENT

NONPHARMACOLOGIC THERAPY

Avoidance of alcohol, histamine, nitroglycerin, and tobacco during clusters

ABORTIVE Rx

- Inhalation of 100% oxygen by face mask for 15 min often aborts an attack.
- About 75% of users of triptans (sumatriptan, zolmitriptan) will be pain free within 20 minutes. Only injectable and nasal formulations achieve a rapid response to be efficacious.
- Cafergot, octreotide, intranasal lidocaine, or dihydroergotamine may abort an attack or prevent one if given just before a predictable episode. Acute episode is typically resolved before oral analgesics become effective, although indomethacin and other NSAIDs may also be effective in prolonged attacks.
- Capsaicin nasal spray, available as a homeopathic OTC preparation, may be effective in aborting some cluster episodes, although double-blind, randomized, controlled trials are lacking due to lack of inert placebo.

PROPHYLAXIS Rx

Various medications have been tried without great success, although good responses may be obtained in up to 50% of cases. Examples include:

- Valproic acid: start at 500 mg/day
- Topiramate: up to 50 mg bid
- Verapamil: up to 480 mg/day as tolerated. Verapamil can be used as first-line prophylactic therapy and can also be used to treat chronic cluster headaches.
- Lithium: 200 mg tid with frequent monitoring and adjustment to maintain therapeutic serum level of 0.4 to 1 mEq/L. Equally effective as verapamil, but with more side effects
- Methysergide: 1 to 2 mg tid; requires familiarity with the potential adverse effects and use of "drug holidays" to decrease risk of fibrosis
- Ergotamine tartrate: 3 to 4 mg/day during clusters
- Prednisone: 60 mg PO daily for 1 wk followed by taper; headaches can return during taper
- Greater and lesser occipital nerve blocks, with the use of local anesthetics including lidocaine and bupivacaine along with steroids like Depo-Medrol, dexamethasone, or triamcinolone, may be used to shorten the duration of the cluster period. Consensus guidelines from the American Headache Society have been published recently.
- There is emerging evidence for benefit of a sphenopalatine ganglion block that may be available at some centers, for treatment and prophylaxis of cluster attacks.

DISPOSITION

Headache-free periods tend to increase with increasing age.

REFERRAL

Refractory cluster headaches may require referral to a headache specialist.

PEARLS & CONSIDERATIONS

COMMENTS

- Cluster headaches are divided into episodic (attacks lasting up to 1 yr with more than 1 mo pain-free periods) and chronic (>1 yr without remission). Episodic cluster headache is six times more common than the chronic form.
- Home oxygen therapy is reasonable for cluster headache sufferers.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Cluster Headaches (Patient Information)

AUTHOR: **SIDDHARTH KAPOOR, M.D.**

SUGGESTED READINGS

Ekbom K, Hardebo JE: Cluster headache: aetiology, diagnosis and management, *Drugs* 62(1):61, 2002.

Goadsby PJ: Trigeminal autonomic cephalalgias: pathophysiology and classification, *Rev Neurol (Paris)* 161:692, 2005.

Headache Classification Committee of the International Headache Society: the international classification of headache disorders, *Cephalgia* 24:s1, 2004.

May A: Cluster headache: pathogenesis, diagnosis, and management, *Lancet* 366:843, 2005.

Weaver, Agostoni J: Cluster headache, *Am Fam Physician* 88(2):122–128, 2013.

BASIC INFORMATION

DEFINITION

Cocaine is an alkaloid derived from the coca plant *Erythroxylum coca,* native to South America, which contains approximately 0.5% to 1% cocaine. The drug produces physiologic and behavioral effects when administered orally, intranasally, intravenously, or by inhalation after smoking. Cocaine has potent pharmacologic effects on dopamine, norepinephrine, and serotonin neurons in the central nervous system (CNS) involving alteration and blockade of cellular membrane transport and prevention of reuptake. Cocaine's second action involves the blockage of voltage-gated sodium ion membrane channels, which is responsible for its anesthetic effect. The mechanisms by which cocaine may induce myocardial ischemia or infarction are described in Fig. EC1-87. Table C1-39 describes the pharmacokinetics of cocaine according to route of administration.

SYNONYMS

Cocaine hydrochloride: topical solution (FDA approved as a topical anesthetic)
Crack: this is produced when the hydrochloride molecule is removed by ether extraction, which frees the basic cocaine molecule or "free base." Heating does not destroy the free base; rather, it melts at 98 °F and vaporizes at higher temperatures allowing it to be smoked.
Freebase: aqueous solution of cocaine hydrochloride converted to a more volatile base state by the addition of alkali, thereby extracting the cocaine base in a residue or precipitate
Street names include Bernice, Blow, C, Carrie, Cecil, Charlie, Coke, Dust, Dynamite, Flake, Gin, Girl, Gold dust, Green gold, Jet, Powder, Star dust, Paradise, Pimp's drug, Snow, Stardust, White girl, Yay, Yayo
Liquid lady = alcohol + cocaine
Speedball = heroin + cocaine
Street measures: hit (2 to 200 mg), snort, line, dose, spoon (approximately 1 g)

ICD-9CM CODES

304.2 Cocainism

ICD-10CM CODES

T40.5 Poisoning, cocaine
F14.20 Cocaine dependence, uncomplicated

EPIDEMIOLOGY & DEMOGRAPHICS

- The 1993 National Household Survey on Drug Abuse estimated that 4.5 million Americans used cocaine in 1992, with 1.3 million reporting use at least monthly. When reviewed in 1998, this had not changed significantly.
- Of note between 1993 and 1994, intravenous cocaine and heroin abusers accounted for a major new group of persons with HIV in several metropolitan areas.
- In 1999 an estimated 25 million Americans admitted that they used cocaine at least once—3.7 million the previous year and 1.5 million currently.
- The 2010 National Survey on Drug Use and Health indicates that there were 1 million individuals aged 12 yr or older who had dependence or abuse of cocaine in the preceding year. This compares with 1.1 million in 2009, 1.4 million in 2008, and 1.6 million in 2007.
- The most recent National Survey on Drug Use and Health (2012) reports that there were 1.6 million individuals aged 12 yr or older who had dependence or had abuse of cocaine in the preceding year compared with 1.4 million in 2011.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

PHASE I:
- CNS: euphoria, agitation, headache, vertigo, twitching, bruxism, unintentional tremor
- Nausea, vomiting, fever, hypertension, tachycardia

PHASE II:
- CNS: lethargy, hyperreactive deep tendon reflexes, seizures (status epilepticus)
- Sympathetic overdrive: tachycardia, hypertension, hyperthermia
- Incontinence

PHASE III:
- CNS: flaccid paralysis, coma, fixed dilated pupils, loss of reflexes
- Pulmonary edema
- Cardiopulmonary arrest

Psychological dependence manifests with habituation, paranoia, and hallucinations (cocaine "bugs").

CNS: Cerebral ischemia and infarction, cerebral arterial spasm, cerebral vasculitis, cerebral vascular thrombosis, subarachnoid hemorrhage, intraparenchymal hemorrhage, seizures, cerebral atrophy, movement disorders, and hyperthermia

Cardiac: Acute myocardial ischemia and infarction (Table C1-40), arrhythmias (Table C1-41), and sudden death, dilated cardiomyopathy and myocarditis, infective endocarditis, aortic rupture, acceleration of coronary atherosclerosis

Pulmonary: Inhalation injuries (secondary to smoking crack cocaine): cartilage and nasal septal perforation, oropharyngeal ulcers; immunologically mediated diseases: hypersensitivity pneumonitis, bronchiolitis obliterans; pulmonary vascular lesions and hemorrhage, pulmonary infarction, pulmonary edema secondary to left ventricular failure, pneumomediastinum, and pneumothorax

Gastrointestinal: Gastroduodenal ulceration and perforation; intestinal infarction or perforation, colitis

Renal: Acute renal failure secondary to rhabdomyolysis and myoglobinuria; renal infarction; focal segmental glomerulosclerosis

Obstetric: Placental abruption, low infant weight, prematurity, microcephaly

Psychiatric: Anxiety, depression, paranoia, delirium, psychosis, suicide

Adulterants such as levamisole (an immunomodulator) and clenbuterol (a beta-adrenergic

TABLE C1-39 Pharmacokinetics of Cocaine According to Route of Administration

Route of Administration	Onset of Action	Peak Effect	Duration of Action
Inhalation (smoking)	3-5 sec	1-3 min	5-15 min
Intravenous	10-60 sec	3-5 min	20-60 min
Intranasal or other mucosal	1-5 min	15-20 min	60-90 min

From Bonow RO et al: *Heart Disease,* ed 9, Philadelphia, 2012, Saunders.

TABLE C1-40 Characteristics of Patients with Cocaine-Induced Myocardial Infarction

Dose of Cocaine
Five or six lines (150 mg), up to 2 g
Serum concentration, 0.01-1.02 mg/liter
Frequency of Use
Reported in chronic, recreational, and first-time users
Route of Administration
Occurs with all routes of administration
75% of reported MIs occurred after intranasal use
Age
Mean, 34 yr (range, 17-71 yr)
20% younger than 25 yr
Sex
80-90% male
Timing
Often within minutes of cocaine use
Reported as late as 5-15 hr after use

From Bonow RO et al: *Heart disease*, ed 9, Philadelphia, 2012, Saunders.

TABLE C1-41 Cardiac Dysrhythmias and Conduction Disturbances Reported with Cocaine Use

Sinus tachycardia
Sinus bradycardia
Supraventricular tachycardia
Bundle branch block
Complete heart block
Accelerated idioventricular rhythm
Ventricular tachycardia
Ventricular fibrillation
Asystole
Torsades de pointes
Brugada pattern (right bundle branch block with ST-segment elevation in leads V_1, V_2, and V_3)

From Bonow RO et al: *Heart disease,* ed 9, Philadelphia, 2012, Saunders.

agonist) have been found mixed with cocaine. Levamisole can cause agranulocytosis, leukoencephalopathy, and cutaneous vasculitis leading to necrosis of the skin. Clenbuterol may cause tachycardia, hyperglycemia, and hypokalemia.

ETIOLOGY

Cocaine may be absorbed through different routes with varying degrees of speed:

- Nasal insufflation/snorting: 2.5 min
- Smoking: <30 sec
- Oral: 2 to 5 min
- Mucosal: <20 min
- Intravenous injection: <30 sec

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Methamphetamine ("speed") abuse
- Methylenedioxyamphetamine ("ecstasy") abuse
- Cathione ("khat") abuse
- Lysergic acid diethylamide (LSD) abuse

WORKUP

Physical examination and laboratory evaluation

LABORATORY TESTS

- Toxicology screen (urine): cocaine is metabolized within 2 hr by the liver to major metabolites, benzoylecgonine and ecgonine methyl ester, which are excreted in the urine. Metabolites can be identified in urine within 5 min of IV use and up to 48 hr after oral ingestion.
- Blood: CBC, electrolytes, glucose, BUN, creatinine, calcium.
- Arterial blood gas analysis.
- ECG.
- Serum creatine kinase and troponin concentration.

Rx TREATMENT

There is no specific antidote, and at present, no drug therapy is uniquely effective in treating cocaine abuse and dependence. Modifying cocaine's pharmacokinetic properties by sequestering or hydrolyzing it in serum and limiting its access to its sites of action may prove helpful by using a bacterial cocaine esterase, currently investigational. Adulterants (such as levamisole and clenbuterol, discussed earlier), contaminants, and other drugs may be admixed with street cocaine and should be kept in mind with patients presenting with unusual manifestations. Amantadine may provide effective treatment for cocaine-dependent patients with severe cocaine withdrawal symptoms, as well as the other dopamine agonist bromocriptine (1.5 mg PO tid), which may alleviate some of the symptoms of craving associated with acute cocaine withdrawal.

ACUTE GENERAL Rx

Acute cocaine toxicity requires following advanced poisoning treatment and life support. A suspected "body packer" should have an abdominal radiograph to detect the continued presence of cocaine-containing condoms in the intestinal tract. If present, gentle catharsis with charcoal and mineral oil should be performed with ICU admission and monitoring.

SPECIFIC TREATMENT

INHALATION: Wash nasal passages

AGITATION:

- Check STAT glucose
- Diazepam 15 to 20 mg PO or 2 to 10 mg IM or IV for severe agitation

HYPERTHERMIA:

- Check rectal temperature, creatine kinase, electrolytes
- Monitor with continuous rectal probe; bring temperature down to 101 °F within 30 to 45 min

RHABDOMYOLYSIS:

- Vigorous hydration with urine output at least 2 ml/kg
- Mannitol or bicarbonate for rhabdomyolysis resistant to hydration

SEIZURE MANAGEMENT (STATUS EPILEPTICUS):

- Diazepam 5 to 10 mg IV over 2 to 3 min; may be repeated every 10 to 15 min.
- Lorazepam 2 to 3 mg IV over 2 to 3 min; may be repeated.
- Phenytoin loading dose 15 to 18 mg/kg IV at a rate not to exceed 25 to 50 mg/min under cardiac monitoring.
- Phenobarbital loading dose 10 to 15 mg/kg IV at a rate of 25 mg/min; an additional 5 mg/kg may be given in 30 to 45 min if seizures are not controlled.
- For refractory seizures, consider:
  1. Pancuronium 0.1 mg/kg IV
  2. Halothane general anesthesia
  3. Both require EEG monitoring to determine brain seizure activity.

HYPERTENSION: Cocaine-induced hypertension usually responds to benzodiazepines. If this fails:

- Consider arterial line for continuous blood pressure monitoring
- Avoid the use of calcium channel blockers because they may potentiate the incidence of seizures and death, especially in body packers.
- The use of beta-blockers may exacerbate cocaine-induced vasoconstriction.
- Phentolamine (unopposed adrenergic effects) or nitroglycerin may be required.
- If diastolic pressure >120 mm Hg: hydralazine hydrochloride 25 mg IM or IV; may repeat q1h.
- If hypertension is uncontrolled or hypertensive encephalopathy is present: sodium nitroprusside initially at 0.5 mg/kg/min not to exceed 10 mg/kg/min.

CHEST PAIN:

- Chest radiograph, ECG, cardiac enzymes.
- Benzodiazepines for agitation.
- Acetylsalicylic acid and nitroglycerin for ischemic pain. (Aspirin is contraindicated if dissection is suspected.)
- Percutaneous transluminal coronary angioplasty possibly better than thrombolysis for cocaine-associated myocardial infarction.
- Phentolamine will reverse cocaine-induced vasoconstriction and may be administered 5 to 10 mg every 5 to 10 minutes.
- The use of beta-adrenergic blockers remains controversial because of the unopposed alpha-adrenergic effects of cocaine.
- If beta-blockers are to be used, this should be preceded by administration of phentolamine to prevent unopposed alpha-adrenergic stimulation. Many authors recommend not using beta-blockers until the cocaine has been systemically eliminated.

VENTRICULAR ARRHYTHMIAS (CONSIDERATIONS):

- Antiarrhythmic agents should be used with caution during the early period after cocaine exposure as a result of their proarrhythmic and proconvulsant effects.
- Lidocaine 1.5 mg/kg IV bolus followed by IV infusion (controversial: may be proarrhythmic and proconvulsant).
- Termination of ventricular arrhythmias may be resistant to lidocaine and even cardioversion.
- $NaHCO_3$– is under investigation in cocaine-mediated conduction abnormalities and rhythm disturbances.
- In a cardiac arrest situation secondary to cocaine toxicity, vasopressin offers a theoretical advantage over epinephrine as it increases coronary blood flow and myocardial oxygen availability.

DISPOSITION

Although many patients who use cocaine may not require treatment because of the short half-life of the drug, others may require specific treatment for possible cocaine-related complications.

REFERRAL

Consider psychotherapy or behavioral therapy once stable. There is some evidence that topiramate 300 mg orally daily added to cognitive behavioral therapy may be beneficial in patients with severe withdrawal symptoms.

PEARLS & CONSIDERATIONS

- Cocaine-induced vasoconstriction may be exacerbated by the use of selective and nonselective beta-adrenergic blocking agents.
- The use of lidocaine in treating ventricular arrhythmias may precipitate seizures and further arrhythmias.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Cocaine Abuse and Dependence (Patient Information)
Drug Abuse (Patient Information)
Abuse, Drug (Related Key Topic)

AUTHOR: **SAJEEV HANDA, M.D.**

SUGGESTED READINGS

Centers for Diseases Control and Prevention (CDC): atypical reactions associated with heroin use – five states, January-April 2005, *MMWR Morb Mortal Wkly Rep* 54(32):793, 2005.

Dinwahar N, Woods JH, Sunahara RK: Bacterial cocaine esterase: a protein-based therapy for cocaine overdose and addiction, *Future Med Chem* 4(2):137–150, 2012.

Gross RL, Brucker J: A novel cutaneous vasculitis syndrome induced by levasimole contaminated cocaine, *Clin Rheumatol* 30(10):1385, 2011.

Field JM: *Advanced cardiovascular life support resource text for instructors and experienced providers*, 2008. 259–287.

Jones JH, Wier WB: Cocaine associated chest pain, *Med Clin North Am* 89(6):1323, 2005.

Lange RA, Hillis LD: Cardiovascular complications of cocaine use, *N Engl J Med* 345:351, 2001.

Mokhlesi B, Corbridge T: Adult toxicology in critical care: part II: specific poisonings, *Clin Chest Med* 123(3):897, 2003.

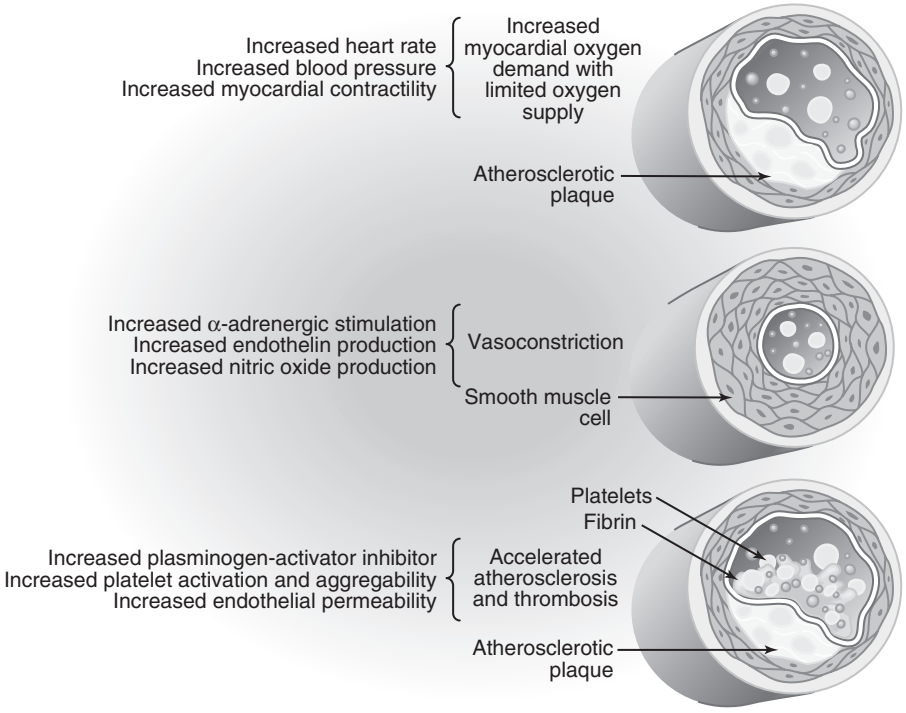

FIGURE EC1-87 The mechanisms by which cocaine may induce myocardial ischemia or infarction. Cocaine may cause increase in the determinants of myocardial oxygen demand when oxygen supply is limited *(top),* when intense vasoconstriction of the coronary arteries occurs *(middle)*, or when accelerated atherosclerosis and thrombosis are present *(bottom).* (From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine*, ed 8, Philadelphia, 2010, Saunders.)

BASIC INFORMATION

DEFINITION

Coccidioidomycosis is an infectious disease caused by inhaling the spores of the fungus *Coccidioides immitis.* Clinical syndromes range from subclinical pulmonary disease to pneumonia and disseminated disease mostly in immunocompromised hosts. Most cases occur in the southwest part of the U.S.

SYNONYMS

San Joaquin Valley fever

ICD-9CM CODES

114.0 *Coccidioides* pneumonia
114.1 Cutaneous or extrapulmonary (primary) coccidioidomycosis
114.3 Disseminated or prostate coccidioidomycosis
114.5 Pulmonary coccidioidomycosis
114.2 Coccidioidal meningitis
114.4 Chronic coccidioidomycosis

ICD-10CM CODES

B38.9 Acute pulmonary coccidioidomycosis
B38.3 Cutaneous coccidioidomycosis
B38.89 Other forms of coccidioidomycosis
B38.2 Pulmonary coccidioidomycosis, unspecified
B38.4 Coccidioidomycosis meningitis
B38.1 Chronic pulmonary coccidioidomycosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Estimated annual infection rate 150,000 persons, predominantly in southwest U.S. and appears to be rising due to increased population and construction in the area.

PEAK INCIDENCE: Seasonal in endemic areas with the highest risk being in the dry season after a rainy season as the mold lies a few inches below desert surface in soil and can become aerosolized.

PREVALENCE: 28.65 cases per 1 million population in the southwest U.S. in 2002 based on patients requiring hospital admission.

PREDOMINANT SEX: Males, between the ages of 25 and 55 yr

Clinical disease more severe in older children and adults

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The clinical manifestations vary widely according to the host, the severity of the illness, and location of dissemination.
- Asymptomatic infections or illness consistent with a nonspecific upper respiratory tract infection in at least 60%.
- Symptoms of primary infection—cough, malaise, fever, chills, night sweats, anorexia, weakness, and arthralgias (desert rheumatism)—in remaining 40% within 3 wk of exposure.
- Erythema nodosum and erythema multiforme more common in women.
- Scattered rales and dullness on percussion.
- Spontaneous improvement within 2 wk of illness, with complete recovery usual.
- Pulmonary nodules and cavities in <10% of those patients with primary infection; half of these patients asymptomatic.
- In a small portion of these patients: a progressive pneumonitis, often with a fatal outcome.
- Immunocompromised or diabetic patients may progress to chronic pulmonary disease.
- Over many years, granulomas rupture, leading to new cavity formation and continued fibrosis, often accompanied by hemoptysis.
- Disseminated or extrapulmonary disease in approximately 0.5% of acutely infected patients.
  1. Early signs of probable dissemination: fever, malaise, hilar adenopathy, and elevated ESR persisting in the setting of primary infection.
  2. Most organs are susceptible to dissemination, with heart and GI tract generally spared.
- Musculoskeletal involvement: bone lesions often unifocal, ribs, long bones, and vertebral lesions are common.
  1. Joint lesions predominantly unifocal, most commonly involving the ankle and knee, and often accompanying adjacent sites of osteomyelitis.
- Meningeal involvement: headache, fever, weakness, confusion, lethargy, cranial nerve defects, seizures; meningeal signs often minimal or absent.
- Cutaneous involvement: variable lesions—pustules, papules, plaques, nodules, ulcers, abscesses, or verrucous proliferative lesions.
  1. Dissemination and fatal outcomes most common in men, pregnant women, neonates, immunocompromised hosts, and individuals of dark-skinned races, especially those of African, Filipino, Mexican, and Native American ancestry.

ETIOLOGY

- *Coccidioides immitis* is endemic to North and South America.
- In the U.S., endemic areas coincide with the Lower Sonoran Life Zone, with semiarid climate, sparse flora, and alkaline soil in Arizona, California, New Mexico, and Texas.
- Fungus exists in the mycelial phase in soil, having barrel-shaped hyphae (arthroconidia). Arthrospores are aerosolized and deposit in the alveoli, then fungus converts to thick-walled spherule.
- Internal spherical spores (endospores) are released through spherule rupture and mature into new spherules (parasitic cycle).
- Fungus incites a granulomatous reaction in host tissue, usually with caseation necrosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute pulmonary coccidioidomycoses:
  1. Community-acquired pneumonias caused by *Mycoplasma* and *Chlamydia*
  2. Granulomatous diseases, such as *Mycobacterium tuberculosis* and sarcoidosis
  3. Other fungal diseases, such as *Blastomyces dermatitidis* and *Histoplasma capsulatum*
- Coccidioidomas: true neoplasms

WORKUP

Suspected in patients with a history of residence or travel in an endemic area, especially during periods favorable to spore dispersion (e.g., dust storms and drought followed by heavy rains)

LABORATORY TESTS

- CBC to reveal eosinophilia, especially with erythema nodosum
- Routine chemistries: usually normal but may reveal hyponatremia
- Elevated serum levels of IgE; associated with progressive disease
- CSF cell counts and chemistry: pleocytosis with mononuclear cell predominance associated with hypoglycorrhachia and elevated protein level
- Definitive diagnosis based on demonstration of the organism by culture from body fluids or tissues
  1. Greatest yield with pus, sputum, synovial fluid, and soft tissue aspirations, varying with the degree of dissemination
  2. Possible positive cultures of blood, gastric aspirate, pleural effusion, peritoneal fluid, and CSF, but less frequently obtained
  3. Lab personnel are at risk of infection by inhalation on opening culture plates so lab should be notified the disease is suspected, but it is not contagious from person to person.
- Serologic evaluations
  1. Latex agglutination and complement fixation
  2. Elevated serum complement-fixing antibody (CFA) titers ≥1:32 strongly correlated with disseminated disease, except with meningitis where lower titers seen
  3. In meningeal disease: CFA detected in CSF except with high serum CFA titers secondary to concurrent extraneural disease
  4. Enzyme-linked immunosorbent assay (ELISA) against a 33-kDa spherule antigen to detect and monitor CNS disease
- PCR
- Skin test: currently not available, and its use was limited as patients with severe disease may be anergic. Skin testing may still have use in epidemiologic surveys.

IMAGING STUDIES

Chest x-ray:

- Reveals unilateral infiltrates, hilar adenopathy, or pleural effusion in primary infection
- Shows areas of fibrosis containing usually solitary, thin-walled cavities that persist as residua of primary infection
- Possible coccidioidoma, a coinlike lesion representing a healed area of previous pneumonitis

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive care in mild symptomatic disease
- In patients with extrapulmonary manifestations involving draining skin, joint, and soft tissue infection: local wound care to avoid possible bacterial superinfection

ACUTE GENERAL Rx

- In general, drug therapy is not required for patients with asymptomatic pulmonary disease and most patients with mild symptomatic primary infection.
- Chemotherapy is indicated under the following circumstances:
  1. Severe symptomatic primary infection
  2. High serum CFA titers
  3. Persistent symptoms >6 wk
  4. Prostration
  5. Progressive pulmonary involvement
  6. Pregnancy
  7. Infancy
  8. Debilitation
  9. Concurrent illness (e.g., diabetes, asthma, COPD, malignancy)
  10. Acquired or induced immunosuppression
  11. Racial group with known predisposition for disseminated disease
- Fluconazole
  1. Most commonly, oral therapy with 400 mg/day up to 1.2 g/day appears to be the drug of choice for meningeal and deep-seated mycotic infections.
  2. In patients with AIDS, fluconazole may be considered the drug of choice for initial and maintenance therapy.
  3. All patients with coccidioidal meningitis should continue azole therapy indefinitely.
- Itraconazole
  1. 400 to 600 mg/day achieves 90% response rate in bone, joint, soft tissue, lymphatic, and genitourinary infections.
  2. Itraconazole may be more efficacious than fluconazole in the treatment of skeletal (bone) infections.
- Posaconazole is a new triazole that has recently been approved for use for systemic mycoses such as coccidioidomycosis; its relative efficacy compared to other agents will need additional clinical study.
- For pulmonary infections, treatment with either fluconazole or itraconazole, given for 6 to 12 wk, appears to be equal in efficacy.
- Amphotericin B is the classic therapy for disseminated extraneural disease, dose 0.6 to 1 mg/kg/day, qd for the first week then 0.8 mg/kg every other day, for a total dose of 1 to 2.5 g or until clinical and serologic remission is accomplished.
  1. Local instillation into body cavities such as sinuses, fistulae, and abscesses has been adjunct to therapy.
  2. Liposomal amphotericin B is probably equally effective.
  3. Duration of therapy for extraneural disease is undefined but probably about 1 yr.
- With meningeal disease: fluconazole 400 to 1000 mg PO q24h indefinitely
  1. Intrathecal amphotericin B is the alternate treatment modality, given alone or preceding the use of oral agents.
  2. Begin in doses of 0.01 to 0.025 mg/day, gradually increasing the dose as tolerated, to 0.5 mg/day with the patient in Trendelenburg's position.
  3. If given via Ommaya reservoir, as in ventriculitis, dose may be increased to 1.5 mg/day if tolerated.
  4. Concomitant parenteral therapy with amphotericin B is used for simultaneous extraneural disease as standard doses and with purely meningeal disease in smaller doses, although not strictly indicated.
  5. Intrathecal therapy is usually given three times a week for at least 3 mo, then discontinued or gradually tapered until once every 6 wk through 1 yr of therapy.
  6. Patients need routine monitoring of CSF, CFA, cell count, and chemistries for at least 2 yr following cessation of therapy.
- For osteomyelitis, soft tissue closed-space infections, and pulmonary fibrocavitary disease: surgical debridement, drainage, or resection, respectively, in addition to oral azole therapy or parenteral administration of amphotericin B.

CHRONIC Rx

For chronically immunocompromised patients, lifelong therapy with oral azoles or amphotericin B

DISPOSITION

- Prognosis for primary symptomatic infection is good.
- Immunocompromised patients are most likely to have disseminated disease and higher morbidity and mortality.

TABLE C1-42 Risk Factors for Poor Outcome in Young Patients with Active Coccidioidomycosis

Primary Infections
Severe, prolonged (≥6 wk), or progressive infection
Risk Factors for Extrapulmonary Dissemination
Primary or acquired cellular immune dysfunction (including patients receiving tumor necrosis factor inhibitors)
Neonates, infants, the elderly
Male sex (adult)
Filipino, African, Native American, or Latin American ethnicity
Late-stage pregnancy and early postpartum period
Standardized complement fixation antibody titer >1:16 or increasing titer with persisting symptoms
Blood group B
HLA class II allele-DRBI*1301

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

- Risk factors for poor outcome in patients with active coccidioidomycosis are described in Table C1-42.

REFERRAL

- To surgeon for the evaluation of chronic hemoptysis, enlarging cavitary lesions despite chemotherapy and intrapleural rupture, osteomyelitis, and other synovial or soft tissue closed space infections
- For neurosurgical consultation in patients with meningeal disease to establish the delivery route of intrathecal drug therapy

PEARLS & CONSIDERATIONS

COMMENTS

- Although coccidioidomycosis is a great imitator, a diagnosis will become apparent if a high degree of suspicion is maintained and appropriate testing (serologic testing, cultures, and histology) is performed.
- Infected body fluids contained within a closed moist environment (e.g., sputum in a specimen cup) provide the opportunity for the fungus to revert to its hyphal form whereby spores may be made airborne on opening of the container. This is a biohazard for laboratory personnel. Purulent drainage into a cast, allowing conversion of fungus to the saprophytic phase, has been responsible for acute disease when the cast was opened and the spores were unintentionally made airborne.
- Patients with a remote history of exposure, especially if immunosuppressed by medication or disease, may reactivate primary disease and suffer rapid dissemination.
- Although cardiac disease is rare, constrictive pericarditis in the setting of disseminated coccidioidomycosis has been documented and is potentially fatal.
- Organ transplant recipients may develop disease if the transplant donor has unrecognized active coccidioidomycosis at the time of death.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Coccidioidomycosis (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Adam RD et al.: The spectrum and presentation of disseminated coccidioidomycosis, *Am J Med* 122:770–777, 2009.

Anstead GM, Graybill JR: Coccidiomycosis, *Infect Dis Clin North Am* 20:621–643, 2006.

Blair JE et al.: Coccidioidomycosis in patients with hematologic malignancies, *Arch Intern Med* 165(1):113–117, 2005.

Parish JM, Blair JE: Coccidioidomycosis, *Mayo Clin Proc* 83(3):343–349, 2008.

Szeyco LA et al.: Vertebral coccidiodomycosis: presentation and multidisciplinary management, *Am J Med* 125:304–314, 2012.

Wang CY et al.: Disseminated coccidioidomycosis, *Emerg Infect Dis* 11(1): 177–179, 2005.

BASIC INFORMATION

DEFINITION

Cogan's syndrome is an autoimmune inner ear disorder that is temporally associated with interstitial keratitis and is thought to be the result of an underlying systemic vasculitis.

SYNONYMS

Cogan syndrome

ICD-9CM CODES
370.52 Cogan's syndrome
ICD-10CM CODES
H16.3 Interstitial and deep keratitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: No population studies are available for incidence calculation. More than 100 cases have been described in the literature.
PREVALENCE: No population studies are available for prevalence analysis.
PREDOMINANT SEX: No gender preference.
PREDOMINANT AGE: Median age of onset is 25 yrs.
GENETICS: Unknown.
RISK FACTORS: None.

PHYSICAL FINDINGS & CLINICAL PRESENTATION (Table EC1-43)

- Clinical hallmarks: Cogan's syndrome is characterized by an acute or subacute or recurrent onset of inner ear loss of function resembling Meniere's disease (tinnitus, vertigo, and gradual hearing loss). The resultant hearing loss typically is bilateral. This is temporally related to the onset of a nonsyphilitic keratitis manifested as pain, redness, and blurry vision in the affected eye. Keratitis and cochleovestibular symptoms should occur within 2 yr of each other. Systemic vasculitis features are marked by large-vessel vasculitis and can occur in up to 10% of patients. Systemic vasculitis features are marked by large vessel vasculitis and can occur in up to 10% of patients. This leads to aortic regurgitation. Medium vessel vasculitis resembling polyarteritis nodosa to small vessel vasculitis manifestations are possible.
- Constitutional: fever, headache, weight loss, malaise
- Ocular: redness, pain, and blurred vision as a result of interstitial keratitis (72% to 100%). Scleritis or episcleritis (23%).
- Hearing/Vestibular: hearing loss to deafness, usually bilateral (100%), vertigo (90%), tinnitus (80%). Imbalance with associated nausea, vomiting.
- Cardiovascular: aortitis (aortic aneurysm, aortic insufficiency)
- Musculoskeletal: arthralgia, arthritis, myalgia
- Gastrointestinal: abdominal pain (13% to 16%)
- Renal: hematuria (7%), glomerulonephritis (3%)
- Dermatologic: cutaneous nodules, rash

TABLE EC1-43 Systemic Manifestations of Cogan's Syndrome

Manifestations	Percentage of Cases (%)
Fever	25
Fatigue	20
Arthralgias/myalgias	15
Arthritis	15
Weight loss	15
Abdominal pain	10
Gastrointestinal bleeding	10
Lymphadenopathy	10
Hepatomegaly	10
Splenomegaly	10
Central nervous system findings	5
Pleuritis	5
Rash	5
Peripheral nervous system findings	<5
Polychondritis	<5

From Hochberg MC et al: *Rheumatology,* ed 4, St Louis, 2008, Mosby.

ETIOLOGY

The exact etiology of Cogan's syndrome is unknown. It is an autoimmune disease, which is supported by the binding of autoantibodies from patients with Cogan's syndrome to the cochlea in mice in passive transfer studies. Infection is thought to be a trigger for Cogan's syndrome. Some HLA loci, including HLA-B17, HLA-A9, HLA-Bw35, and HLA-Cw4, correlate with the disorder.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infectious diseases
  1. Syphilis
  2. Tuberculosis, Lyme disease, chlamydia, leprosy, brucellosis, mumps, EBV, herpes zoster, and herpes simplex; rubeola should be considered in the differential for interstitial keratitis
- Rheumatology
  1. ANCA-associated vasculitis: granulomatosis with polyangiitis (Wegener's granulomatosis)
  2. Takayasu's arteritis
  3. Giant cell arteritis
  4. Rheumatoid arthritis with vasculitis
  5. Polyarteritis nodosa
  6. Behçet's disease
  7. Sarcoidosis
- Neurology
  1. Susac syndrome
- Neoplastic
  1. Lymphoma (CNS)
- Miscellaneous
  1. Vogt-Koyanagi-Harada syndrome

LABORATORY TESTS

- Inflammatory markers are often elevated, including the erythrocyte sedimentation rate (ESR) and C-reactive protein.
- Complete blood cell count with differential; may show leukocytosis.
- ANCA serology test to exclude ANCA-associated vasculitis.
- Serologic test result should be negative for syphilis.

IMAGING STUDIES

- MRI with gadolinium of the brain to rule out noninner ear causes for acute or subacute hearing loss and vestibular dysfunction. Brain MRI can range from normal to gadolinium enhancement of the vestibular-cochlear structures.
- Magnetic resonance angiography (MRA) of the aorta and its proximal branches may be used to assess for vascular inflammation. This can be supportive of large vessel vasculitis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cochlear implant

ACUTE GENERAL Rx

- Treatment guidelines are based on grade C (fair evidence from ancillary studies) recommendations.
- Eye symptoms: Topical corticosteroids, mydriatics may be considered.
- Fluconazole vestibuloauditory symptoms: Oral prednisone 1 to 2 mg/kg/day is recommended.
- Vasculitis symptoms: Oral prednisone 1 to 2 mg/kg/day is recommended. Oral or intravenous cyclophosphamide should be considered for life-threatening features.

CHRONIC Rx

- Methotrexate or azathioprine may be considered as steroid-sparing agent.

DISPOSITION

- Ocular outcomes are good.
- Hearing loss may occur in up to 50% of cases.

REFERRAL

- Refer to ophthalmologist for complete ocular examination, including slit-lamp examination.
- Refer to rheumatologist for all patients with suspected disease.
- Refer to audiologist for complete hearing assessment.
- Refer to otolaryngologist for confirmation of sensorineural hearing loss.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **SAMUEL H. POON, M.D.**

SUGGESTED READINGS

Antonios N et al.: Cogan syndrome: an analysis of reported neurological manifestations, *Neurologist* 18:55–63, 2012.

Cogan DG: Syndrome of nonsyphilitic interstitial keratitis and vestibuloauditory symptoms, *Arch Ophthalmol* 33:144–149, 1945.

Greco A et al.: Cogan's syndrome: an autoimmune inner ear disease, *Autoimmun Rev* 12:396–400, 2013.

BASIC INFORMATION

DEFINITION

Colorado tick fever is an acute, self-limited febrile illness caused by infection with a Coltivirus.

ICD-9CM CODES
066.1 Colorado tick fever
ICD-10CM CODES
A93.2 Colorado tick fever

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence: approximately 330 cases reported per year in the U.S.
- Demographics: children and adults of both genders.
- Geography: Rocky Mountains at elevations of 4000 to 10,000 feet. Sporadic cases have been reported from areas of California outside the range of *Dermacentor andersoni.*
- Colorado has the highest incidence (Fig. EC1-88).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Incubation: 3 to 4 days is usual but can be up to 14 days
- First symptoms: fever, chills, severe headache, severe myalgias, and hyperesthetic skin
- Initial signs and symptoms:
  1. Tick bite
  2. Fever and chills
  3. Headache
  4. Myalgias
  5. Weakness
  6. Prostration and indifference
  7. Injected conjunctivae
  8. Erythematous pharyngitis
  9. Lymphadenopathy
  10. Maculopapular or petechial rash

These first symptoms last for 1 wk or less but 50% of patients have a febrile relapse 2 to 3 days after an initial remission. Weakness and fatigue may persist for several months after the acute phase(s). This chronic phase is more likely in older patients.

In children, 5% to 10% of cases are complicated by aseptic meningitis. In adults, rare complications include pneumonia, hepatitis, myocarditis, and epididymo-orchitis. Vertically transmitted fetal infection is possible.

ETIOLOGY

- Infectious agent: Coltiviruses; 7 species, including three in the U.S.
- Vector: wood tick, *D. andersoni.*
- Pathogenesis: human transmission occurs by tick bite. Tick season spans from March to September. The virus infects marrow erythrocytic precursors, explaining the protracted disease course because viremia lasts for the lifespan of the infected red blood cell.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rocky Mountain spotted fever
- Influenza
- Leptospirosis
- Infectious mononucleosis
- CMV infection
- Pneumonia

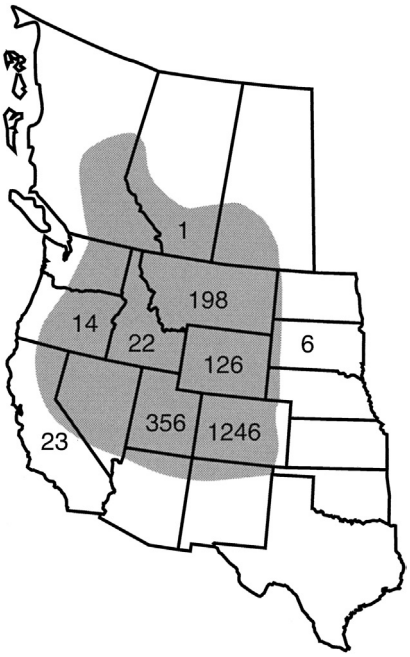

FIGURE EC1-88 Geographic distribution of *Dermacentor andersoni* (wood ticks) and reported cases of Colorado tick fever, 1990-1996, United States and Canada. (From Mandell GL: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 6, New York, 2005, Churchill Livingstone.)

- Hepatitis
- Meningitis
- Endocarditis
- Scarlet fever
- Measles
- Rubella
- Typhus
- Lyme disease
- Immune thrombocytopenic purpura (ITP)
- Thrombotic thrombocytopenic purpura (TTP)
- Kawasaki disease
- Toxic shock syndrome
- Vasculitis

WORKUP

Consider Colorado tick fever in the presence of the above symptoms associated with travel to an endemic area coupled with a history of tick exposure.

LABORATORY TESTS

- Complete blood count
  1. Leukopenia
  2. Atypical lymphocytes
  3. Moderate thrombocytopenia
- Virus identification in red blood cells by indirect immunofluorescence
- Serology with enzyme-linked immunosorbent assay, neutralization, or complement fixation

TREATMENT

- No specific therapy, although Coltiviruses are sensitive to ribavirin
- Bed rest, fluids, acetaminophen
- Avoid aspirin because of thrombocytopenia
- Prevention: tick avoidance measures

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Jaffar FM et al.: Recombinant VP-7-based enzyme-linked immunosorbent assay for detection of immunoglobulin G antibodies to Colorado tick fever virus, *J Clin Microbiol* 41:2102, 2003.

Tsai TF: Coltiviruses (Colorado tick fever). In: (editor: Mandell G.L.; et al.) Principles and practice of infectious diseases. ed 6 Churchill Livingstone: Philadelphia.

BASIC INFORMATION

DEFINITION

Colorectal cancer (CRC) is a neoplasm arising from the luminal surface of the large bowel; locations include descending colon (40% to 42%), rectosigmoid and rectum (30% to 33%), cecum and ascending colon (25% to 30%), and transverse colon (10% to 13%).

ICD-9CM CODES
154.0 Colorectal cancer
ICD-10CM CODES
C18 Malignant neoplasm of colon
C18.2 Malignant neoplasm of colon, ascending colon
C18.4 Malignant neoplasm of colon, transverse colon
C18.6 Malignant neoplasm of colon, descending colon
C18.7 Malignant neoplasm of colon, sigmoid colon
C19 Malignant neoplasm of rectosigmoid junction

EPIDEMIOLOGY & DEMOGRAPHICS

- CRC is the third most common cancer and the second leading cause of cancer deaths in the U.S. (>160,000 new cases and >55,000 deaths/yr).
- Peak incidence is in the seventh decade of life. The lifetime risk for development of CRC is 1 in 17, with 90% of cases occurring after age 50 yr.
- 50% of rectal cancers are within reach of the examiner's finger, and 50% of colon cancers are within reach of the flexible sigmoidoscope.
- CRC accounts for 14% of all cases of cancer (excluding skin malignancies) and 14% of all yearly cancer deaths.
- Risk factors:
  1. Hereditary polyposis syndromes
  2. Familial polyposis (high risk)
  3. Gardner's syndrome (high risk)
  4. Turcot's syndrome (high risk)
  5. Peutz-Jeghers syndrome (low to moderate risk)
  6. Inflammatory bowel disease (IBD), both ulcerative colitis and Crohn's disease
  7. Family history of "cancer family syndrome"
  8. Heredofamilial breast cancer and colon carcinoma
  9. History of previous colorectal carcinoma
  10. Women undergoing irradiation for gynecologic cancer
  11. First-degree relatives with colorectal carcinoma
  12. Age >40 yr
  13. Possible dietary factors (diet high in fat or meat, beer drinking, reduced vegetable consumption); prolonged high consumption of red and processed meat may increase the risk for cancer of the large intestine
  14. Hereditary nonpolyposis colon cancer (HNPCC): autosomal dominant disorder characterized by early age of onset (mean age, 44 yr) and right-sided or proximal colon cancers, synchronous and metachronous colon cancers, mucinous and poorly differentiated colon cancers; accounts for 1% to 5% of all cases of CRC
  15. Previous endometrial or ovarian cancer, particularly when diagnosed at an early age
  16. The gut bacterium *Fusobacterium nucleatum* has been linked to CRC. Researchers have shown that it contains a unique receptor that binds to the colorectal cells, stimulating inflammation and carcinogenesis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination may be completely unremarkable.
- Digital rectal examination can detect approximately 50% of rectal cancers.
- Palpable abdominal masses may indicate metastasis or complications of colorectal carcinoma (abscess, intussusception, volvulus).
- Abdominal distention and tenderness are suggestive of colonic obstruction.
- Hepatomegaly may be indicative of hepatic metastasis.

ETIOLOGY

CRC can arise through two mutational pathways: microsatellite instability or chromosomal instability. Germline genetic mutations are the basis of inherited colon cancer syndromes; an accumulation of somatic mutations in a cell is the basis of sporadic colon cancer.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Diverticular disease
- Strictures
- IBD
- Infectious or inflammatory lesions
- Adhesions
- Arteriovenous malformations
- Metastatic carcinoma (prostate, sarcoma)
- Extrinsic masses (cysts, abscesses)

WORKUP

The clinical presentation of colorectal malignancies is initially vague and nonspecific (weight loss, anorexia, malaise). It is useful to divide colon cancer symptoms into those usually associated with the right side of the colon and those commonly associated with the left side of the colon because the clinical presentation varies with the location of the carcinoma.

- Right side of colon:
  1. Anemia (iron deficiency from chronic blood loss).
  2. Dull, vague, and uncharacteristic abdominal pain may be present, or patient may be completely asymptomatic.
  3. Rectal bleeding is often missed because blood is mixed with feces.
  4. Obstruction and constipation are unusual because of large lumen and more liquid stools.
- Left side of colon:
  1. Change in bowel habits (constipation, diarrhea, tenesmus, pencil-thin stools).
  2. Rectal bleeding (bright red blood coating the surface of the stool).
  3. Intestinal obstruction is frequent because of small lumen.

Early diagnosis of patients with surgically curable disease (Dukes A/B) is necessary because survival time is directly related to the stage of the carcinoma at the time of diagnosis. Appropriate screening recommendations are discussed in Section V.

CLASSIFICATION AND STAGING

Dukes and UICC classification for CRC:
A. Confined to the mucosa-submucosa (stage I)
B. Invasion of muscularis propria (stage II)
C. Local node involvement (stage III)
D. Distant metastasis (stage IV)

TNM Classification:

Stage	TNM Classification
I	T1-2, N0, M0
IIA	T3, N0, M0
IIB	T4, N0, M0
IIIA	T1-2, N1, M0
IIIB	T3-4, N1, M0
IIIC	T(any), N2, M0
IV	T(any), N(any), M1

LABORATORY TESTS

- Positive fecal occult blood test (FOBT): Many primary care physicians use single digital FOBT as their primary screening test for CRC. Single FOBT has low specificity for detecting human hemoglobin, is a poor screening method for CRC (sensitivity, 4.9%), and is inappropriate as the only test because negative results do not decrease the odds of advanced neoplasia. The American College of Gastroenterology recommends fecal immunochemical test (FIT) as a replacement for guaiac-based FOBT for CRC detection. FIT measures intact human globin protein (as opposed to heme) in the stool. It detects more advanced adenomas than FOBT. Fecal DNA testing is emerging as a newer screening method for CRC. It detects colonic cells shed into the fecal stream that possess specific genetic or epigenetic changes and has a reported sensitivity of 97% and a specificity of 90% for CRC stages I to III. In trials involving asymptomatic persons at average risk for colorectal cancer, multitarget stool DNA testing detects significantly more cancers than FIT but has more false-positive results. Cost ($599) and rate of false positives are the main obstacles inhibiting broader adoption of fecal DNA testing. A recent clinical study in asymptomatic persons ≥50 years old at average risk for colorectal cancer revealed that one time screening with stool DNA test (Cologuard) detected 92% of cases

of colorectal cancer, but it detected less than half of advanced precancerous lesions and produced a substantial number of false-positive results.[1]

- Microcytic anemia on CBC may be indicative of chronic blood loss.
- Increased plasma carcinoembryonic antigen (CEA) level: CEA should not be used as a screening test for CRC because it can be increased in patients with many other conditions (smoking, IBD, alcoholic liver disease). A normal CEA result does not exclude the diagnosis of CRC.

IMAGING STUDIES

- Colonoscopy with biopsy (primary assessment tool): The American College of Physicians (ACP) recommends that patients should be offered a colonoscopy beginning at age 50 yr, and it should be repeated every 10 yr in average-risk patients. Screening is recommended in African Americans beginning at 45 yr of age. Persons with only one first-degree relative with CRC or advanced adenomas diagnosed at 60 yr or older may be screened as at average risk. A family history of small tubular adenomas in first-degree relatives is not considered to increase the risk for CRC. The U.S. Preventive Services Task Force guidelines state that screening should not be routinely recommended in persons older than 75 yr, and it should not be recommended at all in persons older than 85 yr. If persons between the ages of 75 and 85 yr have never undergone screening, the decision about screening should be individualized according to health status. The ACP recommends that clinicians stop screening for colorectal cancer in adults over age 75 yr or in adults with a life expectancy of <10 yr. Table C1-44 describes CRC screening and surveillance recommendations.
- Computed tomography colonoscopy (CTC) virtual colonoscopy (VC) uses helical (spiral) CT scanning to generate a two- or three-dimensional virtual colorectal image (Fig. EC1-89). CTC does not require sedation, but, like optical colonoscopy, it requires some bowel preparation (either bowel cathartics or ingestion of iodinated contrast medium with meals during the 48 hr before CT) and air insufflation. It also involves substantial exposure to radiation. In addition, patients with lesions detected by VC will require traditional colonoscopy. Compared with colonoscopy, CTC sensitivity for detection of polyps >10 mm ranges from 70% to 96%, and specificity ranges from 72% to 96%. CTC has replaced double-contrast barium enema as the radiographic screening alternative when patients decline colonoscopy.
- Capsule endoscopy allows visualization of the colonic mucosa but is not recommended as a screening procedure because its sensitivity for detecting colonic lesions is low compared with colonoscopy.
- CT scanning of the abdomen, pelvis, and chest assists in preoperative staging.
- PET scanning can display functional information and is accurate in the detection of CRC and its distant metastases. Combined PET/CT scanners are increasingly more available and are useful to detect and characterize malignant lesions. Colonography composed of a combined modality of PET and CT is a newer diagnostic modality that can provide whole-body tumor staging in a single session.

[1]The Medical Letter on Drugs and Therapeutics, October 13, 2014; 56(1453):100-101.

TABLE C1-44 Colorectal Cancer (CRC) Screening and Surveillance Recommendations*

Indication	Recommendations
Average risk	Beginning at age 50 yr: Colonoscopy every 10 yr Computed tomographic colonography every 5 yr Flexible sigmoidoscopy every 5 yr Double-contrast barium enema every 5 yr Stool blood testing annually or stool DNA testing acceptable but not preferred
One or two first-degree relatives with CRC at any age or adenoma at age <60 yr	Colonoscopy every 5 yr beginning at age 40 yr, or 10 yr younger than earliest diagnosis, whichever comes first
Hereditary nonpolyposis CRC	Genetic counseling and screening† Colonoscopy every 1 to 2 yr beginning at age 25 yr and then yearly after age 40 yr‡
Familial adenomatous polyposis and variants	Genetic counseling and testing† Flexible sigmoidoscopy yearly beginning at puberty‡
Personal history of CRC	Colonoscopy within 1 yr of curative resection; repeat at 3 yr and then every 5 yr if normal
Personal history of colorectal adenoma	Colonoscopy every 3 to 5 yr after removal of all index polyps
Inflammatory bowel disease	Colonoscopy every 1 to 2 yr beginning after 8 yr of pancolitis or after 15 yr if only left-sided disease

*Recommendations proposed by the American Cancer Society and U.S. Multi-Society Task Force on Colorectal Cancer; recommendations for average-risk patients also endorsed by the American College of Radiology.
†Whenever possible, affected relatives should be tested first because of potential false-negative results.
‡Screening recommendation for individuals with positive or indeterminate tests as well as for those who refuse genetic testing.
From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.

Rx TREATMENT

GENERAL Rx

- Surgical resection: 70% of CRCs are resectable for cure at presentation; 45% of patients are cured by primary resection. Stage I and II tumors are curable by surgical resection, and up to 73% of cases of stage III can be cured by surgery combined with adjuvant chemotherapy.
- The backbone of chemotherapy treatment of CRC is fluorouracil (FU). Leucovorin (folinic acid) enhances the effect of FU and is given concomitantly. Adjuvant chemotherapy with combination of 5-FU and levamisole substantially increases cure rates for patients with stage III colon cancer and should be considered standard treatment for all such patients and selected patients with high-risk stage II colon cancer (adherence of tumor to an adjacent organ, bowel perforation, or obstruction).
- Radiation therapy is a useful adjunct to FU and leucovorin therapy for stage II or III rectal cancers.
- When given as adjuvant therapy after a complete resection in stage III disease, FU increases overall 5-yr survival rate from 51% to 64%. The use of adjuvant FU in stage II disease (no involvement of regional nodes) is controversial because 5-yr overall survival is 80% for treated or untreated patients, and the addition of FU only increases the probability of a 5-yr disease-free interval from 72% to 76%. For patients with standard-risk stage III tumors (e.g., involvement of one to three regional lymph nodes), both FU alone and FU with oxaliplatin (Eloxatin, an inhibitor of DNA synthesis) are reasonable choices. In general, reversible peripheral neuropathy is the main side effect of FU plus oxaliplatin. The oral fluoropyrimidine capecitabine (Xeloda) is a prodrug that undergoes enzymatic conversion to FU. It is an effective alternative to IV FU as adjuvant treatment for stage III colon cancer because it has a lower incidence of mouth sores and bone marrow suppression. It does, however, have an increased incidence of palmar-plantar erythrodysesthesia (hand-foot syndrome).
- Irinotecan (Camptosar), a potent inhibitor of topoisomerase I, a nuclear enzyme involved in the unwinding of DNA during replication, can be used to treat metastatic CRC refractory to other drugs, including 5-FU; it may offer a few months of palliation but is expensive and is associated with significant toxicity.
- Oxaliplatin (Eloxatin), a third-generation platinum derivative, can be used in combination with FU and leucovorin (FL) for patients with metastatic CRC whose disease has recurred or progressed despite treatment with FL plus irinotecan. FL plus oxaliplatin should be considered for high-risk patients with stage III cancers (e.g., more than three involved regional nodes [N2] or tumor invasion beyond the serosa [T4 lesion]).
- Laboratory studies have identified molecular sites in tumor tissue that may serve as

specific targets for treatment by using epidermal growth factor receptor (EGFR) antagonists and angiogenesis inhibitors. The monoclonal antibodies cetuximab (Erbitux), panitumumab (Vectibix), and bevacizumab (Avastin) have been approved by the FDA for advanced CRC. Bevacizumab is an angiogenesis inhibitor that binds and inhibits the activity of human vascular endothelial growth factor. Cetuximab and panitumumab are EGFR blockers that inhibit the growth and survival of tumor cells that overexpress EGFR. Cetuximab has synergism with irinotecan, and its addition to irinotecan in patients with advanced disease resistant to irinotecan increases the response rate from 10% when cetuximab is used alone to 22% with combination of cetuximab and irinotecan. The addition of bevacizumab to FL in patients with advanced CRC has been reported to increase the response rate from 17% to 40%. Severe dermatologic toxicity can occur with both cetuximab and panitumumab.

- The liver is generally the initial and most common site of CRC metastases. Resection of metastases limited to the liver is curative in more than 30% of selected patients. In patients who undergo resection of liver metastases, postoperative treatment with a combination of hepatic arterial infusion of floxuridine and IV FU improves the outcome at 2 yr. Trials comparing hepatic resection (HR) and radiofrequency ablation (RFA) in the treatment of solitary colorectal liver metastases reveal that HR has better outcome; however, in tumors <3 cm, RFA can be recommended in patients who are not surgical candidates due to comorbidities or when the liver met is poorly localized anatomically.

CHRONIC Rx

Follow-up is indicated with:

- Physician visits with a focus on the clinical and disease-related history, directed physical examination guided by this history, coordination of follow-up, and counseling every 3 to 6 mo for the first 3 yr, then decreased frequency thereafter for 2 yr
- Colonoscopy yearly for the initial 2 yr, then every 3 yr
- Baseline CEA level can be obtained; if elevated, it can be used after surgery as a measure of completeness of tumor resection or to monitor tumor recurrence. If used to monitor tumor recurrence, CEA should be obtained every 3 to 6 mo for up to 5 yr. The role of CEA for monitoring patients with resected colon cancer has been questioned because of the small number of cures attributed to CEA monitoring despite the substantial cost in dollars and physical and emotional stress associated with monitoring.

DISPOSITION

The 5-yr survival rate varies with the stage of the carcinoma:

- Dukes:
  1. Dukes A 5-yr survival rate >80%
  2. Dukes B 5-yr survival rate 60%
  3. Dukes C 5-yr survival rate 20%
  4. Dukes D 5-yr survival rate 3%
- TNM classification:

Stage	TNM Classification	5-yr Survival Rate
I	T1-2, N0, M0	>90%
IIA	T3, N0, M0	60-85%
IIB	T4, N0, M0	60-85%
IIIA	T1-2, N1, M0	25-65%
IIIB	T3-4, N1, M0	25-65%
IIIC	T(any), N2, M0	25-65%
IV	T(any), N(any), M1	5-7%

- Overall 5-yr disease-free survival rate has increased from 50% to 63% during the past two decades.
- High-frequency microsatellite instability in CRC is independently predictive of a relatively favorable outcome and reduces the likelihood of metastases.
- In patients with Dukes C (stage III) CRC, there is improved 5-yr survival among women treated with adjuvant chemotherapy (53% with chemotherapy vs. 33% without) and among patients with right-sided tumors treated with adjuvant chemotherapy.
- Retention of 19q alleles in microsatellite-stable cancers and mutation of the gene for the type I receptor for tumor growth factor B1 in cancers with high levels of microsatellite instability point to a favorable outcome after adjuvant chemotherapy with FU-based regimens for stage II colon cancer.
- Expression patterns of microRNA are systemically altered in colon adenocarcinomas. High miR-21 expression is associated with poor survival and poor therapeutic outcome.
- Guanylyl cyclase 2 C (GUCY2C) has been identified as a marker expressed by colorectal tumors that could reveal occult metastases in lymph nodes. Expression of GUCY2C in histologically negative lymph nodes appears to be independently associated with time to recurrence and disease-free survival in patients with lymph nodes free of tumor cells by histopathology (pN0) in CRC.
- The optimal timing from surgery to initiation of adjuvant chemotherapy is unknown. Meta-analysis of available literature suggests that longer time to adjuvant chemotherapy is associated with worse survival rates among patients with resected CRC.
- Regular aspirin use after the diagnosis of CRC has been reported to be associated with lower risk for CRC-specific and overall mortality, especially among individuals with tumors that overexpress cyclooxygenase-2. Regular aspirin use is associated with lower BRAF-wild type colorectal cancer but not with BRAF-mutated cancer risk. All aspirin doses starting with 75 mg daily had similar effects on CRC incidence and mortality.

REFERRAL

- Surgical referral for resection
- Oncology referral for adjuvant chemotherapy in selected patients
- Radiation oncology referral for patients with stage II or III rectal cancers

PEARLS & CONSIDERATIONS

COMMENTS

- Metastases of tumor cells to regional lymph nodes is the single most important prognostic factor in patients with colon cancer.
- Decreased fat intake to 30% of total energy intake, increased fiber, and fruit and vegetable consumption may reduce CRC risk. Recent literature reports, however, do not support a protective effect from dietary fiber against CRC in women.
- Chemoprophylaxis with aspirin (81 mg/day) reduces the incidence of colorectal adenomas in persons at risk.
- Statins inhibit the growth of colon cancer lines. Use of statins is associated with a 47% relative reduction in the risk for CRC. Additional trials are necessary to investigate the overall benefits of statins in preventing CRC.
- The National Cancer Institute has published consensus guidelines for universal screening for HNPCC in patients with newly diagnosed CRC. Tumors in mutation carriers of HNPCC typically exhibit microsatellite instability, a characteristic phenotype caused by expansion or contraction of short nucleotide repeat sequences. These guidelines (Bethesda Guidelines) are useful for selective patients for microsatellite instability testing. Screening patients with newly diagnosed CRC for HNPCC is cost effective, especially if the benefits to their immediate relatives are considered.
- Expression of guanylyl cyclase C mRNA in lymph nodes is associated with recurrence of CRC in patients with stage II disease. Analysis of guanylyl cyclase mRNA expression by reverse transcription polymerase chain reaction may be useful for CRC staging.
- The use of either annual or biennial FOBT significantly reduces the incidence of CRC.
- The detection of mutations in the *APC* gene from stool samples is a promising new modality for early detection of colorectal neoplasms.
- *KRAS* mutations are consistently associated with reduced overall and progression-free survival and increased treatment failure.

EVIDENCE

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SUGGESTED READINGS

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RELATED CONTENT

Colon Cancer (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Purpose:
The addition of cetuximab to irinotecan, fluorouracil, and leucovorin (FOLFIRI) as first-line treatment for metastatic colorectal cancer (mCRC) was shown to reduce the risk of disease progression and increase the chance of response in patients with *KRAS* wild-type disease. An updated survival analysis, including additional patients analyzed for tumor mutation status, was undertaken.

Patients and Methods:
Patients were randomly assigned to receive FOLFIRI with or without cetuximab. DNA was extracted from additional slide-mounted tumor samples previously used to assess epidermal growth factor receptor expression. Clinical outcome according to the tumor mutation status of *KRAS* and *BRAF* was assessed in the expanded patient series.

Results:
The ascertainment rate of patients analyzed for tumor *KRAS* status was increased from 45% to 89%, with mutations detected in 37% of tumors. The addition of cetuximab to FOLFIRI in patients with *KRAS* wild-type disease resulted in significant improvements in overall survival (median, 23.5 v 20.0 months; hazard ratio [HR], 0.796; $P = .0093$), progression-free survival (median, 9.9 v 8.4 months; HR, 0.696; $P = .0012$), and response (rate 57.3% v 39.7%; odds ratio, 2.069; $P < .001$) compared with FOLFIRI alone. Significant interactions between *KRAS* status and treatment effect were noted for all key efficacy end points. *KRAS* mutation status was confirmed as a powerful predictive biomarker for the efficacy of cetuximab plus FOLFIRI. *BRAF* tumor mutation was a strong indicator of poor prognosis.

Conclusions:
The addition of cetuximab to FOLFIRI as first-line therapy improves survival in patients with *KRAS* wild-type mCRC. *BRAF* tumor mutation is an indicator of poor prognosis. Ⓐ

Abstract[2]

Background:
In the Medical Research Council (MRC) COIN trial, the epidermal growth factor receptor (EGFR)-targeted antibody cetuximab was added to standard chemotherapy in first-line treatment of advanced colorectal cancer with the aim of assessing effect on overall survival.

Methods:
In this randomised controlled trial, patients who were fit for but had not received previous chemotherapy for advanced colorectal cancer were randomly assigned to oxaliplatin and fluoropyrimidine chemotherapy (arm A), the same combination plus cetuximab (arm B), or intermittent chemotherapy (arm C). The choice of fluoropyrimidine therapy (capecitabine or infused fluouroracil plus leucovorin) was decided before randomisation. Randomisation was done centrally (via telephone) by the MRC Clinical Trials Unit using minimisation. Treatment allocation was not masked. The comparison of arms A and C is described in a companion paper. Here, we present the comparison of arm A and B, for which the primary outcome was overall survival in patients with KRAS wild-type tumours. Analysis was by intention to treat. Further analyses with respect to NRAS, BRAF, and EGFR status were done. The trial is registered, ISRCTN27286448.

Findings:
1630 patients were randomly assigned to treatment groups (815 to standard therapy and 815 to addition of cetuximab). Tumour samples from 1316 (81%) patients were used for somatic molecular analyses; 565 (43%) had KRAS mutations. In patients with KRAS wild-type tumours (arm A, n = 367; arm B, n = 362), overall survival did not differ between treatment groups (median survival 17.9 months [IQR 10.3 to 29.2] in the control group vs 17.0 months [9.4 to 30.1] in the cetuximab group; HR 1.04, 95% CI 0.87 to 1.23, p = 0.67). Similarly, there was no effect on progression-free survival (8.6 months [IQR 5.0 to 12.5] in the control group vs 8.6 months [5.1 to 13.8] in the cetuximab group; HR 0.96, 0.82 to 1.12, p = 0.60). Overall response rate increased from 57% (n = 209) with chemotherapy alone to 64% (n = 232) with addition of cetuximab (p = 0.049). Grade 3 and higher skin and gastrointestinal toxic effects were increased with cetuximab (14 vs 114 and 67 vs 97 patients in the control group vs the cetuximab group with KRAS wild-type tumours, respectively). Overall survival differs by somatic mutation status irrespective of treatment received: BRAF mutant, 8.8 months (IQR 4.5 to 27.4); KRAS mutant, 14.4 months (8.5 to 24.0); all wild-type, 20.1 months (11.5 to 31.7).

Interpretation:
This trial has not confirmed a benefit of addition of cetuximab to oxaliplatin-based chemotherapy in first-line treatment of patients with advanced colorectal cancer. Cetuximab increases response rate, with no evidence of benefit in progression-free or overall survival in KRAS wild-type patients or even in patients selected by additional mutational analysis of their tumours. The use of cetuximab in combination with oxaliplatin and capecitabine in first-line chemotherapy in patients with widespread metastases cannot be recommended. Ⓐ

Abstract[3]

Background:
Robotic colorectal surgery may solve some of the problems inherent to conventional laparoscopic surgery (CLS). We sought to evaluate the advantages of robot-assisted laparoscopic surgery (RALS) using the da Vinci Surgical System over CLS in patients with benign and malignant colorectal diseases.

Methods:
PubMed and Embase databases were searched for relevant studies published before July 2011. Studies clearly documenting a comparison of RALS with CLS for benign and malignant colorectal diseases were selected. Operative and postoperative measures, resection margins, complications, and related outcomes were evaluated. Weighted mean differences, relative risks, and hazard ratios were calculated using a random-effects model.

Results:
The meta-analysis included 16 studies comparing RALS and CLS in patients with colorectal diseases and 7 studies in rectal cancer. RALS was associated with lower estimated blood loss in colorectal diseases ($P = 0.04$) and rectal cancer ($P < 0.001$) and lower rates of intraoperative conversion in colorectal diseases ($P = 0.03$) and rectal cancer ($P < 0.001$) than CLS. In patients with colorectal diseases, however, operating time ($P < 0.001$) and total hospitalization cost ($P = 0.06$) were higher for RALS than for CLS.

Conclusions:
RALS was associated with reduced estimated blood loss and a lower intraoperative conversion rate than CLS, with no differences in complication rates and surrogate markers of successful surgery. Robotic colorectal surgery is a promising tool, especially for patients with rectal cancer. Ⓐ

Abstract[4]

Objective:
We report a multicentered randomized controlled trial across Australia and New Zealand comparing laparoscopic-assisted colon resection (LCR) with open colon resection (OCR) for colon cancer.

Background:
Colon cancer is a significant worldwide health issue. This trial investigated whether the short-term benefits associated with LCR for colon cancer could be achieved safely, without survival disadvantages, in our region.

Methods:
A total of 601 patients with potentially curable colon cancer were randomized to receive LCR or OCR. Primary endpoints were 5-year overall survival, recurrence-free survival, and freedom from recurrence rates, compared using an intention-to-treat analysis.

Results:
On April 5, 2010, 587 eligible patients were followed for a median of 5.2 years (range, 1 week to 11.4 years) with 5-year confirmed follow-up data for survival and recurrence on 567 (96.6%). Significant differences between the 2 trial groups were as follows: LCR patients were older at randomization, and their pathology specimens showed smaller distal resection margins; OCR patients had some worse pathology

parameters, but there were no differences in disease stages. There were no significant differences between the LCR and OCR groups in 5-year follow-up of overall survival (77.7% vs 76.0%, $P = 0.64$), recurrence-free survival (72.7% vs 71.2%, $P = 0.70$), or freedom from recurrence (86.2% vs 85.6%, $P = 0.85$).

Conclusions:

In spite of some differences in short-term surrogate oncological markers, LCR was not inferior to OCR in direct measures of survival and disease recurrence. These findings emphasize the importance of long-term data in formulating evidence-based practice guidelines. Ⓐ

Evidence-Based References

Van Cutsem E et al.: Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor and mutation status, *J Clin Oncol* 29:2011–2019, 2011. Ⓐ

Maughan TS et al.: on behalf of the MRC COIN Trial Investigators: Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial, *Lancet* 377:2103–2114, 2011. Ⓐ

Yang Y, Wang F, Zhang P, et al.: Robot-assisted versus conventional laparoscopic surgery for colorectal disease, focusing on rectal cancer: a meta-analysis, *Ann Surg Oncol* 19:3727–3736, 2012. Ⓐ

Bagshaw PF et al.: the Australasian Laparoscopic Colon Cancer Study Group: Long-term outcomes of the Australasian randomized clinical trial comparing laparoscopic and conventional open surgical treatments for colon cancer: the Australasian Laparoscopic Colon Cancer Study Trial, *Ann Surg* 256:915–919, 2012. Ⓐ

SUGGESTED READINGS

Biaggi JJ et al.: Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer, *JAMA* 305(22):2335–2342, 2011.

Chan AT et al.: Aspirin use and survival after diagnosis of colorectal cancer, *JAMA* 302(6):649–659, 2009.

Dahabreh IJ et al.: Systematic review: anti-epidermal growth factor receptor treatment effect modification by KRAS mutations in advanced colorectal cancer, *Ann Intern Med* 154:37–49, 2011.

De Roock W et al.: Association of KRAS p. G13D mutation with outcome in patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab, *JAMA* 304(16):1812–1820, 2010.

Gill S et al.: Colorectal cancer, *Mayo Clin Proc* 82:114–129, 2007.

Hur H et al.: Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver metastases, *Am J Surg* 197:728–736, 2009.

Imperiale TF et al.: Multitarget stool DNA testing for colorectal-cancer screening, *N Engl J Med* 370:1287–1297, 2014.

Johnson CD et al.: Accuracy of CT colonography for detection of large adenomas and cancers, *N Engl J Med* 359:1207–1217, 2008.

Jonker DJ et al.: Cetuximab for the treatment of colorectal cancer, *N Engl J Med* 357:2040–2048, 2007.

Levi Z et al.: A qualitative immunochemical fecal occult blood test for colorectal neoplasia, *Ann Intern Med* 146:244–255, 2007.

Liebman DA: Screening for colorectal cancer, *N Engl J Med* 361:1179–1187, 2009.

Markowitz SD, Bertagnolli M: Molecular basis of colorectal cancer, *N Engl J Med* 361:2449–2460, 2009.

Nishihara R et al.: Aspirin use and risk of colorectal cancer according to BRAF mutation status, *JAMA* 309(24):2563–2571, 2013.

Primrose JN et al.: Effect of 3 to 5 years of scheduled CEA and CT follow-up to detect recurrence of colorectal cancer, *JAMA* 311:263, 2014.

Qaseem A et al.: Screening for colorectal cancer: a guidance statement for the American College of Physicians, *Ann Intern Med* 156:378–386, 2012.

Rex DK et al.: for the American College of Gastroenterology: American College of Gastroenterology guidelines for colorectal cancer screening, *Am J Gastroenterology* 104(3):740, 2009.

Rothwell PM et al.: Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomized trials, *Lancet* 376:1741, 2010.

Schetter AJ et al.: MicroRNA expression profiles associated with prognosis and therapeutic outcome in colon adenocarcinoma, *JAMA* 299(4):425–436, 2008.

Van Gossum et al.: Capsule endoscopy versus colonoscopy for the detection of polyps and cancer, *N Engl J Med* 361:264–270, 2009.

Waldman SA et al.: Association of GUCY2C expression in lymph nodes with time to recurrence and disease-free survival in PNO colorectal cancer, *JAMA* 301(7):745–752, 2009.

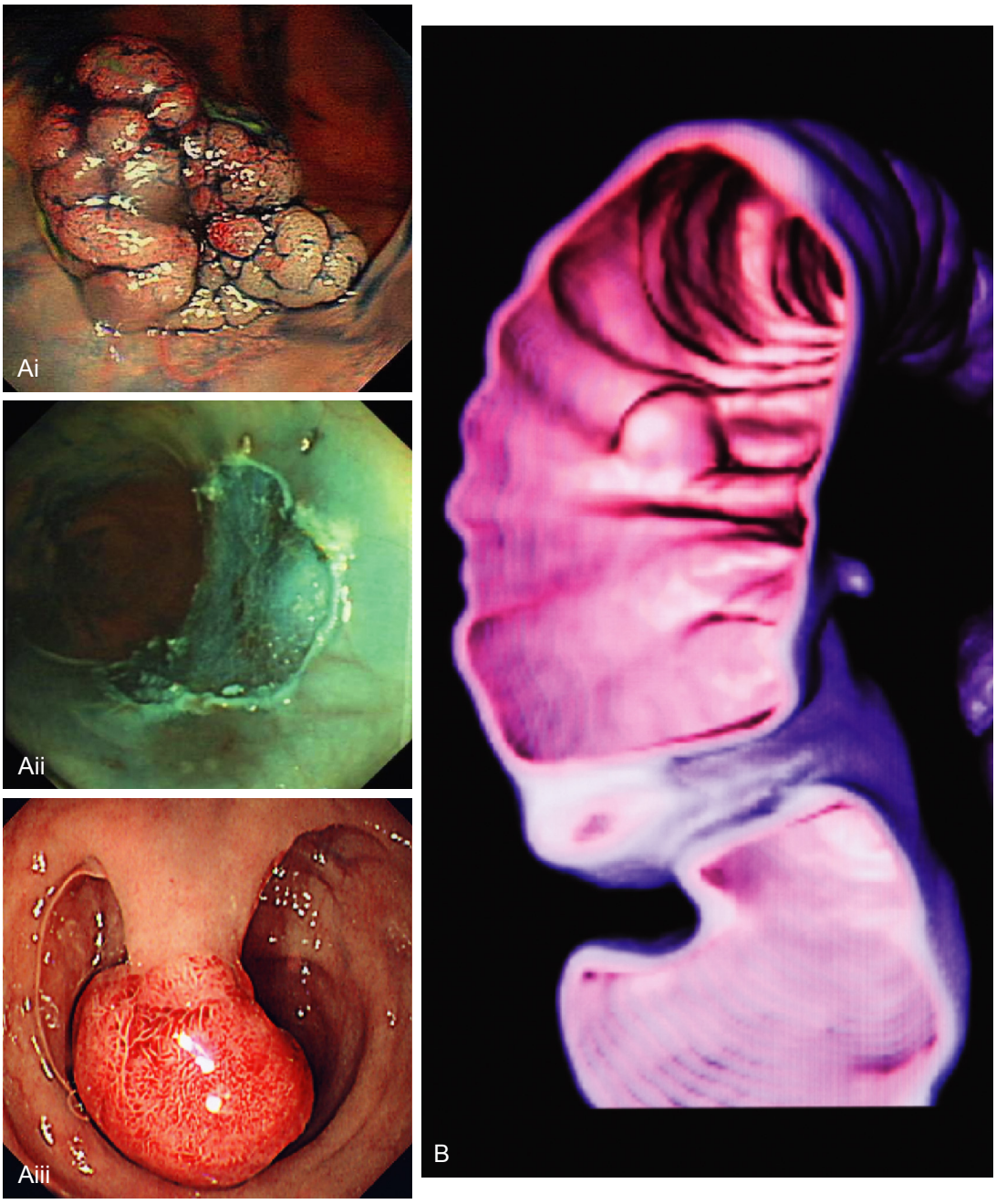

FIGURE EC1-89 Colon polyps seen at (Ai–iii) colonoscopy and (B) computed tomography (CT) colonography. Aii is after endoscopic resection of the polyps in Ai. (From Ballinger A: *Kumar & Clark's essentials of medicine*, ed 5, Edinburgh, 2012, Saunders.)

BASIC INFORMATION

DEFINITION

Compartment syndrome is a condition that occurs when elevated pressure within a limited space compromises the circulation, with increased risk of irreversible damage to its contents and their function. Acute compartment syndrome is a surgical emergency.

ICD-10CM CODES

958.90	Compartment syndrome unspecified
958.90	Compartment syndrome, not otherwise specified
T79.A0	Compartment syndrome, unspecified, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

- Occurs most commonly after acute trauma, especially with long bone fractures, comprising 75% of cases.
- It usually occurs in persons <35 yr.
- Incidence is higher in males.
- It can occur in other parts, such as the foot, thigh, gluteal region, and abdomen.
- Supracondylar fractures in children can commonly lead to compartment syndrome.
- 6% to 9% of open tibial fractures are complicated by compartment syndrome.
- It is seen in all races and ethnicities.

PATHOPHYSIOLOGY

Compartment syndrome occurs when the blood flow is less than the tissue metabolic demands, causing tissue injury. It occurs when the intracompartmental pressure increases limiting venous outflow with rising venous pressure, resulting in compromise of the local circulation and tissue hypoxia with decreased arteriovenous pressure gradient. Venous congestion additionally leads to tissue edema and interstitial pressure, and the compartment pressure continues to increase. Compartment pressure able to cause the condition ranges between 10 and 30 mm Hg of diastolic pressure.

Different conditions are known to cause compartment syndrome:

- Conditions that limit compartment volume, such as when patients have fracture casts, when sedated or comatose patients lie on a limb for a prolonged period, or when patients have tight dressings that are applied externally.
- Conditions that cause increased compartment content, such as bleeding in the compartment from vascular injury or diathesis, fractures or finger injuries, reperfusion after ischemic injury such as embolectomy and arterial bypass grafting, severe bruising of muscle, and thermal or electrical burn injuries.
- Other injuries, such as extravasation of intravenous fluids, injection of recreational drugs, and snake bites.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Signs and symptoms are usually apparent but can be unreliable and can lead to delayed diagnosis. Acute compartment syndrome can worsen within hours; therefore serial examination is important in a patient with suspected compartment syndrome. Patients with tense painful limbs are considered to have acute compartment syndrome; however, diagnosis is confirmed with the assessment of elevated compartment pressure. Clinical signs and symptoms include the following:

- Pain disproportional to injury (the earliest sign)
- Constant deep pain and pain that is referred to the compartment on passive stretching of the muscles of the affected compartment (Fig. C1-90*A*)
- Reduced sense of touch or sensation (hypesthesia) within the territory of the nerve passing the compartment (in acute anterior compartment syndrome, the patient may have hypesthesia in the territory of the first webspace)
- Tense and swollen compartment (Figs. C1-90*B* and *C*)
- Muscle weakness
- Paresis (late finding) that suggests permanent muscle damage
- Capillary refill can be slow but normal.
- Peripheral pulses that are normally palpable even in severe conditions
- Tingling and numbness in the affected limb. Hypesthesia or paresthesia should be evaluated with pinprick, light touch, and two-point discrimination tests.
- Difficulty moving the extremities.

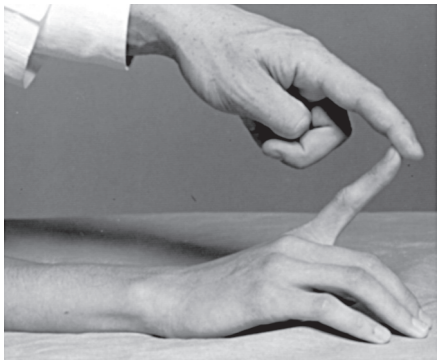

FIGURE C1-90A Passive extension of the digit causes pain referred to the compartment. (From Browner BD et al [eds]: *Skeletal trauma,* ed 4, Philadelphia, 2009, Saunders.)

FIGURE C1-90B Acute compartment syndrome of the leg. (From Browner BD et al [eds]: *Skeletal trauma,* ed 4, Philadelphia, 2009, Saunders.)

DIAGNOSIS

Diagnosis is based on clinical signs and symptoms along with compartment pressure. Compartment pressure testing may be unnecessary if the diagnosis is clinically obvious.

DIFFERENTIAL DIAGNOSIS

- Muscle strains
- Cellulitis
- Gangrene
- Peripheral vascular injury
- Necrotizing fasciitis
- Stress fractures
- Deep vein thrombosis and thrombophlebitis
- Tendinitis
- Muscle contusion
- Tarsal tunnel syndrome
- Posterior ankle syndrome
- Popliteal artery impingement
- Claudication
- Tumor
- Venous insufficiency

LABORATORY TESTS

Diagnosis is based on clinical findings and the measurement of compartment pressures. Laboratory values are not useful in the diagnosis of compartment syndrome. Laboratory studies are important, though, for other diagnoses or associated conditions.

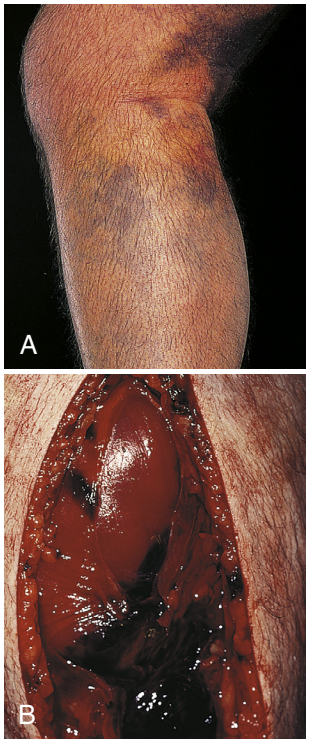

FIGURE C1-90C A, Severe calf swelling due to anterior and posterior compartment syndromes after ischemia-reperfusion. **B,** Appearance after emergency fasciotomy. Note edematous muscle and hematoma. (Courtesy Michael J. Allen, FRCS, Leicester, UK. From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

- CBC with differential for evaluation of infection
- Creatine phosphokinase (CK) levels, which can rise as muscle injury develops
- Metabolic panel for the assessment of electrolytes and renal function
- Coagulation profile for bleeding diathesis
- Urinalysis for rhabdomyolysis
- Urine and serum myoglobin levels

IMAGING STUDIES

- Direct intracompartmental pressure measurement can be done by handheld manometer, wick or slit catheter technique, and simple needle manometer system. Compartment syndrome is diagnosed when the difference between diastolic blood pressure and compartment pressure (Δ pressure) is ≤30 mm Hg.
- Ultrasonography can be used to rule out deep vein thrombosis, or Doppler ultrasonography can be used to evaluate blood flow to the extremity. Arteriography should be used to evaluate the adequate blood flow through a compartment.
- Near-infrared spectroscopy and technetium-99m methoxyisobutylisonitrile scintigraphy can also be used.
- Radiography can be used on the affected limb for fracture or foreign body evaluation.

Rx TREATMENT

Treatment goal is to keep intracompartmental pressure low and prevent tissue injury (Fig. C1-90*D*).

NONPHARMACOLOGIC THERAPY

- Immediate relieving of all external pressure on the affected compartment
- Removal of casts, splints, and dressings
- Placing limb at heart level to avoid decreased or increased blood flow

ACUTE GENERAL Rx

- Analgesics for pain
- Hyperbaric oxygen
- Hypotension can worsen tissue ischemia and thus should be treated with IV isotonic saline.
- Fasciotomy of the affected compartment is indicated if there has been >6 hr of limb ischemia, or immediate decompression should be performed when the compartment pressure > 30 to 35 mm Hg.
- Measurement of compartment pressure is not necessary to perform fasciotomy if clinical suspicion is high depending on history and clinical examination.
- When compartment pressures are trending downward, it is often safe to hold fasciotomy emergently, provided the Δ pressure is also improving.

CHRONIC Rx

- Aftercare of fasciotomy wound: Wound is inspected after 48 hours and dead tissue is removed.
- Wounds are left open, requiring later skin grafting or delayed wound closure.
- Opsite sheet and boot lace techniques are also used for closing fasciotomy wounds.
- Concomitant fractured bones should also be stabilized with plating, external fixation, or intramedullary nailing.

DISPOSITION

With early diagnosis and treatment, the prognosis is excellent for recovery of the muscles and nerves inside the compartment. The following conditions can be prevented:

- Permanent nerve damage/paralysis
- Muscle contracture
- Gangrene
- Amputation
- Muscle necrosis
- Fracture nonunion
- Rhabdomyolysis that leads to renal failure
- Compartment syndrome that can occur in open fractures
- Permanent nerve injury, which can occur after 12 to 24 hr of compression; mortality rates in patients who need fasciotomy is ≈15%.

REFERRAL

Patients with suspected compartment syndrome should be referred promptly to orthopaedic and general surgery.

PEARLS & CONSIDERATIONS

- Universal precautions and aseptic measures are necessary for patients undergoing fasciotomy because the risk of local and systemic infection is high with the procedure.
- Invasive monitoring techniques should be undertaken with adequate analgesia so that patient immobility is ensured while the pressure is measured.
- Injection of local anesthetics into the compartment can increase the pressure and pain and therefore should be avoided.
- Patients with fracture casts should be informed about the risks of swelling, and patients should also be encouraged to wear appropriate equipment while playing sports.
- A history of coagulation disorders and the use of anticoagulants should be mentioned in a patient's medical history.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

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RELATED CONTENT

Compartment Syndrome (Patient Information)

AUTHOR: **SYEDA M. SAYEED, M.D.**

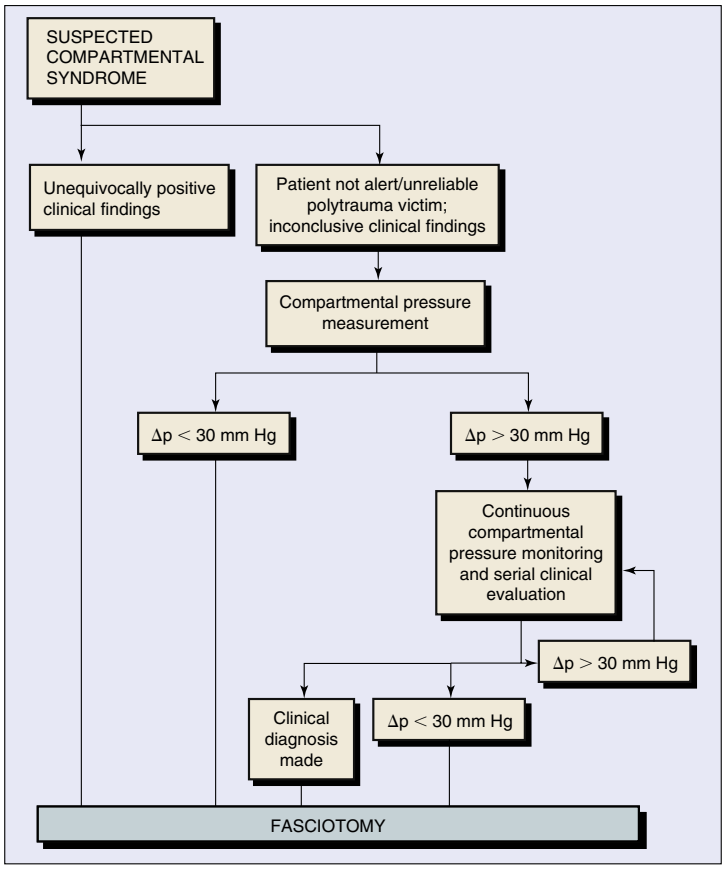


FIGURE C1-90D Algorithm for management for a patient with suspected compartment syndrome. Δp is defined as the difference between the diastolic pressure and the measured compartment pressure in mm Hg as documented by McQueen and Court-Brown. (From Browner BD et al [eds]: *Skeletal trauma,* ed 4, Philadelphia, 2009, Saunders.)

EVIDENCE

Abstract[1]

Objectives:

To determine the current incidence of postinjury abdominal compartment syndrome (ACS), the effect of intraabdominal hypertension (IAH) on trauma outcomes, and the independent predictors of postinjury IAH.

Design:

Prospective cohort study.

Setting:

University-affiliated level 1 trauma center.

Patients:

Eighty-one consecutive shock/trauma patients admitted to the intensive care unit (mean [SD] values: age, 41[2] years; 70% male; injury severity score, 29 [1]; base deficit, 6 [0.5] mmol/L; lactate level, 29.73[4.5] mg/dL; transfusions of packed red blood cells, 5 [0.5] U in first 24 hours; mortality rate, 2.5%; and multiple organ failure [MOF], 6%) had second hourly intraabdominal pressure (IAP) monitoring.

Main Outcome Measures:

Intensive care unit length of stay, ACS, IAH, MOF, mortality.

Results:

The mean (SD) IAP was 14(1) mm Hg. No patients developed ACS. Sixty-one patients (75%) had sustained IAH. Both patients with IAH and those without had similar demographics and injury severity. Patients with IAH had worse metabolic acidosis (P =.02), received more crystalloids (P =.03), and underwent laparotomy more frequently (P =.005). One patient with IAH and one without died. MOF occurred in 1 patient without IAH (5%) vs 4 with IAH (7%). The mean (SD) intensive care unit length of stay was 11(3) days in patients without IAH vs 8(1) days in those with IAH. Intraabdominal hypertension was poorly predictive of MOF (odds ratio, 1.17; 95% confidence interval, 0.96-1.43; P =.13). Of the 30 variables in multiple logistic regression analysis, only base deficit, laparotomy, and emergency department crystalloids were identified as weak predictors of IAP greater than 12 mm Hg. No predictors were found for the clinically more relevant IAP greater than 15 mm Hg and IAP greater than 18 mm Hg.

Conclusions:

Most of the severe shock/trauma patients developed sustained IAH. Based on univariate and multivariate analyses, there was no difference in outcomes between the trauma patients with IAH and those without. Multiple logistic regression analysis failed to show IAH as a predictor of MOF. The attenuation of the deadly ACS to a less deleterious IAH could be considered a success of the last decade in trauma and critical care. Ⓐ

Evidence-Based Reference

Balogh ZJ et al.: Mission to eliminate postinjury abdominal compartment syndrome, *Arch Surg* 146:938–943, 2011. Ⓐ

SUGGESTED READINGS

Allen MJ et al.: Intracompartmental pressure monitoring of leg injuries: an aid to management, *J Bone Joint Surg Br* 67:53, 1985.

Elliott KG, Johnstone AJ: Diagnosing acute compartment syndrome, *J Bone Joint Surg Br* 85(5):625, 2003.

Gelberman RH et al.: Compartment syndromes of the forearm: diagnosis and treatment, *Clin Orthop* 161:252, 1981.

Hope MJ, McQueen MM: Acute compartment syndrome in the absence of fracture, *J Orthop Trauma* 18(4):220–224, 2004.

Lee BY et al.: Management of compartmental syndrome: diagnosis and surgical considerations, *Am J Surg* 148:383, 1984.

McQueen MM et al.: Acute compartment syndrome. Who is at risk? *J Bone Joint Surg Br* 82(2):200, 2000.

Rizvi S, Catenacci M: Responding promptly to acute compartment syndrome, *Emerg Med* 40:12, 2008.

BASIC INFORMATION

DEFINITION

Complex regional pain syndrome (CRPS) is a pain disorder characterized by constant and intense limb pain associated with vasomotor and neurosensory abnormalities, skin changes, and demineralization of bone. CRPS has been divided into type I, in which there is usually an initiating noxious event but no distinct nerve lesion, and type II, in which a definable (usually traumatic) nerve lesion exists. CRPS type I generally correlates with the syndrome formerly known as reflex sympathetic dystrophy (RSD), and CRPS type II equates with what was previously termed causalgia. The term *shoulder-hand syndrome* has been used to describe CRPS in the setting of myocardial infarction or ischemia.

SYNONYMS

Reflex sympathetic dystrophy
Shoulder hand syndrome
CRPS

ICD-9CM CODES
337.20 Dystrophy, sympathetic (posttraumatic) (reflex)
ICD-10CM CODES
M89.0 Algoneurodystrophy
G90.59 Complex regional pain syndrome I of other specified site

EPIDEMIOLOGY & DEMOGRAPHICS

The incidence and prevalence of CRPS are not known. It occurs in adults and children. Common situations in which CRPS is seen include extremity trauma, burns, stroke, and orthopedic and podiatric procedures. Immobilization of the limb often precedes the development of symptoms. CRPS in the setting of myocardial infarction seems to be decreasing, presumably due to early mobilization and more effective pain control.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

CRPS is divided into three stages:

1. Acute stage (occurring within hours to days after the injury).
   - Burning or aching pain occurring over the injured extremity.
   - Hyperalgesia (exaggerated response to nociceptive stimuli).
   - Edema.
   - Dysthermia.
   - Increased hair and nail growth.
2. Dystrophic stage (3 to 6 months after injury).
   - Burning pain radiating both distally and proximally from the site of injury.
   - Brawny edema (Fig. EC1-91).
   - Hyperhidrosis.
   - Hypothermia and cyanosis.
   - Muscle tremors and spasms.
   - Increased muscle tone and reflexes.
3. Atrophic stage (6 months after injury).
   - Spread of pain proximally.
   - Allodynia (pain response to stimuli that are not normally painful).
   - Cold, pale, cyanotic skin.
   - Tropic skin changes with subcutaneous atrophy.
   - Contractures.

ETIOLOGY

The exact pathogenetic mechanisms underlying CRPS have not been fully elucidated, but most theories include the formation of an abnormal reflex arc in the sympathetic nervous system that is modulated by cortical centers to produce peripheral vascular disturbances. Persistent pain in the peripheral nervous system is modulated by inflammatory neuropeptides including substance P, which has been shown to be elevated in the serum of patients with CRPS-I. Increased concentrations of tumor necrosis factor and IL-6 have been demonstrated in the skin of patients with CRPS-I, and immune abnormalities such as reduced numbers of CD8-positive T lymphocytes have also been seen.

DIAGNOSIS

Criteria proposed for the diagnosis of CRPS type I include:

- An initiating noxious event, spontaneous pain or alloying/hyperalgesia disproportionate to the inciting event.
- Evidence of edema, skin blood flow, or sweating abnormality in the region of the pain.
- Absence of other conditions that could explain the symptoms.

Tests such as nuclear medicine bone scanning, nerve conduction testing, and plain radiographs are often indicated to confirm the diagnosis and rule out other possibilities.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes nerve entrapment syndromes such as cervical radiculopathy, myofascial pain syndromes, and fibromyalgia.

WORKUP

- Bone scintigraphy (Fig. EC1-92) shows decreased perfusion of the affected areas if done soon after the onset of symptoms. If done after 6 weeks of symptoms, bone scan may show increased uptake in the region of the peripheral joints of the involved extremity.
- Electrophysiologic testing is useful to identify nerve injury in patients with type II CRPS.
- Plain radiographs show diffuse patchy osteopenia.
- Skin temperature measurements can be used as a diagnostic test.
- Autonomic testing, although not commonly done, has been proposed.
  1. Measuring resting sweat output.
  2. Measuring resting skin temperature.
  3. Quantitative sudomotor axon reflex test.

TREATMENT

Treatment of CRPS is largely empiric, based mostly on anecdotal reports, extrapolation from drug trials for other painful conditions, and clinical experience. Therapy should be tailored to stage of disease progression and severity of symptoms.

NONPHARMACOLOGIC THERAPY

- Physical therapy.
- Patient education.

PHARMACOLOGIC THERAPY

Suggested regimens:

Stage 1
- Tricyclic antidepressants (amitriptyline 25 to 150 mg or doxepin 5 to 20 mg).
- Prednisone 1 mg/kg for 2 weeks, then taper by 10 mg every 2 weeks.
- Alendronate 70 mg PO weekly.

Stage II
- Topical capsaicin.
- Gabapentin 300 mg tid.
- Regional nerve blocks.

Stage III
- Sympathetic ganglion blocks.
- Refer to multidisciplinary pain center.

NOTE: High-dose vitamin C may decrease the incidence of CRPS following wrist fracture and foot and ankle surgery or trauma.

DISPOSITION

Spontaneous remission can occur after several weeks to months.

REFERRAL

Cases in which the diagnosis is not clear or there is suboptimal response to therapy should promptly be referred to a multidisciplinary pain clinic.

PEARLS & CONSIDERATIONS

COMMENTS

- CRPS is a common clinical entity without clear definition, pathophysiologic features, or treatment.
- Early mobilization in high-risk situations is important for prevention of CRPS.
- Prompt diagnosis and aggressive physical and pharmacologic therapy may prevent progression to chronic, intractable pain.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **BERNARD ZIMMERMANN, M.D.**

SUGGESTED READINGS

Dowd GSE et al.: Complex regional pain syndrome with special emphasis on the knee, *J Bone Joint Surg Br* 89-B(3):285–290, 2007.

Goebel A et al.: Intravenous immunoglobulin treatment of the complex regional pain syndrome, *Ann Intern Med* 152:152–158, 2010.

Krumova EK et al. Long-term skin temperature measurements—a practical diagnostic tool in complex regional pain syndrome, *Pain* 140(1):8–22 (Epub 2008).

Low AK et al.: Pediatric complex regional pain syndrome, *J Pediatr Orthop* 27(5):567–572, 2007.

Reuben SS, Buvanendran A: Preventing the development of chronic pain after orthopaedic surgery with preventive multimodal analgesic techniques, *J Bone Joint Surg Am* 89(6):1343–1358, 2007.

Shibuya N et al.: Efficacy and safety of high-dose vitamin C on complex regional pain syndrome in extremity trauma and surgery: systematic review and meta-analysis, *J Foot Ankle Surg* 52:62–66, 2013.

Teasdall RD et al.: Complex regional pain syndrome (reflex sympathetic dystrophy), *Clin Sports Med* 23(1):145, 2004.

Tran DQH et al.: Treatment of complex regional pain syndrome: a review of the evidence, *J Can Anesth* 57:149–166, 2010.

FIGURE EC1-91 Complex regional pain syndrome affecting the lower limb, showing marked swelling and color change. (Reproduced with permission from Salford Royal NHS Foundation Trust.)

FIGURE EC1-92 Reflex sympathetic dystrophy in a patient with a history of right wrist fracture. Three-phase bone scintigraphy shows increased tracer delivery to the right distal upper extremity diffusely *(arrow)* on flow *(top)* and blood pool *(middle)* images. Delayed images *(bottom)* reveal diffuse abnormal uptake in the wrist *(arrow)* and increased activity in a juxtaarticular distribution *(arrowheads).* (From DeLee D, Drez D: *DeLee and Drez's orthopaedic sports medicine,* ed 2, Philadelphia, 2003, Saunders.)

BASIC INFORMATION

DEFINITION

- Concussion is a mild traumatic brain injury that manifests with self-limited symptoms at the less severe end of the brain injury spectrum.
- It is a complex pathophysiologic process affecting the brain, induced by traumatic biomechanical forces. It may be caused by a direct blow to the head, face, neck, or elsewhere on the body with an "impulsive" force transmitted to the head.
- Concussion typically results in the rapid onset of short-lived impairment of neurologic function that resolves spontaneously. It may result in neuropathologic changes, but the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury.
- The fourth International Conference on Concussion (2012) defines concussion as "a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces," characterized by the following features: (1) caused by a direct blow to the head or blow to the body that transmits an "impulsive" force to the head; (2) results in rapid onset of short-lived neurotic impairment that resolves spontaneously; (3) variable clinical symptoms that may not include loss of consciousness; (4) symptoms that largely reflect a functional disturbance rather than structural injury (thus, no abnormalities are seen on standard structural neuroimaging studies); and (5) symptom resolution that typically follows a sequential course but may be prolonged in a small percentage of cases.[1]

SYNONYMS

Sports-related mild traumatic brain injury (mTBI)

ICD-9CM CODES

850.0 Concussion (no loss of consciousness)
850.11 Concussion (loss of consciousness of ≤30 min)
850.9 Concussion unspecified

ICD-10CM CODES

S06.0 Concussion

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 3.8 million sports- and recreation-related concussions occur each year in the U.S. It is estimated that as many as 50% of concussions go unreported.

PREVALENCE: Each year, U.S. emergency departments treat an estimated 135,000 sports- and recreation-related TBIs, including concussions, among children ages 5 to 18.

PREDOMINANT SEX AND AGE: Children and teens are more likely to get a concussion and take longer to recover than adults. Limited studies have shown that in sports that are played by both men and women, women are at more risk of sustaining a concussion.

[1]McCrory P et al.: Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012. *Clin J Sport Med* 23:89-117, 2013.

RISK FACTORS: High-impact sports and recreation; six times more likely in organized sports than leisure physical activity. Individuals who have sustained a concussion previously are at a higher risk of sustaining another concussion. Athletes with a body mass index (BMI) >27 kg/m^2 and those who train <3 hr/wk are also at greater risk.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

See Table C1-45.

ETIOLOGY

- Concussion occurs when rotational or angular acceleration forces are applied to the brain, resulting in shear strain of the underlying neural elements, including altered autonomic function and impaired control of cerebral blood flow.
- This may be associated with a blow to the skull; however, direct impact to the head is not required.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Migraine

TABLE C1-45 Symptoms and Signs of Concussion

Mental Status Changes
Amnesia
Confusion
Disorientation
Easily distracted
Excessive drowsiness
Feeling dinged, stunned, or foggy
Impaired level of consciousness
Inappropriate play behaviors
Poor concentration and attention
Seeing stars or flashing lights
Slow to answer questions or to follow directions

Physical or Somatic
Ataxia or loss of balance
Blurry vision
Decreased performance or playing ability
Dizziness
Double vision
Fatigue
Headache
Lightheadedness
Nausea, vomiting
Poor coordination
Ringing in the ears
Seizures
Slurred, incoherent speech
Vacant stare/glassy-eyed
Vertigo

Behavior or Psychosomatic
Emotional lability
Irritability
Low frustration tolerance
Personality changes
Nervousness, anxiety
Sadness, depressed mood

From Patel DR et al: Sports related concussions in adolescents, *Pediatr Clin N Am* 57:652, 2010.

- Cervical strain
- Posttraumatic vestibular injury

WORKUP

- Sideline assessment:
  1. No athlete with a suspected concussion should return to play that day.
  2. Neurologic assessment using a standardized tool, such as s SCAT3 (Sports Concussion Assessment Tool), which includes the BESS (Balance Error Scoring System) and Maddocks Questions or SAC (Standardized Assessment of Concussion) (Fig. C1-93)
  3. Monitor for deterioration; no athlete should be left alone
- Neurocognitive testing:
  1. Computer-based programs, such as ImPACT, ANAM, CogSport
  2. Neuropsychiatric testing administered by a neuropsychologist
- Gait/balance testing with a tool such as the Balance Error Scoring System (BESS)
- When used in combination, symptom assessment, balance assessment, and neurocognitive testing provide a sensitivity of >90% for the identification of concussion.
- Consider the Buffalo Concussion Treadmill Test, which identifies physiologic dysfunction in concussion, rules out other diagnoses, and can quantify a safe level of activity in concussion recovery.

IMAGING STUDIES

- CT imaging is indicated in any athlete with a Glasgow Coma Scale score of ≤15 or a rapidly changing neurologic exam.
- Imaging should be reserved for athletes in whom intracerebral bleeding is suspected; PECARN guidelines.

TREATMENT

ACUTE GENERAL Rx

- Removal from game
- Physical rest
  1. No return to play until asymptomatic for 24 hr
  2. Follow return-to-play guidelines (Table C1-46)
- Cognitive rest to limit symptoms
  1. Modifications at school
  2. Modifications at home/recreation
  3. Encourage sleep

CHRONIC Rx

See "Postconcussive Syndrome"

DISPOSITION

- Table C1-46 summarizes the American Academy of Neurology, American Medical Society for Sports Medicine, and International Conference on Concussion recommendations on returning to play after a concussion.
- If concussion symptoms occur with activity at one level, the athlete should stop the activity, rest until symptoms resolve, and then restart his or her progression at the level that did not elicit symptoms.

NAME: _____

AGE: ___ SEX: ___ EXAMINER: _____

Nature of Injury: _____

Date of Exam: _____ Time: _____ No. _____

1) ORIENTATION:

Month: _____	0	1
Date: _____	0	1
Day of Week: _____	0	1
Year: _____	0	1
Time (within 1 hour): _____	0	1

Orientation Total Score _____ /5

2) IMMEDIATE MEMORY: (all 3 trials are completed regardless of score on trials 1 & 2; score equals sum across all 3 trials)

LIST	TRIAL 1		TRIAL 2		TRIAL 3	
Elbow	0	1	0	1	0	1
Apple	0	1	0	1	0	1
Carpet	0	1	0	1	0	1
Saddle	0	1	0	1	0	1
Bubble	0	1	0	1	0	1
Total						

Immediate Memory Score _____ /15

3) CONCENTRATION:

Digits Backward: (if correct, go to next string length. If incorrect, read trial 2. Stop after incorrect on both trials.)

4–9–3	6–2–9	0	1
3–8–1–4	3–2–7–9	0	1
6–2–9–7–1	1–5–2–8–6	0	1
7–1–8–4–6–2	5–3–9–1–4–8	0	1

Months in Reverse Order: (entire reverse sequence correct for 1 point)
DEC–NOV–OCT–SEP–AUG–JUL
JUN–MAY–APR–MAR–FEB–JAN 0 1

Concentration Total Score _____ /5

EXERTIONAL MANEUVERS (when appropriate):

5 jumping jacks
5 push-ups
5 sit-ups
5 knee-bends

4) DELAYED RECALL

Elbow	0	1
Apple	0	1
Carpet	0	1
Saddle	0	1
Bubble	0	1

Delayed Recall Score _____ /5

SUMMARY OF TOTAL SCORES:

Orientation	_____	/5
Immediate Memory	_____	/15
Concentration	_____	/5
Delayed Recall	_____	/5
OVERALL TOTAL SCORE	_____	**/30**

FIGURE C1-93 Standardized assessment of concussion (SAC). (Redrawn from McCrea M et al: Standard assessment of concussion in football players. *Neurology* 48:586–588, 1997.)

TABLE C1-46 Graduated Return to Play Protocol

Rehabilitation Stage	Functional Exercise at Each Stage of Rehabilitation	Objective of Each Stage
1. No activity	Complete physical and cognitive rest	Recovery
2. Light aerobic exercise	Walking, swimming, or stationary cycling, keeping intensity <70% maximum predicted heart rate No resistance training	Increase heart rate
3. Sport-specific exercise	Skating drills in ice hockey, running drills in soccer No head impact activities	Add movement
4. Noncontact training drills	Progression to more complex training drills, e.g., passing drills in football and ice hockey May start progressive resistance training	Exercise, coordination, and cognitive load
5. Full contact practice	After medical clearance, participate in normal training activities	Restore confidence and assess functional skills by coaching staff
6. Return to play	Normal game play	

From Putukian M: The acute symptoms of sports-related concussion: diagnosis and on-field management, *Clin Sports Med* 30(58), 2011.

- There are no evidence-based guidelines for disqualifying or retiring an athlete from sport after a concussion. Each case should be individually considered.

REFERRAL

Sports-medicine physician, neuropsychology or concussion center

PEARLS & CONSIDERATIONS

PREVENTION

- Preparticipation evaluations for all athletes
- Preparticipation neurocognitive and balance testing to establish a baseline
- There is currently no evidence to support the use of concussion prevention headbands or mouth guards.

PATIENT/FAMILY EDUCATION

Centers for Disease Control and Prevention: http://www.cdc.gov/concussion/support.html

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Concussion (Patient Information)
Traumatic Brain Injury (Related Key Topic)

AUTHORS: **PETER J. SELL, D.O.,** and **AMITY RUBEOR, D.O.**

SUGGESTED READINGS

Centers for Disease Control and Prevention. www.cdc.gov/TraumaticBrainInjury/causes.html.

Giza CC et al.: Summary of evidence-based guideline update: evaluation and management of concussion in sports: report of the guideline development subcommittee of the American Academy of Neurology, *Neurology* 80:2250–2257, 2013.

Halstead ME et al.: Sports-related concussion in children and adolescents, *Pediatrics* 126(3):597–615, 2010.

Harmon KG: American Medical Society for Sports Medicine position statement: concussion in sport, *Clin J Sport Med* 23:1–18, 2013.

Leddy JJ et al.: Use of graded exercise testing in concussion and return-to-activity management, *Current Sports Medicine Reports* 12(6):370–376, 2013.

Lovell M: The management of sports-related concussion: current status and future trends, *Clin Sports Med* 28:95–111, 2009.

McCrory P et al.: Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012, *Br J Sports Med* 47:250–258, 2013.

McCrory P et al.: Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012. *Clin J Sport Med* 23:89–117, 2013.

Meehan WP et al.: Sports-related concussion, *Pediatrics* 123:114–123, 2009.

O'Kane JW et al.: Concussion among female middle-school soccer players, *JAMA Pediatrics* 168:258–264, 2014.

Patel DR et al.: Sports related concussions in adolescents, *Pediatr Clin N Am* 57:649–670, 2010.

Purcell L et al.: Sports-related concussion in pediatric athletes, *Clin Pediatr* 47(2):106–113, 2008.

Putukian M: The acute symptoms of sports-related concussion: diagnosis and on-field management, *Clin Sports Med* 30:49–61, 2011.

BASIC INFORMATION

DEFINITION

Conduct disorder (CD) is a repetitive and persistent pattern of behaviors in which either the basic rights of others are violated and/or major age-appropriate societal rules are violated. Classified under the DSM-5 category "disruptive, impulse control, and conduct disorders."

For childhood onset:
ICD-9CM and DSM-5 CODES
312.81
ICD-10CM CODES
F91.1
For adolescent onset:
ICD-9CM and DSM-5 CODES
312.32
ICD-10CM CODES
F91.2

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1% (12 mo span, National Comorbidity Survey-Replication [NCS-R])
PREVALENCE: Approximately 2% to 10%; NCS-R: 9%. Disruptive behavior disorders are considered the most common reason for referral of children to mental health providers.
PREDOMINANT SEX: More common in males (4:1 preadolescence and 2:1 postadolescence). It is unclear if CD females are underrepresented, as diagnostic criteria were validated on male samples. Nonconfrontational aggression and promiscuity are examples of possible gender-specific criteria that, at this time, have unknown predictive validity.
PREDOMINANT AGE: Most common onset in early adolescence. Median age of onset is 11 yr.
GENETICS: Risk increased if parent or sibling with disorder.
RISK FACTORS: There are various temperamental (including lower-than-average intelligence, especially verbal), family-level (including parental rejection or neglect, early institutional living, frequent caregiver changes, large family size, parental criminality or substance use), and community-level (including peer rejection, association with delinquent peer group, exposure to violence) risk factors.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The DSM-5 lists 15 possible behavioral manifestations of CD, grouped into four categories: aggression to people and animals, destruction of property, deceitfulness or theft, and serious violations of rules. Three of the 15 behaviors are required to have occurred in the last 12 mo, and one behavior must have occurred in the last 6 mo.
- Specifiers describe the age of onset and the severity of the disorder.
- New to the DSM-5 is an additional specifier addressing issues relating to intent and reaction to the behaviors, including the following options: "With limited prosocial emotions," "lack of remorse or guilt," "callous-lack of empathy," "unconcerned about performance," and "shallow or deficient affect."
- CD represents a heterogeneous group with respect to presentation, etiology, severity, and course.
- Symptom severity often progresses over time with age (i.e., lying and truancy to sexual assault and robbery).
- Aggressive youth are more likely to interpret as negative or hostile the intent of neutral others and are more likely to believe that conflict can be adequately resolved via aggression.
- Poor frustration tolerance, irritability, temper outbursts, and recklessness are often associated with CD.
- Slow resting heart rate associated with reduced autonomic response to fear is the most replicated of all biologic markers for conduct problems.

ETIOLOGY

Estimated population variance in antisocial behavior accounted for by:
1. Genes: 50%
2. Environmental factors shared among family members: 20%
3. Environmental factors unshared among family members: 20% to 30%

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Oppositional defiant disorder
- ADHD
- Mood disorder
- Adjustment disorder
- Substance abuse, dependence, intoxication, or withdrawal
- Post-traumatic stress disorder
- Antisocial personality disorder (for those >18 yr)
- Adaptive behavior or subcultural delinquency

WORKUP

Diagnosis is made based on history, including individual and family interviews as well as collateral data from additional sources (e.g., parents, teachers, other medical providers, therapist).

LABORATORY TESTS

Consider urine toxicology for possible substance use comorbidity.

IMAGING STUDIES

None indicated; however, both structural and functional differences have been noted in certain areas of the brain in individuals with CD.

TREATMENT

Initial treatment of CD should include psychosocial and environmental interventions aimed at decreasing the frequency and severity of delinquent behaviors. If the interventions listed here are not effective, or if serious concerns exist regarding safety or impairment in functioning, pharmacologic interventions targeting specific symptoms (e.g., aggression) or comorbid disorders (e.g., ADHD, anxiety disorders, or mood disorders) may help. There are currently no medications approved by the FDA for the treatment of CD.

NONPHARMACOLOGIC THERAPY

- Parent management training
- Cognitive problem-solving skills training (including elements of social skills, conflict resolution, anger management, impulse control, and vocational training).
- Multisystemic therapy (MST).
- Social skills training.
- Individual psychotherapy.
- Family psychotherapy.
- Higher levels of care such as a hospital or acute residential setting may be required for stabilization if acute safety concerns develop in the context of CD, such as severe aggression.
- Legal involvement and/or out-of-home-placements may be necessary to monitor safety of both the patient and the community.

PHARMACOLOGIC THERAPY

Medication may be considered as an adjunct to behavioral treatment or in cases where comorbidity is a factor. There is some evidence for symptom improvement with trials of several classes of psychotropic medications—including stimulants, mood stabilizers, atypical antipsychotics, antidepressants, and alpha-2 agonists—all of which seem to target aggressive symptoms in particular; medication, however, should never be used alone or as first-line treatment for CD.

DISPOSITION

- Approximately half of those with early onset of CD persist with antisocial behaviors into adulthood. There is no reliable way to predict which 50% will persist.
- Approximately half of those with early onset of CD do not develop antisocial personality disorder in adulthood. This subgroup is at higher risk for depression, anxiety, and social isolation as adults.
- Approximately 85% of those with adolescent onset of CD do not demonstrate lifetime persistent violence, convictions, and incarcerations. However, adult prognosis may often include substance abuse and crimes that go largely undetected.

PEARLS & CONSIDERATIONS

COMMENTS

- Treatment noncompliance is common.
- Expect 30% treatment noncompliance rate.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **HASSAN M. MINHAS, M.D., ELIZABETH A. LOWENHAUPT, M.D.**, and **SARAH L. XAVIER, D.O.**

SUGGESTED READINGS

Blair RJ, Leibenluft E, Pine DS: Conduct disorder and callous-unemotional traits in youth. *N Engl J Med* 371:2207–2216, 2014.

Frick P: Developmental pathways to conduct disorder: implications for future directions in research, assessment, and treatment, *J Clin Child Adolesc Psychol* 41(3):378–389, 2012.

Frick PJ, Nigg JT: Current issues in the diagnosis of attention deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder, *Annu Rev Clin Psychol* 8:77–107, 2012.

Murray J, Farrington DP: Risk factors for conduct disorder and delinquency: key findings from longitudinal studies, *Can J Psychiatry* 55(10):633–642, 2010.

Pardini DA, Fite PJ: Symptoms of conduct disorder, oppositional defiant disorder, attention-deficit/hyperactivity disorder, and callous-unemotional traits as unique predictors of psychosocial maladjustment in boys: advancing an evidence base for DSM-V, *J Am Acad Child Adolesc Psychiatry* 49(11):1134–1144, 2010.

BASIC INFORMATION

DEFINITION

Condyloma acuminatum is a sexually transmitted viral disease of the vulva, vagina, and cervix caused by the human papillomavirus (HPV). 90% of genital warts are caused by HPV 6 or 11.

SYNONYMS

Genital warts
Venereal warts
Anogenital warts

ICD-9CM CODES
078.11 Condyloma acuminatum
ICD-10CM CODES
A63.0 Anogenital (venereal) warts

EPIDEMIOLOGY & DEMOGRAPHICS

- Seen mostly in young adults, with peak age of onset of 16 to 25 yr
- A sexually transmitted disease spread by skin-to-skin contact
- Highly contagious, with 25% to 65% of sexual partners developing it
- Virus shed from both macroscopic and microscopic lesions
- Average incubation time is 2 mo (range, 1 to 8 mo)
- Predisposing conditions: diabetes, pregnancy, local trauma, and immunosuppression (e.g., transplant recipients, those with HIV infection)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Usually found in genital area but can be present elsewhere
- Lesions usually in similar positions on both sides of perineum
- Initial lesions pedunculated, soft papules about 2 to 3 mm in diameter, 10 to 20 mm long; may occur as single papule or in clusters
- Size of lesions varies from pinhead to large cauliflower-like masses (Fig. EC1-94)
- Usually asymptomatic, but if infected can cause pain, odor, or bleeding
- Vulvar condyloma more common than vaginal and cervical
- Four morphologic types: condylomatous, keratotic, papular, and flat warts
- Intraanal anal warts are observed predominantly in persons who have had receptive anal intercourse.

ETIOLOGY

- HPV DNA types 6 and 11 usually found in exophytic warts and have no malignant potential
- HPV types 16 and 18 usually found in flat warts and are associated with increased risk of malignancy
- Recurrence associated with persisting viral infection of adjacent normal skin in 25% to 50% of cases

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Abnormal anatomic variants or skin tags around labia minora and introitus
- Dysplastic warts

WORKUP

- Colposcopic examination of lower genital tract from cervix to perianal skin with 3% to 5% acetic acid
- Biopsy of vulvar lesions that lack the classic appearance of warts and that become ulcerated or do not respond to treatment
- Biopsy of flat, white, or ulcerated cervical lesions

LABORATORY TESTS

- Pap smear
- Cervical cultures for Neisseria gonorrhoeae and Chlamydia
- Serologic test for syphilis
- HIV testing offered
- Wet mount for trichomoniasis, Candida albicans, and Gardnerella vaginalis
- Testing for diabetes (blood glucose)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Keep genital area dry and clean.
- If present, keep diabetes well controlled.
- Use of condoms recommended to prevent spread of infection to sexual partner.

ACUTE GENERAL Rx

Factors that influence selection of treatment include wart size, wart number, anatomic site of wart, wart morphology, patient preference, cost of treatment, convenience, adverse effects, and provider experience.

Keratolytic agents:

- Podophyllin (Podofilox 0.5% solution or gel)
  1. Acts by poisoning mitotic spindle and causing intense vasospasm
  2. Applied directly to lesion weekly and washed off in 6 hr
  3. Used in minimal vulvar or anal disease
  4. Applied cautiously to nonkeratinized epithelial surfaces
  5. Contraindicated in pregnancy
  6. Discontinued if lesions do not disappear in 6 wk; switch to other treatment
- Sinecatechin 15% ointment
  1. Applied tid (0.5 cm strand of ointment to each wart)
  2. Should not be continued longer than 16 wk
- Trichloroacetic acid (30% to 80% solution)
  1. Acts by precipitation of surface proteins
  2. Applied twice monthly to lesion
  3. Indicated for vulvar, anal, and vaginal lesions; can be used for cervical lesions
  4. Less painful and irritating to normal tissue than podophyllin
- 5-Fluorouracil
  1. Causes necrosis and sloughing of growing tissue
  2. Can be used intravaginally or for vulvar, anal, or urethral lesions
  3. Better tolerated; 3 g (two thirds of vaginal applicator) applied weekly for 12 wk
  4. Possible vaginal ulceration and erythema
  5. Patient's vagina examined after four to six applications
  6. 80% cure rate

Physical agents:

- Cryotherapy with liquid nitrogen or cryoprobe
  1. Can be used weekly for 3 to 6 wk
  2. 62% to 79% success rate
  3. Not suitable for large warts
- Laser therapy
  1. Done by physician with necessary expertise and equipment
  2. Painful; requires anesthesia
- Electrocautery or excision
  1. For recurrent, very large lesions
  2. Local anesthesia needed

Immunotherapy:

- Interferon
  1. Injected intralesionally at a dose of 3 million U/m^2 three times weekly for 8 wk
  2. Side effects: fever, chills, malaise, headache
- Imiquimod 5% cream at night, 3× per wk up to 16 wk increases wart clearance after 3 mo
- Interferon, topical: increases wart clearance at 4 wk

DISPOSITION

- Follow-up exam every 6 to 12 mo, as needed.
- Correct and consistent male condom use might lower the chances of giving or getting genital HPV, but such use is not fully protective because HPV can infect areas that are not covered by a condom.

PREVENTION

- Routine vaccination of females at age 11 or 12 through age 26.
- Routine vaccination of males at age 11 or 12 through age 21 (up to age 26 for men who have sex with men or are immunocompromised patients).
- Gardasil vaccinates against types 6, 11, 16, and 18
- Cervarix vaccinates against types 16 and 18.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Genital Warts (Patient Information)
Warts (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READING

Centers for Disease Control and Prevention: *Sexually transmitted diseases guidelines, 2010*, MMWR Recomm Rep 59 (RR-12). 2010.

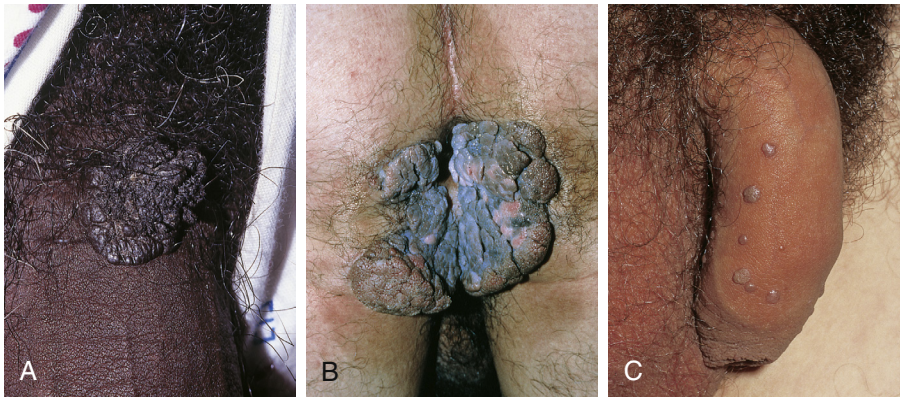


FIGURE EC1-94 Condyloma acuminatum. A, Scattered, flesh-colored or hyperpigmented, smooth or verrucous papules or erythematous macules along the shaft of the penis, scrotum, and perianal area are characteristic. The term *bowenoid papulosis* is used when the histologic picture of a lesion resembles Bowen's disease. **B,** Perianal condyloma acuminatum. The viral particles causing perianal condyloma may have originated from warts elsewhere on the body and been transmitted via the patient's own hands, or they may have been contracted during anal sex. **C,** Condyloma acuminatum. Multiple lesions on the shaft of the penis. (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

BASIC INFORMATION

DEFINITION

Congenital adrenal hyperplasia (CAH) is a spectrum of disorders resulting from a deficiency or complete lack of one of the enzymes in the cortisol synthesis pathway. These autosomal-recessive genetic disorders are usually characterized by cortisol deficiency and virilization, with or without salt wasting.

SYNONYMS

21-hydroxylase deficiency (equivalent to CYP21A2 deficiency)
11β-hydroxylase deficiency
3β-hydroxysteroid dehydrogenase deficiency
17-hydroxylase deficiency
Lipoid adrenal hyperplasia
Adrenal virilism
Adrenogenital syndrome
Virilizing adrenal hyperplasia

ICD-9CM CODES
255.2 Adrenogenital disorders; hyperplasia, congenital adrenal
ICD-10CM CODE
E25.0 Congenital adrenogenital disorders associated with enzyme deficiency

EPIDEMIOLOGY & DEMOGRAPHICS

- About 95% of cases of CAH are caused by 21-hydroxylase deficiency, of which two thirds are the salt-wasting form.
- Autosomal recessive inheritance.
- The "classic" form presents in childhood, nonclassic is mild or late onset.
- Incidence is estimated at about 1:10,000 to 1:20,000 live births (Hispanic >American Indian >white >black >Asian).
- Most common cause of ambiguous genitalia in 46,XX females.

CLINICAL PRESENTATION

"Classic" salt-wasting form (impaired cortisol and aldosterone synthesis):

- Adrenal crisis in first weeks of life with vomiting, poor weight gain, lethargy, dehydration, hyponatremia, hyperkalemia, and elevated plasma renin.
- Females are born with ambiguous genitalia that often leads to diagnosis before adrenal crisis occurs.
- Males may have greater penile size and smaller testes than expected during childhood. Males may also develop adrenal rests, or ectopic islands of adrenal cortical tissue in the testes, in childhood and may experience infertility as adults.
- If patients survive infancy, their overall life expectancy is not compromised.
- Both males and females may exhibit rapid growth in childhood due to early epiphyseal closure, which then results in short stature in adulthood.
- Precocious puberty is common in both males and females.

"Classic" non-salt-wasting or simple virilizing form (impaired cortisol synthesis only):

- Females present with ambiguous genitalia at birth.
- The normal appearance of male genitalia in the simple virilizing form makes this a difficult diagnosis in male infants.
- Characterized by precocious puberty, short stature, and testicular adrenal rests, as in the salt-wasting form.

"Nonclassic" or mild, late-onset form (varying degrees of androgen excess):

- Usually presents in adolescence or adulthood and is not detected on newborn screening.
- Often asymptomatic but can be associated with mild virilization.
- PCOS-like symptoms occur in women (hirsutism, oligomenorrhea, acne, infertility, insulin resistance, and abnormal menses).
- Associated with infertility in males.

ETIOLOGY

In 21-hydroxylase deficiency, the pathways for aldosterone production (from the conversion of progesterone to deoxycorticosterone) and cortisol production (from the conversion of 17-hydroxyprogesterone to 11-deoxycortisol) by the cP450 enzyme 21-hydroxylase are interrupted. The production of ACTH is thus stimulated by a negative feedback mechanism, leading to adrenal hyperplasia and mineralocorticoid deficiency as the intermediaries in aldosterone and cortisol synthesis are shunted to the androgen biosynthesis pathway (Fig. EC1-95*A* and *B*). A recombination event between the active CYP21A2 gene on chromosome 6p21.3 and the CYP21A1 pseudogene is thought to create the deficient 21-hydroxylase enzyme.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Precocious puberty
- Polycystic ovarian syndrome (PCOS)
- Androgen resistance syndromes
- Pseudohermaphroditism
- Mixed gonadal dysgenesis
- Testicular carcinoma
- Leydig cell tumors
- Adrenocortical carcinoma
- Addison's disease
- Pituitary adenoma

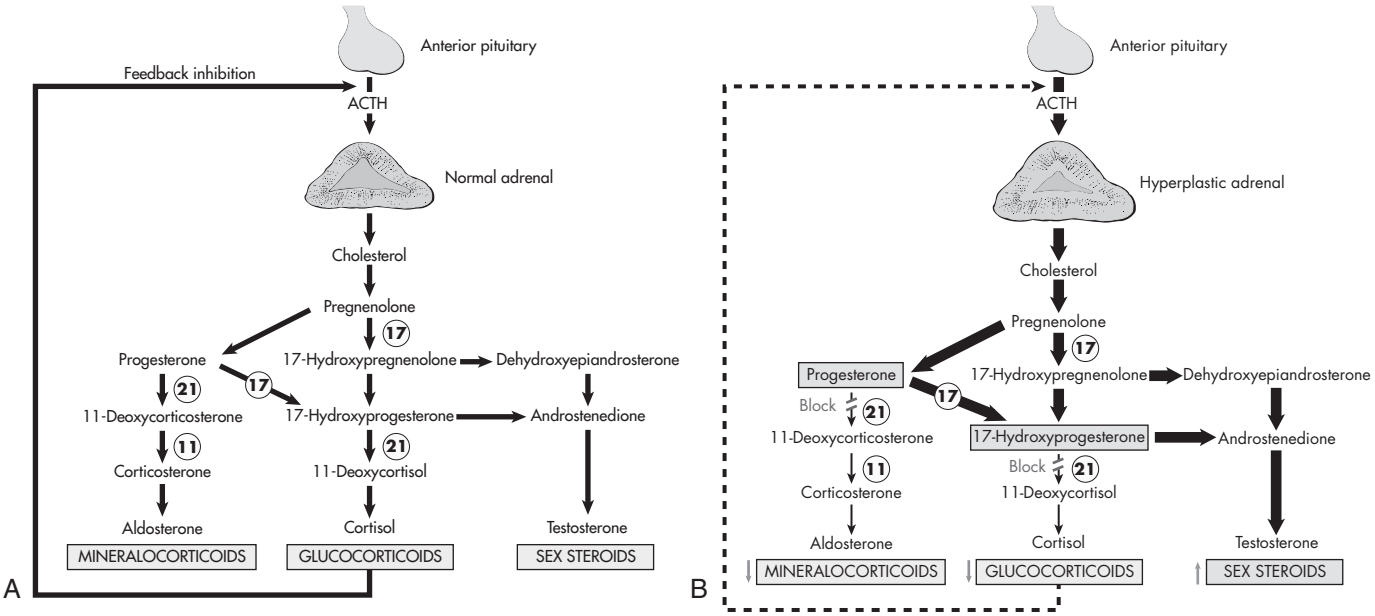


FIGURE EC1-95 A, Normal adrenal steroidogenesis. **B,** Consequences of C-21 hydroxylase deficiency. (From Cotran R et al [eds]: *Robbins pathologic basis of disease,* ed 6, Philadelphia, 1999, Saunders, p 1158.)

LABORATORY TESTS

- Prenatal: chorionic villus sampling for history; genetic testing or measurement of 17-hydroxyprogesterone if family history.
- Serum 17-hydroxyprogesterone level, which is included in the newborn screen in all states, is the first-line test for suspected CAH.
- Adrenocorticotropin (ACTH) stimulation test is the next step to confirm the diagnosis and identify type of CAH.
- Additional tests that may be useful include plasma renin activity, aldosterone level, and electrolytes.

IMAGING STUDIES

- Abdominal ultrasound to evaluate adrenal glands can accelerate diagnosis.
- Ultrasound to identify a uterus in cases of ambiguous genitalia.
- Ultrasound is preferred to rule out testicular adrenal rest tumors (found in classic and nonclassic forms) and should be done beginning in adolescence.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Surgical correction of ambiguous genitalia may be necessary.
- Monitoring: serum 17-hydroxyprogesterone and androstenedione, renin, electrolytes, blood pressure, bone age and density, Tanner staging, growth velocity, weight.
- Bilateral laparoscopic adrenalectomy with lifelong glucocorticoid and mineralocorticoid replacement (controversial).
- Gene therapy (hypothetical).
- Psychological counseling.

CHRONIC Rx

- Glucocorticoids to partially suppress adrenal androgen secretion. During periods of physiologic stress may need to be doubled or tripled.
  1. In children, hydrocortisone is preferred due to its short half-life, which minimizes the risk of iatrogenic short stature. Once patients are fully grown, long-acting glucocorticoids can be used.
  2. Adolescents/adults: dexamethasone 0.25 to 0.75 mg PO QHS (also used to treat adrenal rests) or prednisone 5 to 7.5 mg/day in 2 divided doses.
- Mineralocorticoids (e.g., fludrocortisone) to normalize electrolytes and plasma renin activity.
  1. In infants, salt supplementation is also required.
- Treatment of simple virilizing form: similar to salt-wasting form but mineralocorticoid replacement is unnecessary.
- Treatment of nonclassic form:
  1. In adolescent and adult women: oral contraceptives, glucocorticoids, and/or antiandrogens.
  2. In children and adult males, usually no treatment is necessary.
  3. Prenatal glucocorticoid treatment is controversial but may decrease virilization in female fetuses.

PEARLS & CONSIDERATIONS

COMMENTS

- Consider the diagnosis of classic salt-wasting CAH in infants with failure to thrive.
- There is believed to be an increased prevalence of CAH in patients diagnosed with adrenal "incidentalomas"—adrenal gland lesions detected unexpectedly on imaging, usually by MRI or CT scanning.
- Cushing's syndrome may result from overtreatment of CAH with glucocorticoids.
- Patients with CAH may suffer from gender identity disorders and sexual dysfunction.
- Table EC1-47 summarizes diagnosis and treatment of CAH.

PREVENTION

- Prenatal: Early CVS sampling. Use of dexamethasone 20 to 25 mg/kg daily beginning at 5- to 8-wk gestation for female fetuses only is controversial because long-term studies are unavailable.
- Neonatal screening.
- Genetic counseling.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **ELIZABETH BROWN, M.D.**, and **PATRICK NSEREKO, M.D.**

TABLE EC1-47 Diagnosis and Treatment of Congenital Adrenal Hyperplasia

Disorder	Affected Gene and Chromosome	Signs and Symptoms	Laboratory Findings	Therapeutic Measures
21-Hydroxylase deficiency, classic form	*CYP21* 6p21.3	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH, ↑↑ Baseline and ACTH-stimulated 17-hydroxyprogesterone	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia, ↑ Plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in females	↑ Serum androgens	Vaginoplasty and clitoral recession
		Postnatal virilization in males and females	↑ Serum androgens	Suppression with glucocorticoids
21-Hydroxylase deficiency, nonclassic form	*CYP21* 6p21.3	May be asymptomatic; precocious adrenarche, hirsutism, acne, menstrual irregularity, infertility	↑ Baseline and ACTH-stimulated 17-hydroxyprogesterone. ↑ Serum androgens	Suppression with glucocorticoids
11β-Hydroxylase deficiency	*CYP11B1* 8q24.3	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH	Glucocorticoid (hydrocortisone) replacement
			↑↑ Baseline and ACTH-stimulated 11-deoxycortisol and deoxycorticosterone	
		Ambiguous genitalia in females	↑ Serum androgens	Vaginoplasty and clitoral recession
		Postnatal virilization in males and females	↑ Serum androgens	Suppression with glucocorticoids
		Hypertension	↓ Plasma renin, hypokalemia	Suppression with glucocorticoids
3β-Hydroxysteroid dehydrogenase deficiency, classical form	*HSD3B2* 1p13.1	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH, ↑↑ Baseline and ACTH-stimulated D5 steroids (pregnenolone, 17-hydroxy pregnenolone, DHEA)	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia, ↑ Plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in females and males	↑ DHEA, ↓ androstenedione, testosterone, and estradiol	Surgical correction of genitals and sex hormone replacement as necessary, consonant with sex of rearing
		Precocious adrenarche, disordered puberty	↑DHEA, ↓ androstenedione, testosterone, and estradiol	Suppression with glucocorticoids
17α-Hydroxylase/17,20-lyase deficiency	*CYP17* 10q24.3	Cortisol deficiency (corticosterone is an adequate glucocorticoid)	↓ Cortisol, ↑ ACTH, ↑ DOC, corticosterone. Low 17α-hydroxylated steroids; poor response to ACTH	Glucocorticoid (hydrocortisone) administration
		Ambiguous genitalia in males	↓ Serum androgens; poor response to hCG	Orchidopexy or removal of intraabdominal testes; sex hormone replacement consonant with sex of rearing
		Sexual infantilism	↓ Serum androgens or estrogens	Sex hormone replacement consonant with sex of rearing
		Hypertension	↓ Plasma renin; hypokalemia	Suppression with glucocorticoids
Congenital lipoid adrenal hyperplasia	*STAR* 8p11.2	Glucocorticoid deficiency	↑ ACTH, Low levels of all steroid hormones, with decreased or absent response to ACTH	Glucocorticoid (hydrocortisone) replacement
		Mineralocorticoid deficiency (salt-wasting crisis)	Hyponatremia, hyperkalemia, ↓ Aldosterone, ↑ plasma renin	Mineralocorticoid (fludrocortisone) replacement; sodium chloride supplementation
		Ambiguous genitalia in males	Decreased or absent response to hCG in males	Orchidopexy or removal of intraabdominal testes; sex hormone replacement consonant with sex of rearing
		Poor pubertal development or premature ovarian failure in females	↑ FSH, ↑LH, ↓ estradiol (after puberty)	Estrogen replacement
P450 oxidoreductase deficiency	*POR* 7q11.3	Glucocorticoid deficiency	↓ Cortisol, ↑ ACTH, ↑ Pregnenolone, ↑ progesterone	Glucocorticoid (hydrocortisone) replacement
		Ambiguous genitalia in males and females	↑ Serum androgens prenatally, ↓ androgens and estrogens at puberty	Surgical correction of genitals and sex hormone replacement as necessary, consonant with sex of rearing
		Maternal virilization. Antley-Bixler syndrome	Decreased ratio of estrogens to androgens	

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

SUGGESTED READINGS

Pezzuti IL, Barra CB, Mantovani RM, Januário JN, Silva IN: A three-year follow-up of congenital adrenal hyperplasia newborn screening, *J Pediatr (Rio J)*, 2014.

Falhammar H et al.: Clinical outcomes in the management of congenital adrenal hyperplasia, *Endocrine* 41(3):355–373, 2012.

Speiser PW et al.: Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline, *J Clin Endocrinol Metab* 95:4133–4160, 2010.

BASIC INFORMATION

DEFINITION

The term *conjunctivitis* refers to an inflammation of the conjunctiva resulting from a variety of causes, including allergies and bacterial, viral, and chlamydial infections.

SYNONYMS

"Red eye"
Pink eye
Acute conjunctivitis
Subacute conjunctivitis
Chronic conjunctivitis
Purulent conjunctivitis
Pseudomembranous conjunctivitis
Papillary conjunctivitis
Follicular conjunctivitis
Newborn conjunctivitis

ICD-9CM CODES
372.30 Conjunctivitis, unspecified
ICD-10CM CODES
H10.9 Unspecified conjunctivitis
B30 Viral conjunctivitis
H10.0 Mucopurulent conjunctivitis
H10.1 Acute atopic conjunctivitis
H10.4 Chronic conjunctivitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 1.6% to 12% in *newborns*
PREVALENCE (IN U.S.):

- Allergic conjunctivitis (Fig. C1-96), the most common form of ocular allergy, is usually associated with allergic rhinitis and may be seasonal or perennial.
- Bacterial or viral conjunctivitis is often seasonal and can be extremely contagious.

PREDOMINANT AGE: Occurs at *any* age. Most cases in adults are due to viral infection. Children are more prone to develop bacterial conjunctivitis than viral forms.
PEAK INCIDENCE: More common in the spring and fall, when *viral* infections and pollens increase

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Infection and chemosis of conjunctivae with discharge. Gluing of the eyelids and no itching is more indicative of a bacterial cause (Fig. C1-97).
- Cornea is clear or can be involved.
- Vision is often normal but can be blurred.

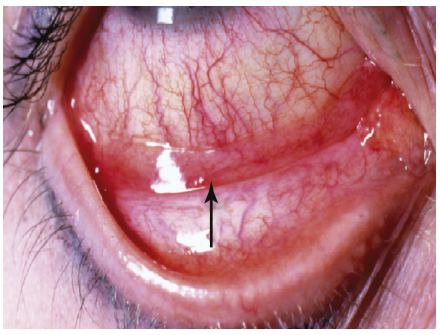


FIGURE C1-96 Allergic conjunctivitis. *Arrow* indicates area of chemosis in the conjunctivitis. (From Adkinson NF Jr et al [eds]: *Middleton's allergy principles and practice,* ed 7, vol 2, Philadelphia, 2008, Mosby.)

ETIOLOGY

- Bacterial: *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* in children; *Staphylococcus* species in adults. Gram-negative infections are more common in contact lens wearers. Gonococcal ophthalmia neonatorum is caused by *Neisseria gonorrhoeae* acquired by exposure of the neonatal conjunctivae to infected cervicovaginal secretions during delivery.
- Viral: most common overall cause of infectious conjunctivitis.
- Chlamydial.
- Allergic.
- Traumatic.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute glaucoma
- Corneal lesions
- Acute iritis
- Episcleritis
- Scleritis
- Uveitis
- Canalicular obstruction

WORKUP

- History and physical examination
- Reports of itching, pain, and visual changes

LABORATORY TESTS

Cultures are useful if not *successfully* treated with antibiotics; initial culture is usually not necessary, since normal conjunctival flora interferes with helpful culture results.

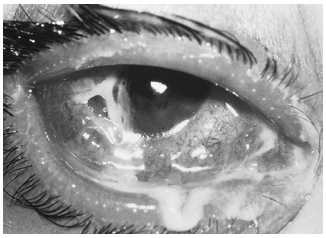


FIGURE C1-97 Bacterial conjunctivitis. Purulent discharge and conjunctiva hyperemia suggest bacterial conjunctivitis. Viral conjunctivitis produces watery discharge, foreign body sensation, preauricular lymphadenopathy, and conjunctival follicles seen on slit lamp examination. (Reproduced with permission from the American Academy of Ophthalmology. From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Warm compresses if infective conjunctivitis.
- Cold compresses if irritative or allergic conjunctivitis.
- Contact lenses should be taken out until an infection is completely resolved. Nondisposable lenses should be cleaned thoroughly as recommended by the manufacturer, and a new lens case should be used. Disposable contact lenses should be thrown away.

ACUTE GENERAL Rx

- The majority of cases of bacterial conjunctivitis are self-limiting and no treatment is necessary in uncomplicated cases.[1] Antibiotic drops (e.g., levofloxacin, ofloxacin, ciprofloxacin, tobramycin, gentamicin ophthalmic solution, 1 or 2 drops q2 to 4h) are indicated for complicated bacterial conjunctivitis, in conjunctivitis caused by gonorrhea or chlamydia, and in bacterial conjunctivitis in contact lens wearers.
- Caution: be careful with ophthalmic corticosteroid treatment, and avoid unless sure of diagnosis; corticosteroids can exacerbate infections and have been associated with increased intraocular pressure and cataract formation.
- An oral antihistamine (cetirizine, loratadine, desloratadine, or fexofenadine) is effective in relieving itching.
- Mast cell stabilizers (e.g., ketotifen, olopatadine, azelastine bid) are effective for allergic conjunctivitis. Others include Elestat, Optivar, and Patanol.
- Bepotastine, alcaftadine, azelastine, epinastine, and ketotifen are H1-antihistamines and mast cell stabilizers effective for topical treatment of itching associated with allergic conjunctivitis. The topical NSAID ketorolac (0.5%, 1 drop qd) is also useful in allergic conjunctivitis. Table C1-48 describes topical ophthalmic medications for allergic conjunctivitis.
- Antihistamine/decongestant combinations such as pheniramine/naphazoline (Visine A), available over the counter, are more effective than either agent alone but have a short duration and can result in rebound vasodilatation with prolonged use. Others include Naphcon-A, Albalon~A, and Opcon-A.

CHRONIC Rx

- Depends on cause.
- If allergic, nonsteroidals such as ketorolac, and bromfenac ophthalmic solution; mast cell stabilizers such as Patanol and Zaditor are useful for improving ocular itching in patients with allergic conjunctivitis.
- If an infection, use antibiotic drops (see "Acute General Rx").
- Dry eyes need artificial tears (Restasis) or lacrimal duct plugs when indicated.

DISPOSITION

Follow carefully for the first 2 wk to ensure secondary complications do not occur. Otitis media

[1]Azari AA, Barney NP: Conjunctivitis, a systematic review of diagnosis and treatment, *JAMA* 310(16):1721-1729, 2013.

TABLE C1-48 Topical Ophthalmic Medications for Allergic Conjunctivitis

Generic Drug Name (Trade Name)	Mechanism of Action and Dosing	Cautions and Adverse Events
Azelastine hydrochloride 0.05% (Optivar)	Antihistamine Children ≥3 yr: 1 gtt bid	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Emedastine difumarate 0.05% (Emadine)	Antihistamine Children ≥3 yr: 1 gtt qid	Soft contact lenses should not be worn if the eye is red. Wait at least 10 min after administration before inserting soft contact lenses.
Levocabastine hydrochloride 0.05% (Livostin)	Antihistamine Children ≥12 yr: 1 gtt bid-qid up to 2 wk	Not for use in patients wearing soft contact lenses during treatment.
Pheniramine maleate 0.3% or 0.025%	Antihistamine/vasoconstrictor	Avoid prolonged use (>3 to 4 days) to avoid rebound symptoms. Not for use with contact lenses.
Naphazoline hydrochloride (Naphcon-A, Opcon-A)	Children >6 yr: 1 to 2 gtt qid	
Cromolyn sodium 4% (Crolom, Opticrom)	Mast cell stabilizer Children >4 yr: 1 to 2 gtt q4-6h	Can be used to treat giant papillary conjunctivitis and vernal keratitis. Not for use with contact lenses.
Lodoxamide tromethamine 0.1% (Alomide)	Mast cell stabilizer Children ≥2 yr: 1 to 2 gtt qid up to 3 mo	Can be used to treat vernal keratoconjunctivitis. Not for use in patients wearing soft contact lenses during treatment.
Nedocromil sodium 2% (Alocril)	Mast cell stabilizer Children ≥3 yr: 1 to 2 gtt bid	Avoid wearing contact lenses while exhibiting the signs and symptoms of allergic conjunctivitis.
Pemirolast potassium 0.1% (Alamast)	Mast cell stabilizer Children >3 yr: 1 to 2 gtt qid	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Epinastine hydrochloride 0.05% (Elestat)	Antihistamine/mast cell stabilizer Children ≥3 yr: 1 gtt bid	Contact lenses should be removed before use. Wait at least 15 min after administration before inserting soft contact lenses. Not for the treatment of contact lens irritation.
Ketotifen fumarate 0.025% (Zaditor)	Antihistamine/mast cell stabilizer Children ≥3 yr: 1 gtt bid q8-12h	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Olopatadine hydrochloride 0.1%, 0.2% (Patanol, Pataday)	Antihistamine/mast cell stabilizer Children ≥3 yr: 1 gtt bid (8 hr apart), 1 gtt qid	Not for treatment of contact lens–related irritation; the preservative may be absorbed by soft contact lenses. Wait at least 10 min after administration before inserting soft contact lenses.
Ketorolac tromethamine 0.5% (Acular)	NSAID Children ≥3 yr: 1 gtt qid	Avoid with aspirin or NSAID sensitivity. Use ocular product with caution in patients with complicated ocular surgeries, corneal denervation or epithelial defects, ocular surface diseases (e.g., dry eye syndrome), repeated ocular surgeries within a short period of time, diabetes mellitus, or rheumatoid arthritis; these patients may be at risk for corneal adverse events that may be sight threatening. Do not use while wearing contact lenses.

NSAID, Nonsteroidal antiinflammatory drug.
Modified from Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

can develop in 25% of children with *H. influenzae* conjunctivitis. Bacterial keratitis occurs in 30/1000 contact lens wearers.

REFERRAL

To ophthalmologist if symptoms are refractory to initial treatment. Indications for urgent referral are severe eye pain or headache, photophobia, decreased vision, and contact lens use.

PEARLS & CONSIDERATIONS

COMMENTS

- Red eyes are not simply conjunctivitis when the patient has significant pain or loss of sight. However, it is usually safe to treat pain-free eyes and the normal-seeing red eye with lid hygiene and topical treatment.
- Use caution with patients wearing soft contact lenses, infants, and the elderly.
- Do not use steroids indiscriminately; use only when the diagnosis is certain.
- Bacterial conjunctivitis is generally self-limiting. Over 60% of persons will improve with placebo within 2 to 5 days.

RELATED CONTENT

Conjunctivitis (Patient Information)

AUTHOR: **R. SCOTT HOFFMAN, M.D.**

Contact Dermatitis PTG EBM

BASIC INFORMATION

DEFINITION

Contact dermatitis is an acute or chronic skin inflammation, usually eczematous dermatitis resulting from exposure to substances in the environment. It can be subdivided into "irritant" contact dermatitis (nonimmunologic physical and chemical alteration of the epidermis) and "allergic" contact dermatitis (delayed hypersensitivity reaction).

SYNONYMS

Irritant contact dermatitis
Allergic contact dermatitis

ICD-9CM CODES
692 Contact dermatitis and other eczema
ICD-10CM CODES
L23 Allergic contact dermatitis
L23.0 Allergic contact dermatitis due to metals
L23.1 Allergic contact dermatitis due to adhesives
L23.2 Allergic contact dermatitis due to cosmetics
L23.3 Allergic contact dermatitis due to drugs in contact with skin
L23.4 Allergic contact dermatitis due to dyes
L23.5 Allergic contact dermatitis due to other chemical products
L25.9 Unspecified contact dermatitis, unspecified cause

EPIDEMIOLOGY & DEMOGRAPHICS

- 20% of all cases of dermatitis in children are caused by allergic contact dermatitis.
- Rhus dermatitis (poison ivy, poison oak, and poison sumac) is responsible for most cases of contact dermatitis.
- Frequent causes of irritant contact dermatitis are soaps, detergents, and organic solvents.
- Chemical irritants (e.g., cutting fluids used in machining, solvents) account for most cases of irritant contact dermatitis. Occupational skin diseases are second only to traumatic injuries as the most common types of occupational disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Clinical presentation varies with the responsible agent and affected area of skin.

IRRITANT CONTACT DERMATITIS:

- Mild exposure may result in dryness, erythema, and fissuring of the affected area (e.g., hand involvement in irritant dermatitis caused by exposure to soap (Fig. EC1-98), genital area involvement in irritant dermatitis caused by prolonged exposure to wet diapers).
- Eczematous inflammation may result from chronic exposure.

ALLERGIC CONTACT DERMATITIS:

- Poison ivy dermatitis can present with vesicles and blisters; linear lesions (as a result of dragging of the resins over the surface of the skin by scratching) are a classic presentation.
- The pattern of lesions is asymmetric; itching, burning, and stinging may be present.
- The involved areas are erythematous, warm to touch, swollen, and may be confused with cellulitis.

ETIOLOGY

- Irritant contact dermatitis: cement (construction workers), rubber, ragweed, malathion (farmers), orange and lemon peels (chefs, bartenders), hair tints, shampoos (beauticians), rubber gloves (medical, surgical personnel)
- Allergic contact dermatitis: poison ivy, poison oak, poison sumac, rubber (shoe dermatitis), nickel (jewelry), balsam of Peru (hand and face dermatitis), neomycin, formaldehyde (cosmetics)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Impetigo
- Lichen simplex chronicus
- Atopic dermatitis
- Nummular eczema, dyshidrotic eczema
- Seborrheic dermatitis
- Inverse psoriasis, palmoplantar psoriasis
- Scabies
- Tinea pedis

WORKUP

- Medical history: gradual onset versus rapid onset, number of exposures, clinical presentation, occupational history.
- Physical examination: contact dermatitis in the neck may be caused by necklaces, perfumes (Fig. EC-99), after-shave lotion. Involvement of the axillae is often secondary to deodorants, clothing. Face involvement can occur with cosmetics, airborne allergens, aftershave lotion.

LABORATORY TESTS

- Patch testing has a sensitivity and specificity of 70% to 80%. It is useful to confirm the diagnosis of contact dermatitis; it is indicated only when inflammation persists despite appropriate topical therapy and avoidance of suspected causative agent; patch testing should not be used for irritant contact dermatitis because this is a nonimmunologic-mediated inflammatory reaction.
- Dermoscopy and microscopy when suspecting scabies and mites.
- A potassium hydroxide (KOH) preparation may be useful if suspecting tinea or Candida infection.

TREATMENT

NONPHARMACOLOGIC THERAPY

Avoidance of suspected allergens

ACUTE GENERAL Rx

- Removal of the irritant substance by washing the skin with plain water or mild soap within 15 min of exposure is helpful in patients with poison ivy, poison oak, or poison sumac dermatitis.
- Cold or cool water compresses for 20 to 30 min 5 to 6 times a day for the initial 72 hr are effective during the acute blistering stage.
- Topical steroids (clobetasol 0.05%, triamcinolone 0.1%) are effective for acute localized allergic contact dermatitis lesions. Lower-potency topical steroids are preferred on face, anogenital regions, and flexural surfaces to minimize risk of skin atrophy. Oral corticosteroids (e.g., prednisone 20 mg bid for 6 to 10 days) are generally reserved for severe, widespread dermatitis.
- IM steroids (e.g., Kenalog) are used for severe reactions and in patients requiring oral corticosteroids but unable to tolerate PO.
- Oral antihistamines (e.g., hydroxyzine 25 mg q6h) will control pruritus, especially at night; calamine lotion is also useful for pruritus; however, it can lead to excessive drying.
- Colloidal oatmeal (Aveeno) baths can also provide symptomatic relief.
- Patients with mild to moderate erythema may respond to topical steroid gels or creams.
- Patients with shoe allergy should change their socks at least once a day; use of aluminum chloride hexahydrate in a 20% solution (Drysol) qhs will also help control perspiration.
- Use hypoallergenic surgical gloves in patients with rubber and surgical glove allergy.

DISPOSITION

Allergic contact dermatitis generally resolves within 2 to 4 wk if re-exposure to allergen is prevented.

REFERRAL

For patch testing in selected patients, see "Laboratory Tests."

PEARLS & CONSIDERATIONS

COMMENTS

Commercially available corticosteroid dose packs should be avoided, because they generally provide an inadequate amount of medication.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Contact Dermatitis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Topical agents indicated for the treatment of superficial wounds have the potential to cause irritation or allergic contact dermatitis, particularly when applied to an impaired skin barrier.

Objective:

We sought to compare the irritancy potential of 5 topical wound care products commonly used in dermatologic practice on normal and compromised skin.

Methods:

Agents tested included Aquaphor Healing Ointment (AHO) (Beiersdorf Inc, Wilton, CT); bacitracin; Biafine Topical Emulsion (BTE) (OrthoNeutrogena, Los Angeles, CA); Neosporin (Poly/Bac/Neo) (Johnson & Johnson, New Brunswick, NJ); and Polysporin (Poly/Bac) (Johnson & Johnson). Study 1 assessed cumulative irritation using a modified human repeat insult patch test on normal back skin with an induction phase (test materials applied under occlusive patch 9 times at 48- to 72-hour intervals) and a challenge phase (test materials applied to original and naïve sites for 48 hours, 12 to 24 days postinduction). Irritation was graded for erythema and type IV allergy skin responses. Study 2 assessed the acute irritation potential of agents on tape-stripped ("wounded") back skin. Test sites were graded for erythema, transepidermal water loss, and skin color (Chroma Meter a*) (Minolta, Osaka, Japan) at 48 and 72 hours poststripping.

Results:

In study 1, cumulative irritation testing in 108 subjects classified AHO, bacitracin, Poly/Bac/Neo, and Poly/Bac as "mild," and BTE as "probably mild." In study 2 at 72 hours, mean clinical grading scores were significantly higher for BTE and Poly/Bac/Neo than AHO. Transepidermal water loss and colorimeter a* values were significantly lower for AHO and bacitracin compared with BTE. No allergic contact dermatitis was seen in either study.

Conclusions:

Patch test studies demonstrated that BTE showed the greatest irritancy potential in both normal and compromised skin whereas AHO showed the least.Ⓐ

Abstract[2]

Background:

It has been found that patch testing with 15 μL formaldehyde 2·0% aq. detects twice as many allergies as by testing with 1·0%. The clinical relevance of positive patch test reactions is often difficult to determine. Repeated open application tests are simple to do and help to evaluate the significance of patch test results.

Objectives:

To study the clinical relevance of contact allergy to formaldehyde detected by 2·0% formaldehyde (0·60 mg cm(−2)) but not by 1·0%.

Methods:

Eighteen patients positive to formaldehyde 2·0% but negative to 1·0%, and a control group of 19 patients with dermatitis but without allergy to parabens, formaldehyde, and formaldehyde releasers were included in the study. Formaldehyde 2000 p.p.m., the maximum concentration permitted in leave-on cosmetics according to the EU Cosmetics Directive, was added to a batch of moisturizer preserved with parabens. The same batch without formaldehyde served as a control. The study was double-blinded and randomized. The patients were provided with both moisturizers and instructed to apply one of them twice a day on a marked-out 5×5-cm area on the inside of one upper arm and the other moisturizer on the other arm. Reading of the test sites was done once a week for a maximum of 4 weeks.

Results:

In the control group there were no allergic reactions to either of the moisturizers. Nine of 17 formaldehyde-allergic patients reacted with an allergic reaction to the moisturizer which contained formaldehyde ($P<0·001$). No positive reactions were observed to the moisturizer without formaldehyde.

Conclusions:

Our results demonstrate that contact allergy to formaldehyde 2·0% may be clinically relevant.Ⓐ

Abstract[3]

Background:

Multiple studies have evaluated diverse allergens in paediatric populations. Consensus is still lacking on which allergens are most commonly implicated in allergic contact dermatitis.

Objectives:

To evaluate the proportion of positive reactions for allergens tested in children and to identify allergens with positive reactions in at least 1% of them.

Methods:

This was a systematic review of studies in PubMed (1966-2010) investigating allergens in at least 100 enrolled children. Proportions of positive reactions for each allergen were combined with random effects models across studies.

Results:

We included 49 studies with available data on 170 allergens. Each study tested a median of two allergens. Among the 94 allergens evaluated by at least two studies, 58 had estimates of positive reactions of at least 1% by random effects calculations, and for 21 of them the 95% confidence interval ensured that the proportion of positive reactions was at least 1%. The top five allergens tested by at least two studies included nickel sulfate, ammonium persulfate, gold sodium thiosulfate, thimerosal, and toluene-2,5-diamine (p-toluenediamine). For most allergens, the proportion of positive reactions was higher in studies published after 1995 than in earlier studies (p=0.0065).

Conclusions:

This meta-analysis offers guidance on which allergens are most prevalent in the paediatric population and should have priority for inclusion in standardized allergen series.Ⓐ

Abstract[4]

Background:

Dimethylfumarate is a potent contact sensitizer with antimicrobial and mold-preventing effects. Sofa dermatitis has affected hundreds of patients who are exposed to dimethylfumarate in sachets designed to prevent mold in furniture being stored or transported. A case of allergic contact dermatitis developed in a man who came into contact with dimethylfumarate in a leather sofa.

Case Report:

Man, 49, had widespread pruritic erythematous dermatitis of 2 weeks' duration that had begun on his thighs but now extended to the back, buttocks, and arms. The affected skin sites had been in contact with a sofa purchased 6 months previously, so a diagnosis of allergic contact dermatitis was made. Oral prednisone and avoidance of contact with the sofa resulted in healing of the dermatitis, but in 4 weeks the patient developed hyperpigmented areas at the resolved dermatitis sites. Biopsy of the sites showed no melanocytes. Patch tests with the baseline Spanish contact dermatitis research group series, textile dyes, and footwear series yielded a nonrelevant positive result for wood alcohols. A positive result was obtained from patch testing with dimethylfumarate. However, the patch test site did not develop depigmentation. After 2 years of follow-up, the depigmented areas remained. The patient reported no personal or family history of vitiligo or other autoimmune disease. Depigmentation after contact eczema has been reported in various settings, such as occupationally or after the private use of sensitizing agents such as phenol and cathecol derivatives or sulfhydryl compounds. The lack of vitiligo history makes this less likely, but the repeated exposure to dimethylfumarate for 6 months, the location of the acquired depigmented areas at sites where contact dermatitis had been, and the temporal association suggested leukoderma after dimethylfumarate dermatitis.

Conclusions:

Contact leukoderma is characterized by the loss of pigment after exposure to chemicals that produce specific, selective melanocytopenia. Either

allergic dermatitis or toxic depigmenting effects can precede contact leukoderma. The exact mechanism by which the pigmentary change occurs is unknown. It may result from a melanocytotoxic effect independent of its sensitizing potential. Genetic susceptibility and the nature of the chemical contribute to the severity of the lesions. Dimethylfumarate should be added to the list of substances that can cause depigmentation.Ⓐ

Evidence-Based References

Trookman NS et al.: Irritation and allergy patch test analysis of topical treatments commonly used in wound care: evaluation on normal and compromised skin, *J Am Acad Dermatol* 64:S16–S22, 2011. Ⓐ

Hauksson I et al.: Clinically relevant contact allergy to formaldehyde may be missed by testing with formaldehyde 1·0, *Br J Dermatol* 164:568–572, 2011. Ⓐ

Bonitsis NG et al.: Allergens responsible for allergic contact dermatitis among children: a systematic review and meta-analysis, *Contact Dermatitis* 64:245–257, 2011. Ⓐ

Vives R et al.: Leucoderma after Chinese sofa dermatitis, *Contact Dermatitis* 64:58–62, 2011. Ⓐ

SUGGESTED READING

Usatine RP, Riojas M: Diagnosis and management of contact dermatitis, *Am Fam Physician* 82(3):249–255, 2010.

FIGURE EC1-98 Hand dermatitis from a cleanser. The doctor should always consider allergic contact dermatitis in a patient presenting with an eczematous eruption. The hands are a common site for both allergic and irritant contact dermatitis, because they come into contact with so many things. This patient was allergic to an ingredient in the cleanser used at work. (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

FIGURE EC1-99 Perfume and medicament allergy. Multiple allergies are often found. This patient developed a reaction first to a perfume and then to a topical medication applied to soothe the initial rash. (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

BASIC INFORMATION

DEFINITION

Contraception refers to the various modalities that a sexually active couple use to prevent pregnancy. These options can be either medical or nonmedical and used by men or women or both. An algorithm for helping couples select a contraceptive method is described in Fig. EC1-100. Online Appendices A-F summarize U.S. medical eligibility criteria for contraceptive use. The options are as follows:

- No contraception (unprotected intercourse) failure rate 85% both typical use and perfect use
- Abstinence
  1. 12.4% of unmarried men
  2. 13.2% of unmarried women
  3. More frequently practiced before age 17 yr
  4. No intercourse experienced by 13% of women ages 30 to 34 yr
  5. Failure rate 0%
- Withdrawal
  1. Used in only 2% of sexually active women
  2. Failure rate with perfect use, 4%; with typical use, 19%
- Rhythm method (natural family planning)
  1. Failure rate with perfect use, 1% to 9%; with typical use, 20%
  2. Symptothermal type: mucus method and ovulation pain combined with basal body temperature
  3. Ovulation (Billings' method): takes into account mucus quality
  4. Basal body temperature method: uses biphasic temperature chart
  5. Lactation amenorrhea method: effective in fully breastfeeding women, especially 70 to 100 days after delivery; depends on number of feedings per day
- Barriers
  1. Diaphragm and cervical cap: failure rate 5% to 9% in nulliparous women, 20% in multiparous women
  2. Female condom: failure rate with perfect use, 5.1%; with typical use, 12.4%; FDA labeling states 25% failure rate
  3. Male condom: failure rate with perfect use, 3%; with typical use, 12%
  4. Spermicides (aerosols, foam, jellies, creams, tabs): failure rate with perfect use, 3%; with typical use, 21%
- Oral contraceptives
  1. Failure rate with perfect use, <1%; with typical use, 3%
  2. Come in combinations of estrogen/progestin or as progestin only
- Hormonal implants and injectables
  1. Implanon (etonogestrel) implant 2-yr cumulative pregnancy rate 0.05%. Nexplanon is essentially the same as Implanon but with a barium sulfate core for easier radiologic detection and a preloaded applicator to facilitate insertion.
  2. Depo-Provera: failure rate 0.3% in first year of use
  3. Lunelle failure rate 0.2% in first year
  4. Nestorone-releasing single implant: not yet available
  5. Jadelle implant: Successor to the Norplant implant, which has been discontinued in the U.S. The Jadelle implant is not available in the U.S.
- Mini pill (progesterone only pill)
  1. Failure rate with typical use, 1.1% to 13.2%
  2. With perfect use, 5 pregnancies per 1000 women
- Emergency postcoital contraception
  1. Decreases pregnancy rate by 75% with women treated immediately postcoitally
  2. Involves dedicated hormonal (Plan B, which contains levonorgestrel) use or intrauterine device (IUD) insertion
- IUD (available over the counter in some states)
  1. Progestasert: failure rate with perfect use, 2%; with typical use, 3%
  2. Copper T (30-A): failure rate with perfect use, 0.8%; with typical use, 3%
  3. Levonorgestrel Intrauterine System (Mirena)
     - 1-yr failure rate, 1%
     - 5-yr cumulative failure rate, 0.71 per 100 women
- Female sterilization (tubal ligation): failure rate with perfect use, 0.2%; with typical use, 3%
- Male sterilization (vasectomy): failure rate of 0.1% in first year
- Vaginal ring (Nuva ring): failure rate pearl index 0.77
- Contraceptive patch (Ortho Evra): failure rate 0.4% to 0.7%

SYNONYMS

Birth control
Family planning

ICD-9CM CODES	
V25.01	Oral contraceptives
V25.02	Other contraceptive measures
V25.09	Family planning
V25.1	IUD
V25.2	Sterilization
ICD-10CM CODES	
Z30.011	Encounter for initial prescription of contraceptive pills
Z30.018	Encounter for initial prescription of other contraceptives
Z30.09	Encounter for other general counseling and advice on contraception
Z30.430	Encounter for insertion of intrauterine contraceptive device
Z30.2	Encounter for sterilization

DIAGNOSIS

WORKUP

- Thorough medical history
- Thorough surgical history
- Obstetric history (was fertility desired with conception?)
- Gynecologic history, including:
  1. History of previous sexually transmitted diseases
  2. Number of partners
  3. Previous difficulties with contraception
  4. Frequency of intercourse
- Family history

LABORATORY TESTS

- Pap smear
- Cultures, aerobic and *Chlamydia*
- Pregnancy test if suspected pregnancy
- Lipid profile if family history of premature vascular event

TREATMENT

NONPHARMACOLOGIC THERAPY

- Male condoms
  1. 95% latex (rubber), 5% skin or natural membrane
  2. Proper use: place on an erect penis and leave ½-inch empty space at the tip of the condom; use with non–oil-based lubricants
  3. Effectiveness increased when used with spermicides
- Female condoms
  1. Composed of polyurethane, with one end open and one end closed
  2. Proper use: place closed end over cervix, open end hanging out of vagina to cover penis and scrotum
  3. Highly effective against HIV
- Spermicides
  1. Types: nonoxynol, octoxynol
  2. Forms: jellies, creams, foams, suppositories, tablets, soluble films
  3. Proper use: put in immediately before intercourse; may be used with other barrier methods
- Diaphragm and cervical cap
  1. Must be fitted by practitioner, used with contraceptive gels, and refitted with weight gain or loss of 4.5 kg. Must also be refit after pregnancy.
  2. Diaphragm sizes: 50 to 105 mm; cervical cap sizes 26, 28, and 30 mm
  3. The correct fit allows the woman to remain ambulatory without feeling the device
  4. Proper use of diaphragm: put in immediately before intercourse and keep in for 6 hr after intercourse; must not remain in the vagina for longer than 24 hr
  5. Proper use of cervical cap: fit over the cervix exactly; must not remain in place for longer than 48 hr
- Lactation amenorrhea method
  1. Depends on number of feedings per day; effective as birth control for 6 mo if 15 or more feedings, lasting 10 min each, are accomplished daily. If woman meets criteria (e.g., breastfeeding only source of infant feeding) 0.5%-2.0% failure rate in the first 6 months after delivery.
  2. Not a common practice in the U.S.
- Withdrawal

1. Withdrawal of the penis from the vagina before ejaculation
2. Depends on self-control, but even with withdrawal high typical use failure rate.

- Rhythm method
  1. Depends on awareness of physiology of male and female reproductive tracts
  2. Sperm viable in vagina for 2 to 7 days
  3. Ovum life span 24 hr
- Sterilization
  1. Male:
     - Vasectomy to interrupt vas deferens and block passage of sperm to seminal ejaculate
     - Scalpel and nonscalpel techniques available
     - More easily performed procedure than female sterilization and does not require general anesthesia
  2. Female:
     - Leading method of birth control in U.S. in women older than 30 yr
     - Interrupts fallopian tubes, blocking passage of ovum proximally and sperm distally through tube
     - Several types; modified Pomeroy done during cesarean section or interval laparoscopic using clips (Filshie, Hulka) or banding
     - Essure-tubal occlusion through hysteroscopic placement of micro-inserts into the fallopian tubes.

ACUTE GENERAL Rx

- Combination oral contraceptives
  1. Taken daily for 21 days, pill-free interval of 7 days
  2. Less than 50 mcg ethinyl estradiol in most common combination oral contraceptives; progestins most commonly used in combination pills are norethindrone, levonorgestrel, norgestrel, norethindrone acetate, ethynodiol diacetate, norgestimate, or desogestrel; triphasic combination oral contraceptives (give varying doses of progestin and estrogens throughout cycle); monophasic oral contraceptives: offer same dose of progestin and estrogen throughout cycle, taken daily at same time; estrophasic pill (constant progesterone with variation of estrogen throughout the cycle)
  3. If pill taken with antibiotics, efficacy affected by inadequate gastrointestinal absorption in most cases; only rifampin truly reduces pill's effectiveness
  4. Increased body weight decreases effectiveness
  5. Table EC1-49 describes oral contraceptive formulations available in the United States. Guidelines for use of combination estrogen-progestin contraceptives in women 35 years of age and older are described in Table EC1-50
- Mini pill
  1. Progestin only; taken without a break
  2. Causes much irregular bleeding because of the lack of estrogen effect on the lining of the uterus
  3. Table EC1-51 provides a summary and recommendations for progestin-only oral contraceptive use
- Hormonal implants and injectables
  1. Implanon/Nexplanon
     - Single etonogestrel-secreting device that is inserted underneath the skin
     - Among the most effective contraceptive available
     - Approved by FDA in 2006 and effective over 3-yr period
  2. Depo-Provera
     - Medroxyprogesterone acetate given every 3 mo in IM injection form
     - Major side effect: irregular bleeding
     - Fertility return possibly delayed up to 1 year or longer after last injection
     - Table EC1-52 provides a summary and recommendations for depot medroxyprogesterone acetate (DMPA) use
  3. Lunelle: monthly injectable administered intramuscularly. Contains 0.5 ml aqueous, 5 mg estradiol cypionate, and 25 mg medroxyprogesterone acetate
- Postcoital contraception
  1. Done on emergency basis, usually as a result of noncompliance with birth control or failure of birth control (e.g., condom breakage) at the time of ovulation
  2. Methods:
     - Hormonal methods:
       - Levonorgestrel is available either as two 0.75 mg tablets taken 12 hr apart (next choice) or as a 1.5 mg tablet taken once (Plan B, one step). It is indicated for emergency contraception to be used within 72 hr after unexpected intercourse. It can be obtained OTC by women >15 yr of age and by prescription by younger patients
       - Ulipristal (ELLA) is a progesterone-receptor agonist/antagonist available by prescription only. It is a 30-mg, single-dose tablet and can be taken up to 5 days after unexpected intercourse
       - Copper IUD insertion within 5 days of coitus
- IUD
  1. Device inserted into uterus to prevent sperm and ovum from uniting in fallopian tube
  2. Types available in the U.S.:
     - ParaGard (Copper T/30-A): a polyethylene T wrapped with a fine copper wire effective for 10 yr
     - Mirena Levonorgestrel Intrauterine System: a T-shaped system with a chamber that contains levonorgestrel. Releases 20 mcg/day; is effective for 5 yr
- Vaginal ring (NuvaRing)
  1. Provides daily dose of 120 mcg of etonogestrel and 15 mcg ethinyl estradiol
  2. Stays in vagina 3 wk and is removed the fourth for a contraceptive-free interval analogous to the placebo pills in oral contraceptive pills
  3. Increased body weight decreases effectiveness
- Contraceptive patch (Ortho-Evra)
  1. Provides low daily dose of steroids
  2. Releases a progestin and estrogen (ethinyl estradiol)
  3. Patch size 20 cm^2
  4. Each patch contains 6 mg norelgestromin and delivers an estimated continuous systemic dose of 150 mcg norelgestromin and 20 mcg of ethinyl estradiol; common dose 250 mcg/day progestin and 25 mcg/day estrogen
  5. Worn 3 out of 4 wk
  6. Increased body weight decreases effectiveness
  7. Concern for increased risk of thromboembolic events

CHRONIC Rx

- With all the previously mentioned types of birth control, patient is followed up at least yearly, or as necessary, if problems arise.
- Full history, physical examination, and Pap smear, including cultures when needed, are performed yearly.
- Patients with medical problems are followed up approximately every 6 mo when taking hormonal therapy.

DISPOSITION

- Follow yearly or more frequently according to patient's side effects.
- Tailor birth control to patient according to different needs or side effects present at different times in life. Effective counseling also requires an understanding of a woman's preference and medical risks, benefits, side effects, and contraindications of each contraceptive method.

COMMENTS

- With hormonal contraception, if neurologic or cardiac symptoms arise, stop method immediately, evaluate, and refer to internist when appropriate.
- The effectiveness of long-acting reversible contraception (IUDs and implants) is superior to that of contraceptive pills, patch, or ring and is not altered in adolescents and young women.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Contraception (Patient Information)
Emergency Contraception (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

EVIDENCE

Abstract[1]

Objective:
To compare the risk of non-fatal venous thromboembolism in women receiving oral contraceptives containing drospirenone with that in women receiving oral contraceptives containing levonorgestrel.

Design:
Nested case-control and cohort study.

Setting:
The study was based on information from PharMetrics, a United States based company that collects information on claims paid by managed care plans.

Participants:
The study encompassed all women aged 15 to 44 years who received an oral contraceptive containing either drospirenone or levonorgestrel after 1 January 2002. Cases were women with current use of a study oral contraceptive and a diagnosis of venous thromboembolism in the absence of identifiable clinical risk factors (idiopathic venous thromboembolism). Up to four controls were matched to each case by age and calendar time.

Main Outcome Measures:
Odds ratios comparing the risk of non-fatal venous thromboembolism in users of the two contraceptives; incidence rates and rate ratios of nonfatal venous thromboembolism for users of each of the study contraceptives.

Results:
186 newly diagnosed, idiopathic cases of venous thromboembolism were identified in the study population and matched with 681 controls. In the case-control analysis, the conditional odds ratio for venous thromboembolism comparing use of oral contraceptives containing drospirenone with use of those containing levonorgestrel was 2.3 (95% confidence interval 1.6 to 3.2). The incidence rates for venous thromboembolism in the study population were 30.8 (95% confidence interval 25.6 to 36.8) per 100 000 woman years among users of oral contraceptives containing drospirenone and 12.5 (9.61 to 15.9) per 100,000 woman years among users of oral contraceptives containing levonorgestrel. The age-adjusted incidence rate ratio for venous thromboembolism for current use of oral contraceptives containing drospirenone compared with those containing levonorgestrel was 2.8 (2.1 to 3.8).

Conclusions:
The risk of non-fatal venous thromboembolism among users of oral contraceptives containing drospirenone seems to be around twice that of users of oral contraceptives containing levonorgestrel, after the effects of potential confounders and prescribing biases have been taken into account. Ⓐ

Abstract[2]

Context:
Combinations of testosterone (T) and nestorone (NES; a nonandrogenic progestin) transdermal gels may suppress spermatogenesis and prove appealing to men for contraception.

Objective:
The objective of the study was to determine the effectiveness of T gel alone or combined with NES gel in suppressing spermatogenesis.

Design and Setting:
This was a randomized, double-blind, comparator clinical trial conducted at two academic medical centers.

Participants:
Ninety-nine healthy male volunteers participated in the study.

Interventions:
Volunteers were randomized to one of three treatment groups applying daily transdermal gels (group 1: T gel 10 g + NES 0 mg/placebo gel; group 2: T gel 10 g + NES gel 8 mg; group 3: T gel 10 g + NES gel 12 mg).

Main Outcome Variable:
The main outcome variable of the study was the percentage of men whose sperm concentration was suppressed to 1 million/ml or less by 20-24 wk of treatment.

Results:
Efficacy data analyses were performed on 56 subjects who adhered to the protocol and completed at least 20 wk of treatment. The percentage of men whose sperm concentration was 1 million/ml or less was significantly higher for T + NES 8 mg (89%, $P < 0.0001$) and T + NES 12 mg (88%, $P = 0.0002$) compared with T + NES 0 mg group (23%). The median serum total and free T concentrations in all groups were maintained within the adult male range throughout the treatment period. Adverse effects were minimal in all groups.

Conclusion:
A combination of daily NES + T gels suppressed sperm concentration to 1 million/ml or less in 88.5% of men, with minimal adverse effects, and may be further studied as a male transdermal hormonal contraceptive. Ⓐ

Evidence-Based Reference

Jick SS et al.: Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data, *BMJ* 340:d2151, 2011. Ⓐ

Ilani N, Roth MY, Amory JK, et al.: A new combination of testosterone and nestorone transdermal gels for male hormonal contraception, *J Clin Endocrinol Metab* 97:3476–3486, 2012. Ⓐ

SUGGESTED READINGS

Bosworth MC et al.: An update on emergency contraception, *Am Fam Phys* 89(7):545–550, 2014.

Spencer A et al.: Helping women choose appropriate hormonal contraception: update on risks, benefits, and indications, *Am J Med* 122:497–506, 2009.

Steinbrook R: Science, politics, and over-the-counter emergency contraception, *JAMA* 307:365, 2012.

Winner B et al.: Effectiveness of long-acting reversible contraception, *N Engl J Med* 366:1998–2007, 2012.

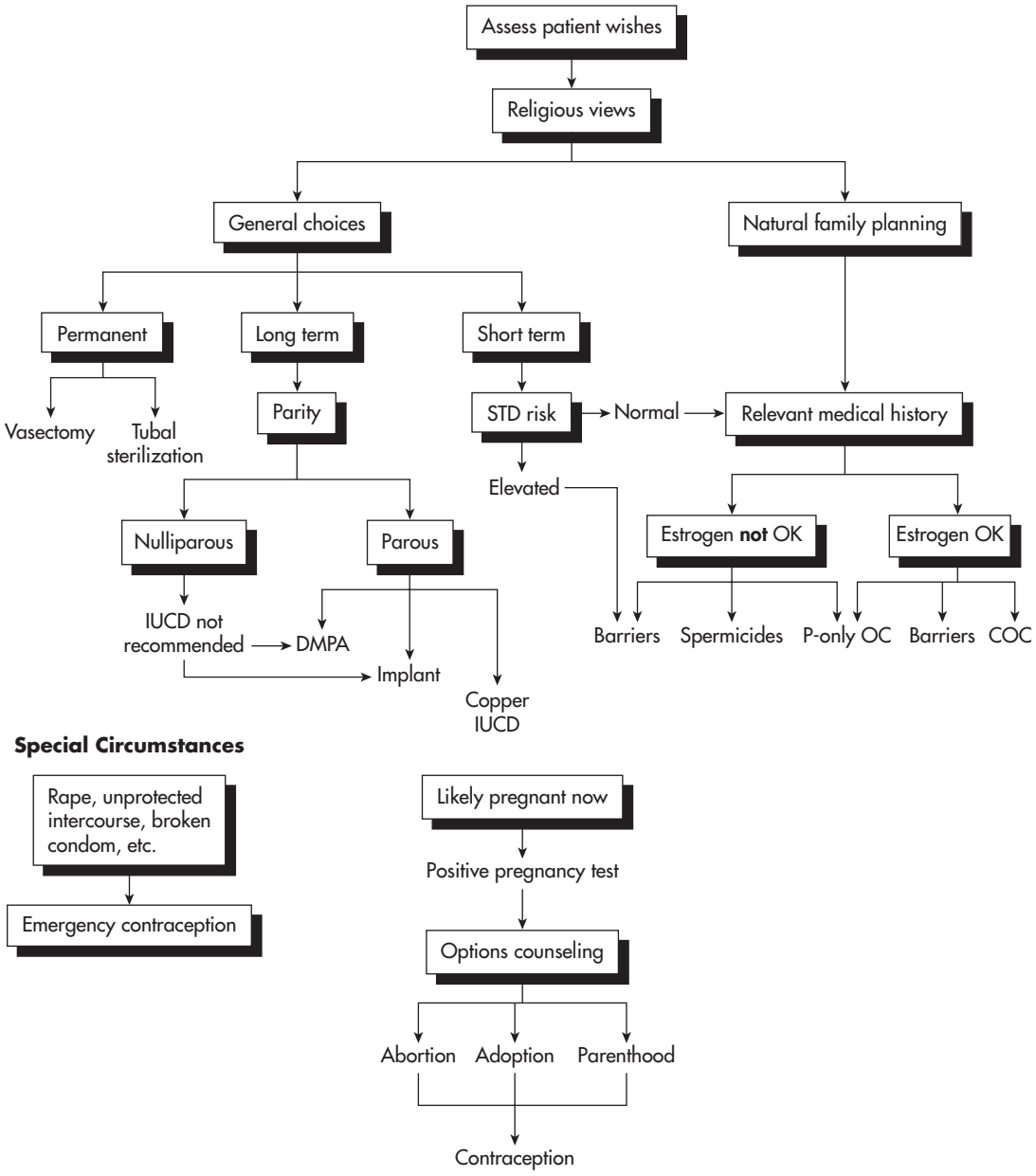


FIGURE EC1-100 Helping couples select a contraceptive method. *DMPA,* Depot medroxyprogesterone acetate; *IUCD,* intrauterine contraceptive device; *OC,* combination estrogen-progestin oral contraceptive; *P-only OC,* progestin-only oral contraceptive; *STD,* sexually transmitted disease. (From Copeland LJ: *Textbook of gynecology,* ed 2, Philadelphia, 2000, Saunders.)

TABLE EC1-49 Oral Contraceptive Formulations Available in the United States

	Name	Estrogen	Progestin	Progestin Dose (mg)
EE, 50 μg monophasic	Ovcon 50*	EE	Norethindrone	1.0
	Ortho-Novum 1/50*	Mestranol	Norethindrone	1.0
	Norinyl 1 + 50*	Mestranol	Norethindrone	1.0
EE, 35 μg monophasic	Femcon Fe†	EE	Norethindrone	0.4
	Modicon*	EE	Norethindrone	0.5
	Brevicon*	EE	Norethindrone	0.5
	Ovcon 35*	EE	Norethindrone	0.4
	Ortho-Cyclen*	EE	Norgestimate	0.25
	Demulen 1/35*	EE	Ethynodiol diacetate	1.0
	Ortho-Novum 1/35*	EE	Norethindrone	1.0
	Norinyl 1 + 35*	EE	Norethindrone	1.0
EE, 35 μg biphasic	Ortho-Novum 10/11*	EE	Norethindrone	0.5/1.0
EE, 35 μg triphasic	Ortho-Novum 7/7/7*	EE	Norethindrone	0.5/0.75/1.0
	Ortho Tri-Cyclen*,‡	EE	Norgestimate	0.18/0.215/0.25
	Tri-Norinyl*	EE	Norethindrone	0.5/1.0/0.5
	Estrostep*,‡	EE (20/30/35)	Norethindrone acetate	1.0
EE, 30 μg monophasic	Loestrin 1.5/30*	EE	Norethindrone acetate	1.5
	Ortho-Cept*	EE	Desogestrel	0.15
	Desogen*	EE	Desogestrel	0.15
	Lo-Ovral*	EE	Norgestrel	0.3
	Nordette*	EE	Levonorgestrel	0.15
	Levlen*	EE	Levonorgestrel	0.15
	Yasmin*	EE	Drospirenone	3.0
EE, 30 μg triphasic	Triphasil*	EE (30/40/30)	Levonorgestrel	0.05/0.075/0.125
	Tri-Levlen*	EE (30/40/30)	Levonorgestrel	0.05/0.075/0.125
Extended cycle (84 active tablets)	Seasonale*	EE	Levonorgestrel	0.150
Extended cycle (84 estrogen/progestin tablets, 7 tablets 10 μg EE)	Seasonique	EE	Levonorgestrel	0.150
EE, 25 μg	Cyclessa*	EE	Desogestrel	0.10/0.125/0.150
	Ortho Tri-Cyclen Lo	EE	Norgestimate	0.18/0.215/0.25
EE, 20 μg monophasic	Loestrin 1/20*	EE	Norethindrone acetate	1.0
	Levlite*	EE	Levonorgestrel	0.1
	Alesse*	EE	Levonorgestrel	0.1
21 Hormonally active tablets (2 inert tablets, 5 tablets 10 μg EE)	Mircette*	EE	Desogestrel	0.15
24 Hormonally active tablets	Yaz‡,§	EE	Drosperinone	3.0
	Loestrin 24Fe	EE	Norethindrone acetate	1.0
Extended cycle (84 estrogen/progestin tablets, 7 tablets 10 μg EE)	LoSeasonique	EE	Levonorgestrel	0.1
28 Hormonally active tablets	Lybrel	EE	Levonorgestrel	0.09
Progestin-only	Micronor*		Norethindrone	0.35

*Generic versions available.
†Chewable tablets.
‡Indicated for the treatment of acne in women desiring to use oral contraception.
§Indicated for the treatment of premenstrual dysphoric disorder in women desiring to use oral contraception.
EE, Ethinyl estradiol.
From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders, Elsevier.

TABLE EC1-50 World Health Organization (WHO) and American College of Obstetrics and Gynecology (ACOG) Guidelines Regarding Use of Combination Estrogen-Progestin Contraceptives (Oral Contraception, Ring, Patch) in Women 35 Years of Age and Older

Variable	ACOG Guidelines	WHO Guidelines
Obesity	Progestin-only or intrauterine contraception* may be safer	Benefit usually outweighs risks†
Smoker	Progestin-only or intrauterine contraception* should be used	Risk unacceptable
Hypertension	Progestin-only or intrauterine contraception* should be used	Risk unacceptable
Diabetes	Progestin-only or intrauterine contraception* should be used	Risk unacceptable
Migraine	Progestin-only or intrauterine contraception* should be used	Risk unacceptable
None of the above risk factors	Healthy, nonsmoking women doing well on a combination contraceptive can continue their method until age 50-55 yr, after weighing the risks and benefits	For women ≥40 yr, the risk of cardiovascular disease increases with age and may also increase with use of combined hormonal contraceptives. In the absence of other adverse clinical conditions, combined hormonal contraceptives may be used until menopause.

*Includes progestin-only oral contraception, depot medroxyprogesterone acetate (DMPA), contraceptive implants, copper intrauterine devices (IUDs), and progestin-releasing IUDs.
†Obesity in women age 35 and older not specifically addressed.
From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders, Elsevier.

TABLE EC1-51 Summary and Recommendations for Progestin-Only Oral Contraceptive Use

1. Progestin-only contraception is an option for women in whom an estrogen-containing contraceptive is either contraindicated or causes additional health concerns.
2. Ovulation is not consistently suppressed; the main contraceptive actions of progestin-only oral contraception are effects on cervical mucus and the endometrium.
3. The typical user failure rate with progestin-only oral contraception is estimated to be >8%. Women choosing progestin-only oral contraception are often subfertile as a result of breast-feeding or older reproductive age, so the failure rate in these populations may be lower than in more fertile populations.
4. It is essential that the pill be taken at the same time each day to maximize contraceptive efficacy.
5. Menstrual irregularities are common in users of progestin-only oral contraception and represent the most frequent cause for contraceptive discontinuation.

From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders, Elsevier.

TABLE EC1-52 Summary and Recommendations for Depot Medroxyprogesterone Acetate (DMPA) Use

1. DMPA is an excellent method of contraception for women who desire a long-term, reversible contraceptive method.
2. DMPA primarily acts by inhibiting follicular maturation and ovulation through inhibition of gonadotropin secretion. It also affects cervical mucus.
3. DMPA is available in two formulations: 150 mg/1 ml for IM injection and 104 mg/0.65 ml for SC injection.
4. The ideal time to initiate DMPA is within 5 days of the onset of menses to ensure absence of pregnancy. The dose is repeated every 3 months, with a 2-week grace period.
5. Although DMPA does not permanently affect endocrine function, return of fertility may be delayed.
6. Thorough, candid counseling about side effects is important. Women who are well informed when they choose this method of contraception are much more likely to become highly satisfied users with high continuation rates.
7. Menstrual changes occur in all women using DMPA and are the most frequent cause for discontinuation.
8. Because DMPA induces amenorrhea, it can be used for managing a variety of gynecologic and nongynecologic disorders, such as menorrhagia, dysmenorrhea, and iron deficiency anemia.
9. There is no high-quality evidence that use of DMPA increases the risk of developing cancer, cardiovascular disease, or sexually transmitted infection. DMPA use significantly reduces the risk of developing endometrial cancer.
10. There is an association between current DMPA use and decreased bone mineral density; losses in bone mineral density are temporary, reverse after discontinuation of DMPA, and have not been linked to postmenopausal osteoporosis or fractures.

From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders, Elsevier.

Recommendations and Reports

Appendix A

Summary Chart of *U.S. Medical Eligibility Criteria for Contraceptive Use, 2010*

Key:
1. No restriction (method can be used)
2. Advantages generally outweigh theoretical or proven risks
3. Theoretical or proven risks usually outweigh the advantages
4. Unacceptable health risk (method not to be used)

Updated June 2012. This summary sheet only contains a subset of the recommendations from the US MEC. For complete guidance, see: http://www.cdc.gov/reproductivehealth/unintendedpregnancy/USMEC.htm.

Most contraceptive methods do not protect against sexually transmitted infections (STIs). Consistent and correct use of the male latex condom reduces the risk of STIs and HIV.

Condition	Sub-condition	Combined pill, patch, ring		Progestin-only pill		Injection		Implant		LNG-IUD		Copper-IUD	
		I	C	I	C	I	C	I	C	I	C	I	C
Age		Menarche to <40=1		Menarche to <18=1		Menarche to <18=2		Menarche to <18=1		Menarche to <20=2		Menarche to <20=2	
		≥40=2		18-45=1		18-45=1		18-45=1		≥20=1		≥20=1	
				>45=1		>45=2		>45=1					
Anatomic abnormalities	a) Distorted uterine cavity									4		4	
	b) Other abnormalities									2		2	
Anemias	a) Thalassemia	1		1		1		1		1		2	
	b) Sickle cell disease†	2		1		1		1		1		2	
	c) Iron-deficiency anemia	1		1		1		1		1		2	
Benign ovarian tumors	(including cysts)	1		1		1		1		1		1	
Breast disease	a) Undiagnosed mass	2*		2*		2*		2*		2		1	
	b) Benign breast disease	1		1		1		1		1		1	
	c) Family history of cancer	1		1		1		1		1		1	
	d) Breast cancer†												
	i) current	4		4		4		4		4		1	
	ii) past and no evidence of current disease for 5 years	3		3		3		3		3		1	
Breastfeeding (see also Postpartum)	a) < 1 month postpartum	3*		2*		2*		2*					
	b) 1 month or more postpartum	2*		1*		1*		1*					
Cervical cancer	Awaiting treatment	2		1		2		2		4	2	4	2
Cervical ectropion		1		1		1		1		1		1	
Cervical intraepithelial neoplasia		2		1		2		2		2		1	

Appendix A (*Continued*)

Summary Chart of *U.S. Medical Eligibility Criteria for Contraceptive Use, 2010*

Condition	Sub-condition	Combined pill, patch, ring		Progestin-only pill		Injection		Implant		LNG-IUD		Copper-IUD	
		I	C	I	C	I	C	I	C	I	C	I	C
Cirrhosis	a) Mild (compensated)	1		1		1		1		1		1	
	b) Severe† (decompensated)	4		3		3		3		3		1	
DVT/PE	a) History of DVT/PE, not on anticoagulant therapy												
	i) higher risk for recurrent DVT/PE	4		2		2		2		2		1	
	ii) lower risk for recurrent DVT/PE	3		2		2		2		2		1	
	b) Acute DVT/PE	4		2		2		2		2		2	
	c) DVT/PE and established on anticoagulant therapy for at least 3 months												
	i) higher risk for recurrent DVT/PE	4*		2		2		2		2		2	
	ii) lower risk for recurrent DVT/PE	3*		2		2		2		2		2	
	d) Family history (first-degree relatives)	2		1		1		1		1		1	
	e) Major surgery												
	(i) with prolonged immobilization	4		2		2		2		2		1	
	(ii) without prolonged immobilization	2		1		1		1		1		1	
	f) Minor surgery without immobilization	1		1		1		1		1		1	
Depressive disorders		1*		1*		1*		1*		1*		1*	

Appendix A (*Continued*)

Summary Chart of *U.S. Medical Eligibility Criteria for Contraceptive Use, 2010*

Condition	Sub-condition	Combined pill, patch, ring		Progestin-only pill		Injection		Implant		LNG-IUD		Copper-IUD	
		I	C	I	C	I	C	I	C	I	C	I	C
Diabetes mellitus	a) History of gestational diabetes mellitus only	1		1		1		1		1		1	
	b) Non-vascular disease												
	(i) non-insulin dependent	2		2		2		2		2		1	
	(ii) insulin dependent†	2		2		2		2		2		1	
	c) Nephropathy/ retinopathy/ neuropathy†	3/4*		2		3		2		2		1	
	d) Other vascular disease or diabetes of >20 years' duration†	3/4*		2		3		2		2		1	
Endometrial cancer†		1		1		1		1		4	2	4	2
Endometrial hyperplasia		1		1		1		1		1		1	
Endometriosis		1		1		1		1		1		2	
Epilepsy†	(see also Drug Interactions)	1*		1*		1*		1*		1		1	
Gallbladder disease	a) Symptomatic												
	(i) treated by cholecystectomy	2		2		2		2		2		1	
	(ii) medically treated	3		2		2		2		2		1	
	(iii) current	3		2		2		2		2		1	
	b) Asymptomatic	2		2		2		2		2		1	
Gestational trophoblastic disease	a) Decreasing or undetectable ß-hCG levels	1		1		1		1		3		3	
	b) Persistently elevated ß-hCG levels or malignant disease†	1		1		1		1		4		4	
Headaches	a) Non-migrainous	1*	2*	1*	1*	1*	1*	1*	1*	1*	1*	1*	
	b) Migraine												
	i) without aura, age <35	2*	3*	1*	2*	2*	2*	2*	2*	2*	2*	1*	
	ii) without aura, age ≥35	3*	4*	1*	2*	2*	2*	2*	2*	2*	2*	1*	
	iii) with aura, any age	4*	4*	2*	3*	2*	3*	2*	3*	2*	3*	1*	

Appendix A (*Continued*)

Summary Chart of *U.S. Medical Eligibility Criteria for Contraceptive Use, 2010*

Condition	Sub-condition	Combined pill, patch, ring		Progestin-only pill		Injection		Implant		LNG-IUD		Copper-IUD	
		I	C	I	C	I	C	I	C	I	C	I	C
History of bariatric surgery†	a) Restrictive procedures	1		1		1		1		1		1	
	b) Malabsorptive procedures	COCs: 3 P/R: 1		3		1		1		1		1	
History of cholestasis	a) Pregnancy-related	2		1		1		1		1		1	
	b) Past COC-related	3		2		2		2		2		1	
History of high blood pressure during pregnancy		2		1		1		1		1		1	
History of pelvic surgery		1		1		1		1		1		1	
HIV	High risk	1		1		1*		1		2	2	2	2
	HIV infected (see also Drug Interactions)†	1*		1*		1*		1*		2	2	2	2
	AIDS (see also Drug Interactions) †	1*		1*		1*		1*		3	2*	3	2*
	Clinically well on therapy	If on treatment, see Drug Interactions								2	2	2	2
Hyperlipidemias		2/3*		2*		2*		2*		2*		1*	
Hypertension	a) Adequately controlled hypertension	3*		1*		2*		1*		1		1	
	b) Elevated blood pressure levels (properly taken measurements)												
	(i) systolic 140-159 or diastolic 90-99	3		1		2		1		1		1	
	(ii) systolic ≥160 or diastolic ≥100†	4		2		3		2		2		1	
	c) Vascular disease	4		2		3		2		2		1	
Inflammatory bowel disease	(Ulcerative colitis, Crohn's disease)	2/3*		2		2		1		1		1	
Ischemic heart disease†	Current and history of	4		2	3	3		2	3	2	3	1	
Liver tumors	a) Benign												
	i) Focal nodular hyperplasia	2		2		2		2		2		1	
	ii) Hepatocellular adenoma†	4		3		3		3		3		1	
	b) Malignant†	4		3		3		3		3		1	
Malaria		1		1		1		1		1		1	

Appendix A (*Continued*)

Summary Chart of *U.S. Medical Eligibility Criteria for Contraceptive Use, 2010*

Condition	Sub-condition	Combined pill, patch, ring		Progestin-only pill		Injection		Implant		LNG-IUD		Copper-IUD	
		I	C	I	C	I	C	I	C	I	C	I	C
Multiple risk factors for arterial cardiovascular disease	(such as older age, smoking, diabetes and hypertension)	3/4*		2*		3*		2*		2		1	
Obesity	a) ≥30 kg/m^2 BMI	2		1		1		1		1		1	
	b) Menarche to <18 years and ≥30 kg/m^2 BMI	2		1		2		1		1		1	
Ovarian cancer†		1		1		1		1		1		1	
Parity	a) Nulliparous	1		1		1		1		2		2	
	b) Parous	1		1		1		1		1		1	
Past ectopic pregnancy		1		2		1		1		1		1	
Pelvic inflammatory disease	a) Past, (assuming no current risk factors of STIs)												
	(i) with subsequent pregnancy	1		1		1		1		1	1	1	1
	(ii) without subsequent pregnancy	1		1		1		1		2	2	2	2
	b) Current	1		1		1		1		4	2*	4	2*
Peripartum cardiomyopathy†	a) Normal or mildly impaired cardiac function												
	(i) <6 months	4		1		1		1		2		2	
	(ii) ≥6 months	3		1		1		1		2		2	
	b) Moderately or severely impaired cardiac function	4		2		2		2		2		2	
Postabortion	a) First trimester	1*		1*		1*		1*		1*		1*	
	b) Second trimester	1*		1*		1*		1*		2		2	
	c) Immediately post-septic abortion	1*		1*		1*		1*		4		4	
Postpartum (see also Breastfeeding)	a) <21 days	4		1		1		1					
	b) 21 days to 42 days												
	(i) with other risk factors for VTE	3*		1		1		1					
	(ii) without other risk factors for VTE	2		1		1		1					
	c) >42 days	1		1		1		1					

Appendix A (*Continued*)

Summary Chart of *U.S. Medical Eligibility Criteria for Contraceptive Use, 2010*

Condition	Sub-condition	Combined pill, patch, ring		Progestin-only pill		Injection		Implant		LNG-IUD		Copper-IUD	
		I	C	I	C	I	C	I	C	I	C	I	C
Postpartum (in breastfeeding or non-breastfeeding women, including post-cesarean section)	a) <10 minutes after delivery of the placenta									2		1	
	b) 10 minutes after delivery of the placenta to < 4 weeks									2		2	
	c) ≥4 weeks									1		1	
	d) Puerperal sepsis									4		4	
Pregnancy		NA*		NA*		NA*		NA*		4*		4*	
Rheumatoid arthritis	a) On immunosuppressive therapy	2		1		2/3*		1		2	1	2	1
	b) Not on immunosuppressive therapy	2		1		2		1		1		1	
Schistosomiasis	a) Uncomplicated	1		1		1		1		1		1	
	b) Fibrosis of the liver†	1		1		1		1		1		1	
Severe dysmenorrhea		1		1		1		1		1		2	
STIs	a) Current purulent cervicitis or chlamydial infection or gonorrhea	1		1		1		1		4	2*	4	2*
	b) Other STIs (excluding HIV and hepatitis)	1		1		1		1		2	2	2	2
	c) Vaginitis (including trichomonas vaginalis and bacterial vaginosis)	1		1		1		1		2	2	2	2
	d) Increased risk of STIs	1		1		1		1		2/3*	2	2/3*	2
Smoking	a) Age <35	2		1		1		1		1		1	
	b) Age ≥35, <15 cigarettes/day	3		1		1		1		1		1	
	c) Age ≥35, ≥15 cigarettes/day	4		1		1		1		1		1	
Solid organ transplantation†	a) Complicated	4		2		2		2		3	2	3	2
	b) Uncomplicated	2*		2		2		2		2		2	
Stroke†	History of cerebrovascular accident	4		2	3	3		2	3	2		1	

Appendix A (*Continued*)

Summary Chart of *U.S. Medical Eligibility Criteria for Contraceptive Use, 2010*

Condition	Sub-condition	Combined pill, patch, ring		Progestin-only pill		Injection		Implant		LNG-IUD		Copper-IUD	
		I	C	I	C	I	C	I	C	I	C	I	C
Superficial venous thrombosis	a) Varicose veins	1		1		1		1		1		1	
	b) Superficial thrombophlebitis	2		1		1		1		1		1	
Systemic lupus erythematosus†	a) Positive (or unknown) antiphospholipid antibodies	4		3		3	3	3		3		1	1
	b) Severe thrombocytopenia	2		2		3	2	2		2*		3*	2*
	c) Immunosuppressive treatment	2		2		2	2	2		2		2	1
	d) None of the above	2		2		2	2	2		2		1	1
Thrombogenic mutations†		4*		2*		2*		2*		2*		1*	
Thyroid disorders	Simple goiter/ hyperthyroid/ hypothyroid	1		1		1		1		1		1	
Tuberculosis† (see also Drug Interactions)	a) Non-pelvic	1*		1*		1*		1*		1		1	
	b) Pelvic	1*		1*		1*		1*		4	3	4	3
Unexplained vaginal bleeding	(suspicious for serious condition) before evaluation	2*		2*		3*		3*		4*	2*	4*	2*
Uterine fibroids		1		1		1		1		2		2	
Valvular heart disease	a) Uncomplicated	2		1		1		1		1		1	
	b) Complicated†	4		1		1		1		1		1	
Vaginal bleeding patterns	a) Irregular pattern without heavy bleeding	1		2		2		2		1	1	1	
	b) Heavy or prolonged bleeding	1*		2*		2*		2*		1*	2*	2*	
Viral hepatitis	a) Acute or flare	3/4*	2	1		1		1		1		1	
	b) Carrier/Chronic	1	1	1		1		1		1		1	

Appendix A (*Continued*)

Summary Chart of *U.S. Medical Eligibility Criteria for Contraceptive Use, 2010*

Condition	Sub-condition	Combined pill, patch, ring		Progestin-only pill		Injection		Implant		LNG-IUD		Copper-IUD	
		I	C	I	C	I	C	I	C	I	C	I	C
Drug Interactions													
Antiretroviral therapy	a) Nucleoside reverse transcriptase inhibitors	1*		1		1		1		2/3*	2*	2/3*	2*
	b) Non-nucleoside reverse transcriptase inhibitors	2*		2*		1		2*		2/3*	2*	2/3*	2*
	c) Ritonavir-boosted protease inhibitors	3*		3*		1		2*		2/3*	2*	2/3*	2*
Anticonvulsant therapy	a) Certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine)	3*		3*		1		2*		1		1	
	b) Lamotrigine	3*		1		1		1		1		1	
Antimicrobial therapy	a) Broad spectrum antibiotics	1		1		1		1		1		1	
	b) Antifungals	1		1		1		1		1		1	
	c) Antiparasitics	1		1		1		1		1		1	
	d) Rifampicin or rifabutin therapy	3*		3*		1		2*		1		1	

Abbreviations: AIDS = acquired immunodeficiency syndrome; BMI = body mass index; C = continuation of contraceptive method; COC = combined oral contraceptive; Cu-IUD = copper-containing intrauterine device; DVT = deep venous thrombosis; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; I = initiation of contraceptive method; LNG-IUD = levonorgestrel-releasing intrauterine device; NA = not applicable; PE = pulmonary embolism; STI = sexually transmitted infection; VTE = venous thromboembolism.

Source: Modified from CDC. Summary chart of U.S. medical eligibility criteria for contraceptive use. Atlanta, GA: CDC; 2012. (Available at http://www.cdc.gov/reproductivehealth/UnintendedPregnancy/USMEC.htm)

* Please see the complete guidance for a clarification to this classification: www.cdc.gov/reproductivehealth/unintendedpregnancy/USMEC.htm.

† Condition that exposes a woman to increased risk as a result of unintended pregnancy.

Appendix B

When to Start Using Specific Contraceptive Methods

Contraceptive method	When to start (if the provider is reasonably certain that the woman is not pregnant)	Additional contraception (i.e., back-up) needed	Examinations or tests needed before initiation*
Copper-containing IUD	Anytime	Not needed	Bimanual examination and cervical inspection†
Levonorgestrel-releasing IUD	Anytime	If >7 days after menses started, use back-up method or abstain for 7 days.	Bimanual examination and cervical inspection†
Implant	Anytime	If >5 days after menses started, use back-up method or abstain for 7 days.	None
Injectable	Anytime	If >7 days after menses started, use back-up method or abstain for 7 days.	None
Combined hormonal contraceptive	Anytime	If >5 days after menses started, use back-up method or abstain for 7 days.	Blood pressure measurement
Progestin-only pill	Anytime	If >5 days after menses started, use back-up method or abstain for 2 days.	None

Abbreviations: BMI = body mass index; HIV = human immunodeficiency virus; IUD = intrauterine device; STD = sexually transmitted disease; U.S. MEC = *U.S. Medical Eligibility Criteria for Contraceptive Use, 2010*.

* Weight (BMI) measurement is not needed to determine medical eligibility for any methods of contraception because all methods can be used (U.S. MEC 1) or generally can be used (U.S. MEC 2) among obese women (Box 2). However, measuring weight and calculating BMI (weight [kg]/height $[m]^2$) at baseline might be helpful for monitoring any changes and counseling women who might be concerned about weight change perceived to be associated with their contraceptive method.

† Most women do not require additional STD screening at the time of IUD insertion if they have already been screened according to CDC's *STD Treatment Guidelines* (available at http://www.cdc.gov/std/treatment). If a woman has not been screened according to guidelines, screening can be performed at the time of IUD insertion, and insertion should not be delayed. Women with purulent cervicitis or current chlamydial infection or gonorrhea should not undergo IUD insertion (U.S. MEC 4). Women who have a very high individual likelihood of STD exposure (e.g., those with a currently infected partner) generally should not undergo IUD insertion (U.S. MEC 3) (Box 2). For these women, IUD insertion should be delayed until appropriate testing and treatment occurs.

Appendix C

Examinations and Tests Needed Before Initiation of Contraceptive Methods

The examinations or tests noted apply to women who are presumed to be healthy. Those with known medical problems or other special conditions might need additional examinations or tests before being determined to be appropriate candidates for a particular method of contraception. The *U.S. Medical Eligibility Criteria for Contraceptive Use, 2010* (U.S. MEC), might be useful in such circumstances (*5*). The following classification was considered useful in differentiating the applicability of the various examinations or tests:

Class A: essential and mandatory in all circumstances for safe and effective use of the contraceptive method.

Class B: contributes substantially to safe and effective use, but implementation may be considered within the public health and/or service context; risk of not performing an examination or test should be balanced against the benefits of making the contraceptive method available.

Class C: does not contribute substantially to safe and effective use of the contraceptive method.

These classifications focus on the relationship of the examinations or tests to safe initiation of a contraceptive method. They are not intended to address the appropriateness of these examinations or tests in other circumstances. For example, some of the examinations or tests that are not deemed necessary for safe and effective contraceptive use might be appropriate for good preventive health care or for diagnosing or assessing suspected medical conditions.

No examinations or tests are needed before initiating condoms or spermicides. A bimanual examination is necessary for diaphragm fitting. A bimanual examination and cervical inspection are needed for cervical cap fitting.

TABLE. Examinations and tests needed before initiation of contraceptive methods

	Contraceptive method and class							
Examination or test	Cu-IUD and LNG-IUD	Implant	Injectable	CHC	POP	Condom	Diaphragm or cervical cap	Spermicide
Examination								
Blood pressure	C	C	C	A*	C	C	C	C
Weight (BMI) (weight [kg]/ height [m]^2)	—†	—†	—†	—†	—†	C	C	C
Clinical breast examination	C	C	C	C	C	C	C	C
Bimanual examination and cervical inspection	A	C	C	C	C	C	A§	C
Laboratory test								
Glucose	C	C	C	C	C	C	C	C
Lipids	C	C	C	C	C	C	C	C
Liver enzymes	C	C	C	C	C	C	C	C
Hemoglobin	C	C	C	C	C	C	C	C
Thrombogenic mutations	C	C	C	C	C	C	C	C
Cervical cytology (Papanicolaou smear)	C	C	C	C	C	C	C	C
STD screening with laboratory tests	—¶	C	C	C	C	C	C	C
HIV screening with laboratory tests	C	C	C	C	C	C	C	C

Abbreviations: BMI = body mass index; CHC = combined hormonal contraceptive; Cu-IUD = copper-containing intrauterine device; DMPA = depot medroxyprogesterone acetate; HIV = human immunodeficiency virus; LNG-IUD = levonorgestrel-releasing intrauterine device; POP = progestin-only pill; STD = sexually transmitted disease; U.S. MEC = *U.S. Medical Eligibility Criteria for Contraceptive Use, 2010*.

* In cases in which access to health care might be limited, the blood pressure measurement can be obtained by the woman in a nonclinical setting (e.g., pharmacy or fire station) and self-reported to the provider.

† Weight (BMI) measurement is not needed to determine medical eligibility for any methods of contraception because all methods can be used (U.S. MEC 1) or generally can be used (U.S. MEC 2) among obese women (Box 2). However, measuring weight and calculating BMI at baseline might be helpful for monitoring any changes and counseling women who might be concerned about weight change perceived to be associated with their contraceptive method.

§ A bimanual examination (not cervical inspection) is needed for diaphragm fitting.

¶ Most women do not require additional STD screening at the time of IUD insertion if they have already been screened according to CDC's *STD Treatment Guidelines* (available at http://www.cdc.gov/std/treatment). If a woman has not been screened according to guidelines, screening can be performed at the time of IUD insertion and insertion should not be delayed. Women with purulent cervicitis or current chlamydial infection or gonorrhea should not undergo IUD insertion (U.S. MEC 4). Women who have a very high individual likelihood of STD exposure (e.g., those with a currently infected partner) generally should not undergo IUD insertion (U.S. MEC 3). For these women, IUD insertion should be delayed until appropriate testing and treatment occurs.

Appendix D

Routine Follow-Up After Contraceptive Initiation

These recommendations address when routine follow-up is recommended for safe and effective continued use of contraception for healthy women. The recommendations refer to general situations and might vary for different users and different situations. Specific populations that might benefit from more frequent follow-up visits include adolescents, those with certain medical conditions or characteristics, and those with multiple medical conditions.

TABLE. Routine follow-up after contraceptive initiation

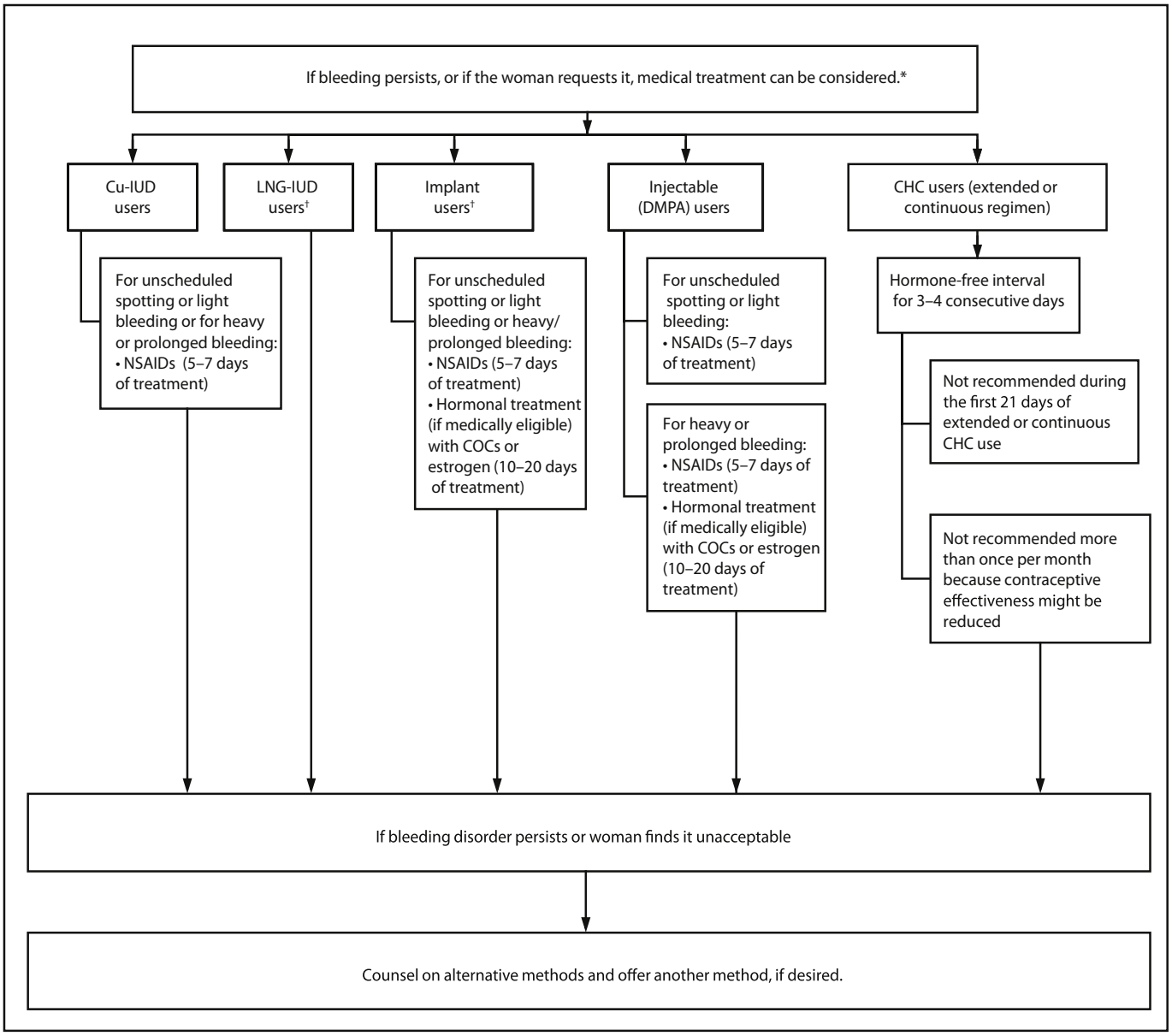
	Contraceptive method				
Action	**Cu-IUD or LNG-IUD**	**Implant**	**Injectable**	**CHC**	**POP**
General follow-up					
Advise women to return at any time to discuss side effects or other problems or if they want to change the method. Advise women using IUDs, implants, or injectables when the IUD or implant needs to be removed or when a reinjection is needed. No routine follow-up visit is required.	X	X	X	X	X
Other routine visits					
Assess the woman's satisfaction with her current method and whether she has any concerns about method use.	X	X	X	X	X
Assess any changes in health status, including medications, that would change the method's appropriateness for safe and effective continued use based on U.S. MEC (i.e., category 3 and 4 conditions and characteristics) (Box 2).	X	X	X	X	X
Consider performing an examination to check for the presence of IUD strings.	X	—	—	—	—
Consider assessing weight changes and counseling women who are concerned about weight change perceived to be associated with their contraceptive method.	X	X	X	X	X
Measure blood pressure.	—	—	—	X	—

Abbreviations: CHC = combined hormonal contraceptive; Cu-IUD = copper-containing intrauterine device; HIV = human immunodeficiency virus; IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing intrauterine device; POP = progestin-only pill; U.S. MEC = *U.S. Medical Eligibility Criteria for Contraceptive Use, 2010*.

Recommendations and Reports

Appendix E

Management of Women with Bleeding Irregularities While Using Contraception



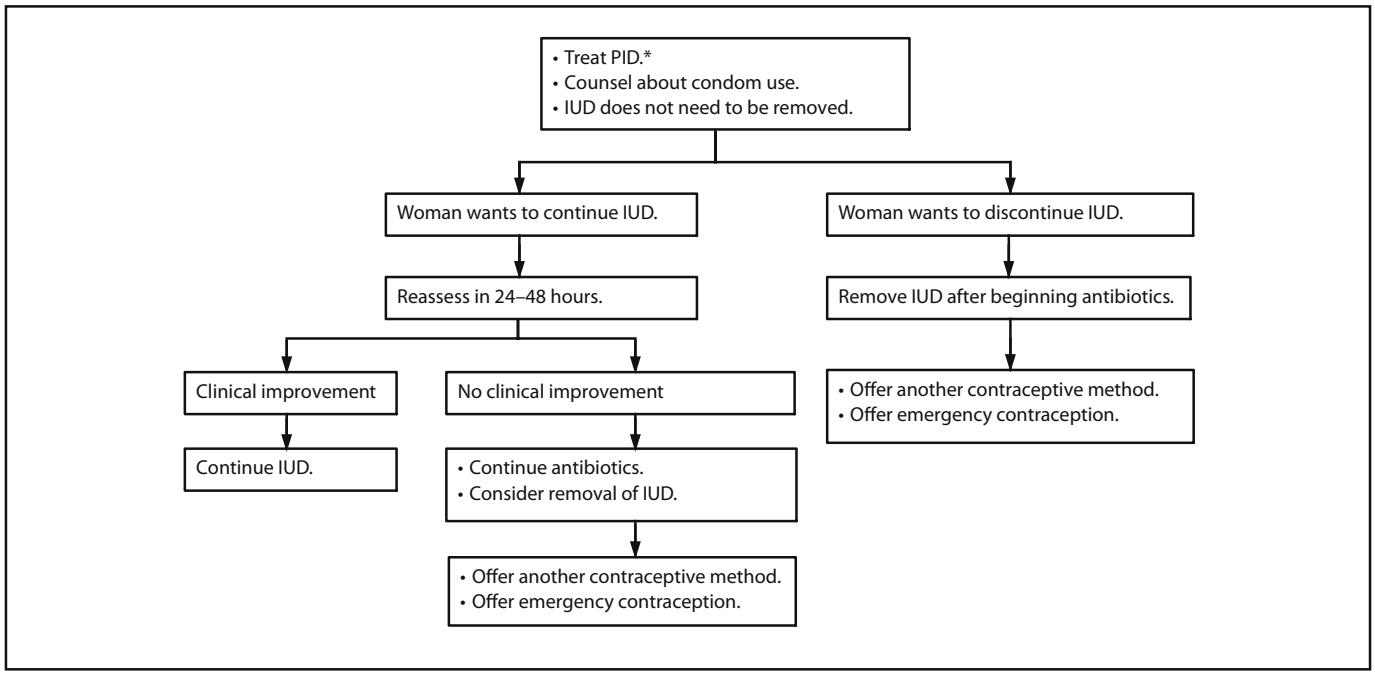
Abbreviations: CHC = combined hormonal contraceptive; COC = combined oral contraceptive; Cu-IUD = copper-containing intrauterine device; DMPA = depot medroxyprogesterone acetate; LNG-IUD = levonorgestrel-releasing intrauterine device; NSAIDs = nonsteroidal antiinflammatory drugs.

* If clinically warranted, evaluate for underlying condition. Treat the condition or refer for care.

† Heavy or prolonged bleeding, either unscheduled or menstrual, is uncommon.

Appendix F

Management of the IUD when a Cu-IUD or an LNG-IUD User Is Found to Have Pelvic Inflammatory Disease



Abbreviations: Cu-IUD = copper-containing IUD; IUD = intrauterine device; LNG-IUD = levonorgestrel-releasing IUD; PID = pelvic inflammatory disease.
* Treat according to CDC's *STD Treatment Guidelines* (available at http://www.cdc.gov/std/treatment).

BASIC INFORMATION

DEFINITION

Conversion disorder (functional neurologic symptom disorder) is a diagnosis of exclusion that presents with one or more symptoms of altered voluntary motor or sensory function that cannot be explained by medical evaluation or a culturally sanctioned behavior or experience. The symptom or deficit is not intentionally produced, distinguishing conversion disorder from factitious disorder or malingering. Conversion disorder is usually characterized by a single symptom that is sporadic, such as paralysis, blindness, numbness, or the inability to speak. Symptoms may have been preceded by a psychological conflict or stressor that may or may not be remembered and may have happened recently or in the distant past. The conversion symptom is presumed to express and manage the psychological distress, or "convert" the distress into a neurologic symptom. There is no well-validated physiologic model for conversion disorder, but advances in neuroscience and neuroimaging may reveal new etiologies.

SYNONYMS

Nonepileptic seizure
Psychogenic movement disorder
Hysterical neurosis (historical)

ICD-9CM and DSM-5 CODES
300.01
ICD-10CM CODES
F44-F44.7 (depending on symptoms)
F44.9 Dissociative (conversion) disorder, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence ~5 to 10/100,000 in general population, 20 to 100/100,000 in hospital inpatients
- All ages, including early childhood, but rare in children younger than 10 years old

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Presents with a motor symptom (e.g., paralysis, aphonia, difficulty swallowing), or a sensory symptom (loss of sensation, double vision, blindness, deafness), or a nonepileptic seizure, or a combination of these symptoms.
- Physical exam findings that are incompatible with neurologic diseases, such as Hoover sign (weakness of hip extension returns to normal strength with contralateral hip flexion against resistance), weakness of plantar flexion on the exam table in an individual able to walk on tiptoes, positive tremor entrainment test, normal EEG or closed eyes with resistance to opening during nonepileptic seizure, or tunnel vision.
- Symptoms tend to occur in isolation (compared with multisystem involvement in somatization disorder).
- The symptoms or signs persist whether the patient is observed or unobserved, though are typically worse when the patient is attentive to them.
- May last from hr to yr and usually sporadic.
- May occur in the context of documented medical illness (e.g., a patient with epileptic seizure may also have psychogenic seizure).
- May have comorbid axis I or axis II disorders, commonly depression, generalized anxiety, or PTSD.

ETIOLOGY

- Complex interplay of neurologic and psychologic factors is not well-understood.
- Presumed to be preceded by psychological conflict or stressor that is completely or partially unconscious, but this is not necessary for diagnosis.
- Functional brain imaging studies suggest alterations in processing of sensory and motor signals.
- Associated with psychiatric comorbidities, most commonly depression, anxiety, PTSD, and personality disorders (most commonly histrionic, borderline, or narcissistic).
- Associated with preexisting neurological illness.
- Associated with physical injury.

DIAGNOSIS

Diagnosis is specific to symptom type:
- Nonepileptic seizure
- Weakness or paralysis
- Abnormal movement (tremor, dystonic movement, myoclonus, gait disorder)
- Swallowing symptom
- Speech symptom (e.g., dysphonia, slurred speech)
- Anesthesia or sensory loss
- Special sensory symptom (e.g., visual, olfactory, auditory)
- Mixed symptoms

DIFFERENTIAL DIAGNOSIS

Broad differential diagnosis depending on presenting signs and symptoms, including movement disorders, seizure, stroke, spinal disorders, autoimmune disorders, vitamin B_{12} deficiency, migraine, dystonia, limbic encephalopathy, stiff person syndrome, HIV, somatic symptom disorder, factitious disorder, and malingering.

LABORATORY TESTS

- Laboratory tests or procedures needed to rule out other medical conditions (e.g., EEG for seizures, EMG for lower motor neuron paralysis, optokinetic drum test in blindness).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Education about illness including explanation and diagnosis. A multidisciplinary treatment team including a neurologist and psychiatrist can be helpful for some patients.
- Cognitive behavioral therapy is often the treatment of choice, although evidence is mixed.
- A long tradition of psychodynamic therapy exists but has not been validated by controlled trials.
- Treatment success has been associated with a caring, long-term relationship between patient and physician and a safe, nonconfrontational approach, with the exception of psychogenic seizure for which empathic confrontation and acceptance of disease is advocated as a foundation of treatment.
- Physical and occupational therapy can help "retrain" the patient in normal behaviors and is important for maintaining strength and function in extended cases of paralysis.
- Studies have shown no additional benefit to hypnosis, although case records describe successful treatment with hypnosis.
- Transcranial magnetic stimulation (TMS) has shown therapeutic benefit in recent small studies.
- Family therapy and group therapy.

GENERAL Rx

- Antidepressants may be helpful for underlying mood or anxiety disorders.
- Inpatient treatment may be required depending on acuity, comorbidities, and functional impairment.

DISPOSITION

Long-term follow-up essential for recurrent conversion symptoms and underlying mood disorders.

PEARLS & CONSIDERATIONS

COMMENTS

- Good prognostic factors: sudden onset, presence of psychological stressors at onset, short duration between diagnosis and treatment, high level of intelligence, absence of other psychiatric or medical disorders.
- Poor prognostic factors: severe disability, long duration of symptoms, age >40 yr at onset, and convulsions or paralysis as presenting symptoms.
- Differentiation between conversion, somatization, dissociative, factitious, and malingering disorders, as well as organic versus functional etiologies, can be challenging.
- Studies show an association between sexual trauma and conversion symptoms, although evidence does not support causality due to confounding and methodologic factors.
- Although not well demonstrated, some argue that conversion and somatized symptoms are more prevalent in cultures without an articulated concept of affective disorder or in which mental illness is highly stigmatized.
- A strong therapeutic alliance is an essential treatment component.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Conversion Disorder (Patient Information)

AUTHOR: **KAILA COMPTON, M.D., PH.D.**

SUGGESTED READINGS

Abyek S et al.: The neuropsychiatry of conversion disorder, *Curr Opin Psychiatry* 21(3):275–280, 2008.

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, ed 5, American Psychiatric Publishing: Arlington.

Ballmeier M et al.: Conversion disorder revisited, *Functional Neurology* 20:105, 2005.

Binder M et al.: Psychogenic nonepileptic seizures, *Neuropsychol Rev* 17:405, 2007.

Carson AJ et al.: Functional (conversion) neurological symptoms: research since the millennium, *J Neurol Neurosurg Psychiatry* 83:842, 2012.

Crimlisk H et al.: Slater revisited: 6 year follow up study of patients with medically unexplained motor symptoms, *BMJ* 316:582–586, 1998.

Feinstein A: Conversion disorder: advances in our understanding, *CMAJ* 183:915–920, 2011.

Halligan PW et al. In: Contemporary approaches to the study of hysteria. Oxford University Press: Oxford.

Hallet M et al.: *Psychogenic movement disorders and other conversion disorders*, Cambridge, 2011, Cambridge University Press.

Pollack TA et al.: A systematic review of transcranial magnetic stimulation in the treatment of functional (conversion) neurological symptoms, *J Neurol Neurosurg Psychiatry* 85:191, 2014.

BASIC INFORMATION

DEFINITION

Cor pulmonale is an alteration in the structure and function of the right ventricle (RV) from pulmonary hypertension caused by diseases of the upper or lower airways, lungs, or pulmonary vasculature. It is a state of cardiopulmonary dysfunction that may result from multiple etiologies rather than a specific disease state. Right-sided heart failure resulting from primary disease of the left heart and congenital heart disease are not considered in this disorder.

SYNONYMS

Acute cor pulmonale
Chronic cor pulmonale

ICD-9CM CODES
415.0 Cor pulmonale, acute
416.9 Cor pulmonale, chronic
ICD-10CM CODES
I26.0 Pulmonary embolism with acute cor pulmonale
I27.81 Cor pulmonale (chronic)

ETIOLOGY

Acute cor pulmonale is a disorder in which the right ventricle (RV) is dilated and the muscular wall is stretched thin, usually as a result of acute pulmonary embolism. This may present with often life-threatening cardiogenic shock, or death, but if the patient survives the initial event, then the RV often recovers and cor pulmonale no longer exists after several weeks.

Chronic cor pulmonale is hypertrophy of the right ventricle caused by increased afterload in the pulmonary circuit, resulting in either acute or chronic right ventricular failure depending on the time course of the elevation in pulmonary vascular resistance. Mechanisms leading to pulmonary hypertension and thus predisposing to the development of cor pulmonale include:

- Pulmonary vasoconstriction leading to increased RV afterload, often resulting from conditions causing alveolar hypoxia and/or respiratory acidosis (e.g., high altitude/hypobaric hypoxia, obstructive sleep apnea/obesity-hypoventilation syndrome, chronic obstructive pulmonary disease). In pulmonary arterial hypertension (PAH), pulmonary vasoconstriction may occur in the absence of a primary cause of hypoxemia, due to imbalances between vasoconstrictor and vasodilator expression in the pulmonary circulation.
- Anatomic reduction or remodeling of the pulmonary vascular bed leading to increased RV afterload (e.g., emphysema, interstitial lung disease, pulmonary emboli, pulmonary arterial hypertension)
- Increased blood viscosity leading to increased RV afterload (e.g., polycythemia related to chronic hypoxemia, polycythemia vera, Waldenström's macroglobulinemia)
- Chronic thrombotic and/or embolic disease

PHYSICAL FINDINGS & CLINICAL PRESENTATION

No symptoms are specific for cor pulmonale. Typically, the symptoms depend on the underlying disease process. The symptoms are most often a result of right ventricular failure:

- Dyspnea, fatigue, chest pain, or syncope with exertion (from pulmonary hypertension, RV ischemia, and impaired cardiac output)
- Right upper quadrant abdominal pain and anorexia (from passive hepatic congestion)
- Hoarseness (caused by compression of the left recurrent laryngeal nerve by dilation of the main pulmonary artery; known as *Ortner's syndrome*)
- Signs of right ventricular failure: jugular venous distention, peripheral edema, hepatic congestion, ascites, and a right ventricular third heart sound
- Signs of associated tricuspid regurgitation: holosystolic murmur heard best along the left parasternal border (augments during inspiration), prominent V-wave on jugular venous pulse, and pulsatile hepatomegaly (in severe tricuspid regurgitation)
- Pulmonary hypertension will increase the intensity of the pulmonic component of S2, which may be narrowly split
- Rarely, cough and hemoptysis

DIAGNOSIS

WORKUP

Search for an underlying pulmonary process resulting in pulmonary hypertension:

- Left ventricular dysfunction should be excluded in initial assessment with an echocardiogram.
- Worldwide, chronic mountain sickness is an important cause of cor pulmonale.
- 80% to 90% of cor pulmonale cases are attributable to chronic obstructive pulmonary disease (COPD) and should include complete pulmonary function tests (PFTs).
- Consideration of obstructive sleep apnea, chronic thromboembolic disease, pulmonary arterial hypertension, and musculoskeletal disease should be given in the absence of parenchymal lung disease.
- A MUGA RVEF of <40-45% is considered abnormal, but RVEF is not a good marker of RV function because it is afterload-dependent. Raised PAP and PVR will decrease the measured RVEF.

LABORATORY TESTS

- Complete blood count may show erythrocytosis from chronic hypoxia.
- Arterial blood gas levels confirm hypoxemia and acidosis or hypercapnia.
- BNP may be elevated from RV dilation.
- Connective tissue disorder workup to exclude scleroderma, lupus, rheumatoid arthritis
- HIV testing

IMAGING STUDIES

- Chest radiograph may show underlying pulmonary disease and evidence of pulmonary hypertension (e.g., enlargement of the pulmonary arteries or right atrium and right ventricular dilation or "pruning" of the peripheral vasculature) (Fig. C1-101).
- ECG (Fig. C1-102) may reveal right ventricular hypertrophy with R/S ratio >1 in leads V_1 and R/S ratio <1 in leads V_5,V_6, right atrial enlargement (P-pulmonale), right-axis deviation, or the triad of $S_1Q_3T_3$ indicative of RV strain.
- Echocardiogram to detect right ventricular enlargement and/or hypertrophy and estimate pulmonary artery pressure.

FIGURE C1-101 Chest radiography in a patient with severe intrinsic pulmonary vascular disease demonstrating enlargement of the main pulmonary artery, right ventricle, and right atrium. (From Crawford MH et al [eds]: *Cardiology,* ed 2, St Louis, 2004, Mosby.)

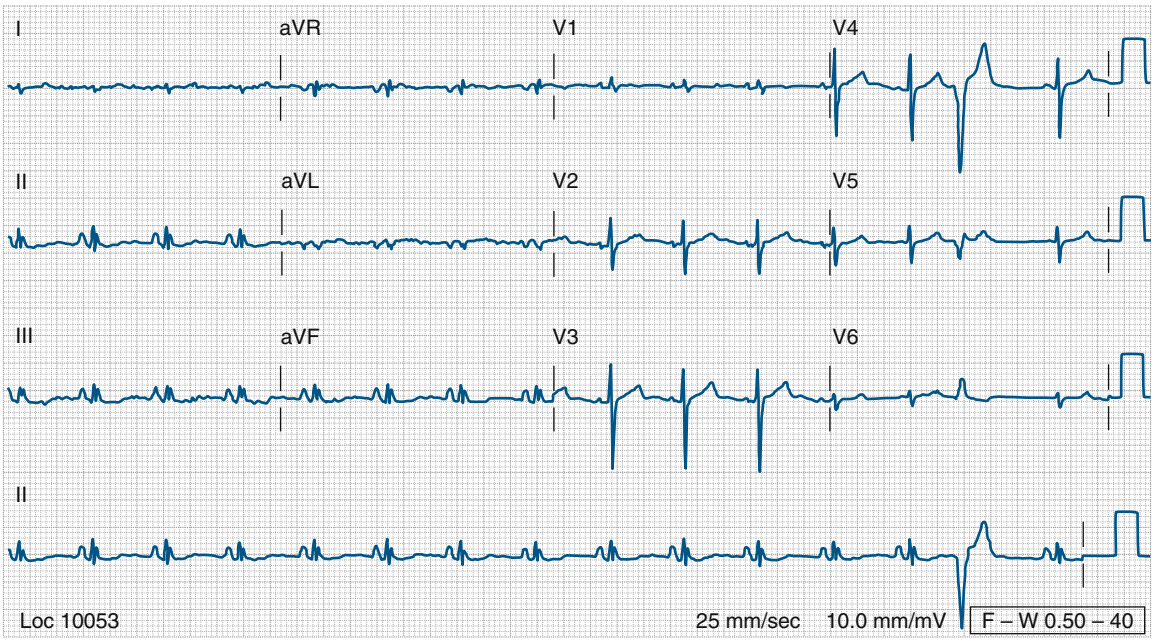


FIGURE C1-102 An electrocardiogram in a patient with chronic cor pulmonale reveals prominent "p pulmonale" and other characteristic features (see text). (From Mason, RJ: *Murray & Nadel's textbook of respiratory medicine*, ed 5, Philadelphia, 2010, Saunders.)

- Perfusion scintigraphy (VQ scan) to rule out chronic thromboembolic pulmonary hypertension (CTEPH)
- Cardiac MRI can accurately measure right ventricular dimensions and function.
- Right-sided heart catheterization measures pulmonary artery pressures and pulmonary vascular resistance. It can also determine response to oxygen or vasodilators. Importantly, right heart catheterization allows assessment of pulmonary capillary wedge pressure, allowing right heart failure from pulmonary venous hypertension due to left heart disease to be ruled out.
- Chest CT can assess for pulmonary parenchymal disease and embolus in the pulmonary vasculature.

Rx TREATMENT

The treatment of cor pulmonale is directed toward the underlying etiology while also reversing hypoxemia, improving right ventricular contractility, decreasing pulmonary artery vascular resistance, and improving pulmonary hypertension. Table C1-53 summarizes therapeutic strategies for cor pulmonale.

NONPHARMACOLOGIC THERAPY

- Supplemental oxygen to correct hypoxemia is an important management step in the treatment of cor pulmonale related to hypoxemia. Goal O_2 sat of more than 90% is recommended.
- Continuous positive airway pressure is used in patients with obstructive sleep apnea.
- Sodium and fluid restriction in setting of edema from RV failure
- Phlebotomy is reserved as adjunctive therapy in patients with polycythemia (hematocrit >55%) who have acute decompensation of cor pulmonale or remain polycythemic despite long-term oxygen therapy. Phlebotomy has been shown to decrease mean pulmonary artery pressure and pulmonary vascular resistance.
- Low-level aerobic exercise, avoiding heavy physical exercise, or isometric exercises that may cause syncope

ACUTE GENERAL Rx

- Pulmonary embolism is the most common cause of acute cor pulmonale (see "Pulmonary Embolism"). The treatment is anticoagulation, hemodynamic support, and consideration of thrombolytics. Catheter-based thrombectomy or surgical embolectomy are potential salvage therapies in patients who cannot receive anticoagulation or thrombolysis, or whose condition continues to deteriorate despite thrombolytics and anticoagulation.
- Acute cor pulmonale may also be seen in cases of acute respiratory distress syndrome (ARDS), related to hypercapnia/acidosis, hypoxic pulmonary vasoconstriction, and the effects of mechanical ventilation. The treatment is supportive care for ARDS with low tidal volume ventilation. Extracorporeal membrane oxygen support (ECMO) while awaiting lung recovery from ARDS may also be helpful in maintaining blood oxygenation. Venoarterial ECMO can provide hemodynamic support as well as blood oxygenation.
- In patients with preexisting cor pulmonale, acute pulmonary illnesses or hypoxia can increase pulmonary hypertension and worsen right ventricular function. The underlying exacerbating conditions should be treated.
- Careful attention to fluid balance is important in the management of acute decompensated right heart failure. Both overhydration and overdiuresis should be avoided, with careful monitoring of intake and output, electrolytes and creatinine, and hemodynamics.
- Intravenous inotropes may be employed to support right heart contractility in decompensated right heart failure.
- In acutely decompensated right heart failure due to pulmonary arterial hypertension, IV prostanoid medications are the treatment of choice. Oral pulmonary vasodilators may also be added to the IV prostanoids, but should not be initiated as monotherapy in patients with advanced right heart failure from PAH.

CHRONIC Rx

The long-term use of oxygen therapy results in decreased clinical right heart failure and improved pulmonary hemodynamics in hypoxic patients.

Indications for oxygen in COPD patients include the following:

1. Resting $PaO_2 \leq 55$ mm Hg on arterial blood gas
2. Resting PaO 56–59 mm Hg if clinical presence of right heart failure with dependent edema, P pulmonale on EKG
3. Desaturation to $SpO_2 \leq 88\%$ on oximetry with activity or at night

- Right ventricular volume overload should be treated with loop diuretics (e.g., furosemide) and potassium-sparing diuretics such as spironolactone.
- Anticoagulation with warfarin has been shown to have a proven survival benefit in patients with idiopathic pulmonary arterial hypertension and is recommended in other causes of cor pulmonale as well, with a target international normalized ratio (INR) of

TABLE C1-53 Therapeutic Strategies for Cor Pulmonale

Diet and Lifestyle
Smoking cessation
Weight loss
Sodium restriction
Judicious exercise training
Structured rehabilitation and breathing training programs
Avoidance of overexertion
Avoidance of pregnancy
Avoidance of high altitudes
Interventions
Treatment of underlying condition
COPD (bronchodilators, corticosteroids, antibiotics, oxygen)
Interstitial lung disease (immunosuppression, oxygen, interferon gamma [investigational])
Sleep-disordered breathing and alveolar hypoventilation disorders (CPAP, BiPAP, surgery)
Chronic exposure to high altitudes (return to sea level)
Chronic thromboembolic disease (anticoagulation, inferior vena cava filters, thromboendarterectomy)
Supplemental oxygen
Pulmonary vasodilators
Anticoagulation
Diuretics
Digitalis glycosides (chronic therapy)
Nonglycoside inotropes (low-dose dobutamine or dopamine in acute severe right heart decompensation with hypoperfusion)
Lung volume-reduction surgery
Lung transplantation
Heart-lung transplantation (PAH secondary to complex congenital heart disease)
Percutaneous blade-balloon atrial septostomy (investigational)
Severe right-sided heart failure
Recurrent syncope

BiPAP, Bilevel positive airway pressure; *CPAP*, continuous positive airway pressure; *PAH*, pulmonary arterial hypertension.
(From Mason, RJ: *Murray &Nadel's textbook of respiratory medicine*, ed 5, Philadelphia, 2010, Saunders.)

1.5-2.5, unlike the target for thromboembolic disease, provided there are no obvious contraindications to long-term anticoagulation but can cause toxicity and arrhythmias.
- Digoxin, though controversial, may be employed as an oral inotropic agent to improve right heart contractility and control atrial arrhythmias.
- Selective oral or parenteral pulmonary vasodilators such as oral calcium channel blockers (CCBs), prostanoids, and endothelin receptor blockers may be used after a right heart catheterization that establishes pulmonary hypertension. If vasoreactivity to calcium channel blockers is established, CCBs may be used to combat pulmonary hypertension. However, if there is no vasoreactivity, prostanoids such as epoprostenol or treprostinil or endothelin receptor blockers such as bosentan may be tried. However, such agents have been shown to be beneficial in the treatment of idiopathic PAH, PAH related to connective tissue disease, and PAH due to congenital heart disease. Pulmonary vasodilators are sometimes considered in other forms of PAH when primary disease management strategies have failed to improve right heart failure.
- Phosphodiesterase inhibitors such as sildenafil and tadalafil are newer vasodilators that improve symptoms, functional class, and mean pulmonary artery pressures as alternatives or in addition to prostanoids.
- Pulmonary thromboendarterectomy may be curative in the special case of cor pulmonale due to chronic thromboembolic pulmonary hypertension.
- Atrial septostomy is a salvage option for patients with ongoing decompensated right heart failure from PAH despite pulmonary vasodilators. Such patients should undergo rapid assessment for possible transplantation.
- Lung transplantation or heart-lung transplantation should be considered in the setting of cor pulmonale from lung diseases or from pulmonary vascular disease.

DISPOSITION

Patients with cor pulmonale should have regular assessment of their functional class (e.g., NYHA or WHO functional class); worse functional class indicates a poorer prognosis. Other poor prognostic features include high right atrial pressure, impaired cardiac output, presence of hyponatremia, elevated BNP levels, low systemic blood pressure, and poor exercise tolerance as demonstrated by a 6-minute walk test.

REFERRAL

Patients with pulmonary disease who have progressed to cor pulmonale should be followed up by a pulmonologist and a tertiary care center that specializes in treatment of advanced pulmonary hypertension.

PEARLS & CONSIDERATIONS

- Identification and treatment of the underlying cause of cor pulmonale is key
- Prognosis and treatment are related to the underlying cause, whereas the presence of cor pulmonale is merely a marker of the underlying disease severity.
- Right heart catheterization is the gold standard to establish diagnosis and to determine treatment, including response to calcium channel blockers, prostanoids, and endothelin receptor blockers.

COMMENTS

There is increasing interest in selective pulmonary vasodilators to improve right ventricular heart function in patients with cor pulmonale outside of the setting of idiopathic PAH, PAH related to connective tissue disease, and PAH related to congenital heart disease. However, more data on the safety and efficacy of these agents, especially in the setting of hypoxemic lung disease, is needed.

The importance of maintaining or improving right heart function, rather than solely lowering pulmonary pressures, is becoming increasingly apparent in the therapeutic management of patients with pulmonary hypertension and right heart failure.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pulmonary Hypertension (Related Key Topic)

AUTHOR: **RABIA ARSHAD, M.D.**

SUGGESTED READINGS

Campo A et al.: Outcomes of hospitalisation for right heart failure in pulmonary arterial hypertension, *Eur Respir J* 38(2):359–367, 2011.

Champion HC et al.: Comprehensive invasive and noninvasive approach to the right ventricle pulmonary circulation unit: state of the art and clinical and research implications, *Circulation* 120:992–1007, 2009.

Forfia PR et al.: Hyponatremia predicts right heart failure and poor survival in pulmonary arterial hypertension, *Am J Respir Crit Care Med* 177(12):1364–1369, 2008.

Lehrman S et al.: Primary pulmonary hypertension and cor pulmonale, *Cardiol Rev* 10(5):265–278, 2002.

Shah SJ: Pulmonary hypertension, *JAMA* 308(13):1366–1374, 2012.

Weitzenblum E: Chronic cor pulmonale, *Heart* 89(2):225–230, 2003.

BASIC INFORMATION

DEFINITION

A corneal abrasion is a loss of surface epithelial tissue of the cornea caused by trauma.

SYNONYMS

Corneal erosion
Corneal contusion

ICD-9CM CODES
918.1 Corneal abrasion
ICD-10CM CODES
S05.00XA Injury of conjunctiva and corneal abrasion without foreign body, unspecified eye, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): A universal problem. Corneal abrasions comprise 8% of all eye presentations in primary care.
PEAK INCIDENCE: Childhood through active adulthood and older and debilitated patients
PREDOMINANT AGE: Any age

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Haziness of the cornea
- Disruption of the corneal surface (Fig. C1-103)
- Redness and injection of the conjunctiva
- Pain
- Light sensitivity
- Tearing
- Gritty feeling
- Pain on opening or closing eyes
- Sensation of a foreign body

ETIOLOGY

- Trauma (direct mechanical event)
- Foreign body
- Contact lenses
- Chemical or flash ultraviolet burns

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute-angle glaucoma
- Herpes ulcers and other corneal ulcers
- Foreign body in the cornea (be certain it is not a keratitis)
- Infective keratitis

WORKUP

- Fluorescein staining, slit lamp evaluation. After fluorescein staining of the cornea, an abrasion will appear yellow under normal light and green in cobalt blue light.
- Assessment of visual acuity. Vision loss requires referral.
- Intraocular pressure
- Rule out corneal laceration
- Rule out other eye pathology. Inspect anterior chamber for blood (hyphema) or pus (hypopyon). If present, refer immediately to ophthalmologist.
- Examine for foreign bodies and remove them if present.
- Confirm red reflex to rule out significant globe injury.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Bandage contact lens can help to speed healing for large epithelial abrasions.
- Warm compresses.
- Pressure dressing (patching) is controversial. Although eye patching traditionally has been recommended in the treatment of corneal abrasions, several studies show that patching does not help and may hinder healing.
- Removal of any foreign particles if present.

ACUTE GENERAL Rx

- Topical antibiotics such as 10% sulfacetamide or ofloxacin 0.3% solution 2 drops qid are commonly prescribed to prevent bacterial superinfection, but evidence for their use is lacking. Ointment forms are often used (e.g., erythromycin, bacitracin ophthalmic QID) to also improve corneal surface lubrication. Antipseudomonal topical antibiotics are, however, recommended for contact lens–related abrasions.
- Pressure patching of eye with eyelid closed is no longer recommended because it can result in decreased oxygen delivery, increased moisture, and a higher chance of infection.
- Cycloplegics such as 5% homatropine are often prescribed to relieve ciliary muscle spasm; however, their benefit has been questioned and they are no longer routinely recommended.
- Topical nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., diclofenac 0.1% or ketorolac 0.5%) 1 drop qid may be used for pain relief.
- Oral NSAIDs may be used for severe pain.

DISPOSITION

Follow-up in 24 hr and then every 3 days until abrasion has cleared and vision has returned to normal. Less frequent follow-up is appropriate for abrasions ≤4 mm or for uncomplicated abrasions.

REFERRAL

To ophthalmologist if patient has no relief within 24 hr or for patients with deep eye injuries, foreign bodies that cannot be removed, or suspected recurrent corneal erosion.

PEARLS & CONSIDERATIONS

COMMENTS

- Never give the patient topical anesthetic to use at home because these can cause decompensation of the cornea, severe delay of epithelial healing, and permanent damage.
- Corticosteroid drops (e.g., dexamethasone, prednisolone) should be avoided, since they can delay healing and exacerbate some corneal infections (herpes viral keratitis, pseudomonas, and fungal ulcers)
- Most corneal abrasions heal in 24 to 48 hr and rarely progress to corneal erosion or infection.
- Improvement in pain is a good indication of corneal epithelial healing. Severe worsening of pain could indicate corneal bacterial infection (keratitis) and should be evaluated urgently.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Corneal Foreign Body or Abrasion (Patient Information)

AUTHOR: **R. SCOTT HOFFMAN, M.D.**

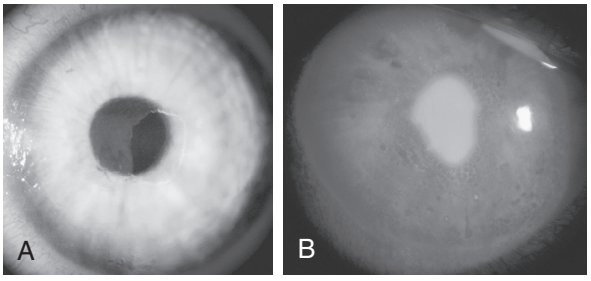


FIGURE C1-103 Corneal epithelial abrasion. A, Epithelial defect without fluorescein highlighting the defect. An irregularity in the otherwise smooth corneal surface is the key to identifying the defect if no fluorescein is available. **B,** Classic fluorescein staining of an epithelial defect. (From Palay D [ed]: *Ophthalmology for the primary care physician,* St Louis, 1997, Mosby.)

SUGGESTED READINGS

Wilson SA, Last A: Management of corneal abrasions, *Am Fam Physician* 70(1):123, 2004.

Wipperman JL, Dorsch JN: Evaluation and management of corneal abrasions, *Am Fam Physician* 87(2):114–120, 2013.

Corneal Ulceration EBM ALG

BASIC INFORMATION

DEFINITION

Corneal ulceration refers to the disruption of the corneal surface and/or deeper layers caused by trauma, contact lenses infection, degeneration, or other means.

SYNONYMS

Infectious keratitis with ulceration
Bacterial keratitis with ulceration
Viral keratitis with ulceration
Fungal keratitis with ulceration

ICD-9CM CODES
370.0 Corneal ulcer NOS
ICD-10CM CODES
H16.009 Unspecified corneal ulcer, unspecified eye

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Four to six cases per month seen by an average general ophthalmologist
PREVALENCE (IN U.S.): Common
PREDOMINANT SEX: Either
PREDOMINANT AGE: All ages

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Localized, well-demarcated, infiltrative lesion with corresponding focal ulcer (Fig. C1-104) or oval, yellow-white stromal suppuration with thick mucopurulent exudate and edema. Usually red, angry-looking eye with infiltration in surrounding area of cornea.
- Eye possibly painful, with conjunctival edema and infection (pain is a helpful indicator of progression or improvement in infectious keratitis).
- Sterile neurotrophic ulcers with tissue breakdown and no pain.

ETIOLOGY

- Complication of contact lens wear, trauma, or diseases such as herpes simplex keratitis or keratoconjunctivitis sicca. Often associated with collagen vascular disease and severe exophthalmus and thyroid disease.
- Viral causes often contagious.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- *Pseudomonas* and pneumococcus and other bacterial infection—virulent
- *Moraxella, Staphylococcus, α-Streptococcus* infection—less virulent
- Herpes simplex infection or disease caused by other viruses
- Contact lens ulcers differ
- Autoimmune keratitis (e.g., peripheral ulceration with RA, SLE)
- Acute angle closure glaucoma

WORKUP

- Fluorescein staining, slit lamp
- Appearance often typical
- Differentiate carefully with contact lens wearers
- Note previous eye surgery or laser vision correction

LABORATORY TESTS

Microscopic examination and culture of scrapings are indicated for vision-threatening keratitis (lesions are large or central location in the cornea)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Warm compresses for blepharitis, eyelid hygiene
- Bandage contact lenses
- Patching
- Stop contact lens wearing

ACUTE GENERAL Rx

- An ophthalmic emergency, refer to ophthalmologist same day
- Intense antibiotic and antiviral therapy may be needed for infectious keratitis
- Topical antibiotics (often broad coverage, new generation fluoroquinolones)
- Nonsteroidal anti-inflammatory drugs and cycloplegic may help with comfort
- Bacterial infection: subconjunctival cefazolin or gentamicin (topical Zymar, Vigomax, etc.)
- Fungal infection: hospitalization and topical application of antifungal agents
- Herpes: viral keratitis can have similar symptoms, should avoid steroid drops unless diagnosis is near certain and showing improvement, since viral keratitis can worsen with steroid

DISPOSITION

Ideally treated by an ophthalmologist if the patient does not rapidly respond to antibiotics (within 24 hr)

PEARLS & CONSIDERATIONS

- Always stop contact lens wearing.
- Always refer ulcers to ophthalmologist.
- Never treat with topical anesthetics or steroids.

COMMENTS

Do not use topical steroids because herpes, fungal, or other ulcers may be aggravated, leading to perforation of the cornea. Antibiotics may delay response and result in overgrowth of nonbacterial (fungal and amoebic) pathogens.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fig. E3-52 Approach to the patient with corneal disorders (Algorithm)

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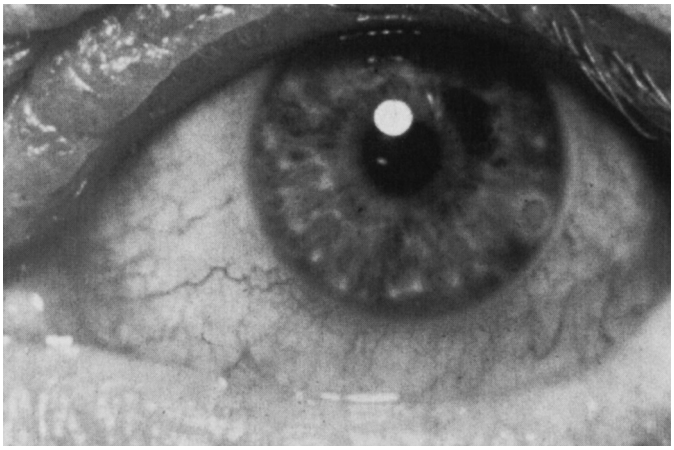

FIGURE C1-104 Peripherally located corneal ulcer. (From Marx JA [ed]: *Rosen's emergency medicine,* ed 5, St Louis, 2002, Mosby.)

EVIDENCE

Abstract[1]

Purpose:

To determine whether topical corticosteroids as adjunctive therapy for bacterial keratitis improves long-term clinical outcomes.

Design:

Randomized, placebo-controlled, double-masked clinical trial.

Methods:

This multicenter trial compared 1.0% prednisolone sodium phosphate to placebo in the treatment of bacterial keratitis among 500 patients with culture-positive ulcers receiving 48 hours of moxifloxacin before randomization. The primary endpoint was 3 months from enrollment, and 399 patients were evaluated at 12 months. The outcomes examined were best spectacle-corrected visual acuity (BSCVA) and scar size at 12 months. Based on previous results, regression models with adjustments for baseline status and/or causative organism were used for analysis.

Results:

No significant differences in clinical outcomes by treatment group were seen with the prespecified regression models (BSCVA: _0.04 logMAR, 95% CI, _0.12 to 0.05, P = .39; scar size: 0.03 mm, 95% CI, _0.12 to 0.18, P = .69). A regression model including a Nocardia-treatment arm interaction found corticosteroid use associated with a mean 1-line improvement in BSCVA at 12 months among patients with non-Nocardia ulcers (_0.10 logMAR, 95% CI, _0.19 to _0.02, P = .02). No significant difference was observed in 12-month BSCVA for Nocardia ulcers (0.18 logMAR, 95% CI,_0.04 to 0.41, P = .16). Corticosteroids were associated with larger mean scar size at 12 months among Nocardia ulcers (0.47 mm, 95% CI, 0.06-0.88, P = .02) and no significant difference was identified by treatment for scar size for non-Nocardia ulcers (_0.06 mm, 95% CI, _0.21 to 0.10, P = .46).

Conclusions:

Adjunctive topical corticosteroid therapy may be associated with improved long-term clinical outcomes in bacterial corneal ulcers not caused by Nocardia species. Ⓐ

Evidence-Based References

Srinivasan M: for the Steroids for Corneal Ulcers Trial Group: The Steroids for Corneal Ulcers Trial (SCUT): Secondary 12-Month Clinical Outcomes of a Randomized Controlled Trial, *Am J Ophthalmol* 157:327–333, 2014. e3Ⓐ

Srinivasan M, Mascarenhas J, Rajaraman R, et al.: Corticosteroids for bacterial keratitis: the Steroids for Corneal Ulcers Trial (SCUT), *Arch Ophthalmol* 130:143–150, 2012. Ⓐ

SUGGESTED READINGS

Price FW: New pieces for the puzzle: nonsteroidal anti-inflammatory drugs and corneal ulcers, *J Cataract Refract Surg* 26(9):1263, 2000.

Schaefer F et al.: Bacterial keratitis: a prospective clinical and microbiological study, *Br J Ophthalmol* 85(7):42, 2001.

Stretton S et al.: Corneal ulceration in pediatric patients: a brief overview of progress in topical treatment, *Paediatr Drugs* 4(2):95, 2002.

Varaprasathan G et al.: Trends in the etiology of infectious corneal ulcers at the F.I. Proctor Foundation, *Cornea* 23(4):360, 2004.

BASIC INFORMATION

DEFINITION

Coronary artery disease (CAD) is a clinical syndrome that suggests limitation of coronary blood flow to the myocardium as a result of flow-limiting atherosclerotic lesions. It is characterized by exertional symptoms as described below.

This topic addresses only stable CAD. Acute coronary syndromes (ACS), angina pectoris, and myocardial infarction are addressed as separate topics elsewhere.

SYNONYMS

Atherosclerotic heart disease
CAD
Chronic stable angina
Stable ischemic heart disease

ICD-9CM CODE
414.01 Coronary atherosclerosis of native coronary artery
ICD-10CM CODE
I25.1 Atherosclerotic heart disease
I25.0 Atherosclerotic cardiovascular disease

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Increases with age.
PEAK INCIDENCE: Increases in age in women but peaks in men between the ages of 55 and 65 years.
PREVALENCE: 15.4 million Americans ≥20 years of age have CAD, and this includes 6.4% of US adults ≥20 years of age. CAD prevalence is 7.9% for men and 5.1% for women.
PREDOMINANT SEX AND AGE: Male predominance, no predominant age.
RISK FACTORS: Age, male sex, hypertension, hyperlipidemia, diabetes mellitus, obesity, tobacco use, family history, peripheral vascular disease. Coronary plaque, especially noncalcified plaque, is more prevalent and extensive in HIV-infected men, independent of CAD risk factors.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Left anterior chest discomfort often described as squeezing, choking, heavy, and occasionally hot or cold sensations.
- Associated symptoms include fatigue, dyspnea, weakness, lightheadedness, nausea, diaphoresis, altered mental status, and syncope.
- Angina typically lasts 3 to 5 minutes but usually does not last more than 30 minutes.
- Women and diabetics may not present with classic symptoms, but may manifest more frequently with dyspnea.
- Elicited by physical exertion, emotional stress, cold exposure, consumption of heavy meal, smoking.

ETIOLOGY

- Myocardial ischemia caused by the impairment of coronary blood flow secondary to coronary atherosclerosis that has built up over decades or nonatheromatous coronary artery disease, including Prinzmetal angina and congenital abnormalities of the coronary arteries in their origin or distribution.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS OF ACUTE CHEST PAIN

- Cardiovascular causes
  - Aortic dissection.
  - Pericarditis.
  - Coronary arterial vasospasm.
- Pulmonary causes
  - Pneumothorax.
  - Pneumonia.
  - Pleuritis.
  - Pulmonary embolism.
- Gastrointestinal causes
  - Esophageal spasm.
  - Esophagitis.
  - GERD.
  - Cholecystitis.
  - Choledocholithiasis.
  - Cholangitis.
  - Peptic ulcer.
  - Pancreatitis.
- Chest wall causes
  - Rib fracture.
  - Sternoclavicular arthritis.
  - Herpes zoster.
  - Costochondritis.
- Psychiatric causes
  - Anxiety disorders.

WORKUP

- See Fig. C1-105

LABORATORY TESTS

- Focused metabolic studies to rule out noncardiac causes.
- Complete blood count can help rule out anemia-related chest discomfort.
- Fasting cholesterol panel is important in assessment of control of lipid-related risk factors.
- Hemoglobin A1c is important to follow glycemic control.
- High sensitivity C-reactive protein.

IMAGING STUDIES

- Electrocardiogram (ECG) is important for assessing for prior cardiac injury.
- Exercise treadmill test (ETT) is the gold standard to assess physiologic cardiac stress response if the patient is able to exercise and has a normal baseline ECG.
- Stress tests combined with imaging is the next best option if ETT cannot be performed due to physical limitation or if baseline ECG is abnormal.
- Echocardiogram to assess left ventricular ejection fraction (LVEF).
- Coronary artery calcium (CAC) score: can be used to improve CVD risk classification. The CAC is estimated from noncontrast CT images (radiation exposure 0.9 to 1.1 mSv of radiation, digital mammogram radiation is 0.44 mSv). Normal coronary arteries do not have plaques or calcium, and the normal score is 0. A CAC score of 300 or higher or 75th percentile or higher for age, sex, and ethnicity is considered a high risk. According to the recent ACC/AHA guidelines, CAC is most appropriate among adults with an estimated 10-year ASCVD risk <7.5% in whom questions remain about whether statin therapy is indicated. A CAC score >75th percentile for age, sex, and ethnicity is considered high risk and would justify revising a patient's risk upward.
- Those with high-risk features (Box C1-4) should undergo coronary angiography to assess coronary anatomy for revascularization.
- Cardiac computed tomography angiography is an emerging imaging modality that can be considered as an alternative to stress testing.
- Coronary angiography is useful for both diagnostic and therapeutic interventions if there is evidence of significant ischemia by noninvasive assessment or progressive symptoms despite optimal medical therapy (as below).

TREATMENT

- See Fig. C1-106.
- Successful treatment of CAD entails minimizing the likelihood of major adverse cardiac events (MACE), which include death, myocardial infarction, need for emergent coronary artery bypass grafting, or target lesion revascularization, while maximizing health and function.

NONPHARMACOLOGIC THERAPY

LIFESTYLE MODIFICATION:
- ≥150 min/wk of moderate-intensity activity or ≥75 min/wk of vigorous-intensity activity or a combination thereof (for adults) as 1 of the 7 components of ideal cardiovascular health.
- Mediterranean diet with a focus on vegetables, fruit, fish, whole grains, and olive oil has proven to reduce cardiovascular events to a degree greater than low-fat diets and equal to or greater than the benefit observed in statin trials.
- Smoking cessation.
- Weight reduction can reduce various risk factors with improved lipid and glycemic control.

THERAPEUTIC INTERVENTIONS:
- Enhanced external counterpulsation is used for refractory cases.
- Transmyocardial laser revascularization (TMLR) may relieve symptoms in refractory angina. The mechanics by which TMLR reduces angina is not well understood.
- Coronary angiography with PCI or CABG for patients on optimal medical therapy with persistent symptoms.

ACUTE GENERAL Rx FOR ANGINA

- Rest.
- Sublingual nitroglycerin if rest does not provide adequate relief.

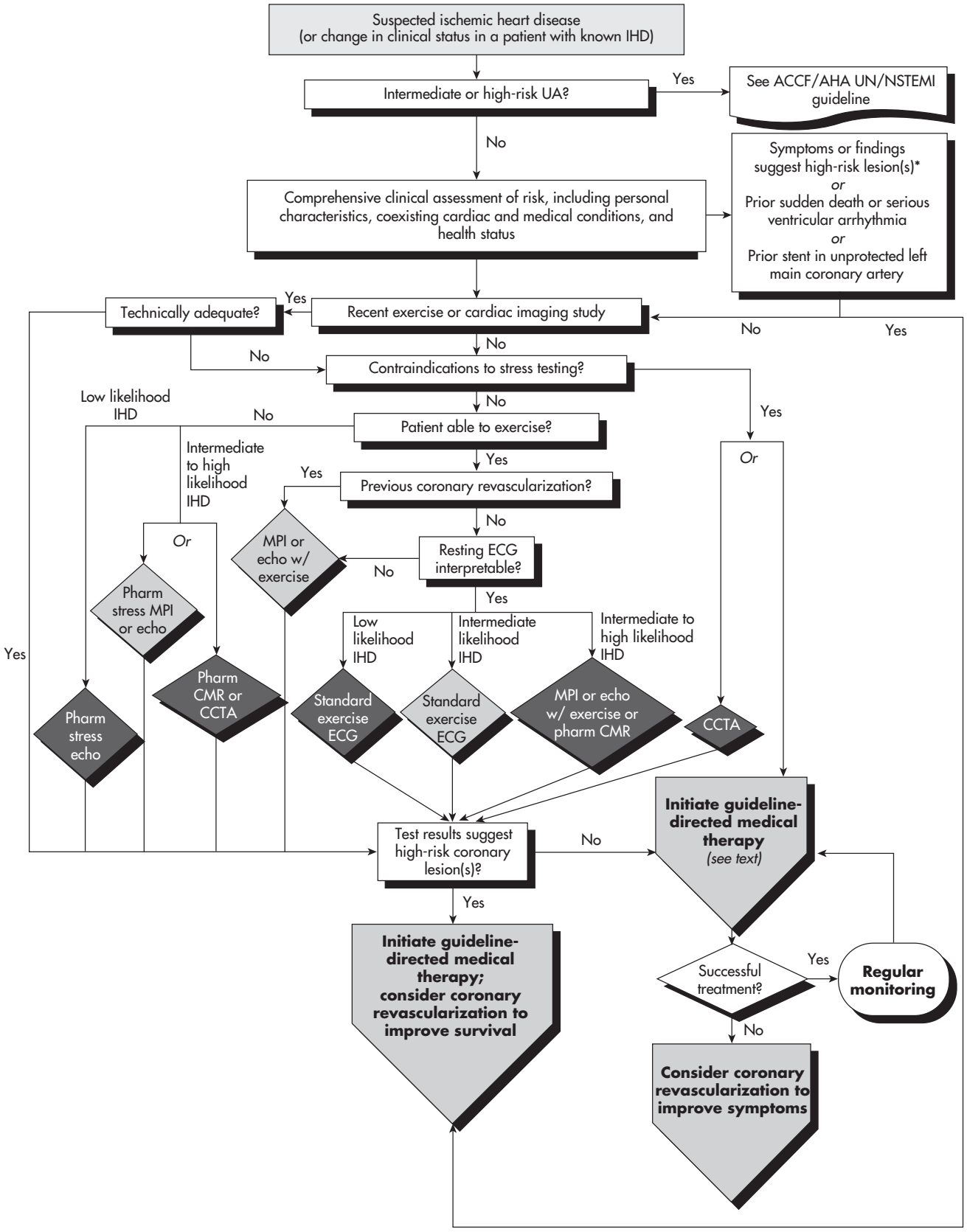

FIGURE C1-105 Diagnosis of patients with suspected ischemic heart disease.
*CCTA is reasonable only for patients with intermediate probability of IHD. *CCTA,* Computed coronary tomography angiography; *CMR,* cardiac magnetic resonance; *ECG,* electrocardiogram; *Echo,* echocardiography; *IHD,* ischemic heart disease; *MI,* myocardial infarction; *MPI,* myocardial perfusion imaging; *Pharm,* pharmacologic; *UA,* unstable angina; *UA/NSTEMI,* unstable angina/non–ST-elevation myocardial infarction. (From 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, *J Am Coll Cardiol* 60:e44-e164, 2012.)

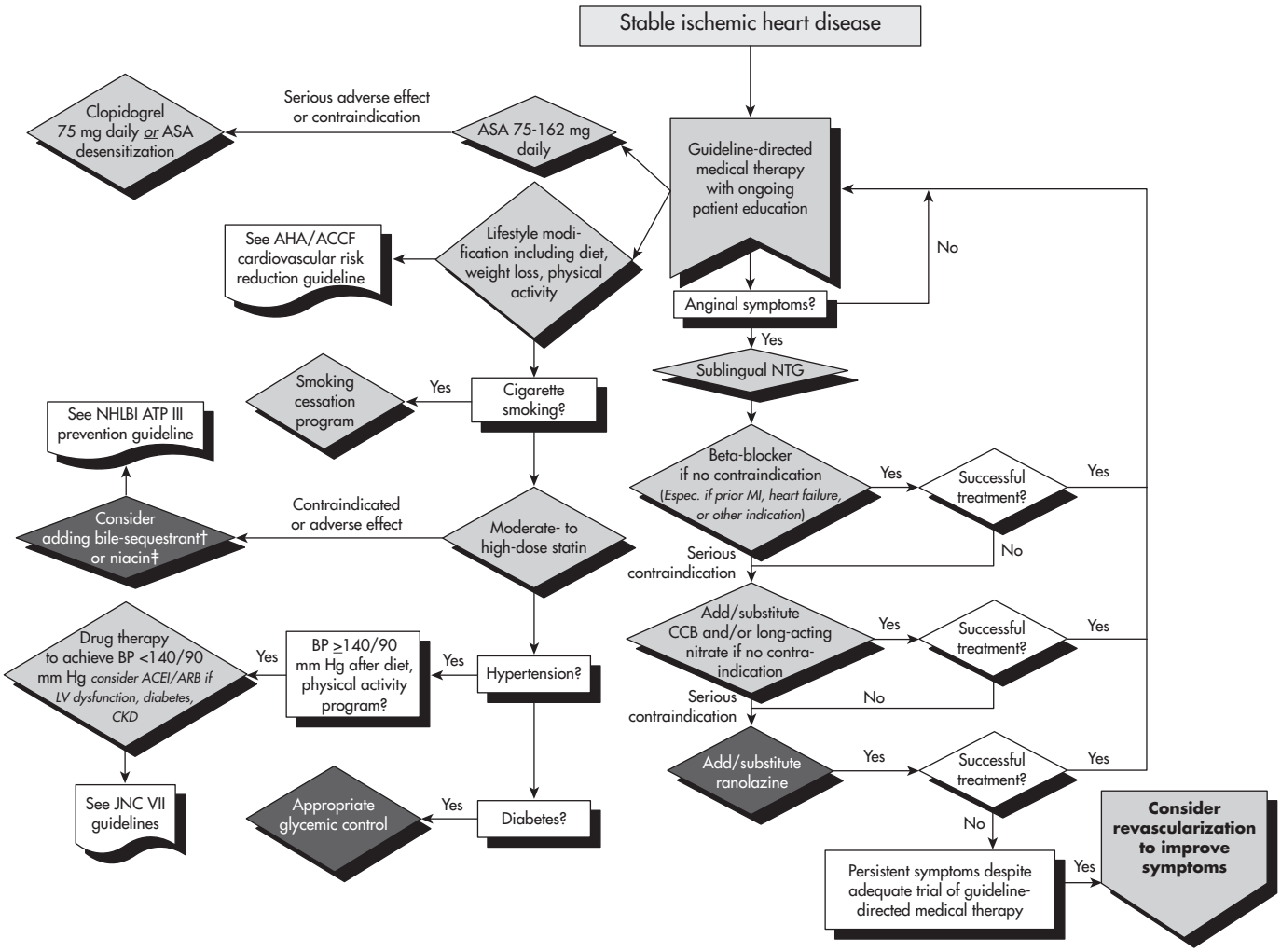

FIGURE C1-106 Algorithm for guideline-directed medical therapy for patients with SIHD.*

*The algorithms do not represent a comprehensive list of recommendations (see text for all recommendations).

†The use of bile acid sequestrant is relatively contraindicated when triglycerides are ≥200 mg/dl and is contraindicated when triglycerides are ≥500 mg/dl.

‡Dietary supplement niacin must not be used as a substitute for prescription niacin. *ACCF,* American College of Cardiology Foundation; *ACEI,* angiotensin-converting enzyme inhibitor; *AHA,* American Heart Association; *ARB,* angiotensin-receptor blocker; *ASA,* aspirin; *ATP III,* Adult Treatment Panel 3; *BP,* blood pressure; *CCB,* calcium channel blocker; *CKD,* chronic kidney disease; *HDL-C,* high-density lipoprotein cholesterol; *JNC VII,* Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; *LDL-C,* low-density lipoprotein cholesterol; *LV,* left ventricular; *MI,* myocardial infarction; *NHLBI,* National Heart, Lung, and Blood Institute; *NTG,* nitroglycerin. (From 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons, *J Am Coll Cardiol* 60:e44-e164, 2012.)

CHRONIC Rx

- Antianginal therapy
  1. Nitrates (isosorbide mononitrate and isosorbide dinitrate). These medications treat ischemia by venodilation to decrease preload, dilate epicardial coronary arteries, and recruit coronary collaterals. Furthermore, they attenuate platelet aggregation. Although they do not influence survival or decrease cardiovascular death in patients with chronic CAD, they do lower the rate of angina frequency and increase time to ischemic ECG findings on treadmill testing.
  2. Beta-adrenergic antagonists (metoprolol, atenolol, carvedilol, or any other beta-blockers with the exception of those with intrinsic sympathomimetic activity). These medications work to relieve angina by decreasing myocardial oxygen demand by reducing heart rate, blood pressure, and contractility. Drugs should be titrated to a heart rate of 50 to 60 beats/min at rest and ≤100 beats/min with exercise
  3. Calcium channel blockers (CCBs; amlodipine or verapamil). The antianginal efficacy of CCBs is comparable to beta-blockers; however, the efficacy of monotherapy for reducing MI or cardiac death has not been demonstrated.
  4. Ranolazine. This is a selective inhibitor of late sodium influx into myocytes, which leads to decreased myocardial contractility. It can be used in combination with beta-blockers and significantly reduces time to onset of angina and exercise performance (CARISA trial). Although it rarely may cause QT prolongation, it has not been linked to any clinically important arrhythmias.
  5. May benefit from combination therapy of the above.
- Antiplatelet therapy
  1. Aspirin therapy (71-162 mg/day).
  2. Clopidogrel for those intolerant to aspirin therapy.
  3. Combination of aspirin and clopidogrel does not reduce cardiovascular events (CHARISMA trial).
  4. Newer antiplatelet drugs such as prasugrel and ticagrelor have been studied in ACS but not in stable CAD.

BOX C1-4 Noninvasive Risk Stratification

High risk (>3% annual mortality rate)
1. Severe resting left ventricular dysfunction (LVEF <35%).
2. High-risk treadmill score (≤–11).
3. Severe exercise left ventricular dysfunction (exercise LVEF <35%).
4. Stress-induced large perfusion defect (particularly if anterior).
5. Stress-induced multiple perfusion defects of moderate size.
6. Large, fixed perfusion defect with LV dilation or increased lung uptake (thallium-201).
7. Stress-induced moderate perfusion defect with LV dilation or increased lung uptake (thallium-201).
8. Echocardiographic wall motion abnormality (involving >2 segments) developing at low dose of dobutamine (≤10 mg/kg/min) or at a low heart rate (<120 beats/min).
9. Stress echocardiographic evidence of extensive ischemia.

Intermediate risk (1% to 3% annual mortality rate)
1. Mild/moderate resting left ventricular dysfunction (LVEF 35% to 49%).
2. Intermediate-risk treadmill score (score between –11 and <5).
3. Stress-induced moderate perfusion defect without LV dilation or increased lung intake (thallium-201).
4. Limited stress echocardiographic ischemia with a wall motion abnormality only at doses of dobutamine involving ≤2 segments.

Low risk (<1% annual mortality rate)
1. Low-risk treadmill score (≥5).
2. Normal or small myocardial perfusion defect at rest or with stress.
3. Normal stress echocardiographic wall motion or no change of limited resting wall motion abnormalities during stress.

From ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012: Appropriate use criteria for coronary revascularization focused update: A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography, *J Am Coll Cardiol* 59:857-881, 2012.

- Statins
  1. HMG-CoA reductase inhibitors (statins) (atorvastatin, rosuvastatin) with high-intensity therapy for a target LDL reduction of >50% if safely achieved in high-risk patients; if not a candidate for high-intensity therapy, patient should receive at least moderate-intensity statin therapy that lowers LDL by 30% to 50% as advised by the new ATP IV cholesterol guidelines from the 2013 ACC/AHA expert panel.
- ACE-inhibitors (captopril, enalapril, lisinopril) are a class I recommendation for patients with chronic CAD with LV dysfunction LVEF < 40% or diabetes and a class II recommendation for CAD patients without these features.

CORONARY ARTERY REVASCULARIZATION

- Patients with symptoms refractory to optimal medical therapy (OMT) as above or those with high clinical, stress testing, or an angiographic risk profile and suitable coronary anatomy may benefit from revascularization with either PCI (percutaneous coronary intervention) or CABG (coronary artery bypass graft) surgery.
- ACC/AHA class I indications for CABG surgery in chronic CAD patients include the following:
  1. High grade (>50%) left main CAD.
  2. Left main CAD-equivalent anatomy including >70% luminal stenosis in the left anterior descending artery and left circumflex arteries.
  3. Three-vessel disease with LVEF <50%.
  4. Single- or two-vessel CAD with a large area of viable myocardium at risk.
  5. Severe angina despite medical therapy if CABG can be performed with acceptable risk.
- PCI has not been shown to reduce long-term rates of MI and death in patients with stable chronic CAD and therefore has no class I indications in this group. PCI is suitable in patients with suitable anatomy with refractory or lifestyle-limiting angina who have failed OMT. Recent trials such as the COURAGE Trial have demonstrated no significant difference between OMT and PCI in overall survival, MI, and ACS over 5 years in patients with chronic stable CAD.
- The SYNTAX trial, which used a numerical score based on qualitative plaque features on angiography, showed that surgical revascularization was associated with a lesser risk of stroke and major cardiac events if the SYNTAX score was high (>33).
- The FREEDOM trial showed that in diabetic patients with multivessel disease, CABG is superior to PCI with drug-eluting stents in chronic CAD and should remain the revascularization strategy of choice in this patient population. CABG resulted in lower rates of death and MI but a higher risk of stroke. This is true for patients with either insulin-dependent or non–insulin-dependent DM.

DISPOSITION

- Coronary artery disease is a common chronic condition with which many patients can live for years with good symptom control on optimal medical therapy.

REFERRAL

- Cardiovascular disease specialist.

PEARLS & CONSIDERATIONS

COMMENTS

- The transition from stable coronary artery disease to unstable angina must be carefully monitored. Symptoms of concern include more frequent episodes of chest pain, chest pain that is less responsive to nitroglycerin, or first episode of chest pain. Regarding unstable angina, please refer to section on acute coronary syndromes.
- JDL efflux capacity (the ability of HDL to accept cholesterol from macrophages) is inversely associated with the incidence of cardiovascular efforts and may become a useful new biomarker.[1]

RELATED CONTENT

Coronary Artery Disease (Patient Information)
Acute Coronary Syndrome (Related Key Topic)
Angina Pectoris (Related Key Topic)
Hyperlipidemia (Related Key Topic)
Myocardial Infarction (Related Key Topic)

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[1] Rohatgi A et al: HDL cholesterol efflux capacity and incident cardiovascular events, *N Engl J Med* 311:2383-2393, 2014.

SUGGESTED READINGS

Abrams J: Chronic stable angina, *N Engl J Med* 352:2524–2533, 2005.

Dalen JE, Devries S: Diets to prevent coronary heart disease 1957–2013: What have we learned? *Am J Med* 127:364–369, 2014.

Estruch R et al.: Primary prevention of cardiovascular disease with a Mediterranean diet, *N Engl J Med* 368:1279–1290, 2013.

Fihn SD et al.: 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: executive summary, *J Am Coll Cardiol* 60:2564–2603, 2012.

Goff DC Jr et al.: ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology /American Heart Association Task Force on Practice Guidelines, *Circulation*, 2013.

Nabel EG, Braunwald E: A tale of coronary artery disease and myocardial infarction, *N Engl J Med* 366:54–63, 2012.

Polonsky TS et al.: Coronary Artery Calcium score, *JAMA* 312:837–838, 2014.

Post WS et al.: Associations between HIV infection and subclinical coronary atherosclerosis, *Ann Intern Med* 160:458–467, 2014.

Wolk MJ et al.: ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection of stable ischemic heart disease, *J Am Coll Cardiol* 63:380–406, 2014.

BASIC INFORMATION

DEFINITION

Clinical condition characterized by pain and tenderness at costochondral or chondrosternal joints of the anterior chest wall without obvious swelling or induration.

SYNONYMS

Anterior chest wall syndrome
Chest wall pain syndrome
Costosternal syndrome
Parasternal chondrodynia

ICD-9CM CODES
733.6 Costochondritis
ICD-10CM CODES
M94.0 Chondrocostal junction syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Fairly common, comprises approximately 28% of undifferentiated noncardiac chest pain patients.
PREDOMINANT SEX: Women more than men.
PREDOMINANT AGE: >40 years of age.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

SYMPTOMS:

- Anterior chest wall pain, usually described as sharp, aching, or pressure-like. Pain is usually aggravated by coughing, sneezing, deep inspiration, or any chest wall movement.
- Pain is usually self-limited.
- May radiate to arms and shoulders mimicking cardiac pain.

SIGNS:

- Reproducible tenderness of costochondral (mostly second through fifth) or costosternal junction without localized swelling or induration.
- Pain on crossed-chest adduction of arm and backward extension of arm from 90 degrees of abduction signifies pain of musculoskeletal origin. Reproduction of symptoms during dry needling also suggests pain from musculoskeletal origin.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Usually self-limited and benign; however, it needs to be distinguished from other potentially serious conditions.

- Cardiac pain: primary concern; ischemic chest pain, acute pericarditis, aortic dissection.
- Gastrointestinal: gastroesophageal reflux disease.
- Pulmonary embolism, pneumonia, pneumothorax.
- Musculoskeletal (Table C1-54): Tietze's syndrome, cervical or thoracic spine disease, fibromyalgia, arthritis.
- Involvement of ribs by trauma, infections *(Candida albicans)* or neoplasms (breast cancer, prostate cancer, sarcoma, plasma cell cytoma, non-Hodgkin's lymphoma).
- Miscellaneous: fibromyalgia syndrome, panic attack.

WORKUP

- A diagnosis of exclusion for chest pain after ruling out more serious conditions including cardiac chest pain. Key to diagnosis are a detailed history, a meticulous physical examination, and a few rationally selected diagnostic studies, including electrocardiogram and chest x-ray to rule out cardiopulmonary causes. Usefulness of nuclear scanning with technetium-99m scintigraphy, gallium, or bone scanning to assist diagnosis of costochondritis is not clear.

TREATMENT

ACUTE GENERAL Rx

- Often self-limiting, so reassurance is important.
- Symptomatic treatment includes local application of heat, minimizing of activities that aggravate symptoms, stretching exercises for chest wall muscles, and nonsteroidal anti-inflammatory drugs or acetaminophen.
- Refractory cases can be treated with local injections of combined lidocaine and corticosteroid (may be a useful diagnostic and therapeutic tool). Dry needling by a trained physical therapist may be helpful.
- Recurrent costochondritis may respond to sulfasalazine; however, there are no clinical trials on pharmacologic therapy for costochondritis.

PEARLS & CONSIDERATIONS

Presence of costochondritis in a patient with chest pain does not exclude more serious problems including cardiac pain. Further testing is required as clinically indicated.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Costochondritis (Patient Information)

AUTHOR: **ASHA SHRESTHA, M.D.**

TABLE C1-54 Musculoskeletal Chest Pain

Disorder	Clinical Features	Comments
Tietze's syndrome	Painful swelling of usually 2nd or 3rd costochondral junctions.	Less common than costochondritis; commonly affects young people of either sex. Exact cause is unknown, but a traumatic pathogenesis has been associated. The disease course is mostly self-limited. Non-Hodgkin's lymphoma of medial clavicular head has been reported to mimic Tietze syndrome.
Costochondritis	Pain and tenderness at the costochondral or chondrosternal junctions without a notable swelling. The 2nd-5th costal cartilages are most commonly involved.	Certain maneuvers like "crowing rooster" maneuver (extension of the cervical spine and traction on the posteriorly extended arm) and traction on the adducted arm with head rotated to ipsilateral side may reproduce the pain.
Slipping rib syndrome	Pain at the lower costal cartilages, associated with increased mobility of the anterior end of a costal cartilage. Most commonly affects 10th rib and occasionally 8th and 9th ribs.	Maneuver such as hooking the fingers under the anterior costal margin and pulling the rib cage anteriorly may produce a palpable click of the cartilages slipping over one another.
Cervical, thoracic disc disease	Referred regional pain from affected areas. Often aggravated by spine motion and may be accompanied by radicular pain into arm if cervical origin or along intercostal nerve if thoracic origin. Symptoms reproduced by Spurling's maneuver (steady pressure to head causing increased axial loading on the nerve root).	May mimic chest disease if spinal complaints are minimal and referred or radicular symptoms predominate.
Fibromyalgia	Widespread pain with multiple other peripheral tender points.	Female/male ratio of 9:1. Prevalent age 30-50 yr. Frequently associated with tension headache, irritable bowel syndrome, and psychiatric symptoms.
Sternoclavicular or manubriosternal joint involvement in osteoarthritis, inflammatory conditions (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis), and infection	Dull, aching local pain with tenderness. Occasional bony joint enlargement with soft tissue swelling.	Crepitus may rarely be present.

SUGGESTED READINGS

Adel G et al.: Musculoskeletal chest wall pain, *Can Med Assoc J* 133:379–389, 1985.

Biundo J.J. Jr. Disorders of the anterior chest wall. In: Klippel J.H. editor, Primer on the rheumatic diseases, ed 13 Springer: New York.

Calabro JJ: Costochondritis, *N Engl J Med* 296:946–947, 1997.

Ferri F.F. Practical guide to the care of the medical patient. ed 7 Mosby: St Louis.

Freeston J et al.: Can early diagnosis and management of costochondritis reduce acute chest pain admissions? *J Rheumatol* 31:2269, 2004.

Fruergaard P et al.: The diagnoses of patients admitted with acute chest pain but without myocardial infarction, *Eur Heart J* 17(7):1028–1034, 1996.

Jenson S: Musculoskeletal causes of chest pain, *Am Fam Physician* 30:834, 2001.

Proulx AM, Zryd T: Costochondritis: diagnosis and treatment, *Am Fam Physician* 80(6):617–620, 2009.

Ringstrom E, Freedman J: Approach to undifferentiated chest pain in emergency department: a review of recent medical literature and published practice guidelines, *Mt Sinai J Med* 73(2):499–505, 2006.

Rovetta G et al.: Stretching exercises for costochondritis pain, *G Ital Med Lav Ergon* 31(2):169–171, 2009.

Westrick RB et al.: Evaluation and treatment of musculoskeletal chest wall pain in a military athlete, *Int J Sports Phys Ther* 7(3):323–332, 2012.

Wise CM et al.: Musculoskeletal chest wall syndromes in patients with noncardiac chest pain: a study of 100 patients, *Arch Phys Med Rehabil* 72:147–149, 1992.

Craniopharyngioma PTG ALG

BASIC INFORMATION

DEFINITION

Craniopharyngiomas are tumors arising from squamous cell remnants of Rathke's pouch, located in the infundibulum or upper anterior hypophysis.

SYNONYMS

Subset of nonadenomatous pituitary tumors

ICD-9CM CODES
237.0 Craniopharyngioma
ICD-10CM CODES
D44.3 Neoplasm of uncertain behavior of pituitary gland

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Occurs at all ages; peak during the first 2 decades of life, with a second small peak occurring in the sixth decade.
PREDOMINANT SEX:
- Both sexes are usually equally affected.
- Craniopharyngiomas are the most common nonglial tumors in children and account for 3% to 5% of all pediatric brain tumors.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The typical onset is insidious and a 1- to 2-year history of slowly progressive symptoms is common.
- Presenting symptoms are usually related to the effects of a sella turcica mass. Approximately 75% of patients report headache and have visual disturbances.
- The usual visual defect is bitemporal hemianopsia. Optic nerve involvement with decreased visual acuity and scotomas and homonymous hemianopsia from optic tract involvement may also occur.
- Other symptoms include mental changes, nausea, vomiting, somnolence, or symptoms of pituitary failure. In adults, sexual dysfunction is the most common endocrine complaint, with impotence in men and primary or secondary amenorrhea in women. Diabetes insipidus is found in 25% of cases. In children, craniopharyngiomas may present with dwarfism.
- More than 70% of children at the time of diagnosis present with growth hormone deficiency, obstructive hydrocephalus, short-term memory deficits, and psychomotor slowing.

ETIOLOGY

Craniopharyngiomas are believed to arise from nests of squamous epithelial cells that are commonly found in the suprasellar area surrounding the pars tuberalis of the adult pituitary.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Pituitary adenoma.
- Empty sella syndrome.
- Pituitary failure of any cause.
- Primary brain tumors (e.g., meningiomas, astrocytomas).
- Metastatic brain tumors.
- Other brain tumors.
- Cerebral aneurysm.

LABORATORY TESTS

- Hypothyroidism (low FT_4, FT_3 with high thyroid-stimulating hormone).
- Hypercortisolism (low cortisol) with low adrenocorticotropic hormone.
- Low sex hormones (testosterone, estriol) with low follicle-stimulating hormone and luteinizing hormone.
- Diabetes insipidus (hypernatremia, low urine osmolarity, high plasma osmolarity).
- Prolactin may be normal or slightly elevated.
- Pituitary stimulation tests may be required in some cases.

IMAGING STUDIES

- MRI (Fig. C1-107) or head CT if MRI is contraindicated. MRI features include a multicystic and solid enhancing suprasellar mass. Hydrocephalus may also be present if the mass is large. CT usually reveals intratumoral calcifications.
- Visual field testing for bitemporal hemianopsia.

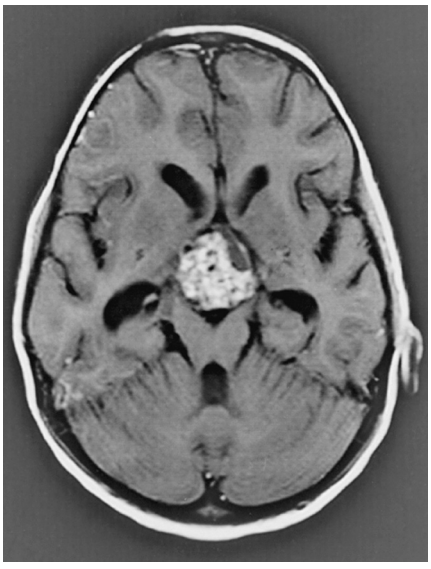

FIGURE C1-107 MRI scan of a craniopharyngioma, demonstrating a cystic contrast-enhancing mass in the suprasellar area extending upward and compressing the hypothalamus. (From Goetz CG: *Textbook of clinical neurology,* Philadelphia, 1999, Saunders.)

- Skull film may show:
  1. Enlarged or eroded sella turcica (50%)
  2. Suprasellar calcification (50%)

TREATMENT

GENERAL Rx

- Traditionally, surgery has been the main treatment for craniopharyngioma. However, radiation treatment instead of surgery may be an option in selected cases.
- Surgical resection (curative or palliative).
  1. Transsphenoidal surgery for small intrasellar tumors.
  2. Subfrontal craniotomy for most patients.
- Overall prognosis is good with 80% to 90% chance of permanent cure.
- Postoperative radiation.
- Intralesional ^{32}P irradiation or bleomycin for unresectable tumors. Long-term complications of radiation include secondary malignancies, optic neuropathy, and vascular injury.

PROGNOSIS

- Overall prognosis is good with 80%-90% chance of permanent cure.
- Operative mortality rate: 3% to 16% (higher with large tumors).
- Postoperative recurrence rate: <20% of cases after total resection and 60% of cases after subtotal resection. Most recurrences occur within the first 2 yr after surgery.
- 5-yr and 10-yr survival: 88% and 76%, respectively, with surgery and radiation.
- The most important factors that correlate with prognosis are the extent of resection and postoperative radiation.
- Long-term post-treatment hormonal, visual, and neurological problems occur in a significant percentage of patients.

RELATED CONTENT

Craniopharyngioma (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

BASIC INFORMATION

DEFINITION

Creutzfeldt-Jakob disease (CJD) is a progressive, fatal, dementing neurologic illness caused by an infectious protein agent known as a *prion.*

SYNONYMS

Transmissible spongiform encephalopathy.
Mad cow disease.
Prion disease.
Bovine spongiform encephalopathy.

OTHER PRION DISEASES

Fatal familial insomnia
Kuru
Gerstmann-Sträussler-Scheinker syndrome (GSS)

ICD-9CM CODES
046.1 Creutzfeldt-Jakob disease
ICD-10CM CODES
A81.00 Creutzfeldt-Jakob disease, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence of one per 1 million population per year.
- Peak age 60 yr (range, 16 to 82 yr)—sporadic cases are seen in an older population while the variant subtype is commonly seen in younger patients.
- 5% to 10% familial, remaining cases are sporadic; iatrogenic cases (corneal or liver transplants, dura mater allograft, human pituitary extract, blood or blood product transfusion, reused medical equipment such as EEG depth electrodes) are very rare—about 1%; variant CJD is caused by ingestion of meat from cows with prion disease and is more commonly seen in Great Britain but recent cases from Canada and France have also been reported.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Cognitive deficits: Patients present with cognitive deficits (dementing illness—memory loss, behavioral abnormalities, higher cortical function impairment), usually a subacute rapid progressive encephalopathy or dementia. Prodromal symptoms such as fatigue, depression, weight loss, and disorders of sleep and appetite may be seen in about one third of patients. Early stages are characterized by confusion with hallucinations, delusions, and agitation.
- More than 80% will have myoclonus—generalized and exaggerated by startle.
- Pyramidal tract signs (weakness), cerebellar signs (clumsiness), and extrapyramidal signs (parkinsonian features) are seen in more than 50% of the cases.
- Less common features include cortical visual abnormalities, abnormal eye movements, vestibular dysfunction, sensory disturbances, autonomic dysfunction, lower motor neuron signs, and seizures.

ETIOLOGY

Small proteinaceous infectious particle (prion): Noninfectious prion protein (PrP) is a cellular protein found on the surfaces of neurons. Normal function is not known. This normal protein is converted to a protease-resistant infectious agent by the infectious prion protein.

- Normal prion protein (PRNP) gene is found on human chromosome 20.
- Methionine and valine distribution on codon 129 of the PRNP determines the six clinical phenotypes of CJD.

DIAGNOSIS

- Definite CJD: neuropathologically confirmed spongiform encephalopathy in a case of progressive dementia.
- Probable CJD: history of rapidly progressive dementia (<2 yr) with typical EEG and with at least two of the following clinical features: myoclonus, visual or cerebellar dysfunction, pyramidal or extrapyramidal features, akinetic mutism.
- Possible CJD: same as probable CJD without EEG findings.

DIFFERENTIAL DIAGNOSIS

- Other progressive dementias (Alzheimer's disease, frontotemporal dementia, Lewy body dementia, and vascular dementia).
- Infectious (viral, HIV, fungal, TB, Whipple's disease).
- Inflammatory/autoimmune (CNS vasculitis, Hashimoto's encephalopathy, SSPE).
- Metabolic (vitamin deficiency, endocrine).
- Cancers (CNS lymphoma, gliomatosis cerebri, paraneoplastic).
- Other conditions, toxic (heavy metal poisoning).

A clinical algorithm for the evaluation of dementia is described in Section III, "Dementia."

WORKUP

- Evaluate for treatable causes of dementia (see "Alzheimer's Disease").
- Brain biopsy is gold standard for diagnosis, but it is usually not performed because there is no treatment or cure.
- Lumbar puncture with spinal fluid analysis for presence of 14-3-3 protein or human prion protein (PrP^{Sc}).
- Recent guidelines issued by the American Academy of Neurology states that clinicians should order assays for 14-3-3 in patients with rapidly progressive dementia, strong suspicion of sporadic CJD, and an uncertain diagnosis (pretest probability 20% to 90%). The test has a high false-positive and false-negative rate due to its presence in other chronic noninflammatory dementing diseases.

LABORATORY TESTS

- Presence of periodic sharp wave complexes on EEG in cases of rapidly progressive dementia has a sensitivity of 67% and a specificity of 86%.
- In cases of probable or possible CJD, presence of the 14-3-3 protein in CSF has a 95% positive predictive value with its absence having a 92% negative predictive value. Test for presence of human prion protein (PrP^{Sc}) in CSF has been reported to be 83% sensitive and 100% specific. Repeated testing for 14-3-3 protein increases the probability of a positive result. Enolase and neopterin in CSF are the other nonspecific markers that may have adjunct diagnostic value.
- Recent reports indicate that testing of nasal brushings using RT-QuIC, an ultrasensitive, multiwall plate-based fluorescence assay involving PrP^{CJD}–seeded polymerization of recombinant PrP into amyloid fibrils is accurate in diagnosing CJD.
- PRP^{Sc} can also be detected in urine samples obtained from patients with variant CJD.
- The National Prion Disease Pathology Surveillance Center at Case Western Reserve University performs specific diagnostic tests free of charge and acts as a reporting center to the CDC.

IMAGING STUDIES

MRI scan can show areas of restricted diffusion in the basal ganglia and cerebral cortex. MRI diffusion-weighted imaging has a sensitivity of 92.3% and a specificity of 93.8% only in cases of rapidly progressive dementia. T2-weighted imaging may also show subtle hyperintensities in the lenticular nuclei in about 82% of cases.

TREATMENT

NONPHARMACOLOGIC THERAPY

Full-time caregiver and/or nursing home: Social work can be helpful with end-of-life discussions, family counseling, and optimizing appropriate home services. Proper disposal of medical equipment and avoidance of organ transplants from these patients prevent transmission of the disease.

ACUTE GENERAL Rx

No known therapy.

CHRONIC Rx

No known therapy.

DISPOSITION

The disease is fatal. Mean duration of illness is 8 mo (range, 1 to 130 mo). One in 7 survives to 1 yr, and 1 in 30 survives to 2 yr. Better survival found in younger age at onset of disease and female gender. Increased survival may be falsely reported due to coexisting dementias such as Alzheimer's with earlier onset of dementia than CJD.

REFERRAL

- Neurology for evaluation of any rapidly progressive dementia.
- Social work.

PEARLS & CONSIDERATIONS

COMMENTS

- A diagnosis of CJD should be considered in patients with rapid progression of dementia from unknown causes.
- Exposure to human or animal nervous tissues increases the odds of CJD in patients presenting with progressive dementia.
- Related diseases in human beings: kuru, fatal familial insomnia, Gerstmann-Sträussler-Scheinker syndrome, new-variant CJD.
- Related diseases in animals: scrapie, bovine spongiform encephalopathy (mad cow disease).

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **ARUN SWAMINATHAN, M.B.B.S**. and **SACHIN KEDAR, M.B.B.S., M.D.**

EVIDENCE

Abstract[1]

Background:

Variant Creutzfeldt-Jakob disease (vCJD) is a fatal neurodegenerative disorder originating from exposure to bovine-spongiform-encephalopathy-like prions. Prion infections are associated with long and clinically silent incubations. The number of asymptomatic individuals with vCJD prion infection is unknown, posing risk to others via blood transfusion, blood products, organ or tissue grafts, and contaminated medical instruments. We aimed to establish the sensitivity and specificity of a blood-based assay for detection of vCJD prion infection.

Methods:

We developed a solid-state binding matrix to capture and concentrate disease-associated prion proteins and coupled this method to direct immunodetection of surface-bound material. Quantitative assay sensitivity was assessed with a serial dilution series of 10^{-7} to 10^{-10} of vCJD prion-infected brain homogenate into whole human blood, with a baseline control of normal human brain homogenate in whole blood (10^{-6}). To establish the sensitivity and specificity of the assay for detection of endogenous vCJD, we analysed a masked panel of 190 whole blood samples from 21 patients with vCJD, 27 with sporadic CJD, 42 with other neurologic diseases, and 100 normal controls. Samples were masked and numbered by individuals independent of the assay and analysis. Each sample was tested twice in independent assay runs; only samples that were reactive in both runs were scored as positive overall.

Findings:

We were able to distinguish a 10^{-10} dilution of exogenous vCJD prion-infected brain from a 10^{-6} dilution of normal brain (mean chemiluminescent signal, 1.3×10^5 [SD 1.1×10^4] for vCJD vs 9.9×10^4 [4.5×10^3] for normal brain; $p<0.0001$)—an assay sensitivity that was orders of magnitude higher than any previously reported. 15 samples in the masked panel were scored as positive. All 15 samples were from patients with vCJD, showing an assay sensitivity for vCJD of 71.4% (95% CI 47.8-88.7) and a specificity of 100% (95% CIs between 97.8% and 100%).

Interpretation:

These initial studies provide a prototype blood test for diagnosis of vCJD in symptomatic individuals, which could allow development of large-scale screening tests for asymptomatic vCJD prion infection. Ⓐ

Evidence-Based Reference

Edgeworth JA et al.: Detection of prion infection in variant Creutzfeldt-Jakob disease: a blood-based assay, *Lancet* 377:487–493, 2011. Ⓐ

SUGGESTED READINGS

Atarashi R et al.: Ultrasensitive human prion detection in cerebrospinal fluid by real-time quaking-induced conversion, *Nat Med* 17:175, 2011.

Knight RSG, Will RG: Prion disease, *J Neurol Neurosurg Psychiatry* 75:36, 2004.

Masters CL et al.: Creutzfeldt-Jakob disease: patterns of worldwide occurrence and the significance of familial and sporadic clustering, *Ann Neurol* 5:177, 1979.

Matsui Y et al.: Development of an ultra-rapid diagnostic method based on heart-type fatty acid binding protein levels in the CSF of CJD patients, *Cell Mol Neurobiol* 30(7):991–999, 2010.

Moda F et al.: Prions in the urine of patients with variant Creutzfeldt-Jakob disease, *N Engl J Med* 371:530–539, 2014.

Orru CD et al.: A test for Creutzfeldt – Jakob disease using nasal brushings, *N Engl J Med* 371:519–529, 2014.

Shiga Y et al.: Diffusion-weighted MRI abnormalities as an early diagnostic marker for Creutzfeldt-Jakob disease, *Neurology* 63:443, 2004.

Steinhoff BJ et al.: Accuracy and reliability of periodic sharp wave complexes in Creutzfeldt Jakob disease, *Arch Neurol* 53:162, 1996.

Torres M et al.: Altered prion protein expression pattern in CSF as a biomarker for Creutzfeldt-Jakob disease, *PLoS One* 7(4):e36159, 2012.

BASIC INFORMATION

DEFINITION

Crohn's disease is an inflammatory disease of the bowel of unknown etiology, most commonly involving the terminal ileum and manifesting primarily with diarrhea, abdominal pain, fatigue, and weight loss.

SYNONYMS

Regional enteritis
Inflammatory bowel disease (IBD)

ICD-9CM CODES
555.9 Crohn's disease, unspecified site
555.0 Crohn's disease, small intestine
555.1 Crohn's disease involving large intestine

ICD-10CM CODES
K50.90 Crohn's disease, unspecified, without complications
K50.00 Crohn's disease of small intestine without complications
K50.10 Crohn's disease of large intestine without complications

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE

- One case per 1000 persons; most common in whites and Jews.
- Crohn's disease affects approximately 380,000 to 480,000 persons in the United States.
- Incidence: bimodal with a peak in the third decade of life and another in the fifth decade.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Abdominal tenderness, mass, or distention.
- Chronic or nocturnal diarrhea.
- Weight loss, fever, night sweats.
- Hyperactive bowel sounds in patients with partial obstruction, bloody diarrhea.
- Delayed growth and failure of normal development in children.
- Perianal and rectal abscesses, multiple sinuses and scarring (Fig. EC1-108), mouth ulcers, cobblestone appearance of oral mucosa (Fig. EC1-109), and atrophic glossitis.
- Extraintestinal manifestations (Table EC1-55): joint swelling and tenderness, hepatosplenomegaly, erythema nodosum, clubbing, tenderness to palpation of the sacroiliac joints.
- Symptoms may be intermittent with varying periods of remission.

ETIOLOGY

Unknown. Pathophysiologically, Crohn's disease involves an immune system dysfunction.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Ulcerative colitis (see Table C1-56).
- Infectious diseases (tuberculosis, *Yersinia, Salmonella, Shigella, Campylobacter*).
- Parasitic infections (amebic infection).
- Pseudomembranous colitis.
- Ischemic colitis in elderly patients.
- Lymphoma.
- Colon carcinoma.
- Diverticulitis.
- Radiation enteritis.
- Collagenous colitis.
- Fungal infections *(Histoplasma, Actinomyces).*
- Gay bowel syndrome (in homosexual patient).
- Carcinoid tumors.
- Celiac sprue.
- Mesenteric adenitis.

LABORATORY TESTS

- Decreased hemoglobin and hematocrit from chronic blood loss, effect of inflammation on bone marrow, and malabsorption of vitamin B_{12}.
- Hypokalemia, hypomagnesemia, hypocalcemia, and low albumin in patients with chronic diarrhea.
- Vitamin B_{12} and folate deficiency.
- Elevated erythrocyte sedimentation rate.
- Positive anti–*Saccharomyces cerevisiae* antibodies.
- Elevated INR (due to vitamin K malabsorption).
- Fecal calprotectin has been reported as useful in screening of patients with suspected IBD. Based on a pretest probability of 32% in adults, an abnormal calprotectin test result increases the posttest probability to 91%, and a normal result reduces the probability of IBD to 3%. False elevations may occur with other gastrointestinal diseases such as bacterial, viral, and protozoal causes of infective diarrhea.

ENDOSCOPIC EVALUATION

Endoscopic features of Crohn's disease include asymmetric and discontinued disease, deep longitudinal fissures, cobblestone appearance, and presence of strictures. Crypt distortion and inflammation are also present. Granulomas may be present.

IMAGING STUDIES

- CT of abdomen may show thickening of the terminal ileum (Fig. C1-110) and is helpful in identifying abscesses and other complications.
- Barium imaging studies are essentially outdated examinations. When performed, they reveal deep ulcerations (often longitudinal and transverse) and segmental lesions (skip lesions, strictures, fistulas, cobblestone appearance of mucosa caused by submucosal inflammation); "thumbprinting" is common, and "string sign" in terminal ileum may be noted. Although the diagnosis may be suggested by radiographic studies, it should be confirmed by endoscopy and biopsy when possible.
- Magnetic resonance enterography (MRe) is superior to other imaging modalities in its ability to distinguish active from chronic

TABLE C1-56 Differentiating Features

	Ulcerative Colitis	Crohn's Disease
Site of involvement	Only involves colon Rectum almost always involved	Any area of the gastrointestinal tract Rectum usually spared
Pattern of involvement	Continuous	Skip lesions
Diarrhea	Bloody	Usually nonbloody
Severe abdominal pain	Rare	Frequent
Perianal disease	No	In 30% of patients
Fistula	No	Yes
Endoscopic findings	Erythematous and friable Superficial ulceration	Aphthoid and deep ulcers Cobblestoning
Radiologic findings	Tubular appearance resulting from loss of haustral folds	String sign of terminal ileum RLQ mass, fistulas, abscesses
Histologic features	Mucosa only Crypt abscesses	Transmural Crypt abscesses, granulomas (about 30%)
Smoking	Protective	Worsens course
Serology	p-ANCA more common	ASCA more common

ASCA, Anti–*Saccharomyces cerevisiae* antibodies; *p-ANCA,* perinuclear antineutrophil cytoplasmic antibody; *RLQ,* right lower quadrant.
From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine*, ed 8, Philadelphia, 2010, Saunders.

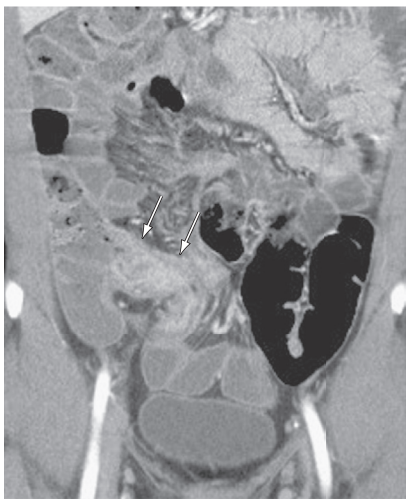

FIGURE C1-110 Coronal reformat from a contrast-enhanced computed tomographic scan shows thickening in the terminal ileum with enhancement *(arrows)* suggestive of Crohn's disease. (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.)

fibrotic disease. It is, however, more expensive.
- In 5% to 10% of patients with IBD, a clear distinction between ulcerative colitis and Crohn's disease cannot be made. In general, Crohn's disease can be distinguished from ulcerative colitis by the presence of transmural involvement and the frequent presence of noncaseating granulomas and lymphoid aggregates on biopsy.

Rx TREATMENT

The medical management of Crohn's disease is based on disease activity. According to Hanauer and Sanborn, disease activity can be defined as follows:
- Mild to moderate disease: The patient is ambulatory and able to take oral alimentation. There is no dehydration, high fever, abdominal tenderness, painful mass, obstruction, or weight loss of >10%.
- Moderate to severe disease: Either the patient has not responded to treatment for mild to moderate disease or has more pronounced symptoms, including fever, significant weight loss, abdominal pain or tenderness, intermittent nausea and vomiting, or significant anemia.
- Severe fulminant disease: Either the patient has persistent symptoms despite outpatient steroid therapy or has high fever, persistent vomiting, evidence of intestinal obstruction, rebound tenderness, cachexia, or evidence of an abscess.
- Remission: The patient is asymptomatic or without inflammatory sequelae, including patients responding to acute medical intervention.

NONPHARMACOLOGIC THERAPY

- Nutritional supplementation is needed in patients with advanced disease. Total parenteral nutrition may be necessary in selected patients.
- Low-residue diet is necessary when obstructive symptoms are present.
- If diarrhea is prominent, increased dietary fiber and decreased fat in the diet are sometimes helpful.
- Psychotherapy is useful for situational adjustment crises. A trusting and mutually understanding relationship and referral to self-help groups are very important because of the chronicity of the disease and the relatively young age of the patients.
- Avoid oral feedings during acute exacerbation to decrease colonic activity: a low-roughage diet may be helpful in early relapse.

ACUTE GENERAL Rx

- Corticosteroids are used to induce remission. They have been the mainstay for treating moderate to severe active Crohn's disease. Prednisone 40 to 60 mg/day is useful for acute exacerbation. Steroids are usually tapered over approximately 2 to 3 mo. Some patients require a low dose for a prolonged period of maintenance.
- Steroid analogues are locally active corticosteroids that target specific areas of inflammation in the gastrointestinal tract. Budesonide is available as a controlled-release formulation and is approved for mild to moderate active Crohn's disease involving the ileum and/or ascending colon. The adult dose is 9 mg qd for a maximum of 8 wk.
- Immunosuppressants such as azathioprine or mercaptopurine are used for maintenance of remission. Methotrexate is an alternative agent.
- Metronidazole 500 mg qid may be useful for colonic fistulas and treatment of mild to moderate active Crohn's disease. Ciprofloxacin 1 g qd has also been found to be effective in decreasing disease activity.
- TNF inhibitors are agents useful to induce remission and maintain remission in patients with moderate to severe Crohn's disease. Infliximab, a chimeric monoclonal antibody targeting tumor necrosis factor-α, is effective in the treatment of enterocutaneous fistulas. This medication can induce clinical improvement in 80% of patients with Crohn's disease refractory to other agents. It can be used in combination with other medications such as azathioprine in patients with severe Crohn's disease. A PPD test should be done before using this medication. Adalimumab and certolizumab are other TNF inhibitors also effective in inducing remissions and may be useful in adult patients with Crohn's disease who cannot tolerate infliximab or have symptoms despite receiving infliximab therapy.
- Natalizumab, a selective adhesion-molecule inhibitor, has been reported to be effective in increasing the rate of remission and response in patients with active Crohn's disease. It is effective for patients in whom anti-TNF therapy has been unsuccessful. Vedolizumab is another IV integrin receptor antagonist reecently FDA approved for moderate to severe Crohn's disease who have not responded or cannot tolerate standard treatment.
- Hydrocortisone enema bid or tid is useful for proctitis.
- Most patients who have anemia associated with Crohn's disease respond to iron supplementation. Erythropoietin is useful in patients with anemia refractory to treatment with iron and vitamins.

CHRONIC Rx

- Monitor disease activity with symptom review and laboratory evaluation (complete blood count and sedimentation rate).
- Liver tests and vitamin B_{12} levels monitored on a yearly basis.

DISPOSITION

One tenth of patients have prolonged remission, three quarters have a chronic intermittent disease course, and one eighth have an unremitting course.

REFERRAL

- Surgical referral is needed for complications such as abscess formation, obstruction, fistulas, toxic megacolon, refractory disease, or severe hemorrhage. Approximately 40% to 50% of patients will require some type of bowel surgery within the first 5 years of Crohn's disease. A conservative surgical approach is necessary because surgery is not curative. Multiple surgeries may also result in short bowel syndrome.

EBM EVIDENCE

available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Crohn's Disease (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Objectives:
To assess the effectiveness and safety of zoledronate (ZOL) in preventing glucocorticoid therapy-associated bone loss in patients with acute flare of Crohn's disease (CD) in a randomized, double-blind, placebo-controlled trial.

Methods:
Forty CD patients starting a glucocorticoid therapy (60mg prednisolone per day) for acute flare (CD activity index (CDAI) >220) were randomized to compare the effect of ZOL (4mg intravenous, *n*=20) or placebo (*n*=20) on change in lumbar bone mineral density (BMD). All patients received calcium citrate (800mg) and colecalciferol (1,000IU) daily. Dual energy X-ray absorptiometry (DXA) of the lumbar spine (L1–L4) was performed at baseline and day 90. Follow-up examinations at day 1/7/14/30 and 90 included laboratory tests and adverse event/serious adverse events reports.

Results:
Thirty-six patients were available for per-protocol analysis. With placebo (n=18), a decrease in BMD was seen (T-score: –0.98±0.8, day 0 and –1.25±0.77, day 90, *P*=0.06), with ZOL (*n*=18) BMD increased (–1.15±1.02, day 0 and –0.74±1.09, day 90, *P*=0.03). The change in BMD under placebo (–0.26±0.21) vs. ZOL (+0.41±0.19) was highly significant (*P*=0.006). In all, 14 out of 18 patients with ZOL had an increase in BMD (+0.64±0.48), 12 of 18 with placebo a decrease (–0.50±0.39). Changes of clinical findings and laboratory results of inflammation (leukocytes, platelets, and C-reactive protein) were the same in and between groups throughout the study. With ZOL, serum bone degradation marker β-Cross-Laps decreased. Study medication was safe and well tolerated.

Conclusions:
ZOL is effective in preventing glucocorticoid therapy-induced bone loss in patients with acute flare of CD and should be considered whenever a glucocorticoid therapy is started in CD patients. Ⓐ

Abstract[2]

Background:
Treatment options for fistulizing Crohn's disease (CD) are limited.

Aim:
To examine whether fistula closure is maintained at week 26 following treatment with certolizumab pegol.

Methods:
Patients with draining fistulas at baseline from PRECiSE 2 (*n*=108) received open-label induction with certolizumab pegol 400mg at weeks 0 (baseline), 2 and 4. Response was defined as ≥100-point decrease from baseline in the Crohn's Disease Activity Index. Nonresponders (50/108) were excluded. At week 6, responders with draining fistulas (N=58) were randomised to certolizumab pegol 400mg (n=28) or placebo (n=30) every 4weeks across weeks 8–24. Fistula closure was evaluated throughout the study, with a final assessment at week 26.

Results:
The majority of patients (55/58) had perianal fistula. At week 26, 36% of patients in the certolizumab pegol group had 100% fistula closure compared with 17% of patients receiving placebo (P=0.038). Protocol-defined fistula closure (≥50% closure at two consecutive post-baseline visits ≥3 weeks apart) was not statistically significant (P=0.069) with 54% and 43% of patients treated with certolizumab pegol and placebo achieving this end point, respectively.

Conclusion:
Continuous treatment with certolizumab pegol improves the likelihood of sustained perianal fistula closure compared with placebo. Ⓐ

Evidence-Based References

Klaus J et al.: A single dose of intravenous zoledronate prevents glucocorticoid therapy-associated bone loss in acute flare of Crohn's disease, a randomized controlled trial, *Am J Gastroenterol* 106:786–793, 2011. Ⓐ.

Schreiber S et al.: Randomised clinical trial: certolizumab pegol for fistulas in Crohn's disease—subgroup results from a placebo-controlled study, *Aliment Pharmacol Ther* 33:185–193, 2011. Ⓐ.

SUGGESTED READINGS

Abraham C, Cho JH: Inflammatory bowel disease, *N Engl J Med* 361:2066–2078, 2009.

Baumgart DC, Carding SR: Inflammatory bowel disease: cause and immunobiology, *Lancet* 369:1627, 2007.

Baumgart DC, Carding SR: Inflammatory bowel disease: clinical aspects and established and evolving therapies, *Lancet* 369:1641, 2007.

Colombel JF et al.: Infliximab, azathioprine, or combination therapy for Crohn's disease, *N Engl J Med* 362:1383–1395, 2010.

Sandborn WJ et al.: Adalimumab induction therapy for Crohn disease previously treated with infliximab, *Ann Intern Med* 146:829, 2007.

Sandborn WJ et al.: Certolizumab pegol for the treatment of Crohn's disease, *N Engl J Med* 357:228, 2007.

Van Rheenen PF et al.: Fecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis, *BMJ* 341:c3369, 2010.

FIGURE EC1-108 Crohn's disease affecting the skin of the buttocks, with multiple sinuses and scarring. This patient had a lesion of pyoderma gangrenosum when first seen and developed inflammatory plaques with the appearance of Sweet disease on the trunk (with the novel feature of a Koebner reaction into recent scars). (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

FIGURE EC1-109 Crohn's disease of the oral mucosa. In this fairly quiescent example, there is a granular cobblestoned appearance. Some patients have more aggressive fissured and ulcerated plaque lesions. (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

TABLE EC1-55 Extraintestinal Manifestations of Inflammatory Bowel Disease

Feature or Disease	Crohn's	Ulcerative Colitis
Peripheral arthritis	~15%	~10%
Axial or sacroiliac arthritis	~15%-20%	~10%-15%
Septic arthritis	Rare	Not reported
Skin		
Erythema nodosum	Up to 15%	<15%
Erythema multiforme	Rare	?
Pyoderma gangrenosum	0.5%-2%	0.3%-0.4% in severe disease
Aphthous ulcers	Rare	1%-8%
Nephrolithiasis (oxalate)	<15%	?
Amyloidosis	Very rare	Not reported
Liver disease	3%-5%	7%
Uveitis	13%	4%
Vasculitis	Takayasu's	<5%
Clubbing of fingers	Yes	1%-5%
Increased prevalence of asthma	Yes	Yes
Increased prevalence of multiple sclerosis	No	Yes

From Firestein GS, Budd RC, Gabriel SE, et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.

BASIC INFORMATION

DEFINITION

Cryoglobulins are serum immunoglobulins that precipitate when cooled and redissolve when heated. A classification of cryoglobulins is described in Table EC1-57. Cryoglobulinemia is a clinical syndrome that results from systemic inflammation caused by cryoglobulin-containing immune complexes. Mixed cryoglobulinemia is a vasculitis of small and medium-sized arteries and veins due to the deposition of complexes of antigen, cryoglobulin, and complement in the vessel walls.

SYNONYMS

Cryoglobulinemic vasculitis
Cryoproteinemia
Mixed cryoglobulinemia
Essential cryoglobulinemia

ICD-9CM CODES
273.2 Cryoglobulinemia, cryoglobulinemic vasculitis (CV), mixed cryoglobulinemia (MC)
ICD-10CM CODES
D89.1 Cryoglobulinemia

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:
- Prevalence of mixed cryoglobulinemia is approximately 1:100,000.
- More than 50% of patients with HCV are found to have mixed cryoglobulinemia.
- Three types: I (monoclonal), II (IgM monoclonal and IgG polyclonal), and III (polyclonal).

PREDOMINANT SEX AND AGE: Female:male ratio of 3:1.
PREDOMINANT AGE: Mean age reported is 42 to 52 yr.
RISK FACTORS: Hepatitis C virus (HCV) infection, connective tissue disorders, lymphoproliferative disorders.

FIGURE C1-111 Cryoglobulinemia. (From Hoffman R et al: *Hematology, basic principles and practice*, ed 6, New York, 2013, Elsevier.)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- ***Meltzer triad*** of purpura, arthralgias/myalgia, and weakness.
- Other symptoms include dyspnea, cough, numbness, abdominal pain, acrocyanosis.
- Hypertension, hepatosplenomegaly, Raynaud's phenomenon, and in severe cases, distal necrosis and ulcerations of lower limbs (Fig. C1-111).

ETIOLOGY

- Intravascular deposition of cryoglobulins leads to ischemic insults in territory supplied by vasa nervorum.
- Necrotizing vasculitis caused by cryoglobulin precipitation.
- Infections: HCV, mycosis fungoides, HBV, Epstein-Barr virus, cytomegalovirus, *Treponema pallidum, Mycobacterium leprae,* and in post-streptococcal glomerulonephritis.
- Lymphoproliferative disorders: chronic lymphocytic leukemia, Waldenström's macroglobulinemia, multiple myeloma.
- Connective tissue disorders: rheumatoid arthritis, systemic lupus erythematosus (SLE), scleroderma, Sjögren's syndrome, vasculitis.
- Renal diseases including proliferative glomerulonephritis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Antiphospholipid syndrome, SLE, lupus, Churg-Strauss syndrome, cirrhosis, glomerulonephritis, Goodpasture syndrome, hemolytic uremic syndrome, hepatitis, lymphoma, sarcoidosis, Waldenström's hypergammaglobulinemia.

WORKUP

History and physical examination; laboratory tests; imaging tests depending on patients' presentations.

LABORATORY TESTS

- Serum cryoglobulins, rheumatoid factor, serum complement, hepatitis C titers, urinalysis, CBC, ALT, AST, BUN, creatinine.
- Electromyogram/nerve conduction studies may demonstrate axonal changes and distal muscle denervation.
- Sural nerve and skin biopsy.

IMAGING STUDIES

Chest x-ray for pulmonary involvement, CT to study for malignancy, and angiography for vasculitis.

TREATMENT

- Immunosuppressive therapies such as corticosteroids are the mainstay treatment for mixed cryoglobulinemia.
- In patients with HCV, IFN-α can be added. The treatment of HCV-related mixed cryoglobulinemia is difficult due to the multifactorial origin and polymorphism of the syndrome. Therapy is aimed at eradicating the HCV infection, suppressing B-cell clonal expansion and cryoglobulin production and ameliorating symptoms
- Combination of pegylated IFN-α with ribavirin results in 77% remission.
- Variable success rate with plasma exchange, intravenous immunoglobulin, and anti-CD20 (rituximab) treatments.

NONPHARMACOLOGIC THERAPY

Avoidance of cold exposure

ACUTE GENERAL Rx

NSAIDs in those with general fatigue and arthralgia; see "Treatment" for further management.

DISPOSITION

Overall prognosis is worse with concomitant renal disease. Mean survival rate is ~50% at 10 yr.

REFERRAL

Consider referring to a nephrologist if there is renal involvement; hematologist in those with lymphoproliferative disorders; gastroenterologist/hepatologist in hepatitis; rheumatologist in connective tissue disease cases; and consider clinical immunologist in severe cases.

PEARLS & CONSIDERATIONS

COMMENTS

Always look for underlying causes for cryoglobulinemia.

PREVENTION

Avoidance of cold exposure, avoidance of late complications.

PATIENT/FAMILY EDUCATION

Inform patients about early signs/symptoms of cryoglobulinemia so that treatments can be rendered before the development of complications.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **QUANG P. LE, M.D., M.P.H.**

SUGGESTED READINGS

Cacoub P et al.: Anti-CD 20 monoclonal Ab (Rituximab) for tx for cryoglobulinemic vasculitis: where do we stand? *Ann Rheum Dis* 67(3):283–287, 2008.

Carlson JA et al.: Cutaneous vasculitis update: small vessel neutrophilic vasculitis syndromes, *Am J Dermatopathol* 28(6):486–506, 2006.

Chacko JM et al.: Paraproteinemic neuropathies, *J Clin Neuromuscul Dis* 7(4):185–197, 2006.

Crowson AN et al.: Small vessel cutaneous vasculitis, *Pathol Case Rev* 12(5): 205–213, 2007.

Iannuzzella F et al.: Management of hepatitis C virus-related mixed cryoglobulinemia, *Am J Med* 123:400–408, 2010.

TABLE EC1-57 Classification of Cryoglobulins

Type	Composition	Associated Disease
I	Monoclonal IgG, IgA, or IgM	Multiple myeloma (IgG, IgM) Chronic lymphocytic leukemia Waldenstrom macroglobulinemia Idiopathic monoclonal gammopathy Lymphoproliferative disorders
II	Polyclonal IgG and monoclonal IgM (with rheumatoid factor activity)	Hepatitis C virus Neoplasms: chronic lymphocytic leukemia, diffuse lymphoma, B lymphocytic neoplasia Essential
III	Polyclonal IgG and polyclonal IgM	Infections: viral (hepatitis B and C, Epstein-Barr virus, cytomegalovirus), bacterial (endocarditis, leprosy, poststreptococcal glomerulonephritis), parasitic (schistosomiasis, toxoplasmosis, malaria) Autoimmune disorders: systemic lupus erythematosus, rheumatoid arthritis Lymphoproliferative disorders Chronic liver disease Essential

From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

BASIC INFORMATION

DEFINITION

Cryptococcosis is an infection caused by the fungal organism *Cryptococcus neoformans.*

SYNONYMS

C. neoformans var. *neoformans* infection
C. neoformans var. *gatti* infection
C. neoformans var. *grubii* infection

ICD-9CM CODES
117.5 Cryptococcosis
ICD-10CM CODES
B45.9 Pulmonary cryptococcosis
B45.1 Cerebral cryptococcosis
B45.2 Cutaneous cryptococcosis
B45.3 Osseous cryptococcosis
B45.7 Disseminated cryptococcosis
B45.9 Cryptococcosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN THE UNITED STATES):
- 0.8 cases/million persons/year; *C. neoformans* is an important opportunistic infection in patients with deficits in cell-mediated immunity.
- 6% to 7% in HIV-infected persons with AIDS.

PEAK INCIDENCE: 20 to 40 yr (parallel to AIDS epidemic).
PREDOMINANT SEX: Equal sex distribution when corrected for HIV status.
PREDOMINANT AGE: Less than 2 yr of age; 20 to 40 yr of age.
NEONATAL INFECTION: Very uncommon.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- More than 90% present with meningitis; almost all have fever and headache.
- Meningismus, photophobia, mental status changes are seen in approximately 25%.
- Increased intracranial pressure.
- Most common infections outside the CNS:
  1. In the lungs (fever, cough, dyspnea).
  2. In the skin (cellulitis, papular eruption).
  3. In the lymph nodes (lymphadenitis).
  4. Potential involvement of virtually any organ.

ETIOLOGY

- Caused by the fungal organism *C. neoformans.*

There are 3 varieties of *Cryptococcus* spp. and 4 capsular serotypes: Serotype A is *Cryptococcus neoformans* var. *grubii* and Serotype D is known as *Cryptococcus neoformans* var. *neoformans*. Both cause disease primarily in immunocompromised patients. Serotype B and C are known as *C. neoformans* var. *gatti.* This organism causes disease primarily in normal hosts.

- Infection originates by inhalation into the respiratory tract followed by dissemination to the CNS in most cases, usually without recognizable lung involvement.
- Almost always in the setting of AIDS or other disorders of cellular immune function.
- Neutropenia alone poses a much lower risk of significant cryptococcal infection.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Subacute meningitis (caused by *Listeria monocytogenes, Mycobacterium tuberculosis, Histoplasma capsulatum,* viruses).
- Intracranial mass lesion (neoplasms, toxoplasmosis, TB).
- Pulmonary involvement confused with *Pneumocystis jiroveci* pneumonia when diffuse or confused with TB or bacterial pneumonia when focal or involving the pleura.
- Skin lesions confused with bacterial cellulitis or molluscum contagiosum.

WORKUP

- Lumbar puncture to exclude cryptococcal meningitis.
- CT scan of the head when focal lesion or increased intracranial pressure is suspected.
- Biopsy of enlarged lymph nodes and skin lesions if feasible.

LABORATORY TESTS

- Culture and India ink stain (60% to 80% sensitive in culture-proven cases [Fig. C1-112]) examination of the CSF in all cases when CNS involvement is suspected.
- Blood and serum cryptococcal antigen assay (>90% sensitivity and specificity).
- Culture and histologic examination of biopsy material.
- HIV.

IMAGING STUDIES

- CT scan or MRI of the head if focal neurologic involvement is suspected.
- Chest x-ray examination to exclude pulmonary involvement.

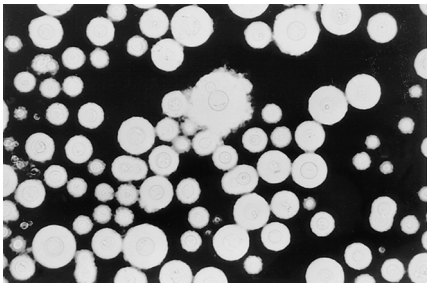

FIGURE C1-112 India ink preparation of cerebrospinal fluid revealing encapsulated cryptococci. Note the large capsules surrounding the smaller organisms. (From Andreoli TE [ed]: *Cecil essentials of medicine,* ed 4, Philadelphia, 1997, Saunders.)

TREATMENT

ACUTE GENERAL Rx

- Induction therapy for CNS disease (meningitis) is initiated with IV amphotericin B (0.5 to 0.8 mg/kg/day) with flucytosine 37.5 mg/kg PO q6h until afebrile and cultures negative (≈6 wk), then stop amphotericin B/flucytosine and start fluconazole 200 mg PO q24h or fluconazole 400 mg PO q24h for 8-10 wk or longer (up to 2 yr) to reduce relapse rate.
- Alternative: IV fluconazole for initial therapy in patients unable to tolerate amphotericin B.
- If symptomatic increased intracranial pressure, consider multiple therapeutic lumbar taps or intraventricular shunt.

CHRONIC Rx

- Fluconazole (200 to 400 mg PO qd) is highly effective in preventing a relapse in HIV-infected patients; development of resistance may occur. Itraconazole is an alternative agent.
- Immune reconstitution syndrome following the institution of HAART can cause transient worsening of meningitis and necessitate the use of a short course of corticosteroids.

DISPOSITION

Without maintenance therapy, relapse rate is >50% among AIDS patients.

REFERRAL

- For consultation with infectious diseases specialist in all cases.
- For neurologic consultation if level of consciousness is depressed or focal lesion is present.

PEARLS & CONSIDERATIONS

Cryptococcal meningitis can be remarkably insidious in nonimmunocompromised patients.

COMMENTS

Cryptococcosis is considered an AIDS-defining infection; thus all patients should be HIV tested.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Cryptococcosis (Patient Information)

AUTHOR: **PHILIP A. CHAN, M.D., M.S.**

SUGGESTED READINGS

Chayakulkeeree M, Perfect JR: Cryptococcosis. *Infect Dis Clin North Am* 20:507–544, 2006.

Lui G et al.: Cryptococcosis in apparently immunocompetent patients, *QJM* 99(3):143, 2006.

Perfect JR et al.: Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the Infectious Diseases Society of America, *Clin Infect Dis* 50:291–322, 2010.

Sperry BW et al.: A case of cryptogenic dyspnea: disseminated cryptococcosis, *Am J Med* 127:707–710, 2014.

BASIC INFORMATION

DEFINITION

Cryptorchidism is the incomplete or improper descent of the testis (testes) into the scrotum during fetal development. Testes that can be manually manipulated into the scrotum and that remain there without traction until cremasteric reflexes are induced are called *retractile.* Testes previously located but no longer palpable in the scrotum are called *ascended testes.*

SYNONYMS

Undescended testis

ICD-9CM CODES
752.51 Cryptorchidism
ICD-10CM CODES
Q53.9 Undescended testicle, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Cryptorchidism is the most common genitourinary disorder of male children.
- Occurs in approximately 30% of premature and 5% of term male infants. In 10%, it can be bilateral.
- Spontaneous descent occurs in 35% to 43% of newborn boys with congenital cryptorchidism, usually before 3 months of age.
- Increased rates with premature birth, low birth weight, twins, and family history of cryptorchidism.
- Associated with Kallman's and Prader-Willi syndromes, pituitary hypoplasia, testicular feminization, prune belly syndrome, cystic fibrosis, myelomeningocele, and Reifenstein syndrome.
- With retractile testes there is a reported 2% to 45% risk of subsequent ascent leading to an undescended testis.

CLINICAL PRESENTATION

- Typically asymptomatic and is noted incidentally on screening examination. Undescended testes are at risk for testicular torsion and inguinal hernia.
- The testis may be nonpalpable or palpable in a location along the path of normal descent (Fig. EC1-113) or less commonly ectopic and located in the perineum, femoral canal, superficial inguinal pouch, suprapubic area, or contralateral hemiscrotum.
- In 80% the undescended testis is palpable in the inguinal canal.
- Associated with infertility and a threefold increased risk of testicular cancer. Risk of infertility is the greatest for a child with bilateral intraabdominal testes and longer duration of cryptorchidism.

ETIOLOGY

Normal testicular descent is a complex interplay among mechanical (gubernaculums, vas deferens and testicular vessel length, cremasteric muscles, and abdominal pressure), hormonal (gonadotropin, testosterone, dihydrotestosterone, and mullerian inhibiting substance), and neural (ilioinguinal and genitofemoral nerves) factors.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Retractile testis
- Ascended testis
- Atrophic testis
- Vanished testis

WORKUP

- Physical examination:
  1. When done in a warm room with warm hands, can identify presence, absence, and location of palpable testes.
  2. Should be done with the patient in the supine, sitting, and standing positions with adequate cremasteric relaxation to differentiate true cryptorchidism from retractile testes.
  3. Often associated with an indirect inguinal hernia as the tunica vaginalis fails to close above the testis.
  4. An enlarged contralateral testis in the presence of a nonpalpable undescended testis is suggestive of but not definitive for testicular atrophy/absence.

If there are bilateral nonpalpable undescended testes, first rule out congenital adrenal hyperplasia (CAH). If no CAH, then rule out disorders of sexual development (DSD). Mullerian inhibiting substance (MIS or antimüllerian hormone) should be measured, and consider additional hormonal testing to evaluate for anorchia, that is, human chorionic gonadotropin (hCG) stimulation test and determination of the follicular stimulating hormone level.

- If the follicular stimulating hormone level is three times normal and there is no increase in testosterone in response to hCG, functional testes are absent.

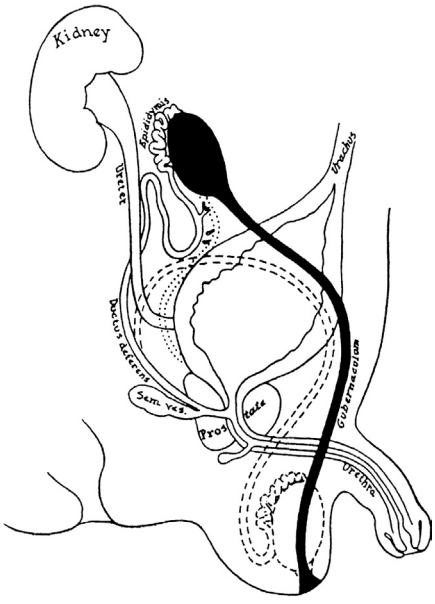

FIGURE EC1-113 The path of testicular descent. (Reproduced with permission from Sarnat HB, Sarnat MS: Disorders of muscle in the newborn. In Moss AJ, Stern L [eds]: *Pediatrics update,* ed 4, New York, 1983, Elsevier-North Holland.)

IMAGING

Imaging is not routinely recommended in the evaluation of undescended testis.

- Ultrasound: sensitivity of 76%, specificity of 100%, accuracy of 84%.
- MRI: sensitivity of 86% and specificity of 79%. CT results are inconsistent.

TREATMENT

- Repeat examination at 3 mo of age because many testes will descend spontaneously. Spontaneous descent is rare after 3 mo of age.
- Treatment is primarily surgical, rarely hormonal.
- Referral to an appropriate specialist if spontaneous descent does not occur by 6 months of age. Earlier orchiopexy may improve testicular function and decrease the risk of testicular cancer. Orchiopexy allows testicular self-examination and detection of testicular cancer should it occur.

HORMONAL Rx

- Hormonal therapy (hCG) is not recommended in the American Urological Association Guidelines for the treatment of cryptorchidism.

SURGICAL Rx

- For the palpable undescended testis, orchiopexy, the surgical placement of an undescended testis into the scrotum, is the standard approach, performed between 6 mos and 1 yr of age in a healthy child.
- In the setting of a nonpalpable undescended testis, laparoscopy/abdominal exploration is recommended to identify the presence or absence of a testis and the location of the testis if present and to determine the length of the testicular vessels.
- A two-stage approach is recommended for an intraabdominal testis with short vessels. The testicular vessels are clipped laparoscopically in the first stage, and the testis is brought into the scrotum in the second stage, typically 6 months after the first stage.

DISPOSITION

- Earlier orchiopexy may decrease the risk of malignancy and infertility.
- Lifelong testicular examinations after puberty.

REFERRAL

Early referral to a pediatric urologist/pediatric surgeon

PEARLS & CONSIDERATIONS

Regular testicular examinations should be performed in infants and children, particularly those with retractile testes, because ascent of scrotal testis can occur.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Undescended Testicle (Patient Information)

AUTHOR: **PAMELA ELLSWORTH, M.D.**

SUGGESTED READINGS

Acerini CL, Miles HL, Dunger DB et al.: The descriptive epidemiology of congenital and acquired cryptorchidism in a UK infant cohort, *Arch Dis Child* 94(11):868–872, 2009.

Barthold JS, Gonzalez R: The epidemiology of congenital cryptorchidism, testicular ascent and orchidopexy, *J Urol* 170:2396, 2003.

Kolon TF, Herndon A, Baker LA, Baskin LS, Baxter CG, Cheng EY, Diaz M, Lee PA, Seashore CJ, Tasian GE, Barthold JS: Evaluation and treatment of cryptorchidism: AUA Guidelines. Available at http://www.auanet.org/education/guidelines/cryptorchidism. cfm.

Lee P: Fertility after cryptorchidism: epidemiology and other outcome studies, *Urology* 66:427, 2005.

Patil KK et al.: Laparoscopy for impalpable testes, *BJU Int* 95:704, 2005.

Pettersson A et al.: Age at surgery for undescended testis and risk of testicular cancer, *N Engl J Med* 356:1835, 2007.

Thomas JC, DeMarco RT et al.: Incidence of testicular ascent in boys with retractile testes, *J Urol* 178:172, 2007.

Wagner-Mahler K, Kurzenne JY, Delattre I et al.: Prospective study on the prevalence and associated risk factors of cryptorchidism in 6246 newborn boys from Nice area, France, *Int J Androl* 34:e499, 2011.

Walsh TJ et al.: Prepubertal orchiopexy for cryptorchidism may be associated with lower risk of testicular cancer, *J Urol* 178(4 pt 1):1440, 2007.

BASIC INFORMATION

DEFINITION

The intracellular protozoan parasite *Cryptosporidium parvum* is associated with gastrointestinal disease and diarrhea, especially in AIDS patients or immunocompromised hosts. It is also associated with sporadic infections and waterborne outbreaks in immunocompetent hosts.

Other species, including *C. hominis, C. felis, C. muris,* and *C. meleagridis,* are now described to be pathogens as well.

SYNONYMS

Cryptosporidiosis

ICD-9CM CODES
007.4 Cryptosporidia infection
ICD-10CM CODES
A07.2 Cryptosporidiosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:
- Approximately 2% in industrial countries, 5% to 10% in developing countries
- 10% to 20% of HIV patients in the United States may excrete cyst

PREVALENCE: Worldwide, especially third world countries; associated with poor hygiene as a waterborne pathogen
PREDOMINANT SEX: Male = female.
TRANSMISSION:
- Person to person (daycare, family members).
- Animal to person (pets, farm animals).
- Environmental (water-associated outbreaks, including travel associated with swimming in or drinking contaminated water or eating contaminated food).
- May be significant pathogen causing diarrhea in AIDS.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Spectrum of illness ranging from asymptomatic to severe enteritis.
- Usually limited to gastrointestinal tract.
- Diarrhea, severe abdominal pain (2 to 28 days).
- Impaired digestion, dehydration.
- Fever, malaise, fatigue, nausea, vomiting.
- Pneumonia if aspirated.

ETIOLOGY

C. hominis, C. parvum, C. felis, C. muris, C. meleagridis

DIAGNOSIS

Clinical presentation of acute gastrointestinal illness, especially associated with HIV or with travel and waterborne outbreaks.

DIFFERENTIAL DIAGNOSIS

- *Campylobacter*
- *Clostridium difficile*
- *Entamoeba histolytica*
- *Giardia lamblia*
- *Salmonella*
- *Shigella*
- Microsporidia
- Cytomegalovirus
- *Mycobacterium avium*

Disease may cause cholecystitis, reactive arthritis, hepatitis, pancreatitis, pneumonia in immunocompromised or HIV-infected patients.

WORKUP

- Stool evaluation looking for characteristic oocyst by modified acid-fast stain (Fig. C1-114).
- Direct immunofluorescence using monoclonal antibodies is the gold standard for stool exams.
- HIV.

TREATMENT

- May be self-limited in normal host over several weeks. Antidiarrheal agents Pepto-Bismol, Kaopectate, or loperamide may give symptomatic relief.
- Pharmacologic treatment with antibiotics has been largely unsatisfactory in AIDS patients. Antiviral therapy is the treatment of choice to restore the immune system. Oocyst excretion reduction has been shown with nitazoxanide 500 mg PO bid for 3 days in immunocompetent patients. If treatment fails, consider a trial of paromomycin, metronidazole, or trimethoprim/sulfamethoxazole. However, these medications have not been approved for treatment of *Cryptosporidium.*
- Nitazoxanide elixir has been approved for the treatment of cryptosporidiosis in children ages 1 to 11 yr.
- Biliary cryptosporidiosis can be treated with antiretroviral therapy in the HIV setting.

DISPOSITION

- A self-limited disease in immunocompetent patients with complete recovery over 2 to 3 weeks.
- Chronic arthralgia, headache, malaise, and weakness may persist after cryptosporidial infection even in immunologically normal people.
- If severe and prolonged disease (>30 days), testing for HIV and other immunocompromised states is appropriate along with a referral to an infectious disease specialist or gastroenterologist.

REFERRAL

- To an infectious disease specialist if symptoms persist and if HIV infection is found.
- To a gastroenterologist if chronic malabsorption or biliary or pancreatic complications occur.

PEARLS & CONSIDERATIONS

- Chronic cryptosporidiosis (>30 days of diarrhea from *Cryptosporidium* spp. infection) in a patient with HIV is an AIDS-qualifying opportunistic infection.
- *Cryptosporidium hominis* has a limited host range (humans), whereas *Cryptosporidium parvum* has a wide host range including humans, horses, cattle, other domesticated animals, and wild animals; both species present a similar illness in humans.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **PHILIP A. CHAN, M.D., M.S**

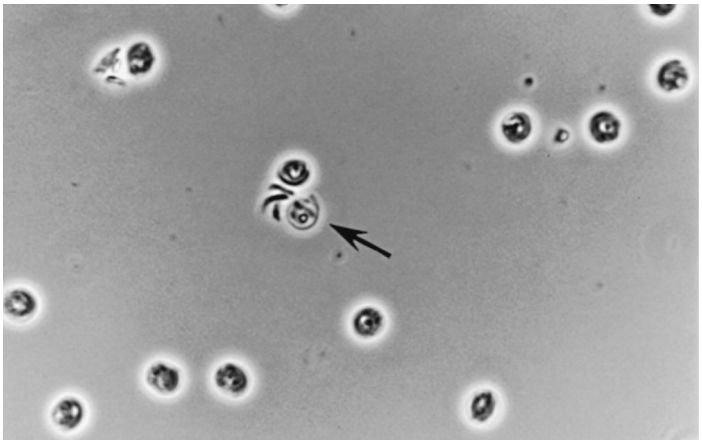

FIGURE C1-114 Human stool-derived Cryptosporidium oocysts. Excysting oocyst (arrow) is releasing three of its four sporozoites. (Phase-control microscopy ×630.) (From Gorbach SL: *Infectious diseases*, ed 2, Philadelphia, 1998, Saunders.)

SUGGESTED READINGS

Centers for Disease Control and Infection: Cryptosporidiosis outbreak at a summer camp, North Carolina, 2009, *MMWR Morb Mortal Wkly Rep* 60:918–922, 2011.

Hunter PR et al.: Health sequelae of human cryptosporidiosis in immunocompetent patients, *Clin Infect Dis* 39(4):504–510, 2004.

Smith HV, Corcoran GD: New drugs and treatment for cryptosporidiosis, *Curr Opin Infect Dis* 17(6):557, 2004.

Cubital Tunnel Syndrome PTG

BASIC INFORMATION

DEFINITION

Cubital tunnel syndrome is a compression neuropathy of the ulnar nerve as it traverses the cubital tunnel at the elbow (Fig. C1-115). It is the second most common entrapment neuropathy of the upper extremity.

ICD-9CM CODES
354.2 Cubital tunnel syndrome
ICD-10CM CODES
G56.2 Lesion of ulnar nerve, unspecified upper limb

EPIDEMIOLOGY & DEMOGRAPHICS

Males and females equally affected. Cubital tunnel syndrome is, after carpal tunnel syndrome, the second most common compression neuropathy of the upper extremity.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Paresthesias, numbness along distribution of ulnar nerve (little finger and medial half of ring finger); pain is less common.
- Positive Tinel's sign at elbow over the ulnar groove—highest negative predictive value.
- Positive elbow flexion test (flexion of elbow with wrist extended for 30 sec may reproduce symptoms).
- Pressure provocation test (direct pressure over cubital tunnel for 60 sec elicits symptoms).
- "Scratch collapse" test—positive if temporary loss of external rotation resistance after examiner scratches over the compressed ulnar nerve; due to allodynia.
- Signs of old trauma or elbow instability (valgus stress).
- Ulnar nerve may be subluxable over medial epicondyle with elbow motion.

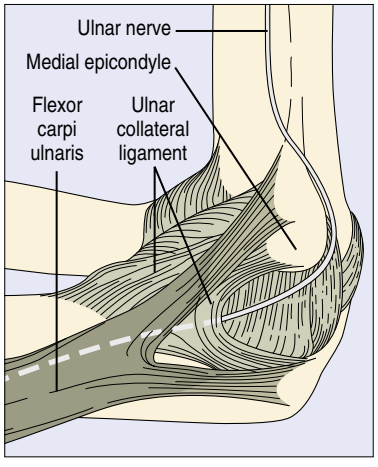

FIGURE C1-115 The cubital tunnel. The fibro-osseous canal is formed by the medial epicondyle, ulnar collateral ligament, and flexor carpi ulnaris muscle. Elbow flexion decreases the volume of the channel. (From Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.)

- Weakness/atrophy of intrinsic musculature of hand in longstanding cases (Fig. C1-116).
- "Intrinsic minus" or claw hand; due to paralysis of lumbricales and interossei (clawing usually worse in ring and small fingers).
- Masse's sign—hand appears flattened due to hypothenar muscle paralysis.
- Wartenberg's sign—due to weakness of interossei: weak adduction of small finger.
- Froment's sign—compensation by thumb flexor (flexor pollicis longus, median-nerve innervated) for diminished thumb pinch strength (paralysis of adductor pollicis, which is innervated by ulnar nerve).

ETIOLOGY

- Previous trauma, fractures.
- Chronic pressure over ulnar groove from occupational stress, unusual elbow positioning.
- Cubitus valgus deformity.
- Subluxation of ulnar nerve.
- Repeated stretching during throwing motion.
- Elbow synovitis, osteophytes.
- Local muscular hypertrophy.
- Increased cubital tunnel pressure, particularly in elbow flexion.
- Symptoms develop due to local nerve ischemia.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Tardy ulnar palsy.
- Medial epicondylitis.
- Other peripheral neuropathies.
- Carpal tunnel syndrome.
- Cervical radiculopathy.
- Ulnar nerve compression at wrist (Guyon's canal).

WORKUP

Diagnosis can usually be established clinically. Provocative tests have inconsistent sensitivity and specificity. These tests are operator dependent and may have substantial inter-rater variation.

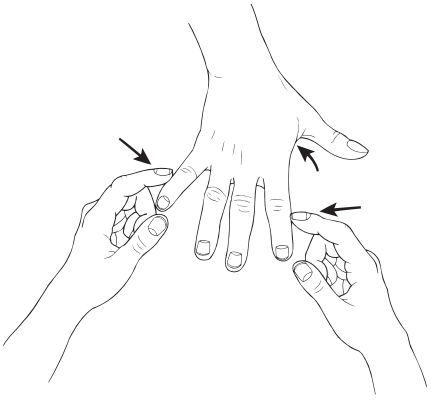

FIGURE C1-116 Testing for intrinsic (ulnar) motor weakness (fanning the fingers against resistance). Always look for atrophy of the first dorsal interosseus *(curved arrow)* when ulnar nerve lesions are suspected. (From Mercier LR: *Practical orthopedics*, ed 5, St Louis, 2000, Mosby.)

IMAGING STUDIES

- Routine roentgenograms may be helpful in ruling out other conditions.
- Electrodiagnostic studies: nerve conduction tests and electromyography are useful to confirm the clinical diagnosis and can help localize site of compression.
- Musculoskeletal ultrasound can be a valuable adjunct to diagnosis and may identify the structural etiology of nerve compression. Because of the real-time nature of ultrasound evaluation, dynamic testing can be done and ulnar nerve subluxation may be observed during elbow flexion and extension motions.
- On ultrasound, there was strong correlation found between greater ulnar nerve cross-sectional area at the elbow and presence of cubital tunnel syndrome, using electrodiagnostic criteria as the reference standard.

TREATMENT

ACUTE GENERAL Rx

- Activity modification, avoiding prolonged/repetitive flexion.
- Elbow pads to relieve pressure, splints limiting flexion.
- Physical therapy.

DISPOSITION

- There is tendency toward spontaneous recovery with mild/moderate or intermittent symptoms if provocative causes are avoided.
- If muscle atrophy has developed, recovery of strength may be incomplete despite treatment.

REFERRAL

Surgical referral needed in cases of failed medical management. Patients with constant symptoms or muscle atrophy usually require surgical treatment. Surgical treatment can consist of ulnar nerve in situ decompression, partial medical epicondylectomy and endoscopic ulnar nerve decompression, or anterior transposition of the ulnar nerve (subcutaneous, intramuscular, or submuscular).

PEARLS & CONSIDERATIONS

Patients with cubital tunnel syndrome are 4 times more likely to present with atrophy than those with carpal tunnel syndrome. Surgical decompression has been shown to be successful and may be adequate in most cases. More recently, endoscopic decompression techniques have been described. Ulnar nerve transposition and medial epicondylectomy are other surgical options.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Cubital Tunnel Syndrome (Patient Information)

AUTHOR: **CANDICE YUVIENCO, M.D.**

SUGGESTED READINGS

Hutchison RL, Rayan G: Diagnosis of cubital tunnel syndrome, *J Hand Surg Am* 36(9):1519–1521, 2011. Epub May 7, 2011.

Iba K et al.: The relationship between the pressure adjacent to the ulnar nerve and the disease causing cubital tunnel syndrome, *J Shoulder Elbow Surg* 17:585, 2008.

Keith J, Wollstein R: A tailored approach to the surgical treatment of cubital tunnel syndrome, *Ann Plast Surg* 66(6):637–639, 2011.

Nashel D.J. Entrapment neuropathies. In: (editor: Hochberg M.C.; et al.) Rheumatology. Mosby: St Louis.

Palmer BA, Hughes TB: Cubital tunnel syndrome, *J Hand Surg* 35A:153, 2010.

Radunovic G et al.: Ultrasound assessment of the elbow, *Medical Ultrasonography* 14(2):141–146, 2012.

Sanjay N et al.: A demographic analysis of cubital tunnel syndrome, *Ann Plast Surg* 64:177, 2010.

Svernlov B et al.: Conservative treatment of the cubital tunnel syndrome, *J Hand Surg* 34B:201, 2009.

Trehan SK et al.: Cubital tunnel syndrome: diagnosis and management, *Medicine and Health/Rhode Island* P5(11), 2012.

Yoon JS et al.: Ulnar nerve and cubital tunnel ultrasound in ulnar neuropathy at the elbow, *Arch Phys Med Rehabil* 89:887, 2008.

BASIC INFORMATION

DEFINITION

- Cushing's syndrome is the occurrence of clinical abnormalities associated with glucocorticoid excess as a result of exaggerated adrenal cortisol production or long-term glucocorticoid therapy.
- Cushing's disease is Cushing's syndrome caused by pituitary adrenocorticotropic hormone (ACTH) excess.

ICD-9CM CODES
255.0 Cushing's disease or syndrome
ICD-10CM CODES
E24 Cushing syndrome
E24.2 Drug-induced Cushing syndrome
E24.3 Ectopic ACTH syndrome
E24.8 Other Cushing syndrome
E24.9 Cushing syndrome, unspecified
E24.9 Pituitary-dependent Cushing's disease

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Hypertension.
- Central obesity with rounding of the facies (moon facies); thin extremities.
- Hirsutism, menstrual irregularities, hypogonadism.
- Skin fragility, ecchymoses, red-purple abdominal striae (Fig. EC1-117), acne, poor wound healing, hair loss, facial plethora, hyperpigmentation (with ACTH excess).
- Psychosis, emotional lability, paranoia.
- Muscle wasting with proximal myopathy.

NOTE: The previous characteristics are not commonly present in Cushing's syndrome caused by ectopic ACTH production. Many of these tumors secrete a biologically inactive ACTH that does not activate adrenal steroid synthesis. These patients may have only weight loss and weakness.

ETIOLOGY

- Iatrogenic from long-term glucocorticoid therapy (common).
- Pituitary ACTH excess (Cushing's disease; 60%).
- Adrenal neoplasms (30%).
- Ectopic ACTH production (neoplasms of lung, pancreas, kidney, thyroid, thymus; 10%).
- Table EC1-58 summarizes the incidence of tumors associated with the ectopic adrenocorticotropic hormone syndrome.
- A classification of causes of Cushing's syndrome is described in Table C1-59.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Alcoholic pseudo-Cushing's syndrome (endogenous cortisol overproduction).
- Obesity associated with diabetes mellitus.
- Adrenogenital syndrome.

WORKUP (Table EC1-60)

- In patients with a clinical diagnosis of Cushing's syndrome the initial screening test is the overnight dexamethasone suppression test:
  1. Dexamethasone 1 mg PO given at 11 PM.
  2. Plasma cortisol level measured 9 hr later (8 AM).
  3. Plasma cortisol level <5 mcg/100 ml excludes Cushing's syndrome.
- Serial measurements (two or three consecutive measurements) of 24-hr urinary free cortisol and creatinine (to ensure adequacy of collection) are undertaken if overnight dexamethasone test is suggestive of Cushing's syndrome. Persistent elevated cortisol excretion (>300 mcg/24 hr) indicates Cushing's syndrome.
- The low-dose (2 mg) dexamethasone suppression test is useful to exclude pseudo-Cushing's syndrome if the previous results are equivocal. Corticotropic-releasing hormone (CRH) stimulation after low-dose dexamethasone administration (dexamethasone-CRH test) is also used to distinguish patients with suspected Cushing's syndrome from those who have mildly elevated urinary free cortisol level and equivocal findings.
- The high-dose (8 mg) dexamethasone test and measurement of ACTH by radioimmunoassay are useful to determine the etiology of Cushing's syndrome.
  1. ACTH undetectable or decreased and lack of suppression indicate adrenal cause of Cushing's syndrome.
  2. ACTH normal or increased and lack of suppression indicate ectopic ACTH production.
  3. ACTH normal or increased and partial suppression suggest pituitary excess (Cushing's disease).

Bilateral inferior petrosal sinus sampling (BIPSS) can be used to distinguish pituitary Cushing's disease from the ectopic ACTH syndrome (Fig. C1-118).

LABORATORY TESTS

- Hypokalemia, hypochloremia, metabolic alkalosis, hyperglycemia, hypercholesterolemia.
- Increased 24-hr urinary free cortisol (>100 mcg/24 hr).

IMAGING STUDIES

- CT scan or MRI of adrenal glands in suspected adrenal Cushing's syndrome (Fig. EC1-119).
- MRI of pituitary gland with gadolinium is the preferred procedure for localizing a pituitary edema in suspected pituitary Cushing's syndrome.
- Additional imaging studies to localize neoplasms of the lung, pancreas, kidney, thyroid, or thymus in patients with ectopic ACTH production.

TREATMENT

GENERAL Rx

The definitive treatment of Cushing's syndrome is surgical removal of the tumor causing excessive production of cortisol:

- Pituitary adenoma: transsphenoidal microadenomectomy is the therapy of choice in adults. Pituitary irradiation is reserved for patients not cured by transsphenoidal surgery. In children, pituitary irradiation may be considered as initial therapy because 85% of children are cured by radiation. Stereotactic radiotherapy (photon knife or gamma knife) is effective and exposes the surrounding neuronal tissues to less irradiation than conventional radiotherapy. Total bilateral adrenalectomy is reserved for patients not cured by transsphenoidal surgery or pituitary irradiation.
- Adrenal neoplasm:
  1. Surgical resection of the affected adrenal.
  2. Glucocorticoid replacement for approximately 9 to 12 mo after the surgery to allow time for the contralateral adrenal gland to recover from its prolonged suppression.

TABLE C1-59 Classification of Causes of Cushing's Syndrome

ACTH-Dependent Causes
Cushing's disease (pituitary-dependent)
Ectopic ACTH syndrome
Ectopic CRH syndrome
Macronodular adrenal hyperplasia
Iatrogenic (treatment with 1-24 ACTH)
ACTH-Independent Causes
Adrenal adenoma and carcinoma
Primary pigmented nodular adrenal hyperplasia and Carney's syndrome
McCune-Albright syndrome
Aberrant receptor expression (gastric inhibitory polypeptide, interleukin-1β)
Iatrogenic (e.g., pharmacologic doses of prednisolone, dexamethasone)
Pseudo-Cushing's Syndromes
Alcoholism
Depression
Obesity

ACTH, Adrenocorticotropic hormone; *CRH,* corticotropin-releasing hormone.
From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

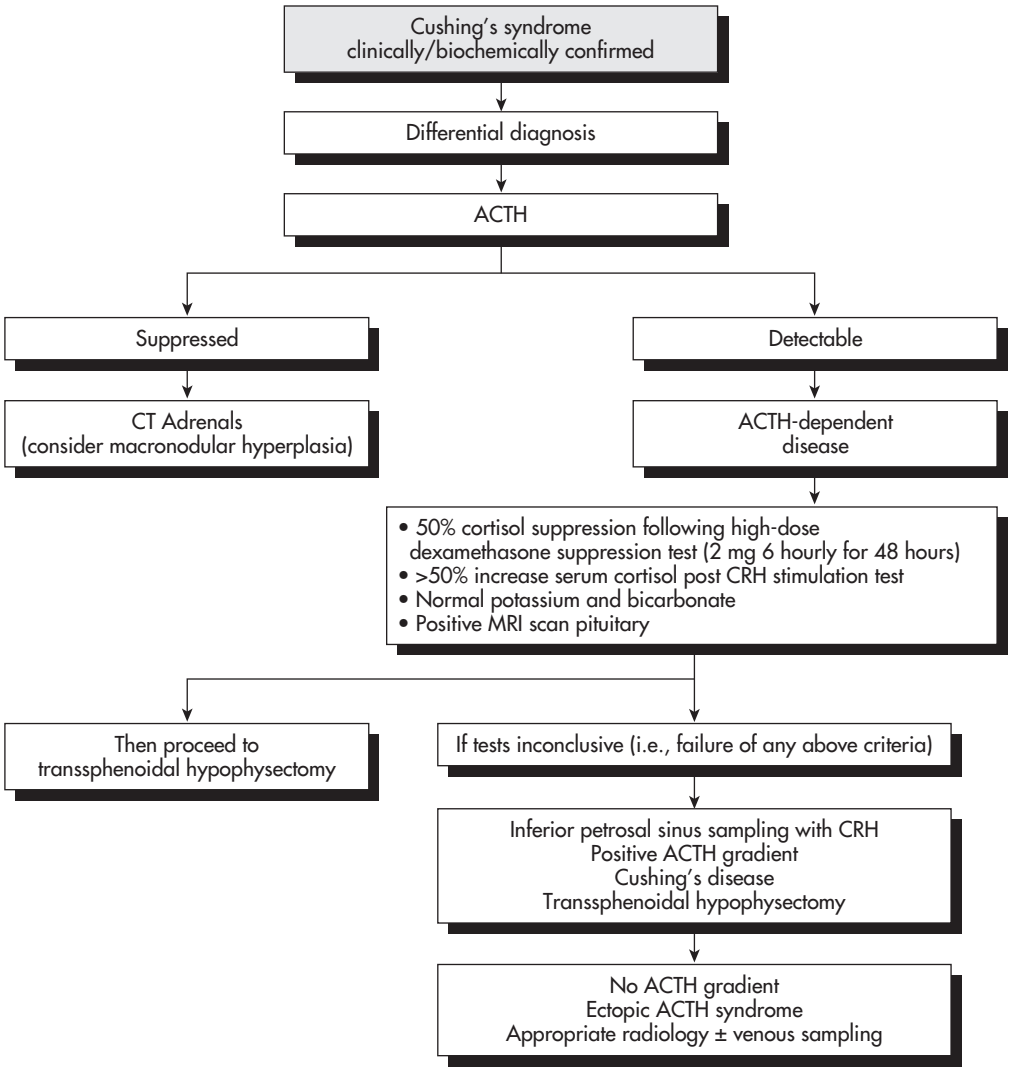

FIGURE C1-118 The tests to uncover the cause of Cushing's syndrome are debatable and differ in any given center depending on many factors, including familiarity and turnaround time of hormone assays and local expertise in techniques such as inferior petrosal sinus sampling. Depicted here is an algorithm in use within many endocrine units based on the reported sensitivity and specificity of each endocrine test. *ACTH,* Adrenocorticotropin; *CT,* computed tomography; *MRI,* magnetic resonance imaging. (From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

3. In nonsurgical candidates, suppression of adrenal steroid production can be accomplished with ketoconazole. Mifepristone, an antiprogestin, can also be used for control of hyperglycemia secondary to hypercortisolism in adults with endogenous Cushing's syndrome. It should be avoided in women who are or who could become pregnant.

- Bilateral micronodular or macronodular adrenal hyperplasia: bilateral total adrenalectomy.
- Ectopic ACTH:
  1. Surgical resection of the ACTH-secreting neoplasm.
  2. Control of cortisol excess with metyrapone, aminoglutethimide, mifepristone, or ketoconazole.
  3. Control of the mineralocorticoid effects of cortisol and 11-deoxycorticosteroid with spironolactone.
  4. Bilateral adrenalectomy: a rational approach to patients with indolent, unresectable tumors.

DISPOSITION

Prognosis is favorable in patients with surgically amenable disease.

PEARLS & CONSIDERATIONS

COMMENTS

- A single midnight serum cortisol level (normal diurnal variation leads to a nadir around midnight) >7.5 mcg/dl has been reported as 96% sensitive and 100% specific for the diagnosis of Cushing's syndrome.
- Screening for multiple endocrine neoplasia type I should be considered in patients with Cushing's disease.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Cushing's Syndrome (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READING

Boscaro M, et al.: The diagnosis of Cushing's syndrome, *Arch Intern Med* 160:3045, 2000.

FIGURE EC1-117 Clinical features of Cushing's syndrome. A, Centripetal and some generalized obesity and dorsal kyphosis in a 30-year-old woman with Cushing's disease. **B,** Same patient as in **A** showing moon facies, plethora, hirsutism, and enlarged supraclavicular fat pads. **C,** Facial rounding, hirsutism, and acne in a 14-year-old girl with Cushing's disease. **D,** Central and generalized obesity and moon facies in a 14-year-old boy with Cushing's disease. **E** and **F,** Typical centripetal obesity with livid abdominal striae seen in a 41-year-old woman **(E)** and a 40-year-old man **(F)** with Cushing's syndrome. **G,** Striae in a 24-year-old patient with congenital adrenal hyperplasia treated with excessive doses of dexamethasone as replacement therapy. **H,** Typical bruising and thin skin of a patient with Cushing's syndrome. In this case, the bruising occurred without obvious injury. (From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

TABLE EC1-58 Tumors Associated with the Ectopic Adrenocorticotropic Hormone Syndrome

Tumor Type	Approximate Incidence (%)
Small-cell lung carcinoma	50
Non–small-cell lung carcinoma	5
Pancreatic tumors (including carcinoids)	10
Thymic tumors (including carcinoids)	5
Lung carcinoids	10
Other carcinoids	2
Medullary carcinoma of thyroid	5
Pheochromocytoma and related tumors	3
Rare carcinomas of prostate, breast, ovary, gallbladder, colon	10

From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

TABLE EC1-60 Tests Used in the Diagnosis and Differential Diagnosis of Cushing's Syndrome

Diagnosis—Does the Patient Have Cushing's Syndrome?
Circadian rhythm of plasma cortisol
Urinary free cortisol excretion*
Low-dose dexamethasone suppression test*
Differential Diagnosis—What Is the Cause of Cushing's Syndrome?
Plasma ACTH
Plasma potassium, bicarbonate
High-dose dexamethasone suppression test
Metyrapone test
Corticotropin-releasing hormone
Inferior petrosal sinus sampling
CT, MRI scanning of pituitary, adrenals
Scintigraphy
Tumor markers

ACTH, Adrenocorticotropic hormone; *CT,* computed tomography; *MRI,* magnetic resonance imaging.
*Valuable outpatient screening tests (see text).
From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

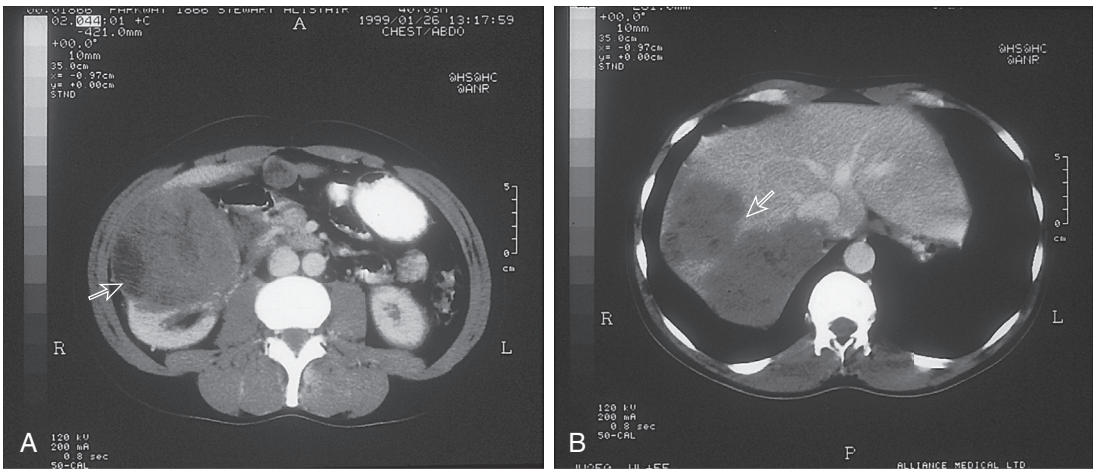

FIGURE EC1-119 Computed tomographic scan of a patient with rapidly progressing Cushing's syndrome caused by an adrenal carcinoma. An irregular right adrenal mass is shown in **(A),** and a large liver metastasis in **(B).** (From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

EVIDENCE

Abstract[1]

ACTH

Objective:

Twenty-four-hour urinary free cortisol (UFC) sampling is commonly used to evaluate Cushing's syndrome. Because there are few data on UFC variability in patients with active Cushing's disease, we analysed baseline UFC in a large patient cohort with moderate-to-severe Cushing's disease and assessed whether variability correlates with hypercortisolism severity. These data will help clinicians establish the minimum number of UFC samples required to obtain reliable data.

Design:

Observational study (enrollment phase of Phase III study).

Methods:

Patients (n = 152) with persistent/recurrent or de novo Cushing's disease and mean UFC (mUFC) ≥1·5×ULN (normal: 30–145 nmol/24 h) were included. Mean UFC level was calculated from four 24-h urine samples collected over 2 weeks.

Results:

Over 600 24-h UFC samples were analysed. The mUFC levels of samples 1 and 2 and samples 3 and 4 were 1000 nmol/24 h (SD 1872) and 940 nmol/24 h (SD 2148), respectively; intrapatient coefficient of variation (CV) was 38% for mUFC. The intrapatient CV using all four samples was 52% (95% CI: 48–56). The intrapatient CV was 51% (95% CI: 44–58) for samples 1 and 2, 49% (95% CI: 43–56) for samples 3 and 4 and 54% (95% CI: 49–59) for samples 1, 2 and 3. Variability in mUFC increased as UFC levels increased. There were no correlations between UFC and clinical features of hypercortisolism.

Conclusions:

There is intrapatient variability of approximately 50% in 24-h UFC measurements, which is relevant to targets set to estimate any treatment effect. Analysing more than two 24-h collection periods in individual patients does not result in a relevant decrease in variability. Interestingly, UFC levels did not correlate with hypercortisolism severity.

Current guidelines recommend a combination of late-night cortisol, dexamethasone suppression testing, and urinary free cortisol for the screening of hypercortisolism. Each of these has its own advantages and disadvantages. With respect to urinary free cortisol, variations in assays as well as collection errors are among the major problems. Because urinary free cortisol is the only parameter widely accepted for the follow-up of Cushing syndrome during medical treatment, standardization of collection and establishment of reference ranges is of major interest.

This study analyzed variability of urinary free cortisol with repeated sampling in a large cohort of patients with confirmed Cushing disease. Interestingly, even four 24-hour urine collections demonstrated a relevant variability of approximately 50%, without any major improvement compared with two or three collection periods. Because of the relevant variability, only changes of more than 50% in urinary free cortisol may present real treatment effects outside of chance variability.

These results clearly indicate the need for better tools for assessment of disease activity in Cushing disease to allow for optimal management of therapy.

Another major finding relates to the lack of significant correlation between urinary free cortisol and various clinical indicators of hypercortisolism, calling into question the use of biochemical parameters alone to follow patients with Cushing disease. Ⓑ

Evidence-Based Reference

1. Petersenn S, Newell-Price J, Findling JW, et al.: High variability in baseline urinary free cortisol values in patients with Cushing's disease, *Clin Endocrinol* 80:261–269, 2014. Ⓑ

BASIC INFORMATION

DESCRIPTION

Cutaneous larva migrans (CLM) is a syndrome defined clinically and parasitologically by subcutaneous larval migration of nematodes. Creeping eruption is the cardinal manifestation. It includes neither diseases in which creeping eruption is due to non-larval forms of parasites nor diseases without creeping eruptions from subcutaneous migration of larval parasites. As animal hookworms are the most common cause, some people use the term "hookworm-related cutaneous larva migrans" (HrCLM) instead. Table EC1-61 describes other clinical syndromes associated with unusual helminth infections in humans.

SYNONYMS

CLM
Creeping eruption
Plumber's itch
Creeping verminous dermatitis
Sand worm eruption
Duck hunter's itch
Hookworm-related cutaneous larva migrans
HrCLM

ICD-9CM CODES
126.9
ICD-10CM CODES
B76.8 Other hookworm diseases
B76.9 Hookworm disease, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Commonly seen in tropical and subtropical countries. In the United States it is most prevalent in southeastern states. Florida tops among these states.
- More often seen in children than adults.
- Has no racial or sexual predilection.
- Peak incidence is seen during rainy season.
- Second to pinworm among helminth infection in developed countries.
- Most common tropically acquired dermatosis.
- Most common imported ectoparasites in travelers returning to the United States after a holiday.

RISK FACTORS

Hobbies and occupations that involve contact with warm, moist, sandy soil
- Tropical/subtropical climate travels
- Barefoot beach goers/sunbathers
- Children playing in sandboxes
- Carpenter, electrician, plumber, farmer, gardener, pest exterminator

ETIOLOGY

- Animal hookworms
- *Ancylostoma braziliense* (commonest cause)
- *Ancylostoma caninum*
- *Uncinaria stenocephala*
- *Bunostomum phlebotomum*
- *Pelodera strongyloides*
- *Gnathostoma* species
- *Strongyloides stercoralis*
- *Spirurina* species

PATHOGENESIS

The infection is usually acquired via skin contact with the soil or sand contaminated with feces of infected dogs or cats. The filariform larva is the infective form. It penetrates the skin and migrates within the epidermis by releasing protease and hyaluronidase. The inflammatory reaction along the cutaneous tract of their migration results in creeping eruptions. The larvae are believed to lack the collagenase enzymes required to penetrate the basement membrane to invade the dermis. In contrast to cats or dogs, humans are incidental host. Thus the larvae are unable to complete their natural cycles in humans. The larvae die without treatment and are resorbed within weeks to months of invasion. This explains why CLM is a self-limiting disease and rarely has systemic features.

CLINICAL FEATURES

- Often associated with a history of sunbathing, walking barefoot on a beach, or similar activity in a tropical location.
- Incubation period is around 1 to 6 days.
- Intense pruritus at the site of invasion within hours of invasion.
- Many patients report a stinging sensation, which they may misinterpret as a puncture or insect bite.
- Erythematous papules develop at the larval penetration site. Feet, buttocks, and thighs are most commonly affected anatomical locations.
- The most frequent and cardinal finding of HrCLM is *creeping dermatitis* (Fig. EC1-120), which takes a few days to develop. It is defined as an erythematous, slightly elevated, linear, or serpiginous track that is 3 mm in width and may be up to 15 to 20 cm in length. The mean number of lesions per person varies from 1 to 3. The creeping track associated with the larva migration may extend a few millimeters to few centimeters daily. These eruptions last 2 to 8 wk without treatment.
- Edema and vesicobullous lesions along the course of the larva.
- Rare presentation is hookworm folliculitis. It is characterized by numerous (20-100) follicular, erythematous, and pruritic papules and pustules, located mainly in the buttocks. Generally numerous short tracks are seen arising from these follicular lesions.

TABLE EC1-61 Clinical Syndromes Associated with Unusual Helminth Infections in Humans

Clinical Syndrome	Parasite	Usual Host
Visceral larva migrans	*Toxocara canis*	Canines
	Toxocara cati	Felines
	Baylisascaris procyonis	Raccoons
Eosinophilic gastroenteritis	*Anisakis* spp.	Sea mammals
	Phocanema spp.	Sea mammals
	Ancylostoma caninum	Canines
Cutaneous larva migrans	*Ancylostoma braziliense*	Canines, felines
	Ancylostoma caninum	Canines, felines
	Uncinaria stenocephala	Canines, felines
Eosinophilic meningitis	*Angiostrongylus cantonensis*	Rats
	Gnathostoma spinigerum	Felines, other mammals
Pulmonary or cutaneous nodules	*Dirofilaria* spp.	Canines, other mammals
Abdominal angiostrongyliasis	*Angiostrongylus costaricensis*	Cotton rats
Capillariasis	*Capillaria philippinensis*	Birds
Diarrhea	*Nanophyetus salmincola*	Mammals, birds
Swimmer's itch	*Trichobilharzia* spp.	Birds

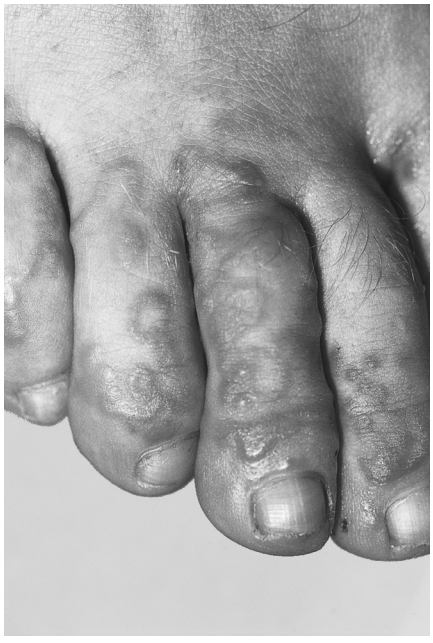

FIGURE EC1-120 Cutaneous larva migrans ("creeping eruption") due to invasion of infective larvae of the dog hookworm *Ancylostoma caninum*. This condition may be mistaken for infestation with the larvae of ectoparasitic arthropods. The lesions respond rapidly to treatment with albendazole or ivermectin. (From Cohen J, Powderly WG: *Infectious diseases,* ed 2, St Louis, 2004, Mosby.)

- In case of rare pulmonary involvement, dry cough and wheezing develop a week after the dermal invasion.

Dx DIAGNOSIS

Diagnosis is made on clinical grounds and history of potential exposure. Clinical characteristics of the creeping trails (length, width, speed of migration, location, duration) help differentiate HrCLM from other causes of creeping dermatitis.

- Blood tests are not necessary for diagnosis. Theoretically, blood test could detect eosinophilia and elevated IgE level.
- Biopsy specimens usually show an eosinophilic inflammatory infiltrate, but not the migratory parasite. For this reason, biopsy is not indicated to establish the diagnosis. Nonetheless, in case of hookworm folliculitis, skin biopsy specimens may reveal nematode larvae in the follicular canal.
- Stool studies and serology are not helpful.
- Radiograph of chest is indicated when migratory pulmonary infiltrates are suspected.
- A new technology, optical coherence tomography, has been found to identify the larva in the epidermis, allowing direct removal.

DIFFERENTIAL DIAGNOSIS

- Superficial thrombophlebitis.
- Mondor's disease.
- Lichen striatus.
- Phytophotodermatitis.
- Herpes zoster.
- Migratory myiasis.
- Scabies.
- Loiasis.
- Dracunculiasis.
- Cercarial dermatitis.
- Onchocerciasis.
- Dirofilariasis.
- Contact dermatitis.
- Creeping hair.
- Jelly fish stings.
- Fascioliasis.
- Bacterial folliculitis.
- Tinea pedis/corporis.
- Impetigo.
- Erythema chronicum migrans of Lyme disease.
- Ground itch.
- Toxocariasis.

Rx TREATMENT

- Oral albendazole and ivermectin are the first line of drugs.
- Oral administration is preferred in presence of extensive lesions or when topical application fails.
- Topical application should cover the tracks and area covering up to 2 cm from the leading edge.
- Albendazole should be given (400 mg orally per day for 3 to 5 days).
- At times, when oral drugs are contraindicated, topical 10% albendazole creams are applied twice a day for a period of 10 days.
- Ivermectin should be given (200 mcg/kg given as a single dose).
- Thiabendazole should be given (25 to 50 mg/kg divided into twice-daily doses for 2 days).
- Because of its higher side effect profile when given orally, it is more often applied topically (10% to 15% cream or aqueous suspension of 500 mg/5 ml) four times a day for 5 to 10 days.
- Mebendazole should be given (100 mg orally twice for 3 days).
- Cryotherapy with liquid nitrogen is obsolete. It is ineffective as the larva is usually located 1 to 2 cm beyond the visible end of the trail, and the larva is capable of withstanding temperature as low as –21° C for more than 5 minutes. Moreover, this procedure is painful and can lead to chronic ulcerations.
- Specific antihelminthic therapy for pulmonary involvement is generally not required since the illness is usually mild and self-limiting.
- In the case of hookworm folliculitis, treatment is more difficult than traditional form and necessitates repeated courses of oral antihelminthic agents.
- Antihistamines and topical steroids relieve intense pruritus.
- Antibiotics are indicated for bacterial superinfection.
- Generally there should be no attempt to extract the worm.

COMPLICATIONS

- Secondary bacterial infection
- Erythema multiforme
- Migratory eosinophilic pneumonitis (Loeffler syndrome)
- Eosinophilic enteritis

PROGNOSIS

Self-limiting benign disease. Even without treatment most cases resolve within 4 to 8 weeks.

PREVENTION

- Prohibit pets such as dogs and cats walking on the beaches in tropical areas.
- Avoid allowing pets in the sandbox.
- Deworm household pets.
- Clean up pet droppings.
- Protective foot wear while walking on the beach.
- Avoiding tropical beaches frequented by dogs and cats.
- When lying on tropical beaches potentially frequented by dogs and cats, areas of sand washed by the tide are preferable to dry sand, and mattresses are preferable to towels.
- Towels and clothes should not touch the ground when hung up for drying.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **HEMANT K. SATPATHY, M.D.**

SUGGESTED READINGS

Epidemiological and clinical characteristics of hookworm related cutaneous larva migrans, *Lancet Infect Dis* 8:302–309, 2008.

Hookworm-related cutaneous larva migrans, *J Travel Med* 14(5):326–333, 2007.

BASIC INFORMATION

DEFINITION

Cystic fibrosis (CF) is an autosomal recessive disorder characterized by dysfunction of exocrine glands.

ICD-9CM CODES
277.0 Cystic fibrosis
ICD-10CM CODES
E84.9 Cystic fibrosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- CF is the most common fatal hereditary disorder of whites in the United States (one case per 2500 whites) and second most common life-shortening childhood-onset inherited disorder in the United States, behind sickle cell disease.
- Median age at diagnosis is 5.3 mo. Median survival is 30 yr.
- Carrier screening is associated with a decrease in incidence of CF.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Failure to thrive in children
- Increased anterior/posterior chest diameter
- Basilar crackles and hyperresonance to percussion
- Digital clubbing
- Chronic cough
- Abdominal distention
- Greasy, smelly feces

ETIOLOGY

Chromosome 7 gene mutation (*CFTR* gene) resulting in abnormalities in chloride transport and water flux across the surface of epithelial cells; the abnormal secretions cause obstruction of glands and ducts in various organs and subsequent damage to exocrine tissue (recurrent pneumonia, atelectasis, bronchiectasis, diabetes mellitus, biliary cirrhosis, cholelithiasis, intestinal obstruction, increased risk of gastrointestinal malignancies).

TABLE C1-62 Diagnostic Criteria for Cystic Fibrosis (CF)

Presence of typical clinical features (respiratory, gastrointestinal, or genitourinary)
OR
A history of CF in a sibling
OR
A positive newborn screening test
PLUS
Laboratory evidence for CFTR (CF transmembrane regulator) dysfunction:
- Two elevated sweat chloride concentrations obtained on separate days
- OR
- Identification of two CF mutations
- OR
- An abnormal nasal potential difference measurement

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Immunodeficiency states
- Celiac disease
- Asthma
- Recurrent pneumonia

WORKUP

A diagnosis of CF requires a positive quantitative pilocarpine iontophoresis test with one or more phenotypic features consistent with CF (e.g., chronic suppurative obstructive lung disease, pancreatic insufficiency) or documented CF in a sibling or first cousin. Table C1-62 describes diagnostic criteria for CF. Conditions suggesting the diagnosis of CF in adults and recommended diagnostic studies are described in Table C1-63.

LABORATORY TESTS

- Pilocarpine iontophoresis (sweat test): diagnostic of CF in children if sweat chloride is >60 mmol/L (>80 mmol/L in adults) on two separate tests on consecutive days. Repeat testing may be necessary because not all infants have sufficient quantities of sweat for reliable testing. Table C1-64 describes conditions associated with false-positive and false-negative sweat test results.
- DNA testing may be useful for confirming the diagnosis and providing genetic information for family members.
- Sputum culture and sensitivity and Gram stain (frequent bacterial infections with *Staphylococcus aureus, Pseudomonas aeruginosa* [most common virulent respiratory pathogen], *Haemophilus influenzae*). Bronchoalveolar lavage (BAL) is used at times to aid in the early diagnosis of pulmonary infection in non-expectorating patients. However, evidence for its clinical benefit is lacking. Trials have shown that among infants diagnosed with CF, BAL-directed therapy did not result in a lower prevalence of *P. aeruginosa* infection or lower total CF-CT score when compared with standard therapy at age 5 years.
- Low albumin level, increased 72-hr fecal fat excretion.
- Pulse oximetry or arterial blood gases: hypoxemia.
- Pulmonary function studies: decreased total lung capacity, forced vital capacity, pulmonary diffusing capacity.

TABLE C1-63 Approach to Diagnosis of Cystic Fibrosis in Adult Patients

Conditions Suggesting the Diagnosis of Cystic Fibrosis in Adults
Recurrent pancreatitis
Male infertility
Chronic sinusitis
Nasal polyposis
Nontuberculous mycobacterial infection
Allergic bronchopulmonary mycosis
Bronchiectasis
Recommended Diagnostic Studies
Sweat electrolyte determination
Extended CFTR mutation analysis
Nasal potential difference
High-resolution CT scan to identify bronchiectasis
CT scan of sinuses for polyposis
Sputum induction or bronchoalveolar lavage to identify bacterial and fungal pathogens

CFTR, Cystic fibrosis transmembrane conductance regulator; *CT,* computed tomography.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

IMAGING STUDIES

- Chest x-ray (Fig. C1-121): may reveal focal atelectasis, peribronchial cuffing, bronchiectasis, increased interstitial markings, hyperinflation
- High-resolution chest CT scan: bronchial wall thickening, cystic lesions, ring shadows (bronchiectasis)

TABLE C1-64 Conditions Associated with False-Positive and False-Negative Sweat Test Results

With False-Positive Results
Eczema (atopic dermatitis)
Ectodermal dysplasia
Malnutrition/failure to thrive/deprivation
Anorexia nervosa
Congenital adrenal hyperplasia
Adrenal insufficiency
Glucose-6-phosphatase deficiency
Mauriac syndrome
Fucosidosis
Familial hypoparathyroidism
Hypothyroidism
Nephrogenic diabetes insipidus
Pseudohypoaldosteronism
Klinefelter syndrome
Familial cholestasis syndrome
Autonomic dysfunction
Prostaglandin E infusions
Munchausen syndrome by proxy
With False-Negative Results
Dilution
Malnutrition
Edema
Insufficient sweat quantity
Hyponatremia
Cystic fibrosis transmembrane conductance regulator (CFTR) mutations with preserved sweat duct function

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

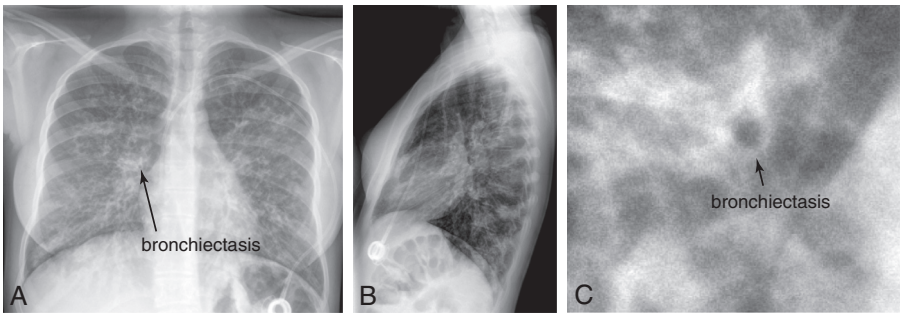

FIGURE C1-121 Cystic fibrosis. Cystic fibrosis is aptly named. Chest x-ray findings include increased interstitial density of fibrosis and cystic changes of lung parenchyma similar to chronic obstructive pulmonary disease. Bronchiectasis (dilation of bronchi, potentially eroding into bronchial arteries and presenting with hemoptysis) may be visible on chest x-ray as large and thickened bronchioles particularly when viewed in short axis (when bronchioles are oriented perpendicular to the frontal plane). This I5-year-old with cystic fibrosis presented with cough and dyspnea. Does she have pneumonia? Comparison with prior x-rays showed no changes. **A,** Posterior-anterior chest x-ray. **B,** Lateral chest x-ray. **C,** Close-up from A showing bronchiectasis. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Postural drainage and chest percussion.
- Encouragement of regular exercise and proper nutrition.
- Psychosocial evaluation and counseling of patient and family members.

ACUTE GENERAL Rx

- Antibiotic therapy based on results of Gram stain and culture and sensitivity of sputum (PO quinolones for *Pseudomonas,* cephalosporins for *S. aureus,* IV aminoglycosides [tobramycin] plus ceftazidime or ticarcillin for life-threatening *Pseudomonas* infections). Inhaled antibiotics (aztreonam or tobramycin) can also be used and can achieve high airway concentration with lower systemic side effects. Macrolides are also active against *Pseudomonas aeruginosa.* For *S. aureus* infection, use oxacillin or nafcillin 2 g IV p4h if MSSA; if dealing with MRSA, use IV vancomycin 1 g q12h. A recent study using azithromycin maintenance in children with CF for 6 mo found less use of additional antibiotics and improvement in some aspects of pulmonary function. Additional studies may be necessary to determine if azithromycin should be used as a primary therapy or rescue treatment.
- Bronchodilators for patients with airflow obstruction.
- Long-term pancreatic enzyme replacement.
- Alternate-day prednisone (2 mg/kg) possibly beneficial in children with CF (decreased hospitalization rate, improved pulmonary function); routine use of corticosteroids not recommended in adults; among children with CF who have received alternate-day treatment with prednisone, boys, but not girls, have persistent growth impairment after treatment is discontinued.
- Proper nutrition and vitamin supplementation.
- Recombinant human deoxyribonuclease (DNase [dornase alfa]) 2.5 mg qd or bid given by aerosol for patients with viscid sputum. It lowers the viscosity of sputum. It is useful to improve mucociliary clearance by liquefying difficult-to-clear pulmonary secretions. It is, however, very expensive; it is most beneficial in patients with forced vital capacity values >40% of predicted. Its cost can be decreased by using alternate-day rhDNase therapy.
- Intermittent administration of inhaled tobramycin has been reported beneficial in CF.
- Newer treatment modalities involve increasing the activity of CF transmembrane conductance regulator (CFTR) protein. Ivacaftor (a CFTR potentiator) is FDA approved for oral treatment of CF in patients 6 years and older with the G551D mutation (5% of patients with CF). It can decrease the frequency of pulmonary exacerbations and improve lung function. Dose is 150 mg PO BID. Cost is a significant limiting factor.
- Treatment of impaired glucose tolerance and diabetes mellitus.

CHRONIC Rx

Pneumococcal and influenza vaccination

DISPOSITION

- Bronchiectasis develops early in the course of cystic fibrosis, being detectable in infants as young as 10 wk of age, and is persistent and progressive. Recent data[1] reveal that neutrophil elastase activity in BAL fluid in early life is associated with early bronchiectasis in children with cystic fibrosis.
- More than 50% of children with CF live beyond age 20 yr. During the past 2 decades, survival among patients with late-stage CF has lengthened substantially. Survival has impaired at the rate of 1.8% annually during the past decade. This is believed due to increased use of NBH DNase.
- Lung transplantation is the only definitive treatment; 3-yr survival after transplantation exceeds 50%.
- Obstructive azoospermia is present in >98% of postpubertal males.
- The SERPINA Z allele is a risk factor for liver disease in CF. Patients that carry the Z allele are at a greater risk of developing severe liver disease with portal hypertension.

[1]Sly PD et al: Risk factors for bronchiectasis in children with cystic fibrosis, *N Engl J Med* 368:1963-1970, 2013.

REFERRAL

- For lung transplantation in selected patients. Indications for lung transplantation are FEV_1 <30% of predicted, rapidly progressive respiratory deterioration, increasing number of hospital admissions, massive hemoptysis, recurrent pneumothorax, arterial partial pressure of oxygen <55 mm Hg, arterial partial pressure of carbon dioxide >50 mm Hg, multiresistant organisms, wasting. Young female patients should be referred earlier because of overall poor prognosis.
- For screening of family members with DNA analysis.

PEARLS & CONSIDERATIONS

COMMENTS

- Clinicians should think of CF in any patient with bronchiectasis plus any of the following: male infertility, recurrent idiopathic pancreatitis, recurrent nasal polyposis.
- Genetic testing for CF should be offered to adults with a positive family history of CF, couples currently planning a pregnancy, and couples seeking prenatal care.
- Inhalation of hypertonic saline (5 ml of 7% sodium chloride qid) has been reported to produce a sustained acceleration of mucus clearance and improved lung function.
- The prevalence of MRSA in the respiratory tract of individuals with CF has increased dramatically over the past decade and is associated with worse survival.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Cystic Fibrosis (Patient Information)
Bronchiectasis (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Background:
VX-809, a cystic fibrosis transmembrane conductance regulator (CFTR) modulator, has been shown to increase the cell surface density of functional *F508del-CFTR* in vitro.
Methods:
A randomised, double-blind, placebo-controlled study evaluated the safety, tolerability and pharmacodynamics of VX-809 in adult patients with cystic fibrosis (n = 89) who were homozygous for the F508del-*CFTR* mutation. Subjects were randomised to one of four VX-809 28 day dose groups (25, 50, 100 and 200 mg) or matching placebo.
Results:
The type and incidence of adverse events were similar among VX-809- and placebo-treated subjects. Respiratory events were the most commonly reported and led to discontinuation by one subject in each active treatment arm. Pharmacokinetic data supported a once-daily oral dosing regimen. Pharmacodynamic data suggested that VX-809 improved CFTR function in at least one organ (sweat gland). VX-809 reduced elevated sweat chloride values in a dose-dependent manner ($p = 0.0013$) that was statistically significant in the 100 and 200 mg dose groups. There was no statistically significant improvement in CFTR function in the nasal epithelium as measured by nasal potential difference, nor were there statistically significant changes in lung function or patient-reported outcomes. No maturation of immature *F508del-CFTR* was detected in the subgroup that provided rectal biopsy specimens.
Conclusions:
In this study, VX-809 had a similar adverse event profile to placebo for 28 days in *F508del-CF*TR homozygous patients, and demonstrated biologic activity with positive impact on CFTR function in the sweat gland. Additional data are needed to determine how improvements detected in CFTR function secondary to VX-809 in the sweat gland relate to those measurable in the respiratory tract and to long-term measures of clinical benefit.
Clinical Trial Number:
NCT00865904. Ⓐ

Abstract[2]

Background:
Increasing the activity of defective cystic fibrosis transmembrane conductance regulator (CFTR) protein is a potential treatment for cystic fibrosis.
Methods:
We conducted a randomized, double-blind, placebo-controlled trial to evaluate ivacaftor (VX-770), a CFTR potentiator, in subjects 12 years of age or older with cystic fibrosis and at least one *G551D-CFTR* mutation. Subjects were randomly assigned to receive 150 mg of ivacaftor every 12 hours (84 subjects, of whom 83 received at least one dose) or placebo (83, of whom 78 received at least one dose) for 48 weeks. The primary end point was the estimated mean change from baseline through week 24 in the percent of predicted forced expiratory volume in 1 second (FEV_1).
Results:
The change from baseline through week 24 in the percent of predicted FEV_1 was greater by 10.6 percentage points in the ivacaftor group than in the placebo group ($P<0.001$). Effects on pulmonary function were noted by 2 weeks, and a significant treatment effect was maintained through week 48. Subjects receiving ivacaftor were 55% less likely to have a pulmonary exacerbation than were patients receiving placebo, through week 48 ($P<0.001$). In addition, through week 48, subjects in the ivacaftor group scored 8.6 points higher than did subjects in the placebo group on the respiratory-symptoms domain of the Cystic Fibrosis Questionnaire–revised instrument (a 100-point scale, with higher numbers indicating a lower effect of symptoms on the patient's quality of life) ($P<0.001$). By 48 weeks, patients treated with ivacaftor had gained, on average, 2.7 kg more weight than had patients receiving placebo ($P<0.001$). The change from baseline through week 48 in the concentration of sweat chloride, a measure of CFTR activity, with ivacaftor as compared with placebo was −48.1mmol per liter ($P<0.001$). The incidence of adverse events was similar with ivacaftor and placebo, with a lower proportion of serious adverse events with ivacaftor than with placebo (24% vs. 42%).
Conclusions:
Ivacaftor was associated with improvements in lung function at 2 weeks that were sustained through 48 weeks. Substantial improvements were also observed in the risk of pulmonary exacerbations, patient-reported respiratory symptoms, weight, and concentration of sweat chloride. (Funded by Vertex Pharmaceuticals and others; VX08-770-102 Clinical Trials.gov number, NCT00909532.) Ⓐ

Abstract[3]

Better treatment of obstructed small airways is needed in cystic fibrosis. This study investigated whether efficient deposition of dornase alfa in the small airways improves small airway obstruction.

In a multicentre, double-blind, randomised controlled clinical trial, cystic fibrosis patients on maintenance treatment with 2.5 mL dornase alfa once daily were switched to a smart nebuliser and randomised to small airway deposition (n = 24) or large airway deposition (n = 25) for 4 weeks. The primary outcome parameter was forced expiratory flow at 75% of forced vital capacity ($FEF_{75\%}$).

FEF75% increased significantly by 0.7 SD (5.2% predicted) in the large airways group and 1.2 SD (8.8% pred) in the small airways group. Intention-to-treat analysis did not show a significant difference in treatment effect between groups. Per-protocol analysis, excluding patients not completing the trial or with adherence <70%, showed a trend ($p = 0.06$) in FEF75% Z-score and a significant difference ($p = 0.04$) between groups in absolute FEF75% (L·s−1) favouring small airway deposition.

Improved delivery of dornase alfa using a smart nebuliser that aids patients in correct inhalation technique resulted in significant improvement of FEF75% in children with stable cystic fibrosis. Adherent children showed a larger treatment response for small airway deposition. Ⓐ

Abstract[4]

Life expectancy in cystic fibrosis (CF) has improved substantially over the last 75 years, with a median predicted survival now approaching 40 years. This improvement has resulted largely from therapies treating end-organ manifestations. In an effort to develop drugs that would target the underlying defects in the CF transmembrane conductance regulator (CFTR), the Cystic Fibrosis Foundation embarked on a bold initiative in which it established collaborations with biopharmaceutical companies to support early-stage efforts to discover new medicines for CF. This has led to the development and clinical trial testing of several novel drugs targeting specific CFTR mutations. One drug, ivacaftor, was recently approved by the US Food and Drug Administration for the approximately 4% of patients with CF who have the *G551D* gating mutation. Drugs targeting *F508 del CFTR* and premature termination codons, which would be applicable to 90% of patients with CF, are undergoing clinical trials. The impact of such drugs on CFTR biomarkers, such as sweat chloride and nasal potential difference, suggests that they may reset the clinical trajectory of CF, but their effect on long-term outcomes will remain unknown for many years. Nevertheless, development of CFTR-targeted drugs represents an important milestone in CF, perhaps revolutionizing the care of these patients in a fundamental way. Ⓐ

Evidence-Based References

Clancy JP et al.: Results of a phase IIa study of VX-809, an investigational CFTR corrector compound, in subjects with cystic fibrosis homozygous for the mutation, *Thorax* 67:12–18, 2012. Ⓐ

Ramsey BW, et al.: VX08-770-102 Study Group. A CFTR potentiator in patients with cystic fibrosis and the mutation, *N Engl J Med* 365:1663–1672, 2011. Ⓐ

Bakker EM et al.: Improved treatment response to dornase alfa in cystic fibrosis patients using controlled inhalation, *Eur Respir J* 38:1328–1335, 2011. Ⓐ

Clancy JP, Jain M: Personalized medicine in cystic fibrosis: dawning of a new era, *Am J Respir Crit Care Med* 186:593–597, 2012. Ⓐ

SUGGESTED READINGS

Accurso FJ et al.: Effect of VX-770 in persons with cystic fibrosis and the G551D-CFTR mutation, *N Engl J Med* 363:1991–2003, 2010.

Bartlett JR et al.: Genetic modifiers of liver disease in cystic fibrosis, *JAMA* 302(10):1076–1083, 2009.

Castellani C et al.: Association between carrier screening and incidence of cystic fibrosis, *JAMA* 302(23):2573–2579, 2009.

Dasenbrook EC et al.: Association between respiratory tract MRSA and survival in cystic fibrosis, *JAMA* 303(23):2386–2392, 2010.

George PM et al.: Improved survival at low lung function in cystic fibrosis: cohort study from 1990 to 2007, *BMJ* 342(d1008), 2011.

Ramsey B. et al.: A CFTR potentiator in patients with cystic fibrosis and the G551D mutation, *N Engl J Med* 365:1663–1672, 2011.

Stoltz DA et al: Origins of cystic fibrosis lung disease. *N Engl J Med* 372:351–362, 2015.

Wainwright CE et al.: Effect of bronchoalveolar lavage-directed therapy on Pseudomonas aeruginosa infection and structural lung injury in children with cystic fibrosis, *JAMA* 306(2):163–171, 2011.

BASIC INFORMATION

DEFINITION

Cysticercosis is an infection caused by the tissue deposition of larval forms of the pork tapeworm *Taenia solium. T. solium* cysts, or cysticerci, may accumulate in any human tissue, including the eyes, spinal cord, skin, muscle, heart, and brain. Central nervous system (CNS) involvement is common and is known as neurocysticercosis. Humans most commonly acquire cysticercosis via fecal-oral transmission from human tapeworm carriers or via ingestion of larval cysts in infected pork or tapeworm eggs in contaminated water or soil. Larvae in the gastrointestinal tract migrate hematogenously to tissues, where they encyst, forming cysticerci.

SYNONYMS

Cysticerciasis
Taeniasis
Pork tapeworm

ICD-9CM CODES	
123.1	Cysticercosis
ICD-10CM CODES	
B69	Cysticercosis
B69.0	Cysticercosis of central nervous system
B69.1	Cysticercosis of eye
B69.81	Myositis in cysticercosis
B69.89	Cysticercosis of other sites
B69.9	Cysticercosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- *T. solium* infection is worldwide in distribution. Tapeworm infection and cysticercosis are endemic in developing countries where pigs are raised as a food source, including developing countries of Central America, South America, and parts of Africa and Asia.
- Serologic studies from endemic areas of Latin America have demonstrated seroprevalence rates of 4% to 24% in native populations.
- Neurocysticercosis is most common in the United States in states with large immigrant populations from countries where the disease is endemic.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- After ingestion of *T. solium* eggs or cysts, humans may remain asymptomatic for years.
- Cysticerci in muscles and skin may form asymptomatic "cold" nodules without erythema or tenderness that may calcify and be seen on radiographs.
- Neurocysticercosis, the presence of cysts within the brain parenchyma, is usually asymptomatic. Symptoms develop due to the inflammatory response to degeneration of cysts, which can result in focal encephalitis, vasculitis, chronic meningitis, and cranial nerve palsies.
- Seizures are the most common manifestation of neurocysticercosis, occurring in 70% to 90% of symptomatic cases. Headache and focal neurologic deficits can also occur.
- In 10% to 20% of cases of neurocysticercosis, cysts lodge within the ventricular system and result in obstructive hydrocephalus, causing acute intracranial hypertension. Symptoms are caused by the presence of the parasite itself, ependymal inflammation, and/or fibrosis, each of which blocks the circulation of cerebrospinal fluid (CSF). Death may occur from progressive hydrocephalus, cerebral edema, or intractable seizures.
- Ocular cysticercosis occurs in less than 5% of infections and is generally asymptomatic. Inflammation in response to degenerating cysticerci may result in chorioretinitis, vasculitis, or retinal detachment, threatening vision.

ETIOLOGY

- *T. solium* has a complex two-host life cycle.
- Humans are the only definitive host and harbor the adult worm in the intestine (taeniasis). However, both humans and pigs can serve as intermediate hosts and harbor the larvae or cysticerci.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Epilepsy of unknown etiology.
- Migraine.
- CNS vasculitis.
- Primary neoplasia of CNS.
- Chronic CNS infections, including toxoplasmosis, coccidioidomycosis, tuberculosis, and cryptococcosis.
- Brain abscess.
- CNS involvement with sarcoidosis or systemic lupus erythematosus.

WORKUP

Comprehensive clinical history: obtain information on current and previous travel and residence, including geographic area, sanitary conditions, and consumption of undercooked pork.

LABORATORY TESTS

- Definitive diagnosis is based on the histopathologic demonstration of cysticerci in the tissue involved.
- Peripheral eosinophilia is usually absent.
- Stool examination for ova and proglottids of *T. solium* is insensitive and not specific for the diagnosis of cysticercosis.
- CSF examination in neurocysticercosis is usually unremarkable, but may demonstrate pleocytosis, with lymphocytic or eosinophilic predominance, low glucose, and elevated protein.
- Serologic testing is supportive of a suspected diagnosis of cysticercosis. Antibody detection by enzyme-linked immunoelectrotransfer blot (EITB) assay has a sensitivity of 98% and a specificity of 100% in patients with more than one cyst, but has less predictive value in patients with a single cyst, in which up to 38% can be falsely negative. Antibodies detected by EITB can persist for years after successful therapy, limiting the usefulness of this assay in following patients after treatment. In endemic regions, a negative test is useful in ruling out disease but a positive result is a marker of exposure, not necessarily symptomatic infection.
- Newer enzyme-linked immunosorbent assays can detect circulating cysticercus antigens in blood and CSF, providing a marker of viable organisms, even when CNS lesions are calcified and presumed to be inactive. This method may be particularly useful in monitoring patients following therapy. Antigen levels usually fall within 3 months of successful treatment.
- Polymerase chain reaction (PCR) detection of *T. solium* DNA has been developed, with a reported sensitivity of 96.7%, but is not widely available.

IMAGING STUDIES

- Plain radiographs of the extremities may reveal calcified cysts in patients with soft tissue or muscle involvement.
- For diagnosis of neurocysticercosis, CT and MRI are most commonly used.
- Brain CT (Fig. C1-122) has a sensitivity and specificity of 95% and can identify living cysticerci, which appear as hypodense lesions, as well as degenerating cysts, which appear as isodense or hyperdense lesions with surrounding edema. CT is the best method for detecting calcification associated with prior infection, which suggests inactivity.
- Brain MRI is the most accurate technique to assess the extent of infection, location, and evolutionary stage of the parasites. MRI provides detailed images of living and degenerating cysts, perilesional edema, as well as small cysts or those located in the ventricles, brainstem, and cerebellum. However, MRI has a low sensitivity for detecting calcified lesions, which are the most common neuroimaging finding in endemic populations.

TREATMENT

ACUTE GENERAL Rx

Asymptomatic cysticercosis:

- There is no evidence that administering antiparasitic therapy is beneficial.

Symptomatic neurocysticercosis:

The goals of treatment are to control seizures and mass effect from cysticercal lesions, control intracranial hypertension, and reduce the size of active cysts.

- Treatment decisions in neurocysticercosis should be individualized. Initial measures should focus on the symptomatic management considering antiparasitic therapy when appropriate.
- Patients with active lesions, with evidence of surrounding edema and/or inflammation, generally warrant treatment with antiparasitics, corticosteroids, and anticonvulsants.

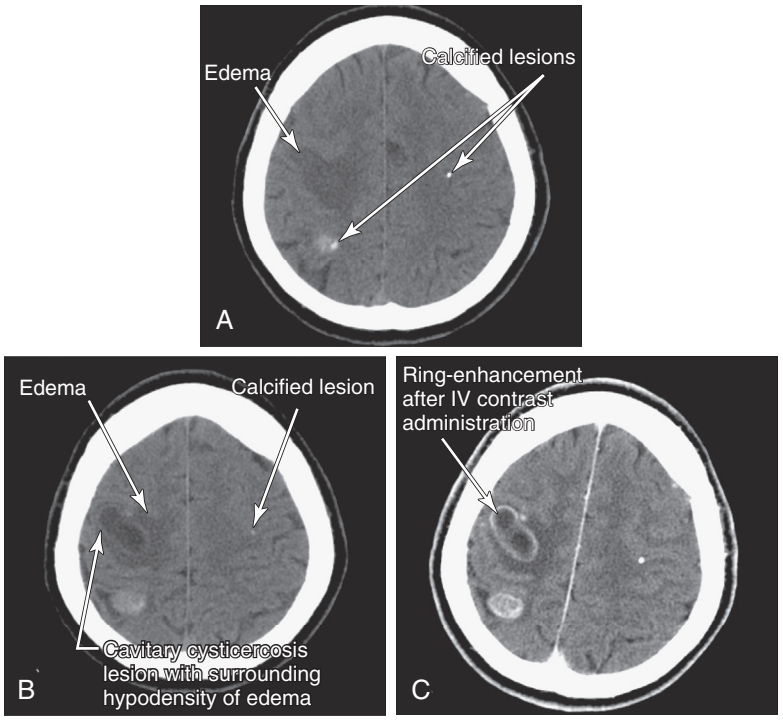

FIGURE C1-122 Neurocysticercosis. This 40-year-old Bolivian male presented with left-hand weakness. **A-B,** Noncontrast head CT, brain windows. **C,** CT with contrast moments later—compare this with image **B.** A slice through the same level of the brain before contrast administration. Hypodense lesions are present, with surrounding hypodensity *(dark gray)* representing edema. Scattered calcifications are also seen, which are a common feature of old neurocysticercosis lesions. Administration of IV contrast leads to ring enhancement, a feature of many infectious and inflammatory conditions, including neurocysticercosis, brain abscess, and toxoplasmosis. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

1. Patients who have seizures or are considered at risk for recurrent seizures based on imaging should be treated with anticonvulsants.
2. Corticosteroids may decrease inflammation and edema, and should be given whenever antiparasitic therapy is given.
3. Antiparasitic therapy is indicated in the treatment of symptomatic patients with multiple viable brain parenchymal cysticerci. Despite treatment, only 30% to 50% of lesions resolve within 6 months.
4. Calcified cysticerci are generally inactive and do not warrant antiparasitic treatment.
5. Antiparasitic therapy is often unnecessary in patients with single cysts, which are usually self-limited and resolve spontaneously within 6 months.

Antiparasitic therapy:

1. Patients with viable parenchymal or subarachnoid cysts should be treated with albendazole 15 mg/kg/day PO divided twice daily for 7 days or praziquantel 50 mg/kg/day divided three times daily for 28 days. Albendazole is preferred since praziquantel management is more complicated due to an interaction with anticonvulsants such as phenytoin. Patients should receive prednisolone (2 mg/kg/day) or dexamethasone (0.15 mg/kg/day) orally before initiation of antiparasitic therapy. Antiparasitics should be used cautiously in patients with massive cysticercal infection of the brain parenchyma (≥50 cysts) or cysticercal encephalitis. These patients should be managed initially with corticosteroids, and perhaps mannitol, to control intracranial hypertension. Once the inflammation and edema have resolved by MRI, antiparasitics can be administered.
2. Albendazole is considered to be the drug of choice due to slightly better efficacy, greater availability, fewer drug interactions, and lower cost.
3. Combination therapy with praziquantel (50 mg/kg/day) and albendazole (15 mg/kg/day) with dexamethasone (0.1 mg/kg/day) has recently been demonstrated to be more efficacious than albendazole and steroids alone for cyst resolution; seizures persisted despite treatment in many cases.

Surgical therapy:

1. Surgery may be indicated in patients with obstructive hydrocephalus or giant cysts with associated intracranial hypertension.
2. Minimally invasive neurosurgery (neuroendoscopy) for cyst removal and ventricular shunt formation has greatly improved the management of intraventricular neurocysticercosis.
3. Extraparenchymal neurocysticercosis, including ocular, subarachnoid, and intraventricular disease, carries a poor prognosis and requires a more aggressive approach. When feasible, complete surgical excision of lesions remains the definitive therapy.

CHRONIC RX

- Prolonged antiparasitic therapy does not improve outcomes in neurocysticercosis and may delay calcification of lesions. Antiepileptic medications should be continued for 2 years or 6 to 12 months after CT/MRI resolution of viable cysts, before tapering. In some cases, antiepileptic therapy needs to be continued indefinitely.
- Rare patients with neurocysticercosis develop chronic or recurrent perilesional inflammation, requiring long-term, high-dose steroid therapy. Methotrexate has been reported to be of use as a steroid-sparing agent in this setting.

DISPOSITION

- In seizure-free, stable neurocysticercosis, outpatient management is appropriate.
- Patients with seizures should be restricted from driving.

REFERRAL

- Infectious diseases consultation.
- Neurology consultation in patients with seizures.
- Neurosurgical consultation if extraparenchymal neurocysticercosis or obstructive hydrocephalus is present.

PREVENTION

- Eradication of taeniasis/cysticercosis is possible with implementation of meat inspection, improvement of pig husbandry, and improvement of socioeconomic conditions in endemic areas.
- A porcine vaccine against *T. solium* has been developed and successfully implemented in Peru, Mexico, and Australia.
- There is currently no human vaccine to prevent tapeworm infection or cysticercosis.

PATIENT & FAMILY EDUCATION

- Pork should be inspected for the presence of cysticerci, which are visible in raw meat.
- Pork must be well cooked.
- Proper disposal of human excreta and handwashing are of utmost importance to break the transmission cycle in households.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Cysticercosis (Patient Information)

AUTHORS: **ELENI PATROZOU, M.D.,** and **STACI A. FISCHER, M.D.**

SUGGESTED READINGS

Almeida CR et al.: Taenia solium DNA is present in the cerebrospinal fluid of neurocysticercosis and can be used for diagnosis, *Eur Arch Psychiatry Clin Neurosci* 256(5):307–310, 2006.

Alonso ZV et al.: Parasite antigen in serum predicts the presence of viable brain parasites on patients with apparently calcified cysticercosis only, *Clin Infect Dis* 57:e154–e159, 2013.

Cantey PT et al.: Neglected parasitic infections in the United States: Cysticercosis, *Am J Trop Med Hyg* 90(5):805–509, 2014.

Castillo Y et al.: Urine antigen detection for the diagnosis of human neurocysticercosis, *Am J Trop Med Hyg* 80(3):379–383, 2009.

Das K et al.: Role of antiparasitic therapy for seizures and resolution of lesions in neurocysticercosis patients: an 8 year randomized study, *J Clin Neurosci* 14:1172–1177, 2007.

Deckers N, Dorny P: Immunodiagnosis of Taenia solium taeniosis/cysticercosis, *Trends Parasitol* 26(3):137–144, 2010.

Del Brutto OH et al.: Meta-analysis: cysticidal drugs for neurocysticercosis: albendazole and praziquantel, *Ann Intern Med* 145:43, 2006.

Garcia HH et al.: Efficacy of combined antiparasitic therapy with praziquantel and albendazole for neurocysticercosis: a double-blind, randomized controlled trial, *Lancet Infectious Diseases* 14:687–695, 2014.

Garcia HH, DelBrutto OH: Neurocysticercosis: updated concepts about an old disease, *Lancet Neurol* 4:653–661, 2005.

Garcia HH et al.: Cysticercosis of the central nervous system: how should it be managed? *Curr Opin Infect Dis* 24:423–427, 2011.

Garcia HH et al.: A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis, *N Engl J Med* 350:249, 2004.

Garcia HH et al.: Strategies for the elimination of taeniasis/cysticercosis, *J Neurol Sci* 262:153–157, 2007.

Garcia HH et al.: New concepts in the diagnosis and management of neurocysticercosis (Taenia solium), *Am J Trop Med Hyg* 72:3, 2005.

Garcia HH et al.: Taenia solium cysticercosis, *Lancet* 362:547–556, 2003.

Gonzalez AE et al.: Short report: vaccination of pigs to control human neurocysticercosis, *Am J Trop Med Hyg* 72:837–839, 2005.

Kaur S et al.: Combination therapy with albendazole and praziquantel versus albendazole alone in children with seizures and single lesion neurocysticercosis: a randomized, placebo-controlled double blind trial, *Pediatr Infect Dis J* 28:403–406, 2009.

Kimura-Hayama ET et al.: Neurocysticercosis: radiologic-pathologic correlation, *Radio Graphics* 30:1705–1719, 2010.

Michelet L et al.: Human neurocysticercosis: comparison of different diagnostic tests using cerebrospinal fluid, *J Clin Microbiol* 49(1):195–200, 2011.

Mitre E et al.: Methotrexate as a corticosteroid-sparing agent in complicated neurocysticercosis, *Clin Infect Dis* 44:449–553, 2007.

Nash TE et al.: Treatment of neurocysticercosis: current status and future research needs, *Neurology* 67:1120–1127, 2006.

Pardini AX et al.: Cysticercus antigens in cerebrospinal fluid samples from patients with neurocysticercosis, *J Clin Microbiol* 39(9):3368–3372, 2001.

Rajshekhar V: Surgical management of neurocysticercosis, *Int J Surg* 8:100–104, 2010.

Rodriguez S et al.: Detection of Taenia solium antigens and anti-T. solium antibodies in paired serum and cerebrospinal fluid samples from patients with intraparenchymal or extraparenchymal neurocysticercosis. Cysticercosis Working Group in Peru, *J Infect Dis* 199:1345–1352, 2009.

Takayanagui OM et al.: Clinical aspects of neurocysticercosis, *Parasitol Int* 55:S111–S115, 2006.

Tsang VC et al.: An enzyme-linked immunoelectrotransfer blot assay and glycoprotein antigens for diagnosing human cysticercosis (Taenia solium), *J Infect Dis* 159:50–59, 1989.

Wallin MT, Kurtzke JF: Neurocysticercosis in the United States: review of important emerging infection, *Neurology* 63:1559–1564, 2004.

BASIC INFORMATION

DEFINITION

Infection with cytomegalovirus (CMV), a herpes virus, is common in the general population, with multiple mechanisms for transmission, often during childhood and adolescence. CMV is associated with pregnancy and can be a congenital disease. CMV is also associated with immunocompromised states and may be life threatening.

SYNONYMS

CMV
Heterophil-negative mononucleosis
Cytomegalic inclusion disease virus

ICD-9CM CODES
078.5 CMV infection
771.1 Congenital or perinatal CMV infection
V01.7 Exposure to CMV

ICD-10CM CODES
B25.9 Cytomegaloviral disease, unspecified
P35.1 Congenital cytomegalovirus infection
Z20.820 Contact with and (suspected) exposure to varicella

EPIDEMIOLOGY & DEMOGRAPHICS

- Seroprevalence is widespread: 40% to 100% antibody positivity in adults.
- Increased infection develops perinatally, in day care exposure, and then during reproductive age, related to sexual activity.

ROUTES OF TRANSMISSION

- Blood transfusions.
- Sexually (STDs) via uterus, cervix, and semen.
- Perinatally via breast milk.
- Transplant of organs—bone marrow, kidneys, liver, heart, or lung.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

CHILDREN: Congenital—25% of infected children with symptoms if congenital:
- Petechial rash.
- Jaundice and/or hepatosplenomegaly.
- Lethargy.
- Respiratory distress.
- CNS involvement, seizures.

Postnatal acquisition:
- CMV mononucleosis.
- Pharyngitis, croup, bronchitis, pneumonia.

HEALTHY ADULTS: Common
- May be asymptomatic.
- CMV mononucleosis similar to EBV mononucleosis.
- Fever—lasting 9 to 30 days—mean of 19 days.

Less common
- Exudative pharyngitis.
- Lymphadenopathy, hepatitis, splenomegaly.
- Interstitial pneumonia (rare).
- Nonspecific rash.
- Thrombocytopenia/hemolytic anemia.

Rare
- Guillain-Barré syndrome.
- Meningoencephalitis.
- Myocarditis.

IMMUNOSUPPRESSED PATIENTS:
- Febrile mononucleosis.
- GI ulcerations, hepatitis, pneumonitis, retinitis, encephalopathy, meningoencephalopathy.
- HIV associated—dementia, demyelination, retinitis, acalculous cholecystitis, adrenalitis, diarrhea, enterocolitis, esophagitis.
- Diabetes associated with pancreatitis.
- Adrenalitis associated with HIV.

ETIOLOGY

CMV infection can remain latent, reactive with immunosuppression.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Congenital:
- Acute viral, bacterial, parasitic infections including other congenitally transmitted agents (toxoplasmosis, rubella, syphilis, pertussis, croup, bronchitis).

Acquired:
- EBV mononucleosis.
- Viral hepatitis—A, B, C.
- Cryptosporidiosis.
- Toxoplasmosis.
- *Mycobacterium avium* infections.
- Human herpesvirus 6.
- Acute HIV infection.

WORKUP

- Laboratory confirmation combined with clinical findings often with leukopenia, thrombocytopenia, lymphocytosis.
- Serology:
  1. Detection of CMV-IgM antibodies suggests recent infection. CMV-IgG antibodies usually appear 2 to 3 weeks after infection.
  2. Molecular amplification tests: options include PCR assays on plasma, leukocytes and whole blood, nucleic acid sequence based amplification (NASBA), and Hybrid Capture System CMV DNA test. These tests are used in immunocompromised, AIDS, and transplant patients.
- Cultures: using human fibroblast cultures of blood, CSF, urine, BAL, and biopsy specimens but can take 1 to 6 weeks.
- Funduscopic—necrotic patches with white granular component of retina.
- Biopsy—"owl's eye" inclusion bodies on tissue sample.
- HIV.

IMAGING STUDIES

- Chest radiograph—if pneumonitis suspected, consider bronchoscopy.
- Endoscopy—if GI involvement.
- CT scan/MRI—if CNS involvement.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Strict hand washing and standard precautions limit CMV transmission in health care facilities.
- Antiretroviral therapy (ART) in patients with CD4 count $<50/mm^3$ for the goal of CD4 $>100/mm^3$ for a 3- to 6-mo period.

ACUTE GENERAL Rx

For compromised hosts with CMV retinitis or pneumonitis:
- Ganciclovir 5 mg/kg q12h IV x 14 to 21 days, then valganciclovir: 900 mg PO q24h or alternative regimen.
- Ganciclovir intraocular implant plus valganciclovir 900 mg PO q24h or alternative regimen.
- Foscarnet 90 mg/kg q12h x 14 to 21 days, then 90 mg to 120 mg/kg IV q24h or alternative regimen.
- Cidofovir 5 mg/kg IV q day x 14 days, then 5 mg/kg IV q 2 weeks.
- Fomivirsen-salvage therapy for CMV retinitis 300 μg injected into vitreous.

DISPOSITION

- CMV infection in patients who are immunocompromised (especially those with AIDS, bone marrow and solid organ transplant recipients, and disorders of cell-mediated immune function) will need expert, long-term follow-up by an infectious disease specialist or immunologist familiar with the care of such patients.
- CMV mononucleosis, hepatitis, pharyngitis, etc. in immunologically normal hosts are usually self-limiting infections requiring no special follow-up plans.

REFERRAL

- To an ophthalmologist if CMV retinitis is present.
- To an infectious disease specialist or AIDS specialist for patients who are HIV-positive with CMV disease.
- To a cellular immunologist or transplant specialist in the case of CMV infection in a transplant recipient.
- To a pediatric infectious disease specialist for congenital CMV infection.

PEARLS & CONSIDERATIONS

CMV is ubiquitous in the environment and is asymptomatically shed by latently infected persons with CMV infection, making it difficult to protect patients who are immunocompromised from acquiring this infection.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

EVIDENCE

Abstract[1]

Background:

Congenital cytomegalovirus (CMV) infection is an important cause of hearing loss, and most infants at risk for CMV-associated hearing loss are not identified early in life because of failure to test for the infection. The standard assay for newborn CMV screening is rapid culture performed on saliva specimens obtained at birth, but this assay cannot be automated. Two alternatives—real-time polymerase chain reaction (PCR)–based testing of a liquid-saliva or dried-saliva specimen obtained at birth—have been developed.

Methods:

In our prospective, multicenter screening study of newborns, we compared real-time PCR assays of liquid-saliva and dried-saliva specimens with rapid culture of saliva specimens obtained at birth.

Results:

A total of 177 of 34 989 infants (0.5%; 95% confidence interval [CI], 0.4 to 0.6) were positive for CMV, according to at least one of the three methods. Of 17 662 newborns screened with the use of the liquid-saliva PCR assay, 17 569 were negative for CMV, and the remaining 85 infants (0.5%; 95% CI, 0.4 to 0.6) had positive results on both culture and PCR assay. The sensitivity and specificity of the liquid-saliva PCR assay were 100% (95% CI, 95.8 to 100) and 99.9% (95% CI, 99.9 to 100), respectively, and the positive and negative predictive values were 91.4% (95% CI, 83.8 to 96.2) and 100% (95% CI, 99.9 to 100), respectively. Of 17 327 newborns screened by means of the dried-saliva PCR assay, 74 were positive for CMV, whereas 76 (0.4%; 95% CI, 0.3 to 0.5) were found to be CMV-positive on rapid culture. Sensitivity and specificity of the dried-saliva PCR assay were 97.4% (95% CI, 90.8 to 99.7) and 99.9% (95% CI, 99.9 to 100), respectively. The positive and negative predictive values were 90.2% (95% CI, 81.7 to 95.7) and 99.9% (95% CI, 99.9 to 100), respectively.

Conclusions:

Real-time PCR assays of both liquid- and dried-saliva specimens showed high sensitivity and specificity for detecting CMV infection and should be considered potential screening tools for CMV in newborns. (Funded by the National Institute on Deafness and Other Communication Disorders.) Ⓐ

Abstract[2]

Background:

Cytomegalovirus end-organ disease can be prevented by giving ganciclovir when viraemia is detected in allograft recipients. Values of viral load correlate with development of end-organ disease and are moderated by preexisting natural immunity. Our aim was to determine whether vaccine-induced immunity could do likewise.

Methods:

We undertook a phase-2 randomised placebo controlled trial in adults awaiting kidney or liver transplantation at the Royal Free Hospital, London, UK. Exclusion criteria were pregnancy, receipt of blood products (except albumin) in the previous 3 months, and simultaneous multiorgan transplantation. 70 patients seronegative and 70 seropositive for cytomegalovirus were randomly assigned from a scratch-off randomisation code in a 1:1 ratio to receive either cytomegalovirus glycoprotein-B vaccine with MF59 adjuvant or placebo, each given at baseline, 1 month and 6 months later. If a patient was transplanted, no further vaccinations were given and serial blood samples were tested for cytomegalovirus DNA by real-time quantitative PCR (rtqPCR). Any patient with one blood sample containing more than 3000 cytomegalovirus genomes per mL received ganciclovir until two consecutive undetectable cytomegalovirus DNA measurements. Safety and immunogenicity were coprimary endpoints and were assessed by intention to treat in patients who received at least one dose of vaccine or placebo. This trial is registered with ClinicalTrials.gov, NCT00299260.

Findings:

67 patients received vaccine and 73 placebo, all of whom were evaluable. Glycoprotein-B antibody titres were significantly increased in both seronegative (geometric mean titre 12 537 (95% CI 6593–23 840) versus 86 (63–118) in recipients of placebo recipients; p<0·0001) and seropositive (118 395; 64 503–217 272) versus 24 682 (17 909–34 017); p<0.0001) recipients of vaccine. In those who developed viraemia after transplantation, glycoprotein-B antibody titres correlated inversely with duration of viraemia (p = 0.0022). In the seronegative patients with seropositive donors, the duration of viraemia (p = 0.0480) and number of days of ganciclovir treatment (p = 0.0287) were reduced in vaccine recipients.

Interpretation:

Although cytomegalovirus disease occurs in the context of suppressed cell-mediated immunity post-transplantation, humoral immunity has a role in reduction of cytomegalovirus viraemia. Vaccines containing cytomegalovirus glycoprotein B merit further assessment in transplant recipients.Ⓐ

Evidence-Based References

Boppana SB et al.: National Institute on Deafness and Other Communication Disorders CHIMES Study: Saliva polymerase-chain-reaction assay for cytomegalovirus screening in newborns, *N Engl J Med* 364:2111–2118, 2011. Ⓐ

Griffiths PD et al.: Cytomegalovirus glycoprotein-B vaccine with MF59 adjuvant in transplant recipients: a phase 2 randomised placebo-controlled trial, *Lancet* 377:1256–1263, 2011. Ⓐ

SUGGESTED READINGS

Asberg A et al.: Valganciclovir for the prevention and treatment of CMV in solid organ transplant recipients, *Expert Opin Pharmcother* 11:1159–1166, 2010.

Hodson E et al.: Antiviral medications to prevent cytomegalovirus disease and early death in recipients of solid-organ transplants: a systematic review of randomised controlled trials, *Lancet* 365:2105–2115, 2005.

Nichols W et al.: Recent advances in the therapy and prevention of CMV infections, *J Clin Virology* 16(1):25–40, 2000.

Plosa EJ et al.: Cytomegalovirus infection, *Pediatr Rev* 33:156–163, 2012.

Razonable R: Cytomegalovirus infection after liver transplantation: current concepts and challenges, *World J Gastroenterol* 14(31):4849–4860, 2008.

BASIC INFORMATION

DEFINITION

Venous thromboembolism is any thromboembolic event occurring within the venous system. Deep vein thrombosis (DVT) is the development of thrombi in the deep veins of the extremities or pelvis.

SYNONYMS

DVT
Venous thromboembolism (VTE) (VTE includes DVT and pulmonary embolism [PE])
Deep venous thrombosis
VTE

ICD-9CM CODES

451.1	Thrombosis of deep vessels of lower extremities
451.83	Thrombosis of deep veins of upper extremities
541.9	Deep vein thrombosis of unspecified site

ICD-10CM CODES

I80.29	Phlebitis and thrombophlebitis of other deep vessels of lower extremities
I80.293	Phlebitis and thrombophlebitis of other deep vessels of lower extremity, bilateral
I80.8	Phlebitis and thrombophlebitis of other sites
I80.9	Phlebitis and thrombophlebitis of unspecified site

EPIDEMIOLOGY & DEMOGRAPHICS

- Annual incidence of VTE is 0.1% to 0.27%, affecting up to 5% of the population during their lifetimes.
- The risk of recurrent thromboembolism is higher among men than women.
- About 5% to 15% of persons with untreated DVT die from pulmonary embolism.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pain and swelling of the affected extremity
- In lower extremity DVT: leg pain on dorsiflexion of the foot (***Homans' sign***)
- Physical examination may be unremarkable in early DVT

ETIOLOGY

The etiology is often multifactorial (prolonged stasis, coagulation abnormalities, vessel wall trauma). The following are risk factors for DVT:

- Prolonged immobilization (>3 days)
- Postoperative state
- Trauma to pelvis and lower extremities for lower extremity DVT; central line placement for upper extremity DVT
- Birth control pills, high-dose estrogen therapy; conjugated equine estrogen but not esterified estrogen is associated with increased risk of DVT; estrogen plus progestin is associated with doubling the risk of venous thrombosis. The use of bevacizumab is also significantly associated with an increased risk of developing DVT in cancer patients receiving this drug.
- Visceral cancer (lung, pancreas, alimentary tract, genitourinary tract)
- Age >60 yr
- History of thromboembolic disease
- Hematologic disorders (e.g., factor V Leiden mutation [FVL], antithrombin III deficiency, protein C deficiency, protein S deficiency, heparin cofactor II deficiency, sticky platelet syndrome, G20210A prothrombin mutation, lupus anticoagulant, dysfibrinogenemias, anticardiolipin antibody, hyperhomocysteinemia, concurrent homocystinuria, high levels of factors VIII, XI, and single nucleotide polymorphisms [SNPs] such as CYP4V2)
- Pregnancy and early puerperium
- Obesity (BMI >30)
- Congestive heart failure
- Surgery, fracture, or injury involving lower leg or pelvis
- Plaster cast immobilization
- Surgery requiring >30 min of anesthesia
- Gynecologic surgery (particularly gynecologic cancer surgery)
- Recent travel (within 2 wk, lasting ≥2 hr). Every 2 hr spent traveling increases VTE risk by 18%.
- Smoking and abdominal obesity
- Central venous catheter or pacemaker insertion
- Superficial vein thrombosis (10% risk of DVT within 3 mo), varicose veins
- Collagen vascular disease
- Nephrotic syndrome
- Myeloproliferative disorders
- Preoperative basiss
- Long-term exposure to particulate air pollution is also associated with altered coagulation function and DVT risk.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Postphlebitic syndrome
- Superficial thrombophlebitis
- Ruptured Baker's cyst
- Cellulitis, lymphangitis, Achilles tendinitis
- Hematoma
- Muscle or soft tissue injury, stress fracture
- Varicose veins, lymphedema
- Arterial insufficiency
- Abscess
- Claudication
- Venous stasis

WORKUP

- The clinical diagnosis of DVT is inaccurate. Pain, tenderness, swelling, or color changes are not specific for DVT.
- Clinical prediction rules can be used to establish pretest probability of DVT. The Wells prediction rules for DVT and for pulmonary embolism are described in Box D1-1. These rules perform better in younger patients without a history of DVT and in those without comorbidities. In younger patients without associated comorbidities and a low pretest probability using Wells criteria and a negative high-sensitivity D-dimer test, the diagnosis of DVT can be reasonably excluded.
- Compression ultrasonography (CUS; Fig. ED1-1) is preferred as the initial study to diagnose DVT in patients with intermediate to high pretest probability. An initial negative test limited to the proximal leg should be repeated after 5 days (if the clinical suspicion of DVT persists) to exclude DVT that is propagating proximally from the calf. Comprehensive ultrasonography (whole-leg CUS) is a more extensive test that examines the deep veins from the inguinal ligament to the level of the malleolus. Literature reports indicate that it may be safe to withhold anticoagulation after negative results on comprehensive duplex ultrasonography in nonpregnant patients with a suspected first episode of symptomatic DVT of the leg.

LABORATORY TESTS

- Laboratory tests are not specific for DVT. Baseline prothrombin time (INR), partial thromboplastin time, and platelet count

BOX D1-1 Wells Prediction Rule for Diagnosing Deep Venous Thrombosis: Clinical Evaluation Table for Predicting Pretest Probability of Deep Venous Thrombosis*

Clinical Characteristic	Score
Active cancer (treatment ongoing, within previous 6 mo, or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden >3 days or major surgery within 12 wk requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis at least as likely as deep venous thrombosis	22

*Clinical probability: low, ≤0; intermediate, 1-2; high, ≥3. In patients with symptoms in both legs, the more symptomatic leg is used.

Reprinted from Wells PS et al: Value assessment of pretest probability of deep-vein thrombosis in clinical management, *Lancet* 351:1795-1798, 1997.

should be obtained on all patients before starting anticoagulation. D-dimer testing is sensitive but not specific for DVT. A negative result (D-dimer <0.5 mcg/ml) can exclude the diagnosis, but a positive result (≥0.5 mcg/ml) mandates additional testing with venous ultrasonography.

- Use of D-dimer assay by ELISA is useful in the management of suspected DVT. The combination of a normal D-dimer study on presentation together with a normal compression venous ultrasound is useful to exclude DVT. DVT can be ruled out in patients who are clinically unlikely to have DVT and who have a negative D-dimer test. Compressive ultrasonography can be safely omitted in such patients. Fig. ED1-2 is an algorithm for the diagnosis of DVT.
- Laboratory evaluation of young patients with DVT, patients with recurrent thrombosis without obvious causes, and those with a family history of thrombosis should include protein S (both total and free PS), protein C, fibrinogen, antithrombin III level, lupus anticoagulant, anticardiolipin antibodies, anti-b2 glycoprotein1, factor V Leiden, factor VIII, factor IX, and fasting plasma homocysteine levels. HIT antibody may also be useful in the correct context (heparin exposure and abrupt onset of unexplained decrease in platelet count, whether thrombocytopenic or not). It is important to remember that the lupus anticoagulant assay and antithrombin, protein C, protein S, and dysfibrinogenemia testing cannot be properly interpreted if the patient is already on warfarin, whereas anticardiolipin antibody test, prothrombin G20210A factor VII:C, factor V Leiden, and PT polymorphism can be performed when the patient is on warfarin.

IMAGING STUDIES

- Compression ultrasonography (CUS) is generally preferred as the initial study because it is noninvasive and can be repeated serially (useful to monitor suspected acute DVT); it offers good sensitivity for detecting proximal vein thrombosis (in the popliteal or femoral vein) (see Fig. ED1-1). Its disadvantages are poor visualization of deep iliac and pelvic veins and poor sensitivity in isolated or nonocclusive calf vein thrombi. Whole-leg compression ultrasound can generally exclude proximal and distal DVT in a single evaluation. Withholding anticoagulation following a single negative whole-leg CUS is associated with a relatively low risk of venous thromboembolism (3.5% of inpatients will develop DVT) during a 3-mo follow-up.
- Contrast venography is the gold standard for evaluation of DVT of the lower extremity. It is, however, invasive and painful. Additional disadvantages are the increased risk of phlebitis, new thrombosis, renal failure, and hypersensitivity reaction to contrast media; it also gives poor visualization of the deep femoral vein in the thigh and the internal iliac vein and its tributaries.
- Magnetic resonance direct thrombus imaging (MRDTI) is an accurate noninvasive test for diagnosis of DVT. It is particularly useful in suspected DVT patients with leg casts, which prevent CUS, and in pregnant patients with positive D-dimer and negative CUS (Fig. ED1-3). Current limitations are its cost and lack of widespread availability.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Gradual resumption of normal activity. Immobility promotes stasis and propagation of DVT. Patients should get up and walk as tolerated. The theoretical risk that ambulation may dislodge thrombi in the legs, precipitating PE, is unfounded.
- Patient education on anticoagulant therapy and associated risks.

ACUTE GENERAL Rx

- Initial treatment of DVT requires therapeutic doses of heparin (low-molecular-weight heparin [LMWH] or unfractionated). LMWH is preferred due to ease of administration, less hemorrhage, and significantly fewer deaths. Unfractionated heparin is recommended in patients with renal insufficiency because LMWH is predominantly excreted in the urine.
- LMWH is generally administered for 5 to 7 days. Recommended dose of enoxaparin is 1 mg/kg q12h SC. Once-daily fondaparinux, a synthetic analogue of heparin, is also as effective and safe as twice-daily enoxaparin in the initial treatment of patients with symptomatic DVT. Once systemic anticoagulation is initiated, vitamin K antagonist warfarin or oral factor V inhibitors are initiated. When using warfarin, it is normally started on the same day as heparin and is titrated to maintain an INR between 2 and 3. Warfarin therapy at 10 mg daily for 2 days may be initiated in healthy patients with acute DVT. This higher dose helps to achieve therapeutic INR sooner and decreases LMWH doses needed as compared to the 5 mg/day dose. After ≥5 days, heparin is stopped and warfarin is continued as monotherapy. Long-term LMWH may be preferable to warfarin in patients with cancer or those whose INR is difficult to control. Alternatives to warfarin may include the oral factor Xa inhibitors rivaroxaban, apixaban, or edoxaban, or dabigatran, a direct oral thrombin inhibitor. These new anticoagulants are noninferior to warfarin, do not require periodic lab monitoring, and have a relatively low bleeding risk. They may eventually become preferred agents for extended treatment of venous thromboembolism.
- Outpatient treatment of DVT is appropriate for patients without prior DVT, thrombophilic conditions, or substantial comorbidity, but not for those who are pregnant or likely not to adhere to therapy.
- Exclusions from outpatient treatment of DVT include patients with potential high complication risk (e.g., hemoglobin <7, platelet count <75,000, guaiac-positive stool, recent cerebrovascular accident or noncutaneous surgery, noncompliance).
- Compression stockings are effective in reducing the incidence of postthrombotic syndrome and should be used starting within 1 mo of proximal DVT and continued for at least 1 yr after diagnosis.
- Insertion of an inferior vena cava filter to prevent pulmonary embolism is recommended in patients with contraindications to anticoagulation (e.g., hemorrhagic stroke, active internal bleeding, pregnancy), HIT in a patient with an active VTE/PE, recurrent PE despite adequate anticoagulant therapy, emergent surgery in patient with DVT, presence of free-floating iliofemoral thrombus, lower IVC thrombosis (incipient embolization), and chronic pulmonary (thromboembolic) hypertension with limited pulmonary reserve.
- Thrombolytic therapy (streptokinase) can be used in rare cases (unless contraindicated) in patients with extensive iliofemoral venous thrombosis and a low risk of bleeding. There are concerns about hemorrhagic complications related to the large doses of thrombolytics required in systemic thrombolysis for DVT (2% to 10% risk of major hemorrhagic complications).
- Other treatment modalities for DVT include surgical thrombectomy and catheter-directed thrombolysis (CDT). Thromboreduction by surgical thrombectomy is effective but invasive and expensive. CDT is also invasive, carries a bleeding risk, and will require ICU admission.

CHRONIC Rx

- The optimal duration of anticoagulant therapy varies with the cause of DVT and the patient's risk factors. The risk of recurrence is low if VTE is provoked by surgery, intermediate if provoked by a nonsurgical risk factor, and high if unprovoked. These risks should determine whether patients with VTE should undergo short-term vs. indefinite treatment.
- Therapy for 3 mo is generally satisfactory in patients with reversible risk factors (low-risk group). A high D-dimer level measured after 3 mo of anticoagulation in patients with unprovoked DVT should favor a longer duration of therapy. The American College of Chest Physicians Guidelines suggests that patients with first unprovoked VTE receive indefinite anticoagulation unless their bleeding risk is high.
- The risk of recurrence in patients with a first unprovoked VTE who have negative D-dimer results is not low enough to justify stopping stopping anticoagulant therapy in men but may be low enough in some cases to justify stopping therapy in women who were taking estrogen at the time of initial VTE.[1]
- Anticoagulation for 6 mo is recommended for patients with idiopathic venous thrombosis or medical risk factors for DVT (intermediate-risk group). About 20% of patients with unprovoked venous thromboembolism have a recurrence within 2 yr after the withdrawal of oral anticoagulant therapy. Use of daily low-dose aspirin after discontinuation of

[1]Kearon C et al: D-Dimer testing to select patients with a first unprovoked venous thromboembolism who can stop anticoagulant therapy: A cohort study. *Ann Intern Med* 162:27-34, 2015.

anticoagulant treatment may provide a modest reduction in DVT risk.
- Indefinite anticoagulation is necessary in patients with DVT associated with active cancer; long-term anticoagulation is also indicated in patients with inherited thrombophilia (e.g., deficiency of antithrombin III, protein C or S antibody), high factor VIII levels, antiphospholipid antibody, and those with recurrent episodes of idiopathic DVT (high-risk group). Long-term anticoagulation should also be considered in the presence of comorbidities such as paroxysmal nocturnal hemoglobinuria (PNH), SLE (especially with nephrotic syndrome), some myeloproliferative disorders, IBD, and Cushing's syndrome.
- Measurement of D-dimer after withdrawal of oral anticoagulation may be useful to estimate the risk of recurrence in selected patients. In patients with a first unprovoked DVT, positive D-dimer test results after cessation of anticoagulation predict recurrence, regardless of test timing or patient's age. Patients with a first spontaneous DVT and a D-dimer level <250 mg/ml after withdrawal of oral anticoagulation have a low risk of DVT recurrence. Risk is lower in women than in men. Recent trials show that in patients who have completed at least 3 mo of anticoagulation for a first episode of unprovoked DVT and after approximately 2 yr of follow-up, a negative D-dimer result is associated with a 3.5% annual risk of recurrent disease, whereas a positive D-dimer result is associated with an 8.9% annual risk for recurrence. Hence, elevated D-dimer levels would be an indication for prolonged therapy (for 1 or 2 more yr at a minimum).
- The presence of residual thrombosis on ultrasonography when warfarin therapy is discontinued is also associated with an increased risk for subsequent recurrent DVT; a recent trial showed that tailoring the duration of anticoagulation on the basis of the persistence of residual thrombi on ultrasonography may reduce the rate of recurrent DVT. Additional trials are needed before this approach can be adapted for all patients.
- Patients with DVT and pulmonary embolism are at high risk of recurrence whenever anticoagulation is discontinued; therefore, many experts recommend prolonged anticoagulation in this population group, especially if other risk factors for recurrence are present.

PEARLS & CONSIDERATIONS

COMMENTS

- When using heparin, there is a risk of heparin-induced thrombocytopenia (HIT) (with unfractionated more so than with LMWH). Platelet count should be obtained initially and repeated every 3 days while on heparin.
- ***PROPHYLAXIS OF DVT:*** Recommended in all patients at risk (e.g., low-molecular-weight heparin [enoxaparin 30 mg SC bid or fondaparinux 2.5 mg SC daily] after major trauma, post surgery of hip and knee; enoxaparin 40 mg SC qd post-abdominal surgery in patients with moderate to high DVT risk; gradient elastic stockings alone or in combination with intermittent pneumatic compression [IPC] boots following neurosurgery). Graduated compression stockings (GCSs) are effective for preventing air-travel-related DVT and in reducing the risk of DVT in patients hospitalized for conditions other than stroke. The type of GCSs is also important because proximal DVT occurs more often in patients with stroke who wear below-knee stockings than in those who wear high-length stockings. The new oral anticoagulants (rivaroxaban, apixaban, etc.) are effective for thromboprophylaxis after THR and TKR. However, their clinical benefits over LMWH are marginal, they are more expensive, and they lack antidotes for timely reversal in case of bleeding.
- ***RECURRENT THROMBOEMBOLISM:*** The risk of recurrent venous thromboembolism in heterozygous carriers of factor V Leiden and a first spontaneous venous thromboembolism is similar to that of non-carriers of factor V Leiden; therefore, heterozygous patients should receive secondary thromboprophylaxis for a similar length of time as patients without factor V Leiden.
- ***POSTTHROMBOTIC SYNDROME:*** Approximately 20% to 50% of patients with DVT develop postthrombotic syndrome characterized by leg edema, pain, venous ectasia, skin induration, and ulceration. Patients with extensive DVT and those with more severe postthrombotic manifestations 1 month after DVT have poorer long-term outcomes. Recent trials have shown that compression stockings after DVT do not prevent postthrombotic syndrome.
- Exercise following DVT is reasonable because it improves flexibility of the affected leg and does not increase symptoms in patients with postthrombotic syndrome.
- Previously undiagnosed cancer is frequent in patients with newly diagnosed DVT. A cancer screening strategy should be considered in all patients with unprovoked venous thromboembolism.
- ***UPPER EXTREMITY DVT:*** It is less common than lower extremity DVT and is seen more frequently in patients requiring central venous catheters or wires. It confers risk for mortality, recurrent thromboembolic events, and post-thrombotic syndrome similar to that of lower extremity DVT. It is classified as primary upper extremity DVT ***(Paget-Schroetter syndrome)***, defined as a thrombus in the axillary and subclavian veins in absence of identifiable thrombosis risk factors. It accounts for 20% of upper extremity DVT cases and may be due to an underlying anatomic abnormality at the thoracic outlet in combination with local hypercoagulability due to venous stretching or perivascular fibrosis from recurrent venous compression. Secondary upper extremity DVT is defined as any DVT related to a predisposing factor (e.g., insertion of central venous catheter, wires, or other devices, malignancy). In patients with secondary upper extremity DVT removal of the catheter is not routinely recommended but is warranted if there is a catheter malfunction or infection, if anticoagulation therapy is contraindicated or has failed, or if the catheter is no longer needed. Anticoagulation therapy in upper extremity DVT consists of use of vitamin K antagonists except in patients with cancer, for whom low-molecular-weight heparin is preferred. Optimal duration of anticoagulation treatment in upper extremity DVT is 3 to 6 mo (including in those in whom a central catheter has been removed).
- ***REVERSAL OF ANTICOAGULATION:*** Vitamin K (1 mg PO or 2 mg IV) can be used to reverse elevated INR (3 to 6) when elective or urgent procedures are needed. The administration of vitamin K can take more than 24 hr to fully restore vitamin K dependent coagulation factors II, VII, IX, and X. The American College of Chest Physicians recommends the following guidelines for managing elevated INRs or bleeding in patients receiving vitamin A antagonist therapy:
  1. INR between 4.5 and 10 and no significant bleeding: omit dose and monitor the next day, routine use of vitamin K is not recommended
  2. INR >10 and no significant bleeding: hold vitamin K antagonist, give 5 to 10 mg orally of vitamin K. Monitor the next day and use additional vitamin K if necessary. Resume therapy at lower dose when INR therapeutic.
  3. Serious bleeding at any elevation of INR: hold vitamin K antagonist and supplement with prothrombin complex concentrates (PCC). Give vitamin K (10 mg by slow IV infusion over 30 min to reduce the risk of anaphylaxis). Vitamin K1 can be repeated every 12 hr. PCC composition in the United States (3-factor PCC) includes clotting factors II, IX, and X but minimal amounts of factor VII (unlike PCC products available outside of the United States [4-factor PCC], which have a significant amount of factor VII). In order to replace the low factor VII some clinicians in the United States will also give fresh frozen plasma (FFP) in addition to vitamin K and PCC in patients with life-threatening warfarin-related bleeding.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

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RELATED CONTENT

Deep Vein Thrombosis (DVT) (Patient Information)
Antiphospholipid Antibody Syndrome (Related Key Topic)
Hypercoagulable State (Related Key Topic)
Pulmonary Embolism (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Background:
Some patients with acute VTE who may previously have been exposed to heparin products have unrecognized antibodies implicated in heparin-induced thrombocytopenia (HIT). Antibody prevalence and patient consequences upon exposure to heparin, low-molecular-weight heparin, and fondaparinux are uncertain.

Methods:
In this secondary analysis, we tested patients in the Matisse VTE studies at study entry for heparin-dependent antibodies and further tested patients with enzyme-linked immunosorbent assay (ELISA)-positive results for platelet-activating antibodies. We compared the risk of HIT (>50% fall in platelet count, heparin-dependent antibodies, no contradicting features) between patients treated with heparin (either unfractionated or low molecular weight [enoxaparin]) vs those who received fondaparinux. Comparison groups for thrombocytopenia occurrence comprised patients with ELISA-positive, platelet-activating, antibody-positive results; ELISA-positive, but platelet-activating antibody-negative results; and randomly selected antibody-negative results.

Results:
A total of 127 of 3,994 patients (3.2%) had ELISA-positive results at baseline, but only 14 (0.4%; 95% CI, 0.2%-0.6%) had platelet-activating antibodies. Among these 14, 4 treated with unfractionated or low-molecular-weight heparin developed HIT compared with zero of 10 fondaparinux-treated patients (OR, 95; 95% CI, 8-1,123; $P < .001$). This frequency (4 of 4, 100%) significantly differed from that of both heparin-treated patients whose results were ELISA positive but platelet-activating antibody negative and from heparin-treated antibody-negative control subjects (zero of 15 and zero of 27, respectively; $P < .001$ for both).

Conclusions:
Of patients with VTE, 0.4% had pathologic platelet-activating heparin-dependent antibodies rather than the 3.2% detected by the recommended cutoff of the commercial ELISA. Among study patients with acute VTE who had platelet-activating antibodies, treatment with fondaparinux reduced the risk of precipitating rapid-onset HIT.Ⓐ

Abstract[2]

Background:
In haemodynamically stable patients with acute symptomatic pulmonary embolism (PE), studies have not evaluated the usefulness of combining the measurement of cardiac troponin, transthoracic echocardiogram (TTE), and lower extremity complete compression ultrasound (CCUS) testing for predicting the risk of PE-related death.

Methods:
The study assessed the ability of three diagnostic tests (cardiac troponin I [cTnI], echocardiogram, and CCUS) to prognosticate the primary outcome of PE-related mortality during 30 days of follow-up after a diagnosis of PE by objective testing.

Results:
Of 591 normotensive patients diagnosed with PE, the primary outcome occurred in 37 patients (6.3%; 95% CI, 4.3% to 8.2%). Patients with right ventricular dysfunction (RVD) by TTE and concomitant deep vein thrombosis (DVT) by CCUS had a PE-related mortality of 19.6%, compared with 17.1% of patients with elevated cTnI and concomitant DVT and 15.2% of patients with elevated cTnI and RVD. The use of any two-test strategy had a higher specificity and positive predictive value compared with the use of any test by itself. A combined three-test strategy did not further improve prognostication. For a subgroup analysis of high-risk patients, according to the pulmonary embolism severity index (classes IV and V), positive predictive values of the two-test strategies for PE-related mortality were 25.0%, 24.4%, and 20.7%, respectively.

Conclusions:
In haemodynamically stable patients with acute symptomatic PE, a combination of echocardiography (or troponin testing) and CCUS improved prognostication compared with the use of any test by itself for the identification of those at high risk of PE-related death.Ⓐ

Abstract[3]

Purpose:
Young individuals with occlusive, proximal-limb deep vein thrombosis (DVT) who have acutely increased plasma levels of factor VIII and D-dimer are at high risk for postthrombotic syndrome (PTS) when treated with conventional anticoagulation alone. The present report is an evaluation of experience with adjunctive percutaneous mechanical thrombolysis (PMT) and/or percutaneous pharmacomechanical thrombolysis (PPMT) in such patients.

Patients and Methods:
Among 95 children 11–21 years of age enrolled in a prospective cohort of venous thromboembolism between March 1, 2006, and November 1, 2009, 16 met eligibility criteria and underwent PMT/PPMT, typically with adjunctive catheter-directed thrombolytic infusion (CDTI) of tissue-type plasminogen activator given after the procedure.

Results:
Median age was 16 years (range, 11 to 19 years). Thirteen cases (81%) involved lower limbs. Underlying stenotic lesions were disclosed in 53%, with endovascular stents deployed in all cases of May–Thurner anomaly. There were no periprocedural major bleeding events and one symptomatic pulmonary embolism. Technical success rate was 94%. Early (<30 days) locally recurrent DVT developed in 40% of cases, of which 83% were successfully treated with repeat lysis. Late recurrent DVT rate (median follow-up duration, 14 months; range, 1 to 42 mo) was 27%. Cumulative incidence of physically and functionally significant PTS at 1 to 2 years was 13%.

Conclusions:
This experience provides preliminary evidence that PMT/PPMT with adjunctive CDTI can be used safely and effectively in adolescent subjects with DVT at high risk for PTS.Ⓐ

Abstract[4]

Objective:
Rates of venous thromboembolism as high as 58% have been reported after trauma, but there is no widely accepted screening protocol. If Medicare adds venous thromboembolism to the list of "preventable complications," they will no longer reimburse for treatment, which could have devastating effects on many urban centers. We hypothesized that prescreening with a risk assessment profile followed by routine surveillance with venous duplex ultrasound could identify asymptomatic venous thromboembolism in trauma patients.

Design:
Prospective, observational trial with waiver of consent.

Setting:
Level I trauma center intensive care unit.

Patients:
At admission, 534 patients were prescreened with a risk assessment profile.

Interventions:
Patients (n = 106) with risk assessment profile scores >10 were considered high risk and received routine screening venous duplex ultrasound within 24 hrs and weekly thereafter.

Results:
In prescreened high-risk patients, 20 asymptomatic deep vein thromboses were detected with venous duplex ultrasound (19%). An additional ten venous thromboembolisms occurred, including six symptomatic deep vein thromboses and four pulmonary emboli, resulting in an overall venous thromboembolism rate of 28%. The most common risk factors discriminating venous thromboembolism vs. no venous thromboembolism were femoral central venous catheter (23% vs. 8%), operative intervention >2 hrs (77% vs. 46%), complex lower extremity fracture (53% vs. 32%), and pelvic fracture (70% vs. 47%), respectively (all $P < .05$). Risk assessment profile scores were higher in patients with venous thromboembolism (19 ± 6 vs. 14 ± 4, $P = .001$). Risk assessment profile score (odds ratio 1.14) and the combination of pelvic fracture requiring operative intervention >2 hrs (odds ratio 5.75) were independent predictors for development of venous thromboembolism. The rates of venous thromboembolism for no chemical prophylaxis (33%), unfractionated heparin (29%), dalteparin (40%), or inferior vena cava filters (20%) were not statistically different ($P = .764$).

Conclusions:
Medicare's inclusion of venous thromboembolism after trauma as a "never event" should be questioned. In trauma patients, high-risk assessment profile score and pelvic fracture with prolonged operative intervention are independent predictors for venous thromboembolism development, despite thromboprophylaxis. Although routine venous duplex ultrasound screening may not be cost-effective for all trauma patients, prescreening using risk assessment profile yielded a cohort of patients with a high prevalence of venous thromboembolism. In such high-risk patients, routine venous duplex ultrasound and/or more aggressive prophylactic regimens may be beneficial.

Abstract[5]

Background:
The most effective agent for prophylaxis against venous thromboembolic disease after total joint arthroplasty (TJA) remains unknown. The paucity of literature comparing different methods of pulmonary embolism (PE) prophylaxis and fear of litigation make it difficult for surgeons to abandon the use of aggressive chemical prophylaxis.
Questions/Purposes:
We compared the (1) overall frequency of symptomatic PE, (2) risk of symptomatic PE after propensity matching that adjusted for potentially confounding variables, and (3) other complications and length of stay before and after propensity matching in patients undergoing TJA at our institution who received either aspirin or warfarin prophylaxis.
Methods:
A total of 28,923 patients underwent TJA between January 2000 and June 2012 at our institution, had either aspirin (325 mg twice daily; 2800 patients) or warfarin prophylaxis (26,123 patients), and were registered in our institutional electronic database. The incidence of symptomatic PE, symptomatic deep vein thrombosis (DVT), hematoma formation, infection, wound complications, and mortality up to 90 days postoperatively was collected from the database. We performed multivariate analysis and 3:1 and 5:1 propensity score matching for comorbid and demographic variables.
Results:
The overall symptomatic PE rate was lower ($p < 0.001$) in patients receiving aspirin (0.14%) than in the patients receiving warfarin (1.07%). This difference did not change after matching. The aspirin group also had significantly fewer symptomatic DVTs and wound-related problems and shorter hospital stays, which did not change after matching.
Conclusions:
After publication of the American Academy of Orthopaedic Surgeons' guidelines, some surgeons have utilized aspirin as thromboprophylaxis after TJA. Based on our findings from a large institutional database, aspirin offers suitable prophylaxis against symptomatic PE in selected patients.Ⓐ

Abstract[6]

Trunk, Genitalia, and Extremities
Background:
Abdominoplasty is one of the highest risk plastic surgery procedures for venous thromboembolism complications (VTE). Current recommendations for VTE prophylaxis are sequential compression devices (SCDs) in the OR and optional use of subcutaneous heparin after surgery. Subcutaneous heparin has been shown to be safe in other surgical groups. However, the large raw surface areas and dissection involved in abdominoplasty has been a relative contraindication for preoperative chemoprophylaxis. However, the period while the patient is under general anesthesia and immediately following the procedure is likely the highest risk time period for VTEs. The purpose of this study is to determine if preoperative chemoprophylaxis is safe in these patients.
Methods:
All patients undergoing abdominoplasty by the senior author from January 1, 2005 to January 1, 2012 were retrospectively reviewed. All patients whose operation took place between January 1, 2005 and January 18, 2008 were given SCDs before the induction of anesthesia and heparin (unfractionated) 5000 units SQ on call to the OR. All patients whose operation took place between January 19, 2008 and January 1, 2012 received enoxaparin (low molecular weight heparin) 40 mg SQ on call to the OR and then daily for 2 days postoperatively. These groups were evaluated in regards to overall complication rate, incidence of VTE, and bleeding complications.
Results:
A total of 151 patients underwent abdominoplasty during the study period. One hundred one patients received the SCD/heparin protocol and 50 had the enoxaparin protocol. The groups were similar in regard to pre-morbid conditions and risk factors for VTE. There were no VTEs diagnosed in either group. The overall incidence of any complication was similar between the 2 groups (19% vs. 14%, $P = 0.503$) and similar to other published series. The most common complications were seroma, cellulitis, and minor wound dehiscence. The incidence of bleeding complications was similar between the 2 groups (1% vs. 0%, $P = 1.0$).
Conclusions:
The use of preoperative chemoprophylaxis in patients undergoing abdominoplasty can be done without an increase in bleeding complications or overall complication rate. Furthermore, enoxaparin can also be used preoperatively and continued for 2 more days during the period of time of maximum immobility with easy administration for outpatients via use of a prescription home use kit.Ⓐ

Evidence-Based References

Warkentin TE et al.: Prevalence and risk of preexisting heparin-induced thrombocytopenia antibodies in patients with acute VTE, *Chest* 140:366–373, 2011.Ⓐ

Jiménez D et al.: Combinations of prognostic tools for identification of high-risk normotensive patients with acute symptomatic pulmonary embolism, *Thorax* 66:75–81, 2011.Ⓐ

Goldenberg NA et al.: Percutaneous mechanical and pharmacomechanical thrombolysis for occlusive deep vein thrombosis of the proximal limb in adolescent subjects: Findings from an institution-based prospective inception cohort study of pediatric venous thromboembolism, *J Vasc Interv Radiol* 22:121–132, 2011.Ⓐ

Thorson CM, Ryan ML, Van Haren RM, et al.: Venous thromboembolism after trauma: a never event?, *Crit Care Med* 40:2967–2973, 2012.Ⓐ

Raphael IJ, Tischler EH, Huang R, et al. Aspirin: An alternative for pulmonary embolism prophylaxis after arthroplasty? Clin *Orthop Relat Res* 472:482-488 (2014).

Campbell W, Pierson J, Cohen-Shohet R, et al Maximizing chemoprophylaxis against venous thromboembolism in abdominoplasty patients with the use of preoperative heparin administration. *Ann Plast Surg* 72:S94-S96 (2014).Ⓑ

SUGGESTED READINGS

Adams S et al.: Comparative effectiveness of new oral anticoagulants and standard thromboprophylaxis in patients having total hip or knee replacement, *Ann Int Med* 159:275–284, 2013.

Agnelli G et al.: Apixaban for extended treatment of venous thromboembolism, *N Engl J Med* 368:699–708, 2013.

Antithrombotic therapy and prevention of thrombosis 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines, *Chest* 141(suppl 2), 2012.

Baccarelli A et al.: Exposure to particulate air pollution and risk of deep vein thrombosis, *Arch Intern Med* 168(9):920, 2008.

Brighton TA et al.: Low-dose aspirin for preventing recurrent venous thromboembolism, *N Engl J Med* 367:1979–1987, 2012.

Becattini C et al.: Aspirin for preventing the recurrence of venous thromboembolism, *N Engl J Med* 366:1959–1967, 2012.

Buller HR et al: Fracture XI antisense oligonucleotide for prevention of venous thrombosis. *N Engl J Med* 372:232–240, 2015.

Carrier M et al.: Systematic review: the Trousseau syndrome revisited: should we screen extensively for cancer in patients with venous thromboembolism, *Ann Intern Med* 149:323–333, 2008.

Chan WS et al.: A red blood cell agglutination D-dimer test to exclude deep venous thrombosis in pregnancy, *Ann Intern Med* 147:165–170, 2007.

Cohen AT et al.: Rivaroxaban for thromboprophylaxis in acutely ill medical patients, *N Engl J Med* 368:513–523, 2013.

Douketis J et al.: Patient-level meta-analysis: effect of measurement timing, threshold, and patient age on ability of D-dimer testing to assess recurrence risk after unprovoked venous thromboembolism, *Ann Intern Med* 153:523–531, 2010.

Francis CW: Prophylaxis for thromboembolism in hospitalized medical patients, *N Engl J Med* 356:1438–1444, 2007.

Galioto NJ et al.: Recurrent venous thromboembolism, *Am Fam Phys* 83(3):293–300, 2011.

Iorio A et al.: Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor, *Arch Intern Med* 170(19):1710–1716, 2010.

Johnson SA et al.: Risk of deep vein thrombosis following a single negative whole-leg compression ultrasound, *JAMA* 303(5):438–445, 2010.

Kahn SR et al.: Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis, *Ann Intern Med* 149:698–707, 2008.

Kahn SR et al.: Compression stockings to prevent post-thrombotic syndrome: A randomized placebo-controlled trial, *Lancet* 383(9920):880–888, 2014.

Kucher N: Deep-vein thrombosis of the upper extremity, *N Engl J Med* 364:861–869, 2011.

Landerfeld CS: Noninvasive diagnosis of deep vein thrombosis, *JAMA* 300:1696, 2008.

Lassen MR et al.: Apixaban versus enoxaparin for thromboprophylaxis after hip replacement, *N Engl J Med 363* 2529, 2010.

Linkins LA et al.: Selective D-dimer testing for diagnosis of a first suspected episode of deep venous thrombosis, *Ann Intern Med* 158:93–100, 2013.

Mai C, Hunt D: Upper-extremity DVT: a review, *Am J Med* 124:402–407, 2011.

Marik PE, Plante LA: Venous thromboembolic disease and pregnancy, *N Engl J Med* 359:2025–2033, 2008.

Nallur SR et al.: Risk of venous thromboembolism with the angiogenesis inhibitor bevacizumab in cancer patients, *JAMA* 300(19):2277–2285, 2008.

Pautas E et al.: Reversal of overanticoagulation in very elderly hospitalized patients with an INR above 5.0: 24 hour INR response after vitamin K administration, *Am J Med* 124:527–533, 2011.

Piazza G, Goldhaber SZ: Improving clinical effectiveness in thromboprophylaxis for hospitalized medical patients, *Am J Med* 122:230–232, 2009.

Polareti G et al.: D-dimer testing to determine the duration of anticoagulation therapy, *N Engl J Med* 355:1780–1789, 2006.

Prandoni P et al.: Residual thrombosis on ultrasonography to guide the duration of anticoagulation in patients with deep vein thrombosis, *Ann Intern Med* 150:577–585, 2009.

Qaseem A et al.: Current diagnosis of venous thromboembolism in primary care: a clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians, *Ann Intern Med* 146:454–458, 2007.

Sachdeva A et al.: Elastic compression stockings for prevention of deep vein thrombosis, *Cochrane Database Syst Rev* 7:CD001484, 2010.

Segal JB et al.: Management of venous thromboembolism: a systematic review for a practice guideline, *Ann Intern Med* 146:211–222, 2007.

Sevestre MA et al.: Outcomes for inpatients with normal findings on whole-leg ultrasonography: a prospective study, *Am J Med* 123:158–165, 2010.

Snow V et al.: Management of venous thromboembolism: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians, *Ann Intern Med* 146:204–210, 2007.

Sweeney J: Venous thromboembolism: duration, IVC filters, and hypercoagulable workup. Medicine & Health, *Rhode Island* 94(4):99–104, 2011.

The CLOTS Trial Collaboration: Thigh-length versus below-knee stockings for deep venous thrombosis prophylaxis after stroke, *Ann Intern Med* 153:553–562, 2010.

The EINSTEIN Investigators: Oral rivaroxaban for symptomatic venous thromboembolism, *N Engl J Med* 363:2499, 2010.

The van Gogh investigators: Idraparinux versus standard therapy for venous thromboembolic disease, *N Engl J Med* 357:1094–1104, 2007.

Ullinjian A et al: Safety and feasibility of a diagnostic algorithm combining clinical probability D-dimer testing and ultrasonography for suspected upper extremity deep venous thrombosis: A prospective management study. *Ann Int Med* 160:451–457, 2014.

Verhovsek M et al.: Systematic review: D-Dimer to predict recurrent disease after stopping anticoagulant therapy for unprovoked venous thromboembolism, *Ann Intern Med* 149:481–490, 2008.

Wells PS et al.: Treatment of venous thromboembolism, *JAMA* 311(7):717–728, 2014.

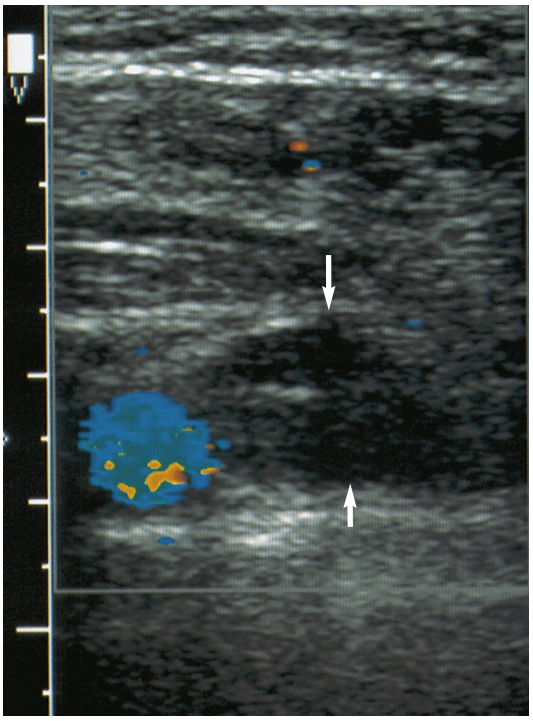
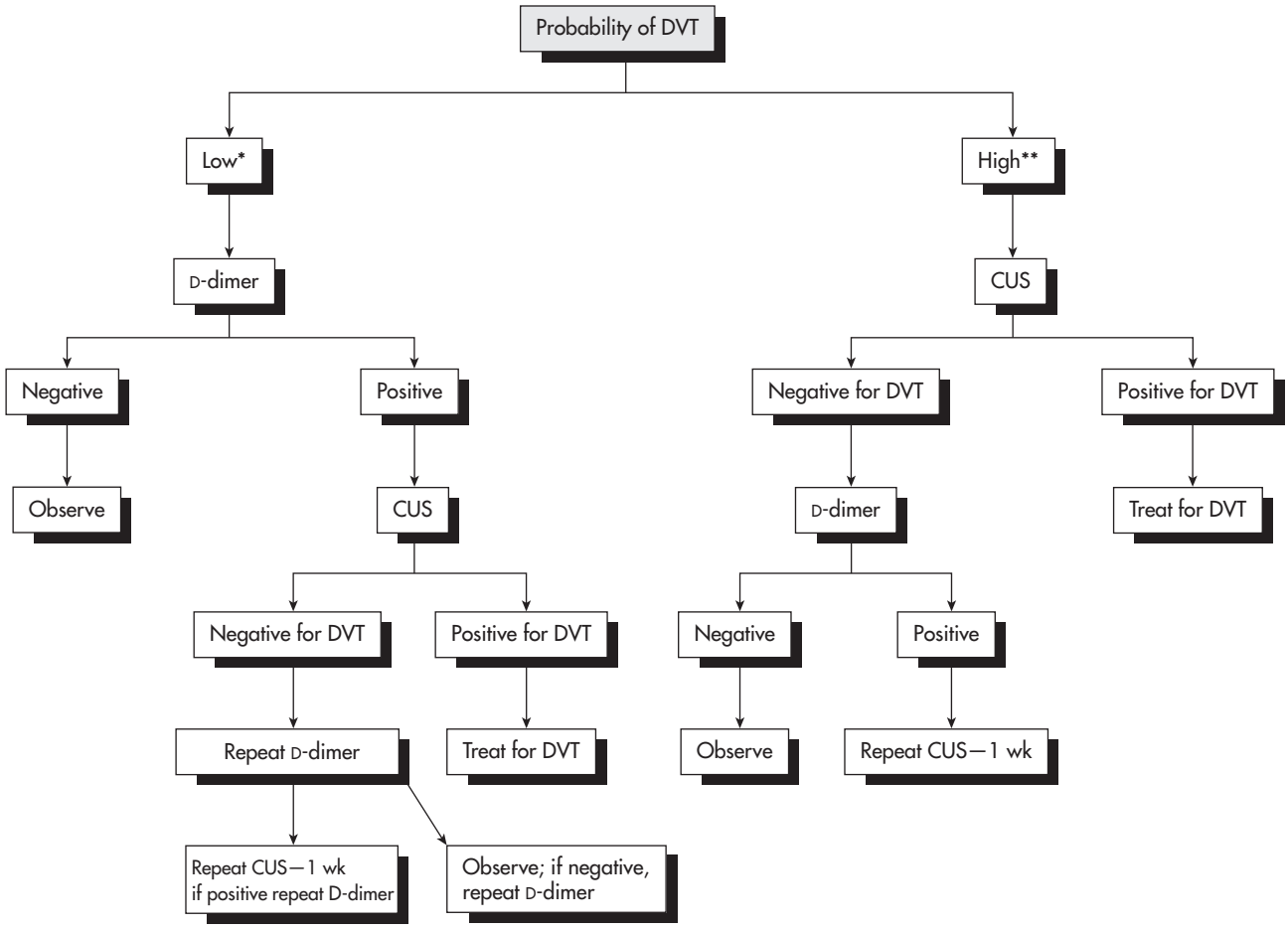


FIGURE ED1-1 Doppler ultrasound appearance of deep vein thrombosis. The superficial femoral vein is filled with echogenic material representing thrombus and no flow can be identified in the vein on Doppler evaluation. Flow can be identified in the adjacent artery on color Doppler evaluation *(arrows)*. (From Crawford MH, DiMarco JP, Paulus WJ [eds.]: *Cardiology*, ed 2, St. Louis, 2004, Mosby.)



*Low probability
None of features of high probability and an alternative diagnosis likely

**High probability
1. History of active cancer
2. History of prolonged immobilization
3. History recent surgery
4. History recent leg trauma
5. Previous history of thromboembolic disease
6. Family history of thromboembolic disease
7. BCP use
8. History recent long travel
9. Exam positive for swelling and tenderness compared to other extremity

FIGURE ED1-2 Diagnostic approach to deep vein thrombosis. *BCP,* Birth control pill; *CUS,* compressive ultrasound; *DVT,* deep vein thrombosis.

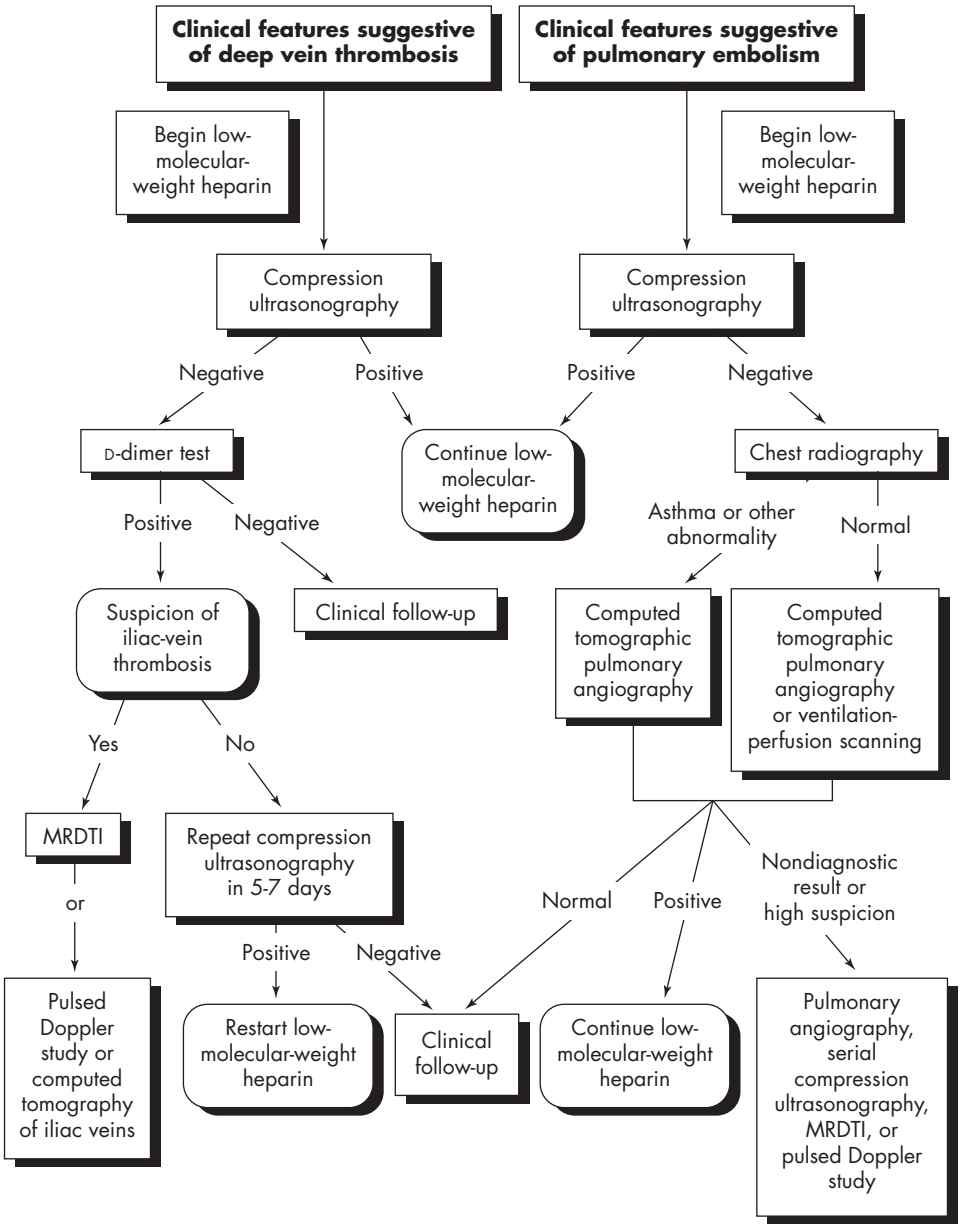


FIGURE ED1-3 Diagnostic algorithm for suspected deep vein thrombosis and pulmonary embolism during pregnancy. If compression ultrasonography was negative, low-molecular-weight heparin was discontinued. *MRDTI,* Magnetic resonance direct thrombus imaging. (From Marik PE, Plante LA: Venous thromboembolic disease and pregnancy, *N Engl J Med* 359:2027, 2008.)

BASIC INFORMATION

DEFINITION

Delayed puberty is clinically defined as the absence of or incomplete development of secondary sexual characteristics by an age at which 95% of the population begins to mature sexually. For girls, a delay is defined as an absence of breast development by age 13 or primary amenorrhea by age 16. For boys, a delay is classified as an absence of testicular enlargement by age 14.

SYNONYMS

Pubertal delay

ICD-9CM CODES
259.0 Delay in sexual development and puberty, not elsewhere classified
ICD-10CM CODES
E30.0 Delayed puberty

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: The actual prevalence and incidence for children presenting with delayed puberty is unknown. Delayed puberty is more common in boys.

GENETICS: Constitutional pubertal delay (CPD) often runs in families. Although specific gene mutations have yet to be identified, studies have shown that 50% to 75% of patients with CPD have at least one parent who experienced a delay in puberty. The inheritance pattern for CPD is thought to be autosomal dominant.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Girls with pubertal delay have an absence of breast development by age 13, absence of menarche by age 16, or absence of menarche within 3 years of thelarche. Boys with pubertal delay show no evidence of testicular enlargement, further defined as testes <2.5 cm, by age 14. Absence of pubic and/or axillary hair is common, as is lack of growth spurt.
- Patients with a constitutional delay in puberty are short in stature with a normal growth rate and otherwise good health.
- Boys often fall below the 10th percentile on a height chart with normal rate of growth between 4 and 6 cm per yr.

ETIOLOGY

Causes for pubertal delay (Fig. D1-4) can be separated into four categories (from most to least common):

1. Constitutional delay, which is a temporary delay in puberty that is seen mostly in boys and is genetic. Patients are typically short in stature with normal growth rate and appropriate skeletal age.
2. Functional hypogonadotropic hypogonadism secondary to malnutrition or chronic disease. Celiac sprue, inflammatory bowel disease (IBD), hypothyroidism, diabetes mellitus, cystic fibrosis, and eating disorders such as anorexia nervosa are examples of illnesses that may cause a temporary, reversible delay in puberty. Clinical suspicion is warranted when underweight children present with pubertal delay.
3. Hypergonadotropic hypogonadism caused by primary gonadal failure. Congenital disorders such as cryptorchidism; chromosomal disorders such as gonadal dysgenesis, Klinefelter's syndrome, and Turner's syndrome; and acquired causes secondary to chemotherapy, pelvic radiation, and gonadal surgery are organic dysfunctions that result in gonadal failure despite adequate hypothalamic-pituitary function. In this group of disorders, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels are elevated yet cannot stimulate ovaries and testicles to produce estrogen and testosterone, respectively, leading to hypogonadism and absence of secondary sex characteristics.
4. Permanent hypogonadotropic hypogonadism secondary to genetic or acquired defects along the hypothalamic-pituitary-gonadal (HPG) axis. Kallmann's syndrome is a genetic mutation in *KAL1* on the X chromosome and is responsible for the migration of gonadotropin-releasing hormone and olfactory neurons into the hypothalamus. Children with Kallmann's syndrome typically present with pubertal delay and anosmia. Other mutations such as *FGFR1* and *DAX1* have been linked to congenital gonadotropin deficiencies and pubertal delay. Acquired defects such as hemochromatosis, sickle cell anemia, and pituitary tumors can cause delayed puberty and other hypothalamic syndromes, including Prader-Willi. Table ED1-1 provides a classification of puberty and sexual infantilism.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Normal or low serum LH and FSH

- Constitutional pubertal delay
- Functional hypogonadotropic hypogonadism
  1. Malnutrition or eating disorder
  2. Strenuous exercise
  3. Chronic illness (e.g., hypothyroidism, celiac disease, IBD, cystic fibrosis)
- Hypopituitarism
  1. Panhypopituitarism
  2. Isolated gonadotropin deficiency
  3. Kallmann's syndrome (associated with anosmia)
  4. Prader-Willi syndrome
- Hyperprolactinemia
  1. Pituitary adenoma
  2. Drug-associated (e.g., cannabis, cocaine)

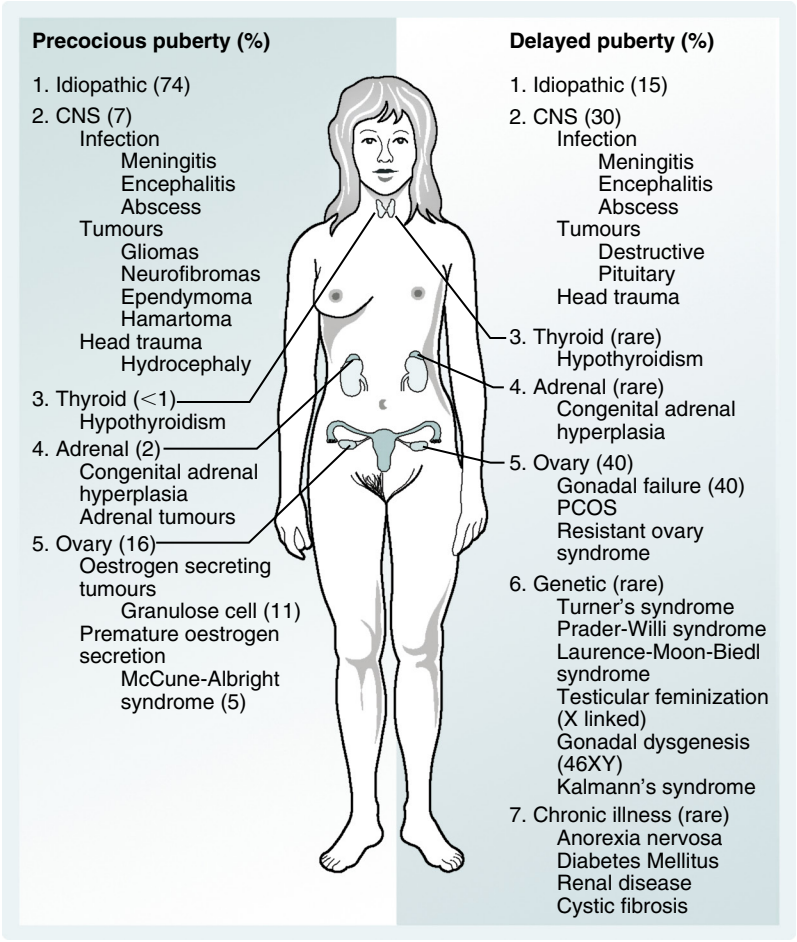


FIGURE D1-4 Causes of precocious puberty and delayed puberty. (From Pariseai M: Gynaecological endocrinology. In, *Obstetrics and Gynaecology*, St. Louis, 2008, Mosby.)

Increased serum gonadotropins
- Hypergonadotropic hypogonadism
  1. Turner's syndrome (gonadal dysgenesis)
  2. Klinefelter's syndrome
  3. Gonadal dysgenesis
  4. Noonan syndrome
  5. Bilateral gonadal failure
     1. Primary testicular failure
     2. Anorchia
     3. Premature ovarian failure
     4. Resistant ovary syndrome
     5. Radiation, chemotherapy
     6. Trauma
     7. Infections (e.g., mumps, orchitis)

Other conditions
- Androgen sensitivity syndrome
- Steroidogenic enzyme defects

WORKUP

- Given the extensive differential diagnosis for pubertal delay, a systematic and focused approach is necessary. Table ED1-2 describes differential diagnostic features of delayed puberty and sexual infantilism. A careful history, including family and social history, can identify eating, exercise habits, chronic illnesses, weight loss, poor weight gain, changes in bowel habits, and parental history of pubertal delay. Figs. D1-5 and D1-6 describe an algorithm for the evaluation of delayed puberty in males and females.
- Growth measurement should include height and weight, a growth chart to assess rate of growth, and calculation of the sex-adjusted midparental height that represents the statistically probable adult height for the child.
  1. For boys, add 2.5 inches (6.5 cm) from the mean of the parents' heights. For girls, subtract 2.5 inches (6.5 cm) from the mean of the parents' heights.
  2. Physical exam can reveal signs of sexual maturation, stigmata of congenital syndromes, and nutritional deficiencies. It is important to include a neurologic (visual fields, ophthalmologic), thyroid, respiratory, cardiovascular, and abdominal examination, in addition to evaluation of the Tanner stages of sexual characteristics.

LABORATORY TESTS

- Serum LH, FSH, testosterone, and estradiol can help distinguish disorders of congenital or acquired gonadal failure from other causes. By the age of 10 to 12 yr gonadal failure produces elevated levels of serum LH and FSH. If levels are low or normal, constitutional delay is the most common diagnosis.
- Chromosomal analysis is indicated if there is a suspicion of gonadal dysgenesis or Klinefelter's syndrome.
- Screening studies include complete blood count, erythrocyte sedimentation rate, prolactin, thyroid-stimulating hormone, and free thyroxine level.
- Endocrinologist may incorporate further studies such as IGF-1 to screen for growth hormone disorders and GnRH stimulation testing.

IMAGING STUDIES

Bone age skeletal radiograph of the left hand and wrist determines skeletal age, which is delayed in constitutional delay and GnRH deficiency. MRI of the head should be considered if there is high clinical suspicion for tumors of pituitary or hypothalamic origin. Pelvic ultrasound can be helpful in detecting intraabdominal testes and evaluating müllerian anatomy.

Rx TREATMENT

- Treat underlying cause.
- Constitutional delay can be managed with reassurance that the delay will have no effect on the final adult height or overall development. Short-term hormonal therapy can be used to hasten puberty if the delay is causing severe psychosocial difficulties. Oxandrolone orally can be given daily or IM depot testosterone q6wk for 3-6 mo for boys to improve velocity of growth. Girls can receive oral estradiol once daily for 3-6 mo.

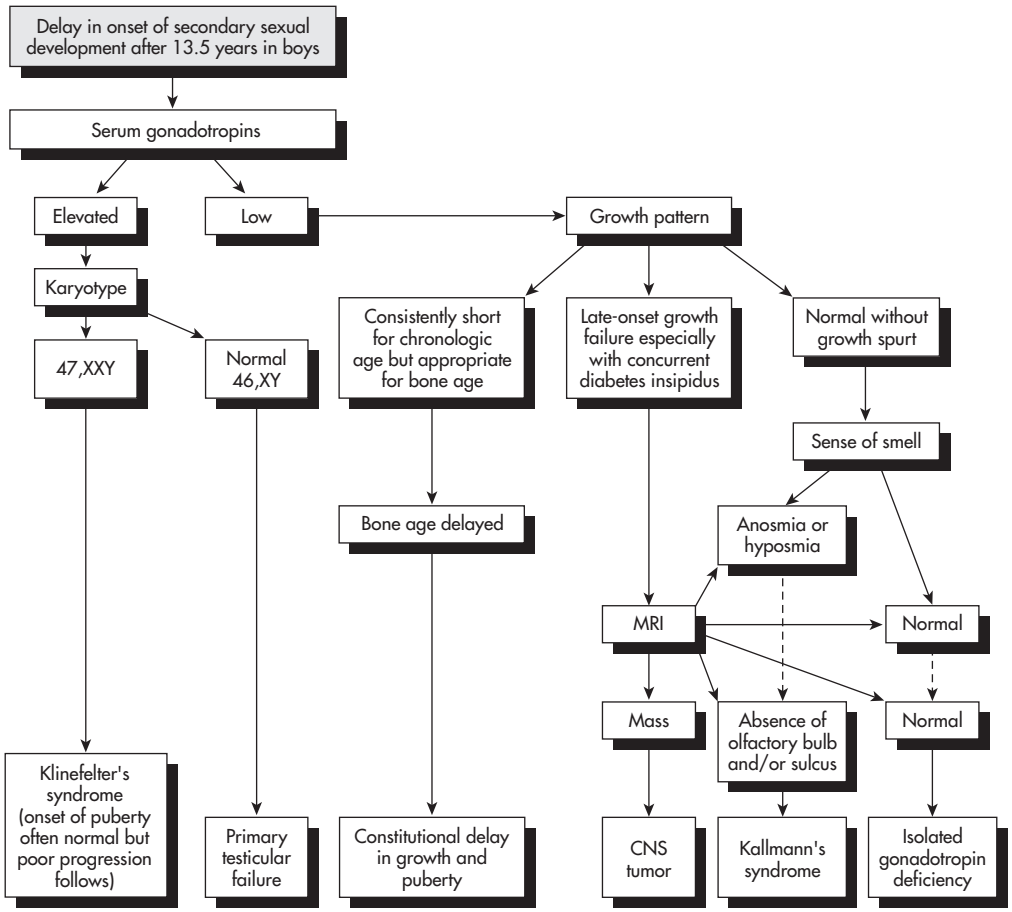


FIGURE D1-5 Flow chart for the evaluation of delayed puberty in boys. (From Melmed S et al: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders)

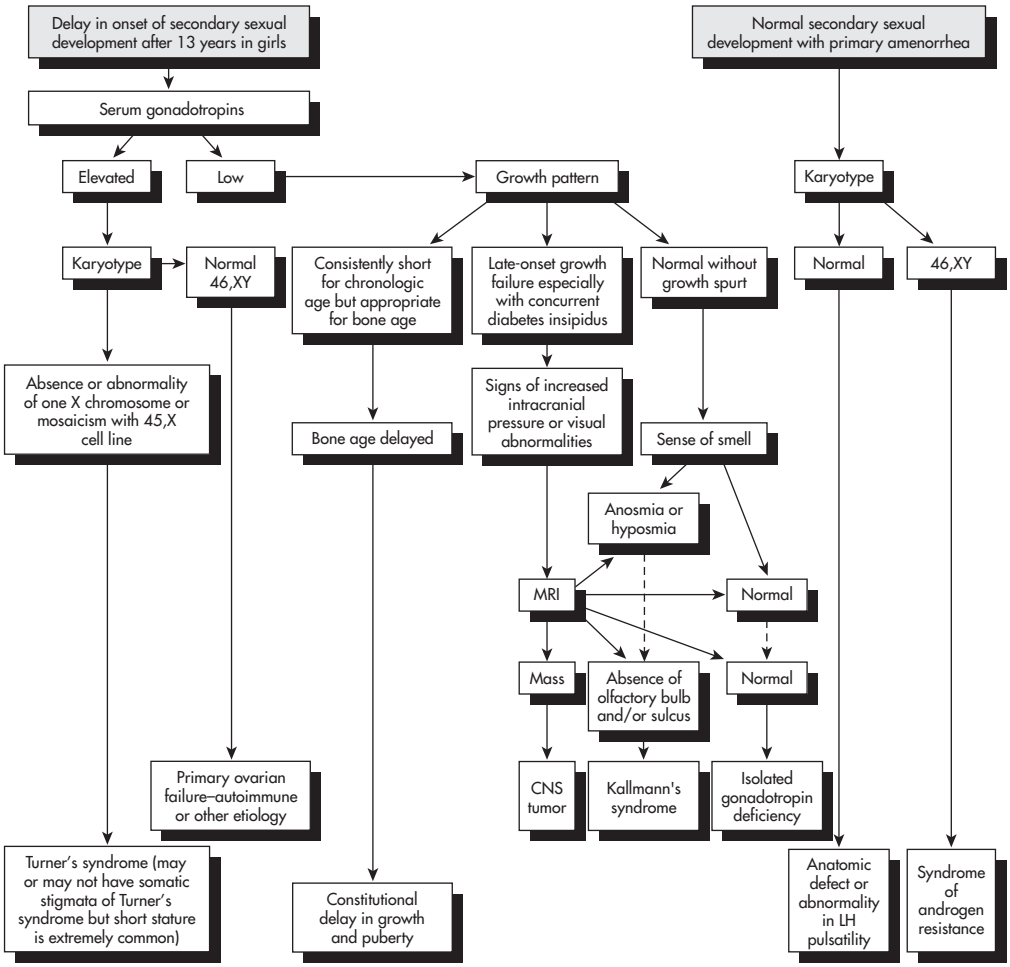


FIGURE D1-6 Flow chart for the evaluation of delayed puberty in girls. (From Melmed S et al: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders)

- Malnutrition and chronic disease can best be treated by correcting the underlying etiology. A short (3-6 mo) treatment course, as described above, may be indicated for children with psychosocial difficulties.
- Permanent causes of pubertal delay can be treated by inducing puberty with testosterone for boys and estrogen plus progesterone for girls.
- Patients with Turner's syndrome will need adjunct growth hormone with or without oxandrolone.
- Gonadotropin deficiency or hypogonadism may require lifelong sex steroid replacement.
- Psychosocial evaluation, support, and treatment as needed.
- Table ED1-3 summarizes the management and treatment of delayed puberty.

REFERRAL

Pediatric endocrinology

PEARLS & CONSIDERATIONS

COMMENTS

- Constitutional delay is the most common cause of pubertal delay and is often associated with a positive family history in parents and/or siblings, but it is a diagnosis of exclusion, so other causes, such as Turner's syndrome and systemic disorders, need to be ruled out first.
- Bone age demonstrates more clearly than chronologic age how far an individual has progressed toward maturity and predicts the potential for further growth.
- No studies reliably differentiate constitutional delay from gonadotropin deficiency.

PATIENT & FAMILY EDUCATION

- The Magic Foundation, a support group for patients and their families (http://www.magicfoundation.org)
- The American Academy of Family Physicians (http://www.aafp.org)
- American Academy of Pediatrics (http://www.aap.org)
- Pediatric Endocrine Society (http://www.lwpes.org)
- Nemours Foundation (kiddshealth.rog/teen/sexual_health/changing_body/puberty)
- www.noonansyndrome.org

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Delayed Puberty (Patient Information)

AUTHORS: **STEPHANIE A. CURRY, M.D.,** and **RACHAEL M. BIANCUZZO, M.D.**

SUGGESTED READINGS

Bakker B et al.: Pubertal development and growth after total-body irradiation and bone marrow transplantation for haematological malignancies, *Eur J Pediatr* 159:31–37, 2000.

Blondell RD et al: Disorders of puberty, Am Fam Physician. Available at http://www.aafp.org/afp/990700ap/209.html. Accessed July 2009.

Harrington J, Palmert MR: Clinical review: Distinguishing constitutional delay of growth and puberty from isolated hypogonadotropic hypogonadism: critical appraisal of available diagnostic tests, *J Clin Endocrinol Metab* 97:3056–3067, 2012.

Lazar L, Phillip M: Pubertal disorders and bone maturation, *Endocrinol Metab Clin North Am* 41(4):805–825, 2012.

Master-Hunter T, Heiman D: Amenorrhea: evaluation and treatment, *Am Fam Physician* 73:1376–1382, 2006.

Mauras N: Strategies for maximizing growth in puberty in children with short stature, *Pediatr Clin North Am* 58(5):1167–1179, 2011.

Palmert MR, Dunkel L: Delayed puberty, *N Engl J Med* 166:443–453, 2012.

Rosen D, Foster C: Delayed puberty, *Pediatr Rev* 27:9, 2001.

Rugarli EI, Ballabio A: Kallmann syndrome: from genetics to neurobiology, *JAMA* 270:2713–2716, 1993.

Sedlmeyer IL, Palmort MR: Delayed puberty: analysis of a large case series from an academic center, *J Clin Endocrinol Metab* 87:1613–1620, 2002.

Segal TY et al.: Role of gonadotropin-releasing hormone and human chorionic gonadotropin stimulation tests in differentiating patients with hypogonadotropic hypogonadism from those with constitutional delay of growth and puberty, *J Clin Endocrinol Metab* 94:780–785, 2009.

TABLE ED1-1 Differential Diagnostic Features of Delayed Puberty and Sexual Infantilism

Condition	Stature	Plasma Gonadotropins	GnRH Test LH Response	Plasma Gonadal Steroids	Plasma DHEAS	Karyotype	Olfaction
Constitutional delay in growth and adolescence	Short for chron. age, usually appropriate for bone age	Prepubertal, later pubertal	Prepubertal, later pubertal	Low, later normal	Low for chron. age, appropriate for bone age	Normal	Normal
Hypogonadotropic Hypogonadism							
Isolated gonadotropin deficiency	Normal, absent pubertal growth spurt	Low	Prepubertal or no response	Low	Appropriate for chron. age	Normal	Normal
Kallmann's syndrome	Normal, absent	Low	Prepubertal or no response	Low	Appropriate for chron. age	Normal	Anosmia; pubertal growth spurt or hyposmia
Idiopathic multiple pituitary hormone deficiencies	Short stature and poor growth since early childhood	Low	Prepubertal or no response	Low	Usually low	Normal	Normal
Hypothalamic-pituitary tumors	Late-onset decrease in growth velocity	Low	Prepubertal or no response	Low	Normal or low for chron. age	Normal	Normal
Primary Gonadal Failure							
Syndrome of gonadal dysgenesis (Turner's syndrome) and variants	Short stature since childhood	High	Hyperresponse for age	Low	Normal for chron. age	45,X or variant	Normal
Klinefelter's syndrome and variants	Normal to tall	High	Hyperresponse at puberty	Low or normal	Normal for chron. age	47,XXY or variant	Normal
Familial XX or XY gonadal dysgenesis	Normal for age	High	Hyperresponse	Low	Normal for chron. age	46,XX or 46,XY	Normal

chron., Chronologic; *DHEAS*, dehydroepiandrosterone sulfate; *GnRH*, gonadotropin-releasing hormone; *LH*, luteinizing hormone.
From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.

TABLE ED1-2 Classification of Delayed Puberty and Sexual Infantilism

Idiopathic (Constitutional) Delay in Growth and Puberty (Delayed Activation of Hypothalamic LRF Pulse Generator)

Hypogonadotropic Hypogonadism: Sexual Infantilism Related to Gonadotropin Deficiency

CNS Disorders

Tumors

- Craniopharyngiomas
- Germinomas
- Other germ cell tumors
- Hypothalamic and optic gliomas
- Astrocytomas
- Pituitary tumors (including MEN-1, prolactinoma)

Other Causes

- Langerhans' histiocytosis
- Postinfectious lesions of the CNS
- Vascular abnormalities of the CNS
- Radiation therapy
- Congenital malformations especially associated with craniofacial anomalies
- Head trauma
- Lymphocytic hypophysitis

Isolated Gonadotropin Deficiency

- Kallmann's syndrome
- With hyposmia or anosmia
- Without anosmia
- LHRH receptor mutation
- Congenital adrenal hypoplasia (*DAX1*mutation)
- Isolated LH deficiency
- Isolated FSH deficiency
- Prohormone convertase 1 deficiency (PCI)

Idiopathic and Genetic Forms of Multiple Pituitary Hormone Deficiencies Including PROP1 Mutation

Miscellaneous Disorders

- Prader-Willi syndrome
- Laurence-Moon and Bardet-Biedl syndromes
- Functional gonadotropin deficiency
- Chronic systemic disease and malnutrition
  1. Sickle cell disease
  2. Cystic fibrosis
  3. Acquired immunodeficiency syndrome (AIDS)
  4. Chronic gastroenteric disease
  5. Chronic renal disease
  6. Malnutrition
  7. Anorexia nervosa
  8. Bulimia
- Psychogenic amenorrhea
- Impaired puberty and delayed menarche in female athletes and ballet dancers (exercise amenorrhea)
- Hypothyroidism
- Diabetes mellitus
- Cushing's disease
- Hyperprolactinemia
- Marijuana use
- Gaucher's disease

Hypergonadotropic Hypogonadism

Males

- The syndrome of seminiferous tubular dysgenesis and its variants (Klinefelter's syndrome)
- Other forms of primary testicular failure
  1. Chemotherapy
  2. Radiation therapy
  3. Testicular steroid biosynthetic defects
  4. Sertoli-only syndrome
  5. LH receptor mutation
  6. Anorchia and cryptorchidism
- Trauma/surgery

Females

- The syndrome of gonadal dysgenesis (Turner's syndrome) and its variants
- XX and XY gonadal dysgenesis
- Familial and sporadic XX gonadal dysgenesis and its variants
- Familial and sporadic XY gonadal dysgenesis and its variants
- Aromatase deficiency
- Other forms of primary ovarian failure
- Premature menopause
- Radiation therapy
- Chemotherapy
- Autoimmune oophoritis
- Galactosemia
- Glycoprotein syndrome type 1
- Resistant ovary
- FSH receptor mutation
- LH/hCG resistance
- Polycystic ovarian disease
- Trauma/surgery
- Noonan's or pseudo-Turner's syndrome
- Ovarian steroid biosynthetic defects

CNS, central nervous system; *hCG*, human chorionic gonadotropin; *LHRH*, luteinizing hormone–releasing hormone; *LRF*, luteinizing hormone–releasing factor; *MEN*, multiple endocrine neoplasia.

From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.

TABLE ED1-3 Management and Treatment of Delayed Puberty

Objective

- Determine site and etiology of abnormality
- Induce and maintain secondary sexual characteristics
- Induce pubertal growth spurt
- Prevent the potential short-term and long-term psychological, personality, and social handicaps of delayed puberty
- Ensure normal libido and potency
- Attain fertility

Therapy

Concerned But Not Anxious or Socially Handicapped Adolescent

- Reassurance and follow-up (tincture of time)
- Repeat evaluation (including serum testosterone or estradiol) in 6 mo

Psychosocial Handicaps, Anxiety, Highly Concerned

Therapy for 4 mo

- *Boys:* testosterone enanthate 100 mg IM q4wk at 14-14.5 yr of age, or overnight transdermal testosterone patch
- *Girls:* ethinyl estradiol 5-10 mg/day PO or conjugated estrogens 0.3 mg/day PO or overnight ethinyl estradiol patch at 13 yr of age

No therapy for 4-6 mo; reevaluate status including serum testosterone or estradiol; if indicated repeat treatment regimen

From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.

BASIC INFORMATION

DEFINITION

The American Psychiatric Association's *Diagnostic and Statistical Manual*, 5th edition (DSM-5) defines delirium as:

- Disturbance of consciousness with reduced ability to focus, sustain, or shift attention.
- The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of a day.
- An additional disturbance in cognition (e.g., memory deficit, disorganization, language, visuospatial ability, or perception).
- A change in cognition or development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.
- There is evidence from history, physical exam, or lab findings that the disturbance is caused by medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.

SYNONYMS

Acute confusional state
Toxic or metabolic encephalopathy

THEORIES REGARDING PATHOPHYSIOLOGY

- Neuroinflammation, with increased permeability of the blood-brain barrier.
- Acetylcholine deficiency.
- Other neurotransmitter imbalances, including excesses of norepinephrine, serotonin, and, most important, dopamine.

CLASSIFICATION

Hyperactive, hypoactive, and mixed subtype.

ICD-9CM CODES
780.09 Delirium
ICD-10CM CODES
F05 Delirium, not induced by alcohol and other psychoactive substances
F05.9 Delirium, unspecified
F06.0 Organic hallucinosis
F05.8 Other delirium
F05.0 Delirium not superimposed on dementia
F05.1 Delirium superimposed on dementia

EPIDEMIOLOGY & DEMOGRAPHICS

Nearly 30% of older patients experience delirium at some time during the hospital course. In old surgical patients, the risk varies from 10% to 50%. Hypoactive is more common. Delirium is the most common mental disorder in patients with medical illness. Any age, race, or gender can be affected. Pediatric delirium is often missed but remains important because delirium is associated with longer hospital stays, decreased cognitive performance, and increased mortality. Risk factors include extremes of age, severe pain, illicit substance use, surgery, dementia, and kidney or liver failure (Tables ED1-4 and D1-5).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- One of the earliest symptoms is change in level of awareness and ability to focus, sustain, or shift attention. Symptoms may differ both among patients and within one patient. Family members or caregivers report that the patient "isn't acting quite right." Symptoms may include poor attention, sleepiness, agitation, or psychosis.
- Acuteness of presentation helps in differentiating delirium with dementia. Change in cognition, perceptual problems (such as visual, auditory, or somatosensory hallucination usually with lack of insight), memory loss, disorientation, difficulty with speech and language. It is important to ascertain from family member or caregivers the patient's level of functioning before onset of delirium.
- Elderly patients with delirium often do not look sick, but patients with delirium are sick by definition.
- There is often a prodrome phase that later blends into hypoactive delirium or erupts into an agitated confusional state.
- Physical examination should be performed, focusing on signs of infection, dehydration, or chronic disease that may be exacerbated. Vital signs are key. Consider using the Mini-Mental Status Exam or the Montreal Cognitive Assessment.
- Fig. ED1-7 describes an algorithm for evaluation of mental status changes in an older patient.

ETIOLOGY

Can be multifactorial; often falls into one of the following categories:

- Drugs: benzodiazepines are the worst offenders, but other drugs such as narcotics, anticholinergics, beta-blockers, steroids, nonsteroidal anti-inflammatory drugs, digoxin, cimetidine can cause delirium; also, withdrawal states such as alcohol withdrawal or benzodiazepine withdrawal can cause delirium.
- Infection or inflammation.
- Metabolic: kidney or liver failure, thyroid, adrenal, or glucose dysregulation, anemia, vitamin deficiency such as Wernicke's encephalopathy or vitamin B_{12} deficiency, inborn metabolic errors such as porphyrias or Wilson's disease.
- Stress: surgery, sleep problems, pain, fever, hypoxia, anesthesia, environmental changes, fecal or urinary retention, burns.
- Fluids, electrolytes, nutrition (FEN): dysregulation of calcium, magnesium, potassium, or sodium; dehydration; volume overload; altered pH.
- Brain disorder: CNS infection, head injury, hypertensive encephalopathy.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Primary psychiatric illness.
- Focal syndromes.
- Dementia.
- Sundowning.
- Nonconvulsive status epilepticus.

Remember, delirium may coexist with any of the above. Table D1-6 describes clinical factors that help differentiate delirium and dementia from psychiatric disease.

LABORATORY TESTS

- Complete blood count, electrolytes, liver function tests, ammonia, drug levels (digoxin, lithium).
- Toxicology screen, urinalysis, urine culture.
- Thyroid function tests, vitamin B_{12}, and folate levels.
- Rapid plasma reagin for syphilis, blood, urine, and spinal fluid culture.
- Arterial blood gas.
- Lumbar puncture is mandatory when cause of delirium is not obvious.

IMAGING STUDIES

- Consider head CT (to look for bleed, trauma, tumor, atrophy, dementia, stroke)
- Chest radiograph (to look for tumor, infection).

TABLE D1-5 Mnemonic for Risk Factors for Delirium and Agitation

IWATCHDEATH	DELIRIUM
Infection	**D**rugs
Withdrawal	**E**lectrolyte and physiologic abnormalities
Acute metabolic	**L**ack of drugs (withdrawal)
Trauma/pain	**I**nfection
Central nervous system pathology	**R**educed sensory input (blindness, deafness)
Hypoxia	**I**ntracranial problems (CVA, meningitis, seizure)
Deficiencies (vitamin B_{12}, thiamine)	**U**rinary retention and fecal impaction
Endocrinopathies (thyroid, adrenal)	**M**yocardial problems (MI, arrhythmia, CHF)
Acute vascular (hypertension, shock)	
Toxins/drugs	
Heavy metals	

CHF, Congestive heart failure; *CVA,* cerebrovascular accident; *MI,* myocardial infarction.
From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

TABLE D1-6 Clinical Factors That Help Differentiate Delirium and Dementia from Psychiatric Disease

Characteristic	Delirium	Dementia	Psychiatric Illness
Symptoms			
Age at onset	<12 or >40 yr	Usually elderly, >50 yr	13-40 yr
Onset	Acute	Gradual or insidious	Gradual
Symptom course	Rapid, fluctuating	Stable and progressive	Stable
Duration	Days to weeks	Months to years	Months to years
Reversibility	Usually	Rarely	Rarely
History			
Past medical history	Substance abuse, medical illness	Comorbid conditions of aging	Previous psychiatric history
Family history	Unusual	History of dementia	History of psychiatric illness
Physical Examination			
Vital signs	Usually abnormal	Usually normal	Usually normal
Involuntary activity	May have tremors, asterixis, etc.	None unless coexistent disease	None
Mental Status			
Affect	Emotional lability	Flat affect with advanced disease	Flat affect
Orientation	Usually impaired	Impaired with advanced disease	Rarely impaired
Attention	Impaired	Slow to focus	Disorganized
Hallucinations	Primarily visual	Rare	Primarily auditory
Speech	Slow, incoherent, dysarthric	Usually coherent	Usually coherent
Consciousness	Decreased to impaired	Normal (clear)	Alert
Intellectual function	Usually impaired	Impaired	Intact

From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

ELECTROENCEPHALOGRAM

- To exclude seizure, confirm diagnosis of metabolic encephalopathy.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- The most important consideration is to keep the patient safe by using a variety of methods, including frequent reorientation.
- A quiet, restful, simplified environment with cues to time and location such as clock or calendar is helpful, as well as consistent staff providing both personal and medical care. If possible, encourage familiar family members and friends to keep the patient company.
- Early mobilization and minimized use of physical restraints (use of physical restraints if necessary to ensure safety).
- Visual and hearing aids for patients with these impairments.

ACUTE GENERAL Rx

- Reverse any treatable cause, such as volume repletion for patients with dehydration, antibiotics for urinary tract infection.
- Haloperidol can be used with caution to control agitation, with doses ranging from 0.25 to 2 mg IM/IV twice daily, repeating the dose every 20 to 30 min until patient has calmed and using lower doses for the elderly.
- Risperidone 0.5 mg twice daily (off-label use, non-FDA approved) can also be used with caution with a slow increase to desired dose, not to exceed 1.0 to 2.0 mg.
- Avoid benzodiazepines and meperidine. Drug toxicity accounts for approximately 30% cases of delirium.

CHRONIC Rx

Delirium is not a chronic condition; if assessing a more long-term mental status change, consider other diagnoses.

DISPOSITION

Requires frequent monitoring often necessitating hospital level of care to ensure safety and assess etiology.

REFERRAL

Consider neurologic or psychiatric consultation if not improved in several days or in complicated cases.

PEARLS & CONSIDERATIONS

COMMENTS

Although benzodiazepines are frequently used in hospitalized patients for sedation and are the mainstay of therapy for alcohol withdrawal, they must be used with caution in the elderly because they can have a paradoxical effect on agitation.

PREVENTION

- Avoid polypharmacy as much as possible.
- Optimize chronic medical conditions.
- Provide frequent reorientation and a soothing environment for high-risk patients (e.g., lights on during the day, off at night; open curtains during the day so patient can see the weather).
- In patients over 70 without dementia, regular exercise has been associated with lower risk for developing delirium, and early return to physical activity can improve outcomes in ill patients.

PATIENT & FAMILY EDUCATION

Inform about the above preventive techniques, especially polypharmacy risks.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Delirium Tremens (Related Key Topic)

AUTHORS: **CRISTINA ANTONIO PACHECO, M.D.,** and **POOJA VERMA, M.D.**

SUGGESTED READINGS

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. ed 4 American Psychiatric Association Press: Washington DC.

Hughes CG et al.: Pathophysiology of acute brain dysfunction: what's the cause of all this confusion? *Curr Opin Crit Care* 18:518, 2012.

Kang JH et al.: Comprehensive approaches to managing delirium in patients with advanced cancer, *Cancer Treat Rev* 39:105, 2013.

Kelly P, Frosch E: Recognition of delirium on pediatric hospital services, *Psychosomatics* 53:446, 2012.

O'Mahany R et al.: Synopsis of the National Institute for Health and Clinical Excellence guideline for prevention of delirium, *Ann Intern Med* 154:746–751, 2011.

TABLE ED1-4 Risk Factors for Agitation and Delirium

Age <70 years	BUN/creatinine ratio ≥18
Transfer from a nursing home	Renal failure, creatinine <2.0 mg/dl
History of depression	Liver disease
History of dementia, stroke, or epilepsy	Congestive heart failure
Alcohol abuse within past month	Cardiogenic or septic shock
Tobacco use	Myocardial infarction
Drug overdose or illicit drug use	Infection
HIV infection	CNS pathology
Psychoactive medications	Urinary retention or fecal impaction
Hypo- or hypernatremia	Tube feeding
Hypo- or hyperglycemia	Rectal or bladder catheters
Hypo- or hyperthyroidism	Physical restraints
Hypothermia or fever	Central line catheters
Hypertension	Malnutrition or vitamin deficiencies
Hypoxia	Procedural complications
Acidosis or alkalosis	Visual or hearing impairment
Pain	Sleep disruption
Fear and anxiety	

BUN, Blood urea nitrogen; *CNS,* central nervous system; *HIV,* human immunodeficiency virus.
From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

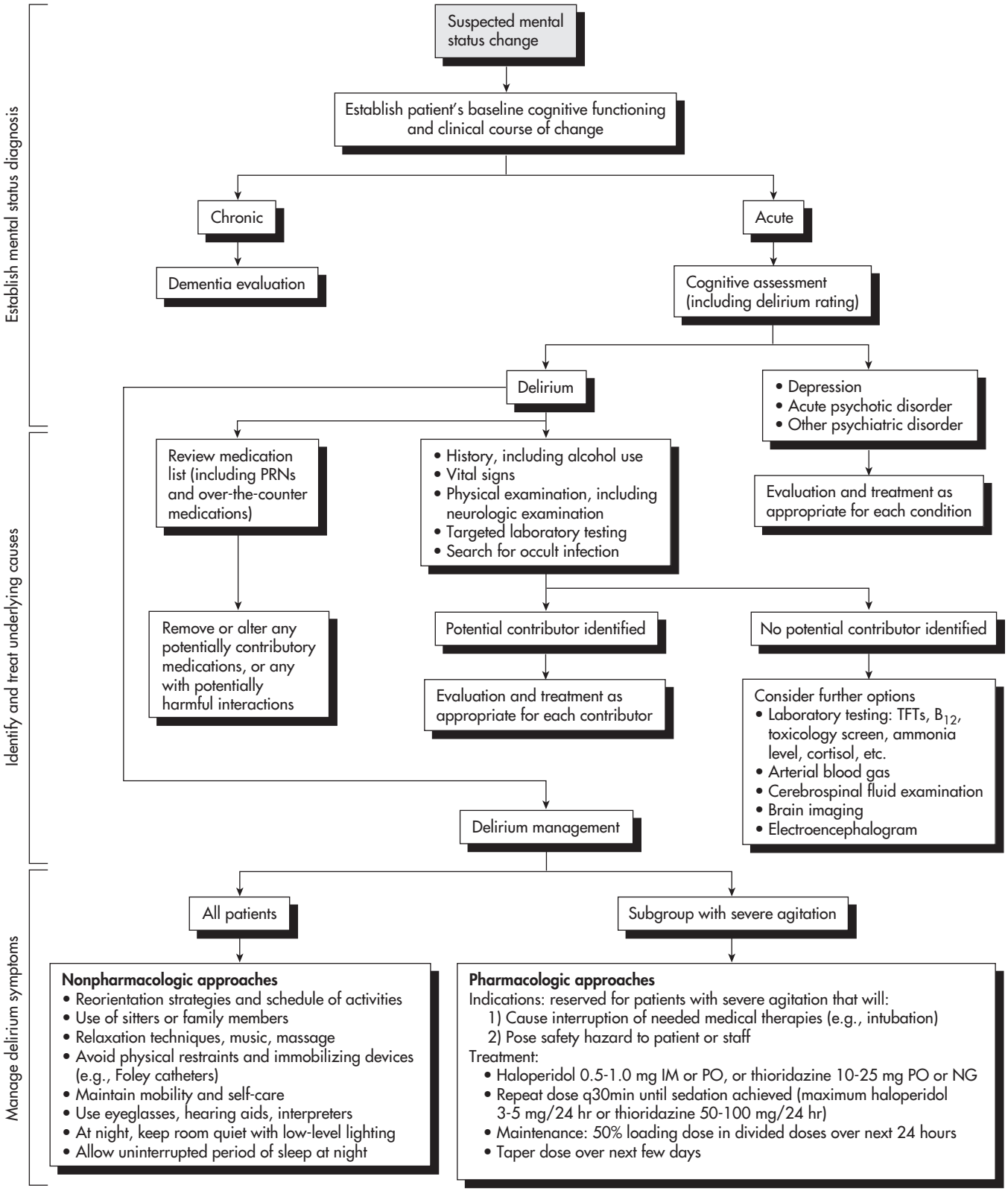


FIGURE ED1-7 Algorithm for evaluation of suspected mental status change in an older patient. *IM,* Intramuscular; *NG,* nasogastric; *PO,* by mouth; *PRN,* as needed; *TFTs,* thyroid function tests. (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

Delirium Tremens PTG

BASIC INFORMATION

DEFINITION

Delirium tremens, also known as withdrawal delirium, is overactivity of the central nervous system after cessation of alcohol intake. The time interval is variable; it usually occurs within 1 wk after reduction or cessation of heavy alcohol intake and persists for 1 to 3 days.

SYNONYMS

Withdrawal delirium
Alcohol withdrawal syndrome
DTs
Alcoholic delirium

ICD-9CM CODES
291.00 Alcohol withdrawal delirium
ICD-10CM CODES
F10.231 Alcohol dependence with withdrawal delirium

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Up to 500,000 cases annually, 3% to 5% of patients who are hospitalized for alcohol withdrawal meet the criteria for withdrawal delirium
PEAK INCIDENCE: 30 yr and older
PREDOMINANT SEX: Male
PEAK AGE: Teenage years and older
GENETICS: More common with patients who have relatives who are alcoholics

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Ethanol withdrawal styptoms usually begin within 8 hours after blood alcohol levels decrease, peak at about 72 hours, and are markedly reduced by days 5-7 of abstinence.
- Initially: anxiety, insomnia, tremulousness
- Early: tachycardia, sweating, anorexia, agitation, headache, gastrointestinal distress
- Late: seizures, visual hallucinations, delirium

ETIOLOGY

Alcoholism

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Coexisting illness.
- Trauma.
- Drug use.

WORKUP

- Frequent rating of symptoms (hallucinations, tremor, sweating, agitation, orientation).
- The Clinical Institute Withdrawal Assessment-Alcohol (CIWA-A) scale can be used to measure the severity of alcohol withdrawal. It consists of the 10 following items:
  1. Nausea.
  2. Tremor.
  3. Autonomic hyperactivity.
  4. Anxiety.
  5. Agitation.
  6. Tactile disturbances.
  7. Visual disturbances.
  8. Auditory disturbances.
  9. Headache.
  10. Disorientation.

  The maximum score is 67. Scores <8 indicate mild symptoms; scores 8-15 indicate moderate withdrawal symptoms; and scores >15 indicate severe withdrawal symptoms.

LABORATORY TESTS

- Electrolytes (including magnesium, phosphate).
- Close monitoring of glucose levels.
- Drug screen (blood and urine).

IMAGING STUDIES

CT scan of head if there is a history of head trauma.

TREATMENT

NONPHARMACOLOGIC THERAPY

Refer to drug rehabilitation program after patient recovers.

ACUTE GENERAL Rx

- Admission to a detoxification unit where patient can be observed closely.
- Vital signs q30min initially (neurologic signs, if necessary).
- Use of lateral decubitus or prone position if restraints are necessary.
- Nothing by mouth: nasogastric tube for abdominal distention may be necessary but should not be routinely used.
- Vigorous hydration (4 to 6 L/day): IV with glucose (Na^+, K^+, PO_4^{-3}, and Mg^{2+} replacement). May be necessary in some patients but commonly there is little support for routine administration of magnesium. Use vigorous hydration with caution in patients with CHF.
- Vitamins: thiamine 500 mg infused IV over the course of 30 minutes daily for 3 days. The initial dose of thiamine should precede the administration of IV dextrose; multivitamins (may be added to the hydrating solution).
- Sedation (sedation can be achieved using fixed-dose regimen or individualized benzodiazepine administration [see CIWA-Ar score] in Alcohol-Related Disorders):
  1. Initially: lorazepam 8 mg IM/IV every 15 minutes as needed, after the patient has received 16 mg. If delirium is still severe, administer an 8 mg bolus IV, then administer 10-30 mg/hr.[1]
  2. Maintenance (individualized dosage): chlordiazepoxide, 50 to 100 mg PO q4 to 6h, lorazepam 2 mg PO q4h, or diazepam 5 to 10 mg PO tid; withhold doses or decrease subsequent doses if signs of oversedation are apparent.
  3. Midazolam is also effective for managing DTs. Its rapid onset (sedation within 2 to 4 min of IV injection) and short duration of action (approximately 30 min) make it an ideal agent for titration in continuous infusion.
- In addition to benzodiazepines, administer medications such as the antipsychotic agent haloperidol for uncontrolled agitation or hallucinations (0.5-5 mg IV/IM every 30-60 minutes as needed for severe agitation or hallucinations, not to exceed 20 mg.
- Treatment of seizures: diazepam 2.5 mg/min IV until seizure is controlled (check for respiratory depression or hypotension) may be beneficial for prolonged seizure activity; IV lorazepam 1 to 2 mg q2h can be used in place of diazepam. In general, withdrawal seizures are self-limited and treatment is not required; the use of phenytoin or other anticonvulsants for short-term treatment of alcohol withdrawal seizures is not recommended.
- Diagnosis and treatment of concomitant medical, surgical, or psychiatric conditions.

CHRONIC Rx

Alcoholics Anonymous has the best record in breaking addiction, but the results are still disappointing.

DISPOSITION

Refer to drug rehabilitation program.

REFERRAL

If cardiac arrhythmias are prominent or respiratory distress develops.

PEARLS & CONSIDERATIONS

COMMENTS

- This is a potentially lethal disease if not carefully treated. Mortality rate is 15% in untreated patients, and approximately 1% to 6% of hospitalized patients who have withdrawal delirium die.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Delirium Tremens (Patient Information)
Alcoholism (Related Key Topic)
Delirium (Related Key Topic)
Wernicke's Syndrome (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

[1]Schuckit MA: Recognition and management of withdrawal delirium (delirium tremens). *N Engl J Med* 371:2109-2113, 2014.

SUGGESTED READING

Kosten TR, O'Connor PG: Management of drug and alcohol withdrawal, *N Engl J Med* 348:1786, 2003.

Schuckit MA: Recognition and management of withdrawal delirium (delirium tremons). *N Engl J Med* 371:1786-2113, 2014.

BASIC INFORMATION

DEFINITION

A fixed belief characterized by a person's preoccupation that his or her skin is infested by insects, worms, or other living organisms.

SYNONYMS

Ekbom syndrome
Morgellon's disease

ICD-9CM and DSM-5 CODES
297.1
ICD-10CM CODES
F22.0 Delusional disorder

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Unknown
PEAK INCIDENCE: Occurs more often later in life
PREVALENCE: Unknown
PREDOMINANT SEX AND AGE: For patients less than age 50, the male/female ratio is 1:1; for patients older than 50, females predominate by a ratio of 3:1
GENETICS: Unknown
RISK FACTORS: None known

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients complain of living organisms infesting their skin, sometimes including mucosal tissues.
- Patients have often been to specialists, including dermatologists, allergists, and infectious disease specialists.
- Patients may bring in samples of skin or hair, stating that they have looked at tissue under a microscope and have seen organisms. These samples are often brought in a matchbox ("matchbox sign") or wrapped in plastic wrap ("Saran sign"). This is generally called the "specimen sign."
- Skin may show areas of excoriation.

ETIOLOGY

Unknown: Thought to be mediated through dopaminergic pathways in the brain given the known etiology of other psychotic disorders and the ability of cocaine use to create symptoms of formication (see below).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Primary psychiatric disorders include formication, in which patients experience crawling and biting sensations on their skin, although they are not delusional about the cause.
- Substance abuse should be considered: case reports exist of cocaine and amphetamine use leading to these delusions.
- Neuropsychiatrically, B_{12} deficiency, diabetic neuropathy, cardiovascular disease, multiple sclerosis, hyperthyroidism, and brain lesions can all cause similar delusions.
- Other medical causes that deserve workup include primary skin lesions, systemic diseases that may present with skin lesions, and disorders of infestation.

WORKUP

- Skin biopsy may exclude dermatitis herpetiformis (although many patients have already been to their primary care doctor and dermatologist and have had a skin biopsy done, likely many times).
- Mineral oil preparation may exclude scabies, and a microscopic examination may exclude louse infestation.
- Thorough history is likely to yield the very fixed nature of the belief and an unwillingness to come to terms with the lack of findings on the exam.

LABORATORY TESTS

- Pruritus workup: iron studies, LFTs, CBC, UA, TSH, Chem 7, Folate, B_{12}
- Lumbar puncture (especially when multiple sclerosis is highly suspected)
- CRP (especially when an infectious etiology is suspected)
- Urine toxicology screen to evaluate substance use

IMAGING STUDIES

- Head CT, without contrast
- MRI

TREATMENT

- Antipsychotics have been shown to lead to full to partial remission in 60% to 100% of cases.
- Classically, Orap was the treatment of choice, although it has been associated with QTc prolongation.
- Multiple studies describe the use of second-generation antipsychotics, but these have been shown to cause weight gain and metabolic syndrome.
- Numerous antipsychotics have a black box warning about the risk of sudden death in the elderly and must be administered carefully for patients who have issues with QTc.
- Given all of these issues, a careful risk/benefit analysis is needed, including the assistance of family members of elderly patients.

NONPHARMACOLOGIC THERAPY

- Given the fixed nature of the belief, patients often refuse referral to a mental health specialist.
- A treatment (e.g., permethrin) should not be recommended "just in case" because it may reinforce the patient's belief.
- Repeat visits with medical providers may be helpful to provide assurance and prevent harm from further workup.

ACUTE GENERAL Rx

Antipsychotics (Table D1-7)

COMPLEMENTARY & ALTERNATIVE MEDICINE

There is no evidence on the use of complementary or alternative medicine for this disorder.

REFERRAL

Referral to an outpatient psychiatrist may be helpful, but patients are often resistant.

PREVENTION

No preventive measures have been identified.

PATIENT/FAMILY EDUCATION

Psychoeducation may be helpful for the patient and family, although resistance from the patient can be expected.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Alcohol-Related Disorders (Related Key Topic)
Cocaine Overdose (Related Key Topic)
Delirium (Related Key Topic)
Schizophrenia (Related Key Topic)

AUTHOR: **ANTHONY GALLO, M.D.**

TABLE D1-7 Antipsychotics

Antipsychotic Drug	Dosage
Haloperidol	0.5-10 mg PO bid
Pimozide	2-12 mg PO qam
Perphenazine	4-16 mg PO tid
Olanzapine	2.5-10 mg PO bid
Aripiprazole	2.5-20 mg PO qam
Quetiapine	12.5-200 mg PO bid
Ziprasidone	20-80 mg PO bid
Risperidone	0.5-3 mg PO bid

SUGGESTED READINGS

Stanciu C et al.: Delusional infestation following misuse of prescription stimulants. Psychosomatics. In Press.

Kaplan H, Sadock B. Comprehensive textbook of clinical psychiatry. Williams & Wilkins: Baltimore.

Lepping P et al.: Antipsychotic treatment of primarily delusional parasitosis, *Br J Psychiatry* 191:198–205, 2007.

Dementia with Lewy Bodies EBM

BASIC INFORMATION

DEFINITION

A neurodegenerative disease characterized by dementia concurrent with or preceding parkinsonian symptoms typically by 1 yr with other core features including fluctuations in attention and alertness and recurrent visual hallucinations. Diagnostic criteria for dementia syndrome associated with Lewy body pathology are described in Box D1-2. The disease characteristically responds to cholinesterase inhibitors, is relatively unresponsive to L-dopa, and is very sensitive to neuroleptics.

SYNONYMS

Lewy body dementia
Diffuse Lewy body disease
Lewy body type senile dementia
Cortical Lewy body disease

ICD-9CM CODES
Lewy bodies
331.82 [294.11] with behavioral disturbance
331.82 [294.10] without behavioral disturbance
ICD-10CM CODES
G31.83 Dementia with Lewy bodies

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Accounts for 10% to 22% of all dementias.
PEAK INCIDENCE: Affects individuals in their sixth decade or older.
PREVALENCE: Estimated 0.7% of individuals older than age 65.
PREDOMINANT SEX AND AGE
- Sex: Male predominance
- Mean age of onset: 75 yr. On average, 10 yr greater for dementia with Lewy bodies (DLB) than Parkinson's disease (PD).

GENETICS
- Most cases are sporadic with a discordance among monozygotic twins, which suggests that environment or other epigenetics play a major role in the incidence of DLB.
- Multiplication of alpha-synuclein gene (SNCA) has been reported in families with DLB.
- Other factors include glucocerebrosidase genetic mutations, high prevalence of Lewy bodies with presenilin-1 mutations, and polymorphisms of the coding region for the synuclein genes.

RISK FACTORS
- Male sex
- Advanced age

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Importance of recognizing DLB relates to its pharmacologic management, including responsiveness to cholinesterase inhibitors, sensitivity to side effects of neuroleptics, and relative unresponsiveness to L-dopa.
- Insidious onset of dementia with core features of fluctuations in cognition, recurrent visual hallucinations, and extrapyramidal motor symptoms, along with other features either suggestive or supportive of the clinical diagnosis. Refer to "Revised Criteria for the Clinical Diagnosis of Dementia with Lewy Bodies" (McKeith I et al, *Neurology,* 2005).
- Detailed neuropsychological assessment demonstrates a characteristic profile of impairments in visuoperceptual, attentional, and executive functions, which reflects a combination of cortical and subcortical damage.

ETIOLOGY

- SNCA is a protein normally found at the synapse with a role in vesicle production. In its insoluble form, SNCA aggregates into Lewy bodies found at the cortical and subcortical levels.
- Lewy bodies (Fig. D1-8) are round, eosinophilic, intracytoplasmic inclusions in the nuclei of neurons.
- Cortical Lewy bodies are found in deep cortical layers of the anterior frontal and temporal lobes, the cingulate gyrus, and insula.
- As in PD, Lewy bodies aggregate in the following structures: substantia nigra, locus coeruleus, raphe nuclei, nucleus basalis of Meynert, and brainstem nuclei.
- Figure D1-9 shows the relationships among the subtypes of dementia.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Similar to Parkinson's disease with dementia, including fluctuation in neuropsychological function, neuropsychiatric features, and extrapyramidal motor features
- Diagnosis of DLB when dementia occurs before or concurrently with extrapyramidal features—arbitrarily set as the "1-yr rule" vs. Parkinson's disease with dementia, which occurs after 1 yr
- Dementia: Alzheimer's disease (AD), vascular dementia
- Parkinsonian features: progressive supranuclear palsy, multisystem atrophy, corticobasal degeneration
- Rapidly progressive form: Creutzfeldt-Jakob disease. Lack of cerebellar signs may help distinguish DLB from classic CJD (but not variant form of CJD)
- Psychiatric features: late-onset psychosis or depression with psychotic features
- Hallucinations with fluctuations in consciousness: temporal lobe epilepsy (TLE)

WORKUP

- Lumbar puncture to rule out underlying chronic infections. Protein 14-3-3 may be present in both DLB and CJD.
- EEG to rule out potential TLE. However, either DLB or TLE may show nonspecific slowing or periodic complexes.

LABORATORY TESTS

- Rule out other potential reversible causes for dementia including:
  1. Hormonal dysregulation: thyroid stimulating hormone, free thyroxine
  2. Vitamin deficiency: thiamine, cyanocobalamin, folate

BOX D1-2 Diagnostic Criteria for the Dementia Syndrome Associated with Lewy Body Pathology

The cognitive disturbance is of insidious onset and is progressive, based on evidence from the history or serial cognitive examination
The presence of at least two of the following:
- Parkinsonism (rigidity, resting tremor, bradykinesia, postural instability, parkinsonian gait disorder)
- Prominent, fully formed visual hallucinations
- Substantial fluctuations in alertness or cognition
- Rapid eye movement sleep behavior disorder
- Severe worsening of parkinsonism by antipsychotic drugs

The disturbance is not better accounted for by a systemic disease or another brain disease

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

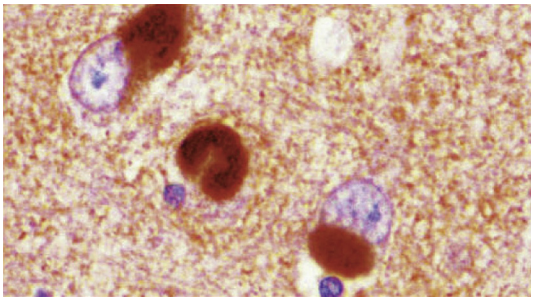


FIGURE D1-8 Cortical Lewy bodies present in cerebral cortex, as opposed to Parkinson's disease without dementia, in which Lewy bodies are found in the substantia nigra. Immunostain for Alpha synuclein is characteristic for Lewy body immunohistological profile. (From MacDonald, AB: Spirochetal cyst forms in neurodegenerative disorders, hiding in plain sight. *Medical Hypotheses* 67(4) 819–832, 2006.)

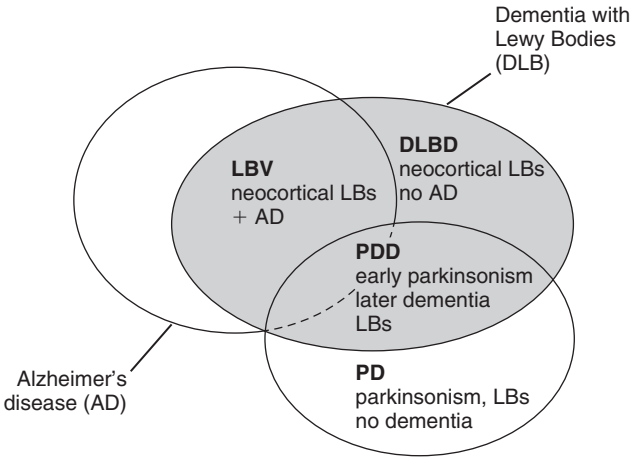


FIGURE D1-9 Relationships among Alzheimer's disease (AD), the three subtypes of dementia with Lewy bodies (DLB), and Parkinson's disease (PD). Parkinsonism refers to the clinical symptoms of PD (hypokinesia, tremor, and muscular rigidity). *LBV*, Lewy body variant of Alzheimer's disease; *DLBD*, diffuse Lewy body disease; *PD*, Parkinson's disease; *PDD*, Parkinson's disease dementia; *LBs*, Lewy bodies. (From Lewis, KA et al: Abnormal neurites containing C-terminally truncated α-synuclein are present in Alzheimer's disease without conventional Lewy body pathology. *The American Journal of Pathology* 177(6) 3037–3050, 2010.)

3. Vascular risk factors: lipid profile, Hgb A_{1c}, homocysteine, syphilis (FTA-ABS), or ApoE genotype

IMAGING STUDIES

- MRI typically shows a relative preservation of the hippocampi and medial temporal lobe volumes (as found in AD) but generalized atrophy and white matter changes.
- Functional imaging including single photon emission computed tomography (SPECT) demonstrates hypoperfusion of the occipital region.

Rx TREATMENT

Patient and caregiver education on benefits, side effects, and limitations of treatment is very important. Based on the preference of the patient and caregiver, a fine balance between psychosis and Parkinsonism features confounds the treatment choices.

NONPHARMACOLOGIC THERAPY

- Social interaction and environmental novelty may improve cognitive dysfunction and psychiatric features often exacerbated by low levels of arousal and attention.
- Behavioral methods, such as avoiding previously exposed environmental triggers known to cause anxiety, agitation, or aggression.
- Physical therapy, mobility aids, and daily exercise.

ACUTE GENERAL Rx

Neuroleptic for disabling, persistent psychotic features despite initiation of a cholinesterase inhibitor. A very low dose of an atypical antipsychotic (quetiapine 12.5 mg daily) may be started after patient/caregiver education regarding the sensitivity to neuroleptics.

CHRONIC Rx

- Cholinesterase inhibitors for cognitive and behavioral symptoms. Rivastigmine (6 to 12 mg per day orally or 9.5 mg per day by transdermal patch) has shown in RCT a significant reduction in anxiety, delusions, and hallucinations, as well as significantly improved performance on neuropsychological testing.
- Antiparkinson medications for disabling parkinsonian features. L-Dopa is reported to be more effective with fewer side effects than dopamine agonists. Begin at a low dose of L-dopa (25/100 mg tid), and slowly titrate over several weeks as tolerated and according to response.
- Selective serotonin reuptake inhibitors are commonly used for depression.
- If REM sleep disorder remains disabling (or patient has not responded to an atypical antipsychotic initiated for psychosis), a trial of low-dose clonazepam (0.25 to 0.5 mg) or melatonin (3 mg) at bedtime remains an option.
- Orthostatic hypotension may be aided by nonpharmacologic therapy, such as supportive stockings, or pharmacologically by midodrine and/or fludrocortisone.
- Memantine demonstrated an improvement in clinical global measure and remains well tolerated but may worsen hallucinations or delusions.
- Avoid anticholinergics (including tricyclic antidepressants) and benzodiazepines.

DISPOSITION

- Survival resembles the progression of AD, but a minority of cases may have a rapid disease course.
- Progression in cognitive decline, similar to AD, by an approximate 10% per year on cognitive testing.

REFERRAL

DLB requires a multidisciplinary approach including the general practitioner, neurologist, neuropsychologist, and/or neuropsychiatrist.

PEARLS & CONSIDERATIONS

COMMENTS

- Clinical presentation helps differentiate DLB from AD. AD presents with early signs of anterograde episodic memory loss without the benefit of recognition on neuropsychological testing due to cortical atrophy at the medial temporal lobe region.
- Vascular dementia may also present with evidence of frontal-subcortical features but typically without the core features listed in the criteria above.
- Bed partners may report that individuals with DLB "act out their dreams," sometimes violently, leading to sleeping in separate beds. A history of REM sleep behavior may precede the diagnosis by many years.

PATIENT/FAMILY EDUCATION

- Visual hallucinations (VH) typically consist of innocuous, well-formed, detailed images of animate figures. Unless VH lead to a potential threat to self or others, avoid antipsychotics due to the sensitivity of neuroleptics. Family/friends are often more alarmed by the VH than the patient with DLB.
- Apathy is a common clinical feature of DLB and mimics changes in mood, including depression, or excessive daytime somnolence. These features are often noticed by family/friends.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **D. BRANDON BURTIS, D.O.,** and **GLEN FINNEY, M.D.**

EVIDENCE

Abstract[1]

Objective:

To assess the ability of 5 cerebrospinal fluid (CSF) biomarkers to differentiate between common dementia and parkinsonian disorders.

Design:

A cross-sectional, clinic-based study.

Participants:

Cerebrospinal fluid samples (N = 453) were obtained from healthy individuals serving as controls and from patients with Parkinson disease (PD), PD with dementia (PDD), dementia with Lewy bodies (DLB), Alzheimer disease (AD), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), or corticobasal degeneration (CBD).

Setting:

Neurology and memory disorder clinics.

Main Outcome Measures:

Cerebrospinal fluid biomarker levels in relation to clinical diagnosis.

Results:

Cerebrospinal fluid levels of α-synuclein were decreased in patients with PD, PDD, DLB, and MSA but increased in patients with AD. Cerebrospinal fluid levels of β-amyloid 1-42 were decreased in DLB and even further decreased in AD. Cerebrospinal fluid levels of total tau and hyperphosphorylated tau were increased in AD. Multivariate analysis revealed that these biomarkers could differentiate AD from DLB and PDD with an area under the curve of 0.90, with α-synuclein and total tau contributing most to the model. Cerebrospinal fluid levels of neurofilament light chain were substantially increased in atypical parkinsonian disorders (ie, PSP, MSA, and CBD), and multivariate analysis revealed that the level of neurofilament light chain alone could differentiate PD from atypical parkinsonian disorders, with an area under the curve of 0.93.

Conclusions:

Ascertainment of the α-synuclein level in CSF somewhat improves the differential diagnosis of AD vs DLB and PDD when combined with established AD biomarkers. The level of neurofilament light chain alone may differentiate PD from atypical parkinsonian disorders. Ⓐ

Evidence-Based Reference

Hall S et al.: Accuracy of a panel of 5 cerebrospinal fluid biomarkers in the differential diagnosis of patients with dementia and/or parkinsonian disorders, *Arch Neurol* 69:1445–1452, 2012. Ⓐ

SUGGESTED READINGS

Aarsland D et al.: Marked neuroleptic sensitivity in dementia with Lewy bodies and Parkinson's disease, *J Clin Psychiatry* 66:633–637, 2005.

Barber R et al.: MRI volumetric study of dementia with Lewy bodies: a comparison with AD and vascular dementia, *Neurology* 54:1304, 2000.

Hofer A et al.: The role of alpha-synuclein gene multiplications in early-onset Parkinson's disease and dementia with Lewy bodies, *J Neural Transm* 112:1249, 2005.

McKeith I. Pharmacologic management of DLB. In: (O'Brien J et al, editor:) Dementia with Lewy bodies. Dunitz: London, pp. 183–192.

McKeith I.. Dementia with Lewy bodies and Parkinson's disease dementia. In: (Growdon J et al, editor:) The dementias 2. Butterworth Heinemann: Philadelphia, pp. 216–238.

McKeith I et al.: Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium, *Neurology* 65:1863, 2005.

McKeith I et al.: Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study, *Lancet* 356:2031, 2000.

Molloy S et al.: The role of levodopa in the management of dementia with Lewy bodies, *J Neurol Neurosurg Psychiatry* 76:1200, 2005.

O'Brien KK et al.: Regulation of attention and response to therapy in dementia by butyrylcholinesterase, *Pharmacogenetics* 13:231, 2003.

BASIC INFORMATION

DEFINITION

Dengue fever (DF) is an infectious disease endemic in most tropical and subtropical countries (Fig. ED1-10). It may be the most widespread arboviral illness worldwide. The causative agent is the dengue virus, a single positive-stranded RNA virus of the Flaviviridae family, which has four distinct but closely related serotypes (DEN-1, DEN-2, DEN-3, DEN-4). Dengue virus is transmitted by the *Aedes* mosquito. The primary vector is *Aedes aegypti*; the secondary vector is *Aedes albopictus*. Box ED1-3 describes the World Health Organization case classification of dengue.

SYNONYMS

Classic dengue fever
Dengue
Dengue hemorrhagic fever
Dengue shock syndrome

ICD-9CM CODES
061 Dengue
065.4 Mosquito-borne hemorrhagic fever
ICD-10CM CODES
A90 Dengue fever [classical dengue]
A91 Dengue hemorrhagic fever

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Attack rates during epidemics range from 1 to 10/1000 per year and as high as 292/1000 among children in hyperendemic countries. 30-fold increased incidence over the past 30 yr. Fig. ED1-11 illustrates the number of cases of dengue fever and hemorrhagic fever in the United States in 2010.

PREVALENCE: Worldwide, 50 to 100 million dengue infections are diagnosed yearly. Dengue shows cyclical variation with large outbreaks every 3 to 5 yr. DF is confirmed in up to 8% of febrile travelers returning from the tropics.

RISK FACTORS: Travel to endemic regions. Few locally acquired U.S. cases have been documented in Texas, Hawaii, and Florida (see Fig. ED1-11). The majority of indigenous cases presented as uncomplicated fever and a minor percentage developed dengue hemorrhage fever (DHF) or dengue shock syndrome (DSS). Local transmission has also been reported in recent years in Europe (Southern France, Croatia, and Portugal).

ETIOLOGY

After bite by infected mosquito, the virus replicates in regional lymph nodes, then spreads by blood and the lymphatic system to other tissues. Incubation period is typically 4 to 7 days (range, 3 to 14 days). Most important risk factors for development of severe disease (DHF/DSS) are young age, female sex, prior infection, and viral genotype. Majority of DHF/DSS cases occur during secondary heterologous (different from first exposure) infection, or during primary infection in infants born to dengue-immune mothers. In such cases, non-neutralizing cross-reactive antibodies facilitate viral entry into cells generating higher viral burdens and stronger inflammatory responses. Additionally, T memory cells from a previous infection are preferentially expanded due to a lower threshold of activation compared with naïve T cells of higher affinity to the current serotype. This results in suboptimal clearance of the virus and quicker, more robust cytokine production leading to increased vascular permeability and plasma leakage. "Asian" genotypes DEN-2 and DEN-3 are associated with severe disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Clinical presentation ranges from asymptomatic infection to shock syndrome.

Symptomatic DF infection can be classified into three categories:

1. Undifferentiated fever
2. Classic DF: characterized by acute febrile illness accompanied by symptoms such as headache, retroorbital pain, fatigue, mild respiratory and gastrointestinal symptoms, and myalgias/arthralgias ("break bone fever"); DF usually follows an incubation period of 3 to 14 days and fever typically lasts 5 to 7 days; physical findings may include a maculopapular rash (Fig. ED1-12), lymphadenopathy, pharyngeal erythema, and injected conjunctivae; some patients may experience development of hemorrhagic manifestations with petechiae, purpura (Fig. ED1-13), and rarely, epistaxis, gum bleeding, and gastrointestinal bleeding; during pregnancy, DF has been associated with increased risk for premature labor and birth, uterine hemorrhage, intrautero death, neonatal death, and maternofetal transmission
3. DHF/DSS: occurs in less than 3% of infected individuals; early course is similar to presentation of classic dengue, but 4 to 7 days after onset of illness, plasma leakage with hemorrhagic manifestations develops resulting in hypoproteinemia, peripheral edema, ascites, pleural and cardiac effusions, and is suggested by a hematocrit increase of 20% during course of illness; thrombocytopenia is also a hallmark, with resultant clinical manifestations such as petechiae, ecchymosis, mucosal hemorrhage, and GI bleeding; may progress to DSS with circulatory collapse, manifested by rapid/weak pulse, profound hypotension, and pulse pressure of <20 mm Hg; warning signs for DHF/DSS include mucosal bleed, abdominal pain, persistent vomiting, abrupt defervescence, change in mental status, and respiratory distress

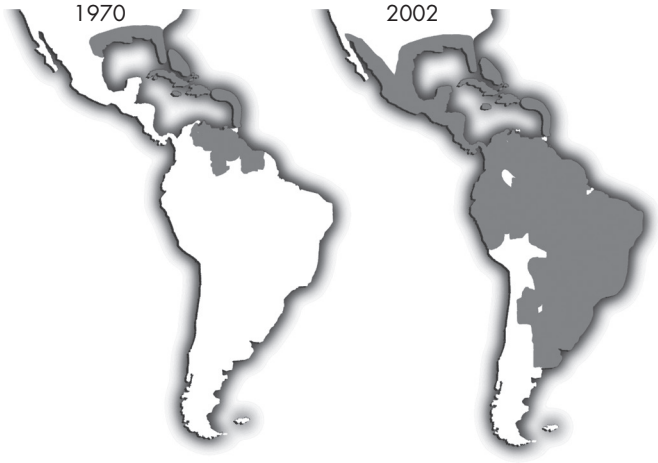


FIGURE ED1-10 Distribution of *Aedes aegypti* in the Americas in 1970 (at the end of the mosquito eradication program) and in 2002. (Source: CDC and PAHO; from Mandell GL et al: *Principles and practice of infectious diseases,* ed 6, Philadelphia, 2005, Saunders.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Influenza.
- Measles.
- Rubella.
- Epstein-Barr virus.
- West Nile virus.
- HIV conversion.
- Malaria.
- Typhoid.
- Leptospirosis.
- Chikungunya.
- Rickettsial diseases.
- Early severe acute respiratory syndrome.
- Other viral hemorrhagic fevers.

DHF is defined by the following World Health Organization (WHO) criteria:

1. Fever lasting 2 to 7 days.
2. Hemorrhagic tendency (spontaneous bleeding or positive tourniquet test).
3. Thrombocytopenia.
4. Evidence of plasma leakage.

WORKUP

- Suspicion for DF based on travel, exposure history, and clinical presentation.
- Tourniquet test can be performed to look for hemorrhagic manifestations; inflate blood pressure cuff midway between systolic and

diastolic blood pressure for 5 min; the test result is positive when more than 20 petechial hemorrhages per square inch are counted on the forearm.

LABORATORY TESTS

- CBC, liver function tests, chemistries.
- Additional laboratory tests based on differential diagnoses (e.g., malaria smears, monospot/Epstein-Barr virus titers, HIV testing).
- With compatible exposure history and symptom profile, positive anti–dengue IgM suggests recent infection, whereas positive anti–dengue IgG may indicate past infection
- Confirm diagnosis with a fourfold increase of IgG and IgM between acute (<6 days after illness onset) and convalescence titers; IgM capture enzyme-linked immunosorbent assay (ELISA) commonly used, but test is negative early in the course of disease.
- Identification of DENV from serum by reverse transcriptase polymerase chain reaction (distributed by Centers for Disease Control and Prevention to departments of health laboratories).

IMAGING STUDIES

As dictated by clinical course.

Rx TREATMENT

No specific pharmacologic treatment for dengue.

NONPHARMACOLOGIC THERAPY

- Treatment is based on supportive measures.
- Mortality rate from DHS/DSS is improved by early and correct fluid replacement.

ACUTE GENERAL Rx

- Monitor platelet count and hematocrit at least daily.
- Patients with platelet counts <100,000 have increased risk for DHF and should be monitored as inpatients.
- Hematocrit increase of 20% suggests substantial plasma loss for which patients should be admitted for intensive care and intravenous fluid replacement.
- Fever should be managed with acetaminophen; aspirin and NSAIDs should be avoided because of their anticoagulant properties.

DISPOSITION

- Classic dengue is usually self-limiting and rarely fatal.
- Of an estimated 500,000 cases of DHF/DSS admitted early, the mortality rate is approximately 2.5%.
- Mortality rate for DHF/DSS is as high as 20% without proper treatment but decreases to <1% with prompt recognition and appropriate treatment.

REFERRAL

- Infectious disease consultation for suspicion of DF.
- Referral/transfer to center experienced with DHF/DSS if available.

! PEARLS & CONSIDERATIONS

COMMENTS

- Health care providers should consider dengue infection in any traveler returning from endemic areas who presents with fever.
- Given the incubation period, dengue infection can be ruled out if onset of symptoms begins 2 wk after individual leaves endemic area.
- Asymptomatic dengue infections are common; however, immunity that results from primary infection increases the risk for DHF/DSS during subsequent infections.
- Serologic testing is complicated by cross-reactions with flaviviruses (including vaccines for yellow fever and Japanese encephalitis).
- Contact the Dengue Branch at the Centers for Disease Control and Prevention for additional information and testing (http://www.cdc.gov/ncidod/dvbid/misc/db.htm).

PREVENTION

- There is no approved vaccine against dengue, but in recent phase 3 efficacy trials, a recombinant live, attenuated, tetravalent dengue vaccine (CYD-TDV) was efficacious against virologically confirmed dengue (VCD) and sever VCD and led to fewer hospitalizations in five Latin American countries where dengue is endemic.[1]
- For travelers, the most effective preventive measure is avoidance of mosquito bites by using protective clothing and insect repellents containing DEET.
- *Aedes* mosquitoes primarily bite during the day and typically live in urban areas.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **VALERIA FABRE, M.D., CLAUDIA RODRIGUEZ CABRERA, M.D.,** and **JOSEPH A. DIAZ, M.D., M.P.H.**

[1]Villar L et al: Efficacy of a tetravalent dengue vaccine in children in Latin America. N Engl J Med 372:113-123, 2015.

BOX ED1-3 World Health Organization Case Classification of Dengue, 2009.

Dengue

Acute febrile illness, live in or travel to endemic region, with two or more of the following:
- Headache and/or retro-orbital pain.
- Nausea and/or vomiting.
- Rash
- Aches and pains.
- Tourniquet test positive.
- Leukopenia.
- Any warning signs (abdominal pain, persistent vomiting, fluid accumulation, mucosal bleeding, lethargy, liver enlargement, increase in hematocrit, falling platelet count with laboratory confirmation).

Severe Dengue Including Dengue Shock Syndrome

Severe capillary permeability and plasma leakage leading to dengue shock syndrome.
Fluid accumulation and respiratory distress.
Severe bleeding.
Severe organ involvement (liver, central nervous system, heart, kidneys, and others).

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

SUGGESTED READINGS

Basurko C et al.: Maternal and fetal consequences of dengue fever during pregnancy, *Eur J Obstet Gynecol Reprod Biol* 147:29–32, 2009.

Centers for Disease Control and Prevention (CDC): Dengue and dengue hemorrhagic fever. Available at http://www.cdc.gov/dengue/clinicalLab/index.html. Accessed August 2013.

Centers for Disease Control and Prevention (CDC): Locally acquired dengue, Key West, Florida 2009-2010, *MMWR Morb Mortal Wkly Rep* 59:577, 2010.

Dejnirattisai W et al.: Cross-reacting antibodies enhance dengue virus infection in humans, *Science* 328:745–748, 2010.

Marchand E et al.: Autochthonous case of dengue in France, *Eurosurveillance* 18, October 2013.

Simmons CP et al.: Dengue, *N Engl J Med* 366:1423–1432, 2012.

Tomashek K.. Dengue fever (DF) and dengue hemorrhagic fever (DHF), CDC traveler's health yellow book.. Available at http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/dengue Accessed August 2014.

Villar L et al: Efficacy of a tetravalent dengue vaccine in children in Latin America. *N Engl J Med* 372:113–123, 2015.

World Health Organization. Dengue and severe dengue. Available at http://www.who.int/mediacentre/factsheets/fs117/en. Accessed August 2014.

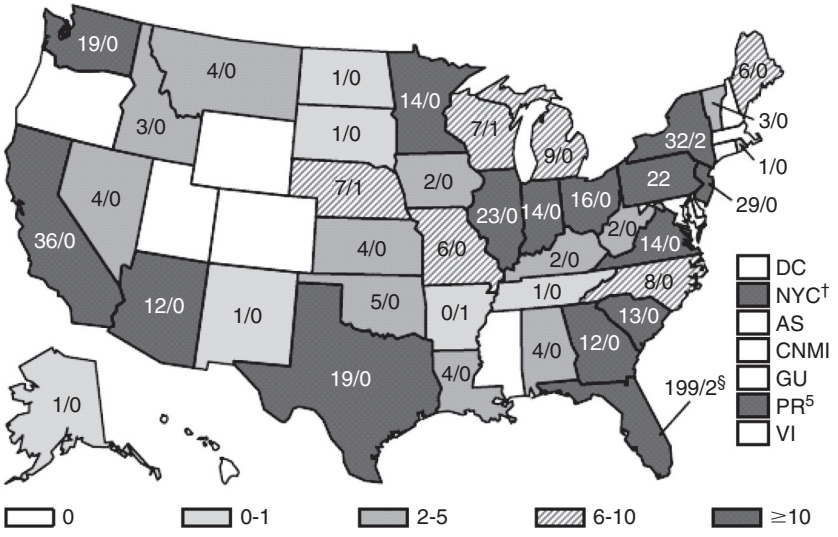


FIGURE ED1-11 Dengue fever and dengue hemorrhagic fever. Number of reported cases, by location of residence—United States and U.S. territories, 2010. (From Centers for Disease Control and Prevention: Summary of notifiable diseases—United States, 2010, *MMWR Morb Mortal Wkly Rep* 59[53]:1-111, 2012. Data from the Division of Vector-Borne Diseases, National Center for Emerging and Zoonotic Infectious Diseases [ArboNET Surveillance]).

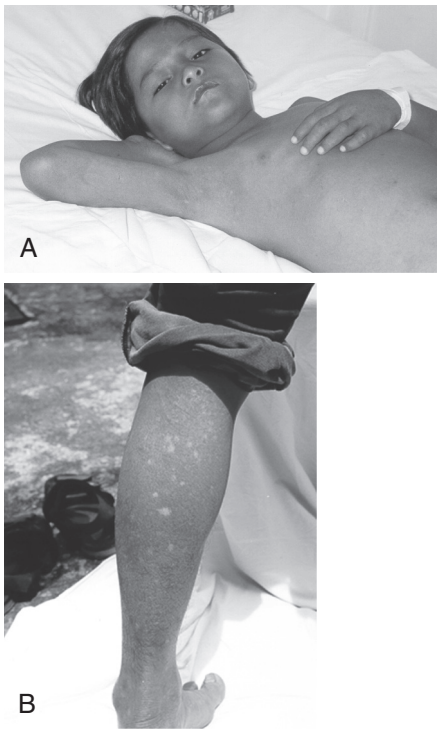


FIGURE ED1-12 Characteristic skin manifestations in convalescent dengue. A, Early convalescent macular diffuse rash occurring in the first week after recovery. **B,** Typical convalescent rash with "islands of white in a sea of red." (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

FIGURE ED1-13 Acute skin manifestations of dengue. A, Characteristic minor bleeding near injection sites. **B,** Rash in established dengue shock syndrome. C, Severe bleeding following IV injection. Staff should press after IV injections for 5 minutes to ensure that bleeding stops. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

Dependent Personality Disorder

BASIC INFORMATION

DEFINITION

Dependent personality disorder (DPD) is characterized by a pervasive and excessive need to be taken care of that leads to submissive and clinging behavior and fears of separation. DPD begins by early adulthood and causes significant distress or impairment in multiple domains of functioning. Individuals must meet five or more of the following criteria:

1. Difficulty making routine decisions without an excessive amount of advice and reassurance from others.
2. Need others to assume responsibility for most major areas of their life.
3. Difficulty expressing disagreement with others because of fear of loss of support or approval.
4. Difficulty initiating or completing projects on own because of a lack of self-confidence in abilities rather than lack of motivation or energy.
5. Excessive attempts to obtain nurturance and support from others.
6. Feel uncomfortable or helpless when alone because of exaggerated fears of being unable to care for self.
7. Urgently seek another relationship when a close relationship ends.
8. Unrealistically preoccupied with being left to take care of self.

SYNONYMS

None

ICD-9CM and DSM-5 CODES
301.6
ICD-10CM
F60.7 Dependent personality disorder

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 0.5% in general population. Dependent traits, as opposed to the disorder itself, are among the most frequently reported in outpatient mental health clinics.
PREDOMINANT SEX: Female (2:1) in clinical settings.

CLINICAL PRESENTATION

- Early onset and chronic course. Impairment is frequently mild.
- On interview, will defer excessively to partner or parent.
- Indecision in routine decisions.
- Depend on a parent or spouse to decide where they should live, work, and recreate and who they should befriend.
- Need for others to function for them goes beyond age-appropriate and situation-appropriate requests for assistance.
- Will agree with objectionable opinions, submit to unreasonable requests, and not express appropriate anger or disappointment for fear of alienating the person without whom they believe they cannot function.
- Convinced that they are not capable of independent function and present themselves as inept.
- Often do not develop independent living skills, perpetuating their dependency.
- Social relations tend to be limited to those few people on whom the person depends.

ETIOLOGY

Chronic physical illness or separation anxiety disorder may predispose for DPD.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Dependency and personality changes arising as a consequence of an Axis I disorder.
- Dependency arising as a consequence of a general medical condition.
- Most common comorbid Axis I conditions are major depressive and other mood disorders, anxiety disorders, including social phobia, and adjustment disorder.
- Most common comorbid personality disorders are histrionic, avoidant, and borderline. Each of these disorders is characterized by dependent features. DPD is distinguished by its predominantly submissive, reactive, and clinging behavior.

WORKUP

- History: collateral information is essential to establishing the presence of longstanding interpersonal pattern in multiple domains of the patient's life.
- Physical examination.
- Mental status examination.

LABORATORY TESTS

Tests necessary to rule out medical causes of personality changes.

IMAGING STUDIES

Tests necessary to rule out medical causes of personality changes.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cognitive-behavioral and psychodynamic psychotherapy to diminish and better contain anxiety and to help patients develop sense of self as competent and requisite assertiveness skills.
- Psychodynamic psychotherapy to help develop improved self-concept and interpersonal functioning.

ACUTE GENERAL Rx

Benzodiazepines to control highly anxious states.

CHRONIC Rx

Selective serotonin reuptake inhibitors (SSRIs) and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) for comorbid depression, social phobia, other anxiety disorders, and agoraphobia.

DISPOSITION

- Chronic course; severity is variable.
- Impairments often mild.
- At increased risk for major depression, social phobia, and other anxiety disorders, including panic and agoraphobia.

REFERRAL

- If pharmacotherapy or psychotherapy is contemplated.
- If patient's functioning is impaired.

PEARLS & CONSIDERATIONS

COMMENTS

- DPD patients fear illness will lead to abandonment by others.
- This fear of simultaneous helplessness and abandonment intensifies neediness and may lead to dramatic demands for urgent medical attention.
- When physicians do not respond as wanted, angry outbursts may ensue.
- Medical care can also become a means by which dependency needs are met. As a result, some of these patients may unconsciously or consciously prolong their illness for primary gain.
- Physicians often react to the extreme neediness with avoidance or overengagement, leading to burnout.
- Management guidelines:
  1. Overall strategy is to provide reassurance and allay fear of abandonment.
  2. Specific strategies include scheduling frequent visits, noncontingent care (i.e., scheduling visits regardless of whether ill or not).
  3. Establish firm and realistic limits to availability as early as possible in treatment.
  4. Enlist other members of health care team for support.
  5. Encourage patient to develop additional "outside" support systems.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **JOHN Q. YOUNG, M.D., M.P.P.**

SUGGESTED READINGS

Quirk SE et al.: Personality disorders and physical comorbidities in adults from the United States: data from the National Epidemiologic Survey on Alcohol and Related Conditions, *Social Psychiatry Psychiatr Epidemiol*, Oct. 15 2014.

Angstman KB et al.: Personality disorders: review and clinical application in daily practice, *Am Fam Phys* 84(11):1253–1260, 2011.

Disney KL: Dependent personality disorder: a critical review, *Clin Psychol Rev* 33(8):1184–1196, 2013.

BASIC INFORMATION

DEFINITION

Major depression is an episodic, frequently recurring syndrome. The diagnosis requires that five of nine criteria be present for 2 wk. One of these nine criteria must be either a persistent depressed mood or pervasive anhedonia (loss of interest or pleasure in all, or almost all, usual interests or activities). Other symptoms include sleep disturbance (insomnia or hypersomnia), appetite loss/gain or weight loss/gain, fatigue, psychomotor retardation or agitation, difficulty concentrating or indecisiveness, feelings of guilt or worthlessness, and recurrent thoughts of death or suicidal ideation.

SYNONYMS

Unipolar affective disorder
Clinical depression
Melancholia
Manic-depressive illness, depressed type
Depressive episode

Codes depend on whether the episode is single or recurrent, and also on clinical severity.

ICD-9CM and DSM-5 CODES
296.2x-296.3x
ICD-10CM CODES
F32.9 Depressive episode, unspecified
F33.0 Recurrent depressive episode, current episode mild
F33.1 Recurrent depressive disorder, current episode moderate
F33.2 Recurrent depressive disorder, current episode severe without psychotic symptoms
F33.3 Recurrent depressive disorder, current episode severe with psychotic symptoms
F33.4 Recurrent depressive disorder, currently in remission
F33.9 Recurrent depressive disorder, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

LIFETIME RISK (IN U.S.): 10% of men, 20% of women
PREVALENCE (IN U.S.): Point prevalence in a community sample is 3% of men, 4.5% to 9.3% of women, and 1% of children. Prevalence of 20% to 40% in patients with comorbid medical conditions.
PREDOMINANT SEX: Female/male ratio 2:1
PREDOMINANT AGE: 25 to 44 yr; 5% of adolescents
PEAK INCIDENCE: 30 to 40 yr; 13% of postpartum women
GENETICS
- Clear evidence of familial predominance
- Prevalence is 2 to 3 times greater among first-degree relatives.
- Concordance among monozygotic twins approximately 50%
- No established pattern of inheritance; MDD with anxious features may be uniquely associated with family history of bipolar disorder, but further studies are needed.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical evaluation facilitated by organizing the major symptoms into four hallmarks: (1) depressed mood, (2) anhedonia, (3) physical symptoms (sleep disturbance, appetite problem, fatigue, psychomotor changes), and (4) psychological symptoms (difficulty concentrating or indecisiveness, guilt or worthlessness, and suicidal ideation).
- A stressful life event, typically a serious loss, may trigger a depressive episode. DSM-5 recommends that clinical judgment be used to determine if depression in the context of a loss should be used to determine if a diagnosis of a disorder is warranted.
- Patients often present with somatic complaints such as pain, fatigue, insomnia, dizziness, headache, or gastrointestinal problems. Somatic complaints may be reported more frequently among certain ethnic groups than depressed mood, increasing risk for underdetection in these groups.
- May be associated with mood-congruent delusional thinking (paranoid and melancholic themes).
- May be associated with active or passive suicidal ideation.
- Serious misconduct may appear in adolescents.
- May be underdiagnosed in elderly patients, with signs and symptoms attributed to normal aging.
- May be underdiagnosed in medically ill patients, with signs and symptoms attributed to medical illness or considered appropriate reaction to medical condition.

ETIOLOGY

- A heterogeneous group of disorders probably arising from various etiologies.
- Genetic and environmental experiences, and their interaction, each contribute.
- Significant psychosocial stressors, especially loss, often trigger depression, particularly for first episodes.
- Numerous biologic correlates have been identified, though none is considered causative or diagnostic. Genes that influence the production and reuptake of serotonin, norepinephrine, and dopamine, as well as nerve cell growth in brain regions underlying memory and emotional processing, are of greatest interest. Abnormalities in brain regions underlying executive functioning, emotion regulation, and reward processing, as well as irregularities in cortisol responding and inflammation, appear to play a role.
- Cognitive risk factors include a pessimistic style of explaining negative events, a tendency to ruminate, and biases in processing emotional information and events.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Anxiety disorders (e.g., social phobia, PTSD, obsessive compulsive disorder), substance abuse, and personality disorders often present with depressive symptoms.
- Important to determine if a depressive episode is part of major depression or part of bipolar disorder.
- Important to distinguish from adjustment disorder. Depression in the context of a stressful life event is diagnosed as major depressive disorder if the symptom criteria are met and adjustment disorder if the symptom criteria are not met. There is no evidence that medication is effective for adjustment disorder.
- Approximately 10% to 15% of depression caused by general medical illnesses, such as Alzheimer's disease, Parkinson's disease, stroke, end-stage renal failure, cardiac disease, HIV infection, and cancer.
- Some medical conditions present as depression (e.g., hypothyroidism, hyperthyroidism or neurosyphilis).
- Premenstrual dysphoric disorder.
- In elderly, depression often coexists with dementia.

WORKUP

- Careful medical history is required
- Physical examination reveals no specific diagnostic signs of depression
- Mental status examination
- Self-report scales can assist in screening.
- Commonly used validated screening tools include the 15-item Geriatric Depression Scale in the elderly and the Patient Health Questionnaire (PHQ)-2 and PHQ-9. The PHQ-2 has a 97% sensitivity and 67% specificity in adults. If it is positive for depression, the PHQ-9 should be administered. The PHQ-9 has a 61% sensitivity and 94% specificity for depression in adults.

LABORATORY TESTS

- No laboratory studies are diagnostic.
- The following can assist in ruling out other confounding issues:
  1. Routine blood chemistry evaluation
  2. CBC with differential
  3. Thyroid function studies
  4. Vitamin B_{12} levels

IMAGING STUDIES

With unusual presentations (e.g., associated with new-onset severe headache, focal neurologic signs, a cognitive or sensory disturbance), the following may be performed:
- EEG (diffuse slowing indicates metabolic encephalopathy)
- Anatomic brain imaging (CT scan or MRI)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Good evidence that cognitive-behavioral therapy is as effective as antidepressant medication in achieving significant reduction or remission (Table D1-8).
- Problem solving and interpersonal psychotherapies have efficacy rates of 50% to 60%.
- "New wave" cognitive-behavioral therapies (e.g., acceptance and commitment therapy, mindfulness-based CBT) have demonstrated efficacy, but as of yet it is unknown whether they are superior to traditional CBT.
- By 12 wk, psychotherapy and medication approaches are equally effective.
- Augmentation of standard depression treatment with CBT to address insomnia was found to significantly improve response rates.
- Patients with severe symptoms should generally not be treated by psychotherapy alone.
- Evidence, although mixed, that combined psychotherapy and medication may be more effective than either treatment alone. Psychotherapy or augmentation with psychotherapy may reduce the risk for future recurrences compared to medication alone.
- Factors, including history of childhood maltreatment, presence of precipitant stressful life events, family psychiatric history, the presence of anhedonia, and depression severity, may affect treatment response and risk of recurrence. Numerous genetic and neurobiological variables that predict treatment response have been identified, but as of yet there are no universally accepted markers that can aid clinicians in matching individuals to particular medications or interventions.

ACUTE GENERAL Rx

- Concurrent medical or psychiatric illnesses, history of prior response, cost, patient preference, and side effects should be considered when selecting initial treatment. Fig. ED1-14 describes guidelines for the treatment of depression in the primary care setting.
- Antidepressants are helpful in approximately 60% to 70% of cases, though sustained remission rates are lower.
- Selective serotonin reuptake inhibitors (SSRIs) generally are first-line.
- According to the STAR-D trial, approximately 30% achieve remission with the first prescribed medication after 3 months of treatment. Another 25% to 30% respond to treatment, but do not achieve remission. Treatment-refractory patients should be switched to another SSRI or to another class of medication, offered adjunctive medication such as bupropion, or referred for evidence-based counseling. Approximately 25% more patients will achieve remission with this secondary intervention.
- Response to antidepressants for many patients is seen as early as 2 wk, and among patients showing little to no response, the odds of later response decrease the longer patients remain unimproved.
- To date no benefit of combining antidepressants as first-line treatment. Also no clear advantage has been identified for switching medications within vs. across different classes, or to switching vs. augmentation.
- Therapy should be continued for 4 to 9 mo after the full remission of symptoms.
- Electroconvulsive therapy is the most effective means available for the treatment of severe, refractory depression. Transcranial magnetic stimulation has also shown evidence of efficacy though the magnitude of effects is more variable and to date electroconvulsive therapy has shown superior efficacy.
- Antipsychotic medication should be added for psychotic depression. Antipsychotic medication has also been shown to be helpful in augmenting antidepressants for nonpsychotic depression.
- Ketamine found to be rapidly effective in treatment-resistant depression. However, treatment remains experimental and effects do not persist.

CHRONIC Rx

Long-term treatment, in some cases, lifelong recommended for multiple depressive episodes, an episode duration longer than 2 yr, a severe episode or significant suicidality, or a strong family history of severe depression or bipolar disorder.

DISPOSITION

- Major depression is often a relapsing and remitting illness.
- Physical symptoms predict a favorable response to biologic intervention.
- Additional episodes experienced by >50% after one episode, with each additional episode linked to increased risk for subsequent episodes.
- Without treatment, episodes last an average of 6 to 12 mo; risk of recurrence higher without treatment.
- For many depressed individuals, subthreshold residual symptoms are present between episodes and define the majority of an individual's course of depression. Such symptoms may lead to impairment and warrant prolonged treatment.

REFERRAL

- If treatment refractory
- If patient suicidal or psychotic
- For suspected bipolar depression

TABLE D1-8 Treatments of Depression

Name of Psychotherapy	Approach
Cognitive psychotherapy	Identify and correct negativistic patterns of thinking.
Interpersonal psychotherapy	Identify and work through role transitions or interpersonal losses, conflicts, or deficits.
Problem-solving therapy	Identify and prioritize situational problems; plan and implement strategies to deal with top-priority problems.
Psychodynamic psychotherapy	Use therapeutic relationship to maximize use of the healthiest defense mechanisms and coping strategies.

From Goldman L et al: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

PEARLS & CONSIDERATIONS

COMMENTS

- All threats of suicide should be taken very seriously. Clinicians can use the mnemonic SAL: Is the method specific? Is it available? Is it lethal?
- Rule out bipolar affective disorder before initiating antidepressant medication. Screening scales for bipolar disorder can be helpful in primary care settings to identify patients at increased risk for bipolar disorder, although unclear benefit in mental health settings.
- Many patients and families reluctant to acknowledge depression because of stigma.
- A two-question screener is as effective as longer instruments. A positive answer to either question warrants a full assessment.
  1. Over the past 2 weeks, have you ever felt down, depressed, or hopeless?
  2. Over the past 2 weeks, have you felt little interest or pleasure in doing things?
- Depression screening programs without treatment programs are unlikely to improve depression outcomes.
- Strict monitoring of patients who initiate antidepressant therapy is necessary both for safety and to ensure optimal treatment. Use of self-report scales to measure symptom severity are helpful in monitoring outcome and may result in improved outcomes.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Bipolar Disorder (Related Key Topic)
Depression (Patient Information)

AUTHORS: **MARK ZIMMERMAN, M.D.,** and **CATHERINE D'AVANZATO, Ph.D.**

EVIDENCE

Abstract[1]

Objective:
The authors assessed whether clinical and psychosocial factors in depressed adolescents at baseline predict suicide attempts and nonsuicidal self-injury over 28 weeks of follow-up.

Method:
Participants were 164 adolescents with major depressive disorder taking part in the Adolescent Depression Antidepressants and Psychotherapy Trial (ADAPT). Clinical symptoms, family function, quality of current personal friendships, and suicidal and nonsuicidal self-harm were assessed at baseline. Suicidal and nonsuicidal self-harm thoughts and behaviors were assessed during 28 weeks of follow-up.

Results:
High suicidality, nonsuicidal self-injury, and poor family function at entry were significant independent predictors of suicide attempts over the 28 weeks of follow-up. Nonsuicidal self-injury over the follow-up period was independently predicted by nonsuicidal self-injury, hopelessness, anxiety disorder, and being younger and female at entry.

Conclusion:
Both suicidal and nonsuicidal self-harm persisted in depressed adolescents receiving treatment in the ADAPT study. A history of nonsuicidal self-injury prior to treatment is a clinical marker for subsequent suicide attempts and should be as carefully assessed in depressed youths as current suicidal intent and behavior. Ⓐ

Abstract[2]

Objective:
Two antidepressant medication combinations were compared with selective serotonin reuptake inhibitor monotherapy to determine whether either combination produced a higher remission rate in first-step acute-phase (12 weeks) and long-term (7 months) treatment.

Method:
The single-blind, prospective, randomized trial enrolled 665 outpatients at six primary and nine psychiatric care sites. Participants had at least moderately severe nonpsychotic chronic and/or recurrent major depressive disorder. Escitalopram (up to 20 mg/day) plus placebo, sustained-release bupropion (up to 400mg/day) plus escitalopram (up to 20 mg/day), or extended-release venlafaxine (up to 300 mg/day) plus mirtazapine (up to 45 mg/day) was delivered (1:1:1 ratio) by using measurement-based care. The primary outcome was remission, defined as ratings of less than 8 and less than 6 on the last two consecutive applications of the 16-item Quick Inventory of Depressive Symptomatology—Self-Report. Secondary outcomes included side effect burden, adverse events, quality of life, functioning, and attrition.

Results:
Remission and response rates and most secondary outcomes were not different among treatment groups at 12 weeks. The remission rates were 38.8% for escitalopram-placebo, 38.9% for bupropion-escitalopram, and 37.7% for venlafaxine-mirtazapine, and the response rates were 51.6% to 52.4%. The mean number of worsening adverse events was higher for venlafaxine-mirtazapine (5.7) than for escitalopram-placebo (4.7). At 7 months, remission rates (41.8%–46.6%), response rates (57.4%–59.4%), and most secondary outcomes were not significantly different.

Conclusion:
Neither medication combination outperformed monotherapy. The combination of extended-release venlafaxine plus mirtazapine may have a greater risk of adverse events. Ⓐ

Abstract[3]

Objective:
To evaluate the efficacy and further establish the safety profile of oral once-daily vilazodone, a potent and selective serotonin 1A receptor partial agonist and reuptake inhibitor, in the treatment of major depressive disorder (MDD).

Method:
This phase 3, randomized, double-blind, placebo-controlled, 8-week study (conducted March 2008–February 2009) enrolled 481 adults with *DSM-IV-TR*-defined MDD. Patients received vilazodone (titrated to 40 mg/d) or placebo. The primary efficacy endpoint was change in Montgomery–Asberg Depression Rating Scale (MADRS) total score from baseline to end of treatment. Secondary efficacy measures included MADRS and 17-item Hamilton Depression Rating Scale (HDRS-17) response and change in HDRS-17, HDRS-21, Hamilton Anxiety Rating Scale (HARS), Clinical Global Impressions-Severity of Illness (CGI-S), and Clinical Global Impressions-Improvement (CGI-I) scores. The Changes in Sexual Functioning Questionnaire (CSFQ) was administered at baseline and week 8.

Results:
Vilazodone-treated patients had significantly greater improvement (P = .009) according to the MADRS than placebo patients (intent-to-treat; least-squares mean changes: −13.3, −10.8). MADRS response rates were significantly higher with vilazodone than placebo (44% vs. 30%, P = .002). Remission rates for vilazodone were not significantly different based on the MADRS (vilazodone, 27.3% vs. placebo, 20.3%; P = .066) or HDRS-17 (vilazodone, 24.2% vs. placebo, 17.7%; P = .088). Vilazodone-treated patients had significantly greater improvements from baseline in HDRS-17 (P = .026), HDRS-21 (P = .029), HARS (P = .037), CGI-S (P = .004), and CGI-I (P = .004) scores than placebo patients. Rates of discontinuation due to adverse events were 5.1% (vilazodone) and 1.7% (placebo). The most common adverse events (vilazodone vs. placebo) were diarrhea (31% vs. 11%), nausea (26% vs. 6%), and headache (13% vs. 10%). Treatment-related effects on sexual function as measured by the CSFQ were small and similar to placebo. Effects on weight were no different from placebo.

Conclusion:
Vilazodone 40 mg/d was well tolerated and effective in adult patients with MDD.

Trial Registration:
clinicaltrials.gov Identifier: NCT00683592 Ⓐ

Evidence-Based References

Wilkinson P et al.: Clinical and psychosocial predictors of suicide attempts and nonsuicidal self-injury in the Adolescent Depression Antidepressants and Psychotherapy Trial (ADAPT), *Am J Psychiatry* 168:495–501, 2011. Ⓐ

Rush AJ et al.: Combining Medications to Enhance Depression Outcomes (CO-MED): acute and long-term outcomes of a single-blind randomized study, *Am J Psychiatry* 168:689–701, 2011. Ⓐ

Khan A et al.: A randomized, double-blind, placebo-controlled 8-week study of vilazodone, a serotonergic agent for the treatment of major depressive disorder, *J Clin Psychiatry* 72:441–447, 2011. Ⓐ

SUGGESTED READINGS

Feldman MD et al.: Let's not talk about it: suicide inquiry in primary care, *Ann Fam Med* 5(5):412, 2007.

Maurer DM: Screening for depression, *Am Fam Physician* 85(2):139–144, 2012.

O'Connor E et al.: Screening for depression in adult patients in primary care settings: a systematic evidence review, *Ann Intern Med* 151:793–803, 2009.

Stewart DE et al.: Depression during pregnancy, *N Engl J Med* 365:1605–1611, 2011.

Trivedi MD et al.: Medication augmentation after the failure of SSRIs for depression, *N Engl J Med 354* 1243, 2006.

Zimmerman M: Misuse of the Mood Disorders Questionnaire as a case-finding measure and a critique of the concept of using a screening scale for bipolar disorder in psychiatric practice, *Bipolar Disord* 14:127–134, 2012.

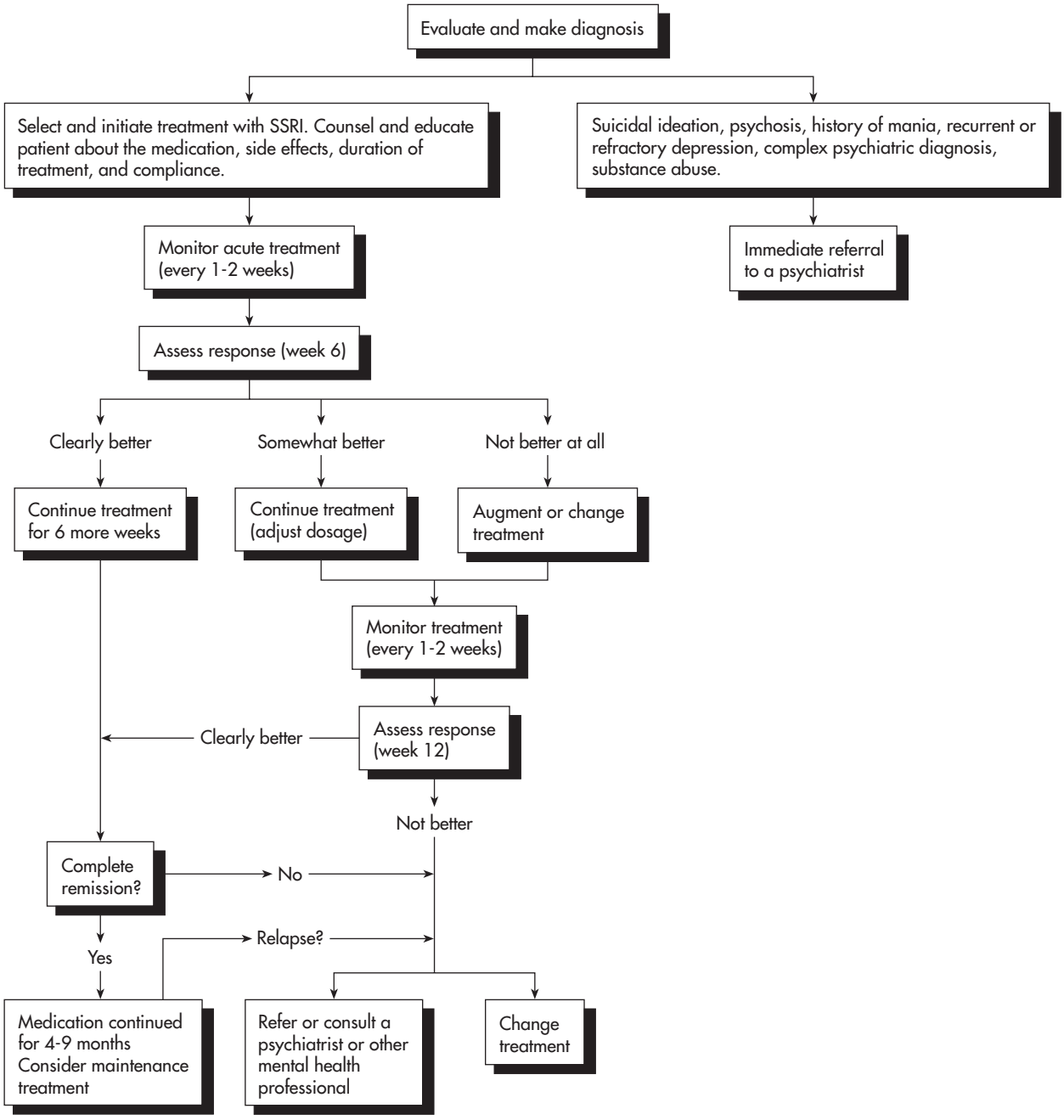


FIGURE ED1-14 Guidelines for the treatment of depression in the primary care setting. Time of assessment (weeks 6 and 12) rests on very modest data. It may be necessary to revise the treatment plan earlier for patients who fail to respond. *SSRI,* Selective serotonin reuptake inhibitor. (From *AHCPR* quick reference guide of clinicians. No. 5: Depression in primary care: detection, diagnosis and treatment, 1993; and American Psychiatric Association: *Diagnostic and statistical manual of mental disorders,* ed 4, Washington, DC, 1994, American Psychiatric Association.)

BASIC INFORMATION

DEFINITION

De Quervain's tenosynovitis refers to painful inflammatory process of the first dorsal retinacular compartment containing abductor pollicis longus and extensor pollicis brevis tendons.

SYNONYMS

Stenosing tenosynovitis of the radial styloid process
Stenosing tenovaginitis of the first dorsal compartment
De Quervain's disease
De Quervain's tendonitis
De Quervain's stenosing tenosynovitis
Tendinosis

ICD-9CM CODES

727.04	Radial styloid tenosynovitis, de Quervain disease
727.0	Synovitis and tenosynovitis
727.05	Other tenosynovitis of hand and wrist

ICD-10CM CODES

M65.4	Radial styloid tenosynovitis [de Quervain]
M65.9	Synovitis and tenosynovitis, unspecified
M65.849	Other synovitis and tenosynovitis, unspecified hand

EPIDEMIOLOGY & DEMOGRAPHICS

- More common in women than in men (10:1)
- Usually occurs between the ages of 30 and 50
- Associated with rheumatoid arthritis (RA)
- Can be seen in new mothers or daycare providers due to holding the babies with an outstretched thumb
- Seen more frequently in certain occupations involving repetitive wrist motion (e.g., clerical, assembly, and manual labor)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pain over the styloid process of the radius with grasping and isometric thumb abduction
- Pain may radiate up to the volar aspect of the wrist or to the thumb
- Swelling on the radial styloid
- Tenderness and swelling of the first extensor (dorsal) compartment.
- Positive Finkelstein's test (Fig. D1-15)
- Crepitance
- Rarely, numbness of dorsum of thumb
- Absence of local heat on examination

ETIOLOGY

- Repetitive use or overuse of the hand and thumb involving pinching with the thumb while moving wrist in radial and ulnar directions causing thickening of the fibrous tendon sheath (e.g., typing, writing, nailing, golfing, fly-fishing, etc.).
- Acute trauma to the first extensor dorsal compartment.
- Inflammatory joint conditions like rheumatoid arthritis (RA) and conditions causing calcium apatite deposition.

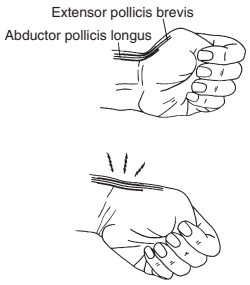


FIGURE D1-15 Finkelstein's test is positive in de Quervain's stenosing synovitis. Ulnar flexion of the wrist produces pain over the dorsal compartment containing the extensor pollicis brevis and abductor pollicis longus. (From Noble J [ed]: *Textbook of primary care medicine,* ed 2, St Louis, 1996, Mosby.)

DIAGNOSIS

- The diagnosis of de Quervain's tenosynovitis is based on the clinical triad of:
  1. Tenderness over the radial styloid
  2. Swelling over the first dorsal retinacular compartment
  3. Pain on ulnar movement of the wrist with the thumb adducted and flexed (Finkelstein's test; see Fig. D1-15).
- Consideration can be given to injecting 1.5 ml of 1% Xylocaine into the tenosynovial sac, and if all three physical signs resolve, the diagnosis is confirmed, allowing for differentiation from carpometacarpal (CMC) osteoarthritis (OA).
- Finkelstein maneuver can also be present in first CMC joint OA; therefore it should also be evaluated if this test is positive.

DIFFERENTIAL DIAGNOSIS

- Carpal tunnel syndrome
- Arthritis (e.g., degenerative OA or RA)
- Gout
- Infiltrative tenosynovitis
- Radiculopathy
- Compression neuropathy (e.g., superficial branch of the radial nerve "bracelet syndrome")
- Ganglia
- Infection (e.g., tuberculosis, bacterial)
- Scaphoid fracture
- Intersection syndrome

LABORATORY TESTS

- ESR is usually normal in patients with de Quervain's tenosynovitis.
- Arthrocentesis to rule out gout (crystals) and infection (Gram stain, culture of aspirate).

IMAGING STUDIES

- Imaging of wrist and thumb not necessary unless fracture or arthritis suspected.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Rest
- Avoid repetitive movements of hand or thumb
- Splinting (thumb spica)
- Icing (4 to 6 times a day for 15 min)
- Physiotherapy

ACUTE GENERAL Rx

- Corticosteroid injection using 20 to 40 mg triamcinolone acetonide and 1% Xylocaine is effective in relieving pain.
- NSAIDs (ibuprofen 800 mg tid or naproxen 500 mg bid)
- Topical hydrocortisone on the radial styloid for mild conditions

CHRONIC Rx

- Once signs of active inflammation have resolved after 3-4 wk, gentle stretching exercises involving abductor and extensor tendons usually help recovery.
- Surgical release is generally reserved for patients not responding to NSAIDs and corticosteroid injection therapy.
- Surgery includes first extensor (dorsal) compartment release with or without tenosynovectomy.

DISPOSITION

- ~90% of patients have relief of symptoms with either single or multiple steroid injections.
- Rarely, steroid injection use can cause infection and tendon rupture.
- Accidental injection of the glucocorticoid in the subcutaneous tissue instead of sheath of first extensor (dorsal) compartment should be avoided to prevent fat and dermal atrophy.
- If left untreated, can lead to fibrosis and decrease in mobility (stenosing tenosynovitis).
- Surgical control of symptoms achieved in 90% of referred cases
- Complications of surgery include:
  1. Radial nerve damage
  2. Paresthesia (10%)
  3. Neuroma
  4. Scarring
- Recovery rates are higher with early treatment to ~80% after 6 wk but <40% after 4 yr.

PEARLS & CONSIDERATIONS

- Steroid injection is generally recommended after failure of conservative treatment for 2 to 6 wk.
- Pain relief usually noted within 48 hr, with patient becoming asymptomatic 1 to 2 wk after corticosteroid injection.
- If no improvement by 6 wk post second corticosteroid injection, refer to orthopedic hand surgeon.
- Without treatment it will not improve and can get worse.
- Condition can recur if triggering activity continues.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

De Quervain's Tenosynovitis (Patient Information)

AUTHORS: **SYEDA M. SAYEED, M.D., and UZMA NASIR, M.D.**

SUGGESTED READINGS

Asif M, Ilyas AM, et al.: Surgical treatment for de Quervain's tenosynovitis, *J Hand Surg* 34:928–929, 2009.

Bouras Y et al.: Surgical treatment in de Quervain's tenosynovitis, *Ann Chir Plast Esthet* 55:42–45, 2010.

Capasso G, Testa V, Maffulli N, et al.: Surgical release of de Quervain's stenosing tenosynovitis postpartum: can it wait? *Int Orthop* 26:23, 2002.

Graham JB, Hulkower SD, Bosworth M: Are steroid injections effective for tenosynovitis of the hand? *J Fam Pract* 56(12):1045–1047, 2007.

Ilyas AM et al.: De Quervain tenosynovitis of the wrist, *J Am Acad Orthop Surg* 15(12):757–764, 2007.

Jirarttanphochai K et al.: Treatment of de Quervain disease with triamcinolone injection with or without nimesulide A randomized, double-blind, placebo-controlled trial, *J Bone Joint Surg Am* 86-A:2700, 2004.

Mellor SJ, Ferris BD: Complications of a simple procedure: de Quervain's disease revisited, *Int J Clin Pract* 54(2):76, 2000.

Richie CA, Briner Jr WW: Corticosteroid injection for treatment of de Quervain's tenosynovitis: a pooled quantitative literature evaluation, *J Am Board Fam Pract* 16:102, 2003.

Dermatitis Herpetiformis

BASIC INFORMATION

DEFINITION

Dermatitis herpetiformis (DH) is an autoimmune blistering disease that is considered to be a cutaneous manifestation of celiac disease (CD). It is associated with gluten-sensitive enteropathy in nearly all cases, although only 20% of patients have gastrointestinal symptoms. Approximately 25% of patients with CD will have DH.

SYNONYMS

Duhring disease

ICD-9CM CODES
694.0 Dermatitis herpetiformis
ICD-10CM CODES
L13.0 Dermatitis herpetiformis

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE (IN U.S.): 11.2 cases per 100,000 persons; prevalence for CD is one in 133 adults
PREDOMINANT SEX: Male predominance (2:1); however, female predominance in children
PREDOMINANT AGE: Fourth decade of life, but can occur at any age
PREDOMINANT RACE: Most common in Caucasians of Northern European ancestry
GENETICS: Both CD and DH have a strong genetic component. Eleven percent of patients with DH have a first-degree relative with either DH or CD. Specific HLA genes (involved in processing gliadin antigen in genetically susceptible individuals) have also been shown to predispose to developing DH (HLA-DQ2 in 90%, DQ8 in the remaining 10%). However, less than 50% of genetic predisposition is attributed to HLA genes.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Classically, small fragile clusters ("herpetiform" vesicles) distributed symmetrically on extensor surfaces (elbows, knees, scalp, back, and buttocks) (Fig. D1-16). However, due to intense pruritus, pinpoint erosions and excoriations are often the most prominent findings on examination, with intact vesicles rare.
- Spontaneous improvement with cyclic exacerbations is common.
- Celiac-type enamel defects to permanent teeth, oral vesicles, or palmoplantar purpura have been reported as potential associated findings.

PATHOGENESIS

CD and DH are both autoimmune-mediated by IgA class autoantibodies. Dietary gluten is central to the pathogenesis in both. It is hypothesized that gluten byproduct, gliadin, complexes with tissue transglutaminase (tTG) in the gut, binding as an antigen to HLA-DQ2 on T-cells, creating an immune response resulting in anti-tTG IgA antibodies (i.e., anti-endomysial antibodies) in the blood result. However, unlike CD, patients with DH also have high-affinity antibodies against epidermal transglutaminase (eTG). Antigenetic cross-reactivity has been hypothesized.

DIAGNOSIS

Physical examination and routine histopathology are often suggestive of DH; however, direct immunofluorescence (DIF) of a perilesional skin biopsy has pathognomonic findings and is the gold standard for diagnosis. Fig. D1-17 describes an approach to the patient with suspected dermatitis herpetiformis.

DIFFERENTIAL DIAGNOSIS

- Clinically and histologically, the differential diagnosis includes linear IgA dermatosis, bullous pemphigoid, and bullous lupus. These diagnoses can be differentiated by DIF on perilesional skin biopsy
- Other clinical diagnoses to consider:
  1. Scabies (check for interdigital burrows, involvement of genitalia)
  2. Arthropod bite (papular urticaria over exposed areas)
  3. Eczematous dermatitis (ill-defined, weeping erythematous plaques)
  4. Herpes simplex or zoster infection (painful, not symmetric)
  5. Generalized pruritus (no blister history)

WORKUP, LABORATORY TESTS

- Evaluation for gastrointestinal symptoms, family history of DH or CD, and pruritus should be sought in patients with suspected DH
- **Lesional skin biopsy:** will demonstrate a neutrophil-rich subepidermal bulla and rule out many conditions.
- **DIF of normal-appearing perilesional skin biopsy:** will demonstrate pathognomonic IgA deposits localized to the dermal papillae and dermal-epidermal junction in a granular pattern.
- Checking for circulating antibodies in the blood (anti-gliadin, anti-endomysial, or anti-reticulin IgA antibodies) is not recommended as part of the diagnostic workup for DH. However, they can be helpful in confirming the diagnosis of DH in cases where linear IgA cannot be excluded on DIF.

TREATMENT

A gluten-free diet (GFD) and dapsone are considered first-line therapy and are often started in conjunction.

1. GFD improves symptoms of both GI and skin disease, with GI responding quicker (skin responds after 2 months).
2. Dapsone results in improvement of skin manifestations within days but does not treat GI manifestations. Dapsone is often tapered over time, while lifelong gluten avoidance is often necessary.
   A recent small study demonstrated that a GFD alone was comparable to a gluten-free diet plus dapsone in the treatment of DH; hence GFD is an essential component in the treatment of DH.

NONPHARMACOLOGIC THERAPY

- First line: GFD
  1. Avoid barley, rye, wheat (rice, corn, and oats okay)
  2. Consultation with a dietitian recommended
  3. Most patients need to follow diet indefinitely; however, cases of spontaneous remission have been reported.
- Second line: elemental diet (controversial)
  1. Can consider elemental diet (avoidance of whole proteins) in those patients who do not adequately respond to a strict GFD; however, data are limited.

ACUTE GENERAL Rx

- First line: dapsone
  1. Initial dose 25-50 mg PO daily with gradual increase to an average maintenance dose of 0.5-1 mg/kg daily (often maintenance dose of 100 mg daily).

FIGURE D1-16 Dermatitis herpetiformis is an immunologically mediated blistering disease. There is a strong association of dermatitis herpetiformis with HLA-B8, DR3. Gluten-sensitive enteropathy is a common associated finding. The lesions are grouped (herpetiform) and extremely pruritic. (From Callen JP [ed]: *Color atlas of dermatology,* ed 2, Philadelphia, 2000, Saunders.)

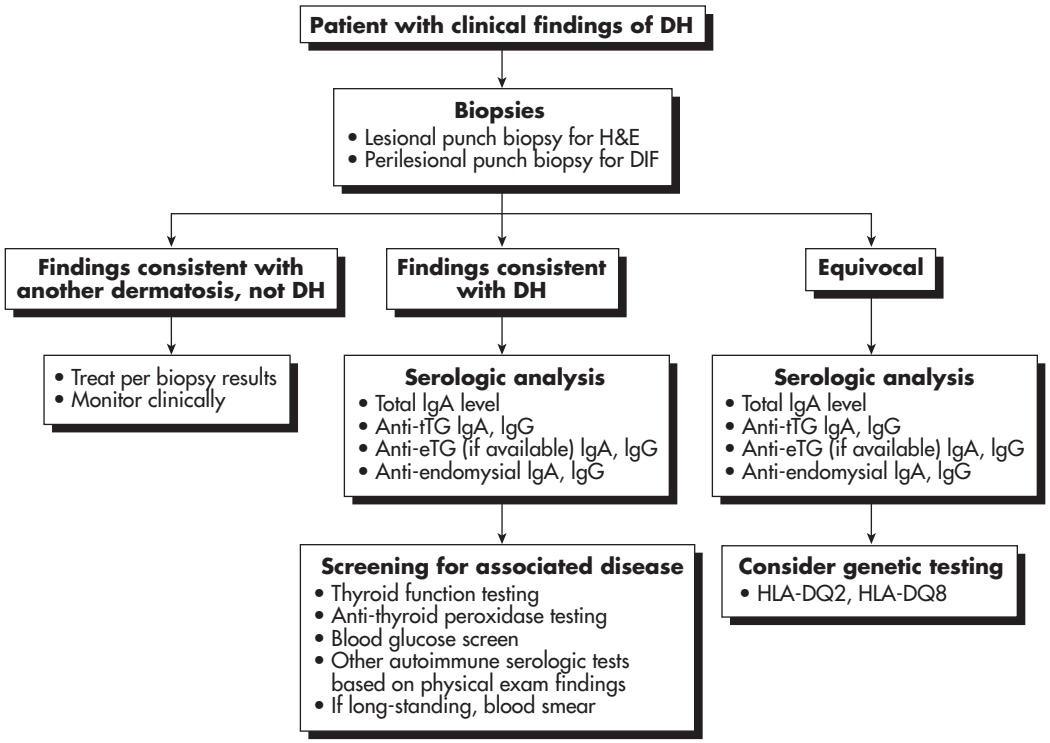


FIGURE D1-17 Approach to the patient with suspected dermatitis herpetiformis. (From Bolotin D, Petronic-Rosic V: Dermatitis herpetiformis: Part II. Diagnosis, management, and prognosis. *J Am Acad Dermatol* 64(6), 1027–1033, 2011.)

2. Clinical monitoring weekly is recommended to optimize dose (optimal dose is when 1-2 new lesions/wk)
3. Caution: dapsone may produce hemolysis (especially if G6PD deficiency), agranulocytosis, methemoglobinemia, systemic drug hypersensitivity reaction (DRESS), and a peripheral neuropathy.
4. Baseline labs: CBC, LFTs, G6PD levels. After the initiation of therapy, monitor CBC every week ×1 month, then every other week ×2 months, monthly ×4 months, then every 3-4 months. Monitor LFTs every 3-4 months.

- Second-line alternatives
  1. Sulfapyridine (500-1500 mg/day) or sulfasalazine (500-1000 mg bid) may be substituted in cases of dapsone intolerance.
  2. Reported efficacy in uncontrolled studies and case reports have suggested efficacy with tetracyclines, nicotinamide, cyclosporine, colchicine, and heparin
- Symptomatic relief for pruritus
  1. Potent and superpotent topical corticosteroids (atrophy with prolonged use, limit to 14 days per month), non-sedating antihistamines twice daily, sedating antihistamines at bedtime, sarna lotion

CHRONIC Rx

- As DH is considered to represent the cutaneous manifestations of CD, lifelong avoidance of gluten is typically recommended. Information about educational resources, such as national and local support groups, should be provided (www.celiac.org).
- Patients with DH and CD have an increased risk of developing Hashimoto's thyroiditis, non-Hodgkin lymphoma, and GI lymphomas. An increased incidence of other autoimmune disorders (type 1 diabetes mellitus, pernicious anemia, Addison's disease, vitiligo, systemic lupus erythematosus, rheumatoid arthritis, and Sjögren's syndrome) and osteoporosis have also been reported.
  1. Screening for thyroid disease (TSH, antithyroid peroxidase antibody titers) is typically recommended
  2. Screening for autoimmune connective tissue diseases should be considered if suspicious signs or symptoms
  3. Routine screening for GI lymphomas is controversial

REFERRAL

- Dermatologist for skin biopsy and management of cutaneous disease
- Gastroenterologist for evaluation of CD
- Nutritionist to educate patients about gluten-free diet
- National support groups (www.celiac.org) and local support groups

PEARLS & CONSIDERATIONS

- Classic areas involved are those that are exposed if in a "fetal position."
- Lesions may be worsened by iodides and certain NSAIDs; systemic steroids ineffective.
- Location of biopsies is important! False-negative DIF can result if biopsies are taken from lesional skin (should be taken from normal-appearing skin adjacent to lesion) as diagnostic IgA deposits are usually destroyed by the blistering process.
- GFD results in reduced IgA in skin on DIF (with eventual disappearance) and reduced anti-endomysial antibodies in the blood. Hence, serologies (e.g., anti-endomysial antibodies) can be used to monitor degree of compliance to dietary gluten restriction.
- Some studies have suggested a possible protective effect of GFD against intestinal lymphoma. First-degree relatives do not appear to be at increased risk for GI or systemic lymphomas in the absence of DH or CD.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Celiac Disease (Related Key Topic)

AUTHORS: **LISA PAPPAS-TAFFER, M.D.,** and **IRIS L. TONG, M.D.**

SUGGESTED READINGS

Bolotin D, Rosic V: Dermatitis herpetiformis part I: Epidemiology, pathogenesis, and clinical presentation, *J Am Acad Dermatol* 64(6):1017–1024, 2011.

Bolotin D, Rosic V: Dermatitis herpetiformis part II: Diagnosis, management, and prognosis, *J Am Acad Dermatol* 64(6):1027–1033, 2011.

Cardones AR, Hall RP: Management of dermatitis herpetiformis, *Dermatol Clin* 29:631–636, 2011.

Hull CM et al.: Elevation of IgA antiepidermal transglutaminase antibodies in dermatitis herpetiformis, *Br J Dermatol* 159:120, 2008.

Jaskowski TD et al.: Novel screening assay performance in pediatric celiac disease and adult dermatitis herpetiformis, *JPGN* 51(1):19–23, 2010.

Nino M et al.: A long-term gluten-free diet as an alternative treatment in severe forms of dermatitis herpetiformis, *J Dermatol Treat* 13:10–12, 2007.

Paek SY et al.: Remission in dermatitis herpetiformis, *Arch Dermatol* 147(3):301–305, 2011.

Samasca G et al.: IgG-F-actin antibodies in celiac disease and dermatitis herpetiformis, *Roum Arch Microbiol Immunol* 69(4):177–182, 2010.

BASIC INFORMATION

DEFINITION

Diabetes insipidus is a polyuric disorder resulting from insufficient production of vasopressin (pituitary [neurogenic] diabetes insipidus) or unresponsiveness of the renal tubules to vasopressin (nephrogenic diabetes insipidus).

ICD-10CM CODES
253.5 Diabetes insipidus
ICD-10CM CODES
E23.2 Diabetes insipidus

EPIDEMIOLOGY & DEMOGRAPHICS

GENETICS:

- Nephrogenic diabetes insipidus can be inherited as a sex-linked recessive trait.
- There is also a rare autosomal-dominant form of neurogenic diabetes insipidus.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Central diabetes insipidus is usually abrupt in onset whereas in compulsive water drinking there is a more vague history of onset
- Nocturia is unusual in compulsive water drinkers and more common in central diabetes insipidus
- Polyuria: urinary volumes ranging from 2.5 to 6 L/day
- Polydipsia (predilection for cold or iced drinks)
- Neurologic manifestations (seizures, headaches, visual field defects)
- Evidence of volume contractions

NOTE: The physical findings and clinical manifestations are generally not evident until vasopressin secretory capacity is reduced to <20% of normal.

ETIOLOGY

Neurogenic diabetes insipidus:

- Idiopathic
- Neoplasms of brain or pituitary fossa (craniopharyngiomas, metastatic neoplasms from breast or lung)
- Posttherapeutic neurosurgical procedures (e.g., hypophysectomy)
- Head trauma (e.g., basal skull fracture)
- Granulomatous disorders (sarcoidosis or tuberculosis)
- Histiocytosis (Hand-Schüller-Christian disease, eosinophilic granuloma)
- Familial (autosomal dominant); some cases autosomal recessive
- Other: interventricular hemorrhage, aneurysms, meningitis, postencephalitis, multiple sclerosis, Guillain-Barré syndrome

Nephrogenic diabetes insipidus:

- Drugs: lithium, aminoglycosides, antivirals amphotericin B, demeclocycline, methoxyflurane anesthesia
- Familial: X-linked
- Metabolic: hypercalcemia or hypokalemia
- Other: sarcoidosis, amyloidosis, pyelonephritis, polycystic disease, sickle cell disease, postobstructive, low-protein diets (protein malnourishment)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Diabetes mellitus, nephropathies
- Primary polydipsia, medications (e.g., chlorpromazine)
- Osmotic diuresis (glucose, mannitol, anticholinergics)
- Psychogenic polydipsia, electrolyte disturbances

WORKUP

- The diagnostic workup is aimed at showing that polyuria is caused by the inability to concentrate urine and determining whether the problem is the result of decreased vasopressin or insensitivity to vasopressin. This is done with the water deprivation test (Table ED1-9):
  1. After baseline measurement of weight, vasopressin, plasma sodium, and urine and plasma osmolarity, the patient is deprived of fluids under strict medical supervision.
  2. Frequent (q2h) monitoring of plasma and urine osmolarity follows.
  3. The test is generally terminated when plasma osmolarity is >295 mOsm/kg or the patient loses ≥3.5% of initial body weight.
  4. Diabetes insipidus is confirmed if the plasma osmolarity is >295 mOsm/kg and the urine osmolarity is <500 mOsm/kg.
  5. To distinguish nephrogenic from neurogenic diabetes insipidus, the patient is given 5 U of vasopressin and the change in urine osmolarity is measured. A significant increase (>50%) in urine osmolarity after administration of vasopressin is indicative of neurogenic diabetes insipidus.
- A diagnostic algorithm for diabetes insipidus is described in Fig. ED1-18.

LABORATORY TESTS

- Decreased urinary specific gravity (≤1.005)
- Baseline plasma osmolality >295 mOsm/kg is suggestive of central diabetes mellitus whereas values below 270 mOsm/kg favor compulsive water drinking. Decreased urinary osmolarity (usually <200 mOsm/kg) even in the presence of high plasma osmolality
- Hypernatremia, increased plasma osmolarity, hypercalcemia, hypokalemia

IMAGING STUDIES

MRI of the pituitary if neurogenic diabetes insipidus is confirmed

TREATMENT

NONPHARMACOLOGIC THERAPY

- Patient education regarding control of fluid balance and prevention of dehydration with adequate fluid intake or IV D_5W
- Daily weight

ACUTE GENERAL Rx

Therapy varies with the degree and type of diabetes insipidus (Table ED1-10).

- Neurogenic diabetes insipidus:
  1. Desmopressin acetate (DDAVP) 20-40 mcg qd intranasally in 1 to 3 divided doses or in tablet form 0.1 to 1.2 mg. Usual oral dose is 0.1 to 1.2 mg/day in 2 to 3 divided doses. Desmopressin is also available in injectable form given as 2 to 4 mcg/day SC or IV in 2 divided doses.
  2. Vasopressin tannate in oil: 2.5 to 5 U IM q24 to 72h; useful for long-term management because of its long half-life.
  3. In mild cases of neurogenic diabetes insipidus, polyuria may be controlled with HCTZ 50 mg qd (decreases urine volume by increasing proximal tubular reabsorption of glomerular infiltrate).
- Nephrogenic diabetes insipidus:
  1. Removal of the underlying cause. However, prolonged lithium therapy can lead to irreversible nephrogenic diabetes insipidus even after lithium therapy is withdrawn.
  2. Amiloride 5 mg/day for lithium-related disease
  3. Low-sodium diet and chlorothiazide to induce mild sodium depletion

CHRONIC Rx

Patients should be aware of the danger of dehydration and the need for liberal water intake.

REFERRAL

Endocrinology consultation for diagnostic testing

PEARLS & CONSIDERATIONS

COMMENTS

- Patients should be instructed to wear a medical identification tag or bracelet identifying their medical illness.
- In central diabetes insipidus, the use of DDAVP has become the standard of care. Extensive clinical experience has shown it to be both safe and effective in the treatment of this disorder.
- The treatment of nephrogenic diabetes insipidus is more complicated than the central form, and opinion varies among experts in the field. Consultation with a specialist is always recommended in this setting.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Diabetes Insipidus (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READING

Sands JM, Bichet DG: Nephrogenic diabetes insipidus, *Ann Intern Med* 144:186, 2006.

TABLE ED1-9 Water Deprivation Test

Diagnosis	Urine Osmolality with Water Deprivation (mOsm/kg H_2O)	Plasma AVP after Dehydration	Increase in Urine Osmolality with Exogenous AVP
Normal	>800	>2 pg/ml	Little or none
Complete central diabetes insipidus	<300	Undetectable	Substantial
Partial central diabetes insipidus	300-800	<1.5 pg/ml	>10% of urine osmolality after water deprivation
Nephrogenic diabetes insipidus	<300-500	>5 pg/ml	Little or none
Primary polydipsia	>500	<5 pg/ml	Little or none

AVP, Arginine vasopressin.
From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

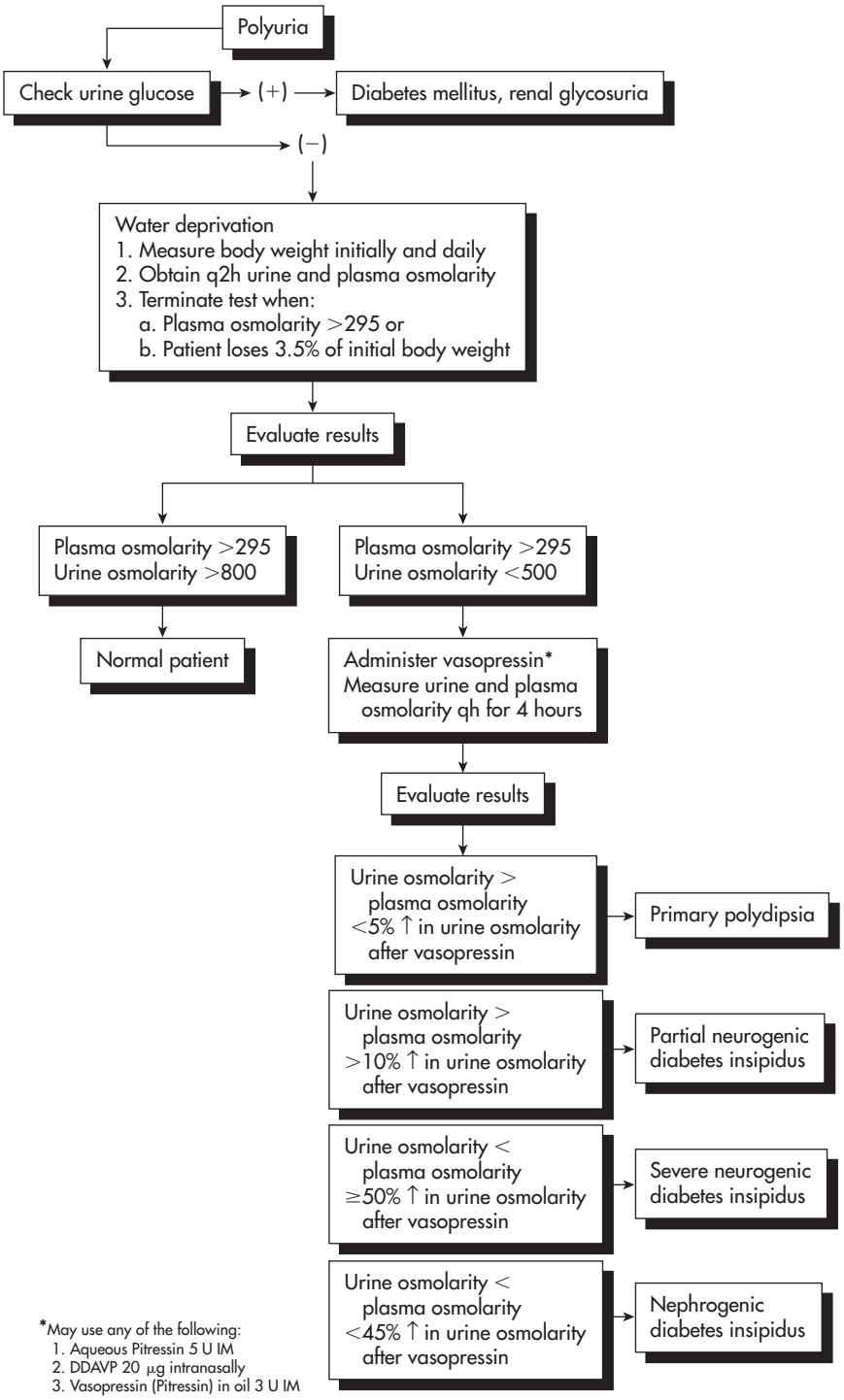


FIGURE ED1-18 Diagnostic flowchart for diabetes insipidus. (From Ferri F: *Practical guide to the care of the medical patient*, ed 8, St Louis, 2011, Mosby.)

TABLE ED1-10 Treatments for Diabetes Insipidus

Type of Diabetes Insipidus	Drug	Dose
Complete central	DDAVP	10-20 g intranasally every 12-24 hr
Partial central	Aqueous vasopressin	5-10 U subcutaneously every 4-6 hr
	Chlorpropamide	250-500 mg/day
	Clofibrate	500 mg 3-4 times daily
	Carbamazepine	400-600 mg/day
Nephrogenic	Thiazide diuretics	5 mg/day
	NSAIDs	
	Amiloride (for lithium-related disease)	
Gestational	DDAVP	As for complete central

DDAVP, Desmopressin; *NSAIDs,* nonsteroidal anti-inflammatory drugs.
Adapted from Lanese D, Teitelbaum I: Hypernatremia. In Jacobson HR et al (eds): *The principles and practice of nephrology,* Philadelphia, 1998, Mosby.

Diabetes Mellitus PTG ALG EBM

BASIC INFORMATION

DEFINITION

- Diabetes mellitus (DM) refers to a syndrome of hyperglycemia resulting from many different causes (see "Etiology"). It is broadly classified into type 1 and type 2 DM. The terms "insulin-dependent" and "non–insulin-dependent" diabetes are obsolete because when a person with type 2 diabetes needs insulin, he or she remains labeled as type 2 and is not reclassified as type 1. Table D1-11 provides a general comparison of the two types of DM.
- The American Diabetes Association (ADA) defines DM as follows:
  1. A fasting plasma glucose (FPG) ≥126 mg/dl, which should be confirmed with repeat testing on a different day. Fasting is defined as no caloric intake for at least 8 hr.
  2. Symptoms of hyperglycemia and a casual (random) plasma glucose ≥200 mg/dl. Classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss.
  3. An oral glucose tolerance test (OGTT) with a plasma glucose ≥200 mg/dl 2 hr after a 75 g (100 g for pregnant women) glucose load.
  4. A hemoglobin A_{1c} (HbA1c) value ≥6.5%.
- Individuals with glucose levels higher than normal but not high enough to meet the criteria for diagnosis of DM are considered to have "prediabetes," the diagnosis of which is made as follows:
  1. A fasting plasma glucose 100 to 125 mg/dl; this is referred to as impaired fasting glucose.
  2. After OGTT, a 2-hr plasma glucose 140 to 199; this is referred to as impaired glucose tolerance.
  3. A hemoglobin A_{1c} value 5.7% to 6.4%.
- Table D1-12 describes diagnostic categories for DM and at-risk states.

SYNONYMS

IDDM (insulin-dependent diabetes mellitus)
NIDDM (non–insulin-dependent diabetes mellitus)
Type 1 diabetes mellitus (insulin-dependent diabetes mellitus)
Type 2 diabetes mellitus (non–insulin-dependent diabetes mellitus)

ICD-9CM CODES
250.0 Diabetes mellitus (NIDDM)
250.1 Insulin-dependent diabetes mellitus without complication (IDDM)

ICD-10CM CODES
E11.5 Type 2 diabetes mellitus with peripheral circulatory complications
E11.6 Type 2 diabetes mellitus with other specified complications
E11.7 Type 2 diabetes mellitus with multiple complications
E11.8 Type 2 diabetes mellitus with unspecified complications
E11.9 Type 2 diabetes mellitus without complications

EPIDEMIOLOGY & DEMOGRAPHICS

- DM affects 9% to 10% of the U.S. population. Prevalence rates vary considerably by race/ethnicity.
- Incidence rate increases with age, varying from 2% in persons age 20 to 44 yr to 18% in persons 65 to 74 yr. Type 2 DM can have a long presymptomatic phase, leading to a 4- to 7-yr delay in diagnosis.
- Diabetes accounts for 8% of all legal blindness in the United States and is the leading cause of end-stage renal disease (ESRD).
- Patients with diabetes are 2-4 times more likely than nondiabetic patients to experience development of cardiovascular disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

1. Physical examination varies with the presence of complications and may be normal in early stages
2. Diabetic retinopathy:
   a. Nonproliferative (background diabetic retinopathy):
      (1) Initially: microaneurysms, capillary dilation, waxy or hard exudates, dot and flame hemorrhages, atrioventricular shunts
      (2) Advanced stage: microinfarcts with cotton wool exudates, macular edema
   b. Proliferative retinopathy: characterized by formation of new vessels, vitreous hemorrhages, fibrous scarring, and retinal detachment
3. Cataracts and glaucoma occur with increased frequency in patients with diabetes
4. Diabetic neuropathy
   a. Distal sensorimotor polyneuropathy
      (1) Symptoms include paresthesia, hyperesthesia, or burning pain involving bilateral distal extremities, in a "stocking-glove" distribution. This can progress to motor weakness and ataxia.
      (2) Physical examination may reveal decreased pinprick sensation, sensation to light touch, vibration sense, and loss of proprioception. Motor disturbances such as decreased deep tendon reflexes and atrophy of interossei muscles can also be seen.
   b. Autonomic neuropathy:
      (1) GI disturbances: esophageal motility abnormalities, gastroparesis, diarrhea (usually nocturnal)

TABLE D1-11 General Comparison of the Two Types of Diabetes Mellitus

	Type 1	Type 2
Previous terminology	Insulin-dependent diabetes mellitus (IDDM), type I, juvenile-onset diabetes	Non–insulin-dependent diabetes mellitus, type II, adult-onset diabetes
Age of onset	Usually <30 yr, particularly childhood and adolescence, but any age	Usually >40 yr, but any age
Genetic predisposition	Moderate; environmental factors required for expression; 35%-50% concordance in monozygotic twins; several candidate genes proposed	Strong; 60-90% concordance in monozygotic twins; many candidate genes proposed; some genes identified in maturity-onset diabetes of the young
Human leukocyte antigen associations	Linkage to DQA and DQB, influenced by DRB (3 and 4) (DR2 protective)	None known
Other associations	Autoimmune; Graves' disease, Hashimoto's thyroiditis, vitiligo, Addison's disease, pernicious anemia	Heterogenous group, ongoing subclassification based on identification of specific pathogenic processes and genetic defects
Precipitating and risk factors	Largely unknown; microbial, chemical, dietary, other	Age, obesity (central), sedentary lifestyle, previous gestational diabetes
Findings at diagnosis	85-90% of patients have one and usually more autoantibodies to ICA512/IA-2/IA-2b, GAD_{65}, insulin (IAA)	Possibly complications (microvascular and macrovascular) caused by significant preceding asymptomatic period
Endogenous insulin levels	Low or absent	Usually present (relative deficiency), early hyperinsulinemia
Insulin resistance	Only with hyperglycemia	Mostly present
Prolonged fast	Hyperglycemia, ketoacidosis	Euglycemia
Stress, withdrawal of insulin	Ketoacidosis	Nonketotic hyperglycemia, occasionally ketoacidosis

GAD, Glutamic acid decarboxylase; *IA-2/IA-2b,* tyrosine phosphatases; *IAA,* insulin autoantibodies; *ICA,* islet cell antibody; *ICA512,* islet cell autoantigen 512 (fragment of IA-2).
From Andreoli TE (ed): *Cecil essentials of medicine,* ed 6, Philadelphia, 2005, Saunders.

TABLE D1-12 Diagnostic Categories*: Diabetes Mellitus and At-Risk States

	2-HOUR (75-g) OGTT RESULT		
Fasting Plasma Glucose Level	**<140 mg/dl**	**140-199 mg/dl**	**≥200 mg/dl**
<100 mg/dl	Normal	IGT†	DM
100-125 mg/dl	IFG†	IGT† *and* IFG†	DM
≥126 mg/dl	DM	DM	DM
HbA_{1C} Level	**<5.7%**	**5.7-6.4%**	**≥6.5%**
	Normal	High-risk†	DM

*These diagnostic categories are based on the combined fasting plasma glucose level and a 2-hour, 75-g oral glucose tolerance test (OGTT) result. Note that a confirmed random plasma glucose level of 200 mg/dl or higher in the appropriate clinical setting is diagnostic of diabetes and precludes the need for further testing.
†May be referred to as prediabetes.
DM, Diabetes mellitus; *IFG,* impaired fasting glucose; *IGT.* impaired glucose tolerance.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

(2) Genitourinary (GU) disturbances: neurogenic bladder (hesitancy, weak stream, and dribbling), impotence
(3) Cardiovascular (CV) disturbances: orthostatic hypotension, tachycardia, decreased heart rate variability (HRV). Decreased heart rate variability is associated with increased cardiac mortality, independent of ejection fraction.

c. Polyradiculopathy: painful weakness and atrophy in the distribution of ≥1 contiguous nerve roots.
d. Mononeuropathy involving cranial nerves III, IV, or VI or peripheral nerves can also occur.

5. Diabetic nephropathy: pedal edema, pallor, weakness, uremic appearance
6. Foot ulcers: occur in 15% of individuals with diabetes (annual incidence rate 2%) and are the leading causes of hospitalization; they are usually secondary to a combination of factors, including peripheral vascular insufficiency, repeated trauma (unrecognized because of sensory loss), and superimposed infection.
   a. Patient symptoms are usually less than would be expected from clinical findings, due to loss of sensation related to peripheral neuropathy.
   b. Comprehensive foot exams include visual inspection, assessment of pedal pulses, and assessment of protective sensation using a 10-g monofilament to test sensation.
   c. Prevention of foot ulcers in an individual with diabetes includes strict glucose control, patient education, prescription footwear, intensive podiatric care, and evaluation for surgical interventions
7. Neuropathic arthropathy (Charcot's joints): bone or joint deformities from repeated trauma (secondary to peripheral neuropathy; Fig. ED1-19).
8. Necrobiosis lipoidica diabeticorum: plaque-like reddened areas with a central area that fades to white-yellow found on the anterior surfaces of the legs (Fig. ED1-20); in these areas, the skin becomes very thin and can ulcerate easily.

ETIOLOGY

IDIOPATHIC DIABETES: Type 1 DM: results from beta-cell destruction, usually leading to absolute insulin deficiency

- Hereditary factors:
  1. Islet cell antibodies (found in 90% of patients within the first yr of diagnosis)
  2. Higher incidence of human leukocyte antigen (HLA) types DR3, DR4
  3. 50% concordance rate in identical twins
- Environmental factors: viral infection (possibly Coxsackie virus, mumps virus)

Type 2 DM: results from insulin resistance and a progressive defect in insulin secretion.

- Hereditary factors: 90% concordance rate in identical twins
- Environmental factors: obesity, sedentary lifestyle, high carbohydrate content in food

DIABETES SECONDARY TO OTHER FACTORS

- Hormonal excess: Cushing's syndrome, acromegaly, glucagonoma, pheochromocytoma
- Drugs: glucocorticoids, diuretics, oral contraceptives
- Insulin receptor unavailability (with or without circulating antibodies)
- Pancreatic disease: pancreatitis, pancreatectomy, hemochromatosis, cystic fibrosis
- Genetic syndromes: maturity onset diabetes of the young (MODY, monogenetic diabetes accounting for 2% to 5% of diabetes), familial hyperlipidemias, myotonic dystrophy, lipoatrophy
- Gestational diabetes (GDM): diabetes diagnosed during pregnancy that is due to pregnancy-related insulin resistance

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Diabetes insipidus
- Stress hyperglycemia
- Diabetes secondary to hormonal excess, drugs, pancreatic disease

LABORATORY TESTS

- Diagnosis of DM is made on the basis of the following tests:
  1. Fasting glucose ≥126 mg/dl on two occasions
  2. Non-FPG ≥200 mg/dl and symptoms of DM
  3. OGTT (75 g glucose load for nonpregnant individuals) with 2-hr value >200 mg/dl
  4. Glycosylated hemoglobin (HbA_{1c}) ≥6.5%
- Screening for prediabetes and diabetes in asymptomatic patients (see Table D1-13):
  1. Should be considered in adults of any age who are overweight (body mass index [BMI] >25 kg/m^2) or obese (BMI >30) and who have one or more additional risk factors for diabetes.
  2. In those who are without these risk factors, testing should begin at age 45 yr.
  3. If screen is normal, repeat testing should be carried out at least at 3-yr intervals.
- Detection and diagnosis of gestational diabetes mellitus (GDM)
  1. Screen for GDM using risk factor analysis and use of an OGTT. Pregnant women who are not known to have diabetes should be screened for gestational diabetes at 24 to 48 weeks' gestation with a 75 g oral glucose tolerance test. A diagnosis of GDM is made if any of the following levels of plasma glucose are exceeded: ≥92 mg/dl (5.1 mmol/L) when fasting, ≥80 mg/dl (10 mmol/L) at 1 hour, or ≥153 mg/dl (8.5 mmol/L) at 2 hours.
  2. Women with GDM should be screened for diabetes 6 to 12 wk postpartum and should be followed with subsequent screening for the development of diabetes or prediabetes at least every 3 yr
- Screening for diabetic nephropathy (Fig. ED1-21)
  1. Screening should be done at diagnosis and then yearly for type 2 diabetes and 5 yr after diagnosis then yearly in type 2 diabetics.
  2. Screening can be performed using a albumin:creatinine ratio (microalbumin) in a random spot urine collection or by measurement of a 24 hr urine collection for albumin, and creatinine clearance. The urine albumin to creatinine ratio (ACR) is independently associated with mortality at all levels of estimated glomerular filtration rate (eGFR) in older adults with diabetes.
  3. The diagnosis of microalbuminuria (ACR 30-299 mg/24 hr) should be based on 2 to 3 elevated levels within a 3- to 6-mo period because there is a marked variability in day-to-day albumin excretion. Patients with overt macroalbuminuria (>300 mg albumin/24 hr or albumin:creatinine ratio >300) should be followed by urine protein:creatinine ratio.
- A fasting serum lipid panel, serum creatinine, and electrolytes should be obtained yearly on all adult patients with diabetes.
- Self-monitoring of blood glucose (SMBG) is crucial for assessing the effectiveness of the management plan. The frequency and timing of SMBG varies with the needs and goals of each patient. In most patients with type 1 DM and pregnant women taking insulin, SMBG is recommended at least 3 times/day. In patients with type 2 DM not on insulin, recommendations are unclear for SMBG, but testing once or twice/day is acceptable in most patients.

TABLE D1-13 Criteria for Diabetes Screening in Asymptomatic Individuals

1. Testing should be considered in all adults who are overweight (BMI >25 kg/m2*) and have additional risk factors:
   - Physical inactivity
   - A first-degree relative with diabetes
   - High-risk ethnic population (e.g., African American, Hispanic American, Native American, Asian American, Pacific Islander)
   - Delivered a baby weighing more than 9 lb or diagnosed with gestational diabetes mellitus
   - Systemic hypertension (blood pressure >140/90 mm Hg or on antihypertensive therapy)
   - High-density lipoprotein cholesterol level <35 mg/dl or triglyceride level >250 mg/dl
   - Polycystic ovary syndrome
   - Hemoglobin A_{1c} ≥5.7%, impaired glucose tolerance or impaired fasting glucose on prior testing
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
   - History of cardiovascular disease
2. If none of the above criteria are present, screening for diabetes should begin at age 45 yr.
3. If the results are normal, screening should be repeated at least every 3 yr. Depending on initial results and risk status, more frequent testing may need to be considered.

*In some ethnic groups, such as Asians, at-risk body mass index (BMI) may be lower.
Modified from American Diabetes Association, Diagnosis and classification of diabetes mellitus *Diabetes Care* 33(Suppl. 1):S14, 2010. Borrowed from Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

- Screening for thyroid dysfunction (TSH level), Vitamin B_{12} deficiency, and celiac disease should be considered in type 1 diabetes due to the increased frequency of other autoimmune diseases in these individuals.

Rx TREATMENT

- Type 1 diabetes requires immediate initiation of insulin therapy.
- The ADA and European Association for the Study of Diabetes recommend lifestyle intervention (diet and exercise) and metformin initiation (unless contraindication exist such as serum creatinine levels ≥1.5 mg/dL in males or ≥1.4 mg/dL in females or patients ≥30 years of age with reduced renal function as measured by creatinine clearance.) at the time of diagnosis of type 2 diabetes. Therapy should then be augmented with additional agents (including early initiation of insulin therapy) to achieve adequate glycemic control.
- In Type 1 diabetes, intensive glycemic control (HbA1c <7) has been shown in randomized controlled trials (RCT) to reduce the risk of microvascular (neuropathy, retinopathy, nephropathy) and macrovascular (cardiovascular events) complications.
- In Type 2 diabetes, intensive glycemic control (HbA1c <7) has been shown in RCT to reduce the risk of microvascular complications. While intensive glucose control reduced the risk of some cardiovascular disease outcomes (such as nonfatal MI), it did not reduce the risk of cardiovascular death or all cause mortality and increased the risk of severe hypoglycemia.
- It is important to remember that tight glycemic control may burden patients with complex treatment programs, hypoglycemia, weight gain, and costs. Clinicians should individualize HbA1c targets so that they are reasonable and reflect patients' personal and clinical contexts and their informed values and preferences. A target HbA1c >7 is reasonable for motivated new diabetic patients with long life expectancies, whereas less stringent controls (HbA1c 7.5 or higher) may be reasonable in elderly patients with limited life expectancy and elevated risk of hypoglycemia.

NONPHARMACOLOGIC THERAPY

1. Diet
   a. Calories
      (1) The patient with diabetes can be started on 15 calories/lb of ideal body weight; this number can be increased to 20 calories/lb for an active person and 25 calories/lb if the patient does heavy physical labor.
      (2) The calories should be distributed as 45% to 65% carbohydrates, <30% fat, with saturated fat limited to <7% of total calories, and 10% to 30% protein. Daily cholesterol intake should not exceed 300 mg.
      (3) The emphasis should be on complex carbohydrates rather than simple and refined starches, and on polyunsaturated instead of saturated fats in a ratio of 2:1.
   b. Seven food groups
      (1) The exchange diet of the ADA includes bread or starches, meat or proteins, vegetables, fruits, fats, milk, and free foods (e.g., black tea, sugar-free gelatin).
      (2) The name of each exchange is meant to be all-inclusive (e.g., cereal, muffins, spaghetti, potatoes, rice are in the bread group; meats, fish, eggs, cheese, peanut butter are in the protein group).
      (3) The glycemic index compares the increase in blood sugar after the ingestion of simple sugars and complex carbohydrates with the increase that occurs after the absorption of glucose; equal amounts of starches do not give the same increase in plasma glucose (pasta equal in calories to a baked potato causes less of an increase than the potato); thus, it is helpful to know the glycemic index of a particular food product.
      (4) Fiber: Insoluble fiber (bran, celery) and soluble globular fiber (pectin in fruit) delay glucose absorption and attenuate the postprandial serum glucose peak; they also appear to reduce the increased triglyceride level often present in patients with uncontrolled diabetes. A diet high in fiber should be emphasized (20 to 35 g/day of soluble and insoluble fiber).
   c. Other principles
      (1) Modest sodium restriction to 2400 to 3000 mg/day. If hypertension is present, restrict to <2400 mg/day; if nephropathy and hypertension are present, restrict to <2000 mg/day.
      (2) Moderation of alcohol intake recommended (≤2 drinks/day in men, ≤1 drink/day in women).
      (3) Non-nutritive artificial sweeteners are acceptable in moderate amounts.
2. Exercise: increases the cellular glucose uptake by increasing the number of insulin receptors. The following points must be considered:
   a. Exercise program must be individualized and built up slowly. Consider beginning with 15 min of low-impact aerobic exercise 3 times per wk and increasing the frequency and duration to 30 to 45 min of moderate aerobic activity (50% to 70% of maximum age predicted heart rate) to 3 to 5 days/wk.
      (1) In the absence of contraindications, resistance training three times per wk should be encouraged.
   b. Insulin is more rapidly absorbed when injected into a limb that is then exercised, and this can result in hypoglycemia.
   c. Physical activity can result in hypoglycemia if medication dose or carbohydrate consumption is not modified. Ingestion of additional carbohydrates is recommended if pre-exercise glucose levels are <100 mg/dl.
3. Weight loss: to ideal body weight if the patient is overweight. Recent trials have shown that although weight loss has many positive health benefits for people with type 2 DM, such as slower decline in mobility, it does not reduce the number of cardiovascular events.
4. Screening for nephropathy, neuropathy, and retinopathy: annual serum creatinine and urine albumin excretion; initial comprehensive eye examination and at least annually thereafter
5. Diabetes self-management education: could also address psychosocial issues
6. Self-monitoring of blood glucose should occur three to four times per day for patients using multiple insulin injections or on insulin pump therapy
7. Perform HbA1c at least two times a year in patients who are meeting treatment goals and who have stable glycemic control
   1. HbA1c quarterly in patients whose therapy has changed or who are not meeting glycemic goals
   2. The HbA1c goal for nonpregnant adults in general is <7%
   3. In the elderly, those with comorbidities, or those at risk for complications from hypoglycemia, a more moderate glycemic target (HbA1c 7-8) may be appropriate

GENERAL Rx

- When the previous measures fail to normalize the serum glucose, oral hypoglycemic agents should be added to the regimen in type 2 DM. Tables D1-14 and D1-15 compare therapies for type 2 DM and classes of antihyperglycemic agents.
- The primary mechanism of metformin is to decrease hepatic glucose production and improve insulin sensitivity. Because metformin does not produce hypoglycemia when used as a monotherapy, it is preferred initially for most patients. Metformin reduces mean HbA1c level by 1.1%. It is contraindicated in patients with severe renal insufficiency with an estimated glomerular filtrate rate <30 ml/min, heart failure, or other clinical states of hypoperfusion, and in patients with significant liver disease.
- Sitagliptin, saxagliptin, vildagliptin, and linagliptin inhibit the enzyme DPP-4, responsible for inactivation and degradation of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These drugs, known as "gliptins," raise blood incretin levels, thereby inhibiting glucagon release and lowering blood glucose levels. When used with metformin they do not cause hypoglycemia and are preferred over sulfonylureas as second line agents. Cost is a major barrier to their use.
- Exenatide and liraglutide are glucagon-like peptide-1 (GLP-1) agonists. They are incretin mimetics that stimulate release of insulin from pancreatic beta cells and can be used as adjunctive therapy for patients with type 2 DM. GLP-1 agonists are not indicated in type 1 DM and are contraindicated in patients with severe renal impairment. Cost is a barrier to their use.
- Acarbose and miglitol inhibit pancreatic amylase and small intestinal glucosidases, thereby delaying carbohydrate absorption in the gut and reducing associated post-prandial hyperglycemia. The major side effects are flatulence, diarrhea, and abdominal cramps.
- Sulfonylureas increase insulin secretion and work best when given before meals. All sulfonylureas are contraindicated in patients who are allergic to sulfa.
- Pramlintide is a synthetic analog of human amylin, which is synthesized by pancreatic beta cells and cosecreted with insulin in response to food intake. It suppresses glucagon secretion and slows stomach emptying and can be used as an adjunctive treatment for patients with type 1 or type 2 DM who inject insulin at mealtime. Nausea is its major side effect.
- Thiazolidinediones (pioglitazone and rosiglitazone) increase insulin sensitivity and have been used in the therapy of type 2 diabetes. Serum transaminase levels should be obtained before starting therapy and monitored periodically. Thiazolidinediones, in general, result in moderate weight gain and increase the risk for heart failure and osteoporosis/fractures. Rosiglitazone has an FDA black box warning for heart failure exacerbations and myocardial

TABLE D1-14 Comparison of Therapies for Type 2 Diabetes

Property	Lifestyle	Insulins	Sulfonylureas	Metformin	α-Glucosidase Inhibitors	Glitazones	Glinides	Exenatide	Pramlintide
Target tissue	Muscle or fat	Beta cell supplement	Beta cell	Liver	Gut	Muscle	Beta cell	Various	Brain
ΔHbA_{1c} (%) as (monotherapy)	Variable	1->2	1-2	1-2	0.5-1	0.5-2	Re: 1-2 N: 0.5-1	~1	~0.5
Fasting effect	Good	Excellent	Good	Good	Poor	Good	Re: Moderate N: Poor	Poor	Poor
Postprandial effect	Good	Excellent	Good	Good	Excellent	Good	Re: Good N: Excellent	Excellent	Excellent
Severe hypoglycemia	No	Yes	Yes	No	No	No	Re: Yes N: No	No	No
Dosing interval	Continuous	qd to continuous	qd to tid	bid or tid	bid to qid	P: qd Ro: qd or bid	tid to qid with meals	bid	tid
ΔWeight (lb/yr)	+1	+3	+1 to 3	0 to –6	0 to –10	+1 to 13	+1 to 3	–6 to –12	–3 to –6
ΔInsulin	Variable	Increase	Increase	Modest decrease	Modest decrease	Decrease	Increase	Increase	None
ΔLDL	Minimal decrease	Minimal decrease	None	Decrease	Minimal decrease	Increase	None	None	None
ΔHDL	Minimal increase	None	None	Increase	None	Increase	None	Decrease	None
ΔTG	Minimal decrease	Decrease	None	Decrease	Minimal decrease	P: Decrease Ro: None	None	Decrease	None
Common problem	Recidivism, injury	Hypoglycemia, weight gain	Hypoglycemia, weight gain	Transient GI	Flatulence	Weight gain, edema, anemia	Hypoglycemia	GI	GI
Rare problem	—	—	—	Lactic acidosis	—	Hepatotoxicity?	—	—	—
Contraindications	None	None	Allergy	Renal failure, Liver failure, CHF (>80 yr old)	Intestinal disease	Hepatocellular disease	—	None	None
Cost ($/mo)	0-200	30-450	10-15	30-60	40-80	75-180	70-110	170-200	200-400
Maximum effective dose	—	1-2 U/kg per day	maximum or double starting	1000 mg bid	50 mg tid	P: 45 mg qd Ro: 4 mg bid	Re: 2 mg tid N: 120 mg tid	10 μg bid	120 μg ac

Δ, Change; *ac,* before food; *CHF,* congestive heart failure; *GI,* gastrointestinal disturbance; *HbA_{1c},* glycosylated hemoglobin; *HDL,* high-density lipoprotein; *LDL,* low-density lipoprotein; *N,* nateglinide; *P,* pioglitazone; *Re,* repaglinide; *Ro,* rosiglitazone; *TG,* triglycerides.

From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

TABLE D1-15 Classes of Antihyperglycemic Therapy

Class	Representative Agents	Major Action	HbA_{1c} Lowering (%)	Fasting or Prandial Effect	Usual Dosing Frequency (Doses/Day)	Route	Hypoglycemia	Weight Effect	CVD Risk Factor Benefits	Important Contraindications	Daily Cost ($)
Lifestyle	—	Broad	>1	Both	—	—	No	Loss	Yes	—	—
Biguanide	Metformin	Liver sensitizer	>1	Fasting	1-2	Oral	No	Neutral	Modest	Renal or hepatic failure	<$1
Sulfonylurea	Glimepiride, glipizide	Insulin secretagogue	>1	Fasting	1-2	Oral	Yes	Gain	Negligible	—	<<$1
Meglitinide	Repaglinide	Insulin secretagogue	>1	Both	With meals	Oral	Yes	Gain	Negligible	—	~$5
Benzoic acid–derived	Nateglinide	Insulin secretagogue	<1	Prandial	With meals	Oral	Minimal	Minimal	Negligible	—	~$5
Basal insulin	NPH, glargine, detemir	Insulin supplement/substitute	>1	Fasting	1	SQ	Yes++	Gain++	Lowers TG	—	~$5
Bolus insulin	R, lispro, aspart, glulisine	Insulin supplement/substitute	>1	Prandial	With meals	SQ	Yes++	Gain++	Lowers TG	—	~$5
Thiazolidinediones	Pioglitazone, rosiglitazone	Peripheral sensitizer	>1	Fasting	1	Oral	No	Gain++	Variable (see text)	Heart or liver failure	~$5
α-Glucosidase inhibitors	Acarbose, miglitol	Slow carbohydrate absorption	<1	Prandial	With meals	Oral	No	Neutral	Negligible	—	~$3
Amylinomimetics	Pramlintide	Broad	<1	Prandial	With meals	SQ	No	Loss	Negligible	—	~$10
GLP1 receptor agonists	Exenatide	Broad	~1	Prandial	2	SQ	No	Loss	Modest with weight loss	Pancreatitis, renal failure	~$9
Long-acting GLP1 receptor agonists	Liraglutide, albiglutide, dulaglutide	Broad	>1	Both	1	SQ	No	Loss	Lowers BP	Pancreatitis, medullary thyroid cancer	~$13
DPP4 inhibitors	Sitagliptin, saxagliptin	Improved insulin/ glucagon secretion	<1	Both	1	Oral	No	Neutral	Negligible	Pancreatitis	~$7
Bile acid sequestrants	Colesevelam	Uncertain	<1	Prandial	1-2	Oral	No	Neutral	Lowers LDL	Hypertriglyceridemia	~$9
$SGlT_2$ inhibitor	Canagliflozin, dapagliflozin	Decrease renal glucose reabsorption, increase urinary glucose excretion	<1	Both	1	Oral	No	Loss	Negligible	Volume dilution	~$10

BP, Blood pressure; *CVD,* cardiovascular disease; *LDL,* low-density lipoprotein; *$SGLT_2$,* sodium-glucose co-transporter 2; *SQ,* subcutaneous; *TG,* triglyceride.
Modified from Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.

ischemia. Pioglitazone and rosiglitazone cause increased incidence of bladder cancer.

- Sodium-glucose co-transporter 2 ($SGLT_2$) inhibitors (e.g., canagliflozin, dapagliflozin) have recently been approved by the FDA for oral treatment of type 2 DM. By inhibiting $SGLT_2$, these medications decrease glucose reabsorption, increase urinary glucose excretion, and lower blood glucose levels ({down arrow} HbA_{1C} by 0.7%). Side effects include increased risk of genital mycotic infections, UTIs, and volume depletion. Higher cost and limited drug formulary availability are limiting factors.
- Combination therapy of various hypoglycemic agents is commonly used when monotherapy results in inadequate glycemic control.
- Insulin is indicated for the treatment of all type 1 DM and for type 2 DM patients whose condition cannot be adequately controlled with diet and oral agents. The American College of Endocrinology and the American Association of Clinical Endocrinologists recommend initiation of insulin therapy in patients with type 2 diabetes and an initial HbA1c level >9%, or if the diabetes is uncontrolled despite optimal oral glycemic therapy. Insulin therapy may be initiated as augmentation, starting at 0.3 unit/kg, or as replacement, starting at 0.6 to 1.0 unit/kg. Table D1-16 describes commonly used types of insulin.
  1. The risks of insulin therapy include weight gain, hypoglycemia, and in rare cases, allergic or cutaneous reactions.
  2. Replacement insulin therapy should mimic normal release patterns.
     a. Approximately 50% to 60% of daily insulin can be given as a long-acting insulin (NPH, ultralente, glargine, detemir) injected once or twice daily
     b. The remaining 40% to 50% can be short-acting (regular) or rapid-acting (lispro, aspart, glulisine) to cover mealtime carbohydrates and correct increased current glucose levels.
- Continuous subcutaneous insulin infusion (CSII, or insulin pump) provides comparable or slightly better control than multiple daily injections. It should be considered for diabetes presenting in childhood or adolescence and during pregnancy. The guidelines for insulin pump therapy from the American Association of Diabetes Educators include "frequent and unpredictable fluctuations in blood glucose" and "patient perceptions that diabetes management impedes the pursuit of personal or professional goals."
- Low-dose aspirin (ASA; 81 mg/day) has been proven to lower the risk of subsequent myocardial infarction, stroke, or vascular death in secondary prevention studies. The ADA recommends low-dose aspirin for primary prevention in diabetic patients with one additional cardiovascular risk factor, including age older than 40 yr, cigarette smoking, hypertension, obesity, albuminuria, hyperlipidemia, and family history of coronary artery disease.
- Measure fasting lipid profile at least annually in adults.
  1. All patients with diabetes with one or more additional risk factors for cardiovascular disease should be on statin therapy together with lifestyle modification regardless of baseline lipid levels.
  2. Diabetic patients aged 40 to 75 with LDL cholesterol of 70 to 189 mg/dl and without clinical atherosclerotic cardiovascular disease (ASCVD) should receive at least moderate-intensity statin therapy and consider high-intensity statin therapy if 10-year ASCVD risk is >=7.5%.
- Aggressive antihypertensive therapy is recommended to keep systolic blood pressure (BP) <130 and diastolic BP <80 mm Hg. Use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) to decrease albuminuria and for prevention of progression of kidney disease should be considered regardless of presence of hypertension. Combination therapy with an ACE inhibitor and an ARB should be avoided due to increased risk of adverse effects among patients with diabetic nephropathy.
- Bariatric surgery should be considered in adults with BMI >35 kg/m^2 and type 2 diabetes, especially if the diabetes is difficult to control with lifestyle and pharmacologic therapy.
- Treat hypoglycemia in a conscious person with glucose tab or gel 15 to 20 g, and intramuscular injection of glucagon if unconscious. Patient and family members should be instructed on the administration of glucagon for individuals at significant risk for severe hypoglycemia.

TABLE D1-16 Types of Insulin[a]

Preparation	Brand	Onset (hr)[b]	Peak (hr)	Duration (hr)[c]	Route
Insulin Aspart	NovoLog[d]	<0.25	1-3	3-5	SC, IV, CSII
Insulin Aspart Protamine/Insulin Aspart	NovoLog Mix 70/30[d]	<0.25	1-4	24	SC
Insulin Detemir	Levemir	1	None	24	SC
Insulin Glargine	Lantus[d]	1.1	None	≥24	SC
Insulin Glulisine	Apidra[d]	≤0.25	1	2-4	SC, IV
Insulin Lispro	Humalog[d]	<0.25	1	3.5-4.5	SC
Insulin Lispro Protamine/Insulin Lispro	Humalog Mix 75/25[d]	≤0.25	0.5-1.5	24	SC
	Humalog Mix 50/50[d]	≤0.25	1	16	SC
Insulin Injection Regular (R)	Humulin R[f]	0.5	2-4	6-8	SC, IM, IV
	Novolin N[e]	0.5	2.5-5	8	SC, IM, IV
Insulin Isophane Suspension (NPH)/ Regular Insulin (R)	Humulin 70/30[f]	0.5	2-12	24	SC
	Humulin 50/50[f]	0.5	3-5	24	SC
	Novolin 70/30[e]	0.5	2-12	24	SC
Insulin Isophane Suspension (NPH)	Humulin N[f]	1-2	6-12	18-24	SC
	Novolin N[e]	1.5	4-12	24	SC

[a]Injectable insulins listed are available in a concentration of 100 U/ml; Humulin R, in a concentration of 500 U/ml for SC injection. SC injection only is available by prescription from Lilly for insulin-resistant patients who are hospitalized or in need of medical supervision.
[b]Onset for injectable formulations is always for the subcutaneous (SC) route. All times are approximate.
[c]Maximum effect occurs between these times; actual effect may last longer.
[d]Recombinant human insulin analogue (using *E. coli*).
[e]Recombinant (using *S. cerevisiae*).
[f]Recombinant (using *E. coli*).
CSII, Continuous subcutaneous infusion; *IM,* intramuscularly; *IV,* intravenously.

DISPOSITION

- Diabetic retinopathy occurs in nearly 15% of patients with diabetes after 15 yr of diagnosis and increases 1%/yr after diagnosis. Retinal laser photocoagulation and vitrectomy are effective treatment modalities. Prevention is best accomplished by strict glucose and BP control. Early blockade of the renin-angiotensin system has been shown to slow progression of retinopathy in patients with type 1 diabetes.
- The frequency of neuropathy in patients with type 2 diabetes approaches 70% to 80%. It can be subdivided into sensorimotor neuropathy and autonomic neuropathy. Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, is effective and FDA approved for relief of diabetic peripheral neuropathy. Pregabalin and gabapentin (900 to 3600 mg/day) are also effective for the symptomatic treatment of peripheral neuropathic pain. Topical capsaicin, 5% lidocaine transdermal patches, amitriptyline, and carbamazepine are also modestly effective.
- Diabetic gastroparesis is most often seen in patients who have had diabetes for at least 10 yr and typically have retinopathy, neuropathy, and nephropathy. Major manifestations are postprandial fullness, nausea, vomiting, and bloating. Pharmacologic therapy involves prokinetic agents (metoclopramide). Endoscopic injection of botulinum toxin into the pylorus and gastric electrical stimulation (using f electrodes placed laparoscopically in the muscle wall of the stomach antrum and connected to a neurostimulator) represent newer approaches to nonpharmacologic therapy.

- Nephropathy: The first sign of renal involvement in patients with DM is most often microalbuminuria, which is classified as incipient nephropathy. Before the current period of intensive glycemic control and blood pressure with ACE inhibitors and angiotensin receptor blockade, it was suggested that 25% to 45% of diabetic patients would develop clinically evident renal disease (proteinuria) and 4% to 17% would progress to end-stage renal disease. In the current era of intensive glycemic and blood pressure control and ACE/ARB use, clinically evident diabetic nephropathy has declined to 9% and end-stage renal disease 2% to 7%.
- Infections are generally more common in patients with diabetes because of multiple factors, such as impaired leukocyte function, decreased tissue perfusion secondary to vascular disease, repeated trauma because of loss of sensation, and urinary retention secondary to neuropathy.
- Prevention/delay of type 2 diabetes: Patients with prediabetes should achieve weight loss of 5% to 10% of body weight and increase physical activity to at least 150 min/wk of moderate activity such as walking. Metformin therapy may be considered in those at high risk, especially if they have hyperglycemia (HbA1c ≥6) despite lifestyle interventions.

REFERRAL

- Patients with diabetes should be advised to have annual ophthalmologic examinations. In type 1 DM, ophthalmologic visits should begin within 3 to 5 yr of diagnosis, whereas type 2 DM patients should be seen from disease onset.
- Podiatric care can significantly reduce the rate of foot infections and amputations in patients with DM. Noninfected neuropathic foot ulcers require debridement and reduction of pressure.
- Nephrology consultation in all cases of proteinuria, hyperkalemia, uncontrolled BP, and when GFR has decreased to <30 ml/min/1.73 m^2.

PEARLS & CONSIDERATIONS

COMMENTS

- Because normalization of serum glucose level is the ultimate goal, every patient with diabetes should measure his or her blood glucose with commercially available glucometers unless contraindicated by senility or blindness.
- Underinsured children and those with psychiatric illness are at greater risk for acute complications in type 1 DM and require frequent monitoring and aggressive risk management with diet, exercise, and periodic laboratory evaluation.
- Significant sustained weight loss using bariatric surgery has been reported as effective in achieving remission of type 2 diabetes in morbidly obese patients. Bariatric surgery may be considered for adults with BMI >35 kg/m^2 and type 2 DM, especially if diabetes or associated comorbidities are difficult to control with lifestyle and pharmacologic therapy.
- Cigarette smoking predicts incident type 2 diabetes. For a smoker at risk for diabetes, smoking cessation should be coupled with strategies for diabetes prevention and early detection.
- Glycemic control in hospitalized patients: The American College of Physicians (ACP) recommends against using intensive insulin therapy to strictly control blood glucose in non-surgical intensive care unit (SICU)/medical intensive care unit (MICU) in patients with or without DM. The ACP recommends a target blood glucose level of 140 to 200 mg/dl if insulin therapy is used.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Diabetes Mellitus Type 1 (Patient Information)
Diabetes Mellitus Type 2 (Patient Information)
Diabetic Ketoacidosis (Related Key Topic)
Diabetic Polyneuropathy (Related Key Topic)
Diabetic Retinopathy (Related Key Topic)
Gestational Diabetes Mellitus (Related Key Topic)
Hyperosmolar Hyperglycemic Syndrome (Related Key Topic)

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EVIDENCE

Abstract[1]

Background:
The role of weight training in the primary prevention of type 2 diabetes mellitus (T2DM) is largely unknown.
Methods:
To examine the association of weight training with risk of T2DM in US men and to assess the influence of combining weight training and aerobic exercise, we performed a prospective cohort study of 32,002 men from the Health Professionals Follow-up Study observed from 1990 to 2008. Weekly time spent on weight training and aerobic exercise (including brisk walking, jogging, running, bicycling, swimming, tennis, squash, and calisthenics/rowing) was obtained from questionnaires at baseline and biennially during follow-up.
Results:
During 508 332 person-years of follow-up (18 years), we documented 2278 new cases of T2DM. In multivariable-adjusted models, we observed a dose-response relationship between an increasing amount of time spent on weight training or aerobic exercise and lower risk of T2DM ($P < .001$ for trend). Engaging in weight training or aerobic exercise for at least 150 minutes per week was independently associated with a lower risk of T2DM of 34% (95% CI, 7%-54%) and 52% (95% CI, 45%-58%), respectively. Men who engaged in aerobic exercise and weight training for at least 150 minutes per week had the greatest reduction in T2DM risk (59%; 95% CI, 39%-73%).
Conclusions:
Weight training was associated with a significantly lower risk of T2DM, independent of aerobic exercise. Combined weight training and aerobic exercise conferred a greater benefit. A

Abstract[2]

Background:
Physical activity (PA) is considered a cornerstone of diabetes mellitus management to prevent complications, but conclusive evidence is lacking.
Methods:
This prospective cohort study and meta-analysis of existing studies investigated the association between PA and mortality in individuals with diabetes. In the EPIC study (European Prospective Investigation Into Cancer and Nutrition), a cohort was defined of 5859 individuals with diabetes at baseline. Associations of leisure-time and total PA and walking with cardiovascular disease (CVD) and total mortality were studied using multivariable Cox proportional hazards regression models. Fixed- and random-effects meta-analyses of prospective studies published up to December 2010 were pooled with inverse variance weighting.
Results:
In the prospective analysis, total PA was associated with lower risk of CVD and total mortality. Compared with physically inactive persons, the lowest mortality risk was observed in moderately active persons: hazard ratios were 0.62 (95% CI, 0.49-0.78) for total mortality and 0.51 (95%CI, 0.32-0.81) for CVD mortality. Leisure-time PA was associated with lower total mortality risk, and walking was associated with lower CVD mortality risk. In the meta-analysis, the pooled random-effects hazard ratio from 5 studies for high vs low total PA and all-cause mortality was 0.60 (95% CI, 0.49-0.73).
Conclusions:
Higher levels of PA were associated with lower mortality risk in individuals with diabetes. Even those undertaking moderate amounts of activity were at appreciably lower risk for early death compared with inactive persons. These findings provide empirical evidence supporting the widely shared view that persons with diabetes should engage in regular PA. A

Abstract[3]

Complications
Objective:
The incidence of type 1 diabetes complications appears to be decreasing, but the relative contributions of risk factors are unclear. We thus estimated the effect of modifiable risk factors on the incidence of a composite end point, major outcomes of diabetes (MOD).
Methods:
The Pittsburgh Epidemiology of Diabetes Complications (EDC) Study was used to derive two cohorts based on diabetes diagnosis year (1960 to 1969 and 1970 to 1980). Baseline exam data in the current analysis for the 1960s group were collected in 1986 to 1988 and for the 1970s in 1996 to 1998. Each group was followed for 8 years for MOD incidence (diabetes-related death, myocardial infarction, revascularization procedure/blockage ≤50%, stroke, end-stage renal disease, blindness, and amputation). Assessed risk factors include the following: HbA1c, hypertension, microalbuminuria, BMI, hypercholesterolemia, and smoking. Accelerated failure time models were used to estimate the acceleration factor.
Results:
MOD incidence decreased in the 1970s cohort (15.8% [95% CI 11.6 to 21.4]) compared with the 1960s (22.6% [17.0 to 29.1]) over the 8-year follow-up ($P = 0.06$). Hypertension and microalbuminuria were associated with significantly accelerated MOD incidence in both cohorts ($P < 0.01$ for both). High HbA1c ($P = 0.0005$), hypercholesterolemia ($P = 0.01$), and current smoking ($P = 0.003$) significantly accelerated the incidence of MOD in the 1960s but not 1970s cohort. BMI was not associated with MOD in either cohort.
Conclusions:
These results suggest that hypertension and microalbuminuria remain important predictors of complications that are not being adequately addressed. A

Abstract[4]

Objective:
To assess whether intermittent real-time continuous glucose monitoring (CGM) improves glycemic control and pregnancy outcome in unselected women with pregestational diabetes.
Methods:
A total of 123 women with type 1 diabetes and 31 women with type 2 diabetes were randomized to use real-time CGM for 6 days at 8, 12, 21, 27, and 33 weeks in addition to routine care, including self-monitored plasma glucose seven times daily, or routine care only. To optimize glycemic control, real-time CGM readings were evaluated by a diabetes caregiver. HbA1c, self-monitored plasma glucose, severe hypoglycemia, and pregnancy outcomes were recorded, with large-for-gestational-age infants as the primary outcome.
Results:
Women assigned to real-time CGM (n = 79) had baseline HbA1c similar to that of women in the control arm (n = 75) (median 6.6 [range 5.3 to 10.0] vs. 6.8% [5.3 to 10.7]; $P = 0.67$) (49 [34 to 86] vs. 51 mmol/mol [34 to 93]). Forty-nine (64%) women used real-time CGM per protocol. At 33 weeks, HbA1c (6.1 [5.1 to 7.8] vs. 6.1% [4.8 to 8.2]; $P = 0.39$) (43 [32 to 62] vs. 43 mmol/mol [29e66]) and self-monitored plasma glucose (6.2 [4.7 to 7.9] vs. 6.2 mmol/L [4.9 to 7.9]; $P = 0.64$) were comparable regardless of real-time CGM use, and a similar fraction of women had experienced severe hypoglycemia (16 vs. 16%; $P = 0.91$). The prevalence of large-for-gestational-age infants (45 vs. 34%; $P = 0.19$) and other perinatal outcomes were comparable between the arms.
Conclusions:
In this randomized trial, intermittent use of real-time CGM in pregnancy, in addition to self-monitored plasma glucose seven times daily, did not improve glycemic control or pregnancy outcomes in women with pregestational diabetes.
Current treatment of diabetes in pregnancy relies on intermittent self-monitoring of blood glucoses using finger sticks to monitor capillary blood glucoses.
Continuous glucose monitoring (CGM) systems are a relatively new technology that allow frequent glucose measurements (every 5 minutes) and the ability to monitor glucose trends in real time. Whereas there has been great optimism that the more liberal use of CGM systems will improve outcomes in diabetic pregnancy, the evidence speaks

otherwise. Voormolen,[5] after a systematic review concluded "Current evidence on the efficacy of CGM on improving glycemic control during pregnancy as well as on the effectiveness on pregnancy outcome is limited to two randomized controlled trials (RCTs) with contradicting results. Evidence on the cost effectiveness is lacking. Further proper RCTs on the effectiveness and cost-effectiveness of CGM in pregnancy are required before wide implementation in practice." Nonetheless many investigators believe that there is a huge potential for their use in research and clinical practice and trials. It is anticipated that CGMs will improve detection of both hyperglycemia and hypoglycemia and help stabilize glucose levels so that HbA1c levels can be kept at reasonable levels.

In Secher et al's randomized trial, CGM did not improve glucose control compared with multiple glucose measurements. HbA1c, self-monitored plasma glucose values, and plasma glucose profiles of biochemical hypo- or hyperglycemia were similar throughout pregnancy in women using real-time CGM versus control subjects for the entire study population Sixteen percent of women in each group experienced hypoglycemia. The inevitable conclusion from the trial is that CGM is not ready for prime time. It may be helpful in selected cases. Intensive focus in gestational diabetes needs to be directed at diet, including carbohydrate counting and control of weight gain.

Starikov et al.[6] posed the question as to whether the HbA1c in the first trimester would predict adverse pregnancy outcomes. The frequencies of composite maternal adverse pregnancy outcomes (birth at <37 weeks, preeclampsia, and medically indicated birth <39 weeks), and composite fetal adverse pregnancy outcomes (shoulder dystocia, Apgar scores <7 at 5 minutes, small for gestational age [SGA], large for gestational age [LGA], and stillbirth) were compared between HbA1c categories (<6.5, 6.5 to e7.4, 7.5 to e8.4, and $≤8.5%). There was an increased risk of shoulder dystocia in those women with HbA1c ≤$8.5% but otherwise no statistically significant correlations. However, the teaching remains that tight control of blood sugars before conception reduces the prevalence of birth defects in insulin-dependent diabetics. This practice should be continued.[7]

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Evidence-Based References

Grnøtved A Rimm EB, Willett WC, et al.: A prospective study of weight training and risk of type 2 diabetes mellitus in men, *Arch Intern Med* 172:1306–1312, 2012. Ⓐ

Sluik D, Buijsse B, Muckelbauer R et al.: Physical activity and mortality in individuals with diabetes mellitus: a prospective study and meta-analysis, *Arch Intern Med* 172:1285–1295, 2012. Ⓐ

Miller RG, Secrest AM, Ellis D et al.: Changing impact of modifiable risk factors on the incidence of major outcomes of type 1 diabetes: The Pittsburgh Epidemiology of Diabetes Complications Study, *Diabetes Care* 36:3999–4006, 2013. Ⓑ

Secher AL, Ringholm L, Andersen HU, et al.: The effect of real-time continuous glucose monitoring in pregnant women with diabetes: a randomized controlled trial, *Diabetes Care* 36:1877–1883, 2013. Ⓐ

Voormolen DN, DeVries JH, Evers IM, Mol BW, Franx A: The efficacy and effectiveness of continuous glucose monitoring during pregnancy: a systematic review, *Obstet Gynecol Surv* 68:753–763, 2013.

Starikov RS, Inman K, Chien EK, et al.: Can hemoglobin A1c in early pregnancy predict adverse pregnancy outcomes in diabetic patients? *J Diabetes Complications* 28:203–207, 2014.

Cordua S, Secher AL, Ringholm L, Damm P, Mathiesen ER: Real-time continuous glucose monitoring during labour and delivery in women with type 1 diabetes - observations from a randomized controlled trial, *Diabet Med* 30:1374–1381, 2013.

SUGGESTED READINGS

American Diabetes Association Position Statement: Standards of medical care in diabetes-2010, *Diabetes Care* 33:S1, January 2010.

Balducci J et al.: Effect of an intensive exercise intervention strategy on modifiable cardiovascular risk factors in subjects with type 2 DM, *Arch Intern Med* 170(20):1794–1803, 2010.

Culver A et al.: Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative, *Arch Intern Med* 172(2):144–152, 2012.

Esposito K et al.: Effects of a Mediterranean-style diet on the need for antihyperglycemic drug therapy in patients with newly diagnosed type 2 diabetes, *Ann Intern Med* 151:306–314, 2009.

Fried LF et al.: Combined angiotensin inhibition for the treatment of diabetic nephropathy, *N Engl J Med* 369:1892–1903, 2013.

Inzucchi SE: Diagnosis of diabetes, *N Engl J Med* 367:542–550, 2012.

Inzucchi SE: Management of hyperglycemia in the hospital setting, *N Engl J Med* 355:1903, 2006.

Inzucchi SE et al.: Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association and the European Association for the Study of Diabetes, *Diabetes Care* 35:1364, 2012.

Kanji JN et al.: Does this patient with diabetes have large-fiber peripheral neuropathy, *JAMA* 303:1526–1532, 2010.

Kavanagh BP, McCowen KC: Glycemic control in the ICU, *N Engl J Med* 363: 2540–2546, 2010.

Kelly TN: Systematic review: Glucose control and cardiovascular disease in type 2 diabetes, *Ann Intern Med* 151:394–403, 2009.

Mauer M et al.: Renal and retinal effects of enalapril and losartan in type 1 diabetes, *N Engl J Med* 361:40–51, 2009.

Montori V, Fernandez-Balsells M: Glycemic control in type 2 diabetes: time for an evidence-based about-face? *Ann Intern Med* 150:803–808, 2009.

Mooradian A et al.: Narrative review: a rational approach to starting insulin therapy, *Ann Intern Med* 145:125, 2006.

Nauck M: Incretin-based therapies for type 2 diabetes mellitus: properties, functions, and clinical implications, *Am J Med* 124:S3–S18, 2011.

O'Hare A et al.: Prognostic implications of the urinary albumin to creatinine ratio in veterans of different ages with diabetes, *Arch Intern Med* 170(11):930–936, 2010.

Petnick A: Insulin management of type 2 diabetes mellitus, *Am Fam Phys* 84(2):183–190, 2011.

Pickup JC: Insulin-pump therapy for type 1 diabetes mellitus, *N Engl J Med* 366:1616–1624, 2012.

Pignone M et al.: Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation, *Circulation* 121:2694, 2010.

Qaseem A et al.: Use of intensive insulin therapy for the management of glycemic control in hospitalized patients: a clinical practice guideline from the American College of Physicians, *Ann Intern Med* 154:260–267, 2011.

Rejeski WJ et al.: Lifestyle change and mobility in obese adults with type 2 diabetes, *N Engl J Med* 366:1209–1217, 2012.

Ripsin CM et al.: Management of blood glucose in type 2 diabetes mellitus, *Am Fam Phys* 79(1):29–36, 2009.

The DCCT/EDIC Research Group: Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes, *N Engl J Med* 365:2366, 2011.

The Task Force on Diabetes and Cardiovascular Diseases of the European Society of Cardiology (ESC) and of the European Association for the Study of Diabetes (EASD): Guidelines on diabetes, pre-diabetes, and cardiovascular disease: executive summary, *Eur Heart J* 28:88–136, 2007.

Yeh HC et al.: Smoking, smoking cessation, and risk for type 2 diabetes mellitus, *Ann Intern Med* 152:10–17, 2010.

FIGURE ED1-19 Diabetic neuropathy of the hindfoot. Destruction of the joint with collapse and fragmentation. (From Hochberg MC et al [eds]: *Rheumatology*, ed 3, St Louis, 2003, Mosby.)

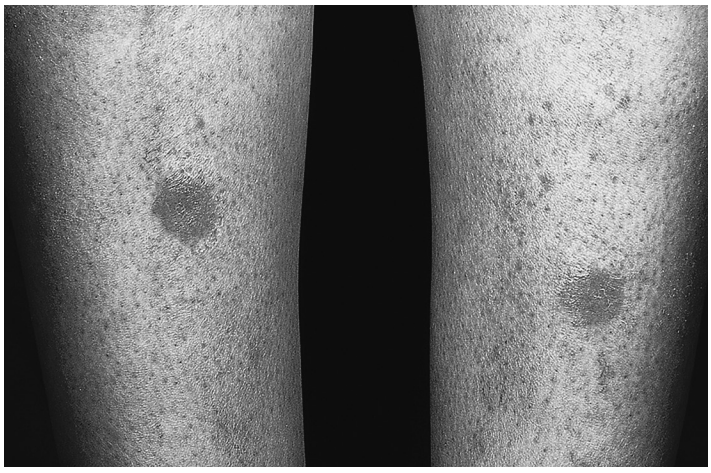

FIGURE ED1-20 Necrobiosis lipoidica: symmetrical early lesions with erythema. (Courtesy of the Institute of Dermatology; from McKee PH et al [eds]: *Pathology of the skin with clinical correlations,* ed 3, St Louis, 2005, Mosby.)

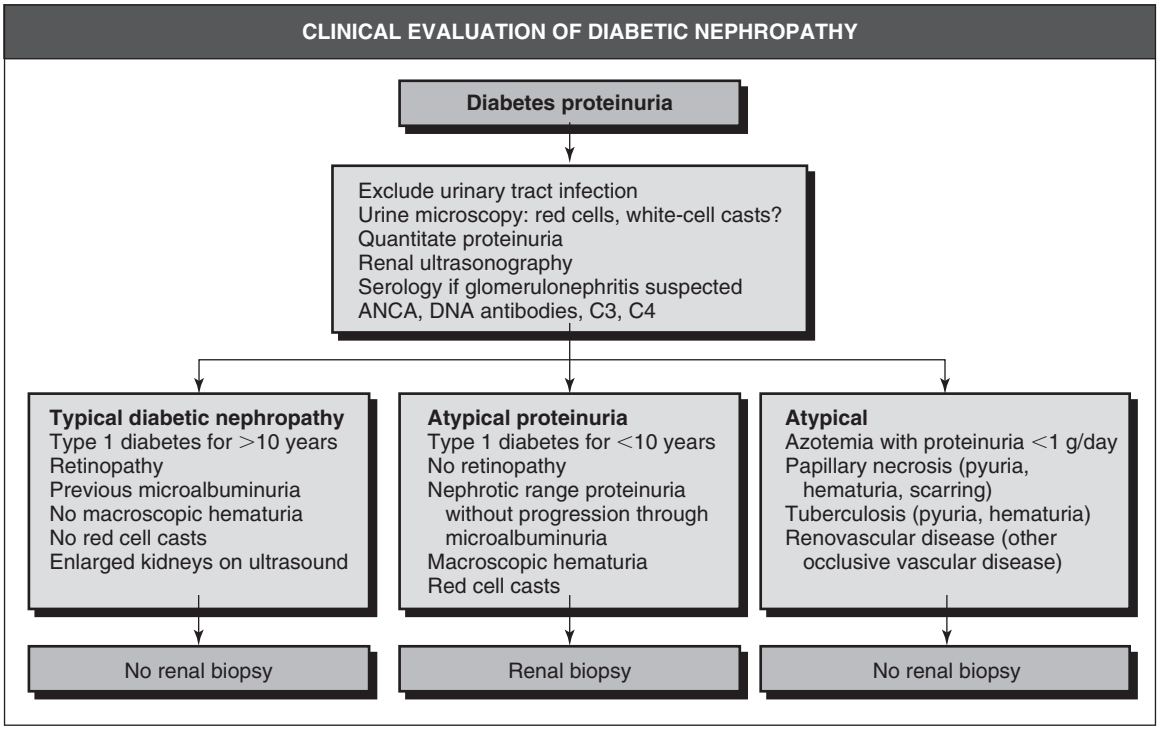

FIGURE ED1-21 Clinical evaluation of diabetic renal disease. *ANCA,* Antineutrophil cytoplasmic antibody. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

BASIC INFORMATION

DEFINITION

Diabetic foot infections (DFIs) are a common and potentially serious problem in persons with diabetes. They usually arise from either a skin ulceration that occurs secondarily to peripheral neuropathy or in a wound caused by some form of trauma. The infection usually involves one or more bacteria and can spread to contiguous tissues including bone, causing an osteomyelitis.

SYNONYMS

Diabetic foot ulcer

ICD-9CM CODES

250.80 Diabetes with other specified manifestations, type II or unspecified type, not stated as uncontrolled

707.15 Ulcer of other part of foot

ICD-10CM CODES

E10.5 Diabetes mellitus with peripheral circulatory complications

E10.6 Diabetes mellitus with other specific complications

E11.621 Type 2 diabetes mellitus with foot ulcer

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: DFIs are the most common cause of hospitalizations for diabetic patients. They account for 20% of all hospital admissions. Nearly one in six patients will die within a year of their infection.

PEAK INCIDENCE: More common in Hispanics, African Americans, and Native Americans due to increased rates of diabetes in those populations

PREVALENCE: 25 million people in the United States have diabetes, of which 15% to 25% will develop a foot ulcer in their lifetime and more than 50% of these will become infected.

PREDOMINANT SEX AND AGE: Females greater than males

RISK FACTORS

- Diabetes greater than 10 years
- Poor glucose control
- Peripheral neuropathy: altered protective sensation and altered pain response
- Diabetic angiopathy: atherosclerotic obstruction of larger vessels leading to peripheral vascular disease
- Evidence of increased local pressure: callus or erythema

PHYSICAL FINDINGS & CLINICAL PRESENTATION

A. Based on guidelines by Infectious Diseases Society of America, infection is present if obvious purulent drainage and/or the presence of two or more signs of inflammation
1. Erythema
2. Pain
3. Tenderness
4. Warmth
5. Induration

B. Systemic signs of infection include:
1. Anorexia, nausea/vomiting
2. Fever, chills, night sweats
3. Change in mental status and recent worsening of glycemic control

C. Various classifications exist but Wagner's Classification is one of most used:
0: Pre-ulcerative area without open lesion
1: Superficial ulcer (partial/full thickness)
2: Ulcer deep to tendon, capsule, bone
3: Stage 2 with abscess, osteomyelitis, or joint sepsis
4: Localized gangrene
5: Global foot gangrene

D. Etiology: most diabetic foot infections are polymicrobial (can involve 5-7 different bacteria) and depend on the extent of involvement
1. Superficial infections are likely due to gram-positive skin bacteria:
   a. *Staphylococcus aureus*, includes methicillin-resistant *S. aureus* (MRSA)
   b. *Streptococcus agalactiae* (group B streptococcus) and *Streptococcus pyogenes* (group A streptococcus)
   c. Coagulase-negative *Staphylococcus*
2. Infections that are deep, chronically infected, or previously treated are likely to be polymicrobial:
   a. Include above bacteria plus enterococci, gram-negative rods including
   b. *Pseudomonas aeruginosa* and anaerobes
   c. With gangrene can expect more anaerobic bacteria such as *Clostridia* and *Bacteroides* species
   d. Patients with multiple admissions can have more resistant bacteria such as ESBL-type resistant gram-negative rod bacteria, MRSA, and *Acinetobacter*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Other inflammatory conditions that can mimic diabetic foot infections include:

- Crystal-associated arthritis such as gout
- Trauma
- Acute Charcot arthropathy from long-standing diabetes
- Venous stasis ulcers
- Deep vein thrombosis

WORKUP

Evaluation of a patient with a DFI involves determining the extent and severity of the infection, identifying the underlying factors that predispose to the infection, and determining the microbiologic etiology.

Physical Examination

- Vital signs: fever, chills, hypotension, tachycardia can be present.
- Detailed wound description: length, width, and depth of wound, consistency of drainage, character of wound base: granular fibrous necrotic
- Determination of osteomyelitis: highly likely if bone visible. A positive probe test to bone has a sensitivity of 66% and specificity of 85% in diagnosing bone infection.
- Necrotizing infections may present with cutaneous bullae, soft tissue gas, foul odor, and skin discoloration (Fig. D1-22).
- Severe infections may present with gangrene, tissue necrosis, and evidence of tissue ischemia, all of which may be limb threatening.

LABORATORY TESTS

Important to obtain at baseline and to assess response to therapy

- Fewer than 50% of patients have an elevated WBC.
- Determine BUN/Cr, acidosis, hemoglobin A_{1C}, and blood sugar.
- Acute phase reactants: Sed rate and CRP are markers for inflammation.
  1. Sed rate >70 increases probability of bone infection.
- Serum prealbumin and albumin are markers for nutritional status and ability to heal.
- An ulcer size larger than 2 cm^2 is indicative of osteomyelitis.
- Gram stains and cultures: superficial cultures should not be obtained as they may contain colonizing bacteria and instead deep tissue cultures (aerobic and anaerobic) should be obtained.

IMAGING STUDIES

- Plain film x-ray evaluates bones and soft issues and can detect presence of tissue gas, which would represent an emergent situation (Fig. D1-23).
- Osteomyelitis appears as radiolucencies, periosteal reaction, and destructive changes. Plain films are 67% specific and 60% sensitive for osteomyelitis.
- Bone scan: Indium-111 or technetium-99 can distinguish acute and chronic infections.

FIGURE D1-22 Foot: Severe diabetic foot infection with significant tissue swelling and necrosis.

FIGURE D1-23 X-ray: Significant soft tissue swelling in midfoot with numerous gas bubbles seen in the soft tissues.

- CT and MRI: MRI is the most sensitive and specific test to detect osteomyelitis and abscess formation.

OTHER DIAGNOSTIC TESTS

- Noninvasive vascular studies: Ankle brachial index (ABI): <0.90 or >1.30 indicates peripheral arterial disease
- Transcutaneous oxygen (TcPO2) tension measurements: predictive of wound healing failure at levels below 25 mm Hg

Rx TREATMENT

Empiric antibiotic regimen should be started based on likely pathogens suspected and severity of disease. Wound management and debridement including surgical consultation are important as well.

NONPHARMACOLOGIC THERAPY

- Good nutrition will promote wound healing.
- Glycemic control will promote healing.
- Fluid and electrolyte balance will improve healing.

ACUTE GENERAL TREATMENT

Wound management

- Debridement of callus and necrotic tissues by wound care specialist or surgeon and at times may require multiple debridements.
- Wound dressing: to absorb exudates and promote healing. Many products are available but none has been proven superior and include:
  1. Enzymes
  2. Gels
  3. Hydrocolloids
  4. Antiseptics containing iodine or silver salts
  5. Honey
- Relieve pressure on the foot: casts or special shoes.
- Amputation or revascularization procedures such as angioplasty or bypass grafting may be necessary.

Antibiotic management

- Prior to receiving culture results an empiric antibiotic regimen should be started as soon as possible to cover skin bacteria, gram-negative rods, and anaerobes. Options for intravenous therapy include:
- Piperacillin-tazobactam: 3.375 g IV q6h with normal kidney function. Will cover gram-negative rods including *Pseudomonas aeruginosa*, streptococci, anaerobes, and *Staphylococcus aureus.* Adjust dose based on CrCl.
- Meropenem: 1 g IV q8h with normal kidney function has comparable coverage as piperacillin-tazobactam. Similar agents include imipenem and doripenem.
- Third-generation cephalosporin such as cefepime, 2 g IV q8h, or ceftriaxone, 2 g IV qd, have excellent gram-negative coverage and for anaerobic coverage add metronidazole, 500 mg IV q8h, or clindamycin 900 mg IV q8h. Cefepime will cover *Pseudomonas aeruginosa* but ceftriaxone will not.
- For penicillin-allergic patients a combination of ciprofloxacin, 400 mg IV q12h, plus metronidazole or clindamycin is an option. Aztreonam is another option for gram-negative rod coverage, 2 g IV q8h.
- If MRSA suspected need to add IV vancomycin, 15-20 mg/kg IV q8-12h, depending on age and CrCL and follow trough levels to keep above 15. Other options include daptomycin, 4 mg/kg IV qd, which does not have to be adjusted for CrCL or linezolid, 400-600 mg IV q12h.
- If VRE suspected options include tigecycline, 100-mg IV load dose, then 50 mg IV q12h, which also covers MRSA and gram-negative rods but not *Pseudomonas aeruginosa,* or can use daptomycin or linezolid.
- If ESBL gram-negative bacteria are suspected then options include meropenem or ertapenem, 1 g IV qd, or tigecycline.
- Once culture results are known can tailor antibiotics to more specific agent.
- Oral antibiotics used for milder infections include: amoxicillin-clavulanate, 875 mg PO q12h, will cover gram-negative rods, streptococci, and anaerobes, or ciprofloxacin plus metronidazole or clindamycin. Bactrim will cover MRSA and MSSA and some gram-negative rods.

CHRONIC TREATMENT

- Length of therapy: highly variable depending on the severity of the infection. In general 2 to 4 weeks of antibiotics is sufficient. If bone infection suspected or documented may need 4-8 weeks of antibiotics preferably intravenous via a peripherally inserted central line (PICC line).
- Surgical debridement may also be necessary for several weeks.

COMPLEMENTARY MEDICINE

- Hyperbaric oxygen (HBO): Used as an adjunct to antibiotics, debridement, and revascularization in the therapy of chronic, nonhealing wounds associated with diabetes. HBO acts by:
  1. Inducing vasoconstriction and reducing vasogenic edema
  2. Facilitating fibroblast activity, angiogenesis, and wound healing
  3. Killing anaerobic bacteria and augmenting neutrophil bactericidal activity
- Negative pressure wound therapy (wound vac): controlled, subatmospheric pressure applied to an open wound can accelerate healing and closure.
  1. An open cell foam insert is cut to fit the open wound and then secured under a clear, vapor-permeable, plastic dressing.
  2. Tubing extends from the sponge to a disposable collection canister.
  3. A portable pump applies 125 mm Hg of controlled suction to the system. The subatmospheric pressure (suction) is equally distributed across the open wound and evacuates stagnant fluid from the wound.

DISPOSITION

- Following up on sed rates, CRP, BUN/CR, and levels of vancomycin if that antibiotic used.
- Surgical or wound center care follow-up.
- HBO usually involves multiple sessions over several weeks.
- Wound vac is applied for weeks and requires periodic nursing follow-up.

REFERRAL

- Infectious disease consultant for antibiotic management.
- Surgeon or wound care center for surgical treatments.
- Endocrinologist for good diabetes care.
- Vascular surgeon for angioplasty or bypass procedures.

! PEARLS & CONSIDERATIONS

- In a meta-analysis of randomized controlled trials on the outcome of DFIs, there was a 22.7% treatment failure rate.
- Patients should be advised to seek prompt medical attention as these infections can progress rapidly to gangrene.

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SUGGESTED READINGS

Hobizal K, Wukich D: Diabetic foot infections: current concept review, *Diabet Foot Ankle* 3:10, 2012. 3402/dfa.v3i0.18409.

Lipsky BA et al.: 2012 Infectious Diseases Society of America clinical practice guideline for the diagnosis and treatment of diabetic foot infections, *Clin Infect Dis* 54, 2012 (15 June).

Paola D, Faglia E: Treatment of diabetic foot ulcer: an overview strategies for clinical approach, *Curr Diabetes Rev* 2(4):431–446, 2006.

BASIC INFORMATION

DEFINITION

Diabetic ketoacidosis (DKA) is a life-threatening complication of diabetes mellitus resulting from absolute insulin deficiency or insulin resistance with relative insulin deficiency. It is characterized by the presence of an anion gap metabolic acidosis, ketonemia, and hyperglycemia. Patients often present with severe dehydration and altered sensorium.

SYNONYMS

DKA

ICD-9CM CODES
250.1 Diabetic ketoacidosis
ICD-10CM CODES
E10.10 Type 2 diabetes mellitus with other specified complication

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE/PREVALENCE: 6 episodes per 10,000 individuals with diabetes; it accounts for 8% to 29% of all hospital admissions of patients with diabetes

PREDOMINANT AGE: 36% in persons younger than age 30, 27% in persons 30 to 60 years of age, 23% in persons 51 to 70 years of age, and 14% occurring in persons older than 70 years.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Evidence of dehydration (tachycardia, hypotension, dry mucous membranes, sunken eyeballs, poor skin turgor)
- Altered mental status
- Tachypnea with air hunger (Kussmaul's respiration)
- Fruity breath odor (caused by acetone)
- Lipemia retinalis in some patients
- Possible evidence of precipitating factors (infected wound, pneumonia)
- Abdominal tenderness in some patients

ETIOLOGY

- Metabolic decompensation in individuals with diabetes is frequently precipitated by an infectious process (up to 40%).
- Poor compliance with insulin therapy and severe medical illness (e.g., pancreatitis, cardiovascular events) are other common causes.
- There is a subgroup of type 2 diabetics who have ketosis-prone diabetes. These persons are often black or Latino, overweight, middle aged, males with a family history of diabetes or newly diagnosed diabetes. This subgroup represents 20% to 50% of persons with DKA.
- Cocaine abuse has been reported as a risk factor for DKA in adult and teenage patients, particularly in patients with multiple admissions.
- Lack of education of primary caregiver (mother, sibling), as well as deficiencies in proper monitoring of blood glucose, correct administration of insulin, supervision of insulin pump maintenance, and monitoring of diabetic caloric restraints are causes of recurrent episodes of DKA.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hyperosmolar nonketotic state
- Alcoholic ketoacidosis
- Uremic acidosis
- Metabolic acidosis caused by methyl alcohol or ethylene glycol
- Salicylate poisoning

WORKUP

- Laboratory evaluation (see "Laboratory Tests") to confirm diagnosis and evaluate precipitating factors
- Identification of "trigger," such as infection (blood cultures, urine cultures, chest radiographs), pancreatitis (pancreatic enzymes), or myocardial ischemia (ECG, cardiac enzymes)

LABORATORY TESTS

- Glucose level demonstrates severe hyperglycemia (serum glucose generally >250 mg/dl)
- Arterial blood gases demonstrate metabolic acidosis: arterial pH usually <7.30 with Pco_2 <40 mm Hg
- Serum ketonemia (b-hydroxybutyrate >300 mmol/L), ketonuria, and glycosuria
- Serum electrolytes:
  1. Serum bicarbonate is usually <15 mEq/L.
  2. Serum potassium (K^+) may be low, normal, or elevated. There is always significant total body potassium depletion regardless of the initial potassium level.
  3. Serum sodium is usually decreased as a result of hyperglycemia, dehydration, and lipemia. Assume 1.6-mEq/L decrease in extracellular sodium for each 100-mg/dl increase in glucose concentration.
  4. Calculate the anion gap (AG): $AG = Na^+ - (Cl^- + HCO^-_3)$
  5. In DKA, the anion gap is increased (<12) because of high levels of ketones.
  6. Mixed metabolic disturbances demonstrating anion gap metabolic acidosis overlapping with metabolic alkalosis may be present; this is common in patients with DKA with persistent vomiting.
- CBC with differential, urinalysis, and urine and blood cultures to rule out infectious precipitating factor
- Serum calcium, magnesium, and phosphorus; the plasma phosphate and magnesium levels may be significantly depressed and should be rechecked within 12 hr because they may decrease further with correction of DKA
- Blood urea nitrogen and creatinine generally reveal significant dehydration and acute kidney injury.
- A pregnancy test should be performed in all female patients of child-bearing years who present with DKA.
- Amylase, lipase, and liver enzymes should be checked in patients with abdominal pain.

IMAGING STUDIES

- Chest radiographs are helpful to rule out pneumonia. The initial chest film may be negative if the patient has significant dehydration. Repeat chest x-ray after 24 hr if pulmonary infection is strongly suspected.
- Additional imaging, such as CT scanning or abdominal ultrasound, should be considered in the presence of physical exam findings, such as abdominal tenderness.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Monitor mental status, vital signs, and urine output hourly until improved, then monitor every 2 to 4 hours.
- Fingersticks should be checked every 1 to 2 hours while patient is on an insulin drip.
- Basic metabolic panel should be checked every 2 to 4 hours to monitor for anion gap closure (see "Acute General Rx").

ACUTE GENERAL Rx (Fig. D1-24)

Fluid replacement (usual deficit is 6 to 8 L):

1. Do not delay fluid replacement until laboratory results have been received. Fluid deficits are typically 100 ml/kg of body weight. The total fluid administered should not exceed 4 $L/m^2/24$ hours for fear of causing cerebral edema (CE). One rule of thumb is to deliver fluids (deficit and maintenance) over a period of 48 hours if serum osmolality is >360 mOsm/L.
2. The initial fluid replacement should be with 0.9% normal saline (NS) to expand vascular volume and ensure blood pressure stabilization and organ perfusion. In patients with severe hypernatremia (serum sodium >160 mEq/L), 0.45% normal saline infusion can be used. Careful monitoring for fluid overload is necessary in elderly patients and those with a history of congestive heart failure.
3. The rate of fluid replacement varies with the age of the patient and the presence of significant cardiac or renal disease.
   1. The usual rate of infusion is 1 L of 0.9% NS over the first hour, followed by 15 ml/kg/hr 0.9% NS during the second hour. Then change to 0.45% NS at 15 ml/kg/hr to replenish free water.
   2. Switch to dextrose D5 0.45% NS when serum glucose is <250 to prevent hypoglycemia and introduce additional glucose substrate (necessary to suppress lipolysis and ketogenesis).

Insulin administration:

1. The patient should be given an initial loading IV bolus of 0.1 U/kg regular insulin followed by a constant infusion at a rate of 0.1 U/kg/hour. Insulin replacement should generally not be started until serum potassium is >3.3 mEq/L to prevent life-threatening hypokalemia.
2. Monitor serum glucose every 1 to 2 hr while patient is on insulin drip, then every 2 to 4 hr.
3. The goal is to decrease serum glucose level by 80 mg/dl/hour (after an initial decline

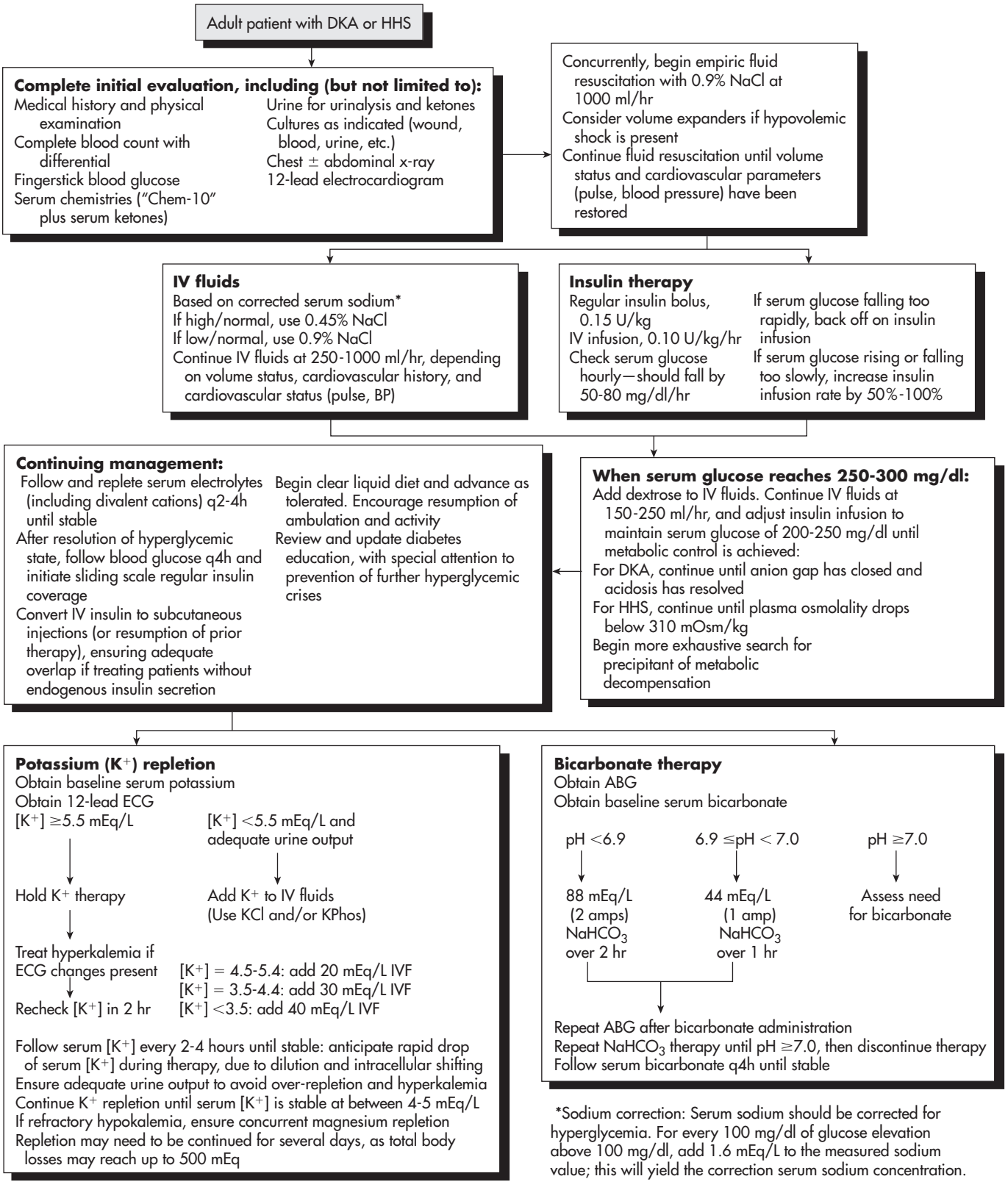

FIGURE D1-24 Management of diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS). *ABG*, Arterial blood gas; *ECG*, electrocardiograph. (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine*, ed 23, Philadelphia, 2008, Saunders.)

because of rehydration); if the serum glucose level is not decreasing at the expected rate, double the rate of insulin infusion.

4. When the serum glucose level approaches 250 mg/dl, decrease the rate of insulin infusion to 2 to 3 U/hour and continue this rate until the patient has received adequate fluid replacement, HCO_3- is close to normal, and ketones have cleared. After target glucose levels are achieved, it usually takes 5 to 7 hr for ketosis to clear. Young children and adolescents have greater levels of human growth hormone, resulting in a prolonged time lag for plasma glucose to reach above levels. Patients with infection and fever have higher metabolic requirements and may need 15% to 20% more insulin than the usual starting dose.
5. Prior to stopping the IV insulin infusion, administer an SC dose of insulin (dose varies with the patient's demonstrated insulin sensitivity). Short (regular) or rapid-acting (aspart, lispro, glulisine) insulins should be administered SC 1 to 2 hr before stopping IV insulin infusion. Intermediate (NPH) or long-acting (glargine, detemir) insulins should be administered 2 to 4 hr before stopping IV insulin infusion.
6. In individuals with newly diagnosed diabetes, the total daily insulin dose to maintain metabolic control ranges from 0.5 to 0.8 U/kg/day. Approximately half of this dose should be given as intermediate or long-acting insulin, and half of this dose should be given as mealtime or prandial insulin, provided the patient is eating.

Electrolyte replacement:

- Potassium replacement: the average total potassium loss in DKA is 300 to 500 mEq.
- K^+ can be supplemented as chloride- and phosphate-containing solutions.
  1. The rate of replacement varies with the patient's serum potassium level, degree of acidosis (decreased pH, increased potassium level), and renal function (potassium replacement should be used with caution in patients with renal failure).
  2. As a rule of thumb, potassium replacement can be guided by presenting serum K level. If K is <3.3, give KCl 20 to 30 mEq/L of intravenous fluid (IVF) until K is >3.3. If K is 3.3 to 5.3, give KCl at 10 to 30 mEq/L IVF to maintain a K of >4. If K is >5.3, hold potassium supplementation until K is <5.3.
  3. Monitor serum potassium level hourly for the first 2 hours, then monitor q2 to 4h.
- Phosphate replacement: If the serum PO_4 is <1.5 mEq/L, give 2.5 mg/kg IV over 6 hours of elemental phosphate. Routine replacement of phosphate (in the absence of laboratory evidence of significant hypophosphatemia) is not indicated. Rapid IV phosphate administration can cause hypocalcemia.
- Magnesium replacement: Replacement is indicated only in the presence of significant hypomagnesemia or refractory hypokalemia/hypocalcemia.

Bicarbonate therapy:

- Routine use of bicarbonate in DKA is contraindicated because it can worsen hypokalemia and can cause cerebral edema. Bicarbonate therapy should be considered only if the arterial pH is <6.9 and HCO_3- is <5.
- In these patients, 44 to 88 mEq sodium bicarbonate can be added to 1 L of 0.45% NS q2-4h until pH increases to >7.
- Use of bicarbonate therapy is particularly dangerous in the pediatric population. Children with DKA are at increased risk for cerebral edema. Bicarbonate therapy in children with DKA should be limited to those with severe circulatory failure and a high risk for cardiac decompensation resulting from profound acidosis.

PREVENTION

- Provide information/education for teachers, parents, school staff, and caregivers on how to recognize children with undiagnosed diabetes.
- Review sick day management; increase home blood glucose monitoring, education on how to measure urinary or fingerstick ketones, compliance with insulin; and maintain adequate hydration and nutrition.

DISPOSITION

- Average mortality rate in DKA is 5% to 10%.
- In children <10 yr, DKA causes 70% of diabetes-related deaths.
- Cerebral edema (CE) occurs in 1% of episodes of DKA in children and is associated with a mortality rate of 40% to 90%.

REFERRAL

In general, patients with DKA should be admitted to the intensive care unit on an insulin drip. Alert patients who are able to take fluids orally and have mild DKA occasionally can be treated with short-acting insulin analogues under observation and sent home. The American Diabetes Association admission guidelines are a plasma glucose level >250 mg/dl with arterial pH <7.30, serum bicarbonate level <15 mEq/L, and a moderate or greater level of ketones in the serum or urine.

PEARLS & CONSIDERATIONS

COMMENTS

- Although DKA occurs more commonly in type 1 diabetes mellitus, a significant proportion (>20%) occurs in patients with type 2 diabetes, particularly under conditions of extreme stress, severe infection or surgery, and marked hyperglycemia (results in glucose toxicity).
- 30% to 40% of DKA admissions involve patients with newly diagnosed diabetes.
- Potential complications of DKA therapy include hypoglycemia, cerebral edema, cardiac arrhythmias, shock, myocardial infarction, and acute pancreatitis.
- Risk factors for cerebral edema include age <5 yr, high initial BUN, hyperventilation to a $Paco_2$ of <22 mm Hg, and presenting arterial pH of <7.00. It presents 4 to 8 hours after start of rehydration therapy. Presentation may be abrupt with sudden severe headache, vomiting, sudden hypertension, and obtunded sensorium. First management response to CE is to elevate head of the patient to 30-degree angle, IV mannitol, intubation and hyperventilation, and, finally, cutting back of the maintenance fluid to 75%.
- Underinsured children and those with psychiatric illness are at greater risk for DKA.
- Subcutaneous administration of rapid-acting insulin analogues may be reasonable alternatives to IV regular insulin infusion for treating uncomplicated DKA.
- DKA can occur with blood glucose <350 mg/dl in the setting of poor oral intake or pregnancy.
- Ketones can be positive in starvation or with heavy alcohol intake; DKA can coexist with other causes of metabolic acidosis such as lactic acidosis.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Diabetes Mellitus (Related Key Topic)
Hyperosmolar Hyperglycemic Syndrome (Related Key Topic)

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SUGGESTED READINGS

Argus MS et al.: Continuous noninvasive end-tidal CO_2 monitoring in pediatric inpatients with diabetic ketoacidosis, *PediatrDiabetes* 7:196, 2006.

Cole RP: Heparin treatment for severe hypertriglyceridemia in diabetic ketoacidosis, *Arch Intern Med* 169(15):1439–1441, 2009.

Halperin M et al.: Strategies to diminish the danger of cerebral edema in pediatric diabetes, *Pediatr Diabetes* 7:191, 2006.

Kamel KS, Halperin ML: Acid-base problems in diabetic ketoacidosis, *N Engl J Med* 372:546–554, 2015.

Kitabchi AE et al.: Hyperglycemic crises in diabetes mellitus: diabetic ketoacidosis and hyperglycemic hyperosmolar state, *Endocrinol Metab Clin North Am* 35:725–751, 2006.

Koul PB: Diabetic ketoacidosis: a current appraisal of pathophysiology and management, *Clin Pediatr (Phila)* 48:135, 2009.

Mazer M et al.: Is subcutaneous administration of rapid-acting insulin as effective as intravenous insulin for treating diabetic ketoacidosis? *Ann Emerg Med* 53:259–263, 2009.

Newton CA, Raskin P: Diabetic ketoacidosis in type 1 and type 2 diabetes mellitus, *N Engl J Med* 164:1925, 2004.

Westerberg DP: Diabetic ketoacidosis: evaluation and treatment, *Am Fam Physician* 87(5):337–346, 2013.

BASIC INFORMATION

DEFINITION

Diabetic polyneuropathy is a distal symmetric polyneuropathy (DSPN) characterized by numbness, tingling, pain, or weakness that affects the nerves in a stocking-and-glove pattern, beginning in the distal extremities. DSPN leads to substantial pain, morbidity, and impaired quality of life.

SYNONYMS

Distal symmetric polyneuropathy (DSPN)
Diabetic peripheral neuropathy

ICD-9CM CODES
250.6 Diabetes with neurological manifestations
357.2 Polyneuropathy in diabetes
ICD-10CM CODES
E11.40 Type 2 diabetes mellitus with neurological complications
E11.40 Type 2 diabetes mellitus with diabetic neuropathy, unspecified
E11.41 Type 2 diabetes mellitus with diabetic mononeuropathy
E11.42 Type 2 diabetes mellitus with diabetic polyneuropathy
E11.43 Type 2 diabetes mellitus with diabetic autonomic (poly)neuropathy
E11.44 Type 2 diabetes mellitus with diabetic amyotrophy
E11.49 Type 2 diabetes mellitus with other diabetic neurological complication

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: The prevalence of diabetic polyneuropathy varies from 10% to 100% in patients with diabetes mellitus in population-based studies. It is the most common form of peripheral neuropathy in the western world.
RISK FACTORS: Patients with poor glycemic control, diabetic nephropathy, or retinopathy are at increased risk.
PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients most commonly experience numbness and tingling, but may also experience feelings of tightness or a sensation of heat or cold.
- Pain is not uncommon, is often worst at night, and can be burning, aching, shooting, or lancinating in nature.
- These symptoms begin in the feet and may slowly ascend over months to years. Symptoms in the hands do not generally occur until symptoms in the lower extremities have reached the level of the knees. In more severe cases, the symptoms can spread to the trunk and head.
- Neurologic examination reveals early loss of small-fiber modalities resulting in decreased pinprick and temperature sensation, with later involvement of large-fiber modalities leading to a reduction in vibratory and proprioceptive sensation. Ankle reflexes are usually reduced or absent, and more proximal reflexes may also become involved as the neuropathy progresses. Strength is usually normal, but there can be some motor involvement leading to mild weakness and atrophy, which is usually limited to intrinsic foot muscles and ankle dorsiflexors.

ETIOLOGY

Precise etiology is unknown but most likely involves a complex interaction of metabolic derangements and microvascular insults that occur in the setting of diabetes.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Although diabetes is the leading cause of peripheral neuropathy in developed countries, there are numerous other causes requiring further investigation(s).

WORKUP

- A thorough history and neurologic examination are essential to confirm features consistent with a diabetic polyneuropathy and exclude other features that would suggest alternative diagnoses.
- For some patients, neuropathy may be the presenting feature of previously undiagnosed diabetes.
- Electrodiagnostic evaluation to include nerve conduction studies and electromyography can be helpful in confirming the presence, extent, and severity of a neuropathy.
- Patients with DSPN typically have a reduction of amplitudes and slowing of conduction velocities involving sensory and possibly motor nerves in a length-dependent and symmetric fashion.
- Electromyographic examination of distal muscles may reveal fibrillation potentials, positive sharp waves, and large motor unit action potentials, suggestive of denervation and reinnervation.
- Skin biopsy and nerve biopsy are not necessary in the vast majority of cases.
- Fig. D1-25 describes a diagnosis and treatment algorithm of diabetic autonomic neuropathy.

LABORATORY TESTS

- Fasting blood sugar, hemoglobin A1c, and oral glucose tolerance test should all be considered in patients with peripheral neuropathy without a known history of diabetes.
- A focused laboratory evaluation for other common or potentially treatable causes of neuropathy is also indicated: complete blood cell count, complete metabolic panel to include electrolytes and liver function tests, erythrocyte sedimentation rate, vitamin B12 and folate levels, thyroid function tests, serum protein electrophoresis with immunofixation electrophoresis.
- Additional laboratory tests can be considered based on history or exam findings that may suggest other underlying diagnoses, such as anti-nuclear antibodies, extractable nuclear antigens, and rheumatoid factor.

IMAGING STUDIES

- Imaging is not necessary unless there is concern for an alternate or coexisting process based on the history and examination.

TREATMENT

CHRONIC Rx

- Table D1-17 summarizes clinical features, diagnosis, and treatment of diabetic autonomic neuropathy
- Glycemic control: The primary treatment for diabetic polyneuropathy is effective glycemic control, as this may improve or at least slow progression of the neuropathy.
- Symptomatic management: Another aspect of treatment is the symptomatic management of pain and paresthesias. The American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation have developed an evidence-based guideline for the treatment of painful diabetic neuropathy. Pregabalin, an anticonvulsant, is the only agent in the guideline that has been established as effective for painful diabetic neuropathy. Other probably effective agents are listed below:
  1. Topical agents: Lidocaine 5% patch can be applied to painful areas for 12 hours a day, capsaicin 0.075% applied qid.
  2. Anticonvulsants: gabapentin (100 to 1200 mg tid) and pregabalin (50 to 100 mg tid)
  3. Antidepressants: amitriptyline (10 to 100 mg qhs), nortriptyline (25 to 150 mg qhs), duloxetine (60 to 120 mg daily), and venlafaxine (75 to 225 mg/day).
  4. Tramadol (50 mg qid as needed) can be a useful adjunctive analgesic
- Fig. D1-26 describes a treatment algorithm for neuropathic pain after exclusion of nondiabetic etiologies and stabilization of glycemic control

DISPOSITION

The distal sensory loss of diabetic polyneuropathy places patients at increased risk of trauma to the extremities, with the potential for ulceration and infection that could ultimately require amputation if not attended to in a timely fashion.

REFERRAL

- A neurologist can assist in the diagnosis and management of diabetic polyneuropathy.
- Patients with diabetic polyneuropathy should also be evaluated at least annually by a podiatrist and ophthalmologist

PEARLS & CONSIDERATIONS

COMMENTS

- For many patients, a DSPN or other form of diabetic neuropathy may be the initial presentation of previously undiagnosed diabetes.

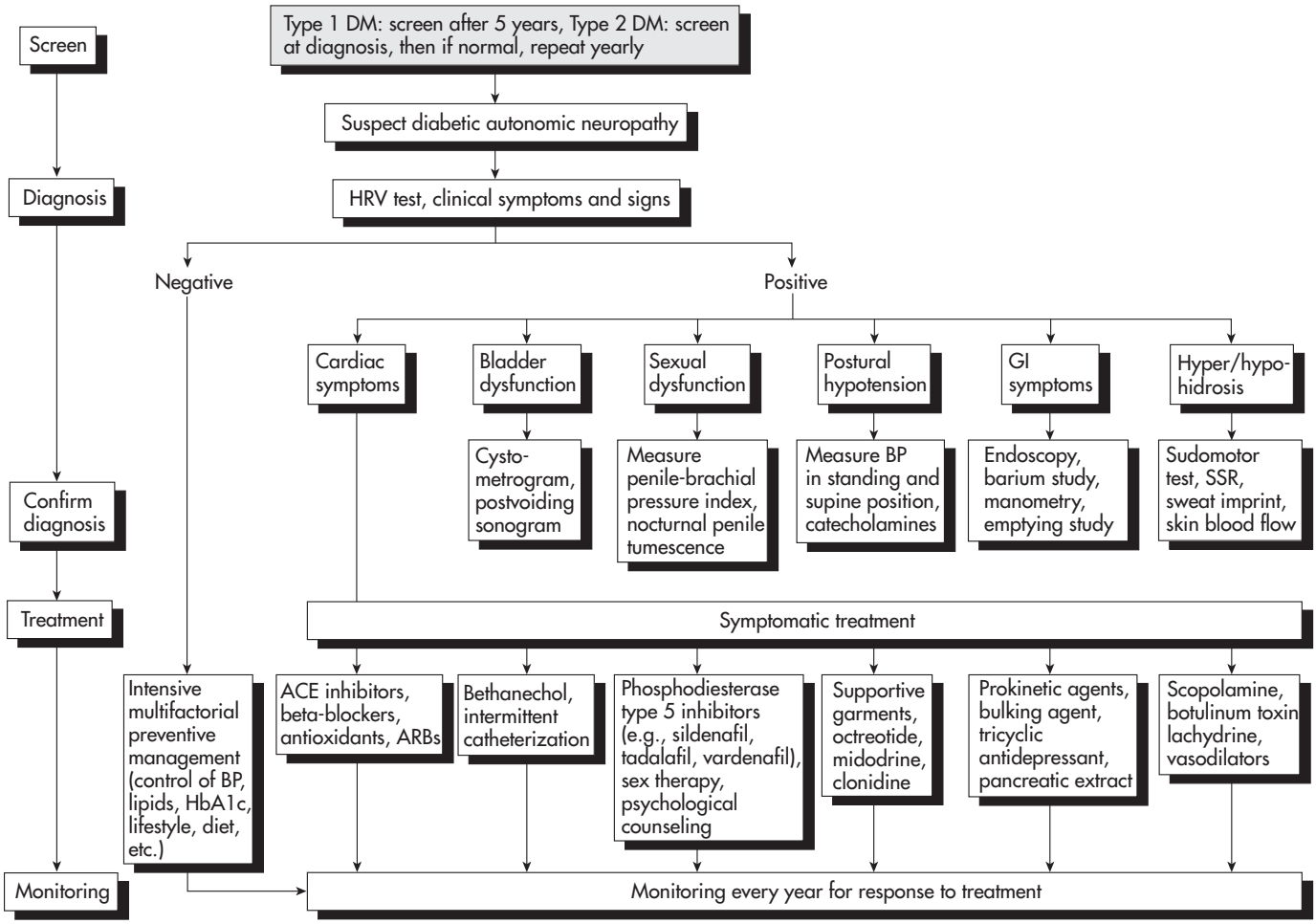

FIGURE D1-25 Diagnosis and treatment algorithm of diabetic autonomic neuropathy. *ACE*, Angiotensin-converting enzyme; *ARBs*, angiotensin receptor blockers; *BP*, blood pressure; *DM*, diabetes mellitus; *GI*, gastrointestinal; *HRV*, heart rate variability; *SSR*, sympathetic skin response. (Modified from Larsen PR et al [eds]: *Williams textbook of endocrinology*, ed 11, Philadelphia, 2008, Saunders.)

- In addition to regular visits with podiatry, patients with diabetic polyneuropathy should be educated on aggressive foot hygiene and the importance of examining their own feet

PATIENT/FAMILY EDUCATION

The following websites are recommended:
http://patienteducationcenter.org/articles/diabetic-neuropathies/
http://www.mayoclinic.com/health/diabetic-neuropathy/DS01045

AUTHOR: **DIVYA SINGHAL, M.D.**

TABLE D1-17 Clinical Features, Diagnosis, and Treatment of Diabetic Autonomic Neuropathy

Symptoms	Tests	Treatments
Cardiac		
Resting tachycardia, exercise intolerance	HRV, MUGA thallium scan, MIBG scan	Graded supervised exercise, ACE inhibitors, β-blockers
Postural hypotension, dizziness, weakness, fatigue, syncope	HRV, supine and standing BP, catecholamines	Mechanical measures, clonidine, midodrine, octreotide, erythropoietin
Gastrointestinal		
Gastroparesis, erratic glucose control	Gastric emptying study, barium study	Frequent small meals, prokinetic agents (metoclopramide, domperidone, erythromycin)
Abdominal pain, early satiety, nausea, vomiting, bloating, belching	Endoscopy, manometry, electrogastrogram	Antibiotics, antiemetics, bulking agents, tricyclic antidepressants, pyloric botulinum toxin, gastric pacing
Constipation	Endoscopy	High-fiber diet, bulking agents, osmotic laxatives, lubricating agents
Diarrhea (often nocturnal alternating with constipation)		Soluble fiber, gluten and lactose restriction, anticholinergic agents, cholestyramine, antibiotics, somatostatin, pancreatic enzyme supplements
Sexual Dysfunction		
Erectile dysfunction	H&P, HRV, penile-brachial pressure index, nocturnal penile tumescence	Sex therapy, psychological counseling, phosphodiesterase inhibitors, PGE_1 injections, devices or prostheses
Vaginal dryness		Vaginal lubricants
Bladder Dysfunction		
Frequency, urgency, nocturia, urinary retention, incontinence	Cystometrogram, postvoid sonography	Bethanechol, intermittent catheterization
Sudomotor Dysfunction		
Anhidrosis, heat intolerance, dry skin, hyperhidrosis	Quantitative sudomotor axon reflex, sweat test, skin blood flow	Emollients and skin lubricants, scopolamine, glycopyrrolate, botulinum toxin, vasodilators
Pupillomotor and Visceral Dysfunction		
Blurred vision, impaired adaptation to ambient light, Argyll-Robertson pupil	Pupillometry, HRV	Care with driving at night
Impaired visceral sensation: silent MI, hypoglycemia unawareness		Recognition of unusual presentation of MI, control of risk factors, control of plasma glucose levels

ACE, acetylcholinesterase; *BP*, blood pressure; *H&P*, history and physical examination; *HRV*, heart rate variability; *MI*, myocardial infarction; *MIBG*, metaiodobenzylguanidine; *MUGA*, multigated angiography; *PGE_1*, prostaglandin E_1.
From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.

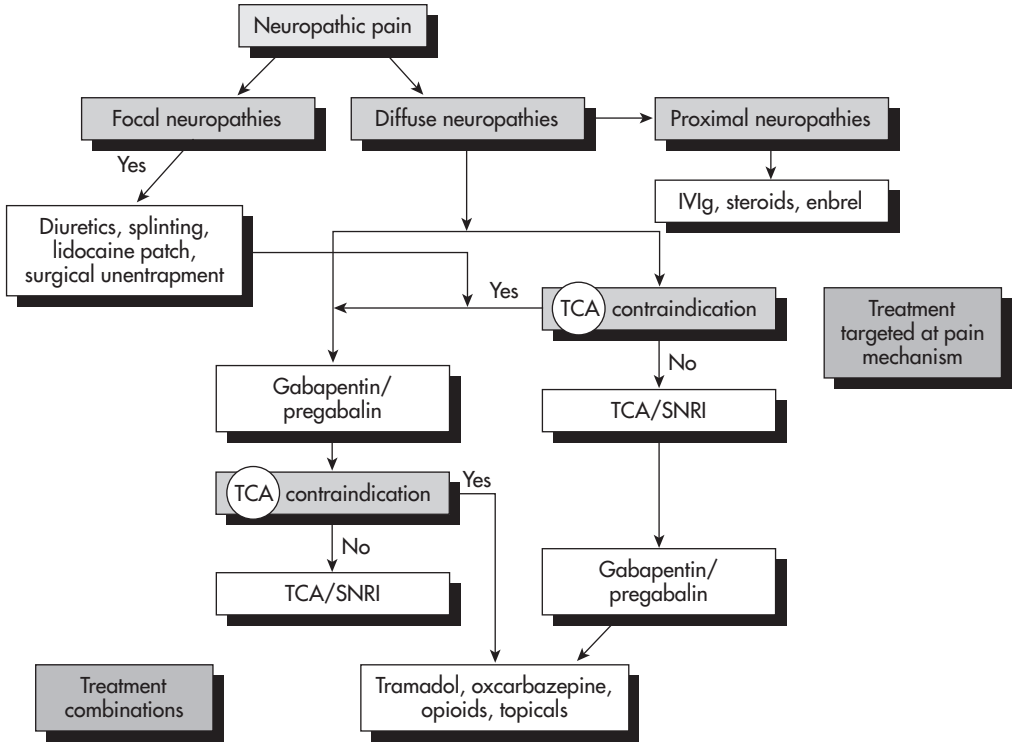

FIGURE D1-26 Treatment algorithm for neuropathic pain after exclusion of nondiabetic etiologies and stabilization of glycemic control. *IVIg*, intravenous immune globulin; *SNRI*, serotonin-norepinephrine reuptake inhibitors; *TCA*, tricyclic antidepressants. (From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.)

SUGGESTED READINGS

Amato AA, Russell JA: Neuromuscular disorders. McGraw-Hill: New York.

Callaghan BC et al.: Diabetic neuropathy: clinical manifestations and current treatments, *Lancet Neurol* 11(6):521–534, 2012.

England JD, Asbury AK: Peripheral neuropathy, *Lancet* 363(9427):2151–2161, 2004.

Smith AG, Singleton JR: Diabetic neuropathy, *Continuum (Minneap Minn)* 18(1):60–84, 2012.

BASIC INFORMATION

DEFINITION

Diabetic retinopathy is an abnormality of the retina associated with diabetes and consisting of microaneurysms, punctate hemorrhages, white and yellow exudates, flame hemorrhages, and neovascular vessel growth and can ultimately end in blindness. Diabetic retinopathy can be classified into two stages: nonproliferative and proliferative (Fig. D1-27 and Table D1-18).

SYNONYMS

Nonproliferative diabetic retinopathy (NPDR)
Proliferative (advanced) diabetic retinopathy (PDR)
Diabetic retinopathy (DR)

ICD-9CM CODES

250.5	Diabetes with ophthalmic manifestations
362.1	Retinopathy, diabetic, background
362.02	Retinopathy, diabetic, proliferative

ICD-10CM CODES

E11.319	Type 2 diabetes mellitus with unspecified diabetic retinopathy with macular edema
E11.39	Type 2 diabetes mellitus with other diabetic ophthalmic complication
H35.00	Unspecified background retinopathy
E11.359	Type 2 diabetes mellitus with proliferative diabetic retinopathy without macular edema

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- Affects 11 million persons. Approximately 40% of patients with diabetes who are over age 40 have retinopathy, including 8.2% who have vision-threatening retinopathy
- A leading cause of blindness in the U.S. between the ages of 20 and 74 yr
- There are 12,000 to 24,000 new cases of diabetic retinopathy-induced blindness each year in the U.S.
- 5000 new cases annually

PEAK INCIDENCE: Begins 10 yr after onset of diabetes

PREVALENCE (IN U.S.): Prevalence of retinopathy increases with duration of diabetes. Found in 18% of people diagnosed with diabetes for 3- to 4-yr duration and in up to 80% of diabetics with a diagnosis of ≥15 yr.

PREDOMINANT SEX: Males and females affected equally

PREDOMINANT AGE: ≥30 yr

GENETICS: Type 1 diabetes: 80% have retinopathy before 30 yr, with 30% having vision-threatening retinopathy.

PHYSICAL FINDINGS & CLINICAL PRESENTATION (Fig. D1-28)

- Microaneurysms
- Hemorrhages
- Exudates
- Macular edema
- Neovascularization
- Retinal detachment (in advanced cases)
- Hemorrhages in the vitreous
- In early cases, patient may not report a visual disturbance
- Figure ED1-29 describes an initial ophthalmic examination flow chart

ETIOLOGY

Vascular endothelial growth factor and erythropoietin have been identified as factors involved in angiogenesis in proliferative diabetic retinopathy. Risk factors for diabetic retinopathy are duration of diabetes, hyperglycemia/glycated hemoglobin value, hypertension, hyperlipidemia, pregnancy, and nephropathy or renal disease. Fig. ED1-30 describes a diabetic retinopathy pathogenesis flow chart.

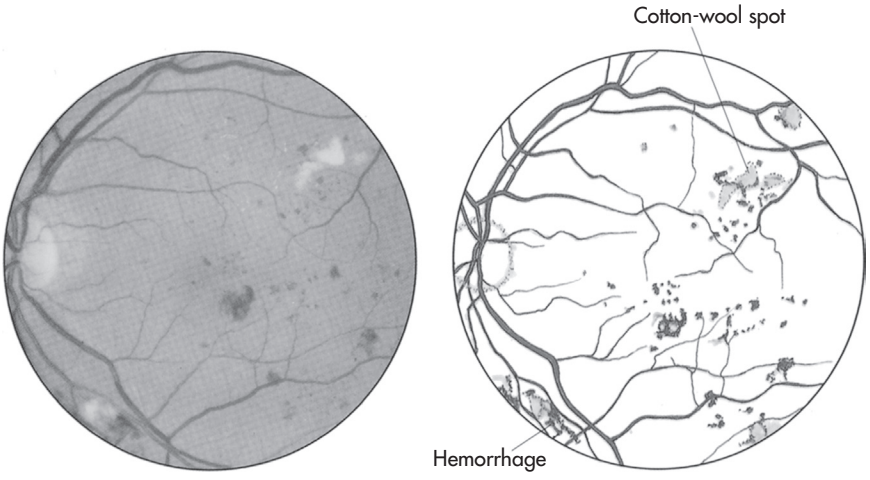

FIGURE D1-27 Background diabetic retinopathy. Note flame-shaped and dot-blot hemorrhages, cotton-wool spots, and microaneurysms. (From Barkaukas VH et al: *Health and physical assessment,* ed 2, St Louis, 1998, Mosby.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Retinal examination: look for background retinopathy, microaneurysms, exudate, macular edema, retinal hemorrhage, proliferative neovascular growth on surface of retina
- Retinal inflammatory diseases
- Tumor
- Trauma
- Arteriosclerotic vascular disease
- Hypertension
- Retinal vascular occlusion

WORKUP

- Fluorescein angiogram
- Frequent retinal examinations

TREATMENT

NONPHARMACOLOGIC THERAPY

- Tight glycemic control remains the cornerstone in the primary prevention of diabetic retinopathy
- Laser treatment (photocoagulation) with proliferative disease or macular edema
- Exercise, diet, sugar and lipids control can slow progression of background retinopathy but have no effect on proliferative retinopathy. Trials have shown that glycemic control and combination treatment of dyslipidemia, but not intensive blood-pressure control, reduce the rate of diabetic retinopathy. Intensive glycemic therapy (vs. standard therapy) lowers the incidence of progressive retinopathy (7.3% vs. 10.4%) but not vision loss (16.3% vs. 16.7%) and can result in excess mortality (ACCORD trial)

ACUTE GENERAL Rx

- Laser therapy: pan-retinal and focal retinal laser photocoagulation reduces the risk of visual loss in patients with severe diabetic retinopathy and macular edema
- Vitrectomy
- Intravitreal injections with VEGF blockers (e.g., Avastin, Lucentis) and/or corticosteroids
- Repair of retinal detachment
- Medical control of disease and complications and associated diseases (e.g., hypertension)

CHRONIC Rx

- Repeated laser treatments may be necessary
- Diet and exercise; good medical control of disease

DISPOSITION

- Retinal examination should be performed on all routine medical visits. Referral if abnormality seen.
- Routine annual eye examination in all patients with diabetes.
- Prognosis is improved with early diagnosis and treatment.

REFERRAL

Refer to ophthalmologist immediately on finding retinal abnormality to institute early treatment.

TABLE D1-18 Abbreviated Early Treatment Diabetic Retinopathy Study Classification of Diabetic Retinopathy

Category/Description	Management
Nonproliferative Diabetic Retinopathy (NPDR)	
No DR	Review in 12 mo
Very mild Microaneurysms only	Review most patients in 12 mo
Mild Any or all of: microaneurysms, retinal hemorrhages, exudates, cotton wool spots, up to the level of moderate NPDR. No IRMA or significant beading	Review range 6-12 mo, depending on severity of signs, stability, systemic factors, and patient's personal circumstances
Moderate • Severe retinal hemorrhages (more than ETDRS standard photograph 2A: about 20 medium-large per quadrant) in 1-3 quadrants *or* mild intraretinal microvascular abnormalities (IRMA) • Significant venous beading can be present in no more than 1 quadrant • Cotton-wool spots commonly present	Review in approximately 6 mo PDR in up to 26%, high-risk PDR in up to 8% within a yr
Severe The 4-2-1 rule; one or more of: • Severe hemorrhages in all 4 quadrants • Significant venous beading in 2 or more quadrants • Moderate IRMA in 1 or more quadrants	Review in 4 mo PDR in up to 50%, high-risk PDR in up to 15% within a yr
Very severe Two or more of the criteria for severe	Review in 2-3 mo High-risk PDR in up to 45% within a yr
Proliferative Diabetic Retinopathy (PDR)	
Mild-moderate New vessels on the disc (NVD) or new vessels elsewhere (NVE), but extent insufficient to meet the high-risk criteria	Treatment considered according to severity of signs, stability, systemic factors, and patient's personal circumstances such as reliability of attendance for review. If not treated, review in up to 2 mo
High-risk • New vessels on the disc (NVD) greater than ETDRS standard photograph 10A (about disc area) • Any NVD with vitreous or preretinal hemorrhage • NVE greater than disc area with vitreous or preretinal hemorrhage (or hemorrhage with presumed obscured NVD/E)	Treatment advised—see text Should be performed immediately when possible, and certainly same day if symptomatic presentation with good retinal view

From Kanski JJ, Bowling B: *Clinical ophthalmology, a systematic approach*, ed 7, Philadelphia, 2010, Saunders.

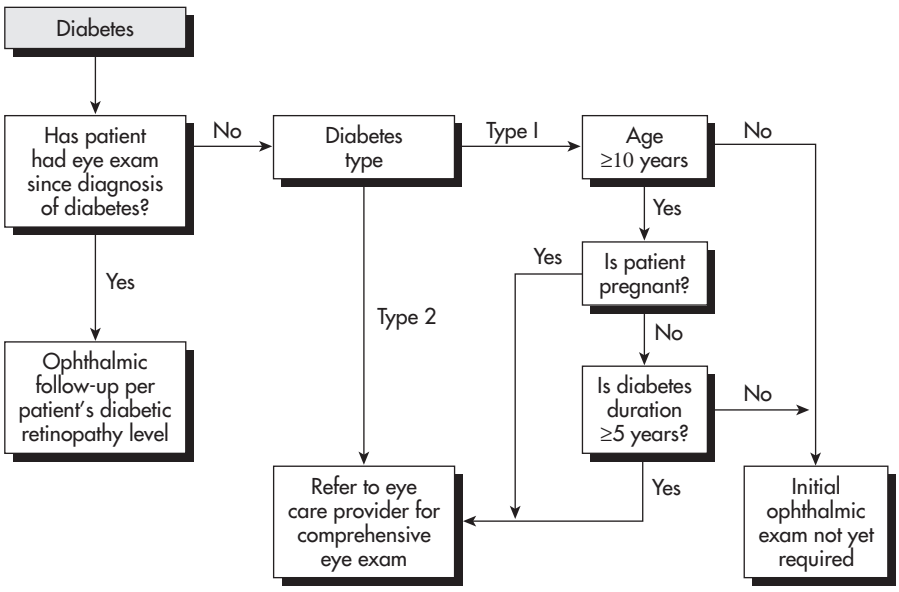

FIGURE D1-28 Initial ophthalmic examination flow chart. Schematic flow chart of major principles involved in determining the timing of initial ophthalmic examination after a diagnosis of diabetes mellitus. These are minimal recommended times. Ocular symptoms, complaints, or other associated medical issues can necessitate earlier evaluation. Guidelines are regularly reevaluated based on new study results. (From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

PEARLS & CONSIDERATIONS

COMMENTS

- Early treatment of severe, nonproliferative, and proliferative retinopathy may minimize complications and visual loss.
- Retinopathy is an independent risk marker for cardiovascular disease in patients with type 2 DM.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Diabetic Retinopathy (Patient Information)
Diabetes Mellitus (Related Key Topic)

AUTHOR: **R. SCOTT HOFFMAN, M.D.**

SUGGESTED READINGS

Antonetti DA et al.: Diabetic retinopathy, *N Engl J Med* 366:1227–1239, 2012.

Bressler NM et al.: Panretinal photocoagulation for proliferative diabetic retinopathy, *N Engl J Med* 365:1520–1526, 2011.

Frank RN: Diabetic retinopathy, *N Engl J Med* 350:48, 2004.

Gimeno-Orna JA et al.: Ability of retinopathy to predict cardiovascular disease in patients with type 2 diabetes mellitus, *Am J Cardiol* 103:1364–1367, 2009.

Mohamed Q et al.: Management of diabetic retinopathy, *JAMA* 298(8):902–916, 2007.

Sjolie AK, Moller F: Medical management of diabetic retinopathy, *Diabetes Med* 21(7):666, 2004.

The ACCORD Study Group and ACCORD Eye Study Group: Effects of medical therapies on retinopathy progression in type 2 diabetes, *N Engl J Med* 363:233–244, 2010.

Watanabe D et al.: Erythropoietin as a retinal angiogenic factor in proliferative diabetic retinopathy, *N Engl J Med* 353:782, 2005.

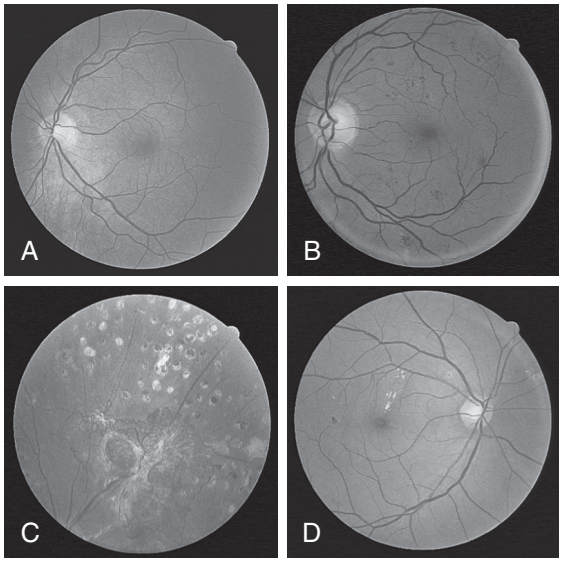

FIGURE ED1-29 Some features of diabetic eye disease. A, The normal macula center and optic disc. **B,** Dot and blot hemorrhages (early background retinopathy). **C,** Multiple frondlike new vessels, the hallmark of proliferative retinopathy. White fibrous tissue is forming near the new vessels, a feature of advanced retinopathy. This eye also illustrates multiple xenon arc laser burns superiorly. **D,** Exudates appearing within a disc-width of the macula are a feature of an exudative maculopathy. (From Ballinger A: *Kumar & Clark's essentials of clinical medicine,* ed 6, Edinburgh, 2012, Saunders.)

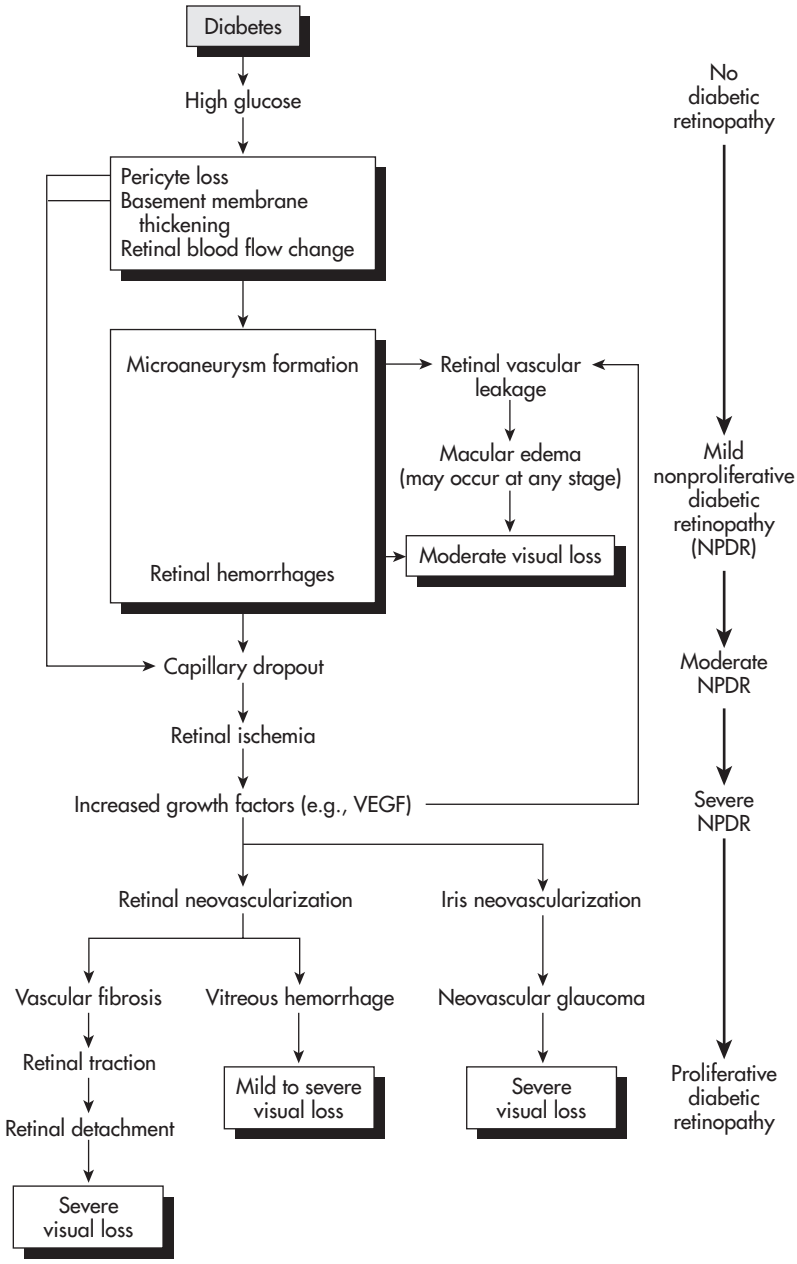

FIGURE ED1-30 Diabetic retinopathy pathogenesis flow chart. The schematic flow chart represents the major preclinical and clinical findings associated with the full spectrum of diabetic retinopathy and macular edema. *VEGF,* Vascular endothelial growth factor. (From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Diffuse idiopathic skeletal hyperostosis (DISH) is a systemic disorder primarily involving the axial skeleton and may involve peripheral entheses. It is characterized by widespread bone proliferation as well as calcification and ossification of soft tissues, including ligaments and their sites of insertion. DISH is also known to be associated with certain metabolic abnormalities.

SYNONYMS

- Ankylosing hyperostosis
- Forestier disease
- DISH

ICD-9CM CODES

721.6 Ankylosing vertebral hyperostosis

ICD-10 CM CODES

M48.10 Ankylosing hyperostosis, site unspecified
M48.11 Ankylosing hyperostosis, occipito-atlanto-axial region
M48.12 Ankylosing hyperostosis, cervical region
M48.13 Ankylosing hyperostosis, cervicothoracic region
M48.14 Ankylosing hyperostosis, thoracic region
M48.15 Ankylosing hyperostosis, thoracolumbar region
M48.16 Ankylosing hyperostosis, lumbar region
M48.17 Ankylosing hyperostosis, lumbosacral region
M48.18 Ankylosing hyperostosis, sacral and sacrococcygeal region
M48.19 Ankylosing hyperostosis, multiple sites in spine

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Prevalence of DISH varies in different populations. Factors such as age, ethnicity, geography and clinical setting affect the prevalence of the disease. Studies have shown DISH is more common in developed nations, although this may be secondary to more frequent use of radiologic imaging in these countries. Higher prevalence rates are seen in men, 10-25% versus 5-15% in women over the age of 50 years. Rates increase with age, with prevalence reported as 35% in men and 26% in women over the age of 70 years

PREDOMINANT SEX AND AGE

- Male predominance with a male to female ratio of 2:1
- Mostly seen in elderly patients, over the age of 50

GENETICS:

- Association with *COL6A1* gene in some populations, which causes ossification of the posterior longitudinal ligament, a condition that is related to DISH

RISK FACTORS

- Obesity
- Type II diabetes mellitus
- Hyperuricemia
- Dyslipidemia
- Hypertension
- Hyperinsulinemia
- Elevated growth hormone levels
- Elevated insulin-like growth factor (IGF-1)
- Chronic vitamin A toxicity/retinoid use

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Patients with DISH are usually asymptomatic or may experience increased stiffness in the spine or peripheral joints. Other symptoms can arise from the extent or location of bone growth. In the spine, osteophytes can obstruct or impinge on other structures or tissues, causing dysphagia (affecting cervical spine), myelopathy, quadriplegia, spinal stenosis and ossification of posterior longitudinal ligament. Spinal stiffening can also lead to decreased range of motion causing a stooped posture as well increase in the risk for fractures. Ligament thickening and shortening can lead to a stiffening arthropathy as well as a painless reduction in range of motion of certain joints. Peripheral enthesopathies are usually asymptomatic as well, but mechanical stresses can injure the entheses and cause pain. In patients with DISH, more pronounced hypertrophic changes than in osteoarthritis (OA) can be seen affecting certain peripheral joints that are not typically associated with OA, such as the metacarpophalangeal joints, elbows, shoulders and ankles. Thoracic spinal involvement, as seen in DISH, is uncommon in OA (refer to chapter on osteoarthritis). In patients with DISH, occurrence of heterotopic ossification, or bone formation at abnormal anatomic sites, can also occur after orthopedic surgery (i.e., hip arthroplasty).

ETIOLOGY

Etiology of DISH is unknown and the cause of bone formation is unclear. Chondrocytes located in entheseal areas become activated and cause changes in the adjacent matrix leading to ossification. Local vascular infiltration in these areas promotes ossification as well.

DIAGNOSIS

Diagnosis of DISH is made by radiographic imaging. Bone formation is typically seen in the thoracic spine, and less frequently in the cervical and lumbar spines. Coarse osteophytes that seem to "flow" between adjacent vertebrae are seen on the right side of the thoracic spine, thought to be subsequent to the pressure effect of the left-sided aorta (Figs. D1-31 and D1-32). Ossification occurs within the overlying anterior longitudinal ligament, preserving the original bone cortex. The intervertebral disc height is preserved in the involved segments. Peripheral bone formation is seen in entheseal areas, especially around the heels (Achilles tendon and plantar fascia), knees (peripatellar ligaments) and elbows (olecranon). Mild to significant hyperostosis or new bone formation can be seen as well, with increased distal finger tuft thickening, increase sesamoid bone size and increased corticol bone thickness. There is no evidence of apophyseal joint ankylosis or sacroiliac involvement.

Resnick and Niwayama criteria: most frequently used and is based on radiographic findings in the spine

- Findings of new bone formation/osteophytes bridging four adjoining vertebral bodies or ossification of the anterolateral longitudinal ligament
- Preserved intervertebral disc height
- Absence of degenerative disc disease, sacroiliac joint or facet joint involvement or changes

Others have proposed different criteria to make the diagnosis, including the presence of peripheral enthesopathy. Currently, new diagnostic criteria are needed to recognize milder forms of the disease, those affecting other parts of the spine, and those beginning to manifest initially with peripheral enthesopathy.

FIGURE D1-31 Large, flowing, right-sided osteophytes of the thoracic spine (**A**). Note the translucent area between the vertebral body and the ossified ligamentous tissue (**B**). (Firestein GS, Budd RC, Gabriel SE, McInnes IB, O'Dell JR: Proliferative bone diseases. *In* Firestein G et al (eds): *Firestein: Kelley's textbook of rheumatology,* 9 ed. Philadelphia, 2013, Elsevier, pp 1680-1691.)

FIGURE D1-32 Severe bulky ossification of the anterior longitudinal ligament of the cervical spine. (Firestein GS, Budd RC, Gabriel SE, McInnes IB, O'Dell JR: Proliferative bone diseases. *In* Firestein G et al (eds): *Firestein: Kelley's textbook of rheumatology,* 9 ed. Philadelphia, 2013, Elsevier, pp 1680-1691.)

Diffuse Idiopathic Skeletal Hyperostosis

DIFFERENTIAL DIAGNOSIS

- Ankylosing spondylitis
- Degenerative disc disease
- Acromegaly

WORK-UP

Diagnosis of DISH is made with radiologic imaging. Patients with the above risk factors (increased weight, BMI, waist circumference and systolic blood pressure) are at risk for cardiovascular disease and workup for this should be pursued.

LABORATORY TESTS

- Routine biochemical tests and an erythrocyte sedimentation rate (ESR) are normal
- Laboratory testing should include evaluation for metabolic syndrome, i.e. fasting glucose or HgbA1c, cholesterol panel, etc.
- Uric acid

IMAGING STUDIES

- Posteroanterior and lateral (Fig. D1-33) X-ray views of the spine
- Computed tomography (CT) or magnetic resonance imaging (MRI) of the spine (not routinely needed unless evaluating for other possible conditions, i.e. spinal stenosis)
- Plain radiographs of peripheral joints

Rx TREATMENT

There is no specific treatment available for DISH

- Weight management
- Treatment and control of components of metabolic syndrome
- Treat cardiovascular risk factors

NONPHARMACOLOGIC THERAPY

- Physical therapy, light exercise
- Heat
- For peripheral enthesopathy pain, local soft applications such as insoles for plantar spurs or orthotics can be used as well as protective bandages at other sites.
- Surgical intervention rarely necessary, unless complications such as dysphagia from cervical osteophytes or spinal stenosis occurs

ACUTE GENERAL Rx

- Analgesics and nonsteroidal anti-inflammatory medications (NSAIDs)
- Local corticosteroid injections

CHRONIC Rx

- Pain management as above
- Prevention of heterotopic ossification after orthopedic surgical procedures: NSAIDs, anti-vitamin K, and irradiation.

SUGGESTED READINGS

Available at www.experconsult.com

RELATED CONTENT

Ankylosing Spondylitis (Related Key Topic)
Osteoarthritis (Related Key Topic)

AUTHOR: **JOANNE SZCZYGIEL CUNHA, M.D.**

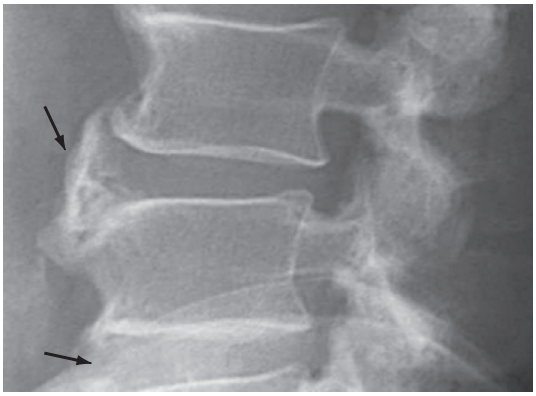

FIGURE D1-33 Diffuse idiopathic skeletal hyperostosis (DISH): lumbar spine. This lateral radiograph of the lumbar spine shows early changes of DISH. Calcifications of the anterior longitudinal spinal ligament *(arrows)* are evident and will eventually evolve into flowing osteophytes extending across multiple spinal levels. (From Firestein GS: *Kelley's textbook of rheumatology*, 9th ed, Philadelphia, 2013, Saunders.)

SUGGESTED READINGS

Firestein GS, Budd RC, Gabriel SE, McInnes IB, O'Dell JR: Proliferative Bone Diseases. In Firestein G et al.: *Firestein: Kelley's Textbook of Rheumatology*, ed 9, Philadelphia, 2013, Elsevier Saunders, pp 1680–1691.

Littlejohn G: Diffuse idiopathic skeletal hyperostosis. In Hochberg MC, et al.: *Rheumatology*, ed 6, Philadelphia, 2015, Elsevier Mosby, pp 1515–1519.

Mader R, Verlaan J, Buskila D: Diffuse idiopathic skeletal hyperostosis: clinical features and pathogenic mechanisms, *Nat Rev Rheumatol* 9:741–750, 2013.

Mader R et al.: Extraspinal manifestations of diffuse idiopathic skeletal hyperostosis, *Rheumatology* 49:1478–1481, 2009.

BASIC INFORMATION

DEFINITION

Digoxin, a cardiac glycoside, is used for the treatment of symptomatic heart failure and ventricular rate control in atrial fibrillation.

Chronic digoxin therapy or acute overdose can cause toxicity. Toxicity can occur even when serum levels are within the therapeutic range.

SYNONYMS

Digitalis overdose
Cardiac glycoside toxicity

ICD-9CM CODES
972.1 Digitalis overdose
ICD-10CM CODES
T46.0X1A Poisoning by cardiac-stimulant glycosides and drugs of similar action, accidental (unintentional), initial encounter

PHARMACOKINETICS

Steady-state levels (not peak levels) correlate with toxicity; digoxin reaches steady state 7 to 10 days after ingestion.
BIOAVAILABILITY: Approximately 80% tablets; 100% capsules or IV
VOLUME OF DISTRIBUTION: 5 to 7 L/kg, highly tissue bound
HALF-LIFE: 36 to 48 hr
EXCRETION: Predominantly renal
THERAPEUTIC LEVEL: 0.5 to 2 ng/ml (0.5 to 0.9 ng/ml suggested in heart failure); check level 1 wk after starting therapy or changing dose. Sample should be drawn at least 6 hr after last dose.

EPIDEMIOLOGY & DEMOGRAPHICS

- Digoxin toxicity remains common despite decline in digoxin use, likely because of its narrow therapeutic range. Occurs in up to 5% of individuals on therapy.
- Factors that potentiate toxicity (may increase level or modify cardiac sensitivity): advanced age, female gender, renal insufficiency, cardiac or pulmonary disease, hypokalemia, hyperkalemia, hypomagnesemia, hypercalcemia, hypernatremia, acid-base disturbance, hypoxia, hypothyroidism, volume depletion and drugs that affect elimination (ACE inhibitors, amiodarone, clarithromycin, cyclosporine, diltiazem, erythromycin, itraconazole, ketoconazole, NSAIDs, rifampin, spironolactone, SSRIs, tetracyclines, quinidine, verapamil, and herbal supplements), coingestion of cardiotoxic drugs (beta-blockers, calcium channel blockers, tricyclic antidepressants).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Cardiac, gastrointestinal, and central nervous systems are affected. Fatigue, malaise, and weakness are common symptoms. Presentation may differ in acute vs. chronic toxicity. Chronic toxicity is more difficult to recognize because of the nonspecific presentation; visual disturbance and mental status changes may be most prominent.
CARDIAC: Initial presentation often due to proarrhythmic effects, premature ventricular complexes, and bradycardia are common. Can present with almost any dysrhythmia or conduction block.
GASTROINTESTINAL: Anorexia, nausea, vomiting, diarrhea, abdominal pain
CENTRAL NERVOUS SYSTEM
- Headache, dizziness, visual disturbance (flashing lights, halos, blurred vision, scotomas, change in color perception), confusion, hallucinations, delirium, syncope
- Hyperkalemia is usually seen in acute poisoning; hypokalemia is more common in chronic toxicity

ETIOLOGY

Digoxin reversibly inhibits the sodium-potassium ATPase pump, in myocardial cells, increasing extracellular K^+ and intracellular Na^+. This reduces the activity of the Na-Ca exchanger, leading to intracellular accumulation of calcium. This increases myocardial contractility and cardiac output, the positive inotropic effect associated with digoxin therapy. Cardiac glycosides also decrease the heart rate (effect on SA node) and slow conduction through the AV node by increasing vagal tone. Digoxin's neurohormonal effects on the autonomic nervous system also decrease sympathetic activity. Enhanced automaticity of cardiac tissue and depressed conduction lead to the extrasystoles and arrhythmias seen in toxicity.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Other cardiac glycosides:
- Digitoxin
- Deslanoside
- Ouabain

Medications:
- Beta-blockers
- Calcium channel blockers
- Clonidine
- Cyclic antidepressants
- Encainide and flecainide
- Procainamide
- Propoxyphene
- Quinidine

Plants producing digitalis-like glycosides:
- Foxglove
- Oleander
- Lily of the valley

Cardiac conduction abnormalities:
- Sick sinus syndrome
- AV node dysfunction

Electrolyte abnormalities:
- Hyperkalemia

WORKUP

- History: medication changes, herbal supplements, deliberate overdose. In acute toxicity, determine the amount and time of ingestion; possible co-ingestions.
- Physical examination

LABORATORY TESTS

- Chronic toxicity—check stat digoxin level. Acute toxicity—check digoxin level 6 hr after ingestion (initial high levels may not be toxic, as tissue redistribution will occur)
- Potassium, BUN, creatinine, magnesium, calcium, glucose
- Serial ECG (Figs. ED1-34, ED1-35, and ED1-36)
- Almost any arrhythmia can occur, but simultaneous increased automaticity of cardiac tissue and conduction delay in the AV node should raise suspicion. Findings suggestive of toxicity include the following:
  1. Frequent premature ventricular complexes, bigeminy, shortening of the QT interval with a scooped or downsloping ST-T complex (Fig. ED1-37)
  2. Bradyarrhythmias
  3. AV block
  4. Atrial tachycardia with AV block
  5. Junctional rhythms
  6. Ventricular arrhythmias: Ventricular tachycardia, ventricular fibrillation, bidirectional ventricular tachycardia (alternating QRS axis)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Ensure adequate airway, IV access
- Continuous cardiac monitor, pulse oximetry

ACUTE GENERAL Rx

DECREASE TOXICITY:
- Acute poisoning: single dose of activated charcoal if within 2 hr of ingestion.
- Treat hypokalemia and hypomagnesemia; both potentiate toxicity.
- Most life-threatening complications of digoxin toxicity are treated with digoxin-specific antibody fragments (Fab).
- Digoxin-specific Fab fragments (DigiFab):
  1. Specific antibodies that bind to digoxin and to a lesser extent other cardiac glycosides. By binding to free digoxin, the plasma digoxin level decreases, facilitating dissociation of digoxin from the Na^+, K^+-ATPase.
  2. Initial response usually seen within 30 min and complete reversal usually occurs within 4 hr
  3. Indications: hyperkalemia (>5.0 mEq/L), hemodynamic instability, severe arrhythmias, massive overdose (acute ingestion of >10 mg digoxin; acute ingestion resulting in steady-state serum level >10 ng/ml; chronic toxicity with level >6 ng/ml), coingestion of cardiotoxic drugs or plants containing cardiac glycosides
  4. Dosing: 1 vial of Fab fragments binds 0.5 mg of digoxin. Round up when calculating number of vials to administer
     a. Acute ingestion of known amount: number of vials = (ingested digoxin [mg] × B)/0.5; B= bioavailability for tablets (0.8) and capsules or IV (1.0)

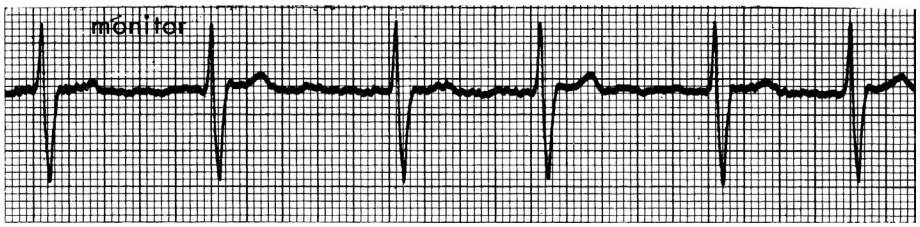

FIGURE ED1-34 Ventricular bigeminy caused by digoxin toxicity. Ventricular ectopy is one of the most common signs of digoxin toxicity. The underlying rhythm here is atrial fibrillation. (From Goldberger AL [ed]: *Clinical electrocardiography*, ed 5, St Louis, 1994, Mosby.)

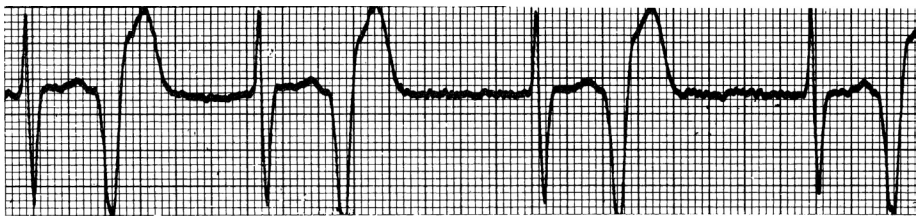

FIGURE ED1-35 Ventricular bigeminy caused by digoxin toxicity. In this figure, each normal QRS is followed by a ventricular premature beat. (From Goldberger AL [ed]: *Clinical electrocardiography*, ed 5, St Louis, 1994, Mosby.)

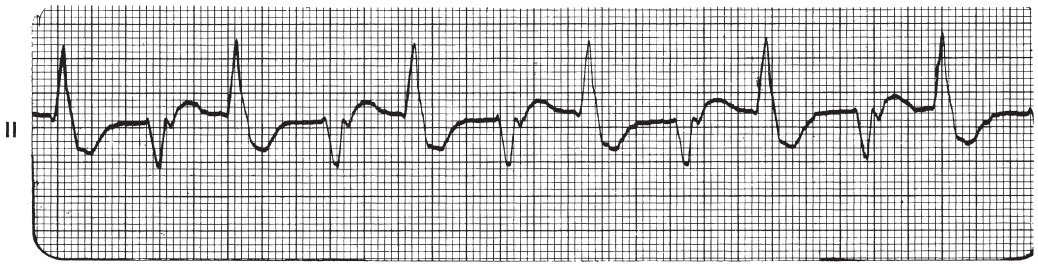

FIGURE ED1-36 This digoxin-toxic arrhythmia is a special type of ventricular tachycardia (bidirectional tachycardia) with QRS complexes that alternate in direction from beat to beat. No P waves are present. (From Goldberger AL [ed]: *Clinical electrocardiography,* ed 5, St Louis, 1994, Mosby.)

b. Chronic ingestion: number of vials = (serum digoxin level [ng/ml] × weight [kg]/100
c. If neither the amount ingested nor steady-state serum level is known, treat empirically:
   (i) Acute intoxication: 10 vials and repeat in 30 min if inadequate response
   (ii) Chronic toxicity: 6 vials

NOTE: Underdosing of Fab fragments may result in rebound toxicity as free digoxin is released from tissue stores. In chronic toxicity without life-threatening symptoms, consider giving half the calculated dose initially to decrease the risk of exacerbating underlying heart disease.

5. After use of Fab fragments, the free digoxin level decreases, but the measured digoxin level may increase because most assays measure free and bound digoxin levels. Serum levels are unreliable for days.
6. Renal elimination: half-life of inactive complex is 15 to 20 hr. Elimination of complex is prolonged in renal failure; may get recurrence of toxicity days later (complexes may dissociate before excretion), so require monitoring for >72 hr. Can use plasma exchange or plasmapheresis to remove Fab-digoxin complex.
7. Class C for pregnancy.
8. Adverse effects of treatment:
   a. May undo desirable action of digoxin and exacerbate heart failure or increase ventricular response in previously controlled atrial fibrillation.
   b. Hypotension
   c. Hypokalemia (as toxicity is corrected, potassium moves back into the cell and hypokalemia can develop): monitor potassium level hourly for several hours.
   d. Allergic reactions (higher if history of prior use): serum sickness.

- Hemodialysis and hemoperfusion: not useful because of extensive tissue binding and large volume of distribution.
- Digoxin toxicity not requiring Fab fragments: hospitalize with cardiac monitoring. Monitor potassium and digoxin concentrations; serial EKGs.

COMPLICATIONS: These recommendations are temporizing measures until digoxin-specific Fab fragments can be given.

Hyperkalemia: due to redistribution; treatment to lower K^+ not recommended unless life threatening because hypokalemia may occur once toxicity is corrected with Fab fragments.

Hypotension: IV fluids

Bradycardia and heart block:

- Atropine
- Cardiac pacing: use with caution, may precipitate life-threatening ventricular arrhythmias

Supraventricular and ventricular tachycardia:

- Lidocaine or phenytoin: decrease ventricular automaticity without slowing AV node conduction
- Avoid quinidine, bretylium, procainamide, and verapamil; may increase ventricular arrhythmias/AV node block
- Elective electrocardioversion is relatively contraindicated because it may precipitate ventricular fibrillation

DISPOSITION

- Good with prompt treatment
- Chronic poisoning is associated with higher mortality rate than acute poisoning

REFERRAL

American Association of Poison Control Centers: 800-222-1222

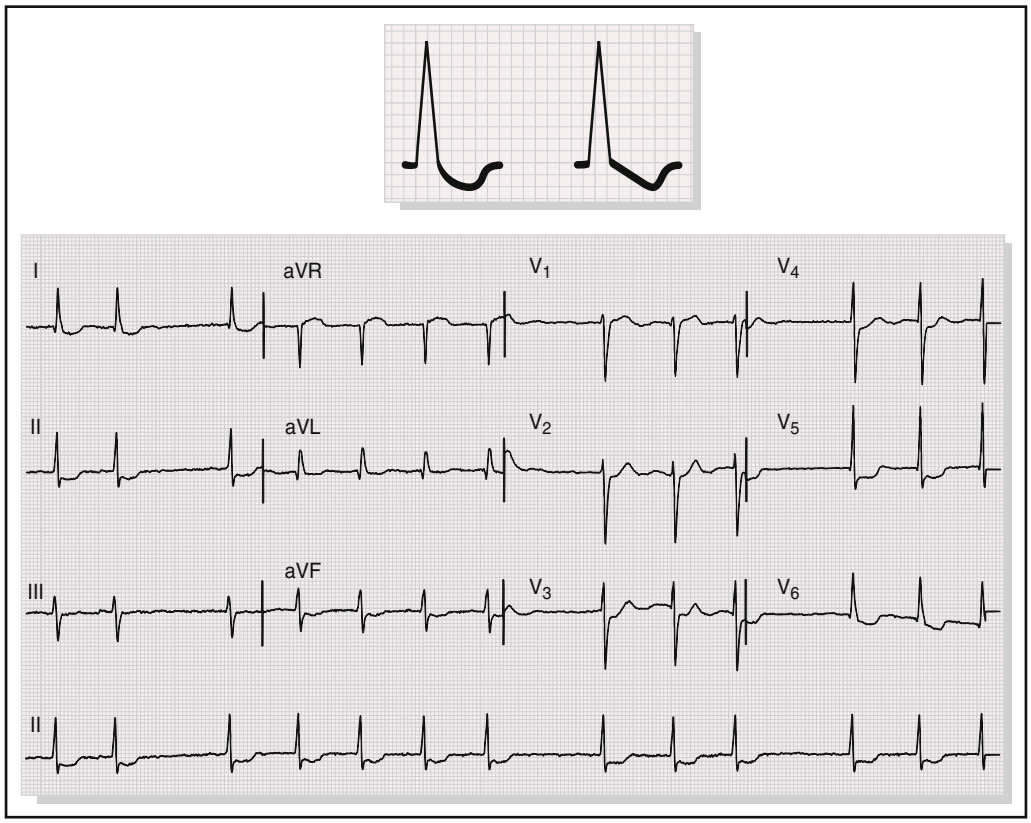

FIGURE ED1-37 *Top panel*, digitalis effect. Digitalis glycosides characteristically produce shortening of the QT interval with a scooped or downsloping ST-T complex. *Bottom panels*, Digitalis effect in combination with digitalis toxicity. The underlying rhythm is atrial fibrillation. A group beating pattern of QRS complexes with shortening of the R-R intervals is consistent with nonparoxysmal junctional tachycardia with exit (AV Wenckebach) block. ST-segment depression and scooping (lead V6) are consistent with the digitalis effect, although ischemia or left ventricular hypertrophy (LVH) cannot be excluded. Findings are strongly suggestive of digitalis excess; the serum digoxin level was higher than 3 ng/ml. The digitalis effect does not necessarily imply digitalis toxicity, however. (Top panel from Goldberger AI: *Clinical electrocardiography*, ed 6, St. Louis, 1999, CV Mosby.) (From Bonow RO [et al.]: *Braunwald's heart disease*, ed 9, Philadelphia, 2012, Saunders.)

PEARLS & CONSIDERATIONS

- High index of suspicion is necessary; the signs and symptoms of toxicity often are similar to those of the underlying disease.
- To minimize toxicity, digoxin levels should be checked if the patient's condition changes (e.g., weight loss, worsening renal function) or an interacting drug is started or stopped.
- Hyperkalemia in acute toxicity is suggestive of significant poisoning (reflects amount of Na^+, K^+-ATPase poisoning) and is associated with increased mortality.
- Falsely elevated digoxin levels may be seen in pregnant women, renal failure, hepatobiliary disease, and CHF due to the presence of an endogenous digoxin-like substance.
- Severe toxicity from ingestion of nondigoxin cardiac glycosides (plants, etc.) may present with low digoxin levels because of low cross-reactivity between these substances and the digoxin assay. Empiric dosing of Fab fragments should be used to treat these poisonings.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **SUDEEP KAUR AULAKH, M.D.**

SUGGESTED READINGS

Antman EM et al.: Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments, *Final report of a multicenter study Circulation* 81:1744, 1990.

Bauman JL et al.: Mechanisms, manifestations, and management of digoxin toxicity in the modern era, *Am J Cardiovasc Drugs* 6(2):77, 2006.

Obreli-Neto PR et al.: Adverse drug reactions caused by drug-drug interactions in elderly outpatients: a prospective cohort study, *Eur J Clin Pharmacol* 68:1667, 2012.

Yancy CW et al.: ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 128 (16):e240, 2013.

BASIC INFORMATION

DEFINITION

Diphtheria is an infection of the mucous membranes or skin caused by *Corynebacterium diphtheriae.*

Rarely, a similar disease can be caused by other *Corynebacterium* species, which may elaborate a toxin similar to toxigenic *C. diphtheriae.*

SYNONYMS

Pharyngeal diphtheria
Wound diphtheria
Diphtheric cardiomyopathy
Diphtheric polyneuropathy

ICD-9CM CODES
032.9 Diphtheria
ICD-10CM CODES
A36.9 Diphtheria, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Since 1980 the incidence in the U.S. has been about 0.001 cases per 1,000,000 population due to widespread vaccination
PREDOMINANT AGE: Adult years (in the U.S.)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

RESPIRATORY DIPHTHERIA:

- Commonly presenting as pharyngitis, but any part of the respiratory tract may be involved, including the nasopharynx, larynx, trachea, or bronchi
- Areas of gray or white exudate coalescing to form a "pseudomembrane" that bleeds when removed
- Possible fever and dysphagia
- Complications: respiratory tract obstruction and pneumonia
- Systemic effects of the toxin: myocarditis and polyneuritis (frequently involving a bulbar distribution), less often nephritis
- Occurs mostly in nonimmune individuals; usually milder and less likely to be complicated in those adequately immunized

CUTANEOUS DIPHTHERIA:

- Usually complicates existing skin lesion (i.e., impetigo or scabies)
- Resembles the underlying condition or presents as a nonhealing ulcer with a grayish membrane

ETIOLOGY

- Caused by *C. diphtheriae,* an aerobic, gram-positive rod
- Transmitted by close contact through droplets of nasopharyngeal secretions
- Symptomatic disease of the respiratory system caused by toxin-producing strains (tox^+)
- Systemic effects of toxin: ranging from nausea and vomiting to polyneuropathy, nephritis, myocarditis, and vascular collapse
- Presence of strains not producing toxin (tox^+) in the respiratory tract of asymptomatic carriers and in skin lesions of cutaneous diphtheria
- Humans are the only known reservoir for *C. diphtheriae.*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Streptococcal pharyngitis
- Viral pharyngitis
- Mononucleosis

WORKUP

- Presence of a pseudomembrane in the oropharynx suggestive of diagnosis (not always present)
- Gram stains of secretions to show club-shaped organisms, which appear as "Chinese letters"
- Nasolaryngoscopy to identify lesions in the nares, nasopharynx, larynx, or tracheobronchial tree

LABORATORY TESTS

- Cultures of mucosal lesions or of nasal discharge
  1. Positive culture for *C. diphtheriae* confirms the diagnosis.
  2. Laboratory is notified of the suspected diagnosis so that appropriate culture medium (Tinsdale agar) is used.
- Testing of all isolated organisms for toxin production. The CDC Pertussis and Diphtheria Lab offers culture, toxin testing, PCR, and serology; phone 404-639-1231.

Repeat cultures should be obtained two weeks after completing therapy to ensure eradication of the bacteria.

IMAGING STUDIES

Chest x-ray to rule out pneumonia

TREATMENT

NONPHARMACOLOGIC THERAPY

- Intubation or tracheostomy if signs of respiratory distress occur
- Nasogastric or parenteral nutrition in those with bulbar signs
- ICU monitoring for patients with signs of systemic toxicity
- Cardiac pacing in patients with heart block
- Respiratory isolation

ACUTE GENERAL Rx

- Administration of diphtheria antitoxin once a clinical diagnosis is made
- If tests for hypersensitivity to horse serum are negative: 20,000 to 40,000 units for pharyngeal/laryngeal disease present less than 48 hr, 40,000 to 60,000 units for nasopharyngeal disease, and 80,000 to 120,000 units for greater than 3 days of illness or diffuse neck swelling ("bull-neck") (available via the CDC)
- IV infusion of antitoxin over 60 min
- Serum sickness in 10% of treated individuals; those with hypersensitivity to horse serum should be desensitized before administration of antitoxin
- Antibiotics to eradicate the organism in carriers or patients
- For respiratory diphtheria:
  1. Erythromycin 500 mg qid PO or IV (clarithromycin and azithromycin are acceptable alternatives) or IV penicillin G 25,000 to 50,000 units/kg to a maximum of 1.2 million units bid for 14 days. The course may be completed orally when able.
  2. Carriers or patients with cutaneous disease: erythromycin 500 mg PO qid or IM penicillin.
  3. Patients should be given diphtheria toxoid vaccine during convalescence as disease does not interfere with immunity.
- Patients should be appropriately isolated: droplet precautions for respiratory cases, contact for cutaneous cases.
- Contacts should be screened for prophylactic antibiotics.

CHRONIC Rx

Antibiotics to limit toxin production and eradicate carrier state, thereby preventing transmission

DISPOSITION

Complete recovery with adequate supportive measures and antitoxin

REFERRAL

- Hospitalization and referral to an infectious disease specialist for all suspected patients
- To an otolaryngologist for evaluation in cases of respiratory diphtheria
- All cases reported to the public health authorities

PEARLS & CONSIDERATIONS

COMMENTS

- Most cases are imported by travelers in epidemic areas, so recent epidemics in Eastern Europe are a cause for concern. A widespread epidemic of diphtheria began in 1990 in the former Soviet Union.
- Vaccination with diphtheria toxoid (attenuated toxin) is safe and effective in the form of DPT or Td; Td boosters should be given to adults every 10 yr. A new formulation of Tdap vaccine with reduced amounts of diphtheria toxoid and acellular pertussis antigens is available; it is well tolerated in clinical trials and provides excellent protection in adolescents and adults.
- According to serologic studies, 20% to 60% of U.S. adults >20 yr of age are susceptible to diphtheria.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **PATRICIA CRISTOFARO, M.D.**

SUGGESTED READINGS

ACIP Childhood/Adolescent Immunization Work Group: Recommended immunization schedule for persons aged 0 thru 18 yrs–US 2013, *MMWR Surveill Summ* 62(Suppl 1):2, 2013.

Advisory Committee on Immunization Practices: Recommended immunization schedule for adults aged 19 years and older–US 2013, *MMWR Surveill Summ* 62(Suppl 1):9, 2013.

Berrington J, Fenton A: Immunization responses in preterm infants who receive postnatal steroid treatment, *Pediatrics* 114(4):1127, 2004.

Centers for Disease Control and Prevention: Notes from the field: respiratory diphtheria-like illness caused by toxigenic Corynebacterium ulcerans—Idaho, 2010, *MMWR Morb Mortal Wkly Rep* 60(77), 2011.

Dittmann S et al.: Successful control of epidemic diphtheria in the states of the Former Union of Soviet Republics: lessons learned, *J Infect Dis* 181(Suppl 1):S10, 2000.

Kadirova R et al.: Clinical characteristics and management of 676 hospitalized diphtheria cases, Kyrgyz Republic, 1995, *J Infect Dis* 181(1):S110, 2000.

Kneen R et al.: Clinical features and predictors of diphtheritic cardiomyopathy in Vietnamese children, *Clin Infect Dis* 39:1591, 2004.

Kneen R et al.: Penicillin vs. erythromycin in the treatment of diphtheria, *Clin Infect Dis* 27:845, 1998.

Lowe CF et al.: Cutaneous diphtheria in the urban poor population of Vancouver, British Columbia: a 10-year review, *J Clin Microbiol* 49(7), 2011.

Tiwari TS et al.: Investigations of two cases of diphtheria-like illness due to toxigenic Corynebacterium ulcers, *Clin Infect Dis* 46:395, 2008.

Wagner KS et al.: Diphtheria in the United Kingdom, 1986-2008: the increasing role of Corynebacterium ulcerans, *Epidemiol Infect* 138:1519, 2010.

BASIC INFORMATION

DEFINITION

Discoid lupus erythematosus (DLE) refers to a chronic inflammatory autoimmune skin disorder that can lead to significant disfiguration and scarring. It can be associated with systemic lupus erythematosus (SLE).

SYNONYMS

Chronic cutaneous lupus erythematosus (CLE)

ICD-9CM CODES

695.4 Lupus erythematosus
Erythematosus (discoid)
Erythematosus (discoid), not disseminated

ICD-10CM CODES

L93.0 Discoid lupus erythematosus
L93.2 Other local lupus erythematosus

EPIDEMIOLOGY & DEMOGRAPHICS

- Slightly more common in African Americans than in Asians or whites
- CLE is two to three times more likely in women than in men
- Approximately 5% to 10% of patients presenting with DLE will develop SLE; those with widespread, numerous lesions are more likely to progress

PHYSICAL FINDINGS & CLINICAL PRESENTATION

General:

- Early lesions: single or multiple erythematous or violaceous, discrete papules or plaques with scale, often extending into dilated hair follicles (Fig. D1-38)
- Older lesions: peripheral hyperpigmentation with scarring, central depigmentation (Fig. ED1-39), and telangiectasia

Anatomic distribution:

- Commonly involves the scalp, face, ears, and extensor surface of the arms
- Mucosal and nail involvement is also possible

Lesion configuration:

- Irregularly grouped, confluent and disfiguring plaques

Lesion morphology:

- Plaque lesions with scale
- Follicular plugging
- Atrophy
- Irreversible, scarring alopecia (34%)
- May be associated with other clinical findings of SLE (e.g., oral ulcers, arthritis, pleuritis, pericarditis)

ETIOLOGY

Unknown, but thought to be an autoimmune-mediated disorder

DIAGNOSIS

Clinical findings and skin biopsy are used to establish the diagnosis of DLE

DIFFERENTIAL DIAGNOSIS

Psoriasis, lichen planus or lichen planopilaris, dermatophyte infections, photosensitivity eruption, sarcoidosis, subacute CLE, rosacea, dermatomyositis, cutaneous T-cell lymphoma

LABORATORY TESTS

- Complete blood count is usually normal in isolated DLE, but a small percentage of patients may show low-grade anemia
- Blood urea nitrogen and creatinine are normal in isolated DLE
- Erythrocyte sedimentation rate is elevated in active disease
- Urinalysis may show proteinuria
- Antinuclear antibody positive in 30% to 40% of patients with isolated DLE
- Anti-Ro (SS-A) autoantibodies are present in 1% to 3% of patients
- dsDNA antibodies are uncommon
- Complement levels may be low in rare instances
- Histology of skin reveals hyperkeratosis with follicular plugging, a thickened basement membrane, and a perivascular, interstitial, and appendageal lymphocytic infiltrate

FIGURE D1-38 Classic discoid lupus erythematosus of the face. Note central scarring and erythematous hyperkeratotic borders. (From Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.)

TREATMENT

NONPHARMACOLOGIC THERAPY

Avoid sun exposure by using protective clothing and a broad-spectrum sunscreen of SPF >30

ACUTE GENERAL Rx

1. Topical steroids: intermediate- to high-potency steroids are needed; use caution when applying to the face
2. Intralesional steroids: triamcinolone acetonide 2.5 to 5.0 mg/ml with 1% Xylocaine
3. Topical calcineurin inhibitors: pimecrolimus 1% cream and tacrolimus 0.1% ointment
4. Antimalarial drugs are first-line systemic therapy for cutaneous lupus: hydroxychloroquine sulfate 400 mg PO qd
5. Avoid use of systemic glucocorticoids in patients with isolated DLE because of risks of side effects

CHRONIC Rx

1. Chloroquine 250 to 500 mg PO qd
2. Additional options are methotrexate, mycophenolate mofetil, and cyclosporine.
3. Thalidomide 100 to 300 mg PO before sleep, with water, and >1 hr after meals for refractory CLE
4. Azathioprine 1 mg/kg/day PO for 6 to 8 wk, increase by 5 mg/kg q4 wk until response is seen or dose reaches 2.5 mg/kg/day
5. Dapsone: 100 mg/day

DISPOSITION

If untreated, DLE can lead to significant and permanent atrophy and scarring of the skin.

REFERRAL

Dermatology, rheumatology

PEARLS & CONSIDERATIONS

- Cutaneous lesions account for four of the 11 criteria in the diagnosis of SLE (e.g., malar rash, discoid rash, photosensitivity, and oral ulcers).
- Rarely, patients with DLE may develop nonmelanoma skin cancer in areas of disease.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Discoid Lupus Erythematosus (Patient Information)
Systemic Lupus Erythematosus (Related Key Topic)

AUTHORS: **KACHIU LEE, B.A.,** and **JESSICA CORWIN, M.D., M.P.H.**

EVIDENCE

Abstract[1]

Background:
Antimicrobial peptides (AMPs) are small effector molecules of the innate immune system with well-known antimicrobial activity. Skin infections rarely occur in patients with cutaneous lupus erythematosus (CLE), and AMP expression in CLE has not been previously evaluated.

Objectives:
We aimed to determine the expression of several important AMPs in 3 different subtypes of CLE.

Methods:
Skin lesions were analyzed for the gene and protein expression of human β-defensin (hBD)-1, -2, and -3; RNase-7; the cathelicidin LL-37; and psoriasin (S100A7) using real-time reverse transcriptase polymerase chain reaction and immunohistochemistry.

Results:
Skin biopsy specimens of 96 study participants including 47 patients with CLE (15 patients with discoid lupus erythematosus [LE], 11 patients with subacute CLE, and 21 patients with LE tumidus), 34 patients with psoriasis, and 15 healthy control subjects were evaluated in this study. HBD-2, hBD-3, LL-37, and psoriasin were significantly more highly expressed in CLE as compared with healthy controls, and most AMPs were significantly more highly induced in subacute CLE as compared with discoid LE and LE tumidus. AMP gene expression paralleled well with AMP protein expression in CLE and controls. Subacute CLE and discoid LE showed a similar correlation of AMP gene expression (significant correlations between hBD-1 and RNase-7, hBD-2 and hBD-3, hBD-2 and psoriasin, and hBD-3 and psoriasin).

Limitations:
The relatively small number of samples and the lack of analysis of the lesional bacterial colonization are a limitation.

Conclusions:
Several AMPs are increased in CLE at both gene and protein levels. This could explain the low prevalence of skin infections in CLE. It remains to be elucidated whether AMPs play a pathogenic role in CLE. Ⓐ

Evidence-Based Reference

Kreuter A et al.: Expression of antimicrobial peptides in different subtypes of cutaneous lupus erythematosus, *J Am Acad Dermatol* 65:125–133, 2011. Ⓐ

SUGGESTED READINGS

Callen JP: Lupus erythematosus, discoid, *e-Medicine Journal*, May 25, 2010. Available at http://www.emedicine.com.

Fabri P et al.: Cutaneous lupus erythematosus: diagnosis and management, *Am J Clin Dermatol* 4(7):449, 2003.

Pramatorov KD: Chronic cutaneous lupus erythematosus—clinical spectrum, *Clin Dermatol* 22(2):113, 2004.

Rothfield NR et al.: Lupus erythematosus: systemic and cutaneous manifestations, *Clin Dermatol* 24(5):348, 2006.

Werth V: Clinical manifestations of cutaneous lupus erythematosus, *Autoimmune Rev* 4(5):296, 2005.

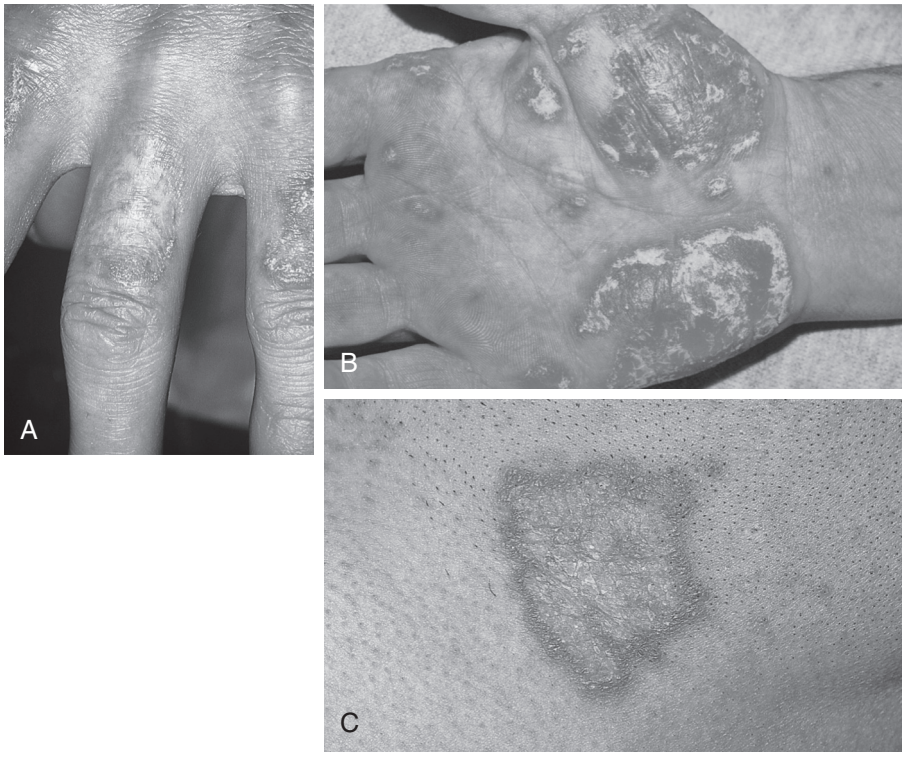

FIGURE ED1-39 Discoid lupus. Discoid lupus erythematosus on the finger **(A),** palm **(B)** (an uncommon site), and beard area **(C)**. A grayish color centrally is a common feature, due to the combination of disruption of pigment, which is caused by inflammation at the dermo-epidermal junction, and the subsequent atrophy. Note the scaling, follicular scarring, and follicular plugging in these pictures. (**A** from Lawrence CM, Cox NH: *Physical signs in dermatology,* ed 2, London, 2002, Mosby; **B** and **C** from White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

Disseminated Intravascular Coagulation PTG

BASIC INFORMATION

DEFINITION

Disseminated intravascular coagulation (DIC) is an acquired thromboembolic disorder characterized by generalized activation of the clotting mechanism, which results in the intravascular formation of fibrin and ultimately thrombotic occlusion of small and midsize vessels.

SYNONYMS

Consumptive coagulopathy
DIC
Defibrination syndrome

ICD-9CM CODES
286.6 Disseminated intravascular coagulation
ICD-10CM CODES
D65 Disseminated intravascular coagulation [defibrination syndrome]

EPIDEMIOLOGY & DEMOGRAPHICS

More than 50% of cases are associated with gram-negative sepsis or other septicemic infections.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Wound site bleeding, epistaxis, gingival bleeding, hemorrhagic bullae
- Petechiae, ecchymosis, purpura (Fig. ED1-40)
- Dyspnea, localized rales, delirium
- Oliguria, anuria, gastrointestinal bleeding, metrorrhagia

ETIOLOGY

- Infections (e.g., gram-negative sepsis, Rocky Mountain spotted fever, malaria, viral or fungal infection)
- Obstetric complications (e.g., dead fetus, amniotic fluid embolism, toxemia, abruptio placentae, septic abortion, eclampsia, placenta previa, uterine atony)
- Tissue trauma (e.g., burns, hypothermia rewarming)
- Neoplasms (e.g., adenocarcinomas [gastrointestinal, prostate, lung, breast], acute promyelocytic leukemia)
- Quinine, cocaine-induced rhabdomyolysis
- Liver failure
- Acute pancreatitis
- Transfusion reactions
- Respiratory distress syndrome
- Toxins (snake bites, amphetamine overdose)
- Other: systemic lupus erythematosus (SLE), vasculitis, aneurysms, polyarteritis, cavernous hemangiomas
- Box ED1-4 describes underlying conditions associated with DIC.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hepatic necrosis: normal or elevated factor VIII concentrations
- Vitamin K deficiency: normal platelet count
- Hemolytic uremic syndrome
- Thrombotic thrombocytopenic purpura
- Renal failure, SLE, sickle cell crisis, dysfibrinogenemias
- HELLP syndrome (**h**emolysis, **e**levated **l**iver function tests, and **l**ow **p**latelets)

WORKUP

Diagnostic workup includes laboratory screening to confirm the diagnosis and exclude conditions noted in the differential diagnosis (Figs. D1-41 and D1-42). Workup is also aimed at distinguishing DIC progression (acute vs. chronic), chief manifestations (thrombotic or hemorrhagic), and extent (localized or systemic). The International Society on Thrombosis and Haemostasis scoring system for DIC is described in Box ED1-5.

LABORATORY TESTS

- Peripheral blood smear generally shows red blood cell fragments (schistocytes) and low platelet count.
- Coagulation factors are consumed at a rate in excess of the capacity of the liver to synthesize them, and platelets are consumed in excess of the capacity of the bone marrow megakaryocytes to release them. Diagnostic characteristics of DIC are decreased fibrinogen level; thrombocytopenia; and increased prothrombin time (PT), partial thromboplastin time (PTT), TT, fibrin split products, bleeding time, and D-dimer.
- Coagulopathy secondary to DIC must be differentiated from that secondary to liver disease or vitamin K deficiency.
  1. Vitamin K deficiency manifests with prolonged PT and normal PTT, TT, platelet, and fibrinogen level; PTT may be elevated in severe cases.
  2. Patients with liver disease have abnormal PT and PTT; TT and fibrinogen are usually normal unless severe disease is present; platelets are usually normal unless splenomegaly is present.
  3. Factors V and VIII are low in DIC, but they are normal in liver disease with coagulopathy.

IMAGING STUDIES

Imaging studies are generally not useful. Chest radiographs may be helpful to exclude infectious processes in patients with pulmonary symptoms such as dyspnea, cough, or hemoptysis.

TREATMENT

NONPHARMACOLOGIC THERAPY

No specific precautions regarding activity level are necessary unless thrombocytopenia is severe.

ACUTE GENERAL Rx

- Correct and eliminate underlying cause (e.g., antimicrobial therapy for infection, removal of necrotic bowel, evacuation of uterus in obstetric emergencies).
- Give replacement therapy with fresh frozen plasma (FFP) and platelets in patients with significant hemorrhage:
  1. FFP 10 to 15 ml/kg can be given with a goal of normalizing international normalized ratio.
  2. Platelet transfusions are given when platelet count is <10,000 (or higher if major bleeding is present).
  3. Cryoprecipitate 1 U/5 kg is reserved for hypofibrinogen states.
  4. Antithrombin III treatment may be considered as a supportive therapeutic option in patients with severe DIC. Its modest results and substantial cost are limiting factors.
- Heparin therapy at a dose lower than that used in venous thrombosis (300 to 500 U/hr) may be useful in selected cases to increase neutralization of thrombin (e.g., DIC associated with acute promyelocytic leukemia, purpura fulminans, acral ischemia).

CHRONIC Rx

Follow-up management includes coagulation screening to assess factor replacement therapy. Laboratory abnormalities generally correct with treatment of the underlying disorder. Long-term laboratory monitoring is not required.

DISPOSITION

Mortality rate in severe DIC exceeds 75%. Death generally results from progression of the underlying disease and complications such as acute renal failure, intracerebral hematoma, shock, or cardiac tamponade.

REFERRAL

Hematology consultation is recommended in all cases of DIC.

PEARLS & CONSIDERATIONS

COMMENTS

The treatment of chronic DIC is controversial. Low-dose SC heparin and/or combination antiplatelet agents such as aspirin and dipyridamole may be useful.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Disseminated Intravascular Coagulation (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

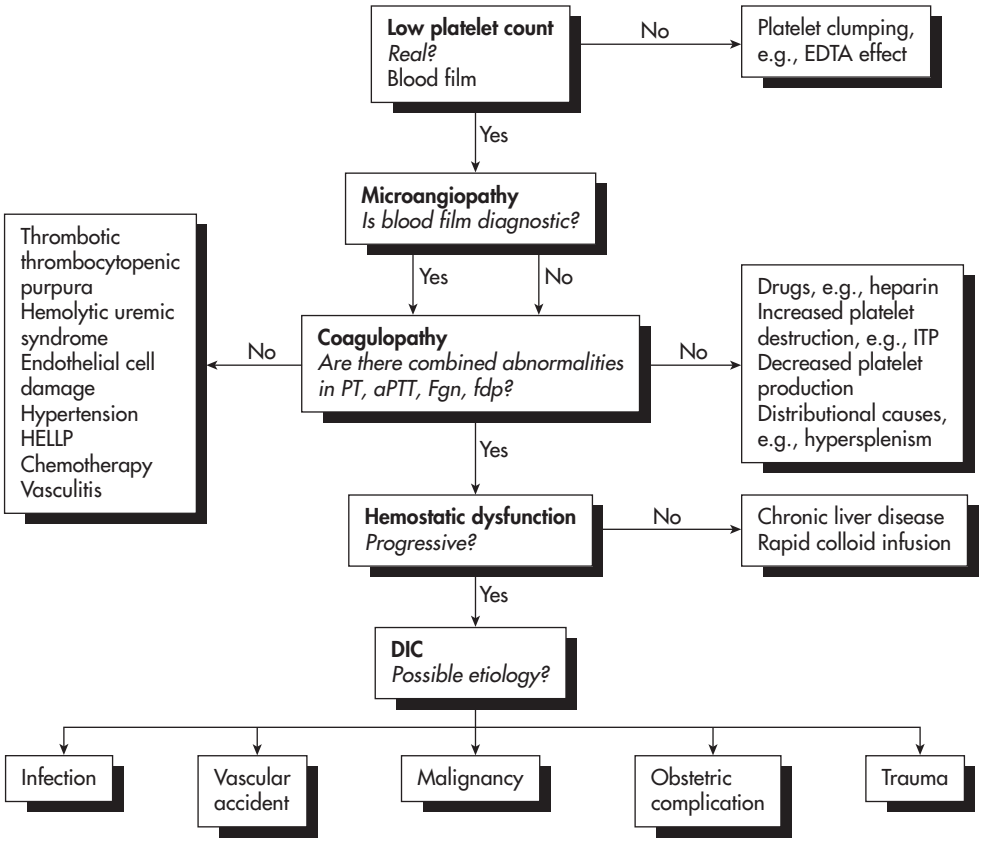

FIGURE D1-41 Differential diagnostic algorithm for disseminated intravascular coagulation (DIC). *aPTT,* Activated partial thromboplastin time; *EDTA,* ethylenediaminetetraacetic acid; *ITP,* idiopathic thrombocytopenic purpura; *PT,* prothrombin time. (From Young NS et al [eds]: *Clinical hematology,* St Louis, 2006, Mosby.)

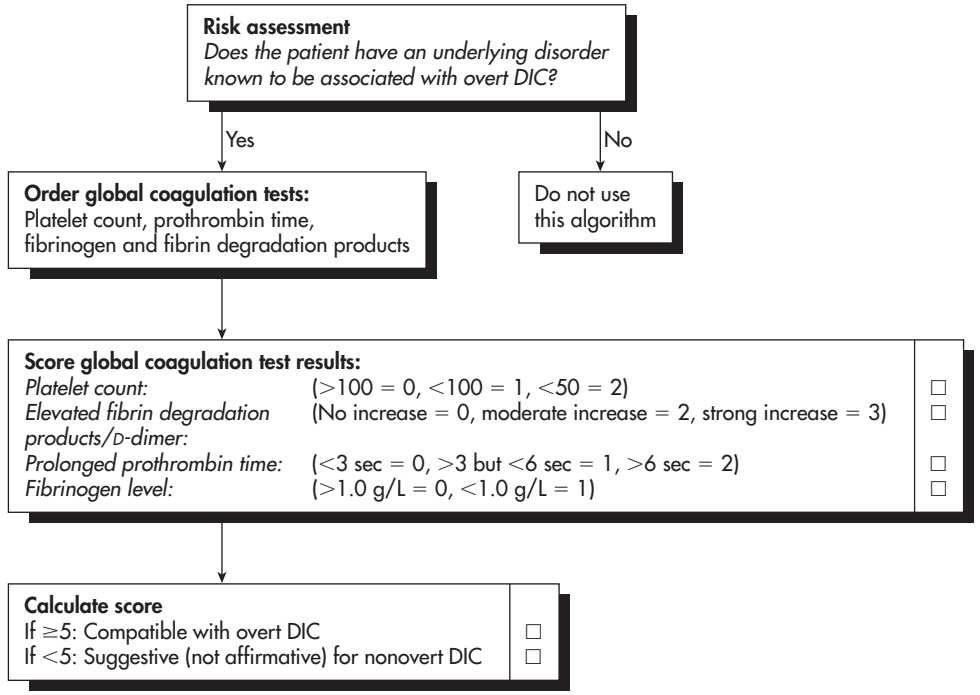

FIGURE D1-42 Laboratory testing and diagnosis of overt disseminated intravascular coagulation (DIC). (From Young NS et al [eds]: *Clinical hematology,* St Louis, 2006, Mosby.)

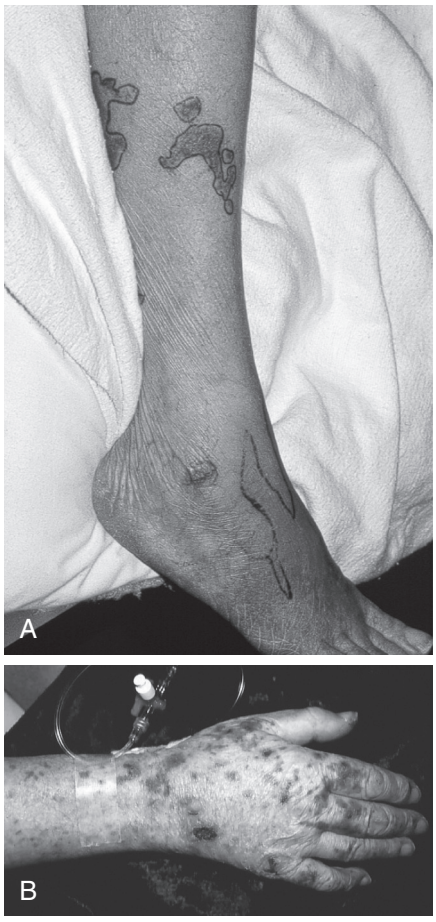

FIGURE ED1-40 Disseminated intravascular coagulation (DIC). A and **B,** DIC causing a livedo patterning of necrotic areas. (*B* courtesy of Dr. G. Dawn. From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

BOX ED1-4 Underlying Conditions Associated with Disseminated Intravascular Coagulation

Acute and Subacute
- Infection
- Gram-negative bacteria
- Encapsulated gram-positive bacteria
- Viruses (e.g., varicella)
- Obstetric complications
- Abruptio placentae
- Amniotic fluid embolism
- Sepsis
- Saline-induced abortion
- Malignancies
- Leukemia, lymphoma
- Tissue injury
- Burns
- Heat stroke

Chronic
- Malignancies
- Solid tumors
- Obstetric complications
- Dead fetus syndrome
- Localized intravascular coagulation
- Aortic aneurysm
- Hemangiomas (Kasabach-Merritt syndrome)
- Advanced liver disease
- LeVeen shunt
- Fatty liver of pregnancy

From Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

SUGGESTED READINGS

Hunt BJ et al.: Bleeding and coagulopathies in critical care, *N Engl J Med* 370:846–859, 2014.

Toh CH, Hoots WK: The scoring system of the Scientific and Standardisation Committee on Disseminated Intravascular Coagulation of the International Society on Thrombosis and Haemostasis: a 5-year overview, *J Thromb Haemost* 5:604–606, 2007.

BOX ED1-5 International Society on Thrombosis and Haemostasis Scoring System for Disseminated Intravascular Coagulation (DIC)

Overt DIC

1. Risk assessment: Does the patient have an underlying disorder known to be associated with DIC (see Box ED1-4)?
   If yes, proceed. If no, do not use the algorithm.
1. Order global coagulation test: platelet count, soluble fibrin monomers of fibrin degradation products, prothrombin time, fibrinogen.
2. Score global coagulation test results as follows:
   Platelet count:
   - >100 × 10^9/L = 0
   - <100 × 10^9/L = 1
   - <50 × 10^9/L = 2

   Score = ____
3. Fibrin-related marker:
   No increase = 0
   Moderate increase = 2
   Strong increase = 3
   Score = ____
4. Prolongation of prothrombin time:
   <3 seconds = 0
   >3 seconds >6 seconds = 1
   >6 seconds = 2
   Score = ____
5. Fibrinogen level:
   <1.0 gram/L = 0
   >1.0 gram/L = 1
   Score = ____
6. Calculate score.
   If total score ≥5, compatible with overt DIC, repeat scoring daily.
   If total score >5, suggestive of nonovert DIC, repeat in 1 to 2 days
   Score = ____

Nonovert DIC

1. Risk assessment: Does the patient have an underlying condition associated with DIC (see Box ED1-4)?
   Yes = 1
   No = 0
   Score = ____
2. **Major criteria**
   Platelet count:
   - >100 × 10^9/L = 0
   - <100 × 10^9/L = 1

   plus
   - Increasing count = -1
   - Stable count = 0
   - Decreasing count = 1

   Score = ____
3. PT prolongation:
   >3 seconds = 0
   <3 seconds = 1
   plus
   Increasing value = 1
   Stable value = 0
   Decreasing value = -1
   Score = ____
4. Soluble fibrin or FDP:
   Normal = 0
   Raised = 1
   plus
   Increasing value = 1
   Stable value = 0
   Decreasing value = -1
   Score = ____
5. **Specific criteria**
   Antithrombin:
   - Normal = -1
   - Low = 1

   Score = ____

   Protein C:
   - Normal = -1
   - Low = 1

   Score = ____

   TAT complexes:
   - Normal = -1
   - High = -1

   Score = ____
6. Calculate total score. **Score** = ____

FDP, Fibrin/fibrinogen degradation products; *TAT,* thrombin-antithrombin.
From Taylor FBJ et al: Toward definition, clinical and laboratory criteria and a scoring system for disseminated intravascular coagulation, *Thromb Haemost* 86:1327-1330, 2001.

BASIC INFORMATION

DEFINITION

Dissociative disorders (DDs) are a cluster of disorders that feature a disturbance in identity, memory, perception, and consciousness. Subtypes of DDs include: dissociative identity disorder (DID), dissociative amnesia (DA), dissociative fugue (DF), and depersonalization/derealization disorder (DPD).

SYNONYMS

DD
DID
DA
DF
DPD

ICD-9 CM CODES

300.12 Dissociative amnesia
300.13 Dissociative fugue
300.14 Dissociative identity disorder
300.6 Depersonalization disorder
300.15 Dissociative disorder not otherwise specified

ICD-10 CM CODES

300.14 Dissociative identity disorder
300.12 Dissociative amnesia
300.13 Dissociative amnesia with dissociative fugue
300.6 Depersonalization/derealization disorder
300.15 Other specified dissociative disorder
300.15 Dissociative disorder, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence: Limited research documents incidence rates of DDs. These incidence estimates vary greatly based on the instrument utilized and the sample studied.
- Peak incidence: Age of peak incidence varies by the type of DD.
- Prevalence: The prevalence of DDs is thought to be between 0.1% and 1.0% of the general population.
- Predominant sex and age: Females are diagnosed with DDs more frequently than males. Diagnoses may be made among individuals of all ages. Whereas DID is thought to begin in childhood during the course of severe and/or prolonged trauma, other DDs are thought to begin within the immediate context of stressful events at any age.
- Genetics: There is some evidence that biologic differences may play a role the likelihood of dissociation following the experience of trauma.
- Risk factors: DDs have been linked to experiencing overwhelming stress, such as witnessing or experiencing traumatic events.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- **Dissociative amnesia (DA)**: Loss of autobiographic memory for previous experiences, or before a certain point in time. Types of DA include:
  - Localized amnesia: Inability to recall a specific (traumatic) period of time.
  - Selective amnesia: Inability to recall parts, but not all, of a specific period of time.
  - Systematized amnesia: Inability to recall categoric memories, but not memory loss in chronologic order such as with localized amnesia.
  - Continuous amnesia: Anterograde loss of memory, or inability to remember successive events as they occurred.
  - Generalized (global) amnesia: Inability to recall one's whole life, including personal details.
  - Thematic amnesia (as seen in DID & DDNOS): As identity states change, ability to recall specific periods of time is altered.
- **Dissociative fugue (DF):** DF carries all the same characteristics and features as DA, with the distinguishing feature of sudden and unplanned purposeful travel away from one's home.
- **Dissociative identity disorder (DID):** Formerly referred to as *multiple personality disorder* (MPD), patients appear to possess two (or more) distinct identities or personality states, associated with the patient's consciousness, perception, thoughts, and actions.
- **Depersonalization disorder (DPD):** Also known as *derealization disorder,* DPD is a state where patients believe that they have been altered in some way, or that they are no longer real. Features include persistent and recurring experiences of feeling detached from one's own body and mental processes (i.e., one observing oneself as an outsider). Reality testing remains intact.
- **Dissociative disorders not otherwise specified (DDNOS):** Some dissociative symptoms of varying degrees, but not meeting clinical diagnostic criteria for a distinct diagnosis.

ETIOLOGY

- DDs are thought to develop after experiencing severe emotional or physical trauma. There is limited understanding of the neurobiologic underpinnings of DDs. However, data indicating that individuals with DPD report blunted reactions to arousing stimuli suggest that DDs may be due to problems in connections between sensory systems (i.e., eyesight, hearing) and the limbic system. Other studies indicate variations in serotonin, endogenous opioid, and glutamate systems among individuals with DPD. Other studies document decreased blood flow in the right frontotemporal cortex of individuals with DA.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- DDs should be distinguished from acute substance intoxication, withdrawal, or substance-induced persisting amnestic disorder.
- Symptoms due to the physiologic consequences of a medical condition should be diagnosed as a mental disorder NOS due to a general medical condition.
- DA should be distinguished from amnestic disorder due to a brain injury, seizure disorders, delirium, dementia, age-related cognitive decline, and nonpathologic forms of amnesia (i.e., amnesia for sleep, memory loss).
- DA and DPD should not be diagnosed separately if symptoms occur only during the course of DF.
- DPD should not be diagnosed when symptoms occur only during a panic attack, or in the context of panic disorder, specific phobia, or post-traumatic or acute stress disorders.
- If fugue symptoms occur only in the context of DID, DF should not be diagnosed separately.
- DID diagnosis takes precedence over diagnosis of other DDs (i.e., DA, DF, DPD).
- Purposeful travel that occurs during a manic episode should be distinguished from a DF.
- Differential diagnosis should also consider schizophrenia and other psychotic disorders, bipolar disorder with rapid cycling, anxiety disorders, somatization disorders, and personality disorders.
- Amnesia for trauma may also occur in post-traumatic stress disorder and acute stress disorder
- Clinicians may also consider malingered amnesia and malingered fugue states

WORK-UP

Diagnosis is made based on structured clinical interviews such as Dissociative Disorders Interview Schedule (DDIS), or the Structured Clinical Interview for Dissociative Disorders (SCID-D). The Dissociative Experiences Scale (DES) is a self-questionnaire diagnostically useful in DDs. Diagnosis also includes a review of personal history and symptoms as well as ruling out any physical injury (i.e., head trauma).

TREATMENT

There are currently no FDA-approved drugs for the treatment of DDs. Clinicians may consider FDA-approved medications (i.e., antianxiety medications, antidepressants, or antipsychotics) to treat co-occurring mood and anxiety symptoms associated with DDs.

NONPHARMACOLOGIC THERAPY

Psychotherapy for DDs generally proceeds in three phases. Phase 1 includes stabilization and symptom control, education about treatment, affect and impulse regulation skill building, increasing awareness of dissociated self-states, and establishment of a therapeutic alliance. Phase 2 includes processing of traumatic memories, resolution of trauma-related cognitive distortions, and development of a narrative of traumatic experiences. Phase 3 involves a resolution of dissociated self-state and a focus on current and future life issues.

ACUTE GENERAL Rx

It is believed that a critical component of early treatment is the provision of a safe therapeutic environment. Identification of triggers associated with the onset of dissociation is useful. Controversy exists regarding the use of hypnosis for the purpose of recovering memories.

CHRONIC Rx

All stages of treatment may include: psychoeducation, skill-building, alliance building, processing of reactions to therapy, emotion regulation, management of relationships, and stabilization. Grounding techniques, containment (i.e., imagery aimed at decreasing the intrusiveness of a memory), skill building (i.e., relaxation training and self-affirmation), and cognitive behavioral interventions (i.e., addressing irrational beliefs).

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Research is lacking on complementary and alternative medicine for DDs.

DISPOSITION

Treatment should be delivered in the least restrictive environment possible to ensure patient safety. Patients who have comorbid psychiatric/medical diagnoses; who are experiencing suicidal or homicidal ideation, plans, or intention; or who are severely ill may require partial or inpatient hospitalization for the purpose of stabilization.

REFERRAL

Patients are treated by a mental health clinician.

PEARLS & CONSIDERATIONS

COMMENTS

- Symptoms of DDs (i.e., derealization, dissociation) are seen in many other psychiatric disorders (e.g., panic disorder, PTSD). Incidence of dissociative symptoms following severe trauma is high. However, for most individuals dissociative symptoms subside on their own within a few weeks following a traumatic event.
- Treatment approach may vary by the specific type of DD. Rigorous empiric studies assessing the treatment of specific DDs are lacking. For example, no randomized treatment studies have investigated the effectiveness of hypnosis in treating acute DA. Additionally, for chronic DA, pharmacologic facilitated intervention for the retrieval of memories (i.e., utilization of sodium pentobarbital, or administration of intravenous lorazepam) is not well researched.

PREVENTION

Data are lacking on the prevention of DDs, but the prevention of child maltreatment may be useful in this regard.

PATIENT/FAMILY EDUCATION

International Society for the Study of Trauma and Dissociation (http://www.isst-d.org)

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED TOPICS

Acute Stress Disorder (Related Key Topic)
Post-Traumatic Stress Disorder (Related Key Topic)

AUTHORS: **LINDSAY M. ORCHOWSKI, Ph.D.,** and **DANIEL W. OESTERLE, B.S.**

SUGGESTED READINGS

Becker-Blease K et al.: A genetic analysis of individual differences in dissociative behaviors in childhood and adolescence, *J Child Psychol Psychiatry* 45:522–532, 2004.

Foote B et al.: Prevalence of dissociative disorders in psychiatric outpatients, *Am J Psychiatry* 163:623–629, 2006.

International Society for the Study of Trauma and Dissociation: Guidelines for treating dissociative identity disorder in adults, third revision, *J Trauma Dissociation* 12:115–187, 2011.

Kihlstrom JF: Dissociative disorders, *Annu Rev Clin Psychol* 1:227–253, 2005.

Diverticular Disease (Diverticulosis, Diverticulitis) PTG

BASIC INFORMATION

DEFINITION

- Colonic diverticula are herniations of mucosa and submucosa through the muscularis (Fig. ED1-43). They are generally found along the colon's mesenteric border at the site where the vasa recta penetrates the muscle wall (anatomic weak point).
- *Diverticulosis* is the asymptomatic presence of multiple colonic diverticula.
- *Diverticulitis* is an inflammatory process or localized perforation of diverticulum.

ICD-9CM CODES
562.10 Diverticulosis of colon
562.11 Diverticulitis of colon
ICD-10CM CODES
K57.30 Diverticulosis of large intestine without perforation or abscess without bleeding
K57.32 Diverticulitis of large intestine without perforation or abscess without bleeding

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence of diverticulosis in the general population is 35% to 50%.
- Diverticulosis is more common in Western countries, affecting >30% of people >40 yr and >50% of people >70 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination in patients with diverticulosis is generally normal.
- Painful diverticular disease can present with left lower quadrant (LLQ) pain, often relieved by defecation; location of pain may be anywhere in the lower abdomen because of the redundancy of the sigmoid colon.
- Diverticulitis can cause muscle spasm, guarding, and rebound tenderness predominantly affecting the LLQ.

ETIOLOGY

- Diverticular disease is believed to be secondary to low intake of dietary fiber.
- Recent studies indicate a pathogenetic role for inflammation in diverticulitis that may be similar to that of IBS, IBD, or both, based on common histologic findings such as granulomas, infiltrating lymphocytes, TNF, histamine, and matrix metalloproteinases.[1]

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Irritable bowel syndrome
- IBD
- Carcinoma of colon
- Endometriosis
- Ischemic colitis
- Infections (pseudomembranous colitis, appendicitis, pyelonephritis, PID)
- Lactose intolerance
- Celiac disease

[1]Morris AM et al: Sigmoid diverticulitis: a systematic review, *JAMA* 311(3):287-297, 2014.

LABORATORY TESTS

- WBC count in diverticulitis reveals leukocytosis with left shift.
- Microcytic anemia can be present in patients with chronic bleeding from diverticular disease. MCV may be elevated in acute bleeding secondary to reticulocytosis.

PROCEDURES: Colonoscopy should be avoided during acute diverticulitis due to the risk of perforation. It can generally be performed after 6 wk to rule out the presence of cancer and IBD.

IMAGING STUDIES

- A CT scan of the abdomen (Fig. ED1-44) is recommended as the initial radiologic examination to diagnose acute diverticulitis. It can also diagnose diverticulosis. It has a sensitivity of 93% to 97% and a specificity approaching 100% for diverticulitis. Typical findings are thickening of the bowel wall, fistulas, or abscess formation. CT may also reveal other disease processes (e.g., appendicitis, tuboovarian abscess, Crohn's disease) accounting for lower abdominal pain
- Evaluation of suspected diverticular bleeding:
  1. Arteriography if the bleeding is faster than 1 ml/min (advantage: the possible infusion of vasopressin directly into the arteries supplying the bleeding, as well as selective arterial embolization; disadvantages: its cost and invasive nature)
  2. Technetium-99m sulfa colloid
  3. Technetium-99m labeled RBC (can detect bleeding rates as low as 0.12 to 5 ml/min)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Increase in dietary fiber intake and regular exercise to improve bowel function. However, recent studies have challenged the common view that fiber intake protects against diverticulosis
- NPO and IV hydration in severe diverticulitis; NG suction if ileus or small bowel obstruction is present

ACUTE GENERAL Rx

TREATMENT OF DIVERTICULITIS:

- Mild case: broad-spectrum PO antibiotics (e.g., ciprofloxacin 750 mg bid or levofloxacin 750 mg bid or trimethoprim/sulfamethoxazole DS bid to cover aerobic component of colonic flora *and* metronidazole 500 mg q6h for anaerobes) and liquid diet for 7 to 10 days are commonly prescribed. However, randomized trials and cohort studies have shown that antibiotics are not as beneficial as previously thought and that mesalamine might be useful.[1]
- Severe case: NPO and aggressive IV antibiotic therapy
  a. Ampicillin-sulbactam 3 g IV q6h *or*
  b. Piperacillin-tazobactam 4.5 g IV q8h *or*
  c. Ciprofloxacin 400 mg IV q12h plus metronidazole 500 mg IV q6h *or*
  d. Ticarcillin-clavulanate 3.1 g IV q6h
- Life-threatening case: imipenem 500 mg IV q6h *or* meropenem 1 g IV q8h
- Surgical treatment (laparoscopic preferred over open colectomy) consisting of resection of involved areas and reanastomosis (if feasible); otherwise a diverting colostomy with reanastomosis performed when infection has been controlled; surgery should be considered in patients with:
  1. Repeated episodes of diverticulitis (two or more)
  2. Poor response to appropriate medical therapy (failure of conservative management)
  3. Abscess or fistula formation
  4. Obstruction
  5. Peritonitis
  6. Immunocompromised patients, first episode in young patient (<40 yr old)
  7. Inability to exclude carcinoma (10% to 20% of patients diagnosed with diverticulosis on clinical grounds are subsequently found to have carcinoma of the colon)

DIVERTICULAR HEMORRHAGE:

1. Bleeding is painless and stops spontaneously in the majority of patients (60%); it is usually caused by erosion of a blood vessel by a fecalith present within the diverticular sac.
2. Medical therapy consists of blood replacement and correction of volume and any clotting abnormalities.
3. Colonoscopic treatment with epinephrine injections, bipolar coagulation, or both may prevent recurrent bleeding and decrease the need for surgery.
4. Surgical resection is necessary if bleeding does not stop spontaneously after administration of 4 to 5 U of PRBCs or recurs with severity within a few days; if attempts at localization are unsuccessful, total abdominal colectomy with ileoproctostomy may be indicated (high incidence of rebleeding if segmental resection is performed without adequate localization).

DISPOSITION

- The risk of recurrence among patients with uncomplicated diverticulitis is 32% to 36%. Most patients with diverticulitis respond well to antibiotic management and bowel rest. Up to 30% of patients with diverticulitis will eventually require surgical management.
- Diverticular bleeding can recur in 15% to 20% of patients within 5 yr.

REFERRAL

GI referral for colonoscopy 4-6 wk after resolution of symptoms. In patients who have complications from diverticulitis, colonoscopy is not necessary after radiologically proven uncomplicated diverticulitis. Surgical referral when considering resection.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Diverticulitis (Patient Information)
Diverticulosis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Jacobs DO: Diverticulitis, *N Engl J Med* 357:2057–2066, 2007.
Perry AF et al.: A high-fiber diet does not protect against asymptomatic diverticulosis, *Gastroenterology* 142:266, 2012.
Wilkins T et al.: Diagnosis and management of acute diverticulitis, *Am Fam Physician* 87(9):612–620, 2013.

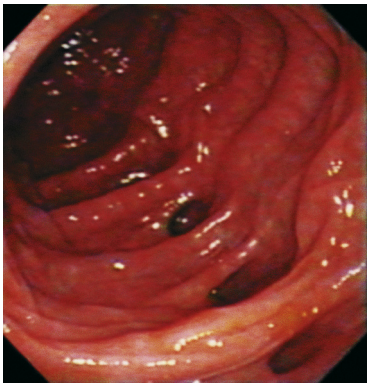

FIGURE ED1-43 Colonoscopic appearance of diverticular disease affecting the sigmoid colon. (From Forbes A et al: *Atlas of clinical gastroenterology,* ed 3, Edinburgh, 2005, Elsevier.)

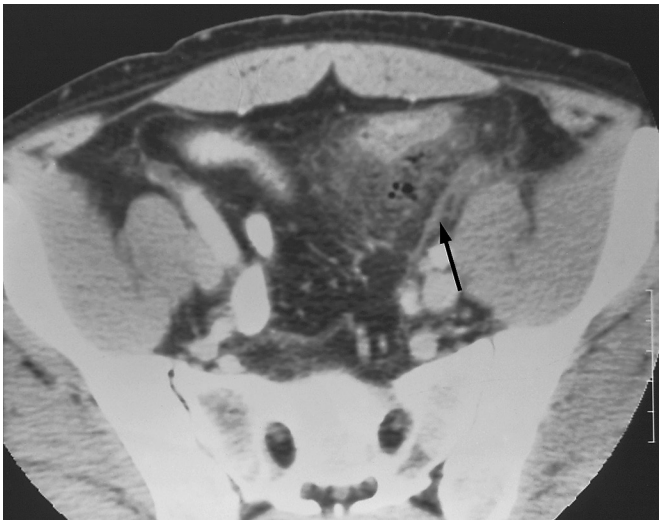

FIGURE ED1-44 Sigmoid diverticulitis. Enhanced CT shows haziness associated with extraluminal air in the sigmoid mesocolon due to perforated diverticulitis, also manifested as a thickened sigmoid wall. Thickening at the root of the sigmoid mesocolon is also present *(arrow)*. (From Grainger RG et al [eds.]: *Grainger and Allison's diagnostic radiology,* ed 4, Philadelphia, 2001, Churchill Livingstone.)

BASIC INFORMATION

DEFINITION

Down syndrome is a disorder characterized by mental retardation and multiple organ defects and is caused by a chromosomal abnormality (trisomy 21).

SYNONYMS

Trisomy 21
Mongolism

ICD-9CM CODES
758.0 Down syndrome
ICD-10CM CODES
Q90.9 Down syndrome, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 1 in 800 births
PEAK INCIDENCE: Newborn
PREVALENCE (IN U.S.): 300,000 persons
PREDOMINANT SEX: Male/female ratio of 1.3:1.0
PREDOMINANT AGE: Newborn to early adulthood
GENETICS: Nondisjunction causing trisomy 21

PHYSICAL FINDINGS & CLINICAL PRESENTATION

(Fig. D1-45)
- Microcephaly
- Flattening of occiput and face
- Upward slant to eyes with epicanthal folds
- Brushfield spots on iris
- Broad, stocky neck

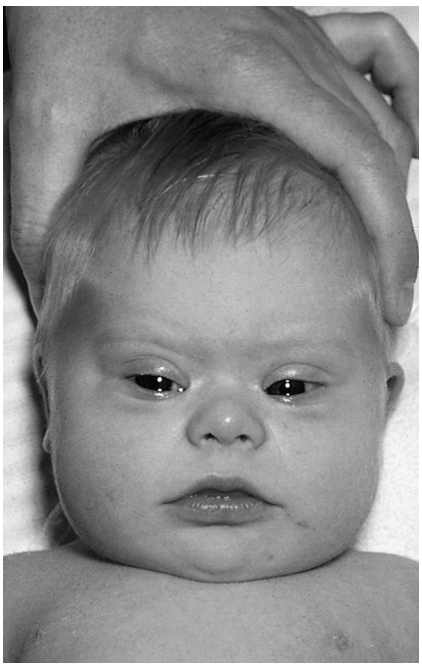

FIGURE D1-45 Down syndrome. Note depressed nasal bridge, epicanthal folds, mongoloid slant of eyes, low-set ears, and large tongue. (From Zitelli BJ, Davis HW: *Atlas of pediatric physical diagnosis,* ed 3, St Louis, 1997, Mosby.)

- Small feet, hands, digits
- Single palmar crease
- Hypotonia
- Short stature
- Associated with congenital heart disease, malformations of the GI tract, cataracts, hypothyroidism, hip dysplasia, obstructive sleep apnea, infantile spasms, moyamoya disease, and myeloproliferative disorders
- About half of children with Down syndrome are born with congenital heart disease, with the most common lesions being atrial septal defect and ventricular septal defect
- Persistent primary congenital hypothyroidism is found in 1 in 141 newborns with Down syndrome, as compared with 1 in 4000 in the general population
- Ophthalmologic disorders increase in frequency with age; >80% of children aged 5 to 12 yr have disorders that need monitoring or intervention, such as refractive errors, strabismus, or cataracts
- Renal and urinary tract abnormalities

ETIOLOGY

Nondisjunction of chromosome 21

DIAGNOSIS

- The American College of Obstetrics and Gynecology recommends offering fetal chromosomal screening to all pregnant women regardless of age due to improvements in noninvasive screening methods.
- Combined use of serum screening and fetal ultrasound testing for thickened nuchal fold has 85% detection rate with 5% false-positive results. Second-trimester serum screening in combination with maternal age is improved with use of multiple serum markers
- Prenatal cytogenic diagnosis by amniocentesis or chorionic villus sampling
- Postnatal chromosomal karyotype

DIFFERENTIAL DIAGNOSIS

- Congenital hypothyroidism
- Other chromosomal abnormalities

WORKUP

Postnatal chromosomal karyotype

TREATMENT

- Thyroid screen at birth, at age 6 mo, and yearly thereafter
- Echocardiogram in all newborns and cardiac assessment of adolescents for development of mitral valve prolapse
- Treatment consists of vigilant monitoring for comorbid states, such as obesity, hypothyroidism, leukemia, hearing loss, and valvular heart disease
- Prevention of obesity with low-calorie, high-fiber diet
- Auditory brain stem responses in all newborns and aggressive testing for hearing loss in children with chronic otitis media
- Ophthalmologic assessment by age 6 mo for congenital cataracts and annual examinations for monitoring of refractive errors and strabismus
- Regular dental care
- Pelvic examination of women who are sexually active or who have menstrual problems
- Dermatologic issues such as folliculitis can become problematic in adolescents and require topical antibiotics and careful attention to hygiene

DISPOSITION

Most children with Down syndrome live at home. As these individuals reach adulthood, those with higher functioning sometimes live in supervised settings away from their families.

REFERRAL

Down syndrome clinics use a preventive checklist to anticipate many clinical challenges.

PEARLS & CONSIDERATIONS

COMMENTS

- Screening for atlantoaxial subluxation is controversial.
- Most patients experience neuropathologic changes typical of Alzheimer's disease. Presenting symptoms include seizures, focal neurologic signs, and apathy. If Alzheimer's disease is suspected, screen for treatable diseases such as depression or hypothyroidism.
- This syndrome accounts for approximately one third of moderate-to-severe cases of mental retardation.
- Individuals with Down syndrome have a wide range of function, but all will have decrease in intelligence quotient (IQ) in first decade of life.
- Deficiency of language production relative to other areas of development often causes substantial impairment.
- Though increased maternal age is a risk factor, most children with Down syndrome are born to women younger than 35 yr.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Down Syndrome (Trisomy, Mongolism) (Patient Information)

AUTHOR: **MAITREYI MAZUMDAR, M.D., M.P.H., M.SC.**

SUGGESTED READINGS

ACOG Practice Bulletin No. 77 Screening for fetal chromosomal abnormalities: *Obstet Gynecol* 109(1):217–227, 2007.

Allred SK et al.: Second trimester serum tests for Down's syndrome screening, *Cochrane Database Syst Rev* 6:CD009925, 2012.

Ball RH et al.: First- and second-trimester evaluation for Down syndrome, *Obstet Gynecol* 110(1):10–17, 2007.

Lott IT, Head E: Down syndrome and Alzheimer's disease: a link between development and aging, *Ment Retard Dev Disabil Res Rev* 7(3):172, 2001.

Patterson D, Costa AC: Down syndrome and genetics—a case of linked histories, *Nat Rev Genet* 6(2):137, 2005.

Roizen NJ: Medical care and monitoring for the adolescent with Down syndrome, *Adolesc Med* 13(2):345, 2002.

BASIC INFORMATION

DEFINITION

Dumping syndrome refers to a constellation of postprandial symptoms resulting from rapid delivery of hypertonic stomach contents into the small bowel that is most often caused by gastric surgery, such as procedures for peptic ulcer disease and gastric bypass.

SYNONYMS

Postgastrectomy syndrome
Rapid gastric emptying

ICD-9CM CODES
564.2 Postgastric surgery syndromes
ICD-10CM CODES
K91.1 Postgastric surgery syndromes

EPIDEMIOLOGY & DEMOGRAPHICS

Incidence is 10% of all patients having gastric surgery.

- Vagotomy and pyloroplasty (8.5% to 20%)
- Vagotomy and antrectomy (4% to 27%)
- Subtotal gastrectomy (10% to 40%)
- Parietal cell vagotomy (3% to 5%)
- Gastric bypass surgeries (up to 50%)
- Males and females are affected equally

PHYSICAL FINDINGS & CLINICAL PRESENTATION

1. Early dumping syndrome: symptoms start within 1 hr after eating food:
   - No symptoms in fasting state
   - Nausea, vomiting, and belching
   - Epigastric fullness, cramping, and diarrhea
   - Dizziness, flushing, diaphoresis, and syncope
   - Palpitations and tachycardia
2. Late dumping syndrome: symptoms occurring 1 to 3 hr after eating:
   - Diaphoresis
   - Irritability
   - Difficulty in concentration
   - Tremulousness

ETIOLOGY

Dumping syndrome occurs almost exclusively in patients who have had gastric surgery.

- Systemic symptoms in early dumping syndrome are thought to be partially due to hypovolemia caused by rapid shifts of fluid from the intravascular space into the lumen of the bowel.
- Increase in vasoactive substances related to rapid gastric emptying is thought to play a role in dumping syndrome.
- Late dumping symptoms are thought to be due to reactive hypoglycemia.

DIAGNOSIS

A detailed clinical history and evidence of prior gastric surgery are necessary for the diagnosis.

DIFFERENTIAL DIAGNOSIS

- Pancreatic insufficiency
- Inflammatory bowel disease
- Afferent loop syndromes
- Bile acid reflux after surgery
- Bowel obstruction
- Gastroenteric fistula

WORKUP

Diagnosis is typically made on clinical grounds. In certain clinical settings, where patients exhibit symptoms with no prior history of gastric surgery, oral glucose challenge and imaging studies may be pursued and aid in establishing the diagnosis.

LABORATORY TESTS

Oral glucose challenge test:

- After overnight fasting, oral intake of 50 g of glucose is followed by serial measurements of heart rate, serum glucose, and hydrogen breath test every 15 to 30 min for 3 to 6 hrs. A 30-min hematocrit can also be taken.
- An increase in the heart rate >12 beats/min and a rise in hydrogen breath excretion have a sensitivity of 94% and specificity >92%. An increase of >3% in the 30-min hematocrit is also suggestive of a positive test. A nadir blood glucose <3.3 mmol/L (<59 mg/dl) was present in 75% of late dumpers.

IMAGING STUDIES

- Upper GI series properly defines anatomy.
- Scintigraphic imaging documents rapid gastric emptying and may be useful in patients with dumping syndrome and no prior history of gastric surgery.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Diet modification
  1. Divide caloric intake over six small meals
  2. Limit fluid intake with meals (try to avoid fluids 30 min before meals and following meals)
  3. Decrease carbohydrate intake and avoid simple sugars
  4. Increase/supplement dietary fibers
  5. Avoid milk/milk products

ACUTE GENERAL Rx

- Acarbose 50 mg PO daily can be tried if dietary modification does not help.
- Octreotide 25 to 50 mg SC 30 min before meals is effective in relieving symptoms of dumping syndrome.
- Pectin and guar have been used to increase viscosity of intraluminal contents and relieve symptoms from rapid emptying and absorption.

CHRONIC Rx

- Surgery is considered in patients with severe symptoms refractory to the above-mentioned dietary and acute general treatment.
- Surgical procedures include: reconstruction of the pylorus, converting Billroth II to a Billroth I anastomosis, and a Roux-en-Y reconstruction.
- In severe cases, can consider depot long-acting-release octreotide, given as 10 mg intramuscularly every 4 wk for symptom relief.

DISPOSITION

- Dumping syndrome improves with time. Approximately 1% to 2% of patients will continue to have significant symptoms several months after surgery.
- Dietary modification effectively treats the majority of patients.

REFERRAL

- A gastrointestinal specialist consult is recommended in patients suspected of having dumping syndrome.
- If medical management is unsuccessful, a general surgical consultation is warranted.

PEARLS & CONSIDERATIONS

COMMENTS

- The majority of patients usually manifest with early dumping symptoms or a combination of early and late symptoms. Few have late dumping symptoms alone.
- Octreotide has an inhibitory effect on the release of insulin and other vasoactive substances released by the gut. It also works by decreasing gastric emptying.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **MARK F. BRADY, M.D., M.P.H., M.M.S.**

SUGGESTED READINGS

Hasler WL: Dumping syndrome, *Curr Treat Options Gastroenterol* 5(2):139, 2002.

Li-Ling J, Irving M: Therapeutic value of octreotide for patients with severe dumping syndrome: a review of randomized controlled trials, *Postgrad Med J* 77(909):441, 2001.

Mine S et al.: Large-scale investigation into dumping syndrome after gastrectomy for gastric cancer, *J Am Coll Surg* 211(5):628–636, 2010.

Parrish CR et al.: Dietary nutritional recommendations for patients with dumping syndrome (rapid gastric emptying), *Digestive Health Matters* 15(02):15, 2006.

Tack J et al.: Pathophysiology, diagnosis and management of postoperative dumping syndrome, *Nat Rev Gastroenterol Hepatol* 6(10):583–590, 2009.

Ukleja A: Dumping syndrome: pathophysiology and treatment, *Nutr Clin Pract* 20(5):517, 2005.

Dupuytren's Contracture PTG EBM

BASIC INFORMATION

DEFINITION

Dupuytren's contracture is a disease of the palmar fascia characterized by nodular fibroblastic proliferation that often results in progressive contractures of the fascia and flexion deformity of the fingers.

Dupuytren's diathesis is a more aggressive presentation of the disease. Risk factors include >40 yr, strong family history, bilateral involvement, and ectopic manifestations like plantar and penile fibromatosis.

ICD-9CM CODES
728.6 Dupuytren's contracture
ICD-10CM CODES
M72.0 Palmar fascial fibromatosis [Dupuytren]

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Varies depending on ethnicity. The disorder is more common in Scandinavians; some Northern Europeans have a 25% prevalence after the age of 60.
PREVALENT SEX: Male/female ratio of 3.5 to 9:1, becomes 1:1 after age 80 yr.
PREVALENT AGE: 40 to 60 yr
RISK FACTORS: Age >40 yr, positive family history, diabetes mellitus, alcoholism, smoking, HIV infection
GENETICS: Aberrations in genes encoding proteins in the Wnt-signaling pathways are believed to be implicated in the process of fibromatosis in Dupuytren's disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Usually asymptomatic
- Most common complaints: deformity and interference with the use of the hand by the flexed, contracted fingers (Fig. ED1-46)
- Process usually begins on the ulnar side of the hand, often starting at the ring finger; other fingers can be involved
- Isolated, painless nodules that eventually harden and mature into a longitudinal cord that extends into the finger
- Later stages: fibrous cord begins to contract and pull the finger into flexion
- Skin pitting, atrophic grooves
- Tabletop test of Hueston: place hand and fingers prone on a table. Test is positive if hand won't go flat (Fig. D1-47). Surgery is generally not indicated if test is negative
- A staging classification for Dupuytren's contracture is described in Table D1-19.

ETIOLOGY

Unknown.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Soft tissue tumor
- Tendon cyst

WORKUP

The typical case is easily diagnosed clinically. Plain radiographs may be useful to rule out bony abnormalities.

TREATMENT

- Avoidance of repetitive hand trauma; measures include the use of gloves and damping tape to widen grips.
- Stretching exercises.
- Radiotherapy.
- Intralesional corticosteroid injection can be effective in early stages and provide better results in combination with percutaneous needle aponeurotomy.
- Enzymatic fasciotomy by *Clostridium histolyticum* collagenase injection for early, less severe cases: collagenase *C. histolyticum* (Xiaflex) is the first FDA-approved, nonsurgical treatment option for adult Dupuytren's contracture patients with a palpable cord that is highly effective and well tolerated.
- Surgery is usually performed when the metacarpophalangeal joint contracture exceeds 30 degrees or when the proximal interphalangeal joint has any degree of contracture. Another indication for surgery is if there is neurovascular damage of the finger. Percutaneous needle aponeurotomy performed in the office represents an alternative to surgery.

DISPOSITION

Rate of development is variable.

REFERRAL

Evaluation by hand or plastic surgeon if joint contracture begins to develop or for excision of rare nodule that is painful (at any stage)

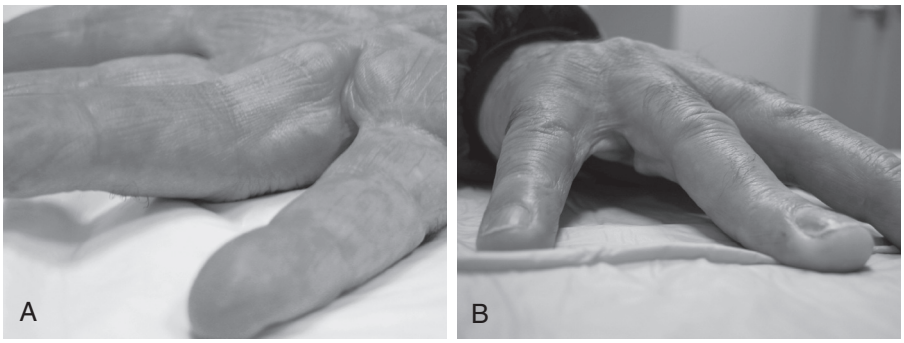

FIGURE D1-47 Dupuytren's contracture of the ring finger. A, Pitting of the skin and a longitudinal cord can be seen causing metacarpophalangeal (MCP) joint flexion. **B**, Contracture/flexion deformity at the MCP joint keeps this patient from flattening his hand against a flat surface. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

TABLE D1-19 Staging Classification for Dupuytren's Contracture (Woodruff, 1998)

Stage	Description	Management
1	Early palmar disease with no contracture	Leave alone
2	One finger involved, with only metacarpophalangeal joint contracture	Surgery
3	One finger—metacarpophalangeal joint 1 proximal interphalangeal joint	Surgery difficult
4	Stage 3 1 more than one finger involved	Surgery prolonged and only partly successful
5	Finger-in-palm deformity	Consider amputation

From Parvizi J: *High-yield orthopedics,* Philadelphia, 2010, Saunders.

PEARLS & CONSIDERATIONS

COMMENTS

- Dupuytren's contracture develops earlier and more often in certain families.
- Approximately 5% of patients develop a similar condition elsewhere, such as Peyronie's disease or Ledderhose disease (involvement of the plantar fascia).
- Tender knuckle pads *(Garrod's knuckle pad)* over the dorsal aspect of the PIP joints may also be present.
- Individuals with these additional findings are considered to have Dupuytren's diathesis, and their disease is generally more severe and recurrent.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Dupuytren's Contracture (Patient Information)

AUTHOR: **DANIEL E. MENDEZ-ALLWOOD, M.D.**

EVIDENCE

Abstract[1]
General
Background:
The present study was undertaken to assess the health-related quality of life in patients with Dupuytren's disease who undergo palmar fasciectomy.
Methods:
A prospective cohort of patients with Dupuytren's disease undergoing palmar and/or digital fasciectomy were recruited from the practice of three plastic surgeons in Hamilton, Ontario, Canada. After written informed consent was obtained, participants were asked to complete three health-related quality-of-life questionnaires (i.e., Short Form-36, Michigan Hand Outcomes Questionnaire, and Health Utility Index Mark 3) at five time points: at 1 week and 1 day preoperatively, and at 1, 3, 6, and 12 months postoperatively. Ranges of motion and grip strength measurement were also recorded.
Results:
For the 26 patients in the study, the multiattribute scores of the Health Utility Index Mark 3 improved from 0.80 before surgery to 0.83 at 12 months postoperatively ($p > 0.05$). There was no difference in the Short Form-36 scores, but the Michigan Hand Outcomes Questionnaire scores improved from 74 at 1 week preoperatively to 90 at the 12-month postoperative visit ($p < 0.001$).
Conclusions:
Patients who undergo palmar fasciectomy for Dupuytren's disease experience a substantial improvement in their health-related quality of life 12 months after surgery. In the authors' study population, a benefit of 0.85 quality-adjusted life-year within 12 months was observed. This can be translated as follows: the average patient who undergoes palmar fasciectomy gains the equivalent of approximately 14.4 days (0.48 months) in perfect health by undergoing palmar fasciectomy. Ⓐ

Evidence-Based Reference

1. Thoma A, Kaur MN, Ignacy TA, et al.: Health-related quality of life in patients undergoing palmar fasciectomy for Dupuytren's disease, *Plast Reconstr Surg* 133:1411–1419, 2014. Ⓐ

SUGGESTED READINGS

Badalamente et al.: Efficacy and safety of injectable mixed collagenase subtypes in the treatment of Dupuytren's contracture, *J Hand Surg Am* 32(6):767–774, 2007.
Bayat A: Connective tissue diseases: a nonsurgical therapy for Dupuytren disease, *Nat Rev Rheumatol* 6:7, 2010.
Chen N et al.: A systematic review of outcomes of fasciotomy, aponeurotomy and collagenase treatments for Dupuytren's contracture, *Hand* (6)250–255, 2011.
Dolman GH et al.: Wnt signaling and Dupuytren's disease, *N Engl J Med* 365:307–317, 2011.
Khashan M et al.: Dupuytren's disease: review of the current literature, *Open Orthop J* 5(Suppl 2):283–288, 2011.
McMillan C et al.: Steroid injection and needle aponeurotomy for Dupuytren contracture: a randomized, controlled study, *J Hand Surg Am* 37:1307–1312, 2012.
Rayan GM: Dupuytren's disease: anatomy, pathology, presentation, and treatment, *J Bone Joint Surg Am* 89A(189), 2007.
Thurston AJ: Dupuytren's disease, *J Bone Joint Surg Br* 85B(4):469, 2003.
Trojian TH, Chu SM: Dupuytren's disease: diagnosis and treatment, *Am Fam Physician* 76(86), 2007.

FIGURE ED1-46 Dupuytren's contracture. A flexion deformity of the finger is present, with nodular thickening of the fascia to the ring finger.

BASIC INFORMATION

DEFINITION

Dysfunctional uterine bleeding (DUB) describes abnormal uterine bleeding in the absence of disease in the pelvis, pregnancy, or medical illness. Parameters of normal menstrual function are described in Box D1-6. Specific types of abnormal bleeding include the following:

- Hypermenorrhea: excessive bleeding amount during normal duration of regular menstrual cycles
- Hypomenorrhea: decreased bleeding amount in regular menstrual cycles
- Menorrhagia: regular normal intervals, excessive flow and duration
- Metrorrhagia: irregular intervals, excessive flow and duration
- Menometrorrhagia: irregular or excessive bleeding during menstruation and between periods
- Oligomenorrhea: intervals >35 days
- Polymenorrhea: intervals <21 days

These terms, while commonly used in practice, increasingly are felt to be confusing. In fact, The FIGO Menstrual Disorders Working Group has been working since 2009 to eliminate many of the confusing and overlapping terms and create simpler definitions that can be intuitively understood by medical professionals and lay people alike. The term *dysfunctional uterine bleeding* was initially used in 1935 but has never been clearly defined and has been used as both a diagnosis and a symptom. It is generally understood to be a term of exclusion when no other cause of bleeding has been established. FIGO recommends that the three diagnoses (disturbances of molecular control of menses, HPO axis abnormalities, and disorders of hemostasis) be grouped under the nonstructural causes of abnormal uterine bleeding. However, these new FIGO terms have not yet made their way into common usage. In addition, the ICD-9 codes have not been updated to reflect this new usage.

SYNONYMS

DUB

ICD-9CM CODES

626 Disorders of menstruation and other abnormal bleeding from female genital tract
626.2 Hypermenorrhea
626.1 Hypomenorrhea
626.2 Menorrhagia
626.6 Metrorrhagia
626.2 Menometrorrhagia
626.1 Oligomenorrhea
626.2 Polymenorrhea

ICD-10CM CODES

N92.5 Other specified irregular menstruation
N92.0 Excessive and frequent menstruation with regular cycle
N91.5 Oligomenorrhea, unspecified
N92.1 Excessive and frequent menstruation with irregular cycle
N94.6 Dysmenorrhea, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Most cases of DUB occur in postmenarchal and perimenopausal age groups.
- During reproductive age, <20% of abnormal bleeding results from anovulatory DUB.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- A clinical diagnosis of exclusion
- Thorough physical and pelvic examination to exclude the other causes of abnormal bleeding
  1. Includes thyroid, breast, liver, presence or absence of ecchymotic lesions
  2. Patient possibly obese and hirsute (polycystic ovarian disease)
  3. No evidence of any vulvar, vaginal, cervical lesions, uterine (fibroid) or ovarian tumor, urethral caruncle, urethral diverticula, hemorrhoids, anal fissure, colorectal lesions
  4. Bimanual pelvic examination: normal-sized or slightly enlarged uterus

ETIOLOGY

- 90% is caused by anovulation.
- 10% is ovulatory in origin; can be caused by dysfunction of corpus luteum or midcycle bleeding.
  - Section II describes the various causes of abnormal uterine bleeding.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Pregnancy-related cause
- Anatomic uterine causes:
  1. Leiomyomas
  2. Adenomyosis
  3. Polyps
  4. Endometrial hyperplasia
  5. Cancer
  6. Sexually transmitted diseases
  7. Intrauterine contraceptive devices
- Anatomic nonuterine causes:
  1. Cervical neoplasia, cervicitis
  2. Vaginal neoplasia, adhesions, trauma, foreign body, atrophic vaginitis, infections, condyloma
  3. Vulvar trauma, infections, neoplasia, condyloma, dystrophy, varices
  4. Urinary tract: urethral caruncle, diverticulum, hematuria
  5. Gastrointestinal tract: hemorrhoids, anal fissure, colorectal lesions
- Systemic diseases:
  1. Exogenous hormone intake
  2. Coagulopathies: von Willebrand's disease, thrombocytopenia, hepatic failure
  3. Endocrinopathies: thyroid disorder, hypothyroidism and hyperthyroidism, diabetes mellitus
  4. Renal diseases
- Section II describes a differential diagnosis of vaginal bleeding abnormalities.

BOX D1-6 Parameters of Normal Menstrual Function

Cycle interval (days)	21-35
Duration of flow (days)	2-8
Blood loss/cycle (ml)	30-80

From Carlson KJ et al: *Primary care of women,* ed 2, St Louis, 2002, Mosby.

WORKUP

- A detailed history and thorough physical examination, including a pelvic examination to exclude causes mentioned above.
- Clinical algorithms for the evaluation of vaginal bleeding are described in Section III, "Bleeding, Vaginal."

LABORATORY TESTS

- Complete blood count with platelets; possible iron-deficiency anemia or thrombocytopenia
- Prothrombin; partial thromboplastin and bleeding time if coagulopathy is suspected
- Serum human chorionic gonadotropin
- Chemistry profile, including liver function tests
- Thyroid profile
- Stool testing for occult blood
- Urinalysis for hematuria
- Pap smear
- Cultures for gonorrhea and *Chlamydia*
- Serum gonadotropins and prolactin
- Serum androgens
- Endometrial biopsy in women, especially if there exists a longstanding history of anovulatory bleeding, such as fewer than 3 menstrual cycles per year
- Hysterogram and hysteroscopy
- von Willebrand's panel, particularly in perimenarchal women

IMAGING STUDIES

- Pelvic ultrasound, including measurement of endometrial thickness and assessment of myometrial or endometrial defects
- Fluid contrast ultrasound (also called saline sonogram, sonohysterogram, saline infusion sonogram, and various other names). Distends the uterine cavity so that "filling defects" of the endometrium can be assessed. Such a filling defect may represent an endometrial polyp, uterine fibroid, or neoplasm.

TREATMENT

NONPHARMACOLOGIC THERAPY

Increase iron intake in the form of pills and a diet rich in iron.

ACUTE GENERAL Rx

- Progestational agents (see Box D1-7)
  1. Progesterone in oil, 100 to 200 mg
  2. Medroxyprogesterone acetate, 20 to 40 mg qd for 15 days
  3. Megestrol acetate, 40 to 120 mg daily in divided doses for 15 days

BOX D1-7 Equivalent Daily Doses of Oral Progestins for the Treatment of Dysfunctional Uterine Bleeding

Medroxyprogesterone acetate (Provera, Cycrin)	10 mg
Micronized progesterone (Prometrium)	400 mg
Norgestrel (Ovrette)	150 μg
Norethindrone acetate (Micronor, Nor-QD)	0.7 to 1.0 mg

From Carlson KJ et al: *Primary care of women,* ed 2, St Louis, 2002, Mosby.

4. Oral contraceptives: any oral contraceptive pill, 1 tablet qid for 5 to 7 days, followed by 1 tablet low-dose estrogen qd for 21 days; causes withdrawal bleeding; should then be on cyclical Provera or continue on oral contraceptives

- Estrogens
  1. Conjugated estrogen (Premarin) 25 mg IV q4h until bleeding is under control (in cases of severe or life-threatening bleeding); maximum three doses
  2. For prolonged bleeding that is not life threatening: Premarin 1.25 mg (Estrace 2 mg) q4h for 24 hr, followed by Provera to bring on withdrawal bleeding; then sequential regimen of estrogen and progestin (Premarin 1.25 mg qd for 24 days, Provera 10 mg for last 10 days) or oral contraceptives
- Surgical treatment
  1. Hysteroscopy with or without dilation and curettage (D&C)
  2. Endometrial ablation
  3. Hysterectomy

CHRONIC Rx

- Progestational agents
  1. Medroxyprogesterone acetate 10 mg qd for 12 days, then cyclically to induce monthly withdrawal bleeding
  2. Norethindrone 2.5 to 10 mg qd for 12 days
  3. Depo-Provera 150 mg IM and then 150 mg every 3 mo
  4. Oral contraceptives, 1 tablet qd either cyclically or continuously using only active pills
  5. Levonorgestrel-releasing intrauterine device (Mirena, currently has an FDA indication for heavy menstrual bleeding in women who use an IUD for contraception)
- Letrozole or clomiphene citrate: patients with anovulatory bleeding who want to become pregnant. Recent studies suggest that progesterone withdrawal may be counterproductive in patients wishing to start ovulation induction regimen. Pregnancy rates lower when patients undergo withdrawal compared to when random ovulation induction start utilized. A recent large, multicenter trial demonstrated that letrozole is superior to clomiphene citrate in ovulation induction in PCOS women. Human menopausal gonadotropin (HMG) can be used for women who do not ovulate with oral agents or who have hypothalamic dysfunction.
- Others
  1. Antiprostaglandins
  2. Danazol (rarely used due to side-effect profile)
  3. Gonadotropin-releasing hormone analogues (GnRH)
  4. Tranexamic acid (Lysteda) is an antifibrinolytic agent recently FDA approved for cyclic heavy menstrual bleeding. Dosage in normal renal function is 3900 mg daily (650 mg tablets, 2 tablets tid) for up to 5 days during menses
- Surgical treatment
  1. D&C and hysteroscopy
  2. Endometrial ablation
  3. Hysterectomy

DISPOSITION

Cyclical treatment on birth control pills or Provera for several cycles, then discontinue pill and watch patient for onset of regular menses

REFERRAL

To gynecologist in case of failure of treatment

TABLE D1-20 Management of Dysfunctional Uterine Bleeding (DUB)

Bleeding Pattern	Cause	Treatment
Ovulatory DUB		
Heavy menstrual bleeding	Imbalance in endometrial prostacyclins and prostaglandins	Nonsteroidal antiinflammatory drugs Combination oral contraceptive pill Progestin intrauterine device Endometrial ablation
Midcycle spotting	Periovulatory estrogen decline	None
Delayed menses	Persistent corpus luteum	None (rule out pregnancy)
Anovulatory DUB		
Irregular menses	Unopposed estrogen stimulation of endometrium	Combination oral contraceptive pill Cyclic progestins Endometrial ablation
Postmenopausal bleeding	Endometrial atrophy	Hormone replacement therapy Endometrial ablation

From Carlson KJ, Eisenstat SA et al: *Primary care of women,* ed 2, St Louis, 2002, Mosby.

PEARLS & CONSIDERATIONS

COMMENTS

- Table D1-20 describes management options for DUB.
- Patient education material may be obtained from the American College of Obstetricians and Gynecologists, 409 12th Street SW, Washington, DC 20024-2188; phone 202-638-5577.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fig. 3-33 Evaluation of ovulatory bleeding (Algorithm)
Fig. 3-34 Evaluation of anovulatory bleeding (Algorithm)
Dysfunctional Uterine Bleeding (Patient Information)
Endometrial Cancer (Related Key Topic)
Uterine Fibroids (Related Key Topic)

AUTHORS: **MANDEEP K. BRAR, M.D.** and **RUBEN ALVERO, M.D.**

SUGGESTED READING

Mihm LM et al.: The accuracy of endometrial biopsy and saline sonohysterography in the determination of the cause of abnormal uterine bleeding, *Am J Obstet Gynecol* 186:858, 2002.

BASIC INFORMATION

DEFINITION

Dysmenorrhea is pain with menstruation, usually cramping and usually centered in the lower abdomen. It is defined as *primary dysmenorrhea* when there is no associated organic pathology and *secondary dysmenorrhea* when there is demonstrable organic pathology.

SYNONYMS

Menstrual cramps
Painful periods

ICD-9CM CODES
625.3 Dysmenorrhea
ICD-10CM CODES
N94.3 Primary dysmenorrhea
N94.5 Secondary dysmenorrhea
N94.6 Dysmenorrhea, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Approximately 50% of menstruating women are affected by dysmenorrhea, with approximately 10% of them having severe dysmenorrhea with incapacitation for 1 to 3 days/mo.
- Dysmenorrhea is most common in the age group from 20 to 24 yr, and primary dysmenorrhea usually appears within 6 to 12 mo after menarche.
- Dysmenorrhea is more common in women who have menarche at an earlier age and in those with a longer duration of menstruation.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Sharp, crampy, midline, lower abdominal pain without a lower quadrant or adnexal component but possible radiation to the lower back and upper thighs
- Unremarkable pelvic examination in nonmenstruating patient
- Accompanying symptoms: nausea, vomiting, headaches, anxiety, fatigue, diarrhea, fainting, and abdominal bloating
- Cramps usually lasting <24 hr and seldom lasting >2 to 3 days
- Secondary dysmenorrhea: dyspareunia is a common complaint, and bimanual pelvic-abdominal examination may demonstrate uterine or adnexal tenderness, fixed uterine retroflexion, uterosacral nodularity, a pelvic mass, or an enlarged, irregular uterus

ETIOLOGY

Prostaglandin $F_2\alpha$ is the agent responsible for dysmenorrhea. It stimulates uterine contractions and cervical stenosis (narrowing) and increases vasopressin release. Behavior and psychological factors have also been implicated in the etiology of primary dysmenorrhea. Primary dysmenorrhea only occurs in ovulatory cycles. Secondary dysmenorrhea is usually caused by endometriosis, adenomyosis, leiomyomas and, less commonly, chronic salpingitis, intrauterine device (IUD) use, or congenital or acquired outflow tract obstruction, including cervical stenosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Adenomyosis
- Adhesions
- Allen-Masters syndrome
- Cervical structures or stenosis
- Congenital malformation of müllerian system
- Ectopic pregnancy
- Endometriosis
- Endometritis
- Imperforate hymen
- IUD use
- Leiomyomas
- Ovarian cysts
- Pelvic congestion syndrome, pelvic inflammatory disease
- Polyps
- Transverse vaginal septum
- Interstitial cystitis

WORKUP

- Primary dysmenorrhea: characteristic history, physical examination normal with the absence of an identifiable cause of pelvic pain
- Secondary dysmenorrhea: history of onset generally >2 yr after menarche; physical examination may reveal uterine irregularity, cul-de-sac tenderness, or nodularity or pelvic masses

LABORATORY TESTS

- No specific tests diagnostic for dysmenorrhea
- Elevated white blood cell count in the presence of infection
- Human chorionic gonadotropin to rule out ectopic pregnancy

IMAGING STUDIES

- Ultrasound scan of the pelvis to evaluate the presence of leiomyomas, ovarian cysts, or ectopic pregnancy
- Hysterosalpingogram or saline ultrasonography to assess the uterine cavity to rule out endometrial polyps or submucosal or intraluminal leiomyomas
- Cystoscopy for evaluation of interstitial cystitis

TREATMENT

NONPHARMACOLOGIC THERAPY

- Applying heat to the lower abdomen with hot compresses, heating pads, or hot water bottles seems to offer some relief.
- Offer reassurance that this is a treatable condition.

ACUTE GENERAL Rx

- Nonsteroidal anti-inflammatory drugs such as ibuprofen 400 to 600 mg q4 to 6h or naproxen sodium 500 mg q12h, mefenamic acid 500 mg initial dose followed by 250 mg q6h prn
- Oral contraceptives cyclically or continuously (taking only active pills), primarily in women with primary dysmenorrhea
- Nifedipine 30 mg qd in difficult cases of dysmenorrhea
- Vitamin E supplements may reduce pain compared to placebo
- Magnesium supplements have been found likely to be beneficial
- Thiamine supplements may reduce pain
- The Chinese herbal remedy toki-shakuyaku-san may be effective in reducing pain. However, few studies have been of good quality
- Secondary dysmenorrhea: treatment directed to the specific underlying condition; surgery may be indicated if pathology is found on physical examination or by imaging

CHRONIC Rx

Acupuncture and transcutaneous electrical nerve stimulation may be tried. However, there is not enough evidence to support the use of yoga, acupuncture, or massage. In cases in which medical therapy has not worked, laparoscopy or other surgical treatments should be considered depending on the secondary cause of the dysmenorrhea. A directed physical examination, looking for gynecologic masses or nodularity, should be performed. Nontraditional approaches such as acupuncture have been tried with relief in some patients. The levonorgestrel IUD has been shown to effectively reduce pain in women with primary dysmenorrhea.

DISPOSITION

The majority of patients are satisfactorily treated with good outcomes. Possible chronic complications with primary dysmenorrhea that has not been adequately treated can lead to anxiety and depression. With certain causes of secondary dysmenorrhea, infertility can become a problem.

REFERRAL

If a secondary cause of dysmenorrhea is revealed, refer to the appropriate specialist for further medical or surgical treatment (e.g., gynecologist, urogynecologist, pain management center).

RELATED CONTENT

Dysmenorrhea (Patient Information)
Dyspareunia (Related Key Topic)
Endometriosis (Related Key Topic)
Premenstrual Syndrome (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

BASIC INFORMATION

DEFINITION

Persistent and/or recurrent pain associated with sexual activity that causes marked distress or interpersonal conflict.

SYNONYMS

Painful intercourse

ICD-9CM CODES

625.0 Pain associated with female genital organs

302.76 Sexual deviations and disorders with functional dyspareunia, psychogenic dyspareunia

ICD-10CM CODES

N94.1 Dyspareunia

F52.6 Dyspareunia not due to a substance or known physiological condition

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE (IN U.S.): Affects 10% to 20% of women

PREDOMINANT SEX: Female

AT-RISK POPULATION: No consistent findings regarding:

- Age
- Parity
- Educational status
- Race
- Income
- Marital status

RISK FACTORS: Lower:

- Frequency of intercourse
- Levels of desire and arousal
- Orgasmic response
- Physical and emotional satisfaction
- General happiness

HISTORICAL FACTORS:

- Pain parameters
  1. Character
  2. Location (Introital, middle, deep)
  3. Onset
  4. Duration
  5. Timing
  6. Chronicity
  7. Cyclicity
  8. Recurrence
- Gynecologic history
  1. History of sexually transmitted disease
  2. History of herpes simplex virus (HSV) or human papillomavirus (HPV)
  3. Other sexual dysfunctions
  4. Prior abdominal or gynecologic surgery
  5. Prior pelvic or abdominal radiation
  6. History of endometriosis, fibroids
  7. History of genital or uterine prolapse
  8. History of gynecologic infection
  9. History of pelvic pain
  10. History of menopausal symptoms
  11. Sexual misinformation
- Obstetric history
  1. Lacerations
  2. Episiotomy
- General medical causes
  1. History of chronic diseases
  2. Gastrointestinal or genitourinary symptoms
  3. Medications
  4. History of psychological disorders
  5. History of dermatologic condition
  6. Religious beliefs
  7. Generalized anxiety

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Primary versus secondary dyspareunia
  1. Latter with history of pain-free coitus
- Visual inspection of lower genital tract
  1. Discoloration
  2. Ulcerations
  3. Discharge
  4. Prolapse
  5. Dysplastic changes
  6. Infestations
- Physical examination
  1. Sensitivity to light touch
  2. Tenderness to palpation
  3. Genital prolapse
     a. Uterus
     b. Bladder
     c. Cervix
     d. Vagina
     e. Adnexa
     f. Rectum
     g. Bowel
  4. Longitudinal or transverse vaginal septum
  5. Levator muscle tone
  6. Evidence of previous surgery
  7. Vaginal length, depth, caliber constrictions: Assess for shortened or absent vagina

ETIOLOGY

- Pathology or alteration or reduction of genital-associated tissue
- Psychosocial factors
- Marital or relationship discord
- History of sexual abuse

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Congenital deformities (septa/agenesis)
- Imperforate hymen
- Menopausal changes
- Atrophic tissue
- Impaired lubrication
- Psychogenic
- Vaginismus
- Inadequate foreplay
- Endometriosis
- Levator ani myalgia
- Chronic pelvic pain
- Previous surgery (posterior colporrhaphy, perineorrhaphy)
  1. Alteration in vaginal length, depth, caliber
  2. Adhesions
- Infectious
  1. HPV
  2. HSV
  3. Candidiasis
  4. *Tinea cruris*
  5. Acute or chronic salpingitis or endometritis
- Pelvic carcinoma
- Previous radiation
- Adnexal attachment or tubal prolapse
- Pelvic tumor
- Uterine prolapse, malposition, enlargement, or retroversion
- Genital prolapse
- Cystocele, rectocele, enterocele
- Urethral or bladder pathology
- Pelvic congestion (controversial)
- Vulvar vestibulitis
- Postcoital cystitis
- Broad ligament pathology
- Neuroma at the site of previous episiotomy
- Previous sexual abuse
- Vulvodynia
- Contact or allergic dermatitis
- Vitamin A, B, or C deficiency
- Equestrian dyspareunia
- Interstitial cystitis
- Pudendal neuralgia
- Myofascial pain syndrome
- Rectal pathology
- Structural abnormalities or alterations
  1. Muscle
  2. Bone
  3. Ligament

WORKUP

- History and physical examination are key
- If needed:
  1. Colposcopy
  2. Cystoscopy
  3. Consider laparoscopy for unexplained deep dyspareunia

LABORATORY TESTS

- Erythrocyte sedimentation rate
- White blood cell count
- Wet mount
- Cultures
  1. Cervical
     a. Gonorrhea
     b. *Chlamydia*
  2. Vaginal
  3. Lesions
  4. Urine
- Vulva, vaginal, or cervical biopsy
- Pap smear
- HSV antibodies
- Gonadotropin levels

IMAGING STUDIES

Pelvic or abdominal ultrasonography. Transvaginal ultrasonography provides for greater resolution of uterus and ovaries due to proximity to pelvic organs. MRI when diagnosis is unclear with other diagnostic modalities (Fig. D1-48).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Patient education
- Discontinue exacerbating activity and irritants
- Lubrication with coitus
- Coital position changes to reduce deep thrust discomfort
- Warm or cool soaks

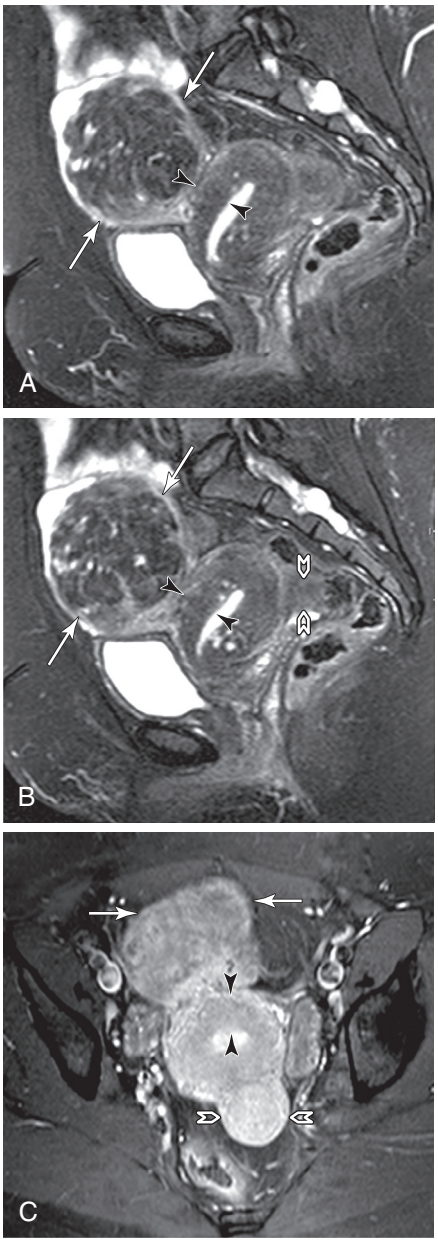

FIGURE D1-48 Adenomyosis and leiomyomata in a 41-year-old woman with pelvic pain, irregular menses, menorrhagia, and dyspareunia. **A** and **B,** Sagittal T2-weighted fat-suppressed images show a large anterior subserosal fibroid with mixed but predominantly low signal *(arrows)* and a smaller posterior subserosal fibroid with low to intermediate signal *(chevrons).* There is also widening of the junctional zone *(black arrowheads)* with areas of increased T2 signal, indicative of adenomyosis. **C,** Axial three-dimensional gradient echo postcontrast image with fat suppression shows enhancement of the leiomyomata *(white arrowheads and chevrons)* and the thickened junctional zone *(black arrowheads).* (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.)

- Reassurance to patient of nonmalignant condition
- Psychosocial interventions
  1. Systemic desensitization techniques
  2. Behavior modification
- Vaginal dilators
- Vaginal muscle exercises and relaxation techniques
- Excision of pathologic tissue
- Surgical correction of altered, reduced, or deformed tissues

ACUTE GENERAL Rx

- Topical lidocaine, non-hormonal moisturizers and lubricants
- Corticosteroids
- Antiinfective agents if vaginitis found
- Trigger point injections
- Massage/physical therapy
- Acupuncture
- Transcutaneous electrical nerve stimulation
- Stress reduction techniques
- Safe sexual practices
- Hormonal replacement therapy. The FDA has recently approved ospemifene, an oral estrogen agonist/antagonist for treatment of moderate to severe dyspareunia in postmenopausal women with suspected vaginal atrophy.
- Antiviral agents
- Intralesional interferon
- Mild analgesics
- Antidepressants

CHRONIC Rx

All the previous plus:

- Set supportive visits as needed
- Oral contraceptives
- Regular sexual activity
- Balanced diet
- Vitamin supplementation
- Proper hygiene

DISPOSITION

Most patients will have a reduction and/or resolution of their symptoms by using the appropriate therapeutic approaches.

REFERRAL

As with other chronic pain conditions, a multidisciplinary approach using the expertise of psychologists, dermatologists, gynecologic surgeons, infectious disease specialists, or urologists is helpful.

PEARLS & CONSIDERATIONS

- Dyspareunia is a symptom complex resulting from a multitude of etiologies, some of which act simultaneously.
- Uncovering the etiology of dyspareunia is predominantly based on a comprehensive history and physical examination.
- The differential diagnoses can be sorted into superficial, intermediate, and deep dyspareunia categories.
- As with the physical evaluation of any painful condition, attempt—by precise touching (moistened cotton swab), palpation, or applied pressure—to reproduce the patient's chief complaint.
- Performing a one-finger pelvic examination without concurrent abdominal palpation allows a more precise assessment of the source of genital pain.
- Individualize therapy.
- Initiate and maintain an honest diagnosis and compassionate demeanor with the patient and her partner.
- Be open minded, approachable, nonjudgmental, and diligent in your search for a solution to help these often silently suffering patients.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Painful Intercourse (Patient Information)
Dysmenorrhea (Related Key Topic)
Endometriosis (Related Key Topic)

AUTHORS: **DAVID I. KURSS, M.D.,** and **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Hawton RL: Female dyspareunia, *BMJ* 328(7452):1357, 2004.
Helm LJ: Evaluation and differential diagnosis of dyspareunia, *Am Fam Physician* 63:1535, 2001.
Nichols D. Reoperative gynecologic and obstetric surgery. ed 2. Mosby: St Louis.
Seehusen DA et al.: Dyspareunia in women, *Am Fam Physician* 90(7):465–470, 2014.

Dyspepsia, Nonulcerative ALG

BASIC INFORMATION

DEFINITION

Nonulcerative dyspepsia is a term used to describe signs and symptoms of persistent or recurrent dyspepsia centered in the upper abdomen that have no identifiable organic cause

SYNONYMS

Nonulcer dyspepsia
Functional dyspepsia
Idiopathic dyspepsia

ICD-9CM CODES
536.8 Nonulcerative dyspepsia
ICD-10CM CODES
K30 Functional dyspepsia

EPIDEMIOLOGY & DEMOGRAPHICS

- Up to 25% of the general population will experience dyspepsia each year. Of these, 75% will have no evident causative agent.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Typical clinical presentation is dyspepsia without findings on physical examination to explain the symptoms

ETIOLOGY

The etiology and pathophysiology are still unclear. Research is focused on abnormalities of gastric motor function and visceral hypersensitivity, as well as

- *Helicobacter pylori* infection
- Psychosocial factors—associated with anxiety and depression

RISK FACTORS

Risk factors include:

- Genetic predisposition: homozygous GNB3 gene.
- Dietary habits such as caffeine, alcohol, or smoking.
- Medications such as NSAIDs, calcium channel blockers, methylxanthines, alendronate, orlistat, acarbose, and potassium supplements.
- Psychological disorders such as anxiety, depression, somatization, or personal history of childhood sexual or physical abuse.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Nonulcerative dyspepsia is diagnosed when all other organic causes have been excluded, including:

- PUD
- Gastroesophageal reflux
- Gastric/esophageal/other abdominal cancers
- Biliary tract disease
- Gastroparesis, including diabetic gastroparesis
- Pancreatitis
- Medications (i.e., NSAIDs, erythromycin)
- Metabolic disturbances (i.e., hypercalcemia, heavy metals, or hyperkalemia)
- Ischemic bowel disease
- Systemic disorders (i.e., eosinophilic gastritis, Crohn's disease, sarcoidosis, celiac disease, thyroid disorders)

DIAGNOSIS

Developed in 2006 in conjunction with the American Gastroenterological Association, the Rome III criteria lists the following factors, which must be present at least 3 months and first noticed within 6 months of diagnosis:

- At least one of the following:
  - Postprandial fullness, *or*
  - Early satiety, *or*
  - Epigastric pain, *or*
  - Epigastric burning
- *and* no evidence of structural disease likely to explain the symptoms

WORKUP

The American Gastroenterological Association, as well as the Maastricht III and the IV European consensus, suggest the following:

- The pattern of symptoms overlaps considerably for all types of dyspepsia; therefore, the history and physical should focus on finding specific symptoms that help exclude other causes of dyspepsia.
- Endoscopy should be performed only in patients >55 years old and in younger patients with alarming symptoms (e.g., weight loss, progressive dysphagia, recurrent vomiting, evidence of gastrointestinal bleeding, or family history of cancer) presenting with new-onset dyspepsia. Findings consistent with diagnosis of nonulcerative dyspepsia are not conclusive, no presence of *H. pylori*, no signs of gastroesophageal reflux disease, no mucosal inflammation. NOTE: Patients <55 years old and without any alarming symptoms can be treated without endoscopy.

LABORATORY TESTS

H. pylori: Laboratory methods include serologic tests*, monoclonal stool antigen, or urea breath test.

TREATMENT

ACUTE GENERAL Rx

PHARMACOLOGIC THERAPY: Primary treatment is usually initiated with proton pump inhibitors (PPIs), which can be started without performing endoscopy, especially if the patient comes from a population with low prevalence of *H. pylori* infection. If symptoms persist, a trial of antidepressants can be started.

Treatment of accompanying symptoms includes:

Predominant Symptom	Possible Etiology	Medication Recommended
Nausea	Motility dysfunction	Prokinetic agent
Bloating	Motility dysfunction	Simethicone and/or prokinetic agent
Pain	Mucosal disease or *H. pylori* infection	Antibiotic trial
Somatic complaints	Psychosocial	Psychotropic medication trial

Medication categories:

- Antacids (i.e., aluminum hydroxide, calcium carbonate)
- Gas-reducing agents, such as those containing simethicone
- H_2-receptor antagonists (i.e., cimetidine)
- PPIs (i.e., omeprazole)
- Prokinetic agents (i.e., metoclopramide)
- Antidepressants (i.e., selective serotonin receptor inhibitors)
- *H. pylori* therapy/antibiotic therapy (various antibiotic regimens, usually 1 PPI) if *H. pylori* present

CHRONIC Rx

Controversy currently exists around the long-term use of PPIs. Due to the high association with psychological factors, patients with functional dyspepsia should undergo psychological intervention, even if there is good response to pharmacotherapeutic approaches.

COMPLEMENTARY & ALTERNATIVE THERAPIES

Peppermint and caraway oil may be helpful, as well as acupuncture; however, no definitive trials have been performed.

REFERRAL

- Referral to gastroenterology if patient has alarming symptoms (such as GI bleeding, dysphagia, odynophagia, unexplained anemia, change in appetite, and weight loss) or when endoscopy is indicated—although controversy exists about the workup of younger patients.
- Referral to cardiology if cardiac etiology suspected.

PEARLS & CONSIDERATIONS

PREVENTION

Avoid excessive amounts of caffeine, alcohol, smoking, or long-term use of steroids and NSAIDs.

PATIENT AND FAMILY EDUCATION

http://www.mayoclinic.com/health/stomach-pain/DS00524

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fig. 3-65 Approach to the patient with dyspepsia (Algorithm)

AUTHORS: **ALVARO M. RIVERA, M.D., and NADINE MBUYI, M.D.**

*Serologic testing for *H. pylori* has a low predictive value because colonization is lifelong; it can therefore determine prevalence better than incidence.

SUGGESTED READINGS

Dickerson LM et al.: Evaluation and management of nonulcer dyspepsia, *Am Fam Physician* 70(1), 2004.

Fennerty MB et al.: Short- and long-term management of heartburn and other acid-related disorders, *J Fam Pract* 58(suppl):S1–S12, 2009.

Geeraerts B et al.: Functional dyspepsia: past, present and future, *J Gastroenterol* 43(251), 2008.

Lloyd RA, McClellan DA: Update on the evaluation and management of functional dyspepsia, *Am Fam Physician* 83(5):547–552, 2011.

Malfertheiner P et al.: for the European Helicobacter Study Group. Management of Helicobacter pylori infection—the Maastricht IV/Florence Consensus Report, *Gut* 61(5):646–664, 2012.

Malfertheiner P, et al.: Guidelines for the management of Helicobacter pylori infection. Summary of the Maastricht III 2005 consensus report, *Bus Brief Eur Gastroenterol Rev* 59–63, 2005.

Quigley EMM et al.: Dyspepsia, *Curr Opin Gastroenterol* 24(692), 2008.

Rome III Criteria: http://www.romecriteria.org/assets/pdf/19_RomeIII_apA_885-898.pdf and http://www.romecriteria.org/criteria/

Soo S, Moayyedi P, Deeks J et al.: Psychological interventions for non-ulcer dyspepsia, *Cochrane Database Syst Rev* 2:CD001960, 2005.

Tack J, Bisschops R, Sarnelli G: Pathophysiology and treatment of functional dyspepsia, *Gastroenterology* 127:1239–1255, 2003.

Tack J, Talley NJ, Camilleri M et al.: Functional gastroduodenal disorders, *Gatroenterology* 120:1466–1479, 2006.

Talley NJ: American Gastroenterological Association medical position statement: evaluation of dyspepsia, *Gastroenterology* 129(5):1753–1755, 2005.

BASIC INFORMATION

DEFINITION

The term "dysphagia" is derived from the Greek words *dys* (with difficulty) and *phagia* (to eat). It is characterized by abnormal transfer of food from mouth to the stomach, which may involve the oral, pharyngeal, or esophageal stages of swallowing.

ICD-9CM CODES
782.2 Dysphagia
ICD-10CM CODES
R13.10 Dysphagia, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- This is seen in 10% of individuals above the age of 50 yr. Its prevalence increases with advancing age.
- Nearly 12% of hospitalized patients have symptoms of dysphagia.
- Up to 30% to 60% of nursing home patients have some form of dysphagia.
- Special populations, including patients with head injury, stroke, or Parkinson's disease, have 30% to 50% prevalence of oropharyngeal dysphagia.

ETIOLOGY

- Oropharyngeal
  1. Neuromuscular causes
     1. Stroke.
     2. Parkinson's disease.
     3. Multiple sclerosis.
     4. Myasthenia gravis.
     5. Amyotrophic lateral sclerosis.
     6. CNS tumors.
     7. Muscular dystrophy.
     8. Thyroid dysfunction.
     9. Polymyositis and dermatomyositis.
     10. Sarcoidosis.
     11. Cerebral palsy.
     12. Head trauma.
     13. Metabolic encephalopathy.
     14. Dementia.
     15. Bell's palsy.
  2. Structural causes
     1. Oropharyngeal tumors.
     2. Zenker's diverticulum.
     3. Infection of pharynx or neck (mucositis from *Candida,* herpes, and CMV).
     4. Thyromegaly.
     5. Prior surgery or radiotherapy.
     6. Osteophytes and other spinal disorders.
     7. Proximal esophageal webs.
     8. Congenital anomalies (e.g., cleft palate).
     9. Poor dentition.
- Esophageal
  1. Neuromuscular disorders
     1. Achalasia.
     2. Diffuse esophageal spasm.
     3. Nutcracker esophagus.
     4. Hypertensive lower esophageal sphincter.
     5. Ineffective esophageal motility.
     6. Scleroderma.
     7. Reflex-associated dysmotility.
  2. Structural disorder
     1. Peptic stricture.
     2. Esophageal rings and webs.
     3. Diverticuli.
     4. Carcinoma and benign tumors.
     5. Foreign bodies.
     6. Vascular compression.
     7. Mediastinal masses.
     8. Spinal osteophytes.
     9. Mucosal injury (from pills, infection, gastroesophageal reflux disease [GERD], etc.).

PATHOGENESIS

The inability to swallow is caused either by a problem in strength or coordination of the muscles required to move material from the mouth to stomach or by a fixed obstruction somewhere between the mouth and the stomach.

CLINICAL FEATURES

Oropharyngeal dysphagia
- Problem arises within 2 seconds of initiating the voluntary phase of swallowing.
- Typical symptoms include drooling, spillage of food, postnasal regurgitation, difficulty in initiation of swallowing, sialorrhea, sensation of food stuck in the neck, coughing or choking during swallowing, the need to swallow repeatedly to clear food or fluid from the pharynx, dysphonia, nasal speech, hoarseness of voice, and dysarthria.
- A thorough physical examination including that of the nervous system, oral cavity, and the head/neck is very important in patients with oropharyngeal dysphagia.

Esophageal dysphagia
- Problem usually arises several seconds after swallowing.
- Patients often complain of food being stuck in lower substernal area.
- Dysphagia to solids suggests mechanical obstruction.
- Neuromuscular causes result in dysphagia to both solids and liquids. Particularly, patients with achalasia tend to drink a lot of fluids while eating or apply maneuvers such as straightening the back, raising their arms over their heads, or standing to increase intraesophageal pressure to facilitate the emptying of food into the stomach.
- Oftentimes, ingestion of very cold or very hot foods precipitates the dysphagia associated with neuromuscular disorder.
- Delayed regurgitation of food, heartburn, and chest pain are usually present.
- Weight loss is usually associated with malignancy or achalasia.
- Symptoms are intermittent in patients with esophageal dysphagia from benign causes of structural obstruction or diffuse esophageal spasm. However, it is progressive in patients with peptic stricture, esophageal carcinoma, scleroderma, and achalasia.
- In patients with structural obstruction, when the luminal diameter is more than 18 to 20 mm, they are rarely symptomatic, whereas those with a diameter of less than 13 mm are nearly always symptomatic.
- These patients with esophageal dysphagia usually do not have any characteristic physical findings.

DIAGNOSIS

Laboratory evaluation
- CBC.
- Thyroid studies.
- Nutritional assessment by checking serum protein and albumin levels.
- Other studies based on specific clinical conditions.

Special studies
- Oropharyngeal dysphagia
  1. Videofluoroscopy is the first test often ordered in evaluation of patients with oropharyngeal dysphagia.
  2. Double contrast modified barium swallow study (Fig. ED1-49).
  3. Fiberoptic flexible nasopharyngeal laryngoscopy is mandatory in all cases when a structural lesion, particularly malignancy, is suspected.
  4. Pharyngeal and upper esophageal manometry (Fig. ED1-50) is occasionally of value to predict which patients will have a favorable outcome from cricopharyngeal myotomy or dilation.
  5. Radiography of head and neck when indicated.
- Esophageal dysphagia
  1. Barium esophagography should precede upper endoscopies to identify patients at risk from potential perforation with an endoscopy and to help plan fluoroscopically guided dilation. It is often the first step in evaluating patients with dysphagia, especially if an obstructive lesion is suspected.
  2. EGD.
  3. Esophageal manometry is indicated if no abnormality is identified by barium study or EGD.
  4. Esophageal pH monitoring in patients with suspected reflux disease.
  5. Endoscopic ultrasonography.
  6. Radiograph, CT, and MRI of chest.

DIFFERENTIAL DIAGNOSIS (Fig. D1-51)

- Globus pharyngeus.
- Odynophagia.
- Phagophobia.
- GERD.

TREATMENT

- Treatment should be approached with the help of specialists of multiple disciplines (ENT, head and neck surgeon, radiologist, speech pathologist, physical therapist, dietitian, gastroenterologist, physical medicine and rehabilitation specialist, dentist, neurologist, etc.).

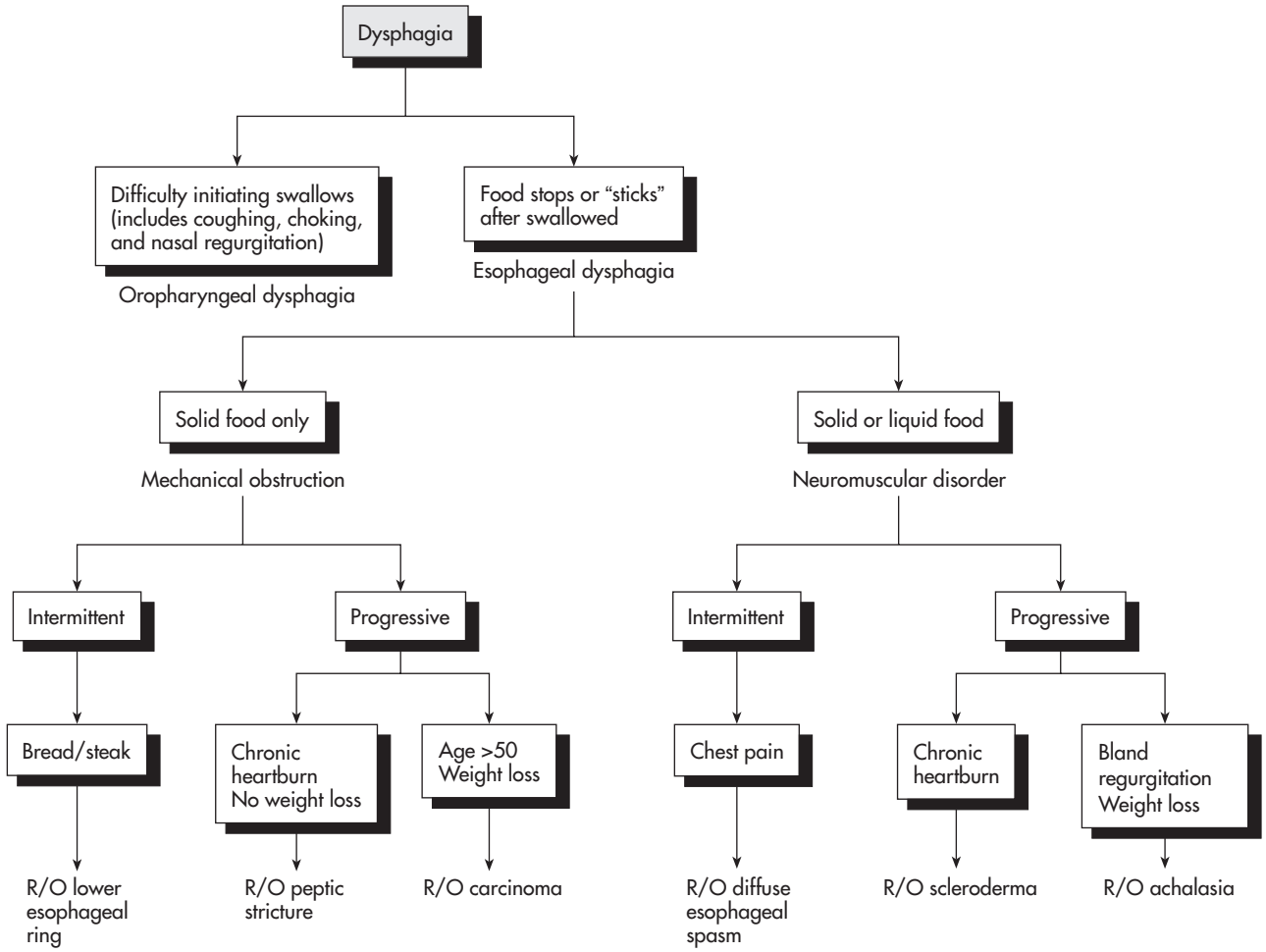

FIGURE D1-51 Differential diagnosis of dysphagia. *RO,* Rule out. (Modified from Andreoli TE [ed]: *Cecil essentials of medicine,* ed 7, Philadelphia, 2008, Saunders.)

- Goal of therapy is airway protection and maintenance of nutrition.
- Alteration of food consistency, volume, and delivery rate plays a major role.
- The goal of direct therapy is to change swallowing physiology with medical treatment of primary disease, maxillofacial prosthesis, and cricopharyngeal myotomy.
- Indirect therapies include exercise programs for tongue coordination and chewing under the guidance of a speech therapist.
- Maintenance of oral feeding often requires compensatory techniques such as chin-tuck position, rotation of head to the affected side, tilting of head to the strong side, and lying on one's back or on one's side during swallowing.
- Some of the voluntary maneuvers applied include supraglottic swallow, effortful swallow, Mendelson maneuver, Shaker exercise, and the Heimlich maneuver.
- Placement of nasogastric tube, jejunostomy tube, or percutaneous endoscopic gastrotomy (PEG) tube is considered for enteral feeding when other measures fail and the patient remains at significant risk for aspiration or nutrition becomes compromised.
- Treatment of associated GERD should not be forgotten.
- Surgery for chronic aspiration may involve tracheostomy, medialization, laryngeal suspension, laryngeal closure, and/or laryngotracheal separation-diversion.
- Other measures include esophageal dilation removal of foreign body, esophageal resection, chemotherapy, radiotherapy, endoscopic ablation of tumor, photodynamic therapy, esophageal prosthesis/stents, diverticulectomy, intrasphincteric injection of botulinum toxin, surgical myotomy, and others. Smooth muscle relaxants such as nitrates and calcium channel blockers have been used to effectively treat patients with diffuse esophageal spasm and nutcracker esophagus.
- Several scales have been suggested to determine patients' functional outcome. One of them is the "Swallowing Rating Scale."

COMPLICATIONS

- Dehydration.
- Malnutrition.
- Aspiration pneumonia.
- Airway obstruction.
- Death resulting from pulmonary complications.

PROGNOSIS

- Depends on the etiology.
- Nursing home patients with oropharyngeal dysphagia and a history of aspiration have an approximately 45% mortality rate over 1 yr.
- All patients, especially the elderly, should take their medications with a full glass of water while in upright position well before bedtime.
- Dysphagia should be considered an alarm symptom, indicating the need for immediate evaluation.

PATIENT EDUCATION

Elderly patients with dysphagia should not attribute their symptoms to aging.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Dyspepsia, Nonulcerative (Related Key Topic)
Esophageal Tumors (Related Key Topic)
Gastroesophageal Reflux Disease (Related Key Topic)

AUTHOR: **HEMANT K. SATPATHY, M.D.**

EVIDENCE

Abstract[1]

Background:

Many experts consider laparoscopic Heller's myotomy (LHM) to be superior to pneumatic dilation for the treatment of achalasia, and LHM is increasingly considered to be the treatment of choice for this disorder.

Methods:

We randomly assigned patients with newly diagnosed achalasia to pneumatic dilation or LHM with Dor's fundoplication. Symptoms, including weight loss, dysphagia, retrosternal pain, and regurgitation, were assessed with the use of the Eckardt score (which ranges from 0 to 12, with higher scores indicating more pronounced symptoms). The primary outcome was therapeutic success (a drop in the Eckardt score to ≤3) at the yearly follow-up assessment. The secondary outcomes included the need for retreatment, pressure at the lower esophageal sphincter, esophageal emptying on a timed barium esophagogram, quality of life, and the rate of complications.

Results:

A total of 201 patients were randomly assigned to pneumatic dilation (95 patients) or LHM (106). The mean follow-up time was 43 months (95% confidence interval [CI], 40 to 47). In an intention-to-treat analysis, there was no significant difference between the two groups in the primary outcome; the rate of therapeutic success with pneumatic dilation was 90% after 1 year of follow-up and 86% after 2 years, as compared with a rate with LHM of 93% after 1 year and 90% after 2 years (P=0.46). After 2 years of follow-up, there was no significant between-group difference in the pressure at the lower esophageal sphincter (LHM, 10 mm Hg [95% CI, 8.7 to 12]; pneumatic dilation, 12 mm Hg [95% CI, 9.7 to 14]; P=0.27); esophageal emptying, as assessed by the height of barium-contrast column (LHM, 1.9 cm [95% CI, 0 to 6.8]; pneumatic dilation, 3.7 cm [95% CI, 0 to 8.8]; P=0.21); or quality of life. Similar results were obtained in the per-protocol analysis. Perforation of the esophagus occurred in 4% of the patients during pneumatic dilation, whereas mucosal tears occurred in 12% during LHM. Abnormal exposure to esophageal acid was observed in 15% and 23% of the patients in the pneumatic-dilation and LHM groups, respectively (P=0.28).

Conclusions:

After 2 years of follow-up, LHM, as compared with pneumatic dilation, was not associated with superior rates of therapeutic success. (European Achalasia Trial Netherlands Trial Register number, NTR37, and Current Controlled Trials number, ISRCTN56304564.) Ⓐ

Evidence-Based Reference

Boeckxstaens GE: for the European Achalasia Trial Investigators. Pneumatic dilation versus laparoscopic Heller's myotomy for idiopathic achalasia, *N Engl J Med* 364:1807–1816, 2011. Ⓐ

SUGGESTED READINGS

Lind C: Dysphagia: evaluation and treatment, *Gastroenterol Clin North Am* 32(2):553–575, 2003.

Logemann J: Oropharyngeal dysphagia and nutritional management, *Curr Opin Clin Nutr Metab Care* 10(5):611–614, 2007.

Saud BM, Szyjkowski RD: A diagnostic approach to dysphagia, *Clin Fam Pract* 6(3):525–546, 2004.

FIGURE ED1-49 Barium swallow demonstrating a benign peptic stricture in a patient with gastroesophageal reflux disease and dysphagia. (From Talley NJ, Martin C: *Clinical gastroenterology: a practical problem-based approach,* ed 2, Sydney, 2006, Churchill Livingstone.)

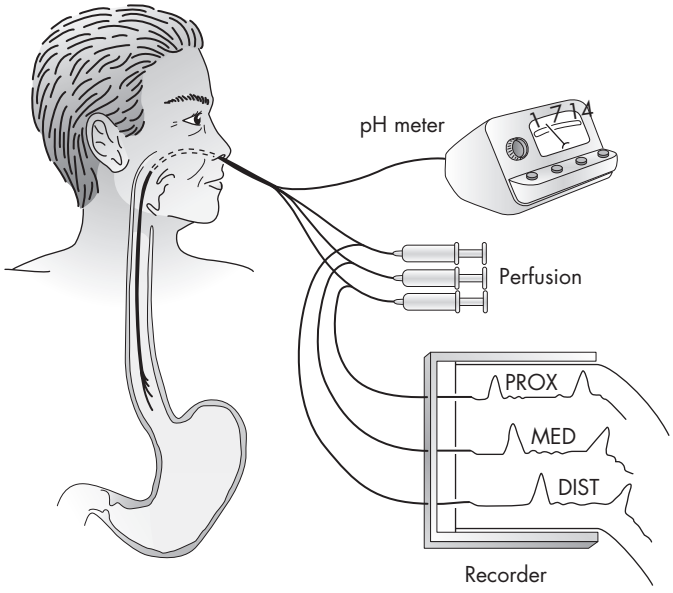

FIGURE ED1-50 Combined manometric-pH recording system used in the evaluation of esophageal function. The triple-lumen perfused recording catheter measures intraluminal pressures from three levels in the esophagus. Measurements are made in terms of centimeters from the nostrils to the proximal opening of the recording catheter *(PROX).* The medial catheter *(MED)* records pressures 5 cm distal to the proximal opening and the distal catheter *(DIST)* 5 cm below this. The intraesophageal pH electrode is used to document gastroesophageal reflux. (From Townsend CM et al: *Sabiston textbook of surgery,* ed 17, Philadelphia, 2004, Saunders.)

BASIC INFORMATION

DEFINITION

Dystonia refers to a group of disorders characterized by involuntary muscle contractions (sustained or spasmodic) that lead to abnormal body movements or postures. Dystonia can be generalized or focal, of early (<20 yr) or late onset, and primary or secondary.

SYNONYMS

Blepharospasm
Oromandibular (orofacial) dystonia
Spasmodic (limb or axial) dystonia
Torticollis
Writer's cramp

ICD-10CM CODES

G24 Dystonia
G24.1 Idiopathic familial dystonia
G24.0 Drug induced dystonia
G24.3 Spasmodic torticollis

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Estimated at one in 3000 persons.
PREDOMINANT SEX: Cervical dystonia has a 3:2 female preponderance.
PREDOMINANT AGE:

- Onset of focal cervical dystonia is usually in the fifth decade.
- Hereditary forms may have an onset in childhood or adulthood and tend to be more severe.

GENETICS: Autosomal-dominant, autosomal-recessive, and X-linked forms of dystonia have been identified. Ashkenazi Jews are particularly susceptible to primary early-onset dystonia.

CLINICAL PRESENTATION

Focal dystonias produce abnormal sustained muscle contractions in a single region of the body:

- Neck (***torticollis***): most commonly affected site with a tendency for the head to turn to one side.
- Eyelids (***blepharospasm***): involuntary closure of the eyelids that leads to excessive eye blinking, sometimes with persistent eye closure and functional blindness.
- Mouth (***oromandibular dystonia***): involuntary contraction of muscles of the mouth, tongue, or face.
- Hand (***writer's cramp***) (Fig. D1-52).

Generalized dystonia affects multiple areas of the body and can lead to marked joint deformities.

- Isolated foot dystonia is very rare and may suggest an underlying parkinsonian disorder or brain structural abnormality.

ETIOLOGY

- Exact pathophysiology of primary dystonia is unknown but believed to involve abnormalities of basal ganglia. Specifically, reduced and abnormal patterns of neuronal activity in the basal ganglia result in disinhibition of the motor thalamus and cortex, leading to abnormal movement.
- Fifteen hereditary forms have been described, including the severe progressive form, dystonia musculorum deformans.
- Secondary dystonia results from central nervous system (CNS) disease of the basal ganglia (stroke, demyelination, hypoxia, trauma), Huntington's disease, Wilson's disease, Parkinson syndromes, and lysosomal storage diseases.
- Acute dystonia can occur with drugs that block dopamine receptors, such as phenothiazines or butyrophenones.
- Tardive dyskinesia can result from long-term treatment with antiemetics (e.g., phenothiazines), antipsychotics (e.g., haloperidol), levodopa, anticonvulsants, or ergots.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Parkinson's disease.
- Progressive supranuclear palsy.
- Wilson's disease.
- Huntington's disease.
- Drug effects.
- Table D1-21 describes selected causes of primary and secondary dystonia in childhood.

WORKUP

History (family history, birth history, trauma, medication use, age of onset, and temporal pattern), physical examination to determine associated features (weakness, myoclonus, tremor) and to determine pattern of dystonia—focal (single body region), segmental (two or more body contiguous body regions), multifocal (two or more noncontiguous body regions), generalized (involving the trunk and at least two other sites), or hemidystonia (involving more regions but restricted to one body side).

FIGURE D1-52 Focal dystonia of the distal right arm. (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, Saunders.)

LABORATORY TESTS

- Usually not helpful for diagnosis.
- Serum ceruloplasmin if Wilson's disease is suspected.
- Genetic testing (DYT gene mutations, inborn errors of metabolism, or mitochondrial disease) if indicated.

IMAGING STUDIES

- Primary dystonias are generally not associated with structural CNS abnormalities. CT scan or MRI of brain if a CNS lesion is suspected as a cause of secondary dystonia.
- Electrophysiologic testing can provide diagnostic support for the diagnosis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Heat, massage, physical therapy to relieve pain
- Splints to prevent contractures

ACUTE GENERAL Rx

For acute dystonic reactions to phenothiazines/butyrophenones, use diphenhydramine 50 mg IV or benztropine 2 mg IV. For patients presenting for subacute or chronic dystonia, a trial of L-dopa can be useful in distinguishing dopa-responsive dystonia from other causes.

CHRONIC Rx

- For treatment of drug-induced dystonia, slowly withdraw offending agents (antiemetics, antipsychotics most commonly).
- For generalized dystonia, a trial of carbidopa/levodopa may be beneficial and diagnostic of dopa-responsive dystonia.
- Trihexyphenidyl or benztropine may be helpful in up to 50% of tardive dystonias; these are the mainstay of treatment for generalized dystonias not responsive to dopa.
- Diazepam, clonazepam, or baclofen may be helpful.
- Injections of botulinum toxin into the affected muscles are the standard treatment for focal dystonias. Both type A and type B toxins produced by *Clostridium botulinum* block cholinergic transmission at the neuromuscular junction by inhibiting release of acetylcholine.
- Surgical procedures, including denervation, myectomy, rhizotomy, thalamotomy (pallidotomy), or deep brain stimulation, may be helpful for severe, refractory cases, depending on the etiology.
- Intrathecal baclofen can be useful for spastic or truncal dystonia.

DISPOSITION

Spontaneous remission of focal cervical dystonia can occur, but dystonia is generally progressive and pharmacologic therapy is often ineffective.

REFERRAL

Neurology and/or neurosurgery for severe or refractory cases.
Physical therapy for maintaining flexibility.

PEARLS & CONSIDERATIONS

COMMENTS

- Avoid triggers/exacerbating factors.
- Early physical therapy and splinting to prevent contractures.
- Consider botulism injections or deep brain stimulation surgery for severe or refractory dystonia and for focal dystonias.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **LYNN MCNICOLL, M.D.** and **JULIE L. ROTH, M.D.**

TABLE D1-21 Selected Causes of Primary and Secondary Dystonia in Childhood

Diagnosis	Additional Clinical Features
Aicardi-Goutieres syndrome	Encephalopathy, developmental regression Acquired microcephaly Sterile pyrexias Lesions on the digits, ears (chilblain) Epilepsy CT: calcification of the basal ganglia
Alternating hemiplegia of childhood	Episodic hemiplegia/quadriplegia Abnormal ocular movements Autonomic symptoms Epilepsy Global developmental impairment Environmental triggers for spells
Aromatic amino acid decarboxylase deficiency (AADC)	Developmental delay Oculogyric crises Autonomic dysfunction Hypotonia
ARX gene mutation (X-linked)	Male Cognitive impairment Infantile spasms, epilepsy Brain malformation
Benign paroxysmal torticollis of infancy	Episodic Cervical dystonia only Family history of migraine
Complex regional pain syndrome	Lower limb involvement Prominent pain
Dopa-responsive dystonia (DRD)	Diurnal variation
Drug-induced dystonia	
Dystonia-deafness optic neuropathy syndrome	Sensorineural hearing loss in early childhood Psychosis Optic atrophy in adolescence
DYT1 dystonia	Lower limb onset followed by generalization
Glutaric aciduria type 1	Macrocephaly Encephalopathic crises MRI: striatal necrosis
GM1 gangliosidosis type 3	Short stature, skeletal dysplasia Orofacial dystonia Speech/swallowing disturbance Parkinsonism MRI: putaminal hyperintensity
Huntington disease (HD)	Parkinsonism Epilepsy Family history of HD
Kernicterus	Jaundice in infancy Hearing loss Impaired upgaze Enamel dysplasia MRI: hyperintense lesions in the globus pallidus
Leigh syndrome	Motor delays, weakness, hypotonia Ataxia, tremor Elevated lactate MRI: bilateral symmetric hyperintense lesions in the basal ganglia or thalamus
Lesch-Nyhan syndrome (X-linked)	Male Self-injurious behavior Hypotonia Oromandibular dystonia, inspiratory stridor Oculomotor apraxia Cognitive impairment Elevated uric acid
Myoclonus dystonia	Myoclonus Head, upper limb involvement
Niemann-Pick type C	Hepatosplenomegaly Hypotonia Supranuclear gaze palsy Ataxia, dysarthria Epilepsy Psychiatric symptoms
Neuroacanthocytosis	Oromandibular and lingual dystonia
Neurodegeneration with brain iron accumulation	Cognitive impairment Retinal pigmentary degeneration, optic atrophy
Rapid onset dystonia parkinsonism (DYT12)	Acute onset Distribution face>arm>leg Prominent bulbar signs
Rett syndrome	Female Developmental regression following a period of normal development Stereotypic hand movements Acquired microcephaly Epilepsy
Spinocerebellar ataxia 17 (SCA17)	Ataxia Dementia, psychiatric symptoms Parkinsonism
Tics	Stereotyped movements Premonitory urge, suppressible
Tyrosine hydroxylase deficiency	Infantile encephalopathy, hypotonia Oculogyric crises, ptosis Autonomic symptoms Less diurnal fluctuation than DRD

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

SUGGESTED READINGS

Albanese A, Bhatia K, Bressman SB, et al.: Phenomenology and classification of dystonia: a consensus update, *Mov Disord* 28:863, 2013.

Defazio G et al.: Epidemiology of primary dystonia, *Lancet Neurol* 3:673, 2004.

Simpson D et al.: Assessment: botulism neurotoxin for the treatment of movement disorders (an evidence-based review): report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, *Neurology* 70:1699, 2009.

Tarsy D, Simon DK: Dystonia, *N Engl J Med* 355:818, 2006.

BASIC INFORMATION

DEFINITION

Echinococcosis is a chronic infection caused by the larval stage of several animal cestodes (tapeworms) of the genus *Echinococcus.*

SYNONYMS

Hydatid disease

ICD-9CM CODES
122.9 *Echinococcus* infection
ICD-10CM CODES
B67.90 Echinococcosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Seen primarily in immigrants, but local transmission can occur in southwestern U.S., California, and Alaska.
PEAK INCIDENCE: Presumed to be acquired in childhood or early adulthood in most cases.
PREVALENCE (IN U.S.): See Incidence
PREDOMINANT SEX: Male = female
PREDOMINANT AGE: 0 to 50 yr of age

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Signs of an enlarging mass lesion in a visceral site such as the liver, lungs, kidneys, bone, or CNS
- Occasional cyst rupture causing allergic manifestations such as urticaria, angioedema, or anaphylaxis that bring the patient to medical attention
- Incidental discovery of cysts by abdominal or thoracic imaging studies performed for other reasons

ETIOLOGY

- Four species of *Echinococcus: E. granulosus, E. multilocularis, E. oligarthrus,* and *E. vogeli.*
  1. *E. granulosus* is the cause of cystic hydatid disease.
  2. *E. multilocularis* and *E. vogeli* are the causes of alveolar and polycystic disease.
- The disease is transmitted to humans by infected canines (domestic or wild dogs, wolves, foxes), which are the definitive hosts, and seen most commonly in livestock-producing areas of the Middle East, Africa, Australia, New Zealand, Europe, and the Americas, including the southwestern U.S., whereby sheep, goats, camels, or cattle serve as intermediate hosts to humans. Humans are incidental hosts and do not play a role in the transmission cycle.
- The adult tapeworm resides in the small intestine of the canine definitive hosts. Eggs are then shed in the feces of infected canines; human infection occurs by ingestion of viable eggs in contaminated food from intermediate hosts or direct fecal-oral transmission.
- After ingestion of the eggs by intermediate hosts or humans, eggs hatch and release onchospheres, which migrate through intestinal mucosa to definitive organs and develop into enlarging fluid-filled cysts known as hydatid cysts (metacestode). The cyst is acellular and is surrounded by fibroblasts and lymphocytic infiltrate (Fig. EE1-1).
- It is common in many areas of the world, especially the Middle East.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cystic neoplasms (see Table E1-1)
- Abscess (amebic or bacterial)
- Congenital polycystic disease

WORKUP

- Antibody assay
- Imaging study (CT scan [Fig. E1-2], ultrasonography)
- Classification (Fig. E1-3): Table E1-2 describes the World Health Organization Informal Working Group on Echinococcosis classification of hepatic echinococcal cysts.
- Histologic examination of cyst or contents obtained by aspiration or resection (if possible) to confirm diagnosis

LABORATORY TESTS

Antibody assays (ELISA or Western blot) available through CDC: 80% to 100% sensitive and 88% to 96% specific for liver cysts, but less accurate for cysts in other sites, such as lung. A PCR assay is now available for problematic cases. Eosinophilia is not consistently seen and thus not a reliable test.

IMAGING STUDIES

Ultrasonography, CT, and MRI:
- All are extremely sensitive for the detection of cysts, especially in the liver.
- All lack specificity and are inadequate to establish the diagnosis of echinococcosis with certainty.

TREATMENT

ACUTE GENERAL Rx

- Albendazole 400 mg PO bid followed by percutaneous aspiration-injection-reaspiration (PAIR) for uncomplicated larval cysts. It consists of puncture (P) and needle aspirate (A) of cyst content followed by inspiration (I)

TABLE E1-1 Hepatic Cyst Disease: Differential Features on Imaging Studies

Characteristics	Hydatid Cyst	Congenital Cyst	Cystadenoma
Configuration	Cyst within cyst	Single or multiple ± septations	Single ± septations
Wall character	Thick, uniform ± calcification	Thin, uniform	Mural nodules
Cyst contents	Daughter cysts Hydatid sand	Low density	Low density

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

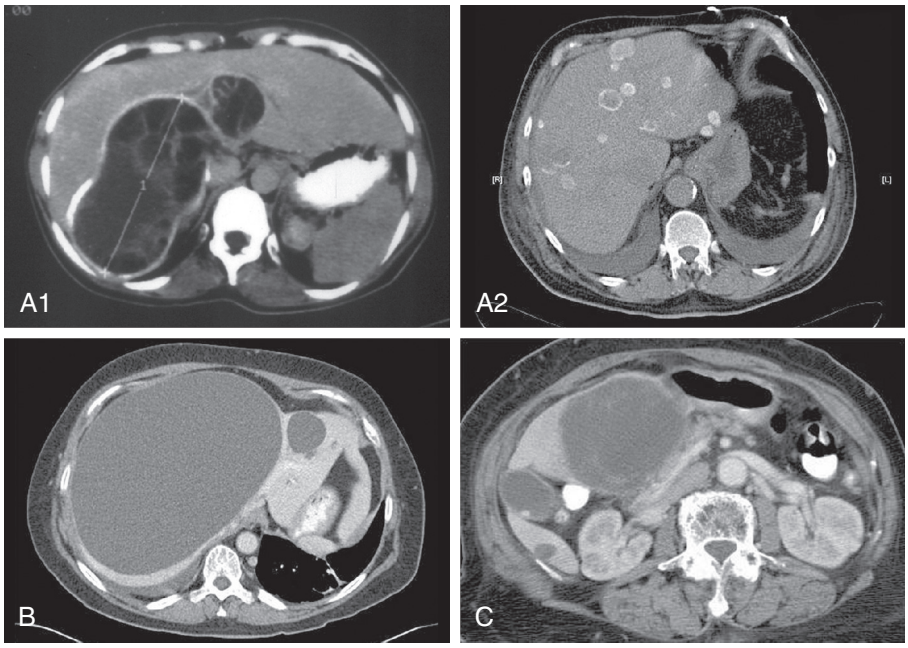

FIGURE E1-2 A comparison of computed tomography scans. A, Hepatic echinococcal cysts. **B,** Congenital cyst. **C,** Cystadenoma. For echinococcal cyst. **A1** demonstrates a single cyst with calcification and daughter cyst caused by *E. granulosa.* **A2** shows multiple small cysts characteristic of *E. multilocularis* infection. (Courtesy Barbara M. Kadell, MD, Professor of Radiology, David Geffen School of Medicine at University of California, Los Angeles. From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

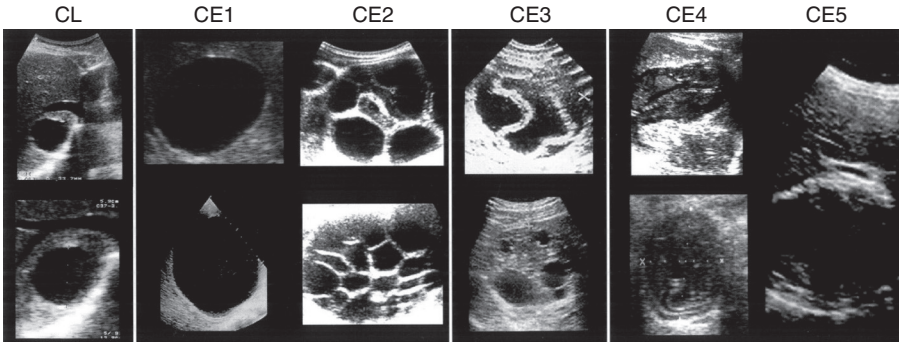

FIGURE E1-3 WHO Informal Working Group on Echinococcosis standardized ultrasound classification of cystic echinococcosis. CL lesions are cystic lesions lacking a distinct wall and may have other diagnoses. CE1 lesions are cystic lesions with a visible wall that may demonstrate protoscolices ("hydatid sand"). CE2 lesions include internal septation. CE3 lesions may be detached from the wall or have daughter cysts with internal thickening. CE4 lesions are heterogeneous lesions with degeneration. CE5 lesions show thick calcification. (From Goldman L, Schafer AI: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Saunders.)

TABLE E1-2 WHO-IWGE Classification of Hepatic Echinococcal Cysts

Type of Cyst	Status	Ultrasound Features	Remarks
CL	Active	Signs not pathognomonic, unilocular, no cyst wall	Usually early stage, not fertile; differential diagnosis necessary
CE 1	Active	Cyst wall, hydatid sand	Usually fertile
CE 2	Active	Multivesicular, cyst wall, rosette-like	Usually fertile
CE 3	Transitional	Detached laminated membrane, "water lily" sign, less round, decreased intracystic pressure	Starting to degenerate, may produce daughter cyst
CE 4	Inactive	Heterogeneous hypoechogenic or hyperechogenic degenerative contents; no daughter cyst	Usually no living protoscolices; differential diagnosis necessary
CE 5	Inactive	Thick, calcified wall, calcification partial to complete; not pathognomonic but highly suggestive of diagnosis	Usually no living protoscolices

WHO-IWGE, World Health Organization Informal Working Group on Echinococcosis.
From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

of hypertonic saline (15%-30%) or absolute alcohol, waiting 20 to 30 minutes, then reaspirating (R) with final irrigation. Albendazole is continued for 28 days. Cure rate is 96%.
- Surgical resection: cure rate 90%
- Alternatives to albendazole include mebendazole and praziquantel alone or in combination with mebendazole.

DISPOSITION

- Long-term follow-up is necessary following surgical or medical therapy because of the potential for late relapse.
- Antibody assays and imaging studies are repeated every 6 to 12 mo for several years following successful surgical or medical therapy.

REFERRAL

All patients for evaluation for possible surgical resection of cysts versus PAIR

PEARLS & CONSIDERATIONS

COMMENTS

Cyst resection, if indicated, should be performed by surgeons experienced with this procedure.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Echinococcosis (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Brunetti E, Junghanss T: Update on cystic hydatid disease, *Curr Opin Infect Dis* 22(5):497–502, 2009.

Eckert J, Deplazes P: Biological, epidemiological, and clinical aspects of echinococcosis, a zoonosis of increasing concern, *Clin Microbiol Rev* 17(1):107, 2004.

McManus DP, Gray DJ, Zhang W, Yang Y: Diagnosis, treatment and management of echinococcosis, *BMJ* 344:e3866, 2012.

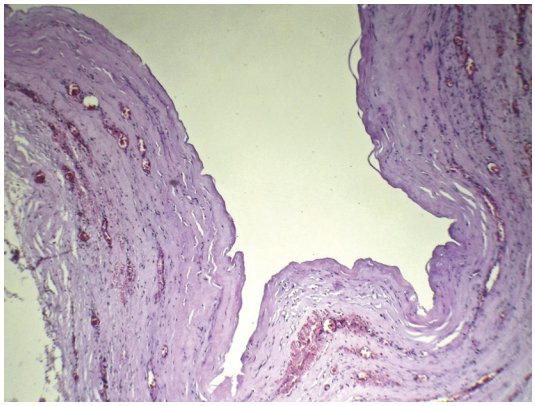

FIGURE EE1-1 Echinococcosis. The cyst is acellular and is surrounded by fibroblasts and lymphocytic infiltrate. (From Prieto-Granada CN, Lobo AZC, Mihm MC, Jr: Skin infections. In Kradin, RL (ed.): *Diagnostic pathology of infectious disease*; Philadelphia, 2010, Elsevier, pp 519–616.)

BASIC INFORMATION

DEFINITION

Eclampsia is the occurrence of seizures or coma in a woman with preeclampsia, occurring at >20 wk of gestation or <48 hr postpartum. Atypical eclampsia occurs at <20 wk of gestation or as much as 14 days postpartum.

SYNONYMS

Toxemia
Seizures of pregnancy

ICD-9CM CODES
642.6 Eclampsia
ICD-10CM CODES
O15.9 Eclampsia, unspecified as to time period

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: One case per 150 to 3000 pregnancies; 2% to 4% of those with preeclampsia.
GENETICS: Increased incidence with a first-degree relative (sister or mother) having had eclampsia.
RISK FACTORS: Multifetal gestation (3.6% in twin gestation), molar pregnancy, nonimmune hydrops fetalis, uncontrolled hypertension, preexisting hypertension, renal disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Seizure begins as facial twitching, then spreads to generalized tonic-clonic state, with cessation of respiration followed by a postictal period of amnesia, agitation, and confusion.
- 40% have severe hypertension, 40% have mild to moderate hypertension, and 20% are normotensive.
- Generalized edema with rapid weight gain (>2 lb/wk) may be one of the earliest signs of eclampsia.
- Persistent occipital headache and hyperreflexia with clonus occur in 80% of patients with eclampsia; epigastric pain occurs in 20% of these patients.

ETIOLOGY

- Exact etiology unknown.
- Common pathway relates to abnormalities in autoregulation of cerebral blood flow. This may involve transient vasospasm, ischemia, cerebral hemorrhage, and edema occurring by a mechanism involving hypertensive encephalopathy, decreased colloid osmotic pressure, and prostaglandin imbalance.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Preexisting seizure disorder.
- Metabolic abnormalities (hypoglycemia, hyponatremia, hypocalcemia).
- Substance abuse.
- Head trauma, infection (meningitis, encephalitis).
- Intracerebral bleeding or thrombosis.
- Amniotic fluid embolism.
- Space-occupying brain lesions or neoplasms.
- Pseudoseizure.
- Hypertensive encephalopathy.
- Venous or arterial thrombosis, arterial embolism.
- Posterior reversible vasoconstriction syndrome.
- Vasculitis, angiopathy.

WORKUP

- Rule out other causes of seizures during pregnancy.
- Atypical presentations such as prolonged postictal state; status epilepticus; gestational age <20 wk or >48 hr postpartum; or signs of meningitis, substance abuse, or severe uncontrolled hypertension should prompt a search for other seizure etiologies.

LABORATORY TESTS

- Proteinuria: severe (49%), mild to moderate (29%), absent (22%).
- HCT: elevated as a result of hemoconcentration.
- Platelet count: decreased; LFTs elevated in HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count).
- BUN and creatinine: elevated with renal involvement.
- Serum electrolytes, glucose, calcium, toxicology profile: rule out other causes of seizures.
- Hyperuricemia: >6.9 mg/dl found in 70% of eclamptics.
- ABG: maternal acidemia and hypoxia.

IMAGING STUDIES

- CT scan or MRI indicated in atypical presentation, suspected intracerebral bleeding, or focal neurologic deficit.
- There are abnormal findings, including cerebral edema, hemorrhage, and infarction, in 50% of patients.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Airway protection (risk of aspiration)
- Supportive care during acute event

ACUTE GENERAL Rx

- Maintain airway, adequate oxygenation, and IV access.
- Fetal resuscitation, involving maternal oxygenation, left lateral positioning, and continuous fetal heart rate monitoring, is needed.
- Magnesium sulfate is the drug of choice. Give magnesium sulfate 6 g IV load over 20 min, then 3 g/hr maintenance, for recurrent seizure prophylaxis. If repeated convulsions, may give an additional 2 g IV over 3 to 5 min. Approximately 10% to 15% of patients will have a second seizure after initial loading dose. Check magnesium level 1 hr after loading dose, then q6h (therapeutic range 4 to 7 mEq/L). Clinical signs of progressive Mg^{2+} toxicity, such as loss of reflexes, should also be followed. Respiratory and cardiac arrest occur at extremely high levels. Antidote for toxicity is calcium gluconate 10 ml of 10% solution. Phenytoin has been used as an alternative in patients in whom magnesium sulfate is contraindicated (renal insufficiency, heart block, myasthenia gravis, hypoparathyroidism).
- Give sodium amobarbital 250 mg IV over 3 min for persistent seizures.
- Treat blood pressure if >160 mm Hg/110 mm Hg with labetalol 20- to 40-mg IV bolus, hydralazine 10 mg IV, or nifedipine 10 to 20 mg sublingual q20 min.
- Evaluate patient for delivery.

CHRONIC Rx

- The first priority is stabilization of the mother in terms of adequate oxygenation, hemodynamics, and laboratory abnormalities, such as associated coagulopathies.
- Cervical status and gestational age should be assessed. If unfavorable cervix and <30 wk of gestation, consider C-section; otherwise consider induction.
- Controlled epidural is the anesthesia of choice for labor or C-section.
- Avoid general anesthesia in uncontrolled hypertension to minimize risk of catastrophic cerebral events.

DISPOSITION

The maternal mortality rate for eclampsia averages 5% to 6%. Morbidity rate is 25%, including placental abruption (10%), maternal apnea with fetal asphyxia, aspiration pneumonia, pulmonary edema (4%), renal failure, cardiopulmonary arrest, and coma.

REFERRAL

Because of the potential for serious permanent maternal and fetal sequelae, all cases should be managed by a team approach of obstetrician, neonatologist, and intensivist.

PEARLS & CONSIDERATIONS

COMMENTS

- Eclampsia antepartum, 50%; intrapartum, 20%; and postpartum, 30%.
- Postseizure there is an associated period of fetal bradycardia from 1 to 9 min; if there is evidence of fetal compromise beyond that time, consider alternative etiologies such as placental abruption (23% incidence).

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Eclampsia (Patient Information)
HELLP Syndrome (Related Key Topic)
Preeclampsia (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Duley L: Evidence and practice: the magnesium sulphate story, *Best Pract Res Clin Obstet Gynaecol* 19(1):57, 2005.

Schroeder BM: ACOG practice bulletin on diagnosing and managing preeclampsia and eclampsia, *Am Fam Physician* 66:330, 2002.

Sibai BM: Diagnosis, prevention, and management of eclampsia, *Obstet Gynecol* 105(2):402, 2005.

BASIC INFORMATION

DEFINITION

An ectopic pregnancy (EP) occurs when a fertilized ovum implants outside the endometrial lining of the uterus.

SYNONYMS

Abdominal pregnancy (0.03% to 1%)
Cervical pregnancy (0.5%)
Interstitial pregnancy (1% to 2%)
Ovarian pregnancy (1%)
Tubal pregnancy (97%)

ICD-9CM CODES
633 Ectopic pregnancy
ICD-10CM CODES
000.9 Ectopic pregnancy, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- 1% to 2% of pregnancies
- 13% of maternal deaths

PREVALENCE (IN U.S.): Increasing number of EPs; 17,800 reported cases in 1970 and currently over 100,000 reported cases/year.
RISK FACTORS: Previous salpingitis, previous EP, previous tubal ligation, previous tuboplasty, intrauterine device use, progestin-only pill, assisted reproductive techniques

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Abdominal tenderness: 95%.
- Adnexal tenderness: 87% to 99%.
- Peritoneal signs: 71% to 76%.
- Adnexal mass: 33% to 53%.
- Enlarged uterus: 6% to 30%.
- Shock: 2% to 17%.
- Amenorrhea or abnormal vaginal bleeding: 75%.
- Shoulder pain: 10%.
- Tissue passage: 6% to 7%.

ETIOLOGY

- Anatomic obstruction to zygote passage.
- Abnormalities in tubal motility.
- Transperitoneal migration of the zygote.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Corpus luteum cyst.
- Rupture or torsion of ovarian cyst.
- Threatened or incomplete abortion.
- Pelvic inflammatory disease.
- Appendicitis.
- Gastroenteritis.
- Dysfunctional uterine bleeding.
- Degenerating uterine fibroids.
- Endometriosis.

WORKUP

1. The classic presentation of EP includes the triad of abnormal vaginal bleeding, pelvic pain, and an adnexal mass. Fig. E1-4 describes a diagnostic approach to suspected EP. Fig. E1-5 *(top)* describes potential sites of ectopic implantations. Consider in all women with abdominopelvic pain and a positive pregnancy test.
2. Transvaginal ultrasound.
3. Quantitative serum human chorionic gonadotropin level.
4. Laparoscopy in equivocal situations and possibly for treatment.

LABORATORY TESTS

- Quantitative human chorionic gonadotropin (QhCG): if normal intrauterine pregnancy (IUP), 85% have doubling time of 2 days. If abnormal gestation, will show <66% increase of QhCG within 2 days. However, 13% of ectopic pregnancies have a normal doubling time.
- Progesterone: decreased production in EP; <5 ng/ml strongly predictive of abnormal pregnancy. If >25 ng/ml, strongly predictive of normal IUP.
- Dropping hematocrit associated with tubal rupture, resolving EP, or abnormal intrauterine pregnancy.
- Leukocytosis.

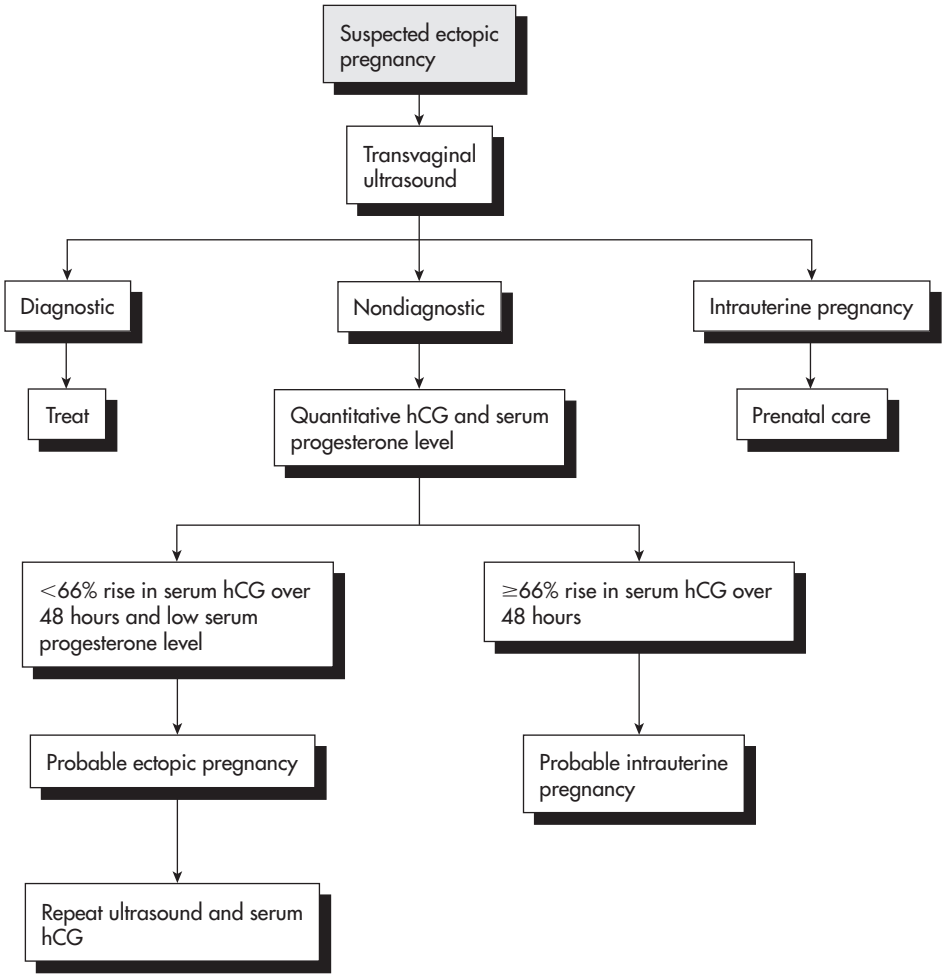

FIGURE E1-4 Ectopic pregnancy. *hCG*, Human chorionic gonadotropin.

IMAGING STUDIES

- Ultrasound: presence of an IUP makes EP extremely unlikely. However, if the patient used assisted reproductive technologies, a heterotopic pregnancy (a pregnancy in the uterus as well as in the fallopian tube) is much more likely to occur (Fig. E1-5*A* and *B*). A repeat ultrasonographic examination 2 to 7 days after presentation may identify the location of a pregnancy that was not identified on initial ultrasonographic examination.
- If QhCG >6000 mIU/ml, should see IUP on abdominal scan; QhCG >1500 mIU/ml for transvaginal scan. Since transvaginal ultrasonography is overwhelmingly the preferred modality for imaging, the latter value is clearly the discriminatory threshold that is used in diagnosis.
- Findings on ultrasound in EP include:
  1. Empty uterus.
  2. Adnexal mass.
  3. Cul-de-sac fluid.
  4. Fetal sac in tube.
  5. Fetal cardiac activity in adnexa.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Surgery can be performed by laparoscopy if patient is stable or, rarely, by laparotomy if patient is very unstable. Salpingiosis is the direct injection of chemotherapy into the EP by laparoscopy, transvaginal ultrasound, or hysteroscopy. Direct injection of methotrexate, and possibly KCl if there is active cardiac activity, may be performed when the pregnancy is in a location where there is high morbidity, such as the cervix or cornu.

- Conservative surgery, salpingostomy or segmental resection, depends on tubal location and size of EP.
- Salpingectomy should be considered in the following circumstances:
  1. Ruptured tube.
  2. Future fertility not desired.
  3. Recurrent EP in the same tube.
  4. Uncontrolled hemorrhage.

ACUTE GENERAL Rx

- If the patient is stable and compliant, consider medical management with methotrexate. Patient should not have contraindications to methotrexate such as hepatic or renal disease, thrombocytopenia, leukopenia, or significant anemia. There should be no evidence of hemoperitoneum on transvaginal ultrasound. EP should be <3.5 cm mass with QhCG <6,000 to 15,000 mIU/ml, but these are relative contraindications. Presence of cardiac activity in the fetus is also a relative contraindication to methotrexate.
- Most common regimen is methotrexate 50 mg/m^2 of body surface area. May require second dose or surgical intervention if QhCG increases or plateaus (<15% drop) when comparing values from the fourth through seventh day after treatment (day 1 is the day that methotrexate is given). Absolute contraindications to methotrexate include breast feeding, preexisting blood dyscrasias, known sensitivity to methotrexate, active pulmonary disease, chronic liver disease, alcoholism, laboratory evidence of immunodeficiency, renal disease, and peptic ulcer disease.

CHRONIC Rx

Persistent EP results from residual trophoblastic tissue or secondary implantation after conservative surgery. There is a 5% incidence of persistent EP with conservative treatment.

DISPOSITION

If diagnosed and treated early (before rupture), prognosis is excellent for good recovery. Monitor QhCG weekly until negative. Use reliable contraception until hCG is negative. With subsequent pregnancies, follow QhCG and perform early ultrasound to confirm IUP. There is a 12% recurrence rate for EP.

REFERRAL

Should obtain gynecologic consultation if EP is suspected.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Ectopic Pregnancy (Patient Information)
Spontaneous Miscarriage (Related Key Topic)
Vaginal Bleeding During Pregnancy (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

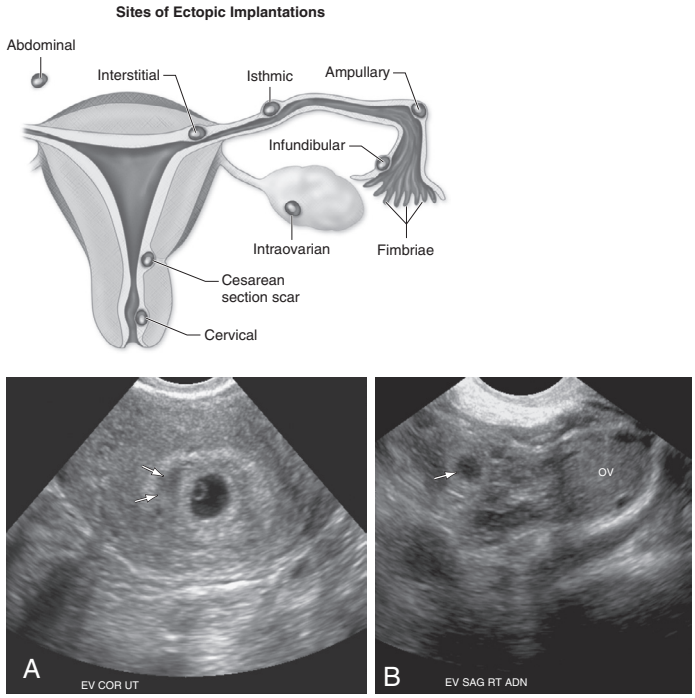

FIGURE E1-5 *Top*, Schematic drawing depicting implantation sites of ectopic pregnancies. **A** and **B,** Heterotopic pregnancy. This pregnant patient presented with vaginal bleeding at 5 to 6 wk of gestational age. **A,** Transverse transvaginal ultrasound (TVUS) image of the uterus reveals an intrauterine gestational sac containing a yolk sac. Note small subchorionic hemorrhage (*arrows*), most likely accounting for the vaginal bleeding. **B,** Sagittal TVUS image of the right adnexa reveals an echogenic tubal ring (*arrow*) clearly separate from the right ovary (*OV*), which was surgically confirmed to be an ectopic pregnancy. (From Fielding JR et al: *Gynecologic imaging*, Philadelphia, 2011, Saunders.)

SUGGESTED READINGS

Barnhart KH: Ectopic pregnancy, *N Engl J Med* 361:379–387, 2009.

Della-Giustina D, Denny M: Ectopic pregnancy, *Emerg Med Clin North Am* 21(3):565, 2003.

Gracia CR, Barnhart KT: Diagnosing ectopic pregnancy: decision analysis comparing six strategies, *Obstet Gynecol* 97(3):464, 2001.

BASIC INFORMATION

DEFINITION

Ehlers-Danlos syndrome (EDS) refers to a group of inherited, clinically variable, and genetically heterogeneous connective tissue disorders. EDS is characterized by skin hyperextensibility, skin fragility, joint laxity, and joint hyperextensibility.

ICD-9CM CODES
756.83 Ehlers-Danlos syndrome
ICD-10CM CODES
Q79.6 Ehlers-Danlos syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- The prevalence of EDS is estimated to be approximately one in 5000 births, although it is somewhat higher in African Americans.
- There are several distinct forms of EDS (see Table EE1-3).
- Classic and hypermobility EDS are most prevalent. Classic EDS accounts for approximately 80% of reported cases.
- Vascular EDS is the most dangerous because it is associated with spontaneous rupture of medium and large arteries and hollow organs, especially the large intestine and uterus
  1. Occurs in 4% of patients with EDS.
  2. Vascular events typically occur between the third and fifth decade.
- In most cases, transmission is autosomal dominant except for some unclassified forms of EDS (previously known as type V and type IX, which are X-linked; type X is autosomal recessive).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Classic (previously types I and II): Patients have moderate-to-severe skin hyperelasticity; easy scarring and bruising ("cigarette-paper scars"); smooth, velvety skin and subcutaneous spheroids (small, firm, cyst-like nodules) along shins or forearms; hyperextensibility ("Gorlin's sign": ability to touch tip of tongue to nose); and joint hypermobility (Fig. EE1-6) and dislocation. Patients have complications such as hernias, pelvic organ prolapse, premature arthritis, and cervical insufficiency
- Hypermobility (type III): most frequent form, causing recurrent joint dislocations, often leaving a patient unable to walk. Chronic limb/joint pain is a prominent feature. Skin involvement is less prominent
- Vascular (type IV): Cardinal features include distinctive facial features (pinched nose, thin lips, tight skin, hollow cheeks, lobeless ears), acrogeria, thin, translucent skin, excessive bruising, and most importantly, rupture of vessels and viscera including arterial, intestinal, and uterine walls. Vessels most prone to rupture are abdominal aorta and its branches, great vessels of aortic arch, and large arteries

FIGURE EE1-6 Joint hyperextensibility in classic Ehlers-Danlos syndrome. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

TABLE EE1-3 Types of Ehlers-Danlos Syndrome

Type	Prior Classification	Name	Genetics	Etiology	Clinical Features
Classic	EDS I	Gravis	AD	30% of cases caused by null allele	Soft skin with scars for *COL5A1* or *COL5A2* Hypermobile joints Easy bruising
Classic	EDS II	Mitis	AD	30% of cases caused by null allele for *COL5A1* or *COL5A2*	Less severe form of type I EDS
Hypermobility	EDS III	Hypermobile	AD	Unknown	Soft skin without scars Marked mobility of large and small joints
Vascular	EDS IV	Vascular	AD (AR)	Defects of type III collagen	Translucent skin Marked bruising Ruptured arteries, uterus, bowel Normal joint mobility
Unclassified	EDS V	X-linked	XL	Unknown	Similar to EDS II
Kyphoscoliosis	EDS VI	Ocular-scoliotic	AR		Skin soft and extensible
		VIA—decreased lysyl hydroxylase case type		Defects in lysyl hydroxylase	Scoliosis Ocular fragility
		VIB—decreased lysyl hydroxylase case type		Unknown	Hypermobile joints
Arthrochalasia	EDS VII	Arthrochalasis multiplex congenita			
		VIIA—α1(I) type	AD	α1(I) DE6	Congenital hip dislocation
		VIIB—α2(I) type	AD	α2(I) DE6	Hypermobile joints
Dermatosparaxis		VIIC—enzyme deficiency	AR	Deficient procollagen *N*-proteinase	Skin soft without scars
Unclassified	EDS VIII	Periodontitis type	AD	Unknown	Generalized periodontitis Skin soft and extensible Easy bruising Hypermobile joints
Unclassified	EDS X	Fibronectin	AR	Fibronectin	Mild joint hypermobility Easy bruising Abnormal platelet aggregation

AD, Autosomal dominant; *AR,* autosomal recessive.
Modified from Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

of limbs. Spontaneous rupture of organs occurs in the sigmoid colon, spleen, liver, and uterus. Facial features are often not prominent in children, and vascular EDS is usually not diagnosed until adulthood. Vascular rupture, GI perforation, or other organ rupture are presenting signs in 70% of adults with vascular EDS; presentation is often dramatic and unexpected. Average age for first major arterial or GI complication is 23 years of age.

- Kyphoscoliotic (type VI): rare; characterized by marked muscular hypotonia, osteopenia, joint hypermobility, progressive scoliosis, ocular fragility and possible globe rupture, mitral valve prolapse, and aortic dilation.
- Arthrochalasia (types VIIA and VIIB): prominent joint hypermobility with subluxations, congenital hip dislocation, skin hyperextensibility, and tissue fragility.
- Dermatosparaxis (type VIIC): severe skin fragility with decreased elasticity, bruising, hernias.
- Unclassified types: type V: X-linked recessive, similar to classic EDS with skin fragility but less joint hypermobility and bruising. Type IX: classic characteristics. Type VIII: classic characteristics and severe periodontal disease. Type X: mild classic characteristics, mitral valve prolapse. Type XI: joint instability.

ETIOLOGY

- Defects of collagen in extracellular matrices of multiple tissues (skin, tendons, blood vessels, and viscera) underlie all forms of EDS.
- Classic EDS is associated with defects in type V collagen, corresponding to mutations of *COL5A* genes.
- Vascular EDS involves a deficiency in type III collagen, and several studies suggest that mutations of gene *COL3A1* lead to this deficiency.
- Arthrochalasia EDS results from a defect in type I collagen, caused by mutations in the *COL1A1* and *COL1A2* genes.

DIAGNOSIS

Diagnosis is based solely on clinical criteria. It is important to identify patients with vascular EDS because of the grave consequences of the disease.

- Clinical criteria for vascular EDS: two of four major diagnostic criteria establish the diagnosis; >1 minor criterion supports but is not sufficient to establish the diagnosis.
- Major criteria:
  1. Arterial rupture.
  2. Intestinal rupture.
  3. Uterine rupture.
  4. Family history of EDS.
- Minor criteria:
  1. Thin, translucent skin.
  2. Easy bruising.
  3. Characteristic facial features (thin, delicate, and pinched nose, hollow cheeks, prominent staring eyes): occur in <30% of patients with vascular EDS.
  4. Small joint hypermobility.
  5. Skin hyperextensibility.
  6. Spontaneous pneumothorax/hemothorax.
  7. Tendon or muscle rupture.
  8. Early-onset varicose veins.
  9. Carotid-cavernous fistula.
  10. Talipes equinovarus (clubfoot).

DIFFERENTIAL DIAGNOSIS

- Marfan's syndrome.
- Osteogenesis imperfecta.
- Autosomal dominant cutis laxa.
- Familial joint hypermobility.

WORKUP

Diagnosis is based solely on clinical criteria.

LABORATORY TESTS

- Biochemical and gene testing for known molecular defects recommended to confirm the diagnosis in vascular EDS.
- Plain radiographs may reveal calcified nodules along the shin or forearms corresponding to the subcutaneous spheroids.
- Echocardiogram can identify mitral valve prolapse and aortic dilation.

TREATMENT

- All patients should receive genetic counseling about the mode of inheritance of their EDS.
- Management of most skin and joint problems should be conservative and preventive. Joint hypermobility and pain in EDS usually does not require surgical intervention. Physical therapy to strengthen muscles is helpful. Surgical repair and tightening of joint ligaments can be performed, but ligaments frequently will not hold sutures. Surgical intervention should be considered on an individual basis.
- For patients with vascular EDS:
  1. Special surgical care is required because of increased tissue friability.
  2. Patients should be advised to avoid contact sports.
  3. Elevated blood pressure should be aggressively treated with beta-blockers, given the risk of arterial dissection.
  4. A β_1-selective agent with partial β_2-agonist activity, celiprolol, has been shown to decrease the incidence of arterial rupture or dissection in a small study.
  5. In the case of bleeding, desmopressin should be considered as it stimulates release of endothelial von Willebrand's factor and of aminocaproic acid to counteract fibrinolysis.

DISPOSITION

Prognosis varies according to type of EDS. For vascular EDS:

- 25% will have a complication by age 25 yr; >80% will have a complication by age 40 yr.
- Most vascular complications consist of arterial dissections.
- Vascular events typically occur between the third and fifth decade.
- Median age of survival is 48 years. Most deaths are related to arterial rupture.

REFERRAL

Referral to dermatology for skin biopsy to confirm diagnosis of vascular EDS and to cardiology, orthopedic surgery, general surgery, and physical therapy as needed.

PEARLS & CONSIDERATIONS

- Women with vascular EDS should be counseled about the risk of uterine, intestinal, and arterial rupture.
  1. Pregnancy is associated with up to a 25% mortality rate; however, successful childbirth is possible.
  2. There is a 50% chance that the child will be affected.
- Family members of patients with EDS should be recommended for evaluation for EDS and genetic testing/counseling.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Ehlers-Danlos Syndrome (Patient Information)

AUTHOR: **IRIS L. TONG, M.D.**

SUGGESTED READINGS

Bergqvist D, Bjorck M, Wanhainen A: Treatment of vascular Ehlers-Danlos syndrome: a systematic review, *Ann Surg* 258(2):257–261, 2013.

Beridze N, Frishman W: Vascular Ehlers-Danlos syndrome: pathophysiology, diagnosis, and prevention and treatment of its complications, *Cardiol Rev* 20(1):4–7, 2012.

Callewert B et al.: Ehlers-Danlos syndromes and Marfan syndrome, *Best Pract Res Clin Rheumatol* 22(1):165–189, 2008.

Fernandes NF, Schwartz RA: A "hyperextensive" review of Ehlers-Danlos syndrome, *Ped Dermatol* 82:242, 2008.

Gawthrop G et al.: Ehlers-Danlos syndrome, *BMJ* 335:448–450, 2008.

Ong K et al.: Celiprolol increases the elasticity of the radial artery in vascular Ehlers-Danlos syndrome: a randomized controlled clinical trial, *Arch Cardiovas Dis* 102(Suppl 1):S99, 2009.

Parapia LA, Jackson C: Ehlers-Danlos syndrome–a historical review, *Br J Haematol* 141:32–35, 2008.

Pyeritz R: Ehlers-Danlos syndrome, *N Engl J Med* 342(10):730, 2000.

Ehrlichiosis and Anaplasmosis PTG

BASIC INFORMATION

DEFINITION

Human monocytic ehrlichiosis (HME) and human granulocytic anaplasmosis (HGA) are tick-borne rickettsial diseases. HGA was formerly known as human granulocytic ehrlichiosis (HGE). Table E1-4 describes the agent, vector, and geographic prevalence of these diseases.

SYNONYMS

Human granulocytic ehrlichiosis (HGE)
Ehrlichiosis
Human monocytic ehrlichiosis (HME)
Human granulocytic anaplasmosis (HGA)
Anaplasmosis
Ehrlichia phagocytophila
Anaplasma phagocytophilum

ICD-9CM CODES
082.8 Other tick-borne rickettsiosis
ICD-10CM CODES
A77.40 Ehrlichiosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Highest overall incidence in Rhode Island (36.5 per 1 million), New York, New Jersey, Connecticut, Wisconsin, Minnesota, and northern California; >3000 cases identified in the United States since 2006.
PREDOMINANT SEX: Males outnumber females by 2 to 1.
PREDOMINANT AGE: Most severe disease 50 to 70 yr
PEAK INCIDENCE: Occurs throughout the year, with peak incidence between May and July and again in November.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most common initial symptoms
  1. Fever
  2. Chills, rigor
  3. Headache
  4. Myalgia
- Subsequent symptoms
  1. Anorexia, nausea
  2. Arthralgia
  3. Cough
  4. Confusion (meningoencephalitis in 20% of patients with HME)
  5. Abdominal pain
  6. Rash (erythematous to pustular) <30% in HME, uncommon in HGA
- Complications
  1. Hepatitis
  2. Interstitial pneumonitis; acute respiratory distress syndrome
  3. Renal and respiratory failure
  4. Demyelinating polyneuropathy
  5. Toxic shock–like syndrome
  6. Life-threatening opportunistic infections

ETIOLOGY

- The causative agents are *Ehrlichia chaffeensis* and *Anaplasma phagocytophilum*
- Vector
  1. Almost certainly tick-borne, recently confirmed to be rarely transmitted by infected blood (including nosocomial infection).
  2. Transmitted by *Ixodes scapularis* in the northeastern states and *Amblyomma americanum* in the south central, southeastern, and mid-Atlantic states. Fig. E1-7 illustrates the life cycles of human monocytic ehrlichiosis (HME, with *Ehrlichia chaffeensis*) and human granulocytic ehrlichiosis (anaplasmosis).
  3. Tick exposure reported in >90% of patients, with ~60% reporting tick bite.
- Mammalian host: deer, horses, dogs, white-footed mice, cattle, sheep, goats, bison
- Host inflammatory and immune responses define final spectrum of disease beyond granulocytes, including hepatitis, interstitial pneumonitis, and nephritis with mild azotemia
- Between 6% and 21% of patients with HGE also have serologic evidence of other *Ixodes* spp. tick-borne diseases: Lyme disease or babesiosis
- Recovery is usual outcome; fatality rate of HGE is about 1%
- ICU care required: 7%

TABLE E1-4 Ehrlichioses and Anaplasmoses

Disease	Agent	Vector	Geographic Repartition
American monocytic ehrlichiosis	*Ehrlichia chaffeensis*	*Amblyomma americanum*	South central, southeastern, mid-Atlantic coastal states
Human granulocytic ehrlichiosis	*Anaplasma phagocytophilum*	*Ixodes ricinus*	Europe, China
		Ixodes scapularis	Northeast, upper Midwest, northern California
E. ewingii	*Ehrlichia ewingii*	*Amblyomma americanum*	South central, southeastern, mid-Atlantic coastal states
Japanese monocytic ehrlichiosis	*Neorickettsia sennetsu*	Helminth of the gray mullet?	Japan
E. canis	*Ehrlichia canis*	*Rhipicephalus sanguineus*	Venezuela

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rocky Mountain spotted fever, Colorado tick fever, Q fever, relapsing fever
- Babesiosis
- Leptospirosis
- Lyme disease
- Tularemia
- Typhoid fever, paratyphoid fever
- Brucellosis
- Viral hepatitis
- Meningococcemia
- Infectious mononucleosis
- Hematologic malignancy
- TTP (thrombotic thrombocytopenic purpura)
- Table E1-5 describes clinical clues suggesting a diagnosis of a tick-borne illness manifesting as a nonspecific febrile illness

WORKUP

- Acute blood samples for Giemsa-stained smears
- CBC (leukopenia, thrombocytopenia), liver function (elevated), BUN/creatinine
- Acute serum samples for serology. Antibodies are seldom detected at time of acute infection (they usually appear 2-4 weeks following clinical illness).
- Chest radiograph examination
- Bone marrow rarely needed

LABORATORY TESTS

- Polymerase chain reaction (PCR) to facilitate early diagnosis: detection of *Ehrlichia* DNA in blood or CSF by PCR
- Giemsa-stained smear demonstrating morulae of the organism within granulocytes (sensitivity 20% to 75%) (Fig. E1-8)
- CBC: progressive leukopenia and thrombocytopenia with nadir near day 7
- C-reactive protein concentration is generally elevated
- Liver function tests (LFTs): increase in hepatic transaminases, lactate dehydrogenase, and alkaline phosphatase
- Elevated plasma creatinine concentration may be seen
- Serologic titer (IFA) >80 or fourfold increase in titer to *E. equi* antigen
- Culture on the first 7 days of illness; not readily available in most clinical laboratories

IMAGING STUDIES

- Chest radiograph examination to show interstitial pneumonitis (unusual)
- MRI of the brain

TREATMENT

ACUTE GENERAL Rx

- Immediate therapy to limit extent of acute illness and complication
- Doxycycline: 100 mg twice a day for 7 to 14 days is therapy of choice for adults and children >8 yr (4 mg/kg/day in 2 divided doses).

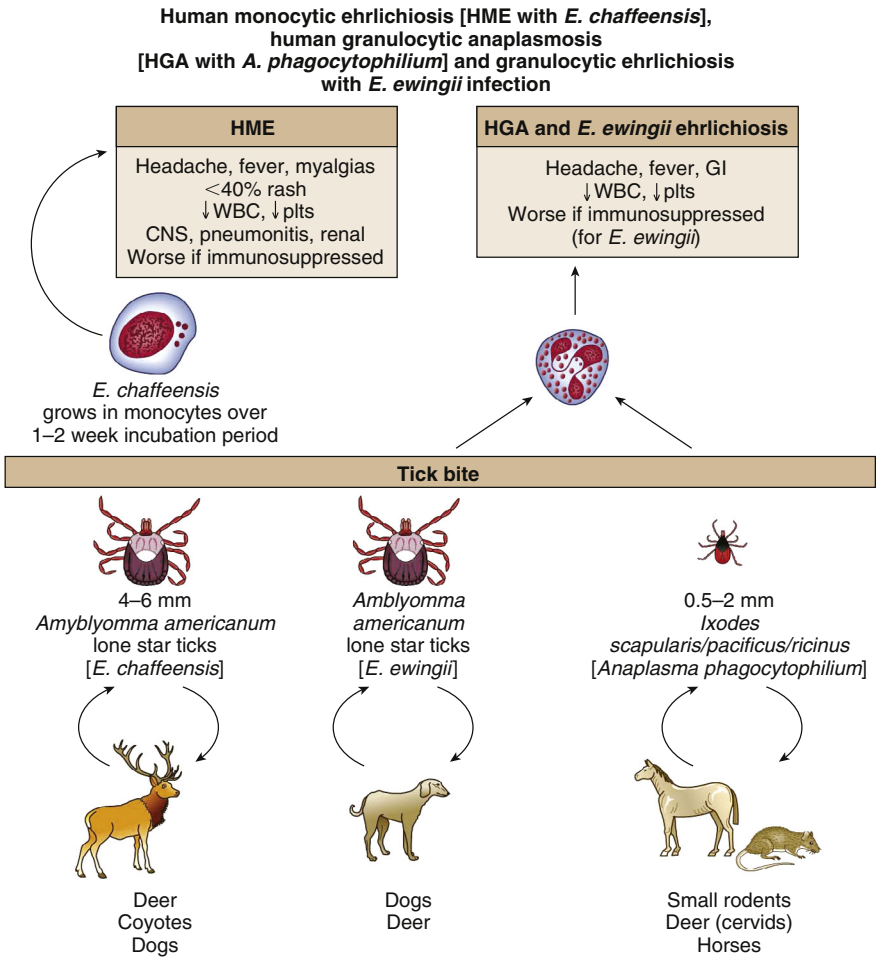

FIGURE E1-7 Life cycles of human monocytic ehrlichiosis (HME, with *Ehrlichia chaffeensis*) and human granulocytic ehrlichiosis (anaplasmosis, HGA with *Anaplasma phagocytophilum*) or infection with *E. ewingii*. *CNS*, Central nervous system; *GI*, gastrointestinal; *WBC*, white blood cell count. (From Dumler JS: Ehrlichioses and anaplasmosis. In Guerrant RL, Walker DH, Weller PF (eds) *Tropical infectious diseases: principles, pathogens and practice*, 3rd ed, Philadelphia, 2011, Elsevier, pp. 339-343.)

TABLE E1-5 Clinical Clues (History, Physical Examination, or Laboratory) Suggesting the Diagnosis of a Tick-Borne Illness Manifesting as a Nonspecific Febrile Illness*

Disease	Clues
Anaplasmosis	Faint rash possible Low white blood cell or platelet count Elevated hepatic transaminases
Babesiosis	Findings of hemolysis History of splenectomy Presence of faint rash, hepatomegaly, or splenomegaly
Lyme disease	Careful skin examination for any rash consistent with erythema migrans Bradycardia from heart block Associated seventh nerve palsy or lymphocytic meningitis
Colorado tick fever	Saddle-back fever curve
Rocky Mountain spotted fever	Maculopapular or petechial rash Normal white blood cell count or low platelet count Hyponatremia Peripheral edema
Relapsing fever	Recurring episodes of fever with afebrile intervals
Tularemia	Acrally located ulcer Regional lymphadenopathy Possible associated pneumonia

*Apart from an epidemiologic context suggesting a tick-borne disease.

- Rifampin: 300 mg twice a day for 7 to 10 days can be used in pregnancy and for children <8 yr at 10 mg/kg twice per day
- Most patients defervesce within 24 to 48 hr given appropriate treatment.

PROGNOSIS

Poor prognostic indicators include:

- Advanced age
- Concomitant chronic illness (such as diabetes mellitus, collagen-vascular disease)
- Lack of diagnosis recognition
- Delayed onset of specific antibiotic therapy
- Concomitant HIV or organ transplant status

DISPOSITION

- Repeat CBC every 2 to 4 wk until normal.
- A new pathogenic *Ehrlichia* species, close relative of *E. muris* has been identified in Minnesota and Wisconsin. Organism-specific PCR and serologic testing can be used for identification.

REFERRAL

For consultation with infectious diseases specialist in suspected cases

PEARLS & CONSIDERATIONS

COMMENTS

- Duration of time tick must be attached to produce illness as few as 4 hr
- Delay in antibiotic treatment results in poorer outcome. Antibiotic treatment should be initiated as soon as infection is suspected.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Anaplasmosis (Patient Information)

AUTHOR: **PATRICIA CRISTOFARO, M.D.**

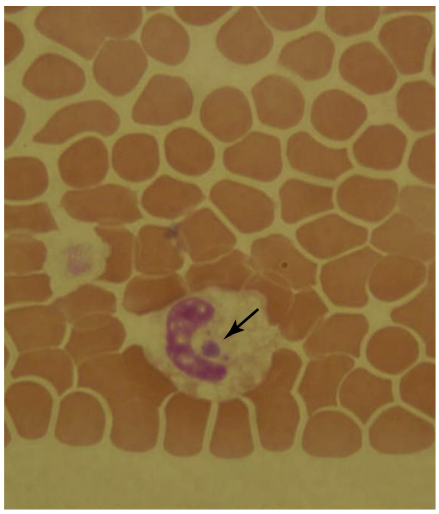

FIGURE E1-8 White blood cells infected with the agent of human granulocytic ehrlichiosis (*Anaplasma phagocytophilum*). (Courtesy Dr. Daniel Caplivski, Division of Infectious Diseases, Mount Sinai School of Medicine.)

SUGGESTED READINGS

Bakken JS et al.: Human granulocytic anaplasmosis, *Infect Dis Clin North Am* 22:433, 2008.

Bakken JS et al.: Human granulocytic ehrlichiosis, *Clin Infect Dis* 31:554, 2000.

Blanco JR et al.: Human granulocytic ehrlichiosis in Europe, *Clin Microbiol Infect* 8:763, 2002.

CDC: Summary of Notifiable Diseases-US, 2010, *MMWR Rep* 59:1, 2012.

CDC: Anaplasmosis and ehrlichiosis–Maine 2008, *MMWR Rep* 58:1033, 2009.

CDC: Anaplasma phagocytophilum transmitted through blood transfusion–Minnesota, 2007, *MMWR Rep* 57:1145, 2008.

Chapman AS et al.: Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis–US, *MMWR Recomm Rep* 55:1, 2006.

Dhand A et al.: Human granulocytic anaplasmosis during pregnancy: case series and literature review, *Clin Infect Dis* 45:589, 2007.

Dumier JS et al.: Ehrlichioses in humans: epidemiology, clinical presentation, diagnosis, and treatment, *Clin Infect Dis* 45(Suppl 1):S45, 2007.

Krause PJ et al.: Successful treatment of human granulocytic ehrlichiosis in children using rifampin, *Pediatrics* 112:e252, 2003.

Moss WJ, Dumler JS: Simultaneous infection with Borrelia burgdorferi and human granulocytic ehrlichiosis, *Pediatr Infect Dis J* 22(1):91, 2003.

Pritt B et al.: Emergence of a new pathogenic *Ehrlichia* species, Wisconsin and Minnesota, 2009, *N Engl J Med* 365:422–429, 2011.

Singh-Behl D et al.: Tick-borne infections, *Dermatol Clin* 21(2):237, 2003.

Walls JJ et al.: Improved sensitivity of PCR for diagnosis of human granulocytic ehrlichiosis using epank1 genes of *Ehrlichia phagocytophilia*-group ehrlichiae, *J Clin Microbiol* 38:354, 2000.

Weil AA et al.: Clinical findings and diagnosis in human granulocytic anaplasmosis: a case series from Massachusetts, *Mayo Clin Proc* 87(3):233–239, 2012.

Wormser GP et al.: The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America, *Clin Infect Dis* 43:1089, 2006.

Ejaculation and Orgasm Disorders PTG

BASIC INFORMATION

DEFINITION

Clinically significant disorders of ejaculation include failure of emission, retrograde ejaculation, premature ejaculation, delayed ejaculation, painful ejaculation, hematospermia, and anorgasmia. Failure of emission occurs when semen is not propulsed into the urethra during orgasm, resulting in a dry ejaculate. Retrograde ejaculation is a backward flow of semen into the bladder. Premature ejaculation refers to ejaculation that occurs sooner than desired, either before or shortly after penetration, causing distress to either one or both partners. Hematospermia is the appearance of blood in the ejaculate. Anorgasmia is the inability to achieve orgasm in a timely manner.

SYNONYMS

Ejaculatory dysfunction
Retarded or delayed ejaculation
Early or rapid ejaculation
Inhibited ejaculation
Anejaculation

ICD-9CM CODES
608.82 Hematospermia
608.87 Ejaculation, retrograde
608.89 Painful ejaculation
306.59 Ejaculation, psychogenic
302.75 Ejaculation, premature
302.74 Orgasm inhibited male (psychosexual)

ICD-10CM CODES
N53.14 Retrograde ejaculation
R36.1 Hematospermia
F45.8 Other somatoform disorders
F52.4 Premature ejaculation
F52.32 Male orgasmic disorder

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Not well understood, due to variability in definitions and reporting.
PEAK INCIDENCE: Not well understood.
PREVALENCE: Premature ejaculation is the most prevalent male sexual complaint, affecting 20%-30% of men, and may be primary (lifelong) or acquired. Retarded or delayed ejaculation is the least common, least studied, and least understood of the male sexual dysfunctions.
PREDOMINANT SEX AND AGE: These disorders have been reported among men aged 18-70 years.
GENETICS: No known genetic predisposition.
RISK FACTORS: Men with ejaculatory dysfunction of any type usually indicate higher levels of relationship stress, sexual dissatisfaction, anxiety about sexual performance, and general health issues, compared to sexually functional men.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Failure of emission: no ejaculate is produced during orgasm. Physical findings may reveal nervous system dysfunction (e.g., spinal cord injury); may present with infertility (e.g., ejaculatory duct obstruction).
- Retrograde ejaculation: little or no ejaculate is expelled out of the urethra at orgasm. Patients may report cloudy postcoital urine. Physical examination is usually normal; may present with infertility.
- Premature ejaculation: ejaculation occurs sooner than desired, either before or shortly after penetration. Physical examination is normal. Up to 30% of patients may report concomitant erectile dysfunction.
- Delayed ejaculation: ejaculation requires prolonged sexual stimulation, often 30 minutes or longer. Physical examination is normal.
- Painful ejaculation: perineal, scrotal, or testicular pain during or shortly after ejaculation. Physical examination may demonstrate pain on examination of external genitalia, or with digital rectal examination; may present with infertility.
- Hematospermia: reddish-brown ejaculate, usually painless. Physical findings are usually unremarkable; not associated with malignancy.
- Anorgasmia: patient is not able to achieve orgasm despite appropriate stimulation.

ETIOLOGY

- Retrograde ejaculation may be caused by anatomic abnormalities of the bladder neck, or nerve injury affecting the bladder neck sphincter.
- Retrograde ejaculation or failure of emission may result from functional abnormalities, such as spinal cord injury, diabetes mellitus, retroperitoneal surgery, transurethral prostate surgery, urethral strictures, alpha-blocker therapy, antipsychotics, multiple sclerosis, and peripheral neuropathy.
- Premature and delayed ejaculation represent opposite ends of the spectrum of ejaculatory disorders. The underlying etiology is complex and multifactorial, and includes organic and psychogenic contributions.
- Causes of painful ejaculation may be infectious (e.g., epididymo-orchitis, urethritis, prostatitis), obstructive (e.g., vasectomy, prostatectomy, hernia repair), or psychological.
- Hematospermia may be idiopathic, secondary to prolonged abstinence, or due to infection or inflammation of the genitourinary tract.
- Anorgasmia may be caused by spinal cord injury, psychological factors, dysfunctional sexual techniques, or medications, particularly serotonin reuptake inhibitors.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Erectile dysfunction
- Low seminal fluid volume attributable to hypogonadism or ejaculatory duct obstruction
  1. Inflammatory disorders of the genitourinary tract
  2. Hypoactive sexual desire

LABORATORY TESTS

- Fig. E1-9 describes an algorithm for the evaluation of the patient with low-volume or absent (aspermia) ejaculate.
- For a low-volume ejaculate, post-ejaculate urine should be evaluated for the presence of spermatozoa to differentiate failure of emission from retrograde ejaculation.
- Hematuria, in the setting of hematospermia or painful ejaculation, may signal an underlying inflammatory disorder or a malignancy and should prompt a complete evaluation.
- A fasting blood glucose test may be considered if diabetes is suspected as a cause of lack of emission or retrograde ejaculation.
- Urinalysis, urine culture, and screening for sexually transmitted diseases, when indicated, can rule out an infectious etiology of painful ejaculation.

IMAGING STUDIES

Transrectal ultrasonography or pelvic MRI can rule out ejaculatory duct obstruction or absence of the seminal vesicles.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Retrograde ejaculation and failure of emission do not require treatment unless fertility is desired.
- In the setting of retrograde ejaculation, viable sperm can be recovered from the post-ejaculate urine and used for intrauterine insemination or in vitro fertilization.
- Premature ejaculation can improve with psychotherapy and behavioral interventions (e.g., "coronal squeeze" or "start-and-stop" technique) and effective partner communication. These approaches may be more effective when combined with pharmacologic therapy.
- Idiopathic hematospermia may be followed expectantly and is usually self-limited to 10 to 15 ejaculations.
- Anorgasmia caused by serotonin reuptake inhibitors usually improves with withdrawal of the medication. Sexual therapy and counseling can improve anorgasmia caused by dysfunctional sexual techniques or psychological issues. Vibratory or electrical stimulation of emission is helpful in selected cases.

ACUTE GENERAL Rx

- Retrograde ejaculation: pharmacologic therapy is only effective in patients without an anatomic disturbance of the bladder neck. Sympathomimetic medications (phenylpropanolamine, ephedrine, pseudoephedrine) and imipramine may be useful in converting retrograde ejaculation to antegrade ejaculation.
- Failure of emission: may be converted to retrograde ejaculation by oral sympathomimetic therapy, as listed above.
- Premature ejaculation: selective serotonin reuptake inhibitors (SSRI) (e.g., sertraline, fluoxetine) and the tricyclic antidepressant clomipramine can successfully delay ejaculation when taken daily. Dapoxetine, a short-acting SSRI,

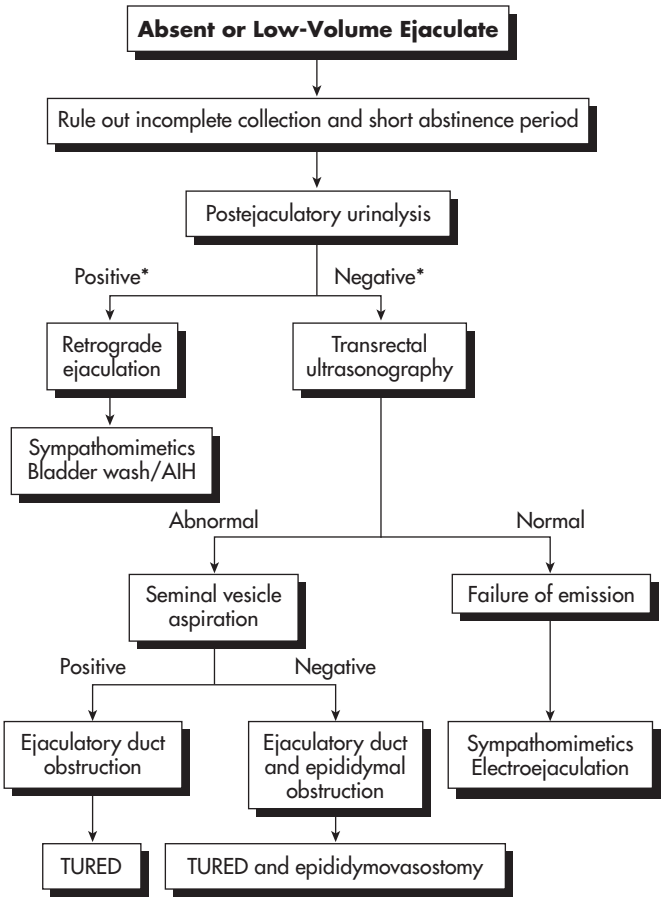

FIGURE E1-9 Algorithm for the evaluation of the patient with low-volume or absent (aspermia) ejaculate. *AIH*, Artificial insemination using husband's sperm; *TURED*, transurethral resection of the ejaculatory ducts. *See text. (From Wein AJ; Male infertility. In Wein AJ et al (eds): *Campbell-Walsh Urology*; Philadelphia, 2007, Elsevier.)

may be used as an "on-demand" treatment for premature ejaculation. Topical anesthetics such as lidocaine cream and topical sprays have been used with variable success. The use of phosphodiesterase inhibitors (PDE5i) (e.g., sildenafil, vardenafil, tadalafil) with SSRIs may be beneficial in men with concomitant erectile dysfunction and premature ejaculation.

- Antimicrobial treatment (if indicated), NSAIDs, and muscle relaxants may help decrease discomfort associated with painful ejaculation.
- The use of the pharmacologic therapies listed above for the treatment of various disorders of ejaculation is strictly off label and does not carry FDA approval.

CHRONIC Rx

Rarely, painful ejaculation due to long-standing obstructive causes may show improvement with surgical intervention (e.g., vasectomy reversal).

The pharmacologic therapies listed previously can also be used for the chronic treatment of disorders of ejaculation and orgasm.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

- A variety of nutritional supplements and herbs have been used for the treatment of erectile dysfunction, but their benefit for the specific treatment of ejaculation and orgasm disorders is unknown.
- Acupuncture and traditional Chinese medicine may be helpful in treating underlying hormonal imbalances.
- Yoga and meditation can reduce the effects of stress and relieve anxiety about sexual dysfunction.
- Therapeutic massage can decrease stress.

DISPOSITION

Prognosis varies with etiology. Ejaculatory dysfunction attributable to sexual techniques or psychological issues can improve with psychotherapy. Pharmacologic treatment is helpful in treating premature, retrograde, or painful ejaculation.

REFERRAL

All fertility issues and suspected anatomic problems should be referred to a urologist. Professional psychotherapy should be considered for appropriate patients.

PEARLS AND CONSIDERATIONS

COMMENTS

Ejaculatory and orgasmic disorders are common male sexual dysfunctions and include failure of emission, retrograde ejaculation, premature ejaculation, delayed ejaculation, painful ejaculation, hematospermia, and anorgasmia

PREVENTION

Preventing sexually transmitted infections and treating other inflammatory disorders of the genitourinary tract may be of some benefit in reducing the incidence of these sexual disorders.

PATIENT/FAMILY EDUCATION

These sexual disorders can exert a significant psychological burden on affected men and their partners. A combination of pharmacologic and nonpharmacologic therapies, including a urologic and psychologic evaluation, when indicated, may be helpful in the treatment of these complaints.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Erectile Dysfunction (Patient Information)
Erectile Dysfunction (Related Key Topic)

AUTHORS: **AKANKSHA MEHTA, M.D.,** and **MARK SIGMAN, M.D.**

SUGGESTED READINGS

McMahon CG et al.: Standard operating procedures in the disorders of orgasm and ejaculation, *J Sex Med* 10:204–229, 2013.

Mulhall J.P.. Premature ejaculation. In: (Wein A et al., editor) Campbell-Walsh urology. ed 10 Saunders: Philadelphia.

Rowland D et al.: Disorders of orgasm and ejaculation in men, *J Sex Med* 7:1668–1686, 2010.

Serefoglu EC et al.: An evidence-based unified definition of lifelong and acquire premature ejaculation: report of the second International Society for Sexual Medicine Ad Hic Committee for the Definition of Premature Ejaculation, *J Sex Med* 11:1423–1441, 2014.

BASIC INFORMATION

DEFINITION

Injuries or wounds that occur as a result of contact with an electrical current or lightning.

ICD-9CM CODES
994.8 Electrical shock, nonfatal
ICD-10CM CODES
W87 Exposure to unspecified electric current
W86 Exposure to other specified electric current
W85 Exposure to electric transmission lines
X33 Victim of lightning

EPIDEMIOLOGY & DEMOGRAPHICS

- Causes approximately 1000 deaths annually, with two thirds occurring in persons between ages 15 and 40 yr.
- Most electrical injuries in children occur at home (e.g., oral burns from electrical appliances).
- Most electrical injuries in adults are occupationally related. They rank fifth as a cause of occupational death.
- Account for 4% to 6.5% of all admissions to burn units.
- Lightning strikes kill on average 100 people annually.
  1. Eight of every 10 lightning strike victims are male; 75% of lightning deaths in the United States occur in the South and Midwest.
  2. 25% of lightning deaths are work related.
- Electronic weapons (stun gun and Taser) are capable of causing fatal cardiac arrhythmias.
- Table E1-6 compares lightning injuries with high-voltage electrical injuries.

TABLE E1-6 Lightning Injuries Compared with High-Voltage Electrical Injuries

Factor	Lightning	High Voltage
Energy level	30 million volts, 50,000 Å	Usually much lower*
Time of exposure	Brief, instantaneous	Seconds
Pathway	Flashover, orifice	Deep, internal
Burns	Superficial, minor	Deep, major injury
Renal	Rare myoglobinuria or hemoglobinuria	Myoglobinuric renal failure common
Fasciotomy	Rarely if ever necessary	Common, early, and extensive
Blunt injury	Explosive thunder effect	Falls, being thrown

*Range is 500 V up to millions of volts in transmission lines.
From Auerbach P: *Wilderness medicine, expert consult* Premium Edition—Enhanced Online

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Cognitive changes: depending on the extent of injury, the patient may be unconscious, seizing, or confused and unable to present a history.
- Extensive skin burns (>10% of the body surface).
  1. Located over the entry and exit sites (Fig. E1-10).
  2. Most common entry sites are the hands and skull.
  3. Most common exit sites are the heels.
  4. "Kissing burns" over the flexor creases.
  5. Oral burns are common in children; bleeding from the labial artery may present 7 to 10 days after the injury.
  6. Charring at the contact site (Fig. EE1-11).
- Asystole or ventricular fibrillation may be the initial cardiac rhythm.
- Bone fractures and periosteal burns.
- Compartment syndrome from severe muscle tissue damage.
- Headaches, memory disturbances.
- Weakness and paresthesias.
- Otologic injury, conductive hearing loss from tympanic membrane rupture or ossicular disruption.
- Rhabdomyolysis and myoglobin-induced acute tubular necrosis.
- Vascular injury from coagulation of small vessels or compartment syndrome.
- Box EE1-1 summarizes the immediate and delayed effects of lightning injuries.

ETIOLOGY

- Electricity causes tissue injury by converting electrical energy into heat or by blunt trauma from being thrown from the electrical source or from continuous muscle contraction (tetany).
- The effects of electricity are determined by seven factors: type of current, amount of current, pathway of current, duration, area of contact, resistance of the body, and voltage.
- Tissue damage is greater with higher voltage and longer duration of contact.

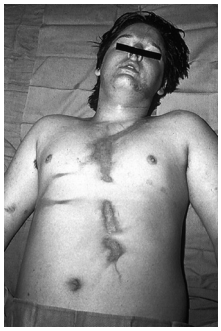

FIGURE E1-10 The arborescent current markings on the face, neck, and anterior trunk of this young patient, which are characteristic of lightning injury, healed without the need for grafting. Note the focal lesions on the right arm, indicating the spread of the current that produced the marks on the right anterolateral aspect of the chest wall. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

- Direct current (DC) contact causes a single muscle contraction, throwing the patient away from the source. Alternating current (AC) contact precipitates a tetanic contraction, not allowing the patient to withdraw from the source and prolonging the duration of contact. AC contact is more ominous than DC contact.
- Electrical injuries are arbitrarily divided into high-voltage (>1000 volts) and low-voltage (<1000 volts) burns. Low-voltage burns involve almost exclusively either the hands or oral cavity. High-voltage injuries have a wide variety of systemic manifestations.
- The entry and exit path of the electrical current determines which tissues are affected.
- Box E1-2 describes the mechanisms of lightning injury.

DIAGNOSIS

WORKUP

Physical examination may not reveal the extent of damage that has occurred. Detailed testing to determine the extent of internal organ damage is indicated. In lightning injuries, male victims may have scrotal (on the undersurface of the scrotum) and penile burns, which may often be overlooked. Hemorrhage behind the eardrum with or without perforation is not uncommon. An otoscopic examination is indicated in all lightning strike victims.

LABORATORY TESTS

- Complete blood count.
- Blood chemistry profile including electrolytes.
- Blood urea nitrogen and creatinine.
- Arterial blood gas analysis.
- Myoglobin.
- Creatinine kinase with isoenzyme fractionation.
- Urinalysis, including screening for myoglobinuria.
- Liver function tests.
- Type and cross-match.
- ECG.

IMAGING STUDIES

- Radiographs: any suspicious area for bone fractures.
- CT scan of the head and cervical spine in patients with suspected head injury, coma, or neurologic deficit.

TREATMENT

NONPHARMACOLOGIC THERAPY

- At the scene: ensure the electrical power source of injury is turned off before approaching patients.
- Basic and advanced cardiac life support with cervical spine precautions. Prolonged cardiopulmonary resuscitation should be undertaken regardless of the initial cardiac rhythm.
- Cardiac monitoring.
- Oxygen.
- Tetanus prophylaxis.

BOX E1-3 Myths Commonly Cited as Facts in Litigation

These apply to electrical injury as well as lightning injury.

Behavior of Current in the Body

- Current seeks earth.
- Current seeks the path of lowest resistance.
- Nerve tissue is a good conductor, or alternatively, current is preferentially conducted by nerve tissue.
- When a person touches a source of potential, current flows through the skin to other parts of the skin in contact with the same conductor (i.e., current passage is local only).

The Severity of Electric Shock

Myth: If the following are absent, the shock cannot be severe and no deleterious effect can result:

- Being thrown (i.e., if a person is not thrown, the shock is not severe).
- Burns (i.e., if burns are not present, the shock is not severe).
- If the only surface change is a blister, the shock was not severe.
- Entry and exit wounds:
  - Must be present.
  - Demonstrate the current path.
  - If not present, indicate no shock occurred.
- Fuses being blown (i.e., if a fuse does not blow, the shock is not severe enough to harm a victim).
- Low voltage cannot harm.
- Electroconvulsive therapy does not give long-term post–electric-shock symptoms (also false), so any other electric shock cannot be harmful.

Investigations

- If computed tomography (CT) and magnetic resonance imaging (MRI) scans are normal, there are no injuries.
- Negative investigations (e.g., nerve conduction study, electroencephalogram, CT, MRI) mean a victim has not sustained an electric shock.
- Neuropsychological testing is objective and easily interpreted.
- Burns of electrical origin can be distinguished on histologic examination.

Remote Symptoms

- Remote symptoms do not exist.
- Remote symptoms are proportional to the size of the shock.
- Symptoms of the shock that are not present immediately after the shock are not related to it.
- A person getting remote symptoms was psychologically vulnerable all the time.

Miscellaneous

- Litigation increases the potency of the claimed symptoms. Corollary: resolving litigation terminates symptoms.
- Medical specialists understand electricity or lightning.
- Electrical experts can predict lightning or electrical injury.
- A diagnosis of depression, post-traumatic stress disorder, adjustment disorder, and so on negate an electrical injury causation.
- Residual current devices (RCDs) eliminate the possibility of all shocks. Corollary: a shock occurring when an RCD breaks the circuit cannot be severe.

(From Auerbach P: *Wilderness medicine, expert consult* Premium Edition—Enhanced Online Features and Print, Philadelphia, 2012, Saunders, Elsevier.)

BOX E1-2 Mechanisms of Lightning Injury

Electrothermal Effects

1. Direct strike.
2. Contact potential.
3. Side flash, sometimes called "splash" (1 to 3 may include surface arcs over the body surface).
4. Step voltage (also termed "Earth potential rise" or "ground current").
   a. Transmitted through the ground.
   b. Surface arcing.
5. Upward streamer current (also called "fifth mechanism").

Blunt Force Trauma Effects

1. Barotrauma.
2. Concussive injury.
3. Musculoskeletal injury from muscle contraction, falls.

(From Auerbach P: *Wilderness medicine, expert consult* Premium Edition—Enhanced Online Features and Print, Philadelphia, 2012, Saunders, Elsevier.)

ACUTE GENERAL Rx

- IV fluids to maintain urine output of 50 to 100 ml/hr (IV hydration should be reassessed with central nervous system expert in patients at risk of developing cerebral edema).
- Alkalinization of the urine (sodium bicarbonate 50 mEq in 1 L of normal saline) in patients with or at risk of myoglobinuria.
- Furosemide 20 to 40 mg PO or IV and/or mannitol 12.5 g/kg/hr may be used to force diuresis.
- Seizures are treated in the standard fashion.
- Treat burns with sulfadiazine silver dressings.

CHRONIC Rx

- Hospitalization is indicated in patients with high-voltage injuries, extensive burns, central nervous system symptoms, myonecrosis (creatine kinase level more than twice normal, high serum myoglobin levels, or myoglobinuria), new cardiac arrhythmia or ECG changes, or any internal organ damage.
- Ophthalmology consultation at the follow-up to screen for cataract formation (occurs within 1 to 24 mo of a high-voltage electrical injury in 5% to 20% of patients).

DISPOSITION

- Patients with severe burns should be transferred to the regional burn center.
- Complications of electrical injuries include:
  1. Infection.
  2. Renal failure from rhabdomyolysis.
  3. Seizure disorder.
  4. Fasciotomies.
  5. Amputation.
- Delayed neurologic damage may present as ascending paralysis, amyotrophic lateral sclerosis, or transverse myelitis weeks to years after the injury.
- Vascular damage may also present in a delayed fashion.

REFERRAL

- Referrals to general surgery, burn surgery, trauma surgery, orthopedic surgery, and/or critical care specialists as appropriate in any patient that meets hospitalization criteria. Ophthalmology and ear-nose-throat specialist referral may be indicated.
- Plastic surgery is recommended in children with oral burns.

PEARLS & CONSIDERATIONS

COMMENTS

- The size of external skin burns can often underestimate the degree of internal injury.
- Lightning Strike and Electric Shock Survivors International is a support group that serves people from around the world who have sustained an electric injury (http://www.lightning-strike.org).
- Home safety education provided one to one in a clinical setting or at home, especially with the provision of safety equipment, is effective in increasing the range of safety practices.
- Box E1-3 describes myths regarding electrical and lightning injury commonly cited as facts in litigation.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Electrical Injury (Patient Information)

AUTHORS: **ROBERT M. KIRCHNER, M.D.** and **PAUL GORDON, M.D.**

SUGGESTED READINGS

Bailey B et al.: Cardiac monitoring of high-risk patients after an electrical injury: a prospective multicentre study, *Emerg Med J* 24(5):348–352, 2007.

Edlich RF et al.: Modern concepts of treatment and prevention of electrical burns, *J Long Term Eff Med Implants* 15(5):511–532, 2005.

Kendrick D et al.: Home safety education and provision of safety equipment for injury prevention, *Cochrane Database Syst Rev* 1:CD005014, 2007.

Spies C, Trohman RG: Narrative review: electrocution and life-threatening electrical injuries, *Ann Intern Med* 145(7):531, 2006.

Zafren K et al.: Lightning injuries: prevention and on-site treatment in mountains and remote areas. Official guidelines of the International Commission for Mountain Emergency Medicine and the Medical Commission of the International Mountaineering and Climbing Federation (ICAR and UIAA MEDCOM), *Resuscitation* 65(3):369–372, 2005.

BOX EE1-1 Lightning Injuries

Immediate

- Cardiac arrest and cardiac injuries.
- Pulmonary injuries.
- Neurologic signs.
- Seizures.
- Deafness.
- Confusion, amnesia.
- Blindness.
- Dizziness.
- Contusion from shock wave.
- Chest pain, muscle aches.
- Tympanic membrane rupture.
- Headache, nausea, postconcussion syndrome.

Delayed

- Neurologic symptoms and signs.
- Neuropsychological changes.
- Memory deficits.
- Attention deficit.
- Coding and retrieval problems.
- Distractibility.
- Personality changes.
- Irritability.
- Chronic pain.
- Seizures.

(From Auerbach P: *Wilderness medicine, expert consult* Premium Edition—Enhanced Online Features and Print, Philadelphia, 2012, Saunders.)

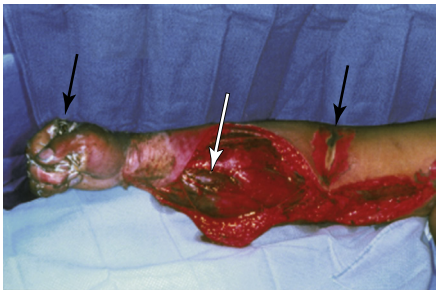

FIGURE EE1-11 Charring at the contact site in the first web space and at the site of arcing in the antecubital space *(black arrows)* of a victim of electric injury. The fixed flexion deformity of the thumb and other digits is characteristic of severe high-voltage injury to the hand and forearm. The severity of the injury is indicated by the marked edema of the forearm muscles, bulging above the cut edges of the fasciotomy incision, and by the patchy dark discoloration of the muscles of the arm and the forearm, particularly the deeper muscle exposed in the central portion of the forearm incision *(white arrow)*. (From Goldman L, Schafer AI: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Saunders.)

BASIC INFORMATION

DEFINITION

Emergency contraception (EC) can prevent pregnancy soon after unprotected intercourse, sexual assault, or failure or improper use of a birth control method. EC reduces the risk of pregnancy when used up to 120 hr (5 days) after unprotected sex but is more effective if used earlier.

MECHANISM: The primary mechanism of all EC pills is inhibition or delay of ovulation. Emergency insertion of the copper IUD may prevent fertilization or implantation.

EFFECTIVENESS: The copper IUD prevents 99% of expected pregnancies and should be considered the first line option for all women of childbearing age. Oral ulipristal acetate and levonorgestrel prevent the majority of expected pregnancies after unprotected intercourse. Ulipristal acetate is more effective than levonorgestrel, particularly in overweight and obese patients.

SYNONYMS

Morning-after pill, postcoital contraception

ICD-9CM CODES

V25.03 Emergency contraceptive counseling and treatment
V25.09 Family planning

ICD-10CM CODES

Z30.012 Encounter for prescription of emergency contraception
Z30.09 Encounter for other general counseling and advice on contraception

EPIDEMIOLOGY & DEMOGRAPHICS

Approximately 49% of all pregnancies and more than 82% of teen pregnancies in the United States are unintended. An estimated 1.7 million unintended pregnancies could be prevented annually if EC use were widespread.

DIAGNOSIS

LABORATORY TESTS

- If there is doubt about whether a patient is already pregnant from intercourse that occurred more than 2 wk previously, a pregnancy test may be helpful. However, there is no need for a pregnancy test before administering EC pills. Delays in administration of the medication will reduce its efficacy. The medication in EC pills will not harm an established pregnancy.
- A pregnancy test should be done before insertion of a copper IUD.

TREATMENT

ACUTE GENERAL Rx

- Administer EC as soon as possible after unprotected intercourse. All forms of EC reduce the risk of pregnancy when used up to 5 days after unprotected intercourse but are more effective if used earlier. EC pills function by delaying ovulation, so it is important to counsel patients to abstain or use a barrier method for 2 weeks following EC use in order to avoid a later cycle pregnancy.
- Copper IUD for EC.
  1. Emergency insertion of the copper IUD is the most effective option for EC.
  2. Ideal for women who desire effective long-term contraception and have no contraindications to IUD insertion.
  3. A pregnancy test should be done before IUD insertion.
- Emergency contraceptive pills (see Table EE1-7)
  1. Ulipristal acetate (Ella).
     1. Single dose 30 mg ulipristal acetate, a progesterone-receptor modulator.
     2. More effective than levonorgestrel EC. Prescription is required.
  2. Levonorgestrel (Next Choice, Plan B One-Step)
     1. Total dose 1.5 mg levonorgestrel
     2. A single dose is equally effective and causes no more side effects than two divided doses.
     3. Likely ineffective in overweight and obese women (BMI >25).
     4. Plan B One-Step available over the counter without age restrictions.
     5. Next Choice One Dose, My Way, generic levonorgestrel available "behind the counter" without a prescription for ages 17 and over.
  3. Combined estrogen/progestin contraceptive pills:
     1. Least effective method with highest incidence of side effects.
     2. Two doses, 12 hr apart, of 100 to 120 mcg ethinyl estradiol and 0.5 to 0.6 mg levonorgestrel (or 1.0 to 1.2 mg norgestrel) per dose.
     3. Prescription is required, but if patient uses combined oral contraceptives she may have the product on hand.
     4. The Emergency Contraception website provides instructions for using available combined oral contraceptive pills for EC. http://ec.princeton.edu/questions/dose.html#dose
- Side effects:
  1. Levonorgestrel and ulipristal: combined estrogen-progestin EC will cause nausea in 50% of women and vomiting in 20%. Side effects resolve within 1 to 2 days. Anti-nausea medication such as meclizine 25 mg orally is recommended 1 hr before taking combined estrogen-progestin EC.
- Contraindications:
  1. Few contraindications to EC exist other than hypersensitivity to the product. EC pills will not affect an established pregnancy.
  2. There are no other evidence-based medical contraindications to the use of EC pills. The benefits of EC in preventing pregnancy generally outweigh the theoretical risks for women with contraindications to long-term use of combined hormonal contraception, such as thromboembolic disease, smoking after age 35, heart disease, or liver disease. Nonestrogen containing EC is preferable for all women because of better efficacy, but particularly for those with any of these conditions or who are breastfeeding. EC is not indicated for breastfeeding women ≤6 weeks postpartum as ovulation is extremely unlikely.

CHRONIC Rx

Because EC pills are less effective than other forms of contraception, they are not recommended as an ongoing method of contraception. The copper IUD is highly effective for EC and can be kept in place to prevent pregnancy for up to 12 yr.

DISPOSITION

After using EC, most women will have their menses within 1-2 weeks of the expected date. If a woman's next expected menses are delayed by more than 3 weeks, a pregnancy test should be done.

PEARLS & CONSIDERATIONS

COMMENTS

- Copper IUD is the most effective form of EC and is the only method that provides users with long-term contraception.
- All forms of EC pills reduce the risk of pregnancy up to 5 days after unprotected intercourse, with ulipristal acetate being the most effective. Delayed ovulation can result in a later cycle pregnancy, therefore patients should use a barrier method for 2 weeks following EC pill use.
- EC pills are less effective in overweight and obese women. Levonorgestrel EC appears ineffective for women with BMI >25 kg/m^2,

TABLE EE1-7 Emergency Contraceptive Pills Available in the United States

	Emergency Contraception Pills	
Brand	**Dose**	**Dose**
Ella	1 pill	30 mg ulipristal acetate
Plan B One-Step	1 pill	1.5 mg levonorgestrel
Next Choice One Dose	1 pill	1.5 mg levonorgestrel
My Way	1 pill	1.5 mg levonorgestrel
Levonorgestrel	2 pills	1.5 mg levonorgestrel

and ulipristal acetate appears ineffective for those with BMI >35kg/m^2. The copper IUD is highly effective regardless of BMI.
- A pregnancy test is not necessary before administering EC pills because the medicines will not harm an existing pregnancy.
- Advanced prescription of EC pills at routine visits may increase timely use of EC and does not decrease the use of more reliable means of contraception. Health care providers who speak with the pharmacist directly are more likely to ensure timely distribution of EC pills to their patients.
- Levonorgestrel EC is available without a prescription. Plan B One-Step is over the counter without age restrictions, and other brands are available behind the counter for ages 17 years and above.

PREVENTION

- Patients should begin an effective method of birth control immediately after using EC. Hormonal contraceptives can be started the day after EC is administered. Abstinence or a barrier method should be used for 2 wk.
- EC should be offered to all women after sexual assault.

PATIENT & FAMILY EDUCATION

- EC website: http://ec.princeton.edu/index.html

SUGGESTED READINGS

Batur P: Emergency contraception: separating fact from fiction, *Cleve Clin J Med* 79:771–776, 2012.

Brache V et al.: Ulipristal acetate prevents ovulation more effectively than levonorgestrel: analysis of pooled data from three randomized trials of emergency contraception regimens, *Contraception*, 2013. epub ahead of print.

Cheng L et al.: Interventions for emergency contraception, *Cochrane Database Syst Rev* 8:CD001324, 2012.

Stewart F et al. Emergency contraception. In: (editor: Hatcher R.; et al.) Contraceptive technology. Ardent Media, Inc.: New York, pp. 87–116.

Trussell J et al. Emergency contraception. In: (editor: Hatcher R.; et al.) Contraceptive technology. Ardent Media, Inc.: New York, pp. 113–145.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Contraception (Related Key Topic)

AUTHORS: **MELISSA NOTHNAGLE, M.D., M.SC.** and **JENNIFER BUCKLEY, M.D.**

BASIC INFORMATION

DEFINITION

An accumulation of pus in the pleural space, most often caused by bacterial infection.

SYNONYMS

Infected pleuritis
Infected pleural effusion
Purulent pleural effusion

ICD-9CM CODES
510.9 Empyema, lung
ICD-10CM CODES
J86 Pyothorax
A16.5 Empyema due to tuberculosis

EPIDEMIOLOGY & DEMOGRAPHICS

- Empyema is most commonly a complication of bacterial pneumonia, especially in association with pneumococcal or anaerobic infection (40% to 60% of cases of empyema).
- Occurs as a complication of thoracic surgery (<20% of cases).
- Penetrating chest trauma (4% to 10% of cases).
- Bronchopleural fistulae resulting from malignancy or lung biopsy.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- May be abrupt or chronic and insidious depending on the etiologic agent and host factors.
- Typically presents as progressive pleuritic chest pain, persistent fever, and other sustained signs and symptoms of infection.
- In anaerobic empyema, particularly that caused by the actinomycetes, the clinical picture is dominated by systemic symptoms and signs: weight loss, malaise, and low grade fever.
- A slowly enlarging chest wall mass.
- As a complication of thoracic trauma or surgery, empyema typically results from contamination of blood within the pleural space several days following the event.
- The physical findings of empyema are those of pleural effusion. Decreased breath sounds and dullness to percussion over the involved part of the thorax is typical. Systemic signs include fever, tachycardia, leukocytosis, and warmth and erythema over the involved area.

ETIOLOGY

Infection of the lung parenchyma spreading to pleural space caused by

- *Streptococcus pneumoniae.*
- *Haemophilus influenzae.*
- *Staphylococcus aureus.*
- *Legionella* species.
- *Mycobacterium tuberculosis.*
- *Actinomyces* spp.
- A variety of oral anaerobic bacteria have been cultured in 36% to 37% of empyemas: *Bacteroides fragilis*, *Prevotella* species, *Fusobacterium nucleatum*, and *Peptostreptococcus* are the most common.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Uninfected parapneumonic effusion.
- Congestive heart failure.
- Malignancy involving the pleura.
- Tuberculous pleurisy.
- Collagen vascular disease (particularly rheumatoid lung and systemic lupus erythematosus).

LABORATORY TESTS

- Complete blood count; arterial blood gas.
- Blood cultures.
- Pleural fluid analysis in empyema has the characteristics of an exudate with a ratio of pleural fluid to serum protein >0.5 or pleural fluid to serum LDH >0.6. Characteristically, empyema fluid is grossly purulent with visible organisms on Gram stain with glucose <50 mg/dl and pH <7. These findings justify immediate drainage by chest tube or surgery because of the high risk of loculation and progressive systemic infection.

IMAGING STUDIES

- Chest x-ray (Fig. E1-12*A*).
- Lateral decubitus view to establish the presence of free fluid in the pleural space.
- Computed tomography (Fig. E1-12*B*) to establish the presence of fluid loculation, underlying mass lesions, and other intrathoracic pathology.

TREATMENT

NONPHARMACOLOGIC THERAPY

Prompt drainage by thoracostomy (chest tube) or open thoracotomy. Video-assisted thorascopic surgery (VATS) has greatly improved surgical management of empyemas.

ACUTE GENERAL Rx

- Maintenance of drainage until infection controlled.
- Antibiotics directed at suspected or proven bacterial or fungal pathogens. Initial regimens include cefotaxime or ceftriaxone for suspected *S. pneumoniae* or group A *Streptococcus,* nafcillin or oxacillin for suspected methicillin-sensitive *S. aureus,* vancomycin or linezolid for suspected MRSA, ceftriaxone for suspected *H. influenzae,* and clindamycin plus ceftriaxone when suspecting anaerobes.
- Thoracoscopy or instillation of thrombolytic agents (streptokinase or urokinase) may be considered in refractory, loculated empyema.

CHRONIC Rx

- If thorough drainage cannot be accomplished, open thoracotomy with pleural decortication may be required.
- Lung function should be monitored following completion of therapy.

DISPOSITION

Hospitalization with supplemental oxygen with ventilatory support if necessary

REFERRAL

Consultation by infectious diseases, pulmonary, or thoracic surgery specialists as needed.

PEARLS & CONSIDERATIONS

COMMENTS

- Empyema caused by actinomycetes may present with erosion through the chest wall and formation of a fistulous tract.
- Nosocomial infection caused by relatively resistant bacterial or fungal pathogens may result in empyema in patients with indwelling thoracostomy tubes.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

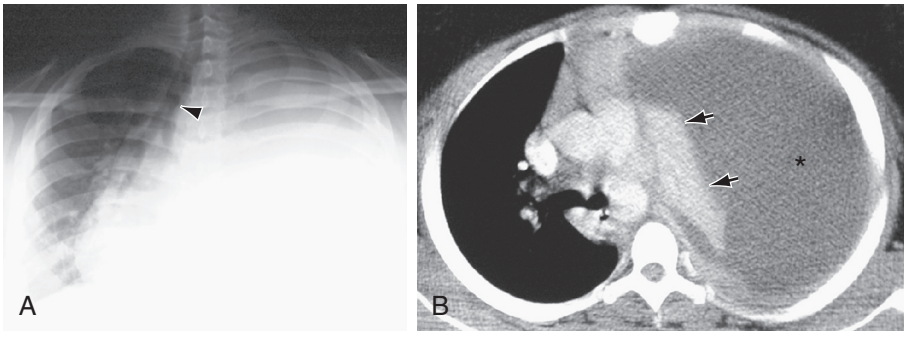

FIGURE E1-12 Empyema and pneumonia in a teenager. A, Chest radiograph shows opacification of the left thorax. Note shift of mediastinum and trachea *(arrowhead)* to right. **B,** Thoracic CT scan shows massive left pleural effusion *(asterisk).* Note the compression and atelectasis of the left lung *(arrows)* and shift of the mediastinum to the right. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

SUGGESTED READINGS

Jaffe A, Cohen G: Thoracic empyema, *Arch Dis Child* 88(10):839, 2003.

Lardinois D et al.: Delayed referral and gram-negative organisms increase the conversion thoracotomy rate in patients undergoing video-assisted thoracoscopic surgery for empyema, *Ann Thorac Surg* 79(6):1851, 2005.

Lee SF et al.: Thoracic empyema: current opinion in medical and surgical management, *Curr Opin Pulm Med* 16(3):194–200, 2010.

Melloni G et al.: Decortication for chronic parapneumonic empyema: results of a prospective study, *World J Surg* 28(5):488, 2004.

Wilcox ME et al.: Does this patient have an exudative pleural effusion ? The rational clinical examination systematic review, *JAMA* 311(23):2422–2431, 2014.

Zahid I et al.: Comparison of video-assisted thoracoscopic surgery and open surgery in the management of primary empyema, *Curr Opin Pulm Med* 17(4):255–259, 2011.

BASIC INFORMATION

DEFINITION

Acute viral encephalitis is an acute febrile syndrome with evidence of meningeal involvement and of derangement of the function of the cerebrum, cerebellum, or brain stem.

SYNONYMS

Arboviral encephalitis
Brain stem encephalitis
Acute necrotizing encephalitis
Rasmussen encephalitis
Encephalitis lethargica

ICD-9CM CODES
049.9 Viral encephalitis, NOS
ICD-10CM CODES
A86 Unspecified viral encephalitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): About 20,000 cases/yr are reported to the CDC. In 2012 there was an increase in the number of cases of West Nile virus infection in the U.S.
PEAK INCIDENCE: Any age
PREVALENCE (IN U.S.): Unknown
PREDOMINANT SEX: Male = female
PREDOMINANT AGE: Any age
GENETICS: No specific genetic or congenital predisposition

ETIOLOGY

- Can be caused by a host of viruses, with herpes simplex the most common virus identified.
- Arboviruses transmitted by mosquitoes include Eastern equine encephalitis, Western equine encephalitis, St. Louis encephalitis, Venezuelan equine encephalitis, California virus encephalitis, Japanese B encephalitis, Murray Valley and West Nile encephalitis. Tick-borne diseases include Russian spring-summer encephalitis, Powassan encephalitis, and other lesser known agents.
- Also implicated: rabies-causing agents, CMV, Epstein-Barr, varicella-zoster, echo virus, mumps, adenovirus, coxsackie, rubeola, and herpes viruses.
- Meningoencephalitis: acute retroviral infection
- In the U.S., the most commonly identified etiologies are herpes simplex virus, West Nile virus, and the enteroviruses.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Initially, fever and evidence of meningeal irritation
- Headache and stiff neck
- Later, development of signs of cortical dysfunction: lethargy, coma, stupor, weakness, seizures, facial weakness, as well as brainstem findings
- Cerebellar findings: ataxia, nystagmus, hypotonia, myoclonus, cranial nerve palsies, and abnormal tendon reflexes
- Patients with rabies: hydrophobia, anxiety, facial numbness, psychosis, coma, or dysarthria
- Rarely, movement disorders, such as chorea, hemiballismus, or dystonia
- Recall of a prodromal viral-like illness (this finding is not at all uniform)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bacterial infections: brain abscess, toxic encephalopathies, TB
- Protozoal infections
- Behçet's disease
- Lupus encephalitis
- Sjögren's syndrome
- Multiple sclerosis
- Syphilis
- Cryptococcus
- Toxoplasmosis
- Brucellosis
- Leukemic or lymphomatous meningitis
- Other metastatic tumors
- Lyme disease
- Cat-scratch disease
- Vogt-Koyanagi-Harada syndrome
- Mollaret's meningitis

WORKUP

- Lumbar puncture to reveal pleocytosis, usually lymphocytic, although neutrophils may be seen early on
- Usually, elevated CSF protein
- Normal or low CSF glucose
- In herpes simplex encephalitis: RBCs and xanthochromia
- Selected tests on CSF fluid in viral encephalitis are described in Table E1-8
- EEG changes showing periodic high-voltage sharp waves in the temporal regions and slow wave complexes suggestive of herpes encephalitis (Fig. E1-13).
- CT scan and MRI to reveal edema and hemorrhage in the frontal and temporal lobes
- Temporal lobe involvement suggests herpes simplex encephalitis
- Basal ganglia and thalami are areas involved as generally seen in Eastern equine encephalitis
- With West Nile infection, MRI changes have shown changes in basal ganglia, thalami, mesial temporal structures, brain stem, and cerebellum
- Arboviral infections suspected during outbreaks in specific areas
- Rising titers of neutralizing antibodies from the acute to the convalescent stage demonstrated but often not helpful in the acutely ill patient
- Polymerase chain reaction (PCR) that amplifies DNA from the CSF for herpes simplex encephalitis
- Rarely, brain biopsy to assist in the diagnosis; viral culture of cerebral tissue obtained if biopsy done
- Classic herpetic skin lesions suggestive of herpes encephalitis
- In diagnosing arboviral encephalitis:

TABLE E1-8 Selected Tests for Viral Encephalitis

Organism/Syndrome	Test	Comment
West Nile Virus		
West Nile encephalitis	IgM in CSF	Diagnostic of CNS invasive disease or acute flaccid paralysis
Herpes Simplex Virus Type 1		
Herpes simplex encephalitis	PCR in CSF	Sensitive and specific in the acute phase
	CSF–serum antibody ratio	Useful 2 weeks to 3 months after onset
Herpes Simplex Virus Type 2		
Neonatal encephalitis	PCR in CSF	Confirmatory, high sensitivity
Relapsing meningitis	PCR in CSF	Sensitive and specific in first 3 days of illness
Varicella-Zoster Virus		
Meningoencephalitis	PCR in CSF	Confirmatory when used with clinical and spinal fluid findings; sensitivity unclear
Epstein-Barr Virus		
EBV encephalitis	PCR in CSF	Suggests CNS invasion by virus
JC Virus		
Progressive multifocal leukoencephalopathy	PCR in CSF	Diagnostic but incompletely (70%) sensitive
Cytomegalovirus		
CMV ventriculitis	PCR in CSF	Sensitive and specific

CMV, Cytomegalovirus; *CNS,* central nervous system; *CSF,* cerebrospinal fluid; *EBV,* Epstein-Barr virus; *PCR,* polymerase chain reaction.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2011, Saunders.

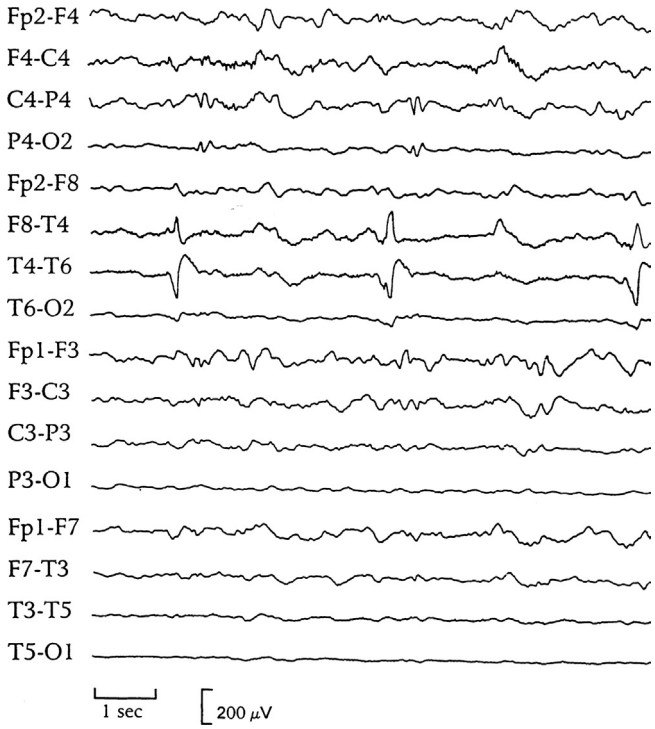

FIGURE E1-13 Repetitive complexes occurring in the right temporal region of a child with herpes simplex encephalitis. (From Goetz CG, Pappert EJ: *Textbook of clinical neurology,* Philadelphia, 1999, Saunders.)

1. Presence of antiviral IgM within the first few days of symptomatic disease; detected and quantified by ELISA
2. Unusual to recover an arbovirus from the blood or CSF

LABORATORY TESTS

- Aside from the lumbar puncture, most other laboratory studies are nonspecific.
- Skin lesions and urine may be cultured for herpes simplex and CMV.

Rx TREATMENT

ACUTE GENERAL Rx

- Supportive care, frequent evaluation, and neurologic examination
- Ventilatory assistance for patients who are moribund or at risk for aspiration
- Avoidance of infusion of hypotonic fluids to minimize the risk of hyponatremia
- For patients who develop seizures: anticonvulsant therapy and follow-up in a critical care setting
- For comatose patients:
  1. Aggressive care to avoid decubitus ulcers, contractures, and DVT
  2. Close attention to weights, input/output, and serum electrolytes
- Acyclovir 30 mg/kg/day IV total dose divided in q8 hour intervals for 14 days for herpes simplex encephalitis
- Short courses of corticosteroids to control brain edema and prevent herniation
- In patients with suspected rabies:
  1. Human rabies immune globulin (HRIG) should be given at a dose of 20 U/kg.
  2. Active immunization may be stimulated by rabies vaccine, which is grown on a human diploid cell line (HDCV) and has reduced the number of doses needed to five.
  3. If suspect animal is a dog or cat and can be found, observe closely for 10 days to detect rabid behavior; any significant illness in the animal should promptly initiate humane sacrifice of the animal with the brain submitted to local or state health departments for pathology and immunologic testing for rabies. Any wild animal suspected of rabies should be humanely sacrificed, if possible, and submitted for rabies testing immediately.
  4. If signs are seen, animal should be euthanized and its brain examined for signs of rabies.
- No specific pharmacologic therapy for most other viral pathogens

CHRONIC Rx

Some patients may develop permanent neurologic sequelae; these patients will benefit from intensive rehabilitation programs, including physical, occupational, and speech therapy.

DISPOSITION

- Patients with suspected encephalitis of any cause should generally be admitted for initial diagnostic workup and specific treatment (if available).
- Long-term management of patients with significant neurologic sequelae from encephalitis (e.g., memory defects, depression, difficulty with organization of thoughts, movement disorders) may benefit from rehabilitation services, home care, or nursing home placement.

REFERRAL

- To a neurologist for initial workup and management
- To an infectious disease specialist for diagnostic and therapeutic plan
- To a rehabilitation service for long-term evaluation and convalescent services

PEARLS & CONSIDERATIONS

- West Nile virus encephalitis occurs primarily in elderly patients >65 years of age.
- Rabies may occur months after contact with the rabid animal, and the exposure (especially bat rabies) may have been seemingly insignificant and even inapparent.
- Experimental therapies are worthy of consideration for some forms of viral encephalitis (e.g., immune plasma, ribavirin, interferons), and expert consultation should be obtained early on for possible treatment interventions with promising experimental therapies (e.g., Milwaukee protocol for rabies).

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Rabies (Related Key Topic)
West Nile Virus Infection (Related Key Topic)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Denizot M et al.: Encephalitis due to emerging viruses: CNS innate immunity and potential therapeutic targets, *J Infect* 65(1):1–16, 2012.

Frenkel LM: Challenges in the diagnosis and management of neonatal herpes simplex virus encephalitis, *Pediatrics* 115(3):795–797, 2005.

Kennedy PG: Viral encephalitis, *J Neurol* 252(3):268, 2005.

Lim SM et al.: West Nile virus: immunity and pathogensis, *Viruses* 3(6):811–828, 2011.

Long SS: Encephalitis diagnosis and management in the real world, *Adv Exp Med Biol* 697:153–173, 2011.

Roos KL: Fatal encephalitis due to rabies virus transmitted by organ transplantation, *Arch Neurol* 62(6):855–856, 2005.

Sellal F, Stoll-Keller F: Rabies: ancient yet contemporary cause of encephalitis, *Lancet* 365(9463):921–923, 2005.

Tunkel AR et al.: The management of encephalitis: Clinical Practice Guidelines by the Infectious Diseases Society of America, *Clin Infect Dis* 47:303–327, 2008.

BASIC INFORMATION

DEFINITION

Encephalopathy is a clinical syndrome of global cognitive impairment characterized by impaired arousal, inattention, and disorientation.

SYNONYMS

Delirium, acute confusional state

ICD-9CM CODES
348.3 Encephalopathy, NOS
348.30 Encephalopathy, unspecified
348.31 Encephalopathy, metabolic
348.39 Encephalopathy, other
349.82 Encephalopathy, toxic

ICD-10CM CODES
G93.40 Encephalopathy, unspecified
G93.41 Metabolic encephalopathy
G93.49 Other encephalopathy
G92 Toxic encephalopathy

EPIDEMIOLOGY & DEMOGRAPHICS

POINT PREVALENCE: 1.1% of adults in the general population >55 yr, 10% to 40% of hospitalized elderly, and 60% of nursing home patients >75 yr; 100,000 to 200,000 cases annually with anoxic encephalopathy
RISK FACTORS: Age, cancer, AIDS, terminal illness, bone marrow transplant, surgery

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The essential feature of encephalopathy is the patient's inability to maintain a coherent stream of thought or action.
- The history may often suggest a waxing and waning of the level of arousal and general cognitive ability.
- Because toxins and metabolic disturbances are common causes of encephalopathy, the history should focus on exposure to toxins (especially medications) and symptoms suggesting a concurrent illness such as a urinary tract infection or pneumonia.
- Common to all encephalopathies is a fluctuating level of arousal, poor attention, and disorientation.
- Some patients may appear agitated and others lethargic.
- Delusions (fixed false beliefs) and hallucinations are common.
- Asterixis (negative myoclonus) is common.
- Other physical findings may vary depending on the underlying cause of encephalopathy, such as fever, ascites, jaundice, or tachycardia.

ETIOLOGY

The final common pathway of all causes of encephalopathy is widespread, neuronal dysfunction from structural or functional causes. Many conditions are reversible and carry a good prognosis if treated in a timely manner.

- Organ failure (e.g., hepatic encephalopathy, hypoxia, hypercapnia, uremia)
- Infection: systemic (e.g., urinary tract, pneumonia, sepsis) or involving the central nervous system (e.g., meningitis, encephalitis)
- Toxin ingestion or withdrawal (e.g., alcohol, medications [especially psychotropics and neuroleptics], recreational drugs)
- Metabolic disturbances: hyperosmolar states, hypernatremia, hyponatremia, hyperglycemia, hypoglycemia, hypercalcemia, hypophosphatemia, acidosis, alkalosis, inborn errors of metabolism
- Endocrinopathy: hyperthyroidism, hypothyroidism, Cushing's syndrome, adrenal insufficiency, pituitary failure
- Neoplasm: tumors of the central nervous system, primary or metastatic; also effect of distant tumors (e.g., paraneoplastic limbic encephalitis)
- Nutritional deficiency, mostly in alcoholics and chronically ill patients, such as vitamin B_1 deficiency (Wernicke's encephalopathy)
- Seizures: postictal state, nonconvulsive status epilepticus, complex partial seizures, absence seizures
- Trauma: concussion, contusion, subdural hematoma, epidural hematoma, diffuse axonal injury
- Vascular: ischemic and hemorrhagic strokes, vasculitis, venous thrombosis
- Postanoxic encephalopathy
- Psychiatric disease: acute psychosis, depression with psychiatric features
- Acute disease: acute disseminating myelitis, tumefactive multiple sclerosis
- Other: hypertensive encephalopathy, postoperative status, sleep deprivation

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Differential diagnosis for encephalopathy is broad. It is typically helpful to distinguish toxic metabolic causes from primary neurologic causes.

- Dementia: distinguished from encephalopathy by a history of slowly progressive cognitive decline over time (fluctuating cognitive function is rare except in diffuse Lewy body disease).
- Hypersomnia
- Aphasia: distinguished from encephalopathy by virtue of it representing a specific disorder of language rather than a global disturbance of cognitive function.
- Depression
- Psychosis: some overlap with encephalopathy because delusions and hallucinations may be common to both.
- Mania
- Vegetative state from cerebral injury; these patients appear awake (eyes are open) but there is no content to their consciousness.
- Akinetic mutism: these patients do not talk and do not move; there is little fluctuation in their state and there is no asterixis or other focal deficit.
- Locked-in syndrome: may be distinguished from encephalopathy by the presence of fixed neurologic deficits (e.g., paralysis of all four limbs); however, the patient is aware of his or her environment.

WORKUP

The best tool in the evaluation of encephalopathy is a good history and physical exam, which will help tailor the remainder of the diagnostic workup. Interview family members and other providers to identify preceding events, medication changes, and medical history. Evaluate focal deficits.

LABORATORY TESTS

- General chemistry: electrolytes, glucose, creatinine, ammonia, blood urea nitrogen, transaminases, amylase, lipase
- Arterial blood gases
- Complete blood count
- Drug screen and alcohol level (must order ethylene glycol separately if suspected)
- Lumbar puncture if meningitis, encephalitis, or subarachnoid hemorrhage with negative imaging is suspected
- HIV testing
- Endocrine testing: cortisol level, thyroid function test
- Urinalysis and microscopy

IMAGING STUDIES

- Chest radiograph to rule out pneumonia
- Head CT to rule out bleeding, hydrocephalus, tumors
- Brain MRI with diffusion-weighted images for suspected encephalitis, tumors, and acute strokes
- Magnetic resonance angiography/venography for strokes, arterial dissection, venous thrombosis
- Conventional angiography for central nervous system (CNS) vasculitis and aneurysms
- EEG: evaluate for subclinical status epilepticus

TREATMENT

The encephalopathy itself is a symptom of these underlying problems. In general, it is best to avoid treating the symptom of encephalopathy with antipsychotics or sedatives.

- The best approach is to treat the underlying toxic or metabolic disturbance.
- Thiamine supplementation
- Glucose for hypoglycemia
- Antibiotics in cases of infections (choose an agent with good CNS penetration in cases of primary CNS infections)
- Insulin in hyperglycemic conditions (e.g., diabetic ketoacidosis, hyperosmolar nonketosis, and sepsis)
- Ensure hemodynamic stability (blood pressure and heart rate)

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Delirium (Related Key Topic)
Encephalitis, Acute Viral (Related Key Topic)
Hepatic Encephalopathy (Related Key Topic)

AUTHOR: **JOSHUA CHALKELY, M.S., D.O.**

SUGGESTED READINGS

Agrawal A et al.: Secondary prophylaxis of hepatic encephalopathy in cirrhosis: an open-label, randomized controlled trial of lactulose, probiotics, and no therapy, *Am J Gastroenterol* 107:1043, 2012.

Bass N et al.: Rifaximin treatment in hepatic encephalopathy, *N Engl J Med* 362:1071–1081, 2010.

Riordan SM, Williams R: Gut flora and hepatic encephalopathy in patients with cirrhosis, *N Engl J Med* 362:1140–1141, 2010.

BASIC INFORMATION

DEFINITION/DIAGNOSTIC CRITERIA

DSM-5[1] defines encopresis as:

A. Reverted passage of feces into inappropriate places (e.g., clothing, floor), whether involuntary or intentional.

B. At least one such event occurs each month for at least three months.

C. The behavior is not attributable to the physiological effects of a substance (e.g., laxatives) or another medical condition except through a mechanism involving constipation.

Encopresis may be classified into two types based on published guidelines of the Multinational Working Teams to Develop Criteria for Functional Disorders (Rome III). Definition of functional retentive encopresis requires two of six criteria: 2 or fewer defecations per week, at least 1 episode of incontinence after acquisition of toileting skills, history of excessive fecal retention and or painful or hard bowel movements, presence of large fecal mass in the rectum, history of large diameter stools that may obstruct the toilet. Nonretentive encopresis is fecal incontinence without evidence of constipation or fecal retention in the absence of underlying disease process that explains the symptoms.

SYNONYMS

Stool/fecal incontinence
Soiling

ICD-9CM and DSM-5 CODES
307.7 Encopresis
ICD-10CM CODES
R15 Fecal incontinence
F98.1 Non-organic (psychogenic) encopresis

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Preschool age (though also occurs during school age and adolescence).
PREVALENCE (IN U.S.): 1.5% to 7.5% of children 4 to 12 yr old.
PREDOMINANT SEX: More often in males (estimates range from 1.9:1 to 9:1).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most children are toilet-trained for stool by age 4. Traditionally, in primary encopresis, fecal continence is never fully established; in secondary encopresis, soiling is preceded by a period of fecal continence. However, definitions of "primary" vs. "secondary" do not reliably correlate with etiology or outcome.
- Constipation and withholding of stool are significant factors in 80% to 90% of cases ("retentive encopresis"). In 10% to 20%, constipation is not a factor ("nonretentive" encopresis).
- When constipation is longstanding, soft or liquid stool may flow around the retained feces, resulting in overflow incontinence. This may occur several times per day and mistakenly be interpreted as diarrhea.
- Children may report a lack of awareness of stool passage when longstanding constipation/impaction has resulted in loss of rectal tone and sensation. Furthermore, some children habituate to the odor.

ETIOLOGY

- Approximately 96% of children have bowel movements between three times daily to once every other day. When bowel movements are less frequent, stool becomes drier and harder and much more uncomfortable or painful to pass. Children may avoid the discomfort or pain by avoiding elimination, resulting in worsening constipation and overflow incontinence.
- Constipation may begin gradually as a result of a decrease in elimination frequency or more acutely after an illness or changes in diet.
- Toilet training practices that increase anxiety may also play a role in stool retention, the development of constipation, and eventual encopresis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hirschsprung's disease
- Endocrine disease (hypothyroidism)
- Cerebral palsy
- Myelomeningocele
- Pseudoobstruction
- Anorectal lesions (rectal stenosis)
- Malformations
- Trauma
- Rectal prolapse
- Celiac disease
- Hypothyroidism
- Medications

WORKUP

- History: frequency of elimination, character of the stool, associated pain, and presence of enuresis (with which it is frequently associated).
- Evaluate for other developmental or psychiatric problems.
- Common physical findings in retentive encopresis: abdominal fecal mass, stool-impacted rectum, loose anal sphincter, fecal material in the perianal area, anal tags or fissures.
- Perform a complete neurologic examination to exclude sensorineural or spinal cord abnormalities.

LABORATORY TESTS

- Consider thyroid function tests, celiac screening tests, electrolytes, calcium, urinalysis, urine culture.
- If concerned about the possibility of Hirschsprung's disease, obtain rectal biopsy.

IMAGING STUDIES

- Abdominal imaging to determine extent of obstruction or megacolon.
- Anorectal manometric studies or barium enema can support suspicion of Hirschsprung's disease.

TREATMENT

ACUTE GENERAL Rx

- Disimpaction is a necessary first step, by oral or rectal route (or combination).
- For oral disimpaction, polyethylene glycol, magnesium citrate, or high doses of mineral oil are effective (avoid use of mineral oil in patients at risk for aspiration).
- Adding stimulant laxatives such as senna or bisacodyl can sometimes make oral disimpaction more effective.
- For rectal disimpaction, phosphate soda, saline, or mineral oil enemas are effective.
- If oral and rectal disimpaction fail, admission to the hospital might be necessary for a Golytely bowel clean-out via a nasogastric tube.
- When medical workup determines no constipation ("nonretentive encopresis"), consider toilet-training routines or referral to behavioral health provider.

CHRONIC Rx

- Prevent recurrence of constipation with oral stool softeners (e.g., polyethylene glycol or lactulose) or stool lubricants (mineral oil).
- In immediate postdisimpaction period (1 mo after treatment), stimulant laxatives may be needed if bowel tone remains low; taper use as quickly as possible to avoid dependence.
- Dietary modifications, such as improving fluid and fiber intake, help improve bowel regularity.
- Family documentation of stool passage, including location and amount, helps inform medication changes and best times for toilet sitting.
- Praise and other incentives for positive toileting routines and medication adherence can help maintain good bowel habits. Balanced diet and increased fiber intake/supplementation may help.
- Formal behavioral treatment (education, reinforcement of treatment adherence, exercises to improve anal sphincter control) increases treatment success. Biofeedback is advocated by some, with 1-yr results comparable to behavioral treatment. Adjunctive Internet-based interventions that incorporate behavioral therapy and medical management are beginning to show promise.

DISPOSITION

Encopresis may be self-limited or relatively brief in duration; may require prolonged maintenance therapy. Relapses are common.

REFERRAL

Behavioral family therapy should be considered for patients who do not respond to medical treatment within a few months or who have significant contributing psychiatric or family factors.

[1]American Psychiatric Association: *Desk reference to the diagnostic criteria from DSM-5*, Arlington, VA, 2013, American Psychiatric Association.

PEARLS & CONSIDERATIONS

- Educate parents and children about constipation and encopresis and defuse negative interactions.
- Emphasize it may need prolonged maintenance therapy and relapses are common.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Encopresis (Patient Information)

AUTHORS: **CAROLINA S. CEREZO, M.D.,** and **WENDY A. PLANTE, PH.D.**

SUGGESTED READINGS

Constipation Guideline Committee of the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition: Evaluation and treatment of constipation in infants and children: recommendation of the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition, *J Ped Gastroenterol, Hepatol, Nutr* 43(3):e1–e13, 2006.

Culbert TP, Banez GA: Integrative approaches to childhood constipation and encopresis, *Pediatr Clin North Am* 54(6):927, 2007.

Hyman PE, Milla PJ, Benninga MA et al.: Childhood functional gastrointestinal disorders: neonate/toddler, *Gastroenterology* 130:1519, 2006.

Rasquin A, Di Lorenzo C, Forbes D et al.: Childhood functional gastrointestinal disorders: child/adolescent, *Gastroenterology* 130:1527, 2006.

Endocarditis, Infective ALG EBM PTG

BASIC INFORMATION

DEFINITION

Infective endocarditis is an infection of the endocardial surface of the heart or mural endocardium. Box E1-4 describes the modified Duke criteria for the diagnosis of infective endocarditis.

ACUTE ENDOCARDITIS: Usually caused by *Staphylococcus aureus, Streptococcus pyogenes, S. pneumoniae,* and *Neisseria* organisms; classic clinical presentation of high fever, positive blood cultures, vascular and immunologic phenomenon

SUBACUTE ENDOCARDITIS: Usually caused by viridans streptococci in the presence of valvular pathology; less toxic, often indolent presentation with lower fevers, night sweats, fatigue

ENDOCARDITIS IN INJECTION DRUG USERS: Often involving *S. aureus* or *Pseudomonas aeruginosa* with variation that may be geographically influenced; tricuspid (Fig. E1-14) or multiple valvular involvement; high mortality rate of 50% to 60%

PROSTHETIC VALVE ENDOCARDITIS (EARLY): Usually caused by *S. aureus* (leading cause of PVE) within 2 mo of valve replacement; other organisms include *S. epidermidis,* gram-negative bacilli, diphtheroids, *Candida* organisms

PROSTHETIC VALVE ENDOCARDITIS (LATE): Typically develops >60 days after valvular replacement; involved organisms similar to early prosthetic valve endocarditis, including viridans streptococci, enterococci, and group D streptococci

NOSOCOMIAL ENDOCARDITIS: Secondary to intravenous catheters, TPN lines, pacemakers; coagulase-negative staphylococci, *S. aureus,* and streptococci most common

Non-HACEK gram-negative bacillus endocarditis is not primarily a disease of injection drug users. More than half of all cases are associated with health care contact

SYNONYMS

Bacterial endocarditis
Subacute bacterial endocarditis (SBE)
Endocarditis

ICD-9CM CODES

421.0 Infective endocarditis
996.61 Prosthetic valve endocarditis

ICD-10CM CODES

I33.0 Acute and subacute infective endocarditis
I33.9 Acute endocarditis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 5 to 7.9 cases/100,000 persons/yr.
PEAK INCIDENCE: Females: often <35 yr old; males: 45 to 65 yr old.
NOSOCOMIAL ENDOCARDITIS: 14% to 28% of cases.
PREVALENCE (IN U.S.): 0.3 to 3 cases/1000 hospital admissions.
PREDOMINANT SEX: Male < female.
PREDOMINANT AGE: 45 to 65 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical manifestations of infective endocarditis are described in Table E1-9.
- Fever may be variable in presentation; may be high, hectic, or absent.
- Fever, chills, fatigue, and rigors occur in 25% to 80% of patients.
- Heart murmur may be absent in right-sided endocarditis.
- Embolic phenomenon with peripheral manifestations is found in 50% of patients.
- Skin manifestations include petechiae, Osler nodes (Fig. EE1-15), splinter hemorrhages, Janeway lesions (Fig. EE1-16).
- Splenomegaly is more common with subacute course.

ETIOLOGY

Staphylococcal infection is now the leading cause of native or prosthetic valve infection. Variation in incidence may occur that is influenced by the patient's risk for developing infection. Risk factors include hemodialysis (8%), IV drug use (10%), mitral regurgitation (43%), aortic regurgitation (26%), and rheumatic heart disease (3.3%).

ACUTE ENDOCARDITIS:
- *S. aureus*
- *S. lugdunensis*
- *S. pneumoniae*
- Streptococcal species and groups A through G
- *Haemophilus influenzae*

SUBACUTE ENDOCARDITIS:
- Viridans streptococci (alpha-hemolytic).
- *S. bovis.*
- Enterococci.
- *S. aureus.*

ENDOCARDITIS IN INJECTION DRUG USERS:
- *S. aureus.*
- *P. aeruginosa.*
- *Candida* spp.
- Enterococci.

PROSTHETIC VALVE ENDOCARDITIS (EARLY):
- *S. epidermidis.*
- *S. aureus.*
- Gram-negative bacilli.
- Group D streptococci.

FIGURE E1-14 Tricuspid valve endocarditis. There are large vegetations on the leaflets and the chordae tendineae. (From Crawford MH et al [eds]: *Cardiology,* ed 2, St Louis, 2004, Mosby.)

BOX E1-4 Modified Duke Criteria for the Diagnosis of Infective Endocarditis*

Major Criteria

Positive blood cultures for infective endocarditis.
Typical microorganism for infective endocarditis from two separate blood cultures in the absence of a primary focus: *Streptococcus viridans, Streptococcus bovis.*
HACEK group: *Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella kingae*
Community-acquired *Staphylococcus aureus* or enterococci
Persistently positive blood cultures, defined as recovery of a microorganism consistent with infective endocarditis from blood cultures drawn more than 12 hr apart or all of three or the majority of four or more separate blood cultures, with first and last drawn at least 1 hr apart
Single positive blood culture for *Coxiella burnetii* or antiphase IgG antibody titer >1:800
Evidence for endocardial involvement
TTE (TEE in prosthetic valve) showing oscillating intracardiac mass on a valve or supporting structures, in the path of regurgitant jet or on implanted material, in the absence of an alternative anatomic explanation, *or*
Abscess, *or*
New partial dehiscence of prosthetic valve.

Minor Criteria

Predisposition (e.g., prosthetic valve, intravenous drug use).
Fever: 38° C.
Vascular phenomena.
Immunologic phenomena.
Microbiologic evidence: positive blood culture but not meeting major criteria.

TEE, Transesophageal echocardiogram; *TTE,* transthoracic echocardiogram.

From Ballinger A: *Kumar & Clark's essentials of clinical medicine,* ed 6, Edinburgh, 2012, Saunders.
*Adapted from Li JS et al: Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis, *Clin Infect Dis* 30:633-638, 2000.

TABLE E1-9 Clinical Manifestations of Infective Endocarditis Myalgia/Arthralgia

Symptoms	Patients Affected (%)	Signs	Patients (%)
Fever	80	Fever	90
Chills	40	Heart murmur	85
Weakness	40	Changing murmur	5-10
Dyspnea	40	New murmur	3-5
Sweats	25	Embolic phenomenon	>50
Anorexia	25	Skin manifestations	18-50
Weight loss	25	Osler nodes	10-23
Malaise	25	Splinter hemorrhages	15
Cough	25	Petechiae	20-40
Skin lesions	20	Janeway lesion	<10
Stroke	20	Splenomegaly	20-57
Nausea/vomiting	20	Septic complications	20
Headache	20	(e.g., pneumonia, meningitis)	
Myalgia/arthralgia	15	Mycotic aneurysms	20
Edema	15	Clubbing	12-52
Chest pain	15	Retinal lesion	2-10
Abdominal pain and delirium/coma	15	Signs of renal failure	10-25
Delirium/coma	10-15		
Hemoptysis	10		
Back pain	10		

From Mandell GL et al: *Principles and practice of infectious diseases*, ed 6, Philadelphia, 2005, Churchill Livingstone.

PROSTHETIC VALVE ENDOCARDITIS (LATE):
- *S. epidermidis.*
- Viridans streptococci.
- *S. aureus.*
- Enterococci and group D streptococci.

NOSOCOMIAL ENDOCARDITIS:
- Coagulase-negative staphylococci
- *S. aureus*
- Streptococci: viridans, group B, enterococcus

HACEK ORGANISMS:
- Fastidious gram-negative bacilli.
- *H. parainfluenzae.*
- *H. aphrophilus.*
- *A. actinomycetemcomitans.*
- *Cardiobacterium hominis.*
- *Eikenella corrodens.*
- *Kingella kingae.*

RISK FACTORS
- Poor dental hygiene.
- Long-term hemodialysis.
- Diabetes mellitus.
- HIV infection.
- Mitral valve prolapse.

DX DIAGNOSIS

DIFFERENTIAL DIAGNOSIS
- Brain abscess.
- FUO.
- Pericarditis.
- Meningitis.
- Rheumatic fever.
- Osteomyelitis.
- *Salmonella.*
- TB.
- Bacteremia.
- Pericarditis.
- Glomerulonephritis.

WORKUP
Physical examination to evaluate for the previous physical findings followed by laboratory testing (see "Laboratory Tests"). Fig. E1-17 describes a diagnostic evaluation of suspected endocarditis. The modified Duke criteria for diagnosis of endocarditis defines "major criteria" as persistently positive blood cultures of organisms typical of endocarditis or endocardial involvement (new valvular regurgitation or positive echocardiogram). "Minor criteria" are defined as presence of predisposing condition or injection drug use, fever, embolic vascular pneumonia (e.g., glomerulonephritis, rheumatoid factor), or positive blood cultures not meeting major criteria. Definite endocarditis is 2 major criteria or 1 major criteria and 3 minor criteria or 5 minor criteria or presence of organisms by culture or histologic examination of a vegetation.

LABORATORY TESTS
- Blood cultures: three sets in first 24 hr.
- More culturing if patient has received prior antibiotic.
- CBC (anemia possibly present, subacute).
- WBC (leukocytosis is higher in acute endocarditis).
- ESR and C-reactive protein (elevated).
- Positive rheumatoid factor (subacute endocarditis).
- Proteinuria, hematuria, RBC casts.

IMAGING STUDIES
- Echocardiogram: two-dimensional. Transthoracic echocardiography (TTE) (Fig. EE1-18) is noninvasive and more easily available but has less-than-optimal sensitivity (50%-80%) for endocarditis.
- Transesophageal echocardiography (TEE): more sensitive in detecting vegetations and preferred diagnostic modality. It is especially helpful with prosthetic valves or in detecting perivalvular disease.
- Electrocardiogram: look for cardiac conduction abnormalities, injury pattern, or evidence of pericarditis—any such new findings are suggestive of myocardial abscess.

RX TREATMENT

Initial IV antibiotic therapy (before culture results) is aimed at the most likely organism. The American Heart Association has developed guidelines based on the most frequently encountered bacteria.

- **Native valve** endocarditis caused by penicillin-susceptible *S. viridians, S. bovis,* and other streptotcocci (MIC of penicillin ≤0.12 mcg/ml)**:** Pen G 12-18 million U IV q24h continuous or divided q4h for 4 weeks **or** ceftriaxone 2 g IV or IM q day for 4 weeks for penicillin allergic patients. Vancomycin at 30 mg/kg per 24 hr in 2 equally divided doses assuming normal kidney function, for 4 weeks.
- **Native valve** endocarditis caused by strains of viridians streptococci and *S. bovis* relatively resistant to penicillin (MIC >0.12 mcg/ml): Pen G: 24 million units per 24 hr IV either continuously or in 4 or 6 equally divided doses for 4 weeks **or** ceftriaxone 2 g per 24 hr IV or IM for 4 weeks **plus** gentamicin 3 mg/kg per 24 hr IV or IM in one dose or in 2 to 3 equally divided doses for two weeks or monotherapy with vancomycin 30 mg/kg per 24 hr IV in 2 equally divided doses for 4 weeks not to exceed 2 g per 24 hr unless concentrations in serum too low.
- **Native valve** endocarditis due to *Staphylococcus:*
  1. **MSSA:** nafcillin (or oxacillin) 12 per 24 hr IV in 4 or 6 equally divided doses for 6 weeks **plus** optional addition of gentamicin 3 mg/kg per 24 hr IV or IM in 2 or 3 equally divided doses for 3 to 5 days **or** cefazolin 6 g per 24 hr IV in 3 equally divided doses for 6 weeks, **plus** optional addition of gentamicin 3 mg/kg per 24 hr IV or IM in 2 or 3 equally divided doses for 3 to 5 days. A newer antibiotic daptomycin has an indication for right-sided endocarditis with MSSA at 6 mg/kg IV q24h.
  2. **MRSA:** vancomycin 30 mg/kg per 24 hr in 2 equally divided doses for 6 weeks; not to exceed 2 g per 24 hr unless concentrations in serum are low.
- For culture negative native valve endocarditis one of the following regimens is suggested: ampicillin-sulbactam: 12 g per 24 hr IV in

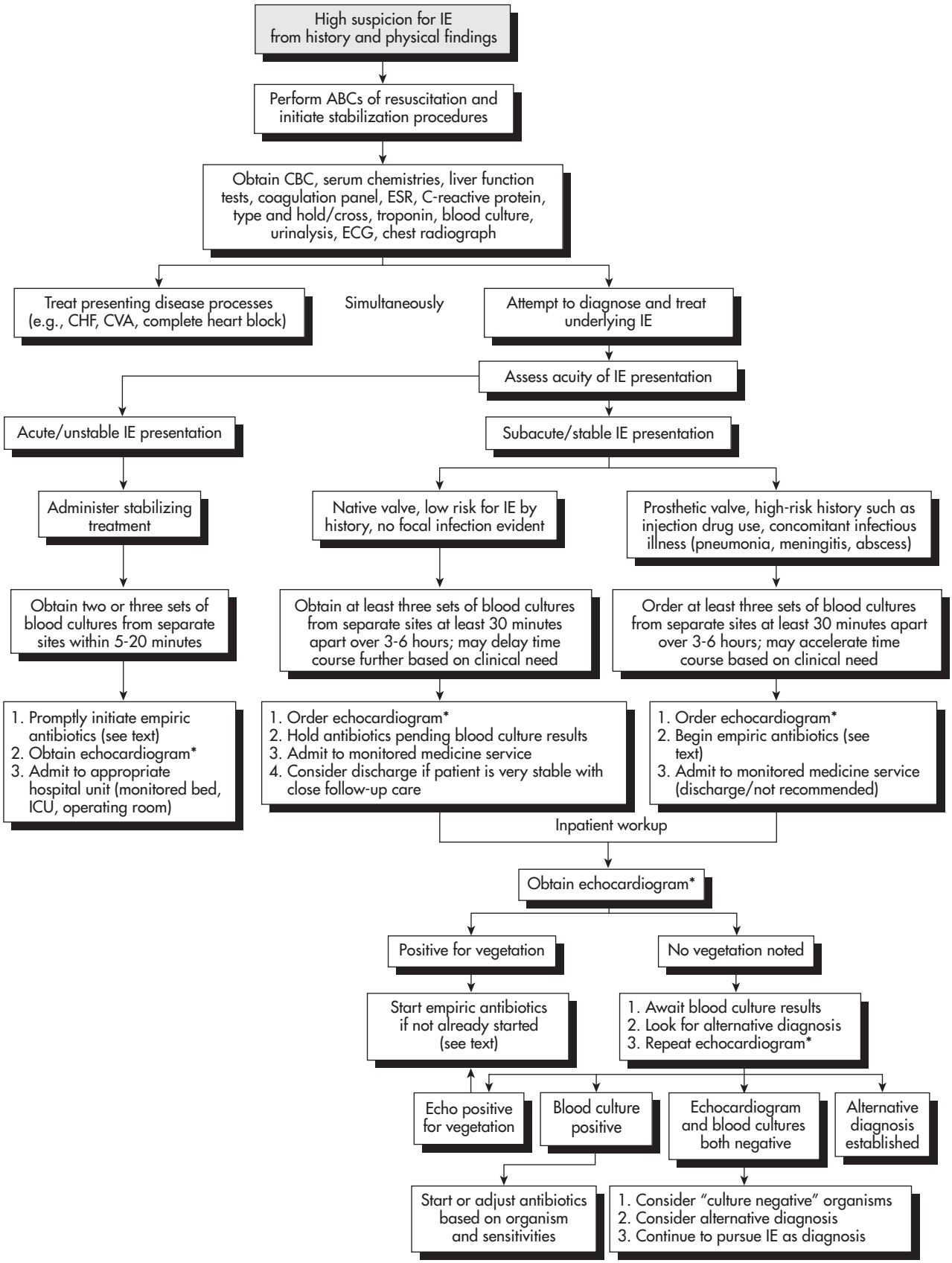

FIGURE E1-17 Diagnostic algorithm for the emergency department management of patients in whom infective endocarditis (IE) is suspected. *Echocardiography can be performed via either the transthoracic (TTE) or transesophageal (TEE) technique. TEE is more invasive but is more sensitive for detecting vegetations and complications of IE, such as perivalvular abscesses; it is recommended for prosthetic valves; for situations in which optimal visualization by TTE will be difficult, such as emphysema and morbid obesity; for high suspicion of IE but normal TTE findings; and for high suspicion of a complication of IE, such as perivalvular abscess. Normal findings with either technique do not exclude IE if clinical suspicion is high. Echocardiograms can be repeated in an attempt to identify problems such as vegetations and abscesses that may not be noted initially. *ABCs*, Airway, breathing, and circulation; *CBC*, complete blood count; *CHF*, congestive heart failure; *CVA*, cerebrovascular accident; *ECG*, electrocardiogram; *ESR*, erythrocyte sedimentation rate; *ICU*, intensive care unit. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

4 equally divided doses for 4 to 6 weeks **plus** gentamicin 3 mg/kg per 24 hr IV or IM in 3 equally divided doses for 4 to 6 weeks **or** vancomycin 30 mg/kg per 24 hr IV in 2 equally divided doses for 4 to 6 weeks; not to exceed 2 g per 24 hr unless concentrations in serum low **plus** gentamicin 3 mg/kg per 24 hr IV or IM in 3 equally divided doses for 4 to 6 weeks **plus** ciprofloxacin 1000 mg per 24 hr orally or 800 mg per 24 hr IV in 2 equally divided doses for 4 to 6 weeks.

- For treatment of native valve endocarditis due to HACEK organisms: ceftriaxone 2 g per 24 hr IV or IM in 1 dose for 4 weeks **or** ampicillin-sulbactam 12 g per 24 hr IV in 4 equally divided doses for 4 weeks **or** ciprofloxacin 1000 mg per 24 hr orally or 800 mg per 24 hr IV in 2 equally divided doses for 4 weeks
- **Patients with prosthetic valves** endocarditis:
- methicillin-susceptible strains: nafcillin or oxacillin 12 g per 24 hr IV in 6 equally divided doses for at least 6 weeks **plus** rifampin 900 mg per 24 hr IV or orally in 3 equally divided doses for at least 6 weeks **plus** gentamicin 3mg/kg IV or IM in 2 or 3 equally divided doses for 2 weeks.
- Methicillin-resistant strains: vancomycin 30 mg/kg per 24 hr in 2 equally divided doses for at least 6 weeks **plus** rifampin 900 mg per 24 hr IV or orally in 3 equally divided doses for at least 6 weeks **plus** gentamicin 3 mg/kg per 24 hr IV or IM in 2 or 3 equally divided doses for 2 weeks.

Antibiotic therapy after identification of the organism should be guided by susceptibility testing, preferably by formal testing by MIC (minimum inhibitory concentration).

DISPOSITION

- The patient may need outpatient IV antibiotic therapy, and arrangements need to be made to ensure safe vascular access and continuity of care with outpatient IV therapy team.
- Long-term follow-up is essential after therapy has ended; relapse of endocarditis may occur.
- Prophylaxis with antibiotics will be needed before dental procedures as a previous episode of endocarditis increases the risk of recurrent endocarditis associated with transient bacteremia from dental procedures.

REFERRAL

- To an infectious disease specialist.
- To a cardiologist or a cardiac surgeon if evidence of heart failure, refractory infection, myocardial abscess, valve disruption, or major embolic events occur.
- The timing and indications for surgical intervention to prevent systemic embolism in infective endocarditis remain controversial. Trials have shown that early surgery in patients with infective endocarditis and large vegetations significantly reduced death and embolic events by decreasing the risk of systemic embolism.

PEARLS & CONSIDERATIONS

COMMENTS

For endocarditis prophylaxis refer to Section V.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Endocarditis (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

EVIDENCE

Abstract[1]

Introduction:

Early identification of prognostic factors is essential to improve the grim prognosis associated with left-sided infective endocarditis. This group identified three independent risk factors obtained within 72 hr of admission, (*Staphylococcus aureus,* heart failure and periannular complications) for in hospital mortality or urgent surgery in a series of 317 patients diagnosed at five tertiary centers (derivation sample). A stratification score was constructed for the test cohort by a simple arithmetic sum of the number of variables present. The goal was to validate this model internally and externally in a prospective manner with two different cohorts of patients.

Methods:

The appropriateness of the model was tested prospectively on predicting events in two cohorts of patients with left-sided endocarditis: internally with the 263 consecutive patients diagnosed at the same centers where the model was derived (internal validation sample), and externally with 264 patients admitted at another hospital (external validation sample).

Results:

The discriminatory power of the model, expressed as the area under the receiver operating characteristic curve was similar between derivation and both validation samples (internal 0.67 vs 0.68, p=0.79; external 0.67 vs p=0.74, p=0.09). There was a progressive, significant pattern of increasing event rates as the risk stratification score increased in both validation cohorts ($p<0.001$ by $\chi 2$ for trend).

Conclusions:

The early risk stratification model derived, based on variables obtained within 72 hr of admission, is applicable to different populations with left-sided endocarditis. A simple bedside assessment tool is provided to clinicians that identifies patients at high risk of having an adverse event. Ⓐ

Evidence-Based Reference

Lopez J et al.: Internal and external validation of a model to predict adverse outcomes in patients with left-sided infective endocarditis, *Heart* 97:1138–1142, 2011. Ⓐ

SUGGESTED READINGS

Babu E et al.: *Staphylococcus lugdunensis*: The coagulase negative Staphylococcus you don't want to ignore, *Expert Rev Anti Infect Ther* 9(10):901–907, 2011.

Cecchi E et al.: Are the Duke criteria really useful for the early bedside diagnosis of infective endocarditis? Results of a prospective multicenter trial, *Ital Heart J* 6(1):41–48, 2005.

Cha R et al.: Bactericidal activities of daptomycin, quinupristin-dalfopristin, and linezolid against vancomycin-resistant Staphylococcus aureus in an in vitro pharmacodynamic model with simulated endocardial vegetations, *Antimicrob Agents Chemother* 47(12):3960–3963, 2003.

Fowler VG et al.: Daptomycin versus standard therapy for bacteremia and endocarditis caused by Staphylococcus aureus, *N Engl J Med* 355(7):653, 2006.

Hoen B, Duval X: Infective endocarditis, *N Engl J Med* 368:1425–1433, 2013.

Kang DH et al.: Early surgery versus conventional treatment for infective endocarditis, *N Engl J Med* 366:2466–2473, 2012.

McDonald JR et al.: Enterococcal endocarditis: 107 cases from the international collaboration on endocarditis merged database, *Am J Med* 118(7):759, 2005.

Morpeth S et al.: Non-HACEK gram-negative bacillus endocarditis, *Ann Intern Med* 147:829–835, 2007.

Morris AJ et al.: Gram stain, culture, and histopathological examination findings for heart valves removed because of infective endocarditis, *Clin Infect Dis* 36(6):697–704, 2003.

Patrick T et al.: Complexity and subtlety of infective endocarditis, *Mayo Clin Proc* 82(5):615–621, 2007.

Pierce D et al.: Infectious endocarditis: diagnosis and treatment, *Am Fam Physician* 85(10):981–986, 2012.

Wang A et al.: Contemporary clinical profile and outcome of prosthetic valve endocarditis, *JAMA* 297:1354–1361, 2007.

FIGURE EE1-15 Osler nodes. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

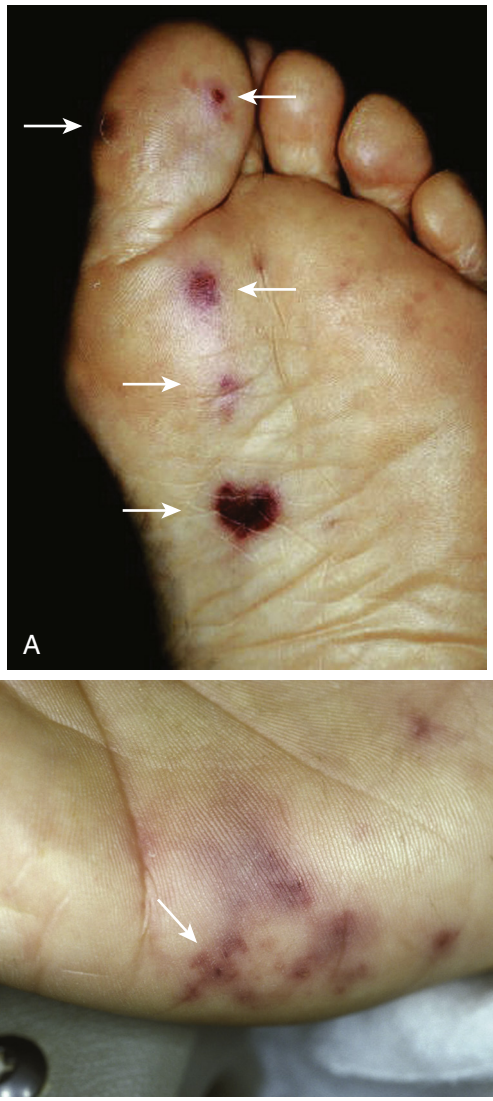

FIGURE EE1-16 Janeway lesions. These nontender, often hemorrhagic lesions *(arrows)* are most commonly associated with *Staphylococcus aureus* endocarditis. They result from septic microembolization. The lesions are usually macular to slightly nodular and involve the soles **(A)** and the thenar and hypothenar eminences of the palms **(B).** (From Mandell GL, Bennett JE, Dolin R [eds]: *Principles and practice of infectious diseases,* ed 6, Philadelphia, 2005, Churchill Livingstone; **B,** courtesy Marc E. Grossman, MD, FACP.)

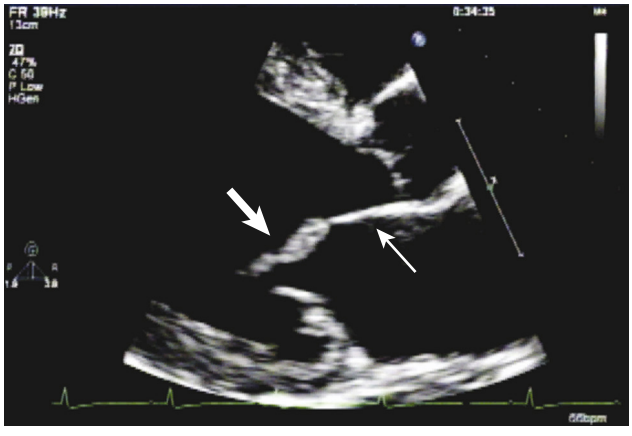

FIGURE EE1-18 Valvular vegetations. This parasternal long view on a transthoracic echocardiogram shows a large vegetation *(thick arrow)* on the mitral valve *(thin arrow).* The *large arrow* is in the left ventricle and the *thin arrow* is in the left atrium. (Courtesy Mark Goldberger, MD.)

Endometrial Cancer EBM PTG

BASIC INFORMATION

DEFINITION

Endometrial cancer (EC) is a malignant transformation of endometrial stroma and/or glands typified by irregular nuclear membranes, nuclear atypia, mitotic activity, loss of glandular pattern, and irregular cell size. The two main histologic subcategories of EC, endometrioid and nonendometrioid EC, show unique molecular aberrations and differing clinical behaviors.

SYNONYMS

Uterine cancer (some forms)

ICD-9CM CODES
182 Malignant neoplasm of body of uterus
ICD-10CM CODES
C54.1 Malignant neoplasm of endometrium
C55 Malignant neoplasm of uterus, part unspecified
C54.9 Malignant neoplasm of corpus uteri, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 21.2 cases per 100,000 persons; approximately 30,000 new cases annually. It is the most common gynecologic malignancy in the U.S.
PREDOMINANCE: Median age at onset: 60 yr; only 5% occur in women <40 yr
RISK FACTORS: Obesity, diabetes, nulliparity, early menarche and late menopause, unopposed estrogen therapy, tamoxifen use, oligoovulation with chronic unopposed estrogen exposure such as with polycystic ovary syndrome (PCOS), endometrial atypical hyperplasia, endometrial polyps (malignancy is found in 3.6% of endometrial polyps)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Abnormal uterine bleeding or postmenopausal bleeding in 90%
- Pyometra or hematometra
- Abnormal Pap smear

ETIOLOGY

Endogenous or exogenous chronic unopposed estrogen stimulation of the endometrium

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Atypical hyperplasia
- Other genital tract malignancy
- Uterine polyps
- Atrophic vaginitis
- Granuloma cell tumor
- Fibroid uterus

WORKUP

- Complete history and physical examination
- Endometrial biopsy or dilation and curettage
- Assessment of operative risk
- Staging (Table E1-10)

LABORATORY TESTS

- Complete blood count
- Chemistry profile including liver function tests
- Consider CA-125 level

IMAGING STUDIES

- Chest x-ray
- CT scan, and/or pelvic ultrasound (Fig. E1-19)
- Endovaginal ultrasound (Fig. E1-20) in postmenopausal women with vaginal bleeding

TREATMENT

NONPHARMACOLOGIC THERAPY

- Surgery is the mainstay of treatment, with or without radiation, depending on tumor stage and grade. Laparoscopic surgery for early-stage EC is as safe and effective as laparotomy. Robotic laparoscopy procedures have increased significantly in recent years for this indication.
- Surgery generally consists of pelvic washings, total abdominal hysterectomy and bilateral salpingo-oophorectomy, omental biopsy, and selective pelvic and periaortic lymphadenectomy, depending on stage and grade.
- Brachytherapy and/or teletherapy are added in an advanced stage.
- Chemotherapy (cisplatin, Adriamycin) or tamoxifen may also be used, especially for advanced or recurrent endometrial cancers.
- Aromatase inhibitors, currently primarily used for breast carcinoma, are being investigated as adjuvant therapy for endometrial cancer.
- Hormonal therapy is an option for some young women with early stage EC who wish to preserve fertility. This choice should be discussed with a gynecologic oncologist.

ACUTE GENERAL Rx

- A thorough workup should be completed before any therapy for EC.
- Surgery is the treatment of choice.

CHRONIC Rx

- Physical and pelvic examination every 3 mo for 2 yr, then every 6 mo for 2 yr, annually thereafter
- Yearly Pap smear
- Hormone replacement (combination) a consideration in low-risk patients (stage I or early stage II)

DISPOSITION

The majority of cases present early, and the 5-yr survival is generally good:

Stage I (Fig. E1-21)	75%-100%
Stage II	65%
Stage III	40%
Stage IV	10%

Some histologic types (clear cell, serous papillary) have worse survival rates.

TABLE E1-10 FIGO Staging of Endometrial Carcinoma

Stage	Definition	Stage at Presentation	Pelvic Nodes	5-Year Survival
I_A	Tumor limited to the endometrium	73%	>20%	85%
I_B	Growth that has invaded <50% of myometrial thickness			
I_C	Growth that has invaded >50% of myometrial thickness			
II_A	Endocervical glandular involvement only	11%	20%	65%
II_B	Cervical stroma involved			
III_A	Invades sero-serosal surface of uterus, 6 adnexa, 6 positive washings	13%	35%	40%
III_B	Vaginal metastases			
III_C	Metastases to pelvic or para-aortic nodes			
IV_A	Tumor invasion of bladder and/or bowel	3%	50%	10%
IV_B	Distant metastases including intra-abdominal and/or inguinal lymph nodes			

Histopathology: Degree of Differentiation

Uterine adenocarcinoma should be grouped according to the degree of differentiation as follows:
G1 – 5% or less of a solid growth pattern
G2 – 6%-50% of a solid growth pattern
G3 – More than 50% of a solid growth pattern

From Drife J, Magowan B: *Clinical obstetrics and gynecology*, Philadelphia, 2004, Saunders.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Endometrial Cancer (Patient Information)
Dysfunctional Uterine Bleeding (Related Key Topic)
Uterine Malignancy (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

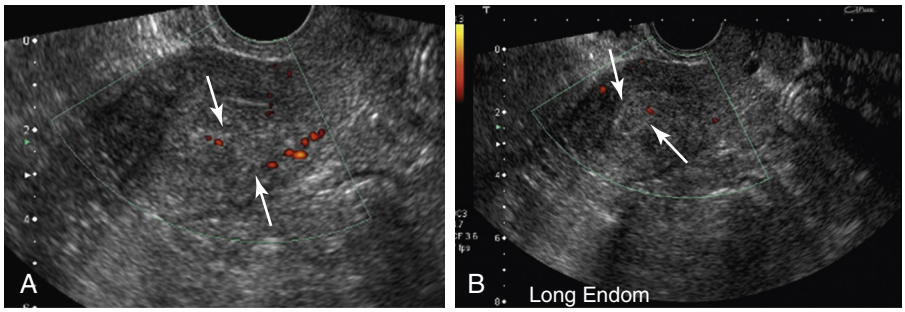

FIGURE E1-19 A 48-year-old woman with endometrial carcinoma. A, Endovaginal ultrasound (US) showing thickened, heterogeneous, cystic, and vascular hyperechoic tissue filling the endometrial cavity *(arrows)*. **B,** Second, sagittal US image showing the same. (From Fielding JR et al: *Gynecologic imaging*, Philadelphia, 2011, Saunders.)

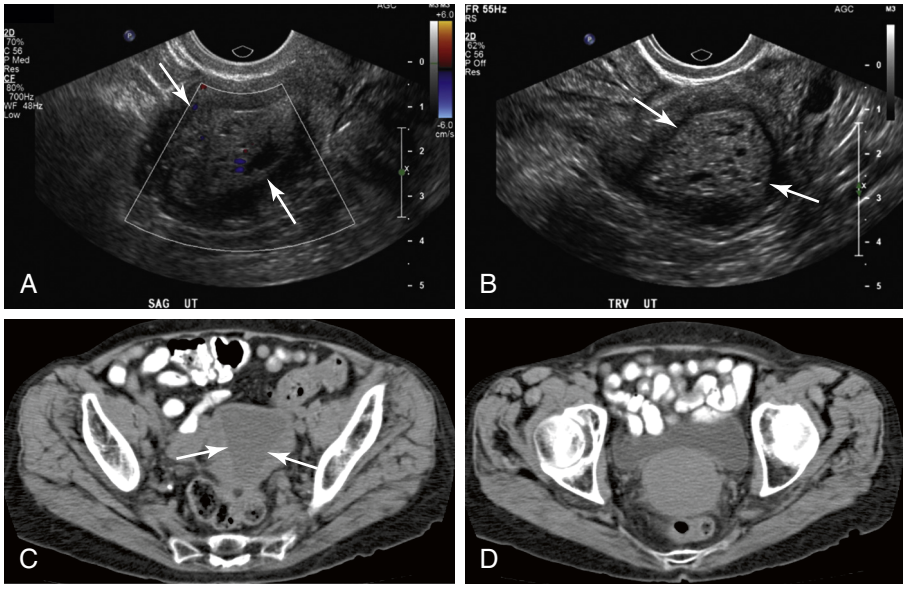

FIGURE E1-20 A 56-year-old woman with endometrial carcinoma. A, Sagittal ultrasound (US) image showing thickened cystic echogenic soft tissue filling the endometrial cavity *(arrows)*. **B,** Axial US image showing thickened cystic echogenic soft tissue filling the endometrial cavity *(arrows)*. **C,** Non–contrast-enhanced axial computed tomographic (CT) image showing low-attenuation tissue filling the endometrial canal *(arrows)* in a postmenopausal patient. Note fundal thinning. **D,** Non–contrast-enhanced axial CT image showing cervical soft tissue fullness. (From Fielding JR et al: *Gynecologic imaging*, Philadelphia, 2011, Saunders.)

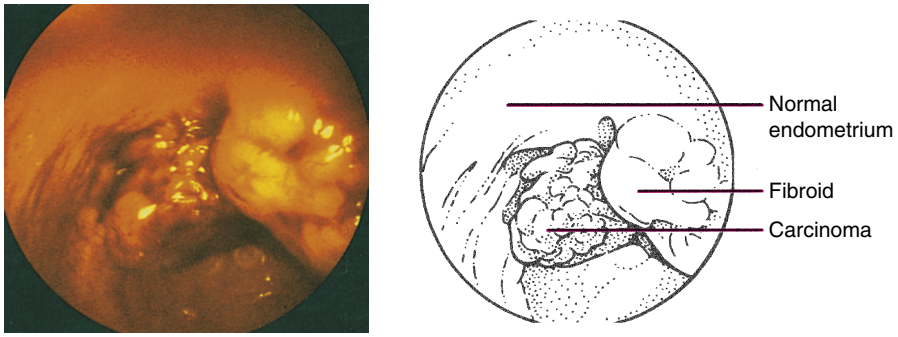

FIGURE E1-21 Stage I endometrial carcinoma. A small carcinoma can be seen adjacent to a uterine fibroid in this hysteroscopy photograph. Occasionally, a tumor this small may be missed on curettage. (From Skarin AT: *Atlas of diagnostic oncology*, 4th ed, St Louis, 2010, Mosby.)

EVIDENCE

Abstract[1]

Objective:

To determine the cost effectiveness of total laparoscopic hysterectomy (TLH) versus total abdominal hysterectomy (TAH) in early stage endometrial cancer alongside a multicenter randomized controlled trial (RCT).

Methods:

An economic analysis was conducted in 279 patients (TLH n=185; TAH n=94) with early stage endometrial cancer from a societal perspective, including all relevant costs over a three month time horizon. Health outcomes were expressed in terms of major complication-free rate and in terms of utility based on women's response to the EQ-5D. Comparisons of costs per major complication-free patient gained and costs with utility gain and costs were made, using incremental cost effectiveness ratios.

Results:

The mean major complication-free rate and median utility scores were comparable between TLH and TAH at three months. TLH is more costly intraoperatively (Δ$1.129) and less costly postoperatively in-hospital (Δ$–1.350) compared to TAH. Incremental costs per major complication-free patient were $–52. Higher cost ($249) were generated while no gains in utility (–0.02) were observed for TLH compared to TAH. Analyzing utility at six weeks, incremental costs per additional point on the EQ-5D scale were $1.617.

Conclusion:

TLH is cost effective compared to TAH, based on major complication-free rate as measure of effect. Along with future cost saving strategies in laparoscopy, TLH is assumed to be cost effective for both effect measures. Therefore and due to comparable safety, TLH should be recommended as a standard-of-care surgical procedure in early endometrial cancer. Ⓐ

Evidence-Based Reference

Bijen CB et al.: Cost effectiveness of laparoscopy versus laparotomy in early stage endometrial cancer: a randomised trial, *Gynecol Oncol* 121:76–82, 2011. Ⓐ

SUGGESTED READINGS

Amant F et al.: Endometrial cancer, *Lancet* 366(9484):491, 2005.

Bakkum-Gamez JN et al.: Current issues in the management of endometrial cancer, *Mayo Clin Proc* 83(1):97–112, 2008.

Basen-Engquist K et al.: Physical activity and obesity in endometrial cancer survivors: associations with pain, fatigue, and physical functioning, *Am J Obstet Gynecol* 200:288.e1–288.e8, 2009.

Lee SC et al.: The oncogenic potential of endometrial polyps: a systematic review and meta-analysis, *Obstet Gynecol* 116:1197, 2010.

Tabor A et al.: Endometrial thickness as a test for endometrial cancer in women with postmenopausal vaginal bleeding, *Obstet Gynecol* 99:529, 2002.

Zullo F et al.: Laparoscopic surgery vs laparotomy for early stage endometrial cancer: long-term data of a randomized controlled trial, *Am J Obstet Gynecol* 200:296.e1–296.e9, 2009.

BASIC INFORMATION

DEFINITION

Endometriosis is defined as the presence of functioning endometrial glands and stroma outside the uterine cavity (Fig. E1-22).

ICD-9CM CODES
617.9 Endometriosis
ICD-1-CM CODES
N80.9 Endometriosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:
- Endometriosis affects 10% of reproductive-aged women.
- Women with dysmenorrhea: 40% to 60%.
- Subfertile women: 20% to 30%.
- Incidence peaks at approximately 40 yr.

MOST COMMON AGE AT DIAGNOSIS: 25 to 29 yr.

GENETICS:
- Multifactorial inheritance pattern.
- 6.9% occurrence rate in first-degree female relatives.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Classic triad is dysmenorrhea, dyspareunia, and infertility.
- Presence of pelvic pain not correlated with the total area of endometriosis, type of lesion, or volume of disease, but is correlated with the depth of infiltration.
- Other symptoms include abnormal bleeding (premenstrual spotting, menorrhagia), cyclic abdominal pain, intermittent constipation/diarrhea, dyschezia, dysuria, hematuria, and urinary frequency.
- Rare manifestations: catamenial hemothorax, bloody pleural effusion, massive ascites occurring during menses.
- Most severe discomfort is associated with lesions >1 cm in depth.
- Bimanual examination may reveal tender uterosacral ligaments, cul-de-sac nodularity, induration of the rectovaginal septum, fixed retroversion of the uterus, adnexal mass, and generalized or localized tenderness.

ETIOLOGY

- Reflux and direct implantation theory: retrograde menstruation with implantation of viable endometrial cells to surrounding pelvic structures (Sampson's theory).
- Coelomic metaplasia theory: transformation of multipotential cells of the coelomic epithelium into endometrium-like cells.
- Vascular dissemination theory: transport of endometrial cells to distant sites by the uterine vascular and lymphatic systems.
- Autoimmune disease theory: disorder of immune surveillance allows growth of endometrial implants.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Ectopic pregnancy.
- Acute appendicitis.
- Chronic appendicitis.
- Pelvic inflammatory disease (PID).
- Pelvic adhesions.
- Hemorrhagic cyst.
- Hernia.
- Psychologic disorder.
- Irritable bowel syndrome.
- Uterine leiomyomata.
- Adenomyosis.
- Nerve entrapment syndrome.
- Scoliosis.
- Muscular/skeletal strain.
- Interstitial cystitis.

WORKUP

- Thorough history and physical examination, including inquiry about physical and emotional abuse. Defining diagnosis of endometriosis can be made only by histology of lesions that have been removed surgically.
- Laparoscopy for definitive diagnosis.
- Revised American Fertility Society (renamed American Society for Reproductive Medicine) scale to classify endometriosis (since 1985):

Stage I	Minimal
Stage II	Mild
Stage III	Moderate
Stage IV	Severe

LABORATORY TESTS

Cancer antigen 125 (CA125): limited overall value in the diagnosis of endometriosis
- Also elevated in ovarian epithelial neoplasm, myomas, adenomyosis, acute PID, ovarian cysts, pancreatitis, chronic liver disease, menstruation, and pregnancy.
- CA125 value >35 U/ml: positive predictive value of 0.58 and a negative predictive value of 0.96 for the presence of endometriosis.

IMAGING STUDIES

- Ultrasound: for evaluating adnexal mass; ultrasound characteristics may suggest endometriomas versus other benign or malignant ovarian conditions but persistent solid or cystic-solid ovarian masses require definitive tissue diagnosis with laparoscopy.
- MRI:
  1. Highly accurate in detecting endometriomas.
  2. Limited sensitivity in detecting diffuse pelvic endometriosis, especially if sessile lesions.
- CT scan may show adnexal masses of varying density (Fig. E1-23).

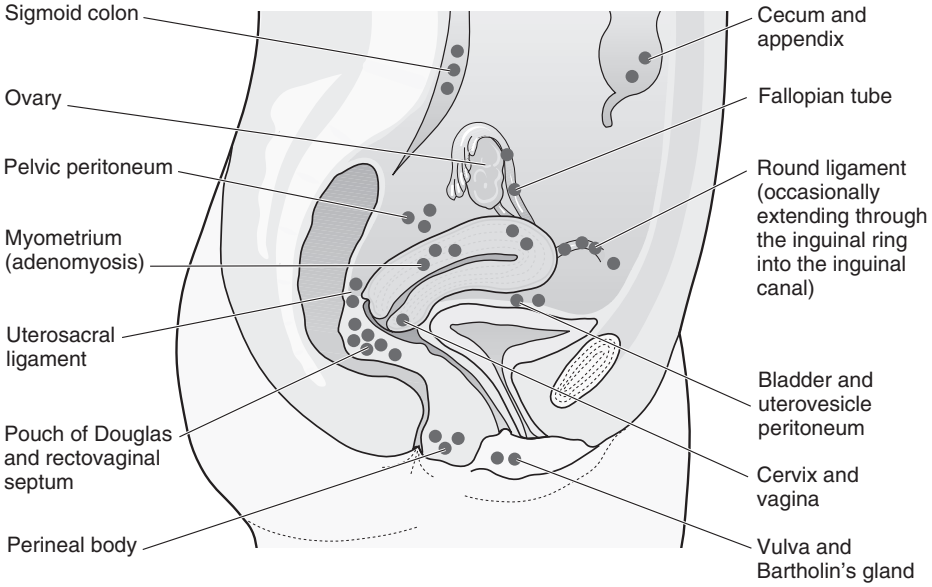

FIGURE E1-22 Common sites for endometriotic deposits in the pelvis. (From Drife J, Magowan B: *Clinical obstetrics and gynecology,* Philadelphia, 2004, Saunders.)

TREATMENT

NONPHARMACOLOGIC THERAPY

Expectant management (observation for 5 to 12 mo) for stage I or stage II endometriosis-associated infertility. Evaluation should take place if the couple meet the diagnostic criteria for infertility.

ACUTE GENERAL Rx

Nonsteroidal anti-inflammatory drugs for symptomatic relief of dysmenorrhea.

CHRONIC Rx

PHARMACOLOGIC MANAGEMENT: Estrogen-progesterone:
- State of "pseudopregnancy" created by continuous (discarding pill pack when placebo pills remaining and starting active pills from new pill pack) use of combination oral contraceptives for minimum of 6 mo and continuing indefinitely.

- Breakthrough bleeding treated by administering conjugated estrogens 1.25 mg/day for 2 wk.

Progestins:

- Medroxyprogesterone acetate 10 to 30 mg orally qd and occasionally up to 100 mg orally qd.
- Alternatively, 100 mg IM q2wk for four doses, followed by 200 mg IM monthly for 4 mo.
- Breakthrough bleeding treated with ethinyl estradiol (20 mcg/day) or conjugated estrogens (1.25 mg/day) for 1 to 2 wk.
- Comparison with danazol: progestins cost less, have a more tolerable side-effect profile, and have comparable efficacy with regard to pain relief and so are often the first-line drug. Very little justification for the use of danazol.

Gonadotropin-releasing hormone (GnRH) agonists:

- Use usually limited to 6-12 mo due to hypoestrogenic effects such as osteopenia or osteoporosis but can be given longer in certain circumstances, particularly when paired with estrogen add-back therapy. Referral to specialist strongly advised.
- Leuprolide acetate depot 3.75 mg IM monthly or 11.25 mg IM q3mo or nafarelin 200 mcg nasal puffs bid or goserelin 3.6 mg SC monthly.
- As effective as danazol for relief of pelvic pain.
- Add-back therapy for protection against vasomotor symptoms and bone loss: norethindrone acetate 5 mg PO qd alone or in combination with conjugated estrogen 0.625 mg orally qd.
- Add-back therapy allows gonadotropin-releasing hormone (GnRH) agonist use to be extended to 1 yr based on limited studies available

Alternative therapies for inhibition of estrogen action currently under investigation are:

- Aromatase inhibitors: anastrozole, letrozole.
- SERM: raloxifene.
- Agents enhancing cell-mediated immunity are cytokines (interleukin-12 and interferon-α2b).
- Immunomodulators (loxoribine, levamisole).
- Anti-inflammatory: pentoxifylline.

SURGICAL MANAGEMENT:

Conservative:

- Directed at enhancing fertility or treating pain unresponsive to first-line medical treatment.
- Usually accomplished through laparoscopy.
- Removal or destruction of endometriotic implants by excision, electrocautery, or laser.
- Cystectomy for endometrioma; must remove cyst wall to be effective long-term.
- Laparoscopic uterosacral nerve ablation for midline pain such as dysmenorrhea or dyspareunia (evidence does not support its use).
- Unless pregnancy is desired, patient is usually started on GnRH agonist therapy or continuous OCP immediately after surgery.
- For those desiring pregnancy, surgery alone results in significant increase in fertility.

Definitive:

- Directed at relieving endometriosis-associated pain.
- Total abdominal hysterectomy with bilateral salpingo-oophorectomy and complete excision or ablation of endometriosis.
- Thorough abdominal exploration to ensure removal of all disease.
- Must be prepared to manage possible gastrointestinal and urinary tract endometriosis.
- 90% effective in pain relief; patient must be counseled that pain relief is not guaranteed.
- Estrogen replacement therapy (ERT) to be considered in all women undergoing definitive surgical management; after ERT, recurrence rate is 0% to 5% in women with endometriosis confined to the pelvis but 18% in women with bowel involvement.
- Concern for malignant degeneration exists in implants if unopposed estrogen is used after definitive surgical therapy.

MANAGEMENT OF ENDOMETRIOSIS-ASSOCIATED INFERTILITY:

Conservative surgery:

- Yields significantly higher pregnancy rate than does expectant management, in part because of correction of mechanical factors such as adhesions.

Assisted reproductive technologies:

- Can be used to circumvent unknown mechanism of endometriosis-associated infertility.
- Superovulation with clomiphene citrate or human menopausal gonadotropins; clomiphene citrate results in threefold pregnancy rate over either danazol or expectant management.
- Further improvement with intrauterine insemination combined with superovulation.
- In vitro fertilization if above procedures are unsuccessful.

DISPOSITION

Tends to recur unless definitive surgery is performed, and should be considered a chronic condition.

REFERRAL

To a reproductive endocrinologist for advanced surgical management or infertility management.

PEARLS & CONSIDERATIONS

COMMENTS

Patient information can be obtained through the following organizations: Endometriosis Association, 8585 North 76th Place, Milwaukee, WI 53223, 414-355-2200 or 800-992-ENDO; Women's Reproductive Health Network, P.O. Box 30167, Portland, OR 97230-9067 or 503-667-7757.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Dysmenorrhea (Related Key Topic)
Dyspareunia (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

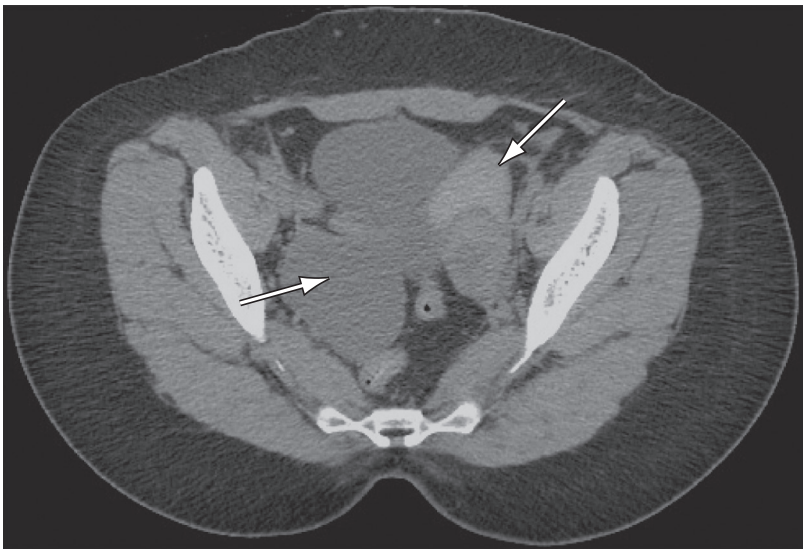

FIGURE E1-23 Computed tomographic scan demonstrates adnexal masses of varying density, subsequently proven to be endometriomas. (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.)

SUGGESTED READINGS

ACOG: Updated guideline on diagnosis and treatment of endometriosis, *Obstet Gynecol*, July 2010. Available at http://journals.lww.com/greenjournal/citation/2010/07000/practice_bulletin_no__114__management_of.41.aspx.

Bulun SE: Endometriosis, *N Engl J Med* 360:268–279, 2009.

Giudice LC: Endometriosis, *N Engl J Med* 362:2389–2398, 2010.

Olive DL: Gonadotropin-releasing hormone agonists for endometriosis, *N Engl J Med* 359:1136, 2008.

Schrager S et al.: Evaluation and treatment of endometriosis, *Am Fam Physician* 87(2):107–113, 2013.

Winkel CA: Evaluation and management of women with endometriosis, *Obstet Gynecol* 102(2):397, 2003.

BASIC INFORMATION

DEFINITION

Endometritis is defined as a uterine infection after delivery or abortion.

SYNONYMS

Endomyometritis
Metritis

ICD-9CM CODES
615.9 Endometritis
ICD-10CM CODES
O85 Puerperal sepsis
O86 Other puerperal infections
O86.1 Other infection of genital tract following delivery
O86.8 Other specified puerperal infections

EPIDEMIOLOGY & DEMOGRAPHICS

- Overall rate of postpartum infection: estimated between 1% and 8%.
- Most common genital tract infection after delivery.
- Usually presents early in postpartum period; more commonly seen after cesarean section than vaginal delivery; also seen with an incomplete abortion (spontaneous abortion, legal abortion, or illegal abortion).
- More common in preterm deliveries.
- Possible after any uterine manipulation in the presence of undiagnosed cervicitis or vaginitis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Postpartum oral temperature >37.8° C.
- Localized uterine tenderness, purulent or foul lochia; physical examination revealing uterine or parametrial tenderness.
- Nonspecific signs and symptoms such as malaise, abdominal pain, chills, and tachycardia.

ETIOLOGY

Endometritis is usually associated with multiple organisms: group A or B streptococci, *Staphylococcus aureus* and *Bacteroides* species, *Neisseria gonorrhoeae, Chlamydia trachomatis,* enterococci, *Gardnerella vaginalis, Escherichia coli,* and *Mycoplasma.*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Causes of postoperative or postprocedural infections

WORKUP

Diagnosis based on symptoms of fever, malaise, abdominal pain, uterine tenderness, and purulent, foul vaginal discharge.

LABORATORY TESTS

Complete blood count, blood cultures, and uterine culture

IMAGING STUDIES

Ultrasound (Fig. E1-24) may be useful if retained products are considered a possible source of infection.

TREATMENT

ACUTE GENERAL Rx

Treatment options include doxycycline plus one of the following:
1. Cefoxitin.
2. Ticarcillin-clavulanate.
3. Ertapenem.
4. Imipenem-cilastatin.
5. Meropenem.
6. Ampicillin-sulbactam.
7. Piperacillin-tazobactam.

- An alternative regimen is clindamycin plus aminoglycoside or ceftriaxone.
- Regimen should be continued for at least 48 hr after substantial clinical improvement. If response is not adequate (Table E1-11), check cultures and treat with appropriate antibiotics.

CHRONIC Rx

Watch for recurrent infection.

DISPOSITION

With appropriate antibiotic therapy, 95% to 98% cure rate.

REFERRAL

For patients who do not respond within 48 to 72 hr of appropriate antibiotic therapy, obtain an infectious disease consultation or gynecologic consultation.

AUTHOR: **RUBEN ALVERO, M.D.**, and **GEORGE T. DANAKAS, M.D.**

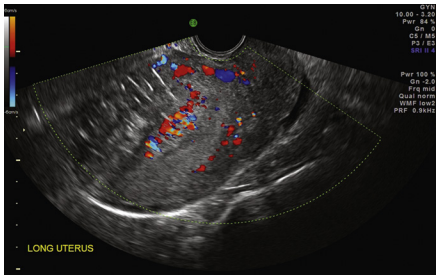

FIGURE E1-24 Endometritis. Patient with uterine tenderness and fever 7 days after classic cesarean section for premature rupture of membranes, chorioamnionitis, and fundic presentation at 27 weeks' gestational age. Sagittal transvaginal ultrasound shows increased vascularity within the endometrium, which can be seen with endometritis. Linear echogenic foci within the anterior myometrium likely represent air and suture material in the vertical uterine incision. Patient's symptoms resolved with antibiotics. (From Fielding JR et al: *Gynecologic imaging*, Philadelphia, 2011, Saunders.)

TABLE E1-11 Identified Causes of Poor Response to Antibiotic Therapy in Patients with Endometritis

Cause	Approximate Prevalence (%)
Infected mass, including abscess, hematoma, septic pelvic thrombophlebitis, pelvic cellulitis, retained placenta	40-50
Resistant organisms, commonly enterococci, in a patient receiving clindamycin-aminoglycoside or a cephalosporin	20
Additional cause, including catheter phlebitis, inadequate dose of antibiotics	10
No cause evident but response to empirical change in antibiotic therapy	20-30

From Gorbach SL: *Infectious diseases,* ed 2, Philadelphia, 1998, Saunders.

BASIC INFORMATION

DEFINITION

Enuresis refers to the voiding of urine into clothes or in bed that is either voluntary or involuntary in individuals who are expected to be continent (>5 yr of age). The diagnosis is made if voiding occurs at least twice a week for 3 months. Primary enuresis refers to enuresis without a period of continence, whereas secondary enuresis occurs after a 6-month period of normal bladder control.

SYNONYMS

Urinary incontinence
Bedwetting

ICD-9CM and DSM-5 CODES
307.6 Enuresis
ICD-10CM CODES
F98.0 Non-organic enuresis

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Ages 5 to 10 yr. 5 to 7 million children in the U.S. have enuresis.
PREVALENCE (IN U.S.)
- Age 5 yr: 7% of males and 3% of females.
- Age 10 yr: 3% of males and 2% of females.
- Ages 15 and older: 1% of males and females.

PREDOMINANT SEX: Twice as many males as females at all ages
PREDOMINANT AGE: Highest prevalence at age 5 with a steady decrease thereafter at a rate of approximately 12% to 15% per year
GENETICS:
- Approximately 75% of children with enuresis have a first-degree relative with enuresis.
- Almost twice as common in monozygotic than dizygotic twins.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Three enuresis subtypes are defined in DSM-5:
- Nocturnal only (also known as monosymptomatic enuresis): occurs in each sleep stage in proportion to the time spent in the particular stage. May occur during transition from deep sleep to REM and is without other lower urinary tract symptoms.
- Diurnal only (also referred to as urinary incontinence): more frequent in girls and rarely after age 9 yr; voiding occurs in early afternoon on school days. Within this subtype, individuals have "urge incontinence" with sudden symptoms of urgency and detrusor instability or "voiding postponement" where individuals ignore urges until the point of incontinence.
- Combined nocturnal and diurnal.

ETIOLOGY

- Enuresis often correlates with other maturational delays, particularly language, motor skills, and social development.
- May be related to toilet training issues, stress (secondary enuresis), inability to concentrate urine, altered smooth muscle physiology, small bladder capacity, or dysfunction of the arousal system.
- Diurnal enuresis associated with a higher rate of urinary tract infections.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- The pathophysiology of primary enuresis involves the inability to awaken from sleep in response to full bladder, or a decreased functional capacity of the bladder with possible excessive nighttime urine production.
- May be associated with encopresis and sleep disorders such as sleep terrors; much less likely to be a primary psychological disorder.
- Organic causes of enuresis include diabetes mellitus, diabetes insipidus, bladder outlet obstruction, small bladder capacity, detrusor instability, urethral valves, meatal stenosis, cerebral palsy, spina bifida, pelvic mass, impacted stool, sedating medications, nocturnal seizures, and obstructive sleep apnea.

WORKUP

- History and physical examination to rule out anatomic abnormalities. Fluid intake and voiding diaries may be useful.
- Children frequently experience shame, so gentleness and care must be exercised when questioning or examining the child.
- Observation of voiding stream is useful.

LABORATORY TESTS

- Urinalysis with specific gravity and urine culture if white cells or nitrites to rule out infection.
- Serum studies to rule out diabetes, electrolyte abnormalities, or renal dysfunction.

IMAGING STUDIES

- In complicated cases, or if there is evidence of obstructive sleep apnea, sleep studies may be useful.
- If an anatomic abnormality is suspected, urologic imaging, including voiding cystourethrogram and renal sonogram is possibly indicated: an abdominal x-ray may demonstrate stool retention; MRI of the spine if evidence of abnormalities of lower spine or perineum is found on examination.

TREATMENT

NONPHARMACOLOGIC THERAPY

Behavioral treatment:
- Alarm and pad technique: up to 80% cure rate, although 30% relapse.
- Scheduled voiding to reduce the frequency of enuretic episodes.
- Motivational therapy including sticker or star charts to reward child for dry nights.
- Punishment for enuresis is not effective.

ACUTE GENERAL Rx

- Desmopressin (DDAVP) administered orally at bedtime significantly reduces the incidence of bedwetting (the intranasal preparation is associated with a greater risk for water intoxication and is not recommended).
- Tricyclic antidepressants (imipramine): efficacy supported by randomized control trials. Use with care in children, given the side effect profile.
- Serotonin reuptake inhibitors: lack of adequate trials is notable.
- Indomethacin suppositories may reduce normal prostaglandin inhibitory effects on antidiuretic hormone.
- Table E1-12 summarizes medications commonly used for treatment of monosymptomatic nocturnal enuresis. Fig. E1-25 describes an algorithm for management of pediatric enuresis and voiding dysfunction.

TABLE E1-12 Medications for Treatment of Monosymptomatic Nocturnal Enuresis

Generic Name (Trade Name)	Dosage Formulation	Dosage Regimen	Mechanisms of Action	Comments
Desmopressin acetate (DDAVP)	Tablets: 0.1 mg, 0.2 mg	0.2 mg PO qhs, increasing up to 0.4 mg	Decreased urine volume Possible effect on sleep arousal through its action as a central nervous system neurotransmitter	Risk of water intoxication (headache, seizures); hence, limit fluids 1 hr before and 3 hours after the dose Stop treatment during illness or conditions necessitating increased fluid intake
Imipramine hydrochloride (Tofranil)	Tablets: 10 mg, 25 mg, 50 mg; Tofranil PM capsule 75, 100, 125, 150 mg	1.5-2 mg/kg 2 hr before bedtime, not to exceed 50 mg in children less than 12 yr and 75 mg in older children	Anticholinergic effect on bladder Increased resistance of bladder outlet Possible central inhibition of micturition reflex Possible effect on sleep arousal by central noradrenergic facilitation	Can cause sleep disturbance, mood alteration, decreased appetite Risk of cardiac arrhythmia with overdose

Modified from Chandra MM: Enuresis and voiding dysfunction. In Burg FD et al (eds): *Current pediatric therapy,* ed 18, Philadelphia, 2006, Saunders.

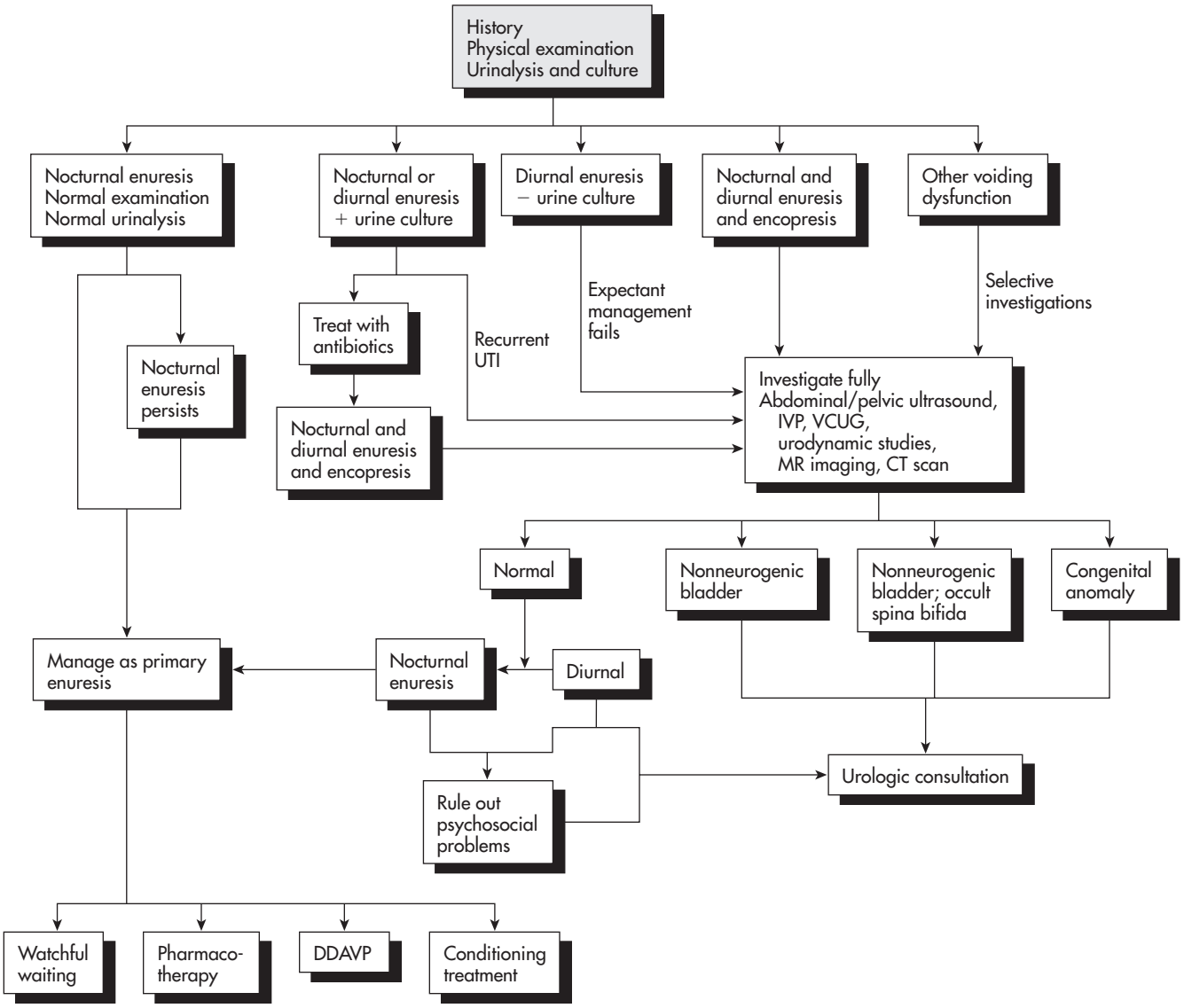

FIGURE E1-25 Algorithm of management of pediatric enuresis and voiding dysfunction. *CT,* Computed tomography; *DDAVP,* desmopressin acetate; *IVP,* intravenous pyelogram; *MR,* magnetic resonance; *UTI,* urinary tract infection; *VCUG,* voiding cystourethrogram. (From Nseyo UO [ed]: *Urology for primary care physicians,* Philadelphia, 1999, Saunders.)

DISPOSITION

- After age 5 yr, the rate of spontaneous remissions is approximately 12% to 15% per year.
- The disorder usually resolves by adolescence. However, effective treatment spares considerable misery.
- Fewer than 1% will have enuresis as adults.

REFERRAL

- If coexisting, a psychiatric condition complicates the course of treatment.
- Referral to a pediatric urologist is indicated for primary enuresis refractory to therapy and for selected secondary causes (e.g., urinary tract malformations, neurologic disorders).

PEARLS & CONSIDERATIONS

Illness, hospitalization, and family stressors may precipitate recurrent enuresis after a period of dryness.

PATIENT & FAMILY EDUCATION

American Academy of Pediatrics www.healthychildren.org/English/ages-stages/toddler/toilet-training/Pages/default.aspx

Kidshealth http://kidshealth.org/parent/general/sleep/enuresis.html

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Bedwetting (Patient Information)

AUTHORS: **CATHLEEN ADAMS, M.D.** and **MARTA MAJCZAK, M.D.**

SUGGESTED READINGS

Baird DC, Seehusen DA, Bode DV: Enuresis in children: a case-based approach, *Am Fam Physician* 90(8):560–568, 2014.

Makari J, Ruston HG: Nocturnal enuresis, *Am Fam Physician* 73(9):1611, 2006.

Ramakrishnan K: Evaluation and treatment of enuresis, *Am Fam Physician* 78(4):489–496, 2008.

Robson WL: Clinical practice. Evaluation and management of enuresis, *N Engl J Med* 360(14):1429–1436, 2009.

Van Dommelen P et al.: The short- and long-term effects of simple behavioral interventions for nocturnal enuresis in young children: a randomized controlled trial, *J Pediatr* 154(5):662–666, 2009.

BASIC INFORMATION

DEFINITION

Eosinophilic fasciitis (EF) is a rare inflammatory disease of the skin and subcutaneous tissue that is initially characterized by erythema, edema, and eosinophilia in peripheral blood. This condition starts with symmetrical erythema, edema, and induration of an extremity or trunk and later may progress to sclerosis of the dermis and subcutaneous fascia leading to contractures.

SYNONYMS

Shulman's syndrome
Diffuse fasciitis with eosinophilia

ICD-9CM CODES
728.89 Eosinophilic fasciitis
ICD-10CM CODES
M35.4 Diffuse (eosinophilic) fasciitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Males and females are affected equally.
- Most common in the fourth and fifth decades.

CLINICAL PRESENTATION

- Initial presentation consists of acute erythema, swelling, and induration of the skin that is accompanied by eosinophilia.
  1. Extremities usually symmetrically involved.
  2. Upper more commonly affected than lower extremities.
  3. Face, hands, and feet are spared.
  4. Sunken veins may be seen when the extremity is elevated (Fig. EE1-26). The groove sign marks the borders of different muscle groups.
  5. Skin may appear deeply rippled (peau d'orange).
- Arthritis was found in 40% of cases in one series.
- Cranial and peripheral neuropathy (carpal tunnel syndrome, mononeuritis multiplex) may occur.
- Myalgia and weakness are common. Inflammatory myositis is uncommon.
- Constitutional symptoms such as weight loss or asthenia may be present at the onset.
- Hematologic abnormalities other than eosinophilia are present in 10% of cases in one series, including aplastic anemia, amegakaryocytic thrombocytopenia, myeloproliferative disorders, and hematologic malignancies.
- The presence of Raynaud's phenomenon and visceral involvement is more suggestive of systemic sclerosis or other scleroderma-like disorders than EF.

ETIOLOGY

The etiology is unknown. Most cases are considered idiopathic. Eosinophil granule products may contribute to the development of fascia fibrosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Systemic sclerosis.
- Systemic or localized scleroderma.
- Scleroderma-like disorders.
- Chemical-induced sclerosis.
- Eosinophilia-myalgia syndrome.
- Porphyria cutanea tarda.
- Chronic Lyme borreliosis.

WORKUP

- Physical examination to confirm characteristic distribution.
- Skin biopsy that penetrates to muscle is mandatory for diagnosis:
  1. Epidermis is usually normal.
  2. Dermis may demonstrate mild inflammation with lymphocytes, histiocytes, plasma cells, and eosinophils with some fibrosis.
  3. Moderate inflammation of subcutaneous tissue and sclerosis of fat septa.
  4. Muscle demonstrates perivascular mixed inflammatory cell infiltrate.

LABORATORY TESTS

- Peripheral eosinophilia in up to 70% during the acute phase of the disease.
- Elevated erythrocyte sedimentation rate (29%).
- Hypergammaglobulinemia (35%).
- Creatine kinase is usually normal even in patients with myalgia.
- Occasional thrombocytopenia, anemia.
- Serum antinuclear antibodies are negative.

IMAGING STUDIES

- MRI is the best study in assessing patients with suspected EF.
- Increased T2 signal in the subcutaneous and deep fascia with enhancement of these structures on T1 images after gadolinium administration. Gadolinium-containing contrast agents should be avoided in patients with renal function impairment (GFR <15-30 ml/min) to avoid developing nephrogenic systemic fibrosis.

TREATMENT

ACUTE GENERAL Rx

- Although no controlled trials exist, corticosteroids (prednisone 0.5 to 1 mg/kg/day) lead to a partial or complete response in 70% to 90% of patients, but the duration and extent of symptom reduction are variable. From 3 to 6 months should be sufficient to assess the effectiveness. The dose can be increased up to 1.5 mg/kg in cases resistant to the initial dose.
- In resistant cases, methotrexate, hydroxychloroquine, mycophenolate mofetil, psoralen plus ultraviolet A photochemotherapy, cyclosporine, antithymocyte globulin, D-penicillamine, infliximab, intravenous immune globulin, and sulfasalazine have been successfully used in some patients.

CHRONIC Rx

Surgery is sometimes required to reduce contractures and maintain function.

DISPOSITION

- Prognosis is generally good with not uncommon spontaneous regression and response to steroids.
- Contractures are common.
- 10% may develop blood dyscrasias.

REFERRAL

To dermatology for biopsy to make definitive diagnosis. Functional impairment requires surgical evaluation.

FIGURE EE1-26 Eosinophilic fasciitis. This 29-year-old butcher had to stop working because of a generalized painful induration of his skin. Fingers were spared. As he raised his forearms, the collapsed veins appeared as grooves (the "groove sign"), which is pathognomonic of eosinophilic fasciitis. His condition subsided 4 years later, leaving joint contractures. (From Canoso J: *Rheumatology in primary care,* Philadelphia, 1997, Saunders.)

PEARLS & CONSIDERATIONS

COMMENTS

- EF is a rare inflammatory disorder of unknown etiology with symmetric painful edema and induration of the arms and legs with peripheral eosinophilia.
- Rapid onset, progression, and good response to systemic corticosteroids are characteristic of the disease.
- Prognosis is usually good.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **ETSUKO AOKI, M.D., PH.D.**

SUGGESTED READINGS

Mosconi S et al.: Eosinophilic fasciitis (Shulman syndrome), *Dermatology* 205(2):204, 2002.

Moulton SJ et al.: Eosinophilic fasciitis: spectrum of MRI findings, *AJR Am J Roentgenol* 184(3):975, 2005.

Lebeaux D et al.: Eosinophilic fasciitis (Shulman disease): new insights into the therapeutic management from a series of 34 patients, *Rheumatology* 51(3):557, 2012.

BASIC INFORMATION

DEFINITION

Eosinophilic pneumonias (EPs) are a group of disorders characterized by pulmonary infiltrates, pulmonary parenchymal eosinophilia, and possibly peripheral blood eosinophilia. They manifest by different radiologic and clinical syndromes.

SYNONYMS

Simple pulmonary eosinophilia
Chronic eosinophilic pneumonia
Acute eosinophilic pneumonia
Churg-Strauss syndrome
Idiopathic hypereosinophilic syndrome
Allergic bronchopulmonary aspergillosis
Parasite-induced, fungal-induced, and drug-induced pulmonary eosinophilia

ICD-9CM CODES
518.3 Eosinophilic pneumonia
ICD-10CM CODES
J82 Pulmonary eosinophilia, not elsewhere classified

EPIDEMIOLOGY & DEMOGRAPHICS

Vary depending on the specific cause

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fever, cough, and shortness of breath
- Vary depending on the specific cause

ETIOLOGY

SIMPLE PULMONARY EOSINOPHILIA (LÖFFLER'S SYNDROME):
- Transient pulmonary infiltrates
- Symptoms range from asymptomatic to dyspnea and dry cough
- Usually idiopathic
- May be secondary to parasitic infection or drugs (nitrofurantoin, penicillin)
- Remove the offending agent
- If idiopathic and severe symptoms, then give glucocorticoid therapy

IDIOPATHIC ACUTE EP:
- Absence of infection or other cause
- Acute onset of fever, cough, dyspnea (<1 mo); often presents with acute respiratory failure, requiring intensive care
- Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and IgE may be elevated but nonspecific
- Bilateral diffuse infiltrates on chest radiograph
- High-resolution CT scan of the chest may demonstrate patchy ground glass with reticular infiltrates; small pleural effusions present in two thirds of cases
- Pleural fluid analysis reveals elevated pH and high eosinophil count
- Hypoxemia (PaO_2 <60)
- Lung eosinophilia >25% on bronchoalveolar lavage (BAL)
- Pulmonary function test can demonstrate restrictive dysfunction with reduction in diffusion capacity
- Associations: recent onset of tobacco smoking, World Trade Center dust, Scotchguard inhalation, tear gas, gasoline, indoor renovation work, multiple medications, firework smoke, cocaine
- Steroids lead to rapid improvement, though there is no consensus about ideal dosing strategy

IDIOPATHIC CHRONIC EP:
- Absence of infection or other cause
- Presentation over weeks to months
- Productive cough, dyspnea, malaise, weight loss, night sweats, and fever (with or without hemoptysis/chest pain)
- Progressive pulmonary infiltrates
- "Photographic negative" pulmonary edema (peripheral alveolar infiltrates) is pathognomonic but only present in 25% of cases; high-resolution CT of the chest may reveal atelectasis, pleural effusions, lymphadenopathy, and septal line thickening
- Blood eosinophilia not always present
- ESR, CRP, platelets, and IgE may be elevated but are nonspecific
- Diagnose by BAL (up to 90% of cases will have 60% eosinophils) or lung biopsy
- Spontaneous remission in 10% of cases
- Treatment with glucocorticoids is rapidly effective
- Relapses are common when glucocorticoids tapered
- Prevalence of patients with asthma

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA):
- Hypersensitivity reaction to *Aspergillus fumigatus*
- Occurs most often in patients with asthma and atopy (up to 13% of the asthma population)

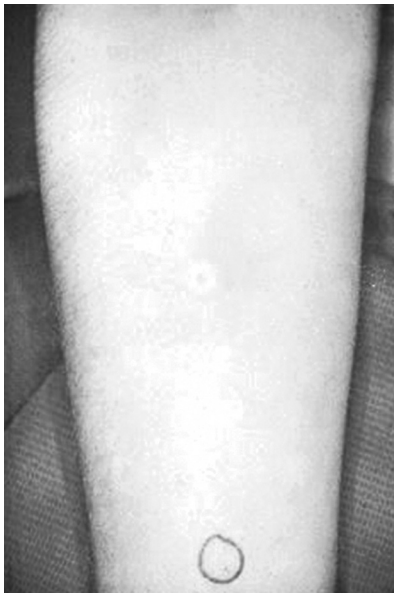

FIGURE EE1-27 A positive prick test with *Aspergillus fumigatus* in a patient with allergic bronchopulmonary aspergillosis. The wheal and erythema reaction at 15 min after performing the skin test. (From Fireman P: *Atlas of allergies and immunology,* ed 3, St Louis, 2006, Mosby.)

- Fever, flulike symptoms, myalgias, lassitude, persistent cough and wheezing, hemoptysis, and/or expectoration of brown-black mucous plugs
- A patient with chronic asthma with a component of bronchiectasis and pulmonary infiltrates should be evaluated carefully for ABPA
- Chest radiograph: infiltrates (sometimes migratory) and atelectasis, reflecting endobronchial mucous inspissation ("finger in glove")
- Blood and sputum eosinophilia
- Diagnosis by
  1. *Aspergillus* isolation from multiple sputum samples
  2. Positive skin test to *Aspergillus* (Fig. EE1-27)
  3. Elevated serum IgE
  4. *Aspergillus*-specific IgE and IgG
  5. Serum eosinophilia >1000 cells/mL

The disease has been characterized by a staging system:
Patients do not necessarily proceed from one stage to another.

Stage I	Acute phase
Stage II	Remission
Stage III	Exacerbation
Stage IV	Glucocorticoid-dependent ABPA
Stage V	End-stage (fibrotic) ABPA

- Treatment: systemic corticosteroids are the mainstay of treatment. Antifungals may provide additional benefit in modulating airway fungal burden and are recommended for use in patients with relapse or glucocorticoid-dependent disease
- Development of bronchiectasis portends a worse prognosis
- Response to therapy and activity of disease may be monitored by measuring IgE levels, which will decrease by 35% to 50% when a patient is in remission

TROPICAL PULMONARY EOSINOPHILIA:
- Onset of asthma, fever, paroxysmal cough and bronchospasm, marked blood eosinophilia
- Basilar reticulonodular and alveolar infiltrates
- High serum IgE levels
- Presumed etiology: filariasis

PULMONARY VASCULITIS (ALLERGIC GRANULOMATOSIS AND ANGIITIS OR CHURG-STRAUSS SYNDROME):
- Vasculitis and necrotizing granulomatous inflammation that involves many organ systems in the setting of asthma
- Blood eosinophilia and elevated IgE
- Antineutrophilic cytoplasmic antibody may be positive in up to two thirds of patients; antinuclear antibody, rheumatoid factor, and ESR also may be elevated
- Common symptoms include cough, dyspnea, sinusitis, allergic rhinitis; other symptoms depend on other organs involved
- Pulmonary function test may reveal obstructive dysfunction
- Organ and systems involved include lungs, heart (including refractory coronary vasospasm), skin, gastrointestinal, renal, neurologic

The pathogenesis is not clearly known. Several infectious agents (*Aspergillus, Candida, Ascaris, Actinomyces*), bird exposure, cocaine, and drugs (sulfonamides used together with antiserum, diflunisal, macrolides, diphenylhydantoin) have been considered potential triggers.

HYPEREOSINOPHILIC SYNDROME:

- A disease of persistently elevated eosinophils (>6 mo) with no known cause
- Cardiac problems are the prominent clinical feature with mural thrombi and endocardial/myocardial fibrosis
- Hepatosplenomegaly is common
- Fever, cough, weight loss, wheezing, CNS abnormalities
- May have a myeloproliferative or a lymphocytic etiology
- Diagnosis of exclusion
- Check echocardiogram
- Treat with steroids if symptoms or cardiac abnormalities
- Several potential targets for treatment are currently under investigation, including IL-5, IL5-R, CD2 binding protein, IgE, and IL-4/IL-13 receptor.

DRUG- OR TOXIN-INDUCED EP:

- Can have several different clinical presentations, including simple pulmonary eosinophilia, chronic, or acute
- Symptoms resolve when offending drug is removed
- Described causes of drug/toxin-induced EP: antibiotics, NSAIDs, amiodarone, bleomycin, captopril, gold salts, iodine, methotrexate, venlafaxine, daptomycin, benzbromarone, smoke, illicit drugs, radiation exposure
- BAL to exclude infection or other lung disease
- Laboratory evaluation rarely diagnostic

DIAGNOSIS

- Diagnosis varies depending on specific cause of pneumonia.
- Usually involves chest radiograph, CT, peripheral eosinophil count, BAL, and possibly lung biopsy.

DIFFERENTIAL DIAGNOSIS

- Tuberculosis
- Brucellosis
- Fungal diseases
- Parasitic infection *(Ascaris, Strongyloides)*
- Idiopathic pulmonary fibrosis
- Bronchiolitis obliterans and organizing pneumonia
- Radiation pneumonitis
- Bronchogenic carcinoma
- Hodgkin's disease
- Immunoblastic lymphadenopathy
- Rheumatoid lung disease
- Sarcoidosis

WORKUP

Physical examination, laboratory tests, imaging, bronchoscopy

LABORATORY TESTS

- WBC counts are often normal
- Often blood eosinophilia
- Elevated eosinophil count on BAL

IMAGING STUDIES

Chest radiograph may show a variety of infiltrates depending on the cause of EP. CT demonstrates a more characteristic pattern and distribution of parenchymal opacities than chest radiograph.

TREATMENT

- Varies depending on the cause.
- Remove offending agent or treat with appropriate antibiotic.
- Steroids may be helpful in many cases; doses and length of treatment depend on etiology of symptoms and response to treatment.
- There have been recent case reports of successful use of omalizumab (Xolair) as a steroid-sparing agent in the treatment of chronic eosinophilic pneumonia, though this practice is not well-examined in the literature to date.
- Supportive respiratory care.

DISPOSITION

Prognosis is good if offending agent can be removed or an infectious etiology treated. Glucocorticoids have a good effect, but relapse often recurs with tapering in chronic idiopathic cases.

REFERRAL

To pulmonologist if a BAL or lung biopsy is needed to establish the diagnosis

PEARLS & CONSIDERATIONS

- History (including travel) and physical examination are most important. Temporal association of eosinophilia and pulmonary abnormalities is an important diagnostic clue.
- Coccidioidomycosis and *Aspergillus* can present as eosinophilic lung disease and are important to recognize because steroid therapy can produce progressive infection.
- *Aspergillus* from respiratory specimens does not always indicate true infection and may be colonization.
- Blood eosinophilia $>1 \times 10^9$ eosinophils/L or BAL >25% is helpful in narrowing diagnosis.
- Integrating the clinical, radiologic, and pathologic findings facilitates the initial and differential diagnoses of various eosinophilic lung diseases.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Aspergillosis (Related Key Topic)
Churg-Strauss Syndrome (Related Key Topic)

AUTHOR: **KRISTINA KRAMER, M.D.**

SUGGESTED READINGS

Agarwal R: Allergic bronchopulmonary aspergillosis, *Chest* 135:805, 2009.

Alam M: Chronic eosinophilic pneumonia: a review, *South Med J* 100(1):49, 2007.

Allen J: Acute eosinophilic pneumonia, *Semin Resp Crit Care Med* 27(2):142, 2006.

Allen JN et al.: The eosinophilic pneumonias, *Semin Resp Crit Care Med* 23(2):127, 2002.

Cottin V et al.: Eosinophilic lung diseases, *Immunol Allergy Clin N Am* 32:557, 2012.

Hara A et al.: Drug-induced eosinophilic pneumonia with pulmonary alveolar hemorrhage caused by benzbromarone, *Intern Med* 49(5):435–438, 2010.

Janz DR et al.: Acute eosinophilic pneumonia: a case report and review of the literature, *Crit Care Med* 37:1470, 2009.

Jeong YJ: Eosinophilic lung diseases: a clinical, radiologic and pathologic overview, *Radiographics* 27:617, 2007.

Kaya H et al.: Omalizumab as a steroid-sparing agent in chronic eosinophilic pneumonia, *Chest* 142(2):513, 2012.

Lal Y, Assimacopoulos A: Two cases of daptomycin-induced eosinophilic pneumonia and chronic pneumonitis, *Clin Infect Dis* 50(5):737–740, 2010.

Marchand E: Idiopathic chronic eosinophilic pneumonia, *Semin Resp Crit Care Med* 27(2):134, 2006.

Miller BA et al.: Acute eosinophilic pneumonia secondary to daptomycin: a report of three cases, *Clin Infect Dis* 50(11):e63–e68, 2010.

Mochimaru H, et al.: Clinicopathological differences between acute and chronic eosinophilic pneumonia, *Respirology* 10(1):76–85, 2005.

Simon HU et al.: Refining the definition of hypereosinophilic syndrome, *J Allergy Clin Immunol* 126:45–49, 2010.

Solomon J: Drug, toxin, and radiation therapy-induced eosinophilic pneumonia, *Semin Resp Crit Care Med* 27(2):192, 2006.

Tsigkaropoulou E et al.: Venlafaxine-induced acute eosinophilic pneumonia, *Gen Hosp Psychiatry* 33(4):411, 2011.

Uchiyama H et al.: Alterations in smoking habits are associated with acute eosinophilic pneumonia, *Chest* 133:1174, 2008.

Wechsler ME: Pulmonary eosinophilic syndromes, *Immunol Allergy Clin North Am* 27:477–492, 2007.

Wechsler ME et al.: Novel targeted therapies for eosinophilic disorders, *J Allergy Clin Immunol* 130:563–567, 2012.

BASIC INFORMATION

DEFINITION

Epicondylitis is inflammation (tendinosis) of the myotendinous junction of the common extensors (commonly the extensor carpi radialis brevis tendon) at the lateral epicondyle or the flexor pronator group (commonly the flexor carpi radialis and pronator teres) at the medial epicondyle of the elbow.

SYNONYMS

Tennis elbow (lateral epicondylitis)
Golfer's elbow (medial epicondylitis)
Elbow tendinosis
Elbow tendinopathy
Epicondylalgia
Elbow tendinitis

ICD-9CM CODES
726.31 Medial epicondylitis
726.32 Lateral epicondylitis
723.4 Radial nerve neuralgia
ICD-10CM CODES
M77.00 Medial epicondylitis, unspecified elbow
M77.10 Lateral epicondylitis, unspecified elbow

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- Prevalence is 1% to 3% in the general population.
  1. Tennis players who play >2 hr a day have a two to four times greater risk of developing epicondylitis compared with general population.
  2. Smoking, obesity, repetitive movement for at least 2 hr daily, and forceful activity are also risk factors in the general population.
- The lateral side is involved more often than the medial.

PREVALENT AGE AND SEX:

- Affects women more often than men.
- More common in individuals 40 to 60 years old.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Main symptom is of pain in lateral or medial elbow.
  1. Pain is typically related to activity.
  2. Local tenderness is experienced over the affected epicondyle.
- Pain can be reproduced by administering a forced elbow extension test (Fig. E1-28), offering resistance against wrist extension (Fig. E1-29), or inducing flexion in the affected area.

ETIOLOGY

- Epicondylitis is thought to be secondary to a chronic tendinosis rather than an acute inflammatory process.
- Overuse likely causes tendinous micro-tears, resulting in inflammation, degeneration, immature repair, and tendinosis.

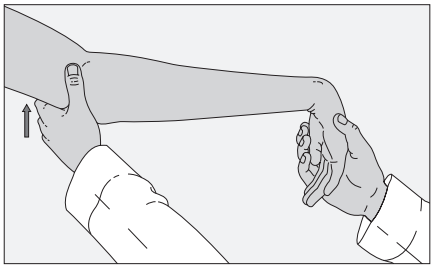

FIGURE E1-28 Forced elbow extension test. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

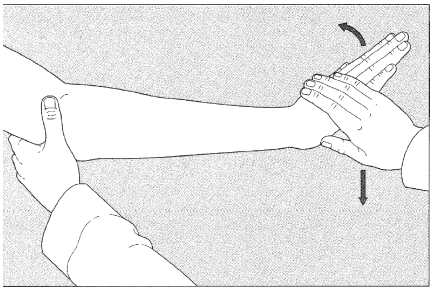

FIGURE E1-29 Resisted wrist extension to test for lateral epicondylitis. The examiner asks the patient to try to extend the wrist but prevents movement by fixing the wrist; this puts tension on the lateral epicondyle without moving the elbow and reproduces the pain of lateral epicondylitis. (From Klippel J et al [eds]: *Primary care rheumatology,* London, 1999, Mosby.)

- Disorganization of normal collagen by invading fibroblasts in association with an immature vascular reparative response and the absence of inflammatory cells is termed angiofibroblastic tendinosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cervical radiculopathy.
- Intraarticular elbow pathology (osteoarthritis, osteochondritis dissecans, loose body).
- Radial tunnel syndrome (compression of the posterior interosseous nerve).
- Cubital tunnel syndrome (compression of the median nerve).
- Tumors.
- Avascular necrosis.
- Medial collateral ligament instability.
  1. Thoracic outlet syndrome.
  2. Ulnar neuritis.
  3. Valgus extension overload.

IMAGING STUDIES

- Plain radiography is useful to evaluate osteoarthritis, osteochondrosis dissecans, or other bony abnormalities.
- Musculoskeletal (MSK) ultrasonography is not very sensitive; epicondylitis appears as a thickening or thinning of the tendon, as well as decreased echogenicity and poor definition of tendon.
- Magnetic resonance imaging (MRI) is the gold standard in detecting epicondylitis. MRI is the most sensitive test, showing tendon thickening and high T2 signal intensity.

TREATMENT

- Rest, restricted activities, and proper technique during sports activities.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) can be used topically or orally but usually provide only short-term relief.
- Local steroid/lidocaine injection can be considered; however, recent trials have called into question the efficacy of corticosteroid injections for epicondylitis.
- Counterforce brace/wrist orthoses.
- Acupuncture has been found to be beneficial in some cases.
- Local injection of platelet-rich plasma (PRP) has been investigated to a limited extent for use in the treatment of lateral epicondylitis with some evidence of improvement in pain and function.
- Physical therapy and eccentric exercise provides short-term relief.
  1. Injection of botulinum toxin A at the myotendinous junction has been found to be helpful in a small randomized-control trial.
- Patients with refractory symptoms after 6 months of nonoperative management may benefit from surgical intervention.

DISPOSITION

- Epicondylitis is self-limited in most cases. Resolution of symptoms may take months to years.
- Prognosis is worse in the following conditions:
  1. The dominant hand is involved.
  2. Patient experiences high physical strain at work.
  3. Duration of symptoms is more than 3 months.
  4. Patient experiences severe pain at presentation and concomitant neck pain.

REFERRAL

If symptoms do not respond to injections or a 6-month trial of conservative therapy, surgical referral is appropriate.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Epicondylitis (Tennis Elbow, Golfer's Elbow) (Patient Information)

AUTHOR: **WAFFIYAH AFRIDI, M.D.**

EVIDENCE

Abstract

Importance:
Corticosteroid injection and physiotherapy, common treatments for lateral epicondylalgia, are frequently combined in clinical practice. However, evidence on their combined efficacy is lacking.

Objective:
To investigate the effectiveness of corticosteroid injection, multimodal physiotherapy, or both in patients with unilateral lateral epicondylalgia.

Design, Setting, and Patients:
A 2 × 2 factorial, randomized, injection-blinded, placebo-controlled trial was conducted at a single university research center and 16 primary care settings in Brisbane, Australia. A total of 165 patients aged 18 years or older with unilateral lateral epicondylalgia of longer than 6 weeks' duration were enrolled between July 2008 and May 2010; 1-year follow-up was completed in May 2011.

Interventions:
Corticosteroid injection (n = 43), placebo injection (n = 41), corticosteroid injection plus physiotherapy (n = 40), or placebo injection plus physiotherapy (n = 41).

Main Outcome Measures:
The 2 primary outcomes were 1-year global rating of change scores for complete recovery or much improvement and 1-year recurrence (defined as complete recovery or much improvement at 4 or 8 weeks, but not later) analyzed on an intention-to-treat basis ($P<.01$). Secondary outcomes included complete recovery or much improvement at 4 and 26 weeks.

Results:
Corticosteroid injection resulted in lower complete recovery or much improvement at 1 year vs placebo injection (83% vs 96%, respectively; relative risk [RR], 0.86 [99% CI, 0.75-0.99]; $P = .01$) and greater 1-year recurrence (54% vs 12%; RR, 0.23 [99% CI, 0.10-0.51]; $P <.001$). The physiotherapy and no physiotherapy groups did not differ on 1-year ratings of complete recovery or much improvement (91% vs 88%, respectively; RR, 1.04 [99% CI, 0.90-1.19]; $P = .56$) or recurrence (29% vs 38%; RR, 1.31 [99% CI, 0.73-2.35]; $P = .25$). Similar patterns were found at 26 weeks, with lower complete recovery or much improvement after corticosteroid injection vs placebo injection (55% vs 85%, respectively; RR, 0.79 [99% CI, 0.62-0.99]; $P <.001$) and no difference between the physiotherapy and no physiotherapy groups (71% vs 69%, respectively; RR, 1.22 [99% CI, 0.97-1.53]; $P = .84$). At 4 weeks, there was a significant interaction between corticosteroid injection and physiotherapy ($P = .01$), whereby patients receiving the placebo injection plus physiotherapy had greater complete recovery or much improvement vs no physiotherapy (39% vs 10%, respectively; RR, 4.00 [99% CI, 1.07-15.00]; $P = .004$). However, there was no difference between patients receiving the corticosteroid injection plus physiotherapy vs corticosteroid alone (68% vs 71%, respectively; RR, 0.95 [99% CI, 0.65-1.38]; $P = .57$).

Conclusion and Relevance:
Among patients with chronic unilateral lateral epicondylalgia, the use of corticosteroid injection vs placebo injection resulted in worse clinical outcomes after 1 year, and physiotherapy did not result in any significant differences. Ⓐ

Abstract[2]

Background:
Elbow tenderness and pain with resisted wrist extension are common manifestations of lateral epicondylar tendinopathy, also known as tennis elbow. Previous studies have suggested platelet-rich plasma (PRP) to be a safe and effective therapy for tennis elbow.

Purpose:
To evaluate the clinical value of tendon needling with PRP in patients with chronic tennis elbow compared with an active control group.

Study Design:
Randomized controlled trial; Level of evidence, 2.

Methods:
A total of 230 patients with chronic lateral epicondylar tendinopathy were treated at 12 centers over 5 years. All patients had at least 3 months of symptoms and had failed conventional therapy. There were no differences in patients randomized to receive PRP (n = 116) or active controls (n = 114). The PRP was prepared from venous whole blood at the point of care and contained both concentrated platelets and leukocytes. After receiving a local anesthetic, all patients had their extensor tendons needled with or without PRP. Patients and investigators remained blinded to the treatment group throughout the study. A successful outcome was defined as 25% or greater improvement on the visual analog scale for pain.

Results:
Patient outcomes were followed for up to 24 weeks. At 12 weeks (n = 192), the PRP-treated patients reported an improvement of 55.1% in their pain scores compared with 47.4% in the active control group (P = .163). At 24 weeks (n = 119), the PRP-treated patients reported an improvement of 71.5% in their pain scores compared with 56.1% in the control group (P = .019). The percentage of patients reporting significant elbow tenderness at 12 weeks was 37.4% in the PRP group versus 48.4% in the control group (P = .143). Success rates for patients at 12 weeks were 75.2% in the PRP group versus 65.9% in the control group (P = .104). At 24 weeks, 29.1% of the PRP-treated patients reported significant elbow tenderness versus 54.0% in the control group (P = .009). Success rates for patients with 24 weeks of follow-up were 83.9% in the PRP group compared with 68.3% in the control group (P = .037). No significant complications occurred in either group.

Conclusion:
No significant differences were found at 12 weeks in this study. At 24 weeks, however, clinically meaningful improvements were found in patients treated with leukocyte-enriched PRP compared with an active control group. Ⓐ

Evidence-Based References

Coombes BK et al.: Effect of corticosteroid injection, physiotherapy, or both on clinical outcomes in patients with unilateral lateral epicondylalgia: a randomized controlled trial, *JAMA* 309:461–469, 2013. Ⓐ

Mishra AK, Skrepnik NV, Edwards SG et al.: Efficacy of platelet-rich plasma for chronic tennis elbow: a double-blind, prospective, multicenter, randomized controlled trial of 230 patients, *Am J Sports Med* 42:463–471, 2014. Ⓐ

SUGGESTED READINGS

Bunata RE et al.: Anatomic factors related to the cause of tennis elbow, *Bone Joint Surg Am* 89:2007, 1955.

Johnson GW et al.: Treatment of lateral epicondylitis, *Am Fam Physician* 76:843–848, 2007.

Rahman Shiri et al.: Lateral and medial epicondylitis: role of occupational factors, *Best Pract Res Clin Rheumatol* 25:43–57, 2011.

Shiri R et al.: Prevalence and determinants of lateral and medial epicondylitis: a population study, *Am J Epidemiol* 164(11):1065, 2006.

Smidt N et al.: Lateral epicondylitis in general practice: course and prognostic indicators of outcome, *J Rheumatol* 33:2053, 2006.

Smidt N et al.: Corticosteroid injections, physiotherapy, or wait-and-see policy for lateral epicondylitis: a randomized controlled trial, *Lancet* 359:657, 2002.

Tosti R et al.: Lateral epicondylitis of the elbow, *Am J Med Apr* 126(4):357. e1–e6, 2013.

Von Hofwegen C et al.: Epicondylitis in the athlete's elbow, *Clin Sports Med Oct* 29(4):577–597, 2010.

Walz DM et al.: Epicondylitis: pathogenesis, imaging, and treatment, *Radiographics* 30:167, 2010.

BASIC INFORMATION

DEFINITION

- Epididymitis is an inflammatory reaction of the epididymis caused by either an infectious agent or local trauma. In most cases of acute epididymitis, the testis is also involved (orchitis).
- Epididymitis is considered chronic if lasting ≥6 wk. Chronic epididymitis has been subcategorized into inflammatory chronic epididymitis, obstructive chronic epididymitis, and chronic epididymalgia.

SYNONYMS

Nonspecific bacterial epididymitis
Sexually transmitted epididymitis

ICD-9CM CODES
604 Orchitis and epididymitis
ICD-10CM CODES
N45.1 Epididymitis
A54.00 Gonococcal infection of lower genitourinary tract, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Cause of >600,000 visits to physicians per year
PEAK INCIDENCE: Sexually active years
PREDOMINANT SEX: Exclusive to males
PREDOMINANT AGE: All ages affected but usually in sexually active men or older males
CONGENITAL: Congenital urologic structural disorders possibly predisposing to infections

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Tender swelling of the scrotum with erythema, usually unilateral testicular pain and tenderness
- Dysuria and/or urethral discharge
- Fever and signs of systemic illness (less common)
- Pain and redness on scrotal examination
- Hydrocele or even epididymoorchitis, especially late
- Chronic draining scrotal sinuses with a "beadlike" enlargement of the vas deferens in tuberculous disease

ETIOLOGY

- In young, sexually active men (<35 years of age), the most common infectious agents isolated are *Neisseria gonorrhoeae* and *Chlamydia trachomatis*.
- In older men (>35 years of age) or with underlying urologic disease:
  1. Gram-negative aerobic rods are predominant (i.e., *Escherichia coli*).
  2. Similar organisms are found in men following invasive urologic procedures.
  3. Gram-positive cocci are rarely seen in these groups.
  4. Mycobacteria may also be a cause of epididymitis.
- Young, prepubertal boys may present with epididymitis caused by coliform bacteria; almost always a complication of underlying urologic disease such as reflux.
- In AIDS patients, CMV and *Salmonella* epididymitis have been described. CMV may have a negative urine culture. Toxoplasmosis and *Cryptococcus* should also be considered as a cause of epididymitis in AIDS patients.
- Chronic infectious epididymitis is mostly frequently seen in conditions associated with granulomatous reaction; mycobacterium tuberculosis is the most common granulomatous disease affecting the epididymis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Orchitis
- Testicular torsion, trauma, or tumor
- Epididymal cyst
- Hydrocele
- Varicocele
- Spermatocele
- Testicular torsion should be considered in all cases.

WORKUP

- Consideration of a full assessment of the urologic tract in patients with bacterial infection, especially if recurrent
- If discharge is present, cultures and Gram stain smear of urethral exudate. Gram stain will demonstrate ≥5 WBC per oil immersion field.
- In sexually active men: gonococcal cultures of the throat and rectum possibly of value
- If testicular torsion a consideration: radionuclear imaging
- Examination of first void uncentrifuged urine for leukocytes if the urethral Gram stain is negative. Positive leukocyte esterase test on first-void urine or microscopic examination of first-void urine sediment will demonstrate ≥10 WBC per high power field. A culture and Gram-stained smear of this urine specimen should be obtained along with nucleic acid amplification studies (ligase chain reaction [LCR]) from urine samples for gonorrhea and *Chlamydia* spp.
- Imaging with sonogram

LABORATORY TESTS

- Urinalysis and urine culture if dysuria is present or if urinary tract infection is suspected
- Screening test for syphilis, chlamydia, and gonorrhea in sexually active men
- HIV testing and counseling
- PPD placed and chest x-ray viewed if TB suspected (rare cases)
- Rarely, biopsy to ensure the diagnosis of tuberculous epididymitis

TREATMENT

ACUTE GENERAL Rx

- Ice packs and scrotal elevation for relief of pain
- Analgesia with acetaminophen with or without codeine or NSAIDs
- Antibiotics to cover suspected pathogens. Empiric therapy is indicated before laboratory test results are available.
- Recommended regimens are ceftriaxone 250 mg IM in a single dose plus doxycycline 100 mg bid for 10 days. For acute epididymitis most likely caused by enteric organisms, treatment options are levofloxacin 500 mg qd × 10 days or ofloxacin 300 mg bid × 10 days.
- Best treatment for older men with gram-negative bacteriuria: ofloxacin 300 mg PO bid for 10 days or levofloxacin 500 mg PO qd for 10 days
- *Pseudomonas* covered by ciprofloxacin PO or IV or cefepime (2 g IV q12h)
- Consider ampicillin-sulbactam, 3rd-generation cephalosporin, ticarcillin-clavulanate, or piperacillin-tazobactam in toxic-appearing patients.
- Surgical aspiration of local abscesses or even open surgical drainage
- Diabetics: especially prone to develop more extensive scrotal infections, including Fournier's gangrene
- Reinforcement of compliance with antibiotics to avoid partial treatment

CHRONIC Rx

- Repair of underlying structural defects is considered especially if infections are severe or recur.
- Surgical repair of reflux in young boys should be undertaken promptly and at a young age when possible.
- Sex partners of patient should be referred for evaluation and treatment.

DISPOSITION

Usually self-limited (≤6 wk duration in most cases)

REFERRAL

- If abscess or chronic structural problems suspected
- If another diagnosis, such as testicular torsion, is suspected

PEARLS & CONSIDERATIONS

- Recurrent epididymitis in sexually active men is usually related to failure to simultaneously treat sexual partners for STDs.
- Recurrent epididymitis in non-sexually active men is generally related to structural-anatomic defects in the genitourinary system or relapsing disease from inadequate initial treatment or antimicrobial resistance.
- Tuberculous epididymitis fails to respond to seemingly adequate antimicrobial therapy even without characteristic radiographic changes on chest films.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Epididymitis (Patient Information)

AUTHOR: **PHILIP A. CHAN, M.D., M.S.**

SUGGESTED READINGS

Abul F, et al.: The acute scrotum: a review of 40 cases, *Med Princ Pract* 14(3):177, 2005.

Tracy CR, Steers WD, Costabile R: Diagnosis and management of epididymitis, *Urol Clin North Am* 35(1):101–108, 2008.

Trojian TH, Lishnak TS, Heiman D: Epididymitis and orchitis: an overview, *Am Fam Physician* 79(7):583–587, 2009.

BASIC INFORMATION

DEFINITION

Epidural hematoma (EDH) is the accumulation of blood in the potential space surrounding the brain, between the dura mater and the inner surface of the skull.

SYNONYMS

Extradural hematoma/hemorrhage
EDH

ICD-9CM CODES
432.0 Nontraumatic extradural hemorrhage
852.5 Extradural hemorrhage following injury without intracranial wound
852.5 Extradural hemorrhage following injury with open intracranial wound

ICD-10CM CODES
S06.4 Epidural hemorrhage
I62.1 Non-traumatic extradural hemorrhage

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Exact incidence is unknown; however, it is found in 1% to 4% of traumatic head injury cases and 5% to 15% of autopsy series.
PREDOMINANT SEX AND AGE: Male > female
PEAK INCIDENCE: Peak incidence among adolescents and young adults. It is rarely found in patients older than 50-60 years old.
GENETICS: There is a role for genetics in spontaneous (nontraumatic) EDH caused by coagulopathies and vascular malformations.
RISK FACTORS: Head trauma, especially in cases involving skull fracture.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- History of head trauma is present.
- Signs and symptoms vary depending on severity.
- Symptoms: altered mental status, nuchal rigidity, headache, drowsiness, confusion, aphasia, photophobia, and paralysis
- Signs: transient loss of consciousness, followed by a "lucid interval" in 47% of cases, in which the patient is free of any neurologic signs or symptoms. This is followed by clinical deterioration including, vomiting, lethargy, confusion, or seizures. Other signs include focal neurologic deficits such as paralysis of limbs, unequal pupils, and coma. Signs of increased intracranial pressure could be found including the Cushing reflex of hypertension, bradycardia, and respiratory distress. External signs of skull fracture—lacerations, ecchymoses, cerebrospinal fluid (CSF) rhinorrhea or otorrhea—may be observed. Skull fractures can be found in 75%-95% of EDH patients.

ETIOLOGY

- Traumatic: commonly caused by arterial injury (the middle meningeal artery) (Fig. E1-30) but may also be injury of the anterior meningeal artery, a dural arteriovenous (AV) fistula at the vertex, or from venous bleeding
- Nontraumatic: caused by an infection/eroding abscess, coagulopathy, hemorrhagic tumors, vascular malformations, postsurgical procedures, and in special populations (e.g., pregnant women, patients receiving hemodialysis)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

In the setting of head trauma: subdural hematoma, subarachnoid hemorrhage, cerebral contusion, brain laceration, diffuse brain swelling

WORKUP

- Imaging is the mainstay of diagnosis.
- Serial head CT is the test most commonly used due to its simplicity, widespread use, and availability. Typical appearance is a "lens shaped," or "lentiform" hyperdensity (Fig. E1-31). Box E1-5 describes CT findings of EDH.
- Note: Head CT is not conclusive in 8% of cases possibly due to severe anemia, early scanning (before blood has time to accumulate), and severe hypotension.
- Brain MRI: more sensitive. Indicated in situations in which there is a strong clinical suspicion but no evidence of EDH on head CT (Fig. E1-32).
- Angiography: rarely necessary but may be used to evaluate an underlying vascular lesion.
- NOTE: lumbar puncture (LP) is contraindicated in EDH due to risk of brain stem herniation.

LABORATORY TESTS

- Laboratory tests are helpful as adjunct to diagnosis but are not the mainstay of diagnosis or treatment.
- CBC may be helpful to evaluate for anemia, although in an acute onset of bleeding, hemoglobin levels can be normal.
- Other tests: renal functions, electrolytes, liver functions, INR may be helpful depending on the case scenario.

TREATMENT

Acute symptomatic EDH is a neurologic emergency that requires surgical treatment to prevent permanent brain injury.

NONPHARMACOLOGIC THERAPY

- Immediate surgical decompression, ideally within 1-2 hr after traumatic event
- Craniotomy and hematoma evacuation is the treatment of choice. When indicated, identify and ligate the bleeding vessel.
- Burr hole evacuation: this involves drilling a hole in the skull to evacuate the hematoma. It is a lifesaving procedure that is indicated if surgical expertise is limited.

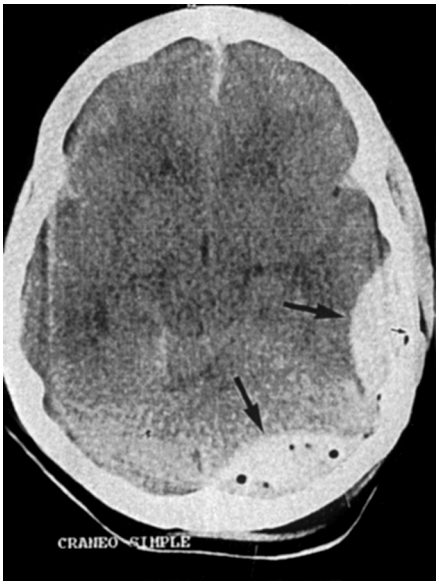

FIGURE E1-31 Head CT showing two epidural hematomas in 23-year-old involved in a motor vehicle accident. Note air bubbles that are a result of linear fracture in the left temporal bone *(short arrow)*.

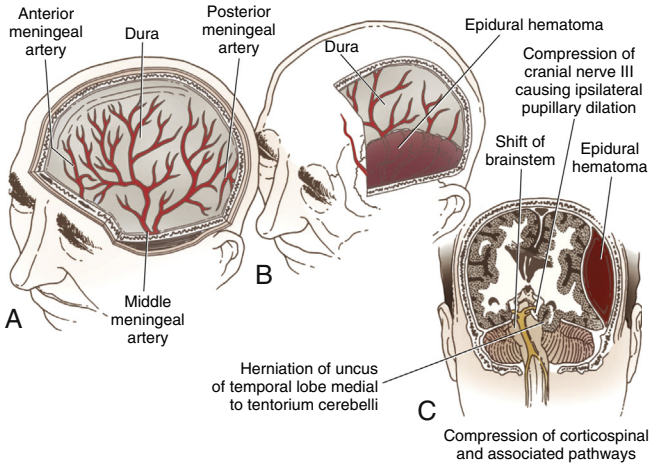

FIGURE E1-30 Epidural hematoma is typically caused by trauma resulting in laceration of the middle meningeal artery. **A,** The middle meningeal artery. The typical traumatic epidural hematoma is caused by a laceration of this vessel. **B** and **C,** A linear fracture of the squamous portion of the temporal bone has torn the middle meningeal artery, which has resulted in an epidural hematoma. (From Rothrock, JC: Neurosurgery. In Rothrock, JC (ed): *Alexander's care of the patient in surgery*, 13th edition, Philadelphia, 2007, Elsevier.)

Epidural Hematoma

BOX E1-5 CT Findings of Epidural Hematoma

- CT appearance: variable white to gray on brain windows
- Location: peripheral to brain, variable but usually temporal region
- Shape: biconvex disc or lens
- Pearl: does not cross suture lines
- White swirl sign means active bleeding
- Significance: may cause mass effect and herniation
- Look for midline shift
- Look for effacement of ventricles and sulci
- Surgical indications: 15-mm thickness or 5-mm midline shift

From Broder JS: *Diagnostic imaging for the emergency physician*, Philadelphia, 2011, Saunders.

FIGURE E1-32 Epidural hematoma on MRI. Coronal T2-weighted images show hypointense biconvex extraaxial collection in the left temporal region.

ACUTE GENERAL Rx

- Cardiopulmonary resuscitation and assessment for disability.
- Medical resuscitation maneuvers: head elevation, hyperventilation, monitoring of vital signs and avoidance of hypotension and hyperthermia, sedation if necessary.
- Medications: osmotic diuresis with IV mannitol, cerebrosedating medications, antiepileptics may be used to treat or, in some situations, prevent seizures. The patient should also be started on a proton pump inhibitor to decrease risks of developing an upper gastrointestinal bleed.
- Reversing anticoagulation should be weighed in terms of advantages versus disadvantages.
- NOTE: glucocorticoid therapy is *not* indicated following head injury and may be related to increased mortality.
- Evaluation for surgery: the best available evidence points toward advantages of decompression procedures. Nonoperative treatment may only be indicated if the patient has no symptoms, no focal neurologic deficit, no coma (Glasgow coma score >8), and EDH volume is less than 30 ml by CT scan, with clot thickness <15 mm and midline shift of less than 5 mm.
- Nonoperative treatment involves close monitoring, hourly neurologic checks, and serial head CT scans.

CHRONIC Rx

- There is a risk of permanent brain damage whether the disorder is treated or not. Most recovery occurs in the first 6 months with some improvement over 2 years.
- Children have a tendency to recover more quickly.
- Patients should be educated on rehabilitative exercises and to alert medical professionals in the event of new neurologic symptoms.
- Support and encouragement to patient and family should always be provided.

REFERRAL

Clinical nurse practitioners, pastoral care staff, and social workers to help patients and families are also appropriate.

PEARLS & CONSIDERATIONS

- Acute symptomatic EDH is a neurologic emergency.
- EDH should be suspected in any patient with a history of blow to the head leading to a period of loss of consciousness.
- Initial resuscitation is extremely important, but surgery is the mainstay of treatment for acute symptomatic EDH.

PREVENTION

Should be directed toward preventing head trauma: use of appropriate safety equipment (e.g., helmets, hard hats, safe driving, avoiding diving into unknown depths)

PATIENT/FAMILY EDUCATION

Online head injury support groups are helpful: www.headinjury.com/linktbisup.htm, www.headinjury.com/, www.dailystrength.org/c/Brain-Injury/support-group.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **SCOTT M. SOUTHER, M.D.**

SUGGESTED READINGS

Bullock MR et al.: Surgical management of acute epidural hematomas, *Neurosurgery* 58:S7, 2006.

Kucharczyk J, Moseley E: Imaging of head trauma. In Imaging of the nervous system diagnostic and therapeutic applications. vol. II Mosby: Philadelphia.

Nelson JA: Local skull trephination before transfer is associated with favorable outcomes in cerebral herniation from epidural hematoma, *Acad Emerg Med* 18:78–85, 2011.

BASIC INFORMATION

DEFINITION

Epiglottitis is a rapidly progressive cellulitis of the epiglottis and adjacent soft tissue structures with the potential to cause abrupt airway obstruction, which can be life-threatening.

SYNONYMS

Supraglottitis
Cherry-red epiglottitis

ICD-9CM CODES
464.30 Epiglottitis
ICD-10CM CODES
J05.1 Acute epiglottitis

EPIDEMIOLOGY

INCIDENCE (IN U.S.): Due to vaccination against *Haemophilus influenzae* type B, this is a rare infection in children estimated at between 0.6 to 0.8 per 100,000 in one study and for adults at 1.6 per 100,000.
PEAK INCIDENCE: Now highest in children ages 6 to 12
PREDOMINANT SEX: Males

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Irritability, fever, dysphonia, and dysphagia.
- Respiratory distress, with child tending to lean up and forward.
- Often, drooling or oral secretions.
- Often, presence of tachycardia and tachypnea.
- On visualization, edematous and cherry-red epiglottis.
- Often, no classic barking cough as seen in croup.
- Possibly fulminant course (especially in children), leading to complete airway obstruction.

ETIOLOGY

- In children, *Haemophilus influenzae* type b, still most common cause but now rare due to vaccination *Streptococcus pyogenes,* (group A Streptococcus) *Streptococcus pneumoniae, Staphylococcus aureus* (includes MRSA).
- In adults, *Streptococcus pyogenes* (group A Streptococcus), *H. influenzae* (can be isolated from blood and/or epiglottis [about 26% of cases]).
- Pneumococci, streptococci, and staphylococci are also implicated.
- Role of viruses in epiglottitis unclear.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Croup.
- Angioedema.
- Retropharyngeal or peritonsillar abscess.
- Diphtheria.
- Foreign body aspiration.
- Lingual tonsillitis.

WORKUP

- Cultures of blood and urine.
- Lateral neck radiograph to show an enlarged epiglottis, ballooning of the hypopharynx, and normal subglottic structures (Fig. E1-33).
  1. Radiographs are of only moderate sensitivity and specificity and take time to perform.
  2. Visualization of the epiglottis may be safer in adults than in children.
- Cultures of the epiglottis.

LABORATORY TESTS

- CBC: may reveal a leukocytosis with a shift to the left.
- Chest radiograph examination: may reveal evidence of pneumonia in close to 25% of cases.
- Cultures of blood, urine, and the epiglottis, as noted previously.

TREATMENT

ACUTE GENERAL Rx

- Maintenance of adequate airway is critical. Fig. EE1-34 describes the optimal assessment and management of upper airway obstruction caused by epiglottitis or severe croup. It is crucial to have a tracheostomy set "at bedside."
- Early placement of an endotracheal or nasotracheal tube in a child is advised.
- Closely follow the adult patient, if no signs of airway obstruction, and defer intubation.
- In children, visualization and intubation are best done in the most controlled environment.
- *H. influenzae* in children is much less common in large part due to the HIB vaccine.

Empiric antibiotics:

1. **In children:** use cefotaxime 50 mg/kg IV q8h or ceftriaxone 50 mg/kg IV q24h *plus* vancomycin for its coverage of MRSA. If penicillin allergy, use levofloxacin 10 mg/kg IV q24h *plus* clindamycin 7.5 mg/kg IV q6h.
2. **In adults:** ceftriaxone 2 g IV q24h or cefotaxime *plus* vancomycin.

If possible, obtain cultures before initiating antibiotics.

If there is an unvaccinated child for *H. influenzae* at home (or in a day care center) who is >4 yr and living with an index case, give close family contacts of the patient (including adults) rifampin 20 mg/kg/day for 4 days (up to 600 mg/day) for prophylaxis.

Role of epinephrine or corticosteroids in the management of epiglottitis is not firmly established.

DISPOSITION

Invasive *H. influenzae* infections and epiglottitis are reportable illnesses; this may be particularly important in recognizing an outbreak in a day care center with unvaccinated children.

REFERRAL

- Close cooperation between the pediatrician or internist, anesthesiologist, and otorhinolaryngologist, especially when epiglottis is visualized and when the patient requires endotracheal intubation.
- Best managed in a critical care setting or ICU.

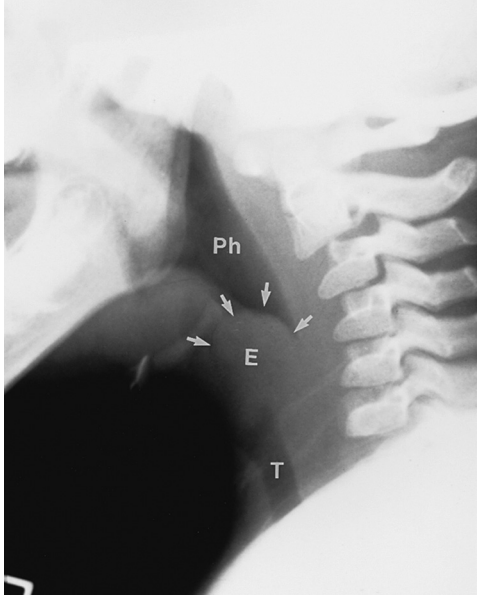

FIGURE E1-33 Epiglottitis. A lateral soft tissue view of the neck shows a ballooned pharynx *(Ph)* with swollen epiglottis *(E)* in the shape of a large thumbprint *(arrows). T,* Trachea. (From Mettler FA [ed]: *Primary care radiology,* Philadelphia, 2000, Saunders.)

PEARLS & CONSIDERATIONS

The incidence of epiglottitis has diminished markedly since the introduction of the conjugate vaccine against *H. influenzae* serotype B into routine childhood immunization.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Epiglottitis (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Alcaide MK, Bisno AL: Pharyngitis and epiglottitis, *Infect Dis Clin North Am* 21(2):449–469, 2007.

Hafidh MA et al.: Acute epiglottitis in adults: a recent experience with 10 cases, *J Laryngol Otol* 120(4):310, 2006.

Loftis L: Acute infectious upper airway obstructions in children, *Semin Pediatr Infect Dis* 17(2):5–10, 2006.

Sobol SE, Zapata S: Epiglottitis and croup, *Otolaryngol Clin North Am* 41:551–566, 2008.

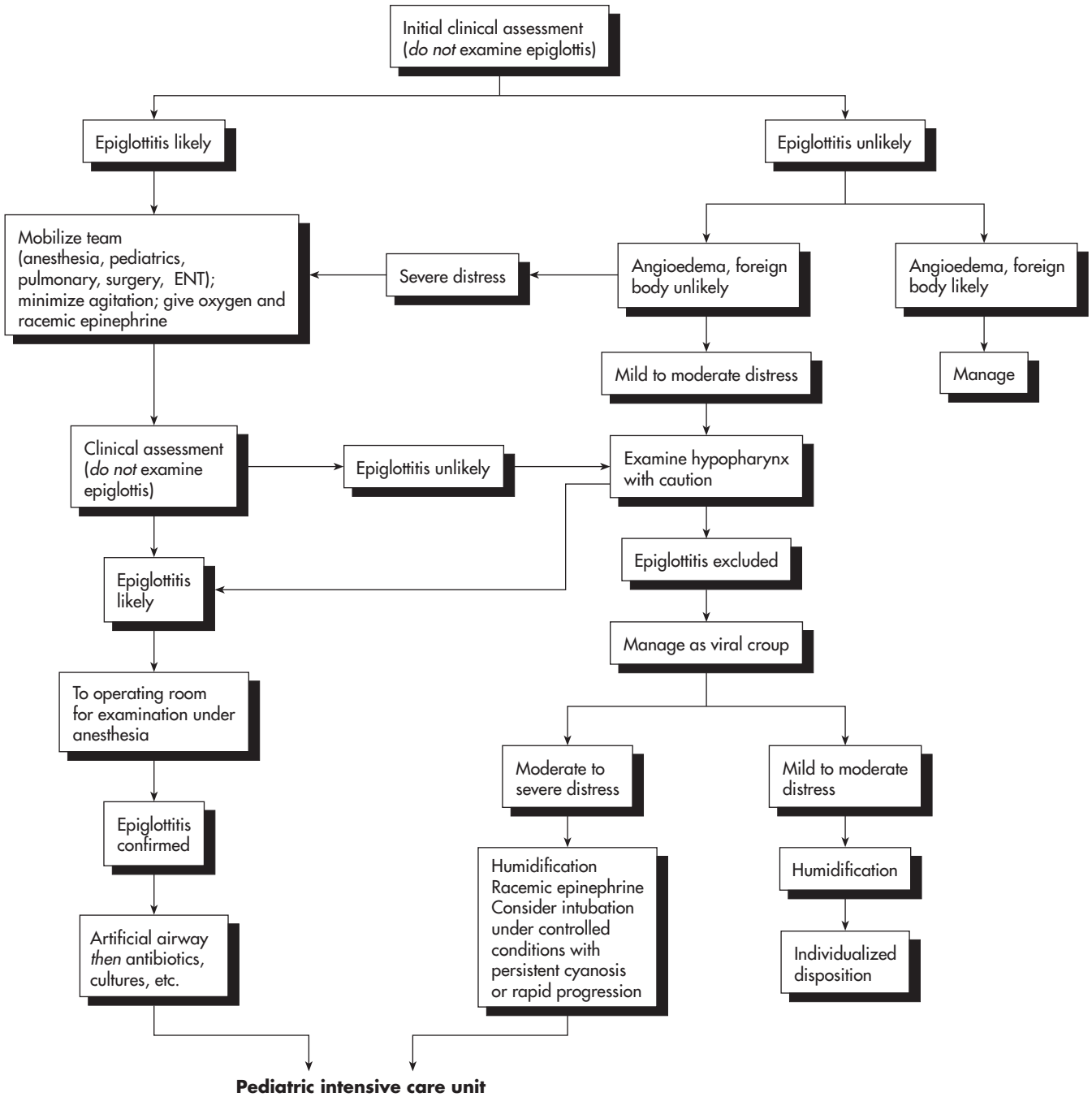

FIGURE EE1-34 Optimal assessment and management of upper airway obstruction caused by epiglottitis or severe croup. Care must be individualized to reflect resources and logistic issues within a given institution. *ENT,* Ear, nose, throat. (From Barkin RM et al: *Emergency pediatrics,* St Louis, 1999, Mosby.)

Episcleritis PTG

BASIC INFORMATION

DEFINITION

Episcleritis is an inflammation of the episclera (Fig. E1-35), the thin layer of vascular elastic tissue between the sclera and conjunctiva.

ICD-9CM CODES
379.0 Scleritis and episcleritis
ICD-10CM CODES
H15.1 Episcleritis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Relatively rare in an ophthalmologic practice.
PEAK INCIDENCE: Most common in middle and old age.
PREDOMINANT SEX: None.
PREDOMINANT AGE: 40s.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Red, vascular injection of conjunctiva with engorged and enlarged blood vessels beneath the conjunctiva (Fig. E1-36).

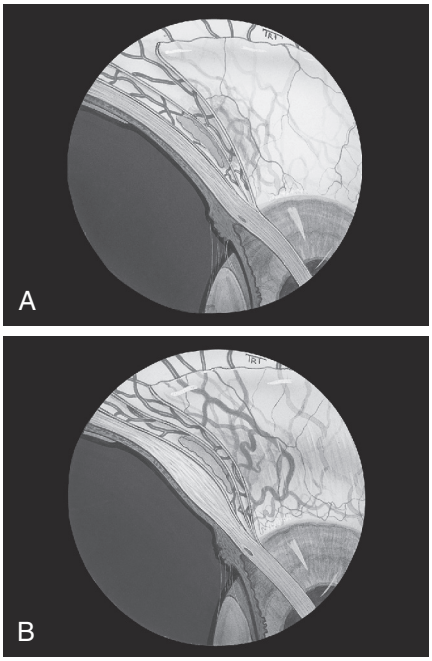

FIGURE E1-35 A, Episcleritis with maximal vascular congestion of the superficial episcleral plexus; **B,** scleritis with scleral thickening and maximal vascular congestion of the deep vascular plexus. (From Kanski JJ, Bowling B: *Clinical ophthalmology, a systematic approach,* ed 7, Philadelphia, 2010, Saunders.)

- Pain in area of inflammation that is usually localized (severe pain suggests deeper inflammation, see Scleritis).

ETIOLOGY

Associated with collagen-vascular diseases, vasculitis, trauma; often nonspecific

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute glaucoma.
- Conjunctivitis.
- Scleritis.
- Subconjunctival hemorrhage.
- Congenital or lymphoid masses.
- The differential diagnosis of "red eye" is described in Section II.

WORKUP

Eye examination, general check-up for collagen-vascular disease or other autoimmune diseases.

LABORATORY TESTS

Studies for collagen-vascular disease (e.g., ANA, ESR, RF).

TREATMENT

NONPHARMACOLOGIC THERAPY

Warm compresses.

ACUTE GENERAL Rx

- Topical steroids, 1% prednisolone if no glaucoma; nonsteroidal eye drops if there is a tendency for glaucoma.
- Nonsteroidal anti-inflammatory drugs (NSAIDs): treat underlying systemic disease.

CHRONIC Rx

NSAID eye drops (diclofenac eye drops, ketorolac ophthalmic solution).

DISPOSITION

Close follow-up needed.

REFERRAL

To ophthalmologist if patient unresponsive to treatment after a few days.

PEARLS & CONSIDERATIONS

COMMENTS

- Can be associated with collagen-vascular disease.
- May occur with systemic autoimmune disease. Workup for autoimmune disease is often negative, more likely with scleritis (50%). Ask about other symptoms to find autoimmune disorders, helps to guide workups.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Episcleritis (Patient Information)

AUTHOR: **R. SCOTT HOFFMAN, M.D.**

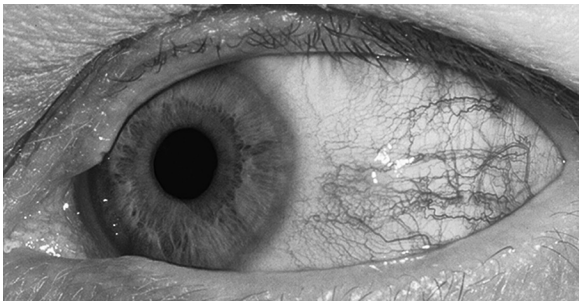

FIGURE E1-36 Nodular episcleritis in a patient with gout. (From Palay D [ed]: *Ophthalmology for the primary care physician,* St Louis, 1997, Mosby.)

SUGGESTED READINGS

Jabs DA et al.: Episcleritis and scleritis: clinical features and treatment results, *Am J Ophthalmol* 130(4):469, 2000.

Paresio CE, Meier FM: Systemic disorders associated with episcleritis and scleritis, *Curr Opin Ophthalmol* 12(6):471, 2002.

Shaw C et al.: Rheumatoid arthritis and ocular involvement, *J Indian Med Assoc* 101(9):537, 2003.

BASIC INFORMATION

DEFINITION

Epistaxis is defined as bleeding from the nose or nasal hemorrhage and is classified as either anterior or posterior.

SYNONYMS

Nosebleed

ICD-9CM CODES
784.7 Epistaxis
ICD-10CM CODES
R04.0 Epistaxis

EPIDEMIOLOGY & DEMOGRAPHICS

- Epistaxis accounts for one of every 200 emergency department visits in the U.S. annually.
- It increases in frequency after age 20 yr and reaches the highest levels among the elderly population.
- More than 80% of cases of epistaxis are anterior in origin (Little's area) and occur from Kiesselbach's plexus.
- Only 5% of patients with epistaxis have posterior bleeds.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Nosebleed
- Hypotension and hemodynamic instability with acute, severe epistaxis

ETIOLOGY

- Approximately 90% of epistaxis events are idiopathic.
- Common identifiable causes are:
  1. Cold, dry environment
  2. Trauma (nose picking, accidents, and physical altercations)
  3. Structural deformities (septal deviations or spurs, chronic perforations)
  4. Inflammatory (rhinosinusitis, nasal polyposis)
  5. Allergies
  6. Foreign bodies in the nasal cavity
  7. Tumors (juvenile angiofibroma)
  8. Irritants
  9. Hypertension
  10. Coagulopathy (hemophilia, von Willebrand's disease, thrombocytopenia)
  11. Osler-Weber-Rendu disease
  12. Renal failure
  13. Drugs: aspirin, nonsteroidal antiinflammatory drugs, warfarin, alcohol, sildenafil, and tadalafil
  14. Blood vessel disorders (connective tissue disease, hereditary hemorrhagic telangiectasia)
  15. Pseudoaneurysm and aneurysm of the internal carotid artery might present as epistaxis

DIAGNOSIS

A good attempt should be made to directly visualize the source of bleeding to confirm the diagnosis and determine the best treatment. Fig. E1-37 illustrates anatomical sites for epistaxis.

DIFFERENTIAL DIAGNOSIS

Pseudoepistaxis must be ruled out. Common extranasal sites of bleeding that can simulate epistaxis include:
1. Pulmonary hemoptysis
2. Bleeding esophageal varices
3. Tumor bleeding from the pharynx, larynx, or trachea

WORKUP

The workup should include laboratory blood testing to exclude obvious causes. Type and cross in anticipation of transfusion if the bleeding is severe.

LABORATORY TESTS

- Hemoglobin and hematocrit
- Platelet count
- Blood urea nitrogen and creatinine
- Coagulation studies (prothrombin time and partial thromboplastin time)
- Type and crossmatching of blood products

IMAGING STUDIES

Radiographic studies are usually not helpful.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Digital compression or pinching of the lower soft cartilaginous part of the nose for 10 min is the method of choice.
- Use cotton or tissue plug.
- The patient should be sitting and leaning forward, breathing through the mouth, allowing blood to flow out of the nostrils as opposed to bending backward, which would allow the blood to flow down the throat.
- Application of cold compresses to the bridge of the nose to cause a vasoconstrictive effect; the patient may also suck on ice to achieve this effect.

ACUTE GENERAL Rx

Anterior epistaxis:
- Local vasoconstriction is performed by moistening a cotton pledget with either:
  1. 4% lidocaine with 1:1000 epinephrine
  2. 4% lidocaine with 1% phenylephrine (Neo-Synephrine)
  3. 4% lidocaine with 0.05% oxymetazoline (Afrin)
  4. 4% cocaine or cocaine 25% in paraffin base ointment and inserting the pledget into the nasal cavity with bayonet forceps.
- Cauterization with silver nitrate or trichloroacetic acid is performed once hemostasis is achieved.

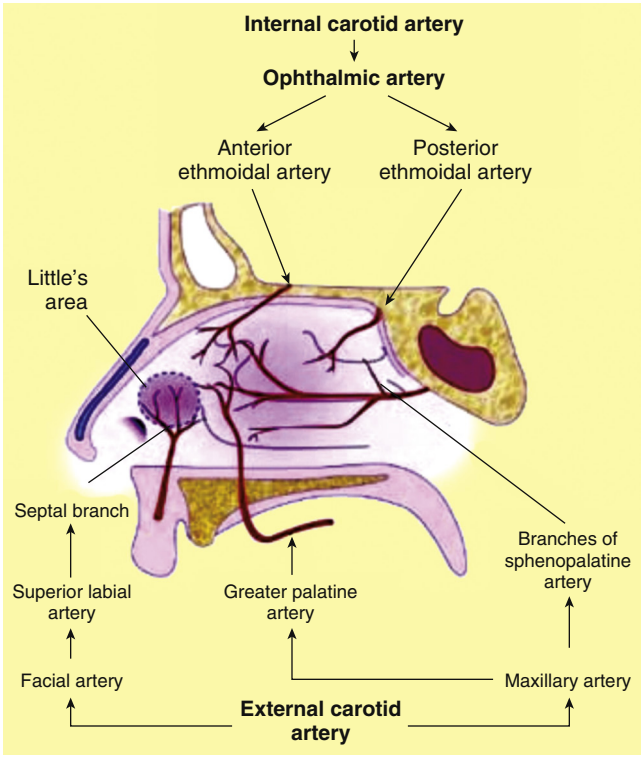

FIGURE E1-37 Anatomical sites for epistaxis. (From McLarnon CM, Carrie S: Epistaxis. *Surgery (Oxford)* 30(11): 584–589, 2012.)

- Anterior nasal packing is needed when local measures are unsuccessful. Nasal packing is performed under local anesthesia and is done by inserting Vaseline gauze strips in layers from the floor of the nasal cavity to the front entrance of the nasal orifice. Enough pressure is placed to tamponade the epistaxis.
- Other commercially available nasal packing uses sponge packs that expand when exposed to blood or moisture and can be used for anterior epistaxis.

Posterior epistaxis:

- Posterior nasal packing
  1. Commercially available nasal sponge packing can be applied
  2. Rolled gauze technique
- Foley catheter balloon insertion into the nasopharynx can be tried in patients with posterior epistaxis.

Newer agents in the treatment of epistaxis:

- Quick clot hemostatic agent, available OTC. When it comes in contact with blood in and around a wound, it absorbs the smaller water molecules from the blood to promote rapid clotting
- FloSeal hemostatic matrix, a combination of human thrombin, gelatin matrix, and calcium chloride, which are mixed together and placed at bleeding site
- Recombinant factor VIIa, generally reserved for uncontrolled epistaxis

CHRONIC Rx

- If acute treatment fails to stop the bleeding or the site of bleeding cannot be located, electrocautery or endoscopic cauterization can be used.
- Electrocautery is performed after suitable anesthesia, such as application of a topical anesthetic followed by local anesthetic injection. Only one side of the nasal septum should be cauterized at a time because perforation can result from bilateral cauterization.
- Arterial ligation or embolization has been used in refractory posterior epistaxis.
- For cases involving irritated or inflamed mucosa, a conservative regimen of triamcinolone 0.025%, Nemdyn, Nasalate, or equivalent cream should be applied once a week, combined with nightly application of a small quantity of petroleum jelly to the septum before bedtime.

DISPOSITION

- Most cases of anterior epistaxis from Kiesselbach's plexus can be stopped by nasal compression and local vasoconstriction or cauterization.
- Nasal packing with gauze or sponge can control 90% of anterior epistaxis.
- Anterior and posterior packs are removed in 2 to 3 days. Hospital admission should be considered in patients who cannot be expected to return for prompt follow-up because prolonged packing increases the risk of pressure necrosis, toxic shock syndrome, sinus infections, and other complications.
- Although rare, epistaxis can lead to death by aspiration of blood, hemodynamic compromise from rapid excessive blood loss, or toxic shock syndrome.

REFERRAL

- If epistaxis cannot be controlled, an ear-nose-throat (ENT) specialist should be called for assistance.
- ENT specialist should be consulted in any patient with posterior epistaxis requiring posterior packing.

PEARLS & CONSIDERATIONS

COMMENTS

- Silver nitrate cauterization, if done on both sides of the nasal septum, can lead to septal perforation and should be discouraged.
- If anterior nasal packing is done, broad-spectrum antibiotics (e.g., amoxicillin-clavulanate 250 mg PO tid or trimethoprim-sulfamethoxazole 1 tablet PO bid) are used until the anterior packs are removed. Although it is customary to place patients on antibiotics to prevent sinusitis from obstruction, there is no proof that this is effective.
- Complications of nasal packing include:
  1. Aspiration
  2. Dislodged packing
  3. Infection
  4. Nasal trauma
- Traditional risk factors for epistaxis, including nasal perforation, nasal septum deviation, rhinitis, sinusitis, and upper respiratory tract infection, do not increase the risk of recurrent epistaxis. Significant risk factors for recurrent epistaxis include congestive heart failure, diabetes mellitus, hypertenstion, and a history of angina. Warfarin use also increases risk of recurrence, independent of INR. Aspirin and clopidogrel do not increase the risk of recurrent epistaxis.[1]

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Nosebleeds (Patient Information)

AUTHOR: **TANYA ALI, M.D.**

[1] Abrich V, Brozek A, Boyle TR, et al.: Risk factors for recurrent spontaneous epistaxis, *Mayo Clin Proc* 89(12):1636-1643, 2014.

SUGGESTED READINGS

Dai A, Jurges E: The problem with nose bleeds, *Emerg Med J* 22(8):596, 2005.
Leong SC et al.: No frills management of epistaxis, *Emerg Med J* 22(7):470, 2005.
Pallin DJ et al.: Epidemiology of epistaxis in U.S. emergency departments, 1992 to 2001, *Ann Emerg Med* 46(1):77, 2005.
Pope LE, Hobbs CG: Epistaxis: an update on current management, *Postgrad Med J* 81(955):309, 2005.

BASIC INFORMATION

DEFINITION

Epstein-Barr virus infection refers to a disease caused by Epstein-Barr virus (EBV), a human herpesvirus.

SYNONYMS

Infectious mononucleosis (IM)
Kissing disease

ICD-9CM CODES
075 Mononucleosis
ICD-10CM CODES
B27.90 Infectious mononucleosis, unspecified without complication

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 5 cases/100,000 persons per yr of IM.
PREDOMINANT SEX: Neither, although peak incidence occurs about 2 yr earlier in women.
PREDOMINANT AGE:
- Clinical evidence of IM: occurs most commonly at ages 15 to 24 yr.
- EBV infection: occurs earlier in life in lower socioeconomic groups.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most EBV infections either are asymptomatic or cause a nonspecific viral illness.
- Incubation period is 1 to 2 mo, possibly followed by a prodrome of anorexia, low-grade fever, malaise, headache, and chills; after several days, clinical triad of pharyngitis, moderate to high fever, and adenopathy may appear, accompanied by fatigue and malaise.
- Pharyngitis is usually the most severe symptom; white or necrotic exudates are common.
- Symmetrical lymphadenopathy is most prominent in the posterior more than anterior cervical region but may be diffuse.
- Splenomegaly (50% of cases) is possible, most commonly during the second week of illness.
- Maculopapular or morbilliform rash is uncommon but will occur in patients who receive ampicillin. Patients may have palatal petechiae, periorbital, or palpebral edema. Mucocutaneous oral hairy leukoplakia (OHL), which is associated with intense EBV replication and the action of EBV-encoded proteins such as latent membrane protein-1, may occur.
- Possible IM presentation: fever and adenopathy without pharyngitis.
- Nausea, vomiting, and anorexia are frequent in patients with IM, probably reflecting mild hepatitis encountered in 90% of infected individuals.
- Although complications such as spleen rupture, airway obstruction, and malignancy may be severe and fatal, they are uncommon and tend to resolve completely.
- Hematologic involvement includes hemolytic or aplastic anemia, thrombocytopenia, thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome, and disseminated intravascular coagulation (DIC). Pneumonia, myocarditis, pancreatitis, mesenteric adenitis, myositis, and glomerulonephritis may occur as well. Nervous system involvement includes Guillain-Barré syndrome, facial nerve palsy, meningoencephalitis, aseptic meningitis, transfer myelitis, peripheral neuritis, and optic neuritis.
- IM is usually a self-limited illness. Acute symptoms resolve in 1 to 2 wk, but symptoms of malaise and fatigue often persist for months.
- EBV is related to lymphoproliferative syndromes in transplant recipients and in AIDS patients.
- Increasing evidence showing an association between EBV infection and African Burkitt's, B-cell, T-cell lymphoma, and nasopharyngeal carcinoma. Table EE1-13 describes EBV-associated malignancies.

ETIOLOGY

- EBV is a ubiquitous virus.
- Infection during childhood is much less likely to cause significant illness.
- Frequency of IM in late adolescence is attributed to the onset of social contact between the sexes.
- Close personal contact is usually necessary for transmission, although EBV is occasionally transmitted by blood transfusion; transfer via saliva while kissing may be responsible for many cases.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Heterophile-negative IM caused by cytomegalovirus (CMV).
- Although clinical presentation similar, CMV more frequently follows transfusion.
- Bacterial and viral causes of pharyngitis.
- Toxoplasmosis.
- Acute retroviral syndrome of HIV.
- Lymphoma.
- Lyme disease.

WORKUP

Heterophile antibody and CBC with blood smear. Table EE1-14 describes frequently determined EBV-specific antibodies.

LABORATORY TESTS

- Increased WBC common, with a relative lymphocytosis of more than 50% and neutropenia identified.
- Hallmark of IM: atypical lymphocytes of more than 10% (not pathognomonic) are found.
- Mild thrombocytopenia is present.
- Falling hematocrit signals the possibility of splenic rupture or immune hemolytic anemia.
- Elevated hepatocellular enzymes and cryoglobulins are found in most cases.
- Heterophile antibody:
  1. As measured by the monospot test, may be positive at presentation or may appear later in the course of illness.
  2. Negative test is repeated in 1 wk if clinical suspicion is high.
  3. A positive test has been reported with primary HIV infection.
- Viral capsid antigen (VCA) IgG and IgM are rarely used for diagnosis, but better value in children because heterophile antibody is negative in most children younger than 8 years.
- PCR DNA for CMV is the test of choice in transplant recipients who develop lymphoproliferative syndromes.

IMAGING STUDIES

Chest radiograph examination:
- May rarely show infiltrates.
- Possible elevated left hemidiaphragm with splenic rupture.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive including rest.
- Splenectomy if rupture occurs.
- Transfusions for severe anemia or thrombocytopenia.

ACUTE GENERAL Rx

- Pharmacologic therapy is not indicated in uncomplicated illness.
- Avoid aspirin due to the risk of Reye's syndrome.
- Avoid ampicillin and amoxicillin as their use can frequently precipitate a nonallergic rash.
- Use of steroids is suggested in patients who have severe thrombocytopenia, hemolytic anemia, impending airway obstruction resulting from enlarged tonsils, or fulminant liver failure. Prednisone 60 to 80 mg PO qd for 3 days, then tapered over 1 to 2 wk.
- Although it may reduce initial viral shedding, there is little evidence to support the use of antiviral agents such as acyclovir in the management of IM.

CHRONIC Rx

An extremely rare, chronic form of IM with persistent fevers and fatigue has been described and should be differentiated from chronic fatigue syndrome, which is not related to EBV.

DISPOSITION

Eventual resolution of all symptoms.

REFERRAL

If more than mild illness.

PEARLS & CONSIDERATIONS

COMMENTS

Avoidance of contact sports during the first month of illness because splenic rupture can occur even in the absence of clinically detectable splenomegaly.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Epstein-Barr Virus Infection (Patient Information)
Mononucleosis (Related Key Topic)

AUTHOR: **MONZR M. AL MALKI, M.D.**

SUGGESTED READINGS

Bauer CC et al.: Serum Epstein-Barr virus DNA load in primary Epstein-Barr virus infection, *J Med Virol* 75(1):54, 2005.

Crum NF: Epstein-Barr virus hepatitis: case series and review, *South Med J* 99(5):544, 2006.

Ebell MH: Epstein-Barr virus: infectious mononucleosis, *Am Fam Physician* 70:1279, 2004.

Kaygusuz I et al.: The role of viruses in idiopathic peripheral facial palsy and cellular immune response, *Am J Otolaryngol* 25(6):401, 2004.

Ozyar E et al.: Prognostic role of Ebstein-Barr virus latent membrane protein-1 and interleukin-10 expression in patients with nasopharyngeal carcinoma, *Cancer Invest* 22(4):483, 2004.

Thorley-Lawson DA, Gross A: Persistence of the Epstein-Barr virus and the origins of associated lymphomas, *N Engl J Med* 350:1328, 2004.

Vernon SD et al.: Preliminary evidence of mitochondrial dysfunction associated with post-infective fatigue after acute infection with Epstein-Barr virus, *BMC Infect Dis* 6:15, 2006.

TABLE EE1-13 Epstein-Barr Virus (EBV)-Associated Malignancies

Malignancy	EBV Frequency (%)
Hodgkin disease	~40
Non-Hodgkin lymphomas	
Burkitt's lymphoma	20-95
Diffuse large B-cell lymphoma and $CD30^+$ $Ki\text{-}1^+$ anaplastic large cell lymphoma	10-35
Lymphomatoid granulomatosis	80-95
T-cell–rich B-cell lymphoma	20
Angioimmunoblastic lymphoma	>80
T-cell, NK-cell, and T/NK-cell lymphomas	30-90
Nasopharyngeal carcinoma	>95
Gastric adenocarcinoma	5-10
Pyothorax-associated lymphoma	>95
Leiomyosarcoma in immunocompromised patients	>95

From Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

TABLE EE1-14 Frequently Determined EBV-Specific Antibodies

Antibody Specificity	Positive in IM (%)	Time of Appearance in IM	Persistence	Comments
Viral Capsid Antigen				
VCA-IgM	100	At clinical presentation	4-8 weeks	Highly sensitive and specific; of major diagnostic utility
VCA-IgG	100	At clinical presentation	Lifelong	Useful for documentation of past EBV infection
Early Antigen				
Anti-D	70	Peaks 3-4 weeks after onset	3-6 months	Correlates with disease severity; seen in NPC patients
Anti-R	Low	2 weeks to several months after onset	2 months to >3 years	Occasionally seen with unusually severe cases; seen in African Burkitt's lymphoma patients
EBNA	100	3-4 weeks after onset	Lifelong	Presence excludes primary EBV infection

EBNA, EBV nuclear antigen; *EBV,* Epstein-Barr virus; *IM,* infectious mononucleosis; *NPC,* nasopharyngeal carcinoma; *VCA,* viral capsid antigen.
Adapted from Schooley RT: Epstein-Barr virus (infectious mononucleosis). In Mandell GL et al (eds): *Principles and practice of infectious diseases,* Philadelphia, 2010, Churchill Livingstone.

BASIC INFORMATION

DEFINITION

Erectile dysfunction (ED) is the persistent inability to achieve or sustain a penile erection of adequate rigidity to make intercourse possible or satisfactory.

SYNONYMS

ED
Impotence
Male erectile disorder
Sexual dysfunction (a nonspecific term)

ICD-9CM and DSM-5 CODES
607.84 Impotence of organic origin
ICD-10CM CODES
N48.4 Impotence of organic origin
F52.2 Failure of genital response
F52.9 Unspecified sexual dysfunction, not caused by organic disorder or disease

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE (IN U.S.):
- Increases with age and presence of vascular comorbidities.
- Approximately 8% in the 20s to 30s, 18% in the 50s, 25% in the 60s, 37% in the 70s, 80% in the 80s.

PREDOMINANT SEX: By definition, only in males
PREDOMINANT AGE: Increases with age
RISK FACTORS: Age, coronary artery disease, peripheral vascular disease, hypertension, diabetes mellitus, hypercholesterolemia, prostate surgery, neurologic injury, numerous medications, alcohol, smoking or drug abuse, obesity, obstructive sleep apnea, restless leg syndrome, systemic sclerosis

ETIOLOGY

- Most cases are caused by organic problems related to neurologic, hormonal, or vascular abnormalities or prescription or recreational drugs. In organic ED nocturnal penile tumescence is generally abnormal.
- Psychogenic ED results from mental stress, depression, widower syndrome, and performance anxiety. Characterized by normal nocturnal penile tumescence and otherwise negative test results.
- Vascular disease: history of hypertension (HTN), peripheral vascular disease, ischemic heart disease, diabetes, smoking. In approximately 40% of men >50 yr, the primary cause of ED is related to atherosclerotic disease, diabetes mellitus (DM), neuropathy, or vascular disease.
- Medication side effects: antihypertensives such as thiazides and clonidine, guanethidine or methyldopa (consider change to ACE inhibitors and calcium channel blockers with lower reported incidence of ED); antiandrogens such as spironolactone, finasteride, ketoconazole; cimetidine (but not ranitidine or famotidine); antidepressants such as selective serotonin reuptake inhibitors [SSRIs]; and antipsychotics.
- Alcohol and nicotine use.
- Recreational drugs, including cocaine, heroin, amphetamines, and marijuana. These may increase libido but impair performance.
- Hormonal dysfunction such as testosterone deficiency (decreases libido and erection), hypothyroidism or hyperthyroidism, hyperprolactinemia, and adrenal insufficiency.
- Neurogenic causes including spinal cord lesions, cortical lesions, and peripheral neuropathies.
- Bicycling has possible, but controversial, association; this may be due to prolonged pressure on the pudendal and cavernosal nerves or compromised blood flow to the cavernosal artery, resulting in penile numbness and impotence.
- Trauma or pelvic surgeries such as radical prostatectomy or cystectomy.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- A useful tool to diagnose/evaluate ED severity is the Sexual Health Inventory for Men.
- Distinguish psychogenic from organic ED.
- Evaluate for underlying etiology of organic ED and comorbid psychiatric condition.

WORKUP

- Clinical history should include time course (abrupt onset may correlate with reversible cause such as medications, psychosocial stress, psychiatric complaint, trauma. Nonsustained erection may be secondary to anxiety or vascular steal syndrome), cause (psychogenic vs. organic), and change in libido.
- Report of spontaneous nocturnal or morning erections indicate intact neurologic reflexes and penile blood flow.
- Decreased libido may indicate endocrinologic or psychogenic cause.
- If possible, interview partner regarding sexual function.
- Medical and social history should address cardiac disease symptoms and risk factors (HTN, DM, hyperlipidemia, smoking, and substance abuse), pelvic surgery, medications, and mental health.
- Physical examination to check blood pressure, visual field defects to evaluate for pituitary tumors; femoral and peripheral pulses, femoral bruits; gynecomastia; neuronal damage (genital sensation, cremasteric reflex); direct penile damage (e.g., plaque formation such as Peyronie's disease); prostate examination; or testicular atrophy and other secondary sexual characteristics.

LABORATORY TESTS

Screen for diabetes mellitus with fasting glucose. Consider lipid panel, thyroid-stimulating hormone, morning serum testosterone (free and total). If decreased testosterone, check prolactin, follicle-stimulating hormone, and luteinizing hormone.

IMAGING STUDIES

Imaging studies are rarely performed except in situations of pelvic trauma or surgery.

OTHER STUDIES

- Nocturnal penile tumescence testing very specific for distinguishing psychogenic versus organic causes.
- Neurogenic etiologies examined by the cremasteric reflex (inner-thigh touch elicits scrotal contraction), the bulbocavernosus reflex, or the pudendal-evoked response.
- Intracorporeal injection of prostaglandin E_1 to distinguish vascular and nonvascular etiologies (erection is achieved in patients with normal vascular systems). If no erection with direct injection of vasoactive substance, consider duplex ultrasound of penile vasculature.
- In patients without an obvious cause of ED, consider screening for cardiovascular disease prior to starting treatment.

TREATMENT (Fig. E1-38)

NONPHARMACOLOGIC THERAPY

- Various psychotherapeutic approaches: cognitive-behavioral therapy preferred; success rates decrease with advancing age and duration of symptoms.
- Psychosexual therapy (sex therapy and couples therapy) is first line for psychogenic ED. Psychosexual therapy may be used as for adjunctive therapy in ED from any cause to address contributing social and relationship issues.
- Mechanical vacuum devices (function by drawing blood into corpus cavernosum) are 70% to 90% effective but are difficult to use.
- Incorporate vascular risk factor reduction including counsel on diet, exercise, smoking cessation, ETOH intake and screening/treatment for HTN, insulin resistance, and hypercholesterolemia as appropriate. Trials have shown that lifestyle modification and pharmacotherapy for cardiovascular risk factors are effective in improving sexual function in men with ED.

ACUTE GENERAL Rx

- First-line treatment: In setting of sexual stimulation, three selective phosphodiesterase type 5 (PDE5) inhibitors prolong nitric oxide–induced vasodilation by increase of intracavernosal cyclic guanosine monophosphate levels. Sildenafil (Viagra) and vardenafil (Levitra, Staxyn) can be taken 30 to 60 min before sexual activity, and both are effective for about 4 hr. Tadalafil (Cialis) can be taken several hours before sexual activity (although 50% respond within 30 min) and lasts up to 36 hr. All three PDE5 inhibitors have similar efficacy and tolerability, but tadalafil has a longer duration of action and is

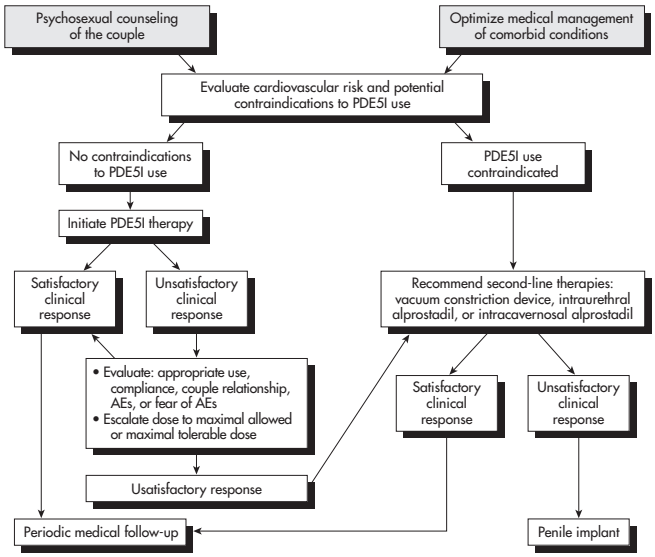

FIGURE E1-38 An algorithmic approach to the treatment of erectile dysfunction in men. *AE,* Adverse effects; *PDE5I,* phosphodiesterase 5 inhibitor. (From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

less affected by high-fat meals and alcohol. Counsel patients to avoid high-fat meals and excessive alcohol when taking PDE5 inhibitors, as they may impede effectiveness.

- With PDE5 inhibitors, avoid concomitant use of nitrates (absolute contraindication), drugs that inhibit or induce cytochrome P450 CYP3A4, and drugs that prolong the QT interval. Caution in men on alpha-adrenergic blocker therapy because of concern for hypotension; start the lowest dose of PDE5 inhibitor. Caution in men who have had myocardial infarction in the past 6 mo, resting hypotension or uncontrolled hypertension, unstable angina, positive exercise stress test or poor exercise tolerance. Counsel on side effects of headache, flushing, dyspepsia, nasal congestion, changes in color perception (including blue vision for sildenafil and vardenafil but not tadalafil), sudden hearing loss, and priapism (rare). Nonarteritic anterior ischemic optic neuropathy is also a rare association with sildenafil and tadalafil. Consider counseling on safe sexual practices when prescribing PDE5 inhibitors.
- Second-line treatment if PDE5 inhibitors fail: self-injection with intraurethral alprostadil (prostaglandin E_1 [medicated urethral suppository]) applied into meatus of penis before intercourse; or intracavernosal injections of vasodilators (e.g., papaverine or prostaglandin E_1 pellet). Consider combining intraurethral alprostadil with sildenafil. Relatively high success with self-injection, but attrition is high (Table EE1-15).
- Second-line treatment alternative: vacuum constriction pump; has variable satisfaction rate.

CHRONIC Rx

- Psychosexual therapy is helpful as an adjunctive treatment.
- Psychogenic impotence: PDE5 inhibitors are effective in patients with depression because tissues, nerves, hormones, and vasculature are normal. Full psychologic evaluation is recommended before starting treatment. If not responding to other therapies, consider yohimbine (modest efficacy), which acts by blocking presynaptic alpha$_2$-adrenergic receptors, thereby increasing cholinergic and decreasing adrenergic tone (caution in patients with heart disease due to possible tachycardia and hypertension).
- For men not responding to other approaches: surgical implantation of penile prosthesis.
- Testosterone therapy in men with low testosterone (i.e., hypogonadal); evaluate for prostate cancer before prescribing testosterone.
- Aerobic exercise may improve ED along with pharmacologic treatment.

DISPOSITION

- Psychogenic-acquired ED will remit spontaneously in 15% to 30% of cases.
- Lifelong ED is usually a chronic and unremitting condition.
- Situational ED may remit with changes in social environment but usually recurs.

REFERRAL

- Refer if psychotherapy, sex therapy, or invasive organic treatment required
- Refer to urology if PDE5 inhibitors fail or sudden onset occurs after penile trauma

PEARLS & CONSIDERATIONS

- ED is commonly evaluated and treated by primary care physician; refer to urologist if oral therapy fails or surgery is required.
- PDE5 inhibitors are treatment of choice for most causes of ED. Main contraindications are nitrate use and decompensated cardiac disease. Caution in patients on alpha-adrenergic blockers and with blood pressures at extreme ends (significant hypotension or hypertension).
- For optimal response, patients should be appropriately informed of proper use, precautions, and adverse effects of PDE5 inhibitors. Try six to eight times at optimal doses before declaring PDE5 inhibitors a failure. Consider switching among the three PDE5 inhibitors if one fails.
- Men with ED are at increased risk of coronary, cerebrovascular, and peripheral vascular diseases. Screen for cardiovascular risk factors in these patients.

EVIDENCE

available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Erectile Dysfunction (Patient Information)

AUTHORS: **CINDY LAI, M.D.,** and **JONATHAN DUONG, M.D.**

EVIDENCE

Abstract[1]

Introduction:
Erectile dysfunction (ED) impacts both members of the couple. Female partners of men with ED are more likely to report reduced sexual quality of life than women whose partners do not have ED.

Aim:
To assess vardenafil efficacy in men with ED and determine the effects of treatment on their female partner's sexual quality of life.

Methods:
Study participants comprised men aged 18–64 years with ED and their female partners. Eligible men had ED of ≥6 months' duration and a female partner who was motivated to support their ED treatment. Eligible women had a total Female Sexual Function Index score >23.55, indicating absence of significant sexual dysfunction. Following a 4-week screening period, men were randomized to treatment with vardenafil 10 mg or placebo, which could be titrated to 20 or 5 mg after 4 weeks.

Main Outcomes Measures:
Primary efficacy variables were question 3 of the Sexual Encounter Profile questionnaire (SEP3) and the quality-of-life domain of the modified Sexual Life Quality Questionnaire (mSLQQ-QOL).

Results:
The intent-to-treat population included 343 couples, with 168 and 175 men receiving vardenafil or placebo, respectively. Vardenafil treatment significantly improved both erection maintenance and the female partners' sexual quality of life. Least squares (LS) mean SEP3 overall success rates after 12 weeks of treatment were 9.5 (baseline) vs. 67.2 (week 12) and 12.4 (baseline) vs. 24.2 (week 12) in the vardenafil and placebo groups, respectively ($P<0.0001$). In female partners, LS mean mSLQQ-QOL scores were 28.8 (baseline) vs. 68.2 (last observation carried forward [LOCF]) in the vardenafil group and 24.6 (baseline) vs. 40.5 (LOCF) in the placebo group ($P<0.0001$).

Conclusions:
Vardenafil treatment of men with ED improved both their erectile function and the sexual quality of life of their female partners. Ⓐ

Abstract[2]

Nitric oxide (NO) generated by neuronal NO synthase (nNOS) initiates penile erection, but has not been thought to participate in the sustained erection required for normal sexual performance. We now show that cAMP-dependent phosphorylation of nNOS mediates erectile physiology, including sustained erection. nNOS is phosphorylated by cAMP-dependent protein kinase (PKA) at serine (S)1412. Electrical stimulation of the penile innervation increases S1412 phosphorylation that is blocked by PKA inhibitors but not by PI3-kinase/Akt inhibitors. Stimulation of cAMP formation by forskolin also activates nNOS phosphorylation. Sustained penile erection elicited by either intracavernous forskolin injection, or augmented by forskolin during cavernous nerve electrical stimulation, is prevented by the NOS inhibitor L-NAME or in nNOS-deleted mice. Thus, nNOS mediates both initiation and maintenance of penile erection, implying unique approaches for treating erectile dysfunction. Ⓐ

Abstract[3]

Objective:
To prospectively assess the safety and effectiveness of the investigational phosphodiesterase 5 inhibitor avanafil to treat erectile dysfunction in men with diabetes mellitus.

Patients and Methods:
This 12-week, multicenter, double-blind, placebo-controlled study conducted between December 15, 2008, and February 11, 2010, randomized 390 men with diabetes and erectile dysfunction 1:1:1 to receive avanafil, 100 mg (n = 129), avanafil, 200 mg (n = 131), or placebo (n = 130). Coprimary end points assessed changes in the percentage of sexual attempts in which men were able to maintain an erection of sufficient duration to have successful intercourse (Sexual Encounter Profile [SEP] 3), percentage of sexual attempts in which men were able to insert the penis into the partner's vagina (SEP 2), and International Index of Erectile Function erectile function domain score.

Results:
Compared with placebo, least-squares mean change from baseline to study end in SEP 3, SEP 2, and International Index of Erectile Function erectile function domain score were significantly improved with both avanafil, 100 mg ($P \leq .002$), and avanafil, 200 mg ($P < .001$). Additional analyses indicated that successful intercourse could be initiated in 15 minutes or less though more than 6 hours after avanafil dosing. Adverse events most commonly reported with avanafil treatment were headache, nasopharyngitis, flushing, and sinus congestion.

Conclusion:
Avanafil was safe and effective for treating erectile dysfunction in men with diabetes and was effective as early as 15 minutes and more than 6 hours after dosing. The adverse events seen with avanafil were similar to those seen with other phosphodiesterase 5 inhibitors. Trial Registration:clinicaltrials.gov Identifier NCT00809471. Ⓐ

Abstract[4]

Purpose:
We evaluated the improvement in erectile dysfunction and lower urinary tract symptoms as well as the safety of once-daily administration of 50 mg mirodenafil in men with erectile dysfunction.

Materials and Methods:
A total of 226 patients visited for treatment of erectile dysfunction and were recruited for the study. Of these men 180 met the study inclusion criteria after completing a 2-week screening period (visit [V]1). The patients were randomly allocated into 2 groups. Group 1 (90 patients) received 50 mg mirodenafil once daily and group 2 (90 patients) received a placebo daily. Blood pressure, heart rate, IIEF-5 (5-item version of the International Index of Erectile Function), and SEP (Sexual Encounter Profile) questions 2 and 3 were assessed at 4 (V2), 8 (V3) and 12 weeks after the start of treatment (V4). I-PSS (International Prostate Symptom Score), maximal flow rate and post-void residual volume were also assessed for the evaluation of lower urinary tract symptoms.

Results:
Of the 180 patients 71 in group 1 and 63 in group 2 completed the 12-week clinical trial. IIEF-5 and I-PSS significantly improved in group 1 ($P<0.001$ for both). Facial flushing was the most common adverse effect, followed by headaches. Notably there were no statistically significant differences in either of the variables related to the cardiovascular system.

Conclusions:
Once-daily administration of 50 mg mirodenafil was efficacious and safe for the treatment of erectile dysfunction and lower urinary tract symptoms. Ⓐ

Abstract[5]

Objective:
To evaluate the effectiveness and cost-effectiveness of simvastatin on erectile function and health-related quality of life in men aged ≥40 years with erectile dysfunction (ED).

Patients and Methods:
ED is common in men aged ≥40 years and impacts upon their overall health-related quality of life and that of their partners. Men aged ≥40 years who were not receiving lipid-lowering or antihypertensive medication and not at high cardiovascular risk were recruited from 10 general practices in the East of England. In total, 173 eligible men with untreated ED were randomized to double-blind treatment with 40 mg of simvastatin or placebo once daily for 6 months. Data were collected at three points over 30 weeks. The main outcome was erectile function (International Index of Erectile Function-5 score). Secondary outcomes included male ED-specific quality of life (MED-QoL), quality-adjusted life years (QALYs) using the generic Euroqol measure (EQ-5D), endothelial function, cardiovascular risk, cholesterol, and health service costs.

Results:
There was no significant difference in erectile function between the simvastatin and placebo groups (mean change, 1.28 vs 0.07, $z = 1.1$, $P = 0.27$), although a significant improvement in MED-QoL was observed (5% vs 2%, $z = 2.09$, $P = 0.04$). Both 10-year cardiovascular risk and low-density lipoprotein were reduced (cardiovascular risk, $z = -3.67$, $P < 0.001$; low-density lipoprotein, $z = -5.46$, $P < 0.001$), with no

consistent change in endothelial function. The frequency of sexual encounters is correlated with improved erectile function. The joint distribution of costs and QALY benefits indicates that the probability of simvastatin being cost-effective for willingness-to-pay thresholds of £20,000 and £30,000 is 86% and 83%, respectively.

Conclusions:

Identifying men with ED provides an opportunity to modify future cardiovascular risk and to improve MED-QoL by treating them with 40 mg of simvastatin. The joint analysis of costs and QALY benefits suggests that there is high probability that simvastatin is a cost-effective strategy in men with ED. Ⓐ

Evidence-Based Reference

Martín-Morales A et al.: Improvement in sexual quality of life of the female partner following vardenafil treatment of men with erectile dysfunction: a randomized, double-blind, placebo-controlled study, *J Sex Med* 8:2831–2840, 2011. Ⓐ

Hurt KJ, Sezen SF, Lagoda GF, et al.: Cyclic AMP-dependent phosphorylation of neuronal nitric oxide synthase mediates penile erection, *Proc Natl Acad Sci U S A* 109:16624–16629, 2012. Ⓐ

Goldstein I, Jones LA, Belkoff LH, et al.: Avanafil for the treatment of erectile dysfunction: a multicenter, randomized, double-blind study in men with diabetes mellitus, *Mayo Clin Proc* 87:843–852, 2012. Ⓐ

Chung JH, Kang DH, Oh CY, et al.: Safety and efficacy of once daily administration of 50 mg mirodenafil in patients with erectile dysfunction: a multicenter, double-blind, placebo controlled trial, *J Urol* 189:1006–1013, 2013. Ⓐ

Trivedi D, Kirby M, Wellsted DM, et al.: Can simvastatin improve erectile function and health-related quality of life in men aged ≥40 years with erectile dysfunction? Results of the Erectile Dysfunction and Statins Trial [ISRCTN66772971], *BJU Int* 111:324–333, 2013. Ⓐ

SUGGESTED READINGS

Beckman T et al.: Evaluation and medical management of erectile dysfunction, *Mayo Clin Proc* 81(3):385–390, 2006.

Gupta BP et al.: The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction, *Arch Intern Med* 171(20):1797–1803, 2011.

Heidelbaugh JJ: Management of erectile dysfunction, *Am Fam Physician* 81(3):305–312, 2010.

McVary KT: Clinical practice: erectile dysfunction, *N Engl J Med* 357(24): 2472–2481, 2007.

McVary KT: Erectile dysfunction, *N Engl J Med* 357:2472–2481, 2007.

Melnik T et al.: Psychosocial interventions for erectile dysfunction, *Cochrane Database Syst Rev* 3, 2007. CD004825.

Rosenberg MT: Diagnosis and management of erectile dysfunction in the primary care setting, *Int J Clin Pract* 61:1198, 2007.

TABLE EE1-15 Guidelines for Intracavernosal Therapy

1. Do not prescribe intracavernosal therapy to men who have psychiatric disorders, hypercoagulable states, or sickle cell disease; who are receiving anticoagulant therapy; or who are unable to comprehend the risks or take appropriate action should complications occur.
2. Designate a physician or a urologist to be available to handle emergencies related to complications of intracavernosal injections, such as prolonged erection and priapism.
3. Instruct the patient in the injection technique, the risks of intracavernosal therapy, and the steps to be taken in the event of prolonged erection or priapism.
4. Administer the first injection in the office, and observe the blood pressure and heart rate response. This provides an excellent opportunity for educating the patient, observing adverse effects, and determining whether the patient will respond to intracavernosal therapy.
5. Start with a low dose of alprostadil and titrate the dose based on the erectile response and the duration of erection. Adjust the dose of alprostadil to achieve an erection that is sufficient for sexual intercourse but does not last more than 30 min.
6. If the erection does not abate in 30 min, the patient should be instructed to take a tablet of pseudoephedrine or terbutaline (Brethine) or an intracavernosal injection of phenylephrine. If this is not effective, the patient should call the designated physician or urologist and go to the emergency room.

From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders, Elsevier Inc.

BASIC INFORMATION

DEFINITION

Erysipelas is a type of cellulitis caused by infection of the superficial layers of the skin and cutaneous lymphatics. Erysipelas is characterized by redness, induration, and a sharply demarcated, raised border.

SYNONYMS

St. Anthony's fire

ICD-9CM CODES
035 Erysipelas
ICD-10CM CODES
A46 Erysipelas

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT AGE: Occurs most often in the young or old
RISK FACTORS: Patients with impaired lymphatic or venous drainage (mastectomy, saphenous vein harvesting) and immunocompromised patients. Athlete's foot is a common portal of entry.
RECURRENCE RATE: Relatively common

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Distinctive red, warm, tender skin lesion with induration and a sharply defined, advancing, raised border (Fig. E1-39).
- Most common sites are lower extremities and face.
- Systemic signs of infection (fever) are often present.
- Vesicles or bullae may develop.
- After several days lesions may appear ecchymotic.
- After 7 to 10 days desquamation of affected area may occur.

ETIOLOGY

- Usually group A β-hemolytic streptococci
- Less often group B, C, or G streptococci
- Rarely *Staphylococcus aureus*

COMPLICATIONS

- Abscess
- Necrotizing fasciitis
- Thrombophlebitis
- Gangrene
- Metastatic infection

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other types of cellulitis
- Necrotizing fasciitis
- Deep vein thrombosis
- Contact dermatitis
- Erythema migrans (Lyme disease)
- Insect bite
- Herpes zoster
- Erysipeloid
- Acute gout
- Pseudogout

WORKUP

History, physical examination, and laboratory evaluation

LABORATORY TESTS

Diagnosis is usually made by characteristic clinical setting and appearance.

- Complete blood count and white blood cell count often elevated
- Blood cultures positive in 5% of patients
- Gram stain and culture of any drainage from skin lesions
- Culture of aspirated fluid from leading edge of skin lesion has low yield

IMAGING STUDIES

- Not routinely indicated
- Duplex ultrasound for patients suspected of having deep vein thrombosis
- CT scan or MRI for patients with suspected necrotizing fasciitis

TREATMENT

NONPHARMACOLOGIC THERAPY

- Elevation of the affected limb
- Warm compresses

ACUTE GENERAL Rx

Typical erysipelas of extremity in nondiabetic patient:

- PO: penicillin V 500 mg qid
- IV: penicillin G (aqueous) 1 to 2 million units q6h. Use vancomycin 15 mg/kg IV q12h in penicillin-allergic patients.

NOTE: Use azithromycin in patients allergic to penicillin.

Facial erysipelas (include coverage for *Staphylococcus aureus*):

- PO dicloxacillin 500 mg q6h
- IV nafcillin or oxacillin 2 g q4h
- IV vancomycin 1 g q12h
- Daptomycin 4 mg/kg IV q24h
- Linezolid 600 mg IV q12h

DISPOSITION

Prognosis is good with antibiotic treatment but recurrence is common.

REFERRAL

For surgical debridement for patients with necrotizing fasciitis or for drainage of abscess

PEARLS & CONSIDERATIONS

- Consider early surgical referral when necrotizing fasciitis suspected. Consider skin biopsy when not responding to appropriate antibiotics.
- Look for tinea pedis as portal of entry in erysipelas of lower extremities. Treat if present.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Erysipelas (Patient Information)
Cellulitis (Related Key Topic)

AUTHOR: **GAIL M. O'BRIEN, M.D.**

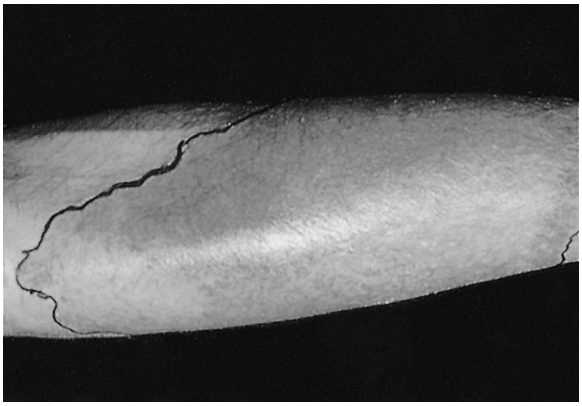

FIGURE E1-39 Erysipelas. Note well-demarcated erythematous plaque on arm. (From Goldstein B [ed]: *Practical dermatology,* ed 2, St Louis, 1997, Mosby. Courtesy Department of Dermatology, University of North Carolina at Chapel Hill.)

SUGGESTED READING

Falagas M et al.: Narrative review: diseases that masquerade as infectious cellulites, *Ann Intern Med* 142(1):47, 2005.

BASIC INFORMATION

DEFINITION

Erythema multiforme is an inflammatory disease characterized by eruption of annular, maculopapular lesions with dark raised, erythematous, or vesiculobullous center surrounded by a pale zone. It is believed to be caused by immune complex formation and subsequent deposition in the skin and mucous membranes. It is considered a hypersensitivity reaction to infection or drugs.

SYNONYMS

EM

ICD-9CM CODES
695.1 Erythema multiforme
ICD-10CM CODES
L51.9 Erythema multiforme, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT AGE: 20 to 40 yr.
RISK FACTORS: Often associated with herpes simplex and other infectious agents, drugs, or connective tissue diseases.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Prodromal symptoms are mild or absent. Itching or burning at the site of eruption may occur.
- Symmetric skin lesions with a classic "target" appearance (caused by the centrifugal spread of red maculopapules to circumference of 1 to 3 cm with a purpuric, cyanotic, or vesicular center) are present (Fig. E1-40). The papules may enlarge into plaques measuring a few centimeters in diameter with a dark or red central portion. Target lesions may not be apparent for several days.
- Lesions are most common on the back of the hands and feet and extensor aspect of the forearms and legs. Trunk involvement can occur in severe cases.
- Urticarial papules, vesicles, and bullae may also be present and generally indicate a more severe form of the disease.
- Individual lesions heal in 1 to 2 wk without scarring.
- Bullae and erosions may also be present in the oral cavity.

ETIOLOGY

- Immune complex formation and subsequent deposition in the cutaneous microvasculature may play a role in the pathogenesis of erythema multiforme.
- The majority of cases follow outbreaks of herpes simplex virus 1 and 2.
- *Mycoplasma pneumoniae,* fungal infections, medications (bupropion, sulfonamides, penicillins, nonsteroidal anti-inflammatory drugs, barbiturates, phenothiazines, hydantoins).
- In >50% of patients no specific cause is identified.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Chronic urticaria.
- Secondary syphilis.
- Pityriasis rosea.
- Contact dermatitis.
- Pemphigus vulgaris.
- Lichen planus.
- Serum sickness.
- Drug eruption.
- Granuloma annulare.
- Polymorphic light eruption.
- Viral exanthema.

WORKUP

- Medical history with emphasis on drug ingestion.
- Laboratory evaluation in patients with suspected collagen-vascular diseases.
- Skin biopsy when diagnosis is unclear.

LABORATORY TESTS

- Complete blood count with differential.
- Antinuclear antibody.
- Serology for *Mycoplasma pneumoniae,* HSV-1, HSV-2.
- Urinalysis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Mild cases generally do not require treatment; lesions resolve spontaneously within 1 mo.
- Potential drug precipitants should be removed.

ACUTE GENERAL Rx

- Treatment of associated diseases (e.g., acyclovir for herpes simplex, erythromycin for *Mycoplasma* infection).
- Prednisone 40 to 80 mg/day for 1 to 3 wk may be tried in patients with many target lesions; however, the role of systemic steroids remains controversial.
- Levamisole, an immunomodulator, may be effective in the treatment of patients with chronic or recurrent oral lesions (dose is 150 mg/day for 3 consecutive days used alone or in combination with prednisone).
- IV immunoglobulins in severe cases.

DISPOSITION

The rash generally evolves over a 2-wk period and resolves within 3 to 4 wk without scarring. A severe bullous form can occur (see entry for "Stevens-Johnson Syndrome").

REFERRAL

Hospital admission in patients with suspected Stevens-Johnson syndrome

PEARLS & CONSIDERATIONS

COMMENTS

The risk of recurrence of erythema multiforme exceeds 30%. Recurrence may be treated with valacyclovir 500 to 1000 mg/day, famciclovir 125 to 250 mg/day, or acyclovir 400 mg bid. Dapsone, antimalarials, azathioprine, or cyclosporine use is reserved for cases resistant to antivirals.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Erythema Multiforme (Patient Information)
Stevens-Johnson Syndrome (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

FIGURE E1-40 Iris and arcuate lesions of erythema multiforme. Note erythematous lesions with multiform configurations: target, arcuate, and vesicles. (From Noble J et al: *Textbook of primary care medicine,* ed 2, St Louis, 1995, Mosby.)

SUGGESTED READINGS

Lamoreux M et al.: Erythema multiforme, *Am Fam Physician* 74:2006, 1883.
Patel NN, Patel DN: Erythema multiforme syndrome, *Am J Med* 122:623–625, 2009.

Erythema Nodosum PTG

BASIC INFORMATION

DEFINITION

Erythema nodosum (EN) is an acute, tender, erythematous, nodular skin eruption resulting from inflammation of subcutaneous fat, often associated with bruising. It is the most common form of panniculitis.

ICD-9CM CODES
695.2 Erythema nodosum
ICD-10CM CODES
L52 Erythema nodosum

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Two to three cases/100,000 persons per yr.
PREDOMINANT SEX: Female/male ratio of 3 to 4:1.
PREDOMINANT AGE: 25 to 40 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute onset of tender nodules typically located on the shins (Fig. E1-41) and occasionally seen on the thighs and forearms.
- The nodules are usually 1/8 to 1 inch in diameter but can be as large as 4 inches; they begin as light red lesions, then become darker and often ecchymotic. The nodules heal within 8 wk without ulceration.

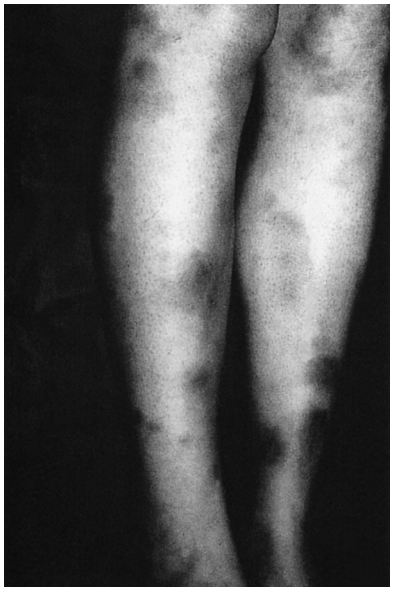

FIGURE E1-41 Erythema nodosum. (From Arndt KA et al: *Cutaneous medicine and surgery, vol 1,* Philadelphia, 1997, Saunders.)

- Associated findings:
  1. Fever.
  2. Lymphadenopathy.
  3. Arthralgia.
  4. Signs of the underlying illness.

ETIOLOGY

Cell-mediated hypersensitivity reaction is seen more frequently in persons with human leukocyte antigen (HLA) B8. The lesion results from an exaggerated interaction between an antigen and cell-mediated immune mechanisms leading to granuloma formation. Up to 55% of cases of EN are idiopathic.

Infections:

- Bacteria
  1. Streptococcal pharyngitis (28% to 48%).
  2. *Salmonella* enteritis.
  3. *Yersinia* enteritis.
  4. Psittacosis.
  5. *Chlamydia pneumoniae* infection.
  6. *Mycoplasma* pneumonia.
  7. Meningococcal infection.
  8. Gonorrhea.
  9. Syphilis.
  10. Lymphogranuloma venereum.
  11. Tularemia.
  12. Cat-scratch disease.
  13. Leprosy.
  14. Tuberculosis.
- Fungi
  1. Histoplasmosis.
  2. Coccidioidomycosis.
  3. Blastomycosis.
  4. *Trichophyton verrucosum.*
- Viruses
  1. Cytomegalovirus.
  2. Hepatitis B.
  3. Epstein-Barr virus.
- Drugs (3% to 10%)
  1. Sulfonamides.
  2. Penicillins.
  3. Oral contraceptives.
  4. Gold salts.
  5. Prazosin.
  6. Aspirin.
  7. Bromides.
- Sarcoidosis (11% to 25%).
- Inflammatory bowel disease.
- Cancer, usually lymphoma.
- Ankylosing spondylosis and reactive arthropathies (e.g., associated with inflammatory bowel disease)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Insect bites.
- Posttraumatic ecchymoses.
- Vasculitis.
- Weber-Christian disease.
- Fat necrosis associated with pancreatitis.
- Necrobiosis lipoidica.
- Scleroderma.
- Lupus panniculitis.
- Subcutaneous granuloma.

WORKUP

- Physical examination.
- Diagnosis of underlying illness by history, physical examination, and laboratory tests as indicated.

LABORATORY TESTS

- Erythrocyte sedimentation rate.
- Throat culture and antistreptolysin O titer.
- PPD.
- Others depending on index of suspicion (e.g., stool culture and evaluation for ova and parasites in patients with diarrhea and gastrointestinal symptoms).
- Skin biopsy in doubtful cases:
  1. Early lesion: inflammation and hemorrhage in subcutaneous tissue.
  2. Late lesion: giant cells and granulomata.

IMAGING STUDIES

Chest radiograph to rule out sarcoidosis and tuberculosis.

TREATMENT

- The disease is self-limited and treatment is symptomatic. EN nodules develop in pretibial locations and resolve spontaneously over several weeks without scarring or ulceration.
- Treatment of underlying disorders.
- Avoidance of contact irritation of affected areas.
- Nonsteroidal anti-inflammatory drugs for pain.
- Systemic steroids (prednisone 1 mg/kg of body weight/day, tapered over several days) may be useful in severe cases if underlying risk of sepsis and malignancy have been excluded.

PROGNOSIS

Typical case:

- Pain for 2 wk.
- Resolution within 8 wk.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Erythema Nodosum (Patient Information)
Sarcoidosis (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READING

Schwartz RA, Nervi S: Erythema nodosum: a sign of systemic disease, *Am Fam Physician* 75:695–700, 2007.

BASIC INFORMATION

DEFINITION

Esophageal tumors include both benign and malignant neoplasms of the esophageal mucosa and wall. Carcinomas of the esophageal epithelium, both squamous cell and adenocarcinoma, are by far the most common tumors of the esophagus (see Table E1-16). Rare esophageal tumors include both malignant (spindle cell, small cell, sarcoma, lymphoma) and benign neoplasms (leiomyoma, papilloma, and fibrovascular polyps). Approximately 15% of esophageal tumors arise in the proximal esophagus, 50% in the middle third of the esophagus, and 35% in the lower third.

SYNONYMS

Neoplasm of the esophagus.
Malignancy of the esophagus.

ICD-10CM CODES

C15.X Malignant neoplasm of the esophagus (X defines location)
C15.3 Malignant neoplasm of upper third of esophagus
C15.4 Malignant neoplasm of middle third of esophagus
C15.5 Malignant neoplasm of lower third of esophagus
D00.2 Carcinoma of esophagus, in situ

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Varies widely worldwide. It is the eighth most common incident cancer and the seventh leading cause of cancer death worldwide. Rates are increasing every decade and are highest in the Asian esophageal cancer belt, extending from the Caspian Sea to northern China, with certain high-incidence pockets in Finland, Ireland, southeast Africa, and northwest France. Incidence has increased sixfold since 1975. Rates of squamous cell carcinoma are decreasing while rates of adenocarcinomas are dramatically increasing.

PREVALENCE: In the United States, >18,000 new cases and >15,000 deaths per year, making it the seventh leading cause of death by cancer among men. The majority are diagnosed at an advanced stage (unresectable or metastatic disease).

RACE, AGE, & SEX PREDOMINANCE: In the United States, squamous cell esophageal cancer is more common among blacks than whites, whereas adenocarcinoma is more common in whites than blacks. The overall male/female ratio is 3 to 4:1; the highest male/female ratio is in the Hispanic population. It usually develops in the seventh and eighth decades and is associated with lower socioeconomic status.

GENETICS: Increasing evidence shows that genetics may play a role by increasing susceptibility to esophageal cancer. One well identified disease condition associated with esophageal cancer is tylosis (focal non-epidermolytic palmoplantar keratoderma), linked to loss of heterozygosity on chromosome 17q. Familiar clustering of Barrett's esophagus and the recent identification of germline mutations in affected sibling pairs support a genetic link to esophageal adenocarcinoma.

TABLE E1-16 Classification of Esophageal Cancer

Epithelial
Squamous cell
Ordinary squamous cell
Verrucous squamous cell
Spindle cell (carcinosarcoma)
Adenocarcinoma
Ordinary
Adenoacanthoma
Mucoepidermoid
Adenoid cystic
Small cell
Melanoma
Choriocarcinoma
Metastatic Disease
Lymphoma
Sarcoma

From Abeloff MD: *Clinical oncology,* ed 3, Philadelphia, 2004, Churchill Livingstone.

CLINICAL PRESENTATION

Symptoms and signs:
- Dysphagia (74%): initially occurs with solid foods and gradually progresses to include semisolids and liquids; latter signs usually indicate incurable disease with tumor involving more than 60% of the esophageal circumference. May be felt as chest pain.
- Unintentional weight loss: usually of short duration. Losing >10% of body mass predicts poor outcome.
- Hoarseness: suggests recurrent laryngeal nerve involvement.
- Odynophagia and halitosis: unusual symptoms.
- Cervical adenopathy: usually involving supraclavicular lymph nodes.
- Dry cough: suggests tracheal involvement.
- Aspiration pneumonia: caused by development of a fistula between the esophagus and trachea.
- Iron deficiency anemia, related to chronic GI blood loss.
- Massive hemoptysis or hematemesis: results from the invasion of vascular structures.
- Advanced disease spreads to lymph nodes, liver, lungs, peritoneum, and pleura.
- Hypercalcemia: associated with squamous cell carcinoma from secretion of a parathyroid-like tumor peptide.

Clinical findings:
- Fifty to sixty percent of patients present with locally advanced, regional, or metastatic disease.

ETIOLOGY

Pathogenesis of esophageal cancers is attributable to chronic recurrent oxidative damage from any of the following etiologic agents, which cause inflammation, and esophagitis, increased cell turnover, and, ultimately, initiation of the carcinogenic process.

ETIOLOGIC AGENTS: Squamous cell carcinoma
- Excess alcohol consumption is strongly associated with squamous cell esophageal cancer in the United States; hard liquor is associated with a higher incidence than wine or beer.
- Tobacco and alcohol synergistically increase risk for squamous cell cancer.
- Other ingested carcinogens:
  1. Nitrates (converted to nitrites): South Asia, China.
  2. Smoked opiates: Northern Iran.
  3. Fungal toxins in pickled vegetables.
  4. Betel nut chewing.
- Mucosal damage:
  1. Long-term exposure to extremely hot tea (>70° C).
  2. Lye ingestion.
- Radiation-induced strictures.
- Achalasia: incidence of esophageal cancer is seven times greater in this population.
- Host susceptibility as a result of precancerous lesions:
  1. Plummer-Vinson syndrome (Paterson-Kelly): glossitis with iron deficiency.
  2. Congenital hyperkeratosis and pitting of palms and soles (tylosis).
- Human papillomavirus infection (particularly types 16 and 18) has been variably detected in squamous cell carcinoma of the esophagus, sometimes associated with p53 tumor suppressor gene mutations.
- Questionable relationship with prolonged bisphosphonate use (≥10 prescriptions, or use >3 yr).
- Possible association with celiac sprue or dietary deficiencies of molybdenum, selenium, zinc, vitamin A.

ADENOCARCINOMA:
- Smoking may increase the risk of developing adenocarcinoma, particularly in patients with Barrett's.
- Obesity, hiatal hernia, and diets lacking in fresh fruit and vegetables and high in fat (particularly from red meat and processed foods).
- Chronic GERD leading to Barrett's metaplasia and adenocarcinoma via immune cell infiltration and production of inflammatory mediators and reactive oxygen species. The annual rate of transformation from Barrett's to adenocarcinoma is <0.5%.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Achalasia.
- Scleroderma of the esophagus.
- Diffuse esophageal spasm.
- Esophageal rings and webs.

LABORATORY TESTS

Complete blood cell count, blood chemistry, liver enzymes. No biomarkers are available currently to diagnose, monitor, or predict outcomes.

IMAGING STUDIES

Imaging studies are important not only for diagnosis but for accurate staging (Fig. E1-42):
- Esophagogastroduodenoscopy (EGD) (Fig. EE1-43) should be performed initially to

visualize smaller tumors, which may be missed by esophagogram, and to allow histopathologic confirmation.
- Endoscopic inspection of the larynx, trachea, and bronchi may identify concomitant cancers of head, neck, and lung ("triple endoscopy").
- Endoscopic ultrasonogram (EUS) (Fig. EE1-43) is the most accurate method for locoregional staging: to determine the depth of tumor invasion and to assess for and possibly obtain fine needle aspiration biopsies of suspicious lymph nodes.
- Double-contrast esophagogram effectively identifies large esophageal lesions (Fig. EE1-44).
  1. In contrast to benign esophageal leiomyomata, which cause narrowing with preservation of normal mucosal pattern, esophageal carcinomas cause ragged ulcerating mucosal changes in association with deeper infiltration.
- Chest and abdominal CT and/or integrated CT-PET scans can determine tumor spread for preoperative staging and may help restage patients after initial induction therapy.
- Staging laparoscopy may alter treatment plans in 20% to 30% of cases by more accurately staging regional lymph nodes and detecting occult peritoneal metastases.

STAGING

Table E1-17 describes the TNM staging system for cancer of the esophagus from the American Joint Committee on Cancer Criteria.

Rx TREATMENT

TREATMENT OF ALL STAGES OF ESOPHAGEAL CANCER

SURGICAL RESECTION:

- Surgical resection of squamous cell carcinoma and adenocarcinoma of the middle esophagus and lower third of the esophagus is an acceptable initial modality of treatment for local and resectable disease in the absence of widespread metastasis detected by CT-PET and transesophageal ultrasound (T1 and T2 tumors). Gastric pull-through or colonic interposition typically is used to provide luminal continuity.
- Endoscopic mucosal resection may replace radical surgical resection in very early tumors with no lymph node involvement (Tis or T1a), but a recent Cochrane review found no studies comparing endoscopic treatment vs. surgery. This may be performed in conjunction with ablative therapies, including radiofrequency ablation, thermal ablation techniques, or photodynamic therapy.
- Complications of surgery:
  1. Anatomic fistula (usually with colon interposition, subphrenic abscesses).
  2. Respiratory complications.
  3. Cardiovascular complications are most common, including MI, CVA, and PE.
  4. Mortality is lower and clinical outcomes are better at high-volume hospitals and with minimally invasive surgery.

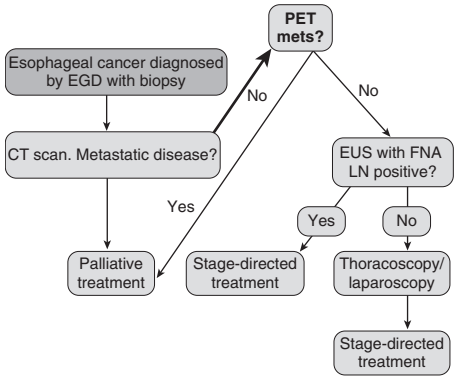

FIGURE E1-42 Algorithm for staging esophageal cancer. *CT,* Computed tomography; *EGD,* esophagogastroduodenoscopy; *mets,* metastases; *PET,* positron emission tomography. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

TABLE E1-17 TNM Staging System for Cancer of the Esophagus (American Joint Committee on Cancer Criteria)

Primary Tumor (T)*	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia†
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.
Lymph Node (N)‡	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in 7 or more regional lymph nodes
Distant Metastasis (M)	
MX	Metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

*(1) At least maximal dimension of the tumor must be recorded and (2) multiple tumors require the T(m) suffix.
†High-grade dysplasia includes all noninvasive neoplastic epithelia that was formerly called carcinoma in situ.
‡Number must be recorded for total number of regional nodes sampled and total number of reported nodes with metastasis.
From Edge S et al (eds): *AJCC cancer staging manual,* ed 7, New York, 2010, Springer.

PRE-TREATMENT PATIENT PREPARATION

The patient needs to stop smoking and drinking alcohol if at all possible. Before neoadjuvant or definitive chemoradiation, the patient should have placement of an intravenous access device (port-a-cath or PICC line) and a feeding tube (J-tube is preferable before surgical resection).

RADIATION THERAPY:

- Squamous cell carcinomas are more radiosensitive than adenocarcinoma. Radiation achieves good local control but is generally only used as monotherapy in a palliative mode for obstructive symptoms in patients with unresectable or advanced cancer or those with multiple comorbidities that limit treatment. It is best used for cervical esophageal tumors, but response rates are best when combined with chemotherapy.
- Radiation therapy in the preoperative/neoadjuvant setting is taken to a total dose of 40 to 50 Gy. For definitive therapy, the dose range is 50 to 65 Gy.
- Palliative radiation therapy for bone metastasis is also effective.
- Complications of radiation therapy: These can now best be avoided by 3D conformal radiation therapy.
  1. Esophageal stricture, fistula formation, radiation-induced pulmonary fibrosis, and transverse myelitis are the most common.
  2. Radiation-induced cardiomyopathy and skin changes are rare.

COMBINATION CHEMOTHERAPY, RADIATION Rx, & SURGICAL Rx:

- Chemotherapy is most often given with concurrent radiation therapy (chemoradiation). Chemotherapy acts as a radiosensitizer and makes tumor cells more vulnerable to the effects of ionizing radiation thus improving tumoricidal effects on cancer. Neoadjuvant chemoradiation followed by surgery is the most common approach for patients with resectable disease, but employed primarily for patients with stage IIA or higher disease. Five-year survival is improved with neoadjuvant chemoradiation (39%) versus surgery alone (16%). Several trials have now shown that preoperative chemoradiation improves survival among patients with potentially curable esophageal or esophagogastric junction cancer. Neoadjuvant chemotherapy alone is another option for locally advanced disease, but results are not as good as neoadjuvant combined therapy.
- Chemoradiation combined with surgery should be offered to late stage I (T1bN0 or higher), stage II, and stage III esophageal cancer patients as the current standard of care. In several studies, preoperative chemoradiation plus surgery significantly improved local control, reduced recurrence, and reduced mortality compared with surgery alone in patients with resectable esophageal cancer. Trimodality therapy is the preferred treatment for most esophageal cancers.

- Chemoradiation alone may be offered as the definitive treatment for patients who are not surgical candidates.
- Combination chemotherapy utilizing a platinum doublet (platinum agent plus second chemotherapeutic agent) can achieve significant tumor reduction in 30% to 60% of patients. Cisplatin oxaliplatin or carboplatin is usually given with 5-FU (5-fluorouracil) or paclitaxel to obtain the desired tumoricidal effects.
- Capecitabine in combination with either cisplatin or oxaliplatin is as effective as 5FU in the neoadjuvant or definitive treatment setting.
- Complications of chemotherapy primarily include mucositis, nausea, vomiting, diarrhea, myelosuppression, nephrotoxicity, ototoxicity, and neurotoxicity. These can occur to varying degrees and are certainly more significant in the elderly and otherwise infirmed.
- Postoperative adjuvant chemotherapy with or without radiation therapy may be offered to node-positive patients who underwent initial surgery alone.

TREATMENT OF UNRESECTABLE, LOCALLY ADVANCED, OR METASTATIC DISEASE

- Combination chemotherapy regimens as a rule have a higher response rate than single agent therapy. Response rates can be as high as 50% but that does not always translate into prolonged survival.
- Neoadjuvant chemotherapy regimens can also be utilized in locally advanced or metastatic settings. Cisplatin is probably the most active agent, and this combined with 5FU can yield response rates shown in several studies of 20% to 50%. If a taxane is added to this regimen in the metastatic setting, the triple drug regimen can lead to a prolongation in disease progression by about 2 months, which may translate into prolonged survival. However, the patients have to be carefully chosen for this triple drug regimen because of increased toxicity. Other active double regimens can combine cisplatin with irinotecan, etoposide, or gemcitabine. Again, capecitabine can be substituted for 5FU in these regimens.

TARGETED MOLECULAR THERAPY

- Ramucirumab is the first recombinant monoclonal antibody of the IgG1 class that acts as a vascular endothelial growth factor receptor 2 (VEGFR-2) antagonist. Its only indication is in metastatic gastric or gastroesophageal cancer treatment. It binds VEGF and thereby blocks binding of VEGFR ligands and inhibits ligand proliferation and migration of endothelial cells. Ultimately it inhibits angiogenesis. It is indicated for second line therapy following treatment with either a 5FU or platinum-containing chemotherapy regimen. This has been used as first line therapy in conjunction with paclitaxel with an overall response rate of 28%.
- Trastuzumab, in combination with cisplatin and 5FU, can be used as first line therapy for metastatic esophageal cancer in patients with HER-2 overexpressing adenocarcinoma. Approximately 22% of adenocarcinomas will overexpress the type II epidermal growth factor receptor HER2. There is high concordance between HER2 results from the primary tumor and metastatic sites. The overall response rate is 47%.
- Cetuximab, an epidermal growth factor receptor (EGFR) inhibitor, is being studied in combination with more traditional chemotherapy to treat squamous cell carcinomas. It is not considered part of the standard approach to treatment and should be reserved for clinical trials.

FOLLOW-UP CARE

For patients who have received treatment, the majority of recurrences develop within 12 months. Clinical monitoring, along with lab tests, imaging, and endoscopic evaluation where appropriate (particularly with preoperative Barrett's), are usually performed for postoperative surveillance, without clear benefit in earlier detection or decreased mortality. For patients who have undergone definitive therapy, it is recommended that endoscopic surveillance be performed every 3 months for the first year, and then annually. Biopsies should be taken of any mucosal surface changes. Palliative procedures such as repeated endoscopic dilation, endoscopic ablation, endoscopic mucosal resection, photodynamic therapy, brachytherapy, feeding tube insertion, or placement of expandable metal stents or polyvinyl prostheses to bypass tumors have been used for unresectable patients. The morbidity and mortality associated with resection in patients with advanced disease and/or for palliation argues against offering this modality to most of these patients.

SURVIVORSHIP

- Overall 5-yr survival given all stages at presentation, including patients inoperable secondary to existing comorbidities, is 15% (39% for localized disease, 21% for regional disease, and 4% for distant disease).
- Endoscopic therapy for highly selected stage 0 or stage I patients with disease limited to the submucosa may have 5-year survival rates of 70% to 90%.
- Surgical resection without neoadjuvant treatment: 5-yr survival rate is 5% to 30%, with higher survival (up to 45% to 50%) in early stage cancers.
- Radiation therapy without chemotherapy or surgery: 5-yr survival rate of 6% to 20%.
- Chemoradiation without surgery: 5-year survival up to 30%.
- Combined trimodality treatment: up to 45% to 50% 5-year survival rates (all stages of disease treated).
- Patients with stage IV disease receive palliative chemotherapy with a median survival of less than 1 year.

REFERRAL

- To gastroenterologist for endoscopy for patients with dysphagia, odynophagia, or unexplained weight loss, or for palliative care.
- To medical oncologist for evaluation of preoperative chemotherapy and care of the metastatic patient.
- To radiation oncologist for palliative therapy if tumor is unresectable or obstruction is present.
- To hospice if appropriate.

PEARLS & CONSIDERATIONS

COMMENTS

More than 50% of patients with esophageal cancer are diagnosed when the disease is metastatic or unresectable.

PREVENTION

- A diet high in fruits, vegetables, and antioxidants may be associated with lower risk of esophageal cancer.
- Avoid tobacco and excessive alcohol use.
- Avoid ingested toxins known to cause esophageal cancers.
- Aspirin may have a chemopreventive role in Barrett's but is only currently recommended for patients with other (e.g., cardiac) indications.
- There is no evidence that vitamins, Chinese herbal regimens, or green tea prevent esophageal cancer.
- Screening the general population is not recommended. If Barrett esophagus is detected, regularly scheduled surveillance endoscopies are necessary, with consideration for radiofrequency or other ablation therapy if dysplasia is detected.

PATIENT/FAMILY EDUCATION

Provide education and support about the likely prognosis because most esophageal cancers are diagnosed at an advanced stage.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Barrett Esophagus (Related Key Topic)
Esophageal Cancer (Patient Information)

AUTHORS: **HARLAN G. RICH, M.D.,** and **ANTHONY G. THOMAS, D.O.**

EVIDENCE

Abstract[1]

Background:

The clinical value of synbiotics in patients undergoing esophagectomy remains unclear. This study investigated the effects of synbiotics on intestinal microflora and surgical outcomes in a clinical setting.

Methods:

We studied 70 patients with esophageal cancer who were scheduled to undergo esophagectomy. They were randomly allocated to 2 groups: 1 group received synbiotics before and after surgery, and the other did not. Fecal microflora and organic acid concentrations were determined. Postoperative infections, abdominal symptoms, and duration of systemic inflammatory response syndrome (SIRS) were recorded.

Results:

Of the patients, 64 completed the trial (synbiotics, 30; control, 34). The counts of beneficial bacteria and harmful bacteria in the group given synbiotics were significantly larger and smaller, respectively, than those in the control group on postoperative day (POD) 7. The concentrations of total organic acid and acetic acid were higher in the synbiotics group than in the control group ($P < .01$), and the intestinal pH in the synbiotics group was lower than that in the control ($P < .05$) on POD 7. The rate of infections was 10% in the synbiotics group and 29.4% in the control group ($P = .0676$). The duration of SIRS in the synbiotics group was shorter than in the control group ($P = .0057$). The incidence of interruption or reduction of enteral nutrition by abdominal symptoms was 6.7% in the synbiotics group and 29.4% in the control group ($P = .0259$).

Conclusion:

Perioperative administration of synbiotics in patients with esophagectomy is useful because they suppress excessive inflammatory response and relieve uncomfortable abdominal symptoms through the adjustment of the intestinal microfloral environment.

In an era when there is intense focus on postoperative complications, infections, and the pressure to shorten hospital stays, this report promises to significantly impact these issues. Esophagectomy is associated with relatively high complication rates and extended hospitalization. This group from Japan reports on the use of synbiotics to address these concerns. Synbiotics are a combination of helpful bacteria, including *Lactobacillus* and *Bifidobacterium,* along with the prebiotics, which include nondigestive food constituents that selectively alter the growth and activity of bacteria. Prebiotics comprise galactooligosaccharides, fructooligosaccharides, and inulin. This randomized study enrolled 70 patients scheduled for esophagectomy to the perioperative administration of a synbiotic (Yakult BL) versus control bacteria. Patients who received the synbiotic had lower infection rates, shorter postoperative ileus, and less perioperative inflammatory response. This was accompanied by alternations in colonic flora and fewer postoperative complaints of abdominal discomfort. Although the difference in infection rates just missed statistical significance, a 3-fold reduction was noted. The utility of synbiotics for other extensive operations like hepatobiliary surgery, liver transplantation, and colectomy has been reported. This simple intervention with synbiotics may be an important approach to address many issues with our most complex surgical patients.

J. Hines, M.D. Ⓐ

Evidence-Based Reference

Tanaka K et al.: Impact of perioperative administration of synbiotics in patients with esophageal cancer undergoing esophagectomy: a prospective randomized controlled trial, *Surgery* 152:832–842, 2012. Ⓐ

SUGGESTED READINGS

Arnott SJ et al.: Preoperative radiotherapy for esophageal carcinoma, *Cochrane Database Syst Rev* 4:CD001799, 2005.

Cunningham D et al.: Capecitabine and oxaliplatin for advanced esophagogastric cancer, *N Engl J Med* 358:36–46, 2008.

Green S et al.: Surgery versus radical endotherapies for early cancer and high grade dysplasia in Barrett's oesophagus, *Cochrane Database Syst Rev* 2:CD007334, 2009.

Kranzfelder M et al.: Meta-analysis of neoadjuvant treatment modalities and definitive non-surgical therapy for oesophageal squamous cell cancer, *BrJ Surg* 98:768–783, 2011.

Layke JC, Lopez PP: Esophageal cancer: a review and update, *Am Fam Physician* 73:2187–2192, 2006.

Rustgi AK, El-Serag HB: Esophageal carcinoma, *N Engl J Med* 371:2499–2509, 2014.

Sharma P: Barrett's esophagus, *N Engl J Med* 361(26):48–56, 2009.

Van Hagen P et al.: Preoperative chemoradiotherapy for esophageal or junctional cancer, *N Engl J Med* 366:2074–2084, 2012.

Wiedmann WM et al.: New and emerging combination therapies for esophageal cancer, *Cancer Manag Res* 27:133–146, 2013.

Wong R, Malthaner R: Combined chemotherapy and radiotherapy (without surgery) compared with radiotherapy alone in localized carcinoma of the esophagus, *Cochrane Database Syst Rev* 1:CD002092, 2006.

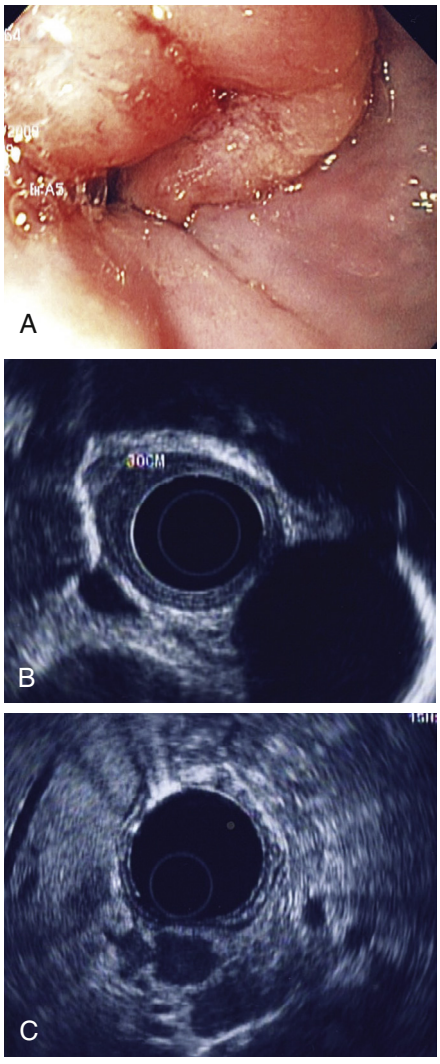

FIGURE EE1-43 Esophageal cancer. A, Endoscopic picture of malignant esophageal stricture. **B,** EUS image showing T3 lesion. **C,** Malignant celiac lymphadenopathy. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

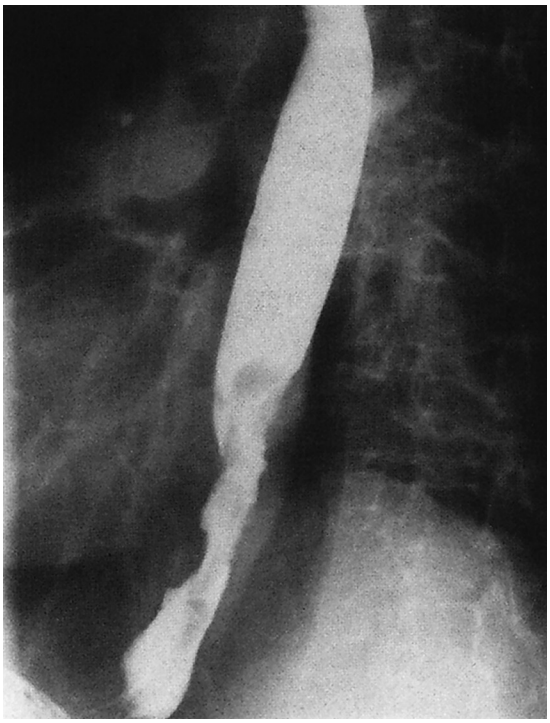

FIGURE EE1-44 Barium swallow demonstrating the classic findings in cancer of the distal third of the esophagus. (Reprinted from Noble J [ed]: *Primary care medicine,* ed 2, St Louis, 1996, Mosby.)

Esophageal Varices EBM

BASIC INFORMATION

DEFINITION

Esophageal varices are dilated submucosal veins that occur in patients with underlying portal hypertension, function as a shunt between the portal venous and systemic venous circulation, and can result in severe upper GI hemorrhage.

ICD-9CM CODES
- 85.00 Esophageal varices without bleeding
- I85.01 Esophageal varices with bleeding
- I85.10 Secondary esophageal varices without bleeding
- I85.11 Secondary esophageal varices with bleeding

ICD-10CM CODES
- I85.00 Esophageal varices without bleeding
- I85.01 Esophageal varices with bleeding

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE

- Esophageal varices: 5%-15% per year in patients with cirrhosis
- Hemorrhage:
  1. One third of all patients with varices will develop hemorrhage.
  2. Variceal hemorrhage occurs in 25%-40% of patients with cirrhosis
  3. The risk of bleeding from varices is approximately 15% at 1 year.
  4. Survivors of an episode of active bleeding have a 70% risk of recurrent hemorrhage within 1 year.

PREVALENCE: Approximately 50% of patients with cirrhosis have varices at the time of diagnosis.

RISK FACTORS: Cirrhosis, low platelet count and advanced Child-Pugh class, hepatitis C with advanced fibrosis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Often asymptomatic until acute upper GI hemorrhage: hematemesis, hypovolemia
- No physical findings specific for esophageal varices
- Stigmata of cirrhosis and portal hypertension may be evident: palmar erythema, telangiectasias, gynecomastia, testicular atrophy, jaundice, caput medusae, lower extremity edema, ascites, splenomegaly, hemorrhoids, asterixis

ETIOLOGY

- Portal hypertension results from obstruction to portal venous outflow, and varices subsequently develop in order to decompress the hypertensive portal vein and return blood to the systemic circulation.
- Varices may appear when portal vein pressures rise above 10-12 mm Hg.
- Cirrhosis is the most common cause of portal hypertension.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Budd-Chiari syndrome, cirrhosis, portal vein thrombosis, schistosomiasis, Wilson's disease
- Other causes of upper GI bleeding: duodenal or gastric ulcers, gastric cancer, Mallory-Weiss tear

WORKUP

Upper endoscopy, laboratory tests, and imaging

LABORATORY TESTS

- CBC
  1. Anemia (blood loss, nutritional deficiencies, alcohol myelosuppression)
  2. Thrombocytopenia (hypersplenism, alcohol myelosuppression)
- Renal function panel
  1. BUN: often increased in setting of upper GI bleeding
  2. Creatinine: often elevated by hypovolemia, monitor for hepatorenal syndrome
  3. Sodium: dilutional hyponatremia
- Heme-positive stools
- Type and Crossmatch: in preparation for blood transfusion
- INR/PT and PTT: coagulation factors produced in liver and may be prolonged in liver disease or impairment
- Liver function tests: ALT/AST may be normal in cirrhotic patients due to longstanding fibrosis; elevated alkaline phosphatase and a direct hyperbilirubinemia may be present if cholestatic liver disease is present
- Serum albumin: severe liver disease results in hypoalbuminemia

IMAGING STUDIES (Fig. E1-45)

Invasive:
- Esophagogastroduodenoscopy (EGD) (upper endoscopy):
  1. In all patients with cirrhosis, screen for the presence or absence of varices and determine subsequent risk for variceal hemorrhage.
  2. In patients with compensated cirrhosis who do not have varices, screening is repeated every 2 to 3 years.
  3. In patients with decompensated cirrhosis (ascites, hepatic encephalopathy, variceal hemorrhage, or jaundice), it is repeated every year or at the time of first decompensation.
  4. Emergently performed if there is evidence of acute upper GI bleeding to diagnose and treat variceal hemorrhage.

Noninvasive:
- Esophagography with barium can diagnose esophageal varices.
- Capsule endoscopy can also diagnose esophageal varices, although sensitivity is not yet established.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Endoscopic variceal ligation (Fig. E1-46) is an alternative to nonselective beta-blockers for primary prophylaxis against variceal hemorrhage.
  1. Typically for patients with medium or large varices at highest risk for hemorrhage (Child-Pugh B/C or red wale markings viewed on endoscopy)
  2. Usually 2-4 sessions
  3. May not be a permanent solution because varices can recur after initial eradication
  4. Associated with significant complications, including hemorrhage from banding-induced ulcerations
     1. Therefore should be performed by endoscopists with expertise in prophylactic banding
     2. First surveillance endoscopy 1-3 months after obliteration, then every 6-12 months indefinitely

ACUTE GENERAL Rx

- Variceal hemorrhage: acute hemodynamic resuscitation with packed red blood cell transfusion, correct coagulopathy and thrombocytopenia, airway protection and intubation as necessary, antibiotics (ceftriaxone or norfloxacin) for SBP prophylaxis, octreotide maintained for 2-5 days in conjunction with endoscopic therapy
- EGD to treat bleeding esophageal varices by esophageal band ligation or sclerotherapy

CHRONIC Rx

Primary prophylaxis:
- Nonselective beta-blockers such as propranolol (20 mg twice daily) and nadolol (40 mg once daily)
  1. Increase as tolerated for goal heart rate of approximately 55 beats/min
  2. Blocks the adrenergic dilatory tone in mesenteric arterioles, resulting in unopposed alpha-adrenergic mediated vasoconstriction and therefore a decrease in portal inflow

Secondary prophylaxis:
- All patients with compensated cirrhosis who have bled from esophageal varices should receive esophageal band ligation and beta-blockers, unless beta-blockers are contraindicated.
  1. Transjugular intrahepatic portosystemic shunt or surgical shunt may be performed if bleeding from esophageal varices continues or recurs despite this dual therapy.
- For patients with decompensated cirrhosis there is evidence, although limited, against the use of prophylactic beta-blockers due to the risk for increased mortality.

REFERRAL

Consultation with a gastroenterologist is recommended in all patients with cirrhosis or portal hypertension in order to screen for esophageal varices.

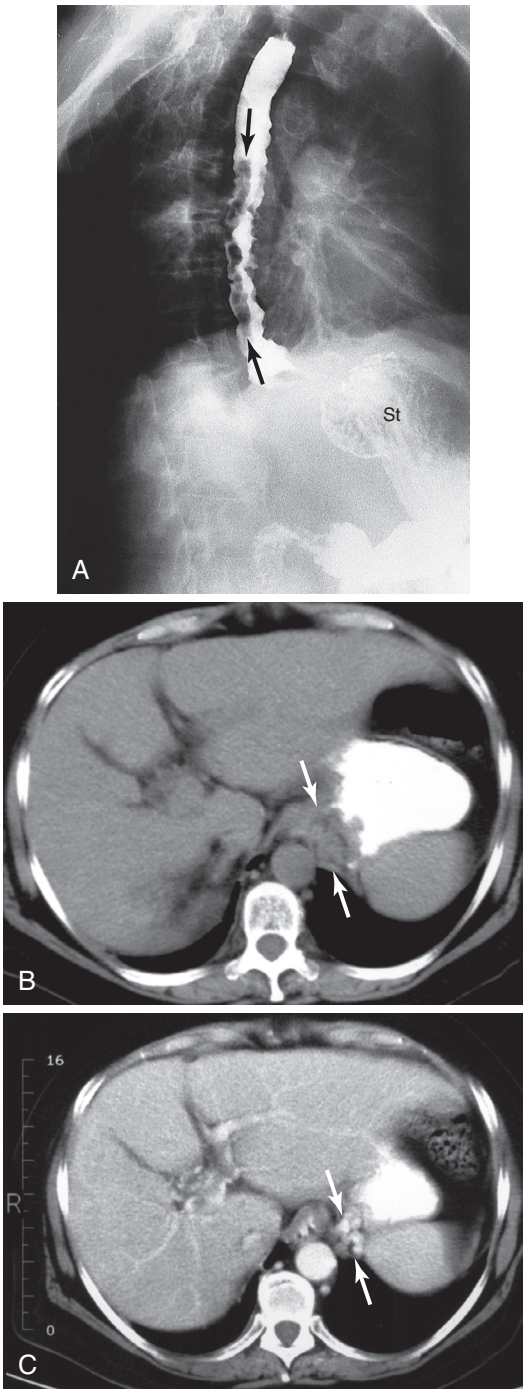

FIGURE E1-45 Esophageal varices. In an oblique view from an upper gastrointestinal examination (**A**) performed on an alcoholic patient, a large, dark, wormlike filling density *(arrows)* is seen in the distal esophagus. It is caused by varices protruding into the lumen of the esophagus. The stomach (*St*) also is seen. Varices also can be seen on computed tomography (CT) scan. On a CT scan without intravenous contrast (**B**), they are seen as small rounded structures *(arrows),* and they may indent the fundus of the stomach. When intravenous contrast is given (**C**), they enhance and become whiter *(arrows).* (From Mettler FA: *Essentials of radiology*, 3rd ed, Philadelphia, 2014, Saunders.)

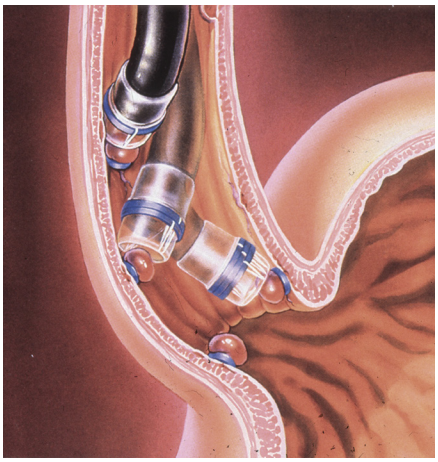

FIGURE E1-46 Esophageal varices. Endoscopic band ligation performed with a multiple-band ligating device. The endoscopist makes circumferential contact between the end of the ligating device and the varix to be ligated. Endoscopic suction draws the varix into the device, after which the elastic band is ejected to ensnare the varix. The ligated tissue sloughs after 3 to 5 days, leaving a shallow ulceration that generally heals within 1 week. (Courtesy Bard Endoscopic Technologies, Billerica, Mass.)

PEARLS & CONSIDERATIONS

Besides variceal size, risk factors for variceal hemorrhage include Child-Pugh class B/C or variceal red wale markings on endoscopy.

PREVENTION

Treatment of the underling liver disease may help to prevent variceal development. However, treatment with nonselective beta-blockers is not recommended because they do not prevent the development of varices.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Cirrhosis (Related Key Topic)
Portal Hypertension (Related Key Topic)

AUTHOR: **ADAM J. WEINBERG, M.D.**

EVIDENCE

Abstract[1]

Background & Aims:

Gastric variceal bleeding is severe and is associated with high mortality. We compared the efficacy of cyanoacrylate injection and beta-blockers in primary prophylaxis of gastric variceal bleeding.

Methods:

Cirrhotics with large gastroesophageal varices type 2 with eradicated esophageal varices or large isolated gastric varix type 1, who had never bled from gastric varix, were randomised to cyanoacrylate injection (Group I, n=30), beta-blockers (Group II, n=29) or no treatment (Group III, n=30). Primary end-points were bleeding from gastric varix or death.

Results:

The actuarial probability of bleeding from gastric varices over a median follow-up of 26months was 13% in Group I, 28% in Group II (p=0.039), and 45% in Group III (p=0.003). The actuarial probability of survival was higher in the cyanoacrylate compared to the no-treatment group (90% vs. 72%, p=0.048). The median hepatic venous pressure gradient (HVPG) was increased in Group I (14–15mmHg, p=0.001) and III (14–16mmHg, p=0.001) but decreased in Group II (14 to 12mmHg, p=0.001) during follow-up. Size of gastric varix >20mm, a MELD score ≥17, and presence of portal hypertensive gastropathy predicted 'high risk' of first bleeding from gastric varices.

Conclusions:

Primary prophylaxis is recommended in patients with large and high risk gastric varices to reduce the risk of first bleeding and mortality. Cyanoacrylate injection is more effective than beta-blocker therapy in preventing first gastric variceal bleeding. Ⓐ

Evidence-Based Reference

Mishra SR et al.: Primary prophylaxis of gastric variceal bleeding comparing cyanoacrylate injection and beta-blockers: a randomized controlled trial, *J Hepatol* 54:1161–1167, 2011. Ⓐ

SUGGESTED READINGS

Garcia-Tsao G et al.: Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis, Practice Guidelines Committee of the American Association for the Study of Liver Diseases, Practice Parameters Committee of the American College of Gastroenterology, *Hepatology* 46(3):922–938, 2007.

Guadalupe G, Bosch J: Management of varices and variceal hemorrhage in cirrhosis, *N Engl J Med* 362:823–832, 2010.

BASIC INFORMATION

DEFINITION

A predominantly postural and action tremor that is bilateral and tends to progress slowly over the years in the absence of other neurologic abnormalities.

SYNONYMS

Benign essential tremor
Familial tremor

ICD-9CM CODES
333.1 Essential tremor
ICD-10CM CODES
G25.0 Essential tremor

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT AGE: Can begin at any age, but incidence increases after age 40 yr. Prevalence is 6% to 9% for those >60 yr.
GENETICS: No gender or racial predominance.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients complain of tremor that is most bothersome when writing or holding something such as a newspaper or trying to drink from a cup. Worsens under emotional distress.
- Tremor, 4 to 12 Hz, bilateral postural and action tremor of the upper extremities. May also affect the head, voice, trunk, and legs. Typically it is the same amplitude throughout the action, such as bringing a cup to the mouth. No other neurologic abnormalities on examination except difficulty with tandem gait. Patients often note improvement with intake of small amounts of alcohol.

ETIOLOGY

Often an inherited disease, autosomal dominant; sporadic cases without a family history are frequently encountered

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS (see Table E1-18)

- Parkinson's disease—tremor is usually asymmetric, especially early on in the disease, and is predominantly a resting tremor. Patients with Parkinson's disease will often also have increased tone, decreased facial expression, slowness of movement, and shuffling gait.
- Cerebellar tremor—an intention tremor that increases at the end of a goal-directed movement (such as finger to nose testing). Other associated neurologic abnormalities include ataxia, dysarthria, and difficulty with tandem gait.
- Drug-induced—there are many drugs that enhance normal, physiologic tremor. These include caffeine, nicotine, lithium, levothyroxine, β-adrenergic bronchodilators, amiodarone, valproate, and SSRIs.
- Wilson's disease—wing-beating tremor that is most pronounced with shoulders abducted, elbows flexed, and fingers pointing toward each other. Usually there are other neurologic abnormalities including dysarthria, dystonia, and Kayser-Fleischer rings on ophthalmologic examination.
- Physiologic tremor

WORKUP

- Essential tremor is a clinical diagnosis
- All imaging studies (MRI, CT) are unnecessary unless there are other associated neurologic abnormalities
- Obtain TSH (rule out hyperthyroidism)
- In patients younger than 40 yr with other neurologic abnormalities, send ceruloplasmin, serum Cu, 24-hr urine Cu to rule out Wilson's disease

TREATMENT

Treat essential tremor when it is functionally impairing. Treatments are up to 75% effective.

NONPHARMACOLOGIC THERAPY

- Stress management
- Minimize use of caffeine if consumption is correlated with worsened symptoms.
- Small quantities of alcohol at social functions may be beneficial.

ACUTE GENERAL Rx

Propranolol (20 to 40 mg) may be used in preparation for specific event.

CHRONIC Rx

First-line agents:
- Propranolol/Inderal LA: usual starting dose is 30 mg. The usual therapeutic dose is 160 to 320 mg. Although not contraindicated, they must be used with caution in those with asthma, depression, cardiac disease, and diabetes.
- Primidone: usual starting dose is 12.5 to 25 mg qhs. Usual therapeutic dose is between 62.5 and 750 mg daily (assuming side effects are tolerated). Sedation and nausea are common at treatment initiation.
- Topiramate: 25 mg qhs, may titrate up to about 400 mg

Other agents:
- Gabapentin: 400 mg qhs, usual therapeutic dose is 1200 to 3600 mg
- Alprazolam: 0.75 to 2.75 mg
- Botulinum toxin injected focally may decrease tremor
- Atenolol, sotalol

SURGICAL Rx

Thalamic deep brain stimulation (or possibly thalamotomy) contralateral to side of tremor is reserved for resistant tremor or for patients who do not tolerate drug therapy.

DISPOSITION

Patients should be reassured that the condition is not associated with other neurologic disabilities; however, it can become quite functionally disabling over time.

REFERRAL

This is a condition that usually can be treated by the primary care physician; however, if patient fails first-line therapies then patient should be referred to specialists for other drug trials and other possible surgical options.

PEARLS & CONSIDERATIONS

- Essential tremor is the most common of all movement disorders.
- In addition to motor dysfunction, essential tremor can cause significant psychological impact on patients in social situations.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Essential Tremor (Patient Information)

AUTHOR: **U. SHIVRAJ SOHUR, M.D., PH.D.**

TABLE E1-18 Overlapping Features of Various Types of Tremor

Feature	Parkinson's Syndrome	Cerebellar Tremor	Essential Tremor
Present at rest	Yes	No	Yes
Increased tone	Yes	No	No
Decreased tone	No	Yes	No
Postural abnormality	Yes	Yes	No
Head involvement	Yes	Yes	Yes
Intentional component	No	Yes	Yes
Incoordination	No	Yes	No

From Remmel KS et al: *Handbook of symptom-oriented neurology,* ed 3, St Louis, 2002, Mosby.

SUGGESTED READINGS

Abboud H et al.: Essential tremor: choosing the right management plan for your patient, *Cleve Clin J Med* 78:821, 2011.

Deuschel G, Volkmann J: Tremors: differential diagnosis, pathophysiology, and therapy. In (editors: Jankovic J, Tolosa E.) Parkinson's disease and movement disorders. ed 4, pp. 270–291.

Elias WS, Shah BB: Tremor, *JAMA* 311(9):948–954, 2014.

Louis ED: Essential tremor, *N Engl J Med* 345(12):887, 2001.

Zesiewicz TA et al.: Phenomenology and treatment of tremor disorders. In Hurtig H, Stern M, editors: Neurologic clinics: movement disorders 19:3, 2001, pp 651–680.

BASIC INFORMATION

DEFINITION

Factitious disorder occurs when an individual falsifies physical or psychological signs or symptoms or induces injury or disease with identified deception. The individual presents himself or herself to others as ill, impaired, or injured. The individual may create signs or symptoms by (1) lying, (2) simulating (e.g., putting drops of blood into a urine sample), or (3) actually creating disease (e.g., injecting bacteria or medications). The primary aim is to achieve the patient role, and the behavior persists even in the absence of apparent external rewards such as monetary rewards or obtaining narcotics. More is known about factitious physical disorder so this chapter will focus on that entity.

The individual may seek invasive diagnostic testing, surgery, or treatment. Munchausen's syndrome is the most severe variant of factitious physical disorder and is characterized by exaggerated lying (pseudologia fantastica), sociopathy, geographic wandering from hospital to hospital, and a continuous life of patienthood.

SYNONYMS

Factitious disorder.
Munchausen's syndrome (the most severe variant of factitious disorder).
Munchausen by proxy (factitious disorder created in another person, usually a child).
Deliberate disability.
Hospital addiction syndrome.
Artifactual illness.
Peregrinating problem patients.
Dermatitis artefacta.
Surreptitious illness.

ICD-9CM and DSM-5 CODES
300.19 Other and unspecified factitious illness
ICD-10CM CODES
F68.10 Intentional production or feigning of symptoms or disabilities, either physical or psychological (factitious disorder)

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Unknown
PEAK INCIDENCE: 30 to 40 yr
PREVALENCE (IN U.S.): Unknown but considerable in specific illnesses. For example, 3.3% of patients with fever of unknown origin have a factitious disorder.
PREDOMINANT SEX: Male/female ratio of 2:1 for Munchausen's syndrome but 1:2 for individuals with non-Munchausen type of factitious physical disorder.
PREDOMINANT AGE: 30 to 40 yr.
GENETICS: No genetic predisposition known.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- False complaints or self-inflicted injury or symptoms without clear secondary gain. The intentional aspect of the disorder is often evident, such as injecting bacteria to produce infection or taking medication to produce an abnormality.
- Presentation may be acute and dramatic, but the condition can be a chronic, recurring problem.
- Workup is usually negative for naturally occurring organic etiology.
- Clinical picture is atypical for the natural history of disease (e.g., an infection that does not respond to multiple courses of appropriate antibiotics).

ETIOLOGY

- A history of significant childhood illness; physical or sexual abuse is thought to predispose.
- Personality disorders and psychodynamic factors often play a significant role.

DIAGNOSIS

The diagnosis can be made by (1) direct observation of fabrication, (2) the presence of signs or symptoms that contradict laboratory testing, (3) nonphysiologic response to treatment, (4) the presence of physical evidence of fabrication (e.g., syringes at the bedside), and (5) recurrent patterns of illness exacerbation (e.g., just before discharge) or failure to follow the natural history of disease (e.g., a wound that does not heal for no apparent reason).

DIFFERENTIAL DIAGNOSIS

- Malingering: falsifying an illness for a clear secondary gain (e.g., financial gain or avoidance of unwanted duties).
- Somatoform disorders or hypochondriasis: these disorders are produced unconsciously and are not intentionally produced.
- Self-injurious behavior is common in many other psychiatric conditions; in those conditions the patients confess the intentional self-harm and describe motivating factors. The main intent is the self-harm and not to attain the patient role, as occurs in factitious disorder.
- May also present as Munchausen by proxy, in which a mother (86% of time) or other caregiver induces illness in a child (52% between ages of 3 and 13 yr) for the purpose of obtaining medical attention or some other psychological need. Mothers often have a history of somatoform, factitious, or personality disorder themselves.

WORKUP

- Dictated by the presenting complaints.
- No specific tests for Munchausen's syndrome.
- Diagnosis may be made when the patient is caught in the act of lying or inducing an injury. The diagnosis often rests on organic workup failing to reveal a plausible natural organic disease. The failure of usual, or even extensive, treatment to ameliorate a condition is an important clue.

LABORATORY TESTS

- Laboratory testing often reveals inconsistencies.
- Other laboratory abnormalities may reflect the underlying factitious behavior (e.g., hypokalemia in an individual surreptitiously taking furosemide).

TREATMENT

NONPHARMACOLOGIC THERAPY

Two major approaches:
- Nonpunitive confrontation. Primary physician and psychiatrist conjointly meet with patient and say, "You must be in a lot of distress to be harming yourself as we believe you have been. We would like to help you deal with your distress more adaptively and get you into psychiatric treatment."
- Avoid overt confrontation with patient but provide him or her with a face-saving way to recover. For example, a therapeutic double bind would involve saying, "There are two possibilities here, one is that you have a medical problem that should respond to the next intervention we do, or two, you have a factitious disorder. The outcome will give us the answer."
- Munchausen's syndrome is the most severe variant and may be virtually impossible to treat except to avoid further invasive and iatrogenic disease.

ACUTE GENERAL Rx

Treatment of comorbid psychiatric disorders may be helpful. Treatment with antidepressants or psychotherapy may ameliorate the factitious behavior. Multidisciplinary staff meetings are useful to ventilate feelings and develop cohesive treatment plans.

DISPOSITION

- After being confronted with their behavior, patients may cease factitious behavior, but they more commonly seek other physicians or hospitals, as in the Munchausen variant. Other factitious disorder patients may enter psychotherapy, particularly when they have been given a face-saving approach with avoidance of a humiliating confrontation.
- Extensive medical workups and exploratory surgery are frequent.

REFERRAL

Always obtain psychiatric referral. Risk management attorneys and hospital ethicists may contribute to challenging decision making in these patients.

PEARLS & CONSIDERATIONS

Think of factitious disorders whenever there is an unexplained medical course that continues to repeat despite appropriate treatment, particularly in patients associated with the health care field. There is current consideration of whether factitious disorders should be classified in the upcoming DSM-5 as a subset of somatoform disorders. This possibility is related to the challenge of discriminating whether an illness state is being consciously (factitious) or unconsciously (somatoform) produced. Future research will investigate the utility of this possible change in classification.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hypochondriasis (Related Key Topic)

AUTHOR: **STUART J. EISENDRATH, M.D.**

SUGGESTED READINGS

Birman MV, Lee DH: Factitious disorders of the upper extremity, *J Am Acad Orthop Surg* 20(2):78–85, 2012.

Dimsdale J et al.: The proposed diagnosis of somatic symptom disorders in DSM-V to replace somatoform disorders in DSM-IV—a preliminary report, *J Psychosom Res* 66(6):473–476, 2009.

Eisendrath SJ, Telischak KS: Factitious disorders: potential litigation risks for plastic surgeons, *Ann Plast Surg* 60(1):64–69, 2008.

Kanaan RA, Wessely SC: Factitious disorders in neurology: an analysis of reported cases, *Psychosomatics* 51(1):47–54, 2010.

BASIC INFORMATION

DEFINITION

Failure to thrive (FTT) describes a delay in growth and development among children. FTT is a cluster of symptoms rather than a specific disease.

SYNONYMS

Pediatric undernutrition
Faltering growth
Weight faltering
Growth failure
FTT

ICD-9CM CODES

263.0 Malnutrition of moderate degree
263.1 Malnutrition of mild degree
263.2 Arrested development following protein-calorie malnutrition
263.8 Other protein-calorie malnutrition
263.9 Unspecified protein-calorie malnutrition
779.34 Failure to thrive in newborn
783.2 Abnormal loss of weight and underweight
783.21 Loss of weight
783.22 Underweight
783.4 Lack of expected normal physiologic development in childhood
783.40 Unspecified lack of normal physiologic development
783.41 Failure to thrive
783.43 Short stature

ICD-10CM CODES

R62.51 Failure to thrive (child)

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: FTT is a common problem, though its incidence in the community is unclear. A total of 1% to 5% of inpatient pediatric admissions are for evaluation of FTT.
PREDOMINANT SEX AND AGE: FTT most commonly occurs among children ages 6 to 12 months, with 80% presenting before 18 months of age. Most FTT patients present before 3 years of age. Males and females are equally affected.
RISK FACTORS: Poverty is the single greatest risk factor. Nonmedical: poverty, food insecurity, social isolation, neglect, and physical or emotional abuse. Medical: Intrauterine growth restriction (IUGR), prematurity, medical conditions leading to inadequate food intake, food malabsorption, or increased metabolic demand.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Children have blunted growth in height, weight, head circumference, or any combination of these. Children may have pallid, dry, or cracked skin, sparse hair growth, poorly developed musculature, lack of subcutaneous fat, swollen abdomen, or evidence of vitamin deficiencies.

ETIOLOGY

FTT is the result of inadequate nutrition, which may be due to a wide range of medical or psychosocial causes. FTT can be thought of as stemming from inadequate nutritional intake, malabsorption of nutrients, or increased caloric expenditure, though the actual cause is commonly multifactorial.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Inadequate nutritional intake: food insecurity, poor parent knowledge of child's needs, formula dilution, excessive juice, breastfeeding difficulties, neglect, behavioral feeding problem, oromotor dysfunction, developmental delay, emesis, gastroesophageal reflux, volvulus, increased intracranial pressure, genetic disease (trisomy 13, 18, 21), and psychiatric conditions
- Malabsorption: cystic fibrosis, celiac disease, food protein insensitivity or intolerance, and inflammatory bowel disease
- Increased metabolic demand: insulin resistance, congenital infection, other infection, genetic syndrome, hyperthyroidism, chronic disease, and malignancy

WORKUP

- Evaluation should include the child's eating habits, caloric intake, parent-child interactions, psychosocial history, and review of systems. Fig. F1-1 illustrates an algorithm for management of a child with failure to thrive (FTT).
- Height, weight, and weight-to-length measurements are most sensitive, whereas head circumference and body mass index (BMI) may be useful. Common FTT criteria for children younger than 2 years are below, but clinical judgment should be used because normal causes and biologic variants may exist.
  - Length, weight, or BMI below the 3rd or 5th percentile on more than one consecutive visit
  - Weight that drops below two major percentile lines
  - Weight less than 80% of the ideal weight for age
  - Weight-to-length below the 5th percentile or weight-for-length less than 70% to 79% of the median
  - Weight velocity below the 3rd or 5th percentile
  - Weight less than 70% of the 50th percentile; may require hospitalization
- Obtain caliper measurements of skinfold thickness and midarm muscle circumference.
- Observation of a meal being taken to assess potential feeding difficulties.
- A 3-day food diary is helpful, as well as consultation by a nutritionist, to calculate the child's intake of energy, protein, vitamins, and minerals.
- Assess stool frequency, consistency, quantity, as well as fat, blood, or mucus content.
- Routine hospitalization for FTT evaluation is not recommended. Rarely, hospitalization for observed feedings and further workup is warranted.

LABORATORY TESTS

- Laboratory tests have limited utility in screening for FTT unless a specific underlying medical cause is suspected.
- Consider CBC with red blood cell indices, complete chemistry panel, celiac screening, stool examination for fats or reducing substances, or sweat chloride testing. If clini-

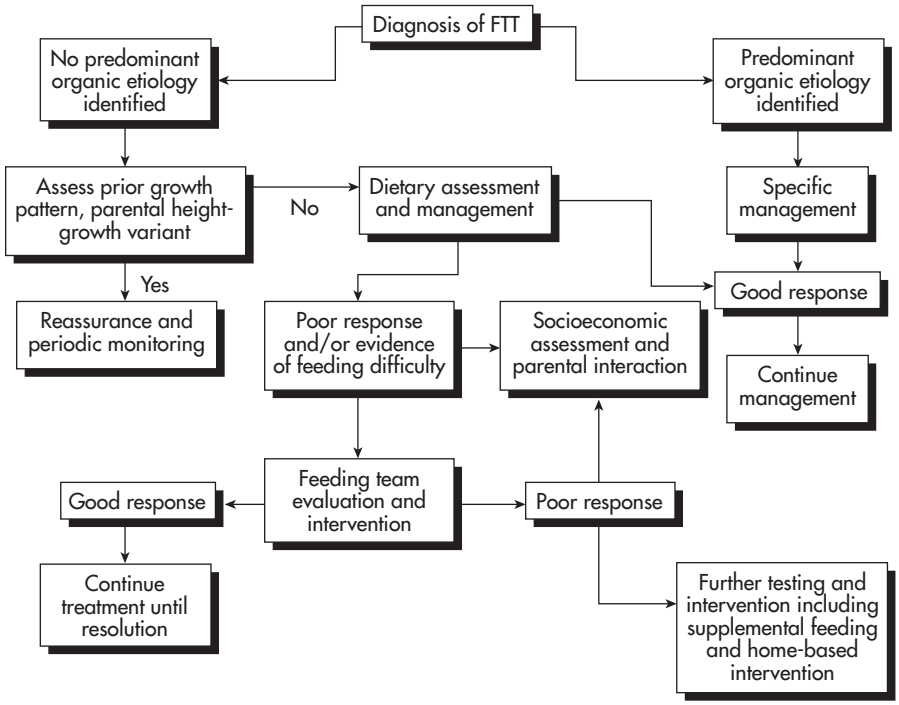

FIGURE F1-1 Algorithm for management of a child with failure to thrive (FTT). (Shashidhar H, Tolia V: Failure to Thrive. *In* Wyllie R, Hyams, JS (eds): *Pediatric Gastrointestinal and Liver Disease,* 4th ed, Philadelphia, 2011, Elsevier, pp. 136–145.e3.)

cally indicated, thyroid function and growth hormone level can be checked.

IMAGING STUDIES

Imaging tests are not routinely performed but may be warranted depending on underlying medical cause.

Rx TREATMENT

Identification and management of underlying causes should be implemented. In cases in which there is no underlying medical condition, providing nutrition repletion will, by definition, correct FTT. A multidisciplinary team (including, but not limited to, social workers, occupational/speech therapists, nutritionists/dietitians, nurses, advanced practice nurses, and pediatricians) should be used.

NONPHARMACOLOGIC THERAPY

- Add calorie-dense foods or increase the number of feedings.
- Enteral feeding, percutaneous endoscopic gastrostomy (PEG), and nasogastric feeding tubes can be used to accelerate weight gain, and results should be seen within 2 to 7 days. Caloric intake should be titrated up to goal over 5 to 7 days. Caloric goals by age group: 0 to 6 months: 108 kcal/kg/day, 6 to 12 months: 98 kcal/kg/day, and 1 to 3 years: 102 kcal/kg/day.
- Swift restoration of nutrition can lead to life-threatening refeeding syndrome, where shifts in electrolyte balance (low phosphate, magnesium, potassium), fluid balance (edema), hypoglycemia, and impaired heart function can occur. Calories must therefore be titrated slowly to goal with close monitoring.
- Treat underlying medical conditions, including mental health disorders.
- Assist with family psychosocial stressors.
- Follow up closely, including home nursing visits.
- In cases where economic, psychosocial, or parental issues are suspected and the child's growth is not maintained, state and federal legislation regarding reporting to child protection services must be followed.

ACUTE GENERAL Rx

Multivitamins including iron and zinc

CHRONIC Rx

Nutrient repletion with the goal of accelerated growth should be continued for 4 to 9 months

DISPOSITION

Children with FTT commonly remain small in height and weight. Studies consistently find that children with FTT are more prone to long-term cognitive, learning, and behavioral abnormalities.

REFERRAL

- Indicated based on the cause of FTT
- Hospitalization should be considered in cases of FTT in which a child is less than 70% of predicted weight for length, where outpatient management has failed, when a suspicion of abuse or neglect exists, where signs of traumatic injury are present, or where serious impairment of the child's caregiver is evident.

PEARLS & CONSIDERATIONS

COMMENTS

- FTT is a common childhood symptom encountered in the outpatient and inpatient pediatric populations, is caused by undernutrition, and is associated with inadequate nutritional intake, malabsorption, or increased metabolic demand.
- A thorough multidisciplinary approach to assessment, diagnosis, and management should be used to manage nutrient status and any underlying cause(s).
- Child height/length, weight, and weight-for-length measurements with comparison to standard growth curves are useful in the identification of potential cases of FTT.
- FTT treatment should include restoration of nutrition along with treatment of the underlying cause(s), including psychosocial factors.
- Although FTT can usually be managed effectively in the outpatient setting, specific indications for inpatient treatment should be considered.

PREVENTION

Nutritional counseling and anticipatory guidance should be provided at each well-child visit. Enlist dietitians and visiting nurses to provide support to families with children at high risk of FTT.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **GRAYSON W. ARMSTRONG, B.A.**

SUGGESTED READINGS

Black MM et al.: Early intervention and recovery among children with failure to thrive: follow-up at age 8, *Pediatrics* 120(1):59–69, 2007.

Cole SZ, Lanham JS: Failure to thrive: an update, *Am Fam Physician* 83(7):829–834, 2011.

Fuentebella J, Kerner JA: Refeeding syndrome, *Pediatr Clin North Am* 56(5):1201–1210, 2009.

Jaffe AC: Failure to thrive: current clinical concepts, *Pediatr Rev* 32(3):100–108, 2011.

King C, Davis T: Nutritional treatment of infants and children with faltering growth, *Eur J Clin Nutr* 64(Suppl 1):S11–S13, 2010.

Rogol AD, Hayden GF: Etiologies and early diagnosis of short stature and growth failure in children and adolescents, *J Pediatr* 164(Suppl 5):S1–14, 2014.

Shields B et al.: Weight faltering and failure to thrive in infancy and early childhood, *Br Med J* 325:e5931, 2012.

Falls in the Elderly ALG EBM

BASIC INFORMATION

DEFINITION

A fall is an "event which results in a person coming to rest inadvertently on the ground and other than a consequence of the following: loss of consciousness, sudden onset of paralysis, or epileptic seizure" (Kellogg International Work Group, *Danish Medical Bulletin,* 34, 1-24).

SYNONYMS

Syncope
Collapse

ICD-9CM CODES
Accidental fall (E880-E888.9)
ICD-10CM CODES
E880-E888.9 Accidental fall

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE

- Trauma is the fifth leading cause of death in persons >65 years of age, and falls are responsible for 70% of accidental deaths in persons ≥75 yr.
- The incidence of falls among community-dwelling older adults is 30% to 40%. Two thirds of falls in the community are preventable; 6% to 7% of these falls result in fracture.
- The incidence of falls for nursing home and hospitalized older adults is three times the rate of community-dwelling older adults. Over 50% of nursing home residents fall during their stay.
- 20% to 30% of older adults who fall suffer significant injury leading to immobility, dependence, and an increased risk of early death.

HEALTHCARE COST

- In 2006, patients ≥65 had over 2.1 million visits to the ED for injurious falls, which was 10.5% of all ED visits among the elderly and 29.6% of these visits required hospital admission. In those that were admitted, the mean length of stay was 5.5 days with a mean cost of $10,800. The aggregate hospital cost for those requiring admission in 2006 was $6.8 billion. (Source: Healthcare Cost and Utilization Project).

PREDOMINANT SEX & AGE

- Fall-related mortality is highest among older white men followed by white women, black men, and black women.
- The incidence rates of falls increase with advancing age.
- Older adults ≥85 years are 10 to 15 times more likely to have a fracture compared with those aged 60 to 65 years.

RISK FACTORS: Four groups of risk factors for falls have been identified (Table F1-1):

1. Intrinsic factors inherent in the older adult who falls.
2. Extrinsic factors circumstantial to the older adult who falls.
3. Falls in nursing homes.
4. Situational or the activity in which the older adult is engaged in when a fall occurs.

CLINICAL PRESENTATION

- Older adults who fall may present with minor soft tissue injuries, such as lacerations or bruising, hip fracture, or head trauma; however, most falls are not reported unless an injury has occurred.
- If an older adult presents for medical attention for a fall or reports recurrent falls in the past year or difficulties in walking or balance, a multifactorial fall risk assessment should be completed.
- The multifactorial fall risk assessment should include:
  1. Focused history: A detailed history of events and circumstances surrounding fall, relevant risk factors including review of medications, acute and chronic medical problems (e.g., osteoporosis, urinary incontinence, and cardiovascular disease), and whether the fall was witnessed.
  2. Physical examination
     1. Vital signs including orthostatics.
     2. Cardiovascular examination assessing for arrhythmias, carotid bruits, or new murmurs.
     3. Neurologic examination including vision assessment, evaluation of lower extremity strength, peripheral nerves, proprioception, and testing of cortical, extrapyramidal, and cerebellar function.
     4. Gait and balance assessment: "Get up and go test" is a rapid assessment that will quickly tell you if the patient needs rehabilitation and what to work on. (Ask patient to stand from a seated position without use of hands, walk 10 feet forward, turn around, and return to chair and sit).
     5. Musculoskeletal exam with attention to joints of lower extremity, feet and footwear.
  3. Functional assessment including the older adult's activities of daily living skills, use of adaptive equipment, and fear of falling
  4. Environmental assessment of home safety

ETIOLOGY

- Falls are a multifactorial syndrome resulting from the cumulative effects of impaired gait and balance, aging, polypharmacy, depression, cognitive impairment, acute medical illness, or environmental factors (Fig. EF1-2).

TABLE F1-1 Risk Factors for Falls in the Elderly

Intrinsic

Aging

Age-related decline in vestibular function might lead to loss of balance, dizziness, and falls. Aging of the vision system (e.g., glaucoma, cataracts, retinopathy) may result in decreased visual acuity, inability to discriminate dark/light, and decreased spatial perception.

Cardiac

Cardiac arrhythmias, carotid sinus hypersensitivity, neurocardiogenic syncope

Neurologic

Parkinson's disease, normal pressure hydrocephalus (NPH), sensory neuropathy, dementia/impaired cognition, cervical myelopathy, senile gait disorder, prior stroke (One third of the elderly have abnormal position sense)

Musculoskeletal

Lower extremity weakness, impaired knee extension and ankle plantar flexion strength contribute to abnormalities in gait velocity and step length, deconditioning, arthritis, foot abnormalities (such as bunions, calluses, or nail abnormalities)

Vascular

Vertebrobasilar insufficiency, postural hypotension, postprandial hypotension

Metabolic

Hypoglycemia, hypothyroidism, hyponatremia

Psychiatric

Depression

Medications

Use of more than four medications may be associated with an increased risk of falls. Medications that may increase fall risk include benzodiazepines, sleeping medications, neuroleptics, antidepressants, anticonvulsants, class I antiarrhythmics, and antihypertensives (Rao, 2005).

Extrinsic

Environmental

Environmental hazards cause >50% of falls in the elderly (cords, furniture, small objects, ill-fitting shoes, slippery surfaces, loose rugs, uneven steps, optical patterns on escalators). Majority occurs with mild-moderate activity (walking, stepping up/down, changing position); 70% occur at home and 10% on stairs (descending > ascending).

Nursing Home Falls

20% have a cardiovascular cause (hypotension: drug induced, postprandial, postural, or bradycardia)
5% are the result of an acute illness such as PNA, febrile illness, UTI, CHF.
3% are from an overwhelming intrinsic event such as syncope, seizure, stroke, psychoactive drugs.

Situational

Tripping over obstacles, carrying heavy items, descending/ascending stairs, rapid turning, reaching overhead, climbing ladders, ill-fitting shoes, lack of assistive devices

- Most falls among community-dwelling older adults are due to environmental factors, whereas falls among nursing home residents are a result of confusion, gait impairment, or postural hypotension.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Falls are often a nonspecific symptom of an acute illness (such as delirium, urinary tract infection, acute anemia, or pneumonia) or an exacerbation of a chronic disease (chronic heart failure [CHF] or chronic obstructive pulmonary disease [COPD]). The mnemonic "DELIRIUMS" can be used to assess the differential diagnosis in acute delirium. (**D**rugs, **E**motional [depression], **L**ow PaO_2 [CHF, COPD], **I**nfection, **R**etention [urinary, fecal], **I**ctal status, **U**nder nutrition/hydration, **M**etabolic, **S**ubdural/Sensory [all neurologic causes] workup).

WORKUP

- Older adults presenting with a noninjurious fall need a detailed history and physical exam to identify acute medical illnesses and potential modifiable risk factors. Laboratory and neuroimaging studies may be necessary if the history and physical exam indicate a specific problem. ECG and Holter monitoring may be considered if cardiac arrhythmia is suspected.
- See Fig. EF1-2.

LABORATORY TESTS

CBC, stool guaiac, blood chemistries, thyroid function, liver function, vitamin B_{12} level, folate level, erythrocyte sedimentation rate, vitamin D level, drug levels, and urinalysis depending on physical/historical findings.

IMAGING STUDIES

- CT or MRI of the brain or cervical spine films in the presence of neurologic or gait impairment.
- Chest x-ray if pulmonary pathology (pneumonia, pulmonary edema) is suspected.
- Consider ECG, echocardiography, or Holter monitor if suspicious for structural cardiac abnormality or syncope.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Physical therapy evaluation for gait and balance training, evaluation of appropriate assisted devices (e.g., cane, walker), the use of fall prevention equipment (e.g., low beds, bed alarms).
- Home safety assessment: studies show that 50% of recurrent fallers fell doing the same activity that caused them to fall the first time. This can be prevented by creating a home safety evaluation checklist (preferably done by family member to improve compliance) or arranging for a home safety inspection by a visiting nurse or occupational therapist.
- Minimization or discontinuation of certain medications associated with falls (psychotropics).
- Customized exercise program to improve strength, gait, and balance
- Evaluation of proper footwear, hard sole, and low heel height.

ACUTE GENERAL Rx

Hospitalization may be necessary for treatment of hip fracture, subdural hematoma, lacerations, or trauma as well as the treatment of underlying cause of the fall such as infection, metabolic disturbances, cardiovascular (e.g., carotid sinus hypersensitivity, vasovagal syndrome, bradyarrhythmias, and tachyarrhythmias) or neurologic abnormality.

CHRONIC Rx

- Screen and treat for osteoporosis as low bone density increases the risk of hip or other fractures.
- Optimize treatment of chronic illnesses such as CHF, COPD, osteoarthritis, Parkinson's disease, dementia, postural hypotension, and visual problems.
- Vitamin D supplementation of at least 800 IU per day. Epidemiological studies reveal that compared with usual care, short-term intervention with oral nutritional supplementation and dietetic counseling significantly decrease falls in malnourished older adults.

COMPLEMENTARY & ALTERNATIVE MEDICINE

T'ai chi has been shown to reduce the risk of falls in community-dwelling study participants.

DISPOSITION

Falls increase the older adult's risk of hospitalization, institutionalization, and mortality.

REFERRAL

- Referral may be appropriate to cardiologist, ophthalmologist, neurologist, or podiatrist depending on the presence of a specific condition.
- Consider referral to physical therapist for gait and balance training, evaluation for assisted device, or strengthening program.

PEARLS & CONSIDERATIONS

COMMENTS

- Fear of falling may lead to restriction of activities, social isolation, and dependence.
- Older adults with four or more risk factors have a 78% chance of falling.
- Mortality from falls has increased by 42% over the past decade.

PREVENTION

The U.S. Preventive Services Task Force recommends exercise or physical therapy and vitamin D supplementation to prevent falls in community-dwelling adults aged ≥65 who are at increased risk for falls. It does not recommend automatically performing an in-depth multifactorial risk assessment in conjunction with comprehensive management of identified risks to prevent falls in community-dwelling adults aged 65 or older because the likelihood of benefit is small. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the balance of benefits and harms on the basis of the circumstances of prior falls, comorbid medical conditions, and patient values.

SCREENING

The "get up and go test" is a quick assessment of balance and gait. A more in-depth screening tool for falls is the Tinetti gait and balance assessment, which evaluates normal and adaptive ability to maintain balance when rising from a chair, standing with eyes closed, turning, and receiving a sternal nudge. It also evaluates several components of gait (step height, postural sway, path deviation). The test is scored on the patient's ability to perform specific tasks. Scoring is done on a 3-point scale with a range of 0 to 2. Individual scores are combined to form three measures: an overall gait assessment score (maximum score = 12), an overall balance assessment score (maximum score = 16), and a gait and balance score (maximum score = 28). In general, patients who score below 19 are at high risk for falls, and those who score 19-24 are at risk for falls.

PATIENT/FAMILY EDUCATION

Providing education and information for the patient and caregiver regarding fall prevention strategies in addition to multifactorial risk reduction strategies

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **SEAN H. UITERWYK, M.D., ALICIA J. CURTIN, PH.D.** and **KEITH BRENNAN, M.D.**

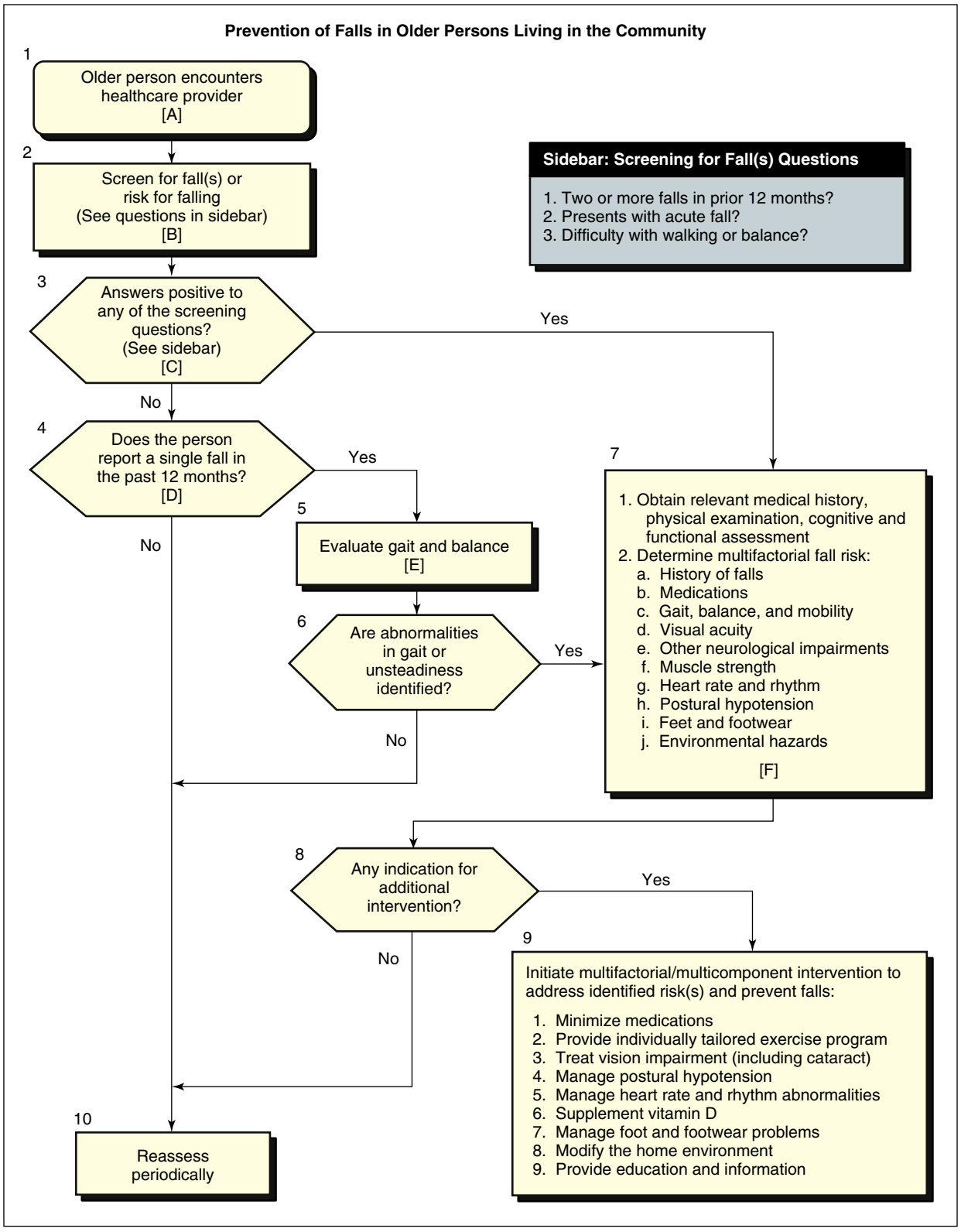

FIGURE EF1-2 Guideline for the prevention of falls in older persons living in the community. (From Panel on Prevention of Falls in Older Persons, American Geriatrics Society and British Geriatrics Society: Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons, *J Am Geriatr Soc* 59:148-157, 2011.)

EVIDENCE

Abstract[1]

Questions:

Do primary care interventions reduce risk for falls in older adults living in the community? What are the adverse effects?

Review Scope:

Included studies compared fall-prevention interventions with a control group in community-dwelling, older adults (mean age ≥65y); were conducted in primary care or similar settings; assessed falling or falls as primary or secondary outcomes; and were good or fair quality (US Preventive Services Task Force quality criteria). Outcomes were number of participants who fell and harms.

Review Methods:

MEDLINE, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessments, and Web sites (1991 to Oct 2007) were searched for good-quality systematic reviews; 1 was selected. MEDLINE, CINAHL, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews (2002 to Feb 2010) were searched for English-language, randomized, controlled trials (RCTs) published after the selected systematic review and reporting intervention efficacy. MEDLINE and CINAHL (1992 to Feb 2010) were searched for trials reporting harms. 54 RCTs (n = 26 102) met the selection criteria: 19 (n = 7099) assessed multifactorial assessment and management programs, 18 (n = 3986) assessed exercise or physical therapy, 9 (n = 5809) evaluated vitamin D (daily oral dose range, 10IU to 1000IU; median, 800IU), 4 (n = 1437) assessed vision correction procedures, 3 (n = 2348) assessed home-hazard modification, and 1 each assessed medication assessment and withdrawal (n = 48) or clinical education or behavioral counseling (n = 310).

Main Results:

Vision correction procedures did not reduce falls (data not reported). Harms were not consistently reported.

Conclusion:

In older community-dwelling adults, exercise/physical therapy and vitamin D each reduce risk for falls; results for other primary care interventions are mixed. Ⓐ

Evidence-Based Reference

Kiel DP: Exercise/physical therapy and vitamin D each reduce risk for falls in older community-dwelling adults, *Ann Intern Med* 154:JC4–JC5, 2011. Ⓐ

SUGGESTED READINGS

Centers for Disease Control and Prevention: *Home & recreational safety: falls—older adults*. Available from: http://www.cdc.gov/homeandrecreationalsafety/falls/index.html. Accessed March 6, 2013.

Greenhouse AH et al. Falls among the elderly. In: (editors: Albert ML Knoefel J.E.) Clinical neurology of aging. ed 2 Oxford University Press: New York.

Michael YL et al.: Primary care-relevant interventions to prevent falling in older patients: A systematic evidence review for the U.S. Preventive Services Task Force, *Ann Intern Med* 153:815–825, 2010.

Moncada LV: Management of falls in older persons: a prescription for prevention, *Am Fam Phys* 84(11):1267–1276, 2011.

Moyer VA: Prevention of falls in community-dwelling older adults: U.S. Preventive Services Task Force recommendation statement, *Ann Intern Med* 157:197–204, 2012.

Neelemaat F et al.: Short-term oral nutritional intervention with protein and vitamin D decreases falls in malnourished older adults, *J Am Geriatr Soc* 60(4):691–699, 2012.

Panel on Prevention of Falls in Older Persons. American Geriatrics Society and British Geriatrics Society: Summary of the Updated American Geriatrics Society/British Geriatrics Society clinical practice guideline for prevention of falls in older persons, *J Am Geriatr Soc* 59:148–157, 2011.

Rao S: Prevention of falls in older patients, *Am Fam Physician* 72:81–88, 2005.

Sherrington C et al.: Effective exercise for the prevention of falls: a systematic review and meta-analysis, *J Am Geriatr Soc* 56(12):2234–2243, 2008.

Tinetti ME: Preventing falls in the elderly, *N Engl J Med* 348:42–49, 2003.

U.S. Preventive Services Task Force: *Prevention of falls in community-dwelling older adults*. http://www.uspreventiveservicestaskforce.org/uspstf11/fallsprevention/fallsprevrs.htm. Accessed March 6, 2013.

Wolf SL et al.: Intense tai chi exercise training and fall occurrences in older, transitionally frail adults: a randomized, controlled trial, *J Am Geriatr Soc* 51:1693–1697, 2003.

Familial Adenomatous Polyposis and Gardner's Syndrome

BASIC INFORMATION

DEFINITION

Familial adenomatous polyposis (FAP) is an inherited disorder manifesting with numerous adenomatous polyps (Fig. F1-3) mainly in the large intestine. Gardner's syndrome is a subset of familial adenomatous polyposis, with prominent extraintestinal manifestations. It is a highly penetrant autosomal-dominant condition characterized by the following:

- Adenomatous intestinal polyps
- Soft tissue tumors
- Osteomas

SYNONYMS

Familial adenomatous polyposis
Gardner's syndrome

ICD-9CM CODES
211.3 Familial adenomatous polyposis
ICD-10CM CODES
D12.5 Benign neoplasm of sigmoid colon
D12.4 Benign neoplasm of descending colon
D12.3 Benign neoplasm of transverse colon
D12.2 Benign neoplasm of ascending colon
D12.6 Benign neoplasm of colon, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- FAP occurs in approximately 1 in 10,000 births.
- FAP accounts for <1% of all colorectal cancers.
- Individuals develop hundreds to thousands of adenomatous colorectal polyps.
- Polyps usually present in adolescence.
- 100% lifetime risk for colorectal cancer; most diagnosed by 40 yr of age.
- Gastric, duodenal, periampullary, and small bowel polyps occur but have lower malignant potential.
- Increased risk for other tumors: desmoid (15%), duodenal/periampullary (7%), thyroid (2%), brain (1%), childhood hepatoblastoma (1%), nasopharyngeal angiofibroma (benign), pancreatic (2%), adrenal adenoma (10%), and gastric (1%).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Phenotypic variability is seen in individuals and families with the same mutation. Soft tissue and bone abnormalities may precede intestinal disease. These findings are reported in at least 20% of individuals with FAP.

- Congenital hypertrophy of the retinal pigment epithelium (CHRPE): benign fundus lesions, usually present at birth
- Dental abnormalities: supernumerary or unerupted teeth
- Soft tissue lesions: epidermal or sebaceous cysts, fibromas, lipomas, desmoid tumors (benign, locally invasive, aggressive connective tissue tumor)
- Osteomas (benign bone growths): skull, mandible, long bone
- Anemia, occult blood in stool, bowel obstruction, weight loss

ETIOLOGY

- Gardner syndrome is caused by mutations of the tumor suppressor gene adenomatous polyposis coli *(APC)* on chromosome 5q21-q22; more than 1000 diseases causing mutations identified. The site of the mutation may explain the prominent extraintestinal lesions found in Gardner's syndrome.
- FAP and "attenuated FAP" are caused by APC gene defects, autosomal recessive FAP is caused by MUTYH gene defects. De novo mutations are responsible for approximately 20% of FAP cases. These may be due to germline mutations or somatic cell mosaicism, which is seen when a new mutation occurs in the APC gene post-fertilization and is present in only a subset of cell types or tissues.

DIAGNOSIS

In individuals with a family history, more than 100 adenomatous colorectal polyps, CHRPE lesions, or genetic testing confirms diagnosis. In those without a family history, more than 100 adenomatous colorectal polyps suggest the diagnosis and genetic testing confirms it.

DIFFERENTIAL DIAGNOSIS

- Turcot's syndrome
- Attenuated FAP
- MUTYH-associated polyposis
- Peutz-Jeghers syndrome
- Juvenile polyposis syndrome
- Hereditary mixed polyposis syndrome
- Hyperplastic polyposis

WORKUP

History, physical examination, laboratory tests, imaging studies

DIAGNOSTIC SCREENING OPTIONS

GENETIC TESTING

NOTE: Genetic counseling should be performed and written informed consent obtained before testing. Refer to a specialized center for counseling and evaluation.

- Should be offered to first-degree relatives of affected individuals (with an identified mutation) at age 10 to 12 yr and clinically suspected individuals.
- Able to identify a mutation in approximately 80% of families. To ensure that the family has a detectable mutation, test an affected family member first.
- If positive in the affected individual, the test can differentiate with 100% accuracy affected and unaffected family members. If negative in the affected individual, screening family members will not be useful in determining disease status.
- If no known family history exists, screening the clinically suspected individual is reasonable. A positive test rules in FAP but a negative test does not rule it out.
- Numerous testing techniques available; may require multiple tests to identify the mutation.

SIGMOIDOSCOPY

- Individuals with a positive genetic test: annual flexible sigmoidoscopy beginning at 10 to 12 yr of age.
- Untested at-risk family members or patients from families with an unidentified *APC* mutation: annual flexible sigmoidoscopy beginning at 10 to 12 yr until 25 yr of age, then decreasing frequency until age 50 yr, when age-appropriate guidelines may be followed.
- Once adenomatous polyps are detected, patients should undergo colonoscopy and evaluation for colectomy.
- Negative genetic test in patients from families with an identified mutation: average risk screening.

CHRPE: Lesions occur in up to 80% of families and are a reliable indicator of affected status in these families.

TREATMENT

- Prophylactic colectomy or proctocolectomy: timing determined by polyp number, size, and degree of dysplasia.
- Consider celecoxib therapy to reduce polyposis.
- Screening of remaining GI tract and screening for extraintestinal manifestations must continue after colectomy.
  1. Annual physical examination: history, examination (including thyroid), and blood tests
  2. Upper endoscopy to screen for gastric/duodenal polyps: baseline at age 20 yr (earlier if colon polyps detected) and repeated every 1 to 5 yr based on findings
  3. Some recommend annual thyroid ultrasound
  4. Other possible cancer sites imaged if symptoms occur or if these cancers have occurred in relatives
- Treat soft tissue lesions and osteomas for symptoms or cosmetic concerns. Treat desmoid tumors if they pose a risk to adjacent structures.

DISPOSITION

- 100% chance of colorectal cancer in untreated individuals. Many other neoplasms occur at higher rates.
- Metastatic colorectal cancer is the leading cause of death (58%), followed by desmoid tumors (11%) and duodenal/periampullary adenocarcinoma (8%).

REFERRAL

- Patients should be managed at centers with expertise in FAP, including a gastroenterologist, medical geneticist, and surgeon.
- Genetic counselors can be found at www.nsgc.org.
- Genetic testing sites can be found at www.genetests.org.

PEARLS & CONSIDERATIONS

- Management should be individualized based on genotype, phenotype, and individual preferences.
- Sulindac (NSAID) and celecoxib (COX-2 inhibitor) cause polyp regression in individuals with FAP. Celecoxib is FDA approved for this indication. Cancer risk remains; neither replaces colon resection for cancer prevention. Small studies suggest combination therapies and dietary supplements may also be effective in reducing polyposis.
- Desmoid tumors usually present in the 30s, frequently occur in the abdomen, and are difficult to treat with high rates of recurrence. Growth and recurrence are stimulated by surgery.
- Screen children of affected parents (from infancy to age 10 yr) with alpha-fetoprotein level, liver enzymes, and liver ultrasound to rule out hepatoblastoma.
- Preimplantation and prenatal genetic testing is available.

FIGURE F1-3 Familial adenomatous polyposis with innumerable adenomatous polyps, increasing in size and density from proximal *(upper left)* to distal *(lower right)*. (From Skarin AT: Atlas of diagnostic oncology, 4th ed, St. Louis, 2010, Mosby.)

SUGGESTED READINGS

available at www.expertconsult.com

RELATED CONTENT

Colorectal Cancer (Related Key Topic)
Peutz-Jeghers syndrome and other polyposis syndromes (Related Key Topic)

AUTHOR: **SUDEEP KAUR AULAKH, M.D.**

SUGGESTED READINGS

Galiatsatos P et al.: Familial adenomatous polyposis, *Am J Gastroenterol* 101:385, 2006.

Grover S et al.: Prevalence and phenotypes of APC and MUTYH mutations in patients with multiple colorectal adenomas, *JAMA* 308:485, 2012.

Kim B et al.: Chemoprevention in familial adenomatous polyposis, *Best Pract Res Clin Gastroenterol* 25:607, 2011.

Leiden Open Variation Database http://chromium.liacs.nl/LOVD2/colon_cancer/home.php?select_db=APC Accessed July 4, 2014.

Macrae F et al.: Familial adenomatous polyposis, *Best Pract Res Clin Gastroenterol* 23:197, 2009.

Vasen HF et al.: Guidelines for the clinical management of familial adenomatous polyposis (FAP), *Gut* 57:704, 2008.

Winawer S et al.: Colorectal cancer screening and surveillance: clinical guidelines and rationale–update based on new evidence, *Gastroenterology* 124:544, 2003.

Febrile Seizures PTG ALG

BASIC INFORMATION

DEFINITION

Febrile seizures are seizures that occur in febrile children (fever of at least 100.4° F [38° C]) between the ages of 6 and 60 mo in the absence of infection of the central nervous system (CNS), metabolic disturbance, or history of neonatal seizures or a previous unprovoked seizures. Febrile seizures are subdivided into 2 categories: simple and complex. Simple febrile seizures last <15 min, are generalized (without a focal component), and occur once in a 24-hr period, whereas complex febrile seizures are prolonged (>15 min), show focal neurologic signs, or occur more than once in 24 hr.

SYNONYMS

Febrile convulsions

ICD-9CM CODES
780.6 Febrile seizures
ICD-10CM CODES
R56.0 Febrile convulsions

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Febrile seizures are the most common seizures of childhood. 2% to 5% of children will have a febrile seizure by age 60 mo. Simple febrile seizures represent 65% to 90% of febrile seizures.
PREDOMINANT SEX AND AGE: Slightly more common in boys than girls.
PEAK INCIDENCE: 6 to 60 mo
PREVALENCE: Represents up to 18% of all pediatric epilepsy syndromes

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Children with febrile seizures have normal physical and neurologic examinations.
- Viral illnesses are the predominant cause of febrile seizures.

ETIOLOGY

- Viral infections are a common cause of fever that triggers febrile seizures.
- Febrile seizures tend to occur in families. Although clear evidence exists for a genetic basis of febrile seizures, the mode of inheritance is unknown.
- Febrile seizures are likely multifactorial with genetic and environmental factors.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- CNS infection (i.e., meningitis).
- Epilepsy.

WORKUP

- It is important to first investigate whether an underlying infection exists. Fig. EF1-4 describes guidelines for febrile seizure evaluation.
- In patients with simple self-limited febrile seizures with rapid return to consciousness and a normal neurologic examination, further workup is not routinely recommended.
- In patients with complex febrile seizures, laboratory workup and brain imaging are recommended.
- EEG is not routinely recommended in the evaluation of a neurologically healthy child with simple partial seizures.

LABORATORY TESTS

- Routine blood workup (CBC with differential, CMP, electrolytes), blood and urine cultures are often performed, but there is no evidence that these tests are necessary for identifying the cause of a simple febrile seizure.
- CSF analysis: lumbar puncture guidelines (American Academy of Pediatrics).
- Lumbar puncture should be performed in children with febrile seizures and signs and symptoms of meningitis (e.g., neck stiffness, Kernig sign, Brudzinski sign), or if the patient history or examination suggests the presence of meningitis or intracranial infection.
- In infants 6 to 12 months of age with febrile seizures, lumbar puncture is an option if they have not received the recommended *Haemophilus influenza* type b (Hib) or pneumococcal vaccinations, or if their immunization status is unknown.
- Lumbar puncture is also considered an option in children with febrile seizures pretreated with antibiotics.

IMAGING STUDIES

- MRI of the brain is not required in the routine evaluation of patients with simple febrile seizures.
- Imaging of the brain should be considered in children with complex febrile seizures and in children with focal neurologic deficits.
- CT scans of the head should be avoided in children, if possible, due to exposure to radiation and the relative low yield of the test compared with MRI. CT scans of the head are reserved for neurologic emergencies and are adjusted for weight in children.

TREATMENT

Febrile seizures do not usually require antiepileptic drug treatment.

NONPHARMACOLOGIC THERAPY

Not applicable

GENERAL Rx

Symptomatic treatment of fever.

CHRONIC Rx

No chronic treatment for febrile seizures is recommended.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Not applicable.

DISPOSITION

- Treatment is not recommended.
- Febrile seizures should stop by age 60 mo.
- Risk of recurrence in the first 2 years after an initial febrile seizure is 15% to 70%.

REFERRAL

Patients with recurrent febrile seizures need to be referred for a consultation by a pediatric neurologist.

PEARLS & CONSIDERATIONS

COMMENTS

- It is crucial to find out the etiology of the fever and to treat it appropriately.
- Patient with seizures and fever after age 60 mo are not classified as febrile seizures.

PREVENTION

Antipyretics do not reduce the recurrence risk of febrile seizures. However, fever should be treated and worked up independently of the diagnosis of febrile seizures.

PATIENT & FAMILY EDUCATION

- Children with febrile seizures do not need antiepileptic drug treatment.
- Patient education and information can be obtained at the Epilepsy Foundation: www.epilepsyfoundation.org. Parents should be reassured that children without underlying developmental problems will usually not have lasting neurologic effects from febrile seizures.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fever Seizures (Patient Information)

AUTHOR: **PATRICIO SEBASTIAN ESPINOSA, M.D., M.P.H.**

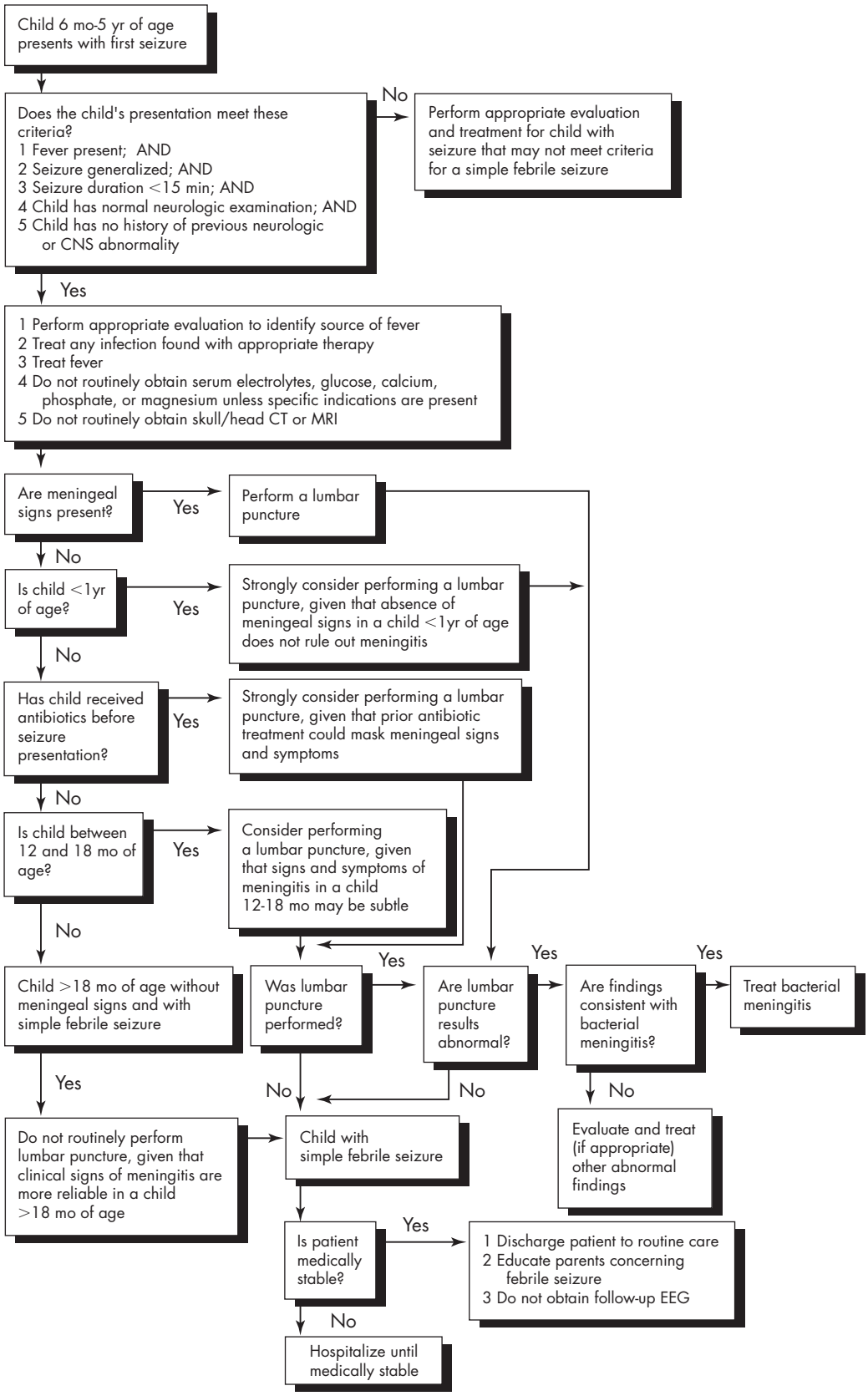

FIGURE EF1-4 Guidelines for febrile seizure evaluation. (From Custer JW, Rau RE: *The Harriet Lane handbook*, ed 18, St Louis, 2009, Mosby.)

SUGGESTED READINGS

Berg AT et al.: Predictors of recurrent febrile seizures: a prospective cohort study, *Arch Pediatr Adolesc Med* 151(4):371–378, 1997.

Graves RC et al.: Febrile seizures: risks, evaluation, and prognosis, *Am Fam Physician* 85(2):149–153, 2012.

Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures American Academy of Pediatrics: Febrile seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures, *Pediatrics* 121(6):1281–1286, 2008.

Subcommittee on Febrile Seizures; American Academy of Pediatrics, Neurodiagnostic evaluation of the child with a simple febrile seizure, *Pediatrics* 127(2):389–394, 2011.

BASIC INFORMATION

DEFINITION

Felty's syndrome (FS) is originally defined as the triad of seropositive rheumatoid arthritis (RA), splenomegaly, and neutropenia. The hallmark of FS is a persistent, idiopathic neutropenia, which is defined as a neutrophil count <1500/mm^3. Splenomegaly is extremely variable in its extent and no longer required as an absolute diagnostic requirement. It is an extraarticular manifestation of seropositive RA in which recurrent local and systemic infections are the major source of morbidity and mortality.

ICD-9CM CODES
714.1 Felty's syndrome
ICD-10CM CODES
M05.00 Felty's syndrome, unspecified site

EPIDEMIOLOGY & DEMOGRAPHICS

- The lifetime risk of FS for a patient initially diagnosed with RA is estimated to be 1% to 3%. The prevalence has been steadily declining over the past two decades.
- 60% to 80% are women.
- Recognized in patients in their late 40s or early 50s who have had RA for 10 yr or more.
- Rare in African Americans because of the infrequency of HLA-DRB1*0401 in this population.

CLINICAL PRESENTATION

- Splenomegaly and neutropenia are rarely present before the arthritis.
- Articular involvement is usually severe in patients with FS; however, one third may have relatively inactive synovitis. Yet erythrocyte sedimentation rate (ESR) is almost always significantly elevated even in patients with inactive synovitis.
- Degree of splenomegaly varies and may be detectable only by imaging studies; degree of splenomegaly has no correlation with the degree of neutropenia.
- Patients with FS have a greater frequency of extraarticular manifestations (rheumatoid nodules, vasculitis, skin lesions, pleuropericarditis, etc.) than other patients with RA.
- Mild hepatomegaly is common (up to 68%).
- Patients with FS have a twentyfold increased frequency of bacterial infections compared with other RA patients.

ETIOLOGY

The pathogenesis of FS is probably multifactorial, including immune dysfunction causing the imbalance of production and destruction of granulocytes.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Systemic lupus erythematosus.
- Large granular lymphocytic (LGL) leukemia.
- Drug reaction.
- Myeloproliferative disorders.
- Lymphoma/reticuloendothelial malignancies.
- Cirrhosis with portal hypertension.
- Sarcoidosis.
- Tuberculosis.
- Amyloidosis.
- HIV infection.

LABORATORY TESTS

- There is no single diagnostic test for FS.
- Complete blood count with differential to detect neutropenia, mild to moderate anemia, and mild to moderate thrombocytopenia.
- High ESR, C-reactive protein (CRP).
- Rheumatoid factor: and anticyclic citrullinated peptide (CCP) antibody; positive in 94% and 77%, respectively, usually with high titer.
- Autoantibody levels are more frequently elevated in FS.
- Antinuclear antibody (ANA): positive in 67%; antihistone antibody: positive in 83%; antineutrophil cytoplasmic antibody (ANCA): positive in 77%; anti-glucose-6-phosphate isomerase antibody: positive in 92%.
- HLA-DRB1*0401: positive in 98%.
- Immunoglobulins: level may be higher than in RA patients, complement level may be lower than in RA patients.
- Peripheral blood smear and bone marrow examination are often necessary to exclude other cause of neutropenia. It usually shows myeloid hyperplasia with maturation arrest.

IMAGING STUDIES

Ultrasonography or CT scan may be useful in diagnosing splenomegaly but is not necessary.

TREATMENT

ACUTE GENERAL Rx

- Splenectomy
  1. Usually reserved for patients with profound neutropenia (<1000/mm^3) and severe recurrent infections despite drug therapy and biologic agents.
  2. Acutely reverses hematologic abnormalities.
  3. 25% to 30% will have recurrent neutropenia, but the granulocyte count usually remains above the presplenectomy level.
  4. Improvement in frequency of recurrent infection is variable and not correlated with degree of hematologic improvement.
- Disease-modifying antirheumatic drug (DMARD): second-line drugs for RA may improve the neutropenia in FS for patients who have already been on DMARD therapy.
  1. Methotrexate: series of studies with small numbers of patients treated with low-dose oral pulse therapy suggest efficacy in FS. Granulocyte count may begin to rise within several weeks in responders. Also effective for articular disease.
  2. Gold salt: good hematologic response in 60%, partial response in 20%. The recovery of neutrophil count is usually slow.
  3. Penicillamine, sulfasalazine, hydroxychloroquine: limited experience; not first choice for FS.
- Corticosteroids
  1. Overwhelming infection is the main barrier to the use of corticosteroids.
  2. Prednisone 30 mg/day or more can elevate the neutrophil count, but this effect is often not sustained when the dose is reduced.
  3. Pulse dosing is a potential alternative for short-term elevation of neutrophils.
- Others
  1. Limited experience with cyclophosphamide, cyclosporine, azathioprine, leflunomide, anti–tumor necrosis factor (TNF)-alpha antibody, rituximab, lithium, and testosterone.
- Granulocyte colony-stimulating factor/granulocyte-macrophage colony-stimulating factor
  1. Improves neutrophil count but not arthritis and anemia of FS.
  2. May be useful as adjunctive therapy during serious infection or in preparation for surgery.

DISPOSITION

- Poor prognosis with recurrent infections because of neutropenia. The average mortality after diagnosis is 25% in 5 years.
- Articular involvement can be severe in FS.

REFERRAL

- To hematologist for treatment of neutropenia.
- To rheumatologist for treatment of RA.

PEARLS & CONSIDERATIONS

COMMENTS

- Recurrent infections are the major cause of death.
- Neutropenia of FS can be effectively treated with disease-modifying antirheumatic drugs, the widest experience being with methotrexate.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hypersplenism (Related Key Topic)
Rheumatoid Arthritis (Related Key Topic)

AUTHOR: **ETSUKO AOKI, M.D., PH.D.**

SUGGESTED READINGS

Balint GP et al.: Felty's syndrome, *Best Pract Res Clin Rheumatol* 18:631, 2004.

Bartels CM et al.: Changing trends in serious extra-articular manifestations of rheumatoid arthritis among United States veterans over 20 years, *Rheumatology* 49:1670, 2010.

Burks EJ et al.: Pathogenesis of neutropenia in large granular lymphocyte leukemia and Felty's syndrome, *Blood Rev* 20:245, 2006.

Capsoni F et al.: Primary and secondary autoimmune neutropenia, *Arthritis Res Ther* 7:208, 2005.

Narvaez J et al.: Biological agents in the management of Felty's syndrome: A systemic review, *Semin Arthritis Rheum* 41658, 2012.

BASIC INFORMATION

DEFINITION

- Adverse effects of alcohol on developing humans represent spectrum of structural anomalies and behavioral and neurocognitive disabilities, most accurately termed fetal alcohol spectrum disorder (FASD) (Table F1-2).
- Children at severe end of spectrum defined as having fetal alcohol syndrome (FAS).

ICD-9CM CODES
760.71 Fetal alcohol syndrome
ICD-10CM CODES
P04.3 Newborn (suspected to be) affected by maternal use of alcohol

EPIDEMIOLOGY & DEMOGRAPHICS

- Alcohol considered to be most common teratogen to which the fetus is liable to be exposed.
- 10% report drinking alcohol during pregnancy and 2% to 4% admit to binge drinking.
- Most common form of mental retardation in the United States.
- Prevalence is 1 to 2/1000 live births across the United States.
- Each year 40,000 babies are born with FASD.

RISK FACTORS

- Advanced maternal age (>30 yr).
- High parity.
- African-American, Alaskan Natives, and Native Indian race.
- Binge drinking (>4 drinks per occasion).
- History of prior affected child.
- Genetic susceptibility.
- Undernutrition.
- Low socioeconomic group.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Typical features:

- Growth retardation.
  1. Prenatal or postnatal.
  2. Height and/or weight <10%.
- Facial dysmorphia
  1. Smooth philtrum.
  2. Thin vermilion border.
  3. Small palpebral fissure (<10%).
  4. Others: epicanthic folds, ptosis of eyelids, flat nasal bridge and midface, upturned nose, railroad track ears, and so forth.
- CNS abnormalities
  - Structural
    1. Head circumference, 10%.
    2. Clinically significant brain abnormalities observable through imaging.
  - Neurologic
    1. Neurologic problems not due to a postnatal insult or fever.
  - Functional
    1. Intellectual deficit.
    2. Cognitive or developmental deficits.
    3. Executive function deficits.
    4. Motor function delays.
    5. Problem with attention and hyperactivity.
    6. Social skills.
    7. Other problems such as sensory, pragmatic language, and memory.

Rare birth defects:

- Cardiac
  1. Ventricular septal defect (VSD).
  2. Atrial septal defect (ASD).
  3. Tetralogy of Fallot.
  4. Aberrant great vessels.
- Skeletal
  1. Radioulnar synostosis.
  2. Hypoplastic nails.
  3. Clinodactyly.
  4. Shortened fifth digit.
  5. Pectus excavatum and carinatum.
  6. Klippel-Feil syndrome.
  7. Hemivertebrae.
  8. Camptodactyly.
  9. Scoliosis.
- Renal
  1. Aplastic kidneys.
  2. Dysplastic kidneys.
  3. Ureteral duplication.
  4. Hypoplastic kidneys.
  5. Hydronephrosis.
  6. Horseshoe kidneys.
- Ocular
  1. Strabismus.
  2. Refractive problems.
  3. Retinal vascular abnormalities.
- Auditory
  1. Conductive hearing loss.
  2. Neurosensory hearing loss.
- Others
  1. Hockey stick–like palmar crease.

TABLE F1-2 Institute of Medicine's Diagnostic Criteria for Fetal Alcohol–Related Abnormalities

Category 1	
FAS with confirmed maternal alcohol exposure	Presence of classic triad of growth retardation, characteristic facial dysmorphology, and neurodevelopmental abnormalities. This is often defined as full-blown FAS.
Category 2	
FAS without confirmed maternal alcohol exposure	Triad in category 1 is present without confirmed maternal drinking
Category 3	
Partial FAS with confirmed maternal alcohol exposure	Presence of some of the characteristic facial anomalies plus growth retardation or CNS neurodevelopmental abnormalities or behavioral/cognitive abnormalities
Category 4	
FAS with confirmed maternal alcohol exposure and alcohol-related birth defects	Some congenital anomalies as a result of alcohol toxicity
Category 5	
FAS with confirmed maternal alcohol exposure and alcohol-related neurodevelopmental disorder	Evidence of CNS neurodevelopmental abnormalities, a complex pattern of behavioral/cognitive abnormalities, or both, but not necessarily any obvious physical changes

CNS, Central nervous system; *FAS,* fetal alcohol syndrome.

ETIOLOGY

- Prenatal damage comes about primarily by direct action of ethanol or its metabolites (e.g., acetaldehyde) on the fetus.
- Exact damaging mechanism is unclear.
- Although the damaging effect of alcohol is different in the various phases of pregnancy, it is by no means limited to first trimester.
- No exact dose-response relationship between alcohol consumed during prenatal period and extent of damage inflicted on infant.
- An occasional drink during pregnancy carries no risk to the fetus, but no level of drinking is known to be safe during pregnancy.
- The least significant effect recognized at 2 drinks/day is smaller birth weight (160 g less than average).
- Until 4 to 6 drinks/day are consumed, no additional subtle clinical features are evident.
- Most children who have FAS have been born to frankly alcoholic mothers whose intake is ≥8-10 drinks/day, and those who engage in binge drinking.
- The risk of serious problem in the offspring of a chronically alcoholic woman is ~30% to 50%; the greatest risk is mental retardation.

SECONDARY DISABILITIES

- Mental health problems.
- Dependent living.
- Employment problems.
- Disruptive school problems.
- Trouble with law.
- Confinement.
- Inappropriate sexual behavior.
- Alcohol or drug problems.

DIAGNOSIS

- It is a diagnosis of exclusion.
- Diagnosis is difficult prenatally and at birth. Most cases are not diagnosed until school age.
- As the characteristic facial features tend to become decreasingly recognizable as the child reaches adolescence, the diagnosis becomes increasingly difficult with advancing age.

- Prenatal exposure to alcohol is not sufficient to warrant a diagnosis. According to the CDC, diagnosis of FAS requires 3 specific findings and history of prenatal alcohol exposure:
  1. Growth restriction (intrauterine or postnatal)
  2. CNS involvement
  3. Documentation of all three facial abnormalities (smooth philtrum, thin vermilion border, and short palpebral fissure)
- Imaging recommendation during pregnancy with alcohol exposure:
  1. High-risk anatomy scan.
  2. Serial growth scan.
  3. Fetal echocardiogram at 22 to 24 weeks' intrauterine pregnancy.
- Measurement of the ethyl esters of fatty acids in the meconium and hair of the newborn can substantiate maternal alcohol exposure.
- In school-aged children, the diagnostic process should include a thorough psychological evaluation that assesses multiple domains. Also, supplement the observation by obtaining standardized testing through early intervention programs, public schools, and psychologists in private practice.

DIFFERENTIAL DIAGNOSIS

- Other causes of symmetric growth retardation including intrauterine infection and aneuploidy.
- Aneuploidy (T21, T18, T13).
- Syndromes with overlapping features of FAS:
  1. Fetal anticonvulsant syndrome.
  2. Maternal phenylketonuria.
  3. Toluene embryopathy.
  4. Velocardiofacial syndrome (deletion 22q11).
  5. Williams syndrome.
  6. Dubowitz syndrome.
  7. Cornelia de Lange syndrome.

Rx TREATMENT

- As there is no cure for FAS, we need to emphasize prevention.
- For women who are planning pregnancy or who could become pregnant, the United States Surgeon General recommends the safest course: to avoid alcohol entirely during pregnancy.
- Women of childbearing age who are not pregnant should drink ≤7 alcoholic drinks/wk and ≤3 drinks on any one occasion.
- Preconception counseling should be offered to women of childbearing age who are at risk for an alcohol-exposed pregnancy.
- Screen all pregnant women for alcohol use.
- The National Institute on Alcohol Abuse and Alcoholism recommends that any woman who reports drinking >7 drinks/wk or >3 drinks on a given day be further assessed for alcohol-related problems.
- The T-ACE (Table F1-3) and TWEAK (Table F1-4) questionnaires are used to identify women drinking enough to potentially damage the fetus. The CAGE questionnaire is less sensitive for screening pregnant women.
- Effective treatment alternatives for women who screen positive for hazardous alcohol use include brief interventions to promote reductions in alcohol use and that facilitate referral to specialized treatment programs.
- Discontinuation or reduction of alcohol consumption at any point in pregnancy may be beneficial.
- The use of alcohol-containing tonics and medications should be avoided. This applies to medications with an alcohol base when the concentration exceeds 10%.
- Alcoholism is one of the few situations in which pregnancy interruption may be discussed with the patient as it may result in FAS.
- Early diagnosis and appropriate treatment may decrease secondary disabilities and recurrence in future pregnancies.
- A child should be referred for full FAS evaluation when substantial prenatal alcohol use by the mother has been confirmed (>7 drinks/wk, >3 drinks on multiple occasions, or both).
- If substantial prenatal exposure is known, with no other positive criteria, the physician should document exposure and closely monitor the child's growth and development.

TABLE F1-3 T-ACE Questions*

T (tolerance)	How many drinks does it take to make you feel high? (3 or more drinks = 2 points)
A (annoyed)	Have people annoyed you by criticizing your drinking? (Yes = 1 point)
C (cut down)	Have you felt you ought to cut down on your drinking? (Yes = 1 point)
E (eye opener)	Have you ever had to drink first thing in the morning to steady your nerves or to get rid of a hangover? (Yes = 1 point)

*A score of 2 or more indicates heavy or problem drinker. Its sensitivity is 70% and specificity is 85%.

TABLE F1-4 TWEAK*

T (tolerance)	How many drinks does it take before you begin to feel the first effects of alcohol? (3 or more drinks = 2 points)
W (worried)	Have close friends or relatives worried about your drinking in the past year? (Yes = 2 points)
E (eye opener)	Do you sometimes take a drink in the morning when you first get up? (Yes = 1 point)
A (amnesia)	Has a friend or family member ever told you about things you said or did while you were drinking that you could not remember? (Yes = 1 point)
K (kut down)	Do you sometimes feel the need to cut down on your drinking? (Yes = 1 point)

*A total of 3 or more points indicates the woman is likely to be a heavy or problem drinker. Its sensitivity is 79% and specificity is 83%.

- When information about prenatal exposure is unknown, a child should be referred for full FAS if any of the following conditions are present: (1) all three dysmorphic facial features (smooth philtrum, thin vermilion border, and small palpebral fissure), (2) one or more of these facial features with growth deficit, (3) one or more facial features with one or more CNS abnormalities, (4) one or more dysmorphic facial features with growth deficit and one or more CNS abnormalities, or (5) any report of concern by a caregiver or parent that a child has or may have FAS.
- Infants and children who are diagnosed with FAS should be evaluated by a physician who is knowledgeable and competent in the evaluation of neurodevelopment and psychosocial problems associated with the diagnosis.
- A multidisciplinary team including a clinical geneticist, developmental pediatrician, mental health professional, social worker, and education specialist is often necessary for management.
- Treatment options include:
  1. Medications to help with symptoms
  2. Behavior and education therapy
     - Friendship training
     - Specialized math training
     - Executive function training
     - Parent-child interaction training
     - Parenting and behavior management training
  3. Parenting training
     - Concentrate on child's strengths and talents
     - Accept child's limitations
     - Be consistent with everything
     - Use concrete language and examples
     - Use stable routine that does not change daily
     - Keep everything simple
     - Be specific (i.e., say exactly what you mean)
     - Structure your child's world to provide a foundation for daily living
     - Use visualized aids, music, and hands-on activities to help your child learn
     - Use positive reinforcement often
     - Supervise
     - Repeat, repeat, and repeat
  4. Emphasis on the following protective factors helps reduce the effects and also assists people with this condition to reach their full potential:
     - Diagnosing before 6 yr
     - Living in stable nurturing home environment in school years
     - Absence of violence
     - Involvement in special education and social services
  5. Alternative approaches such as biofeedback, auditory training, relaxation therapy, visual imagery, yoga/exercise, acupuncture/acupressure, massage, Reiki, energy healing, animal-assisted therapy, and so forth may play a role.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **HEMANT K. SATPATHY, M.D.**

SUGGESTED READING

Koren G et al.: Fetal alcohol spectrum disorder, *CMAJ* 169:1181–1185, 2003.
Online resources: http://fascenter.samhsa.gov, http://www.cdc.gov/ncbddd/fas, http://depts.washington.edu/fasdpn, http://www.nofas.org.

BASIC INFORMATION

DEFINITION

Fever of undetermined origin (FUO) was defined by Petersdorf and Beeson in 1961 as an illness characterized by temperatures >38.3° C (101° F) on several occasions for >3 wk with no known cause despite extensive workup.

- Persistence for >2 wk separates an FUO from an insignificant viral illness.
- Traditionally, diagnosis was made only after a 1-wk inpatient workup. In contemporary practice, much of the workup is performed as an outpatient.

Table F1-5 provides a summary of definitions and major features of subtypes of FUO.

SYNONYMS

Fever of unknown origin

ICD-9CM CODES
780.6 Pyrexia of undetermined origin
ICD-10CM CODES
R50.9 Fever, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- The incidence of undiagnosed FUO dropped to <10% in the 1950s, but has steadily increased since then.
- True FUOs are uncommon.

CLINICAL PRESENTATION

Fever 38.3° C (101° F or higher) on several occasions >3 wk.

ETIOLOGY

- Infection (16%).
  1. Abscess: abdominal, pelvic.
  2. Tuberculosis.
  3. HIV infection.
  4. Nosocomial: urinary tract infection, pneumonia, line-related bacteremia, *Clostridium difficile* colitis, sinusitis.
  5. Bacterial endocarditis (especially caused by difficult-to-isolate organisms).
  6. Biliary tract infection.
  7. Osteomyelitis, vertebral and mandibular.
  8. Less common infections: Q fever, leptospirosis, psittacosis, tularemia, secondary syphilis, gonococcemia, chronic meningococcemia, Whipple's disease, yersiniosis, fungal infections.
- Malignancy (7%): lymphoma (especially non-Hodgkin lymphoma), leukemia, renal cell carcinoma, hepatocellular carcinomas, other tumors metastatic to liver.
- Noninfectious inflammatory disease (22%).
  1. Adult Still's disease (young to middle-aged patients).
  2. Temporal arteritis (elderly patients).
  3. Other vasculitis: polyarteritis nodosa, Takayasu's arteritis, Wegener's granulomatosis, mixed cryoglobulinemia.
- Other.
  1. Drug-induced fever.
  2. Inflammatory bowel disease.
  3. Sarcoidosis.
  4. Pulmonary embolism.
  5. Alcoholic hepatitis.
- No diagnosis

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Factitious fever

WORKUP

- Accurate history and careful physical examination are essential. Fig. EF1-5 describes an approach to the patient with FUO.
- Laboratory tests and imaging dependent on medical history clues and physical findings.
- When in doubt, perform another complete history and physical examination. Examples of subtle physical findings in patients with FUO are described in Table F1-6.

MEDICAL HISTORY CLUES

- Fever duration, tempo; inciting factors.
- Rash, myalgia, weight loss, pain.
- Sick contacts.
- Past medical history: tuberculosis, HIV, malignancies, surgeries.
- Medications.

TABLE F1-5 Summary of Definitions and Major Features of the Four Subtypes of Fever of Undetermined Origin

Feature	Classic FUO	Health Care–Associated FUO	Immune-Deficient FUO	HIV-Related FUO
Definition	>38.0° C, >3 wk, >2 visits or 1 wk in hospital	≥38.0° C, >1 wk, not present or incubating on admission	≥38.0° C, >1 wk, negative cultures after 48 hr	≥38.0° C, >3 wk for outpatients, >1 wk for inpatients, HIV infection confirmed
Patient location	Community, clinic, or hospital	Acute care hospital	Hospital or clinic	Community, clinic, or hospital
Leading causes	Cancer, infections, inflammatory conditions, undiagnosed, habitual hyperthermia	Health care–associated infections, postoperative complications, drug fever	Majority due to infections, but cause documented in only 40%-60%	HIV (primary infection), typical and atypical mycobacteria, CMV, lymphomas, toxoplasmosis, cryptococcosis, immune reconstitution inflammatory syndrome (IRIS)
History emphasis	Travel, contacts, animal and insect exposure, medications, immunizations, family history, cardiac valve disorder	Operations and procedures, devices, anatomic considerations, drug treatment	Stage of chemotherapy, drugs administered, underlying immunosuppressive disorder	Drugs, exposures, risk factors, travel, contacts, stage of HIV infection
Examination emphasis	Fundi, oropharynx, temporal artery, abdomen, lymph nodes, spleen, joints, skin, nails, genitalia, rectum or prostate, lower limb deep veins	Wounds, drains, devices, sinuses, urine	Skinfolds, IV sites, lungs, perianal area	Mouth, sinuses, skin, lymph nodes, eyes, lungs, perianal area
Investigation emphasis	Imaging, biopsies, sedimentation rate, skin tests	Imaging, bacterial cultures	CXR, bacterial cultures	Blood and lymphocyte count; serologic tests; CXR; stool examination; biopsies of lung, bone marrow, and liver for cultures and cytologic tests; brain imaging
Management	Observation, outpatient temperature chart, investigations, avoidance of empirical drug treatments	Depends on situation	Antimicrobial treatment protocols	Antiviral and antimicrobial protocols, vaccines, revision of treatment regimens, good nutrition
Time course of disease	Months	Weeks	Days	Weeks to months
Tempo of investigation	Weeks	Days	Hours	Days to weeks

CMV, Cytomegalovirus; *CXR,* chest radiograph; *FUO,* fever of undetermined origin.
Adapted from Mandell GL, Bennett JE, Dolin R (eds): *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 7, Philadelphia, 2010, Churchill Livingstone. Borrowed from Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

- Family history: tuberculosis, malignancies, familial Mediterranean fever.
- Social history: daily routine, rural versus urban, pets and animal contacts, arthropod bites, recent and remote travel, socioeconomic status, occupation, military service, sexual history.

PHYSICAL FINDINGS

- HEENT (head, ears, eyes, nose, throat): sinus tenderness, dental abscesses, funduscopic lesions.
- Neck: adenopathy, palpable thyroid.
- Lungs: auscultate for rales.
- Heart: murmur.
- Abdomen: organomegaly
- Rectal: prostate tenderness.
- Pelvic: cervical motion tenderness, fundal or adnexal masses or pain; inguinal adenopathy.
- Extremities: clubbing, splinter hemorrhages; tenderness or fluctuance at IV access site.
- Musculoskeletal: joint effusions.
- Skin: rashes, wounds.

LABORATORY TESTS

- Most FUO workups include:
  1. Blood cultures (three sets from different sites).
  2. Complete blood count with differential.
  3. Erythrocyte sedimentation rate or C-reactive protein.
  4. Urinalysis with microscopic exam and culture.
  5. Transaminases.
  6. Serum lactate dehydrogenase.
  7. PPD testing.
- Consider
  1. HIV antibody testing.
  2. Creatinine phosphokinase.
  3. Rheumatoid factor.
  4. Serum protein electrophoresis.
  5. Lumbar puncture.
  6. Thyroid function testing.
  7. Stool culture and *C. difficile* assay.
  8. Biopsy (bone marrow, skin, liver lymph nodes, pleural, etc., based on clinical and laboratory findings).
  9. Antinuclear antibody testing.

May need to repeat tests at regular intervals until diagnosis is established.

IMAGING STUDIES

- Most workups eventually include chest radiograph and abdominal CT scan.
- Further imaging is based on medical history clues and physical findings.
- FDG-PET is very sensitive to detect anatomic sites of inflammation or malignancy. It may help to identify sites requiring further investigation. Further data are needed to evaluate efficacy.

TABLE F1-6 Examples of Subtle Physical Findings Having Special Significance in Patients with Fever of Undetermined Origin

Body Site	Physical Finding	Diagnosis
Head	Sinus tenderness	Sinusitis
Temporal artery	Nodules, reduced pulsations	Temporal arteritis
Oropharynx	Ulceration	Disseminated histoplasmosis
	Tender tooth	Periapical abscess
Fundi or conjunctivae	Choroid tubercle	Disseminated granulomatosis*
	Petechiae, Roth's spot	Endocarditis
Thyroid	Enlargement, tenderness	Thyroiditis
Heart	Murmur	Infective or marantic endocarditis
Abdomen	Enlarged iliac crest lymph nodes, splenomegaly	Lymphoma, endocarditis, disseminated granulomatosis*
Rectum	Perirectal fluctuance, tenderness	Abscess
	Prostatic tenderness, fluctuance	Abscess
Genitalia	Testicular nodule	Periarteritis nodosa
	Epididymal nodule	Disseminated granulomatosis
Lower extremities	Deep venous tenderness	Thrombosis or thrombophlebitis
Skin and nails	Petechiae, splinter hemorrhages, subcutaneous nodules, clubbing	Vasculitis, endocarditis

*Includes tuberculosis, histoplasmosis, coccidioidomycosis, sarcoidosis, and syphilis.
From Mandell GL et al (eds): *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 7, Philadelphia, 2010, Churchill Livingstone.

Rx TREATMENT

ACUTE GENERAL Rx

Antibiotics and other treatment indicated only after definitive or highly probable diagnosis is established unless patient is neutropenic, severely ill, or septic.

DISPOSITION

In some cases a diagnosis is not made for years. At 5-yr follow-up, mortality rate among patients with undiagnosed FUO was only 3.2% in one study.

REFERRAL

To an infectious disease specialist, hematologist, or rheumatologist if no diagnosis after thoughtful workup.

PEARLS & CONSIDERATIONS

COMMENTS

Because of improvements in imaging and laboratory tests, fewer cases of FUO are attributed to infectious causes and more are diagnosed as attributable to tumors and collagen-vascular diseases.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fever of Unknown Origin (Patient Information).

AUTHOR: **ETSUKO AOKI, M.D., PH.D.**

SUGGESTED READINGS

Bleeker-Rovers CP et al.: A prospective multicenter study on fever of unknown origin: the yield of a structured diagnostic approach, *Medicine (Baltimore)* 86(26), 2007.

Knockaert DC et al.: Long-term follow-up of patients with undiagnosed fever of unknown origin, *Arch Intern Med* 156(6), 1996.

Hayakawa K et al.: Fever of unknown origin: An evidence-based review, *Am J Med Sci* 344(307), 2012.

Vanderschueren S et al.: From prolonged febrile illness to fever of unknown origin: the challenge continues, *Arch Intern Med* 163:1033–1041, 2003.

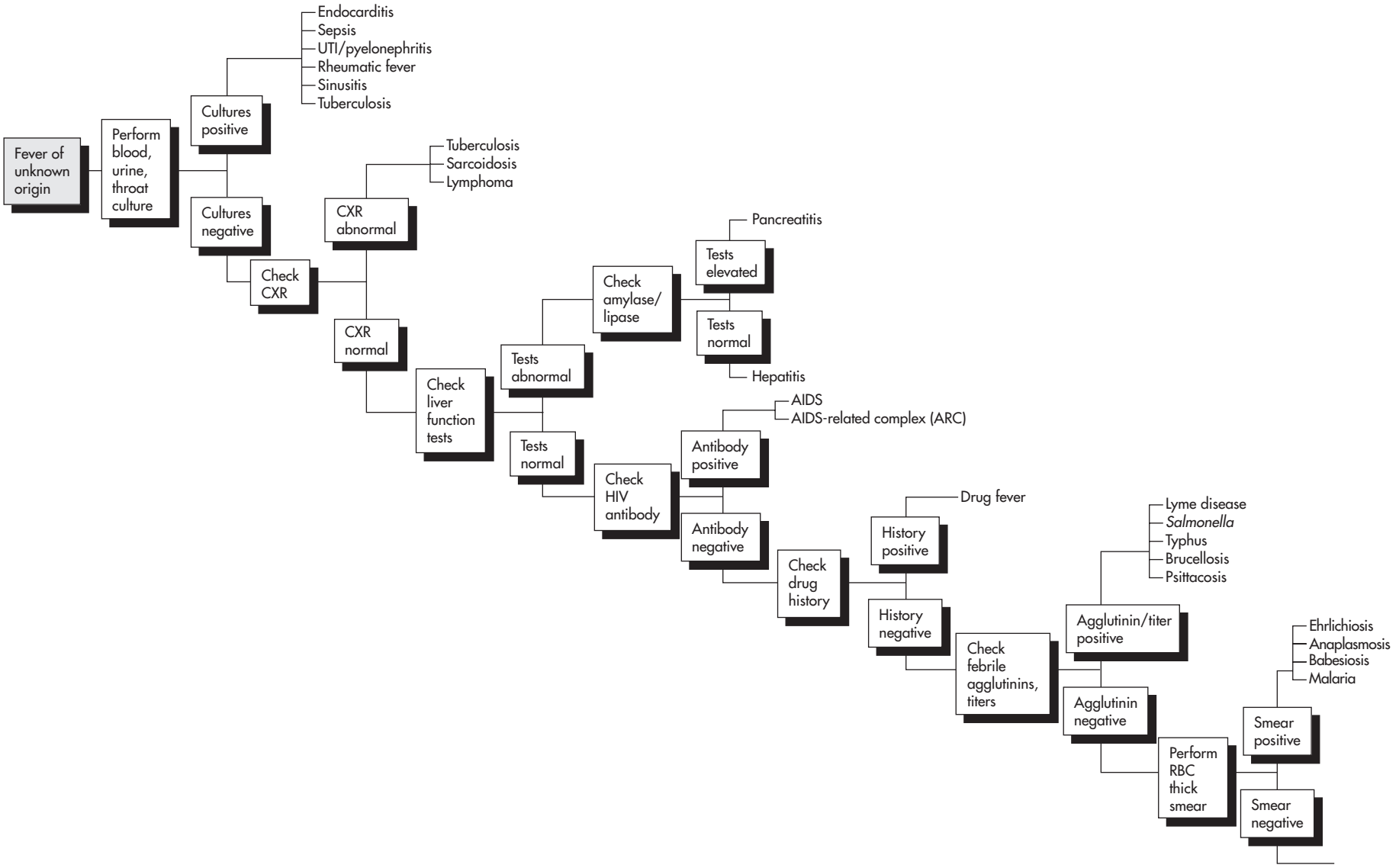

FIGURE EF1-5 Approach to the patient with fever of undetermined origin. *AIDS*, Acquired immunodeficiency syndrome; *ANA*, antinuclear antibody; *CT*, computed tomography; *CXR*, chest x-ray; *ESR*, erythrocyte sedimentation rate; *GI*, gastrointestinal; *HIV*, human immunodeficiency virus; *RBC*, red blood cell; *UTI*, urinary tract infection. (Modified from Healey PM: *Common medical diagnosis: an algorithmic approach*, ed 3, Philadelphia, 2000, Saunders.)

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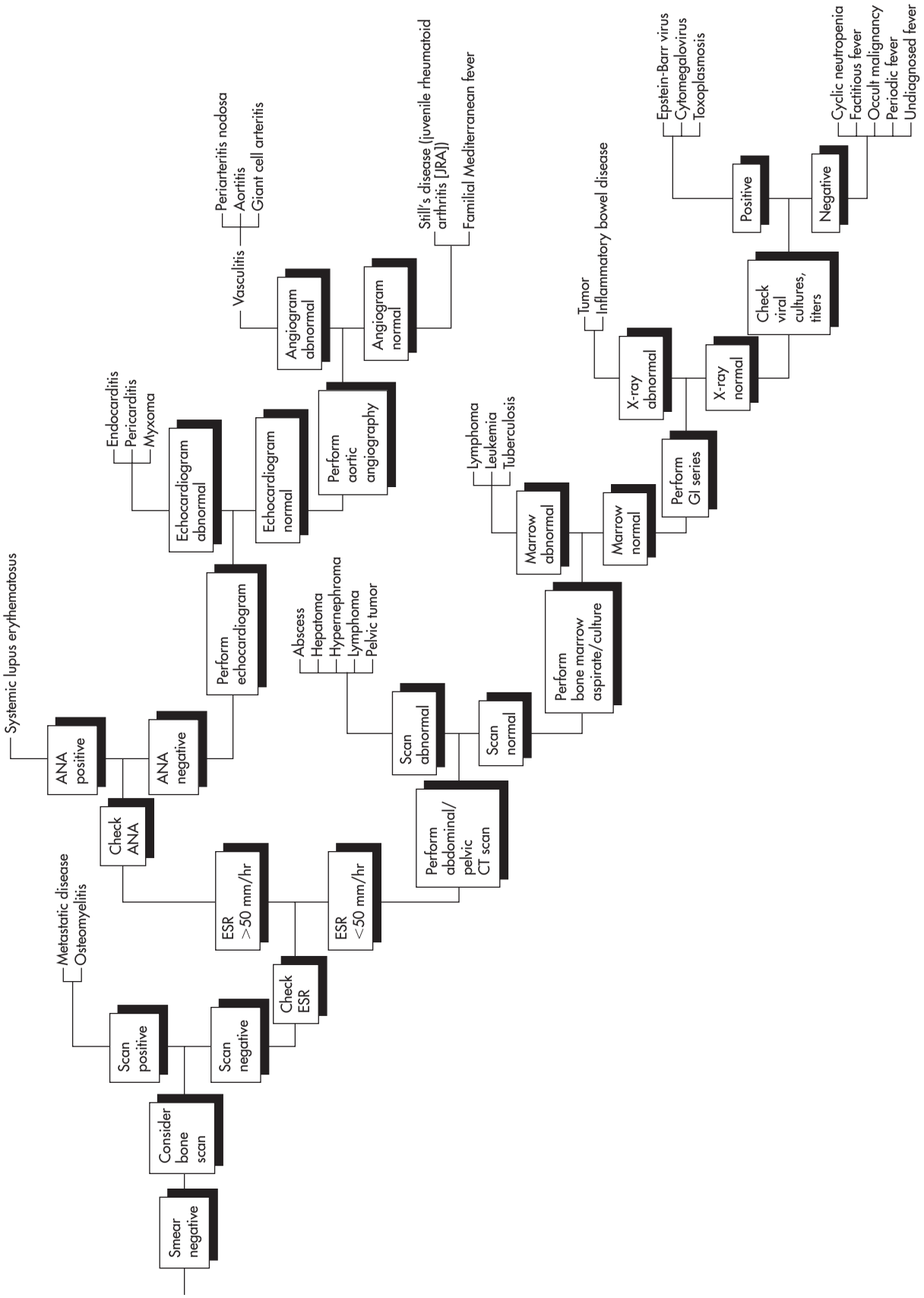


FIGURE EF1-5 (Continued)

BASIC INFORMATION

DEFINITION

Fibrocystic breast disease (FCD) is a "non-disease" that includes nonmalignant breast lesions such as microcystic and macrocystic changes, fibrosis, ductal or lobular hyperplasia, adenosis, apocrine metaplasia, fibroadenoma, papilloma, papillomatosis, and other changes. Atypical ductal or lobular hyperplasia is associated with a moderate increase in breast cancer risk.

SYNONYMS

Cystic changes.
Chronic cystic mastitis.
Mammary dysplasia.

ICD-9CM CODES
610.0 Solitary cyst of the breast
610.1 Fibrocystic disease of the breast
ICD-10CM CODES
N60.09 Solitary cyst of unspecified breast
N60.19 Diffuse cystic mastopathy of unspecified breast

EPIDEMIOLOGY & DEMOGRAPHICS

- Ubiquitous in premenopausal women after 20 yr of age
- Palpable nodular changes in the breast termed FCD clinically; such changes observable in more than half of adult women aged 20 to 50 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Tender breasts.
- Nodular areas.
- Dominant mass.
- Thickening.
- Nipple discharge.
- Can vary with menstrual cycle.

ETIOLOGY

- Although it is frequently seen and diagnosed, mechanism of development is not understood.
- Because it is found in the majority of healthy breasts, it is regarded as a nonpathologic process.
- With hormone replacement therapy, the condition may be carried into menopause.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Table F1-7 differentiates breast masses. Characteristics of breast masses suspect for cancer (90% sensitivity, 40% to 60% specificity) are fixed mass, poorly defined mass, and hard mass.

WORKUP

- Exclude breast carcinoma if breast mass, thickening, discharge, and/or pain are present.
- Perform biopsy of suspected area for histologic confirmation.

IMAGING STUDIES

Mammography and ultrasound studies required:
- For mammographic changes (suspicious densities, microcalcifications, architectural distortion): careful evaluation, including possibly biopsy to exclude breast cancer.
- Ultrasound study: to establish cystic nature of clinical or mammographic mass lesion.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Not considered a "disease" and does not require treatment.
- Surgical intervention diagnostic to eliminate possibility of breast cancer.
- Periodic physician examination to monitor patients with FCD who have pronounced nodular features.
- Aspiration for palpable cysts (NOTE: Cysts often recur; repeat aspiration is not always required unless pain is a problem).

ACUTE GENERAL Rx

The majority of women require no treatment.

CHRONIC Rx

For breast pain:
- Danocrine (Danazol): limited success reported but significant side effect profile of medication.
- Bromocriptine or tamoxifen: used less frequently.
- Limited caffeine intake: not as successful in controlling pain or nodularity as originally suggested.

DISPOSITION

- Careful evaluation to exclude suspicious changes for breast cancer, then reassurance and periodic reevaluation as required.
- Regular self-examination, annual physician examination, and annual mammograms for women with atypical ductal or lobular hyperplasia.

REFERRAL

- For further evaluation and/or biopsy if there are suspicious changes that may be associated with FCD (including changing of dominant mass or thickening, persistent or spontaneous discharge, suspicious mammographic changes or lesions).
- To alleviate anxiety associated with breast symptoms or changes.

RELATED CONTENT

Breast Cancer (Related Key Topic)
Fibrocystic Breast Changes (Patient Information)
Mastodynia (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

TABLE F1-7 Differentiation of Breast Masses

Characteristic	Cystic Disease	Benign Adenoma	Malignant Tumor
Patient age	25-60 years	10-55 years	25-85 years
Number	One or more	One	One
Shape	Round	Round	Irregular
Consistency	Elastic, soft to hard	Firm	Stony hard
Delimitation	Well delimited	Well delimited	Poorly delimited
Mobility	Mobile	Mobile	Fixed
Tenderness	Present	Absent	Absent
Skin retraction	Absent	Absent	Present

From Swartz, MH: *Textbook of physical diagnosis,* ed 7, Philadelphia, 2014, Saunders.

BASIC INFORMATION

DEFINITION

Fibromyalgia (FM) is a disorder characterized by chronic, widespread pain related to central sensitization. Key features also include fatigue, sleep disturbance, and tenderness.

ICD-9CM CODES
729.0 Rheumatism, unspecified and fibrositis
729.1 Myalgia and myositis, unspecified
ICD-10CM CODES
M79.7 Fibromyalgia

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 2% to 8% of the U.S. population.
PREDOMINANT SEX: Female/male ratio of 7:1.
PREDOMINANT AGE: 30 to 50 years.

PHYSICAL FINDINGS

Tender points (Fig. F1-6) or generalized tenderness.

ETIOLOGY

- Unknown. Genetic and environmental factors predispose individuals to FM. Evidence suggests that both the ascending and descending pain pathways operate abnormally, resulting in central amplification of pain signals, analogous to the "volume control setting" being turned up too high. Familial associations of FM provide strongest evidence that reflect both these factors.
- In those predisposed, FM may be precipitated by stressful events such as abuse, injury from accidents, illnesses including autoimmune disorders, infections, surgical procedures, and psychological stressors.
- Psychosocial and neuroendocrine factors also influence symptom expression.
- "Fibrositis" is a term no longer used as there was no inflammation found in connective tissues, contrary to what was previously thought to be the cause of widespread pain.

PATHOGENESIS

- Augmented pain and sensory processing is a hallmark, resulting in diffuse pain, allodynia (pain brought on by nonpainful stimuli), and hyperalgesia (more intense and prolonged pain perception).
- Afflicted persons show altered physiologic responses to painful stimulation at spinal and supraspinal levels.
- Brain neuroimaging studies found differences in brain structure, neurochemical concentrations, and functional brain networks in FM compared with control subjects.
- Pain augmentation may also result from a loss of tonic inhibition by descending inhibitory pathways from the brain to the spinal cord.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Presence of any of the disorders mentioned below does not necessarily exclude a diagnosis of FM because it may coexist with many conditions.
- Other functional somatic or "central sensitivity" syndromes: myofascial pain, chronic fatigue, irritable bowel, headache/migraines, chronic pelvic and bladder pain disorders, and temporomandibular disorder.
- Disorders that can mimic FM and must be ruled out include: hypothyroidism, rheumatic diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, osteoarthritis, inflammatory myopathies), infection.
- Mood and anxiety disorders.
- Sleep disorders (e.g., sleep apnea, restless leg syndrome).
- Neurologic disorders.
- Medications: statin-induced muscle pain, opioid-induced hyperalgesia.

WORKUP

- Thorough history, physical examination, and appropriately selected laboratory or imaging studies can usually differentiate FM from connective tissue or other systemic diseases.
- Chronic (>3 mo), widespread pain is the hallmark symptom of FM, but fatigue, tenderness, depression/anxiety, nonrestorative sleep, cognitive difficulties (the so-called "fibrofog"), and functional impairment are other key symptoms.
- The 1990 American College of Rheumatology (ACR) FM Classification Criteria was used for clinical studies:
  1. Chronic, widespread pain in all four quadrants of the body and the axial skeleton.
  2. Pain on digital palpation of at least 11 of 18 tender points (see Fig. F1-6).
- The 2010 ACR preliminary diagnostic criteria for FM do not require a tender point examination; it requires the exclusion of other disorders that would otherwise explain the pain.
- A diagnostic screening tool (Fibromyalgia Diagnostic Screen) developed by Arnold and colleagues was found to accurately screen for FM. This tool includes a patient self-reported questionnaire and an abbreviated physical examination with targeted lab tests.

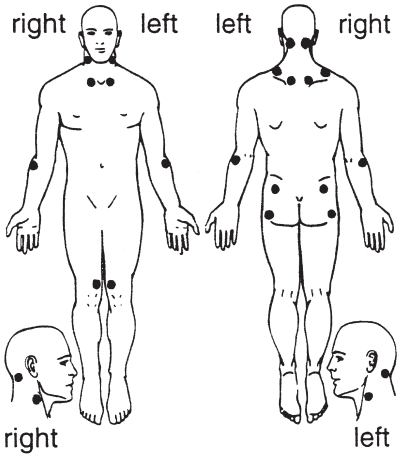
LABORATORY TESTS

- Selective use of ancillary tests complements the history and physical examination in the diagnosis of FM. Testing should be highly focused on the exclusion of FM mimickers or suspected concurrent diseases.
- Complete blood cell count, routine chemistries, thyroid-stimulating hormone (TSH), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are normal in FM.
- Routine testing for antinuclear antibody (ANA) and/or rheumatoid factor should be avoided unless history and physical examination suggest an autoimmune disease.

TREATMENT

GENERAL Rx (Fig. F1-7)

- Best approach may be to combine drug and nondrug therapies.
- FM can be due to abnormalities in many different neurotransmitter systems, thus, approaches and treatment responses may be varied.
- Best evidence for tricyclics (low-dose amitriptyline and cyclobenzaprine), serotonin-norepinephrine reuptake inhibitors (milnacipran and duloxetine), and gabapentinoids (gabapentin and pregabalin).
- Second-tier drug classes include SSRIs.
- "Start low, go slow" approach is best to avoid side effects from medications.
- The only analgesic that has demonstrated efficacy in FM has been tramadol, either alone or in combination with acetaminophen.
- No evidence that NSAIDs or corticosteroids are effective in FM.
- Avoid narcotic use. There is concern that opioid use and abuse may aggravate chronic widespread pain.



1. Occiput
2. Low cervical
3. Trapezius
4. Supraspinatus
5. Second rib
6. Lateral epicondyle
7. Gluteal
8. Greater trochanter
9. Knees

FIGURE F1-6 The sites of the 18 tender points of the 1990 American College of Rheumatology criteria for the classification of fibromyalgia. (From Conn R: *Current diagnosis*, ed 9, Philadelphia, 1997, Saunders.)

- Nonpharmacologic: strong evidence to support exercise, cognitive behavioral therapy, and patient education.

DISPOSITION

- The pain and symptoms of FM can wax and wane, vary in physical location and in intensity day to day; many patients continue to have chronic pain and fatigue regardless of therapy.
- Disability rates vary from 9% to 44%.

REFERRAL

Referral to rheumatology, neurology, mental health professionals, physical medicine and rehabilitation, including physical therapy, may be helpful for a multidisciplinary team approach.

PEARLS & CONSIDERATIONS

Myofascial pain syndrome may represent a localized form of FM. It is associated with trigger points (rather than tender points as seen in FM). Some patients with myofascial pain syndrome may progress to FM.

COMMENTS

FM occurs frequently in patients with some rheumatic diseases such as rheumatoid arthritis, ankylosing spondylitis, and systemic lupus erythematosus, in which prevalence of FM may reach 20%.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fibromyalgia (Patient Information)

AUTHOR: **CANDICE YUVIENCO, M.D.**

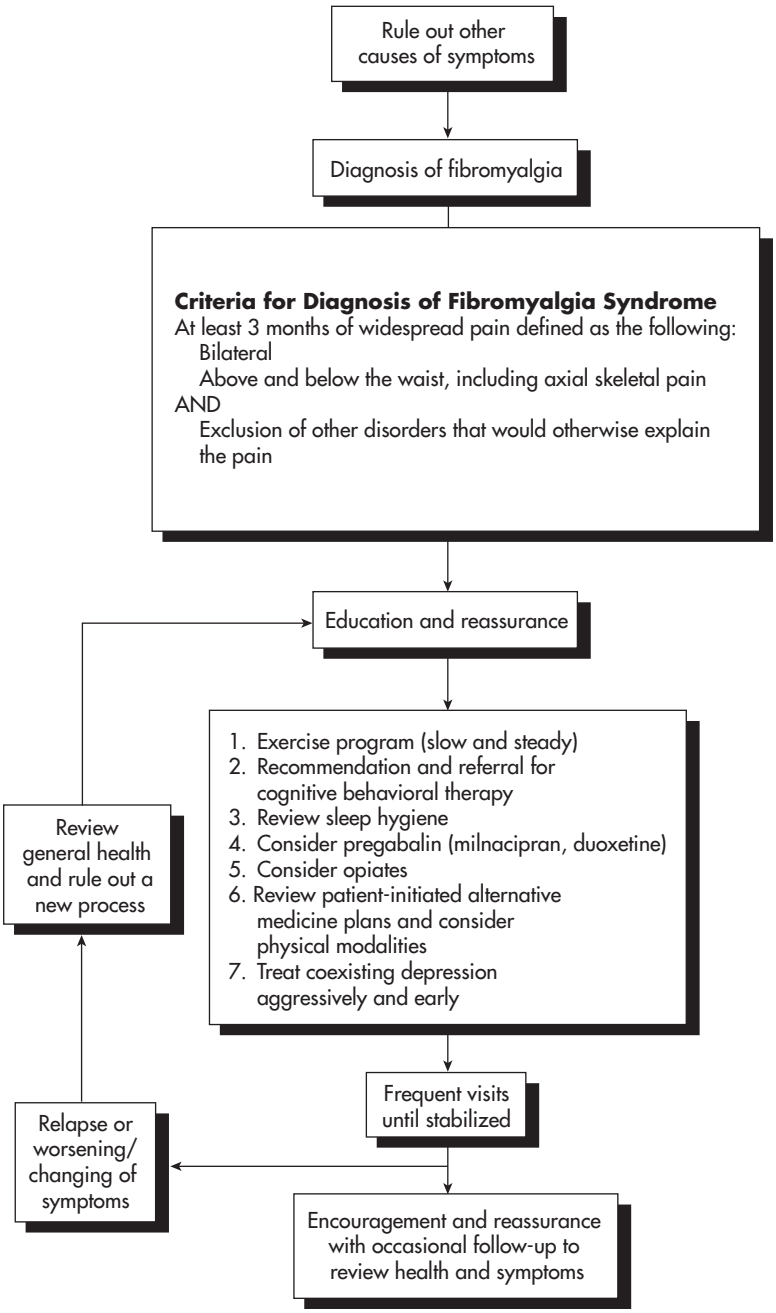


FIGURE F1-7 Treatment algorithm for fibromyalgia. (Modified from Harris ED et al: *Kelley's textbook of rheumatology*, ed 7, Philadelphia, 2005, Saunders.)

EVIDENCE

Abstract[1]

The objective of this project was to determine the relationship between cigarette smoking and the reporting of chronic pain syndromes among participants in the Kentucky Women's Health Registry. Data was analyzed on 6,092 women over 18 years of age who responded to survey questions on pain and smoking. The chronic pain syndromes included in the analysis were fibromyalgia, sciatica, chronic neck pain, chronic back pain, joint pain, chronic head pain, nerve problems, and pain all over the body. Analyses controlled for age, body mass index, and Appalachian versus non-Appalachian county of residence. Results showed that women who were daily smokers reported more chronic pain (defined as the presence of any reported chronic pain syndromes) than women who were never smokers (adjusted odds ratio [aOR]=2.04 and 95% confidence interval [CI] 1.67, 2.49). An increased risk was also seen for "some-day" smokers (aOR 1.68, 95% CI 1.24, 2.27), and former smokers (aOR 1.20, 95% CI 1.06, 1.37), though with less of an association in the latter group. This study provides evidence of an association between chronic pain and cigarette smoking that is reduced in former smokers. Ⓐ

Abstract[2]

To assess the analgesic efficacy of the *N*-methyl-d-aspartate receptor antagonist S(+)-ketamine on fibromyalgia pain, the authors performed a randomized double blind, active placebo-controlled trial. Twenty-four fibromyalgia patients were randomized to receive a 30-min intravenous infusion with S(+)-ketamine (total dose 0.5mg/kg, n=12) or the active placebo, midazolam (5mg, n=12). Visual Analogue Pain Scores (VAS) and ketamine plasma samples were obtained for 2.5 h following termination of treatment; pain scores derived from the fibromyalgia impact questionnaire (FIQ) were collected weekly during an 8-week follow-up. Fifteen min after termination of infusion the number of patients showing a reduction in pain scores >50% was 8 *vs.* 3 (P<0.05), at t=180min 6 *vs.* 2 (ns), at the end of week-1 2 *vs.* 0 (ns) and at end of week-8 2 *vs.* 2 in the ketamine and midazolam groups, respectively. Ketamine effect on VAS closely followed ketamine plasma concentrations. For VAS and FIQ scores no significant differences in treatment effects were observed in the 2.5-h following infusion or during the 8-week follow-up. Side effects as measured by the Bowdle questionnaire (which scores for 13 separate psychedelic symptoms) were mild to moderate in both study groups and declined rapidly, indicating adequate blinding of treatments. Efficacy of ketamine was limited and restricted in duration to its pharmacokinetics. The authors argue that a short-term infusion of ketamine is insufficient to induce long-term analgesic effects in fibromyalgia patients. Ⓐ

Evidence-Based References

Mitchell MD et al.: Association of smoking and chronic pain syndromes in Kentucky women, *J Pain* 12:892–899, 2011. Ⓐ

Noppers I et al.: Absence of long-term analgesic effect from a short-term S-ketamine infusion on fibromyalgia pain: a randomized, prospective, double blind, active placebo-controlled trial, *Eur J Pain* 15:942–949, 2011. Ⓐ

SUGGESTED READINGS

Arnold LM et al.: Development and testing of the fibromyalgia diagnostic screen for primary care, *J Womens Health (Larchmont)* 21:231–239, 2012.

Choy E et al.: A systematic review and mixed treatment comparison of the efficacy of pharmacological treatments for fibromyalgia, *Semin Arthritis Rheum* 41(3):335–345, 2011.

Clauw DJ; Fibromyalgia a clinical review. *JAMA* 311(15):1547–1555.

Clauw DJ et al.: The science of fibromyalgia, *Mayo Clin Proc* 86(9):907–911, 2011.

Fitzcharles MA et al.: Opioid use, misuse, and abuse in patients labeled as fibromyalgia, *Am J Med* 124:955–960, 2011.

Foerster B et al.: Cerebral blood flow alterations in pain-processing regions of patients with fibromyalgia using perfusion MR imaging, *Am J Neuroradiol* 32:1873–1878, 2011.

Goldenberg D: Clinical manifestations and diagnosis of fibromyalgia in adults, *UpToDate version* 19(2), May 2011.

Goldenberg D et al.: Management of fibromyalgia syndrome, *JAMA* 292:2388–2395, 2004.

Hawkins RA: Fibromyalgia: a clinical update, *J Am Osteopath Assoc* 113:680–689, 2013.

Mease P: Fibromyalgia syndrome: review of clinical presentation, pathogenesis, outcome measures, and treatment, *J Rheumatol Suppl* 75:6–21, 2005.

Wolfe F et al.: The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee, *Arthritis Rheum* 33(2):160–172, 1990.

Wolfe F et al.: The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity, *Arthritis Care Res* 62:600, 2010.

Yunus MB: Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes, *Semin Arthritis Rheum* 36:339–356, 2007.

Fifth Disease (Parvovirus B19 Infection) PTG

BASIC INFORMATION

DEFINITION

Parvovirus B19 is a small, nonenveloped ssDNA virus that belongs to the *Erythrovirus* genus of the *Parvoviridae* family. It was first discovered in 1975 when units of blood were being screened for hepatitis B and was read as a false positive result (sample 19 in panel B). It causes a spectrum of human disease, from asymptomatic to fatal, depending on the underlying host. Classically, it has been associated with erythema infectiosum (EI), or "fifth disease," the fifth in a series of six viral exanthems that commonly affect school-aged children and are named in order of the dates they were first described. In addition, parvovirus B19 causes a variety of diseases in fetuses, adults, and the immunocompromised.

SYNONYMS

Parvovirus B19
Erythema infectiosum
Fifth disease

ICD-9CM CODES
057.0 Erythema infectiosum (fifth disease)
079.83 Parvovirus B19
ICD-10CM CODES
B08.3 Erythema infectiosum [fifth disease]

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Between 1% and 9% of pregnancies are affected by B19 infection, up to 1 in 200 units of blood are contaminated by B19, 16% of schoolteachers and 9% of daycare workers and homemakers are infected with B19 during epidemics. The infection rate of household contacts may be as high as 50%.
PEAK INCIDENCE: Temperate climates between late winter and early summer, often in cycles of local epidemics that peak every 3 to 10 yr.
PREVALENCE: 15% of school-aged children and 30% to 85% of adults have demonstrated protective IgG antibodies to parvovirus B19.
PREDOMINANT AGE: 5 to 18 yr
RISK FACTORS: Exposure to school-aged children, immunosuppression, congenital or acquired hematologic abnormalities, blood transfusion, tissue transplantation.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Approximately 25% of those infected are asymptomatic, 50% have nonspecific flulike symptoms, and 25% have the classic symptoms of B19 infection, including rash and/or arthralgias.
- Parvovirus B19 is the most common viral agent associated with rashes in school-aged children. EI is characterized by a bright red, nontender rash most prominent on the cheeks with a circumoral pallor producing the classic "slapped face" appearance (Fig. F1-8), which is often followed by a reticular, lacelike rash on the trunk and extremities. This is typically a transient, self-limited illness that begins with a prodrome of flulike symptoms, such as fever, malaise, myalgias, coryza, headache, nausea, and diarrhea, and ends with the malar rash once viremia has resolved and antibody production has occurred.
- Polyarthralgias and polyarthritis are more commonly seen in adults (especially women) and typically involve symmetric small joints of the extremities. The arthritis is nonerosive. Joint symptoms usually resolve within 3 wk but may rarely become persistent or recurrent. A rash develops in 75% of infected adults, but less than 20% have the classic "slapped face" rash seen in EI. The rash may be exacerbated by changes in temperature, sunlight, exercise, or emotional stress.
- B19 infection during pregnancy can result in fetal anemia, nonimmune hydrops fetalis, miscarriage, or fetal loss. Pregnant women with B19 infection have a 30% chance of fetal transmission. The risk of fetal loss is 5% to 10% and greatest when fetal infection occurs in the first 20 wk of gestation.
- In patients with congenital or acquired hematologic abnormalities, B19 infection can cause severe anemia or transient aplastic crisis, which is usually manifested as pure red cell aplasia and may be fatal. Chronic infection and anemia have been described in patients with leukemia and other cancers, HIV, or congenital immunodeficiency and in recipients of tissue transplantation.
- B19 has also been associated with immune thrombocytopenic purpura, vasculitis, nephritis, lymphadenitis, meningitis, encephalitis, and fulminant liver disease and is the most prevalent pathogen responsible for acute myocarditis, which progresses to dilated cardiomyopathy in 21% of cases.

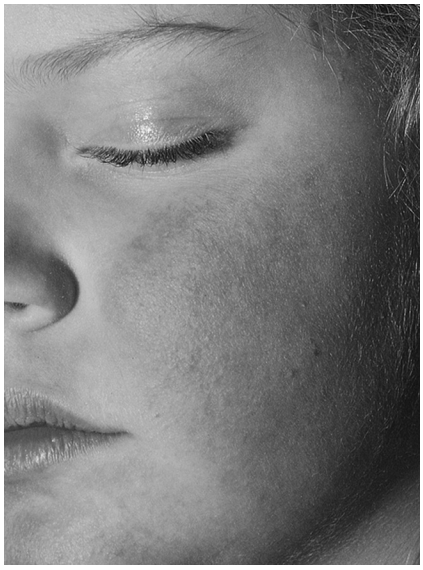


FIGURE F1-8 Fifth disease (erythema infectiosum). Facial erythema "slapped face." The red plaque covers the cheek and spares the nasolabial and the circumoral region. (From Habif TP: *Clinical dermatology: a color guide to diagnosis and therapy,* ed 3, St Louis, 1996, Mosby.)

ETIOLOGY, INFECTIVITY, & TRANSMISSION

B19 preferentially infects, replicates in, and is directly cytotoxic to erythroid progenitor cells, which may result in profound anemia or pure red cell aplasia. Viremia and the period of greatest infectivity occur 7 to 10 days after exposure and last about 1 wk in immunocompetent individuals, after which time antibody production begins and typical symptoms of rash and arthralgias manifest. Transmission is thought to occur primarily through droplet exposure, as well as person-to-person contact, fomites, vertical transmission, and hematogenous transmission. Because of its nonenveloped capsid, parvovirus B19 is heat stable and difficult to inactivate with solvent detergents, often leading to contamination of blood products.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Juvenile rheumatoid arthritis (Still's disease)
- Rubella, measles (rubeola), and other childhood viral exanthems
- Mononucleosis
- Lyme disease
- Acute HIV infection
- Drug eruption

WORKUP

Diagnosis can be made by typical clinical presentation in well children. Laboratory tests may be required for confirmation in immunosuppressed populations, those with severe anemia or transient aplastic crisis (TAC), and pregnant women.

LABORATORY TESTS

- Parvovirus B19 viral DNA polymerase chain reaction (PCR): Nucleic acid antigen testing (NAAT) of B19 DNA by PCR is the most sensitive method of infection detection and the preferred method for diagnosis in immunocompromised individuals, fetuses, immunocompetent patients with suspected persistent infection, and blood products.
- Parvovirus B19 IgM and IgG: Parvovirus B19 IgM enzyme immunoassay is widely available and the preferred method of diagnosis in immunocompetent individuals. IgM can be found within 7 to 10 days of exposure and may persist for several months. IgG antibodies are detectable about 15 days after exposure and persist long-term.
- Complete blood count (CBC) and reticulocyte count: CBC evaluation ranges from mild to profound classically normocytic normochromic anemia. Reticulocytes are markedly decreased or absent in pure red cell aplasia. White blood cell and platelet counts are typically unchanged. Fig. F1-9 illustrates investigations for parvovirus B19 infection in pregnancy.
- Bone marrow biopsy: Bone marrow examination in patients with pure red cell aplasia demonstrates complete or near-complete absence of red cell precursors. Characteristic giant proerythroblasts containing large eosinophilic nuclear inclusions can be seen.

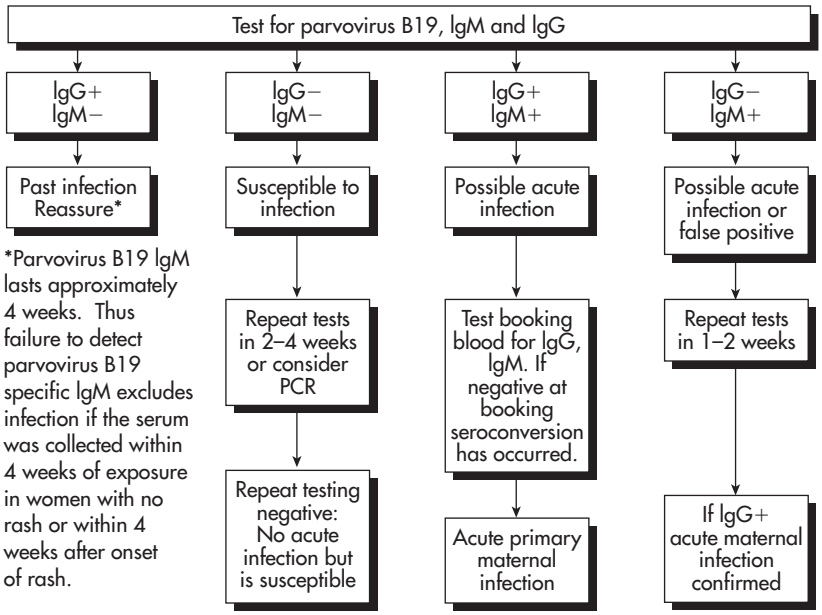


FIGURE F1-9 Investigations for parvovirus B19 infection. (From Stephen G, Gillham J: Fetal infection: a pragmatic approach to recognition and management. *Obstetrics, Gynaecology & Reproductive Medicine* 22(10): 299–303, 2012.)

- Prenatal testing: Fetal nuchal translucency measurement and ductus venosus Doppler velocimetry may indicate the presence of severe fetal anemia. Ultrasound may show fetal edema, ascites, pleural effusions, and cardiomegaly in hydrops fetalis.

Rx TREATMENT

NON-PHARMACOLOGIC THERAPY

- Treatment for Fifth disease is generally supportive because the majority of B19 infections are asymptomatic or mild and self-limited; nonsteroidal antiinflammatory drugs may be used for relief of joint symptoms, antipyretics for fever, and adequate hydration.

ACUTE GENERAL TREATMENT

- No antiviral drug is available.
- Blood transfusion is often required in cases of severe anemia and pure red cell aplasia until red blood cell (RBC) production returns; intrauterine transfusion may be required in fetal infection.
- Initiation of antiretroviral therapy (ART) has been associated with resolution of B19-induced anemia in HIV-infected patients.
- Bone marrow transplantation has been used in individuals with nonresolving aplastic crisis.
- The mainstay of fetal therapy is delivery, which may be followed by resuscitation and ventilation in cases of severe hydrops.

CHRONIC GENERAL TREATMENT

- IV immunoglobulin (IVIG) treatment may be considered for immunocompromised patients with chronic B19 infection and chronic anemia.

DISPOSITION

- B19 infection is typically self-limited, with symptoms usually resolving within a few weeks and most often requiring only supportive care.
- Children in whom EI develops are no longer contagious and may attend school and daycare.
- Patients in whom persistent arthritis with or without joint erosion develops should be evaluated by a rheumatologist.
- In immunocompetent patients, anemia is typically transient with spontaneous resolution and return of RBC production in days to weeks. In patients with hematologic abnormalities, however, anemia may be severe and may be the result of transient aplastic crisis or pure red cell aplasia, which warrant immediate hematologic evaluation and transfusion.
- Patients with TAC or chronic parvovirus B19 infection pose a risk for nosocomial spread and, when hospitalized, should be isolated with droplet precautions.
- Patients with chronic infection and anemia may require evaluation for possible IVIG treatment.
- Pregnant women with B19 infection have a 30% risk of fetal transmission; they should undergo close monitoring of fetal health and development and may require fetal transfusion or referral to a tertiary care center for delivery in the case of hydrops fetalis.
- Vaccines have not progressed beyond phase I/II clinical trials.

REFERRAL

- To hematologist if signs of marrow suppression
- To rheumatologist if signs of severe or erosive arthritis
- To cardiologist if suspicion of myocarditis

PEARLS & CONSIDERATIONS

- Generally self-limited disease lasting up to 3 wk in immunocompetent individuals
- Symmetric arthritis involving small joints is common in adults, whereas facial rash is common in children
- Can cause severe anemia with or without transient aplastic crisis that may become chronic in patients with hematologic abnormalities, immunocompromise, or malignancy and those after transplantation.
- Infection during pregnancy can cause fetal anemia, hydrops fetalis, or fetal loss.

PREVENTION

- Hand-washing and not sharing food or drinks during epidemics.
- Testing of plasma pools and blood products for B19 contamination.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fifth Disease (Patient Information)

AUTHORS: **ANTONELLA FINE, M.D.,** and **DOMINICK TAMMARO, M.D.**

SUGGESTED READINGS

Oiwa H et al.: Clinical findings in parvovirus B19 infection in 30 adult patients in Kyoto, *Mod Rheumatol* 21(1):24–31, 2011.

Young NS: Parvovirus B19, *N Engl J Med* 350(6):586, 2004.

BASIC INFORMATION

DEFINITION

Filariasis is a general term for an infection caused by subcutaneous nematodes (roundworms) of the genera *Wuchereria* and *Brugia,* found in the tropical and subtropical regions of the world. The disease is variably characterized by acute lymphatic inflammation or chronic lymphatic obstruction associated with intermittent fevers or recurrent episodes of dyspnea and bronchospasm.

SYNONYMS

Lymphatic filariasis
Elephantiasis

ICD-9CM CODES
125.0 Bancroftian
125.1 Brugian
125.9 Filariasis
ICD-10CM CODES
B74.0 Filariasis due to *Wuchereria bancrofti*
B74.1 Filariasis due to *Brugia malayi*
B74.9 Filariasis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Unknown
INCIDENCE (GLOBAL): Lymphatic filariasis is endemic in 72 countries; 40 million people have clinical manifestations, 15 million have elephantiasis, and 25 million men have genital swelling (usually hydrocele) from filariasis.
PEAK INCIDENCE: Unknown
PREDOMINANT SEX: Male
PREDOMINANT AGE: For both males and females, risk is greatest between the ages of 15 and 35 yr.

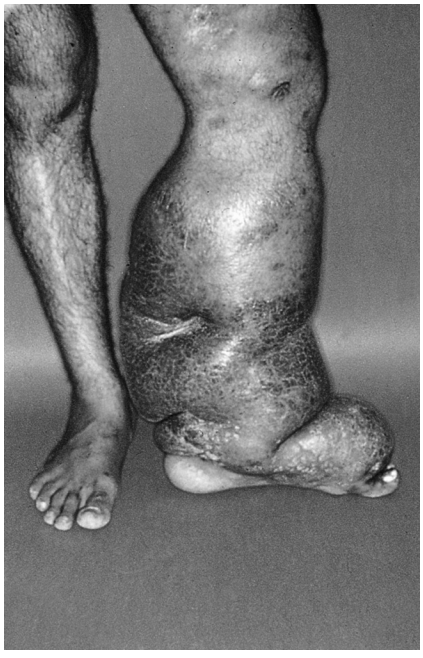


FIGURE EF1-10 Filariasis that eventually leads to elephantiasis. Note massive swelling of the extremity. (From Goldstein B [ed]: *Practical dermatology,* ed 2, St Louis, 1997, Mosby.)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical manifestations result from acute lymphatic inflammation or chronic lymphatic obstruction.
- Many patients are asymptomatic despite the presence of microfilaremia.
- Episodes of lymphangitis and lymphadenitis are associated with fever, headache, and back pain.
- Acute funiculitis and epididymitis or orchitis may also be present; all usually resolve within days to weeks but tend to recur.
- Chronic infections may be associated with lymphedema, most commonly manifested by hydrocele.
- It is a progressive disease, leading to nonpitting edema and brawny changes that may involve a whole limb (Fig. EF1-10).
- Elephantiasis occurs in about 10% of patients, with skin of the scrotum or leg becoming thickened and fissured; patient is thereafter plagued by recurrent ulceration and infection.
- Chyluria, a condition that develops when lymphatic vessels rupture into the urinary tract, may occur.

ETIOLOGY

Caused by one of three types of nematode parasite, all of which are transmitted to humans by *Culex, Anopheles, Aedes, Mansonia* spp. mosquitoes.

- *W. bancrofti:* distributed in Africa, areas of Central and South America, the Pacific Islands, and the Caribbean Basin. This is the cause of over 90% of cases.
- *B. malayi:* restricted to Southeast Asia.
- *B. timori:* confined to the Indonesian archipelago.

After bite of an infected mosquito:

- Filarial larvae move into lymphatic vessels and nodes, settling and maturing over 3 to 15 mo into adult male and female worms (Fig. EF1-11). *Wolbachia* bacteria are needed for filarial development.
- After fertilization, the female nematode produces large numbers of larvae or microfilariae that enter into the bloodstream via the lymphatics.
- Nocturnal periodicity, characteristic of *B. malayi,* is an increased presence of microfilariae in the circulation during the night.
- Microfilariae of *W. bancrofti* are maximal during late afternoon.
- Most microfilariae remain in the body as immature forms for 6 mo to 2 yr.
- Infected larvae are ingested by mosquitoes, then transmitted to humans, where the microfilariae mature into new adult worms. Humans are the definitive hosts.

Acute and chronic inflammatory and granulomatous changes in the lymphatic channels:

- Result from complex interaction of adult worms and host's immune systems.
- Eventually lead to fibrosis and obstruction.
- Most likely to develop into obstructive lymphatic disease with recurrent exposure over many years.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Elephantiasis is distinguished from other causes of chronic lymphedema, including Milroy's disease, postoperative scarring, and lymphedema of malignancy.

WORKUP

Diagnosis is suspected in individuals who have resided in endemic areas for at least 3 to 6 mo or more and complain of recurrent episodes of lymphangitis, lymphadenitis, scrotal edema, or thrombophlebitis, with or without fever.

LABORATORY TESTS

- Demonstration of microfilariae on a blood smear via Giemsa or Wright Stain for definitive diagnosis

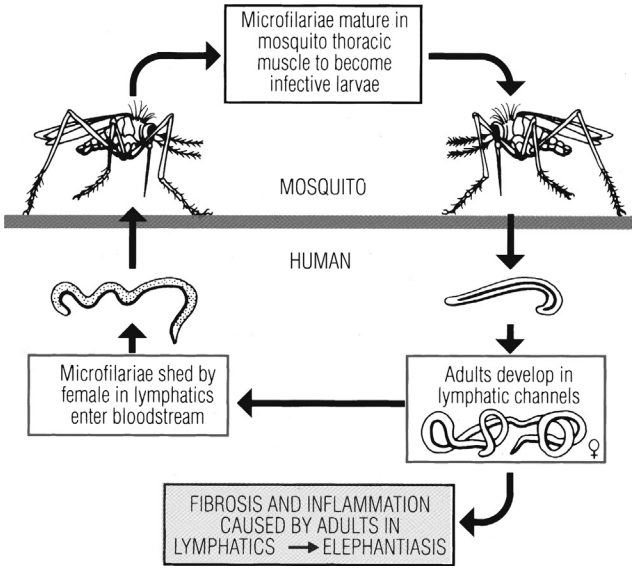


FIGURE EF1-11 Lifecycle of lymphatic filariasis. (From Souhami RL, Moxham J: *Textbook of medicine,* ed 4, London, 2002, Churchill Livingstone.)

- For patients from southeastern Asia: blood sample drawn at night, especially between 10 PM and 2 AM
- Occasionally, microfilaremia in chylous urine or hydrocele fluid.
- Prominent eosinophilia only during periods of acute lymphangitis or lymphadenitis.
- Serologic tests for antibody, including enzyme-linked immunosorbent assay and indirect fluorescent antibody (often unable to distinguish among the various forms of filariasis or between acute and remote infection).
- Immunoassays (such as circulating filaria antigen [CFA]) only available for *W. bancrofti:* more successful in antigen detection in patients who are microfilaremic than in those who are amicrofilaremic.

IMAGING STUDIES

- Chest radiograph: reticular nodular infiltrates (tropical pulmonary eosinophilia syndrome).
- In men proven to be microfilaremic, scrotal ultrasonography to aid in the detection of adult worms.
- Compared with adults, children with filariasis have more sleep disturbances, fewer tender points, and a better prognosis.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Standard of care for elephantiasis:
  1. Elevation of the affected limb
  2. Use of elastic stockings
  3. Local foot care
- General wound care for chronic ulcers and prevention of secondary infection

ACUTE GENERAL Rx

- Diethylcarbamazine citrate (DEC) to reduce microfilaremia by 90%.
  1. Effect on adult worms, especially those of the *Wuchereria* species, less certain.
  2. Given in an oral dose of 6 mg/kg PO qd in 3 divided doses × 14 days or 6 mg/kg/day as single PO dose daily × 14 days *plus* doxycycline 200 mg/day × 6 weeks (to decrease number of *Wolbachia* and number of microfilaria).
  3. DEC should not be used if coinfection with Loa loa or onchocerciasis suspected due to adverse reactions and these two diseases should be treated first.
- Ivermectin alone or in combination with diethylcarbamazine citrate to decrease microfilaremia
- Both drugs are similar in efficacy and tolerability; advantage of ivermectin: administration in a single oral dose of 200 to 400 μg/kg. Side effects of these drugs include severe hypotensive reactions with dizziness, headache, fever, and vomiting, especially in patients with high microfilarial loads.
- World Health Organization (WHO) recommendation: DEC given as a single dose, alone or (preferably) in combination with ivermectin as treatment in endemic areas.
- Antibacterial agents (a penicillin or cephalosporin) may be indicated to treat coexisting bacterial soft tissue infection (cellulitis or lymphangiitis), which frequently complicates filariasis of the lower extremities.

CHRONIC Rx

- Surgical drainage of hydroceles
- No satisfactory therapy for those patients with chyluria

DISPOSITION

Rarely fatal, but the psychological impact of limb and scrotal deformities associated with elephantiasis is substantial.

REFERRAL

To a surgeon for management of hydrocele.

PEARLS & CONSIDERATIONS

- Studies in endemic areas suggest that filarial-specific IgG1 is associated with amicrofilaremic states highest in children, regardless of sex.
- Levels of IgE and IgG4 increase with age and are associated with increased levels of microfilaremia.

COMMENTS

Individuals who intend to travel or reside in endemic areas should be advised to institute preventive measures such as the use of netting and insect repellents containing DEET, especially at night when mosquitos transmitting disease are most active.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Hoerauf A: Filariasis: new drugs and new opportunities for lymphatic filariasis and onchocerciasis, *Curr Opin Infect Dis* 21(6):673–681, 2008.

Mendoza N et al.: Filariasis: diagnosis and treatment, *Dermatol Ther* 22(6): 475–490, 2009.

Molyneux DH: Tropical lymphedemas—control and prevention, *N Engl J Med* 366:1169–1171, 2012.

Pal BK et al.: Lymphatic filariasis: possible pathophysiological nexus with oxidative stress, *Trans R Soc Trop Med Hyg* 100(7):650, 2006.

Ramaiah KD et al.: The prevalences of *Wuchereria bancrofti* antigenemia in communities given six rounds of treatment with diethylcarbamazine, ivermectin or placebo tablets, *Ann Trop Med Parasitol* 97(7):737, 2003.

Watanabe K et al.: Bancroftian filariasis in Nepal: a survey for circulating antigenemia of Wuchereria bancrofti and urinary IgG4 antibody in two rural areas of Nepal, *Acta Trop* 88(1):11, 2003.

BASIC INFORMATION

DEFINITION

Folliculitis is inflammation of the hair follicle as a result of infection, physical injury, or chemical irritation.

SYNONYMS

Sycosis barbae

ICD-9CM CODES

704.8 Other specified diseases of hair and hair follicles

ICD-10CM CODES

L72.9 Follicular cyst of skin and subcutaneous tissue, unspecified
L73.1 Pseudofolliculitis barbae
L73.8 Other specified follicular disorders
L66.3 Perifolliculitis capitis abscedens

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Staphylococcal folliculitis is the most common form of infectious folliculitis; it occurs most commonly in persons with diabetes.

PREDOMINANT SEX: Sycosis barbae occurs most frequently in men who have commenced shaving.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The lesions generally consist of painful yellow pustules surrounded by erythema; a central hair is present in the pustules. Furuncles with pus may be present (Fig. F1-12).
- Patients with sycosis barbae may initially present with small follicular papules or pustules that increase in size with continued shaving; deep follicular pustules may occur surrounded by erythema and swelling; the upper lip is frequently involved.
- "Hot tub" folliculitis occurs within 1 to 4 days after the use of a hot tub with poor chlorination. It is characterized by papules and pustules (Fig. F1-13) with surrounding erythema generally affecting the torso, buttocks, and limbs.

ETIOLOGY

- Staphylococcus infection (e.g., sycosis barbae), *Pseudomonas aeruginosa* ("hot tub" folliculitis.)
- Gram-negative folliculitis *(Klebsiella, Enterobacter, Proteus)* associated with antibiotic treatment of acne.
- Chronic irritation of the hair follicle (use of cocoa butter or coconut oil, chronic irritation from workplace).
- Initial use of systemic corticosteroid therapy (steroid acne), eosinophilic folliculitis (AIDS patients), *Candida albicans* (immunocompromised patients).
- *Pityrosporum orbiculare.*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Pseudofolliculitis barbae (ingrown hairs).
- Acne vulgaris.
- Dermatophyte fungal infections.
- Keratosis pilaris.
- Cutaneous candidiasis.
- Superficial fungal infections.
- Miliaris.

WORKUP

Physical examination and medical history (e.g., use of hot tub: "hot tub" folliculitis; adolescent patients who have started shaving: sycosis barbae; use of occlusive topical steroid therapy: *Staphylococcus* folliculitis).

LABORATORY TESTS

- Generally not necessary.
- Gram stain is useful to identify the infective organisms in infectious folliculitis and to differentiate infectious folliculitis from noninfectious.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Prevention of chemical or mechanical skin irritation.
- Glycemic control in diabetics.
- Proper chlorination of hot tubs and spas.
- Shaving with a clean razor.

ACUTE GENERAL

- Cleansing of the area with chlorhexidine and application of saline compresses to involved area.
- Application of 2% mupirocin ointment or 1% Retapamulin ointment for bacterial folliculitis affecting a limited area (e.g., sycosis barbae).
- Treatment of severe cases of *Pseudomonas* folliculitis with ciprofloxacin.
- Treatment of *S. aureus* folliculitis with dicloxacillin 250 mg qd for 10 days.

CHRONIC Rx

- Chronic nasal or perineal *S. aureus* carriers with frequent folliculitis can be treated with rifampin 300 mg bid for 5 days.
- Mupirocin or Retapamulin ointment applied to nares bid is also effective for nasal carriers.

DISPOSITION

- Most cases of bacterial folliculitis resolve completely with proper treatment.
- Steroid folliculitis responds to discontinuation of steroids.

PEARLS & CONSIDERATIONS

COMMENTS

Patients should be instructed in good personal hygiene and avoidance of sharing razors, towels, and washcloths.

RELATED CONTENT

Folliculitis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

FIGURE F1-12 Rupture and discharge of pus in a furuncle. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

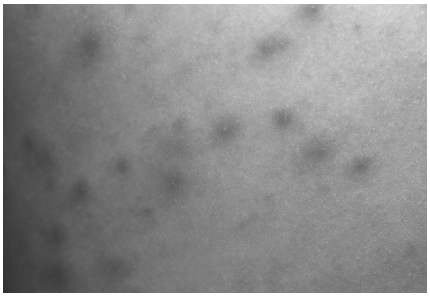


FIGURE F1-13 Papules and pustules in hot tub folliculitis. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Food allergies are divided into IgE-mediated and immunologically mediated non-IgE reactions. They include a spectrum of disorders that involve adverse immunologic responses to dietary antigens.

ICD-9CM CODES

447.1 Allergic rhinitis due to food
558.3 Allergic gastroenteritis and colitis
693.1 Dermatitis due to food taken internally
995.60 Anaphylactic reaction due to unspecified food
995.7 Other adverse food reactions, not elsewhere classified

ICD-10CM CODES

T78.0 Adverse food reaction (including anaphylactic shock)
T78.1 Other adverse food reactions, not elsewhere classified
L27.2 Dermatitis due to ingested food

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Food allergies have a cumulative incidence of 6% to 8% for the first 3 yr of life.

PREVALENCE:

- Overall prevalence is 1% to 2% in general population, ~3.9% -8% in children.
- Patient self-reported food allergies have a prevalence of 12% to 13%, demonstrating the importance of objective measures in assessing food allergies.
- Nearly 40% of children with food allergy have a history of severe reactions that, if not treated immediately with proper medication, can lead to hospitalization or even death.[1]
- There is insufficient evidence to conclude a racial predilection (Greenhawt, 2013).

PREDOMINANT SEX: Males are more affected than females among children, and among adults, females are more frequently affected.

GENETICS: Children with parents or close relatives with allergies may have a tendency to become allergic to foods.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- IgE-mediated reactions: (within minutes to a few hours) pruritus, urticaria or angioedema, atopic dermatitis, GI symptoms, conjunctival injection, sneezing, nasal congestion, rhinorrhea, bronchospasm, and anaphylaxis
- Non–IgE-mediated reactions: food-induced enterocolitis, celiac disease, Crohn's disease, dermatitis herpetiformis, and pulmonary reactions such as Heiner syndrome. These illnesses are discussed separately.
- Signs, symptoms, and presentation reflect specific allergic manifestation, but in food allergies there is a reproducible temporal relationship to ingested food allergens.

[1]Gupta RS et al: The prevalence, severity, and distribution of childhood food allergy in the United States, *Pediatrics* 128(l):e9-e17, 2011.

ETIOLOGY

Failure to establish tolerance to food antigens. IL-33 mediated epithelial permeability and Th2 skewing result in sensitization to food proteins which are presented to primed T cells.

DIAGNOSIS

- Thorough history and physical exam should be performed.
- The temporal relationship and reproducibility of the symptoms are most important to establishing the diagnosis.
- A review of ingredient labels may be helpful.
- Confirmatory testing can include skin testing or in vitro testing.
- Skin prick testing (SPT): positive predictive value <50%, but negative predictive value >95%. Thus a negative skin test effectively rules out an IgE-mediated process.
- In vitro testing: RAST testing: Historically it is less sensitive than skin testing, but sensitivity has improved with cut off points indicating a positive predictive value of 95% for allergies to eggs, milk, peanuts, wheat, and fish.
- Atopy patch test: used in conjunction with RAST and skin testing in multiallergic children to plan widening the elimination diet. However, it is not recommended in the routine evaluation of food allergies.
- Double-blind, placebo-controlled food challenges are the gold standard test for determining food allergies. These need to be done in a supervised and controlled setting.
- In summary, if the history and lab tests are suggestive of a specific food allergy, that food should be confirmed by SPT, RAST, or food challenge and, once confirmed, eliminated from the diet.

DIFFERENTIAL DIAGNOSIS

- Gastrointestinal disorders
- Irritable bowel syndrome
- Carcinoid syndrome
- Giardiasis
- Structural abnormalities like hiatal hernia, pyloric stenosis, Hirschsprung's disease, tracheoesophageal fistula
- Disaccharidase deficiencies: lactase, sucrase-isomaltase complex, glucose-galactose complex
- Pancreatic insufficiency: cystic fibrosis
- Gallbladder disease
- Peptic ulcer disease
- Malignancy
- Metabolic disorders
- Galactosemia
- Phenylketonuria
- Pharmacologic-related conditions
- Gustatory rhinitis
- Auriculotemporal syndrome (facial flush from tart food)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Elimination diet should be used in conjunction with nutritional counseling. Fig. F1-14 illustrates an algorithm for the management of food allergy
- Formula-fed infants: brief trial of hydrolyzed milk formula as most children with milk allergy induced skin symptoms will respond to the change of formula. Nonresponders may require amino acid–based formula.
- In older children: elimination of one to two suspected foods is appropriate for 2 wk or longer and then reintroducing the foods to determine if symptoms recur.

ACUTE GENERAL Rx

- Antihistamines (both H_1 and H_2 antihistamines), albuterol if wheezing, epinephrine and glucocorticoids in patients with anaphylaxis.
- Patients with documented IgE-mediated reactions should receive and be counseled on the use of epinephrine autoinjector.

NEW TREATMENTS FOR FOOD ALLERGIES

- Oral and sublingual immunotherapy may play a role in management of food allergies, but this is currently under investigation.
- Recombinant vaccines and other immunomodulatory strategies are under development, although monoclonal anti-IgE antibody has shown benefit in adults with peanut allergy.

PEARLS & CONSIDERATIONS

- Eczema that develops in first 6 to 12 mo of life is usually the first manifestation of atopy.
- Egg allergy or sensitization is the strongest recognized predictor of respiratory allergies in children and asthma in adults.
- Neither the size of the wheal in skin prick testing nor the IgE antibody level correlates with severity. However, there may be increased positive predictive value with larger wheals and higher titers.
- Consultation with trained dietitian is critical to avoid potentially adverse nutritional consequences in children with multiple food allergies.
- Skin testing is the preferred method for identifying food-specific IgE. RAST is useful if there is chance of severe food reaction causing risk to the patient.
- American Academy of Pediatrics recommends avoiding influenza vaccine in patients with severe systemic allergic reactions to egg. Skin prick testing using influenza vaccine containing egg is recommended before vaccination in children with egg allergy and asthma. Skin prick testing not required before MMR vaccine in children with egg allergy.

COMMENTS

- Milk allergy usually resolves by age 5. Risk factors for persistence are early cutaneous manifestations following milk ingestion, development of other atopic conditions, and persistence of milk-specific high IgE titers. Soy milk is recommended for these children, keeping in mind that about 15% of these children can develop soy allergy.
- Egg allergy has been thought to resolve in 66% of children by 5 yr of age and in 75% of children by 7 yr of age. Trials have shown

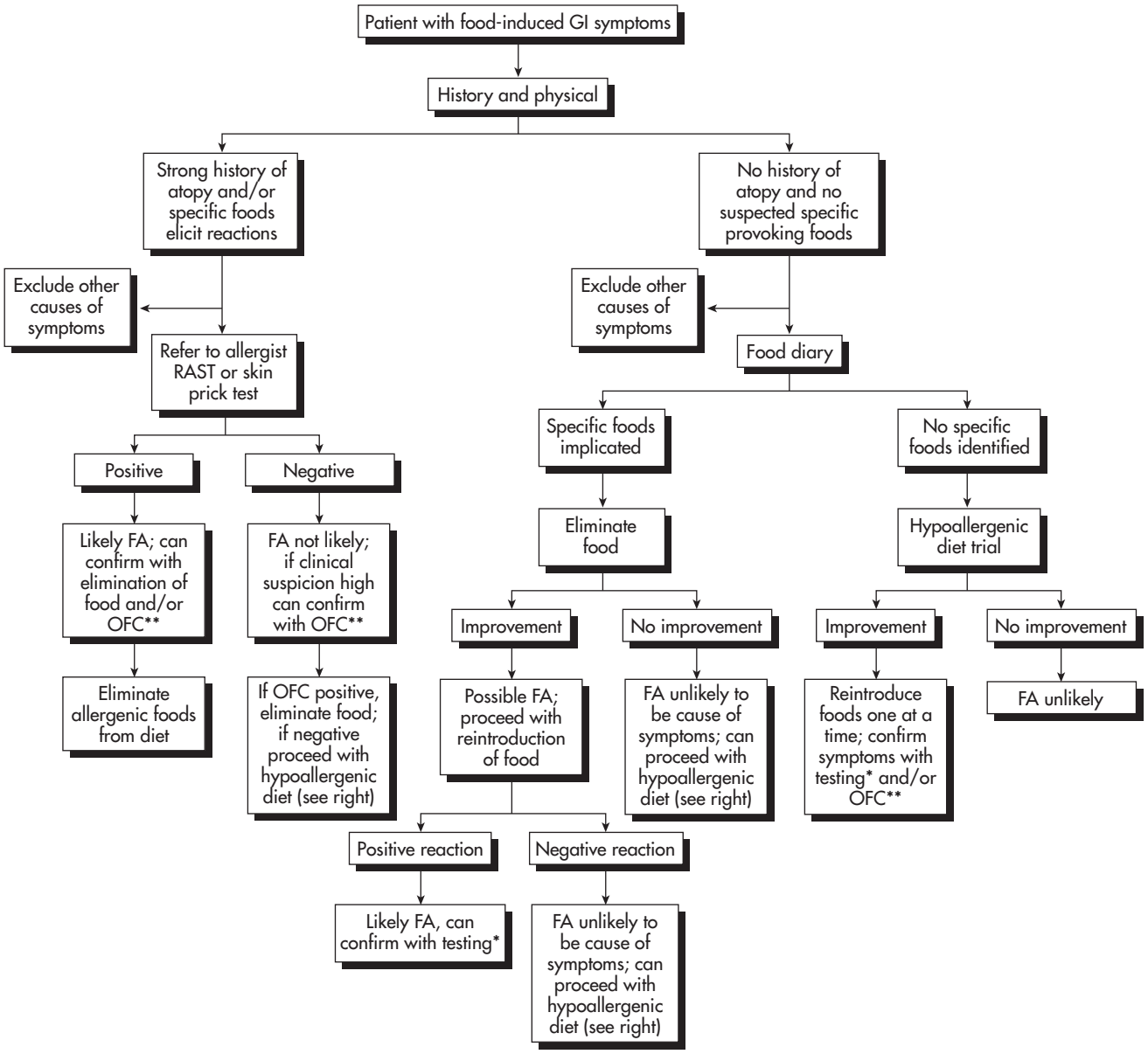


FIGURE F1-14 Algorithm for the management of food allergy. *Testing indicates skin-prick testing, radioallergosorbent tests (RAST), IgG_4 assay, and/or patch testing. Note that clinical symptoms must be associated with the food(s) that test positive before the food(s) should be eliminated from the diet. **Oral food challenge (ofc) involves reintroducing the food and observing for signs/symptoms of food allergy (fa). Treatment of food allergy involves elimination of the causative food(s) from the diet. (From Stephen G, Gillham J: Fetal infection: a pragmatic approach to recognition and management. *Obstetrics, Gynaecology & Reproductive Medicine* 22(10) 299–303, 2012.)

that oral immunotherapy can desensitize a high proportion of children with egg allergy and induce sustained unresponsiveness in a clinically significant subset.
- Wheat allergy found to resolve by 5 yr of age and soybean allergy by 2 yr of age.

PREVENTION

- There is conflicting evidence regarding the protective effect of breastfeeding on food allergies.
- There is no evidence to suggest that exclusive breastfeeding for 6 mo or more is superior to exclusive breastfeeding for 4 to 6 mo in terms of developing food allergies.
- In high-risk infants who are not exclusively breast fed, there is limited evidence to suggest that feeding with hydrolyzed formula compared to cow's milk formula reduces allergies.
- Currently, there is no evidence to support the use of prebiotics, probiotics, or synbiotics for the prevention of allergic diseases.
- No current evidence exists to support delaying the introduction of solid foods beyond 4 to 6 mo.
- The early introduction of peanuts significantly decreases the frequency of the development of peanut allergy among children at high risk for this allergy and modulated immune responses to peanuts.[1]

PATIENT/FAMILY EDUCATION

Information can be found on American Academy of Allergy, Asthma and Immunology (www.aaaai.org), the Food Allergy and Anaphylaxis Network (www.foodallergy.org), and the Anaphylaxis Campaign (www.anaphylaxis.org.uk).

REFERRAL

Patients may be referred to an allergy/immunology specialist when the diagnosis is uncertain or if avoidance measures are not successful.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Food Allergies (Patient Information)

AUTHOR: **LUKE BARRÉ, M.D.**

[1]DuToit G et al.: Randomized trial of peanut consumption in infants at risk for peanut allergy, *N Engl J Med* 372:803-13, 2015

SUGGESTED READINGS

Bock SA: Diagnostic evaluation, *Pediatrics* 111(6 pt. 3):1638–1644, 2003.

Bock SA, Sampson HA: Double blind placebo controlled food challenge as an office procedure: a manual, *J Allergy Clin Immunol* 82(6):986–997, 1988.

Boyce JA et al.: Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-Sponsored Expert Panel, *J Allergy Clin Immunol* 126(suppl):S1–S58, 2010.

Burks AW et al.: Oral immunotherapy for treatment of egg allergy in children, *N Engl J Med* 367:233–243, 2012.

Bush RH: Approach to patients with symptoms of food allergy, *Am J Med* 121:376–378, 2008.

DuToit G et al.: Randomized trial of peanut consumption in infants at risk for peanut allergy, *N Engl J Med* 372:803–13, 2015.

Greenhawt ME: Racial and ethnic disparity in food allergy in the United States: a systematic review, *J Aller Clin Immunol*378–386, 2013.

Grimshaw KE et al.: Infant feeding and allergy prevention: a review of current knowledge and recommendations, *A EuroPrevall state of the art paper. Allergy* 64(10):1407–1416, 2009.

Gupta RS et al.: Childhood food allergies: current diagnosis, treatment, and management strategies, *Mayo Clin Proc* 88(5):512–526, 2013.

Kagan RS: Food allergy: an overview, *Environ Health Perspect* 111(2):223–225, 2003.

Lack G: Clinical practice: food allergy, *N Engl J Med* 359(12):1252–1260, 2008.

Muraro A et al.: The management of anaphylaxis in childhood: position paper of the European Academy of Allergology and Clinical Immunology, *Allergy* 62(8):857–871, 2007.

NIAID-Sponsored Expert Panel: Guidelines for the diagnosis and management of food allergy in the United States: Report of the NIAID-Sponsored Expert Panel, *J Allergy Clin Immunol* 126(6):S1–S68, 2010.

Sampson HA: Atopic dermatitis, *Ann Allergy* 69:469–479, 1992.

BASIC INFORMATION

DEFINITION

Food poisoning is an illness caused by ingestion of food contaminated by bacteria and/or bacterial toxins. Table F1-8 describes pathogenic mechanisms in bacterial foodborne disease.

SYNONYMS

Enterotoxin-poisoning
Epidemic vomiting disease

ICD-9CM CODES
See specific illness.
ICD-10CM CODES
A05.9 Bacterial foodborne intoxication, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- Estimated range of 6 to 8 million cases/yr.
- CDC reported 13,405 foodborne disease outbreaks from 1998 to 2008 in the United States.
- Majority of identifiable causes are bacterial, although more than 250 known diseases can be transmitted through food.

PEAK INCIDENCE: Varies with specific organism.

- Summer: *Staphylococcus aureus, Salmonella, Shigella* spp.
- Summer and fall: *Clostridium botulinum, Vibrio parahaemolyticus.*
- Spring and fall: *Campylobacter jejuni.*
- Winter: *Clostridium perfringens, Yersinia enterocolitica.*

PREDOMINANT AGE: Varies with specific agent.
NEONATAL INFECTION: Rare but severe with *Shigella* and *Salmonella* spp.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Any combination of GI symptoms and fever.
- Specific organisms suspected on the basis of the incubation period and predominant symptoms (Table EF1-9), although a great deal of overlap exists.
  1. Short incubation period (1 to 6 hr): involve the ingestion of preformed toxin; noninvasive.
     a. *S. aureus:* nausea, profuse vomiting, and abdominal cramps common; diarrhea possible, but fever uncommon; usually resolves within 24 hr; foods implicated in outbreaks include meats, mayonnaise, and cream pastries.
     b. *B. cereus:* two forms, a short incubation (emetic) form (characterized by vomiting and abdominal cramps in virtually all patients, diarrhea in one third of patients, fever uncommon) and a long incubation (diarrheal) form; illness usually mild, resolves within 12 hr; unrefrigerated rice most often implicated as vehicle.
  2. Moderate incubation period (8 to 16 hr): involves the in vivo production of toxin; noninvasive.
     a. *C. perfringens:* severe crampy abdominal pain and watery diarrhea common; fever and vomiting unlikely; symptoms usually resolving within 24 hr; outbreaks invariably related to cooked meat or poultry that is allowed to cool without refrigeration; most cases in the fall and winter months. *C. perfringens* is the third most common cause of foodborne illness in the United States.
     b. *B. cereus:* diarrheal (or long incubation) form most commonly beginning with diarrhea, abdominal cramps, and occasionally vomiting; fever uncommon; usually resolves within 24 hr; the responsible food is usually fried rice.
  3. Long incubation period (>16 hr): some toxin-mediated, some invasive.
- Toxin-producing organisms include:
  (1) *C. botulinum:* should be considered when a diarrheal illness coincides with or precedes paralysis; severity of illness related to the quantity of toxin ingested; characteristic cranial nerve palsies progressing to a descending paralysis; fever usually absent; usually associated with home-canned foods.
  (2) Enterotoxigenic *E. coli* (ETEC): most common cause of travelers' diarrhea; after 1- to 2-day incubation period, abdominal cramps and copious diarrhea occur; vomiting and fever uncommon; usually resolves after 3 to 4 days; vehicle usually unbottled water or contaminated salad or ice.
  (3) Enterohemorrhagic *E. coli* (EHEC): can cause severe abdominal cramps and watery diarrhea, which may eventually become bloody; bacteria (strain O157:H7) are noninvasive; no fever; illness may be complicated by hemolytic-uremic syndrome; associated with contaminated beef.
  (4) *V. cholerae:* varies from a mild, self-limited illness to life-threatening cholera; diarrhea, nausea, and vomiting, abdominal cramps, and muscle cramps; no fever; severe cases may progress to shock and death within hours of onset; survivors usually have resolution of symptoms in 1 wk; U.S. cases are either imported or result from ingestion of imported food.
- Invasive organisms include:
  (1) *Salmonella:* associated most often with nontyphoidal strains; incubation period generally 12 to 48 hr; nausea, vomiting, diarrhea, and abdominal cramps typical; fever possible; outbreaks of gastroenteritis related to contaminated poultry, meat, and dairy products.
  (2) *Shigella:* asymptomatic infection possible, but some with fever and watery diarrhea that may progress to bloody diarrhea and dysentery; with mild illness, usually self-limited, resolves in a few days; with severe illness, may develop complications; transmission usually from person to person but can occur via contaminated food or water.
  (3) *C. jejuni:* the most common food-borne bacterial pathogen; incubation period is about 1 day, then a prodrome of fever, headache, and myalgias; intestinal phase marked by diarrhea associated with fever, malaise, and abdominal pain; diarrhea mild to profuse and bloody; usually resolves in about 7 days, but relapse is possible; associated with undercooked meats and poultry, unpasteurized dairy products, and drinking from freshwater streams.
  (4) *Y. enterocolitica* and *Y. pseudotuberculosis:* infrequent causes of enteritis in the United States; children affected more often than adults; fever, diarrhea, and abdominal pain lasting 1 to 3 wk; some with mesenteric adenitis that mimics acute appendicitis; contaminated food or water is usually responsible.
  (5) *V. parahaemolyticus:* In the United States, most outbreaks in coastal states or on cruise ships during the summer months; incubation period usually >1 day, followed

TABLE F1-8 Pathogenic Mechanisms in Bacterial Foodborne Disease

Preformed Toxin	Toxin Production in Vivo	Tissue Invasion	Toxin Production and/or Tissue Invasion
Staphylococcus aureus	*Clostridium perfringens*	*Campylobacter jejuni*	*Vibrio parahaemolyticus*
Bacillus cereus (short incubation)	*B. cereus* (long incubation)	*Salmonella*	*Yersinia enterocolitica*
Clostridium botulinum	*C. botulinum* (infant botulism)	*Shigella*	
	Enterotoxigenic *Escherichia coli*	Invasive *E. coli*	
	Vibrio cholerae 01 or 0139		
	V. cholerae non-01		
	Shiga toxin–producing *E. coli*		

From Mandell GL et al: *Principles and practice of infectious diseases,* ed 6, Philadelphia, 2005, Churchill Livingstone.

by explosive watery diarrhea in the majority of cases; nausea, vomiting, abdominal cramps, and headache also common; fever less common; usually resolves by 1 wk; related to ingestion of seafood.

(6) Enteroinvasive *E. coli* (EIEC): a rare cause of disease in the United States; high incidence of fever and bloody diarrhea; may resemble bacillary dysentery.

(7) *V. vulnificus:* may cause serious, often fatal illness in persons with chronic liver disease; GI symptoms usually absent, but fever, chills, hypotension, and hemorrhagic skin lesions possible; patients with liver disease or at increased risk of developing liver disease should avoid eating raw oysters.

ETIOLOGY

Classically categorized as either inflammatory (invasive) or noninflammatory:

- Noninflammatory: *B. cereus, S. aureus, C. botulinum, C. perfringens, V. cholerae,* enterotoxigenic *E. coli* (ETEC), and enterohemorrhagic *E. coli* (EHEC); toxin-producing organisms that are noninvasive; fecal leukocytes are not seen.
- Inflammatory: *Campylobacter,* enteroinvasive *E. coli* (EIEC), *Salmonella, Shigella, V. parahaemolyticus,* and *Yersinia;* cause disease by invasion of intestinal tissue; fecal leukocytes are seen.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Gastroenteritis caused by viruses (Norwalk, Noro, or rotavirus), parasites *(Amoeba histolytica, Giardia lamblia),* or toxins (ciguatoxins, mushrooms, heavy metals).

LABORATORY TESTS

- Test stool for fecal leukocytes to help narrow the differential diagnosis:
  1. Send stool for culture and for ova and parasites.
  2. Send stool for *C. difficile* toxin in patients with current or recent antibiotic use.
  3. NOTE: Some pathogens are not identified on routine stool culture; laboratory should be advised if *Yersinia, C. botulinum, Vibrio,* or enterohemorrhagic *E. coli* (O157:H7) are suspected.
  4. Finding *B. cereus, C. perfringens,* or *E. coli* in stool is of little value, because these may be part of the normal bowel flora.
- If botulism suspected, send food, serum, and stool for toxin assay.
- Blood cultures are needed for all febrile patients.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Adequate rehydration is the mainstay of therapy.

ACUTE GENERAL Rx

- Gastroenteritis caused by the following organisms requires no antimicrobial treatment: *B. cereus, S. aureus, C. perfringens, V. parahaemolyticus, Yersinia,* and enterohemorrhagic and enteroinvasive *E. coli.*
- The usual cause of traveler's diarrhea is enterotoxigenic *E. coli.* Although usually a self-limited illness, antibiotics can shorten the course in patients with fever or dysentery.
  1. Azithromycin 1000 mg in a single oral dose or
  2. SMX/TMP one DS tab bid for 3 days or
  3. Ciprofloxacin 500 mg PO bid for 3 days.
- The mainstay of therapy for cholera is fluid replacement. Antibiotics should be given to decrease shedding and duration of illness.
  1. Doxycycline 300 mg in a single dose or 100 mg PO bid for 3 days.
  2. SMX/TMP one DS tab bid for 3 days.
- Treatment is not indicated for *Salmonella* gastroenteritis. Patients who are at high risk of developing bacteremia may be treated for 48 to 72 hr (see "Salmonellosis").
- Although shigellosis tends to be a self-limited illness, antibiotics shorten the course of illness and may limit transmission of the illness (see "Shigellosis").
- Those with moderate or severe *Campylobacter* diarrhea may benefit from treatment.
  1. Azithromycin 500 mg qd for 3 days or
  2. Erythromycin 500 mg PO qid for 5 days or
  3. Ciprofloxacin 500 mg PO bid for 5 days.
- *V. vulnificus* sepsis should be treated with:
  1. Doxycycline 100 mg IV bid for 2 wk.
  2. Ceftazidime 2 g IV q8h for 2 wk.
- For suspected botulism, antitoxin should be administered early (see "Botulism").

CHRONIC Rx

Patients with *Salmonella* infections may become carriers and may require treatment (see "Salmonellosis").

DISPOSITION

- Most infections are self-limited and do not require therapy.
- In immunocompromised host or patient with underlying disease, serious complications are possible.
- Postinfectious syndromes are important with some infections:
  1. Reiter's syndrome: *Salmonella, Shigella, Campylobacter, Yersinia* spp.; more common in genetically susceptible host (HLA-B27+).
  2. Guillain-Barré syndrome: *Campylobacter* spp.

REFERRAL

If more than a mild illness.

PEARLS & CONSIDERATIONS

COMMENTS

- Grossly underreported and undiagnosed.
- All cases to be reported to the local health department.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Bacterial Food Poisoning (Patient Information)
Salmonellosis (Related Key Topic)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Allos BM, et al.: Surveillance for sporadic foodborne disease in the 21st century: the FoodNet perspective, *Clin Infect Dis* 38(suppl 3):pS115, 2004.

Centers for Disease Control and Prevention (CDC): Surveillance for food borne disease outbreaks—United States. 1998-2008.

MMWR Morb Mortal Wkly Rep 62, Number SS2-June 2013 Chiang YC, et al.: PCR primers for the detection of staphylococcal enterotoxins K, L, and M and survey of staphylococcal enterotoxin types in *Staphylococcus aureus* isolates from food poisoning cases in Taiwan, *J Food Prot* 69(5):1072, 2006.

DuPont HL: Acute infectious diarrhea in immunocompetent adults, *N Engl J Med* 370:1532–1540, 2014.

Ikeda T, et al.: Mass outbreak of food poisoning disease caused by small amounts of staphylococcal enterotoxins A and H, *Appl Environ Microbiol* 71(5):2793, 2005.

Saito N, et al.: An outbreak of food poisoning caused by an enteropathogenic *Escherichia coli* O115:H19 in Miyagi Prefecture, *Jpn J Infect Dis* 58(3):189, 2005.

TABLE EF1-9 Major Food-Borne Microbes by the Principal Presenting Gastrointestinal Symptom in Immunocompetent Adults

	Organism	Source/Vehicles	Incubation Period	Diagnosis	Recovery
Vomiting	*Staphylococcus aureus*	Prepared food (e.g., sandwiches)	2-4 h	Diagnosis usually clinical for all organisms	<24 h
	Bacillus cereus	Rice, meat	1-6 h		2-3 days
	Norovirus	Shellfish, prepared food	24-48 h		2-3 days
Watery diarrhea	*Clostridium perfringens*	All by contaminated food and water	8-22 h	Stool culture	2-3 days
	Enterotoxigenic *Escherichia coli* (ETEC)		24 h		1-4 days
	Enteric viruses		Variable		Variable
	Cryptosporidium parvum and C. hominis		5-28 days		7-14 days
	Cyclospora cayetanensis		7 days		Weeks to months
	Yersinia enterocolitica		2-14 h		1-22 days
	Vibrio cholerae		Hours–6 days		2-3 days
Diarrhea with blood (dysentery)	*Campylobacter jejuni*	Cattle and poultry—meat, milk	48-96 h	Stool culture	3-5 days
	Nontyphoidal *Salmonella*	Cattle and poultry—eggs, meat	12-48 h		3-6 days, may be up to 2 weeks
	Enterohemorrhagic *E. coli* (usually serotype O157:H7)*	Cattle—meat, milk	12-48 h		10-12 days
	Shigella spp.	Contaminated food and water	24-48 h		7-10 days
	Vibrio parahaemolyticus	Contaminated seafood	2-48 h		1-12 days
Nongastrointestinal manifestations	*Clostridium botulinum* paralysis due to neuromuscular blockade	Environment—bottled or canned food	18-24 h	Toxin in food or feces	10-14 days
	Listeria monocytogenes meningitis	Contaminated packaged chilled foods	Up to 6 weeks	CSF culture	Variable

*A low threshold for suspecting *E. coli* O157 infection in gastroenteritis is vital because it can cause serious complications. Between 1% and 15% progress to hemolytic uremic syndrome (acute kidney injury, hemolytic anemia, thrombocytopenia). Antibiotics are contraindicated in *E. coli* O157 infection.

From Ballinger A: *Kumar & Clark's essentials of clinical medicine,* ed 6, Edinburgh, 2012, Saunders.

BASIC INFORMATION

DEFINITION

Friedreich's ataxia is the most common hereditary neurodegenerative ataxic disorder, caused by degeneration of dorsal root ganglions, posterior columns, spinocerebellar and corticospinal tracts, and large sensory peripheral neurons.

ICD-9CM CODES
334.0 Friedreich's ataxia
ICD-10CM CODES
G11.1 Early-onset cerebellar ataxia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Estimated at one in 30,000 whites
PEAK INCIDENCE: 8 to 15 yr
PREVALENCE (IN U.S.): Two to four per 100,000. Carrier rate 1:120 to 1:160; lower prevalence in Asians and people of African descent.
PREDOMINANT SEX: Males and females affected equally
GENETICS: Autosomal recessive; 96% of affected patients are homozygous and 4% are compound heterozygous (two different mutations). Trinucleotide repeat expansion accounts for 94% to 98% of cases, whereas point mutations account for 2% to 6% of cases.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Onset of progressive appendicular and gait ataxia, with absent muscle stretch reflexes in the lower extremities.
- With disease progression (within 5 yr): dysarthria, distal loss of position and vibration sense, pyramidal leg weakness, areflexia in all four limbs, and extensor plantar responses.
- Common findings: progressive scoliosis, distal atrophy, pes cavus, and cardiomyopathy (symmetric concentric hypertrophic form in most cases).
- Insulin-requiring diabetes mellitus may occur in 10% of patients, with glucose intolerance occurring in an additional 10% to 20%.

ETIOLOGY

- Genetic: frataxin gene is localized to the centromeric region of chromosome 9q13.
- Normal sequence has six to 27 repeats; abnormal sequence has 120 to 1700 GAA repeats.
- Frataxin deficiency leads to impaired mitochondrial iron homeostasis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Charcot-Marie-Tooth disease type 2
- Abetalipoproteinemia
- Severe vitamin E deficiency with malabsorption
- Early-onset cerebellar ataxia with retained reflexes
- Autosomal-dominant cerebellar ataxia (spinocerebellar ataxia)

WORKUP

- Diagnostic criteria include electrophysiologic evidence for a generalized axonal sensory or sensorimotor neuropathy.
- ECG may show widespread T-wave inversion and evidence of left ventricular hypertrophy. ECG abnormalities are present in 65% of patients.
- Sural nerve biopsy shows loss of large myelinated fibers.
- Specific gene testing for the expanded GAA trinucleotide repeat.

LABORATORY TESTS

- Electromyography or nerve conduction study
- ECG and echocardiogram
- Peripheral blood smear for acanthocytes
- Lipid profile
- Two-hour glucose tolerance test
- Vitamin E levels (if necessary)

IMAGING STUDIES

MRI of the spinal cord may demonstrate spinal cord atrophy with essentially normal cerebrum, brainstem, and cerebellum (Fig. F1-15).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Surgical correction of scoliosis and foot deformities in selected patients

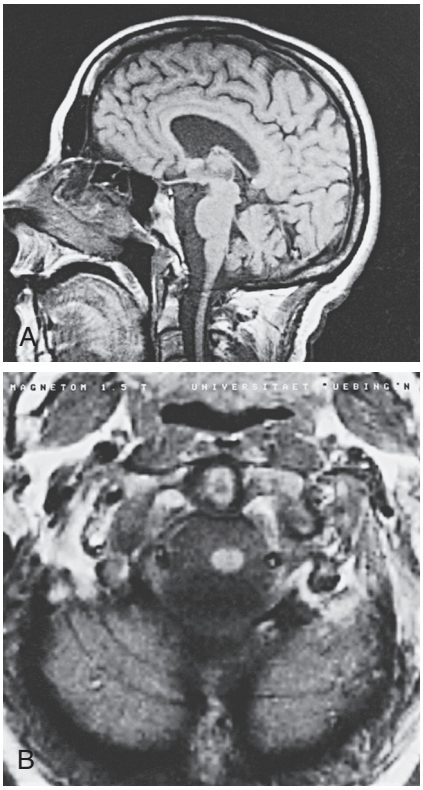


FIGURE F1-15 T1 MRI of the brain (midsagittal section) and spinal cord (axial slice at level of the dens) showing severe shrinkage of the cervical cord, but the cerebellum and brainstem are of normal size. (From Goetz CG: *Textbook of clinical neurology,* Philadelphia, 1999, Saunders.)

- Prosthetic devices as required (e.g., ankle-foot orthosis for footdrop)
- Physical therapy
- Communication devices for patients with severe dysarthria

ACUTE GENERAL Rx

None established.

- An antioxidant, idebenone (short-chain analogue of coenzyme Q10), administered orally at 5 to 20 mg/kg/day with or without vitamin E has demonstrated inconsistent effects on neurologic, cardiac, and psychosocial outcome measures in clinical trials.
- Further research with various antioxidants and iron chelators is ongoing. An open-label pilot study of antioxidants (coenzyme Q10, 400 mg/day, and vitamin E, 2100 U/day) in a small cohort demonstrated slowing in progression of generalized ataxia and kinetic dysfunction and significant improvement in cardiac function with unaltered deterioration in posture, gait, and hand dexterity.

CHRONIC Rx

Chronic management of congestive heart failure is required. Cardiac arrhythmias will warrant pacemaker implantation.

DISPOSITION

- Loss of ambulation typically occurs within 15 yr of symptom onset, and 95% are wheelchair bound by age 45 yr.
- Life expectancy is reduced, particularly if heart disease with or without diabetes mellitus is present.

REFERRAL

- If uncertain about diagnosis
- For genetic counseling (recommended if available)

PEARLS & CONSIDERATIONS

Friedreich's ataxia should be considered in all preadolescent and adolescent children presenting with progressive ataxia. Early recognition of cardiac failure and arrhythmias and institution of appropriate therapy helps prolong survival.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Friedreich's Ataxia (Patient Information)

AUTHOR: **FARIHA ZAHEER, M.D.**

SUGGESTED READINGS

Hart PE et al.: Antioxidant treatment of patients with Friedreich ataxia: four-year follow-up, *Arch Neurol* 62:621, 2005.

Lynch DR et al.: A phase 3, double-blind, placebo-controlled trial of idebenone in Friedreich ataxia, *Arch Neurol* 67:941–947, 2010.

BASIC INFORMATION

DEFINITION

Frostbite represents tissue injury (or death) from freezing and vasoconstriction induced by severe environmental cold exposure.

SYNONYMS

Cold-induced tissue injury.

ICD-9CM CODES
991.3 Frostbite
ICD-10CM CODES
T35.0 Superficial frostbite involving multiple body regions
T34 Frostbite with tissue necrosis
T34.5 Frostbite with tissue necrosis of wrist and hand
T34.8 Frostbite with tissue necrosis of ankle and foot
T34.9 Frostbite with tissue necrosis of other and unspecified sites
T35.4 Superficial frostbite involving multiple body regions
T33.9 Superficial frostbite of unspecified sites, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

- Environmental factors include windchill factor, temperature, duration of exposure, altitude, and degree of wetness. Hands and feet account for 90% of injuries; nose, cheeks, ears, and male genitalia are also more susceptible.
- Host factors include psychiatric illness, neuroleptic and sedative drugs (especially alcohol), immobility, previous frostbite, malnutrition, tobacco use, peripheral neuropathy, peripheral vascular disease, diabetes, exhaustion, and constricting clothing and footwear.

Patients at the extremes of age are at greatest risk, but frostbite is more common in adults aged 30 to 49.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Frostbite may be classified into four degrees of injury severity (determined after rewarming) or, more practically, into *superficial* and *deep* groups. This can only be accurately determined after rewarming as initially most frostbite injuries appear similar.
- *Superficial* frostbite involves the skin and subcutaneous tissue. The frozen part is waxy, white (or mottled), and firm but soft and resilient below the surface when gently depressed. After rewarming, there is an initial hyperemia that may be followed by swelling and formation of superficial blisters with clear or milky fluid within 6 to 24 hr (Fig. F1-16). There is no ultimate tissue loss.
- *Deep* frostbite extends into the dermis and may involve muscles, nerves, tendons, or bones. The skin may be hard or wooden, without tissue resilience. Nonblanching cyanosis, hemorrhagic blisters, tissue necrosis (Fig. F1-17), and gangrene may develop. Affected tissue has a poor prognosis and debridement or amputation is generally required.
- Patients initially feel numbness, prickling, and itching. More severe injury can produce paresthesias and stiffness, with burning or throbbing pain on thawing.

ETIOLOGY

Two mechanisms of tissue injury:

1. Freeze-thaw damage. Intracellular ice crystallization leads to cell membrane lysis and cell death followed by thaw-initiated ischemia-reperfusion injury.
2. Vascular stasis and ischemia. Vessels fluctuate between constriction and dilation (the "hunting response") with associated vascular leak and coagulation; ischemia/infarction ensues from a cascade of inflammatory mediators (prostaglandin F, thromboxane A2, bradykinins, histamine) that contribute to reperfusion injury and thrombus formation and ultimately lead to destruction of the microcirculation and cell death.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Frostnip: a superficial nonfreezing cold injury associated with intense vasoconstriction and characterized by frost forming on the surface of the skin. Transient numbness, tingling, and pallor resolve quickly with warming.
- Pernio (chilblains): self-limited, cold-induced vasculitis associated with purple plaques or nodules, often affecting dorsum of hands and feet; seen with prolonged cold exposure to above-freezing temperatures.
- Cold immersion (trench foot): caused by ischemic injury resulting from sustained, severe vasoconstriction in appendages exposed to wet cold at temperatures above freezing.

WORKUP

- Laboratory work is not indicated unless the patient has systemic hypothermia.
- Imaging with MRA or triple-phase bone scan (with technetium) is recommended within the first 2 days to predict tissue viability in cases of severe frostbite or when thrombolysis is being considered. (MRA has the advantage of showing occluded vessels and viability of surrounding tissues.).

FIGURE F1-16 Large, clear frostbite blisters on the right hand. (From Rosen P [ed]: *Emergency medicine,* ed 4, St Louis, 1998, Mosby.)

TREATMENT (3 PHASES)

1. FIELD MANAGEMENT

- Prioritize treatment of hypothermia (core body temperature <35° C) with systemic and adjunctive rewarming measures if available (e.g., warmed, humidified oxygen, heated IV saline [45° C], and warming blankets) before thawing frostbitten extremities.
  - Shelter patient out of wind and give warm fluids.
- Remove constricting or wet clothing and jewelry from affected digits.
  - Place cold extremity in a companion's armpit or groin for 10 minutes, then replace dry gloves/boots.
- Insulate, splint, and elevate affected areas.
  - Never rub or massage the affected area. Avoid dry heat (e.g., fires and heaters).
- Avoid thawing if there is any risk of refreezing and avoid ambulation on thawed lower extremities (unless only distal toes affected).
- Administer pain medication and topical aloe if available.
- Box EF1-1 describes the Alaska State Guidelines for prehospital treatment of frostbite.

2. REWARMING

- Rapid rewarming is the key objective.
- Immerse affected area in circulating warm water bath with or without a mild antibacterial agent (e.g., chlorhexidene or povidone-iodine) maintained at 37° to 39° C for at least 15 to 30 min up to 1 hour, until all tissues are thoroughly rewarmed and pliable with a red-purple color. Active motion during rewarming is advisable; massage is not.
- Analgesics recommended during rewarming (ibuprofen and possibly narcotics).

3. POST-THAW Rx

- Tetanus prophylaxis and topical antibiotics if potentially contaminated skin wound.
- Consider systemic antibiotics for patients with significant trauma or signs of infection.

FIGURE F1-17 Third- and fourth-degree frostbite with tissue death. Note demarcation beyond the interphalangeal joint. (From Cameron, JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

TABLE F1-10 Frostbite Management: Drugs, Doses, and Modes of Action and Rationale*

Intervention	Dose	Action
Aspirin	75-250 mg orally once daily	Antiplatelet agent, improve rheology
Ibuprofen	400 mg bid or tid orally	Antiprostaglandin effect
Aloe vera gel or cream	With dressing changes every 6 hr	Topical antiprostaglandin effect
Oxygen	2 L/min above 4000 m (13,123 ft) or when Spo_2 is below 90%	Improve tissue oxygenation
Hyperbaric oxygen therapy	2-2.5 atm 1-2 hr daily	Improve tissue oxygenation, improve rheology
Iloprost	2-10 mg/hr IV titrated against side effects	Vasodilator, improve rheology
Nitroglycerin	100 mcg IA single dose	Vasodilator
Papaverine	300 mg over 1 hr IA	Vasodilator
Reserpine	0.1 to 0.25 mg once daily	Vasodilator
Buflomedil	400 mg IV **or** 300 mg bid orally	Vasodilator, improve rheology
Pentoxifylline	400 mg tid orally for 2-6 weeks	Vasodilator, improve rheology
10% Dextran 40	20 mL bolus, 20 mL/hr IV	Improve rheology
t-PA	1 mg/hr IA or IV	Thrombolytic agent
LMW heparin	Prophylactic dosage subcutaneously	DVT prevention, anticoagulant
	Therapeutic dosage subcutaneously	Maintain patency of recently thrombolized vessels
Tetanus prophylaxis		

bid, Twice a day; *DVT,* deep vein thrombosis; *IA,* intra-arterially; *IV,* intravenously; *LMW,* low molecular weight; *Spo_2,* oxygen saturation as measured by pulse oximetry; *tid,* 3 times a day; *t-PA,* tissue plasminogen activator.

*This table is intended to be used as a potential frostbite formulary reference, not as a protocol for treatment. See text for further discussion.

From Auerbach P: *Wilderness medicine, Expert Consult premium edition—enhanced online features and print,* Philadelphia, 2012, Saunders.

- Debride broken clear vesicles and avoid disrupting intact blisters (especially hemorrhagic ones) unless they interfere with mobility.
- Topical aloe vera (a potent anti-prostaglandin agent) q6h and ibuprofen (a thromboxane inhibitor) 400 to 600 mg bid to tid (or daily aspirin) can be given until wounds are healed.
- Thrombolytic therapy. If <24 hr from thawing in a patient with severe frostbite involving an extremity (e.g., extending proximally to PIP joints), imaging (with MRA or technetium bone scan) to assess for arterial compromise followed by intra-arterial or intravenous tPA appears to improve reperfusion considerably and reduce subsequent digit amputation.
- Vasodilator therapy. A prospective study of 47 patients comparing prostacyclin and aspirin with or without tPA showed better results with prostacyclin alone; those authors endorse treatment with aspirin plus prostacyclin and consideration of adding tPA for severe frostbite. A direct comparison of prostacyclin vs tPA has not been done.
- Daily dressing changes with dry, sterile, noncompressive, and nonadherent dressings. Splint and elevate hands and feet to reduce edema and separate digits with cotton gauze. Avoid any abrasion to limit risk of infection.
- Whirlpool hydrotherapy with warm water (37° to 39° C) and an antiseptic for 30 min bid until there is a clear demarcation of necrotic tissues or evidence of tissue healing.
- Gentle, progressive physical therapy after edema resolves.
- Keep site warm, and avoid all vasoconstrictors, including nicotine.
- Dextran, heparin, warfarin, sympathectomy, and hyperbaric oxygen are of potential but unproven benefit.
- Table F1-10 describes drugs used in frostbite management.

DISPOSITION

A majority of patients have long-term residual symptoms, including cold hypersensitivity, neuropathic pain, sensory deficits, hyperhidrosis, secondary Raynaud's disease, localized osteoporosis, edema, hair or nail deformities, and (rarely) arthritis. Treatment with tricyclics, gabapentin, calcium channel blockers, and careful protection from further cold exposure may be helpful.

REFERRAL

- Hospitalize for hypothermia or deep frostbite; a burn unit is best.
- Surgical decisions regarding amputation should be deferred until demarcation of viable tissue is clear (6 to 12 weeks) unless refractory pain, sepsis, or gangrene occurs.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Frostbite (Patient Information)

AUTHOR: **MICHAEL P. JOHNSON, M.D.**

SUGGESTED READINGS

Bruen KJ et al.: Reduction of the incidence of amputation in frostbite injury with thrombolytic therapy, *Arch Surg* 142(6):546, 2007.

Cauchy E, Cheguillaume B: A controlled trial of a prostacyclin and rt-PA in the treatment of severe frostbite, *N Engl J Med* 364:189–190, 2011.

Hallam MJ et al.: Managing frostbite, *BMJ* 341:1151, 2010.

Ingram BJ et al.: Recognition and treatment of freezing and nonfreezing cold injuries, *Am College of Sports Medicine* 12:125–130, 2013.

Handford C et al.: Frostbite: a practical approach to hospital management, *Extrem Physiol Med* 3:7, 2014.

Jurkovich GJ: Environmental cold-induced injury, *Surg Clin North Am* 87(1):247, 2007.

McIntosh S et al.: Wilderness Medical Society practice guidelines for the prevention and treatment of frostbite, *Wild Environ Med* 22:156–166, 2011.

BOX EF1-1 Alaska State Guidelines for Prehospital Treatment of Frostbite

First Responder/Emergency Medical Technician—I, II, III/Paramedic/Small Bush Clinic

Evaluation and Treatment

A Anticipate, assess, and treat the patient for hypothermia, if present.

B Assess the frostbitten area carefully because the loss of sensation may cause the patient to be unaware of soft tissue injuries in that area.

C Obtain a complete set of vital signs and the patient's temperature.

D Remove jewelry and clothing, if present, from the affected area.

E Obtain a patient history, including the date of the patient's last tetanus immunization.

F If there is frostbite distal to a fracture, attempt to align the limb unless there is resistance. Splint the fracture in a manner that does not compromise distal circulation.

G Determine whether rewarming the frostbitten tissue can be accomplished in a medical facility. If it can, transport the patient while protecting the tissue from further injury from cold or impacts.

H If the decision is made to rewarm frostbitten tissue in the field, you should prepare a warm water bath in a container large enough to accommodate the frostbitten tissues without them touching the sides or bottom of the container. The temperature of the water bath should be 99° to 102° F (37° to 39° C).

- Generally, patients with frostbite do not require opiates for pain relief; they occasionally need non-opiate pain medication or anxiolytics. If possible, consult a physician regarding the administration of oral analgesics, such as acetaminophen, ibuprofen or aspirin. Aspirin or ibuprofen may help improve outcomes by blocking the arachidonic acid pathway.
- Immersion injury or frostbite with other associated injuries may produce significant edema and high pain levels. These patients may need opiate pain medications for initial treatment. In this case, advanced life support personnel should administer morphine or other analgesics in accordance with physician-signed standing orders or online medical control.

I A source of additional warm water must be available.

J Water should be maintained at approximately at 99° to 102° F (37° to 39° C) and gently circulated around the frostbitten tissue until the distal tip of the frostbitten part becomes flushed.

K Pain after rewarming usually indicates that viable tissue has been successfully rewarmed.

L After rewarming, let the frostbitten tissues dry in the warm air. Do **not** towel dry.

M After thawing, tissues that were deeply frostbitten may develop blisters or appear cyanotic. Blisters should not be broken and must be protected from injury.

N Pad between affected digits and bandage affected tissues loosely with a soft, sterile dressing. Avoid putting undue pressure on the affected parts.

O Rewarmed extremities should be kept at a level above the heart, if possible.

P Protect the rewarmed area from refreezing and other trauma during transport. A frame around the frostbitten area should be constructed to prevent blankets from pressing directly on the injured area.

Q Do not allow an individual who has frostbitten feet to walk except when the life of the patient or rescuer is in danger. Once frostbitten feet are rewarmed, the patient becomes nonambulatory.

Frozen Shoulder ALG EBM PTG

BASIC INFORMATION

DEFINITION

Frozen shoulder is a clinical diagnosis that describes a stiffened glenohumeral (GH) joint characterized by shoulder pain and restricted passive and active range of motion (ROM) (Fig. F1-18). The condition is categorized as primary or idiopathic when there is no underlying cause. Secondary causes can result from shoulder injuries, shoulder surgery and other surgeries, endocrine disorders such as diabetes mellitus and thyroid disease, autoimmune diseases, neurologic disease such as stroke and Parkinson's disease and antiretroviral therapy used to treat HIV.

SYNONYMS

Adhesive capsulitis
Periarthritis.
Pericapsulitis.
Check-rein shoulder.
Bursitis Duplay.

ICD-9CM CODES
726.0 Adhesive shoulder capsulitis
ICD-10CM CODES
M75.00 Adhesive capsulitis of unspecified shoulder

EPIDEMIOLOGY & DEMOGRAPHICS

- Prevalence of frozen shoulder is 2% to 5% in the general population and a higher incidence of up to 10% to 20% in diabetics.
- Predominant sex: Females are more commonly affected than males.
- There is a peak incidence in the mid-50s.

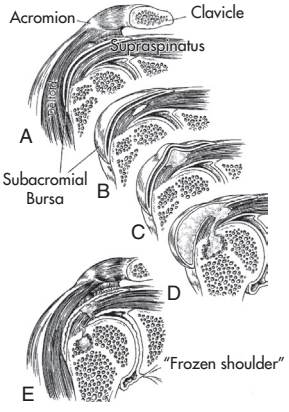


FIGURE F1-18 Sequence of events terminating in frozen shoulder. A, Normal structures of the shoulder. **B,** Supraspinatus tendonitis, sometimes calcific, in the "critical zone." **C,** Spread of inflammation to the tendon sheath and a bulge into the floor of the subacromial bursa. **D,** Rupture into the subacromial bursa and extension of the inflammatory process as an osteitis into the humeral head and greater tuberosity. **E,** Frozen shoulder with involvement of tendons, bursa, capsule, synovium, and muscle with fibrous contracture and markedly diminished volume of the shoulder joint space. (From Noble J [ed]: *Primary care medicine,* ed 2, St Louis, 1996, Mosby.)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The natural history of frozen shoulder occurs in three phases that usually include full resolution of pain and return of function.

- Painful phase: There is a gradual onset of severe shoulder pain that is usually worse at night and difficulty lying on the affected side. This phase may last from weeks up to 10 months.
- Frozen or intermediate phase: Progressive shoulder stiffness and limitation in range of motion that may last for 1 year. Pain usually is less during this phase. In addition to tenderness on palpation of the GH joint, exam findings may include disuse atrophy of the deltoid and supraspinatus, with the arm held in adduction and internal rotation. There is variable loss in the degrees of restricted active and passive shoulder abduction and external rotation.
- Thawing or Recovery phase: Overall improvement in pain and increase in ROM. This may last for 5-24 months.

ETIOLOGY

- The pathology of frozen shoulder is not completely understood. The most agreed-upon theory involves a chronic inflammatory response with fibroblastic proliferation that results in thickening and contraction of the glenohumeral joint capsule and ultimately, significant loss of range of motion of the joint.
- Fig. F1-18 illustrates the sequence of events terminating in frozen shoulder.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Trauma: shoulder sprain, dislocation, glenoid labrum tear, rotator cuff tear.
- Usage, degenerative, and age-related disorders: GH osteoarthritis, avascular necrosis of the humeral head, rotator cuff tendinopathy.
- Mechanical: calcific tendonitis, shoulder impingement or derangement.
- Neoplasm: Pancoast tumor.
- Cervical spondylosis or other cervical disk disease.
- Brachial neuritis.
- Milwaukee shoulder.

WORKUP

- Laboratory studies are not needed but can contribute to the diagnosis if an underlying condition such as diabetes, cardiovascular disease, or thyroid disease is suspected.
- A subacromial injection test helps to distinguish a frozen shoulder from subacromial disorders.
- Radiographic evaluation of the shoulder with plain x-rays, musculoskeletal ultrasound, MRI, or MR arthrography should be considered to rule out other pathologic conditions.
- Characteristic MRI findings can include thickening of the coracohumeral ligament and the joint capsule.
- Musculoskeletal ultrasound can be helpful in demonstrating characteristic soft-tissue findings and limitation in the movement of the supraspinatus tendon during shoulder abduction on dynamic imaging.

TREATMENT

NONPHARMACOLOGIC THERAPY

Patient education is important in prevention and to improve compliance and outcome expectation.

ACUTE GENERAL Rx

- Initial conservative therapy with heat, analgesics (generally NSAIDs), and physical therapy with passive stretching and ROM exercises.
- Course of oral corticosteroids.
- Local or intraarticular steroid and lidocaine injection into the subacromial space with or without hydrodilation.
- When conservative treatment fails, the following surgical methods may be considered:
  1. Shoulder manipulation under anesthesia (rarely needed).
  2. Arthroscopic and, rarely, open capsular release.

DISPOSITION

- The condition is mostly self-limited. Most patients regain 90% of shoulder motion over time and have improved pain, but symptoms can last from several months to more than 3 years.
- Recurrence in the same shoulder is rare, although it can affect the opposite limb in up to 6% to 17% of patients.

REFERRAL

Rheumatology or orthopedic consultation in patients with resistant disease who fail to respond to conservative treatment.

PEARLS & CONSIDERATIONS

COMMENTS

- Arthroscopic shoulder release has been shown to provide beneficial clinical outcome for patients with refractory adhesive capsulitis.

EVIDENCE

Available at www.expertconsult.com.

SUGGESTED READINGS

Available at www.expertconsult.com.

RELATED CONTENT

Frozen Shoulder (Patient Information)
Rotator Cuff Syndrome (Related Key Topic)

AUTHOR: **ANISHKA S. ROLLE, M.D.**

EVIDENCE

Abstract[1]

Background:

A variety of therapeutic interventions is available for restoring motion and diminishing pain in patients with frozen shoulder. An overview article concerning the evidence for the effectiveness of these interventions is lacking.

Objective:

To provide an evidence-based overview regarding the effectiveness of conservative and surgical interventions to treat the frozen shoulder.

Methods:

The Cochrane Library, PubMed, Embase, Cinahl, and Pedro were searched for relevant systematic reviews and randomized clinical trials (RCTs). Two reviewers independently selected relevant studies, assessed the methodologic quality, and extracted data. A best-evidence synthesis was used to summarize the results.

Results:

Five Cochrane reviews and 18 RCTs were included. These reviews and clinical trials studied the effectiveness of oral medication, injection therapy, physiotherapy, acupuncture, arthrographic distension, and suprascapular nerve block (SSNB).

Conclusions:

We found strong evidence for the effectiveness of steroid injections and laser therapy in short-term follow-up and moderate evidence for steroid injections in mid-term follow-up. Moderate evidence was found in favor of mobilization techniques in the short term and long term; for the effectiveness of arthrographic distension alone and as an addition to active physiotherapy in the short term; for the effectiveness of oral steroids compared with no treatment or placebo in the short term; and for the effectiveness of SSNB compared with acupuncture, placebo, or steroid injections. For other commonly used interventions, no or only limited evidence of effectiveness was found. Most of the included studies reported short-term results, whereas symptoms of frozen shoulder may last up to 4 years. High-quality RCTs studying long-term results are clearly needed in this field. Ⓐ

Evidence-Based Reference

Favejee MM et al.: Frozen shoulder: the effectiveness of conservative and surgical interventions—systematic review, *Br J Sports Med* 45(1):49–56, 2011. Ⓐ.

SUGGESTED READINGS

Cohen BL: Treatment of shoulder complaints, *Lancet* 363:492, 2004.

Ewald A: Adhesive capsulitis: a review, *Am Fam Physician* 83(4):417–422, 2011.

Hand GC et al.: The pathology of frozen shoulder, *J Bone Joint Surg Br* 89(B):928, 2007.

Lapner et al.: The stiff shoulder: How, why and when to treat, *Cur Orthop Pract* 19(5):538–541, 2008.

Markenson J: Rheumatic manifestations of endocrine diseases, *Cur Opin Rheumatol* 22:64–71, 2010.

McKeever D: Thawing the frozen shoulder, *Clin Orthop Relat Res* 466:754–755, 2008.

Milgrom C et al.: Risk factors for idiopathic frozen shoulder, *Isr Med Assoc J* 10:361, 2008.

Placzek JD et al.: Theory and technique of translational manipulation for adhesive capsulitis, *Am J Orthop* 33:173, 2004.

Rookmoneea et al.: The effectiveness of interventions in the management of patients with primary frozen shoulder, *J Bone Joint Surg Br* 92(9):1267–1272, 2010.

Tasto JP, Elias DW: Adhesive capsulitis, *Sports Med Arthrosc* 15:216, 2007.

Tonino PM et al.: Complex shoulder disorders: Evaluation and treatment, *J Am Acad Orthop Surg* 17(3):125–136, 2009.

Wong PLK, Tan H: A review on frozen shoulder, *Singapore Med J* 51(9):694–697, 2010.

BASIC INFORMATION

DEFINITION

Fungal meningitis is an infection of the meninges and/or central nervous system that is usually more subacute than acute and caused by a variety of different fungi or molds. The most common causes in the U.S. are *Cryptococcus neoformans* and *Coccidioides immitis* meningitis but there has been a recent multi-state outbreak in the U.S. of fungal central nervous system infections and septic arthritis mostly caused by *Exserohilum rostratum* transmitted via epidural or paraspinal injections of methylprednisolone produced at a single compounding pharmacy. See Table EF1-11. This chapter will cover this outbreak. See chapters on Cryptococcosis and Coccidioidomycosis.

SYNONYMS

Fungal central nervous system infections
Meningitis, fungal

ICD-9CM CODES
321.1 Meningitis in other fungal diseases
ICD-10CM CODES
B37.5+ Candidal meningitis
B38.4+ Coccidioidomycosis meningitis
B40.7 Disseminated blastomycosis
B39.3 Disseminated histoplasmosis capsulati
B47.7 Disseminated sporotrichosis
B45.1 Cerebral cryptococcosis
B46.1 Rhinocerebral mucormycosis
B49 Unspecified mycosis

EPIDEMIOLOGY & DEMOGRAPHICS

- Outbreak started in September 2012
- As of August 2013 there have been 750 cases, including 64 deaths
- Cases have been reported in 20 states but Michigan, Tennessee, and Indiana have had the most cases
- Some 14,000 patients may have been injected with vials of the methylprednisolone that were potentially contaminated with the mold

INCIDENCE: Overall attack rate is calculated at 4.4 cases per 100 persons potentially exposed.
PEAK INCIDENCE: Occurs within 6 wk of receiving an epidural or paraspinal injection of methylprednisolone contaminated with the mold, but cases have been detected after 3 mo.
PREDOMINANT SEX AND AGE:

- Median age of affected patient is 64 yr (range 16 to 92).
- Females represent 60% of the cases.

RISK FACTORS: The source of this outbreak has been traced to a single compounding pharmacy (New England Compounding Center). *E. rostratum* has been detected in two of three implicated lots of unopened vials of preservative-free methylprednisolone.

- 17,000 vials were potentially contaminated.
- 75 health care facilities (hospital and outpatient treatment centers) in 23 states received vials with lots that were subsequently recalled.

TABLE EF1-11 Mycoses as a Cause of Fungal Meningitis

Cryptococcus neoformans and *Cryptococcus gatti*
Coccidioides immitis
Histoplasma capsulatum
Candida albicans and other *Candida* species
Sporothrix schenckii
Blastomyces dermatitidis
Molds: *Scedosporium, Aspergillus*
Molds with dark cell walls containing melanin:
many species including
Cladophialophora
Exophiala species
Exserohilum rostratum

- Infection is only acquired via injection of the steroid and *not* transmitted person to person.
- Eventually all products manufactured at that facility were recalled and the facility closed.
- Contamination was felt to have occurred due to lack of sterility controls in manufacturing.
- Green-black material was visibly seen in 83 of 321 vials from one of the recalled lots.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Most patients present 1 to 4 wk after injection.

- Meningitis, stroke, and injection site infections
  1. Meningitis: new or worsening headache, neck stiffness, photophobia
  2. Stroke: neurologic deficit with weakness, slurred speech, vertigo, ataxia, or diplopia. Stroke usually involves posterior circulation causing a basilar stroke.
  3. Injection site infections: epidural abscess, arachnoiditis, discitis, vertebral osteomyelitis, or persistent back pain
  4. Peripheral joint infections: 35 patients have developed only a peripheral joint infection due to an injection into that joint with a steroid from a contaminated lot
- Pathogenesis: the steroid itself may impair local host defenses and facilitate the fungal infection into the central nervous system. The fungus accesses the CSF and spreads upward to the basal cisterns and then invades the basilar arteries.
- Fever has not been a consistent symptom.
- Some patients were found to have injection site infections on screening MRI but had no clinical symptoms yet.

ETIOLOGY

- Only about a third of the clinical cases have a proven culture result.
- *Exserohilum rostratum* is the documented cause in about 30% of clinical cases.
  1. Part of the Dematiaceae fungi group (darkly pigmented due to melanin)
  2. Found in soil and part of living or dead plant material
  3. Sensitive to voriconazole and amphotericin B but resistant to fluconazole
- Thirteen other mold species have been isolated in patients including *Aspergillus* species, *Alternaria* species, *Cladosporium* species, *Penicillium* species, and other species.
- Four different types of molds were isolated from the contaminated vials.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Meningitis: bacterial, viral, or mycobacterial pathogens
- Stroke: cardioembolic stroke, hemorrhagic stroke
- Tumors of the central nervous system
- Epidural abscess by bacterial pathogens
- Osteomyelitis of bacterial etiology

WORKUP

Should be considered in any patient who has received an injection from a steroid manufactured at New England Compounding Center. Information is available on website: http://www.cdc.gov/hai/outbreaks/meningitis-facilities-map.html

- A negative culture from a clinical specimen does not rule out the infection.
- Local health department should be contacted if case suspected.

LABORATORY TESTS

- CSF: if meningitis suspected perform LP. Obtain at least 10 to 20 ml of CSF.
  1. Obtain routine tests: Gram stain, culture, cell count, protein, glucose
  2. At least 10 cc for fungal culture and hold for a minimum of 2 wk
  3. Send unspun CSF to CDC for a PCR for *E. rostratum*
- Other tests: routine CBC with differential, Bun/Cr, liver function tests

IMAGING STUDIES

Neuroimaging via MRI or MRI/MRA or CT can detect:

- Infarcts/strokes
- Large vessel involvement of the posterior circulation
- Dural and leptomeningeal enhancement
- Arachnoiditis
- Osteomyelitis/discitis of the spine
- Epidural abscess

TREATMENT

There are four cornerstones of the management of mold infections of the CNS: Early diagnosis, administration of antifungal chemotherapy, neurosurgical assessment and intervention, and management of immunologic impairment

ACUTE GENERAL Rx

Will depend on site of infection and severity:

- Meningitis: Voriconazole with or without liposomal amphotericin B
  1. Voriconazole: 6 mg/kg q12h IV for severe cases or oral for mild cases has good

penetration into CSF; side effects include changes in color vision or hallucinations
2. Liposomal amphotericin B (AmBisome): 7.5 mg/kg IV q24h can be added to voriconazole for the most severe cases or for patients who are not responding to voriconazole alone or relapse. Can cause nephrotoxicity that can be ameliorated by giving 1 L of IV normal saline prior to dose.

- Injection site infections: epidural abscess, discitis, vertebral osteomyelitis, etc.
1. Voriconazole: 6 mg/kg q12h IV or oral depending on presentation and can consider adding liposomal amphotericin B at 5-6 mg/kg IV q24h.

CHRONIC Rx

- Meningitis: meningitis therapy should last at least 3 mo, but stroke or severe CNS disease may require 6 mo to one yr. Monitor liver function tests, and obtain a voriconazole trough concentration on day 5 of treatment that should be between >2 mcg/ml and <5 mcg/ml. Monitor for neurologic side effects of voriconazole. For patients on liposomal amphotericin B, kidney function and electrolytes (K+) need to be monitored frequently.
- Injection site infections: therapy should last at least 3 to 6 mo.

DISPOSITION

Mortality has been about 8.8%, and highest risk factor is development of a stroke.

REFERRAL

Infectious diseases physician for guidance on initial and long-term antifungal therapy
Neurologist for evaluation and diagnosis
Neuroradiologist for MRI/MRA interpretation

PEARLS & CONSIDERATIONS

PATIENT & FAMILY EDUCATION

This fungal disease is transmitted by the contaminated steroid injection and is not transmitted person to person and thus not contagious.

RELATED CONTENT

Bacterial Meningitis (Related Key Topic)
Viral Meningitis (Related Key Topic)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Kauffman CA et al.: Fungal infections associated with contaminated methylprednisolone injections, *N Engl J Med* 386:2495–2500, 2013.

McCarthy M et al.: Mold infections of the central nervous system, *N Engl J Med* 371:150–160, 2014.

Pettit AC et al.: The index case for the fungal meningitis outbreak in the United States, *N Engl J Med* 367:2119–2125, 2012.

Ritter JM et al.: *Exserohilum* infections associated with contaminated steroid injections: a clinicopathologic review of 40 cases, *Am J Pathol* 183(3):881–892, 2013.

Smith RM et al.: Fungal infections associated with contaminated methylprednisolone injections, *N Engl J Med* 369:1598–1609, 2013.

BASIC INFORMATION

DEFINITION

Galactorrhea can be defined as inappropriate lactation (in the absence of pregnancy or postpartum state) as a result of nonphysiologic augmentation of prolactin release.

ICD-9CM CODES
611.6 Galactorrhea
ICD-10CM CODES
N64.3 Galactorrhea not associated with childbirth

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Milky discharge from nipples (Fig. G1-1) usually occurring bilaterally.
- Evidence of chest wall irritation from ill-fitting clothing, herpes zoster, or atopic dermatitis may be present.
- Visual field defects (bitemporal hemianopsia) may be present with prolactinomas, particularly if large such as macroadenomas.
- Headaches may also occur in cases of large pituitary adenomas.
- Evidence of acromegaly, Cushing's disease, or hypothyroidism when galactorrhea is caused by these disorders.

ETIOLOGY

- Medications (phenothiazines, metoclopramide, selective serotonin reuptake inhibitors, anxiolytics, buspirone, atenolol, valproic acid, conjugated estrogen and medroxyprogesterone, methyldopa, verapamil, H_2 receptor blockers, octreotide, danazol, tricyclic antidepressants, isoniazid, amphetamine, reserpine, opiates, sumatriptan, rimantadine, oral contraceptive formulations); after infancy, galactorrhea is often medication induced.
- Breast stimulation (prolonged suckling), sexual intercourse.
- Pituitary tumors (prolactinomas, craniopharyngiomas).
- Chest wall irritation from ill-fitting clothing, herpes zoster, atopic dermatitis, burns.
- Hypothyroidism (diminished feedback inhibition increases thyroid-releasing hormone [TRH], which increases prolactin).

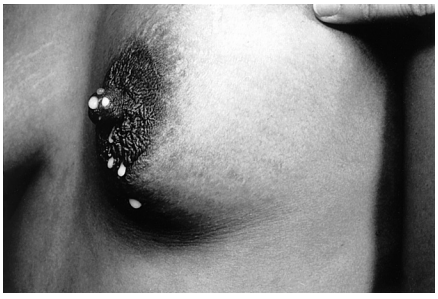


FIGURE G1-1 Galactorrhea. Milk production in a nonpregnant woman resulting from a prolactinoma. (From Haines DE: *Fundamental neuroscience for basic and clinical applications,* ed 3, Philadelphia, 2006, Churchill Livingstone.)

- Increased stress, major trauma.
- Chronic renal failure (decreased prolactin clearance).
- Cushing's disease.
- Herbs (e.g., fennel, red clover, anise, red raspberry, marshmallow).
- Cannabis.
- Spinal cord surgery or injury, or tumors.
- Severe gastroesophageal reflux disease, esophagitis (stimulation of thoracic nerves by the cervical and thoracic ganglia).
- Breast surgery.
- Idiopathic.
- Neonatal ("witch's milk" produced by 2% to 5% of neonates because of precipitous drop in maternal estrogen and progesterone postdelivery).
- Lymphomas, Hodgkin's disease, bronchogenic carcinoma, renal adenocarcinomas.
- Sarcoidosis and other infiltrative disorders.
- Tuberculosis affecting pituitary gland.
- Pituitary stalk resection.
- Multiple sclerosis.
- Empty sella syndrome.
- Acromegaly.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Intraductal papilloma.
- Breast cancer.
- Paget's disease of breast.
- Breast abscess.

WORKUP

- Complete history focusing on menstrual irregularity, infertility, previous pregnancies, duration of galactorrhea, medications, visual complaints, fatigue. Age of onset is also significant (e.g., prolactinoma most common between ages 20 and 35 yr; neonatal galactorrhea is usually secondary to transplacental transfer of maternal estrogen).
- Physical examination: hirsutism, acne, obesity, visual field defects, goiter.
- Breast examination for presence of nodules, evaluation of discharge (milky versus serosanguineous versus purulent).
- Laboratory testing and imaging studies (see "Laboratory Tests")

LABORATORY TESTS

- Prolactin level (elevated, often <200 ng/ml in prolactinoma but may occur at any prolactin level).
- Human chorionic gonadotropin level (positive in pregnancy).
- TSH (elevated in hypothyroidism).
- Blood urea nitrogen, creatinine (elevated in renal failure), glucose (elevated in Cushing's syndrome).
- Urinalysis (hematuria in renal cell carcinoma).
- Microscopic examination of nipple discharge (scant cellular material, numerous fat globules, can be seen without specific staining).

IMAGING STUDIES

- MRI of brain if prolactin level is elevated, amenorrhea is present, or visual field defects are detected on physical examination.
- High-resolution CT of brain with special coronal cuts through the pituitary region may be helpful in patients with contraindications to MRI; however, it may miss small lesions.

TREATMENT

- Discontinuation of potential offending agents.
- Avoidance of excessive breast stimulation.
- Galactorrhea resulting from prolactinoma can be managed medically or with careful surveillance depending on size and growth of tumor, associated symptoms, and prolactin level. Surgical treatment of prolactinomas is usually reserved for medication failures. Please refer to the topic "Prolactinoma" in Section I for additional information.
- No treatment is necessary for normoprolactinemic patients with idiopathic nonbothersome galactorrhea.
- Normoprolactinemic patients with bothersome galactorrhea may respond to low dose dopamine agonist (e.g., cabergoline 0.25 mg twice weekly).

REFERRAL

Endocrine and surgical consultation if prolactinoma is detected

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Galactorrhea (Patient Information)
Pituitary Adenoma (Related Key Topic)
Prolactinoma (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Huang W, Molitch ME: Evaluation and management of galactorrhea, *Am Fam Physician* 85(11):1073–1080, 2012.

Leung A, Pacaud D: Diagnosis and management of galactorrhea, *Am Fam Physician* 70:543, 2004.

Pena KS, Rosenfeld JA: Evaluation and treatment of galactorrhea, *Am Fam Physician* 63:1763, 2001.

BASIC INFORMATION

DEFINITION

A fluid-filled sac (cyst) overlying a tendon sheath or joint.

SYNONYMS

Ganglion

ICD-9CM CODES
727.43 Ganglion
ICD-10CM CODES
M67.4 Ganglion

EPIDEMIOLOGY & DEMOGRAPHICS

- Ganglia are more common in women than men (3:1).
- Can occur at any age, but usually between second and fourth decades of life.
- Most common soft tissue tumor of the hand and wrist.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most ganglia occur on the dorsum of the wrist (50% to 70%) (Fig. G1-2).
- The volar wrist (18% to 20%) is the next most common site.
- Can also involve the proximal digital flexor tendons and the distal interphalangeal joints.
- Left and right hands are equally affected.
- Ganglia are usually solitary, firm, smooth, round, and fluctuant.
- Pain from mass effect or compression against nearby structure may be present (e.g., median nerve and radial nerve).
- Hand numbness may be present.
- Patient may have hand muscle weakness.
- Ganglia usually develop over a period of months but may arise suddenly.

ETIOLOGY

Ganglia are believed to derive from synovial herniation or expansion from the joint capsule or tendon sheath. Repetitive movement as an etiology is uncertain, although it may cause enlargement of the lesion or worsen symptoms.

FIGURE G1-2 Dorsal wrist ganglion. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

DIAGNOSIS

Direct inspection and localization of the cyst often are enough to make the diagnosis of ganglia. Transillumination is an easy method of differentiating ganglia from solid tumors; ganglia transilluminate while solid tumors do not.

DIFFERENTIAL DIAGNOSIS

- Lipoma.
- Fibroma.
- Epidermoid inclusion cyst.
- Osteochondroma.
- Hemangioma.
- Infection (tuberculosis, fungi, and secondary syphilis).
- Gout.
- Rheumatoid nodule.
- Radial artery aneurysm.

WORKUP

The workup of ganglia usually consists of history, physical examination, and x-ray imaging.

LABORATORY TESTS

Blood tests are not specific in the diagnosis of ganglia.

IMAGING STUDIES

- Radiographs of the hand and wrist are taken to rule out other bone or joint abnormalities.
- Ultrasound studies are helpful in the diagnosis of ganglia by demonstrating smooth cystic walls that may be septated.
- CT scan can be done if the ultrasound is equivocal.
- MRI helps differentiate malignant bone lesions from cystic structures.
- Arthrography may demonstrate a communication between the joint and ganglia (not commonly done).

TREATMENT

Expectant treatment is appropriate if the mass is not painful or interfering with motor function.

NONPHARMACOLOGIC THERAPY

- Attempts to rupture the cyst by sharp blows with a book or with finger compression are not recommended.
- Aspiration, heat, and sclerotherapy have been tried but have met with high recurrence rates (60%).

ACUTE GENERAL Rx

- Aspiration at the base with a large-bore needle (18-gauge) followed by injection of 20 to 40 mg of triamcinolone acetonide can be tried.
- This may be repeated if the ganglia recurs (35% to 40%).

CHRONIC Rx

Total ganglionectomy and repair of the defect after tracing its connection to the tendon sheath is effective and the surgical procedure of choice.

DISPOSITION

- Ganglia spontaneously resolve in approximately 40% to 50% of cases.
- Aspiration with steroid injection is successful in approximately 65% of cases.
- Surgery provides cure in 85% to 95% of the cases.
- Complications of ganglia include:
  1. Carpal tunnel syndrome with pain and muscle atrophy.
  2. Radial nerve impingement.
  3. Radial artery compression.
- Complications of ganglion surgery include:
  1. Infection.
  2. Recurrence (5% to 15%), usually from inadequate excision.
  3. Reflex sympathetic dystrophy.
  4. Scar formation.

REFERRAL

It is best to refer patients with symptomatic ganglia to a hand surgeon.

PEARLS & CONSIDERATIONS

- Dorsal ganglia usually originate from the scapholunate ligament.
- Volar ganglia typically originate between the tendons of the flexor carpi radialis and brachioradialis.

COMMENTS

A ganglion's synovial membrane maintains its secretory function. Aspiration of ganglia often demonstrates a viscous, mucinous, clear fluid containing albumin, globulin, and hyaluronic acid.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Ganglia (Patient Information)

AUTHORS: **RYAN W. ZUZEK, M.D.,** and **IMMAD SADIQ, M.D.**

SUGGESTED READINGS

Ho PC et al.: Current treatment of ganglion of the wrist, *Hand Surg* 6(1):49, 2001.
Nahra ME, Bucchieri JS: Ganglion cysts and other tumor related cysts of the hand and wrist, *Hand Clin* 20(3):249, 2004.
Wang AA, Hutchinson DT: Longitudinal observation of pediatric hand and wrist ganglia, *J Hand Surg* 26(4):599, 2001.

BASIC INFORMATION

DEFINITION

Gastric cancer is an adenocarcinoma arising from the stomach.

SYNONYMS

Stomach cancer
Linitis plastica

ICD-9CM CODES
451 Malignant neoplasm of stomach
ICD-10CM CODES
C16 Malignant neoplasm of stomach
C16.0 Malignant neoplasm of cardia of stomach
C16.1 Malignant neoplasm of stomach
C16.2 Malignant neoplasm of body of stomach
C16.3 Malignant neoplasm of pyloric antrum
C16.5 Malignant neoplasm of lesser curvature of stomach, unspecified
C16.6 Malignant neoplasm of greater curvature of stomach, unspecified
C16.8 Malignant neoplasm of overlapping sites of stomach

EPIDEMIOLOGY & DEMOGRAPHICS

- Annual incidence of gastric cancer in the United States is seven cases per 100,000 persons. The incidence is much higher in Japan, with rates as high as 80 cases per 100,000 persons.
- Most gastric cancers arise in the antrum (35%).
- The incidence of distal stomach tumors has greatly declined, whereas that of proximal tumors of the cardia and fundus is on the rise.
- Gastric cancer occurs most commonly in male patients >65 yr (70% of patients are >50 yr).
- Incidence of gastric cancer has been declining over the past 30 yr.
- Male/female ratio is 3:2.
- Familiar diffuse gastric cancer is a disease with autosomal-dominant inheritance in which gastric cancer develops at a young age. Germline truncating mutations in the E-cadherin gene *(CDH1)* are found in these families.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Medical history may reveal complaints of postprandial fullness with significant weight loss (70% to 80%), nausea/emesis (20% to 40%), dysphagia (20%), and dyspepsia, usually unrelieved by antacids; epigastric discomfort, usually lessened by fasting and exacerbated by food intake, is also common.
- Epigastric or abdominal mass (30% to 50%), epigastric pain.
- Skin pallor from anemia.
- Hard, nodular liver: generally indicates metastatic disease to the liver.
- Hemoccult-positive stools.
- Ascites, lymphadenopathy, or pleural effusions: may indicate metastasis.

ETIOLOGY

Risk factors:

- Chronic *Helicobacter pylori* gastritis. Gastric cancer develops in persons infected with *H. pylori* but not in uninfected persons. Those with histologic findings of severe gastric atrophy, corpus-predominant gastritis, or intestinal metaplasia are at increased risk. Persons with *H. pylori* infection and duodenal ulcer are not at risk, whereas those with gastric ulcers, nonulcer dyspepsia, and gastric hyperplastic polyps are. Eradication of *H. pylori* reduces gastric cancer risk.
- Tobacco abuse, alcohol consumption.
- Food additives (nitrosamines), smoked foods, occupational exposure to heavy metals, rubber, asbestos.
- Chronic atrophic gastritis with intestinal metaplasia, hypertrophic gastritis, and pernicious anemia.

FIGURE G1-3 Polypoid gastric cancer. A trilobed polyp is apparent at the angularis. (From Feldman M, Friedman LS, Brandt LJ [eds]: *Sleisenger & Fordtran's gastrointestinal and liver disease: pathophysiology/diagnosis/management,* ed 8, Philadelphia, 2006, Saunders.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Gastric lymphoma (5% of gastric malignancies).
- Hypertrophic gastritis.
- Peptic ulcer.
- Reflux esophagitis.

WORKUP

Upper endoscopy (Fig. G1-3) with biopsy will confirm diagnosis. Endoscopic ultrasonography in combination with CT scanning and operative lymph node dissection can be used in staging of the tumor. Table G1-1 describes staging systems for gastric carcinoma.

LABORATORY TESTS

- Microcytic anemia.
- Hemoccult-positive stools.
- Hypoalbuminemia.
- Abnormal liver enzymes in patients with metastasis to the liver.
- Mutation-specific predictive genetic testing by polymerase chain reaction amplification followed by restriction: enzyme digestion and DNA sequencing for truncating mutations in *CDH1* is recommended in families of patients with familial diffuse cancer because gastric cancer develops in three of every four carriers of a mutant *CDH1* gene.

IMAGING STUDIES

Abdominal CT scan (Fig. G1-4) to evaluate for metastasis (70% accurate for regional node metastases).

TREATMENT

ACUTE GENERAL Rx

- Gastrectomy with regional lymphadenectomy is performed in patients with curative potential (<30% of patients at time of diagnosis). In patients with operable gastric cancer, a perioperative regimen of epirubicin, cisplatin, and infused fluorouracil decreases tumor size and stage and significantly improves progression-free and overall survival. Postoperative adjuvant chemoradiation therapy using 5-fluorouracil (5-FU) and leucovorin is now the standard of care for resected patients able to tolerate such treatment. Postoperative chemotherapy and radiotherapy, compared with surgical resection alone, can extend the survival rate of patients with gastric cancer

TABLE G1-1 Staging Systems for Gastric Carcinoma*

Modified Astler-Coller	TNM	Characteristics
A	TisN0	Nodes negative; lesion limited to mucosa
B1	T1–2N0	Nodes negative; extension of lesion beyond mucosa but still within gastric wall
B2	T3N0	Nodes negative; extension beyond the entire wall (including serosa if present) without adherence to or invasion of surrounding organs or structures
B3	T4N0	Nodes negative; beyond wall with adherence to or invasion of surrounding organs or structures
C1	Tis–2N1–3	Nodes positive; lesion limited to wall
C2	T3N1–3	Nodes positive; extension of lesion through the entire wall (including serosa)
C3	T4N1–3	Nodes positive; beyond wall with adherence to or invasion of surrounding organs or structures

*Comparison of TNM system with a modification of the Astler-Coller rectal system by Gunderson and Sosin.
From Abeloff MD: *Clinical oncology,* ed 3, Philadelphia, 2004, Elsevier.

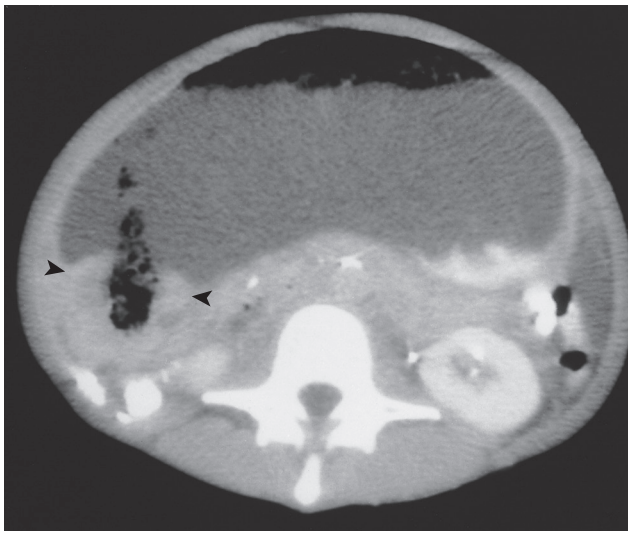


FIGURE G1-4 Gastric outlet obstruction—cancer of the antrum. A markedly distended stomach with an air-fluid level is seen on computed tomography. In this case a mass in the distal end of the antrum is apparent *(arrowheads).* (From Grainger RG, Allison DJ, Dixon AK [eds]. *Grainger & Allison's diagnostic radiology: a textbook of medical imaging,* ed 4, St. Louis, 2001, Churchill Livingstone.)

in those who are able to complete adjuvant therapy.
- When surgical cure is not possible, palliative resection may prolong duration and quality of life.
- Chemotherapy (5-FU, Adriamycin, and mitomycin C) may provide some palliation; however, it generally does not prolong survival. Chemotherapy with docetaxel, cisplatin, and 5-FU can be used for chemotherapy-naive patients with metastatic or locally recurrent gastric cancer. The addition of trastuzumab to cisplatin plus 5-FU or capecitabine may prolong survival in gastric cancer patients expressing HER2.

DISPOSITION

- 5-yr survival rate of gastric carcinoma is 12% overall.
- 5-yr survival for early gastric cancers (usually detected incidentally with endoscopy in populations where screening is recommended) is >35%.

PEARLS & CONSIDERATIONS

COMMENTS

- Gastrectomy patients will need vitamin B_{12} replacement. They are also at risk for dumping syndrome and should be advised to ingest frequent, small meals.
- Prophylactic gastrectomy should be considered in young, asymptomatic carriers of germ-line truncating *CDH1* mutations who belong to families with highly penetrant heredity diffuse gastric cancer.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Stomach Cancer (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READING

Fuccio L et al.: Meta-analysis: Can *Helicobacter pylori* eradication treatment reduce the risk for gastric cancer? *Ann Intern Med* 151:121–128, 2009.

BASIC INFORMATION

DEFINITION

Gastrinoma is a pancreatic or extrapancreatic non-beta islet cell tumor which secretes gastrin. The hypergastrinemic state caused by a gastrinoma results in peptic ulcer disease and is known as Zollinger-Ellison (ZE) syndrome

SYNONYMS

Zollinger-Ellison (ZE) syndrome

ICD-9CM CODES
251.5 Zollinger-Ellison syndrome
ICD-10CM CODES
E16.4 Abnormal secretion of gastrin

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence is unknown, but 0.1% of all duodenal ulcers are believed to be caused by ZE.
- Occurs in both genders and at any age (most common in ages 30 to 50 yr).
- Two thirds of gastrinomas are sporadic, and one third are associated with multiple endocrine neoplasia type 1 (MEN-1), an autosomal-dominant genetic disorder that also includes hyperparathyroidism and pituitary tumors.
- Approximately 60% of gastrinomas are malignant.
- The incidence and prevalence of pancreatic neuroendocrine tumors are increasing. They represent 1.3% of all cases of pancreatic cancer.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The majority of patients (95%) present with symptoms of peptic ulcer (see Section I, "Peptic Ulcer Disease").
- 60% of patients have symptoms related to gastroesophageal reflux disease (see Section I, "Gastroesophageal Reflux Disease").
- One third of patients with ZE have diarrhea and, less commonly, steatorrhea.

The following circumstances warrant suspicion of ZE syndrome:

- Ulcers distal to the first portion of the duodenum.
- Multiple peptic ulcers.
- Ineffective treatment for peptic ulcer disease with the usual drug doses and schedules.
- Peptic ulcer and diarrhea.
- Familial history of peptic ulcer.
- Patients with a personal or family history suggesting parathyroid or pituitary tumors or dysfunction.
- Peptic ulcer and urinary tract calculi.
- Patients with peptic ulcer who are negative for *Helicobacter pylori* and do not have a history of nonsteroidal anti-inflammatory drug use.

ETIOLOGY

- The pathophysiologic manifestations of ZE syndrome are related to the effects of hypergastrinemia. Gastrin stimulates gastric acid secretion, which in turn is responsible for the development of duodenal ulcers and diarrhea. Gastrin also promotes gastric mucosal epithelial cell growth and resulting parietal cell hyperplasia.
- Gastrinomas are usually small (0.1 to 2 cm) but sometimes large (>20 cm) tumors.
- 60% of gastrinomas are malignant, with liver and regional lymph nodes the most common site of metastases. Histology is not a good predictor of the biology of gastrinomas.
- 60% of patients with MEN-1 have gastrinomas.
- 10% of patients with ZE syndrome have islet cell hyperplasia rather than gastrinomas; in 10% to 20% of patients with gastrinoma the tumors cannot be located because of small size.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Peptic ulcer disease (see Section I, "Peptic Ulcer Disease").
- Gastroesophageal reflux disease (see Section I, "Gastroesophageal Reflux Disease").
- Diarrhea (see Section III, "Diarrhea, Acute" and "Diarrhea, Chronic").
- Other endocrine tumors of the pancreas (see Table G1-2).

WORKUP

- Diagnosis of peptic ulcer:
  - Upper gastrointestinal series (may also show prominent gastric rugal folds).
  - Endoscopy
- Gastric acid secretion:
  - Serum gastrin level (fasting) >150 pg/ml (criterion for diagnosis is serum gastrin >1000 pg/ml) (causes of false-positive results: pernicious anemia, renal failure, retained gastric antrum syndrome, diabetes mellitus, rheumatoid arthritis).
- Provocative gastrin level tests:
  - Secretin stimulation.
  - Calcium stimulation.
  - Standard test meal stimulation.
- Gastrinoma localization:
  - Arteriography.
  - Abdominal sonography.
  - Abdominal CT scan.
  - Abdominal MRI/PET scan.
  - Selective portal vein branch gastrin level.
  - Octreotide scan.

TREATMENT

- Surgical resection of the gastrinoma (NOTE: 90% of gastrinomas can be located, resulting in a 40% overall cure rate).
- Total gastrectomy or vagotomy (palliative in some patients).

TABLE G1-2 Characteristics of Endocrine Tumors of the Pancreas

Tumor Type	Major Clinical Symptoms	Predominant Hormone	Islet cell Type	Malignant (%)	Localization	Other Clinical Features
Insulinoma	Hypoglycemia (fasting or nocturnal)	Insulin	β	10	Usually pancreatic; rarely extrapancreatic	Catecholamine excess
Glucagonoma	1. Diabetes mellitus 2. Migratory necrolytic erythema	Glucagon	α	90	Usually pancreatic; rarely extrapancreatic	Panhypoaminoaciduria Thromboembolism Weight loss
Gastrinoma	Recurrent peptic ulcer disease	Gastrin	γ	90	Usually pancreatic but frequently extrapancreatic	Diarrhea/steatorrhea
Somatostatinoma	1. Diabetes mellitus 2. Diarrhea, steatorrhea	Somatostatin	δ	80	Pancreatic and duodenal	Hypochlorhydria Weight loss Gallbladder disease
VIPoma	Watery diarrhea, hypokalemia, achlorhydria (WDHA syndrome)	Vasoactive intestinal polypeptide (VIP)	δ	50	Usually pancreatic but frequently extrapancreatic	Metabolic acidosis Hyperglycemia Hypercalcemia Flushing
PPoma	1. Hepatomegaly 2. Abdominal pain	Pancreatic polypeptide (PP)	PP cells	80	Usually pancreatic; rarely extrapancreatic	Occasional watery diarrhea

(From Besser GM, Cudworth AG: *Clinical endocrinology,* Philadelphia/London, 1987, Lippincott/Gower Medical Publishing, p. 20.15.)

- Medical treatment.
  - Proton pump inhibitors (e.g., omeprazole, lansoprazole).
  - Somatostatin or octreotide.
  - Chemotherapy for metastatic gastrinoma with streptozotocin, 5-fluorouracil, and doxorubicin.
  - Early trials with everolimus, an oral inhibitor of mammalian target of rapamycin (mTOR) have shown antitumor activity in patients with advanced pancreatic neuroendocrine tumors with significant prolongation of progression-free survival and low rates of severe adverse events.
  - Preliminary trials with the tyrosine kinase inhibitor sunitinib have shown encouraging results on prolongation of survival.
- Fig. G1-5 describes a treatment algorithm for gastrinoma.

PROGNOSIS

Five-year survival:
- Two thirds of all patients.
- 20% with liver metastases.
- 90% without liver metastases.

REFERRAL

To gastroenterologist and surgeon.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Gastrinoma (Zollinger-Ellison Syndrome) (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

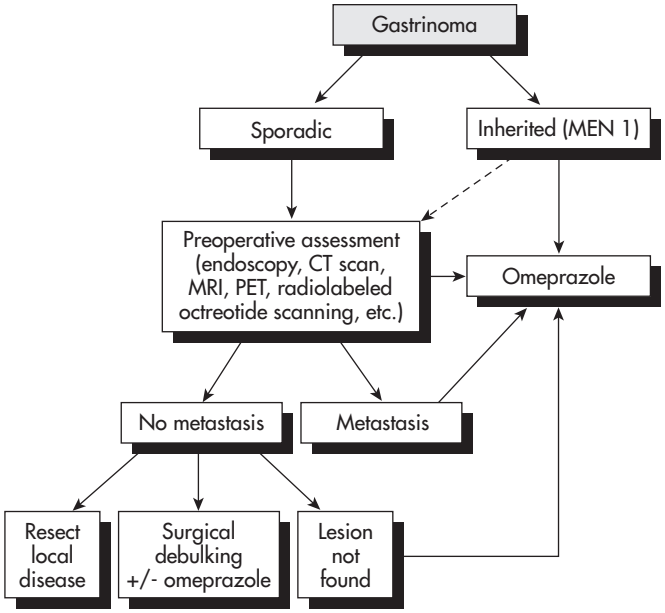


FIGURE G1-5 Treatment algorithm for the management of a patient with gastrinoma. In some circumstances, patients with familial gastrinoma may also be candidates for surgical resection if disease is highly limited *(dotted line). CT,* computed tomography; *MEN 1,* multiple endocrine neoplasia type 1; *MRI,* magnetic resonance imaging; *PET,* positron emission tomography. (From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

EVIDENCE

Abstract[1]

Background:
The multitargeted tyrosine kinase inhibitor sunitinib has shown activity against pancreatic neuroendocrine tumors in preclinical models and phase 1 and 2 trials.

Methods:
We conducted a multinational, randomized, double-blind, placebo-controlled phase 3 trial of sunitinib in patients with advanced, well-differentiated pancreatic neuroendocrine tumors. All patients had Response Evaluation Criteria in Solid Tumors-defined disease progression documented within 12 months before baseline. A total of 171 patients were randomly assigned (in a 1:1 ratio) to receive best supportive care with either sunitinib at a dose of 37.5 mg per day or placebo. The primary end point was progression-free survival; secondary end points included the objective response rate, overall survival, and safety.

Results:
The study was discontinued early, after the independent data and safety monitoring committee observed more serious adverse events and deaths in the placebo group as well as a difference in progression-free survival favoring sunitinib. Median progression-free survival was 11.4 months in the sunitinib group as compared with 5.5 months in the placebo group (hazard ratio for progression or death, 0.42; 95% confidence interval [CI], 0.26 to 0.66; $P < 0.001$). A Cox proportional-hazards analysis of progression-free survival according to baseline characteristics favored sunitinib in all subgroups studied. The objective response rate was 9.3% in the sunitinib group versus 0% in the placebo group. At the data cutoff point, 9 deaths were reported in the sunitinib group (10%) versus 21 deaths in the placebo group (25%) (hazard ratio for death, 0.41; 95% CI, 0.19 to 0.89; $P = 0.02$). The most frequent adverse events in the sunitinib group were diarrhea, nausea, vomiting, asthenia, and fatigue.

Conclusions:
Continuous daily administration of sunitinib at a dose of 37.5 mg improved progression-free survival, overall survival, and the objective response rate as compared with placebo among patients with advanced pancreatic neuroendocrine tumors.
(Funded by Pfizer; ClinicalTrials.gov number, NCT00428597.) A

Evidence-Based Reference

Raymond E et al.: Sunitinib malate for the treatment of pancreatic neuroendocrine tumors, *N Engl J Med* 364:501–513, 2011 . A

SUGGESTED READINGS

Norten JA et al.: Surgery to cure Zollinger-Ellison syndrome, *N Engl J Med* 341:635, 1999.

Raymond E et al.: Sunitinib malate for the treatment of pancreatic neuroendocrine tumors, *N Engl J Med* 364:501–513, 2011.

Yao JC et al.: Everolimus for advanced neuroendocrine tumors, *N Engl J Med* 364:514–523, 2011.

BASIC INFORMATION

DEFINITION

Histologically, *gastritis* refers to inflammation in the stomach. Endoscopically, gastritis refers to a number of abnormal features such as erythema, erosions, and subepithelial hemorrhages. Gastritis can also be subdivided into erosive, nonerosive, and specific types of gastritis with distinctive features both endoscopically and histologically.

SYNONYMS

Erosive gastritis
Hemorrhagic gastritis
Helicobacter pylori gastritis

ICD-9CM CODES
535.5 Gastritis (unless otherwise specified)
535.0 Gastritis, acute
535.3 Alcoholic gastritis
535.1 Atrophic (chronic) gastritis
535.4 Erosive gastritis
535.2 Hypertrophic gastritis

ICD-10CM CODES
K29.70 Gastritis, unspecified, without bleeding
K29.00 Acute gastritis without bleeding
K29.20 Alcoholic gastritis without bleeding
K29.40 Chronic atrophic gastritis without bleeding
K29.60 Other gastritis without bleeding

EPIDEMIOLOGY & DEMOGRAPHICS

- Erosive and hemorrhagic gastritis is most commonly seen in patients taking nonsteroidal anti-inflammatory drugs (NSAIDs), alcoholics, and critically ill patients (usually on ventilator support).
- *H. pylori* infection with gastritis is believed to be present in 30% to 50% of the population; however, the majority are asymptomatic.
- The prevalence of *H. pylori* infection increases with age from <10% in whites <40 yr to >50% in patients >50 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with gastritis generally present with nonspecific clinical signs and symptoms (e.g., epigastric pain, abdominal tenderness, bloating, anorexia, nausea [with or without vomiting]). Symptoms may be aggravated by eating.
- Epigastric tenderness in acute alcoholic gastritis (may be absent in chronic gastritis).
- Foul-smelling breath.
- Hematemesis ("coffee grounds" emesis).

ETIOLOGY

- Alcohol, NSAIDs, stress (critically ill patients usually on mechanical respiration), hepatic or renal failure, multiorgan failure.
- Infection (bacterial, viral).
- Bile reflux, pancreatic enzyme reflux.
- Gastric mucosal atrophy, portal hypertension gastropathy.
- Irradiation.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Peptic ulcer disease.
- Gastroesophageal reflux disease.
- Nonulcer dyspepsia.
- Gastric lymphoma or carcinoma.
- Pancreatitis.
- Gastroparesis.

WORKUP

Diagnostic workup includes a comprehensive history and endoscopy with biopsy.

LABORATORY TESTS

- *H. pylori* testing by urea breath test, stool antigen test (*H. pylori* stool antigen), endoscopic biopsy, or specific antibody test is recommended.
  1. The urea breath test documents active infection (sensitivity and specificity >90%). A new card test for ^{14}C urea has recently been developed, providing a testing option in primary care settings. It uses a flat breath card read by a small analyzer.
  2. The stool antigen test is an enzymatic immunoassay (ELISA) that identifies *H. pylori* antigen in a stool specimen with a polyclonal anti–*H. pylori* antibody. It is as accurate as the urea breath test for diagnosis of active infection and follow-up evaluation of patients treated for *H. pylori.* A negative result on the stool antigen test 8 wk after completion of therapy identifies patients in whom eradication of *H. pylori* was unsuccessful.
  3. Histologic evaluation of endoscopic biopsy samples is considered by many the gold standard for accurate diagnosis of *H. pylori* infection. However, detection of *H. pylori* depends on the site and number of biopsy samples, the method of staining, and experience of the pathologist.
  4. Serologic testing for antibodies to *H. pylori* is easy and inexpensive; however, the presence of antibodies demonstrates previous but not necessarily current infection. Antibodies to *H. pylori* can remain elevated for months to years after infection has cleared; therefore antibody levels must be interpreted in light of patient's symptoms and other test results (e.g., peptic ulcer disease [PUD] seen on upper gastrointestinal series).
- Vitamin B_{12} level in patients with atrophic gastritis.
- Hematocrit (low if significant bleeding has occurred).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of mucosal irritants such as alcohol and NSAIDs
- Lifestyle modifications with avoidance of tobacco and foods that trigger symptoms

ACUTE GENERAL Rx

Eradication of *H. pylori,* when present, can be accomplished with various regimens:

1. Proton pump inhibitor (PPI) bid *plus* amoxicillin 500 mg bid *plus* metronidazole 500 mg for 10 days.
2. PPI bid *plus* clarithromycin 500 mg bid *and* metronidazole 500 mg bid for 10 days. This regimen is useful in those with penicillin allergy.
3. A 1-day quadruple-therapy regimen may be as effective as a 7-day triple-therapy regimen. The 1-day quadruple-therapy regimen consists of two tablets of 262 mg bismuth subsalicylate qd, one 500-mg metronidazole tablet qd, 2 g of amoxicillin suspension qd, and two capsules of 30 mg of lansoprazole.
4. A 5-day treatment with three antibiotics (amoxicillin 1 g bid, clarithromycin 250 mg bid, and metronidazole 400 mg bid) plus either lansoprazole 30 mg bid or ranitidine 300 mg bid is an efficacious, cost-saving option for patients >55 yr with no history of PUD.
5. A combination of levofloxacin 250 mg bid, amoxicillin 1000 mg bid, and a PPI bid for 10 to 14 days can be used as salvage therapy after unsuccessful attempts to eradicate *H. pylori* using other regimens.
   - A 10-day sequential therapy has been reported to be superior to standard triple therapy for eradication of *H. pylori.* It consists of 5 days of treatment with a PPI and one antibiotic (usually amoxicillin) followed by 5-day treatment with the PPI and two other antibiotics (usually clarithromycin and metronidazole).
6. Prophylaxis and treatment of stress gastritis with sucralfate suspension 1 g orally q4-6h, H_2-receptor antagonists, or PPIs in patients on ventilator support.

CHRONIC Rx

- Omeprazole 20 mg/qd in patients receiving long-term NSAIDs.
- Avoidance of alcohol, tobacco, and prolonged NSAID or corticosteroid use.

DISPOSITION

- Undetectable stool antigen 4 wk after therapy accurately confirms cure of *H. pylori* infection in initially seropositive healthy subjects with reasonable sensitivity.
- Surveillance gastroscopy in patients with atrophic gastritis (increased risk of gastric cancer).

RELATED CONTENT

Gastritis (Patient Information)
Helicobacter pylori Infection (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

BASIC INFORMATION

DEFINITION

- Gastroenteritis is a broad term used for various gastrointestinal pathologic states. The main manifestation is diarrhea—often accompanied by nausea, vomiting, malaise, anorexia, fever, abdominal pain, and dehydration.
- Gastroenteritis is a common cause of morbidity/mortality around the world. In the developing world, it is a leading cause of death.

ICD-9CM CODES
009.1 Colitis, enteritis, and gastroenteritis of presumed infectious origin
ICD-10CM CODES
K52.9 Non-infective gastroenteritis and colitis
558.3 Allergic gastroenteritis and colitis
K52.1 Infectious gastroenteritis and colitis
K52.0 Gastroenteritis and colitis due to radiation

EPIDEMIOLOGY & DEMOGRAPHICS

- Frequency is difficult to determine.
- Statistics on sporadic cases of adult viral gastroenteritis are not known
- It is estimated that there are 1.5 billion cases a year worldwide.
- It is the leading cause of death in many developing countries. Children under the age of 5 yr are most vulnerable.

SEX: Higher mortality seen in women.
AGE:

- May occur at any age
- High morbidity and mortality in the very young (younger than 5 yr), the elderly (people aged 65 or older), and the immunosuppressed.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- A well-taken history is important. The onset, duration, and frequency of diarrhea should be noted. The aim of the physical examination is to assess the patient's degree of hydration. This helps to identify the cause of diarrhea and identify patients at risk of complications.

Viral gastroenteritis has a short prodome with vomiting, mild fever, nonbloody and watery diarrhea, usually for 1-4 days.

- Bacterial gastroenteritis presents with high fever, bloody diarrhea, severe abdominal pain, and at least 6 stools in a 24 hours period.
- Patients usually present with:
  - Diarrhea: usually more than 6 stools a day indicates bacterial cause of gastroenteritis
  - Vomiting
  - Abdominal pain
  - Mucus and/or blood in stool: indicating bacterial or parasitic infection
  - Fever
  - Dehydration: this is the main cause of morbidity and mortality. Check for lethargy, dry mucous membrane, poor skin turgor, sunken eyes as signs of dehydration.
  - Malnutrition: this occurs when diarrhea is chronic. There is reduced muscle and fat mass.
  - Abdominal pain: this is a very common symptom in gastroenteritis.
  - Borborygmi: there is significantly increased peristaltic activity, which may cause audible or palpable bowel activity.
  - Perianal erythema: secondary to constantly wet area. Wet buttock and perianal area may result in redness and skin breakdown.

ETIOLOGY

- Bacterial gastroenteritis
  - *Salmonella*
  - *Shigella*
  - *Campylobacter*
  - *Aeromonas* species
  - *Yersinia*
  - Enterohemorrhagic *Escherichia coli*
  - *E. coli*
  - *Clostridium perfringens*
- Viral gastroenteritis (in adults)
  - The caliciviruses such as *Norovirus* genogroup I (e.g., Norwalk), *Norovirus* genogroup II (e.g., South Hampton), *Sapovirus* (e.g., Sapporo).
  - Non-group A *Rotavirus*
  - *Astrovirus*
  - Adenovirus

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Amebiasis
- Appendicitis
- Celiac disease
- Inflammatory bowel disease
- Colon cancer
- Bowel obstruction
- Botulism
- Hemolytic uremic syndrome
- Food poisoning
- Intraabdominal abscess

WORKUP

- In most cases laboratory tests are not indicated.
- Further workup is indicated in patients who:
  1. Have persistent diarrhea
  2. Are extremely dehydrated
  3. Appear seriously ill
  4. Have high fever
  5. Present with severe abdominal pain
  6. Have bloody diarrhea
  7. Have persistent nausea

LABORATORY TESTS

- Routine laboratory tests
  1. Tests such as CBC and BMP may not be indicated in making a diagnosis. However, electrolytes and BUN are indicated in patients with severe diarrhea or dehydration.
  2. CBC is indicated with severe diarrhea or toxicity. WBC is increased in *Salmonella* infection; eosinophilia is present in parasitic infections.
- Stool studies
  1. Presence of blood/leukocytes in stool may indicate inflammatory diarrhea.
  2. In *Salmonella* or *Shigella* infections there is an increased fecal leukocyte.
  3. Stool leukocytes are absent in viral diarrhea.
- Stool culture
  1. Are only useful when positive
  2. Usually not necessary in most cases of diarrhea
  3. Indications for stool cultures include: bloody stools; prolonged, untreated diarrhea; fever; leukocytes in stool; immunosuppressed patients; immunocompromised patients; and patients who have traveled to remote, exotic, or developing nations. It should also be considered in patients with concurrent or very recent use of antibiotics to rule out *Clostridium difficile* infection as a cause of the diarrhea.
- Examination for ova and parasites (O&P) is indicated in immunosuppressed patients, immunocompromised patients, and patients who have traveled to remote, exotic, or developing nations

IMAGING STUDIES

- In patients with suspected bowel obstruction, perforation, or toxic megacolon, abdominal series is warranted.
- Consider CT scan of the abdomen in older patients with severe abdominal pain.

TREATMENT

GENERAL CONSIDERATIONS

- Most infectious diarrhea is self-limited. Fig. G1-6 describes an approach to the management of gastroenteritis.
- It is important to assess the degree of dehydration by checking BP, pulse, HR, skin turgor, mucous membrane, thirst, urine output, and mental status change.
- Oral rehydration therapy is very important in diarrhea treatment.
- Consider intravenous rehydration when oral rehydration fails. Watch out for potassium depletion.
- Early re-feeding decreases recovery time.

Principles of treatment include:

- Rehydration: orally or intravenously, PRN
- Treatment of symptoms such as fever, abdominal pain, nausea, vomiting as needed
- Identify and treat complications

REHYDRATION:

- Oral hydration products include Naturalyte, Rehydralyte.
- Intravenous solutions used include dextrose 5% in 0.5 isotonic NaCl with 50 mEq $NaHCO_3$ and 10-20 mEq KCl.
  1. Indications for IV hydration include intractable vomiting, severe dehydration, change in mental status or consciousness, and ileus.
  2. Oral hydration is not appropriate due to environmental conditions

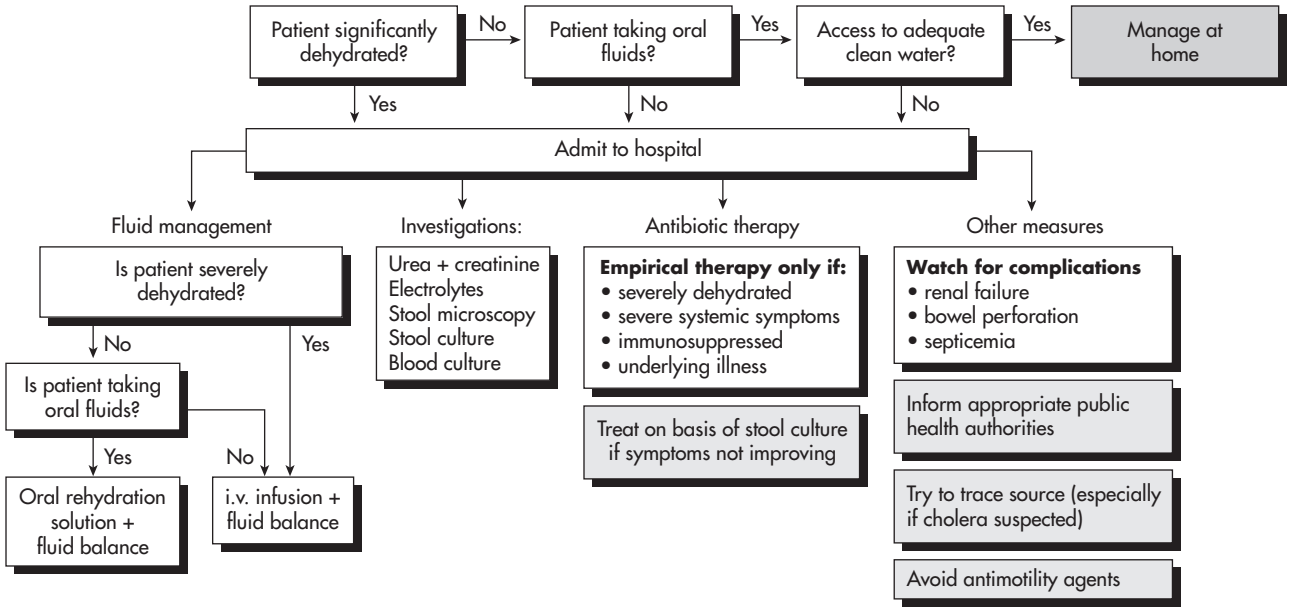


FIGURE G1-6 Management of gastroenteritis. (From Currie G, Douglas G: *Flesh and bones of medicine*, St. Louis, 2011, Mosby, pp 8-9.)

TREATMENT OF SYMPTOMS

- Infectious diarrhea sometimes requires empiric treatment with antibiotics. Food-borne toxigenic diarrhea usually does not.
- Traveler's diarrhea: patients without fever or dysentery may be treated with rifaximin 200 mg thrice daily for 3 days, or ciprofloxacin 500 mg twice daily or 750 mg daily for 1 to 3 days; patients with fever or dysentery can be treated with azithromycin 1000 mg in a single dose.
- *C. difficile* diarrhea and parasitic infestations with *Giardia* or *Entamoeba* are treated with metronidazole.
- Treat severe nausea and vomiting with anti-emetics.
- Antidiarrheal agents may be useful for systemic relief in mild to moderate diarrhea.
- Loperamide (Imodium) or bismuth subsalicylate (Pepto-Bismol) may provide limited relief in traveler's or non-bloody diarrhea.

Dietary measures may include:

- Start with banana, rice, applesauce, toast diet (BRAT diet)
- As early as possible introduce lean meats and clear liquid

In recent years the use of probiotics (non-pathogenic live microorganism) has increased. They are known to provide beneficial effects on the host's health. Beneficial effects have been noted with *Lactobacillus casei GG* and *S. boulardii.*

REFERRAL

Referral to infectious disease or gastroenterologist specialist may be indicated in patients:

- With chronic diarrhea
- In whom a parasitic etiology is suspected
- With *C. difficile* resistant to treatment with metronidazole and vancomycin
- With HIV/AIDS
- Who relapse

PEARLS AND CONSIDERATIONS

PREVENTION

- Perform proper hand washing before and after eating and after each bowel movement to prevent spread to family members.
- Avoid (raw) shellfish served in certain unregulated places.
- Avoid raw or undercooked eggs and/or poultry.
- Wash all produce before consumption.
- For travelers to high-risk areas:
  1. Eat only cooked foods.
  2. Drink hot or carbonated beverages.
  3. Avoid water, raw peeled fruits/vegetables, green leafy vegetables, and street food sold by street vendors.
  4. Vaccines are available for *Salmonella typhi* and *Vibrio cholerae* (the latter provides about 50% protection for 3-6 months).

PATIENT EDUCATION

- Stress the importance of oral rehydration.
- Stress the need for early appropriate feeding.
- Relapse occurs due to dietary noncompliance.
- Travelers to developing areas should be educated on proper avoidance measures and treatment.
- Also stress the importance of good hygiene, hand washing, safe food preparation, and access to clean water as key in preventing gastroenteritis.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Gastroenteritis (Patient Information)

AUTHOR: **DANIEL K. ASIEDU, M.D., Ph.D.**

SUGGESTED READINGS

DuPont HL: Acute infectious diarrhea in immunocompetent adults, *N Engl J Med* 370:1532–1540, 2014.

DuPont HL et al.: Clinical practice. Bacterial diarrhea, *N Engl J Med* 361(16): 1560–1569, 2009. [Medline].

Gastroesophageal Reflux Disease ALG EBM PTG

BASIC INFORMATION

DEFINITION

Gastroesophageal reflux disease (GERD) is a motility disorder characterized primarily by heartburn and caused by the reflux of gastric contents into the esophagus. A current definition is a condition that develops when the reflux of stomach contents causes at least two heartburn episodes per week and/or complications.

SYNONYMS

Peptic esophagitis
Reflux esophagitis
GERD

ICD-9CM CODES
530.81 Gastroesophageal reflux disease
530.1 Esophagitis
787.1 Heartburn
ICD-10CM CODES
K21.9 Gastroesophageal reflux disease without esophagitis
R12 Heartburn

EPIDEMIOLOGY & DEMOGRAPHICS

- GERD is one of the most prevalent gastrointestinal disorders. It is the most common GI diagnosis recorded during visits to outpatient clinics. From 14% to 20% of adults are affected.
- Nearly 7% of persons in the United States have heartburn daily, 20% have it monthly, and 60% have it intermittently. Incidence in pregnant women exceeds 80%.
- Nearly 20% of adults use antacids or over-the-counter H_2 blockers at least once a week for relief of heartburn.

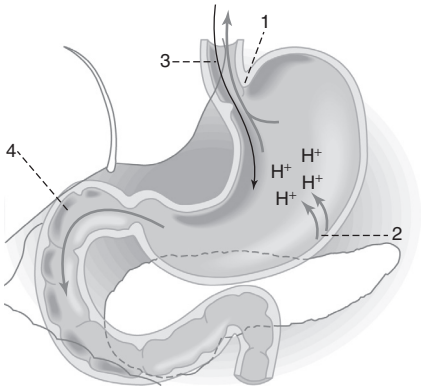


FIGURE G1-7 Pathogenesis of gastroesophageal reflux disease: *(1)* impaired lower esophageal sphincter—low pressures or frequent transient lower esophageal sphincter relaxation; *(2)* hypersecretion of acid; *(3)* decreased acid clearance resulting from impaired peristalsis or abnormal saliva production; *(4)* delayed gastric emptying or duodenogastric reflux of bile salts and pancreatic enzymes. (From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination: generally unremarkable.
- Clinical signs and symptoms: heartburn, dysphagia, sour taste, regurgitation of gastric contents into the mouth.
- Chronic cough and bronchospasm.
- Chest pain, laryngitis, early satiety, abdominal fullness, and bloating with belching.
- Dental erosions in children.

ETIOLOGY

- Incompetent lower esophageal sphincter (LES) (see Fig. G1-7).
- Medications that lower LES pressure (calcium channel blockers, alpha-adrenergic antagonists, nitrates, theophylline, anticholinergics, sedatives, prostaglandins).
- Foods that lower LES pressure (chocolate, yellow onions, peppermint).
- Tobacco abuse, alcohol, coffee.
- Pregnancy.
- Gastric acid hypersecretion.
- Hiatal hernia (controversial) present in >70% of patients with GERD; however, most patients with hiatal hernia are asymptomatic.
- Obesity is associated with a statistically significant increase in the risk for GERD symptoms, erosive esophagitis, and esophageal carcinoma.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Peptic ulcer disease.
- Unstable angina.
- Esophagitis (from infections such as herpes, *Candida*), medication induced (doxycycline, potassium chloride).
- Esophageal spasm (nutcracker esophagus).
- Cancer of esophagus.

WORKUP

- Aimed at eliminating the conditions noted in the differential diagnosis and documenting the type and extent of tissue damage. Generally, when symptoms of GERD are typical and the patient responds to therapy, there is no need for further diagnostic tests to verify the diagnosis.
- Upper GI endoscopy is useful to document the type and extent of tissue damage in persistent GERD and to exclude potentially malignant conditions such as Barrett esophagus. The American College of Physicians recommends endoscopy in the setting of GERD in people with heartburn and alarm symptoms (dysphagia, bleeding, anemia, weight loss, and recurrent vomiting). It is also indicated in people with GERD symptoms that persist despite a therapeutic trial of 4 to 8 weeks of bid PPI therapy in patients with severe erosive esophagus after a 2-month course of PPI therapy to assess healing and rule out Barrett esophagus.
- Fig. EG1-8 describes an approach to patients with heartburn.

LABORATORY TESTS

- 24-hr esophageal pH monitoring and Bernstein test are sensitive diagnostic tests; however, they are not practical and generally not done. They are useful in patients with atypical manifestations of GERD, such as chest pain or chronic cough.
- Esophageal manometry is indicated in patients with refractory reflux in whom surgical therapy is planned.

IMAGING STUDIES

An upper GI series is useful in patients unwilling to have endoscopy or with medical contraindications to the procedure. It can identify ulcerations and strictures; however, it may miss mucosal abnormalities. Only one third of patients with GERD have radiographic signs of esophagitis on an upper GI series.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Lifestyle modifications with avoidance of foods (e.g., citrus- and tomato-based products, onions, spicy foods, carbonated beverages, mint, chocolate, fried foods) and drugs that exacerbate reflux (e.g., caffeine, β-blockers, calcium channel blockers, α-adrenergic agonists, theophylline).
- Avoidance of tobacco and alcohol use.
- Elevation of head of bed (4 to 8 in) with blocks.
- Avoidance of lying down directly after late or large evening meals, consumption of smaller and more frequent meals.
- Weight reduction to BMI <25, decreased fat intake.
- Avoidance of clothing that is tight around the waist.

GENERAL Rx

- Proton pump inhibitors (PPIs) (esomeprazole 40 mg qd, omeprazole 20 mg qd, lansoprazole 30 mg qd, rabeprazole 20 mg qd, or pantoprazole 40 mg qd, or dexlansoprazole 30 mg) are generally safe, tolerated, and highly effective in most patients (Table G1-3).
- H_2 blockers (nizatidine 300 mg qhs, famotidine 40 mg qhs, ranitidine 300 mg qhs, or cimetidine 800 mg qhs) can be used but are generally much less effective than PPIs.
- Antacids (may be useful for relief of mild symptoms; however, they are generally ineffective in severe cases of reflux).
- Prokinetic agents (metoclopramide) are indicated only when PPIs are not fully effective. They can be used in combination therapy; however, side effects limit their use.
- For refractory cases: surgery with Nissen fundoplication. Potential surgical candidates should have reflux esophagitis documented by esophagogastroduodenoscopy and normal esophageal motility as evaluated by manometry. Surgery generally consists of reduction of hiatal hernia when present and placement of a gastric wrap around the gastroesophageal (GE) junction (fundoplication). Although

TABLE G1-3 Drug Therapy for Esophageal Disorders

Agent	Dose
Antacids: Liquid (to Buffer Acid and Increase LESP)	
For example, Mylanta II/Maalox TC (acid-neutralizing capacity, 25 mEq/5 ml)*	15 ml qid 1 hr after meals and at bedtime or as needed
Gaviscon (to Decrease Reflux via a Viscous Mechanical Barrier and Buffer Acid)	
$Al(OH)_3$, $NaHCO_3$, Mg trisilicate, alginic acid	2-4 tablets qid at bedtime or as needed
H_2-Receptor Antagonists (to Decrease Acid Secretion)	
Cimetidine	800 mg bid, 400 mg qid, ≈13 ml bid
Ranitidine	150 mg qid or 10 ml qid; maintenance dose, 150 mg bid, 10 ml bid
Famotidine	20-40 mg bid or 2.5-5 ml bid
Nizatidine	150 mg bid
Proton Pump Inhibitors (to Decrease Acid Secretion and Gastric Volume)†	
Omeprazole	20 mg/day; maintenance dose, 20 mg/day
Lansoprazole	30 mg/day; maintenance dose, 15 mg/day
Pantoprazole	40 mg/day; maintenance dose, 40 mg/day
Rabeprazole	20 mg/day; maintenance dose, 20 mg/day
Esomeprazole	20-40 mg/day; maintenance dose, 20 mg/day
Dexlansoprazole	30-60 mg/day; maintenance dose, 30 mg/day

LESP, Lower esophageal sphincter pressure.
*Patients with reflux are not generally hypersecretors of gastric acid, so the therapeutic doses of antacids are based on their capacity to buffer (normal) basal acid secretion rates of approximately 1 to 7 mEq/hr (mean, 2 mEq/hr) and peak meal-stimulated acid secretion rates of about 10 to 60 mEq/hr (mean, 30 mEq/hr).
†High-dose therapy is a twice-daily administration of the usual daily dose.
From Goldman L, Schafer AI: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Saunders.

laparoscopic fundoplication is now widely used, long-term medical therapy is a better choice for most patients who are willing to remain on daily acid-reduction medication. In patients preferring surgical intervention, surgery should not be advised with the expectation that patients with GERD will no longer need to take antisecretory medications or that the procedure will prevent esophageal cancer among those with GERD and Barrett esophagus.

- Endoscopic radiofrequency heating of the GE junction (Stretta procedure) is a newer treatment modality for GERD patients unresponsive to traditional therapy. Its mechanism of action remains unclear. Endoscopy gastroplasty (EndoCinch procedure) is also aimed at treating GERD. Initial results appear encouraging; however, long-term studies are needed before recommending these procedures.
- Lifestyle modification must be followed for life because this is generally an irreversible condition.

DISPOSITION

- Recurrence of reflux is common if treatment is discontinued.
- The majority of patients respond well to therapy. In patients with chronic GERD, long-term outcomes are similar between medical therapy with PPIs and anti-reflux surgery. Prolonged use of PPIs is associated with increased risk of fractures of hip, wrist, and spine; increased risk of diarrhea from *Clostridium difficile;* pneumonia; and possible iron deficiency from impaired iron absorption. PPIs also block the effects of clopidogrel by inhibiting cytochrome P450 2C19 isozyme. Therefore all PPIs (other than pantoprazole) should be avoided in patients using clopidogrel. H_2 blockers (e.g., ranitidine) can be used for patients with GERD taking clopidogrel.
- Postsurgical complications occur in nearly 20% of patients (dysphagia, gas, bloating, diarrhea, nausea). Long-term follow-up studies also reveal that within 3 to 5 yr, 52% of patients who had undergone antireflux surgery are taking antireflux medications again.

REFERRAL

- There is a strong and probably causal relation between symptomatic prolonged and untreated GERD, Barrett esophagus, and esophageal adenocarcinoma. GI referral for upper endoscopy is needed when there are concerns about associated peptic ulcer disease, Barrett esophagus, or esophageal cancer.
- Patients with Barrett esophagus should undergo surveillance endoscopy with mucosal biopsy every 2 yr or less because the risk of developing adenocarcinoma of esophagus is at least 30 times greater than that of the general population.
- Testing and treating for *Helicobacter pylori* in patients with GERD has not been shown to improve symptoms.
- All children with dental erosions should be evaluated for GERD.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Gastroesophageal Reflux Disease (GERD) (Patient Information)
Achalasia (Related Key Topic)
Dysphagia (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Context:
Gastroesophageal reflux disease (GERD) is a chronic, relapsing disease with symptoms that have negative effects on daily life. Two treatment options are long-term medication or surgery.

Objective:
To evaluate optimized esomeprazole therapy vs standardized laparoscopic antireflux surgery (LARS) in patients with GERD.

Design, Setting, and Participants:
The LOTUS trial, a 5-year exploratory randomized, open, parallel-group trial conducted in academic hospitals in 11 European countries between October 2001 and April 2009 among 554 patients with well-established chronic GERD who initially responded to acid suppression. A total of 372 patients (esomeprazole, n=192; LARS, n=180) completed 5-year follow-up.

Interventions:
A patient group of 266 patients were randomly assigned to receive esomeprazole, 20 to 40 mg/d, allowing for dose adjustments; 288 were randomly assigned to undergo LARS, of whom 248 actually underwent the operation.

Main Outcome Measure:
Time to treatment failure (for LARS, defined as need for acid suppressive therapy; for esomeprazole, inadequate symptom control after dose adjustment), expressed as estimated remission rates and analyzed using the Kaplan-Meier method.

Results:
Estimated remission rates at 5 years were 92% (95% confidence interval [CI], 89%-96%) in the esomeprazole group and 85% (95% CI, 81%-90%) in the LARS group (log-rank P=.048). The difference between groups was no longer statistically significant following best-case scenario modeling of the effects of study dropout. The prevalence and severity of symptoms at 5 years in the esomeprazole and LARS groups, respectively, were 16% and 8% for heartburn (P=.14), 13% and 2% for acid regurgitation (P<.001), 5% and 11% for dysphagia (P<.001), 28% and 40% for bloating (P<.001), and 40% and 57% for flatulence (P<.001). Mortality during the study was low (4 deaths in the esomeprazole group and 1 death in the LARS group) and not attributed to treatment, and the percentages of patients reporting serious adverse events were similar in the esomeprazole group (24.1%) and in the LARS group (28.6%).

Conclusion:
This multicenter clinical trial demonstrated that with contemporary antireflux therapy for GERD, either by drug-induced acid suppression with esomeprazole or by LARS, most patients achieve and remain in remission at 5 years. Ⓐ

Abstract[2]

Objective and Background:
We lack long-term data (>10 years) on the efficacy of antireflux surgery when evaluated within the framework of randomized clinical trials. Hereby we report the outcome of a randomized trial comparing open total (I) and a Toupet posterior partial fundoplication (II) performed between 1983 and 1991.

Methods:
One hundred and thirty-seven patients with gastroesophageal reflux disease were enrolled into the study. The mean follow up has now reached 18 years. During these years 26% had died and 16% were unable to trace for follow up. Symptom outcomes were assessed by the use of validated self-reporting questionnaires.

Results:
Long-term control of heartburn and acid regurgitation (reported as no or mild symptoms) were reported by 80% and 82% after a total fundoplication (I) and corresponding figures were 87% and 90% after a partial posterior fundoplication (II), respectively (n.s.).
The dysphagia scores were low 4.6 ± 1.3 (SEM) in group I and 3.3 ± 0.9 (SEM) in group II (n.s). The point prevalences of rectal flatulence and gas distension related complaints were of similar magnitude in the 2 groups. Twenty-three percentage of the patients in the total fundoplication group noted some ability to vomit compared with 31% in the partial posterior fundoplication group.

Conclusions:
Both a total and a partial posterior fundoplication maintain a high level of reflux control after 2 decades of follow up. The previously reported differences in mechanical side effects, in favor of the partial wrap, seemed to disappear over time. Ⓐ

Abstract[3]

Objectives:
Nocturnal heartburn and related sleep disturbances are common among patients with gastroesophageal reflux disease (GERD). This study evaluated the efficacy of dexlansoprazole MR 30 mg in relieving nocturnal heartburn and GERD-related sleep disturbances, improving work productivity, and decreasing nocturnal symptom severity in patients with symptomatic GERD.

Methods:
Patients (N=305) with frequent, moderate-to-very severe nocturnal heartburn and associated sleep disturbances were randomized 1:1 in a double-blind fashion to receive dexlansoprazole MR or placebo once daily for 4 weeks. The primary end point was the percentage of nights without heartburn. Secondary end points were the percentage of patients with relief of nocturnal heartburn and of GERD-related sleep disturbances over the last 7 days of treatment. At baseline and week 4 final visit, patients completed questionnaires that assessed sleep quality, work productivity, and the severity and impact of nocturnal GERD symptoms.

Results:
Dexlansoprazole MR 30mg (n=152) was superior to placebo (n=153) in median percentage of nights without heartburn (73.1 vs. 35.7%, respectively; P<0.001). Dexlansoprazole MR was significantly better than placebo in percentage of patients with relief of nocturnal heartburn and GERD-related sleep disturbances (47.5 vs. 19.6%, 69.7 vs. 47.9%, respectively; P<0.001), and led to significantly greater improvements in sleep quality and work productivity and decreased nocturnal symptom severity. Adverse events were similar across treatment groups.

Conclusions:
In patients with symptomatic GERD, dexlansoprazole MR 30 mg is significantly more efficacious than placebo in providing relief from nocturnal heartburn, in reducing GERD-related sleep disturbances and the consequent impairments in work productivity, and in improving sleep quality and quality of life. Ⓐ

Evidence-Based References

Galmiche J-P et al.: Laparoscopic antireflux surgery vs esomeprazole treatment for chronic GERD: the LOTUS randomized clinical trial, *JAMA* 305:1969–1977, 2011. Ⓐ

Mardani J et al.: Total or posterior partial fundoplication in the treatment of GERD: results of a randomized trial after 2 decades of follow-up, *Ann Surg* 253:875–878, 2011. Ⓐ

Fass R et al.: The effect of dexlansoprazole MR on nocturnal heartburn and GERD-related sleep disturbances in patients with symptomatic GERD, *Am J Gastroenterol* 106:421–431, 2011. Ⓐ

SUGGESTED READINGS

Hampel H et al.: Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications, *Ann Intern Med* 143(3):199, 2005.

Heidelbaugh JL et al.: Management of gastroesophageal reflux disease, *Am Fam Physician* 68:1311, 2003.

Kahrilas PJ: Gastroesophageal reflux disease, *N Engl J Med* 359:1700–1707, 2008.

Lacy BE et al.: The diagnosis of GERD, *Am J Med* 123:583–592, 2010.

Lundell L et al.: Comparison of outcomes twelve years after antireflux surgery or omeprazole maintenance therapy for reflux esophagitis, *Clin Gastroenterol Hepatol* 7:1292–1298, 2009.

Shaheen NJ et al: Upper endoscopy for GERD: best practice advice from the Clinical Guidelines Committee of the American College of Physicians, Ann Intern Med 157:808–816, 212.

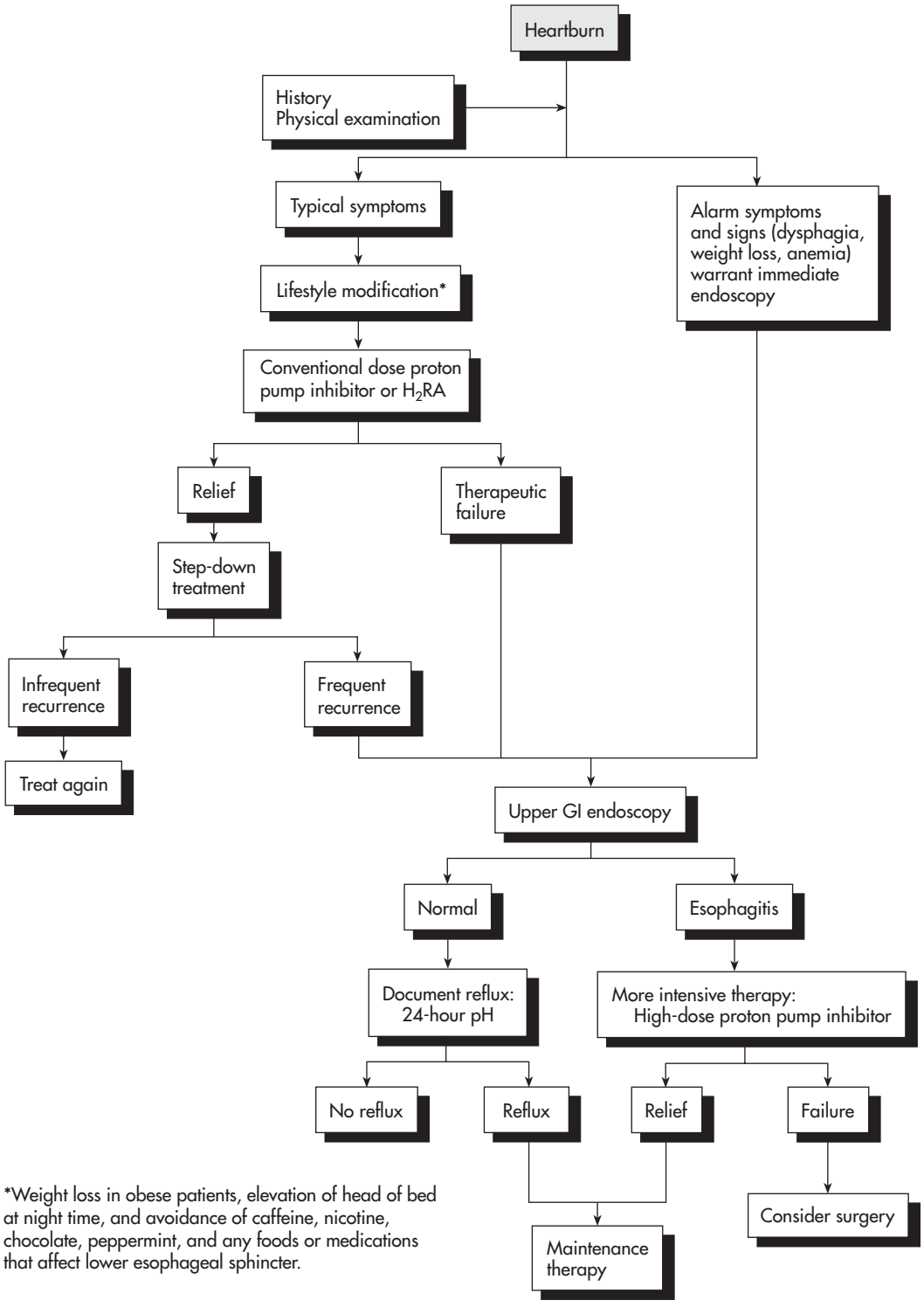


FIGURE EG1-8 Treatment of a patient with heartburn. *GI,* Gastrointestinal; *H_2RA,* H_2 receptor antagonist. (Modified from Sampliner RE: Heartburn. In Greene HL et al [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

BASIC INFORMATION

DEFINITION

Gender nonconformity or transgender identity results when a person's natal or biologic gender (chromosomes, hormones, organs, and secondary sexual characteristics) is incongruent with a person's perceived and asserted core gender identity (innate sense of being male or female). Gender dysphoria implies a notable discomfort and dislike of one's biologic gender and a desire to be physically different from the gender born into or assigned at birth.

Historically, gender and sexuality are related but separate concepts: gender is who a person is and how they identify as male, female, or somewhere on the continuum; sexuality is about who a person is attracted to or engages with intercourse. Although discomfort and dislike of one's biologic and anatomic gender and secondary sexual characteristics are a major component of gender dysphoria disorder, a transgender identity is not limited to dysphoria or psychopathology. Careful evaluation of each patient's unique perspective and gender experience may help guide options for care. Moving from biologic gender to asserted gender identity is known as transition. Transition is typically divided into three types (reversible, partially reversible, and irreversible), but should be tailored to the individual throughout the lifespan.

SYNONYMS

Gender nonconformity
Transgender
Gender dysphoria in children, adolescents, adults
Unspecified gender dysphoria
Transgender or transsexual

Coding:
Adults and Adolescents
ICD-9CM and DSM-5 CODES
302.85
ICD-10CM CODES
259.9 Endocrine disorder NOS
F64.2 Gender identity disorder of childhood
F64.9 Gender identity disorder, unspecified
F64.8 Other gender identity disorder

EPIDEMIOLOGY & DEMOGRAPHICS

DEVELOPMENT & BACKGROUND: Gender development begins as early as 18 months. By age 2 to 4 yr, children understand gender differences and use pronouns such as "him" and "her." Toddlers identify their own gender, and most consider gender a stable personal trait at age 5 to 6 yr. All children partake in gender play and explore gender activities, behaviors, and roles. Gender play does not mean a child is dysphoric, dislikes his or her gender, or identifies as the other gender.

PREDOMINANT AGE

- Gender nonconformity in prepubertal years is more than gender play; nonconforming prepubertal children exhibit *consistent, persistent, and insistent* play, dress, attributes, and activities of the other gender. Some of these children, but not all, experience dysphoria regarding their genitalia or express mild to intense discomfort and dislike of their biologic gender. In the prepubertal years, males who present to medical providers with this experience outnumber females by 3:1.
- With puberty, attaining a mature and adult gender (who you are, your male or female persona) and sexuality (attraction, orientation, behaviors, sexual partner preference) become core developmental tasks of adolescence. At this age, gender nonconforming youth who present for care changes to a ratio of 1:1 male to female.
- Incidence may be heavily associated with cultural expectations. It is generally less acceptable to be a feminized boy than a prepubertal girl who is a "tomboy." A peripubertal spike in gender dysphoria also occurs as pubertal females lose their androgenous appearance, develop breasts, and begin menses.

PREVALENCE: Overall estimates are between 1 in 10,000 to 1 in 100,000 depending on the study and source. Most believe these numbers vastly underestimate prevalence because they originate from adult surgical or gender specialty clinics.

GENETICS: There is no known single or specific genetic basis for gender dysphoria. The disorder has no specific relationships or associations with parent characteristics, socioeconomic status, or race/ethnicity. There may be a link between autism spectrum disorders and gender nonconformity.

RISK FACTORS: No proven risk factors. Most children and adults benefit from medical care models that do not pathologize their innate sense and experience of self. However, children and teens who are gender nonconforming experience higher rates of child abuse, bullying, mental health concerns (e.g., anxiety, depression, suicidality), and substance use. Transgender adult populations have poorer health outcomes, such as depression, anxiety, self-harm and suicide, substance use, underemployment, homelessness, incarceration, and positive HIV status. Poorer health outcomes are explained by using minority stress theory (chronic stress related to stigma and dysphoria) rather than gender variance as a pathology itself.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Prepubertal children present with *consistent, persistent, and insistent* interest and expression of other or opposite-gendered activities and behaviors. Boys may be considered more feminine than their same-age peers; they may prefer to wear long hair, nail polish, makeup, girls' jewelry, and clothing. Girls may be considered "tomboys" and reject wearing dresses and skirts, prefer short hair, wear boys' clothing, and participate in traditionally masculine play and activities. During the school-age years, children become sensitive to social expectations and norms as well as both explicit and implicit criticism, and some may suppress their feelings of being in the wrong body and assume cisgender expression. Many gender dysphoric children who do conform in their gender play and expression, however, still experience underlying problems with biology and identity.

Adolescents and adults may present at any point along the lifespan, though a majority express having cross-gender feelings and identities earlier in life. Many gender dysphoric persons will not present directly with gender dysphoria but present with mood, behavior, or social problems. For many persons, gender dysphoria or the disclosure of gender nonconformity is first elicited as a result of mental health counseling.

DIAGNOSIS

- Gender nonconformity and transgender identity is not considered pathologic or requiring psychiatric evaluation and care. Developmental models instead view gender along a biologic spectrum with diverse presentations and expression. Persons may assert a nonconformity identity without severe self-hatred or significant dysphoric presentation. Psychiatric evaluations are no longer considered necessary or essential to "diagnose" gender nonconforming persons. Transgender individuals may have a range of expression, from an inherent, longstanding belief and feeling that one's psyche is more congruent with the opposite gender, to feeling androgenous and non-gendered, to strongly desiring not to have or to be rid of one's primary and secondary gender's physical characteristics.
- Changes in DSM-5 focus on "gender dysphoria" and inherent distress in one's natal gender and biologic gender characteristics rather than creating a "disorder" of identity. For an individual to be diagnosed with gender dysphoria, marked differences between the individual's natal or assigned gender and expressed/experienced gender must exist for at least six months; cause clinically significant distress or impairment in social, occupational, or other important areas of functioning; with strong and consistent desire to be the other gender. Persons with severe dysphoria and sequelae from the mismatch in biology with identity usually benefit from participating in therapy, building skills to create successful transition plans, and/or obtaining treatment for commonly associated comorbid psychiatric concerns, such as anxiety and depression.
- Gender dysphoria has a chapter in DSM-5 separate from Sexual Dysfunctions and Paraphilic Disorders. Many gender specialists focus on paradigms using physical or endocrine conditions to avoid stigma and allow for improved access to hormonal and surgical therapies.
- DSM-5 changes add a posttransition specifier for people who are living full time as the desired gender identity so as to ensure treatment access for hormone therapy, related surgeries, or counseling.

WORKUP

- Ideally, this interview is in the context of interviewing the individual as a person and part of a holistic health assessment. Persons with various degrees and experience in behavioral health can perform these interviews. While some patients may benefit from additional therapy or psychiatric evaluation, many transgender individuals should not be "required" to seek psychiatric care. Patients may benefit from additional psychiatric services for comorbid mental health concerns, social and emotional skill building, and creating a safe and successful transition plan. Parents of a gender nonconforming child may benefit from receiving support and their own counseling services so that they may successfully focus on the child's issues and needs.
- Clinical interview includes assessment of gender experience from childhood until present; desired name, pronoun, and past and current place on the gender spectrum; past and current attempts to feminize or masculinize with clothing, hair, makeup, hormones, and surgeries; future goals of transitioning, gender identity, and expression. For many children, many parents may provide insight as to early childhood gender identity and expression. For some children, parental distress and denial of a consistent cross-gender identity is the most problematic aspect of providing care.
- Review for known comorbidities by asking mental health specific questions about: depression, anxiety, self-harm (cutting and suicidal ideation), psychiatric hospitalization, substance use. Patient history should also include: sexual attraction and behaviors and risk for sexually transmitted infections and pregnancy; social history, experience of bullying, hate crimes, physical or emotional/verbal abuse, homelessness, joblessness, and survival sex. Resiliency theory also promotes focusing on patient strengths and identifying social support systems.
- An initial visit may include a physical examination depending on the patient's goals. Many gender dysphoric persons are exquisitely uncomfortable with their genitalia and genital examination. If the evaluation is a consultation for information and counseling, an exam may be deferred until the patient is more comfortable and familiar with the provider.
- A general physical examination may be performed as with any new patient, but detailed examination of secondary sexual characteristics (breasts, vulva, penis, testicles) often is deferred at an initial visit. Tanner staging genitalia to determine which peripubertal youth are most appropriate for gonadotropin releasing hormone (GnRH) analogues ("puberty blockers") or cross-gender hormones is important. Those young children who are not peripubertal or those teens who are well into Tanner stage 5 (by chronologic age, years post menarche, or adult secondary sexual characteristics) may be allowed to defer the genital exam during these initial visits.
- Luteinizing hormone is a preferred lab for evaluating prepubertal children and GnRH analogue use, but additional laboratory studies may include follicle stimulating hormone, testosterone, or estradiol. For older youth or adults starting cross-gender hormones, baseline laboratory values include CBC, lipid panel, and liver function tests. Cross-gender hormones may affect hematopoiesis, cholesterol levels, and irritate the liver. Testosterone is useful to measure androgen suppression in asserted women receiving estrogen therapy. Prolactin is an additional baseline lab for continued estradiol therapy has been rarely associated with prolactinoma. Potassium and blood pressure monitoring is useful in transwomen using spironolactone to block male pattern hair growth. Asserted transmales taking testosterone may get routine total testosterone levels with a goal within average adult male range.
- Screening for sexually transmitted infections (urine, rectal, and oral *Chlamydia* and gonorrhea; syphilis; herpes simplex virus; HIV; hepatitis B and C), and pregnancy is indicated according to sexual practices.
- Ancillary testing may include various psychiatric screening and diagnostic tools for comorbid depression, anxiety, suicidality, substance use, and interpersonal violence.
- Additional preventive care screening and testing may be deferred. Over time, patients should receive typical preventive and screening tests for both biologic gender and asserted gender.

Rx TREATMENT

Treatment is determined by patient age and development (including Tanner stage) and desired place on the gender spectrum. Moving from biologic gender to asserted gender identity or transition is typically described as: reversible, partially reversible, and irreversible.

REVERSIBLE TRANSITION

- Social transition includes taking a name and pronoun in the identified gender, as well as clothing, shoes, hair, make-up, and other gender identifying social cues. For prepubertal, androgenous children, social transition does not require hormones, but does require extensive planning for disclosure, social support, and peer- and school-based activities.
- GnRH agonists.
- Blockers in puberty are reversible and best when used at very early Tanner stage II breast and testicular development. When used in early puberty, blockers stop puberty with regression to prepubertal hormones and secondary sexual characteristics. This often "buys time" for additional support and assessment or allowing the family to determine a safe and supportive social transition plan.
- May be used for patients who are at Tanner stage III or IV according to genital exam but are still androgenous in regard to other secondary sex characteristics, such as voice, facial and body hair, bone, muscle, and fat deposition. Blockers can also be used to stop penile function or menses, which can be highly distressing to some gender dysphoric persons.
- Are *completely reversible.* If stopped, a person can continue into biologic puberty with no impact on future gender characteristics or fertility. Most teens who opt to start GnRH agonists to block puberty continue to create a transition plan and eventually move to cross-gender hormones and puberty in their asserted gender. The current literature from the past 30 or more years demonstrates that it is unlikely that an adolescent who is consistently, persistently, and insistently gender nonconforming or transgender will return to his or her natal gender or regret either blockers or cross-gender hormones. This can be both of concern and relief to parents as they determine how to best to support their child.

PARTIALLY REVERSIBLE TRANSITION

- Cross-gender or gender confirming hormone therapies include testosterone for masculinization and estradiol for feminization. Both hormones may have reversible effects on skin, fat deposition, and muscle mass. Irreversible testosterone effects may include masculine voice changes, changes in facial and body hair, and clitoromegaly. Irreversible estradiol effects include aerolar enlargement and breast tissue growth. These changes are usually desired by transgender individuals and desired for continued transition into their asserted gender.
- Estradiol creates softer skin, female body fat deposition (hips/thighs), and breast development. It may impair erectile function, which may or may not be desired because some male-to-female persons still want or depend on penile function (masturbation, sexual relationships, and/or sex work. Estradiol is typically administered sublingually but can be taken intramuscularly, orally, or topically. Topical medicines are expensive and time consuming, run the risk of undesired feminization (or masculinization) of sex partners or others in close physical contact, but are likely have the lowest thromboembolic risks.
- Testosterone masculinizes by inducing male hair patterns, deepening the voice, and inducing male-pattern fat and muscle deposition (bulk and abdominal girth) and clitoromegaly. It can lead to vaginal atrophy, resulting in dyspareunia for transgender female-to-male persons who use the vagina for sex. Testosterone comes in a variety of vehicles, including subcutaneous, intramuscular, and topical. Testosterone is teratogenic in pregnancy. Consent to what we know and do not know is an important part of beginning the cross-gender hormone process. We currently do not have strong guidelines for ongoing preventive care and anticipatory guidance.
- Both sex hormones should not be used in lieu of contraception as current evidence suggests that estrogen or testosterone are not sufficiently effective as a contraceptive.

Nor is future fertility guaranteed, for persons who prioritize having biologic children. Persons taking testosterone who are having unprotected penile-vaginal sex should be counseled and offered birth control in addition to testosterone. Individuals who feel strongly about being about having future genetic children or child bearing may wish to consult reproductive endocrinology and infertility specialists to discuss sperm and oocyte preservation strategies. For male-to-female persons, sperm banking offers future options for biologic children, although at some expense. For female-to-male persons, oocyte banking is extremely expensive and has not yet demonstrated reliable successful outcomes. For many transgender persons, transition to their asserted identity is more important than creating or carrying genetic children. Many transgender persons would prefer to parent or adopt in their identified or asserted gender.

IRREVERSIBLE TRANSITION: Includes mostly surgical options for masculinization (mastectomy and male chest reconstruction, hysterooophrectomy, and orchi-peniplasty) or feminization (orchiectomy-penectomy with vulvovaginal reconstruction, breast implants, and other cosmetic surgeries). Many patients opt for partial surgical transition due to expense. At present, many surgeries are not covered under most insurance plans.

This may change with changes in Federal government recommendations in 2014. The U.S. Department of Health and Human Services Departmental Appeals Board ruled Medicare's categorical exclusion of gender confirmation medical and surgical treatments was unreasonable and contrary to medical standards of care. While Medicare can no longer categorically exclude gender surgeries as it has done since the 1980s, there is, as yet, no consensus or plan for how to include and cover these services by Medicare. Lack of insurance, under-insurance and lack of available providers are additional reasons that many transgender individuals may not opt for irreversible surgical care. Male-to-female genitoplasty surgeons in the United States are rare, and many patients travel overseas for surgical care. Top surgery is more with asserted males seeking specific male chest reconstructive surgeries and asserted females opting for breast implants. It is important to ask specific goals for surgery because they vary by individual patient.

ADDITIONAL THERAPIES: Anti-androgens such as spironolactone prevent male-pattern hair growth. Vocal coaching, tracheal shaving, and other facial feminizing surgeries are some options for male-to-female. Progesterone is used by some asserted females to promote increased breast development, although there is no evidence pointing to side effects or its effectiveness. Topical androgen therapies do not seem to improve clitoral growth. Individual, family, and marital counseling and therapies can be important for dysphoric individuals or for parents and/or partners struggling to unconditionally accept a loved one's transition. Support is important to family members who are involved in a patient's transition. Medications for anxiety, depression, and other mental health concerns may facilitate self-esteem, mood, cognitive function, and social skills building as persons and families negotiate the process of transition. Social support and activity groups may help gender nonconforming persons find a sense of community, feel and become less isolated, and improve transition experiences. Reparative therapy is *universally* rejected as *unethical and harmful* by all the national medical and psychological boards and associations.

DISPOSITION

- Gender is a physical, emotional, social, and cultural construct across the lifespan that every person experiences. Newer paradigms of gender focus on the brain as the most important "source" of gender. When brain and body gender are not congruent a person may experience gender nonconforming or transgender identity. Some transgender individuals experience a severe degree of gender dysphoria, but dysphoria is not a prerequisite for gender nonconforming persons to receive care. Gender dysphoria and social stigma may create lifelong implications for physical, emotional, and social well-being.
- Younger prepubertal gender nonconforming patients may grow up and be cis or transgender, hetero or homosexual. Patients who have early consistent, persistent, insistent dysphoria or cross-gender identification are more likely to continue this into puberty and eventually transition.
- Peripubertal youth who begin hormone blockers are likely to continue to cross-gender hormones and may desire more permanent surgical interventions.
- Youth who are transitioned early both socially and hormonally, and experience puberty in their identified gender, and have family support may have improved ability to be accepted in their asserted gender, decreased suicidality, and less risk of nonmedical use of street hormones and drugs, as well as fewer future surgical interventions.
- Evidence strongly suggests that gender and sexual minorities who have early and consistent parental support, despite being gender and sexually nonconforming, have decreased rates of suicide and substance use.
- For persons experiencing some or all of puberty in their biologic, but not identified gender, cross-gender hormones and/or gender-affirming surgeries offer the promise of living in their asserted gender. For persons who transition later in life, especially in their 30s and older, physical transition and "passing" are more difficult.
- In addition to minority stress and poorer mental health outcomes, being a visual and visible sexual minority has significant and demonstrated social risks for victimization from hate crimes and interpersonal violence, low socioeconomic status, underemployment, and isolation. Early identification and early transition in a person's identified gender, along with a better likelihood of acceptance, may offer significant psychosocial benefits to many gender dysphoric persons.
- Regardless of the timing of transition, safety and ongoing support is a priority in transition planning and important to consider along the lifespan.

REFERRALS

- Providers who are not comfortable with gender or behavioral assessments may want to refer to medical providers with experience and expertise in gender issues and care. This group may include pediatric, family medicine, medicine-pediatrics, endocrinology and psychiatry providers. Similarly, there are therapists and social workers with expertise in gender dysphoria assessment and management.
- There are few contraindications to transitioning for most transgender or gender dysphoric persons. Active psychosis and inability to consent to care would require further psychiatric evaluation but are extremely rare. For older persons, some medical issues involving cardiac, liver, and thromboembolic risks complicate hormone use and need to be taken into consideration.

PEARLS & CONSIDERATIONS

- Periodic assessment of a person's place on the gender spectrum can begin in toddler age children and can continue into adulthood as a potentially effective way of helping identify and support gender dysphoric persons early.
- Early identification and parental support for gender dysphoric and nonconforming persons may lead to improved mental and physical health outcomes.
- Hormone blockers and cross-gender hormones typically offer far more benefit than risk in the treatment of gender dysphoria when a person desires to transition to the opposite gender.
- Federal changes in Health and Human Services may increase access to a variety of services, including gender affirming surgeries, for a growing population of transgender identified persons.

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BASIC INFORMATION

DEFINITION

Tonic clonic seizures are characterized by sudden loss of consciousness, muscle contraction (tonic phase) followed by rhythmic jerking activity (clonic phase).

SYNONYMS

Convulsive seizures
Grand mal seizures

ICD-9CM CODES
345.1 Generalized convulsive epilepsy
ICD-10CM CODES
G40.6 Grand mal seizures, unspecified
G41.0 Grand mal status epilepticus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 30 to 50 cases per 100,000 person-yr (epilepsy incidence).
PEAK INCIDENCE: Not applicable.
PREVALENCE: 5 to 8 cases per 1000 persons (epilepsy incidence).
PREDOMINANT SEX AND AGE: No gender preference.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with tonic clonic seizures usually have normal physical and neurologic examinations.
- During the seizures, the patients are unresponsive and can have violent postures with severe repetitive muscle contractions.
- After the seizure, the patients are usually lethargic and confused.
- Tonic clonic seizures are associated with injuries, bladder incontinence, and tongue biting.
- Focal postictal weakness may point toward a focal neurologic lesion (Todd's paralysis).

ETIOLOGY

- Seizures are a cardinal sign of cortical neurologic injury.
- The etiology of seizures can be idiopathic (likely genetic), cryptogenic (possibly genetic), and symptomatic (due to a neurologic injury/infection).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Convulsive syncope.
- Nonepileptic spells.

WORKUP

- EEG.
- Ambulatory EEG and/or video EEG recommended for patients with diagnostic uncertainty.
- MRI of the brain.

LABORATORY TESTS

- Routine blood workup (CBC, CMP, glucose, electrolytes).
- Urine drug screen.
- Lumbar puncture is recommended in patients with suspicion of meningitis.

IMAGING STUDIES

- Neurodiagnostic imaging studies such as CT of the head or, preferably, MRI of the brain should be performed in all patients with first unprovoked seizure.
- CT scans of the head should be avoided in children due to unnecessary exposure to radiation and the low yield of the test. CT scans of the head are reserved for neurologic emergencies and are adjusted for weight in children.

TREATMENT

- Treatment is based on the type and etiology of seizures (i.e., metabolic disturbance, infectious, etc.).
- Levetiracetam is an effective and well-tolerated antiepileptic drug for treating generalized tonic clonic seizures.
- Valproic acid is better tolerated than topiramate and more efficacious than lamotrigine in patients with generalized and unclassified epilepsy types.
- Valproic acid should be avoided in girls and women with childbearing potential due to the risk of teratogenicity.

NONPHARMACOLOGIC THERAPY

Not applicable.

GENERAL Rx

- First unprovoked seizure with normal imaging, EEG, and laboratory workup requires no treatment.
- Recurrent seizures and seizures with abnormal studies require treatment depending on the etiology.
- Levetiracetam (Keppra): Initial dose 250 to 500 bid, maximum dose 1500 mg bid.
- Valproic acid (Depakote): Initial dose: 10 to 15 mg/kg/day (divided bid), maximum dose 60 mg/kg/day.

CHRONIC Rx

Chronic treatment with antiepileptic drugs is indicated for ≥2 unprovoked seizures or in patients with one seizure with abnormal workup.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Not applicable.

DISPOSITION

- Patients should avoid situations that may cause injuries or accidents in the event of a seizure.
- No driving until seizure-free in accordance with local laws and regulations.

REFERRAL

Patients with epilepsy and seizures should be referred for a consultation by a neurologist, preferably one with epilepsy training.

PEARLS & CONSIDERATIONS

COMMENTS

- It is crucial to understand that tonic clonic seizures can occur in variety of acute neurologic diseases.
- Successful treatment depends on the correct choice of antiepileptic drugs based on the type (partial versus generalized in onset) and etiology of the seizures.
- Valproic acid should be avoided in girls and women with childbearing potential due to the risk of teratogenicity.
- All women of childbearing age taking antiepileptic drugs should take folic acid supplementation (1 to 4 mg/day) for the prevention of neural tube defects.

PREVENTION

Sleep deprivation and alcohol consumption should be avoided.

PATIENT & FAMILY EDUCATION

- Patients with epilepsy have normal lives.
- The goal of treatment is no seizures and no side effects to medications.
- Patient education and information can be obtained at the Epilepsy Foundation: www.epilepsyfoundation.org.
- Pregnant women with epilepsy should visit the Antiepileptic Drug Pregnancy Registry website for information and assistance: www2.massgeneral.org/aed.
- Patients with ongoing seizures are forbidden to drive; check your state regulations and laws regarding driving and epilepsy.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Generalized Tonic-Clonic Seizures (Patient Information)
Status Epilepticus (Related Key Topic)

AUTHOR: **PATRICIO SEBASTIAN ESPINOSA, M.D., M.P.H.**

SUGGESTED READING

Musicco M et al.: Treatment of first tonic-clonic seizure does not improve the prognosis of epilepsy. First Seizure Trial Group (FIRST Group), *Neurology* 49(4):991–998, 1997.

Gestational Diabetes Mellitus (GDM) PTG

BASIC INFORMATION

DEFINITION

- Glucose intolerance that begins, or is first recognized, during pregnancy.
- In the United States, the "two-step" approach is commonly used and is currently endorsed by the American College of Obstetricians and Gynecologists (ACOG) and the National Institutes of Health (NIH). Women are first screened with a 1-hr, nonfasting 50 g oral glucose tolerance test. If the result is ≥ 130 mg/dl, a 3-hr, 100 g oral glucose tolerance test is ordered. The diagnosis is made if two or more of the glucose values are met or exceeded:
  Fasting: 95 mg/dl
  1-hr: 180 mg/dl
  2-hr: 155 mg/dl
  3-hr: 140 mg/dl
- The International Association of Diabetes in Pregnancy Study Group has recommended a simplified "one-step" approach to screening and diagnosing gestational DM (GDM). It involves a fasting 75 g, 2-hr oral glucose tolerance test. A diagnosis of GDM is made if any of the following levels of plasma glucose are exceeded: ≥92 mg/dl when fasting, ≥180 mg/dl at 1 hr, or ≥153 mg/dl at 2 hr. Although this approach is endorsed by the American Diabetes Association, the NIH Consensus on GDM did not endorse these guidelines in 2013 because of increases in the prevalence of GDM, along with corresponding costs and interventions without clear evidence of improvement in outcomes.
- Pregnant women with diabetes mellitus (DM) (gestational or preexisting) are classified according to White's classification (Table G1-4).

SYNONYMS

Gestational diabetes
Diet-controlled gestational diabetes (A1)
Medication-treated gestational diabetes (A2)

ICD-9CM CODES
648.8; if using insulin to treat, add V58.67
ICD-10CM CODES
O99.810 Abnormal glucose complicating pregnancy

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Approximately 5% to 6% of pregnancies using the two-step approach and 15% to 20% using the one-step approach.
PREDOMINANT SEX AND AGE: Women of childbearing age.
GENETICS: Higher rate in women with family history of GDM or type 2 diabetes; specific HLA alleles (DR3 or DR4) predispose to the development of DM type 1 after delivery.

RISK FACTORS

- Obesity.
- Family history of GDM or type 2 diabetes.
- Polycystic ovarian syndrome.
- Multiple gestation.
- Hypertension.
- Chronic systemic steroid use.
- Previous infant weighing >9 lb or with shoulder dystocia.
- Unexplained perinatal loss or malformation.
- Personal history of abnormal glucose tolerance or GDM.
- Hispanic, Native American, African American, Asian or Pacific Islander ethnicity.

POTENTIAL RISK FACTORS

- Limited physical activity the year before pregnancy.
- Prepregnancy diet low in fiber and high in glycemic load.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Suspect GDM if:
- Fetal size greater than dates.
- Macrosomia or polyhydramnios on ultrasound.
- Marked maternal obesity or weight gain.

ETIOLOGY

- During normal pregnancy there is increased insulin resistance because of placental secretion of diabetogenic hormones in the late second and third trimesters. Pancreatic beta-cell secretion increases to compensate for the increased insulin resistance. GDM occurs when this need cannot be met.
- Insulin resistance is also exacerbated by an increase in maternal adipose deposition, decreased exercise, and increased caloric intake.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Preexisting type 1 or 2 DM not previously diagnosed.

WORKUP

- History with focus on personal medical history, prior pregnancy history, and family history.
- Routine prenatal examination.
- Laboratory evaluation (see the following).

LABORATORY TESTS

- "Two-step" approach.
  1. For screening without risk factors, order a 1-hr glucose tolerance test (Nonfasting; 50 g oral glucose load) at 24 to 28 wk.
  2. For screening with risk factors, order at first prenatal visit, then repeat at 24 to 28 wk if initial screen was normal. If abnormal at intake, consider possibility of undiagnosed preexisting DM and check hemoglobin A1c.
- If 1-hr test result is abnormal (≥130 mg/dl), order 3-hr glucose tolerance test (Fasting: 100 g oral glucose load).
  1. Performed after 3 days of unrestricted diet (carbohydrate load is probably not necessary).
  2. Carpenter and Coustan Criteria National Diabetes Data Group Criteria.
  3. GDM is diagnosed if two or more of the glucose values are met or exceeded:

Fasting	≥95 mg/dl	≥105 mg/dl
1-hr plasma glucose	≥180 mg/dl	≥190 mg/dl
2-hr plasma glucose	≥155 mg/dl	≥165 mg/dl
3-hr plasma glucose	≥140 mg/dl	≥145 mg/dl

- If one of four values on 3-hr glucose tolerance test is abnormal, repeat testing in 1 month and consider beginning a diabetic diet.
- "One-step" approach
  1. Rule out overt diabetes at the initial prenatal visit. A diagnosis of diabetes is made if a woman meets any of the following criteria: fasting plasma glucose >126 mg/dl, A1c >6.5%, random plasma glucose >200 mg/dl.
  2. Perform a one-step screening at 24 to 28 wk on all pregnant patients who have not already been diagnosed with diabetes or GDM. This is a 2-hr, 75 g oral glucose tolerance test performed after an overnight fast. A diagnosis of GDM is made if one or more of the following values are met or exceeded:
     Fasting: ≥92 mg/dl
     1-hr plasma glucose ≥180 mg/dl
     2-hr plasma glucose ≥153 mg/dl
- As of January 2014, The U.S. Preventive Services Task Force (USPSTF) recommends screening for gestational diabetes in all pregnant women after 24 weeks' gestation. The current evidence is insufficient to assess the balance between the benefits and harms of screening women for GDM in asymptomatic women before 24 weeks' gestation. Clinicians should discuss early screening

TABLE G1-4 White's Classification for Pregnant Women with Diabetes (Gestational or Preexisting)

Class	Description
A1	DM diagnosed during pregnancy and controlled by diet
A2	DM diagnosed during pregnancy and requiring medication
B	Insulin-requiring DM diagnosed before pregnancy, age >20 yr, lasting <10 yr
C	Insulin-requiring DM, onset at age 10 to 19 yr, with a duration 10 to 19 yr
D	Onset >10 yr or duration >20 yr, or associated with hypertension or background retinopathy
F	DM with renal disease
H	DM with coronary artery disease
R	DM with proliferative retinopathy
T	DM with renal transplant

DM, Diabetes mellitus.

for GDM with their patients and make case-by-case decisions. The discussion should include information about the uncertain benefits and harms as well as the frequency and uncertain meaning of a positive screening test result.
- Women with GDM have an increased risk of developing diabetes during their lifetime. Women with GDM should be screened at 6 to 12 weeks postpartum with a 75 g 2-hour GTT to diagnose impaired glucose tolerance or diabetes.

IMAGING STUDIES

Ultrasound for fetal size at least once at 36 to 37 wk; more frequently (every 3 to 4 weeks) if macrosomia suspected.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Glucose monitoring:
  1. Four times daily: fasting and 2-hr postprandial.
  2. Goals: fasting ≤95 mg/dl; 2-hr postprandial <120 mg/dl.
  3. Can also use 1-hr postprandial goal of <140 mg/dl.
- Dietary modifications aimed at glycemic control:
  1. Follow a low-fat, high-fiber diet; avoid sugar and concentrated sweets; and eat small, frequent meals.
  2. Nutrition counseling for diet that adequately meets the needs of pregnancy but restricts carbohydrates to 35% to 40% of daily calories.
  3. Normal BMI: 30 kcal/kg/day; BMI above 30 to 25 kcal/kg/day and morbid obesity 12 to 14 kcal/kg/day.
- Regular moderate exercise.

PHARMACOLOGIC Rx

Begin if >20% of fasting or postprandial glucose values are elevated after trial of diet control:

- Oral hypoglycemics:
  1. Oral hypoglycemics are equivalent in efficacy to insulin and can be appropriate first-line agents. There is no consistent evidence from randomized trials showing any increase in short-term adverse maternal or neonatal outcomes with oral medications vs insulin. There are no long-term trials available, and both metformin and glyburide may cross the placenta.
  2. Glyburide: begin at 2.5 mg qd and titrate up to a maximum of 20 mg qd (10 mg bid). Increase dose as needed by 2.5 to 5 mg/wk.
  3. Metformin is typically used pre-pregnancy for polycystic ovarian syndrome or preexisting diabetes and may be continued into pregnancy. Studies show that up to 50% of women may require insulin to achieve glycemic control, however, no adverse outcomes have been described. Comparisons of glyburide versus metformin similarly show more women on metformin will require addition of insulin to achieve glycemic control.
- Insulin:
  - There are no randomized controlled trials on insulin regimens, and therapy is largely guided by expert opinion.
  - Insulin may be started first line or added when oral medications have failed to achieve glycemic control.
    1. One commonly used regimen:
       1. Insulin 0.7–1.0 U/kg/day SQ (based on current pregnant weight), with two thirds of the total daily dose given in the morning and one third of the total daily dose given in the evening
       2. One third of each dose is given as short-acting (regular, lispro, or aspart) insulin and the remaining two thirds as NPH insulin
    2. Another option:
       1. If fasting values are elevated, use NPH at bedtime with initial dose of 0.2 U/kg
       2. If postprandial values are elevated, use rapid-acting insulin before meals with initial dose 1.5 U/10 g carbohydrate at breakfast and 1 U/10 g carbohydrate at lunch and dinner
    3. Long-acting insulin such as glargine (Lantus) does not have sufficient data to determine whether it crosses the placenta; it may be continued in persons with preexisting diabetes who are well controlled but is not recommended in patients with newly diagnosed GDM

ANTENATAL TESTING

Antepartum testing is recommended for women with pre-gestational diabetes. There is no consensus regarding antepartum testing in gestational diabetes, and this should be guided by local standards.

ONE COMMONLY USED REGIMEN:

- Class A1: NST/AFI at 40 wk.
- Class A2: weekly NST/AFI beginning at 32 wk or when medications are initiated.
- Poorly controlled diabetes, vascular complications, or hypertension: biweekly NST/AFI beginning at 28 wk and consider admission for initial glycemic control.

TIMING AND ROUTE OF DELIVERY

- Women with preexisting diabetes should be induced at 39 weeks.

ACOG states that there is no evidence-based recommendation that can be made regarding timing of delivery in women with GDM. Decisions should be guided by local standards of care, and well-controlled A1 or A2 women should not be induced before 39 weeks.

- Counseling regarding elective cesarean section at or after 39 weeks if estimated fetal weight is over 4500 g.
- Consider delivery earlier than 39 weeks if poor control or other medical indications such as growth restriction or preeclampsia.

INTRAPARTUM MANAGEMENT

- Goal is normoglycemia (80 to 120 mg/dl) using insulin and D5 lactated Ringer's IV fluid if needed.
- Monitor glucose every 1 to 2 hours.
- Preparation for shoulder dystocia
- If on glyburide, discontinue in labor or 12 hr before a scheduled induction
- If on insulin consider decreased long acting insulin by one third to one half before scheduled induction

Neonatal Management

- Check 30- and 60-min glucose.
- Watch for signs of hypoglycemia, hypocalcemia, hyperbilirubinemia, and polycythemia.

POSTPARTUM MANAGEMENT

- Class A2: check fasting level before discharge; if abnormal, continue checking at home and early follow-up with primary care physician to confirm diagnosis of DM.
- 6-wk postpartum visit: screen for impaired glucose tolerance and diabetes in A1 and A2 women with a 75 g, 2-hr glucose tolerance test
- If no evidence of DM, screen annually for DM and counsel on risk factor modification

REFERRAL

- Nutritionist.
- High-risk obstetrician.
- Maternal-fetal medicine.
- Diabetes educator.

COMPLICATIONS

- Maternal: preeclampsia, future type 2 DM or GDM, operative delivery.
- Fetal: polyhydramnios, macrosomia, shoulder dystocia, birth trauma, congenital malformations.
- Neonatal: hypoglycemia, hypocalcemia, hyperbilirubinemia, polycythemia, perinatal death, future obesity and DM, impaired fine and gross motor functions; increased rates of inattention and hyperactivity.

! PEARLS & CONSIDERATIONS

Trials have shown that although treatment of mild gestational DM did not significantly reduce the frequency of a composite outcome that included stillbirth or perinatal death and several neonatal complications, it did reduce the risks of fetal overgrowth, shoulder dystocia, cesarean delivery, and hypertensive disorders.

PREVENTION

Regular exercise, maintenance of ideal body weight, and high-fiber low-glycemic diet

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Gestational Diabetes (Patient Information)
Diabetes Mellitus (Related Key Topic)

AUTHORS: **MARY BETH SUTTER M.D.**, **NIRALI BORA, M.D.**, **SUSANNA R. MAGEE, M.D., M.P.H.**, and **HEIDI RADLINSKI, M.D., M.P.H.**

SUGGESTED READINGS

AACE Diabetes Mellitus Clinical Practice Guidelines Task Force: AACE diabetes mellitus guidelines. Diabetes and pregnancy, *Endocrinol Pract* 13(suppl 1):55, 2007.

ACOG Practice Bulletin Number 137: Gestational diabetes mellitus, *Obstet Gynecol* 122:406–416, August 2013.

Committee opinion no. 504 screening and diagnosis of gestational diabetes mellitus, *Obstet Gynecol* 118:751–753, 2011.

Donovan L et al.: Screening tests for gestational diabetes: a systematic review for the U.S. Preventive Task Force, *Ann Int Med* 159:115–122, 2013.

International Association of Diabetes and Pregnancy Study Groups; et al: International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy, *Diabetes Care* 33:676–682, 2010.

Landon MB et al.: A multicenter, randomized trial of treatment for mild gestational diabetes, *N Engl J Med* 361:1339–1348, 2009.

Perinatology.com. Clinical calculators for insulin and caloric requirements.

Meneghini L, McDonough B: at www.clinicalmedicinetoday.com.

Serlin D, Lash RW: Diagnosis and management of gestational diabetes mellitus, *Am Fam Physician* 80(1):57–62, 2009.

Turok et al.: Management of gestational diabetes mellitus, *Am Fam Physician* 68:1767, 2003.

Vandorsten JP et al.: NIH consensus development conference: diagnosing gestational diabetes mellitus, *NIH Consens State Sci Statements* 29:1–31, 2013.

BASIC INFORMATION

DEFINITION

Giant cell arteritis (GCA) is a segmental systemic granulomatous arteritis affecting medium and large arteries in individuals >50 yr. Inflammation primarily targets extracranial blood vessels, and although the carotid system is usually affected, pathology in the posterior cerebral artery has been reported.

SYNONYMS

Temporal arteritis
Cranial arteritis
GCA
Horton's disease

ICD-9CM CODES
446.5 Temporal arteritis
ICD-10CM CODES
M31.5 Giant cell arteritis with polymyalgia rheumatica
M31.6 Other giant cell arteritis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 17 to 23.3 new cases per 100,000 persons >50 yr; peak incidence is in patients ages 60 to 80 yr.
PREVALENCE: 200 cases per 100,000 persons; female/male predominance of twofold to fourfold; more common in Caucasians.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

GCA can present with the following clinical manifestations:

TABLE G1-5 Atypical Manifestations of Giant Cell Arteritis

Fever of unknown origin
Respiratory symptoms (especially cough)
Otolaryngeal manifestations
Glossitis
Lingual infarction
Throat pain
Hearing loss
Large-artery disease
Aortic aneurysm
Aortic dissection
Limb claudication
Raynaud's phenomenon
Neurologic manifestations
Peripheral neuropathy
Transient ischemic attack (TIA) or stroke
Dementia
Delirium
Myocardial infarction
Tumorlike lesions
Breast mass
Ovarian and uterine mass
Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
Microangiopathic hemolytic anemia

From Harris ED et al: *Kelly's textbook of rheumatology,* ed 7, Philadelphia, 2005, Saunders.

- Headache, often associated with marked scalp tenderness—noticed while brushing hair (hair comb allodynia).
- Constitutional symptoms (fever, weight loss, anorexia, fatigue).
- Polymyalgia rheumatica (aching and stiffness of the trunk and proximal muscle groups).
- Visual disturbances (transient or permanent monocular or binocular visual loss).
- Intermittent claudication of jaw and tongue on mastication that is especially prominent when solid food such as steak is chewed.
- Table G1-5 describes atypical manifestations of GCA.

Important physical findings in GCA:

- Vascular examination: The temporal artery demonstrates tenderness, decreased pulsation, and nodulation (ropy) (Fig. G1-9); diminished or absent pulses in upper extremities may be seen.

ETIOLOGY

Vasculitis of unknown etiology.

DIAGNOSIS

Clinical history and vascular examination remain cornerstones of diagnosis. An algorithm for diagnosing GCA is described in Fig. G1-10. The American College of Rheumatology has proposed the following criteria for the diagnosis of GCA. Presence of three or more of these criteria in a patient with suspected vasculitis is considered to be diagnostic for GCA.

- Age of onset of symptoms >50 yr.
- New-onset of or new type of localized headache.
- Temporal artery abnormalities including tenderness or decreased pulsation.
- Westergren erythrocyte sedimentation rate (ESR) elevated (typically >50 mm/hr).
- Temporal artery biopsy with vasculitis and mononuclear cell infiltrate or granulomatous changes.

DIFFERENTIAL DIAGNOSIS

- Other vasculitic syndromes.
- Nonarteritic anterior ischemic optic neuropathy (NAION).
- Pituitary apoplexy.
- Primary amyloidosis.
- Transient ischemic attack, stroke.
- Infections.
- Occult neoplasm, multiple myeloma.

LABORATORY TESTS

- ESR elevated although up to 22.5% of patients with GCA have normal ESR before treatment.
- C-reactive protein (CRP) is typically included in laboratory investigation; it may have greater sensitivity than ESR. CRP typically rises before the ESR.

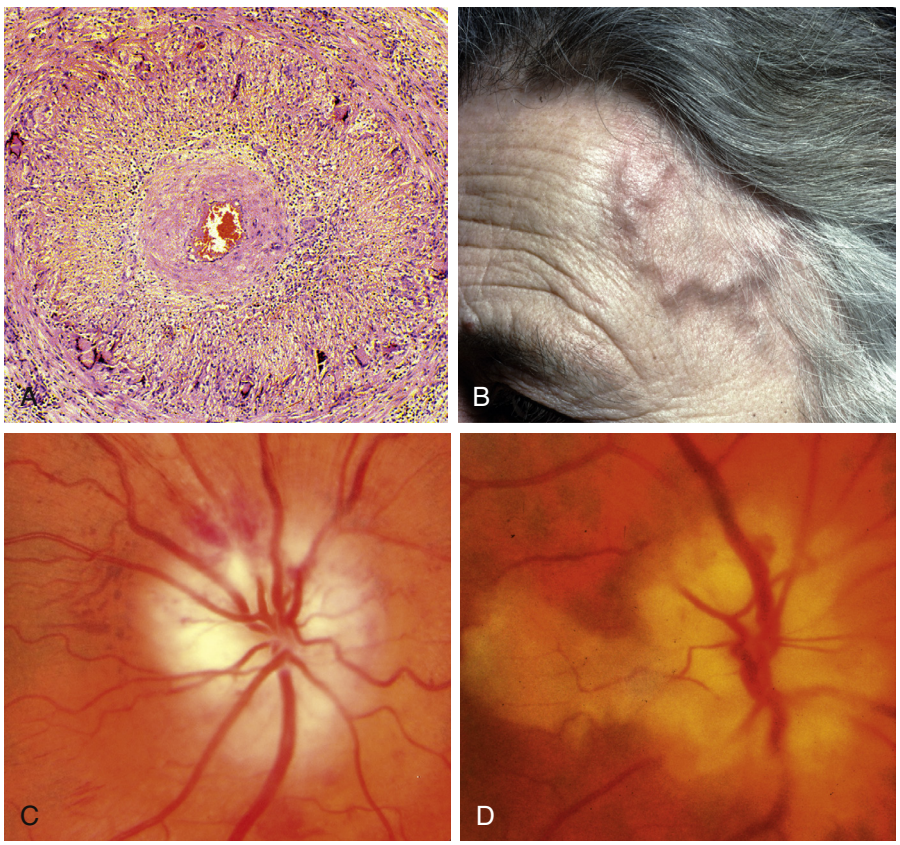


FIGURE G1-9 Giant cell arteritis. A, Histology shows transmural granulomatous inflammation, disruption of the internal elastic lamina, proliferation of the intima, and gross narrowing of the lumen. **B,** The superficial temporal artery is pulseless, nodular, and thickened. **C,** Ischemic optic neuropathy. **D,** Ischemic optic neuropathy and cilioretinal artery occlusion. (From Kanski JJ, Bowling B: *Clinical ophthalmology, a systematic approach,* ed 7, Philadelphia, 2010, Saunders.)

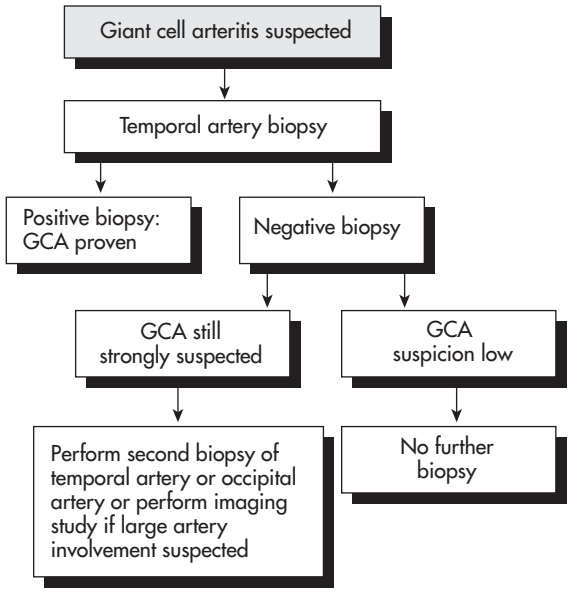


FIGURE G1-10 Algorithm for diagnosing giant cell arteritis (GCA). (From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

- Mild to moderate normochromic normocytic anemia, elevated platelet count.

IMAGING STUDIES

- Color duplex ultrasonography of temporal artery produces three characteristic features—periluminal "halo" over the temporal artery involved, segmental arterial stenosis, and arterial luminal occlusion in severe cases. Clinical utility is not superior to clinical examination with biopsy.
- Contrasted MRI of temporal artery may be performed in patients with contraindications to surgical biopsy of the superficial temporal artery, if treatment with steroids has not been initiated.

Rx TREATMENT

ACUTE GENERAL Rx

- If there is clinical suspicion of GCA, treatment should be initiated without waiting for results of laboratory or imaging studies.
- IV methylprednisolone (250 to 1000 mg for 1 to 3 days) is considered standard of care in patients with severe clinical manifestations such as visual loss from ischemic optic neuropathy.
- Oral prednisone (1 mg/kg/day): high-dose oral regimen should be continued at least until symptoms resolve and ESR returns to normal. Steroid taper is very slow (10% to 20% per month) with monitoring of clinical features as well as ESR and CRP. When dose <10 mg/day, taper by 1 mg/month. Treatment may last up to 2 yr or more.

Corticosteroids are the treatment of choice. There is no evidence for the role of steroid-sparing agents. Methotrexate may be considered as an adjunct treatment.

DISPOSITION

With steroid therapy there is a dramatic improvement of systemic symptoms, but not vision in patients with ischemic optic neuropathy. In one study only 4% of eyes improved in both visual acuity and central visual field.

Management of flares: Repeat prednisone induction if patient experiences severe flare. If mild flare, increase prednisone by 10% to 20%.

REFERRAL

- Surgical or ophthalmologic referral for biopsy of temporal artery.
- Rheumatology referral for long-term immunosuppressive treatment management.

PEARLS & CONSIDERATIONS

- Treatment of GCA should be started if there is clinical suspicion of the disease. This usually includes patients above the age of 55 presenting with a severe headache and systemic features that suggest GCA as well. Physicians should not wait for laboratory or pathologic confirmation before starting treatment as the risk of visual loss increases.
- Temporal artery biopsy should be performed as soon as possible, but within 2 weeks of initiating treatment with steroids.
- Treatment should not be withheld pending temporal artery biopsy.

COMMENTS

- The relation between polymyalgia rheumatica and GCA is unclear, but the two frequently coexist. They are considered to be different points along the gradient or spectrum of the same disease.
- Clinical picture rather than ESR should be the prime yardstick for continuing prednisone therapy. A rising ESR in a clinically asymptomatic patient with normal hematocrit should raise suspicion for alternate explanations (e.g., infections, neoplasms).
- GCA is associated with a markedly increased risk for the development of aortic aneurysm, which is often a late complication and may cause death. Annual chest radiograph in chronic CGA patients has been suggested, as well as emergent chest CT or MRI for clinical suspicion.
- GCA is also associated with increased risk of myocardial infarction, stroke, and peripheral vascular disease.

SUGGESTED READINGS

Available at www.expertconsult.com.

RELATED CONTENT

Giant Cell Arteritis (Patient Information)
Temporal Arteritis (Patient Information)

AUTHORS: **ARUN SWAMINATHAN, M.B.B.S.**, and **SACHIN KEDAR, M.B.B.S., M.D.**

SUGGESTED READINGS

Gold R et al.: Therapy of neurological disorders in systemic vasculitis, *Semin Neurol* 23(2):207, 2003.

Gonzalez-Gay MA: The diagnosis and management of patients with giant cell arteritis, *J Rheumatol* 32:1186, 2005.

Hayreh SR et al.: Visual improvement with corticosteroid therapy in giant cell arteritis, Report of large study and review of the literature *Acta Opththalmol Scand* 80:355, 2002.

Hoffman GS et al.: A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate for giant-cell arteritis, *Arthritis Rheum* 46(5):1309, 2002.

Hunder GG et al.: The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis, *Arthritis Rheum* 33:1122–1128, 1990.

Karassa FB et al.: Meta-analysis: test performance of ultrasonography for giant cell arteritis, *Ann Intern Med* 142:359–369, 2005.

Norborg E, Norborg C: Giant cell arteritis: epidemiological clues to its pathogenesis and an update on its treatment, *Rheumatology* 42:413, 2003.

Salvarani C et al.: Polymyalgia rheumatica and giant-cell arteritis, *N Engl J Med* 347(4):261, 2002.

Smetana GW, Shmerling RH: Does this patient have temporal arteritis? *JAMA* 287:92, 2002.

Tomasson G et al.: Risk for cardiovascular disease early and late after a diagnosis of giant-cell arteritis, *Ann Int Med* 160:73–80, 2014.

Weyand C, Goronzy JJ: Giant-cell arteritis and polymyalgia rheumatica, *N Engl J Med* 371:50–57, 2014.

BASIC INFORMATION

DEFINITION

Giardiasis is an intestinal and/or biliary tract infection caused by the protozoal parasite *Giardia lamblia*. The organism is a widespread zoonotic parasite and frequently contaminates fresh water sources worldwide.

SYNONYMS

Giardiasis
Giardia duodenalis
Giardia intestinalis

ICD-9CM CODES
007.1 Giardiasis
ICD-10CM CODES
A07.1 Giardiasis [lambliasis]

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.)
- Exact incidence unknown. CDC estimates 20,000 cases a year in the U.S.
- Frequently occurs as water-borne outbreaks in international adoptees, travelers, and immunocompromised patients

PREVALENCE (IN U.S.): 4%
PREDOMINANT SEX: Male = female
PREDOMINANT AGE
- Preschool children, especially if in day care
- 20 to 40 yr of age, especially among sexually active homosexual men

PEAK INCIDENCE
- Varies with risk factors, outbreaks, but peak onset from early summer through early fall
- All age groups affected

GENETICS: Familial disposition: Patients with common variable immunodeficiency or X-linked agammaglobulinemia are at increased risk of infection.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- More than 70% with one or more intestinal symptoms (diarrhea, flatulence, cramps, bloating, nausea). Table G1-6 summarizes clinical signs and symptoms of giardiasis
- Incubation period averages 7 to 14 days but can be longer
- Fever in <30%
- Chronic diarrhea, malabsorption, and weight loss, which can be up to 10% of body weight, are common
- GI bleeding is unusual
- Continuous or intermittent symptoms, lasting for 2 to 4 weeks

TABLE G1-6 Clinical Signs and Symptoms of Giardiasis

Symptom	Frequency (%)
Diarrhea	64-100
Malaise, weakness	72-97
Abdominal distention	42-97
Flatulence	35-97
Abdominal cramps	44-81
Nausea	14-79
Foul-smelling, greasy stools	15-79
Anorexia	41-73
Weight loss	53-73
Vomiting	14-35
Fever	0-28
Constipation	0-27

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

- Of infected patients, 20% to 25% are asymptomatic and can shed cysts for months

ETIOLOGY

Infection is acquired by ingestion of viable cysts of the organism, typically in contaminated water or food or by fecal-oral contact. *Giardia* cysts are resistant to chlorination and survive well in cold mountain streams.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other agents of infective diarrhea (amebae, *Salmonella* sp., *Shigella* sp., *Staphylococcus aureus, Cryptosporidium,* etc.)
- Noninfectious causes of malabsorption

WORKUP

- Stool specimen (three specimens yield 90% sensitivity) as a saline suspension or duodenal aspirate for microscopic examination to establish diagnosis and exclude other pathogens
- Immunoassays for *Giardia* sp. Antigens in stool samples such as the DFA or ELISA are now routinely used in most clinical laboratories. These assays are 85% to 98% sensitive and 90% to 100% specific. They also have a faster turnaround time.

LABORATORY TESTS

Serum albumin, vitamin B_{12} levels, and stool fat test to exclude malabsorption

IMAGING STUDIES

- Not necessary unless biliary obstruction is suspected
- In detection of organism, possible interference by barium in stool from radiographic studies

TREATMENT

NONPHARMACOLOGIC THERAPY

Avoidance of milk products to reduce symptoms of transient lactase deficiency that occur in many patients and can last for weeks to months

GENERAL Rx

Adult and pediatric:
- Tinidazole: 2 g single dose (50 mg/kg in children over 3 years of age).
- Metronidazole 250 mg PO three times daily for 5 to 7 days. Pediatric dose: 5 mg/kg tid × 7 days (metronidazole should be avoided in pregnancy).
- Nitazoxanide: aged 12 to 47 mo: 100 mg bid × 3 days. Aged 4 to 11 yr: 200 mg bid × 3 days
- Albendazole 400 mg PO qd x 5 days
- Paromomycin 25 to 35 mg/kg/day in three doses for 5 to 10 days
- Can be used in pregnancy

DISPOSITION

Reinfection is possible.

PEARLS & CONSIDERATIONS

COMMENTS

Travelers to endemic areas (developing world, wilderness areas) should be cautioned to boil drinking water or use water purification tablets. Chronic giardiasis as seen in developing nations can cause delays in growth and development in children due to malabsorption and diarrhea.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Giardiasis (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

DuPont HL: Acute infectious diarrhea in immunocompetent adults, *N Engl J Med* 370:1532–1540, 2014.

Escobedo AA, Cimerman S: Giardiasis: a pharmacotherapy review, *Expert Opin Pharmacother* 8(12):1885–1902, 2007. Aug.

Huang DB, White AC: An updated review on Cryptospridium and Giardia, *Gastroenterol Clin North Am* 35(2):291–314, 2006. Jun.

Muhsen K, Levine MM: A systematic review and meta-analysis of the association between Giardia lamblia and endemic pediatric diarrhea in developing countries, *Clin Infect Dis* 55(Suppl 4):S271–S293, 2012.

Yakoob J et al.: Giardiasis in patients with dyspeptic symptoms, *World J Gastroenterol* 11(42):6667, 2005.

BASIC INFORMATION

DEFINITION

Gilbert's syndrome is an autosomal-dominant disorder characterized by indirect hyperbilirubinemia caused by impaired glucuronyl transferase activity.

SYNONYMS

Gilbert's disease

ICD-9CM CODES
277.4 Gilbert's syndrome
ICD-10CM CODES
E80.4 Gilbert's syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Probable autosomal-dominant disease affecting >5% of the U.S. population
PREDOMINANT SEX: Male/female ratio of 3:1
GENETICS: Most common hereditary hyperbilirubinemia (genotypic prevalence 12%)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- No abnormalities on physical examination other than mild jaundice when bilirubin exceeds 3 mg/dl.
- A family history of unconjugated hyperbilirubinemia may be present.

ETIOLOGY

- Decreased elimination of bilirubin in bile is caused by inadequate conjugation of bilirubin.
- Alcohol consumption and starvation diet can increase bilirubin level.
- The pathogenesis of Gilbert's syndrome has been linked to a reduction in the bilirubin UGT-1 gene *(HUG-Brl)* transcription, resulting from a mutation in the promoter region.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hemolytic anemia.
- Liver disease (chronic hepatitis, cirrhosis).
- Crigler-Najjar syndrome.

WORKUP

- Most patients are diagnosed during or after adolescence, when isolated hyperbilirubinemia is detected as an incidental finding on routine biochemical testing.
- Laboratory evaluation to exclude hemolysis and liver diseases as a cause of the elevated bilirubin level (Table G1-7).

LABORATORY TESTS

Elevated indirect (unconjugated) bilirubin (rarely exceeds 5 mg/dl).

TREATMENT

ACUTE GENERAL Rx

Treatment is generally unnecessary. Phenobarbital (if clinical jaundice is present) can rapidly decrease serum indirect bilirubin level.

DISPOSITION

Prognosis is excellent. Treatment is generally unnecessary.

REFERRAL

Referral is generally not necessary.

PEARLS & CONSIDERATIONS

COMMENTS

- Patients should be reassured about the benign nature of their condition.
- Fasting for 2 days or significant dehydration may raise the bilirubin level and result in the clinical recognition of jaundice.

AUTHOR: **FRED F. FERRI, M.D.**

TABLE G1-7 Characteristic Patterns of Liver Function Tests

Disorder	Bilirubin	Alkaline Phosphatase	AST	ALT	Prothrombin Time	Albumin
Gilbert's syndrome (abnormal bilirubin metabolism)	↑	NL	NL	NL	NL	NL
Bile duct obstruction (pancreatic cancer)	↑↑↑	↑↑↑	↑	↑	↑-↑↑	NL
Acute hepatocellular damage (toxic, viral hepatitis)	↑-↑↑↑	↑-↑↑	↑↑↑	↑↑↑	NL-↑↑↑	NL-↓↓
Cirrhosis	NL-↑	NL-↑	NL-↑	NL-↑	NL-↑↑	NL-↓↓

ALT, Alanine aminotransferase; *AST,* aspartate aminotransferase; *NL,* normal; ↑ increase; ↓, decrease (arrows indicate extent of change: ↑-↑↑↑, slight to large).
From Andreoli TE (ed): *Cecil essentials of medicine,* ed 6, Philadelphia, 2005, Saunders.

BASIC INFORMATION

DEFINITION
Inflammation of the gums covering the maxilla and mandible.

SYNONYMS
None

ICD-9CM CODES
523.1 Chronic gingivitis
523.01 Acute gingivitis
ICD-10CM CODES
K05.0 Acute gingivitis
K05.1 Chronic gingivitis
K05.6 Other disorders of gingiva and edentulous alveolar ridge

EPIDEMIOLOGY & DEMOGRAPHICS
Gingivitis generally occurs in adults.

PHYSICAL FINDINGS & CLINICAL PRESENTATION
- Inflammation is usually painless. Red velvety gingiva may be present (Fig. G1-11).
- Bleeding may occur with minor trauma such as brushing teeth.
- A bluish discoloration of the gums and halitosis are sometimes present.
- Subgingival plaque may be seen on close examination, and in time, there is detachment of soft tissue from the tooth surface.
- Long-standing infection may lead to destructive periodontal disease, which may involve teeth and bones.
- A dramatic form of gingivitis called acute ulcerative necrotizing gingivitis (ANUG or "trench mouth") can occur. This is manifested by acute, painful inflammation of the gingivae, with bleeding, ulceration, and halitosis. At times this is accompanied by fever and lymphadenopathy.
- Linear gingival erythema ("HIV gingivitis") presents as a brightly inflamed band of marginal gingiva. It may be painful, with easy bleeding and rapid destruction.
- Severe periodontitis can occur in patients with diabetes mellitus or HIV infection and in primary HIV infection (acute retroviral syndrome).
- Pregnancy may be associated with an acute form of gingivitis. Gingivae become inflamed and hypertrophic; this is likely the result of hormonal shifts.

ETIOLOGY
- A variety of organisms may be found in the environment of plaque. Anaerobes play a predominant role in periodontal disease.
- Improper hygiene and poorly fitting dentures may contribute to the development of gingivitis.
- Excessive use of tobacco and alcohol may predispose individuals to gingival disease.
- In patients with HIV infection, gram-negative anaerobes, enteric organisms, and yeast predominate.
- Appropriate oral hygiene, such as flossing and tooth brushing, can prevent the accumulation of bacterial plaque; once dense plaque is present, adequate hygiene becomes more difficult.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS
Gingival hyperplasia, which may be caused by long-term use of phenytoin or nifedipine.

WORKUP
Oral examination.

LABORATORY TESTS
Elevated serum glucose in diabetics.

IMAGING STUDIES
Radiographs of the teeth and facial bones may reveal extension of infection to these structures.

TREATMENT

NONPHARMACOLOGIC THERAPY
Removal of plaque, and at times, debridement of soft tissue.

ACUTE GENERAL Rx
- Penicillin VK, 500 mg PO qid for 1 to 2 wk or
- Clindamycin, 300 mg PO qid for 1 to 2 wk.
- For linear gingival erythema, chlorhexidine gluconate rinses and nystatin rinses or troches may be used.

CHRONIC Rx
Extensive or recurrent infection may require periodic evaluation and debridement.

DISPOSITION
Continued inflammation can eventually lead to destruction of teeth and bone.

REFERRAL
Patients should be referred to a dentist or periodontist.

PEARLS & CONSIDERATIONS

COMMENTS
- Presence of periodontal disease is associated with an increased incidence of anaerobic pleuropulmonary infections.
- Existing data support the recommendation to change a toothbrush every 3 mo. Worn brushes seem to be less effective in plaque reduction.

SUGGESTED READINGS
Available at www.expertconsult.com

RELATED CONTENT
Gingivitis (Patient Information)
Gingivitis, Necrotizing Ulcerative (Related Key Topic)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

FIGURE G1-11 Gingivitis in a patient with cicatricial pemphigoid. This pattern of periodontal, chronic, red, velvety gingivitis is very suggestive of this disorder but may occur in other blistering diseases. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

SUGGESTED READINGS

Hodgdon A: Dental and related infections, *Emerg Med Clin North Am* 31(2):465–480, 2013.

Rudiger SG et al.: Dental biofilms at healthy and inflamed gingival margins, *J Clin Periodontol* 29(6):524, 2002.

Sharma NC et al.: Antiplaque and antigingivitis effectiveness of a hexetidine mouthwash, *J Clin Periodontol* 30(7):590, 2003.

Slots J: Human viruses in periodontitis, *Periodontol 2000* 53(1):89–110, 2010.

BASIC INFORMATION

DESCRIPTION

Necrotizing ulcerative gingivitis (NUG) is a distinct painful infectious disease primarily of the interdental and marginal gingiva. It is characterized by a symptom triad that includes gingival pain, ulcer, and bleeding.

SYNONYMS

Trench mouth
Acute necrotizing ulcerative gingivitis (ANUG)
Vincent's stomatitis
Fusospirochetal gingivitis
Acute ulcerative gingivitis

ICD-9CM CODES
101 Acute necrotizing ulcerative gingivitis
ICD-10CM CODES
A69.0 Necrotizing ulcerative stomatitis

EPIDEMIOLOGY

- Unlike in the developing world, NUG is seen rarely in developed countries.
- Occurs in the 2nd and 3rd decades of life in the developed world.
- In contrast, it affects young children more often in developing countries.
- Slightly more prevalent in males than in females because the latter group tend to have better oral hygiene.

RISK FACTORS

- Poor oral hygiene.
- Smoking/chewing tobacco.
- Alcohol use.
- Drug addiction.
- Poor socioeconomic status.
- Psychological stress.
- Preexisting gingivitis.
- Lack of sleep.
- Malnutrition.
- Overcrowding.
- Living near livestock.
- History of prior NUG.
- Recent illness.
- Underlying systemic diseases.
- Acatalasia.
- Various infections such as measles, malaria, and infestation with intestinal parasites.
- Trauma.
- Immunosuppression.
  1. Dermatomyositis (DM).
  2. Steroid use.
  3. HIV/AIDS.
  4. Use of chemotherapeutic drugs.
  5. Leukemia and other malignancies.

ETIOLOGY

- Polymicrobial.
- Often caused by both *Fusobacterium* and spirochetes.

PATHOGENESIS

- Unknown.
- For the most part it appears to result from an opportunistic infection in a host with lowered resistance.

CLINICAL FEATURES

- Onset of the disease is usually sudden.
- Severe gingival pain.
- Gingival tissue is inflamed, edematous, friable, and necrotic; the normal pointed interdental papillae are blunted, but there is no loss of attachment.
- Gingival bleeding with little or no provocation.
- Punched out ulcerations are seen along the interdental papillae around the anterior incisors and posterior molars. A grayish-white pseudomembrane often covers these ulcers. These punched out ulcers along the pseudomembrane are pathognomonic of NUG.
- Other features include
  1. Halitosis.
  2. Alteration in taste, such as a metallic flavor.
  3. Wooden teeth feeling.
  4. Odynophagia.
  5. Fever and fatigue.
  6. Cervical lymphadenopathy.

DIAGNOSIS

- Based on the clinical features.
- WBC may be elevated.
- Gram stain and aerobic/anaerobic culture.
- Dental x-ray or x-ray of face to check on the extent of the disease.
- HIV testing is recommended for patients refractory to antibiotic therapy.

DIFFERENTIAL DIAGNOSIS

- Gingivitis.
- Acute herpetic gingivostomatitis.
- Aphthous stomatitis.
- Chronic periodontal disease.
- Desquamative gingivitis.
- Gonococcal and streptococcal gingivostomatitis.
- Oral candidiasis.
- Ludwig's angina.
- HIV-associated idiopathic ulcerations.

TREATMENT

- Improve oral hygiene by flushing and brushing at least twice a day.
- Improve nutrition and hydrations.
- Eliminate contributing factors such as smoking, alcohol, carbonated beverages, spicy/hot foods, poor nutrition, stress, and so on.
- Antibiotic coverage for 5 to 10 days. Most recommend oral penicillin V 250 to 500 mg orally every 6 to 8 hr and metronidazole 250 to 500 mg orally every 8 hr. Tetracycline is given instead of penicillin in patients allergic to the latter. As an alternative one could give only clindamycin instead of the drug combination of penicillin and metronidazole.
- Rinsing the mouth at least twice a day with warm saline (1/2 teaspoon of salt in 1 cup of water), 0.12% chlorhexidine, or dilute 3% hydrogen peroxide (mixed half and half with water).
- Pain is controlled with oral pain medications and topical application of 2% viscous lidocaine (15 ml oral rinse every 6 to 8 hr as needed) to the inflamed gum.
- Surgical debridement is needed in severe cases.
- Scaling and root planing following the resolution of infection and the acute inflammation.
- At times reconstructive surgery may be needed.

COMPLICATIONS

- Cancrum oris (noma) results when NUG involves the deeper tissue.
- Vincent's angina from the involvement of tonsils and pharynx.
- Necrotizing ulcerative periodontitis.
- Loss of teeth.
- Periodontal abscess.
- Alveolar bone destruction.
- Disfigurement.
- Cellulitis.
- Dehydration/malnutrition.

PROGNOSIS

- Dramatic relief of symptoms within 24 hr of initiating antibiotics and supportive treatment is characteristic.
- Risk of recurrence is high.

PEARLS & CONSIDERATIONS

PREVENTION

- Good oral hygiene.
- Use of power toothbrush is better than a manual brush.
- Good general health including proper nutrition, sleep, and exercise.
- Routine dental checks.
- Avoidance of smoking and alcohol.
- Stress management.

PATIENT EDUCATION

Not a communicable disease.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **HEMANT K. SATPATHY, M.D.**

SUGGESTED READING

Necrotizing ulcerative gingivitis, *Ann Periodontol* 4:65–73, 1999.

BASIC INFORMATION

DEFINITION

Glaucoma is a chronic degenerative optic neuropathy in which the neuro-retinal rim of the optic nerve becomes progressively thinner, thereby enlarging the optic-nerve cup. The classification of glaucoma is based on the appearance of the iridocorneal angle (open angle vs. closed angle) and is further subdivided into primary and secondary types. Primary open-angle glaucoma can occur with or without elevated intraocular pressure (IOP). Normal tension glaucoma refers to primary open-angle glaucoma without elevated intraocular pressure.

SYNONYMS

Primary open-angle glaucoma (POAG)
Open-angle glaucoma (OAG)
Chronic open-angle glaucoma

ICD-9CM CODES
365.1 Open-angle glaucoma
ICD-10CM CODES
H40.1 Primary open-angle glaucoma
H40.8 Glaucoma, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Third most common cause of vision loss (75% to 95% of all forms of glaucoma are open angle)

PEAK INCIDENCE
- Increases after age 40 yr
- Three million cases expected by 2020 because of the rapid increase in aging population

PREVALENCE (IN U.S.)
- Overall prevalence in U.S. population aged >40 yr is estimated to be 1.86%, with 1.57 million white and 398,000 black patients affected.
- 150,000 patients have bilateral blindness.
- Prevalence is higher in diabetics, those with high myopia, and older persons.
- More common in African-American population (three times the age-adjusted prevalence than whites). There is a genetic tendency to OAG; multiple genes have been isolated that are associated with development of high IOP and optic nerve damage.

PREDOMINANT AGE
- Persons >50 yr.
- Can occur in 30s and 40s.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- High intraocular pressures and/or large optic nerve cup (Ocular Hypertension Treatment Study results very important).
- Abnormal visual fields (with advanced glaucoma damage to the optic nerve).
- Open anterior chamber angle—evaluated with gonioscopy.
- Since early treatable stages of OAG normally have no symptoms, it's important to have routine eye exams, especially patients with family history and patients over 60 yr.
- Secondary forms of OAG may exhibit ocular findings such as pseudo-exfoliation, pigment dispersion, blood in anterior chamber, inflammation.

ETIOLOGY

- Uncertain hereditary tendency.
- Topical steroids can induce high IOP and cause glaucoma.
- Trauma.
- Inflammatory (e.g., history of uveitis).
- High-dose oral corticosteroids taken for prolonged periods.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other optic neuropathies.
- Ocular hypertension: IOP is chronically elevated, but not causing optic nerve damage, must monitor closely.
- Secondary glaucoma from inflammation and steroid therapy.
- Trauma.

WORKUP

- Intraocular pressure.
- Slit lamp examination.
- Visual fields.
- Gonioscopy.
- Nerve fiber analysis (e.g., GDx, OCT, and HRT).
- Corneal thickness (thick central cornea will result in possible overestimation of the true physiologic IOP, and vice versa, so this is important information in diagnosis and treatment of OAG).

LABORATORY TESTS

Blood sugar

IMAGING STUDIES

- Optic nerve photography—stereo photographs.
- Visual field testing.
- Laser scan of nerve fiber layer, OCT, HRT. Rarely, MRI of orbits if the glaucoma findings are atypical or suspicious of other causes of optic nerve atrophy.

TREATMENT

ACUTE GENERAL Rx

- β-blockers (e.g., timolol) qd to bid depending on individual response to drug.
- Carbonic anhydrase inhibitors (e.g., Diamox 250 mg qid or 500 mg bid).
- Prostaglandin analogues (latanoprost, bimatoprost, travoprost, tafluprost) are commonly used as first-line treatment. They lower intraocular pressure by 25% to 30% by increasing uveoscleral outflow and reducing aqueous production.
- Alpha-2 agonists and cholinergic agonists.
- Hyperosmotic agents (mannitol) in acute treatment (IV).
- Selective laser trabeculoplasty (SLT) may delay or forestall need for second eyedrop. The effect may be temporary but the laser can be repeated.

CHRONIC Rx

- At least biannual checks of intraocular pressure and adjustment of medication.
- Surgical trabeculectomy and filter valve surgeries can be considered for glaucoma that progresses (optic nerve changes or visual field progression) despite maximal tolerated medical therapies. Recently, minimally invasive glaucoma surgeries (MIGS) have been advocated for IOP control. Some are performed at the time of cataract procedures and some are independent procedures. The effort is to reduce the risks associated with traditional trabeculectomy.

DISPOSITION

Must be followed by ophthalmologist.

REFERRAL

Immediately to ophthalmologist.

PEARLS & CONSIDERATIONS

COMMENTS

- Glaucoma is a serious blinding disease that must be monitored professionally by an ophthalmologist. It is mostly asymptomatic until late in the disease when visual problems arise. Even in developed countries half of glaucoma cases are undiagnosed.
- Risk factors that should prompt referral to an ophthalmologist for evaluation of glaucoma are high intraocular pressure, family history of glaucoma, use of systemic or topical corticosteroids, older age, and black race.
- Vision loss from glaucoma cannot be recovered. Early diagnosis and treatment may minimize visual loss.
- Glaucoma is not solely caused by increased intraocular pressure because approximately 20% of patients with glaucoma have normal intraocular pressure. However, high pressure is definitely a risk factor to be considered. Potential sites of increased resistance to aqueous flow are described in Fig. EG1-12.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Glaucoma (Patient Information)

AUTHOR: **R. SCOTT HOFFMAN, M.D.**

EVIDENCE

Abstract[1]

Purpose:

To investigate clinical characteristics and progression rates of the initial central scotomas (ICS) compared with the initial peripheral scotomas (IPS) in normal-tension glaucoma (NTG) patients.

Methods:

Among NTG patients showing a single hemifield defect and who performed more than five reliable standard visual field (VF) tests, medical records of ICS (involvement of ≥3 adjacent points with P<5% within the central 12°_of fixation and one point with a P < 0.01 within the central 6° of fixation) (n=32) or IPS (no VF abnormality within the central 6° of fixation) (n=34) were retrospectively analyzed. The changes of mean thresholds from 10 zones of the glaucoma hemifield test, central 6° and 12° zones, peripheral zones other than central 6° and 12°, and the entire hemifield were inspected. To calculate the progression rates, linear mixed-effect model was employed.

Results:

There were no significant differences between the two groups in age, gender, ocular factors including baseline/mean treated intraocular pressure, and systemic factors including systolic or diastolic blood pressure/perfusion pressure, mean ocular perfusion pressure (all P > 0.05). There were no significant differences in baseline mean deviation and pattern standard deviation (P>0.05) between the two groups, but VF index was significantly lower in ICS group than in IPS group (P=0.001). The progression rates between the two groups were not significantly different in all zones we investigated (all P> 0.05).

Conclusions:

Newly diagnosed cases of NTG with ICS may not differ from those with IPS in clinical characteristics and progression rates under treatment. B

Evidence-Based Reference

1. Cho H-K, Lee J, Lee M, et al.: Initial central scotomas vs peripheral scotomas in normal-tension glaucoma: clinical characteristics and progression rates, *Eye* 28:303–311, 2014. B

SUGGESTED READINGS

Gordon MO et al.: Baseline factors that predict the onset of primary open-angle glaucoma, *Arch Ophthalmol* 120:714, 2002.

Heijl A et al.: Reduction of intraocular pressure and glaucoma progression: results from the early manifest glaucoma trial, *Arch Ophthalmol* 120:1268, 2002.

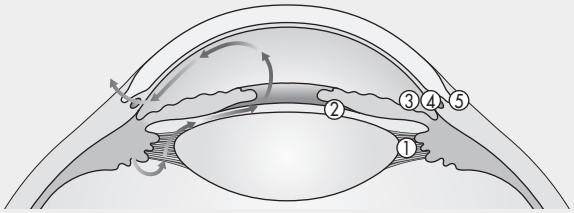
Higginbotham EJ et al.: The Ocular Hypertension Treatment Study: topical medication delays or prevents primary open-angle glaucoma in African American individuals, *Arch Ophthalmol* 122(6):813, 2004.

Kwon YH et al.: Primary open-angle glaucoma, *N Engl J Med* 360:1113–1124, 2009.

Quigley HA Glaucoma: *Lancet* 377:1367–1377, 2011.

Rezaie T et al.: Adult-onset primary open-angle glaucoma caused by mutations in optineurin, *Science* 295:1077, 2002.

Weinreb RN et al.: The pathophysiology and treatment of Glaucoma, *JAMA* 311(18):1901–1911, 2014.



1 Ciliary body processes (when ciliary body swollen by congestion), fibrin debris, vitreous face against the lens equator
2 Pupillary block by anterior position of lens or swollen lens
3 Pretrabecular by neovascular or cellular membranes
4 Trabecular by abnormal accumulation of extracellular matrix
5 Post-trabecular by increased episcleral venous pressure

FIGURE EG1-12 Potential sites of increased resistance to aqueous flow. (From Yanoff M, Duker JS: *Ophthalmology,* ed 2, St Louis, 2004, Mosby.)

Glaucoma, Primary Angle-Closure EBM PTG

BASIC INFORMATION

DEFINITION

Primary angle-closure glaucoma occurs when elevated intraocular pressure is associated with closure of the filtration angle or obstruction in the circulating pathway of the aqueous humor.

SYNONYMS

Acute glaucoma, angle-closure glaucoma (ACG)
Pupillary block glaucoma
Narrow-angle glaucoma
Angle-closure glaucoma

ICD-9CM CODES
365.2 Primary angle-closure glaucoma (PACG)
ICD-10CM CODES
H40.2 Primary angle-closure glaucoma
H40.9 Glaucoma, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):
- 2% to 8% of all patients with glaucoma.
- Higher incidence among those with hyperopia, small eyes, dense cataracts, shallow anterior chambers.

PEAK INCIDENCE: Greater >50 yr; high association with hyperopia, cataracts, and eye trauma
PREDOMINANT SEX: Females are affected more often than males.
PREDOMINANT AGE: 50 to 60 yr.
GENETICS: High family history.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Although angle-closure glaucoma can present with an acute painful crisis associated with blurred vision, more than 75% of patients present with an asymptomatic course with progressive loss of the visual field (similar to that in patients with primary open-angle glaucoma).
- Hazy cornea.
- Narrow angle (Fig. EG1-13).
- Red eyes.
- Pain may be present.
- Injection of conjunctiva.
- Shallow anterior chamber.
- Thick cataract.
- Old trauma.
- Chronic eye infections.

ETIOLOGY

- Narrow angles with acute closure: blockage of circulatory path of the aqueous humor causing increase in intraocular pressure (IOP). ACG occurs more commonly in eyes with shorter axial length (farsightedness), shallower anterior chamber, and a relatively larger lens (enlarging cataract).
- Secondary angle-closure glaucoma resulting from neovascularization of iris, iris tumors, lens induced, iris scarring, trauma, chronic inflammation with scarring, malignant glaucoma with aqueous misdirection

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Open-angle glaucoma: Angle-closure glaucoma is distinguished from open-angle glaucoma by the closure of the angle between the iris and cornea, obstructing outflow of aqueous humor.
- High pressure.
- Optic nerve cupping.
- Shallow chamber.
- Open-angle glaucoma.
- Conjunctivitis.
- Corneal disease, keratitis.
- Uveitis.
- Scleritis.
- Allergies.
- Contact lens wearing with irritation.

WORKUP

Comprehensive eye examination: if one suspects narrow angle or angle closure, avoid pupil dilation since this may exacerbate the attack
- Intraocular pressure.
- Gonioscopy.
- Slit lamp examination.
- Visual field examination.
- GDx examination (laser scan of nerve fiber layer), OCT.
- Optic nerve evaluation.
- Anterior chamber depth.

LABORATORY TESTS

- Blood sugar and complete blood count (if diabetes or inflammatory disease is suspected).
- Visual field.
- GDx nerve fiber analysis, OCT, Heidelberg retinal tomography.

IMAGING STUDIES

- Fundus photography.
- Fluorescein angiography for neovascular disease such as diabetic retinopathy, retinal vein occlusions.
- Ultrasound biomicroscopy and anterior OCT can show relationships of anterior eye structures.

TREATMENT

The goal of treatment is to acutely lower pressure on the eye and keep it down.

NONPHARMACOLOGIC THERAPY

Laser iridotomy early in disease process.

ACUTE GENERAL Rx

- IV mannitol.
- Pilocarpine.
- β-blockers.
- Diamox.
- Laser iridotomy.
- Anterior chamber paracentesis (as emergency treatment).

CHRONIC Rx

- Iridotomy.
- Trabeculectomy.
- Filter valves.
- Other laser procedures.

DISPOSITION

Refer to ophthalmologist immediately.

REFERRAL

If acute angle-closure episode is suspected, should refer emergently to ophthalmologist.

PEARLS & CONSIDERATIONS

COMMENTS

- Do not use antihistamines or vasodilators with narrow-angle glaucoma.
- After iridotomy, the majority of patients will be totally cured and will need no further medication and have no visual loss.
- Lower socioeconomic status and higher levels of social deprivation are risk factors for delayed detection and probable worse outcomes in glaucoma.
- Risk factors that should prompt referral to an ophthalmologist for evaluation of glaucoma are high intraocular pressure, family history of glaucoma, use of systemic or topical corticosteroids, older age, and black race.
- Glaucoma is undiagnosed in 9 out of 10 affected people worldwide and is undiagnosed in 50% of those in developed countries.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Glaucoma (Patient Information).

AUTHOR: **R. SCOTT HOFFMAN, M.D.**

EVIDENCE

Abstract[1]

Aims:

To investigate the relationship between quantitative iris parameters and angle closure disease.

Methods:

Participants with angle closure were recruited prospectively from glaucoma clinics. Anterior segment optical coherence tomography (AS-OCT) was performed under standardized dark conditions. Customized software was used on horizontal AS-OCT scans to measure iris thickness at 750um (IT750) and 2000um (IT2000) from the sclera spur, maximal iris thickness (ITM) and cross-sectional area of the iris (I-Area).

Results:

167 Angle closure (consisting of 50 primary angle-closure (PAC), 73 primary angle closure glaucoma (PACG) and 44 fellow eyes of acute PAC) and 1153 normal participants were examined. After adjusting for age, sex, pupil size and anterior chamber depth, mean IT750 (0.499 vs 0.451mm, p<0.001), IT2000 (0.543 vs 0.479mm, p<0.001), ITM (0.660 vs 0.602mm, p<0.001) and I-Area (1.645 vs 1.570 mm2, p=0.014) were significantly greater in angle closure (combined groups) versus normal eyes. Multivariate adjusted odd ratios (OR) of each parameter for the angle closure as compared with normal eyes were: IT750 OR1.7 (95% CI 1.1 to 2.7, p=0.032); IT2000 OR2.2 (95% CI 1.3 to 3.8, p=0.006) and ITM OR2.2 (95% CI 1.3 to 3.6, p=0.003), respectively, per 0.1 unit increase.

Conclusions:

Increased iris thickness is associated with angle closure. Ⓐ

Evidence-Based Reference

Wang BS, et al.: Increased iris thickness and association with primary angle closure glaucoma, *Br J Ophthalmol* 95:46–50, 2011. Ⓐ

SUGGESTED READINGS

Foster PJ et al.: Defining "occludable" angles in population surveys: drainage angle width, peripheral anterior synechiae, and glaucomatous optic neuropathy in East Asian people, *Br J Opthalmol* 88(4):486, 2004.

Fraser S et al.: Deprivation and late presentation of glaucoma: case control study, *BMJ* 32:638, 2001.

Gazzard G et al.: Intraocular pressure and visual field loss in primary angle closure and primary open angle glaucomas, *Br J Ophthalmol* 87(6):720, 2003.

Kapur SB: The lens and angle-closure glaucoma, *J Cataract Refract Surg* 27(2):176, 2001.

Lam DS et al.: Angle-closure glaucoma, *Ophthalmology* 109:1, 2002.

Quigley HA: Glaucoma, *Lancet* 377:1367–1377, 2011.

Weinreb RN et al.: The pathophysiology and treatment of Glaucoma, *JAMA* 311(18):1901–1911, 2014.

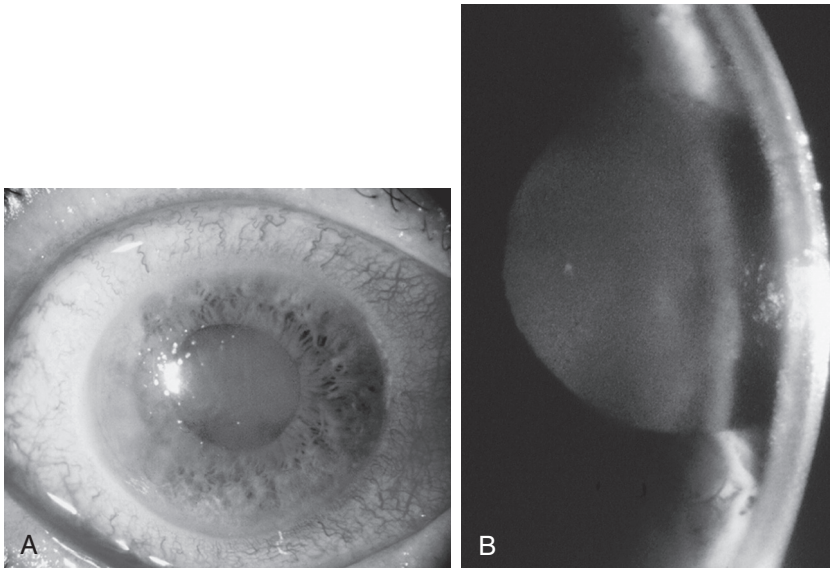


FIGURE EG1-13 Acute angle-closure glaucoma. A, Acutely elevated pressure produces an inflamed eye with corneal edema (note fragmented light reflex) and a mid-dilated pupil. **B,** Slit lamp examination shows a very shallow central anterior chamber (space between cornea and iris) and no peripheral chamber. (From Palay D [ed]: *Ophthalmology for the primary care physician,* St Louis, 1997, Mosby.)

BASIC INFORMATION

DEFINITION

Glenohumeral dislocation (Fig. G1-14) is complete separation or displacement of the humeral head from the glenoid surface (partial separation is termed *subluxation*). Most often the cause is traumatic, and the humeral head dislocates anteriorly and inferiorly. This may cause a tear of the glenoid labrum (the Bankart lesion). Less commonly the head dislocates posteriorly.

Rarely, multidirectional instability may be present in which dislocation or subluxation, often bilateral, may occur in multiple directions, usually the result of excessive joint laxity and generally without trauma.

ICD-9CM CODES

831.01 Anterior
831.02 Posterior
831.03 Inferior
718.31 Recurrent
718.81 Instability

ICD-10CM CODES

S43.016A Anterior dislocation of unspecified humerus, initial encounter
S43.026A Posterior dislocation of unspecified humerus, initial encounter
S43.036A Inferior dislocation of unspecified humerus, initial encounter
M24.419 Recurrent dislocation, unspecified shoulder
M24.819 Other specific joint derangements of unspecified shoulder, not elsewhere classified

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Traumatic:

- The arm is held in external rotation with anterior dislocation and internal rotation with posterior dislocation.
- Little movement is possible without pain.

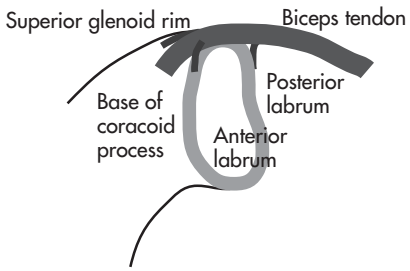


FIGURE G1-14 Glenohumeral dislocation. (From Weissleder R et al: *Primer of diagnostic imaging*, St Louis, 2007, Mosby.)

- The acromion may appear more prominent, and there is absence of the normal "fullness" beneath the acromion.
- The status of the axillary nerve must always be checked (sensation to the mid-deltoid should be assessed).
- The apprehension test may become positive if anterior instability persists (pain and apprehension that the shoulder will dislocate when the relaxed arm is manually placed in the "throwing position" of external rotation and abduction).
- Recurrent episodes of anterior dislocation may occur with minor movement, such as putting on a coat or turning off a light.

Multidirectional:

- Often difficult to diagnose, especially if only subluxation occurs.
- Recurrent episodes of giving out and weakness, often bilateral and without trauma.
- Sulcus sign is often positive (the arms are pulled downward with the patient standing; a sulcus [indentation] will form between the acromion and humeral head, indicating excessive inferior movement of the head).
- Other signs of generalized joint laxity may be present, such as joint hyperextensibility and the ability of the patient to touch the thumb against the flexor aspect of the forearm.

ETIOLOGY

- Trauma.
- Generalized joint laxity (multidirectional).
- Seizures (posterior dislocations).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rotator cuff rupture.
- Frozen shoulder (posterior dislocation).
- Suprascapular nerve paralysis.
- Anterior instability.

IMAGING STUDIES

- Acute shoulder injury: true anteroposterior roentgenogram plus lateral view of the glenohumeral joint, either transaxillary or transcapular.
- MRI: to determine soft tissue status, especially the presence of Bankart lesion or rotator cuff tear; may be indicated after a second episode of dislocation.

TREATMENT

- Reduction of the acute dislocation by gentle straight traction in the relaxed patient followed by light immobilization.
- Gentle limited range-of-motion exercises as pain subsides followed by strengthening exercises at 2 wk.

DISPOSITION

- Recurrence of anterior dislocation is common in the young; these patients may have to avoid the arm position associated with dislocation (external rotation with abduction).
- Primary dislocations in patients >40 yr are not generally complicated by recurrence but may result in shoulder stiffness and associated rotator cuff injuries.
- There is an almost 100% recurrence after the third dislocation.

REFERRAL

Surgical reconstruction may be required in the recurrent dislocator.

PEARLS & CONSIDERATIONS

COMMENTS

- It is important to know if there was an injury involved in the first episode and if a radiograph was taken to determine direction of the dislocation.
- Up to 50% of posterior dislocations are missed by the first examiner, usually the result of an inadequate lateral radiograph of the glenohumeral joint.
- "Voluntary" posterior dislocators should always be treated nonsurgically.
- Sports activities may be resumed when there is pain-free full flexibility and normal strength.
- Multidirectional instabilities are usually treated nonsurgically with strengthening exercises.
- Dislocations in either direction are occasionally overlooked. If the injury is over 2 to 4 weeks old, enough tissue healing will have occurred to make closed reduction fail. Open reduction or arthroplasty will then be needed in the young. Older patients may improve with therapeutic exercises, and the resultant disability is often acceptable.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Purpose:
The purpose of this study was to compare the cost-effectiveness of initial observation versus surgery for first-time anterior shoulder dislocation.

Methods:
The clinical scenario of first-time anterior glenohumeral dislocation was simulated using a Markov model (where variables change over time depending on previous states). Nonoperative outcomes include success (no recurrence) and recurrence; surgical outcomes include success, recurrence, and complications of infection or stiffness. Probabilities for outcomes were determined from published literature. Costs were tabulated from Medicare Current Procedural Terminology data, as well as hospital and office billing records. We performed microsimulation and probabilistic sensitivity analysis running 6 models for 1000 patients over a period of 15 years. The 6 models tested were male versus female patients ages 15 years versus 25 years versus 35 years.

Results:
Primary surgery was less costly and more effective for 15-year-old boys, 15-year-old girls, and 25-year-old men. For the remaining scenarios (25-year-old women and 35-year-old men and women), primary surgery was also more effective but was more costly. However, for these scenarios, primary surgery was still very cost effective (cost per quality-adjusted life year, <$25,000). After 1 recurrence, surgery was less costly and more effective for all scenarios.

Conclusions:
Primary arthroscopic stabilization is a clinically effective and cost-effective treatment for first-time anterior shoulder dislocations in the cohorts studied. By use of a willingness-to-pay threshold of $25,000 per quality-adjusted life year, surgery was more cost effective than nonoperative treatment for the majority of patients studied in the model.

Level of Evidence:
Level II, economic and decision analysis. Ⓐ

Evidence-Based Reference

Crall TS et al.: Cost-effectiveness analysis of primary arthroscopic stabilization versus nonoperative treatment for first-time anterior glenohumeral dislocations, *Arthroscopy* 28:1755–1765, 2012. Ⓐ

SUGGESTED READINGS

Caplan J et al.: Multidirectional instability of the shoulder in elite female gymnasts, *Am J Orthop* 36: 660, 2007.

Cicak N: Posterior dislocation of the shoulder, *J Bone Joint Surg Br* 86B(3):324, 2004.

Hovelius L et al.: Nonoperative treatment of primary anterior shoulder dislocation in patients forty years of age and younger, *J Bone Joint Surg Am* 90(A):945, 2008.

Matsen FA III et al.: Principles for the evaluation and management of shoulder instability, *J Bone Joint Surg Am* 88A:648, 2006.

McFarland EG et al.: The effect of variation in definition on the diagnosis of multidirectional instability of the shoulder, *J Bone Joint Surg Am* 85A:2138, 2003.

O'Connor DR et al.: Painless reduction of acute anterior shoulder dislocations without anesthesia, *Orthopedics* 29:528, 2006.

Owens BD et al.: Incidence of shoulder dislocation in the United States military: demographic consideration from a high-risk population, *J Bone Joint Surg Am* 91:791, 2009.

Robinson CM, Dobson RJ: Anterior instability of the shoulder after trauma, *J Bone Joint Surg Br* 86B(4):469, 2004.

Robinson CN et al.: Redislocation of the shoulder during the first 6 weeks after a primary anterior dislocation: risk factor and results of treatment, *J Bone Joint Surg Am* 84:1552, 2002.

Sachs RA et al.: Can the need for future surgery for acute traumatic anterior dislocation be predicted? *J Bone Joint Surg Am* 89A:1665, 2007.

Sahajpal DT, Zuckerman JD: Chronic glenohumeral dislocation, *J Am Acad Orthop Surg* 16:385, 2008.

Sayegh FE et al.: Reduction of acute anterior dislocations: a prospective randomized study comparing a new technique with the Hippocratic and Kocher methods, *J Bone Joint Surg Am* 91:2775, 2009.

Sileo MJ et al.: Management of acute glenohumeral dislocations, *Am J Orthop* 38(6):282–290, 2009.

Te Slaa RL et al.: The prognosis following acute primary glenohumeral dislocation, *J Bone Joint Surg Br* 1B(86):58, 2004.

Glomerulonephritis, Acute PTG

BASIC INFORMATION

DEFINITION

Acute glomerulonephritis is an immunologically mediated inflammation primarily involving the glomerulus that can result in damage to the basement membrane, mesangium, or capillary endothelium.

SYNONYMS

Postinfectious glomerulonephritis
Acute nephritic syndrome

ICD-9CM CODES
583.9 Glomerulonephritis, acute
ICD-10CM CODES
N00.3 Acute nephritic syndrome with diffuse mesangial proliferative glomerulonephritis
N01.3 Rapidly progressive nephritic syndrome with diffuse mesangial proliferative glomerulonephritis

EPIDEMIOLOGY & DEMOGRAPHICS

- More than 50% of cases involve children <13 yr.
- Glomerulonephritis is the most common cause of chronic renal failure (25%).
- Immunoglobulin A (IgA) nephropathy glomerulonephritis (Berger's disease) is the most common glomerulonephritis worldwide.
- Occurs in 4 out of 100,000 cases.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Edema (peripheral, periorbital, or pulmonary).
- Joint pains, oral ulcers, malar rash (frequently seen with lupus nephritis).
- Dark urine.
- Fatigue, decreased appetite.
- Acute onset of hypertension.
- Findings of palpable purpura in patients with Henoch-Schönlein purpura.
- Heart murmurs may indicate endocarditis.
- Impetigo, skin pallor, palpable purpura, tenderness in the abdomen and/or back, pharyngeal erythema may be present.
- Xanthelasma, alopecia.

ETIOLOGY

Acute glomerulonephritis may be caused by primary renal disease or a systemic disease. A number of pathogenic processes (e.g., antibody deposition, cell-mediated immune mechanisms, complement activation, hemodynamic alterations) have been implicated in the pathogenesis of glomerular inflammation. Medical disorders generally associated with glomerulonephritis are:

- Group A beta-hemolytic *Streptococcus* infection (other infectious etiologies including endocarditis and visceral abscess).
- Collagen-vascular diseases (systemic lupus erythematosus [SLE]).
- Vasculitis (Wegener's granulomatosis, polyarteritis nodosa).
- Idiopathic glomerulonephritis (membranoproliferative, idiopathic, crescentic, IgA nephropathy).
- Goodpasture's syndrome.
- Other cryoglobulinemia (Henoch-Schönlein purpura).
- Drug-induced (gold, penicillamine).

Table G1-8 summarizes primary renal diseases that present as acute glomerulonephritis. Diseases associated with rapidly progressive glomerulonephritis and pertinent laboratory findings are described in Table G1-9.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cirrhosis with edema and ascites.
- Congestive heart failure.
- Acute interstitial nephritis.
- Acute tubular necrosis.
- Severe hypertension.
- Hemolytic-uremic syndrome.
- SLE, diabetes mellitus, amyloidosis, preeclampsia, sclerodermal renal crisis.

WORKUP

Initial evaluation of suspected glomerulonephritis consists of laboratory testing.

LABORATORY TESTS

- Urinalysis (hematuria [dysmorphic erythrocytes and red cell casts], proteinuria).
- Serum creatinine (to estimate glomerular filtration rate [GFR]), blood urea nitrogen.
- 24-hr urine for protein excretion and creatinine clearance (to document degree of renal dysfunction and amount of proteinuria).

TABLE G1-8 Summary of Primary Renal Diseases That Manifest as Acute Glomerulonephritis

Diseases	Poststreptococcal Glomerulonephritis	IgA Nephropathy	Goodpasture Syndrome	Idiopathic Rapidly Progressive Glomerulonephritis
Clinical Manifestations				
Age and sex	All ages, mean 7 yr, 2:1 male	10-35 yr, 2:1 male	15-30 yr, 6:1 male	Adults, 2:1 male
Acute nephritic syndrome	90%	50%	90%	90%
Asymptomatic hematuria	Occasionally	50%	Rare	Rare
Nephrotic syndrome	10%-20%	Rare	Rare	10%-20%
Hypertension	70%	30%-50%	Rare	25%
Acute renal failure	50% (transient)	Very rare	50%	60%
Other	Latent period of 1-3 wk	Follows viral syndromes	Pulmonary hemorrhage; iron deficiency anemia	None
Laboratory findings	↑ ASO titers (70%) Positive streptozyme (95%) ↓ C3-C9; normal C1, C4	↑ Serum IgA (50%) IgA in dermal capillaries	Positive anti-GBM antibody	Positive ANCA in some
Immunogenetics	HLA-B12, D "EN" (9)*	HLA-Bw 35, DR4 (4)*	HLA-DR2 (16)*	None established
Renal Pathology				
Light microscopy	Diffuse proliferation	Focal proliferation	Focal → diffuse proliferation with crescents	Crescentic GN
Immunofluorescence	Granular IgG, C3	Diffuse mesangial IgA	Linear IgG, C3	No immune deposits
Electron microscopy	Subepithelial humps	Mesangial deposits	No deposits	No deposits
Prognosis	95% resolve spontaneously 5% RPGN or slowly progressive	Slow progression in 25%-50%	75% stabilize or improve if treated early	75% stabilize or improve if treated early
Treatment	Supportive	Uncertain (options include steroids, fish oil, and ACE inhibitors)	Plasma exchange, steroids, cyclophosphamide	Steroid pulse therapy

*Relative risk.
ACE, Angiotensin-converting enzyme; *ANCA,* antineutrophil cytoplasmic antibody; *ASO,* anti–streptolysin O; *GBM,* glomerular basement membrane; *GN,* glomerulonephritis; *HLA,* human leukocyte antigen; *Ig,* immunoglobulin; *RPGN,* idiopathic rapidly progressive glomerulonephritis.
From Kliegman RM et al: *Practical strategies in pediatric diagnosis and therapy,* ed 2, Philadelphia, 2004, Saunders.

TABLE G1-9 Diseases Associated with Rapidly Progressive Glomerulonephritis and Pertinent Laboratory Studies

Disease	Studies
Renal Limited	
IgA nephropathy	
Postinfectious glomerulonephritis	Low complement, streptococcal serologies, bacterial cultures
ANCA-associated glomerulonephritis (pauci-immune glomerulonephritis)	ANCA titers
Anti-GBM disease (Goodpasture's syndrome)	Anti-GBM antibodies
Systemic Disorders	
Lupus nephritis	Low complement, ANA, dsDNA antibodies
ANCA-associated small-vessel vasculitis	ANCA titers
Anti-GBM disease	Anti-GBM antibodies
Henoch-Schönlein purpura	None
Cryoglobulinemic vasculitis	Low complement, cryoglobulins, hepatitis C serologies

ANCA, Antineutrophil cytoplasmic antibody; *ANA,* antinuclear antibodies; *dsDNA,* double-stranded DNA; *GBM,* glomerular basement membrane; *IgA,* immunoglobulin A.
From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

TABLE G1-10 Antigens Identified in Glomerulonephritis

Poststreptococcal GN	Streptococcal pyrogenic exotoxin B, plasmin receptor
Anti-GBM disease	α3 type IV collagen (likely induced by molecular mimicry)
IgA nephropathy	Possibly no antigen but rather polymerized polyclonal IgA (?superantigen driven)
Membranous nephropathy	Phospholipase A_2 receptor (idiopathic), neutral endopeptidase in podocyte (congenital), HBeAg (hepatitis associated)
Staphylococcus aureus–associated GN	*Staphylococcus* superantigens induce polyclonal response; not necessarily antigen in glomeruli
Membranoproliferative GN	HCV and HBsAg in hepatitis-associated MPGN
ANCA-associated vasculitis	Proteinase 3 (c-ANCA) and myeloperoxidase (p-ANCA) in neutrophils; antibodies to lysosome-associated membrane protein 2 on endothelial cells (likely induced by molecular mimicry to fimbriated bacterial antigens)

ANCA, Antineutrophil cytoplasmic antibody; *GBM,* glomerular basement membrane; *GN,* glomerulonephritis; *HBeAg,* hepatitis B virus early antigen; *HBsAg,* hepatitis B surface antigen; *HCV,* hepatitis C virus; *IgA,* immunoglobulin A; *MPGN,* membranoproliferative glomerulonephritis.
From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

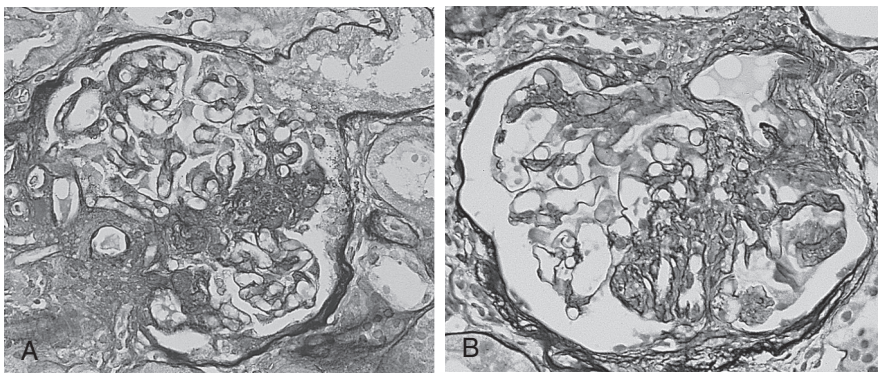


FIGURE G1-15 Light microscopic appearances in focal segmental glomerulosclerosis. Segmental scars with capsular adhesions in otherwise normal glomeruli. A, Periodic acid-Schiff, ×3300. **B,** Methenamine silver stain, ×3300. (Courtesy Dr. D. Davies. From Johnson RJ, Feehally J: *Comprehensive clinical nephrology,* ed 2, St Louis, 2000, Mosby.)

Proteinuria in acute glomerulonephritis typically ranges from 500 mg/day to 3 g/day, but nephrotic-range proteinuria (>3.5 g/day) may be present.
- Spot urine sodium and creatinine for calculation of fractional excretion of sodium (FENa), which is less than 1% in acute glomerulonephritis.
- Serum and urine protein electrophoresis.
- Streptococcal tests (Streptozyme), antistreptolysin O (ASO) quantitative titer (highest in 3 to 5 wk); ASO titer, however, is not related to severity of renal disease, duration, or prognosis.
- Additional useful tests depending on the history: anti-DNA antibodies (rule out SLE), CH_{50} level (if elevated, obtain C_3, C_4 levels), triglycerides, cryoglobulins, hepatitis B and C serologies, antineutrophil cytoplasmic antibody (ANCA), c-ANCA (in suspected cases of Wegener's granulomatosis), p-ANCA found in pauciimmune (lack of immune deposits) idiopathic rapidly progressive glomerulonephritis with or without systemic vasculitis, and antiglomerular basement membrane (type alpha[3] IV collagen) antibodies.
- Hematocrit (decrease in glomerulonephritis) and platelet count (thrombocytopenia in cases of lupus nephritis).
- Anti–glomerular basement membrane antibody (in Goodpasture's syndrome).
- Blood cultures are indicated in all febrile patients.
- Antigens identified in glomerulonephritis are described in Table G1-10.

IMAGING STUDIES

- Chest x-ray: pulmonary congestion, Wegener's granulomatosis, and Goodpasture's syndrome.
- Renal ultrasound if GFR is depressed to evaluate renal size and determine extent of fibrosis. A kidney size of <9 cm is suggestive of extensive scarring and low likelihood of reversibility.
- Echocardiogram in patients with new cardiac murmurs or positive blood cultures to rule out endocarditis and pericardial effusion.
- Renal biopsy and light (Fig. G1-15), electron, and immunofluorescent microscopy to confirm diagnosis.
- Kidney biopsy: generally reveals a granular pattern in poststreptococcal glomerulonephritis and a linear pattern in Goodpasture's syndrome; absence of immune deposits suggests vasculitis. It is useful to determine the degree of inflammation and fibrosis. It is also especially important for patients with rapidly progressive glomerulonephritis, in whom prompt diagnosis and treatment are essential.
- Immunofluorescence: generally reveals C_3. Negative immunofluorescence suggests Wegener's granulomatosis, idiopathic crescentic glomerulonephritis, or polyarteritis nodosa.
- Angiography or biopsy of other affected organs if systemic vasculitis is suspected.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of salt if edema or hypertension is present.
- Low-protein intake (approximately 0.5 g/kg/day) in patients with renal failure.
- Fluid restriction in patients with significant edema.
- Avoidance of high-potassium foods.

ACUTE GENERAL Rx

- Correction of electrolyte abnormalities (hypocalcemia, hyperkalemia) and acidosis (if present).
- Treatment of streptococcal infection with penicillin (or erythromycin in penicillin-allergic patients).
- Furosemide in patients with significant hypertension and/or edema; hydralazine or nifedipine in patients with hypertension.
- Hemodialysis in volume overload, hyperkalemia, uremic symptoms, and encephalopathy.
- Immunosuppressive treatment in patients with heavy proteinuria or rapidly decreasing GFR (high-dose steroids, cyclosporin A, cyclophosphamide); corticosteroids generally not useful in poststreptococcal glomerulonephritis.
- Fish oil (n-3 fatty acids) 12 g/day; may prevent or slow loss of renal function in patients with IgA nephropathy.
- Plasma exchange therapy and immunosuppressive drugs (prednisone and cyclophosphamide); effective in Goodpasture's syndrome.
- Short-term therapy with IV cyclophosphamide followed by maintenance therapy with mycophenolate mofetil or azathioprine. Oral mycophenolate mofetil is also effective in induction therapy in patients with lupus nephritis.
- Mycophenolate mofetil appears superior to azathioprine in maintaining a renal response to treatment and in preventing relapse in patients with lupus nephritis who responded to induction therapy.
- Rituximab and glucocorticoids have been shown to be effective in C3 glomerulonephritis.
- Table G1-11 summarizes suggested management of membranoproliferative glomerulonephritis.

CHRONIC Rx

- Frequent monitoring of urinalysis, serum creatinine, and blood pressure in the initial 12 mo.
- Monitoring for onset of hypertensive retinopathy, encephalopathy.
- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor II blockers (ARBs) are used in patients with proteinuria.
- Aggressive treatment of infections, particularly streptococcal infections.
- Dosage adjustment of all renally excreted medications.

DISPOSITION

- Prognosis is generally related to histology, with excellent prognosis in patients with minimal change in glomerulonephritis and focal segmental proliferative glomerulonephritis. Between 25% and 30% of patients with mesangial IgA disease and membranous glomerulonephritis generally progress to chronic renal failure; <70% of patients with mesangial capillary glomerulonephritis will develop chronic renal failure.
- In general, prognosis is worse in patients with heavy proteinuria, severe hypertension, and significant elevations of creatinine.
- Recovery of renal function occurs within 8 to 12 wk in 95% of patients with poststreptococcal glomerulonephritis.

REFERRAL

- Nephrology consultation. The urgency for referral depends on the GFR. Urgent consultation is recommended if GFR is significantly abnormal or rapidly deteriorating or if the patient has systemic symptoms.
- Surgical referral for biopsy in selected cases.

PEARLS & CONSIDERATIONS

COMMENTS

- Anticoagulation to prevent deep vein thrombosis should be considered in patients with a low level of physical activity.
- Monitoring of lipids and aggressive treatment of hyperlipidemias are recommended.
- Close monitoring of side effects of immunosuppressive drugs and complications of corticosteroids is necessary.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Glomerulonephritis (Patient Information)
Acute Kidney Injury (Related Key Topic)

AUTHORS: **SYEDA M. SAYEED, M.D.,** and **FRED F. FERRI, M.D.**

TABLE G1-11 Suggested Management of Membranoproliferative Glomerulonephritis

Type	Treatment
All types	Supportive therapy following the recommendations discussed in text
Idiopathic MPGN in children	Non-nephrotic proteinuria, normal renal function: follow with 3-month visits Normal renal function and moderate proteinuria (>3 g/day): prednisone 40 mg/m^2 on alternate days for 3 months Nephrotic or impaired renal function: prednisone 40 mg/m^2 on alternate days (80 mg maximum) for 2 years, tapering to 20 mg on alternate days for 3-10 years
Idiopathic MPGN in adults	Non-nephrotic, normal renal function: follow with 3-month visits Nephrotic or impaired renal function: 6-month course of corticosteroid with/without cytotoxic agents (cyclophosphamide) or other drugs used: cyclosporine, tacrolimus, mycophenolate mofetil Rapidly progressive renal failure with diffuse crescents: treat as for idiopathic rapidly progressive glomerulonephritis In the presence of chronic renal failure or nephrotic proteinuria: angiotensin-converting enzyme inhibitors
	Non-nephrotic, normal renal function: treat with interferon alpha based on severity of liver disease (diagnosed by biopsy) Nephrotic syndrome, reduced renal function, or signs of cryoglobulinemia: pegylated interferon alfa-2b (1 mg/kg weekly) and ribavirin (15 mg/kg/day) for 12 months, followed by a short-term course of low-dose corticosteroids; if relapse occurs, consider high-dose interferon alfa (10 million U daily for 2 weeks, then every other day for 6 more weeks) Rapidly progressive renal failure or severe symptoms of vasculitis (heart failure, pulmonary disease): methylprednisolone 1 g daily for 3 days, followed by oral prednisone 60 mg/daily with slow taper during 2-3 months Cyclophosphamide (2 mg/kg/day with adjustment for renal function) and cryofiltration may be added as adjunctive therapy; when the prednisone is reduced to 20 mg/day and the cyclophosphamide is discontinued, add interferon alfa MPGN in the renal or liver transplant recipient: consider course of oral ribavirin (0.6-1 g/day)

MPGN, Membranoproliferative glomerulonephritis.
From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

SUGGESTED READINGS

Contreras G et al.: Sequential therapies for proliferative lupus nephritis, *N Engl J Med* 35:971, 2004.

Dillon JJ, Hladunewich M, Haley WE, et al.: Rituximab therapy for type I membranoproliferative glomerulonephritis, *Clin Nephrol* 77:290, 2012.

Dooley MA et al.: Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis, *N Engl J Med* 365:1886–1895, 2011.

Hricik D et al.: Glomerulonephritis, *N Engl J Med* 339:888, 1998.

Madaio MP, Harrington JT: The diagnosis of glomerular diseases, *Arch Intern Med* 161:25, 2001.

Sethi S, Fervenza FC: Membranoproliferative glomerulonephritis—a new look at an old entity, *N Engl J Med* 366:1118–1131, 2012.

BASIC INFORMATION

DEFINITION

Glossitis is an inflammation of the tongue that can lead to loss of filiform papillae.

ICD-9CM CODES
529.0 Glossitis
ICD-10CM CODES
K14.0 Glossitis

EPIDEMIOLOGY & DEMOGRAPHICS

Glossitis is seen more frequently in patients of lower socioeconomic status, malnourished patients, alcoholics, smokers, elderly patients, immunocompromised patients, and patients with dentures.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The appearance of the tongue varies depending on the etiology of the glossitis (Fig. G1-16*A*). Loss of filiform papillae results in a red, smooth-surfaced tongue.
- The tongue may appear pale in patients with significant anemia.
- Pain and swelling of the tongue may be present when glossitis is associated with infections, trauma, or lichen planus.
- Ulcerations may be present in patients with herpetic glossitis, pemphigus, or streptococcal infection.
- Excessive use of mouthwash may result in a "hairy" appearance of the tongue (Fig. G1-16*B*)

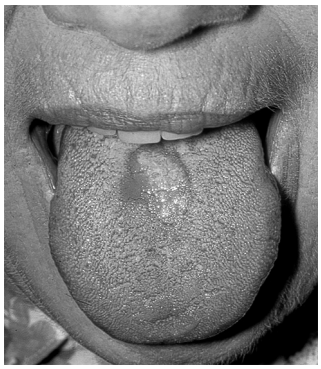


FIGURE G1-16A Median rhomboid glossitis. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

ETIOLOGY

- Nutritional deficiencies (vitamin E, riboflavin, niacin, vitamin B_{12}, iron).
- Infections (viral, candidiasis, tuberculosis, syphilis).
- Trauma (generally caused by poorly fitting dentures).
- Irritation of the tongue from toothpaste, medications, alcohol, tobacco, citrus.
- Lichen planus, pemphigus vulgaris, erythema multiforme.
- Neoplasms.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infections.
- Use of chemical irritants.
- Neoplasms.
- Skin disorders (e.g., Behçet's syndrome, erythema multiforme).

WORKUP

- Laboratory evaluation to exclude infectious processes, vitamin deficiencies, and systemic disorders,
- Biopsy of lesion only when there is no response to treatment,

LABORATORY TESTS

- Complete blood count: decreased hemoglobin and hematocrit, low mean corpuscular volume (MCV) (iron-deficiency anemia), elevated MCV (vitamin B_{12} deficiency).

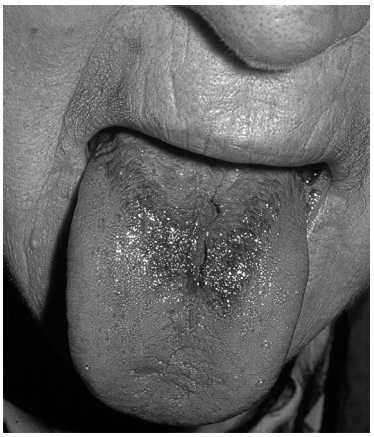


FIGURE G1-16B Black hairy tongue. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

- Vitamin B_{12} level.
- 10% KOH scrapings in patients with white patches suspect for candidiasis.

TREATMENT

NONPHARMACOLOGIC THERAPY

Avoidance of primary irritants such as hot foods, spices, tobacco, and alcohol.

ACUTE GENERAL Rx

Treatment varies with the etiology of the glossitis.

- Malnutrition with avitaminosis: multivitamins.
- Candidiasis: fluconazole 200 mg on day 1, then 100 mg/day for at least 2 wk or nystatin 400,000 U suspension qid for 10 days or 200,000 pastilles dissolved slowly in the mouth four to five times qd for 10 to 14 days.
- Painful oral lesions: rinsing of the mouth with 2% lidocaine viscous, 1 to 2 tablespoons q4h prn; triamcinolone 0.1% applied to painful ulcers prn for symptomatic relief.

CHRONIC Rx

- Lifestyle changes with elimination of tobacco, alcohol, and other primary irritants.
- Dental evaluation for correction of ill-fitting dentures.
- Correction of associated metabolic abnormalities such as hyperglycemia from diabetes mellitus.

DISPOSITION

Most patients experience prompt improvement with identification and treatment of the cause of the glossitis.

REFERRAL

Surgical referral for biopsy of solitary lesions unresponsive to treatment to rule out neoplasm.

PEARLS & CONSIDERATIONS

COMMENTS

If the primary cause of glossitis is not identified or cannot be corrected, enteric nutritional replacement therapy should be considered in malnourished patients.

RELATED CONTENT

Glossitis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

Gonococcal Urethritis ALG PTG

BASIC INFORMATION

DEFINITION

Urethritis is a well-defined clinical syndrome manifested by dysuria, a urethral discharge, or both.

ICD-9CM CODES
597.80 Urethritis, unspecified
098.20 Gonococcal
ICD-10CM Codes
A54.00 Gonococcal infection of lower genitourinary tract, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- The major single specific etiology of acute urethritis is *Neisseria gonorrhoeae,* producing gonococcal urethritis (GCU). Urethritis of all other etiologies is called *nongonococcal urethritis* (NGU).
- NGU is twice as common as GCU in the U.S. NGU is the most common sexually transmitted disease (STD) syndrome occurring in men, accounting for 6 million office visits annually. NGU is more frequently encountered in higher socioeconomic groups. GCU is more common in homosexual males than heterosexual males with acute urethritis.
- *N. gonorrhoeae* is a gram-negative, kidney-shaped diplococcus with flattened opposed margins. The urethra is the most common site of infection in all men. In the United States, the rates of gonorrhea are 40 times higher in black adolescent males than in white adolescent males. In heterosexual men, the pharynx is infected in 7%, and in homosexual men the pharynx is infected in 40% and the rectum in 25%. A single episode of intercourse with an infected partner carries a transmission risk of 20% for males; female partners of an infected male will contract the disease 80% of the time.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms of GCU: urethral discharge and dysuria are the most common symptoms. There is complaint of urethral itching. Prostatic involvement can cause frequency, urgency, and nocturia. It can involve the epididymis through spreading down the vas deferens, causing acute epididymitis.
- Incubation period: 3 to 10 days. Without treatment, urethritis persists for 3 to 7 wk, with 95% of men becoming asymptomatic after 3 mo. GCU is asymptomatic in up to 60% of contacts.
- Signs of GCU: yellow-brown discharge, meatal edema, urethral tenderness to palpation. Rectal bleeding with pus is seen with gonococcal proctitis. Periurethritis leading to urethral stenosis can occur. Disseminated infection can occur. Tenosynovitis and arthritis can occur. Rarely, hepatitis, myocarditis, endocarditis, and meningitis can occur.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- NGU
- Herpes simplex virus

LABORATORY TESTS

- Nucleic acid amplification tests (NAATs): these tests have largely replaced culture in many settings where persons are screened for asymptomatic genital infection. They are not more sensitive than culture for detecting *N. gonorrhoeae* in cervical or urethral specimen; however, they have specificities of >99% and retain sensitivity when used to test voided urine or self-collected vaginal swabs. The performance of NAATs with respect to overall sensitivity, specificity, and ease of specimen transport is better than that of any of the other tests available for the diagnosis of chlamydial and gonococcal infections. NAATs should be used to detect chlamydia and gonorrhea except in cases of child sexual assault involving boys and rectal and oropharyngeal infections in prepubescent girls and when evaluating a potential gonorrhea treatment failure, in which case culture and susceptibility testing might be required.
- Calcium alginate or rayon swab on a metal shaft (not cotton-tipped swabs, which are bactericidal) of the urethra should be performed anywhere from 2 to 4 hr after voiding to prevent bacterial washout with voiding. Gram staining with modified Thayer-Martin media is indicated. Cultures of the pharynx and rectum when indicated.
- Concomitant serologic testing for syphilis on all patients.
- Concomitant *Chlamydia* testing on all patients.
- Offer of HIV counseling and testing to all patients.

TREATMENT

NONPHARMACOLOGIC THERAPY

Behavioral management: avoid intercourse until cure has been attained and sexual partners have been evaluated and treated.

ACUTE GENERAL Rx

- Ceftriaxone 250 mg IM x 1 dose *plus* azithromycin 1 g orally single dose *or* doxycycline 100 mg orally twice/day for 7 days

Alternative regimens:

- Cefixime 400 mg PO x 1 dose *plus* azithromycin 1 g orally single dose *or* doxycycline 100 mg orally twice/day for 7 days *plus* test of cure in 1 wk
- If the patient has severe cephalosporin allergy: azithromycin 2 g in a single oral dose *plus* test of cure in 1 wk
- Resistance to penicillins, fluoroquinolones, sulfonamides, and tetracyclines is now widespread.
- The use of azithromycin as the second antimicrobial is preferred over doxycycline due to the high prevalence of tetracycline resistance.
- The proportion of gonorrhea cases in heterosexual men that are fluoroquinolone resistant (QRNG) has reached 6.7%, an elevenfold increase from 0.6% in 2001. Fluoroquinolone antibiotics are no longer recommended to treat gonorrhea in the U.S.
- Dual treatment for gonococcal and chlamydial infections is based on theory and expert opinion rather than evidence from clinical trials.

CHRONIC Rx

Postgonococcal urethritis (PGU): reinfection is the most common cause of recurrence. Repeat swab and culture of the urethra, pharynx, and rectum (where applicable) are mandatory. Persistence of polymorphonuclear cells (PMNs) with the absence of gram-negative intracellular diplococci suggests a diagnosis of PGU. This occurs when GCU is treated with a regimen that is ineffective against coincident chlamydial infection; it represents NGU after GCU. The syndrome should be treated as NGU. Persistence of *N. gonorrhoeae* by smear or culture requires treatment for *N. gonorrhoeae*.

PEARLS & CONSIDERATIONS

COMMENTS

- Partner notification: the names and contact information of sexual partners should be gathered at the time of the visit and referred to the health department or the patient notifies the contact directly. Expedited partner treatment is recommended by the Centers for Disease Control and Prevention (CDC) and approved in several states. This consists of giving prescriptions to the infected patient for their partner(s) who has not been evaluated by a physician and is unlikely to seek medical care.
- On examination of the urethral smear, the presence of small numbers of PMNs provides objective evidence of urethritis. The complete absence of PMNs on a urethral smear argues against urethritis. If in addition to the PMNs there are gram-negative, intracellular diplococci, the diagnosis of gonorrhea is established.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fig. 3-67 Evaluation of patients with dysuria and/or urethral/vaginal discharge (Algorithm)
Gonococcal Urethritis (Patient Information)

AUTHOR: **RUBEN ALVERO, M.D.,** and **PHILIP J. ALIOTTA, M.D.**

SUGGESTED READINGS

Brill JR: Diagnosis and treatment of urethritis in men, *Am Fam Physician* 81(70): 873–879, 2010.

Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines 2010, *MMWR Morb Mortal Wkly Rep* 59(RR-12), 2010.

Centers for Disease Control and Prevention: Update to CDC's sexually transmitted diseases treatment guidelines. oral cephalosporins no longer a recommended treatment for gonococcal infections, *MMWR Morb Mortal Wkly Rep* 61(31):590–594, 2010, 2012.

MMWR, March 14, 2014, Vol 63/No.2.

BASIC INFORMATION

DEFINITION

Gonorrhea is a sexually transmitted bacterial infection with a predilection for columnar and transitional epithelial cells. It commonly manifests as urethritis, cervicitis, or salpingitis. Infection may be asymptomatic. It differs between males and females in course, severity, and ease of recognition.

SYNONYMS

Gonococcal urethritis
Gonococcal vulvovaginitis
Gonococcal cervicitis
Gonococcal bartholinitis
Clap
GC

ICD-9CM CODES
098 Gonococcal infections
ICD-10CM CODES
A54.9 Gonococcal infection, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- The disease is common worldwide, affects both sexes and all ages, especially younger adults; highest incidence is in inner-city areas, with an estimated 700,000 new cases annually.
- Asymptomatic anterior urethral carriage may occur in 12% to 50% of cases in men.
- Asymptomatic in 50% to 80% of cases in women. Most common dissemination by mucosal passage to fallopian tubes, resulting in pelvic inflammatory disease (PID) in 10% to 15% of infected women. Hematogenous spread may result in septic arthritis and skin lesions. Conjunctivitis rarely occurs but may result in blindness if not rapidly treated. Infection can occur in both men and women in oropharynx and anorectally.
- 700,000 new infections per year (second most commonly reported bacterial STD).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Males: purulent discharge from anterior urethra (Fig. G1-17), with dysuria appearing 2 to 7 days after infecting exposure. May have rectal infection causing pruritus, tenesmus, and discharge or may be asymptomatic.
- Females: initial urethritis or cervicitis may occur a few days after exposure, frequently mild. In approximately 20% of cases uterine invasion occurs after menstrual period with signs and symptoms of endometritis, salpingitis, or pelvic peritonitis. The patient may have purulent discharge or inflamed Skene's or Bartholin's glands.
- Classic presentation of acute gonococcal PID is fever, abdominal and adnexal tenderness, and often absence of purulent discharge. Physical examination may be normal if asymptomatic. Disseminated gonococcal infection may manifest with various skin lesions (Fig. G1-18).

ETIOLOGY

- *Neisseria gonorrhoeae* is the gonococcus. Plasmids coding for β-lactamase render some strains resistant to penicillin or tetracycline. There is an increasing frequency of chromosomally mediated resistance to penicillin, tetracycline, fluoroquinolones, and cefoxitin. In the Far East, high-level resistance to spectinomycin is endemic.
- There are a rising number of cases of quinolone-resistant *N. gonorrhoeae* worldwide, with the expected number to rise in the United States from importation.
- Men who have sex with men are vulnerable to the emerging threat of antimicrobial-resistant *N. gonorrhoeae.*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Nongonococcal urethritis (NGU).
- Nongonococcal mucopurulent cervicitis.
- *Chlamydia trachomatis.*

WORKUP

Diagnosis depends on bacteriologic investigation.

- Nucleic acid amplification tests (NAATs) are preferred testing modalities for the detection of genitourinary infection with *N. gonorrhoeae.* The performance of NAATs with respect to overall sensitivity, specificity, and ease of specimen transport is better than that of any of the other tests available for the diagnosis of gonococcal infections. NAATs should be used to detect gonorrhea except in cases of child sexual assault involving boys and rectal and oropharyngeal infections in prepubescent girls and when evaluating a potential gonorrhea treatment failure, in which case culture and susceptibility testing might be required.[i] NAATs allow testing of the widest variety of specimen types including endocervical swabs, vaginal swabs, urethral swabs (men), and urine (from both men and women).
- Culture: Gonorrhea culture on Thayer-Martin medium (organism is fastidious; requires aerobic conditions with increased carbon dioxide atmosphere; incubate ASAP). Culture has a sensitivity of 95% or more for urethral specimens from men with symptomatic urethritis and 80% to 90% for endocervical infection in women. Gram-negative intracellular diplococci are diagnostic in male urethral smears (Fig. G1-19). There is a false-negative rate of 60% to 70% in female cervical or urethral smears.
  - Concomitant serologic testing for syphilis on all patients.
  - Concomitant *Chlamydia* testing on all patients.
  - Offer of HIV testing and counseling to all patients.

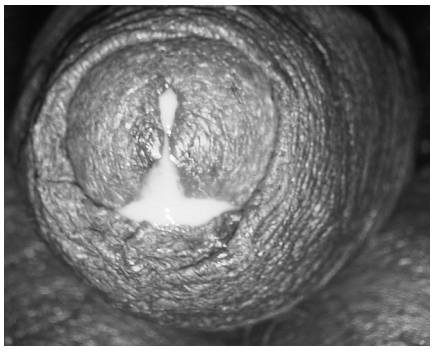


FIGURE G1-17 Purulent urethral discharge from a man with gonococcal urethritis. (From Mandell GL et al: *Principles and practice of infectious diseases,* ed 6, Philadelphia, 2005, Churchill Livingstone.)

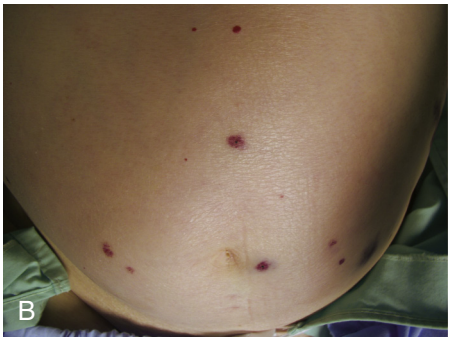


FIGURE G1-18 Disseminated gonococcal infection: skin lesions. A, Macules, papules, and pustules over an ankle. **B,** Hemorrhagic papules localized in trunk. **C,** Hemorrhagic vessel over a distal interphalangeal joint. (**C** Courtesy of Dr. Peter Schlessinger. From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

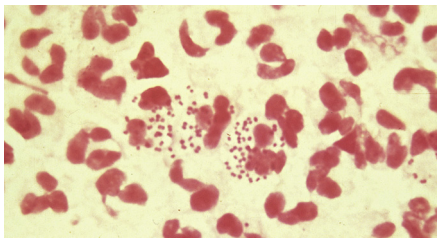


FIGURE G1-19 ***Neisseria gonorrhoeae.*** Gram stain of urethral exudate in gonorrhea, showing intracellular gram-negative reniform diplococci. (Courtesy of Dr S.E. Thompson. From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

LABORATORY TESTS

- Gonorrhea culture on Thayer-Martin medium (organism is fastidious; requires aerobic conditions with increased carbon dioxide atmosphere; incubate ASAP). Culture has a sensitivity of 95% or more for urethral specimens from men with symptomatic urethritis and 80% to 90% for endocervical infection in women.
- NAATs: These tests have largely replaced culture in many settings where persons are screened for asymptomatic genital infection. They are not more sensitive than culture for detecting *N. gonorrhoeae* in cervical or urethral specimen; however, they have specificities >99% and retain sensitivity when used to test voided urine or self-collected vaginal swabs.
- Nonamplified DNA probe tests are less sensitive than culture or NAATs and are not useful in the diagnosis of rectal or pharyngeal infection or for testing urine; however, they are inexpensive, readily available and offered in many laboratories in combination assays for *C. trachomatis.*
- Concomitant serologic testing for syphilis on all patients.
- Concomitant *Chlamydia* testing on all patients.
- Offer of HIV testing and counseling to all patients.

Rx TREATMENT

ACUTE GENERAL Rx

Uncomplicated infections of the cervix, urethra, and rectum. Critical for the practitioner to know local resistance characteristics to best treat the patient:

- Ceftriaxone 250 mg IM × 1 dose *plus* azithromycin 1 g PO single dose *or* doxycycline 100 mg PO bid for 7 days.

Alternative regimens:

- Cefixime 400 mg PO x 1 dose *plus* azithromycin 1 g orally single dose *or* doxycycline 100 mg PO bid for 7 days *plus* test of cure in 1 wk.
- If the patient has severe cephalosporin allergy, then azithromycin 2 g PO single dose *plus* test of cure in 1 wk.

Uncomplicated gonococcal infections of the pharynx:

- Ceftriaxone 250 mg IM x 1 dose *plus* azithromycin 1 g PO single dose *or* doxycycline 100 mg PO bid for 7 days.
- Treatment of the cephalosporin-allergic patient: oral azithromycin 2 gm plus 240 mg IM of gentamicin is effective but has significant side effects (nausea in 28-37% and diarrhea in 18-23% of patients).[1]

DISPOSITION

- Pregnant patients require test of cure (as do those treated with regimens other than ceftriaxone/doxycycline); reculture 4 to 7 days after treatment.
- To reduce development of drug resistance, the CDC has recently modified guidelines and recommends reculture of patients who show continued symptoms despite treatment. These patients should be tested with a culture-based gonorrhea test that can detect antibiotic resistance.
- All sexual partners should be identified, examined, tested, and receive presumptive treatment.

[1] Kirkcaldy RD et al.: The efficacy and safety of gentamicin plus azithromycin and gemifloxacin plus azithromycin as treatment of uncomplicated gonorrhea, *Clin Infect Dis* 59(8):1083-1091, 2014.

REFERRAL

PID requiring hospitalization, disseminated gonococcal infection.

PEARLS & CONSIDERATIONS

COMMENTS

- This is a reportable disease.
- The proportion of gonorrhea cases in heterosexual men who are fluoroquinolone resistant (QRNG) has reached 6.7%, an elevenfold increase from 0.6% in 2001. Fluoroquinolone antibiotics are no longer recommended to treat gonorrhea in the United States.
- The use of azithromycin as the second antimicrobial is preferred over doxycycline due to the high prevalence of tetracycline resistance.
- The U.S. Preventive Services Task Force (USPSTF) recommends screening for gonorrhea in sexually active females 24 years or younger and in older women who are at increased risk for infection. The USPSTF also concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for gonorrhea in men.
- High-intensity counseling on sexual risk reduction has been shown to reduce sexually transmitted infections (STIs) in primary care and related settings.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Gonorrhea (Patient Information)
Cervicitis (Related Key Topic)
Chlamydia Genital Infections (Related Key Topic)
Pelvic Inflammatory Disease (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**, and **PHILIP J. ALIOTTA, M.D.**

SUGGESTED READINGS

Brill JR: Diagnosis and treatment of urethritis in men, *Am Fam Physician* 81(70):873–879, 2010.

Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, 2010, *MMWR Recomm Rep 17* 59(RR-12):1–110, 2010.

Kirkcaldy RD et al.: Neisseria gonorrhoeae antimicrobial resistance among men who have sex with men and men who have sex exclusively with women: the gonococcal isolate surveillance project, 2005-2010, *Ann Intern Med* 158:321–328, 2013.

MMWR, March 14, 2014, Vol 63/No.2.

O'Connor EA et al.: Behavioural sexual risk-reduction counseling in primary care to prevent sexually transmitted infections: a systematic review for the U.S. Preventive Services Task Force, *Ann Intern Med* 161(12):874–883, 2014.

BASIC INFORMATION

DEFINITION

Goodpasture's syndrome is an antiglomerular basement membrane antibody involving the lung and kidney. It is characterized by idiopathic recurrence of alveolar hemorrhage and rapidly progressive glomerulonephritis. It can also be defined by the triad of glomerulonephritis, pulmonary hemorrhage, and antibody to basement membrane antigens.

SYNONYMS

Hypersensitivity angiitis

ICD-9CM CODES
446.2 Goodpasture's syndrome
ICD-10CM CODES
M31.0 Hypersensitivity angiitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Goodpasture's syndrome affects predominantly young, white, male smokers.
- Male/female ratio is 6:1.
- Goodpasture's syndrome accounts for 5% of all cases of rapidly progressive glomerulonephritis.
- 80% of patients are HLA-BR2 positive.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Dyspnea, cough, hemoptysis.
- Skin pallor, fever, arthralgias (may be mild or absent at the time of initial presentation).

ETIOLOGY

Presence of glomerular basement membranes (GBM) antibody deposition in kidneys and lungs with subsequent pulmonary hemorrhage and glomerulonephritis. In the kidneys circulating antibodies bind to the non-collagenous-1 (NC1) domain of type IV collagen in the GBM.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Wegener's granulomatosis.
- Systemic lupus erythematosus.
- Systemic necrotizing vasculitis.
- Idiopathic rapidly progressive glomerulonephritis.
- Drug-induced renal pulmonary disease (e.g., penicillamine).

WORKUP

Laboratory evaluation, diagnostic imaging, immunofluorescence studies of renal biopsy.

LABORATORY TESTS

- Presence of circulating serum anti-GBM antibodies.
- Absence of circulating immunocomplexes, antineutrophils, cytoplasmic antibodies, and cryoglobulins.
- Urinalysis revealing microscopic hematuria and proteinuria.
- Elevated blood urea nitrogen and creatinine from rapidly progressive glomerulonephritis.
- Immunofluorescence studies of renal biopsy material: linear deposits of anti-GBM antibody, often accompanied by C3 deposition.
- Anemia from iron deficiency (from blood loss and iron sequestration in the lungs).

IMAGING STUDIES

Chest radiograph: fluffy alveolar infiltrates, evidence of pulmonary hemorrhage (Fig. G1-20)

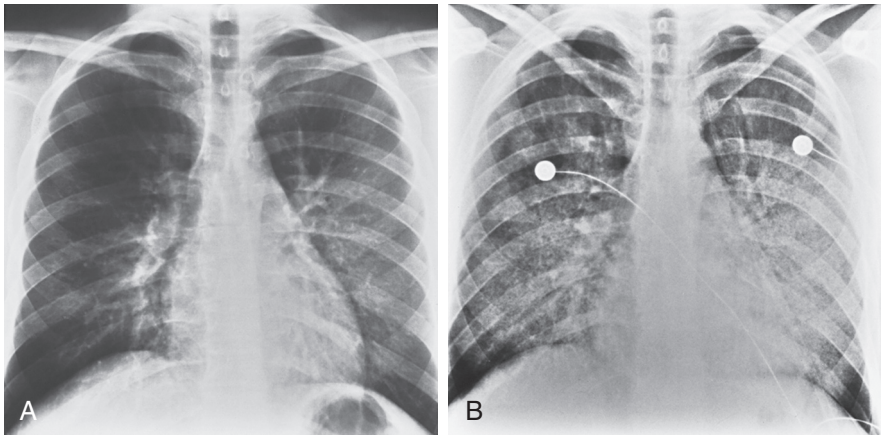


FIGURE G1-20 Goodpasture's syndrome. Posteroanterior chest radiographs several days apart demonstrate consolidation in the left lung **(A),** which progressed to diffuse alveolar disease (consolidation) **(B).** (From McLoud TC [ed]: *Thoracic radiology: the requisites,* St Louis, 1998, Mosby.)

TREATMENT

ACUTE GENERAL Rx

- Combined use of plasmapheresis using albumin replacement for 1 to 2 wk with immunosuppressive therapy with prednisone (1 mg/kg/day) and cyclophosphamide (2 mg/kg/day).
- Dialysis support in patients with renal failure.
- Factors influencing decision to treat or not to treat aggressively in Goodpasture's disease are described in Table G1-12.

DISPOSITION

Life-threatening pulmonary hemorrhage and irreversible glomerular damage are the major causes of death.

REFERRAL

- Referral for renal biopsy to guide the management.
- Consideration for renal transplantation in patients with end-stage renal failure.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Goodpasture's Syndrome (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

TABLE G1-12 Factors Influencing Decision to Treat or Not to Treat Aggressively in Goodpasture's Disease

	Factors Favoring Aggressive Treatment	Factors Against Aggressive Treatment
Pulmonary hemorrhage	Present	Absent
Oliguria	Absent	Present
Creatinine	<5.5 mg/dl (approximately 500 mmol/L)	>5.5-6.5 mg/dl (approximately 500-600 mmol/L) and ANCA negative Severe damage on kidney biopsy No desire for early kidney transplantation
Other factors	Creatinine >5.5-6.5 mg/dl (approximately 500-600 mmol/L) Rapid and recent progression ANCA positive Glomerular damage less severe than expected Crescents recent, nonfibrous Early renal transplantation desired	
Associated disease	Absent	Unusually high risk from immunosuppression

ANCA, Antineutrophil cytoplasmic antibody.
From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

SUGGESTED READINGS

Levy JB et al.: Long-term outcome of anti-glomerular basement membrane antibody disease treated with plasma exchange and immunosuppression, *Ann Intern Med* 134:1033, 2001.

Pedchencko V et al.: Molecular architecture of the Goodpasture autantigen in anti-GBM nephritis, *N Engl J Med* 363:343–354, 2010.

Turner AN: Goodpasture's disease, *Nephrol Dial Transplant* 16:52, 2001.

BASIC INFORMATION

DEFINITION

Gout is a term used to refer to a group of disease states caused by tissue deposition of monosodium urate due to prolonged hyperuricemia. Clinical manifestations of gout include acute and chronic arthritis, soft tissue inflammation, tophus formation, gouty nephropathy, and nephrolithiasis. Untreated hyperuricemia in patients with gout may lead to chronic destructive deforming arthritis.

ICD-9CM CODES
274.00 Gouty arthritis
274.01 Acute gout
274.02 Chronic gout
274.03 Gout with tophus
ICD-10CM CODES
M10 Gout
M10.0 Idiopathic gout
M10.2 Drug induced gout
M10.3 Gout due to impairment of renal function
M10.4 Other secondary gout
M10.9 Gout, unspecified
M10.1 Lead-induced gout

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 5 cases per 1000 persons in the United States. Globally 8 cases per 10,000. Incidence is rising.
PREDOMINANT SEX: Male/female ratio ~4:1.
PREDOMINANT AGE: 30 to 50 yr in men. Older than 60 yr in women.

ETIOLOGY

- Gout is induced by inflammation from monosodium urate (MSU) crystal deposition. The primary risk factor for MSU deposition is hyperuricemia, though local factors such as temperature, pH, and mechanical stress may play a role.
- Hyperuricemia and gout develop from excessive uric acid production, a decrease in the renal excretion of uric acid, or both.
- Primary hyperuricemia results from an inborn error of metabolism and may be attributed to several biochemical defects.
- Secondary hyperuricemia may develop as a complication of acquired disorders (e.g., leukemia) or as a result of the use of certain drugs (e.g., diuretics). Consumption of alcohol, especially beer, increases the risk of gout, and fructose-rich beverage intake is associated with hyperuricemia.

TABLE G1-13 Key Components of Gout Flares

- Marked tenderness and swelling of affected joint
- Acute onset with maximum pain in 4-12 hr
- Recurrent pattern of similar attacks
- Marked impairment of physical function
- Resolution of symptoms within 3-14 days

From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

ACUTE GOUT

- Rapid onset of pain and swelling and erythema of a distal joint and/or periarticular soft tissue. Table G1-13 summarizes key components of gout flares.
- May present as monoarthritis of any joint. Acute gout of the first metatarsophalangeal (MTP) joint (Fig. G1-21) is known as *podagra.*
- 10% to 15% of attacks are polyarticular.
- Spontaneous resolution occurs over days to weeks.

CHRONIC TOPHACEOUS GOUT (FIG. G1-22):

- Insidious onset of painless arthritis and soft tissue swelling.
- Distal small joints characteristic.
- May be confused with nodal osteoarthritis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS OF ACUTE GOUT

- Infectious arthritis.
- Cellulitis.
- Pseudogout.
- Trauma.

DIFFERENTIAL DIAGNOSIS OF CHRONIC GOUT

- Osteoarthritis (especially nodal OA in women).
- Rheumatoid arthritis.
- Psoriatic arthritis.

Section II describes the differential diagnosis of acute monoarticular and oligoarticular arthritis.

WORKUP

Arthrocentesis and examination of synovial fluid

FIGURE G1-21 Podagra or acute gout of the first metatarsophalangeal (MTP) joint is shown. The hyperintense erythema with a dusky hue is characteristic. The area of inflammation usually extends beyond the area of the involved joint. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

LABORATORY TESTS

- Uric acid: All patients with gout are hyperuricemic at some time, but during an acute attack the serum uric acid may be normal or low.
- Synovial aspirate: usually cloudy and markedly inflammatory in nature. Urate crystals in fluid are needle-shaped and strongly negatively birefringent under polarized microscopy (Fig. EG1-23).
- CBC: mild leukocytosis often present.
- Inflammatory markers: ESR and CRP often elevated.

IMAGING STUDIES

- Plain radiography for diagnosis and evaluation. Not generally indicated in typical gout presentation.
- No typical findings in early gouty arthritis but late disease is associated with characteristic punched-out marginal erosions and overhanging edges.
- High frequency ultrasound and dual energy CT may reveal findings supportive of the diagnosis.

TREATMENT OPTIONS FOR ACUTE GOUT

- Nonsteroidal anti-inflammatory medication (see Table G1-14).
  1. Indomethacin 75 mg bid.
  2. Ibuprofen 800 mg tid.
  3. Naproxen 500 mg bid.
  4. Celecoxib 800 mg, then 400 mg/day.
- Low-dose colchicine (less toxic and as effective as traditional high-dose colchicine): 1.2 mg colchicine PO, followed by 0.6 mg PO 1 hr later.
- Intraarticular corticosteroid injection (treatment of choice for monoarticular large joint attack): Triamcinolone hexacetonide 40 mg or equivalent for knee.
- Systemic corticosteroid therapy: Prednisone 40 mg PO for 3 days, then taper over 10 days (effective and safe, but evidence is lacking).

NONPHARMACOLOGIC THERAPY

Lifestyle and dietary modification may be effective in highly motivated patients. Recommendations include reducing ingestion

FIGURE G1-22 Large tophi involving the distal interphalangeal joints are commonly seen in gouty patients with preexisting Heberden's nodes. This is particularly characteristic of late-onset gout. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

of red meat, kidney, liver, yeast extract, shellfish, and overall protein along with restricting alcohol intake. These recommendations should be attempted only in patients with modestly elevated uric acid, as dietary modification can only lower uric acid 1 mg%. Discontinuation of diuretic therapy may help.

PHARMACOLOGIC TREATMENT OF SYMPTOMATIC HYPERURICEMIA

ALLOPURINOL: Allopurinol is very effective and safe when used properly. Correct dosing and patient compliance are essential elements in the prevention of erosive and tophaceous gout. Patients with renal insufficiency are at increased risk for allopurinol hypersensitivity, which manifests as fever, rash, and hepatitis occurring most commonly in the first 3 mo of therapy. The rash may progress to life-threatening toxic epidermal necrolysis if not recognized early.

Traditionally, therapy with allopurinol is initiated several weeks after the acute attack has resolved. However, adding allopurinol at initial presentation may improve long-term compliance without reducing the efficacy of acute treatment. The initial dose should be low (≤100 mg/day depending on creatinine clearance) in patients with renal insufficiency and those with very high uric acid levels. High initial doses are associated with increased incidence of allopurinol hypersensitivity. The serum uric acid should be reevaluated after 4 to 6 wk of therapy, and the allopurinol dose adjusted to reduce the serum uric acid to less than 6 mg%. The most common therapeutic dosage of allopurinol is 300 mg/day, but dose may be increased by 50 to 100 mg every two to three weeks until the target serum uric acid level is achieved. There is evidence that increasing allopurinol doses in patients with renal insufficiency does not result in significant toxicity, but concurrent use with statins and colchicine is associated with a higher incidence of adverse effects. Some authors have reported using doses as high as 800 mg daily without excess toxicity.

FEBUXOSTAT: Novel xanthine oxidase inhibitor that has been shown to be more potent than allopurinol 300 mg daily for reducing serum uric acid. The chemical structure of febuxostat is different from allopurinol, making cross-reactive allergy unlikely. The metabolism of febuxostat is primarily hepatic, which obviates the need for dose adjustments due to renal insufficiency. Some cases of hepatic toxicity have been reported, and it is recommended that liver function tests be monitored periodically. Febuxostat may help preserve renal function in patients with chronic kidney disease (CKD) but has not been tested in patients with severe renal failure.

The primary indication for febuxostat is demonstrated allergy to allopurinol. The cost of febuxostat may be as much as 40 times that of allopurinol.

BENEMID AND SULFINPYRAZONE: These uricosuric agents may only be used in patients with good renal function and urinary uric acid less than 600 mg in a 24-hr collection. Compliance is poor due to necessity of taking drugs more often than once daily.

PEGLOTICASE: Intravenous pegylated uricase was approved by the FDA in 2010 for treatment of severe refractory tophaceous gout. It is a pegylated recombinant mammalian uricase that rapidly degrades urate when given intravenously. Use is limited by very high cost and significant toxicities including frequent gout flares and anaphylaxis.

PATIENT/FAMILY EDUCATION

It is essential that patients, families, physicians, and other members of the health care team appreciate the importance of compliance with a daily allopurinol regimen if recurrent flares and progression to chronic arthritis and tophi are to be avoided. Allopurinol should be discontinued only for symptoms suggesting the hypersensitivity syndrome. It should be continued during flares, medical illnesses, and surgical procedures.

REFERRAL

- Rheumatologist if diagnosis is not clear or therapy is complicated.
- Podiatrist for management of pedal complications.

PEARLS & CONSIDERATIONS

Do not stop allopurinol during hospitalizations, surgery, or acute attacks unless there is evidence of drug allergy.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Gout (Patient Information)
Hyperuricemia (Related Key Topic)

AUTHORS: **BERNARD ZIMMERMANN, M.D.,** and **LUKE BARRÉ, M.D.**

TABLE G1-14 Treatment of Gout

Acute Gout	Interval Gout	Treatment of Hyperuricemia
NSAIDs (preferred): Indomethacin 50 mg qid or ibuprofen 800 mg tid (or other NSAID in full doses). Contraindicated in patients with renal insufficiency and gastrointestinal disorders. *Or* **Colchicine, oral:** 1.2 mg followed by a second dose of 0.6 mg 1 hr later. Contraindicated in patients with renal insufficiency and gastrointestinal disorders *Or* **Intraarticular steroids** (Treatment of choice for large joint monoarthritis): Triamcinolone 40 mg or equivalent for knee *Or* Systemic steroid therapy (for patients in whom NSAIDs and colchicine are contraindicated) Prednisone 30-50 mg PO daily or in divided doses. May use lower dose in diabetic or postsurgical patients.	**Colchicine, oral:** 0.6-1.2 mg/day as prophylaxis against recurrent attacks. **NSAIDs may also be used for prophylaxis.** **Hypouricemic agent:** Indicated for patients with recurrent attacks despite prophylaxis, severe hyperuricemia, presence of tophi, urolithiasis, or gouty arthritis **Other:** Weight loss, reduce alcohol (especially beer), diet low in seafood, red meat, organ meat, and fructose	**Colchicine, oral:** 0.6-1.2 mg/day for 4-6 wk before initiating hypouricemic therapy and for several months afterward to prevent recurrent attacks during initiation of hypouricemic therapy. *And* **Allopurinol:** Initial dose 100 mg/day in patients with renal insufficiency or very high uric acid levels. Increase dose as needed to attain uric acid less than 6 mg/dl. *Or* **Uricosuric agent** (Use only in patients with good renal function and <600 mg uric acid in a 24-hr collection): probenecid, 0.5-1 g bid, or sulfinpyrazone 100 mg tid or qid **Other:** Consider febuxostat for patients allergic to allopurinol. Pegloticase may be useful for selected patients with severe tophaceous gout.

NSAIDs, Nonsteroidal anti-inflammatory drugs.

SUGGESTED READINGS

Conway N, Schwartz ST: Diagnosis and management of acute gout, *Med Health/Rhode Island 92* 11, 2009.

Fox R: Management of recurrent gout, *BMJ 336* 329, 2008.

Jansen TL, et al.: International position paper on febuxostat, *Clin Rheumatol* 29(8):835–840, 2010.

Khanna D, et al.: 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic non-pharmacologic and pharmacologic therapeutic approaches to hyperuricemia, *Arthritis Care and Research* 64(10):1431–1446, 2012.

Krishnan E, et al.: Low-level lead exposure and the prevalence of gout, *Ann Intern Med* 157:233–241, 2012.

Liote F, Ea HK: Recent developments in crystal-induced inflammation: pathogenesis and management, *Curr Rheumatol Rep* 9(3):243, 2007.

Neogi T: Clinical practice: Gout. *N Engl J Med* 364(5):443–452, 2011.

Poon SH, et al.: Approach to the treatment of hyperuricemia, *Med Health/Rhode Island 92* 11, 2009.

Schlesinger N, et al.: Serum urate during acute gout, *J Rheumatol* 36(6):1287–1289, 2009.

Schumacher HR, et al.: Outcome evaluations in gout, *J Rheumatol* 34(6):1381, 2007.

Schumacher Jr HR, et al.: Febuxostat in the treatment of gout: 5-year findings of the FOCUS efficacy and safety study, *Rheumatology* 48:188–194, 2009.

Smith E, et al.: The global burden of gout: estimates from the Global Burden of Disease 2010 study, *Ann Rheum Dis* 73(8):1470–1476, 2014.

Sundy JS, et al.: Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials, *JAMA* 306:711–720, 2011.

Taylor TH, et al.: Initiation of allopurinol at first medical contact for acute attacks of gout: a randomized clinical trial, *Am J Med* 125(11):1126–1134, 2012.

Terkeltaub RA, et al.: High versus low dosing of oral colchicine for early acute gout flare, *Arthritis Rheum* 62:1060–1068, 2010.

Terkeltaub R: Update on gout: new therapeutic strategies and options, *Nat Rev Rheumatol 6* 30, 2010.

Wizenberg T, Buchbinder R: Cochrane Musculoskeletal Group review: acute gout. Steroids or NSAIDs? *J Fam Pract* 58(7):E1, 2009.

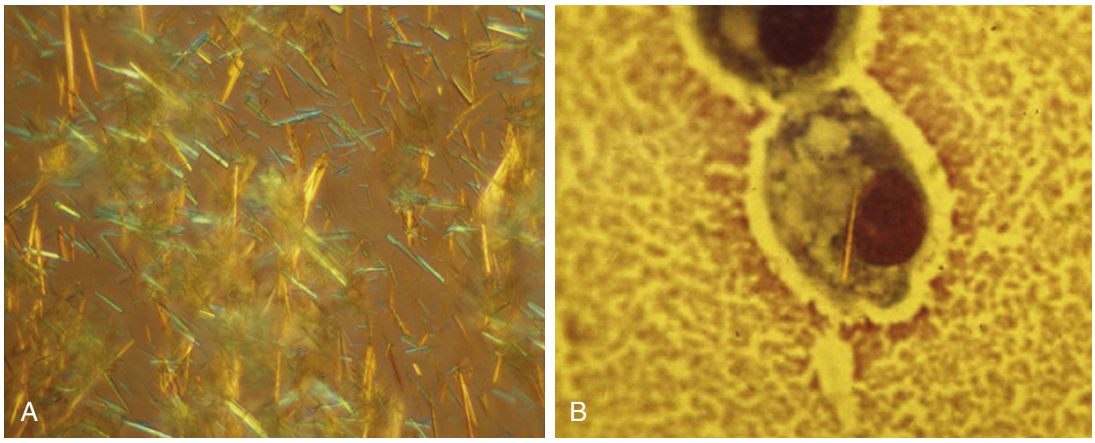


FIGURE EG1-23 A, Urate crystals in the tophus from a patient with gouty arthritis. Crystals are negatively birefringent and needle shaped. **B,** Intracellular urate crystal as seen on Wright stain. (Courtesy H. Ralph Schumacher, Jr.)

Granuloma Annulare PTG

BASIC INFORMATION

DEFINITION

Granuloma annulare (GA) is a chronic, usually self-limited, inflammatory disorder of the dermis that classically presents as arciform to annular plaques located on the extremities.

SYNONYMS

Pseudorheumatoid nodule—subcutaneous granuloma annulare
GA

ICD-9CM CODES
695.89 Granuloma annulare
ICD-10CM CODES
L92.0 Granuloma annulare

EPIDEMIOLOGY & DEMOGRAPHICS

- Most common in children and young adults; most cases of localized GA are diagnosed in patients <30 yr.
- Female predominance (2:1).
- Disseminated form associated with diabetes mellitus.
- Recurrent in 40% of affected individuals.
- A generalized form of GA can occur in up to 15% of patients.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The four main clinical variants of GA are localized (75%), disseminated (>10 lesions), subcutaneous (occurring primarily in children aged 2 to 5 yr), and perforating (rare form manifesting with 1- to 4-mm papules with a central crust).
- Localized GA starts as a small ring of colored skin or pale erythematous papules.
- Lesions coalesce and evolve into annular plaques over several weeks.
- Plaques undergo central involution and increase in diameter over several months (0.5 to 5 cm) (Fig. G1-24).
- Most frequently found on the lateral and dorsal surfaces of the hands and feet.
- Most lesions resolve spontaneously after several months.
- The generalized form of GA is characterized by hundreds to thousands of small, flesh-colored papules in a symmetric distribution on the trunk and extremities.
- Deep dermal GA (subcutaneous GA) presents as large, painless, skin-colored nodules that are frequently mistaken for rheumatoid nodules.

ETIOLOGY

Unknown, but may be related to vasculitis, trauma, monocyte activation, or delayed hypersensitivity.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Tinea corporis.
- Lichen planus.
- Necrobiosis lipoidica diabeticorum.
- Sarcoidosis.
- Rheumatoid nodules.
- Late secondary or tertiary syphilis.
- Arcuate and annular plaques of mycosis fungoides.
- Papular GA can simulate insect bites, secondary syphilis, xanthoma.
- Annular elastolytic giant cell granuloma.

WORKUP

- Diagnosis based on clinical appearance and presentation.
- Biopsy when diagnosis is unclear.

FIGURE G1-24 Granuloma annulare. (From Callen JP [ed]: *Color atlas of dermatology,* ed 2, Philadelphia, 2000, Saunders.)

LABORATORY TESTS

- No laboratory tests will help confirm the diagnosis.
- Biopsy shows focal degeneration of collagen and elastic fibers, mucin deposition, and perivascular and interstitial lymphohistiocytic infiltrate in the upper and middle dermis.

TREATMENT

NONPHARMACOLOGIC THERAPY

Reassurance, given the self-limited and benign nature of GA

CHRONIC Rx

High-potency topical corticosteroids with or without occlusion and intralesional steroid injection into elevated border with triamcinolone 2.5 to 10 mg/ml are useful first-line local therapies.

- Cryosurgery, psoralen ultraviolet-A (UVA) range or UVA-1 therapy, and carbon dioxide laser treatment can also be used.
- Systemic agents (e.g., niacinamide, hydroxychloroquine, chloroquine, cyclosporine, dapsone) are generally reserved for severe cases. Recent case reports indicate positive outcomes with tacrolimus and pimecrolimus and the tumor necrosis factor infliximab.

DISPOSITION

Most lesions resolve spontaneously within 2 yr.

REFERRAL

Dermatology referral recommended for symptomatic, disseminated disease

PEARLS & CONSIDERATIONS

COMMENTS

GA has been described as a paraneoplastic granulomatous reaction to Hodgkin's disease, non-Hodgkin's lymphoma, solid organ tumors, and mycosis fungoides.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Granuloma Annulare (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READING

Cyr PR: Diagnosis and management of granuloma annulare, *Am Fam Physician* 74:1729–1734, 2006.

BASIC INFORMATION

DEFINITION

Granuloma inguinale is a genital ulcerative disease caused by a gram-negative bacterium, *Klebsiella* granulomatis, which may be sexually transmitted, possibly by anal intercourse. It can also be spread through close, long-term, nonsexual contact.

SYNONYMS

Donovanosis

ICD-9CM CODES
099.2 Granuloma inguinale
ICD-10CM CODES
A58 Granuloma inguinale

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Rare in the United States (<100 cases reported annually) and other developed countries
PREVALENCE: Endemic in Australia, India, Caribbean, and Africa; incubation period is variable (1 to 2 wk).
PREDOMINANT SEX: Can affect both males and females.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinically, the disease is commonly characterized as painless, slowly progressive ulcerative lesions on the genitals or perineum without regional lymphadenopathy; subcutaneous granulomas (pseudobuboes) might also occur. The lesions are highly vascular (i.e., beefy red appearance [Fig. EG1-25]) and bleed easily on contact.
- Pathogenic features:
  1. Large, infected mononuclear cell containing many Donovan bodies.
  2. Intracytoplasmic location.

ETIOLOGY

C. granulomatis is a gram-negative bacillus that reproduces within polymorphonuclear cells, plasma cells, and histiocytes, causing the infected cells to rupture 20 to 30 organisms.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Carcinoma.
- Secondary syphilis: condylomata lata.
- Amebiasis: necrotic ulceration.
- Concurrent infections.
- Lymphogranuloma venereum.
- Chancroid.
- Genital herpes.

WORKUP

- Check for clinical manifestations.
  1. Lesions bleed easily.
  2. Lesions sharply defined and painless.
  3. Secondary infection may ensue.
  4. Inguinal involvement may cause pseudobuboes.
  5. Elephantiasis can result from obstruction of lymphatics.
  6. Suppuration and sinus formation are rare in female patients.
- Screen for other sexually transmitted diseases.
- Exclude other causes of lesions.
- Obtain stained, crushed prep from lesion.

A clinical algorithm for evaluation of genital ulcer disease is described in Section III.

Section II describes the differential diagnosis of genital sores.

LABORATORY TESTS

- The causative organism is difficult to culture, and diagnosis requires visualization of dark staining Donovan bodies with Wright stain (observation of Donovan bodies [intracellular bacteria]; organisms in vacuoles within macrophages).
- HIV testing of all patients.

FIGURE EG1-25 Involvement of the penis, with a beefy red, granulomatous ulceration in a patient with granuloma inguinale. (From Goldstein B [ed]: *Practical dermatology,* ed 2, St Louis, 1997, Mosby.)

TREATMENT

ACUTE GENERAL Rx

Recommended regimen:
- Doxycycline 100 mg orally bid ↑ 3 wk minimum.

Alternative regimens:
- Azithromycin 1 g PO/wk ↑ 3 wk.
- Ciprofloxacin 750 mg PO bid ↑ 3 wk.
- Erythromycin base 500 mg PO daily ↑ 3 wk.
- Trimethoprim/sulfamethoxazole, one double-strength tablet PO bid ↑ 3 wk minimum.
- Add gentamicin 1 mg/kg IV q8h if no improvement within the first few days of therapy.

CHRONIC Rx

If there is a poor initial response, extend treatment. Treatment of relapses is often necessary. Patients should be counseled to avoid risky sex practices and not resume having sex until infection is cleared.

DISPOSITION

Follow up clinically until signs and symptoms have resolved, then routine annual or semiannual visits.

REFERRAL

If response is poor, consider referral to infectious disease specialist.

PEARLS & CONSIDERATIONS

COMMENTS

- Sexual partners within 60 days before onset of patient's symptoms should be examined and offered therapy.
- Pregnant women should be treated with erythromycin regimen.
- Patient education material can be obtained from local and state health clinics and also from American College of Obstetricians and Gynecologists.

SUGGESTED READINGS

Available at www.expertconsult.com.

RELATED CONTENT

Granuloma Inguinale (Patient Information)
Chancroid (Related Key Topic)
Lymphogranuloma Venereum (Related Key Topic)
Syphilis (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.,** and **GEORGE T. DANAKAS, M.D.**

SUGGESTED READING

Centers for Disease Control and Prevention: 2010. Sexually transmitted diseases treatment guidelines, *MMWR Morb Mortal Wkly Rep* 59(RR-12), 2010.

BASIC INFORMATION

DEFINITION

Granulomatosis with polyangiitis (GPA) is a multisystem necrotizing vasculitis that generally affects the upper and lower respiratory tracts and the kidneys. It is characterized as an ANCA-associated granulomatous small-vessel vasculitis. Clinical manifestations depend on the tropism of blood vessel involvement and organ systems commonly affected beyond the respiratory tract and kidneys and include neurologic involvement and involvement of the skin and the musculoskeletal systems as well as the gastrointestinal tract.

The disease can also present in a limited form that is generally limited to the upper respiratory tract and can be managed less aggressively than the more diffuse systemic form.

SYNONYMS

Wegener's granulomatosis (WG)

ICD-9CM CODES
446.4 Wegener's granulomatosis
ICD-10CM CODES
M31.3 Wegener's granulomatosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 3/100,000 in recent U.S. epidemiologic studies, equal in men and women, more common in whites.
MEAN AGE AT ONSET: 41 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical manifestations often vary with the stage of the disease and degree of organ involvement; localized disease often has upper respiratory tract involvement without systemic vasculitis, whereas systemic disease stages include early systemic, generalized, and severe disease.
- Frequent manifestations are:
  1. Upper respiratory tract: chronic sinusitis, chronic otitis media, mastoiditis, nasal crusting, obstruction and epistaxis, nasal septal perforation, nasal lacrimal duct stenosis, saddle nose deformities (resulting from cartilage destruction) (Fig. G1-26). Up to 90% of patients with GPA have one or more of these nasal manifestations.
  2. Ears and eyes: sensorineural and conductive hearing loss, episcleritis, scleritis, ulcerative keratitis, proptosis.
  3. Mouth: chronic ulcerative lesions of the oral mucosa, "mulberry" gingivitis.
  4. Lung: nodules, pulmonary infiltrates, cavitary lesions, and frank hemoptysis (6%-85%).
  5. Kidney: rapidly progressive glomerulonephritis (38%-70%), hematuria.
  6. Skin: cutaneous nodules over extensor surfaces of joints, necrotizing skin lesions, palpable purpura (30%-46%).
  7. Nervous system: mononeuritis multiplex and peripheral neuropathies (15%-40%), meningeal inflammation (pachymeningitis), headaches, and CNS involvement (7%-11%).
  8. Muskuloskeletal: monarthritis or polyarthritis (nondeforming), usually affecting large joints (60%).
  9. Constitutional: fever (23%-30%), weight loss >10% (50%), and fatigue (61%).

ETIOLOGY

Unknown; believed to be initially due to granulomatous inflammation that progresses to systemic vasculitis

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other granulomatous lung diseases (e.g., sarcoidosis, lymphomatoid granulomatosis, Churg-Strauss syndrome, necrotizing bronchocentric granulomatosis); the differential diagnosis of granulomatous lung disease is described in Section II. Table G1-15 describes differential diagnostic features of ANCA-associated vasculitis.
- Other ANCA-associated vasculitides, including microscopic polyangiitis.
- Goodpasture's syndrome and other causes of glomerulonephritis (e.g., poststreptococcal nephritis).
- Neoplasms (especially lymphoproliferative disease).
- Bacterial or fungal sinusitis.
- Viral infections.
- Cocaine-induced midline destructive lesions and levamisole-induced vasculitis.
- Other causes of glomerulonephritis (e.g., poststreptococcal nephritis).

WORKUP

- Granulomatosis with polyangiitis should be suspected in a patient presenting with sinus disease that is unresponsive to conventional treatment and/or pulmonary hemorrhage, glomerulonephritis, mononeuritis multiplex resulting in wrist drop or footdrop or progressive migratory arthralgias or arthritis.
- Chest x-ray, laboratory evaluation, PFTs, and tissue biopsy for granulomatous lesions.

LABORATORY TESTS

- ANCA serology: positive immunofluorescence test for cytoplasmic pattern of ANCA (c-ANCA, although between 15% and 40% with diagnosis lack these antibodies). In GPA, ANCAs are predominantly directed against proteinase 3 (anti-PR3), which is the confirmatory

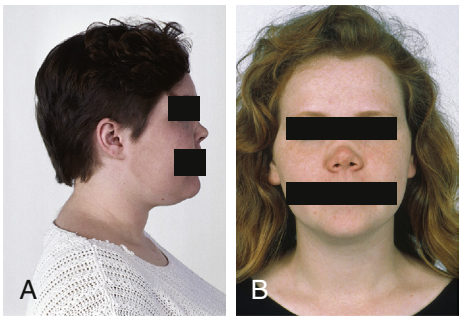


FIGURE G1-26 Saddle-nose deformity in a patient with Wegener's granulomatosis. (From *Kelley's Textbook of Rheumatology*, ed 8, Philadelphia, 2009, Elsevier.)

TABLE G1-15 Differential Diagnostic Features of the Antineutrophil Cytoplasm Antibody–Associated Vasculitides

Feature	Microscopic Polyangiitis	GPA	AGPA	Comments
Glomerulonephritis	+++	+++	+	Progressive renal failure uncommon in AGPA
Pulmonary infiltrates or nodules	++	+++	+++	Asthma and eosinophilia in AGPA
Alveolar hemorrhage	++	++	+	
Upper airway disease	+	+++	++	Ear, nose, and throat disease usually favors GPA
Skin, purpura	+++	+	++	
Peripheral nerve involvement	+	++	+++	Often a prominent feature of AGPA
Central nervous system involvement	+	+	+	

+++, Very commonly seen; ++, seen often; +, uncommon finding; *AGPA*, allergic granulomatosis with polyangiitis; *GPA*, granulomatosis with polyangiitis.
From Firestein GS, et al: *Kelly's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.

laboratory test in a patient with positive ANCA staining on immunofluorescence.
- CBC: anemia, leukocytosis.
- Chemistry: elevated serum creatinine, decreased creatinine clearance.
- Urinalysis: may reveal hematuria, RBC casts, and proteinuria.
- Inflammatory markers: increased ESR, positive rheumatoid factor, and elevated C-reactive protein may be found.

IMAGING STUDIES

- Chest x-ray: may reveal bilateral multiple nodules, cavitary mass lesions, pleural effusion (20%). Up to one third of patients without pulmonary signs or symptoms have an abnormal chest x-ray (Fig. G1-27).
- Computed tomography (Fig. G1-28) or MRI (Fig. EG1-29).
- PFTs: useful in detecting stenosis of the airways.
- Fiberoptic bronchoscopy (endoscopic ENT evaluation): nasal crusting ("golden crusts") are typical on evaluation (Fig. EG1-30).
- Biopsy of one or more affected organs should be attempted; the most reliable source for tissue diagnosis is the lung. Lesions in the nasopharynx (if present) can be easily biopsied but biopsy is positive in only 20%. Biopsy of radiographically abnormal pulmonary parenchyma provides the highest yield (>90%).

FIGURE G1-27 Chest radiograph shows multiple cavitary pulmonary nodules in patient with Wegener's granulomatosis. (From Weinberg SE et al: *Principles of pulmonary medicine,* ed 5, Philadelphia, 2008, Saunders.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Ensure proper airway drainage.
- Give nutritional counseling.

ACUTE GENERAL Rx

- Based on the RAVE trial, rituximab (375 mg/m^2/wk ×4 wk) appears to be more effective than traditional therapy in treating GPA that presents with disease flares and is at least as effective as traditional therapy in treating most ANCA-positive vasculitides for the induction of remission. The RITUXVAS trial concluded that a combined cyclophosphamide-rituximab regimen was noninferior to cyclophosphamide pulsed alone, and rituximab could spare cyclophosphamide pulse dosing and preserve fertility. Both of these studies used concurrent steroid dosing with methylprednisone followed by prednisone.
- Historically, the gold standard for treatment of prednisone 60 to 80 mg/day and cyclophosphamide 20 mg/kg was generally effective and used to control clinical manifestation.
- Potentially useful agents for maintenance therapy include rituximab, methotrexate, azathioprine, and mycophenolate mofetil. The MAINRITSAN trial showed that rituximab may be preferable for maintenance therapy, and the CYCAZAREM (for azathioprine) and LEM (for leflunomide) trials showed that these agents can also be used. The WEGENT study showed oral methotrexate and azathioprine were also noninferior for maintenance than intravenous cyclophosphamide.
- Maintenance therapy should generally be continued for 18 to 24 mo and, if ANCA positivity remains, even as long as 5 years.
- TMP-SMX therapy may represent a useful alternative in patients with lesions limited to the upper or lower respiratory tracts in absence of vasculitis or nephritis. Treatment with TMP-SMX (160 mg/800 mg bid) also reduces the incidence of relapses in patients with granulomatosis with polyangiitis in remission. It is also useful in preventing *Pneumocystis jirovecii* pneumonia (PJP), which occurs in 10% of patients receiving induction therapy. When used for prophylaxis, dose of TMP-SMX (160 mg/800 mg) is 1 tablet three times/wk.
- In patients unable to tolerate TMP-SMX, often because of rash or allergy, PJP prophylaxis can also be achieved with dapsone, atovaquone, or inhaled pentamidine.

DISPOSITION

- Five-year survival with aggressive treatment is approximately 80%; without treatment 2-yr survival is 20%.
- Age >50 yr, impaired renal function, pulmonary involvement at diagnosis, and lack of ENT changes at diagnosis are all associated with worse outcomes and increased mortality rate.
- With standard therapy, remission is achieved by 90% to 94% of patients, but relapse is frequent (from 18% to 40% at 24 mo).

REFERRAL

- Rheumatology referral for continued treatment.
- ENT, surgical referral for biopsy

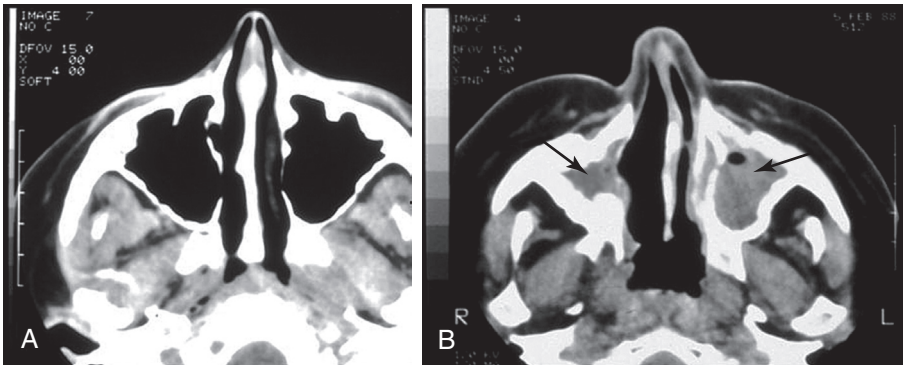


FIGURE G1-28 Computed tomography (CT) scans of the sinuses. A, Normal maxillary sinuses in a recently diagnosed Wegener's granulomatosis (WG) patient. **B,** Sinus CT scan of a patient with long-standing WG: nasal septal deviation to the left, destruction of the medial walls of the right maxillary sinus, opacification of both sinuses with soft tissue densities *(arrows),* and neo-ossification of all maxillary bony structures due to chronic inflammation. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

PEARLS & CONSIDERATIONS

COMMENTS

- Granulomatosis with polyangiitis is characterized by granulomatous lesions and vasculitis involving the respiratory tract, lung, and kidneys.
- C-ANCA levels should not dictate changes in therapy, because they correlate erratically with disease activity.
- The incidence of venous thrombotic events in granulomatosis with polyangiitis is significantly higher than the general population. Clinicians should maintain a heightened awareness of the risks of venous thrombosis and a lower threshold for evaluating patients for possible DVT or pulmonary embolism.
- Disease relapse remains a major problem in the course of the disease.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Wegener's Granulomatosis (Patient Information).

AUTHORS: **AMAR OZA, M.D.**, and **HARALD A. HALL, M.D.**

SUGGESTED READINGS

Finkielman JD et al.: Antiproteinase 3 antineutrophil cytoplasmic antibodies and disease activity in Wegener granulomatosis, *Ann Intern Med* 147(9):611–619, 2007.

Hiemstra TF et al.: Mycophenate mofetil vs. azathioprine for remission maintenance in antineutrophil cytoplasmic antibody-associated vasculitis, *JAMA* 304(21):2381–2388, 2010.

Holle JU et al.: Clinical manifestations and treatment of Wegener's granulomatosis, *Rheum Dis Clin North Am* 36(3):507–526, 2010.

Langford CA: Update on Wegener granulomatosis, *Cleve Clin J Med* 72:689–697, 2005.

Merkel PA et al.: Brief communication: high incidence of venous thrombotic events among patients with Wegener granulomatosis: the Wegener's Clinical Occurrence of Thrombosis (WeCLOT) study, *Ann Intern Med* 142:620–626, 2005.

Stone JH et al.: Rituximab versus cyclophosphamide for ANCA-associated vasculitis, *N Engl J Med* 363:221–232, 2010.

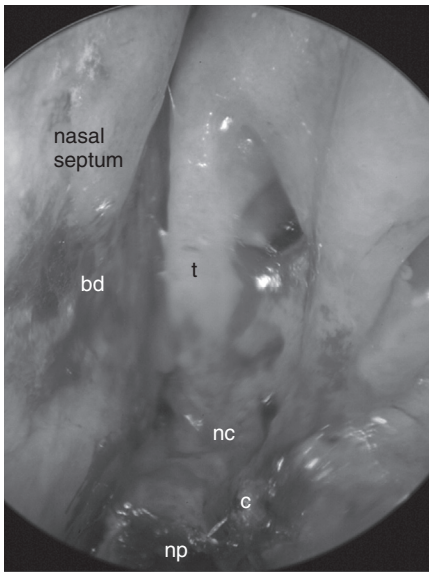


FIGURE EG1-29 Endoscopic view of nasal cavity of GPA patient showing crusting and bloody discharge. (From Holle et al; *Rheum Dis Clin North Am* 36(3):507-526, 2010).

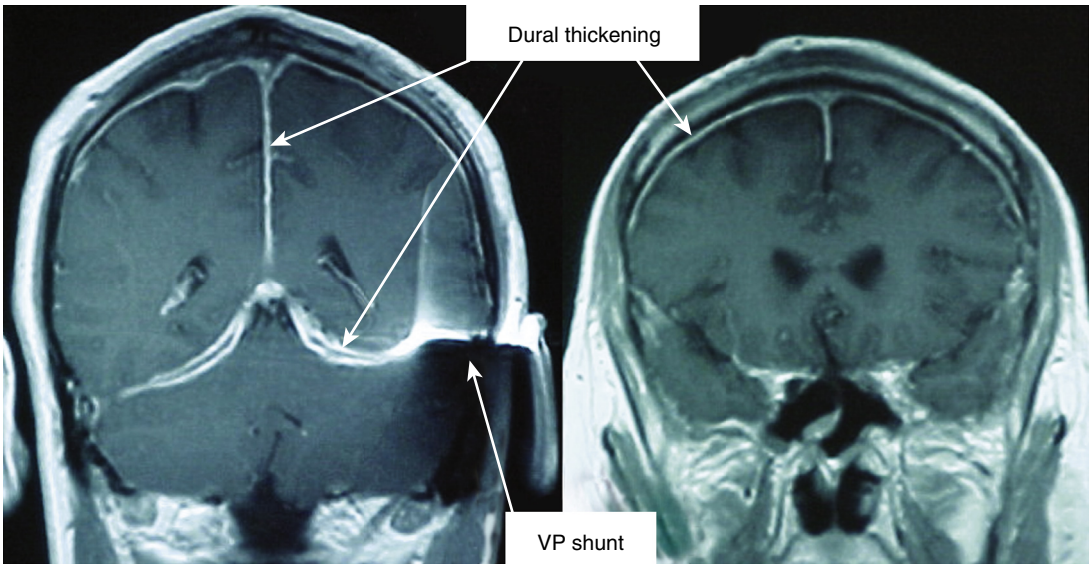


FIGURE EG1-30 Pachymeningitis in a patient with granulomatosis with polyangiitis. Magnetic resonance imaging findings. *VP*, ventriculoperitoneal. (From Firestein GS, et al: *Kelly's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.)

BASIC INFORMATION

DEFINITION

The prototype of granulomatous arthritis is tuberculous arthritis. Atypical mycobacteria, sarcoidosis, and sporotrichosis can cause granulomatous involvement of the synovium, but these entities are much less common.

SYNONYMS

Tuberculous arthritis
Pott's disease

ICD-9CM CODES
711.40 Arthropathy associated with other bacterial disease
730.88 Other infection involving bone
ICD-10CM CODES
M01.1 Tuberculous arthritis (A18.0+)
M01.6 Arthritis in mycoses (B35-B49+)
M01.8 Arthritis in other infections and parasitic diseases classified elsewhere
M00.9 Pyogenic arthritis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: No seasonal predilection.
PREVALENCE (IN U.S.): Unknown.
PREDOMINANT SEX: Male = female.
PREDOMINANT AGE: Rare in childhood.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Often no constitutional symptoms (fever and weight loss).
- Possibly no clinical or radiographic evidence of pulmonary tuberculosis (TB).
- Spinal infection most often in the thoracic or upper lumbar area, with back pain as the most common symptom.
- Considerable local muscle spasm possible.
- Kyphosis and neurologic symptoms resulting from spinal cord compression in advanced disease.
- Chronic monoarticular arthritis in the peripheral joints.
- Single joint involved in 85% of patients.
- Pain, swelling, limitation of motion, and joint stiffness less dramatic than in acute bacterial arthritis; possibly present for months to years.
- Seen more often in persons from developing countries, elderly patients, and hemodialysis patients.

ETIOLOGY

- Hematogenous spread of organisms from a distant site of infection or by direct spread from bone.
- Most commonly affected area: 50% of cases in the spine; next most commonly affected area: large joints (knee and hip).
- Primary infection beginning in the lungs and spreading to the highly vascular synovium.
- Tuberculous osteomyelitis commonly involving an adjacent joint.
- In peripheral joints, a granulomatous reaction in the synovium causing joint effusion and eventual destruction of underlying bone.
- In the spine, infection of the intervertebral disk spreading to adjacent vertebrae.
- Osteomyelitis of vertebrae causing collapse, kyphosis, or gibbous deformity, and possibly paraspinal "cold" abscess.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Sarcoidosis.
- Fungal arthritis.
- Metastatic cancer.
- Primary or metastatic synovial tumors.

WORKUP

- High index of suspicion needed.
- Gold standard: synovial biopsy and culture for bacteria, including acid-fast bacilli, and fungi.
- Joint aspiration and culture of the synovial fluid performed while awaiting biopsy.
- Positive synovial fluid smear for acid-fast bacilli in 20% of cases; positive culture in 80%.
- Elevated synovial fluid protein, low glucose.
- Considerable variation in synovial fluid WBC count, but values of 10,000 to 20,000 cells/mm^3 typical; may be predominantly polymorphonuclear leukocytes.
- Usually positive tuberculin skin test.
- Anergy in elderly patients or in advanced disease.
- In spinal infections, percutaneous or open biopsy to obtain accurate C&S data.

LABORATORY TESTS

Peripheral WBC count and ESR are elevated but nonspecific.

IMAGING STUDIES

- Plain radiographs of the affected joint.
  1. Typically demonstrate bony destruction with little new bone formation.
  2. Osteopenia and soft tissue swelling in early infections.
  3. Later, erosions at the joint margins.
  4. In the spine, disk space narrowing with vertebral collapse (wedging) causing characteristic kyphosis.
- CT scan: useful in early diagnosis of infections of the spine and to detect paraspinal abscess.
- Technetium and gallium scintigraphic scans: may be positive, but do not permit differentiation from inflammation or osteoarthritis.

TREATMENT

NONPHARMACOLOGIC THERAPY

Encourage range-of-motion exercises of the affected joint to prevent contractures.

ACUTE GENERAL Rx

- Combination chemotherapy.
  1. If sensitive TB suspected, give isoniazid 5 mg/kg/day (maximum 300 mg/day) plus rifampin 10 mg/kg/day (maximum 600 mg/day) for at least 6 mo and pyrazinamide 15 to 30 mg/kg/day (maximum 2 g/day) for at least the first 2 mo plus ethambutol 15 to 25 mg/kg/day until sensitivity results are available.
  2. Most patients are treated successfully with chemotherapy alone.
  3. Urgent surgical intervention is necessary if spinal cord compression causes neurologic changes.
- Surgical debridement in cases of extensive bone involvement.

CHRONIC Rx

In longstanding extensive disease, arthrodesis of weight-bearing joints.

DISPOSITION

Loss of cartilage and destruction of underlying bone if treatment is not initiated promptly.

REFERRAL

- To a physician experienced in the management of TB.
- For consultation with an infectious diseases specialist if drug resistance is suspected or documented.
- For neurosurgical and/or orthopedic consultation if neurologic impairment suspected.

PEARLS & CONSIDERATIONS

COMMENTS

As TB has become less prevalent in the United States in the last 10 yr, tuberculous arthritis and osteomyelitis have also become less common. However, due to increase in patients receiving antitumor necrosis factor-alpha therapy, there has been an increase of granulomatous diseases with nontuberculous mycobacteria such as *Mycobacterium avium.*

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Tuberculosis, Military (Related Key Topic)
Tuberculosis, Pulmonary (Related Key Topic)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Crowson AN, Magro C: Interstitial granulomatous dermatitis with arthritis, *Hum Pathol* 35(7):779, 2004.

Gardam M, Lim S: Mycobacterial osteomyelitis and arthritis, *Infect Dis Clin North Am* 19:819–830, 2005.

Smith JW et al.: Infectious arthritis: clinical features, laboratory findings and treatment, *Clin Microbiol Infect* 12(4):309–314, 2006.

Winthrop KL et al.: Nontuberculous mycobacteria infections and anti-tumor necrosis factor-alpha therapy, *Emerg Infect Dis* 10:1556–1561, 2009.

BASIC INFORMATION

DEFINITION

Graves' disease is a hypermetabolic state caused by circulating IgG antibodies that bind to and activate the G-protein–coupled thyrotropin receptor. This activation stimulates follicular hypertrophy and hyperplasia, causing thyroid enlargement as well as increases in thyroid hormone production. It is characterized by thyrotoxicosis, diffuse goiter, and infiltrative ophthalmopathy (edema and inflammation of the extraocular muscles and an increase in orbital connective tissue and fat); infiltrative dermopathy characterized by lymphocytic infiltration of the dermis; accumulation of glycosaminoglycans; and occasionally edema.

SYNONYMS

Thyrotoxicosis

ICD-9CM CODES
242.0 Toxic diffuse goiter
ICD-10CM CODES
E05.00 Thyrotoxicosis with diffuse goiter without thyrotoxic crisis or storm

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE/PREVALENCE: Hyperthyroidism affects 2% of women and 0.2% of men in their lifetimes. More than 80% of these cases are caused by Graves' disease.
PREDOMINANT AGE: Peak incidence is between 40 and 60 yr.
GENETICS: Increased prevalence of HLA-B8 and HLA-DR3 in whites with Graves' disease. Concordance rate is 20% among monozygotic twins.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Tachycardia, palpitations, tremor, hyperreflexia.
- Goiter, exophthalmos (50% of patients), lid retraction, lid lag.
- Nervousness, weight loss, heat intolerance, atrial fibrillation.
- Increased sweating, brittle nails, clubbing of fingers.
- Localized infiltrative dermopathy (1% to 2% of patients) is most frequent over the anterolateral aspects of the legs, commonly over the pretibial area (pretibial myxedema) (Fig. G1-31) but can be found at other sites (especially after trauma).
- Men may have gynecomastia, reduced libido, and erectile dysfunction. Women often have irregular menses.

ETIOLOGY

Autoimmune etiology: the activity of the thyroid gland is stimulated by the action of T cells, which induce specific B cells to synthesize antibodies against thyroid-stimulating hormone (TSH) receptors in the follicular cell membrane.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Anxiety disorder.
- Premenopausal state.
- Thyroiditis.
- Other causes of hyperthyroidism (e.g., toxic multinodular goiter, toxic adenoma).
- Other: metastatic neoplasm, diabetes mellitus, pheochromocytoma.

WORKUP

- The diagnostic workup includes a detailed medical history followed by laboratory and imaging studies and ECG. Patients often present with anxiety, heat intolerance, menstrual dysfunction, increased appetite, and weight loss. Elderly patients can have an atypical presentation (apathetic hyperparathyroidism). For additional information, refer to the topic "Hyperthyroidism."
- Table G1-16 describes the clinical assessment of the patient with Graves' ophthalmopathy.

LABORATORY TESTS

- Increased free thyroxine (T_4) and free triiodothyronine (T_3).
- Decreased TSH.
- Presence of thyroid-stimulating immunoglobulin or thyrotropin-receptor antibodies (useful in selected patients to differentiate Graves' disease from toxic nodular goiter).

IMAGING STUDIES

- 24-hr radioactive iodine uptake (RAIU): increased homogeneous uptake.
- CT or MRI of the orbits (Fig. G1-32) is useful if there is uncertainty about the cause of ophthalmopathy.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Patient education and discussion of therapeutic options.
- Smoking cessation: smoking is associated with an increased risk of progression of Graves' ophthalmopathy.

ACUTE GENERAL Rx

- Antithyroid drugs (ATDs) to inhibit thyroid hormone synthesis or peripheral conversion of T_4 to T_3:
  1. Methimazole or propylthiouracil (PTU) are available. Methimazole is generally preferred because it has a longer half-life, allowing for once-daily dosing. PTU is preferred during pregnancy.
  2. Side effects: skin rash (3% to 5%), arthralgias, myalgias, granulocytopenia (0.5%); rare side effects: aplastic anemia, hepatic necrosis (PTU), cholestatic jaundice.
- Radioactive iodine (RAI):
  1. Treatment of choice for patients >21 yr and younger patients who have not achieved remission after 1 yr of ATD therapy

TABLE G1-16 Clinical Assessment of the Patient with Graves' Ophthalmopathy

Activity Measures*
Spontaneous retrobulbar pain
Pain on attempted up or down gaze
Redness of the eyelids
Redness of the conjunctiva
Swelling of the eyelids
Inflammation of the caruncle and/or plica
Conjunctival edema
Severity Measures
Lid aperture: distance between lid margins in millimeters with the patient looking in the primary position, sitting relaxed, and with distant fixation
Swelling of the eyelids (absent/equivocal, moderate, severe)
Redness of the eyelids (absent/present)
Redness of the conjunctivae (absent/present)
Conjunctival edema (absent, present)
Inflammation of the caruncle or plica (absent, present)
Exophthalmos: measured in millimeters using the same Hertel exophthalmometer and the same intercanthal distance for an individual patient
Subjective diplopia score†
Eye muscle involvement (ductions in degrees)
Corneal involvement (absent/punctate keratopathy/ulcer)
Optic nerve involvement: best-corrected visual acuity, color vision, optic disk, relative afferent pupillary defect (absent/present), plus visual fields if optic nerve compression is suspected

*Based on the seven classic features of inflammation in Graves' ophthalmopathy. The clinical activity score (CAS) is the total number of items present; a CAS ≥3 indicates active ophthalmopathy.
†Subjective diplopia score: 0 = no diplopia; 1 = intermittent (i.e., diplopia in primary position of gaze, when tired, or when first awakening); 2 = inconstant (i.e., diplopia at extremes of gaze); 3 = constant (i.e., continuous diplopia in primary or reading position).
From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

FIGURE G1-31 Chronic pretibial myxedema in a patient with Graves' disease and orbitopathy. The lesions are firm and nonpitting, with a clear edge to feel. (Courtesy of Dr. Andrew Werner, New York, NY.)

2. Contraindicated during pregnancy and lactation
- Surgery: near-total thyroidectomy is rarely performed. Indications: obstructing goiters despite RAI and ATD therapy, patients who refuse RAI and cannot be adequately managed with ATDs, and pregnant women inadequately managed with ATDs.
- Adjunctive therapy: Beta-adrenergic receptor blockers (e.g., atenolol 25 to 100 mg/day) to alleviate the b-adrenergic symptoms of hyperthyroidism (tachycardia, tremor); contraindicated in patients with bronchospasm.
- Graves' ophthalmopathy: methylcellulose eye drops to protect against excessive dryness, sunglasses to decrease photophobia, intraocular and systemic high-dose corticosteroids for severe exophthalmos. Worsening of ophthalmopathy after RAI therapy is often transient and can be prevented by the administration of prednisone. Other treatment options include antiinflammatory and immunosuppressive agents, radiation, and corrective surgical procedures. The administration of the antioxidant selenium (100 μg PO bid) has been recently reported as effective in improving quality of life, reducing ocular involvement, and slowing progression of the disease in patients with mild Graves' orbitopathy. Its mechanism of action is believed to be an effect on the oxygen free radicals and cytokines that play a pathogenic role in Graves' orbitopathy.

CHRONIC Rx

Patients undergoing treatment with ATDs should be seen every 1 to 3 mo until euthyroidism is achieved and every 3 to 4 mo while they are receiving ATDs.

DISPOSITION

- ATDs induce sustained remission in <60% of cases.
- The incidence of hypothyroidism after RAI is >50% within the first year and 2% per year thereafter.
- Complications of surgery include hypothyroidism (28% to 43% after 10 yr), hypoparathyroidism, and vocal cord paralysis (1%).
- Successful treatment of hyperthyroidism requires lifelong monitoring for the onset of hypothyroidism or the recurrence of thyrotoxicosis.
- RAI therapy is followed by the appearance or worsening of ophthalmopathy more often than is therapy with methimazole, particularly in patients who are cigarette smokers. It can be prevented with the administration of prednisone 0.5 mg/kg body weight per day starting 2 to 3 days after RAI, continued for 1 mo, then tapered off over 2 mo.
- Mild to moderate ophthalmopathy often improves spontaneously. Severe cases can be treated with high-dose glucocorticoids, orbital irradiation, or both. Orbital decompression may be used in patients with optic neuropathy and exophthalmos (see "Hyperthyroidism").

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Graves' Disease (Patient Information)
Hyperthyroidism (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

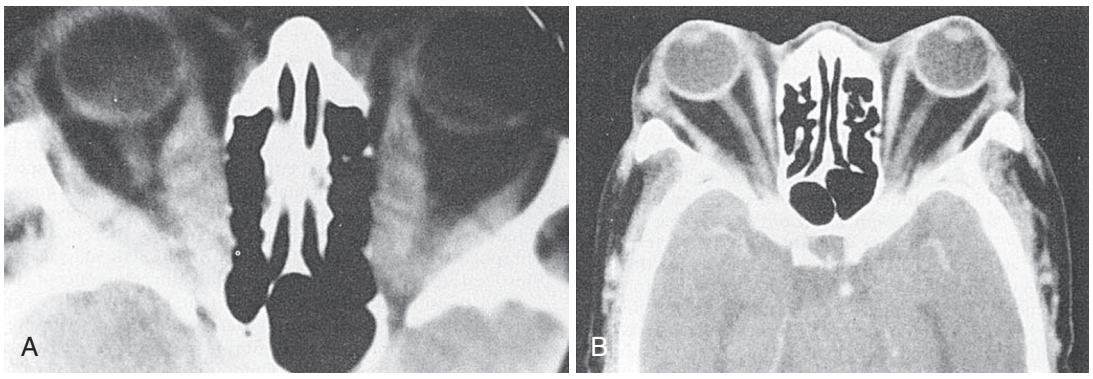


FIGURE G1-32 Computed tomographic scans of orbits in two patients with Graves' orbitopathy. A, Notice the obviously grossly swollen medial rectus extraocular muscles in both orbits and the resulting proptosis. **B**, The patient shows considerable proptosis with only minimal muscle enlargement, suggesting the presence of a large amount of retroorbital fat. (Courtesy of Dr. Peter Som, New York, NY.)

EVIDENCE

Abstract[1]

Background:

Oxygen free radicals and cytokines play a pathogenic role in Graves' orbitopathy.

Methods:

We carried out a randomized, double-blind, placebo-controlled trial to determine the effect of selenium (an antioxidant agent) or pentoxifylline (an antiinflammatory agent) in 159 patients with mild Graves' orbitopathy. The patients were given sodium selenite (100 μg twice daily), pentoxifylline (600 mg twice daily), or placebo (twice daily) orally for 6 months and were then followed for 6 months after treatment was withdrawn. Primary outcomes at 6 months were evaluated by means of an overall ophthalmic assessment, conducted by an ophthalmologist who was unaware of the treatment assignments, and a Graves' orbitopathy–specific quality-of-life questionnaire, completed by the patient. Secondary outcomes were evaluated with the use of a Clinical Activity Score and a diplopia score.

Results:

At the 6-month evaluation, treatment with selenium, but not with pentoxifylline, was associated with an improved quality of life ($P<0.001$) and less eye involvement ($P = 0.01$) and slowed the progression of Graves' orbitopathy ($P = 0.01$), as compared with placebo. The Clinical Activity Score decreased in all groups, but the change was significantly greater in the selenium-treated patients. Exploratory evaluations at 12 months confirmed the results seen at 6 months. Two patients assigned to placebo and one assigned to pentoxifylline required immunosuppressive therapy for deterioration in their condition. No adverse events were evident with selenium, whereas pentoxifylline was associated with frequent gastrointestinal problems.

Conclusions:

Selenium administration significantly improved quality of life, reduced ocular involvement, and slowed progression of the disease in patients with mild Graves' orbitopathy. (Funded by the University of Pisa and the Italian Ministry for Education, University and Research; EUGOGO Netherlands Trial Register number, NTR524). Ⓐ

Evidence-Based Reference

Marcocci C et al.: for the European Group on Graves' Orbitopathy: Selenium and the course of mild Graves' orbitopathy, *N Engl J Med* 364:1920–1931, 2011. Ⓐ

SUGGESTED READINGS

Bahn RS: Graves' ophthalmopathy, *N Engl J Med* 362:726–738, 2010.

Bartalena L, Tanda ML: Graves' ophthalmopathy, *N Engl J Med* 360:994–1001, 2009.

Brent GA: Graves' disease, *N Engl J Med* 358:2594, 2008.

Marsocci C et al.: Selenium and the course of mild Graves' orbitopathy, *N Engl J Med* 364:1920–1931, 2011.

BASIC INFORMATION

DEFINITION

Guillain-Barré syndrome (GBS) is an acute immune-mediated polyradiculoneuropathy (affects nerve roots and peripheral nerves), with predominant motor involvement. It is the most common cause of acute flaccid paralysis in the Western hemisphere and probably worldwide. By definition, maximal clinical weakness occurs within 4 wk of disease onset.

SYNONYMS

AIDP (acute inflammatory demyelinating polyradiculoneuropathy)
Acute polyneuropathy
Ascending paralysis
GBS
Postinfectious polyneuritis

ICD-9CM CODES
357.0 Guillain-Barré syndrome
ICD-10CM CODES
G61.0 Guillain-Barré syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 0.6 to 1.9 cases/100,000 persons annually without geographic variation. Incidence increases with age. A slight peak in incidence occurs between late adolescence and early adulthood. A slight male preponderance (1.25:1) also exists.

PREDISPOSING FACTORS: Viral (HIV, CMV, EBV, influenza) and bacterial *(Campylobacter jejuni, Mycoplasma pneumoniae)* infections; systemic illness (Hodgkin's lymphoma, immunizations). Major antecedents of GBS are described in Box G1-1.

ETIOLOGY

- Unknown
- Preceding infectious illness 1 to 4 wk before disease onset has been noted. The most frequent antecedent infection is *C. jejuni* infection (associated with 30% of cases of GBS and 20% of cases of Miller-Fisher syndrome).
- Humoral and cell-mediated immune attack of peripheral nerve myelin, Schwann cells; sometimes with primary axonal involvement

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symmetric weakness, most commonly involving proximal muscles initially, subsequently involving both proximal and distal muscles; difficulty in ambulating, getting up from a chair, or climbing stairs.
- Depressed or absent reflexes bilaterally.
- Minimal to moderate glove and stocking paresthesias/dysesthesia/anesthesia or back pain.
- Pain (caused by involvement of posterior nerve roots) may be prominent.
- Autonomic abnormalities (bradyarrhythmias or tachyarrhythmias, hypotension or hypertension).
- Respiratory insufficiency (caused by weakness of bulbar/intercostal muscles).

BOX G1-1 Major Antecedents of Guillain-Barré Syndrome

Frequent
Upper respiratory tract infections
Campylobacter jejuni enteritis
Cytomegalovirus infection
Epstein-Barr virus infection
Hepatitis A infection
Hepatitis B infection
Hepatitis C infection
HIV infection

Infrequent
Mycoplasma pneumoniae infection
Haemophilus influenzae infection
Leptospira icterohaemorrhagiae infection
Salmonellosis
Rabies vaccine
Tetanus toxoid
Bacille Calmette-Guérin immunization
Sarcoidosis
Systemic lupus erythematosus
Lymphoma
Trauma
Surgery

Questionable
Hepatitis B vaccine
Influenza vaccine
Hyperthermia
Epidural anesthesia

From Vincent JL et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, Saunders.

- Facial paresis, ophthalmoparesis, dysphagia (secondary to cranial nerve involvement).
- GBS consists of several clinical variants based on the pattern of clinical involvement and electrophysiologic findings. These include:
  1. AIDP (most common form in Europe and North America)
  2. Acute motor axonal neuropathy (AMAN; most prevalent form in China and Japan)
  3. Acute motor and sensory axonal neuropathy (AMSAN; has more severe sensory involvement and is associated with more severe clinical course and poorer prognosis)
  4. Miller Fisher syndrome (MFS; triad of ophthalmoplegia, ataxia, and areflexia)
  5. Acute pandysautonomia (rapid onset of parasympathetic and sympathetic failure without motor or sensory involvement)
  6. Regional variants (e.g., pharyngeal-cervical-brachial GBS, pure ataxic GBS)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Toxic peripheral neuropathies: heavy metal poisoning (lead [microcytic anemia], thallium [alopecia], arsenic [typically accompanied by acute GI illness]), medications (vincristine, disulfiram), organophosphate poisoning, hexacarbon (glue sniffer's neuropathy)
- Nontoxic peripheral neuropathies: acute intermittent porphyria, fulminant vasculitic polyneuropathy, infectious (poliomyelitis, diphtheria, Lyme disease, West Nile virus); tick paralysis
- Neuromuscular junction disorders: myasthenia gravis, botulism, snake envenomations
- Myopathies such as polymyositis, acute necrotizing myopathies caused by drugs
- Metabolic derangements such as hypermagnesemia, hypokalemia, hypophosphatemia
- Acute CNS disorders such as basilar artery thrombosis with brainstem infarction, brainstem encephalomyelitis, transverse myelitis, or spinal cord compression
- Hysterical paralysis or malingering

WORKUP

1. Exclude other causes based on clinical history, examination, and laboratory tests.
2. Lumbar puncture (may be normal in the first 1 to 2 wk of the illness). Typical findings include elevated CSF protein with few mononuclear leukocytes (albuminocytologic dissociation) in 80% to 90% of patients. Elevated CSF cell counts is an expected feature in cases associated with HIV seroconversion.
3. EMG/nerve conduction study (NCS): may be normal in the first 10 to 14 days of the disease. The earliest electrodiagnostic abnormality is prolongation or absence of H-reflexes. NCS evidence of demyelination (prolonged distal latency, conduction velocity slowing, conduction block, temporal dispersion, and prolonged F-waves) in two or more motor nerves confirms diagnosis of AIDP in the appropriate clinical context.

LABORATORY TESTS

- CBC may reveal early leukocytosis with left shift. Electrolytes are tested to exclude metabolic causes.
- Heavy metal testing, urine porphyria screen, creatine kinase, HIV titers, neuroimaging of the brain and spinal cord if diagnosis is uncertain. Nerve root enhancement may be seen on MRI of the lumbosacral spine.
- Antibodies against ganglioside GQ1b may be present in up to 90% of patients with MFS. IgG antibodies against ganglioside GM1 may be associated with AMAN. There are no anti-ganglioside antibodies commonly associated with AIDP.
- In equivocal cases (especially if peripheral nerve vasculitis is a concern), nerve biopsy may aid in confirming a diagnosis of GBS. Sensory nerve biopsy demonstrates segmental demyelination with infiltration of monocytes and T cells into the endoneurium. Axonal loss is commonly seen in sensory nerve biopsy specimens in GBS.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Close monitoring of respiratory function (frequent measurements of vital capacity, negative inspiratory force, and tidal volume) and pulmonary toilet should be done because respiratory failure is the major complication in GBS.
- Frequent repositioning of patient to minimize formation of pressure sores.

- Prevention of thromboembolism with antithrombotic stockings and SC heparin (5000 U q12h) in nonambulatory patients.
- Emotional support and social counseling for patient and family.

ACUTE GENERAL Rx

- Infusion of IV immunoglobulins (IVIG; 0.4 g/kg/day for 5 days). Always check serum IgA levels before infusion to prevent anaphylaxis in IgA deficient patients.
- Early therapeutic plasma exchange (TPE or plasmapheresis: 200 to 250 ml/kg over five sessions every other day), started within 7 days of onset of symptoms, is beneficial in reducing the need for mechanical ventilation in patients with rapidly progressive disease and results in improved rate of recovery. It is contraindicated in patients with cardiovascular disease (recent MI, unstable angina), active sepsis, and autonomic dysfunction.
- There is no proven benefit from combining IVIG and plasma exchange.
- Mechanical ventilation may be needed if FVC is <12 to 15 ml/kg, vital capacity is rapidly decreasing or is <1000 ml, negative inspiratory force <20 cm H_2O, PaO_2 is <70, the patient is having significant difficulty clearing secretions or is aspirating.

CHRONIC Rx

- Ventilatory support may be necessary in 10% to 20% of patients. Adequate fluid/electrolyte support and nutrition are necessary, especially in patients with dysautonomia or bulbar dysfunction.
- Aggressive nursing care to prevent decubitus, infections, fecal impactions, and pressure nerve palsies.
- Monitoring and treatment of autonomic dysfunction (bradyarrhythmias or tachyarrhythmias, orthostatic hypotension, systemic hypertension).
- Treatment of back pain and dysesthesia with low-dose tricyclics, gabapentin, and so on. Opiate narcotics can be used cautiously in the short term but may compound dysautonomia.
- Stress ulcer prevention in patients receiving ventilator support.
- Physical and occupational therapy rehabilitation, including supportive devices.

DISPOSITION

- Mortality rate is approximately 5% to 10% worldwide. Causes of death include cardiac arrest, pulmonary embolism, and fulminant infections. A recent study showed 62% complete motor recovery, 14% mild weakness, 9% moderate weakness, 4% bed-bound or ventilated, and 8% dead at 1 yr. Another study suggested that about 33% of patients were free from sensory symptoms at 1 yr, with residual sensory loss present in the lower extremities in 67% and 36% in the upper extremities. About 32% had to change their work, 30% were unable to function at home as well as they could before the disease, and 52% had to alter their leisure activities 1 yr after GBS onset. Excessive fatigue is a common complaint in patients during the recovery phase of GBS. This may be treated with exercise therapy (e.g., bicycle exercise training).
- Predictors for poor recovery (inability to walk independently at 1 yr): age >60 yr, preceding diarrheal illness, recent CMV infection, fulminant or rapidly progressing course, ventilatory dependence, reduced motor amplitudes (<20% normal), or inexcitable nerves on NCS. Outcomes may also be influenced by complications of medical therapy.
- GBS is typically a monophasic illness. Recurrence may occur in <5% of patients following full recovery.

REFERRAL

Tracheostomy may be necessary in patients with prolonged ventilatory support. Percutaneous endoscopic gastrostomy may be temporarily required.

PEARLS & CONSIDERATIONS

- GBS is the most common cause of acute flaccid paralysis.
- Close monitoring of ventilatory function with respiratory mechanics (FVC and NIF) is of paramount importance in all patients with suspected GBS.

PATIENT/FAMILY EDUCATION

Patient education information may be obtained from the Guillain-Barré Foundation International, The Holly Building, 104 1/2 Forrest Avenue, Narberth, PA 19072; phone: (610) 667-0131; fax: (610) 667-7036; toll-free: (866) 224-3301; E-mail: info@gbs-cidp.org

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **DIVYA SINGHAL, M.D.**

SUGGESTED READINGS

Dimachkie MM et al.: Guillain-Barré syndrome, *Curr Treat Options Neurol* 15(3):338–349, 2013.

Garssen MP et al.: Physical training and fatigue, fitness, and quality of life in Guillain-Barré syndrome and CIDP, *Neurology* 63:2393–2395, 2004.

Fujimura H: The Guillain-Barré syndrome, *Handb Clin Neurol* 115:383–402, 2013.

González-Suárez I et al.: Guillain-Barré syndrome: Natural history and prognostic factors: a retrospective review of 106 cases, *BMC Neurol* 13(1):95, 2013.

Hughes RA et al.: Multidisciplinary Consensus Group: supportive care for patients with Guillain-Barré syndrome, *Arch Neurol* 62:1194–1198, 2005.

van Doorn PA et al.: Immunotherapy for Guillain-Barré syndrome, *Lancet Neurol* 3(2):84, 2004.

Yuki N, Hans-Peter H et al.: Guillain-Barré syndrome, *N Engl J Med* 366:2294–3011, 2012.

BASIC INFORMATION

DEFINITION

Gynecomastia is a benign enlargement of male breast, resulting from proliferation of glandular breast tissue.

ICD-9CM CODES
611.1 Gynecomastia
ICD-10CM CODES
N62 Hypertrophy of breast

EPIDEMIOLOGY

- Most common reason for male breast evaluation.
- Seen in patients of all age groups.
- 60% to 90% of infants have transient gynecomastia due to high estrogenic state of pregnancy.
- Prevalence during adolescence ranges from 4% to 69%. It results from transient increase of estradiol concentration at the onset of puberty.
- Higher incidence in body builders due to use of anabolic steroids.
- 24% to 65% of older men have gynecomastia. It is secondary to decreased testosterone production with advanced age, increased peripheral conversion of testosterone to estrogen, and at times from side effects of medications.

PATHOPHYSIOLOGY

Altered estrogen-androgen balance, in favor of estrogen.

ETIOLOGY

- Physiologic
  Infancy
  Puberty
  Persistent pubertal gynecomastia seen in 25% of cases
  Elderly
- Pathologic
  Idiopathic (25%)
  Increased estrogen production or action
  Testicular tumors (3%)
  Chronic liver disease
  Malnutrition
  Hyperthyroidism
  Adrenal tumors
  Familial gynecomastia

Decreased testosterone production or action (10%)
  Testicular trauma
  Testicular torsion
  Viral orchitis
  Congenital anorchia
  Renal failure (1%)
  Hyperthyroidism (1.5%)
  Malnutrition
  Androgen insensitivity syndrome
  Five-alpha reductase deficiency
  Pituitary tumors
  Kallmann syndrome
  Klinefelter's syndrome

- Medications (10% to 25%)
  Estrogen, gonadotropins, clomiphene, phenytoin, ketoconazole, metronidazole, metoclopramide, alkylating agents, busulfan, methotrexate, cisplatin, cimetidine, ranitidine, omeprazole, flutamide, finasteride, etomidate, HAART therapy, INH, tricyclic antidepressants, phenothiazines, diazepam, haloperidol, calcium channel blocker, ACE inhibitors, spironolactone, digoxin, amiodarone, methyldopa, alcohol, marijuana, heroin, methadone, amphetamine, anabolic steroids
- Table EG1-17 summarizes the various causes of gynecomastia.

CLINICAL FEATURES

- Although gynecomastia is usually bilateral, it could be unilateral.
- Characterized by concentric rubbery to firm disk of tissue, which is often mobile and located directly beneath the areola (Fig. G1-33).
- Pain is usually not severe. Varying degree of tenderness and nipple sensitivity are more common than pain, usually in the first 6 mo.

DIAGNOSIS

- Good history and physical examination including review of all medications the patient is taking is helpful.
- Mammogram is recommended for suspected breast cancer.
- Serum concentration of hCG, LH, testosterone, and estradiol should be measured, preferably in the morning, unless the cause is clearly apparent. There is no uniformity of opinion regarding what biochemical evaluation, if any, should be performed in patients with asymptomatic gynecomastia. Fig. EG1-34 describes an algorithm for evaluation of gynecomastia.

FIGURE G1-33 Gynecomastia. (From Swartz, MH: *Textbook of Physical Diagnosis*, 7th ed, Philadelphia, Saunders, 2014.)

DIFFERENTIAL DIAGNOSIS

- Breast cancer
  1. Mass is usually firm to hard
  2. Unilateral
  3. Eccentric in location
  4. Could be associated with nipple discharge and retraction, lymphadenopathy, and skin dimpling
- Pseudogynecomastia or lipomastia
  1. Characterized by fat deposition without glandular proliferation
  2. Seen in obese men
  3. Bilateral
  4. Remain unchanged over time

TREATMENT

- Observation is recommended for most patients with physiologic gynecomastia. They often regress spontaneously. Reassurance and follow-up examination in 3 to 6 mo usually suffice.
- Treat the underlying cause, and stop the offending medications.
- Treatment is most effective in the early stages (first 6 mo). Medical therapy often fails when given for longstanding (>12 mo) cases because of the presence of fibrosis.
- Potential indications of early therapy include severe breast enlargement, pain, tenderness, and psychological embarrassment. Consider giving tamoxifen 10 mg orally twice a day to these patients for up to 3 mo. It is not FDA-approved for this purpose. It results in regression of gynecomastia in approximately 80% of patients and, of which, only 60% had complete regression. As far as breast symptoms, such as pain and tenderness, some improvement is usually seen within a month of therapy.
- Surgery is offered for symptomatic gynecomastia that does not respond to medical therapy. However, for adolescents, surgery is deferred until puberty is completed. The different surgical options include subcutaneous mastectomy, ultrasound-guided liposuction, and suction-assisted lipectomy.
- For prevention of gynecomastia in patients with prostate cancer using antiandrogen therapy, one could offer tamoxifen or radiotherapy.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Gynecomastia (Patient Information)

AUTHOR: **HEMANT K. SATPATHY, M.D.**

SUGGESTED READINGS

Braunstein GD: Gynecomastia, *N Engl J Med* 357:1229, 2007.
Cordova A, Moschella F: Algorithm for clinical evaluation and surgical treatment of gynecomastia, *J Plast Reconstr Aesthet Surg* 61:41, 2008.
Dickson G: Gynecomastia, *Am Fam Physician* 85(7):716–722, 2012.
Gikas P, Mokbel K: Management of gynecomastia: an update, *Int J Clin Pract* 61:1209, 2007.

TABLE EG1-17 Causes of Gynecomastia

Cause	Examples
Physiologic Causes	
Maternal estrogen exposure	Neonatal gynecomastia
Transient increase in estrogen to androgen concentrations	Pubertal gynecomastia
Estrogen Excess	
Estrogens or estrogen receptor agonists	Estrogens, marijuana smoke, digitoxin, testosterone or other aromatizable androgens
Increased peripheral aromatase activity	Obesity, aging, familial
Estrogen-secreting tumors	Adrenal carcinoma, Leydig or Sertoli cell tumor
hCG-secreting tumors	Germ cell, lung, hepatic carcinoma
hCG treatment	
Androgen Deficiency or Resistance	
Androgen deficiency	Primary or secondary hypogonadism
Hyperprolactinemia causing androgen deficiency	
Androgen resistance disorders	Congenital and acquired androgen resistance
Drugs that interfere with androgen action	Spironolactone, androgen receptor antagonists, marijuana, 5α-reductase inhibitors, histamine 2 receptor antagonists
Systemic Disorders	
Organ failure	Hepatic cirrhosis, chronic kidney disease
Endocrine disorders	Hyperthyroidism, acromegaly, growth hormone treatment, Cushing's syndrome
Nutritional disorders	Refeeding, recovery from chronic illness (hemodialysis, insulin, isoniazid, antituberculous medications, ART)
Idiopathic Causes	
Drugs	ART, calcium channel antagonists, amiodarone, antidepressants (SSRIs, tricyclic antidepressants), alcohol, amphetamines, penicillamine, sulindac, phenytoin, omeprazole, theophylline
Adult–onset idiopathic gynecomastia	
Persistent prepubertal macromastia	

HAART, Highly active antiretroviral therapy; *hCG,* human chorionic gonadotropin; *SSRIs,* selective serotonin reuptake inhibitors.
From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

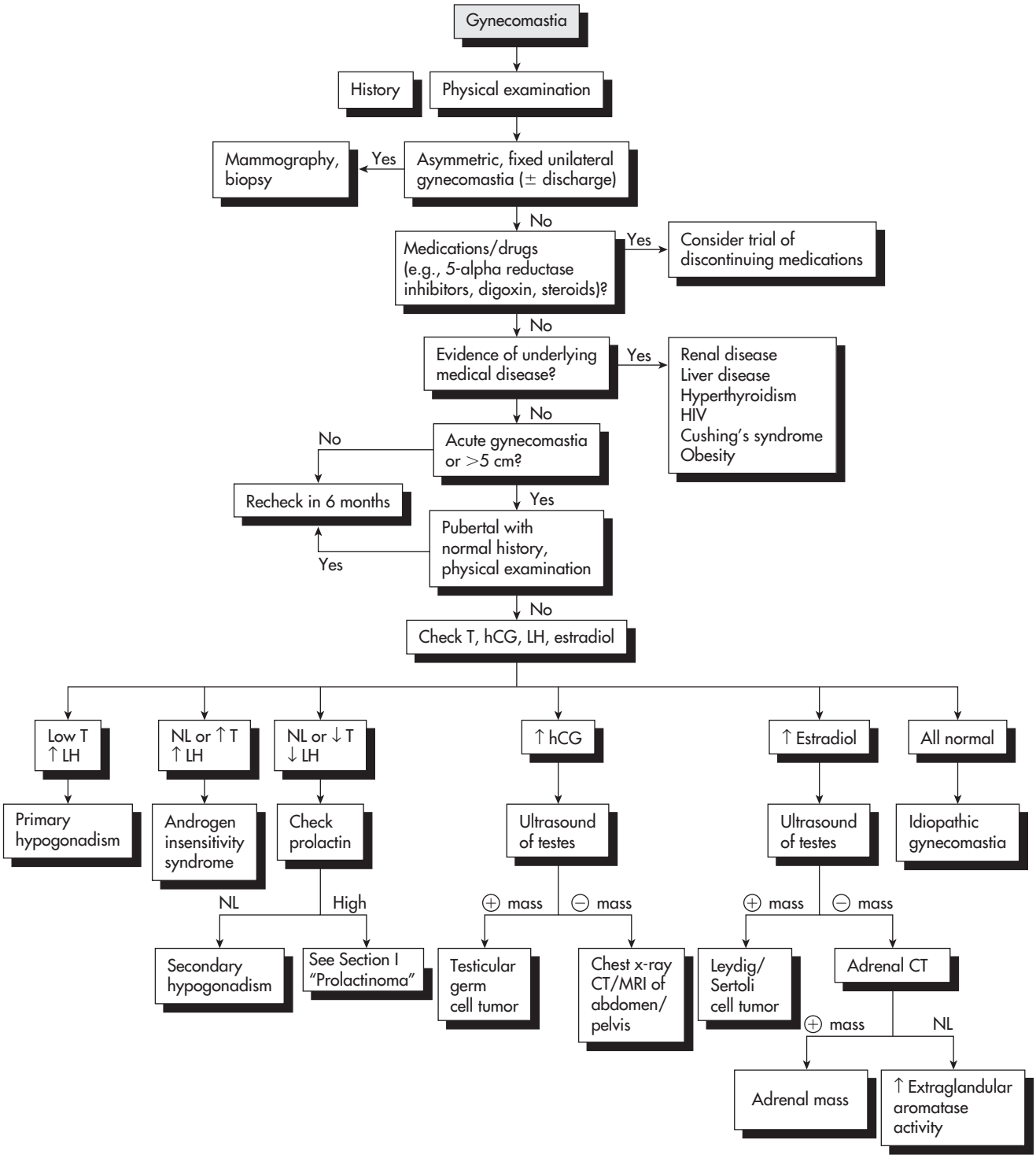


FIGURE EG1-34 Evaluation of gynecomastia. *CT,* Computed tomography; *hCG,* human chorionic gonadotropin; *HIV,* human immunodeficiency syndrome; *LH,* luteinizing hormone; *MRI,* magnetic resonance imaging; *NL,* normal limits; *T,* testosterone. (Modified from Noble J: *Primary care medicine,* ed 3, St Louis, 2001, Mosby.)

BASIC INFORMATION

DEFINITION

Hairy cell leukemia is a lymphoid neoplasm characterized by the proliferation of mature B cells with prominent cytoplasmic projections (hairs).

SYNONYMS

HCL
Leukemic reticuloendotheliosis

ICD-9CM CODES
202.4 Hairy cell leukemia
ICD-10CM CODES
C91.40 Hairy cell leukemia not having achieved remission

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Occurs predominantly in men between ages 40 and 60 yr. Approximately 2% of leukemia cases are of the hairy cell type.
PREDOMINANT SEX: Male/female ratio of 4:1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Usually, splenomegaly (present in >90% of cases) caused by tumor cell infiltration (Fig. EH1-1).
- Pallor, ecchymosis, and evidence of infection if the pancytopenia is severe.
- Weakness, lethargy, and fatigue.
- Infections (resulting from impaired resistance caused by neutropenia) and easy bruising (caused by thrombocytopenia) also common.

ETIOLOGY

Neoplastic disease of the lymphoreticular system of unknown etiology. A heterozygous mutation in BRAF that results in a BRAF V6000E variant protein has been identified in all patients with hairy cell leukemia.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other forms of leukemia.
- Lymphoma.
- Viral syndrome.

WORKUP

Comprehensive history, physical examination, and laboratory evaluation to confirm the diagnosis. Table H1-1 describes major diagnostic features of hairy cell leukemia.

LABORATORY TESTS

- Pancytopenia involving erythrocytes, neutrophils, and platelets is common; anemia is usually present and varies from minimal to severe.
- Hairy cells (Fig. H1-2) can account for 5% to 80% of cells in the peripheral blood. The cytoplasmic projections on the cells are redundant plasma membranes.
- Leukemic cells stain positively for tartrate-resistant acid phosphatase stain.
- A bone marrow biopsy (Fig. EH1-3) is essential for confirmation and to quantify the degree of hairy cell infiltration. Bone marrow may result in a "dry tap" (because of increased marrow reticulin).

TREATMENT

NONPHARMACOLOGIC THERAPY

Approximately 8% to 10% of patients are asymptomatic and have minimal splenomegaly and minor cytopenia. They are usually detected on routine laboratory evaluation and do not require initial therapy. They should, however, be frequently monitored for progression of disease. Patients require treatment when they have significant cytopenias or occasionally recurrent infections from immunocompromise.

ACUTE GENERAL Rx

- Drugs of choice are the purine analogues 2-chloro-2 deoxyadenosine (cladribine) or 2-deoxycoformycin (DCF, pentostatin). They induce complete remissions in up to 85% of patients and partial responses in 5% to 25%.
- Cladribine may be preferred because it is easy to administer (0.14 mg/kg qd for 7 days), has minimal toxicity, and is able to induce complete durable responses with a single course of therapy.
- The anti-CD 22 recombinant immunotoxin BL 22 can induce complete remission in patients with hairy cell leukemia resistant to treatment with purine analogues.

CHRONIC Rx

- Patients should be monitored with periodic examination and laboratory tests for progression of disease.
- Approximately 40% of patients with HCL eventually relapse. Relapsed patients can be re-treated with purine analogues or the monoclonal CD20 antibody rituximab. If the prior response was <18 months in duration, rituximab may be preferred over retreatment with cladribine.

DISPOSITION

Prognosis has become increasingly favorable with the newer agents. Approximately 90% of patients who are treated have a complete or partial response.

REFERRAL

Hematology consultation is recommended in all patients.

TABLE H1-1 Major Diagnostic Features of Hairy Cell Leukemia

Study	Findings
Morphology of hairy cells	Oval or indented nuclei and abundant pale blue cytoplasm Absent or inconspicuous nucleoli Circumferential cell surface "ruffled" projections
Bone marrow biopsy morphology	Diffuse or interstitial bone marrow infiltration, without discrete nodular aggregates Clear cells with "fried egg" or spindled appearance Reticulin fibrosis
Flow cytometry	Clonal B cells expressing *CD103, CD25,* and *CD11c* and lacking *CD5* expression
Immunohistochemistry	Positive for DBA.44, TRAP, and ANXA1

From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.

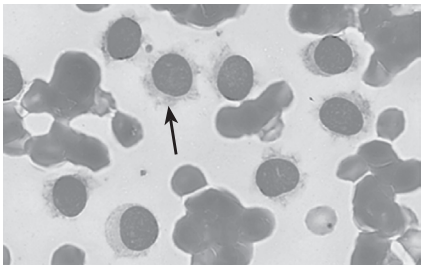


FIGURE H1-2 Hairy cell leukemia. Note the lymphocytes with hairlike cytoplasmic projections surrounding the nucleus. (From Rodak BF: *Diagnostic hematology,* Philadelphia, 1995, Saunders.)

PEARLS & CONSIDERATIONS

COMMENTS

The diagnosis of hairy cell leukemia is occasionally missed and subsequently made by the histopathologist after removal of the spleen for diagnostic purposes.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hairy Cell Leukemia (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Kreitman RJ et al.: Efficacy of the anti-CD 22 recombinant immunotoxin BL 22 in chemotherapy resistant hairy-cell leukemia, *N Engl J Med* 345:241, 2001.

Naik RR et al.: My treatment approach to hairy cell leukemia, *Mayo Clin Proc* 87(1):67–76, 2012.

Tiacci E et al.: BRAF mutations in hairy cell leukemia, *N Engl J Med* 364:2305–2315, 2011.

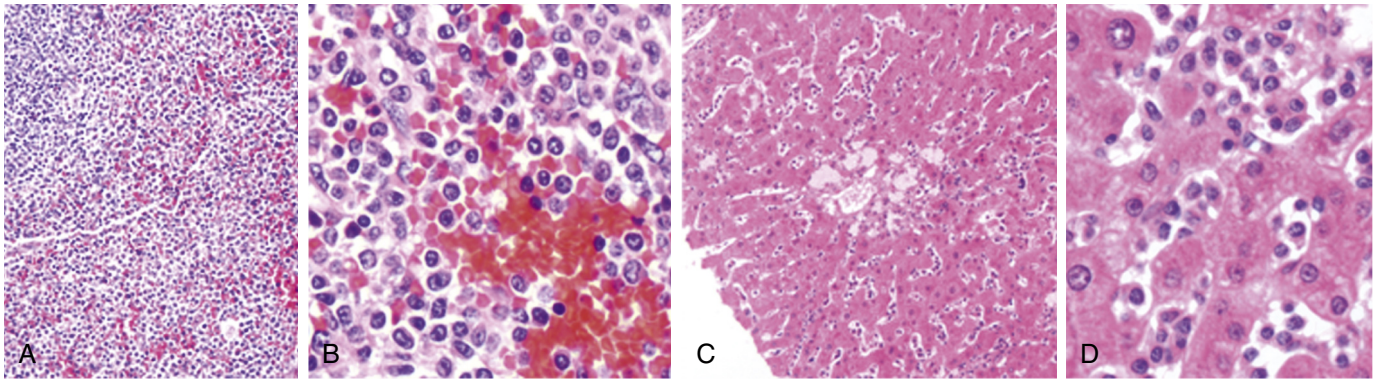


FIGURE EH1-1 Spleen and liver in hairy cell leukemia. The spleen **(A, B)** shows a massive and diffuse infiltrate in the red pulp and depletion of the white pulp. The infiltrate is associated with hemorrhage, which results in red blood cell "lakes" **(B)** (*lower right*). The liver **(C, D)** is frequently involved, and the pattern of infiltration is predominantly sinusoidal. (From Hoffman R et al: *Hematology: basic principles and practice*, ed 5, Philadelphia, 2009, Churchill Livingstone.)

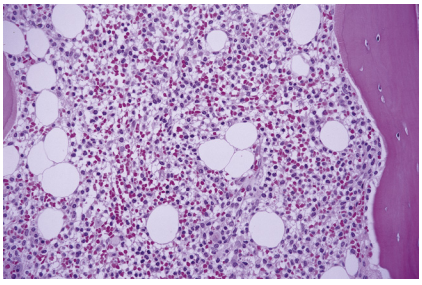


FIGURE EH1-3 Bone marrow trephine biopsy section from a patient with hairy cell leukemia. The bone marrow is hypercellular with a diffuse infiltration by hairy cells. The hairy cell nuclei are widely spaced, separated from each other by a pale, lightly eosinophilic cytoplasm. Many extravasated red blood cells are present between the hairy cells (hematoxylin and eosin stain, 630x). (From Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

BASIC INFORMATION

DEFINITION

Hand-foot-mouth disease (HFMD) is a viral illness characterized by superficial lesions of the oral mucosa and skin of the extremities. HFMD is primarily caused by coxsackie or enterovirus infection and is transmitted primarily by respiratory droplet contact in developed countries and fecal-oral contact in developing countries. Although children are predominantly affected, adults are also at risk. This disease is usually self-limited and benign, although outbreaks in the Asia Pacific region have been increasingly complicated by neurologic and cardiopulmonary sequelae.

SYNONYMS

Vesicular stomatitis with exanthema
Coxsackie virus infection
Enterovirus infection

ICD-9CM CODES
074.0 Hand-foot-mouth disease
ICD-10CM CODES
B08.4 Enteroviral vesicular stomatitis with exanthem

EPIDEMIOLOGY & DEMOGRAPHICS

- Children <5 yr are at the highest risk and have the most severe cases.
- HFMD most often affects children <10 yr.
- HFMD is contagious. Close contacts of affected children, including family members and health care workers, are the most commonly infected adults.
- Infection is spread from person to person by direct contact with saliva, respiratory secretions, fluid in vesicles, or stool.
- A person is most contagious during the first week of illness.
- Outbreaks tend to occur during the summer.
- Infection leads to immunity, but a second episode may occur after infection with a different agent.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms:
- After a 4- to 6-day incubation period, patients may report odynophagia, sore throat, malaise, and fever (38.3° to 40° C).
- 1 to 2 days later the characteristic oral lesions appear (small red spots that blister and may ulcerate).
- In 75% of cases skin lesions on the extremities accompany these oral manifestations (small flat or raised red bumps, sometimes with blisters).
- 11% of adults have cutaneous findings.
- Lesions appear over the course of 1 or 2 days.

Physical findings:
- Oral lesions, usually between five and ten, are commonly found on the tongue, buccal mucosa, gingivae, and hard palate.
- Oral lesions initially start as 1- to 3-mm erythematous macules and evolve into gray vesicles on an erythematous base.
- Vesicles are frequently broken by the time of presentation and appear as superficial gray ulcers with surrounding erythema.
- Skin lesions of the palms of the hands and soles of the feet start as linear erythematous papules (3 to 10 mm in diameter) that evolve into gray vesicles that may be mildly painful (Fig. H1-4). These vesicles are usually intact at presentation and remain so until they desquamate within 2 wk. Although rare, fingernail or toenail loss (nail separation from the nail matrix, otherwise known as onychomadesis) after HFMD (notably with the A6 strain of coxsackie virus) has been reported in children. The nail loss was temporary, and nails grew back without intervention.
- Involvement of the buttocks and perineum is present in 31% of cases.
- In rare cases, encephalitis, meningitis, myocarditis, poliomyelitis-like paralysis, and pulmonary edema may develop. Sporadic acute paralysis and long-term neurologic sequelae have been reported with enterovirus 71.
- Although information is limited, there is no clear evidence that pregnancy outcomes are affected.

ETIOLOGY

- Coxsackie virus group A, type 16, was the first and is the most common cause of HFMD.
- Enterovirus 71 is the second leading cause of HFMD. Enterovirus 71 is neurotropic and has a predilection for the brainstem, leading to more severe cases of the disease. Infection rates have been rising in the Asia Pacific region.
- Coxsackie viruses A5, A6, A7, A9, A10, B1, B2, B3, and B5 have also been implicated.
- Coxsackie A6 has been known to cause a severe skin rash and self-limited nail abnormalities (onychomadesis). Patients with this strain may lack oral lesions.
- Epidemic outbreaks have been reported with coxsackie A16 and enterovirus 71.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Aphthous stomatitis.
- Herpes simplex infection.
- Herpangina.
- Behçet's disease.
- Erythema multiforme.
- Pemphigus.
- Gonorrhea.
- Acute leukemia.
- Lymphoma.
- Allergic contact dermatitis.

WORKUP

The diagnosis is usually made on the basis of history and characteristic physical examination.

LABORATORY TESTS

- Not indicated unless the diagnosis is in doubt.
- Throat culture or stool specimen may be obtained for viral testing but may take from 2 to 4 wk for results.

TREATMENT

ACUTE GENERAL Rx

- Symptomatic therapy is given for this usually self-limited disease.
- There are currently no available approved therapies for more severe cases. Antivirals, steroids, and IV immunoglobulin have been tried for enterovirus 71 infections, but these treatments have not been evaluated in randomized, placebo-controlled studies.

DISPOSITION

Prognosis is excellent except in rare cases of central nervous system or cardiac involvement. Most are managed as outpatients.

REFERRAL

Not usually needed.

PEARLS & CONSIDERATIONS

- Frequent handwashing, disinfection of contaminated surfaces, and washing of soiled articles of clothing can help reduce transmission.
- HFMD has no relation to hoof and mouth disease in cattle.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hand, Foot, and Mouth Disease (Patient Information)

AUTHORS: **ERICA HARDY, M.D., M.M.S.,** and **JENNIFER JEREMIAH, M.D.**

FIGURE H1-4 Hand-foot-mouth disease. Note oval lesions on an erythematous base. (From Goldstein B [ed]: *Practical dermatology,* ed 2, St Louis, 1997, Mosby.)

SUGGESTED READINGS

Centers for Disease Control and Prevention: Notes from the field: severe hand, foot, and mouth disease associated with coxsackievirus a6 – Alabama, Connecticut, California, and Nevada, November 2011-February 2012, *MMWR* 61:213–214, 2012.

Chang LY et al.: Clinical features and risk of pulmonary edema after enterovirus-related hand, foot, and mouth disease, *Lancet* 354(9191):1682, 1999.

Chang LY et al.: Transmission and clinical features of enterovirus 71 infections in household contacts in Taiwan, *JAMA* 291(2):222, 2004.

Chang LY et al.: Neurodevelopment and cognition in children after enterovirus 71 infection, *N Engl J Med* 356:1226–1234, 2007.

Repass GL et al.: Hand, foot and mouth disease: identifying and managing an acute viral syndrome, *Cleveland Clin J Med* 81(9):537–543, 2014.

Ta-Chung L et al.: Diseases caused by enterovirus 71 infection, *Pediatr Infect Dis J* 28(10):904–910, 2009.

Weir E: Foot-and-mouth disease in animals and humans, *Can Med Assoc J* 164(9):1338, 2001.

BASIC INFORMATION

DEFINITION

Hantavirus pulmonary syndrome (HPS) is a severe infectious cardiopulmonary illness usually caused by the Sin Nombre virus (SNV), whose main vector is the deer mouse.

SYNONYMS

Four Corners disease
Hantavirus cardiopulmonary syndrome (HCPS)

ICD-9CM CODES
079.81 Hantavirus
ICD-10CM CODES
B33.4 Hantavirus (cardio)-pulmonary syndrome (HPS) (HCPS)

EPIDEMIOLOGY & DEMOGRAPHICS

- First identified in the United States in 1993, hantavirus has been found throughout the Americas, with most U.S. cases occurring in the Western half of the United States.
- The number of HPS cases reported in the United States through December 31, 2012, was 616. Of these, 585 cases occurred from 1993 onward, following the initial identification of HPS, whereas 31 cases were retrospectively identified. Thirty-six percent of all reported cases have resulted in death.
- The peak incidence to date was in June and July 1993 in the Four Corners region of the United States.
- HPS is more common in the spring and summer.
- HPS is more prevalent among males, most likely because of increased environmental exposure.
- Mean age is 37 yr (range 8 to 83). Not been found at the extremes of age.
- Risk factors include exposure to rodent populations, rural locales, occupations with increased exposure to rodents, and entering infrequently opened structures.

CLINICAL PRESENTATION

- The most common symptoms are fever, headache, nausea, vomiting, cough, shortness of breath, and myalgia. It is not associated with rhinorrhea or nasal congestion.
- The most common signs on physical examination include fever, hypoxemia, and tachypnea. Rash, mucosal bleeding, or peripheral edema is not found with HPS.
- There are two phases of HPS, the prodromal phase and the cardiopulmonary phase, each of which lasts 2 to 7+ days. The prodromal phase is characterized by:
  1. Fever, chills, headache, and myalgias, especially in the legs and back.
  2. Cough, nausea, vomiting, diarrhea, abdominal pain, and general malaise.
  3. Tachypnea, tachycardia, hypoxemia.
- The cardiopulmonary phase has the following characteristics:
  1. Dry cough and dyspnea.
  2. Acute pulmonary edema.
  3. Hypotension.
  4. Decreased cardiac output.
  5. Coagulopathy.

ETIOLOGY

- HPS is most often caused by SNV.
- The main vector is the deer mouse.
- It is transmitted by inhalation of aerosolized feces, urine, or saliva from infected rodents.
- No cases of person-to-person transmission have been reported in the United States.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute respiratory distress syndrome.
- Pneumonia especially atypicals.
- Congestive heart failure.
- Pulmonary edema.
- Acute bacterial endocarditis.
- Gastroenteritis, appendicitis, or cholelithiasis.
- Plague.
- Tularemia (“rabbit fever”).
- Histoplasmosis.
- Coccidioidomycosis.
- Cardiogenic shock.
- HIV/AIDS.
- Myocardial infarction.
- Goodpasture’s syndrome or Granulomatosis with polyangiitis (Wegener).
- Other viral hemorrhagic fevers (see Table EH1-2)

WORKUP

- Diagnosis is made on the basis of clinical criteria (fever, hypoxemia, and bilateral interstitial edema) or autopsy evidence of idiopathic noncardiogenic pulmonary edema, as well as confirmatory laboratory testing.
- Laboratory testing: rapid strip immunoblot assay (RIBA), Western blot, or ELISA, to detect IgM antibodies to SNV or other hantaviruses.
- Complete blood count q8h initially.

TABLE EH1-2 Pathobiologic and Clinical Aspects of Viral Hemorrhagic Fevers

Disease	Incubation Period (days)	Onset	Bleeding	Rash	Jaundice	Heart	Lung	Kidney	CNS	Eye
Filoviridae										
Ebola HF	3-21	Abrupt	++	+++	+	++?	+	+	+	+
Marburg HF	3-21	Abrupt	++	+++	+	++?	+	+	+	+
Arenaviridae										
Lassa fever and Lujo HF[1]	5-16	Gradual	+	++	0	++	+	0	+	0
South American HFs[1]	7-14	Gradual	+++	0	0	++	+	0	+++	0
Bunyaviridae										
HF with renal syndrome	9-35	Abrupt	+++	0	0	++	+	+++	+	0
Hantavirus pulmonary syndrome	7-35	Gradual	0 (except for Andes virus infection)	0	0	+++	+++	+	+	0
Rift Valley fever[2]	2-5	Abrupt	+++	+	++	+?	0	+	++	++
Crimean-Congo HF	3-12	Abrupt	+++	0	++	+?	+	0	+	0
Flaviviridae										
Yellow fever	3-6	Abrupt	+++	0	+++	++	+	++	++	0
Dengue HF	3-15	Abrupt	++	+++	+	++	+	0	+	0
Kyasanur Forest disease	3-8	Abrupt	++	0	0	+	++	0	+++	+
Omsk HF	3-8	Abrupt	++	0	0	+	++	0	+++	+

[1]Data are insufficient to distinguish between the syndromes produced by the various Old and New World arenaviruses.
[2]Hemorrhagic fever, encephalitis, and retinitis may be seen in Rift Valley fever independently of each other.
CNS, Central nervous system; *HF,* hemorrhagic fever; *0,* sign not typically noted/organ not typically affected; +, sign occasionally noted/organ occasionally affected; ++, sign commonly noted/organ commonly affected; +++, sign characteristic/organ involvement severe.

1. All patients manifest thrombocytopenia, and its progression is the most consistent indicator heralding the cardiopulmonary phase of HPS.
2. Differential usually reveals a left shift with atypical, enlarged lymphocytes. White blood cell counts are an unreliable indicator of severity of infection.

- Lactate level >4 mg/dl is associated with a high mortality rate.
- Rapid immunoblot strip assay for SNV antibodies.
- Diagnosis is confirmed by identification of immunoglobulin M and G antibodies to SNV.

IMAGING STUDIES

Chest radiograph: Bilateral diffuse interstitial edema.

Rx TREATMENT

There is no known specific treatment or therapy, only supportive therapy.

NONPHARMACOLOGIC THERAPY

- Intensive care unit admission in tertiary care center.
- Mechanical ventilation with high pulmonary end-expiratory pressure and high Fio_2.
- Pulmonary artery catheterization.
- Extracorporeal membrane oxygenation (ECMO).

ACUTE GENERAL Rx

- Supportive measures.
- Supplemental oxygen.
- Intubation when indicated.
- Hemodynamic monitoring.
- Cautious fluid resuscitation due to potential capillary leak syndrome.
- Early use of vasopressors.
- Initial broad-spectrum antibiotics.
- No definitive antiviral therapy for SNV.

DISPOSITION

- Patients who survive cardiopulmonary phase of HPS have rapid clinical improvement.
- There are no serious sequelae.

REFERRAL

University of New Mexico Hospital is one of the few facilities with experience in ECMO for treatment of HPS. This modality is only for hemodynamically unstable, critically ill patients who do not respond to conventional therapies.

BOX EH1-1 Centers for Disease Control and Prevention Recommendations for Preventing Hantavirus Pulmonary Syndrome

1. Eliminate rodent harborage.
   - Keep cooking, eating, and food storage areas clean.
   - Cover human food and animal feed.
   - Contain and elevate garbage.
   - Seal holes and cracks in dwellings to prevent entrance by rodents.
   - Clear brush and trash from around homes and outbuildings.
2. Control rodent populations by maintaining snap traps and using rodenticides; in areas where plague occurs, control fleas with insecticides.
3. Safely clean up rodent-infested areas.
   - Air out infested spaces before cleanup.
   - Spray areas of infestation and all excreta, nesting, and other materials with household disinfectant or 10% bleach solution. Then, clean up, seal in bags, and dispose.
   - Avoid sweeping, vacuuming, or stirring dust until the area is thoroughly wet with disinfectant.
   - Wear rubber gloves; disinfect gloves before removal, and wash hands afterward.
   - In areas where plague occurs, spray insecticide on trapped rodents and nesting materials to prevent fleas from abandoning rodents to find new hosts.
4. Avoid rodents when outdoors.
   - Do not disturb rodent droppings or camp or sleep near burrows or areas where trash is present.
   - Avoid feeding or handling rodents, even if they appear friendly.

From Auerbach P: *Wilderness medicine, Expert Consult premium edition—enhanced online features and print,* Philadelphia, 2012, Saunders.

PEARLS & CONSIDERATIONS

COMMENTS

- Although rare, HPS should be a consideration in those with acute respiratory illness and a history suggestive of HPS exposure. The combination of thrombocytopenia, left shift, circulating immunoblasts, and hemoconcentration is rare in other viral illnesses.
- Testing for hantavirus should always be considered in cases of thrombocytopenia and fever of unknown origin, especially in areas endemic for the infection.

PREVENTION

Rodent control is the primary way to prevent Hantavirus infection. Box EH1-1 describes CDC recommendations for preventing hantavirus pulmonary syndrome.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **CATHERINE SHAFTS, D.O.** and **ALEEMA PATEL, M.D.**

SUGGESTED READINGS

Centers for Disease Control and Prevention: Reported cases of HPS: HPS in the United States. Available at www.cdc.gov/hantavirus/surveillance/index.html Accessed March 14, 2013.

Denecke B et al.: Hantavirus infection: a neglected diagnosis in thrombocytopenia and fever? *Mayo Clin Proc* 85(11):1016–1020, 2010.

Graziano KL et al.: Hantavirus pulmonary syndrome: a zebra worth knowing, *Am Fam Physician* 66(6):1015–1020, 2002.

Mertz GJ et al.: Diagnosis and treatment of new world hantavirus infections, *Curr Opin Infect Dis* 19(5):437–442, 2006.

Mills JN et al.: Hantavirus pulmonary syndrome—United States: updated recommendations for risk reduction, *MMWR Morb Mortal Wkly Rep* 51(RR09):1–12, 2002.

National Center for Infectious Diseases: Special Pathogens Branch. All about hantaviruses. Available at http://www.cdc.gov/ncidod/diseases/hanta/hps/index.htm Accessed November 2009.

Rhee DK et al.: Breathtaking journey, *N Engl J Med* 367:452–457, 2012.

BASIC INFORMATION

DEFINITION

Health care-associated infections (HAIs) are infections associated with health care, generally occurring more than 2 calendar days after admission to a hospital. Classification criteria are established by the Centers for Disease Control and Prevention's (CDC) National Healthcare Safety Network (NHSN).

SYNONYMS

Nosocomial infections

ICD-9CM CODES	
008.45	*Clostridium difficile*
041.12	MRSA
482.42	MRSA pneumonia
038.12	MRSA septicemia
998.59	Other postoperative infection
999.31	Bloodstream infection due to central venous catheter
997.31	Ventilator-assisted pneumonia
996.31	Due to urethral [indwelling] catheter
ICD-10CM CODES	
A04.7	Enterocolitis due to *Clostridium difficile*
B95.62	Methicillin-resistant *Staphylococcus aureus* infection as the cause of diseases classified elsewhere
J15.212	Pneumonia due to methicillin-resistant *Staphylococcus aureus*
A41.02	Sepsis due to methicillin-resistant *Staphylococcus aureus*
K68.11	Postprocedural retroperitoneal abscess
T80.219A	Unspecified infection due to central venous catheter, initial encounter
J95.851	Ventilator-associated pneumonia
T83.098A	Other mechanical complication of other indwelling urethral catheter, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.)

- Develop in at least 4% of hospitalized patients; over 1.7 million patients previously estimated.
- In 2011, HAIs accounted for more than 75,000 deaths.
- HAIs in the United States cost between $28 and $33 billion annually.
- At least one third of hospital-acquired infections are preventable.
- Leads to increased morbidity and mortality.

PREVALENCE (IN U.S.): Estimated 648,000 patients with at least one HAI/yr in 2011.

PREDOMINANT SEX:

- Overall, approximately equal.
- Elderly women: predominantly nosocomial urinary tract infections.

PREDOMINANT AGE: Newborns and elderly patients (>60 yr) at highest risk.

PEAK INCIDENCE: Varies widely with infection site.

RISK FACTORS: Patients with the following conditions can develop HAIs at any age:

- In ICU.
- Intubation.
- Chronic lung disease.
- Renal disease.
- Comatose.
- Chronic urethral or vascular catheterization.
- Malnutrition.
- Postoperative state.
- Diabetic.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Vary with specific HAIs.

ETIOLOGY

- Bacteria (gram-negative bacteria are responsible for >30% of HAIs).
- Fungi.
- Viruses.

SOURCES AND MODES OF TRANSMISSION:

- Patient's own flora.
  1. Comprises resistant organisms associated with hospitalization.
  2. Frequently maintained thereafter by persistent GI colonization.
- Unwashed hands of staff.
  1. Physicians.
  2. Nurses.
- Invasion of protective defenses (intact skin, respiratory cilia, urinary sphincters, and mucosa).
  1. IV lines/central lines.
  2. Catheters.
  3. Respiratory equipment.
  4. Surgical wounds.
  5. Scopes and other imaging devices.
- Failure to provide adequate negative pressure, high-volume air flow chambers for airborne infection isolation of patients with TB or disseminated herpes zoster/chickenpox.
- Failure to rapidly identify and provide appropriate care (with isolation or precautions) for patients with communicable diseases.
- Food.
- Fomites.
- Personnel attire can become contaminated. Although studies have not yet verified the link between attire contamination and disease transmission, cross-contamination of previously washed hands can occur.
- Inattention to safe injection practices has led to outbreaks of hepatitis and fungal meningitis.
  1. Do not administer medications from a syringe to multiple patients even if the needle is changed.
  2. Use fluid infusion and administration sets (e.g., IV bags/bottles, tubing, connectors) for one patient only and dispose after each use. Do not use bags or bottles as a common source of supply for multiple patients.
  3. Use single-dose vials for parenteral medications whenever possible and do not administer medications from single-dose vials to multiple patients or combine leftover contents for later use.
  4. Single-dose, single-use vials do not have preservative and should be used for a single patient and a single-case/procedure/injection.
  5. When a single dose or single vial is accessed or opened, discard as per manufacturer or at the end of the case or procedure (whichever comes first).
  6. Insulin pens should be used for one single designated person only, even if the needle is changed.

RISKS AMPLIFIED:

- Use of broad-spectrum antibiotics.
  1. Select highly resistant bacteria.
  2. Establish multidrug-resistant bacteria as endemic flora in microenvironments within the hospital.
  3. Consider antibiotic stewardship programs to reduce these risks.
- Highly vulnerable patients with specific risk factors.
  1. Immunosuppression (as a result of therapy, transplantation, AIDS).
  2. Old age.
  3. Postsurgery.
  4. Prolonged surgery.
  5. Chronic lung disease.
  6. Ventilator dependence.
  7. Antacid therapy.
  8. Vascular lines.
  9. Hyperalimentation.
  10. ICU stay.
  11. Recent antibiotic therapy.
- Clustering of seriously ill patients.
  1. Often with wounds or contaminated drainage.
  2. Intensifying probability of cross-infection.

PREVENTION STRATEGIES: Handwashing/hand hygiene between all patient contacts is the single most important method of decreasing HAI:

- Regular soap and water for at least 15 sec.
- Chlorhexidine (particularly good for gram-positive organisms like methicillin-resistant *Staphylococcus aureus* [MRSA]), alcohol handrub or other antiseptic for resistant organisms.
- Purpose of soap and water handwash:
  1. Degrease hand surfaces.
  2. Flush away oils and associated bacteria, removal of visible dirt or body fluids.
- Procedure
  1. Lukewarm water.
  2. Must include all surfaces.
  3. Special attention to areas between fingers and to the dirtier dominant hand (most people reflexively wash the cleaner, nondominant hand more vigorously).
- Alcohol handrubs.
  1. Improve handwashing frequency (less drying to hands, faster, and no need for wash basin and towels for drying).
  2. Significantly reduce HAIs.
  3. Now recommended in essentially all routine health care settings.
  4. Rub hands until dry, approximately 15 sec.
- Environmental cleaning
  1. New supplemental technologies such as hydrogen peroxide vapor or mist or ultraviolet irradiation appear to reduce environmental contamination from *C. difficile*

spores, *Norovirus*, and resistant microorganisms.
2. Clinical equipment should be properly disinfected or sterilized per manufacturer's instructions.
3. High-touch items in patient environment should undergo frequent, thorough disinfection.

METHICILLIN-RESISTANT *STAPHYLOCOCCUS AUREUS* (MRSA)

- Invasive HAIs caused by MRSA decreased 9.4% per year from 2005 through 2008 in the United States.
- Health care-associated MRSA strains are typically resistant to many antibiotics, remaining susceptible to vancomycin and trimethoprim/sulfamethoxazole.
- High-risk factors include dialysis, recent stay in acute or long-term care facilities.
- Control measures include hand hygiene, disinfection of equipment, protective attire for isolation, and standard precautions.
- Community-acquired MRSA (CA-MRSA) is associated with soft tissue, presenting as boils, rash, or so-called spider bite, and typically occurs in patients who have no recent health care or hospital interaction.
- CA-MRSA often not found in nares.
- CA-MRSA can be sensitive to fluoroquinolones, clindamycin, and/or erythromycin in addition to vancomycin and trimethoprim/sulfamethoxazole.

Refer to Methicillin-Resistant Staphylococcus aureus *(MRSA) topic for more information.*

VANCOMYCIN-RESISTANT *ENTEROCOCCUS FAECIUM* (VREF)

- The percentage of HAIs caused by VREF increased more than twentyfold between 1989 and 1993, rising from 0% to 9%. By 2005, VREF, vancomycin-resistant *E. faecalis,* and other vancomycin-resistant species of enterococci had become common and endemic nosocomial pathogens accounting for 15% to 40% of all enterococci isolated in the hospital setting.
- A high percentage of VREF isolated, 80%, are also ampicillin resistant.
- Factors predisposing to VREF colonization or infection include a high percentage of hospital days receiving antibiotic therapy, use of IV, underlying disease, immunosuppression, and abdominal surgery.
- Evidence suggests that the vehicle is the hands of health care workers (HCWs).
- Control measures:
  1. Aggressive isolation of colonized or infected patients.
  2. Restraint in using broad-spectrum antibiotics.
  3. Compliance with hand hygiene best practices.

Refer to the topic "Vancomycin-Resistant Enterococcus" for more information.

CLOSTRIDIUM DIFFICILE

- Causes diarrhea as a result of pseudomembranous colitis.
- Accounts for 15% to 25% of health care-associated diarrhea. Recent survey found *C. difficile* was the third most common HAI and accounted for 70% of gastrointestinal HAIs.
- Warrants contact precautions and disinfection against spores, for example, bleach, supplemental technology (silver, hydrogen peroxide vapor or mist, ultraviolet light).
- Alcohol-based handrub may not eliminate spores of this organism: can use soap and water to wash hands at sink.
- Spores can be dispersed in the air or room environment surrounding patients.
- Treatment is tiered based on severity.
- Rising incidence of *C. difficile* infection with emerging strains that have up to twenty-threefold more toxin production.
- Toxin assays vary widely in ability to detect toxin.
- Only unformed stool specimens should be submitted for laboratory *C. difficile* testing.
- Polymerase chain reaction (PCR) and nucleic acid amplification test/loop mediated isothermal DNA amplification (NAAT/LAMP) are more sensitive test methods than enzyme immunoassay (EIA).
- Antibiotics can predispose persons by altering their normal gut flora.
- Can present in healthy patients with no known risk factors.
- Sometimes causes toxic megacolon or fulminant colitis.

NOROVIRUS

- Patients present with sudden onset of nausea, vomiting, and/or diarrhea.
- Now considered year-round rather than seasonal.
- Disinfection with bleach.
- Often need to isolate exposed persons for average incubation period, such as 3 days, to prevent outbreak.

SURVEILLANCE

- Crucial for early identification of infections. Enables:
  1. Immediate intervention.
  2. Education.
- Prospective, concurrent, hospital surveillance:
  1. Electronic data mining provides accurate review.
  2. Feasible with sophisticated computerized data collection and analysis.
- Targeted surveillance addresses high-risk procedures and patient populations.
- Routine rate calculations and statistical analyses:
  1. Use device-specific days, procedure-specific cases, or patient-days as denominators.
  2. Enhance early recognition of microclusters of infections by body site and by organism.
  3. Facilitate proper early control of potential outbreaks.
- Active surveillance/screening cultures for multi-drug resistant organisms (MDROs); for example, high-risk populations for MRSA.

Dx DIAGNOSIS

MOST COMMON HAI

- Device-associated infections (26%) (central-line associated bloodstream infections, catheter-associated urinary tract infections, and ventilator-associated pneumonias).
- Surgical site and other soft tissue infections (22%).
- Pneumonia (22%).
- Gastrointestinal infections (17%).

HEALTH CARE-ASSOCIATED UTIS:

- General associations:
  1. Indwelling urinary (e.g., Foley) catheters.
  2. Inappropriate catheter care (including opening catheter junctions).
  3. Female sex.
  4. Absence of systemic antibiotics.
- Physical findings:
  1. Fever.
  2. Dysuria.
  3. Leukocytosis.
  4. Pyuria.
  5. Flank or costovertebral angle tenderness.
- Usual organisms:
  1. *E. coli.*
  2. *Candida.*
  3. *Enterococcus.*
  4. *Pseudomonas.*
  5. *Klebsiella.*
  6. *Enterobacter.*
- Sepsis in 1% to 3% of hospital-associated UTIs
- Prevention bundle to eliminate catheter-associated UTIs (CAUTIs):
  1. Use meticulous aseptic technique during insertion and daily perineal care.
  2. Avoid unnecessary urinary catheters; remove promptly.
  3. Never open the catheter-collection tubing junction (keep system closed).
  4. Obtain all specimens using sterile syringe.
  5. Secure the Foley.
  6. Remove Foley catheters as soon as possible.
  7. Substitute intermittent catheterization for Foley catheters.

HEALTH CARE-ASSOCIATED BLOODSTREAM INFECTIONS:

- General associations:
  1. IV lines.
  2. Arterial lines.
  3. Central venous pressure (CVP) lines: lead to catheter-associated bloodstream infection (CLABSI).
  4. Phlebitis.
  5. Hyperalimentation.
  6. Lack of safe injection best practices.
- Fever possibly only presenting sign.
- Exit site of all vascular lines carefully evaluated for:
  1. Erythema.
  2. Induration.
  3. Tenderness.
  4. Purulent drainage.
- Usual organisms for device-associated bacteremia.
  1. *S. aureus* (including MRSA).
  2. *Staphylococcus epidermidis* for long-term IV lines.
  3. *Enterobacter.*
  4. *Klebsiella.*
  5. *Candida* spp.
  6. *Pseudomonas aeruginosa* may come from a water source or reflect cutaneous bacteria.
- Phlebitis in 1.3 million patients yearly.
- Approximately 10,000 annual deaths from IV sepsis.

- Prevention bundle to eliminate central line-associated bloodstream infections (CLABSIs):
  1. Meticulous sterile technique during central catheter line insertion.
  2. Emphasis should be placed on attention to detail, including handwashing, adherence to guidelines for catheter insertion and maintenance, appropriate use of antiseptic solutions such as chlorhexidine (CHG) to prepare the skin before central line insertion.
  3. Modified catheter, for example, antiseptic-coated line, may reduce risk for endoluminal colonization and catheter-related sepsis in subclavian lines.
  4. Decrease use of routine IVs and encourage PO intake.
  5. Avoid using a femoral vein insertion site. Subclavian central line site is associated with lower infection rate than jugular.
  6. Bundle to prevent CLABSIs includes hand hygiene, CHG skin prep for insertion of central lines, full barrier protection for insertion of central lines, removal of unnecessary lines, insertion checklist.
  7. Consider daily CHG baths in ICUs.

HEALTH CARE-ASSOCIATED PNEUMONIAS:

- More common in ICUs.
- General associations:
  1. Aspiration.
  2. Intubation: leads to ventilator-associated events (VAE) or ventilator-associated pneumonia (VAP).
  3. Altered consciousness.
  4. Old age.
  5. Chronic lung disease.
  6. Postsurgery.
  7. Antacids.
  8. Head of bed not elevated.
- Signs of pneumonia common among patients on general wards:
  1. Cough.
  2. Sputum.
  3. Fever.
  4. Leukocytosis.
  5. New infiltrate on chest x-ray examination.
- Signs more subtle in ICUs, because many patients have purulent sputum because of chronic intubation.
  1. Change in sputum character or volume.
  2. Small changes on chest x-ray examination.
- Usual organisms:
  1. *S. aureus* (including MRSA).
  2. *Pseudomonas aeruginosa.*
  3. *Enterobacter.*
  4. *Acinetobacter.*
  5. *Klebsiella.*
- Less common organisms:
  1. *Stenotrophomonas* spp.
  2. *Legionella, Flavobacterium.*
  3. Respiratory syncytial virus (infants).
  4. Adenovirus.
- 1% of hospitalized patients affected.
- Mortality rate high (40%).
- Prevention bundle:
  1. Use meticulous sterile technique during suctioning and handling airway.
  2. Do not routinely change ventilator breathing circuits and components. For heat and moisture exchangers, no more frequently than every 48 hr.
  3. Drain respirator tubing without allowing fluid to return to respirator.
  4. Wash hands routinely to prevent colonization of patients and transfer of organisms among patients.
  5. Use of a bundle to prevent VAEs and VAPs to include: elevate the head of bed, provide deep vein thrombosis (DVT) prophylaxis, provide peptic ulcer disease (PUD) prophylaxis, hold sedation, test for ability to extubate, control glucose, gastric decontamination.
  6. Consider oral mouth care with CHG for vented patients in ICUs.

SURGICAL AND HEALTH CARE-ASSOCIATED SOFT TISSUE INFECTIONS:

- Associations:
  1. Decubitus ulcers.
  2. Surgical site risks: contaminated or dirty/infected, the American Society of Anesthesiologists' (ASA) physical status classification of ASA 3 or 4, duration of surgery over national average, usually 3 hr.
  3. Abdominal surgery.
  4. Presence of drain.
  5. Preoperative length of stay.
  6. Surgeon.
  7. Presence of other infection.
- Physical findings:
  1. Decubitus ulcer with fluctuance at margin or under firm eschar.
  2. Erythema extending >2 cm beyond margin of surgical wound.
  3. Tenderness.
  4. Induration.
  5. Erythema.
  6. Fluctuance.
  7. Purulent drainage.
  8. Dehiscence of sutures.
- Usual organisms:
  1. *S. aureus* (including MRSA).
  2. *Enterococcus.*
  3. *Enterobacter.*
  4. *Acinetobacter.*
  5. *E. coli.*
- Prevention:
  1. Use careful skin care and frequent, proper positioning of patient to prevent decubitus ulcer.
  2. Use meticulous sterile surgical technique.
  3. Use properly washed and sterilized instruments, processed in accordance with manufacturer's instructions. Minimize immediate-use steam sterilization (formerly known as flash sterilization).
  4. Wash hands to decrease colonization when handling postoperative wound.
  5. Limit prophylactic antibiotics to 24 hr perioperatively.
  6. Double-wrap contaminated dressings (hold in gloved hand and evert gloves over dressings) before disposal.
  7. Surgical Care Improvement Project (SCIP) bundle to include antibiotic prophylaxis selection, receipt of antibiotic within 1 hr before surgery, discontinuation of antibiotic within 24 hr of surgery end time, cardiac surgery patients with controlled 6 AM postoperative blood glucose, clip rather than shave prep, postoperative normothermia for colorectal surgery patients, removal of Foley catheter by end of postoperative day 2 (except for urologic, gynecologic, or perineal procedures, or on paralytics, vasopressors/inotropics during ICU stay).
  8. Preadmission nares MRSA screening often beneficial for open heart and orthopedic implants when time is allowed for decolonization, chlorhexidine showers, and appropriate antibiotic prophylaxis selection.

LABORATORY TESTS

- Appropriate to specific HAI and specific patient's condition.
- Cultures generally indicated for proper confirmation of responsible pathogens:
  1. Urine.
  2. Blood.
  3. Sputum.
  4. Soft tissue.
- Molecular analysis of health care-associated epidemics:
  1. Plasmid fingerprinting.
  2. Restriction endonuclease digestion (plasmid and genomic DNA).
  3. Peptide analysis.
  4. Immunoblotting.
  5. Ribosomal RNA (rRNA) typing.
  6. DNA probes.
  7. Multilocus enzyme electrophoresis.
  8. Restriction fragment length polymorphism (RFLP).
  9. PCR.
  10. Provide confirmation of point-source or common strains and corroboration of hypotheses reached utilizing classic epidemiology.

IMAGING STUDIES

Rarely needed for diagnosis of HAI; helpful for deep surgical site infection.

Rx TREATMENT

ACUTE GENERAL Rx

- Appropriate to etiologic organism:
  1. Antibiotic.
  2. Antifungal.
  3. Antiviral.
- Specific therapy determined after careful consideration of resident flora within the microenvironment in which the patient was hospitalized.
  1. Empiric therapy.
  2. Frequently difficult to fashion accurately.
  3. Often undesirable, unless the patient's clinical condition requires urgent treatment.
- Consultation for expert advice regarding antibiotic selection in view of known epidemiologic risks within the hospital. (Hospital Epidemiologist or Infectious Disease Specialist).
- Avoid unnecessary treatment for organisms that are colonizing (no signs or symptoms of infection), but not infecting patients.

- Prevention of spread of communicable diseases.
  1. Isolation or precautions (airborne, droplet, contact isolation precautions, and combinations thereof).
  2. Classic schema (strict, respiratory isolation and contact [skin and wound] precautions) have been replaced by more streamlined revised guidelines (airborne, droplet, contact isolation precautions, and combinations thereof).
  3. Less careful response to some diseases (e.g., hemorrhagic fevers) inadvertently induced by removal of strict isolation category.
  4. Universal/standard precautions to protect HCWs against splash or splatter of blood or body fluids.
  5. Tracking roommates of patients with communicable disease, such as Norovirus or influenza and using precautions during the incubation period.
- Universal/standard precautions used for all patients during all anticipated contacts with blood, body fluids, or secretions.
  1. Gloves.
  2. Goggles/eye shield.
  3. Gowns that prevent blood or potentially infectious materials from passing through.
- Consider aggressive isolation to restrict spread of multidrug-resistant organisms and their plasmids.
  1. MRSA.
  2. VREF.
  3. MDR-GNRs (multidrug-resistant gram-negative rods) can include extended-spectrum β-lactamases (ESBL), carbapenem-resistant Enterobacteriaceae (CRE), some *Acinetobacter baumanni.* New microbiology interpretive criteria (breakpoints) can result in no longer reporting mechanism of resistance.
  4. New Delhi metallo-β-lactamase 1 (NDM-1): these are gram-negative Enterobacteriaceae with a new type of carbapenem-resistance gene.

Refer to the topic "Multidrug-Resistant Gram-Negative Rods (MDR-GNRs)" for more information.

DISPOSITION

The Infection Prevention and Control Service and/or Hospital Epidemiologist should be notified when infectious complications occur in the hospital setting; most, but not all, HAIs are potentially avoidable, and every effort should be taken to minimize the risk of infections associated with health care. Nationwide success in achieving and sustaining zero CLABSIs, zero CAUTIs, and zero VAPs warrant widespread use of infection prevention bundles to target zero HAIs.

REFERRAL

- To infection preventionist.
- To hospital epidemiologist.

PEARLS & CONSIDERATIONS

COMMENTS

- Sharp and splash injuries to staff are relatively rare, but nearly all are preventable.
  1. Nurses incur most injuries.
  2. Usual causes:
     1. Needle sticks.
     2. Scalpel and surgical needle injuries
     3. Blood splashes
  3. Prevention:
     1. Never recap needles.
     2. Dispose of needles only in rigid, impermeable plastic containers.
     3. Clearly announce instrument passes in the operating room and during procedures. Use passing trays.
     4. Use needleless systems for vascular access and neutral displacement central line connectors.
     5. Use gloves, mask, and goggles/eye shield if aerosol or splash is likely.
     6. Never leave needles or other sharp items in beds.
     7. Never dispose of sharp items in regular trash bags.
  4. Infection Prevention and Control or Employee Health staff should be consulted immediately after exposure to determine need for prophylaxis for hepatitis B or HIV.
  5. All clinical staff should be immune to hepatitis B (natural or vaccine).
- Fungi previously considered to be contaminants are now risks for patients with cancer and organ transplantation.
  1. *Candida* spp.
     1. *C. guilliermondii.*
     2. *C. krusei.*
     3. *C. parapsilosis.*
     4. *C. tropicalis.*
  2. *Aspergillus* spp.
  3. *Curvularia* spp.
  4. *Bipolaris* spp.
  5. *Exserohilum* spp.
  6. *Alternaria* spp.
  7. *Fusarium* spp.
  8. *Scopulariopsis* spp.
  9. *Pseudallescheria boydii.*
  10. *Trichosporon beigelii.*
  11. *Malassezia furfur.*
  12. *Hansenula* spp.
  13. *Microsporum canis.*
- Focused, committed efforts by the entire health care staff continuously directed toward prevention:
  1. Each HAI addressed as an opportunity to improve the delivery of safe patient care using always best practices.
  2. Essential for individual staff members to understand that small risks applied to large populations result in a large number of total events (i.e., HAIs).
- Antibiotic stewardship.
  1. Choose appropriate antibiotic.
  2. Minimize vancomycin usage.
  3. Consider procalcitonin to guide antibiotic usage for sepsis.

The Centers for Medicare & Medicaid Services denies inpatient payments for certain HAIs. Total reimbursement is linked to performance by comparing HAI outcome to national benchmark, top percentile and achieved standardized infection ratios (SIR).

- The number of surgical-site *S. aureus* infections acquired in the hospital, particularly cardiac or orthopedic, has been reduced by rapid screening and decolonizing of nasal carriers of *S. aureus* before surgery.
- Universal decolonization of ICU patients for MRSA has been advocated without nares screening as a model to reduce bloodstream infection and MRSA clinical isolates.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Methicillin-Resistant *Staphylococcus aureus* (MRSA) (Related Key Topic).

Multidrug-Resistant Gram-Negative Rods (MDR-GNRs) (Related Key Topic)

Vancomycin-Resistant Enterococcus (VRE) (Related Key Topic)

AUTHOR: **MARLENE FISHMAN WOLPERT, M.P.H., C.I.C.**

EVIDENCE

Abstract[1]

Importance:
Monitoring of residual gastric volume is recommended to prevent ventilator-associated pneumonia (VAP) in patients receiving early enteral nutrition. However, studies have challenged the reliability and effectiveness of this measure.

Objective:
To test the hypothesis that the risk of VAP is not increased when residual gastric volume is not monitored compared with routine residual gastric volume monitoring in patients receiving invasive mechanical ventilation and early enteral nutrition.

Design, Setting, and Patients:
Randomized, noninferiority, open-label, multicenter trial conducted from May 2010 through March 2011 in adults requiring invasive mechanical ventilation for more than 2 days and given enteral nutrition within 36 hours after intubation at 9 French intensive care units (ICUs); 452 patients were randomized and 449 included in the intention-to-treat analysis (3 withdrew initial consent).

Intervention:
Absence of residual gastric volume monitoring. Intolerance to enteral nutrition was based only on regurgitation and vomiting in the intervention group and based on residual gastric volume greater than 250 mL at any of the 6-hourly measurements and regurgitation or vomiting in the control group.

Main Outcome Measures:
Proportion of patients with at least 1 VAP episode within 90 days after randomization, as assessed by an adjudication committee blinded to patient group. The prestated noninferiority margin was 10%.

Results:
In the intention-to-treat population, VAP occurred in 38 of 227 patients (16.7%) in the intervention group and in 35 of 222 patients (15.8%) in the control group (difference, 0.9%; 90% CI, 4.8% to 6.7%). There were no significant between-group differences in other ICU-acquired infections, mechanical ventilation duration, ICU stay length, or mortality rates. The proportion of patients receiving 100% of their calorie goal was higher in the intervention group (odds ratio, 1.77; 90% CI, 1.25-2.51; $P = .008$). Similar results were obtained in the per-protocol population.

Conclusion and Relevance:
Among adults requiring mechanical ventilation and receiving early enteral nutrition, the absence of gastric volume monitoring was not inferior to routine residual gastric volume monitoring in terms of development of VAP. Ⓐ

TrialRegistration.dclinicaltrials.gov Identifier: NCT0113748.

Evidence-Based Reference

Reignier J: for the Clinical Research in Intensive Care and Sepsis (CRICS) Group. Effect of not monitoring residual gastric volume on risk of ventilator-associated pneumonia in adults receiving mechanical ventilation and early enteral feeding: a randomized controlled trial, *JAMA* 309:249–256, 2013. Ⓐ

SUGGESTED READINGS

Bearman G, Bryant K, Leekha S, Mayer J et al.: Healthcare personnel attire in non-operating room settings, *Infect Control Hosp Epidemiol* 35(2):107–121, 2014.

Best EL et al.: The potential for airborne dispersal of *Clostridium difficile* from symptomatic patients, *Clin Infect Dis* 50:1450–1457, 2010.

Bode LG et al.: Preventing surgical-site infections in nasal carriers of Staphylococcus aureus, *N Engl J Med* 362:9–17, 2010.

Calfee DP et al.: Strategies to prevent methicillin-resistant Staphylococcus aureus transmission and infection in acute care hospitals: 2014 Update, *Infect Control Hosp Epidemiol* 35:772–796, 2014.

Centers for Disease Control and Prevention: *2012 CRE Toolkit. Guidance for control of carbapenem-resistant Enterobacteriaceae (CRE)*. Available at http://www.cdc.gov/hai/organisms/cre/cre-toolkit/, 2014. Accessed August 1.

Centers for Disease Control and Prevention: *Antibiotic stewardship—the ultimate return on investment*, Available at http://www.cdc.gov/getsmart/healthcare/learn-from-others/factsheets/antibiotic-use.html, 2014. Accessed August 1.

Centers for Disease Control and Prevention: Carbapenem-resistant Enterobacteriaceae containing New Delhi metallo-beta-lactamase in two patients—Rhode Island, March 2012, *MMWR Morb Mortal Wkly Rep* 61(24):446–448, 2012.

Centers for Disease Control and Prevention (CDC): *Guidelines for hand hygiene in health-care settings, 2002*. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5116a1.htm, 2014. Accessed August 1.

Centers for Disease Control and Prevention: *Management of multidrug-resistant organisms in healthcare settings, 2006*. Available at http://www.cdc.gov/hicpac/mdro/mdro_0.html, 2014. Accessed August 1.

Chapin KC et al.: Comparison of five assays for detection of Clostridium difficile toxin, *J Mol Diagn* 13(4):395–400, 2011.

Clinical and Laboratory Standards Institute (CLSI): *Performance standards for antimicrobial susceptibility testing, 21st informational supplement, CLSI document*, M100–S24. 2014.

Cohen SH et al.: Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA), *Infect Control Hosp Epidemiol* 31(5):431–455, 2010.

Darouiche RO et al.: Chlorhexidine-alcohol versus povidone-iodine for surgical-site antisepsis, *N Engl J Med* 362:18–26, 2010.

Diekema DJ, Climo M: Preventing MRSA infections: finding it is not enough, *JAMA* 299:1190–1192, 2008.

Huang SS et al.: Targeted versus universal decolonization to prevent ICU infection, *N Engl J Med* 368(24):2255–2265, 2013.

Kallen AJ et al.: Health care–associated invasive MRSA infection, 2005-2008, *JAMA* 304(6):641–647, 2010.

Kufelnicka AM, Kirn TJ: Effective utilization of evolving methods for the laboratory diagnosis of Clostridium difficile infection, *CID* 52(12):1451–1457, 2011.

Kumarasamy KK et al.: Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study, *Lancet Infect Dis* 10(9):597–602, 2010.

Magill SS, Edwards JR, Bamberg W, Beldavs ZG et al.: Multistate point-prevalence survey of healthcare-associated infections, *N Engl J Med* 370:1198–1208, 2014. Available at http://www.nejm.org/doi/pdf/10.1056/NEJMoa1306801. Accessed August 28.

National Action Plan to Prevent Healthcare-Associated Infections: Roadmap to Elimination, April 2013. Available at http://www.health.gov/hai/pdfs/hai-action-plan-executive-summary.pdf, 2014. Accessed August 28.

O'Grady NP et al.: Preventing ventilator-associated pneumonia: does the evidence support the practice? *JAMA* 307(23):2534–2538, 2012.

One and Only Campaign for Safe injections: Available at www.oneandonlycampaign.org 2014. Accessed August 6.

Otter JA et al.: The role played by contaminated surfaces in the transmission of nosocomial pathogens, *Infect Control Hosp Epidemiol* 32(7):687–699, 2011.

Peleg AY, Hooper DC: Hospital-acquired infections due to gram-negative bacteria, *N Engl J Med* 362:1804–1813, 2010.

Scott RD: *The direct medical costs of healthcare-associated infection in U.S. hospitals and the benefits of prevention*, Available at http://www.cdc.gov/HAI/pdfs/hai/Scott_CostPaper.pdf, 2014. Accessed August 1.

Society for Healthcare Epidemiology of America (SHEA): *Compendium of strategies to prevent HAIs, 2014 Compendium Update*, Available at http://www.shea-online.org/PriorityTopics/CompendiumofStrategiestoPreventHAIs.aspx, 2014. Accessed August 1.

Heart Block, Complete PTG

BASIC INFORMATION

DEFINITION

Complete heart block (CHB) is the absence of electrical impulse transmission from the atria to the ventricles when atrioventricular (AV) junction is not physiologically refractory, due to a functional impairment of the conduction system, resulting in a bradycardia characterized by AV dissociation. It may be acquired or congenital.

SYNONYMS

Third-degree AV block
CHB
Complete AV block

ICD-9CM CODES
426.0 Complete heart block
ICD-10CM CODES
I44.2 Atrioventricular block, complete

EPIDEMIOLOGY & DEMOGRAPHICS

- The prevalence of CHB is 0.04%.
- The prevalence of CHB increases with age.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Physical examination may be normal. Cannon A waves may appear in the jugular vein periodically due to the right atrium contracting during ventricular systole. Patients may present with the following clinical manifestations:

- Dizziness, palpitations
- Syncope or presyncope (due to reduced cardiac output)
- Fatigue, impaired exercise tolerance
- Mental status changes
- Congestive heart failure
- Angina pectoris
- Some patients may be asymptomatic (e.g., congenital CHB)

ETIOLOGY

- Fibrosis or sclerosis of the conduction system, Lenegre and Lev disease
- Acute myocardial infarction—inferior (14%) or anterior (2%) wall of patients, usually within 24 hours
- Drug effect (digitalis, calcium channel blockers, beta-blockers, amiodarone)
- Cardiomyopathy and myocarditis
- Infiltrative processes of the myocardium (amyloidosis, sarcoidosis, scleroderma, tumor)
- Metabolic abnormalities (hyperkalemia, hypoxia, hypothyroidism)
- Lyme carditis, rheumatoid nodules, polymyositis, Chagas' disease
- Neuromuscular disorders (Becker muscular dystrophy, myotonic muscular dystrophy)
- Congenital (birth from mothers with systemic lupus)
- Hyperkalemia
- Familial: SCN5 sodium channel mutations have been associated with CHB
- Iatrogenic (cardiac surgery, catheter ablation of arrhythmias, percutaneous coronary intervention). Transcatheter aortic valve implantation (TAVI) is shown to be frequently associated with new conduction abnormalities; patients with preexisting right bundle-branch block are at increased risk of CHB (resolves over time in most patients).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- The differential diagnosis includes lesser degree of AV block, automatic junctional rhythms, and nonconducted premature atrial contractions.
- The atrial rate must be faster than the ventricular rate, and episodes of AV dissociation with an accelerated ventricular or junctional pacemaker overtaking the sinus node can often look like heart block on a single electrocardiogram.

WORKUP

- Workup such as routine labs, cardiac biomarkers, and cardiac imaging should be dictated by the clinical circumstances.
- ECG: diagnostic of the disease (Figs. H1-5 and H1-6):
  1. P waves are present with a regular atrial rate that is faster than the ventricular rate.
  2. P waves are not related to the QRS complexes. The PR intervals are variable.
  3. RR intervals are regular.
  4. QRS complexes may be normal with rate of 40 to 60 beats/min (block proximal to His bundle) or wide with a rate of <40 beats/min (block distal to His bundle)—depending on the location of the block in the conduction system.
  5. Complete AV block can result from block at the level of AV node, within the His bundle, or distal to it, in the Purkinje system.

TREATMENT

ACUTE GENERAL Rx

- Initial treatment should focus on the hemodynamic stability and symptoms of the patient.

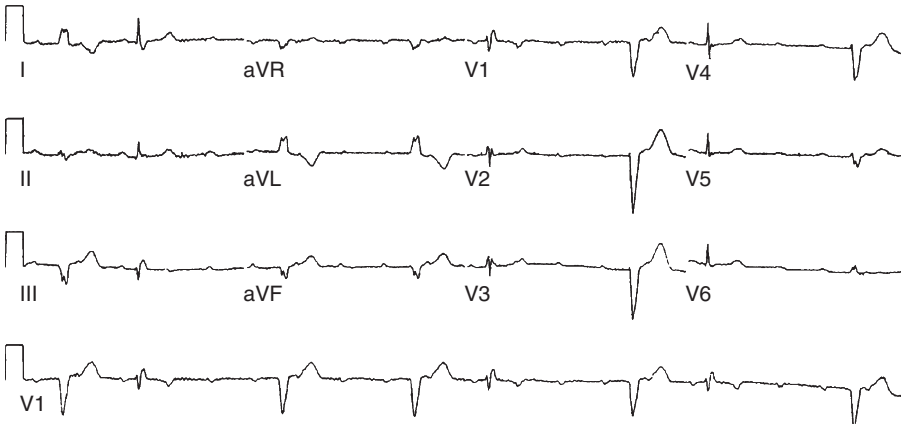


FIGURE H1-6 High-grade atrioventricular block. Note that only three P waves conducted to the ventricle in the whole tracing. Conducted P waves were associated with normal PR intervals and right bundle branch block, a finding suggesting infranodal block. All other P waves were blocked, and ventricular escape rhythm with a left bundle branch block pattern is observed. Note that the block is not caused by retrograde concealment in the atrioventricular node or His-Purkinje system from the ventricular escape complexes because the conducted P waves occurred at a short cycle following the escape complexes. (From Issa Z et al: *Clinical arrhythmology and electrophysiology,* ed 2, Philadelphia, 2012, Saunders.)

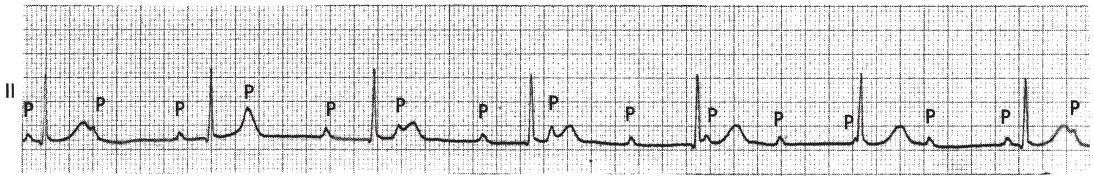


FIGURE H1-5 Third-degree (complete) atrioventricular heart block is characterized by independent atrial (P) and ventricular (QRS) activity. The atrial rate is always faster than the ventricular rate. The PR intervals are completely variable. Some P waves fall on the T wave, distorting its shape. Others may fall in the QRS complex and be "lost." Notice that the QRS complexes are of normal width, indicating that the ventricles are being paced from the atrioventricular junction. (From Goldberger AL [ed]: *Clinical electrocardiography*, ed 5, St Louis, 1994, Mosby.)

- Consider temporary pacemaker insertion if ventricular escape rate is slow (<40 beats/min) and associated with symptoms or hemodynamic compromise.
- CHB as a complication of inferior MI usually only requires temporary pacing; however, a CHB as a result of anterior MI often requires permanent pacing (Table H1-3).
- Acquired CHB usually requires pacing, but patients with congenital CHB often have sufficiently rapid escape rhythm to prevent symptoms and avoid permanent pacemaker implantation.
- Withdraw AV-nodal blocking agents if any.
- Short-term therapy (until adequate pacing therapy is established)
  1. Vagolytic agents such as atropine may be used to increase the rate of the escape rhythm (for AV nodal level blocks)
  2. Catecholamines such as isoproterenol transiently used for a CHB at any site (use with extreme caution or not at all in patients with coronary artery disease or in patients with digitalis toxicity).
- Drugs cannot be relied on to increase HR for more than several hours or days without side effects; therefore, temporary or permanent pacemaker insertion is indicated.
- Symptomatic CHB in the absence of a condition that is likely to resolve is an ACC/AHA/HRS Class I indication for permanent pacemaker (PPM) placement.
- Class 1 indications for PPM placement in asymptomatic patients according to the ACC/AHA guidelines include:
  1. Patients in sinus rhythm, with documented asystolic pauses greater than or equal to 3.0 sec or an escape rate <40 beats/min, or with an escape rhythm that is below the AV node
  2. Patients with atrial fibrillation and bradycardia with one or more pauses of at least 5 sec or longer
  3. After catheter ablation of the AV junction
  4. If cardiomegaly or LV dysfunction is present with ventricular rates of 40 beats/min or faster
  5. Postoperative CHB that is not expected to resolve
  6. When it is associated with neuromuscular diseases, such as Erb dystrophy (limb-girdle muscular dystrophy), Kearns-Sayre syndrome, myotonic muscular dystrophy, and peroneal muscular atrophy
  7. CHB present during exercise in the absence of myocardial ischemia
- Therapy is directed toward the underlying etiology if there is a reversible source (i.e., IV antibiotics for Lyme disease).

TABLE H1-3 Indications for Pacing in AV Block

Class I

1. Third-degree or advanced second-degree AV block at any anatomic level associated with any one of the following conditions:
   - a Symptoms (including heart failure) attributable to AV block (*Level of Evidence: C*)
   - b Arrhythmias and other medical conditions that require drugs that result in symptomatic bradycardia (*Level of Evidence: C*)
   - c Documented periods of asystole >3.0 seconds, any escape rate <40 beats/min, or any escape rhythm below the AV junction (e.g., a wide QRS morphology) in awake, asymptomatic patients in sinus rhythm (*Level of Evidence: C*)
   - d A documented period of asystole >5 seconds in awake, asymptomatic patients in atrial fibrillation (*Level of Evidence: C*)
   - e After catheter ablation of the AV junction (*Level of Evidence: C*)
   - f Postoperative AV block that is not expected to resolve after cardiac surgery (*Level of Evidence: C*)
   - g Neuromuscular diseases, such as myotonic muscular dystrophy, Kearns–Sayre syndrome, Erb (limb-girdle) dystrophy, and peroneal muscular atrophy, with or without symptoms of bradycardia (*Level of Evidence: B*)
2. Asymptomatic third-degree AV block at any anatomic site with an average awake ventricular rate >40 beats/min in patients with cardiomegaly or left ventricular dysfunction
3. Second-degree or third-degree AV block during exercise in the absence of myocardial ischemia (*Level of Evidence: C*)
4. Symptomatic second-degree AV block regardless of type or site of block (*Level of Evidence: B*)

Class IIa

1. Advanced second-degree or third-degree AV block at any anatomic site with an average ventricular rate >40 beats/min in the absence of cardiomegaly (*Level of Evidence: C*)
2. Asymptomatic second-degree AV block at intra- or infra-His levels found at electrophysiologic study (*Level of Evidence: B*)
3. First-degree or second-degree AV block with symptoms similar to those of pacemaker syndrome (*Level of Evidence: B*)
4. Asymptomatic type II second-degree AV block with a narrow QRS. When type II second-degree AV block occurs with a wide QRS, including isolated right bundle branch block, pacing becomes a Class I recommendation. (*Level of Evidence: B*)

Class IIb

1. AV block due to drug use or toxicity when the block is expected to recur even after withdrawal of the drug (*Level of Evidence: B*)
2. Neuromuscular diseases, such as myotonic muscular dystrophy, Kearns–Sayre syndrome, Erb (limb-girdle) dystrophy, and peroneal muscular atrophy with any degree of AV block (including first-degree AV block), with or without symptoms of bradycardia (*Level of Evidence: B*)

Class III

1. Asymptomatic first-degree AV block (*Level of Evidence: B*)
2. Asymptomatic type I second-degree AV block at a site above the His (i.e., the AV node) level or not known to be intra- or infra-Hisian by electrophysiologic study (*Level of Evidence: B*)
3. AV block expected to resolve and unlikely to recur (e.g., drug toxicity, Lyme disease, nocturnally in sleep apnea, early postoperative status, transient increases in vagal tone) (*Level of Evidence: B*)

Bonow RO, et al. *Heart disease*, 9 ed. Philadelphia, 2012, Saunders.

CHRONIC Rx

Patients with PPM need regular follow-up and pacemaker monitoring to ensure proper device functioning.

DISPOSITION

- Mortality is highest in the neonatal period in congenital CHB.
- Prognosis is favorable after insertion of pacemaker and related to the underlying etiology of complete AV block (e.g., myocardial infarction, cardiomyopathy).
- Nonrandomized studies have shown that PPM insertion improves survival in patients with CHB.

REFERRAL

All patients with CHB should be referred to a cardiologist for consideration of temporary and/or PPM implantation.

PEARLS & CONSIDERATIONS

COMMENTS

- Patients should be instructed to avoid activities that may damage the pacemaker (e.g., contact sports).
- Pacemaker manufacturers do not recommend any special restrictions regarding proximity to typical household items.
- The presence of a permanent pacemaker is a strong relative contraindication to MRI, although now certain MRI-compatible pacemakers are available.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Complete Heart Block (Patient Information)

AUTHOR: **BARRY FINE, M.D., Ph.D.**

SUGGESTED READINGS

Bates MG et al.: Postoperative permanent pacemaker implantation in patients undergoing trans-catheter aortic valve implantation: what is the incidence and are there any predicting factors? *Interact Cardiovasc Thorac Surg* 12(2):243–253, 2011.

Epstein AE, ACC/AHA/HRS 2008 et al.: Guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons, *Circulation* 117:e350, 2008.

Kojic EM et al.: The prevalence and prognosis of third-degree atrioventricular conduction block: the Reykjavik study, *J Intern Med* 246(1):81–86, 1999.

Heart Block, Second-Degree PTG

BASIC INFORMATION

DEFINITION

Second-degree heart block or second-degree atrioventricular (AV) heart block is characterized by a failure of one or more, but not all, atrial impulses to conduct to the ventricles. The block may be at any level of AV conduction system. When more than one atrial impulse is present for each ventricular complex, the rhythm may be described as a ratio of the number of atrial impulses to the number of ventricular complexes. Electrocardiographically there are three types of second-degree block:

- Mobitz type I (Wenckebach):
  1. Characterized by a progressive prolongation of the PR interval prior to a blocked nonconducted beat and a shorter PR interval after that blocked beat; the conducted impulse will generally be narrow. The cycle may repeat periodically, leading to "grouped beating."
  2. Site of block is usually AV node (proximal to the His bundle).
- Mobitz type II:
  1. High-grade AV block (3:1, 4:1, or greater)
  2. Characterized by fixed PR intervals before and after blocked beats and is usually associated with a wide QRS morphology (right bundle branch block [RBBB] or left bundle branch block [LBBB] patterns).
  3. Site of block is usually infranodal, especially when QRS is wide.
  4. It has a greater propensity for progressing to third-degree AV block.
- Pure 2:1 conduction patterns cannot be reliably classified as Mobitz type I or type II

SYNONYMS

Wenckebach block (Mobitz type I block)
Mobitz type II block
AV block

ICD-9CM CODES
426.13 Mobitz type I
426.12 Mobitz type II
ICD-10CM CODES
I44.1 Atrioventricular block, second degree

EPIDEMIOLOGY & DEMOGRAPHICS

Mobitz type I block is more common and may occur in individuals with heightened vagal tone or as a side effect of medications, such as β-blockers or calcium channel blockers.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with Mobitz type I are usually asymptomatic. Patients with either type may feel palpitations or the feeling of "missing a beat." Sudden loss of consciousness without warning (Adams-Stokes attack) can occur in patients with Mobitz type II; however, it is much more common in patients with complete heart block.
- Type I block: there is gradual decrease in the intensity of the first heart sound with widening of the a-c interval in the central venous waveform, ending in a pause, and an a wave not followed by a v wave in the neck along with an irregular pulse.
- Type II block: the first heart sound retains a constant intensity, with intermittent ventricular pauses and a waves not followed by v waves in the neck. There is an irregular pulse for most times with intermittent pauses.

ETIOLOGY

- High vagal tone (young patients, athletes at rest)
- Degenerative changes in the AV conduction system
- Ischemia at the AV nodes (type I with inferior wall myocardial infarction [MI] and type II with anterior wall MI)
- Drugs (digitalis, quinidine, procainamide, adenosine, calcium channel blockers [nondihydropyridines], β-blockers)
- Cardiomyopathies, collagen vascular diseases, infiltrative diseases (amyloidosis, sarcoidosis, hematochromatosis)
- Myocarditis/endocarditis (infectious, e.g., Lyme disease, Chagas disease; and noninfectious, e.g., systemic lupus erythematosus)
- Hyperkalemia, hypermagnesemia
- Hypothyroidism
- Prior cardiac valve surgery
- Catheter trauma, catheter ablation for arrhythmias

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

The ECG easily and reliably distinguishes Mobitz type I from Mobitz type II block and from other conduction abnormalities. It should be distinguished from the less common phenomenon of second-degree sinoatrial node exit block.

Mobitz type I block with a normal QRS complex tends to be benign and usually does not progress to more advanced forms of AV conduction within a short period of time because the disease is mostly confined to within the AV node. Mobitz type II block often precedes the development of Adams-Stokes syncope, symptoms are frequent, prognosis is compromised, and progression to third-degree AV block is common and sudden. Thus, type II second-degree AV block with a wide QRS typically indicates diffuse conduction system disease involving even the infranodal His-Purkinje system.

WORKUP

ECG, ambulatory monitoring (Holter or external loop recorders) in selected patients

- Mobitz type I (Fig. H1-7) ECG shows:
  1. Sequential and gradual prolongation of PR interval leading to a nonconducted P wave
  2. Shortened PR interval following the pause as compared to the pre-pause PR interval
  3. Progressive shortening of the R-R interval prior to nonconducted atrial impulse
  4. Usually see "grouped beating" pattern.
- Mobitz type II ECG shows (Fig. H1-8):
  1. Fixed duration of PR interval with constant P-P and R-R intervals
  2. Sudden nonconducted P wave
  3. Abnormal QRS duration or fascicular blocks are common.
- In 2:1 AV block (Fig. H1-9), it cannot be determined based on the 12-lead ECG whether there is Mobitz type I or type II AV block, although a wide QRS complex is suggestive of Mobitz type II.
  1. Administering atropine can improve AV conduction if the AV block is type I or within the AV node; however, if it is infranodal (i.e., type II), the increased sinus rate caused by atropine may worsen the ratio of AV conduction, resulting in worsening bradycardia.
  2. Exercise stress testing may function in the same way as atropine above. If the disease is confined to the AV node, it may improve with exercise, but in cases of Mobitz type II AV block, the degree of AV block will worsen.
  3. Carotid sinus stimulation and other vagal maneuvers may worsen the AV block if it is at the level of the AV node (i.e., Mobitz type I) but will paradoxically improve the ratio of AV conduction by slowing down the sinus rate if it is a Mobitz type II or infranodal AV block.

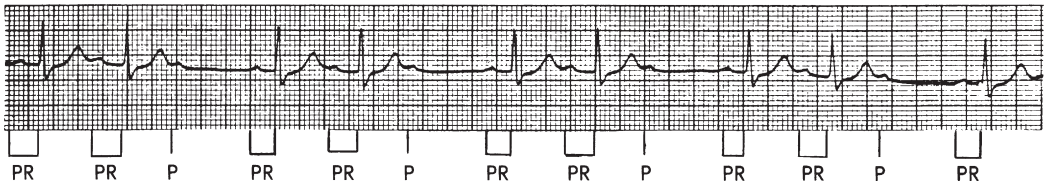


FIGURE H1-7 Wenckebach (Mobitz type I) second-degree atrioventricular block. Notice the progressive increase in PR intervals, with the third P wave in each sequence not followed by a QRS. Wenckebach block produces a characteristically syncopated rhythm with grouping of the QRS complexes (group beating). (From Goldberger AL [ed]: *Clinical electrocardiography,* ed 5, St Louis, 1994, Mosby.)

FIGURE H1-8 Mobitz type II AV block with left bundle branch block (LBBB). Note the fixed P-P intervals with no change in PR intervals followed by a sudden nonconducted P wave. The LBBB indicates infranodal disease in the His-Purkinje system that is suggestive of Mobitz type II block.

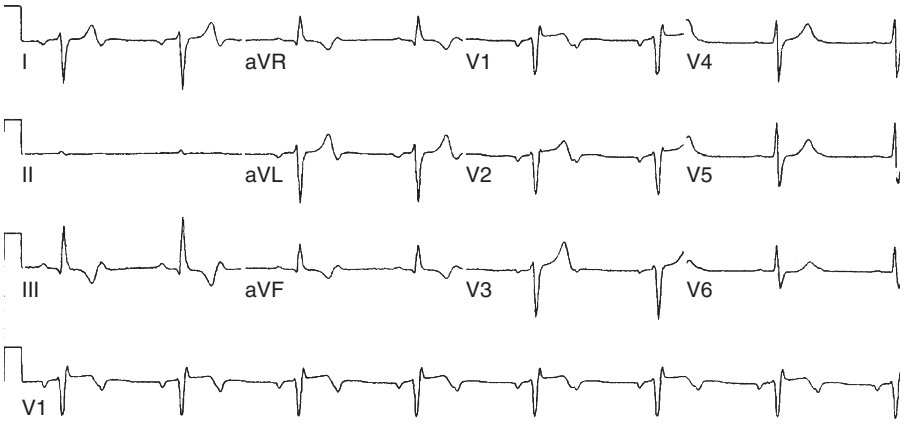


FIGURE H1-9 Second-degree 2:1 atrioventricular block. Notice the short PR interval during conducted complexes and the wide QRS complexes, suggesting block in the His-Purkinje system. (From Issa Z et al: *Clinical arrhythmology and electrophysiology,* ed 2, Philadelphia, 2012, Saunders.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Elimination of drugs that may induce AV block such as digoxin, beta-blockers, and calcium channel blockers

ACUTE GENERAL Rx

- Treatment is usually not necessary unless the resting heart rate is <40 beats per min (bpm) while awake.
- If symptomatic (e.g., dizziness), atropine 1 mg (may repeat once after 5 min) may be tried to increase AV conduction; if no response, trial of dobutamine or isoproterenol may be helpful prior to insertion of a pacemaker.
- Atropine
  1. Reduces heart block due to hypervagotonia but not due to AV node ischemia
  2. Does not increase infranodal conduction (third-degree and second-degree AV block that is below the AV node)
  3. Should be used with caution in Mobitz type II AV block due to possible paradoxical decrease in heart rate (as atrial rate increases, AV conduction decreases)
  4. Is ineffective in heart transplantation patients
- If associated with anterior wall MI and wide QRS complex, consider insertion of a temporary pacemaker.
- Indications for permanent pacemaker (PPM) implantation by ACC/AHA/HRS 2008 guidelines:
  1. Second-degree AV block with associated symptomatic bradycardia regardless of the type or site of the block (class I; level of evidence: B).
  2. Second-degree AV block provoked by exercise in the absence of myocardial ischemia (class I; level of evidence: C).
  3. Asymptomatic second-degree AV block at intra- or infra-His levels found at electrophysiologic study (class IIa; level of evidence: B).
  4. First- or second-degree AV block with symptoms similar to those of pacemaker syndrome or hemodynamic compromise (class IIa; level of evidence: B).
  5. Asymptomatic type II second-degree AV block with a wide QRS, including isolated right bundle-branch block (class I; level of evidence: B).
  6. PPM is not indicated for asymptomatic type I second-degree AV block at supra-His (AV node) level or that which is not known to be intra- or infra-Hisian (class III; level of evidence: C)

DISPOSITION

Prognosis is good with insertion of a pacemaker.

REFERRAL

Referral for pacemaker insertion (see "Acute General Rx")

PEARLS & CONSIDERATIONS

COMMENTS

Patients with symptomatic Mobitz type II should be referred for a pacemaker. Asymptomatic patients should be referred if the AV block worsens with exercise and should be followed up routinely for potential development of high-grade AV block.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Second-Degree Heart Block (Patient Information)

AUTHOR: **AMANDA C. DORAN, M.D., Ph.D.**

SUGGESTED READINGS

Barold SS: Atrioventricular block revisited, *Compr Ther* 28(1):74–78, 2002.

Barold SS, Hayes D: Second-degree atrioventricular block: a reappraisal, *Mayo Clin Proc* 76:44, 2001.

Dhingra RC et al.: The significance of second degree atrioventricular block and bundle branch block: observation regarding site and type of block, *Circulation* 49:638–646, 1974.

Donoso E et al.: Unusual forms of second degree atrioventricular block, including Mobitz type-II block, associated with the Morgagni-Adams-Stokes syndrome, *Am Heart J* 67:150–157, 1964.

Epstein et al.: ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities, *J Am Coll Cardiol* 51:1–62, 2008.

BASIC INFORMATION

DEFINITION

Heart failure (HF) is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. The cardinal manifestations of heart failure are dyspnea and fatigue that can limit exercise tolerance. The pathophysiology of HF is related to progressive activation of the neuroendocrine system to compensate for decreased effective circulating volume, leading to total body volume overload and circulatory insufficiency. These events culminate in the development of pulmonary congestion as well as peripheral edema. Specifically, the renin-angiotensin-aldosterone system (RAAS) is implicated as being activated in HF, leading to volume expansion (sodium retention) and cardiac fibrosis (mediated through angiotensin II). Disordered adrenergic stimulation has also been recognized as a key component of progression of disease. The term "congestive heart failure" (CHF) usually denotes a volume-overloaded status as a result of HF. Given that not all patients have volume overload at the time of the evaluation, "congestive heart failure" should be distinguished from the broader term "heart failure."

CLASSIFICATION: The American College of Cardiology/American Heart Association (ACC/AHA) describes the following four stages of HF. This staging model was designed to emphasize the evolution and progression of HF over a continuum and the preventability of HF in at-risk patients.

Stage A: Patients at high risk (e.g., with hypertension, atherosclerotic disease, diabetes mellitus, metabolic syndrome, cytotoxin, family history) for HF but without structural heart disease or symptoms of HF

Stage B: Patients with structural heart disease (e.g., left ventricular [LV] dysfunction) but without symptoms of HF

Stage C: Patients with structural heart disease with prior or current symptoms of HF

Stage D: Patients with refractory HF requiring specialized interventions

In addition to the ACC/AHA stages described above, the New York Heart Association (NYHA) defines four functional classes of HF designed to describe the symptoms of stage C and D HF. The functional classes are intended to assess the symptoms of HF and may fluctuate with therapy. It should be noted that current guidelines employ the functional classes to aid in determination of appropriate treatment.

I. Asymptomatic or symptomatic only at activity levels that would limit normal individuals
II. Symptomatic with ordinary exertion (e.g., 2 city blocks or 1 flight of stairs in a faster than usual pace)
III. Symptomatic with less than ordinary exertion (e.g., less than 2 city blocks or 1 flight of stairs)
IV. Symptomatic at rest

TERMINOLOGY: HF has been traditionally dichotomized as systolic versus diastolic (see Table H1-4), which has now been replaced with the terms HF with preserved ejection fraction (HFpEF) and HF with reduced ejection fraction (HFREF). Other common classifications include right-sided versus left-sided and high-output versus low-output. Systolic HF or HFREF is defined by the presence of impaired contractility of the LV, as measured by ejection fraction (EF) with clinical signs or symptoms of HF. In contrast, HFpEF or has been described as evidence (clinical) of HF with an EF above 50% with or without evidence of diastolic dysfunction. The term "HF with preserved EF" is preferred over the term "diastolic HF," given that many of the physiologic derangements in this subset of HF are not solely restricted to diastolic function of the heart. Right-sided HF denotes peripheral signs and symptoms of HF without evidence of pulmonary congestion, as opposed to left HF, which typically manifests with pulmonary congestion and subsequent signs and symptoms of right-sided HF. The most common cause of right-sided heart failure is left-sided heart failure. High-output HF involves signs and symptoms of HF but features an elevated cardiac output unable to meet the abnormally high metabolic demands of peripheral tissues, the result of myriad systemic disorders (e.g., systemic arteriovenous fistulas, hyperthyroidism, anemia). The term "acute decompensated HF" (ADHF) refers to worsening of signs or symptoms of HF due to a wide range of causes. Of note, HF is not equivalent to cardiomyopathy or LV dysfunction. These latter terms describe the possible structural or functional reasons for the development of HF, whereas HF is a clinical syndrome characterized by specific symptoms and signs.

SYNONYMS

HF
Congestive heart failure
CHF
Cardiac failure
Cardiogenic shock
Cardiogenic pulmonary edema

ICD-9CM CODES
428.0 Congestive heart failure
ICD-10CM CODES
I50.9 Heart failure, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Of note, there is variability in the reported demographics of HF due to heterogeneous definitions and classifications of HF. African Americans have the highest risk for HF of the demographic groups. Incidence rate is lowest among white women and highest among

TABLE H1-4 Systolic versus Diastolic Heart Failure*

Parameters	Systolic (HFREF)	Diastolic (HFpEF)
History		
Coronary artery disease	+++†	++
Hypertension	++	++++
Diabetes	++	++
Valvular heart disease	++++	+
Paroxysmal dyspnea	++	+++
Physical Examination		
Cardiomegaly	+++	+
Soft heart sounds	++++	+
S_3 gallop	+++	+
S_4 gallop	+	+++
Hypertension	++	++++
Mitral regurgitation	+++	+
Rales	++	+
Edema	+++	+
Jugular venous distention	+++	+
Chest Radiograph		
Cardiomegaly	+++	+
Pulmonary congestion	+++	+++
Electrocardiogram		
Left ventricular hypertrophy	++	++++
Q waves	++	+
Low voltage	+++	-
Echocardiogram		
Left ventricular hypertrophy	++	++++
Left ventricular dilation	++	-
Left atrial enlargement	++	++
Reduced ejection fraction	++++	-

*Certain aspects of the history and physical examination, along with clinical measurements, may help to distinguish diastolic from systolic heart failure. For example, patients with hypertensive heart disease and severe left ventricular hypertrophy often experience heart failure because of diastolic dysfunction.
†*Plus signs* indicate "suggestive" (the number reflects relative weight). *Minus signs* indicate "not very suggestive."
HFpEF, Heart failure with preserved ejection fraction; *HFREF,* heart failure with reduced ejection fraction.
From Zipes DP et al (eds): *Braunwald's heart disease,* ed 7, Philadelphia, 2005, Saunders.

black men, with blacks having a greater 5-yr mortality rate than whites.

- The lifetime risk of developing HF is 20% for Americans ≥40 years of age.
  1. In the United States, HF incidence has largely remained stable over the past several decades, with >650,000 new HF cases diagnosed annually.
- HF is primarily a condition of the elderly. Approximately 80% of patients hospitalized with HF are older than 65 yr. HF is the most common inpatient diagnosis in the U.S. for patients aged >65 yr.
- HF incidence increases with age, rising from approximately 20 per 1,000 individuals 65 to 69 yr to >80 per 1,000 individuals among those >85 yr. Before age 75, the incidence of HF is higher in males, but both sexes are equally affected after this age cutoff.
- In the U.S., 1.1 million hospital discharges and 3.2 million hospitalizations/ambulatory care visits were associated with HF in 2007.
- Prevalence: 5.1 million persons in the U.S. and an estimated 23 million persons worldwide. The prevalence of HF is rising, especially in the elderly, particularly due to aging of the population and improved survival from other conditions.
- In the U.S., more than 550,000 patients annually are diagnosed with HF for the first time. The incidence is higher in the elderly, approaching 1 per 100 persons aged >65 yr per year. Before age 75, the incidence of HF is higher in males but both sexes are equally affected after this age cutoff.
- The estimated (direct and indirect) cost of HF in the U.S. was >$40 billion in 2012, with over half of these costs spent on hospitalizations. The mean cost of HF-related hospitalizations is $23,077 per patient and is higher when HF was a secondary rather than the primary diagnosis.
- HFrEF and HFpEF each make up about half of the overall HF burden.
- Among patients with HF in one large population study, hospitalizations were common after HF diagnosis, with 83% of patients hospitalized at least once and 43% hospitalized at least 4 times. More than half of the hospitalizations were related to non-cardiovascular causes.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The clinical and physical exam findings should be given the highest priority when determining the diagnosis of HF. These signs and symptoms are dependent on the severity of disease, precipitant factor, comorbid conditions, and whether the failure symptoms are predominantly right-sided or left-sided.

- Common clinical manifestations are:
  1. Dyspnea on exertion, that can progress to dyspnea at rest, caused by increasing pulmonary vascular congestion
  2. Orthopnea, caused by increased venous return in the recumbent position and further elevated pulmonary venous pressure
  3. Paroxysmal nocturnal dyspnea (PND) resulting from multiple factors including increased venous return in the recumbent position, decreased Pao_2 and decreased adrenergic stimulation of myocardial function during sleep
  4. Nocturnal angina resulting from increased myocardial oxygen demand (secondary to increased venous return in the recumbent position causing increased preload) in patients with concomitant coronary artery disease (CAD)
  5. ***Cheyne-Stokes respiration*** (alternating phases of apnea and hyperventilation) caused by prolonged circulation time from lungs to brain as a result of impaired cardiac output
  6. Fatigue, lethargy, and decreased functional capacity resulting from low cardiac output and hypoperfusion of peripheral tissues
- Physical examination:
  1. Fine pulmonary crackles, wheezes, tachypnea, hypoxia (due to elevated pulmonary pressures). Crackles may be absent in chronic and longstanding high pulmonary venous pressure because it allows for lymphatic drainage in the lungs to increase.
  2. Tachycardia and narrowed pulse pressure (due to increased sympathetic tone)
  3. S_3 gallop, paradoxical splitting of S_2, jugular venous distention, peripheral edema in dependent tissues, congestive hepatomegaly, ascites, and hepatojugular reflux (due to volume overload)
  4. Perioral and peripheral cyanosis, decreased capillary refill, pulsus alternans, and cool extremities (due to decreased cardiac output)
- Six common clinical presentations identified by European Society of Cardiology of Acute Heart Failure Syndromes:
  1. ADHF presenting with hypertension (SBP >160): the hypertension leads to increased afterload causing pulmonary vascular congestion.
  2. Worsening or decompensation of chronic HF
  3. Flash pulmonary edema
  4. Cardiogenic shock
  5. Acute coronary syndrome (ACS) and ADHF
  6. Isolated RV failure
- Each of these scenarios may require different therapies to effectively stabilize and treat the patient.

Acute precipitants of HF decompensation include noncompliance with salt restriction or medications (most commonly), infection, arrhythmias (e.g., atrial fibrillation), ischemia or infarction, uncontrolled hypertension, new medications (e.g., negative inotropic agents such as calcium channel blockers/antiarrhythmic agents), nonsteroidal anti-inflammatory drugs (NSAIDs), renal dysfunction, toxins (e.g., ethanol and anthracyclines), cardiac surgery, or valvular catastrophe.

ETIOLOGY

LEFT VENTRICULAR FAILURE: The dichotomy of whether HF occurs in the setting of preserved or reduced LV systolic function plays an important role in treatment strategies. Patients with HFpEF may have significant abnormalities in active relaxation and passive stiffness of the LV as well as valvular disease. HF with reduced systolic function denotes poor pump function.

- Abnormal LV systolic function
  1. CAD (acute or chronic ischemia, myocardial infarction [MI], LV aneurysm), the most common cause of cardiomyopathy in the U.S., comprising 50%-75% of patients with HF.
  2. Increased afterload or pressure overload (severe hypertension, aortic stenosis)
  3. Increased preload or volume overload (mitral regurgitation, aortic regurgitation)
  4. Cardiomyopathy: Idiopathic, infiltrative (non-ischemic)
  5. Infectious (Chagas, myocarditis)
  6. Infiltrative (amyloidosis, sarcoidosis, hemochromatosis)
  7. Toxins (ethanol, cocaine, anthracyclines)
  8. Tachycardia induced (e.g., with atrial fibrillation)
- Preserved LV systolic function
  1. Impaired relaxation (myocardial ischemia, diabetes mellitus, metabolic syndrome)
  2. Tachyarrhythmia (featuring reduced diastolic filling time)
  3. Restrictive cardiomyopathy (myocardial stiffness, such as hypereosinophilic syndrome, amyloidosis, hemochromatosis)
  4. High cardiac output (thiamine deficiency, anemia, thyrotoxicosis, arteriovenous malformations)
  5. Increased afterload (uncontrolled hypertension, aortic stenosis, hypertrophic obstructive cardiomyopathy)
  6. Hypervolemia (oliguric renal failure, iatrogenic)

RIGHT VENTRICULAR FAILURE

- Left-sided HF
- Chronic hypoxemic pulmonary disease
- Valvular heart disease (mitral stenosis or regurgitation)
- Pulmonary embolism
- Primary pulmonary hypertension
- Right-to-left shunts that cause systemic hypoxemia (e.g., large patent foramen ovale and tetralogy of Fallot)
- Left-to-right shunts that cause volume overload (e.g., atrial and ventricular septal defects)
- Bacterial endocarditis (right-sided)
- Right ventricular infarction

DX DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- COPD, asthma
- Cirrhosis
- Nephrotic syndrome
- Venous insufficiency
- Pulmonary embolism
- ARDS (adult respiratory distress syndrome)
- Pneumonia
- Heroin overdose

WORKUP

- A flow chart for the evaluation of patients with heart failure is outlined in Fig. H1-10.

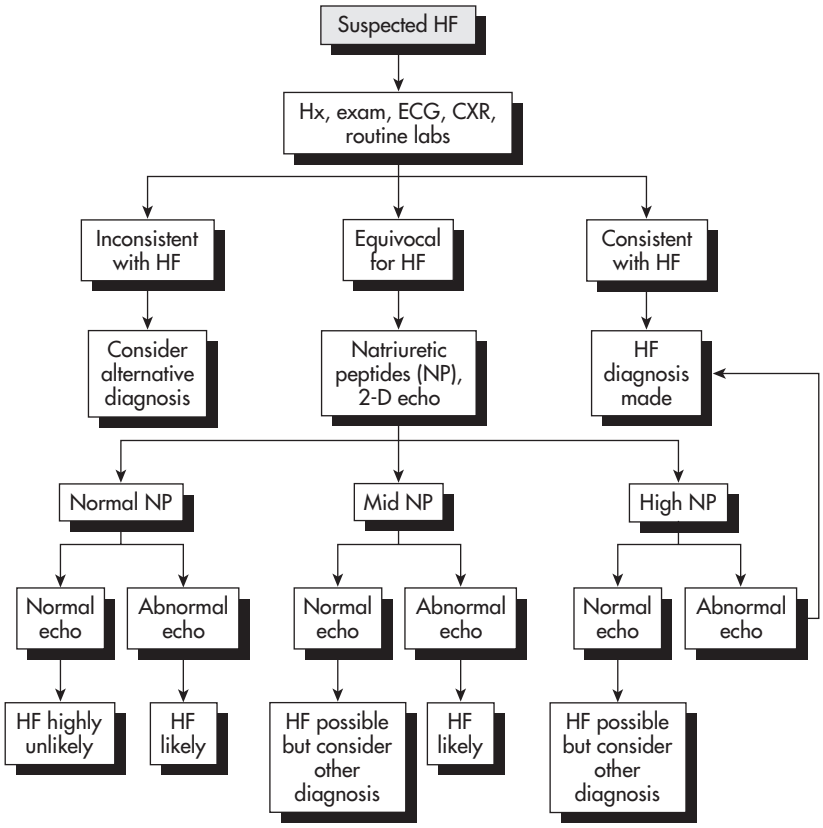


FIGURE H1-10 Flow chart for the evaluation of patients with heart failure. *CXR*, Chest radiograph; *ECG*, electrocardiograph; *echo*, echocardiograph; *HF*, heart failure; *Hx*, history; *NP*, natriuretic peptides. (From Bonow RO et al: *Braunwald's heart disease:a textbook of cardiovascular medicine,* ed 9, St Louis, 2011, Saunders.)

Fig. H1-11 describes the stages and treatment options for heart failure.

- Blood work (to diagnose potentially reversible causes, identify comorbidities, and assess disease severity)
  1. CBC (to evaluate for anemia, infections), urinalysis, blood urea nitrogen (BUN), creatinine, electrolytes (worsening hyponatremia is a marker of disease severity and is associated with higher mortality rates), liver enzymes (hepatic congestion), thyroid function (especially in the elderly or patients with comorbid atrial fibrillation or known thyroid disease)
  2. B-type natriuretic peptide (BNP) is a cardiac neurohormone secreted from the ventricles in response to elevated LV end-diastolic pressure. The sensitivity is low in asymptomatic patients (but elevated BNP levels have been shown to have a negative predictive value up to 90% in symptomatic patients), and BNP elevation generally correlates with severity of disease and parallels closely morbidity and mortality outcome measures. The cleavage remnant n-terminal-pro-BNP (nt-pro-BNP) has a longer half-life and is cleared through the kidneys, making it susceptible to alterations in renal function. A level of <300 pg/mL has an age-independent 98% negative predictive value.
  3. Cardiac biomarkers may be elevated if ischemia is the precipitant factor. However, slight elevations are very common and may not always be due to obstructive coronary disease. These elevations could be due to subendocardial ischemia (due to increased end-diastolic pressure resulting in decreased perfusion) and necrosis, or cardiomyocyte damage from the inflammatory cytokines or oxidative stress. Impaired renal function is very common, and decreased clearance of the biomarkers can contribute to their elevation. Therefore these elevations should be interpreted in the context of the clinical setting. Despite that, in patients with ADHF, a positive cardiac troponin test (from whatever mechanism) is associated with worse prognosis.
  4. Screening for dyslipidemia and glucose intolerance, which are risk factors for CAD.
  5. If hemachromatosis is suspected (specifically in Northern European patients), consider checking a transferrin saturation.
  6. Consider HIV testing in high-risk patients.
- Electrocardiogram (ECG)
  1. Look for signs of prior MI, chamber enlargement, hypertrophy, heart block, arrhythmia, and evidence of pericardial effusion.
  2. More than 25% of patients with HF have some form of intraventricular conduction abnormality that is manifest as an increased QRS duration. The most common pattern seen is left bundle-branch block.
- Chest x-ray (Fig. H1-12)
  1. Evaluate for pulmonary venous congestion, pulmonary edema, pleural effusion, cardiomegaly, chamber dilation, and Kerley B lines.
- Echocardiography
  1. Plays a critical diagnostic role in patients with HF and is useful in assessment of systolic, diastolic, and valvular structure and function
- Exercise stress testing
  1. May be useful in evaluating concomitant ischemic etiologies and assessment of degree of disability in stable compensated patients.
- Cardiac catheterization
  1. Left heart catheterization can help to identify coronary artery disease as a cause of heart failure. Right heart catheterization can help to evaluate intracardiac filling pressures, estimates of valvular areas, presence of intracardiac shunts, and calculation of hemodynamic properties such as cardiac output, systemic vascular resistance, and pulmonary artery wedge pressure to further guide management.
- Cardiac MRI
  1. Useful modality in accurately estimating EF (with less variability than conventional 2D echocardiography). MRI is also useful in excluding pericardial disease, identifying infiltrative disease, and assessing viability in cases of heart failure caused by underlying ischemic heart disease.

Rx TREATMENT

NONPHARMACOLOGIC GENERAL MEASURES

- Assess the etiology and severity of disease. Educate the patient and family about the nature of the disorder. Assess the home setting and if patient has social support to ensure compliance, especially for patients with dementia.
- Identify and correct precipitating factors (e.g., increased sodium load, medication noncompliance, ischemia, infections, anemia, thyrotoxicosis) and address lifestyle modification (e.g., smoking and alcohol cessation, weight reduction, avoiding use of nonsteroidal anti-inflammatory drugs [NSAIDs]). Anemia is common in patients with HF. However, treatments with erythropoiesis-stimulating agents (ESAs) have not shown improved clinical outcomes in patients with systolic HF and mild-to-moderate anemia and are thus not recommended.
- Review list of medications and discontinue the ones that can contribute to HF (e.g., NSAIDs, antiarrhythmic drugs, calcium channel blockers, thiazolidinediones)
- Dietary sodium restriction of <2 g/day is commonly recommended to patients with heart failure and is endorsed by many guidelines.
- Restrict fluid intake to <2 L/day in patients with hyponatremia.
- Caloric supplementation should be provided to patients with advanced HF with weight

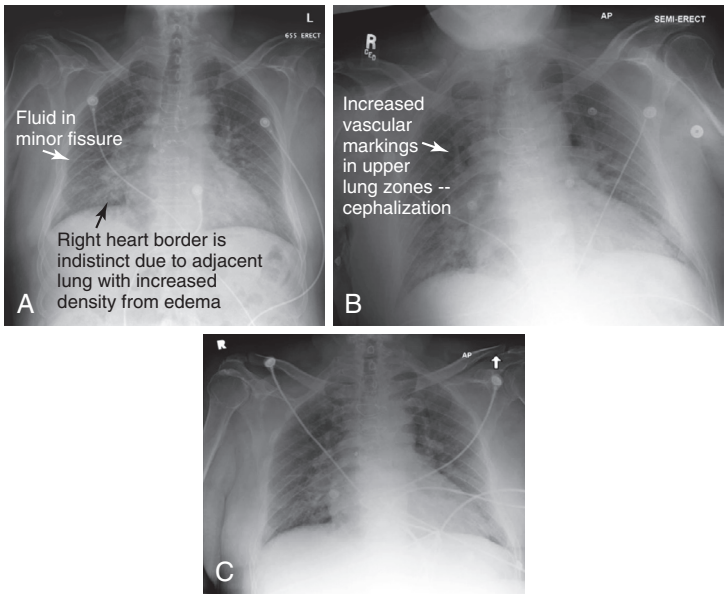


FIGURE H1-12 Congestive heart failure. Mild left ventricular hypertrophy with restricted filling, ejection fraction >55%, and no pericardial effusion. This 63-year-old man with coronary artery disease, chronic renal insufficiency, and diastolic heart failure (ejection fraction >55%) presented multiple times for dyspnea (**A, B,** and **C,** first through third clinical presentations). Each of these three radiographs shows signs of moderate pulmonary edema. The diaphragms and costophrenic angles are clear, suggesting no pleural effusion. The right heart border in all three images is indistinct because of interstitial edema in these locations. Portions of the left heart border are also indistinct. The upper lung fields have a hazy appearance indicating mild edema. Fluid is visible in the minor fissure on all three images. Does the similarity of these radiographs mean that edema is not the cause of the patient's dyspnea? No, he simply presented with pulmonary edema on all three occasions. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

loss and muscle wasting due to cardiac cachexia. Weight loss may reflect cachexia caused by the higher total energy expenditure associated with HF compared with that of healthy sedentary subjects. The diagnosis of cardiac cachexia independently predicts a worse prognosis.

- For patients with coexisting obstructive sleep apnea, continuous positive airway pressure (CPAP) is often recommended after polysomnography, thereby reducing systolic blood pressure and improving LV function.
- Exercise training (or regular physical activity) is recommended as safe and effective for patients with class I to III heart failure who are able to participate to improve functional status. Cardiac rehabilitation is unfortunately an underused preventive measure, although it has been shown to reduce morbidity and mortality.
- Pneumococcal vaccination and annual influenza vaccination.

TREATMENT OF ADHF

- Four phases in treatment of ADHF (Fig H1-11):
  1st phase: initial stabilization and management
  2nd phase: inpatient hospital care
  3rd phase: early discharge planning and care
  4th phase: early post-discharge care

1st phase: Initial stabilization and management

Short-term goals: hemodynamic stabilization, stabilization of respiratory status, symptom relief, optimization of tissue perfusion, and recognition of more immediately life-threatening conditions (e.g., arrhythmias, valvular catastrophe, MI, cardiac tamponade). Initial therapy of ADHF is contingent on appropriate determination of clinical scenario.

Management as per clinical scenario:

1. ADHF-associated hypertension: goal is afterload reduction and decrease of systemic hypervolemia. Mode of treatment: diuresis (IV loop diuretics) and vasodilators (acutely nitrates and morphine followed by treatment with ACE inhibitors or angiotensin receptor blockers [ARBs])
2. Worsening or decompensation of chronic HF (HFREF or HFpEF): goal is control of volume status. Treatment is accomplished with vasodilators and diuretics.
3. Flash pulmonary edema: goal is afterload reduction (vasodilators such as nitrates acutely), respiratory status stabilization, and diuresis (IV loop diuretics). Rate control can be initiated in patients with atrial fibrillation or tachyarrhythmias as it may improve cardiac filling and function.
4. Cardiogenic shock: goal is hemodynamic stabilization. Treatment consists of inotropes + vasopressors ± intraaortic balloon pump ± emergent revascularization if indicated.
5. ACS and ADHF: goal is hemodynamic stabilization + emergent restoration of coronary perfusion. See "Acute Coronary Syndromes."
6. Isolated RV failure: goals are identification of etiology: (1) valvular, (2) pulmonary hypertension, and (3) primary RV failure secondary to ischemia. Treatment: depends on etiology, either corrective surgery vs. treatment of pulmonary hypertension (endothelin antagonists, calcium channel blockers, phosphodiesterase inhibitors) vs. coronary reperfusion therapies.

ACUTE PHARMACOLOGIC TREATMENTS

- Vasodilators are appropriate in most patients with ADHF (contraindicated in cardiogenic shock and severe aortic stenosis)
  1. Nitroglycerin (0.4 to 0.8 mg sublingually every 3 to 5 min, or by intravenous infusion starting at 0.2 to 0.4 mcg/kg/min with subsequent up titration) may be administered in the emergency setting until relative hypotension ensues. Nitrates are contraindicated after use of phosphodiesterase inhibitors such as sildenafil due to risk of hypotension.
  2. Sodium nitroprusside (0.1 to 0.2 mcg/kg/min as an intravenous infusion) is a potent vasodilator with balanced venous and arteriolar effects that usually requires hemodynamic monitoring with an arterial line and may precipitate coronary steal and thiocyanate toxicity (elevated risk in renal failure).
  3. When given intravenously, loop diuretics have an immediate vasodilator effect that provides clinical relief of symptoms before diuresis begins. Due to gut edema and unpredictable patterns of absorption, oral formulation may become less effective. Therefore intravenous formulation should be used in the acute setting. Studies showed no difference in outcome when using bolus dosing vs. continuous IV infusion. Administration of smaller doses of short-acting loop diuretics multiple times daily is preferable to a single large dose because the kidneys can avidly reabsorb sodium after the initial diuresis. However, if a certain dose is not adequate to force diuresis, the dose, rather than the frequency, should be increased until a single effective dose is reached; more frequent doses can be added as needed. Therefore monitoring of urine output, renal function, and electrolytes is key. The addition of a distal tubule inhibitor such as metolazone 30 min prior to loop diuretic dosing has a synergistic effect and often enhances diuresis because it inhibits sodium reabsorption in the distal segment in the face of increased sodium delivery from the loop. Diuretics should be used with caution in patients with aortic stenosis and are contraindicated in patients with severe hypotension or cardiogenic shock.
- Inotropic agents are used for temporary hemodynamic support in cardiogenic shock, but have not been shown to improve survival. Many of these agents have serious associated adverse events including myocardial necrosis and malignant arrhythmias.
  1. Dobutamine (starting at 2.5 to 5 mcg/kg/min) can be used for inotropic support but is associated with increased myocardial oxygen demand and cardiac arrhythmias and may result in hypotension from decreased systemic vascular resistance.
  2. Milrinone (37.5 to 75 mcg/kg loading dose, followed by 0.375 to 0.75 mcg/kg/min) can be used as a vasodilator and

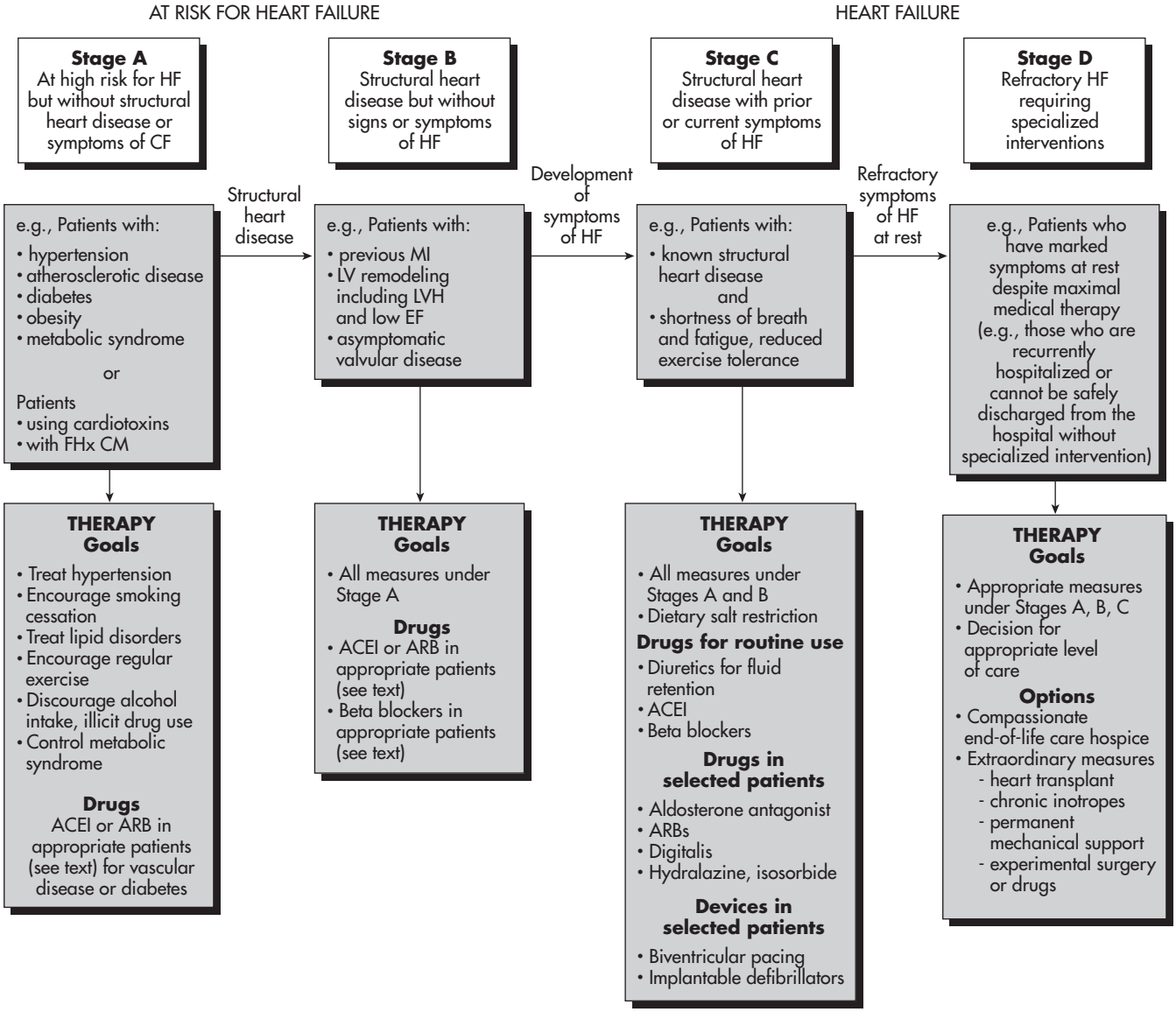


FIGURE H1-11 Stages in the evolution of heart failure (HF) and recommended therapy by stage. *ACEI*, Angiotensin-converting enzyme inhibitor; *ARB*, angiotensin receptor blocker; *EF*, ejection fraction; *FHx CM*, family history of cardiomyopathy; *IV*, intravenous; *LV*, left ventricular; *LVH*, left ventricular hypertrophy; *MI*, myocardial infarction. (From Hunt SA, Baker DW, Chin MH, et al: ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: Executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure]. *J Am Coll Cardiol* 104:2996, 2001.)

inotropic agent, but is associated with increased oxygen demand and cardiac arrhythmias, and may result in hypotension from decreased systemic vascular resistance.

3. Levosimendan is a calcium-sensitizing drug, which also inhibits potassium channels leading to inotropy. However, this agent is not FDA approved for use in the U.S. Currently, this inotrope has been associated with an elevated risk of malignant arrhythmia and higher mortality.

- Renal replacement therapy (can be used as an alternative to pharmacologic diuresis in ADHF when renal function is significantly compromised).
- ACE inhibitors or ARBs, if part of a patient's chronic medication regimen, should be continued in the absence of hypotension, acute renal failure, or hyperkalemia.
- Beta-blockers, if part of a patient's chronic medication regimen, may be continued or reduced in dosage in mild exacerbations of HF but should be discontinued in patients with hypotension or those requiring inotropic support. Beta-blockers should not be initiated in patients who are not on chronic beta-blocker therapy until euvolemia is achieved unless used for rate control.
- Morphine sulfate can cause venodilation and thus reduce cardiac preload. It may be used to reduce patient work of breathing and anxiety, but recent retrospective studies have suggested increased incidence of mechanical ventilation and in-hospital mortality in patients who received morphine.
- If ADHF with preserved EF is suspected, therapy is usually aimed at relief of symptoms and correction of any potential precipitating etiologies (e.g., tachycardia, hypertension, ischemia). Treatment generally involves diuretics to reduce pulmonary congestion with caution to not overdiurese given the need for elevated filling pressures in these patients to ensure adequate stroke volume and cardiac output. Nitrates may be useful in providing symptomatic relief but may precipitate hypotension. Ventricular rate should be controlled in the presence of atrial fibrillation, which, at rapid rates, is poorly tolerated in patients with impaired diastolic filling. Negative inotropic agents such as beta-blockers and calcium channel blockers can be used with caution.

- Nesiritide (recombinant brain natriuretic protein) does not reduce morbidity or mortality (ASCEND-HF trial)
- 2nd phase: Inpatient hospital care

This phase of treatment includes further diuresis and stabilization of volume status. The patient should be carefully brought to euvolemia with daily volume status and electrolyte monitoring. The patient should also be transitioned to oral diuretics when stabilized. Whilst inpatient, the patient should have his/her medical and device management optimized with the therapies discussed later.

3rd phase: Early discharge planning and care

The patient should be transitioned to oral diuretics and be placed on optimum outpatient maintenance therapy, which will be discussed later. If the patient was on IV inotropic therapy, oral regimens should be adjusted while these infusions are tapered off. Prolonged physiologic effects of these IV inotropic agents after their discontinuation before discharge may mask the inadequate diuretic regimen and intolerance to the vasodilator doses. This can result in readmission, especially with milrinone due to its long half-life that can be further prolonged by the common coexisting impaired renal function. Therefore it may be recommended that patients who received inotropic infusions remain hospitalized for at least 48 hours after inotropic agents are discontinued, and optimize the oral regimen.

4th phase: Early post-discharge care

The patient will require re-evaluation and constant monitoring in order to avoid another episode of ADHF. Emphasis should be placed on importance of compliance with instructions regarding dietary restrictions and daily body weight monitoring. Early follow-up should be scheduled as well as outpatient electrolyte monitoring if required after medication adjustments.

CHRONIC TREATMENT OF HF SECONDARY TO SYSTOLIC DYSFUNCTION: The goals of HF therapy are clinical improvement followed by stabilizing, slowing, or even reversing deterioration in myocardial function, and ultimately a reduction in risk of morbidity (including hospitalization rates) and mortality.

- ACE inhibitors
  1. Reduce morbidity and mortality.
  2. Produce both venous and arterial vasodilation acutely, thereby reducing both preload and afterload.
  3. Potential mechanism of long-term benefit is attenuation of RAAS activation and decreased myocardial remodeling and fibrosis.
  4. Used as first-line therapy for asymptomatic LV dysfunction (LVEF <40%) and symptomatic systolic HF (ACC/AHA grades A-D).
  5. Therapy should be initiated at low doses to prevent hypotension and rapidly titrated to higher doses as tolerated.
  6. Contraindications to the use of ACE inhibitors are renal insufficiency (creatinine clearance <30 ml/min), bilateral renal artery stenosis, hyperkalemia, hypotension, or adverse reactions (e.g., angioedema).
- ARBs
  1. Receptor antagonists to the angiotensin II receptor.
  2. Clinical trials have not shown any superiority compared to ACE inhibitors in patients with systolic HF (LVEF <40%).
  3. Reserved for patients who are ACE inhibitor intolerant.
  4. There are conflicting data on the utility of combination therapy with ARBs and ACE inhibitors in addition to beta-blockers for patients who remain symptomatic in the absence of renal dysfunction, hyperkalemia, and outside the post-MI period.
  5. Have a similar contraindication profile to ACE inhibitors. Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful for patients with HFrEF.
- Beta-adrenergic blockers (beta-blockers)
  1. Reduce morbidity and mortality. Such benefits observed with bisoprolol (CIBIS II trial), metoprolol succinate (MERIT-HF trial), and carvedilol (COPERNICUS trial).
  2. Benefit is believed to be conferred by blockade of sympathetic effects of neurohormonal stimulation due to HF.
  3. Are considered first-line therapy for symptomatic patients with systolic HF (NYHA class ≥II and LVEF <35%).
  4. Only carvedilol, bisoprolol, and metoprolol succinate (long acting) have been approved for the medical treatment of chronic HF; these agents are generally started in patients judged to be euvolemic and dosage is to be slowly uptitrated as tolerated.
  5. Adverse effects include worsening HF (due to negative inotropic effects), fatigue, dizziness, bradycardia, hypotension, and bronchospasm.
- Aldosterone receptor antagonists
  1. Reduce morbidity and mortality
  2. Indicated in patients with NYHA class II-IV HF, with LVEF ≤35%, already treated with ACE inhibitors and beta-blockers without significant renal insufficiency or hyperkalemia. Patients with NYHA class II should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be ≤2.5 mg/dL in men or ≤2.0 mg/dL in women (or estimated glomerular filtration rate >30 mL/min/1.73 m2), and potassium should be <5.0 mEq/L. They are also indicated for post-MI patients with EF ≤40% who have either symptomatic HF or diabetes mellitus.
  3. Spironolactone may cause gynecomastia, galactorrhea, and hyperkalemia (especially in patients with baseline renal insufficiency or type 4 renal tubular acidosis). It has been best studied in chronic heart failure with NYHA class III to IV symptoms (RALES study).
  4. Eplerenone is associated with fewer endocrine side effects and has especially been studied in postmyocardial infarction left ventricular dysfunction (EPHESUS trial) and in chronic systolic heart failure with only class II symptoms (EMPHASIS-HF trial).
- Inappropriate use of aldosterone receptor antagonists is potentially harmful because of life-threatening hyperkalemia or renal insufficiency when serum creatinine is >2.5 mg/dL in men or >2.0 mg/dL in women (or estimated glomerular filtration rate <30 mL/min/1.73 m^2), and/or potassium >5.0 mEq/L.
- Diuretics
  1. Are used to maintain euvolemia and to improve symptoms as discussed previously.
  2. Although data on diuretic efficacy are limited, a meta-analysis of a few small trials found that they were associated with reduction in mortality as well as reduced hospitalization for HF.
  3. Of note, loop diuretics with better bioavailability, such as torsemide and bumetanide, may be used in diuretic-resistant patients but are generally more expensive.
- Combination of isosorbide dinitrate and hydralazine
  1. Cause venous (nitrates) and arteriolar (hydralazine) vasodilation resulting in decreased preload and afterload.
  2. The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality for patients self-described as African Americans with NYHA class III–IV HFrEF receiving optimal therapy with ACE inhibitors and beta blockers, unless contraindicated.
  3. A combination of hydralazine and isosorbide dinitrate can be useful to reduce morbidity or mortality in patients with current or prior symptomatic HFrEF who cannot be given an ACE inhibitor or ARB because of drug intolerance, hypotension, or renal insufficiency, unless contraindicated.
  4. Adverse effects of nitrates include hypotension, headaches, and tolerance as well as reflex tachycardial and lupuslike syndrome with hydralazine.
- Digoxin
  1. Positive inotropic and negative chronotropic drug that works by inhibition of the sodium-potassium transmembrane exchange pump and through its vagomimetic action
  2. Commonly used in patients with concomitant atrial fibrillation
  3. Has been shown to reduce HF-related hospitalizations but does NOT confer any mortality benefit (DIG trial). However, there is evidence suggesting that digoxin may actually have an effect on survival that varies with the serum digoxin level; survival was improved when the level was between 0.5 and 0.8 ng/ml (most often in men) and significantly worsened when it was ≥1.2 ng/ml and >0.9 mg/ml in women.
  4. Caution must be used in patients with abnormal renal function to avoid digoxin toxicity and life-threatening arrhythmia. Avoid hypokalemia because potassium

competes with digoxin on the same site of the Na^+-K^+-ATPase pump.

- Cardiac resynchronization therapy (CRT)
  1. Improves morbidity and mortality rates in selected patients.
  2. The presence of a bundle-branch block or other intraventricular conduction delay (IVCD) can cause ventricular dyssynchrony, which induces regional loading disparities and reduces the efficiency of ventricular contraction, thereby further impairing the systolic function of a failing ventricle.
  3. CRT is indicated for patients who have LVEF ≤35%, sinus rhythm, left bundle-branch block with a QRS duration of 150 ms or greater, and NYHA class II, III, or ambulatory IV symptoms on guideline-directed medical therapy. CRT is NOT indicated in patients whose functional status and life expectancy are limited predominantly by chronic noncardiac conditions. Life expectancy should be >1 yr.
  4. In the appropriate subset of patients, CRT in addition to optimal medical therapy has been shown in numerous clinical trials to improve symptoms by at least one NYHA class, improve 6-min walk distance and quality of life, reduce rate of HF-related hospitalization, and reduce rate of all-cause and cardiovascular mortality.
  5. Detailed guidelines for CRT are beyond the scope of this chapter. Consultation with cardiology service may be indicated.
- Implantable cardioverter-defibrillators (ICDs)
  1. Sudden cardiac death (SCD) is a common cause of death in patients with HF in both ischemic and nonischemic cardiomyopathies. Ventricular tachycardia (VT) degenerating into ventricular fibrillation (VF) is the culprit in the majority of patients with SCD, although bradyarrhythmias do also occur with less frequency.
  2. ICD therapy is recommended for primary prevention of SCD to reduce total mortality in selected patients with nonischemic dilated cardiomyopathy or ischemic heart disease at least 40 days post-MI with LVEF ≤35% and NYHA class II or III symptoms on chronic guideline-directed medical therapy, who have reasonable expectation of meaningful survival for >1 year.
  3. Patients with HF who survive an episode of sudden cardiac arrest or experience sustained VT in the presence of LVEF <35% are at high risk for future arrhythmic events and SCD and obtain a mortality benefit from ICD placement for secondary prevention, with or without adjunctive therapies such as antiarrhythmic drugs, radiofrequency ablation, surgery, or transplant.
- In the absence of an indication (e.g., atrial fibrillation), routine use of anticoagulation is currently not recommended in patients with HF. Even with the increased risk for LV thrombus formation in dilated cardiomyopathy and subsequent thromboembolization, data are conflicting about benefits of antithrombotic (antiplatelet or anticoagulant) therapy for primary prevention to reduce thromboembolic events or mortality in patients with systolic HF who are in sinus rhythm (SOLVD, V-HeFT, SAVE, HELAS, and WASH trials). It may be reasonable to consider anticoagulation for secondary prevention in patients with HF who had a prior thromboembolic event; however, risks and benefits should be carefully assessed.
- Antiplatelet agents are recommended for patients with concomitant CAD.
- Statins are not beneficial as adjunctive therapy when prescribed solely for the diagnosis of HF in the absence of other indications for their use.
- Calcium channel blocking drugs are not recommended as routine treatment for patients with HFrEF.
- Omega-3 polyunsaturated fatty acid supplementation is reasonable to use as adjunctive therapy in patients with NYHA class II-IV symptoms and HFrEF or HFpEF, unless contraindicated, to reduce mortality and cardiovascular hospitalizations.
- Percutaneous coronary intervention (PCI) or surgical revascularization should be considered in patients with HF and significant CAD who are revascularization candidates.
- In general, the following sequence of drugs is recommended:
  1. Loop diuretics to provide symptom relief and achieve a euvolemic state.
  2. ACE or ARB started at low doses, then increased to a moderate dose in 1-2 weeks.
  3. Beta-blockers after the patient is stable on ACE/ARB treatment. Start a low dose, then uptitrate to goal based on trial data or maximal dose tolerated. Once achieved, uptitration of ACE or ARB to goal doses can be completed.
- The following drugs can be added in selected patients in the absence of contraindications:
  1. Aldosterone antagonists improve survival in NYHA class II with LVEF <30% or NYHA class III-IV with EF <35%. Kidney function should be stable with eGFR ≥30 ml/min and potassium <5 mEq/L.
  2. Combination of hydralazine with a nitrate in patients (particularly African Americans) with a reduced EF.
  3. Digoxin reduces hospitalizations for HF and controls HR rate in atrial fibrillation. It can also help control symptoms.

CHRONIC TREATMENT OF HF WITH PRESERVED SYSTOLIC FUNCTION

- To date, there is a relative dearth of clinical trials examining effective chronic treatment strategies in this subset of patients with HF. Current therapies are mainly for symptomatic relief.
- Therapy centers on relief of volume overload with judicious diuretic use, treatment of ischemia via coronary revascularization, management of atrial fibrillation, controlling heart rate and blood pressure to prevent acute decompensation, and restriction of sodium and fluid to prevent volume overload.
- Diuretics should be used for relief of symptoms due to volume overload in patients with HFpEF.
- The use of beta-blocking agents, ACE inhibitors, and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF.
- The use of ARBs might be considered to decrease hospitalizations for patients with HFpEF.
- Omega-3 polyunsaturated fatty acid supplementation is reasonable, unless contraindicated, to reduce mortality and cardiovascular hospitalizations.
- There is no evidence to support routine use of nutritional supplements and they are not recommended for patients with HFpEF.
- Surgical options for contributing critical aortic stenosis, constrictive pericarditis, and hypertrophic cardiomyopathy (HCM) should be entertained in appropriate patients.

DISPOSITION

- Annual mortality of systolic HF ranges from 10% in stable patients with mild symptoms to 50% in patients with NYHA class IV disease (a mortality rate rivaling some malignancies). The Seattle Heart Failure Model provides an accurate estimate of 1-, 2-, and 3-year survival before and after different therapies. This model can be useful to assess the need for LV assist device implantation or urgent transplantation. The calculator is available online at http://depts.washington.edu/shfm/.
- Cardiac transplantation has a 5-yr survival rate of ~70% and represents a viable option in selected patients.
- The use of an LV assist device (LVAD) in patients with advanced HF can result in a clinically meaningful survival benefit and improve quality of life in patients who are not candidates for cardiac transplantation. There are two approved uses of LVADs specifically as a bridge to transplant and as destination therapy. There are two major categories of LVAD pulsatile flow devices vs. continuous flow devices. A recent trial (2008) has indicated that continuous flow devices are associated with increased survival as destination therapy as compared to medically managed controls. Interestingly, more recent trials (2010 and 2011) have shown there was no difference in posttransplantation survival between patients who were bridged with continuous-flow VADs vs. no VADs or even between patients bridged with pulsatile vs. continuous-flow VADs.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

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RELATED CONTENT

Congestive Heart Failure (CHF) (Patient Information)

AUTHORS: **MICHAEL RUISI, M.D.,** and **ARAVIND RAO KOKKIRALA, M.D.**

EVIDENCE

Abstract[1]

Background:
Available data suggest that improvement in left ventricular ejection fraction (LVEF) is a major predictor of improved survival in heart failure (HF). Although certain factors are associated with improvements in LVEF in select patients with HF enrolled in clinical trials, relatively little is known about such factors among patients in clinical practice. This study evaluated changes in LVEF and associated factors in outpatients with systolic HF or post-myocardial infarction with reduced LVEF during 24 months of follow-up.

Methods:
IMPROVE HF is a prospective evaluation of a practice-based performance improvement intervention implemented at outpatient cardiology/multispecialty practices to increase use of guideline-recommended care for eligible patients. Data were analyzed by patient groups based on absolute improvement in LVEF (<0%, 0–≤10%, and >10%) from baseline to 24 months and by change in LVEF as a continuous variable.

Results:
A total of 3,994 patients from 155 of 167 practices were eligible for analysis. The overall mean LVEF increased from 25.8% at baseline to 32.3% (+6.4%) at 24 months (P<.001), and 28.6% of patients had a >10% improvement in ejection fraction (from 24.5% to 46.2%, 92% relative improvement). Age, race, and practice setting were similar between the 3 LVEF improvement groups. Multivariate analysis revealed female sex, no prior myocardial infarction, nonischemic HF etiology, and no digoxin use were associated with >10% improvement in LVEF.

Conclusions:
Among patients with HF receiving care in cardiology/multispecialty practices participating in a performance measure intervention, surviving, and having repeat LVEF assessment, close to one third of patients had a >10% improvement in LVEF at 24 months. These findings indicate that HF is not always a progressive disease and that differentiation of the heterogeneous HF phenotypes may set the stage for future research and therapeutic targets. Ⓐ

Abstract[2]

Background:
Nesiritide is approved in the United States for early relief of dyspnea in patients with acute heart failure. Previous meta-analyses have raised questions regarding renal toxicity and the mortality associated with this agent.

Methods:
We randomly assigned 7141 patients who were hospitalized with acute heart failure to receive either nesiritide or placebo for 24 to 168 hours in addition to standard care. Coprimary end points were the change in dyspnea at 6 and 24 hours, as measured on a 7-point Likert scale, and the composite end point of rehospitalization for heart failure or death within 30 days.

Results:
Patients randomly assigned to nesiritide, as compared with those assigned to placebo, more frequently reported markedly or moderately improved dyspnea at 6 hours (44.5% vs. 42.1%, P=0.03) and 24 hours (68.2% vs. 66.1%, P=0.007), but the prespecified level for significance (P≤0.005 for both assessments or P≤0.0025 for either) was not met. The rate of rehospitalization for heart failure or death from any cause within 30 days was 9.4% in the nesiritide group versus 10.1% in the placebo group (absolute difference, −0.7 percentage points; 95% confidence interval [CI], −2.1 to 0.7; P=0.31). There were no significant differences in rates of death from any cause at 30 days (3.6% with nesiritide vs. 4.0% with placebo; absolute difference, −0.4 percentage points; 95% CI, −1.3 to 0.5) or rates of worsening renal function, defined by more than a 25% decrease in the estimated glomerular filtration rate (31.4% vs. 29.5%; odds ratio, 1.09; 95% CI, 0.98 to 1.21; P=0.11).

Conclusions:
Nesiritide was not associated with an increase or a decrease in the rate of death and rehospitalization and had a small, nonsignificant effect on dyspnea when used in combination with other therapies. It was not associated with a worsening of renal function, but it was associated with an increase in rates of hypotension. On the basis of these results, nesiritide cannot be recommended for routine use in the broad population of patients with acute heart failure. (Funded by Scios; ClinicalTrials.gov number, NCT00475852.) Ⓐ

Abstract[3]

Background:
This study assessed the feasibility of a 12-week program of exercise, with and without intramuscular testosterone supplementation, in male patients with chronic heart failure (CHF) and low testosterone status and collected preliminary data for key health outcomes.

Methods:
Male patients with CHF (n ¼, 41; age, 67.2 years; range, 51-84 years) with mean±SD testosterone levels of 10.7±2.6 nmol/L (309±76 ng/dL) were randomly allocated to exercise with testosterone or placebo groups. Feasibility was assessed in terms of recruitment, intervention compliance, and attrition. Outcomes included an incremental shuttle walk test, peak oxygen uptake, muscular strength, echocardiographic measures, N-terminal pro-brain natriuretic peptide, inflammatory markers, depression (Beck Depression Inventory), and health-related quality of life (Minnesota Living with Heart Failure Questionnaire and Medical Outcomes Study Short-Form).

Results:
Attrition was 30% but with 100% compliance to exercise and injections in patients who completed the study. Similar improvements in shuttle walk test (18% vs 19%), body mass (>1.3 kg vs <1.0 kg), and hand grip strength (<2.1 kg vs >2.5 kg) from baseline were observed in both groups. The exercise with testosterone group showed improvements from baseline in peak oxygen uptake (P <.01), Beck Depression Inventory (P <.05), leg strength (P <.05), and several Medical Outcomes Study Short-Form quality of life domains (P <.05), which were generally not apparent in the exercise with placebo group. Echocardiographic measures, N-terminal pro-brain natriuretic peptide, and inflammatory markers were mostly unchanged.

Conclusions:
This study shows for the first time that testosterone supplementation during a program of exercise rehabilitation is feasible and can positively impact a range of key health outcomes in elderly male patients with CHF who have a low testosterone status.

It is now generally accepted that exercise rehabilitation is helpful in patients who have stable congestive heart failure. However, several studies of such patients have found that a substantial part of their disability is caused by a weakness of the skeletal muscles, and it is thus logical to include muscle-strengthening exercises in the rehabilitation program. The practical issue when implementing such a policy is that many of the patients are elderly and lack the levels of testosterone needed for muscle hypertrophy. Stout et al. have now carried out a small-scale randomized, controlled trial of the benefits of including testosterone therapy in a 12-week exercise program for elderly patients with congestive heart failure. All had low total testosterone levels (<15 nmol/L), commonly accepted as the threshold of androgen deficiency. The exercise program was held twice per week, and it included aerobic interval training on a cycle ergometer and resistance exercise for the quadriceps, hamstrings, pectorals, latissimus dorsi, and deltoid muscles. The experimental group also received intramuscular testosterone (100 mg once per fortnight for 12 weeks). Unfortunately, experimental and control groups were not very well matched. On some tests, such as the shuttle walk, the experimental group showed no greater improvement than controls, but on other measures, including peak oxygen intake, leg strength, and mood state, gains were larger in those receiving the testosterone. Possibly, benefits would be greater with larger doses of testosterone, but this might also increase the risk of cardiovascular side effects. Further larger-scale studies seem warranted, using various doses of testosterone and continuing the supplements for longer than 12 weeks. Ⓐ

Abstract[4]

Objectives:
This study investigated the effect of a very long-term exercise training program in chronic heart failure (CHF) patients.

Background:
We previously showed that long-term moderate exercise training (ET) improves functional capacity and quality of life in New York Heart Association class II and III CHF patients.

Methods:
We studied 123 patients with CHF whose condition was stable over the previous 3 months. After randomization, a trained group (T group, n = 63) underwent supervised ET at 60% of peak oxygen consumption (Vo_2), 2 times weekly for 10 years, whereas a nontrained group (NT group, n = 60) did not exercise formally. The ET program was supervised and performed mostly at a coronary club with periodic control sessions twice yearly at the hospital's gym.

Results:
In the T group, peak Vo_2 was more than 60% of age- and gender-predicted maximum Vo_2 each year during the 10-year study (P <.05 vs. the NT group). In NT patients, peak Vo_2 decreased progressively with an average of 52±8% of maximum Vo_2 predicted. Ventilation relative to carbon dioxide output (VE/V_{CO_2}) slope was significantly lower (35±9) in T patients versus NT patients (42±11, P <.01). Quality-of-life score was significantly better in the T group versus the NT group (43±12 vs. 58±14, P <0.05). During the 10-year study, T patients had a significantly lower rate of hospital readmission (hazard ratio: 0.64, P <.001) and cardiac mortality (hazard ratio: 0.68, P <.001) than controls. Multivariate analysis selected peak Vo_2 and resting heart rate as independent predictors of events.

Conclusions:
Moderate supervised ET performed twice weekly for 10 years maintains functional capacity of more than 60% of maximum Vo_2 and confers a sustained improvement in quality of life compared with NT patients. These sustained improvements are associated with reduction in major cardiovascular events, including hospitalizations for CHF and cardiac mortality. Ⓐ

Abstract[5]

Background:
Mineralocorticoid-receptor antagonists improve the prognosis for patients with heart failure and a reduced left ventricular ejection fraction. We evaluated the effects of spironolactone in patients with heart failure and a preserved left ventricular ejection fraction.

Methods:
In this randomized, double-blind trial, we assigned 3445 patients with symptomatic heart failure and a left ventricular ejection fraction of 45% or more to receive either spironolactone (15 to 45 mg daily) or placebo. The primary outcome was a composite of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure.

Results:
With a mean follow-up of 3.3 years, the primary outcome occurred in 320 of 1722 patients in the spironolactone group (18.6%) and 351 of 1723 patients in the placebo group (20.4%) (hazard ratio, 0.89; 95% confidence interval [CI], 0.77 to 1.04; P ¼ 0.14). Of the components of the primary outcome, only hospitalization for heart failure had a significantly lower incidence in the spironolactone group than in the placebo group (206 patients [12.0%] vs. 245 patients [14.2%]; hazard ratio, 0.83; 95% CI, 0.69 to 0.99, P ¼ 0.04). Neither total deaths nor hospitalizations for any reason were significantly reduced by spironolactone. Treatment with spironolactone was associated with increased serum creatinine levels and a doubling of the rate of hyperkalemia (18.7%, vs. 9.1% in the placebo group) but reduced hypokalemia. With frequent monitoring, there were no significant differences in the incidence of serious adverse events, a serum creatinine level of 3.0 mg per deciliter (265 μmol per liter) or higher, or dialysis.

Conclusions:
In patients with heart failure and a preserved ejection fraction, treatment with spironolactone did not significantly reduce the incidence of the primary composite outcome of death from cardiovascular causes, aborted cardiac arrest, or hospitalization for the management of heart failure. (Funded by the National Heart, Lung, and Blood Institute; TOPCAT ClinicalTrials.gov number, NCT00094302.) Ⓐ

Abstract[6]

Objectives:
This study sought to characterize temporal trends in hospitalizations with heart failure as a primary or secondary diagnosis.

Background:
Heart failure patients are frequently admitted for both heart failure and other causes.

Methods:
Using the Nationwide Inpatient Sample (NIS), we evaluated trends in heart failure hospitalizations between 2001 and 2009. Hospitalizations were categorized as either primary or secondary heart failure hospitalizations based on the location of heart failure in the discharge diagnosis. National estimates were calculated using the sampling weights of the NIS. Age- and sex-standardized hospitalization rates were determined by dividing the number of hospitalizations by the U.S. population in a given year and using direct standardization.

Results:
The number of primary heart failure hospitalizations in the United States decreased from 1,137,944 in 2001 to 1,086,685 in 2009, whereas secondary heart failure hospitalizations increased from 2,753,793 to 3,158,179 over the same period. Age- and sex-adjusted rates of primary heart failure hospitalizations decreased steadily from 2001 to 2009, from 566 to 468 per 100,000 people. Rates of secondary heart failure hospitalizations initially increased from 1,370 to 1,476 per 100,000 people from 2001 to 2006, then decreased to 1,359 per 100,000 people in 2009. Common primary diagnoses for secondary heart failure hospitalizations included pulmonary disease, renal failure, and infections.

Conclusions:
Although primary heart failure hospitalizations declined, rates of hospitalizations with a secondary diagnosis of heart failure were stable in the past decade. Strategies to reduce the high burden of hospitalizations of heart failure patients should include consideration of both cardiac disease and noncardiac conditions. Ⓐ

Abstract[7]

Importance:
Small studies suggest that low-dose dopamine or low-dose nesiritide may enhance decongestion and preserve renal function in patients with acute heart failure and renal dysfunction; however, neither strategy has been rigorously tested.

Objective:
To test the 2 independent hypotheses that, compared with placebo, addition of low-dose dopamine (2 mg/kg/min) or low-dose nesiritide (0.005 mg/kg/min without bolus) to diuretic therapy will enhance decongestion and preserve renal function in patients with acute heart failure and renal dysfunction.

Design, Setting, and Participants: Multicenter, double-blind, placebo-controlled clinical trial (Renal Optimization Strategies Evaluation [ROSE]) of 360 hospitalized patients with acute heart failure and renal dysfunction (estimated glomerular filtration rate of 15-60 mL/min/1.73 m2), randomized within 24 hours of admission. Enrollment occurred from September 2010 to March 2013 across 26 sites in North America.

Interventions:
Participants were randomized in an open, 1:1 allocation ratio to the dopamine or nesiritide strategy. Within each strategy, participants were randomized in a double-blind, 2:1 ratio to active treatment or placebo. The dopamine (n ¼ 122) and nesiritide (n ¼ 119) groups were independently compared with the pooled placebo group (n ¼ 119).

Main Outcomes and Measures:
Coprimary end points included 72-hour cumulative urine volume (decongestion end point) and the change in serum cystatin C from enrollment to 72 hours (renal function endpoint).

Results:
Compared with placebo, low-dose dopamine had no significant effect on 72-hour cumulative urine volume (dopamine, 8524 mL; 95% CI, 7917-9131 vs placebo, 8296 mL; 95% CI, 7762-8830 ; difference, 229 mL; 95% CI, _714 to 1171 mL; P ¼.59) or on the change in cystatin C level (dopamine, 0.12 mg/L; 95% CI, 0.06-0.18 vs placebo, 0.11 mg/L; 95%CI, 0.06-0.16; difference, 0.01; 95%CI, _0.08 to 0.10; P ¼.72). Similarly, low-dose nesiritide had no significant effect on 72-hour cumulative urine volume (nesiritide, 8574 mL; 95% CI, 8014-9134 vs placebo, 8296 mL; 95% CI, 7762-8830; difference, 279 mL; 95% CI, _618 to 1176 mL; P ¼.49) or on the change in cystatin C level (nesiritide, 0.07 mg/L; 95% CI, 0.01-0.13 vs placebo, 0.11 mg/L; 95% CI, 0.06-0.16; difference, _0.04; 95% CI, _0.13 to 0.05; P ¼.36). Compared with placebo, there was no effect of low-dose dopamine or nesiritide on secondary end points reflective of decongestion, renal function, or clinical outcomes.
Conclusion and Relevance:
In participants with acute heart failure and renal dysfunction, neither low-dose dopamine nor low-dose nesiritide enhanced decongestion or improved renal function when added to diuretic therapy.
Trial Registration.dclinicaltrials.gov Identifier: NCT01132846. Ⓐ

Evidence-Based References

Wilcox JE et al.: Factors associated with improvement in ejection fraction in clinical practice among patients with heart failure: findings from IMPROVE HF, *Am Heart J* 163:49–56, 2012. e2 Ⓐ

O'Connor CM et al.: Effect of nesiritide in patients with acute decompensated heart failure, *N Engl J Med* 365:32–43, 2011. Ⓐ

Stout M et al.: Testosterone therapy during exercise rehabilitation in male patients with chronic heart failure who have low testosterone status: a double-blind randomized controlled feasibility study, *Am Heart J* 164:893–901, 2012. Ⓐ

Belardinelli R et al.: Ten-year exercise training in chronic heart failure: a randomized controlled trial, *J Am Coll Cardiol* 60:1521–1528, 2012. Ⓐ

Pitt B: for the TOPCAT Investigators Spironolactone for Heart Failure with Preserved Ejection Fraction, *N Engl J Med* 370:1383–1392, 2014. Ⓐ

Blecker S, Paul M, Taksler G, et al.: Heart Failure-Associated Hospitalizations in the United States, *J Am Coll Cardiol* 61:1259–1267, 2013. Ⓐ

Chen HH: for the NHLBI Heart Failure Clinical Research Network: Low-Dose Dopamine or Low-Dose Nesiritide in Acute Heart Failure With Renal Dysfunction: The ROSE Acute Heart Failure Randomized Trial, *JAMA* 310:2533–2543, 2013. Ⓐ

SUGGESTED READINGS

Arnold JM et al.: Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: diagnosis and management, *Can J Cardiol* 22:23, 2006.

Aurigemma GP et al.: Diastolic heart failure, *N Engl J Med* 351:1097–1105, 2004.

Chen HH, et al.: Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction, the Rose Acute Heart Failure Randomized Trial, *JAMA* 310(23):2533–2543, 2013.

Dickstein K et al.: ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESCIM), *Eur Heart J* 29:2388, 2008.

DiNicolantonio JJ et al.: Low sodium versus normal sodium diets in systolic heart failure: systematic review and meta-analysis, *Heart*, 2013 Mar 12. [Epub ahead of print].

Executive summary: HFSA 2006 comprehensive heart failure practice guideline, *J Card Fail* 12:10, 2006.

Felker GM et al.: Diuretic strategies in patients with acute decompensated heart failure, *N Engl J Med* 364:797–805, 2011.

Geraci SA et al.: Office management of chronic systolic heart failure, *Am J Med* 122:239–332, 2008.

Gheorghiade M, Pang PS: Acute heart failure syndromes, *J Am Coll Cardiol* 53:557, 2009.

Heart Failure Society of America et al.: HFSA 2010 Comprehensive Heart Failure Practice Guideline, *J Card Fail* 16:e1–e194, 2010.

Hunt SA et al.: 2009 Focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation, *Circulation* 119:e391, 2009.

John R et al.: Post-cardiac transplant survival after support with a continuous-flow left ventricular assist device: impact of duration of left ventricular assist device support and other variables, *J Thorac Cardiovasc Surg* 140(1):174–181, 2011.

Jondeau G et al.: B-CONVINCED: beta-blocker continuation vs. interruption in patients with congestive heart failure hospitalized for a decompensation episode, *Eur Heart* J30:2186–2192, 2009.

McKelvie RS et al.: Effects of exercise training in patients with heart failure: the Exercise Rehabilitation Trial (EXERT), *Am Heart J* 144(1):23–30, 2002.

McMurray JJ et al.: Angiotensin-Neprilysin inhibition versus enalapril in heart failure, *N Engl J Med* 371:993–1004, 2014.

McMurray JJ: Systolic heart failure, *N Engl J Med* 362(3):228–238, 2010.

McMurray J, Swedber K: Treatment of chronic heart failure: a comparison between the major guidelines, *Eur Heart J* 27:1773, 2006.

Nativi JN et al.: Changing outcomes in patients bridged to heart transplantation with continuous- versus pulsatile-flow ventricular assist devices: an analysis of the registry of the International Society for Heart and Lung Transplantation, *J Heart Lung Transplant* 30(8):854–861, 2011.

Nohria A et al.: Medical management of advanced heart failure, *JAMA* 6(5):628–640, 2002. 287.

O'Connor CM et al.: Effect of nesiritide in patients with acute decompensated heart failure, *N Engl J Med* 365:32, 2011.

Piepoli MF et al.: Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH), *BMJ* 328(7433):189, 2004.

Qaseem A et al.: Treatment of anemia in patients with heart disease: a clinical practice guideline from the American College of Physicians, *Ann Int Med* 159:770–779, 2013.

Roger VL et al.: Heart disease and stroke statistics—2012 update. A report from the American Heart Association, *Circulation* 125(1):188–197, 2012.

Ruschitzka F et al.: Cardiac resynchronization therapy in heart failure with a narrow QRS complex, *N Engl J Med* 369:1395–1405, 2013.

Slaughter MS et al.: Advanced heart failure treated with continuous-flow left ventricular assist device, *N Engl J Med* 361:2241–2251, 2009.

Swedberg K et al.: Treatment of anemia with darbepoetin alfa in systolic heart failure, *N Engl J Med* 368:1210–1219, 2013.

Ware LB et al.: Clinical practice. Acute pulmonary edema, *N Engl J Med* 353:2788, 2005.

Yancy CW et al.: 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, *J Am Coll Cardiol* 62(16):e147–e239, 2013.

Zannad F et al.: Eplerenone in patients with systolic heart failure and mild symptoms, *N Engl J Med* 364:11–21, 2011.

BASIC INFORMATION

DEFINITION

Heat exhaustion and heat stroke are part of a continuum of heat-related illness, and unless factors leading to heat exhaustion are corrected swiftly, affected patients can progress to heat stroke.

- ***Heat exhaustion:*** an illness resulting from prolonged, heavy activity in a hot environment with subsequent dehydration, electrolyte depletion, and rectal temperature >37.8° C but ≤40° C.
- ***Heat stroke:*** a life-threatening heat illness characterized by extreme hyperthermia, dehydration, and neurologic manifestations (core temperature >40° C).

SYNONYMS

Heat illness
Hyperthermia

ICD-9CM CODES
992.0 Heat stroke
992.5 Heat exhaustion
ICD-10CM CODES
T67.5 Heat exhaustion, unspecified
T67.0 Heatstroke and sunstroke
T67.1 Heat syncope
T67.2 Heat cramp
T67.3 Heat exhaustion, anhydrotic
T67.6 Heat fatigue, transient

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Incidence of heat stroke is approximately 20 cases/100,000 population.
PREDOMINANT AGE: Heat exhaustion and stroke occur more frequently in elderly patients, especially those taking diuretics or medications that impair heat dissipation (e.g., phenothiazines, anticholinergics, antihistamines, beta-blockers). Table H1-5 describes factors predisposing to serious heat illness.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Heat exhaustion:

- Generalized malaise, weakness, headache, muscle and abdominal cramps, nausea, vomiting, hypotension, tachycardia.
- Rectal temperature is usually normal.
- Sweating is usually present.

Heat stroke:

- Neurologic manifestations (seizures, tremor, hemiplegia, coma, psychosis, other bizarre behavior).
- Evidence of dehydration (poor skin turgor, sunken eyeballs).
- Tachycardia, hyperventilation.
- Skin is hot, red, and flushed.
- Sweating is often (not always) absent, particularly in elderly patients.
- Classic heat stroke generally develops slowly over days and occurs predominantly in older persons and in those with chronic illness. Exertional heat stroke is more common in young, healthy persons, has a more rapid onset, and is associated with higher core temperatures. Table H1-6 compares classic and exertional heat stroke. Box H1-2 summarizes organ dysfunction seen in patients with heat stroke.

ETIOLOGY

- Exogenous heat gain (increased ambient temperature).
- Increased heat production (exercise, infection, hyperthyroidism, drugs).
- Impaired heat dissipation (high humidity, heavy clothing, neonatal or elderly patients, drugs [phenothiazines, anticholinergics, antihistamines, butyrophenones, amphetamines, cocaine, alcohol, β-blockers]).
- Diuretics, laxatives.
- Fig. EH1-13 describes an algorithm of the pathophysiology of heat stroke.

TABLE H1-5 Factors Predisposing to Serious Heat Illness

Individual Factors
Lack of acclimatization
Low physical fitness
Excessive body weight
Dehydration
Advanced age
Young age
Health Conditions
Inflammation and fever
Viral infection
Cardiovascular disease
Diabetes mellitus
Gastroenteritis
Rash, sunburn, and previous burns to large areas of skin
Seizures
Thyroid storm
Neuroleptic malignant syndrome
Malignant hyperthermia
Sickle cell trait
Cystic fibrosis
Spinal cord injury
Drugs
Anticholinergic properties (atropine)
Antiepileptic (topiramate)
Antihistamines
Glutethimide (Doriden)
Phenothiazines
Tricyclic antidepressants
Amphetamines, cocaine, "Ecstasy"
Ergogenic stimulants (e.g., ephedrine, ephedra)
Lithium
Diuretics
β-Blockers
Ethanol
Environmental Factors
High temperature
High humidity
Little air motion
Lack of shade
Heat wave
Physical exercise
Heavy clothing
Air pollution (nitrogen dioxide)

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infections (meningitis, encephalitis, sepsis).
- Head trauma.
- Epilepsy.
- Thyroid storm.
- Acute cocaine intoxication.
- Malignant hyperthermia.
- Heat exhaustion can be differentiated from heat stroke by the following:
  1. Essentially intact mental function and lack of significant fever in heat exhaustion.
  2. Mild or absent increases in creatine phosphokinase (CPK), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and alanine aminotransferase (ALT) in heat exhaustion.

WORKUP

- Heat stroke: comprehensive history, physical examination, and laboratory evaluation.
- Heat exhaustion: in most cases, laboratory tests are not necessary for diagnosis.

LABORATORY TESTS

Laboratory abnormalities may include the following:

- Elevated BUN, creatinine, hematocrit.
- Hyponatremia or hypernatremia, hyperkalemia or hypokalemia.
- Elevated LDH, AST, ALT, CPK, bilirubin.
- Lactic acidosis, respiratory alkalosis (from hyperventilation).
- Myoglobinuria, hypofibrinogenemia, fibrinolysis, hypocalcemia.

TREATMENT

- Treatment of heat exhaustion consists primarily of placing the patient in a cool, shaded area and providing rapid hydration and salt replacement.
  1. Fluid intake should be at least 2 L q4h in patients without history of CHF.
  2. Salt replacement can be accomplished by using one-quarter teaspoon of salt or two 10-grain salt tablets dissolved in 1 L of water.

BOX H1-2 Organ Dysfunction Seen in Patients with Heat Stroke

Encephalopathy
Rhabdomyolysis
Acute renal failure
Acute respiratory distress syndrome
Myocardial injury
Hepatocellular injury
Intestinal ischemia and infarction
Pancreatic injury
Hemorrhagic complication (e.g., disseminated intravascular coagulation)

From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

3. If IV fluid replacement is necessary, young athletes can be given normal saline IV (3 to 4 L over 6 to 8 hr); in elderly patients, consider using D5½NS IV with the rate titrated to cardiovascular status.

- Patients with heat stroke should undergo rapid cooling.
  1. Remove the patient's clothes and place the patient in a cool and well-ventilated room.
  2. If patient is unconscious, position on his or her side and clear the airway. Protect airway and augment oxygenation (e.g., nasal O_2 at 4 L/min to keep oxygen saturation >90%).
  3. Monitor body temperature every 5 min. Measurement of the patient's core temperature with a rectal probe is recommended. The goal is to reduce the body temperature to 39° C (102.2° F) in 30 to 60 min. Advantages, disadvantages, and efficacy of various cooling methods are described in Table EH1-7.
  4. Spray the patient with a cool mist and use fans to enhance airflow over the body (rapid evaporation method).
  5. Immersion of the patient in ice water, stomach lavage with iced saline solution, intravenous administration of cooled fluids, and inhalation of cold air are advisable only when the means for rapid evaporation are not available. Immersion in tepid water (15° C, 59° F) is preferred over ice water immersion to minimize risk of shivering.
  6. Use of ice packs on axillae, neck, and groin is controversial because they increase peripheral vasoconstriction and may induce shivering.
  7. Antipyretics are ineffective because the hypothalamic set point during heat stroke is normal despite the increased body temperature.
  8. Intubate a comatose patient, insert a Foley catheter, and start nasal O_2. Continuous ECG monitoring is recommended.
  9. Insert at least two large-bore IV lines and begin IV hydration with NS or Ringer's lactate.
  10. Draw initial laboratory studies: electrolytes, complete blood count, blood urea nitrogen, creatinine, AST, ALT, CPK, LDH, glucose, PT (INR), PTT, platelet count, Ca^{2+}, lactic acid, and arterial blood gases.
  11. Treat complications as follows:
      a. Hypotension: vigorous hydration with normal saline or Ringer's lactate.
      b. Convulsions: diazepam 5 to 10 mg IV (slowly).
      c. Shivering: chlorpromazine 10 to 50 mg IV.
      d. Acidosis: use bicarbonate judiciously (only in severe acidosis).
- Observe for evidence of rhabdomyolysis and hepatic, renal, or cardiac failure and treat accordingly.

TABLE H1-6 Comparison of Classic and Exertional Heat Stroke

Patient Characteristics	Classic	Exertional
Age	Young children or elderly	15-55 yr
Health	Chronic illness	Usually healthy
Fever	Unusual	Common
Prevailing weather	Frequent in heat waves	Variable
Activity	Sedentary	Strenuous exercise
Drug use	Diuretics, antidepressants, anticholinergics, phenothiazines	Ergogenic stimulants or cocaine
Sweating	Often absent	Common
Acid-base disturbances	Respiratory alkalosis	Lactic acidosis
Acute renal failure	Uncommon	Common (≈15%)
Rhabdomyolysis	Uncommon	Common (≈25%)
CK	Mildly elevated	Markedly elevated (500-1000 U/L)
ALT, AST	Mildly elevated	Markedly elevated
Hyperkalemia	Uncommon	Common
Hypocalcemia	Uncommon	Common
DIC	Mild	Marked
Hypoglycemia	Uncommon	Common

ALT, Alanine aminotransferase; *AST,* aspartate aminotransferase; *CK,* creatine kinase; *DIC,* disseminated intravascular coagulation.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

DISPOSITION

Most patients recover completely within 48 hr. Central nervous system injury is permanent in 20% of cases. Mortality rate can exceed 30% in patients with prolonged and severe hyperthermia. Delayed access to cooling is the leading cause of morbidity and mortality in persons with heat stroke.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Heat Exhaustion and Heat Stroke (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Becker J, Stewart LK: Heat-related illness, *Am Fam Physician* 83(11):1325–1330, 2011.

Centers for Disease Control and Prevention: Heat illness among high school athletes, U.S. 2005-2009, *MMWR Morb Mort Wkly Rep* 59(32), 2010.

Glazer JL: Management of heat stroke and exhaustion, *Am Fam Physician* 71:2133, 2005.

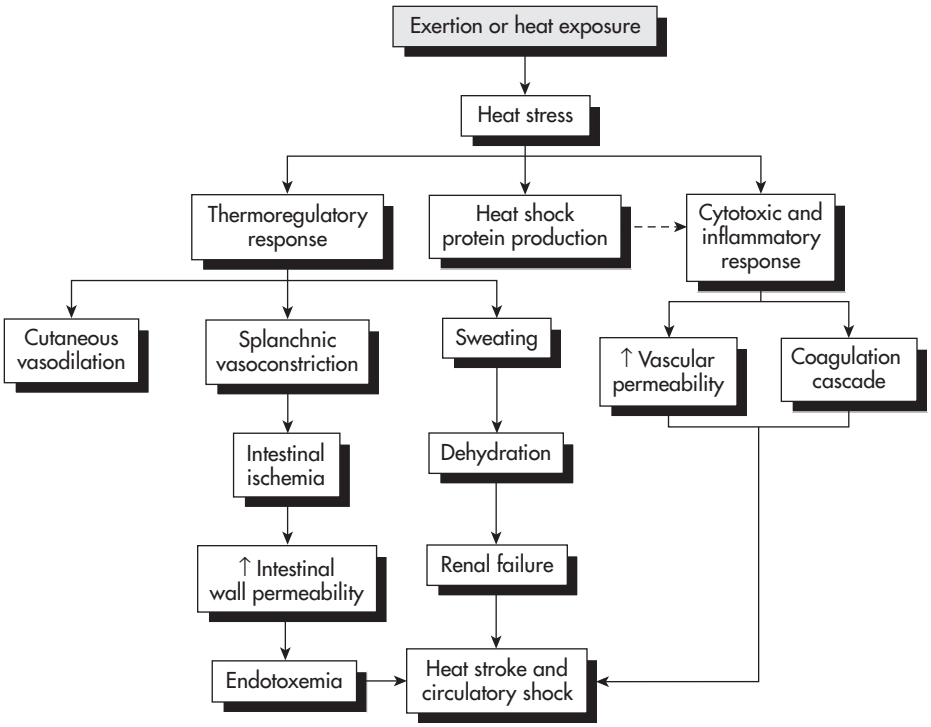

FIGURE EH1-13 Algorithm of the pathophysiology of heat stroke. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

TABLE EH1-7 Advantages, Disadvantages, and Efficacy of Various Cooling Methods

Cooling Method	Advantages	Disadvantages	Effectiveness
Antipyretics		Can worsen liver or renal injury	Not effective (the temperature set-point is not elevated in hyperthermia) Not effective in controlling pathologic inflammation
Evaporative cooling	Noninvasive, easy to monitor, readily available	Labor-intensive—requires constant moistening of skin	Comparison studies show the cooling rate on average to be slower than immersion Published rate range: 0.05-0.31° C/min
Immersion	Noninvasive, rapid	Cumbersome, poorly tolerated, safety questionable if comorbid conditions present, monitoring difficult, shivering and vasoconstriction	Comparison studies show the cooling rate on average to be faster than evaporation Published rate range: 0.04-0.35° C/min
Immersion of the hands and forearms	Noninvasive, easy to perform in the field	Shivering and vasoconstriction	Slower cooling but appropriate for mildly ill patients such as those with heat exhaustion
Ice packing	Noninvasive, readily available	Shivering and vasoconstriction, poorly tolerated	Less effective than immersion or evaporation Some authorities recommend using both evaporation and ice
Cold gastric or peritoneal lavage	Very rapid	Invasive, cumbersome (cold sterile saline needed for peritoneal lavage)	In canine studies, questionably faster than evaporation or immersion
Dantrolene	In theory, decreases heat production by inhibiting muscle contraction		No clear efficacy; it may be more effective for exertional than for classic heat stroke
Benzodiazepines	Treatment of shivering to decrease heat production and heat-induced seizures	Sedation	Whether treatment increases cooling is unknown but may make cooling treatments tolerable Also effective for heat-related seizures

From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

BASIC INFORMATION

DEFINITION

Infection of the human gastric mucosa with the organism *Helicobacter pylori,* a spiral-shaped gram-negative organism with unique features that allow it to survive in the hostile gastric environment.

SYNONYMS

Previously known as *Campylobacter pylori*

ICD-9CM CODES
041.86 *Helicobacter pylori (H. pylori)*
ICD-10CM CODES
B96.81 *Helicobacter pylori (H. pylori)* as the cause of diseases classified elsewhere

EPIDEMIOLOGY & DEMOGRAPHICS

H. pylori is the most common chronic bacterial infection in human beings, probably affecting 50% of the earth's population in all age groups and probably 30% to 40% of the U.S. population. In developing nations, infection is acquired at an earlier age and occurs more frequently.

CLINICAL PRESENTATION

- *H. pylori* causes histologic gastritis in all affected individuals. The majority of cases are asymptomatic and unlikely to proceed to serious consequences.
- *H. pylori* is a causative agent in peptic ulcer disease (PUD), gastric adenocarcinoma, and gastric mucosa-associated lymphoid tissue lymphoma, and may be a risk factor for iron-deficiency anemia and chronic idiopathic thrombocytopenic purpura. It may present with the signs and symptoms of these disorders, including abdominal pain, bloating, anorexia, and early satiety. Fig. H1-14 describes association of *H. pylori* infection and disease states.
- "Alarm symptoms" that should prompt more immediate and aggressive workup include weight loss, dysphagia, protracted nausea or vomiting, anemia, melena, and palpable abdominal mass.

ETIOLOGY

- Route of acquisition is unknown but is presumed to be person to person by oral-oral or fecal-oral exposure.
- The majority of cases are acquired in childhood. Socioeconomic status and living conditions in childhood affect risk of acquisition of infection. These factors include housing density, number of siblings, overcrowding, sharing a bed, and lack of running water.
- *H. pylori* does not invade gastroduodenal tissue, but disrupts the mucous layer, causing the underlying mucosa to be more vulnerable to acid peptic damage.
- What differentiates the subset of patients with *H. pylori* who go on to develop ulcers or cancer remains unclear.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infection with *H. pylori* should be considered in the face of PUD, gastric cancer, gastritis, and gastric MALT lymphoma.
- *H. pylori* should be considered in the differential diagnosis of upper gastrointestinal (GI) tract disease, along with non-ulcer dyspepsia, reflux esophagitis, biliary tract disease, gastroparesis, pancreatitis, and ischemic bowel.

WORKUP

- Workup is indicated in patients with active PUD, a past history of documented peptic ulcer, or gastric MALT lymphoma. The role of routine screening in high-risk populations is not clear. However, numerous studies suggest that *H. pylori* eradication is protective against progression of premalignant lesions. Consider testing for *H. pylori* in patients with idiopathic thrombocytopenic purpura, with otherwise unexplained iron deficiency anemia or unexplained B12 deficiency. Consider a test-and-treat approach in asymptomatic first-degree relatives of gastric cancer patients.
- Routine identification and treatment of *H. pylori* in cases of non-ulcer dyspepsia, gastroesophageal reflux disease (GERD), nonsteroidal antiinflammatory drug (NSAID) use, and in asymptomatic individuals in populations at high risk for gastric cancer is considered controversial, although it may be indicated in specific cases. A test-and-treat strategy may be used in patients younger than 55 with uncomplicated dyspepsia who have no alarm symptoms.
- Results of testing must be interpreted in relation to the individual patient's likelihood of *H. pylori* infection based on demographic risk factors. In the U.S. population, increased probability of infection exists in African Americans, Hispanics/Latinos, immigrants from developing nations, patients with poor socioeconomic status, Native Americans from Alaska, and persons >50 yr.
- Routine screening for *H. pylori* is not indicated in asymptomatic patients who are at low risk of infection.
- Infected patients with functional dyspepsia often benefit from treatment and should be evaluated for *H. pylori.*

LABORATORY TESTS

- Testing may be invasive or noninvasive depending on the need for endoscopy for other indications. There is no indication for endoscopy solely to diagnose *H. pylori.*
- Tests for *H. pylori* are differentiated as active or passive. Active tests provide direct evidence that *H. pylori* infection is currently present and include urea breath testing and stool antigen testing. Passive testing, which includes all serologic testing for *H. pylori,* gives indirect evidence of its presence by detecting the presence of antibodies to the organism. Serologic testing is limited by its inability to distinguish between active current infection and prior infection that has resolved.
- Tests that use urease as a marker (urea breath and stool antigen tests and biopsy for urease activity) may result in false-negative results in patients taking antibiotics, bismuth, or antisecretory therapy, as well as those with active ulcer bleeding. Patients should be off antibiotics for 4 wk and off protein pump

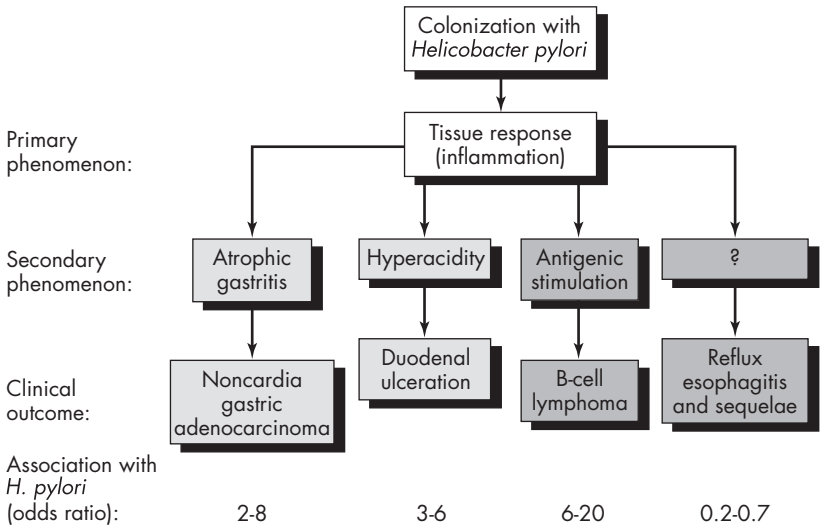

FIGURE H1-14 Association of *Helicobacter pylori* colonization and disease states. After *H. pylori* acquisition, virtually all persons develop persistent colonization that lasts for life. Colonization induces tissue responses termed *chronic gastritis.* This process affects gastric physiology, including glandular structure, acid secretion, and antigen processing, which in turn affect disease risk. Colonization with *H. pylori* increases the risk for certain diseases (duodenal ulcer, gastric ulcer, noncardia gastric adenocarcinoma, and B-cell lymphomas) but appears to decrease the risk for gastroesophageal reflux disease and its complications, including Barrett's esophagus, and adenocarcinoma of the esophagus or gastric cardia. (From Mandell GL et al: *Principles and practice of infectious diseases,* ed 7, Philadelphia, 2010, Churchill Livingstone.)

inhibitors for 2 wk before urea breath or stool antigen testing.
- When diagnostic endoscopy is indicated (for suspicion or follow-up of PUD or gastric MALT), antral biopsy should be tested for urease activity. If urease testing is likely to show a false-negative result because of recent proton pump inhibitor (PPI), bismuth, or antibiotic use or active ulcer bleeding, the sample should undergo histologic examination.
- In cases in which biopsy is not indicated, urea breath testing or stool antigen testing is indicated to evaluate for active infection. The sensitivities and specificities of these two tests are similar (>90%). Urea breath testing is slightly more expensive than stool antigen testing, but both costs are in the modest range. Choice can be made based on patient preference and availability.
- In cases in which biopsy is not indicated, consider using serologic testing as the initial approach. However, in individuals with a low pretest probability of infection, positive results should be confirmed with another testing method.

Rx TREATMENT

ACUTE GENERAL Rx

- Test only patients whom you intend to treat if positive (see "Workup" above). At this time, the value of eradicating *H. pylori* infection is proven in patients with PUD or gastric MALT lymphoma.
- The optimal antibiotic regimen has not been defined. In addition to efficacy, side effects, cost, and ease of administration must be considered.
- Due to increasing resistance to clarithromycin, decisions regarding appropriate regimens should take into account local rates of clarithromycin resistance.
- The following regimens may be considered for first-line therapy:
  1. PPI twice daily, with twice-daily clarithromycin (500 mg) and amoxicillin (1 g) may be used in areas of low clarithromycin resistance.
  2. In cases of penicillin allergy, metronidazole (500 mg bid) may be substituted for amoxicillin.
  3. PPI twice daily, combined with bismuth four times daily, as well as tetracycline (500 mg qid) and metronidazole (250 mg) four times daily, is now recommended as first-line therapy in areas of high clarithromycin resistance. Sequential therapy, consisting of 5 days of treatment with a PPI and one antibiotic (usually amoxicillin) followed by 5-day treatment with the PPI and two other antibiotics (usually clarithromycin and metronidazole), may be used in areas of high clarithromycin resistance when bismuth-based therapy is not available.
- Duration of treatment remains controversial. Extending therapy to 10 to 14 days may improve eradication rates. Use of combination capsules may improve compliance but is likely to be more expensive.
- Prior exposure to a macrolide or metronidazole, for any reason, is associated with increased resistance. A preferable regimen would include medications to which the patient has not been previously exposed.
- Diarrhea and abdominal cramping are commonly observed with many of the regimens. (Probiotics may diminish this effect.) Other side effects may include a metallic taste with metronidazole or clarithromycin, neuropathy, seizures, and disulfiram-like reaction with metronidazole, diarrhea with amoxicillin, photosensitivity with tetracycline, and *Clostridium difficile* infection with any antibiotic exposure. Bismuth may cause black stool and constipation. Tetracycline is contraindicated in pregnant patients.
- 20% of patients may not respond to initial therapy. Optimal retreatment regimens are under investigation. It is important to reinforce compliance. Second-line therapy should be either bismuth-containing quadruple therapy or levofloxacin containing triple therapy (regardless of local clarithromycin resistance patterns). When possible, management of those who do not respond to two courses of therapy should be guided by antimicrobial sensitivity testing.

CHRONIC Rx

- Accepted indications for confirming eradication include *H. pylori*–associated ulcers, MALT lymphoma, and early gastric cancer. It may be considered in those with persistent dyspepsia despite a test-and-treat management strategy (as well as consideration of other causes for the dyspeptic symptoms). Given the increasing prevalence of antibiotic resistance and the decreasing cost of testing, consider confirming eradication of *H. pylori* in all treated patients.
- Serology does not reliably revert to undetectable levels after treatment and should not be used to determine eradication.
- Active tests (urea breath test and stool antigen testing) are preferable. They are equally accurate in confirming eradication, and either may be used depending on availability and patient preference. To reduce the likelihood of false-negative results, testing should be performed at least 4 wk after eradication therapy with PPI and antibiotics or at least 2 wk after the cessation of PPI therapy alone.

DISPOSITION

Consider further evaluation in patients with recurrent symptoms after appropriate treatment.

REFERRAL

- Patients with gastric MALT lymphoma should be followed by a gastroenterologist and oncologist with expertise in the care of lymphoid neoplasms.
- Patients with dyspepsia who have tested positive for *H. pylori* and been treated without resolution should be referred for endoscopy.
- Consider referral for biopsy for culture and sensitivity in patients who have not responded to two attempts at treatment.

PEARLS & CONSIDERATIONS

- Whether *H. pylori* eradication reduces the risk of gastric cancer is unclear.
- Outcomes in PUD and gastric MALT lymphoma are improved with treatment of associated *H. pylori* infection.
- Tests that provide direct evidence of active *H. pylori* infection (urea breath and stool antigen testing) are preferred but may result in false-negative results in patients taking antibiotics, bismuth, or antisecretory agents.
- Serologic testing does not differentiate active from prior infection. It may be useful when active tests are not indicated, particularly in high-risk patients.
- Be aware of high-risk populations in low-prevalence settings, including immigrants from Mexico, South America, Southeast Asia, and Eastern Europe.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Helicobacter pylori Infection (Patient Information)
Gastritis (Related Key Topic)
Peptic Ulcer (Related Key Topic)

AUTHOR: **MARGARET TRYFOROS, M.D.**

SUGGESTED READINGS

Chey W, Wong B: American College of Gastroenterology guideline on the management of *Helicobacter pylori* infection, *Am J Gastroenterol* 102:1808, 2007.

Fuccio L et al.: Meta-analysis: duration of first-line proton pump inhibitor-based triple therapy for *Helicobacter pylori* eradication, *Ann Intern Med* 147:553–562, 2008.

Jafri N et al.: Meta-analysis: sequential therapy appears superior to standard therapy for *Helicobacter pylori* infection in patients naïve to treatment, *Ann Intern Med* 148:923–931, 2008.

Malfertheiner P et al.: for the European Helicobacter Study Group. Management of *Helicobacter pylori* infection—the Maastricht IV/Florence Consensus Report, *Gut* 61(5):646–664, 2012.

McColl KEL: *Helicobacter pylori* infection, *N Engl J Med* 362:1597–1604, 2010.

BASIC INFORMATION

DEFINITION

The HELLP syndrome is a serious variant of preeclampsia. HELLP is an acronym for ***h***emolysis, ***e***levated ***l***iver function, and ***l***ow ***p***latelet count. It is the most frequently encountered microangiopathy of pregnancy. There are three classes of the syndrome based on the degree of maternal thrombocytopenia as a primary indicator of disease severity:

Class 1: Platelets ≤50,000/mm^3
Class 2: Platelets >50,000/mm^3 to 100,000/mm^3
Class 3: Platelets >100,000/mm^3

SYNONYMS

Hemolysis
Elevated liver function
Low platelet syndrome

ICD-9CM CODES
642.50 HELLP, episode of care
642.51 HELLP, delivered
642.52 HELLP, delivered with postpartum complications
642.53 HELLP, antepartum complications
642.54 HELLP, postpartum complications
ICD-10CM CODES
014.2 HELLP syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- Among women with severe preeclampsia, 6% will manifest with one abnormality suggestive of HELLP syndrome, 12% will develop two abnormalities, and approximately 10% will develop all three.
- The HELLP syndrome, like preeclampsia, is rare before 20 wk of gestation.
- One third of all cases occur postpartum; of these, only 80% are typically diagnosed with preeclampsia before delivery.

RISK FACTORS: Women >35 yr, white, multiparity
RECURRENCE RATE: 3% to 25%

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Definitive laboratory criteria remain to be validated prospectively.
- Most commonly used criteria include hemolysis defined by the presence of an abnormal peripheral smear with schistocytes, lactate dehydrogenase (LDH) >600 U/L, and total bilirubin >1.2 mg/dl; elevated liver enzymes as serum aspartate aminotransferase (AST) >70 U/L and LDH >600 U/L; low platelet count as less than 100,000/mm^3.
- Although many women with HELLP syndrome are asymptomatic, 80% report right upper quadrant pain and 50% to 60% present with excessive weight gain and worsening edema.

ETIOLOGY

As with other microangiopathies, endothelial dysfunction, with resultant activation of the intravascular coagulation cascade, has been proposed as the central pathogenesis of HELLP syndrome.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Appendicitis
- Gallbladder disease
- Peptic ulcer disease
- Enteritis
- Hepatitis
- Pyelonephritis
- Systemic lupus erythematosus
- Thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome
- Acute fatty liver of pregnancy
- Box H1-3 summarizes medical and surgical disorders often confused with HELLP syndrome

WORKUP

Because HELLP syndrome is a disease entity based on laboratory values, initial assessment is detailed below.

LABORATORY TESTS

- Initial assessment of suspected HELLP syndrome should include a complete blood count to evaluate platelets, urinalysis, serum creatinine, LDH, uric acid, indirect and total bilirubin levels, and AST/alanine aminotransferase (ALT).
- Tests of prothrombin time, partial thromboplastin time, fibrinogen, and fibrin split products are reserved for women with a platelet count well below 100,000/mm^3.

IMAGING STUDIES

No imaging modalities aid in diagnosis.

TREATMENT

Treatment depends on gestational age of the fetus, severity of condition, and maternal status. Stabilization of the mother is the first priority. Fig. H1-15 describes an algorithm for the management of HELLP syndrome.

ACUTE GENERAL Rx

- Assess gestational age thoroughly. Fetal status should be monitored with nonstress tests, contraction stress tests, and/or biophysical profile.
- Maternal status should be evaluated by history, physical examination, and laboratory testing.
- Magnesium sulfate is administered for seizure prophylaxis regardless of blood pressure.

BOX H1-3 Medical and Surgical Disorders Often Confused With HELLP Syndrome

- Acute fatty liver of pregnancy
- Appendicitis
- Gallbladder disease
- Glomerulonephritis
- Hemolytic uremic syndrome
- Hepatic encephalopathy
- Hyperemesis gravidarum
- Idiopathic thrombocytopenia
- Pyelonephritis
- Systemic lupus erythematosus
- Antiphospholipid antibody syndrome
- Thrombotic thrombocytopenic purpura
- Viral hepatitis
- HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome

(From Gabbe SG: *Obstetrics*, 6th ed, Philadelphia, 2012, Saunders,.)

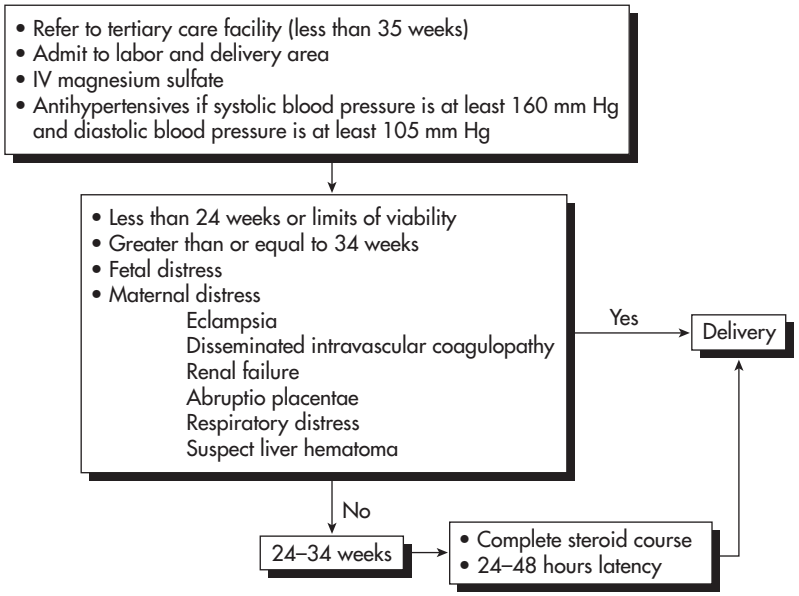

FIGURE H1-15 An algorithm for the management of HELLP syndrome. (From Gabbe SG: *Obstetrics*, 6th ed, Philadelphia, 2012, Saunders.)

- Blood pressure control is achieved with agents such as hydralazine or labetalol.
- Indwelling Foley catheter to monitor maternal volume status and urine output.

CHRONIC Rx

- In pregnancies of 34 wk or with class 1 HELLP syndrome, delivery, either vaginal or abdominal, within 24 hr is the goal.
- In the preterm fetus corticosteroid therapy to enhance fetal lung maturation is indicated.
- Some reports have shown temporary amelioration of HELLP severity with the administration of high-dose steroids measured by increased urine output, improvement in platelet count, and liver function test. However, a 2010 Cochrane review found no benefit of steroids in improving the clinical outcome.
- Judicious use of blood products, especially in those requiring surgery.
- The patient requires intensive observation for 48 hr postpartum; laboratory levels should begin to improve during this time.

DISPOSITION

The natural history of this disorder is a rapidly deteriorating condition requiring close monitoring of maternal and fetal well-being.

REFERRAL

Preterm patients with HELLP syndrome should be stabilized hemodynamically and transferred to a tertiary care center. Term patients can be treated at a local hospital depending on the availability of obstetric, neonatal, and blood banking services.

PEARLS & CONSIDERATIONS

- Not all women with HELLP have hypertension or proteinuria.
- Life-threatening hemorrhage is a rare event in HELLP syndrome. Identifiable risk factors predictive of a major hemorrhage are thrombocytopenia (<100,000/mm^3), AST >70 IU/L, and previous gestations.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Eclampsia (Related Key Topic)
Preeclampsia (Related Key Topic)

AUTHORS: **SONYA S. ABDEL-RAZEQ, M.D.,** and **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Kulungowski AM et al.: Hemolysis, elevated liver enzymes, and low platelets syndrome: when is surgical help needed? *Am J Surg* 198:916–920, 2009.

Norwitz ER et al.: Acute complications of preeclampsia, *Clin Obstet Gynecol* 45(2):308, 2002.

Woudstra DM, Chandra S, Hofmeyr GJ, Dowswell T: Corticosteroids for HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome in pregnancy, *Cochrane Database Syst Rev* 9:CD008148, 2010, http://dx.doi.org/10.1002/14651858.CD008148.pub2. PMID 20824872.

BASIC INFORMATION

DEFINITION

Hemochromatosis is an autosomal-recessive disorder that disrupts the body's regulation of iron and is characterized by increased accumulation of iron in various organs (adrenals, liver, pancreas, heart, testes, kidneys, pituitary) and eventual dysfunction of these organs if not treated appropriately.

SYNONYMS

Bronze diabetes

ICD-9CM CODES
275.0 Hemochromatosis
ICD-10CM CODES
E83.119 Hemochromatosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: In whites, approximately 1 in 385 persons.

PREDOMINANT SEX AND AGE

Generally diagnosed in males in their fifth decade. Diagnosis in females is generally not made until 10 to 20 yr after menopause.

GENETICS

Most common genetic disorder in North European ancestry. Homozygosity for the *C282Y* mutation is now found in approximately 5 of every 1000 persons of European descent.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- In earlier stages patients completely asymptomatic and diagnosed due to abnormal laboratory tests.
- Hepatic dysfunction leading to hepatomegaly, fibrosis, and eventually cirrhosis.
- Arthritis.
- Gonadal insufficiency leading to loss of libido and testicular atrophy.
- Diabetes mellitus: risk greater in patients with family history.
- Iron-induced cardiac disease resulting in cardiomyopathy, heart failure, and arrhythmias.
- Skin pigmentation.

ETIOLOGY

- The majority of the patients diagnosed with hemochromatosis have mutation in the *HFE* gene and are either homozygous for the *C282Y* mutation *(C282Y/C282Y)* or compound heterozygote for the *C282Y* mutation and either the mutation *H63D (C282Y/H63D)* or less commonly the *S65C (C282Y/S65C).*
- The remainder of the patients are classified as non–*HFE*-associated hemochromatosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hereditary anemias with defect of erythropoiesis.
- Cirrhosis, chronic liver disease, porphyria cutanea tarda.
- Repeated blood transfusions.
- African dietary iron overload.

WORKUP

Medical history, physical examination, and laboratory evaluation should be focused on affected organ systems (see "Physical Findings & Clinical Presentation"). Fig. H1-16 outlines evaluation for possible hereditary hemochromatosis in an individual with negative family history. Liver biopsy is the gold standard for diagnosis; it reveals iron deposition in hepatocytes, bile ducts, and supporting tissues.

LABORATORY TESTS

- Transferrin saturation is the best screening test. Values >45% are an indication for further testing.
- Elevated serum ferritin is good evidence of iron overload, but other causes like chronic inflammatory conditions, malignancy, and so forth need to be ruled out as ferritin is also an acute phase reactant.
- Genotypical screening for *C282Y* and *H63D* mutation in *HFE* gene should be done in patients with high transferrin saturation, elevated ferritin, or both.
- Liver biopsy (Fig. H1-17) is the gold standard but is not needed in somebody who has a persistently elevated transferrin saturation, elevated ferritin, or both.
- Hepatic iron index can help differentiate between various causes of iron overload.
- Elevated aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase are seen.
- Hyperglycemia is found.
- Endocrine abnormalities (decreased testosterone, luteinizing hormone, follicle-stimulating hormone) are noted.
- Table H1-8 describes laboratory findings in patients with hereditary hemochromatosis.

IMAGING STUDIES

Routine radiologic imaging is not needed.

TREATMENT

The goal of therapy is the removal of excess iron and maintaining it at a normal or near-normal level.

NONPHARMACOLOGIC THERAPY

Phlebotomy is the treatment of choice.

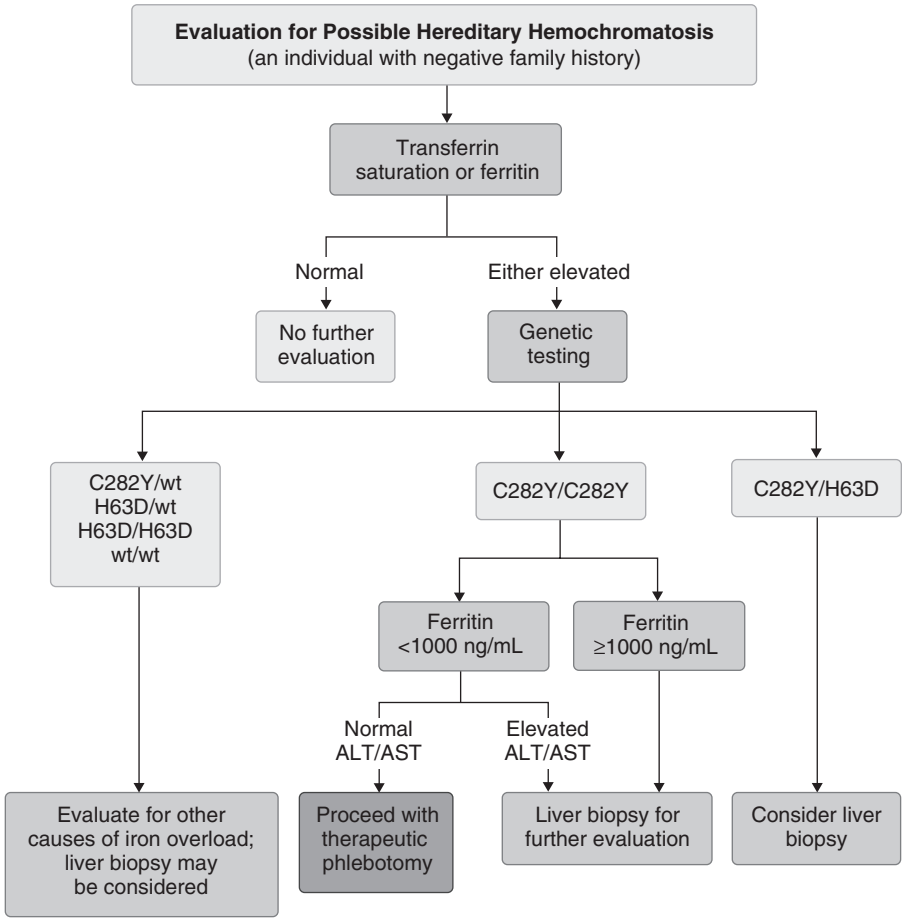

FIGURE H1-16 Algorithm for evaluation of possible hereditary hemochromatosis in a person with a negative family history. *ALT,* Alanine transminase; *AST,* aspartate transminase. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

ACUTE GENERAL Rx

- The timing and frequency of phlebotomy needs to be individualized for each patient.
- For patients with heavy iron overload twice-weekly phlebotomies should be started. In most patients, weekly phlebotomy is adequate.
- The effectiveness of treatment is monitored by periodic ferritin measurement. The goal is to bring ferritin level below 50 ng/ml.
- Patients with iron overload due to transfusion-dependent anemias may not tolerate phlebotomy. For these patients iron chelation may be needed.
- The chelating agent deferoxamine has to be given daily as a 9 to 12-hr IV or SC infusion and compliance is difficult.
- The oral chelating agent deferasirox (Exjade) is effective, but should not be used in patients with high-risk myelodysplastic syndrome because it can cause renal impairment, hepatic impairment, or gastrointestinal hemorrhage, which can be fatal.

CHRONIC Rx

After the ferritin has been brought to less than 50 ng/ml, phlebotomy is needed on an as-needed basis to keep the ferritin at that level.

DISPOSITION

- Serum ferritin measurement is the most useful prognostic indicator of disease severity.
- Prognosis is good if phlebotomy is started early (before onset of cirrhosis or diabetes mellitus); women can have the full phenotypic expression of the disease, including cirrhosis, and should also be aggressively treated.

REFERRAL

For liver biopsy if diagnosis is uncertain.

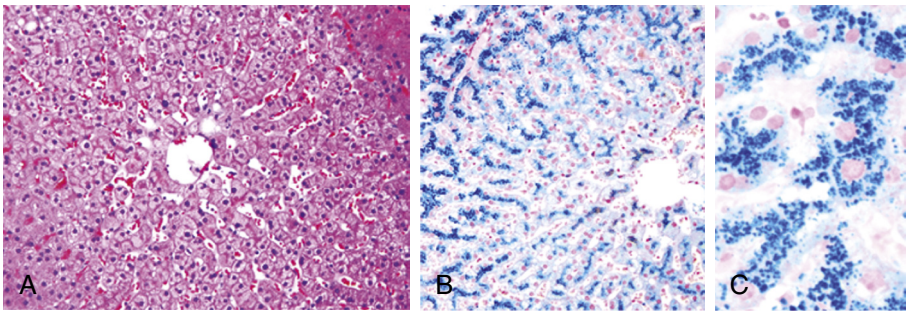

FIGURE H1-17 Hemochromatosis. Liver biopsy sample from a 46-year-old man with homozygous hemochromatosis. Hematoxylin and eosin stain of the liver **(A)** shows intact hepatic architecture. Iron stain **(B, C)** shows marked diffuse iron deposits in the hepatocytes throughout the lobules. A normal liver would show essentially no iron in the hepatocytes. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

TABLE H1-8 Laboratory Findings in Patients with Hereditary Hemochromatosis

		PATIENTS WITH HEREDITARY HEMOCHROMATOSIS	
Measurements	**Normal Subjects**	**Asymptomatic**	**Symptomatic**
Blood (Fasting)			
Serum iron level (μg/dl)	60-180	150-280	180-300
Serum transferrin level (mg/dl)	220-410	200-280	200-300
Transferrin saturation (%)	20-45	45-100	80-100
Serum ferritin level (ng/ml)			
Men	20-200	150-1000	500-6000
Women	15-150	120-1000	500-6000
Genetic (*HFE* Mutation Analysis)			
C282Y/*C282Y*	wt/wt‡	*C282Y*/*C282Y*	*C282Y*/*C282Y*
C282Y/*H63D**	wt/wt	*C282Y*/*H63D*	*C282Y*/*H63D*
Liver			
Hepatic iron concentration			
μg/g dry weight	300-1500	2000-10,000	8000-30,000
μmol/g dry weight	5-27	36-179	140-550
Hepatic iron index†	<1	1 to >1.9	>1.9
Liver histology			
Perls' Prussian blue stain	0, 1+	2+ to 4+	3+, 4+

*Compound heterozygote.
†Calculated by dividing the hepatic iron concentration (in μmol/g dry weight) by the age of the patient (in yr). With the increased use of genetic testing in patients with iron overload, the specificity of the hepatic iron index has diminished.
‡wt/wt: wild type (normal).
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

PEARLS & CONSIDERATIONS

COMMENTS

- Persons who are homozygous for the HFE gene mutation *C282Y* comprise 85% to 90% of phenotypically affected individuals.
- Patients with hemochromatosis and serum ferritin levels <1000 ng/ml are unlikely to have cirrhosis. Liver biopsy to screen for cirrhosis may be unnecessary in such patients.
- Cirrhotic patients must be periodically monitored (ultrasound or CT scan) because of their increased risk of hepatocellular carcinoma.
- *HFE* gene testing for *C282Y* mutation is a cost-effective method of screening relatives of patients with hereditary hemochromatosis. The American College of Gastroenterology recommends genotyping persons who have abnormal iron screening tests and first-degree relatives of those identified with *C282Y* homozygosity.
- Established cirrhosis, hypogonadism, destructive arthritis, and insulin-dependent diabetes mellitus secondary to hemochromatosis cannot be reversed with repeated phlebotomy, but their progress can be slowed.
- In patients who are heterozygotes for *C282Y* or *H63D* mutation, clinically meaningful iron overload does not develop.
- Screening for hepatocellular carcinoma is reserved for those with hereditary hemochromatosis and cirrhosis.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hemochromatosis (Patient Information)

AUTHORS: **BILAL H. NAQVI, M.D.,** and **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Allen KJ et al.: Iron-overload related disease in HFE hereditary hemochromatosis, *N Engl J Med* 358:221–230, 2008.

Crownover BK, Covey CJ: Hereditary hemochromatosis, *Am Fam Physician* 87(3):183–190, 2013.

Phatak P et al.: Hereditary hemochromatosis: time for targeted screening, *Ann Intern Med* 149:270, 2008.

Whitlock EP et al.: Screening for hereditary hemochromatosis: a systematic review for the US Preventive Services Task Force, *Ann Intern Med* 145:209, 2006.

BASIC INFORMATION

DEFINITION

Hemolytic-uremic syndrome (HUS) refers to an acute syndrome characterized by microangiopathic hemolytic anemia, thrombocytopenia, and severe renal failure. "Atypical hemolytic-uremic syndrome" is a genetic, life-threatening, chronic disease of complement-mediated thrombotic microangiopathy.

SYNONYMS

HUS

ICD-9CM CODES
283.11 Hemolytic-uremic syndrome
ICD-10CM CODES
D59.3 Hemolytic-uremic syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- HUS affects mainly children younger than 5 yr with incidence rate of 6.1 cases/100,000.
- Overall incidence is 1 to 2 cases/100,000.
- May be epidemic, most commonly occurring during the summer months in rural populations.
- Most common cause of acute renal failure in children.
- In the United States, 300 to 700 new cases occur each year.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- HUS usually preceded by diarrhea in 90% of cases, bloody in 75%.
- Abdominal pain, vomiting, and fever.
- Neurologic symptoms, principally seizure and somnolence, have been observed in 20% to 25% of cases. Stroke or coma may occur and be associated with significant mortality.
- Hypertension.
- Hepatomegaly and abnormality in liver function tests.
- Anuria or oliguria.
- Glucose intolerance and transient diabetes (10%).

ETIOLOGY

Pathologically, it is thought that thrombin generation (probably the result of accelerated thrombogenesis) and inhibition of fibrinolysis lead to renal arteriolar and capillary microthrombi preceding renal injury.

In children:

- *Escherichia coli* serotype O157:H7 is the leading cause of HUS.
- The infection is acquired by eating undercooked red meat, nonpasteurized milk or milk products, water, fruits, or vegetables. A recent large outbreak of the HUS caused by Shiga toxin–producing *Escherichia coli* O104:H4 in Germany was associated with consumption of contaminated sprouts.
- Other causes of HUS in children and adults are:
  1. Drugs (cyclosporine, mitomycin, tacrolimus, ticlopidine, clopidogrel, cisplatin, quinine, penicillin, penicillamine, oral contraceptives, and quinine used to treat muscle cramps) and toxins.
  2. Infection (*Salmonella, Shigella, Yersinia,* Group A streptococci, *Clostridium difficile, Campylobacter,* coxsackie virus, rubella, influenza virus, Epstein-Barr virus).
  3. HIV-associated thrombotic microangiopathy.
  4. Pneumococcal infection.
- Complement disorders involving factors H, I, and membrane cofactors protein have been associated with cases of nondiarrhea-associated HUS (atypical HUS).
- Mutations that impair the function of thrombomodulin occur in about 5% of patients with atypical HUS.
- Table H1-9 describes a classification of HUS.

DIAGNOSIS

The triad of thrombocytopenia, acute renal failure, and microangiopathic hemolytic anemia establishes the diagnosis of HUS.

TABLE H1-9 Classification of Hemolytic-Uremic Syndrome

Infection-induced
Verotoxin-producing *Escherichia coli*
Shiga toxin-producing *Shigella dysenteriae* type 1
Neuraminidase-producing *Streptococcus pneumoniae*
Human immunodeficiency virus
Genetic
von Willebrand factor-cleaving protease (ADAMTS 13) deficiency
Complement factor H (or related proteins) deficiency or mutation
Membrane cofactor protein (MCP) mutations
Thrombomodulin mutations
Complement factor I mutations
Vitamin B_{12} metabolism defects
Familial autosomal recessive of undefined etiology
Familial autosomal dominant of undefined etiology
Sporadic, recurrent, undefined etiology without diarrhea prodrome
Other Diseases Associated with Microvascular Injury
Systemic lupus erythematosus
Antiphospholipid antibody syndrome
Following bone marrow transplantation
Malignant hypertension
Primary glomerulopathy
HELLP (*h*emolytic anemia, *e*levated *l*iver enzymes, *l*ow *p*latelet count) syndrome
Medication-induced
Calcineurin inhibitors (cyclosporine, tacrolimus)
Cytotoxic, chemotherapy agents (mitomycin C, cisplatin, gemcitabine)
Clopidogrel and ticlopidine
Quinine

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

DIFFERENTIAL DIAGNOSIS

The differential is vast, including all causes of bloody and nonbloody diarrhea because the GI symptoms usually precede the triad of HUS:

- Thrombotic thrombocytopenic purpura.
- Disseminated intravascular coagulation.
- Prosthetic valve hemolysis.
- Malignant hypertension.
- Vasculitis.
- Catastrophic antiphospholipid syndrome.
- Postpartum acute renal failure.
- Scleroderma renal crisis.

WORKUP

The workup for suspected HUS patients includes blood tests and stool cultures.

LABORATORY TESTS

- Anemia (hemoglobin <8 g/dl) with peripheral smear shows the hallmark microangiopathic hemolytic anemia with schistocytes, burr cells, and helmet cells (Fig. H1-18).
- Thrombocytopenia (platelet counts usually <60,000/mm^3).
- Reticulocyte count high.
- LDH level elevated.
- Haptoglobin low.
- Indirect bilirubin elevated.
- Negative Coombs test.
- BUN and creatinine elevated.
- Urinalysis: proteinuria, microscopic hematuria, and pyuria.
- Stool cultures for *E. coli* O157:H7 are positive in more than 90% of cases if obtained during the first week of illness. After the first week, only one third are positive.

IMAGING STUDIES

Imaging studies are not very helpful in the diagnosis of HUS.

TREATMENT

The treatment of HUS is primarily supportive.

NONPHARMACOLOGIC THERAPY

- Blood transfusions are used for severe anemia.

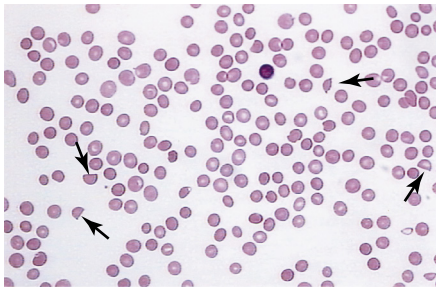

FIGURE H1-18 Hemolytic-uremic syndrome (HUS). Peripheral blood smear from a patient with HUS. The presence of fragmented red blood cells with the appearance of a helmet *(arrows)* is pathognomonic for microangiopathic hemolysis in patients with no evidence of heart valvular disease. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

- Antibiotics and antimotility agents should be avoided and are not indicated for the treatment of *E. coli* O157:H7.
- Correction of electrolyte abnormalities and fluid management should be performed.
- Platelet transfusion is preserved only for patients with HUS who have significant bleed or invasive procedure is required.
- Plasma exchange therapy with immunosuppressive agents has been used in patients with severe CNS involvement. Eculizumab, a monoclonal antibody directed toward complement component C_5, has been approved in adults for treatment of atypical HUS. Trials have shown that eculizumab is effective in inhibiting complement-mediated thrombotic microangiopathy in patients with atypical hemolytic-uremic syndrome.
- Tissue-type plasminogen activator (PAI-1) may have a role in improving renal function in recent studies.

ACUTE GENERAL Rx

Hypertension and seizure control.

CHRONIC Rx

For anuric or oliguric renal failure, dialysis may be required.

DISPOSITION

- Adults presenting with HUS have a worse prognosis than do children with HUS.
- Mortality rate is less than 5%.
- Morbidity includes:
  1. Proteinuria (31%).
  2. Renal insufficiency (31%).
  3. Hypertension (6%).
- Patients with atypical hemolytic-uremic syndrome have a lifelong risk of systemic clinical complications of thrombotic microangiopathy, including damage to multiple organ systems (e.g., the central nervous system, kidneys, heart, and GI tract). Within 1 yr after a diagnosis of this syndrome, up to 5% of patients treated with plasma exchange or infusion sustain permanent renal damage, have progression to end-stage renal disease, or die.

REFERRAL

- The local health department should be notified if *E. coli* O157:H7 has been isolated; large food-borne outbreaks have occurred with commercial beef products and asparagus.
- Consultation with hematology and nephrology specialist is recommended for patients with HUS.

PEARLS & CONSIDERATIONS

COMMENTS

- Children testing positive for the *E. coli* O157:H7 serotype should not return to school or day care facilities until two consecutive stools test negative for the microorganism.
- *E. coli* O157:H7 can be transmitted from person to person; therefore universal precautions and handwashing are recommended in preventing the spread of the infection.
- *E. coli* O111 can also be associated with HUS. In 2008 the largest known U.S. serotype 1 *E. coli* O111 occurred in Oklahoma, causing 341 illnesses. The HUS attack rate in this *E. coli* O111 outbreak was comparable to that for *E. coli* O157-related illness, but most cases occurred among adults. More recently, in May 2011, a large outbreak of diarrhea and HUS caused by an unusual serotype of Shiga toxin–producing *E. coli* (O104:H4) occurred in Germany, with 908 individuals reported with hemolytic-uremic syndrome, and 34 deaths.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hemolytic-Uremic Syndrome (Patient Information)

AUTHORS: **MONZR M. AL MALKI, M.D.,** and **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Buchholz U et al.: German outbreak of *E. coli* O104:H4 associated with sprouts, *N Engl J Med* 365(19), 2011.

Delvaeye M et al.: Thrombomodulin mutations in atypical hemolytic-uremic syndrome, *N Engl J Med* 361:345–357, 2009.

Noris M, Remuzzi G: Atypical hemolytic-uremic syndrome, *N Engl J Med* 361:1676–1678, 2009.

Piercefield EW et al.: Hemolytic uremic syndrome after an *E. coli* O111 outbreak, *Arch Intern Med* 170(18):1656–1663, 2010.

Rasko DA et al.: Origins of the *E. coli* strain causing an outbreak of hemolytic-uremic syndrome in Germany, *N Engl J Med* 365:709–717, 2011.

Razzaq S: Hemolytic uremic syndrome: an emerging health risk, *Am Fam Physician* 74:991, 2006.

Zipfel PF, Skerka C: Complement dysfunction in hemolytic uremic syndrome, *Curr Opin Rheumatol* 18(5):548, 2006.

BASIC INFORMATION

DEFINITION

Hemophilia is a hereditary bleeding disorder caused by low factor VIII coagulant activity (hemophilia A) or low levels of factor IX coagulant activity (hemophilia B).

SYNONYMS

Hemophilia A: Classic hemophilia, factor VIII deficiency hemophilia
Hemophilia B: Christmas disease, factor IX hemophilia

ICD-9CM CODES
286.0 Hemophilia A
286.1 Hemophilia B
ICD-10CM CODES
D66 Hereditary factor VIII deficiency
D67 Hereditary factor IX deficiency

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE/PREVALENCE (IN U.S.): Hemophilia A: 100 cases per 1 million males; hemophilia B: 20 cases per 1 million males. Approximately 400,000 patients have severe hemophilia worldwide.
GENETIC: Both hemophilias have an X-linked recessive pattern of inheritance with only males affected.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The clinical features of hemophilia A and B are generally indistinguishable from each other.
- Bleeding is most commonly seen in joints (knees, ankles, elbows), resulting in hot, swollen, painful joints (Fig. H1-19) and subsequent crippling joint deformity (Fig. H1-20).
- Bleeding can also occur into the muscles and the gastrointestinal tract.
- Compartment syndrome can occur from large hematomas.
- Hematuria may be present.

ETIOLOGY

- Hemophilia A: low factor VIII coagulant (VIII:C) activity; can be classified as mild if factor VIII:C levels are >5%, moderate if levels are 1% to 5%, and severe if levels are <1%.
- Hemophilia B: low levels of factor IX coagulant activity.
- Both disorders are congenital.
- Spontaneous acquisition of factor VIII inhibitors (acquired hemophilia) is rare.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other clotting factor deficiencies.
- Platelet function disorders.
- Vitamin K deficiency.

WORKUP

Patients with mild hemophilia bleed only in response to major trauma or surgery and may not be diagnosed until young adulthood. Diagnostic workup includes laboratory evaluation (see "Laboratory Tests").

LABORATORY TESTS

- Partial thromboplastin time (PTT) is prolonged.
- Reduced factor VIII: C level distinguishes hemophilia A from other causes of prolonged PTT.
- Factor VIII antigen, prothrombin time, fibrinogen level, and bleeding time are normal.
- Factor IX coagulant activity levels are reduced in patients with hemophilia B.
- Coagulation factor activity measurement is useful to correlate with disease severity. Normal range is 50 to 150 U/dl; 5 to 20 U/dl indicates mild disease, 2 to 5 U/dl indicates moderate disease, and <2 U/dl indicates severe disease with spontaneous bleeding episodes.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of contact sports.
- Patient education regarding the disease; promotion of exercises such as swimming.
- Avoidance of aspirin or other NSAIDs.
- Orthopedic evaluation and physical therapy evaluation in patients with joint involvement.
- Hepatitis vaccination.

ACUTE GENERAL Rx

(See Table H1-10).
HEMOPHILIA A:
- Reversal and prevention of acute bleeding in hemophilia A and B are based on adequate

TABLE H1-10 Treatment of Hemophilia

Type of Hemorrhage	Hemophilia A	Hemophilia B
Hemarthrosis*	50 IU/kg factor VIII concentrate† on day 1; then 20 IU/kg on days 2, 3, 5 until joint function is normal or back to baseline. Consider additional treatment every other day for 7-10 days. Consider prophylaxis.	80-100 IU/kg on day 1; then 40 IU/kg on days 2, 4. Consider additional treatment every other day for 7-10 days. Consider prophylaxis.
Muscle or significant subcutaneous hematoma	50 IU/kg factor VIII concentrate; 20 IU/kg every-other-day treatment may be needed until resolved.	80 IU/kg factor IX concentrate‡; treatment every 2-3 days may be needed until resolved.
Mouth, deciduous tooth, or tooth extraction	20 IU/kg factor VIII concentrate; antifibrinolytic therapy; remove loose deciduous tooth.	40 IU/kg factor IX concentrate‡; antifibrinolytic therapy§; remove loose deciduous tooth.
Epistaxis	Apply pressure for 15-20 min; pack with petrolatum gauze; give antifibrinolytic therapy; 20 IU/kg factor VIII concentrate if this treatment fails.ǁ	Apply pressure for 15-20 min; pack with petrolatum gauze; antifibrinolytic therapy; 30 IU/kg factor IX concentrate‡ if this treatment fails.
Major surgery, life-threatening hemorrhage	50-75 IU/kg factor VIII concentrate, then initiate continuous infusion of 2-4 IU/kg/hr to maintain factor VIII >100 IU/dl for 24 hr# then give 2-3 IU/kg/hr continuously for 5-7 days to maintain the level at >50 IU/dl and an additional 5-7 days to maintain the level at >30 IU/dl.¶	120 IU/kg factor IX concentrate‡, then 50-60 IU/kg every 12-24 hr to maintain factor IX at >40 IU/dl for 5-7 days, and then at >30 IU/dl for 7 days.
Iliopsoas hemorrhage	50 IU/kg factor VIII concentrate, then 25 IU/kg every 12 hr until asymptomatic, then 20 IU/kg every other day for a total of 10-14 days.**	120 IU/kg factor IX concentrate‡; then 50-60 IU/kg every 12-24 hr to maintain factor IX at >40 IU/dl until patient is asymptomatic; then 40-50 IU every other day for a total of 10-14 days.# **
Hematuria	Bed rest; 1½ × maintenance fluids; if not controlled in 1-2 days, 20 IU/kg factor VIII concentrate; if not controlled, give prednisone (unless patient is HIV-infected).	Bed rest; 1½ × maintenance fluids; if not controlled in 1-2 days, 40 IU/kg factor IX concentrate‡; if not controlled, give prednisone (unless patient is HIV-infected).
Prophylaxis	20-40 IU/kg factor VIII concentrate every other day to achieve a trough level ≥1%.	30-50 IU/kg factor IX concentrate‡ every 2-3 days to achieve a trough level ≥1%.

*For hip hemarthrosis, orthopedic evaluation tor possible aspiration is advisable to prevent avascular necrosis of the femoral head.
†For mild or moderate hemophilia, desmopressin, 0.3 μg/kg, should be used instead of factor VIII concentrate, if the patient is known to respond with a hemostatic level of factor VIII; if repeated doses are given, monitor factor VIII levels for tachyphylaxis.
‡Stated doses apply for recombinant factor IX concentrate; for plasma-derived factor IX concentrate, use 70% of the stated dose.
§Do not give antifibrinolytic therapy until 4 to 6 hr after a dose of prothrombin complex concentrate.
ǁOver-the-counter coagulation-promoting products may be helpful.
¶Alternatively, give 25 IU/kg every 12 hr to maintain a trough level >50% for 5 to 7 days followed by 25-30 IU/kg for an additional 5 to 7 days to maintain trough >25%.
#Repeat radiologic assessment should be performed before discontinuation of therapy.
**If repeated doses of factor IX concentrate are required, use highly purified, specific factor IX concentrate.
Adapted from Montgomery RR et al: Hemophilia and von Willebrand disease. In Nathan DG, Orkin SH (eds): *Nathan and Oski's hematology at infancy and childhood,* ed 5, Philadelphia, 1998, Saunders.

replacement of deficient or missing factor protein.
- The choice of the product for replacement therapy is guided by availability, capacity, concerns, and cost. Recombinant factors cost two to three times as much as plasma-derived factors, and the limited capacity to produce recombinant factors often results in periods of shortage. In the United States 60% of patients with severe hemophilia use recombinant products.
- Factor VIII concentrates are effective in controlling spontaneous and traumatic hemorrhage in severe hemophilia. The new recombinant factor VIII is stable without added human serum albumin (decreased risk of transmission of infectious agents).
- Alloantibodies (inhibitors) that neutralize factor VIII clotting function occur in nearly 30% of patients with severe hemophilia A after exposure to factor VIII. In these patients, bypassing agents (anti-inhibitor coagulant complex [AICC] and recombinant activated factor VII [rFVIIa]) can be used to treat bleeding. AICC can also be used prophylactically to decrease the frequency of joint and other bleeding events in patients with severe hemophilia A and factor VIII inhibitors.
- Recombinant activated factor VII is useful to stop spontaneous hemorrhages and prevent excessive bleeding during surgery in 75% of patients with inhibitors. Recommended dose is 90 μg/mg of body weight every 2 to 3 hr for treatment of life-threatening hemorrhage. It is, however, very expensive ($1 per μg).
- Desmopressin acetate 0.3 μg/kg q24h (causes release of factor VIII:C) may be used in preparation for minor surgical procedures in mild hemophiliacs.
- Aminocaproic acid (EACA, Amicar) 4 g PO q4h can be given for persistent bleeding that is unresponsive to factor VIII concentrate or desmopressin.

FIGURE H1-19 Acute hemarthrosis of the knee is a common complication of hemophilia. It may be confused with acute infection unless the patient's coagulation disorder is known because the knee is hot, red, swollen, and painful. (From Forbes CD, Jackson WF: *Color atlas and text of clinical medicine,* ed 3, London, 2003, Mosby.)

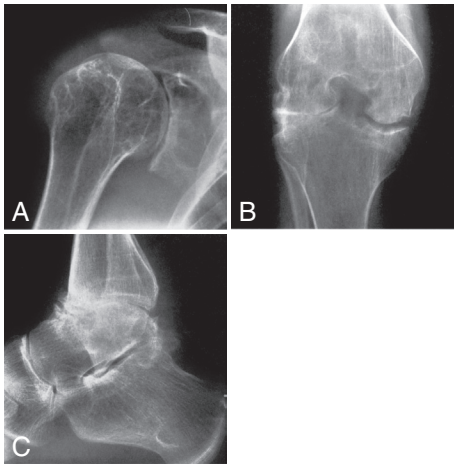

FIGURE H1-20 Radiographic changes associated with hemophilic arthropathy. A, Radiograph of the shoulder showing multiple subchondral cysts in the head of the humerus, an early finding in hemophilic arthropathy. The glenohumeral joint space is fairly well preserved, and range of motion is normal. **B,** Widening of the intercondylar notch and near fusion of the femur and medial tibial condyle in the knee joint affected by hemophilic arthropathy. **C,** Narrowing and fusion of the tibiotalar joint in the ankle. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

HEMOPHILIA B:
- Infuse factor IX concentrates. It is important to remember that factor IX concentrates contain other proteins that may increase the risk of thrombosis with recurrent use. Therefore factor IX concentrates must be used only when clearly indicated.
- Daily administration of oral cyclophosphamide and prednisone without empirical factor VIII therapy is an effective and well-tolerated treatment for acquired hemophilia.

CHRONIC Rx

- The aim of chronic treatment is to prevent spontaneous bleeding and excessive bleeding during any surgical intervention.
- Prophylaxis with recombinant factor VIII can prevent joint damage and decrease the frequency of joint and other hemorrhages in young boys with severe hemophilia A. The estimated annual cost for treatment of one patient with recombinant factor VIII is $300,000.
- Implantation of genetically altered fibroblasts that produce factor VIII is safe and well tolerated. This form is feasible in patients with severe hemophilia. Hemophilia will likely be the first common, severe genetic disease to be cured by gene therapy.

DISPOSITION

- Despite the advent of virally safe blood products and blood treatment programs, nearly 70% of hemophiliacs are HIV seropositive. Survival is of normal expectancy in HIV-negative patients with mild disease.
- Intracranial bleeds are the second most common cause of death in hemophiliacs after AIDS. They are fatal in 30% of patients, occur in 10% of patients, and are generally the result of trauma.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hemophilia (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Leissinger C et al.: Anti-inhibitor coagulant complex prophylaxis in hemophilia with inhibitors, *N Engl J Med* 365:1684–1692, 2011.

Manco-Johnson MJ et al.: Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia, *N Engl J Med* 357:535, 2007.

BASIC INFORMATION

DEFINITION

A hemorrhoid is a varicose dilation of a vein of the superior or inferior hemorrhoidal plexus, resulting from a persistent increase in venous pressure. External hemorrhoids are below the pectinate line (inferior plexus). Internal hemorrhoids are above the pectinate line (superior plexus).

SYNONYMS

Piles

ICD-9CM CODES
455.6 Hemorrhoids
ICD-10CM CODES
K64.9 Unspecified hemorrhoids

EPIDEMIOLOGY & DEMOGRAPHICS

Potential for development of symptomatic hemorrhoids in all adults.
PREVALENCE: ~50% of adults in the United States.
PREDOMINANT SEX: Males and females affected equally.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Painless bleeding with defecation; bleeding is bright red with staining seen on toilet paper.
- Perianal irritation.
- Mucofecal staining of underclothes.
- Acute external hemorrhoids: painful, swollen, and often thrombosed (Fig. H1-21).
- Pain on sitting, standing, or defecating (thrombosed hemorrhoid).
- Prolapse (Fig. H1-22).
- Constipation.
- A classification of internal hemorrhoids is described in Table H1-11.

ETIOLOGY

- Low-fiber, high-fat diet.
- Chronic constipation and straining with defecation.
- High resting anal sphincter pressures.
- Pregnancy.
- Obesity.
- Rectal surgery (i.e., episiotomy).
- Prolonged sitting.
- Anal intercourse.

FIGURE H1-21 Thrombosed external hemorrhoid. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Fissure.
- Abscess.
- Anal fistula.
- Condylomata acuminata.
- Hypertrophied anal papillae.
- Rectal prolapse.
- Rectal polyp.
- Neoplasm (anal cancer, colorectal cancer).
- Inflammatory bowel disease.

WORKUP

- Inspection.
- Digital rectal examination.
- Anoscopy.
- Sigmoidoscopy.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of constipation and straining with defecation.
- Avoidance of prolonged sitting on toilet.

FIGURE H1-22 Prolapsed and thrombosed internal hemorrhoids. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

TABLE H1-11 Classification of Internal Hemorrhoids

Severity (Degree)	Findings
First	No prolapse; painless bleeding
Second	Prolapse with straining and spontaneous reduction Mild discomfort and bleeding
Third	Prolapse with straining, which requires manual reduction Some throbbing pain, itching, bleeding, and mucus discharge
Fourth	Permanent prolapse that cannot be reduced Pain and bleeding common Potential for thrombosis and strangulation

From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

- High-fiber diet (20 to 30 g/day).
- Increased fluid intake (six to eight glasses of water per day).
- Cleaning with mild soap and water after defecation.
- Warm soaks or ice to soothe.
- Sitz baths.

ACUTE GENERAL Rx

- Fiber supplements to provide bulk (psyllium extracts or mucilloids).
- Medicated compresses with witch hazel.
- Topical hydrocortisone (1% to 3% cream or ointment).
- Topical anesthetic spray.
- Glycerin suppositories.
- Stool softeners.
- Surgically remove during first 72 hr after onset.

CHRONIC Rx

- Rubber-band ligation.
- Injection sclerotherapy.
- Photocoagulation.
- Cryodestruction.
- Hemorrhoidectomy.
- Anal dilation.
- Laser or cautery hemorrhoidectomy.
- Observance for complications: thrombosis, bleeding, infection, anal stenosis, or weakness.
- Figs. EH1-23 and EH1-24 illustrate the technique for excision of thrombosed external hemorrhoids.

DISPOSITION

Should resolve, but high rate of recurrence.

REFERRAL

To colorectal or general surgeon for any hemorrhoid that does not respond to conservative therapy.

PEARLS & CONSIDERATIONS

COMMENTS

- Patients need to understand the importance of a healthy diet, regular exercise, and rectal hygiene.
- Stress the importance of avoiding prolonged sitting and straining on the toilet.
- Stress the need not to defer the urge to defecate.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hemorrhoids (Patient Information)
Anal Fissure (Related Key Topic)
Hemorrhoids (Primary Care Procedures in Appendix)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READING

Jacobs D: *Hemorrhoids. N Engl J Med* 371:944–951, 2014.
Zuber TJ: Hemorrhoidectomy for thrombosed external hemorrhoids, *Am Fam Physician 65*:1629, 2002.

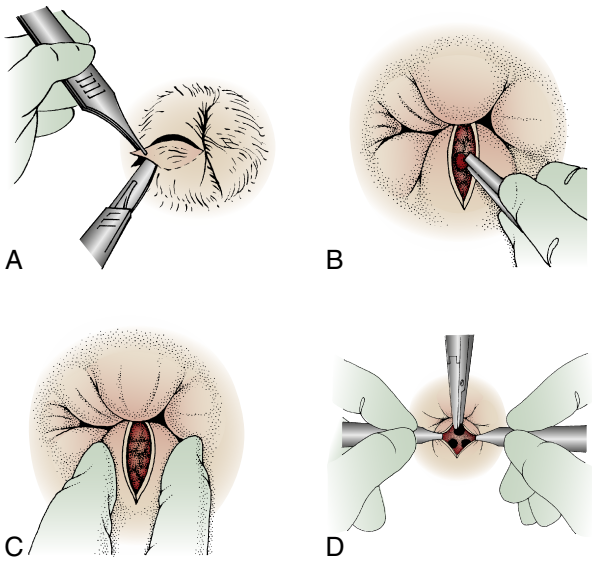

FIGURE EH1-23 Schematic of the technique for excision of thrombosed external hemorrhoids. A, For the unroofing technique, make an elliptical or triangular incision to remove a piece of the overlying skin. To prevent skin tags, do not use a simple linear incision. **B,** Blood clots may extrude spontaneously, but remove the remaining ones with forceps or express them with the fingers **(C). D,** Frequently, multiple clots are present, and they should all be removed. Ask an assistant to provide exposure with forceps if necessary. (From Roberts JR, Hedges JR: *Clinical procedures in emergency medicine,* ed 5, Philadelphia, 2009, Saunders.)

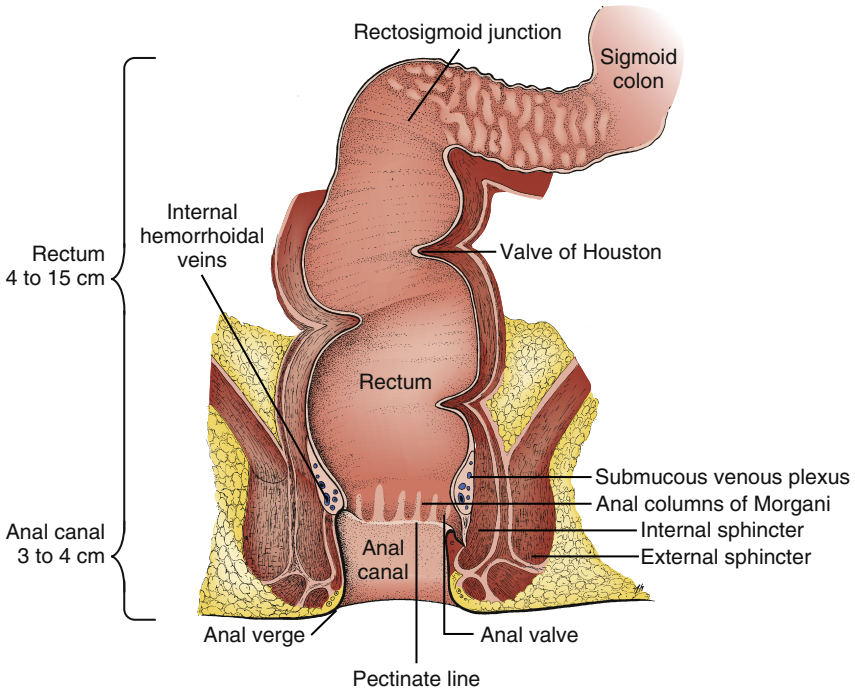

FIGURE EH1-24 Diagram for taping the buttocks. (From Adams JG et al.: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

BASIC INFORMATION

DEFINITION

Hemoptysis is coughing up of blood originating from the lower respiratory tract, ranging from blood-streaked sputum to gross blood. If greater than 100 to 600 ml in 24 hours or if the bleeding rate is >100 mL/hr, it is considered massive hemoptysis.

ICD-9CM CODES
786.3 Hemoptysis
ICD-10CM CODES
R04.2 Hemoptysis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Unknown, varies based on underlying pathology
RISK FACTORS: Tobacco smoking predisposes to lung cancer, a common cause of hemoptysis. Systemic processes (rheumatologic, renal hematologic) may contribute to alveolar hemorrhage or vasculitis. Anticoagulation can worsen bleeding.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Presentation of hemoptysis is variable and can range from minimal blood-tinged sputum to more than 500 ml of gross blood in 24 hr. Other symptoms depend on the underlying etiology and can include cough, sputum production, fever, shortness of breath, weight loss, night sweats, wheezing, and chest pain.
- There are no specific exam findings, but clues to the etiology may be present, for example, focal wheezing, rhonchi or rales on pulmonary exam, murmur of mitral stenosis on cardiac exam.

ETIOLOGY

- There are many potential causes of hemoptysis including airway disease (bronchitis, bronchiectasis, lung neoplasm), infection (necrotizing pneumonia, lung abscess, tuberculosis, fungal infection), inflammatory diseases (Wegener's granulomatosis, Goodpasture's syndrome, lupus), cardiac disease (mitral stenosis after rheumatic heart disease, congenital heart diseases), and others (pulmonary embolism, cocaine use, foreign body, airway trauma, iatrogenic and cryptogenic).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Various potential causes of lower respiratory tract bleeding.
  1. Airway disease (bronchitis, bronchiectasis, lung neoplasm).
  2. Infection (necrotizing pneumonia, lung abscess, tuberculosis, fungal infection).
  3. Inflammatory diseases (Wegener's granulomatosis, Goodpasture's syndrome, lupus).
  4. Cardiac disease (mitral stenosis after rheumatic heart disease, congenital heart diseases).
  5. Pulmonary embolism.
  6. Cocaine use.
  7. Foreign body.
- Bleeding from upper respiratory tract.
- Hematemesis.
- Coagulopathy.

WORKUP

Complete history and physical exam may suggest a particular etiology; important to ask about duration and quantity of hemoptysis and smoking history.

LABORATORY TESTS

- Complete blood count.
- Coagulation profile.
- Serum chemistries including creatinine, urinalysis.
- If indicated, consider vasculitis serologies (i.e., ANA, ANCA, anti-GBM).
- Arterial blood gas to assess oxygenation.
- Sputum for cultures and cytologic studies.

IMAGING STUDIES

- Chest x-ray: all patients with hemoptysis should have a chest x-ray but will likely need additional studies to localize site of bleeding.
- Chest CT: chest CT scan combined with flexible bronchoscopy has the highest yield for localizing the site of bleeding.

TREATMENT

Varies based on underlying etiology and nonmassive versus massive hemoptysis

NONPHARMACOLOGIC THERAPY

Massive hemoptysis:

- Arteriographic embolization of bronchial arteries and/or collateral systemic vessels.
- Surgical resection of affected lung.

ACUTE GENERAL Rx

Massive hemoptysis:

- Stabilize hemodynamic status and oxygenation.
- Reverse any coagulopathy.
- Bronchoscopy can be used to identify cause of hemoptysis (e.g., neoplasm), as well as to help isolate a side/segment of bleeding.
- If site of bleeding is known, place patient with bleeding lung in dependent position to prevent blood from spilling into nonaffected lung.
- Bronchoscopic lavage with iced saline or topical application of epinephrine can be tried as a temporizing measure.
- Bronchoscopic balloon tamponade of bleeding site can be used as temporizing measure.
- Early consultation with interventional radiology and thoracic surgery for definitive intervention is recommended.

Submassive hemoptysis:
For submassive hemoptysis, identify and treat underlying condition. Referral to pulmonologist or hematologist if indicated.

CHRONIC Rx

For patients requiring anticoagulation or antiplatelet therapy for another disorder, consider risks/benefits of continued anticoagulation or antiplatelet therapy.

DISPOSITION

Generally, patients have a good prognosis after an episode of hemoptysis, but those with massive bleeding and/or malignancy tend to have a poorer prognosis.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fig. 3-92 Evaluation of hemoptysis (Algorithm)

AUTHORS: **SARAH TAPYRIK, M.D.,** and **MICHAEL BLUNDIN, M.D.**

SUGGESTED READINGS

Hirshberg B et al.: Hemoptysis: etiology, evaluation and outcome in a tertiary referral hospital, *Chest* 112:440–444, 1997.

Khalil A et al.: Severe hemoptysis of pulmonary arterial origin, *Chest* 133:212–219, 2008.

Jean Baptiste E: Clinical assessment and management of massive hemoptysis, *Critical Care Med* 28(5):1642, 2000.

Henoch-Schönlein Purpura PTG

BASIC INFORMATION

DEFINITION

Henoch-Schönlein purpura (HSP) is a systemic, small-vessel, IgA immune complex–mediated leukocytoclastic vasculitis characterized by a tetrad of palpable purpura (without thrombocytopenia), abdominal pain, renal disease, and arthritis/arthralgias. It may also present with gastrointestinal (GI) bleeding.

SYNONYMS

Anaphylactoid purpura
Allergic purpura

ICD-9CM CODES
287.0 Henoch-Schönlein purpura.
ICD-10CM CODES
D69.0 Allergic purpura.

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Annual incidence of 3 to 26 cases/100,000 population in children. Approximately 1/100,000 in adults
PEAK INCIDENCE: Late autumn to early spring, rarely in summer. Seasonal variation is not seen in adults.
PREVALENCE: Most common vasculitis seen in children and younger age groups; seen in white and Asian populations 3 to 4 times more commonly than black patients.
PREDOMINANT SEX AND AGE: 2:1 male/female ratio. Seen mostly from ages 3 to 12, although can be seen in older adolescents and young adults. 90% of all patients <10 years old.
GENETICS: Recent studies have identified genetic susceptibility factors, but familial recurrence is very rare. An association has been seen with the "Mediterranean fever" (MEFV) gene, HSP seen in up to 7% of gene carriers.

RISK FACTORS

No formally identified risk factors.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Palpable purpura (Fig. H1-25) of dependent areas, especially lower extremities and areas subjected to pressure, such as the beltline in adults or buttocks in toddlers.
- Subcutaneous edema.
- Arthralgias and arthritis in 60 to 85%. Typically oligoarticular, affecting lower extremity and large joints. Periarticular swelling and tenderness also noted.
- GI symptoms are seen in up to two thirds of patients. Common findings are nausea, vomiting, diarrhea, cramping, abdominal pain, hematochezia, and melena. Complications include GI bleeding (20% to 30%), bowel ischemia, intussusception (1%-5%), and bowel perforation (<1%).
- Renal involvement is seen in as many as 80% of older children, usually within the first month of illness. Fewer than 5% progress to end-stage renal failure, a major cause of morbidity. Renal manifestations may range from isolated hematuria or proteinuria to acute nephropathy with renal insufficiency.
- 10% to 20% of male children can present with orchitis that can mimic testicular torsion.

ETIOLOGY

- Presumptive etiology is exposure to a trigger antigen that causes antibody formation.
- Antigen-antibody (immune) complex deposition then occurs in arteriole and capillary walls of skin, renal mesangium, and GI tract. Immunoglobulin (Ig) A deposition is most common.
- Antigen triggers postulated include drugs, foods, immunization, and upper respiratory and other viral illnesses. Group A streptococcal infection is the most common precipitant in children, seen in up to one third of cases. A recent adult case triggered by pantoprazole has also been reported.
- 30% to 65% of cases reviewed in children were preceded by upper unspecified respiratory infection.
- Serologic and pathologic evidence suggests an association between parvovirus B19 and HSP, which may explain observed cases of HSP that do not respond to corticosteroids or other immunosuppressive therapy.
- Case reports have been published describing development of HSP after treatment with a variety of medications including immunosuppressive agents (e.g., etanercept) and more widely used medications such as pantoprazole.

DIAGNOSIS

- Diagnosis is based on the finding of IgA in the affected vessels. Nonthrombocytopenic purpura (see Figure H1-26) is essential to the diagnosis.

TABLE H1-12 Clinical Manifestations of Henoch-Schönlein Purpura

	% at Onset	% during Course
Purpura (nl platelet count)	50	100
Subcutaneous edema	10-20	20-50
Arthritis (large joints)	25	60-85
Gastrointestinal	30	85
Renal	?	10-50
Genitourinary (ddx torsion)	?	2-35
Pulmonary (T_LCO)	?	95
Pulmonary hemorrhage	?	Rare, may be fatal
Central nervous system (headache, organic brain syndrome, seizures)	?	Rare, may be fatal

From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

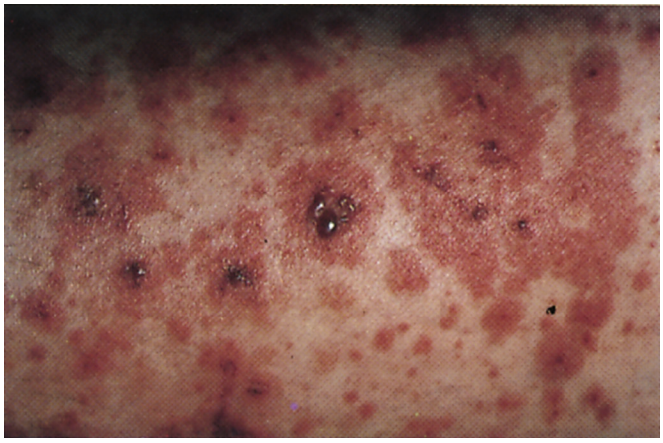

FIGURE H1-25 Palpable purpura in a patient with Henoch-Schönlein purpura. (From Hoffman R et al [eds]: *Hematology: basic principles and practice,* ed 4, Philadelphia, 2005, Saunders.)

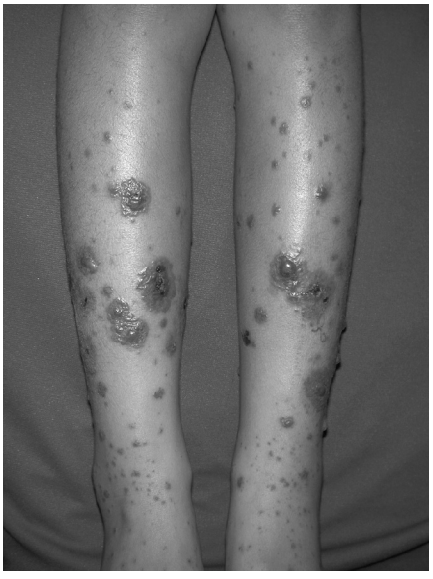

FIGURE H1-26 Extensive palpable purpura over the lower extremities in a 7-yr-old girl with Henoch-Schönlein purpura. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

- Skin manifestations are most common. See Table H1-12 for common clinical manifestations of HSP.
- Skin biopsy shows leukocytoclastic vasculitis. Renal biopsy shows mesangial IgA deposition.
- The presence of two of the following four American College of Rheumatology criteria yields a diagnostic sensitivity of 87.1% and specificity of 87.7%:
  1. Palpable purpura unrelated to thrombocytopenia.
  2. Age <20 yr at onset of first symptoms.
  3. Bowel angina or ischemia.
  4. Granulocytic infiltration of arteriole or venule walls on biopsy.
- In 2010, a European consortium published a set of validated diagnostic criteria that showed 100% sensitivity and 87% specificity. Their criteria described purpura with lower limb predominance and one or more of the following:
  - Abdominal pain.
  - Predominant IgA deposits of histopathology.
  - Arthritis or arthralgia.
  - Renal involvement.

DIFFERENTIAL DIAGNOSIS

- Polyarteritis nodosa.
- Acute abdomen.
- Meningococcemia.
- Thrombocytopenic purpura.
- Hypersensitivity vasculitis.
- Microscopic polyangiitis.
- Wegener granulomatosis.

WORKUP

History, physical examination, laboratory testing, skin or renal biopsy.

LABORATORY TESTS

- Electrolytes, blood urea nitrogen, and creatinine.
- Urinalysis.
- Complete blood count.
- Prothrombin time, fibrinogen, and fibrin degradation products.
- Blood cultures.

Laboratory abnormalities are not specific for HSP, but may help identify complications and rule out other diseases. Leukocytosis and eosinophilia may be seen. IgA levels are elevated in approximately 50% of patients. Glomerulonephritis may be present (microscopic hematuria, proteinuria, and red blood cell casts).

IMAGING STUDIES

Imaging studies are generally not useful in the diagnosis of HSP. Arteriography or magnetic resonance angiography may be helpful in distinguishing from polyarteritis nodosa. Abdominal ultrasound is recommended for patients with severe abdominal pain to detect increased bowel wall thickness, peritoneal fluid, or intussusception.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive care with pain management, adequate hydration, and nutrition is the primary intervention as up to 94% of cases in children and 87% cases in adults will resolve spontaneously.

ACUTE GENERAL Rx

- Prednisone 1 to 2 mg/kg PO daily for two weeks is typically given for severe arthritis and/or abdominal pain. An equivalent dose of methylprednisolone can be used with same efficacy.
- A double-blind, randomized, controlled trial found that early treatment with prednisone reduced abdominal pain and joint symptoms but did not prevent development of renal disease. It was effective in the treatment of renal disease once it was established.
- Corticosteroids and azathioprine may be beneficial if rapidly progressive glomerulonephritis is present. Pulse methylprednisolone therapy has also been proposed in patients with glomerulonephritis, mesenteric vasculitis, or pulmonary involvement. Recent reports describe improvement in rapidly progressive glomerulonephritis and nephrotic-range proteinuria after treatment with mycophenolate mofetil. The combination of cyclosporin A with corticosteroids appears to be effective in inducing remission of nephrotic syndrome in adult patients with HSP nephritis. Recent studies show no benefit to the use of cyclophosamide alone or in combination with steroids in patients with renal manifestations of HSP.

CHRONIC Rx

- Even if renal involvement is not present after initial episode, urinalysis and blood pressure should be checked every 2 to 4 weeks for first 6 months to detect development and progression of kidney disease.

COMPLEMENTARY AND ALTERNATIVE MEDICINE:

- No complementary or alternative treatment modalities proven to be effective for this disease.

DISPOSITION

- Prognosis excellent, with spontaneous recovery of most patients within 4 weeks.
- Hospitalization is recommended for significant GI or renal involvement.
- Increased age of onset generally correlates with morbidity. While end-stage renal disease (ESRD) occurs in 10% to 30% of adult patients with HSP at 15 years, chronic renal insufficiency is the most common long-term morbidity and affects adults more than children.
- Recurrences in up to one third of patients, especially within first 4 to 6 mo after initial episode and most commonly in patients with renal involvement. Recurrences are characteristically less severe than initial episode.

REFERRAL

Rheumatologist; Nephrology or General Surgery consultation based on clinical manifestations

PEARLS & CONSIDERATIONS

- HSP is an IgA-related vasculitis.
- Organ systems involved are skin, joints, GI tract, and kidneys.
- Palpable purpura without thrombocytopenia more common in adults; GI symptoms more common in children.
- GI symptoms and arthritis may precede rash. Skin and renal manifestations occur at same time.
- Most with spontaneous recovery within 4 weeks of onset of symptoms.
- End-stage renal disease occurs in only 5% of patients.
- Steroids have been proven to shorten the duration and intensity of arthritis and GI symptoms, but do not prevent nephritis or recurrences.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Henoch-Schönlein Purpura (Patient Information)

AUTHORS: **JAMES M. FERGUSON, M.D.**, and **DOMINICK TAMMARO, M.D.**

SUGGESTED READINGS

Chartapisak W et al.: Prevention and treatment of renal disease in Henoch-Schönlein purpura: a systematic review, *Arch Dis Child* 94:132–137, 2009.

McCarthy HJ, Tizard EJ: Clinical practice: diagnosis and management of Henoch-Schönlein purpura, *Eur J Pediatr* 169(6):643–650, 2010.

Piram M, Mahr A: Epidemiology of immunoglobulin A vasculitis (Henoch-Schönlein): current state of knowledge, *Curr Opin Rheumatol* 25:171–178, 2013.

Reamy BV et al.: Henoch-Schönlein purpura, *Am Fam Physician* 80(7):697–704, 2009.

BASIC INFORMATION

DEFINITION

There are two forms of heparin-induced thrombocytopenia (HIT). Type 1 HIT is a mild, transient decrease in platelet count that occurs during the first few days of heparin exposure due to platelet agglutination. This form is benign, and the platelet count will return to normal while heparin is continued. This section will refer to Type 2 HIT, an antibody-mediated thrombocytopenia that is associated with a high risk of developing thrombosis.

SYNONYMS

Type II heparin-induced thrombocytopenia
Heparin-induced thrombocytopenia and thrombosis (HITT)
White clot syndrome
Heparin-associated immune thrombocytopenia

ICD-9CM CODES
289.84 Heparin-induced thrombocytopenia (HIT)
ICD-10CM CODES
D75.82 Heparin-induced thrombocytopenia (HIT)

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Occurs in 0.2% to 5% of patients exposed to heparin. Unfractionated heparin is associated with a 5 to 10 times higher risk of HIT compared with low-molecular-weight heparin. Initially, there was an overwhelming underdiagnosis of HIT; however, since the introduction of HIT antibody ELISA test, there is a propensity to overdiagnose HIT irrespective of the clinical scenario.
PREDOMINANT SEX AND AGE: Females are at slightly higher risk than males. More common in adults but may also occur in children.
RISK FACTORS: Longer duration of exposure to heparin, type of heparin (unfractionated heparin has a greater risk), type of patient (surgical patients, especially cardiac and orthopedic surgery, are at higher risk than medical patients).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Suspect in a patient with:
- Exposure to heparin for 4 to 14 days OR who was exposed to heparin in the prior 3 mo.
- Unexplained platelet count decrease to 50% below pretreatment baseline.
- Onset of thrombocytopenia 5 to 10 days after heparin initiation.
- Evidence of acute venous or arterial thrombosis.
- Skin lesions/necrosis at heparin injection sites.
- Acute anaphylactoid reaction during administration of heparin bolus.

ETIOLOGY

Occurs due to the formation of IgG antibodies, directed against heparin in complex with platelet factor 4, which bind to and activate platelets. Activated platelets release platelet factor 4 (leading to more antibody production) and undergo aggregation and premature removal from the circulation (resulting in thrombocytopenia). This platelet activation and antibody formation also can lead to thrombosis. Fig. EH1-27 illustrates the mechanism of HIT.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Thrombocytopenia due to other causes including:
- Sepsis.
- Disseminated intravascular coagulation.
- Thrombocytopenic thrombotic purpura.
- Hemolytic uremic syndrome.
- Drug-induced thrombocytopenia (other than heparin).
- Antiphospholipid antibody syndrome.

WORKUP

HIT is first and foremost a clinical diagnosis that is confirmed with laboratory testing. See Table H1-13 for workup based on pretest probability. If the patient has a low pretest probability score, heparin can be safely continued, and there is no need to send for further testing for HIT. If the patient has a moderate to high pretest probability, HIT testing (Table H1-14), imaging studies for lower-extremity deep venous thrombosis (also consider imaging of upper extremities if swelling is present or venous catheters are in place), cessation of heparin products, and alternative anticoagulation should all be performed.

TABLE H1-13 A Diagnostic and Treatment Approach to Heparin-Induced Thrombocytopenia

Suspicion of HIT Based upon the "**4 T**'s"	Score	Pre-Test Probability Score Criteria 2	1	0
Thrombocytopenia	☐	nadir 20-100, or >50% platelet fall	nadir 10-19, or 30-50% platelet fall	nadir <10, or <30% platelet fall
Timing of onset of platelet fall	☐	day 5-10, or ≤day 1 with recent heparin*	>day 10 or timing unclear (but fits with HIT)	≤day 1 (no recent heparin)
Thrombosis or other sequelae	☐	proven thrombosis, skin necrosis, or ASR†	progressive, recurrent, or silent thrombosis; erythematous skin lesions	none
Other cause of platelet fall	☐	none evident	possible	definite
Total Pre-Test Probability Score	☐	periodic reassessment as new information can change pre-test probability (e.g., positive blood cultures)		

Total Pre-Test Probability Score

High			Moderate		Low				
8	7	6	5	4	3	2	1	0	

Stop heparin‡, give alternative non-heparin anticoagulant argatroban¶ or lepirudin# or danaparoid** (or bivalirudin†† or fondaparinux‡‡) | Physician judgment | Continue (LMW) heparin

Positive test for HIT antibodies ← **HIT Test** → **Negative** test for HIT antibodies

Positive: Continue non-heparin anticoagulant until platelet count recovery

Negative: Consider continuing or switching back to (LMW) heparin ##

Imaging studies for lower-limb DVT†††

Thrombosis***: **If HIT,** continue non-heparin anticoagulant until platelet count recovery, then **cautious coumarin overlap¶¶**

No Thrombosis: **If HIT,** consider anticoagulating until platelet count recovery, even if no thrombosis apparent (± coumarin¶¶)

*recent heparin indicates exposure within the past 30 days (2 points) or past 30-100 days (1 point)
†ASR, acute systemic reaction following *i.v.* heparin bollus
‡stop all heparin, including catheter "flushes" and, possibly, heparin-coated catheters
¶argatroban: approved (U.S., Canada) for isolated HIT and HIT complicated by thrombosis (2 μg/kg/min *i.v.*, adjusted to 1.5-3.0X patient's baseline aPTT or the mean of the laboratory normal range); reduce dose for hepatobiliary compromise: may increase INR more than the other direct thrombin inhibitors, thus requiring care in managing coumarin overlap (see ¶¶ below)
#lepirudin: approved (U.S., Canada, E.U., elsewhere) for treatment of thrombosis complicating HIT (±0.4 mg/kg *i.v.* bolus, then 0.15 mg/kg/h adjusted to 1.5-2.5X patient's baseline aPTT or mean of the laboratory normal range); used (off-label) also to treat isolated HIT (0.1 mg/kg/h, adjusted by aPTT); to avoid overdosing and anaphylaxis, it may be preferable to omit the bolus, and begin as *i.v.* infusion (except when facing life- or limb-threatening thrombosis); reduce dose for renal insufficiency
**danaparoid: usual *i.v.* bolus, 2250 U (body weight 60-75 kg) followed by infusion (400 U/hr for 4 h, then 300 U/h for 4 h, then 200 U/h, adjusted by anti-factor Xa levels); this therapeutic-dose regimen is appropriate both for isolated HIT and for HIT complicated by thrombosis (though higher than approved dose in some jurisdictions); withdrawn from U.S. market (2002)
††bivalirudin: no bolus, *i.v.* infusion 0.15 mg/kg/h adjusted by aPTT; limited experience (off-label)
‡‡fondaparinux: dosing for HIT not established; limited experience (off-label)
¶¶delay coumarin pending substantial platelet count recovery (at least >100, preferably >150); begin coumarin in low doses, with at least 4-5 day overlap, stopping alternative anticoagulant when INR therapeutic for 2 days and platelets recovered
##depending on physician confidence in the laboratory's ability to rule out HIT antibodies (usually, negative PF4-dependent enzyme-immunoassay and/or washed platelet activation assay performed by an experienced laboratory)
***some thrombi may require special treatment, e.g., thrombectomy for large limb artery thrombosis
†††routine ultrasound of lower-limb veins recommended, since many HIT patients have subclinical deep-vein thrombosis (DVT)

From Warkentin TE.; et al. Platelet-endothelial interactions: sepsis, HIT, and antiphospholipid syndrome. *Hematology (Am Soc Hematol Educ Prog)* 497-519, 2003.

TABLE H1-14 Laboratory Assays for Heparin-Induced Thrombocytopenia

Assay	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Functional assay (e.g., serotonin release assay)	88	~100	~100	81
PF4/heparin enzyme immunoassay (ELISA)	95-98	86	93	95

ELISA, Enzyme-linked immunosorbent assay; *PF4,* platelet factor 4.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

Patients with intermediate and high pretest probability but no HIT antibodies or intermediate pretest probability and only weakly positive HIT antibodies (based on optical density, see below) can resume heparin use as HIT is unlikely in these scenarios. Patients with high pretest probability and weakly positive antibodies or intermediate/high pretest probability and moderate to strongly positive antibodies likely have HIT and should be treated as such.

LABORATORY TESTS

These can be broadly divided into immunoassays (high sensitivity) and functional assays (high specificity). In the appropriate clinical setting, testing for HIT antibodies with an enzyme-linked immunosorbent assay, or ELISA, can be useful. This test is very sensitive, but not specific. The majority of patients with positive testing for HIT antibodies will not develop clinical HIT. Thus, HIT antibody testing is more effective for ruling out rather than confirming the diagnosis of HIT. More recently, use of the HIT antibody optical density as well as the immunoglobulin subtypes of the HIT antibody have entered the diagnostic realm. Higher optical density levels are associated with increased likelihood of a positive functional assay, higher pretest probability score, and increased risk of thrombosis. Weakly positive optical densities (0.4 to 1.0) are only rarely associated with functional assay positivity. In contrast, optical densities >2.0 almost always show heparin-dependent platelet activation. Optical densities are thus defined as weakly positive (0.4-1.0), moderately positive (1.0-2.0), or strongly positive (>2.0). The HIT antibody IgG subtype is the pathologic antibody for HIT. Hence, use of IgG-specific ELISA kits increases the test specificity over the polyspecific (IgA/M/G) antibody. Patients with low pretest probability should not have HIT antibody testing performed, while all patients with intermediate and high pretest probability of HIT benefit from HIT antibody testing.

The gold standard test for HIT is to measure heparin-dependent platelet activation via the functional serotonin release assay (14C-SRA). This is both a highly sensitive and specific test. Donor platelets are incubated with radiolabeled serotonin. The platelets internalize the serotonin and are then exposed to the patient's serum and heparin at a therapeutic concentration. If antibodies to the platelet factor 4-heparin complex are present in the patient's serum, the platelets react and released radioactive serotonin is then measured. Availability and turn-around time of this test is dependent on the institution, which can influence the test's clinical utility. Cases where there is intermediate pretest probability, but only a weakly positive HIT antibody score, benefit the most from confirmatory SRA testing. Here, a positive SRA test will argue for HIT while negative SRA tests will suggest absence of HIT.

IMAGING STUDIES

Doppler sonography of the extremities in the correct clinical setting.

Rx TREATMENT

- For patients with a moderate or high pretest probability, discontinue all heparin exposure. Even if the patient does not have a clinically evident thrombosis, he or she is at a 50% risk of developing a clot within the subsequent 30 days. Thus, the patient must be started on an alternate anticoagulant.
- Three agents, all direct thrombin inhibitors, are approved for this indication:
  1. Argatroban (avoid in liver dysfunction).
  2. Lepirudin (avoid in renal dysfunction).
  3. Bivalirudin (bivalirudin is approved only for patients with HIT or at risk of HIT who are undergoing PCI).
- These drugs should be continued as a single agent until the platelet count returns to baseline (generally a platelet count of 150×10^9/L but it is important to consider the individual patient's baseline), then warfarin can be added at a maximum dose of 5 mg/day. This overlap therapy should continue until the platelet count has reached a stable plateau, the INR has reached the intended target (remember that argatroban artificially elevates the INR), and after a minimum overlap of 5 days of both the direct thrombin inhibitor and warfarin. The length of treatment is controversial, but most clinicians agree that 1 month of alternate anticoagulation is sufficient in the absence of thrombosis, while 3 to 6 months of treatment are required in the presence of thrombosis.
- There are emerging data showing efficacy and lower bleeding risk in HIT for fondaparinux when compared with the direct thrombin inhibitors. Fondaparinux is a synthetic pentasaccharide that binds antithrombin, causing long-acting inhibition of activated factor X, but not thrombin. It is not FDA approved for HIT, but its use in HIT in pregnancy has been reported. It can initiate the formation of anti-PF4 antibodies, but it does not support platelet activation by the newly formed immune complexes.

NONPHARMACOLOGIC THERAPY

All nonpharmacologic therapies including surgical procedures.

REFERRAL

Request a hematology consultation.

PEARLS & CONSIDERATIONS

COMMENTS

HIT paradoxically causes thrombocytopenia and *clotting,* not bleeding.

PREVENTION

Consider the use of low-molecular-weight heparin (as opposed to unfractionated heparin) as DVT prophylaxis.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **KALYAN C. MANTRIPRAGADA, M.D., M.P.H., JOHN L. REAGAN, M.D.,** and **ANGELA M. TABER, M.D.**

EVIDENCE

Abstract[1]

Background:

Some patients with acute VTE who may previously have been exposed to heparin products have unrecognized antibodies implicated in heparin-induced thrombocytopenia (HIT). Antibody prevalence and patient consequences upon exposure to heparin, low-molecular-weight heparin, and fondaparinux are uncertain.

Methods:

In this secondary analysis, we tested patients in the MATISSE VTE studies at study entry for heparin-dependent antibodies and further tested patients with enzyme-linked immunosorbent assay (ELISA)-positive results for platelet-activating antibodies. We compared the risk of HIT (>50% fall in platelet count, heparin-dependent antibodies, no contradicting features) between patients treated with heparin (either unfractionated or low molecular weight [enoxaparin]) vs those who received fondaparinux. Comparison groups for thrombocytopenia occurrence comprised patients with ELISA-positive, platelet-activating, antibody-positive results; ELISA-positive, but platelet-activating antibody-negative results; and randomly selected antibody-negative results.

Results:

A total of 127 of 3994 patients (3.2%) had ELISA-positive results at baseline, but only 14 (0.4%; 95% CI, 0.2%-0.6%) had platelet-activating antibodies. Among these 14, four treated with unfractionated or low-molecular-weight heparin developed HIT compared with zero of 10 fondaparinux-treated patients (OR, 95; 95% CI, 8-1,123; $P<.001$). This frequency (four of four, 100%) significantly differed from that of both heparin-treated patients whose results were ELISA positive, but platelet-activating antibody negative, and from heparin-treated antibody-negative control subjects (zero of 15 and zero of 27, respectively; $P<.001$ for both).

Conclusions:

Of patients with VTE, 0.4% had pathologic platelet-activating heparin-dependent antibodies rather than the 3.2% detected by the recommended cutoff of the commercial ELISA. Among study patients with acute VTE who had platelet-activating antibodies, treatment with fondaparinux reduced the risk of precipitating rapid-onset HIT. Ⓐ

Evidence-Based Reference

Warkentin TE, et al.: Prevalence and risk of preexisting heparin-induced thrombocytopenia antibodies in patients with acute VTE, *Chest* 140:366–373, 2011. Ⓐ

SUGGESTED READINGS

Cuker A, Cines DB: How I treat heparin-induced thrombocytopenia, *Blood* 119:2209–2218, 2012.

Kelton JK et al.: Nonheparin anticoagulants for heparin-induced thrombocytopenia, *N Engl J Med* 368:737–744, 2013.

Linkins LA et al.: Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, *Chest* 141(2 suppl):e495S–e530S, 2012.

Warkentin TE et al.: Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition), *Chest* 133:340–380, 2008.

Warkentin TE et al.: Platelet-endothelial interactions: sepsis, HIT, and antiphospholipid syndrome, *Hematology (Am Soc Hematol Educ Prog)* 497–519, 2003.

Warkentin TE et al.: The serological profile of fondaparinux-associated heparin-induced thrombocytopenia syndrome, *Thromb Haemost* 108:394–396, 2012.

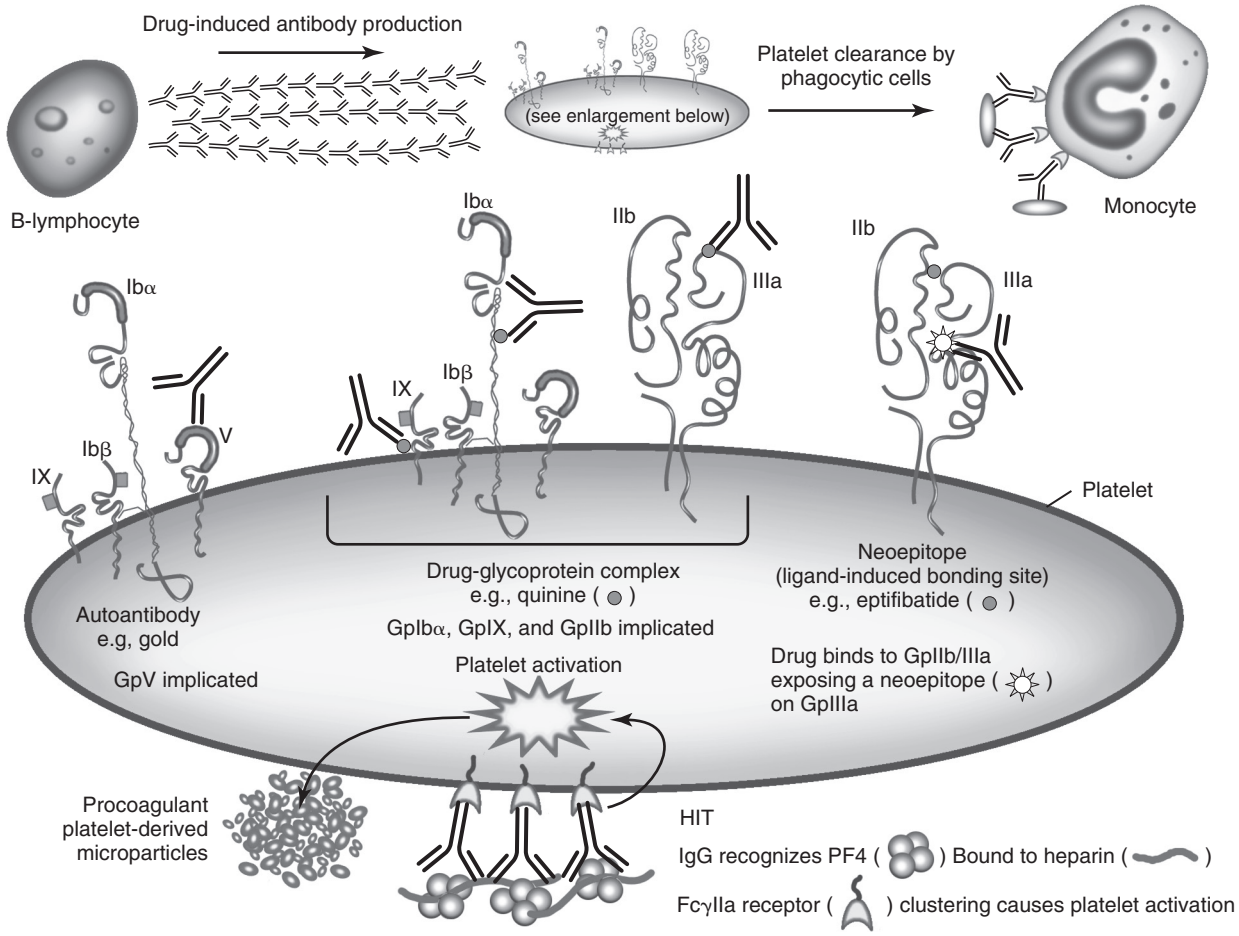

FIGURE EH1-27 Mechanisms of drug-induced immune thrombocytopenia. Four immune thrombocytopenic syndromes are illustrated. On the *bottom* of the schematic platelet, heparin-induced thrombocytopenia (HIT) is illustrated, indicating that IgG antibodies bind to complexes of platelet factor 4 (PF4) and heparin, with the Fc regions of the antibodies binding to the platelet FcγIIa receptors, resulting in platelet activation (including generation of procoagulant, platelet-derived microparticles). On the top of the schematic platelet, three mechanisms are illustrated that lead to increased platelet clearance by phagocytic cells. From *left to right,* these are autoantibody-induced immune thrombocytopenia (e.g., gold-induced antiglycoprotein V [GPV] antibodies); drug-dependent antibodies reactive against drug (or drug metabolite)/platelet glycoprotein complex(es) (e.g., quinine-induced thrombocytopenia, in which drug-dependent antibodies against GPIbα, GPIX, and GPIIb have been implicated, resulting in an antibody/drug/glycoprotein ternary complex); and antibodies against neoepitope(s) formed in the presence of a drug (e.g., eptifibatide-induced immune thrombocytopenia caused by formation of ligand-induced binding site elsewhere on the GPIIb/IIIa complex following eptifibatide binding). Note that preexisting (naturally occurring) antibodies can explain abrupt-onset thrombocytopenia in a patient receiving eptifibatide for the first time. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

Hepatic Encephalopathy PTG EBM

BASIC INFORMATION

DEFINITION

Hepatic encephalopathy is a neuropsychiatric syndrome occurring in patients with severe impairment of liver function and consequent accumulation of toxic products not metabolized by the liver. It is characterized by gradual impairment of the ability to perform mental tasks and to react to external stimuli. ***Minimal hepatic encephalopathy*** refers to patients with hepatic cirrhosis and mild cognitive impairment, but no history of overt encephalopathy.

SYNONYMS

Hepatic coma

ICD-9CM CODES
572.2 Hepatic encephalopathy
ICD-10CM CODES
K72.0 Acute and subacute hepatic failure
K72.1 Chronic hepatic failure
K72.9 Hepatic failure, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE/PREVALENCE: Hepatic encephalopathy occurs in >40% of all cases of cirrhosis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Hepatic encephalopathy can be classified by clinical stages described in Table H1-15.

The physical examination in hepatic encephalopathy varies with the stage and may reveal the following abnormalities:

- Skin: jaundice, palmar erythema, spider angiomata, ecchymosis, dilated superficial periumbilical veins (caput medusae) in patients with cirrhosis.
- Eyes: scleral icterus, Kayser-Fleischer rings (Wilson's disease).
- Breath: fetor hepaticus.
- Chest: gynecomastia in men with chronic liver disease.
- Abdomen: ascites, small nodular liver (cirrhosis), tender hepatomegaly (congestive hepatomegaly).
- Rectal examination: hemorrhoids (portal hypertension), guaiac-positive stool (alcoholic gastritis, bleeding esophageal varices, peptic ulcer disease, bleeding hemorrhoids).
- Genitalia: testicular atrophy in males with chronic liver disease.
- Extremities: pedal edema from hypoalbuminemia.
- Neurologic: flapping tremor (asterixis), obtundation, coma with or without decerebrate posturing.

ETIOLOGY

- Hepatic encephalopathy is thought to be caused mainly by accumulation of unmetabolized ammonia.
- Precipitating factors in patients with underlying cirrhosis (upper gastrointestinal bleeding, hypokalemia, hypomagnesemia, analgesic and sedative drugs, sepsis, alkalosis, increased dietary protein).
- Acute fulminant viral hepatitis.
- Drugs and toxins (e.g., isoniazid, acetaminophen, diclofenac and other NSAIDs, statins, methyldopa, loratadine, propylthiouracil, lisinopril, labetalol, halothane, carbon tetrachloride, erythromycin, nitrofurantoin, troglitazone, herbal products, flavocoxid).
- Reye's syndrome.
- Shock and/or sepsis.
- Fatty liver of pregnancy.
- Metastatic carcinoma, hepatocellular carcinoma.
- Other: autoimmune hepatitis, ischemic venoocclusive disease, sclerosing cholangitis, heat stroke, amebic abscesses.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Delirium caused by medications or illicit drugs.
- Cerebrovascular accident, subdural hematoma.
- Meningitis, encephalitis.
- Hypoglycemia.
- Uremia.
- Cerebral anoxia.
- Hypercalcemia.
- Metastatic neoplasm to brain.
- Alcohol withdrawal syndrome.

WORKUP

Hepatic encephalopathy should be considered in any patient with cirrhosis who presents with neuropsychiatric manifestations. Exclude other etiologies with comprehensive history (obtained from patient, relatives, and others), physical examination, and laboratory and imaging studies. A pertinent history should include exposure to hepatitis, ethanol intake, drug history, exposure to toxins, IV drug abuse, measles or influenza with aspirin use (Reye's syndrome), and history of carcinoma (primary or metastatic). Minimal hepatic encephalopathy may not be obvious on clinical examination, but can be detected with neurophysiologic and neuropsychiatric testing.

LABORATORY TESTS

- Alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase, glucose, calcium, electrolytes, blood urea nitrogen, creatinine, albumin.
- Complete blood count, platelet count, prothrombin time, partial thromboplastin time.
- Serum and urine toxicology screen in suspected medication or illegal drug use.
- Blood and urine cultures, urinalysis.
- Venous ammonia level. Measurement of serum ammonia level is useful in the evaluation of acute liver failure because levels correlate with the severity of encephalopathy and elevated levels are predictive of severe encephalopathy and cerebral edema. It is not useful for the evaluation or screening of hepatic encephalopathy in patients with chronic liver disease because it can neither rule in nor rule out hepatic encephalopathy, and levels do not correlate with the degree of encephalopathy.
- Arterial blood gases.

IMAGING STUDIES

CT scan or MRI of the brain may be useful in selected patients to exclude other etiologies when diagnosis is unclear.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Identification and treatment of precipitating factors.
- Restriction of protein intake (30 to 40 g/day) to reduce toxic protein metabolites.

ACUTE GENERAL Rx

Table H1-16 summarizes the management of fulminant hepatic failure.

Reduction of colonic ammonia production:

- Lactulose 30 ml of 50% solution qid initially; dose is subsequently adjusted depending on clinical response. Ornithine aspartate 9 g tid is also effective. Lactulose may improve hepatic encephalopathy but may be less effective than antibiotics.
- Neomycin 1 g PO q4 to 6h or given as a 1% retention enema solution (1 g in 100 ml of isotonic saline solution); neomycin should be used with caution in patients with renal

TABLE H1-15 Clinical Stages of Hepatic Encephalopathy

Stage	Asterixis	EEG Changes	Clinical Manifestations
I (prodrome)	Slight	Minimal	Mild intellectual impairment, disturbed sleep-wake cycle
II (impending)	Easily elicited	Usually generalized	Drowsiness, confusion, coma/inappropriate behavior, disorientation, mood swings
III (stupor)	Present if patient cooperative	Grossly abnormal slowing of rhythm	Drowsy, unresponsive to verbal commands, markedly confused, delirious, hyperreflexia, positive Babinski sign
IV (coma)	Usually absent	Appearance of delta waves, decreased amplitudes	Unconscious, decerebrate or decorticate response to pain present (stage IVA) or absent (stage IVB)

EEG, Electroencephalogram.
From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.

TABLE H1-16 Management of Fulminant Hepatic Failure

No sedation except for procedures
Minimal handling
Enteric precautions until infection ruled out
Monitor:
- Heart and respiratory rate
- Arterial BP, CVP
- Core/toe temperature
- Neurologic observations
- Gastric pH (>5.0)
- Blood glucose (>4 mmol/L)
- Acid-base
- Electrolytes
- PT, PTT

Fluid balance
- 75% maintenance
- Dextrose 10%-50% (provide 6-10 mg/kg/min)
- Sodium (0.5-1 mmol/L)
- Potassium (2-4 mmol/L)

Maintain circulating volume with colloid/FFP
Coagulation support only if required
Drugs
- Vitamin K
- H_2 antagonist
- Antacids
- Lactulose
- *N*-acetylcysteine for acetaminophen toxicity
- Broad-spectrum antibiotics
- Antifungals

Nutrition
- Enteral feeding (1-2 g protein/kg/day)
- PN if ventilated

BP, Blood pressure; *CVP,* central venous pressure; *FFP,* fresh frozen plasma; *PN,* parenteral nutrition; *PT,* prothrombin time; *PTT,* partial thromboplastin time.
From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.

insufficiency. Metronidazole 250 mg qid may be as effective as neomycin and is not nephrotoxic; however, long-term use can be associated with neurotoxicity.
- A combination of lactulose and neomycin can be used when either agent is ineffective alone.
- The oral antibiotic rifaximin (550 mg PO bid) is effective in reducing the risk of recurrent hepatic encephalopathy in patients with cirrhosis. It can be taken with lactulose, and the combination of lactulose and rifaximin is superior to lactulose alone in reversing hepatic encephalopathy. Rifamaxin has also been shown to be effective in improving psychometric performance and health-related quality of life in patients with minimal hepatic encephalopathy. It is well tolerated but expensive.
- Probiotics (e.g., 1 capsule containing 112.5 billion viable lyophilized bacteria tid) might also be beneficial in altering gut flora to reduce ammonia production.

Treatment of cerebral edema:
- Cerebral edema is often present in patients with acute liver failure, and it accounts for nearly 50% of deaths. Monitoring intracranial pressure by epidural, intraparenchymal, or subdural transducers and treatment of cerebral edema with mannitol (100 to 200 ml of 20% solution [0.3 to 0.4 g/kg of body weight]) given by rapid IV infusion are helpful in selected patients (e.g., potential transplantation patients).
- Dexamethasone and hyperventilation (useful in head injury) are of little value in treating cerebral edema from liver failure.

BOX H1-4 Various Prognostic Criteria Used for Liver Transplantation in Patients with Fulminant Hepatic Failure

King's College Criteria
Acetaminophen overdose:
- Arterial pH <7.3 (irrespective of grade of encephalopathy) or
- PT >100 sec (INR >6.5)
- Serum creatinine >3.4 mg/dl (>300 μmol/L)
- Patients with grade III and IV hepatic encephalopathy

Nonacetaminophen liver injury:
- PT >100 sec (INR >6.5) (irrespective of grade of encephalopathy) or any three of the following variables:
  1. Age <10 or >40 years
  2. Non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions
  3. Jaundice >7 days before onset of encephalopathy
  4. Serum bilirubin 17.4 mg/dl (300 μmol/L)
  5. PT >50 sec

Cliché Criteria
Factor V <20% in persons <30 years or both of the following:
- Factor V <30% in patients >30 years
- Grade III or IV encephalopathy

Serum Gc Globulin Levels
- Decreasing Gc levels due to dying hepatocytes

Serum α-Fetoprotein Level
- Serial increase from day 1 to day 3 has shown correlation with survival

Liver Biopsy[32]
70% necrosis is discriminant of 90% mortality

Gc, Plasma group-specific component protein; *INR,* international normalized ratio; *PT,* prothrombin time.
From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

CHRONIC Rx

- Avoidance of any precipitating factors (e.g., high-protein diet, medications).
- Consideration of liver transplantation in selected patients with progressive or recurrent encephalopathy (Box H1-4). Liver transplantation remains the only curative therapeutic option.

DISPOSITION

Prognosis varies with the underlying etiology of the liver failure and the grade of encephalopathy (generally good for grades 1 or 2; poor for grades 3 or 4). Without proper therapy, the survival rate at 1 yr is 42% and decreases to 23% at 3 yr.

REFERRAL

The early stages of hepatic encephalopathy can be managed in the outpatient setting, whereas stages 3 or 4 require hospital admission.

PEARLS & CONSIDERATIONS

COMMENTS

- Long-acting benzodiazepines should not be used to treat anxiety and sleep disorders in patients with cirrhosis, as they may precipitate encephalopathy.
- Patients not responding to supportive therapy should be evaluated for liver transplantation.
- Not all patients with cirrhosis develop hepatic encephalopathy. It has been shown that 40% of persons with cirrhosis and minimal hepatic encephalopathy do not develop overt hepatic encephalopathy in long-term follow-up. There are genetic factors associated with development of hepatic encephalopathy in patients with cirrhosis. Genetic analyses have shown that glutaminase TACC and CACC haplotypes are linked to the risk for overt hepatic encephalopathy.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hepatic Encephalopathy (Patient Information)
Cirrhosis (Related Key Topic)
Encephalopathy (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Background & Aims:
Patients with cirrhosis and minimal hepatic encephalopathy (MHE) have driving difficulties, but the effects of therapy on driving performance is unclear. We evaluated whether performance on a driving simulator improves in patients with MHE after treatment with rifaximin.

Methods:
Patients with MHE who were current drivers were randomly assigned to placebo or rifaximin groups and followed up for 8 weeks (n = 42). Patients underwent driving simulation (driving and navigation tasks) at the start (baseline) and end of the study. We evaluated patients' cognitive abilities, quality of life (using the Sickness Impact Profile), serum levels of ammonia, levels of inflammatory cytokines, and model for end-stage-liver disease scores. The primary outcome was the percentage of patients who improved in driving performance, calculated as follows: total driving errors = speeding + illegal turns + collisions.

Results:
Over the 8-week study period, patients given rifaximin made significantly greater improvements than those given placebo in avoiding total driving errors (76% versus 31%; $P = .013$), speeding (81% versus 33%; $P = .005$), and illegal turns (62% versus 19%; $P = .01$). Of patients given rifaximin, 91% improved their cognitive performance, compared with 61% of patients given placebo ($P = .01$); they also made improvements in the psychosocial dimension of the Sickness Impact Profile compared with the placebo group ($P = .04$). Adherence to the assigned drug averaged 92%. Neither group had changes in ammonia levels or model for end-stage-liver disease scores, but patients in the rifaximin group had increased levels of the anti-inflammatory cytokine interleukin-10.

Conclusions:
Patients with MHE significantly improve driving simulator performance after treatment with rifaximin, compared with placebo. Ⓐ

Abstract[2]

Background & Aims:
The risk of exacerbating sub-clinical hepatic encephalopathy (HE) by propofol has not been established. The aim of this study is to determine whether the use of propofol, for upper endoscopy in patients with cirrhosis, precipitates subclinical HE.

Methods:
Sixty-one patients with compensated HCV and HBV cirrhosis (CP score 5 to 6) were randomly selected and divided into two groups (intent-to-treat population) matched for age, gender, and BMI. The first group received a single propofol sedation (N = 31, age 57 ± 12, dose range 70 to 100 mg/procedure) and the second group (N = 30, age 56 ± 12, dose 3 to 6 mg/procedure) received a single midazolam sedation, all done by an anesthesiologist. All patients completed number connection test (NCT), cognitive function score, time to recovery, time to discharge sheets, and hemodynamic parameters before sedation, and at discharge from the endoscopy unit, 1 h postprocedure. Thirty control subjects without cirrhosis were matched to the cirrhotic patients who received sedation with regard to age, gender, BMI, and education level.

Results:
A total of 58/61 cirrhotic patients (95%) had sub-clinical encephalopathy before the endoscopy (mean NCT 84.7 ± 77 s, normal <30 s). No patient developed overt HE after sedation. There were no differences between groups in the incidence of adverse effects, cognitive function, MELD score, CP score, oxygen saturation, or respiratory and heart rates before and after sedation. Propofol did not exacerbate minimal HE when compared with midazolam (NCT changed from 87.5 ± 62 s before sedation to 74.2 ± 58 s after sedation in the propofol group versus 72.8 ± 62 s before to 85.6 ± 72 s after sedation in the midazolam group; $p<0.01$). Time to recovery (4.1 ± 1.9 min versus 11.5 ± 5.0 min, $p<0.001$), and time to discharge (38.0 ± 9 min versus 110 ± 42 min, $p<0.001$) were significantly shorter with propofol than midazolam. Pre- and post-procedure NCT (from 25 ± 0 s to 24 ± 20 s), cognitive function score (from 25 to 26), time to recovery (3.5 ± 1.0 min), and time to discharge (35 ± 10 min) did not change in the healthy controls.

Conclusions:
Sedation with propofol has a shorter time recovery and a shorter time to discharge than midazolam and does not exacerbate sub-clinical hepatic encephalopathy in patients with compensated liver cirrhosis. Ⓐ

Evidence-Based References

Bajaj JS et al.: Rifaximin improves driving simulator performance in a randomized trial of patients with minimal hepatic encephalopathy, *Gastroenterology* 140:478–487, 2011. Ⓐ

Khamaysi I et al.: Sub-clinical hepatic encephalopathy in cirrhotic patients is not aggravated by sedation with propofol compared to midazolam: a randomized controlled study, *J Hepatol* 54:72–77, 2011. Ⓐ

SUGGESTED READINGS

Agrawal A et al.: Secondary prophylaxis of hepatic encephalopathy in cirrhosis: an open-label, randomized controlled trial of lactulose, probiotics, and no therapy, *Am J Gastroenterol* 107:1043, 2012.

Ge PS, Runyon BA: Serum ammonia level for evaluation of hepatic encephalopathy, *JAMA* 312:643–644, 2014.

Romero-Gomez M et al.: Variations in the promoter region of the glutaminase gene and the development of hepatic encephalopathy in patients with cirrhosis, *Ann Intern Med* 153:281–288, 2010.

Sharma BC et al.: A randomized, double-blind, controlled trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy, *Am J Gastroenterol* 108:1458, 2013.

Sidhu SS et al.: Rifaximin improves psychometric performance and health-related quality of life in patients with minimal hepatic encephalopathy, *Am J Gastroenterol* 106:307, 2011.

Wakim-Fleming J: Hepatic encephalopathy: suspect it early in patients with cirrhosis, *Cleve Clin J Med* 78:597–604, 2011.

BASIC INFORMATION

DEFINITION

Hepatitis A is generally an acute self-limiting infection of the liver by an enterically transmitted picornavirus, hepatitis A virus (HAV). Infection may range from asymptomatic to fulminant hepatitis.

SYNONYMS

Infectious hepatitis
Short incubation hepatitis
Type A hepatitis
HAV (hepatitis A virus)

ICD-9CM CODES
070.1 Hepatitis A
ICD-10CM CODES
B15.9 Hepatitis A without hepatic coma
B15.0 Hepatitis A with hepatic coma

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE

- Hepatitis A occurs worldwide, affecting 1.4 million people annually and accounting for 20% to 40% of cases of viral hepatitis in the United States.
- The seroprevalence increases with age, ranging from 10% in individuals aged <5 yr to 74% in those aged >50 yr.
- In the United States, average disease rate was ~15 cases/100,000 persons/yr before routine vaccination of all children in certain states. The incidence after 2005 is about 1 case/100,000.
- The incidence is relatively higher in some regions in the United States, including Arizona, Alaska, California, Idaho, Nevada, New Mexico, Oklahoma, Oregon, South Dakota, and Washington.
- At-risk groups include:
  1. Residents and staff of group homes.
  2. Children and employees of day care centers.
  3. People who engage in oral-anal contact, regardless of sexual orientation.
  4. IV drug abusers.
  5. Travel to endemic areas.
  6. Areas of overcrowding, poor sanitation, inadequate sewage treatment.

PREVALENCE

- Approximately three fourths of the U.S. population has serologic evidence of prior infection.
- Anti-HAV prevalence has an inverse relation to income and household size.

PREDOMINANT SEX: None, except higher infection rates seen in homosexual males who engage in oral-anal contact.

PREDOMINANT AGE/PEAK INCIDENCE

- In areas of high rates of hepatitis A, virtually all children are infected while younger than 10 yr, but disease is rare.
- In areas of moderate rates of hepatitis A, disease occurs in late childhood and young adults.
- In areas of low rates of hepatitis A, most cases occur in young adults.

INCUBATION PERIOD: Averages 30 days (15 to 50)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Infection with HAV may have acute or subacute presentation, icteric or anicteric. Severity of illness seems to increase with age (90% of infection in children aged <5 yr may be subclinical).
- A preicteric, prodromal phase of approximately 1 to 14 days; 15% no apparent prodrome. Symptoms are usually abrupt in onset and may include anorexia, malaise, nausea, vomiting, fever, headache, and abdominal pain.
- Less common symptoms are chills, myalgias, arthralgias, upper respiratory symptoms, constipation, diarrhea, pruritus, urticaria.
- Jaundice occurs in >70% of patients.
- The icteric phase is preceded by dark urine.
- Bilirubinuria is typically followed a few days later by clay-colored stools and icterus.

PHYSICAL EXAMINATION

- Jaundice: Peaks in severity 2 wk after onset.
- Hepatomegaly.
- Splenomegaly.
- Cervical lymphadenopathy.
- Evanescent rash.
- Petechiae.
- Cardiac arrhythmias.

COMPLICATIONS

- Cholestasis.
- Fulminant hepatitis.
- Arthritis.
- Myocarditis.
- Optic neuritis.
- Transverse myelitis.
- Thrombocytopenic purpura.
- Aplastic anemia.
- Red cell aplasia.
- Henoch-Schönlein purpura.
- IgA dominant glomerulonephritis.

ETIOLOGY

- Caused by HAV, a 27-nm, nonenveloped, icosahedral, positive-stranded RNA virus.
- Transmission is fecal-oral route, from person to person. Transmission occurs with close contact or with food- or water-borne outbreaks with inadequately purified water or cooked foods. Recent outbreaks have involved green onions and tomatoes.
- Parenteral transmission is considered rare.
- Vertical transmission has also been reported.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other hepatitis virus (B, C, D, E).
- Infectious mononucleosis.
- Cytomegalovirus infection.
- Herpes simplex virus infection.
- Leptospirosis.
- Brucellosis.
- Drug-induced liver disease.
- Ischemic hepatitis.
- Autoimmune hepatitis.

WORKUP

- IgM antibody specific for HAV.
- Liver function tests; ALT and AST elevations are sensitive for liver damage but not specific for HAV.
- Elevated ESR.
- CBC; may find mild lymphocytosis.

LABORATORY TESTS

- Diagnosis confirmed by IgM anti-HAV; it is detectable in almost all infected patients at presentation and remains positive for 3 to 6 mo.
- A fourfold rise in titer of total antibody (IgM and IgG) to HAV confirms acute infection.
- HAV detection in stool and body fluids by electron microscopy.
- HAV RNA detection in stool, body fluids, serum, and liver tissue.
- ALT and AST usually more than 8 times normal in acute infection.
- Bilirubin usually 5 to 15 times normal.
- Alkaline phosphatase minimally elevated but higher level in cholestasis.
- Albumin and prothrombin time are generally normal; if elevated, they may herald hepatic necrosis.
- Fig. H1-28 illustrates the typical course of hepatis A.

IMAGING STUDIES

- Rarely useful.
- Sonogram (fulminant hepatitis).

TREATMENT

- Usually self-limited.
- Supportive care.
- Those with fulminant hepatitis may require hospitalization and treatment of associated complications.
- Activity as tolerated.
- Advise to avoid alcohol and hepatotoxic drugs.
- Patients with fulminant hepatitis should be assessed for liver transplantation.

CHRONIC Rx

No chronic HAV and no chronic carrier state.

DISPOSITION

- Follow-up as outpatient.
- Most patients recover within 2 months of infection, although 10% to 15% of patients will experience a relapse in the first 6 months.
- HAV is a self-limited infection and does not cause chronic hepatitis.

REFERRAL

- To a hepatologist if severe, fulminant hepatitis develops
- To a transplant surgeon if liver transplant becomes a consideration for fulminant hepatitis and liver failure

PEARLS & CONSIDERATIONS

- All cases of hepatitis A should be reported to the public health authorities because food-borne or water-borne outbreaks may occur, and public health efforts (mass vaccination or immunoglobulin therapy) may prevent secondary cases.
- Hepatitis A is a common illness in internationally traveled and developing countries. Pretravel vaccination is strongly recommended for travelers who are HAV susceptible.

PREVENTION

- Improvement in hygiene and sanitation.
- Heating food.
- Avoidance of water and foods from endemic area.

PASSIVE IMMUNIZATION

- Immunoglobulin provides protection against HAV through passive transfer of antibody.
- Preexposure prophylaxis indicated for people traveling to endemic areas (Ig 0.02 or 0.06 ml/kg given IM) and have not received or cannot receive the hepatitis A vaccine before departure. The lower dose is effective for up to 3 mo, and the higher dose is effective for up to 5 mo.
- Postexposure prophylaxis (Ig 0.02 ml/kg given IM) is indicated for people with recent exposure (within 2 wk) to HAV and who have not been previously vaccinated. In high-risk patients, vaccine may be administered with immunoglobulin.

ACTIVE IMMUNIZATION

- There are several inactivated and attenuated hepatitis vaccines; only the inactivated vaccines are currently available for use and they have been found to be safe and highly immunogenic: HAVRIX or VAQTA. These can be used in adults and children older than 12 mo. They are given as a two-dose regimen 6 mo to 1 yr apart. A combined hepatitis A and hepatitis B vaccine called TWINRX is also available.
- Protective antibody levels were reached in 94% to 100% of adults 1 mo after the first dose; similar results have been found for children and adolescents.
- Theoretic analyses of antibody levels estimate duration of immunity to be 10 to 20 yr.
- Vaccine should be considered for persons who are at risk: those traveling to or working in endemic areas, homosexual men, illegal drug users, persons with chronic liver disease, children in areas with high rates of hepatitis A infection.
- The Advisory Committee on Immunization Practices recommends routine hepatitis A vaccination for all children beginning at 12 to 23 mo of age.
- Clinical trials have shown equivalency between use of Ig and hepatitis A vaccine for postexposure prophylaxis in preventing symptomatic hepatitis A in healthy persons 2 to 40 yr of age. The Advisory Committee guidelines now provide for the use of Ig or the vaccine for this population. Those patients who are immunocompromised, have chronic liver disease, or are <1 yr of age should receive Ig.

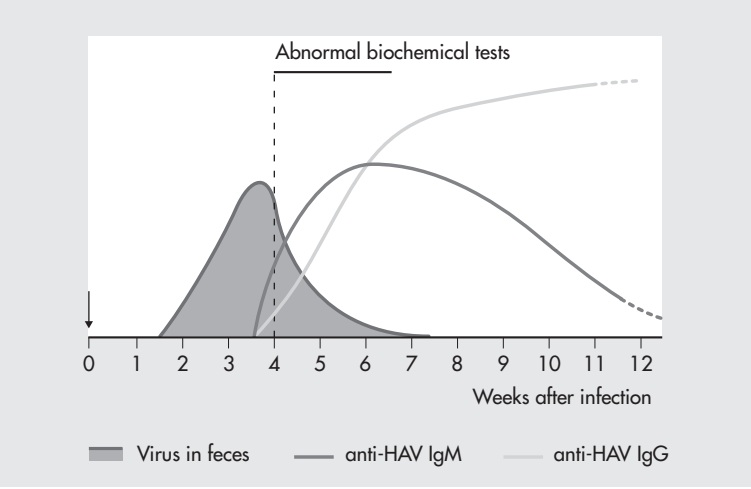

FIGURE H1-28 Course of acute hepatitis A. (From Cohen J, Powderly WG: *Infectious diseases,* ed 2, St Louis, 2004, Mosby.)

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hepatitis A (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Fiore AE et al.: Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR Recomm Rep* 55(RR-7):1, 2006.

Koslap-Petraco MB et al.: Hepatitis A: disease burden and current childhood vaccination strategies in the United States, *J Pediatr Health Care* 22(1):3–11, 2004.

Leach CT: Hepatitis A in the United States, *Pediatr Infect Dis J* 23(6):551, 2004.

Matheny SC: *Hepatitis A. Am Fam Physician* 86(11):1027–1034, 2012.

Victor JC et al.: Hepatitis A vaccine versus immune globulin for postexposure prophylaxis, *N Engl J Med* 357:1685–1694, 2007.

Wu D, Guo CY: Epidemiology and prevention of hepatitis A in travelers, *J Travel Med* 20(6):394–399, 2013.

BASIC INFORMATION

DEFINITION

Hepatitis B is an acute infection of the liver parenchymal cells caused by the hepatitis B virus (HBV).

SYNONYMS

Serum hepatitis
Long incubation (30 to 180 days) hepatitis

ICD-9CM CODES
070.3 Hepatitis B
ICD-10CM CODES
B16 Acute hepatitis
B16.9 Acute hepatitis B without delta agent and without hepatic coma
B16.1 Acute hepatitis B with delta agent (coinfection) without hepatic coma
B18.0 Chronic hepatitis B with delta agent
B18.1 Chronic hepatitis B without delta agent
B19.10 Unspecified viral hepatitis B without hepatic coma

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):
- ~200,000 to 300,000 infections annually in the United States.
- Much higher incidence in Europe (~1 million new cases annually) and in areas of high endemicity.
- In the United States, transmission is mainly horizontal (percutaneous and mucous membrane exposure to infectious blood and other body fluids [e.g., sexual transmission, either homosexual or heterosexual]); also from needle sharing among drug abusers; occupational exposure to contaminated blood and blood products; persons receiving transfusions of blood and blood products; and hemodialysis patients.

NOTE: Improved screening of blood and blood products has greatly reduced, although not eliminated, the risk of posttransfusion HBV infection.
- In areas of high endemicity, transmission is largely vertical (perinatal): HBV exists in the blood and body fluids. Perinatal transmission from HBsAg-positive mothers is as high as 90% unless immunoprophylaxis is given.

PREVALENCE (IN U.S.)
- The WHO estimates that 400 million people worldwide (6% of the population) are chronic HBV carriers. North America, Western Europe, and Australia are areas of low prevalence, <2%. In the United States an estimated 800,000 to 1.4 million people have chronic HBV infection.
- Africa, Asia, and the Western Pacific region are areas of high prevalence, ≥8%.
- Southern and Eastern Europe have intermediate rates, 2% to 7%.
- Chronically infected persons, those with positive HBsAg for >6 mo, represent the major source of infection.
- As many as 95% of infants and children aged <5, who typically have subclinical acute infection, will become chronic HBV carriers.
- Adults are more likely to have clinically evident acute infection, but only 1% to 5% will develop chronic infection.
- ~0.1% of patients with acute infection will develop fulminant acute hepatitis resulting in death.

PREDOMINANT SEX
- Predominant in males because of increased IV drug abuse, homosexuality.
- Females more commonly terminate in chronic carrier state.

PREDOMINANT AGE: 20 to 45 yr.
PEAK INCIDENCE: 30 to 45 yr of age, at rates of 5% to 20%.
GENETICS: Neonatal infection:
- Rare in the United States.
- High (up to 90%) in areas of high endemicity (only 5% to 10% of perinatal infections occur in utero).

PHYSICAL FINDINGS & CLINICAL PRESENTATION (Fig. H1-29)

- Often nonspecific symptoms.
- Profound malaise.
- Many asymptomatic cases.
- Prodrome:
  1. 15% to 20% serum sickness (urticaria, rash, arthralgia) during early HBsAg.
  2. HBsAg-Ab complex disease (polyarteritis nodosa–arthritis, arteritis, glomerulonephritis).
- Hepatomegaly (87%) with right upper quadrant (RUQ) tenderness.
  1. Hepatic punch tenderness.
  2. Splenomegaly: rare (10% to 15%).
- Jaundice, dark urine, with occasional pruritus.
- Variable fever (when present, generally precedes jaundice and rapidly declines following onset of icteric phase).
- Spider angiomata: rare; resolves during recovery.
- Rare polyarteritis nodosa, cryoglobulinemia.

ETIOLOGY

- Caused by HBV (42-nm hepadnavirus with an outer surface coat [HBsAg], inner nucleocapsid core [HBcAg; HBeAg]; DNA polymerase; and partially double-stranded DNA genome). There are eight genotypes (A to H) based on nucleotide sequence. The prevalence of each genotype varies widely.
- Transmission by parenteral route (needle use, tattooing, ear piercing, acupuncture, transfusion of blood and blood products, hemodialysis, sexual contact), perinatal transmission.
- Infection may result from contact of infectious material with mucous membranes and open skin breaks (e.g., HBV is stable and can be transmitted from toothbrushes, utensils, razors, baby toys, assorted medical equipment [respirators, endoscopes]).
- Oral intake of infectious material may result in infection through breaks in the oral mucosa.
- Food or water are virtually never found to be sources of HBV infection.
- Infection occurs primarily in liver, where necrosis probably results from cytotoxic T-cell response, direct cytopathic effect of HBcAg (core antigen), high-level HBsAg (surface antigen) expression, or coinfection with delta (D) hepatitis virus (RNA delta core within HBsAg envelope).
- Recovery (>90%):
  1. Fulminant hepatitis occurring in <1% (especially if coinfected with hepatitis D); 80% fatal.
  2. Unusual (5%) prolonged acute disease for 4 to 12 mo, with recovery.
  3. Overall fatality increases with age and viral inoculation (e.g., transfusions).
- Chronic infection (1% to 2%):
  1. Persistent carrier state without hepatitis (HBsAg positive).
  2. Chronic persistent hepatitis (CPH) (clinically well), or chronic active hepatitis (CAH) (HBsAg positive and HBeAg positive).

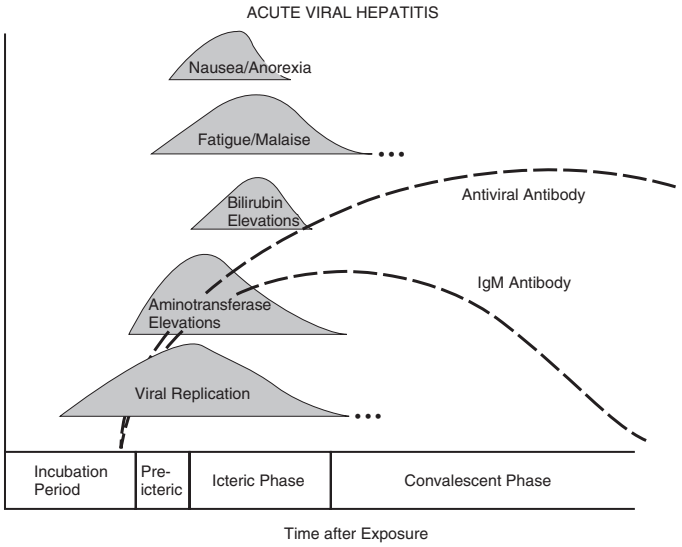

FIGURE H1-29 The typical course of acute viral hepatitis. (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, Saunders.)

3. Cirrhosis.
4. Hepatocellular carcinoma (especially after neonatal infection).
5. Chronic infection: more common following low-dose exposure and mild acute hepatitis, with earlier age of infection, in males, and in immunosuppressed patients.
6. One third to one quarter of chronically infected will develop progressive liver disease (cirrhosis, hepatocellular carcinoma).

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute disease confused with other viral hepatitis infections (A, C, D, E).
- Any viral illness producing systemic disease and hepatitis (e.g., yellow fever, EBV, CMV, HIV, rubella, rubeola, coxsackie B, adenovirus, herpes simplex or zoster).
- Nonviral causes of hepatitis (e.g., leptospirosis, toxoplasmosis, alcoholic hepatitis, drug-induced [e.g., acetaminophen, INH], toxic hepatitis [carbon tetrachloride, benzene]).

WORKUP

- Acute serum specimen for hepatitis B serology (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb), HBDNA by PCR.
- LFTs.
- CBC.
- Liver biopsy: rarely indicated for diagnosis of fulminant viral hepatitis, chronic hepatitis, cirrhosis, carcinoma.

LABORATORY TESTS

- Diagnosis of acute HBV infection is best confirmed by IgM HBcAb in acute or early convalescent serum or by HBDNA by PCR.
  1. Generally, IgM present during onset of jaundice.
  2. Coexisting HBsAg.
- HBsAg and IgG-HBcAb during acute jaundice are strongly suggestive of remote HBV infection and another cause for current illness (Fig. H1-30).
- HBsAb alone is suggestive of immunization response.
- With recovery, HBeAg is rapidly replaced by HBeAb in 2 to 3 mo, and HBsAg is replaced by HBsAb in 5 to 6 mo.
- In chronic HBV hepatitis, HBsAg and HBeAg are persistent without corresponding Ab.
- In chronic carrier state, HBsAg is persistent, but HBeAg is replaced by HBeAb.
- HBcAb develops in all outcomes.
- HBeAg correlation with highest infectivity; appearance of HBeAb heralds recovery.
- LFTs:
  1. ALT and AST: usually more than eight times normal (often 1000 U/L) at onset of jaundice (minimal acute ALT/AST rises often followed by chronic hepatitis or hepatocellular carcinoma).
  2. Bilirubin: variably elevated in icteric viral hepatitis.
  3. Alkaline phosphatase: minimally elevated (one to three times normal) acutely.
- Albumin and prothrombin time:
  1. Generally normal.
  2. If abnormal, possible harbinger of impending hepatic necrosis (fulminant hepatitis).
- WBC and ESR: generally normal.

IMAGING STUDIES

- Rarely useful.
- Sonogram to document rapid reduction in liver size during fulminant hepatitis or mass in hepatocellular carcinoma.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Symptomatic treatment as necessary.
- Activity as tolerated.
- High-calorie diet preferred; often best tolerated in morning.

ACUTE GENERAL Rx

- In most cases of acute HBV infection no treatment necessary; >90% of adults will spontaneously clear infection.
- Hospitalization advisable for any patient in danger from dehydration caused by poor oral intake, whose PT is prolonged, who has rising bilirubin level >15 to 20 μg/dl, or who has any clinical evidence of hepatic failure.
- IV therapy needed (rarely) for hydration during severe vomiting.
- Avoid hepatically metabolized drugs.
- No therapeutic measures are beneficial.
- Steroids not shown helpful.

CHRONIC Rx

- The American Association for the Study of Liver Diseases issued guidelines in 2009 for the evaluation and treatment of hepatitis B.
- The aim of therapy in chronic HBV infection is to eradicate the virus. Treatment is recommended in patients with HbeAg-positive or HbeAg-negative chronic hepatitis and in patients with compensated cirrhosis and HBV DNA > 2000 IU/ml and those with decompensated cirrhosis and detectable HBV DNA by PCR regardless of the serum ALT level.
- The two modalities of therapy available to achieve this goal have been immune modulators (interferon alfa) and antiviral agents in the form of nucleoside analogues (e.g., lamivudine).
- Pegylated interferon alpha (IFN-α) given as a once-a-week SQ injection for 48 wk is a mainstay of therapy and has largely replaced interferon alpha without pegylation, which required daily or thrice weekly injections. Its mechanism of action is to stimulate the immune system to attack HBV-infected hepatocytes, thus inhibiting viral protein synthesis. Dose: 180 μg SQ weekly.
- A 12-mo course of treatment results in a 30% to 40% response with significant reduction of serum HBV DNA, normalization of ALT,

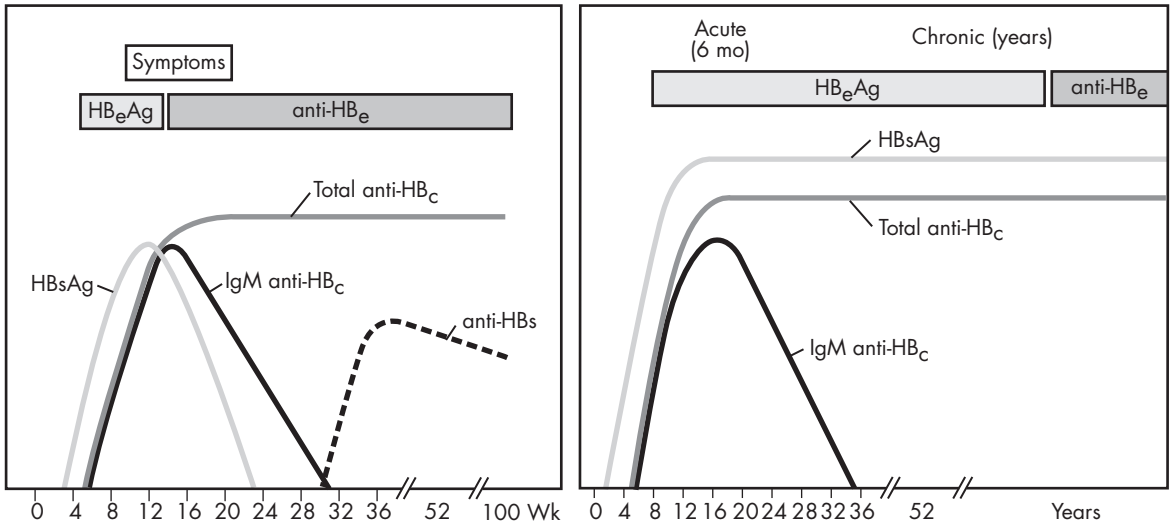

FIGURE H1-30 Typical course of hepatitis B. *Left,* Typical course of acute hepatitis B. *Right,* Chronic hepatitis B. *HBc,* Hepatitis B core; *HBe,* hepatitis B early; *HBsAg,* hepatitis B surface antigen; *IgM,* immunoglobulin M. (From Mandell GL et al: *Principles and practice of infectious diseases,* ed 7, Philadelphia, 2010, Saunders.)

and loss of HBeAg. Seroconversion from HBeAg to HBeAb occurs in 15% to 20%.
- Factors that increase the likelihood of response to IFN-α therapy include:
  1. Adult onset of infection.
  2. High baseline ALT.
  3. Low baseline HBV DNA.
  4. Absence of cirrhosis.
  5. Female.
  6. HBeAg positive.
- Infrequent relapse after successful completion of therapy.
- 80% of patients who lose HBeAg during therapy lose HBsAg in the decade after therapy.
- >50% of patients who do not seroconvert after initial therapy develop a delayed HBeAg seroconversion months to years after therapy.
- Overall incidence of cirrhosis and hepatocellular carcinoma is decreased in those treated with IFN-α.
- IFN-α is successful only in patients with an active immune response; therefore it is not effective in patients with HIV infection and organ transplant patients.
- Asians respond poorly to IFN-α. Patients with genotype A respond well to IFN-α.
- Treatment with IFN-α in general is not well tolerated: side effects include flulike symptoms, injection-site reactions, rash, weight loss, anxiety, depression, alopecia, thrombocytopenia, granulocytopenia, and thyroid dysfunction.
- Nucleoside analogues block viral replication by inhibiting HBV polymerase and require lifelong treatment.
- Lamivudine is the first nucleoside analogue approved for treatment of chronic HBV infection; it has been shown to rapidly reduce HBV replication and suppress HBV DNA to undetectable levels after a few wk of treatment, and treatment for 1 yr is as effective as IFN-α with respect to loss of HBeAg seroconversion to HBeAb and loss of HBV DNA. The high rate of emergence of resistant HBV strains while on therapy has limited the use of lamivudine as a first-line agent (YMDD variants [tyrosine-methionine-aspartate-aspartate]). Dose: 100 mg orally daily with normal kidney function.
- Adefovir dipivoxil: 10 mg orally daily with normal kidney function is a nucleotide reverse transcriptase inhibitor that also has antiviral activity against HBV. It is a prodrug that is converted to the active drug adefovir. It is highly active against HBV and may be useful as a first-line agent or as salvage therapy for patients who are refractory or intolerant to lamivudine. (Nephrotoxicity is a potential side effect, but emergence of resistant strains is less so than with lamivudine.)
- Entecavir is a potent nucleoside agent approved for the treatment of hepatitis B, and it appears to be more effective and to present fewer concerns than lamivudine or adefovir regarding the emergence of resistant strains. Dose: 0.5 mg PO daily for nucleoside-naïve patients and 1 mg PO daily for lamivudine-resistant patients.
- Telbivudine, a thymidine nucleosidase analogue, is more potent than lamivudine or adefovir after 24 wk of treatment but selects for the same resistant strains as lamivudine. Dose: 600 mg PO daily.
- Tenofovir: more potent than adefovir and suppresses lamivudine, telbivudine, or entecavir resistant strains. In the United States it has become a first-line agent. Dose: 300 mg daily with normal kidney function.
- Combination therapy with two or three nucleoside analogues or combination therapy with IFN-α is currently under investigation.
- Liver transplantation (should be considered for fulminant hepatitis).

DISPOSITION

- Follow-up as outpatient.
- Acute disease: usually <6 wk.
- Rare fatalities (fulminant hepatitis).
- Possible chronic carrier state, cirrhosis, hepatocellular carcinoma.

REFERRAL

To infectious disease specialist and gastroenterologist for consultation regarding fulminant hepatitis or prolonged cholestasis, for cases of uncertain etiology, or for treatment of CAH.

PEARLS & CONSIDERATIONS

COMMENTS

- Virus and HBsAg in high titers in blood for 1 to 7 wk before jaundice and for a variable time thereafter.
- Transmission is possible during entire period of HBsAg (and especially during HBeAg) in serum.
- Universal precautions should be followed for all contacts with blood or secretions/excretions contaminated with blood.
- Preventing before exposure:
  1. Lifestyle changes
  2. Meticulous testing of blood supply (although some chronically infected, infectious donors are HBsAg negative).
  3. Sterilization via steam or hypochlorite.
  4. Hepatitis B vaccine for high-risk groups given IM in deltoid to induce HBsAb (response should be confirmed) is protective (>90% effective).
  5. Recommendation for universal childhood immunization with doses at birth, 1 mo, and 6 mo.
- Prevention after exposure:
  1. HBV hyperimmune globulin (HBIG) (0.06 ml/kg IM) given immediately after needlestick, within 14 days of sexual exposure, or at birth, followed by HBV vaccination. A second dose of HBIG is given in 28 days for those refusing vaccine or vaccine nonresponders.
  2. Standard immune globulin: nearly as effective as HBIG
- Preventive therapy with lamivudine or entecavir or tenofovir for patients who test positive for HBsAg and are undergoing chemotherapy may reduce the risk for HBV reactivation and HBV-associated morbidity and mortality,
- Hepatitis B prophylaxis is described in Section V.
- Table H1-17 summarizes interpretation of serologic markers and serum DNA in hepatitis B.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fig. 3-94 A flow diagram showing the use of specific serologic tests for the diagnosis of acute viral hepatitis in relation to the clinical and epidemiologic setting (Algorithm)

Hepatitis B (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

TABLE H1-17 Interpretation of Serologic Markers and Serum DNA in Hepatitis B

	HBsAg	HbeAg	Anti-HBc IgM	Anti-HBc IgG	Anti-HBs	Anti-HBe	HBV DNA*
Acute hepatitis	+	+/–	+				+
Acute hepatitis, window period			+				
Recovery from acute hepatitis			+	+	+	+/–	
Chronic hepatitis	+	+					+
Chronic hepatitis (precore mutant)	+					+	+
Inactive carrier	+					+/–	
Vaccinated					+		

HBsAg, Hepatitis B surface antigen; *HBeAg,* hepatitis Be antigen; *anti-HBc IgM,* hepatitis B core antibody (IgM type); *anti-HBc IgG,* hepatitis B core antibody (IgG type); *anti-HBs,* hepatitis B surface antibody; *anti-HBe,* hepatitis Be antibody; *HBV DNA,* hepatitis B viral DNA.

*HBV DNA $>10^5$ copies/ml.

From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.

EVIDENCE

Abstract[1]

Background:
Despite limited prospective data, it is commonly believed that human immunodeficiency virus (HIV) and hepatitis infections are widespread in the penetrating trauma population, placing healthcare workers at risk for occupational exposure. Our primary study objective was to measure the prevalence of HIV (anti-HIV), hepatitis B (HB surface antigen [HBsAg]), and hepatitis C virus (anti-HCV) in our penetrating trauma population.
Methods:
We prospectively analyzed penetrating trauma patients admitted to Temple University Hospital between August 2008 and February 2010. Patients (n = 341) were tested with an oral swab for anti-HIV and serum evaluated for HBsAg and anti-HCV. Positives were confirmed with Western blot, neutralization immunoassay, and reverse transcription polymerase chain reaction, respectively. Demographics, risk factors, and clinical characteristics were analyzed.
Results:
Of 341 patients, 4 patients (1.2%) tested positive for anti-HIV and 2 had a positive HBsAg (0.6%). Hepatitis C was the most prevalent measured infection as anti-HCV was detected in 26 (7.6%) patients. Overall, 32 (9.4%) patients tested positive for anti-HIV, HBsAg, or anti-HCV. Twenty-eight (75%) of these patients who tested positive were undiagnosed before study enrollment. When potential risk factors were analyzed, age (odds ratio, 1.07, $p = 0.031$) and intravenous drug use (odds ratio 14.4, $p < 0.001$) independently increased the likelihood of anti-HIV, HBsAg, or anti-HCV-positive markers.
Conclusions:
Of our penetrating trauma study population, >9% tested positive for anti-HIV, HBsAg, or anti-HCV although patients were infrequently aware of their seropositive status. As penetrating trauma victims frequently require expedient, invasive procedures, universal precautions are essential. The prevalence of undiagnosed HIV and hepatitis in penetrating trauma victims provides an important opportunity for education, screening, and earlier treatment of this high-risk population. A

Abstract[2]

Background:
Chronic infection with hepatitis B virus and hepatitis delta virus (HDV) results in the most severe form of viral hepatitis. There is no currently approved treatment. We investigated the safety and efficacy of 48 weeks of treatment with peginterferon alfa-2a plus adefovir dipivoxil, peginterferon alfa-2a alone, and adefovir dipivoxil alone.
Methods:
We conducted a randomized trial in which 31 patients with HDV infection received treatment with 180 μg of peginterferon alfa-2a weekly plus 10 mg of adefovir daily, 29 received 180 μg of peginterferon alfa-2a weekly plus placebo, and 30 received 10 mg of adefovir alone weekly for 48 weeks. Follow-up was conducted for an additional 24 weeks. Efficacy end points included clearance of HDV RNA, normalization of alanine aminotransferase levels, and a decline in levels of hepatitis B surface antigen (HBsAg).
Results:
The primary end point—normalization of alanine aminotransferase levels and clearance of HDV RNA at week 48—was achieved in two patients in the group receiving peginterferon alfa-2a plus adefovir and two patients in the group receiving peginterferon alfa-2a plus placebo but in none of the patients in the group receiving adefovir alone. At week 48, the test for HDV RNA was negative in 23% of patients in the first group, 24% of patients in the second, and none of those in the third (P = 0.006 for the comparison of the first and third groups; P = 0.004 for the comparison of the second and third). The efficacy of peginterferon alfa-2a was sustained for 24 weeks after treatment, with 28% of the patients receiving peginterferon alfa-2a plus adefovir or peginterferon alfa-2a alone having negative results on HDV-RNA tests; none of the patients receiving adefovir alone had negative results. A decline in HBsAg levels of more than 1 log10 IU per milliliter from baseline to week 48 was observed in 10 patients in the first group, 2 in the second, and none in the third ($P < 0.001$ for the comparison of the first and third groups and P = 0.01 for the comparison of the first and second).
Conclusions:
Treatment with peginterferon alfa-2a for 48 weeks, with or without adefovir, resulted in sustained HDV RNA clearance in about one quarter of patients with HDV infection. (Funded by Hep-Net [the German Network of Excellence on Viral Hepatitis] and others; Current Controlled Trials number, ISRCTN83587695.) A

Abstract[3]

Background & Aims:
Tenofovir disoproxil fumarate (TDF), a nucleotide analogue and potent inhibitor of hepatitis B virus (HBV) polymerase, showed superior efficacy to adefovir dipivoxil in treatment of chronic hepatitis B through 48 weeks. We evaluated long-term efficacy and safety of TDF monotherapy in patients with chronic hepatitis B who were positive or negative for hepatitis B e antigen (HBeAg+ or HBeAg–).
Methods:
After 48 weeks of double-blind comparison of TDF to adefovir dipivoxil, patients who underwent liver biopsy were eligible to continue the study on open-label TDF for 7 additional years; data presented were collected up to 3 years (week 144) from 85% of participants. Primary efficacy end points at week 144 included levels of HBV DNA and alanine aminotransferase, development of resistance mutations, and presence of HBeAg or hepatitis B surface antigen (HBsAg).
Results:
At week 144, 87% of HBeAg– and 72% of HBeAg+ patients treated with TDF had levels of HBV DNA <400 copies/mL. Among patients who had previously received adefovir dipivoxil and then received TDF, 88% of the HBeAg– and 71% of the HBeAg+ patients had levels of HBV DNA <400 copies/mL; overall, 81% and 74%, respectively, maintained normalized levels of alanine aminotransferase and 34% had lost HBeAg. Amino acid substitutions in HBV DNA polymerase that are associated with resistance to tenofovir were not detected in any patient. Cumulatively, 8% of HBeAg+ patients lost HBsAg. TDF maintained a favorable safety profile for up to 3 years.
Conclusions:
TDF was safe and effective in the long-term management of HBeAg+ and HBeAg– patients with chronic hepatitis B. A

Evidence-Based References

Seamon MJ, et al.: HIV and hepatitis in an urban penetrating trauma population: unrecognized and untreated, *J Trauma* 71:306–311, 2011. A

Wedemeyer H et al.: for the HIDIT Study Group. Peginterferon plus adefovir versus either drug alone for hepatitis delta, *N Engl J Med* 364:322–331, 2011. A

Heathcote EJ et al.: Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B, *Gastroenterology* 140:132–143, 2011. A

SUGGESTED READINGS

Chan HL et al.: Treatment of hepatitis B e antigen-positive chronic hepatitis B with telbivudine or adefovir, *Ann Intern Med* 147:745, 2007.

Chang TT et al.: A comparison of entecavir and lamivudine for HbeAg-positive chronic hepatitis B, *N Engl J Med* 354(10):1001, 2006.

Dienstag JL: Hepatitis B virus infection, *N Engl J Med* 359:1486–1500, 2008.

Elgouhari HM et al.: Hepatitis B virus infection: understanding its epidemiology, course, and diagnosis, *Cleve Clin J Med* 75:881–889, 2008.

Ioannou GN: Hepatitis B virus in the United States: infection, exposure, and immunity rates in a nationally representative survey, *Ann Intern Med* 154:319, 2011.

Lai CL, Yuen MF: Chronic hepatitis B—new goals, new treatment, *N Engl J Med* 359:23, 2008.

Lok AS, McMahon BJ: Chronic hepatitis B (AASLD practice guidelines), *Hepatology* 50:661, 2009.

McMahon BJ et al.: Internist diagnosis and management of chronic hepatitis B virus infection, *Am J Med* 125:1063–1067, 2012.

Pungpapong S et al.: Natural history of hepatitis B virus infection: an update for clinicians, *Mayo Clin Proc* 82(8):967–975, 2007.

Sorrell M et al.: National Institutes of Health Consensus Development Conference Statement: management of hepatitis B, *Ann Intern Med* 150:104–110, 2009.

BASIC INFORMATION

DEFINITION

Hepatitis C is an acute liver parenchymal infection caused by hepatitis C virus (HCV).

SYNONYMS

Transfusion-related non-A, non-B hepatitis (incubation period averages 6 wk, intermediate between hepatitis A and B)

ICD-9CM CODES
070.51 Other viral hepatitis
ICD-10CM CODES
B17.1 Acute hepatitis C
B18.2 Chronic viral hepatitis C
B17.10 Acute hepatitis C without hepatic coma

EPIDEMIOLOGY & DEMOGRAPHICS

Hepatitis C infection is the most common chronic blood-borne infection in the United States. About 3% of baby boomers test positive for the virus. The CDC now recommends testing for hepatitis C for anyone born from 1945 to 1965.
INCIDENCE (IN U.S.): HCV infects more than 185 million individuals worldwide. Approximately 20% of patients chronically infected with HCV progress to cirrhosis.
- 150,000 new cases/yr (37,500 symptomatic; 93,000 later chronic liver disease; 30,700 cirrhosis). The incidence of acute HCV has declined substantially over the past 30 yr (from 7.4/100,000 to 0.7/100,000).
- ~9000 of these ultimately die of HCV infection; most common (40%) cause of nonalcoholic liver disease in the United States

PREVALENCE (IN U.S.)
- Overall prevalence of anti-HCV antibody is 1% to 1.2% (an estimated 2.7 million persons nationwide).
- Highest prevalence in hemophiliacs transfused before 1987 and users of injection drugs, 72% to 90%. Over past 30 yr, blood transfusion as a risk factor declined from 15% of cases to 1.9%.
- Among low-risk groups, prevalence 0.6%.

PREDOMINANT SEX: Slight male predominance.
PREDOMINANT AGE: Highest prevalence in 30- to 49-yr age group (65%).
PEAK INCIDENCE:
- 20 to 39 yr of age.
- African Americans and whites have similar incidence of acute disease; Hispanics have higher rates.
- Prevalence is substantially higher among non-Hispanic blacks than among non-Hispanic whites.

GENETICS: Neonatal infection is rare; increased risk with maternal HIV-1 coinfection.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms usually develop 7 to 8 wk after infection (range of 2 to 26 wk), but 70% to 80% of cases are subclinical.
- 10% to 20% report acute illness with jaundice and nonspecific symptoms (abdominal pain, anorexia, malaise).
- Fulminant hepatitis may rarely occur during this period.
- After acute infection, 15% to 25% have complete resolution (absence of HCV RNA in serum, normal ALT).
- Progression to chronic infection is common, 50% to 84%. 74% to 86% have persistent viremia; spontaneous clearance of viremia in chronic infection is rare. 60% to 70% of patients will have persistent or fluctuating ALT levels; 30% to 40% with chronic infection have normal ALT levels.
- 15% to 20% of those with chronic HCV will develop cirrhosis over a period of 20 to 30 yr; in most others, chronic infection leads to hepatitis and varying degrees of fibrosis.
- 0.4% to 2.5% of patients with chronic infection develop hepatocellular carcinoma (HCC).
- 25% of patients with chronic infection continue to have an asymptomatic course with normal LFTs and benign histology.
- In chronic HCV infection, extrahepatic sequelae include a variety of immunologic and lymphoproliferative disorders (e.g., cryoglobulinemia, membranoproliferative glomerulonephritis, and possibly Sjögren's syndrome, autoimmune thyroiditis, polyarteritis nodosa, aplastic anemia, lichen planus, porphyria cutanea tarda, B-cell lymphoma, others).

ETIOLOGY

- Caused by HCV (single-stranded RNA flavivirus).
- Most HCV transmission is parenteral.
- In the United States, advances in screening of blood and blood products have made transfusion-related HCV infection rare (the risk is estimated to be 0.001% per unit transfused).
- Injecting-drug use accounts for most HCV transmission in the United States (60% of newly acquired cases, 20% to 50% of chronically infected persons).
- Occupational needlestick exposure from an HCV-positive source has a seroconversion rate of 1.8% (range 0% to 7%).
- Nosocomial transmission rates (from surgery and procedures such as colonoscopy and hemodialysis) are extremely low.
- Sexual transmission and maternal-fetal transmission are infrequent (estimated at 5%).
- No identifiable risk in 40% to 50% of community-acquired hepatitis C, but snorting of cocaine by shared use of straw or rolled-up paper has been identified as a risk factor because it causes microscopic bleeding of nasal mucosa.
- HCV infection may stimulate production of cytotoxic T lymphocytes and cytokines (INF-γ), which probably mediate hepatic necrosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other hepatitis viruses (A, B, D, E).
- Other viral illnesses producing systemic disease (e.g., yellow fever, EBV, CMV, HIV, rubella, rubeola, coxsackie B, adenovirus, HSV, HZV).
- Nonviral hepatitis (e.g., leptospirosis, toxoplasmosis, alcoholic hepatitis, drug-induced hepatitis [acetaminophen, INH], toxic hepatitis).

WORKUP

- Acute hepatitis C antibody, viral genotyping, viral titers.
- LFTs; CBC.

NOTE: ALT is an easy and inexpensive test to monitor infection and efficacy of therapy. However, ALT levels may fluctuate or even be normal in active or chronic infection and even with cirrhosis, and ALT may remain elevated even after clearance of viremia.
- Liver biopsy with histologic staging is the gold standard for assessing the degree of disease activity and the likelihood of disease progression, and also to help rule out other causes of liver disease.

LABORATORY TESTS

- Diagnosis is often by exclusion, because it takes 6 wk to 12 mo to develop anti-HCV antibody (70% positive by 6 wk, 90% positive by 6 mo).
- Diagnostic tests include serologic assays for antibodies and molecular tests for viral particles.
  1. Enzyme immunoassay is the test for anti-HCV antibody:
     The current version can detect antibody within 4 to 10 wk after infection.
     False-negative rate in low-risk populations is 0.5% to 1%.
     False negatives also occur in immune-compromised persons, HIV-1, renal failure, HCV-associated essential mixed cryoglobulinemia.
     False positives in autoimmune hepatitis, paraproteinemia, and persons with no risk factors.
- The recombinant immunoblot assay that was previously recommended as a follow-up to positive antibody test is no longer available. The CDC now recommends that anyone who tests positive for HCV antibodies receive a follow-up HCV RNA test.
- Qualitative and quantitative HCV RNA tests using PCR:Lower limit of detection is <43 IU/ml.
- Used to confirm viremia and to assess response to treatment.
- Qualitative polymerase chain reaction (PCR) useful in patients with negative enzyme immunoassay in whom infection is suspected.
- Quantitative tests use either branched-chain DNA or reverse transcription PCR; the latter is more sensitive.
- Viral genotyping can distinguish among genotypes 1, 2, 3, and 4, which is helpful in choosing therapy; most of these tests use PCR (genotypes 1, 2, 3, and 4 predominate in the United States and Europe [genotype 1 is especially common in North America (60% to 75% of Hep C infections in the United States).
- LFTs: ALT and AST may be elevated to more than eight times normal in acute infection; in chronic infection ALT may be normal or fluctuate.
- Bilirubin may be five to 10 times normal.
- Albumin and prothrombin time generally normal; if abnormal, may be harbinger of impending hepatic necrosis.

- WBC and erythrocyte sedimentation rate (ESR) are generally normal.
- HIV testing.

IMAGING STUDIES

Sonogram: rapid liver size reduction during fulminant hepatitis or mass in HCC.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Activity and diet as tolerated, avoid saw palmetto and green tea leaf herbs.

ACUTE GENERAL Rx

- Supportive care.
- Avoid hepatically metabolized drugs.

CHRONIC Rx

Response to therapy is influenced by HCV genotype. Patients with HCV genotype 1 can be treated with sofosbuvir + pegylated interferon + ribavirin because of the shorter duration of therapy and higher rates of sustained virologic response (SVR) (89% to 90%). Simeprevir + pegylated interferon + ribavirin is an alternative for patients with HCV genotype 1 (SVR 79% to 86%). Patients with genotypes 2 and 3 can be treated with sofosbuvir + ribavirin alone (SVR for genotype 2, 12 weeks' duration: 82% to 93%; SVR for genotype 3, 24 weeks' duration 80% to 95%.

- Currently, new all oral regimens of DAAs without interferon or ribavirin are available that have cure rates of more than 95%. These include ledipasvir + sofosbuvir for 12 weeks, daclatasvir + asunaprevir for 12 or 24 weeks and ABT-450/r-ombitasvir and dasabuvir with or without weight-based ribavirin for 12 weeks.
- Liver transplantation:
  1. Hepatitis C is the main indication for liver transplantation in the United States.
  2. It is the only option for patients with deteriorating HCV-related cirrhosis and for some patients with HCC.
  3. Recurrent infection occurs in almost all patients with progressive fibrosis and cirrhosis; as many as 20% progress to cirrhosis within 5 yrs posttransplant.

DISPOSITION

- SVR after treatment among HCV-infected persons at any stage of fibrosis is associated with reduced HCC.
- Periodic abdominal ultrasonography for HCC screening.
- Recent guidelines recommend against measurement of alpha-fetoprotein (AFP) to screen for HCC in patients with chronic hepatitis C due to lack of sensitivity, specificity, and predictive values.

REFERRAL

- To a hepatologist or infectious disease specialist for treatment for hepatitis C.
- To a transplant surgeon for consideration of liver transplant if indicated.

PEARLS & CONSIDERATIONS

- More rapid progression of disease in persons who drink alcohol regularly, persons of advanced age at time of infection, and those coinfected with other viruses (HIV, hepatitis B). All persons with identified HCV infection should receive a brief alcohol screening and intervention as clinically indicated.
- Major depression is a common (20%-40%) side effect of treatment with interferons. Use of the SSRI escitalopram has been found safe and effective for prevention of interferon-associated depression in these patients.
- Regression of cirrhosis has been demonstrated after antiviral therapy in some patients with chronic hepatitis C. Regression is associated with decreased disease-related morbidity and improved survival.
- The presence of interleukin (IL)-28B and HLA class II is independently associated with spontaneous resolution of HCV infection, and single nucleotide polymorphism IL-28B and DQB1*03:01 may explain approximately 15% of spontaneous resolution of HCV infection.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hepatitis C (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Afdhal N et al.: Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection, *N Engl J Med* 370:1889–1898, 2014.

Afdhal N et al.: Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection, *N Engl J Med* 370:1879–1888, 2014.

Bacon BR et al.: Boceprevir for untreated chronic HCV genotype 1 infection, *N Engl J Med* 364:1195, 2011.

Bruix et al.: Management of hepatocellular carcinoma: an update, *Hepatology* 53:1020–1022, 2011.

Chou R et al.: Comparative effectiveness of antiviral treatment of hepatitis C virus infection in adults: a systematic review, *Ann Intern Med* 158:114–123, 2013.

Davila JA et al.: Utilization of surveillance for hepatocellular carcinoma among hepatitis C-virus infected veterans in the United States, *Ann Intern Med* 154:85–93, 2011.

Duggal P et al.: Genome-wide association study of spontaneous resolution of hepatitis C virus infection: data from multiple cohorts, *Ann Intern Med* 158:235–245, 2013.

Kohli A, Shaffer A, Sherman A, Kottilil S: Treatment of Hepatitis C, A systematic review, *JAMA* 312(6):631–640, 2014.

Liang TJ, Ghany MG: Current and future therapies for hepatitis C virus infection, *N Engl J Med* 368:1707–1717, 2013.

Limaye AR et al.: Boceprevir for chronic HCV genotype 1 infection, *N Engl J Med* 365(2):176, 2011.

Lok AS et al.: Preliminary study of two antiviral agents for hepatitis C genotype 1, *N Engl J Med* 366:216, 2012.

Morgan RL et al.: Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma, *Ann Intern Med* 158:328–337, 2013.

Muir AJ: The rapid evolution of treatment strategies for hepatitis C, *AmJ Gastr* 109(5):628–635, 2014.

Pawlotsky JM: New hepatitis C therapies: the toolbox, strategies, and challenges, *Gastroenterology* 146(5):1176–1192, 2014.

Schaefer M et al.: Escatilopram for the prevention of peginterferon alpha2a–associated depression in hepatitis C-infected patients without previous psychiatric disease: a randomized trial, *Ann Intern Med* 157:94, 2012.

Scott JD, Gretch DR: Molecular diagnostics of hepatitis C virus infection, *JAMA* 297:724, 2007.

Sherman KE et al.: Telaprevir in combination with peginterferon alfa2a and ribavirin for 24 weeks or 48 weeks in treatment-naïve genotype 1 HCV patients who achieved an extended rapid viral response, *Hepatology* 52:401A, 2010.

Smith BD et al.: Hepatitis C virus testing of persons born during 1945-1965: recommendations from the Centers for Disease Control and Prevention, *Ann Intern Med* 157:817–822, 2012.

Sterling RK et al.: Frequency of elevated hepatocellular carcinoma (HCC) biomarkers in patients with advanced hepatitis C, *Am J Gastroenterol* 107:64, 2012.

Williams ITo et al.: Incidence and transmission patterns of acute hepatitis C in the United States, 1982-2006, *Arch Intern Med* 171(3):242–248, 2011.

Zeuzem S et al.: Sofosbuvir and ribavirin in HCV genotypes 2 and 3, *N Engl J Med* 370:1993–2001, 2014.

BASIC INFORMATION

DEFINITION

Hepatocellular carcinoma (HCC) is a malignant tumor of the hepatocytes.

SYNONYMS

Hepatoma
HCC

ICD-9CM CODES
155.0 Hepatocellular carcinoma
ICD-10CM CODES
C22.0 Liver cell carcinoma

EPIDEMIOLOGY & DEMOGRAPHICS

Fifth most common cancer worldwide (>500,000 new cases/year) and third most common cause of cancer deaths. Incidence varies worldwide:

- Areas with high rates of hepatitis B and C (Asia, sub-Saharan Africa) have high rates of HCC.
- Males more affected than females, with ratios between 2:1 and 4:1.
- Peak incidence: fifth and sixth decades in Western countries, earlier in areas with perinatal transmission of hepatitis B.
- Incidence rapidly growing in U.S. secondary to chronic hepatitis C infection and obesity leading to nonalcoholic steatohepatitis (NASH).
  1. Incidence: during the past two decades, the incidence of HCC in the U.S. has tripled. The greatest proportional increase in cases has been among Hispanics and whites between 45 and 60 years of age
  2. Mean age of diagnosis approximately 65 yr
  3. HCC is the fastest-rising cause of cancer-related deaths in the United States
- Risk factors:
  1. Chronic hepatitis B infection: accounts for 50% of all cases of HCC and virtually all childhood cases
  2. Chronic hepatitis C infection: markers of HCV infection are found in 80% to 90% of patients with HCC in Japan, 44% to 66% in Italy, and 30% to 50% in the U.S.
  3. Cirrhosis from causes other than viral hepatitis: alcoholic liver disease, nonalcoholic steatohepatitis, primary biliary cirrhosis, hemochromatosis, α1-antitrypsin deficiency, and autoimmune hepatitis
  4. Hepatotoxins: alcohol and aflatoxin B1
  5. Systemic diseases affecting the liver such as tyrosinemia
  6. Obesity and diabetes mellitus

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- One third of patients are asymptomatic. Abdominal pain may be the initial presentation.
- Signs of underlying cirrhosis and portal hypertension are often present.
- Previously compensated cirrhosis with new ascites, encephalopathy, jaundice, or bleeding.
- Paraneoplastic syndromes (hypoglycemia, erythrocytosis, hypercalcemia, severe diarrhea) may be present.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Metastatic tumor to liver
- Intrahepatic cholangiocarcinoma
- Benign liver tumors such as adenomas, focal nodular hyperplasia, and hemangiomas
- Focal fatty infiltration

WORKUP

- History regarding risk factors
- Physical examination with attention to signs of chronic liver disease
- Laboratory evaluation and imaging studies
- Imaging studies: ultrasound for initial screening; 4-phase multidetector CT scan or dynamic contrast-enhanced MRI for HCC diagnosis

LABORATORY TESTS

- Liver function tests
- α-Fetoprotein (AFP) levels can be elevated in 70% of patients (sensitivity, 40% to 65%; specificity, 80% to 94%). An AFP level of 400 ng/ml or greater is highly suggestive of HCC; however, elevations may not be seen in up to 40% of patients with small HCC lesions (<3 cm).

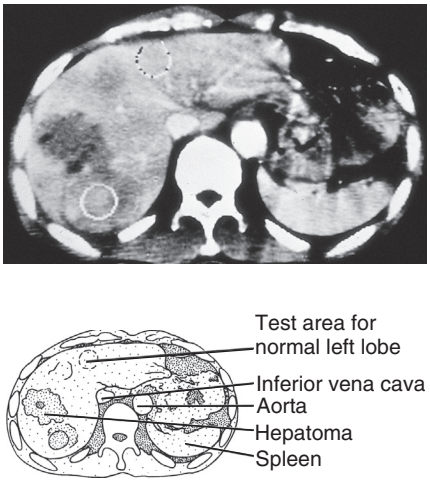

FIGURE H1-31 Hepatoma. CT scan shows a diffuse lesion in the right lobe of an otherwise normal liver. (From Skarin AT: *Atlas of diagnostic oncology,* ed 3, St Louis, 2003, Mosby.)

- Paraneoplastic syndromes associated with HCC may cause hypercalcemia, hypoglycemia, and polycythemia
- Elevated serum HBV DNA level (≥10,000 copies/ml) is a strong risk predictor of HCC independent of HBeAg, serum aminotransferase level, and liver cirrhosis

IMAGING STUDIES

Ultrasound (US), CT scan (Fig. H1-31), or MRI. Ultrasound is most commonly used as a screening test for HCC in high-risk patients every 6 months. Fig. H1-32 shows a laparoscopic view of a cirrhotic liver with a nodular hepatoma.

The following imaging modalities are recommended based on US findings:

- Hepatic lesion <1 cm needs to be followed with a repeat US every 3 months to ensure the lesion does not change change size. If there is no change in size (remains <1 cm) or characteristics after 24 months, the interval for US surveillance can be increased back to every 6 months
- Hepatic lesion >1 cm needs further imaging to confirm the diagnosis of HCC. Either a 4-phase multidetector CT (MDCT) scan or a dynamic contrast-enhanced MR scan is performed. If the chosen imaging modality shows characteristics typical of HCC (hypervascular in the arterial phase with washout in the portal venous or delayed phase) the diagnosis of HCC is confirmed with no need for additional diagnostic testing or biopsy. If the imaging modality is inconclusive or atypical for HCC then the alternate imaging test must be performed (e.g., if the first modality was MRI then the MDCT scan needs to be performed and vice versa). If the second imaging modality is also inconclusive, a biopsy to confirm diagnosis is recommended.

BIOPSY: Percutaneous biopsy under ultrasound or CT scan is obtained in the event that imaging studies are nondiagnostic or atypical for HCC, or if no cirrhosis is present. Negative biopsy results should be followed and the hepatic nodule reassessed every 3 to 6 months until it is no longer seen, enlarges, or shows diagnostic characteristics.

SCREENING: Screening high-risk patients with US every 6 mo is currently recommended to identify HCC at an early stage. The use of AFP in addition to US is currently under debate; though it does increase detection rate it also

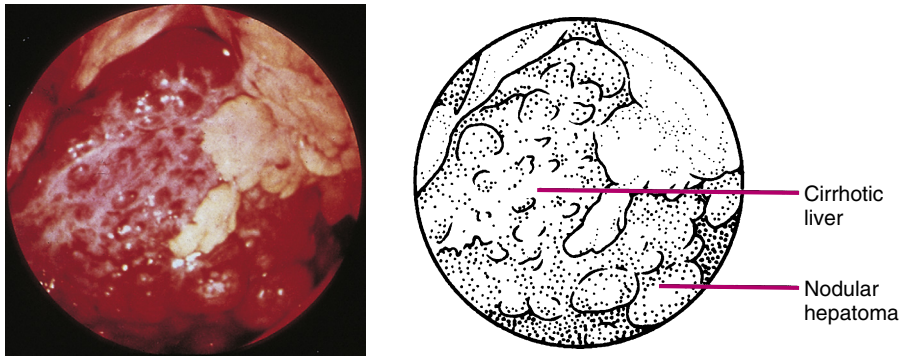

FIGURE H1-32 HEPATOCELLULAR CARCINOMA. Laparoscopic view shows a cirrhotic liver with a nodular hepatoma. (From Skarin AT: *Atlas of Diagnostic Oncology*, ed 4, St Louis, 2010, Mosby.)

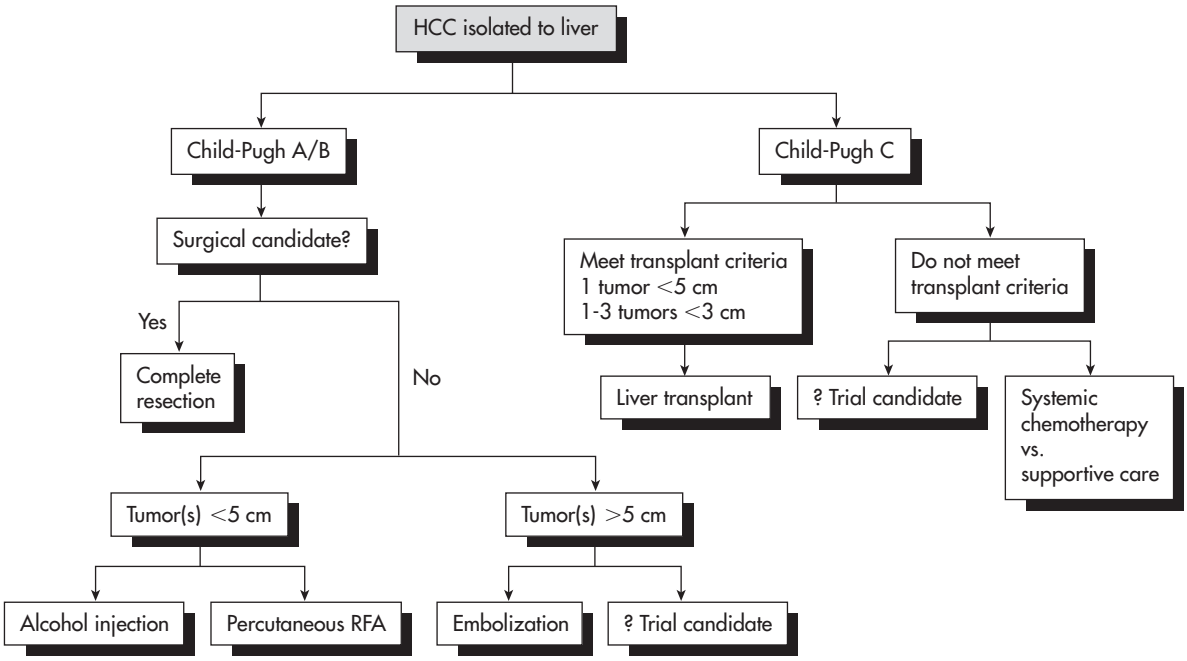

FIGURE H1-33 Treatment algorithm for hepatocellular carcinoma *(HCC).* *RFA,* Radiofrequency ablation. (From Abeloff MD: *Clinical oncology,* ed 3, Philadelphia, 2004, Saunders.)

TABLE H1-18 Milan Criteria of Eligibility for Liver Transplantation

Presence of a tumor ≤5 cm in diameter in patients with single hepatocellular carcinomas
or
≤3 tumor nodules, each 3 cm or less in diameter, in patients with multiple tumors

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

increases false-positive results. The use of AFP alone should be discouraged due to limited sensitivity and specificity. Newer tumor markers are currently under investigation, with plasma microRNA expression the most promising. Patients on transplant waiting lists should be regularly screened for HCC because in the U.S. the development of HCC gives increased priority for liver transplantation. Screening for HCC is recommended in the following groups:

- Hepatitis B carriers (HBsAg positive): Asian males >40 yr, Asian females >50 yr, all cirrhotic hepatitis B carriers, family history of HCC and North American blacks/Africans older than age 20 yr
- Cirrhosis (nonhepatitis B): hepatitis C, alcoholic cirrhosis, hemochromatosis, primary biliary cirrhosis, and possibly α1-antitrypsin deficiency, autoimmune hepatitis, and nonalcoholic steatohepatitis

STAGING: According to the Barcelona Clinic Liver Cancer (BCLC) staging classification, treatment is determined according to stage:

- Early stage (A): asymptomatic single tumor 5 cm or 3 nodules, each ≤3 cm (known as Milan criteria)
- Intermediate stage (B): patients with tumors that exceed early criteria but do not yet show cancer-related symptoms, vascular invasion, or metastases
- Advanced stage (C): patients with mild cancer-related symptoms and/or vascular invasion or extrahepatic spread
- End-stage (D): patients with advanced, symptomatic disease

Rx TREATMENT

- Fig. H1-33 describes a treatment algorithm for HCC.
- Early stage: curative treatment (surgical resection or liver transplantation). Patients who have a single lesion can be offered surgical resection if they are noncirrhotic or have cirrhosis but still have well-preserved liver function, normal bilirubin, and no significant portal hypertension. Liver transplantation is an effective option for patients with HCC corresponding to the Milan criteria (Table H1-18). Living donor transplantation can be offered for HCC if the waiting time is expected to be long. Local ablation is safe and effective therapy for patients who cannot undergo resection or as a bridge to transplantation. With these options, survival at 5 yr ranges from 50% to 70%.
- Intermediate stage: Transarterial chemoembolization (TACE) is recommended as first-line noncurative therapy for nonsurgical patients with large/multifocal HCC who do not have vascular invasion or extrahepatic spread. Median survival with this option exceeds 2 yr.
- Advanced stage: sorafenib, an oral multikinase inhibitor of the vascular endothelial growth factor receptor (VEGF), the platelet-derived growth factor (PDGF) receptor, and Raf, a serine-threonine kinase, has been shown to improve survival and delay disease progression. The SHARP trial included patients with advanced HCC in Child-Pugh A cirrhosis and showed increased median survival from 7.9 to 10.7 mo.
- End stage: palliative care.

DISPOSITION

- For unresectable tumors, prognosis is poor; 5-yr survival after surgical resection ranges from 30% to 50%.
- In the U.S. the 5-year overall survival rate for HCC is 10% to 12%.

REFERRAL

To gastroenterologist for treatment planning

PEARLS & CONSIDERATIONS

PREVENTION

- Universal hepatitis B vaccination in children in endemic areas has been shown to decrease the incidence of HCC.
- Treatment of patients with chronic hepatitis B–associated cirrhosis with lamivudine reduces the incidence of HCC. Treatment with entecavir in chronic hepatitis B-HCC can improve hepatic function and MELD score.
- HCC screening is recommended in high-risk patients because curative therapies are available for small and early HCC.

- The expression patterns of microRNAs in liver tissue in patients with HCC differ between men and women. The miR-26 expression status of such patients is associated with survival and response to adjuvant therapy with interferon alfa.
- Several observational studies have suggested that radiofrequency ablation (RFA) may have survival benefits similar to hepatic resection (HR) in cirrhotic patients affected by HCC who are not candidates for liver transplantation.
- Patients diagnosed with HCC with an AFP >1000 are at increased risk for recurrence after transplantation regardless of tumor size.
- Recent trials have shown that among patients with advanced HCC, treatment with sorafenib plus doxorubicin monotherapy resulted in greater median time to progression-free survival. The degree to which this improvement may represent synergism between sorafenib and doxorubicin remains to be defined.
- There are at least 60 new agents, both TKI (tyrosine kinase inhibitors) and monoclonal antibodies, that are being investigated as targeted therapy for advanced HCC in patients who are intolerant or resistant to sorafenib. The future of therapy for advanced HCC will likely lead to the personalized combination of multiple agents to optimize treatment success.
- SALL4 is a marker for a progenitor subclass of hepatocellular carcinoma with an aggressive phenotype. The absence of SALL4 expression in the healthy adult liver enhances the potential of SALL4 as a treatment target in hepatocellular carcinoma.[1]

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Liver Cancer (Patient Information)

AUTHORS: **PRANITH PERERA, M.D.**, and **JEANETTE G. SMITH, M.D.**

[1]Yong KJ et al: Oncofetal gene SALL4 in aggressive hepatocellular carcinoma, *N Engl J Med* 368: 2266-2276, 2013.

EVIDENCE

Abstract[1]

Background:

Hepatocellular cancer is diagnosed in over half a million persons worldwide each year. Liver cancer is the fifth most common cancer in men and the seventh in women, with 85% of cases occurring in developing countries, especially where infection with hepatitis B (HBV) is endemic: Southeast Asia and sub-Saharan Africa. Rarely does hepatocellular carcinoma manifest before age 40 years and cases peak at about age 70 years. Infection with hepatitis C virus (HCV) is the fastest-rising cause of cancer-related death in the United States. The 5-year survival of HCV-related cancer is less than 12%. The greatest proportional increase in cases is seen in Hispanics and white persons age 45 to 60 years. Risk factors, diagnosis, treatment, and prevention of hepatocellular carcinoma were investigated.

Risk Factors:

The major risk factors for hepatocellular carcinoma are infection with HBV or HCV, alcoholic liver disease, and nonalcoholic fatty liver disease. Less common risk factors are hereditary hemochromatosis, alpha$_1$-antitrypsin deficiency, autoimmune hepatitis, some porphyrias, and Wilson's disease. The distribution of risk factors varies by geographic area and race or ethnic group. Usually the risk factors produce cirrhosis, found in 80% to 90% of patients with hepatocellular carcinoma.

Worldwide, chronic HBV infection is seen in about half of all cases and virtually all pediatric cases. Where HBV infection is transmitted from mother to newborn, up to 90% of infected persons have chronic disease, with HBV often incorporated into host DNA. The risk of hepatocellular carcinoma in persons who are positive for hepatitis B surface antigen (HBsAg) is further increased if the individual is male, elderly, infected for a long time, has a family history of hepatocellular carcinoma, was exposed to aflatoxin, uses alcohol or tobacco, is coinfected with HBV or hepatitis delta virus, has high levels of HBV hepatocellular replication, or is infected with HBV genotype C.

Hepatocellular carcinoma occurs 15 to 20 times more often in persons infected with HCV than those who are not infected. Most of the excess risk is found in those with advanced hepatic fibrosis or cirrhosis. Risk factors for hepatocellular carcinoma in persons infected with HCV include older age at the time of infection, male gender, coinfection with human immunodeficiency virus (HIV) or HBV, and probably diabetes or obesity. Prolonged heavy alcohol use is another strong indicator of higher risk. Coffee drinking may reduce the risk in some areas, such as Japan and southern Europe. It is also related to reduced insulin levels and a lower risk for type 2 diabetes.

Diagnosis:

Noninvasive imaging tests, especially at specialized centers, can be used to diagnose hepatocellular carcinoma in persons with cirrhosis and a focal hepatic mass exceeding 2 cm in diameter. Typical imaging shows areas of early arterial enhancement and delayed washout in the venous or delayed phase of four-phase multidetector computed tomography (CT) or in dynamic contrast-enhanced magnetic resonance imaging (MRI). These changes are related to increased vascularity in the carcinoma. Concordant findings on CT and MRI are recommended if the lesions measure 1 to 2 cm in diameter. An alpha-fetoprotein level of 400 ng/mL or higher is also highly predictive of hepatocellular carcinoma. An image-guided biopsy is considered if the focal hepatic mass has atypical features, the CT and MRI findings do not match, or no cirrhosis is present. A negative biopsy result does not rule out malignant disease; the nodule should be reassessed every 3 to 6 months until it disappears, enlarges, or displays diagnostic characteristics. Risk of tumor seeding along the needle track after biopsy is low. It can be hard to measure liver nodules smaller than 1 cm; it is best to monitor them via ultrasonography (US) every 3 to 6 months for 1 to 2 years.

Treatment:

Choice of treatment is related to cancer stage, resources available, and level of practitioner expertise. Recommendations for staging-guided treatment use systems such as the Barcelona Clinic Liver Cancer staging and the Child-Pugh system. Genomic analysis is used to identify possible prognostic biomarkers, but requires validation. High serum and tissue levels of vascular endothelial growth factor are significantly associated with poor survival, but the clinical usefulness of this is unclear.

Very early stage disease is difficult to diagnose, but surgical resection at this stage produces an overall survival of 90%. Choice of therapy is dictated by severity of liver dysfunction, extent of portal hypertension, and presence of coexisting conditions. Patients with solitary tumors and no portal hypertension can undergo surgical resection. Patients with early-stage hepatocellular carcinoma are best managed with liver transplantation or, if transplantation is not possible, local ablation. For patients with intermediate-stage cancer the best choice is transarterial chemoembolization (TACE), which improves 2-year survival by 20% to 25% compared to conservative treatment. Radioembolization with yttrium-90 microspheres has been used as palliative treatment for patients with Child-Pugh class A cirrhosis and intermediate-stage disease. Radical therapy is not appropriate for patients with advanced-stage disease. Carefully selected patients may have an increased survival with TACE, but the primary treatment option for these patients is oral sorafenib. Other small molecules being studied for use in these patients include bevacizumab and cetuximab. In the terminal stage of disease, which includes cancer symptoms related to liver failure, vascular involvement, or extrahepatic spread, 1-year survival is less than 10%. None of the treatments mentioned is of benefit.

The clinical effectiveness of antiviral therapy for infection with HBV or HCV and for surveillance and treatment is low. Transplantation, resection, and TACE are not widely used. It is difficult to implement surveillance that requires repeated assessments over relatively short time periods and strategies to ensure prompt recall. The diagnostic evaluation is complicated, and curative treatments are often unavailable or quite costly.

Prevention:

All newborns and persons without immunity at high risk for HBV infection should be given HBV vaccine, which is both safe and effective. Antiviral therapy that controls HBV infection in HBsAg-positive patients and that eradicates HCV in patients with viremia may substantially reduce, but does not eliminate, the risk of hepatocellular carcinoma in patients with viral hepatitis. Risk may be reduced by administering either interferon or lamivudine. Persons infected with HCV who do not have cirrhosis and receive interferon-based treatment with a sustained viral response have up to 75% reduction in risk of hepatocellular carcinoma. Maintenance interferon therapy for patients with HCV infection and cirrhosis with no sustained viral response does not reduce the cancer risk. Surveillance is recommended for high-risk patients. One approach is US of the liver and measurement of serum alpha-fetoprotein levels every 6 to 12 months for patients with cirrhosis or advanced hepatic fibrosis regardless of its cause. HBV carriers with or without cirrhosis who are Africans over age 20 years or Asians over age 40 years or who have a family history of hepatocellular carcinoma can also benefit from this approach. Surveillance is not recommended for HCV-infected persons with mild or no hepatic fibrosis. Alpha-fetoprotein levels in serum are inadequate as the only means of surveillance. US has a sensitivity of about 65% and a specificity of over 90% for early detection. CT and MRI are not generally recommended for surveillance because their sensitivity, specificity, and negative and positive predictive values are unknown and because they are expensive and carry risks for radiation exposure, allergic reaction to contrast medium, nephrotoxicity with CT, and nephrogenic fibrosing dermatopathy when gadolinium is used for MRI in patients with renal insufficiency. Ⓐ

Evidence-Based Reference

El-Serag HB: Hepatocellular carcinoma, *N Engl J Med* 365:1118–1127, 2011. Ⓐ

SUGGESTED READINGS

Abou-Alfa GK, et al.: Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma, *JAMA* 304(19):2154–2160, 2010.

Bruix J, Sherman M: AASLD practice guideline. Management of hepatocellular carcinoma: an update. Hepatology, July 2010.

Chen DS, et al.: Serum alpha-fetoprotein in the early stage of human hepatocellular carcinoma, *Gastroenterology* 86(6):1404, 1984.

Cheng BQ, et al.: Chemoembolization combined with radio frequency ablation for patients with hepatocellular carcinoma larger than 3 cm: a randomized controlled trial, *JAMA* 299(14):1669–1677, 2008.

Chien-Jen C, et al.: Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level, *JAMA* 295:65–73, 2006.

Choi GH, et al.: Outcome after curative resection for a huge (10 cm) hepatocellular carcinoma and prognostic significance of gross tumor classification, *Am J Surg* 198:693–701, 2009.

El-Serag H, Rudolph K: Hepatocellular carcinoma: epidemiology and molecular carcinogenesis, *Gastroenterology* 132(7):2557, 2007.

El-Serag HB: Hepatocellular carcinoma, *N Engl J Med* 365:1118–1127, 2011.

Jackson S, et al.: Surveillance of cirrhosis for hepatocellular carcinoma: a cost utility analysis, *Br J Cancer* 98:1166–1175, 2008.

Ji J, et al.: MicroRNA expression, survival, and response to interferon in liver cancer, *N Engl J Med* 361:1437–1447, 2009.

Jin YJ, et al.: Suppressive effects of entecavir on hepatitis B virus and hepatocellular carcinoma, *J Gastroenterol Hepatol* 26(9):1380–1388, 2011.

Llovet JM, et al.: Sorefenib in advanced hepatocellular carcinoma, *N Engl J Med* 359:378–390, 2008.

Marrero JA, et al.: Prognosis of hepatocellular carcinoma: comparison of 7 staging systems in an American cohort, *Hepatology* 41:707–716, 2005.

Molinari M, Helton S: Hepatic resection versus radiofrequency ablation for hepatocellular carcinoma in cirrhotic individuals not candidates for liver transplantation: a Markov model decision analysis, *Am J Surg* 198:396–406, 2009.

Parikh S, Hyman D: Hepatocellular cancer: a guide for the internist, *Am J Med* 120:194, 2007.

Perilongo G, et al.: Cisplatin versus Cisplatin plus Doxorubicin for standard-risk hepatoblastoma, *N Engl J Med* 361:1662–1670, 2009.

Saunders D: Systematic review: The association between obesity and hepatocellular carcinoma—epidemiological evidence, *Aliment Pharmacol Ther* 31(10):1051, 2010.

Sherman M: Recurrence of hepatocellular carcinoma, *N Engl J Med* 359:19, 2008.

Stravitz RT, et al.: Surveillance for hepatocellular carcinoma in patients with cirrhosis improves outcome, *Am J Med* 121:119, 2008.

Trevisani F, et al.: Serum alpha-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease: influence of HBsAg and anti-HCV status, *J Hepatol* 34:570–575, 2001.

Villanueva A, Llovet JM: Targeted therapies for hepatocellular carcinoma, *Gastroenterology* 140(5):1410–1426, 2011.

Zhou J, et al.: Plasma microRNA panel to diagnose hepatitis B virus-related hepatocellular carcinoma, *J Clin Oncol* 29(36):4781, 2011.

Zhu AX, Ghassan KA: Expanding the treatment options for hepatocellular carcinoma, *JAMA* 299:1716, 2008.

BASIC INFORMATION

DEFINITION

Hepatopulmonary syndrome (HPS) is characterized by intrapulmonary vascular dilation in the setting of liver disease causing an increased alveolar-arterial (A-a) gradient.

SYNONYMS

HPS

ICD-9CM CODES
417.9 Unspecified disease of pulmonary circulation
ICD-10CM CODES
I28.9 Disease of pulmonary vessels, unspecified
K76 Other diseases of liver

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Between 5% and 30% of patients with cirrhosis; wide range due to lack of diagnostic criteria.
PREDOMINANT SEX AND AGE: There are no data on gender or age prevalence.
RISK FACTORS: Can occur with any degree or etiology of liver disease but is more common in patients with established cirrhosis and portal hypertension. There is no clear relationship between severity of hepatic dysfunction and level of hypoxemia. One recent study suggests that HPS is more common in patients with history of viral hepatitis than in patients with alcoholic cirrhosis.
GENETICS: There are new data suggesting that genes involved in the regulation of angiogenesis are associated with the risk of HPS.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Dyspnea.
- Platypnea: worsened dyspnea when sitting upright compared with supine position due to further ventilation-perfusion mismatch.
- Orthodeoxia: decreased Pao_2 when the patient is sitting upright compared with supine position due to ventilation-perfusion mismatch.
- Spider angiomata seen in high number.
- Signs of severe hypoxemia (e.g., cyanosis and clubbing of the digits).

ETIOLOGY

Dilation of intrapulmonary arterioles and dilated vascular channels between pulmonary arteries and veins leading to a ventilation-perfusion mismatch and right-to-left shunting (Fig. EH1-34). Research shows that nitric oxide plays a role in vasodilation. The relationship of vasodilation to liver disease is unclear. New areas of research include endothelin-1, which is produced by proliferating cholangiocytes, pulmonary angiogenesis, and opiate receptors' influence on NO production.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Portopulmonary hypertension.
- Cavopulmonary anastomosis.
- Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome).
- Chronic lung disease (i.e., COPD or pulmonary fibrosis) with coexisting liver disease.

WORKUP

- Diagnosis should be suspected in patients with cirrhosis who develop hypoxemia in absence of other causes (e.g., COPD, thromboembolism).
- Workup includes lab testing and imaging studies (see following), but diagnosis is based on clinical findings.

LABORATORY TESTS

- Arterial blood gas at rest, both supine and erect; Pao_2 <80 mm Hg.
- Pulmonary function tests will show nonspecific reduction in DLco.

There is new evidence showing that blood testing for elevated von Willenbrand factor antigen is a good screening test for HPS because it is a surrogate marker for endothelial dysfunction.

IMAGING STUDIES

- The most effective screening tool is transthoracic echocardiogram with bubble study to rule out right-to-left cardiac shunt; microbubble opacification in left atrium shows vasodilation of pulmonary vascular bed.
- Chest x-ray may show nonspecific bibasilar interstitial pattern.
- Scintigraphic perfusion scanning: technetium-99m–labeled albumin found in brain or spleen indicates dilated pulmonary vasculature or cardiac right-to-left shunt.
- Pulmonary angiography rarely used unless there is potential to embolize arteriovenous malformation (AVM).

TREATMENT

Ideal treatment would be targeted against pulmonary vasodilation. Most medications have targeted NO production, the activity of NO synthase or endothelin-1, pulmonary angiogenesis, or even bacterial translocation, but no controlled trials exist. Liver transplantation is the only successful treatment, which leads to improvement in gas exchange or compete resolution in gas exchange in the majority of patients. However, severe hypoxemia with Pao_2 <50 has been associated with a high posttransplant mortality. Some studies have shown benefit of transjugular portosystemic shunting, although it is not currently established treatment. Coil embolization in the setting of pulmonary AVMs is another possible area of treatment.

NONPHARMACOLOGIC THERAPY

Oxygen to correct hypoxemia; Pao_2 will partially correct with administration of supplemental O_2.

ACUTE GENERAL Rx

Correct hypoxemia with supplemental O_2.

CHRONIC Rx

Liver transplantation is the only successful treatment; the majority of patients show improvement in oxygenation at 1 year post transplant. There are some data showing worse outcomes for patients with severe HPS (PaO_2 <50%), but mortality appears to be improving.

COMPLEMENTARY & ALTERNATIVE MEDICINE

One study suggested that garlic supplements might decrease A-a gradient in patients with HPS. Studies of diets containing low amount of L-arginine have not shown benefit.

DISPOSITION

The diagnosis of HPS confers a poor prognosis. Patients with HPS have high mortality and shorter median survival than other patients with liver disease, even after adjusting for severity of liver disease. According to one natural history study, compared with patients with similar severity of liver disease and comorbidities whose 5-yr survival was estimated at 63%, those patients with the diagnosis of HPS had a 5 yr survival rate of 23%.

REFERRAL

- Referral to pulmonologist to help in establishing diagnosis.
- Referral to a liver transplant center.

PEARLS & CONSIDERATIONS

COMMENTS

Consider the diagnosis of HPS in patients with cirrhosis who present with dyspnea without signs of pulmonary edema from fluid overload.

SUGGESTED READINGS

Available at www.expertconsult.com.

RELATED CONTENT

Cirrhosis (Related Key Topic)

AUTHOR: **BEVIN KENNEY, M.D.**

SUGGESTED READINGS

Hoeper MM et al.: Portopulmonary hypertension and hepatopulmonary syndrome, *Lancet* 363:1461, 2004.

Rodriguez-Roisin R, Krowka MJ: Hepatopulmonary syndrome—a liver-induced lung vascular disorder, *N Engl J Med* 358:2378, 2008.

Swanson KL et al.: Natural history of hepatopulmonary syndrome: impact of liver transplantation, *Hepatology* 41:1122, 2005.

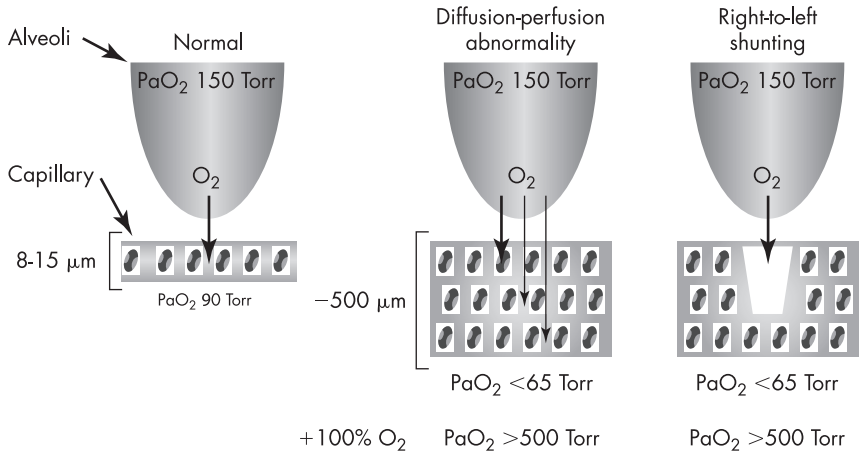

FIGURE EH1-34 Pathophysiology of hypoxemia in hepatopulmonary syndrome. Abnormal intrapulmonary vascular dilation in combination with increased pulmonary blood flow leads to diffusion-perfusion disturbance and arterial hypoxemia, correctable by oxygen supplementation. Most severe intrapulmonary vascular dilation or formation of arteriovenous malformations causes right-to-left shunting only partially correctable by oxygen administration. (From Hoeper MM et al: Portopulmonary hypertension and hepatopulmonary syndrome. *Lancet* 363:1461, 2004.)

BASIC INFORMATION

DEFINITION

Hepatorenal syndrome (HRS) is a condition of intense renal vasoconstriction (see Fig. H1-35) resulting from loss of renal autoregulation occurring as a complication of severe liver disease. Criteria for HRS are:

1. Serum creatinine concentration >1.5 mg/dl or 24-hr creatinine clearance <40 ml/min
2. Absence of shock, ongoing infection, and fluid loss and no current treatment with nephrotoxic drugs
3. Absence of sustained improvement in renal function (decrease in serum creatinine to <1.5 mg/dl after discontinuation of diuretics and a trial of plasma expansion)
4. Absence of proteinuria (<500 mg/day) or hematuria (<50 red blood cells/high-power field)
5. Absence of ultrasonographic evidence of obstructive uropathy or parenchymal renal disease
6. Urinary sodium concentration <10 mmol/L

Tables H1-19 and H1-20 summarize the classic and the revised diagnostic criteria for HRS.

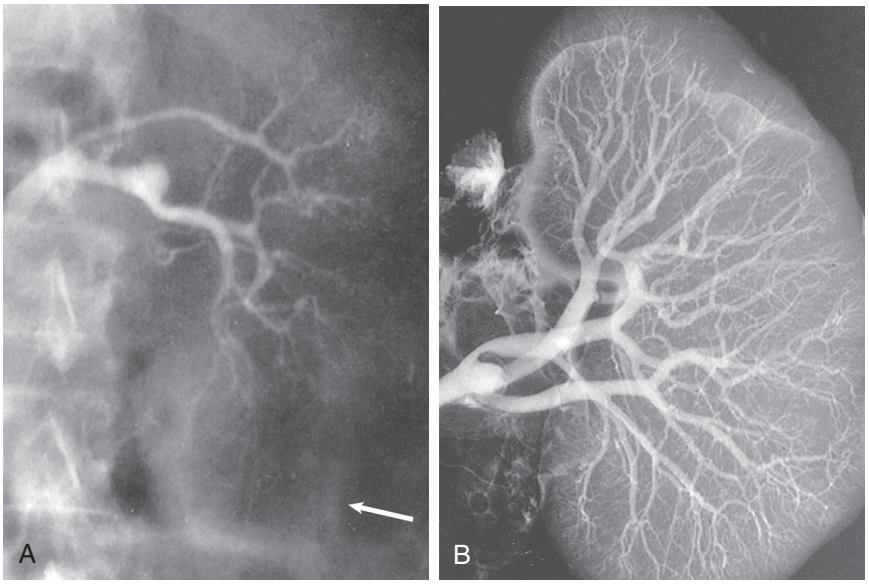

FIGURE H1-35 Hepatorenal syndrome (HRS). A, Renal angiogram (the *arrow* marks the edge of the kidney). **B,** The angiogram carried out in the same kidney at autopsy. Note complete filling of the renal arterial system throughout the vascular bed to the periphery of the cortex. The vascular attenuation and tortuosity seen previously **(A)** are no longer present. The vessels are also histologically normal. This indicates the functional nature of the vascular abnormality in HRS. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

TABLE H1-19 Diagnostic Criteria for Hepatorenal Syndrome

Major Criteria

Chronic or acute liver disease with advanced hepatic failure and portal hypertension
Low glomerular filtration rate, as indicated by serum creatinine >1.5 mg/dl (135 μmol/L) or 24-hr creatinine clearance <40 ml/min
Absence of shock, ongoing bacterial infection, and current or recent treatment with nephrotoxic drugs
Absence of gastrointestinal fluid losses (repeated vomiting or intense diarrhea)
Absence of renal fluid losses (weight loss >500 g/day for several days in patients with ascites without peripheral edema or 1000 g/day in patients with peripheral edema)
No sustained improvement in renal function (decrease in serum creatinine to 1.5 mg/dl [135 μmol/L] or less or increase in creatinine clearance to 40 ml/min or more) following diuretic withdrawal and expansion of plasma volume with 1.5 liters of isotonic saline
Proteinuria <500 mg/day and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease

Additional Criteria

Urine volume <500 ml/day
Urine sodium <10 mmol/L
Urine osmolality greater than plasma osmolality
Urine red blood cells <50 per high-power field
Serum sodium concentration <130 mmol/L

From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

There are two types of HRS (see Table H1-21):

1. Type 1: progressive impairment in renal function as defined by a doubling of initial serum creatinine >2.5 mg/dl in <2 wk
2. Type 2: stable or slowly progressive impairment of renal function not meeting the above criteria

SYNONYMS

Hepatic nephropathy
Oliguric renal failure of cirrhosis
HRS

ICD-9CM CODES
572.4 Hepatorenal syndrome
ICD-10CM CODES
K76.7 Hepatorenal syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

The probability of HRS in patients with cirrhosis is 18% at 1 yr and 39% at 5 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Evidence of cirrhosis is usually present: jaundice, spider angiomas, splenomegaly, ascites, fetor hepaticus, pedal edema.

TABLE H1-20 Revised Diagnostic Criteria for Hepatorenal Syndrome

Cirrhosis with ascites
Serum creatinine >1.5 mg/dl (133 μmol/L)
No improvement in serum creatinine (decrease to a level of 1.5 mg/dl) after at least 2 days with diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day.
Absence of shock
No current or recent treatment with nephrotoxic drugs
Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells per high-power field) and/or abnormal renal ultrasound

From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

TABLE H1-21 Definition of Hepatorenal Syndrome Type 1 and Type 2

Type 1 Hepatorenal Syndrome

Doubling of serum creatinine >2.5 mg/dl (220 μmol/L) or a 50% reduction in 24-hr creatinine clearance to <20 ml/min <2 weeks
Frequently follows a precipitating event (e.g., infection)
Median survival without treatment: 2 weeks

Type 2 Hepatorenal Syndrome

Less rapid renal functional deterioration than type 1
Mainly presents with refractory ascites
Median survival without treatment: 4-6 months

From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

- Hepatic encephalopathy: flapping tremor (asterixis), coma.
- Tachycardia and bounding pulse.
- Oliguria.

ETIOLOGY

An exacerbation of end-stage liver disease, HRS may occur after significant reduction of effective blood volume (e.g., paracentesis, GI bleeding, diuretics) or in the absence of any precipitating factors.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Prerenal azotemia: response to sustained plasma expansion is good (prompt diuresis with volume expansion). Volume challenge (to increase mean arterial pressure) followed by large-volume paracentesis (to increase cardiac output and decrease renal venous pressure) may be useful to distinguish HRS from prerenal azotemia in patients with FENa <1%. In patients with prerenal azotemia, the increase in renal perfusion pressure and renal blood flow will result in prompt diuresis; the volume challenge can be accomplished by giving a solution of 100 g of albumin in 500 ml of isotonic saline.
- Acute tubular necrosis: urinary sodium >30 mEq/L, fractional excretion of sodium (FENa) >1.5%, urinary/plasma creatinine ratio <30, urine/plasma osmolality ratio = 1, urine sediment reveals casts and cellular debris, no significant response to sustained plasma expansion.

WORKUP

Patients with acute azotemia and oliguria in the setting of liver disease should undergo laboratory evaluation to differentiate HRS from acute tubular necrosis and volume challenge to differentiate HRS from prerenal azotemia if FENa <1%.

LABORATORY TESTS

- Obtain serum electrolytes, blood urea nitrogen, creatinine, osmolality, urinalysis, urinary sodium, urinary creatinine, urine osmolality.
- Calculate FENa.
- In HRS: urinary sodium <10 mEq/L, FENa <1%, urinary plasma creatinine ratio >30, urinary plasma osmolality ratio >1.5, urine sediment unremarkable.

IMAGING STUDIES

Renal ultrasound may be indicated if renal obstruction is suspected.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of precipitating factors.
- Transjugular intrahepatic portosystemic shunts may be effective in selected patients, but data are limited.
- Dialysis with molecular adsorbent recirculating systems remains investigational until more data are available.

ACUTE GENERAL Rx

- The only effective treatment of HRS is liver transplantation; ornipressin is used in some liver units to avoid further deterioration of renal function in patients awaiting liver transplantation. In general, dopamine and prostaglandins are ineffective in treating patients with HRS.
- The best approach to the management of HRS based on its pathogenesis is the administration of vasoconstrictor drugs (terlipressin, norepinephrine, midodrine). Terlipressin may improve renal perfusion by reversing splanchnic vasodilation, which is the hallmark of HRS. Encouraging results were found in a recent study using continuous IV noradrenalin in combination with albumin and furosemide. In this study, reversal of HRS was achieved in 10 of 12 patients.
- Treatment of HRS with vasoconstrictors for 5 to 15 days in attempt to reduce serum creatinine to <1.5 mg/dl is as follows:
  1. Administration of one of the following drugs or drug combinations:
     a. Norepinephrine (0.5 to 3.0 mg/hr IV).
     b. Midodrine (7.5 mg PO tid, increased to 12.5 mg tid if needed) in combination with octreotide (100 micrograms SC tid, increased to tid prn).
     c. Terlipressin (0.2 to 2.0 mg IV q4 to 12h).
- Concomitant administration of albumin (1 g/kg IV on day 1, followed by 20 to 40 g daily)

DISPOSITION

Mortality rate exceeds 80%; liver transplantation is the only curative treatment.

REFERRAL

Referral for liver transplantation when indicated (see "Comments").

PEARLS & CONSIDERATIONS

COMMENTS

Liver transplantation may be indicated in otherwise healthy patients (age preferably <65 yr) with sclerosing cholangitis, chronic hepatitis with cirrhosis, or primary biliary cirrhosis. Contraindications to liver transplantation are AIDS, most metastatic malignancies, active substance abuse, uncontrolled sepsis, and uncontrolled cardiac or pulmonary disease.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hepatorenal Syndrome (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Duvoux C et al.: Effects of noradrenalin and albumin in patients with type 1 hepatorenal syndrome: a pilot study, *Hepatology* 36:374, 2002.

Gines P, Schrier RW: Renal failure in cirrhosis, *N Engl J Med* 361:1279–1290, 2009.

Gines P et al.: Management of cirrhosis and ascites, *N Engl J Med* 350:1646, 2004.

BASIC INFORMATION

DEFINITION

Any disorder affecting the peripheral nervous system, including nerve roots, plexuses, and individual peripheral nerves, that has a genetic basis of inheritance and has been or is capable of being transmitted along generations.

There are many different types of hereditary peripheral neuropathies, including Dejerine-Sottas disease, inherited metabolic neuropathies, hereditary sensory and autonomic neuropathies (HSANs), and hereditary motor neuropathies. Most disorders are diagnosed in infancy or childhood; as such, adult clinicians rarely see these patients. For this reason, this chapter discusses only the hereditary motor and sensory neuropathies that an adult clinician might encounter.

SYNONYMS

Charcot-Marie-Tooth (CMT) disease, a.k.a. hereditary motor-sensory neuropathy (HMSN)
Hereditary neuropathy with liability to pressure-sensitive palsies (HNPP)

ICD-9CM CODES
CMT: 356.1
HNPP: 689
ICD-10CM CODES
G60.0 Hereditary motor and sensory neuropathy
G60.8 Other hereditary and idiopathic neuropathies
G60.9 Hereditary and idiopathic neuropathy, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

All CMT: approximately 30 per 100,000
- CMT type 1 (demyelinating pathophysiology): 1 in 2500
- CMT type 2 (axonal pathophysiology): 7 in 1000
- CMT type 4 and CMT-X: rare (either axonal or demyelinating pathophysiology)
  HNPP: 2 to 5 per 100,000

PHYSICAL FINDINGS & CLINICAL PRESENTATION

CMT: Highly variable
- Age at onset earlier for CMT-1 than CMT-2, but both may present from childhood to old age.
- Severely affected patients have severe distal weakness and muscle atrophy with hand (prominently affecting interossei) and foot deformities (pes cavus, high arched feet, hammer toes).
- Mildly affected patients may have only foot deformity (pes cavus) with little or no weakness/sensory loss.
- Legs can be affected greater than arms, and patients will complain of gait abnormalities (steppage), which cause them to trip and fall.
- Sensory complaints (paresthesias, numbness, dysesthesia) are uncommon despite physical findings of impaired sensation.
- Decreased or absent reflexes.
- Some patients may have postural tremor of the upper limbs.

HNPP (a.k.a. tomaculous neuropathy):
- Age at onset is commonly adolescence.
- Disorder is characterized by recurrent entrapment of peripheral nerves with accompanying signs and symptoms (paresthesias and/or weakness in anatomic distributions). Most common are:
  1. Median nerve at the wrist (carpal tunnel syndrome)
  2. Ulnar nerve at the elbow (cubital tunnel syndrome)
  3. Painless brachial plexopathies
  4. Lateral femoral cutaneous nerve (meralgia paresthetica)
  5. Peroneal nerve at the fibular head
- May be associated with a generalized polyneuropathy.

ETIOLOGY

CMT: more than 30 subgroups have been identified and have various chromosomal abnormalities.
- Most common mutation is PMP-22 duplication, giving rise to CMT 1A demyelinating phenotype.
- Other mutations include P0 (demyelinating) and neurofilament light chain mutations (demyelinating or axonal phenotype)—see the following.
- Updated information may be available at http://www.neuro.wustl.edu/neuromuscular.
  HNPP: deletion of chromosome 17p11.2–12.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

CMT: other genetic, metabolic, and multisystem disorders including:
- Spinocerebellar ataxias
- Friedreich's ataxia
- Leukodystrophies
- Refsum's disease (elevated serum phytanic acid)
- Distal spinal muscular atrophies and distal myopathies, which can present with pes cavus and other foot deformities
- Chronic inflammatory demyelinating polyneuropathy (CIDP)

HNPP:
- Hereditary neuralgic amyotrophy (HNA), which typically is painful rather than painless. In addition, in HNA, there is no evidence of generalized polyneuropathy.
- Multifocal motor neuropathy with conduction block (MMNCB)—autoimmune-mediated pure motor neuropathy
- Neuropathy associated with renal failure
- Lead neuropathy
- Neuropathy relating to paraproteinemia (demyelinating pathophysiology)

EVALUATION

CMT
- History of gradual onset symptoms is important to distinguish CMT from other forms of neuropathy.
- Detailed family history with *pedigree* is essential. Consider examination of multiple family members.
- History should evaluate for potential heavy metal exposure.
- History of dysesthesias is uncommon and should prompt search for acquired neuropathy or other inherited neuropathies (e.g., Fabry's disease).

HNPP: genetic testing after identification of multiple entrapment neuropathies on EMG and nerve conduction studies

LABORATORY TESTS

- Neurophysiology: electromyography (EMG) and nerve conduction studies (NCSs) must be done first to determine type of pathophysiology: demyelinating or axonal. This will guide genetic testing.
- NCSs in CMT-1 will reveal demyelinating physiology characterized by very slow conduction velocities (around 15 to 30 m/s) with prolonged distal latencies. Inherited demyelinating disorders can be distinguished from acquired demyelinating disorders (e.g., chronic inflammatory demyelinating polyneuropathy or CIDP) by the presence of conduction block in the latter.
- In HNPP, diffusely prolonged distal latencies with superimposed entrapment neuropathies at common sites will be seen on NCSs.
- EMG will reveal reinnervation characterized by long-duration, large-amplitude, polyphasic motor unit potentials (MUPs) with decreased MUP recruitment.
- Genetic tests are available for some CMT subtypes:
  1. CMT-1A: chromosome 17p11-PMP-22 duplication
  2. CMT-1B: chromosome 1q22-P0 mutation
  3. CMT-2E: chromosome 8p21-neurofilament light chain (NF-L) point mutation
  4. CMT-X: connexin 32 mutations
  5. HNPP: chromosome 17p11 deletion, which includes the PMP-22 gene
- Serum and 24-hour urine levels of heavy metals (arsenic, lead, etc.)
- SPEP, UPEP, immunofixation (for paraprotein).
- Anti-GM1 antibody (positive in ~50% of patients with MMNCB).
- Lumbar puncture may reveal elevated CSF protein in CIDP.
- Peripheral nerve biopsy:
  1. Demyelination with "onion bulb formation." Tomaculae, or focal thickening of myelin sheaths, is seen in HNPP
  2. Generally not indicated unless diagnosis is uncertain

IMAGING STUDIES

- Spine plain films: for evaluation of scoliosis.
- MRI: indicated if dissociative sensory loss (dorsal column dysfunction with intact spinothalamic tract function) or if upper motor neuron findings (spasticity, Babinski's sign, clonus, increased tendon reflexes) are present.
- Exclusion of involvement of brain or spinal cord compressive lesions causing arm or leg weakness.

- Some inherited peripheral demyelinating disorders (i.e., CMT-X) are associated with intracerebral white matter abnormalities on MRI.
- Exclusion of structural, infectious, or inflammatory nerve root pathology.

Rx TREATMENT

There is no known cure for any of these disorders. Management is supportive.

NONPHARMACOLOGIC THERAPY

- Physical therapy (PT) and occupational therapy (OT) to provide assistance with gait and coordination.
- PT and OT might provide walking aid such as ankle foot orthosis (AFO), cane, walker, or wheelchair depending on the severity of the neuropathy.
- Wrist splints for superimposed carpal tunnel syndrome.
- Elbow pads (Heelbo Pads) to cushion the ulnar nerve at the elbow.
- Heel-cord strengthening.
- Stretching exercises.
- Analgesics for pain associated with foot deformity.
- Surgical correction of foot deformities by orthopedic surgeons if indicated.

Vincristine may worsen existing neuropathy (important for oncologist to know if patient develops cancer requiring chemotherapy).

SURGICAL TREATMENT

- Patients with HNPP should probably not undergo surgical decompression of the median nerve at the wrist or the ulnar nerve at the elbow; these nerves are sensitive to manipulation. Poor results have been reported with ulnar nerve transposition.
- Anesthesiologists should be aware of HNPP diagnosis in patients undergoing surgery to prevent compression neuropathies from occurring during surgical procedures.

GENETIC COUNSELING

Must be routinely done for patient and family when diagnosis is established. Many aspects of the patient and family's life are affected, including:

- Future progeny of patient and/or patient's parents or children
- Psychosocial aspects including social functioning, marriage, employment
- Financial needs
- Medical and life insurability

PROGNOSIS

- CMT: slowly progressive, and patients often remain ambulatory until late in life. Life expectancy is normal. Patients with respiratory involvement (i.e., phrenic nerve involvement with diaphragm paresis) may have shorter life expectancy.
- HNPP: benign prognosis.

DISPOSITION

Outpatient care. Routine follow-up appointments should be done initially every 6 mo, and then every 1 to 2 yr.

REFERRAL

- Neurology and/or neuromuscular disease specialist
- Podiatry for recurrent foot problems, including appropriate arches

PEARLS & CONSIDERATIONS

PATIENT & FAMILY EDUCATION

Patients can benefit from use of Muscular Dystrophy Association (MDA) resources.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fig. N1-11 Neuropathic pain, diagnostic approach (Algorithm)

Charcot-Marie-Tooth Disease (Related Key Topic)

AUTHOR: **GAVIN BROWN, M.D.**

EVIDENCE

Abstract[1]

Objective:

To improve understanding of TRPV4-associated axonal Charcot-Marie-Tooth (CMT) neuropathy phenotypes and their debated pathologic mechanism.

Methods:

A total of 17 CMT2C phenotypic families with vocal cord and diaphragmatic involvement and 36 clinically undifferentiated CMT2 subjects underwent sequencing analysis of the coding region of *TRPV4*. Functional studies of mutant proteins were performed using transiently transfected cells for TRPV4 subcellular localization, basal and stimulated Ca^{2+} channel analysis, and cell viability assay with or without channel blockade.

Results:

Two *TRPV4* mutations R232C and R316H from 17 CMT2C families were identified in the ankyrin repeat domains. The R316H is a novel de novo mutation found in a patient with CMT2C phenotype. The family with R232C mutation had individuals with and without vocal cord and diaphragm involvement. Both mutant TRPV4 proteins had normal subcellular localization in HEK293 and HeLa cells. Cells transfected with R232C and R316H displayed increased intracellular Ca^{2+} levels and reversible cell death by the TRPV channel antagonist, ruthenium red.

Conclusion:

TRPV4 ankyrin domain alterations including a novel de novo mutation cause axonal CMT2. Individuals with the same mutation may have nondistinct CMT2 or have phenotypic CMT2C with vocal cord paresis. Reversible hypercalcemic gain-of-function of mutant TRPV4 instead of loss-of-function appears to be pathologically important. The reversibility of cell death by channel blockade provides an attractive area of investigation in consideration of treatable axonal degeneration. Ⓐ

Evidence-Based Reference

Klein CJ et al.: TRPV4 mutations and cytotoxic hypercalcemia in axonal Charcot-Marie-Tooth neuropathies, *Neurology* 76:887–894, 2011. Ⓐ

SUGGESTED READINGS

Chance PF: Genetic evaluation of inherited motor/sensory neuropathy, *Suppl Clin Neurophysiol* 57:228, 2004.

Scott KR, Kothari MJ: Hereditary neuropathies, *Semin Neurol* 25(2):174, 2005.

Washington University Neuromuscular Disease Center. http://www.neuro.wustl.edu/neuromuscular.

BASIC INFORMATION

DEFINITION

Herpangina is a self-limited upper respiratory tract infection associated with a characteristic vesicular rash on the soft palate.

SYNONYMS

Vesicular stomatitis
Acute lymphonodular pharyngitis

ICD-9CM CODES
074.0 Herpangina
ICD-10CM CODES
B08.5 Enteroviral vesicular pharyngitis

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT SEX: Male = female.
PREDOMINANT AGE: 3 to 10 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Characterized by ulcerating lesions typically located on the soft palate (Fig. H1-36).
- Usually fewer than six lesions that evolve rapidly from a diffuse pharyngitis to erythematous macules and subsequently to vesicles that are moderately painful.
- Fever, vomiting, and headache in the first few days of illness but subsiding spontaneously.
- Pharyngeal lesions typical for several more days.

ETIOLOGY

- Most cases caused by coxsackie A viruses (A2, A4, A5, A6, A10).
- Occasional cases caused by other enteroviruses (echovirus and enterovirus 71).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Herpes simplex.
- Bacterial pharyngitis.
- Tonsillitis.
- Aphthous stomatitis.
- Hand-foot-mouth disease.

WORKUP

Diagnosis is typically based on characteristic lesions on the soft palate.

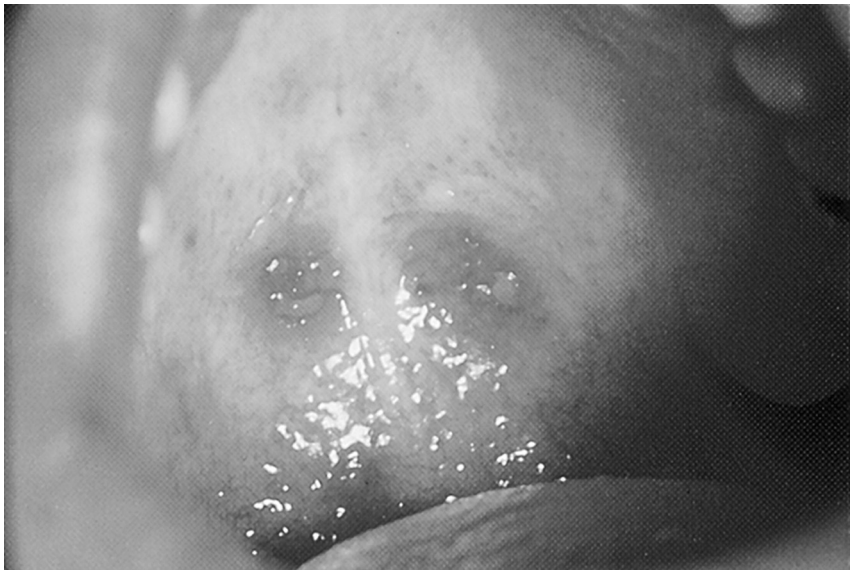

FIGURE H1-36 Herpangina with shallow ulcers in the roof of the mouth. (Courtesy Marshall Guill, M.D. From Goldstein B [ed]: *Practical dermatology,* ed 2, St Louis, 1997, Mosby.)

LABORATORY TESTS

Viral and bacterial cultures of the pharynx to exclude herpes simplex infection and streptococcal pharyngitis if the diagnosis is in doubt.

TREATMENT

- Give symptomatic treatment for sore throat: saline gargles and analgesics, and encourage oral fluids.
- No antiviral therapy indicated; avoid antibacterial agents because they are ineffective, increase cost, might result in side effects, and promote antibiotic resistance.

NONPHARMACOLOGIC THERAPY

Analgesic throat lozenges are helpful in some cases.

ACUTE GENERAL Rx

Antipyretics when indicated.

CHRONIC Rx

Self-limited infection.

DISPOSITION

- Generally, resolution of symptoms within 1 wk.
- Persistence of fever or mouth lesions beyond 1 wk suggestive of an alternative diagnosis (see "Differential Diagnosis").

REFERRAL

For consultation with otolaryngologist or infectious disease specialist if the diagnosis is in doubt.

PEARLS & CONSIDERATIONS

COMMENTS

Household outbreaks may occur, especially during the summer months.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Herpangina (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Chang LY et al.: Outcome of enterovirus 71 infections with or without stage-based management: 1998 to 2002. *Pediatr Infect Dis J* 23(4):327, 2004.

Chang LY et al.: Transmission and clinical features of enterovirus 71 infections in household contacts in Taiwan, *JAMA* 291(2):222, 2004.

Stone MS: Viral exanthems, *Dermatol Online J* 9(3):4, 2003.

Urashima M et al.: Seasonal models of herpangina and hand-foot-mouth disease to simulate annual fluctuations in urban warming in Tokyo, *Jpn J Infect Dis* 56(2):48, 2003.

BASIC INFORMATION

DEFINITION

Herpes simplex is a viral infection caused by the herpes simplex virus (HSV). HSV-1 is associated primarily with oral infections, and HSV-2 causes mainly genital infections. However, either type can infect any site. After the primary infection, the virus enters the nerve endings in the skin directly below the lesions and ascends to the dorsal root ganglia, where it remains in a latent stage until it is reactivated.

SYNONYMS

Genital herpes
Herpes labialis
Herpes gladiatorum
Herpes digitalis

ICD-9CM CODES
054.10 Genital herpes
054.9 Herpes labialis
ICD-10CM CODES
B00.1 Herpesvirus vesicular dermatitis
B00.0 Exzema herpeticum
A60.9 Anogenital herpesviral infection, unspecified
B00.9 Herpesviral infection, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- More than 85% of adults have serologic evidence of HSV-1 infection. The seroprevalence of adults with HSV-2 in the United States is 25%; however, only approximately 20% of these persons recall having symptoms of HSV infection.
- Most cases of eye or digital herpetic infections are caused by HSV-1.
- Frequency of recurrence of HSV-2 genital herpes is higher than HSV-1 oral labial infection.
- The frequency of recurrence is lowest for oral labial HSV-2 infections.
- The incidence of complications from herpes simplex (e.g., herpes encephalitis) is highest in immunocompromised hosts.
- Male circumcision significantly reduces the incidence of HSV-2.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Primary infection
- Symptoms occur from 3 to 7 days after contact (respiratory droplets, direct contact).
- Constitutional symptoms include low-grade fever, headache and myalgias, regional lymphadenopathy, and localized pain.
- Pain, burning, itching, and tingling last several hours.
- Grouped vesicles (Fig. H1-37), usually with surrounding erythema, appear and generally ulcerate or crust within 48 hr.
- The vesicles are uniform in size (differentiating it from herpes zoster vesicles, which vary in size). Scattered erosions covered with exudate may be noted on genitals (Fig. EH1-38).
- During the acute eruption the patient is uncomfortable; involvement of lips and inside of mouth may make it unpleasant for the patient to eat; urinary retention may complicate involvement of the genital area.
- Lesions generally last from 2 to 6 wk and heal without scarring.

Recurrent infection:
- Generally caused by alteration in the immune system; fatigue, stress, menses, local skin trauma, and exposure to sunlight are contributing factors.
- The prodromal symptoms (fatigue, burning and tingling of the affected area) last 12 to 24 hr.
- A cluster of lesions generally evolves within 24 hr from a macule to a papule and then vesicles surrounded by erythema; the vesicles coalesce and subsequently rupture within 4 days, revealing erosions covered by crusts.
- The crusts are generally shed within 7 to 10 days, revealing a pink surface.
- The most frequent location of the lesions is on the vermilion border of the lips (HSV-1), the penile shaft or glans penis and the labia (HSV-2), buttocks (seen more frequently in women), fingertips (herpetic whitlow), and trunk (may be confused with herpes zoster).
- Rapid onset of diffuse cutaneous herpes simplex (eczema herpeticum) may occur in certain atopic infants and adults. It is a medical emergency, especially in young infants, and should be promptly treated with acyclovir.
- Herpes encephalitis, meningitis, and ocular herpes can occur in patients with immunocompromised status and occasionally in normal hosts.

ETIOLOGY

HSV-1 and HSV-2 are both DNA viruses.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Impetigo.
- Behçet's syndrome.
- Coxsackie virus infection.
- Syphilis.
- Stevens-Johnson syndrome.
- Herpangina.
- Aphthous stomatitis.
- Varicella.
- Herpes zoster.

WORKUP

Diagnosis is based on clinical presentation. Laboratory evaluation confirms diagnosis.

LABORATORY TESTS

- Direct immunofluorescent antibody slide tests provide a rapid diagnosis.
- Viral culture is the most definitive method for diagnosis; results are generally available in 1 or 2 days. The lesions should be sampled during the vesicular or early ulcerative stage; cervical samples should be taken from the endocervix with a swab.
- Tzanck smear is a readily available test that will demonstrate multinucleated giant cells. However, it is not a highly sensitive test.
- Pap smear will detect HSV-infected cells in cervical tissue from women without symptoms.
- Serologic tests for HSV: immunoglobulin (Ig) G and IgM serum antibodies. Antibodies to HSV occur in 50% to 90% of adults. The presence of IgM or a fourfold or greater rise in IgG titers indicates a recent infection (convalescent sample should be drawn 2 to 3 wk after the acute specimen is drawn).

TREATMENT

- Table H1-22 summarizes antiviral chemotherapy for HSV infection.
- Topical acyclovir, penciclovir, and docosanol are optional treatments for recurrent herpes labialis, but they are less effective than oral treatments.

DISPOSITION

Most patients recover from the initial episode or recurrences without complications; immunocompromised hosts are at risk for complications (e.g., disseminated herpes simplex infection, herpes encephalitis).

FIGURE H1-37 Herpes simplex. (From Scuderi G [ed]: *Sports medicine: principles of primary care,* St Louis, 1997, Mosby.)

REFERRAL

- Hospital admission in patients with herpes encephalitis or herpes meningitis and in immunocompromised hosts with diffuse herpes simplex infection.
- Ophthalmology referral in patients with suspected ocular herpes.

PEARLS & CONSIDERATIONS

COMMENTS

- Provide patient education regarding transmission of HSV.
- Condom use offers significant protection against HSV-1 infection in susceptible women.
- Patients should be instructed on the use of condoms for sexual intercourse and on avoiding kissing or sexual intercourse until lesions are crusted.
- Patients should also avoid contact with immunocompromised hosts or neonates while lesions are present.
- Proper handwashing techniques should be explained.
- Patients with herpes gladiatorum (cutaneous herpes in athletes involved in contact sports) should be excluded from participation in active sports until lesions have resolved.
- Many new HSV-2 infections are asymptomatic. Since HSV-2 antibody tests have become commercially available, an increasing number of persons have learned that they have genital herpes through serologic testing. Persons with asymptomatic HSV-2 infection shed virus in the genital tract less frequently than persons with symptomatic infection, but much of the difference is attributable to less frequent genital lesions because generally lesions are accompanied by frequent viral shedding.
- Suppressive treatment of HSV-2 infection lowers the incidence of genital lesions by 70% to 80%, but cuts the rate of HSV-2 transmission to uninfected partners by only 50%.
- Trials involving investigational herpes simplex vaccine have found it to be effective in preventing HSV-1 genital disease and infection, but not in preventing HSV-2 disease or infection.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Genital Herpes (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

TABLE H1-22 Antiviral Chemotherapy for Herpes Simplex Virus Infection

Mucocutaneous HSV Infections

Infections in Immunosuppressed Patients

Acute symptomatic first or recurrent episodes: IV acyclovir (5 mg/kg q8h) and oral acyclovir (400 mg qid), famciclovir (500 mg PO tid), or valacyclovir (500 mg PO bid) for 7-10 days are effective. Treatment duration may vary from 7-14 days.

Suppression of reactivation disease: IV acyclovir (5 mg/kg q8h), valacyclovir (500 mg PO bid), or oral acyclovir (400-800 mg 3-5 times per day) prevents recurrences during the immediate 30-day post-transplantation period. Longer-term suppression is often used for persons with continued immunosuppression. In bone marrow and renal transplant recipients, valacyclovir 2 g 4 times daily is also effective in preventing CMV infection. Valacyclovir 4 g 4 times daily has been associated with TTP after extended use in HIV-positive persons. In HIV-infected persons, oral famciclovir (500 mg bid) is effective in reducing clinical and subclinical reactivations of HSV-1 and -2.

Genital Herpes

First episodes: Oral acyclovir (200 mg five times per day or 400 mg tid), oral valacyclovir (1000 mg bid), or famciclovir (250 mg bid) for 10-14 days is effective. IV acyclovir (5 mg/kg q8h for 5 days) is given for severe disease or neurologic complications such as aseptic meningitis.

Symptomatic recurrent genital herpes: Oral acyclovir (200 mg 5 times per day for 5 days, 800 mg PO tid for 2 days), valacyclovir (500 mg bid for 3 or 5 days), or famciclovir (125 mg bid for 5 days). All these therapies are effective in shortening lesion duration.

Suppression of recurrent genital herpes: Oral acyclovir (200-mg capsules bid or tid, 400 mg bid, or 800 mg qd), famciclovir (250 mg bid), or valacyclovir (500 mg or 1000 mg qd or 500 mg bid) prevents symptomatic reactivation. Persons with frequent reactivation (<9 episodes/year) can take 500 mg daily; those with >9 episodes/year should take 1000 mg/daily or 500 mg bid.

Oral-Labial HSV Infections

First episode: Oral acyclovir (200 mg) is given 4 or 5 times per day. Famciclovir (250 mg bid) or valacyclovir (1000 mg bid) has been used clinically.

Recurrent episodes: Valacyclovir 1000 mg bid for 1 day or 500 mg bid for 3 days is effective in reducing pain and speeding healing. Self-initiated therapy with six times daily topical 1% penciclovir cream is effective in speeding the healing of oral-labial HSV; topical acyclovir cream has also been shown to speed healing.

Suppression of reactivation of oral-labial HSV: Oral acyclovir (400 mg bid), if started before exposure and continued for the duration of exposure (usually 5-10 days), prevents reactivation of recurrent oral-labial HSV infection associated with severe sun exposure.

Herpetic Whitlow

Oral acyclovir (200 mg) 5 times daily for 7-10 days.

HSV Proctitis

Oral acyclovir (400 mg five times per day) is useful in shortening the course of infection. In immunosuppressed patients or in patients with severe infection, IV acyclovir (5 mg/kg q8h) may be useful.

Herpetic Eye Infections

In acute keratitis, topical trifluorothymidine, vidarabine, idoxuridine, acyclovir, penciclovir, and interferon are all beneficial. Debridement may be required; topical steroids may worsen disease.

CNS HSV Infections

HSV encephalitis: Intravenous acyclovir (10 mg/kg q8h; 30 mg/kg per day) for 14-21 days is preferred.

HSV aseptic meningitis: No studies of systemic antiviral chemotherapy exist. If therapy is to be given, IV acyclovir (15-30 mg/kg/day) should be used.

Autonomic radiculopathy: No studies are available.

Neonatal HSV infections: Acyclovir (60 mg/kg/day, divided into three doses) is given. The recommended duration of treatment is 21 days. Monitoring for relapse should be undertaken, and some authorities recommend continued suppression with oral acyclovir suspension for 3 to 4 mo.

Visceral HSV Infections

HSV esophagitis: IV acyclovir (15 mg/kg per day). In some patients with milder forms of immunosuppression, oral therapy with valacyclovir or famciclovir is effective.

HSV pneumonitis: No controlled studies exist. IV acyclovir (15 mg/kg per day) should be considered.

Disseminated HSV infections: No controlled studies exist. Intravenous acyclovir (10 mg/kg q8h) nevertheless should be tried. No definite evidence indicates that therapy decreases the risk of death.

Erythema multiforme-associated HSV: Anecdotal observations suggest that oral acyclovir (400 mg bid or tid) or valacyclovir (500 mg bid) suppresses erythema multiforme.

Surgical prophylaxis: Several surgical procedures such as laser skin resurfacing, trigeminal nerve root decompression, and lumbar disk surgery have been associated with HSV reactivation. Intravenous acyclovir (3 mg/kg) and oral acyclovir 800 mg bid, valacyclovir 500 mg bid, or famciclovir 250 mg bid is effective in reducing reactivation. Therapy should be initiated 48 hours before surgery and continued for 3-7 days.

Infections with acyclovir-resistant HSV: Foscarnet (40 mg/kg IV q8h) should be given until lesions heal. The optimal duration of therapy and the usefulness of its continuation to suppress lesions are unclear. Some patients may benefit from cutaneous application of trifluorothymidine or 5% cidofovir gel.

CMV, Cytomegalovirus; *CNS,* central nervous system; *HIV,* human immunodeficiency virus; *HSV,* herpes simplex virus; *TTP,* thrombotic thrombocytopenic purpura.

From Mandell GL et al: *Principles and practice of infectious diseases,* ed 6, Philadelphia, 2005, Churchill Livingstone.

SUGGESTED READINGS

Belshe RB et al.: Efficacy results of a trial of a herpes simplex vaccine, *N Engl J Med* 366:34–43, 2012.

Corey L, Wald A: Maternal and neonatal herpes simplex virus infections, *N Engl J Med* 361:1376–1385, 2009.

Tobian AR et al.: Male circumcision for the prevention of HSV-2 and HPV infections and syphilis, *N Engl J Med* 360:1298–1309, 2009.

Tronstein E et al.: Genital shedding of herpes simplex virus among symptomatic and asymptomatic persons with HSV-2 infection, *JAMA* 305(14):1441–1449, 2011.

Usatine RP, Tinitigan R: Non-genital herpes simplex virus, *Am Fam Physician* 82(9):1075–1082, 2010.

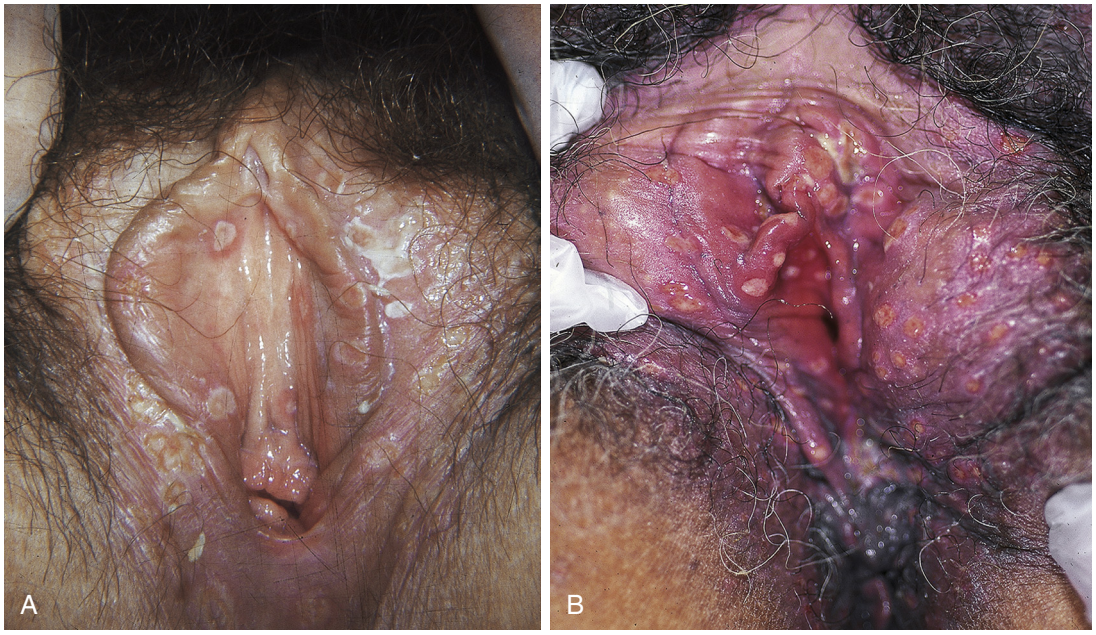

FIGURE EH1-38 Primary herpes simplex. A, Scattered erosions covered with exudate. **B,** Numerous erosions appeared 4 days after contact with an asymptomatic carrier. (From Habif TP: *Clinical dermatology,* ed 4, Philadelphia, 2004, Mosby.)

BASIC INFORMATION

DEFINITION

Herpes zoster is a disease caused by reactivation of the varicella-zoster virus, with spread of the virus alone from the sensory nerve to the dermatome. After the primary infection (chickenpox), the virus becomes latent in the dorsal root ganglia and reemerges when there is a weakening of the immune system (as a result of disease or advanced age).

SYNONYMS

Shingles
HZ

ICD-9CM CODES
053.9 Herpes zoster
ICD-10CM CODES
B02 Herpes zoster
B02.7 Disseminated zoster
B02.8 Zoster with other complications
B02.9 Zoster without complications

EPIDEMIOLOGY & DEMOGRAPHICS

- Herpes zoster occurs during the lifetime of 10% to 20% of the population.
- There is an increased incidence in immunocompromised patients (AIDS, malignancy), the elderly, and children who acquired chickenpox when younger than 2 mo.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pain generally precedes skin manifestation by 3 to 5 days and is generally localized to the dermatome that will be affected by the skin lesions.
- Constitutional symptoms are often present (malaise, fever, headache).
- The initial rash consists of erythematous maculopapules generally affecting one dermatome (thoracic region in majority of cases [Fig. H1-39]). Typically the rash does not cross the midline. Some patients (<30%) may have scattered vesicles outside the affected dermatome. In rare cases the rash can be generalized (Fig. H1-40).
- The initial maculopapules evolve into vesicles and pustules by the third or the fourth day.
- The vesicles have an erythematous base (Fig. EH1-41), are cloudy, and have various sizes (a distinguishing characteristic from herpes simplex, in which the vesicles are of uniform size) and may have a classic appearance of grouped vesicles (Fig. H1-42).
- The vesicles subsequently become umbilicated and then form crusts that generally fall off within 3 wk; scarring may occur.
- Pain during and after the rash is generally significant. Post-herpetic neuralgia occurs after herpes zoster in approximately one third of patients aged 60 years and older and can persist for months or years.
- Secondary bacterial infection with *Staphylococcus aureus* or *Streptococcus pyogenes* may occur.
- Regional lymphadenopathy may occur.
- Herpes zoster may involve the trigeminal nerve (most frequent cranial nerve involved); involvement of the geniculate ganglion can cause facial palsy and a painful ear, with the presence of vesicles on the pinna and external auditory canal (Ramsay Hunt syndrome).

ETIOLOGY

Reactivation of varicella virus (human herpes virus III)

DIAGNOSIS

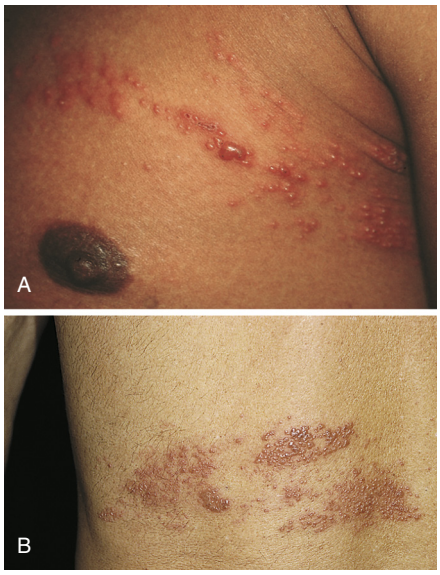

FIGURE H1-39 A and **B,** Herpes zoster lesions in T3 distribution. (From Swartz, MH: *Textbook of physical diagnosis*, 7th ed, Philadelphia, 2014, Saunders.)

FIGURE H1-40 Herpes zoster, generalized. (From Swartz, MH: *Textbook of physical diagnosis*, 7th ed, Philadelphia, 2014, Saunders.)

DIFFERENTIAL DIAGNOSIS

- Rash: herpes simplex and other viral infections
- Pain from herpes zoster: may be confused with acute myocardial infarction, pulmonary embolism, pleuritis, pericarditis, renal colic

LABORATORY TESTS

Laboratory tests are generally not necessary (viral cultures and Tzanck smear will confirm diagnosis in patients with atypical presentation).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Wet compresses (using Burow's solution or cool tap water) applied for 15 to 30 min five to 10 times a day are useful to break vesicles and remove serum and crust.
- Care must be taken to prevent any secondary bacterial infection.

ACUTE GENERAL Rx

- Oral antiviral agents can decrease acute pain, inflammation, and vesicle formation when treatment is begun within 48 hr of onset of rash. Treatment options are:
  1. Valacyclovir 1000 mg tid for 7 days
  2. Famciclovir 500 mg tid for 7 days
  3. Acyclovir 800 mg 5 times daily for 7 to 10 days
- Corticosteroids should be considered in older patients within 72 hr of clinical presentation or if new lesions are still appearing if there are no contraindications. Initial dose is prednisone 40 mg/day decreased by 5 mg/day until finished. When used there is a decrease in the use of analgesics and time to resumption of usual activities, but there is no effect on the incidence and duration of postherpetic neuralgia.
- Immunocompromised patients should be treated with IV acyclovir 500 mg/m^2 or 10 mg/kg q8h in 1-hr infusions for 7 days, with close monitoring of renal function and adequate hydration; vidarabine (continuous 12-hr infusion of 10 mg/kg/day for 7 days) is also effective for treatment of disseminated herpes zoster in immunocompromised hosts.
- Patients with AIDS and transplant recipients may develop acyclovir-resistant varicella-zoster; these patients can be treated with foscarnet (40 mg/kg IV q8h) continued for at

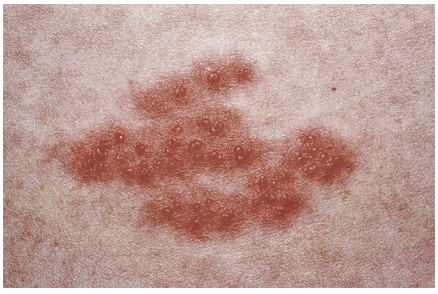

FIGURE H1-42 Herpes zoster. Classic appearance of grouped vesicles. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

least 10 days or until lesions are completely healed.

- Postherpetic neuralgia (Fig. EH1-43)
  1. Gabapentin 100 to 600 mg tid is effective in the treatment of pain and sleep interference associated with postherpetic neuralgia. Other effective agents are pregabalin, duloxetine, and tricyclic antidepressants.
  2. Lidocaine patch 5% is also effective in relieving postherpetic neuralgia. Patches are applied to intact skin after resolution of blisters and crusts to cover the most painful area for up to 12 hr within a 24-hr period.
  3. Capsaicin cream can be useful for treatment of postherpetic neuralgia. It is generally applied 3 to 5 times daily for several weeks after the crusts have fallen off. A topical 8% patch formulation of capsaicin is now available by prescription for postherpetic neuralgia.
  4. Sympathetic blocks (stellate ganglion or epidural) with 0.25% bupivacaine and rhizotomy are reserved for severe cases unresponsive to conservative treatment.

DISPOSITION

- The incidence of postherpetic neuralgia (defined as pain that persists more than 90 days after onset of rash) increases with age (<30% by age 40 yr, >70% by age 70 yr); antivirals reduce the risk of postherpetic neuralgia.
- Incidence of disseminated herpes zoster is increased in immunocompromised hosts (e.g., 15% to 50% of patients with active Hodgkin's disease).
- Immunocompromised hosts are also more prone to neurologic complications (encephalitis, myelitis, cranial and peripheral nerve palsies, acute retinal necrosis). The mortality rate is 10% to 20% in immunocompromised hosts with disseminated zoster.
- Motor neuropathies occur in 5% of all cases of zoster; complete recovery occurs in >70% of patients.
- Rates of HZ recurrence are more frequent than previously reported and are comparable to rates of first HZ occurrence in immunocompetent individuals.

REFERRAL

- Hospitalization for IV acyclovir in patients with disseminated herpes zoster.
- Patients with herpes zoster ophthalmicus should be referred to an ophthalmologist.
- Vaccination: In the absence of the herpes zoster vaccine, persons who live to 85 yr of age have a 50% risk of herpes zoster. Immunocompetent adults ≥60 yr are appropriate candidates for a single dose of varicella-zoster vaccine (VZV) whether or not they have had a previous episode of herpes zoster. Immunization with VZV (Zostavax) boosts waning immunity in older adults and reduces the severity and duration of pain caused by herpes zoster by 61%. Adults who are VZV seronegative (never had varicella) should be immunized against varicella with two doses of varicella vaccine (Varivax). Despite its efficacy and safety, use of this vaccine remains low (<8% of potential recipients).

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Shingles (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Objective:

To present population-based estimates of herpes zoster (HZ) recurrence rates among adults.

Patients and Methods:

To identify recurrent cases of HZ, we reviewed the medical records (through December 31, 2007) of all Olmsted County, Minnesota, residents aged 22 years or older who had an incident case of HZ between January 1, 1996, and December 31, 2001. Kaplan-Meier curves and Cox regression models were used to describe recurrences by age, immune status, and presence of prolonged pain at the time of the incident HZ episode.

Results:

Of the 1669 persons with a medically documented episode of HZ, 95 had 105 recurrences (8 persons with >1 recurrence) by December 31, 2007, an average follow-up of 7.3 years. The Kaplan-Meier estimate of the recurrence rate at 8 years was 6.2%. With a maximum follow-up of 12 years, the time between HZ episodes in the same person varied from 96 days to 10 years. Recurrences were significantly more likely in persons with zoster-associated pain of 30 days or longer at the initial episode (hazard ratio, 2.80; 95% confidence interval, 1.84-4.27; $P<.001$) and in immunocompromised individuals (hazard ratio, 2.35; 95% confidence interval, 1.35-4.08; $P=.006$). Women and anyone aged 50 years or older at the index episode also had a greater likelihood of recurrence.

Conclusion:

Rates of HZ recurrence appear to be comparable to rates of first HZ occurrence in immunocompetent individuals, suggesting that recurrence is sufficiently common to warrant investigation of vaccine prevention in this group. Ⓐ

Evidence-Based Reference

Yawn BP et al.: Herpes zoster recurrences more frequent than previously reported, *Mayo Clin Proc* 86:88–93, 2011. Ⓐ

FIGURE EH1-41 Herpes zoster occurred in this 3-year-old. She had chickenpox at age 18 months. The varicella-zoster virus causes both conditions. Spontaneous resolution can be expected. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

SUGGESTED READINGS

Cohen JI et al.: Herpes zoster, *N Engl J Med* 369:255–263, 2013.

Kimberlin DW, Whitley RJ: Varicella-zoster vaccine for the prevention of herpes zoster, *N Engl J Med* 356:1338, 2007.

Tseng HF et al.: Herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease, *JAMA* 305(2):160–166, 2011.

Yawn B et al.: Herpes zoster recurrences more frequent than previously reported, *Mayo Clin Proc* 86(2):88–93, 2011.

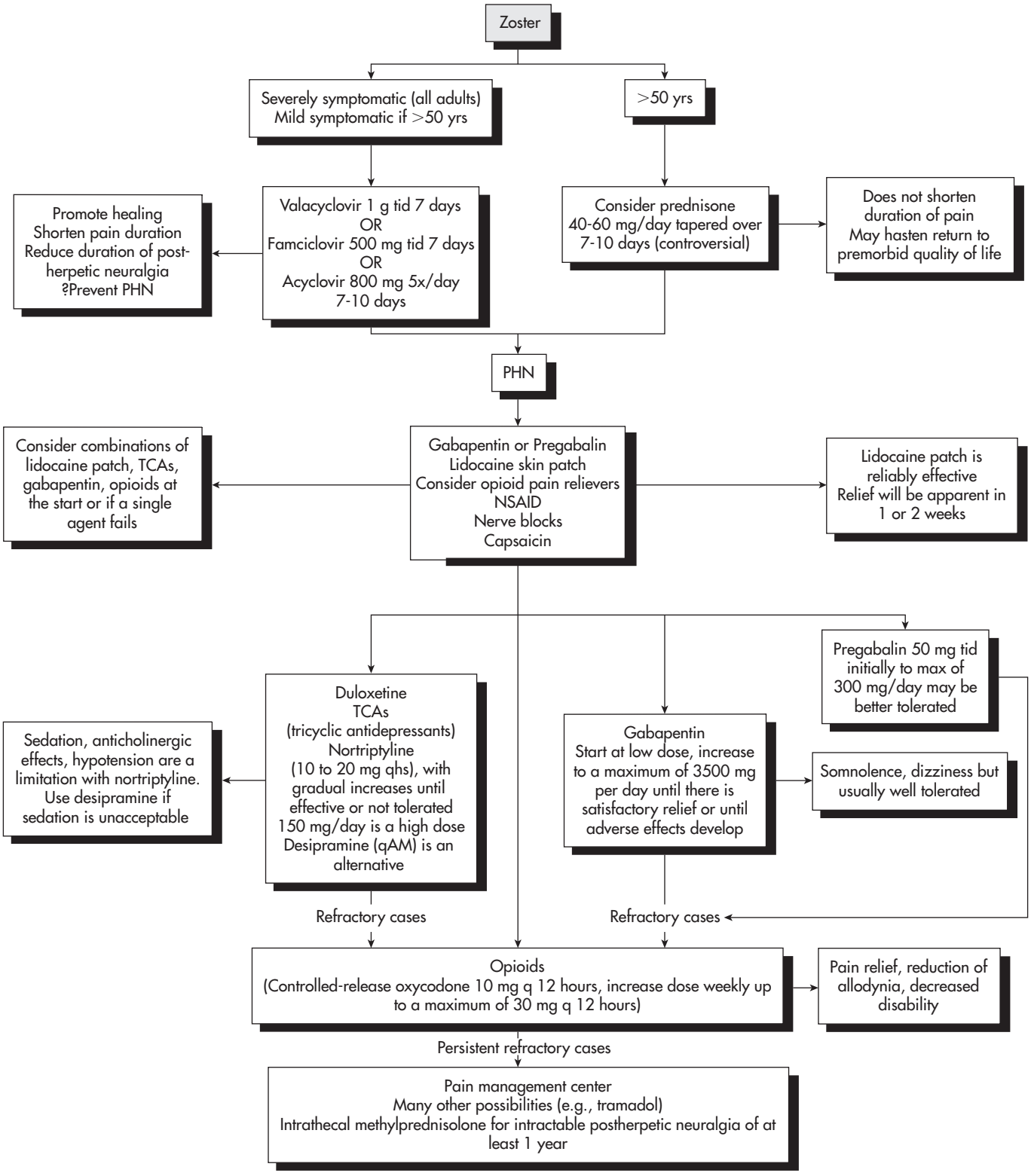

FIGURE EH1-43 Treatment of herpes zoster and postherpetic neuralgia. *NSAID*, Nonsteroidal anti-inflammatory drug; *PHN*, postherpetic neuralgia. (Modified from Habif TA: *Clinical dermatology,* ed 4, St Louis, 2004, Mosby.)

BASIC INFORMATION

DEFINITION

A hiatal hernia is the protrusion of a portion of the stomach into the thoracic cavity through the diaphragmatic esophageal hiatus.

SYNONYMS

Hiatus hernia
Diaphragmatic hernia

ICD-9CM CODES
553.3 Diaphragmatic hernia without obstruction or gangrene
750.6 Congenital hiatal hernia
756.6 Congenital diaphragmatic hernia

ICD-10CM CODES
K44.9 Diaphragmatic hernia without obstruction or gangrene
Q40.1 Congenital hiatus hernia
Q79.0 Congenital diaphragmatic hernia

EPIDEMIOLOGY & DEMOGRAPHICS

- Found in 50% of patients older than 50 yr.
- Prevalence increases with age.
- More prevalent in Western countries than in Africa and Asia.
- Paraesophageal hiatal hernias are more common in women than in men (4:1).
- Associated with diverticulosis (25%), esophagitis (25%), duodenal ulcers (20%), and gallstones (18%).
- More than 90% of patients with endoscopic documentation of esophagitis have hiatal hernias.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Most patients are asymptomatic. If symptoms are present, they resemble those of gastroesophageal reflux disease (GERD).

- Heartburn.
- Dysphagia.
- Regurgitation of gastric contents.
- Chest pain.
- Postprandial fullness.
- GI bleed.
- Dyspnea.
- Hoarseness.
- Wheezing with bowel sounds heard over the left lung base.

ETIOLOGY

- The repetitive stretching of the gastroesophageal (GE) junction with swallowing and actions (e.g., vomiting) or states (e.g., obesity, pregnancy) that increase intraabdominal pressure may cause widening of the hiatus, rupture of the phrenoesophageal ligament, and onset of the hernia.
- Hiatal hernias are classified as:
  1. Type I: Sliding (Fig. H1-44*A*), axial, or concentric hiatal hernia (most common type, 99%). Only the GE junction protrudes into the thoracic cavity and the phrenoesophageal ligament remains intact.
  2. Type II: Paraesophageal or rolling hernia (Fig. H1-44 *B*) (1%). The GE junction stays at the level of the diaphragm, but part of the stomach bulges into the thoracic cavity through a defect in the phrenoesophageal ligament.
  3. Type III: Mixed (rare), a combination of type I and type II.
  4. Type IV: Large defect in hiatus that allows other intraabdominal organs to enter the hernia sac.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Peptic ulcer disease.
- Unstable angina.
- Esophagitis (caused by *Candida,* herpes, NSAIDs, etc.).
- Esophageal spasm.
- Barrett's esophagus.
- Schatzki's ring.
- Achalasia.
- Zenker's diverticulum.
- Esophageal cancer.

WORKUP

- Exclude conditions noted in the differential diagnosis and document the presence of a hiatal hernia. Upper endoscopy may also be needed to exclude abnormal metaplasia, dysplasia, or neoplasia.

LABORATORY TESTS

- Blood tests are not specific.
- Esophageal manometry, although not commonly done, can be used in establishing a diagnosis (low sensitivity, but high specificity when compared with endoscopy).

IMAGING

- Upper gastrointestinal (UGI) barium contrast swallow series: best defines the anatomic abnormality. Demonstration that the gastric cardia is herniated 2 cm above the hiatus is diagnostic. UGI may also reveal a tortuous esophagus (Fig. H1-45). If endoscopy is performed preoperatively, a barium swallow is generally not necessary.
- UGI endoscopy: documents the presence of a hiatal hernia and also excludes commonly associated findings of esophagitis and Barrett's esophagus (recommended at least once during the workup). The >2 cm of gastric rugal fold seen above the margins of the diaphragmatic crura is diagnostic.
- Abdominal ultrasonography: simple, well tolerated. A transdiaphragmatic esophageal diameter of more than or equal to 18 mm is highly suggestive of the presence of a sliding hiatal hernia.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Lifestyle modifications: avoid foods and drugs that decrease lower-esophageal pressure (e.g., caffeine, chocolate, mint, calcium channel blockers, and anticholinergics).
- Weight loss.
- Avoid large quantities of food with meals.
- Sleep with the head of the bed elevated 6 inches.

ACUTE GENERAL Rx

- Antacids may be useful to relieve mild symptoms.
- H_2 antagonists (e.g., cimetidine 400 mg bid, ranitidine 150 mg bid, or famotidine 20 mg bid).
- If significant GERD is present with documented esophagitis, proton pump inhibitors (e.g., omeprazole 20 mg qd or lansoprazole 30 mg qd) are used. Refractory symptoms may require higher doses (e.g., bid dosing).
- Prokinetic agents (e.g., metoclopramide 10 mg taken 30 min before each meal) can be added to an H_2 antagonist or proton pump inhibitor.

CHRONIC Rx

- When indicated, surgery (laparoscopic or open) can be done in patients with refractory symptoms impairing quality of life, or causing intestinal (e.g., recurrent GI bleeds) or extraintestinal complications (e.g., aspiration pneumonia, asthma, or ear-nose-throat complications).

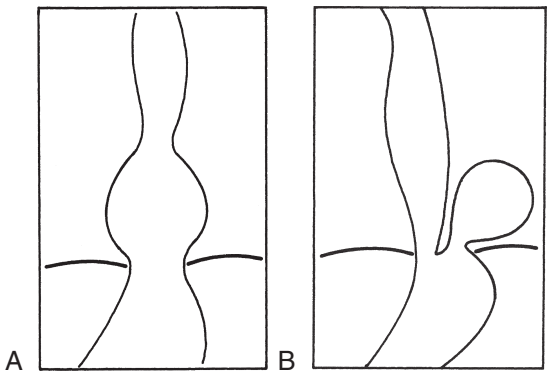

FIGURE H1-44 Types of esophageal hiatal hernia. A, Sliding hiatal hernia, the most common type. **B,** Paraesophageal hiatal hernia. (From Behrman RE: *Nelson textbook of pediatrics,* ed 17, Philadelphia, 2004, Saunders.)

- Prophylactic surgery is a consideration in all paraesophageal hernias because they have a higher incidence of strangulation.

DISPOSITION

- More than 90% of patients having GERD symptoms respond well to medical therapy.
- Complications of hiatal hernias are similar to complications occurring in patients with GERD:
  1. Erosive esophagitis.
  2. Ulcerative esophagitis.
  3. Barrett's esophagus.
  4. Peptic stricture.
  5. GI hemorrhage.
  6. Extraintestinal complications.
  7. Lung collapse or heart failure (severe cases).

REFERRAL

Gastroenterologist: for symptoms refractory to conventional therapy (H_2 antagonists, antacids, and proton pump inhibitors) or having complications previously mentioned.

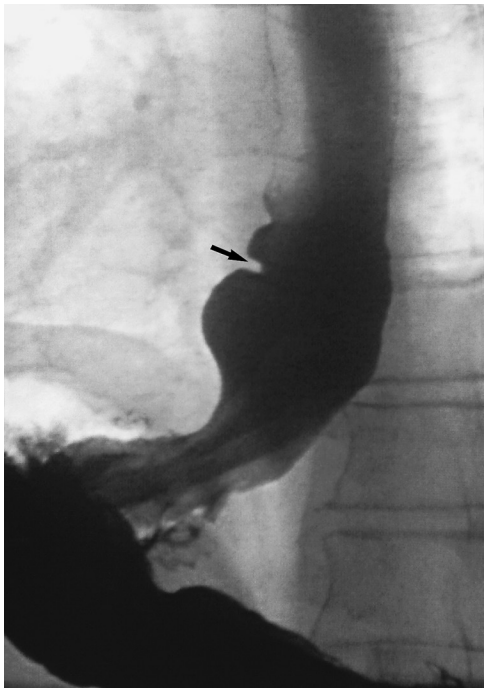

FIGURE H1-45 A sliding hiatal hernia confirmed by the presence of an incisural notch *(arrow)* on the greater curve aspect. (From Grainger RG et al [eds]: *Grainger & Allison's diagnostic radiology,* ed 4, Philadelphia, 2001, Churchill Livingstone.)

PEARLS & CONSIDERATIONS

COMMENTS

- Gastric ulceration and erosions (***Cameron's lesion***) can occur in the paraesophageal hernia pouch and are an uncommon cause of UGI bleeding.
- May cause iron deficiency anemia.
- Gastric volvulus or torsion can also occur and presents as dysphagia and postprandial pain.
- High incidence of esophagitis even after the eradication of *Helicobacter pylori.*
- The appearance of hiatal hernia may resemble a left atrial mass by echocardiography.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hiatal Hernia (Patient Information)

AUTHOR: **MARK F. BRADY, M.D., M.P.H., M.M.S.**

EVIDENCE

Abstract[1]

Objective and Background:
We lack long-term data (>10 years) on the efficacy of antireflux surgery when evaluated within the framework of randomized clinical trials. Hereby we report the outcome of a randomized trial comparing open total (I) and a Toupet posterior partial fundoplication (II) performed between 1983 and 1991.

Methods:
A group of 137 patients with gastroesophageal reflux disease were enrolled into the study. The mean follow up has now reached 18 years. During these years 26% had died and 16% were unable to trace for follow up. Symptom outcomes were assessed by the use of validated self-reporting questionnaires.

Results:
Long-term control of heartburn and acid regurgitation (reported as no or mild symptoms) were reported by 80% and 82% after a total fundoplication (I) and corresponding figures were 87% and 90% after a partial posterior fundoplication (II), respectively (n.s.).
The dysphagia scores were low 4.6 ± 1.3 (SEM) in group I and 3.3 ± 0.9 (SEM) in group II (n.s). The point prevalences of rectal flatulence and gas distension related complaints were of similar magnitude in the 2 groups. Of the total number of patients in the fundoplication group, 23% noted some ability to vomit compared with 31% in the partial posterior fundoplication group.

Conclusions:
Both a total and a partial posterior fundoplication maintain a high level of reflux control after 2 decades of follow up. The previously reported differences in mechanical side effects, in favor of the partial wrap, seemed to disappear over time. Ⓐ

Abstract[2]

Background:
In 2006, we reported results of a randomized trial of laparoscopic paraesophageal hernia repair (LPEHR), comparing primary diaphragm repair (PR) with primary repair buttressed with a biologic prosthesis (small intestinal submucosa [SIS]). The primary endpoint, radiologic hiatal hernia (HH) recurrence, was higher with PR (24%) than with SIS buttressed repair (9%) after 6 months. The second phase of this trial was designed to determine the long-term durability of biologic mesh-buttressed repair.

Methods:
We systematically searched for the 108 patients in phase I of this study to assess current clinical symptoms, quality of life (QOL) and determine ongoing durability of the repair by obtaining a follow-up upper gastrointestinal series (UGI) read by 2 radiologists blinded to treatment received. HH recurrence was defined as the greatest measured vertical height of stomach being at least 2 cm above the diaphragm.

Results:
At median follow-up of 58 months (range 42 to 78 mo), 10 patients had died, 26 patients were not found, 72 completed clinical follow-up (PR, n=39; SIS, n=33), and 60 repeated a UGI (PR, n=34; SIS, n=26). There were 20 patients (59%) with recurrent HH in the PR group and 14 patients (54%) with recurrent HH in the SIS group (p=0.7). There was no statistically significant difference in relevant symptoms or QOL between patients undergoing PR and SIS buttressed repair. There were no strictures, erosions, dysphagia, or other complications related to the use of SIS mesh.

Conclusions:
LPEHR results in long and durable relief of symptoms and improvement in QOL with PR or SIS. There does not appear to be a higher rate of complications or side effects with biologic mesh, but its benefit in reducing HH recurrence diminishes at long-term follow-up (>5 years postoperatively) or earlier. Ⓐ

Evidence-Based References

Mardani J et al.: Total or posterior partial fundoplication in the treatment of GERD: results of a randomized trial after 2 decades of follow-up, *Ann Surg* 253:875–878, 2011. Ⓐ

Oelschlager BK et al.: Biologic prosthesis to prevent recurrence after laparoscopic paraesophageal hernia repair: long-term follow-up from a multicenter, prospective, randomized trial, *J Am Coll Surg* 213:461–468, 2011. Ⓐ

SUGGESTED READINGS

Andujar JJ et al.: Laparoscopic repair of large paraesophageal hernia is associated with low incidence of recurrence and reoperations, *Surg Endosc* 18(3):444, 2004.

Bawahab M et al.: Management of acute paraesophageal hernia, *Surg Endosc* 23(2):255–259, 2009. Epub 2008.

Kahrilas PJ et al.: Approaches to the diagnosis and grading of hiatal hernia, *Best Pract Res Clin Gastroenterol* 22(4):601, 2008.

Linke GR et al.: Is a barium swallow complementary to endoscopy essential in the preoperative assessment of laparoscopic antireflux and hiatal hernia surgery? *Surg Endosc* 22(1):96, 2008.

Menon S, Trudgill N: Risk factors in the aetiology of hiatus hernia: a meta-analysis, *Eur J Gastroenterol Hepatol* 23(2):133–138, 2011.

BASIC INFORMATION

DEFINITION

Hidradenitis suppurativa (HS) is a chronic, relapsing suppurative cutaneous disease affecting skin that bears apocrine glands and manifested by abscesses, fistulating sinus tracts, and chronic infection leading to scarring.

SYNONYMS

Acne inversa
Apocrinitis
Verneuil's disease

ICD-9CM CODES
705.83 Hidradenitis
ICD-10CM CODES
L73.2 Hidradenitis suppurativa

EPIDEMIOLOGY & DEMOGRAPHICS

Onset is postpubertal, with an average age of onset of 23 yr; rates decline after age 55 yr.
PREVALENCE: Overall prevalence in the United States is ~1% to 2%.
PREDOMINANT SEX: Female to male ratio is 3:1.
RISK FACTORS
- Obesity and metabolic syndrome.
- Family history (approximately 30%).
- Hyperandrogenism in women.
- Cigarette smoking.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The diagnosis is primarily clinical based on the development of typical lesions in a characteristic distribution, with a relapsing nature.
- Early symptoms include pain, itching, burning, erythema, and hyperhidrosis.
- Typical lesions include:
  1. Painful erythematous papules and nodules leading to painful abscesses with foul-smelling discharge.
  2. Dermal contractures and ropelike elevation of the skin.
  3. Comedones in the apocrine, gland-bearing skin.
- Classified into Hurley Stages
  1. Stage I: abscesses without sinus tracts or scarring.
  2. Stage II: multiple abscesses plus sinus tracts and scarring.
  3. Stage III: diffuse involvement of entire area with abscesses, sinus tracts, and scarring.
- The axilla is the most common site (Fig. H1-46).
- Less common sites include the inguinal region, the breasts more often in women, and the perineal or perianal skin more often in men.
- There is a strong tendency toward relapse and recurrence.
- There is often a poor response to conventional antibiotics and no pathogens isolated from cultures of lesions.
- The disease is often mistaken for a simple infection and a long delay in diagnosis is common.

ETIOLOGY

- Keratinous materials plug apocrine glands in hair follicles leading to stasis, dilation, rupture, and re-epithelialization.
- Bacteria are trapped and multiply leading to gland rupture with surrounding inflammation and local bacterial infection.
- Over time, repeated nodules and infections cause scarring, which can lead to deep tissue damage and sinus tracts.
- Infectious agents such as *Streptococcus, Staphylococcus,* and *Escherichia coli,* and enteric flora have been identified in cultures, but are likely a secondary component of the disease.
- There is likely a significant genetic component to the disease. An HS spectrum of different phenotypes has been characterized involving genetic factors that are not yet well described but may be important for future therapy.

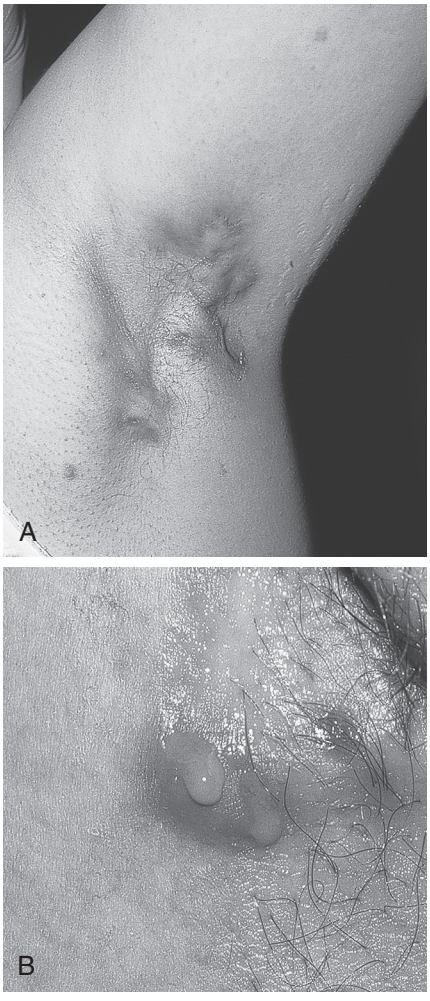

FIGURE H1-46 Hidradenitis suppurativa (HS). **A,** HS of the axilla. This is the classic appearance with inflammatory nodules and scarred areas. This condition is commonly misdiagnosed as a bacterial infection. **B,** HS of the axilla; a close-up view of the draining pus. When intact, the lesions represent sterile abscesses. Once open, they may become secondarily infected. (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

- HS has been associated with other endocrine and autoimmune disorders such as diabetes, Cushing's disease, acromegaly, Crohn's disease, and inflammatory arthritis.
- Metabolic syndrome affects as many as 50% of patients with HS and may exacerbate the associated inflammation.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Follicular pyodermias such as folliculitis, furuncles, carbuncles, and pilonidal cysts.
- Granuloma inguinale.
- Perianal and vulvar manifestations of Crohn's disease.
- Actinomycosis.
- Lymphogranuloma venereum.
- Dermoid, epidermoid, or Bartholin's cysts.
- Tuberculous inflammation of the skin.
- Lymphadenitis.
- Erysipelas.

WORKUP

Primarily a clinical diagnosis based on typical lesion (see "Physical Findings & Clinical Presentation").

LABORATORY TESTS

- Patients with acute lesions may have an elevated erythrocyte sedimentation rate or WBC.
- Febrile and toxic appearing patients should have complete blood count, chemistries, and blood cultures.
- Any pus should be sampled for bacterial culture and sensitivity.

TREATMENT

There is no definitive cure for hidradenitis.

NONPHARMACOLOGIC THERAPY

- Weight loss and control of metabolic syndrome.
- Smoking cessation.
- Avoidance of shaving, depilatory creams, deodorants.
- Warm compresses.
- Incision and drainage of nonpurulent lesions is *not* recommended due to recurrence and scarring.
- Laser therapy, radiotherapy, and cryotherapy currently under study.
- Wide local excision for stage III disease with or without vacuum-assisted closure device.

ACUTE AND CHRONIC Rx

- NSAIDs for inflammation and pain, consider gabapentin, pregabalin, SSRIs for chronic pain management.
- Antibiotics never proven to be effective; however, are mainstay of treatment. Can base treatment on the basis of aspirate culture and sensitivities or empirically.
  1. Clindamycin is the only topical antibiotic proven to be effective in randomized controlled trial and is appropriate for stage I disease.

2. For oral therapy in stage II: consider clindamycin and rifampin in combination. Cephalosporins, dicloxacillin, erythromycin, minocycline, and tetracycline have also been used.
3. Severe, recurrent disease can require up to 3 to 6 mo of antibiotics.

- Oral contraceptives with low androgenic progesterone (norgestimate, desogestrel, or gestodene) for women show mixed effectiveness.
- Isotretinoin has been used with mixed effectiveness.
- Metformin has mixed effectiveness, possibly due to related metabolic syndrome and hyperandrogenism.
- Corticosteroids and other immune suppressants such as cyclosporin, infliximab, and etanercept have been used for stage II disease, with mixed results.
- Adalimumab, an anti–tumor necrosis factor-α antibody given once per week (dose 40 mg/wk) has been used with mixed results, and further studies are needed.

COMPLICATIONS

- Squamous cell carcinoma.
- Scarring leading to restricted limb mobility or lymphedema.
- Rectal or urethral fistulas.
- Psychological effects related to disfiguring nature of disease.

REFERRAL

- Referral to dermatology during stage I to II disease.
- Referral to a surgeon is indicated for stage III disease.

PEARLS & CONSIDERATIONS

COMMENTS

- Patients with hidradenitis are at risk for severe depression, social isolation, and negatively impacted sexuality as a result of their disease.
- There is an average delay in diagnosis of 12 years and most patients are diagnosed in stage II of the disease.
- It is important to maximize nonmedical treatment, start medical treatment, and refer to a surgeon early in the disease course to ensure the best quality of life for patients.
- The only definitive treatment for hidradenitis is wide excision of the involved skin.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **MARY BETH SUTTER, M.D.**

SUGGESTED READINGS

Alikhan A et al.: Hidradenitis suppurativa: a comprehensive review, *J Am Acad Dermatol* 60:539–561, 2009.

Buimer M et al.: Hidradenitis suppurativa, *Br J Surg* 96:350–360, 2009.

Collier F: Diagnosis of hidradenitis suppurativa, *Br Med J* 346:2121–2127, 2013.

Jemec GBE: Hidradenitis suppurativa, *N Engl J Med* 366:158–164, 2012.

Kimball AB et al.: Adalimumab for the treatment of moderate to severe hidradenitis suppurativa, *Ann Intern Med* 157:846–855, 2012.

Rambhatla P et al.: A systematic review of treatments for hidradenitis suppurativa, *Arch Dermatol* 148:439–446, 2012.

Shah N: Hidradenitis suppurativa: a treatment challenge, *Am Fam Physician* 72:1547–1552, 2005. 1554.

BASIC INFORMATION

DEFINITION

High-altitude illness refers to a spectrum of cerebral and pulmonary syndromes related to hypoxemia occurring during rapid ascension to high altitudes. Common acute syndromes include high-altitude pulmonary edema (HAPE), acute mountain sickness (AMS), and high-altitude cerebral edema (HACE). The latter two are thought to represent different points of severity along the same pathophysiologic process in the brain.

SYNONYMS

Altitude sickness
High-altitude headache
Acute mountain sickness
High-altitude pulmonary edema
High-altitude cerebral edema

ICD-9CM CODES
289 Mountain sickness, acute
993.2 High altitude, effects
ICD-10CM CODES
W94 Exposure to high and low air pressure and changes in air pressure
T70.2 Other and unspecified effects of high altitude

EPIDEMIOLOGY & DEMOGRAPHICS

- More than 30 million people are at risk of developing altitude sickness.
- 80% of people who ascend to high altitudes have HAH_2.
- AMS is the most common of the altitude diseases. It affects approximately 40% to 50% of people ascending to 14,000 ft (4200 m) from lowland.
- The incidence of HACE is reported to be 0.1% to 2% at elevations in excess of 12,000 ft (3000 m). HACE is often complicated by concomitant HAPE.
- Men are five times more likely to develop HAPE than are women.
- AMS and HACE affect men and women equally.

PHYSICAL FINDINGS & CLINICAL PRESENTATION (Table EH1-23)

HAH_1
- Headache that develops within 24 hr of ascent.
- Bilateral, frontal or frontotemporal, dull or pressing quality.
- Mild to moderate intensity and aggravated by exertion, movement, straining, coughing, or bending.
- Headache resolves within 8 hr of descent.
- HAH should resolve with analgesics and/or 10 to 15 min of supplementary oxygen.
- Difficult to distinguish from headaches secondary to dehydration.

AMS
- AMS is thought to be a progression of HAH_2.
- Occurs within 6 to 12 hours after rapid ascent to 8000 ft (2500 m) in 10% to 25% of unacclimatized persons.
- Headache is the most common symptom.
- Dizziness and lightheadedness.
- Nausea, vomiting, and loss of appetite.
- Fatigue.
- Sleep disturbance from an exaggerated hyperventilatory phase of Cheyne-Stokes respiration in response to hypoxemia and alkalosis.
- AMS can evolve into HAPE and HACE.
- Retinal hemorrhages can be present from increased blood flow or breakdown in the blood-retina barrier.
- Supplemental oxygen may be used to support the clinical diagnosis.

HAPE (Fig. EH1-47*A*)
- Typically occurs 2 to 4 days after ascent over 8000 ft (2500 m).
- Dyspnea, loss of stamina.
- Dry cough or cough with frothy rust- or pink-tinged sputum.
- Chest tightness.
- Tachycardia, tachypnea, rales, cyanosis.

HACE
- Usually presents several days after AMS.
- Confusion, irritability, drowsiness, stupor, hallucinations, mild fever.
- Headache, nausea, vomiting.
- Truncal ataxia, paralysis, and seizures.
- The sixth cranial nerve is the most commonly affected from the compression of the trunk adjacent to brain swelling.
- Coma and death from brain herniation may develop within hours of the first symptoms.

ETIOLOGY

- During ascent to altitudes above sea level, the atmospheric pressure decreases. Although the percentage of oxygen in the air remains the same, the partial pressure of oxygen decreases with increased altitude, and can cause hypoxemia. Fig. EH1-47*B* illustrates the effect of altitude on alveolar Pao_2 and oxygen saturation.
- Increased cerebral blood flow and the loss of autoregulation of intracranial pressure may contribute to increased cerebral vascular permeability and subsequent brain edema.
- Hypobaric hypoxia can trigger elevated pulmonary pressures, resulting in protein-rich, hemorrhagic exudates into the lung alveoli due to a breakdown in the pulmonary blood-gas barrier (HAPE).
- The body responds to low oxygen partial pressures through a process of acclimatization (see "Comments").

DIAGNOSIS

Made by clinical presentation and physical findings.

DIFFERENTIAL DIAGNOSIS

- Dehydration.
- Carbon monoxide poisoning.
- Hypothermia.
- Infection.
- Substance abuse.
- Congestive heart failure.
- Pulmonary embolism.
- Cerebrovascular accident.
- Box H1-5 summarizes the differential diagnosis of high-altitude illnesses.

WORKUP

Typically the diagnosis is self-evident after history and physical examination. Laboratory tests and imaging studies help monitor cardiopulmonary and central nervous system status in patients admitted to the intensive care unit for pulmonary and/or cerebral edema. In patients with HAPE occurring at lower altitudes (<8000 ft), an evaluation of preexisting pulmonary hypertension or a left-to-right shunt should be considered.

LABORATORY TESTS

Not useful, unless to rule out an alternative diagnosis.

IMAGING STUDIES

- Chest x-ray showing Kerley B-lines and patchy edema (see Fig. EH1-47*A*).
- CT scan of the head showing diffuse or patchy edema.
- MRI of the head showing characteristic intense T2 signal in the white matter.

TREATMENT

Nonpharmacologic Therapy
- Stop the ascent to allow acclimatization or start to descend until symptoms have

BOX H1-5 Differential Diagnosis of High-Altitude Illnesses

Acute mountain sickness and high-altitude cerebral edema	Dehydration, exhaustion, viral or bacterial infection, alcohol hangover, hypothermia, carbon monoxide poisoning, migraine, hyponatremia, hypoglycemia, diabetic ketoacidosis, CNS infection, transient ischemic attack, arteriovenous malformation, stroke, seizures, brain tumors, ingestion of toxins or drugs, acute psychosis
High-altitude pulmonary edema	Asthma, bronchitis, pneumonia, mucus plugging (secondary to previous), hyperventilation syndrome, pulmonary embolus, heart failure, myocardial infarction

CNS, Central nervous system.
From Auerbach P: *Wilderness medicine, expert consult* Premium Edition—Enhanced Online Features and Print, Philadelphia, 2012, Saunders.

resolved. Descent is the definitive treatment and should begin immediately at the first suspicion of HACE.
- Oxygen 4 to 6 L/min is used for severe AMS, HAPE, and HACE.
- Portable hyperbaric bags are useful if available at the site.
- Altitude can cause diuresis that may be mediated by enhanced release of atrial natriuretic peptide. When coupled with the increased fluid loss through increased ventilation, there is a higher risk for dehydration, and adequate hydration should be maintained.

ACUTE PHARMACOLOGIC Rx

- Nonsteroidal anti-inflammatory drugs (e.g., ibuprofen 600 mg every 6 hours, beginning 6 hours before ascending) are effective prophylaxis of traditional altitude sickness and in treating headaches in AMS.
- Acetazolamide 125 to 250 mg PO bid has been effective for both prevention and acute therapy in patients with AMS and HACE.
- Nifedipine 10 mg sublingual followed by long-acting nifedipine 30 mg bid is used for patients with HAPE who cannot descend immediately.
- Dexamethasone 4 mg PO every 6 hr is used in patients with severe AMS, HAPE, or HACE.

CHRONIC Rx

Prevention is the most prudent therapy.
1. Slow, staged ascent to avoid altitude sickness.
2. Start the ascent below 8000 feet.
3. Ascend 1000 feet/day (300 m/day).
4. Spend two nights at the same altitude every 3 days.
5. Sleep at lower heights than the altitude climbed ("climb high, sleep low").
6. Prophylactic therapy with NSAIDs (ibuprofen 600 mg every 6 hours, beginning 6 hours before ascending) or acetazolamide up to 750 mg daily and/or dexamethasone 8 to 16 mg daily decreases the risk of developing AMS (combination may have additive benefit). The drugs should be used until acclimatization occurs.
7. Prophylactic inhalation of a β-adrenergic agonist, salmeterol 125 mcg q12h, or the use of slow-release nifedipine 20 mg bid have both been shown to reduce the risk of HAPE in susceptible individuals.
8. Tadalafil, a long-acting phosphodiesterase inhibitor, has recently been shown to decrease the incidence of HAPE in susceptible individuals.
9. Box H1-6 summarizes field treatment of high-altitude illness.

DISPOSITION

- AMS improves over a period of 2 to 3 days.
- HAPE is the most common cause of death among patients with altitude illnesses.
- More than 60% of patients with HAPE will have recurrence of symptoms on subsequent climbs.
- In HACE, neurologic deficits may persist for weeks but eventually resolve. If coma occurs, prognosis is poor.

BOX H1-6 Field Treatment of High-Altitude Illness

High-Altitude Headache and Mild Acute Mountain Sickness
- Stop ascent, rest, acclimatize at same altitude.
- Symptomatic treatment as necessary with analgesics and antiemetics.
- Consider acetazolamide, 125 to 250 mg bid, to speed acclimatization.
- OR descend 500 m (1640 feet) or more.

Moderate to Severe Acute Mountain Sickness
- Low-flow oxygen, if available.
- Acetazolamide, 125 to 250 mg bid, with or without dexamethasone, 4 mg PO, IM, or IV q6h.
- Hyperbaric therapy.
- OR immediate descent.

High-Altitude Cerebral Edema
- Immediate descent or evacuation.
- Oxygen, 2 to 4 L/min.
- Dexamethasone, 8 mg PO, IM, or IV, then 4 mg q6h.
- Hyperbaric therapy.

High-Altitude Pulmonary Edema
- Minimize exertion and keep warm.
- Immediate descent or hyperbaric therapy.
- Oxygen, 4 to 6 L/min until improving, then 2 to 4 L/min.

If above unavailable, one of the following:
- Nifedipine, 30 mg extended release q12h.
- Sildenafil 50 mg q8h.
- Tadalafil 10 mg q12h.
- Consider inhaled β-agonist.

Periodic Breathing
- Acetazolamide, 62.5 to 125 mg at bedtime as needed.

IM, Intramuscularly; *IV,* intravenously; PO, orally.
From Auerbach P: *Wilderness medicine, expert consult* Premium Edition—Enhanced Online Features and Print, Philadelphia, 2012, Saunders.

REFERRAL

Cardiology and neurology referrals are made in patients with pulmonary edema and central nervous system findings, respectively.

PEARLS & CONSIDERATIONS

COMMENTS

- Acclimatization is the process in which an individual who normally resides at low altitude adapts to hypobaric hypoxia to improve tolerance and performance at higher altitude. These mechanisms include:
  1. An increase in respiratory rates and tidal volume. This hyperventilation allows lowering of arterial carbon dioxide to preserve oxygen delivery, even at extreme altitudes.
  2. An early increase in heart rate and stroke volume to improve oxygen delivery. After 1 wk, both parameters decrease because of diuresis and lower catecholamine levels.
  3. Pulmonary hypertension develops in response to hypoxemia, resulting in improvement of the ventilation-perfusion mismatch but may be maladaptive and lead to the development of HAPE.
  4. Cerebral vasodilation to increase blood flow to the brain.
  5. Rise in hemoglobin and hematocrit. This is a long-term process that takes up to 1 wk to occur in response to the need for improved oxygen delivery.
- Adaptation to altitude is different from acclimatization and refers to physiologic differences in permanent residents at high altitude (e.g., an increased oxygen diffusion capacity).
- High altitude illness can generally be prevented by ascending to 300 to 500 meters per day at altitudes above 3000 meters and including a rest day every 3 to 4 days.
- Risk factors for the development of altitude sicknesses are:
  1. Rapid ascent.
  2. Previous history of altitude sickness.
  3. Strenuous exertion on arrival.
  4. Obesity.
  5. Male gender.
- Physical fitness is not protective against high-altitude illness.
- Both dexamethasone and tadalafil decrease systolic pulmonary artery pressure and may reduce the incidence of HAPE in adults with a history of HAPE. Dexamethasone prophylaxis may also reduce the incidence of AMS in these adults.
- Descent is mandatory for all persons with HACE or HAPE.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Altitude Sickness (Patient Information)

AUTHORS: **JOHANNES STEINER, M.D.,** and **RICHARD REGNANTE, M.D.**

SUGGESTED READINGS

Bartsch P, Swenson ER: Acute high-altitude illness, *N Engl J Med* 368:2296–2302, 2013.

Basnyat B, Murcoch DR: High-altitude illness, *Lancet* 361(2003), 1967.

Fiore DC et al.: Altitude illness: risk factors, prevention, presentation, and treatment, *Am Fam Physician* 82(8):1103–1110, 2010.

Gallagher SA, Hackett PH: High-altitude illness, *Emerg Med Clin North Am* 22(329), 2004.

Hackett P, Rennie D: High altitude pulmonary edema, *JAMA* 287(2275), 2002.

Hackett PH, Roach RC: High-altitude illness, *N Engl J Med* 345(107), 2001.

Lipman GS et al.: Ibuprofen prevents altitude sickness: a randomized controlled trial for prevention of altitude illness with nonsteroidal anti-inflammatories, *Ann Emerg Med* 59(484), 2012.

Maggiorini M et al.: Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema, *Ann Intern Med* 145:497–506, 2006.

Rodway GW et al.: High-altitude related disorders. Part 1. Pathophysiology, differential diagnosis and treatment, *Heart Lung* 32(353), 2003.

West JB: The physiologic basis of high-altitude diseases, *Ann Intern Med* 141(789), 2004.

TABLE EH1-23 Clinical Characteristics of High-Altitude Illnesses

	Clinical Classification			
	HAH	**Mild AMS**	**Moderate to Severe AMS**	**HACE**
Symptoms	Headache only	Headache plus one more symptom (nausea/vomiting, fatigue/lassitude, dizziness or difficulty sleeping) All symptoms of mild severity	Headache plus one or more symptoms (nausea/vomiting, fatigue/lassitude, dizziness or difficulty sleeping) Symptoms of moderate to severe intensity	±Headache Worsening of symptoms seen in moderate to severe AMS
LL-AMS score*	1-3, headache only	2-4	5-15	
Physical signs	None	None	None	Ataxia Altered mental status
Findings	None	None	Antidiuresis Slightly increased body temperature Slight desaturation Widened A-a gradient Elevated ICP White matter edema (CT, MRI)	HAPE common: positive chest radiograph, rales, dyspnea at rest Elevated ICP White matter edema (CT, MRI)
Pathophysiology	Unknown; cerebral vasodilation, trigeminal vascular system?	Unknown; same as HAH?	Vasogenic edema; cytotoxic edema?	Advanced vasogenic cerebral edema; cytotoxic edema?

AMS, Acute mountain sickness; *CT,* computed tomography; *HACE,* high-altitude cerebral edema; *HAH,* high-altitude headache; *HAPE,* high-altitude pulmonary edema; *ICP,* intracranial pressure; *MRI,* magnetic resonance imaging.

*The self-reported Lake Louise AMS score.

From Auerbach P: *Wilderness medicine, expert consult* Premium Edition—Enhanced Online Features and Print, Philadelphia, 2012, Saunders, Elsevier. 978-1-4377-1678-8.

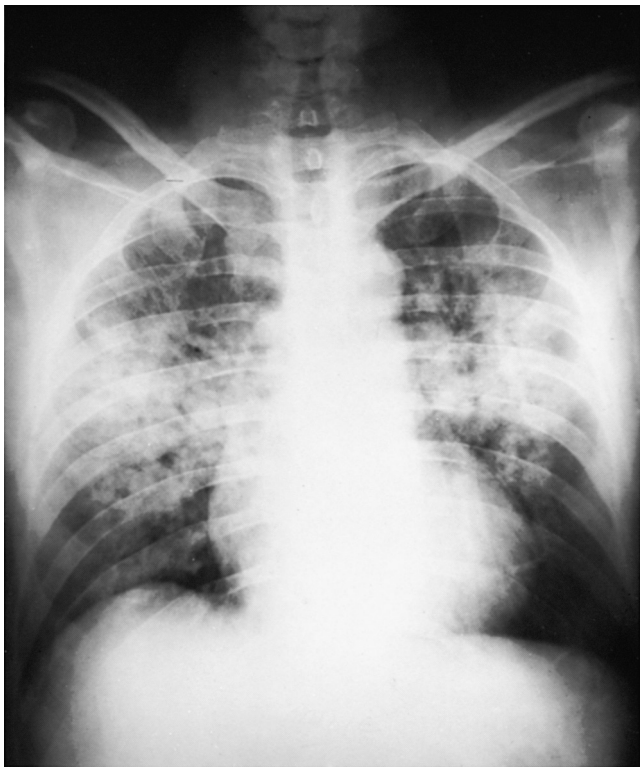

FIGURE EH1-47 A Chest radiograph showing high-altitude pulmonary edema. (From Strauss RH [ed]: *Sports medicine,* ed 2, Philadelphia, 1991, Saunders.)

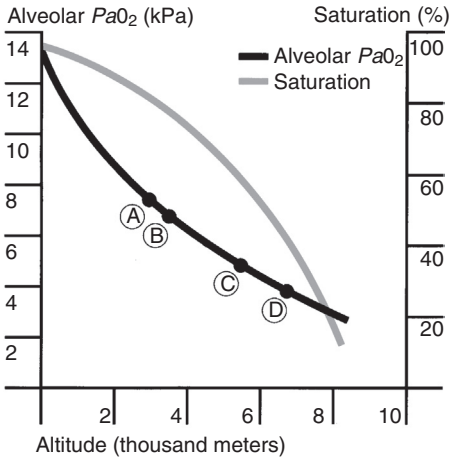

FIGURE EH1-47 B Effect of altitude on alveolar PaO_2 and oxygen saturation. Because of the steep slope of the oxygen dissociation curve, increasing altitude above 5000 m causes abdominal cramps and nausea; **B**, 3500 m (12,000 ft)—headache, nausea, diminished visual acuity, and possible precipitous fall in saturation. In an unacclimated person, acute change occurs at **(B)** 3000 m (10,000 ft)—slightly impaired memory and judgment, increased heart rate pulmonary edema; **C**, 5500 m (18,000 ft)—impaired consciousness after several hours in many people; and **D**, 6750 m (22,000 ft)—loss of consciousness. (From Souhami RL, Moxham J: *Textbook of medicine*, ed 4, London, 2002, Churchill Livingstone.)

BASIC INFORMATION

DEFINITION

Hip fractures are classified as intracapsular or extracapsular. Intracapsular fractures include femoral head and femoral neck fractures (Fig. H1-48). These fractures are further categorized as either displaced or nondisplaced. Extracapsular fractures include intertrochanteric and subtrochanteric fractures, as well as the less common greater and lesser trochanteric fractures. These fractures can be further categorized by the degree of comminution.

SYNONYMS

Hip fracture
Intracapsular fracture
Subcapital fracture
Extracapsular fracture
Intertrochanteric fracture

ICD-9CM CODES	
820.8	Femoral neck fracture
820.2	Peritrochanteric fracture
ICD-10CM CODES	
S72.0	Fracture of neck of femur
S72.1	Pertrochanteric fracture
S72.2	Subtrochanteric fracture
S72.3	Fracture of shaft of femur
S72.4	Fracture of lower end of femur
S72.7	Multiple fractures of femur
S72.8	Fractures of other parts of femur
S72.009A	Fracture of unspecified part of neck of unspecified femur, initial encounter for closed fracture

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Lifetime risk in women ~16%.
PREDOMINANT SEX: Female/male ratio of 3:1.
PREDOMINANT AGE: 90% >60 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Hip or groin pain.
- Affected limb usually shortened and externally rotated in displaced fractures.

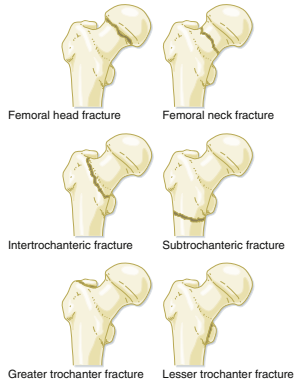

FIGURE H1-48 Types of hip fractures. (From Adams JG.; et al. *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

- Impacted fractures: possibly no deformity and only mild pain with hip motion.
- Mild external bruising.

RISK FACTORS

- Osteoporosis.
- Age >75.
- Gait instability, foot deformities, muscular weakness.
- Sensory impairment.
- Polypharmacy.
- Impaired cognition, depression.
- Use of alcohol or benzodiazepines.
- Orthostatic hypotension.
- Environmental hazards at home (e.g., loose rugs, loose cords).
- Subclinical hyperthyroidism.

ETIOLOGY

- Trauma.
- Age-related bone weakness, usually caused by osteoporosis.
- Increased risk of fractures in elderly (decline in muscle function, use of psychotropic medication, etc.).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- OA of hip, RA of hip.
- Hip dislocation.
- Pathologic fracture.
- Lumbar disk syndrome with radicular pain.
- Insufficiency fracture of pelvis.
- Trochanteric bursitis.
- Septic hip joint.
- Pelvic fracture.
- Lateral femoral cutaneous nerve entrapment (meralgia paresthetica).
- Osteitis deformans (Paget's disease).

WORKUP

Diagnosis is usually obvious based on clinical and radiographic findings (Figs. H1-49 and H1-50). Fig. H1-51 illustrates the Garden classification of femoral neck fractures.

IMAGING STUDIES

- Standard roentgenograms consisting of an anteroposterior view of the pelvis and a cross-table lateral view of the hip to confirm the diagnosis.
- If initial roentgenograms are negative and diagnosis of an occult femoral neck fracture is suspected, hospital admission and further radiographic assessment with either bone scanning or MRI are recommended.
- Bone scanning is sensitive after 48 to 72 hr.

TREATMENT

- Orthopedic consultation.
- Surgery indicated in most cases, usually within 24 hr. Treatment depends on type of fracture:
  1. Femoral neck, non-displaced, impacted valgus: cannulated screws.
  2. Displaced: <50 yr, emergent reduction, cannulated screws; >50 yr: hemiarthroplasty, unipolar versus bipolar or total hip arthroplasty if preexisting degenerative changes
  3. Intertrochanteric: stable, 2 and 3 parts, dynamic hip screw (DHS) versus trochanteric femoral nail (TFN); unstable, 4 parts, subtrochanteric extension, TFN.
  4. Reverse obliquity: TFN, blade plate, dynamic condylar screw, not DHS.
- Deep vein thrombosis prophylaxis (fondaparinux, LMWH, vitamin K antagonist). Mechanical prophylaxis is contraindicated. Prophylaxis is usually continued for 28 to 35 days postop.
- Pain management: effective pain management is a primary goal in hip fracture. Opioid analgesics have a high incidence of delirium and constipation. Nerve blockade is effective in reducing acute pain after hip fracture.
- Prophylactic antibiotics should be initiated before surgery and continued for 24 hours after surgical repair.
- Rehabilitation is a major component of hip fracture treatment and should be initiated on the first postoperative day.
- Conservative therapy in patients who are not surgical candidates (too ill for surgery, bed- or wheelchair-bound patients before injury).

DISPOSITION

- Surgical mortality after hip fracture repair is 2% to 3%. Older adults have a 5- to 8-fold increased risk for all-cause mortality during the first 3 mo after hip fracture. Mortality rate within 1 yr in elderly patients is 25% to 30%. Excess annual mortality persists over time for both women and men, but at any given age, excess annual mortality after hip fracture is higher in men than in women.
- Dementia is a particularly poor prognostic sign.

REFERRAL

For surgical consideration when the diagnosis is made.

PEARLS & CONSIDERATIONS

COMMENTS

- Complications: nonunion, avascular necrosis, DVT, infection, delirium, decubitus ulcers, incontinence, persistent pain, loosening of prosthesis.
- Intracapsular fractures: occasionally occur in nonambulatory patients.
  1. Usually treated nonsurgically, especially in the patient with dementia and limited pain perception.
  2. Early bed-to-chair mobilization and vigilant nursing care to avoid skin breakdown.
  3. Fracture usually pain free in a short time even if solid bony healing does not occur.
- As a result of the increasing life span of the female population, femoral neck fractures are becoming more common. The initial

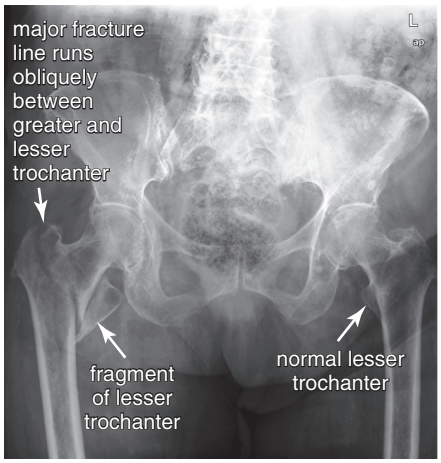

FIGURE H1-49 Intertrochanteric femur fracture: three parts (proximal, distal, and one trochanter). Intertrochanteric femur fractures are common, with the mechanism often being a fall from standing in an elderly patient. The major fracture line usually runs obliquely between the greater and the lesser trochanters. These fractures may have two, three, or four parts classically, although badly comminuted combinations are also possible. Two-part fractures consist of the proximal and distal fragments. Three-part fractures also include a fragment of one trochanter. Four-part fractures include fragments of both trochanters. This 86-year-old female had an unwitnessed fall. She has a typical 3-part fracture, with a fragment of the lesser trochanter visible. Note her generalized severe osteopenia. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

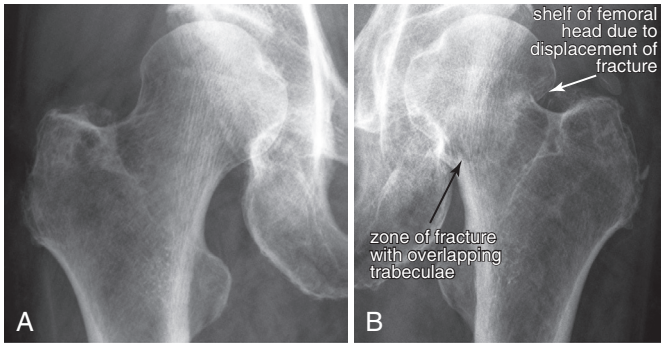

FIGURE H1-50 Femoral neck fracture. This 84-year-old female had an unwitnessed fall. **A,** Normal right hip, osteoporotic. **B,** Left hip, another relatively subtle femoral neck fracture. Note the smudging of the trabeculae of the femoral neck. In addition, the distal fragment has shifted medially, creating an overhanging ledge of the femoral head not seen on the opposite normal side. Some femoral neck fractures are more obvious. (From Broder JS: *Diagnostic imaging for the emergency physician*, Philadelphia, 2011, Saunders.)

physical examination and roentgenographic studies may be completely negative. Groin pain, sometimes quite severe, may be the only early clue to the diagnosis.

- The rate of hip fracture could be reduced by:
  1. Elimination of environmental hazards (poor lighting, loose rugs).
  2. Regular exercise for balance and strength.
  3. Patient education about fall prevention.
  4. Medication review to minimize side effects.
  5. Prevention and treatment of osteoporosis.
- In the United States, hip fracture rates and subsequent mortality among persons aged 65 yr and older are declining, and comorbidities among patients with hip fractures are very expensive ($40,000 in the first year following hip fracture for direct medical costs and $5000 in subsequent years).
- Fragility (or low-trauma) hip fractures, common in elderly patients with reduced bone density, carry a 1-yr mortality of 26%, while another 58% require long-term care in a nursing facility. Previous fragility hip fracture is associated with a second osteoporotic fracture within the subsequent 5 yr.
- Concurrent prolonged use of proton-pump inhibitors (≥1 yr) is associated with reduced effectiveness of alendronate for preventing hip fractures in older adults.

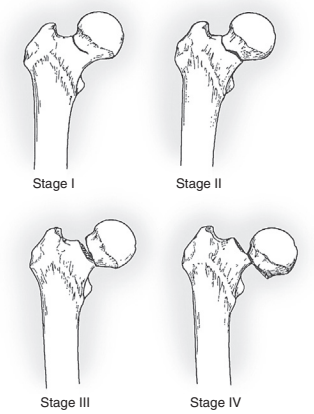

FIGURE H1-51 Garden classification of femoral neck fractures. (From Kyle RF.; Fractures of the hip. In Gustilo RB et al [eds]: *Fractures and dislocations,* St Louis, 1993, Mosby.)

EBM EVIDENCE

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SUGGESTED READINGS

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RELATED CONTENT

Hip Fracture (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

We performed a 4-year follow-up of a randomized controlled trial involving 120 elderly patients with an acute displaced femoral neck fracture who were randomized to treatment with either a bipolar hemiarthroplasty or a total hip arthroplasty. The difference in hip function (as indicated by the Harris hip score) in favor of the total hip arthroplasty group that was previously reported at one year persisted and seemed to increase with time (mean score, 87 compared with 78 at 24 months [p<0.001] and 89 compared with 75 at 48 months [p<0.001]). The health-related quality of life (as indicated by the EuroQol [EQ-$5D_{index}$] score) was better in the total hip arthroplasty group at the time of each follow-up, but the difference was significant only at 48 months (p<0.039). These results confirm the better results in terms of hip function and quality of life after total hip arthroplasty as compared with hemiarthroplasty in elderly, lucid patients with a displaced fracture of the femoral neck. Ⓐ

Abstract[2]

Background: Both intramedullary nails and sliding hip screws are used with good results in the treatment of intertrochanteric and subtrochanteric fractures. The aim of our study was to assess whether use of the TRIGEN INTERTAN nail, as compared with a sliding hip screw, resulted in less postoperative pain, improved functional mobility, and reduced surgical complication rates for patients with an intertrochanteric or subtrochanteric fracture.

Methods: In a prospective, randomized multicenter study, 684 elderly patients were treated with the INTERTAN nail or with a sliding hip screw with or without a trochanteric stabilizing plate. The patients were assessed during their hospital stay and at 3 and 12 months postoperatively. A visual analogue scale (VAS) pain score was recorded at all time points, and functional mobility was assessed with use of the timed Up & Go test. The Harris hip score (HHS) was used to assess hip function more specifically. Quality of life was measured with the EuroQol-5D (EQ-5D). Radiographic findings as well as intraoperative and postoperative complications were recorded and analyzed.

Results: Patients treated with an INTERTAN nail had slightly less pain at the time of early postoperative mobilization (VAS score, 48 versus 52; p = 0.042), although this did not influence the length of the hospital stay and there was no difference at three or twelve months. Regardless of the fracture and implant type, functional mobility, hip function, patient satisfaction, and quality-of-life assessments were comparable between the groups at 3 and 12 months. The numbers of patients with surgical complications were similar for the 2 groups (29 in the sliding-hip-screw group and 32 in the INTERTAN group, p = 0.67).

Conclusions: INTERTAN nails and sliding hip screws are similar in terms of pain, function, and reoperation rates twelve months after treatment of intertrochanteric and subtrochanteric fractures. Ⓐ

Abstract[3]

Hip Fracture

Objective:

Head-preserving fracture care especially for the elderly may be complicated by acetabular screw penetration, cut out, delayed union or femoral head necrosis. The following comparative study analyses whether a new angular stable device may overcome these shortcomings.

Material and Methods:

The Targon FN plate (BBraun/Aesculap, Germany) employs up to 4 angular stable telescoping screws for the fixation of the head fragment. In a prospective study patients with displaced and undisplaced intracapsular femoral neck fractures where treated by closed reduction and fracture fixation using either the Targon FN implant or a standard sliding hip screw (SHS). Patients were followed up clinically, radiographically and via telephone at a mean of follow-up time of 15.5 months.

Results:

A group of 52 patients (mean age: 67 years) with femoral neck fractures were treated with either Targon FN (27 patients) or SHS (25 patients). Time for surgery did not differ within the two groups (56 min Targon FN versus 55 min SHS). 8 patients with SHS (32%) and 4 patients (15%) with Targon FN experienced cut out of the lag screw and received hip replacement ($p < 0.05$). Implant failure occurred after a mean of 1.8 months after SHS and 6.0 months after Targon FN implantation. Final radiographs revealed substantial subsidence in both groups (5.0 mm Targon FN; 9.8 mm SHS, p ¼ 0.055) with a clear trend to less subsidence for the Targon FN group. Furthermore, asymmetrical telescoping of the lag screws occurred in 30% (n=8), complete depletion of telescoping distance in 11% (n=3) in the Targon FN group. Functional assessment using the HHS assessment tool, however, presented with slightly better results for the SHS treatment (87.7 ± 13.9) when compared with Targon FN fixation (69.5 ± 4.5).

Conclusions:

The study revealed less subsidence of the head fragment, lower cut out rate and a lower rate of conversion to hemiarthroplasty after Targon FN fixation in comparison with a standard SHS fixation in a small number of patients with hip fractures. However, this was not accompanied by functional limitations in the SHS group. Ⓑ

Abstract[4]

Introduction:

Immediate total hip replacement (THR) in patients with acetabular fractures is controversial because of concerns about high complication rates. The current article is a systematic review of the literature on the use of acute THR for the treatment of acetabular fractures.

Materials and Methods:

This systematic review included studies published in English between 1992 and 2012 of subjects with acetabular fracture undergoing immediate THR. Outcomes of interest included indications; clinical assessment, including walking ability; comparison with control group; associated procedures, and rate of complications, such as loosening or revision surgery.

Results:

This review identified 6 studies, of which only one included a control group. Acute THR was associated with satisfying outcomes with regard to clinical assessment and walking ability. The comparative study assessed the difference between acute THR and delayed THR in acetabular fractures: improved outcomes were observed in the delayed THR group, although the differences between the two groups were not statistically significant.

Discussion:

According to data reported in the literature, acute primary THR can be successful in patients with poor bone quality, combined acetabular and femoral neck fractures, or pathological fractures and concurrent osteoarthritis of the hip. Relative indications include old age, delayed presentation, substantial medical comorbidities, and pathologic obesity. Clinical outcomes with acute THR were similar to those with delayed THR. Although the results reported in the six studies reviewed here were satisfying overall, there is limited evidence in this area in the existing literature and future prospective investigations are required.

Conclusion:

Data reported in the literature indicate that immediate THR can be successful in appropriately selected elderly patients or patients with extensive osteoporosis, combined acetabular and femoral neck fractures or pathological fractures. There is currently a limited evidence base for THR in patients with acetabular fractures; therefore, physicians' practice and expertise are the most useful tools in clinical practice. Ⓑ

Evidence-Based Reference

Hedbeck CJ et al.: Comparison of bipolar hemiarthroplasty with total hip arthroplasty for displaced femoral neck fractures: a concise four-year follow-up of a randomized trial, *J Bone Joint Surg Am* 93:445–450, 2011. Ⓐ

Matre K et al.: TRIGEN INTERTAN intramedullary nail versus sliding hip screw: a prospective, randomized multicenter study on pain, function, and complications in 684 patients with an intertrochanteric or subtrochanteric fracture and one year of follow-up, *J Bone Joint Surg Am* 95:200–208, 2013. Ⓐ

Eschler A, Brandt S, Gierer P et al.: Angular stable multiple screw fixation (Targon FN) versus standard SHS for the fixation of femoral neck fractures, *Injury* 45:S76–S80, 2014. Ⓑ

De Bellis UG, Legnani C, Calori GM: Acute total hip replacement for acetabular fractures: A systematic review of the literature, *Injury* 45:356–361, 2014. Ⓑ

SUGGESTED READINGS

Abou-Setta AM et al.: Comparative effectiveness of pain management interventions for hip fracture: a systematic review, *Ann Intern Med* 155:234–245, 2011.

Abrahamsen B et al.: Proton pump inhibitor use and the antifracture efficacy of alendronate, *Arch Intern Med* 171:998–1004, 2011.

Amer NA et al.: Early operation on patients with a hip fracture improved the ability to return to independent living, *J Bone Joint Surg Am* 90A:1436, 2008.

Bettelli G et al.: Relationship between mortality and proximal femur fractures in the elderly, *Orthopedics* 26:1045, 2003.

Bogoch ER et al.: Effective initiation of osteoporosis diagnosis and treatment for patients with a fragility fracture in an orthopedic environment, *J Bone Joint Surg Am* 88A:25, 2006.

Brauer CA et al.: Incidence and mortality of hip fractures in the United States, *JAMA* 302(14):1573–1579, 2009.

Christmas C et al.: In the clinic: hip fracture, *Ann Intern Med* 155:11, 2011. ITC6–1.

Clinton J et al.: Proximal humeral fracture as a risk factor for subsequent hip fractures, *J Bone Joint Surg Am* 91:503, 2009.

Feldstein AC et al.: Older women with fractures: patients falling through the cracks of guideline recommended osteoporosis screening and treatment, *J Bone Joint Surg Am* 85A:2294, 2003.

Gardner MJ et al.: Interventions to improve osteoporosis treatment following hip fracture, *J Bone Joint Surg Am* 87A:3, 2005.

Haentjens P et al.: Meta-analysis: excess mortality after hip fracture among older women and men, *Ann Intern Med* 152:380–390, 2010.

Kaufman JD et al.: Barriers and solutions to osteoporosis care in patients with a hip fracture, *J Bone Joint Surg Am* 85A:2003, 1837.

Lawrence VA et al.: Medical complications and outcomes after hip fracture repair, *Ann Intern Med* 162:2053, 2003.

Logan K: Stress fractures in the adolescent athlete, *Pediatr Ann* 36:738, 2007.

Mirchandani S et al.: The effects of weather and seasonality on hip fracture incidence in older adults, *Orthopedics* 28:149, 2005.

Parker MJ et al.: Effectiveness of hip protectors for preventing hip fractures in elderly people, *BMJ* 332:571, 2006.

Parvizi J.; High-yield orthopedics (p. 241). Saunders: Philadelphia.

Radcliff TA et al.: Patient risk factors, operative care, and outcomes among older community-dwelling male veterans with hip fracture, *J Bone Joint Surg Am* 90:34, 2008.

Saunders S, Geraci SA: Outpatient management of the elderly patient following fragility hip fracture, *Am J Med* 124:408–410, 2011.

Schoofs MW et al.: Thiazide diuretics and the risk for hip fractures, *Ann Intern Med* 139:476, 2003.

Tosi LL, Kyle RF: Fragility fractures: the fall and decline of bone health, *J Bone Joint Surg Am* 87A:1, 2005.

Van Helden S et al.: Bone and fall-related fracture risks in women and men with a recent clinical fracture, *J Bone Joint Surg Am* 90:241, 2008.

BASIC INFORMATION

DEFINITION

Hirsutism is the development of stiff, pigmented (terminal) facial and body hair (male distribution) in women as a result of excess androgen production.

SYNONYMS

Excessive hair growth

ICD-9CM CODES
704.1 Hirsutism
ICD-10CM CODES
L68.0 Hirsutism

EPIDEMIOLOGY & DEMOGRAPHICS

- Overall prevalence unknown, estimated 5% to 10% in reproductive age women.
- Race and genetics should be considered. Some distinct ethnic populations have minimal body hair and others (Mediterranean, Middle Eastern, South Asian) have moderate to large amounts of body hair while serum androgen levels are similar.
- Social norms and culture also determine how much body hair is cosmetically acceptable.
- Half of all cases of mild hirsutism do not have hyperandrogenemia. "Patient-important hirsutism" refers to hirsutism causing woman sufficient distress to seek care.
- Incidence and presentation of hirsutism is dependent on underlying cause of androgen excess (see "Differential Diagnosis").
- Most women with hirsutism have polycystic ovary syndrome.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Timing of symptoms: abrupt onset, short duration, rapid progression, progressive worsening, more severe signs of virilization, or later age of onset suggest androgen-producing tumor, late-onset congenital adrenal hyperplasia, or Cushing's syndrome. Weight increases may produce increased androgen production.
- Menstrual history: menarche, cycle regularity and symptoms of ovulation, fertility, and contraception use. Anovulatory cycles are the most common underlying cause of androgen excess.
- Medication use history: some drugs cause hirsutism or produce androgenic effects (danazol, phenytoin, valproic acid, androgenic progestins (e.g., norgestrel), cyclosporin, minoxidil, metoclopramide, phenothiazines, methyldopa, diazoxide, penicillamine).
- Family history: known or suspected family history of hirsutism, congenital adrenal hyperplasia, insulin resistance, polycystic ovary syndrome (PCOS), infertility, obesity, menstrual irregularity may be found.
- Physical exam reveals deepening voice, body habitus, increased muscle mass, galactorrhea; abdominal and pelvic exam.
- Associated cutaneous manifestations (Fig. H1-52) are acne, acanthosis nigricans, striae, hair distribution, location and quantity, frontotemporal balding, muscle mass, clitoromegaly.
- Ferriman-Gallwey scale, a simple, pictorial system of scoring nine body areas, is the most common tool used to quantify hirsutism. It may be unreliable in non-Caucasian women of other ethnicities.

ETIOLOGY

- Presence of hirsutism indicates androgen excess. Total testosterone may be normal, but free testosterone is elevated.
- Androgens induce vellus hair follicles (soft, unpigmented hair) in sex-specific areas (upper lip, chin, midsternum, upper abdomen, back, buttocks) to develop into thicker, more heavily pigmented terminal hairs.
- Anovulatory ovaries are usual source of excess androgens through thecal cell steroidogenesis and conversion of androstenedione to testosterone. The most common cause of hirsutism is polycystic ovary syndrome, which accounts for three out of every four cases.
- Conditions that decrease hepatic production of sex hormone binding globulin (SHBG) decrease protein-bound testosterone and increase free testosterone fraction (e.g., low estrogen, high androgen, and hyperinsulinemic states).
- Late-onset, congenital adrenal hyperplasia enzyme deficiency (most commonly 21-hydroxylase deficiency) produces excess 17 hydroxyprogesterone (17-OHP) and overproduction of androstenedione.
- Rare ovarian tumors primarily derived from Sertoli-Leydig cells, granulosa theca cells, or hilus cells produce excess androgens.
- Rare adrenal tumors produce excess androgens.
- Rare pituitary or hypothalamic tumors produce excess prolactin and can lead to anovulation.
- Box H1-7 summarizes causes of androgen excess in women of reproductive age.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Androgen-independent vellus hair: soft, unpigmented hair that covers entire body
- Hypertrichosis: diffusely increased total body hair (vellus or lanugo-type) not restricted to androgen-dependent areas often an adverse response to a medication or systemic illness (e.g., anorexia nervosa, porphyria, malnutrition, hypothyroidism)
- PCOS 75%
- Idiopathic 5% to 15%
- Congenital adrenal hyperplasia 1% to 8%
- Insulin resistance syndrome 3% to 4%
- Cushing's syndrome <1%
- Drug induced <1%
- Ovarian tumor <1%
- Adrenal tumor <1%
- Hyperthecosis <1%
- Hyperprolactinemia <1%

WORKUP

- Hirsutism is a clinical diagnosis.
- Management of hirsutism is largely independent of the etiology.
- Workup in selected hirsute women is directed to determine underlying cause of androgen excess.
- See specific conditions for more detailed workup of individual diagnoses.

LABORATORY TESTS

Establishing laboratory evidence of excess androgens in women with moderate or severe hirsutism, sudden onset, rapid progression, or associated menstrual dysfunction, central obesity, clitoromegaly, or acanthosis nigricans is an approach consistent with guidelines from the Endocrine Society, the American College of Obstetricians and Gynecologists, the Androgen Excess and Polycystic Ovary Syndrome Society and the American Association of Clinical Endocrinologists.

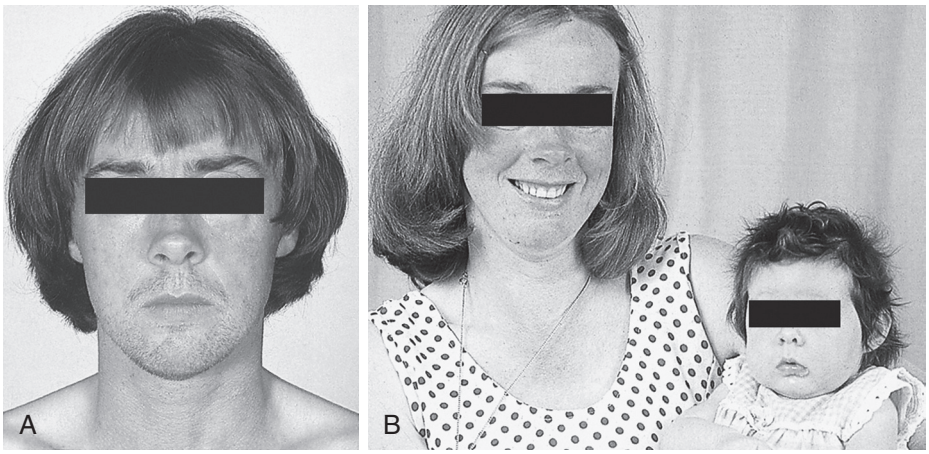

FIGURE H1-52 A patient with an arrhenoblastoma with associated polycystic ovaries before and after treatment. **A,** Before treatment, the patient had marked facial hirsutism. **B,** The patient is shown successfully treated. The tumor was resected and ovulation ensued with clomiphene and human chorionic gonadotropin therapy. (From Besser CM, Thorner MO: *Comprehensive clinical endocrinology,* ed 3, St Louis, 2002, Mosby.)

BOX H1-7 Causes of Androgen Excess in Women of Reproductive Age

Ovarian
Polycystic ovary syndrome (PCOS)
Hyperthecosis (a severe PCOS variant)
Ovarian tumor (e.g., Sertoli-Leydig cell tumor)

Adrenal
Nonclassic adrenal hyperplasia
Cushing's syndrome
Glucocorticoid resistance
Adrenal tumor (e.g., adenoma, carcinoma)

Specific Conditions of Pregnancy
Luteoma of pregnancy
Hyperreactio luteinalis
Aromatase deficiency in fetus

Other
Hyperprolactinemia, hypothyroidism
Medications (danazol, testosterone, anabolizing agents)
Idiopathic hirsutism (normal serum testosterone in an ovulatory woman)
Idiopathic hyperandrogenism (patients who do not fall into any of the other categories listed)

From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

- Total plasma testosterone (normal range 20-60 ng/dl [0.69-2.1 nmol/L]) or free testosterone: early morning on day 4 to 10 of menstrual cycle to screen for testosterone-secreting tumors. If moderately or markedly elevated (total testosterone >150 ng/dl [5.2 nmol/L], free testosterone >2 ng/dl [0.07 nmol/L]) may image adrenals and ovaries for androgen-secreting tumors.

Other laboratory test considerations if appropriate:
- Prolactin: moderately elevated values should prompt imaging of pituitary-hypothalamic region
- 17-OHP (17 α-hydroxyprogesterone): screen for adrenal enzyme deficiencies. Morning value >200 ng/dl in early follicular phase suggests nonclassic (late onset) congenital adrenal hyperplasia due to 21-hydroxylase deficiency and may be confirmed with high-dose (250 mcg) ACTH stimulation test.
- Thyroid-stimulating hormone (TSH): rule out hypothyroidism
- Dehydroepiandrosterone sulfate (DHEA-S): screen for adrenal androgen production as almost entirely produced by adrenals. Levels >700 mcg/dl (13.6 nmol/L) raise suspicion for adrenal androgen-secreting tumor.

Additional laboratory test considerations if appropriate:
- Follicle-stimulating hormone: (FSH): rule out hypoestrogen state (perimenopausal).
- Luteinizing hormone: (LH): typically elevated in PCOS with low or normal FSH.
- 24-hour urinary free cortisol: rule out Cushing's syndrome and overproduction of cortisol.
- Overnight single-dose dexamethasone suppression test: rule out Cushing's syndrome and adrenal hyperfunction.
- Fasting blood sugar (FBS), 2-hr 75-g oral glucose tolerance test, fasting insulin levels: rule out insulin resistance syndrome.

IMAGING STUDIES

Imaging study considerations if appropriate:
- Pelvic ultrasound (high resolution, transvaginal): rule out ovarian tumor if total testosterone is elevated.
- Abdominal CT/MRI: rule out adrenal tumor if elevated DHEA-S.
- Pituitary-hypothalamic region CT/MRI: rule out pituitary tumor if prolactin elevated.
- Laparoscopy/laparotomy: rule out small ovarian tumor in cases of elevated testosterone levels without radiologic evidence of adrenal or ovarian pathology.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Weight reduction: can reduce androgen production indirectly by reducing insulin-stimulated theca cell androgen production and improve menstrual function, and slow hair growth in obese women.
- Cosmetic: temporary.
  1. Shaving: does not stimulate hair growth; lasts days, leaves stubble.
  2. Epilation: electronic plucking.
  3. Bleaching: removes hair pigment. May cause skin irritation.
  4. Mechanical waxing/plucking.
  5. Depilatories: gels, lotions, or creams that chemically disrupt sulfide bonds of hair causing dissolution of hair shaft. No stubble.
  6. Photoepilation (laser and intense pulsed light [IPL]): hair follicles destroyed by wavelengths of light absorbed by melanin. Good for pigmented hair; laser treatment is more effective than shaving, waxing, and electrolysis. It lasts 3 to 6 months as vellus follicles remain and can be converted to terminal pigmented hair under excess androgens.
- Cosmetic: permanent. Electrolysis: destroys individual hair follicles. May be expensive and time consuming.

ACUTE GENERAL Rx

See "Pharmacologic Therapy."

CHRONIC Rx

See "Pharmacologic Therapy."

PHARMACOLOGIC THERAPY

- Usually second-line treatment following nonpharmacologic, physical methods of hair control, and in consideration of patient's comorbidities and risk factors, patient preferences, area of excess hair amenable to treatment, and access and affordability of treatments.
- Pharmacologic treatments categorized as topical, oral contraceptive pills (OCPs), antiandrogens (potential adverse effects on a developing male fetus, so use with reliable contraception), other treatments directed at specific underlying etiology.
- Topical: Eflornithine topical cream 13.9%: unclear mechanism of action; may inhibit ornithine decarboxylase, retarding hair growth. Temporary cosmetic treatment for facial hair. Applied directly to unwanted facial hair bid with at least 8 hr spaced applications. Does not remove hair, rather slows growth. Slow response over 4 to 8 wk. Hair growth returns upon discontinuation of treatment.
- OCPs: Suppress ovarian steroidogenesis and LH through low-dose estrogen and low androgenic progestational agents. Slow response to treatment. Suppresses new hair growth. Established hair unaffected. Low-dose OCPs with low androgenic progestational agents, for example, desogestrel, drospirenone, norgestimate. Avoid norgestrel and levonorgestrel (higher androgenic progestational agents).
- Antiandrogens: Spironolactone: when OCPs unacceptable or may be added for disappointing results after 6 mo of OCP treatment.
  1. Aldosterone-antagonist diuretic inhibits adrenal and ovarian biosynthesis of androgens. May result in ovulation, so consider contraception needs.
  2. Slow response usually 6 mo or more.
  3. 200 mg PO qd, then decrease to 25 to 50 mg qd maintenance.
  4. May cause hyperkalemia.
  5. Anovulatory, unopposed estrogen states require progestin management.

REFERRAL

- To endocrinologist if difficulty in determining diagnosis, achieving therapeutic goals, or resistant to first-line therapies. Pre-pubertal and postmenopausal hirsutism is suspicious for neoplastic or secondary endocrine causes and should be referred for further evaluation.
- Consider referral or consultation for following therapies:

1. Finasteride: antiandrogen, in hair follicle blocks 5α-reductase conversion of testosterone to intranuclearly active 5α-dihydrotestosterone (DHT).
   1. Use only with reliable contraception because DHT necessary for normal male fetus urogenital development.
   2. Not FDA approved for treatment of hirsutism.
   3. 1 to 5 mg PO qd.
2. Flutamide: inhibits androgen uptake and receptor binding
   1. Not recommended by Endocrine Society Clinical Practice Guidelines and not FDA approved for treatment of hirsutism, but used by some European endocrinologists.
   2. Use only with reliable contraception.
   3. Reserved for women with severe, resistant hirsutism because of risk of hepatic dysfunction.
   4. 250 mg PO bid.
3. Cyproterone acetate (not available in the United States): antiandrogen that competes with DHT for binding androgen receptors. Used as progestin component of OCPs outside the United States.

- Other treatments directed at specific underlying etiology:
  1. Metformin/thiazolidinediones: therapy reserved for documented insulin-resistant states.
  2. GnRH agonists: recommended only in women with severe hyperandrogenemia (e.g., ovarian hyperthecosis) with suboptimal response to combination low-dose estrogen/progestin pills and antiandrogen treatment. Inhibits gonadotropin and consequently ovarian androgen and estrogen secretion.
  3. Dexamethasone: adrenal glucocorticoid suppression is reserved for diagnosis of adrenal enzyme deficiency.
  4. Total abdominal hysterectomy/bilateral salpingo-oophorectomy reserved for recalcitrant hirsutism in older female with hyperthecosis and undesired fertility.

PEARLS & CONSIDERATIONS

COMMENTS

- Hirsutism is both an endocrine and cosmetic problem for patients.
- Ovulation induction therapy is indicated in women desiring pregnancy.
- Delay checking serum androgens until oral contraceptives have been discontinued for 2 to 3 mo.
- Evaluation of incidental adrenal mass is always warranted.

SUGGESTED READINGS

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RELATED CONTENT

Hirsutism (Patient Information)

AUTHOR: **RICHARD LONG, M.D.**

SUGGESTED READINGS

Bode D, et al.: Hirsutism in women, *Am Fam Physician* 85(4):373–380, 2012.

Escobar-Morreale HF, et al.: Epidemiology, diagnosis and management of hirsutism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society, *Hum Reprod Update* 18:146, 2012.

Koulouri O, Conway G: A systematic review of commonly used medical treatments for hirsutism in women, *Clin Endocrinol* 68(5):800–805, 2008.

Martin KA, et al.: Evaluation and treatment of hirsutism in premenopausal women: an Endocrine Society Clinical Practice Guideline, *J Clin Endocrinol Metab* 93(4):1105–1120, 2008.

Rosenfield Hirsutism RL: *N Engl J Med* 353(24):2578–2588, 2005.

Histiocytosis X (Langerhans Cell Histiocytosis)

BASIC INFORMATION

DEFINITION

Histiocytosis X, now known as Langerhans cell histiocytosis (LCH), is a rare disorder characterized by the abnormal proliferation of pathologic Langerhans cells. These dendritic cells form characteristic infiltrates with eosinophils, lymphocytes, and other histiocytes found in various organs.

SYNONYMS

Eosinophilic granuloma
Hand-Schüller-Christian disease
Letterer-Siwe disease
Langerhans cell histiocytosis
Langerhans cell granulomatosis
Diffuse reticuloendotheliosis

ICD-9CM CODES
202.5 Acute histiocytosis X
277.89 Chronic histiocytosis X
ICD-10CM CODES
C96.0 Multifocal and multisystemic (disseminated) Langerhans-cell histiocytosis
C96.6 Unifocal Langerhans-cell histiocytosis
D76.3 Other histiocytosis syndromes
C96.5 Multifocal and unisystemic Langerhans-cell histiocytosis

EPIDEMIOLOGY & DEMOGRAPHICS

- LCH is mainly a childhood disorder with a peak incidence from age 1 to 4 yr.
- The annual incidence in the pediatric population is 2 to 5 per million.
- LCH affects males more often than females, 2:1.
- Pulmonary LCH (a localized form more commonly found in adults) has an equal male/female incidence, if not female predominance, possibly because of increased prevalence of smoking in women.
- More common in Caucasians.
- Disseminated LCH usually occurs before 2 yr of age.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical presentation is variable, and ranges from:
  1. A benign isolated bony lesion (eosinophilic granuloma), most often found in children younger than 15 yr of age.
  2. Multiple bone lesions with soft tissue gingival and oral mucosal involvement (Hand-Schüller-Christian disease); generally occurs in children younger than 10 yr of age.
  3. An aggressive disseminated disease infiltrating organs and causing organ dysfunction (Letterer-Siwe disease). This is the rarest form of LCH, affecting mostly children younger than 2 yr.
- Bone lesions (80% to 100%).
  1. May be isolated or multiple.
  2. Painful, often worse at night.
  3. Skull most often involved, followed by long bones; lesions rarely seen in small bones of hands and feet.
  4. Proptosis.
  5. Mastoiditis.
  6. Loose teeth.
  7. Gingival hypertrophy.
- Skin is involved in >80% of patients with disseminated disease and in 30% of patients with less extensive disease.
  1. Seborrhea-like scaling of scalp, petechial and purpuric lesions, ulcers, and bronzing of the skin may occur.
  2. Common sites: scalp, neck, trunk, groin, and extremities.
- Lymphadenopathy (10%): cervical and inguinal.
- Pulmonary disease is very frequent in adults (usually as isolated disease), but can be seen in 23% to 50% of children as well. Lung involvement always occurs as part of the disseminated disease in children.
- Pulmonary involvement may manifest with cough, tachypnea, cyanosis, inspiratory crackles, pleural effusions, or pneumothorax. Diffuse emphysema associated with pulmonary fibrosis is the end stage of a mixed restrictive and obstructive pattern of disease.
- Liver involvement manifesting as hepatomegaly with or without jaundice (50% to 60%).
- Involvement of the biliary tree may be seen as biliary fibrosis or sclerosing cholangitis.
- Splenomegaly (5%).
- CNS involvement occurs in 25% to 35% of patients, most often in those with disseminated disease. The most common cerebral site affected is the hypothalamic-neurohypophyseal region, where infiltration and destruction usually result in diabetes insipidus with insatiable thirst and urination. The second most common site of involvement is the cerebellum.
- Involvement of the thymus, parotid glands, and GI tract has been reported in rare cases.

ETIOLOGY

- The etiology of LCH is unknown, though multiple theories have been proposed.
- Some degree of genetic predisposition has been proposed and recent evidence suggests LCH as a monoclonal proliferative neoplastic disorder in children.
- In adults, pulmonary LCH appears to be primarily an immune-mediated reactive process and has been linked to cigarette smoking. Cigarette smoke had not been observed as a causative factor in other forms of LCH.

DIAGNOSIS

Tissue biopsy of organ lesions reveals pathologic Langerhans cells characterized by the presence of multiple surface nucleoproteins including CD1a, the presence of which establishes definitively histologic diagnosis of LCH. The infiltration by eosinophils forming pseudoabscesses is characteristic.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of histiocytosis syndromes is extensive, including all causes of diabetes insipidus, lytic bone lesions, dermatitis, hepatomegaly, and lymphadenopathy. In regards to histiocytosis syndromes of childhood, there are three classes based on histopathologic findings. Class I histiocytosis (also known as LCH) includes the clinical entities of eosinophilic granuloma, Hand-Schüller-Christian disease, and Letterer-Siwe disease. Class II histiocytoses are non-malignant proliferative disorders that are characterized by accumulation of macrophages. The two major diseases among the class II histiocytoses are hemophagocytic lymphohistiocytosis (FHLH) and infection-associated hemophagocytic syndrome (IAHS). These diseases are grouped together under the term *hemophagocytic lymphohistiocytosis* (HLH) (see Table EH1-24). Class III histiocytoses are

TABLE EH1-24 Distinguishing Characteristics of the Reactive Lymphohistiocytoses

	Genetic History	Virus Infection	Cellular Immune Function	Miscellaneous
HLH, genetic	Autosomal recessive	Possibly associated	↓ CMI ↓ NK cell activity ↓ Monocyte killing ↓ CMI	Perforin deficiency Hypertriglyceridemia, Perforin (PRF1), Munc 13-4 mutations
Secondary infection–associated	Sporadic	Yes	↓ CMI NL or ↑ NK cell in instances associated with EBV ↓ Anomalous EBV-related killing	Coagulopathy early in the course of the disease
XLP	X-linked sporadic	EBV	NL or ↑ NK cell NL or ↑ anomalous EBV-related killing	*SH2DIA* mutation Severe, often fatal hepatitis
SHML	Sporadic	?EBV	Not reported	Autoimmune phenomena
LG	Sporadic	EBV	↓ CMI	Lymphoma development

CMI, Cell-mediated immunity; *EBV,* Epstein-Barr virus; *HLH,* hemophagocytic lymphohistiocytosis; *LG,* lymphomatoid granulomatosis: *NK,* natural killer; *NL,* normal; *SHML,* sinus histiocytosis with massive lymphadenopathy; *XLP,* X-linked lymphoproliferative syndrome.
From Nathan DG et al (eds): *Nathan and Oski's hematology of infancy and childhood,* ed 6, Philadelphia, 2003, Saunders.

malignancies of cells of monotype-macrophage lineage (acute monocytic leukemia) and true malignant histiocytoses.

WORKUP

Baseline evaluation should include bone scan, chest x-ray, skeletal x-ray, abdominal ultrasound, and routine laboratory tests to assess the extent of disease involvement.

LABORATORY TESTS

- CBC is not specific but may reveal cytopenias in patients with bone marrow involvement.
- Electrolytes, BUN, creatinine, urinalysis, and urine and serum osmolality are helpful in the diagnosis of diabetes insipidus during fluid deprivation testing.
- Liver function tests (LFTs) may be elevated in patients with liver involvement.
- Bronchoalveolar lavage may show increased numbers of CD1a-positive histiocytes or Langerhans cells in patients with pulmonary LCH.

IMAGING STUDIES

- Radiograph studies of affected areas show lytic lesions with or without sclerotic margins.
- Radiograph bone survey is done searching for other lesions.
- Bone scan complements the bone survey studies.
- Panoramic dental view of the mandible and maxilla for children with oral involvement.
- Chest radiograph can show interstitial reticulonodular infiltrates. This pattern typically progresses toward frank honeycombing fibrosis later in the course of the disease (Fig. EH1-53).
- High-resolution CT scan of the chest confirms interstitial lung scarring, nodules, and cysts, and represents an excellent noninvasive means for diagnosis and follow-up of pulmonary LCH. Pulmonary cysts are bilateral and symmetric, showing slight upper-lobe predominance with relative sparing of the costophrenic angles.
- CT scans of the temporal bone searching for mastoid, and inner and middle ear involvement.
- Ultrasound of the abdomen may show hepatosplenomegaly.
- Conventional cholangiography or MRI cholangiopancreatography can confirm the presence of disease in patients suspected to have biliary involvement.
- MRI of the brain to visualize the hypothalamic-hypophyseal region in patients suspected of having diabetes insipidus.

Rx TREATMENT

Treatment is still evolving and is based on organ involvement and the extent of disease.

ACUTE GENERAL Rx

Isolated bone lesions can be treated by:

- Curettage of affected site and implantation of allograft bone chips or polymethylmethacrylate.
- Intralesional prednisone or prednisone and vinblastine.
- Bisphosphonates.
- NSAIDs.
- Radiation therapy is useful only for bone lesions of the vertebrae or femoral neck at risk of collapse.

Single skin lesions are treated with:

- Topical steroid (e.g., triamcinolone acetonide) applied bid.
- Nitrogen mustard in 20% solution.
- Surgery.
- Intralesional interferon.
- Isotretinoin.

Treatment of solitary lymph node involvement:

- Excision at the time of diagnosis.
- Systemic oral prednisone.

Treatment for multiple bone lesions, skull base lesions, or multisystem disease includes:

• Vinblastine 6 mg/m^2 IV bolus every wk for 6 mo or etoposide 150 mg/m^2 IV for 3 days every 3 wk for 6 mo and oral prednisone for 6 mo.

CHRONIC Rx

- For severe, high-risk, disseminated cases not responding within 6 wk of initial treatment, salvage therapy, including high dose of the purine analogue cladribine along with high-dose cytosine arabinoside followed by allogeneic blood stem cell transplantation, should be considered. Additionally, liver or lung transplantation might be the treatment of choice for terminal liver and lung failure patients.
- Diabetes insipidus is treated with DDAVP 0.1 to 0.8 mg PO or 1 nasal spray bid to tid.
- Adults with isolated pulmonary LCH do not require aggressive treatment and will benefit from smoking cessation.
- Empirical use of steroids, in either short pulses or longer exposures, has also been suggested in the treatment of pulmonary disease; however, data regarding effectiveness are still limited.
- Lung transplantation has been tried in both children and adults with advanced pulmonary disease and limited lung function, but failure rates are high because of local recurrence after transplantation.

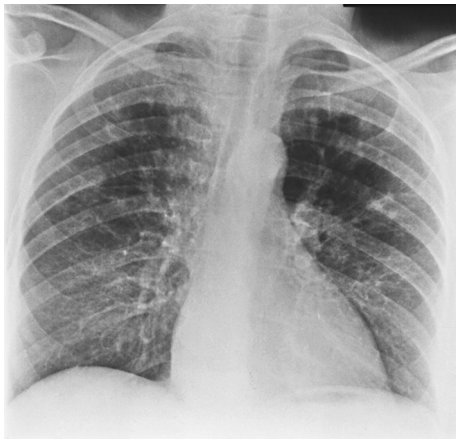

FIGURE EH1-53 Langerhans cell histiocytosis (LCH; histiocytosis X). There is a reticular nodular pattern in the upper lobes. The lung volumes are preserved. (From McLoud TC [ed]: *Thoracic radiology, the requisites,* St Louis, 1998, Mosby.)

DISPOSITION

- Patients with disease localized to only one organ system have a good prognosis and appear to need minimal, if any, treatment. For patients with isolated pulmonary LCH, the 5-yr survival rate is around 80%.
- Patients with disseminated disease have an increased risk for poor outcome, with a reported mortality rate of 10% to 20%, and 50% risk of life-impairing morbidity. A poor prognostic feature is the failure to respond to therapy in the first 6 wk.
- In patients with disseminated LCH and <2 yr of age, the mortality rate is 30%.

REFERRAL

Multidisciplinary approach: pediatric oncologist, radiation oncologists, oral maxillary surgeons, ear-nose-throat specialists, audiology, dermatology, endocrinology, and family counseling.

PEARLS & CONSIDERATIONS

COMMENTS

- The course of LCH is often unpredictable and varies from spontaneous resolution to rapid progression and death, or multiple recurrences and regressions with risk for permanent sequelae.
- The association of LCH with other malignancies (e.g., acute lymphocytic leukemia, acute nonlymphoblastic leukemia, and solid tumors) has been cited.

PREVENTION

Effective antismoking measures may prevent pulmonary LCH.

PATIENT & FAMILY EDUCATION

- Instruct patients to promptly report the development of hemoptysis. This symptom may indicate malignancy or superimposed bacterial/fungal infection, such as *Aspergillus* species infection.
- Educate about the likely etiologic role of cigarette smoking.

SUGGESTED READINGS

Available at www.expertconsult.com

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SUGGESTED READINGS

Abla O et al.: Langerhans cell histiocytosis: current concepts and treatments, *Cancer Treatment Rev* 36(4):354–359, 2010.

Dauriat G et al.: Lung transplantation for pulmonary Langerhans' cell histiocytosis: a multicenter analysis, *Transplantation* 81:746, 2006.

Gadner H et al.: Improved outcome in multisystem Langerhans cell histiocytosis is associated with therapy intensification, *Blood* 111:2556, 2008.

Histiocytosis Association of America. Available at www.histio.org.

Hoover KB et al.: Langerhans cell histiocytosis, *Skeletal Radiol* 36(2):95–104, 2007.

Ladish S.Histiocytosis syndromes of childhood. In: (editor: Kliegman R.M.; et al.) *Nelson textbook of pediatrics*. ed 19 Saunders: Philadelphia.

Stockschlaeder M, Sucker C: Adult Langerhans cell histiocytosis, *Eur J Haematol* 76(5):363–368, 2006.

Weitzman S, Egeler RM: Langerhans cell histiocytosis: update for the pediatrician, *Curr Opin Pediatr* 20:23, 2008.

BASIC INFORMATION

DEFINITION

Histoplasmosis is caused by the fungus *Histoplasma capsulatum* and characterized by a primary pulmonary focus with occasional progression to chronic pulmonary histoplasmosis (CPH) or various forms of dissemination. Progressive disseminated histoplasmosis (PDH) may present with a diverse clinical spectrum, including adrenal necrosis, pulmonary and mediastinal fibrosis, and ulcerations of the oropharynx and GI tract. In those patients coinfected with HIV, it is a defining disease for AIDS.

SYNONYMS

North American histoplasmosis
Ohio Valley fever
Vanderbilt disease

ICD-9CM CODES

115.90 Histoplasmosis
115.94 Histoplasmosis with endocarditis
115.91 Histoplasmosis with meningitis
115.93 Histoplasmosis with pericarditis
115.95 Histoplasmosis with pneumonia
115.92 Histoplasmosis with retinitis

ICD-10CM CODES

B39.9	Histoplasmosis, unspecified
B39.9 with: I39	Endocarditis and heart valve disorders in diseases classified elsewhere
B39.9 with: G02	Meningitis in other infectious and parasitic diseases classified elsewhere
B39.9 with: I32	Pericarditis in diseases classified elsewhere
B39.9 with: J17	Pneumonia in diseases classified elsewhere
B39.9 with: H32	Chorioretinal disorders in diseases classified elsewhere

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- Unknown for acute pulmonary disease
- For CPH, estimated at 1/100,000 cases in endemic areas
- For PDH in immunocompetent adults, estimated at 1/2000 cases of histoplasmosis

PREVALENCE: Unknown

PREDOMINANT SEX: Clinically evident disease is most common in males; male/female ratio of 4:1

PREDOMINANT AGE:

- CPH is most often seen in males >50 yr old with an associated history of COPD.
- Presumed ocular histoplasmosis syndrome (POHS) is seen between ages of 20 and 40 yr.

PEAK INCIDENCE: Unknown

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Conidia are deposited in alveoli then converted to yeast forms where they spread to regional lymph nodes and other organs, especially liver and spleen.
- 1 to 2 wk later, a granulomatous inflammatory response begins to contain the yeast in the form of discrete granulomas.
- Delayed-type hypersensitivity to *Histoplasma* antigens occurs 3 to 6 wk after exposure.
- Clinical disease manifests in various forms, depending on host cellular immunity and inoculum size:
  1. Acute primary pulmonary histoplasmosis
     a. An overwhelming number of patients are asymptomatic.
     b. Most clinically apparent infections manifest by complaints of fever, headache, malaise, pleuritic chest pain, nonproductive cough, and weight loss.
     c. Less than 10%, mainly women, complain of arthralgias, myalgias, and skin manifestations such as erythema multiforme or erythema nodosum.
     d. Acute pericarditis presents in a smaller percentage of patients.
     e. Hepatosplenomegaly is most commonly observed in children.
     f. With particularly heavy exposure, there is severe dyspnea, marked hypoxemia, impending respiratory failure.
     g. Most patients are asymptomatic within 6 wk.
  2. CPH
     a. Presents insidiously with low-grade fever, malaise, weight loss, cough, sometimes with blood-streaked sputum or frank hemoptysis.
     b. Most patients with cavitary lesions present with associated COPD or chronic bronchitis, masking underlying fungal disease.
     c. Tends to worsen preexisting pulmonary disease and further contribute to eventual respiratory insufficiency.
  3. PDH
     a. In both acute and subacute forms, constitutional symptoms of fever, fatigue, malaise, and weight loss are common.
     b. Acute form (seen in infants and children) presents with respiratory symptoms, fever ≥101° F (38.3° C), generalized lymphadenopathy, marked hepatosplenomegaly, and fulminant course resembling septic shock associated with a high fatality rate.
     c. Subacute form is more common in adults and associated with lower temperatures, hepatosplenomegaly, oropharyngeal ulceration, focal organ involvement (including adrenal destruction, endocarditis, chronic meningitis, and intracerebral mass lesions).
     d. Course of subacute form is relentless, with untreated patients dying within 2 yr.
     e. Chronic PDH is found in adults and marked by gradual symptoms of weight loss, weakness, easy fatigability; low-grade fever when present; oropharyngeal ulcerations and hepatomegaly and/or splenomegaly in one third of patients.
     f. Less clinical evidence of focal organ involvement in chronic form than in subacute form.
     g. Natural history of chronic form is protracted and intermittent, spanning months to years.
- Histoplasmoma
  1. A healed area of caseation necrosis surrounded by a fibrous capsule
  2. Usually asymptomatic
- Mediastinal fibrosis
  1. A rare consequence of a fibroblastic process that encases caseating mediastinal lymph nodes producing severe retraction, compression, and distortion of mediastinal structures
  2. Constriction of the bronchi resulting in bronchiectasis, also esophageal stenosis associated with dysphagia, and superior vena cava syndrome
- POHS
  1. Diagnosis characterized by distinct clinical features, including atrophic choroidal scars and maculopathy in patients with histories suggestive of exposure to the fungus (e.g., residence in an endemic area)
  2. Patient complains of distortion or loss of central vision without pain, redness, or photophobia
  3. Usually no evidence of infection except for a positive skin reaction to histoplasmin
- In patients with AIDS
  1. Possible presentation as overwhelming infection similar to acute PDH seen in children
  2. Constitutional symptoms: fever, weight loss, malaise, cough, dyspnea
  3. About 10% with cutaneous maculopapular, erythematous eruptions or purpuric lesions on face, trunk, and extremities
  4. Up to 20% with CNS involvement, manifesting as intracerebral mass lesions, chronic meningitis, or encephalopathy

ETIOLOGY

- *H. capsulatum* is a dimorphic fungus present in temperate zones and river valleys worldwide.
- In the U.S., it is highly endemic in southeastern, mid-Atlantic, and central states.
- Exists as mold at ambient temperature and favors soils enriched with bird or bat droppings.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute pulmonary histoplasmosis
  1. *Mycobacterium tuberculosis*
  2. Community-acquired pneumonias caused by *Mycoplasma* and *Chlamydia*
  3. Other fungal diseases, such as *Blastomyces dermatitidis* and *Coccidioides immitis*
- Chronic cavitary pulmonary histoplasmosis: *M. tuberculosis*
- Histoplasmomas: true neoplasms

WORKUP

- Suspect diagnosis in patients who present with a history of residence or travel in an endemic

area, especially if engaged in occupations (e.g., outside construction or street cleaning) or hobbies (e.g., cave exploring) that increase the likelihood of exposure to fungal spores.
- Suspect diagnosis in immunosuppressed patients with remote history of exposure, especially if associated with characteristic calcifications on chest x-ray.

LABORATORY TESTS

- Demonstration of organism on culture from body fluid or tissues biopsy (Fig. EH1-54) to make definitive diagnosis
  1. Especially high yield in patients with AIDS
  2. Characteristic oval yeast cells in neutrophils with Giemsa stain from peripheral smear
  3. Preparations of infected tissue with Gomori's silver methenamine for revealing yeast forms, especially in areas of caseation necrosis
- Serologic tests, including complement-fixing (CF) antibodies and immunodiffusion assays
- Detection of *Histoplasma* antigen in urine: may be influenced by infections with *Blastomyces* and *Coccidioides*
- In PDH
  1. Pancytopenia
  2. Marked elevations in alkaline phosphatase and alanine aminotransferase (ALT) common
- In chronic meningitis (majority of cases)
  1. CSF pleocytosis with either lymphocytes or neutrophils predominating
  2. Elevated CSF protein levels
  3. Hypoglycorrhachia

IMAGING STUDIES

- Chest radiograph examination in acute pulmonary histoplasmosis
  1. Singular or multiple patchy infiltrates, especially in the lower lung fields
  2. Hilar or mediastinal lymphadenopathy with or without pneumonitis
  3. Diffuse nodular or confluent bilateral miliary infiltrates characteristic of heavier exposure
  4. Infrequent pleural effusions, except when associated with pericarditis
- Chest radiograph examination in histoplasmoma: coin lesion displaying central calcification, ranging from 1 to 4 cm in diameter, predominantly located in the subpleural regions
- Chest radiograph examination in CPH (Fig. EH1-55):
  1. Upper lobe disease frequently associated with cavities
  2. Preexisting calcifications in the hilum associated with peribronchial streaking extending to the parenchyma
- Chest radiograph examination in acute PDH: hilar adenopathy and/or diffuse nodular infiltrates
- CT scan of adrenals to reveal bilateral enlargement and low-attenuation centers

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

For life-threatening disease seen in acute disseminated disease or infection in patients with AIDS: supportive therapy with IV fluids

ACUTE GENERAL Rx

- No drug therapy is required for asymptomatic pulmonary disease.
- A course of therapy with itraconazole 200 mg PO tid for 3 days, then 200 mg/day PO for 6-12 wk may be beneficial in some patients with acute pulmonary distress. Avoid fluconazole because it is not as active.
- Same therapy appropriate for immunocompetent, mild to moderately symptomatic patients with CPH and subacute and chronic forms of PDH, but duration for 6 to 12 mo.
- Use amphotericin B 0.7 to 1 mg/kg IV q day for initial therapy in moderate to severe disease and then transition to oral itraconazole within 1-2 wk. Lipid formulations of amphotericin can be used to avoid nephrotoxicity of amphotericin B.
- (Liposomal amphotericin: 3mg/kg/day IV or amphotericin B lipid complex: 5 mg/kg/day)
- Posaconazole and voriconazole are highly effective as well, but echinocandins such as micafungin are not effective.
- Chronic cavitary pulmonary histoplasmosis: itraconazole 200 mg PO tid for 3 days, then once or twice daily for at least 12 mo.
- CNS histoplasmosis: liposomal amphotericin B, 5 mg/kg/day for a total of 175 mg/kg over 4-6 wk, then itraconazole 200 mg 2-3×/day for at least 12 mo.
- Endocarditis: surgical treatment with excision of infected valve or graft combined with amphotericin for a total dose of 35 mg/kg or 2.5 g.
- For pericardial disease:
  1. Antifungal therapy: no apparent benefit
  2. Best managed with NSAIDs
- For POHS:
  1. Antifungal therapy: no apparent benefit
  2. May respond to laser therapy

CHRONIC Rx

- In patients with AIDS: lifelong suppressive therapy with either itraconazole, given 200 mg PO q day, or IV amphotericin B at a dose of 50 mg once weekly; a triazole compound posaconazole (400 mg PO bid) may be useful in refractory cases, but clinical experience is limited at this point.
- Prophylaxis in HIV-infected patients with <150 CD4 cells/mm^3: itraconazole 200 mg PO qd

DISPOSITION

For those with chronic or progressive disease, especially if immunocompromised, prognosis is dependent on prompt recognition and timely administration of appropriate antifungal drugs.

REFERRAL

- To an infectious disease specialist in suspected cases of disseminated disease, especially if immunocompromised
- To a pulmonologist for patients with CPH form because of progressive respiratory compromise
- To a thoracic surgeon for decompression procedures for progressive mediastinal fibrosis

PEARLS & CONSIDERATIONS

- *H. capsulatum,* variety *duboisii,* also known as African histoplasmosis, is restricted to Senegal, Nigeria, Zaire, and Uganda.
- Unlike *H. capsulatum,* pulmonary forms of *duboisii* are not seen, and the disease is limited to the skin, soft tissues, and bone.

COMMENTS

- Patients living in endemic areas, especially if immunocompromised, should take appropriate respiratory precautions when disposing of bird waste from rooftop or home aviaries.
- Appropriate respiratory precautions should also be taken when leisure traveling to areas that act as a natural haven for the fungus, such as bat caves.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Histoplasmosis (Patient Information)

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SUGGESTED READINGS

Kauffman CA: Histoplasmosis, *Clin Chest Med* 30(2):217–230, 2009.
McKinsey DS, Mckinsey JP: Pulmonary Histoplasmosis, *Semin Respir Crit Care Med* 32(6):735–744, 2011.
Schestatsky P et al.: Isolated central nervous system histoplasmosis in immunocompetent hosts: a series of 11 cases, *Scand J Infect Dis* 38(1):43, 2006.
Weinberg M et al.: Severe histoplasmosis in travelers to Nicaragua, *Emerg Infect Dis* 9(10):1322, 2003.
Wheat LJ, Kauffman CA: Histoplasmosis. *Infect Dis Clin North Am* 17(1):1, 2003.

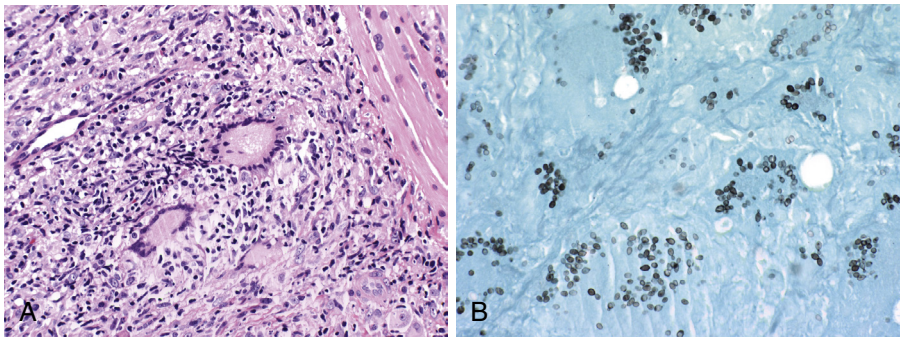


FIGURE EH1-54 A, Photomicrograph shows a tissue biopsy specimen from a patient with slowly progressing disseminated histoplasmosis. Granulomas are well formed, and no organisms are seen. (Hematoxylin and eosin stain ×450.) **B,** Special stains better demonstrate yeast in tissue sections. (Silver methenamine stain; ×450.) (From Mason, RJ: *Murray & Nadel's textbook of respiratory medicine*, 5th ed, Philadelphia, 2010, Saunders.)

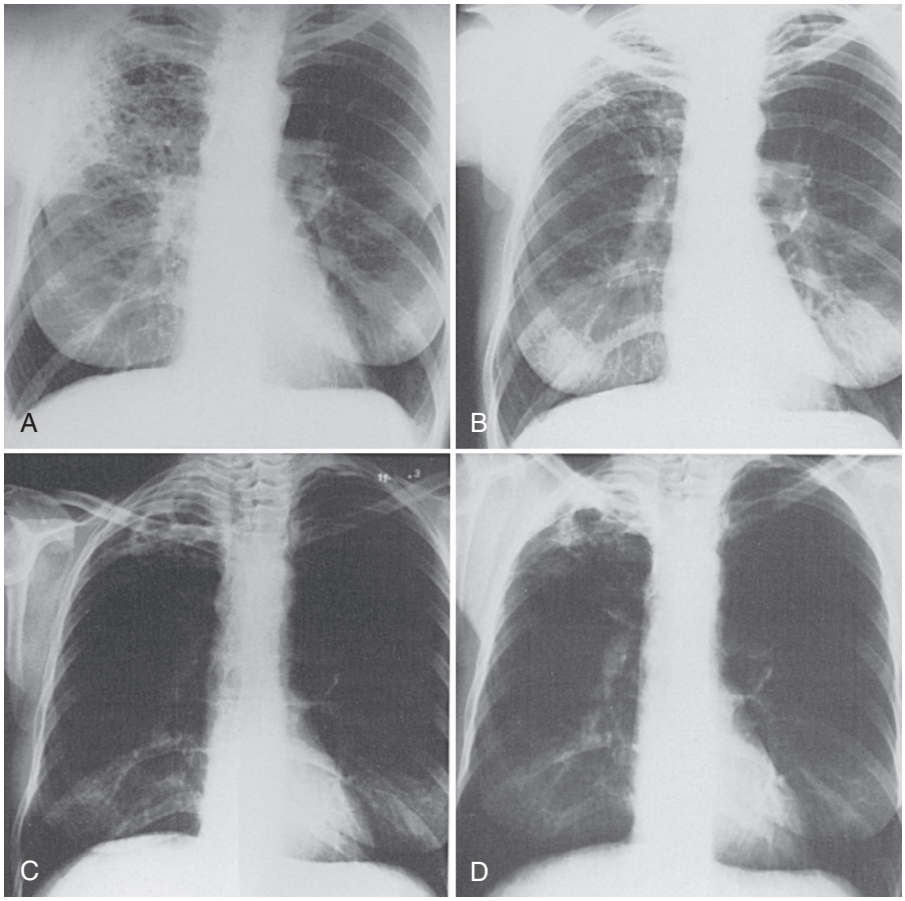


FIGURE EH1-55 The evolution of chronic pulmonary histoplasmosis in a smoker. A, At the onset of the illness, the chest radiograph shows multiple cavity-like air spaces. **B,** Two and one-half years later, fibrosis has occurred with volume loss of the lobe and retraction of the hilum. **C,** A further 17 months later, the entire right upper lobe appears destroyed. **D,** There are signs of continued activity and a residual cavity at the time of diagnosis. The sputum culture was positive for *Histoplasma capsulatum*. (From Mason, RJ: *Murray & Nadel's textbook of respiratory medicine*, 5th ed, Philadelphia, 2010, Saunders.)

BASIC INFORMATION

DEFINITION

Patients with histrionic personality disorder present with a pervasive pattern of excessive emotionality and attention-seeking behavior that generally begins in early adulthood.

SYNONYMS

Hysterical personality disorder
Psycho-infantile personality disorder
Personality disorder (nonspecific)
Personality disorder (trait specified)

ICD-9CM and DSM-5 CODES
301.50 Histrionic personality disorder, unspecified
ICD-10CM CODES
F60.4 Histrionic personality disorder

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE (IN U.S.):

- Diagnosed more often in women (85%); rarely found in men.
- Prevalence: 1% to 3%.

PREDOMINANT SEX: Female. Cultural factors (e.g., attention-seeking behavior not as acceptable in men) may lead to more common diagnosis in women.

PREDOMINANT AGE: Generally begins in early adulthood.

GENETICS: Limited research using interview and self-report methods suggests histrionic personality disorder has a moderate genetic component.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Features include five or more of the following:

1. Is uncomfortable in situations where he or she is not the center of attention.
2. Interaction with others is often characterized by inappropriate sexually seductive or provocative behavior.
3. Displays rapidly shifting and shallow expression of emotions.
4. Consistently uses physical appearance to draw attention to self.
5. Has a style of speech that is excessively impressionistic and lacking in detail.
6. Shows self-dramatization, theatricality, and exaggerated expression of emotion.
7. Is suggestible (i.e., easily influenced by others or circumstances).
8. Considers relationships to be more intimate than they actually are.

ETIOLOGY

- Unknown.
- Hypothesized that childhood events, psychosocial adversity, and genetics are contributory.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Narcissistic and borderline personality disorders share common features.
- Other personality disorders (e.g., antisocial personality disorder, dependent personality disorder)
- Personality change attributable to general medical condition.
- Symptoms in association with chronic substance abuse.

WORKUP

There is no formal test to establish diagnosis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Long-term individual psychotherapy is treatment of choice.
- No controlled psychotherapy studies.
- Unlike other people who have personality disorders, these individuals often seek treatment and exaggerate their symptoms and difficulties in functioning.
- Patients tend to be more emotionally needy and are often reluctant to terminate therapy.

ACUTE GENERAL Rx

- No placebo-controlled trials.
- Care should be given when prescribing medications because of the potential for self-destructive or otherwise harmful behaviors.

DISPOSITION

- Therapeutic approaches should not focus on the long-term personality change, but rather short-term alleviation of specific difficulties and deficits within the person's life.
- Therapeutic approaches that emphasize vague somatic, anxious, or depressive symptoms often fail.
- Patients are likely to be intolerant or drop out of treatment approaches that use delayed gratification.
- Symptoms are moderately stable over adulthood and may remit or decrease in intensity with age.

REFERRAL

Primarily treated by mental health professionals.

PEARLS & CONSIDERATIONS

- This disorder is difficult to treat.
- Like most personality disorders, patients present for treatment only when stress or other situational factors within their lives have made their ability to function and cope effectively impossible.
- Suicidality should be assessed on a regular basis, and suicidal threats and self-mutilation should not be ignored or dismissed.
- An alternative model in DSM-5 section III reconceptualizes histrionic personality disorder as "Personality Disorder, Trait Specified," which rates: (1) impairment in personality functioning (identity, self-direction, empathy, and/or intimacy) and (2) pathologic trait domains such as attention seeking, grandiosity, and manipulativeness.

PATIENT & FAMILY EDUCATION

Group and family therapy approaches are generally not recommended because individuals with this disorder often try to draw attention to themselves and exaggerate every action and reaction.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **MARK ZIMMERMAN, M.D.**, and **THERESA A. MORGAN, PH.D., M.PHIL.**

SUGGESTED READINGS

Gabbard GO: Mind, brain and personality disorders, *Am J Psychiatry* 162:4, 2005.

Kraus G, Reynolds DJ: The "a-b-c's" of the cluster b's: identifying, understanding, and treating cluster b personality disorders, *Clin Psychol Rev* 21(3):345, 2001.

Torgersen S et al.: The heritability of cluster B personality disorders assessed both by personal interview and questionnaire, *J Pers Disord* 17:848–866, 2012.

Verheul R, Herbrink M: The efficacy of various modalities of psychotherapy for personality disorders: a systematic review of the evidence and clinical recommendations, *Int Rev Psychiatry* 19(1):25, 2007.

HIV Cognitive Dysfunction

BASIC INFORMATION

- HIV cognitive dysfunction covers a spectrum of disorders ranging from asymptomatic to clinically severe (including AIDS dementia complex or HIV encephalopathy).
- Cognitive, motor, and behavioral abnormalities

SYNONYMS

HIV-associated neurocognitive disorder

ICD-9CM CODES

042 (for diseases related to HIV; no particular code for HIV cognitive dysfunction)

ICD-10CM CODES

B20 Human immunodeficiency virus [HIV] disease

R41.8 Other and unspecified symptoms and signs involving cognitive functions and awareness

EPIDEMIOLOGY

- Presenting complaint in only 3% of cases
- Incidence: reduced from 60% to 1% since introduction of HIV treatment; however, as more HIV-infected patients live longer, prevalence may be increasing.
- Minor cognitive disorders are more common and seen in 20% of patients; not necessarily progressive
- Rarely precedes clinical evidence of HIV infection

CLINICAL FEATURES

- Cognitive changes: forgetfulness, poor attention and concentration, increased difficulty performing complex tasks, slowed psychomotor speed
- Behavioral changes: apathy, lack of initiative, social withdrawal, irritability, occasionally agitation, psychosis or obsessive compulsive disorder
- Motor problems: clumsiness, unsteady gait, poor balance, tremor, leg weakness
- Progressive/later stages: bedbound, severe dementia, bowel/bladder incontinence
- Subcortical dementia (aphasia, apraxia, and agnosia) is uncommon
- Results from inflammation triggered by HIV itself (not related to opportunistic infection) and immune activation of microglia and brain macrophages
- Clinically may resemble Parkinson's disease
- In children: developmental delay, microcephaly, and spasticity are common

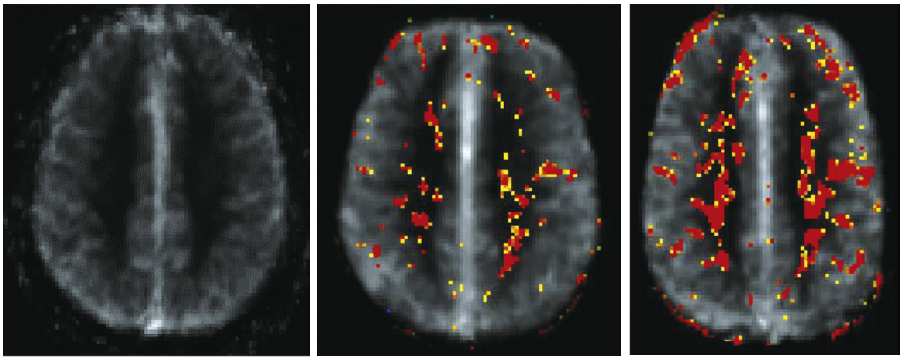
RISK FACTORS

- Low CD4 count (less than 200 cells/mm^3)
- High viral load
- Anemia
- Injection drug use
- Hepatitis C
- Female gender
- Older age

DIAGNOSIS

DIAGNOSTIC EVALUATION

- Diagnosis is based on clinical examination and neuropsychometric tests
- MRI head (Fig. H1-56): diffuse, confluent, periventricular white matter lesions on T2 weighted images with normal T1 images
- Lumbar puncture: CSF analysis helps to rule out opportunistic infections. In HIV-related cognitive dysfunction the CSF may show a nonspecific increase in cell count and protein.
- Potential causes for cognitive impairment that must be ruled out include:
  1. Opportunistic infections (toxoplasmosis, CNS lymphoma)
  2. Vitamin B_{12} deficiency
  3. Substance use
  4. Organic affective disorder (such as depression and mania)
  5. Side effects of prescribed medications



Asymptomatic MCMD HAD

FIGURE H1-56 Perfusion MRI (pMRI) maps showing regions of increasing cerebral blood volume (CBV) with advancing HIV groups: asymptomatic, minor cognitive–motor disorder (MCMD), and HIV-associated dementia (HAD). Areas of red indicate >2 standard deviations elevation in CBV. (Tucker KA et al: Neuroimaging in human immunodeficiency virus infection. *J Neuroimmunol* 157(1–2): 153–162, 2004.)

TREATMENT

Early treatment with antiretroviral therapy (ART) leads to clinical improvement.

PEARLS & CONSIDERATIONS

- Initiation of ART can lead to rapid improvement in cognitive function in early stages (untreated, life span is typically 4 to 6 mo)
- Most common presenting complaint in children infected with HIV
- Mini-mental status examination (MMSE): baseline scores in HIV patients are very helpful
- Usually cognitive symptoms precede motor abnormalities
- Four HIV-related opportunistic infections that commonly cause cognitive impairment are: toxoplasmosis, cryptococcal meningitis, progressive multifocal leukoencephalopathy, and CNS lymphoma

REFERRALS

- Upon diagnosis/clinical suspicion for HIV-associated cognitive dysfunction, referral to neurology is recommended
- Referral to neuropsychology may be considered

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **DIVYA SINGHAL, M.D.**

SUGGESTED READINGS

In Hauser S, Josephson S, editors: Harrison's neurology in clinical medicine. ed 2 McGraw-Hill: Columbus, OH.

Price R: Neurological complications of HIV infection, *Lancet* 348:445–452, 1996.

Ziefert P, Leary M, Boccellari A: AIDS and the impact of cognitive impairment, *UCSF AIDS Health Project*, 1995.

BASIC INFORMATION

DEFINITION

Hodgkin's lymphoma is a malignant disorder of lymphoreticular origin, characterized histologically by the presence of multinucleated giant cells (Reed-Sternberg cells) usually originating from B lymphocytes in germinal centers of lymphoid tissue.

ICD-9CM CODES

201.9 Hodgkin's lymphoma, unspecified
201.0 Hodgkin's paragranuloma
201.4 Hodgkin's lymphoma, lymphocyte predominance
201.5 Hodgkin's lymphoma, nodular sclerosis
201.6 Hodgkin's lymphoma, mixed cellularity
201.6 Hodgkin's lymphoma, mixed cellularity
201.7 Hodgkin's lymphoma, lymphocyte depletion

ICD-10CM CODES

C81.90 Hodgkin lymphoma, unspecified, unspecified site
C81.00 Nodular lymphocyte predominant Hodgkin lymphoma, unspecified site
C81.10 Nodular sclerosis classical Hodgkin lymphoma, unspecified site
C81.20 Mixed cellularity classical Hodgkin lymphoma, unspecified site
C81.30 Lymphocyte depleted classical Hodgkin lymphoma, unspecified site

EPIDEMIOLOGY & DEMOGRAPHICS

- There is a bimodal age distribution (15 to 34 yr and >50 yr).
- Incidence is 4 in 100,000 cases.
- Concordance for Hodgkin's lymphoma in identical twins suggests that a genetic susceptibility underlies Hodgkin's lymphoma in young adulthood.
- There is association between certain HLA haplotypes, especially HLA-A1.
- The disease is more common in males (in childhood Hodgkin's lymphoma, >80% occur in males), whites, and higher socioeconomic groups.
- More common in people living in moderate climates.
- There are >8000 new cases of Hodgkin's lymphoma diagnosed annually in the United States.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Painless palpable lymphadenopathy is the most common presenting symptom.
- Most common site of involvement: neck region.
- Fever and night sweats: fever in a cyclical pattern (days or weeks of fever alternating with afebrile periods) is known as Pel-Epstein fever.
- Unexplained weight loss, generalized malaise.
- Persistent, nonproductive cough.
- Pain associated with alcohol ingestion often because of heavy eosinophil infiltration of the tumor sites is relatively uncommon.
- Generalized pruritus.
- Hepatosplenomegaly in disease below the diaphragm.
- Other: superior vena cava syndrome, spinal cord compression (rare), erythema nodosum, ichthyosis.

ETIOLOGY

Unknown; evidence implicating Epstein-Barr virus remains controversial.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Non-Hodgkin's lymphoma.
- Sarcoidosis.
- Infections (e.g., cytomegalovirus, Epstein-Barr virus, toxoplasmosis, HIV, tuberculosis).
- Drug reaction.

WORKUP

Diagnosis is confirmed by lymph node biopsy. The World Health Organization classifies Hodgkin's lymphoma into two groups: classic Hodgkin's lymphoma (92% to 97%) and nodular lymphocyte-predominant Hodgkin's lymphoma (3% to 8%). Classic Hodgkin's lymphoma has four main histologic subtypes based on the number of lymphocytes, Reed-Sternberg cells, and the presence of fibrous tissue:

1. Nodular sclerosis (60% to 80%) (Fig. EH1-57).
2. Mixed cellularity (15% to 30%) (Fig. EH1-58).
3. Lymphocyte predominance (2% to 7%).
4. Lymphocyte depletion (1% to 6%).

Nodular sclerosis occurs mainly in young adulthood, whereas the mixed cellularity type is more prevalent after age 50 yr.

Staging: Table H1-25 describes the Cotswolds staging classification.

Proper staging requires the following:

- Detailed history (with documentation of "B symptoms" and physical examination).
- Excisional biopsy with histologic, immunophenotypic and immunohistochemical analysis.
- Laboratory evaluation (complete blood count, erythrocyte sedimentation rate, blood urea nitrogen, creatinine, alkaline phosphatase, liver function tests, albumin, lactate dehydrogenase, HIV tests, uric acid), immunophenotypic markers (see Table H1-26). Gene-expression profiling for tumor-associated macrophages is a new biomarker for risk stratification.
- Chest x-ray (posteroanterior and lateral).
- CT scan of chest, abdomen, pelvis, neck.
- Positron emission tomography scan (18-FDG PET scan).
- Bilateral bone marrow biopsy (selected patients).

Box H1-8 summarizes recommended staging procedures for Hodgkin lymphoma.

TREATMENT

ACUTE GENERAL Rx

The main therapeutic modalities are radiotherapy and chemotherapy; the indication for which one varies with pathologic stage and other factors. In general, chemotherapy plus involved-field radiotherapy can be used as standard treatment for Hodgkin's lymphoma in early stages with favorable prognostic features. In patients with unfavorable features, 4 courses of chemotherapy plus involved-field radiotherapy should be the standard treatment. Commonly used therapeutic modalities are:

- Stage I and II: radiation therapy alone (involved-field radiotherapy [35 Gy]) unless a large mediastinal mass is present (mediastinal to thoracic ratio ≥1.3); in the latter case, a combination of chemotherapy and radiation

TABLE H1-25 Cotswolds Staging Classification for Hodgkin's Lymphoma

Classification	Description
Stage I	Involvement of a single lymph node region or lymphoid structure (e.g., spleen, thymus, Waldeyer ring) or involvement of a single extralymphatic site (IE)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (hilar nodes, when involved on both sides, constitute stage II disease); localized contiguous involvement of only one extranodal organ or site and lymph node regions on the same side of the diaphragm (IIE). The number of anatomic regions involved should be indicated by a subscript (e.g., II_3)
III_1	With or without involvement of splenic, hilar, celiac, or portal nodes
III_2	With involvement of paraaortic, iliac, and mesenteric nodes
Stage IV	Diffuse or disseminated involvement of one or more extranodal organs or tissues, with or without associated lymph node involvement
	Designations applicable to any disease stage
A	No symptoms
B	Fever (temperature, >38° C [100.4° F]), drenching night sweats, unexplained loss of >10% of body weight within the preceding 6 mo
X	Bulky disease (a widening of the mediastinum by more than one third of the presence of a nodal mass with a maximal dimension <10 cm)
E	Involvement of a single extranodal site that is contiguous or proximal to the known nodal site

From Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

TABLE H1-26 Selected Immunophenotypic Markers and Histologic Characteristics of Use in the Differential Diagnosis of Hodgkin's Lymphoma and Other Lymphoid Neoplasms

Marker	Classical HL	Nodular Lymphocyte Predominant HL	TCRBCL	ALCL
CD30	+	–	–	+
CD15	+	–	–	–
CD20	–/+*	+	+	–
CD45	–	+	+	+/–
CD79a	–	+	+	–
ALK	–	–	–	+/–
EMA	–	+	+	+
Nodular growth protein	+/–†	+	–	–

+, >90% of cases positive; +/–, majority of cases positive; –/+, minority of cases positive; –, <10% of cases positive; *ALCL,* anaplastic large cell lymphoma; *HL,* Hodgkin's lymphoma; *TCRBCL,* T-cell rich B-cell lymphoma.
*CD20 positivity in classical Hodgkin's lymphoma is quite heterogeneous, with a wide range in brightness of staining.
†In classical Hodgkin's lymphoma, a nodular growth pattern is confined to the nodular sclerosing subtype.
From Abeloff MD: *Clinical oncology*, ed 3, Philadelphia, 2004, Saunders.

TABLE H1-27 Characteristics of the ABVD Regimen

Agents: doxorubicin, bleomycin, vinblastine, dacarbazine
All intravenous, total compliance
80% complete response rate
10% primary refractory disease
60%-65% overall disease-free survival
Most relapses occur within the first 4 yr; however, about 10% of all relapses occur beyond 5 yr
Major side effects are nausea, phlebitis, myelosuppression, less cumulative myelotoxicity than MOPP
No infertility
No leukemia

ABVD, Adriamycin (doxorubicin), bleomycin, vinblastine, dacarbazine; *MOPP,* mechlorethamine, Oncovin (vincristine), procarbazine, prednisone.
From Abeloff MD: *Clinical oncology*, ed 3, Philadelphia, 2004, Saunders.

BOX H1-8 Recommended Staging Procedures for Hodgkin Lymphoma

The following staging procedures are recommended for the initial workup of Hodgkin lymphoma:
1. Adequate surgical biopsy reviewed by an experienced hematopathologist
2. Core-needle biopsy of bone marrow from the posterior iliac crest; needle or surgical biopsy of any suspicious extranodal (e.g., hepatic, osseous, pulmonary, cutaneous) lesions; and cytologic examination of any effusion
3. Detailed history, with attention to the presence or absence of systemic symptoms, and a careful physical examination, emphasizing node chains, size of the liver and spleen, and inspection of Waldeyer ring
4. Routine laboratory tests: complete blood cell count, erythrocyte sedimentation rate, and liver function tests
5. Chest radiographs (posteroanterior and lateral) with measurement of the mass-to-thoracic ratio
6. Neck, chest, and abdominal CT
7. 18-FDG PET scan (Fig. H1-59)

From Hoffman R.; et al. *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

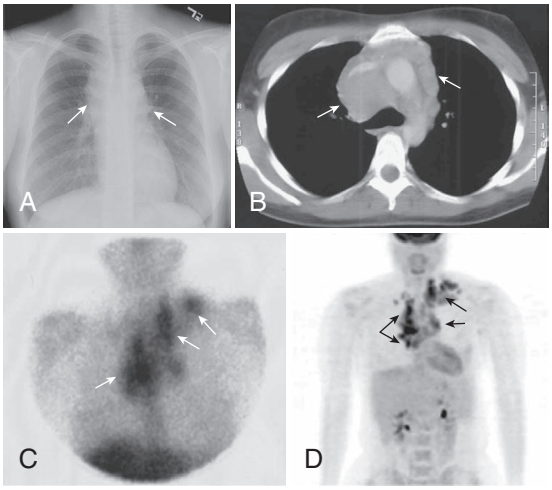


FIGURE H1-59 Imaging of Hodgkin's lymphoma. Bulky Hodgkin's disease as seen on chest radiograph (**A**), computed tomography (CT) of the chest (**B**), gallium scan (**C**), and positron emission tomography (PET) (**D**). The *arrows* indicate sites of disease. Note that the PET and CT scans provide more detailed information than the chest radiograph and gallium scan. (From Goldman L.; Schafer AI. *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

therapy is indicated. Various regimens can be used for combination of chemotherapy. Most oncologists prefer the combination of Adriamycin (doxorubicin), bleomycin, vinblastine, and dacarbazine (ABVD). Table H1-27 describes characteristics of the ABVD regimen. Generally, chemotherapy plus radiation treatment is effective in controlling stage IA or IIA nonbulky lymphoma in a high percentage of patients (>85%), but is associated with late treatment-related deaths. Trials have shown that ABVD therapy alone is associated with a higher rate of overall survival (due to lower rate of death from other causes) when compared with treatment that includes ABVD therapy and subtotal nodal radiation therapy.

- Stage IB or IIB: total nodal irradiation is often used, although chemotherapy is performed in many centers.
- Stage IIIA: treatment is controversial. It varies with the anatomic substage after splenectomy.
  1. III_1A and minimum splenic involvement: radiation therapy alone may be adequate.
  2. III_2 or III_1A with extensive splenic involvement: there is disagreement whether chemotherapy alone or a combination of chemotherapy and radiation therapy is the preferred treatment modality.
  3. IIIB and IVB: the treatment of choice is chemotherapy with or without adjuvant radiotherapy.

Recent trials have shown that in patients with early-stage Hodgkin's lymphoma and favorable prognosis, treatment with two cycles of ABVD followed by 20 Gy of involved-field radiation therapy may be as effective as, and less toxic than, four cycles of ABVD followed by 30 Gy of involved-field radiation therapy. Long-term effects of this approach need to be fully assessed before it becomes standard of care. BEACOPP, an intensified regimen consisting of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, has been advocated by some as the new standard for treatment of advanced Hodgkin's

TABLE H1-28 Definition of Treatment Groups According to the EORTC/GELA and GHSG

Treatment Group	EORTC/GELA	GHSG	NCIC/ECOG
Early-stage favorable	CS I-II without risk factors (supradiaphragmatic)	CS I-II without risk factors	Standard risk group: favorable CSD I-II (without risk factors)
Early-stage unfavorable (intermediate)	CS I-II with ≥1 risk factors (supradiaphragmatic)	CS I, CSIIA ≥1 risk factors; CS IIB with C/D but without A/B	Standard risk group: unfavorable CS I-II (at least one risk factor)
Advanced stage	CS III-IV	CS IIB with A/B;CS III-IV	High-risk group: CS I or II with bulky disease; intraabdominal disease; CS III, IV
Risk factors (RF)	A large mediastinal mass B age ≥50 yr C elevated ESR* D ≥4 involved regions	A large mediastinal mass B extranodal disease C elevated ESR* D ≥3 involved areas	A ≥40 years B not NLPHL or NS histology C ESR ≥50 mm/h D ≥4 involved nodal regions

CS, Clinical stage; *ECOG,* Eastern Cooperative Oncology Group; *EORTC,* European Organization for Research and Treatment of Cancer; *GELA,* Groupe d'Etude des Lymphomes de l'Adulte; *GHSG,* German Hodgkin Study Group; *NCIC,* National Cancer Institute of Canada.
*Erythrocyte sedimentation rate (≥50 mm/h without or ≥30 mm/h with B-symptoms).
From Hoffman R et al: *Hematology, basic principles and practice*, ed 5, New York, 2009, Churchill Livingstone.

TABLE H1-29 Recommendations for the Primary Treatment of Hodgkin's Lymphoma Outside of Clinical Trials

Group	Stage	Recommendation
Early stages (favorable)	CS I-II A/B, no RFs	2 cycles ABVD; 6 cycles EBVP; *or* VBM ± IF RT (20-30 Gy)
	Early stages (unfavorable, intermediate)	4-6 cycles ABVD; BEACOPP-baseline, Stanford V; *or* MOPP/ABV ± IF RT, 20-30Gy
	CS I-II A/B + RFs	
Advanced stages	CS IIB + RFs, CS III A/B, CS IV A/B	6-8 cycles ABVD; MOPP/ABV; ChlVPP/EVA; BEACOPP-escalated *or* BEACOPP-14 ± RT, 20-30 Gy for residual tumor (PET positive) and/or bulk disease

ABVD regimen, Adriamycin (doxorubicin), vinblastine, bleomycin, and dacarbazine; *BEACOPP-baseline* regimen, bleomycin, etoposide, Adriamycin (doxorubicin), cyclophosphamide, Oncovin (vincristine), procarbazine, and prednisone; *BEACOPP-escalated* regimen, bleomycin, etoposide, Adriamycin (doxorubicin), cyclophosphamide, Oncovin (vincristine), procarbazine, prednisone, and G-CSF; *BEACOPP-14* regimen, bleomycin, etoposide, Adriamycin (doxorubicin), cyclophosphamide, Oncovin (vincristine), procarbazine, prednisone, and G-CSF; *ChlVPP/EVA* regimen, chlorambucil, vinblastine, procarbazine, prednisolone, etoposide, vincristine, Adriamycin (doxorubicin); *CS,* clinical stage; *EBVP* regimen, epirubicin, bleomycin, vinblastine, and prednisone; *IF,* involved field; *MOPP* regimen, mechlorethamine, Oncovin (vincristine), procarbazine, and prednisone; *PET,* positron emission tomography; *RF,* risk factors; *RT,* radiation therapy; *Stanford V* regimen, nitrogen mustard, doxorubicin, vinblastine, bleomycin, vincristine, etoposide, and prednisone; *VBM* regimen, vinblastine, bleomycin, and methotrexate.
From Hoffman R et al: *Hematology, basic principles and practice*, ed 5, New York, 2009, Churchill Livingstone.

TABLE H1-30 Prognostic Factors of Importance in Advanced Hodgkin's Lymphoma*

Gender	Male
Age	>45 yr
Stage	IV
Hemoglobin	<105 g/L
White blood cell count	$>15 \times 10^9$/L
Lymphocyte count	$<0.6 \times 10^9$/L or <8% of the white cell differential
Serum albumin	<40 g/L

*Identified by the International Prognostic Factors Project on Advanced Hodgkin's Disease.
From Abeloff MD: *Clinical oncology*, ed 3, Philadelphia, 2004, Saunders.

lymphoma in place of ABVD. Recent trials have shown that treatment with BEACOPP, as compared with ABVD, resulted in better initial tumor control, but the long-term clinical outcome did not differ significantly between the two regimens. In addition, with the use of the escalated BEACOPP regimen, the rate of complications is higher (3% treatment-related death, 20% rate of hospitalization, and 3% rate of secondary leukemia). Thus, if the goal is cure with the least overall toxic effects, especially in elderly population, it is best to favor ABVD therapy, reserving rescue therapy with high-dose chemotherapy and autologous hematopoietic stem-cell transplantation for patients in whom the primary treatment fails. Stanford V (vinblastine, doxorubicin, mechlorethamine, bleomycin, etoposide, vincristine, and prednisone) may be preferred in some cases due to its short administration schedule combining radiation.

- Definitions of treatment groups are described in Table H1-28.
- Recommendations for the primary treatment of Hodgkin's lymphoma outside of clinical trials are described in Table H1-29.

DISPOSITION

- The overall survival at 10 yr is ~60%.
- Cure rates as high as 75% to 80% are now possible with appropriate initial therapy.
- Polyvalent pneumococcal vaccine and other vaccines should be administered especially in patients undergoing splenectomy.
- Poor prognostic features (Table H1-30) include presence of B symptoms, advanced age, advanced stage at initial presentation, mixed cellularity and lymphocyte depletion histology, and increased number of tumor-associated macrophages.
- Chemotherapy significantly increases the risk of leukemia.
- The peak in risk of leukemia is seen approximately 5 yr after the initiation of chemotherapy.
- The risk of leukemia is greater for those who undergo splenectomy and patients with advanced stages of Hodgkin's disease; the risk is unaffected by concomitant radiotherapy.
- Involved-field radiotherapy does not improve the outcome in patients with advanced-stage Hodgkin's lymphoma who have a complete remission after MOPP (mechlorethamine, vincristine, procarbazine, and prednisone)–ABV chemotherapy. Radiotherapy may benefit patients with a partial response after chemotherapy.
- Mediastinal irradiation increases the risk of subsequent death from heart disease caused by sclerosis of the coronary artery from irradiation. Risk increases with high mediastinal doses, minimal protective cardiac blocking, young age at irradiation, and increased duration of follow-up.
- Both chemotherapy and radiation therapy increase the risk of developing secondary solid tumors (Table H1-31).
- Table H1-32 describes potential late complications of Hodgkin's lymphoma treatment and appropriate clinical responses and preventive strategies.

REFERRAL

- To surgery for lymph node biopsy.
- Hematology/oncology.

TABLE H1-31 Second Neoplasms Seen with Increased Frequency After Successful Hodgkin's Lymphoma Treatment

Acute myelogenous leukemia/myelodysplasia
Non-Hodgkin's lymphoma
Melanoma
Soft tissue sarcoma
Adenocarcinoma
Breast
Thyroid
Lung
Stomach and esophagus
Squamous cell carcinoma
Skin
Uterine cervix
Head and neck

From Abeloff MD: *Clinical oncology*, ed 3, Philadelphia, 2004, Saunders.

PEARLS & CONSIDERATIONS

COMMENTS

- Young male patients should consider sperm banking before the initiation of therapy.
- Chemotherapy plus involved-field radiotherapy should be the standard treatment for Hodgkin's disease with favorable prognostic features. In patients with unfavorable features, 4 courses of chemotherapy plus involved-field radiotherapy should be the standard of treatment. After failure of ABVD therapy, more than 60% of patients who have had a relapse and about 30% of patients with initially refractory lymphoma can be reliably cured with high-dose chemotherapy and autologous hematopoietic stem-cell transplantation.
- Preclinical studies suggest that Reed-Sternberg cells exploit the programmed death 1 (PD-1) pathway to evade immune detection. Phase 1 trials with nivolumab, a PD-1 blocking antibody, have shown substantial therapeutic activity and an acceptable safety profile in patients with previously treated relapsed or refractory Hodgkin's lymphoma.[1]

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hodgkin's Lymphoma (Patient Information)

AUTHORS: **SYEDA M. SAYEED, M.D.**, and **FRED F. FERRI, M.D.**

TABLE H1-32 Potential Late Complications of Hodgkin's Lymphoma Treatment and Appropriate Clinical Responses and Preventive Strategies

Risk/Problem	Incidence/Response
Dental caries	Neck or oropharyngeal irradiation can cause decreased salivation. Patients should have careful dental care follow-up and should make their dentist aware of the previous irradiation.
Hypothyroidism	After external beam irradiation that encompasses the thyroid with doses sufficient to cure Hodgkin's lymphoma, at least 50% of patients will eventually become hypothyroid. All patients whose TSH level becomes elevated should be treated with lifelong thyroxine replacement in doses sufficient to suppress TSH levels to low normal. This is also necessary to ensure that the radiation-damaged thyroid is not subjected to long-term stimulation by thyroid-stimulating hormone, which can increase the risk of thyroid neoplasm.
Infertility	ABVD is not known to cause any permanent gonadal toxicity, although oligospermia for 1-2 yr after treatment is common. Direct or scatter radiation to gonadal tissue can cause infertility, amenorrhea, or premature menopause, but this seldom occurs with the current fields used for the treatment of Hodgkin's lymphoma. Thus, with the current chemotherapy regimens and radiation fields used, most patients will not develop these problems. In general, after treatment, women who continue menstruating are fertile, but men require semen analysis to provide a specific answer. High-dose chemoradiotherapy and hematopoietic stem cell transplantation almost always cause permanent infertility in both genders, although some young women occasionally recover fertility.
Impaired immunity to infections	Hodgkin's lymphoma and its treatment can lead to lifelong impairment of full immunity to infection. All patients should be given annual influenza immunization and pneumococcal immunization every 5 years. Patients whose spleen has been irradiated or removed should also be immunized against meningococcal types A and C and *Haemophilus influenza* type B. As for all adults, diphtheria and tetanus immunizations should be kept up-to-date.
Secondary neoplasms	Although uncommon, certain secondary neoplasms occur with increased frequency in patients who have been treated for Hodgkin's lymphoma. These include acute myelogenous leukemia, thyroid, breast, lung, and upper gastrointestinal carcinoma and melanoma, and cervical carcinoma in situ. It is appropriate to screen for these neoplasms for the rest of the patient's life because they might have lengthy induction periods.

ABVD, Adriamycin, bleomycin, vinblastine, dacarbazine; *TSH,* thyroid-stimulating hormone.
From Abeloff MD: *Clinical oncology*, ed 3, Philadelphia, 2004, Saunders.

[1]Ansell SM et al.: PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma, *N Engl J Med* 372:311-319, 2015.

SUGGESTED READINGS

Ansell S, Armitage JO: Management of Hodgkin lymphoma, *Mayo Clin Proc* 81(3):419, 2006.

Armitage JO: Early-stage Hodgkin's lymphoma, *N Engl J Med* 363:653–662, 2010.

Connors JM: Hodgkin's lymphoma, the great teacher, *N Engl J Med* 365:3, 2011.

Diehl V, Thomas RK, Re D et al.: Part II: Hodgkin's lymphoma—diagnosis and treatment, *Lancet Oncol* 5:19, 2004.

Engert A et al.: Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma, *N Engl J Med* 363:640–652, 2010.

Ferme C et al.: Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease, *N Engl J Med* 357:2007, 1916.

Glass C: Role of the primary care physician in Hodgkin lymphoma, *Am Fam Physician* 78(5):615, 2008.

Meyer RM et al.: ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma, *N Engl J Med* 366:399–408, 2012.

Steidl C et al.: Tumor-associated macrophages and survival in classic Hodgkin's lymphoma, *N Engl J Med* 382:875–885, 2010.

Viviani S et al.: ABVD versus BEACOPP for Hodgkin's lymphoma when high-dose salvage is planned, *N Engl J Med* 365:203–212, 2011.

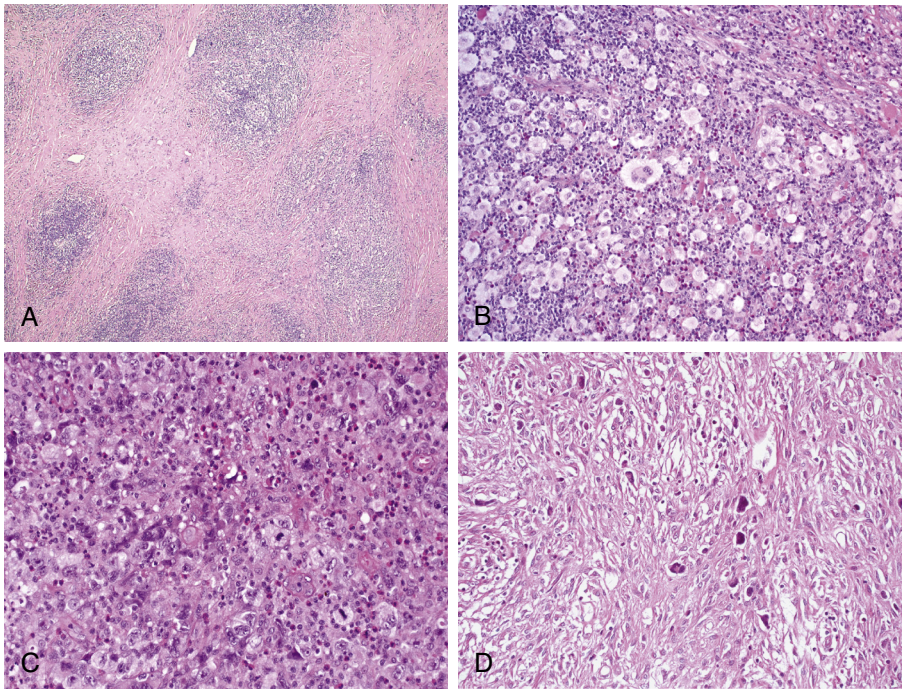


FIGURE EH1-57 Hodgkin's lymphoma. Morphology of classical Hodgkin's lymphoma (CHL). **A,** Nodular sclerosis CHL. Cellular nodules are separated by concentric bands of mature collagen. **B,** Close-up of cellular nodule shows numerous lacunar cells with clear cytoplasm intermingled with lymphocytes, neutrophils, and eosinophils. Note collagen bands rimming the nodule. **C,** Nodular sclerosis CHL grade II. Confluent sheets of neoplastic cells with partly anaplastic features intermingled with a minority of inflammatory cells. This morphology is consistent with the so-called syncytial variant of CHL. **D,** Lymphocyte-depleted CHL, diffuse fibrosis subtype. Neoplastic Reed-Sternberg and Hodgkin cells in a hypocellular background with histiocytes and fibroblasts. This case lacks nodularity and ordered collagen bands. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

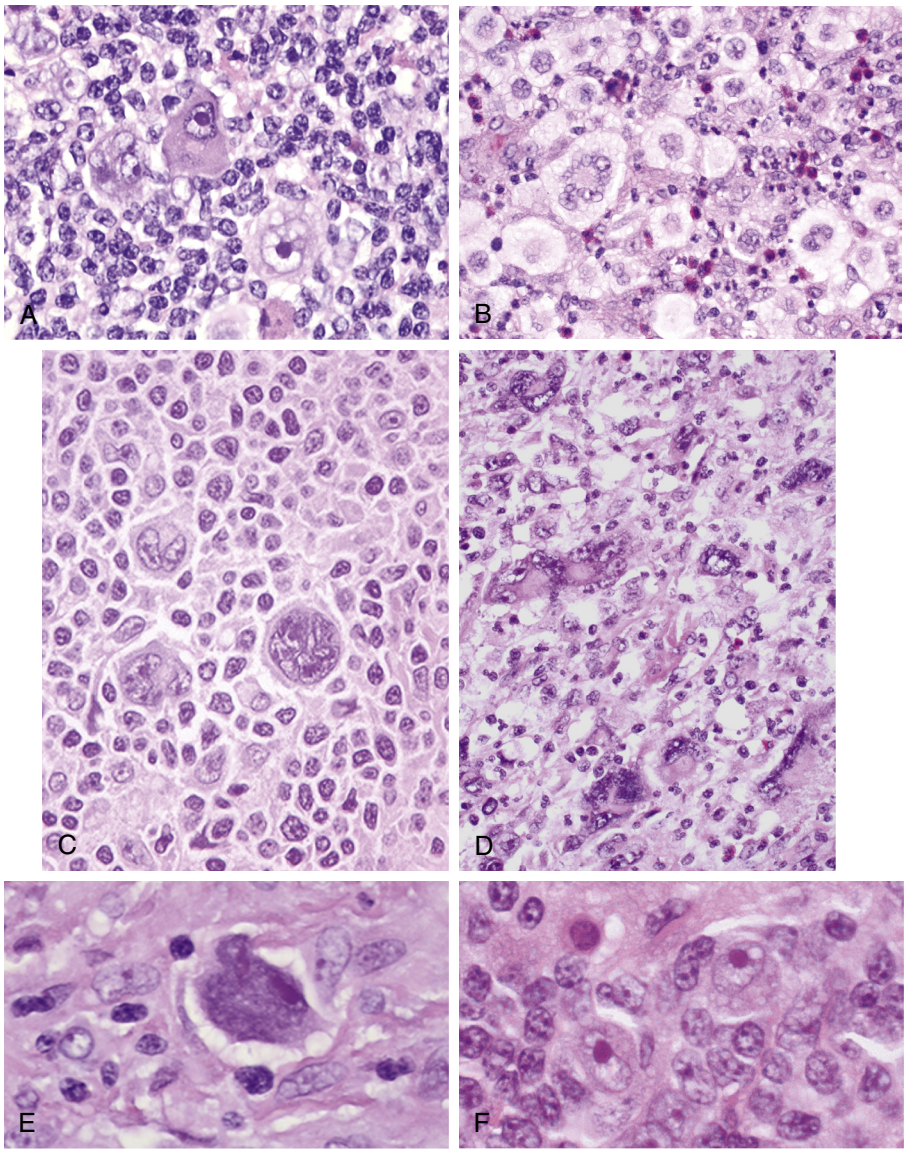


FIGURE EH1-58 Hodgkin's lymphoma. Cytologic features of Reed-Sternberg (RS) cells and Hodgkin cells. **A,** Classic RS cells and variants in mixed cellularity—classical Hodgkin's lymphoma (CHL), with amphophilic cytoplasm, large nuclei with clear karyoplasm, and huge viral inclusion-like nucleoli. **B,** Typical lacunar cells in a case of nodular sclerosis CHL. Note the delicate folded nuclear membranes, less conspicuous nucleoli, and ample clear cytoplasm with threadlike protrusions. **C,** Typical RS cells, including a binuclear variant, in mixed cellularity CHL. **D,** Abundant, sometimes bizarre multinucleated tumor cells in a case of nodular sclerosis grade II. **E,** So-called mummified RS cell with condensed, deeply basophilic cytoplasm. **F,** Two classic mononuclear Hodgkin cells in a case of mixed cellularity CHL. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Hookworm is a parasitic infection of the intestine caused by the soil helminths *Necator americanus* and *Ancylostoma duodenale*.

SYNONYMS

Ground itch
Ancylostoma duodenale infection
Necator americanus infection

ICD-9CM CODES
126.35 Hookworm
ICD-10CM CODES
B76.9 Hookworm disease, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.)

- Varies greatly in different areas of the United States.
- Most common in rural areas of southeastern United States.
- Poor sanitation and increased rainfall increase incidence.

PREVALENCE (IN U.S.): Varies from 10% to 90% in regions where it is found.
PREDOMINANT AGE: Schoolchildren.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Nonspecific abdominal complaints.
- Symptoms related to iron deficiency anemia depending on the amount of iron in the diet and worm burden (these organisms consume host's RBCs).
- Fatigue, tachycardia, dyspnea, and high-output failure.
- Hypoproteinemia and edema from loss of proteins into the intestinal tract.
- Unusual for pulmonary manifestations to occur when the larvae migrate through the lungs.
- Skin rash at sites of larval penetration in some individuals without prior exposure: ground itch.

ETIOLOGY

Two species can cause this disease: *N. americanus* and *A. duodenale. N. americanus* is the predominant cause of hookworm in the United States. They are soil nematodes (geohelminthic infections) that are acquired by skin contact (i.e., bare feet) with contaminated soils in moist, warm climate. Worldwide, over 700 million people are infected.

- Infection occurs via penetration of the skin by the larval form, with subsequent migration via the bloodstream to the alveoli, up the respiratory tract, then into the GI tract (Fig. H1-60).
- *Ancylostoma* spp. infection can also occur via the oral route through ingestion of contaminated water supplies.
- Sharp mouth parts allow for attachment to intestinal mucosa.
- *Ancylostoma* spp. are more likely to cause iron deficiency anemia because they are larger and remove more blood daily from the bowel wall than the other hookworm species, *N. americanus.*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Strongyloidiasis.
- Ascariasis.
- Other causes of iron deficiency anemia and malabsorption.

WORKUP

Examine stool for hookworm eggs. Shedding of eggs starts around 8 weeks after skin penetration in *N. americanum* infections and longer with *A. duodenale,* but eggs are indistinguishable between the two species.

LABORATORY TESTS

CBC to show hypochromic, microcytic anemia; possible mild eosinophilia and hypoalbuminemia.

IMAGING STUDIES

Chest x-ray: generally not helpful, occasionally shows opacities.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Prevention of disease by not walking barefoot and by improving sanitary conditions.
- Vaccines are in development.

ACUTE GENERAL Rx

- Albendazole 400 mg once PO has become preferred treatment.
- Mebendazole 100 mg PO bid for 3 days or as a 500-mg single dose.
- Pyrantel pamoate 11 mg/kg (to max dose of 1 g) PO qd × 3 days.
- Iron supplementation may be helpful in patients with iron deficiency.

DISPOSITION

Easily treated.

REFERRAL

To gastroenterologist and infectious disease specialist if diagnosis uncertain.

PEARLS & CONSIDERATIONS

COMMENTS

- Appropriate disposal of human wastes is important in controlling the disease in areas with a high prevalence of hookworm infestation.
- Wearing shoes will avoid contact with contaminated soils, and the provision of safe water and sanitation for disposing human excreta is important in control of hookworm.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hookworm Infection (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

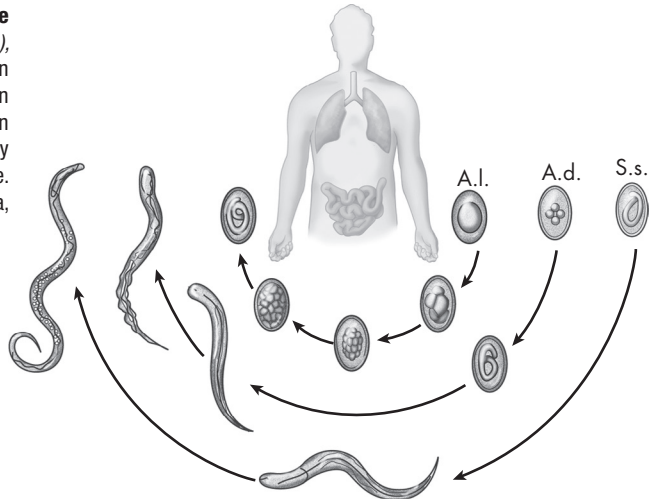


FIGURE H1-60 Life cycle of intestinal nematodes with a migratory phase through the lungs. Eggs are passed with stools in *Ascaris lumbricoides (A.l.), Necator americanus,* or *Ancylostoma duodenale (A.d.),* or they hatch on their way out in *Strongyloides stercoralis (S.s.).* Ascaris eggs mature in soil, and humans are infected upon ingestion of these eggs. With hookworm and strongyloidiasis, humans are infected via skin penetration by filariform larvae. In all three infections, larvae pass through a migratory phase via the lungs before reaching maturity at their final habitat in the small intestine. (From Mandell GL et al: *Principles and practice of infectious diseases,* ed 7, Philadelphia, 2010, Churchill Livingstone.)

EVIDENCE

Abstract[1]

Background and Aims:

The association between hygiene and prevalence of autoimmune disease has been attributed in part to enteric helminth infection. A pilot study of experimental infection with the hookworm *Necator americanus* was undertaken among a group of otherwise healthy people with celiac disease to test the potential of the helminth to suppress the immunopathology induced by gluten.

Methods:

In a 21 week, double-blinded, placebo-controlled study, we explored the effects of *N. americanus* infection in 20 healthy, helminth-naïve adults with celiac disease well controlled by diet. Staged cutaneous inoculations with 10 and 5 infective 3rd stage hookworm larvae or placebo were performed at week –0 and –12 respectively. At week –20, a five day oral wheat challenge equivalent to 16 grams of gluten per day was undertaken. Primary outcomes included duodenal Marsh score and quantification of the immunodominant α-gliadin peptide (QE65)-specific systemic interferon-γ-producing cells by ELISpot pre- and post-wheat challenge.

Results:

Enteric colonisation with hookworm established in all 10 cases, resulting in transiently painful enteritis in 5. Chronic infection was asymptomatic, with no effect on hemoglobin levels. Although some duodenal eosinophilia was apparent, hookworm-infected mucosa retained a healthy appearance. In both groups, wheat challenge caused deterioration in both primary and several secondary outcomes.

Conclusions:

Experimental *N. americanus* infection proved to be safe and enabled testing its effect on a range of measures of the human autoimmune response. Infection imposed no obvious benefit on pathology. Ⓐ

Evidence-Based Reference

Daveson AJ et al.: Effect of hookworm infection on wheat challenge in celiac disease—a randomised double-blinded placebo controlled trial, *PLoS One* 6:e17366, 2011. Ⓐ

SUGGESTED READINGS

Bethony PJ et al.: Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm, *Lancet* 367(9521):1521–1532, 2006 May 6.

Demert DJ et al.: Hookworm vaccines, *Clin Infect Dis* 46(2):282–288, 2008 Jan 15.

Hotez PJ et al.: Hookworm infection, *N Engl J Med* 351(8):799, 2004.

Starr MC, Montgomery SP: Soil-transmitted Helminthiasis in the United States: a systematic review: 1940-2010, *Am J Trop Med Hyg* 85(4):680–684, 2011.

Hordeolum (Stye) PTG

BASIC INFORMATION

DEFINITION

A hordeolum is an acute inflammatory process affecting the eyelid and arising from the meibomian (posterior) or Zeis (anterior) glands. It is most often infectious and usually caused by *Staphylococcus aureus*. When infection involves the meibomian glands, it is called meibomianitis.

SYNONYMS

Stye
Meibomianitis

ICD-9CM CODES
373.11 External hordeolum
373.12 Internal hordeolum
ICD-10CM CODES
H00.019 Hordeolum externum unspecified eye, unspecified eyelid
H00.029 Hordeolum internum unspecified eye, unspecified eyelid

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Unknown.
PREVALENCE (IN U.S.): Unknown.
PREDOMINANT SEX: No gender predilection.
PREDOMINANT AGE: May occur at any age.
NEONATAL INFECTION: Rare in the neonatal period.
PEAK INCIDENCE: May occur at any age.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Abrupt onset with pain and erythema of the eyelid.
- Localized, tender mass in the eyelid (Fig. H1-61).
- May be associated with blepharitis.
- External hordeolum: points toward the skin surface of the lid and may spontaneously drain.
- Internal hordeolum: can point toward the conjunctival side of the lid and may cause conjunctival inflammation.

ETIOLOGY

- 75% to 95% of cases are caused by *S. aureus*.
- Occasional cases are caused by *Streptococcus pneumoniae*, other streptococci, gram-negative enteric organisms, or mixed bacterial flora.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Eyelid abscess.
- Chalazion.
- Allergy or contact dermatitis with conjunctival edema.
- Acute dacryocystitis.
- Herpes simplex infection.
- Cellulitis of the eyelid.

LABORATORY TESTS

- Generally, none are necessary.
- If incision and drainage are performed, specimens should be sent for bacterial culture.

FIGURE H1-61 External stye. (From Palay D [ed]: *Ophthalmology for the primary care physician*, St Louis, 1997, Mosby.)

TREATMENT

NONPHARMACOLOGIC THERAPY

External stye (eyelash follicle): Usually responds to warm compresses and will drain spontaneously

ACUTE GENERAL Rx

- Systemic antibiotics generally not necessary.
- For internal stye, use hot packs *plus* oral dicloxacillin 500 mg qid x 7 days. If suspecting MRSA, use trimethoprim-sulfamethoxazole DS bid in place of dicloxacillin. In patients with hospital-acquired infection, consider linezolid 600 mg PO bid.
- For external stye, topical erythromycin ophthalmic ointment applied to the lid margins two to four times daily until resolution may be helpful in some cases.
- Incision and drainage: rarely needed but should be considered for progressive infections.

DISPOSITION

- Usually sporadic occurrence.
- Possible relapse if resolution is not complete.

REFERRAL

- For evaluation by an ophthalmologist if visual acuity or ocular movement is affected or if the diagnosis is in doubt.
- For surgical drainage if necessary.

PEARLS & CONSIDERATIONS

COMMENTS

Seborrheic dermatitis may coexist with hordeolum.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Stye (Hordeolum) (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Deibel JP, Cowling K: Ocular inflammation and infection, *Emerg Med Clin North Am* 31(2):387–397, 2013.

Hirunwiwatkul P, Wachirasereechai K: Effectiveness of combined antibiotic ophthalmic solution in the treatment of hordeolum after incision and curettage: a randomized, placebo-controlled trial: a pilot study, *J Med Assoc Thai* 88(5):647, 2005.

Kiratli HK, Akar Y: Multiple recurrent hordeola associated with selective IgM deficiency, *J AAPOS* 5(1):60, 2001.

Lindsley K et al.: Interventions for acute internal hordeolum, *Cochrane Database Syst Rev* 9:CD007742, 2010.

BASIC INFORMATION

DEFINITION

Horner's syndrome is the clinical triad of ipsilateral ptosis, miosis, and sometimes facial anhidrosis. Disruption of any of the three neurons in the oculosympathetic pathway (first-order, second-order, or third-order) can cause Horner's syndrome.

SYNONYMS

Oculosympathetic paresis

Raeder's paratrigeminal syndrome: Horner's syndrome of the third-order neuron associated with pain in the trigeminal nerve distribution

ICD-9CM CODES
337.9 Horner's syndrome
ICD-10CM CODES
G90.2 Horner's Syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

Congenital or acquired.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Ptosis is usually mild. It results from loss of sympathetic tone to Müller's muscle, which contributes approximately 2 mm of upper eyelid elevation. Weakness of the corresponding muscle in the lower eyelid causes it to elevate slightly. This combination causes narrowing of the palpebral fissure. Levator function of the eyelid is preserved.
- Miosis results from loss of sympathetic innervation to the iris dilator muscle (Fig. H1-62). The affected pupil reacts normally to bright light and accommodation. Anisocoria is greater in dim light.
  1. Dilation lag: Horner's pupil dilates more slowly than the normal pupil when lights are dimmed (20 versus 5 sec) because it dilates passively as a result of relaxation of the iris sphincter.
- Presence of facial anhidrosis is variable and depends on the site of injury. It occurs with lesions affecting first-order or second-order neurons.
- Congenital Horner's syndrome may result in heterochromia. The affected eye has a lighter-colored iris.
- Acute cases may also present with conjunctival injection from the loss of sympathetic vasoconstriction.

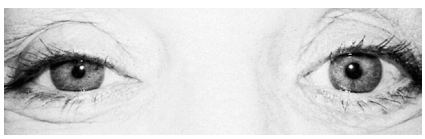


FIGURE H1-62 Horner's syndrome. The mild ptosis (1 to 2 mm) and the smaller pupil (in room light) can be seen on the affected right side. (From Palay D [ed]: *Ophthalmology for the primary care physician,* St Louis, 1997, Mosby.)

ETIOLOGY

Disruption of the ipsilateral sympathetic innervation to the eye and face. Lesions can damage any of the three neurons in the oculosympathetic pathway (Fig. EH1-63). First order neuron lesions are least common but are usually caused by pathology in the hypothalamus, brainstem, or cervical spinal cord. Second order neuron lesions are often caused by disease involving the cervicothoracic spinal cord, lung apex, or anterior neck. Third order neuron lesions are usually seen with disease in the internal carotid artery, skull base, cavernous sinus, or orbital apex. Location is often suggested by the presence of associated findings. Vascular disease and neoplasm must be considered.

Mechanical:
- Syringomyelia.
- Trauma.
- Tumors: benign, malignant head and neck cancers (thyroid, apical lung, mediastinal).
- Lymphadenopathy.
- Neurofibromatosis.
- Cervical rib.

Vascular (ischemia, hemorrhage or arteriovenous malformation):
- Brainstem lesion: commonly occlusion of the posterior inferior cerebellar artery but other arteries may be responsible (vertebral; superior, middle or inferior lateral medullary arteries; superior or anterior inferior cerebellar arteries).
- Carotid artery aneurysm or dissection. Can also be from injury to other major vessels (internal carotid artery, subclavian artery, ascending aorta).
- Cavernous sinus thrombosis.
- Cluster headache, migraine.

Miscellaneous:
- Idiopathic.
- Congenital.
- Demyelination (multiple sclerosis).
- Infection (apical tuberculosis, herpes zoster, Lyme disease).
- Myelitis.
- Pneumothorax.
- Iatrogenic (angiography, internal jugular/subclavian catheter, chest tube, neck or upper thoracic surgery, epidural spinal anesthesia).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Causes of anisocoria (unequal pupils):
- Normal variant.
- Mydriatic use.
- Prosthetic eye.
- Prior eye surgery.
- Unilateral cataract.
- Iritis.

Causes of ptosis are described in Section II.

WORKUP

History, physical examination, pharmacologic testing, imaging.

PHARMACOLOGIC TESTING

- Topical cocaine test: confirms sympathetic denervation (drops dilate normal pupil but not Horner's pupil).
- Topical apraclonidine test: confirms diagnosis (drops reverse anisocoria by causing dilation of Horner's pupil and constriction of normal pupil).
- Topical hydroxyamphetamine test: distinguishes first- and second-order neuron lesions from third-order sympathetic lesions (drops dilate normal pupil and first- or second-order Horner's pupil, but not third-order Horner's pupil). Testing must be delayed >48 hr after topical cocaine or apraclonidine testing.

IMAGING STUDIES

Results of pharmacologic testing as well as accompanying signs and symptoms should guide imaging:
- MRI brain: brainstem (diplopia, vertigo, ataxia); cavernous sinus (eye movement abnormalities, sixth nerve palsy).
- MRI cervical and upper thoracic spinal cord: sensory changes/weakness of extremities, bowel/bladder dysfunction.
- MR or CT angiography (ultrasound is less sensitive): carotid artery dissection (acute Horner's syndrome with face or neck pain).
- CT chest and neck: evaluate lung apex, perivertebral areas, mediastinum if symptoms do not localize to the central nervous system; brachial plexus lesion (arm/hand pain or weakness).

TREATMENT

- Treatment depends on underlying cause.
- Ptosis can be surgically corrected or treated with medication (phenylephrine drops).

REFERRAL

Ophthalmologist for pharmacologic testing to confirm diagnosis and localize lesion.

PEARLS & CONSIDERATIONS

- May be the presentation of a life-threatening condition. Horner's syndrome presenting acutely or associated with pain, trauma, or history of malignancy should be evaluated urgently.
- Normal variant anisocoria:
  1. Occurs in 20% of people.
  2. Usually <1 mm difference between pupils.
  3. Pupils are round and display a normal, brisk constriction and dilation response to light.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Horner's Syndrome (Patient Information)
Lung Neoplasms, Primary (Related Key Topic)

AUTHOR: **SUDEEP KAUR AULAKH, M.D.**

SUGGESTED READINGS

Davagnanam I et al.: Adult Horner's syndrome: a combined clinical, pharmacological and imaging algorithm, *Eye* 27:291, 2013.

Murphy MA et al.: Lyme disease associated with postganglionic Horner syndrome and Raeder paratrigeminal neuralgia, *J Neuro-ophthalmol* 27(2):123, 2007.

Walton KA, Buono LM: Horner syndrome, *Curr Opin Ophthalmol* 14(6):357, 2003.

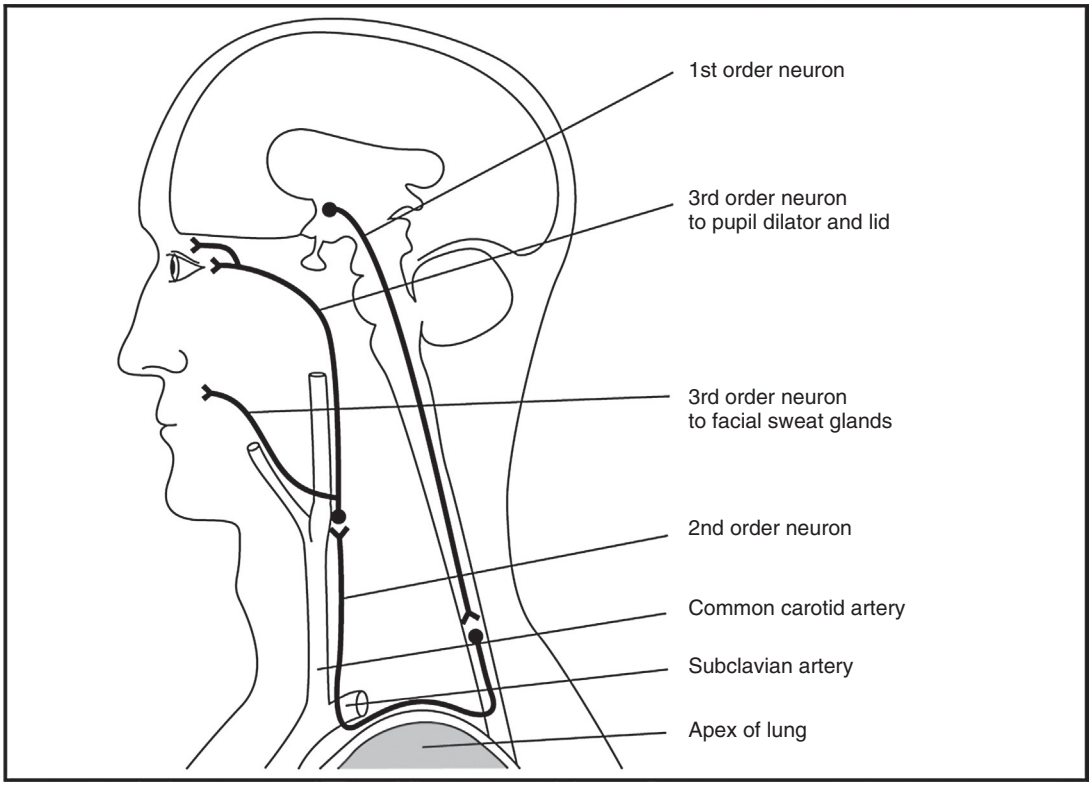


FIGURE EH1-63 Anatomy of sympathetic pathways to the eye. The sympathetic innervation of the eye consists of three neurons connected in series: first order neurons, second order neurons, and third order neurons. The first order neurons (central neurons) extend from the posterior hypothalamus to the C8 to T2 level of the spinal cord. The second order neurons (preganglionic neurons) leave the spinal cord and travel over the lung apex, around the subclavian artery, and along the carotid artery to the superior cervical ganglion. The third order neurons (postganglionic neurons) diverge and take two paths: Those to the pupil and lid muscles travel along the internal carotid artery through the cavernous sinus to reach the orbit; those to the facial sweat glands travel with the external carotid artery to the face. Lesions in any of these neurons cause Horner syndrome and distinct associated physical signs. (From McGee [ed]: *Evidence-based physical diagnosis*, 3rd ed. Philadelphia, 2012, Saunders.)

Hot Flashes PTG

BASIC INFORMATION

DEFINITION

Hot flashes are sudden onset of intense warmth that begins in the neck or face, or in the chest and progresses to the neck and face; often associated with profuse sweating, anxiety, and palpitations.

ICD-9CM CODES
627.2 Hot flashes
ICD-10CM CODES
N95.1 Menopausal and female climacteric states
R23.2 Flushing

EPIDEMIOLOGY & DEMOGRAPHICS

- Hot flashes affect 75% of postmenopausal women.
- Most hot flashes begin 1 to 2 yr before menopause and resolve after 2 yr.
- 15% of women report duration of hot flashes >15 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Profuse sweating and red blotching of skin may be noted during the vasomotor event.
- Palpitations and hyperreflexia may be present during the hot flash.
- Hot flashes typically last 1 to 5 min.
- Each hot flash is associated with increase in temperature, increased pulse rate, and increased blood flow into the hands and face.
- Hot flashes during sleep are common and are referred to as *night sweats.*
- There is considerable variation in the frequency of hot flashes. One third of women report more than 10 flashes per day.

ETIOLOGY

- Dysfunction of central thermoregulatory centers caused by changes in estrogen level at the time of menopause.
- Tamoxifen use.
- Chemotherapy-induced ovarian failure.
- Androgen ablation therapy for prostate carcinoma.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Carcinoid syndrome.
- Anxiety disorder.
- Idiopathic flushing.
- Lymphoma (night sweats).
- Hyperthyroidism.
- Hyperhidrosis.

WORKUP

Evaluation of hot flashes is aimed at excluding the conditions listed in the differential diagnosis.

LABORATORY TESTS

- Follicle-stimulating hormone (FSH), luteinizing hormone, estradiol level. The serum FSH levels rather than estradiol levels are associated with greater severity of hot flashes in older postmenopausal women, suggesting that nonestrogen feedback systems may be important in modulating the severity of hot flashes. It is not necessary to obtain an FSH to make the diagnosis of menopausal status, however. An amenorrheic woman over age 50 with vasomotor symptoms is assumed to have made the menopausal transition and serum markers of menopause are not required to complete the diagnosis.
- Thyroid-stimulating hormone (TSH).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Behavioral interventions such as relaxation training and paced respiration have been reported effective in reducing symptoms in some women.
- Avoidance of caffeine, alcohol, tobacco, and spicy foods may be beneficial.

GENERAL Rx

- Estrogen replacement therapy reduces hot flashes by 80% to 90%. Estrogen therapy, however, is contraindicated in many women, and others are fearful of its use. Potential risks and side effects should be considered before using estrogen in any patient. When using estrogen, it is best to use low dose (e.g., Prempro [conjugated equine estrogen 0.45 mg or 0.3 mg plus medroxyprogesterone 1.5 mg]). Femring is an intravaginal ring that is changed every 3 mo and approved to treat vasomotor symptoms in women who have had a hysterectomy. It provides both local and systemic estrogen.
- Megestrol acetate, a progestational agent, is a safer alternative to estrogen in women with a history of receptor-positive breast or uterine cancer and in men receiving androgen ablation therapy for prostate cancer. Usual dose is 20 mg bid.
- The antidepressant venlafaxine has been reported to be 60% effective in reducing hot flashes and represents an alternative treatment modality in women unable or unwilling to use estrogens. Starting dose is 37.5 mg qd, increased as tolerated up to a maximum of 300 mg/day. Other antidepressants such as desvenlafaxine and escitalopram have also been shown to be effective in reducing the number and severity of menopausal hot flashes. A recent trial showed that paroxetine is also an effective agent for diminishing hot flashes in post-menopausal women and men receiving androgen ablation therapy.
- Duavee is a new FDA-approved treatment of moderate to severe vasomotor menopausal symptoms. It consists of a combination of conjugated estrogens and bazedoxifene, a new selective estrogen receptor modulator (SERM).
- The anticonvulsant gabapentin (300 to 1200 mg/day) represents another nonhormonal alternative in the treatment of hot flashes and can be used alone or in combination with venlafaxine.
- The antihypertensive clonidine is also somewhat effective in reducing the frequency of hot flashes in mild cases. Adverse effects include dry mouth, sedation, and dizziness.
- Vitamin E (800 IU/day) may be effective in patients with mild symptoms that do not interfere with sleep or daily function.
- Soy protein (use of soy extracts that contain plant-derived estrogens [phytoestrogens]) is often used; however, clinical trials have not shown clear efficacy.
- Several classes of herbal remedies are available to patients and are commonly used, generally without significant benefit. Frequently used agents are *Cimicifuga racemosa* (black cohosh, snakeroot, bugbane), *Angelica sinensis,* and evening primrose (evening star). Recent trials using the isopropanolic extract of black cohosh rootstock (Remefemin) did show some improvement in controlling menopausal symptoms. Such alternative medications may be used to treat mild to moderate symptoms, but it is possible that symptomatic improvements may derive in part from a placebo effect.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hot Flashes (Patient Information)
Menopause (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Archer DF et al.: A double-blind, randomly assigned, placebo-controlled study of desvenlafaxine efficacy and safety for the treatment of vasomotor symptoms associated with menopause, *Am J Obstet Gynecol* 200(2):172.e1–172.e10, 2008.

Freeman EW et al.: Efficacy of escitalopram for hot flashes in healthy menopausal women, a randomized controlled trial, *JAMA* 305(3):267–274, 2011.

Huang AJ et al.: Persistent hot flushes in older postmenopausal women, *Arch Intern Med* 168(8):840–846, 2008.

Loprinzi CL et al.: Pilot evaluation of gabapentin for treating hot flashes, *Mayo Clin Proc* 77:1159, 2002.

Loprinzi CI et al.: Pilot evaluation of paroxetine for treating hot flashes in men, *Mayo Clin Proc* 79(10):1247, 2004.

Nelson HD et al.: Nonhormonal therapies for menopausal hot flashes, *JAMA* 295:2057, 2006.

Osmers R et al.: Efficacy and safety of isopropanolic black cohosh extract for climacteric symptoms, *Obstet Gynecol* 105:1074, 2005.

Shanafelt TD et al.: Pathophysiology and treatment of hot flashes, *Mayo Clin Proc* 77:1207, 2002.

Sikon A, Thacker HL: Treatment options for menopausal hot flashes, *Cleve Clin J Med* 71:578, 2004.

Women's Health Initiative Investigators: Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial, *JAMA* 288:321, 2002.

BASIC INFORMATION

DEFINITION

The human immunodeficiency virus (HIV) is a retrovirus that is responsible for causing acquired immunodeficiency syndrome (AIDS). HIV infection does not necessarily mean a person has AIDS.

SYNONYMS

AIDS: The result of progressive HIV infection in with which a person has a weakened immune system and meets specific diagnostic criteria (See "Acquired Immunodeficiency Syndrome" in Section I.)

ICD-9CM CODES
042.9 HIV, unspecified
044.9 HIV, unspecified
ICD-10CM CODES
B20 Human immunodeficiency virus [HIV]

EPIDEMIOLOGY & DEMOGRAPHICS (IN U.S.)

- There are an estimated 1.1 million people infected with HIV in the United States, with approximately 1 out of 6 (15.8%) who do not know they are infected.
- In 2011, there were an estimated 49,273 new HIV infections according to the CDC.
- Greatest incidence is in men who have sex with men (MSM) and minority populations.

PREDOMINANT RISK GROUPS

- Gay, bisexual, and other MSM are the groups most affected by HIV.
- In 2010, MSM accounted for 63% of all new infections according to the CDC.
- HIV disproportionately affects MSM of younger age and black/African American and Hispanic background.
- Heterosexual transmission and injection drug use accounted for 25% and 8% of new HIV infections in 2010, respectively.

RACIAL DATA

- In 2010, blacks/African Americans accounted for 44% of new HIV infections despite being 12% of the U.S. population.
- In 2010, Hispanics/Latinos accounted for 21% of new HIV infections despite being 19% of the U.S. population.

GENETICS

Familial Disposition: Individuals with deletions in the *CCR5* gene are immune from infection with macrophage tropic virus (the predominant virus in sexual transmission). Other genetic variants may contribute to rapid progression or long-term control of the virus once infected. One in 300 individuals infected with HIV is an "elite controller," which means they are able to maintain a normal CD4 count and undetectable viral load through immune control.

Congenital Infection

- 80% of childhood cases are caused by peripartum infection, which may occur in utero, during delivery, or after delivery via breastfeeding.
- No specific congenital abnormalities are associated with HIV infection, although there is a higher risk of spontaneous abortion and low birth weight.

Neonatal Infection

- May occur during delivery or via breastfeeding.
- Typically asymptomatic.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Signs and symptoms are variable with stage of disease. "Stage 0" indicates a very early infection diagnosed when standard markers are converting from negative to positive.
- Acute HIV infection (0 to 3 months, usually within several weeks):
  1. May cause a self-limited mononucleosis-like illness in 50% to 80% of individuals characterized by fever, sore throat, lymphadenopathy, headache, and a rash resembling roseola. Individuals may also be asymptomatic.
  2. In a minority of acute cases, aseptic meningitis, Bell's palsy, or peripheral neuropathy may occur.
  3. Rarely, opportunistic infections such as thrush or *Pneumocystis jiroveci* pneumonia (PJP) may occur.
- Chronic HIV infection is usually characterized by a prolonged asymptomatic phase followed by nonspecific symptoms of lymphadenopathy, fatigue, weight loss, diarrhea, and skin changes including seborrheic dermatitis, localized herpes zoster, and/or fungal infection.
- Advanced disease is characterized by AIDS-associated diseases, including infections and malignancies (see specific disorders).
- HIV infection in women may be associated with lower levels of viral load at comparable degrees of immunosuppression when compared with men. Furthermore, women may, on average, have higher CD4 counts at the time of HIV diagnosis.
- Another special consideration in women infected with HIV is the high incidence of human papillomavirus (HPV) co-infection and risk for cervical cancer. HIV-positive women should be screened for cervical cancer twice in the first year and then annually thereafter if pap smears are normal.
- Co-infection with HIV and hepatitis C is common because of similar transmission risk. Hepatitis C is most commonly transmitted by contaminated needles or blood exposure. Hepatitis C can be transmitted by sex, but the risk is low. Patients with HIV and hepatitis C progress faster to cirrhosis. Patients may already have signs of advanced liver disease at the time of diagnosis.

ETIOLOGY

- HIV is a single-stranded RNA retrovirus (Figure H1-64) that is categorized as type 1 or 2.

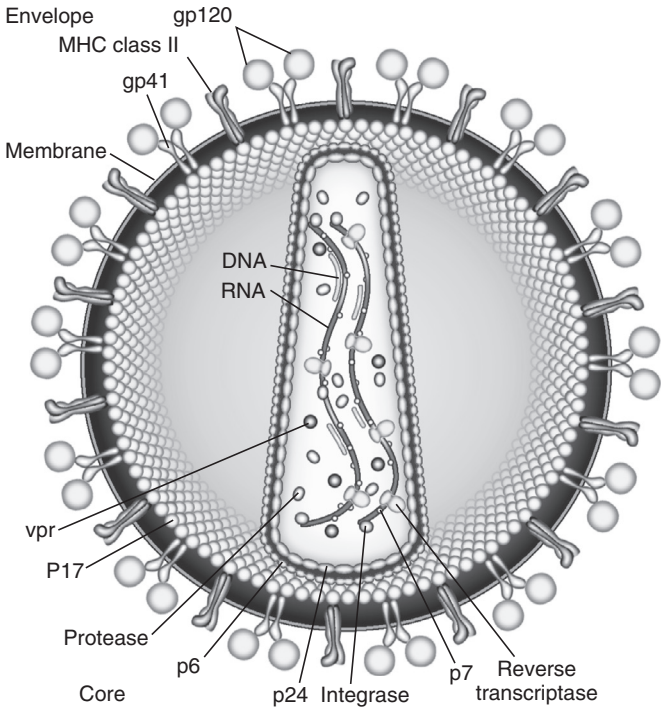


FIGURE H1-64 Structure of the HIV-1 virion. The viral envelope is formed from the host cell membrane, into which the HIV-1 envelope proteins gp41 and gp120 have been inserted and may include several host cell proteins, most significantly the major histocompatibility complex class II proteins. The matrix between the envelope and the core is formed predominantly from gag protein p17. The core contains the viral RNA, closely associated with gag protein p7, in addition to RT and integrase. It has also been proven that virions contain complementary DNA, as shown, synthesized by the RT. The major structural proteins of the core are gag proteins p24 and p6. Also present within the virion are the protease and two cleavage products from the gag precursor protein (p1 and p2, not shown) of undetermined position within the virion. Viral protein R (Vpr) is also packaged in the virion and is thought to be localized within the core, as shown. (From Mandell GL et al: *Principles and practice of infectious diseases*, ed 7, Philadelphia, 2010, Saunders.)

- HIV-1 was derived from transmission of a simian immunodeficiency virus (SIV) from chimpanzees in Central Africa; HIV-2 was derived from an SIV found in sooty mangabey monkeys from West Africa.
- HIV-1 is the predominant pathogenic retrovirus in human populations; HIV-2 has limited distribution (primarily West Africa) and tends to progress less rapidly than HIV-1. HIV-2 should be considered in individuals from West Africa or if sexual partners are from West Africa.
- HIV-1 is transmitted by sexual contact, shared needles, blood transfusion, or from mother to child during pregnancy, delivery, or breastfeeding.
- Primary target of infection: CD4 lymphocytes.
- Direct central nervous system (CNS) involvement: manifests as encephalopathy, myelopathy, or neuropathy in advanced cases.
- Renal failure, rheumatologic disorders, thrombocytopenia, or cardiac abnormalities may be seen in association with HIV-1.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute HIV infection: often diagnosed or confused with mononucleosis or other respiratory viral infections
- Late symptoms: similar to those produced by other wasting/chronic illnesses such as neoplasms, tuberculosis (TB), disseminated fungal infection (such as *Candida*), malabsorption, or depression
- HIV-related encephalopathy: confused with Alzheimer's disease or other causes of chronic dementia (cognitive impairment in HIV infection is described in Section II); myelopathy and neuropathy possibly resembling other demyelinating diseases such as multiple sclerosis.

WORKUP

Since the debut of HIV/AIDS in the 1980s, diagnosis has been established by testing for antibodies to the virus. The Centers for Disease Control and Prevention (CDC) is now recommending routine testing for patients in all health care settings unless the patient declines (opt-out screening). This includes routine testing of pregnant women. It is also recommended that separate written consent should no longer be required, although by law this is being addressed on a state-by-state basis. Generally, all persons aged 13-64 should undergo HIV testing at least once and more frequently (at least once a year) if sexually active.

- An FDA-approved at-home rapid HIV screening test is now available. It uses swabs of oral fluids from upper and lower gums. A positive test requires confirmatory testing in the office. Negative home tests should be repeated within 3 months.

LABORATORY TESTS

HIV antibodies are detected by a two-step technique:

- ELISA (enzyme-linked immunosorbent assay), which is a sensitive screening test.
- Confirmation of positive ELISA tests with more specific assays. The classic confirmatory test is the Western blot, but this is not commonly used anymore.
- Screening ELISA antibody tests will measure HIV-1 and HIV-2 antibodies. Confirmatory tests will generally differentiate between HIV-1 and HIV-2 as well. However, the viral load assays (HIV RNA PCR) are specific only for HIV-1.
- Baseline viral resistance testing is recommended for all newly diagnosed patients with HIV to guide choice of antiretroviral therapy (ART).
- The CD4 count and HIV RNA polymerase chain reaction (PCR) should be measured in all patients.
- The CD4 count is a marker of current immune status.
- The HIV RNA PCR (viral load) is predictive of disease progression.
- Rapid serologic tests have been increasingly used and are useful in specific settings: occupational exposures, pregnant women in labor without previous testing, and patients in high seroprevalence areas (for immediate results). Specimens are either blood or saliva and results are given within 1-20 min. Although sensitivity is high (99%), false-positive tests are more common in low seroprevalence populations. Thus, all positive results must be confirmed with standard serology.
- Early during infection (i.e., acute HIV infection), standard antibody tests may be negative ("window period"). The standard for diagnosing HIV during acute HIV infection is by testing for HIV RNA (viral load).
- In 2014, the CDC released a revised surveillance case definition for HIV infection. This information has been added in the EBM section of this topic.

Fig. H1-65 describes the immunologic response to HIV infection.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Maintenance of adequate nutrition

ACUTE GENERAL Rx

Acute management of opportunistic infections and malignancies (see AIDS-associated disorders, "*Pneumocystis jiroveci*) Pneumonia," "Cryptococcosis," "Tuberculosis," "Toxoplasmosis" elsewhere in this text.)

CHRONIC Rx

All HIV-infected patients should be considered for ART regardless of CD4 cell count. The benefit of ART is well established in preventing progression to AIDS and associated comorbidities. Table H1-33 describes HIV treatment guidelines of the Department of Health and Human Services (DHHS) (www.aidsinfo.nih.gov/guidelines).

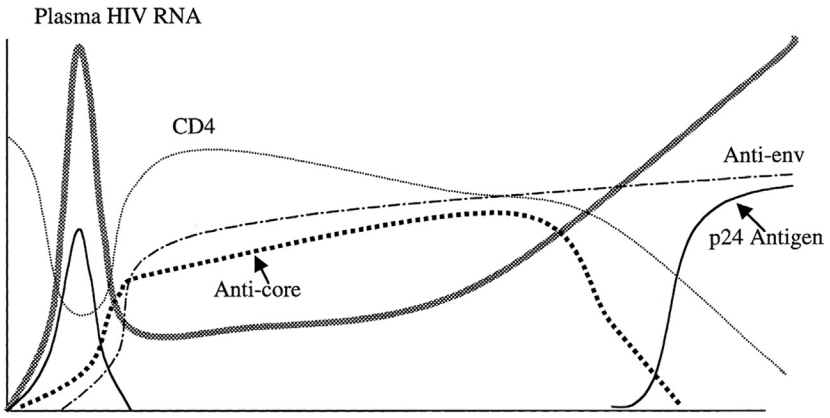


FIGURE H1-65 Course of human immunodeficiency virus infection. (From Mandell GL [ed]: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 6, New York, 2005, Churchill Livingstone.)

TABLE H1-33 When to Initiate Antiretroviral Therapy (ART) in Treatment-Naïve Patients

ART should be initiated in all patients with a history of an AIDS-defining illness or with a CD4 count of <350 cells/mm^3 (AI).
ART is also recommended for patients with CD4 counts between 350 and 500 cells/mm^3 (AII).
ART is recommended for patients with CD4 counts greater than 500 cell/mm^3 (BIII).
ART should also be initiated, regardless of CD4 count, in patients with the following conditions: HIV-associated nephropathy (HIVAN) and HBV coinfection when treatment of HBV is indicated (AII).
A combination ARV drug regimen is also recommended for pregnant women who are not otherwise on treatment, with the goal to prevent perinatal transmission (AI).
Patients initiating ART should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence.
Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy based on clinical and/or psychosocial factors.

Modified from Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1–infected adults and adolescents. Department of Health and Human Services. March 27, 2012. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

Other considerations for initiation of antiretroviral therapy are described in Table H1-34. Prophylaxis to prevent first episode of HIV-related opportunistic disease is described in Table H1-35.

- Therapy is strongly recommended for all patients with symptomatic established HIV disease regardless of the CD4 count. Symptomatic HIV disease is defined as the presence of any of the following: thrush, vaginal candidiasis, herpes zoster, peripheral neuropathy, bacillary angiomatosis, cervical dysplasia in situ, constitutional symptoms such as fever or diarrhea for more than 1 month, ITP, PID, or listeriosis.
- In asymptomatic individuals, ART is now recommended regardless of CD4 cell counts. The updated recommendations are due to the safety and benefit of newer antivirals in preventing AIDS and decreasing both morbidity and mortality. Earlier treatment may also help reduce transmission of the virus to others due to reductions in viral loads.
- ART generally consists of using a 3-drug regimen to treat HIV infection. Classes of antiretrovirals include:
  1. Nucleoside/nucleotide reverse transcriptase inhibitor (NRTI): zidovudine (AZT), lamivudine (3TC), emtricitabine (FTC), tenofovir (TDF), abacavir (ABC), stavudine (D4T), or didanosine (DDI).
  2. Protease inhibitors (PI): lopinavir/ritonavir, atazanavir, fosamprenavir, darunavir, saquinavir, amprenavir, tipranavir, nelfinavir, and indinavir. These PIs may be "boosted" by ritonavir to increase levels.
  3. Nonnucleoside reverse transcriptase inhibitors (NNRTI): Nevirapine, efavirenz, etravirine, delavirdine, or rilpivirine.
  4. Integrase Inhibitors (II): Raltegravir, elvitegravir, and dolutegravir. Raltegravir is a first-line agent according to the DHHS guidelines.
  5. Fusion Inhibitors: Enfuvirtide (T-20). This drug is administered through subcutaneous injections and is only used as part of a salvage regimen for individuals who have failed multiple other regimens.
  6. CCR5 Inhibitors: Maraviroc. Before using this drug, a viral trophism assay should be checked to determine if the virus uses the CCR5 co-receptor to infect cells. If the virus uses the CXCR4 co-receptor, this drug will not be effective.
- Adding a fourth drug to the three-drug regimen does not improve viral suppression or outcomes and is not recommended. Treatment interruptions based upon CD4 responses appear harmful in recent comparative studies versus standard continuous treatment protocols and should be avoided. Antiretroviral regimens for initial therapy are summarized in Table H1-36.
- Typical initial dosing regimen consists of two NRTIs and either a NNRTI, PI, or II. Data support inclusion of lamivudine or emtricitabine as one of the two NRTIs.

  Standard NRTIs include:
- Truvada (tenofovir/emtricitabine) 1 tablet once daily.
  1. Tenofovir: Individuals with underlying renal dysfunction or requiring other nephrotoxic agents may be at increased risk of renal toxicity.
  2. Epzicom (abacavir/lamivudine) 1 tablet once daily
- Abacavir: may be associated with increased risk of myocardial infarction. Before using this drug, individuals should be checked for HLA-B*5701. Individuals with this allele are at higher risk of serious hypersensitivity reactions and this drug should be avoided.
  1. Combivir (Zidovudine/lamivudine) 1 tablet twice daily
  2. Zidovudine: Associated with lipoatrophy and anemia. GI and CNS side effects.

  Standard Backbone Regimens include:
- NNRTIs
  1. Efavirenz 600 mg daily: not recommended for women in the first trimester or those who are contemplating pregnancy. This is considered the preferred agent within the class.
  2. Nevirapine 200 mg two times a day: avoid with CD4 count >250 in men and >350 in women because of the risk of hepatitis. The newer agent rilpivirine had higher virologic failures and should be considered an alternative agent.
  3. Etravirine 200 mg two times a day: This drug is generally used in patients that have failed other regimens. Etravirine retains activity in many patients that have developed resistance against efavirenz and nevirapine.
- PIs (ritonavir boosted)
  1. Lopinavir/ritonavir (200 mg/50 mg) 2 tablets twice a day (or 4 tablets once a day): most likely to cause diarrhea and has the greatest negative effect on triglyceride levels.
  2. Atazanavir and ritonavir (300 mg and 100 mg) 2 tablets a day: lower pill burden, but use with caution with acid reducing agents—can alter absorption. This is considered a preferred PI regimen within the DHHS guidelines.
  3. Fosamprenavir and ritonavir (700 mg and 100 mg) 2 tablets twice a day (or 4 tablets once a day): cannot take fosamprenavir with sulfa allergy.
  4. Darunavir and ritonavir: 800 mg and 100 mg a day. This is considered a preferred PI regimen within the DHHS guidelines.
  5. Saquinavir and ritonavir.
- All these drugs have their own unique, as well as class-specific, side effects and require careful follow-up to achieve optimal antiviral effects. Compliance with the drug regimen and tolerance of common side effects are critically important to maintain drug efficacy. The FDA has approved Triumeq, a fixed-dose combination of the integrase strand inhibitor dolutegravir and the NRTIs abacavir and lamivudine, for once-daily treatment of HIV-1 infection. Antiviral response should be monitored by baseline HIV viral load and CD4 count and repeat measurement at 2 and 4 weeks into treatment and then periodically (every 3 to 6 months) to ensure viral suppression.
- All patients should have genotypic resistance testing upon entry into medical care and before initiation of ART.
- In experienced patients, an antiretroviral regimen should be constructed based on past antiretroviral use and the results of genotypic or phenotypic testing.
- Patients with a CD4 count <200/mm^3 should be given preventive therapy for PJP (see "*Pneumocystis jirovecii [P. carinii]* Pneumonia").
- Evaluation of chronic diarrhea in patients with HIV is described in the AIDS topic in Section I.
- Criteria for discontinuing and restarting opportunistic infection prophylaxis for adults and adolescents with HIV infection is described in Table H1-37.
- HIV infection in a pregnant woman poses special challenges and considerations. Appropriate and timely ART given to mother and newborn has been shown to dramatically reduce the risk of perinatal transmission of HIV. The goal of therapy is to achieve an undetectable viral load. For HIV-infected pregnant women who are already receiving ART: (1) Continue therapy if suppressing viral replication, but avoid use of efavirenz in the first trimester (substitution is recommended in the first trimester); (2) If viremia on therapy, genotypic testing is recommended; (3) Nevirapine should be continued, regardless of CD4 count, if there is viral suppression. For HIV-infected pregnant women who have never received ART: (1) Women who require ART for their own health should start on ART in the first trimester. Most antiretrovirals are safe in pregnancy, however, efavirenz should be avoided because of teratogenicity (Class D), DDI and D4T should be avoided (potential of lactic acidosis), and some protease inhibitors may be dose-altered in pregnancy. Nevirapine should not be initiated in an antiretroviral-naive pregnant patient with CD4 counts >250 because of the risk of hepatotoxicity. (2) Women who do not need ART for their own health should also initiate three-drug therapy, but may do so at the end of the first trimester.

TABLE H1-34 Conditions Favoring More Rapid Initiation of Antiretroviral Therapy

Pregnancy
AIDS-defining conditions
Acute opportunistic infections
Lower CD4 counts (e.g., <200 cells/mm^3)
Rapidly declining CD4 counts (e.g., >100 cells/mm^3 decrease per year)
Higher viral loads (e.g., >100,000 copies/ml)
HIV-associated nephropathy
Hepatitis B/C virus (HBV/HCV) coinfection

Modified from Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1–infected adults and adolescents. Department of Health and Human Services. March 27, 2012. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

TABLE H1-35 Prophylaxis to Prevent First Episode of HIV-related Opportunistic Disease

Pathogen	Indication	First Choice	Alternative
Pneumocystis jiroveci pneumonia (PJP, previously referred to as *Pneumocystis carinii,* PCP)	$CD4^+$ count <200 cells/mm^3 or oropharyngeal candidiasis $CD4^+$ <14% or history of AIDS-defining illness $CD4^+$ count >200 but <250 cells/mm^3 if monitoring $CD4^+$ count every 1-3 mo is not possible	Trimethoprim-sulfamethoxazole (TMP-SMX) double-strength PO daily; *or* single-strength daily	TMP-SMX 1 double-strength PO 3 times weekly; *or* Dapsone 100 mg PO daily or 50 mg PO bid; *or* Aerosolized pentamidine 300 mg via Respirgard II nebulizer every month; *or* Atovaquone 1500 mg PO daily
Toxoplasma gondii encephalitis	*Toxoplasma* IgG–positive patients with $CD4^+$ count <100 cells/mm^3 Seronegative patients receiving PCP prophylaxis not active against toxoplasmosis should have *Toxoplasma* serology retested if $CD4^+$ count declines to <100 cells/mm^3. Prophylaxis should be initiated if seroconversion occurred.	TMP-SMX, 1 double-strength PO daily	TMP-SMX 1 double-strength PO 3 times weekly; *or* TMP-SMX 1 single-strength PO daily; *or* Dapsone 50 mg PO daily + pyrimethamine 50 mg PO weekly + leucovorin 25 mg PO weekly; *or* Dapsone 200 mg PO weekly + pyrimethamine 75 mg PO weekly + leucovorin 25 mg PO weekly;
Mycobacterium tuberculosis infection (TB) (treatment of latent TB infection or LTBI)	(1) Diagnostic test for LTBI, no evidence of active TB, and no prior history of treatment for active or latent TB (2) Diagnostic test for LTBI, but close contact with a person with infectious pulmonary TB and no evidence of active TB (3) A history of untreated or inadequately treated healed TB (i.e., old fibrotic lesions) regardless of diagnostic tests for LTBI and no evidence of active TB	Isoniazid (INH) 300 mg PO daily or 900 mg PO twice weekly for 9 mo—both plus pyridoxine 50 mg PO daily; *or* For persons exposed to drug-resistant TB, selection of drugs after consultation with public health authorities	Rifampin (RIF) 600 mg PO daily × 3-4 mo; *or* Rifabutin (RFB) 300 mg once daily for 4 mo. Be careful of drug interactions with these medications (PIs and NNRTIs).
Disseminated *Mycobacterium avium* complex (MAC) disease	$CD4^+$ count <50 cells/mm^3—after ruling out active MAC infection	Azithromycin 1200 mg PO once weekly; *or* Clarithromycin 500 mg PO bid; *or* Azithromycin 600 mg PO twice weekly	RFB 300 mg PO daily (dosage adjustment based on drug-drug interactions with antiretroviral therapy); rule out active TB before starting RFB
Streptococcus pneumoniae infection	$CD4^+$ count >200 cells/mm^3 and no receipt of pneumococcal vaccine in the past 5 yr $CD4^+$ count <200 cells/mm^3—vaccination can be offered In patients who received polysaccharide pneumococcal vaccination (PPV) when $CD4^+$ count <200 cells/mm^3 but has increased to >200 cells/mm^3 in response to antiretroviral therapy	23-valent PPV 0.5 ml IM × 1 Revaccination every 5 yr may be considered	
Influenza A and B virus infection	All HIV-infected patients	Inactivated influenza vaccine 0.5 ml IM annually	
Histoplasma capsulatum infection	$CD4^+$ count ≤150 cells/mm^3 and at high risk because of occupational exposure or live in a community with a hyperendemic rate of histoplasmosis (>10 cases/100 patient-yr)	Itraconazole 200 mg PO daily	
Coccidioidomycosis	Positive IgM or IgG serologic test result in a patient from a disease-endemic area; and $CD4^+$ count <250 cells/mm^3	Fluconazole 400 mg PO daily Itraconazole 200 mg PO bid	
Varicella-zoster virus (VZV) infection	*Pre-exposure prevention:* Patients with $CD4^+$ count ≥200 cells/mm^3 who have not been vaccinated, have no history of varicella or herpes zoster, or who are seronegative for VZV Note: Routine VZV serologic testing in HIV-infected adults is not recommended. *Postexposure—close contact with a person who has active varicella or herpes zoster:* For susceptible patients (those who have no history of vaccination or of either condition, or are known to be VZV seronegative)	*Pre-exposure prevention:* Primary varicella vaccination (Varivax), 2 doses (0.5 ml SC) administered 3 mo apart If vaccination results in disease because of vaccine virus, treatment with acyclovir is recommended. *Postexposure therapy:* Varicella-zoster immune globulin (VariZIG) 125 IU per 10 kg (maximum of 625 IU) IM, administered within 96 hr after exposure to a person with active varicella or herpes zoster Note: As of June 2007, VariZIG can be obtained only under a treatment IND (1-800-843-7477, FFF Enterprises).	VZV-susceptible household contacts of susceptible HIV-infected persons should be vaccinated to prevent potential transmission of VZV to their HIV-infected contacts. *Alternative postexposure therapy:* Postexposure varicella vaccine (Varivax) 0.5 ml SC × 2 doses, 3 mo apart if $CD4^+$ count >200 cells/mm^3; *or* Preemptive acyclovir 800 mg PO 3×/day for 5 days These two alternatives have not been studied in the HIV population.
Human papillomavirus (HPV) infection	Women aged 11-26 yr. Men aged 11-21 yr	HPV quadrivalent vaccine 0.5 ml IM mo 0, 2, and 6	

Modified from Centers for Disease Control and Prevention. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Disease Society of America, *MMWR Morb Mortal Wkly Rep* 58(RR-4), 2009.

Continued on following page

TABLE H1-35 Prophylaxis to Prevent First Episode of HIV-related Opportunistic Disease—*(Continued)*

Pathogen	Indication	First Choice	Alternative
Hepatitis A virus (HAV) infection	HAV-susceptible patients with chronic liver disease or who are injection-drug users, or men who have sex with men. Certain specialists might delay vaccination until $CD4^+$ count >200 cells/mm^3.	Hepatitis A vaccine 1 ml IM × 2 doses—at 0 and 6-12 mo IgG antibody response should be assessed 1 mo after vaccination; nonresponders should be revaccinated	
Hepatitis B virus (HBV) infection	All HIV patients without evidence of prior exposure to HBV should be vaccinated with HBV vaccine, including patients with $CD4^+$ count <200 cells/mm^3. *Patients with isolated anti-HBc:* consider screening for HBV DNA before vaccination to rule out occult chronic HBV infection	Hepatitis B vaccine IM (Engerix-B 20 μg/ml or Recombivax HB 10 μg/ml) at 0, 1, and 6 mo Anti-HBs should be obtained 1 mo after completion of the vaccine series.	Some experts recommend vaccinating with 40-μg doses of either vaccine.
	Vaccine nonresponders: Defined as anti-HBs <10 IU/ml 1 mo after a vaccination series For patients with low $CD4^+$ count at the time of first vaccination series, certain specialists might delay revaccination until after a sustained increase in $CD4^+$ count with antiretroviral therapy.	Revaccinate with a second vaccine series.	Some experts recommend revaccinating with 40-μg doses of either vaccine.

TABLE H1-36 What Antiretroviral Regimen to Choose for Initial Therapy

Preferred Regimens	Comments
NNRTI-based regimen EFV/TDF/FTC	EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception.
PI-based regimens (in alphabetical order) ATV/r + TDF/FTC DRV/r (once daily) + TDF/FTC	ATV/r should not be used in patients who are on proton pump inhibitors or other antacids.
Integrase inhibitor-based regimen RAL + TDF/FTC Dolutegravir + TDF/FTC Elvitegravir + cobicistat + TDF/FTC	
Preferred regimen for pregnant women LPV/r (twice daily) + ZDV/3TC	
Alternative Regimens	**Comments**
NNRTI-based regimens (in alphabetical order) EFV + ABC/3TC RPV/TDF/FTC RPV + ABC/3TC	NVP should not be used in patients with moderate to severe hepatic impairment (Child-Pugh B or C) Should not be used in women with pre-treatment CD4 >250 cells/mm^3 or men with CD4 >400 cells/mm^3
PI-based regimens (in alphabetical order) ATV/r + ABC/3TC DRV + ABC/3TC FPV/r (once or twice daily) + either ABC/3TC or TDF/FTC LPV/r (once or twice daily) + either [(ABC or ZDV)/3TC] or TDF/FTC	ABC should not be used in patients who test positive for HLA-B*5701 Use with caution in patients with high risk of cardiovascular disease or with pretreatment HIV RNA >100,000 copies/mL Once-daily LPV/r is not recommended in pregnant women.
Integrase inhibitor-based regimens RAL + ABC/3TC Dolutegravir + ABC/3TC	
Acceptable Regimens	
EFV + AZT/3TC NVP + TDF/FTC or ABC/3TC or AZT/3TC RPV + AZT/3TC ATV + ABC/3TC or AZT/3TC ATV/r + AZT/3TC DRV/r + AZT/3TC FPV/r + AZT/3TC LPV/r + AZT/3TC RAL + AZT/3TC MVC + AZT/3TC or TDF/FTC or ABC/3TC	

3TC, Lamivudine; *ABC,* abacavir; *ATV,* atazanavir; *ddI,* didanosine; *DRV,* darunavir; *EFV,* efavirenz; *FPV,* fosamprenavir; *FTC,* emtricitabine; *INSTI,* integrase strand transfer inhibitor; *LPV,* lopinavir; *MRV,* maraviroc; *NNRTI,* nonnucleoside reverse transcriptase inhibitor; *NRTI,* nucleos(t)ide reverse transcriptase inhibitor; *NVP,* nevirapine; *PI,* protease inhibitor; *r,* low dose ritonavir; *RAL,* raltegravir; *RVP,* rilpivirine; *SQV,* saquinavir; *TDF,* tenofovir; *ZDV,* zidovudine.The following combinations in the recommended list are available as fixed-dose combination formulations: ABC/3TC, EFV/TDF/FTC, LPV/r, TDF/FTC, RPV/TDF/FTC, and ZDV/3TC.

Modified from Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1–infected adults and adolescents. Department of Health and Human Services 1-161, 2012. http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

TABLE H1-37 Criteria for Discontinuing and Restarting Opportunistic Infection Prophylaxis for Adults and Adolescents with Human Immunodeficiency Virus Infection

Opportunistic Infection	Criteria for Discontinuing Primary Prophylaxis	Criteria for Restarting Primary Prophylaxis	Criteria for Discontinuing Secondary Prophylaxis/ Chronic Maintenance Therapy	Criteria for Restarting Secondary Prophylaxis/ Chronic Maintenance Therapy
Pneumocystis pneumonia (PJP)	$CD4^+$ count >200 cells/mm^3 for >3 mo in response to ART	$CD4^+$ count <200 cells/mm^3	$CD4^+$ count increased from <200 cells/mm^3 to >200 cells/mm^3 for ≥3 mo in response to ART If PJP is diagnosed when $CD4^+$ count >200 cells/mm^3, prophylaxis should probably be continued for life regardless of $CD4^+$ count rise in response to ART.	$CD4^+$ count <200 cells/mm^3, or if PCP recurred at a $CD4^+$ count >200 cells/mm^3
Toxoplasma gondii encephalitis (TE)	$CD4^+$ count >200 cells/mm^3 for >3 mo in response to ART	$CD4^+$ count <100-200 cells/mm^3	Successfully completed initial therapy, remain asymptomatic of signs and symptoms of TE, and $CD4^+$ count >200 cells/mm^3 for >6 mo in response to ART	$CD4^+$ count <200 cells/mm^3
Microsporidiosis	Not applicable	Not applicable	No signs and symptoms of non-ocular microsporidiosis and $CD4^+$ count >200 cells/mm^3 for >6 mo in response to ART Patients with ocular microsporidiosis should be on therapy indefinitely regardless of $CD4^+$ count.	No recommendation
Disseminated *Mycobacterium avium* complex (MAC) disease	$CD4^+$ count >100 cells/mm^3 for ≥3 mo in response to ART	$CD4^+$ count <50 cells/mm^3	If fulfill the following criteria Completed ≥12 mo therapy, and No signs and symptoms of MAC, and Have sustained (≥6 mo) $CD4^+$ count >100 cells/mm^3 in response to ART	$CD4^+$ count <100 cells/mm^3
Bartonellosis	Not applicable	Not applicable	If fulfill the following criteria Received 3-4 mo of treatment $CD4^+$ count >200 cells/mm^3 for ≥6 mo Certain specialists would discontinue therapy only if *Bartonella* titers have also decreased by fourfold.	No recommendation
Mucosal candidiasis	Not applicable	Not applicable	If used, reasonable to discontinue when $CD4^+$ count >200 cells/mm^3	No recommendation
Cryptococcal meningitis	Not applicable	Not applicable	If fulfill the following criteria Completed course of initial therapy Remain asymptomatic of cryptococcosis $CD4^+$ count ≥200 cells/mm^3 for >6 mo in response to ART Certain specialists would perform a lumbar puncture to determine if cerebrospinal fluid is culture and antigen negative before stopping therapy.	$CD4^+$ count <200 cells/mm^3
Histoplasma capsulatum infection	If used, $CD4^+$ count >150 cells/mm^3 for 6 mo on ART	For patients at high risk for acquiring histoplasmosis, restart at $CD4^+$ count ≤150 cells/mm^3.	If fulfill the following criteria Received itraconazole for ≥1 yr Negative blood cultures $CD4^+$ count >150 cells/mm^3 for ≥6 mo in response to ART Serum *Histoplasma* antigen <2 units	$CD4^+$ count ≤150 cells/mm^3
Coccidioidomycosis	If used, $CD4^+$ count ≥250 cells/mm^3 for ≥6 mo	If used, restart at $CD4^+$ count <250 cells/mm^3	**Only for patients with focal coccidioidal pneumonia:** Clinically responded to ≥12 mo of antifungal therapy $CD4^+$ count >250 cells/mm^3 Receiving ART Suppressive therapy should be continued indefinitely, even with increase in $CD4^+$ count on ART for patients with diffuse pulmonary, disseminated, or meningeal diseases.	No recommendation
Cytomegalovirus retinitis	Not applicable	Not applicable	$CD4^+$ count >100 cells/mm^3 for >3-6 mo in response to ART. Therapy should be discontinued only after consultation with an ophthalmologist, taking into account magnitude and duration of $CD4^+$ count increase, anatomic location of the lesions, vision in the contralateral eye, and the feasibility of regular ophthalmologic monitoring. Routine (every 3 mo) ophthalmologic follow-up is recommended for early detection of relapse or immune restoration uveitis.	$CD4^+$ count <100 cells/mm^3
Isospora belli infection	Not applicable	Not applicable	Sustained increase in $CD4^+$ count to >200 cells/mm^3 for >6 mo in response to ART and without evidence of *I. belli* infection	No recommendation

Modified from Centers for Disease Control and Prevention. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents. Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Disease Society of America. *MMWR Morb Mortal Wkly Rep* 58(RR-4), 2009.

- Zidovudine (AZT) is recommended as a component of ART.
- Therapy should continue through the baby's birth. Zidovudine is given intravenously at the time of labor, regardless of whether it is an existing component of her three-drug regimen. In women with viral loads persistently >1000 copies/ml despite appropriate ART, cesarean section may further lower risk of transmission. Zidovudine (AZT) should also be given to the newborn for the first 6 weeks of life, and mothers should completely avoid nursing.

DISPOSITION

- Ongoing care consisting of frequent medical evaluations and monitoring of CD4 counts and HIV viral loads.
- Long-term care focused on providing up-to-date ART and prophylaxis of PJP and other opportunistic infections, as well as early detection of complications (see Section III)
- Ongoing assessment for cardiovascular risk and other primary prevention interventions.
- Screening for hepatitis A, B, and C. Treatment when indicated. Drugs such as tenofovir and lamivudine have activity against both HIV and hepatitis B and may be used in patients with co-infection.
- Vaccinations including hepatitis A and B (when susceptible), Pneumovax, tetanus/diphtheria/pertussis, and influenza. Box H1-9 summarizes vaccinations in HIV-positive adults.
- Yearly screening for other sexually transmitted infections (chlamydia, gonorrhea, syphilis).
- Consideration of AIDS (lymphomas, HPV) and non-AIDS related (screening for general population, age-specific cancers).

REFERRAL

To a physician knowledgeable and experienced in the management of HIV infection and its complications.

PREVENTION

- Truvada may be used as preexposure prophylaxis (PrEP). Individual who are HIV negative may take Truvada once a day to prevent HIV infection. PrEP has been demonstrated to be effective in MSM, heterosexuals, and injection drug users. Individuals on PrEP should be monitored every 3 months for renal dysfunction, HIV status, and adherence.
- Post-exposure prophylaxis (PEP) is an effective prevention intervention for individuals exposed to HIV infection, either occupationally or through a sexual exposure. PEP should be taken within 72 hours of an exposure and continued for 28 days. Baseline HIV status, renal function, hepatitis B/C, and liver function should be assessed. The recommended first-line regimen is raltegravir and Truvada.

BOX H1-9 Vaccination in HIV-Positive Adults

Generally Avoid
- VZV
- BCG
- Oral polio
- Oral typhoid

Avoid if CD4+ Cells <200
- Yellow fever
- Measles

Give Routinely
- Tetanus/diphtheria (or Tdap)
- Hepatitis B
- *Streptococcus pneumoniae*
- Hib
- Influenza, yearly
- Hepatitis A

Give if Indicated for Travel
- Typhoid Vi
- Meningococcal
- Polio, IPV
- Rabies
- Japanese encephalitis
- Tick-borne encephalitis

From Auerbach P: *Wilderness medicine, expert consult* Premium Edition—Enhanced Online Features and Print, Philadelphia, 2012, Saunders.

PEARLS & CONSIDERATIONS

COMMENTS

- HIV chemoprophylaxis after occupational exposure is described in Section V.
- Analysis of the impact of ART indicates that ART has saved at least 3 million years of life since the introduction into medicine more than 10 years ago.
- ART should be initiated in all HIV-infected individuals regardless of CD4 cell counts.
- Trials involving antiretroviral chemoprophylaxis before exposure for the prevention of HIV acquisition in MSM have shown that oral tenofovir disoproxil fumarate (FTC-TDF) provides protection against acquisition of HIV infection. This is known as *preexposure prophylaxis (PrEP)*. Detected blood levels strongly correlated with the prophylactic effect.
- ART in combination with avoidance of breastfeeding and elective cesarean section in women with viremia reduces risk for mother-to-child transmission.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Human Immunodeficiency Virus (HIV) Infection (Patient Information)

Acquired Immunodeficiency Syndrome (Related Key Topic)

AUTHOR: **PHILIP A. CHAN, M.D., M.S.**

EVIDENCE

Following extensive consultation and peer review, CDC and the Council of State and Territorial Epidemiologists have revised and combined the surveillance case definitions for human immunodeficiency virus (HIV) infection into a single case definition for persons of all ages (i.e., adults and adolescents aged ≥13 years and children aged <13 years). The revisions were made to address multiple issues, the most important of which was the need to adapt to recent changes in diagnostic criteria. Laboratory criteria for defining a confirmed case now accommodate new multitest algorithms, including criteria for differentiating between HIV-1 and HIV-2 infection and for recognizing early HIV infection. A confirmed case can be classified in one of five HIV infection stages (0, 1, 2, 3, or unknown); early infection, recognized by a negative HIV test within 6 months of HIV diagnosis, is classified as stage 0, and acquired immunodeficiency syndrome (AIDS) is classified as stage 3. Criteria for stage 3 have been simplified by eliminating the need to differentiate between definitive and presumptive diagnoses of opportunistic illnesses. Clinical (nonlaboratory) criteria for defining a case for surveillance purposes have been made more practical by eliminating the requirement for information about laboratory tests. The surveillance case definition is intended primarily for monitoring the HIV infection burden and planning for prevention and care on a population level, not as a basis for clinical decisions for individual patients. CDC and the Council of State and Territorial Epidemiologists recommend that all states and territories conduct case surveillance of HIV infection using this revised surveillance case definition.
For the complete document, please visit http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6303a1.htm.

SUGGESTED READINGS

Baeten JM et al.: Antiretroviral prophylaxis for HIV prevention in heterosexual men and women, *N Engl J Med* 367:399–410, 2012.

Boucher HC, Wolbers M, Porter K: 2010 Guidelines for antiretroviral treatment of HIV from the International AIDS Society-USA Panel, *JAMA* 304(17):2010, 1897.

Cain KP et al.: An algorithm for tuberculosis screening and diagnosis in people with HIV, *N Engl J Med* 362:707–716, 2010.

CDC issues new guidelines for community centers: routine HIV testing, counseling update, *AIDS Alert* 26(5):54–56, 2011.

Chou R et al.: Screening for HIV in pregnant women: systematic review to update the 2005 U.S. Preventive Services Task Force recommendation, *Ann Intern Med* 157:719–728, 2012.

Chu C, Selwyn PA: Diagnosis and initial management of acute HIV infection, *Am Fam Physician* 81(100):1239–1244, 2010.

Danel C et al.: CD4-guided antiretroviral treatment interruption strategy in HIV-infected adults in West Africa (Trivacan ANRS 1269 trial): a randomized trial, *Lancet* 367(9527):2006, 1981.

French N et al.: A trial of a 7-valent pneumococcal conjugate vaccine in HIV-infected adults, *N Engl J Med* 362:812–822, 2010.

Gallant JE et al.: Tenofir DF, emtricitabine, and efavirenz vs. zidovidine, lamivudine, and efaverenz for HIV, *N Engl J Med* 354(3):251, 2006.

Grant RM et al.: Pre-exposure chemoprophylaxis for HIV prevention in men who have sex with men, *N Engl J Med* 363:2587–2599, 2010.

Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents: *Developed by the DHHS Panel on Antiretroviral guidelines for Adults and Adolescents—A Working Group of the Office of AIDS Research Advisory Council*, January 10, 2011. Available at: http://AIDSinfo.nih.gov.

Gulick RM et al.: Three- vs four-drug antiretroviral regimens for the initial treatment of HIV-1 infection: a randomized controlled trial, *JAMA* 296(7):769, 2006.

Masur H, Kaplan JE: New guidelines for the management of HIV-related opportunistic infections, *JAMA* 301:2378–2382, 2009.

Riddler SA et al.: Class-sparing regimens for initial treatment of HIV-1 infection, *N Engl J Med* 358(2095), 2008.

Walensky RP et al.: The survival benefits of AIDS treatment in the United States, *J Infect Dis* 194(1):11, 2006. Online at www.cdc.gov/hiv/topics/surveillance/united_states.html.

Walensky RP et al.: Revising expectations from rapid HIV tests in the emergency department, *Ann Intern Med* 149(153), 2008.

BASIC INFORMATION

DEFINITION

Huntington's disease is an autosomal dominant neurodegenerative disorder characterized by involuntary movements, psychiatric disturbance, and cognitive decline.

SYNONYMS

Huntington's chorea

ICD-9CM CODES
333.4 Huntington's chorea
ICD-10CM CODES
G10 Huntington's disease

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Late 30s and 40s, with onsets from ages 2 to 70 yr
PREVALENCE (IN U.S.): 4.1 to 8.4 cases/100,000 persons
PREDOMINANT SEX: Female = male
PREDOMINANT AGE: Adulthood
GENETICS: Autosomal dominant

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Chorea: irregular, rapid, flowing, nonstereotyped involuntary movements. When there is a writhing quality, it is referred to as choreoathetosis. Chorea is present early on and tends to decrease in end stages of disease.
- Dancelike, lurching gait, often caused by chorea.
- Westphal variant: cognitive dysfunction, bradykinesia, and rigidity. This variant is more commonly seen in juvenile-onset Huntington's.
- Oculomotor abnormalities are common early on and include increased latency of response and insuppressible eye blinking.
- Psychiatric disorders (can be present early on): depression is commonly seen as well as obsessive-compulsive behaviors and aggression associated with impaired impulse control.

ETIOLOGY

- Trinucleotide repeat disorder
- The responsible gene is the Huntington gene located on chromosome 4. Its function is not known.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Drug-induced chorea: dopamine, stimulants, anticonvulsants, antidepressants, and oral contraceptives have all been known to cause chorea.
- Sydenham's chorea: decreased incidence with decline of rheumatic fever.
- Benign hereditary chorea: autosomal dominant with onset in childhood; non-progressive and without associated dementia or behavioral problems.
- Senile chorea: possibly vascular in origin.
- Wilson's disease: autosomal recessive; tremor, dysarthria, and dystonia are more common presentations than chorea. A total of 95% of patients with neurologic manifestations will have Kayser-Fleischer rings.
- Postinfectious.
- Systemic lupus erythematosus: can be the presenting feature of lupus (rare).
- Chorea gravidarum: presents during first 4 to 5 mo of pregnancy and resolves after delivery.
- Paraneoplastic: seen most commonly in small-cell lung cancer and lymphoma.

WORKUP

Onset of symptoms in an individual with an established family history requires no additional investigation.

LABORATORY TESTS

- Genetic testing for CAG repeats
- If genetic tests are normal, obtain complete blood count with smear, erythrocyte sedimentation rate, electrolytes, serum ceruloplasmin, 24-hr urinary copper excretion, TFTs, antinuclear antibody, liver function tests, HIV, and ASO titer. Consider paraneoplastic markers.

IMAGING STUDIES

CT scan or MRI scan will show atrophy, most notably in the caudate and putamen. The cortex is involved to a lesser extent. A normal scan does not exclude the diagnosis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive counseling
- Physical and occupational therapy
- Home health care
- Genetic counseling

CHRONIC Rx

- Chorea does not need to be treated unless it is disabling.
- Tetrabenazine (TBZ) is approved by the FDA for the symptomatic treatment of chorea seen in Huntington's disease. It is a reversible inhibitor of the vesicle monoamine transporter type 2 (VMAT-2). It inhibits primarily dopamine and to a lesser degree serotonin and norepinephrine. Side effects include parkinsonism and severe depression.
- Neuroleptics, typical or atypical, can be used for symptomatic management of neuropsychiatric issues and chorea at low doses (e.g., haloperidol 1 to 10 mg/day).
- Amantadine (up to 300 to 400 mg divided tid).
- Depression with suicidal ideation is common; may improve with tricyclic antidepressants or SSRI

DISPOSITION

Relentless course of variable duration leading to progressive disability and death

REFERRAL

- Should refer to psychiatry and neurology for treatment of mood disorders and movement disorders
- Genetic counseling

PEARLS & CONSIDERATIONS

- Suicide rate is fivefold that of the general population.
- The number of repeats does correlate with age of onset but does not clearly correlate with disease severity. Interpretation of number of repeats is still difficult at this time; therefore it is debatable whether to disclose this information to patients.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Huntington's Disease (Patient Information)

AUTHOR: **FARIHA ZAHEER, M.D.**

SUGGESTED READINGS

Bonelli RM et al.: Huntington's disease: present treatments and future therapeutic modalities, *Int Clin Psychopharmacol* 19:51, 2004.

Greenamyre JT: Huntington's disease, making connections, *N Engl J Med* 356: 5, 2007.

Higgins D: Chorea and its disorders, *Neuro Clin* 19(3):707, 2001.

Walker FO: Huntington's disease, *Lancet* 369:218–228, 2007.

BASIC INFORMATION

DEFINITION

A hydrocele is a fluid collection in a serous scrotal space, usually between the layers of the tunica vaginalis (Fig. H1-66). A hydrocele that fills with fluid from the peritoneum is termed *communicating*. This is distinguished from a *noncommunicating* hydrocele by history of variation in size throughout the day and palpation of a thickened cord above the testicle on the affected side. A communicating hydrocele is a small inguinal hernia in which fluid, but not peritoneal structures, traverses the processus vaginalis. In noncommunicating hydrocele, the processus vaginalis was obliterated during development. An abdominoscrotal hydrocele is a rare variant of a hydrocele in which there is a large, tense hydrocele that extends into the lower abdominal cavity.

ICD-9CM CODES
603.9 Hydrocele
ICD-10CM CODES
N43.3 Hydrocele, unspecified
N43 Hydrocele and spermatocele
N43.0 Encysted hydrocele
N43.1 Infected hydrocele
N43.2 Other hydrocele

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms:
- Scrotal enlargement
- Scrotal heaviness or discomfort radiating to the inguinal area
- Back pain

Physical findings:
- Most hydroceles are smooth and nontender. Scrotal distention may make it difficult to palpate the testis, but it is important to palpate the testis because some young men develop a hydrocele in association with a testis tumor
- Transillumination of the scrotum confirms the fluid-filled nature of the mass

ETIOLOGY

Hydroceles may occur as a congenital abnormality in which the processus vaginalis fails to close. In this case an inguinal hernia is virtually always associated with the malformation. Congenital hydroceles are most common in infants (1%-2% of neonates have hydroceles) and children. In adults, hydroceles are more frequently caused by infection, tumor, or trauma. Infection of the epididymis often results in the development of a secondary hydrocele. Tropical infections such as filariasis may produce hydroceles.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Spermatocele
- Inguinoscrotal hernia
- Testicular tumor
- Varicocele
- Epididymitis

IMAGING STUDIES

Scrotal ultrasound is useful to rule out a testicular tumor as the cause of the hydrocele (Fig. H1-67). The acute development of a hydrocele might be associated with the onset of epididymitis, testicular tumor, trauma, and torsion of a testicular appendage. An ultrasound of the scrotum may provide important diagnostic information.

TREATMENT

- No treatment if asymptomatic and testis is believed to be normal. Most congenital hydroceles resolve by 12 months of age following reabsorption of the hydrocele fluid.
- Surgical repair should be considered if the hydrocele is tense and large. Communicating hydroceles should be repaired in the same manner as an indirect hernia. The indications for repair of a noncommunicating hydrocele include failure to resolve and increase in size to one that is large and tense.
- Surgical correction is similar to a herniorrhaphy: an inguinal incision is made, the spermatic cord is identified, the hydrocele fluid is drained, and a high ligation of the processus vaginalis is performed.

PEARLS & CONSIDERATIONS

- The long-term risk of a communicating hydrocele is the development of an inguinal hernia.
- An inguinal hernia/hydrocele is likely if compression of the fluid-filled mass completely reduces the hydrocele.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hydrocele (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

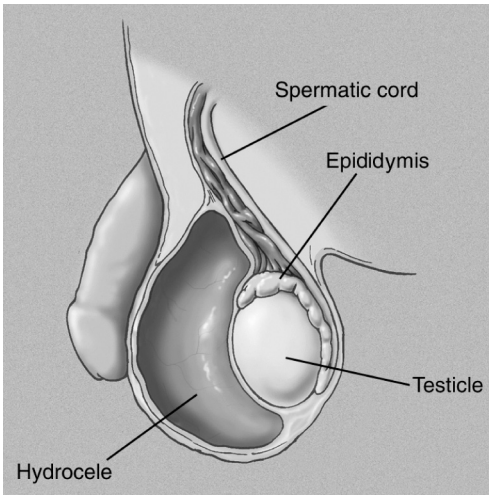


FIGURE H1-66 Schematic representation of the testicle, epididymis, spermatic cord, and a hydrocele. (From Lipshultz LI et al: *Urology and the primary care practitioner,* ed 3, Philadelphia, 2008, Elsevier.)

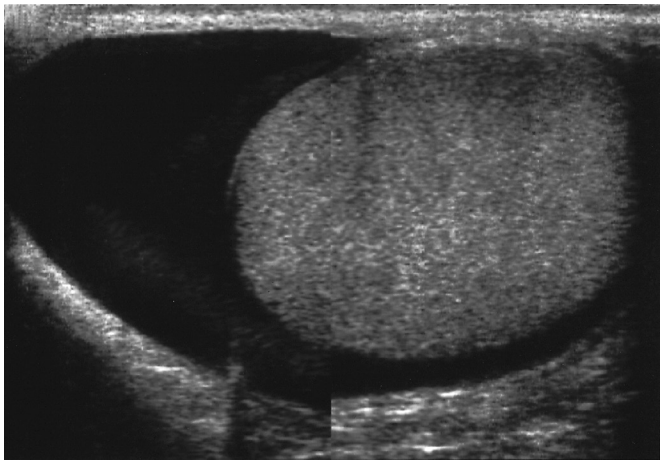


FIGURE H1-67 Longitudinal ultrasound view of normal testis and moderate hydrocele. (From Grainger RG et al [eds.]: *Grainger & Allison's diagnostic radiology,* ed 4, London, 2001, Harcourt.)

SUGGESTED READING

Elder JD: Disorders and anomalies of the scrotal contents. In: (editor: Kliegman R.M.; et al.) *Nelson textbook of pediatrics.* ed 19, Saunders: Philadelphia.

Hydrocephalus, Normal Pressure ALG PTG

BASIC INFORMATION

DEFINITION

Normal pressure hydrocephalus (NPH) is a syndrome of symptomatic hydrocephalus in the setting of normal cerebrospinal fluid (CSF) pressure. The classic clinical triad of NPH includes gait disturbance, cognitive decline, and incontinence.

SYNONYMS

Occult hydrocephalus
Extraventricular obstructive hydrocephalus
Chronic hydrocephalus

ICD-9CM CODES
331.3 Communicating hydrocephalus
ICD-10CM CODES
G91.2 Normal pressure hydrocephalus
G91.8 Other hydrocephalus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The exact incidence is not known. In one study the incidence was found to be 5.5 per 100,000, but it may account for up to 5% of dementia in the U.S. Hospital discharge data suggest approximately 11,500 new cases diagnosed annually (may be overestimated). The prevalence of NPH may be as high as 14% among extended care facility patients.
PREDOMINANT SEX: Males = females
PREDOMINANT AGE: NPH is more common with increasing age.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Gait difficulty: patients often have difficulty initiating ambulation, and the gait may be broad based and shuffling, with the appearance that the feet are stuck to the floor ("magnetic gait" or "frontal gait disorder").
- Cognitive decline: mental slowing, forgetfulness and inattention typically without agnosia, aphasia, or other cortical disturbances.
- Incontinence: initially may have urinary urgency; incontinence later develops. Fecal incontinence also occasionally occurs.
- Gegenhalten (paratonia) or other frontal lobe signs may be seen.

ETIOLOGY

- Approximately 50% of cases are idiopathic; the remaining cases have a variety of causes, including prior subarachnoid hemorrhage, meningitis, head trauma, or intracranial surgery.
- Symptoms are presumed to result from stretching of sacral motor and limbic fibers that lie near the ventricles as dilation occurs.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Alzheimer's disease with extrapyramidal features
- Cognitive impairment in the setting of Parkinson's disease or parkinsonism-plus syndromes
- Diffuse Lewy body disease
- Frontotemporal dementia
- Cervical spondylosis with cord compromise in the setting of degenerative dementia
- Multi-infarct dementia
- HIV dementia

WORKUP

- Large-volume lumbar puncture:
  1. Mental status testing and time to walk a prespecified distance (usually 25 feet) are measured, followed by removal of 40 to 50 ml of CSF.
  2. Retest of mental status and timed walking are done later (sometimes at 1 and 4 hr). Patients who have significant improvement in gait or mental status may have a better surgical outcome; those with mild or negative response can have variable outcomes.
  3. Opening and closing pressure are measured; if pressure is elevated, alternative causes must be considered. Higher *normal* pressure may predict a good outcome from CSF shunting.
- Measurement of CSF outflow resistance by an infusion test or CSF pressure monitoring is sometimes used to help predict surgical outcome. External lumbar drainage (ELD) is being used more commonly.

LABORATORY TESTS

- CSF should be sent for routine fluid analysis to exclude other pathologies.
- CSF biomarkers may be useful in excluding Alzheimer's disease.
- The CSF protein lipocalin-type prostaglandin D synthase (L-PGDS) is being studied as a potential diagnostic biomarker in idiopathic NPH.

IMAGING STUDIES

- CT scan or MRI can be used to document ventriculomegaly. The distinguishing feature of NPH is ventricular enlargement out of proportion to sulcal atrophy (Fig. EH1-68), and typically the frontal horn ratio exceeds 0.50. An algorithm for evaluation of patients with enlarged ventricles is described in Fig. EH1-69.
- MRI has advantages over CT, including better ability to visualize structures in the posterior fossa, visualize transependymal CSF flow (seen as periventricular hyperintensity), and document extent of white matter lesions. On MRI a flow void in the aqueduct and third ventricle ("jet sign"), thinning and elevation of the corpus callosum on sagittal images, rounding of the frontal horns, and a narrow CSF space at the high convexity/midline areas relative to Sylvian fissure size may be seen.
- Isotope cisternography and dynamic MRI studies have not been shown to be superior in predicting shunt outcome.

TREATMENT

There is no evidence that NPH can be effectively treated with medications.

NONPHARMACOLOGIC THERAPY

Response to ventriculoperitoneal shunting is variable. Some patients (variable depending on series reported) show significant improvement from shunting; however, effectiveness of shunting has never been demonstrated in a randomized-controlled trial. Gait is most likely to improve.
Factors that may predict positive outcome with surgery:
- NPH caused by prior trauma, subarachnoid hemorrhage, or meningitis
- History of mild impairment in cognition <2 yr duration
- Onset of gait abnormality before cognitive decline
- Imaging demonstrates hydrocephalus without sulcal enlargement, including normal-sized sylvian fissures and cortical sulci, and absent or mild white matter lesions.
- Transependymal CSF flow visualized on MRI
- Large-volume tap or ELD produces dramatic but temporary relief of symptoms
- High *normal* opening pressure

Factors that may predict negative outcome with surgery:
- Extensive white matter lesions or diffuse cerebral atrophy on MRI
- Moderate to severe cognitive impairment
- Onset of cognitive impairment before gait disorder
- History of alcohol abuse

ACUTE GENERAL Rx

Shunting in selected patients

DISPOSITION

Symptoms of NPH may progress over time. Prompt diagnosis may improve chances for treatment success.

REFERRAL

To neurologist for initial evaluation, including lumbar puncture, followed by neurosurgeon for shunting in appropriate patients

PEARLS & CONSIDERATIONS

Each of the cardinal symptoms of NPH is commonly seen in the elderly and occurs in multiple disease processes; therefore differential diagnoses should always be considered carefully.

CAUTION

Shunt complications, including subdural or intracerebral hematoma, may occur in 30% to 40% of patients.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Normal Pressure Hydrocephalus (Patient Information)

AUTHOR: **TAMARA G. FONG, M.D., PH.D.**

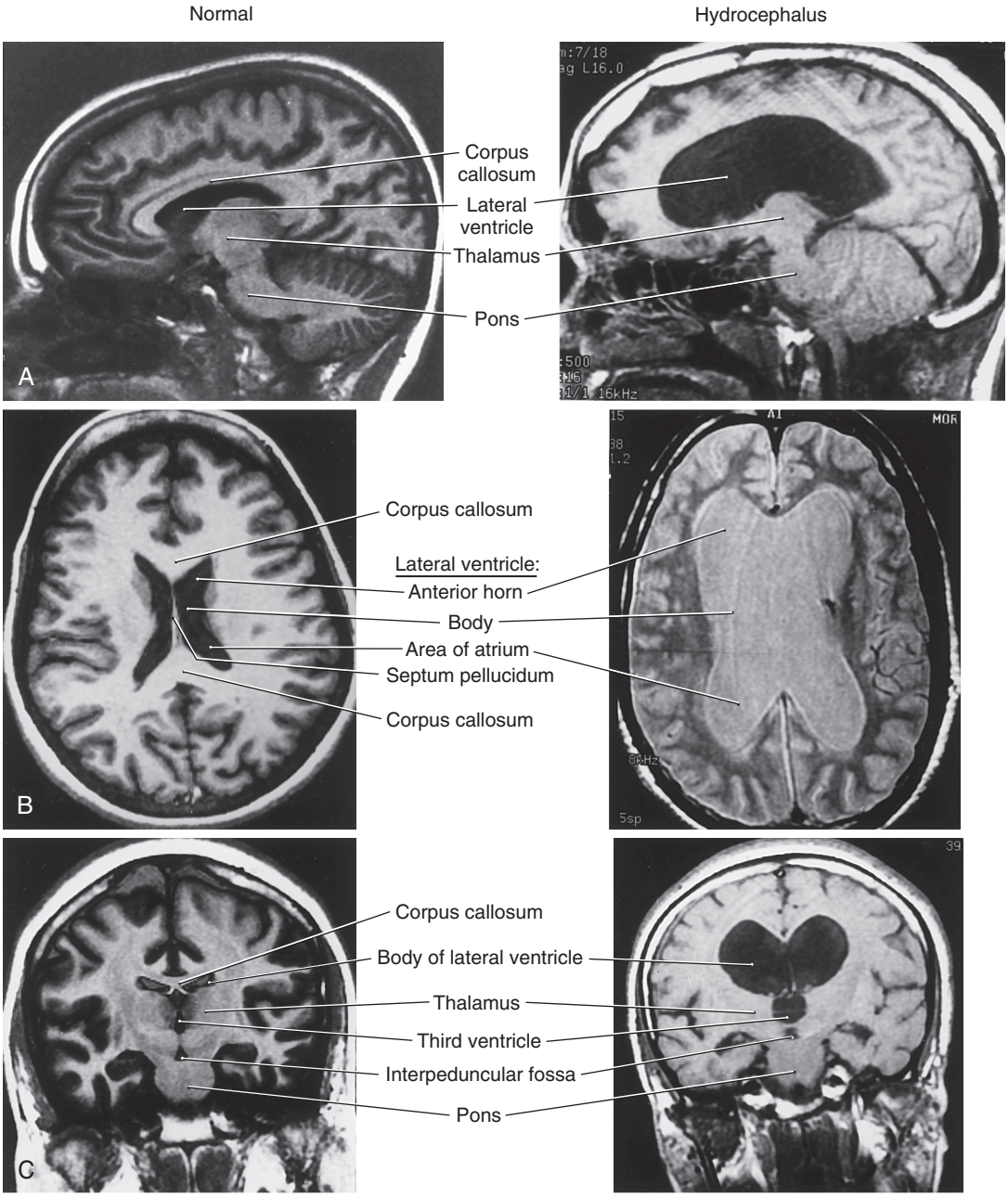


FIGURE EH1-68 Comparison of normal and hydrocephalic brains in sagittal **(A),** axial **(B),** and coronal **(C)** planes as seen on MR images. (From Haines DE: *Fundamental neuroscience for basic and clinical applications,* ed 3, Philadelphia, 2006, Churchill Livingstone.)

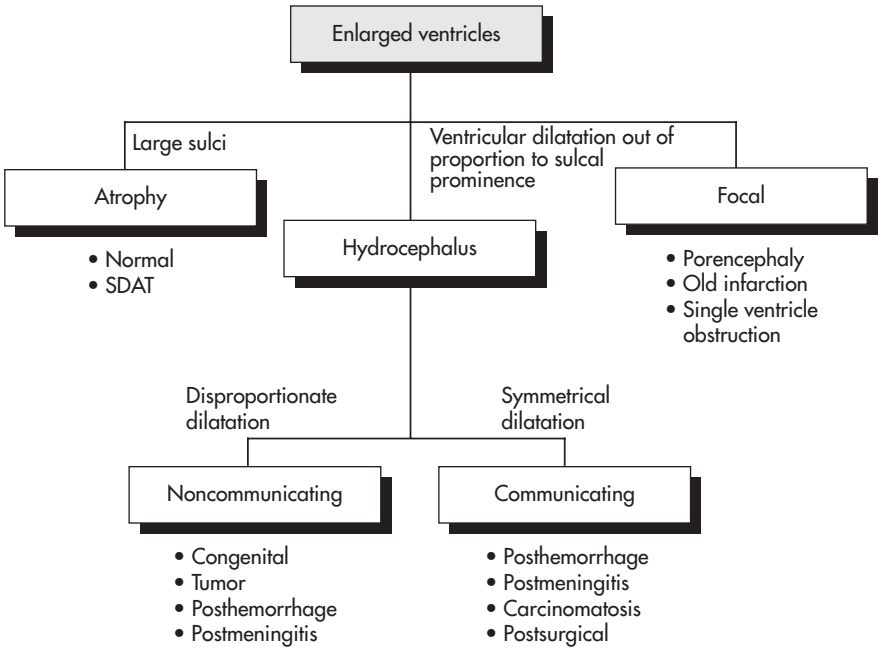


FIGURE EH1-69 Radiographic differential diagnosis of enlarged ventricles. (From Weissleder R et al: *Primer of diagnostic imaging,* ed 5, St. Louis, 2011, Mosby.)

SUGGESTED READINGS

Marmarou A, et al.: The value of supplemental prognostic tests for the preoperative assessment of idiopathic normal-pressure hydrocephalus, *Neurosurgery* 57(suppl 3):17–28, 2005.

Vanneste JA: Diagnosis and management of normal-pressure hydrocephalus, *J Neurol* 247(1):5, 2000.

BASIC INFORMATION

DEFINITION

Hydronephrosis is dilation of the renal pyelocalyceal system, most often as a result of impairment of urinary flow.

SYNONYMS

Hydroureter (dilation of ureter, often seen with hydronephrosis when obstruction is in lower urinary tract)
Urinary tract obstruction

ICD-9CM CODES
591 Acquired hydronephrosis
753.2 Congenital hydronephrosis
ICD-10CM CODES
N13.30 Unspecified hydronephrosis
Q62.39 Other obstructive defects of renal pelvis and ureter

EPIDEMIOLOGY & DEMOGRAPHICS

Children usually have congenital malformations, whereas adults tend to have acquired defects as etiologies.

CLINICAL PRESENTATION

HISTORY:

- Pain is caused by distention of collecting system or renal capsule and is more related to the rate of onset than the degree of obstruction. It can vary in location from flank to the lower abdomen to the testes/labia. Pain in the flank occurring only on micturition is highly suggestive of vesicoureteral reflux.
- Anuria can occur with total obstruction of urinary flow (bilateral hydronephrosis, or unilateral if only one kidney is present).
- Polyuria or nocturia can occur with chronic (incomplete) obstruction because of deleterious effects on renal concentrating ability (nephrogenic diabetes insipidus).
- Urinary frequency, hesitancy, poor stream, and postvoid dribbling are all symptoms that can occur with obstruction at or below the bladder (e.g., prostatic hyperplasia).
- Chronic urinary infections can either result from chronic urinary obstruction (organisms favoring growth with stasis of urine) or lead to conditions (e.g., urine pH changes) that favor stone formation and subsequent obstruction.

PHYSICAL EXAMINATION

- Hypertension can be caused by increased renin release in acute or subacute obstruction.
- Fever or costovertebral angle (CVA) tenderness can suggest urinary tract infection.
- Palpate bladder to detect if distention is present.
- Rectal examination to evaluate prostate for size and nodularity and also to check rectal sphincter tone.
- Pelvic examination to assess for vaginal anatomy, pelvic mass, or pelvic inflammatory disease.
- Penile examination to rule out meatal stenosis or phimosis.
- Bladder catheterization to assess postvoid residual volume if urinary tract obstruction is considered. Should rule out postrenal obstruction in unexplained acute renal failure.

ETIOLOGY

MECHANICAL IMPAIRMENTS

Congenital:

- Ureteropelvic junction narrowing
- Ureterovesical junction narrowing
- Ureterocele
- Retrocaval ureter
- Bladder neck obstruction
- Urethral valve
- Urethral stricture
- Meatal stenosis

Acquired:

- Intrinsic to urinary tract:
  1. Calculi
  2. Inflammation
  3. Trauma
  4. Sloughed papillae
  5. Ureteral tumor
  6. Blood clots
  7. Prostatic hypertrophy or cancer
  8. Bladder cancer
  9. Urethral stricture
  10. Phimosis
- Extrinsic to urinary tract:
  1. Gravid uterus
  2. Retroperitoneal fibrosis or tumor (e.g., lymphoma)
  3. Aortic aneurysm
  4. Uterine fibroids
  5. Trauma (surgical or nonsurgical)
  6. Pelvic inflammatory disease
  7. Pelvic malignancies (e.g., prostate, colorectal, cervical, uterine, bladder)

FUNCTIONAL IMPAIRMENTS

- Neurogenic bladder (often with adynamic ureter) can occur with spinal cord disease or diabetic neuropathy.
- Pharmacologic agents such as alpha-adrenergic antagonists and anticholinergic drugs can inhibit bladder emptying.
- Vesicoureteral reflux may occur.
- Pregnancy can cause hydroureter and hydronephrosis (on the right more often than left) as early as the second month. Hormonal effects on ureteral tone combine with mechanical factors.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Urinary stones
- Neoplastic disease
- Prostatic hypertrophy
- Neurologic disease
- Urinary reflux
- Urinary tract infection
- Medication effects
- Trauma
- Congenital abnormality of urinary tract

LABORATORY TESTS

- Serum blood urea nitrogen and creatinine to assess for renal insufficiency (usually implies bilateral obstruction or unilateral obstruction of a solitary kidney).
- Electrolytes may reveal hypernatremia, hyperkalemia, or distal renal tubular acidosis.
- Urinalysis and examination of sediment may reveal white blood cells, red blood cells, or bacteria in the appropriate setting (e.g., infection, stones), but often the sediment is normal in obstructive renal disease.

IMAGING STUDIES

- Assess kidney and bladder size with ultrasound (Fig. H1-70) as well as contour of collecting system and ureters. Ultrasound is >90% sensitive and specific for hydronephrosis and is noninvasive.
- Abdominal CT scan without IV contrast provides excellent localization of the site of obstruction (Fig. H1-71).
- Magnetic resonance (MR) imaging is an alternative to CT. MR Urography has a similar diagnostic yield to CT but is not yet widely practiced. Poor renal function may preclude the use of gadolinium.
- Once diagnosed, antegrade or retrograde ureterograms can further delineate the point of obstruction.

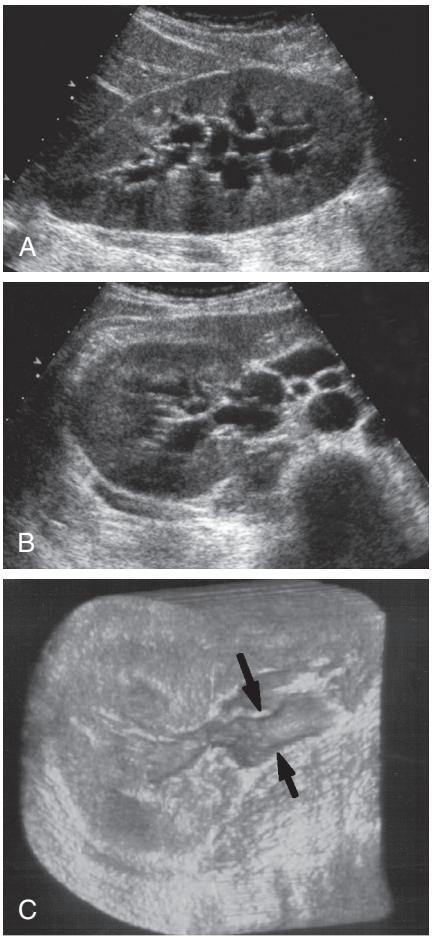


FIGURE H1-70 Renal ultrasound study demonstrating hydronephrosis. A, Sagittal image. **B,** Transverse image. **C,** Transverse three-dimensional surface-rendered image; *arrows* indicate the dilated proximal ureter. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

FIGURE H1-71 CT scan of the abdomen showing a grossly hydronephrotic kidney on the left. *Arrows* mark dilated renal pelvis. Dilated loops of small bowel are seen in the right hypochondrium. Sequential sections demonstrated that the ureter was dilated along its length and that there was a pelvic mass, which was responsible for both bowel and left ureteric obstruction. The mass was subsequently shown to be arising from a carcinoma of the colon. (From Johnson RJ, Feehally J: *Comprehensive clinical nephrology,* ed 2, St Louis, 2000, Mosby.)

- Voiding cystourethrogram is helpful in diagnosing vesicoureteral reflux and obstructions of the bladder neck or urethra.
- Diuretic renogram is sometimes used when there is hydronephrosis without apparent obstruction seen on any of the above studies. A loop diuretic is administered prior to a radionuclide scan. If obstruction is present, there will be slowed transit of the radioisotope during the scan, further dilation of the collecting system, and often reproduction of the patient's symptoms.
- A perfusion pressure flow study should be performed in a symptomatic patient with a negative or equivocal diuretic renogram.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Urgent treatment is required if urinary tract obstruction is associated with urinary tract infection, acute renal failure, or uncontrollable pain.
- Conservative management of calculi with IV fluids, IV antibiotics (if evidence of infection), and aggressive analgesia may be enough to treat acute unilateral urinary tract obstruction depending on the size (90% of stones <5 mm will pass spontaneously).
- Urethral catheter is adequate to relieve most obstructions at or distal to the bladder, but occasionally a suprapubic catheter will be required (e.g., impassable urethral stricture or urethral injury). Neurogenic bladder may require intermittent clean catheterization if frequent voiding and pharmacologic treatments are ineffective.
- Nephrostomy tube can be placed percutaneously to facilitate urinary drainage.
- Extracorporeal shock wave lithotripsy (ESWL) is used to fragment large stones to facilitate spontaneous passage or subsequent extraction. (Note: ESWL is contraindicated in pregnancy.)
- Nephroscopy is performed for extraction of proximal stones under direct visualization.
- Cystoscopy with ureteroscopy is used to remove distal ureteral stones with a loop or basket with or without fragmentation by ultrasonic or laser lithotripsy.
- Ureteral stents can be used for extrinsic and some intrinsic ureteral obstructions.
- Urethral dilation or internal urethrotomy can be used for urethral strictures.
- Nephrectomy or ureteral diversion may be required in severe cases (e.g., malignancy).
- Ureterovesical reimplantation can be used for reflux disease.
- Transurethral retrograde prostatectomy is used for severe obstruction from benign prostatic hypertrophy.
- IV fluid and electrolyte replacement are needed; the patient must be monitored closely during the postobstructive diuresis (usually lasting several days to a week).

ACUTE GENERAL Rx

Antibiotics if indicated

DISPOSITION

Aggressive treatment of infections and early relief of obstruction can usually prevent progressive loss of renal function; however, chronic bilateral obstruction (often from benign prostatic hypertrophy) can lead to chronic renal failure.

REFERRAL

- Urologist consultation early for diagnostic or therapeutic procedures
- Oncologist if a neoplasm is diagnosed
- Gynecologist if pregnancy or female pelvic anatomy is involved

PEARLS & CONSIDERATIONS

COMMENTS

- Not a primary disorder: an underlying etiology should be sought.

PREVENTION

May be achieved through prevention of an underlying potential etiology (e.g., medical or surgical management of benign prostatic hypertrophy before obstruction occurring or medical treatment to avoid formation of renal stones).

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hydronephrosis (Patient Information)

AUTHORS: **SHEENAGH M. BODKIN, M.D.,** and **PAUL A. PIRRAGLIA, M.D., M.P.H.**

SUGGESTED READINGS

EAU/AUA Nephrolithiasis Guideline Panel: *Guideline for the management of ureteral calculi*, Baltimore (M.D). American Urological Association Education and Research, Inc., European Association of Urology, 2007. 61 p. [92 references].

Lameire N et al.: Acute renal failure, *Lancet* 365:417–430, 2005.

Licurse A, Kim MC, Dziura J et al.: Renal ultrasonography in the evaluation of acute kidney injury, *Arch Intern Med* 170(21):1900–1907, 2010.

BASIC INFORMATION

DEFINITION

Hypercholesterolemia refers to a blood cholesterol measurement ≥200 mg/dl.

SYNONYMS

Hypercholesteremia
Dyslipidemia
Type II familial hyperlipoproteinemia

ICD-9CM CODES
272.0 Pure hypercholesterolemia
ICD-10CM CODES
E78.0 Pure hypercholesterolemia

EPIDEMIOLOGY & DEMOGRAPHICS

- Over 105 million (37%) adults in the U.S. have total blood cholesterol levels higher than 200 mg/dl. Of this group, more than 36 million adults have extremely high-risk cholesterol levels over 240 mg/dl (13%).
- For men over the age of 20 years, approximately 48% of white men, 45% of black men, and 50% of Hispanic men have high blood cholesterol.
- For women over the age of 20, approximately 50% of white women, 42% of black women, and 50% of Hispanic women have hypercholesterolemia.
- Prevalence of hypercholesterolemia increases with increasing age.
- According to NHANES data for 2009-2010, about 47% of adults had at least one of three risk factors for cardiovascular disease—uncontrolled high blood pressure, uncontrolled high levels of low-density lipoproteins (LDL) cholesterol, or current smoking.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- A detailed medication history should be performed because some medications may affect lipid levels (e.g., thiazides, corticosteroids, beta-blockers, and estrogens).
- The physical examination should include measurements of BMI and BP, thyroid and liver assessments, and examining peripheral pulses including carotids for bruits.
- Physical findings, particularly in the familial forms may include
  1. Tendon xanthomas
  2. Xanthelasma
  3. Arcus corneae
  4. Arterial bruits (young adulthood)

ETIOLOGY

Primary:
- Genetics
- Obesity
- Dietary intake

Secondary:
- Hypothyroidism
- Diabetes mellitus
- Nephrotic syndrome
- Obstructive liver disease: Hepatoma, extrahepatic biliary obstruction, primary biliary cirrhosis
- Alcohol or tobacco use
- Dysgammaglobulinemia (multiple myeloma, SLE)
- Drugs: Oral contraceptives, progesterone, corticosteroids, thiazide diuretics, β-blockers, androgenic steroids, retinoic acid derivatives, protease inhibitors

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Always consider underlying secondary causes for the elevated cholesterol.
- Patients with very high LDL cholesterol usually have genetic forms of hypercholesterolemia (see *Hyperlipoproteinemia, Primary*). Early detection of these cases and family testing to identify similarly affected relatives is important.
- Metabolic syndrome:
  1. A constellation of lipid and nonlipid risk factors of a metabolic origin
  2. Diagnosed when three or more of the following are present: abdominal obesity (waist circumference >40 in in men and >35 in in women); fasting triglycerides >150 mg/dl; HDL <40 mg/dl in males and <50 mg/dl in females; systolic BP >130 mmHg and diastolic BP >85 mmHg; fasting glucose >110 mg/dl

WHO SHOULD BE SCREENED

- AACE recommends screening of patients >20 yr of age for elevated cholesterol every 5 yr, males >45 yr and females >55 yr of age every 1-2 yr, and >65 yr of age every yr up to 75 yr of age regardless of CAD risk status. Patients above 75 yr of age with multiple CAD risk factors should still continue to get screened annually.
- The USPSTF supports routine screening for men aged >35 yr and women aged >45 yr by measurement of nonfasting total and HDL cholesterol alone.
- In 2010, the USPSTF recommended routine screening for overweight and obesity in persons aged <20 yr.
- In 2011, ACC/AHA recommended screening for hypertriglyceridemia by a nonfasting measurement. A nonfasting level of <200 mg/dl is commensurate with an optimal level of <100 mg/dl and no further testing is required. However, a nonfasting level of >200 mg/dl warrants further testing with a fasting lipid profile.

LABORATORY TESTS

- Obtain a fasting lipid profile.
- Perform a workup for secondary causes if clinically indicated such as TSH, metabolic profile, LFTs, and fasting glucose.

TREATMENT

NONPHARMACOLOGIC THERAPY

- First line of treatment: dietary therapy can result in 5% to 15% reduction in LDL cholesterol level.
- Composition of the **TLC diet:**
  1. Total fat 25% to 30% of total calories
  2. Polyunsaturated fat up to 10% of total calories
  3. Monounsaturated fat up to 20% of total calories
  4. Saturated fats <7% of total calories
  5. Carbohydrate 50% to 60% of total calories
  6. Protein 15% of total calories
  7. No more than 200 mg/day of cholesterol
  8. Fiber 20 to 30 g/day
- Increased physical activity: encourage 30 min of moderately intense physical activity, four to six times a week (e.g., brisk walking, riding stationary bike, water aerobics)
- Maintenance of a healthy weight
- Avoidance of tobacco products
- Counseling on CAD risk factors (Table H1-38)
- Plant-based diets (including stanol-containing margarines, oat bran, and nuts) have shown effectiveness in controlling lipids.

TABLE H1-38 Risk Factors for Heart Disease

1. Cigarette smoking
2. Hypertension (BP ≤140/90 mm Hg or on medications)
3. Low HDL cholesterol (<40 mg/dl)*
4. Family history of premature CHD (<55 yr in first-degree male relative or <65 yr in first-degree female relative)
5. Age (men ≥45 yr, women ≥55 yr)

*HDL cholesterol >60 mg/dl counts as a negative risk factor; its presence removes one risk factor from the total count.

TABLE H1-39 Atherosclerotic Cardiovascular Disease

1. Coronary heart disease: acute coronary syndromes, history of myocardial infarction, stable or unstable angina, coronary or other arterial revascularization
2. Stroke or transient ischemic attack
3. Peripheral arterial disease

ACUTE GENERAL Rx

No acute treatment needed

CHRONIC Rx

- The current guidelines represent a substantial departure from previous recommendations, which were based on LDL levels.
- The new guidelines identify **four high-risk groups** that benefit from statin therapy:
  Patients with clinical ASCVD (atherosclerotic cardiovascular disease) (Table H1-39)
  LDL ≥190 mg/dl
  DM aged 40-75 years and LDL 70-189 mg/dl
  Ten-year risk for ASCVD ≥7.5% and LDL 70-189 mg/dl
- The 10-year risk of ASCVD is calculated with the risk calculator available at http://my.americanheart.org/cvriskcalculator
- ASCVD events are reduced by using the maximum tolerated statin intensity in the above groups shown to benefit the most (Tables H1-40 and H1-41).

TABLE H1-40 Statin Intensity Therapies

High Intensity (Decrease LDL-C ≥50%)	Moderate Intensity (Decrease LDL-C 30%-49%)
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg
—	Simvastatin 20-40 mg
—	Pravastatin 40-80 mg
—	Lovastatin 40 mg
—	Fluvastatin XL 80 mg
—	Fluvastatin 40 mg bid
—	Pitavastatin 2-4 mg

LDL-C, Low-density lipoprotein cholesterol.
From Stone N et al: 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 63(25 Pt. B):2889, 2014.

TABLE H1-41 Statin Benefit Groups and Recommended Therapy

Statin Benefit Group	High Intensity	Moderate Intensity	Additional Testing
Clinical ASCVD	Yes	Consider†	None
Primary LDL-C >190 mg/dl	Yes	Consider†	None
Diabetes without ASCVD and 10-year risk ≥7.5%*	Yes	Consider†	None
Diabetes without ASCVD and 10-year risk <7.5%*	Consider‡	Yes	Case-by-case
Primary prevention and 10-year risk ≥7.5%*	Consider‡	Yes	Case-by-case
Primary prevention and 10-year risk <7.5%*	Consider‡	Consider‡	Case-by-case

ASCVD, Atherosclerotic cardiovascular disease; *LDL-C*, low-density lipoprotein cholesterol.
*Based on Pooled Cohort Risk Equations.
†If age >75 years or not candidate for high intensity.
‡If abnormal high-sensitivity C-reactive protein, coronary artery calcium, ankle-brachial index, lifetime risk.
From Boyden TF et al: Implementing new guidelines in the management of blood cholesterol, *Am J Med* 127:705, 2014.

- Additional factors such as CRP >2 mg/L, primary LDL >160, genetic hyperlipidemias, family history of premature CHD, ABI <0.9, and CAD score >300 Agatston units may be used in patients who are not in one of four statin benefit groups and for whom a decision to initiate statin therapy is otherwise unclear.
- Percent reduction in LDL cholesterol is used as a guide to compliance and adherence to therapy but is not considered a treatment goal.
- Moderate-intensity statin therapy should be continued for individuals >75 years of age for secondary prevention. However, factors such as comorbidities, safety, and priorities of care should be considered before initiating statins for primary prevention of ASCVD.
- Adherence to lifestyle and to statin therapy should be reiterated with patients before the addition of a nonstatin drug.
- Nonstatin therapies do not provide acceptable ASCVD risk reduction benefits compared with their potential adverse effects in ASCVD prevention.
- High-risk patients with a suboptimal response to statins who are unable to tolerate a recommended intensity or who are completely statin intolerant may benefit from the addition of a nonstatin cholesterol-lowering agent.
- The management of metabolic syndrome includes weight reduction, increased physical activity, and treatment of hypertension, elevated triglycerides, and low HDL cholesterol.
- According to recent studies, each 40 mg/dl reduction in LDL cholesterol by statin therapy confers a 20% reduction in ASCVD. In other words, a relative risk reduction of 30% in ASCVD by moderate-intensity therapy and 45% by high-intensity therapy has been approximated.

DISPOSITION AND FOLLOW-UP

- Baseline LFT testing should be done before initiation of statin therapy and as clinically indicated thereafter.
- CK level monitoring is not recommended unless a patient reports muscle weakness or myalgias.
- Statin therapy should be monitored by repeating a lipid profile within 4-12 weeks after initiation of therapy.
- Counseling about behavioral lifestyle changes and risk factors for CHD should be provided at every follow-up visit.
- Adverse effects of statin-associated diabetes varies by statin intensity: 1 excess case of diabetes per 1000 treated individuals with moderate-intensity statin and 3 excess cases of diabetes per 1000 treated individuals with high-intensity statin per year has been reported. Myopathy and hemorrhagic stroke incidence is around 1 excess case per 10,000 treated individuals.
- Per new guidelines, those who develop diabetes during statin therapy should be advised to continue it to reduce their risk of ASCVD events and should adhere to a heart-healthy diet, engage in physical activity, cease tobacco use, and maintain a healthy body weight (Table H1-42).

REFERRAL

Patients with rare lipid disorders, hyperlipoproteinemias, patients resistant to treatment, on complex regimens, and with evidence of disease progression despite treatment should be referred to a lipid specialist.

PEARLS & CONSIDERATIONS

COMMENTS

- The American Academy of Pediatrics (AAP) guideline (*Pediatrics* 122:198, 2008) recommends consideration toward pharmacologic treatment for children with LDL >190 mg/dl or >160 mg/dl if other risk factors are present.
- *HDL cholesterol efflux capacity* refers to the ability of HDL to accept cholesterol from macrophages, which is a key step in reverse cholesterol transport. It is inversely associated with the incidence of cardiovascular events and may be a useful biomarker when added to traditional risk factors.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

High Cholesterol (Patient Information)
Hyperlipoproteinemia, Primary (Related Key Topic)

AUTHOR: **PRIYA BANSAL, M.D., M.P.H.**

TABLE H1-42 Drugs Affecting Lipoprotein Metabolism

Drug Class	Agents and Daily Doses	Lipid/Lipoprotein Effects	Side Effects	Contraindications
HMG-CoA reductase inhibitors (statins)	Lovastatin (10-40 mg) Pravastatin (10-80 mg) Simvastatin† (5-80 mg) Fluvastatin (20-40 mg) Atorvastatin (10-80 mg) Rosuvastatin (5-40 mg) Pitavastatin (2-4 mg)	LDL↓ 20%-60% HDL↑ 5%-15% TG ↓ 7%-30%	Myalgias, myositis Increased liver enzymes New onset diabetes (with intensive therapy) Unproven concerns about memory loss	Active or chronic liver disease Pregnancy Concomitant use of certain drugs*
Bile acid sequestrants	Colestipol (5-20 g) Colesevelam‡ (2.6-3.8 g) Cholestyramine (4-16 g)	LDL↓ 15%-30% HDL↑ 3%-5% TG No change or increase	Gastrointestinal distress, constipation, drug interaction, hypertriglyceridemia Decreased absorption of fat-soluble vitamins	TG >300 mg/dl GI motility disorder
Omega-3 fatty acids	Fish oils (4-6 g)	TG ↓ 45% HDL↑ 13%	Increased bleeding time Nausea	Caution with anticoagulant therapy
Nicotinic acid	Immediate release (niacin) (1.5-3 g) Extended-release (Niaspan) (1-2 g)	LDL↓ 5%-25% HDL↑ 15%-35% TG ↓ 20%-50%	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity	Chronic liver disease Severe gout Diabetes Peptic ulcer disease Pregnancy/lactation
Fibric acids	Gemfibrozil (600 mg bid) Fenofibrate (45-145 mg)	LDL↓ 5%-20% HDL↑ 10%-20% TG ↓ 20%-50%	Dyspepsia Gallstones Myopathy (especially with concomitant use of gemfibrozil and statins)	Severe renal disease (dose adjustment for fenofibrate) Severe hepatic disease Caution with statins Can worsen LDL cholesterol
Ezetimibe (cholesterol absorption inhibitor)	Ezetimibe (10 mg)	LDL↓ 18% HDL↑ 1% TG ↓ 8%	Abdominal pain; myalgias	Liver disease Avoid with resins and fibrates

Modified from The National Cholesterol Education Program, *JAMA* 285:2486, 2001.

*Cyclosporine, macrolide antibiotics, various antifungal agents, and cytochrome P-450 inhibitors (fibrates and niacin should be used with appropriate caution).

†Dosages of 80 mg of simvastatin are no longer recommended. Potential interactions with amlodipine and ranolazine warrant doses ≤2 mg daily.

- Maintain patients on simvastatin 80 mg only if they have been taking this dose for 12 or more months without evidence of muscle toxicity.
- Do not start new patients on simvastatin 80 mg.
- Place patients who do not meet their LDL goal on simvastatin 40 mg on alternative LDL-C-lowering treatment(s) to reach goal.

‡Colesevelam reduces glucose and A1c ~0.5% and has been approved for treatment of diabetes with dyslipidemia.

EVIDENCE

Abstract[1]

Background:
High-density lipoprotein (HDL) may provide cardio-vascular protection by promoting reverse cholesterol transport from macrophages. We hypothesized that the capacity of HDL to accept cholesterol from macrophages would serve as a predictor of atherosclerotic burden.
Methods:
We measured cholesterol efflux capacity in 203 healthy volunteers who underwent assessment of carotid artery intima–media thickness, 442 patients with angiographically confirmed coronary artery disease, and 351 patients without such angiographically confirmed disease. We quantified efflux capacity by using a validated ex vivo system that involved incubation of macrophages with apolipoprotein B–depleted serum from the study participants.
Results:
The levels of HDL cholesterol and apolipoprotein A-I were significant determinants of cholesterol efflux capacity but accounted for less than 40% of the observed variation. An inverse relationship was noted between efflux capacity and carotid intima-media thickness both before and after adjustment for the HDL cholesterol level. Furthermore, efflux capacity was a strong inverse predictor of coronary disease status (adjusted odds ratio for coronary disease per 1-SD increase in efflux capacity, 0.70; 95% confidence interval [CI], 0.59 to 0.83; P<0.001). This relationship was attenuated, but remained significant, after additional adjustment for the HDL cholesterol level (odds ratio per 1-SD increase, 0.75; 95% CI, 0.63 to 0.90; P = 0.002) or apolipoprotein A-I level (odds ratio per 1-SD increase, 0.74; 95% CI, 0.61 to 0.89; P = 0.002). Additional studies showed enhanced efflux capacity in patients with the metabolic syndrome and low HDL cholesterol levels who were treated with pioglitazone, but not in patients with hypercholesterolemia who were treated with statins.
Conclusions:
Cholesterol efflux capacity from macrophages, a metric of HDL function, has a strong inverse association with both carotid intima–media thickness and the likelihood of angiographic coronary artery disease, independently of the HDL cholesterol level. (Funded by the National Heart, Lung, and Blood Institute and others.) Ⓐ

Abstract[2]

Purpose:
Alpha-lipoic acid is an essential cofactor for mitochondrial respiratory enzymes that improves mitochondrial function. We previously reported that alpha-lipoic acid markedly reduced body weight gain in rodents. The purpose of this study was to determine whether alpha-lipoic acid reduces body weight in obese human subjects.
Methods:
In this randomized, double-blind, placebo-controlled, 20-week trial, 360 obese individuals (body mass index [BMI] ≥ 30 kg/m^2 or BMI 27-30 kg/m^2 plus hypertension, diabetes mellitus, or hypercholesterolemia) were randomized to alpha-lipoic acid 1200 or 1800 mg/d or placebo. The primary end point was body weight change from baseline to end point.
Results:
The 1800 mg alpha-lipoic acid group lost significantly more weight than the placebo group (2.1%; 95% confidence interval, 1.4-2.8; *P*<.05). Urticaria and itching sensation were the most common adverse events in the alpha-lipoic acid groups, but these were generally mild and transient.
Conclusion:
Alpha-lipoic acid 1800 mg/d led to a modest weight loss in obese subjects. Alpha-lipoic acid may be considered as adjunctive therapy for obesity. Ⓐ

Abstract[3]

Background:
Hypercholesterolemia is a risk factor for coronary artery disease and closely linked to unstable plaque. Hypoadiponectinemia is frequently observed in patients with metabolic syndrome complicated with macroangiopathy and predicts poor clinical outcome. Spectral analysis of intravascular ultrasonography radiofrequency (IVUS-Virtual Histology [VH]) allows quantitative analysis of plaque composition. The purpose of this study was to verify the effects of low-density lipoprotein (LDL) cholesterol level on plaque morphology, and test the hypothesis that adiponectin influences coronary plaque volume and composition.
Methods:
Preintervention IVUS-VH using a continuous pullback was performed in 92 coronary vessels in 92 patients with coronary artery disease. The morphological distribution of plaque was evaluated prospectively in a 60-mm segment of coronary vessels containing the culprit lesion.
Results:
Serum LDL cholesterol levels correlated positively with necrotic core volume (r = 0.217, *P* = 0.037) and percent necrotic core tissue (r = 0.308, *P* = 0.003), while plasma adiponectin levels correlated negatively with plaque volume (r = –0.297, *P* = 0.004) and necrotic core volume (r = –0.306, *P* = 0.003). Multiple regression analyses showed close association between necrotic core volume and statin-use (β = –21.68, *P* = 0.004) and adiponectin levels (β = –31.25, *P* = 0.038), and that percent necrotic core tissue was influenced by statin-use (β = –4.595, *P* = 0.026) and LDL cholesterol levels (β = 0.092, *P* = 0.031).
Conclusions:
Adiponectin is closely linked to coronary plaque volume. Hypercholesterolemia and hypoadiponectinemia correlate with necrotic core lesions and may contribute to increased risk of coronary plaque vulnerability. Statins can effectively prevent necrotic core plaque formation associated with hypercholesterolemia and hypoadiponectinemia. Ⓐ

Abstract[4]

Objectives:
The aim of this study was to test the hypothesis that elevated nonfasting remnant cholesterol is a causal risk factor for ischemic heart disease independent of reduced high-density lipoprotein (HDL) cholesterol.
Background:
Elevated remnant cholesterol is associated with elevated levels of triglyceride-rich lipoproteins and with reduced HDL cholesterol, and all are associated with ischemic heart disease.
Methods:
A total of 73,513 subjects from Copenhagen were genotyped, of whom 11,984 had ischemic heart disease diagnosed between 1976 and 2010. Fifteen genetic variants were selected, affecting: 1) nonfasting remnant cholesterol alone; 2) nonfasting remnant cholesterol and HDL cholesterol combined; 3) HDL cholesterol alone; or 4) low-density lipoprotein (LDL) cholesterol alone as a positive control. The variants were used in a Mendelian randomization design.
Results:
The causal odds ratio for a 1 mmol/l (39 mg/dl) genetic increase of nonfasting remnant cholesterol was 2.8 (95%confidence interval [CI]: 1.9 to 4.2), with a corresponding observational hazard ratio of 1.4 (95%CI: 1.3 to 1.5). For the ratio of nonfasting remnant cholesterol to HDL cholesterol, corresponding values were 2.9 (95% CI: 1.9 to 4.6) causal and 1.2 (95% CI 1.2 to 1.3) observational for a 1-U increase. However, for HDL cholesterol, corresponding values were 0.7 (95% CI: 0.4 to 1.4) causal and 1.6 (95% CI: 1.4 to 1.7) observational for a 1 mmol/l (39 mg/dl) decrease. Finally, for LDL cholesterol, corresponding values were 1.5 (95% CI: 1.3 to 1.6) causal and 1.1 (95% CI: 1.1 to 1.2) observational for a 1 mmol/l (39 mg/dl) increase.
Conclusions:
A nonfasting remnant cholesterol increase of 1 mmol/l (39 mg/dl) is associated with a 2.8-fold causal risk for ischemic heart disease, independent of reduced HDL cholesterol. This implies that elevated cholesterol content of triglyceride-rich lipoprotein particles causes ischemic heart disease. However, because pleiotropic effects of the genetic variants studied cannot be totally excluded, these findings need to be confirmed using additional genetic variants and/or randomized intervention trials. Ⓐ

Abstract[5]

Background:
Serum proprotein convertase subtilisin/kexin 9 (PCSK9) binds to low-density lipoprotein (LDL) receptors, increasing the degradation of LDL

receptors and reducing the rate at which LDL cholesterol is removed from the circulation. REGN727/SAR236553 (designated here as SAR236553), a fully human PCSK9 monoclonal antibody, increases the recycling of LDL receptors and reduces LDL cholesterol levels.

Methods:

We performed a phase 2, multicenter, double-blind, placebo-controlled trial involving 92 patients who had LDL cholesterol levels of 100 mg per deciliter (2.6 mmol per liter) or higher after treatment with 10 mg of atorvastatin for at least 7 weeks. Patients were randomly assigned to receive 8 weeks of treatment with 80 mg of atorvastatin daily plus SAR236553 once every 2 weeks, 10 mg of atorvastatin daily plus SAR236553 once every 2 weeks, or 80 mg of atorvastatin daily plus placebo once every 2 weeks and were followed for an additional 8 weeks after treatment.

Results:

The least-squares mean (±SE) percent reduction from baseline in LDL cholesterol was 73.2±3.5 with 80 mg of atorvastatin plus SAR236553, as compared with 17.3±3.5 with 80 mg of atorvastatin plus placebo ($P < 0.001$) and 66.2±3.5 with 10 mg of atorvastatin plus SAR236553. All the patients who received SAR236553, as compared with 52% of those who received 80 mg of atorvastatin plus placebo, attained an LDL cholesterol level of less than 100 mg per deciliter, and at least 90% of the patients who received SAR236553, as compared with 17% who received 80 mg of atorvastatin plus placebo, attained LDL cholesterol levels of less than 70 mg per deciliter (1.8 mmol per liter).

Conclusions:

In a randomized trial involving patients with primary hypercholesterolemia, adding SAR236553 to either 10 mg of atorvastatin or 80 mg of atorvastatin resulted in a significantly greater reduction in LDL cholesterol than that attained with 80 mg of atorvastatin alone. (Funded by Sanofi and Regeneron Pharmaceuticals; ClinicalTrials.gov number, NCT01288469.) Ⓐ

Abstract[6]

Objectives:

The aim of this study was to evaluate the safety, tolerability, and effects of AMG 145 on low-density lipoprotein cholesterol (LDL-C) in healthy and hypercholesterolemic subjects on statin therapy.

Background:

Proprotein convertase subtilisin/kexin type 9 (PCSK9) down-regulates surface expression of the low-density lipoprotein receptor (LDL-R), increasing serum LDL-C. AMG 145, a fully human monoclonal antibody to PCSK9, prevents PCSK9/LDL-R interaction, restoring LDL-R recycling.

Methods:

Healthy adults (phase 1a) were randomized to 1 dose of AMG 145: 7, 21, 70, 210, or 420 mg SC; 21 or 420 mg IV; or matching placebo. Hypercholesterolemic adults (phase 1b) receiving low- to moderate-dose statins were randomized to multiple SC doses of AMG 145: 14 or 35 mg once weekly (QW) ×6, 140 or 280 mg every 2 weeks (Q2W) ×3, 420 mg every 4 weeks ×2, or matching placebo. Eleven subjects receiving high-dose statins and 6 subjects with heterozygous familial hypercholesterolemia were randomized to SC AMG 145 140 mg or placebo Q2W ×3.

Results:

In the trials (AMG 145 n = 85, placebo n = 28), AMG 145 reduced LDL-C up to 64% ($P < .0001$) versus placebo after 1 dose ≥21 mg and up to 81% ($P < .001$) with repeated doses ≥35 mg QW. No serious adverse events (AEs) occurred. Overall incidence of treatment-emergent AEs was similar in AMG 145 versus placebo groups: 69% versus 71% (phase 1a); 65% versus 64% (phase 1b).

Conclusions:

In phase 1 studies, AMG 145 significantly reduced serum LDL-C in healthy and hypercholesterolemic statin-treated subjects, including those with heterozygous familial hypercholesterolemia or taking the highest doses of atorvastatin or rosuvastatin, with an overall AE profile similar to placebo. Ⓐ

Evidence-Based References

Khera AV et al.: Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis, *N Engl J Med* 364:127–135, 2011. Ⓐ

Koh EH et al.: Effects of alpha-lipoic acid on body weight in obese subjects, *Am J Med* 124:85.e1–85.e8, 2011. Ⓐ

Kojima S et al.: Hypercholesterolemia and hypoadiponectinemia are associated with necrotic core-rich coronary plaque, *Int J Cardiol* 147:371–376, 2011. Ⓐ

Roth EM et al.: Atorvastatin with or without an antibody to PCSK9 in primary Hypercholesterolemia, *N Engl J Med* 367:1891–1900, 2012. Ⓐ

Dias CS et al.: Effects of AMG 145 on low-density lipoprotein cholesterol levels: results from 2 randomized, double-blind, placebo-controlled, ascending-dose phase 1 studies in healthy volunteers and hypercholesterolemic subjects on statins, *J Am Coll Cardiol* 60:1888–1898, 2012. Ⓐ

SUGGESTED READINGS

de Lemos JA et al.: Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial, *JAMA* 292(1307), 2004.

Grundy SM et al.: Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines, *Circulation* 110:227–239, 2004.

Kenney JF et al.: A pragmatic view of the new cholesterol treatment guidelines, *N Engl J Med* 370:275–278, 2014.

La Rosa JC et al.: Intensive lipid lowering with atorvastatin in patients with stable coronary disease, *N Engl J Med* 352(1425), 2005.

Mosca L et al.: National study of physician awareness and adherence to cardiovascular disease prevention guidelines, *Circulation* 111(499), 2005.

National Cholesterol Education Program: Second Report on the Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults (adult treatment panel IV), *JAMA* 285(2486), 2001.

Pletcher MJ et al.: Non-optimal lipids commonly present in young adults and coronary calcium later in life: The CARDIA (Coronary Artery Risk Development in Young Adults) study, *Ann Intern Med* 153:137–146, 2010.

Rohatgi A et al.: HDL cholesterol efflux capacity and incident cardiovascular events, *N Engl J Med* 371:2383–2393, 2014.

Stone NJ et al.: Treatment of blood cholesterol to reduce atherosclerotic cardiovascular disease risk in adults: synopsis of the 2013 American College of Cardiology/American Heart Association cholesterol guidelines, *Ann Intern Med* 160:339–343, 2014.

Hypercoagulable State PTG

BASIC INFORMATION

DEFINITION

Hypercoagulable state is an inherited or acquired condition associated with an increased risk of thrombosis.

SYNONYMS

Thrombophilia

ICD-9CM CODES
289.8 Hypercoagulable state
ICD-10CM CODES
D68.5 Primary thrombophilia
D68.6 Other thrombophilia
D68.8 Other specified coagulation defects
D68.9 Coagulation defect, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: See Table H1-43.
PREVALENCE, PREDOMINANT SEX, AND AGE: Significant variations in the prevalence rates and thrombotic risks for thrombophilia are reported. This may reflect geographic variation in the prevalence of genetic defects, different populations, or the presence of other unidentified thrombophilic risk factors. When thrombosis occurs, it is often associated with an acquired risk factor (e.g., surgery, pregnancy, oral contraceptive [OC] use). Annual risk of thrombosis is <1%.
GENETICS

- Most people with a genetic defect will not have thrombotic disease.
- Multiple genetic defects are not uncommon (1% to 2% prevalence in patients with idiopathic venous thromboembolism [VTE]); strong synergistic effect when multiple defects are present. Low risk of recurrent thrombosis in patients with a single genetic defect. Approximately half of patients with unprovoked thrombosis have an identifiable inherited thrombophilia.

RISK FACTORS: Family history of thrombosis, increasing age, tobacco use, immobility, surgery, prior history of DVT, pregnancy, hormone replacement therapy, trauma, connective tissue disease, underlying malignancy, medications (Megace, tamoxifen, birth control pills)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Inherited thrombophilia is usually associated with VTE, most commonly deep vein thrombosis (DVT)
- Some acquired thrombophilias are associated with arterial thrombosis. Table EH1-44 describes sites of thrombosis according to coagulation defect.
- Pregnancy complications
- Medical conditions associated with increased risk of thrombosis

ETIOLOGY

See Table H1-45. The differential diagnosis of the patient presenting with thrombosis or thrombotic diathesis is described in Section II. Figure EH1-72 describes components of thrombus formation and actions of various antithrombotic and thrombolytic agents.

- Thrombosis is often a multifactorial process with genetic, environmental, and acquired factors. Table H1-46 describes causes of acquired deficiencies in antithrombin III, protein S, or protein C.
- Thrombotic risk increases with use of OCs or hormone replacement therapy (HRT) and during the pregnancy/postpartum period.
- Adverse pregnancy outcomes may be caused by thrombosis of the uteroplacental circulation.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

INHERITED: Factor V Leiden (FVL) mutation:

- Autosomal-dominant mutation with low penetrance.
- Causes activated protein C resistance (APCR); 90% of APCR is caused by FVL mutation.
- Most common inherited thrombophilia; accounts for 40% to 50% of cases.
- OC use in heterozygous carriers is associated with an eightfold increased risk of VTE compared with noncarriers and a thirty-fivefold increased risk of VTE compared with noncarriers not using OCs.
- May be associated with cardiovascular disease in select high-risk subgroups.

Prothrombin G20210A mutation:

- Autosomal-dominant mutation with low penetrance.
- OC use in heterozygous carriers is associated with a sixteenfold increased risk of VTE compared with noncarriers not using OCs.
- May be associated with cardiovascular disease in select high-risk subgroups and young patients with ischemic stroke.

TABLE H1-45 Potential Prothrombotic States

Congenital
Deficiency of anticoagulants
AT-III, protein C or protein S, plasminogen
Resistance to cofactor proteolysis
Factor V Leiden
High levels of procoagulants
Prothrombin 20210 mutation
Elevated factor VIII levels
Damage to endothelium
Homocysteinemia
Acquired
Obstruction to flow
Indwelling lines
Pregnancy
Polycythemia/dehydration
Immobilization
Injury
Trauma, surgery, exercise
Inflammation
IBD, vasculitis, infection, Behçet syndrome
Hypercoagulability
Pregnancy
Malignancy
Antiphospholipid syndrome
Nephrotic syndrome
Oral contraceptives
L-Asparaginase
Elevated factor VIII levels
Rare Other Entities
Congenital
Dysfibrinogenemia
Acquired
Paroxysmal nocturnal hemoglobinuria
Thrombocythemia
Vascular grafts

AT-III, Antithrombin III; *IBD,* inflammatory bowel disease.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

TABLE H1-43 Hypercoagulable Conditions

	Prevalence in General Population (%)	Prevalence in Population with Thrombosis (%)	A/V Events	Relative Risk of Thrombosis
FVL mutation	5% of whites; rare in nonwhites	12-40%	V	Heterozygous: 3-7; homozygous: 80
Prothrombin G20210A mutation	3% of whites; rare in nonwhites	6-18%	V	3
AT deficiency	0.02%	1-3%	V	20-50
PC deficiency	0.2-0.4%	3-5%	V	7-15
PS deficiency	0.03-0.1%	1-5%	V	5-11
Antiphospholipid antibody syndrome	1-2%	5-21%	V + A	2-11
Hyperhomocysteinemia	5-7%	10%	V + A	3
Elevated factor VIII level	11%	25%	V + A	5

A, Arterial; *AT,* antithrombin; *FVL,* factor V Leiden; *PC,* protein C; *PS,* protein S; *V,* venous.

TABLE H1-46 Causes of Acquired Deficiencies in Antithrombin III, Protein C, or Protein S

Antithrombin III	Protein C	Protein S
Neonatal period	Neonatal period	Neonatal period
Pregnancy	Liver disease	Pregnancy
Liver disease	DIC	Liver disease
DIC	Chemotherapy (CMF)	DIC
Nephrotic syndrome	Acute thrombosis	Inflammatory states
Major surgery		Acute thrombosis
Acute thrombosis		
Treatment with:		
Heparin	Warfarin	Warfarin
L-Asparaginase	L-Asparaginase	L-Asparaginase
Estrogens		Estrogens

CMF, Cyclophosphamide, methotrexate, 5-fluorouracil; *DIC,* disseminated intravascular coagulation.
From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

Protein C, protein S, antithrombin (AT) deficiency:
- Autosomal-dominant inheritance; many mutations identified for each of these conditions.
- Decreased level (type I deficiency) or abnormal function (type II deficiency).
- First episode of thrombosis is usually in young adults.

Protein C and protein S:
- Homozygous condition is very rare; usually associated with lethal thrombosis in infancy.
- Associated with warfarin-induced skin necrosis, which occurs secondary to depletion of vitamin K–dependent anticoagulant factors sooner than procoagulant factors in the first few days of therapy.

AT deficiency:
- Most thrombogenic of the inherited thrombophilias; 50% lifetime risk of thrombosis.
- Homozygous condition is very rare, probably not compatible with normal fetal development.
- Arterial thrombosis can occur rarely.
- Can cause heparin resistance.

Elevated factor VIII level:
- May be an important risk factor for thrombosis in African-American population.
- Increased risk of recurrent thrombosis.
- Genetic etiology is suspected but not yet identified.

Other possible causes: Non-O blood group, dysfibrinogenemia, elevated thrombin-activatable fibrinolysis inhibitor, elevated factor IX and factor XI levels

ACQUIRED: Antiphospholipid antibody syndrome (APS):
- Most common cause of acquired thrombophilia.
- Can present as arterial or venous thrombosis, recurrent pregnancy loss, and adverse pregnancy outcomes.
- Thromboembolic events occur in up to 30% of population; high risk of recurrent thrombosis (up to 70% reported).
- See "Antiphospholipid Antibody Syndrome" for more information.

Hyperhomocysteinemia:
- Can be inherited (most commonly an autosomal recessive mutation in methylene tetrahydrofolate reductase gene) but more frequently acquired; folate, vitamin B_6, or vitamin B_{12} deficiency account for two thirds of cases. Other acquired causes include renal disease, hypothyroidism, malignancy, smoking, and certain medications.
- Acquired causes may be associated with VTE and atherosclerotic disease (cardiovascular, cerebrovascular, and peripheral vascular). Inherited causes may be associated with atherosclerotic disease and adverse pregnancy outcomes.

Conditions associated with increased risk of thrombosis:
- Prior thrombosis
- Trauma
- Medical illness: heart failure, respiratory failure, infection, diabetes mellitus, obesity, nephrotic syndrome, inflammatory bowel disease
- Chronic hemolysis–paroxysmal nocturnal hemoglobinuria, sickle cell anemia
- Pregnancy (sixfold increased risk of VTE), postpartum, OC use (fourfold increased risk, higher risk with third-generation OCs), transdermal contraceptive patch, HRT (twofold increased risk), tamoxifen, raloxifene
- Immobilization, travel
- Surgery (especially orthopedic), central venous catheters
- Hyperviscosity syndromes
- Myeloproliferative disorders
- Malignancy: disease or treatment related
- Heparin-induced thrombocytopenia and thrombosis
- Smoking

WORKUP

- History (presence of conditions or use of medications predisposing to thrombosis, family history of thrombosis), physical examination, laboratory tests, imaging studies.
- Age-appropriate cancer screening.
- No consensus exists regarding screening for thrombophilia; few cost-effectiveness or outcomes data are available. Screening laboratory evaluation for patients suspected of having a biologic defect predisposing to thrombosis is described in Box EH1-10. Thrombophilia screening is probably overused, as results usually don't change management.
- Thrombophilia screening is not recommended for primary prevention of VTE; some advocate testing prior to OC use or pregnancy in women with a strong family history of thrombosis or thrombophilia.
- Screening not recommended if VTE was associated with an identified risk factor. A possible exception is thrombosis associated with pregnancy, the postpartum period, or with OC use.
- Unprovoked VTE:
  1. Screen individuals for APCR, prothrombin G20210A mutation, protein C, protein S, AT deficiency, and APS if any of the following are present: <50 yr of age at first episode of thrombosis, family history of thrombosis, recurrent thrombosis, thrombosis in unusual anatomic location, life-threatening thrombotic event, warfarin-induced skin necrosis, thrombosis in pregnancy/postpartum/with OC use, or characteristic pregnancy complications.
  2. Screen all Caucasians <50 yr of age and all women on HRT for APCR, prothrombin G20210A mutation, and APS.
  3. Screen all others for APS.
- Arterial thrombosis: Screen for APS.
- Note: Routine screening for factor VIII level or hyperhomocysteinemia is not recommended.

TIMING OF WORKUP
- Ideally >3 wk after discontinuation of anticoagulation (except for APS, which requires prolonged anticoagulation).
- Note: Acute thrombosis, anticoagulation, pregnancy, and many medical conditions can affect the results and must be considered in the timing and interpretation of the workup.

LABORATORY TESTS

- CBC with peripheral smear, electrolytes, calcium, renal and liver function tests, prothrombin time/partial thromboplastin time, prostate-specific antigen (in men aged >50 yr), urinalysis
- Note: Genetic counseling and written informed consent should be obtained before genetic testing. Abnormal nongenetic tests should be repeated after 6 wk to decrease false-positive results.
- APCR: APC-resistance assay (using factor V–deficient plasma) and if positive confirm with genetic test for FVL mutation; use genetic test if lupus anticoagulant present.
- Prothrombin G20210A mutation test.
- AT, protein C, and protein S deficiency: functional assays; if decreased perform antigenic assay to determine type of deficiency. Antigenic assays for protein S should measure free and total levels. In protein C and protein S deficiency, the functional assay may be falsely low in the presence of APCR or elevated factor VIII level and falsely high if lupus anticoagulant is present.
- APS: any of the following found on two occasions at least 12 wk apart: lupus anticoagulant or anticardiolipin antibodies or anti–B_2-glycoprotein-I antibodies.
- Hyperhomocysteinemia: fasting plasma homocysteine level (if normal but suspicion

is high, can proceed with methionine loading test and genotyping for methylene tetrahydrofolate reductase).
- Factor VIII level functional assay.

IMAGING STUDIES

Chest radiograph and other tests as appropriate to diagnose thrombosis and rule out associated conditions

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

OC/HRT use and smoking should be avoided.

PROPHYLAXIS

- Prophylactic anticoagulation in high-risk situations.
- Patients with AT deficiency may benefit from antithrombin concentrates in high-risk situations.
- Although homocysteine levels can be lowered with folic acid, vitamin B_6, and vitamin B_{12} supplements, correcting hyperhomocysteinemia does not decrease risk of thrombosis and routine supplementation is not indicated.
- Vitamin E supplements may decrease risk of VTE in women.
- Pregnancy prophylaxis: timing and intensity of therapy is based on the patient's risk (genetic or acquired defect and clinical history). Women with thrombophilia and recurrent adverse pregnancy outcomes may benefit from prophylaxis with heparin and low-dose aspirin.

ACUTE GENERAL Rx

Initial therapy is the same as for individuals without thrombophilia (exceptions for protein C and AT deficiency).

Venous thrombosis:
- Begin low-molecular-weight heparin (LMWH) and warfarin simultaneously. Continue heparin for at least 5 days and until international normalized ratio (INR) is therapeutic for 2 consecutive days; continue warfarin for at least 3 mo. Aim for INR of 2 to 3. Unfractionated heparin (UH) or fondaparinux (factor Xa inhibitor) may be used as alternatives to LMWH. LMWH is preferred over UH (except in patients with massive pulmonary embolism, increased risk of bleeding or renal failure) because of equivalent or superior effectiveness and a better safety profile.
- Novel oral anticoagulants such as the direct thrombin inhibitor dabigatran and the direct Xa inhibitor rivaroxaban have been FDA approved for treatment in acute DVT. They have been found to be noninferior to Coumadin, appear easier to use with fewer drug interactions, and have a trend towards less major bleeding but they still lack a reversal agent.
- Thrombophilia is not associated with a higher risk of recurrent VTE during warfarin therapy, with the exception of cancer patients in whom LMWH for 3 to 6 mo is associated with lower rates of recurrence than warfarin therapy.
- In pregnancy, anticoagulate with heparin throughout pregnancy and for at least 6 wk postpartum. Minimum duration of anticoagulation should be 6 mo. LMWH is preferred over UH. Warfarin may be used postpartum.
- Consider thrombolysis or thrombectomy in patients with massive pulmonary embolism or large proximal lower extremity DVT.

Protein C deficiency:
- Warfarin-induced skin necrosis: Discontinue warfarin, give vitamin K, and start heparin anticoagulation. Consider protein C replacement with protein C concentrate or fresh frozen plasma. Warfarin may be restarted at a low dose (2 mg daily for 3 days and increase by 2 to 3 mg daily until target INR is reached). Continue heparin for at least 5 days and until warfarin-induced anticoagulation is achieved.

AT deficiency:
- AT concentrates may be used if difficulty achieving anticoagulation (heparin resistance), severe thrombosis, or recurrent thrombosis despite adequate anticoagulation.

Arterial thrombosis:
- Anticoagulation and evaluation for thrombolysis or surgery.

CHRONIC Rx

- Optimal duration of anticoagulation remains unknown. Length of therapy may be individualized by assessing the risk of recurrence. Residual thrombosis (on ultrasonography) or elevated D-dimer levels after completion of anticoagulation are associated with an increased risk of recurrence. With these findings, consider prolonging anticoagulation.
- Must consider risk and benefit; risk of major bleeding 2% to 3% annually in general population on anticoagulation but higher in the elderly (7% to 9% per year). Long-term anticoagulation is usually not indicated given the low risk of recurrent thrombosis for most conditions and the bleeding risk associated with anticoagulation.
- Indefinite anticoagulation considered if ≥2 spontaneous thromboses or spontaneous thrombosis associated with any of the following:
  1. Life-threatening thrombosis or thrombosis at an unusual site
  2. More than a single genetic defect
  3. Presence of AT deficiency or APS
- Patients with active cancer may benefit from indefinite anticoagulation.

DISPOSITION

Depends on underlying condition

REFERRAL

Hematology, maternal-fetal medicine, obstetric medicine

PEARLS & CONSIDERATIONS

COMMENTS

- Warfarin therapy effectively reduces the risk of recurrent VTE; when therapy is discontinued VTE risk increases.
- Previous episode of VTE is a major risk factor for recurrence regardless of the presence of thrombophilia. Risk is greatest in the first 2 yr after thrombosis. 20% of all patients with unprovoked VTE have recurrence within 5 yr.
- Genetic risk factors for thrombosis in nonwhites remain largely unknown.
- Interpreting workup: many medical conditions cause acquired abnormalities.
  1. Acute thrombosis may be associated with lupus anticoagulant, increased anticardiolipin antibodies, and elevated factor VIII levels
  2. Heparin therapy: antithrombin levels decrease by up to 30%; can affect lupus anticoagulant testing
  3. Warfarin therapy: cannot measure protein C and protein S (levels and function decrease); antithrombin levels may increase; can affect lupus anticoagulant testing
  4. Protein C, protein S, and antithrombin levels decrease with acute thrombosis (<2 wk), surgery, liver disease, disseminated intravascular coagulation, and chemotherapy. Protein C level also decreases with severe infection but levels increase with age and hyperlipidemia. Protein S and antithrombin levels also decrease with nephrotic syndrome, pregnancy, and estrogen therapy (HRT, OC)
  5. APCR is increased with pregnancy, estrogen therapy (HRT, OCs), and certain cancers; elevated factor VIII level and antiphospholipid antibodies can cause APCR

PREVENTION

Risk of postthrombotic syndrome decreases if compression stockings are worn for at least 1 year, starting in the first month after the DVT.

PATIENT & FAMILY EDUCATION

National Blood Clot Alliance
120 White Plains Road, Suite 100
Tarrytown, NY 10591
http://www.stoptheclot.org/contact.htm

National Collaborative Outreach Project of the Blood Clot Outreach Program at the Hemophilia and Thrombosis Center University of North Carolina at Chapel Hill
http://www.clotconnect.org/about-clot-connect/about

Factor V Leiden Resources
http://www.fvleiden.org/resources/index.html

APS Foundation of America, Inc.
P. O. Box 801
LaCrosse, WI 54602-0801
http://www.apsfa.org/

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Thrombophilia (Patient Information)
Antiphospholipid Syndrome (Related Key Topic)
Deep Vein Thrombosis (Related Key Topic)
Pulmonary Embolism (Related Key Topic)

AUTHORS: **MATTHEW I. QUESENBERRY, M.D.,** and **SUDEEP KAUR AULAKH, M.D.**

SUGGESTED READINGS

Bates SM et al.: Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians evidence-based clinical practice guidelines, *Chest* 133(6 Suppl):844S, 2008.

Glynn RJ et al.: Effects of random allocation to vitamin E supplementation on the occurrence of venous thromboembolism, *Circulation* 116:1497, 2007.

Kearon C et al.: Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians evidence-based clinical practice guidelines, *Chest* 133(6 Suppl):454S, 2008.

Khor B et al.: Laboratory evaluation of hypercoagulability, *Clin Lab Med* 29:339, 2009.

Minichiello T et al.: Diagnosis and management of venous thromboembolism, *Med Clin North Am* 92(2):443, 2008.

Rosendaal FR et al.: Genetics of venous thrombosis, *J Thromb Haemost* 7(1 Suppl):301, 2009.

TABLE EH1-44 Sites of Thrombosis According to Coagulation Defect

Abnormality	Arterial	Venous
Factor V Leiden	-	+
Prothrombin gene mutation	-	+
Antithrombin III deficiency	-	+
Protein C deficiency	-	+
Protein S deficiency	-	+
Lupus anticoagulant	+	+

From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

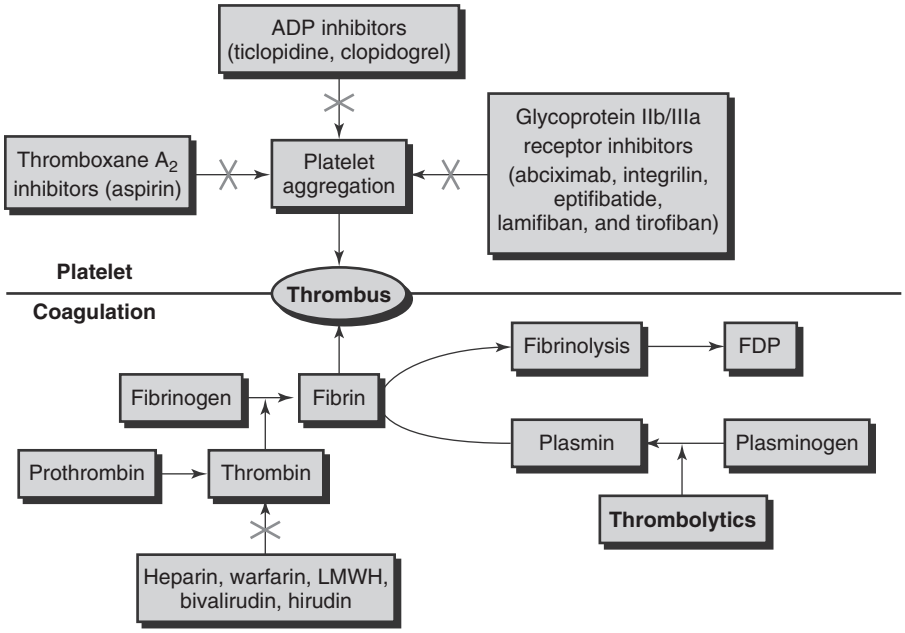


FIGURE EH1-72 Components of thrombus formation and actions of various antithrombotic and thrombolytic agents. *ADP,* Adenosine diphosphate; *FDP,* fibrin degradation products; *LMWH,* low-molecular-weight heparin. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

BOX EH1-10 Screening Laboratory Evaluation for Patients Suspected of Having a Biologic Defect Predisposing to Thrombosis

Test for presence of factor V Arg506Gln
Screen with clotting assay using factor V–deficient plasma and confirm with genetic test for factor V Arg506Gln (factor V Leiden) or obtain genetic test for factor V Arg506Gln (factor V Leiden) only
Genetic test for prothrombin gene mutation (G to A transition at position 20210 in the 3′-untranslated region)
Functional assay of antithrombin III (heparin-cofactor assay)
Functional assays of protein C
Functional assay of protein S/immunologic assays of total and free protein S
Screen for dysfibrinogenemias (immunologic and functional assays of fibrinogen, thrombin time)
Clotting assay for lupus anticoagulant/serologic tests for antiphospholipid antibodies

PTT, Partial thromboplastin time.

From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

BASIC INFORMATION

DEFINITION

Hyperemesis gravidarum is a severe and persistent form of nausea and vomiting resulting in at least a 5% weight loss, dehydration, ketonuria, and electrolyte imbalance, with typical onset at 4 to 8 wk of pregnancy continuing through 14 to 16 wk of pregnancy.

ICD-9CM CODES
643.0 [0,1,3] Mild hyperemesis gravidarum
643.1 [0,1,3] Hyperemesis gravidarum with metabolic disturbance

ICD-10CM CODES
O21.0 Mild hyperemesis gravidarum
O21.1 Hyperemesis gravidarum with metabolic disturbance

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 0.5% to 2% of pregnancies
GENETICS: No genetic disposition
RISK FACTORS: Women with increased placental mass, including molar pregnancy or multiple gestation, family history or personal history of hyperemesis gravidarum, prior miscarriage, nulliparity, preexisting diabetes, hyperthyroid disorder, peptic ulceration or other gastrointestinal disorders, depression, and asthma. Female fetus increases the risk by 1.5-fold.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Weight loss of more than 5% from pregravid weight
- Symptoms—nausea, vomiting, spitting, enhanced olfactory senses, food and/or fluid intolerance, lethargy
- Signs—dehydration, poor skin turgor, dry mucous membranes, ketonuria, anemia, tachycardia, hypotension
- Complications include inadequate caloric intake, nutritional deficiencies, dehydration, and electrolyte abnormalities including hyponatremia, hypocalcemia, hypokalemia, and in severe cases hypochloremic metabolic acidosis or Wernicke's encephalopathy from thiamine deficiency

ETIOLOGY

Unknown but likely multifactorial. Theories include gestational hyperestrogenemia, gastric dysrhythmias, and hyperthyroidism.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Gastrointestinal conditions—gastroenteritis, gastroparesis, achalasia, biliary tract disease, hepatitis, intestinal obstruction, peptic ulcer disease, appendicitis
- Genitourinary tract conditions—pyelonephritis, uremia, ovarian torsion, kidney stones, degenerating uterine leiomyoma
- Metabolic disease—diabetic ketoacidosis, porphyria, Addison's disease, hyperthyroidism
- Neurologic conditions—pseudotumor cerebri, vestibular lesions, migraines, tumors of the central nervous system
- Miscellaneous—drug toxicity or intolerance, psychologic
- Pregnancy-related conditions—acute fatty liver of pregnancy, preeclampsia

WORKUP

Diagnosis is one of exclusion. History and physical examination along with laboratory tests to rule out other causes of vomiting should be performed.

LABORATORY TESTS

- Urinalysis may show elevated specific gravity, ketonuria, or proteinuria
- Liver enzymes (elevated but usually <300 U/L)
- Serum bilirubin (<4 mg/dl)
- Serum amylase or lipase (up to 5× greater than normal)
- BMP, may reveal hyponatremia, hypokalemia, low serum urea
- CBC
- Calcium
- TSH and free T4 (transient hyperthyroidism occurs in 2/3 of women with hyperemesis gravidarum; this is biochemical hyperthyroidism that usually resolves by 18 wk gestation; treatment should not be undertaken without evidence of intrinsic thyroid disease)

IMAGING STUDIES

- Ultrasound to evaluate for multiple gestation or molar pregnancy
- Right upper quadrant ultrasound to evaluate for biliary tract disease

TREATMENT

NONPHARMACOLOGIC THERAPY

- Reassurance and support
- Avoidance of foods and smells that trigger nausea
- Oral ginger root
- Small frequent dry meals
- Eating prior to getting out of bed

ACUTE GENERAL Rx

- Nothing by mouth
- Intravenous fluid and electrolyte replacement with vitamin supplementation
- Thiamine administration prior to giving dextrose to avoid Wernicke's encephalopathy
- Pyridoxine (vitamin B_6)
- Doxylamine 25 mg qhs
- Antiemetics, including promethazine, phenothiazines, metoclopramide, and ondansetron, have been shown to be both safe and effective in improving pregnancy outcome
- Restart oral intake gradually no less than 48 hr after vomiting has stopped

CHRONIC Rx

- Nasogastric feedings are useful alternatives in severe cases
- Total parenteral nutrition may be necessary in life-threatening cases

COMPLEMENTARY AND ALTERNATIVE MEDICINE

- Supportive psychotherapy
- Acupuncture
- Acupressure with use of a wrist band

DISPOSITION

- Infants born to pregnancies complicated by hyperemesis are more likely to be premature and small for gestational age.
- Lower rates of miscarriage have also been documented when comparing pregnancies complicated by hyperemesis gravidarum vs. controls.

PEARLS & CONSIDERATIONS

COMMENTS

Nausea and vomiting in early pregnancy are associated with psychosocial morbidity.

PREVENTION

Taking a multivitamin at the time of conception

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hyperemesis Gravidarum (Patient Information)

AUTHOR: **ALISON PATTERSON, M.D.**

SUGGESTED READINGS

Ismail SK, Kenny L: Review on hyperemesis gravidarum, *Best Practice Res Clin Gastroenterol* 21:755, 2007.

Nausea and vomiting of pregnancy: ACOG Practice Bulletin No. 52, *Obstet Gynecol* 103, 2004.

BASIC INFORMATION

DEFINITION

Hypereosinophilic syndrome (HES) refers to a group of disorders of unknown cause characterized by sustained overproduction of eosinophils, in which eosinophilic infiltration and mediator release cause organ dysfunction.

SYNONYMS

Idiopathic hypereosinophilic syndrome (IHES)

ICD-9CM CODES
288.3 Hypereosinophilic syndrome
ICD-10CM CODES
D72.1 Eosinophilia

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT SEX: Occurs in men more often than women (9:1)
PREDOMINANT AGE: Usually occurs between the ages of 20 and 50 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical presentation of HES may vary from an incidental finding of eosinophilia to sudden onset of cardiac or neurologic symptoms.
- Early presentation includes fatigue, cough, breathlessness, muscle pain, angioedema, rash, and fever.
- Cardiac manifestations (58%) include dyspnea, orthopnea, and signs and symptoms of congestive heart failure (CHF). Including three stages: acute necrotic stage secondary to endocardial infiltration of eosinophils; thrombus formation; and fibrotic stage. This may result in a restrictive or dilated cardiomyopathy and/or valvular heart disease.
- Neurologic manifestations (54%) may be of three types:
  1. Thromboembolic (e.g., cardiac emboli or local vascular thrombosis)
  2. CNS dysfunction: confusion, loss of memory, ataxia, upper motor neuron signs, seizures, and behavior changes
  3. Peripheral neuropathy (most common) may be symmetric or asymmetric, sensory or mixed sensory and motor deficits
- Pulmonary manifestations (40%) include a chronic persistent nonproductive cough, shortness of breath, and dyspnea on exertion. Diffuse or focal infiltrate may present in 20% of cases. Complications may include pulmonary fibrosis, CHF, or pulmonary embolus.
- Cutaneous manifestations (56%) usually include eczema, lichenifications, urticaria, angioedema, or erythematous pruritic papules and nodules.
- GI manifestations (23%) include diarrhea, but findings of gastritis, colitis, pancreatitis, cholangitis, and hepatitis can occur.
- Ocular manifestations (23%) are thought to be the result of retinal microemboli.
- Vascular manifestations include venous or arterial thrombosis of unknown mechanism such as femoral artery occlusion, intracranial sinus thrombosis, and digital gangrene.

ETIOLOGY

- The etiology of HES is unknown and is thought of as a composite of many diseases.
- In some cases, a fusion event generating an abnormal and oncogenic tyrosine kinase (FIP1L1-PDGFRA) appears to be causative especially in males.

DIAGNOSIS

Criteria for the diagnosis of idiopathic HES include:
- Persistent eosinophilia of >1500 eosinophils/mm^3 for more than 6 mo
- Exclusion of other conditions causing eosinophilia (Box EH1-11)
- Signs and symptoms of organ system dysfunction (e.g., heart, liver, lung).

DIFFERENTIAL DIAGNOSIS

The differential includes all causes of peripheral blood eosinophilia. Parasitic infections, coccidioidomycosis, cat-scratch disease, asthma, Churg-Strauss syndrome, allergic rhinitis, atopic dermatitis, drug-induced eosinophilia, aspergillosis, eosinophilic pneumonia, hypersensitivity pneumonitis, HIV, eosinophilic gastroenteritis, inflammatory bowel disease, leukemias (CML and CMML), systemic mastocytosis with eosinophilia.

WORKUP

The workup of a patient who is suspected of having HES should exclude other causes mentioned in the "Differential Diagnosis" section leading to peripheral eosinophilia.

LABORATORY TESTS

- CBC with differential; often the total WBC ranges from 10,000 to 30,000/mm^3 with eosinophilia of 30% to 70%, anemia is present in 50% of the cases, and either thrombocytopenia or thrombocytosis may be noted
- Erythrocyte sedimentation rate (ESR) and rheumatoid factor
- Liver function tests (LFTs), electrolytes, urinalysis, BUN, and creatinine
- HIV assay
- Stools for ova and parasites ×3
- Serologic blood tests for parasitic infections (e.g., *Strongyloides*)
- Total IgE level
- Bone marrow aspirate and biopsy (Figure EH1-73)
- Duodenal aspirate
- ECG
- Tissue biopsies as indicated
- Serum levels of vitamin B_{12}
- Serum levels of tryptase

IMAGING STUDIES

- Chest radiograph may be clear or show infiltrates, effusions, or fibrotic scarring
- CT scan of chest, abdomen, and pelvis
- Echocardiogram (or cardiac MRI for early cardiac involvement) can assess for ventricular function and valvular pathology including regurgitation and thrombi formation

TREATMENT

Treatment is initiated only if there is evidence of organ involvement.

NONPHARMACOLOGIC THERAPY

In patients with hypereosinophilia without organ involvement, serial echocardiograms, blood chemistries, and pulmonary function tests are recommended at 6-mo intervals.

ACUTE GENERAL Rx

- In patients with organ involvement without FIP1L1-PDGFRA fusion, initial therapy is with prednisone 1 mg/kg/day or 60 mg/day in adults.
- Patient's symptoms and peripheral eosinophil counts are monitored.
- Doses may be tapered to alternate-day prednisone use in patients whose eosinophil counts have been suppressed.

CHRONIC Rx

- Patients not responding to corticosteroids, hydroxyurea 1 to 2 g/day may be tried.
- Patient with FIP1L1-PDGFRA fusion with or without organ involvement should be started on tyrosine kinase imatinib or dasatinib for resistant cases.
- If the disease continues to progress, vincristine, etoposide, interferon-α, cyclosporine, and leukapheresis are alternative choices.
- Anticoagulation and/or antiplatelet agents are often used in patients with HES.
- If all else fails, bone marrow transplantation may be considered.

DISPOSITION

- Before the use of cardiac imaging (echo) and cardiac surgeries (valve replacement), patients with HES had a poor prognosis with a mean survival of 9 mo and a 3-yr survival of 12%.
- Deaths usually result from CHF, endocarditis, and systemic emboli.
- 5-yr and 15-yr survival rates are 80% and 42%, respectively.

REFERRAL

HES is a rare and complicated disorder requiring a multidisciplinary approach.

PEARLS & CONSIDERATIONS

COMMENTS

There is still much to be learned about HES. The etiology and exact mechanism of organ damage caused by eosinophils remain unknown.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **MONZR M. AL MALKI, M.D.,** and **GLENN G. FORT, M.D., M.P.H.**

BOX EH1-11 Diseases, Syndromes, and Conditions Commonly Associated with Peripheral Blood Eosinophilia and/or Tissue Eosinophilia

Infectious Agents

Parasitic

Tropical eosinophilia
Visceral larval migrans (VLM, toxocariasis)
Helminth infections
Filariasis *(Wuchereria bancrofti, Brugia malayi)*
Onchocerciasis
Schistosomiasis
Fascioliasis
Paragonimiasis
Strongyloidiasis
Trichinosis
Hookworm
Ascariasis
Echinococcosis/hydatid disease

Nonparasitic

Coccidioidomycosis
Chlamydial pneumonia of infancy
Scarlet fever and pneumococcal pneumonia (convalescent phase)
Cat-scratch disease
Cryptococcosis (CSF eosinophilia) in HIV

Allergic Diseases

Asthma (atopic and intrinsic, nasal polyps, aspirin intolerance syndromes)
Bronchopulmonary aspergillosis
Allergic rhinitis
Urticarias (acute allergic and chronic idiopathic)
Atopic dermatitis
Acute drug (hypersensitivity) reactions (interstitial nephritis, cholestatic hepatitis, exfoliative dermatitis)

Respiratory Tract Disorders

Hypersensitivity pneumonitis (rare)
Allergic bronchopulmonary aspergillosis
Eosinophilic pneumonia
Transient pulmonary infiltrates (Löeffler syndrome)
Prolonged pulmonary infiltrates with eosinophilia (PIE syndromes)
Tropical pulmonary eosinophilia (TPE)
Bronchiectasis
Cystic fibrosis

Endocrinologic Disorders

Addison disease

Gastrointestinal Diseases

Inflammatory bowel disease (IBD)
Eosinophilic gastroenteritis, eosinophilic esophagitis (EE)
Allergic gastroenteritis (young children)
Celiac disease (when associated with EE)

Toxic Reactions to Ingested Agents

Eosinophil myalgia syndrome (L-tryptophan)
Toxic oil syndrome

Reactions to Cytokine Therapies

IL-2 and IL-2 plus lymphokine-activated killer (LAK) cells
GM-CSF for chemotherapy-induced neutropenia

Cutaneous Disorders

Atopic dermatitis
Immunologic skin diseases
Scabies
Eosinophilic cellulitis (Wells syndrome)
Episodic angioedema with eosinophilia
Chronic idiopathic urticaria
Bullous pemphigoid
Herpes gestationis

Immunodeficiency Syndromes

Wiskott-Aldrich syndrome
Selective IgA deficiency with atopy
Hyper-IgE recurrent infection syndrome (Job syndrome)
Swiss-type and sex-linked combined immunodeficiency
Nezelof syndrome
Graft-versus-host disease (GVHD)

Connective Tissue Diseases

Vasculitis/collagen vascular disorders
Hypersensitivity vasculitis
Allergic granulomatosis with angiitis (Churg-Strauss syndrome)
Serum sickness
Eosinophilic fasciitis
Sjögren syndrome
Rheumatoid arthritis (severe)

Neoplastic and Myeloproliferative Diseases and Syndromes

Ovarian carcinoma
Solid tumors (mucin secreting, epithelial cell origin)
Eosinophil leukemia
Idiopathic hypereosinophilic syndrome (HES)
Systemic mastocytosis
Lymphomas (T cell, Hodgkin)
Chronic myelogenous leukemia, acute myelogenous leukemia, MDS (myelodysplastic syndrome)
T-cell lymphocytic leukemia
Myelomonocytic leukemia with bone marrow eosinophilia (M4Eo, inversion 16)
Angioimmunoblastic lymphadenopathy
Angioblastic lymphoid hyperplasia (Kimura disease)

Rare Causes

Chronic active hepatitis
Chronic dialysis
Acute pancreatitis
Postirradiation
Hypopituitarism

Modified and updated from Mahanty S, Nutman TB: Eosinophilia and eosinophil-related disorders. In Middleton EJ et al (eds): *Allergy: principles and practice,* ed 4, St Louis, 1993, Mosby.

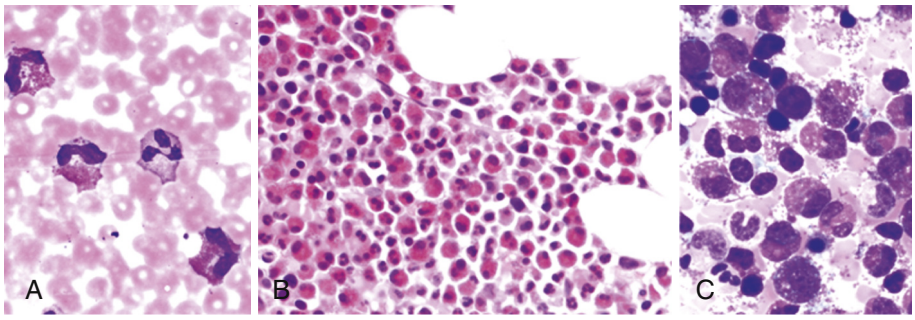


FIGURE EH1-73 Hypereosinophilic syndrome. The illustration is from the case of a 38-year-old woman who was found to have a marked eosinophilia when she presented with headaches, nausea, and vomiting. The WBC was 16,900/μL, with 36% eosinophils **(A)**. The bone marrow was hypercellular and showed sheets of eosinophils **(B)**. On the aspirated material **(C)** eosinophils and eosinophilic precursors accounted for more than 70% of the cells. The patient had no obvious infectious process and no allergies. There was no malignancy associated with eosinophilia such as T-cell lymphoma, Hodgkin lymphoma, or other myeloid disease. Peripheral blood lymphocyte phenotyping showed no abnormal T-cell subset. Cytogenetic analysis showed a normal female karyocyte, and FISH analysis for del 4q12 showed no deletion of CHIC2. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

SUGGESTED READINGS

Katz HT et al.: Pediatric hypereosinophilic syndrome (HES) differs from adult HES, *J Pediatr* 146(1):134, 2005.

Tefferi A et al.: Hypereosinophilic syndrome and clonal eosinophilia: point-of-care diagnostic algorithm and treatment update, *Mayo Clin Proc* 85(2):158–164, 2004.

Hyperlipoproteinemia, Primary EBM PTG

BASIC INFORMATION

DEFINITION

- Primary hyperlipoproteinemia is a group of genetic disorders of the lipid transport proteins in the blood that manifests as abnormally elevated levels of cholesterol, triglycerides, or both in the serum of affected patients.
- Usually defined as total cholesterol, LDL, triglycerides or lipoprotein A levels above 90th percentile or HDL or apo A-1 levels below the 10th percentile for the general population. Figure EH1-74 illustrates the structure of lipoproteins. Plasma lipoprotein composition is described in Table EH1-47.

SYNONYMS

Hyperlipidemia

ICD-9CM CODES
272.4 Hyperlipoproteinemia
272.3 Fredrickson type I
272.0 Fredrickson type IIa
272.2 Fredrickson type IIb, III
272.1 Fredrickson type IV
272.3 Fredrickson type V

ICD-10CM CODES
E78.0 Pure hypercholesterolemia
E78.2 Mixed hyperlipidemia
E78.1 Pure hyperglyceridemia
E78.4 Other hyperlipidemia
E78.3 Hyperchylomicronemia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The most common types are lipoprotein A excess, hypertriglyceridemia, and combined hyperlipidemia.

- Incidence of heterozygous familial hypercholesterolemia: 1:500.
- Incidence of homozygous familial hypercholesterolemia: 1:1 million.
- Familial hypercholesterolemia: autosomal-dominant disorder.
- Familial combined hyperlipidemia: possibly an autosomal-dominant disorder.
- Multifactorial predilection: apparent in majority of affected individuals.

GENETICS

- Familial lipoprotein lipase deficiency: autosomal recessive, resulting in an elevation in the plasma chylomicrons and triglycerides
- Familial apoprotein CII deficiency: autosomal recessive, resulting in increased serum chylomicrons, very-low-density lipoprotein (VLDL), and hypertriglyceridemia
- Familial type 3 hyperlipoproteinemia: single-gene defect requiring contributory factors to manifest
- Familial hypercholesterolemia: autosomal-dominant defect of the LDL receptor, resulting in an elevated serum cholesterol level and normal triglycerides
- Familial hypertriglyceridemia: common, autosomal-dominant defect resulting in elevated VLDL and triglycerides
- Multiple lipoprotein–type hyperlipidemia: autosomal dominant, manifesting as isolated hypercholesterolemia, isolated hypertriglyceridemia, or hyperlipidemia
- Polygenic hypercholesterolemia: multifactorial
- Polygenic hyperalphalipoproteinemia: autosomal dominant or polygenic, causing an elevated high-density lipoprotein
- A classification of lipoprotein disorders is described in Table H1-48.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Familial lipoprotein lipase deficiency: recurrent bouts of abdominal pain in infancy, eruptive xanthomas, hepatomegaly, splenomegaly, lipemia retinalis
- Familial apoprotein CII deficiency: occasional eruptive xanthomas
- Familial type 3 hyperlipoproteinemia: xanthoma striata palmaris or tuberoeruptive xanthomas, xanthelasmas, arterial bruits at a young age, gangrene of the lower extremities at a young age
- Familial hypercholesterolemia: tendon xanthomas, arcus corneae, xanthelasma
- Familial hypertriglyceridemia: associated obesity; eruptive xanthomas can develop with exacerbations

ETIOLOGY

- Genetic defects causing lipid abnormalities
- Environmental influences including diet, drugs, and alcohol intake

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Secondary causes of hyperlipoproteinemias:

- Hypothyroidism
- Diabetes mellitus
- Pancreatitis
- Autoimmune hyperlipoproteinemia
- Nephrotic syndrome
- Biliary obstruction. Table EH1-49 describes the differential diagnosis of hyperlipidemia and dyslipidemia.

WORKUP

- Family history for premature cardiac disease
- Personal history of recurrent pancreatitis
- Detailed physical examination

LABORATORY TESTS:

- Standard lipid profile
- If normal, further testing with measurement of lipoprotein A, apo B, and apo A-1
- Lipoprotein electrophoresis and ultracentrifugation (for phenotypic classification)
- Workup for secondary causes: TSH, fasting glucose, liver function, renal function, urinary protein

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cornerstone of treatment: dietary therapy
  1. TLC diet (**t**herapeutic **l**ifestyle **c**hanges): see "Hypercholesterolemia" topic
- Risk factor reduction includes smoking cessation, treatment of hypertension, exercise
- Familial lipoprotein lipase deficiency and familial apoprotein CII deficiency: fat-free diet
- Remainder of cases, except those with polygenic hyperalphalipoproteinemia: fat- and cholesterol-restricted diets
- Interventions to improve adherence are described in Table H1-50

ACUTE GENERAL Rx

No acute treatment needed.

CHRONIC Rx

- Familial lipoprotein lipase deficiency, polygenic hyperalphalipoproteinemia, or familial apoprotein CII deficiency: no chronic drug therapy
- Familial type 3 hyperlipoproteinemia: usually responds well to secondary causes being treated and diet therapy; if not, fibric acids may be tried
- Familial hypercholesterolemia: HMG-CoA reductase inhibitors, bile acid sequestrants, or niacin
- Familial hypertriglyceridemia: fibric acids (fenofibrate), niacin, omega-3 PUFA-containing fish oil capsules
- Multiple lipoprotein–type hyperlipidemia: drug therapy aimed at the predominant lipid abnormality noted
- Recent data suggest in patients with lipoprotein abnormalities that treatment goals should be based on non-HDL cholesterol rather than LDL cholesterol
- The FDA has approved mipomersen and lomitapide in patients with homozygous familial hypercholesterolemia already taking maximum doses of other lipid-lowering drugs. Both medicines are hepatotoxic and very expensive.
- Table EH1-51 describes the various drugs used to treat hyperlipidemia.

DISPOSITION

- Those with polygenic hyperalphalipoproteinemia: excellent prognosis for longevity
- Those with familial hypercholesterolemia, familial type 3 hypercholesterolemia, or multiple lipoprotein–type hyperlipidemia: even with aggressive treatment, at high risk for accelerated atherosclerosis and coronary artery disease

PEARLS & CONSIDERATIONS

COMMENTS

- Patient information is available through the American Heart Association.
- Lipid-lowering drug therapy is recommended for children ≥10 yr whose LDL-C levels remain extremely elevated after 6 mo to 1 yr of dietary modification. Drug therapy also can be considered for children with LDL-C levels of ≥190 mg/dl.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hypercholesterolemia (Related Key Topic)

AUTHOR: **PRIYA BANSAL, M.D., M.P.H.**

TABLE H1-48 Classification of Lipoprotein Disorders by Phenotypes, Genotypes, and Corresponding Clinical Manifestations

Phenotype (Frederickson Type)	Genotype	Elevated Cholesterol Type	Genetic Defect	Xanthomas	Other Clinical Manifestations
I (rare)	Familial hyperchylomicronemia	Elevated chylomicrons	Familial lipoprotein lipase deficiency, Apo C-II deficiency	Eruptive skin xanthomas	Recurrent abdominal pain, hepatosplenomegaly
IIA	Familial hypercholesterolemia	Elevated LDL	FHC, LDL receptor deficiency	Tendon xanthomas, xanthelasma, tuberous; planar palmar (homozygous)	Premature CAD, arcus corneae, arthritic symptoms
IIB	Familial combined hypercholesterolemia	Elevated LDL and VLDL	Reduced LDL receptor and increased apo B		
III (rare)	Familial dysbetalipoproteinemia	Elevated IDL	Defective apo E2 synthesis	Tuberous, planar (palmar)	Premature CAD and peripheral vascular disease, male > female, obesity, abnormal glucose tolerance, hyperuricemia, aggravated by hypothyroidism, good response to therapy
IV	Familial hyperlipemia	Elevated VLDL	Increased VLDL production	None	CAD and peripheral vascular disease, obesity, abnormal glucose tolerance, hyperuricemia, arthritic
V (rare)	Endogenous hypertriglyceridemia	Elevated VLDL, chylomicrons	Increased VLDL production and reduced LPL	Eruptive	

Apo, Apolipoprotein; *CAD,* coronary artery disease; *FHC,* familial hypercholesterolemia.
Modified from Graber MA: *The family practice handbook,* ed 4, St Louis, 2001, Mosby.

TABLE H1-50 Interventions to Improve Adherence

Focus on the Patient

Simplify medication regimens.
Provide explicit patient instruction and use good counseling techniques to teach the patient how to follow the prescribed treatment.
Encourage the use of prompts to help patients remember treatment regimens.
Use systems to reinforce adherence and maintain contact with the patient.
Encourage the support of family and friends.
Reinforce and reward adherence.
Increase visits for patients unable to achieve treatment goal.
Increase the convenience and access to care.
Involve patients in their care through self-monitoring.

Focus on the Physician and Medical Office

Teach physicians to implement lipid treatment guidelines.
Use reminders to prompt physicians to attend to lipid management.
Identify a patient advocate in the office to help deliver or prompt care.
Use patients to prompt preventive care.
Develop a standardized treatment plan to structure care.
Use feedback from past performance to foster change in future care.
Remind patients of appointments and follow up missed appointments.

Focus on the Health Delivery System

Provide lipid management through a lipid clinic.
Utilize case management by nurses.
Deploy telemedicine.
Utilize the collaborative care of pharmacists.
Execute critical care pathways in hospitals.

From Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), *JAMA* 285:2486-2497, 2001.

EVIDENCE

Abstract[1]

Background:
Patients with homozygous familial hypercholesterolaemia respond inadequately to existing drugs. We aimed to assess the efficacy and safety of the microsomal triglyceride transfer protein inhibitor lomitapide in adults with this disease.

Methods:
We did a single-arm, open-label, phase 3 study of lomitapide for treatment of patients with homozygous familial hypercholesterolemia. Current lipid lowering therapy was maintained from 6 weeks before baseline through to at least week 26. Lomitapide dose was escalated on the basis of safety and tolerability from 5 mg to a maximum of 60 mg a day. The primary endpoint was mean percent change in levels of LDL cholesterol from baseline to week 26, after which patients remained on lomitapide through to week 78 for safety assessment. Percent change from baseline to week 26 was assessed with a mixed linear model.

Findings:
29 men and women with homozygous familial hypercholesterolaemia, aged 18 years or older, were recruited from 11 centres in four countries (USA, Canada, South Africa, and Italy). 23 of 29 enrolled patients completed both the efficacy phase (26 weeks) and the full study (78 weeks). The median dose of lomitapide was 40 mg a day. LDL cholesterol was reduced by 50% (95% CI −62 to −39) from baseline (mean 8.7 mmol/L [SD 2.9]) to week 26 (4.3 mmol/L [2.5]; $P < .0001$). Levels of LDL cholesterol were lower than 2.6 mmol/L in eight patients at 26 weeks. Concentrations of LDL cholesterol remained reduced by 44% (95% CI −57 to −31; $P < .0001$) at week 56 and 38% (−52 to −24; $P < .0001$) at week 78. Gastrointestinal symptoms were the most common adverse event. Four patients had aminotransaminase levels of more than five times the upper limit of normal, which resolved after dose reduction or temporary interruption of lomitapide. No patient permanently discontinued treatment because of liver abnormalities.

Interpretation:
Our study suggests that treatment with lomitapide could be a valuable drug in the management of homozygous familial hypercholesterolaemia. Ⓐ

Abstract[2]

Background:
Heterozygous familial hypercholesterolemia (HeFH) is a common genetic disorder leading to premature coronary artery disease. Despite statins and additional lipid-lowering therapies, many HeFH patients fail to achieve low-density lipoprotein cholesterol (LDL-C) goals. We evaluated mipomersen, an apolipoprotein B synthesis inhibitor, to further lower LDL-C in HeFH patients with coronary artery disease.

Methods and Results:
This double-blind, placebo-controlled, phase 3 trial randomized patients with HeFH and coronary artery disease on maximally tolerated statin and LDL-C ≥2.6 mmol/L (≥100 mg/dL) to weekly subcutaneous mipomersen 200 mg or placebo (2:1) for 26 weeks. The primary end point was percent change in LDL-C from baseline at week 28. Safety assessments included adverse events, laboratory tests, and magnetic resonance imaging assessment of hepatic fat. Of 124 randomized patients (41 placebo, 83 mipomersen), 114 (41 placebo, 73 mipomersen) completed treatment. Mean (95% confidence interval) LDL-C decreased significantly with mipomersen (-28.0% [−34.0% to −22.1%] compared with 5.2% [−0.5% to 10.9%] increase with placebo; $P < .001$). Mipomersen significantly reduced apolipoprotein B (−26.3%), total cholesterol (−19.4%), and lipoprotein(a) (−21.1%) compared with placebo (all $P < .001$). No significant change occurred in high-density lipoprotein cholesterol. Adverse events included injection site reactions and influenza-like symptoms. Five mipomersen patients (6%) had 2 consecutive alanine aminotransferase values 3 times the upper limit of normal at least 7 days apart; none were associated with significant bilirubin increases. Hepatic fat content increased a median of 4.9% with mipomersen versus 0.4% with placebo ($P < 0.001$).

Conclusions:
Mipomersen is an effective therapy to further reduce apolipoprotein B-containing lipoproteins, including LDL and lipoprotein(a), in HeFH patients with coronary artery disease on statins and other lipid-lowering therapy. The significance of hepatic fat and transaminase increases remains uncertain at this time. Ⓐ

Abstract[3]

Background:
There are barriers to fasting lipid screening for at-risk children. Results of studies in adults have suggested that lipid testing might be reliably performed without fasting.

Objective:
To examine population-level differences in pediatric lipid values based on length of fast before testing.

Methods:
We used the National Health and Nutrition Examination Survey (1999 to 2008) to examine total cholesterol (TC), HDL (high-density lipoprotein), LDL (low-density lipoprotein), and triglyceride cholesterol components on the basis of the period of fasting. Young children fasted for varying times before being tested, and children older than 12 years were asked to fast; however, adherence was variable. We used ordinary least-squares regression to test for differences in lipid values that were based on fasting times, controlling for weight status, age, race, ethnicity, and gender.

Results:
TC, HDL, LDL, or triglyceride values were available for 12 744 children. Forty-eight percent of the TC and HDL samples and 80% of the LDL and triglyceride samples were collected from children who had fasted ≥8 hours. Fasting had a small positive effect for TC, HDL, and LDL, resulting in a mean value for the sample that was 2 to 5 mg/dL higher with a 12-hour fast compared with a no-fast sample. Fasting time had a negative effect on triglycerides (β=−0.859; P = 0.02), which resulted in values in the fasting group that were 7 mg/dL lower.

Discussion:
Comparison of cholesterol screening results for a nonfasting group of children compared with results for a similar fasting group resulted in small differences that are likely not clinically important. Physicians might be able to decrease the burden of childhood cholesterol screening by not requiring prescreening fasting for these components. Ⓐ

Evidence Based Reference

Cuchel M: for the Phase 3 HoFH Lomitapide Study investigators Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study, *Lancet* 381:40–46, 2013. Ⓐ

Stein EA et al.: Apolipoprotein B synthesis inhibition with mipomersen in heterozygous familial hypercholesterolemia: results of a randomized, double-blind, placebo-controlled trial to assess efficacy and safety as add-on therapy in patients with coronary artery disease, *Circulation* 126:2283–2292, 2012. Ⓐ

Steiner MJ, Skinner AC, Perrin EM: Fasting might not be necessary before lipid screening: a nationally representative cross-sectional study, *Pediatrics* 128:463–470, 2011. Ⓐ

Guigliano RP, Braunwald E: The year in non-ST-segment elevation acute coronary syndrome, *Circulation* 120:735–742, 2009. Ⓐ

SUGGESTED READINGS

Alawadhi M et al.: Genetic lipoprotein disorders and coronary atherosclerosis, *Curr Atheroscler Rep* 7(3):196, 2005.

McCrindle BW et al.: American Heart Association. Drug therapy of high-risk lipid abnormalities in children and adolescents, *Circulation* 115:1948–1967, 2007.

Brunzell JD: Hypertriglyceridemia, *N Engl J Med* 357:1009–1017, 2007.

National Cholesterol Education Program: Second report on the Expert Panel on Detection, Evaluation and Treatment of High Cholesterol in Adults (Adult Treatment Panel III), *JAMA 285* 2486, 2001.

Sharma M et al.: Systematic review: comparative effectiveness and harms of combination therapy and monotherapy for dysplidemia, *Ann Intern Med* 151:622–630, 2009.

Sveger T, Nordborg K: Apolipoprotein B as a marker of familial hyperlipoproteinemia, *J Atheroscler Thromb* 11(5):286, 2004.

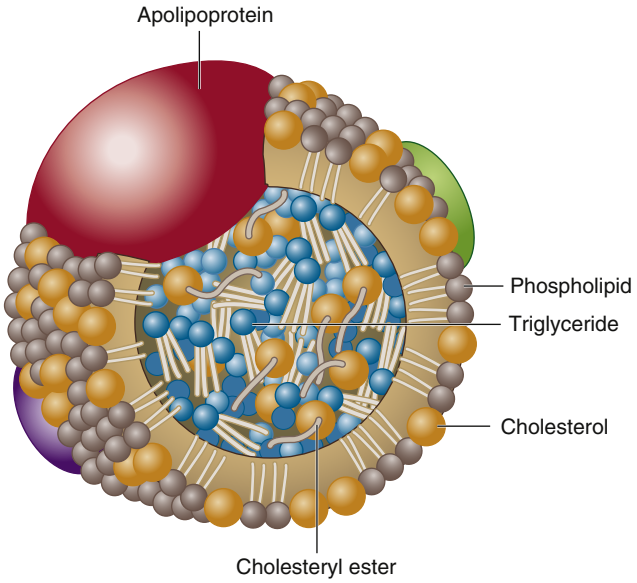


FIGURE EH1-74 Structure of lipoproteins. Phospholipids are oriented with their polar group toward the aqueous environment of plasma. Free cholesterol is inserted within the phospholipid layer. The core of the lipoprotein is made up of cholesteryl esters and triglycerides. Apolipoproteins are involved in the secretion of the lipoprotein, provide structural integrity, and act as cofactors for enzymes or as ligands for various receptors. (From Bonow RO et al: *Heart disease,* ed 9, Philadelphia, 2012, Saunders.)

TABLE EH1-47 Plasma Lipoprotein Composition

Component	Origin	Density (g/ml)	SIZE (NM)	Protein (%)	Cholesterol in Plasma (mmol/L)†	Triglyceride in Fasting Plasma (mmol/L)‡	Apoprotein	
							Major	Other
Chylomicron*	Intestine	<0.95	100-1000	1-2	0.0	0.0	B48	A-I, Cs
Chylomicron remnants*	Chylomicron metabolism	0.95-1.006	30-80	3-5	0.0	0.0	B48, E	A-I, A-IV, Cs
VLDL	Liver	<1.006	40-50	10	0.1-0.4	0.2-1.2	B100	AI, Cs
IDL	VLDL	1.006-1.019	25-30	18	0.1-0.3	0.1-0.3	B100, E	
LDL	IDL	1.019-1.063	20-25	25	1.5-3.5	0.2-0.4	B100	
HDL	Liver, intestine	1.063-1.210	6-10	40-55	0.9-1.6	0.1-0.2	A-I, A-II	A-IV
Lipoprotein(a)	Liver	1.051-1.082	25	30-50			B100, (a)	

*In the fasted state, serum (or plasma) should not contain chylomicrons or their remnants.
†In mmol/L. For mg/dl, multiply by 38.67.
‡In mmol/L. For mg/dl, multiply by 88.5.
From Bonow RO et al: *Heart disease,* ed 9, Philadelphia, 2012, Saunders.

TABLE EH1-49 Differential Diagnosis of Hyperlipidemia and Dyslipidemia

Hypertriglyceridemia	Hypercholesterolemia	Increased Cholesterol and Triglycerides	Low HDL
Primary Disorders			
LPL deficiency	Familial hypercholesterolemia	Familial combined hyperlipidemia	Familial hypoalphalipoproteinemia
ApoCII deficiency	Familial defective apoB100	Dysbetalipoproteinemia	ApoAI mutations
Familial hypertriglyceridemia	Polygenic hypercholesterolemia	Diabetes mellitus	LCAT deficiency
Dysbetalipoproteinemia	Sitosterolemia	Hypothyroidism	ABCA1 deficiency
Secondary Disorders	Hypothyroidism	Glucocorticoids	Anabolic steroids
Diabetes mellitus	Obstructive liver disease	Immunosuppressives	Retinoids
Hypothyroidism	Nephrotic syndrome	Protease inhibitors	
High-carbohydrate diets	Thiazides	Nephrotic syndrome	
Renal failure		Lipodystrophies	
Obesity/insulin resistance			
Estrogens			
Ethanol			
β-Blockers			
Protease inhibitors			
Glucocorticoids			
Retinoids			
Bile acid–binding resins			
Antipsychotics			
Lipodystrophies			
Thiazides			

ABCA1, Adenosine triphosphate–binding cassette transporter 1; *apo,* apolipoprotein; *HDL*, high-density lipoprotein; *LCAT,* lecithin:cholesterol acyltransferase; *LPL,* lipoprotein lipase.
From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

TABLE EH1-51 Drugs Used to Treat Hyperlipidemia

Class and Drugs Available	Dosage	Major Lipoprotein Decreased	Mechanism
Bile Acid Sequestrants			
Cholestyramine	4-12 g bid	LDL	Increase sterol excretion and LDL clearance
Colestipol	5-15 g bid		
Colesevelam	3.75-4.375 qd		
Nicotinic Acid			
Niacin (crystalline)	1-3 g qd	VLDL (LDL)	Decrease VLDL production
Niaspan	500-2000 mg qd		
Fibric Acid Derivatives			
Gemfibrozil	600 mg bid	VLDL (LDL)	Decrease VLDL production; enhance LPL action
Fenofibrate*	34-200 mg qd		
HMG-CoA Reductase Inhibitors			
Lovastatin	10-80 mg qd	LDL	Decrease cholesterol synthesis; increase LDL receptor–mediated removal of LDL
Pravastatin	10-40 mg qd		
Simvastatin	5-80 mg qd		
Fluvastatin	20-80 mg qd		
Atorvastatin	10-80 mg qd		
Rosuvastatin	5-40 mg qd		
Intestinal Cholesterol Absorption Inhibitor			
Ezetimibe	10 mg qd	LDL	Inhibits cholesterol absorption
Omega-3 Fatty Acids			
Lovaza (1-g capsule contains EPA and DHA)	4 g qd	VLDL	Inhibits VLDL production

EPA, Highly concentrated ethyl esters of eicosapentaenoic acid; *DHA,* docosahexaenoic acid; *HMG-CoA,* 3-hydroxy-3-methylglutaryl coenzyme A; *LDL,* low-density lipoproteins; *VLDL,* very-low-density lipoproteins.
*There are several different preparations of fenofibrate with different doses.
From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders, Elsevier Inc.

Hyperosmolar Hyperglycemic Syndrome ALG

BASIC INFORMATION

DEFINITION

Hyperosmolar hyperglycemic syndrome (HHS) is characterized by severe hyperglycemia, hyperosmolarity, profound dehydration, and altered mental status in the absence of ketosis.

SYNONYMS

Hyperosmolar coma
Nonketotic hyperosmolar syndrome
Hyperosmolar nonketotic state
HHS

ICD-9CM CODES
250.2 Hyperosmolar coma
ICD-10CM CODES
E87.0 Hyperosmolality and hypernatremia

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Evidence of extreme dehydration (poor skin turgor, sunken eyeballs, dry mucous membranes)
- Neurologic defects (reversible hemiplegia, focal seizures)
- Orthostatic hypotension, tachycardia
- Evidence of precipitating factors (infection, myocardial ischemia, stroke)
- Suppressed mental status ranging from delirium to obtundation to coma (25% of patients)

ETIOLOGY

- Infections in up to 50% (e.g., pneumonia, urinary tract infection, sepsis)
- New or previously unrecognized diabetes (30%)
- Noncompliance, dose reduction, or recent discontinuation of diabetic medication
- Stress (myocardial infarction, cerebrovascular accident)
- Drugs: diuretics (dehydration), phenytoin, diazoxide (impairs insulin secretion), glucocorticoids, chemotherapeutic agents, calcium channel blockers, total parenteral nutrition, substance abuse (alcohol, cocaine)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Diabetic ketoacidosis
- Stroke
- Encephalitis
- Encephalopathy
- Myxedema coma

LABORATORY TESTS

- Hyperglycemia: serum glucose usually >600 mg/dl, serum/urine ketones absent or "small."
- Hyperosmolarity: serum osmolarity usually >320 mOsm/L.
- Serum sodium: may be low, normal, or high. Because glucose draws fluid from the intracellular space, decreasing the serum sodium, it is necessary to correct sodium for the serum glucose level. The corrected sodium can be obtained by increasing the serum sodium concentration by 1.6 mEq/dl for every 100 mg/dl increase in the serum glucose level over normal.
- Serum potassium: may be low, normal, or high; regardless of the initial serum level, the total body deficit is approximately 5 to 15 mEq/kg.
- Serum bicarbonate: usually >15 mEq/L (average 17 mEq/L).
- Arterial pH: usually >7.3; both serum bicarbonate and arterial pH may be lower if lactic acidosis is present.
- Blood urea nitrogen: generally ranges from 60 to 90 mg/dl due to severe dehydration and pro-renal azotemia.
- Phosphorus: hypophosphatemia (average deficit is 70 to 140 mmol).
- Calcium: hypocalcemia (average deficit is 50 to 100 mEq).
- Magnesium: hypomagnesemia (average deficit is 50 to 100 mEq).
- Complete blood count with differential, urinalysis, and blood and urine cultures should be performed to rule out infectious etiology.
- ECG to rule out a concomitant myocardial infarction.

IMAGING STUDIES

- Chest x-ray is useful to rule out infectious process. The initial x-ray may be negative if the patient has significant dehydration. Repeat chest x-ray after 24 hr of hydration if pulmonary infection is suspected.
- The need for additional imaging, such as CT scans, is determined by biochemical or physical exam findings.

TREATMENT

ACUTE GENERAL Rx

- Vigorous fluid replacement: the volume and rate of fluid replacement are determined by renal and cardiac function. Slower infusion rate may be used initially in patients with compromised cardiovascular or renal status. Frequent clinical monitoring of fluid status is essential.
  - During the first hour, infuse 1000 ml of 0.9% normal saline (NS) to expand the intravascular fluid volume.
  - Infuse a second liter of 0.9% NS in the next hour if the patient is persistently hypotensive.
  - Then begin replacing the free fluid deficit with 0.45% NS at 250 to 500 ml/hr. Taper the 0.45% NS to replace the estimated fluid deficit over 24 to 36 hours.
  - When serum glucose reaches 300 mg/dl, change to 5% dextrose with 0.45% NS.
- Correct hyperglycemia: the goal is to decrease plasma glucose by 50 to 100 mg/dl/hr.
  - Vigorous IV hydration will decrease the serum glucose level in most patients by 80 mg/dl/hr. Insulin should not be administered until serum potassium is >3.3 mEq/L to prevent life-threatening hypokalemia.
  - A regular insulin IV bolus (0.1 units/kg of body weight) is followed by an insulin fusion of 0.1 units/kg/hr, adjusted on an hourly basis as needed, until the serum glucose level approaches 300 mg/dl
  - Before stopping the IV insulin infusion, administer an SC dose of insulin (dose varies with patient's demonstrated insulin sensitivity). Short (regular) or rapid-acting (aspart, lispro, glulisine) insulins should be administered SC 1 to 2 hr before stopping the IV insulin infusion. Intermediate (NPH) or long-acting (glargine, detemir) insulins should be administered SC 2 to 4 hr before stopping IV insulin infusion.
- Total daily insulin doses in insulin-naïve patients range from 0.5 to 0.8 units/kg/day. Approximately half of this dose should be given as intermediate or long-acting insulin, and half of this dose should be given as mealtime or prandial insulin if the patient is eating.
- Replace potassium: monitor potassium every 2 hours until the patient has stabilized. Confirm the patient is not anuric before starting potassium (K) replacement. Rate of K replacement can be based on presenting potassium level. If K is <3.3, give KCl 20 to 30 mEq/L of intravenous fluid (IVF) until K is >3.3. If K is 3.3 to 5.3, give KCl at 10 to 30 mEq/L IVF to maintain a K of >4. If K >5.3, hold potassium supplementation and check K every 2 hours. Continuous telemetry monitoring and hourly measurement of urinary output are recommended.
- Phosphate replacement: replacement can be considered if serum phosphate is <2 mEq/L or there is evidence of phosphate depletion syndrome rhabdomyolysis. In the absence of renal failure, phosphate can be administered at a rate of 0.1 mmol/kg/hr (5 to 10 mmol/hr) to a maximum of 80 to 120 mmol in 24 hr.
- Magnesium replacement, in the absence of renal failure, can be administered IM (0.05 to 0.10 ml/kg of 20% magnesium sulfate) or as IV infusion (4 to 8 ml of 20% magnesium sulfate [0.08 to 0.16 mEq/kg]).

PEARLS & CONSIDERATIONS

COMMENTS

- The typical patient is an elderly or bed-confined diabetic with impaired ability to communicate thirst who is evaluated after an interval of 1 to 2 wk of prolonged osmotic diuresis.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **HILARY B. WHITLATCH, M.D., SAINATH GADDAM, M.D.,** and **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Delaney MF et al.: Diabetic ketoacidosis and hyperglycemic hyperosmolar nonketotic syndrome, *Endocrinol Metab Clin North Am* 29:683–705, 2000.

Kitabchi AE et al.: Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association, *Diabetes Care* 29:2739–2748, 2006.

Stoner GD: Hyperosmolar hyperglycemic state, *Am Fam Physician* 71:1723, 2005.

BASIC INFORMATION

DEFINITION

Hyperparathyroidism is an endocrine disorder caused by excessive secretion of parathyroid hormone (PTH) from the parathyroid glands. Autonomous production of PTH resulting in hypercalcemia defines primary hyperparathyroidism. Secondary hyperparathyroidism occurs when the parathyroid glands appropriately increase PTH production in response to low calcium or vitamin D states. Primary hyperparathyroidism is the focus of this section.

ICD-9CM CODES
252.00 Hyperparathyroidism, unspecified
252.01 Hyperparathyroidism, primary
252.02 Hyperparathyroidism, secondary
ICD-10CM CODES
E21.3 Hyperparathyroidism, unspecified
E21.0 Primary hyperparathyroidism

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 4 cases per 100,000 persons per year. Although malignancy is the most common cause of hypercalcemia in hospitalized patients, primary hyperparathyroidism is the most common cause of hypercalcemia in the outpatient setting.
PREVALENCE: 3 cases/1000 persons
PREDOMINANT SEX AND AGE: Higher prevalence in women (female:male ratio 2:1) and older age (peaks in the seventh decade of life).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The majority of patients with primary hyperparathyroidism are asymptomatic. Diagnosis is usually considered in patients after an incidental discovery of hypercalcemia or during the evaluation for decreased bone mass. The development of symptoms varies with severity and rapidity of disease progression and reflects both the hypercalcemic and hyperparathyroid components of the disease process.

- Cardiovascular: hypertension, shortened QT interval, bradycardia, arrhythmia, valvular calcification, left ventricular hypertrophy, increased mean carotid intima-media thickness.
- GI: anorexia, nausea, vomiting, constipation, abdominal pain, peptic ulcer disease, pancreatitis
- GU: nephrolithiasis, nephrocalcinosis, renal insufficiency, polyuria, nocturia, nephrogenic diabetes insipidus, renal tubular acidosis
- Musculoskeletal: weakness, myopathy, bone pain, osteopenia, osteoporosis, gout, pseudogout, chondrocalcinosis, osteitis fibrosa cystica, subperiosteal bone resorption (Fig. H1-75)
- CNS: confusion, anxiety, fatigue, lethargy, obtundation, depression, coma
- Other: pruritus, metastatic calcifications, band keratopathy

ETIOLOGY

- Most cases of primary hyperparathyroidism are sporadic but it can be associated with rare familial conditions such as multiple endocrine neoplasia (MEN-1 and MEN-2). Mutations in certain genes have been linked to tumor development in both sporadic and familial cases such as hyperparathyroidism-jaw tumor syndrome. Higher prevalence of hyperparathyroidism is noted with head and neck irradiation, chronic low calcium or vitamin D status, and lithium therapy.
- Pathologic characteristics include adenoma (80%-85%), hyperplasia (10%-15%), or carcinomas (<1%-2%).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Secondary hyperparathyroidism precipitated by conditions that result in hypocalcemia
  - Renal calcium loss (i.e., medication: loop diuretics and hypercalcuria)
  - Calcium deficiency
  - Vitamin D deficiency
  - Malabsorption
  - Chronic kidney disease (most common)
  - Pseudohypoparathyroidism (PTH resistance)
  - Inhibition of bone resorption (i.e., bisphosphonates)
- Other causes of hypercalcemia include:
  - Medications: thiazide diuretics, lithium therapy
  - Vitamin D intoxication, milk-alkali syndrome

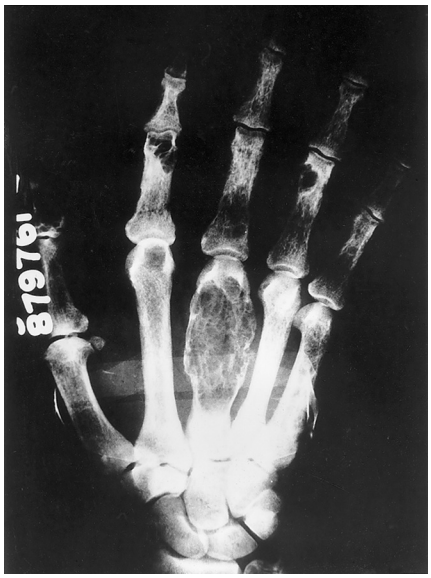


FIGURE H1-75 Radiograph of hand from a patient with severe primary hyperparathyroidism. Note the dramatic remodeling associated with the intense region of high bone turnover in the third metacarpal, in addition to widespread evidence of subperiosteal and trabecular resorption. (Courtesy Fuller Albright Collection, Massachusetts General Hospital. From Larsen PR et al [eds]: *Williams textbook of endocrinology,* ed 10, Philadelphia, 2003, Saunders.)

  - Familial hypocalciuric hypercalcemia (FHH)
  - Renal failure (tertiary hyperparathyroidism)
  - Granulomatous disorders (e.g., sarcoidosis)
  - Malignancy (e.g., lung cancer, lymphoma, multiple myeloma, bone metastasis)
  - Prolonged immobilization

WORK-UP

- Typically, primary hyperparathyroidism is confirmed with an elevated serum calcium and PTH level.
  1. Two measurements of serum calcium are required for the confirmation of hypercalcemia. Total calcium should be corrected for low albumin utilizing the formula: Corrected Calcium = Serum Calcium + 0.8 × 4 – serum albumin). If a reliable laboratory is available, ionized calcium should be considered especially in conditions associated with acid-base disturbances or low albumin states. Patients with primary hyperparathyroidism can also present with normal calcium levels. The most common reason for this finding is concomitant vitamin D deficiency and primary hyperparathyroidism.
  2. The serum intact PTH (iPTH) level is the single best test to evaluate the etiology of hypercalcemia. PTH is elevated or in the high normal range (i.e., inappropriately normal for an elevated calcium state) in primary hyperparathyroidism. PTH is decreased in most other conditions associated with elevated calcium.
- Other causes of hypercalcemia should be ruled out. These are typically associated with low PTH levels. Exceptions include lithium use and FHH.
  - Review medication history to determine lithium, thiazide, vitamin D, or calcium intake.
  - Check 24-hr urine calcium:creatinine to rule out FHH. Urine calcium is usually low in FHH. PTH can be normal or high in FHH.
  - Consider PTH-related peptide (PTHrP) to evaluate hypercalcemia related to malignancies and vitamin D1,25 to assess hypercalcemia secondary to granulomatous diseases or lymphomas.
  - Multiple myeloma and bone metastasis can also result in a high calcium state and therefore must be appropriately evaluated.
- Rule out other causes of elevated PTH (i.e., secondary hyperparathyroidism). Serum calcium is typically low or low-normal in secondary hyperparathyroidism.
  - Check calcium and 25 OH-vitamin D to rule out deficiency states.
  - Check serum creatinine to assess renal function and 24-hr urine calcium and creatinine to evaluate renal loss

LABORATORY TESTS

- Serum calcium (ionized or corrected calcium): normal or elevated in primary hyperparathyroidism
- Serum phosphorus: low or low-normal in primary hyperparathyroidism.

- PTH: elevated or high normal in primary hyperparathyroidism
- 24-hr urine calcium and creatinine to evaluate risk for renal stones and to exclude FHH.
- Serum creatinine to assess GFR and renal status.
- PTHrP and 1,25 OH-vitamin D levels can be considered to rule out other causes of elevated calcium.
- Evaluation of 25 OH-vitamin D is recommended in all patients with hyperparathyroidism. Vitamin D deficiency can result in secondary hyperparathyroidism. Calcium levels are usually in the low-normal range in vitamin D deficiency.
- ECG may reveal shortening of the QT interval secondary to severe hypercalcemia (>12 mg/dl)

IMAGING STUDIES

- Neck imaging is not indicated for diagnosis but is useful for localization before planned parathyroidectomy.
- Parathyroid localization with technetium-99m sestamibi can identify potential adenomas.
- Bone mineral density of the spine, hip, and forearm (distal third) is recommended for all patients with hyperparathyroidism in order to assess the risk for osteoporosis and fragility fractures. Cortical bone loss (i.e., forearm or hip) is greater than trabecular bone loss (i.e., spine) in hyperparathyroidism.
- Renal ultrasound can be considered to assess asymptomatic renal stones.

Rx TREATMENT

Modality of treatment depends on disease progression and which patients are more likely to suffer end-organ effects of hyperparathyroidism or benefit the most from surgery.

NONPHARMACOLOGIC THERAPY

- Surgery is the only definitive treatment for symptomatic primary hyperparathyroidism. Surgery can normalize calcium levels, decrease the risk for kidney stones, improve bone mineral density and fracture risk, and enhance quality of life measures.
  - Indications for parathyroidectomy
    1. All patients younger than 50 yr
    2. Hypercalcemia (Ca >1 mg/dl above upper limit normal)
    3. Creatinine clearance <60 ml/min
    4. Osteoporosis (T-score < –2.5 or prior fragility fracture)
    5. Symptomatic hyperparathyroidism such as history of nephrolithiasis
  - Surgical approaches include:
    1. Bilateral neck exploration under general anesthesia is the conventional surgical approach. An experienced endocrine surgeon cures >95% of patients undergoing bilateral neck exploration. Potential complications include transient and permanent hypocalcemia secondary to hypoparathyroidism and recurrent laryngeal nerve injury.
    2. Minimally invasive parathyroidectomy performed by experienced surgeons is an excellent alternative to conventional surgery. It can be performed under cervical block anesthesia as an outpatient procedure with intraoperative monitoring of PTH before and after removal to document the expected fall after abnormal glands are removed.
- Ablation therapy (e.g., ethanol, angiographic, radiofrequency) can be considered in patients who are not surgical candidates. Limited data are available on efficacy and side effects. Repeat ablations may be required if hypercalcemia persists.
- Medical monitoring is recommended for asymptomatic primary hyperparathyroidism. Majority of patients do not manifest disease progression during observation. However, approximately 25% of asymptomatic patients will require surgery over a 10-yr follow-up period.
  1. Indications for medical monitoring
     1. Clinically asymptomatic and >50 yr old.
     2. Serum calcium level only mildly elevated (<1 mg/dl above upper limit normal)
     3. GFR > 60 ml/min and no nephrolithiasis or nephrocalcinosis
     4. No evidence of osteoporosis
     5. Medically unfit for surgery or refusing surgery
- Symptoms should be assessed regularly. Serum calcium and creatinine should be checked yearly. Bone mineral density may be monitored every 2 yr.
- Medical management
  1. Avoid medications that precipitate hypercalcemia (e.g., thiazide or lithium)
  2. Since inadequate calcium and vitamin D status stimulates PTH, calcium and vitamin D intake should be the same as for patients without hyperparathyroidism (i.e., 1000 mg of elemental calcium and 600-800 IU of vitamin D daily).
  3. Encourage physical activity since immobilization increases bone resorption.
  4. Recommend adequate hydration (at least 2 L) to minimize the risk of nephrolithiasis.

PHARMACOLOGIC THERAPY

For patients who are not surgical candidates, pharmacologic options are available. Indications include symptomatic hyperparathyroidism or osteopenia associated with an increased fracture risk.

- Cinacalcet (Sensipar) is an oral calcimimetic agent that activates the calcium sensing receptor in the parathyroid gland. It decreases PTH production and subsequently serum calcium levels, without significant BMD changes. It is indicated for the treatment of secondary hyperparathyroidism associated with chronic kidney disease, for hypercalcemia associated with parathyroid carcinoma, and for the treatment of severe hypercalcemia in patients with primary hyperparathyroidism who are unable to undergo surgery.
- Agents that inhibit bone resorption such as bisphosphonates (e.g., alendronate, pamidronate, zoledronate), estrogens and selective estrogen receptor modulators (e.g., raloxifene) improve bone mineral density, and decrease calcium levels in patients with hyperparathyroidism. These agents should be considered when fracture reduction is the primary goal.

ACUTE GENERAL Rx

Severe and/or symptomatic hypercalcemia may require hospitalization especially if serum calcium >12 mg/dl. Acute management of hypercalcemia includes:

- Vigorous hydration with IV normal saline (2-4 L/day). Fluid status must be monitored in patients with cardiac dysfunction or renal insufficiency in order to avoid fluid overload.
- Bisphosphonates can effectively decrease calcium levels. Zoledronate (4 mg IV over 15 min) or pamidronate (60-90 mg IV over 4 hr) are both effective. Onset of action is 24 to 48 hr.
- Calcitonin (4 units/kg IM/SC every 12 hr) may be used with bisphosphonates to achieve a more rapid reduction of calcium levels. Onset of action is within hours.

PEARLS & CONSIDERATIONS

COMMENTS

- Parathyroidectomy should be considered for all patients with symptomatic hyperparathyroidism. If surgery is contraindicated or not desired, cinacalcet can be considered.
- Asymptomatic patients can be monitored with serial calcium, creatinine, and bone mineral density measurements. Disease progression may result in surgery.
- Most patients can be managed medically by limiting factors that result in hypercalcemia (e.g., dehydration, immobilization, thiazide diuretics) and maintaining normal calcium and vitamin D intake.
- Patients with osteopenia and high fracture risk may require antiresorptive therapy such as bisphosphonates.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hyperparathyroidism (Patient Information)

AUTHOR: **VICKY CHENG, M.D.**

EVIDENCE

Abstract[1]

Context:

Primary hyperparathyroidism (PHPT) is characterized by elevated serum calcium (Ca) and increased PTH concentrations.

Objective:

The objective of the investigation was to establish the efficacy of cinacalcet in reducing serum Ca in patients with PHPT across a wide spectrum of disease severity.

Design and Setting:

The study was a pooled analysis of data from three multicenter clinical trials of cinacalcet in PHPT.

Patients:

Patients were grouped into three disease categories for analysis based on the following: 1) history of failed parathyroidectomy (n = 29); 2) meeting one or more criteria for parathyroidectomy but without prior surgery (n = 37); and 3) mild asymptomatic PHPT without meeting criteria for either above category (n = 15).

Intervention:

The intervention in this study was treatment with cinacalcet for up to 4.5 yr.

Outcomes:

Measurements in the study included serum Ca, PTH, phosphate, and bone-specific alkaline phosphatase, and areal bone mineral density (aBMD). Vital signs, safety biochemical and hematologic indices, and adverse events were monitored throughout the study period.

Results:

The extent of cinacalcet-induced serum Ca reduction, proportion of patients achieving normal serum Ca (≤10.3 mg/dl), reduction in serum PTH, and increase in serum phosphate were similar across all three categories. Except for decreased aBMD at the total femur noted in the parathyroidectomy group at 1 yr, no significant changes in aBMD occurred. The efficacy of cinacalcet was maintained for up to 4.5 yr of follow-up. AEs were mild and similar across the three categories.

Conclusions:

Cinacalcet is equally effective in the medical management of PHPT patients across a broad spectrum of disease severity, and overall cinacalcet is well tolerated. Ⓐ

Evidence-Based Reference

Peacock M et al.: Cinacalcet HCl reduces hypercalcemia in primary hyperparathyroidism across a wide spectrum of disease severity, *J Clin Endocrinol Metab* 96(1):E9–E18, 2011. Ⓐ

SUGGESTED READINGS

Bilezikian JP: Primary hyperparathyroidism, *Endocr Pract* 18(5):781–790, 2012.

Khan AA et al.: Medical management of primary hyperparathyroidism, *J Clin Den* 16(1):60–63, 2013.

Kunstman JW et al.: Superiority of minimally invasive parathyroidectomy, *Adv Surg* 45:171–189, 2012.

Michels TC, Kelly KM et al.: Parathyroid disorders, *Am Fam Phys* 88(4):249–257, 2013.

Pallan S et al.: Diagnosis and management of primary hyperparathyroidism, *BMJ* 344:e1013, 2012.

BASIC INFORMATION

DEFINITION

Hypersensitivity pneumonitis (HP) is a group of immunologically mediated pulmonary diseases, with or without systemic manifestations (e.g., fever, weight loss), caused by the inhalation of an antigen to which the patient is sensitized and hyperresponsive. Sensitization and exposure alone in the absence of symptoms do not define the disease.

SYNONYMS

Extrinsic allergic alveolitis (EAA)

Some specific examples:

- Bird fancier's lung
- Farmer's lung
- Chemical worker's lung
- Humidifier lung
- Hot tub lung
- Sauna taker's lung
- HP

ICD-9CM CODES

495.9 Pneumonitis, hypersensitivity

ICD-10CM CODES

J67.8 Hypersensitivity pneumonitis due to other organic dust

J67.9 Hypersensitivity pneumonitis due to unspecified organic dust

EPIDEMIOLOGY & DEMOGRAPHICS

- Prevalence and incidence of HP vary considerably.
- Depend on definition and methods to establish diagnosis, intensity of exposure, environmental conditions, and genetic risk factors that remain poorly understood.
- More than 300 causative agents have been identified, and the number continues to grow.
- Causative agents in residential and occupational exposures include birds, mold, humidifiers, fountains, steam irons, dry sausage molds, moldy cheese, contaminated wood, biofilm contained within wind instruments (e.g., trombone, saxophone), and organic and inorganic chemicals, including metalworking fluids. A large series of patients with HP associated with down pillows, feather duvets, and down-upholstered furniture has been published. Likely several genes are involved that cause an exaggerated lung response to an offending agent. The major histocompatibility complex is the most studied thus far.
- A viral connection has been implicated that may enhance clinical exposure to an offending agent.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Vary depending on frequency and intensity of antigen exposure.

- Acute: fever, cough, malaise, and dyspnea 4 to 6 hr after an intense exposure, lasting 18 to 24 hr
- Subacute: insidious onset of productive cough, dyspnea on exertion, anorexia, and weight loss, usually from a heavy, sustained exposure
- Chronic: gradually progressive cough, dyspnea, malaise, and weight loss, usually from low-grade or recurrent exposure
- Physical examination: cyanosis and crepitant rales, possible fever

ETIOLOGY

- Numerous environmental agents, often encountered in occupational settings
- Common sources of antigens: "moldy" hay, silage, grain, or vegetables; bird droppings or feathers (including those found commonly in down pillows, blankets, and upholstered furniture); low-molecular-weight chemicals (e.g., isocyanates); pharmaceutical products

DIAGNOSIS

- Accurate diagnosis is important for differentiating HP from other interstitial disorders because the prognosis and treatment may differ.
- The clinical syndrome is indistinguishable from an acute respiratory infection without a history of illness occurring within hours of exposure to an antigen.
- Need high index of suspicion.
- Detailed occupational and home exposure history is required.
- Lung biopsy is often necessary for diagnosis.

DIFFERENTIAL DIAGNOSIS

Acute Stages	Chronic Stages
Acute bronchopulmonary aspergillosis	Idiopathic pulmonary fibrosis (IPF)
Pulmonary embolism	Bronchiectasis
Asthma	Chronic bronchitis
Aspiration pneumonia	Nonspecific interstitial pneumonia (NSIP)
Recurrent pneumonia	Connective tissue–related lung disease
Bronchiolitis obliterans–organizing pneumonia	
Sarcoidosis	
Churg-Strauss syndrome	
Wegener granulomatosis	

WORKUP

No single radiologic, physiologic, or immunologic test is specific for the diagnosis of HP. HP must be suspected in any patient presenting with cough, dyspnea, fever, and malaise. A thorough history focusing on potential exposures is essential. Table H1-52 describes examples of occupational causes of HP.

Environmental and occupational history questions should ask about grain dusts; animal handling; food processing; cooling towers; fountains; metalworking fluids; symptom improvement away from exposure; pets (particularly birds); hobbies involving chemicals, feathers, or fur; organic dusts; presence of humidifiers, dehumidifiers, or hot tubs/saunas; leaking or flooding indoors; visible fungal growth in living or working environment; feather pillows, bedding, or upholstered furniture.

Major criteria:

- History of symptoms compatible with HP that appear to worsen within hours after antigen exposure
- Confirmation of exposure to the offending agent by history, investigation of the environment, serum precipitin tests to potential agents (often referred to as a "hypersensitivity panel" by many labs), or bronchoalveolar lavage (BAL) antibody
- Compatible changes on chest radiograph or high-resolution CT (HRCT) of the chest
- BAL fluid lymphocytosis (if performed)
- Compatible histologic changes by lung biopsy (if performed): bronchiolocentric interstitial pneumonia, NSIP
- Positive natural challenge (reproduction of symptoms and laboratory abnormalities after exposure to the suspected environment) or controlled inhalation challenge

Minor criteria:

- Basilar crackles
- Decreased diffusion capacity
- Arterial hypoxemia (either at rest or with exercise)

LABORATORY TESTS

- Routine laboratory tests do not make the diagnosis, but typically the erythrocyte sedimentation rate, C-reactive protein, lactate dehydrogenase, and leukocyte count are increased; elevated immunoglobulins IgG and IgM are nonspecific; rheumatoid factor (RF) and immune complexes are often positive; peripheral eosinophil count and serum IgE are generally normal.
- Lactate dehydrogenase (LDH) is increased and tends to decrease with improvement.
- Pulmonary function tests: restrictive ventilatory patterns are typically seen. Decreased FEV_1, decreased forced vital capacity, decreased total lung capacity, decreased diffusing capacity, and decreased static compliance.
- Arterial blood gases show mild hypoxemia (worsens with exercise).
- A-a gradient shows slight increase.
- Serum precipitin test for IgG antibodies against offending antigen detected in serum. It is sensitive but not specific for HP (asymptomatic patients may have IgG antibodies in serum). HP may also be present without a positive precipitin test.
- Skin testing: unclear if helpful. However, some believe it to be a safe, effective, and rapid procedure in the diagnosis and follow-up of patients with HP. Sensitivity is similar to that of the precipitin test but the specificity is higher.

IMAGING STUDIES

Chest x-ray: nonspecific; may be normal in early stage.

- Acute/subacute: bilateral interstitial and alveolar nodular infiltrates in a patchy or homogeneous distribution. Apices are often spared.

TABLE H1-52 Examples of Occupational Causes of Hypersensitivity Pneumonitis

Occupation	Cause
Farmer	Thermophilic actinomycetes in moldy hay
Metal worker	Contamination of metal-working fluids with microorganisms such as *Mycobacteria immunogens* or fungi
Worker exposed to humidifiers	Contamination with microorganisms such as protozoa or fungi
Sugarcane worker	Moldy sugarcane (bagassosis)
Maple bark stripper	Fungi
Chicken or turkey worker	Avian proteins
Pharmaceutical worker	Penicillin
Food handler	Soybeans
Office worker	Microorganisms contaminating air conditioners or humidifiers
Swimming pool attendant	Fungal contamination in sprays around pool area
Animal worker	Rat proteins
Mushroom worker	Fungi
Wheat farmer or handler	Weevil-infested flour
Greenhouse worker	Fungi
Workers spraying urethane paint or adhesives/sealants (or less often, other workers using diisocyanate)	Methylene diphenyl diisocyanate, hexamethylene diisocyanate, toluene diisocyanates
Chemical worker using plastics, resins, paints	Trimellitic anhydride

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

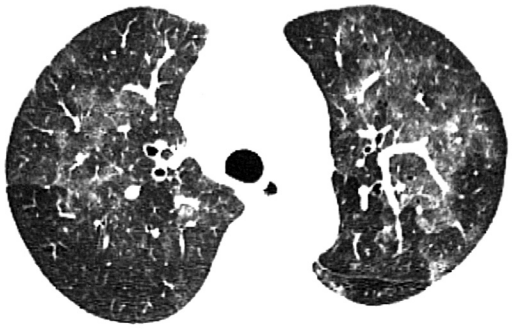


FIGURE H1-76 In this patient with hypersensitivity pneumonitis, patchy ground-glass opacity is visible bilaterally. (From Mason RJ: *Murray & Nadel's textbook of respiratory medicine*, 5th ed, Philadelphia, 2010, Saunders.)

- Chronic: diffuse reticulonodular infiltrates and fibrosis.

High-resolution chest CT scan (Fig. H1-76): no pathognomonic features but demonstrates airspace and interstitial patterns in the acute and subacute stage. The chronic stage reveals honeycombing and bronchiectasis.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Early recognition and avoidance of the causative antigen

ACUTE GENERAL Rx

- Glucocorticoids accelerate initial lung recovery but may have no effect long term (from a controlled study in farmer's lung). No prospective, randomized, placebo-controlled trials for other types of HP or subacute and chronic stages.
- Prednisone 0.5 to 1 mg/kg usually over 1 to 2 wk then tapered over 4 wk. Some patients, particularly those with subacute or chronic presentation, may require a longer course of therapy.

DISPOSITION/PROGNOSIS

Prognosis is generally better in patients with acute or subacute HP, and with the finding of NSIP pathologically. Prognosis is worse in those with older age, desaturation during exercise, and findings of severe fibrosis by lung biopsy.

Acute: 4 to 48 hr
- Clinical: fever, chills, cough, hypoxia, malaise
- HRCT: ground-glass infiltrates
- Immunopathology: poorly formed, noncaseating granulomas or mononuclear cell infiltration in a peribronchial distribution, frequently with giant cells
- Prognosis: good

Subacute: weeks to 4 mo
- Clinical: dyspnea, cough, episodic flares
- HRCT: micronodules, air trapping
- Immunopathology: more well-formed, noncaseating granulomas, bronchiolitis, organizing pneumonia, and interstitial fibrosis
- Prognosis: good

Chronic: 4 mo to years
- Clinical: dyspnea, cough, fatigue, weight loss
- HRCT: fibrosis (possible), honeycombing, emphysema
- Immunopathology: granulomatous pneumonitides may be seen in addition to bronchiolitis obliterans (with or without organizing pneumonia) and honeycombing and fibrosis, lymphocytic infiltration, centrilobular and bridging fibrosis, neutrophil-mediated air space destruction, giant cells

REFERRAL

- Bronchoscopy: BAL provides useful supportive data in the diagnosis of HP. Usually reveals intense lymphocytosis (typically T cells >50%) of predominantly CD8+ suppressor cells. In the acute stage neutrophils predominate, but as the disease progresses to chronic form the ratio of CD4+ to CD8+ cells increases. When fibrosis is present the number of neutrophils increases.
- Lung biopsy: the histopathologic features of HP are distinctive but not pathognomonic. Bronchiolitis and interstitial pneumonitis with granuloma formation typically is seen. Variable degrees of interstitial fibrosis are seen in the chronic form. Chronic HP may be difficult to distinguish from IPF or NSIP pathologically.
- Laboratory inhalation challenge: testing to prove a direct relation between a suspected antigen and disease; extract of antigen is inhaled by nebulizer.

PEARLS & CONSIDERATIONS

A clinical prediction rule using six features has high specificity and sensitivity for the diagnosis of acute and subacute HP:
- Exposure to a known offending agent
- Positive specific precipitating antibody
- Recurrent episodes of symptoms
- Inspiratory crackles
- Symptoms occurring 4 to 8 hr after exposure
- Weight loss

HP occurs more frequently in smokers than nonsmokers (likely from an immunosuppressive effect).

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hypersensitivity Pneumonitis (Patient Information)

AUTHOR: **KRISTINA KRAMER, M.D.**

SUGGESTED READINGS

Churg A: Chronic hypersensitivity pneumonitis, *Am J Surg Pathol* 30(2):201, 2006.

Costabel U et al.: Chronic hypersensitivity pneumonitis, *Clin Chest Med* 33:151–163, 2012.

Fink JN et al.: Needs and opportunities for research in hypersensitivity pneumonitis, *Am J Respir Crit Care Med* 171:792–798, 2005.

Fishwick D et al.: New occupational and environmental causes of asthma and extrinsic allergic alveolitis, *Clin Chest Med* 33:605–616, 2012.

Hanak V et al.: High resolution CT findings of parenchymal fibrosis correlate with prognosis in hypersensitivity pneumonitis, *Chest* 134(1):133–138, 2008.

Lacasse Y et al.: Clinical diagnosis of active hypersensitivity pneumonitis, *Am J Respir Crit Care Med* 168:952–958, 2003.

Lacasse Y et al.: Recent advances in hypersensitivity pneumonitis, *Chest* 142:208–217, 2012.

Metzger F et al.: Hypersensitivity pneumonitis due to molds in a saxophone player, *Chest* 138(3), 2010.

Morrell F et al.: Usefulness of specific skin tests in the diagnosis of hypersensitivity pneumonitis, *J Allergy Clin Immunol* 110(6):939, 2002.

Patel AM et al.: Hypersensitivity pneumonitis: current concepts and further questions, *J Allergy Clin Immunol* 108:661, 2001.

Schuyler M, Cormier Y: The diagnosis of hypersensitivity pneumonitis, *Chest* 111:534, 1997.

Selman M: Hypersensitivity pneumonitis: a multifaceted deceiving disorder, *Clin Chest Med* 25:3, 2004.

BASIC INFORMATION

DEFINITION

Hypersplenism is a syndrome characterized by splenomegaly, cytopenia (one or more of the following: anemia, thrombocytopenia, or leukopenia), and compensatory hyperplastic bone marrow. The cytopenias are correctable with splenectomy.

ICD-9CM CODES
289.4 Hypersplenism
ICD-10CM CODES
D73.1 Hypersplenism

EPIDEMIOLOGY & DEMOGRAPHICS

Most often seen in patients with liver disease, hematologic malignancy, and infection

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms depend on the size of the spleen, rate of growth, and underlying disease.
- History: early satiety, abdominal discomfort or fullness, acute left upper quadrant (LUQ) pain (infarction, sequestration crisis), referred pain to left shoulder
- Physical examination: splenomegaly (normal spleen usually not palpable), LUQ tenderness, presence of a rub in LUQ (suggestive of splenic infarct), stigmata of cytopenias

ETIOLOGY

- Splenomegaly increases the proportion of blood channeled through the red pulp, causing inappropriate splenic pooling of both normal and abnormal blood cells. The size of the spleen determines the amount of cell sequestration. Up to 90% of platelets may be pooled in an enlarged spleen.
- Prolonged sequestration leads to increased destruction of RBCs. Platelets and white blood cells (WBCs) have about normal survival time even when sequestered and may be available if needed.
- Splenomegaly exacerbates cytopenias by dilution, possibly due to plasma volume expansion.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Hypersplenism can be caused by splenomegaly of almost any cause.

- Splenic congestion: cirrhosis (portal hypertension); congestive heart failure; portal, splenic, or hepatic vein thrombosis
- Hematologic causes: hemolytic anemia, spherocytosis, elliptocytosis, sickle cell anemia, thalassemia, extramedullary hematopoiesis, chronic transfusions, following use of granulocyte colony-stimulating factor
- Infections: viral (hepatitis, infectious mononucleosis, cytomegalovirus, HIV/AIDS), bacterial (abscess, endocarditis, sepsis, tuberculosis, salmonella, brucella, Lyme's disease), parasitic (babesiosis, malaria, leishmaniasis, schistosomiasis, toxoplasmosis), fungal
- Malignancy: acute or chronic leukemia, lymphoma, histiocytosis, myeloproliferative diseases (polycythemia vera, essential thrombocythemia, myelofibrosis), metastatic tumors
- Inflammatory diseases: rheumatic fever, rheumatoid arthritis (Felty's syndrome), systemic lupus erythematosus, sarcoid, serum sickness
- Infiltrative diseases: amyloidosis, Gaucher's disease, Niemann-Pick disease, glycogen storage disease
- Anatomic abnormalities: cysts, hemangioma, hamartoma

WORKUP

History (including travel), physical examination, laboratory tests, imaging studies

LABORATORY TESTS

- CBC with differential: cytopenia, neutrophilia (infection)
- Peripheral smear: RBC and WBC morphology (abnormal cells may suggest infection, malignancy, bone marrow disease, rheumatologic disease), organisms (bacteria, malaria, babesiosis)
- Bone marrow aspiration/biopsy: hyperplasia of cytopenic cell lines; hematologic, infiltrative, or infectious disorders
- Tests to diagnose suspected cause of splenomegaly: liver function, hepatitis serology, HIV, rheumatoid factor, antinuclear antibody, tissue biopsy
- Note: red cell mass (^{51}Cr assay) may be used to assess severity of anemia. RBC mass measurement will differentiate true anemia (decrease in RBCs) from dilutional anemia (plasma volume expansion).

IMAGING STUDIES

- Ultrasound: splenic size, presence of cyst or abscess
- CT: estimate volume, obtain structural information: cyst, abscess, malignancy
- MRI: most useful for assessing vascular lesions and infections
- Nuclear medicine: liver-spleen scan: assess anatomy and function; may suggest presence of portal hypertension
- Consider other studies as suggested by history and examination: chest radiograph, echocardiogram, PET scan

TREATMENT

ACUTE GENERAL Rx

- Treat underlying disease
- Splenectomy is considered if:
  1. Indicated for the management of the underlying cause
  2. Persistent symptomatic disease (severe cytopenia) not responding to therapy
  3. Necessary for diagnosis

Risks:

- Infections (especially encapsulated organisms): risk greatest in the first 2 yr after splenectomy. Mortality rate from sepsis is fiftyfold greater in asplenic patients. Attempts to decrease risk include:
  1. Immunization with pneumococcal (PPSV23), meningococcal (2 doses), and *Haemophilus influenzae* vaccines at least 2 wk before splenectomy. Pneumococcal (PCV13) one-time vaccination either 8 wk before or >1 year after PPSV23 vaccination. Revaccination for pneumococcal (PPSV23) in 5 yr and again after 65 yr. Revaccination for meningococcal every 5 yr. Annual influenza vaccination.
  2. Prophylactic antibiotics after splenectomy in highest-risk patients.
  3. Patient education regarding the importance of rapid initiation of antibiotics at the first sign of infection.
- Thromboembolic complications.
- Possible increased risk of atherosclerotic heart disease and cancer.
- Splenectomy should not be performed if the spleen is the main site of hematopoiesis as a result of bone marrow failure (e.g., myelofibrosis).
  - Other options include partial splenectomy, partial splenic embolization, radiofrequency ablation, portosystemic shunting (for congestive splenomegaly).

DISPOSITION

- Cytopenias usually correctable with splenectomy; normal cell counts in a few wk.
- Splenectomy may alleviate portal hypertension.
- Prognosis depends on the underlying disease.

REFERRAL

Hematology

PEARLS & CONSIDERATIONS

- Thrombocytopenia in hypersplenism is usually moderately severe (>50 × 10^9/L) and asymptomatic; severe thrombocytopenia (<20 × 10^9/L) suggests another diagnosis.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hypersplenism (Patient Information)
Felty's Syndrome (Related Key Topic)

AUTHOR: **SUDEEP KAUR AULAKH, M.D.**

SUGGESTED READINGS

CDC Vaccination Recommendations: http://www.cdc.gov/vaccines/schedules/hcp/adult.html

Feng K et al.: Randomized clinical trial of splenic radiofrequency ablation versus splenectomy for severe hypersplenism, *Br J Surg* 98:354, 2011.

Hoffman R et al.: *Hematology: basic principles and practice*, ed 6, Philadelphia, 2013, Elsevier.

Kristinsson SY et al.: Long-term risks after splenectomy among 8,149 cancer-free American veterans: a cohort study with up to 27 years follow-up, *Haematologica* 99(2):392, 2014.

BASIC INFORMATION

DEFINITION

Normal blood pressure (BP) in adults can be defined as systolic BP <120 mm Hg and diastolic <80 mm Hg. *Prehypertension* is defined as systolic BP between 120 to 139 mm Hg or diastolic between 80 to 89 mm Hg. *Stage 1 hypertension* (HTN) is systolic BP from 140 to 159 mm Hg or diastolic BP from 90 to 99 mm Hg. *Stage 2 HTN* is systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg.

SYNONYMS

Essential hypertension
Idiopathic hypertension
High BP

ICD-9CM CODES

401.1	Essential hypertension (HTN)
401.0-9 with 5th digit 1	Renovascular hypertension
405	Secondary hypertension
642	Hypertension complicating pregnancy
437.2	Hypertensive encephalopathy

ICD-10CM CODES

I10	Essential (primary) hypertension
I15.0	Renovascular hypertension
O10.919	Unspecified pre-existing hypertension complicating pregnancy, unspecified trimester
I67.4	Hypertensive encephalopathy

EPIDEMIOLOGY & DEMOGRAPHICS

- Based on NHANES data in 2007 to 2008, between 28-30% of U.S. adults have HTN (approximately 65 million) and only approximately 32.5 million (50%) have it well controlled.
- Worldwide, it's estimated that 41% of people aged 35-70 years have hypertension, and only 46.5% of them are aware (Chow et al).
- Peak prevalence increases with age and was highest among non-Hispanic black adults in the U.S.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Physical examination may be entirely within normal limits except for the presence of elevated BP. A proper initial physical examination on a hypertensive patient should include the following:

- The BP should be measured with an appropriately sized cuff (bladder of the cuff should cover at least two thirds of the circumference of the arm) and in both arms (the higher of the readings being used).
- The BP should be measured twice on each visit, and separated by at least 1 to 2 min to allow the return of trapped blood.
- The patient should be seated in a calm environment with the arm in which BP is measured rested on support level with the heart.
- Postural BP change should always be recorded in elderly to diagnose postural hypotension. This is assessed by taking BP in supine (after 5-minute rest) and standing (after 2 minutes) positions. A drop of ≥20 mm Hg in systolic, a drop of ≥10 mm Hg diastolic BP, or symptoms of cerebral hypoperfusion is suggestive of postural (orthostatic) hypotension.
- A diagnosis of HTN may be established if the BP is markedly elevated (>180/110 mm Hg) or has evidence of end organ damage; otherwise such a diagnosis should wait until BP is found elevated on at least 3 visits, spaced over a period of weeks to months.
- Measure heart rate, height, weight, body mass index, and waist circumference.
- Physical examination should include searching for secondary causes, and sequelae of hypertension.
- Examine skin for the presence of café-au-lait spots (neurofibromatosis), uremic appearance (renal failure), and violaceous striae (Cushing's syndrome).
- Perform careful funduscopic examination; check for papilledema, retinal exudates, hemorrhages, arterial narrowing, arteriovenous compression.
- Examine neck for carotid bruits, distended neck veins, and enlarged thyroid gland.
- Perform extensive cardiopulmonary examination: check for a laterally displaced point of maximal intensity, an S3 or S4, and valvular murmurs.
- Palpate abdomen for renal masses (pheochromocytoma, polycystic kidneys), and auscultate for bruit over the aorta and renal arteries.
- Examine arterial pulses (dilated or absent femoral pulses and BP greater in upper extremities than lower extremities suggest aortic coarctation).
- Look for truncal obesity (Cushing's syndrome) and pedal edema (congestive heart failure [CHF]).
- Table H1-53 provides a guide to evaluation of identifiable causes of HTN. Fig. EH1-77 and Box EH1-12 describe the investigation of suspected endocrine causes of HTN.

ETIOLOGY

- Essential (primary) HTN (85%)
- Drug induced or drug related (5%)
  1. NSAIDs
  2. Oral contraceptives
  3. Corticosteroids
- Renal HTN (5%)
  1. Renal parenchymal disease (3%)
  2. Renovascular HTN (RVH) (<2%)
- Endocrine (<2%)
  1. Primary aldosteronism (0.5%)
  2. Pheochromocytoma (0.2%)
  3. Cushing's syndrome and long-term steroid therapy (0.2%)
  4. Hyperparathyroidism or thyroid disease (0.2%)
- Coarctation of the aorta (0.2%)

DIAGNOSIS

WORKUP

- The objective for the initial evaluation of HTN is to establish the diagnosis and stage of HTN.
- Gather office and nonoffice BP readings, assess presence of target organ damage (TOD), assess the level of global cardiovascular disease risk and produce a plan for individualized monitoring and therapy.

TABLE H1-53 Guide to Evaluation of Identifiable Causes of Hypertension

Suspected Diagnosis	Clinical Clues	Diagnostic Testing
Chronic kidney disease	Estimated GFR <60 ml/min/1.73 m^2 Urine albumin-to-creatinine ratio ≥30 mg/g	Renal sonography
Renovascular disease	New elevation in serum creatinine, marked elevation in serum creatinine with ACEI or ARB, drug-resistant hypertension, flash pulmonary edema, abdominal, or flank bruit	Renal sonography (atrophic kidney), CT or MR angiography, invasive angiography
Coarctation of the aorta	Arm pulses > leg pulses, arm BP > leg BP, chest bruits, rib notching on chest radiography	MR angiography, TEE, invasive angiography
Primary aldosteronism	Hypokalemia, drug-resistant hypertension	Plasma renin and aldosterone, 24-hr urine aldosterone and potassium after oral salt loading, adrenal vein sampling
Cushing's syndrome	Truncal obesity, wide and blanching purple striae, muscle weakness	1 mg dexamethasone-suppression test, urinary cortisol after dexamethasone, adrenal CT
Pheochromocytoma	Paroxysms of hypertension, palpitations, perspiration, and pallor; diabetes	Plasma metanephrines, 24-hr urinary metanephrines and catecholamines, abdominal CT or MR imaging
Obstructive sleep apnea	Loud snoring, large neck, obesity, somnolence	Polysomnography

ACEI, Angiotensin-converting enzyme inhibitor; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *CT,* computed tomography; *GFR,* glomerular filtration rate; *MR,* magnetic resonance; *TEE,* transesophageal echocardiography.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

- Patient counseling and education should be prominent features of the initial evaluation.
- Pertinent history:
  1. Age of onset of HTN, previous antihypertensive therapy
  2. Family history of HTN, stroke, cardiovascular disease
- Diet, salt intake, caffeine, alcohol, drugs (e.g., oral contraceptives, NSAIDs, decongestants, steroids)
- Occupation, lifestyle, pain, socioeconomic status, psychologic factors
- Other cardiovascular risk factors: hyperlipidemia, obesity, diabetes mellitus
- Symptoms of secondary HTN:
  1. Headache, palpitations, excessive perspiration (possible pheochromocytoma)
  2. Weakness, polyuria (consider hyperaldosteronism)
  3. Claudication of lower extremities (seen with coarctation of aorta)
  4. Loud snoring, day-time somnolence, morning confusion (may warrant evaluation for sleep apnea)

LABORATORY TESTS

- Routine laboratory tests recommended before initiating therapy include:
  1. Urinalysis with microscopic evaluation; for signs of glomerulopathy
  2. Basic metabolic panel and calcium; for signs of kidney damage, hypokalemia (primary aldosteronism and Cushing's syndrome), hypercalcemia (hyperparathyroid).
  3. Complete blood count.
  4. Screening for coexisting diseases that may adversely afftect prognosis; hemoglobin a1c or fasting glucose level, serium lipid panel.
  5. Optional tests include measurement of urinary albumin or albumin/creatinine ratio.
- Nonoffice (home, workplace, 24-hr ambulatory) BP determination to establish the pattern of HTN (sustained, "white coat," or "masked" HTN) in selected patients.
- Some general clinical clues for when to screen for secondary HTN include:
  1. Severe or resistant HTN.
  2. An acute rise in BP developing in a patient with previous stable BP.
  3. Age less than 30 years, non-obese, non-black with no family history of HTN.
  4. Malignant or accelerated hypertension.
  5. Age of onset before puberty. If above is suspected, additional tests for secondary HTN should be done including renin, aldosterone, cortisol levels, 24-hr urine metanephrines, and serum catecholamines

IMAGING STUDIES

- ECG: check for presence of left ventricular hypertrophy (LVH) with strain pattern.
- Renal duplex ultrasonography, CT angiography or magnetic resonance angiography of the renal arteries in suspected RVH (renal artery stenosis) may be considered.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Lifestyle modifications (the initial treatment of hypertension should focus on lifestyle modifications):

- Weight loss if overweight (target BMI <25).
- Limit alcohol intake to 1 oz of ethanol per day (<2 drinks/day) in men or 0.5 oz (<1 drink/day) in women.
- Regular aerobic exercise (at least 30 min/day on most days).
- Reduce sodium intake to <100 mmol/day (<1.5 g of sodium/day).
- Maintain adequate dietary potassium (>3500 mg/day) intake in patients with normal kidney function.
- Smoking cessation.
- The BP reduction seen ranges from 2 to 20 mm Hg, most significant with substantial weight loss and the implementation of the Dietary Approaches to Stop Hypertension (DASH) eating plan, which relies on a diet high in fruits and vegetables, moderate in low-fat dairy products, and low in animal protein but with substantial amount of plant protein from legumes and nuts.

ACUTE GENERAL Rx

According to the JNC 8[1]:

- In all patients, initiate pharmacologic treatment if diastolic BP is ≥90 mm Hg. In patients <60 years old, in diabetics, and in those with chronic kidney disease, pharmacologic treatment should be initiated for systolic BP ≥140 mm Hg, whereas in patients ≥60 years, the threshold for pharmacologic treatment for systolic BP has been raised to ≥150 mm Hg.
- In the general non-black population, preferred initial agents are thiazide-type diuretics, angiotensin-converting enzyme inhibitors (ACEi), calcium channel blockers (CCBs), or angiotensin receptor blockers (ARBs). ACEi or ARBs are preferred initial agents in diabetics and those with CKD in this population.
- Preferred initial agents in the black population (including diabetics) are thiazide-type diuretics or CCBs.
- When selecting drugs, try to give once per day dosages to improve compliance. Also consider the cost of the medication, metabolic and subjective side effects, and drug-drug interactions.
- The major advantages and limitations of each class of drugs are described as follows:
  1. Thiazide diuretics:
     a. Advantages: inexpensive, once-daily dosing. Useful in edematous states, CHF, chronic renal disease, elderly patients (decreased incidence of hip fractures in elderly patients)
     b. Disadvantages: significant adverse metabolic effects (hypokalemia), increased risk of cardiac arrhythmias, sexual dysfunction, gout flares, possible adverse effects on lipids and glucose levels
  2. Beta-blockers:
     a. Advantages: ideal in hypertensive patients with ischemic heart disease or status post MI. Favored in hyperkinetic, young patients (resting tachycardia, wide pulse pressure, hyperdynamic heart) and stable CHF patients.
     b. Disadvantages: adverse effect on quality of life (increased incidence of fatigue, depression, impotence), bronchospasm, hypoglycemia, peripheral vascular disease, adverse effects on lipids, masking of signs and symptoms of hypoglycemia in diabetics.
  3. Calcium antagonists:
     a. Advantages: helpful in hypertensive patients with ischemic heart disease. Generally favorable effect on quality of life; can be used in patients with bronchospastic disorders, renal disease, peripheral vascular disease, metabolic disorders, and salt sensitivity. CCBs BP-lowering effect is independent of Na^+ intake.
     b. Disadvantages: diltiazem and verapamil should be avoided in patients with CHF due to systolic dysfunction because of their negative inotropic effects; pedal edema may occur with nifedipine and amlodipine; constipation can be severe in elderly patients receiving verapamil. CCB-related edema is positional in nature, it improves with lying position; additional strategies include switching CCB classes, reducing dosage, giving the medication later in the day, and adding a venodilator (nitrates, an ACE, or an ARB); diuretics may improve edema, but at the expense of a reduction in plasma volume.
  4. ACE inhibitors:
     a. Advantages: first-line therapy for patients with left ventricular dysfunction, helpful in prevention of diabetic renal disease; effective in decreasing LVH, and remodeling.
     b. Disadvantages: cough is a frequent side effect (5% to 20% of patients); hyperkalemia may occur in patients with diabetes or severe renal insufficiency; hypotension may occur in volume-depleted patients; increased risk of renal failure in patients with renal artery stenosis; contraindicated in pregnancy.
  5. ARBs:
     a. Advantages: well tolerated, favorable impact on quality of life; useful in patients unable to tolerate ACE inhibitors because of persistent cough and in CHF and diabetic patients; single daily dose. An episode of renal insufficiency with ACE inhibitors does

[1]James PA et al: 2014 Evidence-based guidelines for the management of high blood pressure in adults. Report from the panel members appointed to the eighth Joint National Committee (JNC8), *JAMA* 311(5):507-520, 2014.

not rule out future therapy with an ARB unless high-grade bilateral renal artery stenosis exists.
   b. Disadvantages: hypotension may occur in volume-depleted patients; hyperkalemia; risk of renal failure in renal artery stenosis; contraindicated in pregnancy.
6. Alpha-adrenergic blockers:
   a. Advantages: no adverse effect on blood lipids or insulin sensitivity; helpful in benign prostatic hypertrophy.
   b. Disadvantages: postural hypotension, sedation; syncope can be avoided by giving an initial low dose at bedtime.
7. Central alpha-antagonists:
   a. Oral clonidine mainstay of therapy for hypertensive urgencies because of the ease of administration and relative safety.
   b. Transdermal clonidine; useful in management of labile HTN, the hospitalized patient who cannot take medications by mouth, and patients subject to early morning BP surges. At equivalent doses, transdermal clonidine is more apt to precipitate salt and water retention than is the case with oral clonidine.
   c. Dose beyond 0.4 mg causes fatigue, sedation and dry mouth, salt and water retention, and rebound HTN upon abrupt termination of the medication.
8. Combined alpha- and beta-adrenergic receptor blockers:
   a. Labetalol, nebivolol, and carvedilol: Use is reserved to treat complicated hypertensive patient when an antihypertensive effect beyond beta-blockade is sought. IV labetalol is used for hypertensive emergencies. Carvedilol is shown to have less adverse effect on glycemic control than metoprolol and to reduce urinary protein excretion in hypertensive diabetic patients.
9. Direct-acting smooth muscle relaxant: Hydralazine
   a. Advantages: beneficial in black patients when used with isosorbide dinitrate.
   b. Disadvantages: may lead to reflex tachycardia, worsening ischemia (best used with nitrates), at higher doses or with renal failure can lead to a reversible drug-induced lupus.
10. Renin inhibitors: newest class of antihypertensives (Aliskiren):
   a. Advantages: generally well tolerated; once-daily dosing; can be used alone or in combination with other antihypertensive agents (avoid combining with ACEI or ARBs given increase of hyperkalemia)
   b. Disadvantages: contraindicated in pregnancy; should not be used in patients with impaired renal function; excessive cost; paucity of cardiovascular outcomes data showing benefit.

TREATMENT OF RENOVASCULAR HYPERTENSION: The therapeutic approach varies with the cause of the RVH (refer to "Renal Artery Stenosis" for additional information).
1. Young patients with fibromuscular dysplasia refractory to medical therapy can be treated with percutaneous transluminal renal angioplasty (PTRA).
2. Medical therapy is advisable in elderly patients with atheromatous RVH; useful agents are:
   a. Beta-blockers: highly effective in patients with elevated plasma renin
   b. ACE inhibitors: highly effective; however, should be avoided in patients with bilateral renal artery stenosis or with a solitary kidney and renal stenosis
   c. Diuretics: often used in combination with ACE inhibitors
3. Surgical revascularization: A recent trial revealed that renal-artery stenting does not confer a significant benefit with respect to the prevention of clinical events when added to comprehensive, multifactorial medical therapy in people with atherosclerotic renal-artery stenosis and hypertension or chronic kidney disease.[2]

HTN DURING PREGNANCY:
1. HTN complicates 5% to 12% of all pregnancies.
2. The American Obstetrical Committee defines BP of 130/80 mm Hg as the upper limit of normal at any time during pregnancy.
3. A rise of 30 mm Hg systolic or 15 mm Hg diastolic is also considered abnormal regardless of the absolute values obtained.
4. Hypertension during pregnancy can be from chronic HTN, gestational HTN, preeclampsia or preeclampsia superimposed on chronic HTN. It is important to distinguish the etiology because the risk to mother and fetus is much greater in preeclampsia.
5. Treatment of chronic HTN during pregnancy is as follows:
   a. Initial treatment with conservative measures (proper nutrition, limited physical activity).
   b. When drug therapy is necessary, initiation of methyldopa, hydralazine, labetalol, or atenolol is preferred. Table H1-54 summarizes drugs used to treat hypertension in pregnancy.
   c. ACE inhibitors can cause fetal and neonatal complications; their use should be avoided in pregnancy.
   d. The safety of CCBs remains unclear.
   e. Diuretics should be used only if there is a specific reason for initiating and maintaining their use (e.g., HTN associated with severe fluid overload or left ventricular dysfunction).

MALIGNANT HTN, HYPERTENSIVE EMERGENCIES, AND HYPERTENSIVE URGENCIES:
Definitions:
1. Malignant HTN occurs with HTN when there are grades III and IV retinopathy (exudates, hemorrhages and papilledema).
   a. The rate of BP rise is a critical factor in the development of malignant HTN.
   b. Complications and mortality rates are much higher in malignant HTN compared to essential HTN.
   c. Requires immediate BP reduction (not necessarily into normal ranges) to prevent or limit target organ disease.
2. Hypertensive emergencies is when the BP elevation causes evidence of impending or progressive organ dysfunction. It requires rapid lowering of BP to prevent end-organ damage.
3. Hypertensive urgencies are significant BP elevations without end-organ damage that should be corrected within 24 hrs of presentation.
   a. Patients are usually treated with oral antihypertensive medications.
   b. Most clinicians suggest lowering the BP to <160 mm Hg/<100 mm Hg or to a level no more than 30% lower than the patient's baseline BP.

Therapy: The choice of therapeutic agents varies with the cause. IV medications are preferred in hypertensive emergencies.
1. Nitroprusside is the drug of choice in hypertensive encephalopathy, HTN and intracranial bleeding, malignant HTN, HTN and heart failure, dissecting aortic aneurysm (used in combination with propranolol); its onset of action is immediate. Because it is metabolized to cyanide, patients should be carefully monitored for toxicity (mental status changes, acidemia).
2. Fenoldopam is a vasodilator agent useful for the short-term (up to 48 hr) management of severe HTN when rapid but quickly reversible reduction of BP is required. It should be avoided in patients with glaucoma.
3. Other commonly used agents are the IV CCBs nicardipine and clevidipine (useful for urgent treatment of HTN in the intensive care unit or operating room), the beta-blocker esmolol (useful in aortic dissection or postoperative HTN), labetalol (combined β-adrenergic and α-blocker useful in patients with coronary disease), phentolamine (useful for catecholamine-related emergencies), IV nitroglycerin (used in patients with cardiac ischemia and hypertensive crisis), and hydralazine (used for hypertensive emergencies in pregnancy).
4. Table H1-55 describes parenteral agents for management of hypertensive emergencies. *The following are important points to remember when treating hypertensive emergencies:*
   a. Introduce a plan for long-term therapy at the time of the initial emergency treatment.
   b. Agents that reduce arterial pressure can cause the kidney to retain sodium and water; therefore the judicious administration of diuretics should accompany their use.
   c. The initial goal of antihypertensive therapy is not to achieve a normal BP, but rather to gradually reduce the BP; cerebral hypoperfusion may occur if the mean BP is lowered >40% in the initial 24 hr.

[2]Cooper CJ et al: Stenting and medical therapy for atherosclerotic renal-artery stenosis, *N Engl J Med* 370:13-22, 2014.

TABLE H1-54 Drugs Used to Treat Hypertension in Pregnancy

DRUG	STARTING DOSE	MAXIMUM DOSE	COMMENTS
Acute Treatment of Severe Hypertension			
Hydralazine	5-10 mg IV every 20 min	20 mg*	Avoid in cases of tachycardia and persistent headaches
Labetalol	20-40 mg IV every 10-15 min	220 mg*	Avoid in women with asthma or congestive heart failure
Nifedipine	10-20 mg oral every 30 min	50 mg*	Avoid in case of tachycardia and palpitations
Long-Term Treatment of Hypertension			
Methyldopa	250 mg bid	4 g/day	
Labetalol	100 mg bid	2400 mg/day	
Nifedipine	10 mg bid	120 mg/day	
Thiazide diuretic	12.5 mg bid	50 mg/day	

*If desired blood pressure levels are not achieved, switch to another drug.
(From Gabbe SG: *Obstetrics*, 6th ed, Philadelphia, 2012, Saunders.)

TABLE H1-55 Parenteral Agents for Management of Hypertensive Emergencies

Agent	Dose	Onset of Action	Precautions
Parenteral Vasodilators			
Sodium nitroprusside	0.25-10 mcg/kg/min IV infusion	Immediate	Thiocyanate toxicity with prolonged use
Nitroglycerin	5-100 mcg/min IV infusion	2-5 min	Headache, tachycardia, tolerance
Nicardipine	5-15 mg/hr IV infusion	1-5 min	Protracted hypotension after prolonged use
Fenoldopam mesylate	0.1-0.3 mcg/kg/min IV infusion	1-5 min	Headache, tachycardia, increased intraocular pressure
Hydralazine	5-10 mg as IV bolus or 10-40 mg IM; repeat every 4-6 hr	10 min IV20 min IM	Unpredictable and excessive falls in blood pressure; tachycardia, angina exacerbation
Enalaprilat	0.625-1.25 mg every 6 hr IV bolus	15-60 min	Unpredictable and excessive falls in blood pressure; acute renal failure in patients with bilateral renal artery stenosis
Parenteral Adrenergic Inhibitors			
Labetalol	20-80 mg as slow IV injection every 10 min, or 0.5-2.0 mg/min IV as infusion	5-10 min	Bronchospasm, heart block, orthostatic hypotension
Metoprolol	5 mg IV every 10 min for three doses	5-10 min	Bronchospasm, heart block, heart failure, exacerbation of cocaine-induced myocardial ischemia
Esmolol	500 mcg/kg IV over 3 min; then 25-100 mg/kg/min as IV infusion	1-5 min	Bronchospasm, heart block, heart failure
Phentolamine	5-10 mg IV bolus every 5-15 min	1-2 min	Tachycardia, orthostatic hypotension

IM, Intramuscular; *IV,* intravenous.
From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.

PEARLS & CONSIDERATIONS

COMMENTS

- For patients with prehypertension, every 20/10 mm Hg increase in BP doubles the risk of cardiovascular events.
- Most patients will require at least two medications for BP control.
- If BP is greater than 20/10 mm Hg above goal, therapy should be initiated with two drugs.
- Resistant HTN: HTN is considered resistant if the BP cannot be reduced below target levels in patients who are compliant with an optimal triple-drug regimen that includes a diuretic. Terms *refractory* and *resistant* are used interchangeably. Causes include pseudohypertension, measurement artifact, medication nonadherence, volume overload, and secondary HTN.
  1. Pseudohypertension in elderly: hardened and sclerotic artery is not compressible hence falsely elevates BP measurement artifact
  2. Measurement artifact: BP taken incorrectly (small cuff, improper support).

  Fig. EH1-78 describes an approach to patients with resistant HTN.
- Renal sympathetic denervation: A recent blinded trial did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 mo after renal artery denervation as compared with a sham control.[3]
- Fig. H1-79 describes an algorithm for evaluation of secondary causes of HTN.
- Barriers to BP control: system issues, provider issues; patient issues, and behavior issues. The rate at which physicians adopt recommended changes based on evidence-based findings can be quite slow and has been properly described as "clinical inertia."
- Indications for specialist referral for patients with HTN are described in Table H1-56.

[3]Bhatt DL et al: A controlled trial of renal denervation for resistant hypertension, *N Engl J Med* 370:1393-1401, 2014.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

High Blood Pressure (Patient Information)
High Blood Pressure–Child (Patient Information)
Renal Artery Stenosis (Related Key Topic)

AUTHORS: **CRAIG L. BASMAN, M.D.**

TABLE H1-56 Indications for Specialist Referral for Patients with Hypertension

Urgent Treatment Needed
Accelerated hypertension (severe hypertension with grade III-IV retinopathy)
Particularly severe hypertension (>220/120 mm Hg)
Impending complications (e.g., transient ischemic attack, left ventricular failure)
Possible Underlying Cause
Any clue in history or examination of a secondary cause (e.g., hypokalemia with increased or high–normal plasma sodium)
Elevated serum creatinine
Proteinuria or hematuria
Sudden onset or worsening of hypertension
Young age (any hypertension <20 years; needing treatment <30 years)
Therapeutic Problems
Multiple drug intolerances
Multiple drug contraindications
Persistent nonadherence or nonconcordance
Special Situations
Unusual blood pressure variability
Possible white coat hypertension
Hypertension in pregnancy

From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

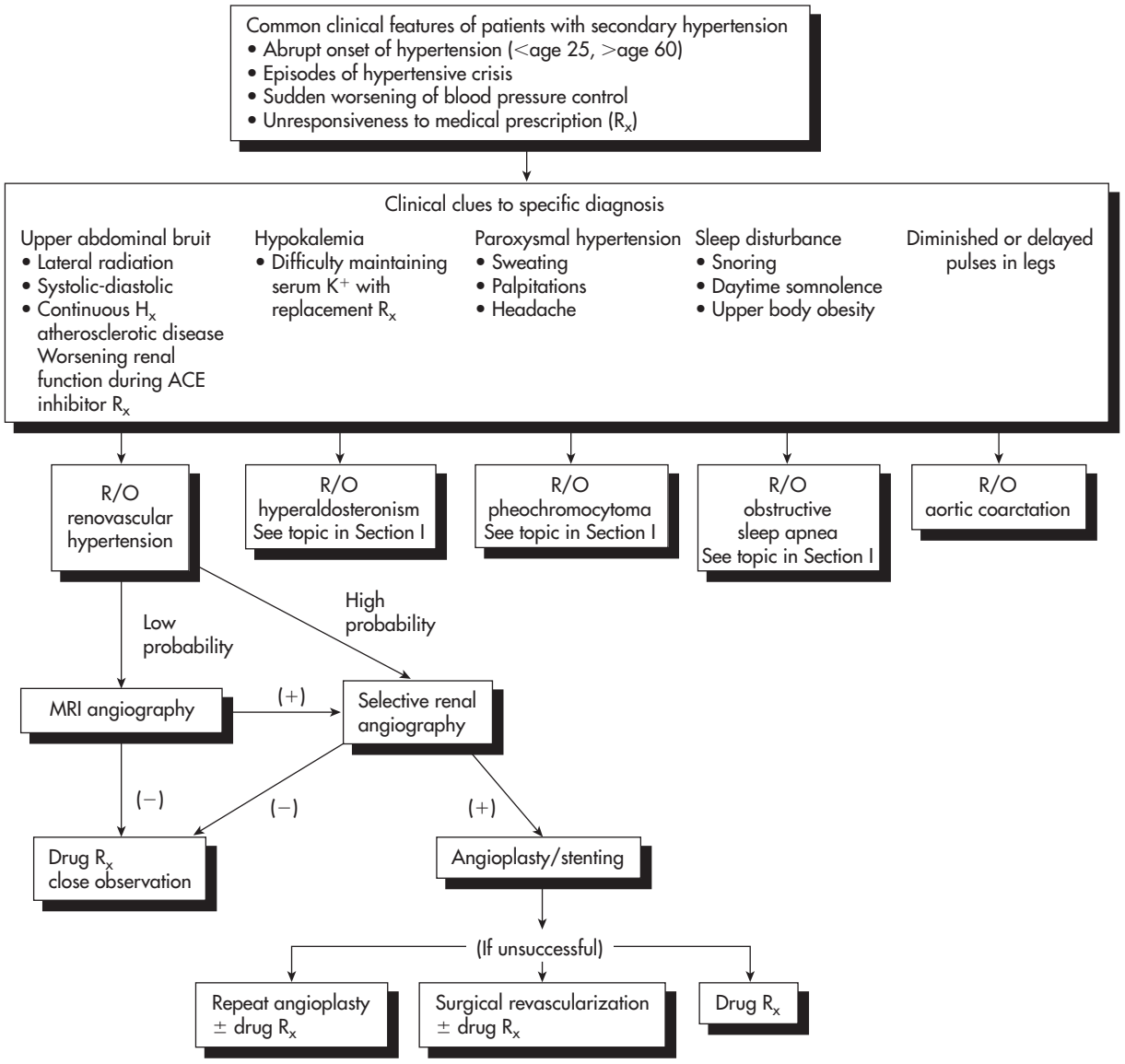


FIGURE H1-79 Algorithm for identifying patients for evaluation of secondary causes of hypertension. *ACE,* Angiotensin-converting enzyme; *Hx,* history; *K,* potassium; *R/O,* rule out. (Modified from Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 23, Philadelphia, 2008, Saunders.)

SUGGESTED READINGS

Arguedes JA et al.: *Treatment blood pressure targets for hypertension (review)* (Issue 3). The Cochrane Collaboration, 2009.

Beckett NS et al.: Treatment of hypertension in patients 80 years of age or older, *N Engl J Med* 358:1887–1898, 2008.

Blood Pressure Lowering Treatment Trialists' Collaboration: Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults. Meta-analysis of randomized trials, *BMJ*, 2008 doi:10.1136.

Chow CK et al.: Prevalence, awareness, treatment and control of hypertension in rural and urban communities in high-, middle- and low-income countries, *JAMA* 310(9):959–968, 2013.

Holdiness A et al.: Renin angiotensin aldosterone system blockade: little to no rationale for ACE inhibitor and ARB combinations, *Am J Med* 124:519, 2011.

Moser M, Setaro JF: Resistant or difficult to control hypertension, *N Engl J Med* 355:385, 2006.

Sacks F, Campos H: Dietary therapy in hypertension, *N Engl J Med* 362:2102–2112, 2010.

Schaer B et al.: Risk for incident atrial fibrillation in patients who receive antihypertensive drugs, *Ann Intern Med* 152(2):78–84, 2010.

Seventh Report of the Joint National Committee on Prevention: Detection, Evaluation, and Treatment of High BP, *JAMA* 289:2560, 2003.

Sica DA: Management of hypertension in the outpatient setting, *Primary Care Clin Office Pract* 5:451–473, 2008.

Silverstein RL et al.: Resistant hypertension, *Primary Care Clin Office Pract* 35:501–513, 2008.

Evidence-Based Guideline for the Management of High Blood Pressure in Adults: report from the panel members appointed to the eighth JNC, *JAMA* 311(5):507–520, 2014.

Elliott WJ: Clincial features in the management of selected hypertensive emergencies, *Prog Cardiovasc Dis* 47(5):316–325, 2006 Mar-Apr.

Vongpatanasin W: Resistant hypertension, A review of diagnosis and management, *JAMA* 311(21), 2014. 226–2224.

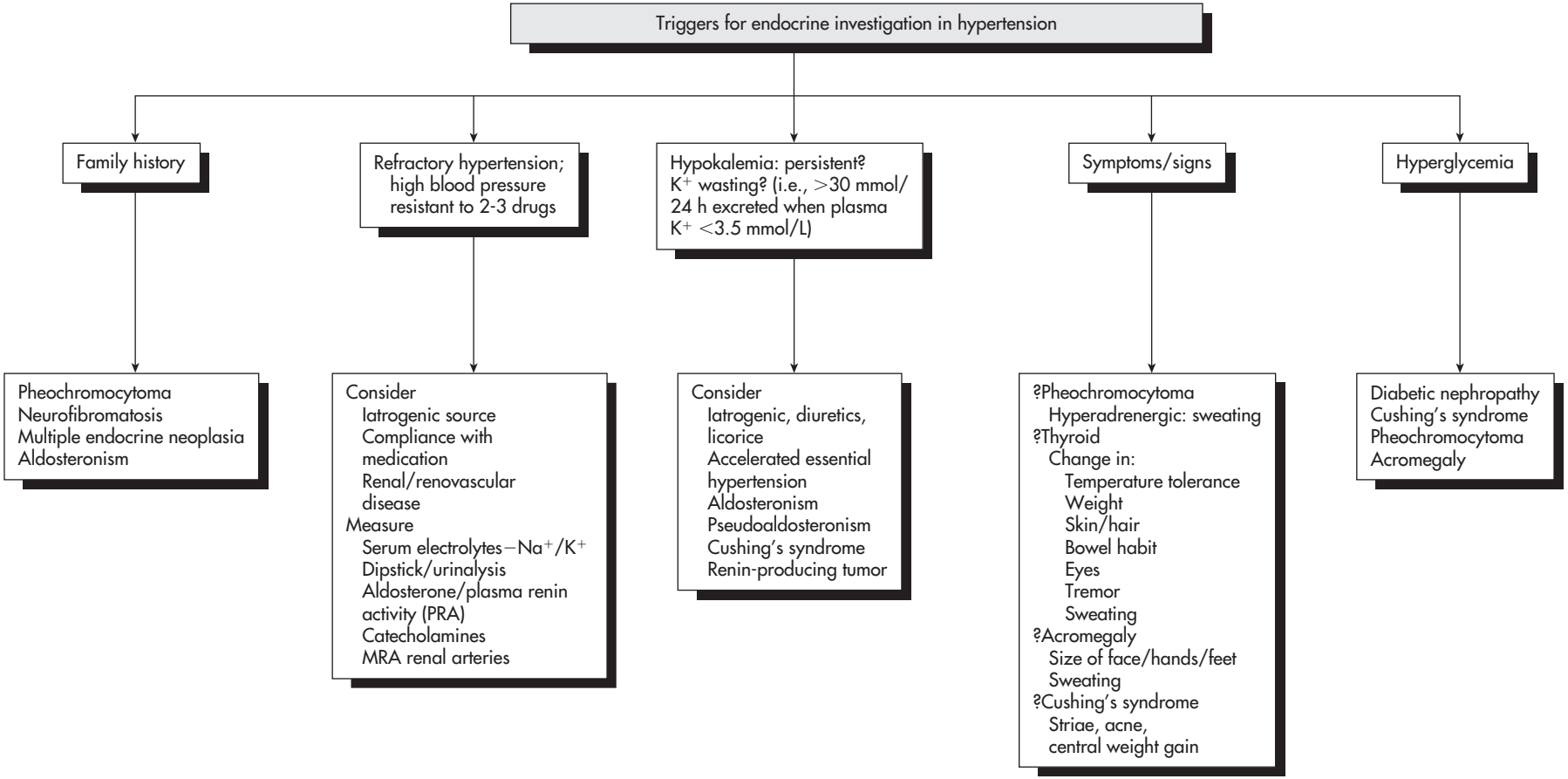


FIGURE EH1-77 Clinical observations suggesting endocrine investigation in hypertension. (From Feehally J et al: *Comprehensive clinical nephrology,* ed 3, St Louis, 2007, Mosby.)

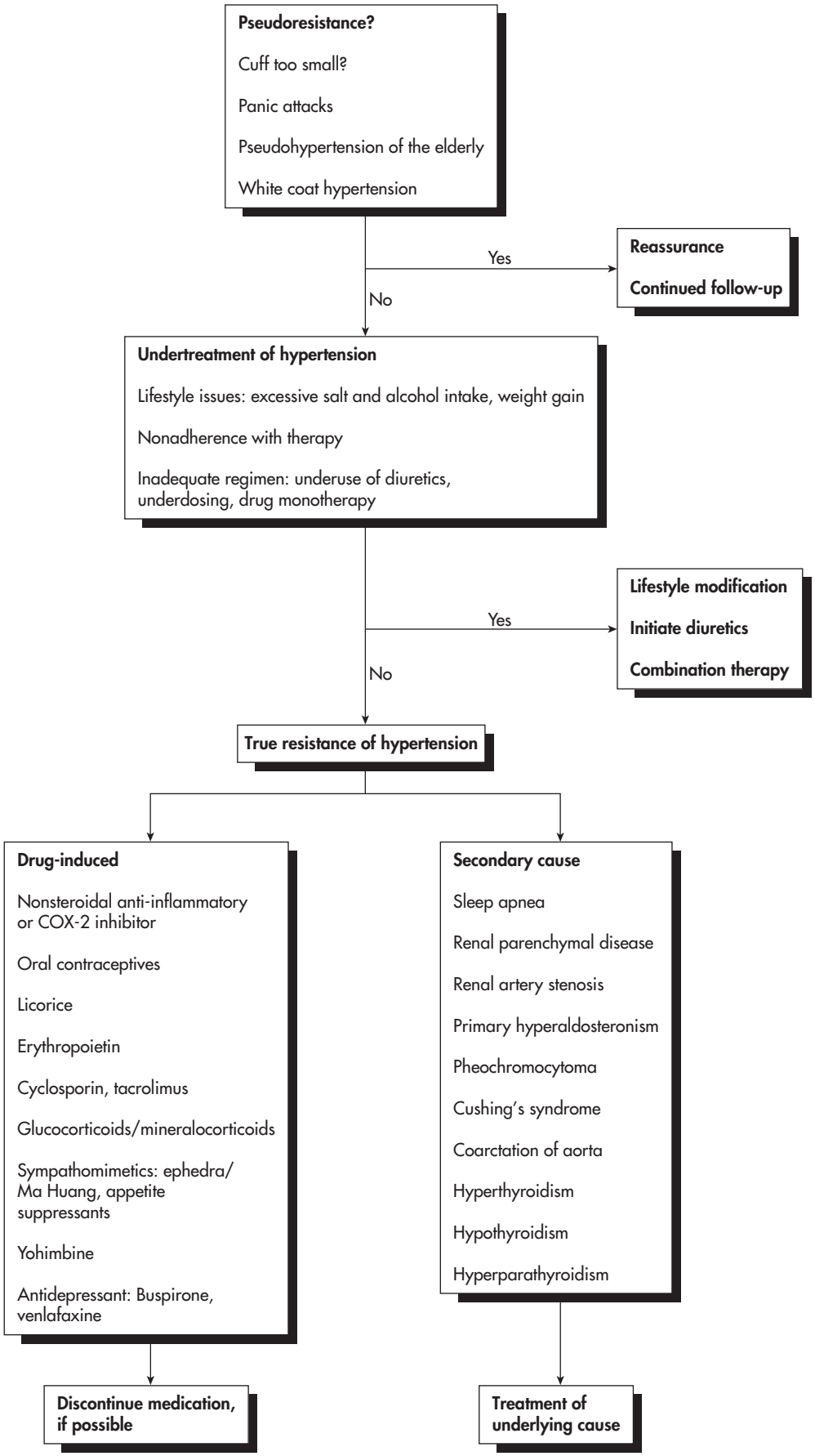


FIGURE EH1-78 Approach to the patient with "resistant" hypertension. (From Crawford MH et al [eds]: *Cardiology,* ed 2, St Louis, 2004, Mosby.)

BOX EH1-12 Causes of Endocrine Hypertension

- Pituitary
  - Cushing's disease
  - Acromegaly
- Adrenal cortex
  - Primary aldosteronism
  - Pseudoaldosteronism
  - Cushing's syndrome
- Adrenal medulla
  - Pheochromocytoma
- Thyroid
  - Hypothyroidism
  - Hyperthyroidism
- Renin-secreting tumors
- Others
  - Hyperparathyroidism?
  - Endothelioma

From Feehally J et al: *Comprehensive clinical nephrology,* ed 3, St Louis, 2007, Mosby.

BASIC INFORMATION

DEFINITION

Hyperthyroidism is a hypermetabolic state resulting from excess thyroid hormone.

SYNONYMS

Thyrotoxicosis

ICD-9CM CODES
242.9 Hyperthyroidism
242.0 Hyperthyroidism with goiter
242.2 Hyperthyroidism, multinodular
242.3 Hyperthyroidism, uninodular

ICD-10CM CODES
E05.90 Thyrotoxicosis, unspecified without thyrotoxic crisis or storm
E05.00 Thyrotoxicosis with diffuse goiter without thyrotoxic crisis or storm
E05.20 Thyrotoxicosis with toxic multinodular goiter without thyrotoxic crisis or storm

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE/PREVALENCE:

- Hyperthyroidism affects 2% of women and 0.2% of men in their lifetimes.
- Toxic multinodular goiter usually occurs in women >55 yr and is more common than Graves' disease in the elderly.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with hyperthyroidism generally present with tachycardia, tremor, hyperreflexia, anxiety, irritability, emotional lability, panic attacks, heat intolerance, sweating, increased appetite, diarrhea, weight loss, menstrual dysfunction (oligomenorrhea, amenorrhea). Presentation may be different in elderly patients (see below).
- Patients with Graves' disease may present with exophthalmos, lid retraction, and lid lag (Graves' ophthalmopathy). The following signs and symptoms of ophthalmopathy may be present: blurring of vision, photophobia, increased lacrimation, double vision, and deep orbital pressure. Clubbing of fingers associated with periosteal new bone formation in other skeletal areas (Graves' acropachy) and pretibial myxedema may also be noted.
- Clinical signs of hyperthyroidism in the elderly may be masked by manifestations of coexisting disease (e.g., new-onset atrial fibrillation, exacerbation of congestive heart failure).

ETIOLOGY

- Graves' disease (diffuse toxic goiter): 80% to 90% of all cases of hyperthyroidism
- Toxic multinodular goiter (Plummer's disease)
- Toxic adenoma
- Iatrogenic and factitious
- Transient hyperthyroidism (subacute thyroiditis, Hashimoto's thyroiditis)
- Rare causes: hypersecretion of thyroid-stimulating hormone (TSH) (e.g., pituitary neoplasms), struma ovarii, ingestion of large amount of iodine in a patient with preexisting thyroid hyperplasia or adenoma (Jod-Basedow phenomenon), hydatidiform mole, carcinoma of thyroid, amiodarone therapy

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Anxiety disorder
- Pheochromocytoma
- Metastatic neoplasm
- Diabetes mellitus
- Premenopausal state

WORKUP

Suspected hyperthyroidism requires laboratory confirmation and identification of its etiology because treatment varies with cause. A detailed medical history will often provide clues to the diagnosis and etiology of the hyperthyroidism. Fig. EH1-80 describes a diagnostic approach to suspected hyperthyroidism.

LABORATORY TESTS

- Elevated free thyroxine (T_4)
- Elevated free triiodothyronine (T_3): generally not necessary for diagnosis
- Low TSH (unless hyperthyroidism is a result of the rare hypersecretion of TSH from a pituitary adenoma)
- Thyroid autoantibodies useful in selected cases to differentiate Graves' disease from toxic multinodular goiter (absent thyroid antibodies)

IMAGING STUDIES

- 24-hr radioactive iodine uptake (RAIU) is useful to distinguish hyperthyroidism from iatrogenic thyroid hormone synthesis (thyrotoxicosis factitia) and from thyroiditis.
- An overactive thyroid shows increased uptake, whereas a normal underactive thyroid (iatrogenic thyroid ingestion, painless or subacute thyroiditis) shows normal or decreased uptake.
- The RAIU results also vary with the etiology of the hyperthyroidism:
  1. Graves' disease: increased homogeneous uptake
  2. Multinodular goiter: increased heterogeneous uptake
  3. Hot nodule: single focus of increased uptake
- RAIU is also generally performed before the therapeutic administration of radioactive iodine to determine the appropriate dose.

TREATMENT

NONPHARMACOLOGIC THERAPY

Patient education regarding thyroid disease and discussion of the therapeutic options. Patients should be informed that radioiodine, antithyroid drugs, and surgery are all reasonable treatment options for hyperthyroidism. It is crucial for the physician to have a detailed discussion with the patient about the benefits and risks relative to lifestyle, patients' values, and coexisting conditions.

ACUTE GENERAL Rx

ANTITHYROID DRUGS (THIONAMIDES): Propylthiouracil (PTU) and methimazole inhibit thyroid hormone synthesis by blocking production of thyroid peroxidase (PTU and methimazole) or inhibit peripheral conversion of T_4 to T_3 (PTU). Methimazole is favored by most endocrinologists because of the potential for hepatic failure with PTU. PTU is preferred in pregnant women because methimazole has been associated with aplasia cutis and with choanal and esophageal atresia. Complete blood count and differential should be obtained before their use.

1. Dosage: methimazole 15 to 30 mg/day given as a single dose; PTU 50 to 100 mg PO q8h.
2. Antithyroid drugs can be used as the primary form of treatment or as adjunctive therapy before radioactive therapy or surgery or afterward if the hyperthyroidism recurs.
3. Side effects: skin rash (3% to 5% of patients), arthralgias, myalgias, granulocytopenia (0.5%). Rare side effects are aplastic anemia, hepatic necrosis from PTU, cholestatic jaundice from methimazole.
4. When antithyroid drugs are used as primary therapy, they are usually given for 6 to 18 mo; prolonged therapy may cause hypothyroidism. Monitor thyroid function every 2 mo for 6 mo, then less frequently.
5. The use of antithyroid drugs before radioiodine therapy is best reserved for patients in whom exacerbation of hyperthyroidism after radioactive iodine therapy is hazardous (e.g., elderly patients with coronary artery disease or significant coexisting morbidity). In these patients the antithyroid drug can be stopped 2 days before radioactive iodine therapy, resumed 2 days later, and continued for 4 to 6 wk.

RADIOIODINE THERAPY (RADIOACTIVE IODINE [RAI; ^{131}I])

1. RAI is the treatment of choice for patients aged >21 yr and younger patients who have not achieved remission after 1 yr of antithyroid drug therapy. RAI is also used in hyperthyroidism caused by toxic adenoma or toxic multinodular goiter.
2. Contraindicated during pregnancy (can cause fetal hypothyroidism) and lactation. Pregnancy should be excluded in women of childbearing age before RAI is administered.
3. A single dose of RAI is effective in inducing a euthyroid state in nearly 80% of patients.
4. There is a high incidence of post-RAI hypothyroidism (>50% within first year and 2%/yr thereafter); these patients should be frequently evaluated for the onset of hypothyroidism (see "Chronic Rx").

SURGICAL THERAPY (SUBTOTAL THYROIDECTOMY):

1. Indicated in obstructing goiters, in any patient who refuses RAI and cannot be adequately managed with antithyroid medications (e.g., patients with toxic adenoma or toxic multinodular goiter), and in pregnant patients who cannot be adequately managed with antithyroid medication or develop side effects

FIGURE H1-81 Characteristic signs of Graves' orbitopathy. A, Subsequently corrected by orbital decompression surgery. **B,** Note the thyroid stare, asymmetry, proptosis, and periorbital edema before correction. (Courtesy Dr. Jack Rootman, University of British Columbia, Vancouver, Canada. From Larsen PR et al [eds]: *Williams textbook of endocrinology,* ed 10, Philadelphia, 2003, Saunders.)

to them. Thyroidectomy can also be considered as primary therapy in refractory cases of amiodarone-induced hyperthyroidism. Thyroidectomy is not indicated for low RAIU hyperthyroidism.

2. Patients should be rendered euthyroid with antithyroid drugs before surgery.
3. Complications of surgery include hypothyroidism (28% to 43% after 10 yr), hypoparathyroidism, and vocal cord paralysis (1%).
4. Most patients should be started on replacement doses of levothyroxine (1.7 mcg/kg/day) before discharge from hospital.
5. Hyperthyroidism recurs after surgery in 10% to 15% of patients.

ADJUNCTIVE THERAPY: Propranolol alleviates the beta-adrenergic symptoms of hyperthyroidism; initial dose is 20 to 40 mg PO q6h; dosage is gradually increased until symptoms are controlled. Major contraindications to propranolol are congestive heart failure and bronchospasm. Diagnosis and treatment of thyrotoxic storm are also discussed in Section I.

CHRONIC Rx

- Patients undergoing treatment with antithyroid drugs should be seen every 1 to 3 mo until euthyroidism is achieved and every 3 to 4 mo while they remain on antithyroid therapy. After treatment is stopped, periodic monitoring of thyroid function tests with TSH is recommended every 3 mo for 1 yr, then every 6 mo for 1 yr, then annually.
- Orbital decompression surgery can be used to correct Graves' orbitopathy (Fig. H1-81). The administration of the antioxidant selenium (100 mcg PO bid) has been recently reported as effective in improving quality of life, reducing ocular involvement, and slowing progression of the disease in patients with mild Graves' orbitopathy. Its mechanism of action is believed to be an effect on the oxygen free radicals and cytokines that play a pathogenic role in Graves' orbitopathy.

DISPOSITION

Successful treatment of hyperthyroidism requires lifelong monitoring for the onset of hypothyroidism or the recurrence of thyrotoxicosis.

REFERRAL

- Endocrinology referral is recommended at the time of initial diagnosis and during treatment.
- Surgical referral in selected patients (see "Surgical Therapy").
- Hospitalization of all patients with thyroid storm.

PEARLS & CONSIDERATIONS

COMMENTS

- Elderly hyperthyroid patients may have only subtle signs (weight loss, tachycardia, fine skin, brittle nails). This form is known as ***apathetic hyperthyroidism*** and manifests with lethargy rather than hyperkinetic activity. An enlarged thyroid gland may be absent. Coexisting medical disorders (most commonly cardiac disease) may also mask the symptoms. These patients often have unexplained congestive heart failure, worsening of angina, or new-onset atrial fibrillation resistant to treatment. See the entry "Graves' Disease" for additional information on diagnosis and treatment.
- Subclinical hyperthyroidism is defined as a normal serum-free thyroxine and free triiodothyronine levels with a TSH level suppressed below the normal range and usually undetectable. These patients usually do not present with signs or symptoms of overt hyperthyroidism. Treatment options include observation or a therapeutic trial of low-dose antithyroid agents for 6 mo to attempt to induce remission.
- ***Thyrotoxic periodic paralysis (TPP)*** is a hyperthyroidism-related hypokalemia and muscle-weakening condition resulting from a sudden shift of potassium into cells. Many patients do not have other symptoms of hyperthyroidism. Typical presentation involves an Asian adult male with acute fatigue and muscle weakness initially presenting in the lower extremities. Physical examination reveals decreased deep tendon reflexes, hypertension, and tachycardia. ECG often reveals U waves, high QRS voltage, and first-degree atrioventricular block. Additional laboratory testing reveals normal acid-base state, hypokalemia with low urinary potassium excretion (spot urinary potassium concentration <20 mEq/L from potassium shift into cells), hypophosphatemia, hypophostaturia, and hypercalciuria. Electromyography during attacks shows low-amplitude compound muscle action potential of the tested muscle. Therapy consists of cautious potassium supplementation (increased risk of rebound hyperkalemia). Use of nonselective beta-blockers (e.g., propranolol) to counteract hyperadrenergic activity, which may be causing TPP, may also be useful.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hyperthyroidism (Patient Information)
Graves' Disease (Related Key Topic)
Thyrotoxic Storm (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Cooper DS: Antithyroid drugs, *N Engl J Med* 352:905, 2005.

Marsocci C et al.: Selenium and the course of mild Graves' orbitopathy, *N Engl J Med* 364:20, 2011.

Reid JR, Wheeler SF: Hyperthyroidism, *Am Fam Physician* 72:623, 2005.

Ross DS: Radioiodine therapy for hyperthyroidism, *N Engl J Med* 364:542–550, 2011.

Shih HL: Thyrotoxic periodic paralysis, *Mayo Clin Proc* 80(10):99, 2005.

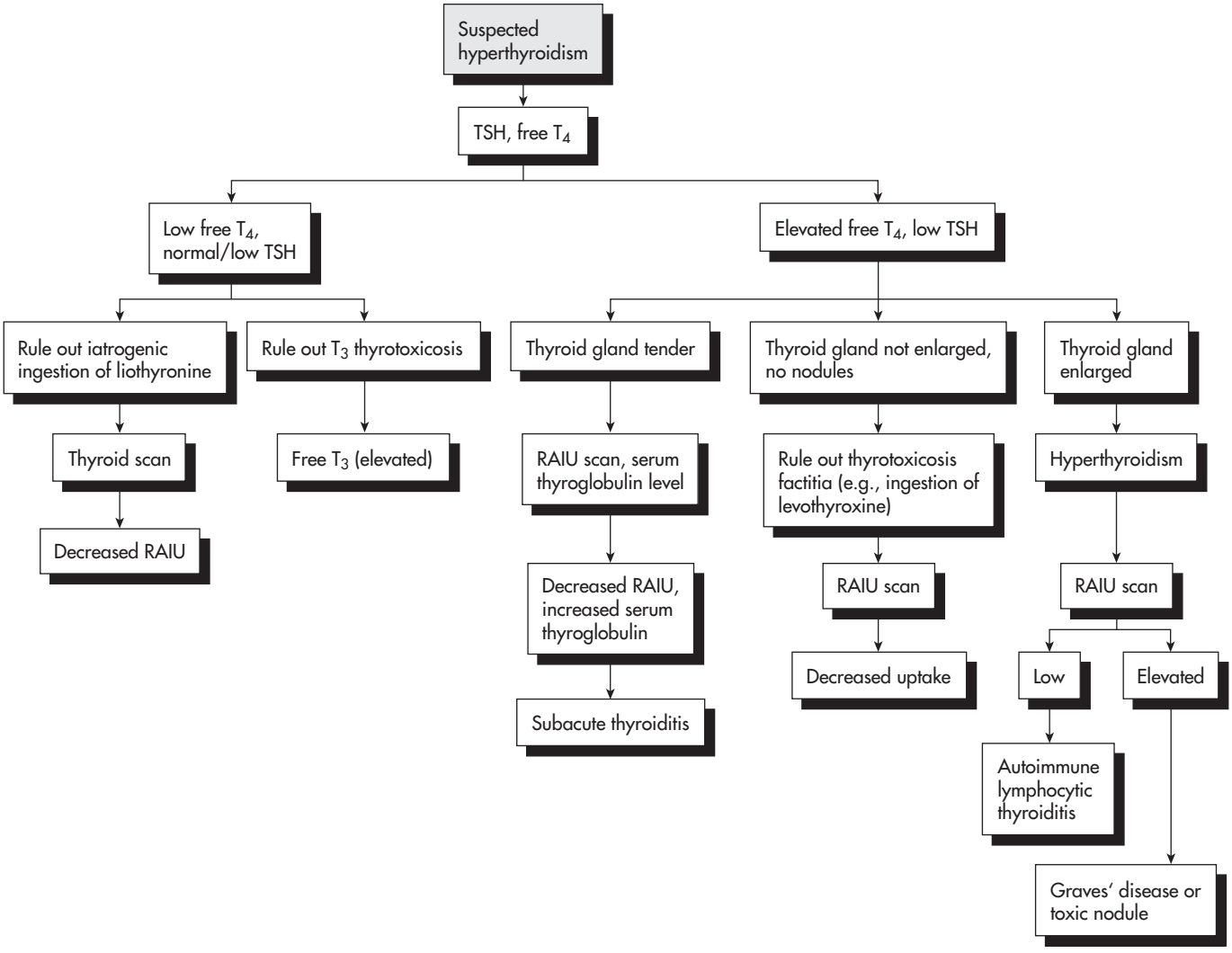


FIGURE EH1-80 Hyperthyroidism. *RAIU,* Radioactive iodine uptake; *TSH,* thyroid-stimulating hormone.

BASIC INFORMATION

DEFINITION

Hypertrophic osteoarthropathy (HOA) is a syndrome of clubbing of the digits, periostosis of long bones, abnormal proliferation of skin, and arthritis. Periostosis is usually involved with pain on palpation of the involved area. HOA may be primary or secondary to other underlying disease processes.

SYNONYMS

- Primary hypertrophic osteoarthropathy:
  1. Pachydermoperiostosis
  2. Idiopathic clubbing
  3. Touraine-Solente-Golé syndrome
- Secondary hypertrophic osteoarthropathy
- HOA

ICD-9CM CODES
731.2 Hypertrophic osteoarthropathy
ICD-10CM CODES
M89.3 Hypertrophy of bone
M89.40 Other hypertrophic osteoarthropathy, unspecified site

EPIDEMIOLOGY & DEMOGRAPHICS

- Fig. H1-82 provides a classification of HOA.
- Primary HOA is a familial autosomal-dominant disease affecting the age group between 1 and 20 years and is rare.
- There is a male/female ratio of 9:1 in occurrence.
- Secondary HOA is more common, typically occurs in adults 55 to 75 years of age. 80% to 90% of secondary HOA is associated with non–small cell lung cancer, most frequently adenocarcinoma; other associated illnesses include:
  1. Pulmonary: mesothelioma, bronchogenic carcinoma, lung abscesses, empyema, bronchiectasis, cystic fibrosis, pulmonary fibrosis, sarcoidosis, arteriovenous malformations
  2. Gastrointestinal: Carcinoma of esophagus or colon, biliary atresia, peptic ulcer disease, inflammatory bowel disease (Crohn's disease, ulcerative colitis), hepatocellular carcinoma, liver cirrhosis, amebiasis
  3. Cardiac: infective endocarditis, right-to-left cardiac shunts, aortic aneurysms, infected aortic bypass graft
  4. Thymoma
  5. Hodgkin lymphoma
  6. Connective tissue diseases
  7. Thyroid acropachy
  8. HIV infection
  9. POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, M component, and skin changes)
  10. Thalassemia
  11. Osteosarcoma
  12. Nasopharyngeal sarcoma
  13. Osteosarcoma

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Primary HOA typically presents with the insidious onset of clubbing of the hands (Fig. H1-83) and feet, described as "spade-like." Finger clubbing is diagnosed by measurement of the digital index (Fig. H1-84). Other signs and symptoms of HOA include:
  1. Joint pain and swelling
  2. Sensation of warmth or burning in the hands and feet
  3. Coarsening of facial features with grooves or depressions in the scalp, ptosis of the lids
  4. Thickening of the arms and legs
  5. Oily skin, diaphoresis, gynecomastia, and acne
  6. Thin and shiny appearance of the skin around the nail bed
  7. Nail convexity with nail "floating" sensation within the soft tissue is noticed on palpation of the base of the nail bed
  8. Edema, warmth, and tenderness of the extremities can be seen
- Secondary HOA patients may present with clinical symptoms before the underlying disorder can be detected. Signs and symptoms are similar to the above in addition to findings related to the underlying disease (e.g., bronchogenic carcinoma, infective endocarditis).
- Patients presenting with painful joints prior to developing clubbing can be misdiagnosed as inflammatory arthritis.

ETIOLOGY

The pathogenesis of HOA is not fully understood; current knowledge suggests that HOA results from the activation of one or more growth factors, such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor, that are normally inactivated in the lungs and systemic circulation.

DIAGNOSIS

Diagnosis is primarily clinical; radiographs and bone scans can help confirm the diagnosis.

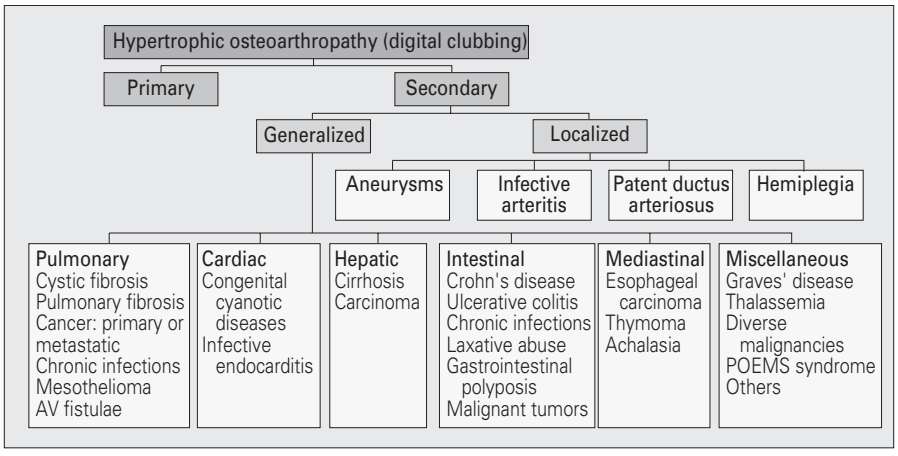


FIGURE H1-82 Classification of hypertrophic osteoarthropathy. *AV,* Arteriovenous; *POEMS,* polyneuropathy, organomegaly, endocrinopathy, monoclonal proteins, and skin changes. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

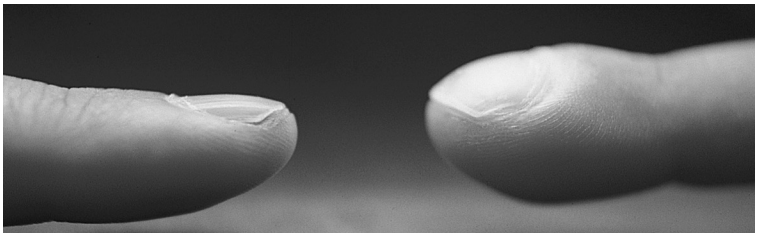


FIGURE H1-83 Clubbing deformity. The finger on the right is clubbed compared with the normal finger shape on the left. (From Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.)

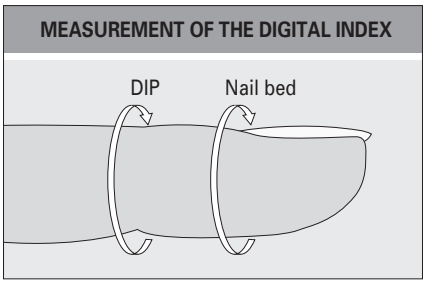


FIGURE H1-84 The digital index. The perimeter of each of the 10 fingers is measured at the nail bed (NB) and at the distal interphalangeal joint (DIP). If the sum of the 10 NB:DIP ratios is more than 10, clubbing is probably present. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

FIGURE H1-85 Hypertrophic osteoarthropathy. Wrist radiograph showing periostosis at the distal ends of the radius and ulna. The coarse, layered appearance is most evident along the diaphyses. The relative sparing of the radial epiphyses is characteristic. (From Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.)

DIFFERENTIAL DIAGNOSIS

Paget's disease, Reiter's syndrome, psoriatic arthritis, syphilitic periostosis, osteoarthritis, rheumatoid arthritis, osteomyelitis, scleromyxedema, and acromegaly.

WORKUP

HOA warrants an investigation into any associated illnesses.

LABORATORY TESTS

- Routine laboratory studies such as blood count, electrolytes, and urine studies are typically normal in primary and secondary HOA.
- Erythrocyte sedimentation rate is elevated in secondary HOA.
- Liver function tests may be abnormal in patients with secondary HOA from gastrointestinal pathology.
- Alkaline phosphatase may be elevated as a result of periostosis of long bones.
- Analysis of the synovial fluid from joint effusions reveals a low white blood cell count with normal viscosity, color, and complement levels.

IMAGING STUDIES

- Radiographs of the long bones show periosteal new bone formation (Fig. H1-85).
- A chest radiograph should be obtained to rule out underlying lung cancer.
- Bone scan with technetium-99m reveals uptake along the long bones, phalanges, and periarticular joint spaces.
- Angiography findings may demonstrate hypervascularization of the finger pads.

Rx TREATMENT

ACUTE GENERAL Rx

- Treatment of primary HOA is symptomatic. Nonsteroidal anti-inflammatory medications such as aspirin, salicylate, ibuprofen, naproxen, indomethacin, corticosteroids, tamoxifen citrate, or retinoids can be used.
- Colchicine can be helpful for the pain due to subperiosteal new bone formation.
- Reconstructive surgery is indicated for correction of gross disfigurement.
- Treatment of secondary HOA is to eradicate the underlying disease (e.g., antibiotics for infective endocarditis, surgery for bronchogenic carcinoma). Correction of heart malformation or removal of an underlying tumor is rapidly followed by regression of HOA.

CHRONIC Rx

In patients with secondary HOA refractory to NSAIDs and aspirin, octreotide (100 mcg subcutaneously twice daily) and bisphosphonates, including pamidronate (1 mg/kg intravenously to a maximum of 60 mg) and zoledronic acid, which inhibit VEGF expression, have significantly reduced pain.

Vagotomy has been tried with some success. However, the definitive treatment is to treat the underlying disease.

DISPOSITION

- Patients with primary HOA typically have symptoms of joint pain and swelling for the early part of their life. However, the disease becomes quiescent thereafter.
- Prognosis and disease course in patients with secondary HOA will depend on the underlying cause. The insidious development of clubbing suggests an infectious process, whereas the rapid progression of clubbing may suggest underlying malignancy.

REFERRAL

Referral should be made to rheumatology when the diagnosis of HOA is suspected and the cause remains unclear.

PEARLS & CONSIDERATIONS

Some cases of primary HOA may later be found to be associated with an underlying disease such as patent ductus arteriosus, Crohn's disease, or myelofibrosis, in which case they become secondary.

COMMENTS

- Infections and intrathoracic malignancies are the most common causes of secondary HOA.
- The periostosis and the extent of involvement do not depend on the form of the disease (primary or secondary), but rather on its duration.
- HOA secondary to infection of an arterial graft has been reported.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **SYEDA M. SAYEED, M.D.**

SUGGESTED READINGS

Amital H et al.: Hypertrophic pulmonary osteoarthropathy: control of pain and symptoms with pamidronate, *Clin Rheumatol* 23(4):330, 2004.

Angel-Moreno Maroto A, Martinez-Quintana E, Suarez-Castellano L, et al.: Painful hypertrophic osteoarthropathy successfully treated with octreotide: the pathogenetic role of vascular endothelial growth factor (VEGF), *Rheumatology* 44:1326–1327, 2005.

Ito T, Goto K, Yoh K et al.: Hypertrophic pulmonary osteoarthropathy as a paraneoplastic manifestation of lung cancer, *J Thorac Oncol* 5:976, 2010.

Martinez-Lavin M et al.: Hypertrophic osteoarthropathy: a palindrome with a pathogenic connotation, *Curr Opin Rheumatol* 20(1):88–91, 2008.

Yao Q et al.: Periostitis and hypertrophic pulmonary osteoarthropathy: report of 2 cases and review of the literature, *Semin Arthritis Rheum* 38(6):458, 2009.

BASIC INFORMATION

DEFINITION

Hyperuricemia may be defined as serum uric acid >7.0 mg/dl in males or >6.0 mg/dl in females. Some persons who are normouricemic by this definition will have levels of uric acid that exceed the limit of solubility of uric acid in tissue. Data from the Framingham study indicate that hyperuricemia increased from 4.8% of the population in the early 1970s to 9.3% in the mid-1980s. Age is an important risk factor in the increasing incidence of hyperuricemia and gout. Women become hyperuricemic at an older age than men due to the uricosuric effect of estrogen. Most people with hyperuricemia are asymptomatic and will remain so; however, 20% of those with serum uric acid >9 mg/dl will develop gout in 5 yr. Hyperuricemia is strongly associated with gout, obesity, diabetes, hypertension, and cardiovascular disease but has not been proven to cause any of these conditions.

ASYMPTOMATIC HYPERURICEMIA

Definition: laboratory evidence of elevated serum uric acid without clinical disease known to be caused by hyperuricemia

ETIOLOGY

Overproduction of uric acid accounts for a minority of cases of hyperuricemia. Most cases are due to decreased renal clearance of uric acid and high dietary purine consumption. Fig. H1-86 describes factors affecting urate balance. Table H1-57 describes a classification of hyperuricemia and gout.

ICD-10CM CODES

E79.0 Hyperuricemia without signs of inflammatory arthritis and tophaceous disease

DIAGNOSIS

EVALUATION

The finding of hyperuricemia should prompt a thorough evaluation of potential causes and related diseases. Fig. EH1-87 describes the evaluation of patients with hyperuricemia. If there is no clinical evidence of gout, nephrolithiasis, or acute kidney injury, the patient may be said to have asymptomatic hyperuricemia. Patients with hyperuricemia should be evaluated for potential causes of elevated uric acid including malignancy, renal insufficiency, toxins, lead toxicity, and dietary indiscretion. If a careful history and physical exam does not reveal an evident cause of persistent hyperuricemia, a 24-hr urine collection for uric acid and creatinine may be considered. Patients with urinary excretion of uric acid >800 mg/24 hr are likely to be overproducers of uric acid and should be investigated more thoroughly for the underlying cause of their hyperuricemia.

TABLE H1-57 Classification of Hyperuricemia and Gout

Impaired Uric Acid Excretion
Primary gout with decreased uric acid clearance
Secondary gout
Clinical conditions
Reduced glomerular filtration rate
Hypertension
Obesity
Systemic acidosis
Familial juvenile hyperuricemic nephropathy
Medullary cystic kidney disease
Lead nephropathy
Drugs
Diuretics
Ethanol
Low-dose salicylates (0.3-3.0 g/day)
Cyclosporine
Tacrolimus
Levodopa
Excessive Urate Production
Primary metabolic disorders
HPRT deficiency
PRPP synthetase overactivity
Glucose-6-phosphatase deficiency
Fructose-1-phosphate aldolase deficiency
Secondary causes
Clinical conditions
Myelo- and lymphoproliferative disorders
Obesity
Psoriasis
Glycogenoses III, V, VII
Drugs and dietary components
Nicotinic acid
Pancreatic extract
Cytotoxic drugs
Red meat, organ meat, shellfish
Alcoholic beverages (especially beer)
Fructose

HPRT, Hypoxanthine-guanine phosphoribosyltransferase; *PRPP,* phosphoribosyl pyrophosphate.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

LABORATORY TESTS

- CBC with differential
- BUN/creatinine
- Urinalysis
- Lipid profile: Consider 24-hr urine collection

TREATMENT

No specific therapy is indicated for most patients with asymptomatic hyperuricemia. Lifestyle and dietary modification are often advisable.

NONPHARMACOLOGIC THERAPY

- Weight loss
- Reduce alcohol intake, especially beer
- Reduce consumption of foods known to be high in purines such as red meat, organ meat, and high-fructose soft drinks.

PEARLS & CONSIDERATIONS

- Research in progress suggests there may be a causal relationship between hyperuricemia and early hypertension.
- Very high levels of serum uric acid may warrant treatment even if asymptomatic.
- Patients with hyperuricemia and a family history of gout should be followed closely for the development of gouty arthritis.
- Hyperuricemia in patients with gout or presence of tophi (Fig. EH1-88) should almost always be treated with urate-lowering medication (see "Gout").

There is evidence suggesting that treatment of hyperuricemia slows the progression of chronic kidney disease in patients without gout.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Gout (Related Key Topic)

AUTHOR: **BERNARD ZIMMERMANN, M.D.**

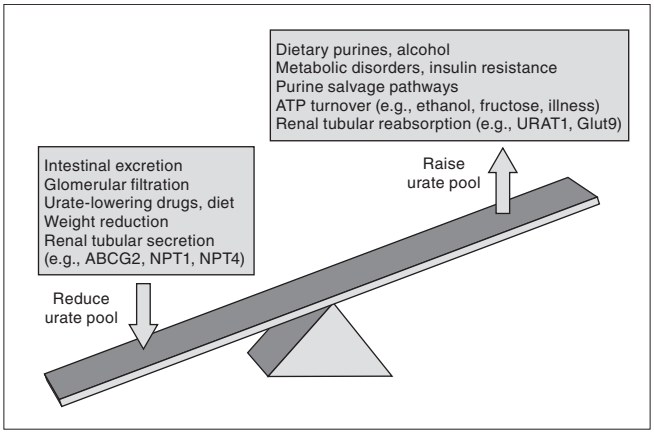


FIGURE H1-86 Factors affecting urate balance. The systemic urate pool and the likelihood of gout are determined by the dynamic balance among dietary purines, endogenous synthesis and recycling, and disposal by the kidney and gut. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

SUGGESTED READINGS

Chen JH et al.: Serum uric acid as an independent risk factor for all-cause, cardiovascular, and ischemic stroke mortality, *Arthritis Rheum* 61:225–232, 2009.

Choi JWJ et al.: Sugar-sweetened soft drinks, diet soft drinks, and serum uric acid level: the third national health and nutrition examination survey, *Arthritis Rheum* 59:109–116, 2008.

Edwards NL: The role of hyperuricemia and gout in kidney and cardiovascular disease, *Cleve Clin J Med 75s s13*, 2008.

Feig DI et al.: Uric acid and cardiovascular risk, *N Engl J Med* 359:1811–1821, 2008.

Krishnan E et al.: Low-level lead exposure and the prevalence of gout, *Ann Intern Med* 157:233–241, 2012.

Neogi T, et al.: Serum uric acid is associated with carotid plaques: the National Heart, Lung, and Blood Institute Family Heart Study, *J Rheumatol* 36:378–384, 2009.

Sachs L et al.: Medical implications of hyperuricemia, *Med Health/Rhode Island 11* 353, 2009.

Siu YP et al.: Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level, *Am J Kidney Dis 47* 51, 2006.

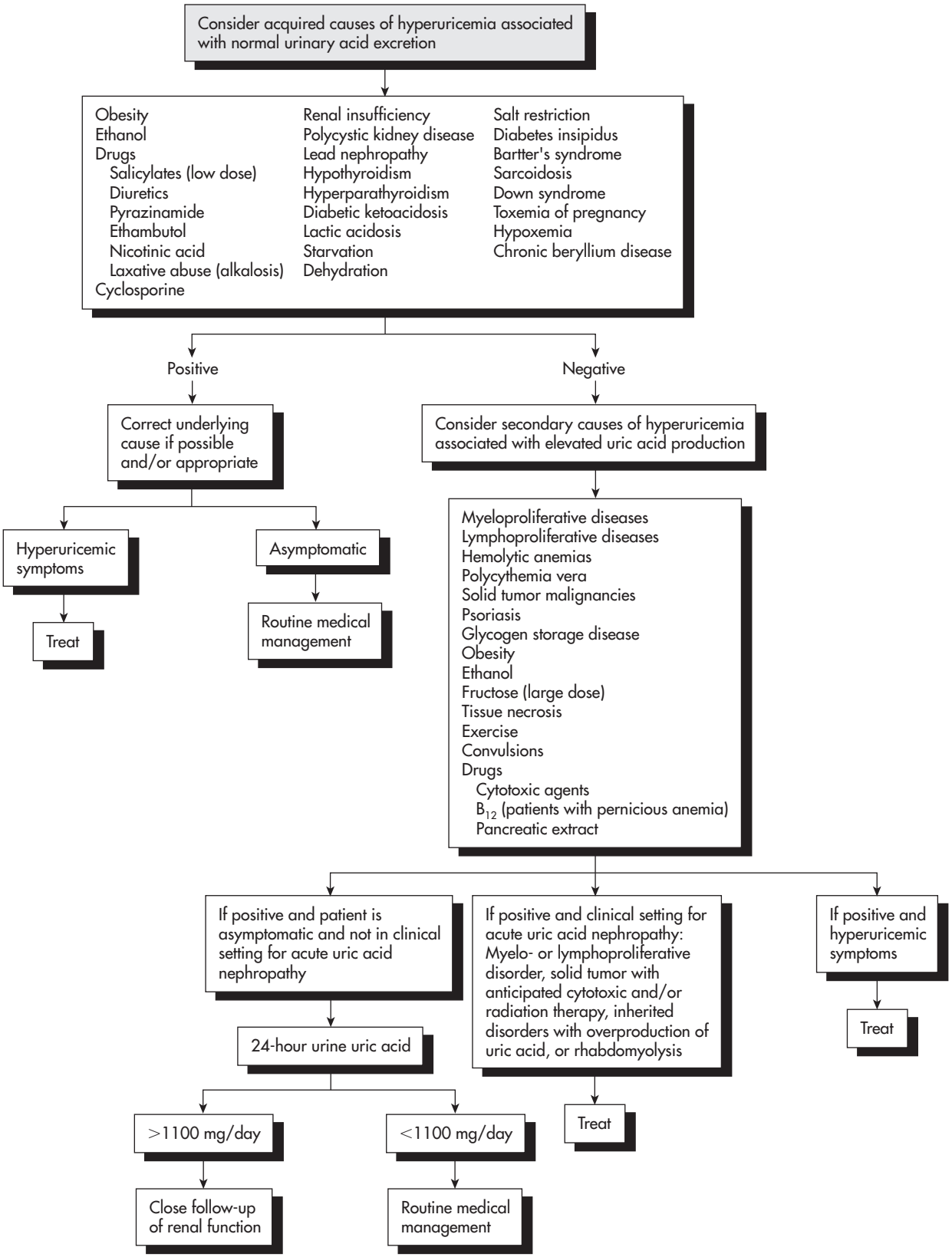


FIGURE EH1-87 Evaluation of patients with hyperuricemia. (From Harris ED et al [eds]: *Kelley's textbook of rheumatology,* ed 7, Philadelphia, 2005, Saunders.)

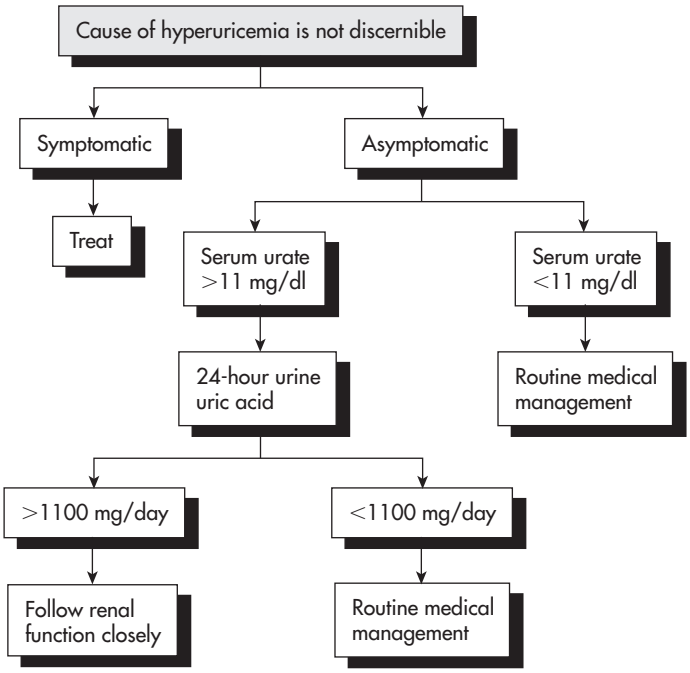


FIGURE EH1-87 (Continued)

FIGURE EH1-88 Tophus of fifth digit with smaller tophus over fourth proximal interphalangeal joint. (From Budd RC et al: *Kelley's textbook of rheumatology,* ed 8, 2009, Saunders.)

BASIC INFORMATION

DEFINITION

Hypoaldosteronism is defined as an aldosterone deficiency or impaired aldosterone function.

ICD-9CM CODES
255.4 Hypoadrenalism
ICD-10CM CODES
E27.40 Unspecified adrenocortical insufficiency
E27.3 Drug-induced adrenocortical insufficiency
E27.9 Disorder of adrenal gland, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

Selective hypoaldosteronism accounts for as many as 10% of cases of unexplained hyperkalemia.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination may be entirely within normal limits.
- Hypertension may be present in some patients.
- Profound muscle weakness and cardiac arrhythmias may be present.

ETIOLOGY

- Hyporeninemic hypoaldosteronism (renin-angiotensin dependent): decreased aldosterone production as a result of decreased renin production; the typical patient has renal disease attributable to various factors (e.g., diabetes mellitus, interstitial nephritis, multiple myeloma).
- Hyperreninemic hypoaldosteronism (renin-angiotensin independent): renin production by the kidneys is intact; the defect is in aldosterone biosynthesis or in the action of angiotensin II. Common causes of this form of hypoaldosteronism are medications (ACE inhibitors, heparin), lead poisoning, aldosterone enzyme defects, and severe illness.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Pseudohypoaldosteronism: renal unresponsiveness to aldosterone. In this condition both renin and aldosterone levels are elevated. Pseudohypoaldosteronism can be caused by medications (spironolactone), chronic interstitial nephritis, systemic disorders (systemic lupus erythematosus, amyloidosis), or primary mineralocorticoid resistance.

WORKUP

Measurement of plasma renin activity after 4 hr of upright posture can differentiate hyporeninemic from hyperreninemic causes. Renin levels in the normal or low range identify cases that are renin-angiotensin dependent, whereas high renin levels identify cases that are renin-angiotensin independent. The diagnosis and etiology of hypoaldosteronism can be confirmed with the renin-aldosterone stimulation test:

- Hyporeninemic hypoaldosteronism: low stimulated renin and aldosterone levels
- End-organ refractoriness to aldosterone action: high stimulated renin and aldosterone levels
- Adrenal gland abnormality: high stimulated renin and low aldosterone levels

LABORATORY TESTS

- Increased potassium, normal or decreased sodium
- Hyperchloremic metabolic acidosis (caused by the absence of hydrogen-secreting action of aldosterone)
- Increased BUN and creatinine (secondary to renal disease)
- Hyperglycemia (diabetes mellitus is common in these patients)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Low-potassium diet with liberal sodium intake (at least 4 g of sodium chloride per day)
- Avoidance of ACE inhibitors and potassium-sparing diuretics

ACUTE GENERAL Rx

- Judicious use of fludrocortisone (0.05 to 0.1 mg PO every morning) in patients with aldosterone deficiency associated with deficiency of adrenal glucocorticoid hormones
- Furosemide 20 to 40 mg qd to correct hyperkalemia of hyporeninemic hypoaldosteronism

DISPOSITION

Prognosis varies with the etiology of hypoaldosteronism and presence of associated disorders.

REFERRAL

Endocrinology referral for renin-aldosterone stimulation test

PEARLS & CONSIDERATIONS

COMMENTS

Treatment of pseudohypoaldosteronism is the same as for hypoaldosteronism; however, effect is limited because of impaired renal sensitivity.

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BASIC INFORMATION

DEFINITION

Male hypogonadism is a clinical syndrome involving subnormal testosterone levels and/or impaired sperm production due to dysfunction at one or both levels of the hypothalamic-pituitary-testicular axis.

SYNONYMS

Testicular dysfunction

ICD-9CM CODES
257 Testicular dysfunction
ICD-10CM CODES
E29 Testicular dysfunction
E29.1 Testicular hypofunction
E29.8 Other testicular dysfunction
E29.9 Testicular dysfunction, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Hypogonadism is the most common clinical disorder of the testis. Incidence is unclear due to the many possible underlying factors, nonspecificity of symptoms, and questions relating to the adequacy of a diagnostic serum total testosterone threshold.

PREVALENCE: Prevalence of hypogonadism increases with aging, obesity, diabetes mellitus, and other comorbidities. The average decrease in serum total testosterone levels in aging men is 1%-2% per year. Prevalence rises to 23% among men in their 70s. However, in population-based surveys of community-dwelling middle-aged and older males, prevalence of hypogonadism is approximately 6%.

GENETICS: Genetic abnormalities underlie a number of hypogonadal disorders including Klinefelter syndrome, Noonan syndrome, hemochromatosis, Kallmann syndrome, and Prader-Willi syndrome.

RISK FACTORS: These are many and include genetic abnormalities; the aging process; pituitary and testicular lesions and disorders; medications; drug abuse; HIV disease; acute illnesses; chronic cardiac, hepatic, renal, and pulmonary diseases; cancer; ionizing radiation; chemotherapy; obesity; and malnutrition.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Sexual (specific)
- Decrease in frequency of erections
- Erectile dysfunction
- Decrease in libido
- Decreased fertility
- Small or shrinking testes
- Gynecomastia
- Diminished sexual hair
- Hot flushes and sweats

Neuropsychologic (less specific)
- Depression
- Inability to concentrate
- Diminished motivation and vitality
- Decrease in self-confidence
- Diminished energy and stamina
- Sleep disturbances

Physical features and findings
- Diminished capacity for physical activity
- Decrease in physical endurance and performance
- Diminished muscle mass and strength
- Increase in body fat
- Decrease or loss of axillary and pubic hair and decrease in shaving frequency
- Fine wrinkling over the lateral aspects of the face
- Breast enlargement with or without tenderness
- Change in consistency and decrease in size of testes
- Fragility fractures
- Anemia

ETIOLOGY

- The importance of a careful history and examination cannot be overstated to determine the etiology of possible hypogonadism. Primary hypogonadism is a result of a decrease in testicular testosterone secretion and/or a decrease in spermatogenesis with an associated increase in gonadotropin levels as in Klinefelter syndrome, cryptorchidism, and following orchitis, testicular trauma, chemotherapy, and irradiation.
- Secondary hypogonadism is due to hypothalamic-pituitary dysfunction, which results in a decrease in testosterone levels and/or spermatogenesis with gonadotropin levels that are subnormal or inappropriately within the normal range.
- Combined primary and secondary hypogonadism is a result of deficits at both the level of the hypothalamic-pituitary axis and testes with variable gonadotropin levels depending upon the predominance of the level of the defect.

DIAGNOSIS (Fig. H1-89)

DIFFERENTIAL DIAGNOSIS

Hypogonadotropic or secondary hypogonadism
- Pituitary dysfunction—hypopituitarism, functioning or nonfunctioning pituitary tumor, lymphocytic hypophysitis, infiltrative disease as with sarcoidosis, hemochromatosis, and histiocytosis X
- Hyperprolactinemia—prolactinoma, medication-related, chronic kidney disease
- Genetic—Kallmann syndrome with anosmia, Prader-Willi syndrome with morbid obesity
- Acute and chronic illnesses, malnutrition, emotional disorders, HIV, sleep apnea, aging, malignancies, obesity, and renal, hepatic, pulmonary, and cardiac diseases
- Opioids, CNS—active medications, glucocorticoid excess, and GnRH analogues (androgen deprivation therapy)

Hypergonadotropic or primary hypogonadism
- Genetic—Klinefelter syndrome, Noonan syndrome, myotonic dystrophy
- Gonadal damage due to drugs, alcohol, radiation, chemotherapy, trauma
- Congenital anorchia (vanishing testis syndrome)
- Cryptorchidism
- Mumps orchitis, HIV orchitis
- Diabetes mellitus
- Hodgkin's disease
- Aging

Combined primary and secondary hypogonadism
- Hemochromatosis, sickle cell disease, thalassemia
- Alcoholism, glucocorticoid therapy, aging
- Chronic cardiac, hepatic, renal, pulmonary diseases, and HIV disease

WORKUP

- Determine the presence or absence of male hypogonadism on the basis of history, clinical manifestations and findings, and documentation of consistently low serum total testosterone levels and/or abnormal seminal fluid analysis.
- Morning serum total testosterone levels should be measured on at least 2 or 3 occasions for confirmation of diagnosis and when necessary followed by measurement of serum free or bioavailable testosterone.
- Serum FSH and LH levels are measured to determine whether hypogonadism is primary, secondary, or a result of combined defects of the hypothalamic-pituitary axis and testis.
- Hormonal assessment of gonadal status should not be done during an acute or subacute illness.

LABORATORY TESTS

- Serum total testosterone is tightly bound to sex hormone binding globulin (SHBG) and weakly bound to circulating albumin. 0.5-3% of serum total testosterone is unbound or free.
- Liquid chromatography tandem mass spectrometry assays for total serum testosterone are more accurate than immunoassays.
- Bioavailable testosterone refers to unbound testosterone plus the testosterone that is loosely bound to albumin.
- Free testosterone, if necessary, is best measured by equilibrium dialysis or centrifugal ultrafiltration.
- An SHBG measurement is helpful in determining the adequacy or normality of a serum total testosterone measurement. Conditions that lower SHBG include obesity, protein-losing states, androgens, hypothyroidism, and familial SHBG deficiency. Increases in SHBG occur in those with hyperthyroidism, hepatitis, cirrhosis, and HIV disease, aging, and by estrogens.
- The lower limit of normal for serum total testosterone in a healthy young male is approximately 240-280 ng/dl and a low-normal serum free testosterone in a young normal male is 9 pg/ml.
- Serum total testosterone levels can vary from day-to-day and there is a diurnal rhythm in young normal males with morning levels that are higher by approximately 20%-25% as compared with levels in the afternoon.
- In elderly males, the diurnal rhythm is diminished with levels approximately 10% lower in the afternoon as compared with morning levels.

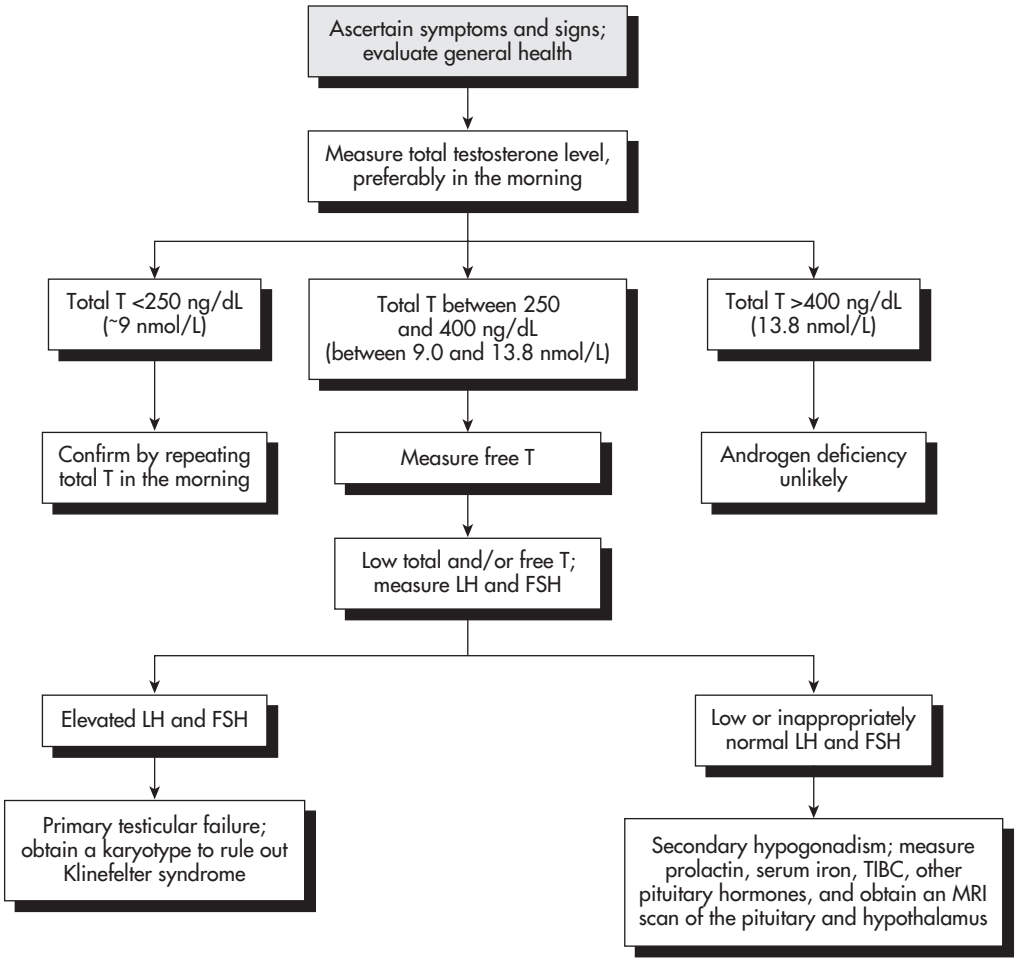

FIGURE H1-89 Algorithm showing an approach for the diagnostic evaluation of adult men suspected of having androgen deficiency. (From Shalender B, Shehzad B: Diagnosis and treatment of hypogonadism in men, *Best Pract Res Clin Endocrin* 25(2):251-270, 2011.)

- Serum FSH and LH measurements are important in delineating primary, secondary, and combined hypogonadism.
- Hypogonadal symptoms are more likely to be seen in those with total serum testosterone level below the lower limit of values for young normal males. Serum total testosterone levels of <150 ng/dl are unequivocally low.
- Transient suppression of total serum testosterone may occur during acute illness, in males that are being treated with glucocorticoid, in those taking opiates or CNS-active medications, in those with malnutrition or poor eating habits, and during excessive physical exercise.
- Quantity and quality of sperm counts and activity can vary in a significant way for a variety of reasons. Therefore, in assessing fertility, seminal fluid analysis should be done on two or more occasions each separated by two or more weeks and on semen collected within an hour of ejaculation after more than two days of abstinence.
- Depending on the clinical picture and examination, other studies may be necessary including a karyotype analysis, for example, for Klinefelter syndrome, or serum prolactin measurement for patients with possible hyperprolactinemia which may be drug-induced, related to a prolactinoma, or to chronic renal disease.

IMAGING STUDIES

- In males with severe androgen deficiency with low serum gonadotropin levels, increased serum prolactin levels, hypopituitarism, severe headaches, and visual defects, an MRI of the pituitary would be appropriate. In males with hypogonadism and a history of fractures, DXA measurements of spine and hip should be obtained to further delineate the status of the skeletal system.

Rx TREATMENT

- Testosterone replacement therapy is indicated when patients have symptoms and signs of hypogonadism and serum testosterone levels that are consistently subnormal with levels of <250 ng/dl. The goal of replacement therapy is to restore serum testosterone levels to within the normal range of values and to have a positive effect on the constellation of hypogonadal symptoms and signs. Subnormal spermatogenesis, if present in such patients, is not affected by testosterone therapy. In patients with hypogonadotropic or secondary hypogonadism, chorionic gonadotropin and/or GnRH therapy can optimize spermatogenesis, whereas, generally in patients with primary hypogonadism, subnormal spermatogenesis and infertility are irreversible.

NONPHARMACOLOGIC THERAPY

- Weight reduction, especially when it appears to be a major factor underlying male hypogonadism.
- Discontinuation of anabolic steroids, CNS-active medications, and narcotic abuse.
- Surgery or radiation therapy for patients with a pituitary functioning or nonfunctioning tumor with visual field abnormality and headaches who are not candidates for further medical therapy or have been unsuccessfully treated with medication.
- Surgery indicated for chronic gynecomastia and, occasionally, in cases with recent-onset gynecomastia that has not responded to testosterone replacement therapy.

CHRONIC THERAPY

Testosterone formulations:

- Parenteral testosterone preparations:
  1. Testosterone enanthate (generic) and testosterone cypionate (Depo-Testosterone and generic) 150 to 200 mg are injected

intramuscularly every 2 weeks. Following injections, there are appreciable fluctuations in serum testosterone, with levels rising within the first several days and a subsequent decrease to normal and in some cases to below normal at the end of the two weeks. As a result of the varying levels of testosterone, patients may have related symptoms. Adjustments in dose and dosing interval may help to alleviate the serum fluctuations and clinical symptoms. Testosterone undecanoate (AUEFD-ENDO) is an injectable depot formulation recently FDA-approved for male hypogonadism. The recommended dosage is 750 mg injected IM at 0 and 4 wk, and then every 10 wk thereafter.

- Topical testosterone preparations:
  1. Testosterone adhesive patch (Androderm) delivers 2.5 or 5 mg of testosterone when applied nightly to the back, abdomen, upper arms, or thighs. Serum testosterone levels rise to within normal range in a few hours after application and, thereafter, are relatively stable. Daily doses of up to 10 mg may be necessary.
  2. Testosterone 1% gels (AndroGel and Testim). Androgel is available in 2.5 g and 5 g gel units that deliver 2.5 mg and 5 mg of testosterone, respectively. The gel is applied daily in the morning by hand over the shoulder, upper arms, or abdomen. Adjustments in dose to 7.5 g or 10 g of gel may be necessary to optimize serum testosterone levels. AndroGel (1.62%) pump is also available for daily application. Testim is available in 5 g and 10 g tubes and with morning applications over the shoulders or arms delivers 5 mg and 10 mg of testosterone, respectively. Both AndroGel and Testim provide relatively stable serum testosterone levels. Two new transdermal formulations, Fortesta and Axiron, are now available and are applied daily by metered dose pumps. With these preparations, care is necessary to avoid skin-to-skin contact exposure with others.
- Testosterone pellets:
  1. 3 to 6 pellets of testosterone each containing 75 mg of testosterone are surgically inserted subcutaneously every 3 to 6 months and provide relatively stable serum testosterone levels. This particular therapy is infrequently used in the United States.

RISKS AND ADVERSE EFFECTS

- Contraindications to testosterone therapy include prostate cancer and breast cancer. Relative contraindications include severe benign prostatic hyperplasia, hematocrit ≥50% at baseline, sleep apnea, and severe congestive heart failure.
- Patients on chronic testosterone therapy need to be followed carefully with prostate and PSA assessments and hematocrit measurements for possible excessive induction of erythrocytosis, initially at 3 to 6 months and at regular intervals thereafter.

REFERRAL

Endocrinology for full endocrine and metabolic assessment and therapy. Urology for further assessment and follow-up of the prostate and for evaluation and therapy of erectile dysfunction. Neurosurgery for evaluation and possible surgery for a pituitary lesion. Plastic surgery for chronic gynecomastia. Reproductive endocrinology for those with an infertility problem.

PEARLS & CONSIDERATIONS

COMMENTS

Male hypogonadism is an important and frequently encountered problem that requires a complete medical history, examination, and hormonal assessment to determine whether a patient has hypogonadism and requires testosterone replacement therapy. Treated patients need to be seen on a regular basis to avoid possible testosterone adverse effects.

AUTHOR: **JOSEPH R. TUCCI, M.D.**

SUGGESTED READINGS

Araujo AB et al.: Prevalence and incidence of androgen deficiency in middle-aged and older men: estimate from the Massachusetts Aging Study, *J Clin Endocrinol Metab* 89:5920–5926, 2004.

Araujo AB et al.: Prevalence of symptomatic androgen deficiency in men, *J Clin Endocrinol Metab* 92:4241–4247, 2007.

Bhasin S et al.: Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society Clinical Practice Guideline, *J Clin Endocrinol Metab* 95(6):2536–2559, 2010.

Handelsman DJ: Mechanism of action of testosterone—unraveling of Gordian knot, *NEJM* 369:1058–1059, 2013.

Morgentaler A et al.: Testosterone therapy and cardiovascular risk: advances and controversies, *Mayo Clin Proc* 90(2):224–251, 2015.

BASIC INFORMATION

DEFINITION

A decrease in parathyroid hormone (PTH) secretion or function results in hypoparathyroidism. In primary hypoparathyroidism, absence or dysfunction of the parathyroid gland results in inadequate PTH secretion and subsequent hypocalcemia and hyperphosphatemia. Surgical hypoparathyroidism is the most common etiology, followed by autoimmune disorders. Individuals with autoimmune polyglandular syndrome 1 typically present in childhood/adolescence with candidiasis, hypoparathyroidism, and adrenal insufficiency. Impaired function of PTH (i.e., PTH resistance) can also cause hypocalcemia and hyperphosphatemia but the measured PTH level is elevated in this circumstance. Maternally transmitted mutation in *GNAS1* gene results in PTH resistance (i.e., pseudohypoparathyroidism). It is associated with characteristic features that include developmental delay, short stature, round facies, and short 4th metacarpal known as Albright's hereditary osteodystrophy (AHO). Paternal transmission manifests with AHO without PTH resistance (i.e., pseudopseudohypoparathyroidism; Table H1-58). Secondary hypoparathyroidism, a condition in which PTH levels are low in response to hypercalcemic states, is discussed in Section IV (see hypercalcemia discussion in the "Calcium" topic).

ICD-9CM CODES
252.1 Hypoparathyroidism
ICD-10CM CODES
E20.0 Idiopathic hypoparathyroidism
E20.1 Pseudohypoparathyroidism
E20.8 Other hypoparathyroidism
E20.9 Hypoparathyroidism, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

The incidence and prevalence of primary hypoparathyroidism depends on the etiology of the condition. Postoperative hypoparathyroidism is the most common etiology and occurs in the setting of thyroid or parathyroid surgery. Transient hypoparathyroidism can be as high as 20% postoperatively but permanent dysfunction is less common (3%). Autoimmune disorders are the second most common cause of hypoparathyroidism in adults (female/male ratio of 1.4:1.0). Autoimmune polyglandular syndrome type I is reported to have an incidence worldwide of 1:1,000,000. Other etiologies of hypoparathyroidism are very rare.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The symptoms of hypoparathyroidism are primarily related to hypocalcemia. The presentation of symptoms varies with the severity and duration of illness.

- Cardiovascular: prolonged QT intervals, QRS and ST segment changes, ventricular arrhythmias
- Musculoskeletal: muscle cramps, laryngospasm, osteomalacia (adults), rickets (children), weakened tooth enamel, osteosclerosis
- CNS: tetany (Chvostek's sign and Trousseau's sign), seizures, paresthesias, visual impairment from cataract formation, altered mental status, papilledema, and basal ganglia calcifications with longstanding disease
- GI: abdominal pain
- Renal: hypercalciuria and nephrolithiasis
- Other: dry scaly skin, brittle nails, dry hair

In addition to the hypocalcemia-related symptoms, syndromes associated with hypoparathyroidism can have distinct clinical findings. Conditions associated with hypoparathyroidism include:

- DiGeorge syndrome: dysmorphic facies, cleft palate
- Pseudohypoparathyroidism: developmental delay, short stature, round face, short 4th metacarpal (Albright's hereditary osteodystrophy)
- Hypoparathyroidism-retardation-dysmorphism syndrome: short stature, microcephaly, microphthalmia, small hands and feet, abnormal teeth
- Hypoparathyroidism-deafness-renal dysplasia syndrome: sensorineural deafness
- Autoimmune polyglandular syndrome type 1: mucocutaneous candidiasis and adrenal insufficiency

ETIOLOGY

There are several etiologies of hypoparathyroidism:

- Developmental defects of the parathyroids
  1. Isolated hypoparathyroidism
  2. Branchial dysembryogenesis (DiGeorge's syndrome)
  3. Hypoparathyroidism-retardation-dysmorphism syndrome
  4. Hypoparathyroidism-deafness-renal dysplasia syndrome
  5. Mitochondrial dysfunction associated with hypoparathyroidism
- Destruction of the parathyroids
  Postoperative hypoparathyroidism
  1. Autoimmune polyglandular syndrome type 1
  2. Radiation to the neck
  3. Infiltrative disease (e.g., metastatic carcinoma, Wilson's disease, hemochromatosis, thalassemia, granulomatous disease)
- Functional and secretory defects of the parathyroids
  1. Activating mutation of the calcium-sensing receptor alters the set point of the receptor and decreases PTH secretion
  2. Activating antibodies to calcium-sensing receptor alters the set point of the receptor and decreases PTH secretion
  3. PTH resistance (i.e., target organs unresponsive to PTH action)
     1. Pseudohypoparathyroidism (PHP): heterogeneous disorder presenting in childhood characterized by hypocalcemia, hyperphosphatemia, and elevated PTH levels. Table H1-59 summarizes the various types of PHP.
     2. Hypermagnesemia and hypomagnesemia

TABLE H1-58 Types of Hypoparathyroidism

Type	Calcium	PO_4	PTH	Comments
Hypoparathyroidism	↓	↑	↓	Surgical removal (most common cause)
Pseudohypoparathyroidism	↓	↑	Ø↑	End-organ resistance to parathyroid hormone and Albright's hereditary osteodystrophy
Pseudo-pseudohypoparathyroidism	Normal	Normal	Normal	Only Albright's hereditary osteodystrophy

Adapted from Weissleder R et al: *Primer of diagnostic imaging,* ed 5, St Louis, 2011, Mosby.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Secondary hypoparathyroidism as a result of hypercalcemia (discussed in the "Hypercalcemia" section)
- Other conditions associated with hypocalcemia. These conditions are usually associated with an elevated PTH hormone level.

WORKUP

- Serum calcium is usually low and phosphorus is elevated
  1. Two measurements of serum calcium are required for the confirmation of hypocalcemia. Total calcium should be corrected for low albumin utilizing the formula: Corrected Calcium = measured calcium + [(4 – albumin) × 0.8]. If a reliable laboratory is available, ionized calcium should be considered especially in conditions associated with acid-base disturbances or low albumin states.
  2. Serum phosphorus is usually high-normal or elevated in primary hypoparathyroidism.
- Serum intact PTH (iPTH) level is the single best test to evaluate the etiology of hypocalcemia. Typically, PTH is decreased in hypoparathyroidism and elevated in most other conditions associated with low calcium levels. However, PTH is also elevated in disorders associated with impaired PTH function (i.e., pseudohypoparathyroidism). Genetic studies as indicated if medical or family history is suggestive.

LABORATORY TESTS

- Total and ionized calcium: low in hypoparathyroidism
- PTH: low in hypoparathyroidism and high in PTH resistance states like pseudohypoparathyroidism

TABLE H1-59 Types of Pseudohypoparathyroidism (PHP)

Disorder	Urinary cAMP Response to PTH	Urinary PO_4 Response to PTH	Other Hormonal Resistance	AHO	Pathophysiology
PHP type 1A	Decreased	Decreased	Yes	Yes	$G_s\alpha$ mutation
Pseudo-PHP	Normal	Normal	No	Yes	$G_s\alpha$ mutation
PHP type 1B	Decreased	Decreased	No	No	*GNAS1* imprinting mutations
PHP type 1C	Decreased	Decreased	Yes	Yes	$G_s\alpha$ activity normal
PHP type 2	Normal	Decreased	No	No	Vitamin D deficiency or myotonic dystrophy in some cases

AHO, Albright's hereditary osteodystrophy; *cAMP*, cyclic adenosine monophosphate; *GNAS1*, portion of the *GNAS* complex locus encoding $G_s\alpha$; $G_s\alpha$, α-subunit of the stimulatory G protein; PO_4, phosphate; *PTH*, parathyroid hormone.
From Melmed: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

- Phosphorus: high-normal or high in hypoparathyroidism
- Magnesium: both hypomagnesemia and hypermagnesemia can cause hypoparathyroidism
- ECG should be considered. Hypocalcemia associated with prolonged QT interval, rarely ST-segment elevations
- 24-hr urine for calcium to evaluate the risk for renal stones

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Parathyroid autotransplantation:

Hypoparathyroidism and subsequent hypocalcemia are common problems after neck exploration for total or near-total thyroidectomy or parathyroidectomy. In cases where there is concern for postoperative hypoparathyroidism, parathyroid autotransplantation of one or two parathyroid glands into the forearm or sternocleidomastoid muscle should be performed to prevent postoperative hypoparathyroidism.

PHARMACOLOGIC THERAPY

The mainstay of treatment for primary hypoparathyroidism is pharmacologic therapy with calcium and vitamin D supplementation. The goals of therapy are to control symptoms and minimize complications of therapy. The aim should be to achieve low-normal serum calcium (8.0-8.5 mg/dl), 24-hr urinary calcium <300 mg/day, and a calcium-phosphorus product <55.

- Vitamin D:
  1. There are several vitamin D preparations available on the market but the treatment of choice for patients with primary hypoparathyroidism is calcitriol. It is an active metabolite that does not require hydroxylation in the liver or kidney and therefore bypasses the PTH-mediated 1-α hydroxylation defect that occurs with hypoparathyroidism.
  2. Dose of 0.25 to 1 μg once or twice daily is usually required to correct hypocalcemia and improve symptoms. Its maximal effect is seen after 10 hr and it lasts for 2 to 3 days.
- Calcium:
  1. Calcium carbonate or calcium citrates are common oral agents used for treatment of hypocalcemia associated with hypoparathyroidism. Calcium carbonate requires an acidic environment for effective absorption, and as a result, it must be taken with food. Its effectiveness is decreased with concomitant use of H_2 blockers or proton pump inhibitors. However, calcium carbonate is cheaper in cost than other calcium supplements and therefore it is first line in the management of hypocalcemia for some patients. The advantage of calcium citrate is that it does not require an acidic environment for effective absorption.
  2. Start with a dose of 500 to 1000 mg of elemental calcium tid and adjust the dose for a desired calcium in the low-normal range.
- Magnesium:
  1. Hypocalcemia is difficult to correct without normalizing magnesium levels.
  2. Magnesium sulfate IV 2 g over 20 min followed by 1 g/hr infusion can be considered in severe deficiency states. Milder deficiencies can be managed with oral magnesium 100 mg tid.
- Thiazide diuretics:
  1. Thiazide diuretics decrease urine calcium excretion and decrease kidney stones. They should be considered in individuals with urine calcium >250 mg/day.
- PTH replacement:
  1. Preliminary studies involving injectable synthetic human PTH(1-34) and PTH (1-84) have been performed with results showing a decrease in urinary calcium excretion, maintenance of serum calcium in the normal range with reduced requirements for calcium and vitamin D supplementation, and increase in bone density at the spine. As expected, injectable PTH decreased forearm BMD.
  2. It is not FDA approved for use in hypoparathyroidism.

ACUTE GENERAL Rx

Severe and/or symptomatic hypocalcemia requires hospitalization. Acute management of hypocalcemia includes:

- Telemetry monitoring for arrhythmias associated with severe hypocalcemia
- IV infusion of calcium gluconate 10 ml of 10% solution to receive a bolus of 90 mg of elemental calcium followed by an infusion of 0.5 to 2 mg/kg/hr until calcium levels are in the low-normal range.

PEARLS & CONSIDERATIONS

COMMENTS

- The mainstay of treatment for primary hypoparathyroidism is calcitriol and calcium supplementation to maintain a goal serum calcium level in the low-normal range. IV calcium should be considered if calcium <7.0 mg/dl. Magnesium levels should be assessed and appropriately replaced in all patients with hypocalcemia. Clinical trials are under way to evaluate the role of recombinant PTH for the treatment of primary hypoparathyroidism.
- In patients undergoing neck exploration, consideration should be given to the parathyroid glands. Autotransplantation of one or more parathyroid glands should be considered when appropriate to prevent postoperative hypoparathyroidism.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **VICKY CHENG, M.D.**

EVIDENCE

Abstract[1]

Context:

Vitamin D therapy for hypoparathyroidism does not restore PTH-dependent renal calcium reabsorption, which can lead to renal damage. An alternative approach, PTH 1-34 administered twice daily, provides acceptable long-term treatment but is associated with nonphysiological serum calcium fluctuation.

Objective:

Our objective was to compare continuous PTH 1-34 delivery, by insulin pump, with twice-daily delivery.

Research Design and Methods:

In a 6-month, open-label, randomized, crossover trial, PTH 1-34 was delivered by pump or twice-daily SC injection. After each 3-month study period, serum and 24-h urine mineral levels and bone turnover markers were measured daily for 3 d, and 24-h biochemical profiles were determined for serum minerals and 1,25-dihydroxyvitamin D(3) and for urine minerals and cAMP.

Study Participants and Setting:

Eight patients with postsurgical hypoparathyroidism (mean ± SD age 46 ± 5.6 yr) participated at a tertiary care referral center.

Results:

Pump vs. twice-daily delivery of PTH 1-34 produced less fluctuation in serum calcium, a more than 50% reduction in urine calcium ($P = 0.002$), and a 65% reduction in the PTH dose to maintain eucalcemia ($P < 0.001$). Pump delivery also produced higher serum magnesium level ($P = 0.02$), normal urine magnesium, and reduced need for magnesium supplements. Finally, pump delivery normalized bone turnover markers and significantly lowered urinary cross-linked N-telopeptide of type 1 collagen and pyridinium crosslinks compared with twice-daily injections ($P < 0.05$).

Conclusion:

Pump delivery of PTH 1-34 provides the closest approach to date to physiological replacement therapy for hypoparathyroidism. Ⓐ

Evidence-Based Reference

Winer KK et al.: Synthetic human parathyroid hormone 1-34 replacement therapy: a randomized crossover trial comparing pump versus injections in the treatment of chronic hypoparathyroidism, *J Clin Endocrinol Metab* 97(2):391–399, 2012. Ⓐ

SUGGESTED READINGS

Bilezikian JP et al.: Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target organ involvement, treatment and challenges for future research, *J Bone Miner Res* 26(10):2317–2337, 2011.

Cusano NE et al.: Mini-review: new therapeutic options in hypoparathyroidism, *Endocrine* 41(3):410–414, 2012.

Rejnmark L et al.: PTH replacement therapy in hypoparathyroidism, *Osteoporosis Int* 24(5):1529–1536, 2013.

Walker Harris V et al.: Postoperative hypoparathyroidism: medical and surgical therapeutic options, *Thyroid* 19(9):967–973, 2008.

BASIC INFORMATION

DEFINITION

Hypopituitarism (from the Latin *pituita,* meaning "phlegm") is the deficiency of one or more of the hormones of the anterior or posterior pituitary gland resulting from diseases of the hypothalamus or pituitary gland. Panhypopituitarism indicates the loss of all the pituitary hormones but is often used in clinical practice to describe patients deficient in growth hormone (GH), gonadotropins, corticotropin, or thyrotropin in whom posterior pituitary function remains intact.

SYNONYMS

Panhypopituitarism
Pituitary insufficiency

ICD-9CM CODES
253.2 Panhypopituitarism
ICD-10CM CODES
E23.0 Hypopituitarism

EPIDEMIOLOGY & DEMOGRAPHICS

Incidence of 4.2 cases per 100,000 persons

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms depend on type of onset, number and severity of hormone deficiencies, their target organs, and age of onset.

- Mass effect of a pituitary tumor can cause headaches and visual disturbances (typically as bitemporal hemianopsia).
- Rhinorrhea.
- Corticotropin deficiency:
  1. Fatigue and weakness, no appetite, abdominal pain, nausea, vomiting, failure to thrive in children, and hyponatremia. If the onset is abrupt, hypotension and shock
- Thyrotropin deficiency:
  1. Fatigue and weakness, weight gain, cold intolerance, anemia, constipation
  2. Bradycardia, hung-up reflexes, pretibial edema, change in voice, and hair loss
- Gonadotropin deficiency:
  1. Loss of libido, erectile dysfunction, amenorrhea, hot flashes, dyspareunia, infertility, gynecomastia, decreased muscle mass, and anemia
- GH deficiency:
  1. Growth retardation in children
  2. Easy fatigue, hypoglycemia
  3. Lean mass is reduced and fat mass is increased, leading to obesity
  4. Decreased bone mineral density, increased low-density lipoprotein cholesterol, obesity, increased inflammatory cardiovascular markers (interleukin-6 and C-reactive protein)
- Hyperprolactinemia:
  1. Galactorrhea, hypogonadism, inability to lactate after delivery
  2. Posterior pituitary (vasopressin; antidiuretic hormone [ADH] deficiency): diabetes insipidus with polyuria, polydipsia, nocturia, hypotension, and dehydration

ETIOLOGY

It can be congenital or acquired:

- Congenital: mutations in transcription factors produce multiple hormonal deficiencies. Mutations in genes produce single hormonal deficiency.
- Acquired: the result of destruction of pituitary cells caused by:
  1. Pituitary apoplexy: hemorrhage or infarction of the pituitary gland. Predisposing factors include diabetes mellitus, anticoagulation therapy, head trauma, and radiation therapy. Sheehan's syndrome: postpartum necrosis, a rare complication after pregnancy.
  2. Infiltrative disease, including sarcoidosis, hemachromatosis, histiocytosis X, Wegener's granulomatosis, lymphocytic hypophysitis, and infection of the pituitary (tuberculosis, mycosis, syphilis).
  3. Primary empty sella syndrome: flattening of the pituitary gland caused by extension of the subarachnoid space and filling of cerebrospinal fluid into the sella turcica.
  4. Pituitary tumors: classified by size (microadenomas, <10 mm; macroadenomas, >10 mm) and function. Prolactin-secreting tumors and nonfunctioning tumors account for the majority of pituitary adenomas.
  5. Suprasellar tumors: craniopharyngiomas are the most common.

DIAGNOSIS

The diagnosis of hypopituitarism is suspected by clinical history and physical findings and is established by blood tests to confirm the presence of hormone deficiency.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is as outlined under "Etiology."

WORKUP

Includes baseline determination of each anterior pituitary hormone followed by dynamic provocative stimulation tests, radiograph imaging, and formal visual field testing. Table H1-60 summarizes testing for assessment of anterior pituitary function.

LABORATORY TESTS

- Corticotropin deficiency:
  1. The presence of a 9:00 am cortisol level >20 mcg/dl or <4 mcg/dl usually confirms sufficiency or deficiency, respectively.
  2. Corticotropin stimulation test using 250 mcg of corticotropin given IV and measuring serum cortisol before and 30 and 60 min after administration. A normal response is an increase in serum cortisol level >20 mcg/dl.
  3. With pituitary disease these test results may be indeterminate, and more dynamic testing such as an insulin-tolerance or metyrapone test may be necessary.
- Thyrotropin deficiency:
  1. Thyroid-stimulating hormone (TSH) and free T_4 measurements
  2. Primary hypothyroidism shows elevated TSH with low free T_4. Secondary hypothyroidism shows normal or low TSH with low free T_4 and low T_3 resin uptake.
- Gonadotropin deficiency:
  1. Follicle-stimulating hormone (FSH), luteinizing hormone (LH), estrogen, and testosterone measurements.
  2. In men, hypogonadotropic hypogonadism is seen with low testosterone levels and normal or low FSH and LH levels (ideally measured at 9:00 AM because of diurnal rhythm). Check free testosterone if patient is obese.
  3. In premenopausal women with amenorrhea, low estrogen with normal or low FSH and LH levels is typically seen.
- GH deficiency:
  1. Insulin-induced hypoglycemia stimulation test using 0.1 to 0.15 unit/kg regular insulin given IV and measuring GH 30, 60, and 120 min after administration. A normal response is a GH level >3 mcg/dl. This test is contraindicated in seizure disorder or ischemic heart disease.
  2. Combination of GH-releasing hormone plus arginine is an alternative test, with a diagnostic threshold of 9 mcg/L.
  3. Because the relation between serum insulinlike growth factor (IGF)-1 and GH levels blurs with age, a normal serum IGF-1 does not exclude the diagnosis in older adults.
- Hyperprolactinemia: prolactin levels may be elevated in prolactin-secreting pituitary adenomas.
- Vasopressin deficiency:
  1. Urinalysis shows low specific gravity.
  2. Urine osmolality is low.
  3. Serum osmolality is high.
  4. Fluid deprivation test over 18 hr with inability to concentrate the urine.
  5. Serum vasopressin level is low.
  6. Electrolytes may show hyponatremia and exclude hyperglycemia.

IMAGING STUDIES

- Imaging is the first step in identifying an underlying cause.
- MRI is more sensitive than CT in visualizing the pituitary fossa, sella turcica, optic chiasm, pituitary stalk, and cavernous sinuses. It is also more sensitive in detecting pituitary microadenomas. CT with contrast can be used if MRI is not available.
- Surveillance scan at baseline and 12 mo thereafter depending on protocol and clinical symptoms.

TREATMENT

Threefold: removing underlying cause (surgery or radiation), treating hormonal deficiencies, and addressing any other repercussions from deficiency. Table H1-61 summarizes replacement therapy for adult hypopituitarism.

TABLE H1-60 Assessment of Anterior Pituitary Function

Test	Dose	Normal Response	Side Effects
ACTH			
Insulin tolerance	0.1-0.15 U/kg IV	Peak cortisol response >18 μg/dl, or ≥5μg/dl	Sweating, palpitation, tremor
Metyrapone	30 mg/kg PO at 11 P.M.	Peak 11-DOC ≥=7 μg/dl Peak cortisol ≤7 μg/dl Peak ACTH >75 pg/ml	Nausea, insomnia, adrenal crisis
CRH stimulation	100 μg IV	Peak ACTH ≥2-4-fold Peak cortisol ≥20 μg/dl or ↑ ≥=7 μg/dl	Flushing
ACTH stimulation	250 μg IV or IM, or 1 μg IV	Peak cortisol ≥20 μg/dl	Rare
TSH			
Serum T_4 (free T_4) Total T_3 TSH—third-generation TRH stimulation	200-500 μg IV	Peak TSH ≥2.5-fold, or ↑ ≥5-6 mU/L (females) or ≥2-3 mU/L (males)	Flushing, nausea, urge to micturate
PRL			
Serum PRL TRH stimulation	200-500 μg IV	PRL ↑ ≥2.5-fold	Flushing, nausea, urge to micturate
LH/FSH			
Serum LH and FSH Serum testosterone GnRH stimulation	100 μg IV	Elevated in menopause and in men with primary testicular failure (otherwise normal) 300-900 ng/ml LH ≥2-3-fold, or ↑ by 10 IU/L FSH ≥1.5-2-fold, or ↑ ≥2 IU/L	Rare
GH			
Insulin tolerance	0.1-0.15 U/kg	GH peak >5 μg/L	Sweating, palpitation, tremor
L-Arginine	Arginine 0.5 g/kg (maximum, 30 g) IV over 30-120 min	GH peak >0.4 μg/L	Nausea
Plus			
GHRH	GHRH 1-5 μg/kg	GH peak >4 μg/L	Flushing

ACTH, Adrenocorticotropic hormone; *CRH,* corticotropin-releasing hormone; *11-DOC,* 11-deoxycorticosterone; *FSH,* follicle-stimulating hormone; *GH,* growth hormone; *GHRH,* growth hormone–releasing hormone; *GnRH,* gonadotropin-releasing hormone; *LH,* luteinizing hormone; *PRL,* prolactin; T_3, triiodothyronine; T_4, thyroxine; *TSH,* thyroid-stimulating hormone; *TRH,* thyrotropin-releasing hormone.

From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders, Elsevier Inc.

TABLE H1-61 Replacement Therapy for Adult Hypopituitarism*

Deficient Hormone
Treatment
Remarks
ACTH
Hydrocortisone: 10-20 mg/day in divided doses Cortisone acetate: 15-25 mg/day in divided doses
TSH
L-Thyroxine: 0.05-0.2 mg/day according to T_4 levels
FSH/LH (in males)
Testosterone enanthate: 200 mg IM q2-3 wk Testosterone skin patch: 2.5-5.0 mg/day (or up to 7.5 mg/day) Testosterone gel: 3-6 g/day
For fertility: hCG three times weekly, or hCG + either FSH or menopausal gonadotropin or GnRH
FSH/LH (in females)
Conjugated estrogen: 0.3-0.625 mg/day Micronized estradiol: 1 mg/day Estradiol valerate: 2 mg Piperazine estrone sulfate: 1.25 mg Estradiol skin patch: 4-8 mg twice weekly
All of the estrogens are administered with progesterone or progestin sequentially or in combination if uterus is present
For fertility: Menopausal gonadotropin, and hCG, or GnRH
Growth hormone
Somatotropin (in adults): 0.2-1.0 mg/day SC Somatotropin (in children): 0.02-0.05 mg/kg per day
Vasopressin
Intranasal desmopressin: 10-20 μg bid Oral DDAVP: 300-600 μg/day, usually in divided doses

ACTH, Adrenocorticotropic hormone; *DDAVP,* desmopressin acetate; *FSH,* follicle-stimulating hormone; *GnRH,* gonadotropin-releasing hormone; *hCG,* human chorionic gonadotropin; *LH,* luteinizing hormone; *T4,* thyroxine; *TSH,* thyroid-stimulating hormone.

From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders, Elsevier Inc.

NONPHARMACOLOGIC THERAPY

- IV fluid resuscitation, correction of electrolyte and metabolic abnormalities with potassium bicarbonate, and oxygen therapy.
- Transsphenoidal surgery for tumors causing specific symptoms.
- Radiation or stereotactic radiosurgery ("gamma knife") for medically unresponsive, surgically unresectable tumors and tumors for which other modalities are contraindicated. It is both safe and effective for recurrent or residual pituitary adenomas.

ACUTE GENERAL Rx

Acute situations such as adrenal crisis or myxedema coma can occur in untreated hypopituitarism and should be treated accordingly with IV corticosteroids (e.g., hydrocortisone 100 to 250 mg bolus followed by hydrocortisone 100 mg IV q6h for 24 hr) and levothyroxine (e.g., 5 to 8 mcg/kg IV over 15 min, then 100 mcg IV q24h).

CHRONIC Rx

Treatment is lifelong:

- Adrenocorticotropic hormone (ACTH) deficiency: hydrocortisone 10 mg PO every morning and 5 mg PO every evening or prednisone 5 mg PO every morning and 2.5 mg PO every evening. Dexamethasone or prednisone is often preferred because of longer duration of action.
- LH and FSH deficiency:
  1. In men, testosterone enanthate or propionate 200 to 300 mg IM every 2 to 3 wk, or transdermal testosterone scrotal patches can be tried.
  2. In women who are not interested in fertility, conjugated estrogen 0.3 to 1.25 mg/day and held the last 5 to 7 days of each month with the addition of medroxyprogesterone 10 mg/day given during days 15 to 25 of the normal menstrual cycle. In those who have secondary hypogonadism and wish to become pregnant, pulsatile gonadotropic-releasing hormone may be of benefit.
- TSH deficiency: levothyroxine 0.05 to 0.15 mg/day.
- GH deficiency:
  1. GH replacement in children is universally accepted.
  2. GH replacement in adults is not generally recommended and requires careful consideration of each individual case. It may have effects on quality of life, body composition, bone density, and cardiovascular risk factors.
  3. Side effects of replacement include peripheral edema, arthralgia, and headaches.
  4. Usual GH dose is between 0.2 and 0.4 mg, determined by the age and gender of a patient and increments of 0.1 mg every 2 to 4 wk until serum IGF-1 is in the upper part of the normal range. Young adults and women taking estrogen require a higher dose.

- ADH deficiency:
  1. Desmopressin (DDAVP) 10 to 20 mcg by intranasal spray or 0.05 to 0.1 mg PO bid is used in patients with diabetes insipidus.
  2. Vasopressin: 5-10 U given IM or SC q6h.

DISPOSITION

- Hormone replacement therapy is adjusted according to serum hormone monitoring.
- If untreated can lead to adrenal crisis, severe hyponatremia and hypothyroidism, metabolic abnormalities, and death.
- Complications: visual deficit, adrenal crisis, susceptibility to infection and other stressors.
- Prognosis: stable patients have a favorable prognosis with replacement hormone therapy. Patients with acute decompensation are in critical condition with a high mortality rate.

REFERRAL

Consultation with an endocrinologist and neurosurgeon for surgical treatment

PEARLS & CONSIDERATIONS

- All patients sustaining moderate to severe head injury should undergo assessment of anterior pituitary function during the acute phase and at 6 mo.
- IGF-1 can be used as a marker of GH deficiency.
- All tests of GH secretion are more likely to give false-positive results in obese patients.
- The GH axis is the most vulnerable to the effects of radiotherapy; doses as low as 18 Gy in children have caused GH deficiency.
- Sequence of hormonal disruption: GH secretion then gonadotropin secretion. TSH and adrenocorticotropic hormone secretion are somewhat resistant.
- Thyroxine supplementation increases the rate of cortisol metabolism and can lead to adrenal crisis, so corticosteroids should be replaced first.
- All patients receiving glucocorticoid replacement therapy should wear proper identification stating the need for this therapy.
- Stress doses of corticosteroids are indicated before surgery or for any medical emergency (e.g., sepsis, acute myocardial infarction).
- Antidiuretic hormone deficiency may be masked if there is ACTH deficiency with symptoms only appearing when cortisol has been replaced.

COMMENTS

- Mineralocorticoid replacement is not necessary in secondary adrenal insufficiency because the renin-angiotensin-aldosterone system is unaffected by pituitary failure.
- Patients with adult-acquired GH deficiency must meet at least two criteria before replacement therapy: a poor GH response to at least two standard stimuli and hypopituitarism from pituitary or hypothalamic damage. The criteria are different in children in whom GH is required for normal growth.
- Prevention of acute decompensation can be accomplished by reminding patients to increase the dose of hydrocortisone in response to stress.
- Medical therapy should precede surgical therapy.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hypopituitarism (Patient Information)

AUTHOR: **SHAHNAZ PUNJANI, M.D.**

SUGGESTED READINGS

American Association of Clinical Endocrinologists: Medical guidelines for clinical practice for growth hormone use in adults and children—2003 update, *Endocr Pract* 9:64, 2003.

Hanberg A: Common disorders of the pituitary gland: hyposecretion versus hypersecretion, *J Infus Nurs* 28(1):36, 2005.

Schneider HJ et al.: Hypopituitarism, *Lancet* 369:1461, 2007.

Sheehan JP et al.: Stereotactic radiosurgery for pituitary adenomas: an intermediate review of its safety, efficacy, and role in the neurosurgical treatment armamentarium, *J Neurosurg* 102(4):678, 2005.

Tagwood A: Hypopituitarism: clinical features, diagnosis, and management, *Endocrinol Metab Clin North Am* 37:235, 2008.

BASIC INFORMATION

DEFINITION

Hypospadias is a developmental abnormality of the penis characterized by:

- Abnormal ventral opening of the urethral meatus anywhere from the ventral aspect of the glans penis to the perineum
- Ventral curvature of the penis (chordee)
- Dorsal foreskin hood

ICD-9CM CODES
752.61 Hypospadias
752.63 Congenital chordee
ICD-10CM CODES
Q54.1 Hypospadias, penile
Q54.2 Hypospadias, penoscrotal
Q54.3 Hypospadias, perineal
Q54.8 Other hypospadias
Q54.9 Hypospadias, unspecified
Q54.4 Congenital chordee

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: One male in 250
GENETICS:

- Pertinent familial aspects of hypospadias include the finding of hypospadias in 6.8% of fathers of affected boys and in 14% of male siblings.
- An 8.5-fold higher rate of hypospadias is reported in monozygotic twins, suggesting insufficient production of human chorionic gonadotropin (hCG) by the single placenta.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Genetics: normal karyotypes are seen with glandular hypospadias; abnormal karyotypes are noted in more severe forms of hypospadias
- Cryptorchidism: 8% to 9% occurrence
- Inguinal hernia: 9% to 10% occurrence
- Hydrocele: 9% to 16% occurrence

PENILE CURVATURE (CHORDEE): Three theories:

1. Abnormal development of the urethral plate
2. Abnormal fibrotic mesenchymal tissue at the urethral meatus
3. Corporal disproportion

ETIOLOGY

Multifactorial:

- Endocrine factors:
  1. Abnormal androgen production
  2. Limited androgen sensitivity in the target tissues
  3. Premature cessation of androgenic stimulation as a result of Leydig cell dysfunction
  4. Insufficient dihydrotestosterone synthesis as a result of deficient 5-alpha reductase enzyme activity
- Arrested development

DIAGNOSIS

WORKUP

Made by observation and examination (Fig. EH1-90)

LABORATORY TESTS

Intersex evaluation should be undertaken if there is associated cryptorchidism. The evaluation should include ultrasound; genitographic studies; and chromosomal, gonadal, biochemical, and molecular studies.

TREATMENT

ACUTE GENERAL Rx

DESIGNATION/CLASSIFICATION:

- Anterior: 33%
- Middle: 25%
- Posterior: 41%

SPECIAL CONSIDERATIONS:

- The major reason for operating on any patient with hypospadias is to correct deformities that interfere with the function of urination and procreation.
- Another reason for intervention is cosmetic concern.
- The American Academy of Pediatrics recommends the best time for surgical intervention to be 6 to 12 mo.

HORMONAL MANIPULATION

- Controversial
- hCG administration is given before repair of proximal hypospadias.
- The effect of hCG administration is decreased hypospadias and chordee severity in all patients, increased vascularity and thickness of the proximal corpus spongiosum.
- Application of topical testosterone increases mean penile circumference and length without any lasting side effects.
- Prepubertal exogenous testosterone does not adversely affect ultimate penile growth.

CHRONIC Rx

Surgical Procedures

- Orthoplasty (correcting penile curvature)
- Urethroplasty
- Meatoplasty
- Glanuloplasty
- Skin coverage

There is no single universally acceptable applicable technique for hypospadias repair.

TYPES OF REPAIR

- Anterior hypospadias: MAGPI, Thiersch-Duplay urethroplasty, glans approximation procedure, tubularized incised plate (TIP) urethroplasty, Mathieu perimeatal flap, Mustarde technique, megameatus intact prepuce, pyramid procedure
- Midlevel hypospadias: TIP, Mathieu flap, onlay island flap (OIF), King procedure
- Posterior hypospadias:
  1. One-stage repair: OIF, double-onlay preputial flap, pedicled preputial flap, transverse preputial island flap
  2. Two-stage repair: orthoplasty to correct chordee followed 6 mo later or longer by Thiersch-Duplay, bladder and/or buccal mucosal hypospadias repair

COMPLICATIONS OF REPAIR: Hematoma, meatal stenosis, fistula, urethral stricture, urethral diverticulum, wound infection, impaired healing, balanitis xerotica obliterans, penile curvature

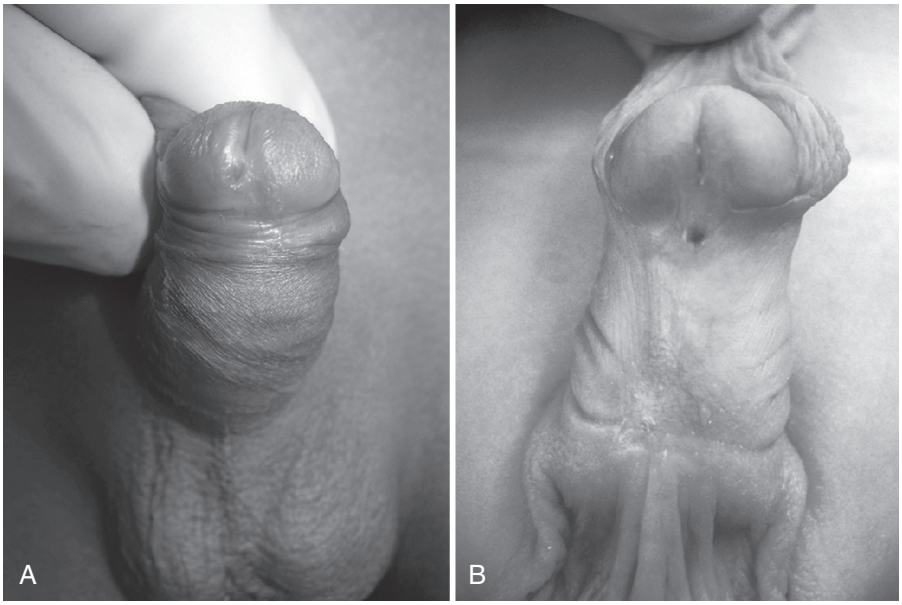

FIGURE EH1-90 Varying forms of hypospadias. A, Glanular hypospadias. **B,** Subcoronal hypospadias. Note the dorsal hood of foreskin. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

PEARLS & CONSIDERATIONS

- Apparent simple isolated hypospadias may be the only visible indication of an underlying abnormality.
- The dorsal hood of redundant foreskin is used in the repair of hypospadias, so the patient with hypospadias and a dorsal hood should not be circumcised.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hypospadias (Patient Information)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

American Academy of Pediatrics: Timing of elective surgery on the genitalia of male children with particular reference to the risks, benefits, and psychological effects of surgery and anesthesia, *Pediatrics* 97:590, 1996.

Belman AB: Hypospadias update, *Urology* 49:166, 1997.

Borer JG, Retik AB: Current trends in hypospadias repair, *Urol Clin North Am* 26(1):15, 1999.

Retik A.B.; Borer J.G. Hypospadias. In: (editor: Walsh P.C.; et al.) *Campbell's urology*. ed 8 Saunders: Philadelphia.

Zaontz MR, Packer MG: Abnormalities of the external genitalia, *Pediatr Clin North Am* 44:1267, 1997.

BASIC INFORMATION

DEFINITION

Hypothermia is a rectal temperature <35° C (95.8° F). Accidental hypothermia is an unintentionally induced decrease in core temperature in the absence of preoptic anterior hypothalamic conditions.

ICD-9CM CODES
991.6 Accidental hypothermia
ICD-10CM CODES
T68 Hypothermia

EPIDEMIOLOGY & DEMOGRAPHICS

- Hypothermia occurs most frequently in the following groups: alcoholics; learning-impaired; patients with cardiovascular, cerebrovascular, or pituitary disorders; those using sedatives or tranquilizers; and elderly patients.
- >700 persons in the United States die from hypothermia annually.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The clinical presentation varies with the severity of hypothermia. Shivering may be absent if body temperature is <33.3° C (92° F) or in patients taking phenothiazines.

Hypothermia may masquerade as cerebrovascular accident, ataxia, or slurred speech, or the patient may appear comatose or clinically dead. Signs of hypothermia are summarized in Box EH1-13.

Physiologic stages of hypothermia:

1. Stage HT I: Mild hypothermia (typical core temperature 32.2° to 35° C [90° to 95° F]): arrhythmias, ataxia
2. Stage HT II: Moderate hypothermia (core temperature 28° to 32.2° C [82.4° to 90° F]):
   a. Progressive decrease of level of consciousness, pulse, cardiac output, and respiration
   b. Fibrillation, dysrhythmias (increased susceptibility to ventricular tachycardia)
   c. Elimination of shivering mechanism for thermogenesis
3. Stage HT III: Severe hypothermia (core temperature ≤28° C to 24° C [82.4° F to 75° F]):
   a. Absence of reflexes or response to pain
   b. Decreased cerebral blood flow, decreased CO_2
   c. Increased risk of ventricular fibrillation or asystole
   d. Vital signs present
4. Stage IV: No vital signs (core temperature < 24° C [75° F])

ETIOLOGY

Exposure to cold temperatures for a prolonged period. Contributing factors include:

1. Drugs: ethanol, phenothiazines, sedative-hypnotics
2. Skin disorders: extensive burns, severe psoriasis, exfoliative dermatitis
3. Metabolic disorders: hypopituitarism, hypothyroidism, hypoadrenalism
4. Neurologic abnormalities: stroke, head trauma, acute spinal cord transection, impaired shivering
5. Other: lack of acclimatization, aggressive fluid resuscitation, sepsis, heat stroke treatment
6. Box EH1-14 summarizes factors predisposing to hypothermia

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- It is crucial to determine an accurate core temperature measurement. Advantages and considerations of various methods to determine core temperature are summarized in Table H1-62.
- Cerebrovascular accident
- Myxedema coma
- Drug intoxication
- Hypoglycemia

LABORATORY TESTS

1. Metabolic and respiratory acidosis are usually present.
   a. When blood cools, the arterial pH increases, oxygen tension (Po_2) increases, and the Pco_2 falls:
      (1). pH increases 0.008 U/° F (or 0.015 U/° C), causing a decrease in temperature.
      (2). Pao_2 increases 3.3%/° F, causing a decrease in temperature. Oxygenation considerations during hypothermia are described in Box H1-15.
      (3). $Paco_2$ decreases 2.4%/° F, causing a decrease in temperature.
   b. Blood gas analyzers warm the blood to 37° C, increasing the partial pressure of dissolved gases, resulting in higher oxygen and carbon dioxide levels and a lower pH than the patient's actual values. Correction of arterial blood gases for temperature is unnecessary as a guide to therapy. The use of uncorrected values also permits reference to the standard acid–base nomograms.
2. A decrease in K^+ initially, then an increase in K^+ with increasing hypothermia; extreme hyperkalemia indicates a poor prognosis.
3. Hematocrit increases (caused by hemoconcentration), decreasing leukocytes and platelets (caused by splenic sequestration).
4. Blood viscosity, increased clotting time

TABLE H1-62 Core Temperature Measurements

Type	Advantages	Considerations
Rectal	Convenient	Insert 15 cm (6 inches)
	Continuous monitoring	Lags during transition from cooling to rewarming
		Falsely elevated with peritoneal lavage
		Falsely low if probe is in cold feces or when lower extremities are frozen
Esophageal	Convenient	Insert 24 cm (9.5 inches) below larynx
	Continuous monitoring	Tracheal misplacement
		Aspiration
		Falsely elevated with heated inhalation
Tympanic	Approximates hypothalamic temperature via internal carotid artery	Probe: tympanic membrane perforation; canal hemorrhage Infrared: unreliable; cerumen effect
Bladder	Convenient	Unreliable
	Continuous monitoring	Falsely elevated with peritoneal lavage
		Falsely low with cold diuresis

From Auerbach P: *Wilderness medicine, expert consult* Premium Edition—Enhanced Online Features and Print, Philadelphia, 2012, Saunders.

BOX H1-15 Oxygenation Considerations During Hypothermia

Detrimental Factors
Oxygen consumption increases with rise in temperature; caution if rapid rewarming; shivering also increases demand
Decreased temperature shifts oxyhemoglobin dissociation curve to the left
Ventilation-perfusion mismatch; atelectasis; decreased respiratory minute volume; bronchorrhea; decreased protective airway reflexes
Decreased tissue perfusion from vasoconstriction; increased viscosity
"Functional hemoglobin" concept: capability of hemoglobin to unload oxygen is lowered
Decreased thoracic elasticity and pulmonary compliance

Protective Factors
Reduction of oxygen consumption: 50% at 28° C (82.4° F); 75% at 22° C (71.6° F); 92% at 10° C (50° F)
Increased oxygen solubility in plasma
Decreased pH and increased $Paco_2$ shift oxyhemoglobin dissociation curve to right

From Auerbach P: *Wilderness medicine,* ed 4, St Louis, 2001, Mosby.

FIGURE H1-91 Hypothermic J waves (Osborne waves) *(arrows)* in an 80-year-old man with core temperature of 86° F (30° C). These waves disappeared with rewarming. (From Morse CD, Rial WY: Emergency medicine. In Rakel RE [ed]: *Textbook of family practice,* ed 4, Philadelphia, 1990, Saunders.)

BOX H1-16 Preparing Hypothermic Patients for Transport

1. The patient must be dry. Gently remove or cut off wet clothing, and replace it with dry clothing or a dry insulation system. Keep the patient horizontal, and do not allow exertion or massage of the extremities.
2. Stabilize injuries (i.e., the spine; place fractures in the correct anatomic position). Open wounds should be covered before packaging.
3. Initiate heated intravenous infusions (IVs) if feasible; bags can be placed under the patient's buttocks or in a compressor system. Administer a fluid challenge.
4. Active rewarming should be limited to heated inhalation and truncal heat. Insulate hot water bottles in stockings or mittens, and then place them in the patient's axillae and groin.
5. The patient should be wrapped. Begin building the wrap by placing a large plastic sheet on the available surface (floor, ground), and on it place an insulated sleeping pad. A layer of blankets, a sleeping bag, or bubble wrap insulating material is laid over the sleeping pad. The patient is then placed on the insulation. Heating bottles are put in place along with IVs, and the entire package is wrapped layer over layer, with the plastic as the final closure. The patient's face should be partially covered, but a tunnel should be created to allow access for breathing and monitoring.

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IMAGING STUDIES

- Chest x-ray: generally not helpful; may reveal evidence of aspiration (e.g., intoxicated patient with aspiration pneumonia)
- ECG: prolonged PR, QT, and QRS segments, depressed ST segments, inverted T waves, atrioventricular block, and hypothermic J waves (Osborne waves) may appear at 25° to 30° C; characterized by notching of the junction of the QRS complex and ST segments (Fig. H1-91).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Treatment of hypothermia varies with the following:
  1. Degree of hypothermia
  2. Existence of concomitant diseases (e.g., cardiovascular insufficiency)
  3. Patient's age and medical condition (e.g., elderly, debilitated patients vs. young, healthy patients)
- General measures:
  1. Secure an airway before warming all unconscious patients; precede endotracheal intubation with oxygenation (if possible) to minimize the risk of arrhythmias during the procedure.
  2. Peripheral vasoconstriction may impede placement of a peripheral intravenous catheter; consider femoral venous access as an alternative to the jugular or subclavian sites to avoid ventricular stimulation.
  3. A Foley catheter should be inserted, and urinary output should be monitored and maintained >0.5 to 1 ml/kg/hr with intravascular volume replacement.
  4. Box H1-16 summarizes measures for preparing hypothermic patients for transport.

ACUTE GENERAL Rx

- Continuous ECG monitoring of patients is recommended. Ventricular arrhythmias can be treated with bretylium; lidocaine is generally ineffective, and procainamide is associated with an increased incidence of ventricular fibrillation in hypothermic patients.
- Correct severe acidosis and electrolyte abnormalities.
- Hypothyroidism, if present, should be promptly treated (see "Myxedema Coma").
- If clinical evidence suggests adrenal insufficiency, administer IV methylprednisolone.

In patients unresponsive to verbal or noxious stimuli or with altered mental status, 100 mg of thiamine, 0.4 mg of naloxone, and 1 ampule of 50% dextrose may be given.

Warm (104° to 113° F [40° to 45° C]), humidified oxygen should also be given if available.

Specific treatment:

1. Mild hypothermia (rectal temperature <32.3° C [90° F]): passive external rewarming is indicated. Place the patient in a warm room (temperature >21° C [69.8° F]), and cover with insulating material after gently removing wet clothing; recommended rewarming rates vary between 0.5° and 20° C/hr but should not exceed 0.55° C/hr in elderly persons.
2. Moderate to severe hypothermia:
   a. Active core rewarming
      (1). Delivery of heat by way of fluids: warm gastrointestinal irrigation (with saline enemas and by nasogastric tube); IV fluids (usually D_5NS without potassium) warmed to 104° to 107.6° F (40° to 42° C), peritoneal dialysis with dialysate heated to 40.5° to 42.5° C.
      (2). Inhalation of heated, humidified oxygen (warmed to 40° C [104° F]) increases core temperature by 1° C (1.8° F) per hr and decreases evaporative heat loss from respiration.
3. Active external rewarming: immersion in a bath of warm water (40° to 41° C); active external rewarming may produce shock because of excessive peripheral vasodilation. Ideal candidates are previously healthy, young patients with acute immersion hypothermia.
4. Extracorporeal blood warming with cardiopulmonary bypass appears to be an efficacious rewarming technique in young, otherwise healthy persons.
5. Patients with cardiac instability and those in cardiac arrest should be transported to a center capable of providing extracorporeal membrane oxygenation (ECMO) unless other conditions (e.g., trauma) require transport to a closer facility.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hypothermia (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Brown DJA et al.: Accidental hypothermia, *N Engl J Med* 367:1830–1838, 2012.

McCullough L, Arora S: Diagnosis and treatment of hypothermia, *Am Fam Physician* 70:2325, 2004.

BOX EH1-13 Signs of Hypothermia

Head, Eye, Ear, Nose, Throat
- Mydriasis
- Decreased corneal reflexes
- Extraocular muscle abnormalities
- Erythropsia
- Flushing
- Facial edema
- Epistaxis
- Rhinorrhea
- Strabismus

Cardiovascular
- Initial tachycardia
- Subsequent tachycardia
- Arrhythmias
- Decreased heart tones
- Hepatojugular reflux
- Jugular venous distention
- Hypotension
- Peripheral vasoconstriction

Respiratory
- Initial tachypnea
- Adventitious sounds
- Bronchorrhea
- Progressive hypoventilation
- Apnea

Gastrointestinal
- Ileus
- Constipation
- Abdominal distention or rigidity
- Poor rectal tone
- Gastric dilation in neonates or in adults with myxedema
- Vomiting

Genitourinary
- Anuria
- Polyuria
- Oliguria
- Testicular torsion

Neurologic
- Depressed level of consciousness
- Ataxia
- Dysarthria
- Amnesia
- Anesthesia
- Areflexia
- Poor suck reflex
- Hypoesthesia
- Antinociception
- Initial hyperreflexia
- Hyporeflexia
- Central pontine myelinolysis

Psychiatric
- Impaired judgment
- Perseveration
- Mood changes
- Peculiar “flat” affect
- Altered mental status
- Paradoxical undressing
- Neuroses
- Psychoses
- Suicide
- Organic brain syndrome
- Anorexia nervosa
- Depression
- Apathy
- Irritability

Musculoskeletal
- Increased muscle tone
- Shivering
- Rigidity or pseudo–rigor mortis
- Paravertebral spasm
- Opisthotonos
- Compartment syndrome

Dermatologic
- Erythema
- Pallor
- Cyanosis
- Icterus
- Scleral edema
- Ecchymosis
- Edema
- Pernio
- Frostnip
- Frostbite
- Panniculitis
- Cold urticaria
- Necrosis
- Gangrene

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BOX EH1-14 Factors Predisposing to Hypothermia

Decreased Heat Production

Endocrinologic Failure
- Hypopituitarism
- Hypoadrenalism
- Hypothyroidism
- Lactic acidosis
- Diabetic and alcoholic ketoacidosis

Insufficient Fuel
- Hypoglycemia
- Malnutrition
- Marasmus
- Kwashiorkor
- Extreme physical exertion

Neuromuscular Physical Exertion
- Age extremes
- Impaired shivering
- Inactivity
- Lack of adaptation

Impaired Thermoregulation

Peripheral Failure
- Neuropathies
- Acute spinal cord transection
- Diabetes

Central or Neurologic Failure
- Cardiovascular accident
- Central nervous system trauma
- Toxicologic effects
- Metabolic failure
- Subarachnoid hemorrhage
- Pharmacologic effects
- Hypothalamic dysfunction
- Parkinson disease
- Anorexia nervosa
- Cerebellar lesion
- Neoplasm
- Congenital intracranial anomalies
- Multiple sclerosis
- Hyperkalemic periodic paralysis

Increased Heat Loss

Environmental
- Immersion
- Nonimmersion

Induced Vasodilation
- Pharmacologic effects
- Toxicologic effects

Erythrodermas
- Burns
- Psoriasis
- Ichthyosis
- Exfoliative dermatitis

Iatrogenic
- Emergency childbirth
- Cold infusions
- Heatstroke treatment

Miscellaneous Associated Clinical States
- Multisystem trauma
- Recurrent hypothermia
- Episodic hypothermia
- Shapiro syndrome
- Infections: bacterial, viral, parasitic
- Pancreatitis
- Carcinomatosis
- Cardiopulmonary disease
- Vascular insufficiency
- Uremia
- Paget disease
- Giant cell arteritis
- Sarcoidosis
- Shaken baby syndrome
- Systemic lupus erythematosus
- Wernicke-Korsakoff syndrome
- Hodgkin’s disease
- Shock
- Sickle cell anemia
- Sudden infant death syndrome

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BASIC INFORMATION

DEFINITION

Hypothyroidism is a disorder caused by the inadequate secretion of thyroid hormone.

SYNONYMS

Myxedema

ICD-9CM CODES

244 Acquired hypothyroidism
243 Congenital hypothyroidism
244.1 Surgical hypothyroidism
244.3 Iatrogenic hypothyroidism
244.8 Pituitary hypothyroidism
246.1 Sporadic goitrous hypothyroidism

ICD-10CM CODES

E03.9 Hypothyroidism, unspecified
E00.9 Congenital iodine-deficiency syndrome, unspecified
E89.0 Postprocedural hypothyroidism
E03.2 Hypothyroidism due to medicaments and other exogenous substances
E01.8 Other iodine-deficiency related thyroid disorders and allied conditions
E07.1 Dyshormogenetic goiter

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE/PREVALENCE: 1.5% to 2% of women and 0.2% of men. Overall, about 1 in 300 persons in the United States has hypothyroidism.
PREDOMINANT AGE: Incidence of hypothyroidism increases with age; among persons older than 60 yr, 6% of women and 2.5% of men have laboratory evidence of hypothyroidism (thyroid-stimulating hormone [TSH] more than twice normal level).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Hypothyroid patients generally present with the following signs and symptoms: fatigue, lethargy, weakness, constipation, weight gain, cold intolerance, muscle weakness, slow speech, slow cerebration with poor memory.
- Skin: dry, coarse, thick, cool, sallow (yellow color caused by carotenemia); nonpitting edema in skin of eyelids and hands (myxedema) secondary to infiltration of subcutaneous tissues by a hydrophilic mucopolysaccharide substance. (Fig. EH1-92*A* and *B*)
- Hair: brittle and coarse; loss of outer third of eyebrows.
- Facies: dulled expression, thickened tongue, thick and slow-moving lips.
- Thyroid gland: may or may not be palpable (depending on the cause of the hypothyroidism).
- Heart sounds: distant, possible pericardial effusion.
- Pulse: bradycardia.
- Neurologic: delayed relaxation phase of the deep tendon reflexes, cerebellar ataxia, hearing impairment, poor memory, peripheral neuropathies with paresthesia.
- Musculoskeletal: carpal tunnel syndrome, muscular stiffness, weakness.

ETIOLOGY

1. Primary hypothyroidism (thyroid gland dysfunction): the cause of >90% of the cases of hypothyroidism
   - Hashimoto's thyroiditis is the most common cause of hypothyroidism after age 8 yr
   - Idiopathic myxedema (nongoitrous form of Hashimoto's thyroiditis)
   - Previous treatment of hyperthyroidism (radioiodine therapy, subtotal thyroidectomy)
   - Subacute thyroiditis
   - Radiation therapy to the neck (usually for malignant disease)
   - Iodine deficiency or excess
   - Drugs (lithium, para-aminosalicylate, sulfonamides, phenylbutazone, amiodarone, thiourea)
   - Congenital (approximately one case per 4000 live births)
   - Prolonged treatment with iodides
2. Secondary hypothyroidism: pituitary dysfunction, postpartum necrosis, neoplasm, infiltrative disease causing deficiency of TSH
3. Tertiary hypothyroidism: hypothalamic disease (granuloma, neoplasm, or irradiation causing deficiency of thyrotropin-releasing hormone)
4. Tissue resistance to thyroid hormone: rare

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Depression
- Dementia from other causes
- Systemic disorders (e.g., nephrotic syndrome, congestive heart failure, amyloidosis)

LABORATORY TESTS

- Increased TSH: TSH may be normal if patient has secondary or tertiary hypothyroidism, is receiving dopamine or corticosteroids, or the level is obtained after severe illness
- Decreased free T_4
- Other common laboratory abnormalities: hyperlipidemia, hyponatremia, and anemia
- Increased antimicrosomal and antithyroglobulin antibody titers: useful when autoimmune thyroiditis is suspected as the cause of the hypothyroidism
- Fig. EH1-92*C* describes a strategy for the laboratory evaluation of patients with suspected hypothyroidism

TREATMENT

NONPHARMACOLOGIC THERAPY

Patients should be educated regarding hypothyroidism and its possible complications. Patients should also be instructed about the need for lifelong treatment and monitoring of their thyroid abnormality.

ACUTE GENERAL Rx

Start replacement therapy with levothyroxine (L-thyroxine) 25 to 100 μg/day, depending on the patient's age and the severity of the disease. Physiologic combinations of L-thyroxine plus liothyronine do not offer any objective advantage over L-thyroxine alone. The levothyroxine dose may be increased every 6 to 8 wk, depending on the clinical response and serum TSH level. Elderly patients and patients with coronary artery disease should be started with 12.5 to 25 μg/day (higher doses may precipitate angina). The average maintenance dose of levothyroxine is 1.7 μg/kg/day (100 to 150 μg/day in adults). The elderly may require <1 μg/kg/day, whereas children generally require higher doses (up to 3 to 4 μg/kg/day). Pregnant patients also have increased requirements. Estrogen therapy may also increase the need for thyroxine. Women with hypothyroidism should increase their levothyroxine dose by approximately 30% as soon as pregnancy is confirmed. Close monitoring of serum thyrotropin levels and adjustment of levothyroxine dose is recommended throughout pregnancy. Table EH1-64 summarizes conditions that alter levothyroxine requirements.

CHRONIC Rx

- Periodic monitoring of TSH level is an essential part of treatment. Patients should be evaluated initially with office visit and TSH levels every 6 to 8 wk until the patient is clinically euthyroid and the TSH level is normalized. The frequency of subsequent visits and TSH measurement can then be decreased to every 6 to 12 mo. Pregnant patients should be checked every trimester.
- For monitoring therapy in patients with central hypothyroidism, measurement of serum free thyroxine (free T_4 level) is appropriate and should be maintained in the upper half of the normal range.

REFERRAL

Admission to the hospital intensive care unit is recommended in all patients with myxedema coma. Additional information on the diagnosis and treatment of this life-threatening complication of hypothyroidism is available under "Myxedema Coma" in Section I.

PEARLS & CONSIDERATIONS

COMMENTS

Subclinical hypothyroidism occurs in as many as 15% of elderly patients and is characterized by an elevated serum TSH and a normal free T_4 level. Subclinical hypothyroidism is associated with an increased risk of coronary heart disease events and mortality, particularly in those with a TSH concentration of 10 mU/L or greater. Treatment is individualized. In general, replacement therapy is recommended for all patients with serum TSH >10 mU/L and with presence of goiter or thyroid autoantibodies.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hypothyroidism (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Background:
Children born to women with low thyroid hormone levels have been reported to have decreased cognitive function.
Methods:
We conducted a randomized trial in which pregnant women at a gestation of 15 weeks 6 days or less provided blood samples for measurement of thyrotropin and free thyroxine (T_4). Women were assigned to a screening group (in which measurements were obtained immediately) or a control group (in which serum was stored and measurements were obtained shortly after delivery). Thyrotropin levels above the 97.5th percentile, free T_4 levels below the 2.5th percentile, or both were considered a positive screening result. Women with positive findings in the screening group were assigned to 150 μg of levothyroxine per day. The primary outcome was IQ at 3 years of age in children of women with positive results, as measured by psychologists who were unaware of the group assignments.
Results:
Of 21,846 women who provided blood samples (at a median gestational age of 12 weeks 3 days), 390 women in the screening group and 404 in the control group tested positive. The median gestational age at the start of levothyroxine treatment was 13 weeks 3 days; treatment was adjusted as needed to achieve a target thyrotropin level of 0.1 to 1.0 mIU per liter. Among the children of women with positive results, the mean IQ scores were 99.2 and 100.0 in the screening and control groups, respectively (difference, 0.8; 95% confidence interval [CI], −1.1 to 2.6; P = 0.40 by intention-to-treat analysis); the proportions of children with an IQ of less than 85 were 12.1% in the screening group and 14.1% in the control group (difference, 2.1 percentage points; 95% CI, −2.6 to 6.7; P = 0.39). An on-treatment analysis showed similar results.
Conclusions:
Antenatal screening (at a median gestational age of 12 weeks 3 days) and maternal treatment for hypothyroidism did not result in improved cognitive function in children at 3 years of age. Ⓐ
Current Controlled Trials Number:
ISRCTN46178175. Funded by the Wellcome Trust UK and Compagnia di San Paulo, Turin.

Abstract[2]

Context:
The incidence of postpartum thyroiditis (PPT) varies widely in the literature. Limited data exist concerning the hormonal status of women with PPT at the end of the first postpartum year.
Objective:
Our aim was to conduct a large prospective study of the incidence and clinical course of PPT.
Design:
A total of 4394 women were screened for thyroid function and thyroid autoantibodies at 6 and 12 months postpartum. Women were classified as being at high or low risk of having thyroid disease before any thyroid testing.
Setting:
The study was conducted at two ambulatory clinics in southern Italy, an area of mild iodine deficiency.
Patients:
A total of 4394 pregnant women were studied.
Intervention:
There was no intervention.
Main Outcome Measures:
We measured incidence, clinical presentation, and course of postpartum thyroiditis.
Results:
The incidence of postpartum thyroiditis was 3.9% (169 of 4384). Women classified as being at high risk for thyroid disease had a higher incidence of PPT than women classified as low risk (11.1 *vs.* 1.9%; odds ratio, 6.69; 95% confidence interval, 4.63, 9.68). Eighty-two percent of the 169 women with PPT had a hypothyroid phase during the first postpartum year. At the end of the first postpartum year, 54% of the 169 women had persistent hypothyroidism.
Conclusions:
One of every 25 women in southern Italy developed PPT. Women at high risk for thyroid disease have an increased rate of PPT. The high rate of permanent hypothyroidism at 1 yr should result in a reevaluation of the widely held belief that most women with PPT are euthyroid at the end of the first postpartum year. Ⓐ

Evidence-Based References

Lazarus JH et al.: Antenatal thyroid screening and childhood cognitive function, *N Engl J Med* 366:493–501, 2012. Ⓐ

Stagnaro-Green A et al.: High rate of persistent hypothyroidism in a large-scale prospective study of postpartum thyroiditis in southern Italy, *J Clin Endocrinol Metab* 96:652–657, 2011. Ⓐ

SUGGESTED READINGS

Escobar-Morreale HF et al.: Thyroid hormone replacement therapy in primary hypothyroidism: a randomized trial comparing L-thyroxine plus liothyronine with L-thyronine alone, *Ann Intern Med* 142:412, 2005.

Gaitonde DY et al.: Hypothyroidism: an update, *Am Fam Phys* 86(3):244–251, 2012.

Rodondi N et al.: Subclinical hypothyroidism and the risk of coronary heart disease and mortality, *JAMA* 304(12):1365–1374, 2010.

Rugge JB et al.: Screening and treatment of thyroid dysfunction: an evidence review for the U.S. Preventive Services Task Force, *Ann Intern Med* 162:35-45, 2015.

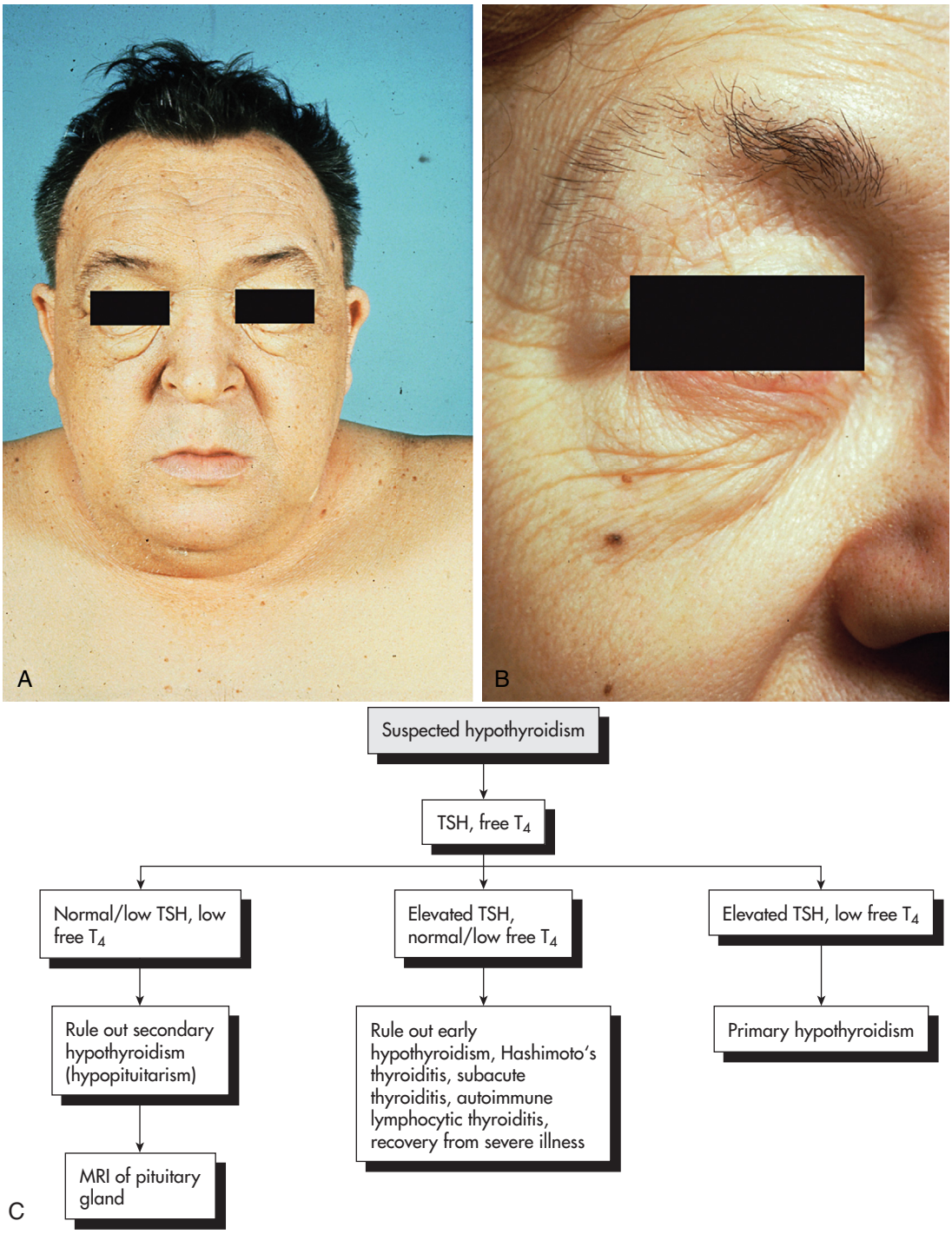


FIGURE EH1-92 **A** and **B,** Typical appearance of patients with moderately severe primary hypothyroidism or myxedema. Notice the dry skin and sallow complexion; absence of scleral pigmentation differentiates the carotenemia from jaundice. Both individuals demonstrate periorbital myxedema. The patient in **B** illustrates the loss of the lateral aspect of the eyebrow, sometimes termed *Queen Anne's sign.* That finding is not unusual in the age group that is commonly affected by severe hypothyroidism and should not be considered to be a specific sign of the condition. **C,** Strategy for the laboratory evaluation of patients with suspected hypothyroidism. The principal differential diagnosis is between primary and central hypothyroidism. The serum thyrotropin (TSH) concentration is the critical laboratory determination that, in general, allows recognition of the cause of the disease. An exception is the individual with a recent history of thyrotoxicosis (and suppressed TSH), in whom a low free thyroxine (T4) level may be associated with a reduced TSH level for several months after relief of the thyrotoxicosis. In patients with primary hypothyroidism, the absence of thyroid peroxidase (TPO) antibodies raises a possible diagnosis of transient hypothyroidism after an undiagnosed episode of subacute or postviral thyroiditis. In such patients, a trial of levothyroxine in reduced dosage after 4 months may reveal recovery of thyroid function, thus avoiding permanent levothyroxine replacement. *MRI,* Magnetic resonance imaging; *TRH,* thyrotropin-releasing hormone. (From Melmed S, et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

TABLE EH1-64 Conditions That Alter Levothyroxine Requirements

Increased Levothyroxine Requirements
Pregnancy
Gastrointestinal Disorders
Mucosal diseases of the small bowel (e.g., sprue)
After jejunoileal bypass and small-bowel resection
Impaired gastric acid secretion (e.g., atrophic gastritis)
Diabetic diarrhea
Drugs That Interfere with Levothyroxine Absorption
Cholestyramine
Sucralfate
Aluminum hydroxide
Calcium carbonate
Ferrous sulfate
Drugs That Increase the Cytochrome P450 Enzyme (CYP3A4) Activity
Rifampin
Carbamazepine
Estrogen
Phenytoin
Sertraline
Drugs That Block T_4-to-T_3 Conversion
Amiodarone
Conditions That May Block Deiodinase Synthesis
Selenium deficiency
Cirrhosis
Decreased Levothyroxine Requirements
Aging (≥65 yr)
Androgen therapy in women

T_4, Thyroxine; *T_3*, triiodothyronine.
From Melmed S, et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

BASIC INFORMATION

DESCRIPTION

ID reaction refers to an acute dermatitis developing at cutaneous sites distant from a primary inflammatory focus and is not explained by the inciting primary inflammation.

SYNONYMS

Autoeczematization

ICD-9CM CODES
692.89 Contact dermatitis and other eczema
ICD-10CM CODES
L30.2 Cutaneous autosensitization
L30.8 Other specified dermatitis
L30.9 Dermatitis, unspecified

EPIDEMIOLOGY

- Exact prevalence in the United States is unknown.
- Seen in all ages.
- Males and females are equally affected.
- No particular race or ethnicity is more vulnerable.

ETIOLOGY

Infection with dermatophytes, mycobacterium, histoplasma, viruses, bacteria, or parasites (e.g., lice).

- Dermatitis such as contact, stasis, or eczematous.
- Other causes include retained sutures, ionizing radiation, blunt trauma.

PATHOGENESIS

Unknown, but possible explanations include:

1. Abnormal immune recognition of autologous skin antigens.
2. Stimulation of normal T cells by altered skin constituents.
3. Lowering of the threshold for skin irritation.
4. Dissemination of infectious antigen resulting in a secondary response.
5. Hematogenous dissemination of cytokines from the primary site of inflammation.

CLINICAL FEATURES

- Usually associated with exacerbation of primary dermatitis.
- Characteristics of the rash in ID reaction include:
  1. Sudden onset of rash appearing within a week or two of primary inflammation.
  2. The rash could not be identified as a common dermatosis.
  3. Lesions are most commonly seen in the side of the fingers. However, ID reaction could be generalized. Particularly in patients with stasis dermatitis, it appears in forearms, thighs, legs, trunk, face (Fig. EI1-1), hands, neck, and feet in descending order of frequency.
  4. Extremely pruritic.
  5. Often symmetric in distribution.
  6. Most of the time it is vesicular.
- It resolves upon treatment of primary inflammation.

DIAGNOSIS

- It is a clinical diagnosis.
- Fungus when suspected could be isolated only from the primary site by using potassium hydroxide or by using fungal culture.
- At times skin biopsy is done. The biopsy findings are not pathognomonic for ID reaction. These include spongiotic epidermal vesicles associated with superficial perivascular lymphocytic infiltration of dermis, which may also contain scattered eosinophils. Most of the lymphocytes in the epidermis are CD3 and CD8 T cells, whereas those in the dermis are primarily CD4 cells.
- Patch testing may be considered to exclude primary or secondary allergic contact dermatitis.

FIGURE EI1-1 ID reaction. Papular eruption of the face associated with severe tinea infection of the hand. (From Kliegman RM.; et al. *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

DIFFERENTIAL DIAGNOSIS

- Atopic dermatitis.
- Contact dermatitis.
- Drug eruptions.
- Dyshidrotic eczema.
- Folliculitis.
- Scabies.
- Dermatophytic infection.
- Viral exanthema.

TREATMENT

- The treatment is best directed toward the inciting cause.
- Medications used for symptomatic treatment of ID reaction include:
  1. Local or systemic steroids.
  2. Local or systemic antihistamines.
  3. Topical or systemic antibiotics for secondary bacterial infection.
  4. Aluminum sulfate or calcium acetate for weeping skin lesions.
  5. Rarely, local or systemic macrolactams (e.g., cyclosporine).

COMPLICATIONS

Secondary bacterial infection.

PROGNOSIS

It almost always resolves within days when the primary dermatitis is adequately treated.

PATIENT EDUCATION

Treat primary dermatitis promptly.

AUTHOR: **HEMANT K. SATPATHY, M.D.**

BASIC INFORMATION

DEFINITION

Idiopathic intracranial hypertension (IIH) is a syndrome of increased intracranial pressure (ICP) without underlying hydrocephalus or mass lesion and with normal cerebrospinal fluid analysis.

SYNONYMS

Pseudotumor cerebri
IIH
Benign intracranial hypertension

ICD-9CM CODES
348.2 Pseudotumor cerebri
ICD-10CM CODES
G93.2 Benign intracranial hypertension

EPIDEMIOLOGY & DEMOGRAPHICS

- Disease of obese women in childbearing age

INCIDENCE

- General population: 1-2 per 100,000 (including children)
- Women (obese females in reproductive age group): 20 per 100,000
- Men: 0.3 to 1.5 cases per 100,000
- Female/male ratio 9:1
- More than 90% of IIH patients are obese
- Mean age at diagnosis is 30 yr

RISK FACTORS

- Obesity
- Medications: vitamin A and retinoids (used in treatment of acne and leukemia), chronic oral medications used for acne (tetracycline, minocycline)
- Systemic conditions: chronic kidney disease, polycystic ovarian syndrome, obstructive sleep apnea

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms:

- Headaches: generalized, throbbing, slowly progressive, worse with straining maneuvers, worse in the morning.
- Transient visual obscuration: a brief blurring of vision or scotomata lasting <30 sec; occurs with postural changes, Valsalva maneuver; may be monocular.
- Double vision: usually due to sixth nerve palsy.
- Pulsatile tinnitus: described as a "whooshing sound" that is synchronous with heartbeat; classic symptom that indicates raised ICP.
- Photopsia: lights, sparkles in the eyes.
- Pain: mainly retro-orbital. Pain may also be located in the shoulders or neck. Could be present without a headache. May be associated with Lhermitte's sign.

Signs

- Papilledema: seen in virtually all cases; usually bilateral but may be asymmetric
- Sixth nerve palsy: seen in approximately 10% to 20% of patients
- Visual field defects: include enlarged physiologic blind spot, nasal field defects, and constricted visual fields. Ninety percent of patients exhibit some form of visual loss on perimetry.
- Loss of central vision: end result of long-standing and untreated IIH

ETIOLOGY

- The exact etiology remains unknown.
- Proposed pathophysiologic mechanisms underlying the raised ICP include increased brain water content, excess CSF production, reduced CSF absorption, and increased cerebral venous pressure either alone or in combination.
- Another proposed mechanism includes abnormal vitamin A metabolism leading to increased CSF retinol levels and decreased CSF absorption at the arachnoid granulations.

DIAGNOSIS

DIAGNOSTIC CRITERIA

MODIFIED DANDY CRITERIA FOR DIAGNOSIS OF IIH:

- Signs and symptoms of raised ICP (listed above)
- Absence of localizing focal neurologic signs (except 6th nerve palsy)
- CSF opening pressure of 25 cm H_2O or more with normal CSF composition
- Normal neuroimaging studies (MRI and MRV brain) including absence of cerebral venous thrombosis; stenosis of transverse sinuses may be seen in IIH without thrombosis.

DIFFERENTIAL DIAGNOSIS

- IIH is a diagnosis of exclusion and criteria listed above have to be satisfied.
- Causes of papilledema include intracranial space-occupying lesions such as tumors, abscesses, hematoma; venous sinus thrombosis; low CSF pressure; carcinomatous meningitis; chronic meningitides such as neurosarcoidosis, CNS lupus, neurosyphilis, cryptococcal meningitis, and tuberculous meningitis.

WORKUP

- Neuroimaging studies: MRI of brain with MR venogram; CT head and CT head venogram when MRI of brain cannot be obtained.
- Lumbar puncture: CSF opening pressure (OP) should be obtained in the lateral decubitus position with the legs stretched and patient relaxed. OP exceeding 25 cm H_2O is considered elevated. CSF composition should be normal.
- Ophthalmologic examination: all patients with IIH need an ophthalmologic examination including visual fields at baseline and follow-up visits.

LABORATORY TESTS

CSF analysis shows normal protein, glucose, and cell count.

IMAGING STUDIES

- MRI of the brain to rule out underlying structural lesions
  1. Absence of specific causes of raised ICP listed above
  2. Empty sella sign often associated with chronic raised ICP but not pathognomonic
- MR or CT venography to exclude cortical venous thrombosis
  1. May show transverse sinus stenosis in IIH without thrombosis. Absence of specific causes of raised ICP listed above.
- CT head
  1. May show slit-like ventricles

TREATMENT

NONPHARMACOLOGIC THERAPY

- Weight loss in obese patients
- Continuous positive airway pressure if obstructive sleep apnea is suspected

ACUTE GENERAL Rx

- Acetazolamide 250 mg to 4 g per day: reduces CSF production by inhibition of carbonic anhydrase, occasionally causing anorexia and resultant weight loss. Dose can be increased to a maximum of 4 g a day in resistant cases with visual loss.
- Furosemide 40 to 120 mg/day in divided doses: apparent mechanism of action is by reduced sodium transport, leading to decreased total CSF volume.
- Topiramate 100 to 400 mg/day: reported to be effective in treatment of IIH. It is a weak carbonic anhydrase inhibitor with weight loss as one of its primary side effects.
- Serial lumbar punctures: SHOULD NOT BE CONSIDERED AS STANDARD TREATMENT OF IIH. LP should be attempted in patients with severe headaches resistant to medical therapy. Goal is to reduce spinal fluid pressure to allow immediate reduction in headache severity. This treatment should be reserved for the most resistant cases and should be used as a conduit to future surgical intervention. Serial LP should not be used as treatment for IIH with progressive visual loss.

CHRONIC Rx

Surgical intervention is indicated in cases of treatment failure and progressive visual loss.

- Optic nerve fenestration: preferred for patients with visual loss and easily controlled headaches. Proposed mechanism is decompression of the optic nerve. Highly effective; however, has been associated with significant number of failure rates.
- CSF shunting: neurosurgical procedure; performed in patients with significant visual deterioration and difficult-to-control headaches. Provides rapid improvement in symptoms; however, reported to have significant rates of shunt revisions because of shunt malfunction.

DISPOSITION

- IIH is a potentially blinding condition, with severe vision loss in 5%-10% of patients; patients should be co-managed by neurologists and ophthalmologists (preferably by a neuro-ophthalmologist). Monthly follow-up is essential until visual fields stabilize.
- All patients with IIH should undergo MR or CT venography to rule out the possibility of venous sinus thrombosis.

REFERRAL

- Neuro-ophthalmologist for serial evaluation of visual fields and fundus photographs
- Nutritionist for weight loss
- General neurologist for the initial workup and eventual treatment of raised ICP

PEARLS & CONSIDERATIONS

COMMENTS

- IIH is a potentially blinding condition.
- IIH is a diagnosis of exclusion.
- IIH is a disease of young obese women.

PREVENTION

Maintenance of ideal body weight is one of the best preventive mechanisms for avoidance of IIH. However, it does occur in patients with normal body weight. In these cases there are no known preventable risk factors.

PATIENT & FAMILY EDUCATION

The combination of weight loss and medical therapy is highly effective in treatment of IIH. Given that most patients with IIH are young and otherwise healthy, high success rates can be accomplished.

SUGGESTED READINGS

Biousse V et al.: Update on the pathophysiology and management of idiopathic intracranial hypertension, *J Neurol Neurosurg Psychiatry* 83:488, 2012.

Friedman D, Jacobson D: Diagnostic criteria for idiopathic intracranial hypertension, *Neurology* 59:1492, 2002.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Diplopia (Section II, Differential Diagnosis)
Optic Atrophy (Section II, Differential Diagnosis)
Papilledema (Section II, Differential Diagnosis)

AUTHOR: **SACHIN KEDAR, M.B.B.S, M.D.**

BASIC INFORMATION

DEFINITION

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic fibrosing interstitial pneumonia with histopathologic characteristics of usual interstitial pneumonia (UIP) occurring in the absence of an identifiable cause of lung injury. Clinically, it is characterized by progressive parenchymal scarring and loss of pulmonary function.

SYNONYMS

Cryptogenic fibrosing alveolitis
IPF
Pulmonary fibrosis
Usual interstitial pneumonia

ICD-9CM CODES
516.3 Idiopathic pulmonary fibrosis
ICD-10CM CODES
J84.112 Idiopathic pulmonary fibrosis

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence: 7-16 cases/100,000 persons worldwide. Clinically IPF affects >50,000 people in the U.S. and accounts for 20-30% of interstitial lung diseases
- Most commonly presents in 5th and 6th decades
- More common in men than women
- More common in current and past smokers
- Familial forms account for 3% to 25% of cases. Genetic variants: include mutations in surfactant protein C and abnormal telomere shortening.
- No distinct geographic distribution; no clear racial predilection

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most present with gradual onset (>6 mo) of exertional dyspnea and nonproductive cough. Progressive dyspnea is usually the most prominent symptom. Cough affects up to 80% of patients with IPF, is frequently disabling, and lacks effective therapy.
- Fine bibasilar inspiratory crackles in >80% of patients, with progression upward as the disease advances.
- Clubbing is found in 25% to 50% of patients.
- Cyanosis and right heart failure (cor pulmonale) may occur late in the disease course.
- Extrapulmonary involvement rarely occurs. Fever and wheezing are rare and suggest alternative diagnosis.
- Fig. I1-2 is a chest radiograph showing diffuse bilateral lower lung perdominant reticular poacities in a patient with IPF.

ETIOLOGY

- Unknown
- Cigarette smoking, environmental exposure, and microaspiration have been associated with IPF.
- Aberrant tissue repair and fibrosis are believed to play a greater role in the pathogenesis than generalized inflammation. Immune system activation and increased vascular permeability contribute to the underlying pathology.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Sarcoidosis
- Drug-induced interstitial lung disease
- Pulmonary manifestations of collagen vascular diseases (e.g., rheumatoid arthritis [RA], systemic sclerosis)
- Hypersensitivity pneumonitis (HP)
- Occupational exposures (e.g., asbestos, silica) may cause pneumoconiosis that mimics IPF
- Other idiopathic interstitial pneumonias:
  1. Desquamative interstitial pneumonia (DIP)
  2. Respiratory bronchitis–interstitial lung disease (RB-ILD)
  3. Acute interstitial pneumonia (AIP)
  4. Nonspecific interstitial pneumonia (NSIP)
  5. Cryptogenic organizing pneumonia (COP)

WORKUP

- Almost all patients have abnormal chest radiograph at presentation, with bilateral reticular opacities most prominent in the periphery and lower lobes. Peripheral honeycombing may be seen.
- High-resolution CT scan shows patchy peripheral reticular abnormalities with intralobular linear opacities, irregular septal thickening, subpleural honeycombing, and may have ground-glass opacities.
- Pulmonary function testing shows restrictive pattern and reduced carbon monoxide diffusion into the lung.
- Six-minute walk test may show reduced exercise tolerance and/or exertional hypoxia.
- Laboratory abnormalities (nondiagnostic): mild anemia; increases in erythrocyte sedimentation rate, lactate dehydrogenase, C-reactive protein; low titer antinuclear antibody seen in up to 30% of patients.
- There is a limited role for bronchoalveolar lavage either in diagnosis or monitoring IPF.
- Gold standard for diagnosis is lung biopsy (open thoracotomy or video-assisted thoracoscopy). Hallmark features: heterogeneous distribution of parenchymal fibrosis against background of mild inflammation (UIP).
- Lung biopsy is critical to distinguish IPF from diseases with better prognosis and treatment options, especially in patients with any atypical features.

TREATMENT

- No proven treatment for at this time, although some recent data appear promising. Evaluation for participation in clinical trials of new therapies may be warranted.
- The antifibrotic agent pirfenidone showed a reduction in disease progression with acceptable side effect profile and was recently FDA approved for IPF
- Nintedanib, a tyrosine kinase inhibitor, has also shown a reduction in disease progression and has been FDA approved.
- In patients with advanced disease, treatment options include supportive care (pulmonary rehabilitation, supplemental oxygen, influenza and pneumococcal vaccination) and potential lung transplantation.
- Treatment of asymptomatic gastroesophageal reflux may be reasonable given association between pulmonary fibrosis and reflux or microaspiration.
- Lung transplantation is the only therapy shown to prolong survival in IPF. Posttransplant 5-yr survival for IPF patients is approximately 40%. Median survival time is longer after bilateral lung transplantation than single lung transplantation but is associated with more complications during the first year.
- Acute exacerbation of IPF, defined as worsening dyspnea (<1 mo), the presence of new opacities on radiograph, and the lack of evidence of infection, has an incidence of 10% to 57%. Progressive respiratory failure may require mechanical ventilation. Treatment

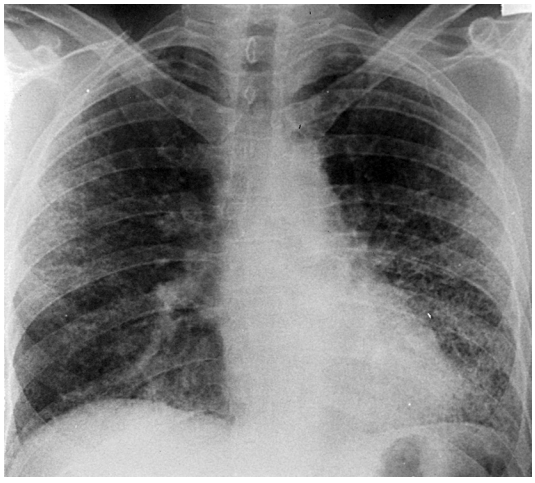


FIGURE I1-2 Chest radiograph shows diffuse bilateral lower lung predominant reticular opacities in a patient with idiopathic pulmonary fibrosis (IPF). (From Mason, RJ: *Murray & Nadel's textbook of respiratory medicine,* 5th ed, Philadelphia, 2010, Saunders.)

often includes high-dose corticosteroids and broad-spectrum antibiotics.

DISPOSITION

- Spontaneous remissions do not occur.
- Natural history includes progressive loss of pulmonary function.
- There is an increased risk of lung cancer.
- Mean survival after the diagnosis of biopsy-confirmed IPF is 2 to 5 yr.
- Respiratory failure is the most common cause of death.

REFERRAL

- To pulmonologist for review of abnormal chest imaging and establishing diagnosis
- Early referral for lung transplant

PEARLS & CONSIDERATIONS

- The course is progressive, with a high mortality rate.
- Among patients with IPF, a common risk polymorphism in MUC5B is associated with improved survival. Further research is necessary to refine the risk estimates and to determine the clinical implications of these findings.[1]
- Critical to differentiate IPF from other interstitial lung diseases because prognosis and response to treatment differ.
- Recent studies have shown an increase in mortality, hospitalizations, and side effects with combination treatment (prednisone/azathioprine/NAC). Trials involving thalidomide, a potent immunomodulary agent, have shown improvement in cough and respiratory quality of life.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

[1]Peljto AL et al: Association between the MUC5B promoter polymorphism and survival in patients with idiopathic pulmonary fibrosis, *JAMA* 309(21):2232-2239, 2013.

RELATED CONTENT

Idiopathic Pulmonary Fibrosis (Patient Information)

AUTHOR: **MICHAEL BLUNDIN, M.D.**

EVIDENCE

Abstract[1]

Rationale:
Several predictors of mortality in patients with idiopathic pulmonary fibrosis have been described; however, there is a need for a practical and accurate method of quantifying the prognosis of individual patients.

Objectives:
Develop a practical mortality risk scoring system for patients with idiopathic pulmonary fibrosis.

Methods:
We used a Cox proportional hazards model and data from two clinical trials (n=1,099) to identify independent predictors of 1-year mortality among patients with idiopathic pulmonary fibrosis. From the comprehensive model, an abbreviated clinical model comprised of only those predictors that are readily and reliably ascertained by clinicians was derived. Beta coefficients for each predictor were then used to develop a practical mortality risk scoring system.

Measurements and Main Results:
Independent predictors of mortality included age, respiratory hospitalization, percent predicted FVC, 24-week change in FVC, percent predicted carbon monoxide diffusing capacity, 24-week change in percent predicted carbon monoxide diffusing capacity, and 24-week change in health-related quality of life. An abbreviated clinical model comprising only four predictors (age, respiratory hospitalization, percent predicted FVC, and 24-week change in FVC), and the corresponding risk scoring system produced estimates of 1-year mortality risk consistent with observed data (9.9% vs. 9.7%; C statistic=0.75; 95% confidence interval, 0.71–0.79).

Conclusions:
The prognosis for patients with idiopathic pulmonary fibrosis may be accurately determined using four readily ascertainable predictors. Our simplified scoring system maybe a valuable tool for determining prognosis and guiding clinical management. Additional research is needed to validate the applicability and accuracy of the scoring system. Ⓐ

Evidence-Based Reference

Du Bois RM et al.: Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis, *Am J Respir Crit Care Med* 184:459–466, 2011. Ⓐ

SUGGESTED READINGS

Horton MR et al.: Thalidomide for the treatment of cough in idiopathic pulmonary fibrosis, *Ann Intern Med* 157:398–406, 2012.

King T et al: A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis, *N Engl J Med* 370: 2083-2092.

Raghu G et al.: An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: Evidence-based guidelines for diagnosis and management, *Am J Respir Crit Care Med* 183:788–824, 2011.

Richeldi L et al.: Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis, *N Engl J Med* 365:1179–1187, 2011.

Richeldi L et al.: Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis, *N Engl J Med* 370:2071–2082, 2014.

Thabut G et al.: Survival after bilateral versus single-lung transplantation for idiopathic pulmonary fibrosis, *Ann Intern Med* 151:767–774, 2009.

BASIC INFORMATION

DEFINITION

Immunoglobulin A (IgA) nephropathy is a proliferative glomerulonephritis associated with predominant deposition of IgA in the mesangium. The diagnostic hallmark of IgA nephropathy is the predominance of IgA deposits, either alone or with IgG, IgM, or both, in the glomerular mesangium.[1]

SYNONYMS

Berger's disease

ICD-9CM CODES
583.81 IgA Nephropathy
ICD-10CM CODES
N02.8 IgA nephropathy
N02.1 IgA nephropathy with glomerular lesion, focal and segmental hyalinosis or sclerosis
N02.3 IgA nephropathy with glomerular lesion, mesangial proliferative (diffuse)
N02.5 IgA nephropathy with glomerular lesion, membrane proliferative (diffuse)

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: It is the most common type of glomerulonephropathy worldwide. The annual incidence of IgA nephropathy among children in the United States is about 0.5 cases per 100,000; however, in Japan, the incidence is 10 times as high.[1]

PREVALENCE: Prevalence rate is lower in the United States (10% to 15%) compared with Asian countries. Lower rates could be explained by a conservative approach by nephrologists in the United States, who are reluctant to do renal biopsy in asymptomatic patients with minimal renal abnormalities. In most reports prevalence rates are expressed as a percentage of cases of primary glomerulonephritis or as a percentage of total series of renal biopsies.
PREDOMINANT SEX AND AGE: It is most prevalent in the second and third decades of life with a male/female ratio of 6:1 in the United States.
GENETICS: Although it is considered a sporadic disease, genetic linkage to locus called *IgAN1* on 6q22 and 6q23 has been shown.
RISK FACTORS: It has a higher association with Asians, whites, and Native Americans and is rarely seen in African Americans.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Two common presentations include (1) recurrent macroscopic hematuria often associated with upper respiratory infection and (2) persistent microscopic hematuria.
- Loin pain may be associated with macroscopic hematuria.
- Physical findings are usually unremarkable, except hypertension seen in 20% to 30% of patients with chronic disease and edema in 5% of patients with nephrotic-range proteinuria.
- Mild proteinuria is common.
- Rarely, IgA nephropathy presents as acute renal failure in 5% of patients and chronic renal failure in 10% to 20% of patients.

ETIOLOGY

- Most cases are idiopathic/primary.
- Secondary causes of IgA nephropathy include Henoch-Schönlein purpura; hepatitis B; alcoholic cirrhosis; celiac disease; inflammatory bowel disease; psoriasis; sarcoidosis; cystic fibrosis; cancer of the lungs, larynx, or pancreas; HIV infection; systemic lupus erythematosus; rheumatoid arthritis; diabetic nephropathy; Sjögren's syndrome; and Reiter's syndrome.
- Fig. I1-3 illustrates the pathogenesis of IgA nephropathy.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Henoch-Schönlein purpura.
- Hereditary nephritis.
- Thin glomerular basement membrane disease.
- Lupus nephritis.
- Poststreptococcal nephritis.
- Secondary causes associated with IgA nephropathy mentioned above.

WORKUP

- The diagnosis is suspected on the basis of clinical history and laboratory data but is confirmed by renal biopsy showing IgA deposits in the mesangium.
- Renal biopsy is restricted to patients with sustained proteinuria >1 g/day or worsening renal function.

LABORATORY TESTS

- Urine analysis showing protein, red blood cells and casts, and white blood cells.
- Serum creatinine may be elevated.
- 24-hour urine assay for quantifying proteinuria and to check creatinine clearance.
- Serum IgA is elevated in only 50% of patients and has no clinical utility.

TREATMENT

Although initially considered a benign disease, IgA nephropathy is now recognized as a common cause of renal failure. Currently there is no cure. Table I1-1 summarizes treatment recommendations for IgA nephropathy.

NONPHARMACOLOGIC THERAPY

- Moderate dietary protein restriction.
- Discourage smoking.

ACUTE AND CHRONIC GENERAL Rx

- Aggressive therapy for hypertension, preferably with angiotensin-converting enzyme (ACE) inhibitors. Goal blood pressure is <125/75 mm Hg in the presence of proteinuria >1 g/day.
- Patients with recurrent gross hematuria or isolated microscopic hematuria, no or minimal proteinuria (<1 g/day), normal blood pressure, and normal kidney function should only be monitored every 6 to 12 mo to assess disease progression.

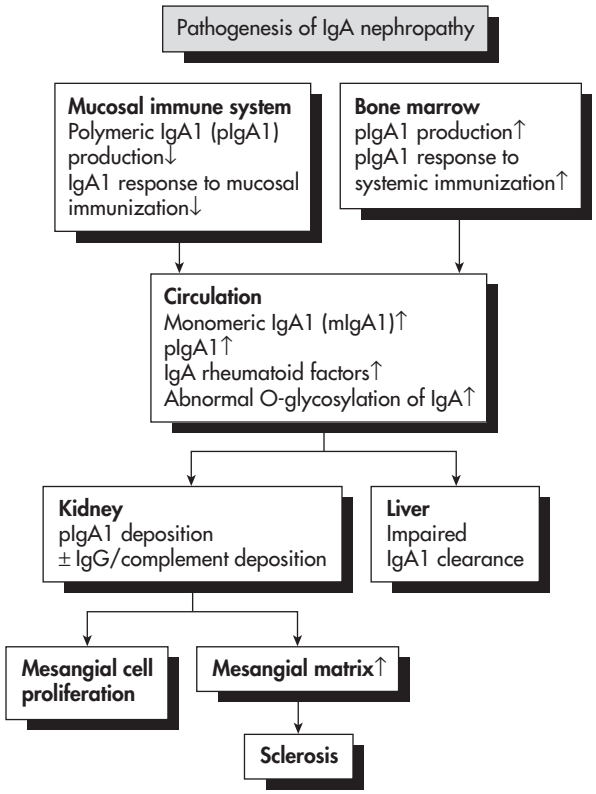


FIGURE I1-3 Pathogenesis of IgA nephropathy. Abnormalities in IgA immunity leading to mesangial IgA deposition and injury. (Modified from Johnson R, Feehally J: *Comprehensive clinical nephrology.* ed 2, St Louis, 2000, Mosby.)

[1]Wyatt RJ, Julian BA: IgA nephropathy, *N Engl J Med* 368:2402-2414, 2013.

- If bouts of recurrent macroscopic hematuria are associated with tonsillitis, tonsillectomy may benefit these patients.
- Patients with persistent proteinuria >1 g/day with or without hypertension are treated with ACE inhibitors and/or angiotensin receptor blockers (ARBs). Steroids are reserved for patients with persistent proteinuria >1 g/day despite ACE and/or ARB administration.
- Patients with nephrotic syndrome, preserved kidney function, and minimal change in disease are treated with steroids for 6 mo.
- Patients with severe renal disease or crescentic, rapidly progressive glomerulonephritis in the absence of changes of chronic kidney disease in biopsy are treated with steroid and cyclophosphamide combination for the first 2 mo, followed by steroids and azathioprine for 2 yr for maintenance treatment.
- Patients with acute renal failure need renal biopsy to rule out acute tubular necrosis, which needs only supportive therapy, from crescentic IgA nephropathy, which needs aggressive medical management.

TABLE I1-1 Treatment Recommendations for IgA Nephropathy

Recurrent Macroscopic Hematuria (Preserved Renal Function)

Aggressive hydration (no role for antibiotics or tonsillectomy).

Macroscopic Hematuria with Acute Kidney Injury

Renal biopsy mandatory if persistent acute kidney injury (see text).
Acute tubular necrosis: supportive measures only.
Crescentic IgA nephropathy.
Induction: Prednisolone 0.5-1 mg/kg/day for up to 8 wk.
Cyclophosphamide 2 mg/kg/day for up to 8 wk.
(no evidence favoring oral or intravenous route—follow local practice).
Maintenance: Prednisolone in reducing dosage.
Azathioprine 2.5 mg/kg/day.

Proteinuria >1 g/24 h (±Microscopic Hematuria)

ACE inhibitor or ARB for urinary protein excretion of >18/day; increase dose depending on blood pressure.

Nephrotic Syndrome with Minimal Change on Light Microscopy

Prednisolone 0.5-1 mg/kg/day (children 60 mg/m2/day) for up to 8 wk, then taper.

Non-nephrotic Proteinuria <1 g/24 h (±Microscopic Hematuria)

ACE inhibitor and/or ARB (maximize dosage or combine to achieve target BP and proteinuria <0.5 g/day).
If proteinuria still >1 g/24 h on maximal supportive therapy and GFR <70 ml/min, consider fish oil (12 g/daily for 6 mo). If further progression of renal failure, consider prednisolone (40 mg/day decreasing to 10 mg by 2 yr).

Hypertension

ACE inhibitors and ARB are agent of first choice—target BP: 130/80 mm Hg if proteinuria <1 g/24 h; 125/75 mm Hg if proteinuria >1 g/24 h

Transplantation

No special measures required

ACE, Angiotensin-converting enzyme; *ARB,* angiotensin receptor blocker; *BP,* blood pressure; *GFR,* glomerular filtration rate.
Modified from Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

BOX I1-1 Prognostic Markers at Presentation in IgA Nephropathy

Clinical
Poor Prognosis
Increasing age
Duration of preceding symptoms
Severity of proteinuria
Hyperuricemia
Hypertension
Renal impairment
Good Prognosis
Recurrent macroscopic hematuria
No Impact on Prognosis
Gender
Serum IgA level

Histopathologic
Poor Prognosis
Glomerular sclerosis
Tubular atrophy
Interstitial fibrosis
Vascular wall thickening
Capillary-loop IgA deposits
No Impact on Prognosis
Intensity of IgA deposits

None of the clinical or histopathologic adverse features, except capillary-loop IgA deposits, are specific to IgA nephropathy.
From Feehally J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

- Kidney transplantation is the treatment of choice for end-stage kidney disease. There is no difference in survival in living versus cadaver donors. At present, kidneys with IgA deposits are not used for transplantation.
- Statins are indicated for all IgA nephropathy patients with dyslipidemia, hypertension, and other cardiovascular risks.
- Role of mycophenolate and plasmapheresis is controversial.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Role of fish oil is controversial.

DISPOSITION

- Complete remission occurs in <10% of patients.
- End-stage renal failure develops in 15% to 20% of patients within 10 yr of onset and in 30% to 35% of patients within 20 yr. Prognostic markers at presentation in IgA nephropathy are described in Box I1-1.
- Poor prognostic indicators include (1) male gender, (2) older age, (3) young age at the onset of the disease, (4) absence of episodes of recurrent macroscopic hematuria, (5) hypertension, (6) extent of renal insufficiency, (7) extent of proteinuria, (8) elevated serum uric acid, and (9) certain histologic changes seen in renal biopsy, such as crescents, glomerulosclerosis, and tubulointerstitial fibrosis or atrophy.
- The serum level of glycan-specific IgG antibodies is correlated with the level of urinary protein excretion and the risk of progression to end-stage renal disease (ESRD) or death.[1]

REFERRAL

Patients with IgA nephropathy are commonly referred to nephrologists.

PEARLS & CONSIDERATIONS

COMMENTS

- IgA nephropathy seems to be a kidney-restricted form of Henoch-Schönlein purpura.
- IgA nephropathy is not an entirely benign condition, even when microhematuria is the only clinical presentation.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **HEMANT K. SATPATHY, M.D.**

SUGGESTED READINGS

Appel GB, Waldman M: The IgA nephropathy treatment dilemma, *Kidney Int* 69:1939, 2006.

Barratt J, Feehally J: Treatment of IgA nephropathy, *Kidney Int* 69:1934–1938, 2006.

BASIC INFORMATION

DEFINITION

Illness anxiety disorder (defined in DSM-5; previously hypochondriasis) is the preoccupation with the fear of having, or the idea that one has, a serious undiagnosed disease, despite a lack of significant corresponding somatic symptoms or medical evidence. Whether or not another medical diagnosis is present, the severity of health-related anxiety is clearly disproportionate to the individual's health status. Existing medical literature (including that referenced here) explores the previously defined disorder hypochondriasis; it is unknown exactly how that evidence applies to illness anxiety disorder.

SYNONYMS

Hypochondriasis

ICD-9CM and DSM-5 CODES
300.70
ICD-10CM CODES
F45.21 Hypochondriasis

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 1% to 5% (based on estimates of DSM-III and DSM-IV disorder hypochondriasis), but may be higher (3-10%) in primary care outpatient settings.
PREDOMINANT SEX: Equal frequency in men and women.
PREDOMINANT AGE: Onset at any age, but most commonly between ages 20 and 30 yr

GENETICS/RISK

No known genetic component. May be more common in less-educated individuals. A comorbid major mental disorder (e.g., generalized anxiety, obsessive-compulsive disorder, or depression) may affect over two-thirds of individuals with illness anxiety disorder; personality disorders and somatic symptom disorders may also be more common.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Somatic symptoms or signs are not present or are only mild; the focus of anxiety is the suspected medical diagnosis itself (i.e., concern for illness rather than symptoms per se).
- Mild somatic symptoms, if present, often include nonpathologic physical signs or sensations (e.g., belching, orthostatic lightheadedness).
- High health anxiety persists despite reassuring clinical evaluation (though without the intensity of a delusion).
- Illness anxiety symptoms often correlate with psychosocial stressors.
- Illness preoccupation lasts at least 6 mo (the specific illness feared may vary).
- Disruption in health-related quality of life and/or social, occupational, or other important areas of functioning.
- Two presentation types: care-seeking (medical attention frequently sought) and care-avoidant (maladaptive avoidance of health care).
- No specific physical examination findings.

ETIOLOGY

Unknown neurobiologic etiology. Serious childhood illness or trauma may be associated with illness anxiety disorder in adulthood.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Underlying medical condition
- Adjustment disorder (health-related anxiety in response to illness)
- Somatic symptom disorder (excessive distress related to somatic symptom[s])
- Body dysmorphic disorder (restricted to a circumscribed concern about appearance)
- Factitious disorder
- Malingering
- Generalized anxiety disorder with health concerns as one worry among others
- Major depressive disorder with health concerns occurring only during depressive episodes
- Psychosis, as may occur with depression and schizophrenia

WORKUP

- History, physical examination, age-appropriate screenings, and laboratory and imaging tests, as appropriate, to exclude underlying medical condition.
- Symptom measures (e.g., Health Anxiety Inventory) may be used for detection and monitoring of severity over time.
- Evaluation for other psychiatric disorders associated with illness anxiety such as depression and generalized anxiety.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Psychotherapy, especially cognitive behavioral therapy (CBT), is the mainstay of treatment, with techniques to alter or restructure maladaptive thinking and behavior. Individual or group CBT, behavioral stress management, and mindfulness-based approaches have demonstrated success.
- Regularly scheduled brief medical appointments not contingent on symptoms
- Avoidance of repeated or non–medically indicated diagnostic testing, referrals, or treatments
- Limit on reading medical texts or websites
- Benign interventions (e.g., exercise, massage)

CHRONIC Rx

- Antidepressants may be helpful even in individuals without features of depression: placebo-controlled trials of fluoxetine and paroxetine suggest benefit.
- Treatment of comorbid psychiatric conditions, if present.

DISPOSITION

Waxing and waning course over decades; recovery rates between 30% and 85%. Positive prognostic factors include shorter duration of illness anxiety and lack of comorbid psychiatric disorder.

REFERRAL

Referral for CBT is the mainstay of treatment; referral to a psychiatrist may be needed in the case of comorbid psychiatric condition.

PEARLS & CONSIDERATIONS

- Psychotherapy and pharmacotherapy may be helpful treatment modalities for individuals open to treatment not directed at the perceived illness.
- In the updated DSM-5, hypochondriasis and related conditions were replaced by two new concepts: somatic symptom disorder (somatic symptoms present, with significant related distress) and illness anxiety disorder (somatic symptoms absent or minimal; concern focused on the idea of illness).

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Somatization Disorder (Patient Information)
Somatization Disorder (Related Key Topic)

AUTHOR: **LUCY KALANITHI, M.D.**

SUGGESTED READINGS

American Psychiatric Association: Somatic symptom and related disorders. In *American Psychiatric Association: Diagnostic and statistical manual of mental disorders*, Arlington, VA, 2013, American Psychiatric Association. (Available at dsm.psychiatryonline.org. Accessed September 3, 2014.

Asmundson FJ et al.: Health anxiety: current perspectives and future directions, *Curr Psychiatry Rep* 12(4):306, 2010.

Barsky AJ, Ahern DK: Cognitive behavior therapy for hypochondriasis: a randomized controlled trial, *JAMA* 291:1464, 2004.

Fallon BA et al.: A double-masked, placebo-controlled study of fluoxetine for hypochondriasis, *J Clin Psychopharmacol* 28(6):638, 2008.

Fink P et al.: The outcome of health anxiety in primary care: a two-year follow-up study on health care costs and self-rated health, *PLoS One* 5(3):e9873, 2010.

Olde Hartman T et al.: Medically unexplained symptoms, somatisation disorder and hypochondriasis: course and prognosis, *J Psychosom Res* 66(5):363, 2009.

Thomson AB, Page LA: Psychotherapies for hypochondriasis, *Cochrane Database Syst Rev* 17(4):CD006520, 2007.

Immune Thrombocytopenic Purpura PTG

BASIC INFORMATION

DEFINITION

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder in which antibody-coated or immune complex–coated platelets are destroyed prematurely by the reticuloendothelial system, resulting in peripheral thrombocytopenia. In primary ITP the thrombocytopenia is isolated, whereas in secondary ITP the condition is associated with other disorders (e.g., SLE, HIV).

ICD-9CM CODES
287.3 Idiopathic thrombocytopenic purpura (ITP)
ICD-10CM CODES
D69.3 Immune thrombocytopenic purpura

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Primary ITP incidence is 10 in 100,000 adults, 5 in 100,000 children.
PREVALENCE: Five to 10 cases per 100,000 persons.
PREDOMINANT SEX: 72% of patients > 10 yr are female; in children, males and females are affected equally.
PREDOMINANT AGE: Children ages 2 to 4 yr and young women (70% are < 40 yr).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The presentation of ITP is different in children and adults:

- Children generally present with sudden onset of bruising and petechiae from severe thrombocytopenia.
- In adults the presentation is insidious; a history of prolonged purpura may be present; many patients are diagnosed incidentally on the basis of automated laboratory tests that now routinely include platelet counts.
- The physical examination may be entirely normal.
- Patients with severe thrombocytopenia may have petechiae, purpura, epistaxis, or heme-positive stool from gastrointestinal bleeding. Life-threatening bleeding is uncommon and generally confined to patients with platelets <10,000 per cubic mm.
- Splenomegaly is unusual; its presence should alert to the possibility of other etiologies of thrombocytopenia.
- The presence of dysmorphic features (skeletal anomalies, auditory abnormalities) may indicate a congenital disorder as the cause of the thrombocytopenia.

ETIOLOGY

Increased platelet destruction caused by autoantibodies to platelet-membrane antigens. Hundreds of medications can cause thrombocytopenia. Drugs commonly implicated are quinidine, heparin, antibiotics (linezolid, vancomycin, sulfonamides, rifampin), platelet inhibitors (tirofiban, abciximab, eptifibatide), cimetidine, NSAIDs, thiazide diuretics, antirheumatic agents (gold salts, penicillamine), acetaminophen, and chemotherapeutic agents (cyclosporine, fludarabine, oxaliplatin).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Falsely low platelet count (resulting from EDTA-dependent or cold-dependent agglutinins).
- Viral infections (e.g., HIV, hepatitis C, mononucleosis, rubella).
- Drug-induced (e.g., heparin, quinidine, sulfonamides).
- Hypersplenism resulting from liver disease.
- Myelodysplastic and lymphoproliferative disorders.
- Pregnancy, hypothyroidism.
- SLE, TTP, hemolytic-uremic syndrome.
- Congenital thrombocytopenia (e.g., Fanconi's syndrome, May-Hegglin anomaly, Bernard-Soulier syndrome)

LABORATORY TESTS

- Complete blood count, platelet count, and peripheral smear: platelets are decreased but are normal in size or may appear larger than normal (Fig. EI1-4). Red blood cells and white blood cells have a normal morphology.
- Additional tests may be ordered to exclude other causes of the thrombocytopenia when clinically indicated (e.g., HIV, ANA, TSH, liver enzymes, bone marrow examination).
- The direct assay for the measurement of platelet-bound antibodies has an estimated positive predictive value of 80% to 83%. A negative test cannot be used to rule out the diagnosis.

IMAGING STUDIES

CT scan of abdomen/pelvis in patients with splenomegaly to exclude other disorders causing thrombocytopenia

TREATMENT

NONPHARMACOLOGIC THERAPY

- Minimize activity to prevent injury or bruising (e.g., contact sports should be avoided).
- Stop any potentially offending drugs (see "Etiology"). Avoid medications that increase the risk of bleeding (e.g., aspirin and other NSAIDs).

ACUTE GENERAL Rx

- Treatment varies with the platelet count, patient's age, and bleeding status (Fig. I1-5).
- Observation and frequent monitoring of platelet count are needed in asymptomatic patients with platelet counts >30,000/mm^3.
- Oral prednisone 1 mg/kg/day in a tapering dose generally for 4 to 6 wk is the most common initial regimen. Methylprednisolone 30 mg/kg/day IV infused over a period of 20 to 30 min (maximum dose of 1 g/day for 2 or 3 days) plus IV immunoglobulin (1 g/kg/day for 2 or 3 days) and infusion of platelets should be given to patients with neurologic symptoms, internal bleeding, or those undergoing emergency surgery.
- Prednisone continued until the platelet count is normalized then slowly tapered off is indicated in adults with platelet counts <20,000/mm^3 and those who have counts <50,000/mm^3 and significant mucous membrane bleeding. Response rates range from 50% to 75%, and most responses occur within the first 3 wk. Oral dexamethasone at a dosage of 40 mg/day for 4 consecutive days has also been reported to induce a high response rate (85%). Continuation of corticosteroids is limited by long-term complications associated with its use (osteoporosis, weight gain, opportunistic infections, emotional lability)
- IV immunoglobulin (0.8 to 1.0 g/kg) is used in patients who have not responded to corticosteroids and often in pregnant patients. It rapidly increases platelet count in nearly 80% of patients, but its effect is transient. Anti-D immunoglobulin, a pooled IgG product derived from the plasma of Rh(D)-negative donors, is also effective. It can be given only to patients who are Rh(D) positive. Usual dose is 50 to 75 mcg/kg.
- Rituximab, a monoclonal antibody directed against the CD20 antigen, is used as a second-line agent. Usual dose is 375 mg/m^2 weekly × 4 wk.
- Splenectomy is considered second-line treatment and should be considered in adults with platelet count <20,000/mm^3 after 6 wk of medical treatment or after 6 mo if more than 10 to 20 mg of prednisone per day is required to maintain a platelet count >30,000/mm^3. In children, splenectomy is generally reserved for persistent thrombocytopenia (>1 yr) and clinically significant bleeding. Appropriate immunizations (pneumococcal vaccine in adults and children, *Haemophilus influenzae* vaccine, meningococcal vaccine in children) should be administered before splenectomy.
- Additional second-line agents are thrombopoietin receptor agonists, azathioprine, cyclosporin A, cyclophosphamide, danazol, dapsone, mycophenolate mofetil, and *Vinca* alkaloids. Romiplostim, a recombinant fusion protein, and the oral thrombopoietin-receptor agonist eltrombopag are effective in increasing platelet count in adult patients with chronic ITP refractory to corticosteroids and/or splenectomy. The American Society of Hematology guidelines revised in 2011 recommend the use of thrombopoietin-receptor agonists for adult patients with ITP at risk for bleeding, who have a contraindication to splenectomy, or do not have a response to at least one other therapy.
- Platelet transfusion is needed only in case of life-threatening hemorrhage.
- Third-line therapy for ITP consists of combination chemotherapy and hematopoietic stem cell transplantation.

DISPOSITION

- More than 80% of children have a complete remission within 8 wk.
- In adults, the course of the disease is chronic; only 5% of adults have spontaneous remission.
- The principal cause of death from ITP is intracranial hemorrhage (1% of children, 5% of adults).

SUGGESTED READINGS

Available at www.expertconsult.com

Immune Thrombocytopenic Purpura (Patient Information).

AUTHOR: **FRED F. FERRI, M.D.**

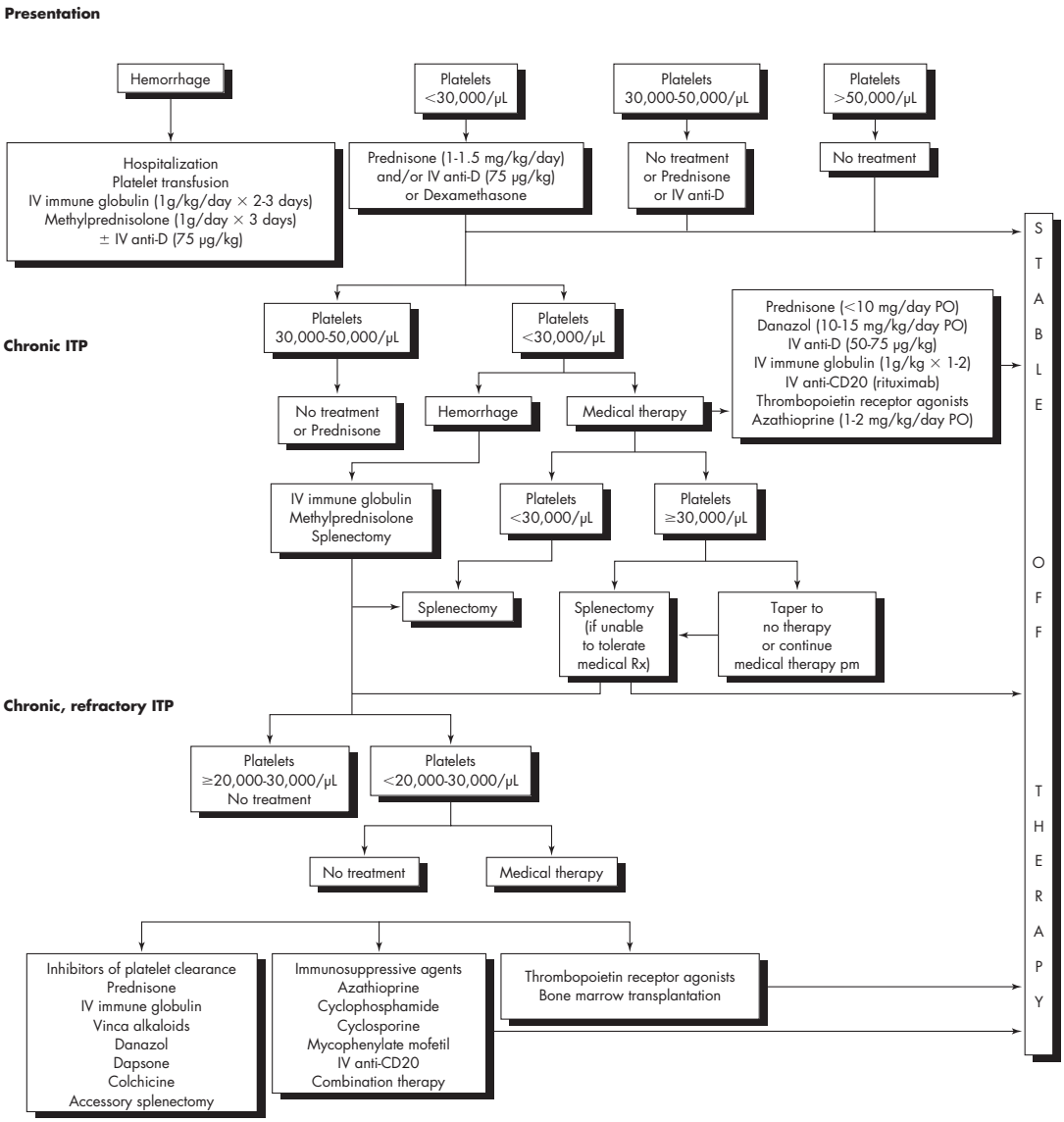


FIGURE I1-5 Treatment algorithm for management of adult-onset immune thrombocytopenic purpura. Some advocate the use of 20,000/mcL as a guideline for therapy. The decision to treat patients with platelet counts lower than 50,000/mcL is based in part on evidence of bleeding, a history of bleeding, comorbid risk factors, lifestyle, and tolerance of therapy. There is no consensus as to duration of steroid therapy. The use of anti-D as initial therapy is appropriate only for Rh(D)-positive individuals who are not markedly anemic or hemolyzing. The goal of medical therapy is to attain a hemostatic platelet count, generally >20,000 to 30,000/mcL. The threshold for treatment depends on comorbid risk factors for bleeding and risk of trauma. Higher platelet counts may be appropriate for surgery or after trauma. Medications can be used individually, but combinations of azathioprine and danazol (or corticosteroids) may provide added benefit and allow lower doses to be used. Intravenous immunoglobulin (IVIG) and anti-D are generally reserved for severe thrombocytopenia unresponsive to oral agents. The decision to proceed to splenectomy depends on intensity of therapy required, tolerance to side effects, risk of surgery, and patient preference. IVIG and/or methylprednisolone may help to increase the platelet count immediately before splenectomy. Laparoscopic and open splenectomy have comparable outcomes. The decision to treat patients who have platelet counts lower than 20,000 to 30,000/mcL after splenectomy involves an assessment of the risk of hemorrhage versus the side effects of each form of therapy. (Modified from Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

SUGGESTED READINGS

George JN: Management of immune thrombocytopenia—something old, something new, *N Engl J Med* 363:1959, 2011.

Imbach P, Crowther M: Thrombopoietin-receptor agonists for primary immune thrombocytopenia, *N Engl J Med* 365:734–741, 2011.

Kuter DJ et al.: Romiplostim or standard of care in patients with immune thrombocytopenia, *N Engl J Med* 363:1889, 2010.

Thota S et al.: Immune thrombocytopenia in adults: an update, *Cleve Clin J Med* 79:641, 2012.

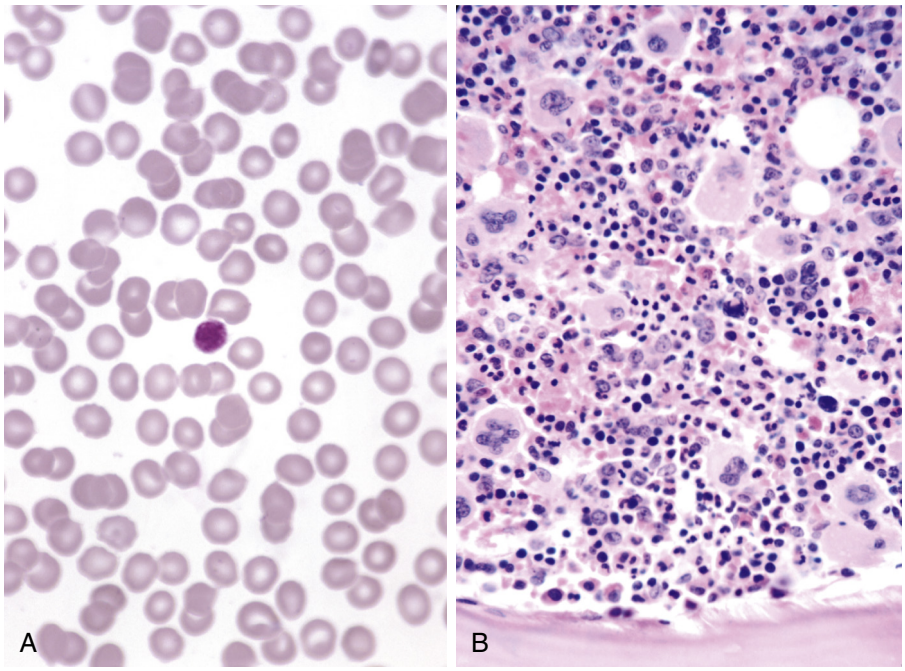


FIGURE EI1-4 Immune thrombocytopenic purpura. A, Peripheral blood smear of immune thrombocytopenic purpura. A single large platelet is seen at the center. Large platelets reflect early release from the bone marrow. **B,** The bone marrow trephine biopsy section contains increased numbers of megakaryocytes. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Impetigo is a superficial skin infection generally caused by *Staphylococcus aureus* and/or *Streptococcus* spp.

Common presentations are bullous impetigo (generally caused by staphylococcal disease) and nonbullous impetigo (from streptococcal infection and possible staphylococcal infection); the bullous form is caused by an epidermolytic toxin produced at the site of infection.

SYNONYMS

Impetigo vulgaris
Pyoderma

ICD-9CM CODES
684 Impetigo
ICD-10CM CODES
L01.00 Impetigo, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

Impetigo is the most common bacterial skin infection in children 2 to 5 yr of age. Bullous impetigo accounts for 30% of cases and nonbullous for 70% of cases.

- Bullous impetigo is most common in infants and children. The nonbullous form is most common in children ages 2 to 5 yr with poor hygiene in warm climates.
- The overall incidence of acute nephritis with impetigo varies between 2% and 5%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Nonbullous impetigo begins as a single red macule or papule that quickly becomes a vesicle. Rupture of the vesicle produces an erosion of which the contents dry to form honey-colored crusts. Multiple lesions with golden yellow crusts and weeping areas are often found on the skin around the nose, mouth (Figure I1-6), and limbs.

FIGURE I1-6 Multiple crusted and oozing lesions of impetigo. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

- Bullous impetigo is manifested by the presence of vesicles that enlarge rapidly to form bullae with contents that vary from clear to cloudy. There is subsequent collapse of the center of the bullae; the peripheral areas may retain fluid, and a honey-colored crust may appear in the center. As the lesions enlarge and become contiguous with the others, a scaling border replaces the fluid-filled rim; there is minimal erythema surrounding the lesions.
- Regional lymphadenopathy is most common with nonbullous impetigo.
- Constitutional symptoms are generally absent.

ETIOLOGY

- *S. aureus* coagulase positive is the dominant microorganism.
- *S. pyogenes* (group A β-hemolytic streptococci): M-T serotypes of this organism associated with acute nephritis are 2, 49, 55, 57, and 60.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Atopic dermatitis.
- Herpes simplex infection.
- Ecthyma.
- Folliculitis.
- Dermatitis herpetiformis.
- Insect bites.
- Scabies, pediculosis.
- Tinea corporis, cutaneous candidiasis.
- Pemphigus vulgaris and bullous pemphigoid.
- Chickenpox.
- Thermal burns.
- Contact dermatitis.
- Steven Johnson syndrome, Sweet syndrome.

WORKUP

Diagnosis is clinical.

LABORATORY TESTS

- Generally not necessary.
- Gram stain and culture and sensitivity to confirm the diagnosis when the clinical presentation is unclear.
- Sedimentation rate parallel to activity of the disease.
- Increased anti-DNAse B and antihyaluronidase.
- Urinalysis revealing hematuria with erythrocyte casts and proteinuria in patients with acute nephritis (most frequently occurring in children between ages 2 and 4 yr in the southern part of the United States).

TREATMENT

NONPHARMACOLOGIC THERAPY

Remove crusts by soaking with wet cloth compresses (crusts block the penetration of antibacterial creams).

GENERAL Rx

- Application of 2% mupirocin ointment tid for 10 days or retapamulin 1% applied bid for 5 days to the affected area or until all lesions have cleared.
- Oral antibiotics are used in severe cases: commonly used agents are dicloxacillin 250 mg qid for 7 to 10 days, cephalexin 250 mg qid for 7 to 10 days, azithromycin 500 mg on day 1, 250 mg on days 2 through 5, amoxicillin/clavulanate 500 mg q8h.
- Impetigo can be prevented by prompt application of mupirocin or triple-antibiotic ointment (bacitracin, Polysporin, and neomycin) to sites of skin trauma.
- Patients who are carriers of *S. aureus* in their nares should be treated with mupirocin ointment applied to their nares bid for 5 days.
- Fingernails should be kept short, and patients should be advised not to scratch any lesions to avoid spread of infection.

DISPOSITION

Most cases of impetigo resolve promptly with appropriate treatment. Both bullous and nonbullous forms of impetigo heal without scarring.

REFERRAL

Nephrology referral in patients with acute nephritis

PEARLS & CONSIDERATIONS

COMMENTS

- Patients should be instructed on use of antibacterial soaps and avoidance of sharing of towels and washcloths because impetigo is extremely contagious.
- Children attending day care should be removed until 48 to 72 hr after initiation of antibiotic treatment.

SUGGESTED READINGS

Available online at www.expertconsult.com

RELATED CONTENT

Impetigo (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Bangert et al.: Bacterial resistance and impetigo trend: a review, *Pediatr Dermatol* 29(3):431–434, 2012.

Hartman-Adams H et al.: Impetigo: Diagnosis and treatment, *Am Fam Physician* 90(4):229–235, 2014.

BASIC INFORMATION

DEFINITION

Inclusion body myositis (IBM) is the most common myopathy with onset after the age of 50 yr. Although classified among the inflammatory myopathies, its underlying pathophysiology has not yet been delineated.

SYNONYMS

None

ICD-9CM CODES
359.71 Inclusion body myositis
ICD-10CM CODES
G72.41 Inclusion body myositis [IBM]

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 0.22 to 0.79 cases/100,000 persons; uncommon in Asians and African Americans
PREVALENCE: 0.5 to 7.1 cases/100,000 persons
PREDOMINANT SEX: Male/female ratio 1.3:1
PREDOMINANT AGE: 87% older than 50 yr
PEAK INCIDENCE: Seventh decade
RISK FACTORS: None known
GENETICS: Less than 10% of cases familial

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Insidious onset of slowly progressive proximal leg and distal arm weakness.
- Time to diagnosis from symptom onset often lags by years to a decade.
- Functional loss of strength in the legs most often precedes arm weakness.
- The cardinal clinical features include early weakness and atrophy of quadriceps muscles (difficulty climbing stairs, arising from chairs, and getting out of cars) along with wrist and finger flexor muscles (difficulty grasping, opening jars, and turning doorknobs). Ankle dorsiflexion weakness may also be prominent leading to foot drop and tripping.
- When examining strength, side to side asymmetries are seen in one or more muscle groups in the majority of patients. This stands in contrast to the symmetrical, proximal involvement of polymyositis and most muscular dystrophies.
- Dysphagia and/or mild facial weakness are present in over half of cases. Dysphagia may be the presenting symptom.
- Although sensory symptoms are usually lacking, one third have evidence for peripheral neuropathy on physical examination and/or electrodiagnostic testing.
- 10% to 15% of patients have concomitant autoimmune disorders such as systemic lupus erythematosus, Sjögren's syndrome, scleroderma, sarcoidosis, or thrombocytopenia. However, different from polymyositis and dermatomyositis, IBM does not portend an increased risk of heart or lung disease nor cancer.

ETIOLOGY

The pathogenesis of IBM is not known. Inflammatory, degenerative, viral and prion etiologies have been postulated, but none substantiated.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Polymyositis (Table EI1-2)
- Dermatomyositis
- Amyotrophic lateral sclerosis
- Late-onset muscular dystrophies
- Acid maltase deficiency

WORKUP

- Thorough neurologic examination with emphasis on the motor exam is important.
- Nerve conduction studies should be performed to exclude other causes and EMG to document a myopathy.
- The diagnosis of definite IBM requires the following features on muscle biopsy (Fig. EI1-7): (1) inflammation, (2) inflammatory cells invading healthy muscle fibers, (3) vacuoles, and (4) amyloid deposits by Congo red staining, TDP-43 sarcoplasmic staining, or tubulofilaments on electron microscopy.

LABORATORY TESTS

Creatine kinase level (labs for collagen vascular diseases may be obtained after the diagnosis). A complete blood count and coagulation studies should be drawn in anticipation of the muscle biopsy.

IMAGING STUDIES

MRI may reveal atrophy and signal abnormalities in volar forearm muscle groups and quadriceps atrophy with relative preservation of the rectus femoris muscle.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Assistive devices for mobility such as canes, walkers, and wheelchairs are the mainstay of therapy.
- Occasionally knee orthoses or ankle-foot orthoses may improve and prolong ambulation.

ACUTE GENERAL Rx

None

CHRONIC Rx

- Experts have not found clinically significant improvement in functional strength with any pharmacologic therapy. Clinical trials of corticosteroids, methotrexate, intravenous immunoglobulin, anti-T lymphocyte globulin, etanercept, interferon β-1a, and oxandrolone have all failed to demonstrate functional improvements in limb strength.
- A short, small trial of a home exercise program demonstrated mild improvements in strength.
- IBM is generally refractory to therapy.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Some patients choose to self-treat with creatine supplementation, coenzyme Q10, or lithium. There is no evidence supporting these treatments.

REFERRAL

- Patients with suspected IBM should be referred to a neurologist with subspecialty expertise in neuromuscular medicine.
- Physical therapy and occupational therapy consultations help the patient optimize ambulation and fine motor tasks, respectively.
- Speech therapy consultations can assist with symptomatic dysphagia.

PROGNOSIS

Life expectancy is not significantly altered in this late-onset, slowly progressive disorder. Some patients require wheelchair use 10 to 20 yr after disease onset.

PEARLS & CONSIDERATIONS

COMMENTS

A key to diagnosis rests in finding weakness of wrist and/or finger flexors (especially the deep finger flexors at the DIP joints) on examination.

PREVENTION

None known

PATIENT/FAMILY EDUCATION

Patient information and support groups can be found at: www.ninds.nih.gov/disorders/inclusion_body_myositis and http://www.myositis.org.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **MATTHEW P. WICKLUND, M.D.**

EVIDENCE

All randomized, placebo-controlled, double-blind studies have failed to demonstrate functional benefit from any pharmacologic agent. Thus unless the patient has a concomitant autoimmune disorder or an overlap syndrome with either dermatomyositis or polymyositis, treatment with immunosuppressive agents, with their deleterious side effects, should be avoided.

SUGGESTED READINGS

Amato AA, Barohn RJ: Inclusion body myositis: old and new concepts, *J Neurol Neurosurg Psychiatry* 80:1186, 2009.

Amato AA et al.: Inclusion body myositis: clinical and pathological boundaries, *Ann Neurol* 40:581, 1996.

Chahin N, Engel AG: Correlation of muscle biopsy, clinical course, and outcome in PM and sporadic IBM, *Neurology* 70:418, 2006.

Greenberg SA: Inclusion body myositis, *Curr Opin Rheumatol* 23:574, 2011.

Griggs RC et al.: Inclusion body myositis and myopathies, *Ann Neurol* 38:705, 1995.

Neuromuscular Home Page: http://neuromuscular.wustl.edu.

TABLE EI1-2 Clinical and Laboratory Features of Idiopathic Inflammatory Myopathy Subgroups

Diagnostic Features	Dermatomyositis	Polymyositis	Inclusion Body Myositis
Clinical Features			
Age	Children and adults	Adults[a]	Adults >50 yr
Disease onset	Subacute	Subacute	Chronic
Muscle weakness	Proximal	Proximal	Selective pattern[b]
Symmetry	Symmetric	Symmetric	Asymmetric
Systemic features	Yes[c]	Yes[c]	Yes[d]
Skin changes	Yes[e]	No	No
Calcinosis	Yes[f]	Rarely	No
Associated connective tissue disease	Yes[g]	Yes[g]	Yes[h]
Associated malignancy[i]	Yes	Yes	Yes
Laboratory features			
Serum enzymes[j]	Normal to high	Normal to high	Normal to high
Abnormal EMG[k]	Yes	Yes	Yes
Abnormal muscle biopsy	Perifascicular atrophy, capillary depletion, patchy MHC class I expression and microinfarcts	$CD8^+$ T cell invasion of non-necrotic fibers and MHC class I expression on fibers	$CD8^+$ T cell invasion, MHC expression, vacuolated fibers, and tubulofilamentous inclusions in fibers

EMG, electromyogram; *MHC*, major histocompatibility complex.
[a]Rarely in children.
[b]Early involvement of finger flexor, wrist flexor or wrist extensor weakness, and involvement of quadriceps femoris.
[c]Some patients have dysphagia, synovitis, and interstitial lung disease.
[d]Some patients have dysphagia.
[e]Gottron's sign and heliotrope rash.
[f]Especially in children.
[g]Overlap with scleroderma, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, and mixed connective tissue disease.
[h]Associated with Sjögren's syndrome but less frequently associated with other connective tissue diseases.
[i]Dermatomyositis is more frequently associated with cancer than are polymyositis and inclusion body myositis and not overrepresented in polymyositis or inclusion body myositis.
[j]Serum creatine kinase, aspartate transaminase, lactate dehydrogenase, and aldolase vary from normal to very high levels.
[k]Myopathic motor unit potentials with spontaneous discharges in dermatomyositis, with and without spontaneous discharges in polymyositis, and mixed pattern of short- and long-duration motor unit potentials in inclusion body myositis.
From Firestein GS et al: *Kelly's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.

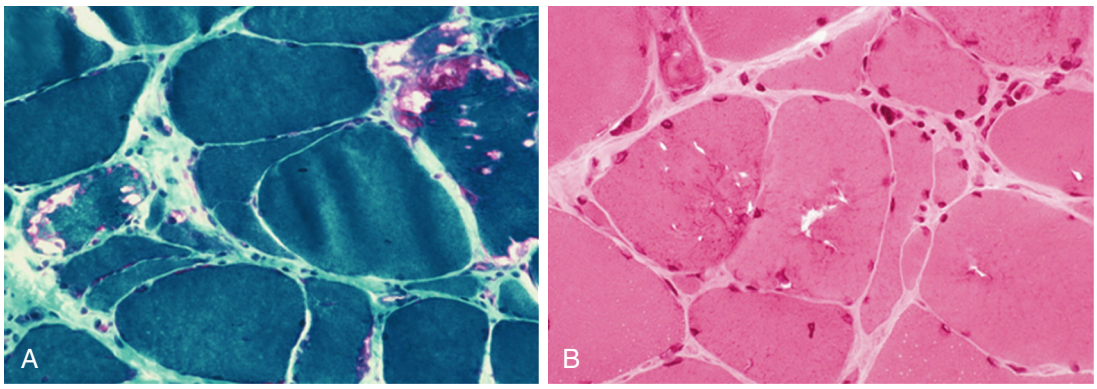


FIGURE EI1-7 Trichrome and hematoxylin and eosin staining of inclusion body myositis biopsy. Note the red-rimmed inclusions **(A)** and marked variation in muscle fiber size (**A** and **B**). (Courtesy Dr. Paul Plotz.)

BASIC INFORMATION

DEFINITION

Fecal incontinence is defined as the involuntary loss of gas or liquid stool (minor incontinence) or the involuntary loss of solid stool (major incontinence).

SYNONYMS

Anal Incontinence
Accidental Bowel Leakage

ICD-9CM CODES
787.6 Incontinence of feces
307.7 Encopresis of non-organic origin
ICD-10CM CODES
R15.9 Full incontinence of feces
F98.1 Encopresis not due to a substance or known physiological condition

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: It affects 0.5% to 1.5% of the population younger than age 65, but >10% older than 65. More common in institutionalized patients.
PREVALENCE: Varies widely depending on definition used and population studied. Estimated 1/12 U.S. adults or about 18 million people. Prevalence increases with age and BMI in women.
PREDOMINANT SEX AND AGE: Slightly more common in females versus males and age >65
RISK FACTORS:
- History of urinary incontinence.
- Cognitive or behavioral dysfunction.
- Structural anorectal abnormalities (e.g., rectal prolapse, surgical trauma).
- Presence of neurologic, psychiatric disease (e.g., depression in females), or diabetes mellitus.
- Poor mobility, poor overall health, and age >70.
- Difficult childbirth with injuries to pelvic floor/obstetric injury.
- Fecal impaction from constipation or diarrhea.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Should inspect perianal area and perform an internal digital rectal exam to evaluate for the presence of fecal material, prolapsing hemorrhoids, chemical dermatitis, scars, fistula or rectal prolapse.
- Assess for anocutaneous reflex. This may be elicited by stroking skin in each perianal quadrant (normal response is a brisk anal wink). Absent reflex is suggestive of nerve damage. Assess resting to squeezing anal tone by asking the patient to bear down.

Ask patient to strain to assess for rectal prolapse or excessive perianal descent.

Etiology
- Usually multifactorial.
- Fecal impaction.
- Neurologic disorders:
  1. History of CVA.
  2. Multiple sclerosis.
  3. Spinal cord lesions.
  4. Diabetes mellitus.
- Anal trauma
  1. Anorectal surgery for hemorrhoids, fistula, and fissures.
  2. Vaginal delivery (anal sphincter tear, trauma to pudendal nerve).

  Radiation treatment.
- Idiopathic.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Fecal encopresis.
- IBS.

WORKUP

- Requires detailed history taking that includes the onset and precipitating events, duration and severity, stool consistency and urgency. Important to evaluate for history of urinary incontinence, anorectal surgery or radiation, neurologic disorders, or prior vaginal deliveries and complete a thorough physical exam. Box EI1-2 describes a structured clinical approach to focal incontinence in older adults.
- Diagnostic workup includes anorectal manometry, endorectal ultrasound (simple and economical), MRI, proctosigmoidoscopy, defecography, pudendal nerve terminal latency, and anal electromyography (EMG).

TREATMENT

- Therapy is focused on three main approaches: medications, biofeedback, and surgery.

Medications focus on decreasing stool frequency and improving consistency, and include loperamide, diphenoxylate/atropine sulfate, methylcellulose, and anticholinergics (hyoscyamine). Phenylephrine gel may increase anal canal resting pressures.

- Solesta is a dextrananomer-hyaluronic gel that was FDA approved in 2011 for the treatment of fecal incontinence in adults who have failed conservative therapy. It consists of four 1 ml injections into the deep submucosal layer of the anal canal, about 5 mm above the dentate line. It is hypothesized that Solesta may narrow the anal canal and allow for better sphincter control.

NONPHARMACOLOGIC THERAPY

- Supportive therapy:
  1. Education, counseling, habit training.
  2. Dietary modifications (e.g., increased fiber and fluid intake, less caffeine).
  3. Modified Kegel exercises.
  4. Anal plugs (poorly tolerated).
- Biofeedback therapy:
  Anal sphincter muscle training and strengthening.
- Surgery:
  1. Overlapping sphincteroplasty (most common).
  2. Anterior overlap repair (usually after obstetric trauma).
  3. Artificial anal sphincter.
  4. Colostomy (if intractable symptoms and/or failed all other therapies).
- Radiofrequency.
- Sacral nerve stimulation.
- Anal electrical stimulation.

REFERRAL

Colorectal surgery

PEARLS & CONSIDERATIONS

COMMENTS

The shame, embarrassment, and stigma associated with fecal and urinary incontinence pose significant barriers to seeking professional treatment, which results in many people who suffer from these conditions without help. Therefore, during routine office visits, asking all patients >70 yr about incontinence may be helpful.

PREVENTION

- Reduce constipation and avoid straining during bowel movements.
- Routine episiotomy is the most easily preventable risk factor for fecal incontinence in females.

PATIENT/FAMILY EDUCATION

http://digestive.niddk.nih.gov/ddiseases/pubs/fecalincontinence/index.aspx

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **DAPHNE SCARAMANGAS-PLUMLEY, M.D.**

SUGGESTED READINGS

Harari D: Constipation and Fecal Incontinence in Old Age. In Fillit HM, Rockwood K, Woodhouse K, editors: *Brocklehurst's Textbook of Geriatrics and Clinical Gerontology*, ed 7, Philadelphia, 2010, Churchill Livingstone.

Landefeld CS et al.: National Institutes of Health State-of-the-Science conference statement: prevention of fecal and urinary incontinence in adults, *Ann Intern Med* 48:449–458, 2008.

Leung FW, Rao SS: Fecal incontinece in the elderly, *Gastroenterol Clin North Am* 38(3):503–511, 2009.

Mellgren A: Fecal incontinence, *Surg Clin N Am* 90(1):185–194, 2010.

Wald A et al.: ACG Clinical Guideline: Management of benign anorectal disorders, *Am J Gastroenterol* 109:1141–1157, 2014.

Van Koughnett JA, Wexner SD: Current Management of fecal incontinence: choosing amongst treatment options to optimize outcomes, *World J Gastroenterol* 19(48):9216–9230, 2013.

BOX EI1-2 Clinical Assessment of Fecal Incontinence in Older Adults

Emphasis in older adults is on a *structured clinical approach* to identify all contributing factors for fecal incontinence.

History

- Duration of fecal incontinence.
- Frequency of episodes.
- Type (constant soiling, small amounts, complete bowel movement).
- Stool consistency (diarrhea, hard stool).
- Unconscious leakage or symptoms of urgency.
- Constipation symptoms/current laxative use.
- Systemic illness (confusion, depression, weight loss, anemia).
- Antibiotic use.

General Examination

- Cognitive and mood assessment.
- Neurologic profile (stroke, autonomic neuropathy, Parkinson's disease).

Toilet Access

- Evaluate ability to use toilet based on muscle strength coordination, vision, limb function, and cognition.
- Place in context of current living environment.

Specific Examination

- Abdominal inspection for distention and tenderness.
- Perineal inspection for skin breakdown, dermatitis, surgical scars.
- Perianal sensation/cutaneous anal reflex.
- Observe for excessive downward motion of the pelvic floor when asking patient to bear down in the lateral lying position.
- Digital examination for stool impaction.
- Digital examination for evaluation of impaired sphincter tone.
  - Anal gaping and/or easy insertion of finger (internal sphincter).
  - Reduced squeeze pressure (external sphincter).
- Ask patient to strain while sitting on commode and observe for rectal prolapse

From Tallis RC.; Fillit HM. (eds): *Brocklehurst's textbook of geriatric medicine and gerontology,* ed 6, London, 2003, Churchill Livingstone.

BASIC INFORMATION

DEFINITION

Urinary incontinence is the involuntary loss of urine.

ICD-9CM CODES

788.3	Incontinence
625.6	Stress incontinence
788.33	Mixed stress and urge incontinence
788.32	Male incontinence
788.39	Neurogenic incontinence
307.6	Nonorganic origin

ICD-10CM CODES

R32	Unspecified urinary incontinence
N39.3	Stress incontinence (female) (male)
N39.46	Mixed incontinence
N39.49	Disorder of urinary system, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE/PREVALENCE: In the general population between the ages of 15 and 64 yr, 1.5% to 5% of men and 10% to 25% of women have incontinence. In the nursing home population, 75% of the population has some degree of incontinence. Nearly 20% of children through the mid-teenage years have episodes of urinary incontinence.

CLINICAL, PSYCHOLOGICAL, & SOCIAL IMPACT

Fewer than 50% of the individuals with incontinence living in the community consult health care providers, preferring to suffer silently, turning to home remedies, commercially available absorbent materials, and supportive aids. As their condition worsens, they become depressed, sacrifice their independence, suffer from recurrent urinary tract infection and its sequelae, limit social interaction, refrain from sexual intimacy, and become homebound. In terms of costs, for all ages living in the community, it is estimated that $7 billion is spent for incontinence annually.

MAJOR TYPES OF INCONTINENCE

- **Transient incontinence:** Incontinence occurring as a result or reaction to an acute medical problem affecting the lower urinary tract. Many of these problems can be reversed with treatment of the underlying problem.
- **Urge incontinence:** Involuntary loss of urine associated with an abrupt and strong desire to void. It is usually associated with involuntary detrusor contractions on urodynamic investigation. In neurologically impaired patients, the involuntary detrusor contraction is referred to as *detrusor hyperreflexia.* In neurologically normal patients the involuntary contraction is called *detrusor instability.*
- **Stress incontinence** (Fig. I1-8): The involuntary loss of urine with physical activities that increase abdominal pressure in the absence of a detrusor contraction or an overdistended bladder. Classification of stress incontinence:
  1. Type 0: Report of incontinence without demonstration of leakage.
  2. Type I: Incontinence in response to stress but with little descent of the bladder neck and urethra.
  3. Type II: Incontinence in response to stress with >2 cm descent of the bladder neck and urethra.
  4. Type III: Bladder neck and urethra wide open without bladder contraction; intrinsic sphincter deficiency; denervation of the urethra. The most common causes include urethral hypermobility and displacement of the bladder neck with exertion, intrinsic sphincter deficiency from failed antiincontinence surgery, prostatectomy, radiation, cord lesions, epispadias, and myelomeningocele.
- **Overflow incontinence:** Loss of urine resulting from overdistention of the bladder with resultant overflow or spilling of the urine. Causes include hypotonic-to-atonic bladder resulting from drug effect, fecal impaction, or neurologic conditions such as diabetes, spinal cord injury, surgery, or vitamin B_{12} deficiency. It is also caused by obstruction at the bladder neck and urethra. In this situation prostatism, prostatic cancer, urethral stenosis, antiincontinence surgery, pelvic prolapse, and detrusor-sphincter dyssynergia cause the incontinence.
- **Functional incontinence:** Involuntary loss of urine resulting from chronic impairments of physical and/or cognitive functioning. This is a diagnosis of exclusion. It consists of simply not getting to the toilet quickly enough due to significant mobility or cognitive impairment. The condition can sometimes be improved or cured by improving the patient's functional status, treating comorbidities, changing medications, and reducing environmental barriers.
- **Mixed stress and urge incontinence:** See Fig. I1-8.
- **Sensory urgency incontinence:** Involuntary loss of urine as a result of decreased bladder compliance and increased intravesical pressures accompanied by severe urgency and bladder hypersensitivity without detrusor overactivity. This is seen with radiation cystitis, interstitial cystitis, eosinophilic cystitis, myelomeningocele, and radical pelvic surgery. Nephropathy can occur as a complication of this vesicoureteral reflux.
- **Sphincteric incontinence:**
  1. *Urethral hypermobility:* The basic abnormality is a weakness of pelvic floor support. Because of this weakness, during increases in abdominal pressure there is rotational descent of the vesical neck and proximal urethra. If the urethra opens concomitantly, stress urinary incontinence ensues. Urethral hypermobility is often present in women who are not incontinent. Its mere presence is not sufficient evidence to make the diagnosis of sphincteric abnormality unless incontinence is shown.
  2. *Intrinsic sphincter deficiency:* There is an intrinsic malfunction of the sphincter itself. It is characterized by an open vesical neck at rest and a low leak point pressure (<65 cm water). Urethral hypermobility and intrinsic sphincter deficiency may coexist in the same patient. Causes of intrinsic sphincter deficiency are previous pelvic surgery, antiincontinence surgery, urethral diverticulectomy, radical hysterectomy, abdominoperineal resection of the rectum, urethrotomy, Y-V plasty of the vesical neck, myelodysplasia, anterior spinal artery syndrome, lumbosacral disease, aging, and hyperestrogenism.

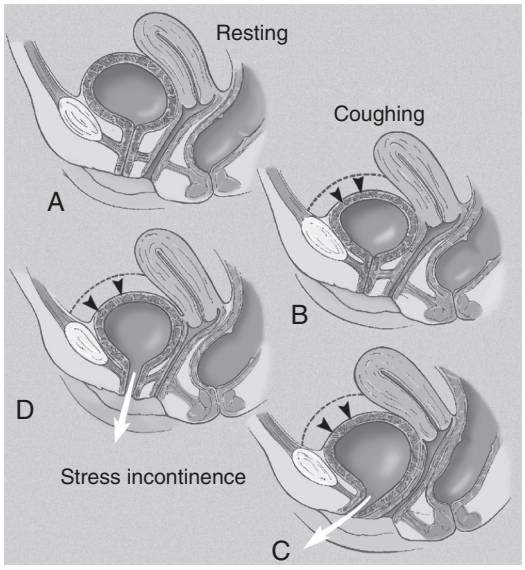


FIGURE I1-8 A, Bladder and urethra in normal position. **B,** Intra-abdominal pressure transmitted to the bladder. **C,** Bladder and urethra in abnormal position with loss of support (hypermobile). **D,** Loss of urethral closure. (From Lipshultz LI.; et al. *Urology and the primary care practitioner.* ed 3, Philadelphia, 2008, Elsevier.)

DIAGNOSIS

HISTORY

- History of present illness, psychosocial factors, congenital disorders, access issues for the physically challenged, neurologic disorders, and disorders pertinent to the urologic tract.

- Review of prescription and nonprescription medications.
- Voiding diary to assess total voided volume, frequency of micturition, mean volume voided, largest single volume, diurnal distribution, nature and severity of incontinence.

WORKUP

- Physical examination including general examination, gait of the patient (neuromuscular deficits), estrogen status, vaginal examination to include the periurethral region, evaluation for cystocele, rectocele, and enterocele.
- Pelvic floor strength assessment.
- Rectal examination to assess sphincter tone and bulbocavernosus reflex.
- Neurologic examination.
- Postvoid residual check with bladder scan or catheter.

LABORATORY TESTS

Urinalysis, urine culture, urine cytology, blood urea nitrogen, creatinine.

IMAGING STUDIES

- Radiography: a KUB (kidney, ureter, and bladder) to assess bony skeleton.
- CT or intravenous pyelography (IVP) to rule out upper tract abnormalities, developmental anomalies, bladder configuration, and fistula.
- Renal ultrasound if contrast study is contraindicated.

SPECIALIZED STUDIES

Simple cystometrogram, complex urodynamics for leak point pressures and uroflowmetry, endoscopic evaluation, cystogram.

Rx TREATMENT

- The recommended approach to urinary incontinence is a stepped care plan, initiating with noninvasive behavioral modifications. In nonresponders pharmacologic interventions and devices are tried next, and finally surgical intervention in those with persistent incontinence refractory to other therapies.
- Transient incontinence: treatment of underlying medical conditions and behavioral therapy to include habit training and timed voiding.
- Urge incontinence: anticholinergic and antimuscarinic agents (tolterodine, oxybutynin, trospium chloride, fesoterodine, darifenacin, solifenacin). Anticholinergics bind to muscarinic receptors in the bladder and relax detrusor smooth muscle but can cause dry mouth, constipation, confusion, and cognition abnormalities in the elderly. Other treatment modalities include biofeedback, Kegel exercises, and surgical removal of obstructing or other pathologic lesions. A recent trial comparing oral anticholinergic therapy and onabotulinum toxin A by injection shows similar reductions in the frequency of daily episodes of urgency urinary incontinence. The group receiving onabotulinum toxin A was less likely to have dry mouth and more likely to have complete resolution of urgency urinary incontinence but higher rates of transient urinary retention and urinary tract infections. Mirabegron is a beta-3 adrenergic agonist recently FDA approved for overactive bladder. It is better tolerated than anticholinergic agents but has significant drug interactions and can cause urinary retention.
- Stress incontinence: pelvic floor muscle training (PFMT), Kegel exercises. Duloxetine improves incontinence rates and quality of life but does not cure incontinence. It can be tried if PFMT has been unsuccessful. PFMT is considered first-line therapy for stress incontinence and is also beneficial in mixed urge and stress incontinence. Midurethral-sling surgery is generally advocated when physiotherapy is unsuccessful. However, a recent trial[1] revealed that for women with stress incontinence, initial midurethral-sling surgery, as compared with initial physiotherapy, results in higher rates of subjective improvement and subjective and objective cure at 1 year.
  1. Cystourethropexy (see Table EI1-3): Burch procedure, Raz procedure, Stamey-Raz procedure, Gittes procedure, in situ transvaginal sling, pubovaginal sling with autologous or cadaver graft, laparoscopic Burch procedure, laparoscopic sling, tension-free vaginal tape.
  2. For intrinsic sphincter deficiency: bulking agents (e.g., collagen), sling, and artificial sphincter.
- Overflow incontinence: surgical removal of any obstructing lesions, clean intermittent catheterization, indwelling catheter.
- Functional incontinence: behavioral training to include habit training and timed voiding, incontinence undergarments and pads, external collecting devices, environmental manipulation.
- Mixed urgency and stress incontinence: PFMT and use of measures recommended in the management of stress and urge incontinence.
- Sensory urgency: bladder relaxants (e.g., anticholinergics, muscle relaxants, and tricyclic antidepressants), behavior therapy to include habit training and timed voiding, cystoscopy and hydrodilation.
- Sphincteric deficiency: urethral bulking agents, sling procedure, artificial sphincter, mechanical clamp, external collection devices.
- Botox (onabotulinum toxin A injection; Allergan) has been approved for the treatment of urinary incontinence in patients with neurologic conditions (e.g., spinal cord injury) and those with multiple sclerosis who have overactive bladder.

[1]Labrie J et al: Surgery versus physiotherapy for stress urinary incontinence, *N Engl J Med* 369:1124-1133, 2013.

TABLE I1-4 Transient Causes of Urinary Incontinence (DIAPPERS)

D	Delirium/confusional state
I	Infection—urinary (symptomatic)
A	Atrophic urethritis/vaginitis
P	Pharmaceuticals (diuretics, etc.)
P	Psychological, especially depression
E	Endocrine (hypercalcemia, hypokalemia, glycosuria)
R	Restricted mobility
S	Stool impaction

From Floege J et al. *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

PEARLS & CONSIDERATIONS

COMMENTS

- Weight loss and exercise is helpful for urinary incontinence in obese women. Overweight and obese women with urinary incontinence also have a high prevalence of monthly fecal incontinence (16% found to be associated with low dietary fiber intake after adjustment for other known risk factors for fecal incontinence).
- Transient causes of urinary incontinence in the elderly are described in Table I1-4.
- Other forms of incontinence:
  1. Nocturnal enuresis (ICD-9CM code: 788.3): can be caused by sphincter abnormalities and detrusor overactivity; can occur as idiopathic, neurogenic, and with outlet obstruction
  2. Postvoid dribble (ICD-9CM code: 599.2): a postsphincteric collection of urine seen with urethral diverticulum; can be idiopathic.
  3. Extraurethral incontinence: enterovesical (ICD-9CM codes: 596.1 and 596.2), urethral (ICD-9CM code: 599.1); also known as *fistula*.
- Conditions that predispose to surgical failure: advanced age, postmenopausal state, hysterectomy, prior failed incontinence surgery, concurrent detrusor instability, abnormal perineal electromyography, pelvic radiation

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com.

RELATED CONTENT

Urinary Incontinence (Patient Information)
Pelvic Organ Prolapse (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

EVIDENCE

Abstract[1]

Purpose:
We compared the efficacy and complications of tension-free vaginal tape and tension-free vaginal tape-obturator.

Materials and Methods:
Women with pure urodynamic stress incontinence undergoing only primary continence surgery were randomized to tension-free vaginal tape or tension-free vaginal tape-obturator at 2 centers between March 2005 and March 2007. Primary outcome was objective cure rate at 6 months, defined by a 24 hour pad test of <5 g. Secondary outcomes were the subjective cure rate on the Patient Global Impression of Improvement, quality of life on the King's Healthcare Questionnaire and symptom severity scores on the International Consultation on Incontinence Questionnaire.

Results:
A total of 127 women were recruited. The study was stopped early due to excess leg pain in the tension-free vaginal tape-obturator group. Of the women 66 were randomized to tension-free vaginal tape and 61 were randomized to tension-free vaginal tape-obturator. Analysis was done by intent to treat. The objective and subjective cure rate at 6 months for tension-free vaginal tape versus tension-free vaginal tape-obturator was 69.7% versus 72.1% and 72.7% versus 67.2% ($p = 0.76$ and 0.49, respectively). Cure rates at 1 year were similar but loss to follow-up was high. Objective and subjective cure rates at 1 year for tension-free vaginal tape versus tension-free vaginal tape-obturator were 50% versus 41% and 53% versus 42.6% ($p = 0.31$ and 0.24, respectively). More women complained of leg pain after receiving a tension-free vaginal tape-obturator (26.4% versus 1.7%, $p = 0.0001$). The incidence of perioperative complications was low and similar between the groups. Time to discharge home and time to normal activity were not significantly different.

Conclusions:
Short-term cure rates at 6 months were similar. Tension-free vaginal tape-obturator caused more transient leg pain. Each procedure achieved a high cure rate and a low complication rate. Ⓐ

Abstract[2]

Background:
A relatively common complication after the treatment of localized prostate cancer is urinary dysfunction, with stress urinary incontinence a common occurrence after radical prostatectomy. Even 5 years after surgery, 14% to 28% of patients still report incontinence. New technologies developed to improve this outcome have yet to show benefit. An analysis of behavioral therapy as a method to improve the rate of incontinence after radical prostatectomy raised questions about the effectiveness of all current approaches.

Study Details:
A randomized clinical trial conducted by Goode et al compared 8 weeks of behavioral therapy with or without biofeedback and pelvic floor electrical stimulation with delayed treatment (control). Weekly episodes of urinary incontinence in men whose incontinence had been present for 1 to 17 years were measured. The relative reduction was 55% in the behavioral therapy group and 24% in the control group. In addition, 90% of the men in the behavioral therapy group but only 10% of the men in the control group reported better or much better urinary leakage status than before treatment. Mean urinary leakage episodes declined from 28 to 13 per week with behavioral therapy. In addition, the American Urological Association (AUA-7) symptom index score was improved by 2.5 points with the behavioral intervention. After 6 and 12 months, the AUA-7 symptom score had improved by 4 points in the intervention group.

Analysis:
The improvements reported in this study represent minimal changes. It is questionable whether men would feel satisfied because they had only 2 episodes of urinary incontinence each week. In addition, the 2.5-point improvement in AUA-7 symptom index score represents a slight improvement only, with the 4-point improvement representing the threshold for moderate improvement. Although behavioral therapy appears to improve urinary incontinence after prostatectomy, the degree of improvement is only slightly better than no treatment.

Conclusions:
It may be wise to rethink how best to treat men with post-prostatectomy urinary incontinence. Primary prevention, consisting of increased use of active surveillance in patients with lower-risk disease and selective application of aggressive interventions in patients with worse prognostic variables, may be a better strategy. The use of prostate-specific antigen (PSA) screening identifies many clinically indolent prostate cancers, with rates between 23% and 42%. Aggressive interventions are often undertaken in response to patients', family members', and clinicians' preconceived ideas about cancer in general and prostate cancer in particular; because of financial concerns; and as a result of other obstacles to pursuing active surveillance. If the goal is to reduce the incidence of complications such as urinary incontinence associated with the treatment of localized prostate cancer, it may be best to follow a course of PSA testing and serial prostate biopsies with aggressive treatment delayed until the patient reaches specific pathologic or biochemical milestones. Ⓐ

Abstract[3]

Pharmacologic Therapy

Purpose:
We evaluated the efficacy and safety of flexible dose fesoterodine in medically complex vulnerable elderly subjects with urgency urinary incontinence.

Materials and Methods:
In this 12 week, randomized, double-blind, flexible dose, placebo controlled trial, subjects were community dwelling men and women 65 years old or older. Subjects had scores of 3 or more on the VES-13 (Vulnerable Elders Survey) and 20 or more on the MMSE (Mini-Mental State Examination), and 2 to 15 urgency urinary incontinence episodes and 8 or more micturitions per 24 hours on 3-day baseline diaries. Subjects randomized to fesoterodine received 4 mg once daily for 4 weeks and could then increase to 8 mg based on discussion with the investigator. Subjects receiving 8 mg could decrease the dose to 4 mg at any time (sham escalation and de-escalation for placebo). The primary outcome measure was change in daily urgency urinary incontinence episodes. Secondary outcomes included changes in other diary variables and patient reported quality of life measures. Safety evaluations included self-reported symptoms and post-void residual volume.

Results:
A total of 562 patients were randomized (mean age 75 years, 50.4% age 75 years or greater). Subjects had high rates of comorbidities, polypharmacy and functional impairment. At week 12 the fesoterodine group had significantly greater improvements in urgency urinary incontinence episodes per 24 hours (–2.84 versus –2.20, $p = 0.002$) and most other diary variables and quality of life, as well as a higher diary dry rate (50.8% versus 36.0%, $p = 0.002$). Adverse effects were generally similar to those of younger populations including risk of urinary retention.

Conclusions:
To our knowledge this is the first antimuscarinic study in a community based, significantly older, medically complex elderly population with urgency urinary incontinence. Flexible dose fesoterodine significantly improved urgency urinary incontinence episodes and other outcomes versus placebo, and was generally well tolerated. Ⓐ

Evidence-Based References

1. Teo R et al.: Randomized trial of tension-free vaginal tape and tension-free vaginal tape-obturator for urodynamic stress incontinence in women, *J Urol* 185:1350–1355, 2011. Ⓐ
2. Penson DF: Treatment for postprostatectomy incontinence: is this as good as it gets?, *JAMA* 305:197–198, 2011. Ⓐ
3. Dubeau CE, Kraus SR, Griebling TL et al.: Effect of fesoterodine in vulnerable elderly subjects with urgency incontinence: a double-blind, placebo controlled trial, *J Urol* 191:395–404, 2014. Ⓐ

SUGGESTED READINGS

Goode P et al.: Incontinence in older women, *JAMA* 303:2172–2180, 2010.

Hersh C, Salzman B et al.: Clinical management of urinary incontinence in women, *Am Fam Phys* 87(9):634–640, 2013.

Holdroyd-Leduc JM et al.: What type of urinary incontinence does this woman have? *JAMA* 299(12):1446–1456, 2008.

Markland A et al.: Fecal incontinence in obese women with urinary incontinence: prevalence and role of dietary fiber intake, *Am J Obstet Gynecol* 200:566, 2009.

Myers DL: Female mixed urinary incontinence, A clinical review, *JAMA* 311(19):2007–2014, 2014.

Nelken RS et al.: Randomized trial of estradiol vaginal ring versus oral oxybutynin for the treatment of overactive bladder, *Menopause* 18(9):962–966, 2011.

Nygaard I: Idiopathic urgency urinary incontinence, *N Engl J Med* 363:1156–1162, 2010.

Petrou SP et al.: Botulinum A toxin/dimethyl sulfoxide bladder installation for women with refractory idiopathic detrusor overactivity: a phase study, *Mayo Clin Proc* 84(8):702–706, 2009.

Qaseem A et al.: Nonsurgical management of urinary incontinence in women: A clinical practice guideline from the American College of Physicians, *Ann Intern Med* 161:429–440, 2014.

Richter HE et al.: Retropubic versus transobturator midurethral slings for stress incontinence, *N Engl J Med* 362:2066–2076, 2010.

Rogers RG: Urinary stress incontinence in women, *N Engl J Med* 358:1029–1036, 2008.

Shamliyan TA et al.: Systematic review: randomized controlled trials of nonsurgical treatment for urinary incontinence in women, *Ann Intern Med* 148:459–473, 2008.

Visco AG et al.: Anticholinergic therapy vs. onabotulinumtoxina for urgency urinary incontinence, *N Engl J Med* 367(19):1803–1813, 2012.

TABLE EI1-3 Surgical Treatment of Stress Incontinence

- Anterior colporrhaphy
- Transvaginal needle suspension
  - Pereyra
  - Stamey
  - Gittes
  - Raz
- Abdominal retropubic urethropexy (suspension)
- Marshall-Marchetti-Krantz
  - Burch operation
  - Paravaginal repair
  - Lapides procedure
- Sling procedure
  - Pubovaginal (bladder neck) sling
    - Autologous
      - Rectus abdominis fascia
      - Tensor fascia lata
      - Anterior vagina wall sling
    - Allograft (cadaveric fascia lata fascia)
    - Xenograft
      - Porcine dermis
      - Small intestinal submucosa
    - Synthetic mesh (polypropylene)
  - Tension-free midurethral sling (polypropylene)
    - TVT
    - TVT-O
    - TOT
    - SPARC
- Urethral bulking agent
  - Bovine collagen
  - Carbon-coated zirconium beads
  - Ethylene vinyl alcohol copolymer
  - Calcium hydroxyapatite
- Artificial urinary sphincter

SPARC, Suprapubic arc sling system; *TOT,* trans-obturator tape; *TVT,* tension-free vaginal tape; *TVT-O,* TVT-obturator.

From Lipshultz LI et al: *Urology and the primary care practitioner,* ed 3, Philadelphia, 2008, Elsevier.

BASIC INFORMATION

DEFINITION

Hypotonia typically describes the inability to move or maintain posture against forces that stretch the body, mainly gravity.

SYNONYMS

Floppy infant

ICD-9CM CODES
343.8 Infantile cerebral palsy
ICD-10CM CODES
P94.2 Congenital hypotonia
P94.8 Other disorders of muscle tones of newborn
P94.9 Disorders of muscle tone of newborn, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

Central causes for hypotonia outweigh peripheral causes 3:1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

A detailed history and physical exam are the key tools to localizing the lesion, since the cause can be at any level in the neuraxis, providing an extensive differential.

- Assess tone by observing the fully awake child for body movements, body posture, and signs of decreased in utero movements (hip dislocation, arthrogryposis, plagiocephaly, pectus excavatum).
- When supine, hypotonic infants will lie with their extremities extended and abducted, termed the frog-leg position.
- When pulled gently by the hands from supine toward sitting position, hypotonic infants will have significant head lag and very little resistance to the examiner.
- When held under the arms by the axillae in vertical suspension, hypotonic infants will start to slip through the examiner's hands unlike infants with normal tone.
- If held prone with support under the torso in horizontal suspension, hypotonic infants will fall limply into an "inverted U" position.
- Signs of hypotonia of central origin include abnormal head shape or size, decreased level of consciousness, dysmorphic features, hyperreflexia, seizures, apnea, or abnormal sleep-wake cycles (Table EI1-5). Signs of hypotonia of peripheral origin (i.e., a lesion in the motor unit) include an alert and profoundly weak infant with hyporeflexia and atrophic muscles. Tongue fasciculations and intention tremor are seen with anterior horn disease.
- The rest of the neurologic and general exams can provide pertinent clues to specific diagnoses. Cardiac murmurs, skin lesions, hepatosplenomegaly, and other systemic features help narrow the differentials.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Common central causes
- Acquired brain insult
  1. Infection
  2. Hypoxic encephalopathy
  3. Intracranial hemorrhage
- Brain anomalies: neuromigrational disorders
- Genetic disorders
  1. Prader-Willi syndrome
  2. Down syndrome
  3. Kabuki syndrome
  4. Williams syndrome
  5. MECP2 duplication syndrome
  6. Fragile X syndrome

Peripheral causes of hypotonia in infants
- Anterior horn cell disease
  1. Spinal muscular atrophy
  2. Hypoxic injury
  3. Neurogenic arthrogryposis
- Polyneuropathies (motor or sensory)
  1. Hereditary motor-sensory neuropathy
  2. Charcot-Marie-Tooth disease
  3. Congenital hypomyelinating disorder
- Neuromuscular junction disorders
  1. Infantile botulism
  2. Congenital myasthenia gravis
  3. Transient neonatal myasthenia
- Congenital myopathies
  1. Central core disease
  2. Nemaline rod myopathy
  3. Fiber-type disproportion myopathy
  4. Multi-minicore disease
  5. Myotubular myopathy
- Muscular dystrophies
- Metabolic disorders
  1. Acid maltase deficiency (Pompe's disease)
  2. Cerebrohepatorenal syndrome (Zellweger)
  3. Cytochrome-c oxidase deficiency
  4. Mitochondrial myopathies
  5. Neonatal adrenoleukodystrophy

LABORATORY TESTS

- Evaluate neonate for sepsis
- Electrolytes including glucose, creatinine, calcium
- Liver function tests
- Ammonia level
- Creatinine kinase level
- Lactate
- Consider TORCH titers
- Karyotype or specific genetic testing
- Serum amino acids
- Urine organic acids
- Acylcarnitine/carnitine panel
- Very long chain fatty acids
- EMG/nerve conduction velocity (NCV)
- Muscle biopsy

IMAGING STUDIES

MRI with spectroscopy

TREATMENT

Most of these disorders have no specific treatment.

CHRONIC Rx

- Physical therapy, occupational therapy, and other therapies tailored to the patient's specific needs can provide significant improvement in quality of life and ability to function.
- Respiratory illnesses are common in these children, so vaccinations should be kept up to date.

DISPOSITION

- Long-term outcome varies greatly among different diseases.
- As a general rule, a hypotonic infant who requires mechanical ventilation cannot survive extubation (unless the cause is neonatal myasthenia).

TABLE EI1-5 Localizing Examination Findings

Site of Lesion	Strength	Reflexes	Muscle Mass	Fasciculations
Brain	Normal or slightly impaired	Brisk (decreased after acute injury)	Normal	None
Anterior horn cell	Weak	Decreased	Significant atrophy	Prominent (but not in neonatal period)
Peripheral nerve	Weak	Decreased	Atrophy	None
Neuromuscular junction	Weak	Normal	Normal	None
Muscle	Weak	Decreased or absent	Atrophy or pseudohypertrophy	None

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **KIMBERLY JONES, M.D.**

SUGGESTED READINGS

Fenichel GM: Clinical pediatric neurology: a signs and symptoms approach. ed 6 Saunders: Philadelphia.

Peredo DE, Hannibal MC: The floppy infant: evaluation of hypotonia, *Pediatr Rev* 30:e66–e67, 2009.

BASIC INFORMATION

DEFINITION

Infertility in a reproductive age couple is the inability to conceive after adequate coital attempts have been made for ≥1 yr. In couples where the female partner is >35 yr of age, an evaluation is justified after 6 mo without successful pregnancy.

SYNONYMS

Sterility

ICD-9CM CODES

628.0 Infertility, female, associated with anovulation
628.2 Infertility, female, of tubal origin
628.9 Infertility, of unspecified origin

ICD-10CM CODES

N97.0 Female infertility associated with anovulation
N97.1 Female infertility of tubal origin
N97.9 Female infertility, unspecified
N46 Male infertility

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: The incidence of infertility increases with age. Subtle decreases in female fertility start as early as age 30. The rate of infertility increases dramatically after age 37 and spontaneous pregnancies become extremely uncommon as women reach the mid-40s. There is also a more subtle but still detectable decrease in male fertility that can also start as early as age 30.

PREVALENCE: One in eight reproductive age couples experience infertility. This prevalence is consistent in all developed countries and there is evidence that it is historically stable.

PREDOMINANT SEX AND AGE: By definition this is a diagnosis of reproductive age couples. Infertility increases with aging in both males and females but more dramatically in women. Male factor is responsible in ~40% of couples and the female factor is responsible in ~40% of couples. The remainder of the cases are either combined male and female or unexplained infertility, meaning a clear cause is not identified.

RISK FACTORS: Aging is among the most common of risk factors, predominantly among females. Women are increasingly deferring pregnancy as a result of careers, which is likely associated with the increasing prevalence in certain sectors of the population. Sexually transmitted disease with Chlamydia and gonorrhea is associated with pelvic inflammatory disease, which frequently results in tubal factor infertility. Extremes of weight, especially overweight, are associated with ovulatory dysfunction. Male factor infertility is most commonly idiopathic, although trauma, infection, varicocele, and exposure to environmental toxins may be associated with compromise of semen parameters. Smoking is the most common lifestyle choice that impairs fertility.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Age (both partners).
- Previous fertility, particularly if no pregnancy has occurred in another relationship despite absence of contraception (both partners).
- Absence of secondary sexual characteristics (both partners).
- Irregular or absent menstruation (female).
- Hirsutism, acne, and alopecia suggestive of hyperandrogenism (female).
- Pelvic exam suggestive of uterine abnormality such as fibroids (female).
- Trauma or torsion of the testes (male).
- Small, firm testes (male).

ETIOLOGY

- Advanced age, especially female.
- Pelvic inflammatory disease (results in tubal factor infertility).
- Endometriosis (results in tubal factor infertility).
- Female anatomic (uterine fibroids, polyps, intrauterine adhesions).
- Oligoovulation, most frequently due to polycystic ovarian syndrome (PCOS).
- Idiopathic, both male and female.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Recurrent spontaneous abortion.
- Ineffective attempts at natural conception.
- Sterility due to previous permanent sterilization procedure.

WORKUP

- The components of evaluation depend greatly on whether the female patient is reliably ovulating based on history (regular menses, premenstrual molimina such as breast tenderness) and laboratory testing (midluteal progesterone, basal body temperature testing, urinary LH predictor kits, mid-cycle ovulatory pain [Mittelschmerz], cervical mucus testing). Box EI1-3 and Fig. EI1-9 describe an approach to infertility diagnosis and management.
- Where the menstrual cycle is important in testing, the first day is defined as the first day of full menstrual flow.
- If the female patient does not appear to be ovulating, testing should consist of:
  1. TSH.
  2. Prolactin.
  3. Total testosterone/free testosterone (to assess for PCOS).
  4. Transvaginal pelvic ultrasound to assess for polycystic-appearing ovaries.
  5. 17-Hydroxyprogesterone (to assess for cryptic congenital adrenal hyperplasia).
  6. 2-hr glucose tolerance testing (if the patient has PCOS).
  7. FSH/estradiol/anti-müllerian hormone on the second or third day of the menstrual cycle (if present).
  8. Lipid panel (if the patient has PCOS, secondary to overlap with metabolic syndrome).
  9. Liver function test (if the patient has PCOS, in case treatment with insulin-sensitizing agents indicated).
  10. BUN/creatinine (if the patient has PCOS, in case treatment with insulin-sensitizing agents indicated).
  11. Semen analysis in the male partner.
  12. Hysterosalpingogram (especially if the history suggests previous pelvic infection).
- If the female patient appears to be ovulating, testing should consist of:
  1. Semen analysis in the male partner.
  2. Hysterosalpingogram (Fig. I1-10).
  3. Mid-luteal progesterone, urinary LH predictor kits (to assess for ovulation).
  4. FSH, estradiol, anti-müllerian hormone on day 2 to 3 of menstrual cycle (ovarian reserve testing).
  5. Transvaginal pelvic ultrasound to assess for uterine anomalies and antral follicle count as a measure of ovarian reserve.

LABORATORY TESTS

- Semen analysis, using Kruger strict morphology after 2 to 3 days of abstinence (male).

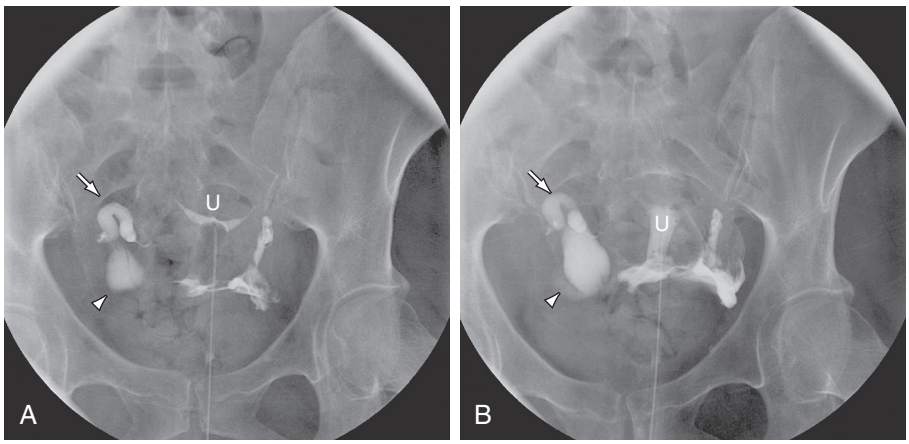


FIGURE I1-10 Hysterosalpingogram spot radiographs early **(A)** and late **(B)** demonstrate a rounded collection of contrast material *(arrowhead)* adjacent to the dilated ampullary portion of the right fallopian tube *(arrow),* caused by peritubal pelvic adhesions related to previous pelvic inflammatory disease. Normal patient left fallopian tube. *U,* Uterus. (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.)

- Day 2 or 3 FSH, estradiol, and anti-müllerian hormone as a measure of ovarian reserve (female).
- Mid-luteal progesterone (ideally 7 days after ovulatory surge). Given variability and absence of a reliable threshold, most practitioners use clinical criteria to diagnose ovulatory dysfunction.
- Urinary LH ovulatory kits.
- See "Workup" for evaluation of couples where the female partner is oligo- or anovulatory.

IMAGING STUDIES

- Hysterosalpingogram (between days 6 and 12 of the menstrual cycle).
- Day 2 or 3 transvaginal pelvic ultrasound to assess uterine abnormalities and to count the number of small antral follicles (2 to 9 mm) as a measure of ovarian reserve. If oligo- or anovulatory, to assess for polycystic-appearing ovary.
- Day 2 or 3 pelvic ultrasound assesses anatomic abnormalities and the number of antral ("resting") follicles; also a means of evaluating ovarian reserve.

Rx TREATMENT

Once the patient presents for evaluation, testing should be completed as quickly as possible, ideally within one menstrual cycle. The couple should follow up with the evaluating provider once all testing is completed and treatment initiated as abnormalities are found.

ACUTE GENERAL Rx

- Male infertility: referral to reproductive endocrinologist if semen analysis is abnormal or hyperprolactinemia is diagnosed. In patients with varicocele, there is insufficient evidence to suggest that corrective surgery will significantly improve birth rates.
- Mild male factor infertility may be treated with intrauterine insemination but more severe forms will usually require assisted reproductive technologies (ART) with intracytoplasmic sperm injection (ICSI) in the laboratory, where sperm is injected directly into the oocyte. ICSI use has increased from 36.4% in 1996 to 76.2% in 2012 with the largest increase among cycles without male factor infertility. Compared with conventional IVF, ICSI use is not associated with improved postfertilization reproductive outcomes, irrespective of male factor infertility diagnosis.[1]
- Tubal factor infertility may be treated surgically if mild and if the female patient is young and can afford the time to attempt pregnancy over multiple menstrual cycles. If the patient is older or if the tubal pathology is moderate to severe, the patient should use in vitro fertilization (IVF) to achieve pregnancy.
- Oligo- or anovulation should be treated with ovulation induction agents. Women with eustrogenic ovulatory dysfunction can be treated with clomiphene citrate as a first-line agent, using 50 mg in the first cycle attempt and increasing the dose by 50 mg up to a maximum dose of 200 mg if the patient fails to ovulate. Increasingly, aromatase inhibitors such as letrozole or anastrazole are being used both for ovulation induction in anovulatory patients and for superovulation in couples with unexplained infertility. A recent multicenter trial found that aromatase inhibitors achieved higher live birth rates than clomiphene citrate. Far less commonly, ovulatory dysfunction is the result of hypothalamic dysfunction. In these patients, once hypothalamic or pituitary abnormalities are excluded with MRI, ovulation can be achieved using injected gonadotropins.
- Uterine anatomic abnormalities such as submucous fibroids, polyps, or intrauterine adhesions should be corrected if they are identified. Fibroids that do not impact the uterine cavity probably do not interfere with fertility. Removal of intramural or subserosal fibroids is reserved for situations in which these cause excessive vaginal bleeding, pain, or pressure.
- Unexplained infertility can be treated empirically using superovulation with clomiphene citrate or gonadotropins combined with intrauterine insemination with partner's sperm. Most providers recommend using clomiphene citrate with insemination as a first-line superovulatory agent because it is inexpensive. After 3 to 4 such cycles, few pregnancies occur and the couple should be advised to become more aggressive. Controversy exists as to whether gonadotropins with insemination or IVF should be used after clomiphene citrate superovulation induction. There is evidence suggesting that moving to IVF in a *fast-track* fashion shortens the time interval to achieving pregnancy.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Acupuncture is widely used by women being treated for infertility. Limited data suggest some benefit, with possible mechanisms of action including increasing blood flow to the uterus. Patients may additionally benefit from the stress relief that acupuncture provides.

DISPOSITION

- Most couples will achieve a pregnancy, provided that they are willing to use aggressive techniques, including ART such as IVF and gamete donation.
- Adoption is also a worthwhile and viable possibility for couples who cannot conceive. These couples should be ready to take on some challenges, such as limited availability of adoptable children, as well as related financial and bureaucratic hurdles.

REFERRAL

Couples should be referred to a reproductive endocrinologist once the complexity of treatment exceeds the comfort level of the provider, whether a family physician, internist, or general gynecologist. Complex ovulation and superovulation induction and ART are usually managed by a board-certified reproductive endocrinologist.

PEARLS & CONSIDERATIONS

COMMENTS

- >2% of all live births in the United States currently are the result of IVF.
- The incidence of heterotopic pregnancy in patients who have undergone IVF is relatively common; identification of a patient with ultrasound-proved intrauterine pregnancy who used ART to conceive should NOT necessarily exclude the possibility of an ectopic gestation.

PREVENTION

- Techniques that reduce the incidence of pelvic inflammatory disease, such as condom use, can reduce pelvic adhesions that are associated with tubal factor infertility.
- Women can be made aware of the fact that delaying pregnancy into the later reproductive years can reduce the chances for successful pregnancy.

PATIENT & FAMILY EDUCATION

Patient support groups such as *Resolve* (www.resolve.org) are available to help couples during evaluation and treatment of infertility, which can be extraordinarily stressful.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Infertility (Patient Information)
Amenorrhea (Related Key Topic)
Pelvic Inflammatory Disease (Related Key Topic)
Polycystic Ovary Syndrome (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

[1]Boulet SL et al.: Trends in use of and reproductive outcomes associated with intracytoplasmic sperm injection, *JAMA* 313(3):255-263, 2015.

EVIDENCE

Abstract[1]

Background:
Randomized controlled trials (RCTs) addressing varicocele treatment are scarce and have conflicting outcomes.

Objective:
To determine whether varicocele treatment is superior or inferior to no treatment in male infertility from an evidence-based perspective.

Design, Setting, and Participants:
A prospective, nonmasked, parallel-group RCT with a one-to-one concealed-to-random allocation was conducted at the authors' institution from February 2006 to October 2009. Married men 20 to 39 yr of age who had experienced infertility ≥1 yr, had palpable varicoceles, and with at least one impaired semen parameter (sperm concentration <20 million/ml, progressive motility <50%, or normal morphology <30%) were eligible. Exclusions included subclinical or recurrent varicoceles, normal semen parameters, and azoospermia. Sample size analysis suggested 68 participants per arm.

Intervention:
Participants were randomly allocated to observation (the control arm [CA]) or subinguinal microsurgical varicocelectomy (the treatment arm [TA]). Semen analyses were obtained at baseline (three analyses) and at follow-up months 3, 6, 9, and 12. The mean of each sperm parameter at baseline and follow-ups was determined.

Measurements:
We measured the spontaneous pregnancy rate (the primary outcome), changes from baseline in mean semen parameters, and the occurrence of adverse events (AE—the secondary outcomes) during 12 mo follow-up; $p < 0.05$ was considered significant.

Results and Limitations:
Analysis included 145 participants (CA: n = 72; TA: n = 73), with a mean age plus or minus standard deviation of 29.3 ± 5.7 in the CA and 28.4 ± 5.7 in the TA ($p = 0.34$). Baseline characteristics in both arms were comparable. Spontaneous pregnancy was achieved in 13.9% (CA) versus 32.9% (TA), with an odds ratio (OR) of 3.04 (95% confidence interval [CI], 1.33–6.95) and a number needed to treat (NNT) of 5.27 patients (95% CI, 1.55–8.99). In CA within-arm analysis, none of semen parameters revealed significant changes from baseline (sperm concentration [$p = 0.18$], progressive motility [$p = 0.29$], and normal morphology [p = 0.05]). Conversely, in TA within-arm analysis, the mean of all semen parameters improved significantly in follow-up versus baseline ($p < 0.0001$). In between-arm analysis, all semen parameters improved significantly in the TA versus CA ($p < 0.0001$). No AEs were reported.

Conclusions:
Our RCT provided level 1b evidence of the superiority of varicocelectomy over observation in infertile men with palpable varicoceles and impaired semen quality, with increased odds of spontaneous pregnancy and improvements. A

Abstract[2]

Hyperprolactinemia is the most common cause of hypogonadotropic anovulation and is one of the leading causes of infertility in women aged 25 to 34. Hyperprolactinemia has been proposed to block ovulation through inhibition of GnRH release. Kisspeptin neurons, which express prolactin receptors, were recently identified as major regulators of GnRH neurons. To mimic the human pathology of anovulation, we continuously infused female mice with prolactin. Our studies demonstrated that hyperprolactinemia in mice induced anovulation, reduced GnRH and gonadotropin secretion, and diminished kisspeptin expression. Kisspeptin administration restored gonadotropin secretion and ovarian cyclicity, suggesting that kisspeptin neurons play a major role in hyperprolactinemic anovulation. Our studies indicate that administration of kisspeptin may serve as an alternative therapeutic approach to restore the fertility of hyperprolactinemic women who are resistant or intolerant to dopamine agonists A

Evidence-Based References

Abdel-Meguid TA et al.: Does varicocele repair improve male infertility? An evidence-based perspective from a randomized, controlled trial, *Eur Urol* 59:455–461, 2011. A

Sonigo C et al.: Hyperprolactinemia-induced ovarian acyclicity is reversed by kisspeptin administration, *J Clin Invest* 122:3791–3795, 2012. A

SUGGESTED READINGS

ACOG Practice Committee: Polycystic ovarian syndrome, *ACOG Practice Bulletin* 108, October 2009.

Alvero R: Assisted reproductive technologies: toward improving implantation rates and reducing high-order multiple gestations, *Obstet Gynecol Surv* 57(8):1–11, 2002.

Boulet SL et al.: Trends in use of and reproductive outcomes associated with intracytoplasmic sperm injection, *JAMA* 313(3):255–263, 2015.

Lindsay TJ, Vitrikas KR: Evaluation and treatment of infertility, *Am Fam Physician* 91(5):308–314, 2015.

Reindollar R et al.: A randomized clinical trial to evaluate optimal treatment for unexplained infertility: The Fast Track and Standard Treatment (FASTT) trial, *Fertil Steril* 94:888–899, 2010.

Wilcox AJ et al.: Timing of sexual intercourse in relation to ovulation-effects on the probability of conception, survival of the pregnancy and sex of the baby, *N Engl J Med* 333:1517, 1995.

BOX EI1-3 Infertility

Diagnostic Imaging	Lab Evaluation
Best Test	***Best Tests***
None	Male: semen analysis Female: endometrial biopsy
Ancillary Tests	***Ancillary Tests***
MRI of pituitary with contrast	FSH, LH
Hysterosalpingography	Prolactin
Testicular ultrasound	Serum testosterone (male) TSH CBC, ESR, FBS Urinalysis, VDRL, *Mycoplasma* culture, chlamydiae serology.

CBC, Complete blood count; *ESR,* erythrocyte sedimentation rate; *FBS,* fasting blood sugar; *FSH,* follicle-stimulating hormone; *LH,* luteinizing hormone; *MRI,* magnetic resonance imaging; *VDRL,* Venereal Disease Research Laboratory (test).
From Ferri FF: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 3, Philadelphia, 2014, Elsevier.

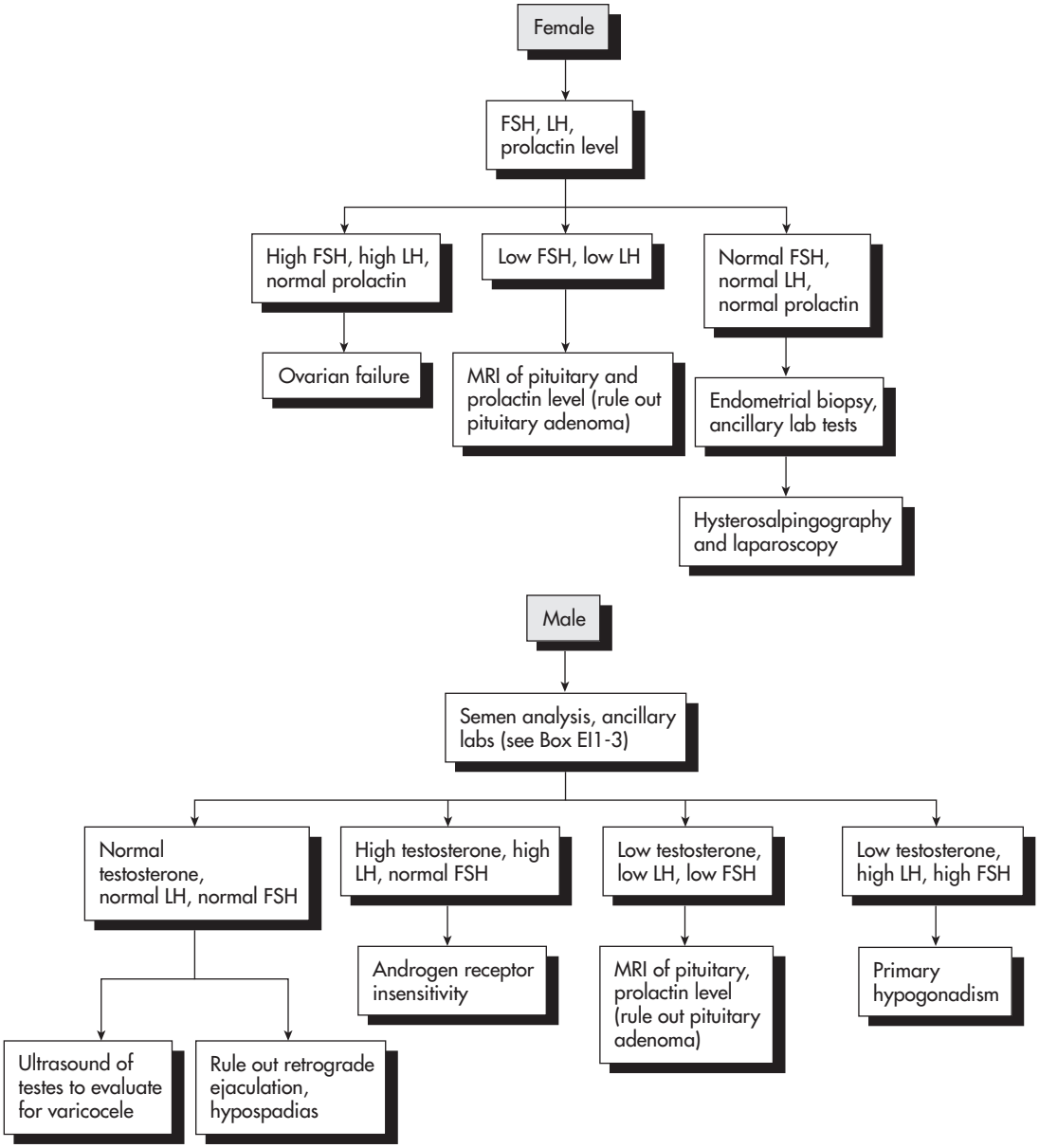


FIGURE EI1-9 Approach to infertility diagnosis and management. *FSH,* Follicle-stimulating hormone; *LH,* luteinizing hormone; *MRI,* magnetic resonance imaging. (From Ferri FF: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 3, Philadelphia, 2014, Elsevier.)

BASIC INFORMATION

DEFINITION

Inflammatory anemia refers to mild to moderately severe anemia (with hemoglobin [Hb] ranging from 7-12 g/dl), associated with chronic infections, inflammatory disorders, and some malignancies. Inflammatory anemia is also commonly referred to as anemia of chronic disease (ACD). The anemia is typically normocytic, normochromic, and hypoproliferative.

SYNONYMS

Anemia of chronic disease (ACD)
Anemia of inflammation
ACD

ICD-9CM CODES
285.21 Anemia in chronic kidney disease
285.22 Anemia in neoplastic disease
285.29 Anemia of other chronic illness
ICD-10CM CODES
D63.8 Anemia in chronic diseases classified elsewhere
D63.0 Anemia in neoplastic disease
D64.8 Anemia, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: The prevalence rate in the elderly ranges from 8% to 44%, with the greatest prevalence in men 85 yr and older.

- Second-most prevalent anemia after iron deficiency anemia
- Perhaps one third of elderly adults with anemia suffer from anemia of chronic disease, anemia of chronic renal failure, or both
  1. 11% of men and 10.2% of women age 65 to 85 yr
  2. >20% of adults older than 85 yr

PREDOMINANT SEX AND AGE: Male sex >85 yr of age

RISK FACTORS:

- Chronic inflammatory conditions like autoimmune disorders (e.g., rheumatoid arthritis, systemic lupus erythematosus, vasculitis and sarcoidosis, inflammatory bowel disease [Crohn's disease/ulcerative colitis])
- Neoplasia (both hematologic cancer and solid tumors)
- Chronic kidney disease
- Infection (acute/chronic—viral, bacterial, parasitic, and fungal)
- Chronic rejection after solid-organ transplantation

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Most patients are asymptomatic but may have general findings like skin pallor and conjunctival pallor.

ETIOLOGY

It is caused by several mechanisms

1. Altered iron homeostasis: Increased uptake and retention of iron within the cells of reticuloendothelial system (RES). Increase in Hepcidin (decreases duodenal iron absorption and blocks iron release from RES)
2. Reduced erythrocyte survival
3. Reduced erythropoietin production (EPO levels can be elevated in ACD, but are relatively low to the level of anemia)
4. Impaired erythropoiesis due to iron restriction and suppressed bone marrow erythroid response to EPO.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Iron deficiency anemia
Other causes of normocytic anemia
  Red blood cell loss or destruction
    Acute blood loss
    Hypersplenism
    Hemolysis
  Decreased red blood cell production
    Primary causes
      Bone marrow hypoplasia or aplasia
      Myelopathies
      Myeloproliferative disease
      Pure red blood cell aplasia
    Secondary causes
      Chronic renal failure
      Liver disease
      Endocrine deficiency states
      Sideroblastic anemia

WORKUP

Detailed history and physical examination. The diagnosis of inflammatory anemia is primarily one of exclusion. The best way to diagnose it is to document an anemia of underproduction in the setting of a systemic, usually inflammatory illness.

LABORATORY TESTS

CBC, reticulocyte count, reticulocyte index, peripheral smear, serum iron level, total iron-binding capacity, transferrin saturation, ferritin, and erythropoietin level. A bone marrow examination is usually not performed for diagnosis but may be necessary to rule out malignancy or infection. Table I1-6 describes laboratory characteristics of inflammatory anemia. Usual findings are as follows:

- Hb levels (typically): 8 to 9.5 g/dl
- Low reticulocyte count (reflecting ineffective erythropoiesis)
- Low serum iron concentration (also low in iron deficiency anemia)
- Low transferrin saturation (also low in iron deficiency anemia)
- Serum ferritin (marker of iron storage and acute phase reactant) normal or increased (Fig. I1-11).
  1. Acute inflammatory states may mimic the hematologic profile of anemia of chronic disease
- Soluble transferrin receptor (sTfR) levels remain within normal limits (elevated in iron deficiency anemia)
  1. TfR index (sTfR/log Ferritin): in patients with normal to high ferritin, it helps to differentiate combined ACD/IDA (>2) from ACD (<1) (Fig. I1-11).
- Hepcidin: low in IDA, elevated in ACD and normal in ACD/IDA.
- Erythropoietin level not very useful. Expected to be low in CKD and doesn't alter the management or ESA dose. In other causes of ACD, EPO levels will start to increase whenever Hb <10g/dl.
- Peripheral smear usually reveals hypochromic normocytic RBCs (Fig. EI1-12*A*). Bone marrow shows that erythroid precursors are present in normal numbers (Fig. EI1-12*B*) and iron stores are increased in stromal histiocytes (Fig. EI1-13).

TREATMENT

Treat the underlying disorder/disease.

TABLE I1-6 Laboratory Characteristics of ACD, IDA, and IDA with Inflammation

	Anemia of Chronic Disease (ACD)	Iron Deficiency Anemia (IDA)	IDA with Inflammation
Mean corpuscular volume (MCV)	72-100 fL	<85 fL	<100 fL
Mean corpuscular hemoglobin concentration (MCHC)	<36 g/dl	<32 g/dl	<32 g/dl
Serum iron	Decreased	Decreased	Decreased
Serum total iron-binding capacity (TIBC)	Typical below mid-normal range	Elevated	Less than upper limit of normal range
Transferrin saturation*	2%-20%	<15% (usually <10%)	<15%
Serum ferritin	>35 μg/L	<35 μg/L	>35 μg/L, <200μg/L
Serum soluble transferrin receptor concentration (sTfR)	Normal (may be increased if serum ferritin > 200 μg/L)	Increased	Increased
TfR index (sTfR/log ferritin)	<1	>2	>2
Hepcidin	High	Low	Normal
Stainable iron in bone marrow	Present	Absent	Absent

*Serum iron/TIBC * 100
From Young NS et al (eds): *Clinical hematology,* St Louis, 2006, Mosby.

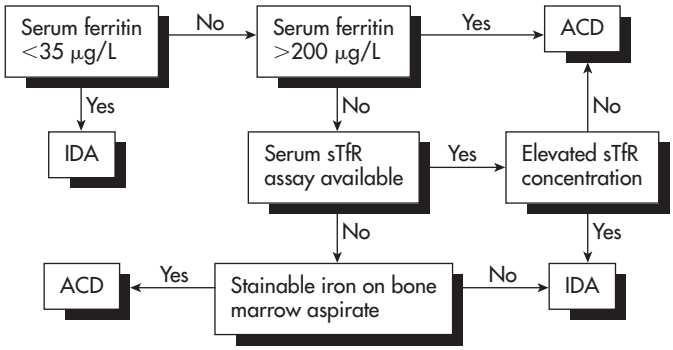


FIGURE I1-11 Differential diagnosis of anemia with low serum iron. *ACD,* Anemia of chronic disease; *IDA,* iron deficiency anemia; *sTfR,* soluble transferrin receptor. (Modified from Young NS et al [eds]: *Clinical hematology,* St Louis, 2006, Mosby.)

ACUTE GENERAL Rx

Blood transfusion is usually reserved for severe anemia (with Hb level <7 g/dl or <8 g/dl in patients with cardiac disease) especially if complicated with ongoing bleeding.

CHRONIC Rx

- Erythropoiesis-stimulating agents (ESA) (epoetin alfa and darbepoetin alfa) are FDA approved for use in patients with anemia resulting from:
  1. CKD
  2. Chemotherapy
  3. Zidovudine therapy.

Data from multiple trials, including pre-dialysis (CHOIR, CREATE, and TREAT) and hemodialysis (NHT) patients, suggest that higher ESA dose and/or higher Hb target are associated with an increase in adverse events (cardiovascular and thromboembolic).

ESA use in patients with cancer was correlated with an increase in tumor progression and mortality. Therefore, ESA should not be used in patients on chemotherapy when the anticipated treatment outcome is cure (NCCN guidelines, 2012 updates).

ESA dose should be individualized for each patient and the lowest sufficient dose to reduce blood transfusions should be used. A Hb target of 10 to 12 is widely acceptable. Supplemental iron: Before initiation of erythropoietin therapy, iron deficiency needs to be ruled out. After starting ESA therapy, ASH/ASCO guidelines recommend periodic monitoring of iron status. When no response to oral therapy, parental iron therapy is to be considered before stating that patient is non-responsive to iron therapy. Maintain a transferrin saturation of >20% and a ferritin ≥100ng/ml.

REFERRAL

Hematology and oncology

PEARLS & CONSIDERATIONS

COMMENTS

The anemia of inflammation, which also includes anemia of critical illness, is a condition that presents similarly to anemia of chronic disease but develops within days of the onset of illness (major surgery, myocardial infarction, sepsis, major trauma). An anemia similar to anemia of inflammation is seen in some elderly patients in the absence of identifiable chronic disease.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **TONY ABDO, M.D.**

SUGGESTED READINGS

American Medical Directors Association (AMDA). Anemia in the long-term care setting. American Medical Directors Association (AMDA): Columbia, Md.

Artz AS, Ershler WB: Anemia in elderly persons, *eMedicine Journal last updated*, Sep 29, 2009. Available at www.emedicine.com.

Bunn HF: End run around Epo, *N Engl J Med* 361:1901–1903, 2009.

Cheng PP et al.: Hepcidin expression in anemia of chronic disease and concomitant iron-deficiency anemia, *Clin Exp Med* 11(1):33–42, 2011.

Chiari MM: Influence of acute inflammation on iron and nutritional status indexes in older inpatients, *J Am Geriatr Soc* 43(7):767–771, 1995.

Cullis JO: Diagnosis and management of anaemia of chronic disease: current status, *Br J Haematol Aug* 154(3):289–300, 2011.

KDIGO: clinical practice guideline for anemia in chronic kidney disease, *Kidney Int Suppl* 2(4):279–335, 2012.

Rizzo JD et al.: ASCO/ASH clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer, *J Clin Oncol* 28(33):4936–5010, 2010.

Tussing-Humphries L et al.: Rethinking iron regulation and assessment in iron deficiency, anemia of chronic disease, and obesity: introducing hepcidin, *J Acad Nutr Diet* 112(3):391–400, 2012.

Weiss G, Goodnough LT: Anemia of chronic disease, *N Engl J Med* 352:1011–1023, 2005.

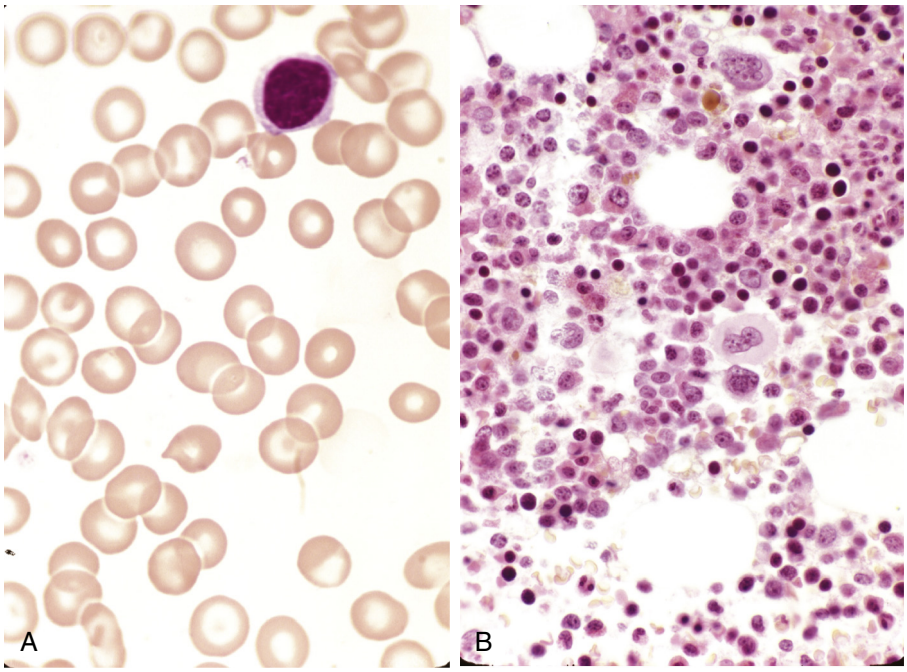


FIGURE EI1-12 Slightly hypochromic normocytic red cells in anemia of chronic disease associated with rheumatoid arthritis **(A).** Bone marrow erythroid precursors are present in normal numbers **(B).** (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

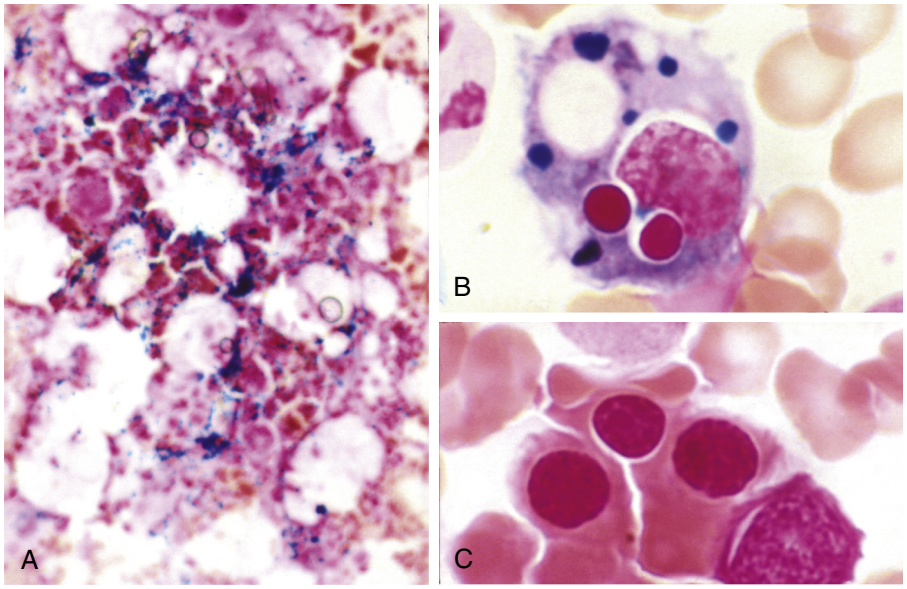


FIGURE EI1-13 In anemia of chronic disease, iron stores are increased in stromal histiocytes (**A** and **B).** Erythroid iron incorporation is decreased or undetectable **(C).** (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Influenza is an acute febrile illness caused by infection with influenza type A or B virus. Seasonal influenza can include the H1N1 virus. Severe acute respiratory syndrome (SARS) is a similar respiratory illness caused by a coronavirus called SARS-associated coronavirus (SARS-CoV). A new novel coronavirus was recognized in two patients in September 2012. This is a very different virus from the SARS agent; the two patients exhibited acute respiratory distress syndrome, renal failure, consumptive coagulopathy, and/or pericarditis. Now called the Middle East respiratory syndrome (MERS-CoV) virus, it has affected patients with connections to several Middle Eastern countries. Death rate has approached 50%. Dromedary camels and their milk are documented to harbor MERS-CoV.

SYNONYMS

Flu
Influenza-like illness (ILI)

ICD-9CM CODES
487 Influenza
487.1 Influenza with other respiratory manifestations
ICD-10CM CODES
J10.1 Influenza due to other identified influenza virus with other respiratory manifestations

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Winter outbreaks lasting 5 to 6 wk.
PREDOMINANT SEX: Male =female.
PREDOMINANT AGE: Attack rates are higher among children than adults, although children are less prone to develop pulmonary complications. During the 2013 to 2014 flu season, there were a high number of hospitalizations of those between 18 and 65 years old with severe morbidity.
INCIDENCE (IN U.S.): Annual incidence of influenza-related deaths is ~36,000 deaths/yr.

PANDEMICS

DEFINITION: Widespread human community-level outbreaks in ≥two countries in one World Health Organization (WHO) region.
HISTORICAL

- In the twentieth century, pandemics occurred from H1N1 resulting in 40 to 100 million deaths worldwide in 1918, 70,000 deaths in the United States in 1957 from H2N2, and 36,000 deaths in the United States in 1968 from H3N2.
- H5N1 emerged in Hong Kong in 1997, quickly infecting poultry and birds. More than 400 humans were infected with avian flu (H5N1) by 2009, but transmission from human to human was not efficient.

Novel influenza A virus:

- The WHO declared the H1N1 outbreaks a public health emergency in April 2009 and announced a global pandemic in June 2009. The U.S. emergency ended in June 2010, and the WHO declared an end to the global pandemic in August 2010.
- H1N1 continues circulation as a seasonal virus.
- The 2009 H1N1 virus affected more young adults than the elderly.
- In 2009 in the United States, it is estimated that there were 43 million to 88 million cases, 192,000 to 398,000 hospitalizations, and as many as 18,000 deaths from H1N1.
- H3N2 variant virus (H3N2v) normally circulates in swine but sometimes infects humans. Infections occurred in 2012 and 2013, mostly associated with exposure to pigs at agricultural fairs. These are not sustained by efficient human-to-human community spread.
- The 2012 H3N2v viruses contained the matrix (M) gene from the 2009 pandemic influenza A (H1N1) virus.
- Influenza A H3N2v clinical presentation is similar to signs and symptoms of uncomplicated seasonal influenza, with vomiting and diarrhea in some pediatric cases. Symptoms can be milder, without fever, lasting 3-5 days.
- Avian influenza A (H7N9) virus caused severe human illness in China from February to May, 2013. Most symptomatic patients are older, male, with underlying conditions, and exposure to poultry. Recommended treatment is oral oseltamivir or inhaled zanamivir as early as possible.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- "Classic flu" is characterized by abrupt onset of fever, headache, myalgias, anorexia, and malaise after a 1- to 2-day incubation period.
- Clinical syndromes are similar to those produced by other respiratory viruses, including pharyngitis, common colds, tracheobronchitis, bronchiolitis, and croup.
- Respiratory symptoms such as cough, sore throat, and nasal discharge are usually present at the onset of illness, but systemic symptoms predominate.
- Elderly patients may experience fever, weakness, and confusion without any respiratory complaints.
- Acute deterioration to status asthmaticus may occur in patients with asthma.
- Influenza pneumonia: rapidly progressive cough, dyspnea, and cyanosis may occur after typical flu onset. This may be caused by primary influenza pneumonia or secondary bacterial pneumonia (often pneumococcal or staphylococcal co-infection).
- For influenza A (H3N2v), children younger than 10 years lack immunity. People ≥ 65 years and those with morbid obesity are at high risk.

ETIOLOGY

- Variation in the surface antigens of the influenza virus, hemagglutinin (HA) and neuraminidase (NA), leading to infection with variants to which immunity is inadequate in the population at risk.
- Droplet transmission by small-particle aerosols and deposited on the respiratory tract epithelium.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Respiratory syncytial virus, adenovirus, parainfluenza virus infection.
- Secondary bacterial pneumonia or mixed bacterial-viral pneumonia.

WORKUP

- The accuracy of clinical diagnosis of influenza on the basis of symptoms alone is limited because symptoms from illness caused by other pathogens can overlap considerably with influenza. Diagnostic tests available for influenza include viral cultures, serology, rapid influenza diagnostic tests (RIDTs), reverse transcription-polymerase chain reaction (RT-PCR), and immunofluorescence assays.
- Virus isolation from nasal or throat swab or sputum specimens is the most rapid diagnostic method in the setting of acute illness.
- Specimens are placed into virus transport medium and processed by a reference laboratory.
- For serologic diagnosis:
  1. Paired serum specimens, acute and convalescent, the latter obtained 10 to 20 days later
  2. Fourfold rises or falls in the titer of antibodies (various techniques) considered diagnostic of recent infection
  3. Commercial rapid influenza diagnostic tests (RIDTs) are available. They can detect influenza virus antigens within 15 minutes of testing. Rapid flu test should be collected as early as possible, ideally within 4 days of onset. False-negative results are common during the flu season. A negative test result does NOT exclude diagnosis of influenza.
  4. Commercial RIDTs cannot determine if an H3N2 is a variant virus; when suspect H3N2v virus infection, send nasopharyngeal swab or aspirate in viral transport medium to state public health laboratory for rRT-PCR testing using CDC FLU rRT-PCR diagnostic panel assay.

LABORATORY TESTS

Septic syndrome presentation: CBC, ABG analysis, blood cultures

IMAGING STUDIES

- Chest x-ray examination when suspecting viral pneumonia: peribronchial and patchy interstitial infiltrates in multiple lobes with atelectasis. Table I1-7 describes x-ray pulmonary findings based on virus type.
- Possible progression to diffuse interstitial pneumonitis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Bed rest.
- Hydration.

ACUTE GENERAL Rx

- Supportive care: antipyretics; avoid use of aspirin in children because of the association with Reye's syndrome.
- Antibiotics if bacterial pneumonia is proved or suspected.
- Amantadine is NOT recommended due to resistant isolates.
- Neuraminidase inhibitors block release of virions from infected cells, resulting in shortened duration of symptoms and decrease in complications; effective against both influenza A and B, including A (H3N2v) for all hospitalized patients, those with severe and progressive illness, and high-risk patients with suspected or confirmed H3N2v.
  1. Zanamivir, administered via inhaler:
     For treatment, 10 mg (2 inhalations of 5 mg each) twice daily for 5 days.
     For prevention in households, 10 mg (2 inhalations of 5 mg each) once daily for 17 days.
     Not recommended in persons with underlying airways disease such as asthma or chronic obstructive pulmonary disease.
  2. Oseltamivir, administered orally:
     For treatment, 75 mg PO twice daily for 5 days.
     For prevention, 75 mg PO once daily for a minimum of 2 wk in an outbreak setting or 7 days after exposure for an adult.
  3. Emergency use authorization by the Centers for Disease Control and Prevention (CDC) for intravenous peramivir during the H1N1 pandemic was terminated in June 2010. Intravenous zanamivir is available in clinical trials or as an emergency investigational new drug.
- Placebo-controlled studies have suggested that antiviral therapy with any of the previously mentioned agents must ideally be initiated within 1 to 2 days of the onset of symptoms and reduces the duration of illness by ~1 day.
- Oseltamivir resistance developed on therapy in individuals with avian flu (H5N1) in Asia, and this is associated with poor outcome.
- Amantadine and rimantadine resistance are documented for novel (H1N1) influenza and H3N2 influenza virus.
- Systemic corticosteroids should not be routinely administered to patients with suspected or confirmed influenza, including H3N2v virus infection, except for patients on chronic corticosteroid therapy for COPD, asthma.

DISPOSITION

Patients are hospitalized if signs of pneumonia are present.

REFERRAL

Infectious disease and/or pulmonary consultation when influenza pneumonia is suspected.

PEARLS & CONSIDERATIONS

COMMENTS

- Prevention of influenza in patients at high risk is an important goal of primary care.
- Vaccines reduce the risk of infection and the severity of illness.
  1. Antigenic composition of the vaccine is updated annually. The northern hemisphere's 2014 to 2015 season trivalent vaccine includes A/Texas/50/2012 (H3N2)-like virus, influenza. A/California/7/2009(H1N1) pdmo9-like virus, and one influenza B-like virus (B/Massachusetts/2/2012-like). Quadrivalent vaccines contain these three antigens, plus an antigen from a second influenza B vaccine virus strain (B/Brisbane/60/2008-like).
  2. Revaccination is recommended annually even for those who received the vaccine in the previous season.
  3. Seasonal influenza vaccine does not provide protection against the influenza A (H3N2v) virus that is associated with agricultural fairs.
  4. Vaccination should be given at the start of the flu season (September-October) for all persons aged ≥6 mo. Vaccination is particularly important for persons who are at increased risk for severe complications from influenza. When vaccine supply is limited, vaccination efforts should focus on the following groups:
     a. All children aged 6 mo to 4 yr (59 mo).
     b. People 50 years and older.
     c. Adults and children with chronic cardiac (except hypertension) or pulmonary (including asthma), renal, hepatic, neurologic, hematologic or metabolic disease (including diabetes mellitus).
     d. Immunocompromised patients (including HIV-infected persons or patients immunosuppressed due to medications).
     e. Women who are or will be pregnant during the influenza season.
     f. Children aged 6 mo to 18 yr who are receiving long-term aspirin therapy.
     g. Residents of nursing homes and other long-term care facilities.
     h. American Indians/Alaska Natives.
     i. Persons who are morbidly obese (BMI ≥40).
     j. Health care workers (HCWs).
     k. Household contacts and caregivers of persons in the previous groups.
  5. Vaccination should be delayed for persons with moderate to severe acute febrile illness. Precautions include:
     a. Guillain-Barré syndrome within 6 wk following a previous dose of influenza vaccine.
     b. Moderate or severe acute illness with or without fever (for trivalent inactivated influenza vaccine).
  6. Contraindication to receiving vaccine is a previous severe allergic reaction to influenza vaccine.
  7. Special efforts should be made to vaccinate high-risk patients <65 yr, only 10% to 15% of whom are vaccinated each year.
  8. HCW vaccination minimizes transmission to patients and coworkers. Some states mandate vaccination of HCWs; some healthcare facilities and other states promote the wearing of face masks by unvaccinated HCWs during the influenza season, particularly when there is widespread flu.
  9. Vaccine efficacy varies by age and by type of circulating virus.
  10. Alternate vaccine formulations.
      1. Intradermal vaccine is available for injection into skin instead of muscle. This uses a smaller needle than the regular flu vaccine and might be preferred by adults aged 18 to 64 yr who do not like shots.

TABLE I1-7 Pulmonary Radiographic Findings Based on Virus Type

Virus	Centrilobular Nodules	Lobar Ground-Glass	Diffuse Ground-Glass	Thickened Interlobular Septa	Consolidation
Influenza	+++	+++	+		+
Epstein-Barr	+	+	+		+
Cytomegalovirus	++	++	++	+	+
Varicella-zoster	+++	+	+		
Herpes simplex	+	+++	+		+++
Measles	++	+	+		+
Hantavirus			+++	+	++
Adenovirus	++	+			+++

From Weissleder R et al: *Primer of diagnostic imaging,* ed 5, St Louis, 2011, Mosby.

2. Nasal spray, live-attenuated influenza vaccine (LAIV) is available for nonpregnant, healthy persons aged 2 to 49 yr. Preferential use of LAIV in healthy children 2 to 8 yr is the anticipated recommendation from ACIP at present. Note: give TIV if recipient has egg allergy or asthma or cares for immunosuppressed persons who require a protective environment.
3. High-dose inactivated vaccine (60 micrograms hemagglutinin each flu strain) is available for persons ≥65 yr. Recent study concludes a significantly improved efficacy using high-dose vaccine.
4. Thimerosal-free vaccine is available.
5. Inactivated influenza vaccine (IIV) can be trivalent or quadrivalent, and egg-based or non-egg-based (cell culture or recombinant hemagglutinin).
6. There is no additional preference for live-attenuated influenza vaccine (LAIV) or IIV.
7. There is no preference for standard dose IIV, high dose IIV (age 65 or over) or intradermal IIV (age 18-64).
8. ACIP guidance for egg allergies:
   - If a person with egg allergy experiences only hives, then administer trivalent recombinant hemagglutinin influenza vaccine (RIV3) if age 18 to 49, or IIV and observe for at least 30 minutes for reaction following vaccine.
   - If a person with egg allergy experiences other symptoms such as cardiovascular (e.g., hypotension), respiratory distress (e.g., wheezing), gastrointestinal (e.g., nausea/vomiting), reaction requiring epinephrine or emergency medical attention, administer RIV3 if age 18 to 49, or refer to a physician with expertise in management of allergic conditions.
   - If there is no known history of exposure to egg, but the person is suspected of having egg allergy, consult with a physician who has expertise in the management of allergies before vaccinating, or give RIV3 (if age 18 to 49).

- Chemoprophylaxis:
  1. Table I1-8 describes antiviral agents for influenza. Oseltamivir and zanamivir are recommended in the United States during the influenza season.
  2. Consider (after the current circulating strain of influenza has been shown to be sensitive):
     a. For high-risk patients in whom vaccination is contraindicated.
     b. When the available vaccine is known not to include the circulating strain.
     c. To provide added protection to immunosuppressed patients likely to have a diminished response to vaccination.
     d. In the setting of an outbreak, when immediate protection of unvaccinated or recently vaccinated patients at high risk of complications is desired. Chemoprophylaxis with antiviral drugs is not recommended for healthy persons exposed to influenza.
  3. Give for 2 wk in the case of late vaccination and for the duration of the flu season in all other patients.
  4. Treatment should not wait for laboratory confirmation of influenza.
  5. Do not give aspirin or aspirin-containing products to children with influenza-like illness due to the risk of Reye's syndrome.
- Other prevention strategies:
  1. Hand hygiene, cough etiquette (cover your cough), respiratory hygiene (use of tissues, facemasks for the ill and proper disposal).
  2. Personal protective equipment (PPE)—wear gloves and gowns as per universal/standard precautions. Per Centers for Disease Control and Prevention, wear facemask, adhering to Droplet Precautions for 7 days after illness onset or until 24 hr after fever and respiratory symptoms are resolved, whichever is longer. Patient placement in a negative pressure room and N95 respirator for health care workers are recommended when conducting aerosol-generating procedures.
  3. Management of ill health care workers—exclude from work until at least 24 hr after they no longer have a fever (without the use of fever-reducing medication). Extended exclusion time period when caring for severely immunocompromised patients.
  4. Standard cleaning and disinfection procedures.
- The Centers for Medicare and Medicaid Services plan to link healthcare worker vaccine acceptance with payment for performance in FY2016.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Influenza (Flu) (Patient Information)

AUTHOR: **MARLENE FISHMAN WOLPERT, M.P.H., C.I.C.**

TABLE I1-8 Antiviral Agents for Influenza

	Amantadine	Rimantadine	Zanamivir	Oseltamivir
Protein target	M2	M2	Neuraminidase	Neuraminidase
Activity	A only (H1N1 and H3N2 are resistant)	A only (H1N1 and H3N2 are resistant)	A and B	A and B
Side effects	CNS (13%) GI (3%)	GI (6%)	? Bronchospasm	GI (9%)
Metabolism	None	Multiple (hepatic)	None	Hepatic
Excretion	Renal	Renal,+ others	Renal	Renal (tubular secretion)
Drug interactions	Antihistamines, anticholinergics	None	None	Probenecid (increased levels of oseltamivir)
Dose adjustments needed	≥65 yr old CrCl <50 ml/min	≥65 yr old CrCl <10 ml/min	None	CrCl <30 ml/min Severe liver dysfunction
Contraindications	Acute-angle glaucoma	Severe liver dysfunction	Underlying airway disease, asthma	
FDA-Approved Indications				
Therapy	Adults and children ≥1 yr old	Adults only	Adults and children ≥7 yr old	Adults and children ≥1 yr old*
Prophylaxis	Yes	Yes	Adults and children ≥5 yr old	Adults and children ≥13 yr old†

CrCl, Creatinine clearance; *FDA*, U.S. Food and Drug Administration; *GI*, gastrointestinal.
*FDA has authorized treatment of S-OIV (novel H1N1) virus with oseltamivir in children ≥3 mo of age.
†FDA has authorized prophylaxis for S-OIV (novel H1N1) virus with oseltamivir in children ≥1 yr.
From Mandell GL et al: *Principles and practice of infectious diseases,* ed 7, Philadelphia, 2010, Churchill Livingstone.

SUGGESTED READINGS

Advisory Committee on Immunization Practices (ACIP) recommends a preference for using nasal spray flu vaccine. Available at http://www.cdc.gov/media/releases/2014/s0625-acip.html Accessed 8/13/14.

Centers for Disease Control and Prevention: What you should know for the 2014-2015 influenza season. Available at http://www.cdc.gov/flu/about/season/flu-season-2014-2015.htm Accessed 8/13/14.

Centers for Disease Control and Prevention. CDC 2011-2012 influenza antiviral medications summary for clinicians. Available at http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm. Accessed 8/1/14.

Centers for Disease Control and Prevention. Updated CDC estimates of 2009 H1N1 influenza cases, hospitalizations and deaths in the United States, April 2009-April 10, 2010. Archived. Available at http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm. Accessed 8/1/14.

Centers for Disease Control and Prevention. ACIP recommends influenza vaccine option for persons with egg allergy. Available at http://www.cdc.gov/media/releases/2013/a0620-FluBlok.html. Accessed 8/1/14.

Centers for Disease Control and Prevention. Interim information for clinicians about human infections with H3N2v virus. Available at http://www.cdc.gov/flu/swineflu/h3n2v-clinician.htm. Accessed 8/14/14.

Centers for Disease Control and Prevention: Prevention and control of seasonal influenza with vaccines, Recommendations of the Advisory Committee on Immunization Practices (ACIP) - United States, 2013 – 2014 season. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6207a1.htm?s_cid=rr6207a1. Accessed 8/1/14.

Centers for Disease Control and Prevention: Evaluation of rapid influenza diagnostic tests for Influenza A (H3N2) virus and update case count – United States, *MMWR early release* Vol. 61(2012), August 10, 2012. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6132a4.htm?s_cid=mm6132a4_e Accessed 8/1/14.

Centers for Disease Control and Prevention. Middle East Respiratory Syndrome. Available at http://www.cdc.gov/coronavirus/mers/index.html. Accessed 8/1/14.

Centers for Disease Control and Prevention. Severe acute respiratory syndrome (SARS). Available at http://www.cdc.gov/sars. Accessed 8/1/14.

DiazGranados CA, Dunning AJ, Kimmel M, Kirby D et al.: Efficacy of high-dose versus standard-dose influenza vaccine in older adults, *N Engl J Med* 371(7):635–645, 2014. August 14.

Gao R et al.: Human infection with a novel avian-origin influenza a (H7N9) virus, *N Engl J Med* 368(20):1888–1897, 2013.

National Center for Immunization and Respiratory Diseases (NCIRD). CDC Netconference: ACIP Influenza Vaccine Recommendations 2013-14 Season. Available at http://www.cdc.gov/vaccines/ed/ciinc/2013-07-25.htm. Accessed 8/ 1/14.

Sampathkumar P: Middle East respiratory syndrome: what clinicians need to know, *Mayo Clin Proc* 89(8):1153–1158, 2014.

Wong KK et al.: Transmissibility of variant influenza from swine to humans: a modeling approach, *Clin Infect Dis* 57(S1):S16–S22, 2013.

World Health Organization. Interim surveillance recommendations for human infection with Middle East respiratory syndrome coronavirus as of 27 June 2013. Available at http://www.who.int/csr/disease/coronavirus_infections/InterimRevisedSurveillanceRecommendations_nCoVinfection_27Jun13.pdf. Accessed 8/1/14.

BASIC INFORMATION

DEFINITION

Avian influenza is a virus originating in birds that has the capacity to infect humans. The prior influenza pandemics of the twentieth century (from the devastating 1918 pandemic (H1N1), in which 40 to 100 million people died, to the lesser pandemics of 1957 (H2N2) and 1968 (H3N3), of 1 to 6 million deaths) were caused by highly virulent, efficiently transmitted influenzas that evolved from avian strains. The highly pathogenic avian influenza A (H5N1), which is capable of only incidentally infecting humans, but with a near 60% mortality rate, has threatened to bring another pandemic flu. H5N1 avian influenza emerged in 1997 in Hong Kong, and by September 2012 had infected worldwide 608 humans with 359 deaths (62 cases in 2011) as it spread via migrating waterfowl from Asia to Europe and Africa. However, the worldwide epidemic of a novel influenza strain in 2009 to 2010 with millions of cases was not with this virus, but with the H1N1 virus, which was a reassortment human-swine-avian virus. See "Influenza."

SYNONYMS

Bird flu
Pandemic flu

ICD-9CM CODES
488 Avian influenza
ICD-10CM CODES
J09 Influenza due to certain identified influenza virus

EPIDEMIOLOGY & DEMOGRAPHICS

Avian influenza A H5N1 is an influenza virus related to those that bring our yearly influenzas, against which populations are routinely vaccinated. Influenza viruses are enveloped RNA viruses with segmented genomes and great antigenic diversity. They are categorized by their core proteins (A, B, C), species of origin (avian, swine, human), geographic site of isolation, serial number, and influenza subtypes based on the major antigenic surface glycoproteins, hemagglutinin (HA), and neuraminidase (NA). Example: H5N1 refers to hemagglutinin subtype 5 and neuraminidase subtype 1.

Often human and avian viruses meet and resort in a pig respiratory system. Southeast Asia is often the birthplace of new flu strains because birds, pigs, and people live in close proximity. It is where avian influenza A H5N1 emerged, first infecting domestic poultry, then wild birds that migrated across Eurasia. It is transmitted directly from birds to their keepers. Antigenic drift or shift may allow avian influenza A H5N1 to gain the ability to be easily transmissible from human to human, transforming it from a highly virulent influenza strain to a pandemic flu.

PREDOMINANT SEX AND AGE: Children and young adults.

RISK FACTORS: Poultry work, possibly swine work (in case of reassortment), travel to affected areas.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Presenting features include fever of at least 100.4° F (38° C) with leukopenia or lymphopenia nearly always followed by viral pneumonia with escalating respiratory distress.
- Ventilatory support is often required within 48 hr of hospitalization for acute respiratory distress syndrome (ARDS).
- Symptom onset is 2 to 5 days after exposure, longer than with human influenza.
- Respiratory symptoms may also be accompanied by watery diarrhea.
- Complications include respiratory failure, renal dysfunction, cardiac compromise, pulmonary hemorrhage, pneumothorax, and multiorgan failure. A common cause of death is superinfection with bacterial pneumonias.

ETIOLOGY

H5N1 resists host antiviral cytokines, inducing excessive host proinflammatory responses. It may cause death by "cytokine storm" rather than by inherent pathogenicity. It attaches to sialic acid molecules via an α2-3 galactose receptor (common in birds) also found in human alveoli, leading to heavy damage to lower lungs. It causes severe pulmonary injury with diffuse alveolar damage. In the bone marrow, there is a reactive histiocytosis with hemophagocytosis that may lead to pancytopenia.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Atypical pneumonia, typical respiratory virus infections (e.g., influenza, respiratory syncytial virus), severe acute respiratory syndrome, upper respiratory infection with conjunctivitis (e.g., adenovirus). Clinical symptoms indistinguishable from other illnesses.

WORKUP

Comprehensive travel, occupational and epidemiologic history.

LABORATORY TESTS

- Aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine, complete blood count should be performed.
- Throat swab within 3 days of onset of symptoms to be sent for viral culture and polymerase chain reaction assay for avian influenza A (H5N1) RNA with appropriate biosafety precautions. The throat swab is more effective than nasal swabs since avian influenza preferentially infects the throat and lower respiratory tract. In the United States the FDA has approved the release of influenza H/A5 (Asian lineage) Virus Real-Time Reverse Transcription-PCR Primer and Probe Set for more than 140 labs in 50 states, which will return preliminary results in 4 hr.
- High-risk patients who must be tested include those with history of travel within 10 days of symptom onset to a country with documented H5N1 avian flu as well as patients with radiographically confirmed pneumonia, ARDS, or severe respiratory illness without alternate etiology.
- Low-risk patients are those who have contact with domestic poultry, or contact with people who have traveled to a country with documented H5N1 avian flu, who have fever >38° C and cough, sore throat, shortness of breath.

IMAGING STUDIES

- Chest x-rays detect infiltrates a median of 7 days after onset of fever. They may be diffuse, multifocal/patchy infiltrates, or interstitial infiltrates, or segmental/lobular consolidation. Progression to respiratory failure is indicated by diffuse bilateral ground-glass infiltrates.
- See "Imaging Studies" in "Acute Respiratory Distress Syndrome" topic.

TREATMENT

Vaccines and antivirals are the usual means for preventing and treating flu, but there are limited supplies worldwide. A subviron H1N1 vaccine was FDA approved in 2007. The traditional means of vaccine production using embryonated hens' eggs has been limited because the bird flu kills the eggs. Promising new vaccine production methods are advancing through the experimental stages, including adenovirus vectors that have the possibility of allowing rapid large-scale production of vaccines.

NONPHARMACOLOGIC THERAPY

- N95 particulate masks prevent person-to-person transmission of H5N1. Surgical masks also likely prevent transmission of the virus as was seen in the H1N1 pandemic.
- In preparation for pandemic flu: increase worldwide surveillance and disease reporting, kill infected birds, increase the numbers of available intensive care unit beds with mechanical ventilators and increase emergency capacity, educate medical personnel and the public, produce vaccines.
- In response, use influenza surveillance, social distancing (school closures), travel restrictions, quarantine, respirator masks, communications networking, and international teamwork to cordon off affected areas.

ACUTE GENERAL Rx

- The neuraminidase inhibitor oseltamivir can reduce the severity and duration of symptoms if treatment is initiated in the first 48 hr after symptom onset.
  1. Treatment: adults 75 mg PO twice daily for 5 days.
  2. Postexposure prophylaxis: 75 mg PO daily for 7 to 10 days.
- H5N1 demonstrates amantadine and rimantadine resistance.

PEARLS & CONSIDERATIONS

PREVENTION

See "Nonpharmacologic Therapy."

PATIENT & FAMILY EDUCATION

The American Council on Science and Health: Avian influenza: what you need to know. Available at http://acsh.org/publications/pubid.1294/pub_detail.asp

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Arabi Y et al.: The critically ill avian influenza A (H5N1) patient, *Crit Care Med* 35(5):1397–1403, 2007.

Brundage JF: Interactions between influenza and bacterial respiratory pathogens: implications for pandemic preparedness, *Lancet Infect Dis* 6:303–312, 2006.

Centers for Disease Control and Prevention. Avian influenza (bird flu). http://www.cdc.gov/flu/avian. Accessed April 22, 2013.

Gambotto A et al.: Human infection with highly pathogenic H5N1 influenza virus, *Lancet* 371(9622):1464–1475, 2008.

Juckett G: Avian influenza: preparing for a pandemic, *Am Fam Physician* 75(5):783–790, 2006.

Singh N et al.: Avian influenza pandemic preparedness: developing prepandemic and pandemic vaccines against a moving target, *Exp Rev Mol Med* 12:e14, 2010.

U.S. Department of Health and Human Services. Flu.gov (avian and pandemic flu information). http://www.pandemicflu.gov. Accessed April 22, 2013.

World Health Organization. Influenza at the human-animal interface (HAI). http://www.who.int/influenza/human_animal_interface/en/. Accessed April 22, 2013.

BASIC INFORMATION

DEFINITION

Insomnia is a disturbance of initiating or maintaining sleep. Restless, nonrestorative sleep may also be described as another specified insomnia. The disturbance occurs despite adequate circumstances and opportunity for sleep and is accompanied by significant distress or impairment in daytime functioning. It should be noted that in the new DSM-5 the diagnosis of primary insomnia has been replaced with insomnia disorder in order to avoid the distinction between primary and secondary forms of the disorder. This paradigm shift relates to widely accepted research in the field suggesting that there is a bidirectional and interactive relationship between insomnia and any coexisting medical and/or mental disorders. As such it suggests that insomnia is deserving of direct clinical attention that may be expected to have beneficial impact on both the insomnia and comorbid disorder as well.

SYNONYMS

Sleeplessness

Sleep disorder, sleep disturbance, dyssomnia (NOTE: The terms *sleep disorder, sleep disturbance,* and *dyssomnia* are generic and can refer to disorders of wakefulness [hypersomnia] or sleep-related behavior disorders [parasomnias])

ICD-9CM and DSM-5 CODES

780.52 Insomnia, unspecified

ICD-10CM CODES

G47.0 Disorders of initiating and maintaining sleep (insomnias)

G47.9 Sleep disorder, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 30% to 45% of adults experience insomnia per year.

PREVALENCE (IN U.S.): 1% to 15% of all adults and 25% of older adults develop persistent insomnia.

PREDOMINANT SEX: More common in women.

PREDOMINANT AGE: Transient insomnia can occur at any age; persistent insomnia is more common after age 60 yr.

GENETICS: Can run in families and may be genetically influenced. Circadian rhythm disorders and narcolepsy have been traced to specific genes.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Difficulty falling asleep, difficulty staying asleep, or early morning awakening.
- Significant distress or impairment in daytime functioning such as fatigue or low energy, sleepiness, cognitive impairments, mood disturbances, or behavioral problems.
- Difficulty occurs despite adequate opportunity for sleep.
- Symptoms may be acute and self-limited, chronic but intermittent, or chronic and frequent.

ETIOLOGY

- Transient insomnia:
  1. Stress.
  2. Illness.
  3. Travel (across time zones).
  4. Environmental disruptions (noise, heat, cold, poor bedding, bed partners, unfamiliar surroundings, etc).
- Persistent insomnia:
  1. Mood and anxiety disorders (depression, hypomania/mania, PTSD).
  2. Psychophysiologic insomnia (conditioned arousal, extended sleep opportunity, sleep effort, poor sleep hygiene).
  3. Sleep-related breathing disorders (e.g., obstructive apnea and hypopnea, increased upper airway resistance).
  4. Chronobiologic (also known as circadian rhythm) disorder (delayed sleep phase, advanced sleep phase, shift work, non-24-hr sleep wake disorder secondary to blindness).
  5. Drug and alcohol abuse.
  6. Restless legs syndrome and periodic leg movements.
  7. Neurodegenerative (Alzheimer's disease, Parkinson's disease, etc).
  8. Medical (pain, GERD, nocturia, orthopnea, medications, etc).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Insomnia disorder is only ruled out when the disorder is seen exclusively during other etiologies (see etiology). It can be precipitated by a "primary" medical mental health, or other sleep-wake disorder but continue as a comorbid condition even after the "primary disorder" has been treated.

WORKUP

- History (with bed partner interview, if possible).
- Sleep diary for 2 wk (sample sleep diary available at http://www.sleepfoundation.org).
- Wrist actigraphy (detects gross limb movements and can distinguish wake from sleep states) and as an adjunct to a diary—provides some objective verification of the diary data.
- Validated sleep-quality rating scale (optional).
  1. Insomnia Severity Index.
  2. Pittsburgh Sleep Quality Index.
  3. Epworth Sleepiness Scale (see Daytime Sleepiness Test at http://www.sleepfoundation.org).

LABORATORY TESTS

- Evaluate for anemia, uremia (for restless legs), thyroid function (if other signs present).
- Polysomnography (in home or in sleep laboratory) is not standard for insomnia but should be reserved for patients whose history suggests specific sleep-related breathing or movement disorders. It is indicated for symptoms suggestive of daytime sleepiness (obstructive sleep apnea, narcolepsy), nonrestorative sleep (periodic leg movements, chronic pain conditions), or sleep behavior suggesting parasomnia (somnambulism, REM sleep behavior).

IMAGING STUDIES

- Not generally helpful for insomnia.
- Brain CT or MRI for severe daytime sleepiness or acute onset.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Sleep hygiene measures (Box I1-4) as a monotherapy is not very effective. More useful combined with procedures described next.
- Cognitive-behavioral therapy for insomnia (CBT-I) has been shown to reduce time to fall asleep and time awake during the night, can reduce reliance on sleep medications, and has shown lasting effects after treatment has been discontinued.
- The standard components that comprise CBT-I are as follows:
  1. Stimulus Control, which addresses the conditioned cues that create arousal when attempting to sleep by restricting activity in bed to sleep and sex and not permitting sleep effort, worrying, watching TV, reading, etc., in bed (reconditioning of this type can take several days or weeks—patients should not come to expect positive changes on the first night)
  2. Sleep Restriction, which increases homeostatic sleep pressure by restricting sleep opportunity to the average amount of total sleep time the patient is getting as determined by baseline sleep diary data. Sleep time is increased incrementally, based on improving sleep efficiency. Note

BOX I1-4 Sleep Habits (Sleep Hygiene Measures) That May Improve Sleep

1. Reduce caffeine, alcohol, or tobacco late in the day or especially evening.
2. Avoid heavy meals at night, but consider a light snack before bed such as toast or a handful of nuts.
3. Increase daytime activity, but avoid exercise within 3 hours of bedtime.
4. Increase daytime exposure to natural light.
5. Take warm bath as part of bedtime ritual.
6. Reduce liquids in the last 4 hours before bedtime.
7. Consider white noise as background sound for the sleep environment.
8. Maintain regular bed and wake times.
9. Go to bed with calm mind; resolve arguments or set a time earlier in the day to review problems and perhaps write down plans, solutions, or things to do.
10. Keep light exposure in the middle of the night to a minimum when awake and attenuate morning light in the bedroom.

that restricted time in bed should never be <4.5 to 5 hr. For the elderly and infirm, average total sleep time plus 30 min is sometimes considered. For patients whose estimated average total sleep time is <4 hr, a diagnosis of paradoxical insomnia should be considered and CBT-I would be contraindicated.

3. Cognitive Therapy, which involves education to address misconceptions and concerns about sleep that serve to increase anxiety. The cognitive model targets unhelpful beliefs and worries about sleep, negative and unwanted thoughts, selective attention bias and monitoring, misperception of sleep and daytime deficits, and counterproductive safety behaviors that are thought to maintain insomnia. These cognitive processes are proposed to be operating *both* night and day.
4. Sleep Hygiene, which is aimed at improving sleep habits (e.g., initiating or maintaining exercise, avoiding heavy meals at night, and avoiding or eliminating caffeine, nicotine, and alcohol intake). Environmental factors can also be addressed (e.g., using white noise and/or light attenuating bedroom). Although disruptive to sleep late in the day, caffeine sometimes can prove useful when used judiciously in the morning and early afternoon to combat the increased fatigue and somnolence that are produced early in therapy with sleep restriction and stimulus control. In addition, exercise contingently applied to daytime fatigue can also help to improve alertness during the day and increase sleep pressure at bedtime.
5. Relaxation Exercises (e.g., progressive muscle relaxation, diaphragmatic breathing) may be considered good adjunctive therapy for insomnia treatment, especially in highly anxious patients, but are not thought to be essential in CBT-I. Increasingly mindfulness-based practices are being effectively utilized alone and in combination with other elements of CBT-I. Mindfulness may be ideally suited to target sleep effort and sleep-related arousal by helping patients to adopt a more flexible and accepting stance toward insomnia.

- Circadian Rhythm Disturbances, such as in shift workers, many blind individuals who lack light-dark cycle to synchronize body clock, adolescents and young adults with delayed sleep phase syndrome, and jet lag can be treated with chronobiologic therapies such as chronotherapy, bright light exposure, melatonin, or melatonin agonists. However, the timing of these interventions can be critical to outcome and constitutes therapies that are very different from standard medical and/or behavioral treatment for insomnia.

ACUTE GENERAL Rx

- Benzodiazepine receptor agonists zolpidem 5 mg and zaleplon 5 mg for sleep-onset insomnia, and zolpidem continuous-release formulation 6.25 to 12.5 mg and eszopiclone 1 to 3 mg for maintenance insomnia.
- Suvorexant is an orexin receptor antagonist recently FDA approved for insomnia. Signaling of orexin neuropeptides sustains wakefulness. Suvorexant promotes sleep by blocking orexin neuropeptides from binding to their receptors. Most common side effect (10%) is next-day somnolence.
- Benzodiazepine sedative-hypnotics (e.g., temazepam 7.5 to 30 mg, triazolam 0.125 to 0.25 mg).
- A low-dose formulation (6 mg) of the tricyclic antidepressant doxepin, brand name Silenor, is also FDA approved for treatment of insomnia associated with sleep maintenance. This dose retains the hypnotic effect of doxepin without the typical tricyclic effects. A generic 10 mg/ml liquid formulation of doxepin is also available.
- In critical care: lorazepam 0.25 to 0.5 mg PO, SL, or IV as needed for sleep. In patients with acute delirium, haloperidol 0.25 to 0.5 mg IV as needed up to 2 mg/day may be less likely to worsen confusion.
- Melatonin agonist ramelteon 8 mg for sleep-onset insomnia when a mild agent without benzodiazepine side effects is desired.
- Avoid antihistamines except for occasional use.
- Optimize treatment of medical symptoms, especially pain.
- Most prescription and over-the-counter medications carry significant risk of adverse events and drug interactions, especially in the geriatric patient. Preferred pharmacotherapeutic agents in the elderly are zolpidem, zalepton, eszopiclone, and ramelteon.

CHRONIC Rx

- Considerable research supports the efficacy of CBT-I, with acute treatment outcomes equivalent to pharmacotherapy, with better long-term outcomes and maintenance of treatment gains. Three sedative-hypnotics—zolpidem continuous release, eszopiclone, and ramelteon—FDA approved for long-term use.
- Some evidence shows that benzodiazepines and benzodiazepine receptor agonists can be used for chronic insomnia on either intermittent or nightly use with moderate risk of tolerance and dependence but low risk of addiction.
- Sedating antidepressants (e.g., trazodone 25 to 150 mg, mirtazapine 7.5 to 30 mg, amitriptyline 25 to 50 mg, doxepin 10 mg) are in widespread use, with limited data on safety and efficacy. Amitriptyline should be avoided in older adults.
- Sedating antipsychotics (e.g., quetiapine 25 to 200 mg, olanzapine 2.5 to 10 mg at night) considered for severe mood or psychotic disorders associated with insomnia.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Melatonin may shorten sleep-onset latency in some individuals. It may have more use in the treatment of circadian rhythm disorders. Timing of administration in these types of cases requires careful consideration and would not be often administered at bedtime.

DISPOSITION

- Transient insomnia: usually self-limited. May require follow-up if stress-related or illness-related because of risk of depression or persistence. Prophylactic education regarding maladaptive sleep practices such as extending time in bed, and/or remaining in bed when unable to sleep, might be helpful in avoiding a more protracted course of insomnia.
- Persistent insomnia: Studies have shown that patients who respond well to CBT-I often continue to maintain gains at 1 and 2-yr follow-ups. Insomnia patients may need periodic follow-up to reinforce good sleep hygiene and stimulus control and for reevaluation of pharmacologic therapies. There is now a compelling amount of evidence that insomnia is associated with significant negative mental and health effects over time, and if left untreated can interfere with treatment gains with other "primary disorders" and increase the chance for relapse.

REFERRAL

- A referral to a behavioral medicine specialist may be required for CBT-I or for circadian rhythm disturbances.
- Excessive daytime sleepiness not obviously caused by insomnia (e.g., narcolepsy, sleep-related breathing disorder).
- Nighttime behavior suggestive of a parasomnia (e.g., somnambulism, REM behavior disorder).
- Severe insomnia not responsive to basic interventions.

PEARLS & CONSIDERATIONS

COMMENTS

CBT-I often results in worse sleep and more fatigue in the short run. Patients often respond to initial worsening of symptoms as a sign of failure; however, they should be encouraged to see this as an important piece of the therapy and to stay the course as new conditioned patterns begin to emerge, sleep efficiency improves, and total sleep time gradually increases. Patients should avoid compensating for lost sleep by extending sleep opportunity in the form of sleeping in or napping. Therefore, early treatment should focus on helping patients to manage daytime fatigue and sleepiness by engaging in activities that help patients stay awake and maintain set bed and wake times.

MODE OF DELIVERY

Access to behavioral sleep medicine specialists can sometimes be limited especially in certain geographic regions. There is now some evidence that the use of Internet-based behavioral interventions for insomnia can have modest effect. Such interventions might

be best thought of as part of a stepped care model in which this is one level of initial treatment. Patients who fail these attempts should still be encouraged to seek more tailored treatment with a specialist, especially when the insomnia is comorbid with other conditions.

PREVENTION

It is estimated that 50% to 70% of individuals demonstrating the syndrome of insomnia (e.g., insomnia symptoms more than 3 days per week for a month along with deleterious daytime sequelae) are still syndromic 1 to 5 years later. Therefore early intervention with medication or education to prevent the development of maladaptive compensatory behaviors (e.g., napping, sleeping late, tossing and turning in bed, avoiding or decreasing daytime activity) may help to reduce the risk of developing persistent insomnia.

PATIENT & FAMILY EDUCATION

The National Sleep Foundation (http://www.sleepfoundation.org) is a comprehensive resource for health care providers and patients.

EBM EVIDENCE

Available at www.expertconsult.com.

SUGGESTED READINGS

Available at www.expertconsult.com.

RELATED CONTENT

Fig. 3-191 Sleep disorders (Algorithm)
Insomnia (Patient Information)

AUTHOR: **DONN POSNER, PH.D., C.B.S.M.**

EVIDENCE

Abstract[1]

Background:

Chronic insomnia is a common health problem with substantial consequences in older adults. Cognitive behavioral treatments are efficacious but not widely available. The aim of this study was to test the efficacy of brief behavioral treatment for insomnia (BBTI) versus an information control (IC) condition.

Methods:

A total of 79 older adults (mean age, 71.7 years; 54 women [70%]) with chronic insomnia and common comorbidities were recruited from the community and 1 primary care clinic. Participants were randomly assigned to either BBTI, consisting of individualized behavioral instructions delivered in 2 intervention sessions and 2 telephone calls, or IC, consisting of printed educational material. Both interventions were delivered by a nurse clinician. The primary outcome was categorically defined treatment response at 4 weeks, based on sleep questionnaires and diaries. Secondary outcomes included self-report symptom and health measures, sleep diaries, actigraphy, and polysomnography.

Results:

Categorically defined response (67% [n = 26] versus 25% [n = 10]; $\chi 2 = 13.8$) (P<.001) and the proportion of participants without insomnia (55% [n = 21] versus 13% [n = 5]; $\chi 2 = 15.5$) (P <.001) were significantly higher for BBTI than for IC. The number needed to treat was 2.4 for each outcome. No differential effects were found for subgroups according to hypnotic or antidepressant use, sleep apnea, or recruitment source. The BBTI produced significantly better outcomes in self-reported sleep and health (group × time interaction, F5,73 = 5.99, *P* <.001), sleep diary (F8,70 = 4.32, *P* <.001), and actigraphy (F4,74 = 17.72, *P* <.001), but not polysomnography. Improvements were maintained at 6 months.

Conclusion:

We found that BBTI is a simple, efficacious, and durable intervention for chronic insomnia in older adults that has potential for dissemination across medical settings.

Trial Registration:

Clinicaltrials.gov Identifier: NCT00177203. Ⓐ

Evidence-Based Reference

Buysse DJ et al.: Efficacy of brief behavioral treatment for chronic insomnia in older adults, *Arch Intern Med* 171:887–895, 2011. Ⓐ

SUGGESTED READINGS

Harvey AG: A cognitive model of insomnia, *Behav Res Ther* 40:869–893, 2002.

Morin CM et al.: Behavioral and pharmacological therapies for late-life insomnia: a randomized control trial, *JAMA* 281(11):991–999, 1999.

Morin CM et al.: Nonpharmacological interventions for insomnia: a meta-analysis of treatment efficacy, *Am J Psychiatry* 151(8):1172–1180, 1994.

Murtagh DR, Greenwood KM: Identifying effective psychological treatments for insomnia: a meta-analysis, *J Consult Clin Psychol* 63(1):79–89, 1995.

Perlis M.L, et al. Cognitive behavioral treatment of insomnia: a session-by-session guide. Springer-Verlag: New York.

Ong JC, Ulmer CS, Manber R: Improving sleep with mindfulness and acceptance: ametacognitive model of insomnia, *Behav Res Ther* 50(11):651–660, 2012.

Ritterband LM et al.: Efficacy of an internet-based behavioral intervention for adults with insomnia, *Arch Gen Psychiatry* 66(7):692–698, 2009.

Roszkowska J, Geraci SA: Management of insomnia in the geriatric patient, *Am J Med* 123:1087–1090, 2010.

Smith MT et al.: Comparative meta-analysis of pharmacotherapy and behavior therapy for persistent insomnia, *Am J Psychiatry* 159(1):5–11, 2002.

BASIC INFORMATION

DEFINITION

Insulinoma is a pancreatic insulin-secreting tumor that leads to inappropriately elevated plasma insulin or proinsulin levels with suppression of hepatic glucose output and subsequent hypoglycemia, especially during periods of fasting.

ICD-9CM CODES
M8151/0 Insulinoma
ICD-10CM CODES
C25.4 Malignant neoplasm of endocrine pancreas
D13.7 Benign neoplasm of endocrine pancreas
D37.7 Neoplasm of uncertain or unknown behavior of other digestive organs (pancreas)

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: One case per 250,000 persons annually. 90% of insulinomas are benign.
PREDOMINANT SEX AND AGE: Insulinomas occur in both sexes (approximately 60% in women) and at all ages. In a Mayo Clinic series, the median age at diagnosis was 50 yr in sporadic cases, but 23 yr in patients with multiple endocrine neoplasia, type 1 (MEN-1).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms typically occur in the morning before breakfast (i.e., fasting hypoglycemia as opposed to reactive hypoglycemia, which is not commonly associated with insulinoma).

Neuroglycopenic Symptoms	*%*
Various combinations of diplopia, blurred vision, sweating, palpitations, or weakness	85
Confusion or abnormal behavior	80
Unconsciousness or amnesia	53
Grand mal seizures	12
Adrenergic Symptoms	*%*
Sweating	43
Tremulousness	23
Hunger, nausea	12
Palpitations	10

ETIOLOGY, PATHOLOGY, PATHOPHYSIOLOGY

- Insulinomas are almost always solitary. Malignant insulinomas account for 5% of the total; they tend to be larger (6 cm). Metastases are usually to the liver (47%), regional lymph nodes (30%), or both.
- Insulinomas are evenly distributed in the head, body, and tail of the pancreas; ectopic insulinomas are rare (1% to 3%). Tumor size: 5% are ≤0.5 cm, 34% are 0.5 to 1 cm, 53% are 1 to 5 cm, and 8% are >5 cm.
- Histologic classification includes insulinoma in 86% of patients, adenomatosis in 5% to 15%, nesidioblastosis in 4%, and hyperplasia in 1%. Adenomatosis consists of multiple macroadenomas or microadenomas and occurs especially in patients with MEN-1. Nesidioblastosis is also a diffuse lesion in which islet cells form as buds on ductular structures.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS (OF FASTING HYPOGLYCEMIA)

Hyperinsulinism:
- Insulinoma.
- Nonpancreatic tumors.
- Severe congestive heart failure.
- Severe renal insufficiency in non-insulin-dependent diabetes.

Hepatic enzyme deficiencies or decreased hepatic glucose output (primarily in infants and children):
- Glycogen storage diseases.
- Endocrine hypofunction.
- Hypopituitarism.
- Addison's disease.
- Liver failure.
- Alcohol abuse.
- Malnutrition.

Exogenous agents:
- Sulfonylureas, biguanides.
- Insulin.
- Other drugs (aspirin, pentamidine).

Functional fasting hypoglycemia:
- Autoantibodies to insulin receptor or insulin.

LABORATORY TESTS

- An overnight fasting blood sugar level combined with a simultaneous plasma insulin, proinsulin, and/or C peptide level will establish the existence of fasting organic hypoglycemia in 60% of patients. Table EI1-9 describes biochemical patterns in patients with various causes of hyperinsulinemic hypoglycemia.
- If single overnight fasting glucose and insulin levels are nondiagnostic, a 72-hr fast is usually done with blood glucose and insulin levels determined at 2-to 4-hr intervals. A total of 75% of patients with insulinoma develop symptoms and a blood sugar level of <40 mg/dl by 24 hr, 92% to 98% develop these by 48 hr, and virtually all patients develop them by 72 hr. The test is considered positive for insulinoma if the plasma insulin/glucose ratio is more than 0.3. If at any point the patient becomes symptomatic, plasma insulin and glucose values should be obtained and IV glucose should be administered.
- The Endocrine Society guidelines for diagnosis of hypoglycemic disorders is based on glucose level <55 mg/dl (<3.1 mmol/L), elevated C-peptide level ≥0.61 ng/ml (≥0.2 nmol/L). Elevated insulin level ≥18 pmol/L, proinsulin level >5 pmol/L, and suppressed β-hydroxy-butyric acid level.
- An "amended" insulin-glucose ratio that accounts for the normal variation in insulin secretion according to prevailing glycemia has been shown to improve diagnostic accuracy of insulinomas. The "amended" insulin-glucose ratio is derived from the simple insulin-glucose ratio by subtracting 30 mg/dl (1.7 mmol/L) from the measured glucose concentrations.

IMAGING STUDIES

- Abdominal CT scan or MRI (Fig. EI1-14) detects half to two thirds of insulinomas (abdominal ultrasound is not effective); should be done only after laboratory tests for insulinoma have confirmed the diagnosis.
- Intraoperative ultrasound.
- Arteriography.
- Octreotide scan (Fig. EI1-15).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Enucleation of single insulinoma.
- Partial pancreatectomy for multiple adenomas.

TABLE EI1-9 Biochemical Patterns in Patients with Various Causes of Hyperinsulinemic Hypoglycemia

Insulin	C Peptide	Proinsulin	Sulfonylurea	Insulin Antibody	Diagnosis
↑	↓	↓	–	–	Exogenous insulin
↑	↑	↑*	–	–	Insulinoma, congenital hyperinsulinism
↑	↑	↑	+	–	Sulfonylurea
↑	↑†,‡	↑†,‡	–	+	Insulin autoimmune
±↑	↓	↓	–	–	Insulin receptor autoimmune‡

*>20% of insulin value.
†Free C peptide and proinsulin ↓.
‡Insulin receptor antibody +.
From Larsen PR et al: *Williams textbook of endocrinology,* ed 10, Philadelphia, 2003, Saunders.

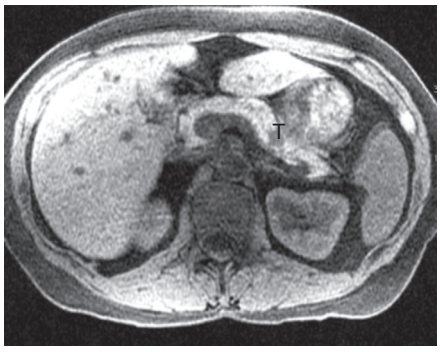


FIGURE EI1-14 MRI shows an insulinoma *(T)* in the tail of the pancreas. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

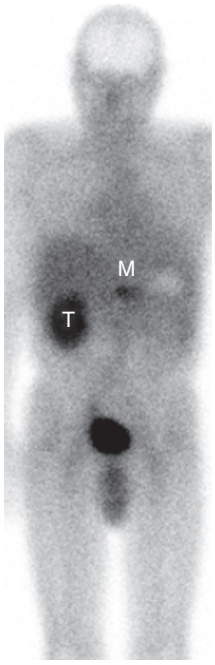


FIGURE EI1-15 Somatostatin receptor scintigraphy demonstrates primary tumor *(T)* and liver metastasis *(M).* (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

ACUTE GENERAL Rx

- Carbohydrate administration.
- Diazoxide directly inhibits insulin release and has an extrapancreatic, hyperglycemic effect that enhances glycogenolysis.
- Lanreotide and octreotide (somatostatin analogues).
- Streptozotocin.

REFERRAL

To an endocrinologist and then to an endocrine surgeon.

SUGGESTED READINGS

Available at www.expertconsult.com.

RELATED CONTENT

Fig. 3-103 Hypoglycemia (Algorithm)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Axelrod L: Insulinoma: cost-effective care in patients with rare disease, *Ann Intern Med* 123:311, 1995.

Cryer PE et al.: Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline, *J Clin Endocrinol Metab* 94:709–728, 2009.

Nauck MA, Meier JJ: Diagnostic accuracy of an "amended" insulin-glucose ratio for the biochemical diagnosis of insulinomas, *Ann Intern Med* 157:767–775, 2012.

BASIC INFORMATION

DEFINITION

Multiple episodes of impulsive verbal or physical aggression out of proportion to perceived stressors or threats

ICD-9CM and DSM-5 CODES
312.34 Intermittent explosive disorder
ICD-10CM CODES
F63.8 Other habit and impulse disorders
F63.9 Habit and impulse disorder, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Unknown
PEAK INCIDENCE: Occurs earlier in life
PREVALENCE: Lifetime prevalence of 6-7%
PREDOMINANT SEX AND AGE: Occurs more so in males and in people under the age of 50
GENETICS: Patients with intermittent explosive disorder (IED) are more likely to have first-degree relatives with the disorder. In addition, adoption and twin studies point to a >50% of the variance in aggression related to genetic factors.
RISK FACTORS: Prior history of violence, exposure to trauma, comorbid depression, anxiety, substance abuse, or cluster B personality disorders.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Several episodes of verbal or physical aggression; the latter may include attacks on others or destruction of physical property.
- The aggression is out of proportion to any perceived stressors or threats.
- The aggression is impulsive.
- The aggression causes distress.
- The aggression is not accounted for by another disease process.
- The patient is at least 6 years of age.

ETIOLOGY

- Potentially an imbalance between aggression, originating from the amygdala and other limbic structures, and orbitofrontal and anterior cingulate cortices. This view is supported by multiple studies involving functional neuroimaging, specifically fMRI.
- From a neurochemical basis, a deficiency in the neurotransmitter serotonin appears involved. Serotonergic agents treat IED (see below) and PET imaging shows a decrease in serotonergic innervation in the anterior cingulate cortex.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Psychiatrically, patients may suffer from mood, anxiety, psychotic, and personality disorders (primarily antisocial and borderline). In addition, patients may be under the effects of substances, or in withdrawal from them.
- Neuropsychiatrically, dementia, delirium, temporal lobe epilepsy, cardiovascular disease, multiple sclerosis, and brain lesions can all cause similar behavior.
- If delirium is expected, a wider, more systemic differential diagnosis should be explored.

WORKUP

- A thorough mental status exam should be performed. In addition, there should be careful consideration for other neuropsychiatric conditions if the history points in that direction.

LABORATORY TESTS

- Urine toxicology screen, as substance abuse is highly comorbid.
- Dementia workup when appropriate: CBC, head CT, Chem 7, B12, TSH, Folate, RPR.
- Delirium workup when appropriate; associated signs and symptoms may be helpful for guidance, especially in clinical settings.

IMAGING STUDIES

- Head CT or MRI, in cases where dementia, delirium, neurovascular disease, or brain lesions are expected. The appropriate test should be ordered depending on the particulars of the case (i.e., MRI to evaluate for MS).
- EEG is indicated to evaluate for seizure-related conditions.

TREATMENT (Table I1-10)

- Selective serotonin reuptake inhibitors (SSRIs) are considered first-line therapy. Multiple studies have been performed on fluoxetine, up to 60 mg per day, though it is not unreasonable to try other SSRIs given similar mechanisms of action. Cost, side effects, drug half-life, and drug-drug interactions need to be considered. Starting at 20 mg per day, and increasing by 10 mg every other week, for a total of a 12 week trial, is recommended.
- Unless there is a contraindication to SSRIs, AEDs should be considered second line, given their potential side effects and toxicities.
- Multiple large trials and meta-analyses also point to the efficacy of phenytoin, lamotrigine, topiramate, and valproate.
- Lithium has also shown to be helpful.
- See Table I1-10 for details related to particular medications.

NONPHARMACOLOGIC THERAPY

- Cognitive-behavioral therapy has been shown to be helpful for patients with IED.
- Patients are taught to examine their thoughts in relation to stressful circumstances.
- Patients can be taught to examine their somatic sensations and change these through relaxation techniques.
- Relapse prevention is focused on helping patients avoid explosive behaviors in the future.

ACUTE GENERAL Rx

- See above.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

There is no evidence on the use of complementary or alternative medicine for this disorder.

REFERRAL

Referral to an outpatient mental health provider should be helpful.

PEARLS & CONSIDERATIONS

PREVENTION

No prevention measures have been identified.

PATIENT/FAMILY EDUCATION

Psychoeducation to the patient and family may be helpful, especially in helping to identify triggers and supporting the use of coping skills.

RELATED CONTENT

Abuse, Drug (Related Key Topic)
Attention Deficit-Hyperactivity Disorder (Related Key Topic)
Bipolar Disorder (Related Key Topic)
Conduct Disorder (Related Key Topic)
Personality Disorders (Related Key Topic)

AUTHOR: **ANTHONY GALLO, M.D.**

TABLE I1-10 Medications for Intermittent Explosive Disorder

Medication	Starting Dose	Blood Level	Adverse Outcomes	Cautionary Notes
Fluoxetine	10 mg PO qAM	N/A	Mania, sexual dysfunction, SIADH.	Caution in patients with bipolar disorder.
Phenytoin	100 mg PO tid	10-20 mcg/ml	Hepatotoxicity, gingival hyperplasia.	Caution in patients with hepatic dysfunction.
Topiramate	50 mg daily	N/A	Sedation.	
Lamotrigine	25 mg daily	N/A	Rash, SJS.	Slow titration schedule.
Valproate	250 mg PO bid	75-125 mcg/ml	Hyperammonemia, pancreatitis. hepatic impairment.	Caution in patients with hepatic impairment.
Carbamazepine	200 mg PO bid	4-12 mcg/ml	Hepatic failure, SJS, blood dyscrasias, SIADH.	Caution in patients with hepatic impairment.
Lithium	300 mg PO bid	0.6-1.2 mEq/L	Hypothyroid, nephrotoxicity.	Caution in patients with renal impairment.

SUGGESTED READINGS

Kaplan H, Sadock B. Comprehensive textbook of clinical psychiatry. Williams and Wilkins: Baltimore.
DSM-5. American Psychiatric Publishing.

BASIC INFORMATION

DEFINITION

The International Continence Society defines interstitial cystitis (IC), otherwise known as painful bladder syndrome, as a clinical syndrome consisting of suprapubic pain related to bladder filling and accompanied by other symptoms such as increased daytime and nighttime frequency in the absence of proven infection or other obvious pathology. The American Urological Association defines interstitial cystitis/bladder pain syndrome (IC/BPS) as an unpleasant sensation perceived to be related to the urinary bladder that is associated with lower urinary tract symptoms >6 weeks' duration, in the absence of infection or other unidentifiable causes.

SYNONYMS

Interstitial cystitis/bladder pain syndrome (IC/BPS)
Painful bladder syndrome
Tic douloureux of bladder

ICD-9CM CODES
595.1 Chronic interstitial cystitis
ICD-10CM CODES
N30.1 Interstitial cystitis (chronic)
N30.9 Cystitis, unspecified
N30.10 Interstitial cystitis (chronic) without hematuria

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 21 cases per 100,000 women and four cases per 100,000 men annually

PREVALENCE

- 197 per 100,000 women and 41 per 100,000 men in the U.S.
- Because the disease is substantially underdiagnosed, it may actually affect one in five women and one in 20 men.
- More than 81% of women diagnosed with chronic pelvic pain and up to 84% of men initially diagnosed with chronic prostatitis actually have IC.
- More than 90% of patients diagnosed with overactive bladder who do not respond to anticholinergics are subsequently diagnosed with IC.

PREDOMINANT SEX AND AGE

- White women constitute 95% of patients with IC.
- Female/male ratio of 5 to 10:1.
- Most prevalent in fourth and fifth decades of life.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Urinary urgency, frequency (>8 in daytime), nocturia (>2 at night), and suprapubic pain are the most common symptoms.
- Suprapubic pain is worse with bladder filling or urinating and relieved after emptying.
- Dyspareunia.
- Symptoms lasting longer than 6 mo.
- Intensity of symptoms waxes and wanes.
- Insidious onset and worsens to the final stage within 5 to 15 yr.
- Exercise, stress, sexual activity, ejaculation, certain foods with high potassium and acids (beer, spices, bananas, tomatoes, chocolate, strawberries, artificial sweeteners, oranges, cranberries, caffeine), menstruation, prolonged sitting, and activation of allergies exacerbate the symptoms.
- Often associated with irritable bowel syndrome, migraine, endometriosis, skin sensitivities, multiple drug allergies, other allergies, vulvodynia, fibromyalgia, chronic fatigue syndrome, systemic lupus erythematosus, and mood disorders.
- Dysphoric mood.
- Lower abdominal tenderness.
- Tender prostate in digital rectal examination.
- Levator ani tenderness in female.
- Tenderness of anterior vaginal wall/bladder neck in female.

ETIOLOGY

Unknown. Fig. I1-16 illustrates a hypothesis for etiologic cascade of painful bladder syndrome/interstitial cystitis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Chronic pelvic pain
- Overactive bladder
- Recurrent urinary tract infection
- Endometriosis
- Pelvic adhesions
- Vulvar vestibulitis
- Vulvodynia
- Urethral pain syndrome
- Chronic nonbacterial prostatitis
- Frequent vaginitis
- Benign prostatic hyperplasia

WORKUP

- IC can be considered a diagnosis of exclusion when no known cause of painful bladder can be identified.
- There is no definite diagnostic test.
- Validated questionnaires such as Pelvic Pain and Urgency/Frequency scale (PUF), O'Leary-Sant symptoms and problem index, and Wisconsin IC scale. PUF is the most commonly used.

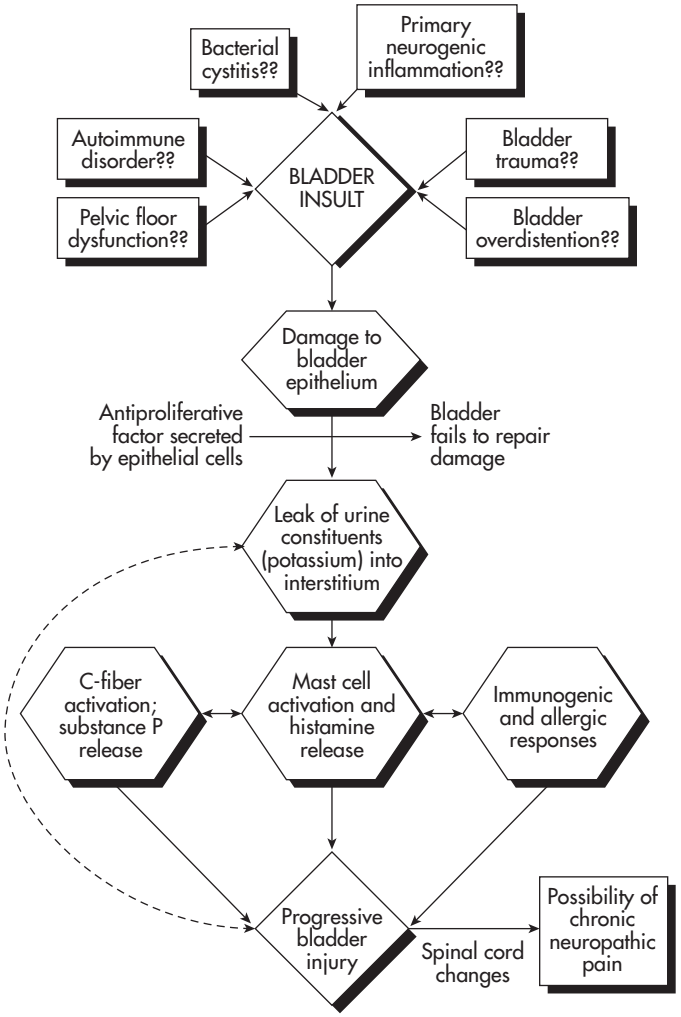


FIGURE I1-16 Hypothesis for etiologic cascade of painful bladder syndrome/interstitial cystitis. (From Wein AJ: Painful bladder syndrome/interstitial cystitis and related disorders. In Wein AJ et al (eds): *Campbell-Walsh urology*, 11th ed, Philadelphia, 2007, Elsevier.)

- Voiding diary shows low-volume (<100 ml) and high-frequency voiding pattern.
- National Institute of Diabetes and Diseases of the Kidney diagnostic criteria misses 60% of IC patients and is not clinically used anymore.
- Anesthetic bladder challenge: with this test the symptoms dissipate on instillation of an anesthetic cocktail into the bladder.
- Cystoscopy and hydrodistention under general anesthesia may show terminal hematuria, glomerulation, Hunner's ulcers, and small bladder capacity of less than 350 ml. Cystoscopy and/or urodynamic testing should be considered when the diagnosis is in doubt, but the tests are not necessary to confirm an IC/BPS diagnosis in uncomplicated cases.
- Bladder biopsy is not essential for diagnosis of IC.
- Parson's potassium sensitivity test (PST).
- Urodynamics are unnecessary in diagnosis of IC.

LABORATORY TESTS

- Urine analysis and culture.
- Urine cytology should be performed if microscopic or gross hematuria is present, or with other risk factors such as smoking, age >40 yr, and other bladder cancer risk factors.
- Culture of sexually transmitted diseases if clinically indicated. Nonbacteriuric patients with pyuria should be screened for *Chlamydia.*
- Urine biomarkers (e.g., antiproliferative factor) are promising but not ready for clinical use.

IMAGING STUDIES

CT or ultrasound of abdomen and pelvis may be considered to rule out other pathology.

Rx TREATMENT

- There is no consensus for optimal management.
- There is no cure for this disease.

NONPHARMACOLOGIC THERAPY

- Avoidance of activities associated with flare-ups
- Avoidance of smoking
- Dietary restriction, avoiding common irritants (e.g., coffee, citrus fruits)
- Physical therapy
- Exercise
- Behavioral therapy
- Bladder retraining
- Biofeedback
- Warm sitz bath, ice, heating pad
- Thiele massage (transrectal and transvaginal manual therapy of pelvic floor muscle) in presence of pelvic floor muscle tenderness and spasm
- Hydrodistention only gives temporary relief, so it is not commonly used anymore

ACUTE AND CHRONIC Rx

- A course of empiric antibiotics if not tried yet. Long-term oral antibiotics are not recommended.
- Oral therapy is tried first.
- Pentosan polysulfate sodium (Elmiron) is the only FDA approved and most effective oral therapy.
- Most treatment takes 3 to 6 mo before maximum benefit is seen.
- Adjunct oral therapy includes tricyclic antidepressants (amitriptyline), cimetidine, antihistaminics (hydroxyzine, montelukast), neuroleptics (gabapentin, topiramate), analgesics (NSAIDs, opioid analgesics), and occasionally antimuscarinics.
- Oral therapies can be used in combination.
- Antihistaminics are preferred for patients with an allergy history or those who show mast cells in bladder biopsy.
- Oral prednisone is used in presence of Hunner's ulcers.
- Other drugs rarely used for IC are cyclosporin A, interleukin-10, imatinib, methotrexate, suplatast, misoprostol, and quercetin.
- Growth factor inhibitors, gene therapy, RDP 58, and vitamin B_3 analogue (BXL 628) may represent future therapies.
- Intravesical treatment is used when oral medications fail, for acute flare-ups, or before the oral medications take full effect.
- Dimethyl sulfoxide (DMSO), heparin, lidocaine, hyaluronic acid, capsaicin, botulinum toxin A, chondroitin sulfate, steroids, and Elmiron are drugs used for intravesical treatment.
- DMSO is the only FDA-approved intravesical treatment.
- DMSO is used less often now because of its side effects, specifically a garlic-like odor or taste on breath or skin that lasts 72 hr after treatment.
- Intravesical therapy typically involves mixture of heparin or Elmiron with lidocaine and sodium bicarbonate.
- Silver nitrate and Clorpactin have fallen out of favor.

SURGERY

- Major surgical intervention is not the mainstay of treatment.
- Patients whose condition is extreme and who are miserable may consider surgery if medications fail.
- Sacral neuromodulation (InterStim) is the current preferred surgical intervention.
- Laser ablation, fulguration, or resection is offered when Hunner's ulcers are seen in cystoscopy.
- Augmentation cystoplasty is not recommended.
- Cystourethrectomy with urinary diversion is rarely done.

COMPLEMENTARY & ALTERNATIVE MEDICINE

- Transcutaneous electric nerve stimulation
- Intravaginal electric nerve stimulation
- Acupuncture
- Urinary chelating agents such as Polycitra-K crystals, Urocit-K
- Prelief, an over-the-counter food additive
- Herbal remedies such as Algnot Plus, CystoProtek, Cysta-Q, aloe vera

DISPOSITION

- Close follow-up every month for 3 mo and every 3 mo thereafter.
- Voiding diary and symptom questionnaire are helpful to monitor response to treatment.

REFERRAL

- Urologist
- Pain specialist
- Physical therapist

PEARLS & CONSIDERATIONS

COMMENTS

- On average these patients see five physicians and endure irritating voiding symptoms for 5 yr before the disease is identified.
- Besides symptom questionnaire and urine analysis, all other diagnostic tests are optional.
- PST is well tolerated.
- Negative cystoscopy does not rule out IC.

PREVENTION

Early identification and timely intervention improve patient outcome.

PATIENT & FAMILY EDUCATION

- IC support groups
- Interstitial Cystitis Association
- Interstitial Cystitis Network

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **HEMANT K. SATPATHY, M.D.**

SUGGESTED READINGS

Chronic pelvic pain in women, *J Reprod Med* 51(3), 2006.

Dimitrakon J et al.: Pharmacologic management of painful bladder syndrome/interstitial cystitis, *Arch Intern Med* 167(18):1922–1929, 2007.

French LM, Bhambore N: Interstitial cystitis/painful bladder syndrome, *Am Fam Phys* 83(10):1175–1181, 2011.

Interstitial cystitis as a disease. a new paradigm emerges, *J Reprod Med* 69(4):S1, 2007.

Myers DL: Interstitial cystitis, *Med Health R I* 92:22–26, 2009.

Randel A: American Urological Association approach to the diagnosis and management of IC/BPS, *Am Fam Physician* 86:97–103, 2012.

BASIC INFORMATION

DEFINITION

The interstitial lung diseases (ILDs) include more than 150 nonmalignant disorders, characterized by varying degrees of damage to the lung parenchyma or interstitium via inflammation and fibrosis. The term "ILD" can be confusing as processes affecting the alveolar space (e.g., pulmonary alveolar proteinosis) are also lumped under the title. A clinical classification of the interstitial lung diseases is summarized in Table I1-11.

SYNONYMS

Interstitial pulmonary disease
ILD
Diffuse parenchymal lung disease (DPLD)

ICD-9CM CODES

136.3 Acute interstitial lung disease
515 Chronic interstitial lung disease
516.30 Idiopathic interstitial pneumonia, NOS
516.31 Idiopathic pulmonary fibrosis

ICD-10CM CODES

J84 Other interstitial pulmonary disease
J84.1 Other interstitial pulmonary disease with fibrosis
J84.8 Other specified interstitial pulmonary diseases
J84.9 Interstitial pulmonary disease, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Varies with type of ILD. The most common type of ILD is idiopathic interstitial fibrosis, with a prevalence of 20 cases/100,000 people in the general population, increasing with age to 175 cases/100,000 people aged 75 yr or older.

PREDOMINANT SEX & AGE: Some ILDs are more common in women, such as those resulting from connective tissue disorders. Lymphangiomyomatosis occurs exclusively in postmenopausal women. ILD caused by occupational exposures are more common in men. Generally, ILD occurs in people >50 yr.

RISK FACTORS: Although many ILDs are categorized as idiopathic, the most common identifiable risk factors include environmental exposures such as silicone, asbestos, or bird droppings; reactions to drugs such as chemotherapeutic agents, radiation therapy, cardiac medications, and some history of connective tissue disease such as rheumatoid arthritis or systemic lupus erythematosus.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Shortness of breath (especially with exertion)
- Dyspnea
- Cough (dry)
- Tachypnea
- Bibasilar end-inspiratory dry crackles
- Pulmonary hypertension
- Cyanosis, clubbing

TABLE I1-11 Clinical Classification of the Interstitial Lung Diseases

CONNECTIVE TISSUE DISEASES
Scleroderma
Polymyositis-dermatomyositis
Systemic lupus erythematosus
Rheumatoid arthritis
Mixed connective tissue disease
Ankylosing spondylitis

TREATMENT-RELATED OR DRUG-INDUCED DISEASES
Antibiotics (nitrofurantoin, sulfasalazine)
Antiarrhythmics (amiodarone, tocainide, propranolol)
Anti-inflammatories (gold, penicillamine)
Anticonvulsants (dilantin)
Chemotherapeutic agents (mitomycin C, bleomycin, busulfan, cyclophosphamide, chlorambucil, methotrexate, azathioprine, BCNU [carmustine], procarbazine)
Therapeutic radiation
Oxygen toxicity
Narcotics

PRIMARY (UNCLASSIFIED) DISEASES
Sarcoidosis
Primary pulmonary Langerhans cell histiocytosis (eosinophilic granuloma)
Amyloidosis
Pulmonary vasculitis
Lipoid pneumonia
Lymphangitic carcinomatosis
Bronchoalveolar carcinoma
Pulmonary lymphoma
Gaucher's disease
Niemann-Pick disease
Hermansky-Pudlak syndrome
Neurofibromatosis
Lymphangioleiomyomatosis
Tuberous sclerosis
Acute respiratory distress syndrome
AIDS
Bone marrow transplantation
Postinfectious
Eosinophilic pneumonia
Alveolar proteinosis
Diffuse alveolar hemorrhage syndromes
Alveolar microlithiasis
Metastatic calcification

OCCUPATIONAL AND ENVIRONMENTAL DISEASES

Inorganic
Silicosis
Asbestosis
Hard-metal pneumoconiosis
Coal worker's pneumoconiosis
Berylliosis
Talc pneumoconiosis
Siderosis (arc welder)
Stannosis (tin)

Organic (hypersensitivity pneumonitis)
Bird breeder's lung
Farmer's lung

IDIOPATHIC FIBROTIC DISORDERS
Acute interstitial pneumonitis (Hamman-Rich syndrome)
Idiopathic pulmonary fibrosis/usual interstitial pneumonia
Familial pulmonary fibrosis
Respiratory bronchiolitis/desquamative interstitial pneumonitis
Cryptogenic organizing pneumonia
Nonspecific interstitial pneumonia
Lymphocytic interstitial pneumonia (Sjögren's syndrome, connective tissue disease, AIDS, Hashimoto's thyroiditis)
Autoimmune pulmonary fibrosis (inflammatory bowel disease, primary biliary cirrhosis, idiopathic thrombocytopenic purpura, autoimmune hemolytic anemia)

AIDS, Acquired immunodeficiency syndrome.
From Mason, RJ: *Murray & Nadel's textbook of respiratory medicine*, 5th ed, Philadelphia, 2010, Saunders.

ETIOLOGY

- Hallmarks of ILD include a restrictive pattern and decreased diffusing capacity for carbon monoxide (DLCO) as demonstrated by pulmonary function testing. The restrictive process can be the result of a number of factors depending on the type of ILD. Different types of ILD are characterized by three distinct patterns:
  1. Acute inflammatory changes, which are potentially reversible
  2. Fibrotic changes
  3. Lung destruction
- Specific changes may be seen:
  1. Granulomatous: accumulation of T lymphocytes, macrophages, and epithelioid cells into granulomas in lung parenchyma
  2. Inflammation and fibrosis: injury to epithelium causes inflammation; if chronic, inflammation spreads to interstitium and vascular areas
- The MUC5B promoter polymorphism has been found to be associated with interstitial lung disease in the general population. Although this association was more apparent in older persons, it did not appear to be influenced by cigarette smoking.[1]

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Congestive heart failure
- Chronic renal failure
- Viral pneumonitis
- Pulmonary embolism
- Pulmonary hypertension

WORKUP

- Well-defined patterns in pulmonary function tests are usually consistent with restrictive defect (decreased FRC, RV, and TLC) owing to decreased lung compliance caused by alveolar wall thickening as a result of inflammation

[1]Hunninghake GM et al: MUC5B promoter polymorphism and interstitial lung abnormalities, *N Engl J Med* 368:2192-2200, 2013.

TABLE I1-12 Histologic Patterns in the Interstitial Lung Diseases and Their Disease Associations

Histologic Patterns	Clinical Associations
Usual interstitial pneumonia	Idiopathic pulmonary fibrosis; connective tissue diseases (uncommon); asbestosis; hypersensitivity pneumonitis; chronic aspiration pneumonia; chronic radiation pneumonitis; Hermansky-Pudlak syndrome; neurofibromatosis
Nonspecific interstitial pneumonia	Idiopathic; connective tissue diseases; drugs; hypersensitivity pneumonitis; diffuse alveolar damage; infections; lymphocytic interstitial pneumonia; AIDS; chronic eosinophilic pneumonia; infections; hemosiderosis; alveolar proteinosis
Diffuse alveolar damage	Acute interstitial pneumonia (Hamman-Rich syndrome); acute respiratory distress syndrome; drugs (cytotoxic agents, heroin, paraquat, ethchlorvynol, aspirin); toxic gas inhalation; radiation therapy; oxygen toxicity; connective tissue disease; infections (*Legionella*, *Mycoplasma*, viral)
Organizing pneumonia	Cryptogenic organizing pneumonia; organizing stage of diffuse alveolar damage; diffuse alveolar hemorrhage; drugs (amiodarone, cocaine); infections; connective tissue diseases; hypersensitivity pneumonitis; eosinophilic pneumonia; Wegener's granulomatosis
Desquamative interstitial pneumonia/respiratory bronchiolitis	Cigarette smoking; idiopathic; connective tissue diseases; primary pulmonary Langerhans cell histiocytosis; asbestosis; hard-metal pneumoconiosis (cobalt); Gaucher's disease; Niemann-Pick disease; Hermansky-Pudlak syndrome; drugs (nitrofurantoin, amiodarone)
Lymphocytic interstitial pneumonia	Idiopathic; hypogammaglobulinemia; autoimmune diseases, including Hashimoto's thyroiditis, lupus erythematosus, primary biliary cirrhosis, Sjögren's syndrome, myasthenia gravis, chronic active hepatitis; AIDS; allogeneic bone marrow transplantation
Eosinophilic pneumonia	Idiopathic acute and chronic; tropical filarial eosinophilia; parasitic infections; allergic bronchopulmonary aspergillosis; allergic granulomatosis of Churg and Strauss; hypereosinophilic syndrome; AIDS
Alveolar proteinosis	Pulmonary alveolar proteinosis; acute silicosis; aluminum dust; AIDS; myeloproliferative disorder
Diffuse alveolar hemorrhage	
With capillaritis	Wegener's granulomatosis; microscopic polyangiitis; systemic lupus erythematosus; polymyositis; scleroderma; rheumatoid arthritis; mixed connective tissue disease; lung transplantation; drugs (retinoic acid, propylthiouracil, Dilantin); Behçet's disease; cryoglobulinemia; Henoch-Schönlein purpura; pauci-immune glomerulonephritis; immune complex glomerulonephritis
Without capillaritis	Idiopathic pulmonary hemosiderosis; systemic lupus erythematosus; Goodpasture's syndrome; diffuse alveolar damage; pulmonary veno-occlusive disease; mitral stenosis; lymphangioleiomyomatosis
Amyloid deposition	Primary amyloidosis; multiple myeloma; lymphocytic interstitial pneumonia
Granuloma	Sarcoidosis; hypersensitivity pneumonitis; pulmonary Langerhans cell histiocytosis; silicosis; intravenous talcosis; berylliosis; lymphocytic interstitial pneumonia; infections

AIDS, Acquired immunodeficiency syndrome.
From Mason, RJ: *Murray & Nadel's textbook of respiratory medicine*, 5th ed, Philadelphia, 2010, Saunders.

and fibrosis. Diffusion capacity is usually reduced also because of inflammation and thickening of alveolar walls, though nonspecific. FEV_1/FVC is usually normal or increased because lung stiffness keeps small airways open, although some conditions (e.g., sarcoidosis) may result in air trapping.

- Bronchoscopy and bronchoalveolar lavage (BAL) may help identify type of ILD. However, their role in defining stage of disease and response to therapy is controversial. Histologic patterns in the interstitial lung diseases and their disease associations are summarized in Table I1-12.
- If laboratory studies and imaging including HRCT fail in yielding a diagnosis, a surgical biopsy is required.
- Fig. I1-17 describes a diagnostic approach to occupational ILD.

LABORATORY TESTS

- ABGs may be normal or show respiratory alkalosis.
- Blood tests for connective tissue diseases, such as antinuclear antibodies, anti-immunoglobulin antibodies (rheumatoid factors), LDH. Laboratory findings in the interstitial lung diseases are summarized in Table I1-13.
- Serum precipitins confirm exposure if hypersensitivity pneumonitis is suspected.
- Antineutrophil cytoplasmic antibodies or antibasement membrane antibodies if vasculitis is suspected.
- Elevation in angiotensin-converting enzyme level in sarcoidosis.

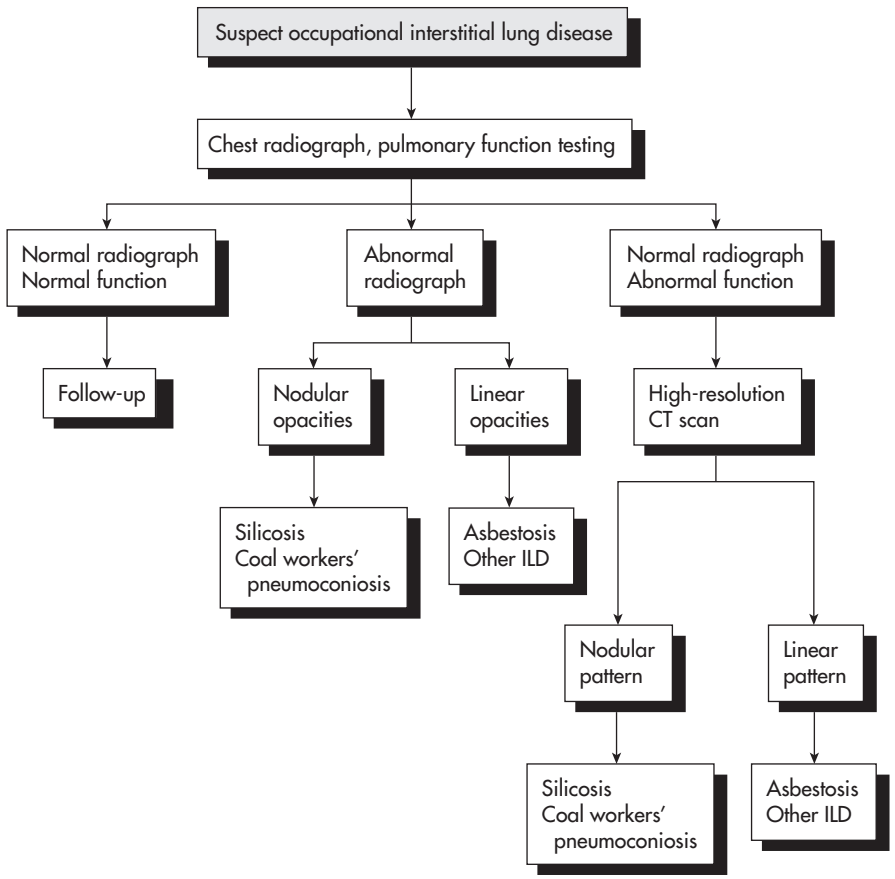


FIGURE I1-17 Diagnostic approach to occupational interstitial lung disease (ILD). *CT,* Computed tomography. (From Goldman L, Ausiello D [eds]: *Goldman's Cecil textbook of medicine,* ed 23, Philadelphia, 2008, Saunders.)

TABLE I1-13 Radiographic Features of the Interstitial Lung Diseases

Feature	Diseases
Upper zone–predominant disease	Radiation pneumonitis; neurofibromatosis; chronic sarcoidosis; pulmonary Langerhans cell histiocytosis; silicosis; chronic hypersensitivity pneumonitis; chronic eosinophilic pneumonia; ankylosing spondylitis; nodular rheumatoid arthritis; berylliosis; drug-induced (amiodarone, gold, BCNU [carmustine]); radiation
Increased lung volumes	Lymphangioleiomyomatosis; chronic sarcoidosis; chronic pulmonary Langerhans cell histiocytosis; tuberous sclerosis; neurofibromatosis
Radiographic honeycomb lung	Idiopathic pulmonary fibrosis; connective tissue disease; asbestosis; drug-induced; lymphocytic interstitial pneumonia; chronic aspiration pneumonia; hemosiderosis; Hermansky-Pudlak syndrome; alveolar proteinosis
Pneumothorax	Pulmonary Langerhans cell histiocytosis; lymphangioleiomyomatosis; tuberous sclerosis; neurofibromatosis
Kerley's B lines	Lymphangitic carcinomatosis; lymphangioleiomyomatosis; left atrial hypertension (mitral valve disease, veno-occlusive disease); lymphoma; amyloidosis
Lymphadenopathy	Sarcoidosis; lymphoma; lymphangitic carcinomatosis; lymphoid interstitial pneumonia; berylliosis; amyloidosis; Gaucher's disease
Pleural disease	Lymphangitic carcinomatosis; connective tissue disease; asbestosis (pleural calcification); lymphangioleiomyomatosis (chylous effusion); drug-induced (nitrofurantoin, radiation); sarcoidosis
Eggshell calcification of lymph nodes	Silicosis; sarcoidosis; radiation

From Mason, RJ: *Murray & Nadel's textbook of respiratory medicine*, 5th ed, Philadelphia, 2010, Saunders.

TABLE I1-14 Laboratory Findings in the Interstitial Lung Diseases

Finding	Diseases
Leukopenia	Sarcoidosis; connective tissue disease; lymphoma; drug-induced
Leukocytosis	Systemic vasculitis; hypersensitivity pneumonitis; lymphoma
Eosinophilia	Eosinophilic pneumonia; sarcoidosis; systemic vasculitis; drug-induced (sulfa, methotrexate)
Thrombocytopenia	Sarcoidosis; connective tissue disease; drug-induced; Gaucher's disease; idiopathic pulmonary fibrosis
Hemolytic anemia	Connective tissue disease; sarcoidosis; lymphoma; drug-induced; idiopathic pulmonary fibrosis
Normocytic anemia	Diffuse alveolar hemorrhage syndromes; connective tissue disease; lymphangitic carcinomatosis
Urinary sediment abnormalities	Connective tissue disease; systemic vasculitis; drug-induced
Hypogammaglobulinemia	Lymphocytic interstitial pneumonia
Hypergammaglobulinemia	Connective tissue disease; sarcoidosis; systemic vasculitis; idiopathic pulmonary fibrosis; asbestosis; silicosis; lymphocytic interstitial pneumonia; lymphoma
Serum autoantibodies	Connective tissue disease; systemic vasculitis; sarcoidosis; idiopathic pulmonary fibrosis; silicosis; asbestosis; lymphocytic interstitial pneumonia
Serum immune complexes	Idiopathic pulmonary fibrosis; lymphocytic interstitial pneumonia; systemic vasculitis; connective tissue disease; pulmonary Langerhans cell histiocytosis
Serum angiotensin-converting enzyme	Sarcoidosis; hypersensitivity pneumonitis; silicosis; acute respiratory distress syndrome; Gaucher's disease
Antibasement membrane antibody	Goodpasture's syndrome
Antineutrophil cytoplasmic antibody	Systemic vasculitis

From Mason, RJ: *Murray & Nadel's textbook of respiratory medicine*, 5th ed, Philadelphia, 2010, Saunders.

IMAGING STUDIES

- Chest x-ray may be normal but commonly shows a bibasilar reticular pattern. Table I1-14 summarizes radiographic features of the interstitial lung diseases.
- High-resolution CT (HRCT) (Fig. I1-18) is the gold standard for evaluating parenchymal opacities seen on chest x-ray; it is also useful for determining potential biopsy sights.
- Echocardiography may be useful to evaluate cardiac function/dilation or to evaluate for pulmonary hypertension.

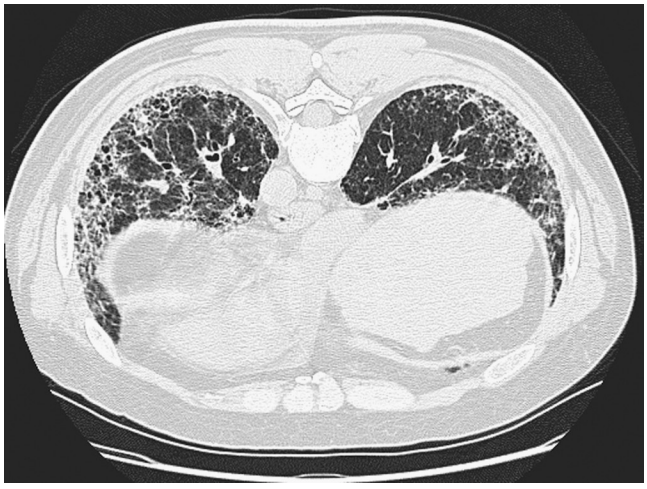


FIGURE I1-18 High-resolution computed tomography scan of the chest shows fibrotic changes in a subpleural distribution with honeycombing consistent with usual interstitial pneumonia. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Avoidance of tobacco and occupational exposures

ACUTE GENERAL Rx

- Supplemental oxygen in patients with hypoxemia is helpful short and long term.
- Glucocorticoids are the mainstay of therapy, but success rate is low, and some guidelines recommend against use, especially long term. Patients should be reevaluated after this initial course of treatment. If they are stable, steroids may be tapered. If not, the same course may be maintained 4 additional wk. If patient's condition continues to decline, may consider adding second agent (cyclophosphamide, azathioprine).

CHRONIC GENERAL Rx

- Respiratory rehabilitation may be of value.
- Lung transplantation may be considered in appropriate patients in severe stages of the disease. Guidelines for referral and transplantation of patients with idiopathic interstitial pneumonia are described in Table I1-15.

REFERRAL

- Surgical referral for biopsy
- Pulmonary referral for bronchoscopy and/or BAL

TABLE I1-15 Guidelines for Referral and Transplantation of Patients With Idiopathic Interstitial Pneumonia

GUIDELINES FOR REFERRAL

1. Histologic or radiographic evidence of UIP irrespective of vital capacity.
2. Histologic evidence of fibrotic NSIP.

GUIDELINES FOR TRANSPLANTATION

1. Histologic or radiographic evidence of UIP and any of the following:
   a. A D_{LCO} <39% predicted.
   b. A ≥10% decrement in FVC during 6 months of follow-up.
   c. A decrease in pulse oximetry below 88% during a 6-MWT.
   d. Honeycombing on HRCT (fibrosis score >2).
2. Histologic evidence of NSIP and any of the following:
   a. A DL_{CO} <35% predicted.
   b. A ≥10% decrement in FVC or 15% decrease in DL_{CO} during 6 months of follow-up.

D_{LCO}, Diffusing capacity for carbon dioxide; *FVC*, forced vital capacity; *HRCT*, high-resolution computed tomography; *6-MWT*, 6-minute walking test; *NSIP*, nonspecific interstitial pneumonia; *UIP*, usual interstitial pneumonia.

From Mason RJ: *Murray & Nadel's textbook of respiratory medicine*, 5th ed, Philadelphia, 2010, Saunders.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Interstitial Pulmonary Disease (Patient Information)

AUTHORS: **GRACE SHIH, M.D., CINDY GLEIT, M.D.,** and **MICHAEL A. MARSH, M.D.**

SUGGESTED READINGS

Fishman A et al.: In *Fishman's pulmonary diseases and disorders.* McGraw-Hill: New York.

Grippi MA: Pulmonary science and medicine. J.B. Lippincott: Philadelphia. In Longo DL, et al editor: Harrison's principles of internal medicine. ed 18, McGraw-Hill Company.

Raghu G et al.: An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management, *Am J Respir Crit Care Med* 183:788–824, 2011.

Raghu G: Idiopathic pulmonary fibrosis: new evidence and an improved standard of care in 2012, *Lancet* 380(9842):699–701, 2012.

Shah NR et al.: A critical assessment of treatment options for idiopathic pulmonary fibrosis, *Sarcoidosis Vasc Diffuse Lung Dis* 22(3):167, 2005.

Swigris JJ et al.: Health-related quality of life in patients with idiopathic pulmonary fibrosis: a systematic review, *Thorax* 60:588, 2005.

BASIC INFORMATION

DEFINITION

Can be classified into two broad categories:

1. Acute interstitial nephritis (AIN): Decrease in renal function resulting from delayed hypersensitivity immune-mediated injury characterized histopathologically with edema and inflammation of the renal interstitium and tubules, classically sparing the glomeruli and blood vessels. Most often drug-induced.
2. Chronic interstitial nephritis: Represents a large and diverse group of disorders characterized by interstitial fibrosis with mononuclear leukocyte infiltration and tubular atrophy. It is a final common pathway of many chronic kidney diseases including chronic bacterial infections, obstruction, and high-grade vesicoureteral reflux. Histopathologically seen as atrophy and fibrosis of the renal interstitium.

SYNONYMS

Acute tubulointerstitial nephritis
Contracted kidney
Cirrhosis of the kidney
Granular kidney
Gouty kidney
Renal sclerosis
Chronic productive nephritis without exudation

ICD-9CM CODES

583 Nephritis and nephropathy not specified as acute or chronic
583.7 Nephritis and nephropathy, not specific as acute or chronic, with lesion of renal medullary necrosis
583.8 Nephritis and nephropathy, not specific as acute or chronic, with other specified pathological lesion in kidney
583.9 With unspecified pathological lesions in the kidney

ICD-10CM CODES

N05.9 Unspecified nephritic syndrome with unspecified morphologic changes
N17.2 Acute kidney failure with medullary necrosis
N05.8 Unspecified nephritic syndrome with other morphologic changes

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Prevalence is significantly underestimated, and the incidence in the US remains unknown. Best available estimates come from measuring the incidence of unexpected AIN at autopsy (<1%), in unselected renal biopsies (1% to 6%), and in renal biopsies selected for patients with acute renal failure (11% to 15%). AIN may comprise 15-20% of all AKI cases.

PREDOMINANT SEX AND AGE: Older patients generally at higher risk given reduced glomerular filtration rates.

PEAK INCIDENCE: Median age at presentation is 65 yr.

RISK FACTORS: Risk of acute interstitial nephritis due to drugs (e.g., NSAIDs, penicillins, sulfa drugs) increases with volume depletion, underlying kidney disease, age >65 yr, congestive heart failure, and diabetes. Some autoimmune disorders are also risk factors.

PHYSICAL FINDINGS & CLINICAL PRESENTATION (Fig. I1-19)

Classic triad of low-grade fever, maculopapular rash, and arthralgias is present in only 5% of cases of AIN. Patients may be asymptomatic or have symptoms such as fever, weight loss, fatigue, abdominal and flank pain, nausea, vomiting, altered mental status, myalgias, headache, oliguria, polyuria and/or nocturia, gross hematuria, nephrotic syndrome, tubulointerstitial nephritis and uveitis (TINU syndrome).

ETIOLOGY

- Drug-induced (70%) usually hypersensitivity reaction occurring about 15 days after exposure to the drug: antibiotics including penicillins, cephalosporins, sulfonamides, rifampin, ciprofloxacin, proton pump inhibitors, NSAIDs, H2 antagonists, anti-neoplastic agents, anticonvulsants, indinavir, mesalamine, allopurinol. Up to 150 agents implicated
- Infection associated (15%) as a primary renal infection or complication of systemic infection
  1. Bacterial: *Corynebacterium diphtheriae, Legionella,* staphylococci, streptococci, *Yersinia*
  2. Viral: Cytomegalovirus, Epstein-Barr virus, hantaviruses, hepatitis C, herpes simplex virus, human immunodeficiency virus, mumps, polyomavirus, influenza A virus
  3. Other: *Mycobacterium, Mycoplasma, Rickettsia,* syphilis, toxoplasmosis
- Idiopathic (10%)
- Immune disorders: systemic lupus erythematosus, Sjögren's, granulomatosis with polyangiitis, and autoimmune pancreatitis

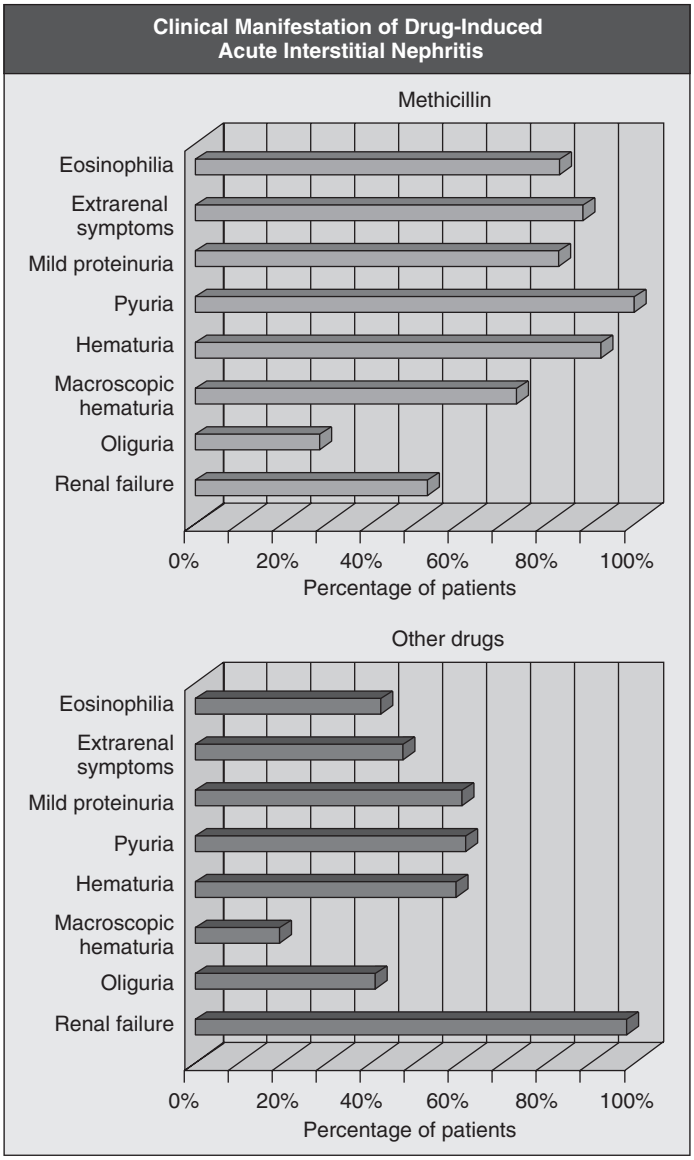


FIGURE I1-19 Clinical manifestations of drug-induced acute interstitial nephritis. Data were pooled from different case reports, including 95 patients with methicillin-induced AIN and more than 200 patients with other drug-induced AIN. Patients with AIN associated with a nephrotic syndrome are not included. (From Floege J, Johnson RJ, Feehally J: *Comprehensive clinical nephrology*, 4th ed, Philadelphia, 2010, Saunders.)

- Neoplastic disorders (multiple myeloma)
- Metabolic diseases (urate nephropathy, hypercalcemic nephropathy, hypokalemic nephropathy, oxalate nephropathy)
- Heavy metals (chronic form)
- Chronic urinary tract obstruction (chronic form)
- Sarcoidosis
- Other rare causes: IgG4 related tubulointerstitial nephritis, hypocomplementemic tubulointerstitial nephritis

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Any other causes of acute renal failure including acute tubular necrosis, glomerulonephritis, hypertensive nephrosclerosis, prerenal azotemia, obstructive nephropathy, renal vascular disease, and various electrolyte abnormalities

WORKUP

Medical history with focus on recent infection, illness, or new medication in the presence of acute to chronic onset of kidney failure; evaluation for underlying infection or insult

LABORATORY TESTS

- Urinalysis and microscopy: white blood cells, microhematuria, glucosuria, eosinophiluria (estimated sensitivity 60% and specificity 85%), proteinuria, phosphaturia, uricosuria, Beta 2 microglobinuria, WBC casts containing eosinophils are characteristic. Detection of eosinophiluria without pyuria is not helpful.
- Serum chemistry profile, rise in plasma creatinine temporally related to administration of offending drug, low serum phosphorus or urate level. Proximal renal tubular acidosis results in bicarbonaturia, and distal renal tubular acidosis results in hyperkalemia.
- Complete blood count with differential (eosinophilia occurs in 50% of AIN patients)
- DLST (drug induced lymphocyte stimulation tests): can be done. Occasionally can be used to identify offending drug in patients on multiple medications, but use may be limited due to expense, time delay, and low availability.
- Renal biopsy is the gold standard for diagnosis but is indicated only when diagnosis is unclear, removal of offending agent does not result in improvement, or steroid initiation is being considered.
- If drug-related AIN is not suspected, laboratory work up for infectious agents, vasculitis, and autoimmune disorders may be warranted based on the clinical context.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Largely supportive; removal of offending agent, if known, will resolve 60% of all cases.

ACUTE GENERAL Rx

- Correct fluid and electrolyte imbalances, maintain adequate hydration and urine output but avoid volume overload.
- Identify and treat infection as indicated.
- Avoid medications that impair renal blood flow.
- Uveitis in TINU syndrome may be asymptomatic; therefore, ophthalmologic exam is needed in idiopathic AIN.
- Initiation of steroids is controversial, but retrospective studies and anecdotal literature have shown that steroid treatment, started within 7 days of diagnosis, may reduce need for chronic dialysis in patients with drug-induced AIN who have not responded to drug withdrawal alone. Steroids are the basis of treatment in idiopathic AIN, AIN associated with systemic disease, and TINU. Dosing is typically pulsed steroids with IV methylprednisolone (250 mg daily ×3 days) followed by 0.5 to 1 mg/kg/day tapering over 4 to 6 weeks.
- Cyclophosphamide, cyclosporine and mycophenolate mofetil have all been used anecdotally in steroid resistant disease.

CHRONIC Rx

- Limit exposure to known nephrotoxic agents.
- Renally adjust medications as indicated by glomerular filtration rate.
- Tight control of blood pressure, diabetes, and cholesterol to preserve kidney function as needed

DISPOSITION

With acute interstitial nephritis (AIN), 60-65% of patients will return to baseline. Partial recovery is seen in 10-20%, and irreversible damage in 5-10%. Relapse is common with reexposure to offending agents.

REFERRAL

Renal consultation is often necessary, especially if there is treatment-resistant disease, the diagnosis is unclear, or biopsy is required.

PEARLS & CONSIDERATIONS

COMMENTS

Acute interstitial nephritis is most often due to drugs; 88% of the time, the drug was started in the past 30 days. In contrast to ATN, early AIN may be associated with polyuria with laboratory evidence of tubular dysfunction; therefore, a high index of suspicion in this clinical setting is essential to early diagnosis.

PREVENTION

Use known offending agents with care, especially in the elderly and those with known underlying kidney disease.

PATIENT/FAMILY EDUCATION

http://www.nlm.nih.gov/medlineplus/ency/article/000464.htm

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **LIORA J. FARBER, M.D., NADEEM MOHAMMED, M.D.**, and **BENJAMIN SAPERS, M.D.**

SUGGESTED READINGS

González E et al.: Early steroid treatment improves the recovery of renal function in patients with drug-induced acute interstitial nephritis, *Kidney Int* 73:940–946, 2008.

Kodner CM, Kudrimoti A: Diagnosis and management of acute interstitial nephritis, *Am Fam Physician* 12:2527–2534, 2003.

Naughton CA: Drug-induced nephrotoxicity, *Am Fam Physician* 78(6):743–750, 2008.

Praga M, Gonzalez E: Acute interstitial nephritis, *Kidney International* 77:956–961, 2010.

Raghavan R, Eknoyan G: Acute interstitial nephritis – a reappraisal and update, *Clinical Nephrology* 82(3):149–162, 2014.

Intraventricular Conduction Delay

BASIC INFORMATION

DEFINITION

Intraventricular conduction delay [IVCD] is a common clinical abnormality related to a conduction disturbance that occurs at the various levels of the branches in the His-Purkinje system. This defect does not meet criteria for right bundle branch, left bundle branch, or hemifascicular blocks (Fig. I1-20). In adults, the QRS duration is >110 ms in adults, in children 4 to 16 yr of age is >100 ms, and in children less than 4 yr of age is >90 ms in the electrocardiogram (ECG). The conduction delay causing the prolonged QRS is considered to take place beyond the Purkinje's myocardial gates and arises from a slowing down in the cell-to-cell conduction.

SYNONYMS

IVCD
Nonspecific intraventricular conduction disturbance
Unspecified intraventricular conduction disturbance
Intraventricular conduction delay
Intraventricular block
Intraventricular conduction defect

ICD-9CM CODES
426.6 Intraventricular block, NOS
ICD-10CM CODES
145.4 Non-specific intraventricular block
145.8 Other specified conduction disorders
145.9 Conduction disorder, unspecified

EPIDEMIOLOGY

- Unknown in general population
- The reported prevalence in military aviators was similar to RBBB at 2:1000.

ETIOLOGY

- Any process that affects the intrinsic ventricular conduction system or slows down the intraventricular conduction can lead to the development of an intraventricular block or conduction delay.
- Nonspecific IVCDs are frequently found in patients with previous myocardial infarction and scar formation, in those who take Class I antiarrhythmic drugs, present left ventricular hypertrophy, and hyperkalemia. IVCD can also be found in the elderly due to myocardial fibrosis caused by apoptosis and the ensuing myocardial fibrosis, as well as in cardiomyopathies of various causes. Etiology can also be unknown in many cases.
- Class IA antiarrhythmics (e.g., procainamide, disopyramide, quinidine) and class IC antiarrhythmics (e.g., flecainide, encainide, and propafenone), amantadine, carbamazepine, cocaine, diphenhydramine, mesoridazine, and thioridazine.
- In addition, propoxyphene and propranolol can also cause IVCD by sodium channel blockade

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Nonspecific IVCD is asymptomatic and is recognizable only through an ECG.

DIAGNOSIS

Usually IVCD is an ECG incidental finding. Lesions of the ventricular conduction system appear as blocks of the bundle branches or fascicles. Ventricular conduction system anomalies can be classified as unifascicular, bifascicular, or trifascicular blocks depending on the site of the lesion or lesions.

DIFFERENTIAL DIAGNOSIS

- Unifascicular block
- Bifascicular block
- Wolff-Parkinson-White (WPW) pattern and variants
- LBBB
- RBBB

WORKUP

Workup such as routine labs, cardiac biomarkers, and cardiac imaging should be targeted at the potential known etiologies and dictated by the clinical circumstances.

Clinical correlation is needed to identify associated cardiac problems. If there is history of heart failure or an abnormal cardiac exam, then an echocardiogram is indicated. If Q waves are present and there is history of myocardial infarction, then an echocardiogram and/or nuclear stress testing is indicated to determine if further therapy should be given to lessen the possibility of heart failure exacerbation, a future myocardial infarction, or other complications. If a Class I antiarrhythmic drug like quinidine or flecainide is being taken that relates temporally to the nonspecific IVCD, then increasing the dosage is not indicated. Blood chemistries can be helpful to assess for hyperkalemia.

TREATMENT

Though cardiac resynchronization therapy has been effective in reducing clinical events in patients with LBBB (LBBB and RBBB are independent predictors of increased risk of cardiac death in patients with HF), patients with IVCDs do not correlate with worsened prognosis nor clinical improvement of heart failure. Therefore, no specific therapy is needed for IVCD. Patients are usually treated for their underlying heart diseases.

PROGNOSIS

In general population, nonspecific IVCD in the ECG is associated with increased all-cause mortality (RR2.01; 1.52-2.66; P <.001), increased cardiac mortality (RR 2.53; CI 1.64-3.90; P <.001) and a markedly elevated risk of sudden arrhythmic death (RR 3.11; CI 1.74-5.54; P = .001. Nevertheless, clinical correlation is needed because prognosis depends on underlying heart disease, if any is present.

REFERRAL

Refer to a cardiologist if there is history of palpitations, dizziness, heart failure, myocardial infarction, or an abnormal cardiac exam.

PEARLS & CONSIDERATIONS

Nonspecific IVCD can be due to drugs such as Class I antiarrhythmic drugs. Nonspecific IVCD can be a normal variant and is not always associated with cardiac pathology. Clinical correlation (history and physical exam) is needed to identify associated cardiac abnormalities. In patients with heart failure, cardiac resynchronization for IVCD does not influence prognosis or clinical improvement.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **CLAUDIA SERRANO-GOMEZ, M.D.**

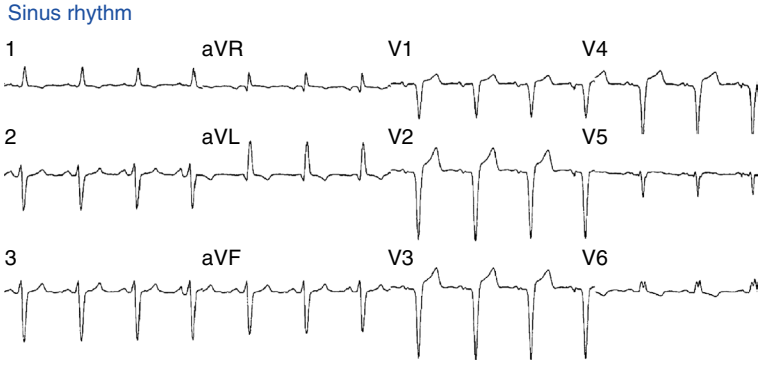


FIGURE I1-20 Normal sinus rhythm baseline with intraventricular conduction delay resembling left bundle branch block (LBBB). (From Issa, Z.F.: Clinical arrhythmology and electrophysiology: a companion to Braunwald's heart disease, 2nd ed, Philadelphia, 2012, Saunders.)

SUGGESTED READINGS

Aro AL et al.: Intraventricular conduction delay in a standard 12-lead electrocardiogram as a predictor of mortality in the general population, *Circ Arrhythm Electrophysiol* 5:704–710, 2011.

Garcia D et al.: Intraventricular conduction abnormality, an electrocardiographic algorithm for rapid detection and diagnosis, *Am J Med* 27:492–502, 2009.

Mirvis DM Goldberger AL. Electrocardiography. In Bonow RO, et al, editors: Braunwald's heart disease: a textbook of cardiovascular medicine, ed 9, Saunders: Philadelphia.

Sipahi I et al.: Effect of QRS morphology on clinical event reduction with cardiac resynchronization therapy: meta-analysis of randomized controlled trials, *Am Heart J* 163:260–267, 2011.

Surawicz B et al.: AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram, part III: intraventricular conduction disturbances, *Circulation* 53(11):976–981, 2009.

Tuzcu EM et al.: Incidence and prognostic significance of intraventricular conduction abnormalities after coronary bypass surgery, *J Am Coll Cardiol* 16:607–610, 1990.

Intraventricular conduction delay in a standard 12-lead electrocardiogram as a predictor of mortality in the general population, *Circ Arrhythm Electrophysiol*, 2011 Oct, 4(5):704–710; http://dx.doi.org/10.1161/CIRCEP.111.963561. Epub 2011.

Differential clinical characteristics and prognosis of intraventricular conduction defects in patients with chronic heart failure. Eur J Heart Fail (2013)10.1093 / eurjhf/hft042. First published online: March 19, 2013.

BASIC INFORMATION

DEFINITION

Anemia is defined as a hemoglobin level 2 standard deviations below normal for age and sex. Iron deficiency anemia is anemia resulting from inadequate iron supplementation or excessive blood loss.

ICD-9CM CODES
280.9 Iron deficiency anemia
648.2 Iron deficiency anemia complicating pregnancy

ICD-10CM CODES
D50.9 Iron deficiency anemia, unspecified
O99.019 Anemia complicating pregnancy, unspecified trimester

EPIDEMIOLOGY & DEMOGRAPHICS

- Dietary iron deficiency occurs often in infants as a result of unsupplemented milk diets. It is also commonly seen in women during their reproductive years, as a result of heavy menstrual periods, and during pregnancy (increased demand).
- Iron deficiency is the most common nutritional deficiency worldwide.
- The prevalence of iron deficiency is greatest among toddlers ages 1 to 2 yr (7%) from inadequate intake and female individuals ages 12 to 49 yr (9% to 16%) from menstrual losses.
- The prevalence of iron deficiency is 2% in adult men, 9% to 12% in non-Hispanic white women, and 20% in black and Mexican American women.
- GI cancer is diagnosed in 10% of elderly patients with iron deficiency anemia.

FIGURE I1-21 Iron deficiency. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St. Louis, 2006, Mosby.)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most patients have normal examination results.
- Skin pallor and conjunctival pallor may be present.
- Signs and symptoms specific for iron deficiency are koilonychias, pica, pagophagia, blue sclera, glossitis, and angular stomatitis (Fig. I1-21).
- Patients with severe anemia can have palpitations, headache, weakness, dizziness, and easy fatigability.

ETIOLOGY

- Blood loss from GI or menstrual bleeding (genitourinary blood loss less often the cause)
- Dietary iron deficiency (rare in adults)
- Poor iron absorption in patients with gastric or small-bowel surgery
- Repeated phlebotomy
- Increased requirements (e.g., during pregnancy)
- Other: traumatic hemolysis (abnormally functioning cardiac valves), idiopathic pulmonary hemosiderosis (iron sequestration in pulmonary macrophages), paroxysmal nocturnal hemoglobinuria (intravascular hemolysis)
- The most common cause worldwide is hookworm infection

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Anemia of chronic disease
- Sideroblastic anemia
- Thalassemia trait
- Lead poisoning

WORKUP

Diagnostic workup consists primarily of laboratory evaluation. Table I1-16 describes laboratory studies differentiating the most common microcytic anemias. Most patients with iron deficiency anemia are asymptomatic in the early stages. With progressive anemia, the major symptoms are fatigue, dizziness, exertional dyspnea, pagophagia (ice eating), and pica. Patient history may also suggest GI blood loss (melena, hematochezia, hemoptysis).

LABORATORY TESTS

- Laboratory results vary with the stage of deficiency.
- Absent iron marrow stores and decreased serum ferritin are the initial abnormalities.
- Decreased serum iron and increased total iron-binding capacity (TIBC) are the next abnormalities.
- Hypochromic microcytic anemia is present with significant iron deficiency.
- Peripheral smear in patients with iron deficiency generally reveals microcytic hypochromic red blood cells (Fig. I1-22) with a wide area of central pallor, anisocytosis, and poikilocytosis when severe.
- Laboratory abnormalities consistent with iron deficiency are low serum ferritin level, increased RBC distribution width with values generally >15, low mean corpuscular volume, low mean corpuscular hemoglobin, increased TIBC, and low serum iron.
- In patients diagnosed with iron deficiency anemia, a GI workup including an upper endoscopy and colonoscopy is recommended to look for source of iron loss.

TABLE I1-16 Laboratory Studies Differentiating the Most Common Microcytic Anemias

Study	Iron Deficiency Anemia	α or β Thalassemia	Anemia of Chronic Disease
Hemoglobin	Decreased	Decreased	Decreased
MCV	Decreased	Decreased	Normal-decreased
RDW	Increased	Normal	Normal-increased
RBC	Decreased	Normal-increased	Normal-decreased
Serum ferritin	Decreased	Normal	Increased
Total Fe binding capacity	Increased	Normal	Decreased
Transferrin saturation	Decreased	Normal	Decreased
FEP	Increased	Normal	Increased
Transferrin receptor	Increased	Normal	Increased
Reticulocyte hemoglobin concentration	Decreased	Normal	Normal-decreased

Fe, Ferritin; *FEP,* free erythrocyte protoporphyrin; *MCV,* mean corpuscular volume; *RBC,* red blood cell; *RDW,* red cell distribution width.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

TREATMENT

The goal of therapy is to supply sufficient iron to correct the low hemoglobin and replenish iron stores.

NONPHARMACOLOGIC THERAPY

Patients should be instructed to consume foods that contain large amounts of iron, such as liver, red meat, and legumes.

ACUTE GENERAL Rx

- Treatment consists of ferrous sulfate 325 mg PO daily for at least 6 mo. Doses higher than 325 mg/day are poorly tolerated. Calcium supplements can decrease iron absorption; therefore, these two medications should be staggered.
- Parenteral iron therapy is reserved for patients with poor tolerance, noncompliance with oral preparations, or malabsorption.
- Transfusion of packed RBCs is indicated in patients with severe symptomatic anemia.

CHRONIC Rx

Patients should be instructed to continue their iron supplements for at least 6 mo or longer to correct depleted body iron stores.

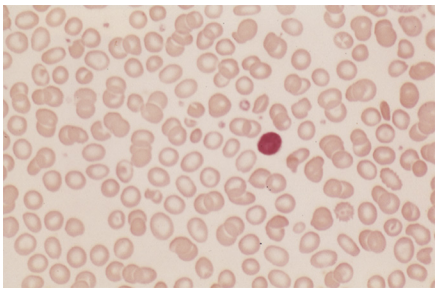


FIGURE I1-22 Iron deficiency anemia. Many of these red blood cells are microcytic (smaller than the nucleus of the normal lymphocyte near the center of the field) and hypochromic (with central areas of pallor that exceed half the diameter of the cells). (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

DISPOSITION

- Most patients respond rapidly to iron supplementation with improvement in CBC and general well-being (Table I1-17). GI side effects from oral iron therapy are common and may require decreased dosage to once every other day or to change to parenteral iron.
- A differential diagnosis of microcytic anemia that fails to respond to oral iron is described in Table I1-18.

REFERRAL

GI referral for evaluation of GI malignancy is recommended in all patients with iron deficiency and suspected GI blood loss.

TABLE I1-17 Responses to Iron Therapy in Iron-Deficiency Anemia

Time after Iron Administration	Response
12-24 hr	Replacement of intracellular iron enzymes; subjective improvement; decreased irritability; increased appetite
36-48 hr	Initial bone marrow response; erythroid hyperplasia
48-72 hr	Reticulocytosis, peaking at 5–7 days
4-30 days	Increase in hemoglobin level
1-3 mo	Repletion of stores

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

TABLE I1-18 Differential Diagnosis of Microcytic Anemia That Fails to Respond to Oral Iron

Poor compliance (true intolerance of iron is uncommon)

Incorrect dose or medication

Malabsorption of administered iron

Ongoing blood loss including gastrointestinal, menstrual, and pulmonary

Concurrent infection or inflammatory disorder inhibiting the response to iron

Concurrent vitamin B_{12} or folate deficiency

Diagnosis other than iron deficiency

- Thalassemias
- Hemoglobin C and E disorders
- Anemia of chronic disease
- Lead poisoning
- Sickle thalassemias, hemoglobin SC disease
- Rare microcytic anemias

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

PEARLS & CONSIDERATIONS

COMMENTS

- Iron deficiency may impair aerobic performance and worsen symptoms in patients with heart failure. Treatment with IV iron in patients with chronic heart failure and iron deficiency has been shown to improve symptoms, quality of life, and functional capacity.
- If the diagnosis of iron deficiency anemia is made, locating the suspected site of iron loss is mandatory.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fig. 3-12 Algorithm for diagnosis of anemias (Algorithm)

Iron Deficiency Anemia (Patient Information)

AUTHORS: **BILAL H. NAQVI, M.D.**, and **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Alleyne A et al.: Individualized treatment for iron-deficiency anemia in adults, *Am J Med* 121:943–948, 2008.

Anker SD et al.: Ferric carboxymaltose in patients with heart failure and iron deficiency, *N Engl J Med* 361:2436–2448, 2009.

Clark SF: Iron deficiency anemia diagnosis and management, *Curr Opin Gastroenterol* 25(2):122–128, 2009. Review.

DeLoughery TG: Microcytic anemia, *N Engl J Med* 371:1324–1331, 2014.

Killip S et al.: Iron deficiency anemia, *Am Fam Physician* 75:671, 2007.

Short MW, Domagalski JE: Iron deficiency anemia: evaluation and management, *Am Fam Physician* 87:98–104, 2013.

BASIC INFORMATION

DEFINITION

Irritable bowel syndrome (IBS) is a chronic functional disorder manifested by alteration in bowel habits and recurrent abdominal pain and bloating. IBS is a symptom complex influenced by a variety of physiologic determinants from gut to brain and back. The ROME III criteria for diagnosis of IBS are:

- Recurrent abdominal pain or discomfort at least 3 days per month in the past 3 mo associated with ≥ two of the following:
  1. Pain is relieved or improved with defecation.
  2. Its onset is associated with a change in the frequency of bowel movement.
  3. Its onset is associated with a change in the form or appearance of the stool.
- The criteria must be fulfilled for at least the past 3 mo with symptom onset at least 6 mo before the diagnosis.

SYNONYMS

Irritable colon
Spastic colon
IBS

ICD-9CM CODES
564.1 Irritable bowel syndrome
ICD-10CM CODES
K58 Irritable bowel syndrome
K58.0 Irritable bowel syndrome
K58.9 Irritable bowel syndrome without diarrhea

EPIDEMIOLOGY & DEMOGRAPHICS

- IBS is the most common functional bowel disorder. An estimated 15 million people in the United States have IBS.
- IBS occurs in 7% to 21% of the general population of industrialized countries and is responsible for >50% of gastrointestinal (GI) referrals. Worldwide adult prevalence is 12%. Incidence increases during adolescence and peaks in third and fourth decades of life.
- Female/male ratio is 2:1. Peak prevalence is from 20 to 39 years of age.
- Nearly 50% of patients have psychiatric abnormalities, with anxiety disorders being most common.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The clinical presentation of IBS consists of abdominal pain and abnormalities of defecation, which may include loose stools, usually after meals and in the morning, alternating with episodes of constipation.
- Physical examination is generally normal.
- Nonspecific abdominal tenderness and distention may be present.

ETIOLOGY

- Unknown
- Associated pathophysiology includes altered GI motility, alteration in gut flora, and increased gut sensitivity
- Risk factors: anxiety, depression, personality disorders, history of childhood sexual abuse, and domestic abuse in women

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Inflammatory bowel disease (IBD)
- Diverticulitis
- Colon malignancy
- Endometriosis
- Peptic ulcer disease
- Biliary liver disease
- Chronic pancreatitis
- Constipation caused by medications (opiates, calcium channel blockers, anticholinergics)
- Diarrhea caused by medications (metformin, colchicine, proton pump inhibitors, antacids, antibiotics)
- Small-bowel overgrowth
- Celiac disease
- Parasites
- Lymphoma of GI tract

WORKUP

Diagnostic workup (Fig. EI1-23) is aimed primarily at excluding the conditions listed in the differential diagnoses. It is important to identify red flags of other diseases, such as weight loss, rectal bleeding, onset in patients >50 yr, fever, nocturnal pain, and family history of malignancy or IBD. Additional red flags include abnormal examination (e.g., mass, enlarged lymph nodes, stool positive for occult blood, muscle wasting) and abnormal laboratory values (anemia, leukocytosis, abnormal chemistry).

Common clinical criteria for diagnosis of IBS are >3 mo of symptoms, including abdominal pain that is relieved by a bowel movement, or pain accompanied by a change in bowel pattern, and abnormality in bowel movement 25% of the time, characterized by two of the following features:

- Abdominal distention
- Abnormal consistency
- Abnormal defecation (e.g., straining, sense of incomplete evacuation)
- Abnormal frequency
- Mucus with bowel movement

LABORATORY TESTS

- Blood work is generally normal. CBC is reasonable to evaluate for anemia. The presence of anemia should alert to the possibility of a colonic malignancy or IBD.
- Testing of stool for ova and parasites should be considered only in patients with chronic diarrhea. Evaluation of stool for *Clostridium difficile* may be helpful in patients with predominant diarrhea symptoms who have recently taken antibiotics.

IMAGING STUDIES

Imaging studies (e.g., flat and upright abdominal radiograph, small-bowel series, sonogram or CT of abdomen and pelvis) are normal and not necessary for diagnosis.

Lower endoscopy is generally normal except for the presence of some spasms. Colonoscopic imaging should be performed only in persons who have alarm features to rule out organic disease and in persons older than 50 yr to screen for colorectal cancer.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Fig. I1-24 illustrates the management of irritable bowel syndrome. The patient should be encouraged to maintain an adequate fiber intake and to eliminate foods that aggravate symptoms. Avoidance of caffeine, dairy products, fatty foods, and dietary excesses is also helpful.
- Cognitive-behavioral therapy is also recommended, particularly in younger patients because psychosocial stressors are important triggers of IBS. Reassurance and education about trigger avoidance and stress management are important.
- Importance of regular exercise and adequate fluid intake should be stressed.

GENERAL Rx

- The mainstay of treatment of IBS is a high-fiber diet. Fiber is helpful for relief of constipation but not for relief of pain. Because symptoms are chronic, the use of laxatives should generally be avoided.
- Soluble fiber (psyllium) is more effective in symptom relief than insoluble fiber (bran). Fiber supplementation with psyllium 1 tbsp bid or calcium polycarbophil (FiberCon) 2 tablets one to four times daily followed by 8 oz of water may be necessary in some patients.
- Patients should be instructed that there might be some increased bloating on initiation of fiber supplementation, which should resolve within 2 to 3 wk. It is important that patients take these fiber products on a regular basis and not only as needed. Fiber is not effective in patients with diarrhea-predominant IBS and may worsen symptoms in these patients.
- Patients who appear anxious can benefit from use of sedatives or selective serotonin reuptake inhibitors (SSRIs). Tricyclic antidepressants in low doses are also effective in some patients with diarrhea-predominant IBS.
- C-2 chloride channel activators: Lubiprostone (Amitiza) is a chloride channel activator that stimulates chloride-rich intestinal fluid secretion and accelerates small intestine and colonic transmit time. It may be effective in chronic constipation-predominant IBS unresponsive to conventional treatment. Usual dose is 8 to 24 mcg bid with food. Side effects include headache and nausea.
- Linaclotide (Linzess) is a guanylate cyclase-C (GC-C) agonist recently FDA approved for IBS with constipation. It stimulates secretion of chloride and bicarbonate into the intestinal lumen, mainly through activation of the CFTR ion channel, resulting in increased intestinal fluid and accelerated transit. Usual dose for IBS is 290 mcg 30 min before eating. The most common adverse effects are diarrhea, abdominal pain, flatulence, and abdominal distension.

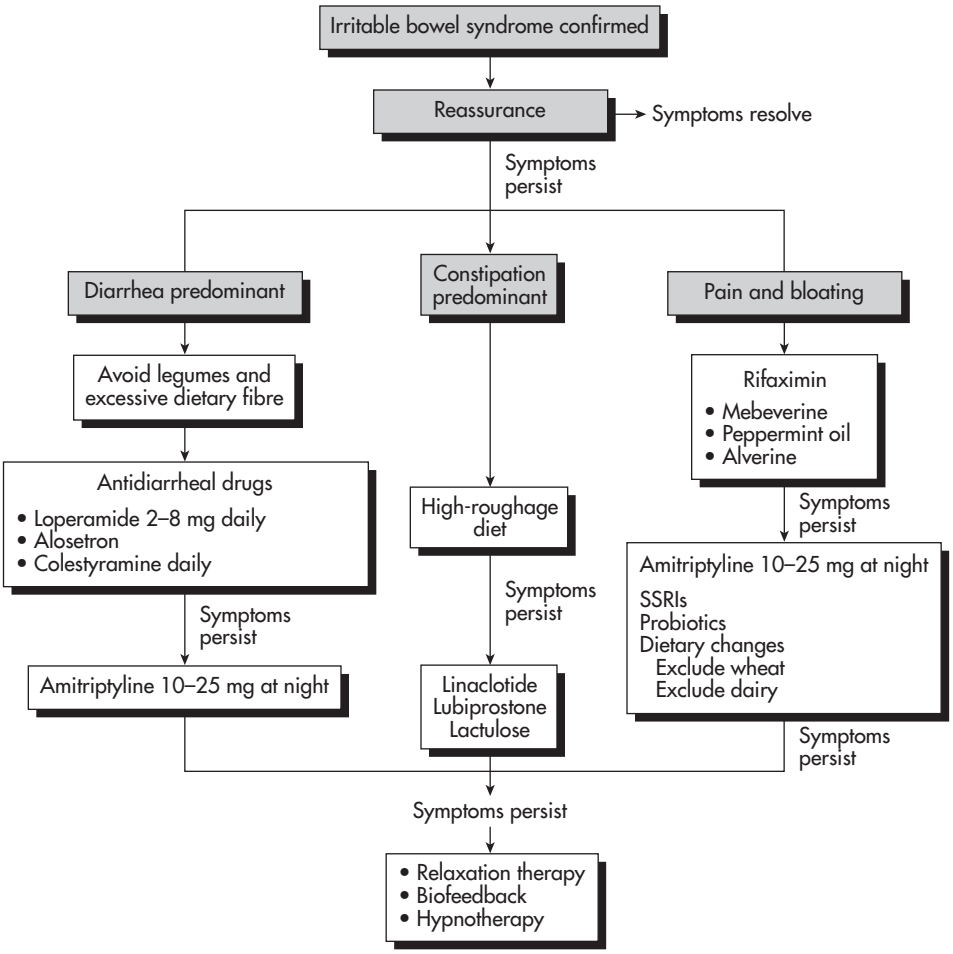


FIGURE I1-24 Management of irritable bowel syndrome. (Modified from Palmer K.R., Penman I.D.: 22 Alimentary tract and pancreatic disease. In Colledge N.R., Walker B.R., Ralston S.H.: *Davidson's principles and practice of medicine*, Philadelphia, 2010, Elsevier.)

- Loperamide is effective for diarrhea. Alosetron, a serotonin type-3 receptor antagonist previously withdrawn because of severe constipation and ischemic colitis, has been reintroduced with limited availability. It is indicated only for women with severe chronic diarrhea-predominant IBS unresponsive to conventional therapy and not caused by anatomic or metabolic abnormality. Starting dose is 1 mg qd.
- Alterations in gut flora have been identified as potentially contributing to IBS (84% of IBS patients have an abnormal lactulose breath test, suggesting small-intestinal bacterial overgrowth). Rifaximin, a gut-selective antibiotic, has been used in recent trials to eradicate bacterial overgrowth (70% eradication rate). A dose of 400 mg tid for 10 days was reported effective in improving IBS symptoms up to 10 wk after discontinuation of therapy. Until additional evidence is available, use of rifaximin or other antibiotics in IBS should be reserved for patients with proven bacterial overgrowth.
- Antispasmodics-anticholinergics (e.g., dicyclomine, hyoscyamine) are often used, but efficacy data from clinical trials are inconclusive.
- Probiotics: Bifidobacteria and some combinations of probiotics have shown some limited efficacy. Lactobacilli do not appear to be effective for the treatment of IBS. Additional data showing efficacy is needed before probiotics can be endorsed for treatment of IBS.
- Antidepressants: SSRIs are more effective than placebo for relief of global IBS symptoms.

DISPOSITION

More than 60% of patients respond successfully to treatment over the initial 12 mo; however, IBS is a chronic, relapsing condition and requires prolonged therapy.

REFERRAL

GI referral is recommended in patients with rectal bleeding, fever, nocturnal diarrhea, anemia, weight loss, or onset of symptoms >40 yr. Consultation is also necessary if specialized diagnostic procedures such as endoscopy are necessary.

PEARLS & CONSIDERATIONS

COMMENTS

- Patients should be educated regarding maintenance of a high-fiber diet and elimination of stressors, which can precipitate attacks of IBS. They should be reassured that their condition does not lead to cancer.
- Recent drug efforts (alosetron, tegaserod) are aimed at serotonergic receptors in the gut because most of the serotonin in the body is found in the GI tract and is believed to be involved in the mediation of visceral sensation and motility.
- Cognitive-behavioral therapy is effective in the treatment of patients with IBS and should be considered as part of the armamentarium against this disorder.
- Some patients with IBS but without celiac disease show symptom improvement on a wheat-free diet. A 2- to 3-week trial of wheat avoidance may be reasonable in patients with treatment-resistant IBS.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Irritable Bowel Syndrome (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Objectives:
Our research group has developed an internet-delivered cognitive behavioral treatment (ICBT) for irritable bowel syndrome (IBS). We compared ICBT with internet-delivered stress management (ISM) for IBS to assess whether the effects of ICBT are specific.
Methods:
This was a randomized controlled trial, including 195 self-referred participants diagnosed with IBS. The treatment interventions lasted for 10 weeks and included an online therapist contact. The ICBT emphasized acceptance of symptoms through exposure to IBS symptoms and related negative feelings. The ICBT also included mindfulness training. The ISM emphasized symptom control through relaxation techniques, dietary adjustments, and problem-solving skills. Severity of IBS symptoms was measured with the gastrointestinal symptom rating scale—IBS version (GSRS-IBS). Credibility of the treatments and expectancy of improvement were assessed with the treatment credibility scale. The participants' perceived therapeutic alliance with their online therapist was measured with the working alliance inventory.
Results:
At post-treatment and 6-month follow-up, 192 (99%) and 169 (87%) participants returned data, respectively. At post-treatment and 6-month follow-up, we found significant differences on the GSRS-IBS, favoring ICBT. The difference on GSRS-IBS scores was 4.8 (95% confidence interval [CI]: 1.2–8.4) at post-treatment and 5.9 (95% CI: 1.9–9.9) at 6-month follow-up. There were no significant differences on the treatment credibility scale or the working alliance inventory between the groups.
Conclusions:
Internet-delivered CBT has specific effects that cannot be attributed only to treatment credibility, expectancy of improvement, therapeutic alliance, or attention. Furthermore, a treatment based on exposure exercises specifically tailored for IBS may be a better treatment option than general stress and symptom management for IBS patients. ICBT is a promising treatment modality for IBS as it can be offered to IBS patients in much larger scale than conventional psychological treatments. Ⓐ

Abstract[2]

Background:
Evidence suggests that gut flora may play an important role in the pathophysiology of the irritable bowel syndrome (IBS). We evaluated rifaximin, a minimally absorbed antibiotic, as treatment for IBS.
Methods:
In two identically designed, phase 3, double-blind, placebo-controlled trials (TARGET 1 and TARGET 2), patients who had IBS without constipation were randomly assigned to either rifaximin at a dose of 550 mg or placebo, three times daily for 2 weeks, and were followed for an additional 10 weeks. The primary end point, the proportion of patients who had adequate relief of global IBS symptoms, and the key secondary end point, the proportion of patients who had adequate relief of IBS-related bloating, were assessed weekly. Adequate relief was defined as self-reported relief of symptoms for at least 2 of the first 4 weeks after treatment. Other secondary end points included the percentage of patients who had a response to treatment as assessed by daily self-ratings of global IBS symptoms and individual symptoms of bloating, abdominal pain, and stool consistency during the 4 weeks after treatment and during the entire 3 months of the study.
Results:
Significantly more patients in the rifaximin group than in the placebo group had adequate relief of global IBS symptoms during the first 4 weeks after treatment (40.8% vs. 31.2%, P = 0.01, in TARGET 1; 40.6% vs. 32.2%, P = 0.03, in TARGET 2; 40.7% vs. 31.7%, P<0.001, in the two studies combined). Similarly, more patients in the rifaximin group than in the placebo group had adequate relief of bloating (39.5% vs. 28.7%, P = 0.005, in TARGET 1; 41.0% vs. 31.9%, P = 0.02, in TARGET 2; 40.2% vs. 30.3%, P<0.001, in the two studies combined). In addition, significantly more patients in the rifaximin group had a response to treatment as assessed by daily ratings of IBS symptoms, bloating, abdominal pain, and stool consistency. The incidence of adverse events was similar in the two groups.
Conclusions:
Among patients who had IBS without constipation, treatment with rifaximin for 2 weeks provided significant relief of IBS symptoms, bloating, abdominal pain, and loose or watery stools. (Funded by Salix Pharmaceuticals; ClinicalTrials.gov numbers, NCT00731679 and NCT00724126.) Ⓐ

Abstract[3]

Objectives:
Physical activity has been shown to be effective in the treatment of conditions, such as fibromyalgia and depression. Although these conditions are associated with irritable bowel syndrome (IBS), no study has assessed the effect of physical activity on gastrointestinal (GI) symptoms in IBS. The aim was to study the effect of physical activity on symptoms in IBS.
Methods:
We randomized 102 patients to a physical activity group and a control group. Patients of the physical activity group were instructed by a physiotherapist to increase their physical activity, and those of the control group were instructed to maintain their lifestyle. The primary end point was to assess the change in the IBS Severity Scoring System (IBS-SSS).
Results:
A total of 38 (73.7% women, median age 38.5 [19–65] years) patients in the control group and 37 (75.7% women, median age 36 [18–65] years) patients in the physical activity group completed the study. There was a significant difference in the improvement in the IBS-SSS score between the physical activity group and the control group (–51 [–130 and 49] vs. –5 [–101 and 118], P = 0.003). The proportion of patients with increased IBS symptom severity during the study was significantly larger in the control group than in the physical activity group.
Conclusions:
Increased physical activity improves GI symptoms in IBS. Physically active patients with IBS will face less symptom deterioration compared with physically inactive patients. Physical activity should be used as a primary treatment modality in IBS. Ⓐ

Evidence-Based References

Ljótsson B et al.: Internet-delivered exposure-based treatment vs. stress management for irritable bowel syndrome: a randomized trial, *Am J Gastroenterol* 106:1481–1491, 2011. Ⓐ

Pimentel M et al.: Rifaximin therapy for patients with irritable bowel syndrome without constipation, *N Engl J Med* 364:22–32, 2011. Ⓐ

Johannesson E et al.: Physical activity improves symptoms in irritable bowel syndrome: a randomized controlled trial, *Am J Gastroenterol* 106:915–922, 2011. Ⓐ

SUGGESTED READINGS

Bijkerk CJ et al.: Soluble or insoluble fiber in irritable bowel syndrome in primary care? Randomized placebo controlled trial, *BMJ* 339:b3154, 2009.

Camiueri M: Peripheral mechanisms in irritable bowel syndrome, *N Engl J Med* 367:1626–1635, 2012.

Carroccio A et al.: Non-celiac wheat sensitivity diagnosed by double-blind placebo-controlled challenge: exploring a new clinical entity, *Am J Gastroenterol* 107:1898–1906, 2012.

Chey WD et al.: Irritable bowel syndrome: a clinical review, *JAMA* 313(9):949–958, 2015.

Drossman DA: The functional gastrointestinal disorders and the Rome III process, *Gastroenterology* 130:1377–1390, 2006.

Ford AC et al.: Will the history and physical examination help establish that irritable bowel syndrome is causing this patient's lower gastrointestinal tract symptoms? *JAMA* 300:1793–1805, 2008.

Marteaus P: Probiotics in functional intestinal disorders and IBS: proof of action and dissecting the multiple mechanisms, *Gut* 59:285–286, 2010.

Mayer EA: Irritable bowel syndrome, *N Engl J Med* 358:1692–1699, 2008.

Mertz HR: Irritable bowel syndrome, *N Engl J Med* 349:22, 2003.

Pimentel M et al.: Rifaximin therapy for patients with irritable bowel syndrome without constipation, *N Engl J Med* 364:22–32, 2011.

Pimentel M et al.: The effect of a nonabsorbed oral antibiotic (Rifaximin) on the symptoms of the irritable bowel syndrome, *Ann Intern Med* 145:557–563, 2006.

Wilkins T et al.: Diagnosis and management of IBS in adults, *Am Fam Physician* 86(5):419–426, 2012.

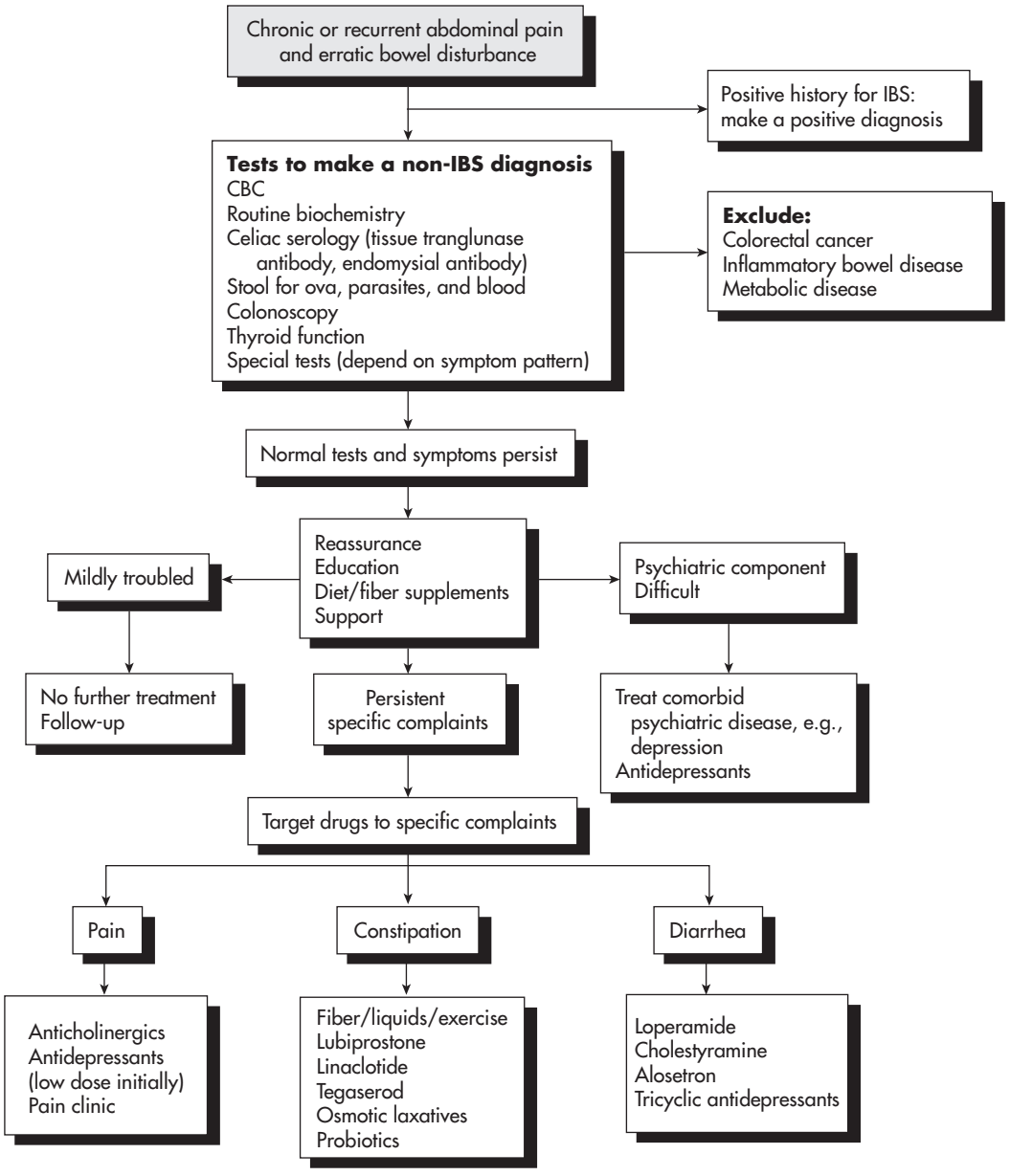


FIGURE EI1-23 Evaluation of suspected irritable bowel syndrome *(IBS).* *CBC,* Complete blood count. (Modified from Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 23, Philadelphia, 2008, Saunders.)

BASIC INFORMATION

DEFINITION

Jaundice is a yellowish discoloration of the sclera (Fig. EJ1-1), skin, and mucous membranes caused by an excessive amount of bilirubin in the bloodstream. Clinically detectable jaundice in adults is a serum bilirubin of 2.5 to 3 mg/dl.

SYNONYMS

Icterus

ICD-9CM CODES
782.4 Jaundice
283.9 Hemolytic jaundice
576.8 Obstructive jaundice
ICD-10CM CODES
R17 Unspecified jaundice

EPIDEMIOLOGY & DEMOGRAPHICS

The prevalent causes of jaundice by age and sex:

- Young adulthood (for either sex): viral hepatitis, Gilbert's disease
- Middle adulthood (for either sex): drug-induced hepatitis and cirrhosis
- Middle-aged and older men: alcoholic liver disease, pancreatic cancer, hepatoma, primary hemochromatosis
- Women: primary biliary cirrhosis, chronic active hepatitis, choledocholithiasis, carcinoma of the gallbladder

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Presentation can vary from an incidental finding to acute and life threatening. History and physical examination give important clues to the underlying condition.

Key history of present illness findings:

- Duration of jaundice
- Associated symptoms: abdominal pain, fever, nausea, malaise, pruritus, chills, changes in urine and stool color, anorexia and/or weight loss

Key social history/exposure findings:

- Alcohol use, injection of illicit drugs, use of hepatotoxic medication or herbal products, blood transfusions, unprotected sex, ingestion of shellfish, travel, occupational exposure to toxins

Key past medical history findings:

- Prior abdominal/biliary surgery, prior episodes of jaundice, prior diagnosis of hepatitis B or C, inflammatory bowel disease

Key physical findings:

- Vital sign abnormalities: fever, hypotension, tachycardia
- Signs of acute disease: abdominal tenderness, splenomegaly, abdominal mass, encephalopathy, Murphy's sign
- Signs of chronic liver disease: palmar erythema, spider angiomas, bruising, gynecomastia, testicular atrophy, ascites, weight loss, Kayser-Fleischer rings (Wilson's), caput medusa, internal hemorrhoids, scleral icterus

ETIOLOGY

Disruption in any of the three phases of bilirubin metabolism can lead to jaundice:

- Prehepatic phase: an increase in heme degradation products from red blood cell catabolism, ineffective erythropoiesis, or breakdown of muscle myoglobin and cytochromes; leads to indirect (unconjugated) hyperbilirubinemia
- Intrahepatic phase: destruction of the hepatocytes or disruption of either of the two separate biochemical processes that conjugate bilirubin in the hepatocyte; may lead to indirect (unconjugated) or direct (conjugated) hyperbilirubinemia
- Posthepatic phase: blockage of the release of water-soluble bilirubin from the hepatobiliary system, preventing excretion into the stool or urine or recycling within the gut flora; leads to direct (conjugated) hyperbilirubinemia

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Prehepatic causes:

- Hemolytic processes (e.g., sickle cell disease, spherocytosis, thalassemia, G6PD, immune hemolysis, HUS), ineffective erythropoiesis (e.g., thalassemia, folate, severe iron deficiency), or large hematoma reabsorption.

Intrahepatic causes:

- If unconjugated hyperbilirubinemia: enzyme metabolism disorders (Gilbert's disease, Crigler-Najjar syndrome), drugs that alter the enzymatic pathways such as rifampin, isoniazid, and probenecid.
- If conjugated hyperbilirubinemia: intrahepatic cholestasis caused by:
  1. Viruses: hepatitis A, B, and C; Epstein-Barr, hemorrhagic viruses (yellow fever, Ebola)
  2. Other infections: bacteria (leptospirosis, MAI), parasites (schistosomiasis, malaria, amebiasis), fungal (blastomyces, histoplasma)
  3. Alcohol: alcoholic hepatitis, alcoholic cirrhosis
  4. Autoimmune: primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis
  5. Hepatotoxic drug-induced: acetaminophen (most common), penicillins (most commonly Augmentin), chlorpromazine, steroids (estrogenic or anabolic), NSAIDs, valproic acid, some herbals such as kava, ma huang, and off-market weight loss supplements
  6. Hereditary/metabolic: sickle cell disease and other RBC dyscrasias, hemochromatosis, Wilson's disease, Dubin-Johnson and Rotor's syndromes, α-antitrypsin deficiency, glycogen storage disease, NASH (non-alcoholic steatohepatitis), porphyria, benign recurrent intrahepatic cholestasis
  7. Systemic disease: invading liver: sarcoidosis, amyloidosis, hemochromatosis, tuberculosis, *Mycobacterium avium intracellulare*
  8. Other: cirrhosis, sepsis, total parenteral nutrition, intrahepatic cholestasis of pregnancy, graft-versus-host disease, environmental toxins, benign postoperative state

Posthepatic causes:

- Intrinsic or extrinsic obstruction of the biliary system
  1. Blockage within hepatobiliary tree: strictures, cholangiocarcinoma, gallbladder cancer, carcinoma of ampulla of Vater, infection (e.g., cytomegalovirus, *Cryptosporidium* in patients with AIDS, parasites), choledocholithiasis
  2. Blockage outside of hepatobiliary tree: pancreatitis, pancreatic carcinoma, pancreatic pseudocyst, lymphoma
- Pseudojaundice: not related to bilirubin but rather resulting from excessive ingestion of foods containing beta carotene (e.g., carrots, melons, squash)

WORKUP

History, physical examination, and first-line lab tests can often clarify diagnosis. Fig. J1-2 describes a clinical approach to jaundice.

LABORATORY TESTS

First-line tests:

Serum total and direct bilirubin

Urinalysis

Liver function tests (AST, ALT, GGTP, alkaline phosphatase), CBC, liver synthetic function (albumin, PT, PTT), pancreatic function (amylase, lipase)

If serum total bilirubin and direct bilirubin are elevated and urine is positive for bilirubin, consider intrahepatic or posthepatic process: If serum total bilirubin is elevated but direct bilirubin is normal (unconjugated hyperbilirubinemia) and urine is negative for bilirubin, consider prehepatic or intrahepatic processes.

- Additional tests if diagnosis unclear:
  1. Screen for hepatitis A, B, and C; if still unclear then consider following options based on H&P
  2. Other viruses: EBV, CMV
  3. Autoimmune disorders: antimitochondrial antibody (elevated in primary biliary cirrhosis); antismooth muscle antibody, ANA (elevated in autoimmune hepatitis); antinuclear cytoplasmic antibody (elevated in primary sclerosing cholangitis)
  4. Ceruloplasmin (elevated in Wilson's disease)
  5. Alpha-1 antitrypsin deficiency (elevated in cirrhosis and emphysema)
  6. Ferritin, Fe saturation (elevated in hemochromatosis)
  7. Blood smear (RBC dyscrasias)
- Diagnosis of exclusion: Gilbert's syndrome

Liver biopsy: essential in diagnosis of chronic hepatitis. Can be used for diagnosis of liver masses but carries a substantial risk.

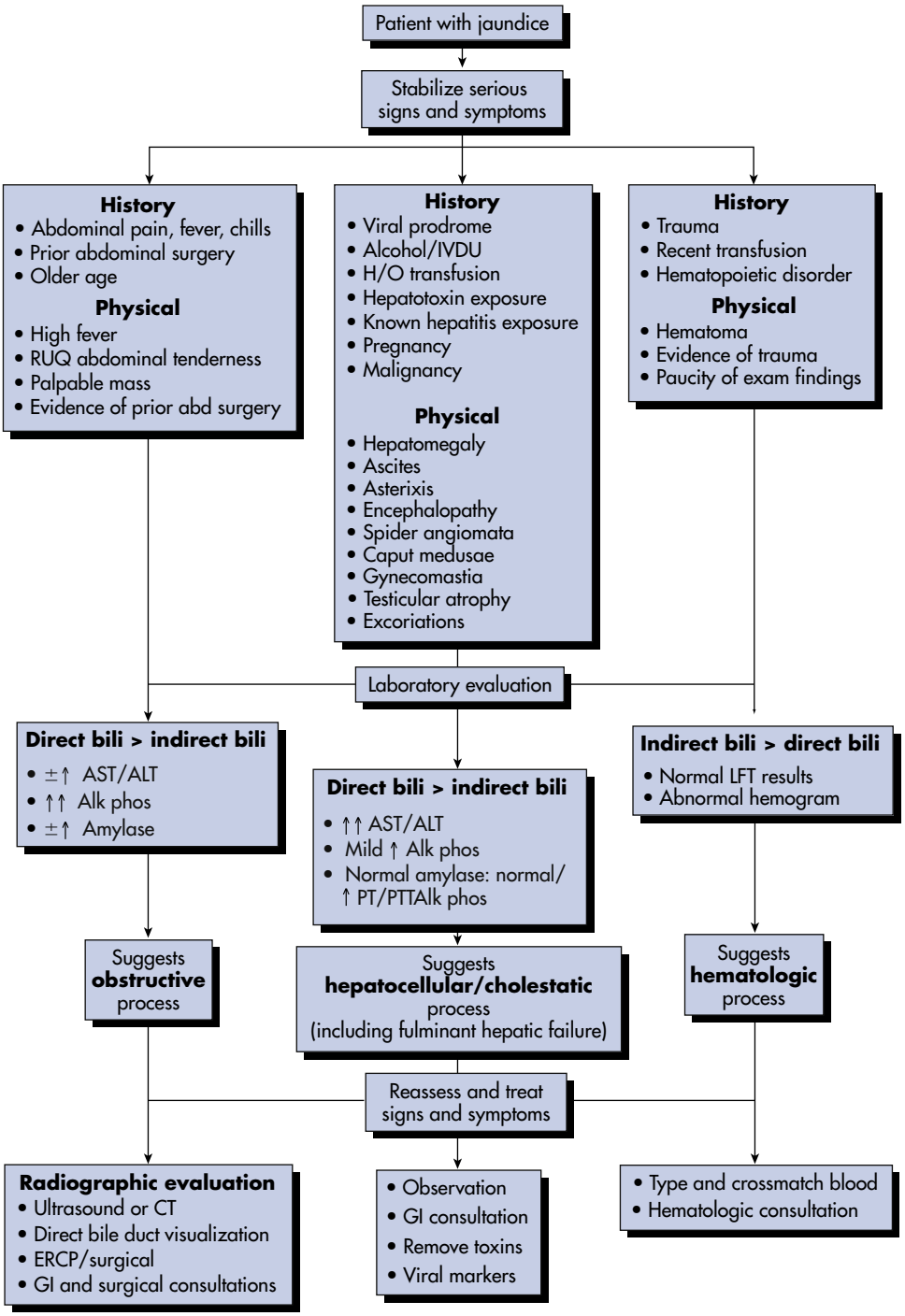


FIGURE J1-2 Management of the patient with jaundice. *Alk phos*, Alkaline phosphatase; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *bili*, bilirubin; *CT*, computed tomography; *ERCP*, endoscopic retrograde cholangiopancreatography; *GI*, gastrointestinal; *H/O*, history of; *IVDU*, intravenous drug use; *LFT*, liver function test; *PT*, prothrombin time; *PTT*, partial thromboplastin time; *RUQ*, right upper quadrant. (From Marx A.J. et al: *Rosen's emergency medicine: concepts and clinical practice*, 7th ed, Philadelphia, 2010, Elsevier)

IMAGING STUDIES

- Abdominal ultrasound: first-line study (Figs. J1-3 and J1-4) may be completed bedside, most sensitive for proximal biliary tract disease; presence of dilated ducts hints at an extrahepatic process
- Abdominal CT: often necessary to elucidate more information on liver, pancreas, and distal biliary system
- Endoscopic retrograde cholangiopancreatography: rarely necessary for diagnostics. Refer to GI consultant
- Percutaneous transhepatic cholangiography: rarely necessary for diagnostics. Refer to GI or surgical consultant
- Magnetic resonance cholangiopancreatography: noninvasive visualization of bile and pancreatic ducts. Refer to GI consultant.
- Endoscopic ultrasound: used for characterization and, if needed, biopsy of any focal lesions found within biliary tree and/or pancreas. Refer to GI consultant

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Depends on underlying cause of the jaundice and clinical stability of the patient. Generally, obstructive causes require surgical treatment, while nonobstructive causes require medical treatment.

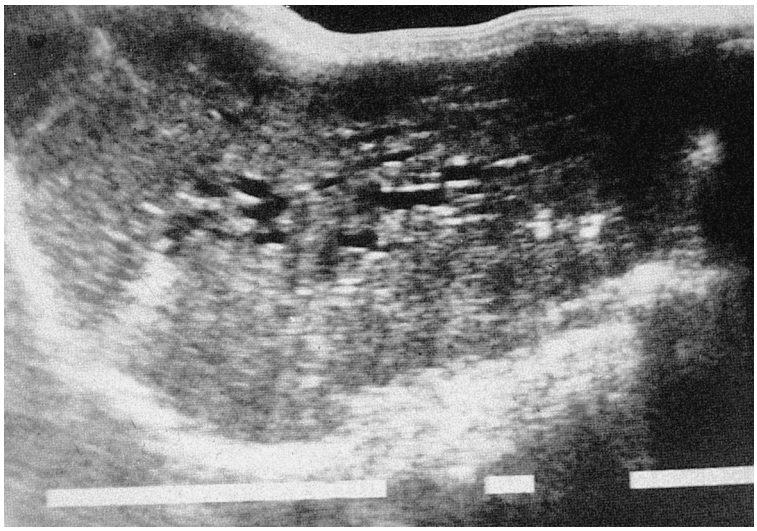


FIGURE J1-3 Ultrasound showing a large calculus in the extrahepatic biliary tree. Dilated bile ducts can be seen to the left. (Courtesy Dr. M.C. Collins. Forbes A et al [eds]: *Atlas of clinical gastroenterology,* ed 3, St Louis, 2005, Mosby.)

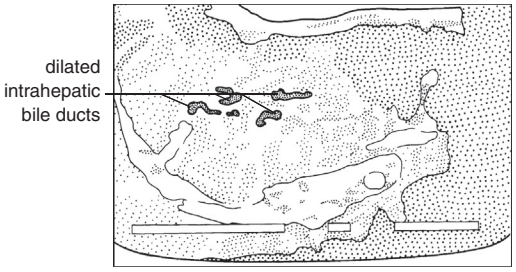


FIGURE J1-4 Schematic representation of ultrasound abnormality seen in Fig. J1-3. (From Forbes A et al [eds]: *Atlas of clinical gastroenterology,* ed 3, St Louis, 2005, Mosby.)

ACUTE GENERAL Rx

Acute, life-threatening illness (e.g., cholecystitis or ascending cholangitis) requires prompt diagnosis with basic labs and bedside diagnostics, with early surgical and GI consultation in conjunction. Suspicious medications should be stopped. Initiate medical management of symptoms with analgesia, IV fluids, correction of coagulopathies, and consideration of antibiotics. *N*-Acetylcysteine can be given for acetaminophen overdose.

CHRONIC Rx

Reversible causes must be ruled out first—suspicious medications and EtOH must be discontinued. Consider GI consult for management of many intrahepatic diseases, such as treatment of hepatitis B or C, Wilson's disease with penicillamine, hemochromatosis with phlebotomy, or for stent insertion with ERCP for post-hepatic obstruction. Consider surgical consult for resection of pancreatic masses, cholecystectomy, etc.

Symptomatic pruritus may be treated with cholestyramine for bilirubin binding or with antihistamines to decrease the itch reflex. Ursodiol to treat primary biliary cirrhosis and for gallstone prevention/dissolution.

PEARLS & CONSIDERATIONS

COMMENTS

- Heed the warning signs of unstable vital signs to diagnose life-threatening illness; early collaboration with surgical and gastroenterology colleagues is helpful in complex patient care scenarios.
- Careful history and physical examination, basic labs, and prompt bedside imaging frequently lead to accurate diagnosis.
- Very high serum bilirubin (>15 mg/dl) is most likely to be seen in cirrhosis. Watch for hepatorenal syndrome in these patients.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Jaundice (Patient Information)

AUTHORS: **ALLA GOLDBURT, M.D.,** and **PAOLO G. PACE, M.A.SC., M.D.**

SUGGESTED READINGS

Livertox database (www.livertox.nih.gov).
In Longo, editor: Harrison's principles of internal medicine. ed 18, McGraw-Hill: New York.
Nguyen KD, Sundaram V, Ayoub WS: Atypical causes of cholestasis, *World J Gastroenterol* 20:28, 2014.
Privette TW et al.: Emergencies of liver, gallbladder, and pancreas, *Emerg Med Clin North Am* 29:293–317, 2011.
Roche SP, Kobos R: Jaundice in the adult patient, *Am Fam Physician* 69:299–304, 2004.
Ryder SD, Beckingham IJ: ABC of diseases of the liver, pancreas and biliary system: other causes of parenchymal liver disease, *BMJ* 322:290–292, 2001.

FIGURE EJ1-1 Jaundice in the adult patient. Jaundice causes yellow sclerae of the eye, and this is often the most readily visible abnormality in mild jaundice, as there is no background melanin or vascular pigment to distract the examiner. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

BASIC INFORMATION

DEFINITION

Juvenile idiopathic arthritis (JIA), previously referred to as juvenile rheumatoid arthritis (JRA), is a diverse spectrum of arthritides presenting before 16 yr of age. The arthritis symptoms must be persistent and objective in ≥1 joints for at least 6 wk with the exclusion of any other known cause.

SYNONYMS

Still's disease
JIA
Juvenile rheumatoid arthritis

ICD-9CM CODES
714.3 Polyarticular juvenile rheumatoid arthritis, chronic or unspecified
ICD-10CM CODES
M08.00 Unspecified juvenile rheumatoid arthritis of unspecified site

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE (IN U.S.): 57 to 220 per 100,000 children.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

JIA is subdivided into seven categories based on the 2001 International League of Associations for Rheumatology (ILAR) classification criteria (subtype characteristics are summarized in Table J1-1).

Systemic onset JIA.
- Arthritis in ≥1 joints with or preceded by fever of at least 2 wk duration that is quotidian (once daily) for at least 3 days and associated with at least one of the following: (1) evanescent erythematous rash (Fig. EJ1-5), (2) generalized lymph node enlargement, (3) hepatomegaly, splenomegaly, or both, and (4) serositis such as pleuritis, pericarditis, or peritonitis.

Oligoarticular JIA (Fig. EJ1-6)
- Arthritis in one to four joints during a 6-mo period of time. There are two subtypes:
  - Persistent: ≤4 joints throughout the disease course.
  - Extended: ≤4 joints during the first 6 mo extending to >4 joints after 6 mo.

Polyarthritis, rheumatoid factor (RF) negative
- Arthritis involves >6 joints during first 6 mo of the disease with negative RF.

Polyarthritis, RF positive
- Arthritis involves >6 joints during first 6 mo of the disease with positive RF on at least two tests run 3 mo apart.
- Anti–cyclic citrullinated (CCP) antibodies may also be present.
- Most likely to extend beyond childhood and most similar to adult rheumatoid arthritis.

Psoriatic arthritis
- Psoriasis and arthritis or psoriasis and ≥2 of the following:
  - Dactylitis, nail pitting, onycholysis, and psoriasis in a first-degree relative.

Enthesitis-related arthritis
- Arthritis and enthesitis or arthritis or enthesitis and ≥2 of the following:
  - Presence of or a history of SI joint pain, positive HLA-B27, boy aged >6 yr, acute anterior uveitis, or history of ankylosing spondylitis, reactive arthritis, sacroiliitis with inflammatory bowel disease or acute anterior uveitis in a first-degree relative.

ETIOLOGY

Idiopathic: Both genetic and environmental triggers thought to play a role.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infection: viral or rheumatic fever.
- Systemic lupus erythematosus (very rare under age 5).
- Malignancy.
- Serum sickness.
- Lyme arthritis.

LABORATORY TESTS

- Increased erythrocyte sedimentation rate and CRP.
- Low-grade anemia.
- Leukocytosis.
- Rheumatoid factor: rarely demonstrable in the serum of children.
- Antinuclear antibodies: often found in children with ocular complications.
- If macrophage activation syndrome suspected in patients with systemic JIA: decreased platelets, WBC, and fibrinogen with high ferritin and liver function tests. Bone marrow biopsy is needed to confirm diagnosis.

TABLE J1-1 Overview of the Main Features of the Subtypes of Juvenile Idiopathic Arthritis

ILAR Subtype	Peak Age of Onset (yr)	Female: Male; % of All JIA	Arthritis Pattern	Extraarticular Features	Investigations	Notes on Therapy
Systemic arthritis	2-4	1:1; ~10% of JIA cases	Polyarticular, often knees, wrists, and ankles; also fingers, neck, and hips	Daily fever; evanescent rash; pericarditis; pleuritis	Anemia; WBC↑↑; ESR↑↑; CRP↑↑; ferritin;↑ platelets↑↑ (normal or ↑ in MAS)	Less responsive to standard treatment with MTX and anti-TNF agents; consider IL-1Ra in resistant cases
Oligoarthritis	>6	4:1; 50%-60% of JIA (but ethnic variation)	Knees ++; ankles, fingers +	Uveitis in ~30%	ANA positive in 60%; other tests usually normal; may have mildly ↑ ESR/CRP	NSAIDs and intraarticular steroids; occasionally require MTX
Polyarthritis, RF negative	6-7	3:1; 30% of JIA cases	Symmetric or asymmetric; small and large joints; cervical spine; TMJ	Uveitis in ~10%	ANA positive in 40%; RF negative; ESR ↑ or; ↑↑ CRP↑/normal; mild anemia	Standard therapy with MTX and NSAIDs, then if nonresponsive, anti-TNF agents or other biologics
Polyarthritis, RF positive	9-12	9:1; >10% of JIA cases	Aggressive symmetric polyarthritis	Rheumatoid nodules in 10%; low-grade fever	RF positive; ESR ↑↑; CRP ↑/normal; mild anemia	Long-term remission unlikely; early aggressive therapy is warranted
Psoriatic arthritis	7-10	2:1; >10% of JIA cases	Asymmetric arthritis of small or medium sized joints	Uveitis in 10%; psoriasis in 50%	ANA positive in 50%; ESR ↑; CRP ↑/normal; mild anemia	NSAIDs and intraarticular steroids; second-line agents less commonly
Enthesitis-related arthritis	9-12	1:7; 10% of JIA cases	Predominantly lower limb joints affected; sometimes axial skeleton (but less than adult AS)	Acute anterior uveitis; association with reactive arthritis and IBD	80% HLA-B27[1]	NSAIDs and intraarticular steroids; consider sulfasalazine as alternative to MTX

ANA, Antinuclear antibody; *AS,* ankylosing spondylitis; *CRP,* C-reactive protein; *ESR,* erythrocyte sedimentation rate; *IBD,* inflammatory bowel disease; *ILAR,* International League of Associations for Rheumatology; *IL-1Ra,* interleukin-1 receptor antagonist; *JIA,* juvenile idiopathic arthritis; *MAS,* macrophage activation syndrome; *MTX,* methotrexate; *NSAID,* nonsteroidal anti-inflammatory drug; *RF,* rheumatoid factor; *TMJ,* temporomandibular joint; *TNF,* tumor necrosis factor; *WBC,* white blood cell count.
From Firestein G et al: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.

IMAGING STUDIES

- Roentgenographic findings (Fig. EJ1-7) are similar to those in adult, with soft tissue swelling and periarticular osteopenia early in the disease.
- Joint destruction (Fig. EJ1-8) is less frequent.
- Bony erosion and cyst formation may be present as a result of synovial hypertrophy.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Proper management requires close cooperation among primary physician, physical and occupational therapists, pediatric rheumatologist, social workers, and orthopedist.

- Rest.
- Physical and occupational therapy.
- Patient and family education.
- Proper diet and weight maintenance (Fig. J1-9).

ACUTE GENERAL Rx

- NSAIDs.
- DMARDs: methotrexate, leflunomide, sulfasalazine.
- Patients with polyarticular disease are less likely to respond to methotrexate if they have longer disease duration, positive ANA, higher level of disability, and bilateral wrist arthritis. It may be reasonable to start with anti-TNF therapy first in these cases.
- Axial involvement is also less likely to respond to methotrexate.
- Biologics:
  1. Tumor necrosis factor blockers such as etanercept and adalimumab.
  2. T-cell modulator CTLA-4 fusion protein, abatacept, is FDA approved for patients with polyarticular JIA who have not responded to anti-TNF therapy.
  3. IL-6 (tocilizumab) and IL-1 inhibitors (anakinra, canakinumab) for systemic JIA.
- Intraarticular steroids can prevent leg length discrepancies in oligoarticular JIA.
- Systemic corticosteroids.

DISPOSITION

- Complete remission occurs in the majority of patients and may occur at any age.
- 70% to 85% of children regain normal function.
- Mortality is three- to fourteen-fold greater than in the general population of the same age. Macrophage activation syndrome is a life-threatening complication in systemic JIA.
- Oligoarticular JIA patients with positive ANA are at the highest risk for blindness due to chronic iridocyclitis and require frequent ophthalmologic monitoring.
- Systemic and localized growth disturbance can lead to generalized growth failure and leg length discrepancies.
- Arthritis of the temporomandibular joint can lead to jaw malformation.

REFERRAL

- Early rheumatology consultation.
- Ophthalmology consultation at diagnosis and regularly thereafter particularly in ANA+, oligoarticular JIA.
- Orthopedic consultation for corrective surgery.

PEARLS & CONSIDERATIONS

COMMENTS

The spontaneous adverse event reports (SERS) in the FDA surveillance system has recently reported a warning for risk of malignancy related to anti-TNF agents in the pediatric population. However, baseline risk of malignancy in children with JIA is unknown and the SERS reporting system has limitations, including incomplete adverse event reporting. Initiation of anti-TNF therapy should be a decision made between families and pediatric rheumatologists.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Juvenile Rheumatoid Arthritis (Patient Information)

AUTHOR: **ELISABETH B. MATSON, D.O.**

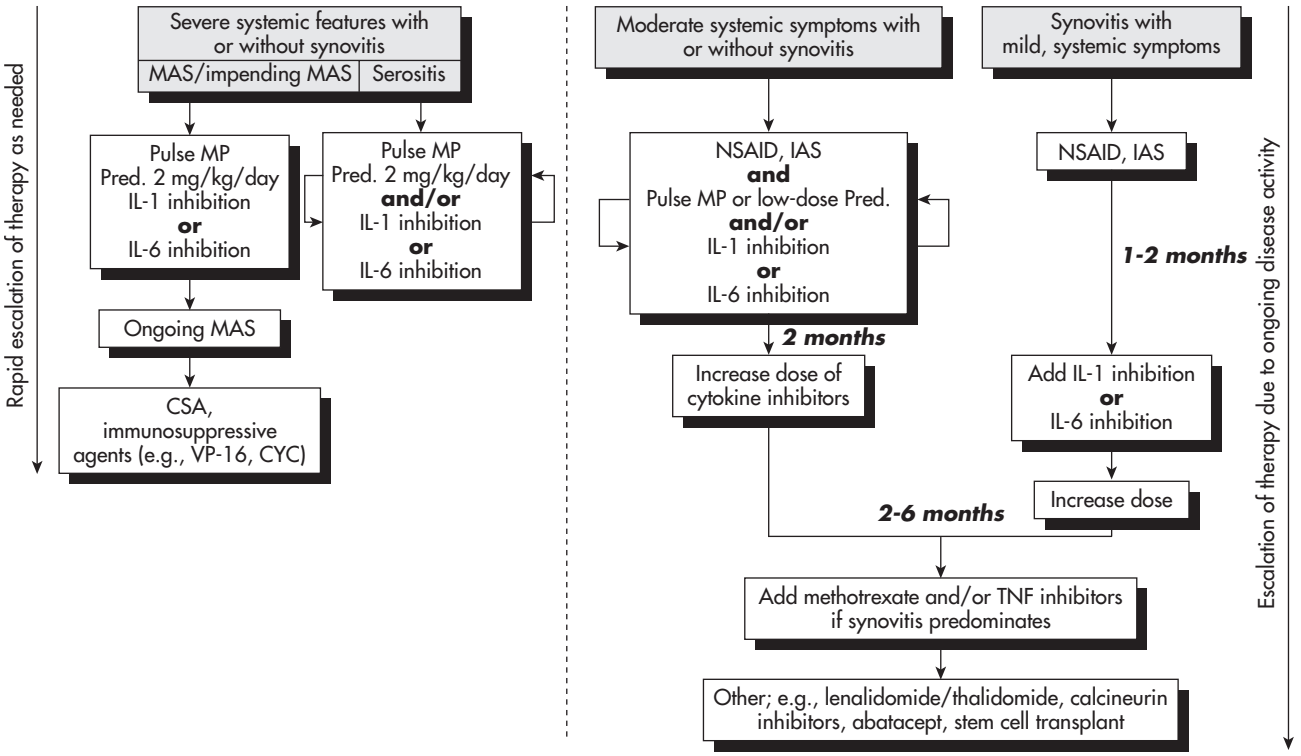


FIGURE J1-9 Systemic juvenile idiopathic arthritis treatment algorithm. The treatment goal is remission of disease activity, both systemic and articular, and is stratified by severity of disease. Algorithm is divided into severe systemic disease manifestations (macrophage activation syndrome [MAS], serositis) or synovitis with milder systemic disease. Currently there is significant variability in practice regarding using corticosteroid as initial systemic therapy or moving directly to inflammatory cytokine inhibitors. At the time of this writing, interleukin (IL)-1 inhibition and IL-6 inhibition are currently in trials, and more information is likely to be available in the future. *CSA*, cyclosporine A; *CYC*, cyclophosphamide; *IAS*, intraarticular steroid; *MP*, methylprednisolone; *NSAID*, nonsteroidal anti-inflammatory drug; *Pred.*, prednisone; *TNF*, tumor necrosis factor. (From Firestein GS et al: *Kelly's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.)

SUGGESTED READINGS

De Benedetti F: Targeting interleukin-6 in pediatric rheumatic diseases, *Curr Opin Rheumatol* 21(5):533, 2009.

De Benedetti F et al.: Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis, *N Engl J Med* 367:2385–2395, 2012.

Feldman DE et al.: Effects of adherence to treatment on short-term outcomes in children with juvenile idiopathic arthritis, *Arthritis Rheum* 57(6):905, 2007.

Glueck D, Gellman H: Management of the upper extremity in juvenile rheumatoid arthritis, *J Am Acad Orthop Surg* 13:254, 2005.

Hashkes PJ et al.: Mortality outcomes in pediatric rheumatology in the U.S., *Arthritis Rheum* 62:599, 2010.

Iesaka K et al.: Orthopedic surgical management of hip and knee involvement in patients with juvenile rheumatoid arthritis, *Am J Orthop* 35:67, 2006.

Ilowite NT: Update on biologics in juvenile idiopathic arthritis, *Curr Opin Rheumatol* 2:613, 2008.

Long AR, Rouster-Stevens KA: The role of exercise therapy in the management of juvenile idiopathic arthritis, *Curr Opin Rheumatol* 22:213, 2010.

Lovell DJ et al.: Adalimumab with or without methotrexate in juvenile rheumatoid arthritis, *N Engl J Med* 359:810–820, 2008.

Martini A, Lovell DJ: Juvenile idiopathic arthritis: state of the art and future perspectives, *Ann Rheum Dis* 69(7):1260, 2010.

Passo MH, Taylor J: Quality improvement in pediatric rheumatology: what do we need to do? *Curr Opin Rheumatol* 20:625, 2008.

Ruperto N et al.: Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial, *Lancet* 372:383–391, 2008.

Ruperto N et al.: Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis, *N Engl J Med* 367:2386–2406, 2012.

Silverman E et al.: Leflunomide of methotrexate for juvenile rheumatoid arthritis, *N Engl J Med* 352:1655, 2005.

Stinson JN et al.: Asking the experts: exploring the self-management needs of adolescents with arthritis, *Arthritis Rheum* 59:65, 2008.

Vilca I et al.: Predictors of poor response to methotrexate in polyarticular-course juvenile idiopathic arthritis: analysis of the PRINTO methotrexate trial, *Ann Rheum Dis* 69:1479, 2010.

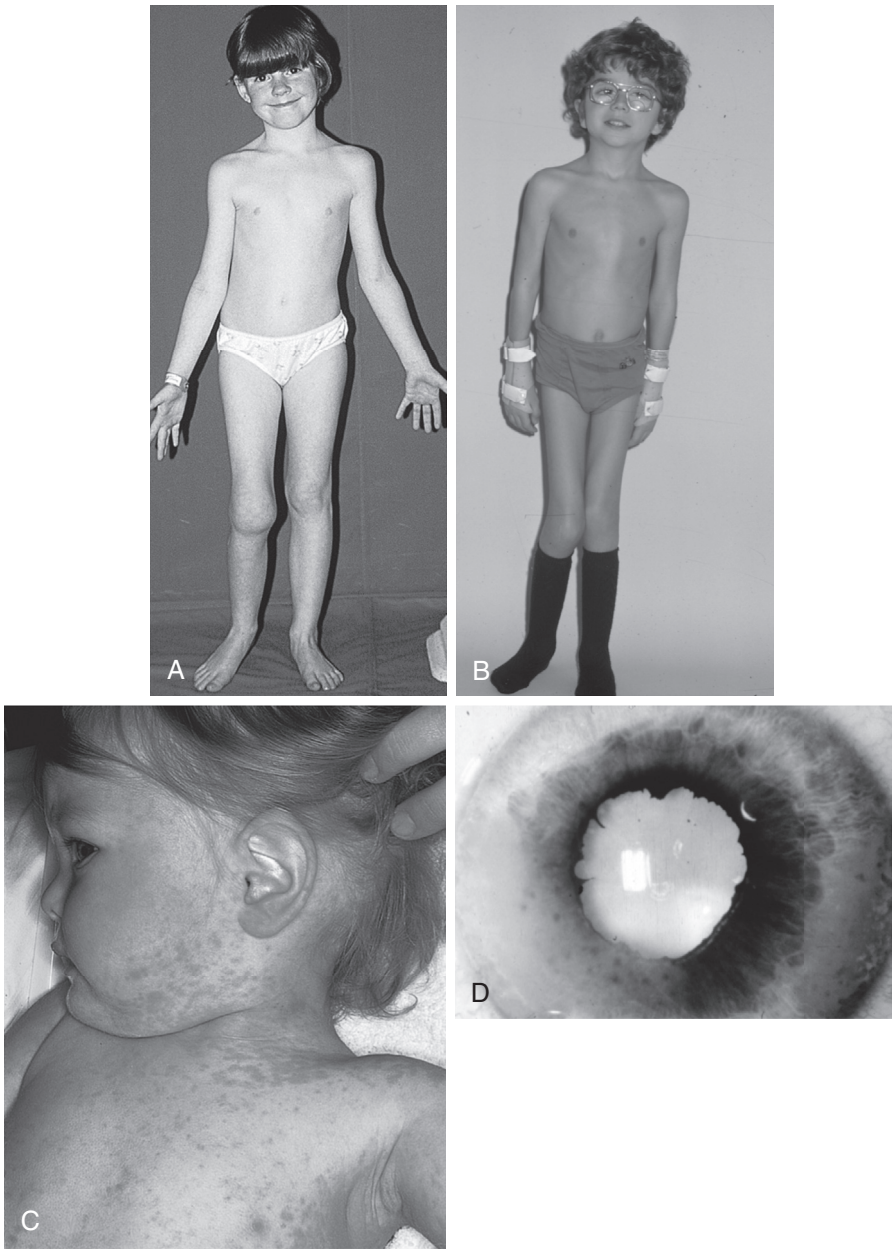


FIGURE EJ1-5 Juvenile idiopathic arthritis. A, Monoarticular disease affecting a knee. **B,** Severe polyarticular disease. **C,** Maculopapular rash in systemic-onset disease. **D,** Band keratopathy and mature cataract in associated chronic anterior uveitis. (From Kanski JJ, Bowling B: *Clinical ophthalmology, a systematic approach,* ed 7, Philadelphia, 2010, Saunders.)

FIGURE EJ1-6 Oligoarticular juvenile idiopathic arthritis with swelling and flexion contracture of the right knee. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

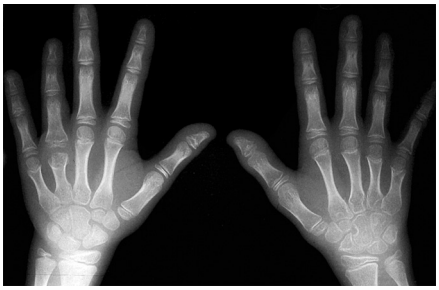


FIGURE EJ1-7 Juvenile idiopathic arthritis (JIA). Oligoarticular-onset JIA in an 8-year-old. Epiphyseal destruction and undergrowth of the third metacarpophalangeal joint of the left hand are seen, as well as overgrowth of the carpal bones of the right wrist compared with the left wrist. Also note the widened appearance of the third phalanges caused by periosteal new bone formation. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

FIGURE EJ1-8 Severe hip disease in a 13-yr-old boy with active, systemic-onset juvenile idiopathic arthritis. Radiograph shows destruction of the femoral head and acetabula, joint space narrowing, and subluxation of left hip. The patient had received corticosteroids systemically for 9 yr. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Kaposi's sarcoma (KS) is a vascular neoplasm most frequently occurring in AIDS patients. It can be divided into the following four subsets:

1. Classic KS: most frequently found in elderly Eastern European and Mediterranean males. It consists initially of violaceous macules and papules with subsequent development of plaques and red-purple nodules. Growth is slow, and most of the patients die of unrelated causes.
2. Epidemic or AIDS-related KS: most frequently occurs in homosexual men. Lesions are generally multifocal and widespread. Lymphadenopathy may be associated.
3. Endemic KS: usually affects African children and adults. An aggressive lymphadenopathic form affects African children in particular.
4. Immunosuppression-associated, or transplantation-associated, KS: usually associated with chemotherapy.

SYNONYMS

KS

ICD-9CM CODES
173.9 Malignant neoplasm of the skin
ICD-10CM CODES
C46.9 Kaposi's sarcoma, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- AIDS-related KS affects >35% of AIDS cases.
- Highest incidence is in homosexual men.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- AIDS-related KS: multifocal and widespread red-purple (Fig. EK1-1) or dark plaques (Fig. K1-2) and/or nodules on cutaneous or mucosal surfaces (Fig. K1-3).
- Generalized lymphadenopathy at the time of diagnosis is present in >50% of patients with AIDS-related KS; the initial lesions have a rust-colored appearance; subsequent progression to red or purple nodules or plaques occurs.
- Most frequently affected areas are the face, trunk, oral cavity, and upper and lower extremities.

ETIOLOGY

A herpesvirus (HHV-8, KS-associated herpesvirus KSHV) has been isolated from patients with most forms of KS and is believed to be the causative agent. It can be transmitted sexually (homosexual or heterosexual activities) and by other forms of nonsexual contact such as maternal-infant transmission (common in African countries).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Stasis dermatitis.
- Pyogenic granuloma.
- Capillary hemangiomas.
- Granulation tissue.
- Postinflammatory hyperpigmentation.
- Cutaneous lymphoma.
- Melanoma.
- Dermatofibroma.
- Hematoma.
- Prurigo nodularis.

The differential diagnosis of cutaneous lesions in patients with HIV infection is described in Section II.

WORKUP

Diagnosis can generally be made on clinical appearance; tissue biopsy will confirm diagnosis.

LABORATORY TESTS

HIV in patients suspected of AIDS.

TREATMENT

NONPHARMACOLOGIC THERAPY

Observation is a reasonable option in patients with slowly progressive disease.

GENERAL Rx

- Excisional biopsy often provides adequate treatment for single lesions and resected recurrences in classic KS.
- Liquid nitrogen cryotherapy can result in complete response in 80% of lesions.
- Interlesional chemotherapy with vinblastine is useful for nodular lesions >1 cm in diameter. Intralesional injection of interferon alfa-2b has also been reported as effective and well tolerated.
- Radiation therapy is effective in non-AIDS KS and for large tumor masses that interfere with normal function.
- Systemic therapy with interferon is also effective in AIDS-related KS and is often used in combination with zidovudine.
- Systemic chemotherapy (vinblastine, bleomycin, doxorubicin, and dacarbazine) can be used for rapidly progressive disease and for classic and African endemic KS.
- Sirolimus (rapamycin), an immunosuppressive drug, is effective in inhibiting the progression of dermal KS in kidney transplant recipients.
- Oral etoposide is also effective and has less myelosuppression than vinblastine.
- Paclitaxel is also effective in patients with advanced KS and represents an excellent second-line therapy.
- Thalidomide, retinoids.

DISPOSITION

- Prognosis is poor in AIDS-related KS. Death is often a result of other AIDS-defining illnesses.
- Prognosis is better in African cutaneous KS and classic sarcoma (patients usually die of unrelated causes).

PEARLS & CONSIDERATIONS

COMMENTS

Immunosuppression-associated KS usually regresses with the cessation, reduction, or modification of immunosuppression therapy in most patients. Similarly, in HIV patients KS responds concurrently with the decrease in serum HIV RNA and increase in the CD4 count.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Kaposi's Sarcoma (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

FIGURE K1-2 Kaposi sarcoma (AIDS). (From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

FIGURE K1-3 Kaposi's sarcoma. More advanced lesions. Note widespread hemorrhagic plaques and nodules. (From Noble J [ed]: *Textbook of primary care medicine,* ed 2, St Louis, 1995, Mosby.)

SUGGESTED READINGS

Stallone G et al.: Sirolimus for Kaposi's sarcoma in renal-transplant recipients, *N Engl J Med* 352:1317, 2005.

FIGURE EK1-1 Kaposi sarcoma (AIDS). (From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

BASIC INFORMATION

DEFINITION

Kawasaki disease (KD) is an acute, febrile illness that predominantly affects children with pathology demonstrating vasculitis of small and medium-size blood vessels with a predilection for the coronary arteries. It is usually a self-limiting condition lasting for an average of 12 days if not treated.

SYNONYMS

Kawasaki syndrome
Mucocutaneous lymph node syndrome
Infantile polyarteritis

ICD-9CM CODES
446.1 Kawasaki disease
ICD-10CM CODES
M30.3 Mucocutaneous lymph node syndrome [Kawasaki]

EPIDEMIOLOGY & DEMOGRAPHICS

- KD is the leading cause of acquired heart disease in children in developed countries including the United States and Japan. Rheumatic disease is still more common in underdeveloped countries.
- Commonly occurs in children <5 yr (80%); peak incidence is in infants aged 6 to 11 mo. Occurrence is rare after late childhood.
- More prevalent in boys than girls (1.5:1).
- The highest incidence is found in Japan (~174 cases/100,000 children).
- Incidence of KD in the United States is 17 to 18 cases/100,000 children <5 yr.
- Temporal clustering and winter to spring predominance have been observed in KD cases in Japan.
- Children of Asian descent have the highest incidence of KD compared with those of European or African descent.
- ~4200 new cases are diagnosed each year in the United States.
- 1% of patients with KD in Japan have a positive family history of KD.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The clinical presentations reflect inflammation of small and medium-sized blood vessels. There is no specific test that is diagnostic for KD so confirmation of the diagnosis is based on clinical criteria. To meet the case definition of KD a child will have fever persisting for >3 days and the presence of at least four of the following five principal features:
  1. Bilateral, painless bulbar conjunctival injection without exudate.
  2. Oral mucosal changes: erythema and fissured lips, strawberry tongue (Fig. EK1-4*B*), diffuse injection of the oropharyngeal mucosae.
  3. Polymorphous exanthema (usually in truncal region) (Fig. EK1-5*A* and *B*).
  4. Extremity changes: (a) acute: erythema and edema of hands and feet (Fig. EK1-4*A*); (b) convalescent: membranous desquamation of fingertips.
  5. Cervical lymph node enlargement (at least one lymph node >1.5 cm in diameter).

Additionally, patients with less than four criteria but evidence of coronary artery aneurysms are diagnosed with KD.

- The fever of KD is mildly responsive to antipyretics and is usually >102.2° F (39° C) and often >104.0° F (40° C). If untreated, it lasts for an average of 12 days.
- The rash of KD can be maculopapular or can take various forms; however, vesicles, bullae, purpura, and petechia are never observed.
- Coronary artery aneurysms can develop in as many as 25% of untreated children between 1 to 4 weeks of illness. This subset of patients can develop ischemic heart disease, myocardial infarction, and congestive heart failure over time, and, occasionally, death. New aneurysms seldom form after 6 weeks. Half of the aneurysms show angiographic regression in 1 to 2 years.
- Morbidity and mortality rates are highest if aneurysm diameter is >8 mm ("giant aneurysms").
- Children with KD who are <1 yr or >6 yr are more likely to develop the cardiac sequelae and are least likely to respond to treatment.
- Patients with fever and some of the classical features of KD but without enough to meet the case definition are diagnosed with atypical or incomplete KD. These patients are more likely to be infants and older children and consequently at higher risk for coronary aneurysms.
- Cervical lymphadenopathy is the most common physical manifestation absent in atypical KD, followed by exanthema and then extremity changes.
- Oral mucosal changes are the most common manifestations of KD affecting approximately 90% of cases (either typical or atypical).
- Patients may also develop sensitivity to light and uveitis along with conjunctival injection.
- Redness and induration can be seen at the site of bacille Calmette-Guérin (BCG) inoculation.
- Beau's lines (transverse grooves of the nails), diarrhea, acute myocarditis, cough, rhinorrhea, dyspnea, arthralgia, and myalgia may also be seen.
- Aseptic meningitis can develop in 40% of cases.
- Interstitial nephritis, acute renal failure in rare cases, KD shock syndrome, and macrophage activation syndrome can also occur.
- Self-limiting arthritis involving large joints including knees, ankles, and hips was reported in 7.5% to 25% of patients.

ETIOLOGY

The cause of KD is not known, although evidence suggests an infectious etiology precipitating an immune-mediated reaction in genetically susceptible individuals.

DIAGNOSIS

Diagnosis of KD is made on the basis of clinical features (see "Physical Findings & Clinical Presentation"). The hallmark of KD is fever lasting >3 days. Typically, the clinical signs appear over the course of several days. Laboratory evaluation may be helpful in making the diagnosis in atypical KD. The timely diagnosis and treatment of KD are important in preventing complications.

DIFFERENTIAL DIAGNOSIS

- Scarlet fever.
- Stevens-Johnson syndrome.
- Drug eruption.
- Henoch-Schönlein purpura.
- Toxic shock syndrome.
- Measles.
- Rocky Mountain spotted fever.
- Epstein-Barr virus, adenovirus, echovirus, and enterovirus.
- Juvenile rheumatoid arthritis.
- Mercury hypersensitivity (acrodynia).
- Leptospirosis.

WORKUP

Clinical findings in addition to laboratory and imaging studies are useful in searching for multiorgan system involvement and complications (e.g., cardiac, lung, liver).

LABORATORY TESTS

Complete blood count commonly shows a normochromic normocytic anemia, elevated white blood cell count with neutrophil predominance, and elevated platelet count, which usually rises by the second week.

- Abnormal liver function tests are found: elevated transaminases (hepatic congestion), elevated bilirubin (gallbladder hydrops), low albumin.
- Inflammatory markers will be increased in KD:
- Elevated erythrocyte sedimentation (ESR) rate is found (often >40 mm/hr and not uncommonly elevated to levels of >100 mm/hr).
- Elevated C-reactive protein (CRP) >3 mg/dL.
- Hyponatremia is associated with increased risk of coronary aneurysms.
- Urinalysis may show sterile pyuria.
- Impaired serum lipid profiles with decreased high-density lipoproteins (HDL) and elevated triglycerides and low-density lipoproteins (LDL) can occur.
- Cerebrospinal fluid (CSF) with increased white cell count without elevated CSF protein is found.
- Arthrocentesis of joints usually demonstrates pleocytosis with 125,000 to 300,000 white cells/mm^3.
- ECG changes (arrhythmias, abnormal Q waves, prolonged PR and/or QT intervals, occasionally low voltage, or ST-T wave changes) can be seen.

IMAGING STUDIES

- Chest radiograph may reveal pulmonary infiltrates; cardiomegaly may also be present.
- Echocardiogram is recommended at the time of illness, and repeat in 6 wk and 6 mo. Echocardiogram should include careful assessment of the coronary arteries for size and aneurysms, mural or intraluminal thrombi, effusions, valve function, and myocardial function.
- Coronary angiogram, computed tomography angiography, and magnetic resonance angiography can be used to visualize the arterial system and the presence of coronary artery aneurysms where echocardiography is nondiagnostic.
- Intravascular ultrasound can assess for luminal irregularities of the coronary arteries.

- Exercise testing with myocardial perfusion studies can be done to assess for coronary blood flow and the presence of myocardial ischemia.

Rx TREATMENT

The goal of treatment of KD in the acute phase is directed at reducing clinical symptoms and reducing inflammation in the systemic and coronary arteries and preventing arterial thrombosis. Long-term therapy in individuals who develop coronary aneurysms is aimed at preventing myocardial ischemia or infarction.

NONPHARMACOLOGIC THERAPY

- Oxygen in selected patients.
- Salt restriction in patients with congestive heart failure.
- Emollient creams for peeling skin and balms for fissured lips.

ACUTE GENERAL Rx

- IV immunoglobulin (IVIG) 2 g/kg over 8 to 12 hr as a single infusion is the treatment of choice in children diagnosed with KD, and ideally should be given within the first 7 to 10 days of the illness.
- Aspirin 80 to 100 mg/kg/day (anti-inflammatory dosing) given in four divided doses until the patient is no longer febrile for 48 hr. Thereafter, aspirin 3 to 5 mg/kg/day (antiplatelet dosing) is continued until laboratory studies (e.g., platelet count, sedimentation rate) return to normal, generally within 6 to 8 wk after disease onset if there are no coronary artery abnormalities or indefinitely if abnormalities are present.
- In patients who do not defervesce within 48 hr or have recrudescent fever after initial IVIG treatment, a second dose of IVIG 2 g/kg IV over 8 to 12 hr should be considered.
- NSAIDs are not effective in the treatment of KD.
- Efficacy of treatment with IVIG along with aspirin is higher than aspirin alone in decreasing risk of coronary artery aneurysms.
- The effect of corticosteroids on coronary artery aneurysms is unclear. Therefore most experts recommend withholding steroids unless fever persists after at least two courses of IVIG. Pulse methylprednisolone at 30 mg/kg daily is given to such patients for 1 to 3 days.
- Other therapies, including urinary trypsin inhibitor (Ulinastatin), pentoxifylline, etanercept, infliximab (monoclonal antibody against tumor necrosis factor-α), plasma exchange, abciximab (platelet glycoprotein IIb/IIIa receptor inhibitor), and immunosuppressive agents such as cyclosporine A have been used, but data are limited on their success.
- Acute coronary thrombosis should be managed with thrombolytic agents under cardiology supervision.
- Most patients with moderate to large aneurysms should be maintained on a second antiplatelet agent.
- Patients with giant coronary artery aneurysms (diameter >8 mm) are maintained on aspirin and warfarin to prevent thrombosis within the aneurysm and myocardial infarction.

CHRONIC Rx

Interventional and surgical procedures can be tried in children who have developed cardiac complications of KD:

- Percutaneous transluminal coronary angioplasty with or without stenting may be performed, but the data are limited.
- Coronary bypass graft surgery using the internal mammary artery or the gastroepiploic artery has met with greater patency success than saphenous vein grafts and is done in those with severe obstructive lesions such as involving the left main coronary artery or multivessel disease.
- Cardiac transplantation is an option and is indicated in patients with:
  1. Severe left ventricular failure.
  2. Malignant arrhythmias.
  3. Multivessel coronary artery disease.
- For patients with persistent giant (≥8 mm) aneurysms, anticoagulation with warfarin for a goal international normalized ratio of 2.0 to 2.5 should be considered.

DISPOSITION

- Mortality rate of children with KD is 0.5% to 2.8%, usually from coronary aneurysm thrombosis and myocardial infarction.
- Death usually occurs in the third to fourth week of the illness.
- Before the use of IVIG, ~25% of all patients with KD developed coronary artery aneurysms; this has fallen to 3%-5% with the use of IVIG.
- ~>50% of coronary artery aneurysms return to normal lumen diameter by 1 to 2 yr after onset of illness.
- Treatment with IVIG has reduced the incidence of coronary aneurysms by 80%.
- Aspirin in high dose decreases the coronary artery involvement to <5% from 25%.
- IVIG has also been shown to improve left ventricular function during the acute stages of the disease.
- Risk factors for the development of coronary aneurysms or giant coronary aneurysms 8 mm or greater are:
  1. Fever lasting >10 days.
  2. Age <1 yr or >6 yr.
  3. Male.
  4. Recurrence of fever.
- Recurrence is in about 1% to 3% of cases most commonly within 1 yr of the initial occurrence.
- Aspirin should be discontinued upon exposure to varicella or influenza to decrease the risk of developing Reye's syndrome.

REFERRAL

Multiple specialists may be consulted to assist in the diagnosis of KD, including dermatology, rheumatology, and infectious disease. Cardiology consultation is recommended in any patient with cardiac involvement and in the long-term follow-up of patients with KD.

PEARLS & CONSIDERATIONS

COMMENTS

- The mechanism of action of IVIG therapy for KD remains unknown.
- Failure of corticosteroids suggests that the inflammatory response is different compared with other vasculitic conditions.
- Increased risk of atherosclerotic heart disease in adulthood is unclear in patients with history of KD during childhood with normal echocardiographic findings.
- Live vaccine (varicella, measles) administration is suggested to be postponed for 11 mo in children treated with IVIG, since it interferes with vaccine immunogenicity.

PREVENTION

- Without a known etiologic agent for KD, primary prevention is not possible.
- Thrombosis leading to myocardial infarction in a stenotic or aneurysmal coronary artery is the leading cause of death in these children and occurs most often in the first year after illness onset. Therefore serial imaging and occasionally stress testing are necessary in patients with significant coronary artery abnormalities (by echocardiography where possible, occasionally by CT coronary angiography or invasive angiography if other imaging is inadequate).

SUGGESTED READINGS

Available at www.expertconsult.com.

RELATED CONTENT

Kawasaki Disease (Patient Information)

AUTHOR: **JONATHAN GINNS, M.D.**

SUGGESTED READINGS

Ayusawa M et al.: Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition), *Pediatr Int* 47:232, 2005.

Burns J.C, et al. Summary of the 8th International Kawasaki Disease Symposium: Presentation of Selected Abstracts. Available at: http://americanheart.org/downloadable/heart/11623189833988th%20IKDS%20summary%20revision.pdf. Accessed September 28, 2009.

Freeman A, Shulman S: Kawasaki disease: summary of the American Heart Association guidelines, *Am Fam Physician* 74:1141, 2006.

Iwashima S et al.: Ulinastatin therapy in Kawasaki disease, *Clin Drug Invest* 27(10):691–696, 2007.

Manlhiot C, Yeung RS, Chahal N, McCrindle BW: Intravenous immunoglobulin preparation type: association with outcomes for patients with acute Kawasaki disease, *Pediatr Allergy Immunol* 21(515), 2010.

Newburger JW et al.: Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis and Kawasaki Disease. Council on Cardiovascular Disease in the Young. American Heart Association, *Circulation* 110:2747–2771, 2004.

Rowley AH, Shulman ST: *Pathogenesis and management of Kawasaki disease Exp Rev AntiInfect Ther* 8(2):197–203, 2010.

Wood LE: Kawsaki disease in children, *Heart* 95:787–792, 2009.

Yellen ES et al.: Performance of 2004 American Heart Association recommendations for treatment of Kawasaki disease, *Pediatrics* 125:e234, 2010.

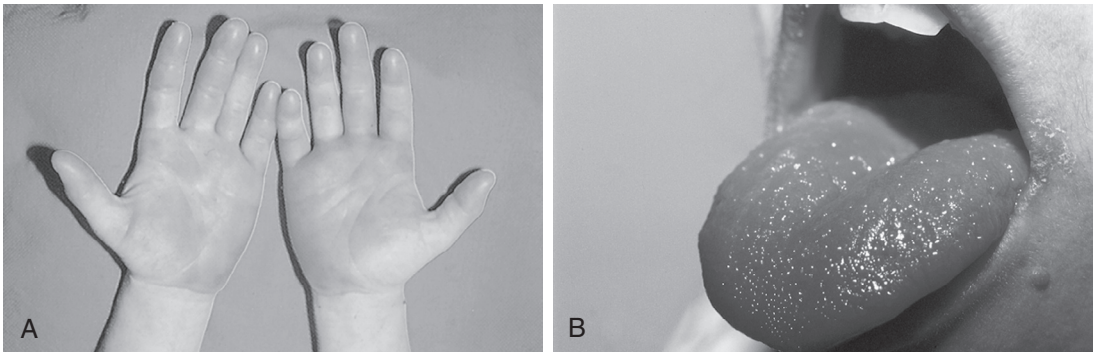


FIGURE EK1-4 A, Erythema of the hands, to be followed by desquamation. **B,** Strawberry tongue in a patient with Kawasaki disease. (**A** courtesy Department of Dermatology, University of North Carolina at Chapel Hill. In Goldstein B [ed]: *Practical dermatology,* ed 2, St Louis, 1997, Mosby. **B** courtesy Marshall Guill, M.D. In Goldstein B [ed]: *Practical dermatology,* ed 2, St Louis, 1997, Mosby.)

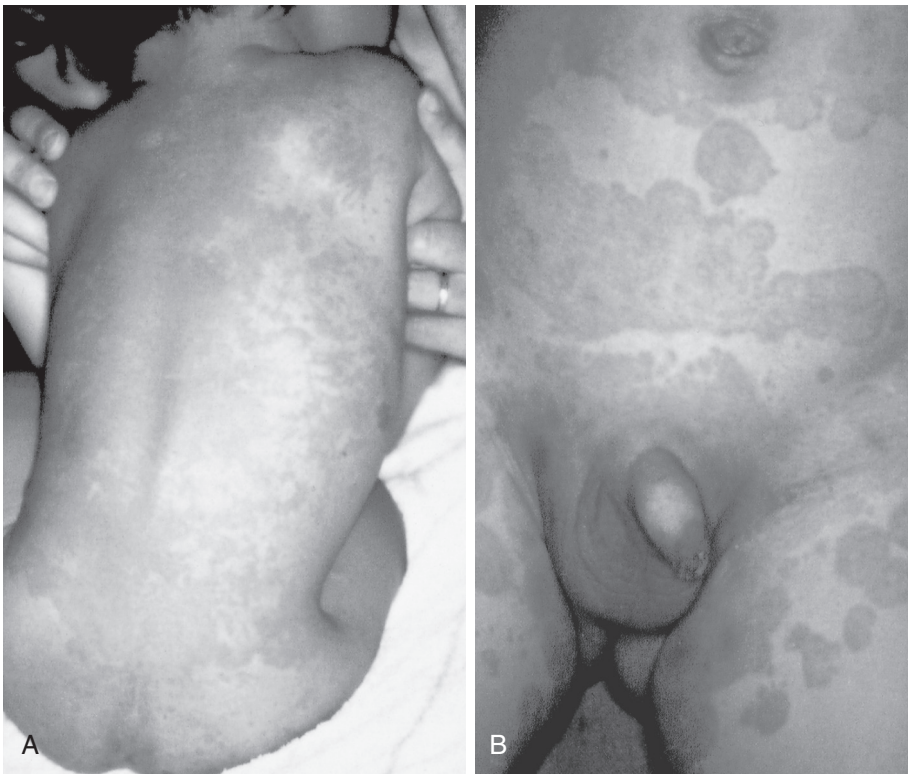


FIGURE EK1-5 Clinical manifestations of Kawasaki disease. **A** and **B,** Polymorphous exanthema.

BASIC INFORMATION

DESCRIPTION

Keloid may be defined as a benign growth of dense fibrous tissue developing from an abnormal healing response to cutaneous injury, extending beyond the original borders of the wound or inflammatory response (Fig. K1-6).

In 1806, Alibert used the term *cheloide,* derived from the Greek *chele,* or crab's claw, to describe lateral growth of tissue into unaffected skin.

ICD-9CM CODES
701.4 Keloid scar
ICD-10CM CODES
L91.0 Hypertrophic scar

EPIDEMIOLOGY

- Keloid is seen 5 to 15 times more often in pigmented ethnic groups than in whites.
- Its prevalence is 16% in blacks and Hispanics.
- The highest incidence is seen in the second decade.
- It affects both sexes equally.
- Combined incidence of keloid and hypertrophic scar ranges from 40% to 70% following surgery to up to 91% following burns.

ETIOLOGY

- Wounds from trauma, surgery, or body piercing (Fig. K1-7).
- Burn.
- Other injuries such as insect bites, vaccination, folliculitis, or acne.
- Rarely can be spontaneous without obvious injury.
- Familial predisposition seen in some patients.

RISK FACTORS

- Family history of keloids.
- Personal history of keloids.
- Blacks, Hispanics, and Asians.
- Pregnancy.
- Puberty.
- Patients with blood group A.
- Injury over bones.

FIGURE K1-6 Keloids. An abnormal reparative reaction to skin injury, keloids are characterized by proliferation of fibroblasts and collagen that extends beyond the margins of the original wound. (From Zitelli BJ, Davis HW: *Atlas of pediatric physical diagnosis,* ed 5, Philadelphia, 2007, Mosby.)

PATHOGENESIS

- Pathophysiology of keloid is not completely understood.
- Caused by benign dermal fibroproliferation because of disorder in the regulation of cellularity during the wound healing process.

CLINICAL FEATURES

- Keloids usually appear within a few months of the injury, in contrast to the hypertrophic scars, which develop within a few weeks. At times it could take up to a year to appear because the growth is slow.
- Keloids are often symptomatic in the early stages. Common complaints are pruritus, burning, pain, and tenderness.
- Keloids are commonly seen on the shoulders, sternum, upper back, nape of neck, ear lobes, mandibular border, and cheek. Hands and feet are often spared.
- Skin lesions vary from papules to nodules to large tuberous lesions. They have the normal skin color most of the time with well-defined borders. Early on they can appear erythematous, whereas older lesions may be hypopigmented or hyperpigmented. They can be firm to hard in consistency with smooth surface and are tender to touch. Hair follicles are absent in these keloids.
- Unlike with hypertrophic scar, in keloids the scar extends beyond the margin of the initial wound.

DIAGNOSIS

Workup is usually not necessary because it is a clinical diagnosis.

- Biopsy is usually avoided because it may increase the keloid size. When biopsy is done, the histology shows randomly organized large collagen fibers in a dense connective tissue matrix. In fact, both major components of extracellular matrix, collagen and glycosaminoglycans, are increased.

DIFFERENTIAL DIAGNOSIS

- Hypertrophic scar.
- Dermatofibroma.
- Dermatofibrosarcoma protuberance.
- Desmoid tumor.
- Foreign body granuloma.
- Scar with sarcoidosis.
- Lobomycosis.

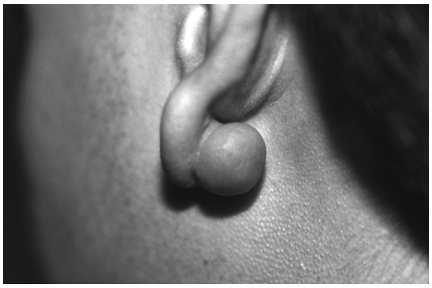


FIGURE K1-7 Keloid of ear lobe after piercing. (From Kliegman RM et al. *Nelson textbook of pediatrics,* Philadelphia, 2011, Saunders.)

TREATMENT

- There is no universally accepted treatment protocol. Prevention is the best strategy.
- Combination treatment is most effective.
- Surgical excision using cold knife followed by intralesional steroids is the preferred method.
- Treatment outcome is the best when it is initiated shortly after the keloid formation.
- Different treatment options include:
  1. Unlike with hypertrophic scars, surgery alone is associated with a 55% to 100% recurrence rate in patients with keloids. Results are significantly better when it is followed by intralesional steroids, radiotherapy, pressure therapy, or silicone application. Both complete and near total excision has been advocated. Few recommend core extirpation. Use of Z-plasties or any wound lengthening techniques is strongly discouraged.
  2. Intralesional steroid every 2 to 4 wk is administered either alone or following surgery. Duration of treatment depends on the treatment response. Triamcinolone is the most studied steroid and is used at a concentration of 10 to 40 mg/ml. Higher concentration is used for denser, more recalcitrant lesions, and those located in trunks or extremities. It could be used in combination with lidocaine to reduce the discomfort. A 27- to 30-gauge needle is used for its administration. To distribute the suspension evenly, it should be injected while continuously advancing the needle. No more than 20 to 30 mg of the drug is used during each treatment. Liquid nitrogen is applied to the injection briefly for 2 to 4 seconds about 10 to 15 min before steroid injection for better dispersal of the steroid and to minimize deposition into surrounding normal tissue. Hypopigmentation, skin atrophy, ulceration, and telangiectasia are the side effects associated with this treatment.
  3. Cryotherapy has been used for smaller lesions. When this treatment is chosen, the entire lesion is treated with 2 to 3 freeze-thaw cycles of 30 second duration each. Most lesions need 2 to 10 treatment sessions at 4-wk intervals. Pain and hypopigmentation are the main adverse events.
  4. Silicone gel sheeting or cushioning can prevent keloids from recurring after surgery. These are applied as soon as reepithelialization is achieved and are worn for at least 12 hr/day for 2 to 4 mo.
  5. Application of pressure by compression devices has been advocated in the treatment of keloids. These compression treatments include button compression, pressure earrings, pressure gradient

garments, ACE bandages, elastic adhesive bandages, compression wraps, Spandex or Elastane bandages, and support bandages. About 24 to 40 mm Hg pressure must be maintained. It must be instituted for long periods (>23 hr/day for 6 to 12 mo) before significant effect can be achieved. Unfortunately, many parts of the body are not amenable to this pressure. Patient discomfort frequently reduces compliance.

6. Radiation following surgery can also reduce the recurrence rate. X-rays of 700 to 1500 cGy in fractions over 5 to 6 treatments are the most frequently used treatment. Radiation is usually initiated within 10 days, preferably within 24 hr of surgery. It is avoided in pediatric and pregnant patients. At times brachytherapy with interstitial iridium 192 is used. Most physicians use radiation only for keloids over the extremities. The reported risk of radiation-induced malignancy is theoretical.
7. **5-**Fluorouracil can be used as an individual agent, following surgery, or in combination with intralesional steroids. Weekly injection of 0.5 to 2 ml at a 50 mg/ml concentration of 5-fluorouracil for 12 wk is the recommended dose.
8. Superiority of laser use to simple excision currently has not been demonstrated.
9. Topical 5% imiquimod cream has some role when used following surgery locally every night for a minimum of 2 mo.
10. Other treatments include Cordran tape, bleomycin, interferon, vitamin A, nitrogen mustard, antihistamines, zinc, tacrolimus, sirolimus, allantoin, botulinum toxin, colchicine, salicylic acid, calcipotriol, NSAIDs, d-penicillamine, relaxin, quercetin, dinoprostone, doxorubicin, ACE inhibitors, hyaluronidase, pentoxifylline, tranilast, mitomycin-C, tamoxifen, silver sulfadiazine, onion extract, vitamin E, intralesional verapamil.

FOLLOW-UP

Because of the high risk of recurrence, a follow-up of at least 12 mo is necessary to fully evaluate the effectiveness of therapy.

PREVENTION

- Avoid nonessential surgery such as body piercing, which carries a high risk for keloid formation.
- LASIK eye surgery and CO_2 laser resurfacing should be avoided in patients with a tendency for keloids.
- Use a laparoscopic approach when surgery is needed.
- Avoid making incisions over joint spaces or over midchest, and ensure that they follow skin creases.
- Handle tissue gently during surgery.
- Ensure good hemostasis intraoperatively.
- Use tension-free primary wound closure.
- Use monofilament, synthetic permanent sutures.
- Use adhesives instead of sutures when possible for closure of wounds.
- Compressive pressure dressing is preferred in high-risk patients following surgery.
- Avoid wound infection.
- Avoid tattoos.
- Aggressively treat inflammatory acnes.

COMPLICATIONS

- Psychological effects secondary to disfigurement.
- Contracture from keloids may result in loss of function if overlying a joint.

PROGNOSIS

- Unlike hypertrophic scars, keloids do not regress with time. However, they may continue to expand in size for decades.
- Regardless of the type of treatment there is a high recurrence rate.
- Keloids never become malignant.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Keloids (Patient Information)

AUTHOR: **HEMANT K. SAPATHY, M.D.**

SUGGESTED READINGS

Al-Attar A et al.: Keloid pathogenesis and treatment, *Plast Reconstr Surg* 117(1):286–300, 2006.

Atiyeh BS et al.: Keloids or hypertrophic scar: the controversy: review of the literature, *Ann Plast Surg* 54(6):676–680, 2005.

Leventhal D et al.: Treatment of keloids and hypertrophic scars: a meta-analysis and review of literature, *Arch Facial Plast* 8(6):362–368, 2006.

Robles DT et al.: Keloids: pathophysiology and management, *Dermatol Online J* 13(3):9, 2007.

Slemp AE et al.: Keloids and scars: a review of keloids and scars, their pathogenesis, risk factors, and management, *Curr Opin Pediatr* 18(4):396–402, 2006.

BASIC INFORMATION

DEFINITION

Klinefelter's syndrome is a congenital disorder in which a 47,XXY chromosome complement is associated with hypogonadism and infertility.

SYNONYMS

47,XXY Hypogonadism

ICD-9CM CODES
758.7 Klinefelter's syndrome
ICD-10CM CODES
Q98.4 Klinefelter syndrome, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: One in 500 men (most common sex chromosome disorder).
GENETICS: The most common mosaic complement is 46,XY/47,XXY. 47,XXY karyotype 48,XXYY, 48,XXXY, or 49,XXXXY have been reported. The manifestations vary in severity by patient (Table EK1-1). This sex chromosome mosaicism is believed to account for the variable presentation. Fertility, although very rare, has been reported in men with Klinefelter's syndrome.

TABLE EK1-1 Clinical Features of Klinefelter's Syndrome

Karyotype	47,XXY
Inheritance	Sporadic; associated with advanced maternal age; nondisjunction during first or second meiotic division in either parent (67% maternal, 33% paternal); mitotic nondisjunction.
Genitalia	Male.
Wolffian duct derivatives	Normal.
Müllerian duct derivatives	Absent.
Gonads	Small, firm testes; seminiferous tubule dysgenesis; azoospermia; Leydig cell hyperplasia.
Habitus	Poor to normal virilization at puberty: gynecomastia; disproportionately long legs.
Hormone profile	Testosterone levels variable but usually decreased; increased levels of plasma LH and FSH postpubertally.

FSH, Follicle-stimulating hormone; *LH,* luteinizing hormone.
From Larsen PR et al: *Williams textbook of endocrinology,* ed 10, Philadelphia, 2003, Saunders.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Classic triad: small firm testes, azoospermia, and gynecomastia.
- Prepubertal: small testes; gonadal volume <1.5 ml is a result of loss of germ cells before puberty.
- Postpubertal: gynecomastia (periductal fat growth) with small, firm testes. Exaggerated growth of the lower extremities results in a decreased crown-to-pubis/pubis-to-floor ratio. There are diminished strength, diminished ability to grow a full beard or mustache, and infertility. Decreased intellectual development and antisocial behavior are believed to occur with high frequency.

ETIOLOGY

- Several postulated mechanisms: nondisjunction during meiosis and mitosis and anaphase lag during mitosis or meiosis.
- Reason: maternal age
  1. The incidence of Klinefelter's syndrome rises from 0.6% when the maternal age is ≤35 yr to 5.4% when the maternal age is >45 yr.
  2. Of note, the extra X chromosome has a paternal origin as often as a maternal origin.

DIAGNOSIS

- Markedly elevated follicle-stimulating hormone levels.
- Total plasma testosterone levels are decreased in 50% to 60% of patients.
- Free testosterone levels are decreased.
- Plasma estradiol is increased, stimulating the increase in levels of testosterone-binding globulin with resultant decrease in the testosterone/estradiol ratio, which is believed to be the cause of gynecomastia.

LABORATORY TESTS

- Normal to low serum testosterone.
- Increased sex hormone–binding globulin (acts to further suppress any available free testosterone).
- Normal to increased estradiol (a result of augmented peripheral conversion of testosterone to estradiol).
- Testis biopsy shows azoospermia, Leydig cell hyperplasia, hyalinization, and fibrosis of the seminiferous tubules. Mosaics may have focal areas of spermatogenesis and, on rare occasions, a sperm may appear in the ejaculate. The extra X chromosome is the pivotal factor controlling spermatogenesis and also affects neuronal function directly, leading to the behavioral abnormalities related to decreased IQ.
- Buccal smear: one sex chromatin body.
- Prepubertal male: Gonadotropin levels are normal.
- Postpubertal male: Gonadotropin levels are elevated even when the testosterone level is normal.
- Disease associations:
  1. Malignancies: breast cancer (20 times >XY men and 20% the rate of occurrence in women), nonlymphocytic leukemia, lymphomas, marrow dysplastic syndromes, extragonadal germ cell neoplasms
  2. Autoimmune disorders: chronic lymphocytic thyroiditis, Takayasu arteritis, taurodontism (enlarged molar teeth), mitral valve prolapse, varicose veins, asthma, bronchitis, osteoporosis, abnormal glucose tolerance testing, diabetes, varicose veins

TREATMENT

- Revolves around three facets of Klinefelter's syndrome:
  1. Hypogonadism: androgen replacement in the form of testosterone.
  2. Gynecomastia: cosmetic surgery.
  3. Psychosocial problems: androgen therapy and educational support.
- After extensive genetic counseling, intracytoplasmic sperm insertion has been used to treat infertility with limited success in mosaic men.

PEARLS & CONSIDERATIONS

COMMENTS

- Androgen therapy should not be used in the case of severe mental retardation.
- Rule out breast and prostate cancer before initiating or continuing androgen therapy.
- Androgen therapy will not improve fertility; it may suppress any spermatogenesis that is taking place within the testes.
- Other causes of primary hypogonadism:
  1. Myotonic muscular dystrophy.
  2. Sertoli cell–only syndrome.
  3. Kartagener's syndrome.
  4. Anorchia.
  5. Acquired hypogonadism.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Klinefelter's Syndrome (Patient Information)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Manning MA, Hoyme HE: Diagnosis and management of the adolescent boy with Klinefelter syndrome, *Adolesc Med State Art Rev* 13(2):367, 2002.
Wattendorg D, Muenke M: Klinefelter syndrome, *Am Fam Physician* 72:2259, 2005.

BASIC INFORMATION

DEFINITION

Korsakoff's psychosis (KP) is a disorder of learning and memory that results from thiamine deficiency. It is classically seen with chronic alcohol abuse and may follow the presentation of Wernicke's encephalopathy (see "Wernicke Syndrome").

SYNONYMS

Korsakoff's syndrome
Wernicke-Korsakoff syndrome
Alcoholic polyneuritic psychosis

ICD-9CM CODES
291.1 Alcohol amnestic syndrome
ICD-10CM CODES
F10.96 Alcohol use, unspecified with alcohol-induced persisting amnestic disorder

EPIDEMIOLOGY & DEMOGRAPHICS

- The incidence of KP is declining as a result of improved patient nutrition and awareness by health professionals.
- More common in males.
- Age of onset evenly distributed between ages 30 and 70.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Impaired retrograde and anterograde memory.
- Remote memory is relatively less impaired on neuropsychiatric testing.
- Confabulation (the fabrication of false memories to fill memory gaps) is common.

ETIOLOGY

KP is the result of thiamine deficiency. Thiamine deficiency is commonly seen in chronic alcoholism and other malnourished populations (anorexia, bariatric surgery, malignancy). It may also occur from prolonged infusion of dextrose-containing fluids without thiamine repletion.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Stroke, trauma, or tumor affecting the temporal lobes or hippocampi
- Cerebral anoxia
- Transient global amnesia
- Dementia of multiple causes

WORKUP

A high index of suspicion should be maintained in chronic alcoholism and malnourished states.

LABORATORY TESTS

- CBC
- Serum chemistries
- Erythrocyte thiamine transketolase concentration before and after replacement with thiamine pyrophosphate

IMAGING STUDIES

MRI brain may show nonspecific T_2 hyperintensities in the diencephalon and mesencephalon but is not pathognomonic. However, MRI/CT may be helpful in ruling out other diagnoses.

TREATMENT

NONPHARMACOLOGIC THERAPY

A supervised environment may be required.

ACUTE GENERAL Rx

- Thiamine 100 mg IV or IM should be given immediately. Avoid oral dosing in acute treatment as malabsorption is prominent.
- Thiamine given acutely in Wernicke's encephalopathy (a disorder of extraocular movements, confusion, and ataxia) may prevent the development of KP.

CHRONIC Rx

- Long-term thiamine replacement.
- Those who suffer from KP rarely recover; therefore one must consider the need for additional support and supervision within the home versus placement in a long-term care facility.

REFERRAL

- Neurology to confirm the diagnosis and rule out other causes.
- Neuropsychiatric testing to assess baseline functioning and further deterioration.

PEARLS & CONSIDERATIONS

COMMENTS

- KP is frequently mis/underdiagnosed.
- Memory problems may persist even in "recovered" patients.
- Replace thiamine in patients at risk, even if clinical symptoms are not evident.
- Prolonged use of dextrose-containing IV fluids without supplemental thiamine may precipitate KP.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Alcoholism (Related Key Topic)
Delirium (Related Key Topic)
Vitamin Deficiency (Related Key Topic)
Wernicke Syndrome (Related Key Topic)

AUTHOR: **ALEXANDRA BOSKE, M.D.**

SUGGESTED READINGS

Cook CC: Prevention and treatment of Wernicke-Korsakoff syndrome, *Alcohol Suppl* 35(suppl):19, 2000.

Martin PR et al.: The role of thiamine deficiency in alcoholic brain disease, *Alcohol Res Health* 27(2):134–142, 2003.

Zubaran C et al.: Wernicke-Korsakoff syndrome, *Postgrad Med J* 78(855):27, 1997.

BASIC INFORMATION

DEFINITION

Labyrinthitis is a peripheral vestibulopathy characterized by acute onset of vertigo usually associated with nausea and vomiting. It may be associated with hearing loss. It may be either serous or purulent.

SYNONYMS

Acute labyrinthitis
Acute vestibular neuronopathy
Vestibular neuronitis
Viral neurolabyrinthitis

ICD-9CM CODES
386.12 Vestibular neuronitis (active and recurrent)
386.3 Labyrinthitis
ICD-10CM CODES
H81.23 Vestibular neuronitis, bilateral
H83.09 Labyrinthitis, unspecified ear

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Most common cause of prolonged spontaneous vertigo associated with nausea at any age
PREDOMINANT AGE: Any

CLINICAL PRESENTATION

- Vertigo, nausea, and vomiting with onset over several hours.
- Symptoms usually peak within 24 hr, then resolve gradually over several weeks.
- During the first day, the patient usually has difficulty focusing the eyes because of spontaneous nystagmus.
- Usually has benign course, with complete recovery within 1 to 3 mo, although older patients may have intractable dizziness that persists for many months.

PHYSICAL FINDINGS

- Nystagmus
- Nausea
- Vomiting
- Vertigo worsening with head movement
- Abnormal caloric ENG tests
- May have hearing loss in the affected ear
- Normal otoscopic exam typically
- Normal neurologic exam; may have signs of vestibular loss, such as a positive head thrust test

ETIOLOGY

Symptoms often preceded for 1 to 2 wk by a viral-like illness. It may be either bacterial or viral, and be either tympanogenic (i.e., resulting from spread of infection into the inner ear from the middle ear, antrum, or petrous apex), meningogenic, or hematogenic from encephalitis or brain abscess. The round window membrane is considered the most likely pathway of inflammatory mediators from the middle to the inner ear that subsequently give rise to labyrinthitis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute labyrinthine ischemia (vascular insufficiency)
- Other forms of labyrinthitis (bacterial and syphilitic)
- Labyrinthine fistula
- Benign positional vertigo
- Meniere's syndrome
- Cholesteatoma
- Drug induced
- Eighth nerve tumor
- Head trauma
- Vertebrobasilar stroke

WORKUP

- Otoscopic examination
- Neurologic examination, with close attention to cranial nerves
- Bedside test of vestibular function, that is, head thrust or head heave test
- Audiogram if symptoms accompanied by hearing loss
- Caloric test if presentation is atypical

LABORATORY TESTS

- Routine laboratory tests are generally not helpful.
- If there is a history of significant emesis, check electrolytes, BUN, and creatinine.

IMAGING STUDIES

- Imaging studies are usually not necessary.
- Contrasted MRI may show enhancement of bony labyrinth. MRI of the brain with and without contrast with fine cuts through the internal auditory canal is indicated if there is an abnormal cranial nerve exam or suspicion of eighth nerve tumor.
- Head CT with fine cuts through temporal bones is indicated if there is a history of trauma or suspicion of cholesteatoma.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Reassurance.
- Initial bed rest, then encourage increase in activity as tolerated.

ACUTE GENERAL Rx

- Phenergan or other antiemetics are typically effective.
- Vestibular suppressant: meclizine 12.5 to 25 mg qid is often used. Scopolamine patch is also effective.
- Methylprednisolone 100 mg per day for 3 days, with slow taper over 3 wk.
- Valacyclovir has not been shown to be helpful.

CHRONIC Rx

No specific chronic therapy

DISPOSITION

Usually does not require hospital admission unless the patient is unable to tolerate oral intake of liquids.

REFERRAL

- Refer if symptoms persist or neurologic abnormalities are present.
- Consider vestibular rehabilitation, particularly in the elderly.

PEARLS & CONSIDERATIONS

COMMENTS

Labyrinthitis is a term that usually implies peripheral vestibulopathy associated with hearing loss. The term *vestibular neuronitis* is typically used when hearing is not affected. Despite this technical distinction, many physicians use these terms interchangeably.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Labyrinthitis (Patient Information)

AUTHOR: **SHARON S. HARTMAN POLENSEK, M.D., PH.D.**

SUGGESTED READINGS

Baloh RW et al.: Neurotology, Continuum, *Lifelong Learning in Neurology* 2(2):37–53, 1996.

Cureoglu S et al.: Round window membrane and labyrinthine pathological changes: an overview, *Acta Otolaryngol* 125(1):9–15, 2005.

Nuti D et al.: Acute vestibular neuritis: prognosis based upon bedside clinical tests (thrusts and heaves), *Ann N Y Acad Sci* 1039:359–367, 2005.

Strupp M et al.: Methylprednisolone, valacyclovir, or the combination for vestibular neuritis, *N Engl J Med* 351(4):322–323, 2004.

Lactose Intolerance PTG

BASIC INFORMATION

DEFINITION

Lactose intolerance is the insufficient concentration of lactase enzyme, leading to fermentation of malabsorbed lactose by intestinal bacteria with subsequent production of intestinal gas and various organic acids, manifesting clinically with diarrhea, abdominal pain, flatulence, or bloating after lactose intake. *Lactose malabsorption* occurs when a substantial amount of lactose is not absorbed in the intestine. *Lactase deficiency* is defined as brush-border lactase activity that is markedly reduced relative to the activity observed in infants.

SYNONYMS

Lactase deficiency
Milk intolerance

ICD-9CM CODES
271.3 Lactose intolerance
ICD-10CM CODES
E73.9 Lactose intolerance, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

Nearly 50 million people in the United States have partial or complete lactose intolerance. There are racial differences, with <25% of white adults being lactose intolerant but >85% of Asian Americans and >60% of African Americans having some form of lactose intolerance.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Abdominal tenderness and cramping, bloating, flatulence.
- Diarrhea.
- Symptoms are directly related to the osmotic pressure of substrate in the colon and occur approximately 2 hr after ingestion of lactose.
- Physical examination: may be entirely within normal limits.

ETIOLOGY

- Congenital lactase deficiency: common in premature infants; rare in term infants and generally inherited as a chromosomal recessive trait.
- Secondary lactose intolerance: usually a result of injury of the intestinal mucosa (Crohn's disease, viral gastroenteritis, AIDS enteropathy, cryptosporidiosis, Whipple's disease, sprue)
- Pancreatic insufficiency.
- Nontropical and tropical sprue.
- Cystic fibrosis.
- Diverticular disease.
- Bowel neoplasm.
- Laxative abuse.
- Celiac disease.
- Parasitic disease (e.g., giardiasis).
- Viral or bacterial infections.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Inflammatory bowel disease.
- Irritable bowel syndrome.

WORKUP

- The diagnosis can usually be made on the basis of the history and improvement with dietary manipulation.
- Diagnostic workup may include confirming the diagnosis with hydrogen breath test and excluding other conditions listed in the differential diagnosis that may also coexist with lactase deficiency.

LABORATORY TESTS

- Lactose breath hydrogen test: a rise in breath hydrogen >20 ppm within 90 min of ingestion of 50 g of lactose is positive for lactase deficiency. This test is positive in 90% of patients with lactose malabsorption. Common causes of false-negative results are recent use of oral antibiotics or recent high colonic enema.
- The lactose tolerance test is an older and less accurate testing modality (20% rate of false-positive and false-negative results). The patient is administered an oral dose of 1 to 1.5 g of lactose/kg body weight. Serial measurement of blood glucose level on an hourly basis for 3 hr is then performed. The test is considered positive if the patient develops intestinal symptoms and the blood glucose level rises <20 mg/dl above the fasting baseline level.
- Diarrhea associated with lactase deficiency is osmotic in nature with an osmotic gap and a pH <6.5.

IMAGING STUDIES

Imaging studies are generally not indicated. A small bowel series may be useful in patients with significant malabsorption.

TREATMENT

NONPHARMACOLOGIC THERAPY

Management consists of reducing lactose exposure by avoiding milk and milk-containing products or using milk in which the lactose has been prehydrolized with lactase. A lactose-free diet generally results in prompt resolution of symptoms. Lactose is primarily found in dairy products but may be present as an ingredient or component of common foods and beverages. Possible sources of lactose include breads, candies, cold cuts, dessert mixes, cream soups, bologna, commercial sauces and gravies, chocolate, drink mixes, salad dressings, and medications. Labels should be read carefully to identify sources of lactose.

ACUTE GENERAL Rx

- Addition of lactase enzyme supplement (Lactaid tablets, Dairy Ease) before the ingestion of milk products may prevent symptoms in some patients. However, it is not effective for all lactose-intolerant patients.
- Lactose-intolerant patients must ensure adequate calcium intake. Calcium supplementation is recommended to prevent osteoporosis.

CHRONIC Rx

Patient education regarding foods high in lactose, such as milk, cottage cheese, or ice cream, is recommended.

DISPOSITION

Clinical improvement with restriction or elimination of milk products.

REFERRAL

GI referral for endoscopic procedures if concomitant GI disorders are suspected.

PEARLS & CONSIDERATIONS

COMMENTS

- There is great variability in signs and symptoms in patients with lactose intolerance depending on the degree of lactase deficiency. Most individuals with presumed lactose malabsorption can tolerate 12 to 15 g of lactose or up to 12 oz of milk daily without symptoms.
- Nondairy synthetic drinks (e.g., Coffee-Mate) and use of rice milk are well tolerated.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Lactose Intolerance (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Shaukat A et al.: Systematic review: effective management strategies for lactose intolerance, *Ann Intern Med* 152:797–803, 2010.

Suchy FA et al.: NIH consensus development conference: lactose intolerance and health. http://consensus.nih.gov/2010/lactosestatement.htm. Accessed April 23, 2013.

Swagerty DL et al.: Lactose intolerance, *Am Fam Physician* 65(2002), 1845.

BASIC INFORMATION

DEFINITION

Lambert-Eaton myasthenic syndrome (LEMS) is a disorder of neuromuscular transmission caused by antibodies directed against presynaptic voltage-gated P/Q calcium channels on motor and autonomic nerve terminals. There are two forms: paraneoplastic (most common) and nonparaneoplastic (autoimmune).

SYNONYMS

Eaton-Lambert syndrome

ICD-9CM CODES
199.1 Malignant neoplasm without specification of site, other
ICD-10CM CODES
G73.1 Lambert-Eaton syndrome (C00-D48+)
G70.8 Other specified myoneural disorders

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Uncertain; estimated at five cases per 1 million persons annually (in U.S.)
PEAK INCIDENCE: Sixth decade
PREVALENCE: Uncertain; estimated at one per 100,000 (in U.S.). Up to 3% of small cell lung cancer (SCLC) patients are estimated to develop LEMS.
PREDOMINANT SEX: Male:female ratio of 2:1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Weakness with diminished or absent muscle stretch reflexes
- Proximal lower-extremity muscles affected most
- Ocular and bulbar muscles less commonly affected
- Transient strength improvement with brief exercise
- Reflexes may be facilitated by repeatedly tapping the tendon or after brief exercise
- Autonomic dysfunction common (dry mouth [75%], sexual dysfunction, blurred vision, constipation, orthostasis, etc.)

ETIOLOGY

- Antibodies directed against presynaptic voltage-gated P/Q calcium channels are present in most patients. The reduction in calcium influx causes a reduction in presynaptic acetylcholine release at motor and autonomic nerve terminals.
- Paraneoplastic forms, usually associated with SCLC, account for 50% to 70% of patients.
- Autoimmune forms, usually in patients with other autoimmune diseases, occur in 10% to 30% of patients.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Myasthenia gravis
- Polymyositis
- Primary myopathies
- Carcinomatous myopathies
- Polymyalgia rheumatica
- Botulism
- Guillain-Barré syndrome

WORKUP

Diagnosis is confirmed on basis of characteristic electrodiagnostic (EMG/NCS) findings: reduced motor amplitudes with normal sensory studies; >10% decrement in motor amplitudes on slow repetitive nerve stimulation (RNS) at 2 to 5 Hz, with >100% increment on fast RNS (20 to 50 Hz) or immediately after 10 sec of maximum exercise (postexercise facilitation).

LABORATORY TESTS

Check P/Q calcium channel antibody titers (commercially available).

IMAGING STUDIES

Screen for an underlying malignancy. Presentation with LEMS may precede diagnosis of SCLC by up to 5 yr; hence chest radiograph or CT of the chest may be required every 6 to 12 mo for SCLC.

TREATMENT

NONPHARMACOLOGIC THERAPY

Symptomatic treatment for autonomic dysfunction.

ACUTE GENERAL Rx

- Anticholinesterase agents (pyridostigmine 30 to 60 mg q4-6h) may yield some improvement.
- Guanidine hydrochloride: start 5 to 10 mg/kg/day up to 30 mg/kg/day in 3-day intervals.
- Plasma exchange (200 to 250 ml/kg over 10 to 14 days) or IV immunoglobulins (2 g/kg divided over 2 to 5 days) often produce significant, temporary improvement.
- Prednisone 1.0 to 1.5 mg/kg/day can be gradually tapered over months to minimal effective dose.
- Azathioprine can be given alone or in combination with prednisone. Give up to 2.5 mg/kg/day. If patient is intolerant, can administer cyclosporine up to 3 mg/kg/day instead.
- 3,4-Diaminopyridine (3,4-DAP) 10 to 20 mg PO qid (maximum of 100 mg/day) may improve muscle strength and reduce autonomic symptoms in up to 85% of patients in uncontrolled series. It is available in Europe and may be available in the U.S. on a compassionate use basis.

CHRONIC Rx

Treat underlying malignancy if present.

DISPOSITION

- Gradually progressive weakness leading to impaired mobility if untreated
- Clinical remission may occur with chronic immunosuppressive therapy in 43% of cases
- Possible substantial improvement with successful treatment of underlying malignancy

REFERRAL

1. Referral to a neurologist is highly recommended because this is a rare disease requiring highly specialized treatment in the context of weighing risk vs. benefit of the different therapeutic options.
2. Referral to specialist centers for 3,4-DAP therapy may be warranted in the U.S.
3. Surgical referral for tumor debulking in paraneoplastic forms necessary.

PEARLS & CONSIDERATIONS

COMMENTS

- Prominent autonomic symptoms (dry eyes, dry mouth, impotence, orthostasis) are often clues to the diagnosis in the appropriate clinical context.
- Many drugs may worsen weakness and should be used only if absolutely necessary. Included are succinylcholine, d-tubocurarine, quinine, quinidine, procainamide, aminoglycoside antibiotics, β-blockers, and calcium channel blockers.

PATIENT INFORMATION

Available through the website http://www.lems.com/resources.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **DIVYA SINGHAL, M.D.**

SUGGESTED READINGS

Dropcho EJ: Remote neurologic manifestations of cancer, *Neurol Clin* 20:85, 2002.

Mahadeva B et al.: Autoimmune disorders of neuromuscular transmission, *Semin Neurol* 28(2):212–227, 2008.

Sanders DB: The Lambert-Eaton myasthenic syndrome diagnosis and treatment, *Ann NY Acad Sci* 998:500, 2003.

Titulaer MJ et al.: Lambert-Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies, *Lancet Neurol* 10(12):1098–1107, 2011.

BASIC INFORMATION

DEFINITION

Laryngeal carcinoma is cancer of the larynx, including the vocal cords (glottis), supraglottis, and subglottis.

SYNONYMS

Laryngeal cancer
Head and neck cancer (subsite); other sites include oral cavity, pharynx, paranasal sinus, and salivary glands

ICD-9CM CODES
231.0 Carcinoma of larynx
ICD-10CM CODES
D02.0 Carcinoma in situ of larynx

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 12,000 new cases per year in the United States.
PEAK INCIDENCE: Sixth decade.
PREDOMINANT SEX: 80% male predominance (current, with past and projected increase in female rates as a result of changing smoking habits).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Glottis: Early diagnosis possible because of voice change (hoarseness). Any voice change of more than 2-wk duration should prompt a laryngeal examination.
- Supraglottis:
  1. No early symptom.
  2. Cervical lymphadenopathy.
  3. Neck pain or ear pain.
  4. Discomfort during swallowing.
  5. Odynophagia.
  6. Later: hoarseness, dysphagia, airway obstruction.
- Subglottis: Even more subtle than supraglottic lesion; the same signs occur, only later in the course.

ETIOLOGY

- Smoking (cigarette, cigar, or pipe).
- Alcohol intake/abuse.
- Diet and nutritional deficiencies.
- Gastroesophageal reflux.
- Voice abuse.
- Chronic laryngitis.
- Exposure to wood dust.
- Asbestosis.
- Exposure to radiation.
- Possible role of human papillomavirus.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Laryngitis.
- Allergic and nonallergic rhinosinusitis.
- Gastroesophageal reflux.
- Voice abuse leading to hoarseness.
- Laryngeal papilloma.
- Vocal cord paralysis attributable to a neurologic condition or entrapment of the recurrent laryngeal nerve caused by mediastinal compression.
- Tracheomalacia.

STAGING:
Supraglottic:
T_1: Tumor limited to one subsite with normal cord mobility.
T_2: Tumor invades mucosa of more than one subsite (e.g., base of tongue, vallecula, pyriform sinus) without fixation of larynx.
T_3: Tumor limited to larynx with vocal cord fixation or invasion of postcricoid area or pre-epiglottis.
T_4: Tumor invades thyroid cartilage or extends into soft tissue of the neck, thyroid, or esophagus.
Glottic:
T_1: Tumor limited to vocal cord with normal mobility.
T_{1a}: Tumor limited to one vocal cord.
T_{1b}: Tumor involves both vocal cords.
T_2: Tumor extends to supra- or subglottis or impairs cord mobility.
T_3: Tumor limited to larynx with cord fixation.
T_4: Tumor invades through cartilage or other tissues beyond larynx.
Stage grouping:
Stage I (one anatomic site within the larynx): T_1, N0, M0.
Stage II (one anatomic region within the larynx): T_2, N0, M0.
Stage III (extending beyond one anatomic region but confined to the larynx): T_3, N0, M0.
T_1, T_2, T_3, N1, M0.
Stage IV (distant metastasis): T_4, N0, N1, M0.
Any T, N2, N3, M0.
Any T, any N or M >0.

WORKUP

- Laboratory: none.
- Endoscopic laryngeal inspection.
- After (and only after) diagnosis of the malignancy, imaging with CT or MRI should be undertaken to stage the disease.

HISTOLOGIC CLASSIFICATION

Epithelial cancers:
- Squamous cell carcinoma in situ.
- Superficially invasive cancer.
- Verrucous carcinoma.
- Pseudosarcoma.
- Anaplastic cancer.
- Transitional cell carcinoma.
- Lymphoepithelial cancer.
- Adenocarcinoma.
- Neuroendocrine tumors, including small cell and carcinoid.

Sarcomas:
- Metastatic malignancies.

TREATMENT

ACUTE GENERAL Rx

- Early stage (T or T_2) has two options:
  1. Conservative surgery (partial laryngectomy) with neck dissection.
  2. Primary radiation.
- Intermediate stage has four options:
  1. Primary radiation alone.
  2. Supraglottic laryngectomy with neck dissection.
  3. Supraglottic laryngectomy with postoperative radiation.
  4. Chemotherapy with radiation.
- Advanced stage:
  1. Chemotherapy and radiation with total laryngectomy reserved for treatment failure.

Glottis:
- Carcinoma in situ.
  1. Microexcision.
  2. Laser vaporization.
  3. Radiation.
- Early stage (T or T_2) has two options:
  1. Voice conservation surgery.
  2. Radiation.
- Intermediate stage (T_3).
  1. Combined radiation and chemotherapy (cisplatin and 5-fluoruracil).
  2. Total laryngectomy for treatment failure.
- Advanced stage (T_4).
  1. Combined radiation and chemotherapy.
  2. Total laryngectomy and neck dissection followed by postoperative radiation in unfavorable lesion or treatment failure.

Subglottis:
- Total laryngectomy and approximate neck surgery to excise the tumor, followed by radiation.

Unresected cancers:
- Induction chemotherapy and radiation followed by neck dissection in chemosensitive tumors, or by laryngectomy and neck dissection in chemoresistant tumors.
- If hypopharyngeal involvement exists: laryngopharyngectomy, neck dissection, and postoperative radiation.

DISPOSITION

Supraglottis 5-yr control:
- T_1: 95% to 100%.
- T_2: 80% to 90%.
- T_3: 65% to 85%.
- T_4: 40% to 55%.

Glottis 5-yr control:
- T_1: 95% to 100%.
- T_2: 50% to 85%.
- T_3: 35% to 85%.
- T_4: 20% to 65%.

RELATED CONTENT

Laryngeal Cancer (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

BASIC INFORMATION

DEFINITION

Laryngitis is an acute or chronic inflammation of the laryngeal mucous membranes.

SYNONYMS

Lower respiratory tract infection

ICD-9CM CODES
464.0 Acute laryngitis
476.0 Chronic laryngitis
ICD-10CM CODES
J04.0 Acute laryngitis
J37.0 Chronic laryngitis

EPIDEMIOLOGY & DEMOGRAPHICS

It is a common illness worldwide in both genders and all age groups, but the diagnosis is imprecise and, therefore, statistics are not readily available with respect to incidence and prevalence.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

ACUTE LARYNGITIS

- Clinical syndrome characterized by the onset of hoarseness, voice breaks, or episodes of aphonia; may also have accompanying sore throat, cough, nasal congestion, and rhinorrhea.
- Usually associated with viral upper respiratory infection.
- Larynx with diffuse erythema, edema, and vascular engorgement of the vocal folds, and occasionally mucosal ulceration.
- In young children subglottis is often affected, resulting in airway narrowing with marked hoarseness, inspiratory stridor, dyspnea, and restlessness.
- Respiratory compromise rare in adults.

CHRONIC LARYNGITIS: Characterized by hoarseness or dysphonia persisting for longer than 2 wk.

ETIOLOGY

ACUTE LARYNGITIS

- Most often caused by viruses so treatment consists of supportive measures as outlined in "Nonpharmacologic Therapy" section.
- Studies evaluating the use of antibiotics (erythromycin, penicillin) in acute laryngitis failed to show objective clinical benefit over placebo so they are not routinely recommended. Antibiotics and other antimicrobials may be indicated in cases in which specific treatable pathogens are identified.
- Avoid decongestants because of their drying effect.
- Guaifenesin may be a useful adjunct as a mucolytic agent.
- In gastroesophageal reflux disease (GERD)-associated laryngitis use acid-suppressive therapy (H_2 blockers, proton pump inhibitors) and nocturnal antireflux precautions.

CHRONIC LARYNGITIS

- Results from any of the following: tuberculosis, usually through bronchogenic spread; leprosy, from nasopharyngeal or oropharyngeal spread; syphilis, in secondary and tertiary stages; rhinoscleroma, extending from the nose and nasopharynx; actinomycosis; cryptococcosis; histoplasmosis; blastomycosis; paracoccidiomycosis; coccidiosis; candidiasis; aspergillosis; sporotrichosis; rhinosporidiosis; parasitic infections including leishmaniasis and *Clinostomum* infection following raw fresh-water fish ingestion.
- Noninfectious causes of both acute and chronic laryngitis include malignancy, voice abuse (singers), GERD, and chemical or environmental irritants such as cigarettes and allergens. Other causes of inflammatory or granulomatous lesions of the larynx include relapsing polychondritis, Wegener's granulomatosis, and sarcoidosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Young children with signs of airway obstruction:
  1. Supraglottitis (epiglottitis).
  2. Laryngotracheobronchitis.
  3. Tracheitis.
  4. Foreign body aspiration.
- Adults with persistent hoarseness, consider noninfectious causes of laryngitis as listed previously.

WORKUP

- History and physical examination: diagnosis is usually apparent.
- Laryngoscopy for severe or persistent cases.
- Laryngeal cultures should be performed if a cause other than acute viral infection is suspected.
- Imaging not indicated unless there is evidence of airway compromise. Obtain plain radiographs of neck, anteroposterior and lateral views, to differentiate laryngitis from acute laryngotracheobronchitis or supraglottitis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Rest the voice.
- Use an air humidifier.
- Ensure adequate hydration. Avoid alcohol and caffeine because of diuretic effect.

ACUTE GENERAL Rx

- Antibiotics and other antimicrobials should generally not be used. They are indicated only when a specific pathogen is isolated; commonly employed antibacterial agents are macrolides; clarithromycin 500 mg by mouth bid for 5 to 7 days or azithromycin 500 mg followed by 250 mg once daily for 4 to 5 days if the cause of laryngitis is found to be *Mycoplasma pneumoniae* or *Chlamydophila pneumoniae* (the new name for what was formerly known as *Chlamydia pneumoniae*).
- Avoid decongestants because of their drying effect.
- Guaifenesin may be a useful adjunct as a mucolytic agent.
- In GERD-associated laryngitis use acid-suppressive therapy (H_2 blockers, proton pump inhibitors) and nocturnal antireflux precautions.

DISPOSITION

Uncomplicated laryngitis is usually benign, with gradual resolution of symptoms.

REFERRAL

- If symptoms persist for >2 wk, refer to otolaryngologist for laryngoscopy.
- Consider referral to gastroenterologist if GERD is suspected.

PEARLS & CONSIDERATIONS

- Most cases of uncomplicated acute laryngitis are viral in origin, and antibacterial agents should not be routinely administered.
- A recent Cochrane analysis in 2013 found no evidence for the use of empiric antibiotics in adults with laryngitis.
- The most difficult clinical challenge is often convincing patients with acute laryngitis that they do not need and will not benefit from antibacterial agents.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Laryngitis (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Dworkin JP: Laryngitis: types, causes, and treatments, *Otolaryngol Clin North Am* 41(2):419–436, 2008.

Ebell MH: Antibiotics for acute laryngitis in adults, *Am Fam Physician* 72:76, 2005.

Mehanna HM et al.: Fungal laryngitis in immunocompetent patients, *J Laryngol Otol* 118(5):379, 2004.

Reveiz L, Cardona AF: Antibiotics for acute laryngitis in adults, *Cochrane Database Syst Rev Mar* 28(3):CD004783, 2013.

Vaezi MF: Laryngeal manifestations of gastroesophageal reflux disease, *Curr Gastroenterol Rep* 10(3):271–277, 2008.

Laryngotracheobronchitis PTG

BASIC INFORMATION

DEFINITION

Acute laryngotracheobronchitis is a viral infection of the upper and lower respiratory tract leading to erythema and edema of the tracheal walls and narrowing of the subglottic region. Laryngotracheitis, which is limited to larynx and trachea, is also known as croup.

SYNONYMS

Croup

ICD-9CM CODES
464.4 Croup
ICD-10CM CODES
J05.0 Acute obstructive laryngitis [croup]

EPIDEMIOLOGY & DEMOGRAPHICS

- Croup is primarily a disease of children occurring between the ages of 1 and 6 yr.
- The peak incidence of croup is between 6 and 36 mo.
- Most cases occur in the fall and represent parainfluenza type 1 viral infection.
- Winter outbreaks usually represent infection by influenza A and B viruses.
- Croup accounts for 10% to 15% of lower respiratory tract infections in young children.
- Boys are affected more often than girls in a ratio of 1.4:1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Most children with croup present with symptoms of an upper respiratory infection for several days.

- Rhinorrhea.
- Cough.
- Low-grade fever.
- Barking cough that usually occurs at night and awakens the child.
- Sore throat.
- Stridor.
- Apprehension.
- Use of accessory muscles of respiration.
- Tachypnea.
- Tachycardia.
- Wheezing.

ETIOLOGY

- Parainfluenza viruses (types 1, 2, and 3) are the most common causes of croup in the United States.

Type 1 is the most common cause of fall and winter outbreaks, with type 2 causing milder disease outbreaks. Parainfluenza type 3, while sporadic, can be more severe than other types.

- Respiratory syncytial virus (RSV) and adenovirus are common causes of croup as well.
- Human coronavirus NL63, rhinoviruses, enteroviruses such as Coxsackie and echovirus.
- Influenza A and B, although not common causes of croup, do lead to more severe cases of the disease.
- *Mycoplasma pneumoniae* (rare).

DIAGNOSIS

The diagnosis of croup is usually based on the characteristic clinical presentation of a young child between the ages of 1 and 6 yr waking up with a barking cough ("seal's bark") and stridor.

DIFFERENTIAL DIAGNOSIS

- Spasmodic croup.
- Epiglottitis.
- Bacterial tracheitis.
- Angioneurotic edema.
- Diphtheria.
- Peritonsillar abscess.
- Retropharyngeal abscess.
- Smoke inhalation.
- Foreign body.

WORKUP

- The workup of a child with croup is to differentiate viral laryngotracheobronchitis from noninfectious causes of stridor, bacterial tracheitis, and epiglottitis caused by *H. influenzae* (Table L1-1).
- The clinical presentation and plain films of the soft tissues of the neck assist in differentiating viral from nonviral and noninfectious causes.

LABORATORY TESTS

- Laboratory tests are not often used to make the diagnosis of viral tracheobronchitis.
- CBC, viral serology, and tissue cultures can be ordered and may detect the infecting agent in up to 65% of cases.
- Pulse oximetry and ABG determination for patients with tachypnea and respiratory distress.

IMAGING STUDIES

- Plain (AP and lateral) films of the soft tissues of the neck (Fig. L1-1) may show the classic radiographic finding of subglottic stenosis or "steeple" sign.
- CT scan of the soft tissues of the neck may be performed in cases in which the differentiation between croup, epiglottitis, and noninfectious causes is more difficult.
- Direct visualization via laryngoscopy may be useful in some situations under a controlled setting.

TREATMENT

Treatment of croup focuses on airway management.

NONPHARMACOLOGIC THERAPY

- Humidified oxygen or humidified air.
- Cool mist.
- Hot steam.

ACUTE GENERAL Rx

- 0.25 to 0.75 ml of 2.25% racemic epinephrine every 20 min is used in children with severe respiratory symptoms, rest stridor, and impending intubation.
- Corticosteroids (e.g., dexamethasone 0.6 mg/kg IV or PO, prednisone 2 mg/kg/day) have been shown to be effective.
- Budesonide, a nebulized corticosteroid given at 4 mg, has been shown to improve symptoms in patients with moderate to severe croup.

DISPOSITION

- Croup is usually benign and self-limited, resolving within 3 to 4 days.
- Complications include:
  1. Airway obstruction.
  2. Otitis media.
  3. Pneumonia.
  4. Dehydration.

REFERRAL

If intubation is needed (rarely), an emergency consultation with ENT and/or anesthesiology is recommended.

PEARLS & CONSIDERATIONS

COMMENTS

- Most patients with croup can be managed at home (e.g., patients without stridor and in no respiratory distress).

TABLE L1-1 Characteristics of Laryngotracheobronchitis, Bacterial Tracheitis, and Epiglottitis

	Laryngotracheobronchitis	Bacterial Tracheitis	Epiglottitis
Age	3 mo to 3 yr	6 mo to 12 yr	12 yr (average)
Onset	Gradual	Intermediate	<24 hr
Fever	Usually low	Usually high	High
Cough	Characteristic "barking"	Characteristic "barking"	None
Sore throat	None	Usually absent	Often severe
Drooling	No	No	Usually
Posture	Any position	Any position	Sitting forward, mouth open, drooling
Voice	Normal	Normal or hoarse	Muffled
Appearance	Nontoxic	Toxic	Toxic
Seasonal distribution	Usually winter, epidemic	Throughout the year	Throughout the year

From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.

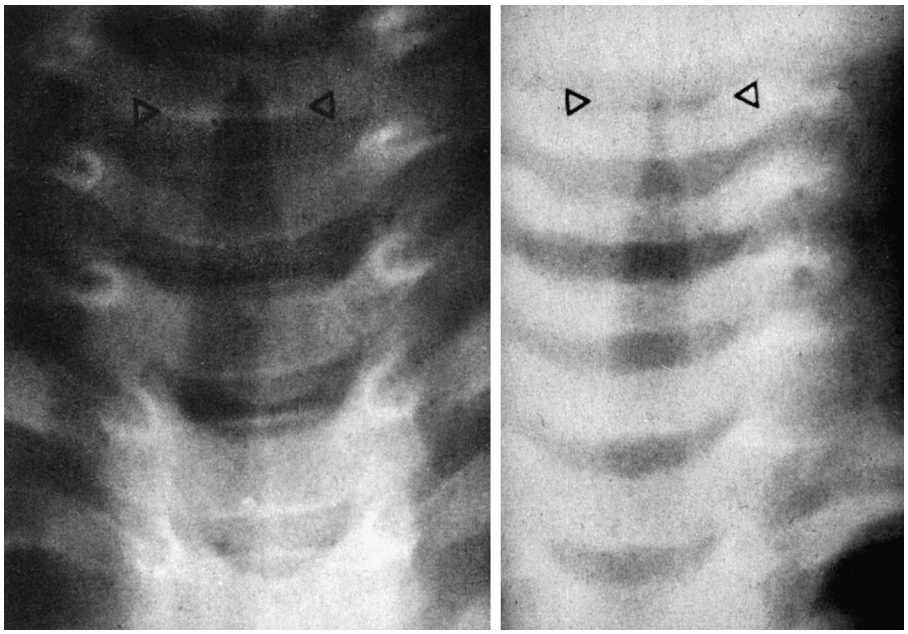


FIGURE L1-1 Laryngotracheobronchitis. Anteroposterior radiograph of the neck. *Left,* A normal tracheal air column (between the *arrows*). *Right,* Trachea narrowed by laryngotracheobronchitis. (From Fuhrman BP et al: *Pediatric critical care,* Philadelphia, ed 4, 2011, Saunders.)

- Hospitalization and observation are required for children with moderate to severe croup (e.g., rest stridor, respiratory distress refractory to the previously mentioned acute treatments). A family history of croup is a risk factor for croup and recurrent croup.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Croup (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Cherry JD: Croup, *N Engl J Med* 358:384, 2008.
Choi J, Lee GL: Common pediatric respiratory emergencies, *Emer Med Clin North Am* 30(2):529–563, 2012.
Zoorob R et al.: Croup: an overview, *Am Fam Physician* 83:1067–1073, 2011.

Lead Poisoning PTG

BASIC INFORMATION

DEFINITION

Lead is a potent, pervasive neurotoxicant. Lead poisoning refers to multisystem abnormalities resulting from excessive lead exposure.

SYNONYMS

Plumbism

ICD-9CM CODES
984.0 Lead poisoning
ICD-10CM CODES
T56.0X1A Toxic effect of lead and its compounds, accidental (unintentional), initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

- Lead poisoning is most common in children ages 1 to 5 yr (17,000 cases/100,000 persons). The highest rates are among blacks, those with low income, and urban children.
- In 1991 the Centers for Disease Control and Prevention (CDC) lowered the definition of a safe blood lead level to <10 mcg/dl of whole blood (a blood lead level of 25 mcg/dl was considered acceptable before 1991).
- It is estimated that >15% of preschoolers in the United States have a blood lead level >15 mcg/dl.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Findings vary with the degree of toxicity. Examination may be normal in patients with mild toxicity.
- Myalgias, irritability, headache, and general fatigue may be present initially.
- Abdominal cramping, constipation, weight loss, tremor, paresthesias and peripheral neuritis, seizures, and coma may occur with severe toxicity.
- Motor neuropathy is common in children with lead poisoning; learning disorders are also frequent.

ETIOLOGY

Chronic, repeated exposure to paint containing lead, plumbing, storage of batteries, pottery, or lead soldering. Concentration of lead is generally highest in lead-based paint on exterior surfaces. Among interior surfaces, windows are most likely to have the highest lead content.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Polyneuropathies from other sources.
- Anxiety disorder, attention deficit disorder.
- Malabsorption, acute abdomen.
- Iron-deficiency anemia.

WORKUP

Laboratory screening: all U.S. children should be considered to be at risk for lead poisoning and should be screened routinely starting at age 1 yr for low-risk children and age 6 mo for high-risk children.

LABORATORY TESTS

- Venous blood lead level: normal level, <5 mcg/dl; levels of 50 to 70 mcg/dl, indicative of moderate toxicity; levels >70 mcg/dl, associated with severe poisoning.
- Mild anemia with basophilic stippling on peripheral smear.
- Elevated zinc protoporphyrin levels or free erythrocyte protoporphyrin level.
- An increased body burden of lead with previous high-level exposure in patients with occupational lead poisoning can be demonstrated by measuring the excretion of lead in urine after premedication with calcium ethylenediamine tetraacetic acid (EDTA) or another chelating agent.

IMAGING STUDIES

- Imaging studies are generally not necessary.
- A plain abdominal film can visualize lead particles in the gut.
- "Lead lines" may be noted on x-ray films of long bones.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Provide adequate amounts of calcium, iron, zinc, and protein in patient's diet.
- Family education on sources of lead exposure and potential adverse health effects.

ACUTE GENERAL Rx

- For children with blood levels of 10 to 19 mcg/dl, the CDC recommends nonpharmacologic interventions (see "Nonpharmacologic Therapy").
- For children with blood levels between 20 and 44 mcg/dl, the CDC recommendations include case management by a qualified social worker, clinical management, environmental assessment, and lead hazard control. Chelation therapy should be considered in children with refractory blood lead levels.

Chelation therapy (Table EL1-2) is indicated in children with blood lead levels >45 mcg/dl:

- Succimer (DMSA) 10 mg/kg PO q8h for 5 days then q12h for 2 wk can be used in patients with levels between 45 and 70 mcg/dl.
- Edetate calcium disodium (EDTA) and dimercaprol (BAL) are effective in patients with severe toxicity.
- Use of both EDTA and DMSA is indicated in children with blood levels >70 mcg/dl.
- d-Penicillamine (Cuprimine) can also be used for lead poisoning, but it is not FDA approved for this condition.

CHRONIC Rx

- Reduce exposure, remove any potential lead sources.
- Correct iron deficiency and any other nutritional deficiencies.
- Recheck blood lead level 7 to 21 days after chelation therapy.

DISPOSITION

Patients with mild to moderate toxicity generally improve without any residual deficits. The presence of encephalopathy at diagnosis is a poor prognostic sign. Residual neurologic deficits may persist in these patients. Chelation therapy seems to slow the progression of renal insufficiency in patients with mildly elevated body lead burden.

REFERRAL

If exposure to lead is work related, it should be reported to the Office of the United States Occupational Safety and Health Administration (OSHA). Follow-up testing is mandatory in all patients after an abnormal screening blood lead level.

PEARLS & CONSIDERATIONS

COMMENTS

- Even blood lead concentrations as low as 5-10 mcg/dl are inversely associated with children's IQ scores at age 3 and 5 yr.
- Screening of household members of affected individuals is recommended.
- In children with blood lead levels of >45 mg/dl, treatment with succimer does not improve scores on tests of cognition, behavior, or neuropsychological function.
- Lead toxicity may delay growth and pubertal development in girls.
- Low-level environmental lead exposure may accelerate progressive renal insufficiency in patients without diabetes who have chronic renal disease. Repeated chelation therapy may improve renal function and slow the progression of renal failure.

SUGGESTED READINGS

Available at www.expertconsult.com.

RELATED CONTENT

Lead Poisoning (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Canfield RL et al.: Intellectual impairment in children with blood lead concentrations below 10 mcg/deciliter, *N Engl J Med 348* 1517, 2003.

Kemper AR et al.: Follow-up testing among children with elevated screening blood lead levels, *JAMA 293* 2232, 2005.

Lin JL et al.: Environmental lead exposure and progression of chronic renal diseases in patients without diabetes, *N Engl J Med 348* 277, 2003.

Selevan SG et al.: Blood lead concentration and delayed puberty in girls, *N Engl J Med 348* 1527, 2003.

TABLE EL1-2 Chelation Therapy

Chelation Agent	Indication	Comments
Dimercaprol (BAL)	BLL >70 mcg/dl Encephalopathy Severe symptoms	Contraindicated in hepatic disease and peanut allergy May cause hemolysis in G6PD deficiency May also cause renal dysfunction
Calcium disodium ethylene-diamine tetraacetic acid	BLL >70 mcg/dl	May cause renal dysfunction Use in conjunction with BAL for BLL >70 mcg/dl—must be given 4 hr after BAL Second-line agent for BLL 45-70 mcg/dl
Succimer	Preferred agent for patients with BLL >45 mcg/dl who are asymptomatic at presentation	May cause transient LFT abnormalities and reversible neutropenia

BLL, Blood lead level; *CBC*, complete blood count; *LFT*, liver function test.
Chelation therapy should be given only in consult with a toxicologist due to the potentially toxic effects.
From Flomenbaum M et al: *Toxicologic emergencies*, ed 8, New York, 2006, McGraw-Hill.

BASIC INFORMATION

DEFINITION

Legg-Calvé-Perthes disease (LCPD) is characterized by circulatory compromise of the immature proximal femoral head leading to avascular necrosis. The classification of LCPD is outlined in Fig. L1-2.

SYNONYMS

Perthes disease
Coxa plana
Capital femoral osteochondrosis
Osteonecrosis of the proximal femoral epiphysis
LCPD

ICD-9CM CODES
732.1 Perthes' disease
ICD-10CM CODES
M91.10 Juvenile osteochondrosis of head of femur [Legg-Calvé-Perthes], unspecified leg

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: One case in 1300 children. More common in Caucasians.
INCIDENCE: One in 1200 children, younger than 15 years of age.
PREDOMINANT SEX: Male/female ratio of 4:1.
PREDOMINANT AGE: 4 to 10 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Initial symptom: usually a mildly painful limp.
- Pain referred down the inner aspect of the thigh to the knee.
- Positive roll test: with the patient in the supine position, rolling of the affected extremity into internal and external rotation elicits guarding, with limited range of motion.
- Pain at the extremes of movement and tenderness over anterior hip join.
- No history of trauma.
- Condition is bilateral in 10% to 20% of patients.

ETIOLOGY

Unknown.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS: UNILATERAL DISEASE

- Transient synovitis.
- Sickle cell disease.
- Septic arthritis.
- Neoplasm.
- Spondyloepiphyseal dysplasia tarda.

BILATERAL DISEASE

- Multiple epiphyseal dysplasia (MED).
- Sickle cell disease.
- Juvenile idiopathic arthritis.

WORKUP

Diagnosis is usually based on the physical findings and eventual radiographic findings.

IMAGING STUDIES

- Plain roentgenography to establish the diagnosis.
- Anteroposterior and frog-leg lateral radiographs (Fig. L1-3).
- Technetium bone scanning to help confirm the diagnosis in early cases.

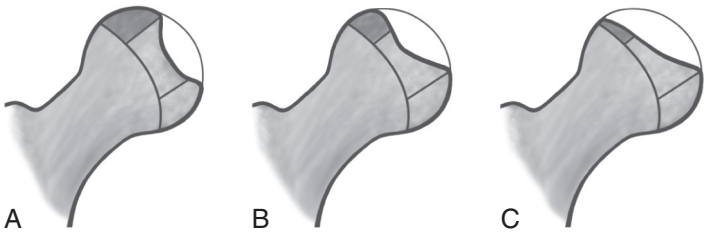


FIGURE L1-2 Lateral pillar classification for Legg-Calvé-Perthes disease. A, There is no involvement of the lateral pillar. **B,** >50% of the lateral pillar height is maintained. **C,** <50% of the lateral pillar height is maintained. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

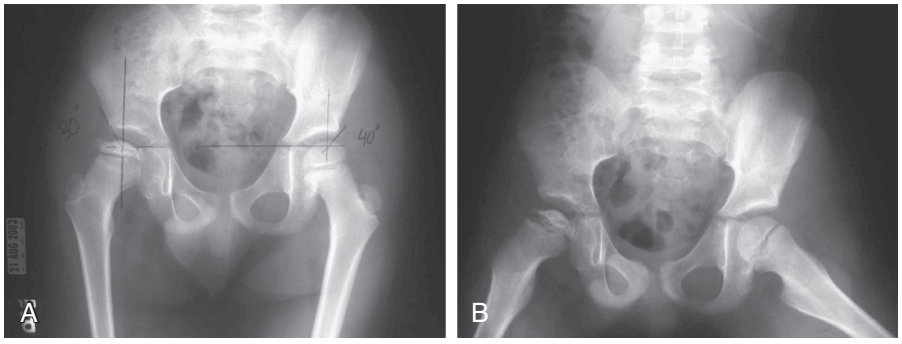


FIGURE L1-3 A, Anteroposterior radiograph of the pelvis shows epiphyseal fragmentation in the right hip, characteristic of the fragmentation phase of Legg-Calvé-Perthes disease. **B,** The frog-leg lateral view demonstrates subchondral fracture, increased density of the femoral head, and some collapse. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

TREATMENT

ACUTE GENERAL Rx

- A brief period of bed rest (1 to 3 days) followed by bracing (except in mild cases).
- Bracing may be required for 2 to 3 yr in a small percent of patients.
- NSAIDs and non-weight-bearing for pain control.
- Range-of-motion physical therapy exercises (physiotherapy).
- Surgical therapy in refractory cases: tenotomy, various osteotomies.

DISPOSITION

- Prognosis depends on age of patient and degree of involvement of the femoral head at onset.
- In patients younger than 6 yr, outcome is generally positive regardless of treatment.
- Patients over the age of 8 yr at onset often have poorer outcomes. Females tend to do worse than males in this age group.
- A few patients eventually develop degenerative arthritis.

REFERRAL

Referral to orthopedics or rheumatology for consultation when diagnosis is suspected.

PEARLS & CONSIDERATIONS

Both the etiology and the treatment of LCPD remain controversial. Treatment recommendations vary widely and continue to evolve. Children >6-8 yr at age of onset may benefit from early surgical intervention.

COMMENTS

There is great uncertainty regarding treatment and its effect on outcome. Bracing may have limited efficacy in augmenting the natural course of the disease.

SUGGESTED READINGS

Available at www.expertconsult.com.

RELATED CONTENT

Legg-Calvé-Perthes Disease (Patient Information)

AUTHOR: **MATTHEW J. STANISHEWSKI, D.O.**

SUGGESTED READINGS

Dillman JR, Hernandez RJ: MRI of Legg-Calvé Perthes disease, *Am J Roentgenol* 193:1394, 2009.

Domzalski ME et al.: The proximal femoral growth plate in Perthes disease, *Clin Orthop Relat Res* 458:150, 2007.

Frick SL: Evaluation of the child who has hip pain, *Orthop Clin North Am* 37:133, 2006.

Gough-Palmer A, McHugh K: Investigating hip pain in a well child, *BMJ* 334:1216, 2007.

Herring JA et al.: Legg-Calvé-Perthes disease: part I: classification of radiographs with use of the modified lateral pillar and Stulberg classifications, *J Bone Joint Surg Am* 86A:2103, 2004.

Herring J et al.: Legg-Calvé-Perthes disease: part II: prospective multicenter study of the effect of treatment on outcome, *J Bone Joint Surg Am* 86A:2121–2134, 2004.

Karimi MT, McGarry T: A comparison of the effectiveness of surgical and nonsurgical treatment of legg-calve-perthes disease: a review of the literature, *Adv Orthop* 490806, 2012.

Poul J: Diagnosis of Legg-Calvé-Perthes disease, *Ortop Traumatol Rehabil* 6(5):604–606, 2004.

Rosenfeld SB et al.: Legg-Calvé-Perthes disease: a review of cases with onset before six years of age, *J Bone Joint Surg Am* 89:2712, 2007.

Vosmaer A et al.: Coagulation abnormalities in Legg-Calvé-Perthes disease, *J Bone Joint Surg Am* 92:121, 2010.

BASIC INFORMATION

DEFINITION

Leishmaniasis is an infectious disease caused by a heterogeneous group of protozoan parasites belonging to the genus *Leishmania* and resulting in a variety of different clinical syndromes. Leishmaniasis parasites are transmitted to humans through sand fly bites.

SYNONYMS

Kala azar
Old world leishmaniasis
New world leishmaniasis

ICD-9CM CODES
085.9 Leishmaniasis
ICD-10CM CODES
B55.9 Leishmaniasis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: ~2 million total new cases and 500,000 visceral cases occur each year with almost 400 million people at risk for the disease.

- Can be classified geographically into new world versus old world disease (Fig. EL1-4).
- Infection can be divided into cutaneous, mucocutaneous, visceral disease.
- Different *Leishmania* species are associated with different patterns of disease.
- Incubation period: from 1 wk to many mo for cutaneous and mucosal leishmaniasis; 2 to 6 mo (range is 10 days to years) for visceral leishmaniasis.
- Mode of transmission: by the female sandfly vector; can also be spread via shared needles, blood transfusions, organ transplants, vertically from the mother to fetus, or sexually.
- Cutaneous leishmaniasis has been reported in U.S. military personnel in Iraq (more than 500 cases from 2002 to 2004).
- Travelers to endemic areas have become infected after <1 week exposure.
- Untreated visceral leishmaniasis is almost always fatal.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Cutaneous syndrome

- Localized cutaneous leishmaniasis: usually presents as an ulcerative skin lesion at the site of the sand fly bite, which resolves within several weeks or months, often leaving a residual scar
- Mucosal leishmaniasis–usually caused by *L. braziliensis;* also known as "espundia"
- Leishmaniasis recidivans
- Diffuse cutaneous leishmaniasis visceral syndrome
- Viscerotrophic leishmaniasis: fever, chronic fatigue, malaise, cough, intermittent diarrhea, and abdominal pain. Signs include adenopathy, hepatosplenomegaly, hyperpigmentation of skin, petechiae, jaundice, edema, and ascites
- Post–kala-azar dermal leishmaniasis: generalized cutaneous rash that is often papular or nodular; severe forms with desquamation of skin and mucosa

ETIOLOGY

- Old world parasite: *Leishmania tropica, L. major, L. aethiopica, L. donovani, L. infantum*
- New world parasite: *L. braziliensis* and *L. mexicana complex, L. chagasi, L. b. guyanensis, L. b. panamensis*
- *L. chagasi* has recently been found to be identical to *L. infantum*
- More than 20 distinct species of *Leishmania* have been described.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Malaria
- African trypanosomiasis
- Brucellosis
- Enteric fever
- Bacterial endocarditis
- Generalized histoplasmosis
- Chronic myelocytic leukemia
- Hodgkin's disease and other lymphomas
- Sarcoidosis
- Hepatic cirrhosis
- Tuberculosis

WORKUP

- Full thickness punch biopsy of a skin lesion
- On biopsy specimen can perform culture and histology
- PCR: SMART Leish PCR, RT-PCR
- Bone marrow bx for visceral disease
- Splenic aspirate often done in resource-poor settings.

LABORATORY TESTS

- CBC: anemia, neutropenia, thrombocytopenia, and eosinopenia
- LFTs: hypergammaglobulinemia, hypoalbuminemia, and hyperbilirubinemia
- Elevated BUN and creatinine
- Specific diagnosis confirmed by intracellular amastigote (Fig. EL1-5) in Giemsa-stained impression smears or sectioned tissue or culture performed in NMN (Novy, MacNeal, Nicolle) or Schneider's medium
- Serologic diagnosis: ELISA, direct agglutination tests, K39 ELISA, PCR, and monoclonal antibody staining of tissue smears; ELISA and DAT on urine specimens
  - Serology is not effective for diagnosis of cutaneous leishmaniasis
- Montenegro skin test: not in use in the US
- Although still a research tool, speciation by PCR would be worth pursuing to distinguish *L. braziliensis* from less aggressive species found in overlapping geographic locations. Urine antigen testing (KATEX), unlike serology, becomes negative after successful treatment, so can be used in follow-up.

TREATMENT

Nonspecific or supportive care
1. Nutritional diet
2. Antimicrobial agents for concurrent infections
3. Blood transfusions
4. Iron and vitamins

Specific antileishmanial therapy

Visceral leishmaniasis
1. Liposomal amphotericin B (Ambisome) in various regimens is the preferred drug for visceral leishmaniasis.
2. Pentavalent antimonials: sodium stibogluconate and sodium antimony gluconate may be used, but resistance has emerged in some geographic areas (e.g., in Asia, northern India, and Nepal).
3. Miltefosine (2.5 mg/kg/day orally in two divided doses for 28 days) is an effective oral choice for cutaneous, mucosal, and visceral disease. Teratogenic in animals, so cannot be used in pregnancy. This medication has now been FDA approved in the U.S.

Extraintestinal leishmaniasis
1. Pentavalent antimony or liposomal amphotericin B
2. Miltefosine

Cutaneous leishmaniasis (mild disease)
1. Paromomycin ointment BID x 20 days
2. Paromomycin (15%)–gentamicin (0.5%) ointment (WR279,396)
3. Cryotherapy with liquid nitrogen
4. Intralesional antimony

Cutaneous leishmaniasis (moderate disease)
1. Miltefosine
2. Sodium stibogluconate (Pentostam)
3. Meglumine antimonate (Glucantime)
4. Fluconazole 200 mg PO qd x 6 weeks
5. Ketoconazole 600 mg PO qd x 30 days
6. Amphotericin B

DISPOSITION

Follow-up examination is important for the early detection and treatment relapse.

REFERRAL

To infectious disease experts for accurate diagnosis and management

PEARLS & CONSIDERATIONS

COMMENTS

- Prevention by reservoir control: destruction of animal reservoir hosts, mass treatment of humans in kala-azar–prevalent areas.
- Prevention by vector control: insecticide spraying in domestic and peridomestic areas.
- Vaccines are in various stages of development and clinical trials. None are licensed or commercially available at this time.
- Co-infection with HIV can lead to more severe disease and/or atypical presentations and requires more intense therapy as well as antiretroviral therapy.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Alvar J et al.: The relationship between leishmaniasis and AIDS: the second 10 years, *Clin Microbiol Rev* 21:334, 2008.

Antinori S et al.: Leishmaniasis among organ transplant recipients, *Lancet Infect Dis* 8:191, 2008.

Bhattacharya SK et al.: Phase 4 trial of miltefosine for the treatment of Indian visceral leishmaniasis, *J Infect Dis* 196:591, 2007.

Centers for Disease Control and Prevention: Update: Cutaneous leishmaniasis in U.S. military personnel—Southwest Central Asia, 2002-04, *MMWR Morb Mortal Wkly Rep* 53:264, 2004.

Ejazi SA, Ali N: Developments in the diagnosis and treatment of visceral leishmaniasis during the last decade and future Prospects, *Expert Rev Anti Infect Ther* 11(1):79–98, 2013.

Jones J et al.: Old world cutaneous leishmaniasis infection in children: a case series, *Arch Dis Child* 90(5):530, 2005.

Machado P: Oral pentoxifylline combined with pentavalent antimony: a randomized trial for mucosal leishmaniasis, *Clin Infect Dis* 44:788, 2007.

Maltezou HC: Drug resistance in visceral leishmaniasis, *J Biomed Biotechnol* 61:7521, 2010. Epub 2009 Nov.

Murray HW et al.: Advances in leishmaniasis, *Lancet* 366:1561, 2005.

Reithinger R, Dujardin JC: Molecular diagnosis of leishmaniasis: current status and future applications, *J Clin Microbiol* 45:21, 2007.

Salah AB et al.: Topical paromomycin with or without gentamicin for cutaneous leishmaniasis, *N Engl J Med* 368:524–532, 2013.

Schwartz E et al.: New world cutaneous leishmaniasis in travellers, *Lancet Infect Dis* 63:342, 2006.

Scott P: Leishmaniasis, a parasitized parasite, *N Engl J Med* 364:1773–1774, 2011.

Solomon M et al.: Liposomal amphotericin B in comparison to sodium stibogluconate for cutaneous infection due to L. braziliensis, *J Am Acad Dermatol* 56:612, 2007.

Sundar S et al.: Comparison of short-course multidrug treatment with standard therapy for visceral leishmaniasis in India: an open-label, non-inferiority, randomized controlled trial, *Lancet* 377:477, 2011.

Sundar S et al.: Single-dose liposomal amphotericin B for visceral leishmaniasis in India, *N Engl J Med* 362:504–512, 2010.

Van Griensven J et al.: Combination therapy for visceral leishmaniasis, *Lancet Infect Dis* 10(3):184–194, 2010.

Van Griennnnsven, Diro E: Visceral Leishmaniasis, *Infect Dis Clin North Am* 26(2):309–322, 2012.

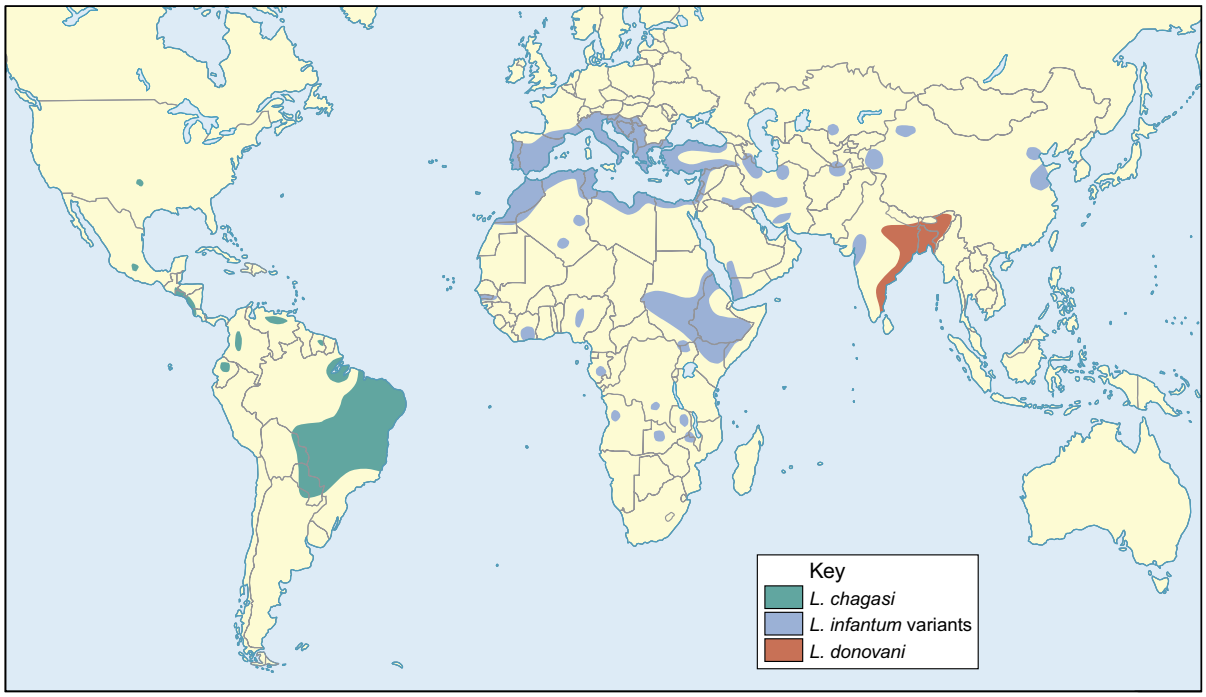


FIGURE EL1-4 Epidemiology of visceral leishmaniases (VL). VL caused by parasites of the *Leishmania donovani–Leishmania infantum* complex occurs in the Mediterranean littorals, the Middle East, and adjacent parts of the former Soviet Union, the Sudan, East Africa, the Indian subcontinent and China, and South America *(Leishmania chagasi).* An arid, warm environment provides ideal ecologic conditions for the breeding of many species of sandfly. Zoonotic kala-azar due to *L. infantum* and *L. chagasi* is commonly associated with dry, rocky, hill country, where cases are typically scattered. In India, *L. donovani* is essentially an anthroponosis. This type of kala-azar may occur in severe epidemic fashion, as can kala-azar in the Sudan. (From Hoffman R: *Hematology, basic principles and practice*, 6th ed, Philadelphia, 2013, Saunders.)

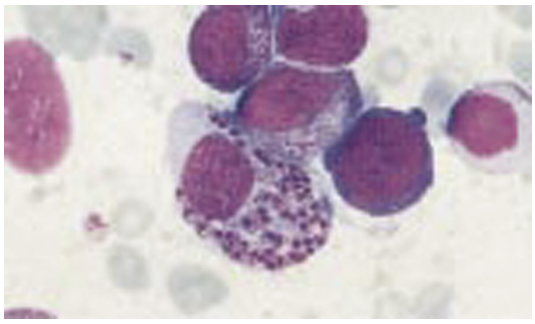


FIGURE EL1-5 *Leishmania infantum* in macrophage from bone marrow. Although typically found in macrophages as shown here, isolated extracellular amastigotes from disrupted host cells are commonly seen in such preparations. (From Hoffman R: *Hematology, basic principles and practice*, 6th ed, Philadelphia, 2013, Saunders.)

BASIC INFORMATION

DEFINITION

Leprosy is a chronic granulomatous infectious disease of humans that primarily affects the skin and peripheral nerves.

SYNONYMS

Hansen's disease

ICD-9CM CODES
030.9 Leprosy
ICD-10CM CODES
A30.9 Leprosy, unspecified
A30.0 Indeterminate leprosy
A30.3 Borderline leprosy
A30.5 Lepromatous leprosy
A30.8 Other forms of leprosy

EPIDEMIOLOGY & DEMOGRAPHICS

- The number of cases worldwide has fallen from >5.4 million cases in 1985 to about 245,000 cases in 2010 according to the World Health Organization (WHO).
- Nearly 75% of the cases of leprosy are found in India, Brazil, Nepal, Mozambique, Madagascar, and Myanmar (see Fig. EL1-6).
- More than 85% of the cases diagnosed in the United States are found among immigrants.
- Annual incidence in the United States is between 50 and 100 new cases per year (Fig. EL1-7).
- Leprosy is more common in men than women (2:1).
- Leprosy can occur at any age but usually is found in young children.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- A skin lesion: most common initial presentation.
- Sensory loss.
- Anhidrosis.
- Neuritic pain.
- Palpable peripheral nerves.
- Nerve damage (most commonly affected nerves are ulnar, median, common peroneal, posterior tibial, radial cutaneous nerve of the wrist, facial, and posterior auricular).
- Muscle atrophy and weakness.
- Foot drop.
- Claw hand and claw toes.
- Lagophthalmos, nasal septal perforation, collapse of bridge of nose (Fig. EL1-8*A*), loss of eyebrows resulting in "leonine" facies.
- Leprosy can present along a spectrum from simple cutaneous skin lesions with minimal sensory loss (Fig. EL1-8*B*) to severe extensive skin involvement, painful neuritis, muscle wasting and contractures, and multiple peripheral nerve damage.

ETIOLOGY

- Leprosy is caused by *Mycobacterium leprae,* an obligate intracellular acid-fast rod.
- The mode of transmission is thought to be through nasal secretions. Spread in humans is thought to occur via the respiratory route or entry through broken skin in patients with multibacillary disease or extensive paucibacillary disease.
- Zoonotic transmission from armadillos has been shown in a few case reports. More common in the southern region of the United States such as Louisiana and Texas.
- The majority of people exposed to patients with leprosy do not develop the disease because of their natural immunity. Variants of genes in the *NOD2*-mediated signaling pathway (which regulates the innate immune response) are associated with susceptibility to infection with *M. leprae.*
- Incubation period is 3 to 7 yr.

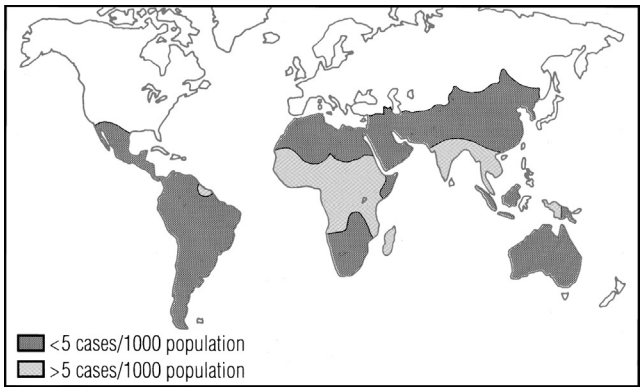


FIGURE EL1-6 Geographic distribution of leprosy. (From Souhami RL, Moxham J: *Textbook of medicine*, ed 4, London, 2002, Churchill Livingstone.)

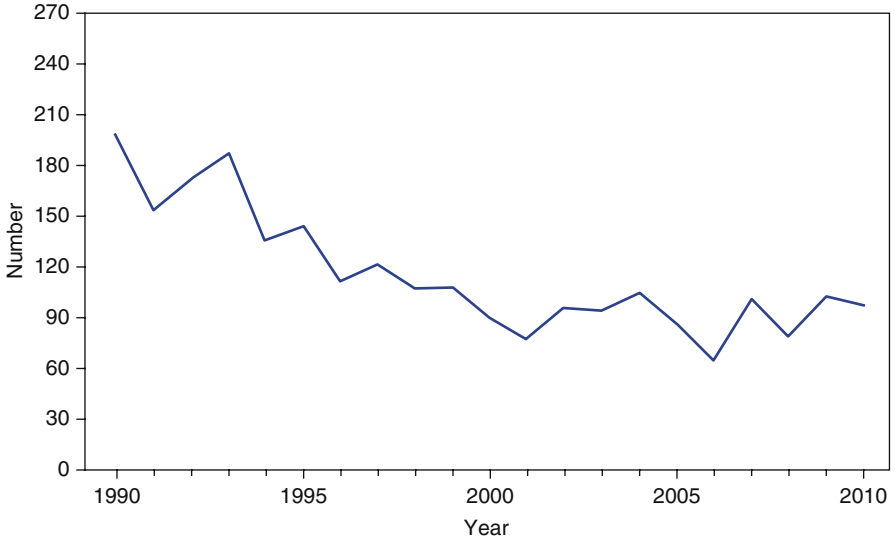


FIGURE EL1-7 Hansen disease (leprosy). Number of reported cases by year—United States, 1990-2010. (From Centers for Disease Control and Prevention: Summary of notifiable diseases—United States, 2010, *MMWR Morb Mortal Wkly Rep* 59:1-111, 2012.)

DIAGNOSIS

- The diagnosis of leprosy relies on a detailed history and physical examination and is established by the demonstration of acid-fast bacilli in skin smears or skin biopsies of the affected sites.
- Leprosy has been classified according to the WHO system into:
  1. Paucibacillary leprosy is defined as <5 skin lesions with no bacilli on skin smear.
  2. Multibacillary leprosy is defined as >5 skin lesions and may be skin-smear positive.
- Leprosy has also been classified by the Ridley-Jopling system based on the type of skin lesions, sensory and motor deficits, and biopsy into:
  1. Indeterminate leprosy.
  2. Tuberculoid leprosy (paucibacillary [few organisms], intense inflammatory reaction; few, well-demarcated skin lesions).
  3. Borderline tuberculoid leprosy.
  4. Borderline lepromatous leprosy.
  5. Lepromatous leprosy (multibacillary [numerous organisms], inadequate host response; diffuse, poorly organized skin lesions).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of leprosy includes sarcoidosis, rheumatoid arthritis, systemic lupus erythematosus, lymphomatoid granulomatosis, carpal

tunnel syndrome, cutaneous leishmaniasis, fungal infections and other causes of hypopigmented, hyperpigmented, and erythematous skin lesions.

WORKUP

Any patient who presents with skin lesions and a sensory or muscle deficit should have a workup for leprosy.

LABORATORY TESTS

- *Mycobacterium leprae* cannot be cultured on artificial media. The bacteria proliferate when injected into the footpads of mice or armadillos and can be used for drug-sensitivity testing.
- Serologic tests, including the antibody to phenolic glycolipid 1 (PGL-1) and bacilli detection in tissue using PCR, are available and used for diagnostic confirmation and research epidemiologic studies.
- Lepromin intradermal skin test is not diagnostic and not for commercial use.
- Skin smears are taken from active sites or most commonly from the earlobe, elbows, or knees and are stained for acid-fast bacilli.
- Skin biopsies of active sites are stained for acid-fast bacilli.
- Peripheral nerve biopsy can be done in patients with sensory loss and no skin lesions. Common nerves biopsied are the radial cutaneous nerve of the wrist and the sural nerve of the ankle.

IMAGING STUDIES

Radiograph studies are usually of no benefit in the diagnosis or treatment of leprosy.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Physical therapy for patients with upper and lower extremity deformities.
- Proper foot care and footwear to prevent ulcer formation.

ACUTE GENERAL Rx

CURRENT STANDARD U.S. REGIMENS: For paucibacillary leprosy:

- Dapsone 100 mg PO q day plus rifampin 600 mg PO q day for 6 mo (World Health Organization regimen), followed by dapsone monotherapy for 3 yr for indeterminate and tuberculoid leprosy and 5 yr for borderline tuberculoid leprosy. The National Hansen's Disease Program (NHDP) recommends dapsone 100 mg/day plus rifampin 600 mg/day PO for 12 months.

For multibacillary leprosy:

Dapsone 100 mg PO q day plus clofazimine 50 mg/day plus rifampin 600 mg PO q day for 2 yr, followed by dapsone monotherapy for 10 yr for borderline and indefinitely for borderline lepromatous or lepromatous.

An alternative regimen consists of dapsone 100 mg/day plus rifampin 600 mg/day plus minocycline 100 mg/day for 24 hours if clofazimine is refused or unavailable.

CHRONIC Rx

- If relapse occurs, the patient is treated with the same medical regimen; drug resistance is low.
- If relapse is from paucibacillary to multibacillary, the medical regimen for multibacillary should be used for therapy.

DISPOSITION

- Relapse is <1% for multibacillary and just over 1% in paucibacillary cases.
- Patients are initially followed up monthly and, when treatment is completed, every 3 to 6 mo for the next 5 to 10 yr.
- Some patients develop reactions known as erythema nodosum leprosum and reversal reaction, usually during treatment.
  1. Erythema nodosum leprosum results in tender nodules and is treated with thalidomide 100 mg qid then tapered with response. Cases not responsive to thalidomide are treated with prednisone 60 to 80 mg q day.
  2. Reactive reaction results in the development of new skin lesions with swelling and erythema of existing lesions. Treatment is with prednisone 60 to 80 mg a day then a taper dose. Clofazimine and dapsone are options. Do not use thalidomide.
  3. Other agents used in the treatment of leprosy include ofloxacin, moxifloxacin, minocycline, and clarithromycin.

REFERRAL

- National Hansen's Disease Programs (NHDP) Center in Baton Rouge, Louisiana, and 15 outpatient clinics in the United States offer consultations and treatment. Telephone: 1-800-642-2477.
- Directly observed therapy (DOT), much like DOT for tuberculosis, is highly desirable and should be used if feasible, at least in the first 6 to 12 mo of therapy.
- Any suspected case of leprosy merits an infectious disease consultation. Consultation with orthopedics, podiatry, ophthalmology, physical therapy, plastic surgery, and psychology are all in order for any of the potential sequelae of the disease.

PEARLS & CONSIDERATIONS

COMMENTS

- The risk of transmission is low in patients with leprosy, and therefore no infection control precautions of hospitalized patients are needed.
- Family members and close contacts need to be examined frequently for the development of lesions.

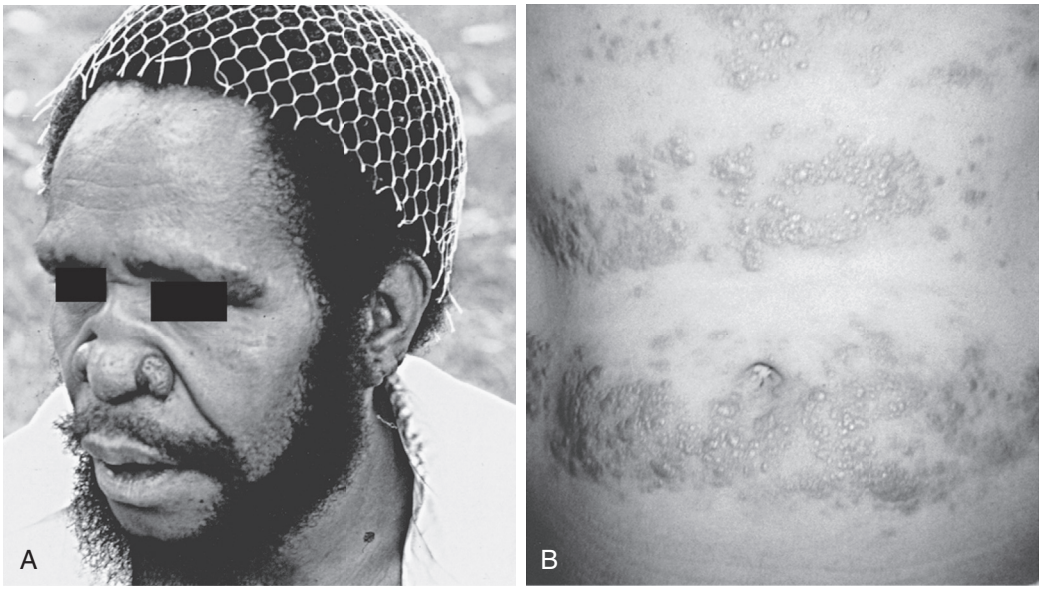


FIGURE EL1-8 A, Advanced lepromatous leprosy with collapse of the nasal septum. **B,** Lepromatous leprosy characterized by extensive papule formation over abdomen. Minimal or no sensory loss is present in the affected areas. (**A** From Gorbach SL: *Infectious diseases*, ed 2, Philadelphia, 1998, Saunders; **B** From Mandell GL: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 5, New York, 2000, Churchill Livingstone.)

- Dapsone or rifampin prophylaxis is not recommended in the prevention of leprosy.
- BCG vaccination has a 50% efficacy in the prevention of leprosy and may be considered.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Leprosy (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

El-Darouti MA: Histopathological study of apparently normal skin of patients with leprosy, *Int J Dermatol* 45(3):292, 2006.

Moet FJ et al.: Physical distance, genetic relationship, age, and leprosy classification are independent risk factors for leprosy in contacts of patients with leprosy, *J Infect Dis* 193(3):346, 2006.

Nolen L et al.: Incidence of Hansen's disease, United States, 1994-2011, *MMWR* 63:969–72, 2014.

Truman RW et al.: Probable zoonotic leprosy in the southern United States, *N Engl J Med* 364:1626–1633, 2011.

Worobec SM: Treatment of leprosy/Hansen's disease in the early 21st century, *Dermatol Ther* 22(6):518–537, 2009.

BASIC INFORMATION

DEFINITION

Leptospirosis is a zoonosis caused by the spirochete *Leptospira interrogans.*

SYNONYMS

Weil's disease

ICD-9CM CODES
100.9 Leptospirosis
ICD-10CM CODES
A27.9 Leptospirosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.)
- 0.05 cases/100,000 persons.
- Significant underestimation because of underreporting.
- Hawaii consistently has the highest reported annual incidence rate in the United States.

PEAK INCIDENCE: Summer months, into the fall.
PREDOMINANT SEX: Male (4:1).
PREDOMINANT AGE: Teenagers and young adults.
GENETICS: Neonatal infection can occur.

PHYSICAL FINDINGS & CLINICAL PRESENTATION (see Table EL1-3)

ANICTERIC FORM
- Milder and more common presentation of disease.
- A self-limited systemic illness with two stages:
  1. Septicemic stage: presents abruptly with fevers, headache, severe myalgias, rigors, prostration, and sometimes circulatory collapse; conjunctival suffusion is common; skin rash, pharyngitis, lymphadenopathy, hepatomegaly, splenomegaly.
  2. Immune stage: occurs a few days after first stage with similar symptoms; hallmark is aseptic meningitis.

ICTERIC LEPTOSPIROSIS (WEIL'S SYNDROME):
1. Denotes severe cases, with symptoms of hepatic, renal, and vascular dysfunction.
2. Biphasic course: persistence of fever, jaundice, and azotemia.
3. Complications: oliguria or anuria, hemorrhage, hypotension, vascular collapse.

ETIOLOGY

Caused by a spirochete, *L. interrogans.*
- Infects a variety of animals, including most mammals.
- Specific serotypes associated with different hosts—pomona in livestock, canicola in dogs, and icterohaemorrhagiae in rodents.
- Organism penetrates skin or mucous membranes through exposure to animal urine or infected water.
- The most important reservoir for the bacteria is rats.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS
- Bacterial meningitis.
- Viral hepatitis.
- Malaria.
- Dengue fever.
- Hanta virus.
- Influenza.
- Legionnaire's disease.

WORKUP

Culture of blood, CSF, and urine:
- Organism can be isolated from blood or CSF during first 10 days of illness.
- Urine should be cultured after first wk and for up to 30 days after onset of illness.
- Serology: ELISA.

LABORATORY TESTS
- Normal or elevated WBCs, at times with leukemoid reactions up to 70,000/mm^3.
- Elevated transaminases or bilirubin.
- Anemia, azotemia, hypoprothrombinemia in those with icteric illness.
- Elevated CK in first phase.
- Meningitis in both phases, but aseptic in second phase.

IMAGING STUDIES

Chest radiographs to show interstitial nonlobar infiltrates.

TREATMENT

NONPHARMACOLOGIC THERAPY
- Supportive.
- Observation for dehydration, hypotension, renal failure, hemorrhage.

ACUTE GENERAL Rx
- Severe illness: IV penicillin G 1.5 million units IV q6h or ceftriaxone 1 to 2 g q24h for 7 days or doxycycline 100 mg IV q12 hrs.

TABLE EL1-3 Signs and Symptoms of Admission in Patients with Leptospirosis in Large Case Series

	Puerto Rico, 1963 *n* = 208	China, 1965 *n* = 168	Vietnam, 1973 *n* = 150	Korea, 1987 *n* = 93	Barbados, 1990 *n* = 88	Seychelles, 1998 *n* = 75	Brazil, 1999 *n* = 193	Hawaii, 2001 *n* = 353	India, 2002 *n* = 74
Percent with:									
Jaundice	49	0	1.5	16	95	27	93	39	34
Anorexia	—	46	—	80	85	—	—	82	—
Headache	91	90	98	70	76	80	75	89	92
Conjunctival suffusion	99	57	42	58	54	—	28.5	28	35
Vomiting	69	18	33	32	50	40	—	73	—
Myalgia	97	64	79	40	49	63	94	91	68
Arthralgia	—	36	—	—	—	31	—	59	12
Abdominal pain	—	26	28	40	43	41	—	51	—
Nausea	75	29	41	46	37	—	—	77	—
Dehydration	—	—	—	—	37	—	—	—	—
Cough	24	57	20	45	32	39	—	—	—
Hemoptysis	9	51	—	40	—	13	20	—	35
Hepatomegaly	69	28	15	17	27	—	—	16	—
Lymphadenopathy	24	49	21	—	21	—	—	—	15
Diarrhea	27	20	29	36	14	11	—	53	—
Rash	6	—	7	—	2	—	—	8	12

From Mandell GL et al: *Principles and practice of infectious diseases,* ed 7, Philadelphia, 2010, Churchill Livingstone.

- Mild illness: doxycycline 100 mg PO bid for 7 days or ampicillin 0.5-1 g IV q6h for 7 days or azithromycin 1 g once, then 500 mg PO qd for 2 days.
- Vitamin K administration if hypoprothrombinemia present.
- Possible Jarisch-Herxheimer reaction when treated with penicillin.

DISPOSITION

- In anicteric leptospirosis, antibiotics can decrease severity and duration of symptoms.
- Icteric leptospirosis, even with supportive therapy, may have a mortality as high as 10%.

REFERRAL

- If more than mild disease.
- If no response to treatment.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Karande S et al.: Acute aseptic meningitis as the only presenting feature of leptospirosis, *Pediatr Infect Dis J* 24(4):390, 2005.

Lau C et al.: Leptospirosis: an emerging disease in travelers, *Travel Med Infect Dis* 8(1):33–39, 2010.

Segura ER et al.: Clinical spectrum of pulmonary involvement in leptospirosis in a region of endemicity, with quantification of leptospiral burden, *Clin Infect Dis* 40(3):343, 2005.

Suputtamongkol Y et al.: An open, randomized, controlled trial of penicillin, doxycycline, and cefotaxime for patients with severe leptospirosis, *Clin Infect Dis* 39(10):1417, 2004.

Toyokawa T et al.: Diagnosis of acute leptospirosis, *Expert Rev Anti Infect Ther* 9(1):111–121, 2011.

Lichen Planus PTG

BASIC INFORMATION

DEFINITION

Lichen planus (LP) refers to an idiopathic inflammatory disease manifesting with a papular skin eruption characteristically found over the flexor surfaces of the extremities, genitalia, and mucous membranes.

SYNONYMS

Lichen
Lichen planus et atrophicus
LP

ICD-9CM CODES
697.0 Lichen planus
ICD-10CM CODES
L43 Lichen planus
L43.0 Hypertrophic lichen planus
L43.1 Bullous lichen planus
L43.9 Lichen planus, unspecified
L43.8 Other lichen planus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: One in every 100 new patients seen in dermatology clinics in the United States is diagnosed with LP.
PREVALENCE: 440 cases/100,000 persons
PREDOMINANT SEX: Found equally between males and females (1:1).
PREDOMINANT AGE: Usually found in people between the ages of 30 and 60 yr.
PREDISPOSING FACTORS:
1. Associated with other autoimmune disorders (e.g., primary biliary cirrhosis, myasthenia gravis, ulcerative colitis, diabetes).
2. Associated with hepatitis C infection.
3. Drug-induced form affects any area of the body surface (e.g., beta-blocker, methyldopa, penicillamine, quinidine, nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, sulfonylurea agents).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The clinical presentation varies depending on the area involved.
History:
- Usually starts on an extremity and may remain localized or spread to involve other areas over a 1- to 4-mo period.
- Pruritic.

Physical findings:
- Anatomic distribution:
  1. Flexor surface of wrists, forearms, shins, and upper thighs.
  2. Neck and back area.
  3. Nails (5% to 10% of patients).
  4. Scalp (lichen planopilaris).
  5. Oral mucosa, buccal mucosa, tongue, gingiva, and lips; oral lichen planus can cause extensive desquamative gingivitis.
  6. Vulva, penis.

Genital mucosa:
- Lesion configuration:
  1. Linear.
  2. Annular (more common).
  3. Reticular pattern noted on oral mucosa and genital area.
- Lesion morphology:
  1. Papules most common presentation (flat, smooth, shiny) (Fig. L1-9)
  2. Hypertrophic
  3. Follicular
  4. Vesicular
- Color:
  1. Dark red, bluish red, purplish-violaceous color is noted in cutaneous LP.
  2. Individual lesions characteristically have white lines visible (Wickham's striae).
  3. Oral and genital LP has a reticular network of white lines that may be raised or annular in appearance.
- Scalp lesions may result in alopecia.

ETIOLOGY

The cause of LP is unknown. It is believed that LP represents a T-cell–mediated inflammatory disorder.

DIAGNOSIS

- Clinical history and physical findings usually establish the diagnosis of LP.
- Skin biopsy (deep shave or punch biopsy of the most developed lesion) can be performed to confirm the diagnosis.

DIFFERENTIAL DIAGNOSIS

- Drug eruption, psoriasis, Bowen's disease, leukoplakia, candidiasis, lupus rash, secondary syphilis, seborrheic dermatitis, chronic graft vs. host disease.

WORKUP

If the diagnosis is questionable, a skin biopsy is performed.

LABORATORY TESTS

Laboratory tests are not specific for the diagnosis of LP. Lipid panels screening is useful since increases in serum triglycerides and decreases in HDL cholesterol are common in patients with LP.

IMAGING STUDIES

Imaging studies are not helpful in diagnosing LP.

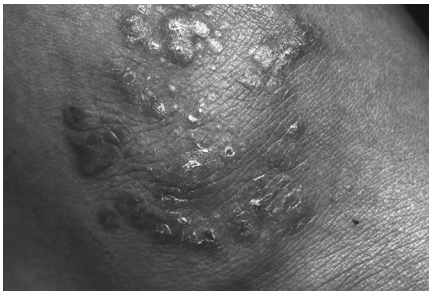


FIGURE L1-9 Flat-topped, purple polygonal papules of the lichen planus. (From Morelli JG: Diseases of the epidermis. In Kliegman RM et al [eds]: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoid scratching.
- Use mild soaps and emollients after bathing to prevent dryness.

ACUTE GENERAL Rx

For cutaneous LP:
- Topical steroids (e.g., triamcinolone acetonide 0.1%, fluocinonide 0.05%, clobetasol propionate 0.05% cream or ointment) with occlusion used twice daily.
- Acitretin 30 mg/day PO for 8 wk.
- Systemic prednisone 30 to 60 mg/day as a starting dose and tapered to 15 to 20 mg/day maintenance for 6 wk.
- Intradermal steroid triamcinolone acetonide 5 mg/ml can be tried for thick hyperkeratotic lesions.
- Hydroxyzine 25 mg PO q6h can be used for pruritus.
- Phototherapy: PUVA or narrow-band ultraviolet B therapy: 2 or 3 times per week, for a total of 12 sessions (i.e., one cycle).

For oral LP:
- Topical steroid fluocinonide in an adhesive base used six times/day for 9 wk.
- Topical calcineurin in steroid-unresponsive cases.
- Topical or systemic retinoids 0.1% retinoic acid in an adhesive base or gel.
- Etretinate 75 mg/day for 2 mo.

CHRONIC Rx

Refer to "Acute General Rx."

DISPOSITION

- Spontaneous remissions of cutaneous LP occur in >65% of cases within the first year.
- Spontaneous remission of oral LP usually occurs by 5 yr.
- Approximately 10% to 20% of patients will have recurrence.

REFERRAL

To dermatologist if diagnosis is unclear

PEARLS & CONSIDERATIONS

COMMENTS

- LP can be remembered as purple, planar, pruritic, polygonal, papules, and plaques (six P's).
- Lesions can develop at the site of prior skin injury (Koebner's phenomenon).
- Although there is an increased risk of squamous cell carcinoma in chronic lesions of mucosal LP, transformation to skin cancer is uncommon.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Lichen Planus (Patient Information)

AUTHOR: **TANYA ALI, M.D.**

SUGGESTED READINGS

Arias-Santiago S et al.: Cardiovascular risk factors in patients with lichen planus, *Am J Med* 124:543–548, 2011.

Chan ES et al.: Interventions for treating oral lichen planus, *Cochrane Database Syst Rev* 2:CD001168, 2000.

Katta R: Lichen planus, *Am Fam Physician* 61(11):3319, 2000.

Le Cleach L, Chosidow O: Lichen planus, *N Engl J Med* 366:723–732, 2012.

BASIC INFORMATION

DEFINITION

Lichen sclerosus is a chronic inflammatory condition of the skin usually affecting the vulva, perianal area, and groin.

ICD-9CM CODES
701.0 Lichen sclerosus
ICD-10CM CODES
L90.0 Lichen sclerosus et atrophicus

EPIDEMIOLOGY & DEMOGRAPHICS

- Most common in postmenopausal women and men between ages 40 and 60 yr.
- More common in females (female/male ratio of 5:1).
- Can occur in children (usually prepubertal girls with involvement of the vulva and perineum).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Erythema may be the only initial sign. A characteristic finding is the presence of ivory-white atrophic lesions on the involved area.
- Close inspection of the affected area will reveal the presence of white-to-brown follicular plugs on the surface (dells).
- When the genitals are involved, the white, parchment-like skin assumes an hourglass configuration around the introital and perianal area ("keyhole" distribution; Fig. L1-10).

Inflammation, subepithelial hemorrhages, and chronic ulceration may develop.
- Dyspareunia, genital bleeding, and anal bleeding are common.

ETIOLOGY

Unknown. There may be an autoimmune association and a genetic familial component.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Localized scleroderma (morphea).
- Cutaneous discoid lupus erythematosus.
- Atrophic lichen planus.
- Psoriasis.

WORKUP

Diagnosis is based on close examination of the lesions for the presence of ivory-white atrophic lesions and typical location.

LABORATORY TESTS

Punch or deep shave biopsy can be used to confirm the diagnosis.

TREATMENT

NONPHARMACOLOGIC THERAPY

Attention to hygiene and elimination of irritants or excessive bathing with harsh soaps.

GENERAL Rx

- Application of clobetasol propionate 0.05% topically bid for up to 4 wk is usually effective. Repeat courses of corticosteroids may be necessary because of the chronic nature of this disorder. Continual application of topical steroids may lead to atrophy of the vulva.
- There is no substantial evidence that use of topical sex hormones (e.g., topical testosterone [2%]) is effective in genital lichen sclerosus.
- Lubricants (e.g., Nutraplus cream) are useful to soothe dry tissues.
- Hydroxyzine 25 mg at bedtime is effective in decreasing nocturnal itching.
- Use of intralesional steroids, etretinate, and surgical management is usually reserved for refractory cases.

DISPOSITION

- The disease persists in approximately one third of patients.
- Most prepubertal girls improve spontaneously at menarche.
- Squamous cell carcinoma can develop within the lesions in 3% to 10% of older patients; therefore periodic examination and biopsy of suspicious areas are indicated.

PEARLS & CONSIDERATIONS

COMMENTS

- Prepubertal lichen sclerosus may be confused with sexual abuse in prepubertal girls and may lead to false accusations and investigations.
- Lichen sclerosus of the vulva (kraurosis vulvae) usually occurs after menopause and is generally chronic. It can be painful and interfere with sexual activity.
- Lichen sclerosus of the penis (balanitis xerotica obliterans) is seen more commonly in uncircumcised males. It affects the glans and prepuce and may lead to stricture if it encroaches into the urinary meatus.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Lichen Sclerosus (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

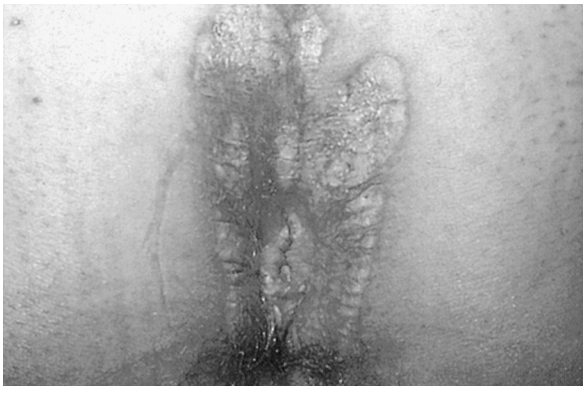


FIGURE L1-10 Lichen sclerosus. Perianal area is thinned and chalk white (keyhole distribution). (Courtesy Department of Dermatology, University of North Carolina at Chapel Hill. From Goldstein BG, Goldstein AO: *Practical dermatology,* ed 2, St Louis, 1997, Mosby.)

SUGGESTED READINGS

Chi CC et al.: Topical interventions for genital lichen sclerosus, *Cochrane Database Syst Rev* 12:CD008240, 2011.

Lichen Simplex Chronicus

BASIC INFORMATION

DEFINITION

Lichen simplex chronicus is neurodermatitis manifesting with localized areas of thickened, hyperplastic scaly skin due to prolonged and severe scratching in patients with no underlying dermatologic condition.

SYNONYMS

Neurodermatitis from rubbing

ICD-9CM CODES
698.3 Lichenification and lichen simplex chronicus
ICD-10CM CODES
L28.0 Lichen simplex chronicus

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Between 35 and 50 yr old.
PREVALENCE: Increased in patients with underlying anxiety disorders.
PREDOMINANT SEX AND AGE:
- Sex: Females > males (2:1).
- Age: Adults over 60.

RISK FACTORS: Anxiety disorders, dry skin, insect bites.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients present with profound pruritus and localized scaly plaques with accentuated skin markings said to resemble tree bark (Fig. L1-11).
- Lichenified circumscribed plaques. Trauma from rubbing and scratching accounts for persistence of the plaque.
- Commonly involved areas include hands and wrists (Fig. L1-12), back and sides of neck, anterior tibias, anogenital areas, and ankles.

ETIOLOGY

- Neurodermatitis.
- Common triggers are excess dryness of skin, heat, sweat, and psychological stress. It can also accompany other conditions such as the fungal infections candidiasis or tinea cruris, or psoriasis, lichen sclerosus, and neoplasia, leading to squamous cell hyperplasia.
- Other causes include atrophic dermatitis and insect bites. Rare cases have shown links to lithium use, hair dye containing PPD, and long-term exposure to vehicle pollution.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Lichen planus.
- Psoriasis.
- Atopic dermatitis.
- Insect bite.
- Nummular eczema.
- Contact dermatitis.
- Stasis dermatitis.

WORKUP

Patient history and skin examination. Skin biopsy when diagnosis is unclear or persistent symptoms.

LABORATORY TESTS

- Not generally necessary.
- Biopsy reveals hyperkeratosis, acanthosis, and mild to moderate lymphohistiocytic inflammatory infiltrate with prominent lichenification.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Patient education is essential to break the itch-scratch cycle and facilitate treatment of any underlying dermatitis.
- Psychotherapy.

ACUTE GENERAL Rx

- Antihistamine hydroxyzine 25 mg at bedtime is effective in decreasing nocturnal itching.
- Topical corticosteroids.
- Intralesional corticosteroids.
- Anxiolytics, SSRIs.
- Oral doxepin (an antidepressant and anxiolytic).
- Mirtazapine.
- Tropical calcineurin inhibitor for vulvar lichenification.

Cyclosporin A

Topical tacrolimus, 0.1% ointment, can be used for sensitive skin, face.

Botulinum intradermal injections.

Alitretinoin, 30 mg daily for 3 mo, has shown some clinical improvement in case studies but needs further investigation as a potential rx.

CHRONIC Rx

Constant irritation of the skin must be avoided. Keeping skin moisturized, a covering to prevent scratching, or nail filing may be necessary.

DISPOSITION

Psychological intervention improves recovery. Regular follow-up visits facilitate long-term management.

REFERRAL

Refer to a psychologist for psychological evaluation and consultation, and a dermatologist in resistant cases.

PEARLS & CONSIDERATIONS

- Significant scratching may occur during nocturnal hours.
- The involved area is always at a site that is easily reached for scratching.
- Chronic scratching can also cause keratinocyte necrosis and the development of amyloid in the papillary dermis, called lichen amyloidosis.

COMMENTS

Patients may be at increased risk for scarring of the skin, changes in skin pigmentation, and bacterial and fungal infections of the involved skin.

PREVENTION

Prevent future incidences by continued therapy, stress management, and avoidance of common triggers and accompanying conditions.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **FRED F. FERRI, M.D.,** and **HEATHER FERRI, D.O.**

FIGURE L1-11 Lichenified skin of the lower extremity caused by habitual rubbing. The confluence of multiple scaling papules has formed a large plaque of palpably thickened skin. (From Ferri FF et al: *Ferri's fast facts in dermatology,* Philadelphia, 2010, Saunders.)

FIGURE L1-12 Long-standing pruritus and scratching resulted in this thickened, hyperpigmented skin on the wrist consisting of numerous 1- to 2-mm papules. This "follicular" pattern is more common in African Americans. (From Ferri FF et al: *Ferri's fast facts in dermatology,* Philadelphia, 2010, Saunders.)

SUGGESTED READINGS

Aschoff R, Wozel A: Topical tacrolimus for the treatment of lichen simplex chronicus, *J Dermatolog Treat* 18(2):115–117, 2007. Available at http://www.ncbi.nlm.nih.gov/pubmed/17520470.

D'Erme A et al. Efficacy of treatment with oral alitretinoin in patient suffering from lichen simplex chronicus and severe atopic dermatitis of hands. Dermatologic therapy Wiley periodicals, Inc.

Felber E: Botulinum toxin in primary care medicine, *J Am Osteopath Assoc* 105(10):609–614, 2006. Available at http://www.jaoa.org/content/106/10/609.full.

Hogan DJ et al.: Lichen simplex chronicus clinical presentation, *Medscape Reference*, 2010. Retrieved via emedicine.medscape.com/article/1123423-overview.

Horn TD et al. In: (editor: Bolognia JL et al.) Dermatology, vol. 2 Mosby: Philadelphia.

Lotti T et al.: Prurigo nodularis and lichen simplex chronicus, *Dermatol Ther* 1(21):42–46, 2008.

Lynch PJ: Lichen simplex chronicus (atopic/neurodermatitis) of the anogenital region, *Dermatol Ther* 17(1):8–19, 2004.

Weyers W et al.: Lichen amyloidosus: a consequence of scratching, *J Am Acad Dermatol* 37(6):923–928, 1997.

BASIC INFORMATION

DEFINITION

Listeriosis is a systemic infection caused by the gram-positive aerobic bacterium *Listeria monocytogenes.*

SYNONYMS

Listerial infection
Granulomatosis infantisepticum

ICD-9CM CODES
027.0 Listeriosis
771.2 Congenital listeriosis
771.2 Fetal listeriosis
665.4 Suspected fetal damage affecting management of pregnancy

ICD-10CM CODES
A32 Listeriosis
A32.0 Cutaneous listeriosis
A32.7 Listerial sepsis
A32.8 Other forms of listeriosis
A32.9 Listeriosis, unspecified
A32.11 Listerial meningitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- *Listeria* meningitis: about 0.7 cases/100,000 persons (fourth most common cause of community-acquired bacterial meningitis in adults)
- In pregnant women: 3.0 cases per 100,000 population
- In general population: 0.29 confirmed cases per 100,000 persons in 2009-2011 in the United States, but 1.3 per 100,000 cases in persons over the age of 65

PREDOMINANT SEX: Pregnant women are more susceptible to *Listeria* bacteremia, accounting for up to one third of reported cases.

PREDOMINANT AGE:

- Pregnant women
- Immunocompromised patients of any age
- Elderly patients are susceptible even in the absence of recognized immunocompromised states

GENETICS: Congenital infection:

- With transplacental transmission, syndrome termed *granulomatosis infantisepticum* in neonate
- Characterized by disseminated abscesses in multiple organs, skin lesions, and conjunctivitis
- Mortality: 33% to 100%

Neonatal infection:

- Infant becoming ill after 3 days of age; mother invariably asymptomatic
- Clinical picture of sepsis of unknown origin

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Infections in pregnancy
1. More common in third trimester
2. Usually present with fever and chills without localizing symptoms or signs of infection

Meningoencephalitis
1. More common in neonates and immunocompromised patients, but up to 30% of adults have no underlying condition
2. In neonates: poor appetite with or without fever possibly the only presenting signs
3. In adults: presentation often subacute, with low-grade fever and personality change as only signs
4. Focal neurologic signs seen without demonstrable brain abscess on CT scan

Cerebritis/rhombencephalitis
1. Headache and fever may be only presenting complaints
2. Progressive cranial nerve palsies, hemiparesis, seizures, depressed level of consciousness, cerebellar signs, respiratory insufficiency may also be seen

Focal infections
1. Ocular infections (purulent conjunctivitis) and skin lesions (granulomatosis infantisepticum) as a result of inadvertent inoculation by laboratory and veterinary personnel
2. Others: arthritis, prosthetic joint infections, peritonitis, osteomyelitis, organ abscesses, cholecystitis

ETIOLOGY

- Direct invasion of skin and eye has been documented, but mechanism of GI entry is unclear.
- Organism's intracellular life cycle explanatory of:
  1. Importance of cell-mediated immunity in host defense
  2. Increased infection in neonates, pregnant women, and immunocompromised hosts

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Meningitis caused by other bacteria, mycobacteria, or fungi
- CNS sarcoidosis
- Brain neoplasm or abscess
- Tuberculous and fungal (especially cryptococcal) meningitis
- Cerebral toxoplasmosis
- Lyme disease
- Sarcoidosis

WORKUP

Dictated by age, end-organ involvement, and immune status

LABORATORY TESTS

- Cultures of blood and other appropriate body fluids
- Variable CSF findings, but neutrophils usually predominate
- Organisms uncommonly seen on Gram stain and may be difficult to identify morphologically
- Monoclonal antibodies, polymerase chain reaction, and DNA probe techniques to detect *Listeria* in foods

IMAGING STUDIES

- If focal cerebral involvement suspected: CT scan or MRI
- MRI most sensitive for evaluation of brainstem and cerebellum

TREATMENT

Empiric therapy should be administered when diagnosis is suspected because overall mortality is 23%.

ACUTE GENERAL Rx

- Drugs of choice:
  1. IV ampicillin 2 g IV q 4 hr for adults. Children: 300 mg/kg per day IV in 4 to 6 divided doses. Infants 8 days to 1 month: 150 to 200 mg/kg per day divided in four doses. For infants ≤7 days: 100 mg/kg per day divided in two doses for infants weighing <2000 g and 150 mg/kg per day divided in three doses for infants weighing more than 2000 g.
  2. IV penicillin 12 to 24 million U/day in divided doses.
- Continuation of therapy for 2 weeks for bacteremia; 2 to 4 weeks for meningitis.
- Alternative (if penicillin allergic): trimethoprim/sulfamethoxazole or vancomycin.
- Gentamicin IV added to provide synergy in meningitis or endocarditis patients of any age.

CHRONIC Rx

Relapses reported, especially in immunocompromised hosts, after 2 wk of therapy.

DISPOSITION

Long-term follow-up of immunodeficiency state.

REFERRAL

Infectious disease consultation for all patients.

PEARLS & CONSIDERATIONS

COMMENTS

- Foodborne cases (1600 cases occur annually with a mortality rate of 16%) have been linked to various products: coleslaw, soft cheeses, unpasteurized milk and milk products, vegetables, undercooked chicken, hot dogs, luncheon meats, refrigerated smoked seafood, and so on.
- Complete decontamination of food products is difficult because *Listeria* is resistant to pasteurization and refrigeration.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Listeriosis (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Allerberger F, Wagner M: Listeriosis: a resurgent foodborne illness, *Clin Microbiol Infect* 16(1):6–23, 2010.

Gottlieb SL et al.: Multistate outbreak of listeriosis linked to turkey deli meat and subsequent changes in U.S. regulatory policy, *Clin Infect Dis* 42(1):29, 2006.

Mylonakis E et al.: Listeriosis during pregnancy: a case series and review of 222 cases, *Medicine* 81:260, 2002.

Pasche B et al.: Sex-dependent susceptibility to Listeria monocytogenes infection is mediated by differential interleukin-10 production, *Infect Immun* 73(9):5952, 2005.

Saunders BD et al.: Molecular epidemiology and cluster analysis of human listeriosis cases in three U.S. states, *J Food Prot* 69(7):1680, 2006.

BASIC INFORMATION

DEFINITION

Long QT syndrome (LQTS) is a disorder of myocardial repolarization characterized by a prolongation of the QT interval on the ECG associated with an increased risk of developing life-threatening ventricular arrhythmias, most commonly torsades de pointes (a specific type of polymorphic ventricular tachycardia), which may lead to ventricular fibrillation and sudden cardiac death (SCD). This syndrome may be either genetic or acquired.

SYNONYMS

LQTS
Congenital forms:
- Jervell and Lange-Nielsen syndrome (associated with deafness)
- Romano-Ward syndrome (associated with normal hearing)

ICD-9CM CODES
427.9 Unspecified cardiac dysrhythmia
ICD-10CM CODES
I45.81 Long QT syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- Congenital LQTS is thought to account for >3000 deaths in childhood per year in the United States.
- Incidence of LQTS is thought to be between 1:2500 and 1:10,000 in the general population, although it has been difficult to estimate due to incomplete penetrance.
- Congenital form associated with deafness is autosomal recessive (Jervell and Lange Nielsen syndrome) and is less common than the autosomal dominant form as well as more severe.
- Congenital form associated with normal hearing (Romano-Ward syndrome) is autosomal dominant. Although inheritance of LQTS is autosomal dominant, female predominance has often been observed and has been attributed to an increased susceptibility to cardiac arrhythmias in women.
- At least 13 different LQTS genes have been identified to date.
- LQTS is more common in women than in men.
- Mortality rate is estimated to be about 1% per year.
- Genetic mutations in the congenital LQTS are described in Table L1-4. Common types of LQTS are described in Table L1-5.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Many episodes are stress mediated.
- Palpitations, presyncope.
- Syncope caused by ventricular tachycardia.
- SCD.
- Seizure.
- Family history of LQTS, but a family history of SCD has not been proved to be a risk factor for SCD in patients with LQTS.
- Abnormal ECG (prolonged QT) in asymptomatic relatives of known case.
- Prolonged QTc interval on ECG (QTc should be >460 ms in women and >440 ms in men).
- In case of congenital LQTS, the presentation of syncope or SCD is typically triggered by exercise and swimming in LQT1 patients, in LQT2 patients by emotion, pregnancy, or noise, and patients with LQT3 are at highest risk of events when at rest or asleep.

ETIOLOGY

- Cardiac repolarization abnormality.
- Congenital cause (hundreds of mutations on more than 10 genes have been identified).
- Most of the gene mutations affect function of ion channels leading to prolonged repolarization (i.e., sodium and potassium channels resulting in either increased Na^+ influx or decreased K^+ efflux). These mutations prolong depolarization and predispose the patient to torsades de pointes.
- Acquired causes:
  1. Drugs: dofetilide, ibutilide, bepridil, quinidine, procainamide, sotalol, amiodarone, ranolazine, disopyramide, phenothiazines and antiemetic agents (droperidol, domperidone), tricyclic antidepressants, antipsychotics (quetiapine, ziprasidone,

TABLE L1-4 Genetic Mutations in Congenital Long QT Syndrome

		Location	Gene	Current	Effect
Romano-Ward syndrome (autosomal-dominant inheritance)	*LQT1*	11p15.5	*KCNQ1* (K^+ channel)	I_{Ks}	↓ Function ↓ Repolarization
	LQT2	7q35-36	*KCNH2* (K^+ channel)	I_{Kr}	↓ Function ↓ Repolarization
	LQT3	3q21-24	*SCN5A* (Na^+ channel)	I_{Na}	↑ Function ↑ Depolarization
	LQT4	4q25-27	*ANK2*	Unknown	Unknown
	LQT5	21q22	*KCNE1* (K^+ channel, subunit minK)	I_{Ks}	↓ Function ↓ Repolarization
Jervell and Lange-Nielsen syndrome (autosomal-recessive inheritance)		11p15.5	*KvLQT1* (K^+ channel)	I_{Ks}	↓ Function ↓ Repolarization
		21q22	*KCNE* 1 (K^+ channel, subunit minK)	I_{Ks}	↓ Function ↓ Repolarization

From Crawford MH et al (eds): *Cardiology,* ed 2, St Louis, 2004, Mosby.

TABLE L1-5 Common Types of Long QT (LQT) Syndrome

	LQT1	LQT2	LQT3
Pathophysiology			
Gene	*KCNQ1 (KvLQT1)*	*KCNH2 (HERG)*	*SCN5A*
Protein	$K_v7.1$	$K_v11.1$	$Na_v1.5$
Ionic current	Decreased I_{Ks}	Decreased I_{Kr}	Increased late I_{Na}
Clinical Presentation			
Incidence of cardiac events	63%	46%	18%
Incidence of SCD	4%	4%	4%
Arrhythmia triggers	Emotional/physical stress (swimming, diving)	Emotional stress, arousal (alarm clock, telephone), rest	Sleep/rest
ECG	Broad-based T wave	Low-amplitude, bifid T wave	Long isoelectric ST segment
QT response to exercise	Attenuated QTc shortening and an exaggerated QTc prolongation during early and peak exercise	Normal QT during exercise but with exaggerated QT hysteresis	Supernormal QT shortening
Management			
Exercise restriction	+++	++	?
Response to beta blockers	+++	+++	?
Potassium supplement	+	++	+
Left cervicothoracic sympathectomy	++	++	++
Response to mexiletine	+	+	++

From Issa Z et al: *Clinical arrhythmology and electrophysiology,* ed 2, Philadelphia, 2012, Saunders.

iloperidone), citalopram, antihistamines, quinolones, azithromycin, astemizole or cisapride given with ketoconazole or erythromycin, clarithromycin, and antimalarials, particularly among patients with asthma or those using potassium-lowering medications; also common in patients receiving methadone.
2. Hypokalemia, hypomagnesemia, hypocalcemia (especially in patients with malabsorption syndrome).
3. Liquid protein diet.
4. Central nervous system lesions.
5. Ischemia.
6. Hypothyroidism.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

See "Syncope." Brugada's syndrome, arrhythmogenic right ventricular dysplasia, and LQTS are major causes of genetic sudden death syndromes (Fig. L1-13).

Diagnostic criteria for the congenital LQTS:

ECG Criteria	
QTc >480 ms	3 points
QTc 460-480 ms	2 points
QTc 450-460 ms (males)	1 point
Torsades de pointes	2 points
T-wave alternans	1 point
Notched T wave in three leads	1 point
Bradycardia	0.5 point
History	
Syncope with stress	2 points
Syncope without stress	1 point
Congenital deafness	0.5 point
Definite family history of long QT	1 point
Unexplained cardiac death in first-degree relative <30 yr	0.5 point

Total score = 4: definite LQTS; total score = 2 to 3: intermediate probability; total score = 1: low probability.

WORKUP

Cardiology referral is recommended for all cases.

Genetic analysis is an essential step for risk stratification of patients with congenital prolonged QT and is important for identification of potential mutation carriers within the proband family. There is evidence for gene-specific triggers of events and therapeutic efficacy. Molecular screening should become part of the routine clinical management of LQTS.

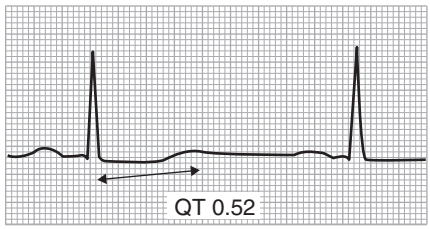
In relatives of known patients with LQTS or in young patients with syncope:

- Stress test may prolong the QT interval or cause T-wave alternans.
- Valsalva maneuver: may prolong the QT interval or cause T-wave alternans.
- Prolonged ECG monitoring with various stimulations aimed at increasing catecholamines and assess for QT prolongation (perform in a setting that can provide resuscitation with α- and β-antagonists readily available).
- Epinephrine-induced prolongation of the QT interval (epinephrine infusion QT stress test)
- Genetic analysis
  1. *LQT1* locus of *KCNQ1* potassium channel gene.
  2. *LQT2* locus of *KCNH2* potassium channel gene.
  3. *LQT3* locus of *SCN5A* sodium channel gene.
  4. These three variants account for >90% of all genotyped LQTS patients, whereas the remaining genes are responsible for a minority of cases.
- Risk stratification for each genetic variant on the basis of gender and QTc: groups are defined on the basis of the probability of the first cardiac event (syncope, cardiac arrest, or sudden death) before the age of 40 years or before therapy. QT interval duration was the strongest predictor of risk for cardiac events; a QTc exceeding 500 ms identifies patients with the highest risk.
  1. High risk (>50% of cardiac event): QTc ≥ 500 ms and LQT1 or LQT2, or male with LQT3.
  2. Moderate risk (30% to 50%): QTc <500 ms in male with LQT3 or in female with LQT2 or LQT3, and female with LQT3 with QTc ≥500 ms.
  3. Low risk (<30%): QTc <500 ms and LQT1 or male LQT2 with QTc <500 ms.
  4. Prophylactic treatment should be considered in all patients with moderate or high risk for cardiac events based on the above risk stratification scheme (Table L1-6).

Rx TREATMENT

NONPHARMACOLOGIC

- Focuses on exclusion of triggers of life-threatening arrhythmia—there are gene-specific triggers for symptoms:
  1. *LQT1* patients experience 90% of lethal events under physical and emotional stress. Swimming and diving should be avoided or performed under supervision.
  2. *LQT2* patients are at highest risk during arousal or emotions, also during sleep and at rest but not at all during exercise; avoid sudden or excessive acoustic stimuli, especially during sleep (e.g., avoid telephone and/or alarm clock in the proximity)—as opposed to *LQT3* patients, in whom 80% of the events occur at rest or while asleep.
- Avoid competitive sports.
- Implantation of an implantable cardioverter-defibrillator (ICD) is recommended according to the ACC/AHA guidelines for patients with a good functional status for more than 1 yr and the following conditions (Table L1-7):
  1. Survivors of cardiac arrest (class 1).
  2. Patients with syncope or ventricular tachycardia while receiving β-blockers (class IIa).
  3. Prophylaxis of SCD with use of β-blocker in patients with characteristics that suggest high risk (such as *LQT2* and *LQT3, QTc >500 ms*) (class IIb).



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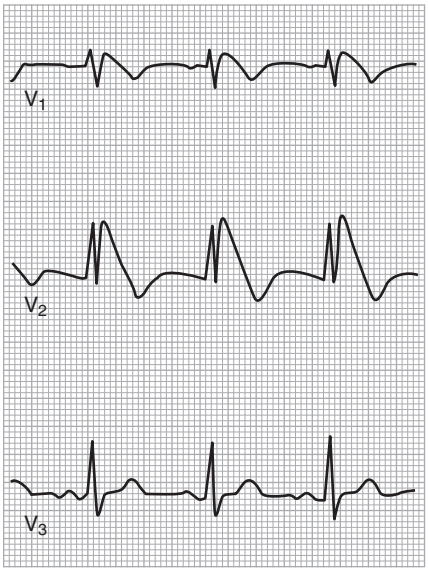

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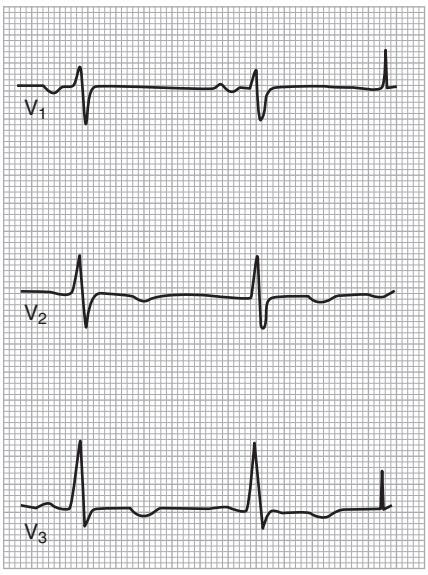

C

FIGURE L1-13 Sinus rhythm electrocardiogram findings in three genetic sudden death syndromes. A, QT prolongation during sinus rhythm in a patient with long QT syndrome. **B,** ST elevation in V_1 and V_2 in a patient with Brugada's syndrome. **C,** T wave inversion in V_1-V_3 in a patient with arrhythmogenic right ventricular dysplasia. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

TABLE L1-6 Cardiac Event Risk Stratification Scheme Based on Genes, Gender, and QTc

	QTc <500 ms		QTc ≥5500 ms	
Genetic Subtype	**Male**	**Female**	**Male**	**Female**
LQT1	Low	Low	High	High
LQT2	Low	Intermediate	High	High
LQT3	Intermediate	Intermediate	High	Intermediate

Probability of the first cardiac event (syncope, cardiac arrest, or sudden death) before the age of 40 years or before therapy. High = >50%, Intermediate = 30%-50%, Low = <30%.

TABLE L1-7 Management of Patients with Long QT Syndrome

Type of Syndrome	Management	Indication
Congenital	Beta-blockers	Asymptomatic patients, symptomatic patients (who do not have bronchospasm)
	Cervicothoracic sympathectomy	Refractory symptoms, especially in pediatric patients
	Cardiac pacing	Refractory symptoms associated with bradycardia, pauses
	Implantable cardioverter-defibrillator	Cardiac arrest, refractory syncope, prophylaxis for moderate- to high-risk patients for cardiac events
Acquired	Elimination of causative drug or condition	All patients
	Magnesium sulfate	Nonsustained ventricular tachycardia, torsades de pointes (even with a normal serum magnesium concentration)
	Administration of potassium (to keep serum K^+ >4.5 mEq/L)	Serum K^+ <4.5 mEq/L
	Maneuvers to increase heart rate (cardiac pacing, isoproterenol)	Bradycardia, arrhythmias refractory to magnesium sulfate

K^+, Potassium.
Adapted from Crawford MH et al (eds): *Cardiology*, ed 2, St Louis, 2004, Mosby.

PHARMACOLOGIC

- With few exceptions (mostly borderline QTc and *LQT1* males aged >25 to 30 yr), all mutation carriers should be treated because of the risk of SCD during first cardiac event. All symptomatic patients should be treated as well.
- Beta-blockers an initial therapy of choice—there are differential responses to β-blocker therapy among different genetic variants; especially effective among LQT1 patients. Studies showed the efficacy of β-blockers with an overall mortality <2% over a mean follow-up exceeding 5 yr.
- In patients with LQT3, mexiletine shortens the QTc and can be given with a β-blocker.
- From 20% to 30% of patients who continue to have symptoms on a β-blocker, the main options are either left cardiac sympathetic denervation (LCSD) or the prophylactic implantation of an ICD.
- In patients with frequent ICD shocks or in those with high risk for SCD where ICD placement cannot be performed, cardiac pacing and/or LCSD may be indicated.
- In patients with recurrent syncope and/or aborted cardiac arrest despite combined ICD and β-blocker, LCSD as adjunctive therapy can be performed.
- Correctable factors including electrolyte disorder—hypokalemia and hypomagnesemia—and avoidance of precipitating drugs that may further prolong the QT interval is mandatory. A complete list of drugs that can potentially prolong QT may be found at www.qtdrugs.org.
- For patients with acquired form and torsades de pointes, IV magnesium and atrial or ventricular pacing are initial choices.
- Table L1-7 summarizes management of patients with LQTS.

PROGNOSIS

In carefully treated patients, mortality is around 0.5% to 1% over 20 years.

The timing and frequency of syncope, QTc prolongation, and gender are predictive of risk for aborted cardiac arrest and SCD during adolescence. Higher risk is present in those with one or two or more episodes of syncope in the last 10 yr compared with those with no syncopal episodes, those with QTc >530 ms, and males aged 10 to 12 yr.

PEARLS & CONSIDERATIONS

COMMENTS

Family history should be assessed for a history of sudden death and other deaths that may have occurred as manifestations of LQTS (e.g., sudden infant death, drowning, and loss of consciousness while driving).

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Long QT Syndrome (Patient Information)
Torsades de Pointes (Related Key Topic)

AUTHOR: **BARRY FINE, M.D., Ph.D.**

SUGGESTED READINGS

Hobbs et al.: Risk of aborted cardiac arrest or sudden cardiac death during adolescence in the long QT syndrome, *JAMA* 296:1249, 2006.

Moss AJ et al.: Effectiveness and limitations of beta blocker therapy in congenital long QT syndrome, *Circulation* 101:616, 2000.

Napolitano C et al.: Genetic testing in the long QT syndrome, *JAMA* 294:2975, 2005.

Priori SG et al.: Risk stratification in the long-QT syndrome, *N Engl J Med* 348:2003, 1866.

Roden DM: Drug-induced prolongation of the QT interval, *N Engl J Med* 350:1013, 2004.

Roden DM: Long QT syndrome, *N Engl J Med* 358:169–176, 2008.

Schwartz PJ et al.: Left cardiac sympathetic denervation in the management of high-risk patients affected by the long QT syndrome, *Circulation* 109:2004, 1826.

Schwartz PJ et al.: Long QT syndrome-phenotype genotype considerations. In: (editor: Zipes D.) Cardiac electrophysiology. ed 4 Saunders: Philadelphia, pp. 651–667.

Schwartz PJ et al.: Pharmacological and non-pharmacological management of the Long QT syndrome: the rationale, *Pharmacol Ther* 131:171–177, 2011.

Zipes DP et al.: ACC/AHA/ESC 2006. Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology, American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death), *J Am Coll Cardiol* 48:e247–e346, 2006.

BASIC INFORMATION

DEFINITION

Lumbar disc syndrome includes diseases resulting from disc disorder, either herniation or degenerative change (spondylosis). Massive disk protrusion may rarely lead to paralysis in the lower extremity, a condition termed *cauda equina syndrome.* Gradual narrowing of the spinal canal (lumbar stenosis), usually from spondylosis, may also cause lower extremity symptoms.

SYNONYMS

Lumbago
Sciatica
Low back pain

ICD-9CM CODES

722.10	Lumbar disc displacement
724.02	Lumbar stenosis
344.60	Cauda equina syndrome
721.3	Lumbar spondylosis

ICD-10CM CODES

M51.26	Other intervertebral disc displacement, lumbar region
M48.06	Spinal stenosis, lumbar region
G83.4	Cauda equina syndrome
M47.817	Spondylosis without myelopathy or radiculopathy, lumbosacral region

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE

- Variable.
- At least one episode in 80% of adults.

PREDOMINANT SEX: Approximately equal.

PREDOMINANT AGE

- Herniation: 20 to 40 yr.
- Stenosis: >40 to 50 yr.
- Disc symptoms: rare <20 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Overlapping clinical syndromes that may result:
  1. Mild herniation without nerve root compression.
  2. Herniation with nerve root compression.
  3. Cauda equina syndrome.
  4. Chronic degenerative disease with or without leg symptoms.
  5. Spinal stenosis.
- Low back pain, often worsened by activity or coughing and sneezing.
- Local lumbar or lumbosacral tenderness.
- Paresthesias, usually unilateral (Fig. EL1-14).
- Restricted low back motion.
- Increased pain on bending toward affected side.
- Weakness and reflex changes (L4—knee jerk and quadriceps, L5—extensor hallucis longus, S1—ankle jerk and toe walking) (Table L1-8).
- Sensory examination usually not helpful.
- Lumbar stenosis that possibly produces symptoms (pseudoclaudication), which are often misinterpreted as being vascular. Pseudoclaudication usually recovers quickly with sitting or spine flexion. (Vascular disease is unaffected by spine position and is typically associated with atrophic skin changes and diminished pulses.)
- Positive straight leg raising test if nerve root compression is present.

ETIOLOGY

Multifactorial.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Soft tissue strain or sprain.
- Tumor.
- Degenerative arthritis of hip.
- Insufficiency fracture of hip or pelvis.

Section II describes the differential diagnosis of common low back pain syndromes. Table L1-9 differentiates the various causes of mechanical low back pain. Red flags for potentially serious underlying causes of low back pain are described in Table L1-10.

WORKUP

In most cases the diagnosis can be established on a clinical basis alone.

IMAGING STUDIES

- Imaging is not warranted for most patients with acute low back pain.
- Plain roentgenograms may be indicated within the first few weeks for persistent pain; they are usually normal in soft disc herniation, but with chronic degenerative disc disease loss of height of the disk space and osteophyte formation can occur.
- MRI (Fig. EL1-15) may be indicated in patients whose symptoms do not resolve or when other spinal pathology may be suspected.
- Electrodiagnostic studies may confirm the diagnosis or rule out peripheral nerve disorders.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Short course (3 to 5 days) of limited physical activity for acute disc herniation with leg pain.
- Physical therapy for modalities plus a careful gradual exercise program. Physical therapists generally use the McKenzie method (see http://www.mckenziemdt.org/approach.cfm or http://www.youtube.com/watch?v=bPz9A4TWMCQ) for the treatment of low back pain).
- Lumbosacral corset brace during rehabilitation process in conjunction with exercise program is beneficial only in some cases.
- Percutaneous electrical nerve stimulation may be beneficial in selected patients with chronic back pain.
- A recent trial of spinal manipulation therapy (SMT) and home exercise with advice (HEA) for subacute and chronic back-related leg pain (BRLP) revealed that SMT plus HEA was more effective than HEA alone after 12 weeks, but at 52 weeks the benefit was sustained only for global improvement, satisfaction, and medication use and not for self-reported low-lack pain, disability, and general health status.

ACUTE GENERAL Rx

- NSAIDs.
- Muscle relaxants for sedative effect.
- Analgesics.
- Injection therapy for low back pain and sciatica has limited clinical benefit and is generally not recommended. Epidural steroid injection for leg symptoms only in selected patients.

DISPOSITION

- Almost all lumbar disc syndromes improve with time.
- Recurrent episodes usually respond to medical management.
- Recovery from the rare paralytic event is often incomplete.

TABLE L1-8 Symptoms and Signs of Common Root Compression Syndromes Produced by Lumbar Disc Prolapse

Root Lesion	Pain	Sensory Loss	Motor Weakness	Reflex Lost	Other Signs
S1	From buttock down back of thigh and leg to ankle and foot	Sole of foot and posterior calf	Plantar flexion of ankle and toes	Ankle jerk	Diminished straight leg raising
L5	From buttock to lateral aspect of leg and dorsum of foot	Dorsum of foot and anterolateral aspect of lower leg	Dorsiflexion of foot and toes	None	As above
L4	Lateral aspect of thigh to medial side of calf	Medial aspect of calf and shin	Dorsiflexion and inversion of ankle; extension of knee	Knee jerk	Positive femoral stretch test

From Ballinger A: *Kumar & Clark's essentials of clinical medicine*, ed 6, Edinburgh, 2012, Saunders.

TABLE L1-9 Mechanical Low Back Pain

	Muscle Strain	Herniated Nucleus Pulposus	Osteoarthritis	Spinal Stenosis	Spondylolisthesis	Scoliosis
Age (yr)	20-40	30-50	>50	>60	20	30
Pain pattern location	Back (unilateral)	Back (unilateral)	Back (unilateral)	Leg (bilateral)	Back	Back
Onset	Acute	Acute (prior episodes)	Insidious	Insidious	Insidious	Insidious
Standing	↑	↓	↑	↑	↑	↑
Sitting	↓	↑	↓	↓	↓	↓
Bending	↑	↑	↓	↓	↑	↑
Straight leg	–	+	–	+ (stress)	–	–
Plain radiography	–	–	+	+	+	+

From Borenstein DG et al: *Low back pain: medical diagnosis and comprehensive management,* ed 2, Philadelphia, 1995, Saunders.

TABLE L1-10 Red Flags for Potentially Serious Underlying Causes of Low Back Pain

Spinal Fracture
- Significant trauma
- Prolonged glucocorticoid use
- Age >50 yr

Infection or Cancer
- History of cancer
- Unexplained weight loss
- Immunosuppression
- Injection drug use
- Nocturnal pain
- Age >50 yr

Cauda Equina Syndrome
- Urinary retention
- Overflow incontinence
- Fecal incontinence
- Bilateral or progressive motor deficit
- Saddle anesthesia

Spondyloarthritis
- Severe morning stiffness
- Pain improves with exercise, not rest
- Pain during second half of night
- Alternating buttock pain
- Age <40 yr

From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.

REFERRAL

- For orthopedic or neurosurgical consultation for intractable pain or significant neurologic deficit.
- Emergency referral for cauda equina syndrome.
- Table L1-11 summarizes indications for surgical referral.

PEARLS & CONSIDERATIONS

Red flags suggesting a more serious condition as a cause of the back pain include:
1. Fever.
2. History of malignancy.
3. Pain at rest.
4. Incontinence.
5. Sudden worsening in level of pain.
6. Weight loss.
7. Significant motor loss, especially if associated with saddle anesthesia.

COMMENTS

- Surgery is most consistently helpful when leg pain (not back pain) predominates.
- No substantial benefit has been shown with oral steroids, traction, epidural corticosteroid injections, or lumbar support.

TABLE L1-11 Indications for Surgical Referral

Disk Herniation
- Cauda equina syndrome (emergency)
- Serious neurologic deficit
- Progressive neurologic deficit
- Greater than 6 weeks of disabling radiculopathy (elective)

Spinal Stenosis
- Serious neurologic deficit
- Progressive neurologic deficit
- Persistent and disabling pseudoclaudication (elective)

Spondylolisthesis
- Serious or progressive neurologic deficit

From Firestein G.S.; et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Lumbar Disc Syndrome (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Background:

Questions remain as to the effect that obesity has on patients managed for symptomatic lumbar disc herniation. The purpose of this study was to determine if obesity affects outcomes following the treatment of symptomatic lumbar disc herniation.

Methods:

An as-treated analysis was performed on patients enrolled in the Spine Patient Outcomes Research Trial for the treatment of lumbar disc herniation. A comparison was made between patients with a body mass index of <30 kg/m^2 (nonobese) (n = 854) and those with a body mass index of ≥30 kg/m2 (obese) (n = 336). Baseline patient demographic and clinical characteristics were documented. Primary and secondary outcomes were measured at baseline and at regular follow-up time intervals up to four years. The difference in improvement from baseline between operative and nonoperative treatment was determined at each follow-up period for both groups.

Results:

At the time of the four-year follow-up evaluation, improvements over baseline in primary outcome measures were significantly less for obese patients as compared with nonobese patients in both the operative treatment group (Short Form-36 physical function, 37.3 compared with 47.7 points [$P < .001$], Short Form-36 bodily pain, 44.2 compared with 50.0 points [$P = .005$], and Oswestry Disability Index, −33.7 compared with −40.1 points [$P < .001$]) and the nonoperative treatment group (Short Form-36 physical function, 23.1 compared with 32.0 points [$P < .001$] and Oswestry Disability Index, −21.4 compared with −26.1 points [$P < .001$]). The one exception was that the change from baseline in terms of the Short Form-36 bodily pain score was statistically similar for obese and nonobese patients in the nonoperative treatment group (30.9 compared with 33.4 points [$P = .39$]). At the time of the four-year follow-up evaluation, when compared with nonobese patients who had been managed operatively, obese patients who had been managed operatively had significantly less improvement in the Sciatica Bothersomeness Index and the Low Back Pain Bothersomeness Index, but had no significant difference in patient satisfaction or self-rated improvement. In the present study, 77.5% of obese patients and 86.9% of nonobese patients who had been managed operatively were working a full or part-time job. No significant differences were observed in the secondary outcome measures between obese and nonobese patients who had been managed nonoperatively. The benefit of surgery over nonoperative treatment was not affected by body mass index.

Conclusions:

Obese patients realized less clinical benefit from both operative and nonoperative treatment of lumbar disc herniation. Surgery provided similar benefit over nonoperative treatment in obese and nonobese patients. Ⓐ

Abstract[2]

Background:

A common complication of spine surgery is postoperative surgical site infection. Recent evidence related to the identification and prevention of such infection was reviewed.

Complications and Interventions. Surgical site infections are costly events associated with no specific identifying features because of the many surgical techniques and approaches as well as patient characteristics and risks for infection. Most cause increased pain after surgery, new-onset neurological signs, and inflammatory changes around the surgical wound, but some produce no overt signs. Infection is confirmed by measuring inflammatory serum mediator levels or using radiographs, magnetic resonance images (MRIs), or other imaging studies as indicated.

Nasal and skin colonization with methicillin-sensitive *Staphylococcus aureus* can be identified using rapid polymerase chain reaction detection and other screening techniques. Treatment is topical intranasal mupirocin two to three times a day for up to 5 days, which eradicates the bacteria and may lower the risk of surgical site infection. Routine scrub-paint solutions of povidone-iodine or combined solutions are standard protocol to eradicate skin flora. Adhesive drapes have not proved effective in reducing the infection rate in spine surgery patients.

Topical antibiotics can be administered directly into wounds. Usually vancomycin is used because it has a slow resorption, low systemic effect, and no local toxicity but can substantially decrease surgical site infections in posterior spine procedures.

Preoperative, early, and postoperative measurement of glucose levels is essential because unrecognized or poorly controlled diabetes carries a higher perioperative risk of complications. Blood glucose control should be optimal, with careful preoperative preparation and multidisciplinary management advised. Blood glucose levels should be maintained at between 90 and 130 mg/dL preprandially and hemoglobin A1C level should be <7.0%.

The spinal implants and instruments used require meticulous cleaning to remove the durable tissues involved in spine surgery from instruments. Mechanical washing by operating-room assistants is vital both during and after surgery. Sterile-processing staff should undergo rigorous training regarding adequate cleaning techniques. Prepackaged sterile implants may also offer protection against infection.

Uncontrolled hemorrhage is more likely in patients with preexisting coagulopathy or other bleeding diathesis and in more complex cases. Allogeneic blood transfusions subject patients to risks for immunologic reactions and infectious disease transmission. Strategies to reduce bleeding include ensuring the abdomen is positioned free of undue pressure to reduce venous oozing into the epidural space, using electrocautery and topical hemostatic agents, using hypotensive and hemodilution anesthetic methods during lumbar spine procedures, injecting recombinant human erythropoietin (when advisable), and using antifibrinolytic agents to slow plasmin-mediated fibrin clot dissolution. Aprotinin, a naturally occurring compound, is associated with more renal toxicity than tranexamic acid and other synthetic lysine analogues and is no longer routinely used. If considerable blood loss is anticipated, intraoperative blood salvage techniques may be employed. The hemostatic regimen chosen should fit the specific situation.

Lumbar spine surgery may predispose the patient to deep vein thrombosis (DVT) and thromboembolic events. The prophylactic measures used against DVT range from mechanical compression stockings to pharmacologic anticoagulation with aspirin, warfarin, or unfractionated or low-molecular-weight heparin. Inferior vena cava filters are a safe, effective method for preventing pulmonary embolism and can be removed when no longer needed. The type of prophylaxis should be the physician's choice.

Complications related to positioning can be avoided by careful consideration of the expected operative time, anticipated amount of blood loss, and complexity of the surgery. The skin, eyes, nerve tissues, and underlying soft tissues can be injured if the patient is not properly positioned and adequately protected from the effects of pressure. Complications associated with poor positioning include peripheral nerve injury, nerve palsies, nerve compression, pain, weakness or numbness, compartment syndrome, and perioperative blindness.

Conclusions:

It is impossible to completely eradicate all complications from lumbar spine surgery, but efforts can be made to minimize their occurrence. It is critical to identify the causes of the various adverse events and manage them effectively.

Evidence-Based Reference

1. Jenis LG, Hsu WK, O'Brien J, et al.: Recent advances in the prevention and management of complications associated with routine lumbar spine surgery, *J Bone Joint Surg Am* 95:944–950, 2013. Ⓑ

SUGGESTED READINGS

Anderson PA et al.: Randomized controlled trials of the treatment of lumbar-disk herniation: 1983-2007, *J Acad Orthop Surg* 16:566, 2008.

Bronfort G et al.: Spinal manipulation and home exercise with advice for subacute and chronic back-related leg pain, *Ann Intern Med* 161:381–391, 2014.

Casazza BA: Diagnosis and treatment of acute low back pain, *Am Fam Physician* 85(4):343–350, 2012.

Chou R et al.: Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society, *Ann Intern Med* 147:478, 2007.

Cole BJ, Schumacher HR: Injectable corticosteroids in modern practice, *J Am Acad Orthop Surg* 13:37, 2005.

Dreyfuss P et al.: Sacroiliac joint pain, *J Am Acad Orthop Surg* 12:255, 2004.

Gregory DS et al.: Acute lumbar disc pain: navigating evaluation and treatment choices, *Am Fam Physician* 78(7):835–842, 2008.

Haig AJ et al.: Electromyographic and magnetic resonance imaging to predict lumbar stenosis, low back pain, and no back symptoms, *J Bone Joint Surg Am* 89A:358, 2007.

Johansson AC et al.: A prospective study of cognitive behavioral factors as predictors of pain, disability, and quality of life one year after lumbar disc surgery, *Disabil Rehabil* 32:521, 2010.

Katz JN: Lumbar disc disorders and low-back pain: socioeconomic factors and consequences, *J Bone Joint Surg Am* 88A(suppl 2):21, 2006.

Lee DH et al.: Clinical nerve conduction and needle electromyography studies, *J Am Acad Orthop Surg* 12:276, 2004.

Madigan L et al.: Management of symptomatic lumbar degenerative disc disease, *J Am Acad Orthop Surg* 17:102, 2009.

Shen FH et al.: Nonsurgical management of acute and chronic low back pain, *J Am Acad Orthop Surg* 14:477, 2006.

Spector LR et al.: Cauda equina syndrome, *J Am Acad Orthop Surg* 16:471, 2008.

Thomas KC et al.: Outcome evaluation of surgical and non surgical management of lumbar disc protrusion causing radiculopathy, *Spine* 32:1414, 2007.

Tribus CB: Degenerative lumbar scoliosis: evaluation and management, *J Am Acad Orthop Surg* 11:174, 2003.

Young IA et al.: The use of lumbar epidural/transforaminal steroids for managing spinal disease, *J Am Acad Orthop Surg* 15:228, 2007.

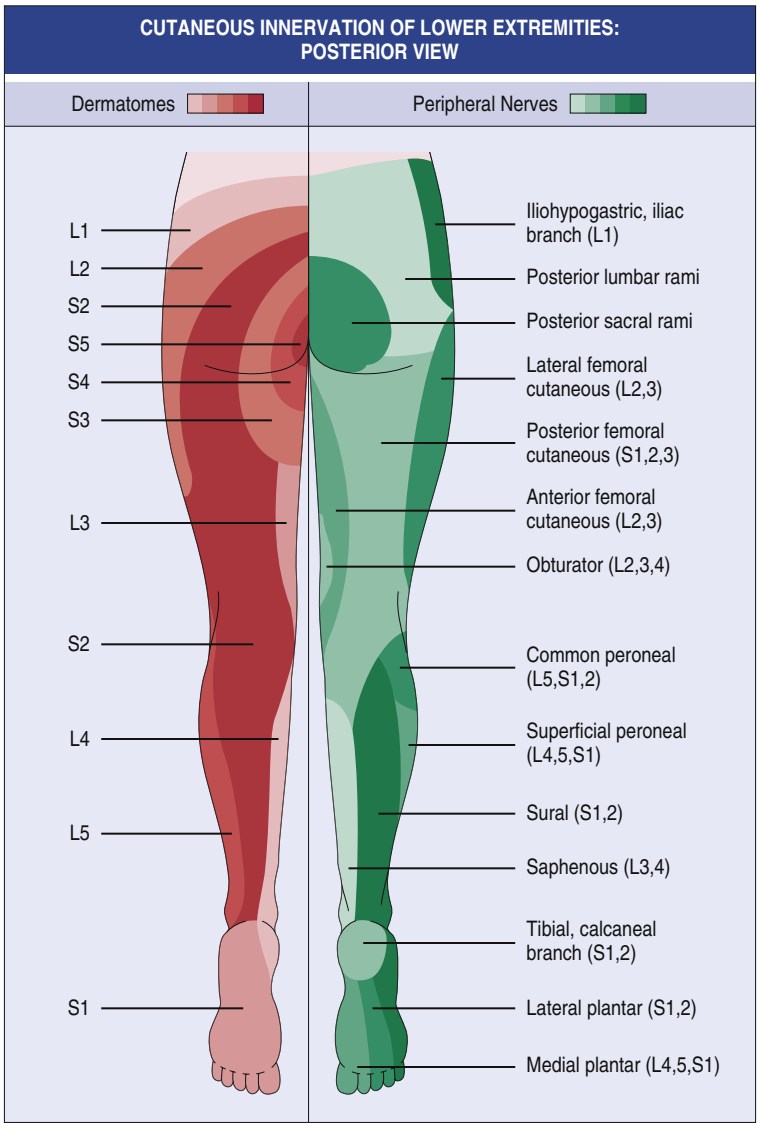

FIGURE EL1-14 Lumbar disk syndrome. Cutaneous sensory innervation. Posterior view of lower extremities illustrating skin areas supplied by nerve roots *(left)* and peripheral nerves *(right).* (From Hochberg M.C.; et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

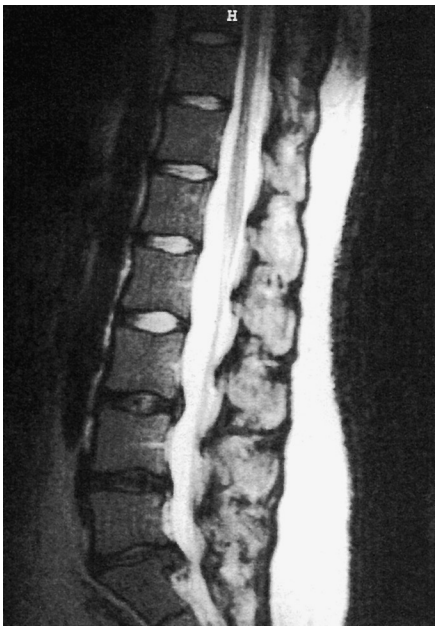

FIGURE EL1-15 MRI showing a prolapsed L5/S1 disk. (From Carr A, Hamilton W: *Orthopedics in primary care,* ed 2, Philadelphia, 2005, Saunders.)

BASIC INFORMATION

DEFINITION

A primary lung neoplasm is a malignancy arising from lung tissue. The World Health Organization distinguishes 12 types of pulmonary neoplasms. The major types are squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and large cell carcinoma. However, the crucial difference in the diagnosis of lung cancer is between small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC) because the prognosis and therapeutic approach are different.

ADENOCARCINOMA: Represents 35% to 40% of lung carcinomas; frequently located in mid-lung and periphery; initial metastases are to lymphatics; frequently associated with peripheral scars; adenocarcinoma is described as preinvasive, minimally invasive, or invasive

SQUAMOUS CELL (EPIDERMOID): 20% to 30% of lung cancers; central location; metastasis by local invasion; frequent cavitation and obstructive phenomena

SMALL CELL (OAT CELL): 20% of lung carcinomas; central location; metastasis through lymphatics; associated with lesion of the short arm of chromosome 3; high cavitation rate

LARGE CELL: 10% to 15% of lung carcinomas; frequently located in the periphery; metastasis to central nervous system and mediastinum; rapid growth rate with early metastasis

LEPIDIC-PREDOMINANT PATTERN (BRONCHOALVEOLAR): 5% of lung carcinomas; frequently located in the periphery; may be bilateral; initial metastasis through lymphatic, hematogenous, and local invasion; no correlation with cigarette smoking; cavitation rare

SYNONYMS

Lung cancer

ICD-9CM CODES

162.9 Malignant neoplasm of bronchus and lung, unspecified

ICD-10CM CODES

C34.90 Malignant neoplasm of unspecified part of unspecified bronchus or lung

EPIDEMIOLOGY & DEMOGRAPHICS

- Lung cancer is responsible for >30% of cancer deaths in males and >25% of cancer deaths in females. It has been the most common cancer in the world since 1985 and is the leading cause of cancer-related death.
- Tobacco smoking is implicated in 90% of cases; second-hand smoke is responsible for approximately 20% of cases.
- There are >200,000 new cases of lung cancer yearly in the U.S., most occurring at age >50 yr (<4% in patients <40 yr).
- Among women there has been a 600% increase in incidence of lung cancer during the past 80 years. The rates of death among women with lung cancer in the U.S. are the highest in the world.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Weight loss, fatigue, fever, anorexia, dysphagia
- Cough, hemoptysis, dyspnea, wheezing
- Chest, shoulder, and bone pain
- Paraneoplastic syndromes (see Table L1-12):
  1. ***Lambert-Eaton myasthenic syndrome:*** myopathy involving proximal muscle groups
  2. Endocrine manifestations: hypercalcemia, ectopic adrenocorticotropic hormone, syndrome of inappropriate excretion of adrenocorticotropic hormone
  3. Neurologic: subacute cerebellar degeneration, peripheral neuropathy, cortical degeneration
  4. Musculoskeletal: polymyositis, clubbing, hypertrophic pulmonary osteoarthropathy
  5. Hematologic or vascular: migratory thrombophlebitis, marantic thrombosis, anemia, thrombocytosis, or thrombocytopenia
  6. Cutaneous: acanthosis nigricans, dermatomyositis
- Pleural effusion (10% of patients), recurrent pneumonias (from obstruction), localized wheezing
- ***Superior vena cava syndrome:***
  1. Obstruction of venous return of the superior vena cava is most commonly caused by bronchogenic carcinoma or metastasis to paratracheal nodes.
  2. The patient usually reports headache, nausea, dizziness, visual changes, syncope, and respiratory distress.
  3. Physical examination reveals distention of thoracic and neck veins, edema of face and upper extremities, facial plethora, and cyanosis.
- ***Horner's syndrome:*** constricted pupil, ptosis, facial anhidrosis caused by spinal cord damage between C8 and T1 as a result of a superior sulcus tumor (bronchogenic carcinoma of the extreme lung apex)
- ***Pancoast tumor:*** a superior sulcus tumor associated with ipsilateral Horner's syndrome and shoulder pain

ETIOLOGY

- Tobacco abuse; the chance of developing lung cancer for a 40-pack-year persistent smoker is 20 times that of someone who never smoked
- Environmental agents (e.g., radon) and industrial agents (e.g., ionizing radiation, asbestos, nickel, uranium, vinyl chloride, chromium, arsenic, coal dust)
- Lung cancer susceptibility and risk increased in inherited cancer syndromes caused by germ-line mutations in p53, retinoblastoma, and germ-line mutation in the epidermal growth factor receptor *(EGFR)* gene; also an association between single-nucleotide polymorphism variation at 15q24-15q25.1 and susceptibility to lung cancer

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Pneumonia
- Tuberculosis (TB)
- Metastatic carcinoma to the lung
- Lung abscess
- Granulomatous disease
- Carcinoid tumor
- Mycobacterial and fungal diseases
- Sarcoidosis
- Viral pneumonitis
- Benign lesions that simulate thoracic malignancy:

TABLE L1-12 Paraneoplastic Syndromes Associated with Bronchogenic Carcinoma

Syndrome	Cell Type	Mechanism
Hypertrophic pulmonary osteoarthropathy and clubbing	All except small cell	Unknown
Hyponatremia	Small cell most common; may be any type	SIADH, ectopic antidiuretic hormone production by tumor
Hypercalcemia	Usually squamous cell	Bone metastases, osteoclast-activating factor, parathyroid hormone–like hormone, prostaglandins
Cushing's syndrome	Usually small cell	Ectopic ACTH production
Lambert-Eaton myasthenic syndrome	Usually small cell	Voltage-sensitive calcium channel antibodies in >75%; affects presynaptic neuronal calcium channel activity
Other neuromyopathic disorders	Small cell most common; may be any type	Antineuronal nuclear antibodies, also known as anti-Hu; others unknown
Thrombophlebitis	All types	Unknown

ACTH, Adrenocorticotropic hormone; *SIADH,* syndrome of inappropriate secretion of antidiuretic hormone.
From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.

1. Lobar atelectasis: pneumonia, TB, chronic inflammatory disease, allergic bronchopulmonary aspergillosis
2. Multiple pulmonary nodules: septic emboli, Wegener's granulomatosis, sarcoidosis, rheumatoid nodules, fungal disease, multiple pulmonary atrioventricular fistulas
3. Mediastinal adenopathy: sarcoidosis, lymphoma, primary TB, fungal disease, silicosis, pneumoconiosis, drug-induced (e.g., phenytoin, trimethadione)
4. Pleural effusion: congestive heart failure, pneumonia with parapneumonic effusion, TB, viral pneumonitis, ascites, pancreatitis, collagen-vascular disease

WORKUP

Workup generally includes chest CT, positron-emission tomographic (PET) scan, and tissue biopsy. Lab tests should include CBC, serum calcium, and liver chemistry studies. Diagnosis and staging of lung cancer should be performed simultaneously to minimize invasive testing.

LABORATORY TESTS

Obtain tissue diagnosis. Various modalities are available:

- Biopsy of any suspicious lymph nodes (e.g., supraclavicular node)
- Flexible fiberoptic bronchoscopy: brush and biopsy specimens are obtained from any visualized endobronchial lesions
- Transbronchial needle aspiration: done with a special needle passed through the bronchoscope; this technique is useful to sample mediastinal masses or paratracheal lymph nodes
- Transthoracic fine-needle aspiration biopsy with fluoroscopic or CT scan guidance to evaluate peripheral pulmonary nodules
- Mediastinoscopy and anteromedial sternotomy in suspected tumor involvement of the mediastinum
- Pleural biopsy in patients with pleural effusion
- Thoracentesis of pleural effusion and cytologic evaluation of the obtained fluid: may confirm diagnosis

IMAGING STUDIES

- Chest x-ray (Fig. L1-16): The radiographic presentation often varies with the cell type. Pleural effusion, lobar atelectasis, and mediastinal adenopathy can accompany any cell types.
- CT scan of chest (Fig. L1-17) is performed to evaluate mediastinal and pleural extension of suspected lung neoplasms. The chest CT should include liver and adrenal glands (common sites of metastases). CT or MRI of brain should be considered in a patient presenting with neurologic symptoms (e.g., headaches, vision disturbances).
- PET with ^{18}F-fluorodeoxyglucose (^{18}FDG-PET) (Fig. L1-18), a metabolic marker of malignant tissue, is superior to CT scan in detecting mediastinal and distant metastases in NSCLC. It is useful for preoperative staging of NSCLC.
- The use of PET-CT for preoperative staging of NSCLC reduces both the total number of thoracotomies and the number of futile thoracotomies but does not affect overall mortality.
- The combination of endoluminal ultrasound (EUS) and endobronchial ultrasound (EBUS) with fine-needle aspiration has been reported to have a 93% sensitivity and 97% specificity for establishing the presence of mediastinal disease in lung cancer patients.

STAGING

After confirmation of diagnosis, patients should undergo staging:

1. The international staging system is the most widely accepted staging system for NSCLC. In this system, stage I (N0 [no lymph node involvement]) and stage II (N1 [spread to ipsilateral bronchopulmonary or hilar lymph nodes]) include localized tumors for which surgical resection is the preferred treatment. Stage III is subdivided into IIIA (potentially resectable) and IIIB. The surgical management

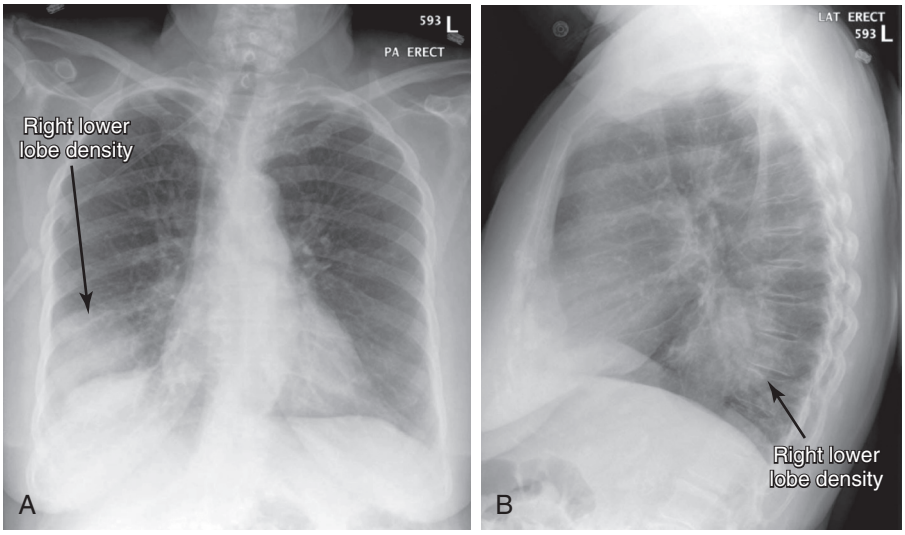

FIGURE L1-16 Lung neoplasm, primary. Lung mass presenting with hemoptysis. **A,** Posterior-anterior (PA) chest x-ray. **B,** Lateral chest x-ray. This 83-year-old female presented with hemoptysis of a quarter-sized clot. Her posterior-anterior chest x-ray shows a rounded right lower lobe density. On the lateral view, this is visible in the retrocardiac space. This density measures 7.6 cm in diameter. Pneumonia, neoplasm, or abscess could have this appearance on chest x-ray. Computed tomography was performed to further delineate the pathology (see Fig. L1-17). (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

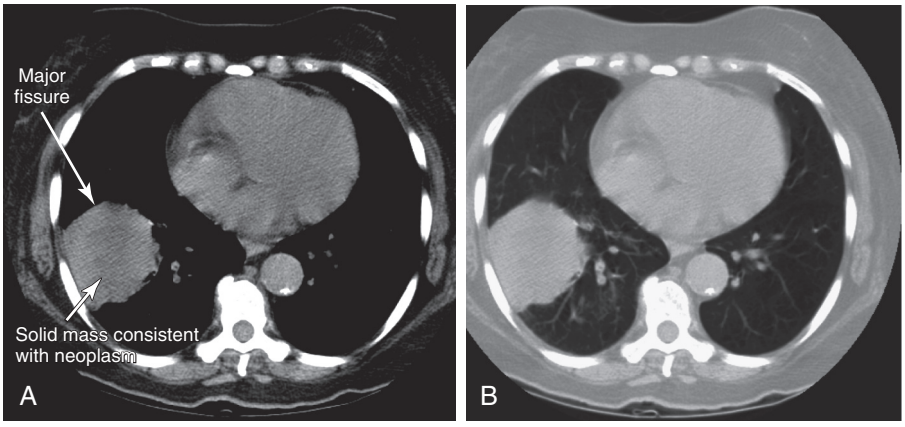

FIGURE L1-17 Lung neoplasm, primary. Lung mass presenting with hemoptysis. Same patient as in Fig. L1-16. Noncontrast computed tomography was performed (contrast was withheld as a consequence of the patient's renal dysfunction) and shows a 6 by 6 cm round lesion abutting the oblique fissure (also called the major fissure) and lateral chest wall. **A,** Soft tissue windows. **B,** Lung windows. On soft tissue windows, the center appears slightly darker, indicating lower density that may represent central necrosis. If IV contrast had been given, an area of necrosis would have failed to enhance. Infection or infarction is technically possible, but a pulmonary neoplasm is the most likely explanation for this lesion. Biopsy showed this to be a moderately differentiated squamous cell carcinoma. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

of stage IIIA disease (N2 [involvement of ipsilateral mediastinal nodes]) is controversial. Only 20% of N2 disease is considered minimal disease (involvement of only one node) and technically resectable. Stage IV indicates metastatic disease. The pathologic staging system uses a tumor/nodal involvement/metastasis system.

2. In patients with SCLC, a more practical accepted staging system is the one developed by the Veterans Administration Lung Cancer Study Group. This system contains two stages:
   a. Limited-stage disease: confined to the regional lymph nodes and to one hemithorax (excluding pleural surfaces)
   b. Extensive-stage disease: spread beyond the confines of limited-stage disease
3. Pretreatment staging procedures for lung cancer patients, in addition to complete history and physical examination, generally include the following tests:
   a. Chest radiograph (posteroanterior and lateral), ECG
   b. Laboratory evaluation: complete blood count, complete metabolic panel, arterial blood gases, pulse oximetry. The identification of molecular signatures of lung cancer to predict prognosis with data from microarray and/or reverse-transcription polymerase chain reaction analysis has been validated in recent trials. A five-gene signature (*DUSP6, MMD, STAT1, ERBB3,* and *LCK*) is closely associated with relapse-free and overall survival among patients with NSCLC. Anaplastic lymphoma kinase (ALK) translocation is found in about 4% to 5% of lung cancers. Detection of mutations in epidermal growth factor receptor (EGFR) in circulating tumor cells from the blood of patients with lung cancer offers the possibility of monitoring changes in epithelial tumor genotypes during the course of treatment
   c. Pulmonary function studies
   d. CT scan of chest and PET scan: a recent Dutch trial revealed a 51% relative reduction in futile thoracotomies for patients with suspected NSCLC who underwent preoperative assessment with PET with the tracer ^{18}FDG-PET in addition to conventional workup
   e. Mediastinoscopy or anterior mediastinotomy in patients being considered for possible curative lung resection
   f. Biopsy of any accessible suspect lesions
   g. CT scan of liver and brain; radionuclide scans of bone in all patients with small cell carcinoma of the lung and patients with NSCLC neoplasms suspected of involving these organs
   h. Bone marrow aspiration and biopsy only in selected patients with small cell carcinoma of the lung. In the absence of an increased lactate dehydrogenase or cytopenia, routine bone marrow examination not recommended
   i. Newer technologies in preoperative staging include endoscopic bronchial ultrasonography and esophageal ultrasonography to guide biopsies; however, cervical mediastinoscopy is standard criterion in preoperative nodal staging (sensitivity >93%, specificity >95%)

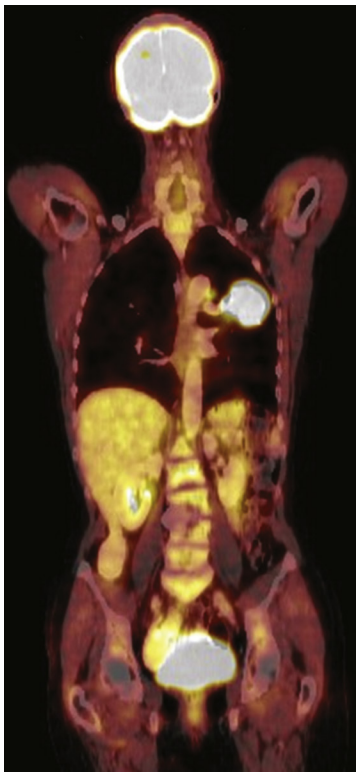

FIGURE L1-18 Whole-body coronal [^{18}F]fluoro-2-deoxy-d-glucose positron emission tomography computed tomography (^{18}FDG-PET-CT) shows intense left upper lobe tracer accumulation (*arrow*) in a patient with bronchogenic carcinoma. Note normal high tracer activity within the brain (*arrowheads*). (From Mason, RJ: *Murray & Nadel's textbook of respiratory medicine*, 5th ed, Philadelphia, 2010, Saunders.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Nutritional support
- Avoidance of tobacco and other substances toxic to the lungs
- Supplemental O_2 prn

ACUTE GENERAL Rx

NON–SMALL CELL CARCINOMA

- Surgical resection is the best hope for cure in patients with operable NSCLC (stage I or II when the patient is a surgical candidate). Lobectomy is the best standard surgical approach. Lesser resections may be necessary in patients with marginal pulmonary reserve. Video-assisted thoracic surgery (VATS) is helpful in decreasing morbidity and shortening hospital stay.
  1. Surgical resection is indicated in patients with limited disease (not involving mediastinal nodes, ribs, pleura, or distant sites). This represents approximately 15% to 30% of diagnosed cases. Stereotactic ablative radiotherapy is a reasonable option for patients with localized NSCLC who are too frail for surgical correction.
  2. Preoperative evaluation includes review of cardiac status (e.g., recent myocardial infarction, major arrhythmias) and evaluation of pulmonary function (to determine if the patient can tolerate any loss of lung tissue). Pneumonectomy is possible if the patient has a preoperative FEV_1 = 2 L or if the maximal voluntary ventilation is >50% of predicted capacity. Individuals with FEV_1 >1.5 L are suitable for lobectomy without further evaluation unless there is evidence of interstitial lung disease or undue dyspnea on exertion. In that case, carbon dioxide diffusion in the lung (DLCO) should be measured. If the DLCO is <80% predicted normal, the individual is not clearly operable.
  3. Preoperative chemotherapy should be considered in patients with more advanced disease (stage IIIA) who are being considered for surgery because it increases the median survival time in patients with NSCLC compared with the use of surgery alone. Gene expression profiles that predict the risk of recurrence in patients with early stage (IA) NSCLC have been identified. These patients are at high risk of recurrence and may also benefit from adjuvant chemotherapy.
  4. Postoperative adjuvant chemotherapy (chemotherapy given after surgical resection of an apparently localized tumor to eradicate occult metastases) with vinorelbine plus cisplatin significantly increases 5-yr survival (69% vs. 54%) in patients with completely resected stage IB or stage II NSCLC and good performance status. Adjuvant chemotherapy is generally indicated for patients with resected stages IIA through IIIA.
- Treatment of unresectable NSCLC:
  1. Radiotherapy can be used alone or in combination with chemotherapy; it is used primarily for treatment of central nervous system and skeletal metastases, superior vena cava syndrome, and obstructive atelectasis. Although thoracic radiotherapy is generally considered standard therapy for stage 3 disease, it has limited effect on survival. Palliative radiotherapy should be delayed until symptoms occur because immediate therapy offers no advantage over delayed therapy and results in more adverse events from the radiotherapy. Conventional radiotherapy fails to durably control the primary lung tumor in nearly 70% of patients and 2-yr survival is less than 40%. Stereotactic body radiation (SBRT) uses several highly focused radiation beams to deliver high doses in 15 treatments and appears to be more effective than conventional radiotherapy, with a survival rate of 55.8% at 3 yr for inoperable early stage lung cancer.
  2. Chemotherapy remains the mainstay of treatment for advanced stage IIIB and stage IV NSCLC. (stage I or II when

the patient is a surgical candidate). Lobectomy is the best standard surgical approach. Lesser resections may be necessary in patients with marginal pulmonary reserve. Video-assisted thoracic surgery (VATS) is helpful in decreasing morbidity and shortening hospital stay. A platinum-based treatment is recommended for fit patients, and single agents can be offered in elderly patients and in those with poor performance status. Various combination regimens are available. Current drugs of choice are paclitaxel plus either carboplatin or cisplatin, cisplatin plus vinorelbine, gemcitabine plus cisplatin, and carboplatin or cisplatin plus docetaxel. The overall results are disappointing, and none of the standard regimens for NSCLC is clearly superior to the others. The addition of bevacizumab to paclitaxel plus carboplatin results in significant survival benefit but carries an increased risk of treatment-related death. Gefitinib and erlotinib are oral inhibitors of *EGFR* tyrosine kinase. Activating mutations in the *EGFR* gene confer hypersensitivity to these medications. Sensitivity of lung neoplasms to these agents is seen primarily in tumors with somatic mutations in the tyrosine kinase domain (more common in adenocarcinomas found in patients who never smoked and in Asian patients). Recent trials revealed that gefitinib is superior to carboplatin-paclitaxel as an initial treatment for pulmonary adenocarcinoma among nonsmokers or former smokers in East Asia. In these patients the presence in the tumor of a mutation of the *EGFR* gene was a strong predictor of a better outcome with gefitinib. The National Comprehensive Cancer Network (NCCN) recognizes erlotinib as an option for second- or third-line therapy in patients with advanced NSCLC who have a performance status of 0 to 3. It also recommends erlotinib monotherapy as first line for patients with an EGFR mutation. Erlotinib can also be used as a salvage treatment in this subgroup and as a maintenance agent for patients with stable or responsive disease after first-line platinum-based chemotherapy. Oncogenic fusion genes consisting of EML4 and anaplastic lymphoma kinase (ALK) are present in a subgroup of NSCLCs, representing 4% to 5% of such tumors. The inhibition of ALK in lung tumors with crizotinib, an orally available small-molecule inhibitor of the ALK tyrosine kinase, has resulted in tumor shrinkage and significant prolonged progression-free survival. Crizotinib was recently approved by the FDA for locally advanced or metastatic NSCLC with ALK translocation, which is found in about 5% of lung cancers. Recent trials[1] have shown that crizotinib is superior to standard chemotherapy in patients with previously treated advanced non–small-cell cancer with ALK rearrangement. Approximately 2% of patients with NSCLC have tumors with genetic rearrangements involving the gene encoding ROS1 proto-oncogenic receptor tyrosine kinase (ROS1). Recent trials have have shown that crizotimb has marked antitumor activity in these patients. Recent trials have shown that ceritinib, a new ALK inhibitor has shown greater anti-tumor potency than crizotinib. Ceritinib was highly active in patients with advanced, ALK–rearranged NSCLC, including those who had had disease progression during crizotinib treatment, regardless of the presence of resistance mutations in ALK.

3. The addition of chemotherapy to radiotherapy improves survival in patients with locally advanced, unresectable NSCLC. The absolute benefit is relatively small, however, and should be balanced against the increased toxicity associated with the addition of chemotherapy.
4. Early initiation of palliative care focusing on management of symptoms, psychosocial support, and assistance with decision making in patients with metastatic NSCLC leads to improved quality of life, longer survival, and less use of aggressive end-of-life care.

SMALL CELL LUNG CANCER:

- Limited-stage disease: standard treatments include thoracic radiotherapy and chemotherapy (cisplatin and etoposide).
- Extensive-stage disease: standard treatments include combination chemotherapy (cisplatin or carboplatin plus etoposide or combination of irinotecan and cisplatin).
- Prophylactic cranial irradiation for patients in complete remission to decrease the risk of central nervous system metastasis.
- Despite high initial response rates, most patients eventually relapse. Topotecan may be an option for these patients.

DISPOSITION

- The 5-yr survival of patients with NSCLC when the disease is resectable is approximately 30%.
- Median survival time in patients with limited-stage disease and SCLC is 15 mo; in patients with extensive stage disease, it is 9 mo. Among patients with metastatic NSCLC, early palliative care results in longer survival and significant improvements in both quality of life and mood.
- Methylation of the promoter region of certain genes (*P16, CDH13, APC,* and *RASSF1A*) in a resected NSCLC specimen is associated with recurrence of the tumor.

[1]Shaw AT et al: Crizotinib versus chemotherapy in advanced ALK-positive lung cancer, *N Engl J Med* 368:2385-2394, 2013.

PEARLS & CONSIDERATIONS

COMMENTS

- CT screening with use of low-dose computed tomography (LDCT) for detection of lung cancer among persons with a heavy history of smoking increases the percentage of lung cancer cases that are diagnosed in stage 1 and reduces mortality from lung cancer. The National Lung Screening Trial (NLST) showed that lung cancer screening with LDCT resulted in a 20% reduction in mortality from lung cancer. New guidelines from the American College of Chest Physicians, the American Society of Clinical Oncology, and the National Comprehensive Cancer Network recommend annual LDCT for those who are current or former smokers aged 55-74. The U.S. Preventive Services Task Force (USPSTF) recommends annual screening for lung cancer with LDCT in adults aged 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. Screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery.[2]
- Quitting smoking is the most effective method to reduce risk for lung cancer. Following smoking cessation, the risk of lung cancer remains higher than normal based on duration and quantity of smoking but does not increase further as in a continuing smoker.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Lung Cancer Diagnosis
Lung Cancer Screening (Patient Information)
Paraneoplastic Syndrome (Related Key Topic)
Superior Vena Cava Syndrome (Related Key Topic)
Horner's Syndrome (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

[2]Moyer VA on behalf of U.S. Preventive Services Task Force: Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement, *Ann Intern Med* 160:330-338, 2014.

SUGGESTED READINGS

Brock MV et al.: DNA methylation markers and early recurrence in stage I lung cancer, *N Engl J Med* 358:1118–1128, 2008.

Cataldo VD et al.: Treatment of non-small cell lung cancer with erlotinib and gefitinib, *N Engl J Med* 364:947–955, 2011.

Fisher B et al.: Preoperative staging of lung cancer with combined PET-CT, *N Engl J Med* 361:32–39, 2009.

Goldstraw P et al.: Non–small-cell lung cancer, *Lancet* 378:1727–1740, 2011.

Gould MK: Clinical practice. Lung-cancer screening with low-does computed tomography, *N Engl J Med* 371:1813–1820, 2014.

Henschke CI et al.: Definition of a positive test result in computed tomography screening for lung cancer, *Ann Intern Med* 185:246–252, 2013.

Herbst RS et al.: Lung cancer, *N Engl J Med* 359:1367–1380, 2008.

Iannettoni MD: Staging strategies for lung cancer, *JAMA* 304:2296, 2010.

Kwak E et al.: Anaplastic lymphoma kinase inhibition in non–small-cell lung cancer, *N Engl J Med* 363:1693, 2010.

Latimer KM, Mott TF: Lung cancer: diagnosis, treatment principles, and screening, *Am Fam Phys*, 81(4):250–256, 2015.

Maemondo M et al.: Gefitinib or chemotherapy for non-small cell lung cancer with mutated EGFR, *N Engl J Med* 362:2380–2388, 2010.

Maheswaran S et al.: Detection of mutations in EGFR in circulating lung cancer cells, *N Engl J Med* 359:366, 2008.

Mok TS et al.: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma, *N Engl J Med* 361:947–957, 2009.

Molina JR et al.: Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship, *Mayo Clin Proc* 83(5):584–594, 2008.

Mostertz W et al.: Age- and sex-specific genomic profiles in non-small cell lung cancer, *JAMA* 303(6):535–543, 2010.

Moyer: VA on behalf of U.S. Preventive Services Task Force: Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement, *Ann Intern Med* 160:330–338, 2014.

Shaw AT et al.: Ceritinib in ALK-rearranged non-small cell lung cancer, *N Engl J Med* 370:1189–1197, 2014.

Shert DY et al.: Small cell lung cancer, *Mayo Clin Proc* 83(3):355–367, 2008.

Silvestri GA: Screening for lung cancer: it works, but does it really work? *Ann Intern Med* 155:537–539, 2011.

Solomon BJ et al.: First-line crizotinib versus chemotherapy in ALK-positive lung cancer, *N Engl J Med*, 371:2167–2177, 2014.

Tammemagi MC et al.: Selection criteria for lung cancer screening, *N Engl J Med* 368:728–736, 2013.

Temel JS et al.: Early palliative care for patients with metastatic non-small cell lung cancer, *N Engl J Med* 363:733–742, 2010.

The National Lung Screening Trial research team: Reduced lung-cancer mortality with low-dose computed tomographic screening, *N Engl J Med* 365:395–409, 2011.

Timmerman R et al.: Stereotactic body radiation therapy for inoperable early stage lung cancer, *N Engl J Med* 303(11):1070–1076, 2010.

Van Meerbeeck J et al.: Small-cell lung cancer, *Lancet* 378:1741–1755, 2011.

BASIC INFORMATION

DEFINITION

Lyme disease is a multisystem inflammatory disorder caused by the transmission of a spirochete, *Borrelia burgdorferi.* Lyme disease is spread by the bite of infected *Ixodes* ticks, taking 36 to 48 hr for a tick to feed and transmit the infecting organism *B. burgdorferi* to the host.

SYNONYMS

Bannworth's syndrome (Europe)
Acrodermatitis chronica atrophicans

ICD-9CM CODES
088.8 Lyme disease
ICD-10CM CODES
A69.20 Lyme disease, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): In the United States, 4.4 cases/100,000 persons; 90% of cases are found in: Massachusetts, Connecticut, Rhode Island, New York, New Jersey, Pennsylvania, Minnesota, Wisconsin, and California. The disease also occurs in Europe and Asia with a different *Ixodes* tick vector.
PEAK INCIDENCE: May to November.
PREDOMINANT SEX: Male = female.
PREDOMINANT AGE: Median age of 28 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Lyme disease may present in the following stages:
- *Early localized stage (incubation period 3-30 days):* early Lyme disease, erythema migrans (EM); skin rash, often at site of tick bite (the CDC has defined EM rash as an expanding red macule or papule that must reach at least 5 cm in size, with or without central clearing); possible fever, myalgias 3 to 32 days after tick bite.
- *Early disseminated stage (incubation period 3-6 weeks):* days to weeks later; multiorgan system involvement, including CNS with aseptic meningitis–type picture or Bell's palsy, joints (arthritis or arthralgias), cardiac including varying degrees of heart block; related to dissemination of spirochete
- *Late stage (incubation period months to years):* mo to yr after tick exposure; affects central and peripheral nervous system, cardiac, joints

Common presenting signs and symptoms include:
- EM (Fig. EL1-19). Most patients with EM (about 80%) have a single lesion but the bacteria can disseminate hematogenously to other sites in the skin and result in often smaller erythema migrans lesions.
- Lymphadenopathy, neck pains, pharyngeal erythema, myalgias, hepatosplenomegaly.
- Patients will complain of malaise, fatigue, lethargy, headache, fever/chills, neck pain, myalgias, back pain.

ETIOLOGY

B. burgdorferi transmitted from bite of an *Ixodes* tick (mostly in the nymph stage, but can also be from adult ticks).

DIAGNOSIS

Clinical presentation, exposure to ticks in endemic area, and diagnostic testing for antibody response to *B. burgdorferi.*

DIFFERENTIAL DIAGNOSIS

- Chronic fatigue/fibromyalgia.
- Acute viral illnesses.
- Babesiosis.
- Ehrlichiosis.

WORKUP

- ELISA testing and if positive or equivocal then followed by a Western blot IgM and IgG (Table L1-13). A Western blot IgM assay is positive if 2 of 3 bands present. The Western blot IgG is positive if 5 of 10 bands present.
- An alternative serologic test is the VlsE C6 ELISA, which detects an IgG response earlier.
- Early disease often difficult to diagnose serologically secondary to slow immune response
- Culturing of skin lesions (EM) and polymerase chain reaction (PCR) of synovial fluid or CSF can also give the diagnosis.

IMAGING STUDIES

- ECG
- Echocardiogram if conduction abnormalities are present with cardiac involvement.
- CT scan, MRI of head for CNS involvement.

TREATMENT

Early localized Lyme disease:
- Doxycycline 100 mg bid or amoxicillin 500 mg tid for 14 days (doxycycline should be avoided in children >8 yr and pregnant females).
- Alternative treatments: cefuroxime axetil 500 mg bid for 14 to 21 days, azithromycin 500 mg PO for 7 to 10 days but should not be used as a first-line agent.
- A single dose of 200 mg doxycycline given within 72 hr of *Ixodes* tick bite can reduce the risk of developing of Lyme disease.

Early disseminated and late persistent infection:
- 28 days of treatment necessary; doxycycline and ceftriaxone appear equally effective for acute disseminated Lyme disease.
- Arthritis: 28 days of doxycycline or amoxicillin plus probenecid.
- Neurologic involvement requires parenteral antibiotics. Those who fail to respond should be treated with IV ceftriaxone or cefotaxime.
- Ceftriaxone 2 g/day IV for 21 to 28 days; alternative: cefotaxime 2 g q8h IV; alternative: penicillin G 5 million U qid.
- Cardiac involvement: IV ceftriaxone or cefotaxime plus cardiac monitoring.
- Prolonged treatment with IV or PO antibiotic therapy for up to 90 days did not improve symptoms more than placebo.

Post–Lyme disease syndrome:
- Antibiotics are not indicated. Antibiotic treatment of patients with persistent unexplained symptoms despite previous antibiotic treatment of Lyme disease provides little, if any, benefit and carries significant risk.
- Supportive care

DISPOSITION

- The patient often needs careful follow-up and supportive care for the arthralgia-neuritis symptoms.
- Repeat episodes of EM in appropriately treated patients are due to reinfection and not to relapse.

REFERRAL

- To a neurologist if significant neurologic complications (meningitis, myelitis, ophthalmoplegia, Bell's palsy).
- To a cardiologist if the patient develops evidence of cardiac conduction disturbances or pericarditis.

PEARLS & CONSIDERATIONS

- A physician diagnosis of classic EM in an endemic region of Lyme disease is sufficient to make a definitive diagnosis.
- In some patients with Lyme disease, nonspecific complaints such as headache, fatigue, and arthralgia may persist for months after appropriate (and ultimately successful) antibiotic treatment.
- There is no evidence of current or previous *Borrelia burgdorferi* infection in most patients evaluated at university-based Lyme disease referral centers. Psychiatric comorbidity and other psychological factors are prominent in the presentation and outcome of some patients who inaccurately ascribe longstanding symptoms to "chronic Lyme disease."

TABLE L1-13 Criteria for Western Blot Interpretation in the Serologic Confirmation of Lyme Disease

Duration of Disease	Isotype Tested	Criteria for Positive Test
First month of infection	IgM	2 of the following 3 bands are present: 23 kD (OspC), 39 kD (BmpA), and 41 kD (Fla)
After first month of infection	IgG	5 of 10 bands are present: 18 kD, 21 kD, 28 kD, 30 kD, 39 kD, 41 kD, 45 kD, 58 kD (not GroEL), 66 kD, and 93 kD

Modified from Centers for Disease Control and Prevention: Recommendations for test performance and interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease, *MMWR Morb Mortal Wkly Rep* 44:590–591, 1995.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Lyme Disease (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Bratton RL et al.: Diagnosis and treatment of Lyme disease, *Mayo Clin Proc* 83(50):566–571, 2008.

Feder HM et al.: A critical appraisal of "chronic Lyme disease," *N Engl J Med* 357:1422–1430, 2007.

Hassett A et al.: Psychiatric comorbidity and other psychological factors in patients with "chronic Lyme disease," *Am J Med* 122:843–850, 2009.

Infectious Disease Clinics of North America: Tick borne diseases part I, *Lyme Disease* 22:195–380, 2008.

Klempner MS et al.: Treatment trials for post-Lyme disease symptoms revisited, *Am J Med* 126:665–669, 2013.

Nadelman RB et al.: Differentiation of reinfection from relapse in recurrent Lyme disease, *N Engl J Med* 367:1883–1890, 2012.

Shapiro ED: Lyme disease, *N Engl J Med* 370:1724–1731, 2014.

Wormser GP et al.: The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America, *Clin Infect Dis* 43:1089–1134, 2006.

Wright WF et al.: Diagnosis and management of Lyme disease, *Am Fam Physician* 85(11):1086–1093, 2012.

FIGURE EL1-19 Erythema migrans rash of Lyme disease. A, Typical macular lesion on left shoulder. **B,** Bull's eye lesion on lateral thigh with central punctum. **C,** Multiple lesions on back. **D,** Lesion with vesicular center on posterior thigh. (Courtesy Juan Salazar, MD, University of Connecticut Health Center.)

Lymphangitis PTG

BASIC INFORMATION

DEFINITION

Lymphangitis refers to the inflammation of lymphatic vessels due to infectious or noninfectious causes. Infectious causes include bacteria, mycobacteria, viruses, fungi, and parasites.

SYNONYMS

Nodular lymphangitis
Sporotrichoid lymphangitis

ICD-9CM CODES
457.2 Lymphangitis
ICD-10CM CODES
I89.1 Lymphangitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Several hundred cases/yr of sporotrichoid lymphangitis; bacterial lymphangitis more common but not reported.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

ACUTE LYMPHANGITIS

- Commonly associated with a bacterial cellulitis.
- Usually develops after cutaneous inoculation of microorganisms into the lymphatic vessels through disrupted skin or as a result of spread from a distal infection.
- May or may not recognize a site of skin trauma (i.e., laceration, puncture, ulcer).
- In hours to days, distal appearance of erythema, edema, and tenderness, with linear erythematous streaks extending proximally to regional lymph nodes.
- Possible lymphadenitis and fever.
- Predisposition to group A streptococcal infection of the skin in those with uncontrolled diabetes mellitus, chronic lymphedema, and superficial fungal infections (e.g., tinea pedis).

SPOROTRICHOID OR NODULAR LYMPHANGITIS

- Includes subcutaneous nodules that develop along the path of involved lymphatics.
- Most commonly results from inoculation of the skin of the hand.
- Usually preceded by well-defined episode of cutaneous inoculation or trauma.
- Lesions apparent from one to several wk after inoculation.
- Initially, nodular or papular lesion; may ulcerate.
- May have frank pus or a serosanguineous discharge.
- Systemic complaints uncommon, but infection with certain microorganisms associated with fever, chills, myalgias, and headache.

ETIOLOGY

- Acute lymphangitis: usually associated with *Streptococcus pyogenes* (group A streptococcus), but staphylococcal organisms are increasingly recognized as a cause of severe soft tissue infections such as lymphangitis, including community-acquired methicillin-resistant *S. aureus* (CA-MRSA).
- Nodular lymphangitis caused by one of several organisms.
  1. *Sporothrix schenckii* ("Rose gardener's disease").
     a. Most common recognized cause in the United States, usually in the Midwest.
     b. Found in soil and plant debris.
  2. *Nocardia brasiliensis:* found in soil.
  3. *Mycobacterium marinum:* associated with trauma related to water (e.g., aquariums, swimming pools, fish).
  4. *Leishmania brasiliensis.*
     a. Protozoal parasite transmitted to humans by sandflies, mostly to travelers in endemic areas.
     b. Small endemic focus in Texas.
  5. *Francisella tularensis.*
     a. Most often in Southern/Midwestern states (Arkansas, Missouri, Oklahoma).
     b. Associated with contact with infected mammals (e.g., rabbits, squirrels) or tick bites.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Nodular lymphangitis.
- Insect or snake bites.
- Filariasis.

WORKUP

- Acute lymphangitis: blood cultures.
- Nodular lymphangitis: various stains and cultures of drainage or biopsy specimens of inoculation sites to make definitive diagnosis.

LABORATORY TESTS

- WBCs possibly elevated with cellulitis.
- Eosinophilia common with helminthic infections.

TREATMENT

NONPHARMACOLOGIC THERAPY

Limb elevation.

ACUTE GENERAL Rx

- Penicillin possibly sufficient, but 1 wk of dicloxacillin or cephalexin 500 mg PO qid commonly used to ensure antistaphylococcal coverage; if CA-MRSA suspected, then use oral Bactrim DS: one PO bid is the best oral agent and with vancomycin 1 g IV every 12 hr being reserved for patients requiring IV therapy.
- If allergic to penicillin:
  1. Clindamycin 300 mg PO qid for 7 days *or*
  2. Erythromycin 500 mg PO qid for 7 days.
  3. Levofloxacin 500 mg PO daily or moxifloxacin 400 mg PO daily for 7 days.
- Nodular lymphangitis: specific therapy directed at etiologic agent.
- For superficial fungal infections: treatment may prevent recurrence of acute lymphangitis.

DISPOSITION

- Acute lymphangitis: usually resolves with therapy.
- Recurrent attacks: may lead to chronic lymphedema of limb, rarely resulting in elephantiasis nostras (nonfilarial elephantiasis).
- Nodular lymphangitis: usually responds to appropriate therapy.

REFERRAL

- If acute lymphangitis is more than a mild disease or if it involves the face.
- If nodular lymphangitis or filariasis is suspected.

PEARLS & CONSIDERATIONS

COMMENTS

- Outside of the United States, initial episodes of filariasis caused by *Brugia malayi* resemble acute lymphangitis.
- Chronic lymphedema or elephantiasis results from recurrent episodes.
- For chronic lymphedema, adherence to limb elevation, compression/support stockings, and adequate glycemic control (for patients with diabetes) all can reduce risk of acute lymphangitis.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Lymphangitis (Patient Information)

AUTHOR: **RUSSELL J. MCCULLOH, M.D.**

SUGGESTED READINGS

DiNubile MJ: Nodular lymphangitis. A distinctive clinical entity with finite etiologies, *Curr Infect Dis* 10(5):404–410, 2008.

Eijnden SV et al.: Gloves and socks lymphangitis associated with acute parvovirus B19 infection, *Pediatr Dermatol* 20(2):184, 2003.

King MD et al.: Emergence of community-acquired methicillin-resistant Staphylococcus aureus USA 300 clone as the predominant cause of skin and soft-tissue infections, *Ann Intern Med* 144(5):309, 2006.

Koehler JE, Duncan LM: A 56-year-old man with fever and axillary lymphadenopathy, *N Engl J Med* 355:1387, 2005.

Kostman JR, DiNubile MJ: Nodular lymphangitis: a distinctive but often unrecognized syndrome, *Ann Intern Med* 118(11):883–888, 1993.

BASIC INFORMATION

DEFINITION

A primary role of the lymphatic system is to transport proteins from the interstitium to the heart. When the transport capacity of the lymphatic system is reduced, proteins accumulate in the interstitium. Accumulated proteins attract water, which creates a high protein swelling in the subcutaneous tissues called lymphedema.

SYNONYMS

Elephantiasis

ICD-9CM CODES

457.0 Lymphedema: secondary to breast cancer
457.1 Lymphedema: secondary to all other causes
757 Lymphedema: primary

ICD-10CM CODES

I97.2 Postmastectomy lymphedema syndrome
I89.0 Lymphedema, not elsewhere classified

EPIDEMIOLOGY & DEMOGRAPHICS

PRIMARY LYMPHEDEMA

- Found in 1.1/100,000 people aged <20 yr.
- Females outnumber males 3.5:1.
- Incidence peaks between ages 12 and 16 (puberty).

SECONDARY LYMPHEDEMA: See specific etiology below.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Lymphedema is a slow onset, progressive disease characterized by an asymmetrical, inflammatory swelling, traveling distal to proximal, that can affect any body part including limbs, trunk, head/neck, and genitals (Fig. L1-20). Box L1-1 summarizes lymphedema staging from the International Society of Lymphology.

FIGURE L1-20 Lymphedema before treatment.

STAGE 0: LATENCY

- Decreased lymphatic system transport capacity due to primary or secondary etiology.
- Subjective complaints of affected body part feeling heavy or achy.
- No objective findings, no apparent swelling.

STAGE I: REVERSIBLE

- Edema is observable, soft, pitting and reversible with elevation.
- No secondary skin changes are present.

STAGE II: SPONTANEOUSLY IRREVERSIBLE

- Skin becomes more firm/fibrotic, therefore less pitting.
- Edema does not reverse to normal with elevation.
- Possibility of infections (cellulitis), wounds, or weeping (lymphorrhea).

STAGE III: ELEPHANTIASIS

- Skin becomes very firm/fibrotic, therefore nonpitting.
- Evidence of substantial skin changes (e.g., papillomas, lobules, *"peau d' orange"*).

ETIOLOGY:

Lymphedema is caused by a reduction in lymphatic system transport and is classified into primary and secondary forms.

Primary Lymphedema

- Occurs when the lymphatic system does not maturate properly during fetal development.
  1. Aplasia.
  2. Hypoplasia.
  3. Hyperplasia.
- Can be familial, genetic, or hereditary.
- Lymphedema congenital: symptoms present at birth.
- Lymphedema praecox: symptoms onset before the age of 35 (commonly during puberty).
- Lymphedema tardum: symptoms onset at the age of 35 or after.

Secondary Lymphedema

- Occurs secondary to a disruption or obstruction of the lymphatic system caused by:
  1. Filariasis (#1 cause worldwide).
  2. Lymph node surgery/radiation due to cancer (#1 cause in the United States).
  3. Other: chronic venous insufficiency (CVI), deep vein thrombosis (DVT), infection, surgery/trauma, lipedema, and obesity.

BOX L1-1 Lymphedema Staging

Stage 0: Latent
- Impaired lymphatic function
- No evident edema; subclinical
- May last months or years before progression

Stage I: Spontaneously Reversible
- Early accumulation of protein-rich fluid
- Pitting edema
- Subsides with elevation

Stage II: Spontaneously Irreversible
- Accumulation of protein-rich fluid
- Pitting edema progresses to fibrosis
- Does not resolve with elevation alone

Stage III: Lymphostatic Elephantiasis
- Nonpitting
- Significant fibrosis
- Trophic skin changes

From International Society of Lymphology: The diagnosis and treatment of peripheral edema: 2009 consensus document of the International Society of Lymphology, *Lymphology* 42(2):51-60, 2009.

DIAGNOSIS

- Lymphedema is primarily a clinical diagnosis made on the basis of past medical history and objective findings that distinguish it from other causes of chronic edema.
- A Stemmer's sign is often used to identify lymphedema (inability to pick up or pinch a fold of skin at the base of the second toe or finger).
- When physical examination is inconclusive, other available imaging tests can help make the diagnosis (see imaging studies below).

DIFFERENTIAL DIAGNOSIS

Other causes of edema that should be ruled out before treatment for lymphedema include cardiac, renal, hepatic, and thyroid dysfunction.

WORKUP

A detailed history and physical examination should help exclude most of the differential diagnoses.

LABORATORY TESTS

- Blood urea nitrogen, creatinine, liver function tests, albumin, urine analysis, and thyroid function tests are obtained to exclude possible systemic causes of edema.
- Genetic testing may be practical in defining a specific hereditary syndrome with a discrete gene mutation such as lymphedema distichiasis (*FOXC2*), Milroy's disease (*VEGFR-3*), Meige's disease, or Klippel-Trenaunay-Weber syndrome.

IMAGING STUDIES

- Lymphoscintigraphy: diagnostic image of choice for lymphedema (if needed).
- Indocyanine green (ICG) fluorescent lymphography: can now be used to identify sentinel nodes, to demonstrate superficial lymph channels and functional lymphatics, to indicate treatment pathways, and to confirm the effectiveness of therapeutic techniques.
- Magnetic resonance imaging (MRI): primarily used in tumor diagnosis.
- Duplex ultrasound: determines venous involvement in the edema.
- Computed axial tomography (CAT): distinguishes between fatty tissue and accumulations of protein-rich fluids.
- Lymphography: phased out in favor of less invasive techniques.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Complete decongestive therapy (CDT) is backed by longstanding research and experience as the primary treatment of choice for lymphedema in both children and adults (Fig. L1-21). It should be delivered by a certified lymphedema therapist (CLT). CDT involves a two-phase treatment program:
  1. Phase 1—Reduce tissue congestion of affected body part with daily treatments:
     1. Manual lymph drainage.
     2. Skin care.
     3. Compression wrapping of limb.
     4. Decongestive exercises.
  2. Phase 2—Maintain decongestion with Home Maintenance Program:
     1. Daily use of elastic and inelastic compression garments that are properly fitted according to circumference and length to prevent lymphedema from returning.
     2. Compression is graduated; most of the compression is distal with decreasing compression in the stocking proximally.
     3. Different knits and compression classes are available for different stages of lymphedema.
     4. Choices of garments include below-the-knee stockings, thigh-high stockings, pantyhose, sleeves, bras, and truncal garments.
- Massage (or any modality that increases blood flow) can have negative effects on lymphedema by increasing vasodilation. Therefore it is contraindicated on the lymphedematous quadrants.
- Compression pumps have not been found to be effective in removing proteins from lymphedematous quadrants.
- Nutritional therapy (reducing the amount of proteins ingested) is ineffective in the treatment of lymphedema.

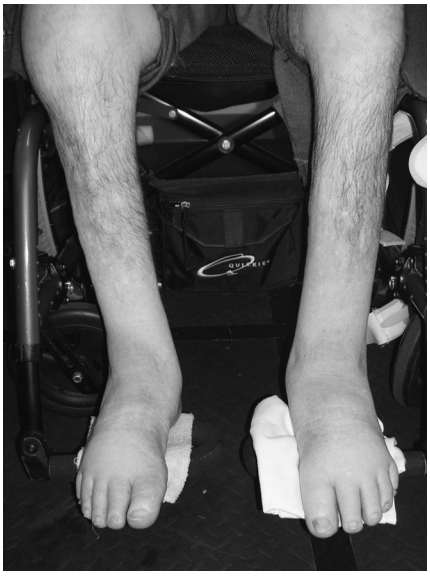

FIGURE L1-21 Lymphedema after treatment.

PHARMACOLOGIC THERAPY

No drugs have been shown to be beneficial in the treatment of lymphedema. Diuretics, in particular, have not been found to be effective in removing proteins from lymphedematous quadrants and may promote the development of volume depletion.

SURGERY

Surgery for lymphedema has been proven largely unsuccessful and should not be considered before CDT. Surgical procedures are divided into two types:

- Physiologic procedures: those performed to improve lymph node drainage (e.g., anastomoses of the lymph system with the venous system, lymph node transplant).
- Excisional or debulking procedures: those performed to excise the subcutaneous tissue (e.g., Charles' procedure, Thompson's procedure, the modified Homans' procedure, and liposuction). Liposuction-circumferential suction-assisted lipectomy represents a newly proposed method to reduce morbidity involved in the traditional excisional techniques.

PEARLS & CONSIDERATIONS

- Lymphedema is a chronic, generally incurable but very manageable condition that requires lifelong care and attention along with psychosocial support.
- Children and adolescents (along with parents and adults) should be encouraged to pursue a normal life, participating in school activities and sports (preferably noncontact, such as swimming).
- Infections such as cellulitis should be treated promptly.
- If the etiology is filariasis caused by the parasites *Wuchereria bancrofti* or *Brugia malayi*, treatment is diethylcarbamazine citrate 5 mg/kg in divided doses for 3 wk.
- Patients with lymphedema commonly manifest psychiatric comorbidities as a result of their disease, such as anxiety, depression, adjustment problems, and difficulty in vocational, domestic, or social domains.
- Lymphedema can be complicated in rare cases by development of lymphangiosarcomata or other cutaneous malignancies.
- Gene therapy to develop new lymphangioses in the affected body parts is a potential clinical remedy in the future.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Lymphedema (Patient Information)

AUTHORS: **FRANK G. FORT, M.D.** and **KATHRYN TAYLOR ANILOWSKI, M.S., P.T., C.L.T.-L.A.N.A.**

SUGGESTED READINGS

International Society of Lymphology: The diagnosis and treatment of peripheral lymphedema: consensus document of the International Society of Lymphology, *Lymphology* 36(2):84, 2003.

Karkkainen MJ et al.: A model for gene therapy of human hereditary lymphedema, *Proc Natl Acad Sci USA* 98(22):12677, 2001.

Murdaca G et al.: Current views on diagnostic approach and treatment of lymphedema, *Am J Med* 125:134–140, 2012.

O'Brien JG et al.: Treatment of edema, *Am Fam Physician* 71(11):2111, 2005.

Rockson SG: Lymphedema, *Am J Med 110* 288, 2001.

BASIC INFORMATION

DEFINITION

Lymphogranuloma venereum (LGV) is a sexually transmitted, systemic disease caused by *Chlamydia trachomatis,* serovars L_1, L_2, or L_3.

SYNONYMS

Tropical bubo
Poradenitis inguinalis
LGV

ICD-9CM CODES
099.1 Lymphogranuloma venereum
ICD-10CM CODES
A55 Chlamydial lymphogranuloma (venereum)

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Rare; <300 cases/year.
PREVALENCE: Endemic in Africa, India, parts of Southeast Asia, South America, and the Caribbean.
PREDOMINANT SEX: Male/female ratio is 5:1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Primary stage:
- Primary lesion caused by multiplication of organism at site of infection.
- Papule, shallow ulcer.
- Herpetiform lesion at site of inoculation (most common).
- Incubation period of 3 to 21 days.
- Most common site of lesion in women: posterior wall, fourchette, or vulva.
- Spontaneous healing without scarring.

Second stage:
- Inguinal syndrome: characteristic inguinal adenopathy.
- Begins 1 to 4 wk after primary lesion.
- Syndrome is the most frequent clinical sign of the disease.
- Unilateral inguinal adenopathy in 70% of cases.
- Symptoms: painful, extensive adenitis (bubo) and suppuration may occur with numerous sinus tracts.
- "Groove sign" signaling femoral and inguinal node involvement (20%); most often seen in men.
- Involvement of deep iliac and retroperitoneal lymph nodes in women may present as a pelvic mass.

Third stage (anogenital syndrome):
- Subacute: proctocolitis.
- Late: tissue destruction or scarring, sinuses, abscesses, fistulas, strictures of perineum, elephantiasis.

ETIOLOGY

Chlamydia trachomatis is the causative agent. There are three serotypes: L1, L2, and L3.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Inguinal adenitis, suppurative adenitis, retroperitoneal adenitis, proctitis, schistosomiasis.
- Section II describes the differential diagnosis of genital sores.

WORKUP

- Diagnosis is based on clinical suspicion and serology, epidemiologic information, and the exclusion of other etiologies for proctocolitis, inguinal lymphadenopathy, or genital or rectal ulcers. Biopsy is contraindicated because sinus tracts develop.
- Screening for other sexually transmitted diseases.
- A clinical algorithm for evaluation of genital ulcer disease is described in Section III, "Evaluation of Patients with Genital Lesions or Ulcers."

LABORATORY TESTS

- Genital and lymph node specimens (i.e., lesion swab or bubo aspirate) can be tested for *C. trachomatis* by culture or direct immunofluorescence, using nucleic acid amplification techniques, including real-time PCR.
- Complement fixation test:
  1. Titer >1:64 in active infection, lower titers may be nonspecific.
  2. Convalescent titers no difference.
- Cell culture of *Chlamydia* aspiration of fluctuant node yields highest rates of recovery.
- Complete blood count: mild leukocytosis with lymphocytosis or monocytosis.
- Elevated sedimentation rate.
- VDRL and HIV screening to rule out other sexually transmitted diseases.

IMAGING STUDIES

- Computed tomography scan for suspected retroperitoneal adenitis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoid milk and milk products while taking medication.
- Practice sexual abstinence.
- Treat sexual partners. Persons who have had sexual contact with a patient who has LGV within 60 days before onset of the patient's symptoms should be examined, tested for urethral or cervical chlamydial infection, and treated with a chlamydia regimen (azithromycin 1 g orally single dose or doxycycline 100 mg orally twice a day for 7 days).

ACUTE GENERAL Rx

- Doxycycline 100 mg PO bid × 21 days.
- Erythromycin base 500 mg PO qid × 21 days.
- Azithromycin 1 g orally once weekly for 3 wk is probably effective.
- Surgical:
  1. Aspirate fluctuant nodes.
  2. Incise and drain abscesses.
- Combination of medical and surgical treatment may be necessary.

CHRONIC Rx

- Longer course of therapy will be needed for chronic or relapsing cases, which may be caused by reinfection and/or inadequate treatment.
- A rectal stricture requires a colostomy.
- Surgery should be considered only after antibiotic treatment.

DISPOSITION

Good prognosis with early treatment, usually resulting in complete resolution of symptoms.

REFERRAL

Surgical consultation if patient develops obstruction, fistula, or rectal stricture. May need referral to plastic surgeon if patient has lymphatic obstruction.

PEARLS & CONSIDERATIONS

COMMENTS

- Pregnant and lactating women should be treated with erythromycin regimen (doxycycline contraindicated in pregnancy).
- Congenital transmission does not occur, but infection may be acquired through an infected birth canal.
- Patient education materials may be obtained through local and state health clinics.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Lymphogranuloma Venereum (Patient Information)

AUTHORS: **RUBEN ALVERO, M.D.**, and **GEORGE T. DANAKAS, M.D.**

SUGGESTED READINGS

Workowski KA et al.: Sexually transmitted diseases treatment guidelines, 2010, *MMWR Recomm Rep* 59(RR-12):1–110, 2010.

BASIC INFORMATION

DEFINITION

Lynch syndrome is a hereditary predisposition to malignancy of the colon that is explained by a germline mutation in a DNA mismatch repair gene.

SYNONYMS

Hereditary non-polyposis colorectal cancer
Hereditary site-specific colon cancer

ICD-9CM CODES
1539 Lynch syndrome
ICD-10CM CODES
C18.9 Malignant neoplasm of colon, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

The lifetime risk for developing colon cancer in the United States is approximately 6%. Of these cases, 2% to 3% may be attributable to Lynch syndrome. The incidence of Lynch syndrome is estimated to be between 1:660 and 1:2000. Lynch syndrome is the most common form of hereditary colon cancer. The average age of diagnosis for Lynch syndrome is 48 years, although diagnosis can occur as early as the 20s or as late as the 70s.

RISK FACTORS: Family history of colon cancer or other hereditary non-polyposis colorectal cancer (HNPCC)-related cancers such as endometrial (up to 40% of women with Lynch syndrome may develop endometrial cancer), biliary tract, ovarian, stomach, upper urinary tract, or brain.

GENETICS: Autosomal-dominant inheritance pattern.

ETIOLOGY

Lynch syndrome is thought to be secondary to germline mutations in DNA mismatch repair genes. The predominant genes involved are *MSH2* and *MLH1,* which are tumor suppressor genes, although other genes have documented involvement *(PMS1, PMS2, MSH6,* and *MLH3).* Mutations in these genes prevent repair of DNA mismatches during DNA replication. This is most prevalent in regions of DNA called microsatellites causing DNA microsatellite instability and leading to an increased risk for malignancy, especially colon cancer. *MSH6* mutations are associated with a markedly lower cancer risk than *MLH1* or *MSH2* mutations.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Changes in bowel habits (prolonged constipation).
- Melena.
- Hematochezia.
- Abdominal pain.
- Unexplained weight loss.
- Decreased appetite.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Familial adenomatosis polyposis.
- Peutz-Jeghers syndrome.
- Juvenile polyposis.
- Nonhereditary colorectal cancer.
- Gardner syndrome.

WORKUP

If an individual presents with numerous adenomatous polyps or has multiple relatives with cancer at a young age, a family history complete with pedigree must be obtained. Clinical diagnosis of the Lynch syndrome can be made with the Amsterdam or Bethesda criteria.

- Revised Amsterdam (II) criteria (must meet all criteria):
  1. HNPCC-associated carrier diagnosis in at least three individuals in the family.
  2. One of the patients is a first-degree family member of two other patients.
  3. Involved patients occur in at least two successive generations with diagnosis of HNPCC.
  4. At least one diagnosis in family of HNPCC was made before age 50.
  5. The diagnoses are histologically confirmed.
  6. Familial adenomatous polyposis is excluded.
- Bethesda criteria (must meet all criteria):
  1. Colorectal cancer before age 50.
  2. Multiple colorectal cancers or other HNPCC-related cancers such as biliary tract, endometrial, stomach, or ovary.
  3. Colorectal cancer with microsatellite instability histology <60 years of age.
  4. Colorectal cancer or HNPCC-related cancer in first-degree relative <50 years of age.
  5. Colorectal cancer or HNPCC-related cancer in at least two first- or second-degree relatives, any age.
- If criteria for the Lynch syndrome are not met, no further analysis is necessary (although a genetic syndrome cannot be definitively excluded and genetic referral may be warranted).

LABORATORY TESTS

- If a patient meets criteria for Lynch syndrome, immunohistochemistry can be performed for the presence or absence of mismatch repair genes *MLH1, MSH2, MSH6,* and *PMS2.* Rarely, *MLH3* is identified.
- Microsatellite instability analysis should also be performed if criteria for Lynch syndrome are met.

TREATMENT

- If the mutation has been identified in a family member, screening for this mutation can be performed via genetic testing. Informed consent must be obtained after a thorough explanation has been provided to each individual.
- Surveillance using colonoscopy can be performed in individuals who screen positive, while those who screen negative can be discharged. The mismatch repair gene that is mutated guides screening.
- According to the Netherlands Surveillance Protocol, for example, individuals with mutations in *MLH1, MSH2,* or *MSH6* should have colonoscopies every 1 to 2 yr starting at age 20 to 25 yr; urine cytology every 1 to 2 yr starting at age 30 to 35 yr; esophagogastroduodenoscopy every 1 to 2 yr starting at age 30 to 35 yr; and, in females, ultrasound of endometrium and CA-125 every 1 to 2 yr starting at age 30 to 35 yr.

REFERRALS

- To gastroenterology for surveillance colonoscopies.
- To genetic counselor if patient satisfies Bethesda criteria.
- To psychologist as necessary for psychological support.

PEARLS & CONSIDERATIONS

- Before genetic testing is instituted, informed consent must be obtained because consequences of this testing include the necessity of lifelong screenings such as colonoscopies.
- The risk of pancreatic cancer is increased in families with Lynch syndrome compared with the U.S. population.

PATIENT & FAMILY EDUCATION

- For information on local genetic counselors, visit the National Society of Genetic Counselors Web site at www.nsgc.org.
- For information on Lynch syndrome, visit www.mayoclinic.com/health/lynch-syndrome/DS00669.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Colorectal Cancer (Related Key Topic)
Gardner's Syndrome (Related Key Topic)
Peutz-Jeghers Syndrome and other Polyposis Syndromes (Related Key Topic)

AUTHORS: **PAUL F. GEORGE, M.D.,** and **JOANNE M. SILVIA, M.D.**

EVIDENCE

Abstract[1]

In current clinical practice, genetic testing to detect Lynch syndrome mutations ideally begins with diagnostic testing of an individual affected with cancer before offering predictive testing to at-risk relatives. An alternative strategy that warrants exploration involves screening unaffected individuals via demographic and family histories, and offering genetic testing to those individuals whose risks for carrying a mutation exceed a selected threshold. Whether this approach would improve health outcomes in a manner that is cost-effective relative to current standards of care has yet to be demonstrated. To do so, we developed a simulation framework that integrated models of colorectal and endometrial cancers with a 5 generation family history model to predict health and economic outcomes of 20 primary screening strategies (at a wide range of compliance levels) aimed at detecting individuals with mismatch repair gene mutations and their at-risk relatives. These strategies were characterized by (i) different screening ages for starting risk assessment and (ii) different risk thresholds above which to implement genetic testing. For each strategy, 100,000 simulated individuals, representative of the U.S. population, were followed from the age of 20, and the outcomes were compared with current practice. Findings indicated that risk assessment starting at ages 25, 30, or 35, followed by genetic testing of those with mutation risks exceeding 5%, reduced colorectal and endometrial cancer incidence in mutation carriers by approximately 12.4% and 8.8%, respectively. For a population of 100,000 individuals containing 392 mutation carriers, this strategy increased quality-adjusted life-years (QALY) by approximately 135 with an average cost-effectiveness ratio of $26,000 per QALY. The cost-effectiveness of screening for mismatch repair gene mutations is comparable to that of accepted cancer screening activities in the general population such as colorectal cancer screening, cervical cancer screening, and breast cancer screening. These results suggest that primary screening of individuals for mismatch repair gene mutations, starting with risk assessment between the ages of 25 and 35, followed by genetic testing of those whose risk exceeds 5%, is a strategy that could improve health outcomes in a cost-effective manner relative to current practice. Ⓐ

Evidence-Based Reference

Dinh TA et al.: Health benefits and cost-effectiveness of primary genetic screening for Lynch syndrome in the general population, *Cancer Prev Res* 4:9–22, 2011. Ⓐ

SUGGESTED READINGS

Bonadona V et al.: Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome, *JAMA* 305(22):2304–2310, 2011.

Hampel H et al.: Screening for the Lynch syndrome (hereditary non-polyposis colorectal cancer), *N Engl J Med* 352:2005, 1851.

Hendriks YM et al.: Management of Lynch syndrome (hereditary nonpolyposis colorectal carcinoma): guide for clinicians, *CA Cancer J Clin* 56:213, 2006.

Kastrinos F et al.: Risk of pancreatic cancer in families with Lynch syndrome, *JAMA* 302(16):1790–1795, 2009.

Ladabaum U et al.: Strategies to identify the Lynch syndrome among patients with colorectal cancer, *Ann Intern Med* 155:69–79, 2011.

Lynch HT et al.: Diagnosis and management of hereditary colorectal cancer syndromes: Lynch syndrome as a model, (Epub 2009 Aug 4) *CMAJ* 181(5):273–280, 2009 Sep 1.

Moreira L: Identification of Lynch syndrome among patients with colorectal cancer, *JAMA* 328(15):1515–1516, 2012.

Power DG et al.: Clinical genetics of hereditary colorectal cancer, *Hematol Oncol Clin N Am* 24:837–859, 2010.

Macular Degeneration EBM PTG

BASIC INFORMATION

DEFINITION

Macular degeneration refers to a group of diseases associated with loss of central vision and damage to the macula. Degenerative changes occur in the pigment, neural, and vascular layers of the macula. Dry macular degeneration is usually ischemic in etiology, and wet macular degeneration is associated with leakage of fluid from blood vessels, usually referred to as *age-related macular degeneration* (ARMD).

ICD-9CM CODES
362.5 Degeneration of macula and posterior pole
ICD-10CM CODES
H35.30 Unspecified macular degeneration

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.)
- Leading cause of irreversible blindness in people ≥50 yr in the developed world.
- Increases with age.
- More than 8 million Americans have AMD. The overall prevalence is projected to increase by >50% by 2020.
- About 10% of patients with AMD have the neovascular form manifested by an often rapid decrease in central visual acuity caused by newly developed leaky vessels arising from the choroid toward the subretinal space.

PEAK INCIDENCE
- Ages 75 to 80 yr
- Dramatically increases in incidence and prevalence with age until ~80% of people ≥75 yr have senile macular degeneration

PREVALENCE (IN U.S.): Varies, but ~5% of people >50 yr have some signs of macular degeneration

PREDOMINANT SEX: Males and females are affected equally (15% of white women >80 yr have severe AMD)

PREDOMINANT AGE: >50 yr

RISK FACTORS:
- Advancing age
- Genetic factors
- History of smoking within past 20 yr
- Dietary factors (low intake of antioxidants and zinc, high fat intake)
- Obesity
- White race

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Decreased central vision
- Macular hemorrhage, pigmentation, edema, atrophy
- The most common abnormality seen in AMD is the presence of drusen, or yellowish deposits deep to the retina; this may be early in the course of disease
- Choroidal neovascular membrane (CNVM) develops with rapid change in vision

ETIOLOGY

- Subretinal neovascular membrane early
- Pigmentary and vascular changes with exudate, edema, and scar tissue development
- Dry-type atrophy of macular pigment epithelium
- The main mediator of neovascularization in wet AMD is the vascular endothelial growth factor (VEGF). It induces angiogenesis and increases inflammation and vascular permeability

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Diabetic retinopathy (with neovascularization, can mimic CNVM)
- Hypertension
- Histoplasmosis and high myopia (less common cause of CNVM)
- Trauma with macular scar

WORKUP

- Complete eye examination, including visual field and fluorescein angiography
- Optical coherence tomography (OCT)

LABORATORY TESTS

Evaluate for diabetes and other metabolic problems as well as vascular diseases

IMAGING STUDIES

- OCT
- Fluorescein angiography

TREATMENT

NONPHARMACOLOGIC THERAPY

- There is no proven treatment for dry AMD.
- Laser treatment to stop progression of disease; photodynamic treatment with verteporfin IV
- Laser (argon) for certain classic membranes (CNVM)
- A high dietary intake of antioxidants, vitamins C and E, and zinc has been reported to substantially reduce the risk of AMD in elderly persons

ACUTE GENERAL Rx

- The introduction of therapies blocking VEGF dramatically changed the management of AMD and it is now standard practice for clinicians to offer intravitreal injections of anti-VEGF agents (ranibizumab, bevacizumab) as first-line treatment for neovascular AMD. Intravitreal administration of ranibizumab, a monoclonal antibody Fab that neutralizes all active forms of VEGF A, has shown to be effective in preventing vision loss and improving mean visual acuity in patients with AMD. It has also been reported to be superior to photodynamic therapy with verteporfin in the treatment of predominantly classic neovascular AMD. Bevacizumab, a monoclonal antibody to VEGF, is also often used off-label as intravitreal therapy. Its cost per intravitreal dose is significantly lower than that of ranibizumab. A major concern regarding anti-VEGF treatment is the potential increased risk of stroke and cardiovascular disease.
- Intravitreous injections of pegaptanib, a more selective anti-VEGF, appear to be less effective therapy in slowing vision loss in neovascular AMD than bevacizumab or ranibizumab. Pegaptanib is administered once every 6 wk by intravitreous injection into one eye.
- Afibercept, a fusion protein that competes for binding of VEGF, has recently been FDA approved for the treatment of wet (neovascular) AMD. It is injected intravitreally every 8 weeks. It appears to be as effective as ranibizumab and bevacizumab but is more expensive.
- Laser photocoagulation therapy may be useful in patients with extrafoveal lesions but is no longer routinely recommended for wet AMD.

CHRONIC Rx

- Laser phototherapy is not recommended for dry AMD.
- Antioxidants and zinc may slow progression of AMD

DISPOSITION

- Follow closely by ophthalmologist, retinal specialist.
- Most bevacizumab or ranibizumab treatment failures are due to missed follow-up visits. Patients should be reminded repeatedly to call if their vision worsens. There should also be a system in place for calling patients who have been lost to follow-up due to the high risk of recurrent neovascularization and vision loss in these patients.

REFERRAL

- To ophthalmologist early in the course of the disease if vision is to be saved
- Immediate referral if any change in vision

PEARLS & CONSIDERATIONS

COMMENTS

- Recent trials with embryonic stem cell transplants have shown promise in macular degeneration.
- Statistically, the vision of only 1 of 10 affected persons can be saved, but the disease is so devastating that vigorous therapy should be considered in all patients.
- Statins plus aspirin may slow progression.
- Vitamins with zinc and antioxidants may slow progression of AMD.
- Quitting smoking significantly reduces the risk of developing AMD.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Macular Degeneration (Patient Information)

AUTHORS: **MELVYN KOBY, M.D.,** and **R. SCOTT HOFFMAN, M.D.**

EVIDENCE

Abstract[1]

Background:
Clinical trials have established the efficacy of ranibizumab for the treatment of neovascular age-related macular degeneration (AMD). In addition, bevacizumab is used off-label to treat AMD, despite the absence of similar supporting data.

Methods:
In a multicenter, single-blind, noninferiority trial, we randomly assigned 1208 patients with neovascular AMD to receive intravitreal injections of ranibizumab or bevacizumab on either a monthly schedule or as needed with monthly evaluation. The primary outcome was the mean change in visual acuity at 1 year, with a noninferiority limit of 5 letters on the eye chart.

Results:
Bevacizumab administered monthly was equivalent to ranibizumab administered monthly, with 8.0 and 8.5 letters gained, respectively. Bevacizumab administered as needed was equivalent to ranibizumab as needed, with 5.9 and 6.8 letters gained, respectively. Ranibizumab as needed was equivalent to monthly ranibizumab, although the comparison between bevacizumab as needed and monthly bevacizumab was inconclusive. The mean decrease in central retinal thickness was greater in the ranibizumab-monthly group (196 μm) than in the other groups (152 to 168 μm, P=0.03 by analysis of variance). Rates of death, myocardial infarction, and stroke were similar for patients receiving either bevacizumab or ranibizumab (P>0.20). The proportion of patients with serious systemic adverse events (primarily hospitalizations) was higher with bevacizumab than with ranibizumab (24.1% vs. 19.0%; risk ratio, 1.29; 95% confidence interval, 1.01 to 1.66), with excess events broadly distributed in disease categories not identified in previous studies as areas of concern.

Conclusions:
At 1 year, bevacizumab and ranibizumab had equivalent effects on visual acuity when administered according to the same schedule. Ranibizumab given as needed with monthly evaluation had effects on vision that were equivalent to those of ranibizumab administered monthly. Differences in rates of serious adverse events require further study. (Funded by the National Eye Institute; ClinicalTrials.gov number, NCT00593450.) Ⓐ

Abstract[2]

Objective:
To evaluate the biologic effects and safety of vascular endothelial growth factor (VEGF) Trap-Eye during a 12-week fixed-dosing period in patients with neovascular (wet) age-related macular degeneration (AMD).

Design:
Multicenter, prospective, randomized, double-masked clinical trial with initial 12-week fixed dosing period. Data were analyzed to week 16.

Participants:
We included 159 patients with subfoveal choroidal neovascularization secondary to wet AMD.

Methods:
Patients were randomized 1:1:1:1:1 to VEGF Trap-Eye during the fixed-dosing phase (day 1 to week 12): 0.5 or 2 mg every 4 weeks (0.5 mg q4wk, 2 mg q4wk) on day 1 and at weeks 4, 8, and 12; or 0.5, 2, or 4 mg every 12 weeks (0.5 mg q12wk, 2 mg q12wk, or 4 mg q12wk) on day 1 and at week 12.

Main Outcome Measures:
The primary endpoint was change from baseline in central retinal/lesion thickness (CR/LT) at week 12; secondary outcomes included change in best-corrected visual acuity (BCVA), proportion of patients with a gain of ≥15 letters, proportion of patients with a loss of >15 letters, and safety.

Results:
At week 12, treatment with VEGF Trap-Eye resulted in a significant mean decrease in CR/LT of 119 μm from baseline in all groups combined (P<0.0001). The reduction in CR/LT with the 2 mg q4wk and 0.5 mg q4wk regimens was significantly greater than each of the quarterly dosing regimens. The BCVA increased significantly by a mean of 5.7 letters at 12 weeks in the combined group (P<0.0001), with the greatest mean gain of >8 letters in the monthly dosing groups. At 8 weeks, BCVA improvements were similar with 2 mg q4wk and 2 mg q12wk dosing. After the last required dose at week 12, CR/LT and visual acuity were maintained or further improved at week 16 in all treatment groups. Ocular adverse events were mild and consistent with safety profiles reported for other intraocular anti-VEGF treatments.

Conclusions:
Repeated monthly intravitreal dosing of VEGF Trap-Eye over 12 weeks demonstrated significant reductions in retinal thickness and improvements in visual acuity and was well-tolerated in patients with neovascular AMD. Ⓐ

Abstract[3]

Purpose: To test whether long-term multivitamin supplementation affects the incidence of cataract or age-related macular degeneration (AMD) in a large cohort of men.
Design: Randomized, double-blind, placebo-controlled trial.
Participants: A total of 14,641 US male physicians aged >50 years.
Intervention: Daily multivitamin or placebo.
Main Outcome Measures: Incident cataract and visually significant AMD responsible for a reduction in best-corrected visual acuity to 20/30 or worse based on self-reports confirmed by medical record review.
Results: During an average of 11.2 years of treatment and follow-up, a total of 1817 cases of cataract and 281 cases of visually significant AMD were confirmed. There were 872 cataracts in the multivitamin group and 945 cataracts in the placebo group (hazard ratio [HR], 0.91; 95% confidence interval [CI], 0.83e0.99; P = 0.04). For visually significant AMD, there were 152 cases in the multivitamin group and 129 cases in the placebo group (HR, 1.19; 95% CI, 0.94e1.50; P = 0.15).
Conclusions: These randomized trial data from a large cohort of middle-aged and older US male physicians indicate that long-term daily multivitamin use modestly and significantly decreased the risk of cataract but had no significant effect on visually significant AMD. Ⓐ

Evidence-Based References

CATT Research Group: Ranibizumab and bevacizumab for neovascular age-related macular degeneration, *N Engl J Med* 364:1897–1908, 2011. Ⓐ

Brown DM: for the CLEAR-IT 2 Investigators Primary endpoint results of a phase II study of vascular endothelial growth factor Trap-Eye in wet age-related macular degeneration, *Ophthalmology* 118:1089–1097, 2011. Ⓐ

Christen WG, Glynn RJ, Manson JE, et al.: Effects of multivitamin supplement on cataract and age-related macular degeneration in a randomized trial of male physicians, *Ophthalmology* 121:525–534, 2014. Ⓐ

SUGGESTED READINGS

The CATT: Research Group: Ranibizumab and bevacizumab for neovascular age-related macular degeneration, *N Engl J Med* 364:1897–1908, 2011.

Schwartz SD et al.: Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies, *Lancet* 385:509–516, 2014.

BASIC INFORMATION

DEFINITION

Malaria is a protozoan disease caused by intraerythrocytic protozoa of the genus *Plasmodium* and transmitted by female *Anopheles* spp. mosquitoes. It is endemic throughout most of the tropics and is characterized by hectic fever and often presents with classic malarial paroxysm. Five species of genus *Plasmodium* usually infect humans (Table M1-1):

- *P. falciparum*
- *P. vivax*
- *P. malariae*
- *P. ovale*
- *P. knowlesi*

SYNONYMS

Periodic fever
Tertian malaria
Quartan malaria
Tropical splenomegaly

ICD-9CM CODES

084.6 Malaria

ICD-10CM CODES

B54 Unspecified malaria
B50.9 *Plasmodium faluparum* malaria, unspecified
B51.9 *Plasmodium vivax* malaria without complications
B52.9 *Plasmodium malariae* malaria without complications
53.0 *Plasmodium ovale* malaria
B53.8 Other parasitologically confirmed malaria, not elsewhere classified

EPIDEMIOLOGY & DEMOGRAPHICS

Global:

- ~300 million cases a year in more than 100 countries
- Around 900,000 deaths per year, with more than 80% of the deaths occurring in children of sub-Saharan Africa
- 3 billion people live in malaria-endemic areas

U.S.:

- ~1500 cases reported to the CDC in the United States each year. In the majority of reported cases, U.S. civilians who acquired infection abroad had not adhered to a chemoprophylaxis regimen that was appropriate for the country in which they acquired malaria.
- More than 50% of the reported cases in the U.S. are *P. falciparum.* On average, there are six deaths per year in the United States.
- Most infections limited to:
  1. Immigrant population
  2. Returned travelers or troops from endemic area
- Occasionally, transmission through exposure to infected blood product or shared intravenous needles by users of injection drugs.
- Congenital transmission is possible.
- Local mosquito-borne transmission has been reported.
- Competent mosquito vectors are present.
  1. *A. albimanus* in eastern United States
  2. *A. freeborni* in western United States

Geographic distribution:

- *P. falciparum:* Sub-Saharan Africa, Papua New Guinea, Solomon Islands, Haiti, Indian subcontinent
- *P. vivax:* Central America, South America, North Africa, Middle East, Indian subcontinent
- *P. ovale:* West Africa
- *P. malariae:* worldwide

Parasite life cycle (Fig. M1-1):

- Human infection begins when a female anopheline mosquito bites (only female anopheline mosquito takes blood meal) and inoculates plasmodial sporozoites into bloodstream. The bite usually occurs between dusk and dawn.
- The sporozoites then travel to liver and invade to hepatocytes.
- In the hepatocytes, the sporozoites mature to tissue schizont or become dormant hypnozoites.
- The tissue schizonts amplify the infection by producing a large number of merozoites (10,000 to 30,000).
- Each merozoite is capable of invading an RBC and can establish the asexual cycle of replication in RBCs.
- Asexual cycles produce and release 24 to 32 merozoites at the end of 48- or 72-hr *(P. malariae)* cycles.
- The hypnozoites are only found in relapsing malaria *P. vivax* or *P. ovale* and may remain dormant for up to 5 yr.
- Eventually some intraerythrocytic parasites develop into gametocytes. Male and female gametocytes are taken up by a female anopheline mosquito with a blood meal where they fertilize in the mosquito gut to produce a diploid zygote that matures to an ookinete; haploid sporozoites are generated that migrate to the salivary gland of the mosquito to infect another human.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fever is the hallmark of malaria, known as malarial paroxysm, initially daily until synchronization of infection after several wk, when fever may occur every other day (tertian) in *P. vivax, P. ovale,* or *P. falciparum* malaria or every third day (quartan) in *P. malariae* malaria. Table M1-2 describes the WHO criteria for severe malaria.
- Classic malarial paroxysm characterized by
  1. Cold stage: abrupt onset of cold feeling associated with rigors, shakes.
  2. Hot stage: high fever (~40° C) associated with restlessness.
  3. Sweating stage: patient defervesces.
- Nonspecific symptoms are
  1. Headache.
  2. Cough.
  3. Myalgia.
  4. Vomiting.
  5. Diarrhea.
  6. Jaundice.
- *P. falciparum:*
  1. Most pathogenic of the four species.
  2. Rapidly progresses to high-level parasitemia.
  3. Important cause of the fatal malaria.

TABLE M1-1 Features of the Five Species of Malaria Known to Cause Disease in Humans

	Plasmodium falciparum	Plasmodium vivax	Plasmodium ovale	Plasmodium malariae	Plasmodium knowlesi
Incubation period (days)	6-25	8-27	8-27	16-40	12
Asexual cycle (hours)	48 (tertian)	48 (tertian)	48 (tertian)	72 (quartan)	24 (tertian)
Relapse	No	Yes*	Yes*	No†	No
Chloroquine resistance	Yes‡	Rare§	No	No‖	No
Characteristic on thin blood film	Rings predominate, multiply infected RBCs, high parasitemia, rings with thread-like cytoplasm, double nuclei, banana-shaped gametocytes	Enlarged RBCs, Schüffner's dots, trophozoite cytoplasm ameboid, 12-24 merozoites in mature schizont	Oval RBCs with fringed edges, Schüffner's dots, trophozoite cytoplasm compact, 6-16 merozoites in mature schizont	Trophozoite cytoplasm compact (band forms), 6-12 merozoites in mature schizont, RBC unchanged	Similar to *P. malariae*, 8-10 merozoites in mature schizont, often in rosette pattern with central clump of pigment

*Relapses may appear months to years after initial infection due to dormant hypnozoites in the liver.
†Although relapse does not occur, *P. malariae* can produce persistent infections that remain below detectable limits in the blood for 20 to 30 years or more.
‡*P. falciparum* resistance to sulfadoxine/pyrimethamine, mefloquine, halofantrine, and artemisinin have also been reported in some areas, along with partial resistance to quinine and quinidine.
§*P. vivax* resistance to chloroquine now reported in some areas of Southeast Asia, Oceania, and South America.
‖Chloroquine-resistant *P. malariae* has also been reported in south Sumatra, Indonesia.
From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

4. Classic malarial paroxysm is usually absent.
5. Incubation period after exposure is 12 days (range: 9 to 60 days).
6. Cytoadherence and resetting of RBCs play central role in pathogenesis.
7. The sequestration of RBCs in vital organs leads to fatal complications.
8. Cerebral malaria is a feared complication.
9. Invades erythrocytes of all ages.
10. Lacks hypnozoites (intrahepatic stage), does not relapse.
11. Blood smear usually shows ring form only.
12. Pigment color is black.
13. Banana-shaped gametocytes; if seen in blood, smear is diagnostic.
14. Chloroquine resistance is widely present.

- *P. vivax:*
  1. Known as tertian malaria: fever occurs every other day.
  2. Duffy blood-group antigen FYA- or FYB-related receptor is needed for attachment to RBC.
  3. FyFy phenotype (most West African) individuals are resistant to *P. vivax* malaria.
  4. Incubation period after exposure is 14 days (range: 8 to 27 days).
  5. Hypnozoites may cause relapse of infection after years.
  6. Infects mainly reticulocytes.
  7. Irregularly shaped large rings and trophozoites, enlarged RBCs, and Schüffner's dots are seen in peripheral blood smear (Fig. M1-2).
  8. Pigment color is yellow-brown.
  9. *P. vivax* from Papua New Guinea have reduced sensitivity to chloroquine.
  10. Primaquine is needed to eradicate the hypnozoites.
- *P. ovale:*
  1. Also known as tertian malaria; fever occurs every other day.
  2. Occurs mainly in tropical Africa.
  3. Incubation period after exposure is 14 days (range: 8 to 27 days).
  4. Hypnozoites may cause relapse of infection.
  5. Infects mainly reticulocytes.
  6. Infected RBC is seen as enlarged, oval shape containing large ring or trophozoites with Schüffner's dots.
  7. Pigment color is dark brown.
  8. Primaquine needed to eradicate the hypnozoites.
  9. No chloroquine resistance has been encountered.
- *P. malariae:*
  1. Known as quartan malaria; fever occurs every third day.
  2. Common cause of chronic malarial infection.
  3. May persist for 20 to 30 yr after leaving the endemic area.
  4. Worldwide distribution.
  5. Incubation period after exposure is 30 days (range: 16 to 60 days).
  6. Lacks hypnozoites (intrahepatic stage).
  7. May persist in blood for many years if treated inadequately.
  8. Chronic infection may cause soluble immune-complex, resulting in nephritic syndrome.

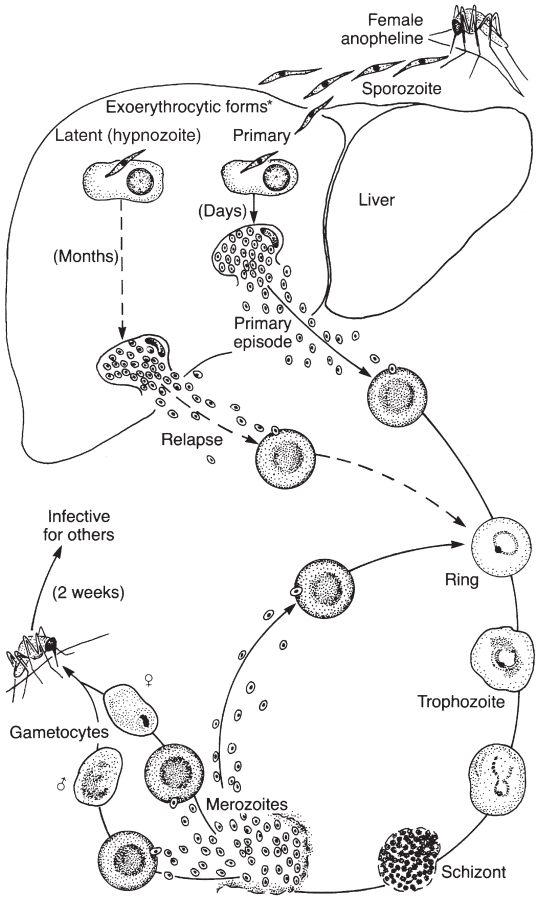

FIGURE M1-1 Life cycle of plasmodia in humans. Exoerythrocytic forms are also called schizonts. (From Gorbach SL: *Infectious diseases,* ed 2, Philadelphia, 1998, Saunders.)

TABLE M1-2 World Health Organization Criteria for Severe Malaria, 2000

Impaired consciousness
Prostration
Respiratory distress
Multiple seizures
Jaundice
Hemoglobinuria
Abnormal bleeding
Severe anemia
Circulatory collapse
Pulmonary edema

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

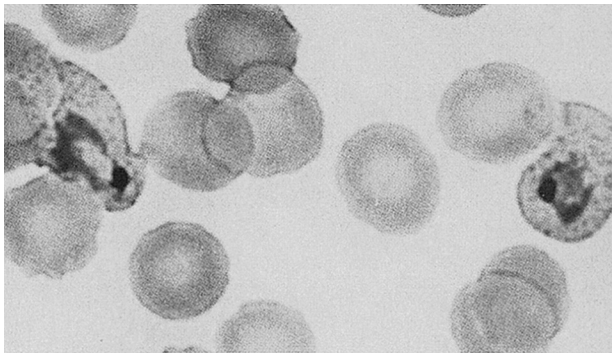

FIGURE M1-2 Giemsa-stained blood smear in *Plasmodium vivax* malaria. Asexual parasites. Note that the parasites are large and ameboid; the infected erythrocytes are the largest cells in the field (because they are reticulocytes), and the erythrocytes contain numerous pink dots (Schüffner's dots) (×2000). (From Klippel JH et al [eds]: *Internal medicine,* ed 5, St Louis, 1998, Mosby.)

9. Infects mainly mature RBCs.
10. Band or rectangular forms of trophozoites are commonly seen in peripheral blood smear.
11. Pigment color is brown-black.

- Cerebral malaria:
  1. Feared complication of *P. falciparum* infection.
  2. Mortality is ~20%.
  3. Pathogenesis is poorly understood.
  4. Ischemia as a result of sequestration of parasites or cytokines induced by parasite toxin(s) is the key debate.
  5. Seizure and altered mental status leading to coma are cardinal manifestation.
  6. Hypoglycemia, lactic acidosis, and elevated circulating TNF-α may be present.
  7. CSF studies: no increase of WBC count or protein, raised lactate concentrate, and increased opening pressure, especially in children, may be present.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Typhoid fever
- Dengue fever
- Yellow fever
- Viral hepatitis
- Influenza
- Brucellosis
- UTI
- Leishmaniasis
- Trypanosomiasis
- Rickettsial diseases
- Leptospirosis

WORKUP

- Clinical diagnosis is notoriously inaccurate.
- Demonstration of malarial parasites in blood smear is essential.
- Newer molecular diagnostic techniques (polymerase chain reaction, rapid diagnostic tests) are promising.

LABORATORY TESTS

- The thick and thin blood film is required to identify malarial parasites. A Giemsa-stained film of the patient's peripheral blood should be examined for parasites as soon as possible.
- The thick smears are more sensitive and primarily used to detect the presence of parasites.
- The thin smears are used for species differentiation and parasite density estimation.
- A patient who is suspected of having malaria but who has no parasite seen in blood smears should have blood smears repeated every 12 to 24 hr for 3 consecutive days.

PREPARATION OF BLOOD SMEAR

- Must be prepared from fresh blood obtained by pricking the fingers.
- The thin smear is fixed in methanol before staining.
- The thick smear is stained unfixed.
- The smear should be stained with a 3% Giemsa solution (pH of 7.2) for 30 to 45 min.
- The parasite density should be estimated by counting the percentage of RBCs infected, not the number of parasites, under an oil immersion lens on thin film.

COMMON ERRORS IN READING MALARIAL SMEARS

- Platelets overlying an RBC
- Misreading artifacts as parasites
- Concern about missing a positive slide

MOLECULAR DIAGNOSIS OF MALARIA

- Rapid diagnostic tests (RDT)
  1. Employ immunochromatographic lateral flow technology for antigen detection.
  2. Thus far only one RDT has been FDA approved: BinaxNOW Malaria test kit.
  3. This kit is based on antigens HRP-2 and aldolase.
  4. For *P. falciparum:* sensitivity 95% and specificity 94%.
  5. For *P. vivax:* sensitivity 69% and specificity 100%.
- Limitations of the BinaxNOW Malaria test:
  1. Not approved for mixed infections
  2. Should not be used for *P. malariae* and *P. ovale* as data are limited
  3. Positive test must be confirmed by microscopy
  4. Negative results require confirmation by thick and thin smears
  5. This test cannot be used to monitor therapy as antigen persists after the elimination of the parasite, causing false positives
- Other diagnostic tests available include:
  1. Tagged monoclonal antibodies for malaria antigen detection
  2. Nucleic acid amplification and detection: PCR can detect parasites down to a level of 1 to 5 parasites per microliter of blood. PCR can detect mixed species infection
  3. Fluorescence microscopy with acridine orange or other staining
  4. Dark field microscopy

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

ANTIMOSQUITO MEASURES

1. Eradication of mosquito breeding places by chemical spray
2. Use of mosquito nets properly in the endemic areas
3. Use of protective clothing
4. Use of insect spray (permethrin), mosquito coils, or repellents such as diethyltoluamide (DEET). For adults, DEET (30% to 50%) is generally protective for at least 4 hr. For smaller children, use DEET at ≤20% concentration.

ACUTE GENERAL Rx

A definitive diagnosis of malaria is essential for specific antimalarial chemotherapy.

NON-FALCIPARUM MALARIA

- Chloroquine 600 mg base (1000 mg chloroquine phosphate) PO loading dose, 6 hr later 300 mg base (500 mg salt), then 300 mg base (500 mg salt) daily for 2 days.
- In the case of *P. vivax* and *P. ovale,* treatment with primaquine 15 mg daily for 14 days is needed to eradicate the exoerythrocytic forms, especially the hypnozoites responsible for relapses.
- G6PD should be measured before primaquine is given. Primaquine is not recommended for those who are glucose-6-phosphate dehydrogenase deficient, because primaquine can cause hemolysis and even death in G6PD-deficient persons. Normal G6PD levels must be documented before using primaquine for either chemoprophylaxis or treatment.
- Chloroquine-resistant *P. vivax* has been documented; in that case, quinine is given.

FALCIPARUM MALARIA

- Chloroquine can be used cautiously for falciparum malaria acquired in chloroquine-sensitive areas (chloroquine is more rapidly effective than quinine).
- Mainstay of treatment is oral quinine sulfate 10 mg (salt)/kg (usually 650 mg) q8h for 3 to 7 days + doxycycline 100 mg PO bid both for 7 days for adults. Pediatrics: quinine sulfate: 10 mg/kg PO tid plus clindamycin: 20 mg/kg per day divided in tid dose both for 7 days.
- Atovaquone-proguanil (Malarone): 250 mg atovaquone/100 mg proguanil): 4 adult tabs PO once a day for 3 days with food in adults or for pediatrics: pediatric tablets (62.5 mg atovaquone/25 mg proguanil) are used based on weight:
- 5 to 8 kg: 2 pediatric tabs PO once daily for 3 days
- 9 to 10 kg: 3 pediatric tabs PO once daily for 3 days
- 11 to 20 kg: 1 adult tab PO once daily for 3 days
- 21 to 30 kg: 2 adult tabs PO once daily for 3 days
- 31 to 40 kg: 3 adult tabs PO once daily for 3 days
- >40 kg: 4 adult tabs PO once daily for 3 days artemether-lumefantrine (Coartem) tablets: 4 tabs PO (at time zero and 8 hr later) then bid × 2 days for a total of six doses. For pediatrics:
- 5 to <15 kg: 1 tablet per dose
- 15 to <25 kg: 2 tablets per dose
- 25 to <35 kg: 3 tablets per dose
- >35 kg: 4 tablets per dose. The child should receive initial dose based on weight, then followed by second dose 8 hr later, then 1 dose PO bid for following 2 days

ALTERNATIVES

- Quinine sulfate plus clindamycin 900 mg tid for 7 days in adults, or
- Mefloquine 750 mg PO then 500 mg PO 6 to 12 hr later in adults

NOTE: Parasitemia may paradoxically rise in the first 24 to 36 hr and is not an indication of treatment failure.

SEVERE FALCIPARUM MALARIA

- It is a medical emergency; intensive care is preferred.
- Measurement of blood glucose, lactate, ABG is important.

- IV quinidine gluconate 10 mg salt/kg loading dose (maximum 600 mg) in NS; infuse slowly over 1 to 2 hr, followed by continuous infusion of 0.02 mg/kg/min until patient can swallow.
- Need to monitor ECG for observation of QT interval as can prolong. Also need to monitor blood pressure and glucose to avoid hypoglycemia.
- Alternatively, IV artesunate: 2.4 mg/kg IV first dose then at 12 and 24 hr followed by 2.4 mg/kg once daily. One recent study showed the superiority of parenteral artesunate over parenteral quinine in adults and children who could not take an oral medication.
- Plasmapheresis is an option for parasitemia >30% or in pregnant women and in elderly with severe malaria.

NOTE: WHO recommends IV artesunate as the treatment of choice for severe malaria in adults and children in area of low transmission. Data on children in high-transmission regions are limited, and WHO recommends treatment with artesunate, artemether, or quinine.

MULTIDRUG-RESISTANT MALARIA

- Mefloquine 1250 mg as a single dose, or
- Halofantrine 500 mg every 6 hr for 3 doses, repeat same course after 1 wk
- Combination therapy usually preferred

DISPOSITION

RISK FACTORS FOR FATAL MALARIA

- Failure to take chemoprophylaxis
- Delay in seeking medical care
- Misdiagnosis

COMPLICATIONS OF MALARIA

- Anemia
- Acidosis
- Hypoglycemia
- Respiratory distress
- DIC
- Blackwater fever
- Renal failure
- Shock

REFERRAL

- To an infectious disease specialist or travel medicine expert for severe malaria complications
- To an intensive care specialist if severe cerebral malaria or other major organ failure develops
- All malaria cases are mandated to be reported to local and state health departments by health care providers or laboratory staff

PEARLS & CONSIDERATIONS

HOST RESPONSE

- The specific immune response to malaria confers protection from high-level parasitemia and disease, but not from infection.
- Asymptomatic parasitemia without illness (premunition) is common among adults in endemic areas.
- Immunity is specific for both the species and the strain of infecting malarial parasites.
- Immunity to all strains is never achieved.
- Normal spleen function is an important host factor because of immunologic as well as filtering functions of the spleen.
- Both humoral and cellular immunity is necessary for protection.
- Polyclonal increase in serum level of IgG, IgM, and IgA occurs in immune individuals.
- Antibody to antigenically variant protein PfEMP1 is important for protection in case of *P. falciparum* malaria.
- Passively transferred IgG from immune individuals has been shown to be protective.
- Maternal antibody confers relative protection of infants from severe disease.
- Genetic disorders (sickle cell disease, thalassemia, and G6PD deficiency) confer protection from death because parasites are unable to grow efficiently in low-oxygen tensions, thus preventing high-level parasitemias.
- Individuals deficient of Duffy factor in RBCs are resistant to infection by *P. vivax.*
- Nonspecific defense mechanisms, such as cytokines (TNF-α, IL-1, -6, -8), also play an important role in protection, causing fever (temperatures of 40° C damage mature parasites) and other pathologic effects.

PREVENTION OF MALARIA: Medications are available for the prophylaxis of malaria and will vary depending on level of chloroquine resistance in a given area.

***Areas free of chloroquine-resistant Falciparum malaria*:** Chloroquine 300 mg base (500 mg chloroquine phosphate) PO/wk. Start 1 wk prior to arrival in malaria area, then weekly while there and for 4 wk on leaving malaria area. Pediatric dose: 8.3 mg/kg (5 mg/kg base). Alternatives for adults include atovaquone-proguanil (Malarone): 1 adult tablet per day starting 1 to 2 days prior to arriving in malaria area, then daily while there and then for 7 days daily on leaving malaria area.

For children, atovaquone-proguanil pediatric tablets based on weight:

11 to 20 kg 1 pediatric tablet
21 to 30 kg 2 pediatric tablets
31 to 40 kg 3 pediatric tablets
>40 kg 1 adult tablet

Areas with chloroquine-resistant Falciparum malaria

- Atovaquone-proguanil (Malarone): dosing as above
- Mefloquine 250 mg (228 mg base) PO/wk, starting 1 wk before arriving in malaria area, weekly while there and then weekly for 4 wk on return. In children, mefloquine dose is based on weight:
- <15 kg 5 mg/kg
- to 19 kg ¼ adult dose
- to 30 kg ½ adult dose
- to 45 kg ¾ adult dose
- >45 kg adult dose
- Doxycycline 100 mg PO/day for adults and children aged >8. Start 1 to 2 days before travel, daily while in malaria area, and then daily for 4 wk on return.

SPECIAL CONSIDERATIONS

- Long-term visitors or travelers
- Children aged <12 yr
- Immunocompromised host
- Pregnant women: chloroquine and mefloquine are safe in pregnancy but not atovaquone-proguanil. Avoid doxycycline and primaquine.

VACCINATION

- No effective and safe vaccine available yet
- A live, attenuated, whole sporozoite vaccine shown to work
- A synthetic peptide (SPf66) vaccine proved ineffective
- New DNA-based vaccines are in development

MALARIA INFORMATION

- CDC Travelers' Health Hotline (877) 394–8747; CDC Travelers' Health Fax (888) 232–3299
- CDC Malaria Epidemiology (770) 488–7788; internet: www.cdc.gov

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Malaria (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

CDC: Malaria surveillance, United States, 2009, *MMWR* 60(3), 2011.

Chen LH et al.: Controversies and misconceptions in malaria prophylaxis for travelers, *JAMA* 297(20):2251–2263, 2007.

Chen LH et al.: Prevention of malaria in long-term travelers, *JAMA* 296(18):2234–2244, 2006.

Griffith KS et al.: Treatment of malaria in the United States, a systematic review, *JAMA* 297:2264–2277, 2007.

Johnson BA, Kalra MG: Prevention of malaria in travelers, *Am Fam Physician* 85(10):973–977, 2012.

Rosenthal PJ: Artesunate for the treatment of severe falciparum malaria, *N Engl J Med* 358:1829–1836, 2008.

Sinclair D et al.: Artesunate versus quinine for treating severe malaria, *Cochrane Database Syst Rev* 13:6, 2012. CD005967.

Wilson MK: Malaria rapid diagnostic tests, *Clin Infect Dis* 54(11):1637–1641, 2012.

BASIC INFORMATION

DEFINITION

Malignant hyperthermia (MH) is a rare and life-threatening subclinical myopathy that can occur in susceptible individuals after exposure to triggering agents, most commonly halogenated anesthetic gases, such as halothane, isoflurane, sevoflurane, and desflurane, or the depolarizing agent, succinylcholine. Initial signs include rising end tidal carbon dioxide (PET CO_2) levels, tachycardia, and skeletal muscle rigidity. Mortality has recently been reported to be 1.4% to 5%, down from 70% in the past. Advanced age, muscularity, comorbidities, and disseminated intravascular coagulation (DIC) increase risk of death.

SYNONYMS

Malignant hyperthermia of anesthesia
Malignant hyperpyrexia
MH

ICD-9CM CODES
995.86 Malignant hyperthermia of anesthesia
ICD-10CM CODES
T88.3 Malignant hyperthermia due to anesthesia, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: In the population as a whole undergoing general anesthesia, the incidence is approximately 1:100,000, depending on the susceptibility of the population and the anesthetics used. It is widely believed that we fail to include a large number of unrecognized events, and that fully half of afflicted patients have had prior uneventful exposures to the same triggering agents. Children account for 42% to 52% of cases, however, any age may be affected.

PREVALENCE: In the general population, the prevalence of susceptibility to MH (MHS) is estimated to be 1:2000. In family cohorts of patients who are susceptible, the prevalence of susceptibility ranges from 1:200 to 1:5000.

PREDOMINANT AGE AND SEX: Male to female ratio of 2:1. Children account for up to half of cases.

GENETICS: Susceptibility to MH is inherited in an autosomal dominant fashion in 50% of cases; the rest presumed to be new mutations. At least 31 mutations on chromosome 19 are known to cause changes in the ryanodine receptor (RYR1) that result in the abnormalities of skeletal muscle calcium homeostasis and susceptibility to MH, with significant clinical variability due to incomplete penetrance and variable expressivity. In approximately 1% of cases, MH susceptibility is due to mutations of the gene on chromosome one coding for the dihydropyridine receptor.

RISK FACTORS: Patients with myopathies due to RYR1 abnormalities, such as central core myopathy, are likely to be MHS and should not receive succinylcholine or volatile anesthetics. Patients with dystrophinopathies such as Duchenne and Becker muscular dystrophy, enzymopathies of skeletal muscle such as McArdle's disease, or exercise and heat-induced rhabdomyolysis, may develop rhabdomyolysis when exposed to these agents, and many authors deem it prudent to use only non-triggering agents. Other syndromes such as osteogenesis imperfecta, myotonia, and neuroleptic malignant syndrome are no longer felt to be associated with MHS.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Within minutes to hours after the triggering anesthetic is administered, the patient develops muscle rigidity and tachycardia that may progress to dysrhythmia, hypotension, and hyperthermia (up to 45° C). Masseter muscle rigidity is common, but is often a normal response to general anesthesia and succinylcholine. The skin may initially be erythematous, progressing to a mottled, cyanotic appearance. Due to increased skeletal muscle metabolism, CO_2 production is increased, leading to elevated mixed venous and arterial pCO_2, and an elevated PET CO_2 in patients who are not breathing spontaneously.
- Muscle injury with an elevated creatine kinase (CK) may lead to rhabdomyolysis and subsequent acute renal failure. Disseminated intravascular coagulation (DIC) may develop.
- Box M1-1 summarizes the findings consistent with MH.

ETIOLOGY

- In contrast to fever due to inflammation where the hyperpyrexia is due to cytokine-induced changes in the hypothalamic set point, MH results from overproduction of heat due to hypermetabolism of skeletal muscle.
- In subjects genetically susceptible to dysregulated calcium release from the sarcoplasmic reticulum, administration of volatile anesthetic gases results in excessively elevated release of sarcoplasmic Ca^{++}, while halothane will inhibit Ca^{++} reuptake, both resulting in unmitigated muscle rigidity and heat production that overwhelms the body's ability to dissipate heat.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Neuroleptic malignant syndrome
- Fever
- Heat stroke
- Thyrotoxicosis
- Pheochromocytoma
- Central nervous system infection or space-occupying lesion
- MDMA (Ecstasy), cocaine, alcohol withdrawal, or amphetamine use
- Serotonin syndrome
- Adverse reaction to MAOIs or anticholinergic drug
- Strychnine poisoning
- Sepsis
- Drug withdrawal
- Rhabdomyolysis
- Transfusion reactions

WORKUP

MH can often be distinguished from other causes of hyperthermia based on history.

LABORATORY TESTS

- If the cause of hyperthermia is uncertain, thyroid function studies, CBC, toxicology screen, and urine vanillylmandelic acid (VMA) may be useful.
- Once the diagnosis is established, it is important to follow electrolytes, especially potassium, calcium, and phosphorus; creatinine; blood urea nitrogen; liver transaminases; and creatinine kinase.
- Prothrombin time and partial thromboplastin time should be followed to evaluate for DIC.

BOX M1-1 Positive Findings Consistent with Malignant Hyperthermia (MH)

History of recent exposure to trigger agent, including volatile anesthetic agents or succinylcholine
Family or personal history of MH susceptibility
Total body rigidity
Masseter spasm
Inappropriately elevated (38.8° C) or rapidly increasing temperature (>1.5° C over 5 min)
Inappropriate tachypnea
Profuse sweating
Mottled, cyanotic skin
Dark urine, urine dipstick testing shows a positive result from blood without red cells in the sediment and no hemolysis
Unexplained, excessive bleeding
Unexplained ventricular tachycardia or fibrillation
Inappropriate hypercarbia (venous $Paco_2$ >65 mm Hg, arterial $Paco_2$ >55 mm Hg) if the patient is receiving positive-pressure ventilation or is spontaneously breathing with greater than normal minute ventilation
Arterial base excess more negative than −8 mEq/L
Arterial pH <7.25
Potassium concentration >6 mEq/L
Creatine kinase >10,000 IU/L

From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.

IMAGING STUDIES

CT scan of the head to evaluate for space-occupying lesion if clinically indicated.

SUSCEPTIBILITY TESTING

Testing for MH susceptibility is not done during the acute event, but can be performed after discharge or preoperatively in patients at risk, such as those with a personal or family history of problems with anesthesia suggestive of MH. Genetic evaluation or the in vitro muscle contracture test can be performed. The latter involves placing a muscle biopsy specimen in a bath of caffeine or halothane. Significant muscle contraction is 97% to 99% sensitive for MH susceptibility, with a specificity of 78% to 94% and a cost of $6 to $10,000. It is performed in only a few sites in the U.S. Genetic testing, while noninvasive, has a sensitivity of <50% and a cost of $1 to $4000. Generally, a positive contracture test leads to genetic testing, unless there is a positive family member, in which case the patient can go directly to genetic testing.

Rx TREATMENT

Immediate discontinuation of potential triggering agents, hyperventilation on an FiO_2 100%, administration of dantrolene, and aggressive cooling are instituted promptly. Based on lab results, sodium bicarbonate to combat and mitigate metabolic acidosis, and dextrose and insulin to treat hyperkalemia may be warranted. ABGs, serum electrolytes, clotting studies, CK, capnography, central venous pressure, and urine output should be followed closely.

NONPHARMACOLOGIC THERAPY

- The patient should be cooled to 38°C. This can be accomplished with ice packs to the axillae and groin, a cooling blanket, a fan with cool mist, or chilled IV fluids. In extreme situations, partial extracorporeal bypass or iced peritoneal lavage have proven helpful.
- Frequent evaluation of core temperature, hemodynamics, and gas exchange are imperative.

ACUTE GENERAL Rx (see *Box M1-2*)

- Dantrolene, which binds to ryanodine receptors and limits calcium release, is the only known antidote for MH. It has no effect on cardiac or smooth muscle, but can cause weakness of the diaphragm and other skeletal muscles. After a loading dose of 2.5 mg/kg IV over 10 minutes, it should be administered at 1mg/kg IV every 5 minutes until elevated PET CO_2, rigidity, and fever abate. Some patients, particularly large muscular ones, may require an initial dose of up to 10 mg/kg.

BOX M1-2 Management of an Acute Malignant Hyperthermia Episode in the Intensive Care Unit

1. Administer high-flow 100% oxygen via a nonrebreathing mask, and consider endotracheal intubation.
2. For ventilated patients, administer an Fio2 of 1.0 and increase minute ventilation to control $Paco_2$.
3. Administer dantrolene (2.5 mg/kg intravenously) over 10 min, and repeat until acidosis and muscle rigidity have resolved. Repeat dantrolene (1 mg/kg) every 6 hr.
4. Initiate cooling with ice packs in the axillae and groin; decrease room temperature; use hypothermia blankets, iced intravenous saline solution (10 mL/kg over 10 min, repeated as needed), and lavage body cavities with cold saline solution if temperature is greater than 39° C. Stop cooling when core temperature falls to 38° C.
5. Correct metabolic acidosis with sodium bicarbonate (1-2 mEq/kg initially), and give subsequent doses based on base excess and body weight.
6. Administer calcium chloride (10 mg/kg) or calcium gluconate (100-200 mg/kg) to cardiotoxicity associated with hyperkalemia.
7. Give regular insulin (0.1 U/kg) and glucose (0.3-0.5 g/kg) to correct hyperkalemia.
8. Administer lidocaine (1 mg/kg) to treat ventricular arrhythmias. Consider amiodarone (5 mg/kg IV) for refractory, stable ventricular tachycardia. Do not delay defibrillation or cardiopulmonary resuscitation if indicated by cardiovascular instability.
9. Maintain urine output of 2 ml/kg/hr with aggressive cold fluid administration, furosemide (0.5-1 mg/kg), and additional mannitol (0.25-0.3 g/kg) if needed.
10. Consider quantitative end-tidal CO_2 monitoring.
11. Monitor core temperature (pulmonary artery, esophageal temperature probe, rectal probe).
12. Place arterial catheter for invasive blood pressure monitoring and frequent blood sampling. Consider central venous catheter and/or pulmonary artery catheter if indicated by cardiovascular instability.
13. Repeat venous blood gas and electrolytes analysis until these normalize. Repeat CK at least every 6 hr while the patient is in ICU and then daily until CK returns to normal. Assess glucose, clotting function, and hepatic and renal functions, and treat symptomatically. Repeat lactic acid measurement after each dantrolene administration.
14. Consider hemodialysis if indicated.
15. Consider intensive care monitoring for at least 24 hr after MH episode or after recrudescence of MH.
16. Refer the patient for muscle caffeine-halothane contracture testing and consider exam of RYR1. Pursue a pathologic diagnosis for other occult myopathies.

CK, Creatine kinase; *ICU,* intensive care unit; *MH,* malignant hyperthermia.

From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.

ONGOING CARE

- Up to 25% of patients will have recrudescence of their symptoms, on average 13+/–13 hours after the initiation of MH. Dantrolene, 1mg/kg IV every 4 to 6 hours or by continuous infusion at 0.1 to 0.3 mg/kg/hr IV is recommended. Additional boluses may be needed for breakthrough signs. Treatment should be continued for 24 to 48 hours.
- Aggressive hydration with forced diuresis and alkalinization of the urine should be instituted for rhabdomyolysis. Observe closely for the development of compartment syndrome.
- Beta-blockers and lidocaine may be useful for dysrhythmias. Verapamil should be avoided as it may significantly depress cardiac function when used with dantrolene.
- Consider sodium bicarbonate for profound metabolic acidosis.

CHRONIC Rx

This is an acute disease, resolving in 24 to 48 hours with appropriate treatment.

The patient should be aware that exercise in excessive heat and/or humidity could trigger an episode of MH.

The patient and their immediate family should be advised to undergo susceptibility testing.

COMPLEMENTARY & ALTERNATIVE MEDICINE

None

DISPOSITION

The patient should be admitted to the Intensive Care Unit for at least 24 hours.

REFERRAL

Anesthesia is presumably involved in the patient's care, so cardiology, renal, and hematologic consultation as appropriate.

PEARLS & CONSIDERATIONS

COMMENTS

MH is a life-threatening condition that requires prompt recognition of the signs and symptoms to minimize illness and end-organ damage. Family or personal history of problems with general anesthesia in the past are clues to susceptibility and should prompt careful pre-operative evaluation. Prophylactic dantrolene is no longer recommended for MH patients undergoing general anesthesia with non-triggering agents.

PATIENT & FAMILY EDUCATION

The patient and their family need to be aware of the diagnosis so that they may undergo susceptibility testing or need to make anesthesia aware of the potential problem during preoperative assessment.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **JOSEPH MEHARG, M.D.,** and **STEPHANIE A. CURRY, M.D.**

SUGGESTED READINGS

Capacchione JF et al.: The relationship between exertional heat illness, exertional rhabdomyolysis, and malignant hyperthermia, *Anesth Analg* 109:1065–1069, 2009.

Glahn KPE et al.: Recognizing and managing a malignant hyperthermia crisis: guidelines from the European Malignant Hyperthermia Group, *Br J Anaesth* 105:417–420, 2010.

Jain G et al.: Malignant hyperthermia in endosulfan poisoning, *Toxicol Int* 19:74–76, 2012.

Johannsen S et al.: Ondansetron-induced muscular contractures in malignant hyperthermia-susceptible individuals, *Anesth Analg* 115:925–928, 2012.

BASIC INFORMATION

DEFINITION

A Mallory-Weiss tear (MWT) is a longitudinal mucosal laceration in the region of the gastroesophageal junction.

SYNONYMS

Mallory-Weiss syndrome

ICD-9CM CODES
530.7 Gastroesophageal laceration-hemorrhage syndrome
530.82 Esophageal hemorrhage
ICD-10CM CODES
K22.6 Mallory-Weiss syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- Accounts for 5% to 15% of cases of upper gastrointestinal (GI) bleeding
- Reported from early childhood to old age; the majority of patients are age 40 to 60 yr
- More common in males
- Alcohol use is present in 30% to 60%

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Vomiting, retching, or vigorous coughing will often, but not always, precede hematemesis.
- Patients may be clinically stable or present with tachycardia, hypotension, melena, hematochezia, epigastric pain, or back pain.
- Bleeding may be self-limited or severe.
- Tears may be seen in association with other upper GI tract lesions, including hiatus hernia (present in as many as 90% of patients), ulcers, and esophageal varices, particularly in alcoholics.

ETIOLOGY

- An acute increase in intraabdominal pressure is transmitted to the esophagus, resulting in mucosal laceration.
- Vomiting may be associated with alcohol use, ketoacidosis, ulcer disease, uremia, pancreatitis, chemotherapy, cholecystitis, pregnancy (in particular associated with hyperemesis gravidarum), myocardial infarction, or the postoperative period.
- Tears may be iatrogenic, related to routine endoscopy (especially in struggling or retching patients, or in association with hiatal hernias), enteroscopy with or without overtubes, esophageal dilation, lower esophageal pneumatic disruption therapy for achalasia, endoscopic submucosal dissection, transesophageal echocardiography, or in association with polyethylene glycol electrolyte colonic lavage preparation.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Esophageal or gastric varices
- Esophagitis or esophageal ulcers (peptic or pill-induced)
- Gastric erosions
- Gastric or duodenal ulcer
- Dieulafoy lesion
- Arteriovenous malformations
- Neoplasms (usually gastric)
- Boerhaave's syndrome

WORKUP

Endoscopy is the diagnostic method of choice.

LABORATORY TESTS

- Complete blood count, prothrombin time, partial thromboplastin time
- Electrolytes, blood urea nitrogen, creatinine, liver function tests, pregnancy test, tests to evaluate for predisposing conditions

IMAGING STUDIES

Upper GI series is usually not sensitive. Patients with concurrent chest pain, dyspnea, shock, or physical examination findings of crepitus or pleural effusion should have a chest radiograph or CT to exclude Boerhaave's syndrome.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive care
- Avoidance of aspirin, nonsteroidal anti-inflammatory drugs, and anticoagulants

ACUTE GENERAL Rx

- Patients with active bleeding or hemodynamic instability require large-bore IVs, fluid resuscitation, and transfusion of blood products (red blood cells, fresh frozen plasma, and platelets) as appropriate.
- Nasogastric decompression and antiemetics may be considered.
- Endoscopic therapy for patients with active or ongoing hemorrhage (Fig. M1-3). Therapeutic modalities include electrocoagulation, injection (e.g., 1:10,000 epinephrine, polidocanol), sclerotherapy (for bleeding associated with esophageal varices), band ligation, or endoscopic hemoclips (therapies may be used alone or in combination) (Fig. EM1-4).
- Arterial embolization in patients with active bleeding who are poor surgical candidates.
- Laparotomy, with gastrotomy and oversewing of the tear, is required in a small percentage of patients with uncontrolled bleeding.

CHRONIC Rx

- Healing will usually occur without specific therapy.
- H_2 blockers or proton pump inhibitors may be given to help facilitate healing but should not be used long term unless appropriate indications are present.

DISPOSITION

- Prognosis is good, with spontaneous cessation of bleeding in upwards of 90% of patients. Endoscopic features can guide treatment. Blatchford score <6 suggests no need for transfusion or endoscopic intervention.
- Delayed rebleeding is described in patients with high-risk stigmata (shock at initial presentation, spurting or oozing at initial endoscopy).
- Death has been reported in 3% to 12%, often in association with severe bleeding and underlying comorbid conditions such as advanced age, coagulopathy, elevated transaminases, thrombocytopenia, alcohol use, presentation with a very low hemoglobin level or melena, and multisystem organ failure.

REFERRAL

- Gastrointestinal referral for endoscopy
- Surgical referral for bleeding unresponsive to endoscopic treatment or in the setting of coexistent perforation

PEARLS & CONSIDERATIONS

Conditions predisposing to retching or vomiting should be identified and treated at presentation.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Mallory-Weiss Tear (Patient Information)

AUTHOR: **HARLAN G. RICH, M.D.**

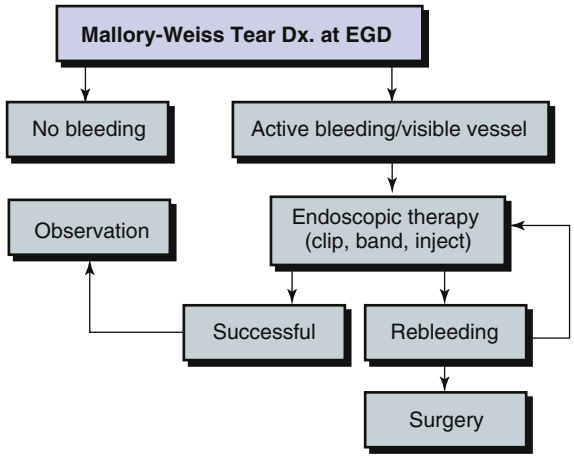

FIGURE M1-3 Treatment algorithm for Mallory-Weiss tear. *EGD,* Esophagogastroduodenoscopy. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

SUGGESTED READINGS

Huang SP et al.: Endoscopic hemoclip placement and epinephrine injection for Mallory-Weiss syndrome with active bleeding, *Gastrointest Endosc* 55:842, 2002.

Kortas DY et al.: Mallory-Weiss tear: predisposing factors and predictors of a complicated course, *Am J Gastroenterol* 96:2863, 2001.

Llach J et al.: Endoscopic injection therapy in bleeding Mallory-Weiss syndrome: a randomized controlled trial, *Gastrointest Endosc* 54:679, 2001.

Park CH et al.: A prospective, randomized trial of endoscopic band ligation vs. epinephrine injection for actively bleeding Mallory-Weiss syndrome, *Gastrointest Endosc* 60:22, 2004.

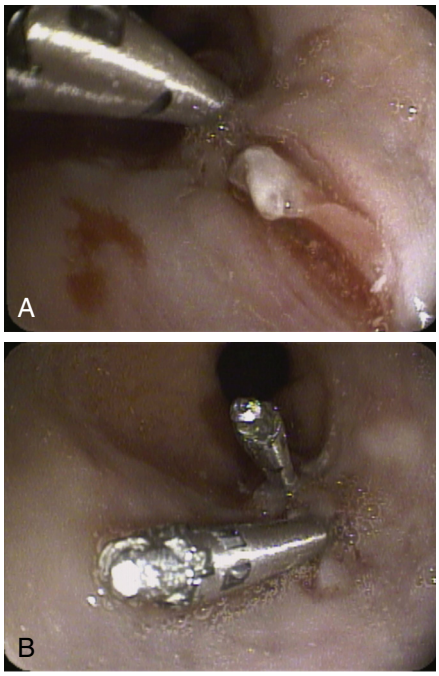

FIGURE EM1-4 Mallory-Weiss tear. A and **B,** Endoscopic views of Mallory-Weiss tear being treated with hemoclips. (Courtesy Isaac Raijman, MD, Associate Professor, Baylor College of Medicine. From Cameron JL, Cameron AM: *Current surgical therapy*, ed 10, Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Marfan's syndrome is an inherited disorder of connective tissue involving the skeleton, cardiovascular system, eyes, lungs, and central nervous system.

ICD-9CM CODES
759.82 Marfan's syndrome
ICD-10CM CODES
Q87.40 Marfan's syndrome, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE:

- One case per 10,000 persons.
- Both sexes are affected equally by this autosomal-dominant syndrome.
- Approximately 30% of cases are a new mutation.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Diagnostic criteria for Marfan's syndrome (Table M1-3):

- Skeleton: joint hypermobility (Fig. M1-5), tall stature (Fig. M1-6*A*), pectus excavatum, reduced thoracic kyphosis, scoliosis, arachnodactyly (Fig. M1-6*B*), dolichostenomelia, pectus carinatum, and erosion of the lumbosacral vertebrae from dural ectasia*
- Eye: myopia, retinal detachment, elongated globe, ectopia lentis*
- Cardiovascular: mitral valve prolapse, endocarditis, arrhythmia, dilated mitral annulus, mitral regurgitation, tricuspid valve prolapse, aortic regurgitation, aortic dissection,* dilation of the aortic root*
- Pulmonary: apical blebs, spontaneous pneumothorax
- Skin and integument: inguinal hernias, incisional hernias, striae atrophicae
- Central nervous system: attention deficit disorder, hyperactivity, verbal-performance discrepancy, dural ectasia, anterior pelvic meningocele*

If the family history is positive for a close relative clearly affected by Marfan's syndrome, manifestations should be present in the skeleton and one of the other organ systems and the diagnosis confirmed by linkage analysis or mutation detection.

If the family history is negative or unknown, the patient should have manifestations in the skeleton, the cardiovascular system, and one other system and at least one of the manifestations indicated by an asterisk in the above lists.

Manifestations are listed within each organ system in increasing specificity for Marfan's syndrome; although none is completely specific, those indicated by an asterisk are the most specific.

ETIOLOGY

Mutations in the gene that encodes fibrillin-1, the major constituent of microfibrils, which form the frame for elastic fibers. All the manifestations of Marfan's syndrome can be explained by the defective microfibrils.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Each of the clinical manifestations of the syndrome may have other causes; however, if the diagnostic criteria are met, the diagnosis is made.

WORKUP

- Echocardiography to establish:
  1. Mitral valve prolapse
  2. Mitral regurgitation
  3. Tricuspid valve prolapse
  4. Aortic regurgitation
  5. Dilation of the aortic root
- Chest radiograph
- Transesophageal echocardiography, chest CT scan, chest MRI, or aortography for suspected aortic dissection
- Chest radiograph for pulmonary apical bullae
- Ophthalmologic examination by ophthalmologist

TREATMENT

- Regular cardiac and aorta monitoring by physical examination and echocardiography.
- Endocarditis prophylaxis.
- Restriction of contact sports, weight lifting, and overexertion.

TABLE M1-3 Diagnostic Criteria for Marfan's Syndrome

In the absence of a family history of MFS, a diagnosis can be reached in 1 of 4 scenarios:
Aortic diameter at Sinuses of Valsalva Z-score ≥2 AND Ectopia Lentis = MFS*
Aortic diameter at Sinuses of Valsalva Z-score ≥2 AND *FBN1* mutation = MFS
Aortic diameter at Sinuses of Valsalva Z-score ≥2 AND Systemic Score ≥7 = MFS*
Ectopia Lentis AND *FBN1* mutation known to associate with aortic aneurysm = MFS

In the absence of a family history of MFS, alternative diagnoses to MFS include:
Ectopia Lentis 6 Systemic Score AND *FBN1* mutation not known to associate with aortic aneurysm or no *FBN1* mutation = Ectopia Lentis syndrome
Aortic diameter at Sinuses of Valsalva Z-score >2 AND Systemic Score 2:5 (with at least one skeletal feature) without Ectopia Lentis = MASS phenotype
Mitral Valve Prolapse AND Aortic diameter at Sinuses of Valsalva Z-score <2 AND Systemic Score <5 without Ectopia Lentis = Mitral Valve Prolapse syndrome

In the presence of a family history of MFS, a diagnosis can be reached in 1 of 3 scenarios:
Ectopia Lentis AND Family History of MFS = MFS
Systemic Score ≥7 AND Family History of MFS = MFS*
Aortic diameter at Sinuses of Valsalva Z-score ≥2 if older than 20 yr or ≥3 if younger than 20 yr AND Family History of MFS = MFS*

Scoring of Systemic Features (in points)†

Wrist AND thumb sign = 3 (wrist OR thumb sign = 1)
Pectus carinatum deformity = 2 (pectus excavatum or chest asymmetry = 1)
Hindfoot deformity = 2 (plain pes planus = 1)
Pneumothorax = 2
Dural ectasia = 2
Protrusio acetabuli = 2
Reduced US/LS AND increased arm/height AND no severe scoliosis = 1
Scoliosis or thoracolumbar kyphosis = 1
Reduced elbow extension = 1
Facial features (3/5) = 1 (dolichocephaly, enophthalmos, downslanting palpebral fissures, malar hypoplasia, retrognathia)
Skin striae = 1
Myopia >3 diopters = 1
Mitral valve prolapse (all types) = 1

Criteria for Causal *FBN1* Mutation

Mutation previously shown to segregate in a Marfan family
Any one of the following *de novo* mutations (with proven paternity and absence of disease in parents):
- Nonsense mutation
- In-frame and out-of-frame deletion/insertion
- Splice site mutations affecting canonical splice sequence or shown to alter splicing on mRNA/cDNA level
- Missense mutation affecting/creating cysteine residues
- Missense mutation affecting conserved residues of the EGF consensus sequence [(D/N)X(D/N)(E/Q)Xm(D/N)Xn(Y/F), with m and n representing variable number of residues; D, aspartic acid; N, asparagine; E, glutamic acid; Q, glutamine; Y, tyrosine; F, phenylalanine]
- Other missense mutations: segregation in family, if possible, + absence in 400 ethnically matched control chromosomes; if no family history, absence in 400 ethnically matched control chromosomes

Linkage of haplotype for n≥6 meioses to the *FBN1* locus

MFS, Marfan's syndrome; *US/LS,* upper segment/lower segment ratio.
*Without discriminating features of Shprintzen-Goldberg syndrome, Loeys-Dietz syndrome, or Ehlers-Danlos syndrome *and* after TGFBR1/2, collagen biochemistry, COL3A1 testing if indicated. Other conditions/genes will emerge with time.
†Maximum total: 20 points; score ≥7 indicates systemic involvement.
From Loeys BL et al: The revised Ghent nosology for the Marfan syndrome, *J Med Genet* 47:476-485, 2010.

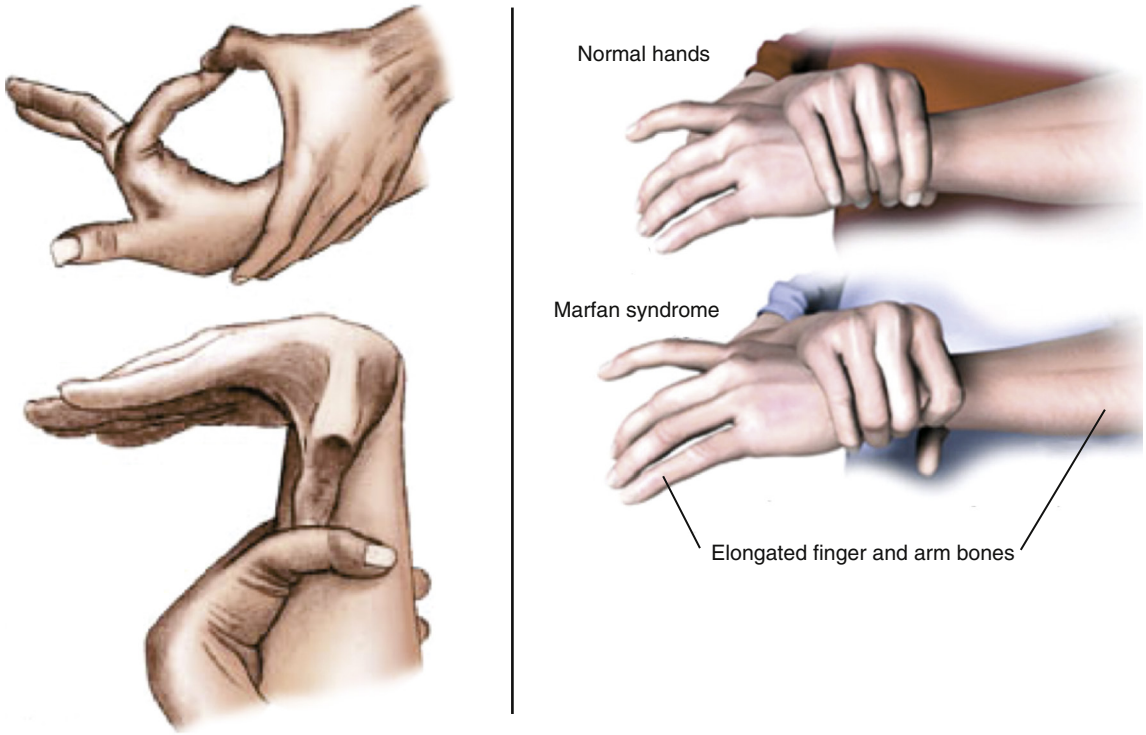

FIGURE M1-5 Marfan syndrome. The Steinberg test (thumb) and the Walker-Murdoch test (wrist) show arachnodactyly. (From Firestein GS et al: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders, Elsevier.)

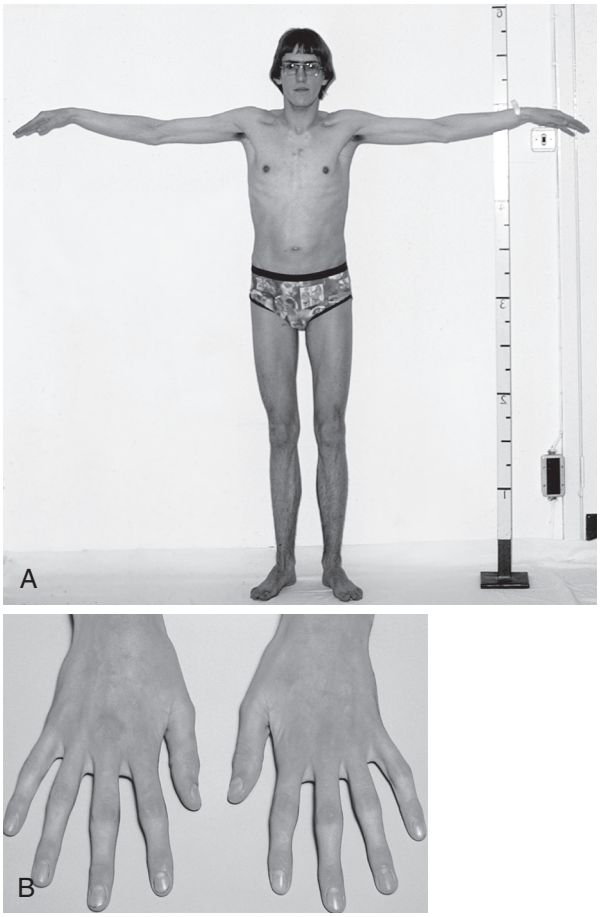

FIGURE M1-6 A, Long limbs compared with the trunk. **B,** Arachnodactyly. (From Kanski JJ, Bowling B: *Clinical ophthalmology, a system approach,* ed 7, Philadelphia, 2010, Saunders.)

- Beta-blockers are commonly prescribed to slow the rate of aortic root dilation. Patients with Marfan's syndrome and associated aneurysm should be receiving beta-blockers unless there is a contraindication to their use. Recent reports indicate that use of angiotensin receptor blockers significantly also slowed the rate of progressive aortic root dilation independent of hemodynamic effects. A recent trial among children and young adults with Marfan's syndrome who were randomly assigned to Losartan or Atenolol found no significant difference in the rate of aortic root dilation between the two treatment groups over a 3 year period. A recent trial among children and young adults with Marfan's syndrome who were randomly assigned to Losartan or Atenolol found no significant difference in the rate of aortic root dilation between the two treatment groups over a 3 year period.[1]
- Genetic counseling.
- Monitor aorta during pregnancy because of the increased risk of dissection.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Marfan's Syndrome (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

[1] Lacro RV, Sleeper LA, et al.: Atenolol versus Losartan in children and young adults with Marfan's syndrome, N Engl J Med 371:2061-71, 2014.

SUGGESTED READINGS

Brooke BS et al.: Angiotensin II blockade and aortic root dilation in Marfan's syndrome, *N Engl J Med* 358:26, 2008.

Selamet Tierney ES et al.: Beta-blocker therapy does not alter the rate of aortic root dilation in pediatric patients with Marfan syndrome, *J Pediatr* 150:77, 2007.

BASIC INFORMATION

DEFINITION

Mastitis is local painful inflammation of the breast that may or may not be accompanied by infection, flulike symptoms, and abscess formation.

ICD-9CM CODES
611.0 Inflammatory disease of the breast
675.1 Postpartum abscess of the breast
675.2 Postpartum nonpurulent mastitis
ICD-10CM CODES
N61 Inflammatory disorders of breast
O91.12 Abscess of breast associated with the puerperium
O91.22 Nonpurulent mastitis associated with the puerperium

EPIDEMIOLOGY & DEMOGRAPHICS

- In lactating mothers, typically occurs in first 3 mo postpartum (74%-95% of cases)
- When severe, mastitis can lead to a breast abscess (5% to 11%) or septicemia
- Delayed diagnosis and treatment of lactational mastitis can lead to discontinuation of breastfeeding, breast tissue damage, recurrence
- In nonlactating women of childbearing age, often presents as granulomatous mastitis (GM)
- In older nonlactating women, often presents as periductal mastitis (PM) and is caused by inflamed milk ducts near the nipple
- Mastitis can also occur in infancy, when breast hypertrophy from maternal hormone leads to infection

PREVALENCE: Lactational mastitis occurs in up to 33% of mothers
PREDOMINANT SEX: Females
RISK FACTORS:
- Previous mastitis
- Milk stasis and missed feedings
- Cracked, fissured, or sore nipples
- Primiparity and infant attachment difficulties
- Cleft lip or palate or short frenulum in infant
- Use of manual breast pump
- Diabetes
- Breast implants
- Nipple piercings

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Warmth, redness, tenderness in breast
- Unilateral or bilateral
- Malaise, myalgias, fevers, chills
- Decreased milk output
- Breast is hard and swollen in a wedge-shaped area
- In PM, breast mass near nipple with retraction or discharge
- In GM, enlarged axillary lymph nodes or sinus tract formation

ETIOLOGY

- In lactational mastitis, milk stasis and irritation of the milk ducts due to local immune response to milk proteins.
  - Bacterial infection of subcutaneous tissue due to breaks in skin.
  - Most commonly, *S. aureus;* less common, *S. epidermidis,* group A beta-hemolytic streptococci, *S. pneumoniae, E. coli, Candida albicans, M. tuberculosis.*
- GM results from inflammation with epithelioid histiocytes and multinucleated giant cells and can be caused by etiologies like tuberculosis, sarcoidosis, foreign body reaction, parasitic and mycotic infections, or idiopathic.
- Neonatal mastitis caused by *S. aureus* or gram-negative enteric bacteria.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Engorgement, plugged duct (see Table M1-4)
- Breast abscess
- Inflammatory or other breast cancer (3% of women diagnosed with breast cancer are lactating)
- Mastitis as a symptom of hyperprolactinemia or galactorrhea
- GM can be manifestation of systemic disease (sarcoidosis, Wegener granulomatosis, GCA, polyarteritis nodosa, TB, syphilis)

WORKUP

- History and clinical exam with thorough breast exam and assessment of axillary nodes and nipple discharge are sufficient for diagnosis
- Recurrent mastitis should include workup for underlying breast disease

LABORATORY TESTS

- Simple lactational mastitis requires no milk culture or laboratory studies
- Obtain midstream sample of milk for culture and sensitivities in refractory mastitis or in MRSA-suspected cases
- CBC and blood cultures in toxic patients
- In abscess formation, culture of drainage or aspirate fluid
- Gram stain and culture indicated in infant mastitis

IMAGING STUDIES

- Not necessary unless refractory mastitis or abscess suspected
- Consider US to evaluate for abscess or mammogram when appropriate to exclude carcinoma
- In GM, mammogram and US-guided FNA are standard

TREATMENT

NONPHARMACOLOGIC THERAPY

- Mainstay of therapy is effective milk removal through continued breastfeeding or pumping
- Consider referral to a certified lactation consultant to improve breastfeeding technique
- Warm compresses, increased fluid intake, good nutrition, and rest
- In abscess formation (10% of women who are treated for bacterial mastitis), surgical drainage or needle aspiration is necessary, followed by antibiotic therapy based on sensitivities of culture

ACUTE GENERAL Rx

- NSAIDs and analgesics (e.g., acetaminophen, ibuprofen). There is insufficient evidence to support or refute the effectiveness of antibiotic therapy. Common regimens include:
- No history of MRSA:
  1. Dicloxacillin 250 mg 4x/d for 7 d
  2. Cephalexin 500 mg 4x/d for 10-14 d
  3. Inpatient nafcillin or oxacillin 2 g IV q4h
  4. Erythromycin may be used in patients allergic to penicillin
- Suspected MRSA or high-risk penicillin allergy:
  1. Trimethoprim/sulfamethoxazole 160 mg/800 mg 2x/d for 10-14 d; should not be used when breastfeeding healthy infants <2 mo or compromised infants
  2. Clindamycin 300 mg 4x/d for 10-14 d
  3. Inpatient: vancomycin 1 g IV q12h
- Oxytocin nasal spray if letdown reflex disturbed
- Consider treatment for candidal infection if bilateral symptoms and infant with thrush
  - Topical clotrimazole for mother and oral nystatin for infant, with careful washing of all pacifiers and nipples
  - If resistant to topical treatment, can consider oral fluconazole; however, data in breastfeeding are limited

TABLE M1-4 Comparison of Findings of Engorgement, Plugged Duct, and Mastitis

Characteristics	Engorgement	Plugged Duct	Mastitis
Onset	Gradual, immediately	Gradual, after feedings	Sudden, after 10 days postpartum
Site	Bilateral	Unilateral	Usually unilateral
Swelling and heat	Generalized	May shift/little or no heat	Localized red, hot, and swollen
Body temperature	<38.4° C	<38.4° C	>38.4° C
Systemic symptoms	Feels well	Feels well	Flulike symptoms

From Lawrence RA, Lawrence RM: *Breastfeeding: a guide for the medical profession,* ed 5, St Louis, 1999, Mosby.

- Infant mastitis typically treated in an inpatient setting with parenteral antibiotics based on results of Gram stain

CHRONIC Rx

- No evidence proving benefit of prophylactic antibiotics to prevent lactational mastitis
- In GM, systemic corticosteroids or wide surgical resection

COMPLEMENTARY & ALTERNATIVE MEDICINE

- Complementary therapies not assessed in prospective studies: *Belladonna, Phytolacca, Chamomilla,* sulfur, *Bellis perennis*
- Several strains of lactobacilli have shown promise as probiotic agents that might be useful in treating mastitis, including *L. fermentum* and *L. salivarius.* These results should be replicated before this approach is adopted widely.

REFERRAL

Refer to surgeon for severe PM or significant lactational abscess that does not resolve with conservative measures

PEARLS & CONSIDERATIONS

COMMENTS

- 25% of breastfeeding mothers with 1 episode of mastitis stop breastfeeding.
- Increasing incidence of MRSA mastitis.
- Lactational mastitis is risk factor for vertical transmission of infections (i.e., HIV-1, CMV, measles, hepatitis B and C).
- When reassessing refractory nonlactational mastitis, the most important consideration is the possibility of cancer.
- Nonlactational mastitis can be a manifestation of systemic disease.
- GM mimics breast cancer both clinically and radiologically (>50% of reported cases are initially mistaken for carcinoma). This includes fine needle aspiration, which is sometimes interpreted as malignant.

RELATED CONTENT

Abscess breast (Related Key Topic)
Fibrocystic breast disease (Related Key Topic)
Mastitis (Related Key Topic)

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **MARY BETH SUTTER, M.D.,** and **ANDRE LEVCHENKO, Ph.D.**

SUGGESTED READINGS

Academy of Breastfeeding Medicine Protocol Committee: ABM Clinical Protocol #4: mastitis. Revision, *May 2008 Breastfeed Med* 3:177–180, 2008.

Amir LH: Managing common breastfeeding problems in the community, *Br Med J* 348:g2954, 2014.

Barbosa-Cesnik C et al.: Lactation mastitis, *JAMA* 289:1609–1612, 2003.

Crepinsek M et al.: Interventions for preventing mastitis after childbirth, *Cochrane Database Syst Rev* 10:CD007239, 2012.

Dixon JM, Khan LR: Breast infection, *Br Med J* 347:f3291, 2013.

Foxman B et al.: Lactation mastitis: occurrence and medical management among 946 breastfeeding women in the United States, *Am J Epidemiol* 55:103, 2002.

Jahanfar S et al.: Antibiotics for mastitis in breastfeeding women, *Cochrane Database Syst Rev* (2), 2013.

Mass S: Breast pain: engorgement, nipple pain and mastitis, *Clin Obstet Gynecol* 47(3):676–682, 2004.

Pouchot J et al.: Granulomatous mastitis: an uncommon cause of breast abscess, *Arch Intern Med* 161:611–612, 2000.

Spencer J et al.: Management of mastitis in breastfeeding women, *Am Fam Physician* 78(6):727–731, 2008.

BASIC INFORMATION

DEFINITION

- Pain in the breast
- Usually cyclic condition but may be noncyclic or extramammary

SYNONYMS

Mastalgia

ICD-9CM CODES
611.71 Mastodynia
ICD-10CM CODES
N64.4 Mastodynia

EPIDEMIOLOGY & DEMOGRAPHICS

- Mastodynia affects up to 70% of women at some time in their reproductive lives.
- Severe cyclic mastodynia lasting more than 5 days/mo and of sufficient intensity to interfere with sexual, physical, social, and work-related activities is reported among 30% of premenopausal women.
- Underlying fear of breast cancer is the reason most of these women seek medical consultation.
- One tenth of women with mastodynia require pain-relieving therapy.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Usually the breasts are normal bilaterally
- Full, tender breasts
- Generalized breast nodularity without discrete lumps
- Chest wall tenderness: extramammary breast pain
- Distinguishing mammary from extramammary pain can be difficult
- With the patient lying on her side so that the breast tissue falls away from the chest wall, tenderness can then be reproduced by direct pressure over the offending site
- Cyclic mastodynia presents in the luteal phase of the menstrual cycle
- Women with cyclic mastodynia tend to have abdominal bloating, leg swelling, and other symptoms of premenstrual syndrome
- Noncyclic mastodynia, on the other hand, is unrelated to the menstrual cycle
- Extramammary breast pain simulates noncyclic mastodynia

ETIOLOGY

- Hormonal imbalance
- Abnormal lipid metabolism
- Premenstrual syndrome (20%)
- Fibrocystic breast disease
- Emotional abuse and anxiety
- Excessive caffeine intake
- Breast cancer (10%)
- Tietze syndrome (idiopathic costochondritis)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- See "Etiology."
- The majority of women with mastodynia have no underlying abnormality.
- Breast fullness and tenderness associated with hormonal changes fluctuate with the menstrual cycle.
- Similarly, breast nodularity, which may or may not be the result of fibrocystic breast disease, also fluctuates with the menstrual cycle.
- Discrete breast lumps need full evaluation to rule out malignancy.
- Tietze syndrome is usually unilateral and may be associated with chest wall swelling.

LABORATORY TESTS

Although hormonal imbalance and abnormal lipid metabolism have been implicated in the etiopathogenesis of mastodynia, there is no good evidence to support any consistent pattern of serum hormonal or lipid profile in women with mastodynia. These tests are therefore not recommended.

IMAGING STUDIES

- Mammography should be part of the baseline investigation if the woman is >35 yr.
- Ultrasound can be performed as needed; it is particularly helpful in the assessment of cystic breast lesions.
- In women <35 yr, imaging investigations are not helpful unless a lump has been palpated clinically. Consideration of family history for breast disease is important.
- There are no radiologic features associated with mastodynia: rather, radiologic investigations are performed to exclude the rare presence of a subclinical carcinoma.

TREATMENT

NONPHARMACOLOGIC THERAPY

- 85% of the women with mastodynia can be reassured after full clinical evaluation.
- The remaining 15% require some form of therapy in addition to reassurance.
- A firm, supportive brassiere designed for postpartum use is particularly helpful if mastodynia is associated with breast swelling.
- Follow a low-fat, high-carbohydrate diet.
- Reduce caffeine intake.

ACUTE GENERAL Rx

- Evening primrose oil, which contains gamma-linolenic acid, has been shown to have some effectiveness and is an acceptable treatment for mastodynia.
- Topical NSAID preparations may confer some benefit and can be prescribed for these women.
- Hormonal therapy is the mainstay of treatment and may include progesterone-only oral contraceptives or cyclic Provera.
- Danazol is the only drug approved by the FDA for the treatment of mastodynia. Danazol has some androgenic and peripheral antiestrogenic effects. Its efficacy is well established, with significant relief of mastodynia in 70% to 93% of cases.
  - Widespread use of danazol is limited because of its adverse side effects. These include menstrual irregularities, depression, acne, hirsutism, and, in severe cases, voice deepening. Women taking danazol should be advised to use effective nonhormonal contraception because of the drug's potential adverse effects on the fetus.
  - The side effects of danazol can be significantly reduced by using a low dose (100 mg daily) and confining treatment to 2 wk preceding menstruation. However, alternatives should be explored.
- Tamoxifen, a synthetic antiestrogen, has also been shown to be effective in the treatment of mastodynia. Although effective in relieving symptoms, its use is extremely limited because of side effects. When used, it should be at a low dosage of 10 mg/day and duration should be limited to 6 mo at a time. In the U.S. this agent is not approved for use in women with mastodynia.
- Bromocriptine is a dopamine-receptor agonist whose primary action is inhibition of prolactin release. It has been used extensively in the treatment of severe cyclic mastodynia and is effective. Again, side effects such as headache and lightheadedness have limited its use.
- Lisuride maleate was recently found to be effective by one study.
- Other hormonal agents that have been reported to be effective in small studies cannot be recommended. Either they have unacceptable side effect profiles or their efficacy is not established. These agents include gestrinone, gonadotropin-releasing hormone analogues, progesterone, and hormone replacement therapy.

CHRONIC Rx

- Longstanding cases of mastodynia can be managed with intermittent low-dose danazol therapy to limit side effects. In between these courses of hormone, nonpharmacologic and nonhormonal therapy can be used.
- Severe, unremitting mastodynia that does not respond to medical treatment may require mastectomy; this is rare.

DISPOSITION

- Cyclic mastodynia resolves spontaneously in 20% to 30% of women.
- Up to 60% of women may develop recurrent symptoms 2 yr after treatment.
- Noncyclic mastodynia responds poorly to treatment but may resolve spontaneously in up to 50% of women.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Breast Pain (Patient Information)
Abscess, Breast (Related Key Topic)
Fibrocystic Breast Disease (Related Key Topic)
Mastitis (Related Key Topic)

AUTHORS: **ALEXANDER B. OLAWAIYE, M.D.,** and **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Colgrave S et al.: Psychological characteristics of women presenting with breast pain, *J Psychosom Res* 50:303, 2001.

Fentiman IS, Hamed H: Assessment of breast problems, *Int J Clin Pract* 55:458, 2001.

Kaleli S et al.: Symptomatic treatment of premenstrual mastalgia in premenopausal women with lisuride maleate: a double-blind placebo-controlled randomized study, *Fertil Steril* 75:718, 2001.

Marchant DJ: Benign breast disease, *Obstet Gynecol Clin North Am* 29:1–20, 2002.

Norlock FE: Benign breast pain in women: a practical approach to evaluation and treatment, *J Am Med Womens Assoc* 57:85, 2002.

BASIC INFORMATION

DEFINITION

Mastoiditis is inflammation of the mastoid process and air cells, a complication of otitis media.

SYNONYMS

Mastoid abscess

ICD-9CM CODES
383.00 Mastoiditis, acute or subacute
383.1 Mastoiditis, chronic
ICD-10CM CODES
H70.0 Acute mastoiditis
H40.1 Chronic mastoiditis
H70.8 Other mastoiditis and related conditions
H70.9 Mastoiditis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Since the introduction of antibiotic therapy and use of broad-spectrum antibiotics, there has been a marked decline in the incidence of acute mastoiditis.
PREDOMINANT SEX: More common in males
PREDOMINANT AGE: 2 mo to 18 yr
PEAK INCIDENCE: Early childhood

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute mastoiditis is usually a complication of acute otitis media.
- Most common presenting symptom is pain and tenderness in the postauricular region.
- Other signs or symptoms include:
  1. Fever
  2. Postauricular erythema and edema
  3. Protrusion of the pinna inferiorly and anteriorly
  4. Tympanic membrane usually intact with signs of acute otitis media
- Complications of acute mastoiditis include:
  1. Subperiosteal abscess (most common complication)
  2. Hearing loss
  3. Facial nerve palsy
  4. Labyrinthitis
  5. Intracranial complications such as hydrocephalus, meningitis, encephalitis, intracranial abscess, and lateral sinus thrombosis
- Chronic mastoiditis is characterized by chronic otorrhea and chronic tympanic membrane perforation.

ETIOLOGY

- Continuity exists between the middle air space and the mastoid cavity.
- Initial hyperemia and edema of the mucosal lining of the air cells result in accumulation of purulent exudate.
- Dissolution of calcium from bony septa and osteoclastic activity in the inflamed periosteum lead to bone necrosis and coalescence of air cells.
- Most common bacterial isolates are:
  1. *Streptococcus pneumoniae*
  2. *Streptococcus pyogenes*
  3. *Haemophilus influenzae*
  4. *Moraxella catarrhalis*
  5. *Staphylococcus aureus*
- Often, there are multiple organisms in chronic mastoiditis, with predominance of anaerobes and gram-negative bacteria.
- *Mycobacterium tuberculosis,* nontuberculous mycobacteria, *Aspergillus,* and *Rhodococcus equi* have been reported in cases of mastoiditis in severely immunocompromised individuals.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Children
  1. Rhabdomyosarcoma
  2. Histiocytosis X
  3. Leukemia
  4. Kawasaki syndrome
- Adults
  1. Fulminant otitis externa
  2. Histiocytosis X
  3. Metastatic disease

WORKUP

A thorough history and physical examination are important in establishing diagnosis.

LABORATORY TESTS

- Fluid for Gram stain and culture may be obtained by myringotomy.
- If there is a perforation in the tympanic membrane with drainage, cultures of this may be taken after carefully cleaning the external canal.

IMAGING STUDIES

- Plain x-rays of the mastoid region may demonstrate clouding or opacification in areas of pneumatization.
- CT scan can demonstrate early involvement of bone (mastoiditis with bone destruction).
- MRI is more sensitive than CT scan in evaluating soft-tissue involvement and is useful in conjunction with CT scan to investigate other complications of mastoiditis.

TREATMENT

NONPHARMACOLOGIC THERAPY

Myringotomy, if the ear is not already draining

ACUTE GENERAL Rx

- Initiated with IV antibiotics directed against the common organisms *S. pneumoniae* and *H. influenzae.* Useful agents are amoxicillin/clavulanate, ceftriaxone, and cefotaxime. If the disease in the mastoid has had a prolonged course, coverage for *S. aureus* with gram-negative enteric bacilli may be considered for initial therapy until results of cultures become available. Add vancomycin if MRSA suspected or nafcillin/oxacillin if culture is positive for *S. aureus*, methicillin susceptible.
- Antibiotics continued until all signs of mastoiditis have resolved
- Directed against enteric gram-negative organisms and anaerobes in chronic mastoiditis
- Indications for mastoidectomy:
  1. Failure to improve after 72 hr of therapy
  2. Persistent fever
  3. Imminent or overt signs of intracranial complications
  4. Evidence of a subperiosteal abscess in the mastoid bone

DISPOSITION

Proceed with mastoidectomy when medical therapy fails.

REFERRAL

- To otorhinolaryngologist:
  1. If diagnosis is in doubt
  2. If aural complications present
  3. To evaluate for surgical intervention
- To neurosurgeon if intratemporal or intracranial extension of infection suspected
  1. Aural complications: bone destruction, subperiosteal abscess, petrositis, facial paralysis, labyrinthitis
  2. Intracranial complications: extradural abscess, lateral sinus thrombophlebitis or thrombosis, subdural abscess, meningitis, brain abscess, otitic hydrocephalus

PEARLS & CONSIDERATIONS

Mastoiditis is particularly difficult to eradicate because the mastoid air cells are poorly vascularized and difficult to drain.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Mastoiditis (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Lin HW et al.: Clinical strategies for the management of acute mastoiditis in the pediatric population, *Clin Pediatr* 49(2):110–115, 2010.

Oestreicher-Kedem Y et al.: Complications of mastoiditis in children at the onset of a new millennium, *Ann Otol Rhinol Laryngol* 114(2):147, 2005.

Taylor MF, Berkowitz RG: Indications for mastoidectomy in acute mastoiditis in children, *Ann Otol Rhinol Laryngol* 113(1):69, 2004.

BASIC INFORMATION

DEFINITION

Measles is a childhood exanthem caused by an RNA virus called *Morbillivirus,* belonging to the family Paramyxoviridae.

SYNONYMS

Rubeola

ICD-9CM CODES
055.9 Measles
055.0 Encephalitis
055.1 Pneumonia
V04.2 Vaccination

ICD-10CM CODES
B05.9 Measles without complication
B05.0 Measles complicated by encephalitis
B05.2 Measles complicated by pneumonia
Z23 Encounter for immunization

EPIDEMIOLOGY & DEMOGRAPHICS

- Before the introduction of an effective vaccine in 1963, measles was one of the most common childhood illnesses. In developing countries, where it mostly strikes children <5 yr, it remains a leading cause of childhood death.
- 30 million cases occur worldwide each year.
- Measles is no longer endemic in the U.S. (Fig. EM1-7). In developed countries, measles outbreaks occasionally occur in adolescents and young adults who have not been immunized (incidence up to 10 per 100,000 person-years).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Incubation: 10 to 14 days (up to 3 wk in adults)
- Prodrome: 2 to 4 days; malaise, fever, rhinorrhea, conjunctivitis, cough
- Exanthem phase: 7 to 10 days
- The fever increases and peaks at 104° to 105° F together with the rash; it persists for 5 or 6 days. The patient's fever decreases over 24 hr.
- Rash: erythematous maculopapular eruption begins behind the ears, progresses to the forehead and neck, then spreads to face, trunk (Fig. EM1-8), upper extremities, buttocks, and lower extremities, in that order. After 3 days the rash fades in the same sequence by becoming copper brown and then desquamating.
- Enanthem: *Koplik spots* are white papules 1 to 2 mm in diameter on an erythematous base. They first appear on the buccal mucosa opposite the lower molar 2 days before the rash and spread over 24 hr to involve most of the buccal and lower labial mucosa (Fig. EM1-9). They fade after 3 days.
- Other symptoms and signs: malaise, anorexia, vomiting, diarrhea, abdominal pain, pharyngitis, lymphadenopathy, and occasional splenomegaly.

Atypical measles (in vaccinated persons):

- Incubation: 10 to 14 days
- Prodrome: 1 to 3 days; high fever and headache
- Rash: maculopapular, urticarial, or petechial rash that begins peripherally and progresses centrally
- Modified measles applies to patients who have received immune serum globulin and develop a milder illness
- Complications (30% of all cases):
  1. Otitis media
  2. Laryngitis, tracheitis
  3. Pneumonia (accounts for 90% of measles deaths)
  4. Encephalitis with lethargy, irritability, and seizures; 60% recover completely, 25% have neurologic sequelae (mental retardation, hemiplegia, paraplegia, epilepsy, deafness), and 15% die
  5. Myocarditis, pericarditis, hepatitis
  6. Complications more common in immunocompromised hosts and persons with AIDS

ETIOLOGY & PATHOGENESIS

- The measles virus is transmitted through the respiratory tract by airborne droplets. Patients shed measles virus from 7 days after exposure to 4-6 days after the onset of rash.
- It initially infects the respiratory epithelium; the patient becomes viremic during the prodromal phase and the virus is disseminated to the skin, respiratory tract, and other organs.
- Viral clearance is achieved by cellular immunity.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other viral infections by enteroviruses, adenoviruses, human parvovirus B-19, rubella (Table EM1-5)
- Scarlet fever
- Allergic reaction
- Kawasaki disease

WORKUP

Knowledge of outbreak, history and physical findings (Koplik spots are diagnostic), laboratory tests

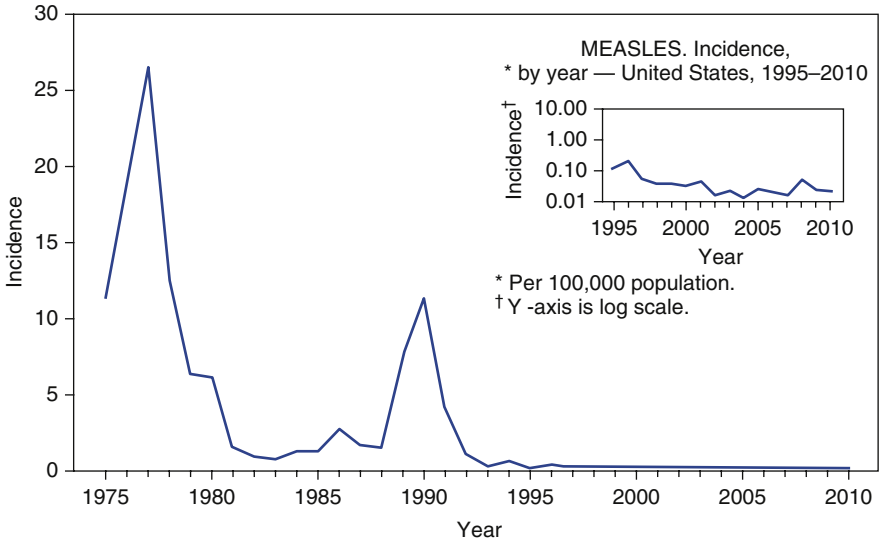

FIGURE EM1-7 Incidence, by year—United States, 1975 to 2010. (From Centers for Disease Control and Prevention: Summary of notifiable diseases—United States, *MMWR Morb Mortal Wkly Rep* 59(53):1-111, 2012.)

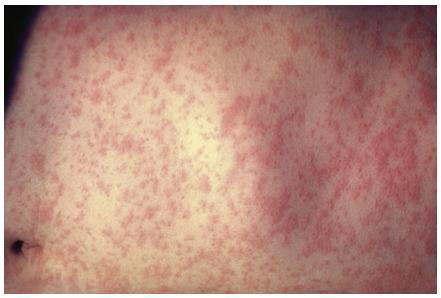

FIGURE EM1-8 Maculopapular rash of measles or rubeola showing coalescence of lesions. (Courtesy CDC/Dr. Heinz F. Eichenwald. From Gabbe SG: *Obstetrics*, 6th ed, Philadelphia, 2012, Saunders.)

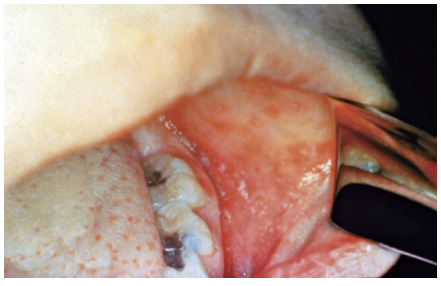

FIGURE EM1-9 Koplik spots on the buccal mucosa during the third day of rash. (From Centers for Disease Control and Prevention: Public Health Image Library, Image #4500, available at http://phil.cdc.gov/phil/details.asp.)

TABLE EM1-5 A Guide to the Differential Diagnosis of Measles

	Conjunctivitis	Rhinitis	Sore throat	Exanthem	Leukocytosis	Specific Laboratory Tests
Measles	++	++	0	+	0	+
Rubella	0	±	±	0	0	+
Exanthem subitum	0	±	0	0	0	+
Enterovirus infection	0	±	±	0	0	+
Adenovirus infection	+	+	+	0	0	+
Scarlet fever	±	±	++	0	+	+
Infectious mononucleosis	0	0	++	±	±	
Drug rash	0	0	0	0	0	0

From Gabbe SG: *Obstetrics*, 6th ed, Philadelphia, 2012, Saunders.

LABORATORY TESTS

- Enzyme-linked immunosorbent assay for measles antibodies, which appear shortly after the onset of the rash and peak 3 to 4 wk later
- Complete blood count: leukopenia
- Cerebrospinal fluid analysis in encephalitis may reveal pleocytosis (lymphocytes) and an elevated protein

IMAGING STUDIES

Chest radiograph if pneumonia is suspected

TREATMENT

- Supportive (hydration, antipyretics for comfort and fever control, airway humidification in patients with respiratory tract involvement). Antiviral therapy is not effective.
- Vitamin A therapy is beneficial in children >6 mo of age with measles who are hospitalized with measles and its complications or have any of the following risk factors: immunodeficiency, clinical evidence of vitamin A deficiency, impaired intestinal absorption, moderate to severe malnutrition, and recent immigration from areas where high mortality rates attributed to measles have been observed. Treatment regimen consists of a single dose of 200,000 IU orally for children >1 yr of age and 100,000 IU for children 6 mo to 1 yr of age.
- Ribavirin is at times used for severe measles pneumonitis; however, it is not licensed in the United States for treatment of measles.

PEARLS & CONSIDERATIONS

PREVENTION

- Passive immunization: human immunoglobulin 0.25 ml/kg IM within 6 days of exposure. Double the dose for immunocompromised persons.
- Active immunization (see Section V).

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Measles (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Mulholland EK: Measles in the United States, *N Engl J Med* 355:5, 2006.

Meckel Diverticulum PTG

BASIC INFORMATION

DEFINITION

Meckel diverticulum is an ileal diverticulum located 100 cm proximal to the cecum. It results from failure of the omphalomesenteric duct to obliterate completely (as it should by the eighth week of gestation).

SYNONYMS

MD

ICD-9CM CODES
751.0 Meckel diverticulum
ICD-10CM CODES
Q43.0 Meckel's diverticulum (displaced) (hypertrophic)

EPIDEMIOLOGY & DEMOGRAPHICS

- Meckel diverticulum, based on autopsy studies and intraoperative evidence, occurs in 0.3% to 4% of the population and is the most prevalent congenital anomaly of the gastrointestinal (GI) tract. Complications occur more frequently in males.
- Most patients who develop symptoms are <10 yr.
- The lifetime risk of complications developing in a case of Meckel diverticulum is 4%.
- In adults, complications (small bowel obstruction [25% to 40%], diverticulitis [20%]) are usually attributable to factors other than heterotopic mucosa.
- Tumors have rarely been reported in symptomatic Meckel diverticulum, with carcinoid being the most common type.

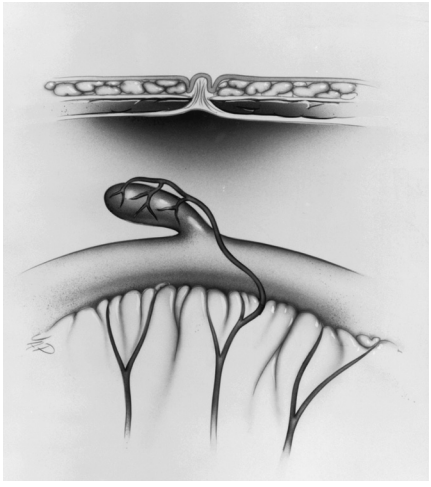

FIGURE M1-10 Typical Meckel diverticulum located on the antimesenteric border. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Painless lower GI bleeding (4%)
- Intestinal obstruction caused by intussusception, volvulus, herniation, or entrapment of a loop of bowel through a defect in the diverticular mesentery (6%)
- Meckel's diverticulitis mimics acute appendicitis (5%)
- Rare primary tumor arising from diverticulum (carcinoid, sarcoma, leiomyoma, adenocarcinoma)
- Asymptomatic (80% to 95%)

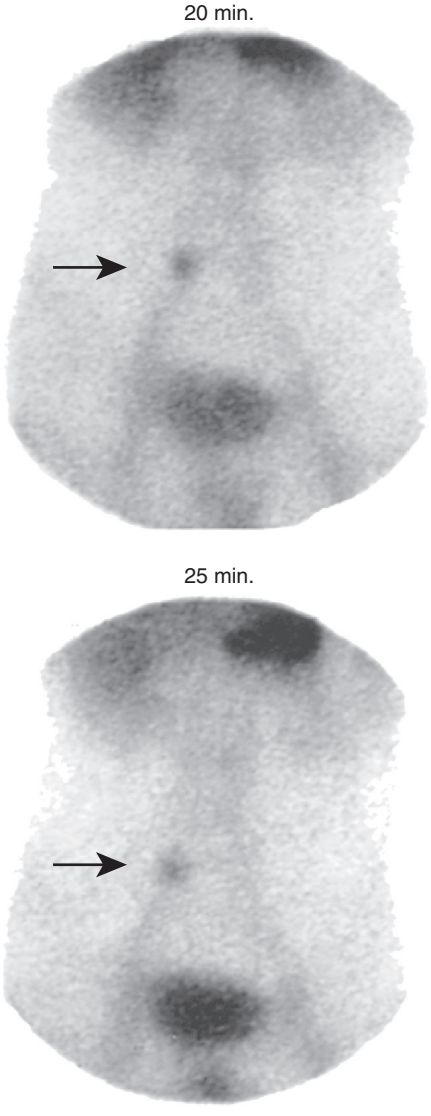

FIGURE M1-11 Meckel scan demonstrating accumulation in the stomach superior bladder (inferior) and in the acid-secreting mucosa of a Meckel diverticulum. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

ETIOLOGY & PATHOGENESIS

- As a remnant of the omphalomesenteric duct, Meckel diverticulum contains all layers of the intestinal wall and has its own mesentery and blood supply (branch of the superior mesenteric artery) (Fig. M1-10).
- The majority of complicated cases of Meckel diverticulum contain ectopic mucosa (75% gastric, 15% pancreatic). It causes ulceration and bleeding of ileal mucosa adjacent to the acidic ectopic gastric secretions. Alkaline secretions of ectopic pancreatic tissue can also cause ulcerations.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Appendicitis
- Crohn's disease
- All causes of lower GI bleeding (polyp, colon cancer, arteriovenous malformation, diverticulosis, hemorrhoids)

WORKUP

- Diagnosis is often made intraoperatively when the preoperative diagnosis is appendicitis.
- Preoperative detection of symptomatic Meckel diverticulum requires a high index of suspicion.
- Meckel scan: In the case of GI bleeding of unknown source, a technetium scan will identify Meckel diverticulum (sensitivity: 85% in children, 62% in adults; specificity: 95% in children, 9% in adults) (Fig. M1-11).
- In patients with suspected small-bowel obstruction, intussusception, or diverticulitis, a CT scan of the abdomen and pelvis is helpful.

TREATMENT

- Surgical resection in symptomatic patients.
- There is controversy regarding the need to remove an incidentally found diverticulum, with most surgeons arguing in favor of resection.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Meckel Diverticulum (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Feller A et al.: Meckel diverticulum, *Arch Intern Med* 163:2093, 2003.
Martin JP et al.: Meckel's diverticulum, *Am Fam Physician* 61:1037, 2000.

BASIC INFORMATION

DEFINITION

Mediastinitis is an infection involving the connective mediastinal tissue that fills the interpleural spaces and surrounds the mediastinal organs. It can be acute or chronic.

SYNONYM(S)

Fibrosing mediastinitis
Sclerosing mediastinitis
Granulomatous mediastinitis

ICD-9CM CODES
519.2 Mediastinitis (acute) (chronic)
ICD-10CM CODES
J98.5 Mediastinitis

EPIDEMIOLOGY

Acute mediastinitis occurs most frequently as a postoperative infection after a median sternotomy and can be a life-threatening infection. Most infections are bacterial in nature.

Chronic mediastinitis is a chronic form of infection in the mediastinum characterized by an invasive and compressive inflammatory infiltrate. It is mostly caused by fungi and some bacteria.

Incidence: Incidence of postoperative mediastinitis ranges from 0.4 to 5%.

Risk Factors:

Mediastinal infections have four possible sources:

- Direct contamination as seen in trauma or surgery (e.g., open heart, esophageal)
- Hematogenous or lymphatic spread
- Extension of infection from the neck or retroperitoneum
- Extension from the lung, pleura, or chest wall

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with acute mediastinitis present with acute onset of fever, tachycardia, chest pain, dysphagia, or respiratory distress. There may be signs of sternal wound infection or cellulitis and/or crepitus and edema of the chest wall.
- Patients with chronic mediastinitis are mostly asymptomatic until symptoms develop related to invasion or obstructions of structures within the mediastinum or adjacent to the mediastinum, such as cough, dyspnea, wheezing, chest pain, dysphagia, or hemoptysis. Complications of chronic or sclerosing mediastinitis include:
  - Superior vena cava syndrome. Histoplasma is the most common nonmalignant cause of this syndrome, marked by edema of face, neck and torso; neck vein distension; and headache.
  - Pulmonary venous or arterial obstruction.
  - Esophageal obstruction, cor pulmonale, constructive pericarditis.
  - Thoracic duct obstruction.

ETIOLOGY

Acute mediastinitis:

- Related to head and neck infections or esophageal perforation
  - Anaerobic bacteria: *Peptostreptococci, Veillonella, Fusobacterium, Actinomyces, Prevotella, Eubacterium, Bacteroides*
  - Aerobic bacteria: *Streptococcus, Staphylococcus, Corynebacterium, Moraxella,* enteric gram-negative rods
  - Fungi: Candida albicans
- Related to cardiothoracic surgery
  - Gram-positive bacteria: *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus*, *Streptococcus*
  - Gram-negative bacteria: *Escherichia coli*, *Enterobacter*, *Klebsiella*, *Proteus*, *Pseudomonas,* other Enterobacteriaceae
  - Fungi: *Candida albicans*

Chronic mediastinitis:

- *Histoplasma capsulatum,* a dimorphic fungus, is the most common and can cause mediastinal granuloma or fibrosing mediastinitis. A leakage of fungal antigens from lymph nodes into the mediastinal space is believed to cause a hypersensitivity reaction and subsequent exuberant fibrotic response.
- Other: *Mycobacterium tuberculosis, Nocardia,* actinomycosis, aspergillosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

For chronic mediastinitis:

- Tumors that can also cause superior vena cava syndrome (e.g., Hodgkin and non-Hodgkin lymphomas, mesothelioma)
- Sarcoidosis
- Behçet syndrome
- Mediastinal fibrosis associated with radiation
- Silicosis

LABORATORY TEST(S)

- CBC with differential, C-reactive protein, and procalcitonin can point to bacterial infection
- Obtain cultures: aerobic and anaerobic bacteria and fungi, intraoperatively or of any purulent drainage
- Pathologic examination: distinguish between cancer and infection for chronic mediastinitis and allow for specific fungal stains on tissues

IMAGING STUDIES

- Chest x-ray: can show diffuse mediastinal widening or evidence of mediastinal abscess, including gas bubbles or fluid level. Pneumomediastinum or pneumothorax can be seen with esophageal perforation.
- Chest CT: can show the same as x-ray but is more sensitive in determining degree of mediastinal involvement and may guide drainage procedures for treatment or diagnosis.
- MRI may be superior to CT for sclerosing mediastinitis.

TREATMENT

NONPHARMACOLOGIC THERAPY

Surgery remains the gold standard treatment of mediastinitis for optimal drainage and debridement.

- Open techniques: debridement of infected tissue and open packing of the wound with delayed closure or use of vacuum-assisted closure for acute mediastinitis
- Closed techniques: debridement of infected tissues, closure of the sternum, and postoperative irrigation through drainage tubes for acute mediastinitis

ACUTE GENERAL Rx

- Intravenous antibiotics: also a cornerstone of therapy but without surgery may fail. Broad-spectrum antibiotics should be used until cultures are finalized. Combination of piperacillin-tazobactam or meropenem plus vancomycin offers good initial coverage for acute mediastinitis. Other options include ciprofloxacin or cefepime for gram-negative rods, linezolid for gram-positive bacteria, metronidazole for anaerobic bacteria.
- Therapy is 2 to 3 weeks, but some cases may require 4 to 6 weeks.

CHRONIC Rx

- There is no definitive cure for chronic fibrosing or sclerosing mediastinitis. Antifungal agents and steroids generally do not work. The goal of therapy is to palliate symptoms by relieving airway, vascular, or esophageal obstruction. Surgery in patients with extensive fibrosis has high morbidity and mortality.

DISPOSITION

- Patients may need extensive wound care and possible vacuum-assisted closure and prolonged intravenous antibiotics.

REFERRAL

- Thoracic surgeon and/or head and neck surgeon for surgery and debridement
- Infectious diseases consultant for antibiotic selection and long-term management

PEARLS & CONSIDERATIONS

COMMENTS

Histoplasma capsulatum is a dimorphic fungus found commonly in bird and bat fecal material and is most prevalent in the Ohio and Mississippi river valleys of the United States.

PREVENTION

Antibiotic prophylaxis should be given within 60 minutes before incision for surgeries requiring sternotomy. Options include cefazolin 1 g IV if <80 kg and 2 g if >80 kg, or cefuroxime 1.5 g IV. If the patient is penicillin allergic or has a history of methicillin-resistant *S. aureus* (MRSA) infection or surgery is to be done in a hospital where MRSA infection is common, use vancomycin 1 g IV.

SUGGESTED READINGS

Available online at www.expertconsult.com

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Athanassiadi K: Infections of the mediastinum, *Thorac Surg Clin* 19:34–37, 2009.

Miyata T et al.: Sclerosing mediastinitis mimicking anterior mediastinal tumor, *Ann Thorac Surg* 88(1):293–295, 2009.

Peikert T et al.: Fibrosing mediastinitis: clinical presentation, therapeutic outcomes, and adaptive immune response, *Medicine* 90:412, 2011.

Meigs' Syndrome

BASIC INFORMATION

DEFINITION

Meigs' syndrome is characterized by the presence of a benign solid ovarian tumor associated with ascites and predominantly right hydrothorax that disappear after tumor removal.

ICD-9CM CODES
620.2 Ovarian mass (unspecified)
789.5 Ascites
511.9 Pleural effusion

ICD-10CM CODES
D27.9 Benign neoplasm of ovary
R18 Ascites
J91.8 Pleural effusion in other conditions classified elsewhere

EPIDEMIOLOGY & DEMOGRAPHICS

- Occurs in <1% of ovarian fibromas (associated with approximately 0.004% of ovarian tumors)
- Most frequently encountered during middle age (average age, approximately 48 yr)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Asymptomatic pelvic mass on bimanual examination
- Intermittent pelvic pain (intermittent torsion)
- Acute pelvic tenderness
- Acute abdominal tenderness
- Abdominal pelvic mass
- Abdominal bloating
- Fluid wave
- Shifting dullness
- "Puddle sign"
- Hyperresonance or flatness to chest percussion, absence of tactile and vocal fremitus
- Absent or loud bronchial breath sounds, rales, mediastinal displacement, tracheal shift
- Weight loss and emaciation

ETIOLOGY

- Not specifically known
- Usually associated with "edematous" fibromas (or other benign ovarian solid tumor) in excess of 10 cm
- Plausible that large fibroma with narrow stalk has inadequate lymphatic drainage; when coupled with intermittent torsion, results in backflow transudation into the peritoneal cavity; accumulated peritoneal ascites then pass to the right pleural cavity by the lymphatics (overloaded thoracic duct) or abdominal pleural commutation (i.e., foramen of Bochdalek)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Abdominal ovarian malignancy
- Various gynecologic disorders:
  1. Uterus: endometrial tumor, sarcoma, leiomyoma ("pseudo-Meigs' syndrome")
  2. Fallopian tube: hydrosalpinx, granulomatous salpingitis, fallopian tube malignancy
  3. Ovary: benign, serous, mucinous, endometrioid, clear cell, Brenner tumor, granulosa, stromal, dysgerminoma, fibroma, metastatic tumor
- Nongynecologic (gastrointestinal tract or genitourinary tract tumor or pathology) causes of pelvic mass
  1. Ascites
  2. Portal vein obstruction
  3. Inferior vena cava obstruction
  4. Hypoproteinemia
  5. Thoracic duct obstruction
  6. Tuberculosis
  7. Amyloidosis
  8. Pancreatitis
  9. Neoplasm
  10. Ovarian hyperstimulation
  11. Pleural effusion
  12. Congestive heart failure
  13. Malignancy
  14. Collagen-vascular disease
  15. Pancreatitis
  16. Cirrhosis

WORKUP

- Clinical condition characterized by ovarian mass, ascites, and predominantly right-sided pleural effusion (the pleural effusion can also be left-sided in a small number of cases)
- Ovarian malignancy and the other causes (see "Differential Diagnosis") of pelvic mass, ascites, and pleural effusion to be considered
- History of early satiety, weight loss with increased abdominal girth, bloating, intermittent abdominal pain, dyspnea, nonproductive cough

LABORATORY TESTS

- Complete blood count to rule out inflammatory process
- Tumor markers (CA-125, hCG, AFP, CEA, LDH) to evaluate malignancy
- Chemical and liver function testing profile to evaluate metabolic or hepatic involvement
- Arterial blood gases if respiratory compromise

IMAGING STUDIES

- Pelvic sonography (color-flow Doppler evaluation of adnexal mass) initially to evaluate pelvic pathology (CT scan or MRI to further delineate neoplastic lesions [Fig. EM1-12])
- Chest x-ray

TREATMENT

NONPHARMACOLOGIC THERAPY

- Informed consent and proper preparation of patient for possible staging laparotomy (total abdominal hysterectomy and bilateral salpingo-oophorectomy, omentectomy, possible bowel resection, pelvic/periaortic lymphadenectomy)
- Bowel prep if considering pelvic malignancy

ACUTE GENERAL Rx

Depending on clinical presentation, size of pelvic mass, amount of ascites, and pleural effusion:

- If pelvic mass <10 cm with minimal ascites/pleural effusion: consider diagnostic laparoscopy (possible exploratory laparotomy) and salpingo-oophorectomy with removal of ovarian fibroma (tumor).
- If pelvic mass >10 cm with moderate/large amount ascites/pleural effusion: consider pleurocentesis if respiratory compromise (cytology: AFB) and exploratory laparotomy with salpingo-oophorectomy and removal of ovarian fibroma (tumor).
- Treat pelvic malignancy, gastrointestinal or genitourinary tumor as indicated.

CHRONIC Rx

- Resolution of ascites and right-sided pleural effusion after removal of ovarian fibroma
- No long-term follow-up for benign ovarian fibroma

DISPOSITION

Excellent progress and complete survival are expected.

REFERRAL

To gynecologist or gynecologic oncologist for evaluation and treatment, especially if malignancy considered or encountered

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Abramov Y et al.: The role of inflammatory cytokines in Meigs' syndrome, *Obstet Gynecol* 99(5 pt 2):917, 2002.

Buttin BM et al.: Meigs' syndrome with an elevated CA 125 from benign Brenner tumors, *Obstet Gynecol* 98(5 pt 2):980, 2001.

Meigs JV, Cass JW: Fibroma of the ovary with ascites and hydrothorax: with a report of seven cases, *Am J Obstet Gynecol* 33:249, 1937.

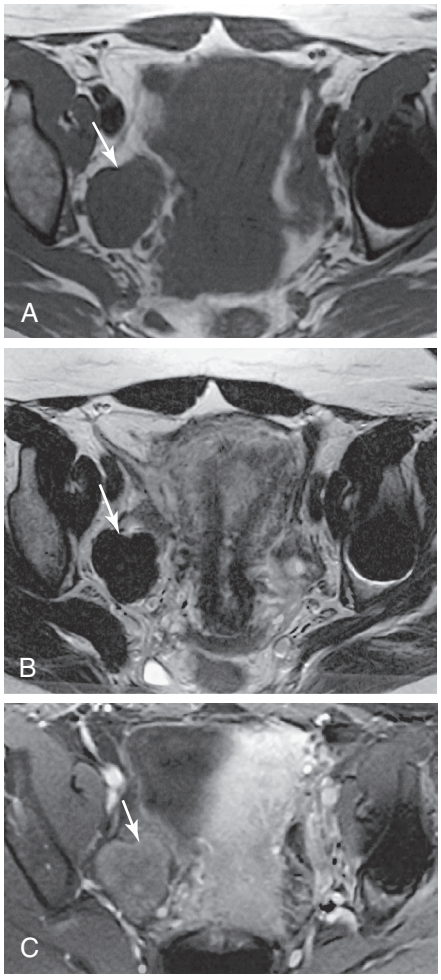

FIGURE EM1-12 Fibroma. A, Axial T1-weighted MRI shows a solid, homogeneously low signal intensity right ovarian mass *(arrow)*, which has well-defined, lobulated borders. **B,** On this T2-weighted axial MRI, the right ovarian mass is also of homogenously low signal *(arrow)*, similar to muscle. **C,** T1-weighted axial MRI obtained after the administration of gadolinium shows the lesion has no significant enhancement *(arrow)*. (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Melanoma is a skin neoplasm arising from the malignant degeneration of melanocytes. It is classically subdivided in four types:

1. Superficial spreading melanoma (70%) (Fig. M1-13*A*)
2. Nodular melanoma (15% to 20%) (Fig. M1-13*B*)
3. Lentigo maligna melanoma (5% to 10%)
4. Acral lentiginous melanoma (7% to 10%)

SYNONYMS

Malignant melanoma
Cutaneous malignant melanoma
CMM

ICD-9CM CODES
172.9 Melanoma of the skin, site unspecified
ICD-10CM CODES
C43.9 Malignant melanoma of skin, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Annual incidence of melanoma is 13 cases per 100,000 persons. By 2015 the estimated lifetime risk of the development of cutaneous melanoma will be 1 in 50.
- Melanoma has doubled and tripled in incidence over the past 25 yr.
- Melanoma is the most common cancer among women ages 20 to 29 yr.
- Melanoma is much more common in whites (17.2/100,000 white men) than in African Americans (1 in 100,000 African American men). Increased risk of developing melanomas is found in patients with fair skin, red hair, light eyes, abundance of freckles, atypical moles or large amount of moles (>50). A personal history of non-melanoma skin cancer or a family history of melanoma also increases the risk.
- Lifetime risk of cutaneous melanoma for white Americans is 1 in 90. White men >50 yr old are the most likely to have rapidly growing melanomas.
- Melanoma is the leading cause of death from skin disease. Although melanoma represents less than 10% of all skin-cancer diagnoses, at least 70% of deaths that are related to skin cancer are attributed to melanoma.
- Median age at diagnosis is 53 yr.
- Superficial spreading melanoma occurs most often in young adults on sun-exposed areas.
- Acral lentiginous melanoma is most often found in Asian Americans and African Americans and is not related to sun exposure.
- Death rate for white men with melanoma is 3 per 100,000.
- 8% to 10% of melanomas arise in people with a family history of the disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Variable depending on the subtype of melanoma:

- Superficial spreading melanoma is most often found on the lower legs, arms, and upper back. It may have a combination of many colors or may be uniformly brown or black.
- Nodular melanoma can be found anywhere on the body, but it most frequently occurs on the trunk on sun-exposed areas. It has a dark-brown or red-brown appearance and can be dome shaped or pedunculated. Lesions are frequently misdiagnosed because they may resemble a blood blister or hemangioma and may also be amelanotic.
- Lentigo maligna melanoma is generally found in older adults in areas continually exposed to the sun and frequently arising from lentigo maligna (Hutchinson's freckle) or melanoma in situ. It might have a complex pattern and variable shape; color is more uniform than in superficial spreading melanoma.
- Acral lentiginous melanoma frequently occurs on soles, subungual mucous membranes, and palms (sole of the foot is the most prevalent site). Unlike other types of melanoma, it has a similar incidence in all ethnic groups.
- The warning signs that the lesion may be a melanoma can be summarized with the ABCDE mnemonic:
  - **A:** Asymmetry (e.g., lesion is bisected and halves are not identical)
  - **B:** Border irregularity (uneven, ragged border)
  - **C:** Color variegation (presence of various shades of pigmentation)
  - **D:** Diameter enlargement (>6 mm)
  - **E:** Evolving (mole changing in size, shape, or color, or mole that differs visibly from surrounding moles ["ugly duckling" sign]) (Fig. M1-14)

ETIOLOGY

- Ultraviolet light is the most important cause of malignant melanoma.
- There is a modest increase in melanoma risk in patients with small nondysplastic nevi and a much greater risk in those with dysplastic lesions.
- The *CDKN2A* gene, residing at the *9p21* locus, is often deleted in people with familial melanoma.
- A mutated signal transduction molecule v-raf murine sarcoma viral oncogene homolog B_1 (BRAF) has been identified in about 50% of patients with metastatic melanoma.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Dysplastic nevi
- Solar lentigo
- Vascular lesions
- Blue nevus
- Basal cell carcinoma
- Seborrheic keratosis

FIGURE M1-14 Subungual melanoma with Hutchinson sign (pigment spreading from under the nail to involve the adjacent skin, usually of the proximal or lateral nail fold). These lesions are thought to emanate from the nail matrix. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

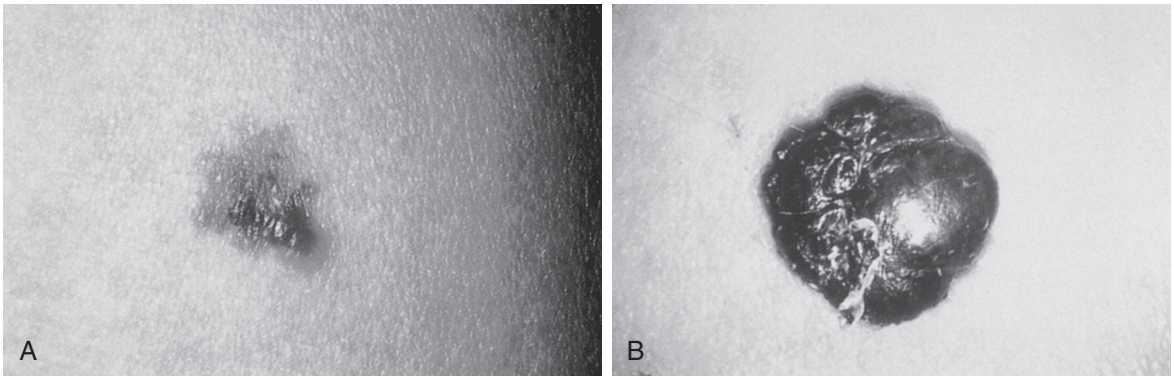

FIGURE M1-13 A, Superficial spreading melanoma. **B,** Nodular melanoma. (From Abeloff MD [ed]: *Clinical oncology,* ed 3, New York, 2004, Churchill Livingstone.)

FIGURE M1-15 Melanoma of the vulva. Benign nevi, vulva melanosis, and melanoma may occur in the vulvar region. Any suspicious pigmented lesion should be biopsied. The patient here is 75 years old. (Courtesy Paul Koonings, M.D. From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

WORKUP

- Dermoscopy (use of an instrument that shines polarized light on skin surfaces and magnifies skin lesions) can increase the accuracy in diagnosing melanoma by 10% to 27%.
- Any suspicious lesion (Fig. M1-15) should be biopsied. Perform excisional biopsy with elliptical excision that includes 1 to 2 mm of normal skin surrounding the lesion and extends to the subcutaneous tissue; incisional punch biopsy is sometimes necessary in surgically sensitive areas (e.g., digits, nose). It is essential that the size of the specimen be adequate to determine the histologic depth of penetration, which is known as the Breslow depth.
- Sentinel lymph node excision (SLNE) is probably the most important diagnostic and potentially therapeutic procedure for patients with melanoma. It should be considered in patients with intermediate (1 to 4 mm) melanomas or high-risk skin tumors to obtain information regarding a patient's subclinical lymph node status with minimal morbidity. The National Comprehensive Cancer Network (NCCN) recommends that sentinel-node biopsy be discussed with and offered to patients classified as stage IB or stage II, and should be considered for patients with stage IA melanoma and "adverse" features that might portend a higher risk of sentinel node involvement (e.g., Clark level IV or V, tumor thickness of 0.75 mm or more, lymphovascular invasion, positive deep margins). Sentinel lymph node biopsy involves the use of radiologic lymphoscintigraphy to map lymphatic drainage from the site of the primary melanoma to the first sentinel lymph node in the region. When properly performed, if the sentinel node is negative the remaining lymph nodes in the region will not have metastases in more than 98% of cases. If the sentinel nodes are negative, no additional regional surgery is recommended. The staging of intermediate thickness (1.2 to 3.5 mm) primary melanomas, according to the results of sentinel node biopsy, provides important prognostic information and identifies patients with nodal metastases whose survival can be prolonged by immediate lymphadenectomy. SPECT/CT is helpful in detecting micrometastatic melanoma. Among patients with clinically lymph node-negative melanoma, the use of SPECT/CT-aided SLNE compared with SNLE alone is associated with a higher frequency of metastatic involvement and a higher rate of disease-free survival.
- The staging system for melanoma adapted by the American Joint Committee on Cancer (AJCC) is as follows:

T*	Thickness of primary tumor
Tis	In situ
T1	≤1.0 mm
T2	1.01-2.0 mm
T3	2.01-4.0 mm
T4	>4.0 mm
N†	Number of positive lymph nodes
N0	0
N1	1
N2	2 or 3
N3	≥4 (or combination of in-transit metastases, satellite lesions, or an ulcerated primary lesion with any number of nodes)
M	Metastases
M0	0
M1	Distant subcutaneous or lymph node metastases
M2	Lung metastases
M3	All other visceral or any distant metastases or an elevated lactate dehydrogenase level not attributable to another cause
Clinical Stage	
0	(T0N0M0)
IA	(T1aN0M0)
IB	(T1bN0M0) (T2aN0M0)
IIA	(T2bN0M0) (T3aN0M0)
IIB	(T3bN0M0) (T4aN0M0)
IIC	(T4bN0M0)
IIIA	(T1-T4aN1bM0)
IIIB	(T1-T4aN2bM0)
IIIC	(AnyT, N2c, M0) (Any T, N3, M0)
IV	(Any T, Any N, >M1)

**a,* Without ulceration; *b,* with ulceration.
†*a,* Micrometastasis; *b,* macrometastases; *c,* in-transit metastases with metastatic lymph nodes.

LABORATORY TESTS

The pathology report should indicate the following:

- Tumor thickness (Breslow microstage).
- Tumor depth: the depth of invasion is the most important histologic prognostic parameter in evaluating the primary tumor.
- Mitotic rate: tabulated as mitoses per square millimeter in the dermal part of the tumor in which most mitoses are identified.
- Radial growth rates versus vertical growth rate: radial growth phase describes the growth of melanoma within the epidermis and along the dermal-epidermal junction.
- Tumor infiltrating lymphocytes have a strong predictive value in vertical growth phase melanomas and are defined as brisk, non-brisk, or absent.
- Histologic regression: characterized by the absence of melanoma in the epidermis and dermis flanked on one or both sides by melanoma.
- Reverse-transcription polymerase chain reaction assay for tyrosine messenger RNA is a useful marker for the presence of melanoma cells. It is performed on sentinel lymph node biopsy and is useful for detection of submicroscopic metastases.
- Identification of somatic mutations in the gene encoding the serine-threonine protein kinase B-RAF (*BRAF*). This mutation is found in approximately 50% of melanomas.

Rx TREATMENT

- Initial excision of the melanoma
- Reexcision of the involved area after histologic diagnosis:
  1. The margins of reexcision depend on the Breslow depth. For melanoma in situ with Breslow depth ≤2.0 mm, recommended surgical margin is 1 cm. If Breslow depth is ≤2.0 mm, margin should be 2 cm. For melanoma in situ, margin should be 5 mm.
  2. Low-risk or intermediate-risk tumors require excision of 1 to 3 cm.
  3. Melanomas of moderate thickness (0.9 to 2.0 mm) can be excised safely with 2-cm margins.
  4. A 1-cm margin of excision for melanoma with a poor prognosis (as defined by a tumor thickness ≥2 mm) is associated with a significantly greater risk of regional recurrence than is a 3-cm margin, but with a similar overall survival rate. Randomized clinical trials have also shown that radical surgery with 2 cm excision margins did not differ from that with 4 cm margins for survival in patients with cutaneous melanoma >2 mm thick.
- Lymph node dissection: recommended in all patients with enlarged lymph nodes. Lymph node evaluation is important in patients with melanoma 1 mm in depth because it determines the overall prognosis and need for therapeutic lymph node dissection or adjuvant treatment.
  1. Elective lymph node dissection remains controversial.
  2. It is indicated with positive sentinel node. It may be considered in those with a primary melanoma between 1 and 4 mm thick (especially in patients >60 yr).

- Adjuvant therapy with interferon alfa-2b (intron A) in patients with metastatic melanoma is approved by the FDA for AJCC stages IIb and III melanoma; however, its statistical benefit remains unclear. Peginterferon alfa-2b (which has a longer duration of action and can be given once a week compared to 3-5 times/week for standard interferon) has now also been FDA approved for adjuvant treatment of node-positive melanoma after surgical resection.
- Dacarbazine and interleukin-2 can be used in metastatic melanoma. Results are generally poor, with median survival time in patients with distant metastatic melanoma approximately 6 mo.
- Recent attention has focused on combinations of dacarbazine and cisplatin with interleukin-2 and interferon-alfa (biochemotherapy). Novel therapeutics involve cancer vaccines and use of granulocyte-macrophage colony-stimulating factor and angiogenesis inhibitors. Preliminary trials involving the stimulation of immune response with vaccines using high-dose interleukin-2 plus the gp100:209-217 (210 M) peptide vaccine in patients with advanced melanoma have shown increased survival. Trials with ipilimumab, an agent that blocks cytotoxic T-lymphocyte–associated antigen 4 to potentiate an antitumor T-cell response, have shown improved overall survival in patients with previously treated metastatic melanoma. Ipilimumab when used with dacarbazine also showed improved overall survival in patients with previously untreated metastatic melanoma.
- In patients who carry the V600E *BRAF* mutation, trials involving treatment with vemurafenib (PLX4032), an oral inhibitor of mutated *BRAF*, have shown complete or partial tumor regression in the majority of patients with metastatic melanoma and improved rates of overall and progression-free survival in patients with previously untreated melanoma. The oral selective MEK inhibitor trametinib has also shown improved rates of progression-free and overall survival among patients who had metastatic melanoma with a BRAF V600E or V600K mutation. Targeted therapy is useful in patients with rapidly growing melanoma with BRAF mutations, but resistance appears in almost all patients and median progression-free survival is 6 to 7 months.
- Some melanomas harbor activating mutations and amplification of the type III transmembrane receptor tyrosine kinase KIT. In these patients with advanced melanomas harboring KIT alterations, treatment with imatinib mesylate results in significant clinical responses in a subset of patients.
- Patients with a history of melanoma should be followed up with skin examinations every 6 mo or sooner if patient detects any new lesions; the assessments usually consist of medical history, physical examination, laboratory values, and chest radiograph.

DISPOSITION

- Prognosis varies with the stage of the melanoma. The 5-yr survival related to thickness is as follows: <0.76 mm, 99% survival; 0.6 to 1.49 mm, 85%; 1.5 to 2.49 mm, 84%; 2.5 to 3.9 mm, 70%; >4 mm, 44%.
- The 5-yr survival in patients with distant metastasis is <10%.
- Treatment of advanced disease consists (in addition to surgical excision and lymph node dissection) of chemotherapy, immunotherapy, and radiation therapy.

PEARLS & CONSIDERATIONS

Phosphodiesterase 5A inhibition by Sildenafil mimics downstream effects of genetic mutations that increase risk for invasive melanoma. A recent study found that age-adjusted absolute risk associated with Sildenafil use was 81 cases per 100,000 person-years.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Melanoma (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Background:
Phase 1 and 2 clinical trials of the BRAF kinase inhibitor vemurafenib (PLX4032) have shown response rates of more than 50% in patients with metastatic melanoma with the BRAF V600E mutation.
Methods:
We conducted a phase 3 randomized clinical trial comparing vemurafenib with dacarbazine in 675 patients with previously untreated, metastatic melanoma with the BRAF V600E mutation. Patients were randomly assigned to receive either vemurafenib (960 mg orally twice daily) or dacarbazine (1000 mg per square meter of body-surface area intravenously every 3 weeks). Coprimary end points were rates of overall and progression-free survival. Secondary end points included the response rate, response duration, and safety. A final analysis was planned after 196 deaths and an interim analysis after 98 deaths.
Results:
At 6 months, overall survival was 84% (95% confidence interval [CI], 78 to 89) in the vemurafenib group and 64% (95% CI, 56 to 73) in the dacarbazine group. In the interim analysis for overall survival and final analysis for progression-free survival, vemurafenib was associated with a relative reduction of 63% in the risk of death and of 74% in the risk of either death or disease progression, as compared with dacarbazine ($P<0.001$ for both comparisons). After review of the interim analysis by an independent data and safety monitoring board, crossover from dacarbazine to vemurafenib was recommended. Response rates were 48% for vemurafenib and 5% for dacarbazine. Common adverse events associated with vemurafenib were arthralgia, rash, fatigue, alopecia, keratoacanthoma or squamous-cell carcinoma, photosensitivity, nausea, and diarrhea; 38% of patients required dose modification because of toxic effects.
Conclusions:
Vemurafenib produced improved rates of overall and progression-free survival in patients with previously untreated melanoma with the BRAF V600E mutation. (Funded by Hoffmann–La Roche; BRIM-3ClinicalTrials.gov number, NCT01006980.) Ⓐ

Abstract[2]

Background:
About 10% of cutaneous malignant melanomas (CMM) occur in individuals with a family history of melanoma. In 20% to 40% of melanoma families germline mutations in CDKN2A are detected. Knowledge of the clinicohistologic characteristics of melanomas and patients from these families is important for optimization of management strategies, and may shed more light on the complex interplay of genetic and environmental factors in the pathogenesis of melanoma.
Objective:
We sought to investigate the clinical and histologic characteristics of CMM in CDKN2A-mutated families.
Methods:
Clinical and histologic characteristics of 182 patients with 429 CMM from families with a founder mutation in CDKN2A (p16-Leiden mutation) were compared with 7512 patients with 7842 CMM from a population-based cancer registry.
Results:
Patients with p16-Leiden had their first melanoma 15.3 years younger than control patients. The 5-year cumulative incidence of second primary CMM was 23.4% for patients with p16-Leiden compared with 2.3% for control patients. The risk of a second melanoma was twice as high for patients with p16-Leiden who had their first melanoma before age 40 years, compared with older patients with p16-Leiden. Unlike control patients, there was no body site concordance of the first and second melanoma in patients with p16-Leiden and multiple primary melanomas. Patients with p16-Leiden had significantly more superficial spreading, and less nodular and lentiginous melanomas.
Limitations:
Ascertainment of patients with p16-Leiden was family based. The study was performed in families with a founder mutation, the p16-Leiden mutation.
Conclusion:
Our findings are consistent with a pathogenic pathway of melanoma development from nevi, starting early and ongoing throughout life, and not related to chronic sun exposure. Ⓐ

Abstract[3]

Objective:
To understand the audiologic and vestibular toxicities associated with adoptive cell immunotherapy (ACI) targeting pigment-pathway antigens on melanoma and to investigate the use of intratympanic steroid injections in the treatment of these toxicities.
Study Design:
Prospective nonrandomized study.
Setting:
Tertiary clinical research center.
Methods:
Thirty-two patients with progressive metastatic melanoma who failed conventional therapy underwent ACI with T cells genetically modified to target MART-1 (n = 18) or gp100 (n = 14). All patients received serial audiometric testing. Vestibular testing was performed on patients with vestibular complaints. Patients with significant deficits received intratympanic steroid injections.
Results:
Of 32 patients, 15 had no hearing change, 9 had mild hearing loss, and 8 had moderate hearing loss following treatment. Ten patients received intratympanic steroid injections for mild (n = 2) or moderate (n = 7) hearing loss or for significant imbalance (n = 1). Of those with mild hearing loss (n = 9), all but 1 recovered to pretreatment hearing levels. Four of 8 patients with moderate hearing loss recovered to baseline hearing levels, and 4 had partial recovery. All 7 patients with posttreatment vestibular complaints had demonstrable vestibular dysfunction. Three of these patients demonstrated recovery to normal vestibular function. The number of modified T cells infused for therapy correlated with the degree of audiovestibular deficit.
Conclusion:
Adoptive cell immunotherapy targeting pigment-pathway cell proteins, a novel therapy for melanoma, can induce hearing loss and vestibular dysfunction. The presumed mechanism of autoimmune attack on normal melanocytes in the cochlear stria vascularis and in the vestibular organs demonstrates the importance of melanocytes in normal inner ear function. Ⓐ

Abstract[4]

Purpose:
Adjuvant pegylated interferon alfa-2b (PEG-IFN- α-2b) was approved for treatment of resected stage III melanoma in 2011. Here, we present long-term follow-up results of this pivotal trial.
Patients and Methods:
In all, 1,256 patients with resected stage III melanoma were randomly assigned to observation (n = 629) or PEG-IFN-α-2b (n = 627) for an intended duration of 5 years. Stratification factors were microscopic (N1) versus macroscopic (N2) nodal involvement, number of positive nodes, ulceration and tumor thickness, sex, and center. Recurrence-free survival (RFS; primary end point), distant metastasis-free survival (DMFS), and overall survival (OS) were analyzed for the intent-to-treat population.
Results:
At 7.6 years median follow-up, 384 recurrences or deaths had occurred with PEG-IFN-α-2b versus 406 in the observation group (hazard ratio [HR], 0.87; 95% CI, 0.76 to 1.00; P = .055); 7-year RFS rate was 39.1% versus 34.6%. There was no difference in OS (P = .57). In stage III-N1 ulcerated melanoma, RFS (HR, 0.72; 99% CI, 0.46 to 1.13; P = .06), DMFS (HR, 0.65; 99% CI, 0.41 to 1.04; P = .02), and OS (HR, 0.59; 99% CI, 0.35 to 0.97; P = .006) were prolonged with PEG-IFN-α-2b. PEG-IFN-α-2b was discontinued for toxicity in 37% of patients.
Conclusion:
Adjuvant PEG-IFN-α-2b for stage III melanoma had a positive impact on RFS, which was marginally significant and slightly diminished versus the benefit seen at prior follow-up (median, 3.8 years). No significant

increase in DMFS or OS was noted in the overall population. Patients with ulcerated melanoma and lower disease burden had the greatest benefit. Ⓐ

Evidence-Based References

Chapman PB, for the BRIM-3 Study Group: Improved survival with vemurafenib in melanoma with BRAF V600E mutation, *N Engl J Med* 364:2507–2516, 2011 Ⓐ.

van der Rhee JI et al.: Clinical and histologic characteristics of malignant melanoma in families with a germline mutation in CDKN2A, *J Am Acad Dermatol* 65:281–288, 2011 Ⓐ

SUGGESTED READINGS

Caravajal RD et al.: KIT as a therapeutic target in metastatic melanoma, *JAMA* 305(22):2327–2334, 2011.

Caroline C et al.: Ipilimumab plus dacarbazine for previously untreated metastatic melanoma, *N Engl J Med* 364:2517–2526, 2011.

Chapman PB et al.: Improved survival with vemurafenib in melanoma with BRAF V600E mutation, *N Engl J Med* 364:2507–2516, 2011.

Flaherty KT: Narrative review: BRAF opens the door for therapeutic advances in melanoma, *Ann Intern Med* 153:587–591, 2010.

Flaherty KT et al.: Inhibition of mutated, activated BRAF in metastatic melanoma, *N Engl J Med* 363:809–819, 2010.

Flaherty KT et al.: Improved survival with MEK inhibition in BRAF-mutated melanoma, *N Engl J Med* 367:107–114, 2012.

Gershenwald JE, Ross MI: Sentinel-lymph-node biopsy for cutaneous melanoma, *N Engl J Med* 364:1738–1745, 2011.

Gillgren P et al.: 2 cm versus 4 cm surgical excision margins for primary cutaneous melanoma thicker than 2 mm: a randomized, multicenter trial, *Lancet* 378:1635–1642, 2011.

Hodi FS et al.: Improved survival with ipilimumab in patients with metastatic melanoma, *N Engl J Med* 363:711–723, 2010.

Li WQ et al.: Sildenafil use and increased risk of incident melanoma in US men: a prospective cohort study, *JAMA Intern Med* 174:964–970, 2014.

Markovic S et al.: Malignant melanoma in the 21st century, *Mayo Clin Proc* 82(3):490, 364; 82(4):490. 2007.

Miller AJ, Mihm MC: Melanoma, *N Engl J Med* 355:51, 2006.

Morton DL: Final trial report of sentinel-node biopsy versus nodal observation in melanoma, *N Engl J Med* 370:599–609, 2014.

Robert C et al.: Improved overall survival in melanoma with combined dabrafenib and trametinib, *N Engl J Med* 372:30–39, 2015.

Schwartzentruber DJ et al.: gp100 peptide vaccine and interleukin-2 in patients with advanced melanoma, *N Engl J Med* 364:2119–2127, 2011.

Shenenberger D: Cutaneous malignant melanoma: a primary care perspective, *Am Fam Physician* 85(2):161–168, 2012.

Sondak VK et al.: Risk-stratified screening for detection of melanoma, *JAMA* 313:616–617, 2015.

Sosman J et al.: Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib, *N Engl J Med* 366:707–714, 2012.

Stoffels I et al.: Association between sentinel lymph node excision with or without pre-operative SPECT/CT and metastatic node detection and disease-free survival in melanoma, *JAMA* 308(10):1007–1014, 2012.

BASIC INFORMATION

DEFINITION

Ménière's disease is a syndrome characterized by recurrent vertigo with fluctuating hearing loss, tinnitus, and fullness in the ear.

SYNONYMS

Endolymphatic hydrops
Lermoyez's syndrome
Idiopathic endolymphatic hydrops

ICD-9CM CODES
386.01 Ménière's disease
ICD-10CM CODES
H81.09 Ménière's disease, unspecified ear

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Varies between 4.3 and 15.3/100,000 persons
PREDOMINANT SEX: Female to male ratio of 1.3:1
PEAK INCIDENCE: Fourth to sixth decade of life

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Hearing may be unilaterally decreased.
- Pallor, sweating, and nausea may occur during a severe attack.
- Usually the patient develops a sensation of fullness and pressure along with decreased hearing and tinnitus in a single ear.
- The patient typically experiences severe vertigo, which peaks within minutes, then slowly subsides over hours.
- May see spontaneous nystagmus on examination.
- Persistent sense of disequilibrium for days is typical after an acute episode
- May have vestibulopathy demonstrable with a positive head thrust test.

ETIOLOGY

- Unknown; viral, autoimmune, and genetic causes have been suggested.
- Endolymphatic hydrops is the postmortem histologic hallmark. Recent research suggests that endolymphatic hydrops may create cytochemical changes which disturb endolymphatic fluid homeostasis leading to spiral ganglion cell death.

DIAGNOSIS

Proposed guidelines by the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) for diagnosis of Ménière's disease:

DIFFERENTIAL DIAGNOSIS

- Acoustic neuroma
- Migrainous vertigo
- Multiple sclerosis
- Autoimmune inner ear syndrome
- Otitis media
- Vertebrobasilar disease
- Labyrinthitis

WORKUP

- Diagnosis is primarily made by history, although further diagnostic tests may help support the diagnosis. Guidelines to define Ménière's disease are described in Table M1-6.
- Audiogram may show sensorineural hearing loss, with lower frequencies primarily affected. Hearing loss may recover either partially or completely after an attack. Recurrent attacks may lead to a persistent and progressive sensorineural hearing loss.
- Electronystagmography may show peripheral vestibular deficit.
- Electrocochleography (ECoG) records the summating potential and action potential of the eighth cranial nerve in response to auditory stimuli and may indicate significant endolymphatic hydrops if the ratio of summating potential to action potential (SP:AP) is greater than 0.35. Unfortunately, sensitivity and specificity of ECoG to diagnosis of Ménière's disease are low, due to their variability related to severity and chronicity of disease.
- More recently, the vestibular-evoked myogenic potential (VEMP), a short latency inhibitory potential of sternocleidomastoid muscle evoked by brief and loud monaural clicks or tone bursts, has been shown to be elevated or absent in some patients with Ménière's disease, reflecting impaired function of the saccule. However, this test also lacks significant sensitivity and specificity to Ménière's disease and has not yet been widely used in the clinical setting.

TABLE M1-6 Guidelines to Define Ménière's Disease

Definition	Symptoms
Certain Ménière's disease	Definite Ménière's disease + histopathologic confirmation
Definite Ménière's disease	≥2 definitive spontaneous episodes of vertigo 20 min or longer Audiometrically documented hearing loss on at least one occasion Tinnitus or aural fullness in the treated ear Other causes excluded
Probable Ménière's disease	One definite episode of vertigo Audiometrically documented hearing loss on at least one occasion Tinnitus or aural fullness in the treated ear Other causes excluded
Possible Ménière's disease	Episodic vertigo without documented hearing loss, or sensorineural hearing loss (SNHL) fluctuating or fixed, with disequilibrium but nonepisodic Other causes excluded

LABORATORY TESTS

No laboratory serologic test is specific for Ménière's disease. A thyroid panel, glucose, hemoglobin A1C, antinuclear antibodies, urinalysis, chemistry panel, Venereal Disease Research Laboratory (VDRL) Test, fluorescent treponemal antibody (FTA-ABS), Lyme disease antibodies, and allergy testing can be ordered to screen for other disorders such as thyroid or autoimmune diseases, diabetes, otorenal syndrome, syphilis, Lyme disease, and allergy-mediated Ménière's disease.

IMAGING STUDIES

- MRI to rule out acoustic neuroma, or other retrocochlear lesion, especially if cerebellar or CNS dysfunction is present
- Recent efforts have shown a role for MRI with intratympanic gadolinium.

TREATMENT

NONPHARMACOLOGIC THERAPY

Limit activity during attacks

ACUTE GENERAL Rx

- Prochlorperazine 5 to 10 mg PO q6h or 25 mg PO bid
- Promethazine 12.5 to 25 mg PO q4 to 6h
- Diazepam 5 to 10 mg IV/PO for acute attack
- Meclizine 25 mg q6h
- Scopolamine patch

CHRONIC Rx

- Diuretics such as hydrochlorothiazide or acetazolamide, salt restriction, and avoidance of caffeine are traditional.
- For refractory cases, intratympanic gentamicin injections to the affected ear, endolymphatic sac surgery

DISPOSITION

- Patients are usually followed by an otoneurologist or ENT specialist.
- Usual course of disease consists of alternating attacks and remissions.
- Majority of patients can be managed medically. Of patients, 10% to 30% will undergo surgical intervention for persistent incapacitating vertigo.

REFERRAL

To an otolaryngologist for surgical intervention if attacks persist despite medical therapy

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Ménière's Disease (Patient Information)

AUTHOR: **SHARON S. HARTMAN POLENSEK, M.D., PH.D.**

SUGGESTED READINGS

Committee on Hearing and Equilibrium of the AAO-HNS: Revised guidelines for the diagnosis and evaluation of therapy in Meniere's disease, *Otolaryngol Head Neck Surg* 113:181–185, 1995.

Le CH et al.: Novel techniques for the diagnosis of Ménière's disease, *Curr Opin Otolaryngol Head Neck Surg* 21:492–496, 2013.

Semaan MT, Megerian CA et al.: Contemporary perspectives on the pathophysiology of Ménière's disease: implications for treatment, *Curr Opin Otolaryngol Head Neck Surg* 18:392–398, 2010.

BASIC INFORMATION

DEFINITION

Meningiomas are generally slow-growing tumors arising from arachnoid cells of the arachnoid villi; 90% are benign.

ICD-9CM CODES
225.2 Cerebral meninges
ICD-10CM CODES
D32.0 Benign neoplasm of cerebral meninges

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 6/100,000 persons/yr; account for about one third of primary brain tumors and are the second most common brain tumor in adults; often underreported.
PREDOMINANT SEX AND AGE: Female/male ratio of almost 3:1 in the brain and up to 6:1 in the spinal cord; male = female in childhood
PEAK INCIDENCE: Males: sixth decade, females: seventh decade, incidence increases with age; rare in childhood
RISK FACTORS: Ionizing radiation results in increased incidence and a shorter latency period. Neurofibromatosis type 2 (NF2) is an autosomal dominant genetic disorder that predisposes to multiple intracranial tumors. Approximately half of all individuals with NF2 have meningiomas, most of which are intracranial. Studies have suggested a link between hormonal factors and development of meningioma. At present, there is no conclusive evidence to support a causal relationship with cell phone usage and subsequent development of meningioma.
GENETICS: Meningiomas may be isolated or found in association with other genetic diseases, such as neurofibromatosis type 2 and familial meningioma. Approximately half of meningiomas have allelic losses involving the *NF2* and *DAL-1* genes. Allelic losses of chromosomes 1p, 2p, 6q, 9q, 10q, 14q, 17p, and 18q may be associated with histologic progression.

TABLE M1-7 Locations and Presentations of Meningiomas

Location	Presenting Manifestation
Parasagittal	Urinary incontinence, dementia, gradual paraparesis, seizures
Lateral convexity	Variable depending on structures compressed, including slow hemiparesis, speech abnormalities
Olfactory groove	Anosmia, visual disturbance, dementia, Foster-Kennedy syndrome
Suprasellar	Hormonal failure, bitemporal hemianopsia, optic atrophy
Sphenoid ridge	Extraocular nerve paresis, exostoses, proptosis, seizures

From Goetz CG, Pappert EJ: *Textbook of clinical neurology,* Philadelphia, 1999, Saunders.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Neurologic symptoms vary with location and size (see Table M1-7); meningiomas can arise from the dura at any site, although most commonly occur within the skull and at sites of dural reflection, such as the cerebral convexities and the falx. Other less common locations include the sphenoid wing, olfactory groove, and optic nerve sheath. Focal symptoms such as vision loss, hearing loss, or mental status change depend on the site of origin and the time course of growth.
- Most common presentation is with a focal or generalized seizure or gradually worsening neurologic deficit. Seizures are present preoperatively in 30% to 40%.
- Typically are slow growing and asymptomatic; many meningiomas are asymptomatic and/or discovered incidentally on a neuroimaging study or at autopsy.

ETIOLOGY

- Meningiomas are thought to arise from a multistep progression of genetic changes.
- Mutations of the *NF2* gene on chromosome 22 are found in patients with neurofibromatosis type 2 and >50% of sporadic meningiomas. This gene is thought to act as a tumor suppressor gene; the protein product, merlin, is also involved in cytoskeletal organization.
- *DAL-1* is another tumor suppressor gene, located on chromosome 18p, that has been identified in a subset of the approximately 40% of sporadic meningiomas with neither the *NF2* gene mutations nor allelic loss of chromosome 22q.
- Cranial radiation may be responsible for some cases following an appropriate latency period from 10 to 20 yr. Meningiomas that result from radiation are generally more aggressive.
- The link with steroid hormones and their receptors is suggested by the increase in growth rate and/or development of meningiomas during pregnancy and increased incidence in women who use postmenopausal hormones or in association with breast carcinomas.

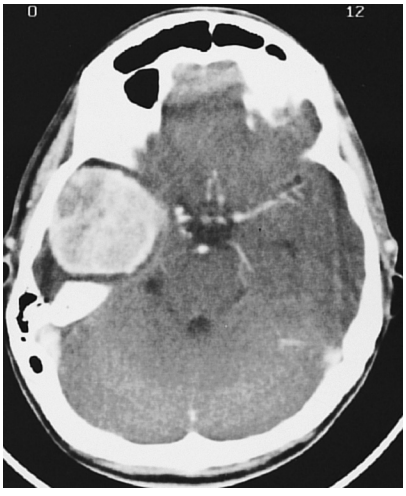

FIGURE M1-16 Contrast-enhanced CT scan demonstrates a large contrast-enhancing right sphenoid wing meningioma. (From Specht N [ed]: *Practical guide to diagnostic imaging,* St Louis, 1998, Mosby.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Other well-circumscribed intracranial tumors that involve the dura or subdural space:
- Acoustic schwannoma (typically at the pontocerebellar junction)
- Ependymoma, lipoma, and metastases within spinal cord
- Metastatic disease from lymphoma/adenocarcinoma, inflammatory disease such as sarcoidosis and Wegener's granulomatosis, or infections such as tuberculosis

WORKUP

Imaging studies with CT or MRI, followed by surgical removal with histologic confirmation

LABORATORY TESTS

According to the World Health Organization (WHO) classification, there are nine benign histologic variants (account for 90% of all meningiomas) and four variants associated with increased recurrence and rates of metastasis. Ninety percent of meningiomas are classified as benign meningiomas or WHO grade I.

IMAGING STUDIES

- Cranial CT scanning or MRI can detect and determine the extent of meningiomas (Fig. M1-16). CT can show hyperostosis and/or intratumoral calcifications. MRI (Fig. M1-17) is the imaging modality of choice to demonstrate

FIGURE M1-17 MRI picture of a posterior fossa meningioma, demonstrated an extra-axial homogeneously contrast-enhanced mass arising from the tentorium and compressing the cerebellar hemisphere. (From Goetz CG, Pappert EJ: *Textbook of clinical neurology,* Philadelphia, 1999, Saunders.)

the dural origin of the tumor in most cases, with the characteristic "tail" sign.
- On nonenhanced scans, meningiomas typically are isodense or slightly hyperdense to brain and are homogeneous in appearance. They show homogeneous contrast enhancement; gadolinium can facilitate imaging of smaller additional lesions that are missed on unenhanced images.
- Indistinct margins, marked edema, mushroomlike projections from tumor, brain parenchymal infiltration, and heterogeneous enhancement are suggestive of more aggressive behavior.
- PET scan may help in predicting the aggressiveness of the tumor and the potential for recurrence, but it is not used routinely.

Rx TREATMENT

Primary management depends on signs or symptoms, age of patient, and location and size of tumor. Observation may be appropriate if tumors are discovered incidentally and/or if growth is indolent and unlikely to cause symptoms.

PHARMACOLOGIC THERAPY

- Although a variety of chemotherapeutic agents have been studied, such as hydroxyurea, there is no established effective systemic therapy.
- Inhibition of hormone receptors, such as progesterone, estrogen, and androgen, has failed to demonstrate clinical benefit.
- Treatment with molecularly targeted approaches, such as angiogenesis inhibition, is currently under way.

NONPHARMACOLOGIC THERAPY

- The mainstay of treatment for meningiomas remains surgical removal. Complete resection is usually attempted, when feasible. After total excision, recurrence rates of 0% to 20% have been observed, while 20% to 50% of patients recur within 5 yr of a subtotal resection.
- Active surveillance to monitor for tumor recurrence is important.
- Radiation therapy is the only validated form of adjuvant therapy and may be beneficial in patients with incomplete resections or inoperable tumors. Stereotactic radiosurgery can provide local control with more limited toxicity.

ACUTE GENERAL Rx

- For lesions that cause significant mass effect, steroids are sometimes used to decrease brain edema.
- Anticonvulsants are used if the patient presents with seizures.

CHRONIC Rx

- Prophylactic use of anticonvulsants is not recommended in patients without a history of seizures.
- There is limited data on the efficacy of traditional chemotherapy, and the evidence is largely anecdotal. The most extensively evaluated agents are hydroxyurea, mifepristone (RU486), and interferon alfa-2b. Recently, somatostatin analogs have been evaluated in multicenter clinical trials.

DISPOSITION

- Estimated surgical mortality is 7%. Significant morbidity and mortality can be observed in meningiomas with otherwise favorable pathology secondary to unfavorable location (e.g., skull base).
- Long-term outcome varies, based on pathology, tumor grade, location, and completeness of resection.
- Most incidentally discovered meningiomas remain asymptomatic and have a slow rate of growth. Calcified tumors may be less likely to progress than noncalcified ones.
- Meningiomas may recur after surgical resection. In addition, some tumors show histologic progression to a higher grade. Features suggesting increased rate of recurrence include multiple allelic chromosomal losses, local brain invasion, high rate of mitosis, and highly anaplastic features.

REFERRAL

- Neurosurgical consultation for all cases
- Neurology, radiation oncology, and oncology depending on presence of other sequelae and in setting of recurrence

PEARLS & CONSIDERATIONS

COMMENTS

- Many meningiomas are discovered incidentally; most are benign and remain asymptomatic.
- "Dural tail" is classic finding on neuroimaging studies.
- Individuals with neurofibromatosis type 2 are at high risk to develop meningiomas.

PATIENT & FAMILY EDUCATION

Meningioma mommas: www.meningiomamommas.org
Meningioma Support and Patient Information Group
National Brain Tumor Society
Meningioma Online Support Group: http://www.brainstrust.org/meningioma.htm

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Meningioma (Patient Information)

AUTHOR: **NICOLE J. ULLRICH, M.D., PH.D.**

SUGGESTED READINGS

Braganza MZ et al.: Ionizing radiation and the risk of brain and central nervous system tumors: a systematic review, *Neuro Oncol* 14:1316, 2012.

Drummond KJ et al.: Meningiomas: updating basic science, management, and outcome, *Neurologist* 10(3):113–130, 2004.

Glantz MJ et al.: Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the Quality Standards Subcommittee of the American Academy of Neurology, *Neurology* 54:1886, 2000.

Mason WP: Stabilization of disease progression by hydroxyurea in patients with recurrent or unresectable meningioma, *J Neurosurg* 97:341, 2002.

Norden AD et al.: Advances in meningioma therapy, *Curr Neurol Neurosci Rep* 9:231, 2009.

Perry A et al. Meningiomas. In: (editor: Louise D.N.; et al.) WHO classification of tumors of the nervous system. IARC Press: Lyon, France, p. 164.

Perry A et al.: Molecular pathogenesis of meningiomas, *J Neurooncol* 70(2):183–202, 2004.

Seizinger JP: Deletion mapping of a locus on human chromosome 22 involved in the oncogenesis of meningioma, *Proc Natl Acad Sci U S A* 84:5419, 1987.

Wiemels J et al.: Epidemiology and etiology of meningioma, *J Neurooncol* 99:307, 2010.

BASIC INFORMATION

DEFINITION

Meningomyelocele is the most common type of neural tube defect and is characterized by herniation of the spinal cord, nerves, or both through a bony defect of the spine.

SYNONYMS

Myelomeningocele
Spina bifida cystica

ICD-9CM CODES
741.9 Meningomyelocele
ICD-10CM CODES
Q05.9 Spina bifida, unspecified
Q05.4 Unspecified spina bifida with hydrocephalus
Q05.7 Lumbar spina bifida without hydrocephalus
Q05.2 Lumbar spina bifida with hydrocephalus
Q05.8 Sacral spina bifida without hydrocephalus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 4.6/10,000 births
PREDOMINANT SEX: Male equals female
PEAK INCIDENCE: Newborn
GENETICS: Environmental and genetic factors have a joint role.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Evident at birth—a sac protruding in the lumbar region (Fig. EM1-18)
- Severity of neurologic deficits depends on the location of the lesion along the neuraxis
- Motor dysfunction in the legs
- Lack of bladder or bowel control
- Often associated with Chiari II malformation and resulting obstructive hydrocephalus

ETIOLOGY

- Failure of neural tube to close completely at about 4 wk gestation
- Associated with maternal valproate use, maternal diabetes and prepregnancy obesity
- Growing recognition of role of environmental chemicals, including organic pollutants
- In the U.S., higher rates of neural tube defects reported among Hispanic women
- A small proportion of cases are associated with chromosomal or single-gene disorders

DIAGNOSIS

- Prenatal diagnosis through ultrasound and MRI is being made more frequently
- Coexisting hydrocephalus detected by measurement of head size, ultrasonography, CT, or MRI

DIFFERENTIAL DIAGNOSIS

- Teratoma
- Meningocele

WORKUP

- Evaluate for hydrocephalus
- Evaluate for other congenital abnormalities, such as congenital heart disease, hydronephrosis, intestinal malformation, club foot, and skeletal deformities

LABORATORY TESTS

Prenatal testing often reveals elevated alpha-fetoprotein in amniotic fluid or maternal serum.

IMAGING STUDIES

- MRI of spine
- X-ray studies of skull exhibit craniolacunia, a honeycombed pattern associated with hydrocephalus (not routinely performed)
- CT or MRI of head: may reveal hydrocephalus

TREATMENT

- Surgical closure of myelomeningocele is performed soon after birth
- Control of hydrocephalus (shunt)
- Management of urinary incontinence (bladder catheterization)

ACUTE GENERAL Rx

- Immediate goal after delivery is to close defect and prevent infection; surgery usually performed within 24 hr of birth
- Shunt placement for obstructive hydrocephalus
- Treatment of seizures, if present

CHRONIC Rx

- Follow closely for development of hydrocephalus
- Bladder catheterization
- Avoid use of latex-containing products to prevent development of latex allergy

DISPOSITION

Followed by a team of specialists including neurosurgeons, urologists, orthopedists, nurses, and physical therapists

PEARLS & CONSIDERATIONS

All mothers of children with neural tube defects should be instructed on nutritional supplementation with folate for future pregnancies.

COMMENTS

- Intrauterine repair of meningomyelocele decreases the incidence of hindbrain herniation and shunt-dependent hydrocephalus in infants, but increases the incidence of premature delivery and is associated with maternal and fetal risks.
- U.S. Public Health Service recommends 400 mg of folate intake per day for all women capable of becoming pregnant for primary prevention of neural tube defects.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **MAITREYI MAZUMDAR, M.D., M.P.H.**

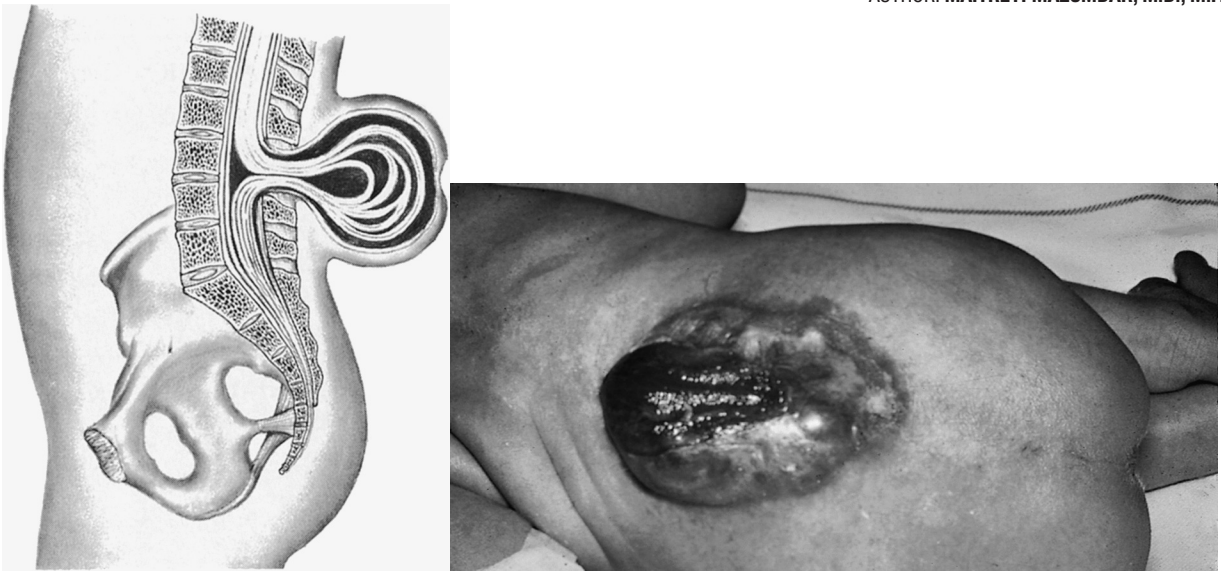

FIGURE EM1-18 Meningomyelocele. (From Wong DL: *Whaley and Wong's nursing care of infants and children*, ed 5, St Louis, 1995, Mosby.)

SUGGESTED READINGS

Adzick NS et al.: A randomized trial of prenatal versus postnatal repair of myelomeningocele, *N Engl J Med* 364:993–1004, 2011.

Adzick NS, Walsh DS: Myelomeningocele: prenatal diagnosis, pathophysiology and management, *Semin Pediatr Surg* 12(3):168, 2003.

Mitchell LE: Epidemiology of neural tube defects, *Am J Med Genet C Semin Med Genet* 135(1):88, 2005.

Spina bifida and anencephaly before and after folic acid mandate—United States. 1995-1996 and 1999-2000, *MMWR Morb Mortal Wkly Rep* 53(17):362, 2004.

BASIC INFORMATION

DEFINITION

Menopause is the permanent cessation of menstrual periods for 1 yr after age 40 yr or permanent cessation of ovulation after lost ovarian activity. It is the reproductive stage of life marked by waxing and waning estrogen levels followed by decreasing ovarian function. Primary ovarian insufficiency (previously also referred to as premature ovarian failure)) and no menstrual periods may also occur because of depletion of ovarian follicles before the age of 40 yr.

SYNONYMS

Change of life
Climacteric ovarian failure

ICD-9CM CODES

627 Premenopausal menorrhagia
627.2 Menopausal or female climacteric states
627.4 States associated with artificial menopause

ICD-10CM CODES

Z78.0 Asymptomatic menopausal state
N95.1 Menopausal and female climacteric states
N95.8 Other specified menopausal and perimenopausal disorders

EPIDEMIOLOGY & DEMOGRAPHICS

- Average age of menopause in the United States is 51 yr.
- Age at which menopause occurs is primarily genetically determined.
- Smokers experience menopause an average of 1.5 yr earlier than nonsmokers.
- More than one third of a woman's life will be spent after menopause.
- Onset of perimenopause is usually in a woman's mid- to late-40s.
- Approximately 4000 women each day begin menopause.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Atrophic vaginitis, which can cause burning, itching, bleeding, dyspareunia
- Either complete cessation of menses or a period of irregular cycles and diminished or heavier bleeding
- Osteoporosis
- Psychological dysfunction:
  1. Anxiety
  2. Depression
  3. Insomnia
  4. Nervousness
  5. Irritability
  6. Inability to concentrate
- Sexual changes, decreased libido, dyspareunia
- Urinary incontinence
- Vasomotor symptoms (hot flashes, flushes), night sweats, cardiovascular disease, coronary artery disease, atherosclerosis, headaches, tiredness, and lethargy. A recent study from the University of Pennsylvania noted that the median duration of moderate-to-severe hot flashes is 10.2 yr but that the length of hot flashes was largely dictated by how early these began in the perimenopause.

ETIOLOGY

- The most common etiology: physiologic, caused by depleted granulosa and theca cells that fail to react to endogenous gonadotropins, producing less estrogen; decreased negative feedback in the hypothalamic pituitary access, increased follicle-stimulating hormone (FSH), and increased luteinizing hormone (LH), which leads to stromal cells that continue to produce androgens as a result of the LH stimulation
- Surgical castration
- Family history of early menopause, cigarette smoking, blindness, abnormal chromosomal karyotype (Turner's syndrome, gonadal dysgenesis), precocious puberty, and left-handedness

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Asherman's syndrome
- Hypothalamic dysfunction
- Hypothyroidism
- Pituitary tumors
- Adrenal abnormalities
- Ovarian abnormalities
- Polycystic ovarian syndrome
- Pregnancy
- Ovarian neoplasm
- Tuberculosis of the endometrium

WORKUP

- If the clinical picture is highly suggestive of menopause, estrogen can be prescribed. If all symptoms resolve, then diagnosis has essentially been made. Before estrogen is prescribed, a complete history and physical examination are needed. If a patient has estrogen-dependent malignancy, unexplained abnormal uterine bleeding, history of thrombophlebitis, or acute liver disease, estrogen therapy is contraindicated.
- Progesterone challenge test: medroxyprogesterone 10 to 20 mg PO or progesterone 100 mg IM to induce withdrawal bleeding. If no withdrawal bleeding is obtained, a hypoestrogenic state is assumed to be present. This test is increasingly controversial even if very commonly performed.
- Physical examination, height, weight, blood pressure, breast examination, and pelvic examination are needed.
- Assess risk for coronary artery disease, osteoporosis, cigarette smoking, personal history, history of breast cancer, liver disease, active coagulation disorder, or any unexplained vaginal bleeding.

LABORATORY TESTS

- FSH, LH, and estrogen levels: markedly elevated FSH and markedly depressed estrogen level constitute laboratory diagnosis of ovarian failure; LH only if polycystic ovarian disease is to be ruled out in a younger patient. It is not necessary to obtain an FSH if the patient fulfills the clinical criteria for menopause. Similarly, since estradiol levels vary during the menstrual cycle, estradiol levels are rarely necessary or informative.
- TSH to rule out thyroid dysfunction and prolactin level if patient has symptoms of galactorrhea and if suspicion of pituitary adenoma exists
- A general chemistry profile to check for any systemic diseases
- Pap smear, endometrial biopsy, or dilation and curettage in patients who have had irregular periods or intermenstrual or postmenopausal bleeding
- Mammogram as recommended by American Congress of Obstetricians and Gynecologists.

IMAGING STUDIES

- CT scan or MRI of sella if pituitary tumor is suspected
- Bone density studies if high-risk condition for osteoporosis exists
- Pelvic ultrasound to check endometrial stripe

TREATMENT

NONPHARMACOLOGIC THERAPY

- A balanced diet: low in fat, with total fat intake being <30% of calories; total calories sufficient to maintain body weight or produce weight loss if that is desired
- Avoidance of smoking and excessive alcohol or caffeine intake
- Exercise: weight-bearing exercise for osteoporosis prevention
- Kegel exercises for strengthening the pelvic floor
- Adequate calcium intake: 1500 mg qd is necessary to maintain zero calcium balance in postmenopausal women
- Change in the ambient temperature (may ameliorate hot flashes and reduce night sweats)
- Vitamin E
- Avoidance of caffeine, alcohol, and spicy foods if they trigger hot flashes
- Vaginal lubricants to help with the dyspareunia attributable to vaginal dryness (e.g., Replens, K-Y Jelly, or Gyne-Moistrin cream)

ACUTE GENERAL Rx

Vasomotor symptoms are best managed with systemic hormone therapy given in the lowest dose and for the shortest period possible. Estrogen replacement in symptomatic patients can be done in a variety of forms, including oral estrogen and transdermal estrogen patch. The lowest effective dose should be prescribed.

- Examples of oral estrogen include:
  1. Conjugated estrogens: start with 0.3 mg qd and increase to 1.25 mg qd depending on symptoms.
  2. Estradiol: start with 0.5 mg qd and increase to 2 mg qd.
  3. Esterified estrogens: start with 0.3 to 1.25 mg qd.

4. Estropipate: start with 0.625 to 2.5 mg qd.
5. Esterified estrogen/testosterone combination: give 1.25 mg and methyltestosterone 2.5 mg (Estratest) and esterified estrogen 0.625 mg and methyltestosterone 1.25 mg (Estratest HS [half-strength]). May improve sexual enjoyment and libido.

- If the patient has had a hysterectomy for benign disease, estrogen alone is sufficient. However, if she still has her uterus, progestin is necessary to prevent endometrial hyperplasia associated with unopposed estrogen which is protective against endometrial cancer. Progestins can be prescribed as continual daily dose or cyclic fashion. Most commonly prescribed progestins include medroxyprogesterone acetate 2.5 mg, 5 mg, and 10 mg; Prometrium 100 mg, 200 mg, and 400 mg; and Aygestin 5 mg. Continuous hormone replacement therapy is preferred because after time the patient should be amenorrheic. Patients should be counseled that they may experience some irregular spotting for the first 6 to 9 mo after starting the hormone replacement therapy. Cyclic therapy will cause withdrawal bleeding.
- Combination oral preparations Femhrt, Prefest, Prempro, Activella, Premphase are commonly used. However, the U.S. Preventive Services Task Force recommends against the use of combined estrogen and progestin for the prevention of chronic conditions in postmenopausal women.
- Transdermal patches can be either estradiol (Estraderm, Vivelle, FemPatch) 0.025 to 0.1 mg applied twice weekly or Climara 0.025 to 0.1 mg used once a week. With these preparations, progesterone should be used in a similar fashion. Apply CombiPatch twice weekly (combination estrogen and progesterone) or Climara Pro once per week (one patch).
- Vaginal creams can be used; these should be reserved for local therapy of atrophic vaginitis. Systemic absorption does occur; however, blood levels are unpredictable. Usual dose 0.5 to 2 g intravaginally daily, cyclically 3 wk on 1 wk off. When symptoms improve, once to twice weekly is adequate maintenance.
- Vagifem estradiol vaginal tablets. Initial dosage: one Vagifem tablet, inserted vaginally, qd for 2 wk. Maintenance dose: one Vagifem tablet, inserted vaginally, twice weekly.
- Femring vaginal ring delivering the equivalent of 0.5 mg/day inserted every 3 mo or Estring 0.0075 mg/day.
- EstroGel 0.06% (estradiol gel) One Pump (1.25 g/day) applied to one arm from wrist to shoulder.
- The FDA contraindications to menopause hormone therapy include the following diseases and disorders: active liver disease; current, past, or suspected breast cancer; active or recent anterior thromboembolic disease (angina, myocardial infarction); known or suspected estrogen-sensitive malignant conditions; known hypersensitivity to the active substance of the therapy or to any of the excipients; porphyria cutanea tarda; previous idiopathic or current venous thromboembolism; undiagnosed genital bleeding; untreated hypertension; untreated endometrial hyperplasia.
- For women in whom estrogen is contraindicated or for those who do not wish to take estrogen, the following regimens can be used:
  1. Serotonin reuptake inhibitors
  2. Depo-Provera 150 mg IM every month (may be helpful in alleviating hot flashes)
  3. Clonidine 0.05 to 0.15 mg PO qd (questionable efficacy) or transdermal clonidine patch
  4. Bellergal-S (questionable efficacy)
- Tibolone significantly improves vasomotor symptoms, libido, and vaginal lubrication. Not available in the U.S.

CHRONIC Rx

Hormone replacement therapy should be used only for the short term unless benefits outweigh the risks of long-term use. As a result of the results of the Women's Health Initiative (WHI), the FDA has instituted a "black box" warning on postmenopausal hormone replacement products suggesting that the lowest dose should be used for the shortest period of time. This necessitates a considered and nuanced counseling session with patients contemplating hormone replacement prior to the initiation of therapy and then on a periodic basis after that, usually at least a yearly basis.

DISPOSITION

If treated, the patient should have resolution of her symptoms and reduced incidence of osteoporosis. Lifelong medical supervision is necessary to monitor adequacy of treatment and prevention of complications. This should include annual Pap smears until the age of 65, pelvic examinations, breast examinations, mammography, and endometrial sampling of any type of abnormal bleeding. If untreated, the vasomotor symptoms will eventually disappear; however, this may take several years in a small percentage of women. Some women who are in their 80s have experienced hot flashes. Urogenital atrophy will continue to worsen. Osteoporosis and coronary artery disease risks will increase with every passing year.

REFERRAL

Most menopausal women are managed by their gynecologists. However, this condition can be managed adequately by the patient's primary care physician who has an interest in treating menopausal women.

PEARLS & CONSIDERATIONS

COMMENTS

- Short-term risks of hormone replacement therapy (HRT) include an eighteenfold increased rise for cholecystitis, three-and-a-half-fold risk of a thrombocardiac event in the first year, and possible increased risk of stroke and myocardial infarction.
- Results of the WHI study found that for every 10,000 women taking HRT (combination of both estrogen and progesterone) for 1 yr (10,000 person-yr), seven more would have coronary events, eight would have more strokes, eight would have more pulmonary emboli, and eight would have earlier breast cancer than would 10,000 women taking placebo. Benefits of HRT were six fewer cases of colorectal cancer and five fewer hip fractures per 10,000 women.
- HRT should not be initiated or continued for the primary or secondary prevention of coronary heart disease.
- Estrogen-replacement therapy or HRT should only be prescribed for patients with sufficient menopausal symptoms that impact the patient's quality of life.
- Interestingly, women who start hormone therapy early in menopause may have cardiac and other benefits. The Women's Health Initiative had an average age at the start of therapy of 61, and this may have skewed the results of the study.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Menopause (Patient Information)
Hot Flashes (Related Key Topic)
Osteoporosis (Related Key Topic)

AUTHORS: **RUBEN ALVERO, M.D.,** and **GEORGE T. DANAKAS, M.D.**

EVIDENCE

Abstract[1]

Context:

The Women's Health Initiative Estrogen-Alone Trial was stopped early after a mean of 7.1 years of follow-up because of an increased risk of stroke and little likelihood of altering the balance of risk to benefit by the planned trial termination date. Postintervention health outcomes have not been reported.

Objective:

To examine health outcomes associated with randomization to treatment with conjugated equine estrogens (CEE) among women with prior hysterectomy after a mean of 10.7 years of follow-up through August 2009.

Design, Setting, and Participants:

The intervention phase was a double-blind, placebo-controlled, randomized clinical trial of 0.625 mg/d of CEE compared with placebo in 10 739 US postmenopausal women aged 50 to 79 years with prior hysterectomy. Follow-up continued after the planned trial completion date among 7645 surviving participants (78%) who provided written consent.

Main Outcome Measures:

The primary outcomes were coronary heart disease (CHD) and invasive breast cancer. A global index of risks and benefits included these primary outcomes plus stroke, pulmonary embolism, colorectal cancer, hip fracture, and death.

Results:

The postintervention risk (annualized rate) for CHD among women assigned to CEE was 0.64% compared with 0.67% in the placebo group (hazard ratio [HR], 0.97; 95% confidence interval [CI], 0.75-1.25), 0.26% vs 0.34%, respectively, for breast cancer (HR, 0.75; 95% CI, 0.51-1.09), and 1.47% vs 1.48%, respectively, for total mortality (HR, 1.00; 95% CI, 0.84-1.18). The risk of stroke was no longer elevated during the postintervention follow-up period and was 0.36% among women receiving CEE compared with 0.41% in the placebo group (HR, 0.89; 95% CI, 0.64-1.24), the risk of deep vein thrombosis was lower at 0.17% vs 0.27%, respectively (HR, 0.63; 95% CI, 0.41-0.98), and the risk of hip fracture did not differ significantly and was 0.36% vs 0.28%, respectively (HR, 1.27; 95% CI, 0.88-1.82). Over the entire follow-up, lower breast cancer incidence in the CEE group persisted and was 0.27% compared with 0.35% in the placebo group (HR, 0.77; 95% CI, 0.62-0.95). Health outcomes were more favorable for younger compared with older women for CHD ($P = .05$ for interaction), total myocardial infarction ($P = .007$ for interaction), colorectal cancer ($P = .04$ for interaction), total mortality ($P = .04$ for interaction), and global index of chronic diseases ($P = .009$ for interaction).

Conclusions:

Among postmenopausal women with prior hysterectomy followed up for 10.7 years, CEE use for a median of 5.9 years was not associated with an increased or decreased risk of CHD, deep vein thrombosis, stroke, hip fracture, colorectal cancer, or total mortality. A decreased risk of breast cancer persisted. Ⓐ

Evidence-Based Reference

LaCroix AZ: for the WHI Investigators: Health outcomes after stopping conjugated equine estrogens among postmenopausal women with prior hysterectomy: a randomized controlled trial, *JAMA* 305:1305–1314, 2011. Ⓐ.

SUGGESTED READINGS

Col NF et al.: Menopause. In the clinic, *Ann Intern Med* 150(7), April 7, 2009. ITC4-1-15.

Freeman EW et al.: Duration of menopausal hot flushes and associated risk factors, *Obstet Gynecol* 117:1095, 2011.

Gambrell RD: The Women's Health Initiative Reports: critical review of the findings, the female patient, *Menopause* 29(11):23, 2004.

Hill DA, Hill SR: Counseling patients about hormone therapy and alternatives for menopausal symptoms, *Am Fam Physician* 82(7):801–807, 2010.

Lacey JV et al.: Menopausal hormone replacement therapy and risk of ovarian cancer, *JAMA* 288:334, 2002.

NIH State of Sciences Panel: NIH State of Sciences Conference Statement: management of menopause related symptoms, *Ann Intern Med* 142:1003, 2005.

Randal A: AACE releases guidelines for menopausal hormone therapy, *Am Fam Physician* 86:864, 2012.

Speroff L: Efficacy and tolerability of a novel estradiol vaginal ring for relief of menopausal symptoms, *Obstet Gynecol* 102(4):823, 2003.

Writing Group for the Women's Health Initiative Investigators: Risks and benefits of estrogen plus progestin in healthy postmenopausal women, *JAMA* 288:321, 2002.

BASIC INFORMATION

DEFINITION

Menorrhagia is menstrual blood loss greater than 80 ml.

Metrorrhagia is bleeding between menses.

Polymenorrhea is bleeding that occurs more often than every 21 days.

Oligomenorrhea is bleeding less than every 35 days.

The new FIGO classification of abnormal uterine bleeding further defines abnormal bleeding by etiology. The acronym PALM-COEIN (polyp, adenomyosis, leiomyoma, malignancy or hyperplasia, coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, or not yet classified) is now used to define abnormal uterine bleeding.

SYNONYMS

Abnormal uterine bleeding
Menometrorrhagia
Dysfunctional uterine bleeding

ICD-9CM CODES
626.2 Menorrhagia
ICD-10CM CODES
N92.0 Excessive and frequent menstruation with regular cycle
N92.1 Excessive and frequent menstruation with irregular cycle
N92.4 Excessive bleeding in the premenopausal period
N92.2 Excessive menstruation at puberty
N92.6 Irregular menstruation, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 30% of women in their lifetime; 5% of medical visits for women
PREDOMINANT SEX AND AGE: Female; peak in adolescence and perimenopausal periods
GENETICS: Von Willebrand disease; hereditary platelet dysfunction disorders; 20% of women at any age have underlying bleeding disorder
RISK FACTORS: genetic predisposition, anticoagulation treatment, obesity

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- History: age, age of menarche or menopause, menstrual bleeding patterns, severity of bleeding, pain, underlying medical conditions, surgical history, use of medications, signs and symptoms of hemostatic disorder including history of heavy bleeding since menarche, postpartum hemorrhage, surgery-related bleeding, bleeding from dental work, easy bruising, epistaxis, and frequent gum bleeding, family history of bleeding disorder
- Physical exam: general findings including excessive weight, signs of polycystic ovarian syndrome (PCOS) (hirsutism and acne), signs of thyroid disease (nodule), signs of insulin resistance (acanthosis nigricans), signs of bleeding disorder including petechiae, ecchymoses, pallor, swollen joints, pelvic examination including external, speculum, and bimanual exam

ETIOLOGY

- Pregnancy/miscarriage
- Endometrial polyps
- Adenomyosis
- Uterine leiomyoma
- Endometrial hyperplasia or carcinoma
- Coagulopathy, inherited or acquired
- Ovulatory dysfunction, most likely PCOS
- Endometrial
- Iatrogenic

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Pregnancy, STD, PCOS, thyroid dysfunction, anovulation due to immature hypothalamic-pituitary-ovarian axis, perimenopausal transition, uterine pathology including endometrial hyperplasia or carcinoma, leiomyoma, adenomyosis, or endometrial polyp, von Willebrand's disease, platelet dysfunction disorder, iatrogenic due to medications including oral contraceptives or anticoagulants (warfarin)

WORKUP

- History
- Physical exam to evaluate for uterine pathology
- Laboratory, pathology, and imaging studies to determine etiology

LABORATORY TESTS

- Pregnancy test
- CBC with platelets to assess for anemia or platelet dysfunction
- TSH to assess for hypothyroidism or hyperthyroidism
- Chlamydia trachomatis testing if high risk for evaluation of pelvic infection
- Evaluation for cyclic menses
- Prothrombin time and partial thromboplastin time
- Testing for von Willebrand disease if clinically suspected (von Willebrand–ristocetin cofactor activity, von Willebrand factor antigen, and factor VIII)
- Endometrial sampling by endometrial biopsy or hysteroscopic sampling for women >45 yr or <45 yr with history of unopposed estrogen (PCOS, obesity), failed medical management, or persistent abnormal bleeding

IMAGING STUDIES

- Transvaginal ultrasound if abnormal exam or persistent symptoms
- Sonohysterography or hysteroscopy if ultrasound not adequate or suspicion for endometrial polyp or submucosal leiomyoma
- Transabdominal ultrasound in adolescents may be considered
- MRI not indicated initially

TREATMENT

NONPHARMACOLOGIC THERAPY

- Dilation and curettage
- Uterine artery embolization
- Hysteroscopic resection of uterine pathology including endometrial polyps and submucosal leiomyoma
- Endometrial ablation
- Hysterectomy

ACUTE GENERAL Rx

- Progestin
- Oral contraceptive pills
- Conjugated estrogens
- Surgical management if indicated including dilation and curettage, uterine artery embolization, or hysterectomy
- Hospitalization to maintain hemostasis and administer blood transfusion if severe menorrhagia

CHRONIC Rx

- Oral contraceptive pills. Can be used cyclically or continuously.
- Levonorgestrel intrauterine device: high degree of efficacy
- Gonadotropin-releasing hormone agonist (goserelin)
- Nonsteroidal anti-inflammatory drugs
- Tranexamic acid, aminocaproic acid
- Danazol (significant side-effect profile requires justification for use; this is rare)
- Surgery for anatomic causes including resection of leiomyoma and hysterectomy
- Endometrial ablation if completed childbearing

REFERRAL

- If concern for uterine pathology as etiology for menorrhagia, referral to a gynecologist for surgical management indicated
- If endometrial sampling reveals endometrial hyperplasia or malignancy, referral to a gynecologist is indicated. Cyclic progestogen therapy is necessary with resampling. If endometrial hyperplasia associated with complex glands or atypia, consultation with gynecologic oncologist is important because of high degree of progression to malignancy.

PEARLS & CONSIDERATIONS

PREVENTION

Weight reduction
Intervention in women with chronic oligo-ovulation due to chronic exposure to unopposed estrogen.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Dysfunctional Uterine Bleeding (Related Topic)

AUTHOR: **ERIN MEDLIN, M.D.**

EVIDENCE

Abstract[1]

Background:

This study compared the efficacy of the levonorgestrel-releasing intrauterine system (LNG-IUS) to low-dose combined oral contraceptive pills (COC) in the management of idiopathic menorrhagia.

Study Design:

A single-center, open, randomized clinical trial. One hundred twelve women complaining of excessive menstruation who desired contraception were randomized to receive LNG-IUS or COC. Treatment failure was defined as the need for medical or surgical treatment during the follow-up. Other outcomes included: menstrual blood loss (MBL) by alkaline hematin and by pictorial blood assessment chart (PBLAC), hemoglobin levels and assessment of lost days in which physical or mental health prevented participating women from performing usual activities.

Results:

At baseline, LNG-IUS ($n = 56$) and COC ($n = 56$) groups were comparable in age (mean ± S.D.) (39.3±6.7 vs. 38.7 ± 5.2 years, $P = .637$), parity (median and range) [3(1-6.4) vs. 3 (2-6), $P = .802$] and BMI (mean ± S.D.) (29.6 ± 5.9 vs. 31.1 ± 5.7 kg/m^2, $P = .175$). Time to treatment failure was longer in LNG compared to COC group with a total of 6 (11%) patients who had treatment failure in the LNG-IUS compared to 18 (32%) in COC group with a hazard ratio of 0.30 (95% CI, 0.15-0.73, $P = .007$). Using alkaline hematin, the reduction in MBL (mean ± S.D.) was significantly more in the LNG-IUS group (87.4 ± 11.3%) compared to the COC group (34.9±76.9%) ($P = .013$). Utilizing PBLAC scores, the reduction in the LNG-IUS (86.6 ± 17.0%) group was significantly more compared to the COC group (2.5 ± 93.2%) ($P < .001$). In the LNG-IUS group, increase in the hemoglobin and ferritin levels (mean ± S.D.) were noted (from 10.2 ± 1.3 to 11.4 ± 1.0 g/dL; $P < .001$; with reduction of the number of lost days (from 6.8 ± 2.6 to 1.6 ± 2.4 days, $P = .003$).

Conclusion:

The LNG-IUS is a more effective therapy for idiopathic menorrhagia compared to COC. Ⓐ

Evidence-Based Reference

Shabaan MM et al.: Levonorgestrel-releasing intrauterine system compared to low dose combined oral contraceptive pills for idiopathic menorrhagia: a randomized clinical trial, *Contraception* 83:48–54, 2011. Ⓐ

SUGGESTED READINGS

Albers JR et al.: Abnormal uterine bleeding, *Am Fam Physician* 69:1915–1926, 2004.

American College of Obstetricians and Gynecologists: Management of anovulatory bleeding, *Practice Bulletin* 14, March 2000.

American College of Obstetricians and Gynecologists: Diagnosis of abnormal uterine bleeding in reproductive-aged women, *Practice Bulletin* 128, July 2012.

Meralgia Paresthetica

BASIC INFORMATION

DEFINITION

Meralgia paresthetica is the term used to describe the condition of pain and/or dysesthesia in the anterolateral thigh due to compression of the lateral femoral cutaneous nerve.

SYNONYMS

Lateral femoral cutaneous nerve entrapment
Bernhardt-Roth syndrome
Skinny pants syndrome—named due to a rise in teenagers wearing skin-tight pants

ICD-9CM CODES
355.1 Meralgia paresthetica
ICD-10CM CODES
G57.1 Meralgia paresthetica

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The incidence rate for males and females is similar.
PEAK INCIDENCE: The mean age at diagnosis is 50 years old.
RISK FACTORS: Obesity, diabetes mellitus and older age are the most commonly associated conditions. Other risk factors include large abdomens, tight belts, tight garments around the waist, pregnancy, and scar tissue near the inguinal ligament**.** Injury during surgery in the region is also an important cause of meralgia paresthetica. Motor vehicle accidents with seat belt injury are a less common but recognized cause. Long periods of leg exercise that increases tension on the inguinal ligament, such as from long distance biking or walking for an extensive period of time, may also cause pressure on the nerve. Alternatively, weight loss or aging may remove protective overlying fat layers so the nerve can squeeze against underwear, belts, or other clothing.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The patient can have numbness and tingling, burning pain, or decreased sensation over the region of the outer upper thigh, which usually presents in a gradual fashion. Sometimes the patient will rub the affected area when discussing the discomfort. There is no motor involvement, as the lateral femoral cutaneous nerve only has sensory fibers. Change in patient position does not always abate the pain, but occasionally it can. Pain spreading across the buttocks or aching in the groin area can sometimes be present. Pain may radiate into the rib cage, groin, thigh, and knee. Often the affected region is more sensitive to light touch than to firm pressure. Hypersensitivity to heat can be present. The patient may mention that warm water from bathing feels like it is burning the affected area.

ETIOLOGY

Meralgia paresthetica mainly results from entrapment of the lateral femoral cutaneous nerve as it passes under the inguinal ligament (Fig. M1-19). However, it can also be compressed within the lumbosacral plexus, abdominal cavity, or in the subcutaneous tissue of the thigh.

DIAGNOSIS

The diagnosis is based mainly on the unique description of pain and the typical location; the sensory abnormalities present on exam in the affected area without neurological abnormalities on the lower half of the affected leg.

DIFFERENTIAL DIAGNOSIS

Lumbar radiculopathy

WORKUP

Most of the time, the diagnosis requires no further testing other than a neurological exam. The lower thigh should also be examined to ensure that it has no neurological abnormalities. Light touch and pinprick examination are usually abnormal in an oval-shaped area on the anterolateral thigh. There should be no abnormality in the straight leg test, or presence of hip, back, or sacroiliac joint involvement. Motor strength distally and deep tendon reflexes should be normal. On occasion, precise diagnosis may require an abdominal and/or pelvic examination to exclude problems in those areas.

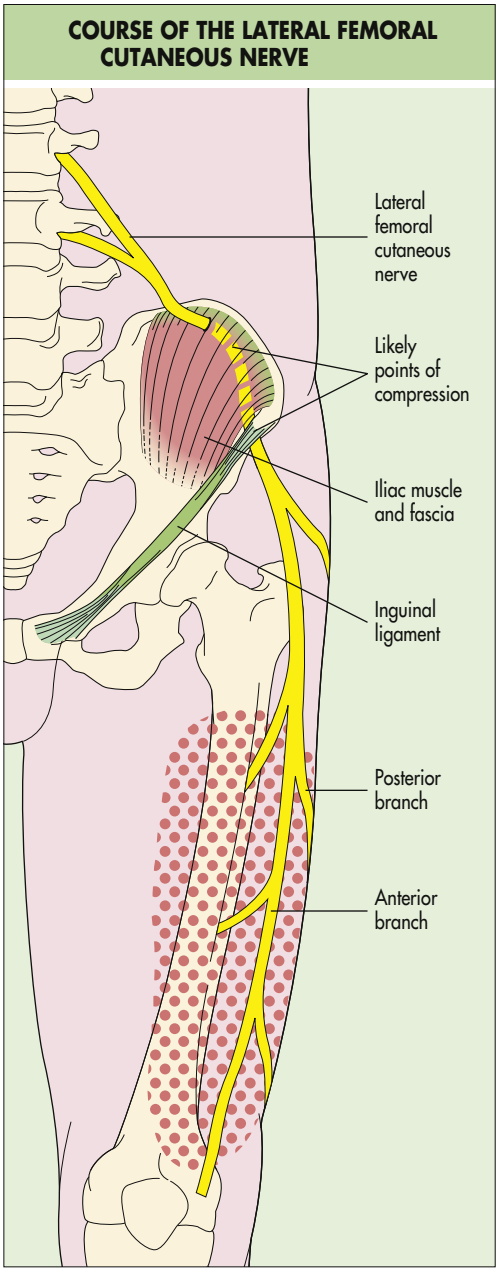

FIGURE M1-19 Course of the lateral femoral cutaneous nerve. The potential for entrapment of the lateral femoral cutaneous nerve can be seen by its course just under the inguinal ligament and medial to the anterior superior iliac spine. (From Hochberg M.C., et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.)

IMAGING/OTHER STUDIES

- X-rays of the hip/pelvis are unnecessary and unrevealing in patients with typical findings of meralgia paresthetica. Lumbar spine imaging can be considered if the patient has unclear symptoms or exam to exclude lumbar spinal stenosis, disk issues, or spondylolisthesis. More advanced imaging, such as CT or MRI scans, can be done to exclude soft tissue causes such as a tumor.
- Nerve conduction and electromyography are rarely necessary. These studies are mainly utilized to exclude radiculopathy or lumbar plexus problems.
- Rarely, an anesthetic nerve block injection, with or without ultrasound guidance, into the lateral femoral cutaneous nerve can be performed. Relief of the pain is confirmatory of the diagnosis of meralgia paresthetica.

Rx TREATMENT

NONPHARMACOLOGICAL THERAPY

Many patients experience sudden discontinuation of their symptoms. Reassurance of the patent regarding the benign nature of the condition is key. Also important is to recommended methods to decrease pressure or compression of the nerve, usually in the groin region.

ACUTE GENERAL THERAPY

- Reassurance of the patient is vital concerning the nonthreatening nature of the condition.
- Methods to reduce compression or pressure on the nerve include avoiding wearing tight garments, undergarments, or belts around the waist. Wearing suspenders rather than belts can be suggested. Weight loss in obese patients, especially in the abdominal region, is also important.

CHRONIC THERAPY

- Persistent symptoms after one to two months despite conservative approach may warrant verification of diagnosis through reexamination of affected area, repeat questioning, and possibly other studies.
- Gabapentin, amitryptiline, phenytoin, and carbamazepine may prove beneficial in reducing the associated neuropathic pain. However, in the majority of patients they are not beneficial.
- Lidocaine patches (must shave affected area first) and titanium dioxide patches can be utilized as additional modes of treatment for more refractory cases.
- Seek appropriate physical therapy, such as stretching and massage, which plays a large role in the management of pain.
- Consultation with an anesthesia specialist specifically for local nerve blockade can be done. Glucocorticoid or local anesthetic, or a mixture of both, can be injected into the appropriate region for temporary relief.
- Surgical opinion can also be obtained for performing surgical nerve decompression or sectioning.
- A few reports have mentioned the utility of radiofrequency nerve ablation in treating the condition, but this has not been studied adequately.

DISPOSITION

This is a self-limited, nonthreatening condition in most patients. Conservative measures are enough for > 90% of patients, but recurrence of symptoms is common.

REFERRAL

- Patients with meralgia paresthetica can often be adequately managed by the primary care physician.
- Referral to anesthesiologist or neurosurgeon may be indicated in refractory cases.

SUGGESTED READINGS

Available at www.expertconsult.com

Author: **SHEFALI MAJMUDAR, D.O.**

SUGGESTED READINGS

Harney D, Patijn J: Meralgia paresthetica: diagnosis and management strategies, *Pain Med* 8(8):669–677, 2007.

Khalil N et al.: Treatment for meralgia paresthetica, *Cochrane Database Syst Rev* 12:CD004159, 2012.

Parisi TJ et al.: Meralgia paresthetica: relation to obesity, advanced age, and diabetes mellitus, *Neurology* 77(16):1538–1542, 2011.

BASIC INFORMATION

DEFINITION

Acute mesenteric lymphadenitis is a syndrome of acute right lower quadrant abdominal pain associated with mesenteric lymph node enlargement and a normal appendix.

ICD-9CM CODES
289.2 Mesenteric adenitis
ICD-10CM CODES
I88.0 Nonspecific mesenteric lymphadenitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence unknown
- Affects mostly children (<18 yr) with no sex preference
- When *Yersinia* enterocolitis is the cause, boys are more frequently involved

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Abdominal pain of variable severity (mild ache to severe colic) beginning in upper abdomen or right lower quadrant; eventually localizes in the right side but not in a precise location (unlike appendicitis)
- In *Yersinia* infection outbreaks (see Table EM1-8), symptoms include abdominal pain (84%), diarrhea (78%), fever (43%), anorexia (22%), nausea (13%), and vomiting (8%)
- Physical findings:
  1. Other lymphadenopathy (20% of cases)
  2. Right lower quadrant tenderness (site of maximal tenderness may vary from one examination to the next)
  3. Guarding (rare)
  4. Mild fever

ETIOLOGY & PATHOGENESIS

- Reactive hyperplasia of lymph nodes that drain the ileocecal region, similar to that seen in inflammatory or allergic conditions. One study reported that approximately two thirds of cases are secondary (reactive) and one third are primary (no demonstrable associated inflammatory process).
- *Yersinia enterocolitica, Y. pseudotuberculosis, Salmonella* species, *Escherichia coli,* and streptococci have been implicated in mesenteric adenitis. Clinical manifestations of yersiniosis are described in Table EM1-9.

DIAGNOSIS

In general, the diagnosis is made on exploration of the abdomen of a patient suspected of having acute appendicitis. On examination the appendix appears normal, and enlarged mesenteric lymph nodes are noted. Excision of an enlarged lymph node with culture and nodal histology may provide information regarding the etiology but is not routinely used.

DIFFERENTIAL DIAGNOSIS

- Acute appendicitis (5% to 10% of patients admitted to hospitals with a diagnosis of appendicitis are discharged with a diagnosis of mesenteric adenitis)
- Crohn's disease

Section II describes the differential diagnosis of right lower quadrant abdominal pain.

LABORATORY TESTS

- Complete blood count may show leukocytosis
- Abdominal sonography and CT scan with IV and oral contrast (Fig. M1-20) may be useful
- Laparotomy if appendicitis is suspected

PROGNOSIS

Recurrent bouts are common; therefore if laparotomy is performed and a normal appendix is found, it should be removed.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **FRED F. FERRI, M.D.**

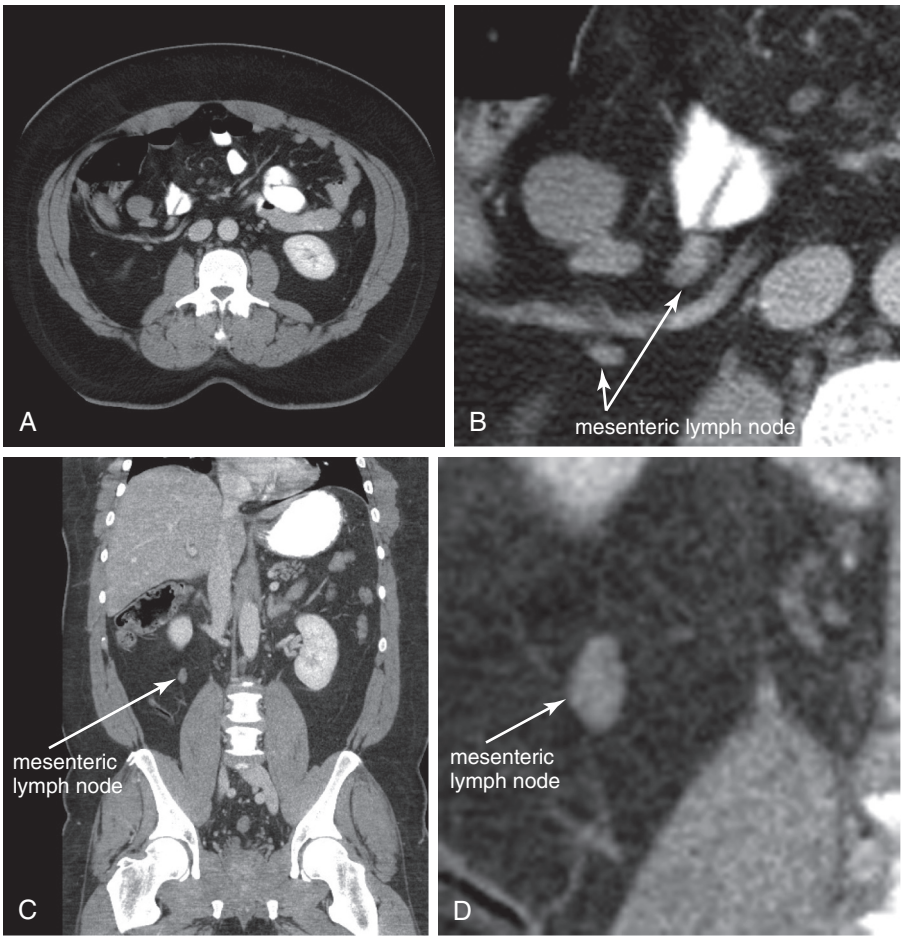

FIGURE M1-20 Mesenteric adenitis, CT with IV and oral contrast, soft-tissue window. Mesenteric adenitis can mimic appendicitis in its clinical presentation. Enlarged lymph nodes are visible on CT. Lymph nodes have soft-tissue density and appear as discrete, rounded structures. On a single image they may appear similar to blood vessels or to the appendix, but on inspection of adjacent images it becomes clear that lymph nodes are rounded, not tubular like a blood vessel or the appendix. **A,** Axial image. **B,** Close-up from **A. C,** Coronal reconstruction. **D,** Close-up from **C.** (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

SUGGESTED READING

Macari M et al.: Mesenteric adenitis: CT diagnosis of primary versus secondary causes, incidence, and clinical significance on pediatric and adult patients, *Am J Roentgenol* 178:853, 2002.

TABLE EM1-8 Symptoms in Four Outbreaks of Mesenteric Adenitis Caused by *Yersinia* Enterocolitis

Location	Japan (110)	Japan (111)	Japan (111)	United States (112)
Serotype	03	03	03	08
Number ill	198	188	544	38
Percentage with				
Abdominal pain	76	86	64	97
Fever	61	76	50	100
Diarrhea	36	60	32	74
Vomiting	12	4	11	—
Percentage undergoing appendectomy	2	—	—	42

From Mandell GL et al: *Principles and practice of infectious diseases,* ed 7, Philadelphia, 2010, Saunders.

TABLE EM1-9 Clinical Manifestations of Yersiniosis

Yersinia enterocolitica	*Yersinia pseudotuberculosis*
Gastroenteritis	Mesenteric lymphadenitis
Mesenteric lymphadenitis	Ulcerative ileitis
Ulcerative ileitis	Septicemia
Septicemia	Erythema nodosum
Hepatic or splenic abscesses	
Reactive polyarthritis (HLA-B27)	
Reiter's syndrome	
Erythema nodosum	
Meningitis	
Exudative pharyngitis	

From Cohen J, Powderly WG: *Infectious diseases,* ed 2, St Louis, 2004, Mosby.

Mesenteric Ischemia, Acute

BASIC INFORMATION

DEFINITION

Acute mesenteric ischemia (AMI) is the sudden onset of intestinal hypoperfusion to all or part of the small bowel caused by emboli, arterial or venous thrombosis (Fig. EM1-21), or vasoconstriction from low-flow states.

ICD-9CM CODES
ICD-557.1 Mesenteric vascular insufficiency
ICD-10CM CODES
K55.0 Acute vascular disorders of intestine

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- AMI accounts for 0.1% of hospital admissions.
- The incidence appears to be increasing, likely due to increased awareness among clinicians and aging of the population. Improved intensive care, and longer survival of sicker patients also contributes to the increasing incidence. The mortality rate is 60% to 85%.

PREDOMINANT SEX AND AGE:

- AMI caused by arterial embolism or thrombosis occurs more frequently in the elderly.
- AMI from mesenteric venous thrombosis often presents in younger age groups.

GENETICS: No specific genetic predisposition but may be related to underlying factors such as cardiac disease, atherosclerosis, and hypercoagulable states.

RISK FACTORS

- Advanced age, atherosclerosis, low cardiac output (especially atrial fibrillation), severe cardiac valvular disease, intraabdominal malignancy.
- In the subgroup of cases caused by venous thrombosis, risk factors include hypercoagulable states, portal hypertension, abdominal infection, blunt trauma, pancreatitis, and portal malignancy.
- Additional risk factors for AMI caused by nonocclusive mesenteric ischemia include recent cardiac surgery, dialysis, and cocaine use.
- Table M1-10 summarizes risk factors for ischemic bowel disease.
- AMI may occur rarely in patients with no identifiable risk factors.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The classic presentation is rapid onset of severe periumbilical pain out of proportion to physical examination findings.
- Nausea and vomiting are commonly associated.
- Initial abdominal examination may be normal, with no rebound or guarding, or may include minimal distention or stool positive for occult blood.
- Later in the course the patient may present with gross distention, absence of bowel sounds, and peritoneal signs. In the elderly, mental status changes may occur.

ETIOLOGY

The pathophysiologic mechanisms that cause AMI include:

- Mesenteric arterial embolism: typically from the left atrium, left ventricle, or cardiac valves. The superior mesenteric artery is most commonly affected.
- Mesenteric arterial thrombosis: often in patients with prior progressive atherosclerotic stenoses, with superimposed abdominal trauma or infection.
- Mesenteric venous thrombosis may occur in the setting of hypercoagulable states (acquired or inherited), blunt trauma, abdominal infection, portal hypertension, pancreatitis, and portal malignancy.
- Nonocclusive mesenteric ischemia is caused by reduced intestinal perfusion, such as may be seen in a patient with an acute cardiovascular disease process being treated with drugs that reduce intestinal perfusion, or with use of ergot, cocaine, or amphetamines.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Initially include other causes of abdominal pain of acute onset, including perforated peptic ulcer and early appendicitis. Ultimately, the varied causes of peritonitis.

TABLE M1-10 Risk Factors for Ischemic Bowel Diseases*

Risk Factor	Arterial Thrombosis	Embolus	Mesenteric Vein Thrombosis	Nonobstructive Mesenteric Ischemia
Advanced age	+	+	+	+
Atherosclerosis	+			
Aortic dissection	+			
Low cardiac output	+	+		+
Congestive heart failure				+
Shock				+
Severe dehydration	+		+	
Cardiac arrhythmias, especially atrial fibrillation		+		+
Severe cardiac valvular disease		+		
Recent myocardial infarction	+			+
Intraabdominal malignancy			+	
Abdominal trauma			+	
Intraabdominal infection			+	
Intraabdominal inflammatory conditions			+	
Parasitic infection (ascariasis)			+	
Hypercoagulable states (venous thrombosis)			+	
Sickle cell anemia			+	
Recent cardiac surgery	+	+		+
Recent abdominal surgery			+	
Vascular aortic prosthetic grafts proximal to the superior mesenteric artery		+		
Hemodialysis				+
Vasculitis	+		+	
Pregnancy			+	
Decompression sickness			+	
Blast lung caused by systemic air embolism		+		
Drugs that cause constriction				
• Digitalis				+
• Cocaine				+
• Amphetamines				+
• Pseudoephedrine				+
• Vasopressin			+†	+
• Estrogen therapy			+	

*A plus sign (+) indicates that the factor is a risk for the disease subtype.
†Especially after sclerotherapy.
From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

WORKUP

- Early diagnosis is key. Treatment success is related to the duration of symptoms prior to diagnosis.
- Consider early laparotomy for diagnosis in cases with a high index of suspicion when imaging is not readily available.

LABORATORY TESTS

- Laboratory test results are nonspecific, especially early in the course. Elevated lactic acid, leukocytosis, acidosis, and elevated hematocrit from hemoconcentration can occur later in the course, often after progression to bowel necrosis has occurred, hence are not useful for early diagnosis.
- When a hypercoagulable state is suspected, workup may include proteins C and S, antithrombin III, and factor V Leiden. This will likely not affect the diagnosis of AMI but may help guide long-term therapy.
- D-dimer testing has been reported to be useful for the early diagnosis of AMI but is very nonspecific.

IMAGING STUDIES

- Biphasic contrast-enhanced CT is the preferred diagnostic mode (Fig. M1-22). It is more easily available and has similar sensitivity to angiography, the prior gold standard test.
- Plain films are normal 25% of the time in the early stages. Suggestive findings may include ileus, bowel wall thickening, or intramural gas.
- Oral contrast should not be used for plain films or CT evaluation, as it will obscure vessels and bowel wall enhancement.

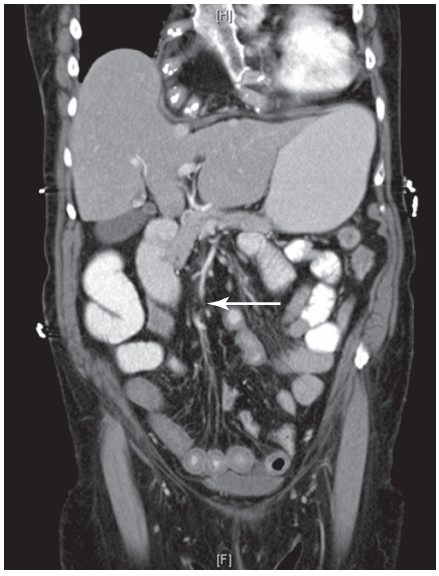

FIGURE M1-22 Mesenteric ischemia, acute. CT after administration of oral and intravenous contrast in patient with embolism to superior mesenteric artery and ischemia of small bowel and right colon. *Arrow* points to embolus in superior mesenteric artery. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

- Doppler ultrasound evaluation of intestinal blood flow is often limited by the presence of air-filled loops of bowel and is not an appropriate part of the diagnostic workup if AMI is the leading working diagnosis.
- Plain CT findings also are commonly nonspecific and more often found late in the course. Portal venous gas or intramural gas may be seen after the development of gangrene; in many cases, even at that advanced stage CT findings remain nonspecific.
- MR angiography may be more useful in cases of mesenteric vein thrombosis causing AMI. It has also been found useful in monitoring the progress of patients with superior mesenteric venous thrombosis who are treated nonsurgically.
- Angiography may be considered if the diagnosis remains unclear after CT or MR imaging.

Rx TREATMENT

- The goal of treatment is to restore blood flow as rapidly as possible to ischemic bowel before the occurrence of infarction.
- Treatment varies depending on etiology.

ACUTE GENERAL Rx

- Initial management should include hemodynamic monitoring and support, correction of acidosis, administration of broad-spectrum antibiotics, and gastric decompression by nasogastric tube.
- Vasoconstricting agents should be avoided.
- Use of systemic anticoagulation is usually indicated in the absence of active bleeding; however, optimal timing of initiation is unclear.

NONPHARMACOLOGIC THERAPY

- Signs of peritonitis mandate early laparotomy and resection of infarcted bowel.
- When workup is positive for major superior mesenteric artery (SMA) embolus, embolectomy is considered standard treatment in the absence of peritoneal signs. Depending on the location and degree of occlusion of the embolus, surgical revascularization, intraarterial infusion of thrombolytics or vasodilators, or systemic anticoagulation may be considered.
- In cases of SMA thrombosis, emergency surgical revascularization is the treatment of choice; stent placement may be a viable alternative.
- Angiography is needed to diagnose nonocclusive mesenteric ischemia before infarct and should be followed up by intraarterial vasodilator infusion. This approach has been shown to significantly reduce mortality rate in this situation.
- In patients with mesenteric vein thrombosis, treatment depends on the presence or absence of peritoneal signs. Laparotomy and resection of infarcted bowel is indicated in more advanced cases. If there are no peritoneal signs, immediate anticoagulant therapy with heparin, and ultimately warfarin, may be adequate treatment.
- In general, percutaneous treatment with lytic therapy, balloon angioplasty, or stenting may be limited by the frequent presence of nonviable bowel, which would require laparotomy despite success with the percutaneous treatment.

CHRONIC Rx

In the subgroup of patients with mesenteric venous thrombosis, prevention of further thrombosis is indicated. The optimal duration of anticoagulation is unclear.

DISPOSITION

- Prognosis is best in AMI due to mesenteric venous thrombosis and after surgical treatment for acute arterial embolism. It remains poor in cases of arterial thrombosis and nonocclusive ischemia.
- With delayed diagnosis, intestinal infarction—resulting in perforation or gangrenous bowel, sepsis, shock, and death—is typical.

REFERRAL

- Early surgical consultation should be considered. There should be no delay with peritoneal signs.
- Surgery may be warranted for diagnostic purposes.

PEARLS & CONSIDERATIONS

COMMENTS

- The diagnosis of AMI should be considered in any patient with acute onset of abdominal pain out of proportion to physical findings, particularly in at-risk patients.
- Early diagnosis, before intestinal infarction occurs, is critical and correlates with improved survival rates.
- In a recent case series, the primary location of the ischemic colitis was in the right, transverse, left, and distal colon in 25%, 10%, 33%, and 25% of cases, respectively; 7% were pancolonic.

PREVENTION

Prevention of the underlying factors, most notably atherosclerotic disease

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Mesenteric Venous Thrombosis (Related Key Topic)

AUTHOR: **MARGARET TRYFOROS, M.D.**

SUGGESTED READINGS

Akyildiz H et al.: The correlation of the D-dimer test and biphasic computed tomography angiography in the diagnosis of acute mesenteric ischemia, *Am J Surg* 197:429–433, 2009.

Berland T, Oldenberg WA: Acute mesenteric ischemia, *Curr Gastroenterol Rep* 10(3):341–346, 2008.

Brandt W et al.: Anatomic patterns, patient characteristics, and clinical outcomes in ischemic colitis: a study of 313 cases supported by histology, *Am J Gastroentrol* 105:2245, 2010.

Offer A et al.: Multidetector CT angiography in the evaluation of acute mesenteric ischemia, *Eur Radiol* 19(1):24–30, 2009.

Schoots IG et al.: Systematic review of survival after acute mesenteric ischaemia according to disease aetiology, *Br J Surg* 91(1):17–27, 2004.

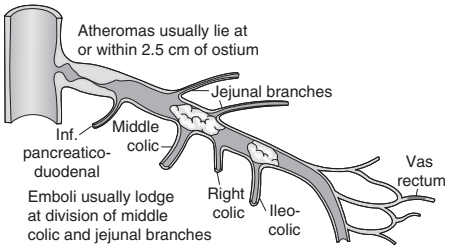

FIGURE EM1-21 Typical location of superior mesenteric artery obstruction in patients with embolic and thrombotic occlusion. (From Donaldson MC: Mesenteric vascular disease. In Braunwald S, Creager MA [eds]: *Atlas of heart diseases*, St Louis, 1996, Mosby.)

Mesenteric Venous Thrombosis

BASIC INFORMATION

DEFINITION

Mesenteric venous thrombosis (MVT) is a thrombotic occlusion of the mesenteric venous system involving major trunks or smaller branches and leading to intestinal infarction in its acute form.

ICD-9CM CODES
557.0 Mesenteric venous thrombosis
ICD-10CM CODES
K55.0 Acute vascular disorders of intestine
K55.1 Chronic vascular disorders of intestine

EPIDEMIOLOGY & DEMOGRAPHICS

Between 5% and 15% of patients with acute mesenteric infarction have MVT. MVT is slightly more common in men than women. The typical age of occurrence is 50 to 60 yr. Table M1-11 summarizes the incidence of ischemic bowel disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Acute MVT:
- Symptoms: abdominal pain in 90% of patients, typically out of proportion to the physical findings. Nausea and vomiting occur in 50% and gastrointestinal (GI) bleeding occurs in 50% (occult) and 15% (gross).
- Physical findings:
  1. Early: abdominal tenderness, decreased bowel sounds, abdominal distention
  2. Later: guarding and rebound tenderness, fever, septic shock
- Subacute MVT:
  - Symptoms: nonspecific abdominal pain for weeks or months
  - Physical findings: none
- Chronic MVT:
  - Symptoms: upper GI hemorrhage from bleeding varices
  - Physical findings: none other than signs of blood loss if significant

ETIOLOGY & PATHOGENESIS

Hypercoagulable states:
Peripheral deep venous thrombosis
Neoplasms
Antithrombin III, protein C, protein S deficiencies
Lupus anticoagulant (antiphospholipid antibody)
Oral contraceptive use, pregnancy
Polycythemia vera
Thrombocytosis
Paroxysmal nocturnal hemoglobinuria
Portal hypertension:
- Cirrhosis
- Inflammation:
- Pancreatitis
- Peritonitis (e.g., appendicitis, diverticulitis, perforated viscus)
- Inflammatory bowel disease
- Pelvic or intraabdominal abscess
- Intraabdominal cancer
- Postoperative state or trauma:
- Blunt abdominal trauma
- Postoperative states (abdominal surgery)

Thrombosis may begin in small mesenteric branches (e.g., in hypercoagulable states) and propagate to the major venous mesenteric trunks or begin in large veins (e.g., in cirrhosis, intraabdominal cancer, surgery) and extend distally. If collateral drainage is inadequate, the intestine becomes congested, edematous, cyanotic, and hemorrhagic and eventually may infarct.

TABLE M1-11 Incidence of Ischemic Bowel Diseases

Disease	Incidence (%)*
Superior mesenteric artery (SMA) embolism:	50
• The SMA is susceptible to embolism because of large vessel caliber and a narrow angle of departure from the aorta.	
• The proximal SMA is most commonly obstructed within 6-8 cm of the aorta	
Nonocclusive ischemia	25
SMA thrombosis	20
Mesenteric venous thrombosis	5

*Percentage of all cases of acute mesenteric ischemia.
From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

All other causes of abdominal pain (e.g., peritonitis, intestinal obstruction, pancreatitis, peptic ulcer disease, gastritis, inflammatory bowel disease, perforated viscus) are also to be considered in the differential diagnosis of GI hemorrhage.

WORKUP

Laboratory tests and imaging studies

LABORATORY TESTS

- Complete blood count: leukocytosis
- Electrolytes: metabolic acidosis (lactic) indicates bowel infarction
- Elevated amylase
- Tests for hypercoagulable status

IMAGING STUDIES

- Abdominal plain radiograph: ileus, ascites, bowel dilation, bowel wall thickening, loop separation, thumbprinting
- Abdominal CT scan (diagnostic in 90%): bowel wall thickening, venous dilation, venous thrombus
- Arteriography if CT scan is not diagnostic
- Diagnosis occasionally made by laparotomy

TREATMENT

- Anticoagulation or thrombolytic therapy
- Laparotomy if intestinal infarction is suspected
- Short ischemic segment: resection
- Long ischemic segment:
  1. Nonviable: resection or close
  2. Viable: intraarterial papaverine and/or thrombectomy followed by "second look" intervention
- Treatment of chronic MVT is the same as for portal hypertension

PROGNOSIS

- Mortality rate of acute MVT: 20% to 50%
- Recurrence rate: 15% to 25%

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Brandt LJ, Smithline AE. Ischemic lesions of the bowel. In: (editor: Feldman M, et al.) Gastrointestinal and liver disease. ed 6 Saunders: Philadelphia.

Kumar S et al.: Mesenteric venous thrombosis, *N Engl J Med* 345:1683, 2002.

BASIC INFORMATION

DEFINITION

Malignant mesothelioma is a neoplasm that originates from the mesothelial surfaces of the pleural cavities (80%) or peritoneal cavities (20%).There are three major histologic subtypes: epithelial (most common), sarcomatous, and mixed (epithelial/sarcomatous).

ICD-9CM CODES
199.1 Malignant mesothelioma, site NOS
ICD-10CM CODES
C45.0 Mesothelioma of pleura
C45.1 Mesothelioma of peritoneum
C45.2 Mesothelioma of pericardium
C45.7 Mesothelioma of other sites
C45.9 Mesothelioma, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Associated with asbestos exposure (all fiber types)
- More than 3000 new cases diagnosed in the United States annually
- More common in men as a result of asbestos exposure in the workplace
- Right-sided involvement is more common
- Incidence of mesothelioma increases with age; median age at presentation is >60 yr
- More than 8 million persons in the United States are currently at risk for mesothelioma because of prior asbestos exposure

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Dyspnea
- Nonpleuritic chest pain
- Fever, weight loss, sweats, fatigue, loss of appetite
- Dysphagia, superior vena cava syndrome, Horner's syndrome in advanced stages
- Auscultation may reveal unilateral loss of breath sounds
- Dullness on percussion may be present

ETIOLOGY

- Asbestos exposure (>70% of patients)
- Other reported potentially causal factors include prior radiation therapy and extravasated Thorotrast, zeolite, and erionite fibers

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Metastatic adenocarcinomas (from lung, breast, ovary, kidney, stomach, prostate)

WORKUP

- Staging evaluation (Fig. M1-23) includes complete history (including occupational history), physical examination, and testing to determine potential operability (CT, bone scan, pulmonary function tests [PFTs])
- Thoracoscopy, pleuroscopy, and open-lung biopsy are useful in obtaining adequate tissue samples for diagnosis
- Pulmonary function tests
- Staging: the International Union Against Cancer (UICC) staging uses the TNM categories to organize mesothelioma in stages I to IV in a manner similar to that used for non–small cell lung cancer

LABORATORY TESTS

- Diagnostic thoracentesis is generally insufficient for diagnosis because pleural effusions may only reveal atypical mesothelial cells.
- Immunohistochemistry is useful to distinguish adenocarcinoma from epithelial malignant mesothelioma (mesotheliomas are generally carcinoembryonic antigen negative and cytokeratin positive).
- Thrombocytosis and anemia may be found on initial laboratory evaluation.
- Fibulin-3 may be useful as a blood and effusion biomarker for pleural mesothelioma. Recent data reveal that plasma fibulin-3 levels can distinguish healthy persons with exposure to asbestos from patients with mesothelioma. In conjunction with effusion fibulin-3 levels, plasma fibulin-3 levels can further differentiate mesothelioma effusions from other malignant and benign effusions.
- Serum osteopontin levels (when available) can also be used to distinguish persons with exposure to asbestos who do not have cancer from those with exposure to asbestos who have pleural mesothelioma.

IMAGING STUDIES

- Chest radiographs may reveal pleural plaques (Figs. EM1-24 and M1-25) or calcifications in the diaphragm.
- CT scans of the chest and abdomen and bone scan are used to assess the extent of disease.

TREATMENT

GENERAL Rx

- Operable patient (epithelial type, no positive nodes, confined to pleura, adequate PFTs): the two surgical techniques for therapeutic intervention are decortication (pleurectomy) and extrapleural pneumonectomy. Postoperative chemotherapy with cisplatin, doxorubicin, and cyclophosphamide and subsequent external-beam radiation are used in some centers with limited success.
- Inoperable patient (disease too extensive, sarcomatous or mixed histology type, poor PFTs): supportive care with or without radiation therapy for symptoms or supportive care plus chemotherapy. Combined modality therapies (surgery, radiation therapy, chemotherapy, and biologics) have also been used to reduce both local and distant recurrences. The combination of pemetrexed (an antimetabolite that inhibits enzymes involved in folate metabolism) and cisplatin is used for chemotherapy of unresectable malignant pleural mesothelioma.
- Intrapleural instillation of cisplatin or biologics (e.g., interferons, interleukin-2) is generally limited to very early disease because it can only penetrate a very limited depth of the tumor and there is a propensity of the pleural space to become progressively obliterated with advancing disease.
- The role of radiation therapy in the treatment of mesotheliomas remains uncertain. It is

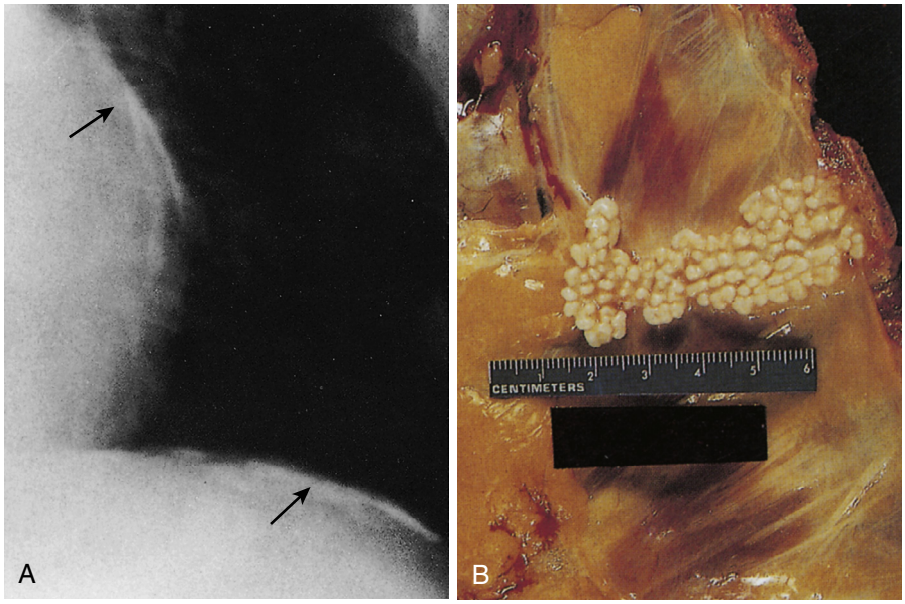

FIGURE M1-25 A, Chest radiograph showing the left lower lung of a 57-year old man demonstrates pericardial and pleural plaques (*arrows*) representing fibrous thickening. These features are common findings indicating pulmonary asbestosis. **B,** Autopsy features of calcified pleural plaques are quite striking. This specimen from a patient with mesothelioma shows focal calcifications on the lateral pleural surface. (Courtesy of Pathology Department, Brigham and Women's Hospital, Boston, MA. From Skarin AT: *Atlas of diagnostic oncology*, 4th ed, St Louis, 2010, Mosby.)

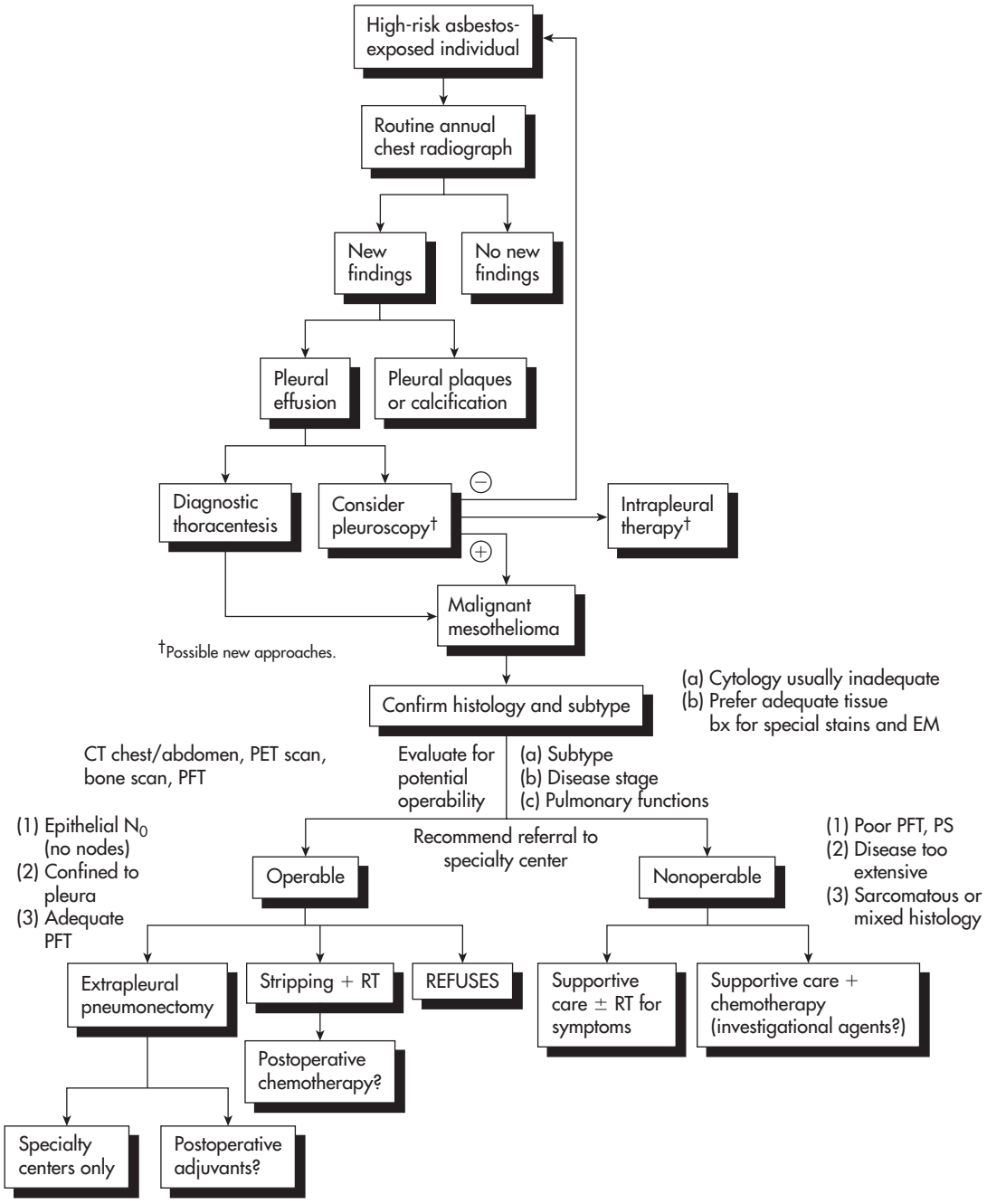

FIGURE M1-23 Evaluation and treatment of mesothelioma. *bx,* Biopsy; *CT,* computed tomography; *EM,* electron microscopy; *PET,* positron emission tomography; *PFT,* pulmonary function test; *PS,* pleural sclerosis; *RT,* respiratory therapy. (From Abeloff MD: *Clinical oncology,* ed 3, New York, 2004, Churchill Livingstone.)

often used for palliation of local pain despite lack of trials to prove its utility.

- Obliteration of the pleural space (pleurodesis) with instillation of tetracycline, bleomycin, or biologic substances such as *Cryptosporidium parvum* into the pleural cavity is often attempted in the treatment of recurrent symptomatic pleural effusions.

DISPOSITION

Median survival is from 6.7 to 21 mo for patients undergoing pleurectomy and ranges from 4 to 21 mo for extrapleural pneumonectomy. Survival is better for patients with the epithelial form.

PEARLS & CONSIDERATIONS

COMMENTS

Patients with early disease should be referred to treatment centers specializing in mesothelioma treatment before attempts are made to obliterate the pleural space with pleurodesis.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Mesothelioma (Patient Information)
Asbestosis (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Pass H et al.: Asbestos exposure, pleural mesothelioma, and serum osteopontin levels, *N Engl J Med* 353:1564, 2005.

Pass H et al.: Fibulin-3 as a blood and effusion biomarker for pleural mesothelioma, *N Engl J Med* 367:1417–1427, 2012.

Robinson B, Lake R: Advances in malignant mesothelioma, *N Engl J Med* 353:1591, 2005.

FIGURE EM1-24 Chest radiograph of patient with mesothelioma. Note several lobulated, pleural-based masses in right hemithorax accompanied by right pleural effusion. (From Weinberg SE et al: *Principles of pulmonary medicine,* ed 5, Philadelphia, 2008, Saunders.)

BASIC INFORMATION

DEFINITION

Hyperglycemia, dyslipidemia, abdominal obesity, and hypertension are critical components of metabolic syndrome. Over the years, many definitions of the syndrome have been proposed and debated (see Table M1-12). In 2009, a consensus statement from several organizations including the International Diabetes Federation (IDF) and American Heart Association defined "metabolic syndrome" as the presence of any three of the following criteria:

- Abdominal waist circumference >94 cm (37 in) in men and >80 cm (31 in) in women (the use of population- and country-specific definitions is suggested; however, until better data are available, IDF recommends using these cutoffs)
- Serum hypertriglyceridemia ≥150 mg/dl (1.7 mmol/L) or drug treatment for elevated triglycerides
- Serum high-density lipoprotein (HDL) cholesterol <40 mg/dl (1 mmol/L) in men and <50 mg/dl (1.3 mmol/L) in women or drug treatment for low HDL-C
- Blood pressure ≥130/85 mm Hg or drug treatment for elevated blood pressure
- Fasting glucose ≥100 mg/dl (5.6 mmol/L) or drug treatment for elevated blood glucose

SYNONYMS

Syndrome X
Insulin resistance syndrome
Obesity dyslipidemia syndrome

ICD-9CM CODES
277.7 Metabolic syndrome
ICD-10CM CODES
E88.81 Metabolic syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- Affects 22% of U.S. adults.
- Prevalence increases with age, affecting more than 40% of individuals >60 yr.

TABLE M1-12 Common Definitions for Metabolic Syndrome

Criterion	NCEP ATP III (3 or more criteria)
Abdominal obesity	Waist circumference
Men	>40 inches (>102 cm)
Women	>35 inches (>88 cm)
Hypertriglyceridemia	>150 mg/dl (≥1.7 mmol/l)
Low HDL	
Men	<40 mg/dl (<1.03 mmol/l)
Women	<50 mg/dl (<1.30 mmol/l)
Hypertension	≥130/85 mm Hg or on antihypertensive medication
Impaired fasting glucose or diabetes	>100 mg/dl (5.6 mmol/l) or taking insulin or hypoglycemic medication

From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

- Increasing prevalence among women, especially in the African American and Mexican American populations.
- Prevalence increases with weight. Metabolic syndrome is noted in 5% of normal weight, 22% of overweight, and 60% of obese individuals.
- Other risk factors include low socioeconomic status, lack of physical activity, high-carbohydrate diet, no alcohol intake, smoking, genetic predisposition, use of atypical antipsychotics, and postmenopausal status.

CLINICAL PRESENTATION

- Obesity, hypertension, dyslipidemia, and hyperglycemia as defined.
  1. Blood pressure: ≥130/85 mm Hg
  2. Abdominal obesity with waist circumference: >94 cm (37 in) in men and >80 cm (31 in) in women
  3. Triglycerides: ≥150 mg/dl (1.7 mmol/L)
  4. HDL: <40 mg/dl (1 mmol/L) in men and >50 mg/dl (1.3 mmol/L) in women
  5. High fasting glucose: ≥100 mg/dl (5.6 mmol/L)
- Patients with the metabolic syndrome are at twice the risk of developing cardiovascular disease and have a sevenfold increase in risk for type 2 diabetes and a 1.5-fold increase in all-cause mortality compared to patients without the syndrome. Other complications include cognitive decline in the elderly, fatty liver disease, polycystic ovary syndrome, obstructive sleep apnea, gout, and chronic kidney disease.
- Focus history on symptoms of diabetes and its complications, obesity and its complications, coronary artery disease (angina), and polycystic ovary syndrome.
- Complete physical examination, including height, weight, waist circumference, and blood pressure.

ETIOLOGY

- Genetic and environmental factors associated with obesity increase the risk of developing metabolic syndrome.
- Abdominal obesity is associated with insulin resistance and hyperinsulinemia.
- Insulin resistance results in ineffective glucose and fatty acid utilization leading to type 2 diabetes mellitus (Fig. M1-26).
- Hyperinsulinemia and inflammatory markers/cytokines play an important role in development of abnormal lipid profile, hypertension, and vascular endothelial dysfunction, which can lead to the development of atherosclerotic cardiovascular disease.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other causes of weight gain or obesity (Cushing's syndrome, hypothyroidism)
- Other causes of hyperlipidemia (familial hyperlipidemia, hypothyroidism)
- Other causes of hypertension (Cushing's syndrome, hyperaldosteronism)
- Other forms of diabetes (type 1)

LABORATORY TESTS

- Fasting lipid profile (total cholesterol, low-density lipoprotein [LDL] cholesterol, HDL cholesterol, and triglycerides)
- Fasting glucose

TREATMENT

NONPHARMACOLOGIC THERAPY

- Lifestyle modification:
  1. Dietary modifications aimed at weight loss
  2. Physical activity of moderate intensity (i.e., brisk walking): 30 min daily
  3. Smoking cessation
- Consider bariatric surgery in the management of obesity:
  1. Body mass index (BMI) ≥40 kg/m^2 in patients who have not responded to diet and exercise (with or without drug therapy).
  2. Individuals with BMI >35 kg/m^2 and comorbidities (hypertension, impaired glucose tolerance, diabetes mellitus, dyslipidemia, sleep apnea) are also potential surgical candidates.

ACUTE GENERAL Rx

- Treat obesity (see "Obesity"): Pharmacologic treatment: consider orlistat and other approved agents in patients who have not responded to diet and exercise if BMI >30 kg/m^2 or a BMI of 27 to 30 kg/m^2 with comorbid conditions. Drug therapy still needs to be in conjunction with diet and exercise.
- Treat hypertension (see "Hypertension"): Systolic blood pressures >130/80 mm Hg: consider angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker as first-line therapy.
- Treat hyperlipidemia: In the 2013 guidelines from the American College of Cardiology and American Heart Association (ACC/AHA), treatment goals for LDL-C and non-HDL-C are no longer recommended and there are no guidelines for treating high triglyceride levels. The new guidelines specify four groups that merit intensive or moderately intensive statin therapy[1]:
  1. People with clinical atherosclerotic cardiovascular disease (ASCVD)
  2. People with LDL-C levels of ≥190 mg/dL
  3. People with diabetes, age 40 to 75
  4. People without diabetes, age 40 to 75 with LDL-C levels 70-190 mg/dL, and a 10-year ASCVD risk of 7.5% or higher as determined by the new risk calculator.[2]
- Treat diabetes:
  1. Goal HgAIC <7.0%
  2. Metformin as first-line therapy to improve insulin sensitivity

[1]Raymond C et al: New cholesterol guidelines: worth the wait? *Clev Clin J Med* 81:11-19, 2014.
[2]American Heart Association: *2013 Prevention Guideline Tools. CV risk calculator.* Available at http://my.americanheart.org/professional/statementsguidelines/preventionguidelines/preventionguidelines_VCM_subhomepage.jsp

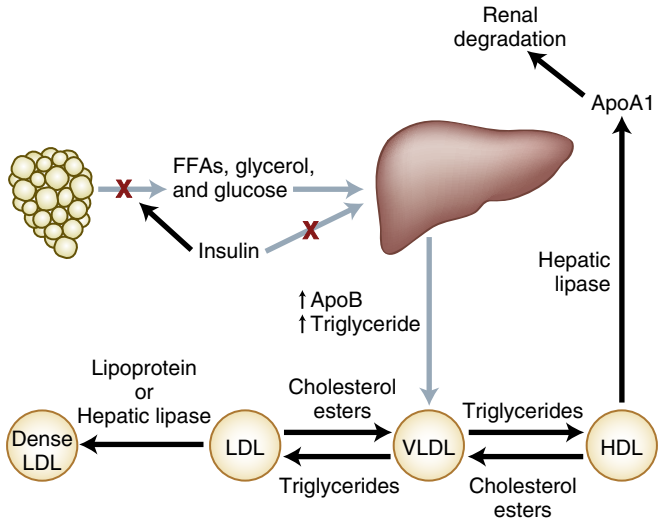

FIGURE M1-26 Insulin resistance and dyslipidemia The suppression of lipoprotein lipase and very-low-density lipoprotein (VLDL) production by insulin is defective in insulin resistance, leading to increased flux of free fatty acids (FFAs) to the liver and increased VLDL production, which results in increased circulating triglyceride concentrations. The triglycerides are transferred to low-density lipoprotein (LDL) and high-density lipoprotein (HDL), and the VLDL particles gain cholesterol esters by the action of the cholesterol ester transfer protein (CETP). This leads to increased catabolism of HDL particles by the liver and loss of apolipoprotein (Apo) A, resulting in low HDL concentrations. The triglyceride-rich LDL particle is stripped of its triglycerides, resulting in the accumulation of atherogenic small, dense LDL particles. (From Melmed S: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

- Treat cardiovascular risk factors:
  1. Consider aspirin. Aspirin should be started in patients with metabolic syndrome and an intermediate or elevated Framingham cardiovascular risk, if there are no contraindications.
  2. Risk can be lowered with weight loss, exercise, smoking cessation, blood pressure control, diabetes management, and treatment of hyperlipidemia.

CHRONIC Rx

- Encourage lifestyle modification as above.
- Pharmacologic and surgical management to maintain therapeutic goals described above.

DISPOSITION

Weight loss can prevent disease progression. Appropriate treatment of obesity, hypertension, hyperlipidemia, and diabetes can improve morbidity and mortality rates.

REFERRAL

- To nutritionist for dietary counseling
- To weight loss and exercise programs
- To endocrinologist if difficulty reaching therapeutic goals
- To bariatric surgeon if patient meets surgical criteria (as noted previously)

PEARLS & CONSIDERATIONS

PREVENTION

- Weight loss is essential for the prevention and treatment of metabolic syndrome.
- Recommend dietary modifications and moderate physical activity.
- Consider pharmacologic and surgical options in select individuals (as above).

PATIENT & FAMILY EDUCATION

- Weight reduction programs, including Weight Watchers, Curves, etc.
- American Diabetes Association: http://www.diabetes.org
- Polycystic Ovarian Syndrome Association: http://www.pcosupport.org
- The Hormone Foundation: http://www.hormone.org

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Obesity (Related Key Topic)
Metabolic Syndrome (Patient Information)

AUTHOR: **GEETHA GOPALAKRISHNAN, M.D.**

SUGGESTED READINGS

Gallagher EJ et al.: The metabolic syndrome. From Grundy SM: Pre-diabetes, metabolic syndrome, and cardiovascular risk, *J Am Coll Cardiol* 59(7): 635–643, 2012.

Leroith D: Pathophysiology of the metabolic syndrome: implications for the cardiometabolic risks associated with type 2 diabetes, *Am J Med Sci* 343(1):13–16, 2012.

BASIC INFORMATION

DEFINITION

The diagnosis of metatarsalgia includes multiple etiologies of pain involving the plantar aspect of the lesser metatarsal heads or metatarsophalangeal joints (Fig. EM1-27).

ICD-9CM CODES
726.7 Metatarsalgia
ICD-10CM CODES
M77.40 Metatarsalgia, unspecified foot

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pain beneath any or all of metatarsal heads 2, 3, 4, and 5
- Pain on metatarsophalangeal joint range of motion
- Often associated with hammertoe deformity and gastrocnemius/soleus equinus
- May include predislocation syndrome
- Common with bunion deformity
- Often obesity, recent weight gain, or increased/change in type of activity

ETIOLOGY

- Primary structural/functional factors, all yielding increased submetatarsal pressure:
  1. Structural: sagittal plane (cavus foot, ankle equinus, pseudoequinus, elongated lesser metatarsal[s] relative to the optimal metatarsal parabola) or frontal plane (relative fixed dorsiflexion or plantarflexion of adjacent metatarsals)
  2. Functional causes yielding transferred pressure (from hypermobile first or fifth rays) or friction (secondary to compensation for transverse plane deformities or lack of sufficient rearfoot mobility).
- Local factors: decreased shock absorption due to hammertoe deformity, predislocation syndrome, translocation of the plantar fat pad, plantar fat pad atrophy.
- Trauma: rupture of plantar plate, metatarsophalangeal joint capsule, or any associated tendon
- Degenerative joint diseases (osteoarthritis, rheumatoid arthritis, psoriatic arthritis, etc.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Interdigital neuroma, most commonly third interspace (Morton's)
- Metatarsal traumatic fracture or stress fracture
- Foreign body, infection/abscess
- Freiberg's infraction, usually of second metatarsal head, frequently in teenage females
- Secondary systemic findings: rheumatoid nodules, gout
- Neoplasms: ganglion cyst, bone tumor
- Skin: verrucous plantaris, intractable plantar keratoma, tinea pedis, etc.
- Neuropathy or peripheral vascular disease

FIGURE EM1-27 Vertical stress test for metatarsophalangeal stability. One of the examiner's hands stabilizes the metatarsal head while the other grasps the proximal phalanx. Examiner attempts to displace the proximal phalanx dorsally. A positive test result is the ability to displace dorsally while reproducing symptoms. (From Scuderi G [ed]: *Sports medicine: principles of primary care,* St Louis, 1997, Mosby.)

SUGGESTED READINGS

Espinosa N et al.: Current concept review: metatarsalgia, *Foot Ankle Int* 29:871, 2008.

Thomas JL et al.: Diagnosis and treatment of forefoot disorders. Section 2. Central metatarsalgia, *J Foot Ankle Surg* 48:2, 2009.

LABORATORY TESTS

As necessary if suspicion of a systemic cause of joint arthritis/destruction

IMAGING STUDIES

- X-rays: rule out fracture, tumor, avascular necrosis, arthritic process/joint disease.
- MRI: evaluate for any plantar plate injury, capsular injury, tendon rupture, or neuroma.
- Bone scan: if stress fracture suspected (may take 2 wk to show up on x-ray).

TREATMENT

- Silicone padding provides symptomatic relief, works well for fat pad atrophy.
- Moleskin or padding will reduce frictional forces without adding bulk for long-term use.
- Custom orthotics with proximal metatarsal pad or submetatarsal cutout to offload.
- Heel lift or shoes with short heel or wedge are effective when equinus is etiology.
- Rocker-bottom to prevent motion in severe or high-risk diabetic patients
- Nonsteroidal anti-inflammatory drugs
- Intraarticular injection if indicated, based on underlying etiology
- **Caution with injection:** risk of plantar plate ruptures; use only if absolutely indicated!

DISPOSITION

Varies depending on etiology

REFERRAL

To podiatric or foot/ankle orthopedic surgeon for biomechanical exam/orthotic management or surgical consultation

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Metatarsalgia (Patient Information)

AUTHOR: **BROOKE E. KEELEY, D.P.M.**

BASIC INFORMATION

DEFINITION

An accidental or intentional ingestion of 1 g/kg of methanol or ethylene glycol is considered lethal, although even small amounts can be toxic. Inhalation and dermal exposures rarely cause toxicity.

SYNONYMS

Antifreeze and moonshine overdose

ICD-9CM CODES
980.1 Toxic effect of methyl alcohol
980.8 Toxic effect of other specified alcohols
ICD-10CM CODES
T51.8 Toxic effect of other alcohols (ethylene glycol)
T51.1 Toxic effect of methanol

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: In 2011, the American Association of Poison Control Centers reported 7014 and 1300 single-exposure cases of ethylene glycol and methanol poisoning, respectively. Most cases reported are in adults older than 19 yr and predominantly males. Accidental exposure is common in children, while alcoholism, polysubstance abuse, depression, and suicide are seen in adults.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical manifestations of both substances depend on the quantity of ingestion, duration of time since the ingestion, and whether coingestion of ethanol or other substances occurs.
- Early ingestions of both substances can mimic ethanol ingestion with nausea, vomiting, inebriation, and CNS depression. Late effects include progressive CNS depression including seizure and coma, as well as both respiratory and cardiopulmonary failure.
- Visual symptoms ranging from blurry or snowy vision to complete visual loss and findings of papillary edema, afferent pupillary defect, retinal hyperemia, and parkinsonian-like syndrome are indicative of methanol poisoning
- Abdominal pain, oliguria, hematuria, calcium oxalate crystalluria, tetany, cranial nerve palsy, and acute kidney injury suggest ethylene glycol toxicity

ETIOLOGY

- Toxicity of these alcohols is related to its metabolites rather than the parent compound
- Sequential metabolism by alcohol and aldehyde dehydrogenase converts methanol to formic acid and ethylene glycol to glycolic acid and oxalate, resulting in toxicity
- Figure M1-28 shows the pathways involved in methanol metabolism
- While methanol metabolites primarily cause retinal injury, ethylene glycol metabolites cause renal tubular injury and calcium oxalate stones
  1. Formic acid prevents oxygen utilization by mitochondria, resulting in an array of organ dysfunction, including within the central nervous system, specifically affecting the retinal and optic neurons and the basal ganglia.
  2. Oxalate forms calcium oxalate renal stones, which are responsible for direct renal injury.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other causes of anion gap metabolic acidosis include lactic acidosis, diabetic/alcoholic ketoacidosis, renal failure, toluene, and salicylate intoxication
- Elevated plasma osmolal gap can also be seen in ethyl alcohol or isopropyl alcohol ingestion and other serious illnesses like septic shock

WORKUP

- Diagnosis depends on history, clinical presentation, and laboratory abnormalities
- Anion gap metabolic acidosis (AG >12 mEq/L) with elevated plasma osmolal gap (>10 mOsm/L) in an appropriate clinical setting should raise the suspicion for methanol or ethylene glycol ingestion. In both intoxications, an osmolar gap will initially be positive, but as the parent compound is converted to its metabolites, the osmolar gap will normalize and the serum anion gap will then be positive.
- Serum methanol and ethylene glycol levels are elevated in respective ingestions.
  1. While those with ethylene glycol ingestion may have fewer toxicities and may present without acidosis, anion gap, or symptoms, the osmolar gap will remain elevated.
- Acute kidney injury, hypocalcemia with prolonged QT interval, and calcium oxalate crystalluria can been seen due to ethylene glycol toxicity
- Wood's lamp fluorescence uses ultraviolet light to detect fluorescein contained in ethylene

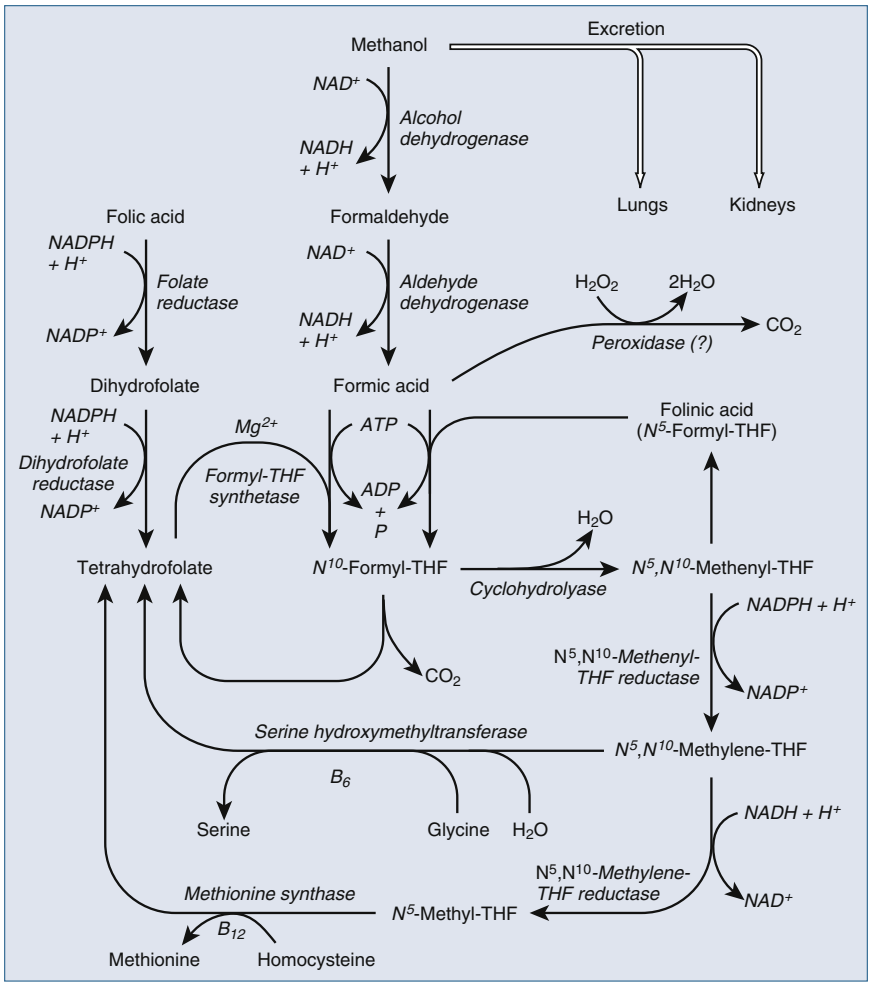

FIGURE M1-28 Metabolic pathways involved in methanol metabolism, showing the role of folate derivatives as enzymatic cofactors operative in the elimination of formic acid. *ADP*, Adenosine diphosphate; *ATP*, adenosine triphosphate; *NAD+* and *NADH*, oxidized and reduced forms of nicotinamide adenine dinucleotide, respectively; *NADP+* and *NADPH*, oxidized and reduced forms of nicotinamide adenine dinucleotide phosphate, respectively; *THF*, tetrahydrofolate. (Adapted from Kruse JA. Methanol poisoning. *Intensive Care Med* 1992;18:391-7, with permission. From Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP: *Textbook of Critical Care*, 6th ed, Philadelphia, 2011, Saunders.)

glycol preparations but lacks sensitivity as not all preparations contain fluorescein and also lacks specificity due to high rate of false positivity

LABORATORY TESTS

- Calculation of the anion gap and serum osmolar gap
  1. Anion gap determination: electrolytes, albumin
  2. Osmolal gap determination: measured and calculated serum osmolality (sodium, BUN, glucose, ± ethanol)
- Arterial blood gas analysis, lactate, calcium, and creatinine kinase
- Creatinine, urine analysis to assess kidney function, tubular injury, and calcium oxalate crystals
- ECG to assess QT interval
- Toxicology screen and quantification: acetaminophen, salicylate, ethanol, methanol, ethylene glycol, and isopropyl alcohol

Rx TREATMENT

High index of suspicion and immediate recognition with early treatment remain crucial to reduce mortality. Box M1-3 describes common commercial products that may contain ethylene glycol.

NONPHARMACOLOGIC THERAPY

- Securing patient's airway, breathing, and circulation and advanced cardiac life support measures instituted as indicated.
- While data are limited, gastric decontamination (charcoal and/or gastric lavage) is of limited use unless done within 1 hr of ingestion as alcohols are rapidly absorbed. Induction of vomiting is contraindicated even in conscious patients given the risks of development of central nervous system depression in these patients.

ACUTE GENERAL Rx

- The principles of therapy include prevention of formation of toxic metabolites, correction of acidosis, and toxin removal.
- Ethanol, as a competitive substrate, and fomepizole, a competitive inhibitor of alcohol dehydrogenase, prevent the formation of toxic metabolites of ethylene glycol and methanol. Fomepizole is preferred over ethanol given the increased incidence of adverse events with ethanol administration, which are likely secondary to the erratic pharmacokinetic profile of ethanol. Volume expansion with isotonic fluids facilitates urinary excretion of the toxins.
- When acidosis is present (pH <7.3), isotonic bicarbonate should be preferentially utilized for volume expansion as reversal of acidosis helps prevent end-organ damage from toxic metabolites. The goal pH range is 7.35-7.45.
- Treatment with medications and/or hemodialysis is continued until the methanol or ethylene glycol concentration is <20 mg/dl.
- Ethanol:
  1. Target ethanol concentration is 100-200 mg/dl requiring close monitoring
  2. Loading dose: 800 mg/kg in a 10% vol/vol solution of D5W which will raise serum ethanol by 100 mg/dl
  3. Maintenance dose: infusion of 80-160 mg/kg/hr based on the levels
- Fomepizole: preferred antidote
- Indications for fomepizole use:
  1. Plasma concentration of methanol or ethylene glycol >20 mg/dl OR
  2. Documented ingestion with an osmolal gap >10 mOsm/L OR
  3. Suspected ingestion with at least two of the following criteria:
  4. Arterial pH <7.3
  5. Serum bicarbonate <20 mEq/L
  6. Osmolal gap >10 mOsm/L
  7. Urinary oxalate crystals in the case of ethylene glycol toxicity
- Fomepizole (4-methylpyrazole) dosing:
  1. Loading dose: 15 mg/kg body weight
  2. Maintenance dose: 10 mg/kg body weight every 12 hr for 4 doses then 15 mg/kg body weight every 12 hr (if blood levels do not reach goal by 48 hr).
  3. During hemodialysis: Add 1 to 1.5 mg/kg body weight per hr
- Hemodialysis should be considered in patients with significant metabolic acidosis (pH <7.25-7.30), renal failure, visual abnormalities, electrolyte imbalances refractory to pharmacologic treatments, hemodynamic instability, and serum concentrations >50 mg/dl.
- Duration of hemodialysis can be estimated using the formula: Time (hr) equals –V ln(5/A)/0.06 k, where V is the Watson estimate of total body water (in liters); A is the initial alcohol concentration (in mmol/L); and k is 80% of the manufacturer's specified urea clearance (in ml/min). Average duration of dialysis in studies was 8.4 ± 3.2 hr.

ADJUNCTIVE Rx

- In cases of ethylene glycol poisoning, thiamine and pyridoxine may decrease oxalic acid formation and shift metabolism to less toxic metabolites.
- Folinic acid at doses of 1 mg/kg given intravenously every 4 to 6 hr may be used to increase the metabolism of formic acid in methanol overdose.
  1. Correct electrolyte abnormalities (hypocalcemia, etc.).
  2. Treat seizures.

DISPOSITION

Transfer to a hospital with intensive care and hemodialysis capability should be considered early in the patient's course.

REFERRAL

- Regional poison center (toxicologist) and nephrology recommended to avoid treatment delays
- Ophthalmology for patients with visual symptoms
- Psychiatry if depression and suicidal ideation
- Detoxification centers for patients with substance abuse

PROGNOSIS

- Coma or seizures at presentation and prolonged severe acidosis correlated with increased mortality
- High osmolal gap and AG gap were associated with high mortality
- Additionally, hyperglycemia may correlate with worse prognosis in methanol poisoning

PEARLS & CONSIDERATIONS

- Profound plasma osmolar gap or anion gap metabolic acidosis should raise suspicion for ethylene glycol and/or methanol ingestion. A high index of suspicion and early treatment remain crucial to reduce mortality. The metabolites of methanol and ethylene glycol cause clinical toxicity rather than the agents themselves.
- Complaints of visual blurring, central scotomata, and blindness suggest methanol poisoning.
- Calcium oxalate crystalluria, oliguria, and hematuria suggest ethylene glycol poisoning.
- Fomepizole is favored over ethanol due to complications associated with ethanol use.
- Emergent hemodialysis is indicated in the setting of end organ damage and severe metabolic acidosis.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fig. 3-153 Algorithm for the management of acute poisoning (Algorithm)

AUTHORS: **NIKUNJKUMAR PATEL, M.D.,** and **SUSIE L. HU, M.D**.

BOX M1-3 Common Commercial Products That May Contain Ethylene Glycol

Paints and lacquers
Polishes and detergents
Inks
Cosmetics
Hydraulic brake fluids
Solar collector fluids
Car wash fluids

Data from Kruse JA: Methanol, ethylene glycol, and related intoxications. In Carlson RW, Geheb MA (eds): *Principles and practice of medical intensive care*, Philadelphia, 1993, Saunders.

EVIDENCE

Abstract[1]

Context:

Methanol and ethylene glycol cause significant mortality post-ingestion. Predicting prognosis based on the biomarkers osmolal gap, anion gap and pH is beneficial.

Objective:

To evaluate the relationship between biomarkers, measured post-methanol and ethylene glycol exposure, and clinical outcomes.

Methods:

A review of the literature identified cases where methanol or ethylene glycol had been ingested and clinical outcomes were recorded. Biomarkers were extracted including osmolal gap, anion gap and pH, with clinical outcomes categorised as recovered, recovered with adverse sequelae and death. Biomarkers were analysed using the Mann–Whitney test for two samples; sensitivity and specificity were evaluated using receiver operating characteristic (ROC) curves.

Results:

In total, 119 cases of methanol and 88 of ethylene glycol poisoning were identified; 21 methanol and 19 ethylene glycol patients died. For methanol ingestion the mean values, for survival compared to death, were 48 (range: 61–38) and 90 (range: 49–159) mOsm/kg water for osmolal gap ($p=0.0052$), 31 (range: 11–50) and 41 (range: 30–53) mmol/L for anion gap ($p=0.0065$) and 7.21 (range: 6.60–7.50) and 6.70 (range: 6.34–7.22) for arterial pH ($p<0.0001$). The area under the ROC curve was highest for arterial pH, 0.94 (95% CI: 0.89–0.99). For ethylene glycol, these were 49 (range: 0–189) and 79 (range: 25–184) mOsm/kg water for osmolal gap ($p=0.050$), 28 (range: 6–48) and 38 (range: 20–66)mmol/L for anion gap ($p=0.0037$) and 7.08 (range: 6.46–7.39) and 6.98 (range: 6.50–7.16) for pH ($p=0.072$), for survival compared to death. The area under the ROC curve was highest for anion gap, 0.73 (95% CI: 0.60–0.87).

Conclusion:

Post-methanol ingestion a large osmolal gap, anion gap and low pH (<7.22) were associated with increased mortality; and pH has the highest predictive value. Post-ethylene glycol ingestion, both osmolal gap and anion gap, were associated with increased mortality. Ⓐ

Evidence-Based Reference

Coulter CV et al.: Methanol and ethylene glycol acute poisonings—predictors of mortality, *Clin Toxicol (Phila)* 49:900–906, 2011. Ⓐ

SUGGESTED READINGS

Barceloux DG et al.: American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning, *J Toxicol Clin Toxicol* 40:415–446, 2002.

Bayliss G: Dialysis in the poisoned patient, *Hemodial Int* 14:158–167, 2012.

Barceloux DG et al.: American Academy of Clinical Toxicology practice guidelines on the treatment of ethylene glycol poisoning, *J Toxicol Clin Toxicol* 37:537–560, 1999.

Brent J: Fomepizole for ethylene glycol and methanol poisoning, *N Engl J Med* 360:2216–2223, 2009.

Bronstein AC et al.: 2009 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 27th Annual Report, *Clin Toxicol* 48:979–1178, 2010.

Coulter CV et al.: Methanol and Ethylene Glycol Acute Poisonings-Predictors of Mortality, *Clin Toxicol* 49:900–906, 2011.

Hirsch DJ et al.: A simple method to estimate the required dialysis time for cases of alcohol poisoning, *Kidney Int* 60:2021–2024, 2001.

Hossein SZ et al.: Hyperglycemia Is a Strong Prognostic Factor of Lethality in Methanol Poisoning, *J Med Toxicology* Vol. 7(3):189–194, 2011.

Jacobsen D, McMartin KE: Antidotes for methanol and ethylene glycol poisoning, *J Toxicol Clin Toxicol* 35:127–143, 1997. From the NIH: Use of folate analogue in treatment of methyl alcohol toxic reactions is studied, *JAMA* 242:1961–1962, 1979.

Kruse J: Methanol and ethylene glycol intoxication, *Crit Care Clin* 28:661–711, 2012.

Lepik K et al.: Adverse drug events associated with the antidotes for methanol and ethylene glycol poisoning: a comparison of ethanol and fomepizole, *Ann Emerg Med* 53:439–450, 2009.

Levine M et al.: Ethylene glycol elimination kinetics and outcomes in patients managed without hemodialysis, *Ann Emerg Med* 59:527–531, 2012.

Liu JL et al.: Prognostic factors in patients with methanol poisoning, *Clin Toxicol* 36:175–181, 1998.

In: Shoemaker W et al, editor: *Textbook of critical care*, ed 2 Saunders: Philadelphia, pp 1177–1178.

Sivilotti ML et al.: for the Methylpyrazole for Toxic Alcohols Study Group: Toxicokinetics of ethylene glycol during fomepizole therapy: implications for management, *Ann Emerg Med* 36:114–125, 2000.

BASIC INFORMATION

DEFINITION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common bacterial pathogen with resistance to many antibiotics. It is defined as a *S. aureus* that shows a minimum inhibitory concentration (MIC) of greater than or equal to 4 mcg/ml to oxacillin. There are now two types of MRSA:

- HA-MRSA: hospital-acquired MRSA, usually multidrug resistant
- CA-MRSA: community-acquired MRSA; an emerging pathogen, usually acquired outside of the hospital setting; resistance may differ from HA-MRSA and is generally susceptible to more antibiotics than HA-MRSA

SYNONYMS

Multidrug-resistant *Staphylococcus aureus*
Oxacillin-resistant *Staphylococcus aureus*

ICD-9CM CODES

041.12 Methicillin-resistant *Staphylococcus aureus* in conditions classified elsewhere and of unspecified site

ICD-10CM CODES

B95.62 Methicillin-resistant *Staphylococcus aureus* infection as the cause of diseases classified elsewhere

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1:3000
PEAK INCIDENCE: Occurs year round; may peak during summer and fall months for CA-MRSA
PREVALENCE: The national rate of MRSA colonization or infection is 46.3 per 10,000 inpatients. Hospital prevalence rate of MRSA is as high as 60% in hospitals, which means that 60% of *S. aureus* strains in that hospital will be MRSA.
PREDOMINANT SEX AND AGE: All ages and both sexes
GENETICS: NA
RISK FACTORS:

- HA-MRSA: hospitalization; invasive medical device; residing in long-term nursing facility
- CA-MRSA: initially seen in young men engaged in athletic activities and in gyms, prisons, military barracks, etc., but has now spread to the entire age spectrum including neonates and the elderly.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- CA-MRSA: can present with skin infection, associated with opening in the skin; red bump, pustule, or boil; erythema, swelling; edema, often fluctuant and very painful
- HA-MRSA: bacteremia; infection associated with intravenous device
  1. Catheters: pneumonia
  2. Skin: cellulitis
  3. Bone: osteomyelitis
  4. Endocarditis
  5. Abscesses: skin or organ
  6. Pneumonia: nosocomial

ETIOLOGY

- CA-MRSA: the most prevalent strain in the US on pulse field electrophoresis (PFGE) is called USA 300
  1. CA-MRSA: common cause of skin and soft tissue infections in the emergency room. It can, however, also cause necrotizing pneumonia, sepsis, osteomyelitis, etc.
  2. Virulence factors particular to CA-MRSA: Panton-Valentine leukocidin (PVL) toxin, alpha-hemolysin toxin, phenol soluble modulins, etc., that enhance ability to cause infection
- HA-MRSA: most strains on PFGE are USA 100 or USA 200 and tend to have multidrug resistance. Patients with HA-MRSA infection have higher mortality and morbidity than patients with a methicillin-sensitive *S. aureus* (MSSA) infection.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Skin: spider bite (many patients with CA-MRSA feel as if they were bitten by a spider)
- Cellulitis: other organism(s) such as streptococci and methicillin-sensitive *S. aureus* (MSSA)
- Pneumonia: not due to MRSA
- Bacteria: not due to MRSA

WORKUP

- Culture of wound, abscess, blood, sputum; rule out colonization; culture of nares or axillae

LABORATORY TESTS

- See above.
- PFGE: usually done only for epidemiologic or outbreak purposes.

IMAGING STUDIES

- Radiographs or computed tomography scan of suspected organ
- Echocardiogram: all adult patients with *S. aureus* bacteremia should undergo echocardiography

TREATMENT

- CA-MRSA: oral antibiotics that may be effective include trimethoprim-sulfamethoxazole, doxycycline, minocycline, or clindamycin; linezolid is another option but very expensive.
- HA-MRSA: intravenous antibiotics, vancomycin, linezolid, daptomycin, tigecycline

NONPHARMACOLOGIC THERAPY

Abscess surgically drained

ACUTE GENERAL Rx

- Trimethoprim-sulfamethoxazole, one double-strength tablet PO bid, is useful in cases of CA-MRSA since 95% of community-acquired MRSA strains are susceptible to it in vitro. Other agents that can be used for CA-MRSA include:
  1. Clindamycin: 300 to 450 mg q6-8h also inhibits toxin production. If strain tests sensitive to clindamycin but resistant to erythromycin, then a D test must be done to ensure there will not be inducible resistance while on therapy with the clindamycin.
  2. Doxycycline: 100 mg PO q12h and minocycline also have some activity against MRSA.
  3. Rifampin: never used alone but can be used with one of the other oral agents
- Vancomycin 15-20 mg/kg IV q8 to 12h is the mainstay of parenteral therapy for MRSA infections. There is an increasing concern of MRSA strains developing tolerance to vancomycin, requiring higher doses to achieve eradication. True vancomycin resistant strains (MIC ≥32 mg/L) remain rare. Vancomycin trough levels of at least 15 to 20 mcg/ml are recommended to treat MRSA infections.
- Linezolid 600 mg PO or IV bid is a synthetic oxazolidinone FDA-approved for MRSA skin and soft tissue infections and pneumonia. It has been shown to be more effective than vancomycin for MRSA pneumonia. However, its cost is more than 10 times as much as vancomycin.
- Daptomycin: 4 mg/kg/day to 6 mg/kg/day IV is approved for skin and soft tissue infections, bacteremia and right-sided endocarditis but should not be used for pneumonia as it is inactivated by pulmonary surfactant.
- Tigecycline: 100 mg IV load, then 50 mg IV q12h, is approved for MRSA skin and soft tissue infections and intraabdominal abscess.
- Ceftaroline is a fifth-generation cephalosporin, also effective against MRSA but only skin and soft tissue infections, not pneumonia: 600 mg IV q12h.

CHRONIC Rx

- Patients with MRSA colonization may have reexposure or may be unable to eradicate colonized state.
- Oral agents used to attempt eradication of colonization are rifampin, tetracycline, and minocycline.

COMPLEMENTARY & ALTERNATIVE MEDICINE

- Mupirocin ointment may be administered to the nares to attempt to decolonize; it can also be applied to infected skin sites.
- Chlorhexidine 2% or 4% wash may be used to lower skin burden of colonization.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

EVIDENCE

Abstract[1]

Background:
Telavancin is a lipoglycopeptide bactericidal against gram-positive pathogens.

Methods:
Two methodologically identical, double-blind studies (0015 and 0019) were conducted involving patients with hospital-acquired pneumonia (HAP) due to gram-positive pathogens, particularly methicillin-resistant *Staphylococcus aureus* (MRSA). Patients were randomized 1:1 to telavancin (10 mg/kg every 24 h) or vancomycin (1 g every 12 h) for 7–21 days. The primary end point was clinical response at follow-up/test-of-cure visit.

Results:
A total of 1503 patients were randomized and received study medication (the all-treated population). In the pooled all-treated population, cure rates with telavancin versus vancomycin were 58.9% versus 59.5% (95% confidence interval [CI] for the difference, −5.6% to 4.3%). In the pooled clinically evaluable population ($n = 654$), cure rates were 82.4% with telavancin and 80.7% with vancomycin (95% CI for the difference, −4.3% to 7.7%). Treatment with telavancin achieved higher cure rates in patients with monomicrobial *S. aureus* infection and comparable cure rates in patients with MRSA infection; in patients with mixed gram-positive/gram-negative infections, cure rates were higher in the vancomycin group. Incidence and types of adverse events were comparable between the treatment groups. Mortality rates for telavancin-treated versus vancomycin-treated patients were 21.5% versus 16.6% (95% CI for the difference, −0.7% to 10.6%) for study 0015 and 18.5% versus 20.6% (95% CI for the difference, −7.8% to 3.5%) for study 0019. Increases in serum creatinine level were more common in the telavancin group (16% vs 10%).

Conclusions:
The primary end point of the studies was met, indicating that telavancin is noninferior to vancomycin on the basis of clinical response in the treatment of HAP due to gram-positive pathogens. Ⓐ

Abstract[2]

Background:
Methicillin-resistant *Staphylococcus aureus* (MRSA) is an important cause of nosocomial pneumonia. Societal guidelines suggest linezolid may be the preferred treatment of MRSA nosocomial pneumonia. We investigated the efficacy of linezolid compared with glycopeptide antibiotics (vancomycin or teicoplanin) for nosocomial pneumonia.

Methods:
This was a systematic review and meta-analysis of English language, randomized, controlled trials comparing linezolid to glycopeptide antibiotics for suspected MRSA pneumonia in subjects >12 years of age. A highly sensitive search of PubMed MEDLINE and Cochrane Central Register of Controlled Trials databases identified relevant studies.

Results:
Eight trials encompassing 1,641 subjects met entry criteria. Linezolid was not superior to glycopeptide antibiotics for end points of clinical success (relative risk [RR] linezolid vs glycopeptide, 1.04; 95% CI, 0.97-1.11; $P = .28$), microbiologic success (RR, 1.13; 95% CI, 0.97-1.31; $P = .12$), or mortality (RR, 0.91; 95% CI, 0.69-1.18; $P = .47$). In addition, clinical success in the subgroup of subjects with MRSA-positive respiratory tract culture (RR, 1.23; 95% CI, 0.97-1.57; $P = .09$) was not significantly different from those without MRSA (RR, 0.95; 95% CI, 0.83-1.09; $P = .48$), P for interaction, 0.07. The risk for adverse events was not different between the two antibiotic classes (RR, 0.96; 95% CI, 0.86-1.07; $P = .48$).

Conclusion:
Randomized controlled trials do not support superiority of linezolid over glycopeptide antibiotics for the treatment of nosocomial pneumonia. We recommend that decisions between linezolid or glycopeptide antibiotics for empirical or MRSA-directed therapy of nosocomial pneumonia depend on local availability, antibiotic resistance patterns, preferred routes of delivery, and cost, rather than presumed differences in efficacy. Ⓐ

Evidence-Based References

Rubinstein E: for the ATTAIN Study Group. Telavancin versus vancomycin for hospital-acquired pneumonia due to gram-positive pathogens, *Clin Infect Dis* 52:31–40, 2011. Ⓐ

Walkey A et al.: Linezolid vs glycopeptide antibiotics for the treatment of suspected methicillin-resistant nosocomial pneumonia: a meta-analysis of randomized controlled trials, *Chest* 139:1148–1155, 2011. Ⓐ

SUGGESTED READINGS

Gould IM et al.: New insights into methicillin-resistant *Staphylococcus aureus* (MRSA) pathogenesis, treatment and resistance, *Int J Antimicrob Agents* 39(2):96–104, 2012.

Holland TL et al.: Clinical management of Staphylococcus aureus bacteremia, a review, *JAMA* 312(13):1330–1341, 2014.

Liv C et al.: Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin resistant *Staphylococcus aureus* infections in adults and children, *Clin Infect Dis* 52:285–292, 2011.

McConeghy K et al.: Agents for the decolonization of methicillin resistant. Staphylococcus aureus, *Pharmacotherapy* 29:263–280, 2009.

Wunderink RG et al.: Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study, *Clin Infect Dis* 54:621–629, 2012.

Microscopic Polyangiitis

BASIC INFORMATION

DEFINITION

Microscopic polyangiitis (MPA) is an ANCA (antineutrophil cytoplasmic autoantibody)-associated small to medium vessel systemic vasculitis. It is characterized by necrotizing, pauci-immune, small vessel vasculitis in the absence of granulomatous inflammation. It commonly affects the kidney and can also affect the lower respiratory tract, skin, nervous system, and gastrointestinal (GI) tract. Renal involvement can lead to glomerulonephritis and renal failure. MPA belongs to a category of vasculitides that also includes granulomatosis with polyangiitis (GPA) and Churg-Strauss syndrome (Table M1-13).

ICD-9CM CODES
446 Polyarteritis nodosa and allied conditions
ICD-10CM CODES
M31.7 Microscopic polyangiitis

SYNONYMS

Microscopic polyarteritis
MPA

TABLE M1-13 Classification Scheme of Vasculitides According to Size of Predominant Blood Vessels Involved

Predominantly Large-Vessel Vasculitides
Takayasu's arteritis
Giant cell arteritis
Cogan's syndrome
Behçet's syndrome*
Predominantly Medium-Vessel Vasculitides
Classic polyarteritis nodosa
Cutaneous polyarteritis nodosa
Rheumatoid vasculitis†
Buerger's disease
Kawasaki disease
Primary angiitis of the central nervous system
Predominantly Small-Vessel Vasculitides
Immune complex mediated
- Cutaneous leukocytoclastic angiitis ("hypersensitivity" vasculitis)
- Henoch-Schönlein purpura
- Urticarial vasculitis
- Cryoglobulinemia†

"ANCA-associated" disorders
- Wegener's granulomatosis†
- Microscopic polyangiitis†
- Churg-Strauss syndrome†

Miscellaneous small-vessel vasculitides
- Connective tissue disorders†
- Paraneoplastic diseases
- Infection
- Inflammatory bowel disease

ANCA, Antineutrophil cytoplasmic antibody.
*May involve small, medium, and large blood vessels.
†Frequent overlap of involvement of small- and medium-sized blood vessels.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

ICD-10CM Codes
M31.7 Microscopic polyangiitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence is 3.6 per 1,000,000 annually in U.S.
- Prevalence is 1 to 2 cases in 100,000.
- More common in Caucasians as compared to African Americans.
- Equally present in both males and females.
- Average age is approximately 50 years depending on the population studied.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Constitutional symptoms like fatigue, fever, "flu-like" symptoms, weight loss, anorexia
- Macroscopic hematuria, proteinuria, edema, decreased urinary output
- Pulmonary symptoms like hemoptysis, cough, dyspnea, pulmonary hemorrhage, pleuritic pain
- Palpable purpura (preferably on dependent areas) 41% and livedo reticularis 12%
- Inflammation of visceral blood and gut vessels causes pain, bloody stools, and perforation
- Kidney involvement 90%
- Weight loss >70%
- Peripheral neuropathy 60%
- Myalgias 50%
- Chest pain, heart failure symptoms
- Ophthalmic involvement including episcleritis, uveitis,conjunctivitis

ETIOLOGY

- Autoimmune process of unknown etiology. ANCA, most specifically those directed at cytoplasmic myeloperoxidase, are felt to contribute to the inflammatory process. Once bound to their cellular epitope, anti-myeloperoxidase (MPO) antibodies likely contribute to degranulation of the neutrophil, which presumably contributes to endothelial injury. Most recently, investigators have demonstrated that anti-MPO antibodies alone can cause necrotizing and crescentic glomerulonephritis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Polyarteritis nodosa
- Kawasaki's disease
- Infective endocarditis
- Lymphoma
- Amyloidosis
- Hypercoagulable states
- Systemic lupus erythematosus
- Paraproteinemias

MPA is distinguished from GPA and Churg-Strauss syndrome by the absence of granuloma formation (Table M1-14) and the absence of asthma and eosinophilia characteristic of Churg-Strauss syndrome.

WORKUP

- Medical history to look for the presence of MPA symptoms
- Physical examination to detect sites of organ involvement and to exclude other illnesses that may have a similar appearance

LABORATORY TESTS

- Laboratory testing may reveal elevated sedimentation rate (ESR), C-reactive protein, leukocytosis, anemia
- Elevated serum blood urea nitrogen (BUN) and creatinine suggestive of renal impairment
- Urinalysis to detect proteinuria, hematuria, erythrocyte casts, abnormal urine sediment
- ANCA positive 82% to 94%
- Perinuclear ANCA directed at myeloperoxidase 60%
- Cytoplasmic ANCA directed at proteinase –3 40%
- Serum complement levels
- Increased aspartate aminotransferase, alanine aminotransferase, and creatine phosphokinase may indicate liver or muscle (skeletal or cardiac) involvement
- Blood cultures to rule out bacterial endocarditis
- Intestinal angina is often a result of mesenteric ischemia and can be assessed using mesenteric angiography when renal function permits
- Tissue for pathology diagnosis is usually required to confirm the diagnosis
- Biopsy of the skin reveals nonspecific leukocytoclastic vasculitis with little or no complement and immunoglobulin on immunofluorescence.
- Kidney biopsy usually reveals necrotizing crescentic glomerulonephritis that is usually pauci-immune on immunofluorescence and necrotizing vasculitis of microscopic vessels (small arteries, arterioles, capillaries, venules) (Figure M1-29).

IMAGING STUDIES

- Chest radiograph would show diffuse parenchymal infiltrates secondary to pulmonary alveolar hemorrhages.
- Computed tomographic (CT) scanning may disclose previously undetected nodules, unsuspected cavitation in nodules, alveolar opacities, large-airway inflammation or stenotic lesions, and pleural-based lesions.
- An EMG may reveal a sensorimotor peripheral neuropathy in patients with neuropathy.
- Electrocardiography is indicated in myocardial infection, pericarditis, and congestive heart failure.
- Gastrointestinal endoscopy and mesenteric angiography in cases of gastrointestinal involvement.

TREATMENT

ACUTE GENERAL Rx

Induction

- Corticosteroids combined with immunomodulatory drugs, such as cyclophosphamide or azathioprine and methotrexate.
- Rituximab is an effective alternative to cyclophosphamide initial treatment as well as for relapse.
- Plasmapheresis is an option for patients with bleeding in the lungs or kidney failure leading to dialysis to remove ANCA.

TABLE M1-14 Names and Definitions of Vasculitis Adopted by the Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitis

Name	Large-Vessel Vasculitis*
Giant cell (temporal arteritis)	Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. Often involves the temporal artery. Usually occurs in patients older than 50 yr and often is associated with polymyalgia rheumatica
Takayasu's arteritis	Granulomatous inflammation of the aorta and its major branches. Usually occurs in patients younger than 50 yr
	Medium-Sized Vessel Vasculitis*
Polyarteritis nodosa (classic polyarteritis nodosa)	Necrotizing inflammation of medium-sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules. Kawasaki's disease arteritis involving large, medium-sized, and small arteries and associated with mucocutaneous lymph node syndrome. Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children
	Small-Vessel Vasculitis*
Wegener's granulomatosis†,‡	Granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels, e.g., capillaries, venules, arterioles, and arteries. Necrotizing glomerulonephritis is common
Churg-Strauss syndrome†,‡	Eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels and associated with asthma and blood eosinophilia
Microscopic polyangiitis (microscopic polyarteritis)†,‡	Necrotizing vasculitis with few or no immune deposits affecting small vessels, e.g., capillaries, venules, or arterioles. Necrotizing arteritis involving small- and medium-sized arteries may be present. Necrotizing glomerulonephritis is very common. Pulmonary capillaritis often occurs
Henoch-Schönlein purpura‡	Vasculitis with immunoglobulin A–dominant immune deposits affecting small vessels, e.g., capillaries, venules, or arterioles. Typically involves the skin, gut, and glomeruli and is associated with arthralgias or arthritis
Essential cryoglobulinemic vasculitis‡	Vasculitis with cryoglobulin immune deposits affecting small vessels, e.g., capillaries, venules, or arterioles, and associated with cryoglobulins in serum. Skin and glomeruli are often involved
Cutaneous leukocytoclastic angiitis	Isolated cutaneous leukocytoclastic angiitis without systemic vasculitis or glomerulonephritis

*_Large artery_ refers to the aorta and the largest branches directed toward major body regions (e.g., to the extremities and the head and neck); _medium-sized artery_ refers to the main visceral arteries (e.g., renal, hepatic, coronary, and mesenteric arteries); and _small artery_ refers to the distal arterial radicals that connect with arterioles (e.g., renal arcuate and interlobular arteries). Note that some small- and large-vessel vasculitides may involve medium-sized arteries; but large- and medium-sized vessel vasculitides do not involve vessels smaller than arteries.

†Strongly associated with antineutrophil cytoplasmic autoantibodies (ANCA).

‡May be accompanied by glomerulonephritis and can manifest as nephritis or pulmonary renal vasculitic syndrome.

From Runge MS, Greganti MA. *Netter's Internal Medicine,* ed 2 (Netter Clinical Science); Philadelphia, 2008, Saunders, p. 1053; Originally adapted from Jennette JC et al: Nomenclature of systemic vasculitides. Proposal of an international consensus conference. *Arthritis Rheum* 37(2):187-192, 1994.

CHRONIC Rx

Maintenance therapy

- Low-dose steroids, azathioprine, methotrexate, and rituximab have been demonstrated to be non-inferior to cyclophosphamide and can be used for maintenance therapy as well although dosing intervals and duration of therapy are still being determined.
- Prophylaxis for opportunistic infections like *Pneumocystis carinii (jiroveci)* pneumonia (PCP) is with low-dose sulfamethoxazole/trimethoprim given as one double-strength tablet three times weekly.

Relapse therapy

- Mild or non-life-threatening relapses while on maintenance therapy can be treated by increasing glucocorticoid dose or azathioprine or methotrexate most commonly.
- In severe cases, treatment is the same as in remission induction; however, rituximab is often preferred over cyclophosphamide.

DISPOSITION

- Poor prognosis if untreated.
- Prompt diagnosis is important to permit initiation of therapy that may be life-saving and organ sparing.
- Renal failure and pulmonary involvement are the major causes of morbidity and mortality.
- With treatment, 2-5-yr survival rates are 74%.

REFERRAL

Nephrology consultation is needed with the diagnosis and management of renal involvement and possible need for dialysis.

Multiple specialists may be consulted depending on system involvement.

PEARLS & CONSIDERATIONS

Relapse occurs in one third of the cases.

PCP occurs in 6% of the patients as a complication of immunosuppressive therapy.

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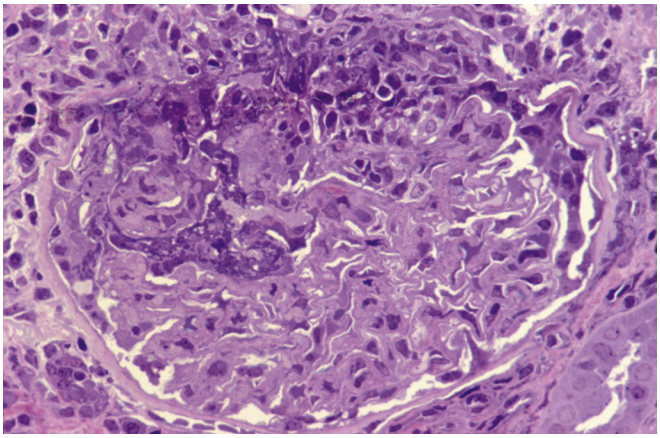

FIGURE M1-29 ANCA-associated crescentic glomerulonephritis. This toluidine blue–stained plastic section demonstrates a glomerulus with a cellular crescent. There is partial obliteration of Bowman's space by a proliferation of epithelial cells and macrophages. All types of crescentic glomerulonephritis appear similar by light microscopy, and immunofluorescence is needed to distinguish among pauci-immune, immune complex, and anti–glomerular basement membrane subtypes. (Courtesy of Dr. J. Myles.) (From Firestein GS et al: *Kelley's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders, p. 1439.)

SUGGESTED READINGS

Falk RJ et al.: Granulomatosis with polyangiitis (Wegener's): an alternative name for Wegener's granulomatosis, *Arthritis Rheum* 63(4):863, 2011.

Hogan SL, Falk RJ: Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis, *Ann Intern Med* 143(9):621, 2005.

Jennette JC et al.: Nomenclature of systemic vasculitides. Proposal of an international consensus conference, *Arthritis Rheum* 37(2):187, 1994.

Pepper RJ, Salama AD: Classifying and predicting outcomes in ANCA-associated glomerulonephritis, *Nephrol Dial Transplant* 27(6):2135, 2012.

Watts R et al.: Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies, *Ann Rheum Dis* 66(2):222, 2007.

BASIC INFORMATION

DEFINITION

Microsporidiosis is an infection caused by single-celled protozoan intracellular spore-forming organisms called Microsporidia. Recent evidence suggests a relationship between microsporidia and fungi. Infections occur more commonly in AIDS patients, travelers, children, organ transplant recipients, contact lens wearers, and the elderly.

SYNONYMS

Enterocytozoon bieneusi infection
Encephalitozoon species infections

ICD-9CM CODES
136.8 Microsporidiosis
ICD-10CM CODES
B60.8 Microsporidiosis
A07.8 Microsporidiosis, intestinal

EPIDEMIOLOGY & DEMOGRAPHICS

Microsporidia exist worldwide in the environment and can infect vertebrate and invertebrate hosts entering via ingestion or inhalation of spores.

PREVALENCE: One European study showed a prevalence of 5%-8% in immunocompetent persons.

In a study of asymptomatic HIV patients, 15% had evidence of microsporidia on small bowel biopsy.

RISK FACTORS

Infections such as a nonbloody watery diarrhea and keratoconjunctivitis in contact lens wearers can occur in normal hosts, but immunocompromised hosts such as AIDS patients, organ transplant recipients, and bone marrow graft recipients are at greater risk for more severe disease and other organ involvement.

ETIOLOGY

- There are 1200 species of Microsporidia, but only 14 infect humans. The four most common are:
  1) *Enterocytozoon bieneusi*
  2) *Encephalitozoon intestinalis*
  3) *Encephalitozoon cuniculi*
  4) *Encephalitozoon hellum*
- These genotypes that infect humans have been identified in domestic, farm, and wild animals and thus may be a form of zoonotic disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Each species of microsporidia has different reported infections:

1) *Enterocytozoon bieneusi* can cause diarrhea, wasting syndrome, cholangitis, rhinitis, or bronchitis.
2) *Encephalitozoon intestinalis* can cause diarrhea, intestinal perforation, cholangitis, nephritis, and keratoconjunctivitis.
3) *Encephalitozoon cuniculi* can cause hepatitis, peritonitis, encephalitis, urethritis, prostatitis, nephritis, sinusitis, keratoconjunctivitis, cystitis, diarrhea, cellulitis, and disseminated infection.
4) *Encephalitozoon hellum* can cause keratoconjunctivitis, sinusitis, pneumonitis, nephritis, prostatitis, urethritis, cystitis, diarrhea, and disseminated infection.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other causes of watery nonbloody diarrhea: *Norovirus, Giardia, Cryptosporidia, Cyclospora,* and *Isospora belli*
- Other causes of keratoconjunctivitis: herpetic keratoconjunctivitis and acanthamoeba keratitis

WORKUP

Consists of the microscopic detection of microsporidia spores (1-2 mcm in diameter) in stool, body fluids, or tissue samples

LABORATORY TEST(S)

- Modified trichrome stain with light microscopy can be used on stool, urine, mucus, or tissues. Spores stain pink against a blue-green background.
- Fluorescent techniques: calcofluor white stain, Uvitex 2B, and Fungi-Fluor kit
- Indirect immunofluorescence
- Serology: detects IgM and IgG antibodies

TREATMENT

ACUTE GENERAL Rx

Treatment will depend on organism and site involved.

1) Encephalitozoonidae species:
   a) Intestinal or disseminated infection: albendazole 400 mg PO bid for 2-4 weeks depending on level of immunosuppression. Children: 15 mg/kg/day PO in divided doses.
   b) Keratoconjunctivitis: topical fumagillin 70 mcg/ml eye drops (2 drops every 2 hours for 4 days, then 2 drops 4 times a day). If associated with intestinal disease, add albendazole 400 mg PO bid for 2-4 weeks depending on degree of immunosuppression.
2) *Enterocytozoon bieneusi:* intestinal or disseminated disease—albendazole is not effective, but one can use fumagillin 20 mg PO tid (although this is not commercially available in the U.S.). Alternative: nitazoxanide 1 g PO bid for 60 days in AIDS patients.

CHRONIC Rx

Antimotility agents are useful to control diarrhea.

REFERRAL

- Infectious diseases physician for ART therapy if HIV+/AIDS
- Ophthalmologist if keratoconjunctivitis is suspected

PEARLS & CONSIDERATIONS

COMMENTS

- Microsporidia infections occur particularly in AIDS patients with CD4+ cell counts <50/ml.
- Microsporidia spores can remain active in the environment for prolonged periods of time (e.g., months).

PREVENTION

The most effective prevention in AIDS patients is to start ART to increase CD4+ count >100/ml; this will result in resolution of symptoms of enteric microsporidiosis (if already present) and serve as a prevention.

SUGGESTED READINGS

Available at www.expertconsult.com

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SUGGESTED READINGS

Anane S, Attouchi H: Microsporidiosis: epidemiology, clinical data and therapy, *Gastroenterol Clin Biol* 34(8-9):450, 2010.

Didier ES, Weiss LM: Microsporidiosis: not just in AIDS patients, *Curr Opin Infect Dis* 24(5):490, 2011.

Didier ES, Weiss LM: Microsporidiosis: current status, *Curr Opin Infect Dis* 19(5):485, 2006.

Garg P: Microsporidia infection of the cornea—a unique and challenging disease, *Cornea* 32(Suppl 1):S33, 2013.

BASIC INFORMATION

DEFINITION

Migraine headaches are recurrent headaches that are either preceded by a focal neurologic symptom (migraine with aura), occur independently without preceding focal neurologic symptoms (migraine without aura), or have atypical presentations (migraine variants). The migraine aura typically is characterized by visual or sensory symptoms that develop over 5 to 60 min. If aura includes motor weakness, the migraine is referred to as hemiplegic. In migraine with and without aura, the headache is typically unilateral, pulsatile, and associated with nausea and vomiting, photophobia, and phonophobia. Migraines that occur ≥15 days every month for ≥3 months are known as chronic; otherwise, they are referred to as episodic.

ICD-9CM CODES	
346	Migraine
ICD-10CM CODES	
G43.909	Migraine, unspecified, not intractable, without status migrainosus
G43.1	Migraine with aura (classical migraine)
G43.0	Migraine without aura (common migraine)
G43.2	Status migrainosus
G43.3	Complicated migraine

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Increases from infancy, peaks during the third decade of life, then decreases
PREVALENCE (IN U.S.): Females: 18%; males: 6%. More than 50% of persons affected by migraine headaches report reduced work or school productivity.
AGE: Peak prevalence between ages of 18 and 49
PREDOMINANT SEX: Female/male ratio of 3:1
GENETICS:

- Familial predisposition: more than 50% of migraine sufferers have an affected family member
- Autosomal-dominant transmission for some rare migraine variants (familial hemiplegic migraine, cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL]); familial hemiplegic migraines have been associated with calcium channelopathy, sodium channelopathy, and Na^+/K^+- ATPase dysfunction.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Normal between episodes
- Normal for migraine without aura.
- Focal motor or sensory abnormalities possible for migraine with aura or migraine variants.
- Common aura types include scintillating scotoma, bright zigzags, homonymous visual disturbance such as paresthesia, speech disturbances, or hemiparesis (familial or sporadic hemiplegic migraine). Other visual phenomena include image distortion or "Alice in Wonderland" effect.

ETIOLOGY

The pathophysiology of migraines is not clearly understood. It is believed that a primary neuronal event results in a trigeminovascular reflex causing neurogenic inflammation. Serotonin, substance P, nitric oxide, and calcitonin gene-related peptide also play a role, but the exact mechanism is unknown. Cortical spreading depression is probably responsible for the aura.

DIAGNOSIS

Migraine without aura:

- Five attacks fulfilling criteria
- Headache attacks lasting 4 to 72 hr
- Headache has at least two of the following characteristics:
  1. Unilateral location
  2. Pulsating quality
  3. Moderate or severe pain intensity
  4. Aggravation or causing avoidance of routine physical activity
- At least one of the following during headache:
  1. Nausea and/or vomiting
  2. Photophobia and phonophobia

Migraine with aura:

- At least two attacks
- Aura consisting of at least one of the following, but no motor weakness:
  1. Fully reversible visual symptoms, including positive and/or negative features
  2. Fully reversible sensory symptoms, including positive and/or negative features
- At least two of the following:
  1. Homonymous visual symptoms and/or unilateral sensory symptoms
  2. At least one aura symptom develops gradually over >5 min and/or different aura symptoms occur in succession over >5 min
- A migraine occurring during or within 60 min of the aura

DIFFERENTIAL DIAGNOSIS

- A diagnosis of migraine is possible only after five recurrent episodes.
- The first or the worst headache should always be investigated and the differential includes headaches from all secondary causes.
- Headache red flags can be remembered by the mnemonic SNOOP:
  1. S: systemic symptoms of fever, weight loss
  2. S: secondary risk factors of immunosuppression from any cause, cancer
  3. N: neurologic deficits, altered consciousness
  4. O: onset is sudden, abrupt, or split second
  5. O: older, age >50 for new-onset headache should be worked up for giant cell arteritis
  6. P: previous headache history is different or there is a change to headache
- Section II describes the differential diagnosis of headaches

WORKUP

- In general, no additional investigation is needed with recurrent, typical attacks with usual age of onset, family history, and a normal physical examination.
- If there is an unusual presentation and/or unexpected findings on examination, investigation for other causes is required.

LABORATORY TESTS

Lumbar puncture for history of abrupt-onset headaches and uncertain diagnosis of migraine

IMAGING STUDIES

- Imaging should be done in patients with headaches and an unexplained abnormal finding on the neurologic examination.
- Imaging should be considered in patients with rapidly increasing headache frequency, history of dizziness or incoordination, headache causing wakening from sleep, or headaches worsening with Valsalva maneuver.

TREATMENT

Consider the use of a headache log/diary to identify triggers of headaches, record efficacy of treatments, and track history of headaches.

NONPHARMACOLOGIC THERAPY

- Avoid any identifiable provoking factors: caffeine, tobacco, and alcohol may trigger attacks, as may dietary or other environmental precipitants (less common)
- Avoid stressors in life and minimize variations in daily routine with regular sleep, meals, and exercise
- Relaxation training, behavioral therapy, and biofeedback. Trials have shown that among young persons with chronic migraine, the use of cognitive behavior therapy (CBT) plus amitriptyline results in greater reductions in days with headaches and migraine-related disability compared with use of headache education plus amitriptyline.[1]

ACUTE ANALGESIC Rx

- Many oral agents are ineffective because of poor absorption from migraine-induced gastric stasis. Non-oral route of administration should be selected in patients with severe nausea or vomiting.
- NSAIDs such as ketorolac, combination analgesics, or barbiturates may be used.

ACUTE ABORTIVE Rx

- IV antiemetic (prochlorperazine, metoclopramide, domperidone): Acute dystonic reactions and akathisia are rare side effects. These are generally not used as monotherapy.
- Ergotamine and ergotamine combinations (PO/PR) and dihydroergotamine (DHE 45) (SC, IV, IM, intranasal) have well-documented efficacy against migraines. DHE is usually administered in combination with an antiemetic drug (Table M1-15).
- Triptans (SC, PO, and intranasal) are now considered the drug class of choice for abortive therapy. Meta-analysis suggests that 10 mg rizatriptan, 40 mg eletriptan, and 12.5 mg almotriptan are most effective.

[1]Powers SW et al: Cognitive behavioral therapy plus amitriptyline for chronic migraine in children and adolescents, *JAMA* 310(24):2622-2630, 2013.

TABLE M1-15 Abortive and Analgesic Therapy for Migraine*

Drug	Route	Dose
Triptans (Serotonin Agonists)		
Sumatriptan	Subcutaneous	6 mg, repeat in 2 hr (max 2 doses/day)
Sumatriptan	Oral	25 mg, 50 mg, 100 mg, repeat in 2 hr (max 200 mg/day)
Sumatriptan	Nasal spray	5 mg, 20 mg, repeat in 2 hr (max 40 mg/day)
Zolmitriptan	Oral	1.25, 2.5 mg, 5 mg, repeat in 2 hr (max 10 mg/day)
Zolmitriptan	Nasal spray	5 mg, repeat in 2 hr (max 10 mg/day)
Zolmitriptan	Orally disintegrating tab	2.5, 5 mg, repeat in 2 hr (max 10 mg/day)
Naratriptan	Oral	1 mg, 2.5 mg, repeat in 4 hr (max 5 mg/day)
Rizatriptan	Oral	5 mg, 10 mg, repeat in 2 hr (max 30 mg/day)
Almotriptan	Oral	6.25 mg, 12.5 mg, may repeat in 2 hr (max 25 mg/day)
Eletriptan	Oral	20 mg, 40 mg, may repeat in 2 hr (max 80 mg/day)
Frovatriptan	Oral	2.5 mg, may repeat in 2 hr (max 7.5 mg/day); may also be used for mini prophylaxis
Ergotamine Preparations		
Ergotamine and caffeine	Oral	2 tablets, may repeat 1 tab q30 min (max 6/day)
Ergotamine and caffeine	Rectal	1 suppository, repeat in 1 hr (max 2/day)
Ergotamine	Sublingual	1 tablet, repeat in 1 hr (max 2/day)
Dihydroergotamine	Intramuscular Subcutaneous Intravenous Nasal spray	0.5-1.0 mg, repeat twice at 1-hr intervals (max 3 mg/attack)
Sympathomimetics (with or without Barbiturates or Codeine)		
Isometheptene+ dichloralphenazone+ acetaminophen	Oral	1 to 2 capsules, repeat in 4 hr (max 8/day)
Nonsteroidal Anti-inflammatory Drugs		
Acetaminophen+ (should not be used alone)	Oral	2 tablets, repeat in 6 hr (max 8/day aspirin+caffeine)
Naproxen	Oral	550-750 mg, repeat in 1 hr (max 3 times/wk)
Meclofenamate	Oral	100-200 mg, repeat in 1 hr (max 3 times/wk)
Flurbiprofen	Oral	50-100 mg, repeat in 1 hr (max 3 times/wk)
Ibuprofen	Oral	200-300 mg, repeat in 1 hr (max 3 times/wk)
Antiemetics		
Promethazine	Oral	50-125 mg
	Intramuscular	No clear benefit in migraine, may be used
Prochlorperazine	Oral	1-25 mg
	Rectal	2.5-25 mg (suppository)
	Intramuscular/IV	5-10 mg, good evidence for strong benefit
Chlorpromazine	Oral	10-25 mg
	Rectal	50-100 mg (suppository)
	Intravenous	Up to 35 mg, use with monitoring, some evidence for good benefit
Trimethobenzamide	Oral	250 mg
	Rectal	200 mg
Metoclopramide	Oral	5-10 mg
	Intramuscular	10 mg
	Intravenous	5-10 mg
Dimenhydrinate	Oral	50 mg

*For side effects and contraindications consult the manufacturer's drug insert before prescribing any of these drugs.
Modified from Wiederholt WC: *Neurology for non-neurologists,* ed 4, Philadelphia, 2000, Saunders.

- Early administration improves effectiveness.
- There is an emerging role for the use of IV magnesium (1 g), IV valproate infusions to abort migraine headaches. IV dexamethasone up to 12 mg may be used for headaches lasting more than 72 hours.
- Greater and lesser occipital nerve blocks may also be performed to alleviate pain in the acute setting. This may be combined with auriculotemporal, supraorbital, and supratrochlear nerve block to achieve anesthesia in the area of perceived pain. Steroids should generally be avoided with these nerve blocks because of lack of benefit.
- Recently an OTC preparation classified as a homeopathic drug has become available. It is derived from capsaicin, is used as a nasal spray, and is reported to be beneficial in both migraine and cluster headaches.
- Single pulse transcranial magnetic stimulation has also been approved by the FDA but is only available in Europe at the current time.

PROPHYLAXIS Rx

- Prophylactic treatment is generally indicated when headaches occur more than once a week or when symptomatic treatments are contraindicated or not effective. They are most effective when initiated during a headache-free period. All prophylaxis should be maintained for at least 3 months before deeming the medication a failure.
- Well-established options for prophylactic treatment include β-blockers (propranolol, timolol, atenolol, metoprolol), tricyclic antidepressants (amitriptyline), and the antiepileptic drugs topiramate and valproic acid.
- Less-established options include calcium channel blockers, selective serotonin reuptake inhibitors, and the antiepileptic drug gabapentin.
- Supraorbital transcutaneous electrical stimulation has been approved by the FDA for prophylaxis of episodic migraine and is widely available with a prescription in Europe and North America.
- The FDA has approved injection of onabotulinum toxin A (Botox) for prevention of headaches in adult patients with chronic migraines only (≥15 headache days/mo for ≥3 mo). The recommended total dose is 155 total units administered intramuscularly every 12 wk divided among 31 sites in head and neck area (frontalis, corrugator, procerus, occipitalis, temporalis, trapezius, cervical paraspinal muscle group). A maximum of 195 units is allowed.
- Surgical treatment for migraine using nerve decompression has been advocated recently but remains highly controversial, with poorly established results. This should be pursued only in collaboration with a headache specialist.

DISPOSITION

With advancing age, many patients will have sustained reduction of migraine headaches.

REFERRAL

To neurologist if uncertain about diagnosis or treatment not effective

PEARLS & CONSIDERATIONS

- Avoid overuse of narcotics, barbiturates, caffeine, and benzodiazepines because they are habit-forming.
- Long-term use of analgesic medications can result in drug-induced or rebound headaches.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Migraine Headache (Patient Information)

AUTHOR: **SIDDHARTH KAPOOR, M.D.**

SUGGESTED READINGS

Buse DC et al.: Assessing and managing all aspects of migraine: migraine attacks, migraine-related functional impairment, common comorbidities, and quality of life, *Mayo Clin Proc* 84(5):422–435, 2009.

Ferrari MD et al.: Oral triptans (serotonin 5-HT1B/1D agonist) in acute migraine treatment: a meta-analysis of 53 trials, *Lancet* 358:1668, 2001.

Ferrari MD et al.: Migraine—current understanding and treatment, *N Engl J Med* 346:257, 2002.

Gilmore B, Magdalena M: Treatment of acute migraine headache, *Am Fam Physician* 83(3):271–280, 2011.

Headache Classification Committee of the International Headache Society: The international classification of headache disorders, *Cephalalgia* 24:s1, 2004.

Jackson JL et al.: Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults, *JAMA* 307(16):1736–1745, 2012.

Laine CL et al.: In the clinic: migraine, *Ann Intern Med* ITC11, 2007.

MacGregor EA: In the clinic, migraine, *Ann Int Med* 159(9):ITC5–1, 2013.

Matchar DB et al. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management of acute attacks. American Academy of Neurology Practice Guideline.. Available at http://www.aan.com/professionals/practice/pdfs/gl0087.pdf.

BASIC INFORMATION

DEFINITION

Significant cognitive impairment in the absence of dementia with preserved activities of daily living (ADLs). Mild cognitive impairment (MCI) is an intermediate state between normal cognitive function and dementia. The main distinctions between MCI and mild dementia are that in the latter, more than one cognitive domain is invariably involved and substantial interference with daily life is evident.*

SYNONYMS

Isolated short-term memory loss
Cognitive impairment not dementia (CIND)
Pre-dementia
Dementia prodrome
Mild neurocognitive disorder
MCI

ICD-9CM CODES
331.83 Mild cognitive impairment, so stated
ICD-10CM CODES
G31.84 Mild cognitive impairment, so stated

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:
- 12 to 15 cases per 1000 person-yr age ≥65
- 51 to 77 cases per 1000 person-yr age ≥75

PEAK INCIDENCE: In the elderly
PREVALENCE: 15% to 25% in those older than age 70.
PREDOMINANT SEX AND AGE: Male, age ≥75
GENETICS: *APOE4* genotype
- Various pathways result in amyloid accumulation and deposition in pre-Alzheimer's presenting as MCI.

RISK FACTORS: Male sex, age, lower socioeconomic status, lower educational level

CLINICAL PRESENTATION

- Subjective memory problems, preferably corroborated by another person.
- Preserved functional status (ADLs).
- Normal general thinking and reasoning skills.
- Subtypes of MCI include amnestic (mainly involves memory loss) vs. nonamnestic with involvement of other cognitive domains (single domain vs. multiple domains).
- Domains affected in MCI include memory, visuospatial skills, language, attention, and executive function.
- Altered sense of smell may be a clue to impending cognitive impairment and has been associated with progression of MCI to dementia.

ETIOLOGY

Neurodegenerative, vascular, traumatic, depression, or due to underlying medical condition

*Knopman Ds, Petersen RC: Mild cognitive impairment and mild dementia: a clinical perspective, *Mayo Clin Proc* 89:1452, 2014.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Delirium
- Dementia
- Depression
- "Reversible" cognitive impairment:
  1. Medication related (anticholinergics)
  2. Hypothyroidism
  3. Vitamin B_{12} deficiency
- Reversible CNS conditions
  1. Subdural hematoma
  2. Normal pressure hydrocephalus
  3. Metastatic disease

WORKUP

History
- Focus on cognitive deficits and impairment.
- Review all medications that may impact cognition (i.e., anticholinergics).
- Rule out depression and delirium.
- Perform functional assessment.

Physical exam
- Check blood pressure
- Neurologic exam to rule out reversible CNS causes of cognitive impairment

Cognitive function testing:

Brief mental status testing using MOCA (Montreal Cognitive Assessment) or SLUMS (Saint Louis University Mental Status) for office screening followed by neuropsychological testing if appropriate for specific deficits in cognitive domains. MOCA may be a better tool in identifying and following MCI with higher sensitivity to monitor cognitive decline in longitudinal monitoring.

LABORATORY TESTS

- Complete blood count
- Comprehensive metabolic profile
- TSH
- Vitamin B_{12}
- Lipids
- At-risk groups should get consideration for rapid plasma reagin (RPR) and HIV evaluation.

IMAGING STUDIES

- CT imaging can detect most reversible CNS conditions leading to cognitive impairment.
- MRI further evaluates vascular, infectious, neoplastic, and inflammatory conditions.

TREATMENT

- There is insufficient evidence to recommend use of cholinesterase inhibitors (Table EM1-16) for MCI. They are not approved for treating MCI, have shown little efficacy in altering progression to dementia, and can have significant side effects.
- Consider treatment with these medications only if memory complaints appear to be affecting day-to-day quality of life in individual patients or in amnestic subtypes of MCI after risk-versus-benefit discussion with patient and family.

NONPHARMACOLOGIC THERAPY

- Role of cognitive rehabilitation to target specific deficits
- Caregiver education and counseling
- Physical and mental exercises to maintain cognition should be recommended

COMPLEMENTARY & ALTERNATIVE MEDICINE

No clear indications for antioxidants, and studies in humans are inconclusive.

DISPOSITION

- Progression to Alzheimer's at the rate of 5% to 15% per year
  1. Risk factors for progression to dementia include presence of vascular risk factors, significant cognitive impairment, depression, and presence of extrapyramidal signs.
- Mortality of those with MCI is twice that of those without MCI.
- Two- to threefold increase in risk of nursing home placement in those with MCI.

REFERRAL

Consider referral to a memory specialist if more than just memory is involved or for further evaluation of specific deficits.

PEARLS & CONSIDERATIONS

COMMENTS

Patients with MCI usually report short-term memory concerns such as misplacing things, not remembering names of people, word-finding difficulties, forgetting day-to-day tasks, not being able to read a book, or not being able to follow a conversation.

MCI becomes clinically relevant when quality of life is affected such as problems making financial decisions and problems with personal day-to-day interactions.

Depression should be ruled out prior to making a diagnosis of MCI since it is highly prevalent in the elderly.

Anticholinergic medication use should be evaluated carefully prior to making a diagnosis of MCI.

PREVENTION

Patients with MCI should be counseled on strategies to prevent progression to dementia. They should remain physically and mentally active, have a well-balanced diet, continue activities that are socially engaging, reduce stress in their lives, and aggressively pursue treatment of vascular risk factors.

PATIENT & FAMILY EDUCATION

- Patients with MCI typically have poor retention and rapid loss of newly learned information.
- For additional information for patients, families, and clinicians: Alzheimer's Association (www.alzheimers.org)

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **BIRJU B. PATEL, M.D.,** and **N. WILSON HOLLAND, M.D.**

SUGGESTED READINGS

Carr DB, Ott BR: The older adult driver with cognitive impairment, *JAMA* 303(16):1632–1641, 2010.

Conti MZ, Vicini-Chilovi B et al.: Odor Identification Deficit Predicts Clinical Conversion from Mild Cognitive Impairment to Dementia Due to Alzheimer's Disease, *Arch Clin Neuropsychol* 28:391, 2013.

Cooper C, Li R et al.: A systematic review of treatments for Mild Cognitive Impairment, *Br J Psychiatry* 203(3):255–264, 2013 September.

Kelley BJ, Petersen RC: Alzheimer's disease and mild cognitive impairment, *Neurol Clin* 25:577–609, 2007.

Kelley RE, Minagar A: Memory complaints and dementia, *Med Clin North Am* 93:389–406, 2009.

Knopman DS, Petersen RC: Mild cognitive impairment and mild dementia: a clinical perspective, *Mayo Clin Proc* 89(10):1452–1459, 2014.

Langa KM, Levine DA: The diagnosis and management of mild cognitive impairment: a clinical review, *JAMA* 312(23):2551–2561, 2014.

Patel BB, Holland NW: Mild cognitive impairment: hope for stability, plan for progression, *Cleve Clin J Med* 78:857, 2012.

Petersen RC et al.: Mild cognitive impairment: a concept in evolution, *J Int Med* 275:214–228, 2014.

Russ TC, Morling JR: Cholinesterase inhibitors for mild cognitive impairment, *Cochrane Database Syst Rev* 9:CD009132, 2012.

Sachs GA et al.: Cognitive impairment: an independent predictor of excess mortality, *Ann Intern Med* 155:300–308, 2011.

Suzuki T et al.: A Randomized Controlled Trial of Multicomponent Exercise in Older Adults with Mild Cognitive Impairment, *PLoS One* 8(4):e61483, 2013.

TABLE EM1-16 Characteristics and Properties of Cholinesterase Inhibitors

Drug Name	Starting Dose	Maintenance Dose	Serum Half-life	Taken with Food?	Elimination
Donepezil	5 mg	10 mg	70 hr	+/–	Hepatic
Rivastigmine pill	1.5 mg bid	6 mg bid	2-8 hr	+	Hepatic
Rivastigmine patch	4.6 mg/24 hr	9.5 mg/24 hr	N/A	N/A	Hepatic
Galantamine	4 mg bid or 8 mg SA daily	12 mg bid or 24 mg SA daily	6-8 hr	+	Hepatic and renal

Adapted from *Physicians' desk reference*, ed 62, Montvale, NJ, 2008, Thomson PDR.

BASIC INFORMATION

DEFINITION

Milk-alkali syndrome is the consumption of large amounts of calcium and alkali, resulting in the triad of hypercalcemia, metabolic alkalosis, and renal insufficiency.

SYNONYMS

Burnett's syndrome (acute form)
Cope's syndrome (subacute form)

ICD-9CM CODES
275.42 Milk-alkali syndrome
ICD-10CM CODES
E83.5 Disorders of calcium metabolism

EPIDEMIOLOGY & DEMOGRAPHICS

In the early 20th century the milk-alkali syndrome was associated with an antacid regimen created by F.W. Sippy that included large amounts of calcium and bicarbonate. With the development of more effective and less toxic treatments, the syndrome virtually disappeared. Since the 1980s, however, there has been a small resurgence of hypercalcemia associated with use of calcium-containing products for the prevention of osteoporosis and the use of calcium bicarbonate rather than aluminum bicarbonate in patients with chronic renal failure. The term milk-alkali syndrome has been used for these more modern cases. The milk-alkali syndrome was the third leading cause of hypercalcemia (12%) in a review of hypercalcemia in hospitalized patients from 1990 to 1993.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Asymptomatic hypercalcemia:
  1. Less than half of cases are detected by an incidental finding of hypercalcemia and occasionally renal failure.
- Symptomatic hypercalcemia:
  1. Symptoms: nausea, vomiting, anorexia, fatigue, vague abdominal pain, nephrolithiasis- and pancreatitis-related pain, constipation, myalgia, confusion, and psychosis. In more chronic cases polyuria and polydipsia may be reported.
  2. Physical examination and further testing: mental status changes such as anxiety, depression, and cognitive dysfunction; shortened QT interval.

ETIOLOGY

Overconsumption of supplemental calcium bicarbonate with reported ranges of 2.5 to 20 g/day, particularly when associated with volume depletion, renal insufficiency, or use of hydrochlorothiazide or calcium-containing substances.

Betel nut chewing, a practice in Asia and the South Pacific, has been associated with a milk-alkali syndrome. Betel nuts are prepared with a compound that can be converted to calcium carbonate.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Hypercalcemia secondary to other causes, including hyperparathyroidism and malignancy

LABORATORY TESTS

- Elevated plasma calcium (wide variation reported).
- Renal insufficiency.
- Elevated plasma bicarbonate and arterial pH, metabolic alkalosis.
- Parathyroid hormone, which is usually suppressed with milk-alkali syndrome, may be elevated, particularly if checked after treatment has begun.
- Phosphate level is variable.

TABLE EM1-17 Potential Sources of Alkali

Alkali/Alkali Precursor	Source
Bicarbonate	$NaHCO_3$: pills, intravenous solutions Proprietary brands, e.g., Alka Seltzer Baking soda $KHCO_3$: pills, oral solutions
Lactate	Ringer's solution, peritoneal dialysis solutions
Acetate Glutamate Propionate	Parenteral nutrition
Citrate	Blood products, plasma exchange, K^+ supplements, alkalinizing agents
Calcium compounds (alkalinizing effect minimal when given by mouth) Acetate Citrate Carbonate	Calcium supplements, phosphate binders

From Johnson RJ, Feehally J: *Comprehensive clinical nephrology,* ed 2, St Louis, 2000, Mosby.

TREATMENT

NONPHARMACOLOGIC THERAPY

Hemodialysis has been indicated for some patients with significant renal failure.

ACUTE GENERAL Rx

- Discontinuation of calcium bicarbonate supplements.
- Aggressive hydration and furosemide if symptomatic hypercalcemia.
- Monitor for rebound hypocalcemia as a result of elevation of parathyroid hormone with treatment.
- Patient education regarding appropriate calcium supplementation. Standard over-the-counter calcium supplements and some antacids contain calcium carbonate.

PROGNOSIS

Hypercalcemia and symptoms resolve with withdrawal of excess calcium supplementation and treatment of hypercalcemia. Acute cases typically resolve in 1 to 2 days while chronic cases will take longer. Patients initially presenting with renal failure may have residual renal insufficiency.

DISPOSITION

Treatment is determined by degree of hypercalcemia and symptoms. Hospital admission is required for patients who require IV hydration and other intensive treatments for hypercalcemia.

REFERRAL

Differentiation from hyperparathyroidism can be difficult and may require the assistance of an endocrinologist. Referral to a nutritionist is generally not required because the excess calcium is from nutritional supplements rather than dietary factors.

PEARLS & CONSIDERATIONS

COMMENTS

Detailed history of dietary supplements and over-the-counter medications (see Table EM1-17) can provide the most important clues. Many patients do not list dietary supplements as a medication.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **MICHELLE S. ANVAR, M.D.**

SUGGESTED READINGS

Abreo K et al.: The milk-alkali syndrome: a reversible form of acute renal failure, *Arch Intern Med* 153:1005, 1993.

Beall DP et al.: Milk-alkali syndrome: a historical review and description of the modern version of the syndrome, *Am J Med Sci* 331(5):233, 2006.

Felsenfeld AJ et al.: Milk-alkali syndrome and the dynamics of calcium homeostasis, *Clin Am J Soc Nephrol* 1:641–654, 2009.

Medarov B: Milk-alkali syndrome, *Mayo Clin Proc* 84(3):261–267, 2009.

Picolos MK et al.: Milk-alkali syndrome is a major cause of hypercalcaemia among non-end-stage renal disease (non-ESRD) in patients, *Clin Endocrinol* 63(5):566, 2005.

Sippy BW: Gastric and duodenal ulcer: medical cure by an efficient removal of gastric juice corrosion, *JAMA* 64:1625, 1915.

Mitral Regurgitation PTG EBM

BASIC INFORMATION

DEFINITION

Mitral regurgitation (MR) is retrograde blood flow into the left atrium resulting from an incompetent mitral valve. This condition can lead to left ventricular (LV) failure as well as increased left atrial and pulmonary pressures, with consequent pulmonary hypertension and right heart failure.

SYNONYMS

Mitral insufficiency
MR

ICD-9CM CODES
424.0 Mitral regurgitation
ICD-10CM CODES
I34.0 Nonrheumatic mitral (valve) insufficiency
I05.1 Rheumatic mitral insufficiency
I05.9 Mitral valve disease, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

The incidence of MR has increased over the past 30 yr; however, this may be due to increasing availability of echocardiography and MR diagnosis rather than any real increase in the prevalence of this condition.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Holosystolic, high-pitched, "blowing" murmur at apex with radiation to base, left axilla, or back; there is a poor correlation between the intensity of the systolic murmur and the degree of regurgitation. However, an early diastolic to mid-diastolic rumble (pseudomitral stenosis) suggests severe MR.
- The murmur of acute MR (e.g., from papillary muscle rupture) can be very soft or inaudible due to a large regurgitant volume entering a noncompliant left atrium, leading to an acute rise in left atrial pressure and thus lack of significant gradient for an audible murmur.
- Hyperdynamic apex, sometimes with palpable LV lift and apical thrill.
- Many patients with mild to moderate MR will remain asymptomatic and without evidence of hemodynamic compromise for years.
- Diminished S1, reflecting failure of valve leaflets to coapt completely, widely split S2 (decreased LV ejection time results in early A2) and presence of an S3
- Symptomatic patients with MR generally present with the following:
  1. Symptoms suggestive of heart failure (fatigue, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema)
  2. Hemoptysis (caused by pulmonary hypertension)
  3. Atrial fibrillation

ETIOLOGY

Primary MR
- Idiopathic myxomatous degeneration of the mitral valve, mitral valve prolapse (most common cause of MR in industrialized countries)
- Papillary muscle dysfunction or rupture (typically as a result of an inferior wall myocardial infarction)
- Ruptured chordae tendineae
- Infective endocarditis
- Calcified mitral valve annulus
- Rheumatic valvulitis (may be combined with mitral stenosis; common in developing countries)
- Systemic lupus erythematosus (Libman-Sacks endocarditis)
- Drugs: fenfluramine, dexfenfluramine, pergolide, cabergoline
- Congenital cleft valve
- Ischemic mitral regurgitation due to papillary muscle dysfunction from multivessel CAD

Secondary MR
- Hypertrophic cardiomyopathy
- LV dilation (e.g., secondary to dilated cardiomyopathy)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hypertrophic cardiomyopathy
- Tricuspid regurgitation
- Aortic stenosis
- Aortic sclerosis
- Ventricular septal defect
- Atrial septal defect

WORKUP

- Diagnostic workup consists of echocardiography, ECG, and chest radiograph; cardiac catheterization sometimes needed to confirm severity of the disease.
- Recent studies suggest that in patients with severe asymptomatic MR and normal LV function, elevations of brain natriuretic peptide (BNP) >105 pg/ml have an independent and additive prognostic value that may identify patients at high risk and aid in the selection of patients for early surgery.

IMAGING STUDIES

- Echocardiography (Fig. M1-30): dilated left atrium, hyperdynamic left ventricle (erratic motion of the leaflet is seen in patients with ruptured chordae tendineae); color flow Doppler will show evidence of MR. The most important aspect of the echocardiographic examination is the quantification of the severity of MR (Table M1-18), LV systolic performance, and estimated right ventricular (RV) systolic pressure vena contracta width >0.6 cm, regurgitant volume >60 ml, regurgitant orifice area >0.40 cm^2 by PISA (proximal isovelocity surface area), and systolic pulmonary vein flow reversal are all echocardiographic criteria of severe MR.
- Chest x-ray:
  1. Left atrial enlargement, LV enlargement
  2. Possible pulmonary congestion, although most often normal

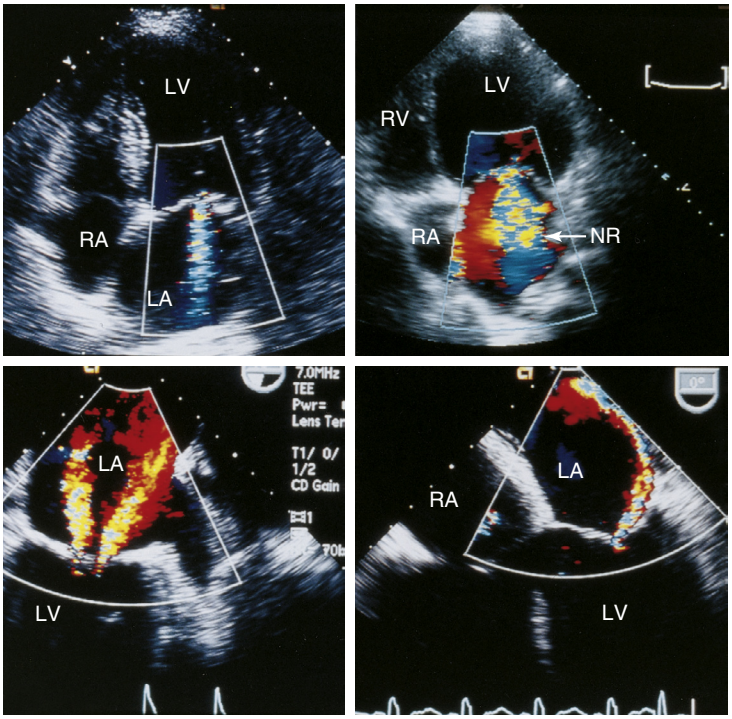

FIGURE M1-30 Mitral regurgitation. Four panels depicting varying degrees of mitral regurgitation; the two *top panels* are apical four-chamber transthoracic views showing, on the *left,* mild mitral regurgitation and, on the *right,* moderate to severe mitral regurgitation. On the *left,* note the relatively narrow jet directed from the tips of the mitral valve toward the posterior left atrial wall. On the right, note the larger jet, filling approximately 40% of the left atrial cavity. The two *bottom panels* are transesophageal echocardiograms. On the *left,* note the mitral regurgitation occurring in two discrete jets and, on the *right,* the highly eccentric jet, which courses along the extreme lateral wall of the left atrium. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. (From Zipes DP et al [eds]: *Braunwald's heart disease*, ed 7, Philadelphia, 2005, Saunders.)

TABLE M1-18 Mitral Regurgitation Severity*

	(Mild)	II	III	IV (Severe)
MR = jet (%LA)	<15	15-30	35-50	>50
Spectral Doppler	Faint	—	—	Dense
Vena contracta	<3 mm	—	—	>6 mm
Pulmonary vein flow	S > D	—	—	Systolic reversed
RV (ml)	<30	30-44	45-59	≥60
ERO (cm^2)	<0.2	0.2-0.29	0.3-0.39	≥0.40
PISA	Small	—	—	Large

D, Antegrade flow in diastole; *ERO,* effective regurgitant orifice; *%LA,* percentage of left atrial area encompassed by the *MR* jet with color flow Doppler; *MR,* mitral regurgitation; *PISA,* proximal isovelocity surface area; *RV,* regurgitant volume; *S,* antegrade flow in systole.

*For some parameters, the observation is valid at the extremes of MR severity and there may be marked overlap in intermediate (grades II, III) MR. In these instances, no value is presented.

From Zipes DP et al (eds): *Braunwald's heart disease,* ed 7, Philadelphia, 2005, Saunders and the 2003 American Society of Echocardiography Guidelines.

- ECG:
  1. Left atrial enlargement
  2. LV hypertrophy
  3. Atrial fibrillation
- Cardiac catheterization: to confirm severity of MR, or to rule out presence of coronary artery disease in patients being evaluated for surgical replacement
- Can consider cardiac MRI in cases where echocardiography is limited or LV function/dimensions are borderline, or when clinical condition and echocardiographic findings are discordant.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Salt restriction

ACUTE GENERAL Rx

- Medical: medical therapy is primarily directed toward treatment of the source or its complications (e.g., atrial fibrillation, ischemic heart disease, infective endocarditis, hypertension, and heart failure).
  1. The utility of afterload reduction (to decrease the regurgitant fraction and to increase cardiac output) depends upon the etiology of MR and the administration of afterload reducers. In acute MR, intravenous nitroprusside has shown some utility. Long-term use of oral afterload reducers (e.g., ACE inhibitors or angiotensin receptor blockers [ARBs]) do not slow the progression of mitral regurgitation, and their use should be only for other indications such as hypertension and LV dysfunction.
  2. Control ventricular response only if atrial fibrillation with rapid ventricular response is present.
  3. Anticoagulants if atrial fibrillation occurs.
- Surgery: Surgery is the only definitive treatment for MR. Although no randomized trial of mitral valve repair vs. replacement exists, repair is favored over replacement in degenerative mitral valve disease due to its lower perioperative risk, improved event-free survival, freedom from complications of prosthetic valves, and better postoperative LV function. It is a class I indication in patients with (Fig. M1-31):
  1. Acute severe MR
  2. Symptomatic patients with severe primary MR despite optimal medical therapy and LVEF >30%, LV dilation, severe MR by echo criteria
  3. Asymptomatic patients with severe MR but with evidence of declining LV function (EF 30% to 60%) or progressive dilation (LV at end-systole >40 mm)
     - Concomitant mitral valve repair or MVR is indicated in patients with chronic severe primary MR undergoing cardiac surgery for other indications
- Surgery is a class IIa (reasonable) recommendation in:
  1. Severe MR with new-onset atrial fibrillation, even if asymptomatic.
  2. Asymptomatic severe MR with pulmonary hypertension (≥50 mm Hg at rest or ≥60 mm Hg during exercise).
  3. Asymptomatic severe MR secondary to flail leaflet.
  4. A recent study of early surgical intervention for severe MR secondary to a flail leaflet in patients with asymptomatic disease shows greater long-term survival and reduced rates of heart failure when compared with medical therapy alone.
     - Asymptomatic severe MR with preserved LVEF (>60%) and size (<40 mm in end-systole) in whom the likelihood of successful repair without residual MR is >95% and operative mortality is <1%.
  5. Surgery is a class IIb recommendation in symptomatic severe MR with severe LV dysfunction or dilatation (LVEF <30% or LV at end-systole >55 mm, respectively) in whom LV dysfunction is not the primary cause for the MR as well as functional MR where it is secondary to LV dysfunction, but in this group there should be NYHA Class III-IV symptoms.
- Quantitative grading of MR is a powerful predictor of the clinical outcome of asymptomatic MR. In general, patients with regurgitant orifice areas of ≥40 mm^2 should be considered for prompt surgery, whereas those with orifices between 20 and 39 mm^2 can be followed closely.
- Percutaneous mitral valve repair methods are currently being investigated, and the MitraClip device is now FDA approved for use in patients with significant symptomatic degenerative MR (>3+) who have too high a risk for surgery. Early data have not demonstrated a significant efficacy in MR reduction compared with surgical replacement; however, it has been shown to improve NYHA functional class and quality of life measures.
- Ischemic MR has been a source of controversy. There has been recent debate as to whether moderate or greater MR should be fixed at the time of revascularization with CABG. A recent NEJM 2014 study looked at moderate ischemic MR and randomized patients to MV repair + CABG versus CABG alone. There was no increase in LV function improvement between groups and, while there was reduced incidence of moderate to severe MR following repair, there were increased number of untoward events like longer bypass time, longer hospitalizations, and more neurologic events. There was no difference in major adverse cardiac or cerebrovascular events deaths, readmissions, or quality of life at one year. Currently the evidence is not in favor of fixing moderate ischemic MR.

DISPOSITION

Prognosis is generally good unless there is significant impairment of left ventricular function or significantly elevated pulmonary artery pressures. Most patients remain asymptomatic for many years (average interval from diagnosis to onset of symptoms is 16 yr). In patients with chronic severe MR, MR is commonly progressive, with onset of other symptoms or left ventricular dysfunction within 6-10 yr. However surgery should be advised well before the onset of symptoms in case of worsening LVEF and LV systolic dimensions and presence of pulmonary hypertension or atrial fibrillation, all of which are poor prognostic signs.

REFERRAL

- Surgical referral in selected patients (see "Acute General Rx"). Emergency surgery is usually necessary in patients with acute MR caused by ruptured papillary muscle or chordae tendineae after myocardial infarction.
- Mitral valve repair can also be accomplished with an investigational procedure that involves the percutaneous implantation of a clip that grasps and approximates the edges of the mitral leaflets at the origin of the regurgitant jet. Preliminary data reveals that although percutaneous repair is less effective at reducing MR than conventional surgery, the procedure

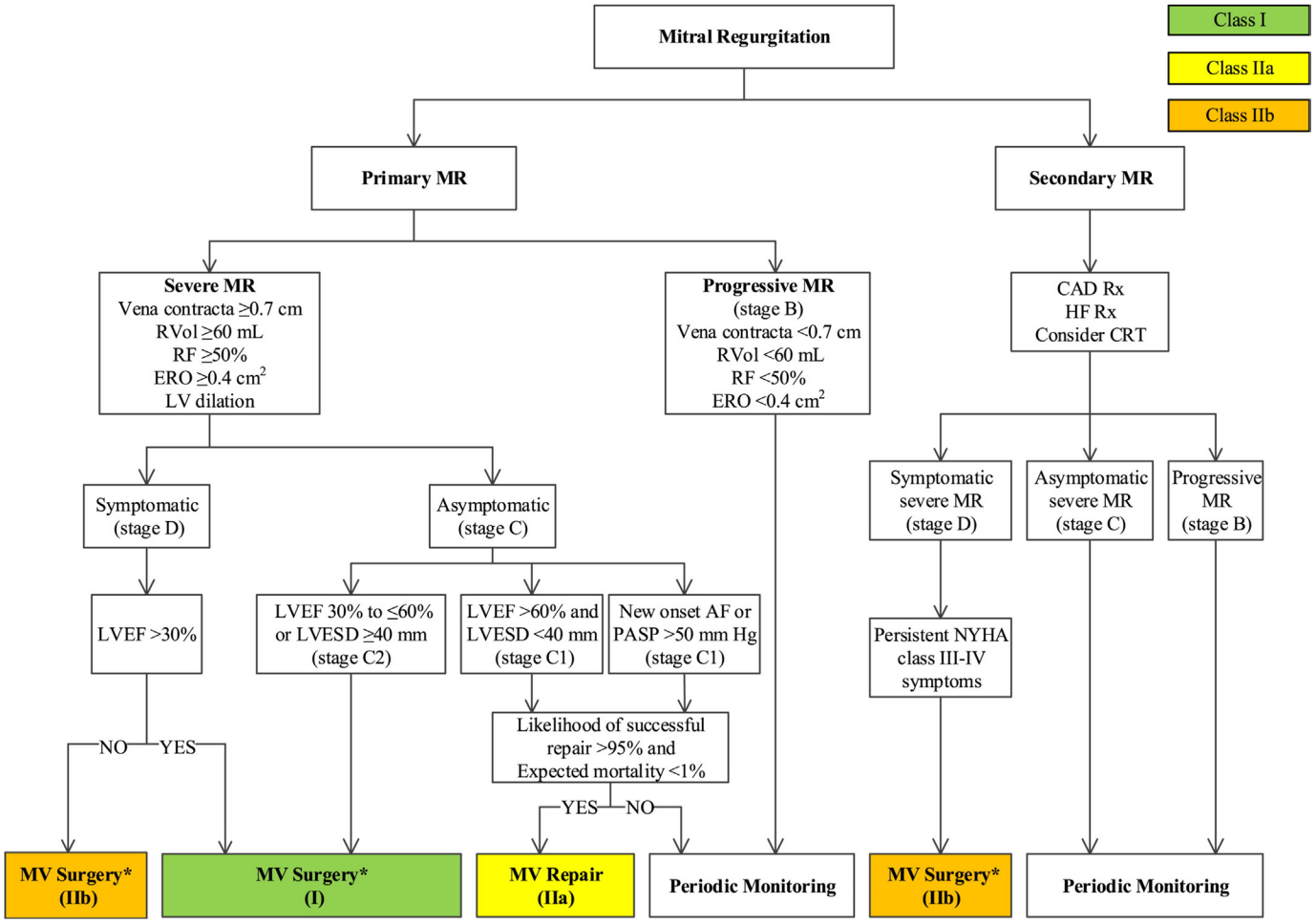

FIGURE M1-31 Indications for Surgery for MR. *Mitral valve repair is preferred over MVR when possible. *AF,* Atrial fibrillation; *CAD,* coronary artery disease; *CRT,* cardiac resynchronization therapy; *ERO,* effective regurgitant orifice; *HF,* heart failure; *LV,* left ventricular; *LVEF,* left ventricular ejection fraction; *LVESD,* left ventricular end-systolic dimension; *MR,* mitral regurgitation, *MV,* mitral valve; *MVR,* mitral valve replacement; *NYHA,* New York Heart Association; *PASP,* pulmonary artery systolic pressure; *RF,* regurgitant fraction; *RVol,* regurgitant volume; and *Rx,* therapy. (From Nishimura R.A.; et al. ACC/AHA guidelines for the management of patients with valvular heart disease, J Am Coll Cardiol 2014;63(22):e57-e185.) doi:10.1016/j.jacc.2014.02.536.)

is associated with superior safety and similar improvements in clinical outcomes.

PEARLS & CONSIDERATIONS

COMMENTS

- Although vasodilators and other agents should be used to treat hypertension in patients with severe mitral regurgitation, there is no evidence that they will delay the need for eventual valve surgery, which is the definitive treatment for severe MR.
- In 2007, the AHA guidelines for prevention of infectious endocarditis were revised and routine antibiotic prophylaxis to undergo dental or other invasive procedures is no longer recommended, unless the patient has prior endocarditis.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Mitral Regurgitation (Patient Information)

AUTHOR: **SHALINE D. RAO, M.D.**

EVIDENCE

Abstract[1]

Background:
Functional mitral regurgitation (MR) is a common finding in heart failure patients with dilated cardiomyopathy and has important prognostic implications. However, the increased operative risk of these patients may result in low referral or high denial rate for mitral valve surgery. Cardiac resynchronization therapy (CRT) has been shown to have a favorable effect on MR. Aims of this study were to (1) evaluate CRT as a therapeutic option in heart failure patients with functional MR and high operative risk and (2) investigate the effect of MR improvement after CRT on prognosis.

Methods and Results:
A total of 98 consecutive patients with moderate-severe functional MR and high operative risk underwent CRT according to current guidelines. Echocardiography was performed at baseline and 6-month follow-up; severity of MR was graded according to a multiparametric approach. Significant improvement of MR was defined as a reduction ≥1 grade. All-cause mortality was assessed during follow-up (median 32 [range 6.0 to 116] months). Thirteen patients (13%) died before 6-month follow-up. In the remaining 85 patients, significant reduction in MR was observed in all evaluated parameters. In particular, 42 patients (49%) improved ≥1 grade of MR and were considered MR improvers. Survival was superior in MR improvers compared with MR nonimprovers (log rank P<0.001). Mitral regurgitation improvement was an independent prognostic factor for survival (hazard ratio 0.35, confidence interval 0.13 to 0.94; $P = 0.043$).

Conclusions:
Cardiac resynchronization therapy is a potential therapeutic option in heart failure patients with moderate-severe functional MR and high risk for surgery. Improvement in MR results in superior survival after CRT. Ⓐ

Abstract[2]

Background:
Mitral-valve repair can be accomplished with an investigational procedure that involves the percutaneous implantation of a clip that grasps and approximates the edges of the mitral leaflets at the origin of the regurgitant jet.

Methods:
We randomly assigned 279 patients with moderately severe or severe (grade 3 + or 4 +) mitral regurgitation in a 2:1 ratio to undergo either percutaneous repair or conventional surgery for repair or replacement of the mitral valve. The primary composite end point for efficacy was freedom from death, from surgery for mitral valve dysfunction, and from grade 3 + or 4 + mitral regurgitation at 12 months. The primary safety end point was a composite of major adverse events within 30 days.

Results:
At 12 months, the rates of the primary end point for efficacy were 55% in the percutaneous-repair group and 73% in the surgery group (P = 0.007). The respective rates of the components of the primary end point were as follows: death, 6% in each group; surgery for mitral valve dysfunction, 20% versus 2%; and grade 3 + or 4 + mitral regurgitation, 21% versus 20%. Major adverse events occurred in 15% of patients in the percutaneous repair group and 48% of patients in the surgery group at 30 days (P <0.001). At 12 months, both groups had improved left ventricular size, New York Heart Association functional class, and quality-of-life measures, as compared with baseline.

Conclusions:
Although percutaneous repair was less effective at reducing mitral regurgitation than conventional surgery, the procedure was associated with superior safety and similar improvements in clinical outcomes. (Funded by Abbott Vascular; EVEREST II ClinicalTrials.gov number, NCT00209274.) Ⓐ

Abstract[3]

Background:
Ischemic mitral regurgitation is associated with increased mortality and morbidity. For surgical patients with moderate regurgitation, the benefits of adding mitral valve repair to coronary artery bypass grafting (CABG) are uncertain.

Methods:
We randomly assigned 301 patients with moderate ischemic mitral regurgitation to CABG alone or CABG plus mitral valve repair (combined procedure). The primary end point was the left ventricular end-systolic volume index (LVESVI), a measure of left ventricular remodeling, at 1 yr. This end point was assessed with the use of a Wilcoxon rank sum test in which deaths were categorized as the lowest LVESVI rank.

Results:
At 1 yr, the mean LVESVI among surviving patients was 46.1 ± 22.4 ml per m^2 of body-surface area in the CABG-alone group and 49.6 ± 31.5 ml per m^2 in the combined-procedure group (mean change from baseline, −9.4 and −9.3 ml per m^2, respectively). The rate of death was 6.7% in the combined-procedure group and 7.3% in the CABG-alone group (hazard ratio with mitral valve repair, 0.90; 95% confidence interval, 0.38 to 2.12; P = 0.81). The rank-based assessment of LVESVI at 1 year (incorporating deaths) showed no significant between-group difference (z score, 0.50; P = 0.61). The addition of mitral valve repair was associated with a longer bypass time (P <0.001), a longer hospital stay after surgery (P = 0.002), and more neurologic events (P = 0.03). Moderate or severe mitral regurgitation was less common in the combined-procedure group than in the CABG-alone group (11.2% vs. 31.0%, P <0.001). There were no significant between-group differences in major adverse cardiac or cerebrovascular events, deaths, readmissions, functional status, or quality of life at 1 year.

Conclusions:
In patients with moderate ischemic mitral regurgitation, the addition of mitral valve repair to CABG did not result in a higher degree of left ventricular reverse remodeling. Mitral valve repair was associated with a reduced prevalence of moderate or severe mitral regurgitation, but an increased number of untoward events. Thus, at 1 yr, this trial did not show a clinically meaningful advantage of adding mitral valve repair to CABG. Longer-term follow-up may determine whether the lower prevalence of mitral regurgitation translates into a net clinical benefit.

(Funded by the National Institutes of Health and the Canadian Institutes of Health Research; ClinicalTrials.gov number, NCT00806988.) Ⓐ

Abstract[4]

Background:
Ischemic mitral regurgitation is associated with a substantial risk of death. Practice guidelines recommend surgery for patients with a severe form of this condition, but acknowledge that the supporting evidence for repair or replacement is limited.

Methods:
We randomly assigned 251 patients with severe ischemic mitral regurgitation to undergo either mitral valve repair or chordal-sparing replacement in order to evaluate efficacy and safety. The primary end point was the left ventricular end-systolic volume index (LVESVI) at 12 months, as assessed with the use of a Wilcoxon rank sum test in which deaths were categorized below the lowest LVESVI rank.

Results:
At 12 months, the mean LVESVI among surviving patients was 54.6 ± 25.0 ml per square meter of body surface area in the repair group and 60.7 ± 31.5 ml per m^2 in the replacement group (mean change from baseline, −6.6 and −6.8 mL per m^2, respectively).

The rate of death was 14.3% in the repair group and 17.6% in the replacement group (hazard ratio with repair, 0.79; 95% confidence interval, 0.42 to 1.47; P = 0.45 by the log-rank test). There was no significant between-group difference in LVESVI after adjustment for death (z score, 1.33; P = 0.18). The rate of moderate or severe recurrence of mitral regurgitation at 12 months was higher in the repair group than in the replacement group (32.6% versus 2.3%, P <0.001). There were no significant between-group differences in the rate of a composite of major adverse cardiac or cerebrovascular events, in functional status, or in quality of life at 12 months.

Conclusions:
We observed no significant difference in left ventricular reverse remodeling or survival at 12 months between patients who underwent

mitral valve repair and those who underwent mitral valve replacement. Replacement provided a more durable correction of mitral regurgitation, but there was no significant between-group difference in clinical outcomes.
(Funded by the National Institutes of Health and the Canadian Institutes of Health; ClinicalTrials.gov number, NCT00807040.) Ⓐ

Evidence-Based References

Van Bommel RJ et al.: Cardiac resynchronization therapy as a therapeutic option in patients with moderate-severe functional mitral regurgitation and high operative risk, *Circulation* 124:912–919, 2011. Ⓐ

Feldman T et al.: for the EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation, *N Engl J Med* 364:1395–1406, 2011. Ⓐ

Smith PK, Michler RE, et al.: Surgical treatment of moderate ischemic mitral regurgitation, *N Engl J Med*, 2014 Nov 18 (Epub ahead of print) Ⓐ

Acker MA, for the CTSN: Mitral valve repair versus replacement for severe ischemic mitral regurgitation, *N Engl J Med* 370:23–32, 2014. Ⓐ

SUGGESTED READINGS

Acker MA et al.: Mitral-valve repair versus replacement for severe ischemic mitral regurgitation, *N Engl J Med* 370:23–32, 2014.

Nishimura RA et al.: ACC/AHA guidelines for the management of patients with valvular heart disease, *J Am Coll Cardiol* 63(22):e57–e185, 2014.

Enriquez-Sarano M et al.: Quantitative determinants of the outcome of asymptomatic mitral regurgitation, *N Engl J Med* 352:875, 2005.

Feldman T et al.: Percutaneous repair of surgery for mitral regurgitation, *N Engl J Med* 364:1395–1406, 2011.

Foster E: Mitral regurgitation due to degenerative mitral valve disease, *N Engl J Med* 363:156–165, 2010.

Otto CM, Salerno CT: Timing of surgery in asymptomatic mitral regurgitation, *N Engl J Med 352* 928, 2005.

Pizarro R et al.: Prospective validation of the prognostic usefulness of brain natriuretic peptide in asymptomatic patients with chronic severe mitral regurgitation, *J Am Coll Cardiol* 54(12):1099–1106, 2009.

Suri RM et al.: Association between early surgical intervention vs watchful waiting and outcomes for mitral regurgitation due to flail mitral valve leaflets, *JAMA* 310(6):609–616, 2013.

BASIC INFORMATION

DEFINITION

Mitral stenosis is a narrowing of the mitral valve orifice that prevents proper opening during diastole and obstruction of blood flow from the left atrium to the left ventricle. Due to thickening of the leaflets there is restricted movement. The cross section of a normal orifice measures 4 to 6 cm^2. Symptoms usually develop with exercise when the orifice measures <2.5 cm^2, and symptoms may develop at rest when the orifice is <1.5 cm^2.

SYNONYMS

MS

ICD-9CM CODES
394.0 Mitral stenosis
ICD-10CM CODES
I05.0 Mitral stenosis
I05.2 Mitral stenosis with insufficiency

EPIDEMIOLOGY & DEMOGRAPHICS

- The predominant cause of mitral stenosis is rheumatic heart disease; however, the occurrence of mitral valve stenosis has decreased worldwide over the past 30 yr (particularly in developed countries) as a result of declining incidence of rheumatic fever due to appropriate antibiotic use.
- Rheumatic heart disease has a predilection for the mitral valve, aortic valve, and to some extent the tricuspid valve.
- The incidence of MS is higher in women (2:1 female-to-male ratio).
- There is high prevalence of rheumatic heart disease in developing countries.
- Outbreaks of rheumatic fever in the U.S. are due to increased virulence of a streptococcal strain or enhanced immigration from where rheumatic heart disease is prevalent.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Dyspnea is the most common symptom along with fatigue and decreased exercise capacity. These symptoms occur due to an inability to increase cardiac output, especially with exercise, and elevated pulmonary capillary wedge pressures, with resultant increase in pulmonary artery pressures.
- The left ventricle is unaffected in pure MS; however, MS often coexists with mitral regurgitation and occasionally with aortic valve dysfunction, both of which can cause left ventricular dysfunction.
- "Mitral facies" which are pinkish-purple patches on the cheek due to low cardiac output and vasoconstriction, usually indicate severe MS.
- Paroxysmal nocturnal dyspnea (PND) and orthopnea secondary to elevated left atrial pressure may occur.
- Acute pulmonary edema may occur after an increase in flow across the mitral valve secondary to an increase in cardiac output or heart rate (exertion, tachyarrhythmias, fever, anemia, etc.).
- Pulmonary hypertension that results from chronically elevated pulmonary capillary wedge pressures can lead to right ventricular (RV) dysfunction and signs and symptoms of right heart failure (hepatomegaly, pulsatile liver, peripheral edema, ascites).
- The left ventricle is typically "protected" in mitral stenosis and exists in a low-pressure state.
- Hemoptysis can be present secondary to rupture of thin-walled dilated bronchial veins due to an abrupt increase in left atrial pressure.
- Systemic embolic events are caused by left atrial thrombi. These are associated with atrial fibrillation 80% of the time, since mitral stenosis leads to left atrial enlargement, which is a predisposing factor to atrial arrhythmias.
- Atrial fibrillation is more prevalent in patients with more severe MS, increasing age, and other valvular abnormalities.
- Chest pain can be caused by RV pressure overload and/or concomitant coronary artery disease in up to 15% of patients.
- Irregularly irregular pulse caused by atrial fibrillation.
- Loud first heart sound (S_1) caused by delayed valve closure preceded by an opening snap and rapid rising left ventricular (LV) pressure.
- A low-pitched rumbling diastolic murmur heard best at the apex. The intensity of the murmur is not related to the severity of the stenosis, but the duration is holodiastolic in severe MS.
- An opening snap (OS) caused by tensing of the valve leaflets after the cusps have opened completely. The OS follows S_2 by 0.03 to 0.14 sec, and the shorter the S_2-OS interval, the more severe the MS, due to the increasing left atrial pressures.
- Prominent A wave on the pulmonary capillary wedge pressure tracing. This is homologous to the prominent A wave seen in systemic venous pressure tracings with tricuspid stenosis.
- A diastolic thrill may be palpable at the apex, especially with the patient in the left lateral recumbent position.
- An RV lift may be palpable at the left sternal border secondary to RV hypertrophy and pulmonary hypertension.
- An accentuated P_2 and/or a soft, early diastolic decrescendo murmur *(Graham Steell murmur)* caused by pulmonary regurgitation may be present in patients with pulmonary hypertension (not specific for mitral stenosis).
- Hoarseness due to the enlargement of the left atrium compressing the recurrent laryngeal nerve.
- Straightening of the left heart border seen on chest radiography indicative of left atrial enlargement.
- Fig. M1-32 shows schematic representations of LV, aortic, and left atrial (LA) pressures, showing normal relationships and alterations with mild and severe MS.

ETIOLOGY

- Rheumatic fever (RF) is the predominant cause of MS. RF causes thickening of the leaflet tips, commissure fusion, and chordal shortening and fusion. This leads to the classic doming of the leaflets in diastole due to fusion of the leaflet tips at the commisures. Rheumatic fever involves the leaflet tips first with progression toward the annulus. This is opposite of mitral annular calcification, which typically starts in the annulus and proceeds out to the leaflet tips, leading to mitral stenosis in severe cases.
- Congenital defect (parachute valve) has the usual two mitral leaflets, but the chordae, instead of diverging to insert into two papillary muscles, converge into one major papillary muscle, which allows little mobility of the leaflets, as in cor triatriatum, in which there is a thin membrane which obstructs the pulmonary vein flow and simulates mitral stenosis.
- Rare causes are severe mitral annular calcification usually seen in end-stage renal disease patients, endomyocardial fibroelastosis, malignant carcinoid syndrome, systemic lupus erythematosus, Whipple disease, Fabry disease, and rheumatoid arthritis.

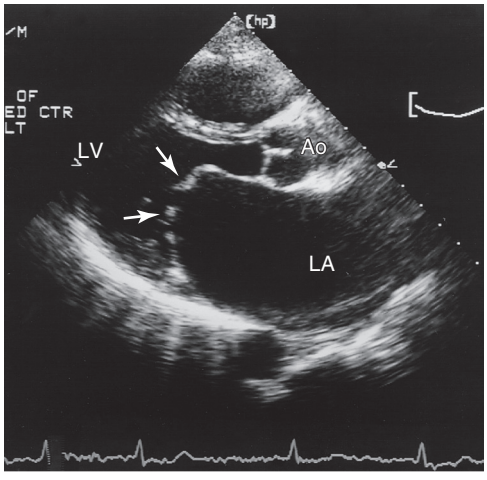

FIGURE M1-32 Mitral stenosis. Parasternal long-axis view of a patient with mitral stenosis and a pliable noncalcified mitral valve leaflet. Note the "doming" motion of the mitral valve leaflets *(arrows).* Valves with these morphologic features are excellent candidates for percutaneous balloon valvotomy. *Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle. (From Zipes DP et al [eds]: *Braunwald's heart disease,* ed 7, Philadelphia, 2005, Saunders.)

- Atrial septal defect in association with rheumatic mitral stenosis is termed Lutembacher syndrome.
- Medications: methysergide

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Left atrial myxoma
- Ball valve thrombus
- Other valvular abnormalities (e.g., tricuspid stenosis, mitral regurgitation)
- Atrial septal defect

WORKUP

Physical examination and echocardiography

IMAGING STUDIES

- Echocardiography (Fig. M1-33):
  1. Two-dimensional echocardiogram can measure valve area by direct planimetry or calculate it by the Doppler pressure half-time method (this may be inaccurate in patients with concomitant diastolic dysfunction or aortic insufficiency and in patients who have recently undergone mitral valvuloplasty) or the continuity equation can be used to calculate the valve area. A valve area less than 1 cm^2 is consistent with severe MS. The transmitral gradient can also be calculated. A mean gradient of >10 mm Hg indicates severe MS. 5-10 mm Hg is consistent with moderate MS, and 0-5 mm Hg is consistent with mild MS or no MS.
  2. Echocardiography will also show a markedly diminished E-to-F slope of the anterior mitral valve leaflet during diastole; there is also fusion of the commissures, resulting in "doming" of the leaflets during diastole.
  3. Grading of leaflet thickness, mobility, calcification, and subvalvular thickening (mitral valvuloplasty score) with a score of 0 to 4 for each characteristic can predict hemodynamic results and outcome of balloon mitral valvuloplasty (a low score of less than 8 is favorable for balloon valvuloplasty and a high score is unfavorable). A score above 8 would favor a surgical approach. In addition, mitral regurgitation that is greater than mild would preclude a balloon mitral valvuloplasty procedure.
  4. Doppler echocardiography can be used to assess for pulmonary hypertension and to give an estimate of the pulmonary artery systolic pressure at rest and with exercise.
  5. Patients with known mitral stenosis: a follow-up echocardiography is recommended to assess for pulmonary artery pressures and valve gradient. (mitral valve area <1.0 cm^2 yearly, mitral valve area <1.5 cm^2 1-2 yr, mitral valve area >1.5 cm^2 every 3-5 yr.
- Chest radiograph:
  1. Straightening of the left cardiac border caused by enlarged left atrium
  2. Left atrial enlargement on lateral chest radiograph
  3. Prominence of pulmonary arteries that indicates pulmonary hypertension
  4. Possible pulmonary congestion and edema (Kerley B lines)
- ECG:
  1. RV hypertrophy; right axis deviation caused by pulmonary hypertension
  2. Left atrial enlargement (broad, biphasic P waves in lead V1 and duration of P-waves >0.11 sec in lead II). This is termed "P-mitrale."
  3. Atrial fibrillation
- Cardiac catheterization:
  1. Allows the measurement of pulmonary artery pressure and transmitral pressure gradients at rest or with exercise (supine biking or raising weights with arms while lying supine).
  2. Allows the measurement of transmitral flow and calculation of the valve area.
  3. Is not routinely recommended for the evaluation of MS but is useful when the echocardiographic findings are nondiagnostic or discrepant with the clinical scenario.
  4. Cardiac catheterization in addition to echocardiography can be used to monitor the hemodynamics during a balloon mitral valvuloplasty procedure.

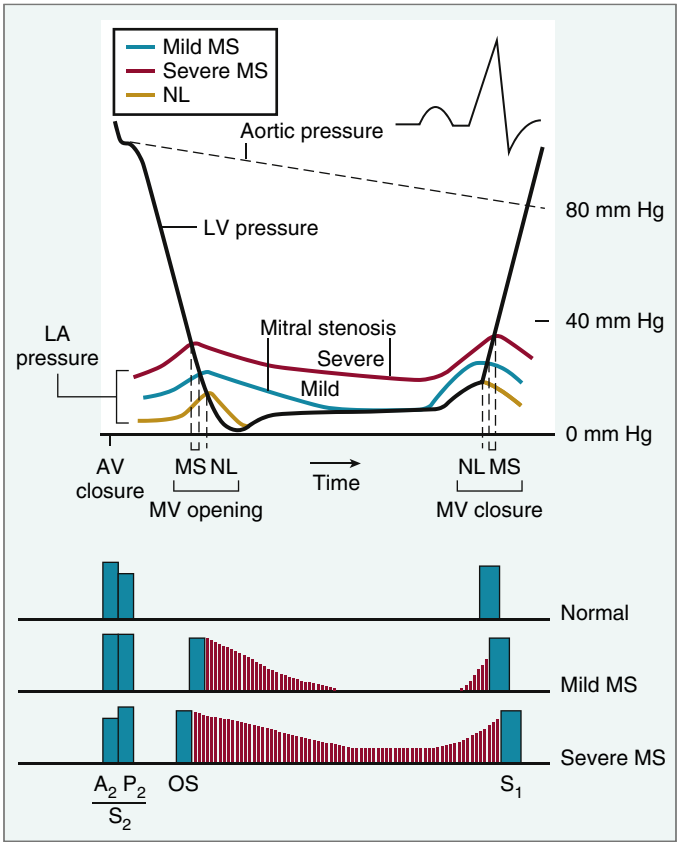

FIGURE M1-33 Schematic representation of LV, aortic, and left atrial (LA) pressures, showing normal relationships and alterations with mild and severe MS. Corresponding classic auscultatory signs of MS are shown at the bottom. The higher left atrial v wave of severe MS causes earlier pressure crossover and earlier MV opening, leading to a shorter time interval between aortic valve (AV) closure and the opening snap (OS). The higher left atrial end-diastolic pressure with severe MS also results in later closure of the mitral valve. With severe MS, the diastolic rumble becomes longer and there is accentuation of the pulmonic component (P_2) of the second heart sound (S_2) in relation to the aortic component (A_2). (From Bonow R.O.: *Heart disease,* 9th ed, Philadelphia, 2012, Saunders.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Decrease level of activity in symptomatic patients and salt restriction if pulmonary congestion is present.

ACUTE GENERAL Rx

- Medical:
  1. Anticoagulation for the prevention of systemic embolic events in patients with MS and:
     1. Atrial fibrillation
     2. Prior embolic event
     3. Documented left atrial thrombus or left atrial appendage thrombus
     4. Severe mitral stenosis if associated with severe left atrial enlargement and spontaneous echo contrast indicating stagnant blood flow (class 2b indication)

TABLE M1-19 Approaches to Mechanical Relief of Mitral Stenosis

Approach	Advantages	Disadvantages
Closed surgical valvotomy	Inexpensive Relatively simple Good hemodynamic results in selected patients Good long-term outcome	No direct visualization of valve Only feasible with flexible, noncalcified valves Contraindicated if MR >2+ Surgical procedure with general anesthesia
Open surgical valvotomy	Visualization of valve allows directed valvotomy Concurrent annuloplasty for MR is feasible	Best results with flexible, noncalcified valves Surgical procedure with general anesthesia
Valve replacement	Feasible in all patients regardless of extent of valve calcification or severity of MR	Surgical procedure with general anesthesia Effect of loss of annular-papillary muscle continuity on LV function Prosthetic valve Chronic anticoagulation
Balloon mitral valvotomy	Percutaneous approach Local anesthesia Good hemodynamic results in selected patients Good long-term outcome	No direct visualization of valve Only feasible with flexible, noncalcified valves Contraindicated if MR >2+

LV, Left ventricular; *MR,* mitral regurgitation.
From Otto CM: *Valvular heart disease*, ed 2, Philadelphia, 2004, Saunders.

2. Ventricular rate control (to increase diastolic filling period) with beta-blockers, non-dihydropyridine calcium channel blockers, or digitalis and aggressive treatment of tachyarrhythmias.
3. Treat congestive heart failure with loop diuretics and sodium restriction.
4. Antibiotic prophylaxis to prevent recurrent rheumatic fever is usually not indicated unless presence of high-risk features such as prior endocarditis, prosthetic heart valves, valvulopathy of the transplanted heart, and certain cases of cyanotic congenital heart disease. Pregnancy in females with advanced MS may be poorly tolerated due to the hemodynamic changes such as increased cardiac output. Whereas pregnant females with mild to moderate MS may tolerate pregnancy very well with medical therapy alone.
5. Pregnancy in females with advanced MS may be poorly tolerated due to the hemodynamic changes such as increased cardiac output. Whereas pregnant females with mild to moderate MS may tolerate pregnancy very well with medical therapy alone.

- Table M1-19 summarizes approaches to mechanical relief of mitral stenosis.
- Percutaneous balloon mitral valvotomy (BMV) is the therapy of choice for symptomatic patients with moderate to severe MS (valve area ≤1.5 cm^2) with a favorable valvuloplasty score, minimal or no mitral regurgitation and no left atrial thrombus. Balloon valvotomy is also indicated in asymptomatic patients with moderate to severe MS that has resulted in pulmonary artery pressures of 50 mm Hg at rest or 60 mm Hg with exercise. Percutaneous BMV is also considered the procedure of choice in pregnant women with rheumatic MS and in NYHA class 3 to 4 heart failure and/or unresponsive to adequate medical treatment. In addition, it is a reasonable option for patients who are at high risk for surgery even when their valve morphology is not ideal (class 2a indication).
- Surgical intervention is indicated for patients with moderate to severe symptomatic MS when BMV is not available or is contraindicated (valvuloplasty score greater than or equal to 8) or the valve is calcified, MR that is more than mild, there is presence of left atrial thrombus and when the surgical risk is acceptable. The surgical approaches include closed mitral valvotomy, open valvotomy and repair (preferred), and mitral valve replacement when repair is not possible.

DISPOSITION

- Prognosis is generally good except in patients with chronic pulmonary hypertension.
- Operative mortality rates for mitral valve replacement are 1% to 5% at most institutions.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Mitral Stenosis (Patient Information)

AUTHOR: **ARAVIND RAO KOKKIRALA, M.D.**

SUGGESTED READINGS

AHA/ACC Guidelines for the management of patients with valvular heart disease, *Circulation* 129:e521–e643, 2014.

Mitral Valve Prolapse PTG

BASIC INFORMATION

DEFINITION

Mitral valve prolapse (MVP) is the bulging of one or both of the mitral valve leaflets into the left atrium during systole. MVP syndrome refers to a constellation of MVP and associated symptoms (e.g., autonomic dysfunction, palpitations) or other physical abnormalities (e.g., pectus excavatum). Table M1-20 describes a classification of mitral valve prolapse.

SYNONYMS

MVP
Mitral click murmur syndrome
Barlow's syndrome

ICD-9CM CODES
424.0 Mitral valve disorders
394.9 Other and unspecified mitral valve diseases
ICD-10CM CODES
I34.1 Mitral valve prolapse
I34.0 Nonrheumatic mitral (valve) insufficiency

EPIDEMIOLOGY & DEMOGRAPHICS

- MVP can be found by echocardiogram in 1% to 4% of the general population, with some studies suggesting that it is more common in women than in men.
- Increased incidence is seen with autoimmune thyroid disorders, Ehlers-Danlos syndrome, Marfan's syndrome, osteogenesis imperfecta, pseudoxanthoma elasticum, pectus excavatum, anorexia nervosa, and bulimia.

TABLE M1-20 Classification of Mitral Valve Prolapse

Mitral Valve Prolapse Syndrome
- Younger age (20-50 yr)
- Predominantly female
- Click or click-murmur on physical examination
- Thin leaflets with systolic displacement on echocardiography
- Associated with low blood pressure, orthostatic hypotension, palpitations
- Benign long-term course

Myxomatous Mitral Valve Disease
- Older age (40-70 yr)
- Predominantly male
- Thickened, redundant valve leaflets
- Mitral regurgitation on physical exam and echocardiography
- High likelihood of progressive disease requiring mitral valve surgery

Secondary Mitral Valve Prolapse
- Marfan syndrome
- Hypertrophic cardiomyopathy
- Ehlers-Danlos syndrome
- Other connective tissue diseases

Modified from Otto CM: *Valvular Heart Disease,* ed 2, Philadelphia, 2004, WB Saunders, p. 369.

- Compared to men, women with MVP have less posterior prolapse (22% vs. 31%), less flail (2% vs. 8%), more leaflet thickening (32% vs. 28%), and less frequent severe mitral regurgitation (MR) (10% vs. 23%).
- Although MVP is more common in women than men, men more often develop severe regurgitation requiring surgical intervention.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Mid to late systolic click, heard best at the apex
- If regurgitation is present, a crescendo mid to late systolic murmur, may be heard that worsens with standing and Valsalva's maneuver
- Timing of click within the cardiac cycle varies with loading conditions within the left ventricle (i.e., may occur earlier with standing or Valsalva and later with squatting or expiration)
- May be associated with small anteroposterior chest diameter, scoliosis, pectus excavatum, or low BMI.
- Most patients with MVP are asymptomatic; symptoms (if present) consist primarily of chest pain, palpitations, fatigue, dyspnea, or and anxiety
- Neurologic abnormalities (e.g., transient ischemic attack [TIA] or stroke) are rare
- A spectrum of arrhythmias, mainly paroxysmal supraventricular tachycardia and atrial and ventricular premature beats, etc., is also observed with mitral valve prolapse. There is also an increased association with Wolff-Parkinson-White syndrome and QT prolongation

ETIOLOGY

- Myxomatous degeneration of connective tissue within mitral valve, usually involving multiple leaflet segments. In contrast, fibroelastic deficiency of single leaflet segment develops in elderly patients.
- Congenital deformity of mitral valve and supportive structures
- Secondary to other disorders of connective tissue such as Ehlers-Danlos, Marfan, or pseudoxanthoma elasticum; association with other connective tissue disorders suggests MVP result of defective embryogenesis in cells of mesenchymal origin

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other valvular abnormalities (especially mitral regurgitation [MR])
- Anxiety/panic disorders
- Pulmonary embolism
- Atypical chest pain

WORKUP

- Medical history and physical examination, with increased suspicion in patients with other findings of connective tissue disorder.
- Two or three-dimensional echocardiography in patients with a systolic click or murmur on careful auscultation.
- Cardiac MRI is an emerging tool for the evaluation and diagnosis of MVP but has not yet been independently validated.
- ECG is most often normal but may show nonspecific ST-T wave changes, prolonged QT interval, or prominent Q waves.

IMAGING STUDIES

Echocardiography (Fig. M1-34) shows one or more leaflets prolapsing >2 mm into the left atrium during systole in a long axis view. Mitral leaflets may be thickened (>5 mm). MR is typically present, though sometimes only during exertion. If moderate or severe MR is present, findings of dilated left atrium, LV dilation and/or dysfunction, and elevated estimated RV systolic pressures may also be present. There is an increased incidence of secundum-type atrial septal defects (ASDs) in patients with MVP, which may also be identified with echocardiography.

TREATMENT

NONPHARMACOLOGIC THERAPY

Avoidance of stimulants (e.g., caffeine, nicotine) in patients with palpitations. Sometimes, reassurance is sufficient to reduce the severity of symptoms in many patients.

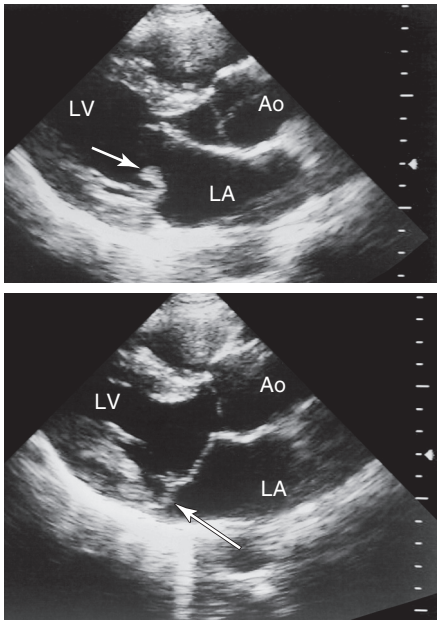

FIGURE M1-34 Mitral valve prolapse. Parasternal long-axis view in diastole *(top)* and systole *(bottom)* in a patient with mitral valve prolapse and myxomatous changes. In the *upper panel,* note the open mitral valve and the diffuse thickening of the posterior mitral valve leaflet *(arrow).* The *lower panel* was recorded in systole. Note that both leaflets prolapse behind the plane of the mitral valve annulus. The prolapse of the posterior leaflet is somewhat more prominent *(arrow). Ao,* Aorta; *LA,* left atrium; *LV,* left ventricle. (From Zipes DP et al [eds]: *Braunwald's heart disease,* ed 7, Philadelphia, 2005, Saunders.)

ACUTE GENERAL Rx

β-blockers may be tried in symptomatic patients (e.g., palpitations, chest pain); they decrease the heart rate and contractility, thus potentially decreasing the stretch on the prolapsing valve leaflets.

CHRONIC Rx

Monitoring for complications:

- Mitral regurgitation (most common complication); on rare occasion may occur acutely due to rupture of chordae tendineae.
- Bacterial endocarditis (risk is three to eight times that of the general population); higher risk in patients with regurgitation than without
- TIA or stroke caused by embolic phenomena (from fibrin and platelet thrombi) in patients with thickened leaflets; risk in young patients is <0.05% per year; if present aspirin (75-325 mg) is indicated for secondary prevention
- Cardiac arrhythmias (the vast majority are supraventricular and benign)
- Sudden death (rare); most often associated with acute flail leaflets or caused by ventricular arrhythmias associated with other structural heart disease
- The incidence of complications of MVP is very low (<1% per year) if mitral leaflet thickness (≤0.5 mm); young patients (age <45 yr) with absence of mitral systolic murmur or MR on Doppler echocardiography, all of which are at low risk for any complications. Table M1-21 describes predictors of clinical outcome in mitral valve prolapse.
- Risk factors that predict higher risk of complications are presence of moderate to severe MR, LV ejection fraction <50%, LA dimension >40 mm, age >50 years

TABLE M1-21 Predictors of Clinical Outcome in Mitral Valve Prolapse

Predictor	Survival	Valve Surgery	Arrhythmias or Sudden Death	Endocarditis
Age	+++	+++	–	–
Gender	++	++	–	–
Leaflet thickness or redundancy	+++	+++	++++	++++
Severity of mitral regurgitation	++++	++++	++++	++++
Systolic click	+	–	–	–
Left ventricular dilation	+	++++	++	–
Left atrial dilation	–	++	+	–

Symbols indicate the relative predictive value of each variable for the listed clinical outcomes on a scale of no predictive value (–) to strongly predictive (++++).
From Bonow RO et al: *Braunwald's heart disease: a textbook of cardiovascular medicine,* Philadelphia, 2012, Saunders.

SURGICAL REFERRAL

Surgical referral may be necessary in patients who develop progressive MR with surgical indications as per guidelines for valvular heart disease (see topic on mitral regurgitation).

PEARLS & CONSIDERATIONS

COMMENTS

- Recent studies suggest that the prevalence of MVP and its propensity to cause symptoms and serious complications have been overestimated in the past.
- The relationship between MVP syndrome and sudden cardiac death is unclear, and the best evidence suggests that there is only a slight risk in subsets of patients with MVP who have severe MR, severe valvular deformity, complex ventricular arrhythmias, QT prolongation, and a history of syncope.
- Asymptomatic patients with MVP and mild or no MR can be evaluated clinically every 3 to 5 yr. High-risk patients (those with symptoms, arrhythmias, or significant regurgitation) should undergo a follow-up examination once a year.
- In 2007, the AHA guidelines for prevention of infectious endocarditis were revised and prophylactic antibiotics are no longer recommended for patients with MVP without previous endocarditis.

PATIENT & FAMILY EDUCATION

www.themitralvalve.org

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Mitral Valve Prolapse (Patient Information)

AUTHOR: **AMANDA C. DORAN, M.D., Ph.D.**

SUGGESTED READINGS

Avierinos JF et al.: Sex differences in morphology and outcomes of mitral valve prolapse, *Ann Intern Med* 149:787–795, 2008.

Bonow RO et al.: 2008 focused update incorporated into the ACC/AHA guidelines for the management of patients with valvular heart disease, *J Am Coll Cardiol* 52:e1, 2008.

Verma S, Mesana TG: Mitral-valve repair for mitral valve prolapse, *N Engl J Med* 361:2261–2269, 2009.

Wilson W et al.: Prevention of infective endocarditis: a guideline from the American Heart Association, *Circulation* 116:1736, 2007.

Mixed Connective Tissue Disease

BASIC INFORMATION

DEFINITION

An overlap syndrome with clinical features seen in systemic lupus erythematosus (SLE), polymyositis (PM), and systemic sclerosis (Scl) in association with high titer of anti U1-RNP antibodies, especially to the 68-70 kD epitope. Not all clinical features are present initially, and it usually takes several years before enough overlapping features are present to be confident that mixed connective tissue disease (MCTD) is the most likely diagnosis. Because of the nonspecific signs and symptoms at presentation, most of the patients may be initially classified as having undifferentiated connective tissue disease.

SYNONYMS

MCTD

ICD-9CM CODES
710.9 Diffuse connective tissue disease NOS
ICD-10CM CODES
M35.1 Other overlap syndrome
M35.9 Systemic involvement of connective tissue, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Variable by population
PREDOMINANT SEX: Female/male ratio of 10:1
PREDOMINANT AGE: Age at onset generally in the second or third decade

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- General: exertional dyspnea, malaise, fatigue, fever

FIGURE M1-35 Sausage-shaped fingers in a patient with mixed connective tissue disease. An identical appearance may be found in patients with early scleroderma and eosinophilic fasciitis. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

- Joints: arthralgias are an early symptom that can evolve to arthritis resembling RA but without severe erosions. Sausage-shaped fingers (Fig. M1-35)
- Skin and mucosa: Raynaud's phenomenon is an early finding. Malar rash, discoid plaques, oral or genital ulcers, sicca symptoms, subcutaneous nodules, abnormal nail fold capillaries
- Muscle: myalgias, inflammatory myopathy (painless weakness)
- Lung: interstitial lung disease leading to pulmonary fibrosis
- Heart: pulmonary hypertension, pericardial effusion (most frequent cardiac manifestation), pericarditis
- Hematopoietic: anemia of chronic disease, lymphopenia, thrombocytopenia
- Gastrointestinal tract: altered motility, mesenteric vasculitis, pancreatitis, hepatitis
- Kidney: membranous glomerulonephritis, diffuse proliferative glomerulonephritis; kidney involvement is uncommon
- Nervous system: trigeminal neuropathy, headache, aseptic meningitis

ETIOLOGY

Autoimmune disorder

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Other connective tissue disorders (SLE, progressive Scl, PM, infection, malignancy)

WORKUP

Table M1-22 summarizes diagnostic criteria.

Alarcon-Segovia: Serologic criterion accompanied by three or more clinical criteria, one of which must be synovitis or myositis (sensitivity 81.3%, specificity 86.2%).

Kahn: Serologic criterion accompanied by Raynaud's phenomenon and at least two of the three remaining clinical criteria.

Once diagnosis is made, screening for pulmonary hypertension is necessary.

LABORATORY TESTS

- Positive antinuclear antibody (ANA) speckled pattern often >1:1280 titer
- U1-RNP antibodies especially to the 68-70 kD antigen (high titers)
- SLE-specific autoantibodies are generally absent.
- Rheumatoid factor and anti-CCP positive (50% to 70%)

TABLE M1-22 Diagnostic Criteria by Alarcon-Segovia and Kahn

	Alarcon-Segovia Criteria	Kahn Criteria
Serology	Anti-RNP at hemagglutination titer of ≥1:1600	High-titer anti-RNP corresponding to a speckled ANA of ≥1:1200
Clinical	Swollen hands Synovitis Myositis Raynaud's phenomenon Acrosclerosis	Swollen fingers Synovitis Myositis Raynaud's phenomenon

TREATMENT

- Considered to be a steroid-responsive disease, especially features seen in SLE and myositis
- Aimed at the specific features of the overlap syndrome
- Arthralgias, arthritis, fatigue, myalgias, and myositis may respond to NSAIDs, antimalarials, and/or steroids. Immunosuppressive medications such as methotrexate, cyclophosphamide, and azathioprine can also be used.
- Intravenous immunoglobulin
- Keeping warm, avoiding beta-blockers, smoking cessation, and dihydropyridine calcium channel blockers can be used for Raynaud's phenomenon
- Pulmonary hypertension and lung disease: Therapies include steroids, cyclophosphamide, low-dose aspirin, anticoagulation, ACE inhibitors, endothelin receptor antagonist, IV prostacyclin, and cyclic GMP phosphodiesterase type 5 inhibitors such as sildenafil and tadalafil.
- Calcium, vitamin D, bisphosphonates, parathyroid hormone analogs, and denosumab are used for bone health

DISPOSITION

- Patients with high titers of U1-RNP antibodies have low prevalence of serious renal disease and life-threatening neurologic disorders.
- Disease-related mortality is usually related to pulmonary hypertension and its cardiac sequelae.

REFERRAL

Rheumatology consultation for clarification and assistance in treatment

PEARLS & CONSIDERATIONS

COMMENTS

Pulmonary arterial hypertension (PAH) is diagnosed by cardiac catheterization. It is the main disease-related cause of death. Early detection of PAH and aggressive treatment may improve prognosis.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Scleroderma (Systemic Sclerosis) (Related Key Topic)

AUTHOR: **DANIEL E. MENDEZ-ALLWOOD, M.D.**

SUGGESTED READINGS

Alarcon-Segovia D et al.: Comparison between 3 diagnostic criteria for mixed connective tissue disease: study of 593 patients, *J Rheumatol* 16:328–334, 1989.

Aringer M, Smolen JS: Mixed connective tissue disease: what is behind the curtain? *Best Pract Res Clin Rheumatol* 21:1037, 2007.

Bennett RM. Overlap syndromes. In: Kelley's textbook of rheumatology. Saunders: Philadelphia, pp. 1381–1399.

Fares WH et al.: Targeted approaches to the treatment of pulmonary hypertension, *Ther Adv Respir Dis* 6(3):147, 2012.

Hoffman RW, Maldonaldo ME: Immune pathogenesis of mixed connective disease: a short analytical review, *Clin Immunol* 128:8, 2008.

Kim P et al.: Treatment of mixed connective tissue disease, *Rheum Dis Clin North Am* 31:549–565, 2005.

Sharp G: The origin of mixed connective disease: a stimulus for autoimmune disease research, *Lupus* 18:1031, 2009.

Tsai YY et al.: Fifteen-year experience of pediatric-onset mixed connective tissue disease, *Clin Rheumatol* 29:53, 2010.

Tzouvelekis A et al.: Effects and safety of mycophenolate mofetil or sodium in systemic sclerosis associated interstitial lung disease: a meta analysis, *Pulm Med* 14:36–37, 2012.

BASIC INFORMATION

DEFINITION

Molar pregnancy is a premalignant gestational disorder. Molar pregnancies are classified as complete or partial based on morphologic and pathologic examination. Both complete and partial molar pregnancies have an abnormal placenta with enlargement and swelling of the chorionic villi and hyperplasia of the villous trophoblastic cells. Most molar pregnancies are complete and are characterized by generalized hydropic villous changes with no fetal tissue. Partial moles are characterized by a mixture of large hydropic villi and normal placental tissue and often have fetal tissue present. The risk of malignant sequelae (gestational trophoblastic neoplasia) for a complete mole is 18% to 29% and for a partial mole is 0% to 11%.

SYNONYMS

Hydatidiform mole
Gestational trophoblastic disease

ICD-9CM CODES
630 Hydatidiform mole
ICD-10CM CODES
001.9 Hydatidiform mole, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 0.57 to 2/1000 pregnancies with wide regional variation
PREDOMINANT SEX AND AGE: Females of reproductive age, highest rates at extremes of reproductive ages
RISK FACTORS: Extremes of reproductive age (<21 and >40 yr), previous molar pregnancy, history of spontaneous abortion

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Complete molar pregnancy:
- 80% to 90% present with vaginal bleeding at 6 to 16 wk gestational age
- 28% with uterine enlargement greater than expected for gestational age
- 8% with hyperemesis gravidarum
- 1% with gestational hypertension in the first or second trimester
- 15% with bilateral theca lutein cysts
- 15% will have a beta hCG >100,000 mIU/ml

Partial molar pregnancy:
- 90% present with an incomplete or missed abortion
- 75% present with vaginal bleeding
- <10% will have a beta hCG of >100,000 mIU/ml

ETIOLOGY

Complete molar pregnancy
- Fertilization of an oocyte with absent or inactive maternal chromosomes and duplication of paternal chromosomes (90% are 46, XX) or fertilization of an empty oocyte with 2 sperm (46, XY or XX)
- Uniform villous enlargement and no development of a fetus

Partial molar pregnancy
- Fertilization of a normal oocyte with 2 sperm (usually 69, XXY)
- Focal villous edema with identifiable fetus

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Complete mole, partial mole, ectopic pregnancy, abortion (incomplete or spontaneous), normal intrauterine pregnancy

WORKUP

- Pelvic exam to evaluate for uterine size and bleeding
- Blood pressure to assess for gestational hypertension or preeclampsia (systolic blood pressure >140 or diastolic blood pressure >90)
- Fig. M1-36 describes an algorithm for the diagnosis and management of molar pregnancy

LABORATORY TESTS

- Quantitative beta human chorionic growth hormone (beta hCG); significantly elevated levels >100,000 will raise suspicion for molar pregnancy
- Complete blood count (CBC) to assess for acute anemia from vaginal bleeding
- Comprehensive metabolic panel to evaluate for renal or liver disease
- TSH to evaluate for hyperthyroidism
- Urinalysis for proteinuria to evaluate for preeclampsia
- Type and screen to evaluate Rh and to prepare for surgery

IMAGING STUDIES

- Pelvic ultrasound (Fig. M1-37)
  1. Complete molar pregnancy will show diffuse vesicular changes with no evidence of fetal tissue and may show theca lutein cysts

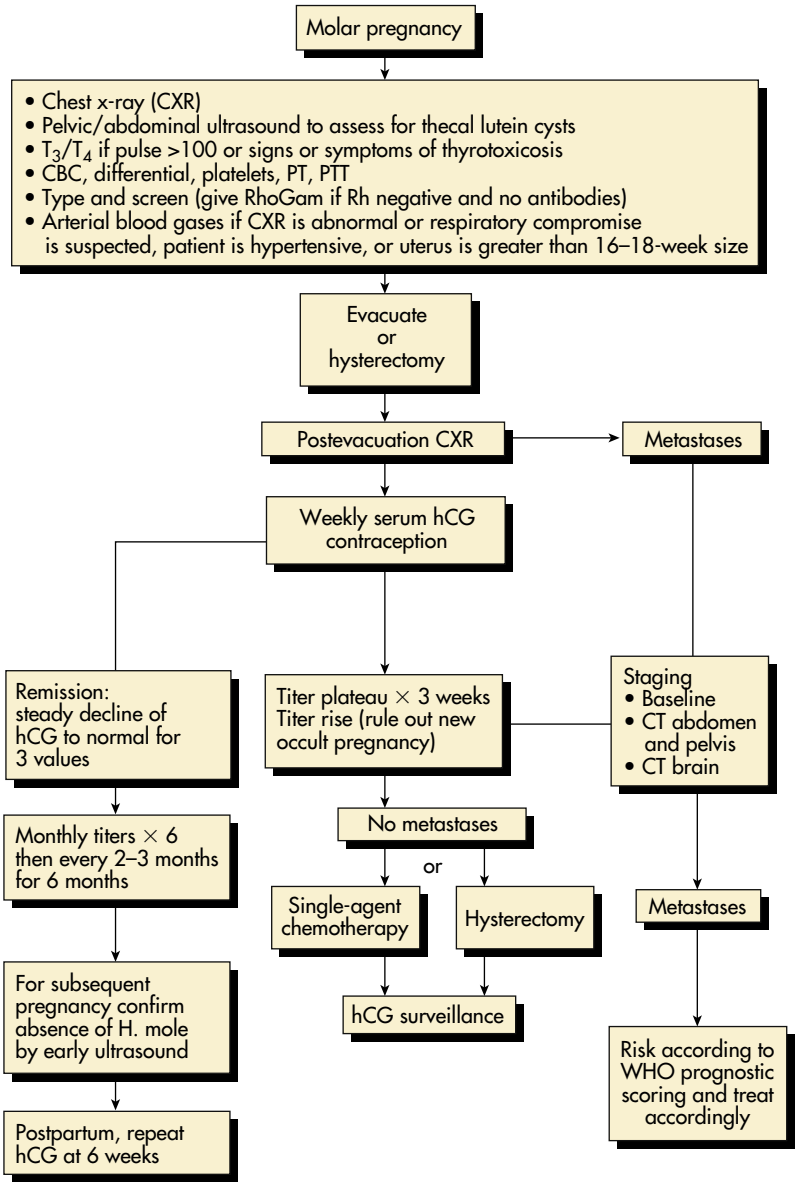

FIGURE M1-36 Algorithm for the management of molar pregnancy. (From Copeland LJ: Gestational trophoblastic neoplasia. In Copeland LJ [ed]: *Textbook of Gynecology*, 2nd ed, Philadelphia, 2000, Saunders.) (From Gabbe SG: *Obstetrics*, 6th ed, Philadelphia, 2012, Saunders.)

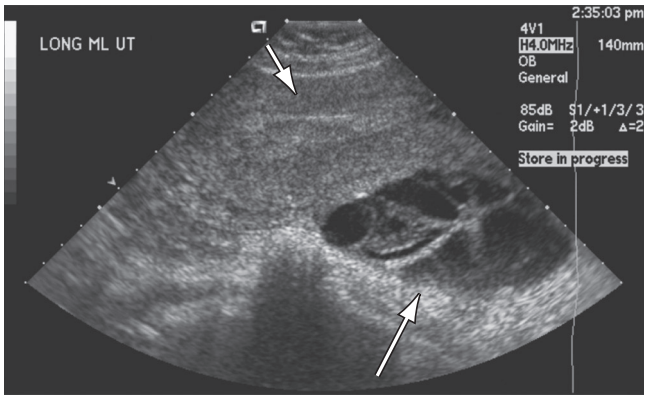

FIGURE M1-37 Endovaginal ultrasound of the theca lutein cyst with early molar pregnancy. Note enlarged anechoic cystic spaces within the ovary *(arrows)*. (From Fielding JR et al: *Gynecology imaging,* Philadelphia, 2011, Saunders.)

2. Partial molar pregnancy will show focal cystic changes in the placenta and fetal tissue may be present

- Baseline chest x-ray to use for comparison if malignant trophoblastic disease develops

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Surgical uterine evacuation with dilatation and curettage (D&C)

ACUTE GENERAL Rx

D&C, Rh immune globulin if Rh negative

CHRONIC Rx & DISPOSITION

If pathology results are consistent with complete or partial mole, patients must be followed to evaluate for trophoblastic neoplasia. 15% to 20% of complete moles and 1% to 5% of partial moles will develop into trophoblastic neoplasia. Quantitative beta hCG should be followed weekly until three consecutive results show normal levels. After that, check quantitative beta hCG every 3 mo for a total of 6 mo. Patients should remain on reliable contraception during this time to prevent confusion from a rising beta hCG in the case of a new pregnancy.

REFERRAL

- If there is concern for a molar pregnancy, the patient should be managed by a gynecologist for uterine evacuation and follow-up.
- If there is a plateau or rise of the beta hCG during follow-up, the patient should be referred to a gynecologic oncologist for treatment with chemotherapy.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Spontaneous Miscarriage (Related Key Topic)
Vaginal Bleeding During Pregnancy (Related Key Topic)

AUTHOR: **LAUREN ROTH, M.D.**

SUGGESTED READINGS

Berkowitz RS, Goldstein DP: Molar pregnancy, *N Engl J Med* 360:16, 2009.

Diagnosis and treatment of gestational trophoblastic disease. ACOG Practice Bulletin No. 53, *Obstet Gynecol* 103, 2004.

Lurain JR: Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole, *Am J Obstet Gynecol* 203(6):531–539, 2010.

BASIC INFORMATION

DEFINITION

Molluscum contagiosum is a viral infection characterized by discrete skin lesions with central umbilication.

SYNONYMS

MC

ICD-9CM CODES
078.0 Molluscum contagiosum
ICD-10CM CODES
B08.1 Molluscum contagiosum

EPIDEMIOLOGY & DEMOGRAPHICS

- Molluscum contagiosum spreads by autoinoculation, scratching, or touching a lesion.
- It usually occurs in young children. It is also common in sexually active adults and patients with HIV infection.
- Incubation period varies between 4 and 8 wk.
- Spontaneous resolution in immunocompetent patients can occur after several months.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The individual lesion appears initially as a small (2-3 mm), flesh-colored, firm, smooth-surfaced papule with subsequent central umbilication. Lesions are frequently grouped (Fig. M1-38). The size of each lesion generally varies from 2 to 6 mm in diameter.
- Typical distribution in children involves the face, extremities, and trunk. Mucous membranes are spared.

FIGURE M1-38 Grouped molluscum. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

- Distribution in adults generally involves pubic and genital areas.
- Erythema and scaling at the periphery of the lesions may be present as a result of scratching or hypersensitivity reaction.
- Lesions are not present on the palms and soles.

ETIOLOGY

Viral infection of epithelial cells caused by a poxvirus, molluscum contagiosum

DIAGNOSIS

Diagnosis is usually established by the clinical appearance of the lesions (distribution and central umbilication). A magnifying lens can be used to observe the central umbilication. If necessary, the diagnosis can be confirmed by removing a typical lesion with a curette and examining the content on a slide after adding potassium hydroxide and gentle heating. Staining with toluidine blue will identify viral inclusions.

DIFFERENTIAL DIAGNOSIS

- Verruca plana (flat warts): no central umbilication, not dome shaped, irregular surface, can involve palms and soles
- Herpes simplex: lesions become rapidly umbilicated
- Varicella: blisters and vesicles are present
- Folliculitis: no central umbilication, presence of hair piercing the pustule or papule
- Cutaneous cryptococcosis in AIDS patients: budding yeasts will be present on cytologic examination of the lesions
- Basal cell carcinoma: multiple lesions are absent
- Cellulitis

WORKUP

Careful examination of the papules

LABORATORY TESTS

Generally not indicated in children. Screening for other sexually transmitted diseases is recommended in all cases of genital molluscum contagiosum.

TREATMENT

GENERAL THERAPY

- Therapy is individualized depending on number of lesions, immune status, and patient's age and preference.
- Observation for spontaneous resolution is reasonable in patients with few, small, nonirritated, and nonspreading lesions. Genital lesions should be treated in all sexually active patients.
- Liquid nitrogen cryotherapy
- Carbon dioxide laser
- Curettage after pretreatment of the area with combination prilocaine 2.5% with lidocaine 2.5% cream (EMLA) for anesthesia is useful for treatment of a few lesions. Curettage should be avoided in cosmetically sensitive areas because scarring may develop.
- Treatments with liquid nitrogen therapy in combination with curettage are effective in older patients who do not object to some discomfort.
- Application of cantharidin 0.7% to individual lesions covered with clear tape will result in blistering over 24 hr and possible clearing without scarring. This medication should be avoided on facial lesions.
- Other treatment measures include use of imiquimod cream or tretinoin 0.025% gel or 0.1% cream at bedtime, daily use of salicylic acid (Occlusal) at bedtime, and use of laser therapy.
- Trichloroacetic acid peel generally repeated every 2 wk for several weeks is useful in immunocompromised patients with extensive lesions.

DISPOSITION

Most patients respond well to the therapeutic modalities listed previously. Spontaneous resolution can occur after 6 to 9 mo in some immunocompetent patients.

REFERRAL

To dermatology when diagnosis is in doubt or in patients with extensive lesions

PEARLS & CONSIDERATIONS

COMMENTS

Genital molluscum contagiosum in children may be indicative of sexual abuse.

RELATED CONTENT

Molluscum Contagiosum (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

Monoclonal Gammopathy of Undetermined Significance (MGUS)

BASIC INFORMATION

DEFINITION

Monoclonal gammopathy of undetermined significance (MGUS) is defined by the presence of a monoclonal protein in persons with no features of multiple myeloma or other malignant gammopathies (Table M1-23). Patients with MGUS have a serum monoclonal protein concentration <3 g/dl, <10% plasma cells on the bone marrow, and no clinical manifestations related to the monoclonal gammopathy.

SYNONYMS

Non-IgM MGUS
IgM MGUS
Light chain MGUS

ICD-9CM CODES
273.1 Monoclonal gammopathy
ICD-10CM CODES
D47.2 Monoclonal gammopathy of undetermined significance (MGUS)

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The annual incidence of MGUS in men is 120 per 100,000 population at age 50 yr and increases to 530 per 100,000 at age 80 yr. The rates for women are 60 per 100,000 at 50 yr and 370 per 100,000 at 80 yr.
PREVALENCE: Prevalence is higher in blacks than in whites
PREDOMINANT SEX AND AGE: Median age of diagnosis is about 70 yr. Prevalence is higher in men than in women.
RISK FACTORS: Race (African American), older age, male sex, exposure to pesticides and family history of MGUS or multiple myeloma

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- MGUS typically detected after a routine blood test reveals an elevated total protein concentration
- Asymptomatic
- Physical exam is normal

ETIOLOGY

- Unknown mechanism
- Characterized by a rearrangement of immunoglobulin genes that results in the production of a monoclonal protein

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Smoldering myeloma (Table EM1-24)
Multiple myeloma
Waldenström's gammaglobulinemia
Secondary monoclonal gammopathies
- Chronic liver disease
- Rheumatologic diseases
- Chronic myelomonocytic leukemia
- Chronic neutrophilic leukemia
- Lichen myxedematosus

Pyoderma gangrenosum

LABORATORY TESTS

Protein studies:
Serum protein electrophoresis (Fig. M1-39)
1. IgG most common, followed by IgM and IgA

24-hour urine protein excretion and urine electrophoresis
Serum and urine immunofixation
Determination of serum free light chain ratio (kappa and lambda free light chains)
Hemoglobin
Serum calcium and creatinine
Examination of the bone marrow aspirate

IMAGING STUDIES

- Skeletal survey
- Bone mineral density resting at baseline (MGUS is associated with increased risk of osteoporosis)

TREATMENT

International Myeloma Working Group Recommendation
1. Risk stratification
   - Abnormal free light chain ratio
   - Bone marrow plasma cells >10%
   - Serum M protein >3 g/dl
   - 1, 2, or 3 risk factors had 5-yr progression rates of 25%, 51%, and 76%, respectively; time to progression 10, 5.1, and 1.9 yr, respectively
2. Follow up by risk category
   - Low risk: every 2-3 yr
   - Intermediate or high risk: after diagnosis, reevaluation at 2-3 mo. If results are stable, reevaluation every 4-6 mo for 1 yr. If results remain stable, reevaluation every 6-12 mo.

Reevaluation consists of:
- Total serum protein–serum electrophoresis
- 24-hour urine protein excretion
- Hemoglobin
- Serum creatinine and calcium

DISPOSITION

- Risk of myeloma at 25 yr is 30%.
- Annual risk of transformation to myeloma depends on type of M protein:
  - Immunoglobulin H MGUS: 1% per year
  - Light-chain MGUS: 0.3% per year
- Risk of infection (bacterial and viral) is twofold compared with healthy controls
- Increased risk of mortality from bacterial infections

REFERRAL

To hematologist/oncologist for evaluation

PEARLS & CONSIDERATIONS

- Approximately 55% of 70-yr-old patients diagnosed as having MGUS have had the condition for more than 10 yr.
- Most patients with MGUS should be monitored every 6 to 12 mo for signs and symptoms of progression.
- There is no indicated treatment.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **KIMBERLY PEREZ, M.D.**

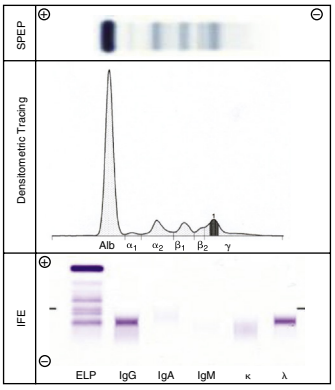

FIGURE M1-39 Serum electrophoresis from a 73-year-old man with monoclonal gammopathy of undetermined significance. The patient has no clinical, hematologic, or imaging evidence of a plasma cell dyscrasia, except for a persistent, modest (0.4 g/dl), single M protein peak on the densitometric tracing *(shaded area, middle panel)* of the serum protein electrophoresis pattern *(SPEP)*. The M protein was identified by immunofixation electrophoresis *(IFE)* as IgGλ, located in the β_2 region of the electrophoresis *(ELP)* pattern. (Courtesy Drs. Frank H. Wians Jr. and Dennis C. Wooten, Department of Pathology, University of Texas Southwestern Medical Center, Dallas. From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

TABLE M1-23 Disease Definitions for the Monoclonal Gammopathies: MGUS and Related Disorders

Type of Monoclonal Gammopathy	Premalignancy with a Low Risk of Progression (1%-2% per year)	Premalignancy with a High Risk of Progression (10% per year)	Malignancy
IgG and IgA (non-IgM) monoclonal gammopathies*	**Non-IgM MGUS** All 3 criteria must be met: Serum monoclonal protein <3 g/dl Clonal bone marrow plasma cells <10%, and Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder	**Smoldering multiple myeloma** Both criteria must be met: Serum monoclonal protein (IgG or IgA) ≥3 g/dl and/or clonal bone marrow plasma cells ≥10%, and Absence of end-organ damage such as lytic bone lesions, anemia, hypercalcemia, or renal failure that can be attributed to a plasma cell proliferative disorder	**Multiple myeloma** All 3 criteria must be met except as noted: Clonal bone marrow plasma cells ≥10% Presence of serum and/or urinary monoclonal protein (except in patients with true nonsecretory multiple myeloma), and Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically Hypercalcemia: serum calcium >11.5 mg/dL or Renal insufficiency: serum creatinine >2 mg/dL or estimated creatinine clearance <40 mL/min Anemia: normochromic, normocytic with a hemoglobin value of >2 g/dL below the lower limit of normal or a hemoglobin value <10 g/dL Bone lesions: lytic lesions or severe osteopenia attributed to a plasma cell proliferative disorder or pathologic fractures
IgM monoclonal gammopathies	**IgM MGUS†** All 3 criteria must be met: Serum monoclonal protein <3 g/dl Clonal bone marrow lymphoplasmacytic cells <10%, and Absence of end-organ damage such as anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder	**Smoldering Waldenström macroglobulinemia** Both criteria must be met: Serum IgM monoclonal protein ≥3 g/dl and/or bone marrow lymphoplasmacytic infiltration ≥10%, and No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder	**Waldenström macroglobulinemia** All criteria must be met: IgM monoclonal gammopathy (regardless of the size of the M-protein), and ≥10% bone marrow lymphoplasmacytic infiltration (usually intertrabecular) by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation and a typical immunophenotype (eg, surface IgM$^+$, CD5$^{+/-}$, CD10$^-$, CD19$^+$, CD20$^+$, CD23$^-$) that satisfactorily excludes other lymphoproliferative disorders including chronic lymphocytic leukemia and mantle cell lymphoma Evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder. **IgM myeloma** All criteria must be met: Symptomatic monoclonal plasma cell proliferative disorder characterized by a serum IgM monoclonal protein regardless of size Presence of 10% plasma cells on bone marrow biopsy Presence of lytic bone lesions related to the underlying plasma cell disorder and/or translocation t(11;14) on fluorescence in situ hybridization.
Light-chain monoclonal gammopathies	**Light-chain MGUS** All criteria must be met: Abnormal FLC ratio (<0.26 or >1.65) Increased level of the appropriate involved light-chain (increased kappa FLC in patients with ratio >1.65 and increased lambda FLC in patients with ratio <0.26) No immunoglobulin heavy-chain expression on immunofixation Clonal bone marrow plasma cells <10%, and Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder	**Idiopathic Bence Jones proteinuria** All criteria must be met: Urinary monoclonal protein on urine protein electrophoresis ≥500 mg/24 h and/or clonal bone marrow plasma cells ≥10% No immunoglobulin heavy-chain expression on immunofixation Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder	**Light-chain multiple myeloma†** Same as multiple myeloma except no evidence of immunoglobulin heavy-chain expression

FLC, Free light chain; *MGUS,* monoclonal gammopathy of undetermined significance.

*Occasionally patients with IgD and IgE monoclonal gammopathies have been described and will be considered to be part of this category as well.

†Note that conventionally IgM MGUS is considered a subtype of MGUS, and similarly light-chain multiple myeloma is considered as a subtype of multiple myeloma. Unless specifically distinguished, when the terms MGUS and multiple myeloma are used in general, they include IgM MGUS and light-chain multiple myeloma, respectively.

From Rajkumar SV et al: Advances in the diagnosis, classification, risk stratification, and management of monoclonal gammopathy of undetermined significance: implications for recategorizing disease entities in the presence of evolving scientific evidence, *Mayo Clin Proc* 85(10):945-948, 2010.

SUGGESTED READINGS

Bladé J: Clinical practice. Monoclonal gammopathy of undetermined significance, *N Engl J Med* 355:2765–2770, 2006.

Greenberg A et al.: Familial monoclonal gammopathy of undetermined significance and multiple myeloma: epidemiology, risk factors, and biological characteristics, *Blood* 119(23):5359, June 2012.

International Myeloma Working Group: Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group, *Br J Haematol* 121:749–757, 2003.

Korde N et al.: Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM): novel biological insights and development of early treatment strategies, *Blood* 117:5573–5581, 2011.

Kyle R et al.: Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management, *Leukemia* 24:1121–1127, 2010.

Kyle R et al.: Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma, *N Engl J Med* 356(25):2582, 2007.

Landgren O et al.: Risk of monoclonal gammopathy of undetermined significance (MGUS) and subsequent multiple myeloma among African-American and white veterans in the United States, *Blood* 107:904–906, 2006.

Therneau TM et al.: Incidence of monoclonal gammopathy of undetermined significance and estimation of duration before first clinical recognition, *Mayo Clin Proc* 87(11):1071–1079, 2012.

Tete S et al.: Immune defects in the risk of infection and response to vaccination in monoclonal gammopathy of undetermined significance and multiple myeloma, *Frontiers in Immunology* 5(257):1, June 2014.

TABLE EM1-24 Diagnostic Criteria for MGUS, Multiple Myeloma, and Other Conditions*

Variable	MGUS	Smoldering Multiple Myeloma	Multiple Myeloma	Waldenström's Macroglobulinemia	Primary Amyloidosis
Bone marrow plasma cells (%)	<10	≥10	≥10	≥10†	<10
	and	And/or	and/or	and	and
Circulating monoclonal protein (g/dl)	<3	≥3	≥3	>3	<3
Clinical manifestations	Absent	Absent	Present‡	Present∫	Present¶

MGUS, Monoclonal gammopathy of undetermined significance.
*Data are from the International Myeloma Working Group.
†The diagnostic criteria included more than 10% lymphoplasmacytoid cells.
‡Clinical features may include increased serum calcium concentrations, renal failure, anemia, skeletal involvement (lytic lesions), recurrent bacterial infections, and extramedullary plasmacytomas.
∫Clinical features included anemia, mucocutaneous bleeding, hepatosplenomegaly, and IgM type of immunoglobulin.
¶Clinical features include fatigue, weight loss, purpura, nephritic syndrome, congestive heart failure, peripheral neuropathy, orthostatic hypotension, and massive hepatomegaly.
From Bladé J: Clinical practice. Monoclonal gammopathy of undetermined significance, *N Engl J Med* 355:2765-2770, 2006.

Mononucleosis PTG

BASIC INFORMATION

DEFINITION

Mononucleosis is a symptomatic infection most commonly caused by Epstein-Barr virus (EBV) and characterized by fever, tonsillar pharyngitis, and lymphadenopathy.

SYNONYMS

Infectious mononucleosis (IM)

ICD-9CM CODES
075 Infectious mononucleosis
ICD-10CM CODES
B27 Infections mononucleosis
B27.0 Gamma herpesviral mononucleosis
B27.1 Cytomegaloviral mononucleosis
B27.8 Other infectious mononucleosis
B27.9 Infectious mononucleosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 500 cases/100,000 persons/yr
PREDOMINANT SEX: Incidence is the same, but occurs earlier in females.
PREDOMINANT AGE: Most common between the ages of 15 and 24 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Following an incubation period of 1 to 2 mo, a prodrome may occur, with fever, chills, malaise, and anorexia for several days. This is followed by the classic triad, which includes pharyngitis, fever, and adenopathy. Although fatigue and malaise may be prominent, pharyngitis is usually the most severe symptom. Tonsillitis with marked tonsillar exudates is common.
- Lymphadenopathy is most prominent in the cervical region but may be diffuse.
- Splenomegaly may occur, most commonly during the second wk of illness.
- Rash is uncommon but will occur in nearly all patients who receive ampicillin or amoxicillin.
- At times, IM can present as fever and adenopathy without pharyngitis. Although complications may be severe, they are uncommon and tend to resolve completely. Involvement of the hematologic, pulmonary, cardiac, or nervous system may occur; splenic rupture is rare. IM is usually a self-limited illness, but symptoms of malaise and fatigue may last months before resolving.

ETIOLOGY

The most common cause of IM is primary infection with EBV. Cytomegalovirus (CMV) can cause a similar disease syndrome, but CMV infection often occurs in infancy or early childhood and is minimally symptomatic. Primary EBV infection during childhood also often causes few or no symptoms; persistent fatigue and recurrent/persistent fevers are the most common reasons parents bring symptomatic children to medical care. Infection during childhood is more common in lower socioeconomic groups. The frequency of IM in late adolescence is attributed to the onset of social contact between the sexes. Close personal contact is usually necessary for transmission. Transfer via saliva while kissing may be responsible for many cases. EBV can persist in the oropharynx of patients with IM for up to 18 mo. Transmission may also occur sexually as EBV can be isolated in cervical epithelial cells and male seminal fluid and can also be transmitted by blood transfusion.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Heterophile-negative IM caused by cytomegalovirus (CMV)
- Bacterial and viral causes of pharyngitis
- Toxoplasmosis
- Acute retroviral syndrome of HIV, lymphoma

WORKUP

Initial testing consists of heterophile antibody (monospot) and CBC with differential. Fig. EM1-40 illustrates a diagnostic algorithm for EBV infection and IM.

LABORATORY TESTS

- Increased WBC is common, with a relative lymphocytosis and neutropenia. Atypical lymphocytes (Fig. EM1-41) are the hallmark of IM, but are not pathognomonic. Mild thrombocytopenia is common. A falling hematocrit may signal splenic rupture or severe immune-mediated hemolytic anemia. Elevated hepatocellular enzymes and cryoglobulins occur in many cases. Heterophile antibody, as measured by the monospot test, may be positive at presentation, or may appear later in the course of illness. A negative test should be repeated if clinical suspicion is high; negative results are common in patients symptomatic for <2 wk and children <4 yr. If this test remains negative for 8 wk, other causes of IM are likely. The monospot usually remains positive for 3 to 6 mo, but can last for 1 yr.
- A positive heterophile test has been reported with primary HIV infection.
- In addition to the heterophile antibody, virus-specific antibodies may result in response to IM. Determination of these EBV-specific antibodies is rarely necessary to diagnose IM, although early diagnosis in monospot negative cases may be made by isolating IgM to the viral capsid antigen, which is usually positive during the acute illness.

IMAGING STUDIES

Chest x-ray may rarely show infiltrates. An elevated left hemidiaphragm may occur in cases of splenic rupture.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive rest is advocated by some, but effect on outcome is not clear.
- Splenectomy if rupture occurs; transfusions for severe anemia or thrombocytopenia

ACUTE GENERAL Rx

- Pharmacologic therapy is not indicated in uncomplicated illness.
- The use of steroids (Fig. EM1-42) is suggested in patients who have severe thrombocytopenia or hemolytic anemia, or impending airway obstruction as a result of enlarged tonsils. Prednisone, 60 to 80 mg PO qid for 3 days, then tapered over 1 to 2 wk. Dexamethasone may also be used for severe tonsillar enlargement. There is no role for antiviral agents such as acyclovir in the management of IM.

CHRONIC Rx

A rare, chronic form of IM with persistent organ infection and inflammation has been described. This should not be confused with chronic fatigue syndrome, which is unrelated to EBV.

DISPOSITION

Eventual resolution of all symptoms is the rule.

REFERRAL

More than mild illness

PEARLS & CONSIDERATIONS

COMMENTS

- Contact sports should be avoided during the first month of illness, because splenic rupture can occur, even in the absence of clinically detectable splenomegaly.
- Between 30% and 75% of college freshmen are seronegative for EBV. Each year nearly 20% of susceptible persons become infected and up to 50% of these persons develop IM.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Mononucleosis (Patient Information)

AUTHOR: **RUSSELL J. MCCULLOH, M.D.**

SUGGESTED READINGS

Auwaerter PG: Infectious mononucleosis: return to play, *Clin Sports Med* 23:485, 2004.

Bauer CC et al.: Serum Epstein-Barr virus DNA load in primary Epstein-Barr virus infection, *J Med Virol* 75(1):54, 2005.

Ebell MH: Epstein-Barr virus: infectious mononucleosis, *Am Fam Physician* 70:1279, 2004.

Luzuriaga K, Sullivan JL: Infectious mononucleosis, *N Engl J Med* 362:1999–2000, 2010.

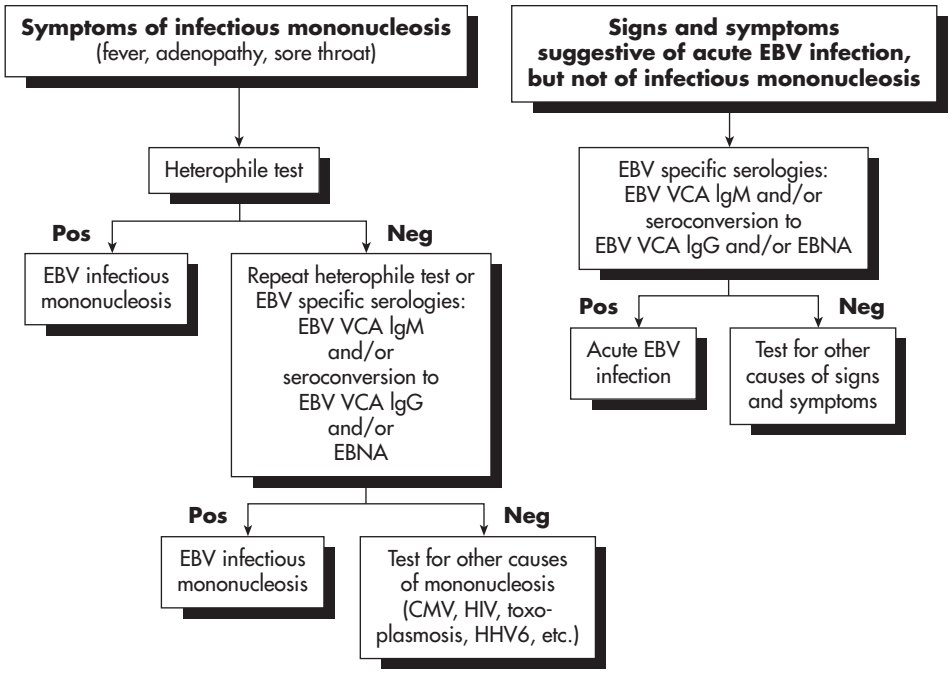

FIGURE EM1-40 Diagnostic algorithm for EBV infection and infectious mononucleosis. *CMV,* Cytomegalovirus; *EBV,* Epstein-Barr virus; *HIV,* human immunodeficiency virus. (From Young NS et al [eds]: *Clinical hematology,* St Louis, 2006, Mosby.)

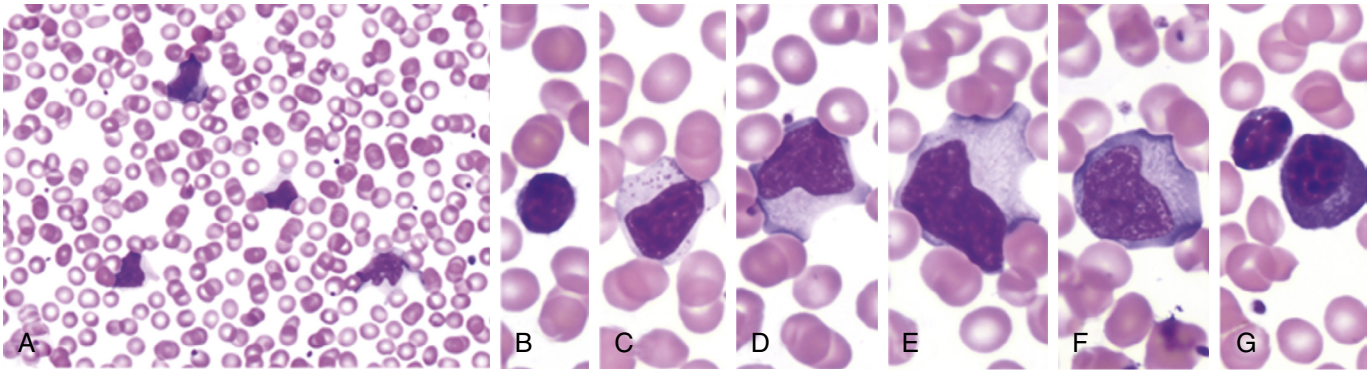

FIGURE EM1-41 Mononucleosis. Peripheral blood smear in infectious mononucleosis. Low power **(A)** shows moderately high white blood cell count and high number of reactive, or "atypical" lymphocytes. Higher power **(B-G)** illustrates spectrum of lymphoid morphology, including small resting lymphocyte **(B)** for comparison, large granular lymphocyte **(C)**, atypical forms **(D, E, F)**, also referred to as "reactive" lymphs, and circulating plasma cell **(G)**. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

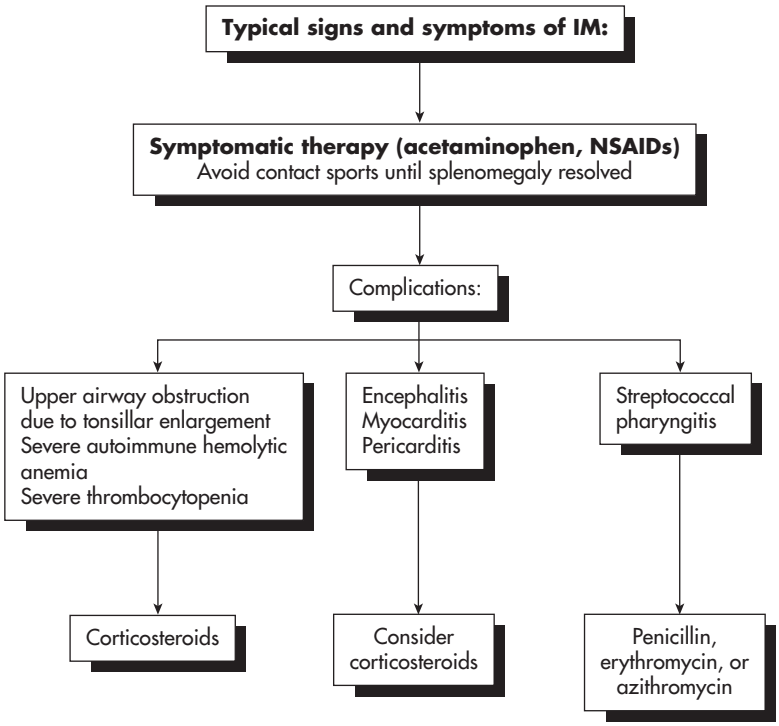

FIGURE EM1-42 Algorithm for management of infectious mononucleosis. *IM,* Infectious mononucleosis; *NSAIDs,* nonsteroidal anti-inflammatory drugs. (From Young NS et al [eds]: *Clinical hematology,* St Louis, 2006, Mosby.)

BASIC INFORMATION

DEFINITION

Morton neuroma is an entrapment neuropathy involving one of the common plantar digital nerves of the foot. This condition manifests as pain in the plantar aspect of the forefoot, often localized between the metatarsal heads.

SYNONYMS

Morton metatarsalgia
Morton toe
Interdigital neuroma
Plantar neuroma
Metatarsal neuralgia
Morton's neuroma

ICD-9CM CODES
355.6 Morton's neuroma
ICD-10CM CODES
G57.6 Lesion of plantar nerve
G57.8 Other mononeuropathies of lower limb
G57.9 Mononeuropathy of lower limb, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Morton neuroma affects one of the common plantar digital nerves located at any of the four interspaces of the foot.
  1. It most commonly affects the third common plantar digital proper nerve, located in the third interspace.
  2. It occurs most frequently in patients who wear tight-fitting, high-heeled shoes.
- Morton neuroma is usually unilateral.
- The condition occurs most frequently in women.
- It usually presents between the fourth and sixth decade of life.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with Morton neuroma will present complaining of pain to the plantar aspect of the foot, typically localized between the metatarsal heads of the affected interspace.
- The pain may be described as stabbing, burning, tingling, or "electric" and may radiate to the digits.
- The pain is exacerbated by the use of tight-fitting shoes. The typical indication of a Morton neuroma is the patient's desire to remove shoes and rub the forefoot.
- The pain can often be recreated by applying pressure at the plantar aspect of the inter space, starting just proximal to the metatarsal heads and proceeding distally.
- Mulder's sign: Compression of the forefoot at the level of the metatarsophalangeal joints, combined with plantar pressure at the affected interspace, elicits a palpable "click."

ETIOLOGY

- Morton neuroma is considered to be an entrapment neuropathy of the affected common digital plantar nerve (Fig. M1-43). The etiology remains obscure.
- The common plantar digital nerves are branches of the medial plantar nerve, coursing distally to supply the digits of the foot, passing just beneath the deep transverse intermetatarsal ligament. The third common plantar nerve is often supplied by a communicating branch of the lateral plantar nerve. This anatomic variation results in a thicker nerve that is more prone to trauma, a reason often cited to explain the prevalence of Morton neuroma in the third common plantar digital nerve.
- The deep transverse intermetatarsal ligament may also be implicated in the cause of a neuroma. If it is thickened or has aberrant bands, it may cause compression of the affected nerve.
- Soft tissue masses, such as a plantar lipoma, may also cause compression of the nerve against the ligament, leading to the formation of a neuroma.
- Histologic examination of resected Morton neuroma exhibits increased neural width, demyelination, intraneural fibrosis, and thickened endoneural capillaries.

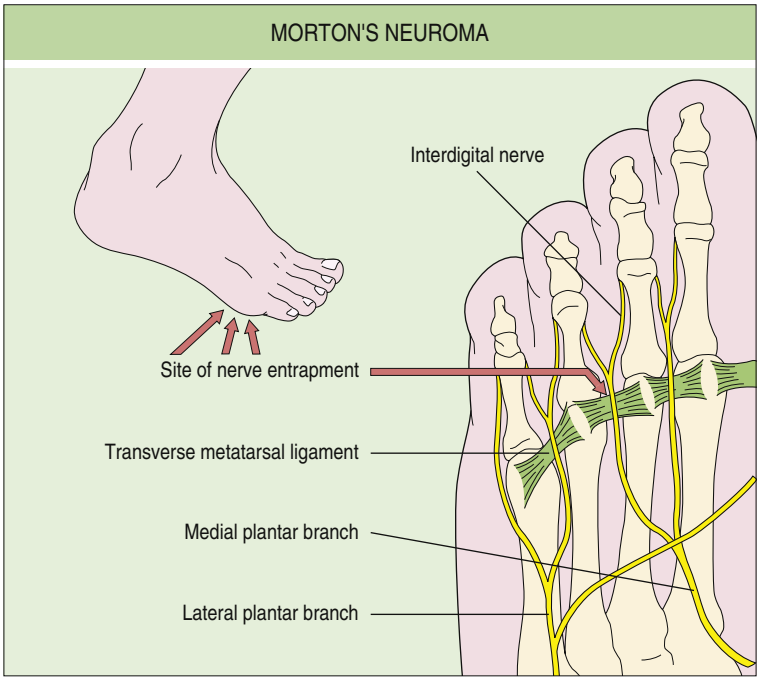

FIGURE M1-43 Morton's neuroma. On the plantar surface of the foot, the interdigital nerve is compressed below the transverse metatarsal ligament and not between the metatarsal heads (plantar view). (From Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.)

DIAGNOSIS

The diagnosis of Morton neuroma is primarily a clinical diagnosis. Laboratory tests and imaging modalities are generally not necessary for diagnosis.

DIFFERENTIAL DIAGNOSIS

- Peripheral neuropathy
- Tarsal tunnel syndrome
- Metatarsal stress fracture
- Freiberg's infraction
- Metatarsophalangeal joint capsulitis
- Osteoarthritis
- Rheumatoid arthritis

WORKUP

Exclude other causes mentioned in "Differential Diagnosis."

LABORATORY TESTS

There is no specific laboratory study that can be used to diagnose Morton neuroma.

IMAGING STUDIES

- Weight-bearing radiographs may be performed to exclude other pathologic conditions.
- MRI may be used to detect and localize a neuroma. The mass is best visualized on a T1-weighted image.
  1. MRI is best for patients with recurrent neuromas and atypical symptoms.
  2. Ultrasound imaging can be used to visualize a neuroma. It will typically present as a hypoechoic mass.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Altering footwear is the first line of treatment.
- Wide shoes with a low heel are recommended.
- A metatarsal pad may also provide relief, as it splays the metatarsal heads, thereby decreasing the pressure on the neuroma.
- If adequate relief is noted with the above, then orthotics may also be considered.

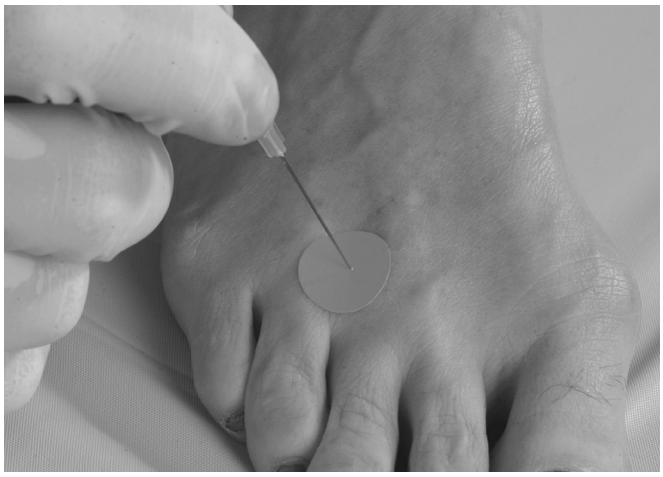

FIGURE M1-44 Injection for interdigital (Morton) neuroma. The area is most easily injected from the dorsal aspect, usually between the metatarsal heads of the third and fourth toes. The area of tenderness is marked, the needle is inserted to 1 inch, and steroid with anesthetic is injected. (From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

ACUTE GENERAL Rx

- If conservative measures are unsuccessful, other treatment options include serial injections (Fig. M1-44) with corticosteroids or a sclerosing agent. The sclerosing solution is commonly composed of bupivacaine and ethyl alcohol. Recent trials[1] showed that corticosteroid injection is a reasonable temporizing intervention for some patients with Morton neuroma. Pain relief was, however, limited, and one third of steroid recipients underwent surgery at some point after 3 mo.
- Nonsteroidal anti-inflammatory agents may also provide relief.

[1]Thomson CE et al: Methylprednisolone injections for the treatment of Morton neuroma: a patient-blinded randomized trial, *J Bone Joint Surg Am* P5:790, 2013.

CHRONIC Rx

- If conservative treatment fails to provide a resolution to symptoms, then surgical intervention should be considered.
- Surgical excision of the neuroma is performed in an operating room under monitored anesthesia care.
- Possible complications of surgery include hematoma formation, numbness, infection, and recurrent neuroma.

DISPOSITION

- Following surgery, patients are often placed on a partial weight-bearing status to the affected foot. Sutures are removed 2 to 3 weeks following the initial surgery. Patients generally return to their previous activity level in 4 to 6 weeks.
- Should a neuroma recur, a second surgical procedure may be performed.

REFERRAL

If surgery is being considered, a consultation with either a podiatrist or a foot and ankle specialized orthopedic surgeon is indicated.

PEARLS & CONSIDERATIONS

COMMENTS

- Dr. Thomas G. Morton is given credit for describing this disorder in 1876.
- Morton neuroma may occur in any of the four interspaces of the foot but most commonly affects the third interspace.
- If conservative treatment and serial injections fail, surgery should be considered for the excision of the neuroma.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Morton's Neuroma (Patient Information)

AUTHOR: **NATHALIA DOOBAY, D.P.M.**

SUGGESTED READINGS

Espinoza N et al.: Alcohol sclerosing therapy is not an effective treatment for interdigital neuroma, *Foot Ankle Int* 32(6):576, 2011.

Farai A, Hosur A: The outcome of using two different approaches for excision of Morton's neuroma, *Chin Med J* 123(16):2195, 2010.

Kay D, Bennett GL: Morton's neuroma, *Foot Ankle Clin* 8(1):49, 2003.

McCluskey LF, Webb LB: Compression and entrapment neuropathies of the lower extremity, *Clin Podiatr Med Surg* 16(1):97, 1999.

Miller S, Nakra A: Morton's neuroma. In Banks A et al, editor: *McGlamry's comprehensive textbook of foot and ankle surgery,* Philadelphia, Lippincott Williams & Wilkins, pp 231–252.

Owens R, Gougoulias N: Morton's neuroma: clinical testing and imaging in 76 feet, compared to a control group, *Foot Ankle Surg* 17(3):197, 2010.

Owens R, Guthrie H: Morton's neuroma: accuracy of clinical assessment, *J Bone Joint Surg (BR)* 93(3):312, 2011.

Schon L, Mann R: Disease of the nerves. In Coughlin M, Mann R, editors: *Surgery of the foot and ankle,* Philadelphia, Mosby, pp 614–636.

Schreiber K et al.: What is the best way to treat Morton's neuroma? *J Fam Practice* 60(3):157, 2011.

BASIC INFORMATION

DEFINITION

Motion sickness is a clinical syndrome associated with motion or perception of motion. Patients with motion sickness suffer perspiration, nausea, vomiting, increased salivation, and generalized malaise in response to movement.

SYNONYMS

Physiologic vertigo

ICD-9CM CODES
994.6 Motion sickness
ICD-10CM CODES
T75.3 Motion sickness

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Common
PEAK INCIDENCE: Any age
PREVALENCE (IN U.S.): Common
PREDOMINANT SEX: Male = female
PREDOMINANT AGE: Any age
GENETICS: Not known to be genetic

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Vomiting
- Sweating
- Pallor

ETIOLOGY

- Motion (e.g., amusement rides, rides in automobiles or planes)
- Exacerbated by anxiety, fumes (e.g., industrial pollutants), visual stimuli
- Fig. M1-45 describes a proposed neural pathway resulting in motion sickness

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute labyrinthitis
- Gastroenteritis
- Metabolic disorders
- Viral syndrome

WORKUP

None necessary in routine case

TREATMENT

NONPHARMACOLOGIC THERAPY

- Fixate on far object
- Cease motion
- Avoid reading
- Avoid alcohol

ACUTE GENERAL Rx

- Scopolamine patch is most effective. It should be applied to a hairless area behind the ear every 3 days prn. It should be applied >4 hr before antiemetic effect is required.
- Over-the-counter oral preparations (e.g., Dramamine) are less effective.
- Meclizine 12.5 to 25 mg q6h may be effective but is very sedating.

CHRONIC Rx

- Rarely chronic
- Symptoms generally resolve completely with cessation of motion exposure.

DISPOSITION

Follow-up is not needed.

REFERRAL

If another diagnosis is suspected (e.g., purulent ear, fever, cranial nerve abnormalities)

PEARLS & CONSIDERATIONS

COMMENTS

- Many patients with migraine report having had severe motion sickness as a child.
- Improved ventilation, avoidance of large meals before travel, semirecumbent sitting, and avoidance of reading while in motion will minimize the risk of motion sickness.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Motion Sickness (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

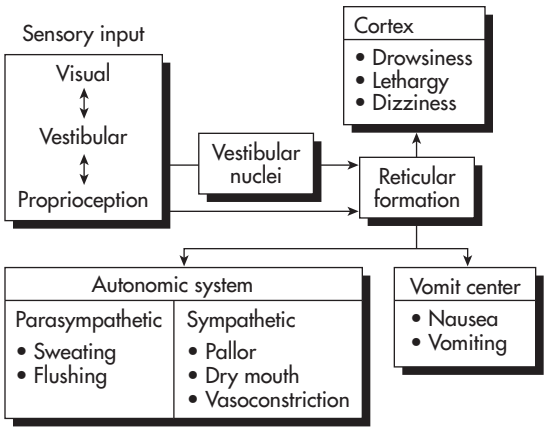

FIGURE M1-45 Proposed neural pathway resulting in motion sickness. (From Kuhn S.M.: Motion sickness. In Keystone J.S., et al: *Travel Medicine*, 2nd ed, Philadelphia, 2008, Elsevier, pp 435–440.)

SUGGESTED READINGS

Koch KL: Illusory self-motion and motion sickness: a model for brain-gut interacting and nausea, *Dig Dis Sci* 48(8 suppl):53S, 1999.

Yates BJ et al.: Physiological basis and pharmacology of motion sickness: an update, *Brain Res Bull* 45(5):395, 1998.

BASIC INFORMATION

DEFINITION

Mucormycosis is a fungal infection by Zygomycetes fungi and includes species in the order Mucorales (*Rhizopus* sp., *Rhizomucor, Cunninghamella, Apophysomyces, Saksenaea, Absidia, Syncephalastrum, Cokeromyces, Mortierella*) and in the order Entomophthorales (*Conidiobolus* and *Basidiobolus*).

ICD-9CM CODES
117.7 Mucormycosis
ICD-10CM CODES
B46.5 Mucormycosis, unspecified
B46.1 Rhinocerebral mucormycosis
B46.0 Pulmonary mucormycosis
B46.3 Cutaneous mucormycosis
B46.4 Disseminated mucormycosis

EPIDEMIOLOGY & DEMOGRAPHICS

- These fungi are ubiquitous in nature and can be found in soil and decaying vegetation. Infection is seen in association with underlying conditions, including diabetes mellitus especially with ketoacidosis, hematologic malignancies, stem cell or solid organ transplants, severe burns or trauma, treatment with deferoxamine or iron overload states, steroid treatment, immunodeficiency states (e.g., AIDS), injection drug use, and malnutrition. Immunocompetent hosts may become infected in tropical climates.
- The fungus gains entry to the body most commonly through the respiratory tract. The spores are deposited in the nasal turbinates and may be inhaled into the pulmonary alveoli. In cases of cutaneous mucormycosis, the spores are introduced directly into the skin lesion.
- After a tornado with winds >200 mph struck Joplin, Missouri, in May 2011, there were 13 confirmed cases of mucormycosis *(Apophysomyces trapeziformis),* including five deaths. While two patients had diabetes, none were immunocompromised. It was felt that the fungus entered through wounds sustained during the tornado. Wooden splinters were found in four patients.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Rhinocerebral-rhinoorbital-paranasal syndrome may present with fever, facial and orbital pain, headache, diplopia, loss of vision, facial or orbital cellulitis, facial anesthesia, cranial nerve dysfunction, black nasal discharge, epistaxis, and seizure. Physical findings in this situation include proptosis; chemosis; nasal, palatal, or pharyngeal necrotic ulcerations; and retinal infarction. Thrombosis of the cavernous sinus or internal carotid artery may occur. This form of mucormycosis is found most commonly in diabetics, primarily in the presence of acidosis, and in patients with leukemia and neutropenia.
- Pulmonary mucormycosis can present with pneumonia, lung abscess, pulmonary infarction, pleurisy, pleural effusion, hemoptysis, chills, and fever. This form of mucormycosis is found most commonly in immunocompromised neutropenic hosts after chemotherapy for hematologic malignancies.
- Gastrointestinal zygomycosis presents with abdominal pain, diarrhea, gastrointestinal hemorrhage, ulcers, peritonitis, and bowel infarction. This form of mucormycosis is found most commonly in patients with extreme malnutrition and is believed to arise from ingestion of spores of the fungi.
- Cutaneous zygomycosis presents as nodular lesions (hematogenous seeding) or a wound infection. It primarily involves the epidermis and dermis after use of occlusive dressings that have not been properly sterilized.
- Cardiac mucormycosis is a form of endocarditis.
- Septic arthritis and osteomyelitis
- Brain abscess occurs most often from extension of the fungus from the nose or paranasal sinuses through adjacent bones in severely debilitated patients.
- Disseminated zygomycosis (rare but uniformly fatal)
- Physical findings depend on the location of the infection.

ETIOLOGY & PATHOGENESIS

The cause of mucormycosis is infection by a fungus of the Zygomycetes class (see "Definition"). Normal host defenses include leukocytes and pulmonary macrophages. Quantitative (e.g., neutropenia) or qualitative (e.g., diabetes mellitus or steroid treatment) disruption in the host defenses predisposes the patient to infection.

DIAGNOSIS

The hallmark of mucormycosis is infarction and necrosis of host tissues that result from invasion of the vasculature by the fungal elements. Black eschars and discharges should be closely evaluated. Diagnosis depends on the demonstration of the organism in the tissue of a biopsy specimen.

DIFFERENTIAL DIAGNOSIS

- Infection of the sites described previously by other organisms (bacterial [including tuberculosis and leprosy], viral, fungal, or protozoan)
- Noninfectious tissue necrosis (e.g., neoplasia, vasculitis, degenerative) of the sites described previously

WORKUP

- Biopsy of infected tissue with direct-light microscopy examination establishes the diagnosis within minutes of the biopsy in the case of nasopharyngeal infection. Fungal hyphae are broad (5- to 15-micron diameter) and irregularly branched and have rare septations, in contrast to molds such as *Aspergillus,* which are narrower, have regular branching, and have many septations.
- Bronchoalveolar lavage or bronchoscopy with biopsy for smear, culture, and histologic examination
- Radiographs and other imaging studies such as CT of symptomatic sites may be required before infection is suspected and tissue specimens are obtained.

TREATMENT

Aggressive correction of underlying disease (e.g., hyperglycemia, high steroid doses, use of immunosuppressive drugs) should be undertaken.

Standard therapy consists of aggressive surgical debridement of involved tissues and antifungal therapy. For invasive mucormycosis recommended treatment is with a lipid formulation of amphotericin B that allows higher doses with less nephrotoxicity. The start dose is 5 mg/kg of liposomal amphotericin B or amphotericin B lipid complex. Doses as high as 10 mg/kg have also been used.

Traditional amphotericin B given IV at a daily dose of 1.0 to 1.5 mg/kg infused over 2 to 4 hr daily for a total of 1 to 4 g can also still be used, but is associated with significant nephrotoxicity and adverse reactions such as fever, chills, myalgias, vomiting, and electrolyte disturbances.

- Other antifungals do not appear to be effective except possibly posaconazole, which may serve as an oral step-down therapy after amphotericin B at a dose of 400 mg bid with a fatty meal.
- Some studies suggest that caspofungin with amphotericin B may be synergistic for *Rhizopus oryzae* infections only.
- The role of colony-stimulating factors remains unclear, beyond that of increasing the neutrophil count in patients with neutropenia.
- Hyperbaric oxygen has been used in some patients but its utility in therapy is still not clear.

PROGNOSIS

- Sinus infection with no underlying disease: 75% survival
- Sinus infection with diabetes: 60% survival
- Sinus infection with renal disease: 25% survival

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Duffy J et al.: Mucormycosis outbreak associated with hospital linens, *Pediatr Infect Dis* 33:472–476, 2014.

Rapidis AD: Orbitomaxillary mucormycosis (zygomycosis) and the surgical approach to treatment: perspectives from a maxillofacial surgeon, *Clin Microbiol Infect Suppl* 5:98–102, 2009.

Spellberg B et al.: Recent advances in the management of mucormycosis: from the bench to bedside, *Clin Infect Dis* 48(12):1743–1751, 2009.

Sun HY, Singh N: Mucormycosis: its contemporary face and management strategies, *Lancet Infect Dis* 11(4):301–311, 2011.

BASIC INFORMATION

DEFINITION

These are gram-negative bacteria that are resistant to at least one antimicrobial in three or more antimicrobial classes (antipseudomonal penicillins, third-generation cephalosporins, fluoroquinolones, carbapenems, and aminoglycosides).

SYNONYMS

CRE: carbapenem-resistant Enterobacteriaceae
ESBL: extended-spectrum beta-lactamases
MDR-GNB: multidrug-resistant gram-negative bacilli
MDRO: multidrug-resistant organisms
NDM-1: New Delhi metallo-beta-lactamase-1

ICD-9CM CODES

V09.9 Infection with drug-resistant microorganisms, unspecified
V09.1 Infection with microorganisms resistant to cephalosporins and other beta-lactam antibiotics

ICD-10CM CODES

Z16.30 Resistance to unspecified antimicrobial drugs
Z16.10 Resistance to unspecified beta lactam antibiotics

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: There is an increasing incidence of these bacteria in hospitals and long-term care facilities in the U.S. and around the world. ESBL bacteria were first discovered in Europe in 1984 and in the U.S. in 1988. CRE bacteria were first described in the late 1990s in the U.S. The NDM-1 bacteria were first noted in 2009 in Sweden in a patient from India.

PREDOMINANT SEX AND AGE: These bacteria can be seen in any age group. They may be more frequent in women due to increased risk of urinary tract sepsis.

RISK FACTORS: In general, these bacteria are more common in hospitals and long-term care facilities, but they are spread nosocomially through patient care and thus are now entering the community, where the incidence is also increasing. Specific risk factors include:

- Length of stay in the hospital
- Length of ICU stay
- Use of central line catheters
- Abdominal surgery
- Presence of gastrostomy or jejunostomy tube
- Prior administration of any antibiotic
- Prior residence in a long-term care facility
- Presence of indwelling urinary catheter

ETIOLOGY

- Several different classes of MDR-GNRs exist based on their resistance mechanism.
  1. ESBL: These bacteria contain enzymes that break open the beta-lactam ring of penicillins, cephalosporins, and aztreonam and thus inactivate antibiotics from those classes. Enzymes conferring resistance include:
     1. TEM beta-lactamases
     2. SHV beta-lactamases
     3. CTX-M beta lactamases
     4. OXA beta-lactamases
     5. These enzymes are plasmid-mediated and thus can spread from one gram-negative bacteria to another, causing outbreaks in a single institution.
  2. CRE: Enzymes conferring resistance include:
     1. Class A beta-lactamases: encoded on chromosomes or plasmids (e.g., *Klebsiella pneumoniae* carbapenamase [KPC], which has caused outbreaks in hospitals around the world)
     2. Class B: metallo-beta-lactamases (e.g., New Delhi metallo-beta-lactamase-1). Encoded on a mobile plasmid that can spread to other gram-negative bacteria.
     3. Class C and Class D beta-lactamases
- *Stenotrophomonas maltophilia*: MDR-GNR that acts as an opportunistic pathogen among mostly hospitalized patients with high morbidity and mortality. It has intrinsic or acquired resistance mechanisms to multiple antibiotic classes and has the ability to adhere to foreign materials and form a biofilm, which escapes host defenses.
- *Acinetobacter* sp. (e.g., *Acinetobacter baumannii*): strains have emerged that are resistant to all commercially available antibiotics. These bacteria have the capability to acquire diverse mechanisms of resistance including:
  1. AmpC beta-lactamases
  2. Beta-lactamases: serine and metallo-beta-lactamases

CLINICAL PRESENTATION

All these resistant bacteria have the capability of causing diverse infections, including

- Pneumonia
- Bacteremia
- Urinary tract sepsis
- Central line–associated infections
- Ventilator-associated pneumonia (VAP)
- Surgical site infections

VAP from *A. baumannii* now accounts for 8.4% of GNR pneumonias in the ICU.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Other gram-negative rods such as:

- *Pseudomonas aeruginosa*
- *Klebsiella pneumoniae* that are not ESBL or CRE by resistance pattern
- *Morganella morgani*
- *Providencia*, *Proteus* sp., *Serratia*

WORKUP

Detection of ESBL and CRE bacteria can pose problems for the clinical microbiology laboratory:

1. To detect ESBL bacteria: automated systems such as Vitek use disk diffusion or broth dilution techniques, or double disk test or E-test strip with clavulanate
2. To detect CRE: modified Hodge test to detect carbapenamase-producing bacteria
3. In 2010, testing guidelines with respect to susceptibility involving several beta-lactam antibiotics were changed to better identify these bacteria via automated systems.

LABORATORY TESTS

Clinical testing is the same in infections from these resistant organisms as with nonresistant organisms:

- Cultures of any wounds, blood, sputum, urine, catheter tips
- CBC, liver function tests, urinalysis

IMAGING STUDIES

Studies depend on the clinical presentation but are similar to those for nonresistant bacteria causing infections.

TREATMENT

Because of multidrug resistance, only a few reliable antibiotics are available to treat these infections.

1. ESBL bacteria: carbapenem antibiotics such as imipenem, meropenem, ertapenem, or the cephalosporin cefoxitin or tigecycline.
2. CRE bacteria: selection of antibiotic will depend on testing but tigecycline may be used clinically. Other alternatives include:
   1. IV colistin
   2. *Stenotrophomonas maltophilia:* only available agents are Bactrim (drug of choice), levaquin, and minocycline
   3. *A. baumannii:* will depend on susceptibility testing, but ampicillin-sulbactam, imipenem or meropenem, or tigecycline can be used for MDR strains. For pan-resistant strains, IV colistin ± rifampin can be used. Inhaled colistin can be used for pneumonia patients.

DISPOSITION

Morbidity and mortality can be quite high with infections from these MDR bacteria.

1. Nosocomial *Acinetobacter* pneumonia carries a mortality rate of 35% to 70%.
2. *Stenotrophomonas* infections carry a mortality rate of 21% to 69%.
3. ESBL infections carry a mortality rate of 3.7% despite therapy with carbapenem antibiotics.

REFERRAL

- Infectious diseases specialist for selection of best antibiotic choice and follow-up
- Microbiologist for specialized testing and interpretation of results
- Pulmonary specialist for severe forms of pneumonia
- Infection control officer to help prevent spread of these bacteria in an institution

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Diekema DJ, Pfaller MA: Rapid detection of antibiotic-resistant organism carriage for infection prevention, *Clin Infect Dis* 56(11):1614–1620, 2013.

Gasink LB, Brennan PJ: Isolation precautions for antibiotic-resistant bacteria in healthcare settings, *Curr Opin Infect Dis* 22:339–344, 2009.

Hebert C, Weber SG: Common approaches to the control of multidrug-resistant organisms other than methicillin-resistant Staphylococcus aureus (MRSA), *Infect Dis Clin North Am* 25:181–200, 2011.

Lim LM et al.: Resurgence of colistin: a review of resistance, toxicity, pharmacodynamics, and dosing, *Pharmacotherapy* 30:1279–1291, 2010.

Maragakis LL: Recognition and prevention of multidrug-resistant gram-negative bacteria in the intensive care unit, *Crit Care Med* 38(8 Suppl):S345–S351, 2010.

Perez F, Van Duin D: Carbapenem-resistant Enterobacteriaceae: a menace to our most vulnerable patients, *Cleve Clin J Med* 80(4):225–233, 2013.

Multifocal Atrial Tachycardia ALG

BASIC INFORMATION

DEFINITION

Multifocal atrial tachycardia (MAT) is a supraventricular, tachyarrhythmia (rate greater than 100 beats/min) with P waves having at least three or more different morphologies and irregular P-P intervals. An isoelectric baseline further differentiates MAT from atrial fibrillation or atrial flutter. Each P wave is thought to originate from a different atrial focus.

SYNONYMS

Chaotic atrial rhythm
Chronic atrial tachycardia
Repetitive multifocal paroxysmal atrial tachycardia
The term *wandering pacemaker* is used for a similar arrhythmia associated with a normal or slow heart rate (<100 beats/min).

ICD-9CM CODES
427.89 Multifocal atrial tachycardia
ICD-10CM CODES
I47.1 Supraventricular tachycardia

EPIDEMIOLOGY & DEMOGRAPHICS

Estimated prevalence in hospitalized patients of 0.05% to 0.32%. Average age is 70s. Usually associated with underlying pulmonary disease with right atrial electromechanical delay. Chronic obstructive pulmonary disease (COPD) is present in approximately 55% of patients with MAT.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms:
- Palpitation
- Lightheadedness
- Syncope
- Symptoms of the underlying pulmonary disease
- Physical findings associated with the underlying pulmonary disease

ETIOLOGY

- Exact mechanism unknown
- Exacerbated by underlying pulmonary disease (COPD, hypoxia, pulmonary embolism, pneumonia), cardiac disease, hypercarbia, acidosis, electrolyte disturbances, digitalis toxicity

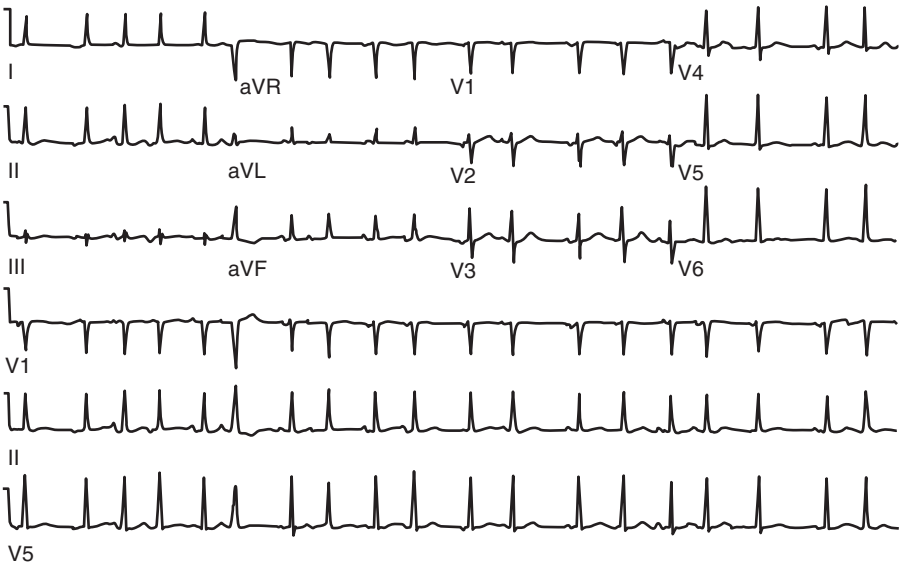

FIGURE M1-46 Surface ECG of multifocal atrial tachycardia. Note the varying morphology of the P waves and the PR intervals. (From Issa Z et al: *Clinical arrhythmology and electrophysiology,* ed 2, Philadelphia, 2012, Saunders.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Atrial fibrillation
- Atrial flutter with variable AV conduction
- Sinus tachycardia
- Paroxysmal atrial tachycardia
- Extrasystole

WORKUP

- ECG (Fig. M1-46)
- Chest x-ray
- Pulmonary function tests
- Electrolytes
- Arterial blood gases
- Digoxin level (if patient on digoxin)

TREATMENT

- Correction and/or improvement in the underlying pulmonary or metabolic dysfunction if possible and avoiding drugs such as digoxin, theophylline, etc.
- Electrolyte repletion, especially magnesium and potassium
- Calcium channel blockers
- β-blockers are typically contraindicated by obstructive lung disease or acute heart failure
- If the arrhythmia is asymptomatic, it can be left untreated
- Direct current cardioversion is ineffective
- No significant role for antiarrhythmics
- In extreme cases of refractory MAT in symptomatic patients who cannot tolerate medical therapy or in MAT resistant to medical therapy, AV nodal ablation with pacemaker implantation has been performed.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **BARRY FINE, M.D., PH.D**

SUGGESTED READINGS

Engel TR, Radhagopalan S: Treatment of multifocal atrial tachycardia by treatment of pulmonary insufficiency: or is it vice versa? *Chest* 117:7–8, 2000.

Link MS: Evaluation and initial treatment of supraventricular tachycardia, *N Engl J Med* 367:1438–1448, 2012.

McCord J, Borzak S: Multifocal atrial tachycardia, *Chest* 113:203, 1998.

BASIC INFORMATION

DEFINITION

Multiple myeloma is a malignancy of plasma cells characterized by clonal proliferation of malignant plasma cells in the bone marrow, monoclonal protein in the blood or urine, and associated organ dysfunction. Diagnostic criteria require the following:

1. Presence of ≥10% plasma cells on examination of the bone marrow (or biopsy of a tissue with monoclonal plasma cells).
2. Monoclonal protein in the serum or urine. Occasional patients without detectable monoclonal protein are considered to have nonsecretory myeloma.
3. Evidence of end-organ damage (***c***alcium elevation, ***r***enal insufficiency, ***a***nemia, or ***b***one lesions [CRAB]).

ICD-9CM CODES
203.0 Multiple myeloma
ICD-10CM CODES
C90.0 Multiple myeloma

EPIDEMIOLOGY & DEMOGRAPHICS

ANNUAL INCIDENCE: Five cases/100,000 persons (blacks affected twice as frequently as whites, males more than females); multiple myeloma accounts for 10% of all hematologic cancers. It is the most common primary bone malignancy. More than 20,000 new cases are diagnosed annually in the United States.
PREDOMINANT AGE: Peak incidence is in the seventh decade at a median age of 70 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The patient usually comes to medical attention because of one or more of the following:

- Bone pain (58%) (back, thorax) or pathologic fractures (30%) caused by osteolytic lesions
- Fatigue (32%) or weakness because of anemia from bone marrow infiltration with plasma cells
- Recurrent infections as a result of impaired neutrophil function and deficiency of normal immunoglobulins
- Nausea and vomiting caused by constipation and uremia
- Delirium resulting from hypercalcemia
- Neurologic complications, such as spinal cord or nerve root compression, blurred vision from hyperviscosity
- Pallor and generalized weakness from anemia
- Purpura, epistaxis from thrombocytopenia
- Evidence of infections from impaired immune system
- Paresthesias (5%), weight loss (24%)
- Swelling on ribs, vertebrae, and other bones

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Metastatic carcinoma
- Lymphoma (B-cell non-Hodgkin lymphoma)
- Bone neoplasms (e.g., sarcoma)
- Monoclonal gammopathy of undetermined significance
- Primary amyloidosis
- Chronic lymphocytic leukemia
- Waldenström's macroglobulinemia

LABORATORY TESTS

- Normochromic, normocytic anemia; rouleaux formation on peripheral smear (Fig. M1-47)
- Hypercalcemia is present in 15% of patients at diagnosis.
- Elevated blood urea nitrogen, creatinine, uric acid, and total protein
- Urine protein immunoelectrophoresis: proteinuria from overproduction and secretion of free monoclonal kappa or lambda chains (Bence Jones protein)
- Serum protein immunoelectrophoresis: tall homogeneous monoclonal spike (M spike) on protein immunoelectrophoresis in approximately 75% of patients (Fig. M1-48); decreased levels of normal immunoglobulins (Ig)
  1. The increased immunoglobulins are generally IgG (70%) and IgA (20%).
  2. Approximately 5–10% of patients have a flat level of immunoglobulins but increased light chains in the urine by electrophoresis.
  3. A small percentage (<2%) of patients have nonsecreting myeloma (no increase in immunoglobulins and no light chains in the urine) but have other evidence of the disease (e.g., positive bone marrow examination).
- Reduced ion gap from the positive charge of the M proteins and the frequent presence of hyponatremia in myeloma patients
- Hyponatremia, serum hyperviscosity (more common with production of IgA)
- Bone marrow examination: usually demonstrates nests or sheets of plasma cells, which comprise >30% of the bone marrow; ≥10% are immature
- Serum beta-2 microglobulin has little diagnostic value; it is useful for prognosis because levels >8 mg/L indicate high tumor mass and aggressive disease.
- Elevated serum levels of lactate dehydrogenase at the time of diagnosis define a subgroup of myeloma patients with very poor prognosis.
- Increased interleukin-6 in serum during active stage of myeloma
- The production of DKK1, an inhibitor of osteoblast differentiation, by myeloma cells is associated with the presence of lytic bone lesions in patients with multiple myeloma.
- Nearly all patients with myeloma present with abnormal chromosomes identified by fluorescence in situ hybridization (FISH). The Mayo Clinic Stratification of Myeloma, for purposes of therapy, identifies high-risk patients (<25% of patients at diagnosis) as those who have any of the following: FISH deletion 17p, FISH translocation 4;14, FISH translocation 14;16, cytogenetic deletion 13q, cytogenetic hypodiploidy, or plasma cell labeling index ≥3%.

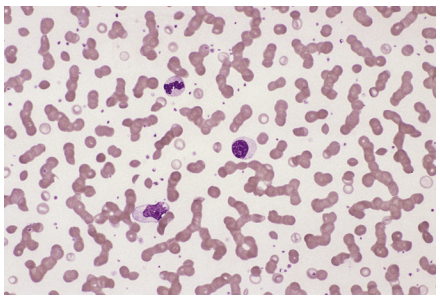

FIGURE M1-47 Increased rouleaux formation is seen in this blood smear from a patient with a large M protein. Marked rouleaux formation is often a clue to the diagnosis of a plasma cell neoplasm, but may also be observed in other conditions (Wright-Giemsa stain). (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

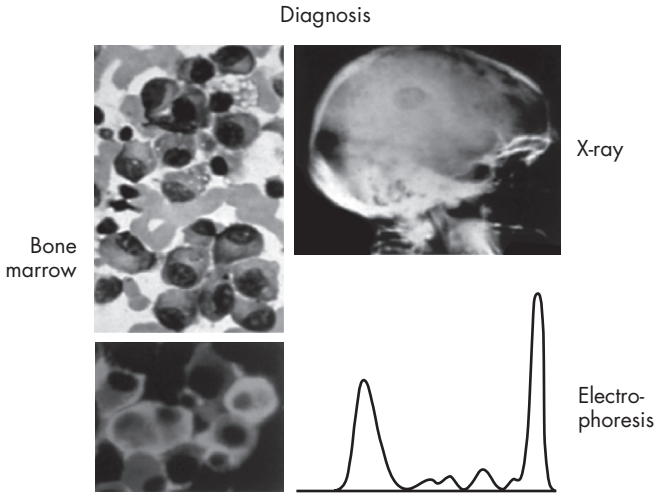

FIGURE M1-48 Common diagnostic features in multiple myeloma. Light chain-restricted plasma cells in a bone marrow aspirate; multiple lytic lesions in a skull radiograph; large monoclonal spike in the g-globulin area in serum electrophoresis. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

TABLE M1-25 Myeloma Staging System

Stage	Criteria
I	All of the following: Hemoglobin >10 g/dl Serum calcium <12 mg/dl Normal bone radiograph or solitary lesion Low M-component production IgG level <5 g/dl IgA level <3 g/dl Urine light chain <4 g/24 hr
II	Fitting neither I nor III
III	One or more of the following: Hemoglobin <8.5 g/dl Serum calcium >12 mg/dl Advanced lytic bone lesions High M-component production IgG level >7 g/dl IgA level >5 g/dl Urine light chains >12 g/24 hr

Subclassification:
A Serum creatinine <2 mg/dl
B Serum creatinine <2 mg/dl

IMAGING STUDIES

Radiograph films of painful areas may demonstrate punched-out lytic lesions or osteoporosis (Fig. M1-48). MRI is the preferred technique for suspected spinal compression or soft tissue plasmacytomas. Bone scans are not useful because lesions are not blastic. PET and MRI scans are emerging as useful tools to detect early bone involvement or extramedullary disease.

STAGING

Table M1-25 describes a historical multiple myeloma staging system. With use of newer tumor biology factors (see "Disposition") that can affect prognosis, along with tumor burden described in Table M1-25 and patient-related factors, it is possible to classify patients in three risk groups (high, intermediate, and standard).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Prevention of renal failure with adequate hydration and avoidance of nephrotoxic agents and dye contrast studies

ACUTE GENERAL Rx

- Treatment strategy is mainly related to age and comorbidities. It is crucial to identify transplant-eligible patients (Fig. M1-49).
  1. Initiation of induction therapy with thalidomide, lenalidomide, or bortezomib plus autologous stem cell transplant (ASCT) for patients <70 yr who do not have substantial heart, lung, renal, or liver dysfunction.
  2. ASCT with a reduced-intensity conditioning regimen should be considered in older patients or those with coexisting conditions.
  3. Conventional therapy combined with thalidomide, lenalidomide, or bortezomib should be administered in patients >70 yr.
- Induction therapy in patients ineligible for transplantation (old age, coexisting conditions, poor physical conditions) includes the following chemotherapeutic agents:
  1. Thalidomide in combination with melphalan and prednisone.
  2. Melphalan, bortezomib, and prednisone
  3. Bortezomib-thalidomide-prednisone
  4. Melphalan-prednisone-lenalidomide (MPR-R)
  5. Lenalidomide and low-dose dexamethasone
- Therapy for relapsed and refractory myeloma:
  1. Lenalidomide plus dexamethasone is a reference treatment for relapsed multiple myeloma.
  2. The proteasome inhibitors bortezomib and carfilzomib are FDA-approved for treatment of refractory multiple myeloma.
  3. Trials have shown that the addition of carfilzomib to lonalidomide and dexamethasone can significantly improve progression-free survival.
  4. If the relapse occurs more than 6 mo after conventional therapy is stopped, the initial chemotherapy regimen can be reinstituted.
  5. Consider autologous stem cell transplantation as salvage therapy in patients who had stem cells cryopreserved early in the course of the disease.
  6. ~15% of patients with newly diagnosed multiple myeloma are recognized incidentally and present without significant symptoms (asymptomatic MM, formerly known as smoldering myeloma). The rate of progression of smoldering myeloma to symptomatic disease is 10% per year for the initial 5 yr, decreasing to 5% for the next 5 yr, and decreasing further to 1.5% per year thereafter. Observation alone is reasonable in these patients because no survival advantage has been demonstrated by treating them.
  7. An exception to this may be in high-risk smoldering myeloma patients.[1] A recent trial[2] has shown that early treatment with lenalidomine plus doxamethasone of patients with high-risk smoldering myeloma delays progression to active disease and increases overall survival.

CHRONIC Rx

- Promptly diagnose and treat infections. Common bacterial agents are *Streptococcus pneumoniae* and *Haemophilus influenzae.* Prophylactic therapy against *Pneumocystis jirovecii* with trimethoprim-sulfamethoxazole must be considered in patients receiving chemotherapy and high-dose corticosteroid regimens. Vaccinate against *S. pneumoniae,* influenza, and *H. influenzae.*
- Control hypercalcemia with IV fluids and corticosteroids. Monthly infusions of the bisphosphonate pamidronate provide significant protection against skeletal complications and improve the quality of life of patients with advanced multiple myeloma. Zoledronic acid at doses of 2 mg and 4 mg in patients with osteolytic lesions has been shown to be as effective as pamidronate in terms of reducing the need for radiation to bone, increasing bone mineral density, and decreasing bone resorption. It can be infused over 15 min for treatment of hypercalcemia of malignancy. Bisphosphonates (pamidronate, zoledronate, and ibandronate) also appear to have an antitumor effect.
- Control pain with analgesics; radiation therapy to treat painful bone lesions or cord compression. Perform surgical stabilization of pathologic fractures. Consider vertebroplasty or kyphoplasty for selected vertebral lesions.
- Treat anemia with erythropoietin.
- Aggressive treatment of reversible causes of renal failure such as dehydration, hypercalcemia, and hyperuricemia.

DISPOSITION

- In patients presenting at an age <60 yr, the 10-year survival is approximately 30%. The median length of survival after diagnosis is now 8 yr. Prognosis is better in asymptomatic patients with indolent or smoldering myeloma. Median survival time is approximately 10 yr in persons with no lytic bone lesions and a serum myeloma protein concentration <3 g/dl. Adverse outcome is associated with increased levels of beta-2 microglobulin, low levels of serum albumin, circulating plasma cells, plasmablastic features in bone marrow, increased plasma cell labeling index, complete deletion of chromosome 13 or its long arm, t (4;14) or t (14;16) translocation, and increased density of bone marrow microvessels. In general any chromosomal abnormality that is detected on standard cytogenetic analysis is associated with a worse outcome than that associated with a normal karyotype.
- Compared with a single autologous stem cell transplantation, double transplantation (two successive autologous stem cell transplantations) improves survival among patients with myeloma, especially those who do not have a very good partial response after undergoing one transplantation.
- Recent trials reveal that among patients with newly diagnosed myeloma, survival in recipients of a hematopoietic stem cell autograft followed by a stem cell allograft from an HLA-identical sibling is superior to that in recipients of tandem stem cell autografts.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Multiple Myeloma (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

[1]Kyle RA et al: Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma, *N Engl J Med* 356:2582-2590, 2007.
[2]Mateos MV et al: Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma, *N Engl J Med* 369:438-447, 2013.

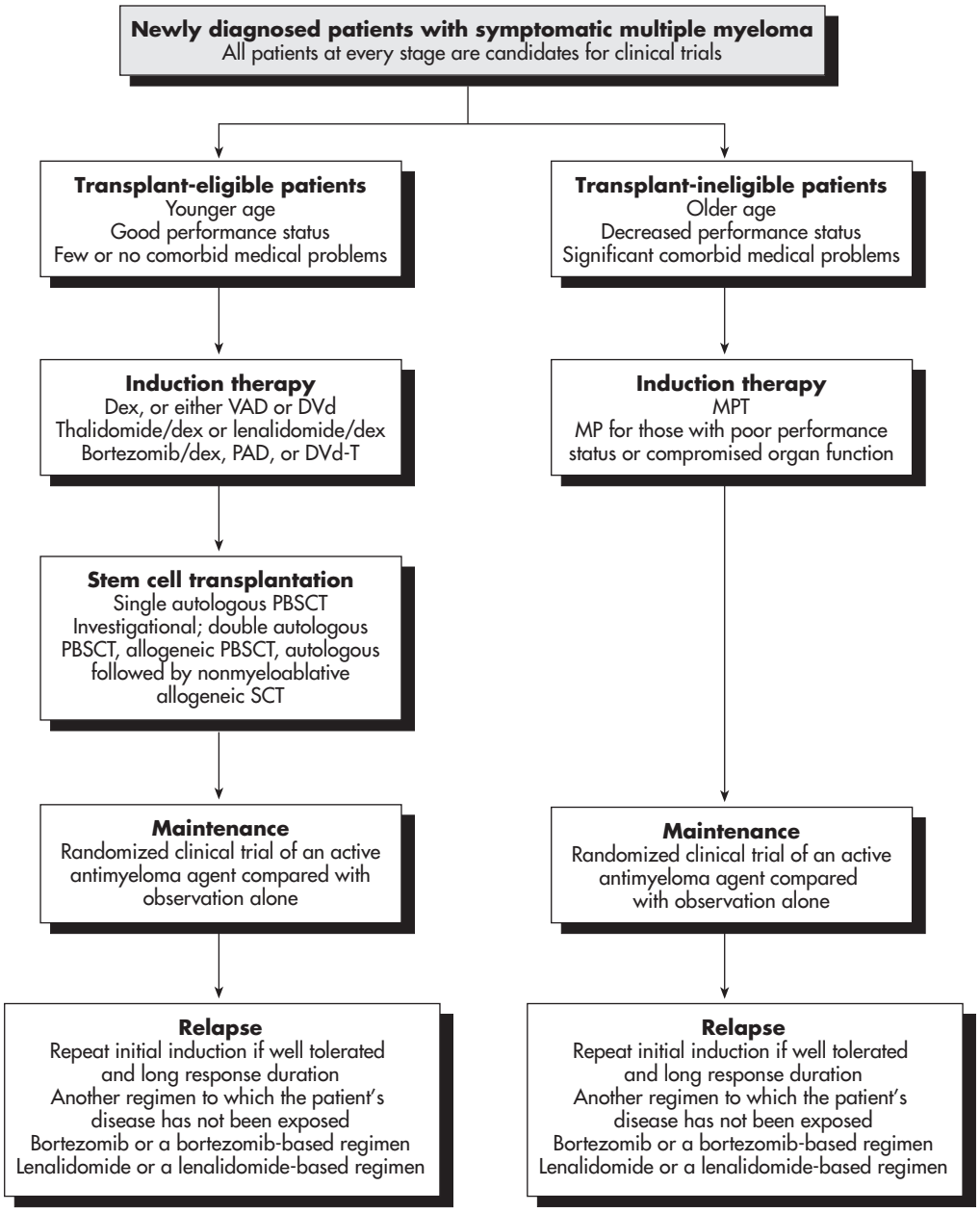

FIGURE M1-49 A treatment algorithm for multiple myeloma. A treatment algorithm for patients who are or are not suitable candidates for stem cell transplantation is presented. Further detail is provided in the text. *Dex,* Dexamethasone; *DVd,* pegylated liposomal doxorubicin with vincristine and oral dexamethasone; *DVd-T,* DVd with thalidomide; *MP,* melphalan and prednisone; *MPT,* melphalan and prednisone with thalidomide; *PAD,* bortezomib with infusional doxorubicin and dexamethasone; *PBSCT,* peripheral blood stem cell transplantation; *SCT,* stem cell transplantation; *VAD,* infusional doxorubicin and vincristine with oral dexamethasone. (Modified from Runge MS, Greganti MA: *Netter's internal medicine,* Philadelphia, 2008, Saunders.)

EVIDENCE

Abstract[1]

Purpose:

This study compared denosumab, a fully human monoclonal anti-receptor activator of nuclear factor kappa-B ligand antibody, with zoledronic acid (ZA) for delaying or preventing skeletal-related events (SRE) in patients with advanced cancer and bone metastases (excluding breast and prostate) or myeloma.

Patients and Methods:

Eligible patients were randomly assigned in a double-blind, double-dummy design to receive monthly subcutaneous denosumab 120 mg (n=886) or intravenous ZA 4 mg (dose adjusted for renal impairment; n=890). Daily supplemental calcium and vitamin D were strongly recommended. The primary end point was time to first on-study SRE (pathologic fracture, radiation or surgery to bone, or spinal cord compression).

Results:

Denosumab was noninferior to ZA in delaying time to first on-study SRE (hazard ratio, 0.84; 95% CI, 0.71 to 0.98; *P*=.0007). Although directionally favorable, denosumab was not statistically superior to ZA in delaying time to first on-study SRE (*P*=.03 unadjusted; *P*=.06 adjusted for multiplicity) or time to first-and-subsequent (multiple) SRE (rate ratio, 0.90; 95% CI, 0.77 to 1.04; *P*=.14). Overall survival and disease progression were similar between groups. Hypocalcemia occurred more frequently with denosumab. Osteonecrosis of the jaw occurred at similarly low rates in both groups. Acute-phase reactions after the first dose occurred more frequently with ZA, as did renal adverse events and elevations in serum creatinine based on National Cancer Institute Common Toxicity Criteria for Adverse Events grading.

Conclusion:

Denosumab was noninferior (trending to superiority) to ZA in preventing or delaying first on-study SRE in patients with advanced cancer metastatic to bone or myeloma. Denosumab represents a potential novel treatment option with the convenience of subcutaneous administration and no requirement for renal monitoring or dose adjustment. Ⓐ

Evidence-Based Reference

Henry DH et al.: Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma, *Clin Oncol* 29:1125–1132, 2011. Ⓐ

SUGGESTED READINGS

Anderson KC et al.: NCCN clinical practice guideline in oncology: multiple myeloma, *J Natl Compr Canc Netw* 7:908–942, 2009.

Attal M et al.: Lenalidomide maintenance after stem-cell transplantation for multiple myeloma, *N Engl J Med* 366:1782–1791, 2012.

Bruno B et al.: A comparison of allografting with autografting for newly diagnosed myeloma, *N Engl J Med* 356:1110, 2007.

Dispenzieri A et al.: Treatment of newly diagnosed multiple myeloma based on Mayo stratification of myeloma and risk-adapted therapy (mSMART): consensus statement, *Mayo Clin Proc* 82(3):323, 2007.

Facon T et al.: Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomized trial, *Lancet* 370:1209–1218, 2007.

Harousseau JL, Moreau P: Autologous hematopoietic stem cell transplantation from multiple myeloma, *N Engl J Med* 360:2645–2654, 2009.

Imrie K et al.: The role of high dose chemotherapy and stem-cell transplantation in patients with multiple myeloma: a practice guideline of the Cancer Care Ontario Practice Guidelines Initiative, *Ann Intern Med* 136:619, 2002.

International Myeloma Working Group: Criteria for the classification of monoclonal gammopathies, multiple myeloma, and related disorders: a report of the International Myeloma Working Group, *Br J Haematol* 121:749–757, 2003.

Kyle RA et al.: Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma, *N Engl J Med* 356:2582, 2007.

Kyle RA, Rajkumar SV: Multiple myeloma, *N Engl J Med* 351:1860–1873, 2004.

McCarthy PL et al.: Lenalidomide after stem-cell transplantation for multiple myeloma, *N Engl J Med* 366:1770–1781, 2012.

Mikhael JR et al.: Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines 2013, *Mayo Clin Proc* 88(4):360–376, 2013.

Nau KC, Lewis WD: Multiple myeloma: diagnosis and treatment, *Am Fam Physician* 78(7):853–859, 2008.

Palumbo A, Anderson K: Multiple myeloma, *N Engl J Med* 364:1046–1060, 2011.

Palumbo A et al.: Autologous transplantation and maintenance therapy in multiple myeloma, *N Engl J Med* 371:895–905, 2014.

Palumbo A et al.: International Myeloma Working Group guidelines for the management of multiple myeloma patients ineligible for standard high-dose chemotherapy with autologous stem cell transplantation, *Leukemia* 23:1716–1730, 2009.

Palumbo A et al.: Bortezomib as induction before autologous transplantation, followed by lenalidomide as consolidation maintenance in untreated multiple myeloma patients, *J Clin Oncol* 28:2314, 2010.

Palumbo A et al.: Continuous lenalidomide treatment for newly diagnosed multiple myeloma, *N Engl J Med* 366:1759–1769, 2012.

Richardson PG et al.: Bortezomib or high dose dexamethasone for relapsed multiple myeloma, *N Engl J Med* 352:2487–2498, 2005.

San Miguel JF et al.: Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma, *N Engl J Med* 359:906–917, 2008.

Stewart AK et al.: Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma, *N Engl J Med* 372:142–152, 2015.

BASIC INFORMATION

DEFINITION

Multiple sclerosis (MS) is a chronic predominantly autoimmune demyelinating disease of the central nervous system (CNS) characterized by subacute neurologic deficit correlating with CNS lesions separated in time and space, excluding other possible disease.

Subtypes include:

- Relapsing-remitting MS (RRMS) (82%): relapses followed by complete or near-complete recovery, 50% to 85% of which later transition to SPMS
- Secondary progressive MS (SPMS): progression of disability with few or no relapses
- Primary progressive MS (PPMS) (18%): progression from the onset, rarely with relapses
- Progressive relapsing or relapsing progressive courses can be incorporated into PPMS or SPMS, respectively.
- Relapses are defined as a subacute onset of neurologic dysfunction that lasts for at least 24 hr.

Rare MS variants include:

- Marburg's disease: MRI reveals a tumorlike lesion with notable edema in one cerebral hemisphere. Pathology shows severe inflammation with necrosis: typically acute onset with a fulminant, often malignant, course.
- Balo's concentric sclerosis: Neuroimaging and pathology show alternating rings of myelination and demyelination, resembling an onion bulb.
- Schilder's diffuse sclerosis: childhood onset with one to two large symmetric lesions
- Relapsing optic neuritis

SYNONYMS

MS
Disseminated sclerosis

ICD-9CM CODES
340 Multiple sclerosis
ICD-10CM CODES
G35 Multiple sclerosis

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: 20 to 40 yr in two thirds of patients; it is the most common permanently disabling disorder of the central nervous system in young adults; mean age of onset is 30 yr, range is infancy to 70 yr.

PREVALENCE: More common in people raised in northern latitudes and in certain genetic clusters. Prevalence per 10,000 varies from 20 in southern Europe to 150-180 in Canada, northern United States, and northern Europe; and <10 in Asia, Central America, and most of Africa. Estimated 400,000 people in the U.S. and 2.5 million people worldwide with MS.

PREDOMINANT SEX & AGE: Female/male ratio is 2 to 3:1.

GENETICS: Frequency of MS in dizygotic twins and siblings is 3% to 5% and 20% to 40% in monozygotic twins. Most common associations include human leukocyte antigen classes I and II *(DRB1*1501, DQA1*0102, DQB1*0602)*, *(DRB1*0405-DQA1*0301-DQB1*0302* in Mediterranean population).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Findings depend on the location of the CNS lesion(s), and may include+

- Common: nonspecific complaints such as fatigue, blurred vision, diplopia, vertigo, falls, hemiparesis, paraparesis, monoparesis, numbness, paresthesias, ataxia, cognitive deficits, depression, sexual dysfunction, and urinary dysfunction
- Visual abnormalities: horizontal nystagmus, visual field defects, ***Marcus Gunn pupil*** (i.e., relative afferent papillary defect—normal direct and consensual light reflexes; however, when swinging flashlight from one eye to the other, direct light causes dilatation of pupil of affected eye), ***internuclear ophthalmoplegia*** (paresis of the adducting eye on conjugate lateral gaze with horizontal nystagmus of the abducting eye [Fig. M1-50])
- Corticospinal tract(s) involvement: leads to upper motor neuron signs such as spasticity, hyperreflexia, clonus, extensor plantar responses, and upper motor neuron pattern of weakness (shoulder abduction, elbow, hand and finger extension, hip and knee flexion, foot dorsiflexion more severely affected)
- Sensory loss: may include partial or full dermatomal loss of pain and temperature, loss of vibration (common) and position sense, and a thoracic band of sensory loss
- Ataxia: intention tremor, dysmetria, dysdiadochokinesis, titubation, inability to tandem gait
- Bladder dysfunction: detrusor hyperreflexia (urge incontinence), flaccidity (neurogenic bladder), and dyssynergia (bladder contracts against a closed sphincter)
- ***Lhermitte's sign:*** flexion of the neck elicits an electrical sensation extending down the spine and occasionally into the extremities
- ***Uhthoff's phenomenon:*** transient worsening of preexisting symptoms with small elevations in body temperature (e.g., during exercise or warm bathing)

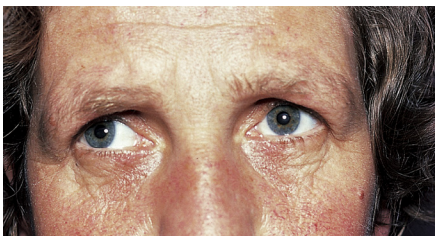

FIGURE M1-50 Internuclear ophthalmoplegia may be an initial feature of brain stem involvement in multiple sclerosis. On lateral gaze to the right, adduction of the left eye is incomplete. On convergence, eye movement was normal. The lesion is in the left medial longitudinal bundle, between the nucleus in the pons and the third nerve nucleus on the opposite side. (From Forbes CD, Jackson WF. *Color atlas and text of clinical medicine,* ed 3, London, 2003, Mosby.)

ETIOLOGY

Remains unknown but multifactorial with evidence for autoimmunity (autoreactive T and B cells), environmental factors, and genetics (Mendelian and epigenetic). Environmental risk factors during childhood include certain viruses (e.g., Epstein-Barr virus and human herpes virus 6), low UV exposure, and month of birth (higher in spring). Other risk factors include low vitamin D level and smoking.

DIAGNOSIS

- MS: based on revised 2010 McDonald criteria (Table M1-26)
- RRMS: see Table M1-26)
- PPMS: insidious progression of disability with a positive CSF and either dissemination in both space and time *or* ongoing progression for at least 1 yr

DIFFERENTIAL DIAGNOSIS

- Autoimmune: acute disseminated encephalomyelitis (ADEM), postvaccination encephalomyelitis
- Degenerative: subacute combined degeneration of the cord (vitamin B_{12} deficiency), amyotrophic lateral sclerosis
- Infections: Lyme disease, neurosyphilis, HIV, tropical spastic paraparesis, progressive multifocal leukoencephalopathy, Whipple's disease
- Inflammatory: systemic lupus erythematosus, vasculitis, sarcoidosis, Sjögren's disease, Behçet's disease, celiac disease

TABLE M1-26 Summary of Revised 2005-2010 McDonald Criteria for Diagnosis of Multiple Sclerosis

RRMS/Clinical Attacks	Clinical Lesions	Paraclinical Testing Needed
2	2	None
2	1	MRI dissemination in space *or* 2 MRI lesions consistent with MS plus positive CSF
1	2	MRI dissemination in time
1	1	MRI dissemination in space *or* 2 MRI lesions consistent with MS plus positive CSF and MRI dissemination in time

Evidence of clinical lesions by physical examination or evoked potentials.
CSF, Cerebrospinal fluid; *MRI,* magnetic resonance imaging; *MRI dissemination in space;* ≥1 T2 lesions in 2 of the 4 typical areas for MS lesions – periventricular, juxtacortical, infratentorial or spinal cord; *MRI dissemination in time,* a new lesion at follow-up MRI at any time, or presence of both an enhancing and nonenhancing lesion at any time.

- Inherited metabolic disorders: leukodystrophies
- Mitochondrial: Leber's hereditary optic neuropathy, mitochondrial encephalopathy, lactic acidosis, and strokelike episodes (MELAS)
- Neoplasms: CNS lymphoma, metastases
- Vascular: subcortical infarcts, Binswanger's disease

WORKUP

- Lumbar puncture for cases that are atypical or do not satisfy the diagnostic criteria for MS. Typical CSF abnormalities may include increased protein (less than 100 mg/dl), mild elevation of mononuclear white blood cells, and increased IgG synthesis rate. 70% of clinically definite MS (CDMS) have elevated CSF immunoglobulin (Ig) G index and 90% have oligoclonal bands. (Serum needs to be sent to lab simultaneously with CSF for both tests.) False-positive results with IgG index and rarely with positive OCBs can be seen in CNS infections, parainfections, vasculitis, and CNS lymphoma.
- Serum: complete blood count, ESR, chemistry panel, liver function tests, ANA, vitamin B_{12}, vitamin D.
- To identify additional lesions, consider collagen vascular serum tests, neuromyelitis optica IgG A, Lyme titre, ACE TSH, free T_4, anti–thyroglobulin A, very-long-chain fatty acids, arylsulfatase A.
- Consider optical coherence tomography or evoked potentials (visual, somatosensory and brain stem auditory evoked response).

IMAGING STUDIES

Head MRI ± gadolinium is recommended in all cases. Fig. EM1-51 illustrate imaging features of MS. MRI of the cervical spine can be helpful. MRI assesses acute and chronic lesions, and atrophy. A normal MRI of the brain does not conclusively exclude MS.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Patient education regarding disease characteristics, treatment options, risks and benefits of treatment, and prognosis. Often patients need intermittent rest periods on a daily basis and when physically active, and avoid exposure to heat, which typically worsens symptoms.

Recommend physical therapy for new weakness, incoordination, or spasticity.

ACUTE GENERAL Rx

Relapses: high-dose IV methylprednisolone (3 to 5 days of 15 mg/kg/day, with a maximum of 1 g/day), often followed by a 7- to 10-day prednisone or methylprednisolone taper. High-dose corticosteroids do not alter the long-term course of disease. May consider IVIG, or plasmapheresis.

CHRONIC Rx

- FDA-approved therapies are only for relapsing MS; there are none yet approved for progressive MS.
- Disease-modifying injection therapy includes interferon beta-1a (IM Avonex, SC Rebif), interferon beta-1b (SC Betaseron, Extavia), and glatiramer acetate (SC Copaxone). Common side effects for Copaxone include injection site reactions and benign chest tightness; no serum studies are needed. Common side effects for interferons include flulike symptoms, liver toxicity, and leukopenia; CBC and LFTs (initially q1mo, then q3mo).
- Disease-modifying oral therapy:
  Typically monthly CBC and liver function tests for 6 mo then q3mo; pregnancy test.
  1. Fingolimod (Gilenya), a sphingosine-1-phosphate receptor modulator and lymphocyte sequester. Possible side effects: liver toxicity, bradycardia with first dose (requiring cardiac monitoring and ECG for at least 8 hr after administration of first dose), arrhythmia, pancytopenia, macular edema (ophtho exam at baseline, 3 months, and thereafter for those with DM or uveitis), and reduced pulmonary function. Obtain VZV serology.
  2. Teriflunomide (Aubagio), reversible inhibitor of pyrimidine synthesis (enzyme dihydroorotate dehydrogenase). Possible side effects: diarrhea, abnormal liver function tests, nausea, and hair loss; pregnancy category X. Serum levels can be measured, and drug can be eliminated by charcoal or cholestyramine. Obtain TB test.
  3. Dimethyl fumarate (Tecfidera), mechanism includes inhibition of transcription of NF-KB. Possible side effects include nausea, abdominal discomfort, and flushing—especially during the first month—and leukopenia.
- Disease-modifying IV therapy:
  1. Natalizumab (Tysabri) is a monoclonal humanized Ab which binds integrin-α4. It has been associated with a higher risk of progressive multifocal leukoencephalopathy (JC virus) than other immunosuppressants. Test for JC virus Ab at least annually (sooner if history of chemotherapy). If positive, PML is still rare but risk increases with increased length of therapy, history of chemotherapy, concomitant immunosuppressants, or interferons.
  2. For rapidly progressive disability or frequent relapses on other maximum therapy, MS specialist may consider mitoxantrone, cyclophosphamide, or rituximab.
- Symptomatic therapy:
- Dalfampridine (Ampyra) is a potassium channel blocker recently approved to improve walking speed in patients with MS.
- Treat spasticity with baclofen or tizanidine. In acute worsening, rule out infection. Onabotulinum toxin type A injection for focal intractable spasticity. Intrathecal baclofen pump for generalized intractable spasticity.
- Treat urge incontinence with anticholinergic/muscarinic therapy such as oxybutynin, tolterodine, or solifenacin. Treat urinary retention with tamsulosin. In both cases, rule out a bladder infection.
- Treat dysesthesias with gabapentin or oxycarbazepine.
- Fatigue: consider amantadine 100 mg bid, modafinil, stimulant, or fluoxetine.
- Tremor: clonazepam, carbamazepine, propranolol, or gabapentin.
- Depression and anxiety are common. Consider referring to both a counselor and psychiatrist.

DISPOSITION

Most patients have complete or near-complete recovery weeks to months after a relapse. Typically, 2 relapses occur in RRMS patient per year (75% will have >1 relapse). Although the rate of disease progression is highly variable, there is higher risk of greater long-term disability with higher relapse rate during the first 2-5 yr, poor recovery from initial relapses, older age of onset, involvement of multiple systems, male sex, African-American, and primary progressive disease.

REFERRAL

- Referral to neurologist is highly recommended. Referral to MS specialist should be considered in cases of poor response to therapy, possibility of IV or cytotoxic treatment, and/or concern for complications of therapies.
- Consider referrals for physical therapy and occupational therapy.
- Consider referral to urology if possible dyssynergia, or not responsive to treatment.

PEARLS & CONSIDERATIONS

- Clinically isolated syndrome (CIS): isolated demyelinating event and assessing risk of CDMS 1) in optic neuritis, if brain MRI is completely normal, there is 20% to 25% chance of CDMS over 15 yrs. 2) In CIS, if there are >2 T2 hyperintensities on brain MRI, there is 84% risk, and if there are >2 Gd + lesions there is a 96% risk of CDMS over 18 months..
- Pseudorelapses may occur with heat, fever, or infections (urinary tract infections common in patients with MS).
- Headache, fever, altered mental status, elevated CSF WBCs, or recurrent relapses over days to weeks, raises concern for CNS infection or ADEM.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Multiple Sclerosis (Patient Information)

AUTHOR: **ALEXANDRA DEGENHARDT, M.D., M.M.Sc**

EVIDENCE

Abstract[1]

Objective.

To evaluate the association between the damage to the anterior and posterior visual pathway as evidence of the presence of retrograde and anterograde trans-synaptic degeneration in multiple sclerosis (MS).

Methods.

We performed a longitudinal evaluation on a cohort of 100 patients with MS, acquiring retinal optical coherence tomography to measure anterior visual pathway damage (peripapillary retinal nerve fiber layer [RNFL] thickness and macular volume) and 3T brain magnetic resonance imaging (MRI) for posterior visual pathway damage (volumetry and spectroscopy of visual cortex, lesion volume within optic radiations) at inclusion and after 1 year. Freesurfer and SPM8 software was used for MRI analysis. We evaluated the relationships between the damage in the anterior and posterior visual pathway by voxel-based morphometry (VBM), multiple linear regressions, and general linear models.

Results.

VBM analysis showed that RNFL thinning was specifically associated with atrophy of the visual cortex and with lesions in optic radiations at study inclusion ($p < 0.05$). Visual cortex volume (β ¼ +0.601, 95% confidence interval [CI] ¼ +0.04 to +1.16), N-acetyl aspartate in visual cortex (β ¼ +1.075, 95% CI ¼ +0.190 to +1.961), and lesion volume within optic radiations (β¼_2.551, 95% CI¼_3.910 to _1.192) significantly influenced average RNFL thinning at study inclusion independently of other confounders, especially optic neuritis (ON). The model indicates that a decrease of 1cm^3 in visual cortex volume predicts a reduction of 0.6μm in RNFL thickness. This association was also observed after 1 year of follow-up. Patients with severe prior ON (adjusted difference¼_3.01, 95% CI¼_5.08 to _0.95) and mild prior ON (adjusted difference ¼_1.03, 95% CI¼_3.02 to +0.95) had a lower adjusted mean visual cortex volume than patients without ON.

Interpretation.

Our results suggest the presence of trans-synaptic degeneration as a contributor to chronic axon damage in MS. Ⓐ

Evidence-Based Reference

Gabilondo I, Martı´nez-Lapiscina EH, Martı´nez-Heras E, et al.: Trans-Synaptic Axonal Degeneration in the Visual Pathway in Multiple Sclerosis, *Ann Neurol* 75:98–107, 2014. Ⓐ

SUGGESTED READINGS

Balcer LJ, Galetta SL: Treatment of acute demyelinating optic neuritis, *Semin Ophthalmol* 17(1):4–10, 2002.

CHAMPS Study Group: MRI predictors of early conversion to clinically definite MS in the CHAMPS placebo group, *Neurology* 59:998, 2002.

Degenhardt A et al.: Clinical prognostic factors in MS: a natural history review, *Nature Rev Neurology* 5(12):672–682, 2009.

Freeman MS et al.: Present and emerging therapies for MS, *Continuum Aug* 19(4):968–991, 2013.

Handunnetthi L et al.: Multiple sclerosis, vitamin D, and *HLADRB1*15*, *Neurology* 74(23):1905–1910, 2010.

Harrison DM: In the clinic: multiple sclerosis, *Ann Intern Med*, 2014.

Jacobs LD et al.: Intramuscular interferon beta-1a therapy, initiated during first demyelinating event in multiple sclerosis, *N Engl J Med* 343:898, 2000.

Lublin FD et al.: Effect of relapses on development of residual deficit in multiple sclerosis, *Neurology* 61:1528–1532, 2003.

O'Connor P et al.: Randomized trial of oral teriflunomide for relapsing MS, *N Engl J Med* 365(14):1293–1303, 2011.

Pelletier D, Hafler DA: Fingolimod for multiple sclerosis, *N Engl J Med* 366:339–347, 2012.

Polman CH et al.: Diagnostic criteria for multiple sclerosis: 2010 revisions to the "McDonald Criteria", *Ann Neurol* 69:292, 2011.

Polman CH et al.: A randomized, placebo-controlled trial of natalizumab for relapsing MS, *N Engl J Med* 354(9):899–910, 2006.

Ramagopalan SV et al.: Epidemiology of MS, *Neurol Clinic* 29(2):207–217, 2010.

Saguil A et al.: Multiple sclerosis: a primary care perspective, *Am Fam Physician* 90(9):644–652, 2014.

Scalfari A et al.: The natural history of MS, study 10: relapses and long-term disability, *Brain* 133:1914–1929, 2010.

Weinshenker BG et al.: The natural history of MS, study 1: a geographically based study, *Brain* 112:1419, 1989.

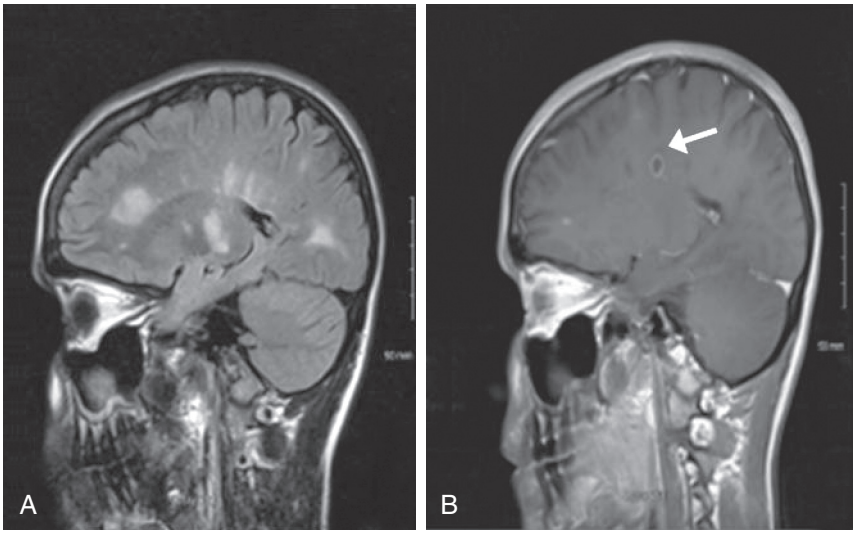

FIGURE EM1-51 Multiple sclerosis. A, Sagittal FLAIR image magnetic resonance scan shows multiple lesions in corpus callosum, "Dawson's fingers" (periventricular fingerlike lesions oriented towards the ventricles), along with ovoid and punctuate lesions in the deep white matter. **B,** Gadolinium-enhanced scan shows an enhancing lesion *(arrow).*

BASIC INFORMATION

DEFINITION

Mumps is an acute generalized viral infection that is usually characterized by nonsuppurative swelling and tenderness of one or both parotid glands. It is caused by mumps virus, a single-stranded RNA paramyxovirus, of which humans are the only natural host.

SYNONYMS

Viral parotitis
Parotitis

ICD-9CM CODES
072.9 Mumps
ICD-10CM CODES
B26.9 Mumps without complication
B26.0+ Mumps orchitis
B26.1+ Mumps meningitis
B26.2+ Mumps encephalitis
B26.3+ Mumps pancreatitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.)
- About 300 infections/yr. Sporadic outbreaks still occur in schools, colleges, military posts, or summer camps started by an unvaccinated person.
- More than 150,000 cases/yr before licensure of mumps vaccine in 1967

PREDOMINANT SEX: Males = females
PREDOMINANT AGE: 75% of disease in teenage years
PEAK INCIDENCE: Late winter and early spring months
GENETICS: Congenital infection:
- First-trimester infection is associated with excessive fetal deaths.
- Second- and third-trimester infection is not associated with increased fetal mortality.

Neonatal infection:
- Uncommon
- Uncommon in infants <1 yr because of passive immunity conferred by placental transfer of maternal antibody

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Prodromal period: includes low-grade fever, malaise, anorexia, and headache
- Parotid swelling (Fig. M1-52) and tenderness; often the first signs of infection:
  1. Progresses over 2 to 3 days, then opposite side may become involved
  2. Unilateral parotitis in 25% of cases
  3. Considerable pain with parotid swelling, causing trismus and difficulty with mastication and pronunciation
  4. Pain exacerbated by eating or drinking citrus and other acidic foods
  5. Possible fever with parotid swelling, ranging up to 40° C
  6. Parotid swelling, usually resolving within 1 wk
- CNS involvement:
  1. May occur from 1 wk before to 2 wk after the onset of parotitis or even in its absence
  2. Meningitis:
     a. Occurs in 1% to 10% of patients with mumps parotitis
     b. Occurs three times more often in males than females
     c. Symptoms: headache, fever, nuchal rigidity, and vomiting
     d. Full recovery with no sequelae
  3. Encephalitis:
     a. May develop early, as a result of direct viral invasion of neurons, or late, around the second wk after onset of parotitis, and is a postinfectious demyelinating process.
     b. Mumps accounted for only 0.5% of viral meningitis.
     c. Symptoms: fever, alterations in the level of consciousness, possible seizures, paresis or paralysis, and aphasia. Fever can be quite high (40° to 41° C).
     d. Cerebellitis and hydrocephalus are serious complications of mumps encephalitis.
     e. May result in permanent sequelae or death.
  4. Other rare neurologic complications include cerebellar ataxia, transverse myelitis, Guillain-Barré syndrome, and facial palsy.
- Epididymoorchitis:
  1. Most common extrasalivary gland complication of mumps in adult men
  2. Occurs in 38% of postpubertal males who have mumps
  3. Most often unilateral but is bilateral in 30% of males who develop this complication
  4. May precede development of parotitis and may be only manifestation of mumps
  5. Two thirds of cases develop during first week of parotitis
  6. Symptoms:
     a. Severe pain, swelling, and tenderness of the testes and scrotal erythema
     b. Fever and chills
  7. Some degree of testicular atrophy in 50% of cases, mo to yr later
  8. Sterility from bilateral orchitis is rare
- Involvement of pancreas and ovaries:
  1. Pancreas: abdominal pain, fever, and vomiting
  2. Ovaries: oophoritis
     a. Occurs in 5% of postpubertal women with mumps
     b. Symptoms include fever, nausea, vomiting, and lower abdominal pain
     c. May rarely result in decreased fertility and premature menopause
- Transient renal impairment: common and manifested by hematuria and polyuria
- Joint involvement:
  1. Migratory polyarthritis is most frequent
  2. Infrequently affects adults with mumps
  3. Occurs rarely in children
  4. Self-limited, with complete resolution
- Deafness:
  1. Most often unilateral, involving high frequencies; may rarely cause bilateral involvement
  2. Most patients recover
  3. Permanent unilateral deafness reported in 1 in 20,000 cases
  4. Labyrinthitis and end lymphatic hydrops also reported
- Myocardial involvement:
  1. Uncommon
  2. Rarely causes progressive and fulminant fatal myocarditis with dilated cardiomyopathy
  3. Refractory arrhythmia and congestive heart failure
  4. Coronary artery involvement
- Eye involvement:
  1. Corneal endotheliitis following mumps parotitis

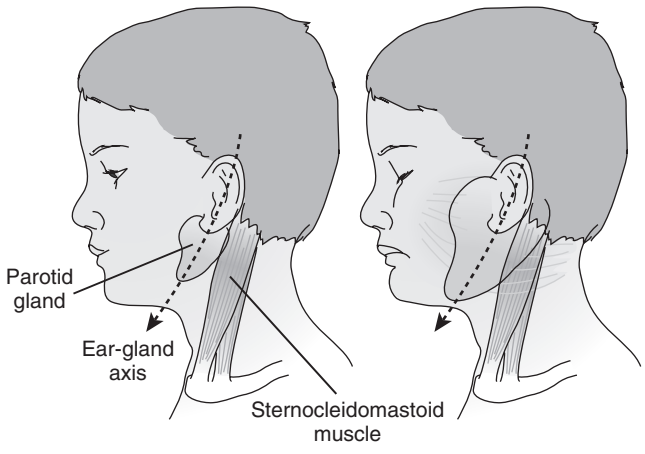

FIGURE M1-52 Schematic drawing of a parotid gland infected with mumps *(right)* compared with a normal gland *(left).* An imaginary line bisecting the long axis of the ear divides the parotid gland into two equal parts. These anatomic relationships are not altered in the enlarged gland. An enlarged cervical lymph node is usually posterior to the imaginary line. (From Mumps [epidemic parotitis]. In Krugman S et al [eds]: *Infectious diseases in children,* ed 6, St Louis, 1977, Mosby.)

ETIOLOGY

- Virus is spread via direct contact, droplet nuclei, fomites, or oral or nasal secretions.
- Patients are contagious from 48 hr before to 9 days after parotid swelling.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other viruses that may cause acute parotitis:
  1. Parainfluenza types 1 and 3
  2. Coxsackie viruses
  3. Influenza A
  4. Cytomegalovirus
- Suppurative parotitis:
  1. Most often caused by *Staphylococcus aureus*
  2. May be differentiated from mumps
     a. Extreme indurations, tenderness and erythema overlying the gland
     b. Ability to express pus from Stensen's duct or massage of parotid
- Other conditions that may occur with parotid enlargement or swelling:
  1. Sjögren's syndrome
  2. Leukemia
  3. Diabetes mellitus
  4. Uremia
  5. Malnutrition
  6. Cirrhosis
- Drugs that cause parotid swelling:
  1. Phenothiazines
  2. Phenylbutazone
  3. Thiouracil
  4. Iodides
- Conditions that cause unilateral swelling:
  1. Tumors
  2. Cysts
  3. Stones causing obstruction
  4. Strictures causing obstruction

WORKUP

- Diagnosis based on history of exposure and physical finding of parotid tenderness with mild to moderate constitutional symptoms.
- Diagnosis is confirmed by a variety of serologic tests or isolation of the virus.

LABORATORY TESTS

- Diagnosis is confirmed by a positive IgM mumps antibody or by fourfold rise between acute and convalescent sera by CF, ELISA, or neutralization tests. However, serologic mumps testing is particularly unhelpful in some vaccinated individuals who can have mumps without having the usual immunoglobulin M (IgM) spike. A polymerase chain reaction (PCR) assay is also available.
- Virus can be isolated from the saliva, usually from 2 to 3 days before to 4 to 5 days after the onset of parotitis. Researchers have shown that many cases labeled as "parotitis" are actually caused by other viruses (EB virus, human herpesvirus 6B, human parainfluenza virus).[1]
- Virus can be cultured from CSF in patients with meningitis during the first 3 days of meningeal findings. More rapid confirmation of mumps in the CSF is IgM antibody capture immunoassay and nested PCR assay.
- Virus can be detected in urine during the first 2 wk of infection.
- WBC:
  1. May be normal or possible mild leukopenia with a relative lymphocytosis
  2. Leukocytosis with left shift with extra–salivary gland involvement, such as meningitis, orchitis, or pancreatitis
- Serum amylase:
  1. Elevated in the presence of parotitis
  2. May remain elevated for 2 to 3 wk
  3. May be differentiated from mumps and parotids by isoenzyme analysis or serum pancreatic lipase
- Mumps meningitis:
  1. CSF WBCs from 10 to 2000 WBC/mm^3 with a predominance of lymphocytes
  2. In 20% to 25% of patients, predominance of polymorphonuclear cells
  3. CSF protein normal or mildly elevated
  4. CSF glucose low, <40 mg/dl, in 6% to 30% of patients

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive treatment
- Adequate hydration and nutrition

ACUTE GENERAL Rx

- Analgesics and antipyretics to relieve pain and fever
- Narcotic analgesics, along with bed rest, ice packs, and a testicular bridge, to relieve pain associated with mumps orchitis
- IV fluids for patients with frequent vomiting associated with mumps pancreatitis or meningitis

[1]Barshey AE et al: Viruses detected among sporadic cases of parotitis, United States 2009-2011, *J Infect Dis* 208:1979, 2013.

DISPOSITION

Most patients recover without incident.

REFERRAL

- To a neurologist if significant neurologic complications develop during or following mumps (myelitis, encephalitis, cranial nerve involvement, cerebellar ataxia, etc.)
- To a cardiologist if viral perimyocarditis develops
- To a urologist if orchitis develops

PEARLS & CONSIDERATIONS

COMMENTS

Prevention:

- Attenuated live mumps virus vaccine has been available since 1967.
  1. Usually given in combination with measles and rubella vaccines (MMR)
  2. Should be given at 12-15 mo of age, and again at 5 to 12 yr
  3. Seroconversion in about 100% of infants given the vaccine
  4. Contraindicated in pregnant women and immunocompromised patients
  5. Patients with asymptomatic HIV infection and patients with symptomatic HIV infection, in the absence of severe immunosuppression, can safely receive mumps, measles, and rubella (MMR) vaccine
  6. Adverse events of vaccination include local pain, indurations, thrombocytopenic purpura, Guillain-Barré syndrome, and cerebellar ataxia
- The CDC and American Academy of Pediatrics (AAP) recommend that patients with mumps stay home from work or school for 5 days after onset of clinical symptoms.
- Because virus may be shed before the onset of parotid swelling, isolation possibly not of great value in limiting spread of infection. Use droplet precautions as per CDC and AAP.
- Mumps is an notifiable disease in all U.S. states.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Mumps (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Barskey AE et al.: Mumps resurgences in the United States: a historical perspective on unexpected elements, *Vaccine* 27:6186–6195, 2009.

Centers for Disease Control and Prevention: Updated recommendations of the Advisory Committee on Immunization Practices (ACIP) for the control and elimination of mumps, *MMWR Morb Mortal Wkly Rep* 55(22):629, 2006.

Dayan GH et al.: Recent resurgence of mumps in the United States, *N Engl J Med* 358:1580, 2008.

BASIC INFORMATION

DEFINITION

Muscular dystrophy (MD) refers to a heterogeneous group of inherited disorders resulting in characteristic patterns of muscle weakness, some with cardiac involvement. Only disorders with childhood or adult onset are considered here (i.e., excluding congenital myopathies).

ICD-9CM CODES
359 Muscular dystrophies and other myopathies
359.1 Hereditary progressive muscular dystrophy
ICD-10CM CODES
G71.0 Muscular dystrophy

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE

- Most common childhood MD is Duchenne's muscular dystrophy (DMD) with an incidence of 1/3500 male births.
- Most common adult MD is myotonic dystrophy with an incidence as high as 1/8000.

GENETICS

- **Dystrophinopathies:** X-linked recessive defect in dystrophin gene resulting in either absence (DMD) or reduced/defective (Becker's MD [BMD]) dystrophin (Fig. M1-53)
- **Myotonic Dystrophy:** Autosomal dominant (AD) CTG trinucleotide repeat (see "Myotonia")
- **Limb-Girdle Muscular Dystrophy:** The majority are autosomal recessive, also autosomal dominant forms. Associated with deficiencies identified in multiple proteins (sarcoglycan, calpain, dystroglycan, and dysferlin may be most common; also may involve telethonin, lamin A/C, myotilin, and caveolin-3)
- **Emery-Dreifuss Muscular Dystrophy:** X-linked recessive defect in nuclear protein emerin or AR/AD defect in inner nuclear lamina proteins lamin A/C
- **Facioscapulohumeral Muscular Dystrophy:** AD; genetic mutation causes deletion of 3.3 kb repeat
- **Oculopharyngeal Muscular Dystrophy:** AD GCG trinucleotide repeat resulting in deficient mRNA transfer from nucleus

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- **Dystrophinopathies:** Proximal arm and leg weakness with hypertrophic calf muscles (Fig. M1-54), delayed motor milestones, cognitive impairment, cardiac involvement, progressive course resulting in respiratory complications and respiratory failure
  1. DMD (Fig. M1-55) onset at 2 to 3 yr old, typically wheelchair-bound by 12 yr
  2. BMD onset at 5 to 15 yr old, ambulatory beyond age 15
- **Myotonic Dystrophy:** Variable age of onset and severity manifesting as predominantly distal weakness with long face, percussion and grip myotonia, temporalis and masseter wasting, ptosis, hypersomnolence, cognitive impairment, and cardiac conduction defects. May be associated with frontal balding, cataracts, impaired glucose tolerance, and male infertility.
- **Limb-Girdle MD:** Phenotypically and genetically heterogenous characterized by proximal hip and shoulder girdle weakness, some genotypes featuring cardiac involvement
- **Emery-Dreifuss MD:** Early adulthood onset with predominantly humeroperoneal weakness, early contractures, and cardiac dysfunction
- **Facioscapulohumeral MD:** Onset typically in late childhood or adolescence with weakness mostly in face and shoulder girdle musculature and possible later, mild involvement of lower extremities
- **Oculopharyngeal MD:** Symptom onset typically in mid-adult life with ptosis, dysphagia, dysarthria, and proximal muscle weakness
- Table M1-27 shows a classification of muscular dystrophies

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Myasthenia gravis, inflammatory myopathy, metabolic myopathy, endocrine myopathy, toxic myopathy, mitochondrial myopathy

WORKUP

- CK
- ECG, Holter monitor, echocardiography
- EMG
- Muscle biopsy with immunohistochemistry useful for diagnosis of dystrophinopathies and limb-girdle MD
- DNA analysis helpful if clinical suspicion is for myotonic, Emery-Dreifuss, facioscapulohumeral, and oculopharyngeal MDs
- Assessment of respiratory parameters, including forced vital capacity (FVC)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Genetic counseling
- Physical, occupational, respiratory, speech therapy as symptoms dictate
- Screening for sleep-disordered breathing with overnight polysomnogram (PSG) if clinically indicated
- Pacemaker placement may be necessary if cardiac conduction defect present

ACUTE GENERAL Rx

Prednisone may modestly prolong ambulation in DMD. A dose of 0.75 mg/kg/day may improve muscle strength and function over 6 months to 2 years. These short-term benefits must be weighed against the side effects of long-term steroid therapy.

CHRONIC Rx

Vigilance to avoid cardiac and respiratory complications, joint contractures

DISPOSITION

Variable course, because severity of phenotype is contingent upon both diagnosis and genotype

REFERRAL

- Surgical referral for correction of scoliosis or contractures may be necessary
- Assessment and follow-up in an MD specialty clinic

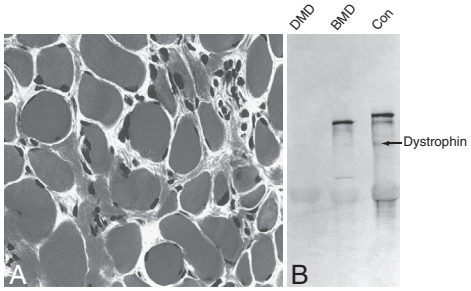

FIGURE M1-53 A, Duchenne muscular dystrophy showing variation in muscle fiber size, increased endomysial connective tissue, and regenerating fibers. **B,** Western blot showing absence of dystrophin in DMD and altered dystrophin size in Becker muscular dystrophy (BMD) compared with control (Con). (Courtesy Dr. L. Kunkel, Children's Hospital, Boston. From Kumar V et al: *Robbins and Cotran pathologic basis of disease,* ed 7, Philadelphia, 2005, Saunders.)

FIGURE M1-54 Becker muscular dystrophy in a 24-year-old male. There is dystrophy of the shoulder girdle and calf pseudohypertrophy. (Courtesy Dr. R. Pascuzzi. From Libby PL et al: *Braunwald's heart disease: a textbook of cardiovascular medicine,* ed 8, Philadelphia, 2007, Saunders.)

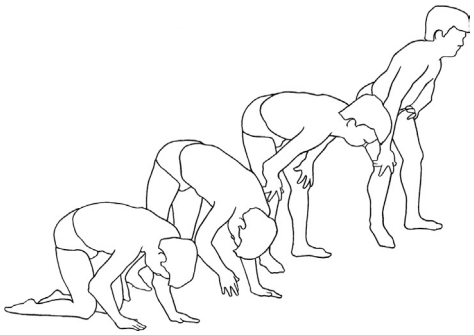

FIGURE M1-55 In Duchenne's muscular dystrophy, the patient will get up from the floor with Gower's maneuver. The boy will "walk up" his body with his hands as he arises. (From Remmel KS et al: *Handbook of symptom-oriented neurology,* ed 3, St Louis, 2002, Mosby.)

PEARLS & CONSIDERATIONS

Formal evaluation by anesthetist is recommended before any operation with general anesthesia in patients with dystrophinopathy.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Muscular Dystrophy (Patient Information)

AUTHOR: **TAYLOR HARRISON, M.D.**

TABLE M1-27 Classification of Muscular Dystrophies

Disease	Genetic Locus	Inheritance	Protein	Outcome
Duchenne/Becker		XR	Dystrophin	Lethal
Emery-Dreifuss		XR	Emerin, lamins A and C	40% lethality
Limb-Girdle Muscular Dystrophies				
LGMD 1A	5q31	AD	Myotilin	With LGMD, less-severe forms can emerge during the first three decades, leading to loss of ambulation after 30 yr of age. The most severe forms start at 3-5 yr of age and progress rapidly.
LGMD 1B	1q11-q21	AD	Laminin A/C	
LGMD 1C	3p35	AD	Caveolin	
LGMD 1D	6q23	AD	—	
LGMD 1E	7q	AD	—	
LGMD 1F	7q32	AD	—	
LGMD 1G	4p21	AD	—	
LGMD 2A	15q15.1-q21.1	AR	Calpain 3	
LGMD 2B	2p13	AR	Dysferlin	
LGMD 2C	13q12	AR	γ-Sarcoglycan	
LGMD 2D	17q12-q21.33	AR	α-Sarcoglycan	
LGMD 2E	4q12	AR	β-Sarcoglycan	
LGMD 2F	5q33-q34	AR	δ-Sarcoglycan	
LGMD 2G	17q11-q12	AR	Telethonin	
LGMD 2H	9q31-q34.1	AR	E3-Ubiquitin ligase (TRIM32)	
LGMD 2I	19q13.3	AR	Fukutin-related protein	
LGMD 2J	2q24.3	AR	Titin	
LGMD 2K	9q34	AR	Protein O-mannosyltransferase	
CMDs with CNS Involvement				
Fukuyama CMD	9q31	AR	Fukutin	LE, 11-16 yr
Walker-Warburg CMD	1p32	AR	O-Mannosyltransferase	LE, <3 yr
Muscle-eye-brain CMD	1p32-34	AR	O-MNAGAT	LE, 10-30 yr
CMDs without CNS Involvement				
Merosin-deficient classic type	6q2	AR	Merosin (laminin A_2)	Many patients never walk; others have an LGMD pattern
Merosin-positive classic type	4p16.3	AR	Selenoprotein N1, collagen VI α_2	Course stabilizes in late childhood; many continue to walk into adulthood
Integrin-deficient CMD	12q13	AR	Integrin α7	Presents early in infancy with hypotonia and delayed milestones
Other Dystrophies				
Facioscapulohumeral	4q35	AD	—	20% wheelchair bound
Oculopharyngeal	14q11.2-q13	AD/AR	Polyadenylate binding protein nuclear 1	Onset: ≈48 yr, 100% symptomatic by age 70
Myotonic dystrophy	19q13.3	AD	DMPK, CCHC-type zinc finger and CNBP	Onset: 50% show signs by age 20; variable severity

AD, Autosomal dominant; *AR*, autosomal recessive; *CCHC*, cysteine and histidine amino acid sequence in this class of zinc finger; *CMD*, congenital muscular dystrophy; *CNBP*, cellular nucleic acid–binding protein; *CNS*, central nervous system; *DMPK*, dystrophia myotonica-protein kinase; *LE*, life expectancy; *LGMD*, limb-girdle muscular dystrophy; *O-MNAGAT*, O-mannose β-1,2-*N*-acetylglucosaminyl transferase; *XR*, X chromosome related.

(From Firestein G.S.: *Kelley's textbook of rheumatology*, 9th ed, Philadelphia, 2013, Saunders.)

SUGGESTED READINGS

Blau HM: Cell therapies for muscular dystrophy, *N Engl J Med* 359:1403–1405, 2008.

Emery AE: Muscular dystrophy into the new millennium, *Neuromuscul Disord* 12(4):843, 2002.

Emery AE: The muscular dystrophies, *Lancet* 359(9307):687, 2002.

Moxley RT 3rd et al.: Practice parameter: corticosteroid treatment of Duchenne dystrophy: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society, *Neurology* 64:13–20, 2005.

Saperstein DS et al.: Clinical and genetic aspects of distal myopathies, *Muscle Nerve* 24(11):1440, 2001.

Mushroom Poisoning (PTG)

BASIC INFORMATION

DEFINITION

Mushroom poisoning is intoxication resulting from ingestion of poisonous mushrooms.

ICD-9CM CODES
988.1 Mushroom poisoning
ICD-10CM CODES
T62.0X1A Toxic effect of ingested mushrooms, accidental (unintentional), initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

- 5% of all mushrooms are poisonous. Distinction between poisonous and edible mushrooms may be difficult even by experienced persons.
- Common poisonous species include *Amanita, Russula, Gyromitra,* and *Omphalotus.*

PHYSICAL FINDINGS & CLINICAL PRESENTATION (Table M1-28)

- *Russula* causes confusion, delirium, visual disturbance, tachycardia, and diarrhea within a few hours of ingestion. Prognosis: spontaneous recovery (mortality rate >1%).
- *Amanita* and *Gyromitra* intoxication begins with symptoms of gastroenteritis (nausea, vomiting, diarrhea, and abdominal cramps) approximately 10 hr after ingestion. *Amanita* then causes cardiomyopathy and hepatic and renal failure. *Gyromitra* produces jaundice and seizures. Both mushrooms are associated with a 50% mortality rate.
- *Omphalotus* causes symptoms of gastroenteritis that subside spontaneously within 24 hr.

ETIOLOGY

- *Amanita* contains cytotoxic substances and isoxazoles that are gamma-aminobutyric acid neurotransmitter analogs.
- *Gyromitra* contains a pyridoxine antagonist that disrupts the gastrointestinal mucosa and causes hemolysis.
- *Russula* contains a cholinergic substance.

TABLE M1-28 Mushroom Groups

Group/Toxin	Representative Example	Clinical Effects
Early onset of symptoms		
Coprine	*Coprinus atramentarius*	Disulfiram reaction with alcohol
GI toxin	Many species	Nausea, vomiting, diarrhea, abdominal pain
Ibotenic acid and muscimol	*Amanita muscaria*	Diverse CNS effects, including hallucinations, seizures, delirium, coma, agitation
Muscarine	*Clitocybe dealbata*	Peripheral cholinergic toxidrome
Psilocybin	*Psilocybe cubensis*	CNS effects, including hallucinations and euphoria
Late onset of symptoms		
Cyclopeptides	*Amanita phalloides*	GI effects followed by hepatotoxicity
Gyromitrin	*Gyromitra esculenta*	GI effects followed by seizures
Orellanine	*Cortinarius orellanus*	GI effects followed by renal toxicity

CNS, Central nervous system; GI, gastrointestinal.
From Marx: Rosen's emergency medicine: *concepts and clinical practice*, 7th ed. Philadelphia, 2010, Elsevier

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Food poisoning
- Overdose of prescription or illegal drug
- Other intoxications
- See topic on specific organ failure (e.g., renal or hepatic failure) for differential diagnosis of those conditions

WORKUP

- History
- Inspection and identification of suspected mushrooms
- Mushroom or gastric content analysis (by thin-layer chromatography or radioimmunoassay)

TREATMENT

- Gastric lavage
- Repeated administration of activated charcoal
- Penicillin G or silibinin can be used for *Amanita* mushroom intoxication. Silibinin interferes with hepatic uptake of alpha-amanitine. IV silibinin is not currently available in the U.S. Where available, it is given at a rate of 5 mg/kg IV over 1 hour, followed by 20 mg/kg/day. An oral form of silibinin is available in health food stores as an extract from milk thistle called silymarin. Dose is 1 g PO qid. IV benzyl penicillin reduces hepatocyte uptake of amatoxin.
- Supportive care as needed (may require respiratory assistance, hemodialysis, or emergency liver transplantation)

RELATED CONTENT

Mushroom Poisoning (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

BASIC INFORMATION

DEFINITION

Myasthenia gravis (MG) is an autoimmune disorder that affects postsynaptic neuromuscular transmission classically mediated by antibodies directed against the nicotinic acetylcholine receptor (AChR) of the neuromuscular junction, resulting in a decrease in functional postsynaptic ACh receptors and consequent weakness. More recently, antibodies against muscle-specific tyrosine kinase (MuSK) have been described, which impact both pre- and postsynaptic function of the neuromuscular junction.

ICD-9CM CODES
358.0 Myasthenia gravis
ICD-10CM CODES
G70.00 Myasthenia gravis without (acute) exacerbation

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 10 to 20 cases annually per 1 million persons. It is the most common disorder of neuromuscular junction transmission.
PEAK INCIDENCE: Female, second to third decades; male, sixth to eighth decades
PREVALENCE (IN U.S.): One per 20,000 persons
PREDOMINANT SEX: Females are affected more often than males (3:2) in adults; they are equally affected in the elderly
GENETICS: Increased frequency of HLA-B8, DR3

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The hallmark of MG is fluctuating weakness worsened with exercise and improved with rest.
- Generalized weakness involving proximal muscles, diaphragm, and neck extensors is common.
- Weakness is confined to eyelids and extraocular muscles in approximately 15% of patients.
- Bulbar symptoms of ptosis, diplopia, dysarthria, and dysphagia are common.
- Reflexes, sensation, and coordination are normal.

ETIOLOGY

Antibody-mediated decrease in nicotinic AChR in the postsynaptic neuromuscular junction resulting in defective neuromuscular transmission and subsequent muscle weakness and fatigue. MuSK antibodies have been recognized since 2001 and present with a similar syndrome to AchR MG although they may have more bulbar weakness, proximal muscle atrophy, and either lack of or paradoxical response to pyridostigmine.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Lambert-Eaton myasthenic syndrome, botulism, medication-induced myasthenia, chronic progressive external ophthalmoplegia, congenital myasthenic syndromes, thyroid disease, basilar meningitis, intracranial mass lesion with cranial neuropathy, Miller-Fisher variant of Guillain-Barré syndrome

WORKUP

- Edrophonium (Tensilon) test (Fig. EM1-56): useful in MG patients with ocular symptoms. Cardiac monitoring and atropine ready at the bedside are essential. Patients with MG may also have a positive ice test (Fig. EM1-57).
- Repetitive nerve stimulation: successive stimulation shows decrement of muscle action potential in clinically weak muscle; may be negative in up to 50%.
- Single-fiber electromyography: highly sensitive; abnormal in up to 95% of patients.
- Serum AChR antibodies found in up to 80% of patients.
- A subset of patients (an estimated 40%-60%) with seronegative MG may have MuSK antibodies.

ADDITIONAL TESTS

- Spirometry to document pulmonary function
- CT scan or MRI with contrast of anterior chest to look for thymoma or residual thymic tissue
- Thyroid-stimulating hormone, free T_4 to rule out thyroid disease

TREATMENT

NONPHARMACOLOGIC THERAPY

- Patient education to facilitate recognition of worsening symptoms and impress need for medical evaluation at onset of clinical deterioration
- Avoidance of selected drugs known to provoke exacerbations of MG (beta-blockers, aminoglycoside and quinolone antibiotics, penicillamine, interferons, class I antiarrhythmics [procainamide, quinidine, etc.])
- Prompt treatment of infections, diet modification, and speech evaluation with dysphagia

ACUTE GENERAL Rx

- Symptomatic treatment with acetylcholinesterase inhibitors:
  1. Pyridostigmine 30 to 60 mg PO q4 to 6h initially; onset of effects is 30 min, duration 4 hr. May be titrated up to 120 mg every 4 hr. GI upset is not uncommon with higher doses and may respond to hyoscyamine.
- Immunosuppressive treatment with corticosteroids, azathioprine, cyclosporine for long-term disease-modifying therapy
  1. Prednisone initiated at 15 to 20 mg qd titrate by 5-mg increments to effect or
  2. dose of 1 mg/kg/day with improvement in 2 to 4 wk and maximal response by 3 to 6 mo
  3. Azathioprine initiated at 50 mg qd titrated to 2 to 3 mg/kg/day with clinical effect in 6 to 12 mo
  4. Cyclosporine initiated at 5 mg/kg/day with clinical effect within 1 to 2 mo
- Plasmapheresis and IV immunoglobulin are short-term options for immunotherapy during an exacerbation.
- Mechanical ventilation is lifesaving in setting of a myasthenic crisis. Consider elective intubation if forced vital capacity <15 ml/kg, maximal expiratory pressure <40 cm H_2O, or negative inspiratory pressure <25 cm H_2O.

SURGICAL Rx

- In thymomatous MG, thymectomy is indicated in all patients. If the tumor cannot be surgically resected, chemotherapy can be considered for prevention of local invasion and symptom relief.
- For nonthymomatous autoimmune MG, thymectomy is an option in select patients, typically <40 yr.

DISPOSITION

Course of disease is highly variable. Mortality rate has decreased from 75% to 4.5% over past 4 decades.

REFERRAL

Surgical referral for thymectomy in selected cases (see "Surgical Rx")

PEARLS & CONSIDERATIONS

- Sustained upward or lateral gaze and arm abduction for 120 sec may be necessary to elicit subtle signs on examination.
- Myasthenic patients can worsen rapidly and warrant close, careful observation during an exacerbation.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Myasthenia Gravis (Patient Information)

AUTHOR: **TAYLOR HARRISON, M.D.**

SUGGESTED READINGS

Hampton T: Trials assess myasthenia gravis therapies, *JAMA* 298:29–30, 2007.
Keesey JC: Clinical evaluation and management of myasthenia gravis, *Muscle Nerve* 29(4):484, 2004.
Li Y, Arora Y, Levin K: Myasthenia gravis: newer therapies open sustained improvement, *Clev Clinic J Med* 80:711–720, 2013.

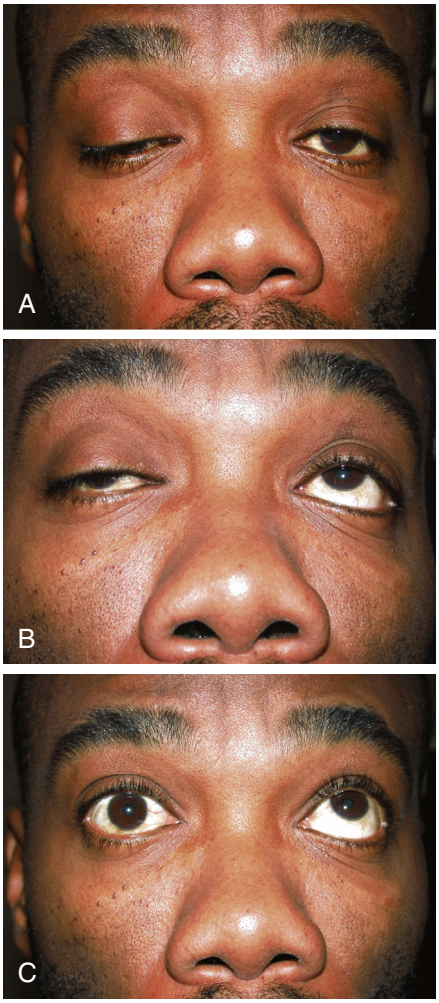

FIGURE EM1-56 Positive edrophonium test in myasthenia gravis. A, Asymmetric ptosis in the primary position. **B,** Defective upgaze. **C,** Following injection of edrophonium, there is marked bilateral improvement of ptosis and modest improvement of left upgaze. (From Kanski JJ et al: *Clinical ophthalmology: a systematic approach,* ed 7, Philadelphia, 2010, Saunders.)

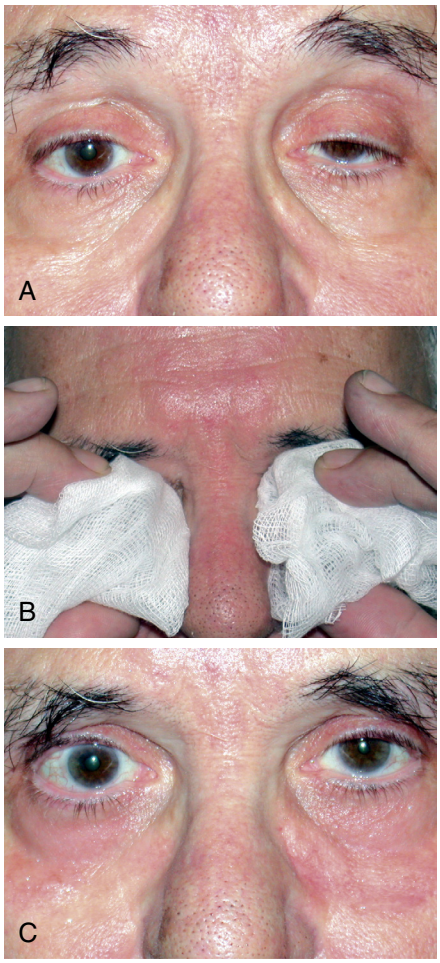

FIGURE EM1-57 Positive ice test in myasthenia gravis. A, Asymmetric ptosis. **B,** Application of ice. **C,** Improvement of ptosis. (Courtesy J. Yanguela. From Kanski JJ et al: *Clinical ophthalmology: a systematic approach,* ed 7, Philadelphia, 2010, Saunders.)

Mycoplasma Pneumonia PTG

BASIC INFORMATION

DEFINITION

Mycoplasma pneumonia is an infection of the lung parenchyma caused by a small bacterium, *Mycoplasma pneumoniae.*

SYNONYMS

Primary atypical pneumonia
Eaton's pneumonia
Walking pneumonia

ICD-9CM CODES
483 *Mycoplasma* pneumonia
ICD-10CM CODES
J15.7 Pneumonia due to *Mycoplasma pneumoniae*

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.)

- It is a frequent cause of community-acquired pneumonia. CDC estimates 2 million cases a yr with 100,000 pneumonia-related hospitalizations.
- Many cases probably resolve without coming to medical attention.
- Incidence is estimated at one case per 1000 persons annually.
- Incidence is estimated to at least triple every (approximately) 5 yr during epidemics.

PEAK INCIDENCE

- Some increased incidence in fall to early winter.
- Seems more prevalent in temperate climates.

PREVALENCE (IN U.S.)

- Estimated to be present in one in every five patients hospitalized for pneumonia (generally a self-limited disease, so its true prevalence is unknown).
- Estimated to cause 7% of all cases of pneumonia and approximately half the cases in those aged 5 to 20 yr.

PREDOMINANT SEX: Equal distribution

PREDOMINANT AGE

- Most commonly affected: school-age children and young adults (ages 5 to 20 yr).
- Occurs in older adults as well, especially with household exposure to a young child.
- More severe infections in affected elderly patients.

GENETICS: Familial disposition:

- None known.
- May be more severe in patients with sickle cell anemia.

Neonatal infection: severe respiratory distress, sometimes requiring intubation, attributed to this disease in infants.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Nonexudative pharyngitis (common).
- Headache, otalgia common.
- Fever may be mild or not present.
- Rhonchi or rales without evidence of consolidation (common) in lower lung zones.
- Associated with bullous myringitis (nonspecific finding; perhaps no more frequently than in other pneumonias).
- Skin rashes in up to one fourth of patients
  1. Morbilliform.
  2. Urticaria.
  3. Erythema nodosum (unusual).
  4. Erythema multiforme (unusual).
  5. Stevens-Johnson syndrome (rare).
- Muscle tenderness (<50% of the patients).
- On examination (and confirmed with testing):
  1. Mononeuritis or polyneuritis.
  2. Transverse myelitis.
  3. Cranial nerve palsies.
  4. Meningoencephalitis.
- Lymphadenopathy and splenomegaly.
- Conjunctivitis.
- Table M1-29 summarizes the clinical manifestations of *Mycoplasma pneumoniae.*

ETIOLOGY

Infection is spread person-to-person via respiratory droplets or secretions with an incubation period of 1 to 4 wk.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- *Chlamydia* (now known as *Chlamydophila) pneumoniae.*
- *Chlamydophila psittaci.*
- *Legionella* spp.
- *Coxiella burnetii.*
- Several viral agents.
- Q fever.
- *Streptococcus pneumoniae.*
- Pulmonary embolism or infarction.

WORKUP

- Chest x-ray.
- Thorough history and physical examination.
- Laboratory tests.
- Evaluation guided by symptoms and findings.

LABORATORY TESTS

- White blood cells (WBCs):
  1. WBC count >10,000/mm^3 in approximately one fourth of patients.
  2. Differential count nonspecific.
  3. Leukopenia rare.
- Cold agglutinins:
  1. Detected in approximately half of the patients.
  2. Also may be found in:
     a. Lymphoproliferative diseases.
     b. Influenza.
     c. Mononucleosis.
     d. Adenovirus infections.
     e. Occasionally, Legionnaires' disease.
  3. Titers typically >1:64.
     a. May be detectable with bedside testing.
     b. Appear between days 5 and 10 of the illness (so may be demonstrable when patient is first examined) and disappear within 1 mo.
- Complement fixation testing assay specific for mycoplasma antigens of paired sera (fourfold rise) or a single titer ≥1:32 in patients with pneumonia and a compatible history:
  1. Considered diagnostic in the appropriate clinical setting.
  2. Other assays include ELISA, antigen capture-enzyme immunoassay, and PCR.
- Culture of the organism from specimens.
  1. Only truly specific test for infection.
  2. Technically difficult and done reliably by few laboratories.
  3. May require weeks to get results.
- Sputum
  1. Often no sputum produced for laboratory testing.
  2. When present, Gram-stained specimens show polymorphonuclear cells without organisms.
- Infection occasionally complicated by pancreatitis or glomerulitis.
- Disseminated intravascular coagulation is a rare complication.
- Electrocardiographic evidence of pericarditis or myocarditis may be present.

IMAGING STUDIES

- Predilection for lower lobe involvement (upper lobes involved in less than a fourth), with radiographic abnormalities frequently out of proportion to those on physical examination (Fig. M1-58).
- Small pleural effusions in approximately 30% of patients.
- Large effusions: rare.
- Infiltrates: patchy, unilateral, and with a segmental distribution, although multilobar involvement may be seen.
- Evidence of hilar adenopathy on chest radiographs in 20% to 25%.

TABLE M1-29 Clinical Manifestations of *Mycoplasma Pneumoniae* Infection

Respiratory tract	Pharyngitis, laryngitis, acute bronchitis, bronchopneumonia
Skin and mucosa	Maculopapular and vesicular exanthema, urticaria, purpura, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome
Central nervous system	Meningitis, meningoencephalitis, acute psychosis, cerebellitis, Guillain-Barré syndrome?
Parenchymatous organs	Pancreatitis, diabetes mellitus, nonspecific reactive hepatitis, subacute thyroiditis?
Miscellaneous	Hemorrhagic bullous myringitis, hemolytic anemia, pericarditis, thromboembolism?

Some association remains uncertain.
From Cohen J, Powderly WG: *Infectious diseases,* ed 2, St Louis, 2004, Mosby.

- Rare cases reported:
  1. Associated lung abscess.
  2. Residual pneumatoceles.
  3. Lobar collapse.
  4. Hyperlucent lung syndrome.

Rx TREATMENT

ACUTE GENERAL Rx

- Therapy: azithromycin 500 mg qd × 3 or 500 mg initially, then 250 mg daily for 4 days for adults. For children: 10 mg/kg in one dose on first day, then 5 mg/kg in one dose for 4 days or clarithromycin: 500 mg bid for 10 days in adults, 15 mg/kg per day in two divided doses for 10 days in children. Alternatives include erythromycin (500 mg qid) for adults or 30 to 40 mg/kg per day in four divided doses in children or doxycycline: 2 to 4 mg/kg per day in one or two divided doses for 10 days, maximum daily dose: 100 to 200 mg, but this agent cannot be used in young children or women of childbearing age. Respiratory fluoroquinolones such as Levaquin or moxifloxacin are alternative agents for treatment in adults but should not be used in young children.
- Therapy shortens the duration and severity of symptoms and may hasten radiographic clearing, but the disease is self-limiting.

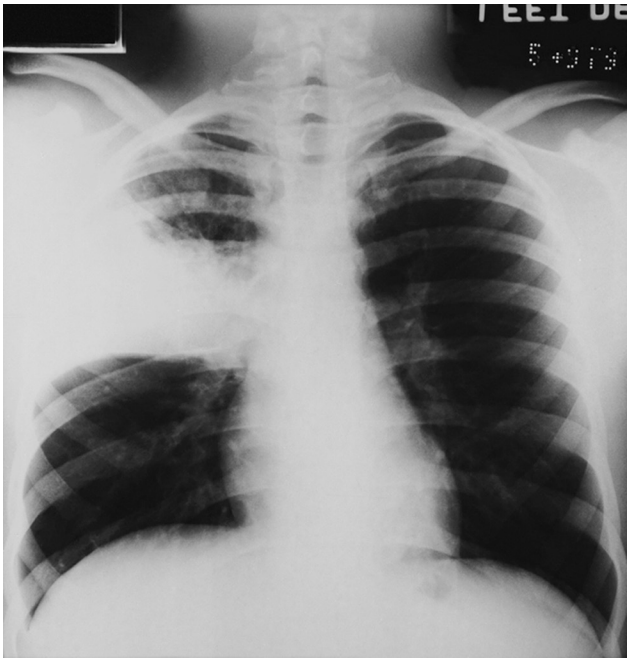

FIGURE M1-58 Localized airspace opacification resulting from *Mycoplasma pneumoniae*. (From Specht N [ed]: *Practical guide to diagnostic imaging,* St Louis, 1998, Mosby.)

CHRONIC Rx

- Effective antimicrobial therapy does not eliminate the organism from the respiratory secretions, which may be positive for weeks.
- Serum antibody response does not necessarily provide lifelong immunity.
- Chronic symptoms do not occur, although clinical relapses may occur 7 to 10 days after the initial response and may be associated with new areas of infiltration.

DISPOSITION

- Clinical improvement is almost universal within 10 days.
- Infiltrates generally clear within 5 to 8 wk.
- Rare deaths are likely attributable to underlying medical diseases.
- Person-to-person spread can be minimized by avoiding open coughing, especially in enclosed areas.

REFERRAL

- Not responding to treatment.
- Severe infection.
- Severe extrapulmonary manifestations.
- Multilobe involvement accompanied by respiratory embarrassment (very rare).

PEARLS & CONSIDERATIONS

COMMENTS

X-ray resolution complete by 8 wk in approximately 90% of patients.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Mycoplasma Pneumonia (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Daxboeck F: Mycoplasma pneumoniae central nervous system infections, *Curr Opin Neurol* 19(4):374–378, 2006.

La Scola B et al.: Mycoplasma pneumoniae: a rarely diagnosed agent in ventilator-acquired pneumonia, *J Hosp Infect* 59(1):74, 2005.

Waites KG, Talkington DF: Mycoplasma pneumoniae and its role as a human pathogen, *Clin Microbiol Rev* 17(4):697, 2004.

Wang K et al.: *Clinical symptoms and signs for the diagnosis of Mycoplasma pneumonia in children and adolescents with community acquired pneumonia*, 2012. Cochrane Database Syst Rev Oct 17(10):CD009175.

BASIC INFORMATION

DEFINITION

Mycosis fungoides refers to a T-cell lymphoproliferative disorder with characteristic cutaneous skin lesions and the potential to disseminate into lymph nodes and viscera.

SYNONYMS

Cutaneous T-cell lymphoma

ICD-9CM CODES
202.1 Mycosis fungoides
ICD-10CM CODES
C84.00 Mycosis fungoides, unspecified site

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence of mycosis fungoides is four cases per 1 million persons.
- ~1000 new cases are diagnosed annually in the United States.
- More commonly affects males than females (2:1).
- Affects blacks more often than whites (2:1).
- Usually found in males ages 40 to 60.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Mycosis fungoides characteristically progresses through three phases:

- A *premycotic phase* featuring scaly, erythematous patches that can last from months to years. During this stage the diagnosis can only be suspected because the histopathologic features are not definitive for mycosis fungoides. Lesions are pruritic and can appear anywhere but are usually found in sun-shielded areas. Parapsoriasis in plaques, poikilodermatous parapsoriasis, parapsoriasis lichenoides, and variegata are skin lesions suspicious of representing premycotic cutaneous T-cell lymphoma.
- The *infiltrative plaque phase* features raised, indurated erythematous palpable plaques that are pruritic and may be associated with alopecia.
  1. Stage IA disease is defined as a patch or plaque skin disease involving <10% of the skin surface area and with absence of blood involvement or with low blood tumor burden (<5% of atypical T cells [Sézary cells] in the peripheral blood).
  2. Stage IB disease (Fig. EM1-59) is defined as a patch or plaque skin disease involving ≥10% of the skin surface area (Fig. M1-60) with absence of blood involvement or low blood tumor burden (<5% Sézary cells).
- The *tumor phase* is characterized by large, lumpy nodules arising from a premycotic patch, plaque, or unaffected skin and represents systemic infiltration and spreading. The tumors can be pruritic and large (>10 cm) and ulceration can occur.
  1. Stage IIA and stage IIB diseases are defined by the presence of tumors with or without clinically abnormal peripheral lymph nodes with absence of blood involvement or low blood tumor burden. In approximately 5% of cases of mycosis fungoides, the presentation may be a diffuse, painful, pruritic erythroderma with Sézary cells (Fig. EM1-61) in the peripheral blood (known as Sézary syndrome) (Fig. EM1-62).
  2. Stage III disease is defined by the presence of generalized erythroderma from the spread of cancer cells through the skin but not yet to the lymph nodes.
- Lymphadenopathy can occur during the plaque or tumor stages and may be regional or diffuse.
  1. Stage IVA disease is defined by a lymph node biopsy showing large clusters of atypical cells, more than six cells, or total effacement by atypical cells.
- Infiltration of the liver, spleen, lungs, bone marrow, kidney, stomach, and brain can occur.
  1. Stage IVB disease is defined by the presence of visceral involvement.

ETIOLOGY

The specific cause of mycosis fungoides is not known. Infection with the retrovirus HTLV-1 has been suspected, given the association of individuals infected with HTLV-1 and those with T-cell leukemia. Other considerations listed but unsubstantiated include environmental toxins (e.g., tobacco, pesticides, herbicides, and solvents) and genetic predisposition.

FIGURE M1-60 Mycosis fungoides. A, Plaques of mycosis fungoides often have a polycyclic appearance. **B,** Tumors are more elevated above the skin surface. By the time tumors supervene, sun-exposed skin, such as the face, is often involved. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

DIAGNOSIS

The diagnosis of mycosis fungoides is established by skin biopsy. This may be difficult to differentiate from other skin lesions in the early phases of the disease (e.g., premycotic patch or early plaque lesions); therefore the diagnosis can only be suspected.

DIFFERENTIAL DIAGNOSIS

- Contact dermatitis
- Atopic dermatitis
- Nummular dermatitis
- Parapsoriases
- Superficial fungal infections
- Drug eruptions
- Psoriasis
- Photodermatitis
- Alopecia mucinosa
- Lymphomatoid papulosis

WORKUP

Any patient who is suspected of having mycosis fungoides should have a staging workup. Prognosis in patients with mycosis fungoides depends on the type of skin lesions and the extent of disease. The workup should focus on:

1. Complete physical examination:
   - The type of skin lesion and the extent of skin involvement of the body (e.g., skin involvement is >10% or <10% of the skin surface)
   - Identification of palpable lymph node (especially those >1.5 cm in largest diameter)
   - Identification of organomegaly (e.g., lungs, liver)
2. Skin biopsy:
   - Biopsy of the most indurated area
   - Immunophenotyping
   - Evaluation for clonality
3. Blood test:
   - Complete blood count with differential, liver function tests, lactate dehydrogenase, chemistry
   - T-cell receptor gene rearrangement
   - Determination of Sézary cell count and/or flow cytometry
4. Radiologic tests
   - Depending on the stage of the disease, chest radiograph; ultrasound; and CT scan of the chest, abdomen, and pelvis alone,

with or without fluorodeoxyglucose positron emission tomography scan

5. Lymph node biopsy
   - Excisional biopsy
   - Biopsy of the largest lymph node
   - If multiple nodes enlarged, order of preference is cervical, axillary, and inguinal areas
   - Histopathology, flow cytometry, T-cell receptor gene rearrangement

Rx TREATMENT

Treatment is guided according to the stage of disease. A treatment algorithm is described in Fig. EM1-63.

NONPHARMACOLOGIC THERAPY

- For dry, cracking skin, emollients (e.g., lanolin and petrolatum) are applied bid.
- Moisturizing lotion (e.g., ammonium lactate) applied bid.
- Topical antibiotics (e.g., bacitracin) are used on ulcerative tumors.

ACUTE GENERAL Rx

- Treatment of patients with stage IA limited patch or plaque phase includes:
  1. Topical agents such as corticosteroids and retinoids are used when cutaneous symptoms develop.
  2. Psoralen ultraviolet A (PUVA) light therapy where 0.6 mg/kg of 8-methoxypsoralen is ingested 1 to 2 hr before exposure of the skin to UVA light (320 to 400 nm). This is done three times per wk and tapered to twice per wk until all the lesions have cleared. This is typically continued for 6 mo with a 90% complete remission rate.
- Treatment of patients with stage IB and IIA disease is similar to stage IA, with topical corticosteroids and retinoids or PUVA.
  1. Total skin electron beam therapy is considered in patients with thick plaques.
  2. Interferon-alpha 5 million units SQ three times weekly can be considered in patients with stage IB or IIA disease.
  3. Retinoids in combination with PUVA are used in refractory cases. Isotretinoin 1 mg/kg per day or acitretin 25 to 50 mg per day is the standard dosing.
- Treatment of patients with stage IIB disease with generalized tumor and plaque disease:
  1. Total skin electron beam therapy in doses of 3000 to 3600 cGy given over 8 to 10 wk followed by adjuvant therapy with topical mustard can be used.
- Patients with advanced disease may receive combination chemotherapy (CHOP, CVP, EPOCH). Allogeneic HSCT should also be considered and may be curative in patients. Alemtuzumab has been reported effective in patients with organ involvement.

CHRONIC Rx

- In patients developing diffuse erythroderma, stage III disease (e.g., Sézary syndrome, extracorporeal photophoresis), 8-methoxypsoralen is ingested and peripheral blood is exposed to UVA through a membrane filter.
- In stage IV disease, interferon and other systemic chemotherapeutic agents (e.g., methotrexate, cyclophosphamide, doxorubicin, vincristine, prednisone) and alemtuzumab are considered.

DISPOSITION

- The patients with limited patch or plaque disease have excellent prognosis with long-term life expectancy that is similar to an age-, sex-, and race-matched control population.
- The patients with generalized patch or plaque without evidence of extracutaneous involvement have a median survival of greater than 11 yr.
- The patients with cutaneous tumor and generalized erythroderma without extracutaneous involvement have a median survival of 3 to 4.6 yr.
- The patients with extracutaneous disease at presentation involving either lymph node or viscera have median survival of 13 mo.

REFERRAL

Any patient with suspected mycosis fungoides should be referred to a dermatologist for definitive diagnosis and initial therapy. Oncology consultation is also indicated in patients with more advanced disease.

TABLE M1-30 Comparison of EORTC and WHO Classifications of Primary Cutaneous Lymphoma

EORTC Classification	WHO Classification
Cutaneous T-Cell Lymphoma	
Indolent clinical behavior	Mycosis fungoides
Mycosis fungoides variants	Mycosis fungoides variants
Follicular mycosis fungoides	Follicular mycosis fungoides
Pagetoid reticulosis	Pagetoid reticulosis
CTCL, large cell, $CD30^+$	Primary cutaneous $CD30^+$ ALCA ($CD30^+$ lymphoproliferative disease, including lymphomatoid papulosis)
Lymphomatoid papulosis	
Aggressive clinical behavior	Sézary syndrome
Sézary syndrome	Peripheral T-cell lymphoma, unspecified (most); extranodal NK/T-cell lymphoma, nasal type
CTCL, large cell, CD30–	
Provisional entities	
CTCL, pleomorphic, small/medium sized	
Subcutaneous panniculitis-like T-cell lymphoma	Subcutaneous panniculitis-like T-cell lymphoma
Cutaneous B-Cell Lymphoma	
Indolent clinical behavior	Extranodal marginal zone B-cell lymphoma
Primary cutaneous immunocytoma (marginal zone B-cell lymphoma)	
Follicle center cell lymphoma (any grade)	
Intermediate clinical behavior	
Primary cutaneous large B-cell	
Lymphoma of the leg	
Provisional Entities	
Primary cutaneous plasmacytoma	Plasmacytoma
Intravascular large B-cell lymphoma	Diffuse large B-cell lymphoma (intravascular)

ALCL, Anaplastic large cell lymphoma; *CTCL,* cutaneous T-cell lymphoma; *EORTC,* European Organization for the Research and Treatment of Cancer; *NK,* natural killer; *WHO,* World Health Organization.
From Hoffman R et al: *Hematology: basic principles and practice*, ed 5, Philadelphia, 2009, Churchill Livingstone.

PEARLS & CONSIDERATIONS

A TNM staging classification of mycosis fungoides has been in use for guiding therapy since 1979. The International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC) recommended revisions to the TNM classification and staging system of cutaneous T-cell lymphoma in 2007. Table M1-30 compares EORTC and WHO classifications of primary cutaneous lymphoma.

COMMENTS

Mycosis fungoides is thought to represent one class of the spectrum of cutaneous T-cell lymphomas.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **TANYA ALI, M.D.**

SUGGESTED READINGS

Foss F: Mycosis fungoides and the Sézary syndrome, *Curr Opin Oncol* 16(5):421, 2004.

Girardi M et al.: The pathogenesis of mycosis fungoides, *N Engl J Med* 350(19):2004, 1978.

Lundin J, Osterborg A: Therapy for mycosis fungoides, *Curr Treat Options Oncol* 5(3):203, 2004.

Olsen E: Revisions to the staging and classification of mycosis fungoides and Sézary syndrome: a proposal of the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC), *Blood* 110(6):1713, 2007.

FIGURE EM1-59 Cutaneous T-cell lymphoma (mycosis fungoides). Note patch, plaque, and tumor stages. (From Noble J [ed]: *Textbook of primary care medicine,* ed 2, St Louis, 1996, Mosby.)

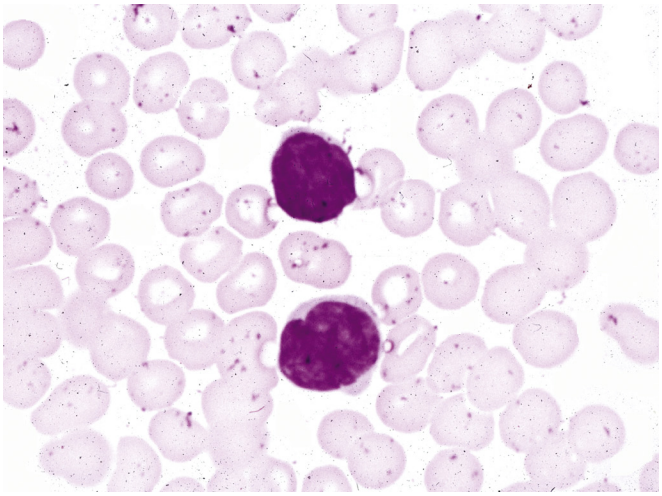

FIGURE EM1-61 Sézary cells in a peripheral blood smear. Recognition of these cells is no longer critical for the diagnosis since the advent of clonality studies and flow cytometry. (From Jaffe et al: *Hematopathology*, ed 1, Philadelphia, 2011, Saunders.)

FIGURE EM1-62 Sézary syndrome presents with erythroderma-diffuse red skin. The term *erythroderma* is overused by clinicians; it should refer to confluent erythema, not just widespread erythematous lesions. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

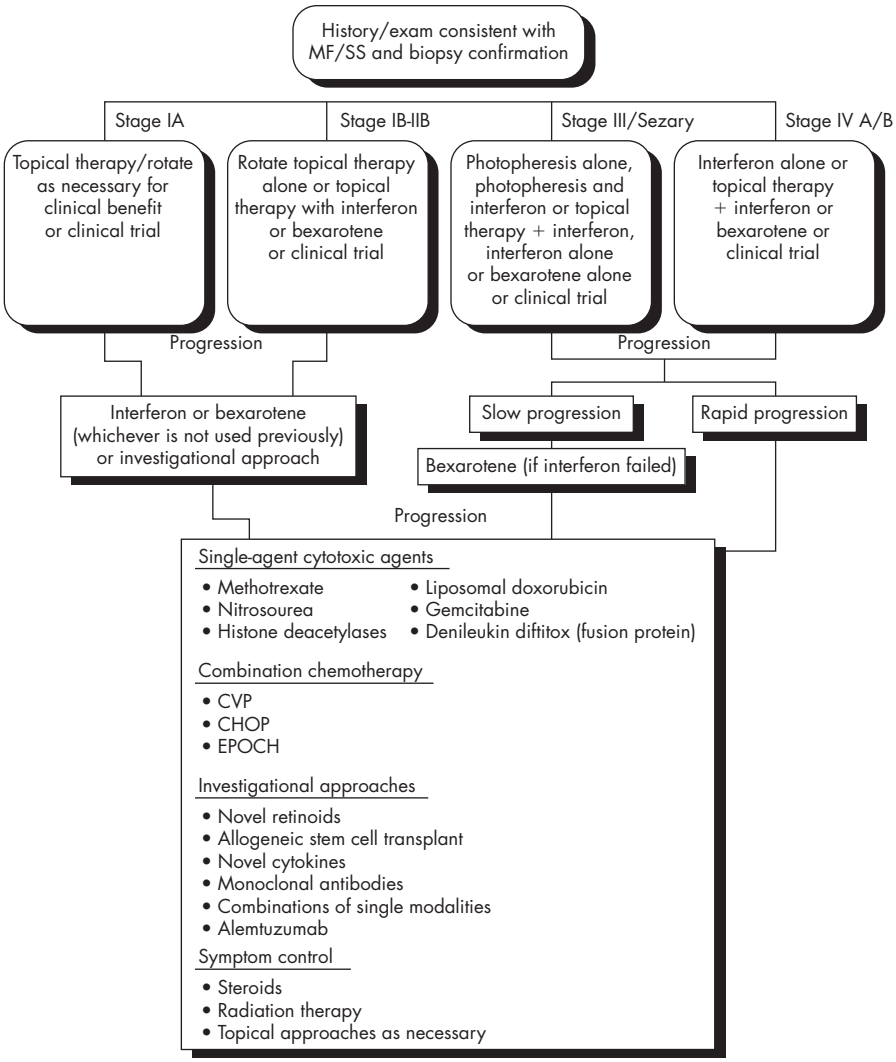

FIGURE EM1-63 Algorithm for care of patients with mycosis fungoides or Sézary syndrome. (Modified from Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

Myelodysplastic Syndrome PTG

BASIC INFORMATION

DEFINITION

Myelodysplastic syndrome (MDS) is a group of acquired clonal disorders affecting the hemopoietic stem cells and characterized by cytopenias with hypercellular bone marrow and various morphologic abnormalities in the hemopoietic cell lines. MDS shows abnormal (dysplastic) hemopoietic maturation. Marrow cellularity is increased, reflecting an effective hematopoiesis, but inadequate maturation results in peripheral cytopenias.

CLASSIFICATION

- Myelodysplasia encompasses several heterogeneous syndromes. The French-American-British (FAB) classification of MDSs is based on the proportion of immature blast cells in the blood and marrow and on the presence or absence of ringed sideroblasts or peripheral monocytosis (Table M1-31). It includes refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, chronic myelomonocytic leukemia, and refractory anemia with excess blasts in transformation.
- In 1999 the World Health Organization modified the FAB by incorporating newer morphologic insights and cytogenetic findings. It includes the disease subtypes refractory anemia, refractory anemia with ringed sideroblasts, refractory cytopenia with multilineage dysplasia, refractory cytopenia with multilineage dysplasia and ringed sideroblasts, refractory anemia with excessive blasts (1, 2), unclassified MDS, and MDS associated with isolated del(5q).

SYNONYMS

MDS
Preleukemia
Dysmyelopoietic syndrome

ICD-9CM CODES
238.7 Myelodysplastic syndrome
ICD-10CM CODES
D46.9 Myelodysplastic syndrome, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Approximately 82 cases/100,000 persons per yr. An estimated 7000 to 12,000 new cases are diagnosed annually in the U.S.
PREDOMINANT AGE: More common in elderly patients; median age, >65 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Splenomegaly, skin pallor, mucosal bleeding, and ecchymosis may be present.
- Patients often present with fatigue.
- Fever, infection, and dyspnea are common.

ETIOLOGY

Unknown. However, exposure to radiation, chemotherapeutic agents, benzene, or other organic compounds is associated with myelodysplasia. Table M1-32 describes predisposing factors and epidemiologic associations of patients with MDS. Recently targeted resequencing of the gene encoding RNA splicing factor 3B, subunit 1 (SF3B1) has shown that mutations in SF3B1 implicate abnormalities of messenger RNA splicing in the pathogenesis of MDS.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hereditary dysplasias (e.g., Fanconi's anemia, Diamond-Blackfan syndrome)
- Vitamin B_{12}/folate deficiency
- Exposure to toxins (drugs, alcohol, chemotherapy)
- Renal failure
- Irradiation
- Autoimmune disease
- Infections (tuberculosis, viral infections)
- Paroxysmal nocturnal hemoglobinuria

WORKUP

Diagnostic workup (Fig. M1-64) includes laboratory evaluation (Table EM1-33) and bone marrow examination (Fig. EM1-65). Cytogenetic analysis (Box EM1-4) by conventional metaphase karyotyping should be performed in patients with MDS. Physical examination, medical history, and laboratory tests aiding in diagnosis of MDS are described in Table M1-34.

TABLE M1-31 French-American-British Classification Criteria

Subtype	Abbreviation	Peripheral Blood	Bone Marrow
Refractory anemia	RA	Blasts <1%	Blasts <5%
Refractory anemia with ringed sideroblasts	RARS	Blasts <1%	Blasts >5%, and >15% ringed sideroblasts
Refractory anemia with excess blasts	RAEB	Blasts <5%	Blasts 5%-20%
Refractory anemia with excess blasts in transformation	RAEB-T	Blasts >5%	Blasts 20%-30% or Auer rods
Chronic myelomonocytic leukemia	CMML	Monocytes >1 × 10^9/L	Any of the above
Acute myelogenous leukemia	AML	Blasts >30%	

From Hoffmann R et al: *Hematology, basic principles and practice*, ed 5, Philadelphia, 2009, Churchill Livingstone.

TABLE M1-32 Predisposing Factors and Epidemiologic Associations of Patients with Myelodysplastic Syndrome

Heritable

Constitutional Genetic Disorders

Trisomy 8 mosaicism
Familial monosomy 7
Down syndrome (trisomy 21)
Neurofibromatosis 1
Germ cell tumors [embryonal dysgenesis del(12p)]

Congenital Neutropenia

Kostmann syndrome
Shwachman-Diamond syndrome

DNA Repair Deficiencies

Fanconi anemia
Ataxia-telangiectasia
Bloom syndrome
Xeroderma pigmentosum
Pharmacogenomic polymorphisms (GSTq1-null)

Acquired

Senescence

Mutagen Exposure

Alkylator therapy (chlorambucil, cyclophosphamide, melphalan, N-mustards)
Topoisomerase II inhibitors (anthracyclines)
β Emitters (32p)
Autologous stem cell transplantation
Environmental/occupational (benzene)
Tobacco
Aplastic anemia
Paroxysmal nocturnal hemoglobinuria

From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Red blood cell transfusions in patients with severe symptomatic anemia

ACUTE GENERAL Rx

- Erythropoietin (10,000 to 40,000 U/wk) in patient with symptomatic anemia.
- DNA methyltransferase inhibitors: Azacitidine (VIDAZA), a pyrimidine nucleoside analogue of cytidine, has been shown to improve the quality of life for patients with MDS and probably prolong survival. Decitabine (Dacogen), another nucleoside analogue, has also been FDA approved for patients with MDS. These agents may also be useful in preventing the transition of MDS to AML.
- Immunomodulators: Lenalidomide (REVLIMID), a novel analogue of thalidomide, has demonstrated hematologic activity in patients with low-rise MDS who have no response to erythropoietin or who are unlikely to benefit from conventional therapy. Lenalidomide can also reduce transfusion requirements and reverse cytologic and cytogenetic abnormalities in patients who have MDS with the 5q31 deletion.
- Allogeneic stem cell transplantation should be considered in patients ≤60 yr because this is the established procedure with cure potential (Fig. M1-66).
- Results of chemotherapy are generally disappointing. Combination chemotherapy regimens (e.g., cytarabine plus doxorubicin) generally induce a complete response in only a minority of patients, and the average duration of response is <1 yr.
- The role of myeloid growth factors (granulocyte colony-stimulating factor [G-CSF], granulocyte-macrophage CSF) and immunotherapy is undefined. In a recent trial, 34% of patients treated with antithymocyte globulin (40 mg/kg for 4 days) became transfusion independent. Response was also associated with a statistically significantly longer survival.

TABLE M1-34 Physical Examination, Medical History, and Laboratory Tests Aiding in Diagnosis of Myelodysplastic Syndrome

Medical History

Duration of symptoms
History of blood disease
History of exposure to occupational toxins or cytotoxic agents
Medication history
Alcohol intake
Comorbid conditions

Physical Examination

Pallor
Petechiae
Purpura
Bruising
Tachypnea
Signs of infection
Splenomegaly

Laboratory Testing

Complete blood count with a manual differential
Reticulocyte count
Vitamin B_{12} and folate levels
Consider methylmalonic acid and red blood cell folate levels
Iron, total iron-binding capacity, and ferritin level
Thyroid-stimulating hormone level
Lactate dehydrogenase
Antinuclear antibody
Coombs test and haptoglobin
Serum erythropoietin level
Human leukocyte antigen (histocompatibility antigens) typing in appropriate patients
Paroxysmal nocturnal hemoglobinuria screen

Bone Marrow Testing

Hematopathology
Percentage of blasts on 200 cell aspirate differential
Presence or absence of Auer rods
Percentage of cellularity of bone marrow biopsy
Iron stain on aspirate (ringed sideroblasts)
Iron stain on biopsy (storage)
Dysplastic features (% and number of dysplastic lineages)
Cytogenetics (karyotype of 20 metaphase cells)
Fluorescent in situ hybridization
Flow cytometry (not useful for quantitation)

From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

CHRONIC Rx

Monitor for infections, bleeding, and complications of anemia. Supportive measures include blood transfusions and erythropoietin for anemia and antibiotics to treat opportunistic infections. Iron overload from frequent transfusions may require iron chelation therapy.

DISPOSITION

- Cure rates in young patients with allogeneic bone marrow transplantation approach 30% to 50%.
- The risk of transformation to acute myelogenous leukemia varies with the percentage of blasts in the bone marrow.
- Advanced age, male sex, and deletion of chromosomes 5 and 7 are associated with a poor prognosis.
- The 1997 International Prognostic Scoring System uses the following three elements for staging: (1) the proportion of myeloblasts in the patient's marrow, (2) the number of blood cell lineage deficits, and (3) the type of chromosomal abnormality present (e.g., poor risk includes abnormalities of chromosome 7; good risk includes clonal loss of the Y chromosome). According to the International Myelodysplastic Syndrome Risk Analysis Workshop, the most important variables in disease outcome are the specific cytogenetic abnormalities, the percentage of blasts in the bone marrow, and the number of hematopoietic lineages involved in the cytopenias.

REFERRAL

Hematology referral in all patients with MDS

PEARLS & CONSIDERATIONS

COMMENTS

- Somatic point mutations in TP53, EZH2, ETV6, RUNX1, and ASXL1 are predictors of poor overall survival in patients with MDS independent of established risk factors. Patients with cytogenetic abnormalities associated with poor prognosis should be considered for aggressive treatment with high-dose chemotherapy and stem cell transplantation.
- Many younger patients who respond to immunosuppressive therapy with drugs such as antithymocyte globulin and cyclosporine have clonal expansions of cytotoxic $CD8^+$ T cells that suppress normal hematopoiesis, as well as expansion of $CD4^+$ helper T-cell subsets that promote and sustain autoimmunity.
- Nearly 50% of the deaths that result from MDS are the result of cytopenia associated with bone marrow failure.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Myelodysplastic Syndrome (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

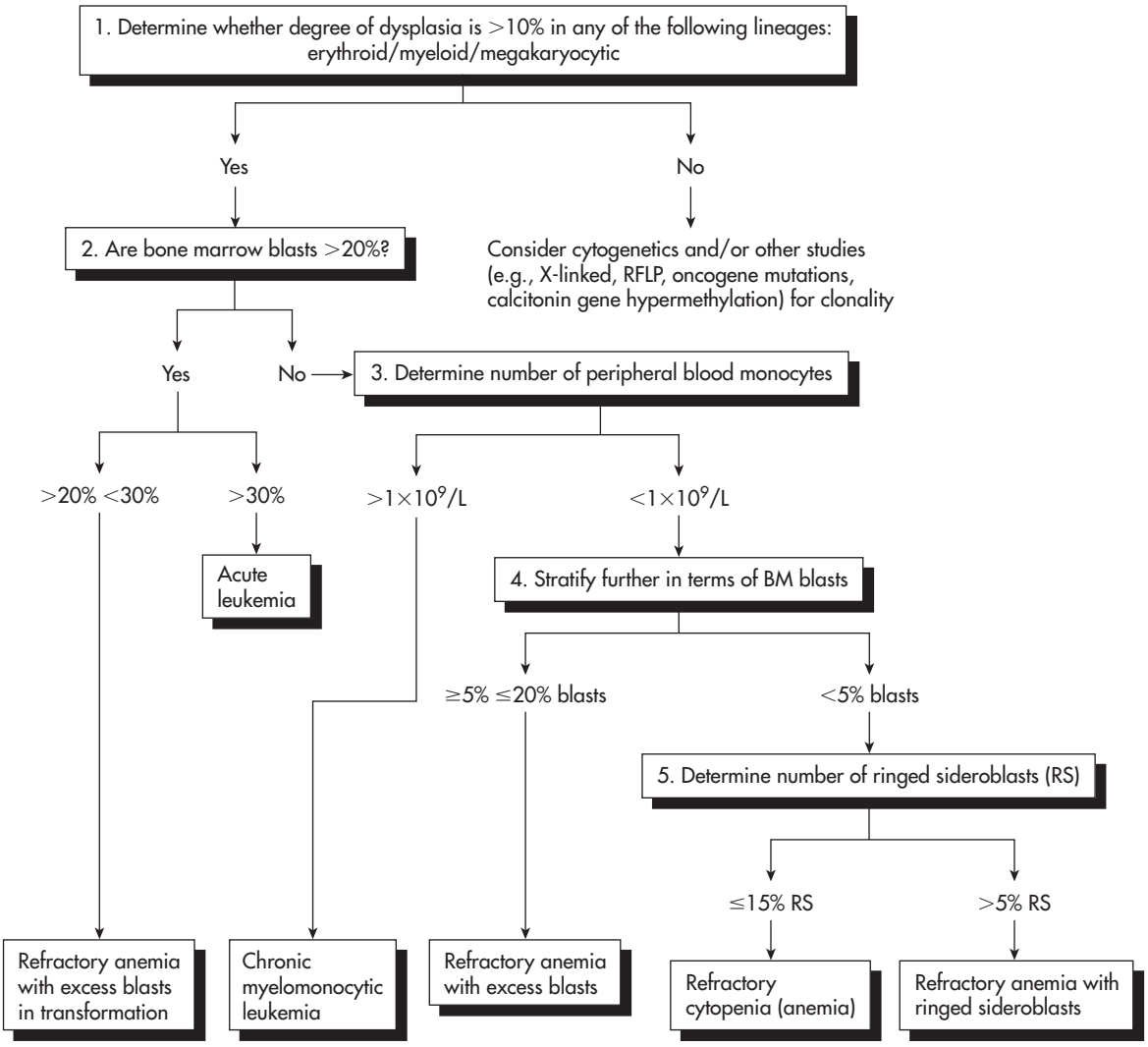

FIGURE M1-64 Myelodysplastic syndrome. *BM blasts,* Bone marrow blastocyst; *RFLP,* restriction fragment length polymorphism. (From Abeloff MD: *Clinical oncology,* ed 3, New York, 2004, Churchill Livingstone.)

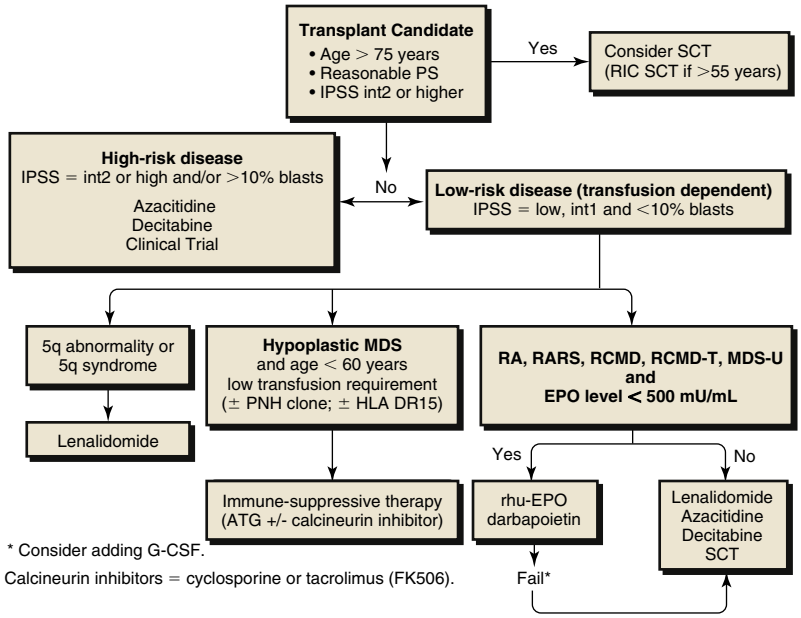

FIGURE M1-66 Algorithm for management of a patient with myelodysplastic syndrome. *PNH,* Paroxysmal nocturnal hemoglobinuria; *PS,* performance status; *RIC,* reduced-intensity conditioning regimen; *SCT,* stem cell transplant. (From Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

SUGGESTED READINGS

Bejar R et al.: Clinical effect of point mutations in myelodysplastic syndromes, *N Engl J Med* 364:2496–2506, 2011.

Griffiths EA, Gore SD: DNA methyltransferase and histone deacetylase inhibitors in the treatment of myelodysplastic syndromes, *Semin Hematol* 45:23–30, 2008.

Haase D: Cytogenetic features in myelodysplastic syndrome, *Ann Hematol* 87:515–526, 2008.

Olnes MJ, Sloand EM: Targeting immune dysregulation in myelodysplastic syndromes, *JAMA* 305(8):814–819, 2011.

Papaemmanuil E et al.: Somatic SF3B1 mutation in myelodysplasia with ring sideroblasts, *N Engl J Med* 365:1384–1395, 2011.

Tefferi A: Myelodysplastic syndromes—many new drugs, little therapeutic progress, *Mayo Clin Proc* 85(11):1042–1045, 2010.

Tefferi A, Vardiman JW: Myelodysplastic syndromes, *N Engl J Med* 361: 1872–1885, 2009.

TABLE EM1-33 Dysplastic Morphologic Features of Myelodysplastic Syndrome

	Peripheral Blood	Bone Marrow
RBCs and precursors	Aniso- and poikilocytosis*	Cloverleaf nuclei and variations
	Dual RBC populations	Megaloblastoid change
	Basophilic stippling	Multinuclearity
	Siderocytes	Vacuolated erythroblasts
		Internuclear bridging
		Pyknotic nuclei
		Irregular hemoglobulinization of precursors
		Howell-Jolly bodies
		Periodic acid Schiff–positive precursors
		Ring sideroblasts, or abnormal sideroblasts with large or multiple siderosomes
Granulocytes and precursors	Acquired (pseudo) Pelger-Huët anomaly	Megaloblastoid change
	Hypogranularity	Hypogranularity
	Hypersegmentation	Myeloperoxidase deficiency
	Ring nuclei	Abnormal localization of immature precursors†
		Nuclear-cytoplasmic asynchrony
		Pseudo–Chédiak-Higashi granules
Platelets and megakaryocytes	Large, vacuolated, or hypogranular platelets	Small mononuclear megakaryocytes
		Larger megakaryocytes with multiple small nuclei
		Hypolobated megakaryocytes
		Large megakaryocytes with large hyperchromic nuclei

RBC, Red blood cell.

*Numerous abnormal forms may be seen, including ovalocyte, elliptocyte, teardrop, target, and fragmented forms.

†In normal marrow, immature myeloid precursors are located adjacent to bony trabeculae and blood vessels. In myelodysplastic syndrome, they may be abnormally located in the center of marrow spaces, hence the descriptive name *abnormal localization of immature precursors*. This finding is not completely specific; for example, it can also be seen in regenerating marrow after an aplastic event.

From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.

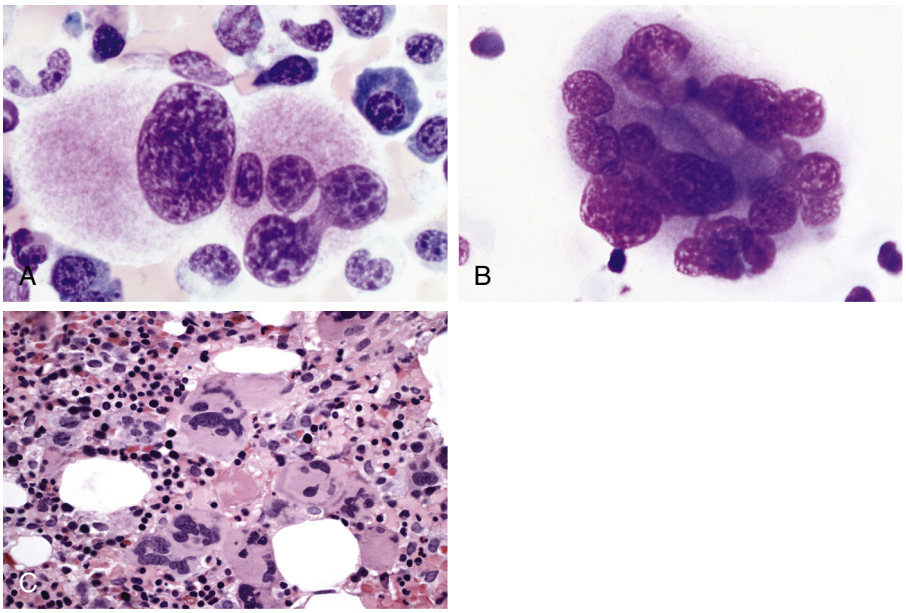

FIGURE EM1-65 Megakaryocytic dysplasia in bone marrow aspirate smears and biopsies in myelodysplastic syndrome. A, Abnormal nuclear features in bone marrow aspirate smears include monolobate and multiple separate small nuclei. **B,** Hyperlobation of megakaryocytic nuclei. **C,** Clustered dysplastic megakaryocytes in a bone marrow biopsy. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2001, Saunders.)

BOX EM1-4 Cytogenetic Abnormalities in Myelodysplastic Syndrome

Gain or loss of chromosomal material
- –7, 7q–
- 5q–, –5
- +8
- +21, –21
- 17p–, –17
- –20, 20q–
- 11q–, +11
- –Y
- 9q–
- +6
- 12p–
- 13q–

Uncommon translocations and inversions
- t(3;3)(q21;q26), inv3(q21q26), t(3;21)(q26;q22) and other 3q21 and 3q26 translocations
- t(1;7)(p11;p11)
- t(2;11)(p21;q23)
- t(11;16)(q23;p13)
- i(17)q, unbalanced and dicentric translocations at 17p

Any acquired clonal cytogenetic abnormality in hematopoietic cells, except characteristic de novo acute myeloid leukemia (AML) translocations*

Complex abnormalities (multiple cytogenetic abnormalities, excluding those characteristic of de novo AML)

*Common de novo AML translocations: t(15;17), t(8;21), inv(16) or t(16;16), t(9;11), t(11;19), t(11;17), t(8;16), t(1:22).
From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.

BASIC INFORMATION

DEFINITION

Myocardial infarction (MI) is a clinical syndrome characterized by symptoms of myocardial ischemia, persistent electrocardiographic (ECG) changes, and release of biomarkers of myocardial necrosis resulting from an insufficient supply of oxygenated blood to an area of the heart. According to the European Society of Cardiology/American College of Cardiology, either one of the following criteria for acute evolving or recent MI satisfies the diagnosis:

1. Detection of the rise and/or fall of cardiac biomarkers (preferably cTn) with at least 1 value above the 99th percentile and with at least 1 of the following:
2. Symptoms of ischemia
3. New, or presumed new, significant ST-T changes or new LBBB. New ST elevation at the J point in at least 2 contiguous leads of ≥2 mm (0.2 mV) in men or ≥1.5 mm (0.15 mV) in women in leads V2–V3 and/or of ≥1 mm (0.1 mV) in other contiguous chest leads or the limb leads
4. Development of pathologic Q waves on the ECG
5. Imaging evidence of new loss of viable myocardium or a new regional wall motion abnormality
6. Identification of an intracoronary thrombus by angiography or autopsy
   - Pathologic findings of acute MI

MI may be classified as ST-segment elevation MI (STEMI) and non–ST-segment elevation MI [NSTEMI]) depending on the ECG findings on MI presentation. This entry discusses STEMI. For a discussion of NSTEMI, see "Acute Coronary Syndromes."

The *European Heart Journal* and the *Journal of the American College of Cardiology* published a new definition of acute MI that includes 5 subtypes of acute MI, imaging tests supporting the diagnosis, and biomarker thresholds after percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

- Type 1: Spontaneous MI related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
- Type 2: MI secondary to ischemia due to either increased oxygen demand or decreased supply (e.g., coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension)
- Type 3: Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, new left bundle branch block, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood
- Type 4a: MI associated with percutaneous coronary intervention
- Type 4b: MI associated with stent thrombosis as documented by angiography or at autopsy
- Type 5: MI associated with coronary artery bypass grafting

SYNONYMS

MI
Myocardial infarction
ST-elevation MI
Heart attack
Acute myocardial infarction
AMI
Coronary thrombosis
Coronary occlusion

ICD-9CM CODES

410.9 Acute myocardial infarction, unspecified site

ICD-10CM CODES

I21 Acute myocardial infarction
I21.0 Acute transmural myocardial infarction of anterior wall
I21.1 Acute transmural myocardial infarction of inferior wall
I21.2 Acute transmural myocardial infarction of other sites
I21.3 Acute transmural myocardial infarction of unspecified site
I21.9 Acute myocardial infarction, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE/PREVALENCE (IN U.S.)

- In 2009, around 683,000 patients were discharged from U.S. hospitals with a diagnosis of acute coronary syndrome (ACS). Community incidence rates as well as mortality rates from STEMI have declined over the past decade, whereas those for NSTEMI have increased. At present, STEMI comprises approximately 25% to 40% of MI presentations. In-hospital (approximately 5% to 6%) and 1-year (approximately 7% to 18%). The most common cause of death in adults over the age of 40 is myocardial infarction. A heart attack takes the life of >1,500,000 people each year just in the United States.
- It is more prevalent in males between the ages of 40 and 65 yr; no predominant sex after the age of 65
- Women comprised 30% of STEMI patients. They experience more lethal and severe first acute MIs than men regardless of comorbidity, previous angina, or age. Being a woman constituted a strong independent predictor of failure to receive reperfusion therapy, have longer reperfusion times, be less often given the standard of care treatment within 24 hours of presentation, and have higher risk for bleeding with antithrombotic therapy.
- At least one fourth of all MIs are clinically unrecognized. Approximately 23% of patients with STEMI in the U.S. have diabetes mellitus, and three quarters of all deaths among patients with diabetes mellitus are related to coronary artery disease. Diabetes mellitus is associated with higher short- and long-term mortality after STEMI. In CRUSADE trial, 7% of eligible patients did not receive reperfusion therapy. The most important factor for not providing reperfusion therapy in eligible patients was increasing age.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Clinical presentation: Myocardial infarction is usually based on a history of chest pain lasting for 20 min or more that does not respond to nitroglycerin. Important clues are history of CAD and radiation of the pain to the neck, lower jaw, or left arm. The pain may not be severe. Some patients may present less-typical symptoms such as nausea/vomiting, shortness of breath, fatigue, palpitations, dizziness, or syncope. These patients, who tend to present typical symptoms later, are more likely to be women, diabetic patients, or elderly patients and less frequently receive reperfusion therapy and other evidence-based therapies than patients with a typical chest pain presentation. Records show that up to 30% of patients with STEMI present with atypical symptoms.

Physical findings:

- Skin may be diaphoretic and exhibit pallor (because of decreased oxygen).
- Rales may be present at the bases of lungs (indicative of heart failure [HF]).
- Cardiac auscultation may reveal an apical systolic murmur caused by mitral regurgitation from papillary muscle dysfunction; S_3 or S_4 may also be present.
- Up to 10% of patients may present with acute pulmonary edema and/or cardiogenic shock.
- Physical examination may be completely normal.

ETIOLOGY

- Coronary atherosclerosis and plaque rupture
- Coronary artery spasm
- Coronary embolism (caused by infective endocarditis, rheumatic heart disease, intracavitary thrombus, atrial fibrillation)
- Periarteritis and other coronary artery inflammatory diseases
- Dissection into coronary arteries (aneurysmal or iatrogenic)
- Calcium supplementation may promote vascular calcification. Studies have shown that calcium supplementation (but not dietary calcium intake) is associated with elevated risk for MI.
- MI with normal coronaries: more frequent in younger patients and cocaine addicts. The risk of acute MI is increased by a factor of 24 during the 60 min after the use of cocaine in persons who are otherwise at relatively low risk. Most patients with cocaine-related MI are young, nonwhite, male cigarette smokers without other risk factors for coronary heart disease who have a history of repeated cocaine use. Blood and urine toxicology screen for cocaine is recommended in all young patients who present with acute MI.
- Hypercoagulable states, increased blood viscosity (polycythemia vera and autoimmune diseases such as systemic lupus)

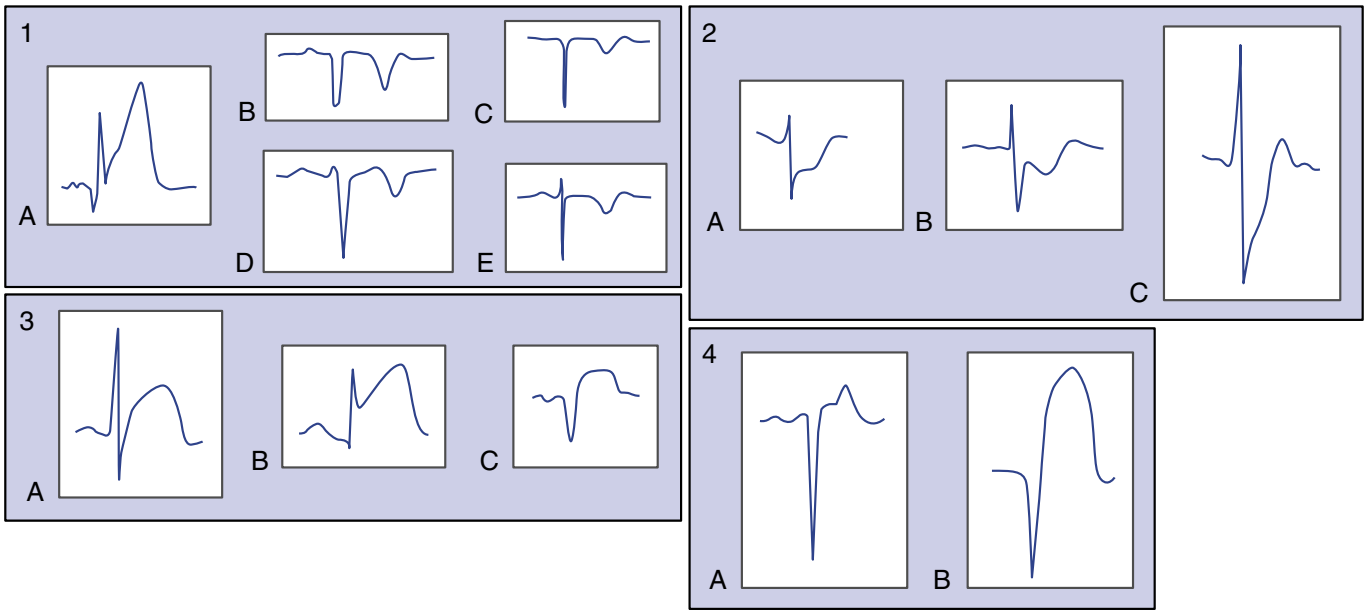

FIGURE M1-67 Electrocardiographic findings of acute myocardial infarction (AMI). 1, T-wave abnormalities of AMI. *A,* Prominent "hyperacute" T wave. *B-E,* T-wave inversions of non-ST-segment elevation MI (NSTEMI). **2,** ST-segment depression. *A,* Flat. *B,* Downsloping. *C,* Upsloping. **3,** ST-segment elevation. *A,* Convex ST-segment elevation. *B,* Obliquely straight ST-segment elevation. *C,* Convex ST-segment elevation. **4,** Pathologic Q waves. *A,* Pathologic Q wave of completed myocardial infarction. *B,* Simultaneous ST-segment elevation with pathologic Q wave 2 hours into the course of ST-segment elevation MI (STEMI). (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

The various causes of myocardial ischemia are described along with the differential diagnosis of chest pain.

LABORATORY TESTS

- Electrocardiogram (Fig. M1-67): a 12-lead ECG should be performed and shown to an experienced emergency physician within 10 min of ED arrival for all patients with chest discomfort (or anginal equivalent) or other symptoms suggestive of STEMI. If the initial ECG is not diagnostic for STEMI but the patient remains symptomatic and there is a high clinical suspicion for STEMI, serial ECGs at 5- to 10-minute intervals or continuous 12-lead ST-segment monitoring should be performed to detect the potential development of ST elevation. In patients with inferior STEMI, right-sided ECG leads should be obtained to look for ST elevation suggestive of right ventricular (RV) infarction. The joint ESC/ACCF/AHA committee for the definition of MI established the definition for the diagnosis of ST-elevation MI, which is considered to be present when there is an ST-segment elevation in two contiguous leads, ≥0.20 mm for men and ≥1.5 mm for women, or ≥1 mm in other leads. ST-segment elevation is measured at 0.08 sec after the J point (the junction between the end of the QRS and the beginning of the ST segment). ECG findings alone, without laboratory results, are sufficient to diagnose STEMI; therefore, treatment should not be delayed until biomarkers are available.
- Cardiac troponin levels: Cardiac-specific troponin T (cTnT) and cardiac-specific troponin I (cTnI) are generally indicative of myocardial injury with increases in serum levels of >99th percentile of a normal reference population. Detection of a rise and fall pattern of the measurements is essential to the diagnosis of AMI. The rise may occur relatively early after muscle damage (3-12 hr), peak at 24-48 hr, and may be present for several days after MI (up to 7 days for cTnI and up to 10 to 14 days for cTnT). cTnT or cTnI tests can be falsely positive in patients with renal failure. Recently, highly sensitive troponin assays (hs-cTnI, hs-cTnT) have also been developed to facilitate an early diagnosis of AMI. Most patients can be diagnosed with AMI within the first 2-3 hours of presentation. However, an initial negative high-sensitivity troponin at the time of presentation is not sensitive enough to completely rule out AMI. MI can be excluded in most patients by 6 hours of presentation, but guidelines suggest serial samples be obtained if there is a high degree of suspicion to definitively rule out MI.
- CK-MB isoenzyme is also a useful marker for MI if troponin levels are not available. It is released in the circulation in amounts that correlate with the size of the infarct. An increased CK-MB value for the diagnosis of MI is defined as a measurement above the 99th percentile of the upper reference limit. Troponin, however, is the preferred marker for the diagnosis of myocardial necrosis because of its increased sensitivity and specificity as compared to CK-MB. This preference was recommended by the 2007 Joint ESC/ACCF/AHA Task Force for the Definition of Myocardial Infarction. Because troponins need 7-14 days to be cleared by the kidneys, they are not sensitive enough to detect a recurrent MI within days from the initial MI. Therefore CK-MB isoenzyme can be useful in such circumstances.

IMAGING STUDIES

- Imaging studies such as a high-quality portable chest x-ray, echocardiography, and a contrast chest CT scan, or an MRI scan should be used to differentiate STEMI from aortic dissection in patients for whom this distinction is initially unclear.

RISK ASSESSMENT

Several risk assessment models are available. Some of the independent predictors of early death from STEMI include age (≥65), Killip class (≥2), time to reperfusion, cardiac arrest, tachycardia (>100 beats/min), hypotension (<100 mm Hg), anterior infarct location, prior infarction, diabetes mellitus, smoking status, renal function, and biomarker findings. Also weight >67 kg, anterior ST elevation or left bundle branch block, and time to treatment >4 hr. The higher the score, the higher the 30-day mortality rate. Risk assessment is a continuous process that should be repeated throughout hospitalization and at time of discharge.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Limit patient's activity: bed rest for the initial 12 to 24 hr; if the patient remains stable, gradually increase activity.
- Diet: nothing by mouth until stable, then a low-salt and a low-cholesterol diet.

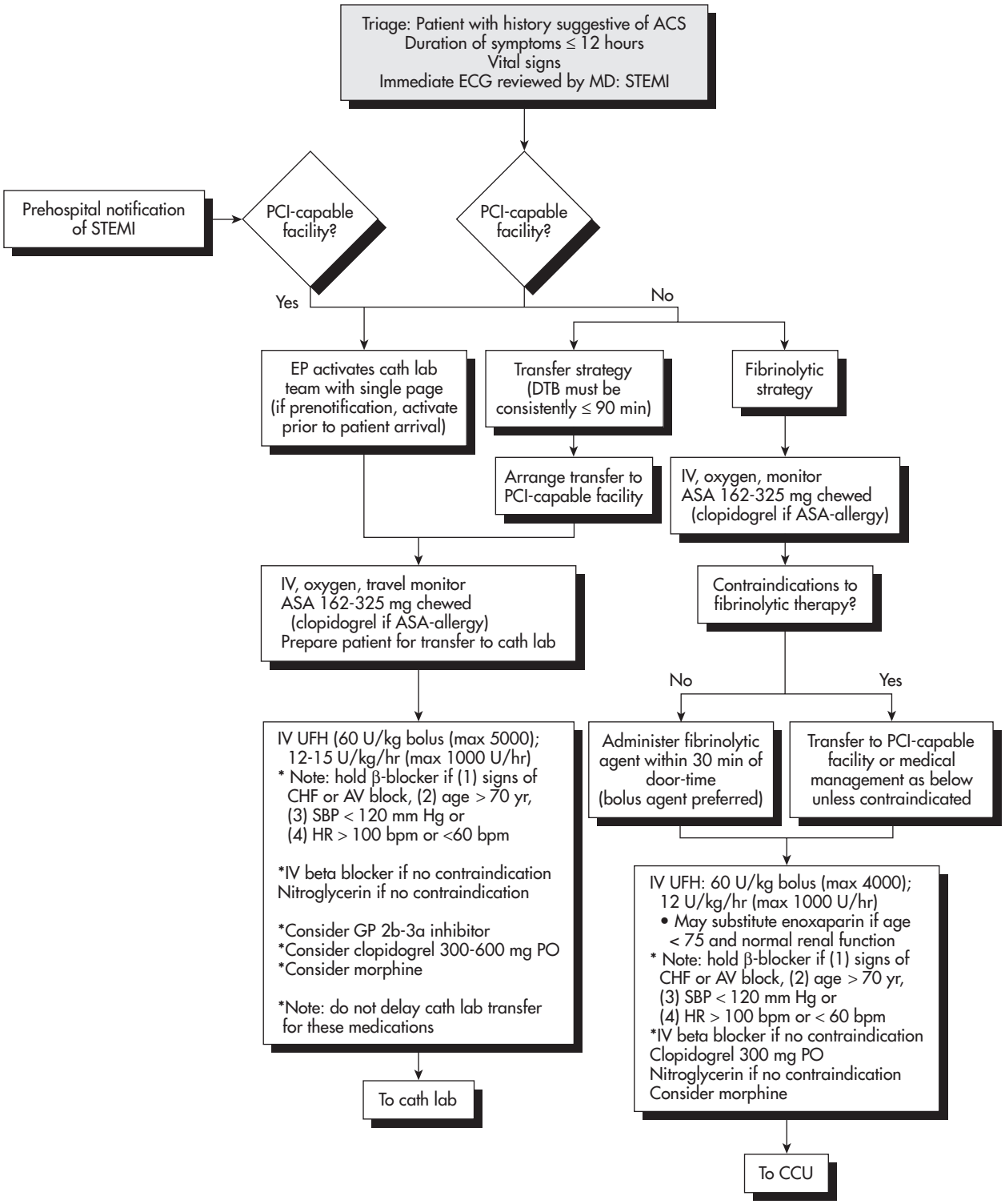

FIGURE M1-68 Assessment and treatment algorithm for ST-segment elevation myocardial infarction (STEMI). *ACS*, Acute coronary syndrome; *ASA*, acetylsalicylic acid; *AV*, atrioventricular; *bpm*, beats per minute; *cath lab*, catheterization laboratory; *CCU*, cardiac care unit; *CHF*, congestive heart failure; *DTB*, door-to-balloon time; *ECG*, electrocardiogram; *EP*, emergency physician; *GP*, glycoprotein; *HR*, heart rate; *IV*, intravenous/intravenous line; *PCI*, percutaneous coronary intervention; *PO*, orally; *SBP*, systolic blood pressure; *UFH*, unfractionated heparin. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

- Patient education to decrease the risk of subsequent cardiac events (proper diet, smoking cessation, regular exercise) should be initiated when the patient is medically stable.

ACUTE GENERAL Rx

- Fig. M1-68 shows a treatment algorithm for STEMI. Assessment and treatment algorithm for non-ST-segment MI is described in Fig. M1-69. Rationale of the treatment of a patient with STEMI is based on "time is muscle." Therefore, all communities should create and maintain a regional system of STEMI care that includes assessment and continuous quality improvement of EMS and

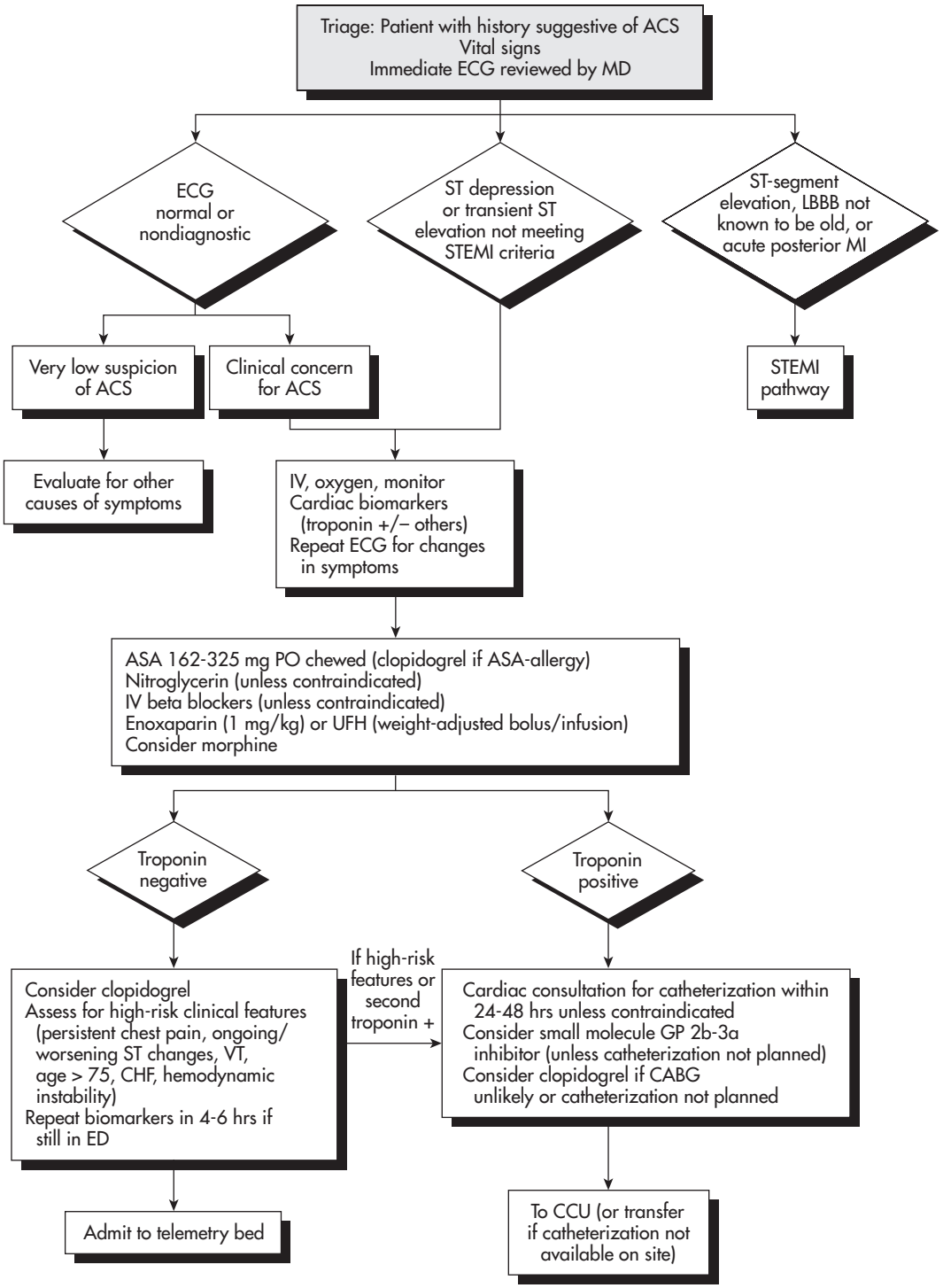

FIGURE M1-69 Assessment and treatment algorithm for non–ST-segment elevation myocardial infarction. *ACS*, Acute coronary syndrome; *ASA*, acetylsalicylic acid; *CABG*, coronary artery bypass grafting; *CCU*, cardiac care unit; *CHF*, congestive heart failure; *ED*, emergency department; *ECG*, electrocardiogram; *GP*, glycoprotein; *IV*, intravenous/intravenous line; *LBBB*, left bundle branch block; *MI*, myocardial infarction; *STEMI*, ST-segment elevation myocardial infarction; *UFH*, unfractionated heparin; *VT*, ventricular tachycardia. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

hospital-based activities. A 12-lead ECG must be done by EMS personnel at the site of first medical contact (FMC).

- Reperfusion therapy should be administered to all eligible patients with STEMI with symptom onset within 12 hours. Indications for primary angioplasty and comparison with fibrinolytic therapy are described in Table M1-35. Primary PCI (Fig. EM1-70) is the recommended method of reperfusion when it can be performed in a timely fashion by experienced operators with an ideal FMC-to-device time system goal of 90 minutes or less. In the absence of contraindications, fibrinolytic therapy (Table M1-36) should be administered to patients with STEMI at non-PCI-capable hospitals when the anticipated FMC-to-device time at a PCI-capable hospital exceeds 120 minutes because of unavoidable delays. It should be administered within 30 minutes of hospital arrival. PCI is superior to thrombolytic therapy and is the standard of care. It is effective and generally results in more favorable outcomes than thrombolytic therapy.
- Primary PCI should be performed in patients with STEMI and persistent ischemic symptoms and who have contraindications to fibrinolytic

TABLE M1-35 Indications for Primary Angioplasty and Comparison with Fibrinolytic Therapy

Indications
Alternative recanalization strategy for ST segment elevation or LBBB acute MI within 12 hr of symptom onset (or >12 hr if symptoms persist)
Cardiogenic shock developing within 36 hr of ST segment elevation/Q wave acute MI or LBBB acute MI in patients >75 yr old who can be revascularized within 18 hr of shock onset
Recommended only at centers performing >200 PCI/yr with backup cardiac surgery and for operators performing <75 PCI/yr
Advantages of Primary PCI
Higher initial recanalization rates
Reduced risk of intracerebral hemorrhage
Less residual stenosis; less recurrent ischemia or infarction
Usefulness when fibrinolysis contraindicated
Improvement in outcomes with cardiogenic shock
Disadvantages of Primary PCI (Compared with Fibrinolytic Therapy)
Access, advantages restricted to high-volume centers, operators
Longer average time to treatment
Greater dependence on operators for results
Higher system complexity, costs

LBBB, Left bundle branch block; *MI,* myocardial infarction; *PCI,* percutaneous coronary intervention (includes balloon angioplasty, stenting).
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

TABLE M1-36 Dosing Regimens of Commonly Used Thrombolytic Agents

Thrombolytic Agents	Dosing Regimen
t-PA (alteplase)	15 mg bolus IV, followed by 0.75 mg/kg body weight (not to exceed 50 mg) over 30 min, followed by 0.5 mg/kg (not to exceed 35 mg) over 60 min
r-PA (reteplase)	Two 10-U IV boluses, given 30 min apart
TNK–t-PA (tenecteplase)	Single bolus IV 0.5 mg/kg (dose rounded to the nearest 5 mg, ranging from 30 to 50 mg)
Streptokinase	1.5 million U IV over 60 min

IV, Intravenous; *PA,* plasminogen activator; *r-PA,* reteplase plasminogen activator; *TNK–t-PA,* tenecteplase tissue plasminogen activator; *U,* units.
From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.

therapy, irrespective of the time delay from FMC, or with cardiogenic shock or acute severe HF irrespective of time delay from myocardial infarction (MI) onset. Coronary stents (drug-eluting or bare-metal) are useful in patients with STEMI.

- Because the effectiveness of thrombolytics is time dependent, these agents should ideally be administered either in the field or within 30 min of the patient's arrival to the emergency department (door-to-needle time). Fibrinolytics therapy: if tissue plasminogen activator (t-PA) or reteplase is used, anticoagulants, such as heparin, are given to increase the likelihood of patency in the infarct-related artery for 48 hr and preferably for the duration of the index hospitalization. In patients receiving fibrinolysis for STEMI, treatment with enoxaparin is superior to treatment with unfractionated heparin for 48 hr but is associated with an increase in major bleeding episodes. In patients receiving streptokinase or APSAC, heparin after thrombolysis is not indicated because it does not offer any additional benefit and can result in increased bleeding complications. Tenecteplase and reteplase are comparable with accelerated infusion recombinant t-PA in terms of efficacy and safety but are more convenient because they are administered by bolus injection. Lanoplase and heparin bolus plus infusion are as effective as tPA with regard to mortality rate, but the rate of intracranial hemorrhage is significantly higher. Absolute contraindications to thrombolytic therapy (Table M1-37) include aortic dissection, active internal bleeding, intracranial neoplasm or arteriovenous malformation, intracranial surgery in the last 6 mo, ischemic stroke in the last yr, head trauma with loss of consciousness in the last 6 mo, surgery in noncompressible location in the last 6 wk, alteration in mental status, and infectious endocarditis. After the administration of thrombolytics, immediate transfer to a PCI-capable facility is advisable without waiting for lytic results.
- Transfer to a PCI-capable hospital: immediate transfer for STEMI patients who develop cardiogenic shock or acute severe HF, irrespective of the time delay from MI onset. Urgent transfer if the patient demonstrates evidence of failed reperfusion or reocclusion after fibrinolytic therapy.
- Coronary angiography should not be performed within the first 2 to 3 hours after administration of fibrinolytic therapy. Coronary artery bypass graft (CABG): urgent CABG is indicated in patients with STEMI and coronary anatomy not amenable to PCI who have ongoing or recurrent ischemia, cardiogenic shock, severe HF, or other high-risk features. CABG is recommended in patients with STEMI at time of operative repair of mechanical defects.
- The use of mechanical circulatory support is reasonable in patients with STEMI who are hemodynamically unstable and require urgent CABG.
- Until the catheterization team is ready or fibrinolytics are administered, medical therapy should be initiated immediately in the emergency department. This includes:
  1. Routine measures
     a. Oxygen: supplemental oxygen should be administered to patients with arterial oxygen desaturation (SaO_2 less than 90%).
     b. Nitroglycerin: increase oxygen supply by reducing coronary vasospasm and decrease oxygen consumption by reducing ventricular preload. Patients with ongoing ischemic discomfort should receive sublingual nitroglycerin every 5 minutes for a total of 3 doses, after which an assessment should be made about the need for intravenous nitroglycerin. Intravenous nitroglycerin is indicated for relief of ongoing ischemic discomfort, control of hypertension, or management of pulmonary congestion. Nitrates should not be administered to patients whose systolic blood pressure is <90 mm Hg or ≥30 mm Hg below baseline or severe bradycardia (<50 beats/min), tachycardia (>100 beats/min), or suspected RV infarction. Nitrates should not be administered to patients who have received a phosphodiesterase inhibitor for erectile dysfunction within the last 24 hr (48 hr for tadalafil).
     c. Adequate analgesia: morphine sulfate 2-4 mg IV initially with increments of 2-8 mg IV at 5- to 10-min intervals can be given for severe pain unrelieved by nitroglycerin. Morphine can reduce the catecholamine surge caused by anxiety and pain, particularly in patients with anterior myocardial infarctions, which in turn can reduce heart rate and PCWP, the increased cardiac workload and oxygen demand, leading to decreased ischemia and pulmonary congestion. Hypotension from morphine can be treated with careful IV hydration with saline solution. If sinus bradycardia accompanies hypotension, use atropine (0.5 to 1.0 mg IV q5min prn to a total dose of 2.5 mg). Respiratory depression caused by morphine can be reversed with naloxone 0.8 mg.

TABLE M1-37 Contraindications to Thrombolytic Therapy in Acute Myocardial Infarction

Absolute
Suspected aortic dissection
Active bleeding*
Any prior cerebral hemorrhage
Intracranial neoplasm
Cerebral aneurysm or arteriovenous malformation
Ischemic cerebrovascular accident within 3 mo
Relative
Bleeding diathesis, coagulopathy, or anticoagulant use
Major surgery within 3 wk
Puncture of a noncompressible vessel, internal bleeding, or head or major body trauma within previous 2 wk
Nonhemorrhagic stroke or gastrointestinal hemorrhage within 6 mo
Proliferative retinopathy
Active peptic ulcer disease
History of chronic, severe, poorly controlled hypertension
Severe uncontrolled hypertension on presentation (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg)
Traumatic or prolonged (>10 min) cardiopulmonary resuscitation
Pregnancy

*Does not include menstrual bleeding.
From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.

Morphine sulfate and nitroglycerine should be avoided in patients with RV involvement who usually present with bradycardia and hypotension. Pain management in these cases should be provided preferentially with meperidine 25-50 mg intravenously q 4h, in combination with phenergan 12.5 mg to prevent nausea and/or vomiting. Blood pressure support with normal saline solution is of critical importance to maintain adequate hemodynamics until optimal revascularization is accomplished.

d. Aspirin 162-325 mg PO should be crushed and chewed to enhance drug absorption and delivery. It should be given as soon as possible and continued indefinitely, at 81 mg daily. Depending on the clinical and ECG findings, if the patient is suspected to have a coronary anatomy that needs CABG rather than PCI, thienopyridine (clopidogrel) should be avoided because it increases the perioperative bleeding risk; otherwise, surgery is deferred for 5-7 days. However, if the coronary artery disease is likely to benefit from PCI alone, then a loading dose of clopidogrel 600 mg or ticagrelor 180 mg PO should be given as early as possible or prasugrel 60 mg as early as possible and no later than 1 hour after PCI. Thienopyridines should be continued for at least 1 yr after STEMI.

1. In patients receiving fibrinolytics only or balloon angioplasty without stent, thienopyridines can be given for as little as 14 d.
2. Beta-adrenergic blocking agents should generally be given to all patients. Beta-blockers are useful to reduce myocardial oxygen consumption and prevent tachyarrhythmias. Early IV beta blockage (in the initial 24 hr) followed by institution of an oral maintenance regimen is also effective in reducing recurrent infarction and ischemia. Oral beta-blockers should be initiated in the first 24 hr in patients with STEMI who do not have any of the following: signs of HF, evidence of a low-output state, increased risk for cardiogenic shock, or other contraindications for its use (bradycardia, PR interval more than 0.24 seconds, second- or third-degree heart block, active asthma, or reactive airways disease).

They should be continued during and after hospitalization for all patients with STEMI and with no contraindications to their use for at least 2 yr. Patients with initial contraindications to the use of beta-blockers in the first 24 hr after STEMI should be reevaluated to determine their subsequent eligibility. It is reasonable to administer intravenous beta-blockers at the time of presentation to patients with STEMI and no contraindications to their use who are hypertensive or have ongoing ischemia.

3. Anticoagulation therapy: STEMI is due to plaque rupture exposing the underlying collagen platelets that are activated and the coagulation cascade is initiated. IV unfractionated heparin or bivalirudin, or subcutaneous enoxaparin or fondaparinux can be used. In patients at high risk of bleeding, use of bivalirudin is reasonable. Anticoagulation therapy is usually continued for 48 hours after administration of lytic therapy unless streptokinase or APSAC is used.
4. Neither facilitation of PCI with reteplase plus abciximab nor facilitation with abciximab alone significantly improves the clinical outcomes compared with abciximab given at the time of PCI in patients with STEMI. In patients with acute MI, treatment with drug-eluting stents is associated with decreased 2-yr mortality rates and a reduction in the need for repeated revascularization procedures compared with treatment including bare-metal stents.

CHRONIC Rx

- Discharge medications in all patients with MI (unless contraindicated) should include antiischemic medications (e.g., nitroglycerin, beta-blocker), lipid-lowering agents, and antiplatelet therapy (aspirin and/or clopidogrel).
- Aspirin, 81 mg (baby dose) PO daily, but should be continued indefinitely unless not tolerated (e.g., GI bleed). Clopidogrel 75 mg PO daily; ticagrelor, 90 mg bid, or prasugrel, 10 mg PO daily, can be combined with aspirin and should be continued without interruption for 30 days after bare-metal stent placement or for 12 months after drug-eluting stent placement, but preferably, if no contraindications, should be given for at least 1 yr and can be discontinued after completion of duration; however, aspirin should be continued indefinitely. Combining thienopyridines with aspirin reduces risk for in-stent restenosis. If there is an elective surgical intervention pending, it is recommended to defer the surgery until completion of the full course of the thienopyridine treatment.
- Angiotensin-converting enzyme inhibitors (ACEIs) should be started within the first 24 hours of STEMI to all patients having STEMI with anterior infarction, pulmonary congestion, or LV EF <40%, in the absence of hypotension. They reduce LV dysfunction and dilation and slow the progression to HF during and after acute MI. Angiotensin receptor blockers should be given to patients who have indication but are intolerant of ACEIs. IV formulations of ACEIs should not be given within the first 24 hours of STEMI due to risk of hypotension. Angiotensin receptor blockers (ARBs) offer no advantage over ACEIs and should be considered only in patients who are intolerant to ACEIs.
  1. Commonly used ACEIs are ramipril 2.5 mg PO qd, captopril 12.5 mg PO bid, enalapril 2.5 mg PO bid, and lisinopril 2.5-5 mg PO qd initially, with subsequent titration as needed. Ramipril is associated with a lower mortality rate than most ACEIs.
  2. ACEIs may be stopped in patients without complications and no evidence of LV dysfunction after 6 to 8 weeks.
  3. ACEIs should be continued indefinitely in patients with impaired LV function (EF <40%) or clinical HF.
- Long-term aldosterone antagonist therapy should be prescribed for post-STEMI patients without significant renal dysfunction (creatinine ≤2.5 mg/dl in men and ≤2.0 mg/dl in women) or hyperkalemia who are already taking an ACEI, a beta-blocker, and have LV EF <40% with symptomatic HF or diabetes.
- Statins should be started as early as possible in all patients with STEMI regardless of lipid

panel, not only for their lipid-lowering effects, but also their anti-inflammatory properties (JUPITER trial), which can stabilize the ruptured plaque. Atorvastatin 80 mg can be used (PROVE IT-TIMI 22 and MIRACL trials). Lipid panel should be checked during the first 24 hr of hospital course and the intensive therapy can be stepped down if appropriate. Goal LDL cholesterol is <70 mg/dl. Consider addition of fenofibrate or niacin if triglycerides are significantly elevated. Recent data showed no improvement in outcome with increasing HDL cholesterol therapy using niacin; therefore its use to decrease HDL cholesterol is questionable.

COMPLICATIONS OF STEMI

Cardiogenic shock: emergent revascularization with either PCI or CABG is the recommended treatment.

Sustained ventricular tachycardia: cardioverter-defibrillator therapy is indicated before discharge in patients who develop sustained ventricular tachycardia/ventricular fibrillation more than 48 hr after STEMI, provided the arrhythmia is not due to transient or reversible ischemia, reinfarction, or metabolic abnormalities.

Pacing in STEMI: temporary pacing is indicated for symptomatic bradyarrhythmias unresponsive to medical treatment and after revascularization. A lot of AV blocks and bradyarrhythmias may be transient and resolve within 2 wk of an MI.

Pericarditis after STEMI: aspirin is recommended for treatment of pericarditis after STEMI. Glucocorticoids and nonsteroidal anti-inflammatory drugs are potentially harmful for treatment of pericarditis after STEMI.

EVALUATION OF POST-MI PATIENTS:

- Noninvasive testing for ischemia should be performed before discharge to assess the presence and extent of inducible ischemia in patients with STEMI who have not had coronary angiography and do not have high-risk clinical features for which coronary angiography would be warranted. It might be considered before discharge to evaluate the functional significance of a noninfarct artery stenosis previously identified at angiography and/or before discharge to guide the postdischarge exercise prescription.
- Assessment of LV function: LV ejection fraction should be measured in all patients with STEMI.

  Echocardiography to rule out presence of mural thrombi in patients suspected of having an extensive infarction (more common with anterior wall MI); contrast echocardiography is added if mural thrombosis is suspected

1. Assessment of risk for sudden cardiac death: patients with an initially reduced LV ejection fraction who are possible candidates for implantable cardioverter-defibrillator therapy should undergo reevaluation of LV ejection fraction <35% and NYHA class II or III heart failure and should then be considered for implanted defibrillator if the life expectancy is >1 yr.

- Cardiac rehabilitation/secondary prevention programs are recommended for patients with STEMI
- Lifestyle risk factors modification

DISPOSITION

The prognosis after MI depends on multiple factors:

- New bundle branch block, Mobitz II second-degree block, and third-degree heart block adversely affect outcome.
- Size of infarct: the larger it is, the higher the post-MI mortality rate. Significant myocardial stunning with subsequent improvement of ventricular function occurs in most patients after anterior MI. A lower level of creatine kinase, an estimate of the extent of necrosis, is independently predictive of recovery of function.
- Site of infarct: inferior wall MI carries a better prognosis than anterior wall MI; however, patients with inferior wall MI and right ventricular involvement have a high risk for arrhythmic complications and cardiogenic shock.
- Ejection fraction after MI: the lower the LV ejection fraction, the higher the mortality rate after MI. The risk of death is higher in the first 30 days after MI among patients with LV dysfunction, HF, or both.
- Presence of post-MI angina indicates a high mortality rate.
- Performance on low-level exercise test: the presence of ST-segment changes during the test is a predictor of high mortality rate during the first year.
- Presence of pericarditis during the acute phase of MI increases mortality rate at 1 yr.
- Type A behavior (competitive drive, ambitiousness, hostility) is associated with a lower mortality rate after symptomatic MI.
- The Killip classification is an independent predictor of all-cause 30-day mortality:
  1. Killip class I includes individuals with no clinical signs of HF. Mortality rate is 6%.
  2. Killip class II includes individuals with rales or crackles in the lungs, S_3 gallop, and elevated jugular venous pressure. Mortality rate is 17%.
  3. Killip class III describes individuals with frank acute pulmonary edema. Mortality rate is 38%.
  4. Killip class IV describes individuals in cardiogenic shock or hypotension (measured as systolic blood pressure <90 mm Hg) and evidence of peripheral vasoconstriction (oliguria, cyanosis, or sweating). Mortality rate is 67%.
- Self-reported moderate alcohol consumption in the year before acute MI is associated with reduced 1-yr mortality rate.
- Discharge medication in patients with MI should include lipid-lowering agents. Statins may also lower vascular inflammation and damage by mechanisms other than reduction of low-density lipoprotein cholesterol. Early initiation of statin treatment in patients with acute MI is associated with reduced 1-yr mortality rate.
- Additional poor prognostic factors include cigarette smoking, history of hypertension or prior MI, presence of ST-segment depression in acute MI, older age, diabetes mellitus, and female sex (especially women >50 yr). Lammintausta and Fonarrow reported that single men and women who live alone have a 60-70% greater risk of a heart attack. Furthermore, the study showed >160% increase in the risk of sudden death in these groups when compared to people who are married or live with family.
- Renal disease, even mild, as assessed by the estimated glomerular filtration rate, is a major risk factor for cardiovascular complications after MI.
- Although black patients with MI have worse outcomes than their white counterparts, these differences did not persist after adjustment for patient factors and site of care.

PEARLS & CONSIDERATIONS

COMMENTS

- Approximately 1.5 million patients undergo PCI in the United States each year. Depending on local practices and the diagnostic criteria used, 5% to 30% of these patients have evidence of a periprocedural MI.
- The 12-lead ECG has low sensitivity for the detection of MI if the culprit lesion is in the left circumflex artery (LCX). If the initial 12-lead ECG is not diagnostic and high clinical suspicion for acute coronary syndrome exists it is reasonable to obtain additional posterior chest leads (V_7 to V_9) to detect LCX occlusion.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Heart Attack (Patient Information)
Acute Coronary Syndrome (Related Key Topic)
Angina Pectoris (Related Key Topic)

AUTHOR: **CLAUDIA SERRANO-GOMEZ, M.D.**

SUGGESTED READINGS

2007 focused update of the ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction, *J Am Coll Cardiol* 51:210–247, 2008.

2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update), J Am Coll Cardiol 54:2205–2241.

2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines, *Circulation* 127:e362–e425, 2013. 10.1161/ CIR.0b013e3182742cf6. Published online before print December 17.

ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction-executive summary: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction), *Circulation* 110:588–636, 2004.

Aquel RA et al.: Usefulness of posterior chest leads for the detection of posterior wall acute myocardial infarction, *Am J Cardiol* 103:159–164, 2009.

Aronow WS: Office management after myocardial infarction, *Am J Med* 123: 593–595, 2010.

Becker RC: Antithrombotic therapy after myocardial infarction, *N Engl J Med* 347:1019, 2002.

Body R et al.: Rapid exclusion of acute myocardial infarction in patients with undetectable troponin using a high-sensitivity assay, *J Am Coll Cardiol* 58:1332–1339, 2011.

Cannon CP et al.: Intensive versus moderate lipid lowering with statins after acute coronary syndromes, *N Engl J Med* 350:1495, 2004.

ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation, *Eur Heart J* 33:2569–2619, 2012.

Heart disease and stroke statistics—2013 update: a report from the American Heart Association, *Circulation* 127:e6–e245, 2013. 10.1161/ CIR.0b013e31828124ad. Published online before print December 12, 2012.

Jeremias A, Gibson M: Narrative review: alternative causes for women's ischemic syndrome evaluation: current status and future research directions: report of the National Heart, Lung, and Blood Institute Workshop: October 2-4, 2002: Section 1: Diagnosis of Stable Ischemia and Ischemic Heart Disease, *Circulation* 109:e44–e46, 2004. 10.1161/ 01.CIR.0000116206.77324.5B.

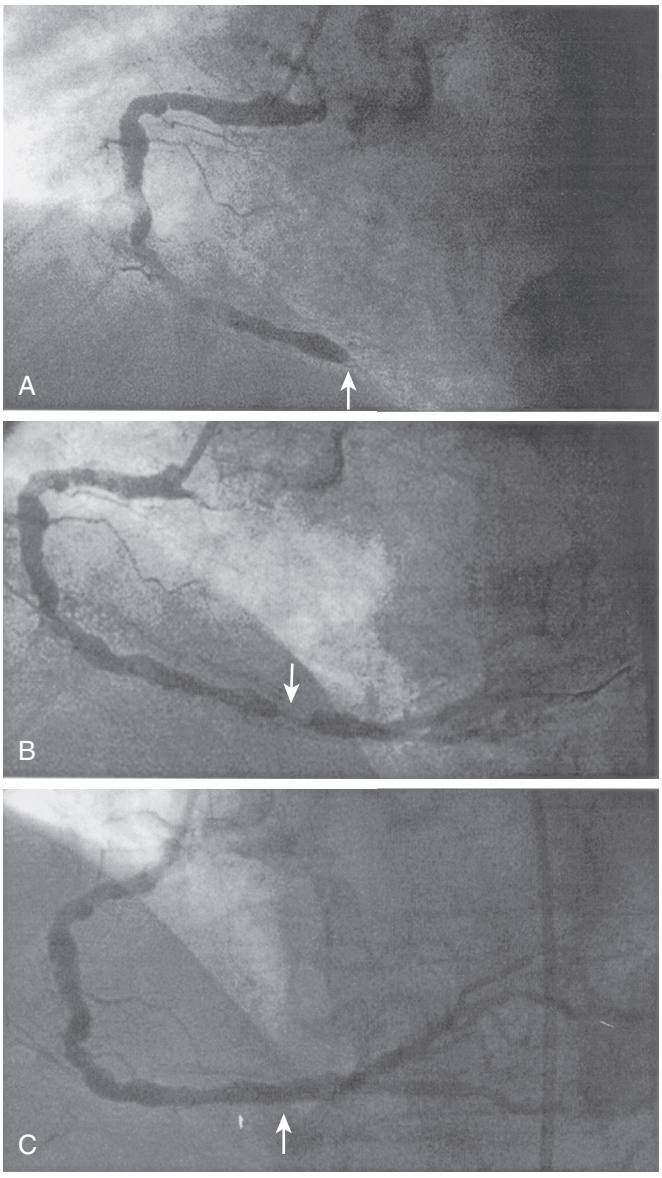

FIGURE EM1-70 Primary coronary angioplasty for acute myocardial infarction. This 50-year-old man presented at midnight with 70 minutes of crushing substernal chest pressure accompanied by inferior ST segment elevation. Emergency angiography performed 45 minutes after arrival found 100% occlusion of the right coronary artery (**A,** *arrow*). Within 10 minutes, a guidewire was negotiated through the obstruction (presumably caused by fresh thrombus), allowing perfusion into the distal vessel and uncovering a high-grade stenotic lesion (**B,** *arrow*). After deployment of a coronary stent (**C,** *arrow*), the stenosis was abolished and significant myocardial damage aborted. (From Goldman L, Schafer AI: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Saunders.)

BASIC INFORMATION

DEFINITION

Myocarditis broadly refers to inflammation of the heart muscle. This may result from exposure to discrete external antigens such as viruses, bacteria, parasites, and drugs or from internal triggers such as autoimmune conditions.

ICD-9CM CODES
429.0 Myocarditis, nonspecific
391.2 Myocarditis, rheumatic
422.91 Myocarditis, viral (except Coxsackie)
074.23 Myocarditis, Coxsackie
422.92 Myocarditis, bacterial

ICD-10CM CODES
I40 Acute myocarditis
I40.0 Infective myocarditis
I40.1 Isolated myocarditis
I40.8 Other acute myocarditis
I40.4 Acute myocarditis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- The incidence of focal myocarditis reported at autopsy is 1% to 9% in asymptomatic patients and 50% in patients infected with HIV.
- Myocarditis is a major cause of sudden unexpected death (as high as 8% to 9%) in young adults <40 years of age, especially in cases of idiopathic dilated cardiomyopathy, where myocarditis may account for 10% to 40% of the cases overall.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Persistent tachycardia out of proportion to fever
- Faint S_1, S_3, and S_4 gallops on auscultation
- Murmur of functional mitral regurgitation and functional tricuspid regurgitation caused by severe left ventricular and right ventricular dilatation
- Pericardial friction rub if associated with pericarditis as in the clinical syndrome of myopericarditis
- Chest pain especially pleuritic and positional when the pericardium is involved.
- Presyncope or syncope secondary to ventricular arrhythmias
- Non-specific viral prodrome and fatigue
- Congestive heart failure (CHF) symptoms that usually manifest with fatigue and decreased exercise capacity
- If myocarditis is severe and diffuse and rapid in evolution, it can present with acute CHF symptoms leading to cardiogenic shock and death.
- Signs of biventricular failure (hypotension, hepatomegaly, peripheral edema, distention of neck veins, S_3 sounds, and pulmonary edema)
- Patients may present with a history of recent flulike syndrome (fever, arthralgias, malaise); children often have a more fulminant presentation than adults. Difficulty breathing is the most common presentation of pediatric myocarditis.
- The most common presentations are dyspnea (72% of patients), chest pain (32%), and arrhythmias (sinus tachycardia, atrial and ventricular premature contractions) (18%).
- Acute coronary syndrome, which can occur because of local coronary spasm and inflammation, which presents on ECG as acute injury pattern or ischemic changes
- Sudden cardiac death from ventricular tachycardia/ventricular fibrillation mediated by inflammation and/or scar, which sets up a re-entry mediated pathway for ventricular arrhythmias

ETIOLOGY

- Infection
  1. Viral (adenovirus, parvovirus B19, hepatitis C virus (HCV), Coxsackie B virus, cytomegalovirus, enterovirus, poliovirus, mumps, HIV, and Epstein-Barr virus, etc.). Viruses are the most common cause of myocarditis in developed countries. In the 1980s and 1990s, enteroviruses were frequently associated with myocarditis and dilated cardiomyopathy. In the past 10 years, however, other viruses such as adenovirus, HCV, parvovirus B19, and herpesvirus 6 (HH6) have emerged as the significant pathogens.
  2. Bacterial (*Staphylococcus aureus, Clostridium perfringens,* diphtheria, and any severe bacterial infection)
  3. *Mycoplasma*
  4. Mycotic (Candida, Mucor, Aspergillus)
  5. Parasitic (*Trypanosoma cruzi*—most common worldwide, *Trichinella, Echinococcus, Amoeba*, *Toxoplasma*)
  6. Rickettsia rickettsii
  7. Spirochetal *(Borrelia burgdorferi*–Lyme carditis)
- Rheumatic fever
- Systemic lupus erythematosus
- Wegener's granulomatosis
- Giant cell arteritis and Takayasu's arteritis
- Drugs (e.g., cocaine, emetine, doxorubicin, sulfonamides, isoniazid, methyldopa, amphotericin B, tetracycline, phenylbutazone, lithium, 5-fluorouracil, phenothiazines, interferon-alfa, tricyclic antidepressants, cyclophosphamides, smallpox vaccination)
- Toxins (carbon monoxide, ethanol, diphtheria toxin, lead, arsenicals)
- Systemic and collagen-vascular disease (scleroderma, sarcoidosis, celiac disease, Sjögren's syndrome, Kawasaki syndrome, etc.)
- Radiation
- Postpartum status
- Post stem cell transplantation

DIAGNOSIS (Table M1-38)

DIFFERENTIAL DIAGNOSIS

- Ischemic cardiomyopathy and other, nonischemic cardiomyopathies
- Acute coronary syndromes
- Valvulopathies
- Infiltrative diseases of the myocardium, such as sarcoidosis, amyloidosis, hemochromatosis, and Chagas' disease.

The differential diagnosis of chest pain is described in Section II.

WORKUP

- Medical history: the clinical presentation of myocarditis is nonspecific and can consist of fatigue, palpitations, dyspnea, precordial discomfort, and myalgias.
- Diagnostic workup includes chest x-ray examination, ECG, laboratory evaluation, echocardiogram, cardiac catheterization, MRI with late gadolinium enhancement, and endomyocardial biopsy (in selected patients on the basis of the likelihood of finding specific treatable disorders such as giant cell myocarditis). Of note, endomyocardial biopsy has a sensitivity of only 10% to 35% using standard histologic criteria. This is due to variability in interpretation and sampling error.

LABORATORY TESTS

- Elevated cardiac troponin is suggestive of myocarditis in patients with clinically suspected myocarditis. Troponin I specificity is 89%; sensitivity is 34% to 53%. A normal level does not rule out the diagnosis.
- Increased creatine kinase (CK) (with elevated MB fraction, lactate dehydrogenase), and aspartate aminotransferase from myocardial necrosis.
- Elevation of cardiac troponin I or T is more common than CK-MB elevation in patients with biopsy-proven myocarditis.
- The elevations of cardiac troponin I were correlated with a short duration (typically less than 1 mo) of CHF symptoms, indicating that the majority of myocardial necrosis occurs early in the disease course.
- Persistent elevations of cardiac biomarkers are indicative of ongoing myocardial necrosis.
- Increased erythrocyte sedimentation rate (nonspecific but may be of value in following the progress of the disease and the response to therapy).
- Increased white blood cell count, again, nonspecific (increased eosinophils if parasitic infection).
- Viral titers (acute and convalescent).
- Cold agglutinin titer, antistreptolysin O titer, blood cultures.
- Lyme disease antibody titer.
- RPR, VDRL.

IMAGING STUDIES

- Chest x-ray: enlargement of cardiac silhouette may be present
- ECG: sinus tachycardia with nonspecific ST-T wave changes unless there is concomitant pericarditis in which the ECG changes are more specific; intraventricular conduction defects and bundle branch blocks are uncommon in typical viral myocarditis but are common manifestations in cardiac sarcoid and idiopathic giant cell myocarditis.

TABLE M1-38 Expanded Criteria for Diagnosis of Myocarditis

Suggestive of myocarditis:	2 positive categories
Compatible with myocarditis:	3 positive categories
High probability of being myocarditis:	all 4 categories positive

(Any matching feature in category = positive for category)

Category I: Clinical Symptoms

Clinical heart failure
Fever
Viral prodrome
Fatigue
Dyspnea on exertion
Chest pain
Palpitations
Presyncope or syncope

Category II: Evidence of Cardiac Structural or Functional Perturbation *in the Absence* of Regional Coronary Ischemia

Echocardiography evidence
Regional wall motion abnormalities
Cardiac dilation
Regional cardiac hypertrophy
Troponin release
High sensitivity (>0.1 ng/mL)
Positive indium In 111 antimyosin scintigraphy
and
Normal coronary angiography *or*
Absence of reversible ischemia by coronary distribution on perfusion scan

Category III: Cardiac Magnetic Resonance Imaging

Increased myocardial T2 signal on inversion recovery sequence
Delayed contrast enhancement after gadolinium-DTPA infusion

Category IV: Myocardial biopsy—Pathologic or Molecular Analysis

Pathology findings compatible with Dallas criteria
Presence of viral genome by polymerase chain reaction or in situ hybridization

DTPA, Diethylenetriamine penta-acetic acid.
(From Bonow R.O., et al.: *Heart disease*, 9th ed, Philadelphia, 2012, Saunders.)

1. Lyme disease and diphtheria cause all degrees of heart block.
2. Changes mimicking acute myocardial infarction can occur with focal necrosis from myocarditis.

- Echocardiogram:
  1. The most useful test in detecting decreased ventricular function in suspected myocarditis even when subclinical.
  2. The spheroid dysfunctional ventricle in acute myocarditis tends to remodel to the more normal elliptical shape over several months.
  3. Dilated and hypokinetic chambers
  4. The dysfunction is generally global but may be regional or segmental as in the case of focal myocarditis.
  5. Abnormal tissue Doppler signal can provide additional evidence for the presence of myocarditis.
  6. The echocardiogram can also be helpful with diagnosing coexisting pericardial involvement.
- Cardiac catheterization and angiography:
  1. To rule out coronary artery disease and valvular disease. Coronary angiography is most commonly normal with no evidence of coronary artery disease.
  2. A right ventricular endomyocardial biopsy can confirm the diagnosis, although a negative biopsy result does not exclude myocarditis owing to the low sensitivity of this test. Recent studies have shown that myocardial biopsy may be unnecessary because immunosuppression therapy based on biopsy results is generally ineffective. However, if idiopathic giant cell myocarditis is suspected, biopsy can confirm this diagnosis, and immunosuppression therapy is often helpful in this patient cohort.
- Cardiac MRI (Fig. M1-71):
  1. Can be used to detect myocardial edema and myocyte injury in myocarditis.
  2. Increased focal or global signal intensity can be used to calculate an edema ratio.
  3. Late gadolinium enhancement (LGE) and the presence of increased focal and global myocardial contrast enhancement relative to skeletal muscle.
  4. Any combination of two of the above has a sensitivity and specificity of 86% and 95%, respectively, and is probably the gold standard for diagnosis of myocarditis today, as opposed to routine biopsy.
  5. Cardiac MRI has demonstrated that myocarditis tends to start as a focal process and becomes a more global process over time, with the extent of myocardial enhancement correlating with clinical status and left ventricular function.
  6. Some viral pathogens have focal involvement of the myocardium. Parvovirus B19 involves the subepicardial lateral wall of the left ventricle. HHV6 and especially the combination of HHV6/parvovirus B19 tend to involve the septum and present with more acute and chronic heart failure symptoms.
  7. The pattern of LGE is different from that in ischemic cardiomyopathy. LGE in myocarditis tends to involve the epicardium with variable extension into the midmyocardium and sparing of the endocardium. This is opposite of ischemic injury, which involves endocardium first with extension outward.
- Indium-111-labeled antimyosin antibody scintigraphy is positive in myocarditis with a sensitivity of up to 65%.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive care is the first line of therapy for patients with myocarditis.
- Restrict physical activity (to decrease cardiac work). Bed rest is advisable during viremia.

ACUTE GENERAL Rx

- Treat underlying cause (e.g., use specific antibiotics for bacterial infection).
- Treat congestive heart failure (CHF) with diuretics, angiotensin-converting enzyme inhibitors (ACE inhibitors), and salt restriction. A beta-blocker may be added once clinical stability has been achieved. Digoxin should be used with caution and only at low doses.
- Patients who are left with an LVEF ≤35% despite optimal medical therapy for 3-9 mo, who have a good functional status, and who have a prognosis >1 yr will benefit from primary prevention therapy with implantable cardioverter-defibrillator (ICD) implantation as in patients with ischemic cardiomyopathy and other nonischemic cardiomyopathies.
- Antiarrhythmics if needed for ventricular arrhythmias. ICD implantation for secondary prevention in patients with life-threatening ventricular arrhythmias who have good functional status and a prognosis >1 yr.
- In patients with chronic CHF from myocarditis, only ACE inhibitors, beta-blockers, and possibly aldosterone receptor antagonists will decrease their mortality in the long term (as with all CHF etiologies).
- Provide anticoagulation to prevent thromboembolism in atrial fibrillation, in severe left ventricular dysfunction with an EF <20%, and in patients with severe segmental wall motion abnormality of the apex.
- Inotropes or mechanical assist devices such as intra-aortic balloon pumps, Impella device, and left ventricular assist device (LVAD) if severe heart failure or if cardiogenic shock persists despite medical therapy.
- Cardiac transplantation in patients with chronic or acute fulminant myocarditis with intractable cardiomyopathy and persistent CHF.
- Corticosteroid use is contraindicated in early infectious myocarditis; it may be justified in only selected patients with intractable CHF, severe systemic toxicity, and severe life-threatening arrhythmias.
- Immunosuppressive drugs (prednisone with cyclosporine/cytoxan or azathioprine) do not

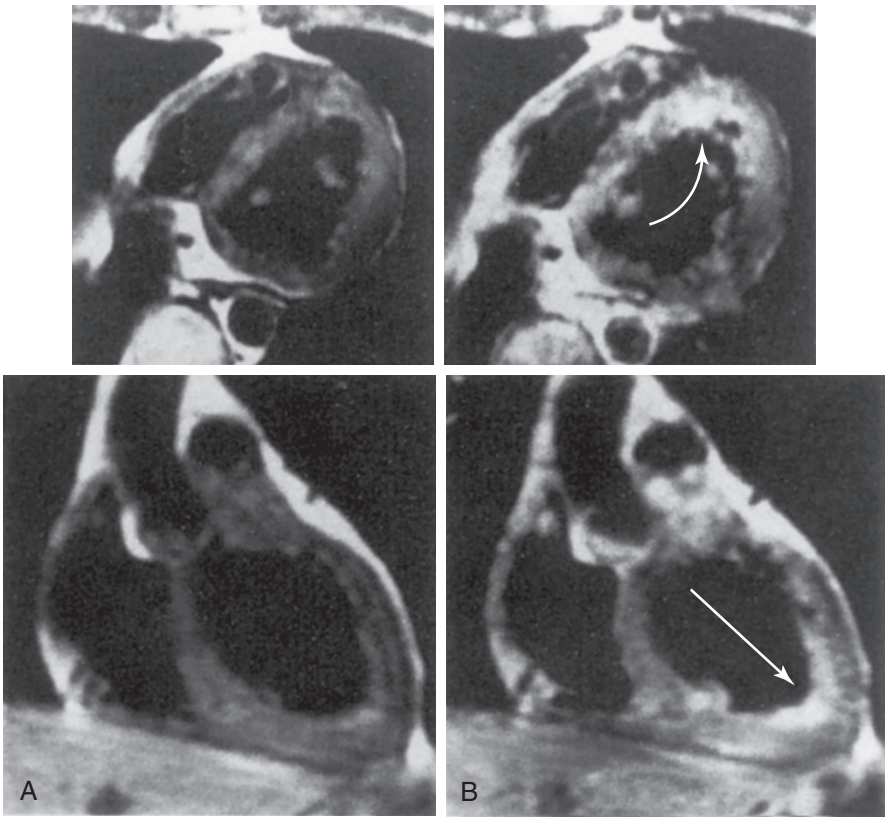

FIGURE M1-71 A, Precontrast T1-weighted transaxial *(upper)* and coronal *(lower)* magnetic resonance images through the left ventricle in a patient with myocarditis. **B,** Postcontrast magnetic resonance images at the same levels after contrast injection. Note enhancement of the myocardial signal in the septum and apical region *(arrows)*. (From Zipes DP et al [eds]: *Braunwald's heart disease*, ed 7, Philadelphia, 2005, Saunders.)

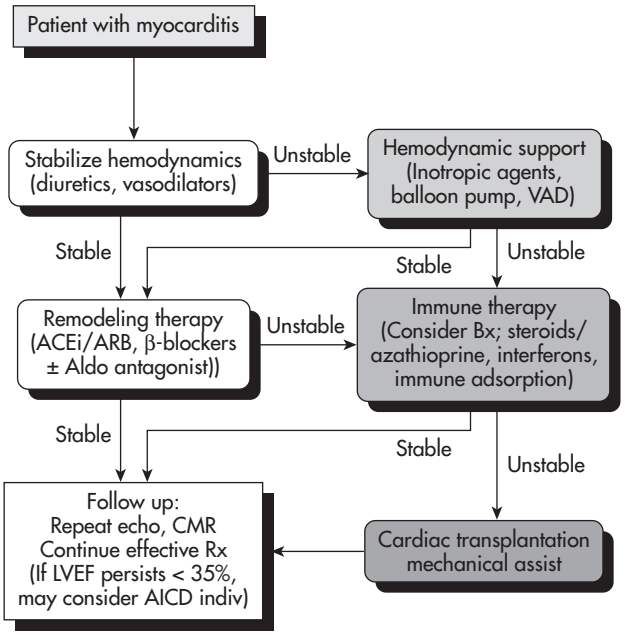

FIGURE M1-72 Treatment algorithms for patients with myocarditis, depending on hemodynamic stability and response to general supportive and remodeling treatment regimen at each step. All patients should have aggressive support and appropriate follow-up. Immune therapy at present is still mainly to support those who have failed to improve spontaneously. *ACEi*, Angiotensin-converting enzyme inhibitors; *AICD*, automatic implantable cardioverter-defibrillator; *Aldo*, aldosterone; *ARB*, angiotensin receptor blockers; *Bx*, biopsy; *CMR*, cardiac magnetic resonance; *indiv*, based on individual assessment of risk versus benefit; *LVEF*, left ventricular ejection fraction; *VAD*, ventricular assist device. (From Bonow RO et al: *Heart disease*, ed 9, Philadelphia, 2012, Saunders.)

have any significant effect on the prognosis of myocarditis and should not be used in the routine treatment of patients with myocarditis. Immunosuppression may have a role in the treatment of myocarditis from systemic autoimmune disease (e.g., lupus, scleroderma), in patients with idiopathic giant cell myocarditis, myocarditis caused by hypersensitivity reactions, or severe hemodynamic compromise.

- In patients with ongoing viral genomic expression, treatment with interferons may improve both symptoms and left ventricular function when compared with standard heart failure therapy and is currently showing promising data in Phase III clinical trials.
- IV immunoglobulins have been studied, but because of lack of efficacy data, at present there is no indication for their use except in some pediatric cases or those refractory to immunosuppressive therapy.
- A treatment algorithm for patients with myocarditis is described in Fig. M1-72.

DISPOSITION

- Most patients with acute myocarditis and mild cardiac involvement have a partial or a full clinical recovery. In some cases, however, the process may continue subclinically with eventual progression to a cardiomyopathy. Therefore all patients with myocarditis should be followed up at least initially at intervals of 1 to 3 mo. Of those with advanced cardiac dysfunction, one third will have residual cardiac dysfunction and 25% may progress to cardiac transplantation or death.
- Prognosis is best for patients with fulminant lymphocytic myocarditis (severe hemodynamic compromise, rapid onset of symptoms, or high fever). These patients tend to have complete recovery with total resolution of myocarditis on repeat biopsy.
- In contrast, patients with giant cell myocarditis have an extremely poor prognosis with a median survival of <6 mo, and most require cardiac transplantation.

REFERRAL

Consider heart transplant if intractable CHF develops.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Myocarditis (Patient Information)

AUTHORS: **PHILLIP RUISI, D.O.,** and **ARAVIND RAO KOKKIRALA, M.D.**

SUGGESTED READINGS

Abdel-Aty H et al.: Diagnostic performance of cardiovascular magnetic resonance in patients with suspected acute myocarditis: comparison of different approaches, *J Am Coll Cardiol* 45(15):1815, 2005.

Cooper LT: Myocarditis, *N Engl J Med* 360:1526–1538, 2009.

Durani Y et al.: Pediatric myocarditis: presenting clinical characteristics, *Am J Emerg Med* 27:942–947, 2009.

Ellis CR, Di Salvo T: Myocarditis basic and clinical aspects, *Card Rev* 15:170–177, 2007.

Mahrholdt H et al.: Presentation, patterns of myocardial damage, and clinical course of viral myocarditis, *Circulation* 114(15):1581, 2006.

Wu LA et al.: Current role of endomyocardial biopsy in the management of dilated cardiomyopathy and myocarditis, *Mayo Clin Proc* 76:1030, 2001.

BASIC INFORMATION

DEFINITION

Myoclonus is defined as sudden, brief, jerky, "shocklike" involuntary movements that can involve the muscles of the extremities, face, or trunk. Positive myoclonus is caused by muscle contraction, whereas negative myoclonus is caused by inhibition of active (such as postural) muscles. Myoclonus is a symptom that can be seen in a number of different neurologic disorders.

ICD-9CM CODES
333.2 Myoclonus
ICD-10CM CODES
G25.3 Myoclonus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1.3/100,000 persons
PREVALENCE: 8.6/100,000 persons
PREDOMINANT SEX AND AGE: No gender preference; age at onset varies by the etiology of the myoclonus.
GENETICS: Varies by etiology, can be hereditary or sporadic

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinically, myoclonus can be classified by its distribution: focal (only one body part involved), multifocal, segmental (spread to adjacent body parts), axial (muscles innervated by one or several spinal levels), or generalized. It can be stimulus-induced or occur at rest.
- Myoclonus can be seen with involvement or lesions of the cerebral cortex, brain stem, spinal cord, or peripheral nerve. The location of the lesion may not always influence the characteristics of the myoclonus.
- Negative myoclonus is typically seen in postural muscles of the legs, causing a "bobbing" while walking. Asterixis is another form of negative myoclonus.

ETIOLOGY

- The causes of myoclonus are numerous and can be grouped into the categories of physiologic, essential, epileptic, and symptomatic.
- Physiologic myoclonus ranges from sleep (hypnic) jerks to exercise-induced myoclonus and can be seen in normal subjects.
- Essential myoclonus occurs in the absence of other neurologic symptoms and is usually autosomal dominant. When dystonia is present, it is called myoclonus-dystonia. The myoclonus is often responsive to alcohol in this condition.
- In epileptic myoclonus, seizures dominate the clinical picture. Syndromes include infantile spasms and juvenile myoclonic epilepsy among others.
- Symptomatic or secondary myoclonus comprises myoclonus in the setting of an underlying neurologic disorder or other precipitant. The number of secondary causes prevents giving a full list, but common etiologies include neurodegenerative diseases (Alzheimer's, atypical forms of parkinsonism), CNS infections (Creutzfeldt-Jakob disease, viral encephalitis), metabolic derangements (uremia, hepatic failure), drug-induced (selective serotonin reuptake inhibitors [SSRIs], tricyclics, lithium), and posthypoxic etiologies.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Tremor: a rhythmic oscillation around a point; slower than myoclonus
- Tic: complex patterned movements that can be suppressed voluntarily for a short time unlike myoclonus, which is simple jerks that are persistent
- Dystonia: patterned contractions of agonist/antagonist muscles causing twisting or pulling; slower than myoclonus
- Chorea: typically slower, writhing, patterned movements
- Psychogenic myoclonus: variable in duration and location, distractible, or entrainable

LABORATORY TESTS

- Evaluate for metabolic precipitants (renal and hepatic function, Mg, Ca, thyroid studies)
- Toxicology screen
- Lumbar puncture if encephalitis is suspected
- Electroencephalography (EEG) to evaluate for epileptic myoclonus

IMAGING STUDIES

MRI of the brain can evaluate for a seizure focus if the myoclonus is epileptic. Creutzfeldt-Jakob disease can show diffusion weighted abnormalities in the striatum and cortex.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Treatment should be directed toward correcting the underlying cause if it is reversible (e.g., hepatic or renal failure).
- Carefully remove or decrease potentially causative medications.

ACUTE GENERAL Rx

For acute treatment of epileptic myoclonus, antiepileptic drugs such as valproic acid, levetiracetam, or clonazepam are helpful.

CHRONIC Rx

- Clonazepam, valproic acid, levetiracetam are typically used for all forms of myoclonus, and often combinations of several medications seem to be more effective.
- If dystonia is present (myoclonus-dystonia), a trial of levodopa is worthwhile although only rarely responsive. Anticholinergics may also help dystonia. Botulinum toxin injections are used for focal dystonias.
- Peripheral focal myoclonus can also be helped by botulinum toxin injections.

DISPOSITION

The ultimate prognosis depends on the etiology of the myoclonus.

REFERRAL

Referral to a general neurologist or movement disorders center is appropriate.

PEARLS & CONSIDERATIONS

COMMENTS

- When myoclonus is seen with parkinsonism, atypical forms of parkinsonism should be high on the differential such as dementia with Lewy bodies, corticobasal degeneration, and multiple system atrophy. Myoclonus is only rarely seen in idiopathic Parkinson's disease.
- Symptomatic palatal myoclonus is a specific syndrome that is often associated with a focal brain-stem lesion. In essential palatal myoclonus (no lesion), ear "clicking" is an additional symptom, which is not seen in the symptomatic form.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **ANDREW DUKER, M.D.**

SUGGESTED READINGS

Borg M: Symptomatic myoclonus, *Clin Neurophys* 36:309–318, 2006.

Caviness JN: Pathophysiology and treatment of myoclonus, *Neurol Clin* 27: 757–777, 2009.

Chang VC, Frucht SJ: Myoclonus, *Curr Treat Options Neurol* 10:222–229, 2008.

Vercueil I: Myoclonus and movement disorders, *Clin Neurophys* 36:327–331, 2006.

Myofascial Pain Syndrome

DEFINITION

- Myofascial pain syndrome is myalgia characterized by trigger point.
- Trigger point: Trigger points are discrete, focal, hyperirritable spots located in a taut band of skeletal muscle. They produce pain locally and in a referred pattern. Muscle involvement is asymmetric and focal.

SYNONYMS

- Chronic myofascial pain (CMP)

ICD-9CM CODES
729.1 Myalgia, myofascial pain syndrome
ICD-10CM CODES
M79.1 Myalgia, myofascial pain syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- Myofascial pain syndrome is a common painful muscle disorder which can affect any sex at any age. About 85% of general population at some point suffered from it during their life time. It also coexists with other chronic pain conditions.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Regional body pain and stiffness; often muscles responsible for body posture are affected. Neck, upper back and lower back muscles are commonly involved including trapezius, scalene, sternocleidomastoid, levator scapulae and quadratus lumborum. Pain is associated with muscle activity or is constant.
- Table M1-39 lists some distinguishing features of myofascial pain and fibromyalgia.
- Limited range of motion and pain-related weakness of affected muscle.
- Twitch response: Brisk contraction of a taut band of skeletal muscle fibers elicited by snapping palpation of a trigger point in that band producing a taut band.
- One or more trigger points asymmetrical location.
- Referred pain from a trigger point to a zone of reference, but not following dermatomal distribution.
- Resolution of the symptoms with lidocaine injection of the trigger point

ETIOLOGY

- Etiology is unknown. There are several proposed histopathologic mechanisms to account for the development of trigger points, but they are lacking scientific evidence. Most researchers agree that acute trauma or repetitive microtrauma may lead to the development of a trigger point.
- Fig. M1-73 lists causes of myofascial pain and dysfunction.
- Lack of exercise, prolonged poor posture, vitamin deficiencies, sleep disturbances, and joint problems may all predispose to the development of micro-trauma.

DIAGNOSIS

- A detailed physical examination and clinical presentation usually make the diagnosis of myofascial pain syndrome.

DIFFERENTIAL DIAGNOSIS

- Fibromyalgia
- Polymyositis
- Migraine
- Tension headache
- Muscle strain
- Bursitis and tendinitis
- Radiculopathies

TABLE M1-39 Distinguishing Features of Myofascial Pain and Fibromyalgia

	Myofascial Pain	Fibromyalgia
Age distribution	20-40 yr	20-50 yr
Gender distribution	Mainly women	Mainly women
Distribution of pain	Localized; usually unilateral	Generalized; bilaterally symmetric
Tender points	Few	Multiple
Trigger points	Uncommon	Common
Fatigue	Localized muscle fatigue	Generalized fatigue
Sleep disturbance	Common	Common

(From Firestein G.S., et al: *Kelley's textbook of rheumatology*, 9th ed, Philadelphia, 2013, Saunders.)

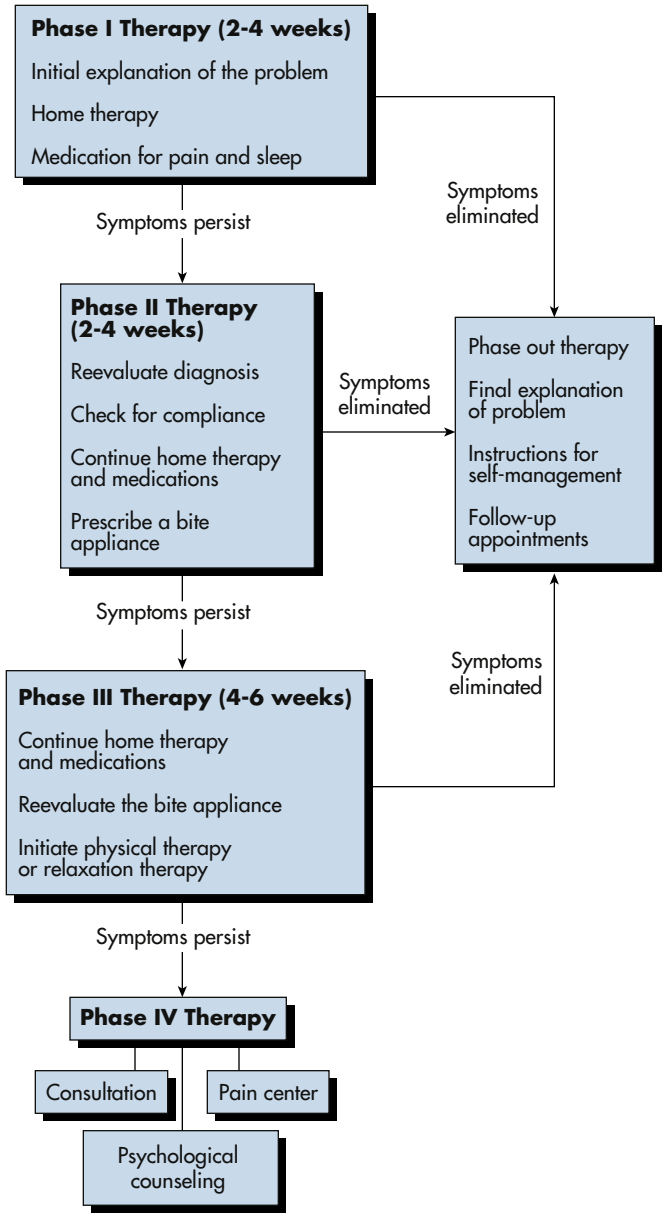

FIGURE M1-73 Management of myofascial pain and dysfunction. Treatments are divided into four phases. If the symptoms are eliminated in any of the first three phases, the ongoing therapy is gradually phased out, and the patient is instructed in continued self-management of the condition. (Modified from Laskin DM, Block S: Diagnosis and treatment of myofascial pain dysfunction [MPD] syndrome, *J Prosthet Dent* 56:75–84, 1986.)

WORK-UP

- Not indicated usually, treatment can be started on clinical grounds alone.

LABORATORY TESTS

- Generally not indicated, except to exclude other causes of myalgia.

IMAGING STUDIES

- Generally not indicated in clear-cut cases of myofascial pain syndrome. Indicated only to exclude other causes of pain (e.g., referred pain).

Rx TREATMENT

- Spray and stretch therapy: involves passive stretching of the affected muscle. Position patient for maximum decrease in muscle tension, identify trigger point and mark them. Apply vapocoolant spray over entire length of the affected muscle. Passively stretch muscle by applying gentle pressure.
- Physical therapy: TENS unit, ultrasound, massage therapy, myofascial release technique.
- Invasive technique: Trigger point injection with 1% lidocaine is the most commonly used technique.
- NSAIDS and muscle relaxants: short term use
- Fig. M1-74 shows the management of myofascial pain and dysfunction.

REFERRAL

A pain management referral is made if trigger point injection is indicated. To physical therapist for increasing ROM and massage therapy.

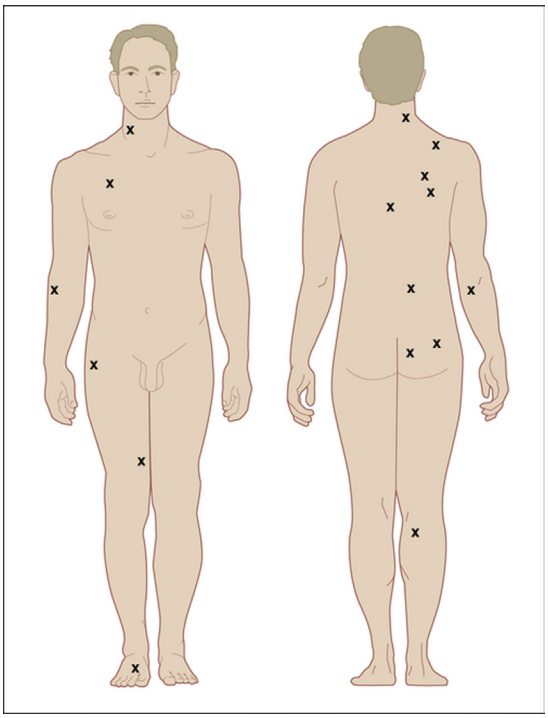

FIGURE M1-74 Most frequent locations of myofascial trigger points. (Adapted from Rachlin E, Rachlin I: *Myofascial pain and fibromyalgia: trigger point management*, ed 2. St Louis, 2002, Mosby.)

PEARLS & CONSIDERATIONS

- Trigger point is commonly misdiagnosed as tender point, which is characteristic finding of fibromyalgia.

Tender point: characterized as non-palpable nodule with symmetric and multiple locations. Tender points are located close to muscle attachment, usually not associated with specific muscle activity. Lacking twitch response and relief of symptoms with localized lidocaine injection.

SUGGESTED READINGS

Available at www.expertconsult.com

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SUGGESTED READINGS

Tsai CT, Hsieh LF, Kuan TS, Kao MJ, Chou LW, Hong CZ: Remote effects of dry needling on the irritability of the myofascial trigger point in the upper trapezius muscle, *Am J Phys Med Rehabil* - 89(2):133–140, Feb 2010.

Karadaş Ö, Gül HL, Inan LE: Lidocaine injection of pericranial myofascial trigger points in the treatment of frequent episodic tension-type headache, *J Headache Pain* 14:44, 2013.

Stephen B. McMahon, Martin Koltzenburg, Irene Tracey, and Dennis C. Turk: Wall & Melzack's Textbook of Pain, Sixth Edition.

Honorio T. Benzon, James P. Rathmell, Christopher L. Wu, Dennis C. Turk, Charles E. Argoff, and Robert W. Hurley: Practical Management of Pain, Fifth Edition.

Frontera Walter R, Silver Julie K, Rizzo Thomas D: *Essentials of Physical Medicine and Rehabilitation: Musculoskeletal Disorders, Pain, and Rehabilitation*, Third Edition, 2002 by Saunders, an imprint of Elsevier Inc, 2008. CHAPTER 104, 520–526, Copyright © 2015.

BASIC INFORMATION

DEFINITION

Inflammatory myopathies are idiopathic diseases of muscle characterized clinically by muscle weakness and pathologically by inflammation and muscle fiber breakdown. The three most common are dermatomyositis (DM), polymyositis (PM), and inclusion body myositis (IBM). See separate topic on "Inclusion Body Myositis" for details regarding the latter.

SYNONYMS

Idiopathic inflammatory myopathies
Myositis syndromes
Polymyositis
Dermatomyositis

ICD-9CM CODES
710.3 Dermatomyositis
710.4 Polymyositis
ICD-10CM CODES
M33.90 Dermatopolymyositis, unspecified, organ involvement unspecified
M33.20 Polymyositis, organ involvement unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

DM:
- Occurs in children and in adults (bimodal age peak)
- Average age at diagnosis is 40 yr in adults. Age range in children: 5 to 14 yr
- More common in females than in males (2:1)
- Incidence 1:100,000
- Prevalence 1 to 10 cases/million in adults and 1 to 3.2 cases/million in children
- Up to one third of patients older than 50 with DM have an associated malignancy

PM:
- Occurs mostly in adults, very rare in children
- Average age at diagnosis >20 yr
- More common in females
- Least common inflammatory myopathy
- Exact incidence unknown

PHYSICAL FINDINGS & CLINICAL PRESENTATION

DM and PM:
- Most patients have a subacute onset over weeks to months.
- Pattern is typically symmetric proximal muscle weakness involving the proximal limbs (shoulder and pelvic girdles).
- Weakness of neck flexion and extension is common.
- Difficulty getting up from a chair, climbing stairs, reaching for objects above head, or combing hair.
- Distal muscle and ocular involvement is uncommon.
- Sensation is preserved.
- Reflexes may be preserved or diminished.
- Dysphagia and dysphonia result from involvement of striated muscle of the pharynx and proximal esophagus.
- Esophageal dysmotility is common in DM.
- Respiratory failure from associated pulmonary fibrosis.
- Cardiac conduction abnormalities can be seen with DM.
- Systemic autoimmune disease occurs frequently in PM, and rarely in DM.
- Skin findings in DM:
  1. Heliotrope rash on the upper eyelids (Fig. M1-75)
  2. Erythematous rash on the face (see Fig. M1-75)
  3. May also involve the back and shoulders (shawl sign), neck and chest (V-shape), knees (Fig. M1-76), and elbows
  4. Photosensitivity
  5. Gottron's papules (violaceous papules overlying dorsal interphalangeal or metacarpophalangeal areas, elbow or knee joints—Fig. M1-77)
  6. Nail cracking, thickening, and irregularity (Fig. M1-78) with periungual telangiectasia (see Fig. M1-77)
  7. Mechanic's hand: fissured, hyperpigmented, scaly, and hyperkeratotic; also associated with increased risk of interstitial lung disease

ETIOLOGY

DM: complex, immune-mediated microangiopathy. Adaptive immune response via humorally mediated complement attack

PM: unknown:
- Cell-mediated immune major histocompatibility-I (MHC-1) process directed against muscle fibers is likely, given biopsy features.
- A viral etiology has been proposed secondary to the presence of autoantibodies to histidyl transferase, anti-Jo-1, and signal recognition particle.

DIAGNOSIS

- Myopathic pattern of muscle weakness
- Characteristic rash in DM
- EMG shows myopathic (small-amplitude, short-duration, polyphasic) motor potentials with early recruitment
- Majority of patients have "irritable" features (fibrillations and positive sharp waves) on EMG
- See "Laboratory Tests."
- Biopsy is required for diagnosis and should confirm inflammation before treatment is started. Table M1-40 describes histologic features of idiopathic inflammatory myopathies. In idiopathic inflammatory myopathies, myopathic features (variation in fiber size, fiber

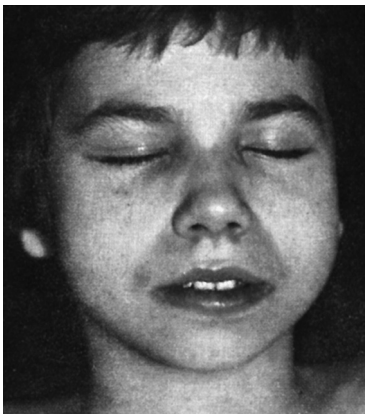


FIGURE M1-75 The facial rash of juvenile dermatomyositis. There is erythema over the bridge of the nose and malar areas, with violaceous (heliotropic) discoloration of the upper eyelids. (From Behrman RE: *Nelson textbook of pediatrics,* ed 17, Philadelphia, 2004, Saunders.)

FIGURE M1-76 Violaceous plaques on the knees in a patient with dermatomyositis (Gottron sign). (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

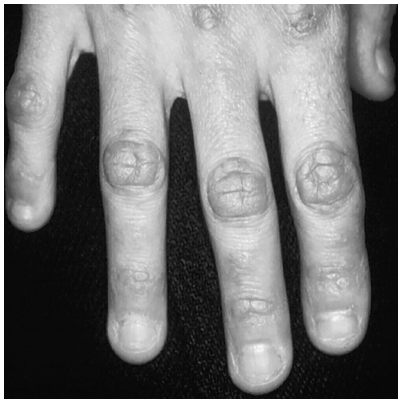


FIGURE M1-77 Dermatomyositis (Gottron's papules). Note erythematous papules over joints and periungual telangiectasias. (From Noble J [ed]: *Textbook of primary care medicine,* ed 2, St Louis, 1996, Mosby.)

FIGURE M1-78 Enlarged nailfold capillaries in a patient with dermatomyositis. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

TABLE M1-40 Histologic Features of Idiopathic Inflammatory Myopathies

Feature	Dermatomyositis	Polymyositis	Inclusion Body Myositis
Necrosis of muscle fibers	+	+	+
Variation in fiber diameter	+	+	+
Regeneration of muscle fibers	+	+	+
Proliferation of connective tissue	+	+	+
Infiltration of mononuclear cells*	+	+	+
Perivascular and perimysial inflammation	+	–/+	–/+
Endomysial inflammation	–/+	+	+
Perifascicular atrophy	+	–	–
Abnormally dilated capillaries	+	–/+	–
Reduced capillary density	+	–/+	–
Deposition of complement on vessel walls	+	–/+	–
Microinfarcts	+	–	–
Invasion of non-necrotic fibers by cytotoxic T lymphocytes and macrophages	–	+	+
Expression of major histocompatibility complex class I on muscle fibers	–/+	+	+
Rimmed vacuoles with amyloid deposits and tubulofilaments†	–	–	+
Angulated or atrophic and hypertrophic fibers	–	–	+
Ragged red or cytochrome oxidase–negative fibers	–	–	+

*Inflammation is absent in a small proportion of polymyositis and dermatomyositis biopsies.
†Also seen in chronic neurogenic conditions and distal myopathies.
From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders, Elsevier.

splitting, fatty replacement of muscle tissue, and increased endomysial connective tissue) should be seen in addition to the following:

1. DM: perifascicular atrophy, MAC deposition along capillaries
2. PM: endomysial infiltrates composed of CD8+ T cells and macrophages invading nonnecrotic muscle fibers that express MHC-I antigen

DIFFERENTIAL DIAGNOSIS

- IBM
- Muscular dystrophies
- Amyloid myoneuropathy
- Amyotrophic lateral sclerosis
- Myasthenia gravis
- Eaton-Lambert syndrome
- Drug-induced myopathies (e.g., quinidine, NSAIDs, penicillamine, HMG CoA-reductase inhibitors)
- Diabetic amyotrophy
- Guillain-Barré syndrome
- Hyperthyroidism or hypothyroidism
- Lichen planus
- Amyopathic DM (rash without weakness)
- DM sine rash (weakness with characteristic biopsy, but no rash)
- Systemic lupus erythematosus (SLE)
- Contact atopic or seborrheic dermatitis
- Psoriasis

LABORATORY TESTS

- Creatine kinase (CK) is the most sensitive muscle enzyme test for muscle breakdown. It should be checked at onset, and serially monitored several times during treatment.
- CK is typically elevated (5-50x normal) in active PM.
- CK may be normal or only slightly elevated in DM.
- Aldolase, AST, ALT, alkaline phosphatase, and LDH may be elevated.
- Anti-Jo-1 antibodies are seen in myositis with associated interstitial lung disease but are not specific for either DM or PM.
- Electrolytes, thyroid-stimulating hormone (TSH), Ca, and Mg should be evaluated to exclude other causes of weakness.
- Check ECG for cardiac involvement.

IMAGING STUDIES

- Chest x-ray is used to rule out pulmonary involvement. If suspicious for pulmonary interstitial disease, a high-resolution CT scan of the chest may be helpful.
- Video fluoroscopy or barium swallow study to look for upper esophageal dysfunction in patients with dysphagia and DM.

Rx TREATMENT

Goal: maintain function, minimize disease/iatrogenic sequelae

NONPHARMACOLOGIC THERAPY

- Sun-blocking agents with SPF 15 or greater for skin protection in patients with DM
- Physical therapy beneficial for gait training and increasing muscle tone and strength
- Occupational therapy assists with activities of daily living
- Speech therapy to monitor patients with swallowing dysfunction

ACUTE GENERAL Rx

- Corticosteroids are the mainstay of therapy. Start prednisone 1 to 2 mg/kg per day, up to a maximum dose of 100 mg/day. Continue until muscle strength improves or muscle enzymes have normalized for at least 4 wk. Begin tapering by 10 mg/mo until 60 mg/day, then slowly taper by 5 mg/mo. Consider every-other-day prednisone treatment at same dose (may decrease side effects).
- Consider IV immunoglobulin (IVIG) if patient fails to improve on prednisone, or muscle enzymes begin rising when tapering off prednisone. See "Chronic Rx" for specific dosage.
- Hydroxychloroquine can be used to treat the cutaneous lesions of DM.
- A treatment algorithm for adult patients with PM and DM is described in Fig. M1-79.

CHRONIC Rx

- Chronic prednisone therapy may be needed for years, but other immunosuppressive ("steroid-sparing") agents may be added early to decrease long-term steroid side effects.
- Azathioprine 2 to 3 mg/kg per day tapered to 1 mg/kg per day once steroid is tapered to 15 mg/day. Reduce dosage monthly by 25-mg intervals. Maintenance dosage is 50 mg/day.
- Methotrexate 7.5 to 10 mg PO/wk, increased by 2.5 mg/wk to total of 25 mg/wk; consider IM dosing if PO is ineffective.
- IV immunoglobulin 2 g/kg total dose over 2 to 5 days.
- IV cyclophosphamide 1 g/M^2 monthly for 6 mo is preferred to oral dosing for refractory cases. However, oral dosing of cyclophosphamide is 1 to 3 mg/kg per day PO or 2 to 4 mg/kg per day in conjunction with prednisone.
- Cyclosporin A: initial dose 2.0 to 2.5 mg/kg bid; long-term maintenance is lowest effective dose.
- Mycophenolate mofetil 500 mg PO bid, titrate to 1500 mg PO bid over 1 to 2 mo.
- Hydroxychloroquine 200 mg PO daily; monitor for visual changes.

DISPOSITION

- 30% to 40% of patients achieve clinical remission with treatment.

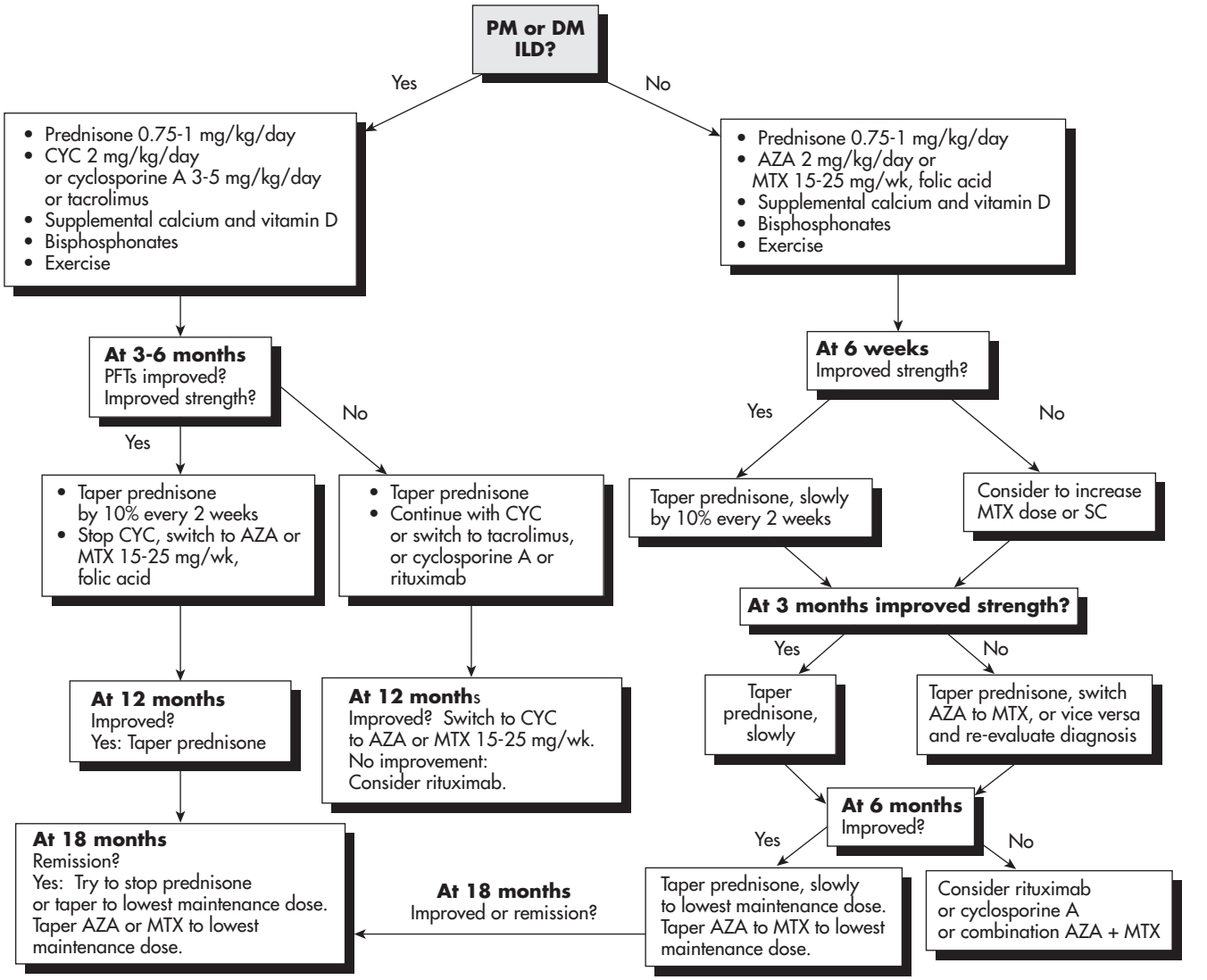


FIGURE M1-79 Treatment algorithm for adult patients with polymyositis (PM) or dermatomyositis (DM). *AZA,* Azathioprine; *CYC,* cyclophosphamide; *ILD,* interstitial lung disease; *MTX,* methotrexate; *PFT,* pulmonary function test; *SC,* subcutaneous. (From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders, Elsevier.)

- In patients with residual weakness, deficits typically remain stable over long-term follow-up.
- 10% experience recurrent disease.
- Serum CK often returns to normal before symptoms improve.
- During exacerbations, enzymes may rise before clinical symptoms appear.
- Poor prognostic indicators include delay in diagnosis, older age, recalcitrant disease, malignancy, interstitial pulmonary fibrosis, dysphagia, leukocytosis, fever, and anorexia.
- Infection, malignancy, and cardiac and pulmonary dysfunction are the most common causes of death.
- With early treatment, 5- and 8-yr survival rates of 80% and 73%, respectively, have been reported.

REFERRAL

Neurology or rheumatology referral should be made to help establish the diagnosis and implement treatment.

PEARLS & CONSIDERATIONS

- Do not implement treatment before muscle biopsy.
- When assessing response to treatment, clinical muscle strength is more important than muscle enzyme tests.
- The concern for malignancies (ovary, lung, breast, GI) associated with DM is legitimate and merits screening in patients older than age 40 at time of diagnosis and every 2 to 3 yr thereafter.
- There does not appear to be any association between juvenile DM and malignancy.
- Overlap syndrome refers to patients with DM who also meet criteria for a connective tissue disorder (e.g., rheumatoid arthritis, scleroderma, SLE).
- In any patient taking steroids, closely monitor for:
  1. Diabetes or glucose intolerance (2-hour oral glucose tolerance test)
  2. Osteopenia/osteoporosis (DEXA scan q6mo)
  3. Cataracts (yearly ophthalmologic appointment)
  4. Hypertension
  5. Psychiatric side effects including depression or psychosis
  6. Poor sleep
  7. Peptic ulcer disease (prescribe H_2 antagonist or proton pump inhibitor)
- Clinical and immune response features can be used for categorizing heterogeneous myositis syndromes and mutually exclusive and stable phenotypes and are useful for predicting clinical signs and symptoms, associated environmental and genetic risk factors, and responses to therapy and prognosis.

RELATED CONTENT

Dermatomyositis and Polymyositis (Patient Information)

AUTHOR: **GAVIN BROWN, M.D.**

BASIC INFORMATION

DEFINITION

Myotonia is a type of muscular dystrophy in which relaxation of a muscle after contraction is delayed or prolonged. The most common type of muscular dystrophy with myotonia is myotonic dystrophy. The nondystrophic myotonias (NDMs) are rare disorders (prevalence 1:100,000) caused by mutations in skeletal muscle chloride and sodium channels with the common clinical feature of myotonia without muscle wasting.[1]

SYNONYMS

Myotonic dystrophy

ICD-9CM CODES
359.2 Myotonic disorders
728.85 Muscle spasm
ICD-10CM CODES
G71.1 Myotonic disorders
M62.89 Other specified disorders of muscle
M62.40 Contracture of muscle, unspecified site

EPIDEMIOLOGY & DEMOGRAPHICS

- Three to five cases/100,000 persons
- Genetic disorder inherited as an autosomal-dominant illness
- Symptoms usually manifest during adolescence or early adulthood. Cases of infantile myotonic dystrophy have been described.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Usual first symptom is distal extremity weakness sometimes associated with muscle stiffness, cramps, or difficulty relaxing grasp.
- Weakness spreads to eventually involve all muscle groups. Flexor neck muscle weakness and masseter and temporal wasting are often prominent features, as is dysarthria.
- Percussion of a muscle produces a slow contraction followed by prolonged relaxation. The myotonic reflex is best tested by percussing the thenar muscles and observing a slow flexion followed by slow relaxation of the thumb.
- As the disease progresses, generalized weakness becomes more pronounced and myotonia becomes less evident.
- Extramuscular involvement:
- Mental retardation of variable severity (may be absent)
- Frontal baldness (Fig. EM1-80)
- Cataracts
- Diabetes mellitus
- Hypogonadism
- Adrenal failure
- Cardiomyopathy
- Infantile myotonic dystrophy presents as neonatal extreme hypotonia with "shark mouth" deformity (upper lip forming an inverted V).

ETIOLOGY & PATHOGENESIS

Genetic disorder encoded on chromosome 19 leading to sustained firing of the muscle membrane, causing prolonged muscle contraction. Myotonic dystrophy 1 (the more common form) is caused by an expanded CTG repeat within the noncoding 3′ untranslated region of the myotonic dystrophy protein kinase *(DMPK)* gene. The less common form (myotonic dystrophy 2) is caused by an expanded CCTG repeat in the first intron of the zinc finger protein 9 *(ZNF9)* gene.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

The disease is limited to muscles and causes hypertrophy and stiffness after rest. Muscle function normalizes with exercise. There is no weakness. Symptoms are exacerbated by exposure to cold.

- Myotonia congenita (Thomsen's disease)
- May be autosomal dominant or recessive (two distinct varieties)
- Paramyotonia congenita (autosomal-dominant disease): weakness and stiffness of facial muscles and distal upper extremities, especially or exclusively on cold exposure
- Muscular dystrophies
- Inflammatory myopathies (polymyositis)
- Metabolic muscle diseases
- Myasthenic syndromes
- Motor neuron disease

WORKUP

- History and physical examination usually sufficient
- Muscle enzymes usually abnormal (creatine phosphokinase, aldolase, aspartate aminotransferase)
- Electromyography: typical myotonic "dive bomber" bursts
- Muscle biopsy: type I fiber atrophy, ring fibers, increased central nucleation

TREATMENT

- Phenytoin
- Quinine
- Quinidine
- Procainamide
- Acetazolamide
- Genetic counseling
- Assistive devices, orthotics
- In recent trials,[1] the use of mexiletine resulted in improvement of patient-reported stiffness in patients with nondystrophic myotonias.

DISPOSITION

- In myotonic dystrophy, death is usually caused by the wasting of skeletal muscle and defects in cardiac function.
- Among patients with myotonic dystrophy type 1, an invasive strategy based on systemic electrophysiological studies and prophylactic permanent pacing is associated with longer survival than a non-invasive strategy.[2]

REFERRAL

To neurologist

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **FRED F. FERRI, M.D.**

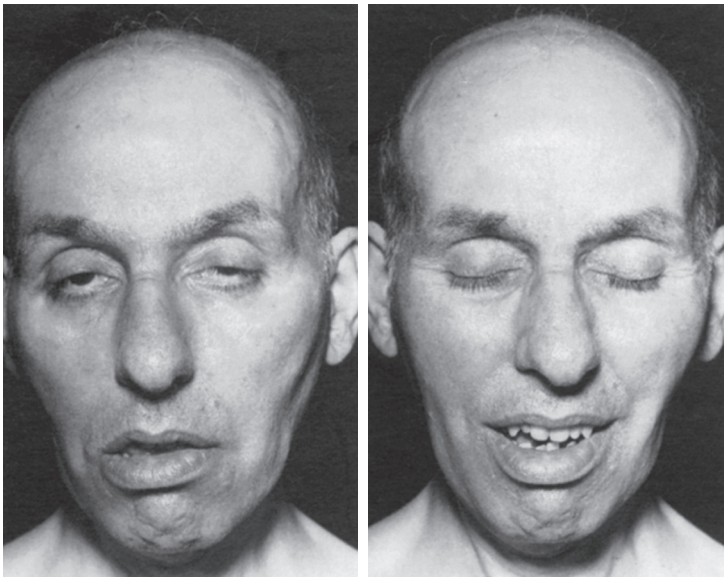


FIGURE EM1-80 Myotonic dystrophy with typical myopathic facies, frontal balding, and sunken cheeks. (From Dubowitz V: *Muscle disorders in childhood,* London, 1995, Saunders.)

[1]Statland JM et al: Mexiletine for symptoms and signs of myotonia in nondystrophic myotonia, *JAMA* 308(13): 1357-1365, 2012.
[2]Wahbi K et al: Electrophysiological study with prophylactic pacing and survival in adults with myotonic dystrophy and conduction system disease, *JAMA* 307(12):1292-1301, 2012.

SUGGESTED READINGS

Cooper TA: A reversal of misfortune for myotonic dystrophy, *N Engl J Med* 355:17, 2006.

Kanadia RN et al.: Reversal of RNA missplicing and myotonia after muscle blind overexpression in a mouse poly (CUG) model for myotonic dystrophy, *Proc Natl Acad Sci U S A* 103:11748, 2006.

BASIC INFORMATION

DEFINITION

Myxedema coma is a life-threatening complication of hypothyroidism characterized by profound lethargy or coma and usually accompanied by hypothermia.

ICD-9CM CODES
244.8 Myxedema, pituitary
244.1 Myxedema, primary
ICD-10CM CODES
E03.5 Myxedema coma
E03.8 Other specified hypothyroidism
E03.9 Hypothyroidism, unspecified

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Mental obtundation, profound lethargy or coma
- Hypothermia (rectal temperature <35° C [95° F]); often missed by using ordinary thermometers graduated only to 34.5° C or because the mercury is not shaken below 36° C
- Bradycardia, hypotension (attributable to circulatory collapse)
- Delayed relaxation phase of deep tendon reflexes, areflexia
- Myxedema facies (Fig. M1-81)
- Alopecia, macroglossia, ptosis, periorbital edema, nonpitting edema, doughy skin
- Bladder dystonia and distention
- Pleural, pericardial, and peritoneal effusions

ETIOLOGY

Decompensation of hypothyroidism from:
- Sepsis
- Exposure to cold weather
- Central nervous system depressants (sedatives, narcotics, antidepressants)
- Trauma, surgery
- Stroke, congestive heart failure, burns
- Intravascular volume contraction (GI blood loss, diuretic use)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Severe depression, primary psychosis
- Drug overdose
- Cerebrovascular accident, liver failure, renal failure
- Hypoglycemia, CO_2 narcosis, encephalitis

WORKUP

Diagnosis of hypothyroidism and exclusion of contributing factors (e.g., sepsis, cerebrovascular accident) with laboratory and radiographic studies (see "Laboratory Tests")

LABORATORY TESTS

- Markedly increased thyroid-stimulating hormone (if primary hypothyroidism), decreased serum free T_4
- Complete blood count with differential, urine and blood cultures to rule out infectious process
- Electrolytes, blood urea nitrogen, creatinine, liver function tests, calcium, glucose
- Arterial blood gases to rule out hypoxemia and carbon dioxide retention
- Cortisol level to rule out adrenal insufficiency
- Elevated CPK
- Hyperlipidemia

IMAGING STUDIES

- CT scan of head in suspected cerebrovascular accident
- Chest x-ray to rule out infectious process

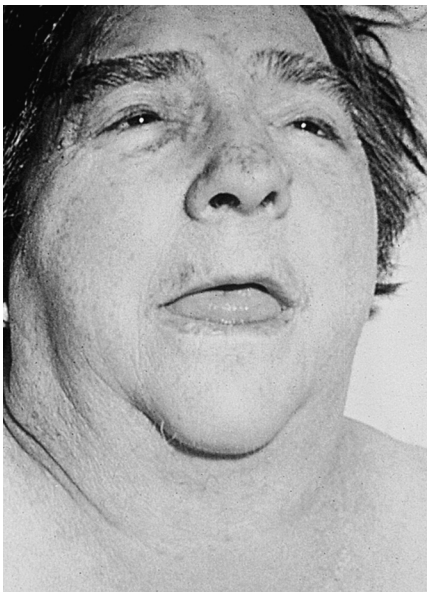


FIGURE M1-81 Myxedema facies. Note dull, puffy, yellowed skin; coarse, sparse hair; temporal loss of eyebrows; periorbital edema; prominent tongue. (Courtesy Paul W. Ladenson, M.D., The Johns Hopkins University and Hospital, Baltimore. In Seidel HM [ed]: *Mosby's guide to physical examination,* ed 5, St Louis, 2004, Mosby.)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Prevent further heat loss; cover the patient but avoid external rewarming because it may produce vascular collapse.
- Support respiratory function; intubation and mechanical ventilation may be required.
- Monitor patient in the intensive care unit.

ACUTE GENERAL Rx

- Give levothyroxine 5 to 8 mcg/kg (300 to 500 mcg) IV infused over 15 min, then 100 mcg IV q24h.
- Glucocorticoids should also be administered until coexistent adrenal insufficiency can be ruled out. Hydrocortisone hemisuccinate 100 mg IV bolus is initially given, followed by 100 mg IV q8h until initial plasma cortisol level is confirmed normal.
- IV hydration with D_5NS is used to correct hypotension and hypoglycemia (if present); avoid overhydration and possible water intoxication because clearance of free water is impaired in these patients.
- Rule out and treat precipitating factors (e.g., antibiotics in suspected sepsis).

CHRONIC Rx

Refer to "Hypothyroidism" in Section I.

DISPOSITION

Mortality rate in myxedema coma is 20% to 50%.

REFERRAL

Endocrinology consultation

PEARLS & CONSIDERATIONS

COMMENTS

If the diagnosis is suspected, initiate treatment immediately without waiting for confirming laboratory results.

RELATED CONTENT

Hypothyroidism (Patient Information)
Hypothyroidism (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

BASIC INFORMATION

DEFINITION

Narcissistic personality disorder (NPD) is characterized by a pattern of grandiosity, need for admiration, and lack of empathy that begins by early adulthood and causes significant distress or impairment in multiple domains of functioning. The individual must meet five or more of the following criteria:

1. Grandiose sense of self-importance. For example, the person may exaggerate achievements and talents or expect recognition as superior without commensurate achievements.
2. Preoccupied with fantasies of unlimited success, power, brilliance, beauty, or ideal love.
3. Views self as "special" and unique and should only associate with other special or highly regarded people and institutions.
4. Requires excessive admiration.
5. Sense of entitlement. For example, unreasonable expectations of especially favorable treatment or automatic compliance with his or her expectations.
6. Interpersonally exploitative.
7. Lacks empathy—unwilling to recognize or identify with the feelings or needs of others.
8. Often envious of others or believes others envious of him or her.
9. Shows arrogant or haughty behaviors.

SYNONYMS

None

ICD-9CM and DSM-5 CODES
301.81
ICD-10CM CODES
F60.8 Other specific personality disorder

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Less than 1% of the general population; estimates range from 2% to 16% in the clinical population
PREDOMINANT SEX: More commonly diagnosed in males (up to 3:1)
PREDOMINANT AGE: 20s and 30s

CLINICAL PRESENTATION

- Patients have an underlying sense of inferiority and inadequacy.
- May be related to the failure of parents or parental surrogates to impart a sense of self-worth.
- To avoid these beliefs and their associated painful effects, patients seek to convince self and others that they are special, the best, or unusually talented.
- Astutely aware of status, pecking order.
- Vulnerability in self-esteem makes these patients exquisitely sensitive to criticism, defeat, or perceived weakness, which in turn can lead to feeling humiliated, degraded, and empty.
- These patients react to perceived slights either with more intense grandiosity- and admiration-seeking or with disdain and rage. Either approach seeks to bolster their sense of self often by devaluing or criticizing the other person.
- Experiences of self-deflation lead to social withdrawal or depressed mood or to feigned humility that protects grandiosity.
- Interpersonal relationships are typically shallow and limited.
- Although ambition and confidence may lead to high achievement, vocational functioning may be disrupted by intolerance for criticism.

ETIOLOGY

- Limited knowledge about role of genetic loading and neurobiologic vulnerability.
- Prevailing hypotheses focus on impaired development of self as "worthy" because of insufficient affirmation and warmth from parents.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Mania and hypomania
- Dysthymia and major depressive episode
- Substance-induced euphoria, especially cocaine abuse
- Histrionic, borderline, antisocial, and paranoid personality disorders share common features and are often comorbid
- Personality changes from a general medical condition, including central nervous system processes in the frontal-temporal regions of the brain

WORKUP

- History: collateral information essential to establishing presence of longstanding interpersonal pattern in multiple domains of the patient's life
- Physical examination
- Mental status examination

LABORATORY TESTS

Tests necessary to rule out medical causes of personality changes

IMAGING STUDIES

Those necessary to rule out medical causes of personality changes

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cognitive-behavioral therapy to help patients control rage, manage perceived criticism, and develop social skills
- Psychodynamic psychotherapy to help develop improved self-concept, affect tolerance, and interpersonal functioning

ACUTE GENERAL Rx

Benzodiazepines or low-dose antipsychotics to control rage

CHRONIC Rx

- Selective serotonin reuptake inhibitors for impulsivity or comorbid depression
- Mood stabilizers if comorbid bipolar or to improve impulse control

DISPOSITION

- Severity is variable and course is chronic. The majority of patients obtain greater functioning in fifth decade and beyond when pessimism replaces grandiosity. Often lifelong difficulty maintaining intimate relationships.
- At increased risk for major depressive disorder and substance abuse or dependence (especially cocaine).

REFERRAL

If pharmacotherapy is contemplated

PEARLS & CONSIDERATIONS

COMMENTS

- Illness threatens these patients' image of superiority.
- To defend against this threat, patients may minimize symptoms or deny presence of illness.
- Patients will commonly demand special treatment from senior and well-known physicians.
- Patients may devalue, criticize, or question the behavior or credentials of the treating physician.
- Management guidelines:
  1. Be respectful and nonconfrontational.
  2. Help patient use self-perceived talents in service of treatment.
  3. Do not personalize patient's devaluation, but understand their criticalness as an attempt to manage their own intense insecurity.
  4. Appeal to the patient's narcissism. In other words, agree with the patient that he or she is "entitled" to appropriate care.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Narcissistic Personality Disorder (Patient Information)

AUTHOR: **JOHN Q. YOUNG, M.D., M.P.P.**

SUGGESTED READINGS

Angstman KB, Rasmussen NH: Personality disorders: review and clinical application in daily practice, *American family physician* 84(11):1253–1260, 2011.

Bartak A, Andrea H, Spreeuwenberg MD et al.: Patients with cluster a personality disorders in psychotherapy: an effectiveness study, *Psychotherapy and psychosomatics* 80(2):88–99, 2011.

Quirk SE et al.: Personality disorders and physical comorbidities in adults from the United States: data from the National Epidemiologic Survey on Alcohol and Related Conditions, *Social psychiatry and psychiatric epidemiology. Oct* 15, 2014.

BASIC INFORMATION

DEFINITION

Narcolepsy is a chronic neurologic sleep disorder characterized by excessive daytime sleepiness and dysregulation of rapid eye movement (REM) sleep. It is the second most common cause of disabling daytime sleepiness after obstructive sleep apnea. Symptoms of REM sleep dysregulation include cataplexy, sleep paralysis, and hallucinations during transition between wake and sleep. Difficulty sleeping with either frequent awakenings or disrupted sleep may also occur.

SYNONYMS

Hypersomnia of central origin
Narcolepsy with cataplexy
Narcolepsy-cataplexy syndrome
Narcolepsy with hypocretin deficiency
Gélineau syndrome

ICD-9CM CODES
347.00 Narcolepsy without cataplexy
347.01 Narcolepsy with cataplexy
ICD-10CM CODES
G47.419 Narcolepsy without cataplexy
G47.411 Narcolepsy with cataplexy

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 0.74/100,000 persons/yr
PREVALENCE: 5 to 50/100,000 people
PREDOMINANT SEX: Males and females are equally affected.
AGE OF ONSET: Peak 15 to 30 yr (range, 10-55 yr)
GENETICS:

- Associated with human leukocyte antigen (HLA) subtypes, specifically, *DQB1*0602,* which is present in 95% of patients with cataplexy and 96% of patients with hypocretin deficiency.
- Risk of narcolepsy increases 20 to 40 times if a family member is affected.
- Monozygotic twin concordance rate is 17% to 36%, thus indicating an incomplete penetrance and suggesting an environmental factor in the disease process.

RISK FACTORS: Anesthesia, head injury, history of meningitis or encephalitis, family history of narcolepsy, tumor, vascular malformations, stroke, and obesity.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Overwhelming urge to sleep with chronic hypersomnia may occur during the day.
- Cataplexy occurs in 60% to 100% of patients with narcolepsy and is reported as a partial or complete loss of voluntary muscle control with preserved consciousness that is precipitated by a strong emotion, more commonly with laughter. This is the most specific symptom and is considered pathognomonic for narcolepsy.
- Hypnagogic (wake to sleep) or hypnopompic (sleep to wake) hallucinations have been reported in 60% to 80% of patients with narcolepsy.
- Sleep paralysis, defined as loss of muscle tone during the transition between sleep and wakefulness, occurs in 60% to 80% of patients with narcolepsy. It may occur with hallucinations and can be interrupted by sensory stimuli.
- Only about one third of patients will have all four symptoms: chronic daytime sleepiness, cataplexy, hypnagogic hallucinations, and sleep paralysis.
- Fragmented sleep is seen in 60% to 80% of narcolepsy patients and can often be mistaken for insomnia or other intrinsic sleep disorder.
- Other symptoms that have been reported in narcolepsy include automatic behavior or semipurposeful movements in 40% of patients and memory disturbance in 50% of patients.

ETIOLOGY

The loss of hypocretin/orexin signaling, genetic factors, and brain lesions are presently identified factors in the development of narcolepsy.
HYPOCRETIN/OREXIN:

- Loss of hypocretin-1 and hypocretin-2 (also known as orexin-A and orexin-B) producing neurons in the lateral hypothalamus.
- Human cerebrospinal fluid (CSF) levels of hypocretin-1 are low to undetectable in narcoleptics with cataplexy.
- Narcolepsy without cataplexy may have a different cause because CSF hypocretin levels are usually normal in these patients, so there may be a completely separate mechanism in these patients, or it may result from less extensive loss of hypocretin neurons or impaired signaling.

SECONDARY ETIOLOGIES:

- Tumors, vascular malformations, and strokes have all been reported to cause secondary narcolepsy.
- Direct injury to the hypocretin neurons or their projections is the most likely cause of secondary narcolepsy due to central nervous system lesions.
- Narcolepsy has been reported in genetic syndromes, including Prader-Willi syndrome and Niemann-Pick disease type C, as well as paraneoplastic syndromes.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Excessive daytime somnolence:

- Autism
- Autosomal dominant cerebellar ataxia, deafness, and narcolepsy
- Behaviorally induced insufficient sleep syndrome
- Central or obstructive sleep apnea (sleep-disordered breathing)
- Circadian rhythm disorder
- Depression
- Diencephalic lesions
- Drug or alcohol abuse
- Hypothyroidism
- Idiopathic hypersomnia with long or short sleep time
- Inadequate sleep hygiene
- Insufficient sleep
- Increased intracranial pressure

Insomnia

- Kleine-Levin syndrome
- Medication effect
- Menstrual-related hypersomnia
- Posttraumatic narcolepsy
- Seizures
- Sleep fragmentation (multiple causes)

Cataplexy:

- Seizures
- Periodic paralysis
- Cardiovascular insufficiency
- Psychogenic (multiple causes)
- Lesions of the hypothalamus or brain stem

WORKUP

- Narcolepsy is often diagnosed by clinical history. The Epworth Sleepiness Scale is very useful in determining the degree of excessive daytime sleepiness (Table N1-1).
- The diagnosis of narcolepsy can be made if there is a clear history of cataplexy in the setting of excessive daytime somnolence, without need for further diagnostic testing. Sleep laboratory testing or possibly laboratory testing is required if these symptoms do not exist.
- The medical history should include questions regarding severity of daytime hypersomnia while also evaluating for sleep-disordered breathing, transient muscle weakness triggered by emotion, hallucinations while falling asleep or upon awakening, and inability to move after awakening. The clinical evaluation should also address symptoms of seizures and paraneoplastic disorders while also asking about previous stroke or genetic disorders. A detailed family history is imperative. Hypothalamic dysfunction such as unexplained weight gain, endocrine abnormalities, circadian dysrhythmias, and autonomic nervous system problems may provide useful insight.
- A thorough examination including a detailed neurologic examination should be performed.
- Nocturnal polysomnography followed by a multiple sleep latency test (MSLT) remains the gold standard for the diagnosis of narcolepsy. A drug screen should also be performed to rule out pharmacologic modulations of sleep.

LABORATORY TESTS

HLA subtyping and CSF hypocretin/orexin levels may be attempted in suspected cases of narcolepsy. CSF hypocretin/orexin analysis is primarily a research tool. CSF hypocretin levels below 110 pg/ml are indicative of narcolepsy, but normal or high CSF hypocretin levels do not exclude the diagnosis.

TREATMENT

NONPHARMACOLOGIC THERAPY

Avoidance of over-the-counter drugs and illicit drugs, optimal sleep hygiene and scheduled daily naps, and psychosocial support can be used for symptoms of excessive daytime somnolence. However, nonpharmacologic therapy is

typically not sufficient for treatment of narcolepsy alone but is often used as adjunct therapy with medications.

PHARMACOLOGIC THERAPY

For excessive daytime somnolence:

- Sodium oxybate: a central nervous system depressant that can be used for the treatment of cataplexy and REM-related symptoms
- Modafinil 200 to 600 mg PO every morning or divided bid
- Armodafinil 150 or 250 mg PO as a single dose in the morning
- Methylphenidate 5 to 15 mg PO bid to tid
- Methylphenidate SR 18 to 54 mg PO every morning or divided bid
- Dextroamphetamine 10 to 60 mg PO qd
- Eldepryl 5 mg PO bid

For cataplexy:

- Sodium oxybate: a central nervous system depressant that can be used for the treatment of cataplexy and REM-related symptoms
- Fluoxetine 20 mg PO qd initially
- Sertraline 25 mg PO qd initially
- Venlafaxine 25 mg PO qd initially
- Clomipramine 25 mg/day initially
- Protriptyline 5 mg tid initially
- Imipramine 25 to 50 mg/day initially
- Desipramine 10 mg bid initially

DISPOSITION

This is a chronic sleep disorder that may worsen for the first few years and then persist for life.

REFERRAL

Because of the complexity of this disorder and its ever-changing management and treatment, patients should be referred to centers or programs with highly trained sleep specialists with expertise caring for these patients, especially if sodium oxybate (Xyrem) therapy is needed.

PEARLS & CONSIDERATIONS

Many narcoleptics report the onset of symptoms beginning in childhood to early adulthood with a long delay of actual diagnosis on the order of 10 to 15 yr. Typically, excessive daytime sleepiness is the initial symptom followed by REM dysregulation (e.g., cataplexy, sleep paralysis, hypnagogic hallucinations). Patients with narcolepsy also have higher than expected incidence of other sleep disorders, including obstructive sleep apnea, periodic limb movements of sleep, and REM sleep behavior disorder.

COMMENTS

Narcolepsy is a rare disorder that is underdiagnosed. Cataplexy is specific for narcolepsy, but other symptoms of REM dysregulation, including sleep paralysis and hypnagogic or hypnopompic hallucinations, can occur even in normal patients. Sleep-onset REM or REM periods on an MSLT may occur as a result of sleep deprivation or withdrawal from REM-suppressing drugs.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Narcolepsy (Patient Information)

AUTHOR: **DON HAYES, JR., M.D., M.S.**

TABLE N1-1 Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to just feeling tired? This refers to your usual way of life in recent time. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation.

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Situation	Chance of Dozing
Sitting and reading	
Watching TV	
Sitting and inactive in a public place (theater or meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after lunch (without alcohol)	
In a car, while stopped for a few minutes in traffic	
Total	

From Johns MW: A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale, *Sleep* 14:540-545, 1991.

SUGGESTED READINGS

Alshaikh MK et al.: Sodium oxybate for narcolepsy with cataplexy: systematic review and meta-analysis, *J Clin Sleep Med* 8(4):451–458, 2012.

Amira SA et al.: Diagnosis of narcolepsy using the multiple sleep latency test: analysis of current laboratory criteria, *Sleep* 8(4):325–331, 1985.

Baumann CR et al.: Hypocretins (orexins) and sleep-wake disorders, *Lancet Neurol* 4(10):673–682, 2005.

Chervin RD et al.: Comparison of the results of the Epworth Sleepiness Scale and the Multiple Sleep Latency Test, *J Psychosom Res* 42(2):145–155, 1997.

Cipolli C et al.: Overnight distribution and motor characteristics of REM sleep behaviour disorder episodes in patients with narcolepsy-cataplexy, *Sleep Med* 12(7):635–640, 2011.

Dauvilliers Y et al.: Narcolepsy with cataplexy, *Lancet* 369(9560):499–511, 2007.

España RA et al.: Sleep neurobiology from a clinical perspective, *Sleep* 34(7):845–858, 2011.

Longstreth WT Jr et al.: The epidemiology of narcolepsy, *Sleep* 30(1):13–26, 2007.

Mignot EJ: A practical guide to the therapy of narcolepsy and hypersomnia syndromes, *Neurotherapeutics* 9(4):739–752, 2012.

Morgenthaler TI et al.: Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin, *Sleep* 30(12):1705–1711, 2007.

Ohayon MM: Narcolepsy is complicated by high medical and psychiatric comorbidities: a comparison with the general population, *Sleep Med* 14(6):488–492, 2013.

Scammell TE: The neurobiology, diagnosis, and treatment of narcolepsy, *Ann Neurol* 53(2):154–166, 2003.

Wise MS et al.: Treatment of narcolepsy and other hypersomnias of central origin, *Sleep* 30(12):1712–1727, 2007.

Zeman A et al.: Narcolepsy and excessive daytime sleepiness, *BMJ* 329(7468):724–728, 2004.

BASIC INFORMATION

DEFINITION

Necrotizing fasciitis is a rapidly spreading bacterial infection of the deep fascia, with associated inflammation, leading to necrosis of subcutaneous tissue planes. This infection can occur in wounds from trauma or surgical wounds or can be spontaneous or idiopathic. There are two clinical types, both of which carry a high rate of morbidity and mortality.

SYNONYMS

Soft tissue gangrene
Flesh-eating bacteria
Fournier's gangrene
Hemolytic streptococcal gangrene

ICD-9CM CODES
728.86 Necrotizing fasciitis
ICD-10CM CODES
M72.6 Necrotizing fasciitis

EPIDEMIOLOGY & DEMOGRAPHICS

Predominant Sex
Male > female.

Predominant Age
6 to 50 yr; less common in children.

EPIDEMIOLOGY

Invasive group A *Streptococcus* infection occurs at a rate of 3.5 cases per 100,000 persons, with a case fatality rate of around 24%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

CLINICAL TYPES OF NECROTIZING FASCIITIS

- Type I necrotizing fasciitis: at least one anaerobic species is isolated in conjunction with one or more facultative anaerobic species, such as streptococci (not group A), *and* members of the Enterobacteriaceae:
- Anaerobic bacteria, most commonly *Bacteroides* or *Peptostreptococcus* spp.
- Enterobacteriaceae: *Escherichia coli*, *Klebsiella* spp., *Proteus* spp., *Enterobacter* spp.
- Usually associated with diabetes or peripheral vascular disease
- Example of type I: Fournier's gangrene of the perineum
- Type II necrotizing fasciitis: Group A *Streptococcus* is isolated alone or in combination with other bacteria, most likely *Staphylococcus aureus.* Also known as hemolytic streptococcal gangrene
1. Example of type II: Invasive group A *Streptococcus*, associated with virulence factors type 1 and type 3 M protein

FIGURE N1-1 Necrotizing fasciitis. The so-called flesh-eating bacteria, group A β-hemolytic Streptococcus, can cause significant tissue destruction rapidly. This 32-year-old woman had pain, erythema, and swelling of the foot followed by necrotic ulceration over a week. There was no history of trauma. (Courtesy Roger Bitar, MD. From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

TABLE N1-2 Classification of Necrotizing Skin, Soft-Tissue, and Muscle Infections

Disease	Bacteriology	Comments
Necrotizing Cellulitis		
Clostridial cellulitis	*Clostridium perfringens*	Local trauma, recent surgery; fascial/deep muscle spared
Nonclostridial cellulitis	Mixed: *Escherichia coli, Enterobacter, Peptostreptococcus* spp., *Bacteroides fragilis*	Diabetes mellitus predisposes; produces foul odor
Meleney's synergistic gangrene	*Staphylococcus aureus,* microaerophilic streptococci	Rare infection; postoperative; slowly expanding, indolent, ulceration in superficial fascia
Synergistic necrotizing cellulitis	Mixed aerobic and anaerobic, including *B. fragilis, Peptostreptococcus* spp.	Diabetes mellitus predisposes; variant of necrotizing fasciitis type I; involves skin, muscle, fat, and fascia
Necrotizing Fasciitis		
Type I	Mixed aerobic and anaerobic; staphylococci, *B. fragilis, E. coli,* group A streptococci, *Peptostreptococcus* spp., *Prevotella, Porphyromonas* spp., *Clostridium* spp.	Usually requires a breach in the mucous membrane layer either through surgery or penetrating injuries or from chronic medical conditions such as diabetes, peripheral vascular disease, malignancy, and anal fissures
Type II	Group A streptococci	Increasing in frequency and severity since 1985; very high mortality; often begins at site of nonpenetrating minor trauma such as a bruise or muscle strain but often no identified precursor Predisposing factors: blunt/penetrating trauma, varicella (chickenpox), intravenous drug abuse, surgical procedures, childbirth, nonsteroidal anti-inflammatory drug use
Myonecrosis		
Clostridial myonecrosis	*Clostridium* spp.	Predisposing factors: deep/penetrating injury, bowel and biliary tract surgery, improperly performed abortion and retained placenta, prolonged rupture of the membranes, and intrauterine fetal demise or missed abortion in postpartum patients. Recurrent gas gangrene occurs at sites of previous gas gangrene.
Streptococcal myonecrosis	Streptococci	
Special Type of Necrotizing Soft-Tissue Infection		
Fournier's gangrene	Polymicrobial, with *E. coli* the predominant aerobe and *Bacteroides* the predominant anaerobe. Other microflora: *Proteus, Staphylococcus, Enterococcus,* aerobic and anaerobic *Streptococcus, Pseudomonas, Klebsiella,* and *Clostridium*	Necrosis of the scrotum or perineum that starts with scrotal pain and erythema and rapidly spreads onto anterior abdominal wall and gluteal muscle. It is more often seen in diabetics and can be associated with trauma.

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

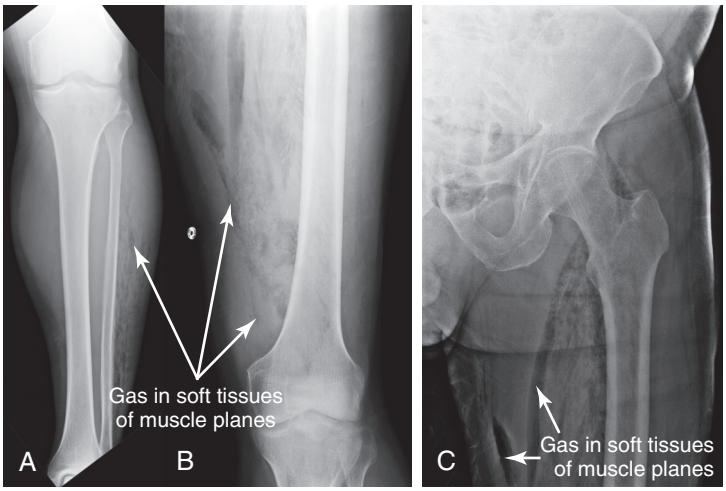


FIGURE N1-2 Necrotizing fasciitis. This 71-year-old man with aplastic anemia presented with fevers to 38.9° C, leg weakness, and extreme leg pain. Initially, the patient was thought to have neuropathic pain and weakness, possibly indicating spinal disease such as epidural abscess. He rapidly developed crepitus of his legs. Radiographs of the patient's legs were obtained, followed by noncontrast CT. **A,** Anterior-posterior (AP) tibia and fibula. **B,** AP femur. **C,** AP hip. Air is seen dissecting in muscle planes of the legs. On radiograph, air appears black. Given the wide distribution of air, a focal abscess is unlikely, and necrotizing fasciitis with gas-producing organisms should be suspected. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

EXAMPLES OF NECROTIZING FASCIITIS

- Fournier's gangrene: Aggressive type I infection of the perineum usually caused by penetration of the gastrointestinal or urethral mucosa by enteric organisms. It can rapidly spread to involve the scrotum, penis, and abdominal wall or gluteal muscles, causing gangrene.
- Clostridial cellulitis: Caused by *Clostridium perfringens* associated by local trauma or surgery and crepitus caused by gas production; generally noted in the skin, with deeper tissues generally spared.

PHYSICAL FINDINGS

Minor skin trauma, toxic-appearing patient:

- Open skin wound.
- Severe pain at injury or surgical site.
- Fever, confusion, weakness, diarrhea.
- Early skin erythema, quickly spreading in hours to days.
- Skin redness changes to purple discoloration.
- Gangrenous skin changes may develop.
- Loosening of skin and subcutaneous skin in association with deep fascial necrosis (Fig. N1-1).
- Muscle involvement, thrombosis of blood vessels, and myonecrosis may develop.
- Bullae and gas formation at site.

ETIOLOGY

- Polymicrobial: mixture of anaerobes and aerobic enteric gram-negative rods.
- Group A streptococci *(S. pyogenes).*
- *S. aureus.*
- C. perfringens.
- Bacteroides fragilis.
- Vibrio vulnificus.
- Methicillin-resistant *S. aureus* (MRSA), especially community-acquired MRSA.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cellulitis.
- Pyomyositis.
- Gas gangrene.
- A classification of necrotizing skin, soft-tissue, and muscle infections is described in Table N1-2.

WORKUP

- Diagnosis of necrotizing fasciitis generally requires incision and probing. In patients with necrotizing fasciitis, there is no resistance to probing subcut and there is fascial plane involvement.
- Laboratory tests:
  1. Complete blood cell count (CBC) with differential
  2. Cultures of skin, soft tissue, or debrided tissue, aerobically and anaerobically. Blood cultures are positive in 60% of patients with type II infections and 20% with type I infections.
- Imaging:
  1. Radiographs show subcutaneous gas in fascial planes (Fig. N1-2).
  2. Computed tomography (CT)/magnetic resonance imaging (MRI) may be helpful because they can detect gas in the tissues.

Rx TREATMENT

- Aggressive surgical debridement of involved necrotic tissues is essential as soon as possible to reduce mortality.
- Fasciotomies of extremities may be necessary.
- Empiric antibiotic treatment:

Type I: Piperacillin/tazobactam; carbapenems such as imipenem, meropenem, or doripenem; and third-generation cephalosporin + metronidazole or aminoglycoside + clindamycin are reasonable choices pending cultures. It is important to always have anaerobic coverage.

Type II: For group A Streptococcus, give intravenous (IV) penicillin G, 4 million U q4h in patients who weigh >60 kg with clindamycin, 600 to 900 mg IV q8h.

1. Clindamycin has the added effect of suppressing toxin production. If MRSA is suspected, add vancomycin, daptomycin, or linezolid.

- Intravenous gammaglobulin (IVIG): 1 g/kg on day 1 and 0.5 g/kg on days 2 and 3 neutralizes circulating streptococcal toxins and has been shown beneficial in severe forms of invasive group A streptococcal infections, although data not definitive.
- Hyperbaric oxygen evaluation as an adjunct to surgery and IV antibiotics.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Cheng NC et al.: Factors affecting the mortality of necrotizing fasciitis involving the upper extremities, *Today* 38(12):1108–1113, 2008.

Edlich RF et al.: Modern concepts of the diagnosis and treatment of necrotizing fasciitis, *J Emerg Med* 39(2):261–265, 2010.

Morgan MS: Diagnosis and management of necrotizing fasciitis: a multiparametric approach, *J Hosp Infect* 75(4):249–257, 2010.

Sarani B et al.: Necrotizing fasciitis: current concepts and review of the literature, *J Am Coll Surg* 208(2):279–288, 2009.

Shimizu T, Tokuda Y: Necrotizing fasciitis, *Intern Med* 49(12):1051–1057, 2010.

Stevens DL, Bisno AL, et al.: Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America, *Clin Inf Dis* 59(2):e10–e52, 2014.

Weaver LK: Hyperbaric oxygen in the critically ill, *Crit Care Med* 39(7):1784–1791, 2011.

Nephroblastoma

BASIC INFORMATION

DEFINITION

Nephroblastoma is a malignant renal tumor derived from primitive metanephric blastoma. Most tumors are unicentric, but some are multifocal in one or both kidneys. Associated anomalies may be present.

SYNONYMS

Wilms' tumor

ICD-9CM CODES
189.0 Nephroblastoma
ICD-10CM CODES
C64 Malignant neoplasm of kidney

EPIDEMIOLOGY & DEMOGRAPHICS

- Pediatric malignancy mean presentation is at 41.5 mo in boys and 46.9 mo in girls.
- Slightly more frequent in girls.
- Incidence rate is 7.9 cases per year per 1 million white children <15 yr (a little over 500 new cases annually in the United States), the incidence is double in black children.
- Associated syndromes (Table N1-3):
  1. Cryptorchidism.
  2. Hypospadias.
  3. Hemihypertrophy with or without the Beckwith-Wiedemann syndrome, aniridia.
  4. Denys-Drash syndrome (nephroblastoma, pseudohermaphroditism, glomerulonephritis).
  5. WAGR syndrome (***W***ilms' tumor, ***a***niridia, ***g***enitourinary malformations, and mental ***r***etardation).
- Familial nephroblastoma occurs in 1.5% (with younger age at diagnosis and more frequent multifocal tumors).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Nephroblastoma often is discovered when a parent notices a mass while bathing or dressing a child, most commonly a child who is approximately age 3 yr, or during a routine physical examination. The mass is unilateral, firm, and nontender and below the costal margin.
- Abdominal swelling and/or pain.
- Nausea.
- Vomiting.
- Constipation.
- Loss of appetite.
- Fever of unknown origin.
- Night sweats.

TABLE N1-3 Syndromes associated with Wilms' Tumor

Syndrome	Clinical Characteristics	Genetic Anomalies
Wilms' tumor, aniridia, genitourinary abnormalities, and mental retardation (WAGR syndrome)	Aniridia, genitourinary abnormalities, mental retardation	Del 11p13 (*WT1* and *PAX6*)
Denys-Drash syndrome	Early-onset renal failure with renal mesangial sclerosis, male pseudohermaphroditism	*WT1* missense mutation
Beckwith-Wiedemann syndrome (BWS)	Organomegaly (liver, kidney, adrenal, pancreas) macroglossia, omphalocele, hemihypertrophy	Unilateral paternal disomy, duplication of 11p15.5 loss of imprinting, mutation of *p57KIP57* Del 11p15.5 *IGF2* and *H19* imprinting control region

From Kliegman RM.; et al. *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

- Hematuria (less common than in adult renal malignancies).
- Malaise.
- High blood pressure that is triggered when the tumor obstructs the renal artery.
- Varicocele.
- Signs of associated syndromes.

ETIOLOGY & PATHOGENESIS

- Three cell types: blastomal, stromal, and epithelial may be present. Structural diversity is characteristic.
- Anaplasia is evidenced by the presence of gigantic polyploid nuclei. The term *focal anaplasia* is used to describe such findings when it is confined within the primary tumor in the kidney.
- Staging:
  Stage I: Tumor limited to the kidney whose capsule is intact. The tumor is completely excised.
  Stage II: Tumor extends beyond the kidney but is completely excised. No peritoneal involvement.
  Stage III: Residual tumor confined to the abdomen after surgery. No hematogenous metastases.
  Stage IV: Hematogenous metastases present.
  Stage V: Bilateral renal involvement at time of initial diagnosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other renal malignancies
  1. Hypernephroma.
  2. Transitional cell carcinoma.
  3. Lymphoma.
  4. Clear cell sarcoma.
  5. Rhabdoid tumor of the kidney.
- Renal cyst.
- Other intraabdominal or retroperitoneal tumors.

LABORATORY TESTS

- Complete blood count.
- Transaminases (alanine aminotransferase, aspartate aminotransferase).
- Alkaline phosphatase.
- Blood urea nitrogen and creatinine.
- Serum calcium.
- Urinalysis.

IMAGING STUDIES

- Renal ultrasound to confirm existence of a solid mass in a kidney.
- Abdominal CT scan with contrast.
- Chest radiograph or CT scan.

TREATMENT

- Surgical resection and surgical staging:
  1. Stages I and II: surgery followed by chemotherapy.
  2. Stages III and IV: surgery followed by radiation and chemotherapy.
- Chemotherapeutic agents used in the treatment of nephroblastoma include vincristine, dactinomycin, and doxorubicin.

PROGNOSIS

- Stage I: 95% survival.
- Stage II: 91% survival.
- Stage III: 91% survival.
- Stage IV: 81% survival.
- Prognosis is better for patients <2 yr.

AUTHOR: **FRED F. FERRI, M.D.**

BASIC INFORMATION

DEFINITION

Multiorgan systemic fibrosis related to gadolinium-based contrast exposure

SYNONYMS

Nephrogenic fibrosing dermopathy
Gadolinium-associated nephrogenic systemic fibrosis

ICD-9CM CODES
710.8 Other specified diffuse diseases of connective tissue
ICD-10CM CODES
M35.5 Multifocal fibrosclerosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1.6% to 4.6%
PREDOMINANT SEX AND AGE: No predilection for sex; often seen in middle age but can involve all age groups
RISK FACTORS: Linear, non-ionically charged gadolinium-based contrast agents including gadodiamide (Omniscan) and gadoversetamide (OptiMARK), along with linear, ionically charged gadopentetate (Magnevist) exposure provide high risk among patients with severe renal dysfunction (Stage 4/GFR <30 ml/min per 1.73 m^2 or worse), including dialysis patients, with the highest risk in patients on peritoneal dialysis or acute kidney injury (AKI), particularly hepatorenal in origin. Proinflammatory states including major surgery, thrombotic events, infection, and malignancy as well as high-dose erythropoietin use in this population are associated with higher risk of nephrogenic systemic fibrosis. Higher than standard dose of gadolinium-based contrast agent is also associated with elevated risk of NSF.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- History of gadolinium-based contrast media in a patient with renal dysfunction (GFR <30 ml/min) or AKI, particularly in those patients with proinflammatory states
- Presentation time varies from day of exposure to several months later, with a median of 11.5 days with up to 8 years after exposure being reported.
- Major criteria include pruritic, erythematous plaques with induration, and joint contractures.
- Minor criteria include superficial plaque, scleral plaques in patients less than 45 years old, and dermal papules.
- Skin presentations typically are symmetric and involve the extremities and trunk, generally sparing the face (Fig. N1-3). Fibrosis can be extradermal, leading to multiorgan dysfunction. For example, fibrosis can lead to respiratory failure from muscular involvement of the diaphragm. It can also affect the eyes and blood vessels.

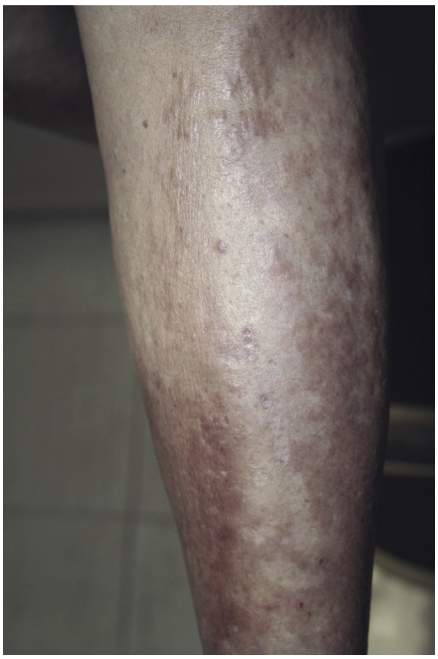


FIGURE N1-3 Red-brown, shiny plaques indicate deeper skin involvement with nephrogenic systemic fibrosis. (From Girardi M.: Nephrogenic systemic fibrosis: a dermatologist's perspective, *J Am Coll Radiol* 5(1):40–44, 2008.)

ETIOLOGY

- Pathophysiology remains unclear, but current postulation is that free gadolinium ions deposit in the tissues after being displaced from its chelating agent and binding to anions forming insoluble salts. Displacement of gadolinium from its chelating agent is postulated to occur more readily in proinflammatory states, allowing the gadolinium to enter the extravascular space. In renal failure, when the duration of gadolinium exposure is highest due to a decreased clearance of gadolinium, tissue deposition is higher. Deposition leads to fibrocyte recruitment and further contribution to the proinflammatory states, leading to further tissue injury and fibrocyte recruitment and ultimately tissue fibrosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Scleroderma

WORKUP

- Skin biopsy

LABORATORY TESTS

- None

IMAGING STUDIES

- None

TREATMENT

No current effective treatment. There are no randomized clinical trials available. Case reports implementing corticosteroids, plasmapheresis, thalidomide, and methotrexate suggest little to no benefit, whereas case reports implementing photopheresis and sodium thiosulfate have shown modest benefit. Hemodialysis can effectively remove gadolinium contrast media, but no current evidence demonstrates that immediate hemodialysis is protective against development of nephrogenic systemic fibrosis. It is reasonable to perform dialysis following gadolinium contrast exposure in patients currently on dialysis. Resolution of renal dysfunction typically also results in the resolution of NSF.

REFERRAL

- Dermatology for biopsy

PEARLS & CONSIDERATIONS

COMMENTS

Given the lack of treatment modalities, prevention of this disease by avoidance of gadolinium-based contrast administration is best among patients with advanced CKD. All patients intended to receive gadolinium-based contrast for renal dysfunction should be screened.

PREVENTION

Unless essential diagnostic information is needed from a gadolinium-based contrast medium, these studies should be avoided in patients with a GFR less than 30 ml per minute per 1.73m^2 or with AKI. Caution should also be used in children under one year and pregnant women.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED TOPICS

Information on gadolinium-based contrast agents: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm142882.htm

AUTHORS: **NIKUNJKUMAR PATEL M.D.,** and **SUSIE L. HU M.D.**

SUGGESTED READINGS

Besheli LD et al.: Current Status of Nephrogenic Systemic Fibrosis, *Clinical Radiology* 69(7):661–668, Jul 2014.

Schlaudecker JD, Bernheisel CR: Gadolinium-associated nephrogenic systemic fibrosis, *Am Fam Physician* 80(7):711–714, 2009.

U.S. Food and Drug Administration: FDA drug safety communication: new warnings for using gadolinium-based contrast agents in patients with kidney dysfunction. Accessed June 10, 2013. http://www.fda.gov/Drugs/DrugSafety/ucm223966.htm, 2010.

BASIC INFORMATION

DEFINITION

Nephrotic syndrome is characterized by high urine protein excretion (>3.5 g/1.73 m^3/24 hr), peripheral edema, and metabolic abnormalities (hypoalbuminemia, hypercholesterolemia). Table N1-4 describes definitions of terms used in idiopathic nephrotic syndrome in adults and children. Fig. N1-4 illustrates the mechanism of nephrotic edema.

ICD-9CM CODES
581.9 Nephrotic syndrome
ICD-10CM CODES
N04.9 Nephrotic syndrome with unspecified morphologic changes

EPIDEMIOLOGY & DEMOGRAPHICS

- Nephrotic syndrome occurs predominantly in children ages 2 to 6 yr (2 new cases/100,000 persons/yr) and in adults of all ages (3 to 4 new cases/100,000 persons/yr).
- Membranous glomerulonephritis is the most common cause of nephrotic syndrome.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Peripheral edema, eyelid edema (Fig. N1-5).
- Ascites, anasarca.
- Hypertension.
- Pleural effusion.
- Typically patients present with severe peripheral edema, exertional dyspnea, and abdominal fullness secondary to ascites. There is a significant amount of weight gain in most patients.

ETIOLOGY

- Idiopathic (may be secondary to the following glomerular diseases: minimal change disease [nil disease, lipoid nephrosis], focal segmental glomerular sclerosis (20% of cases of nephrotic syndrome), membranous nephropathy, membranoproliferative glomerular nephropathy). PLA 2 R is a major antigen in the majority of patients with idiopathic membranous nephropathy. An $HLA\text{-}DQA_1$ allele on chromosome 6p21 is most closely associated with idiopathic membranous nephropathy in persons of white ancestry. This allele may facilitate an autoimmune response against targets such as variants of PLA 2 R1.
- Associated with systemic diseases (diabetes mellitus, systemic lupus erythematosus [SLE], amyloidosis). Amyloidosis and dysproteinemias should be considered in patients >40 yr.

TABLE N1-4 Nephrotic Syndrome (NS): Definitions

	NS DEFINITIONS	
Term	**Adult**	**Pediatric**
Relapse	Proteinuria ≥3.5 g/day occurring after complete remission has been obtained for >1 mo	Albu-stix 3+ or proteinuria >40 mg/m/h occurring on 3 days within 1 wk
Frequently relapsing	2+ relapses within 6 mo	2+ relapses within 6 mo
Complete remission	Reduction of proteinuria to ≤0.20 g/day and serum albumin >35 g/L	<4 mg/m/h on at least 3 occasions within 7 days serum albumin >35 g/L
Partial remission	Reduction of proteinuria to between 0.21 g/day and 3.4 g/day ± decrease in proteinuria of ≥50% from baseline	Disappearance of edema. Increase in serum albumin >35 g/L and persisting proteinuria >4 mg/m/h or >100 mg/m/day
Steroid-resistant	Persistence of proteinuria despite prednisone therapy 1 mg/kg/day × 4 mo	Persistence of proteinuria despite prednisone therapy 60 mg/m × 4 wk*
Steroid-dependent—NS recurs when stop or decrease treatment	Two consecutive relapses occurring during therapy or within 14 days of completing steroid therapy	Two relapses of proteinuria within 14 days after stopping or during alternate day steroid therapy

Definition of terms used in idiopathic nephrotic syndrome in adults and children. The definitions were generated by a consensus of the International Society for Kidney Diseases and the German Pediatric Nephrology Society.
*Or persistence of proteinuria despite prednisone therapy 60 mg m^{-2} × 4 weeks and three methylprednisolone pulses.
From Floege J.; et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

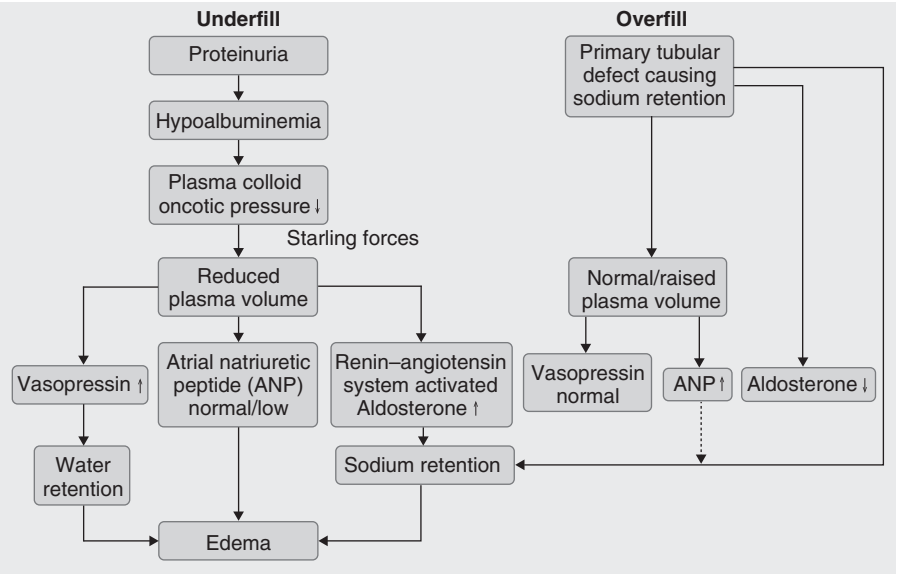


FIGURE N1-4 Mechanisms of nephrotic edema. The kidney is relatively resistant to ANP in this setting, so ANP has little effect in countering sodium retention. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

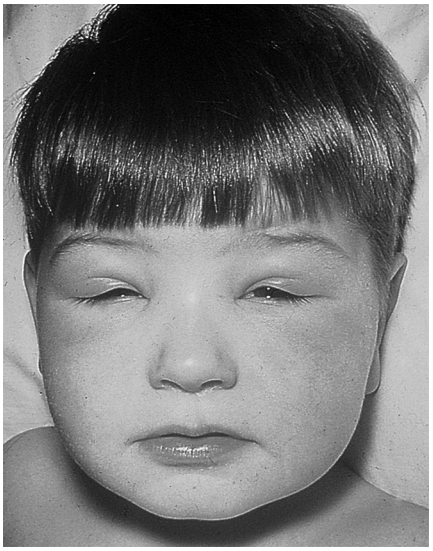


FIGURE N1-5 Nephrotic edema. Periorbital edema in the early morning in a nephrotic child. The edema resolves during the day under the influence of gravity. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

- Majority of children with nephrotic syndrome have minimal change disease (this form also associated with allergy, nonsteroidals, and Hodgkin's disease).
- Focal glomerular disease: can be associated with HIV infection, heroin abuse. A more severe form of nephrotic syndrome associated with rapid progression to end-stage renal failure within months can also occur in HIV seropositive patients and is known as "collapsing glomerulopathy."
- Membranous nephropathy: can occur with Hodgkin's lymphoma, carcinomas, SLE, gold therapy.
- Membranoproliferative glomerulonephropathy: often associated with upper respiratory infections.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other edema states (CHF, cirrhosis).
- Primary renal disease (e.g., focal glomerulonephritis, membranoproliferative glomerulonephritis [MPGN]). The differentiation between nephrotic syndrome and nephritic syndrome is described in Table N1-5. Table N1-6 summarizes primary renal diseases that present as idiopathic nephrotic syndrome.
- Carcinoma, infections.
- Malignant hypertension.
- Polyarteritis nodosa.
- Serum sickness.
- Toxemia of pregnancy.

TABLE N1-5 Differentiation between Nephrotic Syndrome and Nephritic Syndrome

Typical Features	Nephrotic	Nephritic
Onset	Insidious	Abrupt
Edema	++++	++
Blood pressure	Normal	Raised
Jugular venous pressure	Normal/low	Raised
Proteinuria	++++	++
Hematuria	May/may not occur	+++
Red-cell casts	Absent	Present
Serum albumin	Low	Normal/slightly reduced

From Johnson RJ, Feehally J: *Comprehensive clinical nephrology,* ed 2, St Louis, 2000, Mosby.

WORKUP

Diagnostic workup consists of family history and history of drug use or toxin exposure and laboratory evaluation. Renal biopsy is generally performed in individuals with persistent proteinuria in whom the etiology of the proteinuria is unclear.

LABORATORY TESTS

- Urinalysis reveals proteinuria. The presence of hematuria, cellular casts, and pyuria is suggestive of nephritic syndrome. Oval fat bodies (tubular epithelial cells with cholesterol esters) are also found in the urine in patients with nephrotic syndrome.
- 24-hr urine protein excretion is >3.5 g/1.73 m^3/24 hr.
- Abnormalities of blood chemistries include serum albumin <3 g/dl, decreased total protein, elevated serum cholesterol, glucose, azotemia.
- Additional tests in patients with nephrotic syndromes depending on the history and physical examination are ANA, serum and

TABLE N1-6 Summary of Primary Renal Diseases That Present as Idiopathic Nephrotic Syndrome

	Minimal-Change Nephropathy Syndrome	Focal Segmental Sclerosis	Membranous Nephrotic	MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS	
				Type I	Type II
Frequency*					
Children	75%	10%	<5%	10%	10%
Adults	15%	15%	50%	10%	10%
Clinical Manifestations					
Age (yr)	2-6	2-10	40-50	5-15	5-15
Sex	2:1 female	1.3:1 female	2:1 male	Male-female	Male-female
Nephrotic syndrome	100%	90%	80%	60%	60%
Asymptomatic proteinuria	0	10%	20%	40%	40%
Hematuria	10%-20%	60%-80%	60%	80%	80%
Hypertension	10%	20% early	Infrequent	35%	35%
Rate of progression to renal failure	Does not progress	10 years	50% in 10-20 yr	10-20 yr	5-15 yr
Associated conditions	Allergy? Hodgkin's disease, usually none	None			
Laboratory Findings	Manifestations of nephrotic syndrome	Manifestations of nephrotic syndrome	Renal vein thrombosis, cancer, SLE, hepatitis B	None	Partial lipodystrophy
	↑ BUN in 15%-30%	↑ BUN in 20%-40%	Manifestations of nephrotic syndrome	Low C1, C4, C3-C9	Normal C1, C4, low C3-C9
Immunogenetics	HLA-B8, B12 (3.5)†	Not established	HLA-DRW3 (12–32)†	Not established	C3 nephritic factor
Renal Pathology					Not established
Light microscopy	Normal	Focal	Thickened	Thickened	Lobulation
Immunofluorescence	Negative	IgM	Fine	Granular	C3 only
Electron microscopy	Foot process fusion	Foot	Subepithelial	Mesangial	Dense deposits
Response of Steroids	90%	15%-20%	May slow progression	Not established	Not established

*Approximate frequency as a cause of idiopathic nephrotic syndrome. About 10% of adult nephrotic syndrome is due to various diseases that usually present with acute glomerulonephritis.
†Relative risk.
↑, Elevated; *BUN,* blood urea nitrogen; *C,* complement; *GBM,* glomerular basement membrane; *hepatitis B,* hepatitis B virus; *HLA,* human leukocyte antigen; *Ig,* immunoglobulin; *SLE,* systemic lupus erythematosus.
Modified from Goldman L, Ausiello D (eds): *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, Saunders.

urine immunoelectrophoresis, C3, C4, CH-50, LDH, liver enzymes, alkaline phosphatase, hepatitis B and C screening, and HIV.

IMAGING STUDIES

- Ultrasound of kidneys.
- Chest x-ray.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Bed rest as tolerated, avoidance of nephrotoxic drugs, low-fat diet, fluid restriction in hyponatremic patients; normal protein intake unless urinary protein loss exceeds 10 g/24 hr (some patients may require additional dietary protein to prevent negative nitrogen balance and significant protein malnutrition).
- Improved urinary protein excretion and serum lipid changes have been observed with a low-fat soy protein diet providing 0.7 g of protein/kg/day. However, because of increased risk of malnutrition, many nephrologists recommend normal protein intake.
- Strict sodium restriction to help manage peripheral edema.
- Close monitoring of patients for development of peripheral venous thrombosis and renal vein thrombosis because of hypercoagulable state secondary to loss of antithrombin III and other proteins involved in the clotting mechanism.

ACUTE GENERAL Rx

- Furosemide is useful for severe edema (Fig. N1-6).
- Use of ACE inhibitors to reduce proteinuria is generally indicated even in normotensive patients.
- Anticoagulant therapy should be administered as long as patients have nephrotic proteinuria, an albumin level <20 g/L, or both.

The mainstay of therapy is treatment of the underlying disorder:

- Minimal change disease generally responds to prednisone 1 mg/kg/day. Relapses can occur when steroids are discontinued. In these individuals, cyclophosphamide and chlorambucil may be useful.
- Focal segmental glomerulosclerosis: children—empiric therapy with prednisone (60 mg/square meter of BSA) for 4-6 wk because 80% will have glucocorticoid-responsive minimal change disease. Adults receive RAS blockade (ACE inhibitors, ARBs) and dietary sodium restriction. Some genetic forms may respond to empiric therapy with calcineurin inhibitors.
- Membranous glomerulonephritis: prednisone 2 mg/kg/day may be useful in inducing remission. Cytotoxic agents can be added if there is poor response to prednisone.
- MPGN: most patients are treated with steroid therapy and antiplatelet drugs. Despite treatment, the majority of patients will progress to end-stage renal disease within 5 yr.

CHRONIC Rx

- Patients should be monitored for azotemia and should be aggressively treated for hypertension and hyperlipidemia. Furosemide is useful for severe edema. Anticoagulants may be necessary for thromboembolic events. Prophylactic anticoagulation should be considered in patients with membranous glomerulonephritis.
- Oral vitamin D is useful in the treatment of hypocalcemia (because of vitamin D loss).

REFERRAL

Nephrology consultation is recommended in all cases of nephrotic syndrome.

SUGGESTED READINGS

Available at www.expertconsult.com.

RELATED CONTENT

Nephrotic Syndrome (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

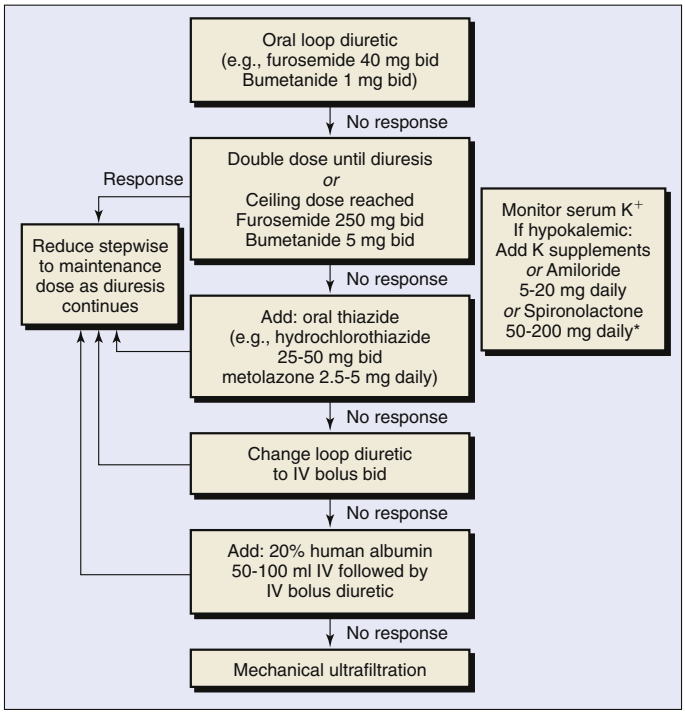


FIGURE N1-6 Management of edema in nephrotic syndrome. Edema is often diuretic resistant, but the response is not predictable. Therefore, stepwise escalation of therapy is appropriate until diuresis occurs. Even when there is anasarca, diuresis should not proceed faster than 2 kg/day in adults to minimize the risk of clinically significant hypovolemia. Mechanical ultrafiltration is rarely required for nephrotic edema unless there is associated renal insufficiency. Spironolactone is less effective in nephrotic syndrome than in cirrhosis and is often poorly tolerated because of gastrointestinal side effects. Spironolactone should be used with great caution if the glomerular filtration rate is very low. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

SUGGESTED READINGS

D'agati VD et al.: Focal segmental glomerulosclerosis, *N Engl J Med* 365:2398–2411, 211.

Stanesco HC et al.: Risk HLA-DQ A2 and PLA2 R1 alleles in idiopathic membranous nephropathy, *N Engl J Med* 364:616–626, 2011.

BASIC INFORMATION

DEFINITION

Neuroblastomas are tumors of postganglionic sympathetic neurons that typically originate in the adrenal medulla or the sympathetic chain/ganglion. Often present at birth, but not diagnosed until later, when the child shows symptoms of the disease. They are almost exclusively a disease of childhood.

ICD-9CM CODES
194.0 Neuroblastoma, unspecified site
ICD-10CM CODES
C74.90 Malignant neoplasm of unspecified part of unspecified adrenal gland

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 8%-10% of all solid tumors of childhood (third most common childhood cancer, after leukemia and brain tumors); 1/10,000 children <15 yr.
PREDOMINANT SEX: Male/female ratio of 1:1.3
PEAK AGE: Early childhood. Mean age of onset is 18 mo; 33% onset by 1 year; 75% onset by 5 year; 97% by 10 year. In rare cases, neuroblastoma can be discovered by fetal ultrasound.
GENETICS: Chromosomal deletions (loss of heterozygosity) found in nearly half of tumors, most commonly localized to chromosomes 1p, 11q, and 14q. Deletion of 1p36 (leading to amplification and overexpression of *N-MYC* protooncogene) associated with poor prognosis. There is a small subset with an autosomal dominant pattern of inheritance. Somatic recurrent mutations (ATRX gene) in tumors from patients with stage 4 neuroblastoma correlate with age at diagnosis and telomere length in children and young adults.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Neuroblastomas can arise anywhere along the sympathetic nervous system. The most common primary site is the adrenal gland (40%), followed by a mass in the abdomen (25%), thorax (15%), neck (5%), and pelvis (5%). In approximately 1% of cases a primary site cannot be identified. 70% to 80% of children have regional lymph node involvement or distant metastases to bone marrow, cortical bone, orbits, liver, and skin at time of presentation.
- Spinal cord/paraspinal: can present with localized back pain, signs of compression—paraplegia, stool/urine retention, scoliosis
- Abdominal mass, pain, or constipation
- Horner's syndrome (ptosis, miosis, anhidrosis)
- Thoracic: difficulty breathing, dysphagia, infections, chronic cough
- Secondary symptoms referable to metastatic disease: fatigue, chronic pain (typically bony pain), pancytopenia, periorbital ecchymosis, proptosis, anorexia, weight loss, unexplained fever, multiple subcutaneous bluish nodules, irritability
- Paraneoplastic syndromes: opsoclonus-myoclonus syndrome (OMS) is described as "dancing eyes, dancing feet," which manifest as myoclonic jerks and chaotic eye movements in all directions. This may be initial presentation before tumor diagnosis; present in 1% to 3% of patients with neuroblastoma; of all patients with opsoclonus-myoclonus, approximately 50% have an underlying neuroblastoma. Patients who present with this syndrome must be evaluated for neuroblastoma; when present, the neuroblastoma often has more favorable biologic features.
  Progressive cerebellar ataxia.
- Abnormal secretion of vasoactive intestinal peptide by the tumor, leading to distention of the abdomen and secretory diarrhea.

DIAGNOSIS

WORKUP

- Careful general physical examination to look for mass
- Biopsy and resection of tumor when possible

LABORATORY TESTS

- Complete blood count, coagulation studies, erythrocyte sedimentation rate.
- 24-hour urine for catecholamines: homovanillic acid (HVA) and vanillylmandelic acid (VMA) are secreted by up to 90% of tumors.
- Nonspecific serum markers such as neuron-specific enolase, lactate dehydrogenase, and ferritin.
- Bone marrow biopsy and aspirate: karyotype, DNA index, *N-MYC* copy number.
- Minimum criteria for diagnosis is based on one of the following: (1) unequivocal pathologic diagnosis made from tumor tissue or (2) combination of bone marrow aspirate with unequivocal tumor cells and increased levels of serum or urinary catecholamine metabolites, as described above.
- Genetic/biologic variables have been studied in children with neuroblastoma, in particular the histology, aneuploidy of tumor DNA, and amplification of the *N-MYC* oncogene within tumor tissue, because treatment decisions may be based on these factors.
  1. Hyperdiploid DNA is associated with favorable prognosis, especially in infants.
  2. *N-MYC* amplification is associated with poor prognosis, regardless of patient age, likely due to association with deletion of chromosome 1p and gain of chromosome 17q.
  3. Other biologic factors studied include profile of GABAergic receptors, expression of neurotrophin receptors, level of telomerase RNA and serum ferritin and lactate dehydrogenase.

IMAGING STUDIES

- Chest x-ray, abdominal plain film, skeletal survey, abdominal and renal/bladder ultrasound
- CT scan or MRI of the chest and abdomen to provide information about regional lymph nodes, vessel invasion, and distant metastases (Fig. N1-7)
- Body scan with ^{131}I-MIBG (meta-iodobenzylguanidine), which is taken up by neuroblasts and is sensitive to metastases in the bone and soft tissue
- Bone scan with Tc-99 MDP to visualize lytic bone lesions and metastases
- Urine catecholamines: elevated in 90% to 95% of patients with neuroblastomas
- STAGING (staged according to the International Neuroblastoma Staging System [INSS])

I. Confined to single organ
IIA. Localized tumor with incomplete gross resection; lymph nodes negative
IIB. Localized tumor with incomplete gross resection; ipsilateral lymph nodes positive
III. Extension across midline, with or without lymph node involvement
IV. Distant metastases to lymph nodes, bone, bone marrow, liver, skin
IVs. Localized primary tumor with dissemination limited to skin, liver, or bone marrow; limited to infants

DIFFERENTIAL DIAGNOSIS

- Other small, round, blue-cell childhood tumors, such as lymphoma, rhabdomyosarcoma, soft tissue sarcoma, and primitive neuroectodermal tumors (PNETs)
- Wilms' tumor. Table N1-7 describes features distinguishing between Wilms' tumor and neuroblastoma.
- Hepatoblastoma. Opsoclonus myoclonus may occur with other tumors such as hepatoblastoma, infections (e.g., Coxsackie virus, Lyme disease, rickettsia, HIV), ingestions (phenytoin,

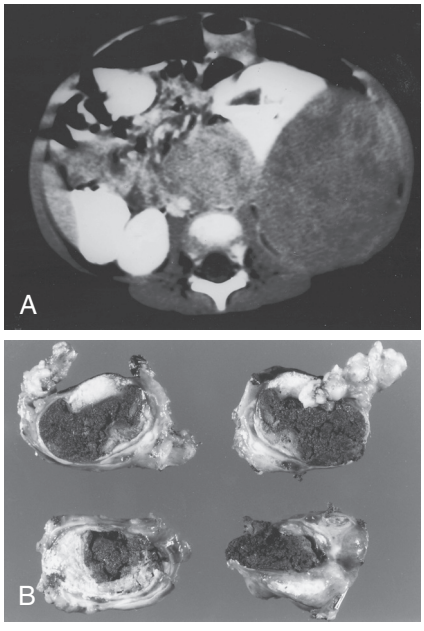


FIGURE N1-7 Computed tomographic scan **(A)** shows adrenal neuroblastoma at diagnosis. Serial sections through adrenal neuroblastoma **(B)** show tumor with large areas of diffuse hemorrhage and calcification. (From Abeloff MD [ed]: *Clinical oncology,* ed 3, Philadelphia, 2004, Saunders.)

amitriptyline, diazepam), toxic exposures, and metabolic derangements (biotin-responsive multiple carboxylase deficiency).

Rx TREATMENT

- Assure patient and family that there is hope for recovery with aggressive treatment.
- Overall, treatment will be determined by several factors, including age at diagnosis, stage of disease, site of primary tumor and metastases, tumor histology, and quantitative DNA content of the tumor.
- Surgery: particularly for low-risk tumors.
- Radiation therapy may be tried for unresectable tumors or tumors that are not responsive to chemotherapy.
- Multiagent chemotherapy is mainstay of treatment (e.g., cisplatinum, etoposide, Adriamycin, cyclophosphamide, carboplatin).
- Autologous bone marrow transplantation following aggressive chemotherapy for stage IV disease or patients who are at highest risk based on presence of disseminated disease or unfavorable markers such as *N-MYC* amplification.
- Novel therapies include immunotherapy using monoclonal antibodies and vaccines that attempt to initiate an immune reaction against the disease and targeting of tumor cells with drugs that induce apoptosis or have antiangiogenic effect. Immunotherapy with ch14.18, a monoclonal antibody against the tumor-associated disialoganglioside GD2, has activity against neuroblastoma. Recent trials have shown that immunotherapy with ch14.18, GM-CSF, and interleukin-2 is associated with a significantly improved outcome as compared with standard therapy in patients with high-risk neuroblastoma. Treatment with MIBG in conjunction with autologous peripheral blood stem cell rescue.
- Adrenocorticotropic hormone (ACTH) treatment is thought to be effective for patients with opsoclonus/myoclonus syndrome.

DISPOSITION

- Overall survival is >40%. Children under the age of 1 yr have a cure rate as high as 90%.
- Approximately 70% of patients with neuroblastoma have metastases at diagnoses.
- Prognosis is related to age at time of diagnosis, clinical stage, and regional lymph node involvement. Children with localized disease and infants <1 year at diagnosis and favorable disease characteristics have better prognosis whereas poorer prognosis is noted in older children with stage IV disease (20% survival compared with >95% in stage I), age >1 year at diagnosis, increased number of *N-MYC* copies, adrenal tumor, and chronic 1p deletion.
- Children treated for neuroblastoma may be at risk for second malignancies, including renal cell carcinoma.

REFERRAL

Multidisciplinary oncology team with experience in treating cancers of childhood and adolescence.

TABLE N1-7 Features Distinguishing Between Wilms' Tumor and Neuroblastoma

Feature	Wilms' Tumor	Neuroblastoma
Age	2-3 years	<2 years
Origin	Kidney	Retroperitoneal neural crest
Renal mass effect	Intrinsic mass effect	External compression
Laterality	10% bilateral	Almost always
Calcification	<15%	85%-95%
Vessel involvement	Renal vein invasion in 5%-10%	Frequent encasement

From Weissleder R et al: *Primer of diagnostic imaging,* ed 5, St Louis, 2011, Mosby.

PEARLS & CONSIDERATIONS

- Neuroblastoma is predominantly a tumor of early childhood that originates in the sites where the sympathetic nervous system tissue is present.
- Symptoms occur due to tumor mass or bone pain from metastases.
- Children can present with classic paraneoplastic neurologic symptoms, including cerebellar ataxia and opsoclonus myoclonus.
- Recent trials have shown a very high rate of survival among patients with intermediate-risk neuroblastoma with biologically based treatment assignment involving a substantially reduced duration of chemotherapy and reduced doses of chemotherapeutic agents as compared with regimens used in earlier trials. These data provide support for further reduction in chemotherapy with more refined risk stratifications.
- Despite recent advances, 50% to 60% of patients with high-risk neuroblastoma have a relapse and currently there are no salvage treatment regimens known to be curative.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Neuroblastoma (Patient Information)

AUTHOR: **NICOLE J. ULLRICH, M.D., PH.D.**

SUGGESTED READINGS

Baker DL et al.: Outcome after reduced chemotherapy for intermediate-risk neuroblastoma, *N Engl J Med* 363:1313–1323, 2010.

Cheung NK et al.: Association of age at diagnosis and genetic mutations in patients with neuroblastoma, *JAMA* 307(10):1062–1071, 2012.

Cohn SL et al.: The International Neuroblastoma Risk Group (INRG) classification system: an INRG Task Force report, *J Clin Oncol* 27:289–297, 2009.

Maris JM: The biologic basis for neuroblastoma heterogeneity and risk stratification, *Curr Opin Pediatr* 17(1):7–13, 2005.

Maris JM: Recent advances in neuroblastoma, *N Engl J Med* 362:2202–2211, 2010.

Pranzatelli MR et al.: Screening for autoantibodies in children with opsoclonus-myoclonus-ataxia, *Pediatr Neurol 27* 384, 2002.

Riley RD et al.: A systematic review of molecular and biological tumor markers in neuroblastoma, *Clin Cancer Res* 10(1 Pt 1):4–12, 2004.

Roberts SS et al.: GABAergic system gene expression predicts clinical outcome in patients with neuroblastoma, *J Clin Oncol* 22(20):4127–4134, 2004.

Rudnick E et al.: Opsoclonus-myoclonus-ataxia syndrome in neuroblastoma: clinical outcome and antineuronal antibodies—a report from the Children's Cancer Group Study, *Med Pediatr Oncol* 36(6):612–622, 2001.

Schilling FH et al.: Neuroblastoma screening at one year of age, *N Engl J Med* 346:1047, 2002.

Shimada H: International neuroblastoma pathology classification for prognostic evaluation of patients with peripheral neuroblastic tumors: a report from the Children's Cancer Group, *Cancer* 92:2451, 2001.

Woods WG et al.: Screening of infants and mortality due to neuroblastoma, *N Engl J Med* 346:1041, 2002.

Yu AL et al.: Anti-GD2 antibody with GM-CSF, interleukin-2 and isotretinoin for neuroblastoma, *N Engl J Med* 363:1324–1334, 2010.

BASIC INFORMATION

DEFINITION

Neurofibromatosis (NF) is an autosomal-dominant disorder affecting bone, the nervous system, soft tissue, and skin. There are three major subtypes of NF disorders: NF type 1 (NF1), NF type 2 (NF2), and schwannomatosis. Schwannomatosis has only recently been recognized as a distinct disorder; currently very little is known about it.

SYNONYMS

NF1: von Recklinghausen disease, peripheral NF
NF2: bilateral acoustic neurofibromatosis, central NF

ICD-9CM CODES
237.70 Neurofibromatosis, unspecified
237.71 Type 1, von Recklinghausen's
237.72 Type 2, acoustic
ICD-10CM CODES
Q85.00 Neurofibromatosis, unspecified
Q85.01 Neurofibromatosis, type 1
Q85.02 Neurofibromatosis, type 2

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence of NF1 (one case/3000 live births), NF2 (one case/25,000 live births).
- Prevalence of NF1 (one case/5000 persons), NF2 (one case/210,000 persons).
- NF1 and NF2 are autosomal dominant; approximately 50% of cases have no family history.
- The two disorders affect approximately 100,000 people in the United States.
- Affects males and females equally.
- NF1 may be associated with optic gliomas, astrocytomas, spinal neurofibromas, pheochromocytomas, and chronic myeloid leukemia.
- NF2 may be associated with meningiomas, spinal schwannomas, and cataracts.
- For schwannomatosis, the incidence is one per 30,000 persons, and the disease is mostly sporadic in nature.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Common features of NF1 include:
  1. Café-au-lait macules (100% of children by age 2 yr).
     a. Hyperpigmented skin lesions (Fig. N1-8) occurring anywhere on the body except the face, palms, and soles.
     b. Appear early in life and increase in size and number during puberty.
     c. Are focal or diffuse.
  2. Axillary and inguinal freckling (70%).
  3. Multiple neurofibromas (Figs. N1-9 and N1-10) can be soft or firm; three subtypes:
     a. Cutaneous: circumscribed, not specific for NF1.
     b. Subcutaneous: circumscribed, not specific for NF1.
     c. Plexiform: noncircumscribed, thick and irregular; can cause disfigurement of supportive structures and specific for NF1.
  4. Lisch nodule (small hamartoma of the iris) found in >90% of adult cases.
  5. Visual defects possibly related to optic gliomas (2% to 5%).
  6. Neurodevelopment problems such as learning disability and mental retardation (30% to 40%).
  7. Skeletal disorders, including long bone dysplasia, pseudoarthrosis, scoliosis, short stature, and decreased bone mineral density.
- Common features of NF2 include:
  1. Hearing loss and tinnitus related to bilateral acoustic neuromas (>90% of adults).
  2. Cataracts (81%).
  3. Headache.
  4. Unsteady gait.
  5. Cutaneous and subcutaneous neurofibromas but fewer than in NF1.
  6. Café-au-lait macules (1%).
- Common features of schwannomatosis include painful multiple schwannomas of the spinal, peripheral, or cranial nerves *except* the vestibular nerve.

ETIOLOGY

- NF1 is caused by DNA mutations located on the long arm of chromosome 17 responsible for encoding the protein neurofibromin.
- NF2 is caused by DNA mutations located in the middle of the long arm of chromosome 22 responsible for encoding the protein merlin, which is a potent inhibitor of glioma growth.
- Both proteins are speculated to act as tumor suppressors.
- The etiology of schwannomatosis remains unclear; however, biallelic NF2 mutations are found in the schwannomas but nowhere else, suggesting that they are secondary mutations.

DIAGNOSIS

- NF1 is diagnosed if the person has two or more of the following features:
  1. Six or more café-au-lait macules >5 mm in prepubertal patients and >15 mm in postpubertal patients.
  2. Two or more neurofibromas of any type or one plexiform neurofibroma.
  3. Axillary or inguinal freckling.
  4. Optic glioma.
  5. Two or more Lisch nodules (iris hamartomas).
  6. Sphenoid wing dysplasia or cortical thinning of long bones, with or without pseudoarthrosis.
  7. A first-degree relative (parent, sibling, or child) with NF1 based on the previous criteria.
- NF2 is diagnosed if the person has either of the following two criteria:
  1. Bilateral eighth nerve masses seen by appropriate imaging studies (e.g., CT, MRI).
  2. A first-degree relative with NF2 and either a unilateral eighth nerve mass or two of the following: neurofibroma, meningioma, glioma, schwannoma, or juvenile posterior subcapsular lenticular opacity.
- Schwannomatosis is diagnosed in an individual >30 yr having either of the following two criteria:
  1. Two nonintradermal schwannomas, no vestibular tumor found on MRI scan, no NF2 mutation.
  2. One nonvestibular schwannoma and a first-degree relative fitting the above criteria.

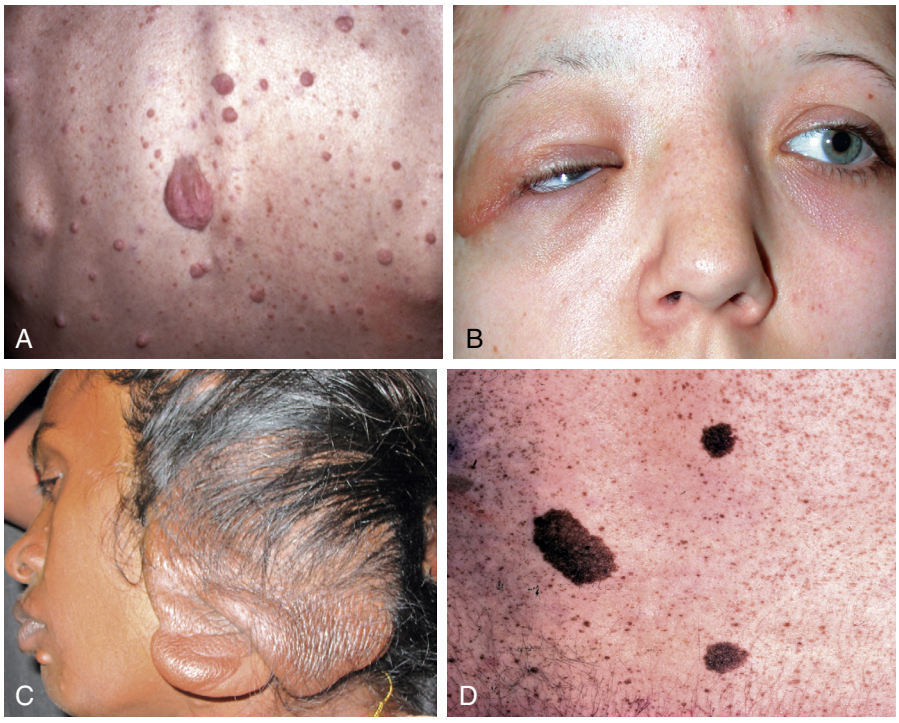


FIGURE N1-8 Systemic features of NF1. A, Discrete neurofibromas. **B,** Nodular plexiform neurofibroma of the eyelid. **C,** Elephantiasis nervosa. **D,** Cafe-au-lait spots. (**C** courtesy S. Kumar Puri.; From Kanski JJ.; Bowling B. *Clinical ophthalmology, a systematic approach.* ed 7, Philadelphia, 2010, Saunders.)

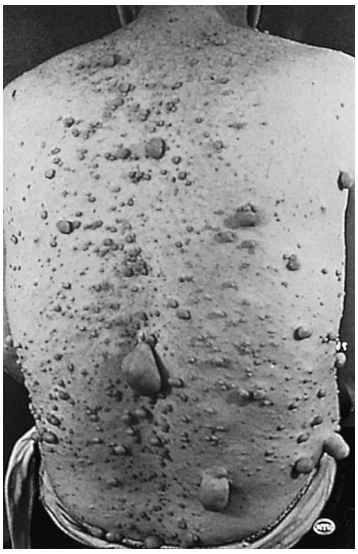


FIGURE N1-9 Nodules. Solid, large (>1 cm), deep-seated mass in dermal or subcutaneous tissues. These nodules are neurofibromas in a patient with neurofibromatosis. (From Goldman L.; Ausiello D. [eds]: *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, Saunders.)

FIGURE N1-10 Type 1 neurofibromatosis: widespread cutaneous neurofibromata are a prominent feature of the classical variant. (Courtesy of R.A. Marsde.; M.D. St George's Hospital, London. From McKee PH, Calonje E, Granter SR [eds]: *Pathology of the skin with clinical correlations,* ed 3, St Louis, 2005, Mosby.)

DIFFERENTIAL DIAGNOSIS

- Abdominal NF.
- Myxoid lipoma.
- Nodular fasciitis.
- Fibrous histiocytoma.
- Segmental NF.

WORKUP

The diagnosis of NF is usually self-evident. Workup is dictated by clinical symptoms in NF1 and usually includes MRI evaluation of the head and spine in NF2 and schwannomatosis. In fact, if NF2 is suspected but no vestibular nerve schwannomas are found, the diagnosis points to schwannomatosis.

LABORATORY TESTS

- Genetic testing is possible in individuals who desire prenatal diagnosis for NF1. There is no single standard test and multiple tests are required. Results can only tell if an individual is affected but cannot predict the severity of the disease due to variable expression.
- In NF2, linkage analysis testing provides a >99% certainty the individual has NF2.

IMAGING STUDIES

- MRI with gadolinium is the imaging study of choice in both NF1 and NF2 patients. MRI increases detection of optic gliomas, tumors of the spine, acoustic neuromas, and "bright spots" believed to represent hamartomas.
- MRI of the spine is recommended in all patients diagnosed with NF2 to exclude intramedullary tumors.

OTHER TESTS

- Wood lamp examination may be useful in patients with very pale skin for visualizing café-au-lait spots.
- Slit-lamp examination is recommended for children >6 yr to confirm the presence of Lisch nodules and subcapsular opacity.

Rx TREATMENT

Treatment is directed primarily at symptoms and complications of NF1 and NF2. As for schwannomatosis, resection should be reserved for tumors that are symptomatic or threaten to cause spinal cord compression.

NONPHARMACOLOGIC THERAPY

- Counseling addressing prognosis and genetic, psychological, and social issues.
- Hearing testing and speech pathology evaluation.

ACUTE GENERAL Rx

- Surgery is usually not done on skin tumors unless cosmetically requested or if suspicion of malignant transformation exists.
- Surgery may be indicated for spinal or cranial neurofibromas, gliomas, or meningiomas.
- Acoustic neuromas can be treated by surgical excision.

CHRONIC Rx

- Radiation may be indicated in optic nerve gliomas and patients whose central nervous system tumors show radiographic progression.
- Stereotactic radiosurgery with a gamma knife may be an alternative approach to surgery for acoustic neuromas.

DISPOSITION

- Prognosis varies according to the severity of involvement.
- There is no cure for NF.

REFERRAL

A multidisciplinary team of consultants is needed in patients with NF, including neurosurgeon, otolaryngologist, dermatologist, neurologist, audiologist, speech pathologist, geneticist, and neuropsychologist.

PEARLS & CONSIDERATIONS

- Friedrich Daniel von Recklinghausen first reported his cases in 1882, although there had been similar accounts dating back to the 1600s.
- A high SPRED1 mutation detection rate has been identified in NF1 mutation-negative families with an autosomal dominant phenotype of CALMs with or without freckling and no other NF1 features.

COMMENTS

For additional information and patient resources, refer to the National Neurofibromatosis Foundation (www.nf.org) or Neurofibromatosis Inc. (www.nfinc.org).

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Neurofibromatosis Type 1 (Patient Information)

AUTHOR: **MARK F. BRADY, M.D., M.P.H., M.M.S.**

SUGGESTED READINGS

Asthagiri et al.: Neurofibromatosis type 2, *Lancet* 373(9679):1974, 2009.

Hersh JH: Health supervision for children with neurofibromatosis, *Pediatrics* 121:633–642, 2008.

Messiaen L et al.: Clinical and mutational spectrum of neurofibromatosis type 1-like syndrome, *JAMA* 302(19):2111–2118, 2009.

Shah KN: The diagnostic and clinical significance of café-au-lait macules, *Pediatr Clin North Am* 57(5):1131–1153, 2010.

Williams VC et al.: Neurofibromatosis type 1 revisited, *Pediatrics* 123(1):124, 2009.

BASIC INFORMATION

DEFINITION

Neuroleptic malignant syndrome (NMS) is a disorder characterized by hyperthermia, muscular rigidity, autonomic dysfunction, and depressed/fluctuating levels of arousal that evolve over 24 to 72 hr. This occurs as an idiosyncratic adverse reaction to medications that affect the central dopaminergic system, usually D2 receptors blockade.

SYNONYMS

NMS

ICD-9CM CODES
333.92 Neuroleptic malignant syndrome
ICD-10CM CODES
G21.0 Malignant neuroleptic syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 0.07% to 0.15% annual incidence in psychiatric population.
PREDOMINANT SEX: More than two thirds of patients are male.
PREDOMINANT AGE: Young and middle-aged adults
PREDISPOSING FACTORS:
- History of intake of dopamine antagonists e.g., antipsychotics

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Syndrome typically begins abruptly while the patient is taking therapeutic (not toxic) dosages of neuroleptics and reaches maximum severity within 72 hr.
- Severe muscle rigidity (hypertonia, cogwheeling, or "lead pipe" rigidity)
- Hyperthermia (38.6° to 42.3° C, usually <40° C)
- Autonomic symptoms: diaphoresis, dysphagia, sialorrhea, skin pallor, urinary incontinence
- Tachycardia, tachypnea
- Labile blood pressure (hypertension or postural hypotension)
- Agitation, catatonia, fluctuating consciousness, obtundation

ETIOLOGY

- Exact etiology is unknown, but it has been suggested that sudden and marked dopamine receptor blockade in nigrostriatal, hypothalamic, mesolimbic, and mesocortical pathways leads to clinical manifestations seen in NMS.
- Neuroleptic drugs have different potencies for inducing NMS:
  1. Typical neuroleptics: high potency, haloperidol; medium potency, chlorpromazine, fluphenazine; low potency, levomepromazine, loxapine
  2. Atypical neuroleptics: low potency, risperidone, olanzapine, clozapine, quetiapine

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Heatstroke, drug-induced states and overdose (Ecstasy abuse, phencyclidine), thyrotoxicosis, pheochromocytoma, serotonin syndrome
- Malignant hyperthermia, catatonia, acute psychosis with agitation
- CNS or systemic infections, including sepsis

WORKUP

Careful drug history

LABORATORY TESTS

- Elevated creatine phosphokinase (CPK) (sensitivity 0.71)
- Urinary myoglobin
- Leukocytosis, usually 10,000 to 40,000/mm^3
- Electrolytes and renal function
- Blood gases
- Drug levels

TREATMENT

NONPHARMACOLOGIC THERAPY

- Stop all neuroleptic drugs and reinstitute any recently discontinued dopaminergic agonists.
- Respiratory support; nutritional support in cases with dysphagia or comatose.
- Careful fluid balance monitoring with adequate hydration (intravenous in severe cases).
- Active cooling (cooling blanket and antipyretics).
- Skilled nursing care is necessary to prevent decubitus ulcers in bed-confined patients.

ACUTE GENERAL Rx

- Bromocriptine, a dopamine receptor agonist, is the mainstay of therapy for patients with NMS. Initial doses of 2.5 to 10 mg are given IV q8h and are increased by 5 mg/day until clinical improvement is seen. The drug should be continued for at least 10 days after the syndrome has been controlled and then tapered slowly.
- Dantrolene therapy can inhibit the excessive muscle contractions that generate myoglobinemia. Initially, patients can be given 0.25 mg/kg IV q6-12h, followed by a maintenance dose up to 3 mg/kg/day. After 2 to 3 days, patients may be given the drug orally (25 to 600 mg/day in divided doses). Oral dantrolene therapy (50 to 600 mg/day) may be continued for several days afterward.
- Amantadine, an NMDA receptor antagonist with possible dopaminergic properties, administered orally at doses of 100 to 200 mg PO bid, has also been shown to reduce mortality in comparison to supportive therapy alone.
- IV benzodiazepines (e.g., diazepam 2 to 10 mg, with total daily dose of 10 to 60 mg) to relax muscles and control agitation.
- Electroconvulsive therapy with neuromuscular blockage in pharmacologically refractory cases. Succinylcholine should not be used because it may cause hyperkalemia and cardiac arrhythmias in patients with rhabdomyolysis or dysautonomia.

CHRONIC Rx

- Respiratory care, nutritional support, and physical therapy may be required in more severe cases.
- Appropriate therapy would be required in patients with persistent neuropsychiatric sequelae of NMS (e.g., antidepressants for depression, cognitive behavioral therapy for cognitive deficits, rehabilitation for contractures).

DISPOSITION

- Mortality rate is currently 5% to 10% despite therapeutic measures. Serious sequelae may occur in a further 20%. Complete recovery occurs in >70% of patients. Causes of death include cardiac arrhythmias, myocardial infarction, renal failure secondary to rhabdomyolysis, seizures, pulmonary edema, and bronchopneumonia.
- Factors adversely affecting mortality are development of renal failure and core temperature >104° F (40° C).
- Late neuropsychiatric sequelae.
- Monitor closely for future complications of pharmacologic therapy.

REFERRAL

If the patient's condition is critical, it is preferable to treat the patient in a medical/neurologic ICU.

PEARLS & CONSIDERATIONS

COMMENTS

- Early detection and diagnosis lead to a more favorable outcome. Refer to recent consensus diagnostic criteria as a guide. Treatment is a medical emergency.
- Sudden withdrawal from dopaminergic agents (such as those used in Parkinson's disease) may lead to "levodopa withdrawal syndrome" that presents with similar clinical manifestations.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **FARIHA ZAHEER, M.D.**

SUGGESTED READINGS

Adityanjee, Sajatovic M, Munshi KR: Neuropsychiatric sequelae of neuroleptic malignant syndrome, *Clin Neuropharmacol* 28:197–204, 2005.

Chandran GJ et al.: Neuroleptic malignant syndrome: case report and discussion, *CMAJ* 169:439, 2003.

Gurrera RJ et al.: An international consensus study of neuroleptic malignant syndrome diagnostic criteria using the Delphi method, *J Clin Psychiatry* 72:1222–1228, 2011.

Kipps CM et al.: Movement disorder emergencies, *Mov Disord* 20:322–334, 2005.

Sueman VL: Clinical management of neuroleptic malignant syndrome, *Psychiatr Q* 72(4):825, 2001.

Ty EB, Rothner AD: Neuroleptic malignant syndrome in children and adolescents, *J Child Neurol* 16(3):157, 2001.

BASIC INFORMATION

DEFINITION

Neuropathic pain is not itself a disease, but rather a symptom that is associated with multiple different diseases. Thus it is not enough to define its presence without searching for a cause. It is defined as the sensation derived from the abnormal discharges of impaired or injured neural structures in either the peripheral or central nervous system. Descriptors include:

- Hyperesthesia: heightened sensitivity to nonpainful stimuli (e.g., light touch)
- Hyperalgesia: heightened sensitivity to painful stimuli (e.g., pinprick), or reduced threshold to feel pain
- Allodynia: pain provoked by a stimulus that is not normally painful

SYNONYMS

Neuralgia

ICD-9CM CODES

782.0 Numbness, paresthesias
729.1 Myositis/myalgia, not otherwise specified
729.2 Neuralgia, neuritis, or radiculitis, not otherwise specified

ICD-10CM CODES

G58.0 Intercostal neuropathy
G58.7 Mononeuritis multiplex
G58.8 Other specified mononeuropathies
G58.9 Mononeuropathy, unspecified
G60.0 Hereditary sensory and motor neuropathy
G61.9 Inflammatory polyneuropathy, unspecified
G62.0 Drug-induced polyneuropathy
G62.1 Alcoholic polyneuropathy
G62.9 Polyneuropathy, unspecified
G63.2 Diabetic polyneuropathy
G63.5 Polyneuropathy in systemic connective tissue disease
G63.8 Polyneuropathy in other diseases classified elsewhere

EPIDEMIOLOGY & DEMOGRAPHICS

- Estimates of the prevalence of neuropathic pain in the general population range from 1.6% to 8.2%.
- Demographics vary widely depending on etiology, for example:
  1. Postherpetic neuralgia: affects elderly, pain seen in almost 100% of cases
  2. AIDS: 30% of patients affected
  3. Diabetes mellitus: 20% to 24% affected (prevalence rates vary, increasing with longer disease duration)
  4. Fabry disease: affects mostly children, pain in 81% to 90% of patients

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- History: localize the disease with questions
  1. Quality (description) of neuropathic pain: burning, hot or cold, "icy hot," "pins and needles," stinging, lancinating, sharp, shooting
  2. Distribution of symptoms may aid in localization (i.e., "stocking-glove" symptoms in generalized neuropathy, numbness in a peripheral nerve territory in focal neuropathy)
  3. Generalized small fiber neuropathy: dysesthesias without numbness common, but many etiologies (e.g., diabetes) cause both small and large fiber dysfunction
  4. Large fiber neuropathy (LFPN): coexisting numbness, hyporeflexia, or weakness may be seen, usually worse distally
  5. Nerve root: coexisting neck or low back pain that radiates along a specific dermatome; most common cause is structural compression
  6. Spinal cord symptoms: coexisting spasticity, bowel or bladder involvement, sensory level
  7. Prior history of thalamic stroke in central thalamic pain syndrome (Dejerine-Roussy syndrome)
  8. Family history may suggest a genetic cause
- Examination: see Table N1-8. Table N1-9 describes joint involvement in neuropathic arthropathy. Fig. N1-11 illustrates a diagnostic approach to neuropathic pain. Fig. N1-12 shows a neuropathic ankle.

ETIOLOGY & LABORATORY EVALUATION (Table N1-10)

- Metabolic: diabetes mellitus; malnutrition and alcoholism; vitamin B_{12} deficiency; thiamine deficiency; porphyria; Fabry's disease
- Inflammatory: immune vasculitides (lupus, Sjögren's syndrome, polyarteritis nodosa, etc.), acute inflammatory demyelinating polyneuropathy (classically presents with ascending weakness and numbness, although pain is also a common feature), chronic inflammatory demyelinating polyneuropathy, sarcoid, multiple sclerosis
- Infiltrative: amyloidosis, paraproteinemias (e.g., monoclonal gammopathy of uncertain significance [MGUS])
- Infectious: postviral (brachial neuritis), HIV/AIDS, HSV, varicella-zoster virus (VZV; postherpetic neuralgia), Lyme disease, leprosy (thickened nerves and skin lesions), syphilis
- Neoplastic and paraneoplastic-carcinomatous infiltration of nerve/nerve root, anti-Hu
- Drugs/toxins: history of exposure to alcohol, chemotherapeutic agents (paclitaxel, vincristine), isoniazid, metronidazole, or heavy metals (thallium, arsenic)

DIAGNOSIS

LABORATORY TESTS

- Fasting blood glucose (FBG)
- 2-hour oral glucose tolerance test (OGTT)
- Vitamin B_1 level
- If B_{12} level normal: serum methylmalonic acid and homocysteine levels
- Serum erythrocyte sedimentation rate (ESR), ANA, SS-A and SS-B, c-ANCA, p-ANCA
- RPR or FTA-ABS
- Serum ACE level (sarcoid)

TABLE N1-8 Examination

Exam Finding	Localization
Pinprick/temperature loss alone	Small fibers only
Pinprick/temperature loss + vibratory/proprioceptive loss	Small and large fibers
Sensory loss and motor dysfunction worse distally than proximal	Large fiber neuropathy
Sensory loss and motor dysfunction along single nerve distribution	Single nerve
Sensory loss and motor dysfunction along multiple single nerves	Multiple mononeuropathies (i.e., mononeuropathy multiplex)
Motor and sensory loss involving multiple nerves belonging to specific region of brachial or lumbar plexus	Plexopathy
Sensory loss along dermatome with multiple myotomal muscles affected	Nerve root lesion
Asymmetric sensory loss without weakness and pseudoathetosis	Dorsal root ganglion
Vibratory/proprioceptive loss without pinprick/temperature loss	Dorsal column dysfunction (from compressive lesion, B_{12} deficiency, or tabes dorsalis from neurosyphilis)
Sensory level with weakness below the level of lesion and long tract signs (spasticity/Babinski's sign)	Spinal cord lesion
Hemisensory hyperalgesia	Contralateral thalamus

TABLE N1-9 Joint Involvement in Neuropathic Arthropathy

Disease	Site of Involvement
Diabetes mellitus	Midtarsal, metatarsophalangeal, tarsometatarsal
Syringomyelia	Shoulder, elbow, wrist
Amyloidosis	Knee, ankle
Congenital sensory neuropathy	Knee, ankle, intertarsal, metatarsophalangeal
Tabes dorsalis	Knee, hip, ankle
Leprosy	Tarsal, tarsometatarsal

From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

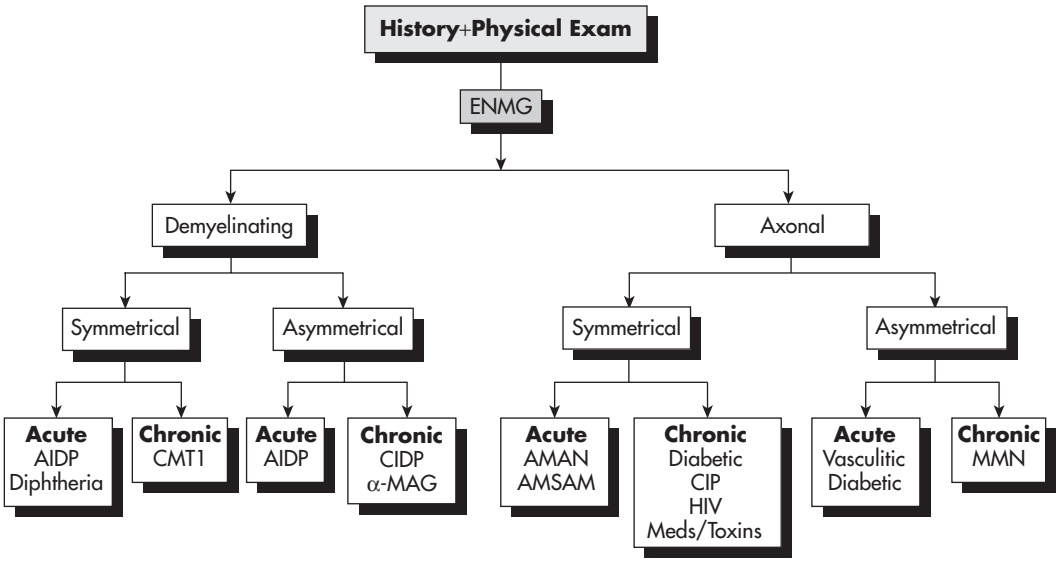


FIGURE N1-11 A systematic approach to evaluate neuropathy. The diseases listed are examples of neuropathies associated with specific neurophysiologic and clinical findings. Diabetic distal, predominantly sensory neuropathies are manifested as chronic axonal neuropathies; acute asymmetric neuropathies can also occur with diabetes. Most neuropathies caused by toxins or by side effects of medication are chronic, symmetric axonal neuropathies. AIDP, AMAN, and AMSAN are subtypes of Guillain-Barré syndrome. These and other examples are discussed in more detail in the text. *AIDP,* Acute inflammatory demyelinating polyradiculoneuropathy; *AMAN*, acute motor axonal neuropathy; *AMSAN*, acute motor and sensory axonal neuropathy; *CIDP*, chronic inflammatory polyradiculoneuropathy; *CIP*, chronic illness polyneuropathy; *CMT1*, Charcot-Marie-Tooth disease type 1, a genetic disorder; *ENMG*, electroneuromyography; *HIV*, human immunodeficiency virus–related neuropathy; *α-MAG*, anti-myelin-associated glycoprotein; *MMN*, multifocal motor neuropathy. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

FIGURE N1-12 Neuropathic ankle. Marked instability of the subtalar and midtarsal joints is seen with collapse on weight bearing. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

- HIV antibody
- SPEP, UPEP, immunofixation
- Urine and stool protoporphyrins, if porphyria is suspected clinically
- Hu antibody: can be seen in both small cell and non–small cell lung cancers, may be positive without evidence of lung cancer
- Lumbar puncture: protein elevation, oligoclonal bands, CSF/serum IgG index, herpes simplex virus (HSV), VZV, Lyme polymerase chain reaction (PCR), VDRL

ELECTROPHYSIOLOGY STUDIES

- Electrophysiologic testing (electromyography with nerve conduction studies): may be normal in small fiber neuropathies or CNS lesion, but is often abnormal in large fiber neuropathies
- Quantitative sensory testing: abnormal in small and large fiber neuropathy
- Evoked potentials (only if suspicion for spinal cord lesion)

PATHOLOGY STUDIES

- Nerve biopsy is occasionally useful in selected cases, particularly when vasculitis, sarcoid, or amyloid neuropathy are in the differential.
- Skin biopsy for intraepidermal nerve fiber (IENF) density may be useful for small fiber neuropathy when other studies are normal.
- Rectal or abdominal fat pad biopsy may show amyloid deposition in systemic amyloidosis.

IMAGING STUDIES

- MRI (with and without contrast):
  1. Of the brain to exclude thalamic pathology if symptoms and signs are consistent with thalamic lesion
  2. Of the spinal cord and nerve roots to exclude structural, inflammatory, neoplastic, or infectious causes
  3. Of the lumbar spine to evaluate for arachnoiditis
- If MRI cannot be performed, consider:
  1. CT of the brain for thalamic pathology
  2. CT myelography of the spinal cord to evaluate for structural/neoplastic disease, but only if clinical signs of spinal or nerve root compromise are present

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Counseling should be initiated at the beginning of therapy to address psychologic issues exacerbating physiologic pain
- Physical therapy: especially in cases of chronic neck and low back pain

ACUTE GENERAL Rx

- Antidepressants:
  1. Tricyclic antidepressants (TCAs): nortriptyline preferred over amitriptyline (fewer anticholinergic side effects with nortriptyline). Begin 25 mg PO qd in adults, or 10 mg qd in elderly. Increase dose by 25 mg every week as tolerated until usual maximal effective dose of 150 mg/day.
  2. Paroxetine: begin 10 mg PO qd, increase by 10 mg/wk to a max dose of 60 mg qd.
  3. Duloxetine: begin 30 mg daily, increase to 60 to 120 mg daily. Duloxetine is effective in diabetic neuropathy, post-herpetic neuropathy, and chemotherapy-induced painful peripheral neuropathy.
- Antiepileptics:
  1. Gabapentin: begin 300 mg PO qd, advance to 300 mg PO tid by the end of the first week. Effective dose: higher than 1600 mg/day. Max dose: 1500 mg PO tid.
  2. Carbamazepine: for trigeminal neuralgia. Begin 400 mg PO bid, increase to tid if necessary. Side effects and drug levels help to determine optimal dosing. Risk of aplastic anemia and hyponatremia (monitor CBC and chemistries).
  3. Oxcarbazepine: better tolerated than carbamazepine. Start 150 mg PO bid and gradually increase to a maximal dose of 600 mg bid.
  4. Lamotrigine: begin 25 mg PO bid, increase slowly (by 100 mg biweekly) until maximum effective dose of 200 to 300 mg PO bid. Risk: Stevens-Johnson syndrome.

TABLE N1-10 Clinical Presentation and Laboratory Findings

Neuropathy Type	Predisposition	Examination Findings	EMG/NCS	Laboratory Analysis
Idiopathic small fiber PN	Age >50	Strength: normal Reflexes: normal Pos/vib: normal Pain/temp: decreased distally	Normal	Serum studies: normal Skin biopsy: abnormal Sudomotor studies: abnormal
Diabetic PN	Longstanding disease Family history	Strength normal to reduced, sensation reduced distally	Abnormal	Abnormal glucose tolerance High fasting glucose
Inherited PN	Family history	Pes cavus, hammer toes, reduced reflexes, sensation reduced distally	Abnormal	Genetic studies may be abnormal, other studies normal
Familial amyloid PN	Family history	Pain/temp loss Reduced reflexes Orthostasis	Abnormal if large fibers affected; also carpal tunnel syndrome	Transthyretin genetic study
Acquired amyloid PN	Monoclonal gammopathy	Pain/temp loss Reduced reflexes Orthostasis	Abnormal if large fibers affected; also carpal tunnel syndrome	SPEP, UPEP, immunofixation abnormal
Fabry's disease	Age Renal failure Strokes	Normal; possible reduced pain/temp sensation	Normal	α-Galactosidase levels in cultured fibroblasts
PN + mixed connective tissue disease	History of lupus, rheumatoid arthritis, Sjögren's syndrome	Reduced reflexes and distal sensation	Abnormal	ANA, RF, SS-A/SS-B may be abnormal
Peripheral nerve vasculitis	Asymmetric disease	Multiple peripheral nerves involved	Abnormal	ANA, RF, SS-A/SS-B, ANCA, cryoglobulins may be abnormal
Paraneoplastic neuropathy	Lung cancer risk factors, chemical exposures	Asymmetric sensory loss, pseudoathetosis, relatively preserved strength	Abnormal	Anti-Hu
Sarcoidosis	Pulmonary sarcoid	Multiple mononeuropathies	Abnormal	Abnormal biopsy, elevated serum ACE, CXR abnormal
Arsenic	Pesticides, copper smelting	Reduced reflexes and distal sensation	Abnormal	Elevated arsenic in plasma, urine, and hair
HIV	Promiscuity, unprotected sex, IV drug abuse, blood transfusion	Variable, but most often reduced reflexes and distal sensation	Abnormal if large fibers involved	HIV antibody

ACE, Angiotensin-converting enzyme; *ANA,* antibody to nuclear antigens; *ANCA,* antineutrophil cytoplasmic antibodies; *CXR,* chest x-ray; *EMG,* electromyography; *HbA1C,* glycosylated hemoglobin; *HIV,* human immunodeficiency virus; *IV,* intravenous; *NCS,* nerve conduction studies; *PN,* polyneuropathy; *Pos,* position sensation; *RF,* rheumatoid factor; *SPEP,* serum protein electrophoresis; *SS-A,* Sjögren syndrome A; *SS-B,* Sjögren syndrome B; *Temp,* temperature sensation; *UPEP,* urine protein electrophoresis; *Vib,* vibration sensation.
Adapted from Mendell JR, Sahenk Z: Painful sensory neuropathy, *N Engl J Med* 348(13):1243, 2003.

5. Pregabalin: begin 50 mg PO tid, increase slowly to 100 to 200 mg PO tid.

- Analgesics:
  1. Tramadol: 150 mg/day (50 mg tid), increase by 50 mg/wk, max 200 to 400 mg/day.
  2. Morphine (oral): 15 to 30 mg q8h, max 90 to 360 mg/day.
  3. Oxycodone: 20 mg q12h, increase by 10 mg/wk, max 40 to 160 mg/day.
  4. Fentanyl patch: 25 to 100 mcg transdermally q3 days.
- Topical anesthetics:
  1. 5% lidocaine patch, apply to area of pain, max three patches every 12 hr.
  2. Capsaicin is inconsistent in its ability to relieve pain and may exacerbate it. Use not recommended.
- Procedural/surgical: this option is considered mostly when the patient suffers from pain secondary to spinal cord or cauda equina injury. Studies are limited and benefit is not completely established. Procedures should be considered only when all other therapeutic modalities have failed. In addition, the patient should be cautioned that surgical procedures may not result in pain relief and may be associated with significant morbidity and even mortality.
  1. Dorsal root rhizotomy
  2. Nerve blocks
  3. Spinal cord stimulator

DISPOSITION

Prognosis depends on multiple factors, including:

- Etiology of pain
- Treatment of any underlying condition
- Initiation of appropriate (often multiple) therapeutic modalities
- Patient compliance with prescribed regimen

Most care is accomplished in the outpatient setting, except when surgery is required.

REFERRAL

- Pain clinic
- Neurology
- Psychiatry
- Psychology
- Physiatry
- Anesthesiology (nerve blocks)
- Neurosurgery if considering surgical management

PEARLS & CONSIDERATIONS

- Factitious disorder and malingering frequently manifest with pain complaints. These are diagnoses of exclusion, and require negative evaluation for organic etiologies before diagnosis is made.
- Peripheral neuropathy in diabetics increases the risk of foot ulceration by sevenfold. Abnormal results in monofilament testing and vibratory perception (alone or in combination with the appearance of the feet, ulceration, and ankle reflexes) are the most helpful sign for the detection of LFPN.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **GAVIN BROWN, M.D.**

EVIDENCE

Abstract[1]

Study Design:
A prospective, randomized, controlled, and double-blind trial.

Objective:
To evaluate the effects of 2 different doses of perioperative pregabalin administration, twice on the day of surgery, on acute postoperative pain after spinal surgery.

Summary of Background Data:
Besides its well-established role on neuropathic pain, pregabalin seems to be a promising adjunct to multimodal analgesic regimen following surgery. No comprehensive data exist regarding the optimal dosage of pregabalin on reducing postoperative pain and opioid consumption in spinal surgery.

Methods:
Patients were randomly assigned to 1 of 3 groups. The placebo group (n=28) received placebo capsules 1 hour before the anesthetic induction and 12 hours after surgery. The pregabalin groups received pregabalin 75 mg (P75 group, n=28) or 150 mg (P150 group, n=28), respectively at the same points. Assessed variables were total amount of administered fentanyl-based intravenous patient-controlled analgesia, pain intensity, and the frequency of rescue analgesic administered during the first 48 hours after surgery, subdivided into the following 4 periods: on arrival of patient to the postanesthesia care unit, 1 to 6 hours, 6 to 24 hours, and 24 to 48 hours.

Results:
The amount of patient-controlled analgesia volume infused until 24 hours ($P = 0.025$) and 48 hours ($P = 0.028$) after surgery was significantly less in the P150 group compared with the control group. The frequency of additional anodynes administered until 6 hours ($P = 0.049$) and 24 hours ($P = 0.045$) after surgery was significantly less in the P150 group compared with the control group.

Conclusion:
Perioperative administration of pregabalin 150 mg before and 12 hours after surgery, but not 75 mg, significantly reduced opioid consumption and the use of additional pain rescue for 48 hours after surgery without significant side effects in patients undergoing spinal fusion surgery. Ⓐ

Abstract[2]

Despite concerted efforts from pharmacologic research into neuropathic pain, many patients fail to achieve sufficient pain relief with medication alone. For this reason, increasing interest centers on neurostimulation techniques. We assessed whether transcutaneous spinal direct current stimulation (tsDCS) modulates conduction in ascending nociceptive spinal pathways. We measured changes induced by anodal and cathodal tsDCS over the thoracic spinal cord on face- and foot-laser evoked potentials (LEPs) and foot-cold pressor test responses in 20 healthy subjects. Whereas anodal tsDCS reduced the amplitude of the N1 and N2 components of foot-LEPs ($P<0.05$) neither anodal nor cathodal tsDCS changed LEPs evoked by face stimulation. Pain tolerance to the cold pressor test was significantly higher after anodal than after cathodal tsDCS ($P<0.05$). Conversely, no difference was found in the pain threshold or pain ratings to the cold pressor test between the two polarity conditions.

Our data suggest that anodal tsDCS over the thoracic spinal cord might impair conduction in the ascending nociceptive spinal pathways, thus modulating LEPs and increasing pain tolerance in healthy subjects. Ⓐ

Evidence-Based References

Kim JC et al.: Effective dose of peri-operative oral pregabalin as an adjunct to multimodal analgesic regimen in lumbar spinal fusion surgery, *Spine* 36:428–433, 2011. Ⓐ

Truini A et al.: Transcutaneous spinal direct current stimulation inhibits nociceptive spinal pathway conduction and increases pain tolerance in humans, *J Pain* 15:1023–1027, 2011. Ⓐ

SUGGESTED READINGS

Kanji JN et al.: Does this patient with diabetes have large-fiber peripheral neuropathy? *JAMA* 303(15):1526–1532, 2010.

Mendell JR, Sahenk Z: Painful sensory neuropathy, *N Engl J Med* 348(13):1243, 2003.

Smith EM et al.: Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial, *JAMA* 309(13):1359–1367, 2013.

BASIC INFORMATION

DEFINITION

Nocardiosis is an infection caused by aerobic actinomycetes found in soil and characterized by lung, soft tissue, or central nervous system (CNS) involvement.

SYNONYMS

Mycetoma
Nocardia

ICD-9CM CODES
039 Actinomycotic infections
039.9 Nocardiosis NOS, of unspecified site
ICD-10CM CODES
A43.0 Pulmonary nocardiosis
A43.1 Cutaneous nocardiosis
A43.8 Other forms of nocardiosis
A43.9 Nocardiosis, unspecified
A42.9 Actinomycosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- *Nocardia* species are found worldwide in the soil.
- Nocardiosis is found most commonly in patients who are immunocompromised (e.g., those receiving steroids or immunosuppressive therapy; those with lymphoma, leukemia, or lung cancer; transplant recipients; and those with pulmonary infections).
- Other underlying conditions associated with nocardiosis are pemphigus vulgaris, Whipple's disease, Goodpasture's syndrome, Cushing's disease, cirrhosis, ulcerative colitis, and rheumatoid arthritis.
- Use of steroids is an independent risk factor for developing nocardiosis.
- Between 500 and 1000 new cases are diagnosed each year in the United States. Approximately 2% of patients with AIDS develop nocardiosis.
- Occurs more commonly in men than in women (2:1).
- Adults are affected more often than children.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Inhalation of *Nocardia* organisms is the most common mode of entry, and pneumonia is the most common presentation, with 75% manifesting with fever, chills, dyspnea, and a productive cough (Fig. EN1-13).
  1. Presentation can be acute, subacute, or chronic.
  2. Nocardiosis should be suspected if soft tissue abscesses or CNS tumors or abscesses form in conjunction with the pulmonary infection.
  3. Pulmonary infection may spread into the pericardium, mediastinum, and superior vena cava.
- Cutaneous disease usually occurs by direct inoculation of the organism as a result of skin puncture by a thorn or splinter, surgery, IV catheter use, or animal scratches or bites manifesting in:
  1. Cellulitis.
  2. Lymphocutaneous nodules appearing along lymphatic sites draining the infected puncture wound.
  3. Mycetoma (Madura foot), a chronic deep nodular infection usually involving the hands or feet that can cause skin breakdown or fistula formation and that spreads along the fascial planes to infect surrounding skin, subcutaneous tissue, and bone.
- The CNS is infected in approximately one third of all cases. Brain abscess is the most common pathologic finding.
- Dissemination of nocardiosis may infect other tissues and organs, including the kidney, heart, skin, and bone.

ETIOLOGY

- The most common *Nocardia* species leading to infection in human beings are:
  1. *N. asteroides* (causing more than 80% of the cases of pulmonary nocardiosis).
  2. *N. brasiliensis* (most common cause of mycetoma).
  3. *N. otitidiscaviarum.*
- *N. asteroides* has two subgroups:
  1. *N. farcinica.*
  2. *N. nova.*

DIAGNOSIS

The diagnosis of nocardiosis requires a high index of suspicion in the proper clinical setting and is confirmed by bacteriologic staining and growth of the organism in culture.

DIFFERENTIAL DIAGNOSIS

There are no pathognomonic findings separating nocardiosis pneumonia from other infectious etiologies of the lung. Diagnoses presenting in a similar manner and often confused for nocardiosis include:

1. Tuberculosis.
2. Lung abscess.
3. Lung tumor.
4. Other causes of pneumonia.
5. Actinomycosis.
6. Mycosis.
7. Cellulitis.
8. Coccidioidomycosis.
9. Histoplasmosis.
10. Aspergillosis.
11. Kaposi's sarcoma.

WORKUP

All patients with suspected nocardiosis need laboratory identification of the microorganism by obtaining sputum in the case of pneumonia, cultures of the infected skin lesions in mycetoma or lymphocutaneous disease, or the sampling of any purulent material (e.g., brain abscess, lung abscess, or pleural effusion).

LABORATORY TESTS

- Blood tests are not very sensitive in the diagnosis of nocardiosis.
- Gram stain shows gram-positive beaded filaments with multiple branches (Fig. EN1-14).
- Gomori methenamine silver staining may detect the organism.
- *Nocardia* species are acid-fast on a modified Ziehl-Neelsen stain.
- *Nocardia* are slow-growing organisms; colony growth in cultures may take up to 2 to 3 wk.

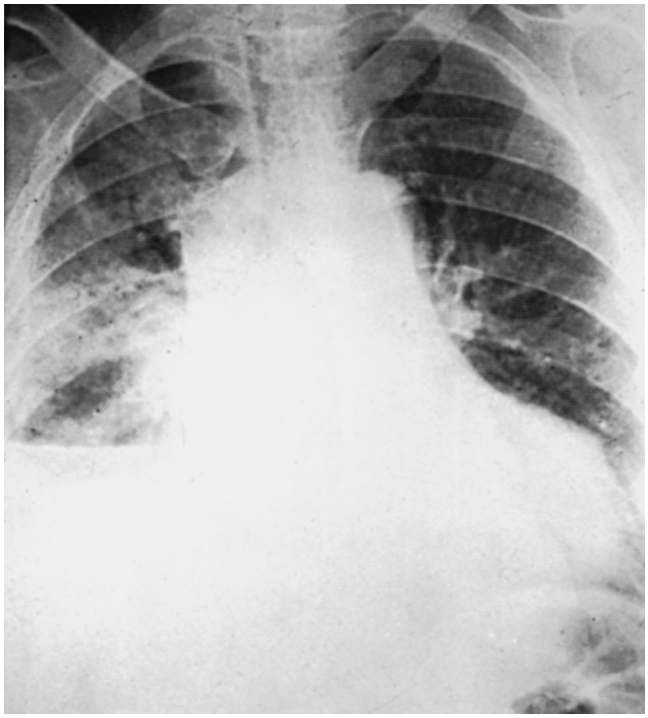


FIGURE EN1-13 Right lower lobe *Nocardia* pneumonia in a kidney transplant recipient. (From Gorbach SL: *Infectious diseases,* ed 2, Philadelphia, 1998, Saunders.)

IMAGING STUDIES

- Chest radiograph may demonstrate infiltrates, densities, nodules, cavitary masses, or multiple abscesses.
- CT scan of the brain is indicated in the appropriate clinical setting to exclude CNS brain abscesses.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive therapy with oxygen in patients with pneumonia.
- Chest physiotherapy.
- For any abscess formation, surgical drainage is indicated (e.g., skin, lung, or brain).

ACUTE GENERAL Rx

- There are no prospective, randomized trials to date highlighting the most effective treatment of nocardiosis. Culture and sensitivity should always be done on the specimen.
- For cutaneous infection, trimethoprim-sulfamethoxazole (TMX-SMX) 5 mg/kg of the trimethoprim component divided in 2 doses.
- *Nocardia* infection that does not involve CNS: TMX-SMX (15 mg/kg/day of TMP component IV in 2-4 divided doses) *plus* (amikacin 7.5 mg/kg q12h). An alternate regimen consists of imipenem 500 mg IV q6h *plus* amikacin 7.5 mg/kg IV q12h.
- In patients with CNS disease, (TMX-SMX 15 mg/kg/day of TMP component IV divided in 2-4 doses) *plus* imipenem 500 mg q6h IV. If multiorgan involvement, add amikacin 7.5 mg/kg q12h. Measure peak sulfonamide levels; target is 100-150 mcg/ml 2 hours post dose. An alternative regimen consists of linezolid 600 mg IV or PO q12h *plus* meropenem 2 g q8h.For infections without involvement of the CNS the patient can be switched to oral therapy after the initial IV therapy for 3-6 weeks or until clinical improvement. For infections involving CNS the initial IV therapy should be continued for minimum of 6 weeks and clear evidence of clinical improvement before switching to combination oral therapy. The combination oral antibiotics that can be used following initial IV therapy include:
  1. TMP/SMX (10 mg/kg per day of the trimethoprim component in two to three divided doses) and/or
  2. Minocycline (100 mg twice daily) and/or
  3. Amoxicillin/clavulinic acid (875 mg) twice daily).
- Alternative drug treatment includes:
  1. Third-generation cephalosporin.
  2. Minocycline 100 to 200 mg bid.
  3. Extended-spectrum fluoroquinolones (moxifloxacin).
  4. Linezolid (use of linezolid >4 wk is associated with hematologic toxicity).
  5. Tigecycline.
  6. Dapsone.

CHRONIC Rx

- Although the optimal duration of therapy has not been determined, long-term therapy is generally recommended for all infections caused by *Nocardia.*
- Patients with cellulitis and lymphocutaneous syndrome are treated for 2 to 4 mo depending on whether there is bone involvement.
- Mycetomas are best treated with antibiotics for 6 to 12 mo but may require surgical drainage.
- Pulmonary and systemic nocardiosis excluding the CNS is treated for at least 6 mo in immunocompromised hosts.
- CNS involvement is treated with drainage and antibiotics for 12 mo.
- All immunosuppressed patients should receive 12 mo of antibiotic therapy.

DISPOSITION

- Patients with pulmonary nocardiosis have a mortality rate of 15% to 30%.
- CNS involvement carries a >40% mortality rate.
- Isolated skin lesions have a low mortality rate.

REFERRAL

Whenever the diagnosis of nocardiosis is suspected, consultation with infectious disease is indicated. Pulmonary evaluation and assistance may be needed in pulmonary nocardiosis. Neurosurgery consultation is indicated in patients with single or multiple brain abscesses.

PEARLS & CONSIDERATIONS

- Nocardiosis does not spread from animal to animal.
- Nocardiosis is not transmitted from person to person.
- Nocardiosis is distinguished by its ability to disseminate to any organ and its tendency to relapse despite appropriate antibiotic therapy.

COMMENTS

Tuberculosis and nocardiosis may coexist in the same patient.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Nocardiosis (Patient Information)

AUTHOR: **TANYA ALI, M.D.**

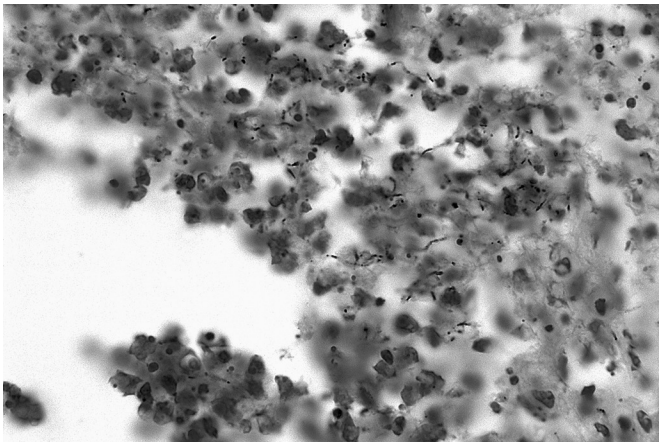


FIGURE EN1-14 *Nocardia* pneumonia. Thin, branching, irregularly staining gram-positive bacilli course through necrotic pulmonary tissue (Brown-Hopps Gram, ×1000). (From Silverberg SG et al [eds]: *Silverberg's principles and practice of surgical pathology and cytopathology,* ed 4, Philadelphia, 2006, Churchill Livingstone.)

SUGGESTED READINGS

Corti ME, Villafane-Fioti MF: Nocardiosis: a review, *Int J Infect Dis* 7(4):243, 2003.
Gilbert DN et al.: The Sanford guide to antimicrobial therapy. ed 42 Antimicrobial Therapy, Inc.
Spelman D: *Treatment of nocardiosis*, UpToDate. www.uptodateonline.com, Apr 3, 2012.
Torres HA et al.: Nocardiosis in cancer patients, *Medicine* 81(5):388, 2002.

BASIC INFORMATION

DEFINITION

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of diseases based on histopathologic findings and representing a morphologic rather than a clinical diagnosis. It is liver disease occurring in patients who do not abuse alcohol and manifesting histologically by mononuclear cells and/or polymorphonuclear cells, hepatocyte ballooning, and spotty necrosis. Nonalcoholic steatohepatitis (NASH) is a subset of NAFLD. A diagnosis of NAFLD is contingent on the following factors:

1. Alcohol consumption in amounts less than those considered hepatotoxic.
2. Absence of serologic evidence of other hepatic diseases or disorders.
3. Liver biopsy showing predominant macrovesicular steatosis or steatohepatitis.

SYNONYMS

Nonalcoholic steatohepatitis (NASH)
NAFLD
Fatty liver hepatitis
Diabetes hepatitis
Alcohol-like liver disease
Laënnec's disease

ICD-9CM CODES
571.8 Fatty liver
ICD-10CM CODES
K76.0 Fatty (change of) liver, not elsewhere classified

EPIDEMIOLOGY & DEMOGRAPHICS

- NAFLD affects 10% to 24% of the general population.
- Increased prevalence in obese persons (57% to 74%), type 2 diabetes mellitus, and hyperlipidemia (primarily hypertriglyceridemia).
- Most common cause of abnormal liver test results in adults in the United States (accounts for up to 90% of cases of asymptomatic ALT elevations).
- 30 million obese adults have steatosis; 8.6 million may have steatohepatitis.
- There is a 3:1 female-to-male predominance.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most patients are asymptomatic.
- Patients may report a sensation of fullness or discomfort on the right side of the upper abdomen.
- Nonspecific complaints of fatigue or malaise may be reported.
- Hepatomegaly is generally the only positive finding on physical examination.
- Acanthosis nigricans may be found in children.

ETIOLOGY

- Insulin resistance is the most reproducible factor in the development of NAFLD. High baseline and continuously increasing fasting insulin levels are independent determinants for future development of NFLD.
- Risk factors are obesity (especially truncal obesity), diabetes mellitus, hyperlipidemia.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Alcohol-induced liver disease (a daily alcohol intake of 20 g in females and 30 g in males [three 12-oz beers or 12 oz of wine] may be enough to cause alcohol-induced liver disease).
- Viral hepatitis.
- Autoimmune hepatitis.
- Toxin- or drug-induced liver disease.

WORKUP

Diagnosis is usually suspected on the basis of hepatomegaly, asymptomatic elevations of transaminases, or "fatty liver" on sonogram of abdomen in obese patients with little or no alcohol use. Liver biopsy will confirm diagnosis and provide prognostic information. It should be considered in patients with suspected advanced liver fibrosis (presence of obesity or type 2 diabetes, AST/ALT ratio 1, age 45 yr).

LABORATORY TESTS

- Elevated ALT, AST: AST/ALT ratio is usually <1, but can increase as fibrosis advances.
- Negative serology for infectious hepatitis; generally normal GGTP and serum alkaline phosphatase.
- Hyperlipidemia (primarily hypertriglyceridemia) may be present.
- Elevated glucose levels may be present.
- Prolonged prothrombin time, hypoalbuminemia, and elevated bilirubin may be present in advanced stages.
- Elevated serum ferritin and increased transferrin saturation may be found in up to 10% of patients; however, hepatic iron index and hepatic iron level are normal.
- Liver biopsy may show a wide spectrum of liver damage, ranging from simple steatosis to advanced fibrosis and cirrhosis.

IMAGING STUDIES

- Ultrasound generally reveals diffuse increase in echogenicity as compared with that of the kidneys; CT scan reveals diffuse low-density hepatic parenchyma.
- Occasionally patients may have focal rather than diffuse steatosis, which may be misinterpreted as a liver mass on ultrasound or CT; use of MRI in these cases will identify focal fatty infiltration.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Weight reduction in all obese patients. The American Gastroenterological Association recommends that the initial target weight loss be 10% of baseline weight at a rate of 1 to 2 lb (0.45 to 0.90 kg) per week.
- Increase physical activity.
- Alcohol has a deleterious effect on NAFLD and should be avoided.

GENERAL Rx

- No medications have been proved to directly improve liver damage from NAFLD.
- Medications to control hyperlipidemia (e.g., fenofibrates for elevated triglycerides) and hyperglycemia (e.g., metformin) can lead to improvement in abnormal liver test results.
- Pioglitazone therapy (30 mg/day) and vitamin E (800 IU/day) provide modest benefits in NASH.

DISPOSITION

- Patients with pure steatosis on liver biopsy generally have a relatively benign course.
- The presence of steatohepatitis or advanced fibrosis on liver biopsy is associated with a worse prognosis.

REFERRAL

- Liver transplantation should be considered in patients with decompensated, end-stage disease; however, in these patients there may be a recurrence of NAFLD posttransplantation.

PEARLS & CONSIDERATIONS

COMMENTS

- NAFLD is closely associated with metabolic disorders, even in nonobese, nondiabetic subjects. It can be considered an early predictor of metabolic disorders, particularly in the normal-weight population. The presence of metabolic syndrome is a strong predictor of NAFLD.
- NAFLD is associated with an increased risk of incident cardiovascular disease that is independent of the risk conferred by traditional risk factors and components of the metabolic syndrome.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fatty Liver (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Angulo P: Nonalcoholic fatty liver disease, *N Engl J Med* 346:1221, 2002.

Bayard M et al.: Nonalcoholic fatty liver disease, *Am Fam Physician* 73:2006, 1961.

Belfort R et al.: A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis, *N Engl J Med* 355:2297, 2006.

Clark JM: Nonalcoholic fatty liver disease, *JAMA* 289:3000, 2003.

Ekstedt M et al.: Long-term follow-up of patients with NAFLD and elevated liver enzymes, *Hepatology* 44:865, 2006.

Hamaguchi M et al.: The metabolic syndrome as a predictor of nonalcoholic fatty liver disease, *Ann Intern Med* 143:722, 2005.

Kim HJ et al.: Metabolic significance of nonalcoholic fatty liver disease in nonobese, nondiabetic adults, *Arch Intern Med* 164:2169, 2004.

Petersen KF et al.: Apolipoprotein C3 gene variants in non-alcoholic fatty liver disease, *N Engl J Med* 362:1082–1089, 2010.

Rhee EJ et al.: Hyperinsulinemia and the development of nonalcoholic fatty liver disease in nondiabetic adults, *Am J Med* 124:69–76, 2011.

Sanyal AJ et al.: Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis, *N Engl J Med* 362:1675, 2010.

Targher G et al.: Risk of cardiovascular disease in patients with nonalcoholic fatty liver disease, *N Engl J Med* 363:1341–1350, 2010.

Nongonococcal Urethritis PTG

BASIC INFORMATION

DEFINITION

Nongonococcal urethritis (NGU) is urethral inflammation caused by any of several organisms.

SYNONYMS

NGU
Urethritis, non gonococcal

ICD-9CM CODES
099.40 Nongonococcal
099.41 Chlamydial
ICD-10 CM Codes
A56.0 Chlamydial infection of lower genitourinary tract
N34.1 Nonspecific urethritis

EPIDEMIOLOGY & DEMOGRAPHICS

- Occurrence is 50% in sexually transmitted disease clinics. *Chlamydia trachomatis* is the most common notifiable disease in the United States, with >1.3 million infections reported to the CDC in 2010.
- NGU most commonly affects men in a higher socioeconomic class, affecting heterosexual men more frequently than homosexual men.
- NGU carries a greater morbidity rate than gonococcal urethritis (GCU).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Incubation period: 2 to 35 days
- Symptoms: dysuria, whitish-clear urethral discharge (Fig. N1-15), and urethral itching. The onset of symptoms in NGU is less acute than GCU. The majority of persons with *Chlamydia trachomatis* infection are not aware of their infection because they do not have symptoms that would prompt them to seek medical care.
- Signs: whitish-clear urethral discharge, meatal edema, and erythema. Infected women manifest pyuria, and the disease can present as acute urethral syndrome.

FIGURE N1-15 Urethral discharge from a man with nongonococcal urethritis. (From Mandell GL et al: *Principles and practice of infectious diseases,* ed 7, Philadelphia, 2009, Churchill Livingstone.)

COMPLICATIONS

Epididymitis in heterosexual men may be linked to nonbacterial prostatitis, proctitis in homosexual men, or Reiter's syndrome.

ETIOLOGY

- Most common agent is *Chlamydia* spp., an obligate intracellular parasite possessing both DNA and RNA, which replicates by binary fission. It causes 20% to 50% of NGU cases. Two species exist:
  1. *Chlamydia psittaci*
  2. *Chlamydia trachomatis* with its 15 serotypes
     Serotypes A through C cause hyperendemic-blinding trachoma.
     Serotypes D through K cause genital tract infection.
     Serotypes L1 through L3 cause lymphogranuloma venereum.
- Other causes of NGU: *Mycoplasma genitalium* (found in 44% of treatment failures); *Ureaplasma urealyticum,* causing 15% to 30% of the cases of NGU; *Trichomonas vaginalis;* and herpes simplex virus. The cause of 20% of the cases of NGU has not been identified.
- Asymptomatic infection occurs in 28% of the contacts of women with chlamydial cervical infection.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- GCU
- Herpes simplex virus
- Trichomoniasis

LABORATORY TESTS

- Requires demonstration of urethritis and exclusion of infection with *N. gonorrhoeae.*
- Nucleic acid amplification tests (NAATs): these tests have replaced culture in many settings where persons are screened for asymptomatic genital infection. The performance of NAATs with respect to overall sensitivity, specificity, and ease of specimen transport is better than that of any of the other tests available for the diagnosis of chlamydial and gonococcal infections. NAATs should be used to detect chlamydia and gonorrhea except in cases of child sexual assault involving boys, rectal and oropharyngeal infections in prepubescent girls, and when evaluating a potential gonorrhea treatment failure, in which case culture and susceptibility testing might be required.
- Chlamydia culture: the appearance of PMNs on urethral smear confirms the diagnosis of urethritis. Because *Chlamydia* is an intracellular parasite of the columnar epithelium, the best specimen for culture is an endourethral swab taken from an area 2 to 4 cm inside the urethra. For culture, a Dacron-tipped swab is used; avoid calcium alginate or cotton swabs. The organism can only be grown in tissue culture, which is expensive.

TREATMENT

Because it is impossible to differentiate among the common etiologies of NGU, the condition is treated syndromically, including in the initial treatment regimen those drugs effective against the common causative agents. In patients with isolated uncomplicated NGU, recommended regimens are azithromycin 1 g orally single dose or doxycycline 100 mg bid × 7 days. In patients with confirmed urethritis and unclear etiology, concurrent treatment for gonorrhea and *Chlamydia* is recommended. In these patients, uncomplicated infections of the urethra can be treated with combination of a single 1-g dose of oral azithromycin or 100 mg doxycycline bid × 7 days *plus*

- Cefixime 400 mg PO × 1 dose or
- Ceftriaxone 250 mg IM × 1 dose

Recommended regimen in pregnancy is azithromycin, 1 g orally as a single dose. Repeat test 3 weeks after completion of treatment to confirm cure.

PEARLS & CONSIDERATIONS

COMMENTS

Partner notification: The names and contact information of sexual partners should be gathered at the time of the visit and referred to the health department or the patient notifies the contact directly. Expedited partner treatment is recommended by the CDC and approved in several states. This consists of giving prescriptions to the infected patient for their partner(s) who has not been evaluated by a physician and is unlikely to seek medical care.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fig 3-67 Evaluation of Patients with Dysuria and/or Urethral/Vaginal Discharge (Algorithm)
Nongonococcal Urethritis (Patient Information)
Cervicitis (Related Key Topic)
Chlamydia Genital Infections (Related Key Topic)

AUTHORS: **RUBEN ALVERO, M.D.,** and **PHILIP J. ALIOTTA, M.D.**

SUGGESTED READINGS

Brill JR: Diagnosis and treatment of urethritis in men, *Am Fam Physician* 81(70):873–879, 2010.

Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, *MMWR Morb Mortal Wkly Rep* 59(RR-12):2010, 2010.

MMWR, 63(2), 2014, March 14.

Sena AC et al.: *Chlamydia trachomatis, Mycoplasma genitalium,* and *Trichomonas vaginalis* infections in men with nongonococcal urethritis: predictors and persistence after therapy, *J Infect Dis* 206:357, 2012.

BASIC INFORMATION

DEFINITION

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of malignancies of the lymphoreticular system.

SYNONYMS

NHL

ICD-9CM CODES
201.9 Lymphoma, non-Hodgkin
ICD-10CM CODES
C85.90 Non-Hodgkin lymphoma, unspecified, unspecified site

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Sixth most common neoplasm (>50,000 new cases annually). Incidence increases with age; majority of patients are above 60 years of age.

In patients with HIV, NHL is the second most common tumor (after Kaposi's sarcoma).

Diffuse large B-cell lymphoma (DLBCL) is the most common type of HIV-associated lymphoma, accounting for 80% to 90% of cases.

- Primary CNS lymphoma (PCNSL) accounts for 2% of the cases of lymphoma in patients with HIV infection, but it accounts for 10% of the cases in patients with a diagnosis of AIDS.
- More common in men than women.
- Higher rates seen in Europe, Australia, and the United States.

PREDOMINANT AGE: Median age at time of diagnosis is 50 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients often present with asymptomatic lymphadenopathy.
- Approximately one third of NHLs originate extranodally. Involvement of extranodal sites can result in unusual presentations (e.g., gastrointestinal tract involvement can simulate peptic ulcer disease).
- Presence of B symptoms like unexplained weight loss, fever, fatigue, and night sweats.
- Aggressive lymphomas have more acute or subacute presentation with increasing size of the mass and B symptoms.
- NHL cases associated with HIV occur predominantly in the brain.
- Pruritus.
- Hepatomegaly and splenomegaly may be present.
- Cough, dyspnea in pulmonary involvement.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hodgkin disease.
- Viral infections.
- Metastatic carcinoma.
- Autoimmune conditions.

A clinical algorithm for evaluation of lymphadenopathy is described in Section III. The differential diagnosis of lymphadenopathy is described in Section II.

WORKUP

Initial laboratory evaluation may reveal only mild anemia and elevated lactate dehydrogenase (LDH) and erythrocyte sedimentation rate (ESR). Proper staging of NHL includes the following:

- A thorough history, physical examination, and excisional or surgical biopsy. Laparoscopic lymph node biopsy can be used on an outpatient basis for most patients with intraabdominal lymphoma.
- Routine laboratory evaluation (complete blood count, flow cytometry, ESR, urinalysis, LDH, blood urea nitrogen, creatinine, serum calcium, uric acid, liver function tests, serum protein electrophoresis).
- β-2 microglobulin levels should be obtained initially (prognostic value) and serially in patients with low-grade lymphomas (useful to monitor therapeutic response of the tumor).
- Serum interleukin levels have prognostic value in diffuse large cell lymphoma.
- HIV testing.
- Tissue biopsy with histologic, immunophenotypic, and genetic studies interpretation.
- Chest x-ray (posteroanterior and lateral).
- Bone marrow evaluation (aspirate and full bone core biopsy) (Fig. EN1-16).
- CT scan of abdomen and pelvis; CT scan of chest if chest x-ray films abnormal.
- Fluorine-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) integrated with CT has emerged as a powerful tool for staging, response evaluation, and posttreatment surveillance in patients with NHL.
- Bone scan (particularly in patients with histiocytic lymphoma).
- Depending on the histopathology (Table EN1-11), the results of the above studies and the planned therapy, some other tests may be performed.

CLASSIFICATION: The working formulation of NHL for clinical use subdivides lymphomas into low grade, intermediate grade, high grade, and miscellaneous (Table N1-12).

STAGING: The Ann Arbor staging system with Cotswold modification is described in Table N1-13. Histopathology has greater therapeutic implications in NHL than in Hodgkin disease. The frequency of indolent lymphomas among all lymphomas is described in Table N1-14. The classification of aggressive lymphomas is described in Table N1-15.

TREATMENT

ACUTE GENERAL Rx

The therapeutic regimen varies with the histologic type and pathologic stage. Following are the commonly used therapeutic modalities:

LOW-GRADE NHL (E.G., NODULAR, POORLY DIFFERENTIATED)

1. Local radiotherapy for symptomatic obstructive adenopathy.
2. Deferment of therapy and careful observation in asymptomatic patients with indolent lymphomas.
3. Single-agent chemotherapy is infrequently used.
4. Combination chemotherapy alone or with radiotherapy: generally indicated only when the lymphoma becomes more invasive, with poor response to less aggressive treatment. Radiation therapy without chemotherapy is not recommended due to increased relapse rate.
5. Monoclonal antibodies directed against B-cell surface antigens can also be used to treat follicular lymphomas resistant to conventional therapy. The anti-CD20 monoclonal antibody rituximab is effective against low-grade NHL in patients who have not received previous treatment. The addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP-R) is generally well tolerated.
6. Ibritumomab tiuxetan, an immunoconjugate that combines the linker-chelator tiuxetan with the monoclonal antibody ibritumomab, can be used as part of a two-step regimen for treatment of patients with relapsed or refractory low-grade, follicular, or transformed B-cell NHL refractory to rituximab.
7. New purine analogs (FLAMP, 2CDA) can be used in salvage treatment of refractory lymphomas. They all have activity in follicular lymphomas.
8. Table N1-16 summarizes treatment strategies for indolent lymphomas.

TABLE N1-16 Treatment Strategies for Indolent Lymphomas

Advanced Stage Disease
"Watchful waiting"
Alkylating agents
Purine analogs
Combination chemotherapy
Chemotherapy + monoclonal antibodies (chemoimmunotherapy)
High dose chemotherapy plus autologous/allogeneic hematopoietic cell transplantation
Reduced intensity conditioning allogeneic transplantation
Palliative radiotherapy
Localized Disease
Radiotherapy
"Watchful waiting"

From Hoffman R et al: *Hematology: basic principles and practice*, ed 5, Philadelphia, 2009, Churchill Livingstone.

INTERMEDIATE- AND HIGH-GRADE LYMPHOMAS (E.G., DIFFUSE HISTIOCYTIC LYMPHOMA): Combination chemotherapy regimens (e.g., CHOP, ProMACE-CytaBOM, MACOP-B, m-BACOD). An anthracycline-containing regimen (such as CHOP) given in standard doses and schedule is generally best for treatment of older patients with advanced stage, aggressive-histology lymphoma who do not have significant comorbid illness.

TABLE N1-12 Classification Systems for Grading Lymphomas

Kiel Classification	Working Formulation	Revised European-American Classification
Low-grade malignancy	Low grade	B-cell lymphomas
Lymphocytic, CLL	A. Malignant lymphoma, small lymphocytic	
Lymphocytic, other	Consistent with CLL	B-CLL/SLL
Lymphoplasmacytoid		Lymphoplasmacytoid lymphoma
Centrocytic	B. Malignant lymphoma, follicular, predominantly small cleaved cell	Follicle center lymphomas
Centroblastic/centrocytic		Marginal zone lymphomas (MALT)
Follicular without sclerosis	Diffuse areas	Mantle cell lymphoma
Follicular with sclerosis	Sclerosis	
Follicular and diffuse, without sclerosis	C. Malignant lymphoma, follicular mixed, small cleaved and large cell	
Follicular and diffuse, with sclerosis	Diffuse areas	Diffuse large B-cell lymphoma
Diffuse	Sclerosis	Primary mediastinal large B-cell lymphoma
Low-grade malignant lymphoma, unclassified	Intermediate grade	Burkitt's lymphoma
High-grade malignancy	D. Malignant lymphoma, follicular	T-cell lymphomas
Centroblastic	Diffuse areas	
Lymphoblastic, Burkitt's type	E. Malignant lymphoma, diffuse small cleaved cell	
Lymphoblastic, convoluted cell type		T-CLL
Lymphoblastic, other (unclassified) immunoblastic		Mycosis fungoides/Sézary syndrome
High-grade malignant lymphoma, unclassified	F. Malignant lymphoma, diffuse mixed, small and large cell sclerosis	
Malignant lymphoma unclassified (unable to specify high grade or low grade)	G. Malignant lymphoma diffuse	Peripheral T-cell lymphoma, unspecified
Composite lymphoma	Large cell	Angioimmunoblastic T-cell lymphoma
	Cleaved cell	Angiocentric lymphoma
	Noncleaved cell	Intestinal T-cell lymphoma
	Sclerosis	Adult T-cell lymphoma/leukemia
	High grade	Anaplastic large cell lymphoma
	H. Malignant lymphoma large cell, immunoblastic	Precursor T-lymphoid lymphoma/leukemia
	Plasmacytoid	
	Clear cell	
	Polymorphous	
	Epithelioid cell component	
	I. Malignant lymphoma lymphoblastic	
	Convoluted cell	
	Nonconvoluted cell	
	J. Malignant lymphoma small noncleaved cell	
	Burkitt's	
	Follicular areas	

B-CLL, B-cell chronic lymphoid leukemia; *CLL,* chronic lymphocytic leukemia; *MALT,* mucosa-associated lymphoid tumor; *SLL,* lymphoid leukemia; *T-CLL,* T-cell CLL.
From Abeloff MD: *Clinical oncology,* ed 3, New York, 2004, Churchill Livingstone.

TABLE N1-13 Ann Arbor Staging System for Lymphomas

Stage*	Cotswold Modification of Ann Arbor Classification
I	Involvement of a single lymph node region or lymphoid structure
II	Involvement of two or more lymph node regions on the same side of the diaphragm (the mediastinum is considered a single site, whereas the hilar lymph nodes are considered bilaterally); the number of anatomic sites should be indicated by a subscript (e.g., II_3)
III	Involvement of lymph node regions on both sides of the diaphragm: III_1 (with or without involvement of splenic hilar, celiac, or portal nodes) and III_2 (with involvement of paraaortic, iliac, and mesenteric nodes)
IV	Involvement of one or more extranodal sites in addition to a site for which the designation E has been used

*All cases are subclassified to indicate the absence (A) or presence (B) of the systemic symptoms of significant fever (>38.0° C [100.4° F]), night sweats, and unexplained weight loss exceeding 10% of normal body weight within the previous 6 months. The clinical stage (CS) denotes the stage as determined by all diagnostic examinations and a single diagnostic biopsy only. In the Ann Arbor classification, the term pathologic stage (PS) is used if a second biopsy of any kind has been obtained, whether negative or positive. In the Cotswold modification, the PS is determined by laparotomy; X designates bulky disease (widening of the mediastinum by >one third or the presence of a nodal mass >10 cm), and E designates involvement of a single extranodal site that is contiguous or proximal to the known nodal site.
From Hoffmann R et al: *Hematology: basic principles and practice*, ed 5, Philadelphia, 2009, Churchill Livingstone.

TABLE N1-14 Frequency of Indolent Lymphomas Among All Lymphomas in the World Health Organization Classification

Follicular lymphoma	22.1%
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue type	7.6%
Small lymphocytic lymphoma/chronic lymphocytic leukemia	6.7%
Mantle cell	6.0%
Splenic marginal zone lymphoma	1.8%
Lymphoplasmacytic lymphoma	1.2%
Nodal marginal zone B-cell lymphoma (±monocytoid B cells)	1.0%

From Hoffman R et al: *Hematology: basic principles and practice*, ed 5, Philadelphia, 2009, Churchill Livingstone.

TABLE N1-15 Classification of Aggressive Lymphomas

B-cell Neoplasms
Precursor B-cell lymphoma
Precursor B lymphoblastic leukemia/lymphoma
Mature B-cell lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma
Mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary effusion lymphoma
Burkitt lymphoma/leukemia
B-cell proliferations of uncertain malignant potential
Lymphomatoid granulomatosis
Posttransplant lymphoproliferative disorder, polymorphic
T-cell and NK-cell Neoplasms
Precursor T-cell
Precursor T lymphoblastic leukemia/lymphoma
Blastic NK cell lymphoma
Mature T-cell and NK-cell lymphoma
Adult T-cell leukemia/lymphoma
Extranodal NK/T cell lymphoma, nasal type
Hepatosplenic T-cell lymphoma
Peripheral T-cell lymphoma, unspecified
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma

NK, Natural killer.
From Hoffman R et al: *Hematology: basic principles and practice*, ed 5, Philadelphia, 2009, Churchill Livingstone.

1. High-dose sequential therapy is superior to standard-dose MACOP-B for patients with diffuse large-cell lymphoma of the B-cell type.
2. Dose-modified chemotherapy should be considered for most HIV-infected patients with lymphoma.
   - Three cycles of CHOP followed by involved-field radiotherapy may be superior to eight cycles of CHOP alone in patients with localized intermediate- and high-grade NHL.
   - High-dose chemotherapy with autologous stem-cell support has been reported to be superior to CHOP in adults with disseminated aggressive lymphoma.
   - The addition of rituximab against CD20 B-cell lymphoma to the CHOP regimen (CHOP-R) increases the complete response rate and prolongs event-free and overall survival in elderly patients with diffuse large B-cell lymphoma without a clinically significant increase in toxicity. Bexxar, a combination of the mononuclear antibody tositumomab and radiolabeled iodine-131, can be used for a single treatment of relapsed follicular NHL in patients who are refractory to rituximab.
   - In patients <61 yr, chemotherapy with three cycles of ACVBP (doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone) followed by sequential consolidation has been reported to be superior to three cycles of CHOP plus radiotherapy for treatment of newly diagnosed aggressive lymphoma (diffuse mixed, diffuse large cell, or immunoblastic according to the working formulation).
   - Granulocyte-colony stimulating factor: may be effective in reducing the risk of infection in patients with aggressive lymphoma undergoing chemotherapy.
   - Radioimmunotherapy with (^{131}I) anti-B1 antibody therapy for NHL either by itself or in combination with other treatments represents a new modality in the armamentarium against lymphomas.
   - Treatment with high-dose chemotherapy and autologous bone marrow transplant: compared with conventional chemotherapy, increases event-free and overall survival in patients with chemotherapy-sensitive NHL in relapse. Recent trials have shown that early autologous stem cell transplantation improves progression-free survival among patients with high intermediate risk or high risk disease who had a response to induction therapy.
   - Combination chemotherapy regimens for NHL are described in Table N1-17.

DISPOSITION

- Patients with low-grade lymphoma, despite their long-term survival (6 to 10 yr average), are rarely cured, and the great majority (if not all) eventually die of the lymphoma, whereas patients with a high-grade lymphoma may achieve a cure with aggressive chemotherapy.
- Complete remission occurs in 35% to 50% of patients with intermediate- and high-grade lymphoma. Prognostic factors include the histiologic subtype, age of patient, and bulk of disease. Table EN1-18 describes the International Prognostic Index for aggressive lymphomas.
- Patients who present with AIDS-related NHL and a low CD4 cell count have a poor prognosis (median duration of survival is 15 to 34 mo). Despite therapeutic advances, the management of HIV-associated lymphomas is challenging due to potential pharmacologic interactions and increased risk of infectious complications. It is important to optimize the CD4 cell count during treatment. Referral to an HIV oncologist is recommended.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Non-Hodgkin's Lymphoma (Patient Information)

AUTHORS: **SYEDA M. SAYEED, M.D.,** and **FRED F. FERRI, M.D.**

TABLE N1-17 Combination Chemotherapy Regimens for Non-Hodgkin Lymphoma

Regimen	Dose	Days of Administration	Frequency
CHOP-R			**Every 21 days**
Cyclophosphamide	750 mg/m^2 IV	1	
Doxorubicin	50 mg/m^2 IV	1	
Vincristine	1.4 mg/m^2 IV*	1	
Prednisone, fixed dose	100 mg PO	1-5	
Rituximab	375 mg/m^2 IV	1	
CVP-R			**Every 21 days**
Cyclophosphamide	1000 mg/m^2 IV	1	
Vincristine	1.4 mg/m^2 IV*	1	
Prednisone, fixed dose	100 mg PO	1-5	
Rituximab	375 mg/m^2 IV	1	
FCR			**Every 28 days**
Fludarabine	25 mg/m^2 IV	1-3	
Cyclophosphamide	250 mg/m^2 IV	1-3	
Rituximab	375 mg/m^2	1	

*Vincristine dose often capped at 2 mg total.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

SUGGESTED READINGS

Ansell S, Armitage JO: Positron emission tomographic scans in lymphoma: convention and controversy, *Mayo Clin Proc* 87(6):571–580, 2012.

Delarue R et al.: Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomised phase 3 trial, *Lancet Oncol* 13:525, 2013.

Gopal AK et al.: PI3Kdelta inhibition by idelalisib in patients with relapsed indolent lymphoma, *N Engl J Med* 370:1008–18, 2014.

Kaminski MS et al.: 131I-tositumomab therapy as initial treatment for follicular lymphoma, *N Engl J Med* 352:441, 2005.

Lens G, Staudt LM: Aggressive lymphomas, *N Engl J Med* 362:1417–1429, 2010.

Maloney DG: Anti-CD20 antibody therapy for B-cell lymphomas, *N Engl J Med* 366:2008–2016, 2012.

Milpied N et al.: Initial treatment of aggressive lymphoma with high-dose chemotherapy and autologous stem cell support, *N Engl J Med* 350:1287, 2004.

Reyes F et al.: ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma, *N Engl J Med* 352:1197, 2005.

Stiff PJ et al.: Autologous transplantation as consolidation for aggressive non-Hodgkin's lymphoma, *N Engl J Med* 369:1681–90, 2014.

Wang CC, Castillo JJ: Management of HIV-associated lymphomas, Medicine and Health, *Rhode Island* 94:4–6, 2011.

TABLE EN1-11 Histologic Features of Non-Hodgkin Lymphomas Involving Bone Marrow

Type of Lymphoma	Incidence of Involvement (%)	Pattern of Involvement*	Cytology	Comments
Small lymphocytic	85	FR, I, D	Small, mature lymphocytes; proliferation centers may be present	Paratrabecular infiltrates essentially rule out this diagnosis
Lymphoplasmacytic	80-100	FR, I, D, FP	Spectrum of cells from lymphocytes to plasma cells; immunoblasts may be present; Dutcher bodies common	Unlike SLL/CLL, occasional paratrabecular infiltrates may be present
Mantle cell	55-95	FR, I, D, FP	Small irregular lymphocytes; may be blastoid; rare cells with prominent nucleoli	Cyclin D1 positive; paratrabecular infiltrates may be present
Follicular	50-60	FP, D, FR, I	Small cleaved lymphocytes usually predominate; large cleaved or noncleaved cells may be present	Characteristically paratrabecular; neoplastic follicles may be apparent
Splenic marginal zone	73-100	FR, I, D, IS	Small lymphocytes with slightly irregular nuclei, condensed chromatin, and abundant cytoplasm	Intrasinusoidal infiltrates often prominent; reactive germinal centers may be present
Low-grade extranodal marginal zone	44	FR, P, I, IS	Small cells with condensed chromatin and scant to moderate amounts of cytoplasm; rare large cells may be admixed	Extent of bone marrow infiltration usually minimal
Nodal marginal zone	30-40	FR, I, P, D	Small cells with condensed chromatin and scant to moderate amounts of cytoplasm	
Diffuse large B cell	15-30	FR, D	Large cells with prominent nucleoli	Prominent component of T lymphocytes with or without histiocytes may be present; immunohistochemistry for B-cell antigens and other markers is essential in these cases; rare cases of large cell lymphoma are intravascular
Burkitt	35-60	I, D	Medium-sized cells with reticular chromatin, multiple small nucleoli, and basophilic cytoplasm; cytoplasmic vacuoles common	Necrosis common; "starry sky" pattern may be seen
Peripheral T cell (unspecified)	80	FR, D	Polymorphic lymphoid population—nuclei often hyperchromatic and irregular; large cells with nucleoli may be present; prominent reactive cell component often intermixed with lymphoma cells	Vascularity and reticulin fibrosis frequently prominent
Anaplastic large cell	4-40	FR, I (scattered cells), D	Large cells with lobulated nuclei, prominent nucleoli, and abundant cytoplasm	Detection rate is higher with immunostaining for CD30 or ALK-1
Hepatosplenic T cell	100	IS	Medium-sized lymphocytes with dispersed chromatin	Lesions may be subtle; immunohistochemistry is often helpful
Lymphoblastic	50-60	I, D	Blastic cells with high mitotic rate	Identical to acute lymphoblastic leukemia
NK/T cell	0-25	I (scattered cells)	Variable size with pleomorphic nuclei	Immunostains or in situ hybridization (EBER) may be necessary to identify lymphoma cells in bone marrow sections

D, Diffuse; EBER, Epstein-Barr virus–encoded RNA; *FP,* focal paratrabecular; *FR,* focal random; *I,* interstitial; *IS,* intrasinusoidal; *NK,* natural killer; *P,* paratrabecular.
*Patterns may be mixed; the most common patterns are listed.
From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.

TABLE EN1-18 International Prognostic Index for Aggressive Lymphomas*

Risk Group	IPI Score	CR Rate (%)	5-yr Overall Survival (%)
Low	0, 1	87	73
Low intermediate	2	67	51
High intermediate	3	55	43
High	4, 5	44	26

CR, Complete response; *IPI,* International Prognostic Index.
*One point is given for the presence of each of the following characteristics: age >60 years, elevated serum lactate dehydrogenase level, Eastern Cooperative Oncology Group performance status ≥ 2, Ann Arbor stage III or IV, and more than two extranodal sites.
From Hoffman R et al: *Hematology: basic principles and practice*, ed 5, Philadelphia, 2009, Churchill Livingstone.

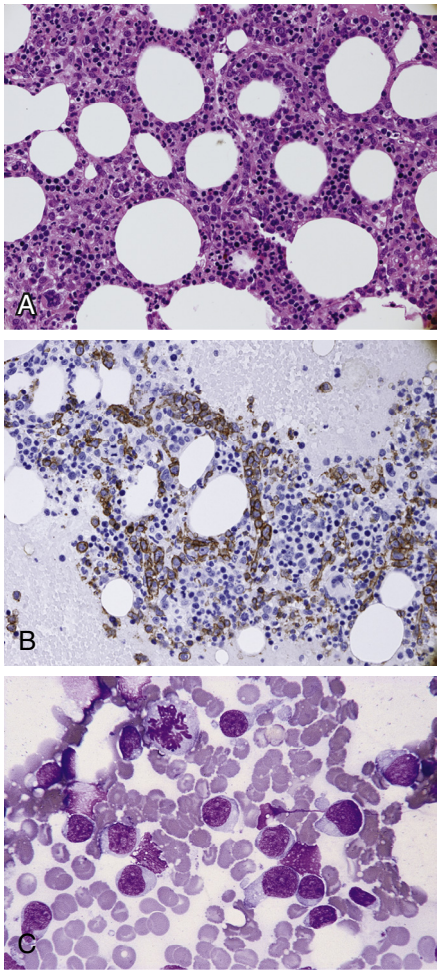


FIGURE EN1-16 Intravascular large B-cell lymphoma in a bone marrow trephine biopsy and bone marrow aspirate. A, Collections of lymphoma cells are present within the sinuses of the hematoxylin-eosin stained section. The infiltrate is subtle and could easily be missed. **B,** CD20 immunostain highlights the intrasinusoidal lymphoma cells. **C,** Lymphoma cells in the bone marrow aspirate are large, with blue-gray cytoplasm; many contain visible nucleoli. (Courtesy Dr. Robert Pooley, Department of Pathology, Little Company of Mary Hospital, Evergreen Park, Ill. From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Obesity refers to having an excess amount of body fat in relation to lean body mass, or a body mass index (BMI) of ≥30 kg/m^2. Overweight is defined as BMI of 25 to 29.9 kg/m^2 and morbid obesity refers to adults with a BMI ≥40 kg/m^2. BMI is used as a surrogate measure of obesity. Abdominal obesity is defined as waist circumference >102 cm (40 inches) in men and >88 cm (35 inches) in women.

ICD-9CM CODES
278.0 Obesity
ICD-10CM CODES
E66.9 Obesity, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- The World Health Organization first recognized obesity as a worldwide epidemic in 1997. As of 2005, 1.6 billion adults worldwide were classified as overweight, 400 million of whom were obese. It is predicted that the combination of overweight and obesity will soon eclipse public health issues such as malnutrition and infectious diseases as the most significant cause of poor health.
- Worldwide, data from the Global Burden of Disease Study from 1980 to 2013, indicate the prevalence of adult obesity has increased from 28.8% to 36.9% in men and 29.8% to 38% in women. The prevalence of children and adolescent obesity has also substantially increased.
- Based on U.S. National Health and Nutrition Examination (NHANES) data from 2009-2010, the prevalence of obesity in the United States was 35.7%. By 2015, it is estimated that two in every five adults and one in every four children in the United States will be obese.
- Based on U.S. NHANES data from 2011 to 2012 the prevalence of abdominal obesity was 54%. Abdominal obesity is closely associated with increased disease risk.
- The present cost of obesity in the U.S. population is estimated at $100 billion annually. Approximately two thirds of people living in the United States are overweight, which is the highest percentage in the world (Marie Ng, 2014).
- For persons with a BMI ≥30 kg/m^2, all-cause mortality is increased by 50% to 100% above that of persons with BMI in the range of 20 to 25 kg/m^2.
- Obesity is an independent risk factor for cardiovascular disease (CVD), type 2 diabetes, hypertension, cancer (particularly colon, prostate, breast, and gynecological malignancies), sleep apnea, degenerative joint disease, thromboembolic disorders, digestive tract diseases (gallstones), and dermatologic disorders.
- Significant morbidity and risk of death are projected to begin in young adulthood, resulting in >100,000 excess cases of CHD by 2035, even with the most modest projection of future obesity.
- When children enter kindergarten, 12.4% are obese, and another 14.9% are overweight. Data show that incident obesity between the ages of 5 and 14 years is more likely to have occurred at younger ages.[1]
- Obesity in adolescence is significantly associated with increased risk of incident severe obesity in adulthood, with variations by sex and race/ethnicity. Overweight or obese adults who were obese as children have increased risk of type 2 DM, dyslipidemia, hypertension, and carotid artery atherosclerosis.
- Obesity is a major preventable cause of death and disability in the United States (the other is tobacco).
- Extensive data indicate that weight loss can reverse or arrest the harmful effects of obesity.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination should assess the degree and distribution of body fat, signs of secondary causes of obesity, and obesity-related comorbidities.
- Increased waist circumference is apparent. Excess abdominal fat is clinically defined as a waist circumference >40 inches (>102 cm) in men and >35 inches (>88 cm) in women (in Asian men and women, >36 inches and >33 inches, respectively).
- Symptoms associated with hypertension, coronary artery disease (CAD), and diabetes (e.g., polyuria, polydipsia, acanthosis nigricans, retinopathy, and neuropathy) may be present.
- Obesity is associated with cardiac hypertrophy, diastolic dysfunction, and decreased aortic compliance, which are independent predictors of cardiovascular risk.
- Joint pain and swelling are associated with degenerative joint disease secondary to obesity.
- The physical exam and ECG often underestimate the presence and extent of cardiac dysfunction in obese patients. Jugular venous distention and hepatojugular reflux may not be seen and heart sounds are frequently distant.
- A large quantity of fluid is present in the interstitial space of adipose tissue, as the interstitial space is ~10% of the tissue wet weight. This excess fluid in this compartment if redistributed into the circulation, can have negative repercussions in obese individuals with heart failure. Obese individuals have higher cardiac output and a lower total peripheral resistance than do lean individuals, and obesity is associated with persistence of elevated cardiac filling pressure during exercise.
- Obesity predisposes to heart failure through several different mechanisms: increased total blood volume, increased cardiac output, LVH, left ventricular diastolic dysfunction, and adipositas cordis (excessive epicardial fat and fatty infiltration of the myocardium).

[1]Cunningham SA et al: Incidence of childhood obesity in the United States, *N Engl J Med*, 370:403-411, 2014.

ETIOLOGY

- The pathophysiology of obesity is complex and poorly understood, but includes social, nutritional, physiologic, psychological, and genetic factors.
- Environmental factors such as a sedentary lifestyle and chronic ingestion of excess calories can cause obesity.
- Obesity may be related to genetic factors, which are thought to be polygenic. Genetic studies with adopted children have demonstrated that they have similar BMIs to their biologic parents but not their adoptive parents. Twin studies also demonstrate a genetic influence on BMI.
- Secondary causes of obesity can result from medications (antipsychotics, steroids, and protease inhibitors being common ones) and neuroendocrine disorders (like Cushing's syndrome and hypothyroidism).

DIAGNOSIS

- BMI will establish the diagnosis of obesity. BMI is defined as the adult's weight in kilograms divided by the square of his or her height—and is closely correlated with total body fat content.
- BMI values can categorize patients into three classes of obesity:
  1. Class I (mild): BMI of 30.0 to 34.9 kg/m^2
  2. Class II (moderate): BMI of 35.0 to 39.9 kg/m^2
  3. Class III (severe): BMI of ≥40 kg/m^2
- Although BMI is commonly used to define obesity, it is not a highly accurate indicator of body fat composition in children, who are undergoing rapid changes in height, or in bodybuilders or athletes who have large amounts of muscle tissue.
- Waist circumference or waist-hip ratio is indicative of visceral adipose tissue/intraabdominal fat, which may be more deleterious than overall overweight or obesity.

DIFFERENTIAL DIAGNOSIS

It is important to evaluate obese patients for secondary medical causes of obesity. Hypothalamic disorders, hypothyroidism, Cushing's syndrome, insulinoma, depression, and drugs (corticosteroids, antidepressants, second-generation antipsychotics, sulfonylureas, and HIV protease inhibitors) can cause obesity. In children, certain genetic conditions, such as Prader-Willi syndrome, are associated with obesity.

WORKUP

History should be obtained regarding weight change, family history of obesity, and eating and exercise behavior. Assessment for eating disorders and depression should be made. Attention should be directed to the use of nutritional supplements, over-the-counter medications, hormones, diuretics, and laxatives. The workup of an obese patient typically requires laboratory work to assess for risks and complications as well as to rule out underlying causative medical conditions. Fig. 01-1 describes the evaluation of patients with suspected endocrine cause of obesity.

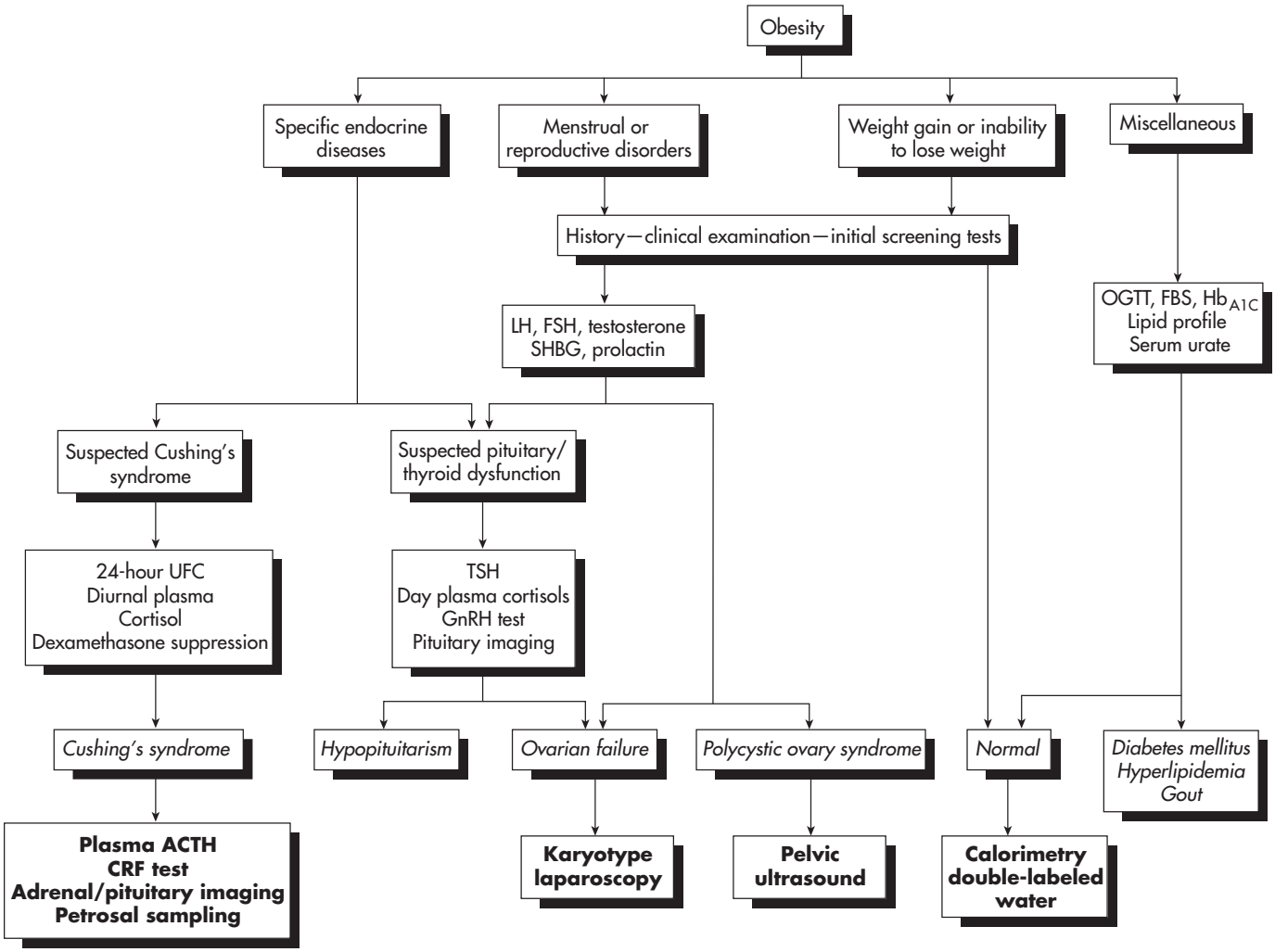


FIGURE 01-1 Endocrine evaluation of obesity. *ACTH,* Adrenocorticotropic hormone; *CRF,* corticotropin-releasing factor; *FBS,* fasting blood sugar; *FSH,* follicle-stimulating hormone; Hb_{A1C} glycohemoglobin; *LH,* luteinizing hormone; *OGTT,* oral glucose tolerance test; *SHBG,* sex hormone-binding globulin; *UFC,* urinary free cortisol. (Modified from Besser CM, Thorner MO: *Comprehensive clinical endocrinology,* ed 3, St Louis, 2002, Mosby.)

LABORATORY TESTS

- Obese patients should be assessed for medical consequences of their obesity by screening for metabolic syndrome. This includes measurement of fasting lipid profile, blood pressure, and waist circumference, and screening for diabetes or prediabetes (oral glucose tolerance test, fasting glucose, or hemoglobin A1C).
- Polycythemia might warrant screening for sleep apnea. Liver function tests should be obtained to screen for hepatic steatosis.
- In the proper clinical setting, thyroid function studies and dexamethasone suppression testing will exclude hypothyroidism and Cushing's syndrome as underlying causes of obesity. If insulinoma is suspected, the patient will need to undergo a 72-hour fast to confirm hypoglycemia with inappropriate insulin secretion.
- Obesity is associated with changes in the ECG, including a reduction in voltage and nonspecific ST-T changes that may interfere with diagnosis of left ventricular hypertrophy (LVH) or CAD.

IMAGING STUDIES

- Several methods are available for determining or calculating total body fat but offer no significant advantage over the BMI. These include measurement of total body water, total body potassium, bioelectrical impedance, and dual-energy x-ray absorptiometry.
- Buoyancy testing is an accurate method for determining total body fat composition.

OTHER STUDIES

Obesity increases the risk of obstructive sleep apnea, which, in turn, increases the risks of hypertension, cardiac arrhythmias, CVD, stroke, and heart failure. Therefore one should have a low threshold to screen obese patients for obstructive sleep apnea via sleep study/polysomnography.

Rx TREATMENT

The National Heart, Lung, and Blood Institute (NHLBI) developed guidelines for selecting treatment strategies for overweight and obese patients based on BMI and comorbidities. They recommend a combination of dietary management, physical activity management, and behavior therapy for anyone with a BMI ≥25 or with a high-risk waist circumference and two or more obesity-associated comorbidities. Pharmacotherapy should be considered for patients with a BMI ≥30 or ≥27 with comorbidities.

Bariatric surgery is indicated for patients with a BMI ≥35 with comorbidities and for any patient with a BMI ≥40 (Table 01-1).

NONPHARMACOLOGIC THERAPY

- The cornerstones for weight management and reduction are calorie restriction, exercise, and behavioral modification. Assessment of patient's willingness to make changes must be evaluated, as treatment is more likely to succeed in motivated patients.
- The NHLBI guidelines recommend an initial diet to produce a calorie deficit of 500 to 1000 kcal/day. This has been shown to reduce total body weight by an average of 8% over 3 to 12 mo.

TABLE O1-1 Weight-Loss Treatment Guidelines from the National Heart, Lung, and Blood Institute*

	BMI				
Treatment	**25.0-26.9**	**27.0-29.9**	**30.0-34.9**	**35.0-39.9**	**>40.0**
Diet, physical activity, behavioral therapy, or all three	Yes	Yes	Yes	Yes	Yes
Pharmacotherapy†		In patients with obesity-related diseases.	Yes	Yes	Yes
Surgery‡				In patients with obesity-related diseases.	Yes

*Data are from www.nhlbi.nih.gov/guidelines/obesity/ob_home.htm. These guidelines are generally consistent with those from the American Heart Association, the American Medical Association, the American Diabetic Association, the Obesity Society (Practical Guide), the American Diabetes Association, the American Academy of Family Physicians, the American College of Sports Medicine, and the American Cancer Society. *BMI* denotes body mass index, calculated as the weight in kilograms divided by the square of the height in meters.

†Pharmacotherapy should be considered only in patients who are not able to achieve adequate weight loss with available conventional lifestyle modifications and who have no absolute contraindications for drug therapy.

‡Bariatric surgery should be considered only in patients who are unable to lose weight with available conventional therapy and who have no absolute contraindications for surgery.

- These guidelines recommend the use of a food diary to focus on dietary substitutes.
- Thirty minutes of moderate-intensity activity on 5 or more days of the week results in health benefits for obese individuals. Moreover, several studies indicate that 60 to 80 min of moderate to vigorous physical activity may provide additional benefit.
- Increased physical activity without caloric restriction (minimal or no weight loss) can reduce abdominal (visceral) adipose tissue and improve insulin resistance.
- The key features of the standard behavioral modification program include goal setting, self-monitoring, stimulus control (modification of one's environment to enhance behaviors that will support weight management), cognitive restructuring (increased awareness of perceptions of oneself and one's weight), and prevention of relapse (weight regain).
- Mammalian sleep is closely integrated with the regulation of energy balance. Trials have shown that the amount of human sleep contributes to the maintenance of fat-free body mass at times of decreased energy intake. Lack of sufficient sleep may compromise the efficacy of typical dietary interventions for weight loss and related metabolic risk reduction.

ACUTE GENERAL Rx

- According to the NHLBI *Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults* and the U.S. Food and Drug Administration (FDA), pharmacotherapy is indicated for:
  1. Obese patients with a BMI ≥30.
  2. Overweight patients with a BMI of ≥27 and concomitant obesity-related risk factors or diseases, such as hypertension, diabetes, or dyslipidemia.
- Pharmacologic treatment options include:
  1. Gastrointestinal lipase inhibitors: Orlistat is the only drug available for long-term treatment of obesity. It blocks the digestion and absorption of ingested dietary fat. It is a reversible inhibitor of pancreatic, gastric, and carboxyl ester lipases and phospholipase A2, which are required for the hydrolysis of dietary fat in the gastrointestinal tract. Side effects include flatulence, fecal incontinence, cramps, and oily spotting. There can also be impairment of absorption of fat-soluble vitamins (A, D, E, K) and beta-carotene. Oxalate-associated acute kidney injury and rare severe liver injury have also been reported.
  2. C serotonin agonists: Lorcaserin is a selective serotonin agonist that acts centrally to reduce appetite, aiding weight loss. Adverse effects include headache, upper respiratory infections, dizziness, and nausea. While there is little evidence of serotonin-associated cardiac valvular disease or pulmonary hypertension (as seen with nonselective serotonergic agonists fenfluramine and dexfenfluramine), long-term data is currently limited.
  3. Sympathomimetic medications: Phentermine and diethylpropion are currently approved for short-term treatment of obesity. They reduce food intake by causing early satiety. Side effects include increased blood pressure and increased pulse. They are Schedule IV drugs with a potential for abuse. Other sympathomimetic drugs that have been removed from the market due to concerns about cardiovascular safety are sibutramine, phenylpropanolamine, and ephedrine.
  4. Antidepressants: While not FDA-approved for treatment of obesity alone, bupropion and fluoxetine are antidepressants that have been associated with modest weight loss. The FDA has recently approved a fixed-dose combination of bupropion with the opioid receptor antagonist naltrexone. It is called Contrave and approved for use as an adjunct to diet and exercise in patients with BMI ≥30 kg/m^2 or a BMI ≥27 kg/m^2 and one or more weight-related comorbidities (e.g., diabetes, hypertension, dyslipidemia).
  5. Antiepileptic drugs: Zonisamide and topiramate (also used in migraine therapy) have been associated with weight loss in clinical trials but are not currently FDA-approved for treatment of obesity alone.
  6. Diabetes drugs: While not FDA-approved for treatment of obesity alone, metformin, pramlintide (synthetic human amylin), and glucagon-like polypeptide-1 agonists (exenatide, liraglutide) have been associated with weight loss in the treatment of individuals with diabetes. Weight loss was also reported in a trial of liraglutide in patients without diabetes.

CHRONIC Rx

- According to the NHLBI guidelines, surgical intervention is an option for selected patients with clinically severe obesity (a BMI ≥40 or a BMI ≥35 with comorbid conditions), when patients are at high risk for obesity-associated morbidity or death, and when less invasive methods of weight loss have failed.
- Eligible patients should also be at an acceptable risk for surgery, well informed, and motivated.
- Bariatric surgery for weight loss falls into one of three general categories:
- Restrictive surgeries limit the amount of food the stomach can hold and slow the rate of gastric emptying. These include vertical banded gastroplasty and laparoscopic adjustable silicone gastric banding LAGB [Fig. EO1-2]). Band slippage is the most common LAGB complication. Other potential complications include port or tubing malfunction, stomal obstruction, band erosion, pouch dilatation, and port infection. Gastric necrosis of the stomach wall is a rarer late complication that results from ischemia caused by a combination of gastric prolapse—the part of the stomach below the band herniates up through the device (Fig. EO1-3)—and pressure from the band. Gastric bypass has better outcomes than gastric band procedures for long-term weight loss, type 2 diabetes control and remission, hypertension, and hyperlipidemia. These procedures have benefits that include: lower perioperative mortality rate, a quicker recovery period, and no malabsorption issues. However, they are not as effective as gastric bypass for weight reduction and comorbidity improvement.
  1. Malabsorptive surgeries reduce nutrient absorption by shortening length of small intestine. These include jejunoileal bypass and the duodenal switch operation (DS).
  2. Restrictive malabsorptive bypass procedures combine the elements of gastric restriction and selective malabsorption. These include Roux-en-Y gastric bypass

(considered the gold standard because of its high level of effectiveness and durability) and biliopancreatic diversion. These procedures have higher rates of comorbidity improvement than restrictive surgeries, but can be complicated by malabsorption and nutritional deficiencies

- Compared with usual care, bariatric surgery is associated with reduced number of cardiovascular deaths and lower incidence of cardiovascular events in obese adults. A study on bariatric surgery patients demonstrated a significant reduction in long-term cardiovascular events. Ten-year follow-up estimated relative risk reductions ranging from 18% to 79% according to the Framingham risk score and 8% to 62% with the PROCAM risk score.
- A recent long-term observational study of obese patients with type 2 diabetes showed that bariatric surgery was associated with higher diabetes remission rates and fewer complications than usual care (Sjostrom et al, 2014).
- Liposuction is removal of fat by aspiration after injection of physiologic saline. This technique reduces the subcutaneous fat but has failed to improve insulin sensitivity or risk factors for CHD.

DISPOSITION

- The incidence of venous thromboembolism in the upper tertile of BMI was 2.42 times that of the lowest BMI tertile. Obese patients have a higher incidence of postoperative thromboembolic events when undergoing noncardiac surgery.
- Obesity may be associated with higher rates of postoperative pulmonary complications and poor wound healing.
- Weight-stable obese subjects have an increased risk of arrhythmias and sudden death even in the absence of cardiac dysfunction.
- Obesity and the cardiac autonomic nervous system are intrinsically related. A 10% increase in body weight is associated with a decline in parasympathetic tone accompanied by a rise in mean heart rate. Conversely, a 10% weight loss in severely obese patients is associated with significant improvement in autonomic nervous system cardiac modulation, including decreased heart rate and increased heart rate variability.
- Postmortem Determinants of Atherosclerosis in Youth (PDAY) study data provided convincing evidence that obesity in adolescents and young adults accelerates the progression of atherosclerosis decades before the appearance of clinical manifestations.
- Obesity accelerates the progression of native coronary atherosclerosis and after coronary artery bypass grafting.
- In older adults, obesity is associated with protection against hip fracture, but this protective effect on bone status does not offset the extensive array of potential adverse effects on conditions common in the older population.

REFERRAL

- Obesity is commonly seen in the primary care setting. If pharmacologic therapy is considered, consultation with physicians specializing in obesity and experienced with the use of the drug is recommended. In addition, consultation with nutritionists and behavioral therapists is helpful. A consultation with general surgery is indicated in patients being considered for surgical intervention.
- Recent trials have shown that among adolescents, use of gastric banding compared with lifestyle intervention results in a greater percentage achieving a loss of 50% of excess weight corrected for age. There were associated benefits to health and quality of life.

PEARLS & CONSIDERATIONS

COMMENTS

- Enhanced weight-loss counseling helps about one third of obese patients achieve long-term, clinically meaningful weight loss.
- The NHLBI launched the Obesity Education Initiative in January 1991. The overall purpose of the initiative is to help reduce the prevalence of overweight along with the prevalence of physical inactivity to reduce the risk of CHD and overall morbidity and mortality rates from CHD.
- The American Medical Association, in association with the Robert Wood Johnson Foundation and the U.S. Department of Health and Human Services, produced a primer for the assessment and management of adult obesity. The primer consists of 10 booklets that offer practical recommendations for addressing adult obesity in the primary care setting and is available free of charge at: http://www.amaassn.org/ama/pub/physician-resources.
- A recent study on BMI and all-cause mortality in a large prospective study suggests that optimal BMI range is between 20 and 24.9 (Patel AV, 2014).
- Recent research indicates that brown adipose tissue represents a natural target for the modulation of energy expenditure. The presence of brown adipose tissue in humans may be quantified with the use of ^{18}F-FDG PET-CT. The amount of brown adipose tissue is inversely correlated with BMI, suggesting a potential role of brown adipose tissue in adult human metabolism.
- Obesity, glucose intolerance, and hypertension in childhood are strongly associated with increased rates of premature death from endogenous causes in this population.
- Recent trials have shown that among persons living in a controlled setting, calories alone account for the increase in fat. Protein affected energy expenditure and storage of lean body mass, but not body fat storage.
- There have been no evidence-based studies supporting combination medical therapy for weight loss.
- Data are lacking for the role of pharmacotherapy and bariatric surgery in the elderly population.

PREVENTION

- Prevention of overweight and obesity involves both increasing physical activity and dietary modification to reduce caloric intake.
- There is compelling evidence that prevention of weight regain in formerly obese individuals requires 60 to 90 min of moderate intensity activity or lesser amounts of vigorous intensity activity.
- Moderate intensity activity of approximately 45 to 60 min per day, or 1.7 physical activity level (PAL), is required to prevent the transition to overweight or obesity. For children, even more activity time is recommended.
- Clinicians can help guide patients to develop personalized eating plans and help them recognize the contributions of fat, concentrated carbohydrates, and large portion sizes.
- Clinicians must work with patients to modify other risk factors such as tobacco use, high glycemic intake, and elevated blood pressure to prevent the long-term chronic disease sequelae of obesity.
- Regular screening of body weight and BMI measurements at routine office visits can help identify early weight gain.

PATIENT & FAMILY EDUCATION

Information can be obtained on the American Obesity Association website (http://www.obesity.org) and the American Medical Association website (http://www.ama-assn.org).

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Obesity, Female (Patient Information)
Obesity, Male (Patient Information)

AUTHOR: **CRAIG L. BASMAN, M.D.**

EVIDENCE

Abstract[1]

Background:
Obesity exacerbates the age-related decline in physical function and causes frailty in older adults; however, the appropriate treatment for obese older adults is controversial.
Methods:
In this 1-year, randomized, controlled trial, we evaluated the independent and combined effects of weight loss and exercise in 107 adults who were ≥65 yrs and obese. Participants were randomly assigned to a control group, a weight-management (diet) group, an exercise group, or a weight-management-plus-exercise (diet–exercise) group. The primary outcome was the change in score on the modified Physical Performance Test. Secondary outcomes included other measures of frailty, body composition, bone mineral density, specific physical functions, and quality of life.
Results:
A total of 93 participants (87%) completed the study. In the intention-to-treat analysis, the score on the Physical Performance Test, in which higher scores indicate better physical status, increased more in the diet–exercise group than in the diet group or the exercise group (increases from baseline of 21% versus 12% and 15%, respectively); the scores in all three of those groups increased more than the scores in the control group (in which the score increased by 1%) (P<0.001 for the between-group differences). Moreover, the peak oxygen consumption improved more in the diet-exercise group than in the diet group or the exercise group (increases of 17% versus 10% and 8%, respectively; P<0.001); the score on the Functional Status Questionnaire, in which higher scores indicate better physical function, increased more in the diet–exercise group than in the diet group (increase of 10% versus 4%, P<0.001). Body weight decreased by 10% in the diet group and by 9% in the diet–exercise group, but did not decrease in the exercise group or the control group (P<0.001). Lean body mass and bone mineral density at the hip decreased less in the diet–exercise group than in the diet group (reductions of 3% and 1%, respectively, in the diet-exercise group versus reductions of 5% and 3%, respectively, in the diet group; P<0.05 for both comparisons). Strength, balance, and gait improved consistently in the diet–exercise group (P<0.05 for all comparisons). Adverse events included a small number of exercise-associated musculoskeletal injuries.
Conclusions:
These findings suggest that a combination of weight loss and exercise provides greater improvement in physical function than either intervention alone. (Funded by the National Institutes of Health;ClinicalTrials.gov number, NCT00146107.) Ⓐ

Abstract[2]

Background:
Consumption of sugar-sweetened beverages may cause excessive weight gain. We aimed to assess the effect on weight gain of an intervention that included the provision of noncaloric beverages at home for overweight and obese adolescents.
Methods:
We randomly assigned 224 overweight and obese adolescents who regularly consumed sugar-sweetened beverages to experimental and control groups. The experimental group received a 1-year intervention designed to decrease consumption of sugar-sweetened beverages, with follow-up for an additional year without intervention. We hypothesized that the experimental group would gain weight at a slower rate than the control group.
Results:
Retention rates were 97% at 1 year and 93% at 2 years. Reported consumption of sugar-sweetened beverages was similar at baseline in the experimental and control groups (1.7 servings per day), declined to nearly 0 in the experimental group at 1 year, and remained lower in the experimental group than in the control group at 2 years. The primary outcome, the change in mean body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) at 2 years, did not differ significantly between the two groups (change in experimental group minus change in control group, –0.3; P = 0.46). At 1 year, however, there were significant between-group differences for changes in BMI (–0.57, P = 0.045) and weight (–1.9 kg, P = 0.04). We found evidence of effect modification according to ethnic group at 1 year (P = 0.04) and 2 years (*P* = 0.01). In a prespecified analysis according to ethnic group, among Hispanic participants (27 in the experimental group and 19 in the control group), there was a significant between-group difference in the change in BMI at 1 year (–1.79, *P* = 0.007) and 2 years (–2.35, *P* = 0.01), but not among non-Hispanic participants (*P* > 0.35 at years 1 and 2). The change in body fat as a percentage of total weight did not differ significantly between groups at 2 years (–0.5%, *P* = 0.40). There were no adverse events related to study participation.
Conclusions:
Among overweight and obese adolescents, the increase in BMI was smaller in the experimental group than in the control group after a 1-year intervention designed to reduce consumption of sugar-sweetened beverages, but not at the 2-year follow-up (the prespecified primary outcome). (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others;ClinicalTrials.gov number, NCT00381160.) Ⓐ

Abstract[3]

AMP-activated protein kinase (AMPK) is an essential sensor of cellular energy status. Defects in the α2 catalytic subunit of AMPK (AMPK α1) are associated with metabolic syndrome. The current study investigated the role AMPK α1 in the pathogenesis of obesity and inflammation using male AMPK α1-deficent (AMPKa1-/-) mice and their wild-type (WT) litter mates. After being fed a high-fat diet (HFD), global AMPK α1-/- mice gained more body weight and greater adiposity and exhibited systemic insulin resistance and metabolic dysfunction with increased severity in their adipose tissues compared with their WT litter mates. Interestingly, upon HFD feeding, irradiated WT mice that received the bone marrow of AMPK α1-/- mice showed increased insulin resistance but not obesity, whereas irradiated AMPK α 1-/- mice with WT bone marrow had a phenotype of metabolic dysregulation that was similar to that of global AMPK α1-/- mice. AMPK α1 deficiency in macrophages markedly increased the macrophage proinflammatory status. In addition, AMPK α1 knockdown enhanced adipocyte lipid accumulation and exacerbated the inflammatory response and insulin resistance. Together, these data show that AMPK α1 protects mice from diet-induced obesity and insulin resistance, demonstrating that AMPK α1 is a promising therapeutic target in the treatment of the metabolic syndrome. Ⓐ

Abstract[4]

Objective:
Obesity leads to severe long-term complications and reduced life expectancy. Roux-en-Y gastric bypass (RYGB) surgery induces excessive and continuous weight loss in (morbid) obesity, although it causes several abnormal anatomical and physiological conditions.
Research Design and Methods:
To distinctively unveil effects of RYGB surgery on ß-cell function and glucose turnover in skeletal muscle, liver, and gut, nondiabetic, morbidly obese patients were studied before (preOP, five female/one male, BMI: 49 ± 3 kg/m^2, 43 ± 2 years of age) and 7 ± 1 months after (postOP, BMI: 37 ± 3 kg/m2) RYGB surgery, compared with matching obese (CONob, five female/one male, BMI: 34 ± 1 kg/m^2, 48 ± 3 years of age) and lean controls (CONlean, five female/one male, BMI: 22 ± 0 kg/m^2, 42 ± 2 years of age). Oral glucose tolerance tests (OGTTs), hyperinsulinemic-isoglycemic clamp tests, and mechanistic mathematical modeling allowed determination of whole-body insulin sensitivity (M/I), OGTT and clamp test ß-cell function, and gastrointestinal glucose absorption.
Results:
PostOP lost (*P*<0.0001) 35 ± 3 kg body weight. M/I increased after RYGB, becoming comparable to CONob, but remaining markedly lower than CONlean (*P*<0.05). M/I tightly correlated (t = -0.611, P<0.0001) with fat mass. During OGTT, postOP showed ≥15% reduced plasma glucose from 120 to 180 min (≤4.5 mmol/L), and 29-fold elevated active glucagon-like peptide-1 (GLP-1) dynamic areas under the curve, which tightly correlated (r = 0.837, *P*<0.001) with 84% increased ß-cell secretion. Insulinogenic index (0 to 30 min) in postOP was ≥29% greater (P<0.04).

At fasting, post-OP showed approximately halved insulin secretion (P<0.05 versus preOP). Insulin-stimulated insulin secretion in post-OP was 52% higher than before surgery, but 1=2 pmol/min^2 lower than in CONob/CONlean (*P*<0.05). Gastrointestinal glucose absorption was comparable in preOP and postOP, but 9 to 26% lower from 40 to 90 min in postOP than in CONob/CONlean (*P*<0.04).

Conclusions:

RYGB surgery leads to decreased plasma glucose concentrations in the third OGTT hour and exaggerated ß-cell function, for which increased GLP-1 release seems responsible, whereas gastrointestinal glucose absorption remains unchanged but lower than in matching controls. Ⓐ

Abstract[5]

Background:

Temporal increases in the consumption of sugar-sweetened beverages have paralleled the rise in obesity prevalence, but whether the intake of such beverages interacts with the genetic predisposition to adiposity is unknown.

Methods:

We analyzed the interaction between genetic predisposition and the intake of sugar-sweetened beverages in relation to body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) and obesity risk in 6934 women from the Nurses' Health Study (NHS) and in 4423 men from the Health Professionals Follow-up Study (HPFS) and also in a replication cohort of 21,740 women from the Women's Genome Health Study (WGHS). The genetic-predisposition score was calculated on the basis of 32 BMI-associated loci. The intake of sugar-sweetened beverages was examined prospectively in relation to BMI.

Results:

In the NHS and HPFS cohorts, the genetic association with BMI was stronger among participants with higher intake of sugar-sweetened beverages than among those with lower intake. In the combined cohorts, the increases in BMI per increment of 10 risk alleles were 1.00 for an intake of less than one serving per month, 1.12 for one to four servings per month, 1.38 for two to six servings per week, and 1.78 for one or more servings per day (*P*<0.001 for interaction). For the same categories of intake, the relative risks of incident obesity per increment of 10 risk alleles were 1.19 (95%confidence interval [CI], 0.90 to 1.59), 1.67 (95% CI, 1.28 to 2.16), 1.58 (95% CI, 1.01 to 2.47), and 5.06 (95% CI, 1.66 to 15.5) (*P* = 0.02 for interaction). In the WGHS cohort, the increases in BMI per increment of 10 risk alleles were 1.39, 1.64, 1.90, and 2.53 across the four categories of intake (*P* = 0.001 for interaction); the relative risks for incident obesity were 1.40 (95% CI, 1.19 to 1.64), 1.50 (95% CI, 1.16 to 1.93), 1.54 (95% CI, 1.21 to 1.94), and 3.16 (95% CI, 2.03 to 4.92), respectively (*P* = 0.007 for interaction).

Conclusions:

The genetic association with adiposity appeared to be more pronounced with greater intake of sugar-sweetened beverages. (Funded by the National Institutes of Health and others.) Ⓐ

Abstract[6]

Background:

Many beliefs about obesity persist in the absence of supporting scientific evidence (presumptions); some persist despite contradicting evidence (myths). The promulgation of unsupported beliefs may yield poorly informed policy decisions, inaccurate clinical and public health recommendations, and an unproductive allocation of research resources and may divert attention away from useful, evidence-based information.

Methods:

Using Internet searches of popular media and scientific literature, we identified, reviewed, and classified obesity-related myths and presumptions. We also examined facts that are well supported by evidence, with an emphasis on those that have practical implications for public health, policy, or clinical recommendations.

Results:

We identified seven obesity-related myths concerning the effects of small sustained increases in energy intake or expenditure, establishment of realistic goals for weight loss, rapid weight loss, weight-loss readiness, physical-education classes, breast-feeding, and energy expended during sexual activity. We also identified six presumptions about the purported effects of regularly eating breakfast, early childhood experiences, eating fruits and vegetables, weight cycling, snacking, and the built (i.e., human-made) environment. Finally, we identified nine evidence-supported facts that are relevant for the formulation of sound public health, policy, or clinical recommendations.

Conclusions:

False and scientifically unsupported beliefs about obesity are pervasive in both scientific literature and the popular press. (Funded by the National Institutes of Health.) Ⓐ

Abstract[7]

Objective:

Given that the repetitive loss and regain of body weight, termed weight cycling, is a prevalent phenomenon that has been associated with negative physiological and psychological outcomes, the purpose of this study was to investigate weight change and physiological outcomes in women with a lifetime history of weight cycling enrolled in a 12-month diet and/or exercise intervention.

Methods:

439 overweight, inactive, postmenopausal women were randomized to: i) dietary weight loss with a 10% weight loss goal (N = 118); ii) moderate-to-vigorous intensity aerobic exercise for 45 min/day, 5 days/week (n = 117); iii) both dietary weight loss and exercise (n = 117); or iv) control (n = 87). Women were categorized as non-, moderate- (≥3 losses of ≥4.5 kg), or severe-cyclers (≥3 losses of ≥9.1 kg). Trend tests and linear regression were used to compare adherence and changes in weight, body composition, blood pressure, insulin, C-peptide, glucose, insulin resistance (HOMA-IR), C-reactive protein, leptin, adiponectin, and interleukin-6 between cyclers and non-cyclers.

Results:

Moderate (n = 103) and severe (n = 77) cyclers were heavier and had less favorable metabolic profiles than non-cyclers at baseline. There were, however, no significant differences in adherence to the lifestyle interventions. Weight-cyclers (combined) had a greater improvement in HOMA-IR compared with non-cyclers participating in the exercise only intervention (*P* = 0.03), but no differences were apparent in the other groups.

Conclusion:

A history of weight cycling does not impede successful participation in lifestyle interventions or alter the benefits of diet and/or exercise on body composition and metabolic outcomes. Ⓐ

Abstract[8]

Background:

Intensive diabetes mellitus therapy of type 1 diabetes mellitus reduces diabetes mellitus complications but can be associated with excess weight gain, central obesity, and dyslipidemia. The purpose of this study was to determine whether excessive weight gain with diabetes mellitus therapy of type 1 diabetes mellitus is prospectively associated with atherosclerotic disease.

Methods and Results:

Subjects with type 1 diabetes mellitus (97% white, 45% female, mean age 35 years) randomly assigned to intensive or conventional diabetes mellitus treatment during the Diabetes Control and Complications Trial (DCCT) underwent intima-media thickness (n = 1015) and coronary artery calcium score (n = 925) measurements during follow-up in the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. Intensive treatment subjects were classified by quartile of body mass index change during the DCCT. Excess gainers (4th quartile, including conventional treatment subjects meeting this threshold) maintained greater body mass index and waist circumference, needed more insulin, had greater intima-media thickness (+ 5%, *P* <0.001 EDIC year 1, *P* =0.003 EDIC year 6), and trended toward greater coronary artery calcium scores (odds ratio, 1.55; confidence interval, 0.97 to 2.49; *P* = 0.07) than minimal gainers. DCCT subjects meeting metabolic syndrome criteria for waist circumference and blood pressure had greater intima-media thickness in both EDIC years (*P* = 0.02 to <0.001); those meeting

high-density lipoprotein criteria had greater coronary artery calcium scores (odds ratio, 1.6; confidence interval, 1.1 to 2.4; $P = 0.01$) during follow-up. Increasing frequency of a family history of diabetes mellitus, hypertension, and hyperlipidemia was associated with greater intima-media thickness with intensive but not conventional treatment.

Conclusions:

Excess weight gain in DCCT is associated with sustained increases in central obesity, insulin resistance, dyslipidemia and blood pressure, as well as more extensive atherosclerosis during EDIC. Clinical Trial Registration: URL for DCCT: http://clinicaltrials.gov; Unique identifier: NCT00360815. URL for EDIC: http://clinicaltrials.gov; Unique identifier: NCT00360893. A

Abstract[9]

Background:

The Diabetes Prevention Program (DPP) lifestyle intervention reduced the incidence of type 2 diabetes mellitus (DM) among high-risk adults by 58%, with weight loss as the dominant predictor. However, it has not been adequately translated into primary care.

Methods:

We evaluated 2 adapted DPP lifestyle interventions among overweight or obese adults who were recruited from 1 primary care clinic and had pre-DM and/or metabolic syndrome. Participants were randomized to (1) a coach-led group intervention (n = 79), (2) a self-directed DVD intervention (n = 81), or (3) usual care (n = 81). During a 3-month intensive intervention phase, the DPP-based behavioral weight-loss curriculum was delivered by lifestyle coach–led small groups or home-based DVD. During the maintenance phase, participants in both interventions received lifestyle change coaching and support remotely—through secure email within an electronic health record system and the American Heart Association Heart360 website for weight and physical activity goal setting and self-monitoring. The primary outcome was change in body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) from baseline to 15 months.

Results:

At baseline, participants had a mean (SD) age of 52.9 (10.6) years and a mean BMI of 32.0 (5.4); 47% were female; 78%, non-Hispanic white; and 17%, Asian/Pacific Islander. At month 15, the Mean ± SE change in BMI from baseline was −2.2 ± 0.3 in the coach-led group versus −0.9 ± 0.3 in the usual care group ($P < 0.001$) and −1.6 ± 0.3 in the self-directed group versus usual care ($P = 0.02$). The percentages of participants who achieved the 7% DPP-based weight-loss goal were 37.0% ($P = 0.003$) and 35.9% ($P = 0.004$) in the coach-led and self-directed groups, respectively, versus 14.4% in the usual care group. Both interventions also achieved greater net improvements in waist circumference and fasting plasma glucose level.

Conclusion:

Proven effective in a primary care setting, the 2 DPP-based lifestyle interventions are readily scalable and exportable with potential for substantial clinical and public health impact. A

Abstract[10]

Recent guidelines on exercise for weight loss and weight maintenance include resistance training as part of the exercise prescription. Yet few studies have compared the effects of similar amounts of aerobic and resistance training on body mass and fat mass in overweight adults. STRRIDE AT/RT, a randomized trial, compared aerobic training, resistance training, and a combination of the two to determine the optimal mode of exercise for obesity reduction. Participants were 119 sedentary, overweight or obese adults who were randomized to one of three 8-mo exercise protocols: 1) RT: resistance training, 2) AT: aerobic training, and 3) AT/RT: aerobic and resistance training (combination of AT and RT). Primary outcomes included total body mass, fat mass, and lean body mass. The AT and AT/RT groups reduced total body mass and fat mass >RT ($P < 0.05$), but they were not different from each other. RT and AT/RT increased lean body mass >AT ($P < 0.05$). While requiring double the time commitment, a program of combined AT and RT did not result in significantly more fat mass or body mass reductions over AT alone. Balancing time commitments against health benefits, it appears that AT is the optimal mode of exercise for reducing fat mass and body mass, while a program including RT is needed for increasing lean mass in middle-aged, overweight/obese individuals.

Evidence-Based Reference

Villareal DT et al.: Weight loss, exercise, or both and physical function in obese older adults, *N Engl J Med* 364:1218–1229, 2011. A

Ebbeling CB et al.: A randomized trial of sugar-sweetened beverages and adolescent body weight, *N Engl J Med* 367:1407–1416, 2012. A

Zhang W et al.: AMP-activated protein kinase $\alpha 1$ protects against diet-induced insulin resistance and obesity, *Diabetes* 61:3114–3125, 2012. A

Anderwald C-H et al.: Alterations in gastrointestinal, endocrine, and metabolic processes after bariatric Roux-en-Y gastric bypass surgery, *Diabetes Care* 35:2580–2587, 2012. A

Qi Q et al.: Sugar-sweetened beverages and genetic risk of obesity, *N Engl J Med* 367:1387–1396, 2012. A

Casazza K et al.: Myths, presumptions, and facts about obesity, *N Engl J Med* 368:446–454, 2013. A

Mason C et al.: History of weight cycling does not impede future weight loss or metabolic improvements in postmenopausal women, *Metabolism* 62:127–136, 2013. A

Purnell JQ: The effect of excess weight gain with intensive diabetes mellitus treatment on cardiovascular disease risk factors and atherosclerosis in type 1 diabetes mellitus: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC) study, *Circulation* 127:180–187, 2013. A

Ma J et al.: Translating the Diabetes Prevention Program lifestyle intervention for weight loss into primary care: a randomized trial, *JAMA Intern Med* 173:113–121, 2013. A

Marie Ng et al.: Global, regional and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis of the Global Burden of Disease Study 2013, *The Lancet* 384(9945):766–781, 2014. A

Patel AV et al.: L Body Mass index and all-cause mortality in a large prospective cohort of White and Black US Adults, *PloS One* 9(10), 2014. A

Sjostrom L et al.: Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications, *JAMA* 311(22):2297–2304, 2014. A

Willis LH et al.: Effects of aerobic and/or resistance training on body mass and fat mass in overweight or obese adults, *J Appl Physiol* 113:1831–1837, 2012. A

SUGGESTED READINGS

Bray GA et al.: Effect of dietary protein content on weight gain, energy expenditure, and body composition during overeating, *JAMA* 307(1):47–55, 2012.

Casazza K et al.: Myths, presumptions, and facts about obesity, *N Engl J Med* 368:446–454, 2013.

DeMaria EJ: Bariatric surgery for morbidly obese, *N Engl J Med* 356:2176, 2008.

Eckel RH: Nonsurgical management of obesity in adults, *N Engl J Med* 358:2008, 1941.

Franks PW et al.: Childhood obesity, other cardiovascular risk factors, and premature death, *N Engl J Med* 362:485–493, 2010.

James WPT et al.: Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects, *N Engl J Med* 363:905–917, 2010.

Juonala M et al.: Childhood adiposity, adult adiposity, and cardiovascular risk factors, *N Engl J Med* 365:1876–1885, 2011.

Kodner C, Hartman DR: Complications of adjustable gastric banding surgery for obesity, *Am Fam Physician* 89(10):813–818, 2014.

Kumanyika SK et al.: Population-based prevention of obesity: the need for comprehensive promotion of healthful eating, physical activity, and energy balance. A Scientific Statement from American Heart Association Council on Epidemiology and Prevention, Interdisciplinary Committee for Prevention (Formerly the Expert Panel on Population and Prevention Science), *Circulation* 118:428–464, 2008.

Ludwig DS: Childhood obesity—the shape of things to come, *N Engl J Med 357* 2325, 2007.

Maggard-Gibbons M et al.: Bariatric surgery for weight loss and glycemic control in nonmorbidly obese adults with diabetes, *JAMA* 309(21):2250–2261, 2013.

Markus P et al.: European Society of Hypertension Working Group on Obesity: Obesity-induced hypertension and target organ damage: current knowledge and future directions, *J Hypertens* 27:207–211, 2009.

Moyer VA et al.: Screening for and management of obesity in adults: U.S. Preventive Services Task Force recommendation statement, *Ann Intern Med* 157:373–378, 2012.

Nedeltcheva AV et al.: Insufficient sleep undermines dietary efforts to reduce adiposity, *Ann Intern Med* 153:435–441, 2010.

O'Brien PE et al.: Laparoscopic adjustable gastric binding in severely obese adolescents, *JAMA* 303(6):519–526, 2010.

Poirier P et al.: Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism, *Circulation* 113:898–918, 2006.

Puzziferri N et al.: Long-term follow-up after bariatric surgery: a systematic review, *JAMA* 312(9):934–942, 2014.

Rao G: Office-based strategies for the management of obesity, *Am Fam Physician* 81:11449–11455, 2010.

Schauer PR et al.: Bariatric surgery versus intensive medical therapy in obese patients with diabetes, *N Engl J Med* 366:1567–1576, 2012.

Sjostrom L et al.: Bariatric surgery and long-term cardiovascular events, *JAMA* 307(1):56–65, 2012.

The NS et al.: Association of adolescent obesity with risk of severe obesity in adulthood, *JAMA* 304(18):2042–2047, 2010.

Wadden TA et al.: A two-year randomized trial of obesity treatment in primary care practice, *N Engl J Med* 365:1969–1979, 2011.

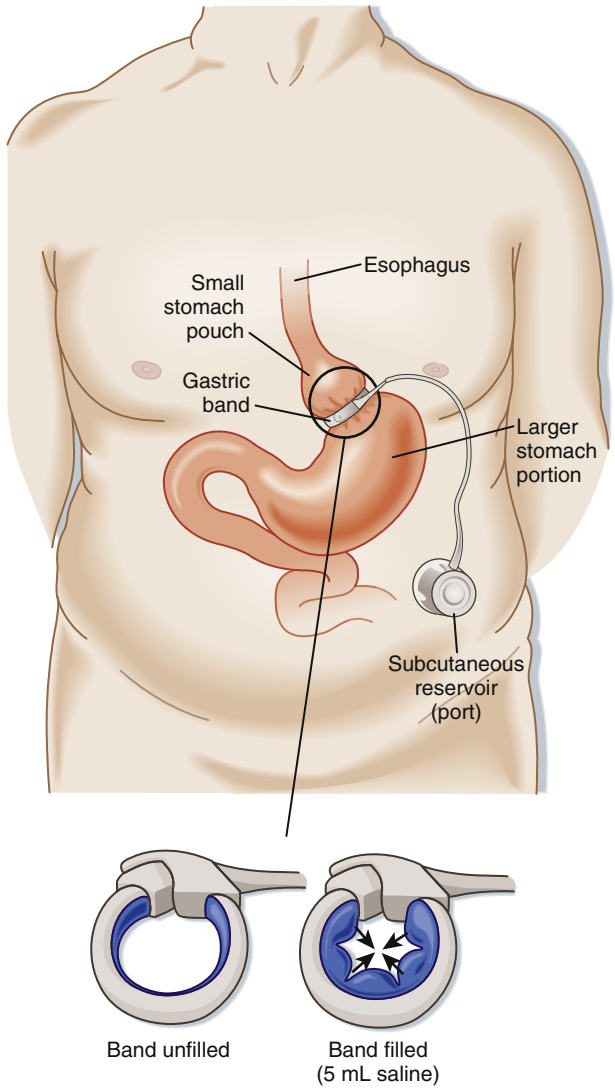


FIGURE EO1-2 Laparoscopic adjustable gastric banding. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

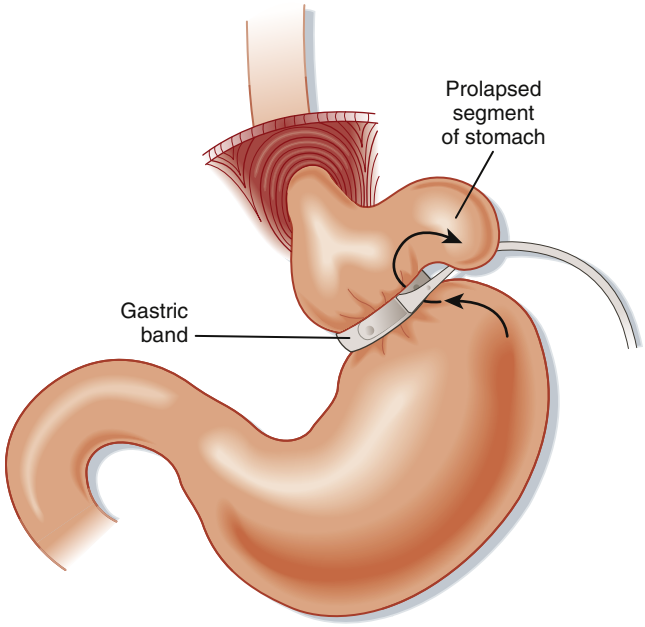


FIGURE EO1-3 Gastric prolapse. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

Obsessive-Compulsive Disorder (OCD) PTG

BASIC INFORMATION

DEFINITION

Obsessive-compulsive disorder (OCD) is characterized by obsessions (recurrent and persistent thoughts, urges, or images experienced as intrusive and unwanted) and/or compulsions (repetitive behaviors or mental acts performed in response to obsessions, or according to rules that must be applied rigidly) that are time-consuming (e.g., >1 hr/day) or cause marked impairment or distress. The symptoms are usually perceived as excessive and unreasonable.

SYNONYMS

OCD

ICD-9CM and DSM-5 CODES
300.3
ICD-10CM CODES
F42 Obsessive-compulsive disorder

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Mean age at onset is 19.6 yr.
12-MONTH PREVALENCE: 1.2% of adults in the United States, international prevalence estimates are similar (1.1% to 1.8%)
PREDOMINANT SEX: Approximately equal distribution between sexes
PREDOMINANT AGE

- Modal age of onset for females is between 20 and 29 yr.
- Modal age of onset for males is between 6 and 15 yr.

DISEASE COURSE

- Condition is chronic with waxing and waning pattern.
- Symptoms typically worsen with stress.
- 15% show progressive deterioration, whereas 5% show an episodic course with little impairment between episodes.

GENETICS

- OCD is a multifactorial familial condition that involves both polygenic and environmental risk factors.
- Rate of concordance is higher in monozygotic (57%) compared with dizygotic (27%) twins.
- Rate of disorder is also much higher in first-degree relatives of individuals with OCD and Tourette's disorder than in the general population.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Persistent and recurrent intrusive and ego-dystonic obsessive ideas, thoughts, urges, or images that are perceived as alien and beyond one's control.
- Frequent experiencing of obsessions related to contamination (e.g., when using the telephone), excessive doubt (e.g., was the door locked?), organization (the need for a particular order), violent impulses (e.g., to yell obscenities in church), or intrusive sexual imagery.
- Compulsive behaviors (e.g., repeated hand washing, checking, rearranging) or mental rituals (e.g., counting, repeating phrases) meant to temporarily ameliorate anxiety caused by obsessions.
- Obsessions and compulsions almost always accompanied by high anxiety and subjective distress. Both are usually seen as excessive and unreasonable.

ETIOLOGY

- Strong evidence of cortico-striato-thalamo-cortical circuit dysfunction.
- OCD onset may be temporally associated with infectious illness of CNS (e.g., Von Economo's encephalitis, Sydenham's chorea).
- OCD may follow head trauma or other premorbid neurologic condition, including birth hypoxia and Tourette's syndrome.
- Serotonergic, dopaminergic, and glutamatergic systems believed important in some ritualistic instinctual behaviors, with dysfunction of these pathways possibly giving rise to OCD.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Obsessive-compulsive personality disorder (OCPD) is a maladaptive personality style defined by excessive rigidity, need for order and control, preoccupation with details, and excessive perfectionism. Unlike OCD, OCPD is ego-syntonic.
- Other psychiatric disorders in which obsessive or intrusive thoughts occur (e.g., body dysmorphic disorder, eating disorders, hypochondriasis, phobias, posttraumatic stress disorder).
- Impulse control disorders (e.g., trichotillomania [hair-pulling disorder], excoriation (skin-picking) disorder, pathologic gambling disorder, compulsive shopping, kleptomania, paraphilias/sexual compulsions).
- Neurologic disorders with repetitive behaviors (e.g., Tourette's syndrome, Sydenham's chorea, torticollis, autism).
- Delusions or psychosis, which may be mistaken for obsessive thoughts; unlike OCD, these individuals do not believe their obsessions are unreal and may likely meet criteria for another psychotic spectrum disorder that fully accounts for the obsessions (e.g., schizophrenia).

WORKUP

- Careful history leading to diagnosis.
- Neurologic examination to rule out concomitant Tourette's or other tic disorder.
- In adolescents and children: psychological testing to reveal learning disabilities.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Treatment will help ~50% of patients achieve partial remission within the first 6 mo.
- Cognitive-behavioral therapy (CBT), especially exposure/response prevention, is successful in up to 70% of patients, but nearly 25% drop out of treatment because of the initial anxiety the exposures create. Best results are found for contamination obsessions and washing compulsions.

GENERAL Rx

- Antidepressants with serotonin reuptake blockade, including clomipramine, fluvoxamine, fluoxetine, paroxetine, sertraline, citalopram and escitalopram, venlafaxine, and duloxetine; optimal dosages are typically at the high end of the prescription range. Risk/benefit/alternatives discussion is crucial (e.g., dose-related risk of QT interval prolongation with clomipramine and citalopram).
- Clonazepam may be helpful in patients with extreme anxiety.
- Most improve with treatment, but few become symptom-free. No response in 15% of patients.
- Likely indefinite treatment. Relapse is common if medications are discontinued.
- Recent studies suggest that combination CBT and pharmacotherapy yields superior outcomes. More severe symptoms warrant combination therapy.
- Patients who do not respond to first-line treatments and those with comorbid psychosis and/or tic disorders may benefit from augmentation with a first- or second-generation antipsychotic medication (e.g., haloperidol, olanzapine, risperidone).
- Surgical intervention (e.g., cingulotomy, deep brain stimulation) is an option for the most extreme, refractory cases.

DISPOSITION

- Most mild to moderate cases can be managed on a regular outpatient basis. Treatment should typically start with SSRI monotherapy with regular follow-up to assess treatment response and side-effect management. Dose should be increased to maximum tolerated.
- Patient and family education may help improve medical adherence and support.

PEARLS & CONSIDERATIONS

Patients with OCD typically have insight regarding the irrationality of their obsessions and compulsions but lack the ability to control them. This may cause intense shame and avoidance of medical care unless patient education and support are provided. Screen for OCD, especially among patients who present with "depression" or "anxiety."

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Obsessive-Compulsive Disorder (OCD) (Patient Information)

AUTHORS: **AGUSTIN G. YIP, M.D., PH.D.** and **JASON M. SATTERFIELD, PH.D.**

SUGGESTED READINGS

American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, DSM-5, Fifth Edition, 2013.

Fineberg NA et al.: Pharmacotherapy of obsessive-compulsive disorder: evidence-based treatment and beyond, *Aust N Z J Psychiatry* 47(2):121–141, 2013.

Grant JE: Obsessive-compulsive disorder, *N Engl J Med* 371:646–653, 2014.

Pauls DL et al.: Obsessive-compulsive disorder: an integrative genetic and neurobiological perspective, *Nature Rev Neurosci* 15(6):410–424, 2014.

Ponniah K et al.: An update on the efficacy of psychological therapies in the treatment of obsessive-compulsive disorders in adults, *J Obsessive Compuls Relat Disord* 2(2):207–218, 2013.

BASIC INFORMATION

DEFINITION

The term *ocular foreign body* refers to a foreign body on the surface of the corneal epithelium.

ICD-9CM CODES
930 Foreign body in external eye
ICD-10CM CODES
T15 Foreign body on external eye
T15.0 Foreign body in cornea
T15.1 Foreign body in conjunctival sac
T15.8 Foreign body in other and multiple parts of external eye
T15.9 Foreign body on external eye, part unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Universal, with a predominance in active people
PEAK INCIDENCE: Childhood through active adult years
PREDOMINANT SEX: Perhaps slightly more common in men
PREDOMINANT AGE: Childhood through active adult years

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pain is most common symptom.
- Causes of most common foreign bodies:
  - Grinding (Fig. 01-4)
  - Drilling
  - Auto repair
  - Working beneath cars
  - Airborne particles, such as blown by fans

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- History of corneal foreign body seen
- Hemorrhage, loss of vision
- Distorted anterior chamber, soft eye
- Corneal abrasion
- Corneal ulceration or laceration
- Glaucoma
- Herpes ulcers
- Infection
- Other keratitis
- Intraocular foreign body

WORKUP

- Fluorescein stain, slit-lamp examination if no foreign body is found
- Ultrasound examination
- Plain radiographs

LABORATORY TESTS

Intraocular pressure to make certain that eye has not been penetrated

IMAGING STUDIES

Occasionally, MRI of the orbits to identify foreign bodies not found by other means. Do not perform MRI if suspect metallic foreign body. Plain radiographs and ultrasound are sufficient.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Remove foreign body
- Treat infection
- Repair eye if ruptured
- Treat corneal abrasion or injury

ACUTE GENERAL Rx

- Saline irrigation
- Removal of foreign body with moist cotton-tipped applicator after instillation of topical anesthetic drops
- Use burr or more aggressive treatment if needed
- Cycloplegics, antibiotics, and pressure dressing after removal of foreign body
- Repair corneal laceration or damaged eye

DISPOSITION

If symptoms persist 24 hr after examination, refer to an ophthalmologist.

REFERRAL

To ophthalmology within 24 hr if patient not completely comfortable

PEARLS & CONSIDERATIONS

COMMENTS

- Make sure foreign body is not intraocular (inside eye).
- Alkaline or acidic chemical foreign bodies can be dangerous; pH test must be performed if either of these is suspected (for all chemical foreign bodies).

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Corneal Foreign Body (Patient Information)

AUTHOR: **R. SCOTT HOFFMAN, M.D.**

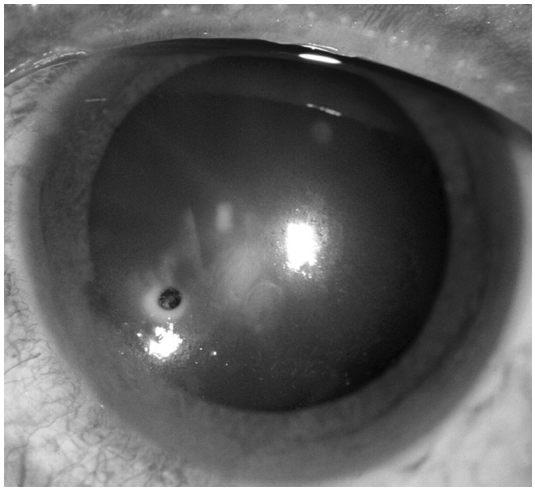


FIGURE 01-4 A small iron foreign body may be seen on external examination. (Courtesy Department of Dermatology, University of North Carolina at Chapel Hill. In Goldstein GB, Goldstein AO: *Practical dermatology,* ed 2, St Louis, 1997, Mosby.)

SUGGESTED READINGS

Pokhrel P, Loftus SA: Ocular emergencies, *Am Fam Physician* 76:829–836, 2007.

Ta CN, Bowman RW: Hyphema caused by a metallic intraocular foreign body during magnetic resonance imaging, *Am J Ophthalmol* 129(4):533, 2000.

BASIC INFORMATION

DEFINITION

Onychomycosis is defined as a persistent fungal infection affecting the toenails and fingernails.

SYNONYMS

Tinea unguium
Ringworm of the nails

ICD-9CM CODES
110.1 Onychomycosis
ICD-10CM CODES
B35.1 Tinea unguium

EPIDEMIOLOGY & DEMOGRAPHICS

- Onychomycosis is most commonly found in people between the ages of 40 and 60 yr.
- Onychomycosis rarely occurs before puberty.
- Incidence: 20 to 100 cases/1000 population.
- Toenail infection is 4 to 6 times more common than fingernail infection.

FIGURE 01-5 Distal subungual onychomycosis in a 5-year-old. Note how heavily infected nails occur adjacent to totally normal nails. Cutting back the big toe's nail plate has revealed the friable subungual debris. This material is the most desirable for culture. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

- Onychomycosis affects men more often than women.
- Occurs more frequently in patients with diabetes, peripheral vascular disease, and any conditions resulting in the suppression of the immune system.
- Occlusive footwear, physical exercise followed by communal showering, and incompletely drying the feet predispose the individual to developing onychomycosis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Onychomycosis causes nails to become thick, brittle, hard, distorted, and discolored (yellow to brown color) (Fig. 01-5). Eventually, the nail may loosen, separate from the nail bed, and fall off (Fig. 01-6).
- Onychomycosis is frequently associated with tinea pedis (athlete's foot).

ETIOLOGY

- The most common causes of onychomycosis are dermatophyte, yeast, and nondermatophyte molds.
- The dermatophyte *Trichophyton rubrum* accounts for 80% of all nail infections caused by fungus.
- *Trichophyton interdigitale* and *Trichophyton mentagrophytes* are other fungi causing onychomycosis.
- The yeast *Candida albicans* is responsible for 5% of the cases of onychomycosis and tends to involve fingernails more than toenails.
- Nondermatophyte molds *Scopulariopsis brevicaulis* and *Aspergillus niger,* although rare, can also cause onychomycosis.
- Onychomycosis is classified according to the clinical pattern of nail bed involvement. The main types are:
  1. Distal and lateral subungual onychomycosis (DLSO)
  2. Superficial onychomycosis
  3. Proximal subungual onychomycosis
  4. Endonyx onychomycosis
  5. Total dystrophic onychomycosis

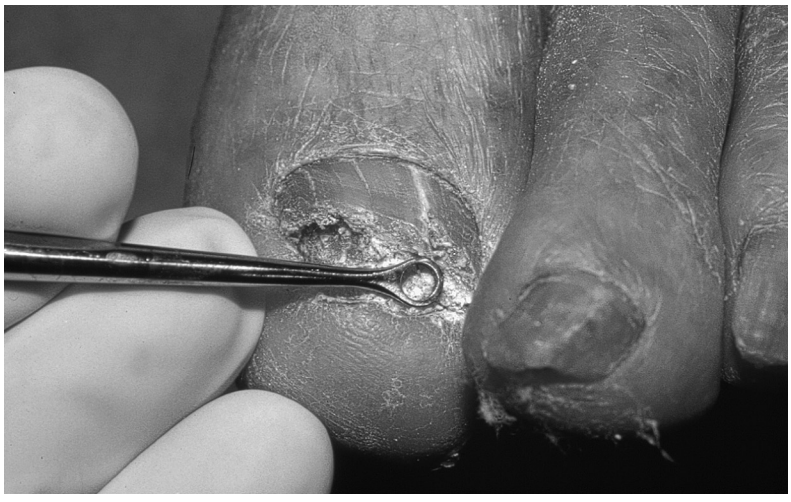


FIGURE 01-6 Collection of nail for culture. The subungual debris is the most valuable material for culture. After the nail is cut back, a curette may be used. Clippings of the nail may be added to the culture. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

DIAGNOSIS

The diagnosis of onychomycosis is based on the clinical nail findings and confirmed by direct microscopy and culture.

DIFFERENTIAL DIAGNOSIS

- Psoriasis
- Contact dermatitis
- Lichen planus
- Subungual keratosis
- Paronychia
- Infection (e.g., *Pseudomonas*)
- Trauma
- Peripheral vascular disease
- Yellow nail syndrome

WORKUP

The workup of suspected onychomycosis is directed at confirming the diagnosis of onychomycosis by visualizing hyphae under the microscope by KOH prep or by culturing the organism. Although the standard for the diagnosis of fungal nail disease is a positive result on microscopic examination and culture of nail clippings with subungual debris or from surface debris in superficial white onychomycosis, treatment is often prescribed in absence of confirmatory findings.

LABORATORY TESTS

- KOH prep: specificity is high but sensitivity is variable
- Fungal cultures on Sabouraud medium: culture may take 4 to 6 wk
- Dermatophyte test medium (DTM): an alternative to Sabouraud's that takes only 3 to 7 days and can be done in office setting. A color change indicates dermatophyte growth.
- Nail plate biopsy with periodic acid–Schiff (PAS) stain
- Blood tests are not specific in the diagnosis of onychomycosis and therefore not useful

IMAGING STUDIES

- Imaging studies are not very specific in making the diagnosis of onychomycosis and not useful.
- If an infection is present and osteomyelitis is a consideration, an x-ray of the specific area and a bone scan may help establish the diagnosis.

CLASSIFICATION

- The Onychomycosis Severity Index (OSI) is a new classification system for grading the severity of onychomycosis.
- The OSI score is obtained by multiplying the score for the area of involvement (range, 0-5) by the score for the proximity of the disease to the matrix (range, 1-5). Ten points are added for the presence of a longitudinal streak or a patch (dermatophytoma) or for >2 mm of subungual hyperkeratosis.
- Mild onychomycosis corresponds to a score of 1-5; moderate to a score of 6-15; severe to a score of 16-35.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Surgical removal of the nail plate is a treatment option; however, the relapse rate is high.
- Prevention of reinfection by wearing properly fitted shoes, avoiding public showers, and keeping feet and nails clean and dry.
- Short-pulse laser therapy is fungicidal and is a newer treatment modality for onychomycosis. Most patients will require 2-4 treatments, each lasting 15-30 minutes. Laser therapy is useful in patients with contraindications to oral agents. It is, however, expensive ($250-$1,000 per treatment) and not covered by most insurance plans.

ACUTE GENERAL Rx

- Topical antifungal creams are used for early superficial nail infections.
  1. Miconazole 2% cream applied over the nail plate bid
  2. Clotrimazole 1% cream bid
  3. Ciclopirox: topical antifungal nail lacquer can be used for moderate onychomycosis that spares the lunula. Success rate <10%
  4. Efinaconazole 10% topical solution is modestly effective in treating toenail onychomycosis due to *Trichophyton rubrum* and/or *Trichophytoin mentagrophytes*. Dosage is 1 drop (2 drops for big toenail) once daily for 48 weeks. Tavaborole 5% is a topical oxaborole also FDA approved for toenail onychomycosis. Cost and formulary are limiting factors with these agents.
- Oral agents.
  1. Terbinafine
     a. For toenails: 250 mg/day for 3 mo
     b. For fingernails: 250 mg/day for 6 wk
  2. Itraconazole
     a. For toenails: 200 mg PO daily for 3 mo
     b. For fingernails: 200 mg PO daily for 6 wk
  3. Fluconazole: not as effective as terbinafine or itraconazole
     a. For toenails: 150 to 300 mg once weekly for 18 to 26 wk
     b. For fingernails: 150 to 300 mg once weekly for 12 to 16 wk
- All oral agents used for onychomycosis require periodic monitoring of liver function blood tests. Patients should be advised to watch for symptoms of drug-induced hepatitis (anorexia, fatigue, nausea, right upper quadrant pain) while taking these oral antifungal agents. They should stop their medication and contact their physician immediately if symptoms occur.
- Itraconazole is contraindicated in patients taking cisapride, astemizole, triazolam, midazolam, and terfenadine. Statins should be discontinued during itraconazole therapy. Itraconazole requires gastric acidity for absorption; patients should be advised not to take oral antacids, H_2 blockers, or proton pump inhibitors while taking itraconazole.
- Fluconazole is contraindicated in patients taking cisapride and terfenadine.
- Oral antifungal agents should not be initiated during pregnancy.

DISPOSITION

- Spontaneous remission of onychomycosis is rare.
- A disease-free toenail is reported to occur in approximately 25% to 50% of patients treated with the oral antifungal agents mentioned previously.

REFERRAL

- Podiatry consultation is indicated in diabetic patients for proper instruction in foot care, footwear, and nail debridement or surgical removal of the toenail.
- Dermatology consultation is indicated in patients refractory to treatment or if another diagnosis is considered (e.g., psoriasis).

PEARLS & CONSIDERATIONS

COMMENTS

- The growth of fungus on an infected nail typically begins at the end of the nail and spreads under the nail plate to infect the nail bed as well.
- Carefully consider the informational insert regarding drug-drug interactions and contraindications before initiating oral antifungal agents.
- Meta-analysis showed cure rates with the oral agents as follows: terbinafine (about 75%), itraconazole (60%-65%), and fluconazole (about 50%).

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Ringworm (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Borenstein E: A review of current research in light-based technologies of podiatric infectious disease states, *J Am Podiatr Med Assoc* 99(4):348–352, 2009.

Carney C et al.: A new classification system for grading the severity of onychomycosis: Onychomycosis Severity Index, *Arch Dermatol* 147(11):1277–1282, 2011.

deBerker D: Fungal nail disease, *N Engl J Med* 360:2108–2116, 2009.

Gupta AK et al.: The use of terbinafine in the treatment of onychomycosis in adults and special populations: a review of the evidence, *J Drugs Dermatol* 4(3):302, 2005.

Gupta AK et al.: Onychomycosis therapy: past, present, future, *J Drugs Dermatol* 9:1109–1113, 2010.

Welsh O et al.: Onychomycosis, *Clin Dermatol* 28(2):151–159, 2010.

BASIC INFORMATION

DEFINITION

- Opioid addiction/dependence is defined as a cluster of cognitive, behavioral, and physiologic symptoms in which the individual continues use of opiates despite significant opiate-induced problems. Opiate dependence is a chronic, relapsing disorder characterized by repeated self-administration that usually results in opiate tolerance, withdrawal, and compulsive drug use. Tolerance is the need to increase dose to achieve the same effect. Dependence may occur with or without the physiologic symptoms of tolerance and withdrawal.
- There are four stages of addiction:
  1. Stage I, acute drug effects: rewarding effects of drug result from neurobiologic changes in response to the acute drug use. Duration varies from hours to days.
  2. Stage II, transformation to addiction: associated with changes in neuronal function that accumulate with repeated administration and diminish over days or weeks after discontinuation of drug use.
  3. Stage III, relapse after extended periods of abstinence: precipitated by an incubation of cue-induced craving (people, places, and things as triggers) and priming (relapse precipitated by drug exposure).
  4. Stage IV, end-stage addiction: vulnerability to relapse endures for years and results from prolonged changes at the cellular level.
- Pseudoaddiction: undertreatment of pain resulting in "opiate-seeking" behaviors such as "doctor shopping" and multiple emergency department visits. These behaviors disappear with adequate treatment of pain.

SYNONYMS

Opiate addiction
Opiate abuse
Narcotic addiction
Narcotic abuse

ICD-9CM CODES
304.7X/304.8X Opioid dependence
ICD-10CM CODES
F11.0 Mental and behavioral disorders due to use of opioids, acute intoxication
F11.2 Mental and behavioral disorders due to use of opioids, dependence syndrome
F11.3 Mental and behavioral disorders due to use of opioids, withdrawal stage
F19.20 Other psychoactive substance dependence, uncomplicated

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: There are 980,000 opiate addicts in the United States; less than one third are in treatment.
PREVALENCE:

- Approximately 6 million persons age ≥12 yr used psychotherapeutic drugs for nonmedical purposes in 2004, which represents 2.5% of the population. Most of them reported abusing opiate pain relievers.
- In 2004, 2.4 million persons age ≥12 yr initiated nonmedical use of prescription pain relievers, surpassing for the first time those who initiated abuse of marijuana (2.1 million).
- Opiate addiction is becoming an adolescent disease. Among twelfth-graders, in 2005, 9.5% reported past-year nonmedical use of oxycodone (Vicodin) and 5.5% reported past-year nonmedical use of oxycodone slow-release tablets (OxyContin).
- The percentage of eighth-, tenth-, and twelfth-graders who have used heroin has more than doubled since the late 1990s. This increase has largely been attributed to decreased price and increased purity in the last decade.

PREDOMINANT SEX: Males abuse opiates more commonly than females, with a male/female ratio of 3:1 for heroin and 1.5:1 for prescription opiates.
PEAK INCIDENCE: The majority of new abusers of opiates are <26 yr.
RISK FACTORS:

- Family history
- Prior history of addiction
- Psychiatric disorders

GENETICS:

- Genetic epidemiologic studies suggest a high degree of heritable vulnerability for opiate dependence.
- Gene polymorphism for dopamine receptor/transporters, opioid receptors, serotonin receptors/transporters, proenkephalin, and catechol-*O*-methyltransferase all appear to be associated with vulnerability to opiate dependence. Future interventions for opiate dependence may include medications identified through genetic research.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination is often noncontributory.
- Small-sized pupils may be the only observable sign of use because only mild tolerance develops for miosis.
- Scars or tracks from chronic IV use may be visible over the veins of the arms, hands, ankles, neck, and breasts.
- Inflamed nasal mucosa or respiratory wheezing may be apparent in patients who are snorting heroin or OxyContin.
- Patients in withdrawal may have more dramatic findings such as tachycardia, hypertension, fever, piloerection (goose flesh), mydriasis, lacrimation, central nervous system (CNS) arousal, irritability, and repeated yawning. In patients with sympathetic overactivity and panic attacks, use of CNS stimulants, such as amphetamines or cocaine, should also be ruled out.
- Although gastrointestinal symptoms of nausea, vomiting, and abdominal pain are common in opiate withdrawal, other causes such as gastroenteritis, pancreatitis, peptic ulcer disease, and intestinal obstruction need to be ruled out.
- The history may provide relevant information in making the diagnosis. Significant findings may include:
  1. A long history of opiate self-administration, typically by the IV or intranasal route but sometimes through smoking as well.
  2. Polysubstance use. Intoxication by drugs other than narcotics (e.g., benzodiazepines, barbiturates) should be ruled out in unconscious patients.
  3. A high incidence of non-opiate-related psychiatric disorders (>80%).
  4. History of problems at work, school, or relationships associated with drug use.
  5. History of legal problems associated with drug use, such as arrest for possession, robbery, or prostitution.
  6. History of interpersonal violence (as perpetrator or victim).
  7. History of physical problems such as skin infections, phlebitis, endocarditis, or liver diseases attributable to acetaminophen toxicity (Vicodin/Percocet) or viral hepatitis. Hepatitis C is the most prevalent blood-borne pathogen. It is present in approximately 90% of opiate-dependent people and is often spread by sharing IV drug paraphernalia or snorting devices. There is also a higher incidence of HIV infection.

ETIOLOGY

Opioid dependence is a biopsychosocial disorder. Pharmacologic, social, genetic, and psychodynamic factors interact to influence abusive behaviors. Pharmacologic factors are especially prominent in opiate addiction because these drugs are strong reinforcing agents because of their euphoric effects and their ability to reduce anxiety and increase self-esteem and the patient's subjective feelings of improved ability to cope with daily challenges.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Psychiatric disorders (e.g., anxiety, depression, bipolar disorder).
- Acute medical illness (e.g., hypoglycemia, seizure disorder, sepsis, renal or hepatic insufficiency) may mimic opiate withdrawal symptoms.

WORKUP

The history is the most important part of the workup. Useful screening tools are the CAGE-AID (Table 01-2), the DAST-10 (Table 01-3) and the CRAFFT (Table 01-4). The CAGE-AID has a sensitivity of 70% and a specificity of 85% when two questions are answered in the affirmative. The DAST-10 can discriminate between current users versus former users. The CRAFFT is a useful screening tool for adolescents. A CRAFFT score of 2 or higher is optimal for identifying any problem (sensitivity 76%, specificity 94%), any disorder (sensitivity 80%, specificity 86%), and drug dependence (sensitivity 92%, specificity 80%).

TABLE O1-2 CAGE-AID

1. Have you ever tried to **C**ut down on your alcohol or drug use?
2. Do you get **A**nnoyed when people comment about your drinking or drug use?
3. Do you feel **G**uilty about things you have done while drinking or using drugs?
4. Do you need an **E**ye-opener to get started in the morning?

Two or more questions answered in the affirmative require further assessment.
AID, adapted to include drugs.
From Bowman S, Eiserman J, Beletsky, L, Stancliff S: Reducing the health consequences of opioid addiction in primary care, Am J Medicine 126, 565-571 (2013).

TABLE O1-3 Drug Abuse Screening Test (DAST-10)

1. Have you used drugs other than those required for medical reasons?
2. Do you abuse more than one drug at a time?
3. Are you unable to stop using drugs when you want to?
4. Have you ever had blackouts or flashbacks as a result of drug use?
5. Do you ever feel bad or guilty about your drug use?
6. Does your spouse (or parents) ever complain about your involvement with drugs?
7. Have you neglected your family because of your use of drugs?
8. Have you engaged in illegal activities in order to obtain drugs?
9. Have you ever experienced withdrawal symptoms (felt sick) when you stopped taking drugs?
10. Have you had medical problems as a result of your drug use (eg, memory loss, hepatitis, convulsions, bleeding)?

Two or more questions answered in the affirmative require further assessment.
(From Bowman S, Eiserman J, Beletsky, L, Stancliff S: Reducing the health consequences of opioid addiction in primary care, The American Journal of Medicine (2013) 126, 565-571.)

- Observation of opiate withdrawal is indicative of opiate addiction.
- Observation of purposeful behaviors such as complaints and manipulations directed at getting more drugs and anxiety during withdrawal is suggestive of opiate addiction.
- Screen blood and urine for opiate metabolites.
- Screen for communicable diseases: HIV, hepatitis B and hepatitis C, tuberculosis.
- Screen for endocarditis in patients with newly diagnosed murmurs.

LABORATORY TESTS

- Urine and serum toxicology screen
- Complete blood count
- Chemistries (alanine aminotransferase, aspartate aminotransferase, serum creatinine): elevated liver function test (LFT) results may be from viral hepatitis or acetaminophen toxicity

TABLE O1-4 CRAFFT Screening Tool for Adolescents

1. Have you ever ridden in a **C**ar driven by someone (including yourself) who was high or had been using alcohol or drugs?
2. Do you ever use alcohol or drugs to **R**elax, feel better about yourself, or fit in?
3. Do you ever use alcohol or drugs while you are by yourself **A**lone?
4. Do you ever **F**orget things you did while using alcohol or drugs?
5. Do your **F**amily or Friends ever tell you that you should cut down on your drinking or drug use?
6. Have you ever gotten into **T**rouble while you were using alcohol or drugs?

Two or more questions answered in the affirmative require further assessment.
(From Bowman S, Eiserman J, Beletsky, L, Stancliff S: Reducing the health consequences of opioid addiction in primary care, The American Journal of Medicine (2013) 126, 565-571.)

- Hepatitis screen: if hepatitis C antibody positive, follow up with hepatitis C polymerase chain reaction (viral load) even in patients with normal LFTs
- HIV
- PPD

IMAGING STUDIES

Generally not helpful in routine diagnosis and treatment. Consider echocardiography in patients with heart murmurs and liver sonography or CT scan in patients with elevated LFTs or who are positive for hepatitis C or B (increased risk of hepatocellular carcinoma).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Brief counseling interventions during a visit with their primary care physician or OB/GYN have proved efficacious in motivating patients for treatment.
- Therapeutic communities (residential).
- 12-step or other self-help groups (e.g., Alcoholics Anonymous, Narcotics Anonymous).
- Relapse prevention (counseling).
- Opioid prevention education (Table O1-5)

ACUTE Rx

- Medical withdrawal (not overdosed).
- Short- (30 days) or long-term (30 to 180 days) protocols.
- Buprenorphine (opioid partial agonist) or methadone (opioid agonist) is initiated in tapering doses.
- Clonidine 0.1 mg bid to tid can be used to minimize autonomic symptoms (sweating) and craving.
- Nonsteroidal anti-inflammatory drugs for body and muscle aches.
- The anticholinergic dicyclomine can be used to minimize gastrointestinal hyperactivity.
- Nonbenzodiazepine hypnotics, low-dose atypical antipsychotics (e.g., quetiapine), or low-dose tricyclic antidepressants are effective for promoting adequate sleep.

TABLE O1-5 Basic Components of Opioid Overdose Prevention Education Curriculum

1. Know the signs of an opioid overdose (e.g., unresponsive, limp, slow, shallow breathing, pale or clammy, finger nails or lips turning blue, gurgling)
2. Call 911
3. Administer rescue breathing
4. Administer naloxone if no response and Emergency Medical Services have not yet arrived
5. Stay with the person until help arrives

From Bowman S, Eiserman J, Beletsky, L, Stancliff S: Reducing the health consequences of opioid addiction in primary care, Am J Med 126, 565-571 (2013).

CHRONIC Rx

Opioid antagonist treatment:

- Naltrexone: does not stabilize neuronal circuitry like partial or full opioid agonists and generally results in poor outcomes, much like Antabuse for alcohol.
- Opioid partial agonist therapy: buprenorphine.
- Opioid agonist therapy: methadone.

NOTE: Buprenorphine and methadone are both metabolized by the cytochrome P450 3a4 and 2d6 l isoenzyme pathways. Prescribers should be aware of multiple possible drug interactions.

PATIENT SELECTION FOR BUPRENORPHINE OR METHADONE

- Appropriate patients for buprenorphine office-based treatment:
  1. Patients interested (highly motivated) in treatment
  2. Have no major contraindications (see following)
  3. Can be expected to be reasonably compliant with treatment
  4. Understand the benefits and risks of buprenorphine treatment
  5. Willing to follow safety precautions
- Less likely to be appropriate for office-based treatment:
  1. Have comorbid dependence on benzodiazepines or other CNS depressants (including ethylene alcohol)
  2. Have significant untreated psychiatric comorbidities
  3. Have active or chronic suicidal or homicidal ideation or attempts
  4. Have multiple previous treatments with frequent relapses
  5. Have poor response to previous treatment with buprenorphine
  6. Have significant medical complications (e.g., hepatic insufficiency, bacterial endocarditis, active tuberculosis)
- Methadone maintenance: narcotic treatment program (clinic setting) indications
- Evidence of opiate addiction >1 yr
- Two failed previous treatment attempts
- Patients not appropriate for office-based treatment

- Eligible without active "use" if prior methadone maintenance patient within previous 2 mo
- Pregnancy

DISPOSITION

- Opioid addiction is a chronic, relapsing disease.
- High rate of relapse after "detox."
- Relapse potential after medically supervised withdrawal from methadone:
  1. 90% after 1 yr stable in treatment
  2. 80% after 3 yr stable in treatment
  3. 70% after 5 yr stable in treatment
- Postmarketing surveillance indicates that the diversion and abuse of prescription opioid medications increased between 2002 and 2010 and plateaued or decreased between 2011 and 2013. These findings suggest that the United States may be making progress in controlling the abuse of opioid analgesics.[1]

REFERRAL

Refer to addiction medicine specialist or narcotic treatment program when the neurobiologic disease of opioid addiction is identified.

[1] Dart RC et al.: Trends in opioid analgesic abuse and mortality in the United States, *N Engl J Med* 372:241-248, 2015.

PEARLS & CONSIDERATIONS

COMMENTS

- Methadone maintenance is the gold standard for the pregnant opiate-addicted patient regardless of the duration of the addiction or prior treatment attempts. Detoxification is contraindicated during pregnancy.
- Breastfeeding is encouraged in mothers on methadone maintenance. The American Academy of Pediatrics statement regarding "Transfer of Drugs and Other Chemicals into Human Milk" has placed methadone into the "usually compatible with breastfeeding" group based on the assumption that maternal urine is monitored to detect use of illicit drugs. The U.S. Department of Health and Human Services also recommends that mothers on methadone be encouraged to breastfeed.
- When a physician identifies a patient as a "drug seeker," it is imperative that the physician avoid abruptly stopping the opiate prescription because this will often result in the patient's buying the drugs illegally. These patients should be counseled and referred for treatment.
- Patients on methadone or buprenorphine who have pain resulting from an acute injury will need pain medication in addition to their daily dose of methadone or buprenorphine. They will require higher than usual doses of pain medications because of opiate receptor blockade attributable to their methadone or buprenorphine use.
- Opiate-dependent patients have a lower pain threshold resulting from hyperalgesia caused by the long-term use of opiates.

PREVENTION

Education is the hallmark of prevention.

- School drug prevention education programs.
- Educate children about their family medical history, including diseases of addiction.
- Address childhood psychiatric disorders to prevent self-medicating.

PATIENT & FAMILY EDUCATION

- Stigma of addictions and treatment often interferes with good treatment.
- Family needs to be educated so they can support the patient's efforts.
- Encourage family meeting with addiction specialist, counselor.
- Recommend support groups for family members. Table 01-6 identifies organizations providing referral information for patients. Recommendations for integrating risk reduction strategies for addressing opioid misuse in the primary care setting are summarized in Table 01-7.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Drug Abuse (Patient Information)

AUTHOR: **STEVEN PELIGIAN, D.O.**

TABLE 01-6 Organizations Providing Referral Information for Patients

Organization	Resources/Website
Substance Abuse and Mental Health Services Administration (SAMHSA)	Opioid treatment program directory: http://dpt2.samhsa.gov/treatment/
Physicians who provide buprenorphine	Buprenorphine physician and treatment program locator: http://buprenorphine.samhsa.gov/bwns_locator/
Pain Action	Chronic pain management materials for patients: www.painaction.org
Substance abuse treatment facilities	Substance Abuse treatment facility locator: http://dasis3.samhsa.gov/
Harm Reduction Coalition	Local risk reduction resources and programs, overdose prevention education, and naloxone prescribing information: http://www.harmreduction.org/
Narcotics Anonymous (NA)	General information and meeting information for NA, a 12-step program modeled after Alcoholics Anonymous: www.na.org

From Bowman S, Eiserman J, Beletsky, L, Stancliff S: Reducing the health consequences of opioid addiction in primary care, Am J Med 126, 565-571 (2013).

TABLE 01-7 Recommendations for Integrating Risk Reduction Strategies for Addressing Opioid Misuse in the Primary Care Setting

Risk Reduction Tools	Type of Client	Delivery Recommendations
Brief substance abuse screening	All clients, particularly those individuals prescribed opioid medications or with a history of substance abuse problems.	Administer CAGE-AID* or similar screening tool as part of routine treatment.
Motivational interviewing	Clients who have identified opioid use or abuse.	Standard procedure may be delivered by primary care provider or other clinic staff.
Comprehensive tools for safer injections, including safer injection education	Clients who have reported, or are suspected of injection drug use. Tools should be available to all patients, not only those identified as drug users.	Resources (including educational materials, syringes, alcohol wipes, etc.) distributed and discussed by the primary care provider or other clinic staff.
Naloxone prescription and distribution	Targeting individuals using illicit or prescribed opioids, including individuals prescribed opioids.	Discussion, prescription of naloxone by the primary care provider; additional education may be delivered by other clinic staff.
Buprenorphine prescription	Targeting individuals using illicit or prescribed opioids, seeking medication assisted treatment.	Discussion and prescription by the primary care provider.

*For a full definition of CAGE-AID, see Table 01-2.

From Bowman S, Eiserman J, Beletsky, L, Stancliff S: Reducing the health consequences of opioid addiction in primary care, Am J Med 126, 565-571 (2013).

SUGGESTED READINGS

Ballantyne JC et al.: Opioid dependence vs addiction, *Arch Intern Med* 172:1342, 2012.

Bowman S et al.: Reducing the health consequences of opioid addiction in primary care, *Am J Med* 126:565–571, 2013.

Daniel A: Acute pain management for patients receiving methadone or buprenorphine therapy, *Ann Intern Med* 144:127, 2006.

Kalinas PW, Volkow ND: The neural basis of addiction: a pathology of motivation and choice, *Am J Psych* 162:1403, 2005.

Krupitsky E et al.: Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicenter randomized trial, *Lancet* 377:1506–1513, 2011.

Olsen Y, Alford D: Chronic pain management in patients with substance use disorders, *Johns Hopkins Advanced Studies in Medicine* 6:110, 2006.

Shapiro B et al.: A primary care approach to substance misuse, *Am Fam Physician* 88(2):113–121, 2013.

Sullivan L, Fiellin DA: Narrative review: buprenorphine for opioid-dependent patients in office practice, *Ann Intern Med* 148:662–670, 2008.

Met Von Korff et al.: Long-term opioid therapy reconsidered, *Ann Intern Med* 155:325–328, 2011.

Wilford B: Principles of addiction medicine. ed 3 American Society of Addiction Medicine: Chevy Chase, MD.

Woody GE et al.: Extended vs short-term buprenorphine-naloxone for treatment of opioid-addicted youth, *JAMA* 300(17):2003–2011, 2008.

Oppositional Defiant Disorder (ODD) PTG

BASIC INFORMATION

DEFINITION

Oppositional defiant disorder (ODD) is an ongoing pattern of angry/irritable mood, argumentative/defiant behavior, or vindictiveness, that is not developmentally appropriate, lasts more than 6 months, and leads to impairment in social, academic, or occupational functioning for a child or adolescent.

SYNONYMS

ODD

ICD-9CM and DSM-5 CODES
313.81
ICD-10CM CODES
F91.3 Oppositional defiant disorder

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE
- Usually diagnosed in school-aged children (roughly ages 6-12)

PREVALENCE
- Ranges from 1% to 16% based on source (community prevalence)

PREDOMINANT SEX AND AGE
- Males more than females
- Highest diagnosis in prepubertal children
- Usually present by age 8

GENETICS
- Some evidence for genetic factors, but studies are not usually specific to ODD (e.g., studies also include conduct disorder or more generally refer to aggressive or delinquent behaviors) and include potential confounding factors (e.g., difficult to distinguish between genetic and environmental contribution)

RISK FACTORS
- Male gender, low socioeconomic status
- The following risk factors have been identified more generally for development of disruptive behavior disorders or aggression:
  1. Family history (especially parental) of aggressive or criminal behaviors
  2. Parental substance abuse
  3. Prenatal or early childhood exposure to toxins (e.g., lead)
  4. Perinatal complications
  5. Head injuries
  6. Cognitive impairment
  7. Learning disabilities
  8. History of abuse or witnessed domestic violence
  9. Overall family instability

PHYSICAL FINDINGS & CLINICAL PRESENTATION

DSM-5 criteria are met when there is a pattern of angry/irritable mood, argumentative/defiant behavior, or vindictiveness for at least 6 months, and four or more symptoms from any category are present
- Angry/irritable mood
  1. Often loses temper
  2. Is touchy or easily annoyed
  3. Is often angry and resentful
- Argumentative/defiant behavior
  1. Often argues with adults
  2. Often actively defies or refuses to comply with requests from authority figures or with rules
  3. Often deliberately annoys others
  4. Often blames others for his or her mistakes/misbehavior
- Vindictiveness
  1. Has been spiteful/vindictive at least twice within the past 6 months

Symptoms are associated with distress in the individual or others, or they negatively impact social, educational, occupational, or other important areas of functioning. Symptoms may not occur only during the course of a psychotic, mood, or substance use disorder. Also, criterion must not be met for disruptive mood dysregulation disorder, and if 18 years or older, for antisocial personality disorder. Symptoms are classified in terms of severity based on whether they are confined to only one setting, e.g., at home or at school (mild), to at least two settings (moderate), and three or more settings (severe). Finally, the DSM-5 specifies that symptoms may not occur only in the context of a sibling relationship.

ETIOLOGY

Multiple hypothetical models have been developed for disruptive behavior disorders and antisocial behaviors in general, including a few focused specifically on ODD that address the complex interaction between various predisposing and protective factors. These models identify some biologic factors (including genetic, structural, toxin exposure, etc.), some child functional factors (including cognitive, social, and neuropsychological deficits), and broad psychosocial factors that focus on parenting styles (including history of physical abuse), peer involvement, and other environmental factors.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Child abuse or neglect
- Learning disorder or other deficits in executive functioning
- Intellectual disability (intellectual developmental disorder)
- Communication disorders (including language disorder, speech sound disorder, childhood-onset fluency disorder, and social communication disorder)
- Attention-deficit/hyperactivity disorder
- Intermittent explosive disorder
- Conduct disorder
- Antisocial personality disorder
- Mood disorder (bipolar disorder or depression)
- Psychotic disorders
- Substance use disorders
- Parent-child relational problem

WORKUP

- Diagnosis is made based on history, including individual and family interviews as well as collateral data from additional sources (parents, teachers, other medical providers, therapist, etc.).

LABORATORY TESTS

- None indicated

IMAGING STUDIES

- None indicated

TREATMENT

Initial treatment of ODD should include psychosocial interventions aimed at changing the maladaptive patterns of interaction between the child or adolescent and his or her family and environment. If the interventions listed here are not effective, or if serious concerns exist regarding safety or impairment in functioning, pharmacologic interventions targeting specific symptoms (such as aggression) or comorbid disorders (such as ADHD, anxiety disorders, or mood disorders) may help. There are currently no medications approved by the FDA for the treatment of ODD.

NONPHARMACOLOGIC THERAPY

- Parent management training
- Cognitive problem-solving skills training
- Social skills training
- Individual psychotherapy
- Family psychotherapy

ACUTE GENERAL Rx

- Medication may be considered as an adjunct to behavioral treatment or in cases where comorbidity is a factor. There is some evidence for symptom improvement with trials of stimulants, mood stabilizers, or atypical antipsychotics, but medication should never be used alone or as first-line treatment for ODD.
- Higher levels of care such as a hospital or acute residential setting may be required for stabilization if acute safety concerns develop in the context of ODD, such as severe aggression.

COMPLEMENTARY & ALTERNATIVE MEDICINE

No evidence-based treatments are available.

DISPOSITION

Most patients with ODD can be managed in an outpatient setting with either standard or intensive, home-based support; treatment should always be provided in the least restrictive setting possible. Hospitalization is sometimes necessary for crisis management only; consideration of different levels of care, including day treatment, therapeutic school settings, or residential facilities, may be appropriate for more severe cases or in situations where the family is not willing or able to participate adequately in the outpatient regimen.

REFERRAL

Consider referral to a mental health provider specializing in the treatment of children,

adolescents, and families (including potentially a child and adolescent psychiatrist) if the patient and family are not responding to basic parenting interventions or are demonstrating significant safety concerns or other evidence of impairment in functioning at home, in school, or in the community.

PEARLS & CONSIDERATIONS

COMMENTS

- Involvement of the family and school is crucial in the management of patients with this disorder.
- Polypharmacy (the prescribing of multiple medications simultaneously) to target the more complicated symptoms of this disorder should be implemented with great caution and only after discrete trials of therapeutic interventions and single medication agents have failed.
- Standardized assessment tools used to identify ADHD, disruptive behavior disorders, and general child and adolescent psychopathology may be helpful in confirming the diagnosis of ODD and/or monitoring progress throughout treatment.
- ODD symptoms are independently associated with increased externalizing symptoms, internalizing symptoms, delinquent behaviors, and social and academic functioning.
- One-time, intensive interventions are not considered effective treatment options (including boot camps, shock incarceration) and may carry additional risks.
- When ODD coexists with attention deficit/hyperactivity disorder, stimulant therapy can reduce the symptoms of both disorders.

PREVENTION

Most effective prevention strategies include both individualized treatment and universal interventions that incorporate a parent-directed component as one of the primary elements. They also may incorporate social-cognitive skills training, academic skills training, proactive classroom management and teacher training, and group therapy. These may take place in schools, clinics, and other community-based settings in addition to targeted clinical work.

PATIENT & FAMILY EDUCATION

ODD: A Guide for Families by the American Academy of Child and Adolescent Psychiatry (http://www.aacap.org/cs/ODD.ResourceCenter)

American Academy of Pediatrics: Healthy Children.org (http://www.healthychildren.org/English/health-issues/conditions/emotional-problems/Pages/Disruptive-Behavior-Disorders.aspx)

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Attention Deficit/Hyperactivity Disorder (Related Key Topic)

Conduct Disorder (Related Key Topic)

AUTHORS: **HASSAN M. MINHAS, M.D.,** and **ELIZABETH A. LOWENHAUPT, M.D.**

SUGGESTED READINGS

Frick PJ, Nigg JT: Current issues in the diagnosis of attention deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder, *Annu Rev Clin Psychol* 8:77–107, 2012.

Quy K, Stringaris A: Oppositional defiant disorder. In Rey JM, editor: *IACAPAP e-Textbook of Child and Adolescent Mental Health*, Geneva, 2012, International Association for Child and Adolescent Psychiatry and Allied Professions.

Pardini DA, Fite PJ: Symptoms of conduct disorder, oppositional defiant disorder, attention-deficit/hyperactivity disorder, and callous-unemotional traits as unique predictors of psychosocial maladjustment in boys: advancing an evidence base for DSM-V, *J Am Acad Child Adolesc Psychiatry* 49:1134–1144, 2010.

BASIC INFORMATION

DEFINITION

- *Optic atrophy* refers to the degeneration of axons of the optic nerve.
- It is a sign indicative of optic nerve insult rather than a distinct disease entity.

SYNONYMS

Unilateral/bilateral optic atrophy

ICD-9CM CODES
377.10 Optic atrophy NOS
377.11 Optic atrophy, primary
377.12 Optic atrophy, post-inflammatory
377.13 Optic atrophy, retinal dystrophy
377.15 Optic atrophy, partial
377.16 Optic atrophy, hereditary
ICD-10CM CODES
H47.2 Optic atrophy

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT SEX: Depends on etiology; <50 yr demyelinating diseases more likely and >50 yr, ischemic optic neuropathy more likely
PREDOMINANT AGE: Variable
PEAK INCIDENCE: Varies depending on cause

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Optic atrophy is identified weeks to months after an initial insult such as optic neuritis, trauma, or ischemia. Frequently, it is noted by the physician during a routine eye exam.
- Asymmetry of disc color is often first subtle finding.
- Temporal part of optic disc is pale initially (Fig. 01-7); later the entire disc becomes pale/white.

FIGURE 01-7 Optic atrophy. Patient's right eye shows atrophy. (Courtesy John W. Payne, M.D., The Wilmer Ophthalmological Institute, The Johns Hopkins University and Hospital, Baltimore. From Seidel HM [ed]: *Mosby's guide to physical examination,* ed 4, St Louis, 1999, Mosby.)

- Optic disc pallor occurs 4 to 6 wk after optic nerve insult.
- Unilateral lesion produces a relative afferent pupillary defect (RAPD): swing flashlight eye to eye; abnormal pupil dilates to direct light.
- Decreased visual acuity, blurred vision, visual field deficits (e.g., central scotoma), abnormal color vision (e.g., red desaturation).

ETIOLOGY

- Optic neuritis—MS, sarcoidosis, infections (syphilis, CMV, HIV, Lyme disease)
- Vascular—ischemic optic neuropathy, central retinal artery occlusion, temporal arteritis
- Compression—glaucoma, pituitary tumor, meningioma, thyroid eye disease
- Hereditary—Leber's hereditary optic neuropathy
- Nutritional, toxic, and metabolic—amiodarone, isoniazid, B_{12} deficiency, tobacco, alcohol
- Trauma

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Optic disc anomalies such as myelinated nerve fibers, "blonde" fundus

WORKUP

- A detailed history to identify onset and course, exposure to risk factors such as toxic/nutritional factors, detailed family history, and associated findings such as headache, eye pain, proptosis, or neurologic deficits
- Ophthalmic examination to document deficits of visual acuity, color vision, contrast sensitivity, and visual fields must be performed. Relative afferent pupillary defect (RAPD) on swinging flashlight examination is sine qua non for unilateral optic nerve disease and must be documented. Absence indicates retinal disease or bilateral lesions.
- General examination and neurologic examination can provide clues to an underlying cause.
- Pertinent laboratory testing as noted below; genetic studies with a consultation can be obtained in cases with a suggestive history. Lumbar puncture should be obtained in patients with unexplained optic atrophy especially with neurologic deficits.
- In the absence of an obvious cause, contrasted MRI of brain and orbits should be obtained to evaluate for demyelinating lesions and compressive lesions of the anterior visual pathways.

LABORATORY TESTS

- Depends on suspected cause: none for trauma, tumor, or MS
- Serum B_{12}
- Autoimmune diseases: ESR, ANA, ACE

IMAGING STUDIES

- MRI of the brain with contrast, fat suppression, and special (thin) cuts through orbits is necessary to identify compressive lesions in all patients with unexplained optic atrophy; especially important in patients with positive predictive factors for abnormal imaging (e.g., young age, progression, bilateral findings).
- If sarcoid is suspected, order chest x-ray.

TREATMENT

ACUTE GENERAL Rx

Treat the underlying cause—discontinue identifiable toxins, use B_{12} replacement, neurosurgical intervention is necessary if tumor is found; consider IV steroids if there is evidence for active demyelinating disease.

CHRONIC Rx

The optic nerve does not regenerate, although symptoms often improve.

DISPOSITION

- Visual loss usually occurs over weeks to months.
- Appointment with neurologist or ophthalmologist

REFERRAL

Depends on the underlying disease process

PEARLS & CONSIDERATIONS

COMMENTS

- An experienced clinician should be able to identify pale optic discs and an RAPD.
- Pupillary dilation with mydriatic agents (e.g., pilocarpine) may be necessary to optimize funduscopic examination.
- Patient education material can be obtained from the National Eye Institute, Department of Health and Human Services, 9000 Rockville Pike, Bethesda, MD 20892.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **SACHIN KEDAR, M.B.B.S., M.D.**

SUGGESTED READINGS

Lee AG et al.: The diagnostic yield of the evaluation for isolated unexplained optic atrophy, *Ophthalmology* 112(5):757, 2005.

Newman NJ, Biousse V: Hereditary optic neuropathies, *Eye* 18(11):1144, 2004.

Van Stavern GP, Newman NJ: Optic neuropathies: an overview, *Ophthalmol Clin North Am* 14(1):61, 2001.

Optic Neuritis EBM

BASIC INFORMATION

DEFINITION

Optic neuritis is an inflammation of the optic nerve resulting in impaired visual function.

SYNONYMS

Optic papillitis
Retrobulbar neuritis

ICD-9CM CODES
377.3 Optic neuritis
ICD-10CM CODES
H46.9 Unspecified optic neuritis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 1 to 5/100,000 person(s) per year; rates vary according to incidence of multiple sclerosis (MS)
PREVALENCE (IN U.S.): Common in patients with MS
PREDOMINANT SEX: Female/male ratio: 1.8:1
PEAK INCIDENCE: 20 to 49 yr, mean 30
GENETICS: Unknown. If due to MS, it is more common in patients with certain HLA blood types and in monozygotic twins of affected siblings.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Presents with acute or subacute (days) visual loss, often accompanied by periocular tenderness that worsens with eye movements.
- **Marcus Gunn pupil** (relative afferent pupillary defect [RAPD]): direct and consensual response is normal; however, when flashlight is swung from eye to eye, the affected eye's pupil dilates to direct light.
- Decreased visual acuity
- Unilateral visual field abnormalities—often a central scotoma (Fig. E01-8)
- Color desaturation; red is most often affected
- Normal orbit and fundus 66% cases; in 33% there is disc edema (Fig. 01-9), uveitis, or periphlebitis.
- May have movement or light-induced phosphenes (flashes of light lasting 1 to 2 sec).

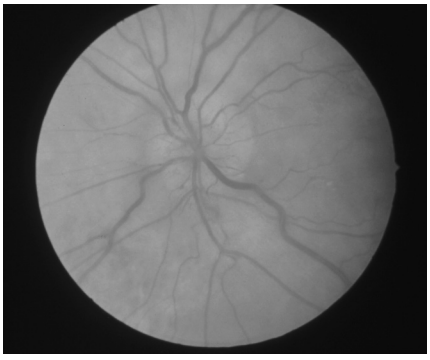


FIGURE 01-9 A case of optic neuritis. The optic disc edema seen here is often not present. Note the otherwise normal fundus. (Courtesy of J. Barton, M.D., Beth Israel Deaconess Medical Center, Boston.)

- Uhthoff's phenomenon (benign exercise- or heat-induced deterioration of vision) is seen in some. Vision may also worsen in bright sunlight.
- Over time the optic disc may atrophy and become pale.

ETIOLOGY

An inflammatory response associated with an infection, autoimmune disease (such as collagen vascular disease, granulomatous disease, MS, or neuromyelitis optica), or, rarely, a mitochondrial disorder

DIAGNOSIS

Consistent clinical presentation and exclusion of alternate ocular pathology, infection, and CNS mass lesions. Classic triad includes loss of vision, retroorbital pain, and dyschromatopsia. 70% of cases are unilateral and 30% bilateral.

DIFFERENTIAL DIAGNOSIS

For optic neuritis (usually with some retroorbital discomfort)
- Inflammatory: MS, neuromyelitis optica (NMO), sarcoidosis, lupus, Sjögren's, Behçet's, postinfectious, postvaccination, neuroretinitis, acute disseminated encephalomyelitis, paraneoplastic, autoimmune optic neuropathy (with retinopathy is ARRONS)
- Infectious: syphilis, TB, Lyme disease, *Bartonella,* HIV, CMV, herpes, helminths, chickenpox, Q fever, periorbital infections, *Toxocara* sp. For optic neuropathy (typically without ocular pain)
- Ischemic: anterior and posterior ischemic optic neuropathies, diabetic papillopathy, branch or central retinal artery or vein occlusion
- Drugs and toxins: arsenic, methanol, ethambutol, cyclosporine, etc.
- Mitochondrial: Leber's hereditary optic neuropathy, other mitochondrial

For loss of vision typically (without ocular pain)
- Mass lesion: pituitary tumor, aneurysm, meningioma, glioma, metastases, carcinomatosis, abscess, hematoma, and sinus mucocele
- Ocular: optic drusen, retinal detachment, vitreous hemorrhage, uveitis, posterior scleritis, neuroretinitis, maculopathies, and retinopathies
- Other: acute papilledema, pseudotumor cerebri, retinal migraine, nonphysiological visual loss

WORKUP

A thorough neurologic examination; recommend dilated ophthalmoscopy.

LABORATORY TESTS

- Recommend CBC, ANA, ACE, ESR.
- Consider HIV Ab, Lyme titer, RPR, other autoimmune or infectious causes.
- Bilateral or recurrent ON: NMO IgG; paraneoplastic CRMP-5-IgG
- Visual field tests

IMAGING STUDIES

- MRI of the brain and orbits (thin section fat-suppressed T_2-weighted) ± gadolinium to look for compressive and infiltrative causes and assess the risk to develop MS. Often enhancement of the optic nerve is seen.
- Consider using optical coherence tomography to follow optic nerve atrophy objectively longitudinally.

TREATMENT

NONPHARMACOLOGIC THERAPY

Assure patient that in most cases there is near complete recovery of vision.

ACUTE Rx

Treat if the visual loss is severe or if there is an abnormal MRI (higher risk of MS). Treatment is with methylprednisolone (MP) 250 mg IV every 6 hr (or 1 g IV daily) for 3 days followed by an oral prednisone taper of 11 days.

CHRONIC Rx

None, unless at significant risk to develop MS. See topic "Multiple Sclerosis."

DISPOSITION

Most often vision is worst at the end of week 1, followed by recovery over months. In the Optic Neuritis Treatment Trial (ONTT), 90% had 20/40 or better vision at 1 yr and 3% had 20/200 or worse. Of initial 20/200 or worse cases, only 5% remained in that group at 6 mo.

REFERRAL

- To neurologist for other neurologic signs and to assess risk of developing MS. In ONTT (Optic Neuritis Treatment Trial), risk of MS >15 yr was 72% with ≥1 lesion(s) on MRI, and 25% with a normal MRI
- To ophthalmologist when atypical features or slowly progressive; urgently when other ocular pathology is present or if vision worsens or does not improve after several wk, or pain is severe

PEARLS & CONSIDERATIONS

- Bilateral optic neuritis suggests a systemic inflammatory disorder, infection, NMO, or paraneoplastic, but can also occur in MS.
- Acute bilateral loss of vision with a severe headache or diplopia should raise concern for pituitary apoplexy and/or giant cell arteritis.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Idiopathic Intracranial Hypertension (Related Key Topic)
Multiple Sclerosis (Related Key Topic)

AUTHOR: **ALEXANDRA DEGENHARDT, M.D., M.M.Sc.**

EVIDENCE

Abstract[1]

Objective:

Optic neuritis (ON) is defined as an inflammation of the optic nerve and provides a useful model for studying the effects of inflammatory demyelination of white matter. The aim of this study was to assess the diffusion changes in both the optic nerve and optic radiation in patients with acute and chronic ON using diffusion tensor (DT) MRI.

Methods:

33 patients with idiopathic demyelinating optic neuritis (IDON) and 33 gender- and age-matched healthy controls were examined with DT-MRI and with T1- and T2-weighted MRI.

Results:

Compared with controls, both first-episode and recurrent patients with IDON in the acute stage showed significantly increased radial diffusivity ($\lambda\perp$) and decreased mean fractional anisotropy (FA) in the affected nerves. Reduced FA, increased $\lambda\perp$, mean diffusivity (MD), and axial diffusivity ($\lambda\parallel$) were determined in patients with subacute IDON. We found no significant difference in the directional diffusivity of optic radiation in patients whose disease had lasted less than 1 year compared with healthy controls. However, significant changes in the FA and $\lambda\perp$ of the optic radiation were detected in patients with disease duration of more than 1 year.

Conclusion:

These results show the great potential and capacity of DT-MRI measures as useful biomarkers and indicators for the evaluation of myelin injury in the visual pathway. Ⓐ

Evidence-Based Reference

Li M et al.: Directional diffusivity changes in the optic nerve and optic radiation in optic neuritis, *Br J Radiol* 84:304–314, 2011. Ⓐ

SUGGESTED READINGS

Beck R et al.: High and low risk profiles for the development of MS within 10 years after optic neuritis, *Arch Ophthalmol* 121(7):944, 2003.

Beck R et al.: Visual function more than 10 years after optic neuritis, *Am J Ophthalmol* 137(77), 2004.

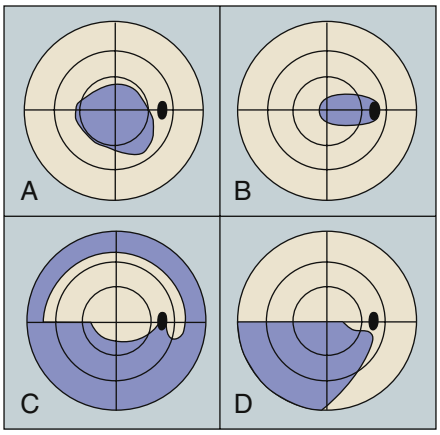


FIGURE EO1-8 Visual field defects in optic neuritis. A, Central scotoma. **B,** Centrocecal scotoma. **C,** Nerve fiber bundle. **D,** Altitudinal. (From Kanski JJ, Bowling B: *Clinical ophthalmology: a systematic approach,* ed 7, Philadelphia, 2010, Saunders.)

BASIC INFORMATION

DEFINITION

Oral cancer is malignant cell formation in the oral cavity and may occur as a primary lesion initiating in any of the oral tissues, by metastasis from a distant site of origin, or by extension from a neighboring anatomic structure such as the nasal cavity or the maxillary sinus.

SYNONYMS

Oropharyngeal cancer
Oral malignant neoplasm

ICD-9CM CODES

140.0-149.0 Code varies with specific anatomic structure

ICD-10CM CODES

C01	Malignant neoplasm of base of tongue
C03	Malignant neoplasm of gum
C04	Malignant neoplasm of floor of mouth
C05	Malignant neoplasm of palate
C06	Malignant neoplasm of other and unspecified parts of mouth
C09	Malignant neoplasm of tonsil
C10	Malignant neoplasm of oropharynx
C11	Malignant neoplasm of nasopharynx
C12	Malignant neoplasm of piriform sinus
C13	Malignant neoplasm of hypopharynx
C14	Malignant neoplasm of other and ill-defined sites of lip, oral cavity and larynx
C14.0	Malignant neoplasm of pharynx, unspecified
C14.2	Malignant neoplasm of Waldeyer's ring
C14.8	Malignant neoplasm of overlapping sites of lip, oral cavity and pharynx

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE & PREVALENCE: Oral and pharyngeal cancer is the sixth most common cancer in the world. An estimated half a million cases are diagnosed annually around the globe and the rates have been rising, particularly in young people and among minorities. In 2011, oropharyngeal squamous cell carcinoma (OP-SCCA) affected >12,000 new patients, with the most common sites being the tonsillar fossa and base of the tongue. In the U.S., the incidence of OP-SCCA linked to alcohol and tobacco use has been declining, whereas those linked to human papillomavirus (HPV), primarily HPV type 16, are on the rise. In developed countries across the world, HPV is increasingly implicated in the growing incidence of oral cancer. In Asian countries where chewing betel nut is customary, oral cancer accounts for up to 40% of cancers in some regions (Ayaz, 2011). Squamous cell carcinoma is the most common malignancy that occurs in the oral cavity. Minor salivary gland cancers, lymphomas, and sarcomas are less common. For more detailed data please see the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute.

PREDOMINANT SEX & AGE:

- Predominantly male, middle aged
- Black males have a higher early incidence in the 50- to 60-yr age group, but with increasing age, white men predominate.

GENETICS: There is no specific genetic factor or translocation, but the human papillomavirus (HPV)–induced oral squamous cell cancer typically seen in younger populations is associated with loss of p53 tumor suppressor due to inactivation by E6 protein from the virus.

RISK FACTORS (FIG. 01-10)

- Tobacco use of any kind
- HPV infection (primarily types 16 and 18)
- Alcohol
- Immune deficiency
- Syphilis
- Radiation
- Vitamin A, C, E deficiency
- Betel nut consumption
- Solar radiation

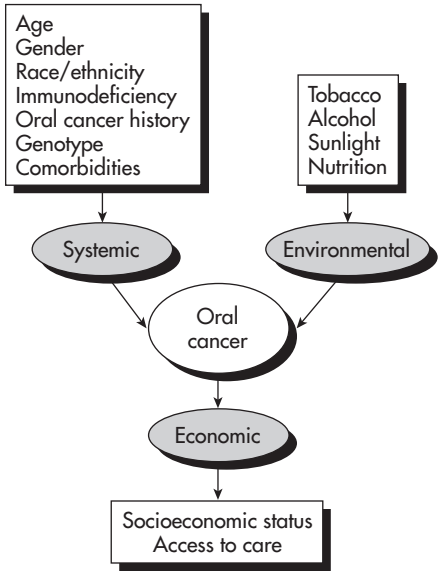


FIGURE 01-10 Risk model for oral cancer. Oral cancer is a multifactorial disease process that includes systemic, environmental, and economic effects. The interplay of these variables ultimately leads to the incidence of this disease. The multifactorial nature of oral cancer should be addressed in the assessment of a patient's risk. (From Jones DL, Rankin KV: Oral cancer and associated risk factors. In Cappelli D Mobley C (eds): *Prevention in clinical oral health care,* St. Louis, 2008, Elsevier, pp 68–77.)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Often starts as a tiny, unnoticed white or red spot or sore anywhere in the oropharyngeal cavity or lip.
- Most lesions begin on the tongue or buccal mucosa.
- Clinically, oral cancer can present as:
  1. Erythroplakia (flat red patch); can mimic inflammatory or traumatic lesions
  2. Leukoplakia (white patch; Fig. 01-11)
  3. Raised lesion
  4. Ulcerated lesion
  5. White warty lesion or growth
- The borders of the oral cavity can be defined as from the skin-vermilion junction of the lips to the junction of the hard and soft palate above and to the line of the circumvallate papilla of the tongue below. The lateral boundary between the oral cavity and oropharynx consists of the anterior tonsillar pillars and glossotonsillar folds.
- Oral cavity cancer can present on the lip, floor of the mouth, oral tongue (anterior two thirds of the tongue), lower alveolar ridge, upper alveolar ridge, retromolar trigone (retromolar gingiva), hard palate, salivary glands, and buccal mucosa.
- Oral cavity tumors often present with local invasion, tissue destruction, and lymph node metastases.

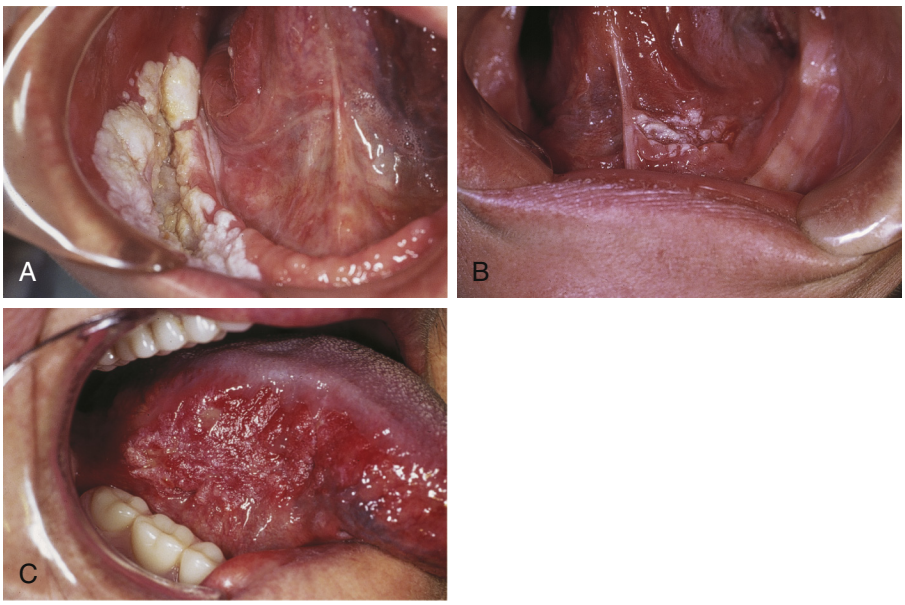


FIGURE 01-11 Squamous cell carcinoma of the oral mucosa. A, Leukoplakia. **B,** Invasive carcinoma of the floor of the mouth. **C,** Invasive carcinoma of the tongue. (Courtesy G. Putnam. In White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

- Oral cancers rarely have distant metastases at the time of presentation, although this may vary depending on the length of time until presentation.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Oral leukoplakia
- Traumatic ulcerative granuloma with stromal eosinophilia, especially on the tongue
- Deep fungal infections
- Chancre of early syphilis and gumma of tertiary syphilis
- Chronic ulcer

WORKUP

- Primary workup includes incisional biopsy with vital staining of the presenting lesion for histopathologic analysis.
- Pretreatment evaluation: tumor size, the extent of invasion, and the presence or absence of regional lymph node metastases are critical for planning treatment.
- Workup includes staging the cancer: The tumor-node-metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC) and the International Union for Cancer Control (UICC) is used to classify lip and oral cavity carcinoma.
- By definition, patients with early (stage I and II) disease have tumors <4 cm in greatest dimension without deep invasion into surrounding structures and have no evidence of lymph node involvement.
- Oral cavity cancers tend to invade bone and soft tissue early in their natural history. Therefore, pretreatment imaging studies, such as magnetic resonance imaging (MRI) and computed tomography (CT), are required in addition to a thorough inspection and deep palpation of the oral cavity.

LABORATORY TESTS

Send biopsy specimen to oral and maxillofacial pathology, head and neck pathology, or general pathology.

IMAGING STUDIES

Consider MRI or CT based on the extent of clinical presentation.

Rx TREATMENT

- Surgery vs. radiation therapy:
  1. Both primary surgery and definitive radiation therapy are options for patients with oral cavity cancer.
  2. Outcomes with primary surgery and definitive radiation therapy appear to be similar based on retrospective studies, but the two modes of treatment have not been compared in randomized controlled trials.
- Surgery is generally favored because it is typically associated with less morbidity than radiation therapy. Surgical therapy traditionally involved wide-exposure approaches (mandibulotomy, transpharyngeal access). Newer surgical techniques allow tumor resection through the mouth. Recently, transoral robotic surgery (TORS) has been developed to improve access to oropharyngeal squamous cell carcinomas with excellent oncologic outcomes.
  1. Acute surgical complications can include infection, bleeding, aspiration, wound breakdown, fistula, and flap loss.
  2. Surgical procedures can cause functional deficits in speech and swallowing, but these adverse effects can be minimized by appropriate reconstruction and prostheses.
- Definitive radiation therapy is reserved for patients who cannot tolerate surgery or for whom surgical resection would result in particularly severe functional impairment.
  1. Radiation therapy can include external beam radiation and brachytherapy.
  2. Radiation therapy side effects include mucositis, skin reaction, loss of taste, dysphagia, and xerostomia.
  3. Late complications can include skin and soft tissue atrophy and fibrosis, osteoradionecrosis, and trismus.
- Close margins, typically defined as <5 mm, are associated with a worse prognosis.
- Adjuvant chemotherapy may also be an option in treatment regimen.

DISPOSITION

- Prognosis depends on the cancer cell type and staging.
- Tumor HPV status is a strong and independent prognostic factor for survival among patients with oropharyngeal cancer.

REFERRAL

Refer to oral and maxillofacial or ear, nose, and throat surgeon.

PEARLS & CONSIDERATIONS

COMMENTS

- Oral and pharyngeal cancer is the sixth most common cancer globally.
- Biopsy is the key for diagnosis.
- Posttreatment surveillance is important.

PREVENTION

- Encourage patients to stop using any type of tobacco and drinking alcohol.
- Examine oral cavities at annual checkups and work up suspicious lesions.

PATIENT & FAMILY EDUCATION

http://globocan.iarc.fr/factsheets/populations/factsheet.asp?uno=900.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Mouth Cancer (Patient Information)

AUTHORS: **PRIYA SARIN GUPTA, M.D., M.P.H.,** and **KEVIN PLUMLEY, M.D., M.P.H.**

EVIDENCE

Abstract[1]

Background:

The evidence on the relationship between coffee intake and cancer of the oral cavity and oesophagus is conflicting and few follow-up studies have been done.

Methods:

A total of 389 624 men and women 40–45 years who participated in a national survey programme were followed with respect to cancer for an average of 14.4 years by linkage to the Cancer Registry of Norway. Coffee consumption at baseline was reported as a categorical variable (0 or <1 cup, 1–4, 5–8, 9+ cups per day).

Results:

Altogether 450 squamous oral or oesophageal cancers were registered during follow-up. The adjusted hazard ratios with 1–4 cups per day as reference were 1.01 (95% confidence interval: 0.70, 1.47), 1.16 (0.93, 1.45) and 0.96 (0.71, 1.14) for 0 or <1 cup, 5–8 and 9+ cups per day, respectively. Stratification by sex, type of coffee, smoking status and dividing the end point into oral and oesophageal cancers gave heterogeneous and non-significant estimates.

Conclusion:

This study does not support an inverse relationship between coffee intake and incidence of cancer in the mouth or oesophagus, but cannot exclude a weak inverse relationship. Ⓐ

Evidence-Based Reference

Tverdal A et al.: Coffee intake and oral–oesophageal cancer: follow-up of 389 624 Norwegian men and women 40-45 years, *Br J Cancer* 105:157–161, 2011. Ⓐ

SUGGESTED READINGS

Ang KK et al.: Human papillomavirus and survival of patients with oropharyngeal cancer, *N Engl J Med* 363:24–35, 2010.

Ayaz B et al.: A clinico-pathological study of oral cancer, *Biomedica* 27:29–32, 2011.

Garewal HS: Chemoprevention of oral cancer: beta-carotene and vitamin E in leukoplakia, *Eur J Cancer Prev* 3:101–107, 1994.

Gillison ML et al.: Prevalence of oral HPV infection in the United States, 2009-2010, *JAMA* 307(7):693–703, 2012.

GLOBOCAN (website) http://globocan.iarc.fr/factsheets/populations/factsheet.asp?uno=900.

Greenberg M.; et al.: Burkett's oral medicine. ed 11 People's Medical Publishing House - USA: Shelton, CT.

Kademani D et al.: Oral cancer, *Mayo Clin Proc* 82(7):878–887, 2007.

Moore EJ et al.: Long-term functional and oncologic results of transoral robotic surgery for oropharyngeal squamous cell carcinoma, *Mayo Clin Proc* 87(3):219–225, 2012.

Neville B.; et al.: Oral and maxillofacial pathology. ed 3, Saunders: Philadelphia.

BASIC INFORMATION

DEFINITION

Oral hairy leukoplakia (OHL) is a painless, white, nonremovable, plaquelike lesion typically located on the lateral aspect of the tongue.

ICD-9CM CODES
528.6 Oral hairy leukoplakia
ICD-10CM CODES
K13.3 Hairy leukoplakia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE AND PREVALENCE: Incidence of Epstein-Barr virus (EBV) seroprevalence is high in individuals who are HIV seropositive. However, OHL occurs in only 25% of these cases.
RISK FACTORS: OHL is usually found in HIV-seropositive individuals (median CD4 count is 468/mL) but may also be identified in smokers and other immunocompromised patients such as transplant recipients (particularly renal) and patients taking steroids. Diagnosing OHL is an indication to institute a workup to evaluate and manage HIV disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Varying morphology and appearance, which may change daily.
- May be unilateral or bilateral.
- White plaques can be small with fine, vertical corrugations on the lateral margin of the tongue (Fig. 01-12). The plaques from OHL are adherent to the tongue surface (in contrast to candidal plaques, which may be easily scraped off).
- Irregular surface; may have prominent folds or projection, occasionally markedly resembling hairs.
- May spread to cover the entire dorsal surface or spread onto the ventral surface of the tongue where the lesions usually appear flat.
- Rarely, lesions can manifest on the soft palate, buccal mucosa, or posterior oropharynx.
- Usually asymptomatic, but some patients have mouth pain, soreness, or a burning sensation; impaired taste; or difficulty eating; others complain of its unsightly appearance.
- OHL may rarely progress to oral squamous cell carcinoma particularly in smokers, which has a poor prognosis.

ETIOLOGY

EBV is implicated in its etiology, and OHL is a result of replication EBV in the epithelium of keratinized cells. OHL differs from most EBV-related diseases in that infection is predominantly lytic rather than latent.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- *Candida albicans.*
- Lichen planus.
- Idiopathic leukoplakia.
- White sponge nevus.
- Dysplasia.
- Squamous cell carcinoma.

WORKUP

Requires physical examination and evaluation of HIV disease

LABORATORY TESTS

The *provisional* diagnosis is clinical and based on:
- Visual inspection.
- Inability to scrape the lesion off the tongue with a blade.
- Failure to respond to antifungal therapy.

The *presumptive* diagnosis requires biopsy and histologic demonstration of:
- Epithelial hyperplasia with hairs.
- Absence of inflammatory cell infiltrate.

The *definitive* diagnosis requires:
- In situ hybridization of histologic or cytologic specimens revealing EBV DNA *or*
- Electron microscopy of specimens revealing herpes-like particles.
- Measurement of the DNA content in cells of oral leukoplakia may be used to predict the risk of oral carcinoma.

NOTE: Specimens obtained from lesions may demonstrate hyphae of *Candida albicans,* which may coexist and potentiate EBV-induced OHL.

TREATMENT

NONPHARMACOLOGIC THERAPY

OHL is usually asymptomatic and requires no specific therapy. It may resolve spontaneously and is generally benign in HIV-seropositive patients.

ACUTE GENERAL Rx

- Antiretroviral therapy (ART) has considerably changed the frequency of oral lesions caused by opportunistic infections in HIV-seropositive individuals.
- Topical retinoids (0.1% vitamin A) may improve the appearance of OHL-affected oral surfaces through their dekeratinizing and immunomodulation effects; however, they are expensive and prolonged use may result in a burning sensation over the treated area.
- Topical podophyllin resin 25% solution has been reported to induce resolution.
- Surgical excision and cryotherapy may help, but the lesions may recur.
- High-dose acyclovir 800 mg five times per day, valacyclovir 1000 mg tid, famciclovir 500 mg tid, ganciclovir 1000 mg tid, or foscarnet 40 mg/kg IV tid will cause lesions to resolve but only temporarily.

PEARLS & CONSIDERATIONS

- OHL may be the presenting sign of patients infected with HIV who are unaware of their status.
- The incidence has decreased significantly in the era of ART.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Leukoplakia (Patient Information)
Epstein-Barr Virus Infection (Related Key Topic)
Human Immunodeficiency Virus (Related Key Topic)

AUTHOR: **SAJEEV HANDA, M.D., S.F.H.M.**

FIGURE 01-12 Oral hairy leukoplakia. Note white verrucoid plaques on the lateral border of the tongue. (From Noble J: *Primary care medicine*, ed 3, St Louis, 2001, Mosby.)

SUGGESTED READING

Sudbo J et al.: DNA content as a prognostic marker in patients with oral leukoplakia, *N Engl J Med* 344:1270, 2001.

BASIC INFORMATION

DEFINITION

Orchitis is an inflammatory process (usually infectious) involving the testicles. Infection may be viral or bacterial and can be associated with infection of other male sex organs (prostate, epididymis, or bladder) or lower urogenital tract or sexually transmitted diseases often via hematogenous spread. Common causes are:

- Viral: mumps—20% postpubertal; coxsackie B virus
- Bacterial: pyogenic via spread from involving epididymis; bacteria include *Escherichia coli, Klebsiella pneumoniae, P. aeruginosa, Staphylococcus, Streptococcus* or *Rickettsia, Brucella* spp.
- Other:
  1. Viral—HIV-associated, CMV
  2. Fungi
     1. Cryptococcosis
     2. Histoplasmosis
     3. *Candida*
     4. Blastomycosis
     5. Syphilis
  3. *Mycobacterium tuberculosis* and *M. leprae*
  4. Parasitic causes: toxoplasmosis, filariasis, schistosomiasis
- Table 01-8 describes a classification of epididymitis and orchitis based on etiology.

SYNONYMS

Epididymo-orchitis
Testicular infection
Testicular inflammation

ICD-9CM CODES
0.72 Mumps
098.13 Acute gonococcal orchitis
095.8 Syphilitic orchitis
016.50 Tuberculous orchitis, unspecified

ICD-10CM CODES
N45.9 Orchitis, epididymitis, and epididymo-orchitis without abscess
A54.1 Gonococcal orchitis
A56.1 Chlamydial orchitis
N51.1 Mumps orchitis

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT SEX: Male
PREDOMINANT ORGANISM: The leading cause of viral orchitis is mumps. The mumps virus rarely causes orchitis in prepubertal males but involves one or both testicles in nearly 30% of postpubertal males.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Testicular pain, unilateral or bilateral swelling
- May have associated epididymitis, prostatitis, fever, scrotal edema, erythema, cellulitis
- Inguinal lymphadenopathy
- Acute hydrocele (bacterial)
- Rare development: abscess formation, pyocele of scrotum, testicular infarction
- Spermatic cord tenderness may be present
- Granulomatous

DIAGNOSIS

Clinical presentation as described previously with possible history of acute viral illness or concomitant epididymitis.

DIFFERENTIAL DIAGNOSIS

- Epididymo-orchitis-gonococcal
- Autoimmune disease
- Vasculitis
- Epididymitis
- Mumps, with or without parotitis
- Neoplasm
- Hematoma
- Spermatic cord torsion

LABORATORY TESTS

- CBC with differential
- Urinalysis
- Viral titer—mumps
- Urine culture
- Ultrasound of testicle to rule out abscess

IMAGING STUDIES

Ultrasound if abscess suspected

TREATMENT

- Dependent on cause
- Viral (mumps): observation; bed rest, ice packs, analgesics, and a scrotal sling for support may provide some relief of discomfort that accompanies mumps orchitis
- Bacterial: empiric antibiotic treatment with parenteral antibiotic treatment until pathogen identified: ceftriaxone (250 mg IM once) plus doxycycline (100 mg PO bid for 10 days), in men <35 yr old to cover *Neisseria gonorrhoeae* and Chlamydia trachomatis. In homosexual men or men >35 yr old: levofloxacin 500-750 mg IV/PO qd for 10-14 days *or* ampicillin-sulbactam *or* third-generation cephalosporin or ticarcillin-clavulanate.
- Surgery for abscess, pyogenic process

DISPOSITION

Follow-up for evidence of recurrence, hypogonadism, and infertility may be needed with bilateral orchitis.

REFERRAL

- To a urologist if surgical drainage is needed
- To an endocrinologist if hypogonadism develops
- To a fertility specialist if infertility develops

PEARLS & CONSIDERATIONS

Consider tuberculous orchitis if symptoms fail to respond to standard antibacterial therapy, even in the absence of chest radiographic evidence of pulmonary tuberculosis.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Orchitis (Patient Information)
Epididymitis (Related Key Topic)
Mumps (Related Key Topic)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

TABLE 01-8 Classification of Epididymitis and Orchitis

Acute Epididymitis or Epididymoorchitis	Granulomatous Epididymitis or Orchitis	Viral Orchitis
Neisseria gonorrhoeae	*Mycobacterium tuberculosis*	Mumps
Chlamydia trachomatis	*Treponema pallidum*	Enteroviruses
Escherichia coli		
Streptococcus pneumoniae	*Brucella* spp.	
Klebsiella spp.	Sarcoid	
Salmonella spp.	Fungal	
Other urinary tract pathogens	Parasitic	
Idiopathic	Idiopathic	

From Cohen J, Powderly WG: *Infectious diseases,* ed 2, St Louis, 2004, Mosby.

SUGGESTED READINGS

Niizuma T et al.: Elevated serum C-reactive protein in mumps orchitis, *Pediatr Infect Dis J* 23(10):971, 2004.

Rajagopal AS: Pseudomonas orchitis in puberty, *Int J STD AIDS* 15(10):707, 2004.

Raynor MC et al.: Urinary infections in men, *Med Clin North Am* 95(1):43–54, 2011.

Trojian TH et al.: Epididymitis and orchitis: an overview, *Am Fam Physician* 79(7):583–587, 2009.

BASIC INFORMATION

DEFINITION

Orthostatic hypotension (OH) is defined as the presence of at least one of the following: a decrease in systolic blood pressure by ≥20 mm Hg or a decrease in diastolic blood pressure by ≥10 mm Hg within 3 min of standing. It is a physical sign that requires further investigation to discern its underlying etiology.

SYNONYMS

Postural hypotension

ICD-9CM CODES
458.0 Orthostatic hypotension
ICD-10CM CODES
I95.1 Orthostatic hypotension

EPIDEMIOLOGY & DEMOGRAPHICS

- The incidence of OH is increased in older people and in those with diseases associated with autonomic dysfunction (e.g., Parkinson disease, diabetes mellitus).
- OH may cause up to 30% of all syncopal events in the elderly, and OH is associated with an increased risk of heart failure among those aged 45 to 55 yr and an increased risk of cardiovascular disease and all-cause mortality among those aged 55 yr and older.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms may include dizziness, lightheadedness, syncope, visual and auditory disturbances, weakness, diaphoresis, pallor, and nausea. OH may also be asymptomatic, especially in older hypertensive patients.
- Associated with increased autonomic activity during meals (from increased splanchnic blood flow), exercise, and hot weather.
- Supine and nocturnal hypertension in patients with OH may indicate an underlying autonomic dysfunction.

ETIOLOGY

- The assumption of an upright posture results in the pooling of approximately 500 ml of blood in the lower extremities due to gravity and decreased venous return, decreased cardiac output, and decreased arterial pressure. The consequent increase in sympathetic tone due to increased carotid baroreceptor activity causes arterial and venous constriction as well as positive inotropic and chronotropic effects, thereby limiting the fall in upright blood pressure. Peripheral vasoconstriction is also mediated by increased activity of the renin-angiotensin system and decreased activity of atrial natriuretic factor.
- Impairment of the baroreceptor reflex, as in central or peripheral autonomic dysfunction and aging, may cause OH because decreased blood pressure cannot be counteracted by the aforementioned regulatory mechanisms.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Common:
- Medications: antihypertensives, antidepressants (tricyclics), antipsychotics (phenothiazines), alcohol, narcotics, barbiturates, insulin, nitrates, PDE-5 inhibitors, alpha-adrenergic antagonists
- Reduced intravascular volume (hemorrhage, dehydration, hyperglycemia, hypoalbuminemia)
- Postprandial effect (especially in the elderly)
- Vasovagal syncope
- Deconditioning
- Central autonomic dysfunction (Parkinson's disease)
- Peripheral autonomic dysfunction (diabetes mellitus, Guillain-Barré syndrome)

Uncommon:
- Central autonomic dysfunction (Shy-Drager syndrome)
- Postganglionic autonomic dysfunction: impaired norepinephrine release
- Autoimmune autonomic dysfunction: nicotinic acetylcholine receptor autoantibodies
- Paraneoplastic autonomic dysfunction: anti-Hu antibodies (in small-cell lung cancer)
- Postural tachycardia syndrome (POTS): usually occurs in young women; an abnormally large increase in heart rate is observed in the upright position caused by increased venous pooling from autonomic dysfunction of the lower extremities, but blood pressure is not affected because of an excess of plasma norepinephrine
- Impaired cardiac output (myocardial infarction, aortic stenosis, arrhythmias)
- Cerebrovascular accident
- Adrenal insufficiency
- Deconditioning
- Carotid sinus hypersensitivity
- Anxiety, panic attacks
- Seizures
- Sepsis
- Idiopathic

WORKUP

- Measure supine blood pressure after the patient has been resting comfortably, stand for 3 min, then measure upright blood pressure. The blood pressure cuff must be held at the level of the right atrium; holding the cuff below this level will result in a 5 to 10 mm Hg underestimation of blood pressure.
- Thorough neurologic examination should be performed.
- Rule out treatable causes (e.g., medications, volume depletion).

LABORATORY TESTS

- Hemoglobin and hematocrit
- Consider when treatable causes of OH have been ruled out:
  1. Blood pressure and heart rate monitoring with a tilt table test
  2. Plasma norepinephrine measurements (to distinguish postganglionic from preganglionic autonomic dysfunction)
  3. Other methods, which use the Valsalva maneuver or measure sweating as indirect means of evaluating the autonomic nervous system

IMAGING STUDIES

None

TREATMENT

NONPHARMACOLOGIC THERAPY

- Patient education (leg crossing, prolonged sitting before first standing in the morning, avoid excessive straining and hot baths)
- High-salt diet (e.g., bouillon cubes); caution if history of heart failure
- Liberal fluid intake
- Take needed antihypertensive medications at different times of the day
- Raise the head of the bed at night
- Compression stockings (to include splanchnic circulation)
- Multiple low-carbohydrate meals to avoid postprandial OH
- Avoid large carbohydrate loads and excess alcohol consumption

ACUTE GENERAL Rx

- Correction of volume status
- Review medication list and attempt to eliminate those potentially contributing to OH

CHRONIC Rx

- Fludrocortisone: 0.1 mg/day (may combine with an alpha-1 agonist to lower the dose of each); monitor for electrolyte disturbances and supine hypertension
- Midodrine (alpha-1 agonist): 10 mg three times a day; monitor for supine hypertension
- Erythropoietin (consider if anemic)
- Caffeine (for postprandial hypotension)

OTHER TREATMENTS

- Pyridostigmine (enhances renal sodium reabsorption): 0.2 to 0.6 mg/day (not FDA approved for this indication)
- Octreotide: 300 to 600 mg/day (not FDA-approved for this indication)
- Indomethacin (prostaglandin inhibitor)
- DDAVP (experimental)

PEARLS & CONSIDERATIONS

COMMENTS

- The presence of OH should always trigger a search for an underlying etiology.
- OH is diagnosed by observing changes in blood pressure, not heart rate.
- Volume depletion should cause an increased heart rate on standing; a lack of heart rate response in this setting suggests autonomic dysfunction.
- Pharmacotherapy with mineralocorticoids may require concomitant potassium replenishment and monitoring for hypertension.

- Evidence to support the efficacy of pharmacologic interventions to treat OH, including midodrine, is limited.
- The etiology of OH is often multifactorial in older patients, but increased susceptibility to volume depletion due to decreased baroreceptor reflexes frequently contributes.
- Evidence suggests that nursing home residents with more stringent SBP control (<140 mm Hg) have a lower risk of OH than nursing home residents with less stringent SBP control.
- The physical examination of patients with dizziness, gait disturbance, and/or falls should include an assessment for OH.
- Because OH may be asymptomatic, physical examination of those at risk must include assessment of blood pressure in both the supine and upright positions.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **TIMOTHY W. FARRELL, M.D.**

SUGGESTED READINGS

Bradley J, Davis K: Orthostatic hypotension, *Am Fam Physician* 68:2393–2398, 2003.

Bush D, Syncope. In: (editors: Pompei P.; Murphy J.) Geriatrics review syllabus: a core curriculum in geriatric medicine. ed 6 American Geriatrics Society: New York, pp. 168–173.

Freeman R: Neurogenic orthostatic hypotension, *N Engl J Med* 358:615–624, 2008.

Gupta V, Lipsitz LA: Orthostatic hypotension in the elderly: diagnosis and treatment, *Am J Med* 120:841–847, 2007.

Jacob G et al.: The neuropathic postural tachycardia syndrome, *N Engl J Med* 343(1008), 2000.

Jones CD et al.: Orthostatic hypotension as a risk factor for incident heart failure: the atherosclerosis risk in communities study, *Hypertension* 59:913–918, 2012.

Logan IC, Witham MD: Efficacy of treatments for orthostatic hypotension: a systematic review, *Age Ageing* 41:587–594, 2012.

Parsaik AK: Midodrine for orthostatic hypotension: a systemic review and meta-analysis of clinical trials, *J Gen Intern Med*, 2013 (epub ahead of print).

Mitka AK et al.: Midodrine for orthostatic hypotension: a systemic review and meta-analysis of clinical trials, *J Gen Intern Med*, 2013 (epub ahead of print).

Valbusa F, Labat C, Salvi P et al.: Orthostatic hypotension in very old individuals living in nursing homes: the PARTAGE study, *J Hypertension* 30:53–60, 2012.

Verwoert G et al.: Orthostatic hypotension and risk of cardiovascular disease in elderly people: the Rotterdam study, *J Am Geriatr Soc* 56:1816–1820, 2008.

Wieling W, Schatz I: The consensus statement on the definition of orthostatic hypotension: a revisit after 13 years, *J Hypertens* 27:935–938, 2009.

BASIC INFORMATION

DEFINITION

Osgood-Schlatter disease is painful swelling of the growing tibial tuberosity in adolescents.

SYNONYMS

Juvenile osteochondrosis

ICD-9CM CODES
732.4 Osgood-Schlatter disease
ICD-10CM CODES
M92.40 Juvenile osteochondrosis of patella, unspecified knee

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 4 cases/100 adolescents.
PREDOMINANT SEX: Male/female ratio of 3:1.
PREDOMINANT AGE: Males: age 12 to 15 yr, females: age 8 to 12 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Gradual onset of pain and swelling of the tibial tubercle.
- Worsening of pain after athletic activity.
- Reproduction of pain with resisted knee extension.

ETIOLOGY

- Repetitive microtrauma and avulsion of the developing ossification center of the tibial tuberosity.
- Anatomic variants such as patella alta.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Stress fracture of the proximal tibia.
- Hoffa disease.
- Sinding-Larsen-Johansson syndrome.
- Patellar tendinitis.

WORKUP

- The diagnosis of Osgood-Schlatter disease is generally made on clinical grounds.
- Imaging to exclude fracture or bony tumors.

IMAGING STUDIES

- Lateral x-rays may show separation and fragmentation of the upper tibial epiphysis (Fig. 01-13).
- Musculoskeletal ultrasound (Fig. 01-14) can also be used and may be helpful in evaluating soft tissue, tendons, and noncalcified cartilage.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Activity modification with increased periods of rest.
- Physical therapy.

ACUTE GENERAL Rx

- Ice, especially after exercise.
- Nonsteroidal anti-inflammatory drugs.
- Quadriceps stretching exercises.

DISPOSITION

- Condition usually heals when the epiphysis closes.
- 90% of patients respond to conservative treatment.
- Recent studies have shown promising results with the use of hyperosmolar dextrose injections in recalcitrant disease.
- Surgery is rarely needed in the treatment of Osgood-Schlatter disease, but can be used for relief of persistent symptoms in which patients have separated ossicles or an abnormally ossified tibial tuberosity.

REFERRAL

Orthopedic consultation is recommended when symptoms persist >6 to 8 weeks with conservative treatment.

PEARLS & CONSIDERATIONS

COMMENTS

Larsen-Johansson disease is a similar disorder. While the diagnosis of Osgood-Schlatter disease is clinical, imaging should be performed to rule out infection, fracture, and malignancy as causes of unilateral anterior knee pain in adolescents.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Osgood-Schlatter Disease (Patient Information)

AUTHOR: **AMY L. LUNDHOLM, D.O.**

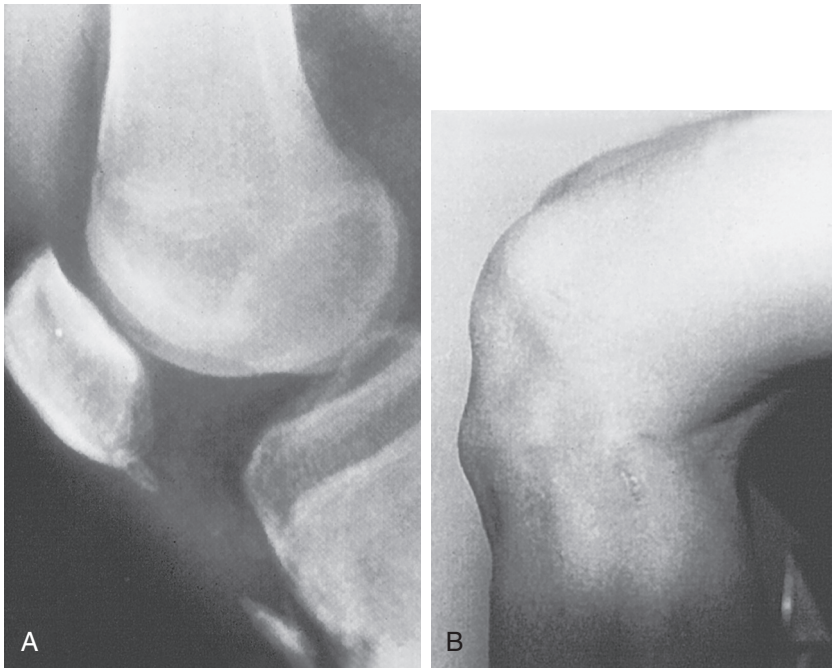


FIGURE 01-13 A, Radiograph of Osgood-Schlatter disease demonstrating thickening of patella tendon, fragmentation of the tibial tubercle, and soft tissue swelling. **B,** Clinical picture of bony prominence anteriorly at the tibial tubercle. (From Scuderi G [ed]: *Sports medicine: principles of primary care,* St Louis, 1997, Mosby.)

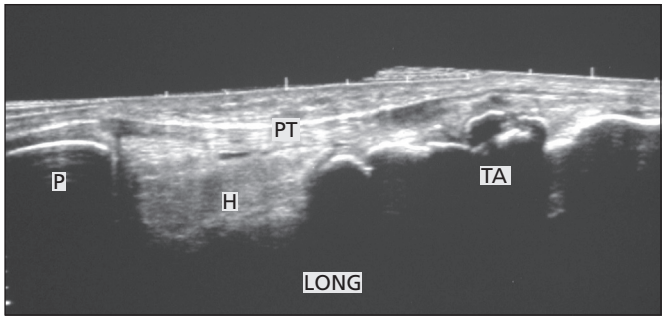


FIGURE 01-14 EFOV of a patient with Osgood-Schlatter disease in the long axis with a knee in extension showing irregularity and fragmentation of the distal tibial apophysis. *P,* Patella; TA, tibial apophysis, PT, patella tendon, H, Hoffa's fat. (From McNally E: *Practical musculoskeletal ultrasound,* ed 1, New York, 2005, Churchill Livingstone, p. 146.)

SUGGESTED READINGS

Duri ZA et al.: The immature athlete, *Clin Sports Med* 21(3):461, 2002.

Frank JB et al.: Lower extremity injuries in the skeletally immature athlete, *J Am Acad Orthop Surg* 15(6):356, 2007.

Pihlajamaki H et al.: Long term outcome after surgical treatment of unresolved Osgood-Schlatter disease in young men, *J Bone Joint Surg* 91(10): 2350–2358, 2009.

Topol GA et al.: Hyperosmolar dextrose injection for recalcitrant Osgood-Schlatter disease, *Pediatrics* 128(5):e1121–e1128, 2011.

BASIC INFORMATION

DEFINITION

Osler-Rendu-Weber syndrome is a disorder characterized by the appearance of multiple telangiectasias on the face, mouth, lips, and other areas.

SYNONYMS

Hereditary hemorrhagic telangiectasia
HHT

ICD-9CM CODES
448.0 Hereditary hemorrhagic telangiectasia
ICD-10CM CODES
I78.0 Hereditary hemorrhagic telangiectasia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1 in 8000 to 16,500
PREVALENCE: Approximately 1.2 million people worldwide
PREDOMINANT SEX AND AGE
- Men = women
- Individual variability

GENETICS: Inherited dominant mutation. Mutations in the endoglin gene, a cell surface component of the transforming growth factor–β (TGF-β) receptor complex, causes this syndrome.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Recurrent epistaxis and gastrointestinal (GI) bleeds due to lesions in the oropharyngeal epithelium and gut.
- Telangiectasia lesions may be present on the lips, tongue (Fig. EO1-15), nasal mucosa, retina, hands, chest, and lower extremities. There may appear to be many erythematous macules and papules.
- Telangiectasias either are round and mildly raised or are stellate without a well-defined border.
- Mucocutaneous lesions are 1 to 4 mm, sharply demarcated red to purple macules, or spiderlike projections. They usually develop at puberty.
- Arteriovenous malformations of the lungs, central nervous system, or liver.
- Multiple arteriovenous (AV) malformations causing liver involvement or atypical cirrhosis are rare but can occur. Liver left-to-right shunting can predispose patients to high-output heart failure.

ETIOLOGY

- Autosomal dominant disorder with incomplete penetrance.
- Mutations in *ENG* and *ACVRLK1* that code for endoglin and ALK, which are TGF-β receptors that function in integrity of vessel structures.
- Type 1 is due to loss of function gene mutation of ENG (9q3).
- Type 2 is due to loss of function gene mutation of *ALK1* (12q13).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Generalized essential telangiectasia
- Unilateral nevoid telangiectasia
- Scleroderma with CREST syndrome
- Rosacea
- Actinic keratosis
- Ataxia telangiectasia
- Venous hypertension
- Cushing syndrome

WORKUP

Diagnosis can generally be made from a detailed history and physical exam, if at least 3 of these 4 criteria are present:
1. Spontaneous recurrent epistaxis
2. Multiple telangiectasias (in multiple sites such as face, mouth, and lips)
3. Internal lesions such as arteriovenous malformations
4. First-degree relative with diagnosed HHT

If 2 criteria are present, there is a possible diagnosis.

LABORATORY TESTS

- Complete blood cell count (CBC), including platelet count, to evaluate anemia and rule out thrombocytopenia; coagulation profile. Patients with this disorder have normal levels of clotting factors and an intact clotting mechanism
- Ferritin level, stool for occult blood
- Endoscopy (upper and lower), angiography

IMAGING STUDIES

- Electron microscopy shows lack of pericytes.
- Chest radiograph

TREATMENT

NONPHARMACOLOGIC THERAPY

- Laser ablation of symptomatic lesions
- GI bleeding prophylaxis
- Angiographic embolization
- Segmental bowel resection
- Surgical correction of AV malformations

ACUTE GENERAL Rx

- Bevacizumab injection 5 mg/kg, intranasal 50 mg spray for epistaxis
- In those without a history of pulmonary AV malformations, tamoxifen 20 mg/d (antiestrogen) or aminocaproic acid (antifibrinolytic) therapies may be considered.
- In severe cases may consider use of agents such as thalidomide.
- Recent studies may suggest the potential use of phosphoinositide 3-kinase inhibitor BKM120.

CHRONIC Rx

Iron replacement for anemia due to blood loss

DISPOSITION

Prognosis depends on areas affected by AV malformations.

REFERRAL

To ENT and vascular surgeon for correction of vascular malformations, gastroenterologist for esophagogastroduodenoscopy

PEARLS & CONSIDERATIONS

- Primary manifestations usually occur before puberty and are characterized as epistaxis. Later, hemorrhages of GI and genitourinary (GU) tracts occur.
- Vascular abnormalities may result in portal hypertension, pulmonary AV malformations with hemoptysis, cerebrovascular accidents, and hematuria in addition to GI bleeding and anemia.
- Genetic screening of first-degree relatives should be performed.
- 5% to 10% of patients have pulmonary AV malformations.
- In two thirds of individuals who have neurologic symptoms, the source is pulmonary AV malformations.
- Those with history or pulmonary AV malformations require antibacterial prophylaxis for surgical or dental operations.
- Approximately 15% to 20% of patients with AV malformations in the lungs present with stroke due to embolic abscesses.

COMMENTS

Affected children may experience recurrent epistaxis before detection of the characteristic skin and mucous membrane lesions.

PREVENTION

Seek genetic counseling if one has a family history of Osler-Rendu-Weber disease.

PATIENT & FAMILY EDUCATION

HHT Foundation International: http://hht.org

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **FRED F. FERRI, M.D.** and **HEATHER FERRI, D.O.**

SUGGESTED READINGS

Guldmann R et al.: Bevacizumab nasal spray: noninvasive treatment of epistaxis in patients with Rendu-Osler disease, *Laryngoscope* 122:952–955, 2012.

Horn TD et al. In: (editor: Bolognia JL et al.) Dermatology. vol. 2 Saunders: Philadelphia.

Sabb C et al.: Hereditary hemorrhagic telangiectasia: clinical features in ENG and ALK1 mutation carriers, *J Thromb Haemost* 5(6):1149–1157, 2007.

Wang XY et al.: Successful treatment of thalidomide for recurrent bleeding due to gastric angiodysplasia in hereditary hemorrhagic telangiectasia, *Eur Rev Med Pharmacol Sci* 17(8):1114–1116, 2013. Apr.

Yaniv E et al.: Anti-estrogen therapy for hereditary hemorrhagic telangiectasia—a long-term clinical trial, *Rhinology* 49(2):214–216, 2011. Jun.

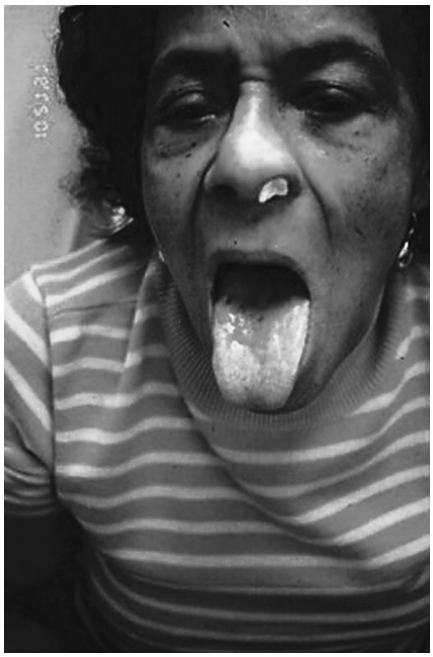


FIGURE E01-15 Multiple telangiectasias are evident on the tongue and in the nose (recent epistaxis in left nostril) of this patient with Osler-Rendu-Weber syndrome. (From Ferri F et al: *Ferri's fast facts in dermatology*, Philadelphia, 2010, Saunders.)

BASIC INFORMATION

DEFINITION

Osteoarthritis (OA) is a progressive disease of the joint representing failed repair of joint damage that results from intraarticular stresses that may be initiated by abnormalities in articular cartilage, subchondral bone, ligaments, menisci (when present), periarticular muscles, peripheral nerves, or synovium. This ultimately results in the breakdown of cartilage and bone, leading to symptoms of pain, stiffness, and functional disability. As a disease, it is aptly defined as structural abnormalities visualized on plain radiographs and MRI (magnetic resonance imaging), while as an illness, it encompasses a symptom complex of pain, aching, discomfort, stiffness, fatigue, and sleep disturbance that results in functional limitation, physical disability, and reduced health-related quality of life.

SYNONYMS

Degenerative joint disease
Osteoarthrosis
Arthrosis

ICD-9CM CODES
715.0 Osteoarthrosis and allied disorders
ICD-10CM CODES
M15.9 Polyarthrosis, unspecified
M17 Gonarthrosis (arthrosis of knee)
M18 Arthrosis of first metacarpal joint
M19 Other arthrosis
M19.8 Other specified arthrosis
M19.9 Arthrosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 2% to 6% of general population
PREDOMINANT SEX: Females slightly more than males in a 2:1 ratio
PREDOMINANT AGE: >50 yr
GENETICS: 39% to 65% heritability rate in twin studies of women who have generalized OA, concordance rate of 0.64 in monozygotic twins.
RISK FACTORS: Nonmodifiable are age, female gender, hormonal status, geographic, genetic, and presence of congenital or developmental conditions. Modifiable risk factors such as obesity, smoking, high bone density, nutritional deficiencies such as vitamin D deficiency, and presence of crystal arthropathies such as gout. Local factors are trauma during physical activities, type of occupation, muscle strength, anatomic malalignment of the lower extremities, as well as biomechanical factors such as knee laxity, leg length discrepancy, and proprioceptive deficits.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Similar symptoms in most forms: stiffness, pain, crepitus
- Joint tenderness, swelling
- Decreased range of motion
- Crepitus with motion
- Bouchard's nodes: bony enlargement on the proximal interphalangeal (PIP) joints of the hand
- Heberden's nodes: bony enlargement of the distal interphalangeal (DIP) joints of the hand (Fig. 01-16)
- Pain with range of motion

ETIOLOGY

- Primary or idiopathic OA can be mono-, oligo-, or polyarticular.
- Secondary OA is due to an identifiable condition such as trauma, type of occupation, developmental, mechanical, metabolic, and inflammatory conditions.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bursitis, tendinitis
- Inflammatory arthritides
- Infectious arthritis
- Crystal arthropathies such as gout and pseudogout
- Rheumatoid arthritis (Fig. 01-17)

WORKUP

- No diagnostic test exists for degenerative joint disease.
- Laboratory evaluation is normal.
- Rheumatoid factor, erythrocyte sedimentation rate, complete blood count, and antinuclear antibody tests may be required if inflammatory component is suggested by history.
- Arthrocentesis of swollen joints: synovial fluid examination is generally normal or noninflammatory in character.

IMAGING STUDIES

- Plain x-ray of the involved joints is the first step and usually of high diagnostic value.
- Roentgenographic evaluation (Fig. E01-18) reveals:
  1. Joint space narrowing
  2. Subchondral sclerosis
  3. New bone formation in the form of osteophytes
- MRI can detect other sources of pain such as synovial thickening, effusions, bone marrow edema, bony attrition, and periarticular lesions.
- Musculoskeletal ultrasound (MSKUS) is emerging as an alternative, fast, and inexpensive modality to identify joint damage, presence of osteophytes, effusions, and noninflammatory synovial proliferation identified using Doppler studies. This is otherwise operator-dependent.

FIGURE 01-16 Osteoarthritis of the distal interphalangeal (DIP) joints. This patient has the typical clinical findings of advanced osteoarthritis of the DIP joints, including large, firm swellings (Heberden's nodes), some of which are tender and red because of associated inflammation of the periarticular tissues and the joint. (From Klippel J et al [eds]: *Primary care rheumatology,* London, 1999, Mosby.)

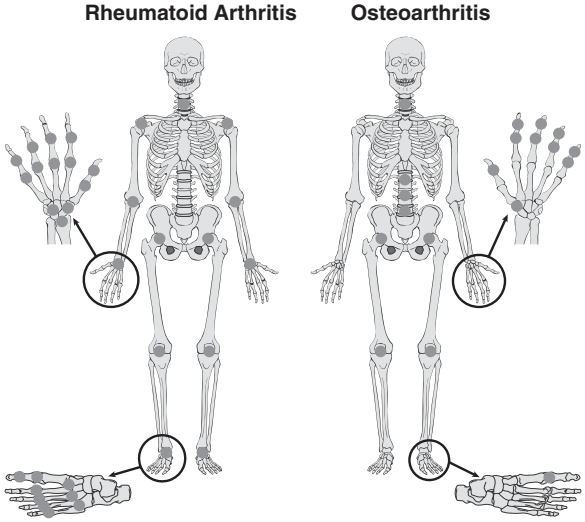


FIGURE 01-17 Distribution of involved joints in the two most common forms of arthritis: rheumatoid arthritis and osteoarthritis. *Shaded circles* are shown over the involved joint areas. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

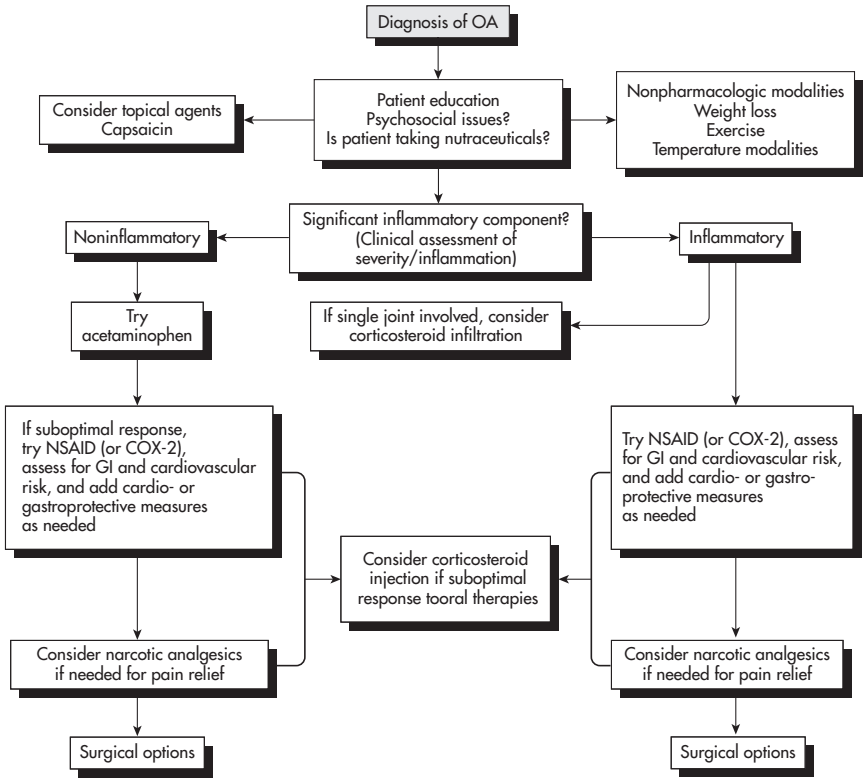


FIGURE 01-19 Algorithm for the management of osteoarthritis (OA). *COX*, Cyclooxygenase; *GI*, gastrointestinal; *NSAID,* nonsteroidal anti-inflammatory drug. (Modified from Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders, Elsevier.)

Rx TREATMENT

- Optimal use of both pharmacologic and nonpharmacologic measures. Fig. 01-19 describes an algorithm for the management of OA.
- Education and reassurance

NONPHARMACOLOGIC THERAPY

HAND OA

- Joint protection techniques
- Assistive devices
- Thermal modalities
- Trapeziometacarpal splints

HIP AND KNEE OA

- Aerobic, aquatic, and resistance exercises
- Weight loss for overweight patients
- Medial wedge insoles for valgus knee
- Subtalar strapped lateral insoles for varus knees
- Patellar taping
- Manual therapy
- Assistive devices such as canes or walkers
- Thermal agents
- Tai chi

ACUTE GENERAL Rx/ PHARMACOLOGIC Rx

- Rest and ice
- Acetaminophen recommended for mild to moderate pain
- May add weak opioids such as tramadol
- Oral and topical NSAIDs. Capsaicin may be used.
- Arthrocentesis of the acutely swollen joint followed by intraarticular steroid injection
- Duloxetine, tramadol if above initial treatment fails
- Opioid analgesics recommended only for severe pain unresponsive to other treatment modalities
- Chronic physical therapy for gentle assisted strengthening exercises
- If considering NSAID as long term, evaluate for risk factors such as age, GI bleed, and cardiovascular (CV) risks. Topical rather than oral NSAIDs are preferred for patients age 75 and older.
- If with risk for GI bleed (age <60 yr), may add PPI or use COX-2 inhibitors
- If with CV risks, consider using naproxen. Ibuprofen may render aspirin ineffective as a cardioprotective agent by interfering with the aspirin-binding site on platelets.
- Nutritional supplements (glucosamine and chondroitin) are unproven. Trials have shown that neither glucosamine sulfate or glucosamine hydrochloride reduces pain compared with placebo in knee or hip osteoarthritis.
- Use of intraarticular hyaluronan injection is controversial. A recent trial in patients with knee OA found viscosupplementation associated with a small and clinically irrelevant benefit and an increased risk for serious adverse events.

DISPOSITION

Progression is not always inevitable, and the prognosis is variable depending on the site and extent of the disease.

REFERRAL

Surgical consultation for patients not responding to nonpharmacologic and pharmacologic management

PEARLS & CONSIDERATIONS

COMMENTS

Surgical intervention is generally helpful in degenerative joint disease. Arthroplasty, arthrodesis, and realignment osteotomy are the most common procedures performed. Arthroscopic debridement (of the knee) appears to be of questionable value. In patients needing hip arthroplasty, resurfacing hip arthroplasty (in which the femoral head is resurfaced with a cap and the neck is preserved) is increasingly popular among younger patients because it results in more hip movement and allows total hip arthroplasty later in the patient's life if necessary.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Osteoarthritis (Patient Information)

AUTHOR: **CRISOSTOMO R. BALIOG, JR, M.D.**

EVIDENCE

Abstract[1]

Background:
An increasing number of young patients are undergoing knee arthroplasties. Thus, the long-term risks of having a knee prosthesis must be evaluated. This study focuses on the potential carcinogenic effects of the prosthesis; it is a long-term follow-up of all patients in Sweden between 1975 and 2006.

Methods:
The incidence of cancer in a total population of operated individuals was compared to the overall national cancer incidence in Sweden by means of standardised incidence ratios. Analysis of cancer latency period was performed to identify potential aetiological factors.

Results:
For male and female patients with rheumatoid arthritis (RA) or osteoarthritis (OA), the overall cancer risks were elevated, ranging from 1.10 (95% confidence interval (CI): 1.03–1.18) for men with OA to 1.26 (1.23–1.29) for men with RA. The greatest increases in risk were observed for the leukaemia subtypes, myelodysplastic syndromes (MDS) and essential thrombocytosis (ET), ranging from 3.31 (1.24–8.83) for ET in men with OA to 7.38 (1.85–29.51) for ET in women with RA. Increases in risk were also observed for breast cancer, prostate cancer and melanoma. The latency analysis revealed elevated risks late in the study period for both solid and haematopoietic cancers. However, only increases in MDS and possibly prostate cancer and melanoma rates appeared to be connected to the operation.

Conclusion:
This study showed that OA and RA arthroplasty patients have a significantly higher risk of cancer than the general population. Elevated risks of MDS and possibly prostate cancer and melanoma indicated a potential connection to exposure to metals in the implant. The observed excessive incidence of ET was likely associated with the inflammatory disease. Ⓐ

Abstract[2]

Objective:
To estimate prospectively any association between measures of physical activity and the risk of either primary knee or hip replacement due to osteoarthritis (OA).

Methods:
Eligible subjects (n=39,023) were selected from participants in a prospective cohort study recruited 1990-1994. Primary knee and hip replacement for OA during 2001-2005 was determined by linking the cohort records to the National Joint Replacement Registry. A total physical activity level was computed, incorporating both intensity and frequency for different forms of physical activity obtained by questionnaire at baseline attendance.

Results:
There was a dose-response relationship between total physical activity level and the risk of primary knee replacement [hazards ratio (HR) 1.04, 95% CI 1.01–1.07 for an increase of 1 level in total physical activity]. Although vigorous activity frequency was associated with an increased risk of primary knee replacement (HR 1.42, 95% CI 1.08–1.86) for 1–2 times/week and HR 1.24 (95% CI 0.90–1.71) for ≥3 times/week), the p for trend was marginal (continuous HR 1.08, 95% CI 1.00–1.16, p=0.05). The frequency of less vigorous activity or walking was not associated with the risk of primary knee replacement, nor was any measure of physical activity associated with the risk of primary hip replacement.

Conclusion:
Increasing levels of total physical activity are positively associated with the risk of primary knee but not hip replacement due to OA. Physical activity might affect the knee and hip joints differently depending on the preexisting health status and anatomy of the joint, as well as the sort of physical activity performed. Ⓐ

Abstract[3]

We retrospectively assessed the value of identifying impinging osteophytes using dynamic computer simulation of CT scans of the elbow in assisting their arthroscopic removal in patients with osteoarthritis of the elbow. A total of 20 patients were treated (19 men and one woman, mean age 38 years (19 to 55)) and followed for a mean of 25 months (24 to 29). We located the impinging osteophytes dynamically using computerized three-dimensional models of the elbow based on CT data in three positions of flexion of the elbow. These were then removed arthroscopically and a capsular release was performed.
The mean loss of extension improved from 23° (10° to 45°) preoperatively to 9° (0° to 25°) post-operatively, and the mean flexion improved from 121° (80° to 140°) pre-operatively to 130° (110° to 145°) post-operatively. The mean Mayo Elbow Performance Score improved from 62 (30 to 85) to 95 (70 to 100) post-operatively. All patients had pain in the elbow preoperatively which disappeared or decreased post-operatively. According to their Mayo scores, 14 patients had an excellent clinical outcome and six a good outcome; 15 were very satisfied and five were satisfied with their post-operative outcome. We recommend this technique in the surgical management of patients with osteoarthritis of the elbow. Ⓐ

Evidence-Based References

Wagner P et al.: Increased cancer risks among arthroplasty patients: 30 year follow-up of the Swedish Knee Arthroplasty Register, *Eur J Cancer* 47:1061–1071, 2011. Ⓐ

Wang Y et al.: Is physical activity a risk factor for primary knee or hip replacement due to osteoarthritis? A prospective cohort study, *J Rheumatol* 38:350–357, 2011. Ⓐ

Miyake J, Shimada K, Oka K, et al.: Arthroscopic debridement in the treatment of patients with osteoarthritis of the elbow, based on computer simulation, *Bone Joint J* 96-B:237–241, 2014. et al Ⓐ

SUGGESTED READINGS

American College of Rheumatology Subcommittee on Osteoarthritis Guidelines: Recommendations for the medical management of osteoarthritis of the hip and knee, *Arthritis Rheum* 43:1905–1915, 2000.

Bannuru RR et al.: Comparative effectiveness of pharmacologic interventions for knee osteoarthritis, *Ann Intern Med* 162:46–54, 2015.

Bedson J, Croft PR: The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature, *BMC Musculoskeletal Disord* 9(116), 2008.

Coggon D et al.: Occupational physical activities and osteoarthritis of the knee, *Arthritis Rheum* 43:1443–1449, 2000.

Costa ML et al.: Total hip arthroplasty versus resurfacing arthroplasty in the treatment of patients with arthritis of the hip joint: single centre, parallel group, assessor blinded, randomized controlled trial, *BMJ* 344:e1247, 2012.

Emkey R, CAPSS-114 Study Group et al.: Efficacy and safety of tramadol/acetaminophen tablets (ultracet) as add-on therapy for osteoarthritis in subjects receiving a COX-2 nonsteroidal anti-inflammatory drug: a multicenter, randomized, double-blind, placebo-controlled trial, *J Rheumatol* 31:150–156, 2004.

Farkouh ME et al.: Comparison of lumaricoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes, randomized controlled trial, *Lancet* 364:675–684, 2004.

Felson DT et al.: The prevalence of knee osteoarthritis in the elderly: the Framingham Osteoarthritis Study, *Arthritis Rheum* 30:914–918, 1987.

Hochberg MC et al.: American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee, *Arthritis Care Res* 64:465–474, 2012.

Hunter DJ: Viscosupplementation for osteoarthritis of the knee, *N Engl J Med* 372:1040–1047, 2015.

Kelly MA et al.: Osteoarthritis and beyond: a consensus on the past, present and future of hyaluronans in orthopedics, *Orthopedics* 26:1064, 2003.

Kirkley A et al.: A randomized trial of arthroscopic surgery for osteoarthritis of the knee, *N Engl J Med* 359:1097, 2008.

Lane NE et al.: OARSI-FDA initiative: defining the disease state of osteoarthritis, *Osteoarthritis Cartilage* 19(5):478–482, 2011.

Leopold S et al.: Corticosteroid compared with hyaluronic acid injections for the treatment of osteoarthritis of the knee, *J Bone Joint Surg* 85:1197, 2003.

Loughlin J: Genetic epidemiology of primary osteoarthritis, *Curr Opin Rheumatol* 13:111–116, 2001.
Moskowitz RW: The 2012 ACR guidelines for osteoarthritis: not a cookbook, *Cleve Clin J Med* 80:26, 2013.
Oliveira SA et al.: Incidence of symptomatic hand, hip and knee osteoarthritis among patients in a health maintenance organization, *Arthritis Rheum* 38(80):1134–1141, 1995.
Pollo FE, Jackson RW: Knee bracing for unicompartmental osteoarthritis, *J Am Acad Orthop Surg* 14:5, 2006.
Raynauld JP et al.: Quantitative magnetic resonance imaging evaluation of knee osteoarthritis progression over two years and correlation with clinical symptom and radiologic changes, *Arthritis Rheum* 50(2):476–487, 2004.
Reichenbach S et al.: Meta-analysis: chondroitin for osteoarthritis of the knee or hip, *Ann Intern Med* 146:580, 2007.
Rutjes AW et al.: Viscosupplementation for osteoarthritis of the knee, *Ann Intern Med* 157:180–191, 2012.
Schimizu M et al.: Clinical and biochemical characteristics after intra-articular injection for the treatment of osteoarthritis of the knee: prospective randomized study of sodium hyaluronate and corticosteroid, *J Orthop Sci* 15:51, 2010.
Teichtahl AJ et al.: Obesity and the female sex, risk factors for knee osteoarthritis that may be attributable to systemic or local leptin biosynthesis and its cellular effects, *Med Hypothesis* 65:312–315, 2005.
Wegman A et al.: Nonsteroidal antiinflammatory drugs or acetaminophen for osteoarthritis of the hip or knee? A systematic review of evidence and guidelines, *J Rheumatol* 31:344, 2004.
Wu D et al.: Efficacies of different preparations of glucosamine for the treatment of osteoarthritis: a meta-analysis of randomized, double-blind, placebo-controlled trials, *Int J Clin Pract* 67:585–594, 2013.

FIGURE E01-18 Osteoarthritis (degenerative joint disease). A, Primary osteoarthritis of the fingers with characteristic cartilage loss, deviations, and spurs of the proximal (Bouchard's nodes) and distal (Heberden's nodes) interphalangeal joints. **B,** Primary osteoarthritis of the carpus showing characteristic involvement of the radial side with cartilage loss, subchondral sclerosis, and small spur formation from the base of the first metacarpal to the distal articular surface of the scaphoid. (From Grainger RG, Allison D: *Grainger & Allison's diagnostic radiology, a textbook of medical imaging,* ed 4, London, 2001, Churchill Livingstone.)

Osteochondritis Dissecans PTG

BASIC INFORMATION

DEFINITION

Osteochondritis dissecans (OCD) refers to a localized necrosis of the bone with detachment of the overlying subchondral bone and cartilage. The suffix "-itis" is a misnomer, as the disease does not involve inflammation.

SYNONYMS

Osteochondrosis

Avascular necrosis (AVN), aseptic necrosis, ischemic necrosis—AVN and OCD have the same pathophysiology; AVN is a more generic term, whereas OCD is used specifically when a detached fragment of bone and/or cartilage is seen on imaging.

ICD-9CM CODE
732.7 Osteochondritis dissecans
ICD-10CM CODES
M93.20 Osteochondritis dissecans of unspecified site

ETIOLOGY & PATHOPHYSIOLOGY

- While the cause remains unknown, predisposing factors have been identified, including genetic predisposition, repetitive microtrauma, and single trauma followed by bone ischemia. The sequence of events likely entails bone injury, hypovascularization with defective repair, bone necrosis with structural collapse, and detachment of the overlying subchondral bone and cartilage.
- OCD is seen more often in children and adolescents and is more commonly associated with repetitive trauma and sports.

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 2 cases/10,000 persons.
PREDOMINANT SEX: Male/female ratio of 3:1.
PREDOMINANT AGE: Typically between 10 and 20 years of age.

CLINICAL PRESENTATION & PHYSICAL FINDINGS

- OCD most commonly affects the knee (75%) followed by the elbow (6%) and the ankle (4%); the other joints are affected in 15% of cases.
- Early lesions cause nonspecific pain with activity.
- As the disease progresses, stiffness and intermittent swelling occurs.
- Range of motion is usually intact in the knees.
- If a loose fragment becomes detached, it can cause locking or catching.
- Physical exam reveals tenderness at the site of the lesion; crepitus may also be present.
- When the knee is involved, a positive Wilson sign can sometimes be found (pain with knee extension and internal rotation); antalgic gait and limp can occur in chronic cases.
- Rare asymptomatic cases have been reported.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Knee: torn meniscus, patellofemoral syndrome, medial plica syndrome, stress fracture.
- Elbow: Panner's disease, Little League elbow, epicondyle fracture, epicondylitis.
- Talus: ankle sprain, os trigonum tarsal coalition.

IMAGING STUDIES

- X-rays including "tunnel views" are the initial test of choice.
- Early, small lesions can look normal or show only increased subchondral bone density.
- The defining lesion of OCD is seen on x-ray as a subchondral bone fragment surrounded by a radiolucent, crescent-shaped line (Fig. 01-20).
- MRI (Fig. 01-21) is the most sensitive test (91%) and is useful to identify OCD in symptomatic patients with normal x-rays.
- Contrast is used to evaluate blood supply to the affected fragment, evaluating stability.

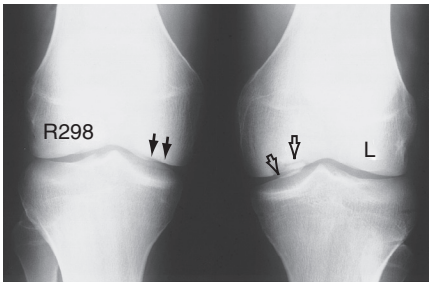


FIGURE 01-20 Bilateral, asymmetrical osteochondritis dissecans with a healed right lesion *(black arrows)* and an unhealed, unstable left lesion *(open arrows)* in a 17-year-old tennis player. (From DeLee D, Drez D [eds]: DeLee and Drez's orthopaedic sports medicine, ed 2, Philadelphia, 2003, Saunders.)

FIGURE 01-21 Osteochondritis dissecans (OCD). A coronal MRI of an OCD lesion of the medial femoral condyle. (From Frontera WR: *Clinical sports medicine: medical management and rehabilitation,* Philadelphia, 2006, Saunders.)

TREATMENT

ACUTE GENERAL Rx

- Conservative management: usually indicated in juvenile OCD without an intraarticular foreign body and for adult patients who have a small, stable fragment.
- Non–weight bearing and immobilization for 4 to 6 wk; physical therapy once healing starts.
- Surgery: indicated for juvenile OCD with a loose body and in cases that fail to improve after 4 to 6 mo of conservative management; also indicated in adults with OCD.

DISPOSITION & PROGNOSIS

- Office follow-ups are initially frequent, every 2 wk.
- X-ray changes should be monitored every 6 wk while immobilized.
- Once bone healing has been seen on x-rays, follow-ups can be spaced every 3 mo.
- Return to activity can be attempted once the patient is pain free and has an intact active full range of motion; it usually takes from 3 to 6 mo.
- Once complete healing occurs, joint function usually returns to normal.
- Complete healing is frequent in skeletally immature children with small lesions (95%), but in adults with larger lesions complete healing is less common (50%).

REFERRAL

- Orthopedic consultation is helpful in most symptomatic children and adults with OCD for staging and management options.
- Surgical options include arthroscopic drilling, fixation with Kirschner wires, special screws, and chondrocyte transplantation.

PEARLS & CONSIDERATIONS

COMMENTS

- Although inflammation is suggested by the name, it has not been shown to be of significance in this disorder. *Osteochondral lesion* or *osteochondrosis dissecans* may be more appropriate terms to describe these disorders.
- Repetitive trauma with ischemic necrosis is the most likely cause.
- The condition is often bilateral, especially in the knee, which could suggest the possibility of an endocrine or genetic basis.
- This condition should always be considered in the patient whose "sprained ankle" does not improve over the usual course of treatment.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Osteochondritis Dissecans (Patient Information)

AUTHOR: **DAN A. CRISTESCU, M.D.**

SUGGESTED READINGS

Bauer M et al.: Osteochondritis dissecans of the ankle: a 20-year follow-up study, *Bone Joint Surg Br* 69(1):93–96, 1987.

Crawford DC, Safran MR: Osteochondritis dissecans of the knee, *J Am Acad Orthop Surg* 14:90, 2006.

Edmonds EW, Polousky J: A review of knowledge in osteochondritis dissecans: 123 years of minimal evolution from König to the ROCK Study Group, *Clin Orthop Rel Res* 471:1118–1126, 2012.

Frank JB et al.: Lower extremity injuries in the skeletally immature athlete, *J Am Acad Orthop Surg* 15:356, 2007.

Maffulli N et al.: Long-term health outcomes of youth sports injuries, *Br J Sports Med* 44:21, 2010.

Peh WC: Osteochondritis dissecans, *Am J Orthop* 33(1):46, 2004.

Polousky JD: Juvenile osteochondritis dissecans, *Sports Med Arthrosc* 19(1): 56–63, 2011.

BASIC INFORMATION

DEFINITION

Osteomyelitis is an acute or chronic infection of the bone secondary to the hematogenous or contiguous source of infection or direct traumatic inoculation, which is usually bacterial.

SYNONYMS

Bone infection

ICD-9CM CODES
730.1 Chronic osteomyelitis
730.2 Acute or subacute osteomyelitis

ICD-10CM CODES
M86 Osteomyelitis
M86.0 Acute hematogenous osteomyelitis
M86.1 Other acute osteomyelitis
M86.2 Subacute osteomyelitis
M86.3 Chronic multifocal osteomyelitis
M86.6 Other chronic osteomyelitis
M86.9 Osteomyelitis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT SEX: Male > female
PREDOMINANT AGE: All ages

PHYSICAL FINDINGS & CLINICAL PRESENTATION

HEMATOGENOUS OSTEOMYELITIS
- Usually occurs in tibia/fibula (children)
- Localized inflammation: often secondary to trauma with accompanying hematoma or cellulitis
- Abrupt fever
- Lethargy
- Irritability
- Pain in involved bone

VERTEBRAL OSTEOMYELITIS
- Usually hematogenous
- Fever: 50%
- Localized pain/tenderness. Back pain is the most common initial symptom (86% of cases)
- Neurologic defects: motor/sensory (sensory loss, weakness, radiculopathy)

CONTIGUOUS OSTEOMYELITIS
- Direct inoculation
- Associated with trauma, fractures, surgical fixation
- Chronic infection of skin/soft tissue
- Fever, drainage from surgical site

CHRONIC OSTEOMYELITIS
- Bone pain
- Sinus tract drainage, nonhealing ulcer
- Chronic low-grade fever
- Chronic localized pain

ETIOLOGY

- *Staphylococcus aureus*
- MRSA: Methicillin-resistant *S. aureus*
- *Pseudomonas aeruginosa*
- Enterobacteriaceae
- *Streptococcus pyogenes*
- *Enterococcus*
- Mycobacteria
- Fungi
- Coagulase-negative staphylococci
- *Salmonella* (in sickle cell disease)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Gaucher's disease
- Bone infarction
- Charcot's joint
- Fracture

WORKUP

- ESR, C-reactive protein
- Blood culturing
- Bone culture. A culture of a biopsy specimen has a significantly higher overall diagnostic yield than does a blood culture. Bone samples should be cultured for aerobic and anaerobic bacteria and for fungi
- Pathologic evaluation of bone biopsy for acute/chronic changes consistent with necrosis or acute inflammation
- PCR analysis of specimens obtained by means of biopsy or puncture may be useful for organisms that are difficult to identify (anaerobic bacteria, *Bartonella* sp., *Kingella kingae*); however, broad-range PCR has suboptimal sensitivity and specificity due to contamination and may not provide sufficient information on the susceptibility of the microorganisms to antibiotics

IMAGING STUDIES

- Bone radiograph examination: initial study but not sensitive in early osteomyelitis as may not show changes for as much as 2 wk
- MRI (Fig. 01-22): most accurate imaging study. CT only if patient has contraindication to MRI
- Triple-phase technetium-99m bone scan (Fig. 01-23). Typically positive within a few days after onset of symptoms but accuracy is lower than that of MRI
- Gallium scan (Ga-67) scintigraphy with single-photon emission CT (SPECT) has higher accuracy than bone scan but is less sensitive for detection of epidural abscess in vertebral osteomyelitis
- Indium-111–labeled leukocyte scintigraphy scan; low sensitivity (<20%) for vertebral osteomyelitis
- Positron-emission tomography (PET) scanning with ^{18}F-fluorodeoxyglucose has high accuracy (similar to MRI) and is useful in patients with metallic implants

TREATMENT

- Surgical debridement in biopsy-positive cases will guide direction for antibiotic therapy. This will vary with type of osteomyelitis. Duration of therapy is usually 6 wk for acute osteomyelitis; chronic osteomyelitis may need a longer course of medication
- *S. aureus:* cefazolin IV, nafcillin IV, vancomycin IV (in patient allergic to penicillin)
- *S. aureus* (methicillin resistant): vancomycin IV, linezolid, daptomycin, or
- *Streptococcus* spp.: ceftriaxone, IV penicillin G in sensitive species
- *P. aeruginosa:* cefepime plus ciprofloxacin, piperacillin/tazobactam plus ciprofloxacin, or imipenem/cilastatin plus aminoglycoside
- Enterobacteriaceae quinolone-susceptible: fluoroquinolone or ceftriaxone
- Enterobacteriaceae quinolone-resistant: carbapenem (such as imipenem, meropenem, or doripenem)

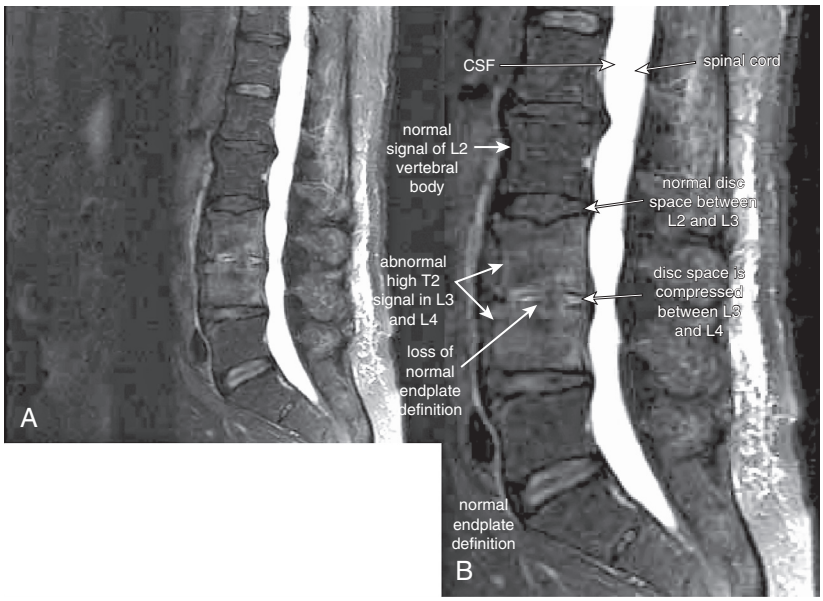


FIGURE 01-22 Osteomyelitis and discitis of L3 and L4. A, T2-weighted fast spin–echo magnetic resonance imaging without contrast demonstrates typical findings of vertebral osteomyelitis and discitis. **B,** Close-up. The inferior endplate of L3 and the superior endplate of L4 are abnormal and ill-defined. The L3 and L4 vertebral bodies show a high T2 signal, indicating an abnormally high fluid content. In comparison, L2 shows a normal marrow signal and appears dark gray due to a normal fat signal. *CSF,* Cerebrospinal fluid. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

- Anaerobes: clindamycin, ticarcillin clavulanate, cefotetan, or metronidazole
- Table 01-9 summarizes antimicrobial therapy for selected microorganisms in osteomyelitis
- Hyperbaric oxygen therapy: may be useful in chronic osteomyelitis
- Wound-assisted vacuum device may help closure of wound
- Surgical debridement of all devitalized bone and tissue
- Immobilization of affected bone (plaster, traction) if bone is unstable

DISPOSITION

Acute hematogenous osteomyelitis usually resolves without recurrence or long-term complications, but contiguous focus osteomyelitis, bone infections from open fractures, or osteomyelitis frequently recurs.

REFERRAL

- To an orthopedic surgeon if chronic osteomyelitis with need for bone debridement, bone grafting, or stabilization of infected tissue adjacent to a bone fracture
- To an infectious disease specialist for appropriate treatment for difficult-to-treat or recalcitrant infections
- To a hyperbaric oxygen chamber service for nonhealing, chronic osteomyelitis

PEARLS & CONSIDERATIONS

- Chronic osteomyelitis is one of the most challenging infections to treat; the high failure rate is a consequence of poor vascular supply, nondistensible bone tissue, and limited penetration of bone tissue.
- The optimal duration of therapy for vertebral osteomyelitis is unclear. Trials comparing 6 weeks to 12 weeks of antibiotic treatment in pyogenic vertebral osteomyelitis showed similar cure rates (91%) in both groups.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Osteomyelitis (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

FIGURE 01-23 Osteomyelitis. Intense accumulation of Tc-99m WBCs in proximal phalanx of fifth digit of left foot at 4 hr after injection. (From Specht N [ed]: *Practical guide to diagnostic imaging,* St Louis, 1998, Mosby.)

TABLE 01-9 Antimicrobial Therapy for Selected Microorganisms in Osteomyelitis or Septic Arthritis in Adults

Microorganism	First Choice*	Alternative Choice
Methicillin/oxacillin/nafcillin-sensitive staphylococci	Nafcillin sodium or oxacillin sodium 1.5-2 g IV q4-6h for 4-6 wk *or* cefazolin 1-2 g IV q8h	Vancomycin 15 mg/kg IV q12h for 4-6 wk
Methicillin/oxacillin/nafcillin-resistant staphylococci (MRSA)	Vancomycin† 15 mg/kg IV q12h *or* daptomycin 6 mg/kg IV q24h	Linezolid 600 mg PO/IV q12h *or* levofloxacin† 500-750 mg PO/IV daily
Penicillin-sensitive streptococci	Aqueous penicillin G 20 × 10^6 U/24 hr IV either continuously or in six equally divided daily doses *or* ceftriaxone 1-2 g IV q24h *or* cefazolin 1-2 g IV q8h	Vancomycin 15 mg/kg IV q12h
Enterococci	Aqueous crystalline penicillin G 20 × 10^6 U/24 hr IV either continuously or in six equally divided daily doses *or* ampicillin sodium 12 g/24 hr IV either continuously or in six equally divided daily doses; the addition of gentamicin sulfate 1 mg/kg IV or IM q8h for 1-2 wk is *optional*	Vancomycin† 15 mg/kg IV q12h; the addition of gentamicin sulfate 1 mg/kg IV or IM q8h for 1-2 wk is *optional*
Enterobacteriaceae, quinolone resistant	Ticarcillin clavulanate, 3.1 g IV q4h or piperacillin/tazobactam, 3.375 g IV q6h	Ceftriaxone 1-2 g IV q24h
Pseudomonas aeruginosa	Cefepime 2 g IV q12h plus ciprofloxacin 400 mg IV q8-12h	Imipenem/cilastatin 1 g IV q8h, plus aminoglycoside

MRSA, Methicillin-resistant *Staphylococcus aureus.*
*Antimicrobial selection should be based on in vitro sensitivity data, as well as allergies, intolerances, and drug interactions in individual patients.
†Doses shown are based on normal renal and hepatic function and may need to be adjusted or serum levels monitored (vancomycin).
Adapted from Berbari EF et al: Osteomyelitis. In Mandell GL et al (eds): *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 7, Philadelphia, 2010, Churchill Livingstone.

SUGGESTED READINGS

Bernard L et al.: Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomized, controlled trial, *Lancet* 385(11):875–882, 2015.

Conrad DA: Acute hematogenous osteomyelitis, *Pediatr Rev* 31(11):464–471, 2010.

Conterno LO, Turchi MD: Antibiotics for treating chronic osteomyelitis in adults, *Cochrane Database Syst Rev Sep* 3(9) CD004439, 2013.

Game FL: Osteomyelitis in the diabetic foot: diagnosis and management, *Med Clin North Am* 97(5):947–956, 2013.

Hatzenbuehler J, Pulling TJ: Diagnosis and management of osteomyelitis, *Am Fam Physician* 84(9):1027–1033, 2011.

Howell WR, Goulston C: Osteomyelitis: an update for hospitalists, *Hosp Pract* 39(1):153–160, 2011.

Lora-Tamayo J, Murillo O: Shorter treatments for vertebral osteomyelitis, *Lancet* 385:836–837, 2015.

Peltola H, Paakkonen M: Acute osteomyelitis in children, *N Eng J Med* 370(4): 352–360, 2014.

Zimmerli W: Vertebral osteomyelitis, *N Engl J Med* 362:1022–1029, 2010.

BASIC INFORMATION

DEFINITION

Osteoporosis is characterized by a progressive decrease in bone mass that results in increased bone fragility and a higher fracture risk. The various types are as follows:

PRIMARY OSTEOPOROSIS: Affects 80% of women and 60% of men with osteoporosis.

- Idiopathic osteoporosis: unknown pathogenesis; may occur in children and young adults
- Type I osteoporosis: may occur in postmenopausal women (ages 51 to 75); characterized by accelerated and disproportionate trabecular bone loss and associated with vertebral body and distal forearm fractures (estrogen withdrawal effect)
- Type II osteoporosis (involutional): occurs in both men and women aged >70 yr; characterized by both trabecular and cortical bone loss and associated with fractures of the proximal humerus and tibia, femoral neck, and pelvis

SECONDARY OSTEOPOROSIS: Affects 20% of women and 40% of men with osteoporosis; osteoporosis that exists as a common feature of another disease process, heritable disorder of connective tissue, or drug side effect (see "Differential Diagnosis")

ICD-9CM CODES
733.0 Osteoporosis

ICD-10CM CODES
M81.0 Age-related osteoporosis without current pathological fracture
M81.4 Drug-induced osteoporosis
M81.5 Idiopathic osteoporosis
M81.6 Localized osteoporosis

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE (IN U.S.)

- <25 million men and women
- Twice as common in women
- Results in 1.5 million fractures annually (70% women)
- Osteoporosis-related fractures in 50% of women and 20% of men aged >65 yr
- Results: institutionalization, death, and costs in excess of $10 billion annually

RISK FACTORS

- Age: each decade after 40 yr associated with a fivefold increased risk
- Genetics:
  1. Ethnicity (white/Asian are affected more often than blacks, with Polynesians affected the least)
  2. Gender (females affected more often than males)
  3. Family history (hip fracture in first-degree relative)
- Environmental factors: poor nutrition, calcium deficiency, physical inactivity, medication (chronic corticosteroid use [>3 mo], PPIs, aromatase inhibitors, anticonvulsants, anticoagulants, SSRIs), tobacco use, alcohol use (>3 drinks/day), traumatic injury, high caffeine intake
- Chronic disease states: estrogen deficiency, androgen deficiency, hyperthyroidism, inflammatory bowel disease, diabetes mellitus, hypercortisolism, cirrhosis, malabsorption, gastrectomy, multiple myeloma

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most commonly silent with no signs and symptoms
- Insidious and progressive development of dorsal kyphosis ***(dowager's hump),*** loss of height, and skeletal pain typically associated with fracture; other physical findings related to other conditions with associated increased risk for osteoporosis (see "Risk Factors")

ETIOLOGY

- Primary osteoporosis: multifactorial, resulting from a combination of factors including nutrition, peak bone mass, genetics, level of physical activity, age of menopause (spontaneous vs. surgical), and estrogen status
- Secondary osteoporosis: associated decrease in bone mass resulting from an identified cause, including endocrinopathies, hypogonadism, hyperthyroidism, hyperparathyroidism, Cushing's syndrome, hyperprolactinemia, acromegaly, diabetes mellitus, gastrointestinal disease, malabsorption, primary biliary cirrhosis, gastrectomy, malnutrition (including anorexia nervosa), and medications (corticosteroids, PPIs, rosiglitazone, pioglitazone)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Malignancy (multiple myeloma, lymphoma, leukemia, metastatic carcinoma)
- Primary hyperparathyroidism
- Osteomalacia
- Paget's disease
- Osteogenesis imperfecta: types I, III, and IV (see also "Epidemiology & Demographics" and "Etiology")

WORKUP

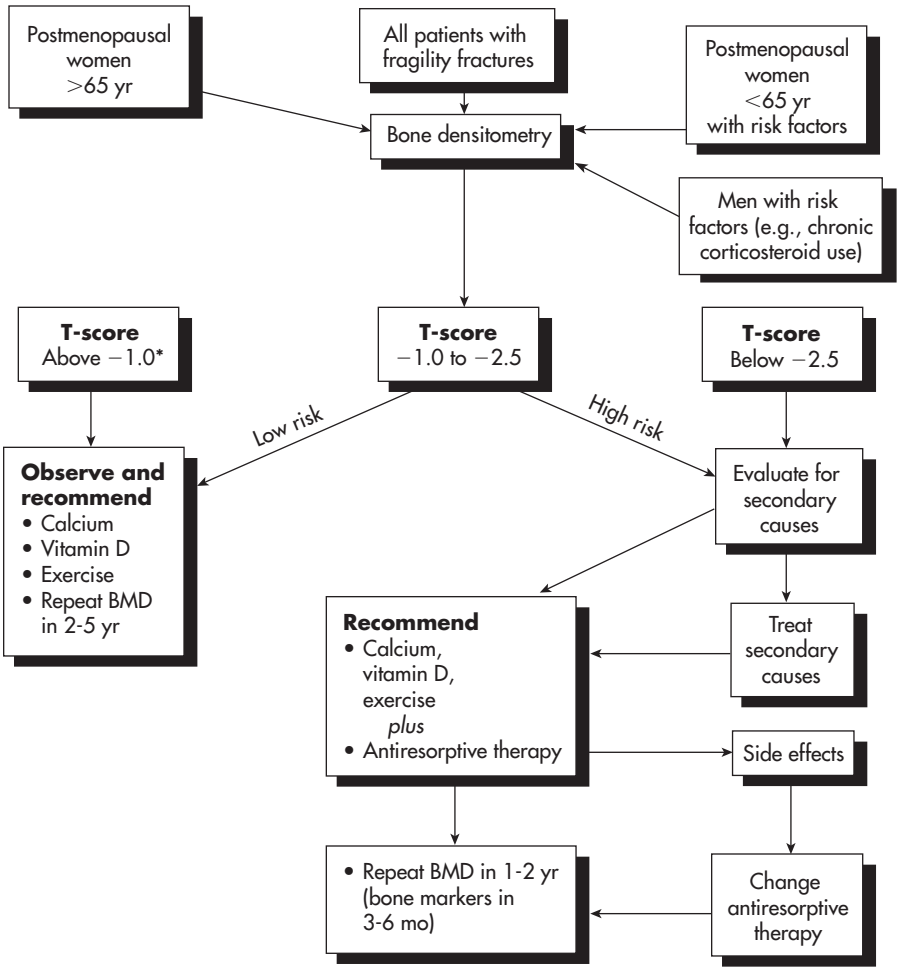
- History and physical examination (20% of women with type I osteoporosis have associated secondary cause), with appropriate evaluation for identified risk factors and secondary causes
- Diagnosis of osteoporosis made by bone mineral density (BMD) determination (BMD should ideally evaluate the hip, spine, and wrist)
  1. Dual-energy x-ray absorptiometry (DEXA) is the gold standard for screening and monitoring changes in BMD due to excellent precision, widespread availability, low cost, and minimal radiation exposure. DEXA is indicated in all women 65 years and older and in postmenopausal women younger than 65 years of age who are at risk for fracture (e.g., weight <127 lbs, parental history of hip fracture, use of medications that cause bone loss, smoking, alcoholism, rheumatoid arthritis, or presence of diseases that cause bone loss).
- Recommendations as to when to repeat bone density testing should be based on initial T scores (Fig. 01-24). Data from the Study of Osteoporotic Fractures indicates that in women with normal bone density or mild osteopenia, repeat testing might not be necessary for another 10-15 yr. For women with moderate osteopenia, a screening interval of 3-5 yr may be appropriate. Annual testing may be indicated for women with advanced osteopenia.

LABORATORY TESTS

- Biochemical profile to evaluate renal and hepatic function, primary hyperparathyroidism, and malnutrition
- CBC: for nutritional status and myeloma
- TSH to rule out the presence of hyperthyroidism
- Vitamin D level. Consideration of 24-hr urine collection for calcium (excess skeletal loss, vitamin D malabsorption/deficiency), creatinine, sodium, and free cortisol (to detect occult Cushing's disease); no need to measure calcitropic hormones (parathyroid hormone, calcitriol, calcitonin) unless specifically indicated
- Biochemical markers of bone remodeling; may be useful to predict rate of bone loss and/or follow therapy response; specific biochemical markers followed (e.g., 3-mo interval) to document normalization as a response to therapy
  1. High-turnover osteoporosis: high levels of resorption markers (lysyl pyridinoline, deoxy lysyl pyridinoline, n-telopeptide of collagen cross-links, C-telopeptide of collagen cross-links) and formation markers (osteocalcin, bone-specific alkaline phosphatase, carboxy-terminal extension peptide of type I procollagen); accelerated bone loss responding best to antiresorptive therapy
  2. Low-normal-turnover osteoporosis: normal or low levels of the markers of resorption and formation (see "high turnover osteoporosis" listed previously); no accelerated bone loss; responds best to drugs that enhance bone formation

IMAGING STUDIES

- BMD determination (see "Workup") should be performed on all women with determined risk factors and/or associated secondary causes; criteria for diagnosis of osteoporosis based on measurement of bone density and T score equivalent cut points are summarized in Table 01-10.
  1. Normal: BMD <1 SD of the young adult reference mean
  2. Osteopenia: BMD 1 to 2.5 SD below the young adult reference mean
  3. Osteoporosis: BMD >2.5 SD below the young adult reference mean
- For patient undergoing treatment: annual BMD to follow response to therapy
- X-ray exam of appropriate part of skeleton to evaluate clinical osteoporotic fracture only



*Patients with fragility fractures and a T-score above −1.0 should be evaluated for other causes of pathologic fracture.

FIGURE 01-24 Diagnosis and management of osteoporosis. The diagram outlines an approach based largely on evidence from studies of postmenopausal white women, with dual-energy x-ray absorptiometry used to measure bone mineral density *(BMD).* Its application to other populations, including patients with secondary osteoporosis and other methods of assessing BMD, is not established. (Modified from Larsen PR et al: *Williams textbook of endocrinology,* ed 11, Philadelphia, 2008, Saunders.)

TABLE 01-10 1994 WHO Criteria for the Diagnosis of Osteoporosis Based on the Measurement of Bone Density and T Score Equivalent Cut Points

Diagnostic Category	Standard Deviations Below the Young-Adult Mean	T Score
Normal	≤1 SD	Equal to or better than −1
Osteopenia (low bone mass)	Between 1 and 2.5 SD	Between −1 and −2.5
Osteoporosis	≥2.5 SD	Equal to or poorer than −2.5
Severe (established) osteoporosis	≥2.5 SD + a fragility fracture	Equal to or poorer than −2.5 + a fragility fracture

From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Prevention:
- Identification and minimization of risk factors
- Appropriate diagnosis and treatment of secondary causes
- Behavioral modification: proper nutrition, physical activity, fracture prevention strategies

ACUTE GENERAL Rx

- Vitamin D supplement: 600 IU/day for persons 19 to 70 years of age and 800 IU/day for persons 71 years and older
- Calcium supplement: The recommended dietary intake of calcium for women 19 to 50 years of age and men 19 to 70 years of age is 1000 mg/day; women older than age 50 and men older than age 70 require 1200 mg/day. Calcium intake above 25000 mg/day (2000 mg/day in persons >50 years of age) should be avoided. Consumption of calcium-rich foods and beverages is the preferred approach to ensuring adequate calcium intake.[1]
- Oral bisphosphonates (ibandronate, alendronate, risedronate): they decrease bone resorption by attenuating osteoclast activity. They are first-line therapy for the treatment of most patients with osteoporosis, with proven efficacy to reduce fracture risk. Ibandronate is given 150 mg once monthly, swallowed whole with 8 oz water on empty stomach, with no oral intake for at least 60 min. Do not lie down for 60 min after dose. Alendronate is given 70 mg once weekly on awakening, with 8 oz water on empty stomach, with no oral intake for at least 30 min. Use 70-mg dose for treatment of postmenopausal osteoporosis and a 35-mg tablet for the prevention of osteoporosis in postmenopausal women. Risedronate is given 35 mg once weekly or 75 mg taken on 2 consecutive days per month on awakening, with 8 oz water on empty stomach, with no oral intake for at least 30 min.
- Raloxifene: 60 mg qd. Selective estrogen-receptor moderator, it has suppressive effects on osteoclast and bone resorption.
- Zoledronic acid: a bisphosphonate given by IV infusion over at least 15 min, 5 mg once/year
- Teriparatide is a recombinant human parathyroid hormone used for postmenopausal women with osteoporosis who are at high risk for fracture. It is also used in men with primary or hypogonadal osteoporosis who are at high risk of fracture. It is administered by injection 20 mcg qd SQ into the thigh or abdominal wall. Use for >2 yr not recommended. It stimulates bone formation and reduces the risk of fracture but may increase the risk of stroke in older women with osteoporosis.
- Denosumab is a human monoclonal antibody that decreases bone resorption by inhibiting the formation and activity of osteoclasts. It was recently approved for treatment of postmenopausal osteoporosis. Dosage is 60 mg subcutaneously every 6 months. Cost of 1 yr of therapy is approximately $2000. Trials[2] have also shown that the monoclonal antibody romosozumab can also increase bone mineral density and bone formation and decrease bone resorption.
- Other FDA-approved drugs (without osteoporosis indication) used to treat osteoporosis:
  1. Calcitriol
  2. Etidronate
  3. Thiazide
- Estrogen (conjugated equine estrogen or equivalent): 0.3 to 0.625 mg/day

[1]Bauer DC: Calcium supplements and fracture prevention, *N Engl J Med* 369:1537-1543, 2013.
[2]McClung MR et al: Romosozumab in postmenopausal women with low bone mineral density, *N Engl J Med* 370:412-420, 2014.

- Progestin: continuous (e.g., 2.5 mg medroxyprogesterone acetate/day or equivalent) or cyclic (e.g., 10 mg medroxyprogesterone acetate days for 10 days each mo or equivalent) coadministered in women with a uterus in place.
- Combination estrogen/alendronate or estrogen-progestin/alendronate may be considered in individualized patients on hormone replacement therapy with identified osteoporosis. BMD baseline obtained before onset of therapy and at 1 yr; decrease of 2% or greater results in dosage adjustment or medication change.
- A recent trial on the effects of lasofoxifene on the risk of fractures showed that in postmenopausal women with osteoporosis, lasofoxifene (0.5 mg/day) decreased risk of vertebral and nonvertebral fractures. It also lowered the risk of ER-positive breast cancer, coronary heart disease, and stroke but it increased the risk of venous thromboembolic events.
- Baseline biochemical markers of remodeling baseline considered; identified high-turnover osteoporosis patients rescreened at 3 mo to document marker return to normal

CHRONIC Rx

- Lifelong disorder requiring lifelong attention to behavior modification issues (nutrition, physical activity, fracture prevention strategies) and compliance with pharmacologic intervention. There is little evidence to guide physicians about long-term bisphosphonate therapy. Evidence is accumulating that the risk of atypical fracture of the femur increases after 5 years of bisphosphonate use. It is reasonable to stop bisphosphonates at 3 to 5 yr in women at the lowest risk (T score better than –2.5 and no fractures) and then monitor patients with markers of bone turnover. Continued treatment may be advisable in those at highest risk.
- Continuing need to eliminate high-risk factors when possible and to diagnose and optimally manage secondary causes of osteoporosis

DISPOSITION

Goal for diagnosis and treatment: identification of women at risk; initiation of preventive measures for all women lifelong; institution of treatment modalities that will result in a decrease in fracture risk; and reduction of morbidity, mortality, and unnecessary institutionalization, thereby improving quality of independent life and productivity.

REFERRAL

- To reproductive endocrinologist, medical endocrinologist, gynecologist, or rheumatologist if unfamiliar with diagnosis and management of osteoporosis
- If multidisciplinary management is required, to other specialties depending on presence of acute fracture and/or secondary associated disorders

PEARLS & CONSIDERATIONS

COMMENTS

- Osteonecrosis of the jaw is a known complication of high-dose IV bisphosphonate therapy for cancer; however, there is considerable debate on whether low-dose bisphosphonates used for osteoporosis can also cause this disorder. Evidence for this is inconclusive.
- Long-term use (>10 yr) of bisphosphonates has been reported to increase risk of atypical subtrochanteric or femoral shaft fractures in several uncontrolled case series. A prodrome of thigh pain, lack of trauma prior to the procedure, and specific radiologic characteristics have been reported. The evidence remains inconclusive. Patients can be reassured that short or intermediate use of bisphosphonates does not increase the risk of atypical femoral fractures. Current strategies should include considering a 12-mo interruption in therapy after 5 yr in patients who are clinically stable and considering teriparatide treatment in individuals who experience an atypical fracture while receiving bisphosphonate therapy.
- Increased risk of esophageal cancer and atrial fibrillation have been reported as possible adverse effects of bisphosphonate therapy.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Osteoporosis (Patient Information)
Biphosphonate-Related Osteonecrosis of Jaw (Related Key Topic)

AUTHORS: **DENNIS M. WEPPNER, M.D.**, and **RUBEN ALVERO, M.D.**

EVIDENCE

Abstract[1]

Objectives:
To assess the effectiveness and safety of zoledronate (ZOL) in preventing glucocorticoid therapy-associated bone loss in patients with acute flare of Crohn's disease (CD) in a randomized, double-blind, placebo-controlled trial.

Methods:
Forty CD patients starting a glucocorticoid therapy (60 mg prednisolone per day) for acute flare (CD activity index (CDAI) >220) were randomized to compare the effect of ZOL (4 mg intravenous, n=20) or placebo (n=20) on change in lumbar bone mineral density (BMD). All patients received calcium citrate (800 mg) and cholecalciferol (1000 IU) daily. Dual energy X-ray absorptiometry (DXA) of the lumbar spine (L1–L4) was performed at baseline and day 90. Follow-up examinations at day 1/7/14/30 and 90 included laboratory tests and adverse event/serious adverse events reports.

Results:
Thirty-six patients were available for per-protocol analysis. With placebo (n=18), a decrease in BMD was seen (T-score: –0.98±0.8, day 0 and –1.25±0.77, day 90, P=0.06), with ZOL (n=18) BMD increased (–1.15±1.02, day 0 and –0.74±1.09, day 90, P=0.03). The change in BMD under placebo (–0.26±0.21) vs. ZOL (+0.41±0.19) was highly significant (P=0.006). In all, 14 out of 18 patients with ZOL had an increase in BMD (+0.64±0.48), 12 of 18 with placebo a decrease (–0.50±0.39). Changes of clinical findings and laboratory results of inflammation (leukocytes, platelets, and C-reactive protein) were the same in and between groups throughout the study. With ZOL, serum bone degradation marker β-Cross-Laps decreased. Study medication was safe and well tolerated.

Conclusions:
ZOL is effective in preventing glucocorticoid therapy-induced bone loss in patients with acute flare of CD and should be considered whenever a glucocorticoid therapy is started in CD patients. Ⓐ

Abstract[2]

The selective cathepsin K inhibitor odanacatib (ODN) progressively increased bone mineral density (BMD) and decreased bone-resorption markers during 2 years of treatment in postmenopausal women with low BMD. A 1-year extension study further assessed ODN efficacy and safety and the effects of discontinuing therapy. In the base study, postmenopausal women with BMD T-scores between –2.0 and –3.5 at the lumbar spine or femur received placebo or ODN 3, 10, 25, or 50 mg weekly. After 2 years, patients (n=189) were rerandomized to ODN 50 mg weekly or placebo for an additional year. Endpoints included BMD at the lumbar spine (primary), total hip, and hip subregions; levels of bone turnover markers; and safety assessments. Continued treatment with 50 mg of ODN for 3 years produced significant increases from baseline and from year 2 in BMD at the spine (7.9% and 2.3%) and total hip (5.8% and 2.4%). Urine cross-linked *N*-telopeptide of type I collagen (NTx) remained suppressed at year 3 (–50.5%), but bone-specific alkaline phosphatase (BSAP) was relatively unchanged from baseline. Treatment discontinuation resulted in bone loss at all sites, but BMD remained at or above baseline. After ODN discontinuation at month 24, bone turnover markers increased transiently above baseline, but this increase largely resolved by month 36. There were similar overall adverse-event rates in both treatment groups. It is concluded that 3 years of ODN treatment resulted in progressive increases in BMD and was generally well tolerated. Bone-resorption markers remained suppressed, whereas bone-formation markers returned to near baseline. ODN effects were reversible: bone resorption increased transiently and BMD decreased following treatment discontinuation. Ⓐ

Abstract[3]

Background:
Parathyroid hormone (PTH) has been shown to increase bone mineral density and to reduce the rate of fractures in patients with osteoporosis and also to improve fracture-healing. The purpose of the present prospective, randomized, controlled study was to evaluate the effect of PTH 1-84 on the course of pelvic fracture-healing and functional outcome in postmenopausal women.

Methods:
Sixty-five patients had a dual x-ray absorptiometry scan, radiographs, and a computed tomography scan to document pelvic fractures. Twenty-one patients received a once-daily injection of 100 μg of PTH 1-84 starting within two days after admission to the hospital, and forty-four patients served as the control group. All patients received 1000 mg of calcium and 800 IU of vitamin D. Computed tomography scans were repeated every fourth week until radiographic evidence of cortical bridging at the fracture site was confirmed. Functional outcome was assessed with use of a visual analog scale for pain and a Timed "Up and Go" test.

Results:
The mean time to fracture healing was 7.8 weeks for the treatment group, compared with 12.6 weeks for the control group ($p<0.001$). At eight weeks, all fractures in the treatment group were healed and four fractures in the control group were healed (healing rate, 100% compared with 9.1%; $p<0.001$). Both the visual analog scale score for pain and the result of the Timed "Up and Go" test improved in the study group as compared with the control group ($p<0.001$).

Conclusions:
In elderly patients with osteoporosis, PTH 1-84 accelerates fracture-healing in pelvic fractures and improves functional outcome. Ⓐ

Abstract[4]

Background:
The distal radius is the most frequent fracture localization in humans. Although younger patients receive a distal radius fracture after an adequate trauma, elderly patients suffer fractures through low-energy mechanisms. Low-energy fractures are hallmarks of osteoporosis. Osteoporotic changes of the distal radius are well described by DXA and peripheral quantitative computed tomography measurements. However, to date, the effects of aging on the microarchitecture of the distal radius have not been investigated.

Methods:
To investigate whether the microarchitecture of the human distal radius shows osteoporotic changes in bone mass and structure during aging, we dissected out 60 complete human distal radii from 30 age- and gender-matched patients at autopsy. Each of the three different age groups (group I: 20–40 years, group II: 41–60 years, group III: 61–80 years) was represented by 10 autopsy cases and 20 specimens (double-sided extraction), respectively. The specimens were analyzed by peripheral quantitative computed tomography, contact-radiography, and histomorphometry.

Results:
We observed a significant age-related decrease in bone mass, bone mineral density and an increase in typical osteoporotic changes of the bone microarchitecture in female distal radius specimens. Comparable observations of age-related changes have not been made in male specimens.

Conclusions:
The distal radius is a location of osteoporosis-specific bone changes. Our data provide evidence for the occurrence of typical osteoporotic changes, especially postmenopausal osteoporotic changes, in the distal radius during aging. Ⓐ

Abstract[5]

Low 25-hydroxyvitamin D (VitD), low sex hormones (SH), and high sex hormone binding globulin (SHBG) levels are common in older men. We tested the hypothesis that combinations of low VitD, low SH, and high SHBG would have a synergistic effect on bone mineral density (BMD), bone loss, and fracture risk in older men. Participants were a random subsample of 1468 men (mean age 74 years) from the Osteoporotic Fractures in Men Study (MrOS) plus 278 MrOS men with incident non-spine fractures studied in a case-cohort design. "Abnormal" was defined as lowest quartile for VitD (<20 ng/mL), bioavailable testosterone (BioT, <163 ng/dL), and bioavailable estradiol (BioE, <11 pg/mL); and highest quartile for SHBG (>59 nM). Overall, 10% had isolated VitD deficiency;

40% had only low SH or high SHBG; 15% had both SH/SHBG and VitD abnormality; and 35% had no abnormality. Compared to men with all normal levels, those with both SH/SHBG and VitD abnormality tended to be older, more obese, and to report less physical activity. Isolated VitD deficiency, and low BioT with or without low VitD, was not significantly related to skeletal measures. The combination of VitD deficiency with low BioE and/or high SHBG was associated with significantly lower baseline BMD and higher annualized rates of hip bone loss than SH abnormalities alone or no abnormality. Compared to men with all normal levels, the multivariate-adjusted hazard ratio (95% confidence interval [CI]) for incident nonspine fracture during 4.6-year median follow-up was 1.2 (0.8-1.8) for low VitD alone; 1.3 (0.9-1.9) for low BioE and/or high SHBG alone; and 1.6 (1.1-2.5) for low BioE/high SHBG plus low VitD. In summary, adverse skeletal effects of low sex steroid levels were more pronounced in older men with low VitD levels. The presence of low VitD in the presence of low BioE/high SHBG may contribute substantially to poor skeletal health. Ⓐ

Abstract[6]

The osteoporosis associated with human hyperthyroidism has traditionally been attributed to elevated thyroid hormone levels. There is evidence, however, that thyroid-stimulating hormone (TSH), which is low in most hyperthyroid states, directly affects the skeleton. Importantly, Tshr-knockout mice are osteopenic. In order to determine whether low TSH levels contribute to bone loss in hyperthyroidism, we compared the skeletal phenotypes of wild-type and Tshr-knockout mice that were rendered hyperthyroid. We found that hyperthyroid mice lacking TSHR had greater bone loss and resorption than hyperthyroid wild-type mice, thereby demonstrating that the absence of TSH signaling contributes to bone loss. Further, we identified a TSH-like factor that may confer osteoprotection. These studies suggest that therapeutic suppression of TSH to very low levels may contribute to bone loss in people. Ⓐ

Abstract[7]

Context:
PTH therapy improves bone mineral density (BMD) and decreases fractures in postmenopausal osteoporosis, but cost and the burden of daily injections limit its use.
Objective:
We evaluated two novel approaches to the use of 6 months of PTH therapy over 2 yr.
Design, Setting, Participants, and Interventions:
We conducted a randomized, double-blinded trial of two combinations of daily PTH (1-84) and monthly ibandronate in 44 postmenopausal women with low bone mass. Participants received either 6 months of concurrent PTH and ibandronate, followed by 18 months of ibandronate (concurrent) or two sequential courses of 3 months of PTH followed by 9 months of ibandronate (sequential) over 2 yr.
Main Outcome Measures:
Bone turnover markers were measured. Areal and volumetric BMD were assessed by dual-energy x-ray absorptiometry and quantitative computed tomography, respectively.
Results:
Over 2 yr, areal BMD at the spine and hip increased similarly in both groups, with 7.5 and 8.2% increases in spine BMD in the concurrent and sequential arms, respectively (difference –0.6%, 95% confidence interval = –3.4-2.1%). Volumetric BMD also increased similarly between groups. With concurrent therapy, mean N-propeptide of type I collagen increased 75% between baseline and month 1 and then declined. With sequential therapy, the second 3-month PTH course increased N-propeptide of type I collagen markedly (209%), although to a lesser absolute degree than the first.
Conclusions:
Six months of PTH (1-84), used over 2 yr with a bisphosphonate in either of our dosing regimens increased BMD substantially. Short PTH courses may provide the benefits of anabolic osteoporosis therapy with reduced burden for patients. Ⓐ

Abstract[8]

Background:
Fractures in men are a major health issue, and data on the antifracture efficacy of therapies for osteoporosis in men are limited. We studied the effect of zoledronic acid on fracture risk among men with osteoporosis.
Methods:
In this multicenter, double-blind, placebo-controlled trial, we randomly assigned 1199 men with primary or hypogonadism-associated osteoporosis who were 50 to 85 years of age to receive an intravenous infusion of zoledronic acid (5 mg) or placebo at baseline and at 12 months. Participants received daily calcium and vitamin D supplementation. The primary end point was the proportion of participants with one or more new morphometric vertebral fractures over a period of 24 months.
Results:
The rate of any new morphometric vertebral fracture was 1.6% in the zoledronic acid group and 4.9% in the placebo group over the 24-month period, representing a 67% risk reduction with zoledronic acid (relative risk, 0.33; 95% confidence interval, 0.16 to 0.70; $P = .002$). As compared with men who received placebo, men who received zoledronic acid had fewer moderate-to-severe vertebral fractures ($P = .03$) and less height loss ($P = .002$). Fewer participants who received zoledronic acid had clinical vertebral or nonvertebral fractures, although this difference did not reach significance because of the small number of fractures. Bone mineral density was higher and bone-turnover markers were lower in the men who received zoledronic acid ($P < 0.05$ for both comparisons). Results were similar in men with low serum levels of total testosterone. The zoledronic acid and placebo groups did not differ significantly with respect to the incidence of death (2.6% and 2.9%, respectively) or serious adverse events (25.3% and 25.2%).
Conclusions:
Zoledronic acid treatment was associated with a significantly reduced risk of vertebral fracture among men with osteoporosis. (Funded by Novartis Pharma; ClinicalTrials.gov number, NCT00439647.) Ⓐ

Abstract[9]

Context:
The acid load imposed by a modern diet may play an important role in the pathophysiology of osteoporosis.
Objective:
Our objective was to evaluate the skeletal efficacy and safety and the effect on fracture prediction of K-citrate to neutralize diet-induced acid loads.
Design and Setting:
We conducted a randomized, double-blind, placebo-controlled trial at a teaching hospital.
Subjects:
Subjects included 201 elderly (>65 yr old) healthy men and women (t-score of –0.6 at lumbar spine).
Intervention:
Intervention was 60 mEq of K-citrate daily or placebo by mouth. All subjects received calcium and vitamin D.
Outcome Measures:
The primary outcome was change in areal bone mineral density (aBMD) at the lumbar spine by dual-energy x-ray absorptiometry after 24 months. Secondary endpoints included changes in volumetric density and microarchitectural parameters by high-resolution peripheral quantitative computed tomography in both radii and both tibiae and fracture risk assessment by FRAX (Switzerland).
Results:
K-citrate increased aBMD at lumbar spine from baseline by 1.7 ± 1.5% [95% confidence interval (CI) = 1.0-2.3, $P < .001$] net of placebo after 24 months. High-resolution peripheral quantitative computed tomography-measured trabecular densities increased at nondominant tibia (1.3 ± 1.3%, CI = 0.7-1.9, $P < .001$) and nondominant radius (2.0 ± 2.0%, CI = 1.4-2.7, $P < .001$). At nondominant radius, trabecular bone volume/tissue volume increased by 0.9 ± 0.8%, (CI = 0.1-1.7), trabecular thickness by 1.5 ± 1.6% (CI = 0.7-2.3), and trabecular number by

1.9 ± 1.8% (CI = 0.7-3.1, for all, $P < 0.05$). K-citrate diminished fracture prediction score by FRAX significantly in both sexes.
Conclusions:
Among a group of healthy elderly persons without osteoporosis, treatment with K-citrate for 24 months resulted in a significant increase in aBMD and volumetric BMD at several sites tested, while also improving bone microarchitecture. Based on the effect on fracture prediction, an effect on future fractures by K-citrate is possible. Ⓐ

Abstract[10]
Background:
Bisphosphonates can adversely affect fracture-healing because they inhibit osteoclastic bone resorption. It is unclear whether bisphosphonates can be initiated safely for patients who have sustained an acute distal radial fracture. The purpose of this randomized study was to determine whether the early use of bisphosphonate affects healing and outcomes of osteoporotic distal radial fractures treated with volar locking plate fixation.
Methods:
Fifty women older than fifty years of age who had undergone volar locking plate fixation of a distal radial fracture and had been diagnosed with osteoporosis were randomized to Group I (n = 24, initiation of bisphosphonate treatment at two weeks after the operation) or Group II (n = 26, initiation of bisphosphonate treatment at three months). Patients were assessed for radiographic union and other radiographic parameters (radial inclination, radial length, and volar tilt) at two, six, ten, sixteen, and twenty-four weeks, and for clinical outcomes that included Disabilities of the Arm, Shoulder and Hand (DASH) scores, wrist motion, and grip strength at twenty-four weeks. The two groups were compared with regard to the time to radiographic union, the radiographic parameters, and the clinical outcomes.
Results:
No significant differences were observed between the two groups with respect to radiographic or clinical outcomes after volar locking plate fixation. All patients obtained fracture union, and the mean times to radiographic union in Groups I and II were similar (6.7 and 6.8 weeks, respectively; $P = 0.65$). Furthermore, the time to radiographic union was not related to osteoporosis severity or fracture type.
Conclusions:
In patients with an osteoporotic distal radial fracture treated with volar locking plate fixation, the early initiation of bisphosphonate treatment did not affect fracture-healing or clinical outcomes. Ⓐ
Level of Evidence:
Therapeutic Level I.

Evidence-Based References

Klaus J et al.: A single dose of intravenous zoledronate prevents glucocorticoid therapy-associated bone loss in acute flare of Crohn's disease, a randomized controlled trial, *Am J Gastroenterol* 106:786–793, 2011. Ⓐ

Eisman JA et al.: Odanacatib in the treatment of postmenopausal women with low bone mineral density: three-year continued therapy and resolution of effect, *J Bone Miner Res* 26:242–251, 2011. Ⓐ

Peichl P et al.: Parathyroid hormone 1-84 accelerates fracture-healing in pubic bones of elderly osteoporotic women, *J Bone Joint Surg Am* 93:1583–1587, 2011. Ⓐ

Beil FT et al.: The distal radius, the most frequent fracture localization in humans: a histomorphometric analysis of the microarchitecture of 60 human distal radii and its changes in aging, *J Trauma* 70:154–158, 2011. Ⓐ

Barrett-Connor E: The association of concurrent vitamin D and sex hormone deficiency with bone loss and fracture risk in older men: the Osteoporotic Fractures in Men (MrOS) Study, *J Bone Miner Res* 27:2306–2313, 2012. for the Osteoporotic Fractures in Men (MrOS) Research Group Ⓐ

Baliram R et al.: Hyperthyroid-associated osteoporosis is exacerbated by the loss of TSH Signaling, *J Clin Invest* 122:3737–3741, 2012. Ⓐ

Schafer AL et al.: Six months of parathyroid hormone (1-84) administered concurrently versus sequentially with monthly ibandronate over two years: the PTH and ibandronate combination study (PICS) randomized trial, *J Clin Endocrinol Metab* 97:3522–3529, 2012. Ⓐ

Boonen S et al.: Fracture risk and zoledronic acid therapy in men with osteoporosis, *N Engl J Med* 367:1714–1723, 2012. Ⓐ

Jehle S et al.: Effect of potassium citrate on bone density, microarchitecture, and fracture risk in healthy older adults without osteoporosis: a randomized controlled trial, *J Clin Endocrinol Metab* 98:207–217, 2013. Ⓐ

Gong HS et al.: Early initiation of bisphosphonate does not affect healing and outcomes of volar plate fixation of osteoporotic distal radial fractures, *J Bone Joint Surg Am* 94:1729–1736, 2012. Ⓐ

SUGGESTED READINGS

Ali T et al.: Osteoporosis in inflammatory bowel disease, *Am J Med* 122:599–604, 2009.

Black DM: Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur, *N Engl J Med* 362:1761–1771, 2010.

Black DM et al.: Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis, *N Engl J Med* 356:2007, 1809.

Boonen J et al.: Fracture risk and zoledronic acid therapy in men with osteoporosis, *N Engl J Med* 367:1714–1723, 2012.

Cadarette SM et al.: Relative effectiveness of osteoporosis drugs for preventing nonvertebral fracture, *Ann Intern Med* 148:637–646, 2008.

Cummings SR et al.: The effects of tibolone in older postmenopausal women, *N Engl J Med* 359:697, 2008.

Cummings SR et al.: Lasofoxifene in postmenopausal women with osteoporosis, *N Engl J Med* 362:686–696, 2010.

Favia G et al.: Osteonecrosis of the jaw correlated to bisphosphonate therapy in nononcologic patients: clinicopathological features of 24 patients, *J Rheumatol* 36:2789, 2009.

Favus MJ: Bisphosphonates for osteoporosis, *N Engl J Med* 363:2027–2035, 2010.

Lewiecki EM: In the clinic: osteoporosis, *Ann Intern Med* 155(1):2011, ITC 1–1.

Liu H et al.: Screening for osteoporosis in men: a systematic review for an American College of Physicians Guideline, *Ann Intern Med* 148:685, 2008.

McClung M et al.: Bisphosphonate therapy for osteoporosis: benefits, risks, and drug holiday, *Am J Med* 126:13–20, 2013.

Ott SM: What is the optimal duration of bisphosphonate therapy? *Clev Clin J Med* 78:619, 2011.

Saag KG et al.: Teriparatide or alendronate in glucocorticoid-induced osteoporosis, *N Engl J Med* 357:2028, 2007.

Schilcher J et al.: Bishosphonate use and atypical fractures of the femoral shaft, *N Engl J Med* 364:1728–1737, 2011.

Sellmeyer DE: Atypical fractures as a potential complication of long-term bisphosphonate therapy, *JAMA* 304(13):1480–1484, 2010.

Sweet MG et al.: Diagnosis and treatment of osteoporosis, *Am Fam Physician* 79(3):193–200, 2009.

Yu EW, Finkelstein JS: Bone density screening intervals for osteoporosis: one size does not fit all, *JAMA* 307:2591–2592, 2012.

BASIC INFORMATION

DEFINITION

Otitis externa refers to a variety of conditions causing inflammation and/or infection of the external auditory canal (and/or auricle and tympanic membrane). There are six subgroups of otitis externa:

1. Acute localized otitis externa (furunculosis)
2. Acute diffuse bacterial otitis externa (i.e., "swimmer's ear")
3. Chronic otitis externa
4. Eczematous otitis externa
5. Fungal otitis externa (otomycosis)
6. Invasive or necrotizing (malignant) otitis externa (Fig. 01-25)

SYNONYMS

See "Definition."

ICD-9CM CODES

38.10 Otitis externa

ICD-10CM CODES

H60.90 Unspecified otitis externa, unspecified ear
H60.2 Malignant otitis externa
H60.3 Other infective otitis externa
H60.5 Acute otitis externa, non-infective
H60.8 Other otitis externa

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):

- Among the most common disorders
- Affects 3% to 10% of patients seeking otologic care

PREVALENCE (IN U.S.)

- Diffuse otitis externa is most often seen in swimmers and in hot, humid climates, conditions that lead to water retention in the ear canal. In the United States, 44% of AOE-related healthcare visits occur June to August.
- Necrotizing otitis externa is more common in elderly, diabetics, and immunocompromised patients.

PREDOMINANT SEX: None

PREDOMINANT AGE

- Occurs at all ages
- Necrotizing otitis externa: typically occurs in elderly: mean age >65 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The two most common symptoms are otalgia, ranging from pruritus to severe pain exacerbated by motion (e.g., chewing), and otorrhea. Patients may also experience aural fullness and hearing loss as a result of swelling with occlusion of the canal. More intense symptoms may occur with bacterial otitis externa, with or without fever, and lymphadenopathy (anterior to tragus). Findings unique to specific forms of the infection include:

- Acute localized otitis externa (furunculosis):
  1. Occurs from infected hair follicles, usually in the outer third of the ear canal, forming pustules and furuncles
  2. Furuncles are superficial and pointing or deep and diffuse
- Impetigo:
  1. In contrast to furunculosis, this is a superficial spreading infection of the ear canal that may also involve the concha and the auricle
  2. Begins as a small blister that ruptures, releasing straw-colored fluid that dries as a golden crust
- Erysipelas:
  1. Caused by group A *Streptococcus*
  2. May involve the concha and canal
  3. May involve the dermis and deeper tissues
  4. Area of cellulitis, often with severe pain
  5. Fever, chills, malaise
  6. Regional adenopathy
- Eczematous or seborrheic otitis externa:
  1. Stems from a variety of dermatologic problems that can involve the external auditory canal
  2. Severe itching, erythema, scaling, crusting, and fissuring possible
- Acute diffuse otitis externa (swimmer's ear):
  1. Begins with itching and a feeling of pressure and fullness in the ear that becomes increasingly tender and painful
  2. Mild erythema and edema of the external auditory canal, which may cause narrowing and occlusion of the canal, leading to hearing loss
  3. Minimal serous secretions, which may become profuse and purulent
  4. Tympanic membrane may appear dull and infected
  5. Usually absence of systemic symptoms such as fever, chills
- Otomycosis:
  1. Chronic superficial infection of the ear canal and tympanic membrane
  2. In primary fungal infection, major symptom is intense itching
  3. In secondary infection (fungal infection superimposed on bacterial infection), major symptom is pain
  4. Fungal growth of variety of colors
- Chronic otitis externa:
  1. Dry and atrophic canal
  2. Typically lack of cerumen
  3. Itching, often severe, and mild discomfort rather than pain
  4. Occasionally mucopurulent discharge
  5. With time, thickening of the walls of the canal, causing narrowing of the lumen
- Necrotizing otitis externa (also known as malignant otitis externa). Typically seen in older patients with diabetes or in patients who are immunocompromised.
  1. Redness, swelling, and tenderness of the ear canal
  2. Classic finding of granulation tissue on the floor of the canal and the bone–cartilage junction
  3. Small ulceration of necrotic soft tissue at bone–cartilage junction
  4. Most common symptoms: pain (often severe) and otorrhea
  5. Lessening of purulent drainage as infection advances
  6. Facial nerve palsy often the first and only cranial nerve defect
  7. Possible involvement of other cranial nerves

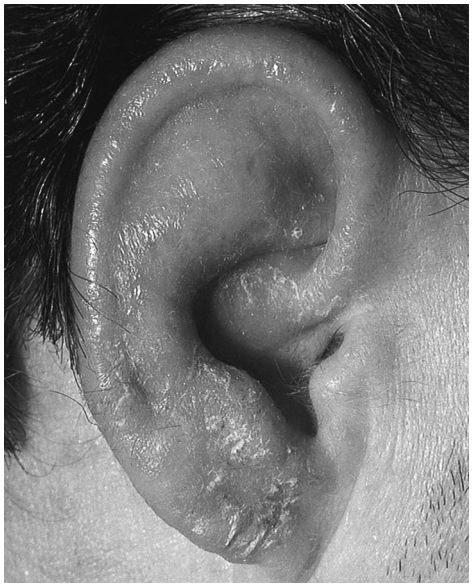


FIGURE 01-25 Malignant external otitis. Severe infection of the ear has occurred after months of chronic inflammation of the pinna. (From Habif TP: *Clinical dermatology: a color guide to diagnosis and therapy,* ed 3, St Louis, 1996, Mosby.)

ETIOLOGY

- Acute localized otitis externa: *Staphylococcus aureus*
- Impetigo:
  1. *S. aureus* including MRSA
  2. *Streptococcus pyogenes*
- Erysipelas: *S. pyogenes*
- Eczematous otitis externa:
  1. Seborrheic dermatitis
  2. Atopic dermatitis
  3. Psoriasis
  4. Neurodermatitis
  5. Lupus erythematosus
- Acute diffuse otitis externa:
  1. Swimming
  2. Hot, humid climates

3. Tightly fitting hearing aids
4. Use of ear plugs
5. *Pseudomonas aeruginosa*
6. *S. aureus* including MRSA

- Otomycosis:
  1. Prolonged use of topical antibiotics and steroid preparations
  2. Uncontrolled diabetes mellitus can contribute to risk
  3. *Aspergillus* (80% to 90%)
  4. *Candida*
- Chronic otitis externa: persistent low-grade infection and inflammation
- Necrotizing otitis externa (NOE):
  1. Complication of persistent otitis externa
  2. Extends through Santorini's fissures, small apertures at the bone-cartilage junction of the canal, into the mastoid and along the base of the skull
  3. *P. aeruginosa*

DX DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute otitis media
- Bullous myringitis
- Mastoiditis
- Foreign bodies
- Neoplasms
- Contact dermatitis
- Eczema
- Ramsey-Hunt syndrome
- Seborrhea
- Otomycosis
- Referred pain

WORKUP

Thorough history and physical examination

LABORATORY TESTS

- Cultures from the canal are usually not necessary unless the condition does not respond to treatment.
- Leukocyte count normal or mildly elevated.
- Erythrocyte sedimentation rate is often quite elevated in malignant otitis externa.

IMAGING STUDIES

- CT scan is the best technique for defining bone involvement and extent of disease in malignant otitis externa.
- MRI is slightly more sensitive in evaluation of soft tissue changes and intracranial extension of infection.
- Gallium scans are more specific than bone scans in diagnosing NOE.
- Follow-up scans are helpful in determining efficacy of treatment.

NOTE: Expert opinion supports history and physical examination as the best means of diagnosis. Persistent pain that is constant and severe should raise the question of NOE (particularly in the elderly, diabetics, and immunocompromised patients).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Cleansing and debridement of the ear canal with cotton swabs and hydrogen peroxide or other antiseptic solution allows a more thorough examination of the ear.
- If the canal lumen is edematous and too narrow to allow adequate cleansing, a cotton wick or gauze strip inserted into the canal serves as a conduit for topical medications to be drawn into the canal. Usually remove wick after 2 days.
- Local heat is useful in treating deep furunculosis.
- Incision and drainage is indicated in treatment of superficial pointing furunculosis.

ACUTE GENERAL Rx

Topical medications:

- An acidifying agent such as 2% acetic acid (Vosol) inhibits growth of bacteria and fungi
- Topical antibiotics (in the form of otic or ophthalmic solutions) or antifungals, often in combination with an acidifying agent and a steroid preparation
- The following are some of the available preparations:
  1. Neomycin otic solutions and suspensions:
     a. With polymyxin-B-hydrocortisone (Cortisporin)
     b. With hydrocortisone-thonzonium (Coly-Mycin S)
  2. Polymyxin-B-hydrocortisone (Otobiotic)
  3. Quinolone otic solutions:
     a. Ofloxacin 0.3% solution (Floxin Otic)
     b. Ciprofloxacin 0.3% with hydrocortisone (Cipro HC)
  4. Quinolone ophthalmic solutions:
     a. Ofloxacin 0.3% (Ocuflox)
     b. Ciprofloxacin 0.3% (Ciloxan)
  5. Aminoglycoside ophthalmic solutions:
     a. Gentamicin sulfate 0.3% (Garamycin)
     b. Tobramycin sulfate 0.3% (Tobrex)
     c. Tobramycin 0.3% and dexamethasone 0.1% (TobraDex)
  6. Chloramphenicol 0.5% otic solution or 0.25% ophthalmic solution (Chloromycetin)
  7. Gentian violet (methylrosaniline chloride 1%, 2%)
  8. Antifungals:
     a. Amphotericin B 3% (Fungizone lotion)
     b. Clotrimazole 1% solution (Lotrimin)
     c. Tolnaftate 1% (Tinactin)
- Topical preparations should be applied qid (bid for quinolones, antifungals), generally for 3 days after cessation of symptoms (average 10 to 14 days total)

Systemic antibiotics:

- Reserved for when the infection has spread beyond the ear canal
- Treatment usually for 10 days with ciprofloxacin 750 mg q12h or ofloxacin 400 mg q12h, or with antistaphylococcal agent (e.g., dicloxacillin or cephalexin 500 mg q6h). Use Bactrim when MRSA suspected or cultured at one DS twice a day instead of cephalexin or dicloxacillin. For malignant otitis externa (due to *Pseudomonas aeruginosa* in >90% of cases), effective agents are imipenem-cilastatin 0.5 g IV q6h or ciprofloxacin 400 mg IV q12h or 750 mg PO q12h or cefepime 2 g q12h.

Treatment for NOE:

- Requires prolonged therapy up to 3 mo; whether to use oral parenteral therapy based on clinical judgment
- Oral quinolones, ciprofloxacin 750 mg q12h or ofloxacin 400 mg q12h may be appropriate initial therapy or used to shorten the course of IV therapy
- Intravenous antipseudomonals with or without aminoglycosides are also appropriate
- Local debridement

Pain control:

- May require NSAIDs or opioids
- Topical corticosteroids to reduce swelling and inflammation

CHRONIC Rx

- Patients prone to recurrent infections should try to identify and avoid precipitants to infection.
- Swimmers should try tight-fitting ear plugs or tight-fitting bathing caps and remove all excess water from the ears after swimming.
- Treat underlying systemic diseases and dermatologic conditions that predispose to infection.

DISPOSITION

Inadequate treatment of otitis externa may lead to NOE and mastoiditis.

REFERRAL

To an otolaryngologist:

- NOE
- Treatment failure
- Severe pain

! PEARLS & CONSIDERATIONS

Otitis externa varies in severity from a mild irritation of the external acoustic canal (swimmer's ear) that resolves spontaneously by simply removing the offending agent (stay out of fresh water or wear ear plugs when swimming) to a life-threatening infection with the risk of intracranial extension, gram-negative bacterial meningitis, and severe neurologic impairment with multiple cranial neuropathy. Do not miss severe malignant otitis externa in patients who are diabetic or immunocompromised.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Otitis Externa (Patient Information)

AUTHOR: **RUSSELL J. MCCULLOH, M.D.**

SUGGESTED READINGS

Block SL: Otitis externa: providing relief while avoiding complications, *J Fam Pract* 54(8):669, 2005.

Carfrae MJ, Kesser BW: Malignant otitis media, *Otolaryngol Clin North Am* 41(3):537–549, 2008.

Kausnik V et al.: Interventions for acute otitis externa, *Cochrane Database Syst Rev* 1: CD004740, 2010.

McCoy SI et al.: Antimicrobial prescribing for otitis externa in children, *Pediatr Infect Dis J* 23(2):181, 2004.

Osguthorpe JD, Nielsen DR: Otitis externa: review and clinical update, *Am Fam Physician* 74:1510, 2006.

Rosenfeld RM1 et al.: Clinical practice guideline: acute otitis externa, *Otolaryngol Head Neck Surg. Feb* 150(1 Suppl):S1–S24, 2014.

Schaefer P, Baugh RF: Acute otitis externa: an update, *Am Fam Physician* 86(11):1055–1061, 2012.

BASIC INFORMATION

DEFINITION

Otitis media is the rapid onset of signs and symptoms of inflammation in the middle ear.

SYNONYMS

Acute suppurative otitis media
Purulent otitis media
Acute otitis media
AOM

ICD-9CM CODES
382.9 Acute or chronic otitis media
381.00 Acute non-suppurative otitis media
ICD-10CM CODES
H65.0 Acute serous otitis media
H65.1 Other acute nonsuppurative otitis media
H65.9 Nonsuppurative otitis media, unspecified
H65.2 Chronic serous otitis media
H65.3 Chronic mucoid otitis media
H65.6 Other chronic nonsuppurative otitis media
H66.0 Acute suppurative otitis media
H66.4 Suppurative otitis media, unspecified
H66.9 Otitis media, unspecified
H66.1 Chronic tubotympanic suppurative otitis media
H66.2 Chronic atticoantral suppurative otitis media

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.)
- Affects patients of all ages but is largely a disease of infants and young children.
- Affects approximately 80% of all children by age 5 yr.
- Occurs three or more times in one third of all children by age 3 yr.
- In 2000, costs associated with otitis media were approximately $5 billion, with 40% of the costs occurring from patients ages 1-3
- From 1995 to 2006, 80% of children diagnosed with otitis media received an antibiotic at initial visit.

PEAK INCIDENCE
- Between 9 and 15 mo
- Second peak between ages 4 and 6 yr
- Fall, winter, early spring (coincident with peak respiratory virus prevalence in the community)

PREDOMINANT SEX: Males

PREDOMINANT AGE
- 47% to 60% of all children have their first episode of otitis media during their first year of life and 80% by their fifth birthday.
- Incidence of infection declines with age; seen infrequently in adults.

GENETICS
Familial disposition:
- Native Americans
- Eskimos
- Australian aborigines
- Those with a strong family history
- Immune globulin G (IgG) or subclass deficiencies

Congenital infection: high incidence in children born with cleft palates and other craniofacial abnormalities

Other risk factors:
- Day care attendance
- Limited or lack of breastfeeding
- Tobacco smoke exposure

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Moderate to severe bulging of the tympanic membrane
- Fluid in the middle ear along with signs and symptoms of local inflammation (Figs. 01-26 and 01-27).
  1. Erythema with diminished light reflex
- As infection progresses, middle ear exudation occurs (exudative phase); the exudate rapidly changes from serous to purulent (suppurative phase).
  1. Retraction and poor motility of the tympanic membrane, which then becomes bulging and convex
- At any time during the suppurative phase the tympanic membrane may rupture, releasing the middle ear contents (otorrhea).
- Erythema of the tympanic membrane without other abnormalities is not a diagnostic criterion for acute otitis media (AOM) because it may occur with any inflammation of the upper respiratory tract, crying, or nose blowing.
- Symptoms:
  1. Rapid- or recent-onset otalgia, ranging from slight discomfort to severe, spreading to the temporal region
  2. Ear stuffiness and hearing loss may precede or follow otalgia
  3. Otorrhea if tympanic membrane has ruptured
  4. Vertigo, nystagmus, tinnitus, fever, lethargy, irritability, nausea, vomiting, anorexia
- After an episode of AOM:
  1. Persistence of effusion for weeks or months (called secretory, serous, or nonsuppurative otitis media)
  2. Fever and otalgia usually absent
  3. Hearing loss possible (10 to 50 dB, with predominant involvement of the low frequencies)

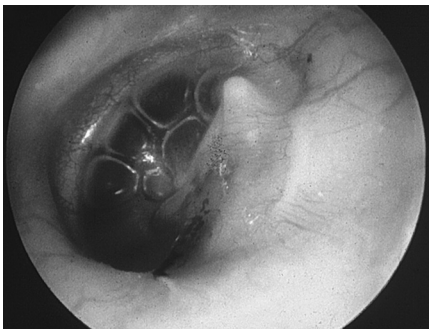


FIGURE 01-26 Otitis media with effusion of left ear. Retracted eardrum, prominent short process of malleus, and air bubbles seen anteriorly through the tympanic membrane. (From Behrman RE: *Nelson textbook of pediatrics,* ed 16, Philadelphia, 1996, Saunders.)

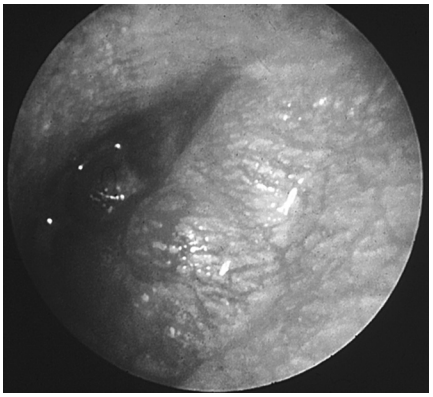


FIGURE 01-27 Acute left otitis media. (From Behrman RE: *Nelson textbook of pediatrics,* ed 16, Philadelphia, 1996, Saunders.)

ETIOLOGY

- Most common etiologic factor is a viral upper respiratory tract infection, which causes inflammation and dysfunction of the eustachian tube and transient aspiration of nasopharyngeal secretions into the middle ear. Bacterial colonization from the nasopharynx in conjunction with eustachian tube dysfunction leads to infection.
- May occasionally develop as a result of hematogenous spread or by direct invasion from the nasopharynx.
- Conjugated pneumococcal vaccination of children has resulted in decreases in *Streptococcus pneumoniae* causing AOM.
- Most common bacterial pathogens:
  1. *S. pneumoniae* causes 30% to 40% of cases and is the least likely of the major pathogens to resolve without treatment
  2. *Haemophilus influenzae* causes up to 50% of cases
  3. *Moraxella catarrhalis* causes 10% to 20% of cases
  4. Of increasing importance, infection caused by penicillin-nonsusceptible *S. pneumoniae* (MIC >0.1 mg/ml), ranging from 8% to 34%. About 50% of PNSSP isolates are penicillin-intermediate (MIC 0.1 to 2.0 mg/ml)
- Viral pathogens:
  1. Respiratory syncytial virus
  2. Rhinovirus
  3. Adenovirus
  4. Influenza
- Others:
  1. *Mycoplasma pneumoniae*
  2. *Chlamydia trachomatis*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Otitis externa
- Otitis media with effusion (OME)
- Referred pain
  1. Mouth
  2. Nasopharynx
  3. Tonsils
  4. Other parts of the upper respiratory tract

- Section II describes the differential diagnosis of earache

WORKUP

Thorough otoscopic examination. Adequate visualization of the tympanic membrane may require removal of cerumen and debris.

- Tympanometry
  1. Measures compliance of the tympanic membrane and middle ear pressure
  2. Detects the presence of fluid
- Acoustic reflectometry
  1. Measures sound waves reflected from the middle ear
  2. Useful in infants >3 mo
  3. Increased reflected sound correlated with the presence of effusion
  4. Tympanometry and acoustic reflectometry are useful in detection of middle ear effusion but do not provide information regarding infection/inflammation

LABORATORY TESTS

- Tympanocentesis
  1. Not necessary in most cases because the microbiology of middle ear effusions has been shown to be quite consistent
  2. May be indicated in:
     a. Highly toxic patients
     b. Patients who do not respond to treatment in 48 to 72 hr
     c. Immunocompromised patients
- Cultures of the nasopharynx: sensitive but not specific
- Blood counts (generally not necessary): usually show a leukocytosis with polymorphonuclear elevation
- Plain mastoid radiographs: generally not indicated; will reveal haziness in the periantral cells that may extend to entire mastoid
- CT or MRI may be indicated if serious complications suspected (meningitis, brain abscess, severe mastoiditis)

Rx TREATMENT

ACUTE GENERAL Rx

Hydration, avoidance of irritants (e.g., tobacco smoke), nasal systemic decongestants, cool mist humidifier

Antimicrobials:

NOTE: Most uncomplicated cases of AOM resolve spontaneously, without complications. Studies have demonstrated limited therapeutic benefit from antibiotic therapy. Watchful waiting is appropriate for children who look well, can be comforted with supportive care, and are old enough to easily evaluate. Children <24 mo with bilateral AOM should receive antibiotic therapy. Children with severe signs or symptoms (moderate or severe otalgia or otalgia for ≥48 hr or temperature ≥39°C) should also receive antibiotic therapy. When opting to use antibiotic therapy:

- Amoxicillin remains the drug of choice for first-line treatment of uncomplicated AOM despite increasing prevalence of drug-resistant *S. pneumoniae.*
- Treatment failure is defined by lack of clinical improvement of signs or symptoms after 3 days of therapy.
- With treatment failure, in the absence of an identified etiologic pathogen, therapy should be redirected to cover:
  1. Drug-resistant *S. pneumoniae*
  2. β-lactamase–producing strains of *H. influenzae* and *M. catarrhalis*
- Agents fulfilling these criteria include amoxicillin/clavulanate, second-generation (e.g., cefuroxime axetil, cefaclor) or third-generation cephalosporins (e.g., oral cefdinir or cefpodoxime or IM ceftriaxone). Do not use cefaclor, cefixime, loracarbef, and ceftibuten given limited activity against pneumococci.
- TMP/SMX and macrolides have been used as first- and second-line agents, but pneumococcal resistance to these agents is rising (up to 25% resistance to TMP/SMX and up to 10% resistance to erythromycin).
- Cross-resistance between these drugs and the β-lactams exists; therefore patients who do not respond to amoxicillin are more likely to have infections resistant to TMP/SMX and macrolides.
- Fluoroquinolones are not indicated as first- or second-line therapy for AOM and should be avoided in young children due to risks of musculoskeletal effects and lack of dosing guidance.
- Treatment should be modified according to cultures and sensitivities when available.
- Generally treatment course is 10 days for children <2 yr and those with severe symptoms, 7 days for children age 2 to 5 yr, and 5 to 7 days for children ≥6 yr.
- Follow up should be tailored to clinical improvement and concern for neurocognitive development delays in at-risk children. Standard follow-up of all cases is no longer required.
- Antibiotic prophylaxis to reduce the frequency of AOM episodes in children with recurrent AOM is not recommended.

NOTE: Effusions may persist for 8 wk or longer in many cases of adequately treated otitis media.

SURGICAL Rx

- No evidence to support the routine use of myringotomy, but in severe cases it provides prompt pain relief and accelerates resolution of infection.
- Purulent secretions retained in the middle ear can lead to increased pressure that may lead to spread of infection to contiguous areas. Myringotomy to decompress the middle ear is sometimes necessary to avoid complications.
- Complications include mastoiditis, facial nerve paralysis, labyrinthitis, meningitis, and brain abscess.
- Other procedures used for drainage of the middle ear include insertion of a ventilation tube and/or simple mastoidectomy.

CHRONIC Rx

- Myringotomy and tympanostomy tube placement for persistent or recurrent middle ear effusion unresponsive to medical therapy for ≥3 mo if bilateral or ≥6 mo if unilateral.
- Adenoidectomy, with or without tonsillectomy, often advocated for treatment of recurrent otitis media, although indications for this procedure are controversial.
- Long-term complications include tympanic membrane perforations, cholesteatoma, tympanosclerosis, ossicular necrosis, toxic or suppurative labyrinthitis, hearing loss, and intracranial suppuration.

DISPOSITION

Patients can be treated at home as outpatients with the rare exception of patients with evidence of local suppurative complications (e.g., meningitis, acute mastoiditis, brain abscess, cavernous sinus, or lateral vein thrombosis).

REFERRAL

- To otorhinolaryngologist if:
  1. Medical treatment failure
  2. Diagnosis uncertain: adults with one or more episodes of otitis media should be referred for ear-nose-throat evaluation to rule out underlying process (e.g., malignancy)
  3. Any of the above-mentioned acute and chronic complications

PEARLS & CONSIDERATIONS

COMMENTS

- Otoscopic findings are critical for accurate AOM diagnosis. AOM microbiology has changed with use of pneumococcal conjugate vaccine (PCV13). Antibiotics are modestly more effective than no treatment but cause adverse effects in 4% to 10% of children. Most antibiotics have comparable clinical success.

Prevention:

- Multiple component conjugate vaccines have helped decrease recurrent episodes of AOM
- Breastfeed and bottle-feed infants in an upright position
- Avoidance of irritants (e.g., tobacco smoke)

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **RUSSELL J. MCCULLOH, M.D.,** and **LAURA NORTON, M.D.**

EVIDENCE

Abstract[1]

Background:
The efficacy of antimicrobial treatment in children with acute otitis media remains controversial.

Methods:
In this randomized, double-blind trial, children 6 to 35 months of age with acute otitis media, diagnosed with the use of strict criteria, received amoxicillin–clavulanate (161 children) or placebo (158 children) for 7 days. The primary outcome was the time to treatment failure from the first dose until the end-of-treatment visit on day 8. The definition of treatment failure was based on the overall condition of the child (including adverse events) and otoscopic signs of acute otitis media.

Results:
Treatment failure occurred in 18.6% of the children who received amoxicillin–clavulanate, as compared with 44.9% of the children who received placebo (P<0.001). The difference between the groups was already apparent at the first scheduled visit (day 3), at which time 13.7% of the children who received amoxicillin–clavulanate, as compared with 25.3% of those who received placebo, had treatment failure. Overall, amoxicillin–clavulanate reduced the progression to treatment failure by 62% (hazard ratio, 0.38; 95% confidence interval [CI], 0.25 to 0.59; P<0.001) and the need for rescue treatment by 81% (6.8% vs. 33.5%; hazard ratio, 0.19; 95% CI, 0.10 to 0.36; P<0.001). Analgesic or antipyretic agents were given to 84.2% and 85.9% of the children in the amoxicillin–clavulanate and placebo groups, respectively. Adverse events were significantly more common in the amoxicillin–clavulanate group than in the placebo group. A total of 47.8% of the children in the amoxicillin-clavulanate group had diarrhea, as compared with 26.6% in the placebo group (P<0.001); 8.7% and 3.2% of the children in the respective groups had eczema (P=0.04).

Conclusions:
Children with acute otitis media benefit from antimicrobial treatment as compared with placebo, although they have more side effects. Future studies should identify patients who may derive the greatest benefit, in order to minimize unnecessary antimicrobial treatment and the development of bacterial resistance. (Funded by the Foundation for Paediatric Research and others; ClinicalTrials.gov number, NCT00299455.) A

Abstract[2]

Background:
Recommendations vary regarding immediate antimicrobial treatment versus watchful waiting for children younger than 2 years of age with acute otitis media.

Methods:
We randomly assigned 291 children 6 to 23 months of age, with acute otitis media diagnosed with the use of stringent criteria, to receive amoxicillin–clavulanate or placebo for 10 days. We measured symptomatic response and rates of clinical failure.

Results:
Among the children who received amoxicillin–clavulanate, 35% had initial resolution of symptoms by day 2, 61% by day 4, and 80% by day 7; among children who received placebo, 28% had initial resolution of symptoms by day 2, 54% by day 4, and 74% by day 7 (P=0.14 for the overall comparison). For sustained resolution of symptoms, the corresponding values were 20%, 41%, and 67% with amoxicillin–clavulanate, as compared with 14%, 36%, and 53% with placebo (P=0.04 for the overall comparison). Mean symptom scores over the first 7 days were lower for the children treated with amoxicillin–clavulanate than for those who received placebo (P=0.02). The rate of clinical failure—defined as the persistence of signs of acute infection on otoscopic examination—was also lower among the children treated with amoxicillin–clavulanate than among those who received placebo: 4% versus 23% at or before the visit on day 4 or 5 (P<0.001) and 16% versus 51% at or before the visit on day 10 to 12 (P<0.001). Mastoiditis developed in one child who received placebo. Diarrhea and diaper-area dermatitis were more common among children who received amoxicillin–clavulanate. There were no significant changes in either group in the rates of nasopharyngeal colonization with nonsusceptible *Streptococcus pneumoniae*.

Conclusions:
Among children 6 to 23 months of age with acute otitis media, treatment with amoxicillin–clavulanate for 10 days tended to reduce the time to resolution of symptoms and reduced the overall symptom burden and the rate of persistent signs of acute infection on otoscopic examination. (Funded by the National Institute of Allergy and Infectious Diseases;ClinicalTrials.gov number, NCT00377260.) A

Abstract[3]

Background:
10 days of amoxicillin/clavulanic acid high dose and 5 days of cefdinir have been the preferred first- or second-line antibiotics for treatment of children with acute otitis media (AOM) since 2004, as recommended by the American Academy of Pediatrics in the USA, but no head-to-head comparison study has been done.

Objective:
The purpose of the study was to compare the clinical efficacy of amoxicillin/clavulanic acid high-dose therapy for 10 days with cefdinir therapy for 5 days for AOM at recommended doses.

Methods:
This was an investigator-blind trial in young children 6-24 months old with no history of recurrent AOM who were randomly assigned to amoxicillin/clavulanic acid (80 mg/kg/day amoxicillin) or cefdinir (14 mg/kg/day), both in two divided doses. The diagnosis of AOM was based on specific clinical criteria by validated otoscopists at two AOM research centres. The outcome measure for clinical cure was resolution of all symptoms and signs of AOM except for persistence of middle-ear effusion at test-of-cure (TOC) 11-14 days after initiation of antibiotic treatment. Clinical failure was defined as persistence of symptoms and signs of AOM and the need for additional antibiotic therapy. Subjects lost to follow up or who had not taken at least 80% of the prescribed medication were classified as having an indeterminate response. Compliance was monitored using Medical Electronic Monitoring System (MEMS) caps and antibiotic bottle volume measurement at the TOC visit. A logistic regression model was used to estimate the association of age with cure rate. Full interactions in terms of age with treatment were included to estimate any age gradient differential.

Results:
A total of 330 children (average age 13.1 months) with AOM were studied. At TOC, 256 children had clinical cure, 69 had clinical failure, and 5 were lost to follow-up. High-dose amoxicillin/clavulanic acid-treated children had a better cure rate (86.5%) than cefdinir-treated patients (71.0%; $P = 0.001$). Cefdinir was correlated with less frequent cure outcomes as children increased in age between 6 and 24 months. The odds ratios for clinical cure per increasing month of age estimated from a logistic regression model for amoxicillin/clavulanic acid high dose and cefdinir treatment groups was 0.992 (95% CI 0.932, 1.056), $P > 0.05$ and 0.932 (95% CI 0.881, 0.986), $P = 0.01$. The differences in the odds ratios are significant at $P < .002$, indicating a stable clinical cure rate across the ages of children studied for amoxicillin/clavulanic acid and decreasing clinical cure rates as children increased in age for cefdinir.

Conclusion:
In children with bona fide AOM for whom clinical outcomes are assessed by validated otoscopists, 10 days of high-dose amoxicillin/clavulanic acid is significantly more effective than 5 days of cefdinir as therapy for AOM. Because of the identified age effect (correlated to child weight), higher doses of cefdinir may have led to a different conclusion; 10 days of cefdinir may also have led to a different conclusion. A

Abstract[4]

Background:
Watchful waiting with the option of delayed antimicrobial treatment for acute otitis media is recommended in several guidelines. Our aim was to study whether delayed, as compared with immediate, initiation of antimicrobial treatment worsens the recovery from acute otitis media in young children.

Methods:
Children (6-35 months) with acute otitis media received either delayed or immediate antimicrobial treatment with amoxicillin-clavulanate for 7 days. The delayed antimicrobial treatment group (n = 53) consisted of placebo recipients from a randomized-controlled trial to whom antimicrobial treatment was initiated after a watchful waiting period. The immediate antimicrobial treatment group (n = 161) consisted of children allocated to receive antimicrobial treatment immediately.
Results:
Improvement during antimicrobial treatment (which includes both symptoms and otoscopic signs) was observed in 91% and 96% of children in the delayed and immediate antimicrobial treatment groups, respectively ($P = .15$). Median watchful waiting period was 48 hours. Delayed initiation of antimicrobial treatment was associated with prolonged resolution of fever, ear pain, poor appetite and decreased activity, but not ear rubbing, irritability, restless sleep or excessive crying. Parents of children in the delayed antimicrobial treatment group missed more work days (mean 2.1 versus 1.2 days, $P = .03$). Diarrhea, vomiting and rash were equally common in both groups.
Conclusions:
Our results indicate that delayed initiation of antimicrobial treatment does not worsen the recovery from acute otitis media, as measured by improvement during treatment. However, watchful waiting before the initiation of delayed antimicrobial treatment might be associated with transient worsening of a child's condition, prolongation of symptoms and economic losses. Ⓐ

Evidence-Based References

Tähtinen PA et al.: A placebo-controlled trial of antimicrobial treatment for acute otitis media, *N Engl J Med* 364:116–126, 2011. Ⓐ

Hoberman A et al.: Treatment of acute otitis media in children under 2 years of age, *N Engl J Med* 364:105–115, 2011. Ⓐ

Casey JR et al.: Comparison of amoxicillin/clavulanic acid high dose with cefdinir in the treatment of acute otitis media, *Drugs* 72:1991–1997, 2012. Ⓐ

Tähtinen PA et al.: Delayed versus immediate antimicrobial treatment for acute otitis media, *Pediatr Infect Dis J* 31:1227–1232, 2012. Ⓐ

SUGGESTED READINGS

Coker TR et al.: Diagnosis, microbial epidemiology, and antibiotic treatment of acute otitis media in children: a systematic review, *JAMA* 304(19):2161–2169, 2010.

Damoiseaux RA et al.: Long-term prognosis of acute otitis media in infancy: determinants of recurrent acute otitis media and persistent middle ear effusion, *Fam Pract* 23(1):40, 2006.

Hoberman A et al.: Treatment of acute otitis media in children under 2 years of age, *N Engl J Med* 364:105–115, 2011.

Klein JO: Is acute otitis media a treatable disease? *N Engl J Med* 364:168, 2011.

Lieberthal AS et al.: The diagnosis and management of acute otitis media, *Pediatrics* 131(3):e964–e999, Mar 2013. 10.1542/peds.2012-3488. Epub 2013 Feb 25.

Pichichero ME: Otitis media, *Pediatr Clin North Am* 60(2):391–407, Apr 2013. 10.1016/j.pcl.2012.12.007.

Plasschaert AL et al.: Trends in doctor consultations, antibiotic prescription, and specialist referrals for otitis media in children: 1995-2003, *Pediatrics* 117(6):1879, 2006.

Ramakrishnan K et al.: Diagnosis and treatment of otitis media, *Am Fam Physician* 76:1650, 2007.

Tähtinen PA et al.: A placebo-controlled trial of antimicrobial treatment for acute otitis media, *N Engl J Med* 364:116–126, 2011.

Venekamp RP et al.: *Antibiotics for acute otitis media in children. Cochrane Database of Systematic Reviews*, 2013. Issue 1. Art. No.: CD000219.

Otosclerosis (Otospongiosis)

BASIC INFORMATION

DEFINITION

Otosclerosis is conductive hearing loss caused by fixation of the stapes, resulting in gradual hearing loss. Approximately 15% of cases affect only one ear.

ICD-9CM CODES
387.9 Otosclerosis

ICD-10CM CODES
H80 Otosclerosis
H80.0 Otosclerosis involving oval window, non-obliterating
H80.1 Otosclerosis involving oval window, obliterating
H80.2 Cochlear otosclerosis
H80.8 Other otosclerosis
H80.9 Otosclerosis, unspecified
H80.93 Unspecified otosclerosis, bilateral

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Most common cause of hearing loss in young adults
PEAK INCIDENCE: Middle age
PREVALENCE (IN U.S.): Five cases per 1000 persons
PREDOMINANT SEX: Male/female ratio of 2:1
PREDOMINANT AGE: Symptoms start between ages 15 and 30 yr, with slowly progressive hearing loss.
GENETICS: Half of cases are dominantly inherited.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Tympanic membrane is normal in most cases (tested with tuning fork).
- Bone conduction is greater than air conduction.
- Weber test localizes to affected ear.

ETIOLOGY

- A disease in which a vascular type of spongy bone is laid down
- Unknown

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hearing loss from any cause: cochlear otosclerosis, polyps, granulomas, tumors, osteogenesis imperfecta, chronic ear infections, trauma.
- A clinical algorithm for evaluation of hearing loss is described in Section III.
- Table EO1-11 describes common types of conductive and sensorineural hearing loss.

WORKUP

Audiometry

LABORATORY TESTS

None, unless infection suspected

IMAGING STUDIES

MRI or CT with specific cuts through inner ear (Fig. EO1-28)

TREATMENT

NONPHARMACOLOGIC THERAPY

Hearing aid only of temporary use

CHRONIC Rx

Progresses to deafness without surgical intervention

DISPOSITION

Referral to ear-nose-throat (ENT) specialist

REFERRAL

To ENT specialist for surgery if moderate hearing loss suspected

PEARLS & CONSIDERATIONS

COMMENTS

A full ENT evaluation in a young or middle-aged person with hearing loss is mandatory unless the cause is obvious (such as trauma or repeated infection).

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **FRED F. FERRI, M.D.**

TABLE EO1-11 Common Types of Conductive and Sensorineural Hearing Loss

Conductive Hearing Loss	Sensorineural Hearing Loss
Otitis media with effusion	Presbycusis (hearing loss with aging)
TM perforation	Ototoxicity
Tympanosclerosis	Ménière's disease
Retracted TM (eustachian tube dysfunction)	Idiopathic loss
Ossicular problems	Noise-induced loss
Otosclerosis	Perilymphatic fistula
Foreign body in ear canal	Hereditary (congenital) loss
Cerumen impaction	Multiple sclerosis
Tumor of the ear canal or middle ear	Diabetes
Cholesteatoma	Syphilis, acoustic neuroma

TM, Tympanic membrane.
From Rakel RE (ed): *Principles of family practice,* ed 6, Philadelphia, 2002, Saunders.

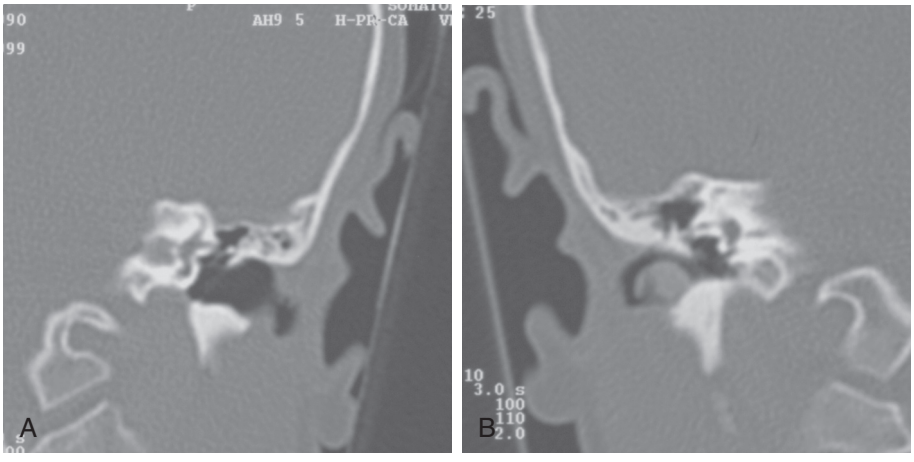


FIGURE EO1-28 A patient with conductive hearing loss. By comparing the normal **(A)** and abnormal **(B)** sides on CT scan, the narrowing of the oval window can be clearly appreciated. This results in fixation of the stapes footplate and conductive hearing loss. (From Grainger RG et al [eds]: *Grainger & Allison's diagnostic radiology,* ed 4, Philadelphia, 2001, Churchill Livingstone.)

SUGGESTED READING

Chole RA, McKenna M: Pathophysiology of otosclerosis, *Otol Neurotol* 22(2):249, 2001.

BASIC INFORMATION

DEFINITION

Ovarian tumors can be benign, requiring operative intervention but not recurring or metastasizing; malignant, recurring, metastasizing, and having decreased survival; or borderline, having a small risk of recurrence or metastases and generally having a good prognosis. An emerging concept is the possibility that many ovarian cancers have origins on nonovarian tissues such as distal fallopian tube and endometriotic implants.

SYNONYMS

Epithelial ovarian cancer
Germ cell tumor
Sex cord stromal tumor
Ovarian tumor of low malignant potential

ICD-9CM CODES
183.0 Malignant neoplasm of ovary
ICD-10CM CODES
C56.9 Malignant neoplasm of unspecified ovary

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 12.9 to 15.1 cases/100,000 persons; ~25,000 new cases annually
PREVALENCE: Median age of 61 yr; peaks at age 75 to 79 yr (54/100,000)
RISK FACTORS: Low parity, delayed childbearing, use of talc on the perineum (unlikely), high-fat diet, fertility drugs (unlikely), Lynch II syndrome (nonpolyposis colon cancer, endometrial cancer, breast cancer, and ovarian cancer clusters in first- and second-degree relatives), breast-ovarian familial cancer syndrome, site-specific familial ovarian cancer.
GENETICS: The greatest risk factors of ovarian cancer are a family history and associated genetic syndromes. Familial susceptibility has been shown with the *BRCA1* gene located on 17q12 to 21. This correlates with breast-ovarian cancer syndrome.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- 60% present with advanced disease
- Abdominal fullness, early satiety, dyspepsia
- Pelvic pain, back pain, constipation
- Pelvic or abdominal mass
- Lymphadenopathy (inguinal)
- Sister Mary Joseph nodule (umbilical mass)

ETIOLOGY

- Can be inherited as site-specific familial ovarian cancer (two or more first-degree relatives have ovarian cancer)
- Breast-ovarian cancer syndrome (clusters of breast and ovarian cancer among first- and second-degree relatives)
- Lynch syndrome
- No family history and unknown etiology in the majority of ovarian cancer cases

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Primary peritoneal cancer mesothelioma
- Benign ovarian tumor
- Functional ovarian cyst
- Endometriosis
- Ovarian torsion
- Pelvic kidney
- Pedunculated uterine fibroid
- Primary cancer from breast, gastrointestinal tract, or other pelvic organ metastasized to the ovary

WORKUP

- Definitive diagnosis made at laparotomy; epithelial ovarian cancer most common type of ovarian cancer
- Careful physical and history, including family history
- Exclusion of nongynecologic etiologies
- Observation of small cystic masses in premenopausal women for regression for 2 mo
- FIGO classification of ovarian carcinoma is described in Table 01-12.

LABORATORY TESTS

- Complete blood count
- Chemistry profile
- CA-125 or lysophosphatidic acid level. Use of these tests for annual screening is controversial. Only about 50% of early-stage ovarian cancers will be associated with elevated CA-125. Additionally, false elevations may occur with uterine leiomyoma, endometriosis, pregnancy, and intraabdominal infections. The PLCO cancer screening trial revealed that annual screening based on CA-125 and vaginal ultrasound is ineffective and diagnostic follow-up of false positives resulted in 15% serious complication rate.
- Consider: human chorionic gonadotropin, inhibin, alpha-fetoprotein, neuron-specific enolase, and lactate dehydrogenase in patients at risk for germ cell tumors.
- A panel of 3 serum biomarkers (apolipoprotein A-1 [ApoA-1], transthyretin [TTR], and transferrin [TF]) has been reported useful in distinguishing normal samples from early-stage ovarian cancer with a sensitivity of 84% and normal samples from late-stage ovarian cancer with a sensitivity of 97%.

IMAGING STUDIES

- Ultrasound
- Chest x-ray
- Mammogram
- CT scan to help evaluate extent of disease (Fig. 01-29)
- Other studies (MRI, intravenous pyelogram, etc.) as clinically indicated

TREATMENT

NONPHARMACOLOGIC THERAPY

Virtually all cases of ovarian cancer involve surgical exploration. This includes:

- Abdominal cytology
- Total abdominal hysterectomy and bilateral salpingo-oophorectomy (except in early stages in which fertility preservation is an issue)
- Omentectomy

TABLE 01-12 FIGO Classification of Ovarian Carcinoma

Stage I	Growth limited to the ovaries:
	Stage IA: Growth limited to one ovary, no ascites and no tumor present on the external surface; capsule intact
	Stage IB: Growth limited to both ovaries, no ascites and no tumor present on the external surface; capsule intact
	Stage IC: Stage 1A or 1B where there is tumor on the surface of either ovary; or with ruptured capsules or with ascites containing malignant cells or positive peritoneal washings. Surgical spillage of a malignant cyst upgrades the patient to IC although it is unlikely that this event affects prognosis.
Stage II	Growth involving one or both ovaries with pelvic extension:
	Stage IIA: Extension and/or metastases to the uterus and tubes
	Stage IIB: Extension to other pelvic tissues
	Stage IIC: Stage IIA or IIB with tumor on the surface of either ovary or positive peritoneal washings or malignant ascites
Stage III	Growth involving one or both ovaries with peritoneal implants outside the pelvis or positive retroperitoneal or inguinal lymph nodes:
	Stage IIIA: Microscopic seeding of abdominal peritoneal surfaces
	Stage IIIB: Macroscopic disease outside the pelvis less than 2 cm in diameter
	Stage IIIC: Abdominal implants greater than 2 cm and/or positive nodes
Stage IV	Growth involving one or both ovaries with distant metastases including parenchymal (but not superficial) liver metastases and pleural effusions containing malignant cells

From Symonds EM, Symonds IM: *Essential obstetrics and gynaecology*, ed 4, London, 2004, Churchill Livingstone.

- Diaphragm sampling
- Selective lymphadenectomy (pelvic and paraaortic nodes)
- Primary cytoreduction with a goal of residual tumor diameter <2 cm
- Bowel surgery, splenectomy if needed to obtain optimal (<2 cm) cytoreduction
- Conventional treatment includes surgical debulking (cytoreduction) followed by chemotherapy. However, patients with low-grade, well-differentiated stage I ovarian cancer do not benefit from adjuvant chemotherapy.

ACUTE GENERAL Rx

- Optimal cytoreduction is generally followed by chemotherapy (except in some early-stage disease).
- Cisplatin-based combination chemotherapy is used for stage II or greater, 6-mo treatment. Compared with IV paclitaxel plus cisplatin, IV paclitaxel plus intraperitoneal cisplatin and paclitaxel improves survival rates in patients with optimally debulked stage III ovarian cancer.
- Chemotherapy regimens continue to change as research continues. Bevacizumab, a humanized antivascular endothelial growth factor monoclonal antibody, has been shown to be effective in improving progression-free survival in women with ovarian cancer. Trials using bevacizumab during and up to 10 months after carboplatin and paclitaxel chemotherapy have shown prolongation of the median progression-free survival by about 4 months in patients with advanced epithelial ovarian cancer. Olaparib, an oral polymerase inhibitor, has shown antitumor activity in patients with high-grade serous ovarian cancer with or without BRCA1 and BRCA2 germline mutations. Trials have shown that olaparib as maintenance treatment significantly improved progression-free survival among patients with platinum-sensitive, relapsed high-grade serous ovarian cancer.
- Second-look surgery when chemotherapy is complete generally is no longer recommended because this procedure has not been shown to improve survival.
- Recent trials have shown that neoadjuvant chemotherapy followed by interval debulking surgery is not inferior to debulking surgery followed by chemotherapy as a treatment option for patients with bulky stage IIIC or IV ovarian carcinoma. Complete resection of all macroscopic disease, whether performed as primary treatment or after neoadjuvant chemotherapy, remains the objective whenever cytoreductive surgery is performed.

CHRONIC Rx

- If CA-125 elevated, may have recurrent disease
- Physical and pelvic examinations every 3 mo for 2 yr, every 4 mo during third year, then every 6 mo
- CA-125 every visit
- Yearly Pap smear

DISPOSITION

- Overall 5-yr survival rates remain low because of the preponderance of late-stage disease:
  1. Stage I and II: 80% to 100%
  2. Stage III: 15% to 20%
  3. Stage IV: 5%
- Younger patients (<50 yr) in all stages have a considerably better 5-yr survival than older patients (40% vs. 15%).
- Among women with high-grade serous ovarian cancer, *BRCA2* mutation, but not *BRCA1* deficiency, is associated with improved survival, improved chemotherapy response, and genome instability compared with *BRCA* wild-type.
- Among patients with invasive epithelial ovarian cancer (EOC), having a germline mutation in *BRCA1* or *BRCA2* is associated with improved 5-yr overall survival. *BRCA2* carriers have the best prognosis.

COMMENTS

- The U.S. Preventive Services Task Force has concluded that current evidence does not show any mortality benefit to routine screening for ovarian cancer with transvaginal ultrasonography or single-threshold serum CA-125 testing and that the harms of such screening are at least moderate.
- Patients at high risk for developing ovarian cancer (BRCA1/BRCA2 gene mutation, hereditary nonpolyposis colorectal cancer syndrome) should consider prophylactic salpingo-oophorectomy after childbearing is complete. If surgery is declined, the National Comprehensive Cancer Network guidelines recommend intensive surveillance with pelvic and abdominal sonogram and serum CA-125 every 6 mo starting at age 35 or 10 yr earlier than cancer diagnosis in family member.

EVIDENCE

available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Ovarian Cancer (Patient Information)
Ovarian Neoplasm, Benign (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

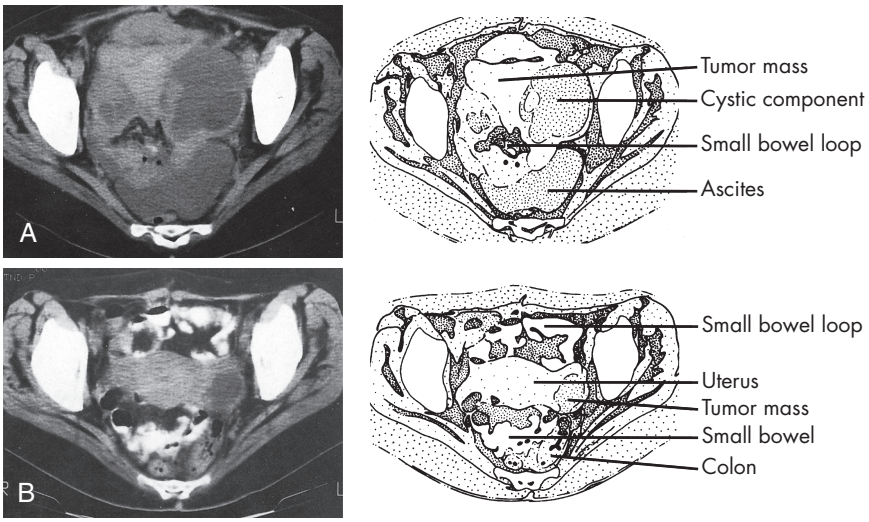


FIGURE 01-29 Response to chemotherapy. A 51-year-old woman presented with a rapid increase in abdominal girth. **A,** On CT scan, she was found to have a 12 x 8 cm ovarian mass with a cystic component; peritoneal involvement was extensive and 6 L of ascites was removed. Pathologic examination showed a poorly differentiated tumor. The tumor was not resectable, and she was treated with combination chemotherapy. After one cycle of therapy, her abdomen returned to normal size. **B,** A CT scan reveals only a small residual ovarian mass. Surgery after four cycles of chemotherapy showed no gross or microscopic tumor. She received four more cycles of chemotherapy but relapsed 1 year later with abdominal metastases. (From Skarin AT: *Atlas of diagnostic oncology,* ed 3, St Louis, 2003, Mosby.)

EVIDENCE

Abstract[1]

Context:
Screening for ovarian cancer with cancer antigen 125 (CA-125) and transvaginal ultrasound has an unknown effect on mortality.

Objective:
To evaluate the effect of screening for ovarian cancer on mortality in the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial.

Design, Setting, and Participants:
Randomized controlled trial of 78 216 women aged 55 to 74 years assigned to undergo either annual screening (n=39 105) or usual care (n=39 111) at 10 screening centers across the United States between November 1993 and July 2001.

Intervention:
The intervention group was offered annual screening with CA-125 for 6 years and transvaginal ultrasound for 4 years. Participants and their health care practitioners received the screening test results and managed evaluation of abnormal results. The usual care group was not offered annual screening with CA-125 for 6 years or transvaginal ultrasound but received their usual medical care. Participants were followed up for a maximum of 13 years (median [range], 12.4 years [10.9-13.0 years]) for cancer diagnoses and death until February 28, 2010.

Main Outcome Measures:
Mortality from ovarian cancer, including primary peritoneal and fallopian tube cancers. Secondary outcomes included ovarian cancer incidence and complications associated with screening examinations and diagnostic procedures.

Results:
Ovarian cancer was diagnosed in 212 women (5.7 per 10 000 person-years) in the intervention group and 176 (4.7 per 10 000 person-years) in the usual care group (rate ratio [RR], 1.21; 95% confidence interval [CI], 0.99-1.48). There were 118 deaths caused by ovarian cancer (3.1 per 10 000 person-years) in the intervention group and 100 deaths (2.6 per 10 000 person-years) in the usual care group (mortality RR, 1.18; 95% CI, 0.82-1.71). Of 3285 women with false-positive results, 1080 underwent surgical follow-up; of whom, 163 women experienced at least 1 serious complication (15%). There were 2924 deaths due to other causes (excluding ovarian, colorectal, and lung cancer) (76.6 per 10 000 person-years) in the intervention group and 2914 deaths (76.2 per 10 000 person-years) in the usual care group (RR, 1.01; 95% CI, 0.96-1.06).

Conclusions:
Among women in the general US population, simultaneous screening with CA-125 and transvaginal ultrasound compared with usual care did not reduce ovarian cancer mortality. Diagnostic evaluation following a false-positive screening test result was associated with complications.

Trial Registration:
clinicaltrials.gov Identifier: NCT00002540. Ⓐ

Evidence-Based Reference

Buys SS: for the PLCO Project Team: Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial, *JAMA* 305:2295–2303, 2011. Ⓐ

SUGGESTED READINGS

Armstrong D et al.: Intraperitoneal cisplatin and paclitaxel in ovarian cancer, *N Engl J Med 354* 34, 2006.

Bolton KL et al.: Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer, *JAMA* 307(4):382–390, 2012.

Burger RA et al.: Incorporation of bevacizumab in the primary treatment of ovarian cancer, *N Engl J Med* 365:2473–2483, 2011.

Buys SS et al.: Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial, *JAMA 305* 2295, 2011.

Clarke-Pearson DL: Screening for ovarian cancer, *N Engl J Med* 361:170–177, 2009.

Ledermanm J et al.: Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer, *N Engl J Med* 366:1382–1392, 2012.

Nosov V et al.: Validation of serum biomarkers for detection of early-stage ovarian cancer, *Am J Obstet Gynecol* 639, 2009. e1–639.e5.

Perren TJ: A phase 3 trial of bevacizumab in ovarian cancer, *N Engl J Med* 365:2484–2496, 2011.

Roett MA, Evans P: Ovarian cancer, an overview, *Am Fam Physician* 80(6):609–616, 2009.

Steinrud L et al.: Hormone therapy and ovarian cancer, *JAMA* 302(3):298–305, 2009.

Vergote I et al.: Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer, *N Engl J Med* 363:943–953, 2010.

Yang D et al.: Association of BRCA1 and BRCA2 mutations with survival, chemotherapy sensitivity, and gene mutator phenotype in patients with ovarian cancer, *JAMA* 306(14):1557–1565, 2011.

Ovarian Neoplasm, Benign PTG

BASIC INFORMATION

DEFINITION

Benign ovarian neoplasms are often clinically indistinguishable from their malignant counterparts. Therefore all persistent adnexal masses must be considered malignant until proven otherwise. Nonneoplastic tumors include:

- Germinal inclusion cyst
- Follicle cyst
- Corpus luteum cyst
- Pregnancy luteoma
- Theca lutein cysts
- Sclerocystic ovaries
- Endometrioma

Neoplastic tumors derived from coelomic epithelium include:

- Cystic tumors: serous cystadenoma, mucinous cystadenoma, mixed forms
- Tumors with stromal overgrowth: fibroma, adenofibroma, Brenner tumor

Tumors derived from germ cells are dermoids (benign cystic teratomas).

ICD-9CM CODES
220 Benign neoplasm of ovary
ICD-10CM CODES
D27.9 Benign neoplasm of unspecified ovary

EPIDEMIOLOGY & DEMOGRAPHICS

- **Reproductive years:**
  1. Most common benign ovarian neoplasms: serous cystadenoma and benign cystic teratoma
  2. Most common adnexal mass: functional cyst
  3. Risk of malignancy increases after age 40 yr.
- **Infants:** adnexal masses are usually follicular cysts attributable to maternal hormone stimulation that regress during first few months of life.
- **Childhood:**
  - Adnexal masses are rare
  - 8% malignant
  - Almost always dysgerminomas or teratomas (germ cell origin)
  - Frequency of malignancy inversely correlated with age
- **Adolescence:**
  - Most common adnexal mass is a functional cyst.
  - Most common neoplastic ovarian tumor is a benign cystic teratoma.
  - Solid/cystic adnexal tumors are rare and almost always dysgerminomas or malignant teratomas.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Usually asymptomatic
- Pelvic pain or pressure
- Dyspareunia
- Abdominal pain ranging from mild to severe peritoneal irritation
- Increasing abdominal girth or distention
- Adnexal mass of pelvic examination
- Children: abdominal or rectal mass

ETIOLOGY

- Physiologic
- Endometriosis
- Unknown

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Ovarian torsion
- Malignancy: ovary, fallopian tube, colon
- Uterine fibroid
- Diverticular abscess, diverticulitis
- Appendiceal abscess, appendicitis (especially in children)
- Tubo-ovarian abscess
- Paraovarian cyst
- Distended bladder
- Pelvic kidney
- Ectopic pregnancy
- Retroperitoneal cyst or neoplasm

WORKUP

- Complete history and physical examination
- Pelvic or rectovaginal examination to reveal firm, irregular, mobile mass
- Laparoscopy or laparotomy to establish diagnosis

LABORATORY TESTS

- Pregnancy test
- Serum tumor markers:
  1. Cancer antigen 125 (CA-125)
  2. Alpha-fetoprotein (endodermal sinus tumor, immature teratoma)
  3. Beta-human chorionic gonadotropin
  4. Lactate dehydrogenase (dysgerminoma)

IMAGING STUDIES

Ultrasound (Fig. 01-30):

- May differentiate adnexal mass from other pelvic masses
- Features that increase risk of malignancy include solid component, papillae, multiple septations or solitary thick septa, ascites, matted bowel, bilaterality, irregular borders
- CT scan with contrast
- Colonoscopy or barium enema, if symptomatic

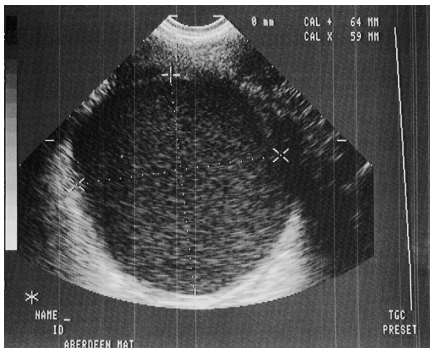


FIGURE 01-30 Ultrasonogram, which reveals a cyst 6.5 cm across, which was found at laparotomy to be an endometrioma, full of altered blood: the so-called chocolate cyst. This may cause cyclical or chronic pelvic pain. (From Greer IA et al: *Mosby's color atlas and text of obstetrics and gynecology*, London, 2000, Harcourt.)

TREATMENT

NONPHARMACOLOGIC THERAPY

Repeat pelvic examination, typically with transvaginal pelvic ultrasound, for premenopausal women in 4 to 6 wk to rule out persistent cyst.

ACUTE GENERAL Rx

Indications for surgery:

- Postmenopausal or premenarchal palpable adnexal mass
- Adnexal mass with suspicious ultrasound features
- Premenopausal woman with persistent cyst >5 cm
- Any adnexal mass >8 cm
- Suspected torsion or rupture

CHRONIC Rx

- Depends on diagnosis
- Possible suppression of formation of new cysts by oral contraceptives

DISPOSITION

Depends on diagnosis

REFERRAL

- If malignancy suspected
- If surgery required

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Ovarian Cysts (Patient Information)

AUTHOR: **RUBEN ALVERO, M.D.,** and **GEORGE T. DANAKAS, M.D.**

SUGGESTED READINGS

Doret M, Raudrant D: Functional ovarian cysts and the need to remove them, *Eur J Obstet Gynecol Reprod Biol* 100:1, 2001.

Kurjak A et al.: Ultrasonic assessment of the peri- and postmenopausal ovary, *Maturitas* 41:245, 2002.

BASIC INFORMATION

DEFINITION

Paget's disease of bone is a focal disorder of chaotic bone remodeling with increased osteoblastic and osteoclastic activity that results in disorganized woven and lamellar bone in one or more skeletal sites. The end result is bone of poor quality that is enlarged, hypervascular, and susceptible to deformation and fracture.

SYNONYMS

Osteitis deformans

ICD-9CM CODES
731.0 Paget's disease (osteitis deformans)
ICD-10CM CODES
M88.9 Osteitis deformans of unspecified bone

EPIDEMIOLOGY & DEMOGRAPHICS

Epidemiologic data suggest an origin of Paget's disease in Great Britain spreading to other areas by English colonists beginning in the seventeenth century. Highest prevalence occurs in Eastern and Western Europe and in those who have emigrated to New Zealand, Australia, South Africa, and North America. Rarely seen in Japanese, Chinese, Asian Indians, sub-Saharan Africans, and Middle Eastern Arabs.

Most commonly diagnosed in those aged >50 yr and rare before 40 yr.

Prevalence estimates of up to 3% of population aged >50 yr and up to 10% in those aged >90 yr.

PREDOMINANT SEX: Variable preponderance of males.
PREDOMINANT AGE: Middle or advanced years.
FAMILIAL INCIDENCE: Common, family history positive in up to 40% of cases.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most common sites of involvement: pelvis, spine, sacrum, femur, skull, tibia (Fig. EP1-1), humerus, scapula.
- Uncommon: hand, foot, fibula.
- Lesions in one (monostotic) or more bones (polyostotic).
- Gradual progression of disease in affected bone(s) with rare appearance at new site(s).
- Many patients are asymptomatic, but up to 40% of patients who come to medical attention present with bone pain.
- Symptoms and signs include bone and articular pain often related to secondary arthritis, bone deformities and enlargement, increased warmth over pagetic bone, skull enlargement, nerve entrapment or compression syndromes, cranial nerve deficits especially deafness, spinal cord compression and vascular steal syndromes, fissure fractures, fractures, and neoplastic degeneration.

ETIOLOGY

Etiology remains unknown

Extensive epidemiologic and laboratory data are in keeping with potential role of paramyxoviral infection of osteoclasts in a genetically susceptible individual with or without documented genetic mutations.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Osteosclerosis
- Hyperphosphatasia
- Familial expansile osteolysis
- Fibrous dysplasia
- Skeletal neoplasm (primary or metastatic)
- Osteomalacia with secondary hyperparathyroidism

LABORATORY TESTS

- Increase in serum alkaline phosphatase or bone-specific alkaline phosphatase
- Increase in urine NTx/creatinine ratio or plasma CTx
- Bone biopsy may be necessary to rule out sarcomatous degeneration or metastatic disease

IMAGING STUDIES (Fig. EP1-2)

Bone scintigraphy is the most sensitive test for delineating the extent and site of pagetic lesions but nonspecific in that areas of uptake may be related to arthritis or metastatic lesions. Radiographs (Fig. P1-3) will further delineate characteristic pagetic changes.

TREATMENT

Indications for therapy include extensive or symptomatic disease; neurologic complications; involvement of weight-bearing bones, skull, vertebrae, and other areas of critical involvement, for example, in proximity to joints; and prevention of excess bleeding from an orthopedic procedure on pagetic bone.

NONPHARMACOLOGIC THERAPY

Optimization of calcium and vitamin D intake and appropriate guidance regarding ambulatory needs.

SPECIFIC THERAPY

Bisphosphonates are the mainstay of therapy and include oral alendronate or risedronate and intravenous pamidronate or zoledronic acid.

- SC salmon calcitonin when bisphosphonates are not tolerated or are contraindicated as in those with GFR of <35 ml/min
- Acetaminophen, aspirin, and nonsteroidal drugs for relief of pain

DISPOSITION

- Without treatment, progression of disease is common
- With treatment, remissions of varying duration in most patients. Bisphosphonates can normalize bone turnover in a high proportion of patients, but evidence that long-term suppression of bone turnover prevents complications or improves the clinical outcome is currently inconclusive.
- Careful and regular clinical and biochemical followup at 3- to 6-mo intervals with necessity of retreatment in patients with continued pagetic activity or reactivation
- With first ever intravenous dose of pamidronate or zoledronic acid, patients may experience a flu-like syndrome for several days that may be prevented with acetaminophen

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Paget's Disease of Bone (Patient Information)

AUTHOR: **JOSEPH R. TUCCI, M.D.**

FIGURE P1-3 Paget's disease of the bone. Frontal radiograph of the pelvis shows marked prominence of the trabeculae in the right ilium, ischium, and pubic bones, with small lytic areas identified as compatible with the later stages of Paget's disease. (From Specht N [ed]: *Practical guide to diagnostic imaging,* St Louis, 1998, Mosby.)

SUGGESTED READINGS

Miller PD et al.: A randomized, double blind comparison of risedronate in the treatment of Paget's disease of bone, *Am J Med* 106:513–520, 1999.

Parvizi J et al.: Surgical management of Paget's disease of bone, *J Bone Min Res* 21(S2):P75–P82, 2006.

Ralston SH: Pathogenesis of Paget's disease of bone, *Bone* 43:819–825, 2008.

Ralston SH: Paget's disease of bone, *N Engl J Med* 368:644–650, 2013.

Reid IR et al.: Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease, *N Engl J Med* 353:898–908, 2005.

Siris ES, Roodman GD: Paget's disease of bone. In: (editor: Rosen C.J.) Primer on the metabolic bone diseases and disorders of mineral metabolism. ed 7 ASBMR: Washington DC, pp. 335–343.

Siris ES et al.: Comparative study of alendronate vs etidronate for the treatment of Paget's disease of bone, *J Clin Endocrinol Metab* 81:961–967, 1996.

Siris ES et al.: Medical management of Paget's disease of bone: indications for treatment and review of current therapies, *J Bone Min Res* 21(S2):94–98, 2008.

Tucci JR: Paget disease of bone, *Curr Opin Endocrinol Diabetes* 11:321–329, 2004.

Whyte MP: Paget's disease of bone, *N Engl J Med* 355:593–600, 2006.

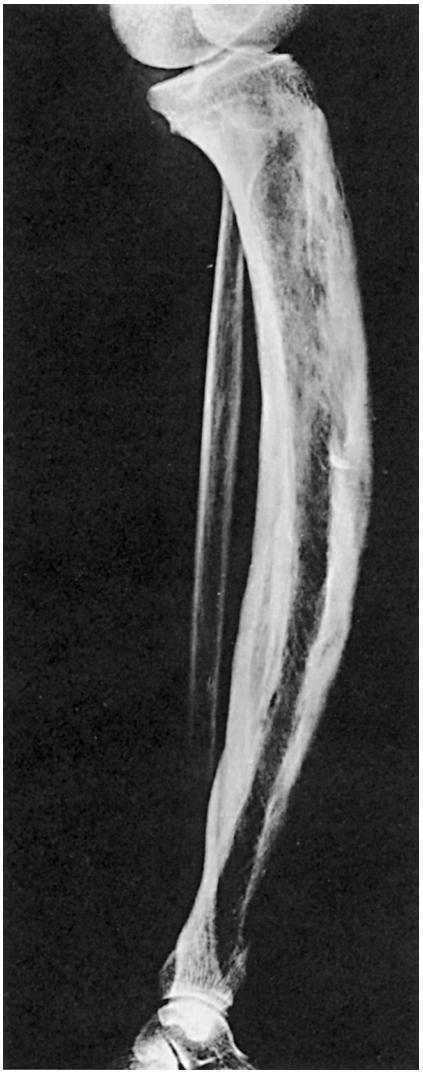


FIGURE EP1-1 Paget's disease of the tibia. Notice the bowing, marked irregularity of the anterior cortex and the flame-shaped lytic lesion of the posterior cortex. (Courtesy of Dr. Ethel S. Siris.)

FIGURE EP1-2 ^{99m}Tc-MDP bone scan shows polyostotic Paget's disease involving the sternum, right scapula, two lumbar vertebral bodies, and right hemipelvis. There may be early pagetic disease in the right skull as well. (From Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.)

Paget's Disease of the Breast PTG

BASIC INFORMATION

DEFINITION

Paget's disease of the breast is a malignant disease that presents itself as a scaly, sore, eroding, bleeding ulcer of the nipple. It represents an extension of a ductal adenocarcinoma of the breast. Microscopically, typical large clear cells (Paget's cells) with pale and abundant cytoplasm and hyperchromatic nuclei with prominent nucleoli are found in the epidermal layer. Paget's disease is more often associated with primary invasive or in situ carcinoma of the breast.

ICD-9CM CODES

174.0 Malignant neoplasm of female breast, nipple, and areola

ICD-10CM CODES

C50.0 Malignant neoplasm of nipple and areola

C50.019 Malignant neoplasm of nipple and areola, unspecified female breast

EPIDEMIOLOGY & DEMOGRAPHICS

- Not common
- Found in one in 100 to 200 breast cancer patients

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Variable; most often reveals an erythematous, irregularly bordered plaque on the nipple.
- Itching or burning nipple and/or reported lump
- Very minimal scaly lesion that may bleed when scales are lifted
- Typical ulcer located on nipple with serous fluid weeping or small amount of bleeding coming from it (Fig. P1-4)
- Palpable carcinoma in the breast of some patients

ETIOLOGY

- Exact origin unknown
- Possibly migration of either in situ or invasive carcinoma cells in breast to nipple skin to produce Paget's disease

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Chronic dermatitis
- Florid papillomatosis of the nipple or nipple adenoma
- Eczema

WORKUP

- Clinically apparent
- Careful breast examination with diagnosis in mind
- Palpable mass or mammographic lesions in 60% to 70% of patients

A clinical algorithm for the evaluation of nipple discharge is described in Section III, "Breast, Nipple Discharge Evaluation."

LABORATORY TESTS

Biopsy of nipple lesion

IMAGING STUDIES

Mammograms to search for possible primary carcinoma

TREATMENT

NONPHARMACOLOGIC THERAPY

- Fewer patients:
  1. Paget's disease of nipple only finding when mammographically negative breast
  2. Consideration of wide excision of nipple with or without radiation
- Other patients: additional invasive or in situ carcinoma recognized
- Either modified mastectomy or breast conservation treatment
- Presence of underlying in situ or invasive carcinoma in mastectomy specimen of majority of patients

ACUTE GENERAL Rx

Systemic adjuvant therapy depending on extent of invasive carcinoma found

DISPOSITION

- Parallel prognosis to that of breast cancer patient without Paget's disease
- Regular follow-up as in other invasive or in situ carcinoma patients

REFERRAL

At outset, all suspicious nipple lesions should be referred for evaluation and treatment.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Paget's Disease of the Breast (Patient Information)
Breast Cancer (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

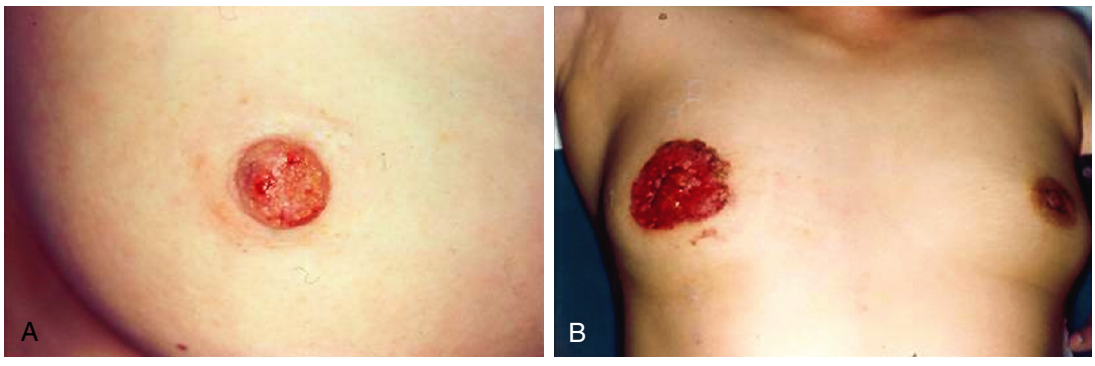


FIGURE P1-4 A and B: Paget disease of the nipple. (Courtesy Sehwan Han, MD.)

SUGGESTED READINGS

Sakoratias GH et al.: Paget's disease of the breast, *Canc Treat Rev* 27(1):9, 2001.

Sakoratias GH et al.: Paget's disease of the breast: a clinical perspective, *Langenbecks Arch Surg* 386(6):444, 2001.

BASIC INFORMATION

DEFINITION

Pancreatic cancer is an adenocarcinoma derived from the epithelium of the pancreatic duct.

ICD-9CM CODES
157.9 Pancreatic cancer
157.0 (head)
157.1 (body)
157.2 (tail)
157.3 (duct)
230.9 (in situ)

ICD-10CM CODES
C25.9 Malignant neoplasm of pancreas, unspecified
C25.0 Malignant neoplasm of head of pancreas
C25.1 Malignant neoplasm of body of pancreas
C25.2 Malignant neoplasm of tail of pancreas
C25.3 Malignant neoplasm of pancreatic duct

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: One case in 10,000 persons annually. In the United States there are >46,000 patients diagnosed with pancreatic cancer and >40,000 deaths yearly. It is the fourth leading cause of cancer-related death in the United States. Less than 20% of patients present with localized, potentially resectable tumors.
PREDOMINANT SEX: Male/female ratio of 2:1
PREDOMINANT AGE: Median age at diagnosis is 71 years

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Presenting symptoms are generally related to location:
Jaundice (60% to 70% of pancreatic cancers are located in the head of the pancreas)
Abdominal pain: generally dull upper abdominal pain or vague abdominal discomfort
Weight loss
Anorexia/change in taste, asthenia
Nausea
Uncommonly: depression, gastrointestinal bleeding, acute pancreatitis (from obstruction of the pancreatic duct), back pain
Trousseau syndrome (hypercoagulability in the setting of malignancy) may be initial presentation in some patients.
Physical findings:
Icterus
Cachexia, temporal wasting
Ascites, peripheral lymphadenopathy, hepatomegaly
Excoriations from scratching pruritic skin

ETIOLOGY

Unknown, but several conditions have been associated with pancreatic cancer:
- Smoking
- Alcoholism
- Genetics: 5% to 10% of patients have a family history of the disease
- Genetic syndromes and associated genes: Hereditary pancreatitis (*PRSS1, SPINK1*), Peutz-Jeghers syndrome (*STK11[LKB1]*), familial atypical multiple mole and melanoma syndrome (*p16*), hereditary breast and ovarian cancer syndromes (*BRACA1, BRACA2, PALB2*), ataxia telangiectasia (*ATM*), Li-Fraumeni syndrome (*P53*)
- Gallstones
- Diabetes mellitus (present in at least 50% of patients with pancreatic cancer)
- Chronic pancreatitis
- Diet rich in animal fat
- Occupational exposure: oil refining, paper manufacturing, chemical industry
- Overweight or obesity during early adulthood is associated with a greater risk of pancreatic cancer and a younger age of disease onset. Obesity at an older age is associated with a lower overall survival in patients with pancreatic cancer.
- Possible increased risk for certain type-2 diabetes medications (GLP-1 receptor agonists and DPP-4 inhibitors)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Common duct cholelithiasis
- Cholangiocarcinoma
- Common duct stricture
- Sclerosing cholangitis
- Primary biliary cirrhosis
- Autoimmune pancreatitis
- Drug-induced cholestasis (e.g., phenothiazines)
- Chronic hepatitis
- Sarcoidosis
- Other pancreatic tumors (islet cell tumor, cystadenocarcinoma, epidermoid carcinoma, sarcomas, lymphomas)

WORKUP

Routine Laboratory Tests	*% Abnormal*
Alkaline phosphatase	80
Bilirubin	55
Total protein	15
Amylase	15
Hematocrit	60

Ca 19-9: Not useful as a screening tool because it may be elevated in other conditions, such as cholestasis, but is useful for therapeutic monitoring and early detection of recurrent disease after treatment

IMAGING STUDIES

Multidetector helical CT with IV administration of contrast is the imaging procedure of choice for initial evaluation. Endoscopic ultrasonography is useful when there is no identifiable mass on CT and diagnosis is strongly suspected and in obtaining tissue for diagnostic purposes. Fine-needle aspiration biopsy combined with endoscopic ultrasonography is the preferred modality for evaluation of cystic or mass lesions to determine malignancy. Endoscopic retrograde cholangiopancreatography (ERCP) is useful in patients with jaundice needing an endoscopic stent to relieve obstruction.

Noninvasive Imaging	*% Abnormal*
Abdominal ultrasonography	60
Abdominal CT scan (with contrast) (Fig. P1-5)	90
Abdominal MRI scan	90
Invasive Imaging	
ERCP	90
CT scan or ultrasonography-guided needle aspiration cytology	90-95

STAGING FOR PANCREATIC CANCER

PRIMARY TUMOR (T)
TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Tumor <2 cm
T2 Tumor >2 cm, confined to the pancreas
T3 Tumor extends locally beyond the pancreas
T4 Tumor involves celiac or superior mesenteric arteries

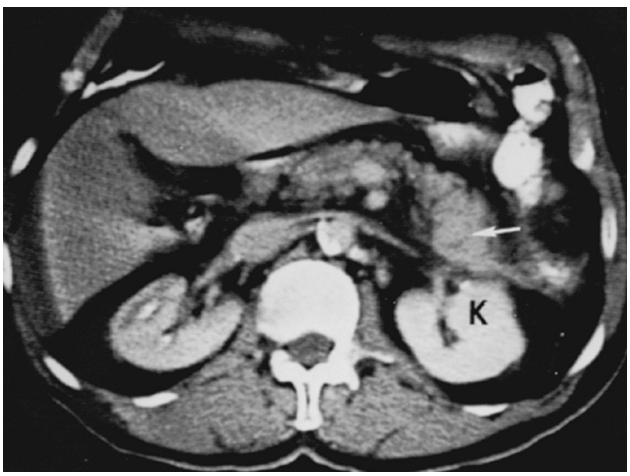


FIGURE P1-5 CT scan of a patient with adenocarcinoma of the body and tail of the pancreas. The tumor *(arrow)* is seen anterior and adjacent to the left kidney *(K)*. At operation, the tumor was invading Gerota's fascia. (From Sabiston D: *Textbook of surgery,* ed 17, Philadelphia, 2005, Saunders.)

LYMPH NODES (N)
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis

DISTANT METASTASES (M)
MX Presence of distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

STAGING GROUP:
IA T1, N0, M0
IB T2, N0, M0
IIA T3, N0, M0
IIB T1-3, N1, M0
III T4, N0-1, M0
IV T1-4, N0-1, M1

A clinical/radiographic staging system for adenocarcinoma of the pancreatic head and uncinate process is described in Table P1-1.

Rx TREATMENT

SURGERY

Curative cephalic pancreatoduodenectomy (Whipple's procedure) for tumors in the head and neck of the pancreas is appropriate for only 10% to 20% of patients whose lesion is <5 cm, solitary, and without metastases. Surgical mortality rate is 5%. Tumors in the body or tail of the pancreas are removed by means of a distal pancreatectomy, which often includes a splenectomy. Adjuvant chemotherapy may improve postoperative survival. An emerging strategy is the use of neoadjuvant preoperative treatment in patients with resectable pancreatic cancer. The addition of gemcitabine to adjuvant fluorouracil and leucovorin chemotherapy has been reported to have a survival benefit for patients with resected pancreatic cancer.

PALLIATIVE SURGERY (FOR BILIARY DECOMPRESSION/ DIVERSION)

Palliative therapeutic ERCP with stents

CHEMOTHERAPY

In patients with advanced disease an accepted approach is the administration of gemcitabine given alone or combined with a platinum agent, the oral EGFR inhibitor erlotinib, or fluoropyrimidine. Combination therapy consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin (FOLFIRINOX) offers increased median survival in metastatic pancreatic cancer when compared to gemcitabine (11.1 mo versus 6.8 mo) but increased toxicity.

- A recent trial revealed that in patients with metastatic pancreatic adenocarcinoma, NAB-paclitaxel plus gemcitabine significantly improved overall survival, progression-free survival, and response rate, but rates of peripheral neuropathy and myelosuppression were increased.[1]
- Investigators have also sought to enhance the immune response against pancreatic cancer with the use of adjuvant therapy. Newer trials incorporating immune checkpoint inhibitors such as the inhibitors to programmed death1 (PD-1) and PD-1 ligand PD-L1 are underway.

RADIATION

- External-beam radiation for palliation of pain.
- Combined chemotherapy and radiation provides a median survival of 11 mo.
- Celiac plexus block by an experienced anesthesiologist provides pain relief in 80% to 90% of cases.

DISPOSITION

- Adjunct chemotherapy has a significant survival benefit in patients with resected pancreatic cancer.
- Recent trials have shown that adjuvant postoperative chemotherapy with gemcitabine significantly delays the development of recurrent disease after complete resection of pancreatic cancer. Among patients with macroscopic complete removal of pancreatic cancer, the use of adjuvant gemcitabine for 6 mo compared with observation alone resulted in increased overall survival as well as disease-free survival. These findings provide strong support for use of gemcitabine in this setting.[2]
- Pancreatic cancer is the most lethal common cancer because it is usually diagnosed at an advanced stage and is resistant to therapy. Median survival for locally unresectable disease is about 1 yr. Median survival for metastatic cancer is 4 to 6 mo.

[1]Von Hoff DD et al: Increased survival in pancreatic cancer with NAB-paclitaxel plus gemcitabine, *N Engl J Med* 369:1691-1703, 2013.
[2]Dettel H et al: Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer, the CONKO-001 randomized trial, *JAMA* 310(14):1473-1481, 2013.

PEARLS & CONSIDERATIONS

COMMENTS

- The U.S. Preventive Services Task Force (USPSTF) recommends against routine screening for pancreatic cancer in asymptomatic adults by abdominal palpation, ultrasonography, or serologic markers. The USPSTF found no evidence that screening for pancreatic cancer is effective in reducing mortality rates. There is potential for significant harm because of the low prevalence of pancreatic cancer, limited accuracy of available screening tests, invasive nature of diagnostic tests, and poor outcome of treatment. As a result, the USPSTF concluded that the harms of screening for pancreatic cancer exceed any potential benefits.
- Recent trials indicate that pancreatic cancer may have a distinct microRNA (miRNA) expression pattern that may differentiate it from normal pancreas and chronic pancreatitis. Current research is aimed at using miRNA expression patterns to distinguish between long- and short-term survivors.
- Alcohol consumption, specifically liquor consumption of three or more drinks per day, increases pancreatic cancer mortality independent of smoking.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pancreatic Cancer (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

TABLE P1-1 Clinical/Radiographic Staging System for Adenocarcinoma of the Pancreatic Head and Uncinate Process

Clinical Stage	>AJCC Stage	TUMOR-VESSEL RELATIONSHIP ON COMPUTED TOMOGRAPHY			
		SMA	Celiac Axis	CHA*	SMV-PV
Resectable (all four are required to be resectable)†	I/II	Normal tissue plane between tumor and vessel	Normal tissue plane between tumor and vessel	Normal tissue plane between tumor and vessel	Patent (may include tumor abutment or encasement)
Borderline resectable (only one of the four required)	III	Abutment	Abutment	Abutment or short segment encasement	May have short segment occlusion if reconstruction possible
Locally advanced (only one of the four required)	III	Encasement	Encasement	Extensive encasement with no technical option for reconstruction	Occluded with no technical option for reconstruction

AJCC, American Joint Commission for Cancer; *CHA,* common hepatic artery; *SMV–PV,* superior mesenteric vein–portal vein confluence. Abutment refers to ≤180 degrees or ≤50% of the vessel circumference; encasement is <180 degrees or <50% of the vessel circumference.
*Assumes normal vascular anatomy; for example, encasement of the CHA is not a limitation in performing PD when there is an uninvolved replaced right hepatic artery arising from the superior mesenteric artery.
†Assumes the technical ability to resect and reconstruct the SMV, PV, or SMV-PV confluence when necessary. Others would consider tumor-vein abutment/encasement, which results in deformity of the vein as borderline resectable.
From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

SUGGESTED READINGS

Abbruzzese JL: Adjuvant therapy for surgically resected pancreatic adenocarcinoma, *JAMA* 299:1066, 2008.

Bloomston M et al.: MicroRNA expression patterns to differentiate pancreatic adenocarcinoma from normal pancreas and chronic pancreatitis, *JAMA* 297:2007, 1901.

Conroy T et al.: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer, *N Engl J Med* 364:1817–1825, 2011.

Freelove R, Walling AD: Pancreatic cancer: diagnosis and management, *Am Fam Physician* 73:485, 2006.

Gaptur S et al.: Association of alcohol intake with pancreatic cancer mortality in never smokers, *Arch Intern Med* 171(5):444–451, 2011.

Hidalgo M: Pancreatic cancer, *N Engl J Med* 362:1605–1617, 2010.

Li D et al.: Body mass index and risk, age of onset, and survival in patients with pancreatic cancer, *JAMA* 301(24):2553–2562, 2009.

Oettle H et al.: Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer, *JAMA* 297:267, 2007.

O'Reilly E: Refinement of adjuvant therapy for pancreatic cancer, *JAMA* 304:1124, 2010.

Regine WF et al.: Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma, *JAMA* 299(9):1019–1026, 2008.

Ryan DP et al.: Pancreatic adenocarcinoma, *N Engl J Med* 371:1039–1049, 2014.

U.S. Preventive Task Force: Screening for pancreatic cancer: a brief evidence update for the USPTS. Available at http://ahrq.gov/clinic/uspstf/uspspanc.htm.

BASIC INFORMATION

DEFINITION

- A **panic attack** is a relatively brief, sudden episode of intense fear or apprehension, often associated with a sense of impending doom and various uncomfortable and disquieting physical symptoms. Panic attacks may be uncued ("out of the blue") or cued (i.e., triggered by a particular object or situation). Panic attacks may be present in a variety of different anxiety-related disorders (e.g., phobias, social anxiety, obsessive-compulsive disorder). Table P1-2 describes criteria for diagnosis of panic attack.
- **Panic disorder** is diagnosed at least after two uncued panic attacks have occurred followed by at least 1 mo (or more) of significant concern about future attacks, worry about their implications, or a major change in behavior related to these attacks. The criteria for diagnosis of panic disorder is summarized in Table P1-3. **Agoraphobia** is anxiety about, and avoidance of, places or situations in which the ability to escape is perceived to be limited or embarrassing or in which help might not be available in the event of having a panic attack.

SYNONYMS

Anxiety attacks
Fear attacks
Ataque de nervios

ICD-9CM and DSM-5 CODES
300.01
ICD-10CM CODES
F41.0 Panic disorder
F40.0 Agoraphobia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 1% 1-mo incidence of panic attacks

TABLE P1-2 Criteria for Diagnosis of a Panic Attack

A discrete period of intense fear or discomfort, in which ≥4 of the following symptoms developed abruptly and reached a peak within 10 min
- Palpitations, pounding heart, or accelerated heart rate
- Sweating
- Trembling or shaking
- Sensations of shortness of breath or being smothered
- Feeling of choking
- Chest pain or discomfort
- Nausea or abdominal distress
- Feeling dizzy, unsteady, light-headed, or faint
- Derealization (feelings of unreality) or depersonalization (being detached from oneself)
- Fear of losing control or going crazy
- Paresthesias (numbness or tingling sensations)
- Chills or hot flashes

From Kliegman RM et al: *Nelson essentials of pediatrics,* ed 5, Philadelphia, 2006, Saunders.

PREVALENCE (IN U.S.)
- 15% to 20% lifetime prevalence of one or more panic attacks.
- Panic disorder is much more uncommon, with a lifetime prevalence of 1.5% to 3.5%; chronicity of condition reflected by a similar 1-yr prevalence rate of 1% to 2%.
- Agoraphobia is relatively rare; 0.3% to 1% lifetime prevalence; 30% to 50% of patients diagnosed with panic disorder also have agoraphobia.

PEAK INCIDENCE
- Chronic condition with a waxing and waning course.
- Bimodal incidence peaks noted, with the first peak between ages 15 and 24 yr and second peak between ages 35 and 44 yr.

PREDOMINANT SEX
- Women more commonly affected (>85% of clinical population).
- Panic disorder twice as common in women.
- Panic disorder with agoraphobia three times as common in women.

PREDOMINANT AGE
- Age of onset is typically late adolescence to mid-30s. Onset earlier in males (24 yr) than females (28 yr).
- Onset after age 45 yr is rare and should raise suspicion of different etiology.

GENETICS
- Risk of developing panic disorder in first-degree relatives of individuals with panic disorder is four to seven times that of general population.
- Findings in twin studies: approximately 60% of contributing factors to panic are genetic.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Panic disorder
- Present either with a panic attack or with fear and anxiety related to anticipation of a future panic attack or its implications.
- Typical presentation: unexpected, untriggered periods of intense anxiety and fear with associated physiologic changes (e.g., palpitations, sweating, tremulousness, shortness of breath, chest pain, gastrointestinal distress, faintness, derealization, paresthesia). This is accompanied by associated fears of dying, heart attack, stroke, passing out, losing control, or losing one's mind. Panic attacks are often described as "the most terrifying" episode an individual has experienced.
- Emergency or physician visits often occasioned by physical symptoms such as chest pain, dizziness, or difficulty breathing. Thirty percent of patients presenting with chest pain have panic disorder.

TABLE P1-3 Criteria for Diagnosis of Panic Disorder

1. Recurrent unexpected panic attacks with associated worry or behavior change
2. Not due to effects of a drug, medication, or medical condition

Agoraphobia:
- Rare complaints to physician. May manifest in missed office visits or tardiness. Patients may request home visits or telephone care.
- Activities usually self-limited by avoiding public situations where the patient believes he or she might experience a panic attack and would be unable to exit readily, such as the following:
  1. Crowded public areas (stores, public transportation, flying, church)
  2. Individual interactions (hairdresser, dentist, neighborhood meetings)
  3. Driving (especially if alone, far from home over bridges, through tunnels, on highways or on isolated roads)
- On exposure to or anticipation of exposure to feared situations, significant anxiety occurs. Anxiety may generate somatic symptoms that trigger a full-blown panic attack. Patients believe that escape from these situations reduces the alarming symptoms, thus reinforcing future avoidance. In actuality, symptom relief stems from adrenaline breaking down in the body after approximately 20 minutes.

ETIOLOGY

Hypotheses (NOTE: There are sufficient data to support each model. Models are not mutually exclusive.)
1. Central dyscontrol of autonomic arousal (typically localized to the locus ceruleus); similar symptoms may be chemically induced with yohimbine, caffeine, or cholecystokinin.
2. Cognitive overreaction (i.e., "catastrophic misinterpretation") to relatively mild or benign physiologic cues that then triggers a genuine autonomic cascade and further misinterpretations.
3. Dysfunction of a central suffocation alarm mechanism; some signs of compensated respiratory alkalosis. Can be experimentally induced with sodium lactate or carbon dioxide.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Medical conditions:
- Endocrinopathies:
  1. Hyperthyroidism
  2. Hyperparathyroidism
  3. Pheochromocytoma
  4. Carcinoid tumor
- Cardiac and respiratory diseases:
  1. Arrhythmias
  2. Myocardial infarction
  3. Chronic obstructive pulmonary disease
  4. Asthma
  5. Mitral valve prolapse
- Metabolic:
  1. Hypoglycemia
  2. Electrolyte imbalances
  3. Porphyria
- Seizure disorders
- Psychiatric disorders (NOTE: Panic attacks are common in a variety of psychiatric disorders. Panic disorder could be conceptualized

as a phobia of the somatic sensations or situations that have become paired with panic attacks.)
1. Phobias (e.g., specific phobia or social phobia). Note that fear of going on a plane because of crashing would be a specific phobia, whereas fear of going on a plane because one is then trapped and worries about panic is more suggestive of panic disorder with agoraphobia.
2. Obsessive-compulsive disorder (cued by exposure to the object of the obsession)
3. Posttraumatic stress disorder (cued by recall of a stressor)
4. Generalized anxiety disorder (cued by excessive worry)

- Therapeutic (theophylline, steroids) and recreational (cocaine, amphetamine, caffeine, diet pills) drugs and drug withdrawal (alcohol, cannabis, barbiturates, benzodiazepines)

WORKUP

- Emergency presentation: cardiac, respiratory, or neurologic symptoms
- History and physical examination to rule out a concomitant medical or substance-related condition

NOTE: Panic disorder and agoraphobia are not diagnoses of exclusion, but exclusion of other conditions is usually required.

LABORATORY TESTS

- Thyroid profile
- Electrolyte measures, including calcium
- Toxicology screen
- ECG
- Acute cases: possible monitoring and cardiac enzymes to rule out arrhythmia or ischemia

IMAGING STUDIES

- For temporal lobe dysfunction (e.g., temporal lesions or as ictal or interictal manifestation of temporal lobe seizures): brain CT scan or MRI or an electroencephalogram in some patients
- Holter monitor to rule out occult or episodic arrhythmias
- Chest x-ray, arterial blood gases, or pulmonary function tests if respiratory compromise suspected

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Cognitive-behavioral therapy (CBT), in particular Panic Controlled Treatment developed by David H. Barlow, PhD, and Michelle G. Craske, PhD, is generally very effective, with strongest results for cognitive restructuring (i.e., challenging catastrophic misinterpretations of somatic symptoms), in vivo or imaginal exposures (i.e., exposure to panic triggers in a controlled graded hierarchical fashion from least to most difficult with the goal of habituation and extinction of the fear response), and interoceptive exposures (i.e., repeated recreation and management of feared somatic sensations via activities such as chair spinning, straw breathing, and hyperventilation). CBT effect sizes are equal to or larger than for pharmacotherapy, attrition rates are lower, and relapse rates are lower. Treatment may take several sessions spread over weeks and may require referral to a behavioral specialist.

Traditionally, exposure therapy has relied upon a "desensitization paradigm" (i.e., habituation), in which the goal is to continue exposing an individual to a feared stimulus until the fear is no longer present (e.g., having a person with panic disorder remain in a shopping mall until anxiety has subsided). The assumption has been that habituation is the active ingredient in learning/fear reduction.

New research by Michelle G. Craske, PhD., suggests that fear habituation itself is not a predictor or mediator of outcomes when treating anxiety disorders. Craske theorizes that fear reduction during a prolonged exposure does not ensure that a person will not re-experience fear when encountering the feared stimulus in the future (e.g., reducing one's fear in a shopping mall does not ensure that one will not experience fear in other shopping malls). Rather, she suggests that strengthening "inhibitory learning' is the central mechanism of action for fear reduction.

Inhibitory learning acts as a competitor to the original fear; therefore, the stronger an exposure, the better it will compete with the original fear and the less likely the original fear will return. Several strategies can be employed to strengthen inhibitory learning. The goal is to violate expectations about the fear a person is going to experience.

The most effective manner to strengthen inhibitory learning is to find ways to surprise a person by violating an expectation multiple times in a single exposure. For example, if a person with panic disorder is conducting an in vivo exposure, combining it with an interoceptive exposure will be more effective (e.g., going to a shopping mall and hyperventilating at the same time).

Because of the element of surprise offered by inhibitory learning, cognitive restructuring occurs following an exposure rather than before it. Practicing cognitive restructuring prior to an exposure has been found to actually weaken an exposure. Craske suggests that varying the contexts of an exposure as much as possible is the most effective way to reduce anxiety (e.g., multiple shopping malls, multiple interoceptive exposures).

ACUTE GENERAL Rx

- Benzodiazepines, particularly alprazolam: highly effective in the acute setting although long-term use is contraindicated for effective outcome.
- Low-dose alprazolam for patients with rare panic attacks and asymptomatic periods (0.25 to 0.5 mg PO or sublingually prn).
- Start patient on selective serotonin reuptake inhibitor (SSRI) or similar agent and taper patient off benzodiazepine by wk 2 to 3.

CHRONIC Rx

- Preferred pharmacologic agents: antidepressants with a significant serotonin reuptake inhibitory action. Generally start at low dose and titrate upward. Minimum treatment duration is 6 to 8 mo, but many patients need to take medications indefinitely.
  1. SSRIs: paroxetine (10 to 60 mg/day), sertraline (50 to 200 mg/day), citalopram (20 to 60 mg/day), escitalopram (5 to 30 mg/day), and fluoxetine (5 to 60 mg/day)
  2. Imipramine (100 to 300 mg/day)
  3. Venlafaxine (75 to 225 mg/day)
- Combination CBT plus SSRI has shown good long-term effects and is somewhat better than antidepressants or CBT alone. Combination CBT plus benzodiazepine does not provide any added benefit and may undermine CBT (interoceptive and in-vivo exposures may be less effective if the benzodiazepine is completely controlling the anxiety).

DISPOSITION

- Typical course is chronic but with significant waxing and waning (common to have long periods of remission).
- Presence of agoraphobia associated with a more chronic course.
- Findings with long-term follow-up studies: 6 to 10 yr after treatment some 30% are in remission, 40% to 50% have improved with residual symptoms, and the remainder are either unchanged or worse.

REFERRAL

- If patients do not respond to an SSRI
- Cognitive-behavioral therapy is the preferred treatment.

PEARLS & CONSIDERATIONS

- Patient and family education is an important first step in the management of panic disorder. Education provides more adaptive explanations for the benign somatic sensations paired with panic. Presentation of genetic information and explanation of the benign nature of the physiology of each of the symptoms the patient experiences serve as a good start to allay fears and reduce stigma.
- Resumption of avoided activities or situations is a positive prognostic sign and may promote further therapeutic gains.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Panic Disorder (Patient Information)

AUTHORS: **JEFFREY P. WINCZE, PH.D,** and **JASON M. SATTERFIELD, PH.D.**

SUGGESTED READINGS

Craske MG, Barlow DH: Mastery of your anxiety and panic: therapist guide (treatments that work). ed 4 Oxford University Press: New York.

Katon WJ: Clinical practice: panic disorder, *N Engl J Med* 354(22):2360, 2006.

Raffa SD et al.: Relapse following combined treatment discontinuation in a placebo-controlled trial for panic disorder, *J Nerv Ment Dis* 196(7):548–555, 2008.

BASIC INFORMATION

DEFINITION

Panniculitis refers to inflammation of subcutaneous fat and is usually associated with a systemic disease. Panniculitis can be separated into groups based on histopathologic findings from a skin biopsy, depending on where the cellular infiltrates are more predominantly located. Panniculitis is classified into lobular or septal panniculitis, based on whether the inflammation is seen in the fat lobules or septae, respectively. It can be further classified based on whether the inflammation is associated with or without vasculitis (Table P1-4). Lastly, the inflammatory infiltrate is examined to determine the types of cells involved, that is, lymphocytes, neutrophils, etc.

SYNONYMS

None

ICD-9CM CODES

729.3 Panniculitis, unspecified

ICD-10CM CODES

M79.3 Unspecified panniculitis
M5400 Panniculitis affecting regions of neck and back, site unspecified
M5401 Panniculitis affecting regions of neck and back, occipito-atlanto-axial region
M5402 Panniculitis affecting regions of neck and back, cervical region
M54.03 Panniculitis affecting regions of neck and back, cervicothoracic region
M54.04 Panniculitis affecting regions of neck and back, thoracic region
M54.05 Panniculitis affecting regions of neck and back, thoracolumbar region
M54.06 Panniculitis affecting regions of neck and back, lumbar region
M54.07 Panniculitis affecting regions of neck and back, lumbosacral region
M54.08 Panniculitis affecting regions of neck and back, sacral and sacrococcygeal region
M54.09 Panniculitis affecting regions, neck and back, multiple sites in spine

EPIDEMIOLOGY & DEMOGRAPHICS

The epidemiology of the various panniculitides varies with each disease process. The most common panniculitis is erythema nodosum (refer to chapter on erythema nodosum). Another common panniculitis seen in the clinical setting is lipodermatosclerosis (LDS), which is usually seen in young, overweight females with associated venous insufficiency.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Skin lesions can appear as nonspecific areas of erythema or erythematous nodules and/or plaques. The nodules can be palpated beneath the dermis. Ulceration, atrophy, and sclerosis can be associated clinical features of these lesions.
- The lesions are frequently painful and tender to palpation.
- Associated constitutional symptoms such as low-grade fevers, malaise, fatigue, myalgias, and arthralgias may be present.
- These skin findings usually are found on the lower limbs; however, the location of these lesions can vary with each specific panniculitis, that is, erythema nodosum is found on the pretibial areas of the lower extremities (Fig. P1-6), erythema induratum occurs on the calf, and lupus panniculitis occurs on the upper arms, shoulders, and face.
- Skin findings tend to evolve as the types of inflammatory cells change over the course of a few days.

ETIOLOGY

Panniculitis can be either primary/idiopathic or secondary. Common secondary etiologies can be classified into the following broad categories:

- Infections: bacterial (streptococci), mycobacterial, fungal, parasitic, and viral.
- Inflammatory/connective tissue disease: erythema nodosum, erythema induratum, lipodermatosclerosis, lupus panniculitis, cutaneous polyarteritis nodosa, dermatomyositis-associated panniculitis.
- Malignancy: subcutaneous panniculitis-like type T cell lymphoma.
- Pancreatic disease: pancreatic panniculitis, which is associated with pancreatitis or pancreatic carcinoma.
- Immunodeficiency states: alpha-1 antitrypsin deficiency panniculitis, which is associated with pulmonary and hepatic disease.
- Trauma: cold panniculitis (due to exposure to the cold), traumatic panniculitis, and factitial panniculitis (due to injection of medication or foreign substances into the subcutaneous fat).
- Deposition: calciphylaxis, gout.

Panniculitis can be a sign of an underlying systemic disease. Lupus panniculitis can occur alone or may present before or after the onset of either discoid lupus erythematosus or systemic lupus erythematosus.

FIGURE P1-6 Erythema nodosum secondary to acute sarcoidosis. (From Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- The skin lesions of panniculitis need to be distinguished from other skin lesions that may manifest similarly, such as insect bites, thrombophlebitis, and cellulitis.
- Disorders affecting the deep dermis or fascia (i.e., plaque morphea, eosinophilic fasciitis), benign or malignant tumors manifesting as subcutaneous nodules, and nodules with deep bruising may have similar clinical findings and be difficult to distinguish from panniculitis.

WORKUP

- Diagnosis of panniculitis depends on a thorough history and physical exam, evaluation of patient's risk factors, skin lesion appearance and distribution, as well as any associated clinical findings.
- If the diagnosis is unclear or needs to be confirmed, a deep skin biopsy should be performed.
- The preferred biopsy is an excisional biopsy. Alternatively, a large 6 to 8 mm punch biopsy may be performed.
- The sample can be classified based on the histopathologic findings characteristic of the sample, such as the location of the inflammation, infiltrate composition, and presence or absence of vasculitis.

Although the above often establishes a diagnosis, there are times when it is difficult to accurately diagnose a specific panniculitis. Different forms of panniculitides have similar clinical findings while others are rare, complicating the presentation. Biopsy specimens may be too superficial to assess for the involvement of the subcutaneous fat or to assess for the presence of a vasculitis. Inflammation of the subcutaneous fat is a changing process, with varying histologic findings as well as physical characteristics of skin lesions based on the stage of evolution. Cellular infiltrates may not be confined to one location in the subcutaneous fat, and may overlap between septa and lobules (Figure P1-7).

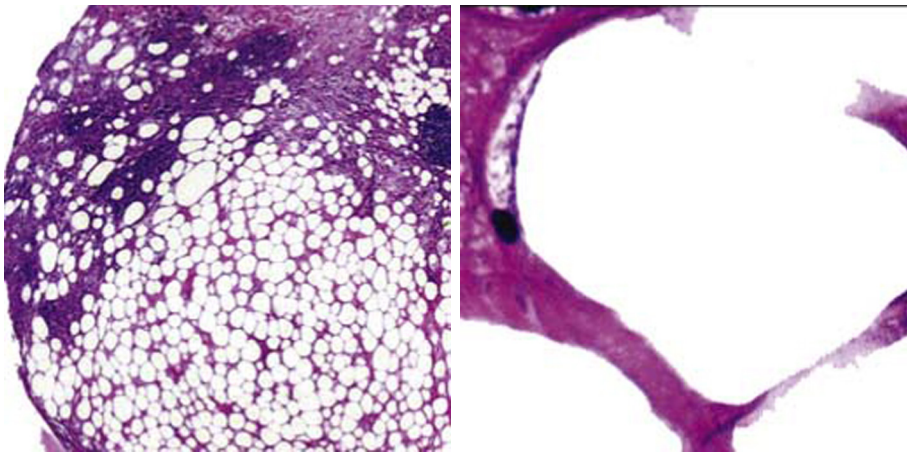


FIGURE P1-7 Mixed lobular and septal panniculitis. (From Hochberg MC et al (eds): Callen JP and Requena L: Cutaneous vasculitis and panniculitis. In *Rheumatology,* ed 6, Philadelphia, 2015, Elsevier Mosby, pp 1350.)

TABLE P1-4 Classification of Panniculitis

I. Without prominent vasculitis
  A. Septal inflammation
    1. Lymphocytic and mixed: erythema nodosum and variants.
    2. Granulomatous: palisaded granulomatous diseases, sarcoidosis, subcutaneous infection: tuberculosis, syphilis.
    3. Sclerotic: scleroderma, eosinophilic fasciitis, lipodermatosclerosis, toxins.
  B. Lobular inflammation
    1. Neutrophilic: infection, ruptured folliculitis and cysts, pancreatic fat necrosis.
    2. Lymphocytic: lupus panniculitis, poststeroid panniculitis, lymphoma/leukemia.
    3. Macrophagic: histiocytic cytophagic panniculitis.
    4. Granulomatous: erythema induratum/nodular vasculitis, palisaded granulomatous diseases, sarcoidosis, Crohn's disease.
    5. Mixed inflammation with many foam cells: α1-antitrypsin deficiency, traumatic fat necrosis.
    6. Eosinophilic: eosinophilic panniculitis, arthropod bites, parasites.
    7. Enzymatic fat necrosis: pancreatic enzyme panniculitis.
    8. Crystal deposits: sclerema neonatorum, subcutaneous fat necrosis of the newborn, gout, oxalosis.
    9. Embryonic fat pattern: lipoatrophy, lipodystrophy.
II. With prominent vasculitis (septal or lobular)
  A. Neutrophilic: leukocytoclastic vasculitis, subcutaneous polyarteritis nodosa, thrombophlebitis, ENL.
  B. Lymphocytic: nodular vasculitis, perniosis, angiocentric lymphomas.
  C. Granulomatous: nodular vasculitis/erythema induratum, ENL, granulomatosis with polyangiitis, Churg-Strauss allergic granulomatosis.
III. Mixed patterns

ENL, Erythema nodosum leprosum.
(From Lee L, Werth V: The skin and rheumatic diseases: panniculitis. In Firestein G et al (eds): *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, Elsevier Saunders, p, 611.)

LABORATORY TESTS

Depending on the suspected underlying disorder, the following workup may be considered:

- Throat swab for rapid streptococcal screen, ASO titer, CBC, PPD, chest radiograph, tissue cultures, and histologic stains for organisms.
- Amylase, lipase.
- Serum alpha-1 antitrypsin level.
- ESR, workup for possible connective tissue disease.
- Further special studies of biopsy sample to determine cell type if malignancy is suspected.

IMAGING STUDIES

- Chest radiography.
- Ankle-brachial index for assessment of peripheral vascular disease.
- Further imaging based on clinical suspicion of disease (i.e., CT scan of abdomen for pancreatitis).

Rx TREATMENT

Treatment of panniculitis is toward treatment of the underlying etiology. Any suspected medications should be discontinued. Appropriate antibiotics to treat underlying infections should be prescribed.

NONPHARMACOLOGIC THERAPY

- Leg elevation, bed rest
- Support stockings

ACUTE GENERAL Rx

- Antiinflammatory medications, such as nonsteroidal antiinflammatory medications (NSAIDs).

CHRONIC Rx

- Based on the underlying disorder. May consider:
- Oral potassium iodide (300 to 900 mg per day).
- Oral corticosteroids.
- Colchicine.
- Hydroxychloroquine.
- Immunosuppressive medications.

REFERRAL

- Dermatology for biopsy of skin lesions.
- Specific specialists based on underlying etiology.

SUGGESTED READINGS

Available online at www.expertconsult.com

RELATED CONTENT

Erythema Nodosum (Related Key Topic)

AUTHOR: **JOANNE SZCZYGIEL CUNHA, M.D.**

SUGGESTED READINGS

Aronson I et al: Panniculitis. In Goldsmith L, et al. (eds): *Fitzpatrick's dermatology in general medicine*, ed 8, McGraw Hill: New York, pp. 732–754.

Callen JP, Requena L: Cutaneous vasculitis and panniculitis. In Hochberg MC, et al. (eds): *Rheumatology*, ed 6, Philadelphia, 2015, Elsevier Mosby, pp 1344–1353.

Lee L, Werth V. The skin and rheumatic diseases: panniculitis. In Firestein G, et al. (eds): *Kelley's textbook of rheumatology*, ed 9, Philadelphia, Elsevier Saunders, pp. 611–612.

James WD, Berger TG, Elston DM: Diseases of subcutaneous fat. In James WD, et al. (eds): *Andrew's Diseases of the Skin Clinical Dermatology*, ed 11, Elsevier Saunders, 2011, pp 477–487.

BASIC INFORMATION

DEFINITION

Paraneoplastic syndromes are a large group of syndromes caused by hormonal, immunologic, or other soluble factors due to the presence of a malignancy. Findings and symptoms are specific to each syndrome. Paraneoplastic syndromes affect most organ systems, predominantly the central and peripheral nervous systems, endocrine system, kidneys, and skin.

ICD-9CM CODES

275.42 Hypercalcemia of malignancy
253.6 Syndrome of inappropriate antidiuretic hormone (SIADH)
255.0 Cushing's syndrome
323 Limbic encephalitis (LE)
334.9 Paraneoplastic cerebellar degeneration (PCD)
358.1 Lambert-Eaton myasthenia syndrome (LEMS)
358.0 Myasthenia gravis (MG)

ICD-10CM CODES

G13.0 Paraneoplastic neuromyopathy and neuropathy
G13.1 Other systemic atrophy primarily affecting central nervous system in neoplastic disease
E83.5 Disorders of calcium metabolism
E73.1 Lambert-Eaton syndrome
E73.2 Other myasthenic syndromes in neoplastic disease

EPIDEMIOLOGY & DEMOGRAPHICS

- Paraneoplastic syndromes may affect as many as 8% of cancer patients.
- See Table P1-5 for epidemiology of each syndrome.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Hypercalcemia of malignancy

- Nausea/vomiting
- Constipation
- Abdominal pain
- Anorexia
- Fatigue
- Altered mental status (from confusion to coma)
- Depression/anxiety
- Renal failure

SIADH

- Headache
- Weakness
- Anorexia
- Nausea
- Vomiting
- Memory impairment, irritability, restlessness
- Mental status changes may progress to obtundation or coma if hyponatremia is >125 mEq/L.

Cushing's syndrome

- Rapid weight gain
- Muscle weakness
- Generalized edema
- Centripetal fat distribution, which often progressed to obesity; limbs are often spared or wasted
- Hypertension
- Characteristic "moon face" due to accumulation of fat deposition in the cheeks
- Skin atrophy, easy bruising, and purple abdominal striae due to skin fragility
- Hyperpigmentation, notably in sun-exposed areas
- Menstrual irregularity, mild hirsutism in women

Limbic encephalitis (LE)

- Slow progression of mood changes
- Hallucinations
- Short-term memory loss
- If hypothalamus is involved, may develop hyperthermia or somnolence.
- Two thirds develop multifocal nervous system involvement.

Paraneoplastic cerebellar degeneration (PCD)

- May develop prodrome of dizziness, nausea, vomiting.
- Ataxia
- Diplopia
- Dysphagia
- Dysarthria

Lambert-Eaton myasthenia syndrome (LEMS)

- Gradual onset of pelvic girdle and lower-extremity weakness, progressing in caudocranial direction
- Hyporeflexia
- Fatigue
- Mild bulbar dysfunction
- Dysautonomia, especially erectile dysfunction

Myasthenia gravis (MG)

- Ocular symptoms: ptosis and diplopia
- Weakness of facial muscles, notably with fatigable chewing
- Lower-extremity weakness that starts distally and progresses proximally
- May progress to involve muscles of respiration and respiratory crisis

Paraneoplastic dermatologic and rheumatologic syndromes

- Acanthosis nigricans
- Dermatomyositis (DM)
- Erythroderma
- Hypertrophic osteoarthropathy
- Leukocytoclastic vasculitis
- Paraneoplastic pemphigus (PNP)
- Polymyalgia rheumatica (PMR)
- Sweet syndrome (acute febrile neutrophilic dermatosis)

ETIOLOGY

Paraneoplastic endocrine syndromes (PES) are due to tumor production of hormones or peptides that lead to metabolic derangements:

Hypercalcemia of malignancy:

Humoral hypercalcemia of malignancy (HHM): 80% of hypercalcemia of malignancy cases. Most commonly due to production of parathyroid hormone–related peptide (PTHrP) in lung and breast cancer (also seen in renal, bladder, and ovarian cancer). More rarely, can see 1,25-dihydroxyvitamin D production from increased 1α-hydroxylase activity in Hodgkin and non-Hodgkin lymphomas or ectopic production of parathyroid hormone (PTH) by the tumor.

Osteolytic activity: 20% of hypercalcemia of malignancy cases. Tumor cells metastasize, infiltrate bone, and produce local factors that stimulate osteoclast activation.

SIADH: production of antidiuretic hormone (arginine vasopressin, atrial natriuretic peptide) by tumor cells

Cushing's syndrome: ectopic ACTH promotes excess production of cortisol and other glucocorticoids from the adrenal glands, which do not respond to normal HPA feedback

TABLE P1-5 Epidemiology of Each Paraneoplastic Syndrome

Condition	Prevalence	Risk Factors
Hypercalcemia of malignancy	Up to 10%-20% of all cancer patients	Squamous cell cancers (lung, head, and neck), breast, kidney, bladder, and ovarian cancers, lymphoma
Syndrome of inappropriate antidiuretic hormone (SIADH)	Up to 1%-2% of all cancer patients Found in 10%-45% of SCLC patients	SCLC
Cushing's syndrome	Approximately 2% in all cancer patients (50% of these are SCLC)	SCLC Pituitary adenoma, benign and malignant adrenal tumors, carcinoid tumors
Limbic encephalitis (LE)	Less than 1%	SCLC Testicular germ cell tumor Breast cancer
Paraneoplastic cerebellar degeneration	Less than 1%	SCLC Hodgkin's lymphoma Breast cancer
Lambert-Eaton myasthenia syndrome (LEMS)	3% of SCLC patients	SCLC, prostate cancer, lymphoma
Myasthenia gravis (MG)	15% of thymoma patients	Thymoma

SCLC, Small cell lung cancer.

Paraneoplastic Syndromes

Paraneoplastic neurologic syndromes (PNS) are due to immune cross-reactivity between tumor cells and components of the nervous system. Tumor-directed antibodies (onconeural antibodies) are produced by the patient in response to a developing cancer. These onconeural antibodies and associated onconeural antigen-specific T lymphocytes inadvertently attack components of the nervous system because of antigenic similarity:

LE, PCD, LEMS, MG: cross-reactive autoantibodies against various components of the central and peripheral nervous system

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Hypercalcemia of malignancy: primary hyperparathyroidism, familial hypocalciuric hypercalcemia, excess calcium intake, vitamin D toxicity, thiazide diuretics. It is important to differentiate between HHM and osteolytic causes of malignancy-associated hypercalcemia because prognosis and response to treatment differ.

SIADH: hypovolemic hyponatremia, reset osmostat, psychogenic polydipsia

Cushing's syndrome: excess glucocorticoid administration, pituitary adenoma, benign or malignant adrenal tumors

LE, PCD, LEMS, MG: multiple sclerosis, stroke, meningitis, encephalitis

WORKUP

- History and physical examination. Box EP1-1 summarizes the evaluation and diagnosis of paraneoplastic syndromes.
- Age-appropriate cancer screening
- EEG, EMG

LABORATORY TESTS

Hypercalcemia of malignancy

- Serum calcium and albumin levels to measure corrected calcium (HHM more common when serum Ca^{2+} >13 mg/dL)
- Ionized serum calcium
- PTH (low to normal)
- PTHrP (elevated)
- 1,25$(OH)_2$D levels (if the above values are inconclusive)

SIADH

- Serum and urine sodium (serum sodium <135 mEq/L or urine sodium >40 mEq/L)
- Serum and urine osmolality (serum osm <280 mOsm/kg of water and/or urine osm >100 mOsm/kg of water)

Cushing's syndrome

- High-dose dexamethasone suppression: 2 mg dexamethasone by mouth every 6 hr for 72 hr, with measurement of urinary 17-hydroxycorticosteroid at 9 A.M. and midnight days 2 and 3
- Low-dose dexamethasone suppression: 1 mg dexamethasone given with measurement of morning serum cortisol
- Dexamethasone suppression test distinguishes pituitary vs. ectopic source of ACTH
- Potassium and glucose should be monitored closely due to increased risk of hypokalemia and hyperglycemia
- **LE:** Anti-Hu, Anti-Ma2, Anti-CRMP5, anti-amphiphysin, CSF analysis
- **PCD:** Anti-Yo, Anti-Hu, Anti-Ma, Anti-Ri, Anti-VGCC, Anti-mGluR1, CSF analysis
- **LEMS:** Anti-VGCC (P/Q), CSF analysis
- **MG:** Anti-AchR, Anti-MuSk, CSF analysis

IMAGING STUDIES

Hypercalcemia of malignancy: CT imaging to evaluate for breast lesion, lung mass, or lymphadenopathy

SIADH: CT imaging to evaluate for brain or lung mass

Cushing's syndrome: CT scan, MRI, or octreotide scan

LE, PCD, LEMS, MG: CT chest, FDG-PET scan, MRI

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Hypercalcemia of malignancy

- Treatment of underlying malignancy, either surgical resection or chemotherapy/radiation of identified tumors
- Fluid resuscitation, typically 1 L bolus followed by 200 to 300 ml/hr to achieve euvolemia; followed by maintenance hydration

SIADH

- Surgical resection of identified tumors
- Fluid restriction

Cushing's syndrome

- Surgical resection of identified tumors

LE, PCD, LEMS, MG

- IVIG
- Plasma exchange

ACUTE GENERAL Rx

Hypercalcemia of malignancy

- Furosemide intravenously once euvolemia has been reached, although clinical efficacy is debatable
- Bisphosphonates, either pamidronate or zoledronic acid intravenous infusions (treatment side effects are renal dysfunction and osteonecrosis of the jaw)
- Calcitonin weight-based dosing, although tachyphylaxis occurs after 48 hours of administration
- Corticosteroids in cases of myeloma and lymphoma
- Hemodialysis in severe cases

SIADH

- If urine sodium is >308 mOsm/kg and patient develops seizure or obtundation, then sodium replacement with hypertonic saline (3%) is indicated
- Sodium should not be corrected at a rate faster than 1 to 2 mEq/L/hr to decrease chances of osmotic demyelination syndrome

Cushing's syndrome

- Management of volume status and blood pressure with diuretics and antihypertensive agents

CHRONIC Rx

- Chronic treatment of all is centered on treatment of the underlying malignancy.

Hypercalcemia of malignancy

- Bisphosphonate therapy every 4 weeks in cases of bone metastasis
- Chronic calcitonin use can be considered

SIADH

- Demeclocycline and vasopressin receptor antagonists (vaptans; conivaptan and tolvaptan, although both are approved for initial administration in hospitalized patients only)
- Cessation of any possible causative medications
- Maintain adequate dietary protein and salt intake

Cushing's syndrome: inhibition of steroid production with ketoconazole, mitotane, metyrapone, aminoglutethimide

LE/PCD: Glucocorticoids, cyclophosphamide, rituximab

LEMS: 3,4-diaminopyridine, pyridostigmine, azathioprine

MG: Pyridostigmine, azathioprine, cyclosporin A, tacrolimus, mycophenolate, rituximab

DISPOSITION

Specific to each condition; however, humoral hypercalcemia of malignancy carries a poor overall prognosis with 30-day mortality of 50%.

REFERRAL

Oncology, endocrinology, neurology, nephrology

PEARLS & CONSIDERATIONS

COMMENTS

- Signs or symptoms of a paraneoplastic syndrome may manifest prior to the identification of a malignancy.
- If paraneoplastic syndrome is suspected, a thorough workup for a tumor is indicated.
- With treatment of the primary tumor, the clinical effects of hypercalcemia of malignancy, SIADH, and Cushing's syndrome may improve or resolve.
- The effects of the neurologic paraneoplastic syndromes can be long-term, due to permanent CNS or PNS damage. In neurologic paraneoplastic syndromes, tumor detection can be difficult, since the immune system, which is causing the syndrome, is also keeping the tumor in check.

PREVENTION

- Smoking cessation
- Age-appropriate cancer screening

PATIENT & FAMILY EDUCATION

Conditions with autoimmune etiology (LE, PCD, LEMS, MG) symptoms may not improve even if tumor is identified and treated, as damage to the nervous system may be sustained or permanent

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **KENNETH D. BISHOP, M.D., Ph.D.** and **JOHN L. REAGAN, M.D.**

SUGGESTED READING

Pelosof LC et al.: Paraneoplastic syndromes: an approach to diagnosis and treatment, *Mayo Clin Proc* 85:838, 2010.

BOX EP1-1 Evaluation and Diagnosis of Paraneoplastic Syndromes

- Characterize abnormality; obtain laboratory studies and biopsy as necessary.
- Carefully elicit any additional symptoms and signs.
- Eliminate common causes.
- If there is no obvious etiology, consider a paraneoplastic syndrome.
- If findings are consistent with a known syndrome, screen for underlying malignancy.
- If signs and symptoms are consistent with a known paraneoplastic syndrome, undertake a search for an unknown primary cancer or recurrence or progression of a known primary tumor.
- Screening should include a careful physical examination with breast, gynecologic, and prostate evaluations; basic hematology, chemistry, and urine studies; chest radiograph; and mammogram.
- Computed tomography (CT) of the abdomen and pelvis or positron emission tomography CT scan is indicated if there are any suspicious symptoms, signs, or laboratory abnormalities. Antibody testing for paraneoplastic neurologic syndromes and/or skin biopsy should be performed as indicated.
- Consider treatment of cancer and/or appropriate palliative treatment, including immunosuppressive therapy for paraneoplastic symptoms when possible.

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders

BASIC INFORMATION

DEFINITION

Paranoid personality disorder (PPD) is characterized by a pattern of pervasive distrust and suspiciousness of others that leads the person to assign malevolence to the motives of others. PPD begins by early adulthood and causes significant distress or impairment in multiple domains of functioning. Individuals must meet four or more of the following criteria:

1. Suspect, without justification, that others are exploiting, harming, or deceiving them.
2. Preoccupied with unwarranted doubts about the loyalty or trustworthiness of friends or associates.
3. Reluctant to confide in others because of unjustified fear that the information will be used against them in a malicious fashion.
4. Infer demeaning or threatening statements from benign remarks or events.
5. Bear grudges for extended periods. For example, PPD patients are unforgiving of perceived or real insults and slights.
6. Perceive attacks on their character that are not apparent to others. Quick to react angrily or to counterattack.
7. Recurrent suspicions, without justification, regarding fidelity of spouse or partner.

SYNONYMS

PPD

ICD-9CM and DSM-5 CODES
301.0
ICD-10CM CODES
F60.0 Paranoid personality disorder

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: From 0.5% to 4.4% in the general population, 10% to 30% in inpatient psychiatric settings, and 2% to 10% in outpatient mental health clinics.
PREDOMINANT SEX: More commonly diagnosed in males in clinical samples.
GENETICS: Increased prevalence of PPD in relatives of probands with schizophrenia and delusional disorder, paranoid type.

CLINICAL PRESENTATION

- Signs of PPD in childhood include solitariness, poor peer relationships, social anxiety, underachievement in school, hypersensitivity, peculiar thoughts and language, and idiosyncratic fantasies.
- As children, these patients may have appeared "odd" or "eccentric" and attracted teasing.
- Their excessive suspiciousness often leads to either overt argumentativeness and recurrent complaining or quiet, hostile aloofness.
- These patients maintain interpersonal distance and may refuse to answer personal questions, saying the information is "nobody's business."
- Misinterpret benign actions by others as malicious assaults. PPD patients may, for example, interpret an honest mistake as a deliberate attempt to harm, a casual humorous remark as a serious character attack, a compliment as a veiled criticism, and an offer of help as a judgment of failure.
- Close relationships are impaired by hypervigilance for threats and associated guardedness. May appear as "cold." Suspiciousness can lead to pathologic jealousy where they gather circumstantial evidence to support contention of betrayal.
- To protect themselves from the perceived malice of others, these patients often maintain a high degree of control of relationships and interactions, constantly questioning the whereabouts, intentions, or actions of the other.
- Often rigid and critical of others but have great difficulty accepting criticism themselves.
- Given their lack of trust of others, PPD patients have an excessive need for self-sufficiency and autonomy.
- Quick to counterattack and may be litigious.
- May join "cults" or groups that share their paranoid belief system.
- In response to stress, may experience very brief psychotic episodes (minutes to hours).

ETIOLOGY

- At this point, limited knowledge about role of genetic loading and neurobiologic vulnerability.
- However, increased prevalence in families of probands with schizophrenia and delusional disorder, paranoid type, suggests possible genetic role.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Schizophrenia, paranoid type, delusional disorder, paranoid type, and mood disorder with psychotic symptoms: require presence of persistent positive psychotic symptoms such as delusions and hallucinations. To give an additional diagnosis of PPD, the personality disorder must be present before the onset of psychotic symptoms and must persist when the psychotic symptoms are in remission.
- Substance-induced paranoia, especially in the context of cocaine, PCP, or methamphetamine abuse or dependence.
- Personality changes caused by a general medical condition that affects the central nervous system.
- Paranoid traits associated with a sensory disability; for example, hearing impairment.
- Increased risk for major depressive disorder, obsessive-compulsive disorder, agoraphobia, and substance abuse or dependence.
- The most common co-occurring personality disorders are schizotypal, schizoid, narcissistic, avoidant, and borderline:
  1. Schizotypal personality disorder includes magical thinking and unusual perceptual experiences.
  2. Schizoid and borderline personality disorders do not have prominent paranoid ideation.
  3. Avoidant personality disorder includes fear of embarrassment.
  4. Narcissistic personality disorder includes the fear that hidden "flaws" or "inferiority" may be revealed.

WORKUP

- History: collateral information is essential to establishing the presence of longstanding interpersonal pattern in multiple domains of the patient's life.
- Physical examination
- Mental status examination

LABORATORY TESTS

Those necessary to rule out medical causes of personality changes

IMAGING STUDIES

Those necessary to rule out medical causes of personality changes

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cognitive-behavioral therapy to help patients control rage, manage perceived criticism, and develop social skills
- Psychodynamic psychotherapy to help patient develop capacity to trust and improve interpersonal functioning.

ACUTE GENERAL Rx

Benzodiazepines or low-dose antipsychotics to control hostility and paranoia

CHRONIC Rx

- Low-dose antipsychotic medication. Increase dose in small increments to minimize risk of side effects.
- Selective serotonin reuptake inhibitors if comorbid depression, obsessive-compulsive disorder, or agoraphobia
- Substance abuse treatment if comorbid dependence

COMPLEMENTARY & ALTERNATIVE MEDICINE

No evidence of efficacy in PPD

DISPOSITION

- Severity is variable and course is chronic. Often lifelong difficulty maintaining intimate relationships.
- At increased risk for major depressive disorder, obsessive-compulsive disorder, agoraphobia, and substance abuse or dependence.
- In some cases, PPD is a prepsychotic antecedent of delusional disorder, paranoid type.

REFERRAL

- If pharmacotherapy or psychotherapy is contemplated
- If patient's social or occupational functioning is impaired

PEARLS & CONSIDERATIONS

COMMENTS

- Illness exacerbates these patients' sense of vulnerability.
- Communicating personal information to the physician challenges the guarded, self-protective approach to others and will often heighten PPD patients' fear that the physician will harm them.
- The encounter with the physician intensifies hypervigilance. As a result, innocuous or even overtly helpful behaviors by the physician may be perceived as manipulating or threatening.
- With the perceived threat, these patients will often confront and challenge the physician on their motives and their rationale for diagnosis and treatment. Conflict and argument are not uncommon.
- Thus establishing an alliance with the patient can be challenging.
- Faced with such a patient, physicians may understandably react defensively to unfounded suspicion or distance and not respond to the patient's concerns. Both responses increase the patient's anxiety and paranoia.
- Management guidelines:
  1. Convey intent "to do no harm."
  2. Address the patient's fears and concerns, no matter how irrational, in a clear, direct, and detailed manner.
  3. Remember that behind the patient's hostility lie fears that are real to him or her.
  4. Maintain a professional and neutral stance.
  5. Responding with too much warmth and friendliness will intensify paranoia.
  6. Give patient detailed and factual information about treatment plan.
  7. Give patient as much control as possible, including maximum participation at each decision node.
  8. Do not personalize patient's hostility and suspicion, but understand his or her distrust as an attempt to manage intense fear.
  9. Validate patient's concerns about the diagnosis or treatment plan.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Paranoid Personality Disorder (Patient Information)

AUTHOR: **JOHN Q. YOUNG, M.D., M.P.P.**

SUGGESTED READINGS

Angstman KB et al.: Personality disorders: review and clinical application in daily practice, *Am Fam Physician* 84:1253–1260, 2011.

Dhawan N, Kunik ME, Oldham J, Coverdale J: Prevalence and treatment of narcissistic personality disorder in the community: a systematic review, *Compr Psychiatry* 51:333–339, 2010.

Quirk SE, El-Gabalawy R, Brennan SL, et al.: Personality disorders and physical comorbidities in adults from the United States: data from the National Epidemiologic Survey on Alcohol and Related Conditions, *Social Psychiatry Psychiatr Epidemiol Oct* 15, 2014. [E-pub ahead of print].

BASIC INFORMATION

DEFINITION

It is important to distinguish between paraphilia and paraphilic disorders. The term *paraphilia* applies to sexual arousal that is repeatedly and intensely stimulated by thoughts and/or behavior elicited by stimuli other than that which is associated with consensual mature human partners. For example, sexual arousal that is repeatedly and intensely stimulated by **activity** such as rubbing up against an unsuspecting person or by a **target preference** such as shoes or diapers would be identified as paraphilia. To meet the DSM-5 criteria for a **paraphilic disorder,** there must be the presence of a paraphilia over at least a 6-month period that is causing distress or impairment to an individual or harm or risk of harm to others. Paraphilia that does not meet DSM-5 criteria is not considered a mental illness, but individuals with paraphilia thoughts and behavior may still present for treatment. It is not unusual for a person to express more than one paraphilic interest.

SYNONYMS

Atypical sexual behavior
Hyper-sexuality
Sexual impulsivity disorder

ICD-9CM and DSM-5 CODES
302.9
ICD-10-CM

F65	Paraphilias
F65.0	Fetishism
F65.1	Transvestic fetishism
F65.2	Exhibitionism
F65.3	Voyeurism
F65.4	Pedophilia
F65.5	Sadomasochism
F65.50	Unspecified
F65.51	Sexual masochism
F65.52	Sexual sadism
F65.8	Other paraphilias
F65.81	Frotteurism
F65.89	Other paraphilias
F65.9	Paraphilia, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The incidence of paraphilias and paraphilic disorders in male and female populations is unknown due to: (1) the secretive nature of the behavior; (2) changes in criterion over time; and (3) differences between cultural definitions of abnormality. It is estimated, however, that only about 1% to 2% of men presenting with paraphilia behavior are distressed by their behavior and meet the criteria of paraphilic disorder.

PEAK INCIDENCE: Although prepubescent individuals can be diagnosed with a paraphilic disorder, diagnosis is usually made post pubescence during late adolescence and early adulthood.

PREVALENCE: Prevalence rates for paraphilia and paraphilic disorders are extremely difficult to report with any certainty. While the seemingly unlimited variety of sexually arousing material available on the internet suggests a wide range of potentially sexually arousing stimulation that human males and females may be interested in, there are no data to accurately describe whether or not such interests are reflective of paraphilia prevalence rates. Studies attempting to provide prevalence rates of paraphilias and paraphilic disorders vary widely in experimental design and clinical definitions leaving little confidence in overall prevalence rates.

PREDOMINANT SEX AND AGE: Males are at a much higher risk than females to experience paraphilias and paraphilic disorders. Although lacking in convincing research, studies estimate the male to female ratio to be 20:1 or greater. Paraphilia behavior can begin in early childhood but is manifested most commonly in late adolescence and early adulthood and may be expressed throughout the life cycle. Paraphilia behavior and paraphilic disorders tend to become less intense and less frequent in older age.

GENETICS: Although the literature points to some possible genetic influences on sexual interest in males and females, it is inconclusive that any genetic influences exist regarding the development of paraphilias or paraphilic disorders.

RISK FACTORS: Possible risk factors associated with paraphilia and paraphilic disorders include:

1. Male gender
2. Low self-esteem in childhood and adolescence
3. Perceived lack of availability of consensual sexual partners
4. Inhibition of normative sexual outlets often related to extreme religiosity or negative sexual messages from parents or care takers
5. Early exposure to paraphilia stimulation and opportunity for repeated exposure

PHYSICAL FINDINGS & CLINICAL PRESENTATION:

1. Usually diagnosed in late adolescence or early adulthood
2. May first be diagnosed in males as erectile dysfunction or delayed ejaculation during consensual sexual relations when paraphilic stimuli are absent
3. May be identified as a result of illegal offenses in some cases such as pedophilia, voyeurism, exhibitionism, or stealing of clothing
4. Paraphilic behavior may be so time consuming or obsessive compulsive that it interferes with work, education, relationships, and/or productivity
5. Certain paraphilic behaviors may put an individual at risk for disease and/or physical harm (self-inflicted or from others)

ETIOLOGY

There are no conclusive theories that satisfactorily explain the etiology of paraphilias and paraphilic disorders. It is quite possible, however, that the combination of biological vulnerability and a conditioned learning process lead to paraphilic interests. Males are more at risk for developing paraphilic behavior perhaps because males are more easily aroused sexually and are more aware of their sexual arousal because of their erectile response. A repeated association of an erection response to certain visual, auditory, olfactory, imagined, or tactile stimuli may condition paraphilia behavior.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Medical: Dementia, Substance Intoxication, Seizures, Dissociative Fugue State, Frontal Parietal Traumatic Brain Injury, Sexsomnia.
- Psychiatric: Manic Episode, Schizophrenia, Dissociative Disorder, Post-Traumatic Stress Disorder, Erotomania Delusion, Non-paraphilic Hyper-sexuality Disorder (i.e., Compulsive Masturbation, Protracted Promiscuity, Cybersex Dependence, Pornography Dependence), Obsessive Compulsive Disorder, Adjustment Disorder, Impulse Control Disorder.

WORKUP

- A very detailed psychosexual developmental history is necessary and must include a review of sexual experiences with others as well as fantasies and stimuli that accompany masturbation. Paraphilic interests are typically first manifested in childhood or adolescence and persist to a greater or lesser degree throughout life. Such interests are often essential for sexual arousal and must be intense and persistent to meet DSM-5 criteria.
- A detailed psychiatric assessment is necessary to make a differential diagnosis and to identify common co-morbid conditions that often accompany paraphilic interests such as low self-esteem and deficits in social skills.
- A physical examination should be performed in cases in which possible physical injury may have resulted from paraphilic behavior such as in cases of masochism or unusual genital, breast, or anal stimulation.
- Information from sexual partners (if available) is helpful for diagnosis and treatment.
- Information regarding the impact of paraphilic behavior on relationships, finances, work productivity, and legal problems is necessary to determine the diagnosis of paraphilic disorder.

TREATMENT

Pharmacologic agents may be used to suppress sexual fantasies, sexual desire, sexual urges, and obsessive compulsive behavior associated with paraphilia. Pharmacologic therapy is used as an adjunct therapy to psychotherapy and not a monotherapy.

PHARMACOLOGIC THERAPY

- Long-acting gonadotropin-releasing hormones: (used for dangerous sex offenders where there is a risk of harm to self or others)

  - Triptorelin (Trelstar)
  - Leuprolide (Lupron)
  - Goserelin (Zoladex)
- Antiandrogens: (used for dangerous sex offenders where there is a risk of harm to self or others).
  - Medroxyprogesterone acetate (Depo-Provera)
  - Spironolactone (Aldactone)
- Selective serotonin reuptake inhibitors (SSRIs): (used for treatment of less serious paraphilia behavior that has obsessive compulsive features)
  - Fluvoxamine (Luvox)
  - Fluoxetine (Prozac)

NONPHARMACOLOGIC THERAPY

Individually tailored therapy that addresses patient needs and comorbid mental health problems combined with a strong alliance with the therapist are important ingredients for successful treatment outcome with paraphilia and paraphilic disorders. Common psychotherapeutic interventions include the following:

- Cognitive behavior therapy
- Social skills training
- Relapse prevention

ACUTE GENERAL Rx

Acute therapy begins with a comprehensive assessment of the intensity, frequency, duration, and topography of the paraphilia and assessment of co-morbid mental health problems. Paraphilic disorders will be determined by the distress level and risk of harm to self and to others. If it is determined that there is a risk of harm then therapy should begin with a consideration of pharmacotherapy in conjunction with psychotherapy. Psychotherapy involves building an alliance with the patient to increase motivation and encourage full disclosure of all aspects of the paraphilia thoughts and behaviors. Therapy typically includes techniques and strategies to suppress and manage paraphilia thoughts and behaviors along with strategies to increase positive social skills, constructive use of time, challenging distortions in thinking, and managing comorbid mental health problems.

CHRONIC Rx

It is unlikely that paraphilia thoughts and desires will remit completely and, therefore, strategies for long-term management should be implemented. In cases of paraphilic disorders, lifetime management involves awareness of all personal risk factors for relapse, plans for managing risks of relapse, building positive support systems, building constructive competing behaviors that interfere with opportunities for expressing and acting on paraphilic behavior and commitment to long-term therapy. **Full remission** of a paraphilic disorder is established if there is a 5-year period without stress or impairment or harm to self or others related to paraphilic behavior.

REFERRAL

Diagnosis complicated by untreated or poorly managed comorbid psychiatric conditions or active substance abuse.

Consultation for individuals with mental retardation or other cognitive impairments should be considered.

PEARLS & CONSIDERATIONS

- Since there is often a great deal of shame associated with paraphilic disorders, health care professionals must be especially sensitive, nonjudgmental, and supportive of patients presenting with problems in this area.
- Treatment of paraphilic disorders should focus on how the paraphilic behavior is impacting relationships, productivity, employment, education, and finances.
- If a significant other is available, he or she should be included in the assessment process in order to add to a comprehensive understanding of the problem and in order to correct any misunderstandings.

SUGGESTED READINGS

Available online at www.expertconsult.com

AUTHOR: **JOHN P. WINCZE, Ph.D.**

SUGGESTED READINGS

Kleinplatz PJ: The paraphilias: an experimental approach to "dangerous" desires. In Binik, Hall, editors: *Principles and practice of sex therapy*, ed 5, New York, 2014, Guilford Press.

Quinsey VL: Pragmatic and Darwinian views of paraphilias, *Arch Sexual Behav* 41:217–220, 2012.

Laws DR, O'Donoghue WT: *Sexual deviance: theory, assessment, and treatment*, New York, 2008, Guilford Press.

www.Emedicine.medscape.com/article/29149-overview.

BASIC INFORMATION

DEFINITION

Idiopathic Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized clinically by rigidity, tremor, postural instability, and slowness of movement (bradykinesia).

SYNONYMS

Paralysis agitans

ICD-9CM CODES

332.0	Idiopathic Parkinson's disease, primary
332.1	Parkinson's disease, secondary

ICD-10CM CODES

G20	Parkinson's disease
G21.11	Neuroleptic induced parkinsonism
G21.1	Other drug-induced secondary parkinsonism
G21.2	Secondary parkinsonism due to other external agents
G21.3	Postencephalitic parkinsonism
G21.4	Vascular parkinsonism
G21.8	Other secondary parkinsonism
G21.9	Secondary parkinsonism, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE

- Affects more than 1 million people in North America. It is the second most common neurodegenerative disease worldwide.
- In age group <40 yr, <5/100,000 are affected.
- In those aged >70 yr, 700/100,000 are affected.
- Highest incidence in whites, lowest incidence in Asians and African Americans

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Tremor (Fig. P1-8)—typically a resting tremor with a frequency of 4 to 6 Hz that is often first noted in the hand as a pill-rolling tremor (thumb and forefinger). Can also involve the leg and lip. Tremor improves with purposeful movement. Usually starts asymmetrically.
- Rigidity—increased muscle tone that persists throughout the range of passive movement of a joint. This, too, is usually asymmetric at onset.
- Akinesia/bradykinesia—slowness in initiating movement
- Postural instability—tested by "pull test." Ask patient to stand in place with back to examiner. Examiner pulls patient back by the shoulders, and proper response would be to take no steps back or very few steps back without falling. Retropulsion is a positive test as is falling straight back. This is not usually severe early on. If falls and postural reflexes are greatly impaired early on, then consider other disorders.
- Masked facies (hypomimia)—face seems expressionless, giving the appearance of depression. Decreased blink; often there is excess drooling.
- Gait disturbance
- Stooped posture, decreased arm swing
- Difficulty initiating the first step; small shuffling steps that increase in speed (festinating gait). Steps become progressively faster and shorter while the trunk inclines further forward.
- Other complaints and findings early on include handwriting becoming smaller (micrographia), and voice becoming softer and often "gruffer" (hypophonia).

ETIOLOGY

- Unknown
- Most cases are sporadic, with age being the most common risk factor, although there is probably a combination of both environmental and genetic factors contributing to disease expression. There are rare familial forms with at least seven different genes identified; these include the parkin gene, which is a significant cause of early-onset autosomal recessive PD and LRRK2, which is the most common cause of familial and sporadic parkinsonism.

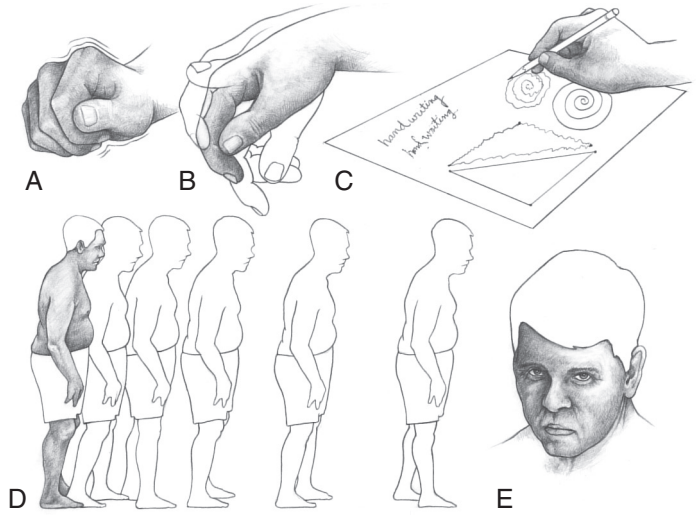


FIGURE P1-8 The parkinsonian syndrome. A, The "pill-rolling" tremor. **B,** Tremor that can worsen with emotional stress. **C,** Handwriting abnormalities, which include micrographia. **D,** Typical posture and gait, which becomes faster (festination). **E,** Lack of facial expression as well as "stare" from decreased blinking. (From Remmel KS et al: *Handbook of symptom oriented neurology,* ed 3, St Louis, 2002, Mosby.)

DIAGNOSIS

A clinical diagnosis can be made based on a comprehensive history and physical examination. The four cardinal signs used to diagnose PD are (mnemonic = TRAP):

1. **T**remor (resting, typically 4-6 Hz)
2. **R**igidity, of the cogwheel type
3. **A**kinesia/bradykinesia—slowness of movement
4. **P**ostural instability—failure of postural "righting" reflexes leading to poor balance and falls

One need not demonstrate all four cardinal signs to make a presumptive diagnosis of PD and begin treatment.

DIFFERENTIAL DIAGNOSIS

- Multiple system atrophy—distinguishing features include autonomic dysfunction (including urinary incontinence, orthostatic hypotension, and erectile dysfunction), parkinsonism, cerebellar signs, and normal cognition.
- Diffuse Lewy body disease—parkinsonism with concomitant dementia: patients often have early hallucinations and fluctuations in level of alertness and mental status.
- Corticobasal degeneration—often begins asymmetrically with apraxia, cortical sensory loss in one limb, and sometimes alien limb phenomenon.
- Progressive supranuclear palsy—tends to have axial rigidity greater than appendicular (limb) rigidity. These patients have early and severe postural instability. Hallmark is supranuclear gaze palsy that usually involves vertical gaze (especially downward) before horizontal.
- Essential tremor—bilateral postural and action tremor
- Secondary (acquired) parkinsonism
  1. Iatrogenic—any of the neuroleptics and antipsychotics. The high-potency D_2-blocker neuroleptics are most likely to cause parkinsonism. Quetiapine is an atypical antipsychotic with lower risk of causing parkinsonism. Metoclopramide can also cause parkinsonism. Abuse of methamphetamine has been recently linked to risk of PD.
  2. Postinfectious parkinsonism—von Economo's encephalitis
  3. Parkinson's pugilistica—after repeated head trauma
  4. Toxins (e.g., MPTP, manganese, carbon monoxide)
  5. Cerebrovascular disease "vascular parkinsonism" (basal ganglia infarcts); often lower limbs (especially gait) affected more than upper extremities

WORKUP

1. Identification of clinical signs and symptoms associated with PD (see "Physical Findings") and elimination of conditions that may mimic it with a comprehensive history and physical examination
2. Routine genetic testing is not recommended.

IMAGING STUDIES

Computed tomographic (CT) scan has almost no role in investigations. Magnetic resonance imaging (MRI) of the head may sometimes distinguish between idiopathic PD and other conditions that present with signs of parkinsonism (see "Differential Diagnosis").

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Physical therapy, patient education and reassurance, treatment of associated conditions (e.g., depression) are important. A safe, practical, and reasonable exercise regimen must be encouraged, individualized to the patient's access to resources and motivation. Recent trials reveal that t'ai chi training is effective in reducing balance impairment and falls and improving functional capacity.
- Avoidance of drugs that can induce or worsen parkinsonism: neuroleptics (especially high potency), certain antiemetics (prochlorperazine, trimethobenzamide), metoclopramide, nonselective MAO inhibitors (may induce hypertensive crisis), reserpine, methyldopa

ACUTE GENERAL Rx

- There continues to be controversy whether levodopa or dopamine agonists should be the initial treatment. In younger patients, agonists are usually the drug of choice; in patients >70 yr, levodopa is typically the preferred initial therapy.
- It is appropriate to initiate pharmacotherapy when required by symptoms; prior practice of waiting for limitation of ADLs is now outdated. Fig. EP1-9 describes an approach to patients with parkinsonism.
- Motor complications do develop during the course of the disease and likely reflect the combination of disease progression together with the side effects of dopaminergic medications.

CHRONIC Rx

- Levodopa therapy
  1. Cornerstone of symptomatic therapy—should be used with a peripheral dopa decarboxylase inhibitor (carbidopa) to minimize side effects (nausea, lightheadedness, postural hypotension). The combination of the two drugs is marketed under the trade name Sinemet. Levodopa therapy has been found to reduce morbidity and mortality in PD patients.
  2. Usual starting dose is 25/100 mg (carbidopa/levodopa) tid 1 hr before (or after) meals.
  3. Controlled-release preparations (e.g., Sinemet CR) are available, but their use should be deferred to a neurologist.
  4. Stalevo (combination Sinemet and entacapone, a COMT inhibitor). Useful for patients with motor fluctuations (wearing off); has no role in treating early patients with PD.
- Dopamine receptor agonists (ropinirole and pramipexole) are not as potent as levodopa, but they are often used as initial treatment in younger patients to attempt to delay the onset of complications (dyskinesias, motor fluctuations) associated with levodopa therapy. These medications are more expensive than levodopa. In general, they cause more side effects than levodopa, including nausea, vomiting, light-headedness, peripheral edema, confusion, and somnolence. They can also cause impulse control behaviors such as hypersexuality, binge eating, and compulsive shopping and gambling. Presence of these must be assessed at each visit.
  1. Ropinirole: initial dose is 0.25 mg tid
  2. Pramipexole: initial dose is 0.125 mg tid
- MAO-B inhibitors can be used as monotherapy early in the disease or as adjunctive therapy in later stages; they have been shown to have milder symptomatic benefit than dopamine agonists or levodopa. Well tolerated and easy to titrate. Concurrent use of stimulants and sympathomimetics should be avoided. Certain food restrictions may apply.
  1. Rasagiline: initial dose is 0.5 mg qd, then 1 mg daily. A recent study, ADAGIO, suggests that 1 mg rasagiline may have disease-modifying benefits, but results must be interpreted with caution.
  2. Selegiline: Usual dose, 5 mg bid with breakfast and lunch. Has amphetamine byproduct so has mild stimulant-like effects, which can be beneficial in some patients.
- Amantadine (unclear mechanism of action, but reported to modulate the dopamine and glutamate systems in the CNS) can be used alone early in the disease. It is especially useful in the treatment of dyskinesias. Dosage is 100 mg tid (titrate q week from 100 mg qd). Must adjust for elderly and renal impairment. The most notable side effect, especially in the elderly, is confusion.
- Anticholinergic agents are only helpful in treating tremor and drooling in patients with PD. Potential side effects include constipation, urinary retention, memory impairment, and hallucinations. They should be avoided in the elderly.
  1. Trihexyphenidyl: initial dose, 1 mg PO tid
  2. Benztropine: usual dose, 0.5 to 1 mg qd or bid

SURGICAL OPTIONS

- Pallidal (globus pallidus interna) and subthalamic deep-brain stimulation (subthalamic nucleus) are currently the surgical options of choice for patients with advanced PD; similar improvement in motor function and adverse effects have been reported after either procedure. Compared with ablative procedures, DBS has the advantage of being reversible and adjustable. Thalamic DBS may be useful for refractory tremor. It improves the cardinal motor symptoms, extends medication "on" time, and reduces motor fluctuations during the day. In general, patients are likely to benefit from this therapy if they show a clear response to levodopa. Therefore, when considering DBS, patients should be evaluated for motor response to levodopa by stopping levodopa overnight and evaluating motor response before and after a dose of levodopa.
- Surgery is often limited to patients with disabling, medically refractory problems, and patients must still have a good response to L-dopa to undergo surgery. Yet for many patients, earlier stimulation might provide an improved motor benefit before disability from other symptoms has occurred and should be considered at an earlier stage of PD. DBS results in decreased dyskinesias, fluctuations, rigidity, and tremor.

DISPOSITION

PD usually follows a slowly progressive course leading to disability over the course of several years. However, every patient will progress individually, and patients should be reassured that this diagnosis does not, by definition, result in being either wheelchair- or bed-bound.

REFERRAL

- Neurology consultation is recommended at initial diagnosis of PD.
- Exercise is important for all patients with PD.
- Participation in outpatient physical therapy program is recommended for patients with moderate to advanced disease.

PEARLS & CONSIDERATIONS

- Asymmetry of symptoms at onset is very useful in distinguishing PD from other causes of parkinsonism.
- Although resting tremor is a common presenting symptom, up to 25% of patients with idiopathic PD do not have classic resting tremor.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Parkinson's Disease (Patient Information)

AUTHOR: **U. SHIVRAJ SOHUR, M.D., PH.D.**

EVIDENCE

Abstract[1]

Background:

Preladenant is an adenosine 2A (A_{2A}) receptor antagonist. In animal models of Parkinson's disease, preladenant monotherapy improves motor function without causing dyskinesia and, as an adjunct to levodopa, it improves motor function without worsening dyskinesia. We aimed to assess the efficacy and safety of preladenant in patients with Parkinson's disease and motor fluctuations who were receiving levodopa and other antiparkinsonian drugs.

Methods:

In this phase 2, dose-finding trial, patients with Parkinson's disease who were receiving levodopa were enrolled and treated at 44 sites in 15 countries between December, 2006, and November, 2008. Assignment to treatment was done centrally with an interactive voice response system, according to a block randomisation schedule that was computer generated by the sponsor. Patients were assigned to receive 1, 2, 5, or 10 mg oral preladenant twice daily, or matching placebo for 12 weeks. Patients, study staff, investigators, and all sponsor personnel were masked to treatment assignment. The primary outcome was change in mean daily off time from baseline to week 12, as assessed by home diaries. Efficacy analysis included all patients who received at least one dose of study drug and had data for assessments after baseline. This trial is registered with ClinicalTrials.gov, number NCT00406029.

Findings:

253 patients were randomised to receive preladenant (1 mg [n = 49], 2 mg [n = 49], 5 mg [n = 49], 10 mg [n = 57]) or placebo (n = 49), of whom 234 on preladenant (1 mg [n = 47], 2 mg [n = 48], 5 mg [n = 45], 10 mg [n = 49]) and placebo (n = 45) were eligible for the efficacy analysis. Mean daily off time from baseline to week 12 was reduced versus placebo in patients on 5 mg preladenant (difference −1.0 h, 95% CI −2.1 to 0.0; p = 0.0486) and 10 mg preladenant (−1.2 h, −2.2 to −0.2; p=0.019). Changes in mean daily off time versus placebo were not significant for 1 mg preladenant (0.2 h, −0.9 to 1.2; p = 0.753) or 2 mg preladenant (−0.7 h, −1.7 to 0.3; p = 0.162). The most common adverse events in the combined preladenant group versus placebo were worsening of Parkinson's disease (22 [11%] *vs* 4 [9%]), somnolence (20 [10%] *vs* 3 [6%]), dyskinesia (18 [9%] *vs* 6 [13%]), nausea (17 [9%] *vs* 5 [11%]), constipation (15 [8%] *vs* 1 [2%]), and insomnia (15 [8%] *vs* 4 [9%]).

Interpretation:

5 and 10 mg preladenant twice daily might be clinically useful to reduce off time in patients with Parkinson's disease and motor fluctuations. Ⓐ

Abstract[2]

Compensatory cerebral mechanisms can delay motor symptom onset in Parkinson's disease. We aim to characterize these compensatory mechanisms and early disease-related changes by quantifying movement-related cerebral function in subjects at significantly increased risk of developing Parkinson's disease, namely carriers of a leucine-rich repeat kinase 2-G2019S mutation associated with dominantly inherited parkinsonism. Functional magnetic resonance imaging was used to examine cerebral activity evoked during internal selection of motor representations, a core motor deficit in clinically overt Parkinson's disease. Thirty-nine healthy first-degree relatives of Ashkenazi Jewish patients with Parkinson's disease, who carry the leucine-rich repeat kinase 2-G2019S mutation, participated in this study.

Twenty-one carriers of the leucine-rich repeat kinase 2-G2019S mutation and 18 non-carriers of this mutation were engaged in a motor imagery task (laterality judgments of left or right hands) known to be sensitive to motor control parameters. Behavioral performance of both groups was matched. Mutation carriers and non-carriers were equally sensitive to the extent and biomechanical constraints of the imagined movements in relation to the current posture of the participants' hands. Cerebral activity differed between groups, such that leucine-rich repeat kinase 2-G2019S carriers had reduced imagery-related activity in the right caudate nucleus and increased activity in the right dorsal premotor cortex. More severe striatal impairment was associated with stronger effective connectivity between the right dorsal premotor cortex and the right extrastriate body area.

These findings suggest that altered movement-related activity in the caudate nuclei of leucine-rich repeat kinase 2-G2019S carriers might remain behaviorally latent by virtue of cortical compensatory mechanisms involving long-range connectivity between the dorsal premotor cortex and posterior sensory regions. These functional cerebral changes open the possibility to use a prospective study to test their relevance as early markers of Parkinson's disease. Ⓐ

Evidence-Based Reference

Hauser RA et al.: Preladenant in patients with Parkinson's disease and motor fluctuations: a phase 2, double-blind, randomised trial, *Lancet Neurol* 10:221–229, 2011. Ⓐ

Van Nuenen BFL et al.: Cerebral pathological and compensatory mechanisms in the premotor phase of leucine-rich repeat kinase 2 parkinsonism, *Brain* 135:3687–3698, 2012. Ⓐ

SUGGESTED READINGS

Connolly BS, Lang EL: Pharmacologic treatment of Parkinson disease, a review, *JAMA* 311(16):1670–1683, 2014.

Follett KA et al.: Pallidal versus subthalamic deep-brain stimulation for Parkinson's disease, *N Engl J Med* 362:2077–2091, 2010.

Goetz C et al.: Evidence-based medical review update: pharmacological and surgical treatments of Parkinson's disease: 2001 to 2004, *Mov Disord* 20:523, 2005.

Kuehl BM: Meth use linked to risk of Parkinson disease, *JAMA* 306:814, 2011.

Li F et al.: T'ai chi and postural stability in patients with Parkinson's disease, *N Engl J Med* 366:511–519, 2012.

Machado A et al.: Deep brain stimulation: what can patients expect from it? *Clev Clin J Med* 79:113, 2012.

Miyasaki J et al.: Practice parameter: initiation of treatment for Parkinson's disease: an evidence-based review, Report of the Quality Standards Subcommittee of the American Academy of Neurology, *Neurology* 58:11–17, 2002.

Okun MS: Deep brain stimulation for Parkinson's disease, *N Engl J Med* 367:1529–1538, 2012.

Samii A et al.: Parkinson's disease, *Lancet* 363(9423):1783, 2004.

Schuepbach WM et al.: Neurostimulation for Parkinson's disease with early motor complications, *N Engl J Med* 368:610–622, 2013.

Suchowersky O et al.: Practice parameter: neuroprotective strategies and alternative therapies for Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology, *Neurology* 66:976–982, 2006.

Tetrud J et al.: Treatment challenges in early stage Parkinson's disease, *Neurol Clin* 22:S19, 2004.

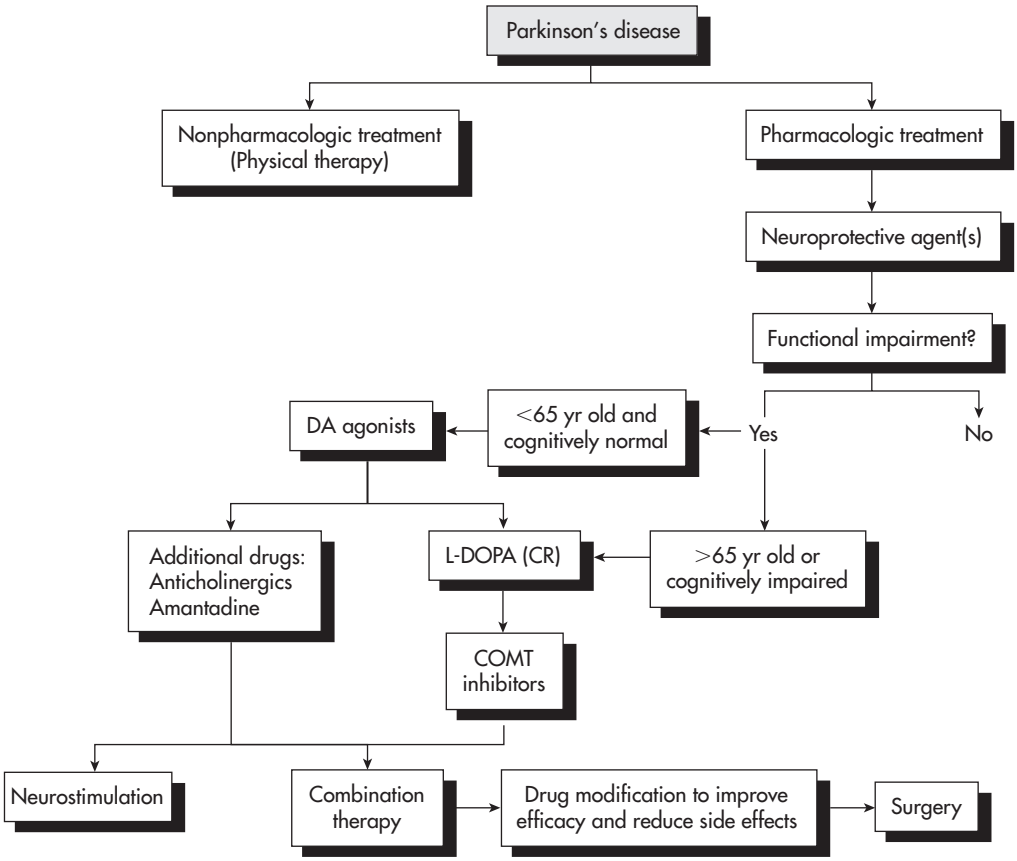


FIGURE EP1-9 Diagrammatic representation of a therapeutic approach to patients with parkinsonism. *COMT,* Catechol-O-methyl transferase; *CR,* controlled release; *DA,* dopamine. (Modified from Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

BASIC INFORMATION

DEFINITION

Paronychia is a localized superficial infection or abscess of the lateral and proximal nail fold. Paronychia may be acute or chronic.

SYNONYMS

Nail bed infection
Nail bed abscess

ICD-9CM CODES
681.9 Paronychia
ICD-10CM CODES
L03.019 Cellulitis of unspecified finger

EPIDEMIOLOGY & DEMOGRAPHICS

- Acute paronychia affects males and females equally.
- Chronic paronychia is more common in females than males (9:1).
- Acute paronychia most often occurs in children.
- Chronic paronychia usually presents in the fifth or sixth decade of life.
- Paronychia is the most common infection of the hand.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute paronychia usually presents with the sudden onset of redness, swelling, and pain with abscess or cellulitis formation in the nail fold. Fluid with purulence is often present.
- Chronic paronychia is insidious, presenting with mild swelling and erythema of the nail folds.
- Acute paronychia usually involves only one finger.
- Chronic paronychia may involve more than one finger.
- Acute paronychia usually involves the thumb.
- Chronic paronychia commonly involves the middle finger.

ETIOLOGY

- Any disruption of the seal between the proximal nail fold and the nail plate can cause paronychial infections.
- Acute paronychia is almost always bacterial in origin (e.g., methicillin-sensitive *Staphylococcus aureus* [most common, but also consider MRSA], *Streptococcus pyogenes, Enterococcus faecalis, Proteus* and *Pseudomonas* species, and anaerobes).
- Chronic paronychia is commonly caused by *Candida albicans* (70%), with bacterial organisms accounting for the remaining 30%.
- Trauma, nail biting, hangnails, diabetes, and long-term exposure to water are common predisposing features of paronychia.

DIAGNOSIS

The diagnosis of paronychia is self-evident on physical examination.

DIFFERENTIAL DIAGNOSIS

- Herpetic whitlow caused by herpes simplex
- Pyogenic granuloma
- Viral warts
- Ganglions
- Squamous cell carcinoma

WORKUP

A workup is usually not pursued unless there is treatment failure.

LABORATORY TESTS

- Gram stain and culture any purulent drainage.
- Potassium hydroxide mount may show pseudohyphae.

IMAGING STUDIES

Radiographs of the digit if concerned about osteomyelitis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- For acute paronychia without purulent drainage, warm soaks tid or qid are helpful. If pus is present, surgical drainage is required (Fig. P1-10).
- For chronic paronychia, avoid frequent immersion in water or exposure to moisture.

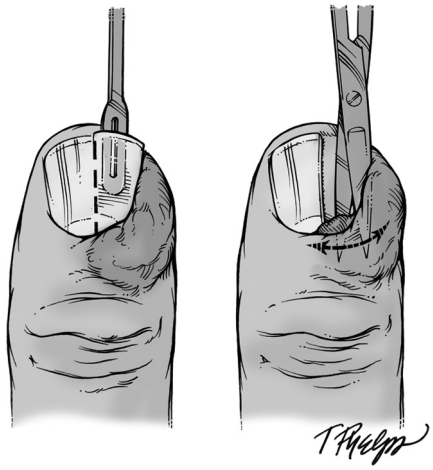


FIGURE P1-10 Surgical drainage of acute paronychia. The lateral nail on the affected side is gently elevated from the nail bed, and a longitudinal strip of nail is removed. If this does not decompress the infection adequately, the margins of the nail fold are opened gently to drain the adjacent soft tissues. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

ACUTE GENERAL Rx

- Trimethoprim-sulfamethoxazole DS 1 PO bid for 7 days is usually the antibiotic of choice for acute paronychia.
- Alternative antibiotic choices include dicloxacillin 500 mg qid, cephalexin 500 mg qid, clindamycin, and amoxicillin-clavulanate potassium.
- Surgical drainage is indicated if purulent discharge is noted.
- A No. 11 blade scalpel is used to lift the lateral perionychium and proximal eponychium off the nail, facilitating drainage.
- If the pus is located beneath the nail, the lateral edge of the nail can be lifted off the nail bed and excised.

CHRONIC Rx

- If no fungal organism is found, tincture of iodine (2 drops bid) helps keep the nail and skin dry.
- Chronic paronychia caused by *Candida albicans* is treated with topical antifungal agents (e.g., miconazole or ketoconazole applied tid).
- Unresponsive cases may be treated with itraconazole or fluconazole, but this should be done in consultation with dermatology and/or infectious disease.
- Surgery may be needed in refractory cases.

DISPOSITION

- Most acute paronychias with appropriate treatment resolve within 7 to 10 days.
- Osteomyelitis is a potential complication of paronychia.
- Untreated chronic paronychia leads to thickening and discoloration with eventual nail loss.

REFERRAL

Chronic paronychia refractory to topical medical therapy is best referred to dermatology and/or infectious disease. A hand surgeon is consulted if abscess drainage or surgery is being considered.

PEARLS & CONSIDERATIONS

COMMENTS

The gastrointestinal tract, including the mouth and bowel, and the genitourinary tract in women are the usual sources of *C. albicans* in chronic paronychia.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Paronychia (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Daniel CR et al.: Managing simple chronic paronychia and onycholysis with ciclopirox 0.77% and an irritant-avoidance regimen, *Cutis* 73(1):81, 2004.

Rigopoulos D et al.: Acute and chronic paronychia, *Am Fam Physician* 77(3): 339–346, 2008.

Shafritz AB, Coppage JM: Acute and chronic paronychia of the hand, *J Am Acad Orthop Sur* 22(3):165–174, 2014.

BASIC INFORMATION

DEFINITION

Paroxysmal cold hemoglobinuria (PCH) is the first, albeit rarest, autoimmune hemolytic anemia to be identified. It is characterized by transient or episodic massive intravascular hemolysis after exposure to cold temperatures. It was first described in patients with secondary or tertiary syphilis, and was classified as acute transient, chronic syphilitic, and chronic non-syphilitic. In modern times, chronic PCH is very rare, usually occurs in the elderly, and is associated with malignancy. Most cases are of the acute transient type, which is usually idiopathic in adults and secondary to a viral syndrome or immunization in children.

SYNONYMS

PCH
Donath-Landsteiner hemoglobinuria

ICD-9CM CODES
283.2 Hemoglobinuria caused by hemolysis from external causes
ICD-10CM CODES
D59.6 Hemoglobinuria due to hemolysis from other external causes

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Estimated at 0.4 cases per 100,000 people
PREVALENCE: Accounts for up to 5% of all adult hemolytic anemias and 30%-40% of childhood cases
PREDOMINANT SEX AND AGE: Mild male sex predilection with reported male-to-female ratio of 2:1 to 5:1
GENETICS: None
RISK FACTORS: Age (most common in young population), infections, and neoplasms have been associated with the development of Donath-Landsteiner antibody.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Within minutes to a few hours after cold exposure, there is a sudden onset of fever, rigors, and chills followed by red to brown urination.
- Associated symptoms include back, leg, and abdominal pain.
- Headaches, nausea, vomiting, diarrhea, and esophageal spasm are common. Oliguria and anuria can develop following renal dysfunction.
- May be associated with Raynaud's phenomenon.
- Associated with cold urticaria.
- Transient splenomegaly and hepatomegaly with jaundice may occur.
- Symptoms and gross hemoglobinuria usually resolve within hours.
- Symptoms believed to be mediated by smooth muscle dysfunction as a result of nitric oxide toxicity associated with hemoglobinemia.

ETIOLOGY

- The exact etiology of the D-L antibody is unknown, but the appearance of the antibody is likely related to infection or malignancy.
- The Donath-Landsteiner antibody is a biphasic, usually polyclonal, immunoglobulin (Ig) G. It is known to bind to various antigens such as I-, i-, p-, Pr-, which are normally present on the red blood cell (RBC) surface, yet the glycosphingolipid P antigen is considered its primary target. It sensitizes RBCs in the cold, and as blood warms to 37° C, complement-mediated hemolysis ensues.
- In children, the appearance of the antibody usually follows the onset of a viral respiratory illness by 1 to 3 wk. Symptoms may persist for several weeks.
- PCH has been associated with multiple infectious pathogens, including syphilis, Haemophilus influenzae, Epstein-Barr virus (EBV), cytomegalovirus (CMV), influenza A, varicella, measles, mumps, adenovirus, parvovirus B19, coxsackie A9, Mycoplasma pneumoniae, and Klebsiella pneumoniae.
- Chronic PCH has also been associated with hematologic and solid organ malignancy such as small cell lung cancer and Hodgkin's and non-Hodgkin's lymphoma.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cold agglutinin disease, paroxysmal nocturnal hemoglobinuria, and malaria
- Other causes of acute massive intravascular hemolysis and myoglobinuria secondary to rhabdomyolysis
- Table EP1-6 differentiates various types of autoimmune hemolytic anemias.

WORKUP

U/A, CBC, peripheral blood smear, hemolysis labs (LDH, total bilirubin, haptoglobin), iron studies, reticulocyte count, indirect Coombs and direct Coombs, complement levels, flow cytometry for PNH testing for the presence of CD55 or CD59 on the RBC membrane if clinically indicated, viral studies (if clinically warranted with thick and thin smear to rule out malaria).

LABORATORY TESTS

- The presence of IgG that reacts with the RBC at reduced temperatures but not at body temperature. In the Donath-Landsteiner test, a patient's serum is incubated with papainized pooled donated RBCs and complement at 4° C, then warmed to 37° C. Lysis is observed in a positive test.
- A more sensitive test involves using radiolabeled monoclonal anti-IgG. This is incubated at 4° C with the patient's serum and donor RBCs. The degree of radioactivity on the separated RBCs will be elevated in PCH compared with a control run at 37° C.
- Elevated bilirubin and lactate dehydrogenase, low haptoglobin, free plasma hemoglobin, low complement (C2, C3, C4).
- Abnormal RBC forms on the peripheral blood smear such as poikilocytosis, spherocytosis, anisocytosis, and nucleated RBCs.
- Erythrophagocytosis by neutrophils and monocytes may be seen.

IMAGING STUDIES

If chronic PCH, imaging could be considered to rule out underlying malignancy as the etiology when clinically warranted.

TREATMENT

NONPHARMACOLOGIC THERAPY

The mainstay of treatment is the avoidance of exposure to cold and presence of supportive care.

ACUTE GENERAL Rx

- In children in particular, transfusion may be necessary because the anemia may become life threatening and hemolysis may be ongoing for several weeks.
- Testing and treatment for underlying secondary condition.
- Hydration and alkalinization of the urine may be necessary to prevent renal failure.
- Steroids, although commonly used, were not shown to be beneficial.
- Plasma exchange therapy with 5% albumin fluid replacement has been successfully employed.
- Splenectomy is not indicated as it plays no role in the pathogenesis of the hemolysis in PCH.
- Treatment with rituximab has resulted in termination of hemolysis in a case report.
- Azathioprine or Cytoxan have also been suggested in case reports.
- In theory eculizumab, the monoclonal antibody directed at complement component 5, is promising but data are lacking. In one case report in a patient with multiple myeloma and PCH, it was ineffective.

CHRONIC Rx

Several case reports suggest that rituximab and immunosuppressants such as azathioprine may be effective. Treatment of the underlying cause such as infection or malignancy may also help in chronic disease.

COMPLEMENTARY & ALTERNATIVE MEDICINE

None

DISPOSITION

- Postinfectious varieties are self-limited.
- Adult idiopathic form is generally manageable by avoiding environmental exposure.

TABLE EP1-6 Characteristics of Autoimmune Hemolytic Anemia

Characteristic	TYPE OF AUTOIMMUNE HEMOLYTIC ANEMIA		
	Warm Autoimmune Hemolytic Anemia	Cold Agglutinin Disease	Paroxysmal Cold Hemoglobinuria
Antibody isotope	IgG, rare IgA, IgM	IgM	IgG
Direct antiglobulin test (DAT) result	IgG and/or C3	C3	C3
Antigen specificity	Multiple, primarily Rh	i/I, Pr	P
Hemolysis	Primarily extravascular	Primarily extravascular	Intravascular
Common disease associations	B-cell neoplasia/lymphoproliferative, collagen-vascular	Viral, neoplasia	Syphilis, viral

From Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

REFERRAL

To hematologist to aid in diagnosis

PEARLS & CONSIDERATIONS

COMMENTS

- PCH is associated with brown or red discoloration of urine after cold exposure in adults or after a viral infection in children.
- PCH can be associated with viral or bacterial infections, including syphilis, *H. influenzae*, EBV, CMV, influenza A, varicella, measles, mumps, and adenovirus, or malignancy, especially in adults.
- PCH can cause life-threatening hemolysis in children.

PREVENTION

None

PATIENT & FAMILY EDUCATION

American Autoimmune Related Diseases Association, Inc.
22100 Gratiot Ave.
East Detroit, MI 48021
Tel: (586) 776-3900
Fax: (586) 776-3903
Tel: (800) 598-4668
Email: aarda@aarda.org
Internet: http://www.aarda.org/

NIH/National Heart, Lung and Blood Institute
P.O. Box 30105
Bethesda, MD 20892-0105
Tel: (301) 592-8573
Fax: (301) 251-1223
Email: nhlbiinfo@rover.nhlbi.nih.gov
Internet: http://www.nhlbi.nih.gov/

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SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **MATTHEW I. QUESENBERRY, M.D.** and **MICHAEL MAHER, M.D.**

SUGGESTED READINGS

Bunch C et al.: Paroxysmal cold haemoglobinuria following measles: immunohematology, *Arch Dis Child* 47(252):299–300, 1972.

Eder AF: Review: Acute Donath-Landsteiner hemolytic anemia, *Immunohematology* 21(2):56, 2005.

Gertz MA: Cold hemolytic syndrome, *Hematology Am Soc Hematol Educ Program*19–23, 2006.

Gertz MA: Management of cold haemolytic syndrome, *Br J Haematol* 138(4): 422–429, Aug 2007.

Goldberg C et al.: Hemoglobinuria, paroxysmal cold, last updated *Emedicine*, 2008.

Koppel A et al.: Rituximab as successful therapy in a patient with refractory paroxysmal cold hemoglobinuria, *Transfusion* 47(10):1902–1904, 2007.

Nakamura H et al.: Donath-Landsteiner antibody of the IgM class with anti-I specificity and possible efficacy of azathioprine therapy in paroxysmal cold hemoglobinuria: a case report, *Rinsho Ketsueki* 31(9):1548–1552, 1990.

Vaglio S et al.: Autoimmune hemolytic anemia in childhood: serologic features in 100 cases, *Transfusion* 47:50–54, 2007.

BASIC INFORMATION

DEFINITION

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal stem disorder characterized by episodes of intravascular hemolysis and hemoglobinuria usually occurring at night. Thrombocytopenia, leukopenia, and recurrent venous thrombosis are also associated with PNH.

SYNONYMS

PNH

ICD-9CM CODES
283.2 Paroxysmal nocturnal hemoglobinuria
ICD-10CM CODES
D59.5 Paroxysmal nocturnal hemoglobinuria [Marchiafava-Micheli]

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence: 2 to 5 per million in the United States
- Affects patients of any age (reported spectrum 6 to 82 yr) but most common in patients aged 30 to 50 yr
- Affects both sexes (slight female predominance) and all races

PHYSICAL FINDINGS & CLINICAL PRESENTATION

1. Initial manifestations
   - Anemia symptoms (35%)
   - Hemoglobinuria (25%)
   - Bleeding (20%)
   - Aplastic anemia (15%)
   - Gastrointestinal symptoms (10%)
   - Hemolytic anemia (10%)
   - Iron-deficiency anemia (5%)
   - Venous thrombosis (5%)
   - Infections (5%)
   - Neurologic symptoms
2. Hemoglobinuria
   - Typically the first morning void reveals dark urine with progressive clearing during the day. The cause for the circadian rhythm is unknown.
3. Hemolysis
   - In addition to the circadian hemolysis and resulting hemoglobinuria, episodes of hemolytic exacerbations can accompany infections, menstruation, transfusion, surgery, iron therapy, and vaccinations. Symptoms of severe hemolysis include chest, back, or abdominal pain, headache, fever, malaise, and fatigue.
4. Aplastic anemia
   - Aplastic anemia may be the presenting manifestation of PNH (therefore PNH must be in the differential diagnosis of aplastic anemia) or may develop as a later complication of PNH.
5. Thrombosis (leading cause of death in PNH; occurs in 40% of patients)
   - Lower extremity deep vein thrombosis (DVT)
   - Subclavian thrombosis
   - Portal or mesenteric vein thrombosis
   - Hepatic vein thrombosis (Budd-Chiari syndrome)
   - Cerebrovascular thromboses
6. Renal failure
   - Acute renal failure associated with massive hemoglobinuria (acute tubular necrosis)
   - Progressive renal failure associated with thrombosis within renal small veins
7. Dysphagia
8. Infections (associated with leukopenia or steroid treatment)
9. Physical findings include:
   - Pallor (anemia)
   - Jaundice (hemolysis)
   - Splenomegaly
   - Unilateral extremity swelling (DVT)
   - Ascites (Budd-Chiari syndrome)

ETIOLOGY & PATHOGENESIS

- Complement-mediated hemolysis; the erythrocytes are abnormally sensitive to acidified serum.
- Patients have two populations of red blood cells (RBCs): some sensitive to hemolysis (PNH III cells) and others not (PNH I cells), in variable proportions (10% to 75% PNH III cells). Approximately 20% PNH III are required for hemoglobinuria to be detectable.
- The RBC defects in PNH are in the membrane proteins as follows:
  1. Decay-accelerating factor deficiency
  2. Membrane inhibitor of reactive lysis deficiency
  3. C-8 binding protein deficiency
- These protein deficiencies are the result of an acquired mutation located in the X chromosome, which regulates glycosyl phosphatidyl inositol (GPI). GPI anchors the above-mentioned proteins in the RBC membrane; GPI-deficient RBCs proliferate as an abnormal clone. Hemolysis is caused by the absence of decay-accelerating factor (CD55) and the membrane inhibitor of reactive lysis (CD59), which are glycosylphosphatidylinositol-dependent complement regulatory proteins.
- The pathophysiology of the relation of PNH and aplastic anemia is unknown.

DIAGNOSIS

It useful to classify PNH patients as either "classical" or "hypoplastic." This can usually be accomplished by ordering a complete blood count, reticulocyte count, LDH level, peripheral blood flow cytometry for PNH, and BM aspirate, biopsy, and cytogenetics. Patients with classical PNH tend to have mild to moderate cytopenias, a normocellular to hypercellular BM, an elevated reticulocyte count, a markedly elevated LDH level, and a relatively large PNH granulocyte population (>30%). In contrast, hypoplastic PNH patients present with manifestations similar to that of aplastic anemia or hypoplastic MDS. These patients typically present with moderate to severe cytopenias, a hypocellular BM (<25% cellularity), a decreased corrected reticulocyte count, a normal or mildly elevated LDH level, and a relatively small (<20%) PNH granulocyte population. Most, but not all, patients can be readily subdivided into classical versus hypoplastic PNH, a distinction that aids with therapeutic decisions

Clinical situations:

- Intravascular hemolysis
- Hemoglobinuria
- Pancytopenia associated with hemolysis
- Iron deficiency associated with hemolysis
- Recurrent venous thrombosis
- Recurrent episodes of abdominal pain, headache, or back pain associated with hemolysis

DIFFERENTIAL DIAGNOSIS

- See "Hemolytic Anemia" in Section I.
- See "Aplastic Anemia" in Section I.
- See "Anemia" algorithm in Section III.

LABORATORY TESTS

- Complete blood count: anemia, leukopenia, thrombocytopenia
- Reticulocytosis
- RBC smear: spherocytes (Fig. EP1-11)
- Negative Coombs test
- Low leukocyte alkaline phosphatase
- Elevated lactate dehydrogenase
- Low serum haptoglobin
- Low serum iron saturation, low ferritin
- Elevated urine hemoglobin, urine urobilinogen, urine hemosiderin
- Positive Ham test (acidified serum RBC lysis)
- Normoblastic hyperplasia on bone marrow aspirate or biopsy
- Assaying granulocytes is the most reliable method of diagnosing PNH because they are not affected by blood transfusions. Identification of GPI-anchored protein deficiency on hematopoietic cells by using monoclonal antibodies or flow cytometry; flow cytometric analysis of granulocytes is the best way to diagnose PNH. Most hematologists prefer to use FLAER over monoclonal antibodies on granulocytes and monocytes because of improved sensitivity and specificity; anti-CD59 is the most reliable marker on erythrocytes.
- Cytogenetic studies are not diagnostic

TREATMENT

- Iron replacement, folic acid supplementation: All patients with classical PNH should be prescribed folic acid (1 to 2 mg/day). Iron supplementation is recommended in those with absent iron stores.
- Eculizumab, a humanized antibody that inhibits the activation of terminal complement components, is an effective therapy for PNH; it reduces intravascular hemolysis, hemoglobinuria, and need for transfusion in patients with PNH. It is very expensive and requires lifelong administration. Vaccination against meningococcus is mandatory before eculizumab administration due to increased susceptibility to neisserial infection.

- Prednisone (0.5 to 1.0 mg/day) for 6 to 8 weeks is helpful to reduce complement activation if eculizumab is unavailable. Danazol 400 mg/day can also decrease hemolysis.
- Transfusions
- Treatment and prevention of thrombosis (heparin, Coumadin)
- Avoidance of oral contraceptives
- Bone marrow transplantation

REFERRAL

To hematologist

PROGNOSIS

- Median survival is 10 to 15 yr.
- 25% survival to 25 yr
- If thrombosis at presentation, only 40% survival to 4 yr
- 1% incidence of leukemia
- 5% incidence of myelodysplastic syndrome
- Death often results from thrombosis or progressive pancytopenia.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Brodsky RA: Narrative review: paroxysmal nocturnal hemoglobinuria: the physiology of complement-related hemolytic anemia, *Ann Intern Med* 148:587–595, 2008.

Hillmen P et al.: The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria, *N Engl J Med* 355:1233, 2006.

Brodsky RA: Paroxysmal nocturnal hemoglobinuria. In Hoffman R, editor: *Hematology, basic principles and practice*, ed 6, Philadelphia, 2013, Saunders.

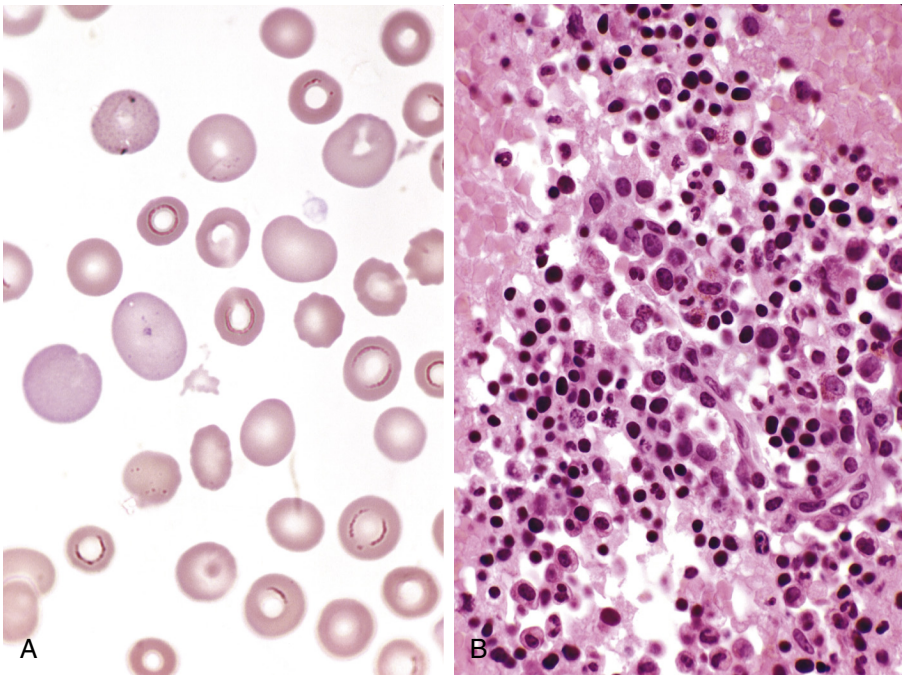


FIGURE EP1-11 Paroxysmal nocturnal hemoglobinuria. A, Large polychromatophilic red cells (shift cells) are seen following an episode of hemolysis. **B,** The bone marrow biopsy shows marked erythroid hyperplasia. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Partial seizures are characterized by focal cortical discharges that provoke seizure symptoms related to the area of the brain involved. Simple partial seizures do not cause impairment of consciousness. However, partial seizures can evolve into complex partial and/or tonic clonic seizures.

SYNONYMS

Simple partial seizures
Focal seizures

ICD-9CM CODES

345.5 Localization-related (focal) (partial) epilepsy and epileptic syndromes with simple partial seizures

ICD-10CM CODES

G40.0 Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset

G40.109 Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with simple partial seizures, not intractable, without status epilepticus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 30 to 50 cases per 100,000 person-yr
PREVALENCE: 5 to 8 cases per 1000 persons
PREDOMINANT SEX AND AGE: No gender preference

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with partial seizures usually have normal physical and neurologic examinations unless the focal seizures are due to a structural abnormality such as a stroke, where the patient will have a neurologic exam consistent with the area of CNS structural damage.
- During partial seizures the patients are conscious, unless there is spread of the epileptic focus causing secondary generalization and unresponsiveness. A focal seizure can evolve to a generalized tonic clonic seizure.
- Patients with partial seizures can experience postictal weakness/paralysis that usually resolves within 24 hr (Todd's paralysis). However, focal neurologic deficits may also be indicative of a structural brain lesion.

ETIOLOGY

- Seizures in general are a cardinal sign of cortical neurologic injury.
- The etiology of partial seizures can be idiopathic (likely genetic), cryptogenic (unknown, possibly genetic), and symptomatic (due to a neurologic injury).
- Frequent causes of partial seizures are tumor, stroke, CNS infections (cysticercosis, abscesses), arteriovenous malformations (AVMs), traumatic brain injury, cortical malformations, and others.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Transient ischemic attack.
- Movement disorders.
- Nonepileptic spells.

WORKUP

- EEG.
- Ambulatory EEG and/or video EEG recommended for patients with diagnostic uncertainty.

LABORATORY TESTS

Routine blood workup (CBC, CMP, glucose, electrolytes) may be considered in appropriate clinical situations.

IMAGING STUDIES

- In the acute setting, a CT scan of the head is high yield to rule out space-occupying lesions.
- MRI of the brain with a defined epilepsy protocol should be performed in all patients with recurrent seizures.
- CT scans of the head should be avoided in children if possible, unless in an emergency setting.

TREATMENT

- Carbamazepine traditionally has been the standard initial drug treatment for partial seizures.
- Lamotrigine and levetiracetam are effective and well-tolerated antiepileptic drugs for treating partial seizures.
- Other antiepileptic drugs (e.g., lacosamide, oxcarbazepine, ezogabine) may be used by an epilepsy specialist in specific cases.
- Surgical treatments (e.g., temporal lobectomy in mesial temporal sclerosis) may be indicated in refractory cases of partial seizures.

GENERAL Rx

- After a first unprovoked seizure with normal examination, imaging, and EEG, no treatment is required.
- Recurrent seizures and seizures with abnormal studies require treatment.

DISPOSITION

- Response to treatment often depends on the etiology of the partial seizures.
- 47% of patients become seizure free with monotherapy and 67% with polytherapy.
- No driving until seizure free in accordance with local laws and regulations.

REFERRAL

Patients with epilepsy and seizures should be referred for a consultation by a neurologist, preferably one with a special interest in epilepsy.

PEARLS & CONSIDERATIONS

COMMENTS

- It is crucial to understand that partial seizures can be due to a variety of neurologic diseases.
- Successful treatment depends on the correct choice of antiepileptic drugs based on patient's gender and comorbidities.
- Valproic acid should be avoided in girls and women with childbearing potential due to the risk of teratogenicity.
- All women in childbearing age taking antiepileptic drugs should take folic acid supplementation (1 to 4 mg/day) for the prevention of neural tube defects.

PREVENTION

- Sleep deprivation and alcohol consumption should be avoided.
- Drug compliance is compulsory to prevent seizure recurrence.

PATIENT & FAMILY EDUCATION

- People with epilepsy can lead normal lives.
- The goal of treatment is no seizures and no side effects to medications.
- Patient education and information can be obtained at the Epilepsy Foundation: www.epilepsyfoundation.org.
- Pregnant women with epilepsy should visit the Antiepileptic Drug Pregnancy Registry website for information and assistance: www2.massgeneral.org/aed.
- Patients with ongoing seizures are forbidden to drive; check your state regulations and laws regarding driving and epilepsy.
- Patients should be counseled on general seizure precautions such as swimming, bathing, and heights.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Partial Motor Seizures (Patient Information)

AUTHOR: **PATRICIO SEBASTIAN ESPINOSA, M.D., M.P.H.**

SUGGESTED READINGS

Marson AG et al.: SANAD Study Group: The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial, *Lancet* 369(9566):1000–1015, 2007.

Wyllie E et al.: *The treatment of epilepsy: principles & practice,* ed 5, Philadelphia, Lippincott Williams & Wilkins.

BASIC INFORMATION

DEFINITION

Patellofemoral pain syndrome is overuse or overload of the patellofemoral region leading to anterior knee pain.

SYNONYMS

PFPS
Retropatellar pain syndrome
Runner's knee
Lateral facet compression syndrome
Idiopathic anterior knee pain

ICD-9CM CODES
719.46 Patellofemoral pain syndrome
ICD-10CM CODES
M22.2 Patellofemoral disorders
M25.569 Pain in unspecified knee

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Estimated >20% of adolescents. PFPS is the most common diagnosis in outpatients presenting with knee pain. PFPS also constitutes 16% to 25% of all injuries to runners.
PREDOMINANT SEX AND AGE: Nearly 2:1 female predominance; disproportionately affects active adolescents and adults in the second and third decades of life.
RISK FACTORS: Increase in physical activity intensity or duration, overuse, joint overload, trauma, anatomic abnormalities, malalignment, patellar hypermobility, quadriceps weakness.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Gradual or acute onset of anterior knee pain
- Sometimes localized under or around the patella
- Also described as a catching sensation under the patella
- Worsened pain with squatting, running, prolonged sitting, or ascending or descending steps
- Effusion implies intraarticular pathology not explained by PFPS
- Pain may be elicited by compression of the patella into the trochlear groove while the leg is extended

ETIOLOGY

No clear consensus; likely multifactorial, including muscle overuse or joint overload with malalignment and/or trauma potentially contributing resulting in imbalances in the forces controlling patellar tracking during knee flexion and extension

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Patellofemoral arthritis
- Patellar instability
- Patellar stress fracture
- Osgood-Schlatter disease
- Articular cartilage injury
- Prepatellar bursitis
- Pes anserine bursitis
- Iliotibial band syndrome
- Plica synovitis
- Chondromalacia
- Bony abnormalities
- Bone tumors
- Patellar tendinopathy
- Other: Referred pain from lumbar spine or hip joint pathology, loose bodies, osteochondritis dissecans, Sinding-Larsen-Johansson syndrome, symptomatic bipartite patella

WORKUP

- PFPS is a clinical diagnosis of exclusion; evaluate and rule out other possibilities on the differential. Dynamic patellar tracking can be assessed by having the patient perform a single leg squat and stand. Physical exam should also include patellar mobility testing (displacement >3 quadrants is considered hypermobile), patellar grind (or inhibition) test (positive test if pain is produced), and patellar tilt test to assess for tightness of the lateral structures.
- Physical exam findings consistent with PFPS include eliciting pain by compression of the patella into the trochlear groove while the leg is extended.

IMAGING STUDIES

- No imaging is necessary in the initial workup.
- Consider plain films if symptoms do not improve after 1 to 2 mo of therapy.

TREATMENT

There is a general lack of consensus. Management should focus on the implementation of a comprehensive rehabilitation program.

NONPHARMACOLOGIC THERAPY

Physical therapy; quadriceps, hamstring, iliotibial band, and calf-stretching exercises; quadriceps and hip abductor strengthening

ACUTE GENERAL Rx

Short-term (2 to 3 wk) nonsteroidal anti-inflammatory drugs or acetaminophen for pain relief; activity modification; ice for 10 to 20 min after activity

CHRONIC Rx

- Physical therapy; strengthening and flexibility exercises; consider arch supports or evaluation for custom orthotics.
- Spontaneous resolution may occur in some cases.

DISPOSITION

Outpatient management

REFERRAL

Consider referral to orthopedics for surgical evaluation as a last resort if conservative therapies fail. Surgical options include release of the lateral retinaculum; articular cartilage procedures; and proximal realignment, usually with anteromedialization of the tibial tubercle.

PEARLS & CONSIDERATIONS

COMMENTS

Treatment is most successful when the patient has a disciplined approach.

PATIENT & FAMILY EDUCATION

The American Academy of Family Practice website www.familydoctor.org contains frequently asked questions, patient information, and example stretching and strengthening exercises. Information is available in English and Spanish.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Knee Pain (Patient Information)
Patellofemoral Pain Syndrome (Patient Information)

AUTHOR: **KATE MAVRICH, M.D.**

EVIDENCE

Abstract[1]

Background:
It is hypothesized that patients with patellofemoral pain syndrome (PFPS) have hip and core muscle weakness leading to dynamic malalignment of the lower extremity. Thus, hip strengthening is a common PFPS treatment approach.

Purpose:
To determine changes in hip strength, core endurance, lower extremity biomechanics, and patient outcomes after proximally focused rehabilitation for PFPS patients.

Study Design:
Case series; Level of evidence, 4.

Methods:
Nineteen women (age, 22.68±7.19 years; height, 1.64±0.07 m; mass, 60.2±7.35 kg) with PFPS participated in an 8-week program to strengthen the hip and core muscles and improve dynamic malalignment. Paired t tests were used to compare the dependent variables between prerehabilitation and postrehabilitation. The dependent variables were pain; functional ability; isometric hip abduction and external rotation strength; anterior, lateral, and posterior core endurance; joint range of motion (ROM; rearfoot eversion, knee abduction and internal rotation, and hip adduction and internal rotation); and peak internal joint moments (rearfoot inversion, knee abduction, and hip abduction and external rotation) during the stance phase of running

Results:
Significant improvements in pain, functional ability, lateral core endurance, hip abduction, and hip external rotation strength were observed. There was also a significant reduction in the knee abduction moment during running, although there were no significant changes in joint ROM.

Conclusion:
An 8-week rehabilitation program focusing on strengthening and improving neuromuscular control of the hip and core musculature produces positive patient outcomes, improves hip and core muscle strength, and reduces the knee abduction moment, which is associated with developing PFPS. Ⓐ

Evidence-Based Reference

Earl JE et al.: A proximal strengthening program improves pain, function, and biomechanics in women with patellofemoral pain syndrome, *Am J Sports Med* 39:154–163, 2011. Ⓐ

SUGGESTED READING

Dixit S et al.: Management of patellofemoral pain syndrome, *Am Fam Physician* 75:194–202, 2007.

Patent Ductus Arteriosus PTG

BASIC INFORMATION

DEFINITION

Patent ductus arteriosus (PDA) is a persistence of the fetal communication between the descending aorta and left pulmonary artery. It is a derivative of the sixth aortic arch. This connection allows for blood to bypass the fetal lungs (which are not participating in gas exchange) and be directed into the descending aorta to supply structures below this region. It usually closes soon after birth under the physiologic effects of elevated oxygen level. Defects can range in size from so small as to be undetectable to large enough to cause volume loading of the left ventricle and pulmonary hypertension.

SYNONYMS

PDA

ICD-9CM CODES
747.0 Patent ductus arteriosus
ICD-10CM CODES
Q25.0 Patent ductus arteriosus

EPIDEMIOLOGY & DEMOGRAPHICS

- Prevalence is 2.9 per 10000 live births. Incidence has increased dramatically due to improved survival of premature infants (especially those born <30 weeks' gestation).
- Female predominance 2:1
- Increased incidence in congenital rubella and with associated cyanotic congenital heart disease

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Loud machinery like murmur appreciated over the left scapula in patients with left to right shunting
  - Widened pulse pressure
- Apex beat is displaced and volume loaded and the precordium is active
- Increased jugular venous pressure (with RV failure)
  - Where the defect has resulted in irreversible pulmonary hypertension, there is no murmur, and cyanosis and clubbing, particularly of the feet (differential cyanosis) will be present
- Exertional dyspnea and fatigue
- Patients with small defects: generally asymptomatic
- Fig. P1-12 shows the anatomy of patent ductus arteriosus.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rule out other causes of continuous murmurs such as aortopulmonary shunts or window, coronary fistula, ruptured sinus of Valsalva aneurysm, and mixed aortic stenosis and regurgitation
- Coarctation of the aorta will have a murmur over the scapula but arm-leg pressure gradient and hypertension.
  - In patients with Eisenmenger syndrome, consider ASD and VSD in the differential diagnosis

WORKUP

- ECG:
  - When the defect is large enough to cause left-sided volume overload there may be LA enlargement, LV hypertrophy
  - When pulmonary hypertension has occurred RAD, RVH and P pulmonale may be present
- Chest x-ray
- Echocardiography
- Cardiac magnetic resonance imaging (MRI), or CT
- Cardiac catheterization

IMAGING STUDIES

- Chest x-ray: cardiomegaly, left heart enlargement, increased pulmonary vascular pattern
- Echocardiography with Doppler flow studies: show the presence of the PDA; can demonstrate the size of the defect, the direction of shunting, and the effect of the PDA on left heart chamber sizes; and can be used to determine if pulmonary hypertension has occurred
- Transesophageal echocardiography is modestly helpful, especially when patients have poor acoustic windows
- Cardiac MRI and CT: may be useful if echo is not diagnostic; the PDA may be directly visualized and its morphology described with either technique. MRI is gold standard for assessing LV size and function, and it can determine whether the left-sided chambers are enlarged and establish the degree of shunting using phase contrast imaging to determine the Qp:Qs noninvasively. MRI is also useful to assess for associated lesions; cardiac CT can offer similar information at the price of radiation exposure
- Cardiac catheterization: Left- and right-heart catheterization can be used when the diagnosis remains in doubt. It can also help to estimate the degree of left to right shunting, establish right-sided pressures, demonstrate the PDA morphology, and attempt closure where technically feasible

TREATMENT

NONPHARMACOLOGIC THERAPY

- NSAIDs (e.g., indomethacin, ibuprofen) may be used to cause PDA closure in the premature infant; the mechanism of action is by inhibition of local prostaglandin synthesis, which is necessary for the duct to remain open in many cases
- Antibiotic prophylaxis is only recommended where there has been previous endocarditis
- Where there is volume overload, patients can be treated with diuretics and digoxin until formal device or surgical closure can be performed
- In older patients with secondary pulmonary hypertension, pulmonary vasodilators can be extremely helpful in improving symptoms and mortality and potentially allowing safe closure of the defect

GENERAL Rx

- Closure of a PDA is considered if there is evidence for volume overload or signs of pulmonary hypertension where the pulmonary pressures have not become excessively high. Additionally, because >95% of PDAs can successfully be closed percutaneously with a low rate of complications, many advocate closing a PDA when there is the presence of an audible murmur. The chief indication for this "prophylactic closure" is the low but non-zero incidence of infective endocarditis in this condition, although there is no clear evidence to support this procedure and controversy remains.

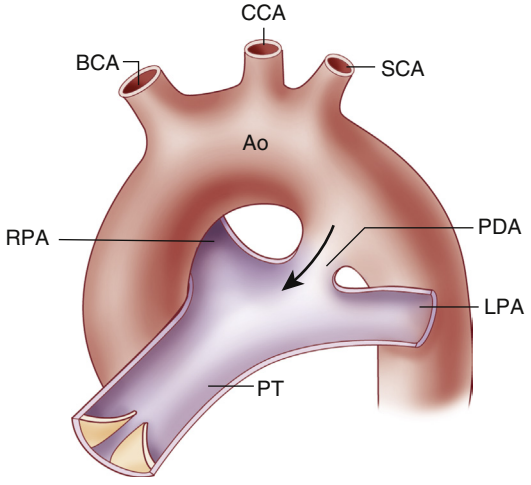


FIGURE P1-12 Anatomy of a patent ductus arteriosus. Note the relationships among the position of the ductus, left subclavian artery, and pulmonary artery bifurcation. *Ao*, Aorta; *BCA,* brachiocephalic; *CCA,* common carotid artery; *LPA,* left pulmonary artery; *PDA,* patent ductus arteriosus; *PT,* pulmonary trunk; *RPA,* right pulmonary artery; *SCA,* subclavian artery. (From Perloff JK, ed. *Clinical recognition of congenital heart disease,* 4th ed, Philadelphia, 1994, Saunders.)

- In patients with pulmonary hypertension, treatment with pulmonary vasodilators should be considered prior to closure.
- Device closure is possible in >95% of cases, and various devices are available for these defects. Use of different types depends on morphology of the defect
- Surgical closure may be performed when a patient is undergoing cardiac surgery for other reasons or when the PDA is not suitable for device closure, such as in the case of very large defects or when the child is too small (<6 kg)

DISPOSITION

- Long-term outcome depends on the size of the lesion and the associated degree of left-to-right shunting. Defects with a small shunt generally do very well, apart from the possibility of endocarditis. Those with moderate shunts may develop left atrial and left ventricular volume overload and shortness of breath or arrhythmias. Those with a very large shunt may develop heart failure early then go on to develop Eisenmenger syndrome (fixed pulmonary hypertension with reversal of shunt causing cyanosis) if unrepaired.
- Endocarditis is uncommon and usually occurs at the site where the high velocity jet lesion enters the PA but generally can be treated medically
- Basic preoperative assessment for patients with adult congenital heart disease (ACHD) should include systemic arterial oximetry, an ECG, chest radiograph, TTE, and blood tests for full blood count and coagulation screen.
- Intracardiac shunts are considered of moderate risk for preoperative evaluation for noncardiac procedure. High-risk features include severe systolic dysfunction (EF <35%), severe pulmonary hypertension (whether primary or secondary), cyanotic heart disease, or severe left-side outlet obstruction.
- Clinical follow-up is recommended for adult patients to exclude residual deficits, pulmonary hypertension and LV dilation and dysfunction, and atrial arrhythmias.
- Infective endocarditis prophylaxis for dental procedures:
  - Prophylaxis is not indicated for an unrepaired PDA.
  - Prophylaxis is indicated for a repaired PDA in the first 6 mo following the repair or where prosthetic material is present and there is a residual defect.
- The estrogen-containing oral contraceptive pill is not recommended in ACHD patients at risk of thromboembolism, such as those with cyanosis related to an intracardiac shunt, atrial fibrillation, severe PAH, or Fontan repair.
- Women with a repaired PDA generally can undergo pregnancy and delivery normally. Those with an unrepaired defect of a size that would ordinarily be repaired are recommended to undergo repair before becoming pregnant

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Patent Ductus Arteriosus (PDA) (Patient Information)

AUTHOR: **JONATHAN GINNS, M.D**

SUGGESTED READINGS

Sommer RJ: Pathophysiology of Congenital Heart Disease in the Adult: Part I: Shunt Lesions, *Circulation* 117:1090–1099, 2008.

Baruteau AE: Transcatheter closure of patent ductus arteriosus: past, present and future, Archives of cardiovascular diseases, 107(2): 122–32

Rao S, Ginns J: Adult Congenital Heart Disease and Pregnancy, *Seminars in Perinatology* 38(5):260–272, 2014.

Warnes CA et al.: ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Adults With Congenital Heart Disease), *J Am Coll Cardiol* 52:e143–e263, 2008.

BASIC INFORMATION

DEFINITION

- Patent foramen ovale (PFO) is a vestige of the fetal circulation, and results from failure of the primum and secundum septa to fuse postnatally. Persistence of the one-way flap valve overlying this foramen ovale allows right to left blood flow when right atrial pressure exceeds that of the left.
- Foramen ovale remains open during intrauterine life, in a valve-like manner, to allow highly oxygenated blood to reach the left atrium from the inferior vena cava. High right atrial pressure in the fetus keeps it open.
- Soon after birth, as the pulmonary circulation fills, the left atrial pressure rises higher than that of the right atrium. This pushes the septum primum against septum secondum, closing the right-to-left pathway through the foramen ovale.

ICD-9CM CODES
745.5 Patent foramen ovale
ICD-10CM CODES
Q21.1 Atrial septal defect

EPIDEMIOLOGY & DEMOGRAPHICS

- PFO fails to close in as much as a fourth of the population.
- PFO has similar frequency among males and females.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most patients with isolated PFO are asymptomatic.
- It cannot be detected on clinical examination.

COMPLICATIONS

- Cryptogenic stroke (particularly <55 yr).
- The proposed mechanism of stroke with PFO includes paradoxical embolization, in situ thrombosis within the canal of the PFO, associated atrial arrhythmia, and concomitant hypercoagulable state.
- Migraine with aura.
- Decompression sickness and air embolism.
- Increases risk of hypoxemia during sleep in patients with obstructive sleep apnea.
- Platypnea-orthodeoxia syndrome (characterized by both dyspnea and arterial desaturation in the upright position with improvement in supine position).
- Increased risk of postoperative atrial fibrillation and hypoxemia, in off-pump coronary artery bypass surgery.

ETIOLOGY

Unknown

DIAGNOSIS

- Testing for PFO is primarily performed in patients with a cerebral ischemic event of uncertain origin.
- A variety of echocardiography modalities have been used to diagnose PFO. These include:
  1. Transthoracic echocardiography (TTE)
  2. Transesophageal echocardiogram (TEE) (Fig. EP1-13)
  3. Transmitral Doppler (TMD)
  4. Transcranial Doppler (TCD) of middle cerebral artery after injection of agitated saline peripherally
- TEE, especially when performed with contrast injected during a cough or Valsalva, is the most sensitive and preferred test for diagnosing PFO.
- Essentially, a PFO is suggested by the presence of echo dropout in the atrial septum visualized in more than one plane during echocardiography. The appearance of microbubbles in the left atrium within three to five cardiac cycles after injection of agitated saline peripherally is considered diagnostic of PFO with associated right-to-left shunt (RLS).
- The diagnosis of PFO is enhanced with multiple intravenous contrast injections with maneuvers that cause transient elevations of right atrial pressure (cough or Valsalva) to enhance RLS.
- TCD has the advantage of being noninvasive and easy to perform at bedside. But it can only detect a right-to-left shunt, not the location of the shunt or other cardiac structural anomalies.

TREATMENT

- Management guidelines from professional societies are shown in Table EP1-7.
- Most patients with a PFO as an isolated finding receive no special treatment. This is because the yearly risk of cryptogenic stroke in healthy persons with PFO may be as low as 0.1%.
- As it is not associated with increased risk for endocarditis, antibiotic prophylaxis is not indicated.

PHARMACOLOGIC TREATMENT

When PFO is associated with an otherwise unexplained neurologic event, traditional treatment has been antiplatelet treatment (e.g., aspirin) therapy alone in low-risk patients and combined with therapeutic anticoagulants (e.g., warfarin) in high-risk patients.

Risk factors associated with a higher risk of complications, particularly stroke, include:

- Coexisting atrial septal aneurysm
- Large PFO
- Spontaneous right-to-left shunting
- Major shunt (>50 bubbles)
- Valsalva-provoking activity preceding the onset of stroke
- Presence of Chiari network (a congenital remnant of the right valve of the sinus venosus)
- Eustachian valves
- Younger age (<55 yr)
- Multiple clinical events or infarcts
- Pulmonary hypertension
- Failure or contraindications to anticoagulants
- High risk for recurrent deep venous thrombosis
- Pulmonary embolism at time of initial event
- Hypercoagulable state

PERCUTANEOUS TRANSCATHETER CLOSURE OF PFO

Percutaneous method of closure is usually preferred over open surgical closure because of invasiveness, procedure time, and patient convenience.

- Indications:
  1. Recurrent cryptogenic stroke due to presumed paradoxical embolism through PFO while on adequate medical treatment with antiplatelets or anticoagulants. The

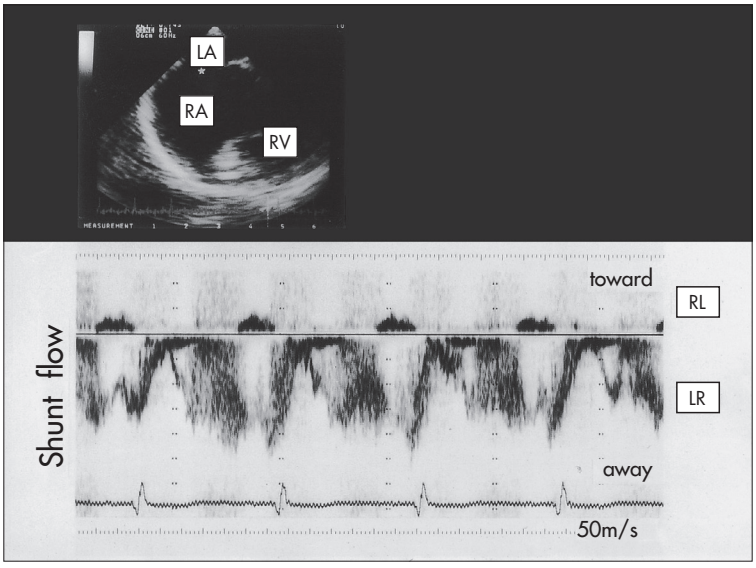


FIGURE EP1-13 Transesophageal echocardiography of an internal defect and pulsed Doppler flow signal. Pulsed Doppler echocardiographic signal is consistent with left-to-right level. *LA,* Left atrium; *RA,* right atrium; *RV,* right ventricle; *LR,* left-to-right shunt signal; *RL,* right-to-left shunt signal. (From Crawford MH et al [eds]: *Cardiology,* ed 2, St Louis, 2004, Mosby.)

American Heart Association and American College of Cardiology have discouraged the use of devices to close a PFO as a means of preventing recurrent stroke. A recent trial (CLOSURE I) revealed that in patients with cryptogenic stroke or TIA who had a PFO, closure with a device did not offer a greater benefit than medical therapy alone for the prevention of recurrent stroke or TIA.

2. In presence of contraindications to anticoagulants
- Contraindications:
  1. Presence of thrombus on the implant site or in the venous system used for access
  2. Active endocarditis or bacteremia
  3. Inadequate size of femoral vein for access
  4. Atrial septal anatomy without an adequate rim to hold the device
  5. Atrial septal anatomy that may result in the occluder obstructing an intracardiac structure
  6. Known hypercoagulable state
  7. Presence of an intracardiac mass or vegetation
- The Food and Drug Administration (FDA) has approved CardioSEAL Septal Occlusion System and Amplatzer PFO Occluder devices for percutaneous PFO closure (Fig. EP1-14).
- Requires SBE prophylaxis and antiplatelets (aspirin and clopidogrel for first 3 mo, followed by aspirin for another 3 mo) for 6 mo postprocedure. During this period of endothelialization, the risk of recurrent stroke is highest.
- The 1-yr rate of recurrent neurologic events ranged from 0% to 5% with percutaneous closure group vs. 4% to 12% with medical therapy group.
- MRI or metal detectors do not affect these implants, as they are not metallic.

TABLE EP1-7 Management Guidelines from Professional Societies

	American Academy of Neurology	American College of Chest Physicians
PFO	1. Evidence is insufficient to determine whether warfarin or aspirin is superior in preventing recurrent strokes or death, but minor bleeding is more frequent with warfarin. 2. There is insufficient evidence to evaluate the efficacy of surgical or endovascular closure.	
PFO alone		1. Antiplatelet therapy recommended over no therapy 2. Antiplatelet therapy suggested over warfarin
PFO with other risk factors		Inadequate data available to allow recommendation of optimal medical therapy vs. endovascular or surgical closure
PFO with concomitant deep vein thrombosis or pulmonary embolism	At least 3 mo of anticoagulation	Anticoagulation recommended

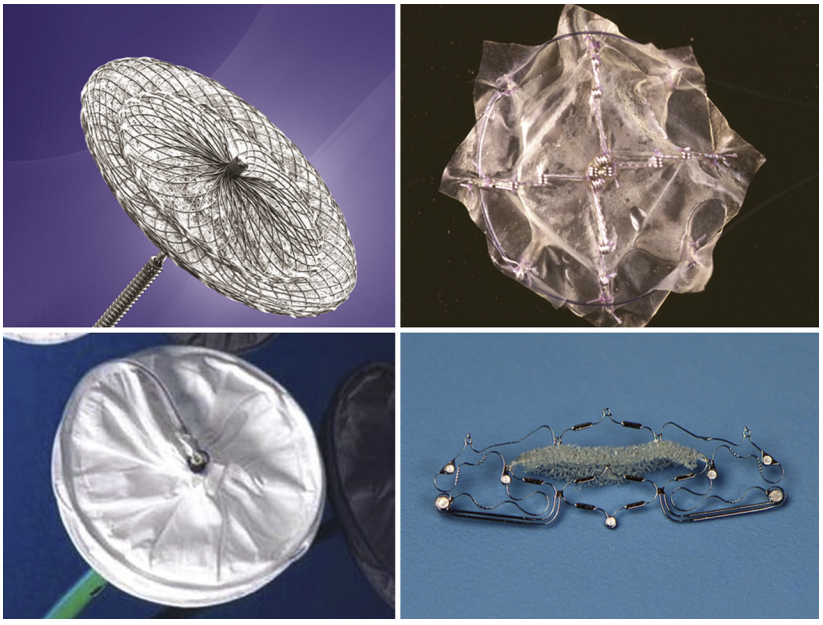


FIGURE EP1-14 Patent foramen ovale occluders. Clockwise from upper left: (1) Amplatzer PFO occluder (AGA Medical, Plymouth, Minn) fashioned of two nitinol alloy disks, each with embedded fabric and connected by a central waist; (2) BioSTAR device (NMT Medical, Boston), which incorporates biodegradable collagenous disks fashioned similarly to its predecessors, the CardioSEAL and StarFlex devices; (3) Coherex device (Coherex Medical, Salt Lake City), which stretches the defect in one dimension while approximating the edges of the defect; and (4) Helex device (WL Gore & Associates, Newark, Del) with a single spiral coil of nitinol wire covered in fabric. (From Bonow RO et al: *Braunwald's heart disease: a textbook of cardiovascular medicine*, Philadelphia, 2012, Saunders.)

SURGICAL CLOSURE (OPEN THORACOTOMY)

Indications:
1. PFO >25 mm in size
2. Inadequate rim of tissue around the defect
3. Percutaneous device failure
4. In presence of other indication for open heart surgery

PEARLS & CONSIDERATIONS

COMMENTS

PFO is found on transesophageal echocardiography in about 50% of young survivors of stroke without clear cause for their stroke. In these patients, it is unclear whether the PFO was the cause of the stroke or whether it was an incidental finding. Trials have shown that closure of a PFO for secondary prevention of cryptogenic embolism did not result in a significant reduction in the risk of recurrent embolic events or death as compared with medical therapy.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **HEMANT K. SATPATHY, M.D.**

SUGGESTED READINGS

Aslam F et al.: Patent foramen ovale: assessment, clinical significance and therapeutic options, *South Med J* 19(12):1367–1372, 2006.

Furlan AJ et al.: Closure or medical therapy for cryptogenic stroke with patent foramen ovale, *N Engl J Med* 366:991–999, 2012.

Horton SC, Bunch TJ: Patent foramen ovale and stroke, *Mayo Clin Proc* 79:79–88, 2004.

Kizer JR, Devereux RB: Patent foramen ovale in young adults with unexplained stroke, *N Engl J Med* 353:2361–2372, 2005.

Maissel WH, Laskey WK: Patent foramen closure devices: moving beyond equipoise, *JAMA* 294(3):366–369, 2005.

Meier B et al.: Percutaneous closure of patent foramen ovale in cryptogenic embolism, *N Engl J Med* 368:1083–1091, 2013.

BASIC INFORMATION

DEFINITION

Medication errors represent failure of intended prescription, dispensation, or administration of desired drug therapy. Medication errors may result in inappropriate medication use or an adverse drug event (ADE) (i.e., direct harm or injury to the patient).

SYNONYMS

Dosing errors or mistakes. Medication errors are not synonymous with ADEs because not all cause harm (a requirement of ADEs).

ICD-9CM CODES
Not applicable
ICD-10CM CODES
NEC T50.9 Wrong drug (given in error)

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE

- 15% of pediatric outpatient prescriptions are either underdosed (7%) or overdosed (8%).
- Nearly 6% of medication orders for a hospitalized child contain an error. One percent of pediatric medication orders will result in a potential ADE. Less than 1% of medication orders for a child will contain an error that ultimately results in harm or injury.

PEAK INCIDENCE: Among outpatient prescriptions, medication errors occur more frequently in children <4 yr compared with older children (20% vs. 13%)
PREVALENCE: Not applicable
PREDOMINANT SEX AND AGE: Children <4 yr
GENETICS: Not applicable
RISK FACTORS

- Patient aged <4 yr
- Off-label (non-FDA approved) medication use
- Prescriptions for analgesics, antiseizure medications, asthma or allergy medications, and antibiotics
- Lack of computerized prescriber order entry (CPOE), standardized order sets, or alert systems
- Infants or children with multiple health care needs or those in intensive care
- Limited parental health literacy, the use of kitchen teaspoons or tablespoons for medication administration, and the use of medication dosing cups (instead of medication oral syringes)
- Errors of hospital medication administration and dispensing may be more common during evening, nighttime, and weekend shifts

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Signs and symptoms of toxicity specific to the current drug regimen
- Lack of clinical efficacy of the current drug regimen

ETIOLOGY

Common sources of pediatric medication errors include:

- Prescribing errors: lack of knowledge of medication; lack of recognition of the age-specific pharmacokinetics of a particular agent; use of medical abbreviations within the prescription or medication order; "look alike, sound alike" substitution errors; doses of liquid medications written as teaspoonfuls or tablespoonfuls
- Calculation errors: mg/kg/*dose* versus mg/kg/*day* dosing recommendations; "tenfold" decimal mistakes such as the use of trailing zeros (1 vs. 1.0) and naked decimals (0.1 vs.1); patient weight in pounds versus kilograms
- Administration errors: lack of patient or caregiver understanding; inappropriate medication administration tools; deviation from the "five rights" (i.e., the *right* drug at the *right* dose for the *right* patient by the *right* route at the *right* time)
- Dispensing errors: inappropriate formulation recommended, prepared or dispensed; use of adult formulations for children

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Iatrogenic adverse drug reaction (unpreventable ADEs)
- Patient nonadherence

WORKUP

Alert from CPOE systems, deviation from standardized order set, or detection on review of prescription or medication order by pharmacist or nurse:

- Immediately discontinue medication order or prescription
- Determine if suspected error has reached the patient
- Assess harm to patient and intervene if necessary
- Determine source of error if possible
- Resume correct drug therapy with appropriate monitoring of efficacy and toxicity
- Report error to institution or facility for tracking and quality improvement purposes
- Report sentinel events to the Joint Commission

LABORATORY TESTS

Supratherapeutic or subtherapeutic serum drug concentrations (if applicable)

TREATMENT

Management of an ADE may include acute treatment of a toxic reaction or long-term management of a suboptimally treated condition. It should always include the workup described above.

ACUTE GENERAL Rx

If the medication error has reached the patient and resulted in an ADE, immediate intervention may be required. Disclosure to the patient or caregiver of an error resulting in harm to the patient is necessary.

CHRONIC Rx

Long-term management of injury or harm resulting from a medication error may be necessary.

DISPOSITION

- Reestablishing trust with the patient or caregiver after an error that resulted in harm to ensure optimal care in the future may be needed.
- The reporting of medication errors should be nonpunitive in nature and intent on individual education and correction of health systems–related flaws.

REFERRAL

Consultation with a pharmacist trained in pediatric pharmacotherapy may improve individual drug therapy and ensure age-specific drug dosing. Interpreters may be necessary to ensure drug information is accurately relayed to non-English-speaking patients or caregivers. Institutional bioethicists or legal counsel may be needed for significant or sentinel events.

PEARLS & CONSIDERATIONS

COMMENTS

- 20% of ADEs occurring in hospitalized children are preventable.
- The most common 10-fold dosing errors involve histamine H_2 antagonist medications and metoclopramide (in children ≤12 mo) and antibiotics or antihistamine-decongestant combination products (in children >12 mo).
- Careful attention must always be focused on the impact growth and development has on the pharmacokinetic characteristics of drugs used in children. A child's dose should not exceed that of an adult. Equations that calculate proportionate doses based on body weight or body surface area do not take into consideration these age-related changes.

PREVENTION

- Health systems management: medication reconciliation at admission and discharge; independent verification of medication orders by pharmacists and administration by nurses; elimination of medical abbreviations within medication orders and prescriptions. Automated clinical decision supports can provide prompts at the time of prescribing or ordering.
- Communication: interdisciplinary cooperation can prevent medication errors. Drug information must be presented and reinforced at a level and in a language understandable to patients or caregivers.
- Education: health care professionals must remain knowledgeable of current standards of care and new drug therapy options.

- Review of drug therapy: reassess prescriptions for accurate age-appropriate dosing and the indication for drug therapy, monitor for efficacy and toxicity, and reconfirm a patient or caregiver's understanding of the drug regimen.

PATIENT & FAMILY EDUCATION

- Caregivers should always remind a child's doctor of any drug allergies or side effects the child has had in the past.
- Caregivers should be instructed on the correct method of measuring liquid medication doses using appropriately gradated oral medication syringes or droppers and to not use common kitchen utensils.
- Do not use over-the-counter cough and cold medicines for children less than 4 yr.
- A list of all the medicines, including over-the-counter products, a child uses should be kept and shared with all the doctors the child sees.
- Caregivers should ask a child's doctor or pharmacist as many questions as needed to ensure understanding.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **BRIAN J. COWLES, PHARM.D.**

SUGGESTED READINGS

Kozer E et al.: Medication errors in children, *Pediatr Drugs* 11:52–54, 2009.

Sharek PJ, Classen D: The incidence of adverse events and medical error in pediatrics, *Pediatr Clin North Am* 53:1067, 2006.

Tham E et al.: Sustaining and spreading the reduction of adverse drug events in a multicenter collaborative, *Pediatrics* 28:e438, 2011.

Wong ICK et al.: Minimising medication errors in children, *Arch Dis Child* 94:161, 2009.

Yin HS et al.: Parents' medication administration errors: role of dosing instruments and health literacy, *Arch Pediatr Adolesc Med* 164:181, 2010.

Yin HS et al.: Unit of measurement used and parent medication dosing errors, *Pediatrics* 134:e354, 2014.

BASIC INFORMATION

DEFINITION

Pediculosis is lice infestation. Human beings can be infested with three kinds of lice: *Pediculus capitis* (head louse), *Pediculus corporis* (body louse), and *Phthirus pubis* (pubic, or crab, louse). Lice feed on human blood and deposit their eggs (nits) on the hair shafts (head lice and pubic lice) and along the seams of clothing (body lice). Nits generally hatch within 7 to 10 days. Lice are obligate human parasites and cannot survive away from their hosts for longer than 7 to 10 days.

SYNONYMS

Lice

ICD-9CM CODES
132.9 Pediculosis
ICD-10CM CODES
B85.2 Pediculosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- There are 6 to 12 million cases of head lice in the United States yearly. The estimated annual direct and indirect cost of head louse infestation in the United States is $1 billion.
- Lice infestation of the scalp is most common in children (girls affected more often than boys).
- Infestation of the eyelashes is most frequently seen in children and may indicate sexual abuse.
- The chance of acquiring pubic lice from one sexual exposure with an infested partner is >90% (most contagious STD known).
- Body lice is most common in conditions of poor hygiene.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pruritus with excoriation may be caused by hypersensitivity reaction, inflammation from saliva, and fecal material from the lice.
- Nits can be identified by examining hair shafts.

FIGURE P1-15 Body louse, *Pediculus humanus* var. *corporis*, as it was obtaining a blood meal from human host. (Courtesy Public Health Image Library, Centers for Disease Control and Prevention. From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

- The presence of nits on clothes is indicative of body lice.
- Lymphadenopathy may be present (cervical adenopathy with head lice, inguinal lymphadenopathy with pubic lice).
- Head lice is most frequently found in the back of the head and neck, behind the ears.
- Scratching can result in pustules and crusting.
- Pubic lice may affect the hair around the anus.

ETIOLOGY

Lice are transmitted by close personal contact or use of contaminated objects (e.g., combs, clothing, bed linen, hats).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Seborrheic dermatitis
- Scabies
- Eczema
- Other: pilar casts, trichonodosis (knotted hair), monilethrix

WORKUP

Diagnosis is made by seeing the lice (Fig. P1-15) or their nits. Combing hair with a fine-toothed comb is recommended because visual inspection of the hair and scalp may miss more than 50% of infestations.

LABORATORY TESTS

Wood's light examination is useful to screen a large number of children: live nits fluoresce, empty nits have a gray fluorescence, nits with unborn louse reveal white fluorescence.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Patients with body lice should discard infested clothes and improve their hygiene.
- Combing out nits is a widely recommended but unproven adjunctive therapy.
- Personal items such as combs and brushes should be soaked in hot water for 15 to 30 min.
- Close contacts and household members should also be examined for the presence of lice.

ACUTE GENERAL Rx

The following products are available for treatment of lice:

- Permethrin: available over the counter (1% permethrin [Nix]) or by prescription (5% permethrin [Elimite]); should be applied to the hair and scalp and rinsed out after 10 min. A repeat application 7 days later is generally not necessary in patients with head lice. It can be applied to clean, dry hair and left on overnight (8 to 14 hours) under a shower cap. Resistance to permethrin is now widespread.
- Malathion, an organophosphate, is effective in head lice. It is available by prescription. Use should be avoided in children ≤2 yr. It is not commonly used because of its objectionable odor, fear of flammability, and prolonged application time (8 to 12 hr).
- Spinosad (Natroba) is a newer FDA-approved product for head lice. It is a topical suspension applied to dry hair for 10 min, then rinsed. It may be repeated 7 days later if necessary. It is more effective than permethrin but also much more expensive. It is safe in pregnancy (category B—no evidence of risk in humans).
- Benzyl alcohol lotion, 5% (Ulesfia) can be used for treatment of head lice in patients >6 mo old. The lotion is applied to dry hair and left on for 10 min. Treatment must be repeated after 7 days because the drug is not ovicidal.
- Eyelash infestation can be treated with the application of petroleum jelly rubbed into the eyelashes three times a day for 5 to 7 days. The application of baby shampoo to the eyelashes and brows three or four times a day for 5 days is also effective. The use of fluorescein drops applied to the lids and eyelashes is also toxic to lice.
- In patients who have previously not responded to treatment or in whom resistance with 1% permethrin cream rinse occurs, a 10-day course of trimethoprim-sulfamethoxazole (TMP-SMX) 8 mg/kg/day in divided doses is an effective treatment for head lice infestation, especially for eyelash infestations with *Phthirus pubis*.
- Ivermectin, an antiparasitic drug, given as an oral dose of 400 mcg/kg of body weight on days 1 and 8, is effective for head lice resistant to other treatments (currently not FDA approved for pediculosis). Ivermectin 0.5% lotion is FDA approved as a single-use topical treatment for head lice in patients 6 mo or older. Cost is more than $200 for 4 oz.

PEARLS & CONSIDERATIONS

COMMENTS

- Patients with pubic lice should notify their sexual contacts. Sex partners within the last month should be treated.
- Parents of patients should also be educated that head lice infestation (unlike body lice) does not indicate poor hygiene.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Lice (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Chosidow O et al.: Oral ivermectin versus malathion lotion for difficult-to-treat head lice, *N Engl J Med* 362:896–905, 2010.

Flinders DC, DeSchweinitz P: Pediculosis and scabies, *Am Fam Physician* 69:341, 2004.

Pariser DM et al.: Topical 0.5% ivermectin lotion for treatment of head lice, *N Engl J Med* 367:1687–1693, 2012.

Roberts RJ: Head lice, *N Engl J Med* 346:1645, 2002.

Stough D et al.: Efficacy and safety of spinosad and permethrin cream rinses for pediculosis capitis, *Pediatrics* 124:e389–e395, 2009.

BASIC INFORMATION

DEFINITION

According to the DSM-5, pedophilic disorder (PD) is one of eight identified paraphiliac disorders. A paraphilic disorder is described as a paraphilia or "any intense and persistent sexual interest other than sexual interest in genital stimulation or preparatory fondling with phenotypically normal, physically mature, consenting human partners," that either causes distress or functional impairment to the individual or entails personal harm or risk of harm to others. The diagnostic criteria for PD include the presence of recurrent, intense sexually arousing fantasies, sexual urges, or behaviors involving sexual activity with a prepubescent child or children (generally age 13 years or younger) that occur over a period of at least 6 months. The individual has acted on these urges or the urges have caused significant distress or interpersonal difficulty. The individual must be at least 16 yr and at least 5 yr older than the object of the sexual interest. DSM-5 subtypes pedophilic disorder into categories based on his/her victim gender preference (males, females, or both), on the exclusivity of the sexual urges (attracted only to children or not), and on his/her relationship with the victim ("limited to incest"). Individuals in late adolescence involved in ongoing sexual relationships with 12- or 13-year-old children are not included for this disorder in DSM-5.

ICD-9CM and DSM-5 CODES
302.2 Pedophilia
ICD-10CM CODES
F65.4 Pedophilia

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Unknown, with likely maximum of 5% in the male population and much smaller in the female population.
ONSET: Around the time of puberty, as adolescents begin to develop sexual interest.
PREDOMINANT SEX: The significant majority of pedophiles are men (females commit roughly 1% to 6% of child sexual assault).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Diagnosis is made by clinical interview and is often complicated by reluctance to disclose symptoms unless the behaviors have already been identified.
- Legal involvement is common and may be the reason for presentation for care.
- Sex offenders have higher rates of *general* crime recidivism than *sexual* crime recidivism. When known child molesters are rearrested, ~40% of their rearrests are for sexual offenses.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Antisocial personality disorder
- Conduct disorder
- Substance use disorder or intoxication
- Obsessive compulsive disorder

WORKUP

Requires comprehensive data from multiple sources, including self-report, past sexual offense convictions, past and present partner report, psychophysiologic assessments, forensic computer analysis, and/or assessment tools. Deviant sexual preferences and lifestyle instability/criminality are strongly associated with general sexual recidivism. Therefore, clinical interview should explore sexual preferences (sex drive, paraphilic interests, victim characteristics), past sexual behaviors (including inquiry into the use of child pornography), and a history of rule violation, substance abuse, and risk taking. It is also important to explore opportunities that the individual has to be around children as well as exploring an individual's strengths and protective factors.

SCALES AND LABORATORY TESTS

- Penile plethysmography: The penile volume or circumference is measured in response to a variety of sexual materials. The result may be a predictor of sexual recidivism for individuals who have committed sexual offenses. However, ~20% to 30% of individuals tested are considered low or nonresponders. Further, in the United States, possession of the viewing material (child pornography) presents a legal dilemma for researchers. Other limitations include its lack of applicability to females, lack of applicability to males with impotence, and ability of individuals to try to suppress sexual feelings via distraction. This form of testing is not currently admissible in court for the purpose of determining guilt.
- Viewing Time: Viewing time is correlated with self-reported sexual interest and phallometric sexual arousal to children. No studies report that this measure predicts recidivism.
- Both of the above tests require the provider to show visual stimuli that may violate U.S. laws around possession of child pornography.
- Scales: For the prediction of general sexual recidivism, the most accurate approach appears to be the use of certain actuarial and mechanical measures. Some of the measures include the Static 99, MNSOST-3, Risk Matrix-2000, and the SVR 20 for adults, or the J-SOAP-II, ERASOR, and J-SORRAT-II for juveniles+. An individual's likelihood to recidivate is estimated based on the average risk of a group of individuals with similar characteristics.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Treatment for sexually aggressive behaviors in general typically incorporates multiple modalities, including individual, group, family, social skills, behavioral, and educational therapies.
- Key elements of treatment include taking responsibility for behaviors, developing empathy for victims, developing skills to prevent re-offending
- General goals of treatment include improved control of deviant behaviors, impulse control, and coping; enhanced conflict resolution, anger management, and social skills; enhanced sense of empathy; understanding of cycle of thoughts, feelings, and events leading to inappropriate behaviors; respect within male-female relationships; and sexual education promoting healthy sexual behaviors (especially when working with juveniles).
- Community interventions might include the education of parents (re: high-risk situations, neighborhood sex offenders) and the education of children (re: assertiveness training, etc.).

PHARMACOLOGIC THERAPY

All used off-label in adults, adolescents, and children

Goals of treatment include suppression and elimination of deviant sexual fantasies, elimination of deviant sexual urges and behaviors, and reduction of risk for recidivism.

Selective serotonin reuptake inhibitors (SSRIs)

- Primary choice in adolescents, since few side effects (especially on adolescent physiological development)
- Case reports and small studies supporting use of fluoxetine, sertraline

Antiandrogens and hormonal agents

- Medroxyprogesterone acetate (MPA)
  1. Most common hormonal agent in the United States
  2. Evidence mostly based on open trials
  3. Reduces sex drive, sexual fantasy, sexual activity
  4. Reduces sex drive, sexual fantasy, sexual activity
  5. Side effects include nausea, vomiting, feminization, weight gain, decreased sperm production, diabetes mellitus, headaches, deep vein thrombosis, hot flashes
  6. Induces testosterone-reductase in the liver, increasing metabolic clearance of testosterone and decreasing plasma testosterone
  7. Also has progestinic effect, leading to reduction of gonadotropin secretion
- Cyproterone acetate (CPA)
  1. Most common in Canada
  2. Antiandrogenic, antigonadotropic, progestinic effects
  3. Principal effect at androgen receptors—blocks intracellular testosterone uptake and metabolism of androgen

4. Similar effects to MPA
5. Effects dose dependent
6. Research indicates decrease in posttreatment recidivism rates for paraphilias
7. Side effects include decreased erections, masturbation, and sexual intercourse; liver dysfunction; adrenal suppression; osteoporosis; osteopenia

- Only should be used rarely by psychiatrists with experience in conjunction with pediatric endocrinologist for severe behaviors (short-term use)

Luteinizing hormone-releasing hormone (LHRH) agonists

- Leuprolide acetate most common in the United States
- Goserelin acetate available, triptorelin acetate likely available soon
- Specifically target paraphilias
- Pharmacologic castration effect
- Not recommended in children <18 yr, only indicated for severe symptoms in adults
- Overstimulation of hypothalamic-pituitary axis leading to inhibition of gonadotropin secretion
- Reduction or elimination of testosterone makes them useful in treating prostate cancer

REFERRAL

Refer to specialty mental health.

PEARLS & CONSIDERATIONS

- Individuals with pedophilia who have had no known risk of prior sexual contacts with children are at unknown risk to offend.
- Physicians must be aware of reporting requirements in their jurisdiction.

SUGGESTED READINGS

Miller L: Sexual offenses against children: patterns and motives, *Aggression Violent Behav* 18(5):506–519, 2013.

Seto MC: Pedophilia, *Annu Rev Clin Psychol* 5:391–407, 2009.

Seto MC, Kingston DA, Bourget D: Assessment of the paraphilias, *Psychiatr Clin North Am* 37(2):149–161, 2014.

White P et al.: *Managements for people with disorders of sexual preference and for convicted sexual offenders*, Cochrane Collaboration, 2009, Wiley.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pedophilia (Patient Information)

AUTHORS: **HASSAN M. MINHAS, M.D, ELIZABETH A. LOWENHAUPT, M.D.,** and **SARAH L. XAVIER, D.O.**

BASIC INFORMATION

DEFINITION

Pelvic inflammatory disease (PID) is a polymicrobial infection of the upper genital tract, including a combination of any of the following:

- Endometritis, salpingitis, tubo-ovarian abscess, or pelvic peritonitis
- Resulting from an ascending lower genital tract infection
- Not related to obstetric or surgical intervention

SYNONYMS

PID
Adnexitis
Pyosalpinx
Salpingitis
Tubo-ovarian abscess

ICD-9CM CODES

614.9 Unspecified inflammatory disease of female pelvic organs and tissue

ICD-10CM CODES

A54.2 Gonococcal pelviperitonitis and other gonococcal genitourinary infections
A56.1 Chlamydial infection of pelviperitoneum and other genitourinary organs
N73.9 Female pelvic inflammatory disease, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE/PREVALENCE

- Estimated 600,000 to 1 million cases annually (United States), affecting primarily young sexually active women
- Diagnosed in 2% to 5% of women seen in sexually transmitted disease clinics
- Very common cause of female infertility and ectopic pregnancy

RISK FACTORS

- Adolescent sexually active females <20 yr
- Previous episode of gonococcal PID
- Multiple sexual partners

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Lower abdominal pain
- Abnormal vaginal discharge
- Abnormal uterine bleeding
- Dysuria
- Dyspareunia
- Nausea and vomiting (suggestive of peritonitis)
- Fever
- Right upper quadrant tenderness (perihepatitis): 5% of PID cases
- Cervical motion tenderness and adnexal tenderness
- Adnexal mass

ETIOLOGY

- *Chlamydia trachomatis*
- *Neisseria gonorrhoeae*
- Polymicrobial infection: *Bacteroides fragilis, Escherichia coli, Gardnerella vaginalis, Haemophilus influenzae, Mycoplasma hominis, Ureaplasma urealyticum*
- *Mycobacterium tuberculosis* (an important cause in developing countries)
- Cytomegalovirus (CMV)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Ectopic pregnancy
- Appendicitis
- Ruptured ovarian cyst
- Endometriosis
- Urinary tract infection (cystitis or pyelonephritis)
- Renal calculus
- Adnexal torsion
- Proctocolitis

WORKUP

Diagnostic considerations:

- Clinical diagnosis is difficult and imprecise. The spectrum of disease ranges from asymptomatic to life-threatening tubo-ovarian abscess. PID should be suspected in at-risk patients who present with pelvic or lower abdominal pain.
- Clinical diagnosis of symptomatic PID has a positive predictive value of 65% to 90% compared with laparoscopy as the standard.
- No single historical, physical, or laboratory finding is both sensitive and specific for the diagnosis of PID.
- Empiric treatment for PID should be initiated in sexually active young women and other women at risk for STDs if they are experiencing pelvic or lower abdominal pain, if no cause for the illness other than PID can be identified, and if one or more of the following minimum criteria are present on pelvic examination:
  1. Uterine tenderness
  2. Adnexal tenderness
  3. Cervical motion tenderness
- The requirement that all three minimum criteria be present before the initiation of empiric treatment could result in insufficient sensitivity for the diagnosis of PID. The presence of signs of lower genital tract inflammation (predominance of leukocytes in vaginal secretions), in addition to one of the three minimum criteria, increases the specificity of the diagnosis.
- Additional criteria to increase the specificity of the diagnosis of PID in women with severe clinical signs:
  1. Oral temperature >38.3° C (101° F)
  2. Abnormal cervical or vaginal discharge
  3. Elevated erythrocyte sedimentation rate (ESR)
  4. Elevated C-reactive protein
  5. Laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*
- Presence of abundant numbers of WBCs on saline microscopy of vaginal fluid.
- Definitive criteria for diagnosing PID warranted in selected cases:
  1. Laparoscopic abnormalities consistent with PID
  2. Histopathologic evidence of endometritis on biopsy. Endometrial biopsy is warranted in women undergoing laparoscopy who do not have visual evidence of salpingitis because endometritis is the only sign of PID in some women
  3. Transvaginal sonography or other imaging techniques showing thickened fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex

LABORATORY TESTS

- Leukocytosis
- Elevated acute phase reactants: ESR >15 mm/hr, C-reactive protein
- Gram stain of endocervical exudate: >30 polymorphonuclear cells per high-power field correlates with chlamydial or gonococcal infection
- Endocervical cultures for *N. gonorrhoeae* and *C. trachomatis*
- Fallopian tube aspirate or peritoneal exudate culture if laparoscopy performed
- Human chorionic gonadotropin to rule out ectopic pregnancy

IMAGING STUDIES

- Transvaginal ultrasound to look for adnexal mass has sensitivity for PID of 81%, specificity of 78%, and accuracy of 80%.
- MRI has sensitivity for PID of 95%, specificity of 89%, and accuracy of 93%. It is useful for establishing the diagnosis of PID and detecting other processes responsible for the symptoms. Disadvantages are its higher cost and limited availability.
- CT scan (Fig. P1-16).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Most patients are treated as outpatients.
- Criteria for hospitalization (CDC, 2006) as follows:
  1. Surgical emergencies such as appendicitis cannot be excluded
  2. Tubo-ovarian abscess
  3. Pregnant patient
  4. Patient is immunodeficient
  5. Severe illness, nausea, or vomiting precluding outpatient management
  6. Patient unable to follow or tolerate outpatient regimens
  7. No clinical response to outpatient therapy

ACUTE GENERAL Rx

Regimens for treatment of PID should also be effective against *N. gonorrhoeae* and *C. trachomatis* because endocervical screening for these organisms does not rule out upper reproductive tract infections.

INPATIENT REGIMENS

Recommended parenteral regimen A

- Cefotetan 2 g IV q12h OR
- Cefoxitin 2 g IV q6h PLUS
- Doxycycline 100 mg PO or IV q12h

Recommended parenteral regimen B

- Clindamycin 900 mg IV q8h PLUS

- Gentamicin loading dose IV or IM (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) q8h. Single daily dosing (3 to 5 mg/kg) can be substituted.

Alternative parenteral regimens

- Ampicillin/sulbactam 3 g IV q6h
- PLUS
- Doxycycline 100 mg PO or IV q12h

OUTPATIENT REGIMENS

Recommended regimen

- Ceftriaxone 250 mg IM in a single dose
- PLUS
- Doxycycline 100 mg PO bid for 14 days
- WITH or WITHOUT
- Metronidazole 500 mg PO bid for 14 days
- OR
- Cefoxitin 2 g IM in a single dose and probenecid, 1 g PO administered concurrently in a single dose

PLUS

- Doxycycline 100 mg PO bid for 14 days
- WITH or WITHOUT
- Metronidazole 500 mg PO bid for 14 days
- OR
- Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime)

PLUS

- Doxycycline 100 mg PO bid for 14 days
- WITH or WITHOUT
- Metronidazole 500 mg PO bid for 14 days

CHRONIC Rx

Hospitalized patients receiving IV therapy:

1. Significant clinical improvement is characterized by defervescence, decreased abdominal tenderness, and decreased uterine, adnexal, and cervical motion tenderness within 3 to 5 days.
2. If no clinical improvement occurs, further diagnostic workup is necessary, including possible surgical intervention.

DISPOSITION

- Long-term sequelae of PID: recurrent PID, chronic pelvic pain, ectopic pregnancy, infertility, Fitz-Hugh-Curtis syndrome (Fig. P1-17)
- Risk of tubal infertility related to episodes of PID: first episode, 8%; second episode, 20%; third episode, 40%
- Essential to evaluate and treat male sex partners

REFERRAL

If there is no clinical improvement with outpatient therapy observed within 72 hr, patient should be hospitalized and gynecology consult requested.

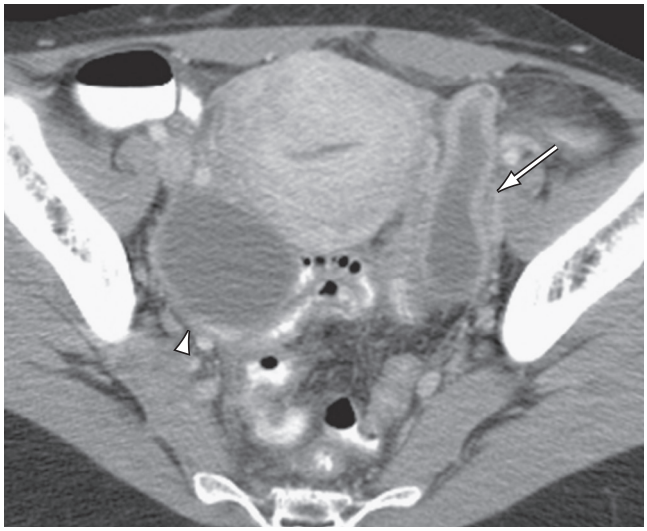


FIGURE P1-16 Pelvic inflammatory disease with pyosalpinx in a 26-yr-old patient. Computed tomographic image through pelvis shows cystic tubular structure with thick enhancing walls *(arrow)* lateral to the uterus, which, in absence of oral contrast, could be mistaken for a loop of small bowel. (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.)

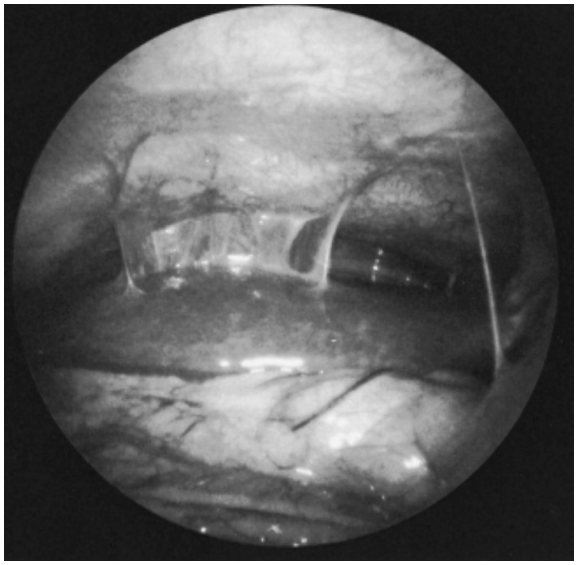


FIGURE P1-17 "Violin string" adhesions are visualized in this patient with Fitz-Hugh-Curtis syndrome. (From Copeland LJ: *Textbook of gynecology,* ed 2, Philadelphia, 2000, Saunders.)

PEARLS & CONSIDERATIONS

COMMENTS

- Maintain a low threshold for the diagnosis of PID.
- Women with documented chlamydial or gonococcal infections have a high rate of reinfection within 6 mo of treatment. Repeat testing of all women who have been diagnosed with chlamydia or gonorrhea is recommended 3 to 6 mo after treatment, regardless of whether their sex partners were treated.
- All women diagnosed with acute PID should be offered HIV testing.
- Male sex partners of women with PID should be examined and treated if they had sexual contact with the patient during 60 days preceding the patient's onset of symptoms. If a patient's last sexual intercourse was >60 days before onset of symptoms or diagnosis, the patient's most recent sex partner should be treated.
- Patients should be instructed to abstain from sexual intercourse until therapy is completed and until they and their sex partners no longer have symptoms.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pelvic Inflammatory Disease (Patient Information)
Abscess, Pelvic (Related Key Topic)
Chlamydia Genital Infections (Related Key Topic)
Gonorrhea (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Centers for Disease Control and Prevention: 2010 sexually transmitted diseases treatment guidelines, *MMWR* 59(RR-12), 2010.

Gradison M: Pelvic inflammatory disease, *Am Fam Physician* 85(8):791–796, 2012.

BASIC INFORMATION

DEFINITION

Pelvic organ prolapse (POP) or *uterine prolapse* refers to the protrusion of the uterus into or out of the vaginal canal. In a first-degree uterine prolapse, the cervix is visible when the perineum is depressed. In a second-degree uterine prolapse, the uterine cervix has prolapsed through the vaginal introitus, with the fundus remaining within the pelvis proper. In a third-degree uterine prolapse (i.e., complete uterine prolapse, uterine procidentia), the entire uterus is outside the introitus. Table P1-8 compares the various types of prolapse.

SYNONYMS

Genital prolapse
Uterine descensus
Uterine prolapse
POP

ICD-9CM CODES
618.8 Genital prolapse
618.1 Uterine descensus
618.8 Pelvic organ prolapse
ICD-10CM CODES
N81.4 Uterovaginal prolapse, unspecified
N81.5 Vaginal enterocele
N81.6 Rectocele
N81.I8 Other female genital prolapse
N81.89 Other female genital prolapse
N81.2 Incomplete uterovaginal prolapse
N81.82 Incompetence or weakening of pubocervical tissue

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Most prevalent in postmenopausal multiparous women.

RISK FACTORS

- Pregnancy, especially POP symptoms during pregnancy
- Labor
- Vaginal childbirth
- Obesity
- Chronic coughing
- Constipation
- Pelvic tumors
- Ascites
- Strenuous physical exertion, especially during pregnancy
- Maternal history of prolapse
- Caucasian race

GENETICS: Increased incidence in women with spina bifida occulta.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pelvic pressure
- Bearing-down sensation
- Bilateral groin pain
- Sacral backache
- Coital difficulty
- Protrusion from vagina
- Spotting
- Ulceration
- Bleeding
- Examination of patient in lithotomy, sitting, and standing positions and before, during, and after a maximum Valsalva effort
- Erosion or ulceration of the cervix possible in the most dependent area of the protrusion

ETIOLOGY

- Vaginal childbirth and chronic increases in intraabdominal pressure leading to detachments, lacerations, and denervations of the vaginal support system
- Further weakening of pelvic support system by hypoestrogenic atrophy
- Direct injury to the levator ani, neurologic injury from stretching of the pudendal nerves
- Some cases from congenital or inherited weaknesses within the pelvic support system
- Neonatal uterine prolapse mostly coexistent with congenital spinal defects

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Occasionally, elongated cervix; body of the uterus remains undescended.
- Diagnosis is based on history and physical examination. Currently there is only one genital tract prolapse classification system that has attained international acceptance and recognition: the patient pelvic organ prolapse quantification (POP-Q) (Boxes P1-2 and P1-3).

WORKUP

- If erosion or ulceration of the cervix is present, a Pap smear followed by a cervical biopsy should be performed if indicated.
- If urinary symptoms are significant, further urodynamic workup is indicated, looking for concurrent cystourethrocele, cystocele, enterocele, or rectocele.

TABLE P1-8 Types of Genital Prolapse

Original Position of Organs	Prolapse	Symptoms (in addition to the general symptoms of discomfort, dragging, the feeling of a "lump" and, rarely, coital problems)
Anterior	Urethrocele Cystocele	Urinary symptoms (stress incontinence, urinary frequency)
Central	Cervix/uterus: 1st, 2nd, and 3rd degree Procidentia	Bleeding and/or discharge from ulceration in association with procidentia
Posterior	Rectocele Enterocele	Bowel symptoms, particularly the feeling of incomplete evacuation and sometimes having to press the posterior wall backwards to pass stool

From Drife J, Magowan B: *Clinical obstetrics and gynaecology,* Philadelphia, 2004, Saunders.

BOX P1-2 Staging of Pelvic Organ Prolapse Based on POP-Q Examination

Stage 0	No prolapse.
Stage I	Most distal prolapse >1 cm above hymenal ring.
Stage II	Most distal point is ≤1 cm above hymenal ring.
Stage III	Most distal point is >1 cm below the hymenal ring but not farther than 2 cm less than the total vaginal length (TVL) (i.e., ≥1 cm but ≤ [TVL – 2] cm).
Stage IV	Complete vaginal eversion.

From Pemberton J (ed): *The pelvic floor,* Philadelphia, 2002, Saunders.

BOX P1-3 Points of Reference for POP-Q

Point A: 3 cm above the hymen on anterior vaginal wall (Aa) or posterior vaginal wall (Ap). Point Aa roughly corresponds with the urethrovesical junction.
Point B: The lowest extent of the segment of vagina between point A and the apex of the vagina. Unlike point A, it is not fixed but will be the same as A if point A is the most protruding point. In maximal prolapse it will be the same as point C.
Point C: The most distal part of the cervix or vaginal vault.
Point D: The posterior fornix, which is omitted in women with prior hysterectomy.
Genital hiatus: From midline external urethral meatus to inferior hymenal ring.
Perineal body: From inferior hymenal ring to middle of anal orifice.
Vaginal length: This should be measured without undue stretching of the vagina.

From Pemberton J (ed): *The pelvic floor,* Philadelphia, 2002, Saunders.

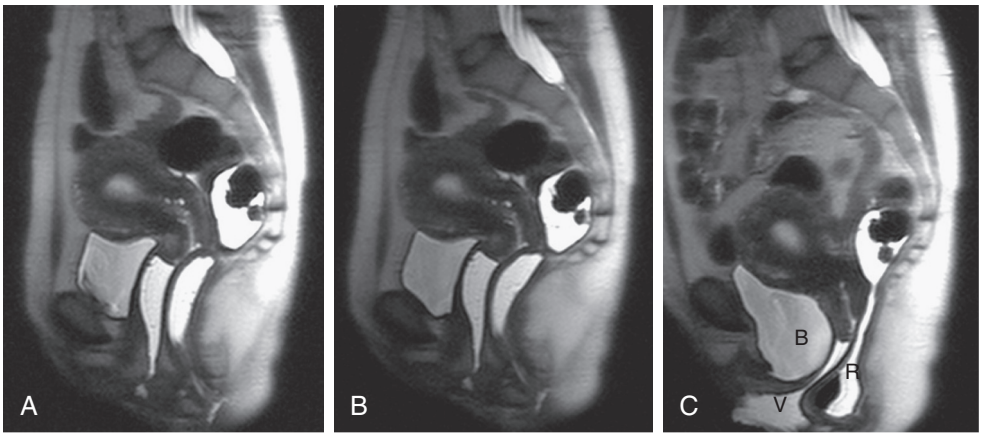


FIGURE P1-18 A, Moderate global pelvic prolapse in a woman with stress urinary incontinence, pelvic heaviness, and constipation after three vaginal deliveries. At rest, all viscera are normally situated in the pelvis. **B**, With Kegel contraction, note that all viscera remain normally situated in the pelvis. **C**, With maximal strain, bladder *(B)*, vagina *(V),* and rectum *(R)* are well below the pelvic floor. (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.)

LABORATORY TESTS
Urine culture

IMAGING STUDIES
Ultrasound if concurrent fibroids need further evaluation, CT or MRI (Fig. P1-18) in symptomatic patients with unclear diagnosis

Rx TREATMENT

NONPHARMACOLOGIC THERAPY
- Prophylactic measures
  1. Diagnosis and treatment of chronic respiratory and metabolic disorders
  2. Correction of constipation
  3. Weight control, nutrition, and smoking cessation counseling
  4. Pelvic muscle exercises
- Supportive pessary therapy
  1. Ring-type pessary useful for first- or second-degree prolapse
  2. Gellhorn pessary preferred for more advanced prolapse
  3. Use of pessaries in conjunction with continuous hormone replacement therapy, unless contraindicated
  4. Perineorrhaphy under local anesthesia possibly needed to support the pessary if the vaginal outlet is very relaxed

ACUTE GENERAL Rx
- Patients who are only infrequently symptomatic: insertion of a tampon or diaphragm for temporary relief when prolonged standing is anticipated
- Neonatal uterine prolapse: simple digital reduction or the use of a small pessary

CHRONIC Rx
- Hormone replacement therapy at the time of menopause helps preserve tissue strength, maintain elasticity of the vagina, and promote the durability of surgical repairs.
- Gold standard for therapy is vaginal hysterectomy.
- Vaginal apex should be well suspended, but a prophylactic sacrospinous ligament fixation is not routinely required.
- If occult enterocele present, McCall culdoplasty is performed.
- If vaginal approach to hysterectomy is contraindicated, abdominal hysterectomy is performed; vaginal apex likewise well supported. Use of laparoscopically assisted approaches, including robotically assisted approaches are increasingly being used. Questions do exist as to whether the robotic approach is cost-effective for this indication.
- Colpocleisis is considered for the elderly patient who is sexually inactive and is a high-risk patient from a surgical point of view; can be done rapidly under local anesthesia with mild sedation if necessary.
- For symptomatic women who desire childbearing: management with pessaries or pelvic muscle exercises is recommended; if surgical correction is required, transvaginal sacrospinous fixation is the preferred method.
- Other surgical options are sling operations and sacral cervicopexy.
- Trials have shown that as compared with anterior colporrhaphy, use of a standardized, trocar-guided mesh kit for cystocele repair results in higher short-term rates of successful treatment but also in higher rates of surgical complications and postoperative adverse events.
- Women without stress incontinence undergoing vaginal surgery for POP are at risk for postoperative urinary incontinence. Use of a prophylactic midurethral sling inserted during vaginal prolapse surgery has been shown to result in a lower rate of urinary incontinence at 3 and 12 months but a higher rate of adverse events (UTIs, major bleeding complications, incomplete bladder emptying).

DISPOSITION
If untreated, uterine prolapse progressively worsens.

REFERRAL
To a gynecologist/urologist if pessary fitting or surgical intervention is needed

PEARLS & CONSIDERATIONS

COMMENTS
- More than 300,000 surgeries are performed annually in the United States for pelvic organ prolapse
- Surgery contraindicated in mild or asymptomatic uterine prolapse because the patient will seldom benefit from the operation although exposed to its risks.
- The Optimal Randomized Trial compared the sacrospinous ligament fixation (SSLF) and uterosacral ligament suspension (ULS) surgical approaches to correct apical prolapse and also whether perioperative behavioral therapy with pelvic floor muscle training (BPMT) improved outcomes of prolapse surgery. The trial showed that two years after vaginal surgery for prolapse and stress urinary incontinence, neither ULS or SSLF was significantly superior to the other for anatomic, functional, or adverse event outcomes. Perioperative BPMT did not improve urinary symptoms at 6 mo or prolapse outcomes at 2 yr.[1]

SUGGESTED READINGS
Available at www.expertconsult.com

RELATED CONTENT
Uterine Prolapse (Patient Information)
Incontinence, Urinary (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

[1]Barber MD et al: Comparison of 2 transvaginal surgical approaches and perioperative behavioral therapy for apical vaginal prolapse, the Optimal Randomized Trial, *JAMA* 311(10):1023-1034, 2014

SUGGESTED READINGS

Altman D et al.: Anterior colporrhaphy versus transvaginal mesh for pelvic-organ prolapse, *N Engl J Med* 364:1826–1836, 2011.

Barber MD et al.: Comparison of 2 transvaginal surgical approaches and perioperative behavioral therapy for apical vaginal prolapse, the Optimal Randomized Trial, *JAMA* 311(10):1023–1034, 2014.

Kuncharapu I et al.: Pelvic organ prolapse, *Am Fam Physician* 81(9):1117–1120, 2010.

Marijke C et al.: Symptomatic pelvic organ prolapse and possible risk factors in a general population, *Am J Obstet Gynecol* 200:184, 2009.

Rapp DE, King AB, Rowe B, et al.: Comprehensive evaluation of anterior elevate system for the treatment of anterior and apical pelvic floor descent: 2-year followup, *J Urol* 191:389–394, 2014.

Thaker R: Management of uterine prolapse, *BMJ* 324:1258, 2002.

Wei JT et al.: A midurethral sling to reduce incontinence after vaginal prolapse repair, *N Engl J Med* 366:2358–2367, 2012.

EVIDENCE

Abstract[1]

Pelvic Prolapse

Purpose:

The Elevate® Anterior and Apical Prolapse Repair System is a polypropylene mesh that is anchored through sacrospinous ligament and obturator fascia fixation points. We present a comprehensive evaluation of this prolapse repair system through 2 years with a focus on safety, operative characteristics, and anatomical, subjective and quality of life outcomes.

Materials and Methods:

A total of 42 women underwent repair of stage II or greater anterior/apical compartment prolapse using the repair system, of whom 2 were lost to followup. Anatomical outcomes were assessed using POP-Q (Pelvic Organ Prolapse Quantification) staging. Subjective and quality of life outcomes were assessed by the validated ICIQ (International Consultation on Incontinence Questionnaire)-VS (Vaginal Symptoms), ICIQ-FLUTS (Female Lower Urinary Tract Symptoms) and IIQ-7 (Incontinence Impact Questionnaire-7). Additional outcomes included a 3-day bladder diary and cough test with outcomes assessed preoperatively, at 6 weeks, and at 1 and 2 years.

Results:

Mean±SD blood loss was 93±55 cc and mean operative time was 58±27 minutes. POP-Q points Aa, Ba and C improved from 0.9, 0.8 and −1.3 preoperatively to −2.1, −2.7 and −6.1 cm at 2 years, respectively (each $p < 0.05$). Four patients experienced anatomical recurrence, which was associated in 2 with symptomatic recurrence on the ICIQ-VS. Statistically significant improvements in the ICIQ-VS, ICIQFLUTS and IIQ-7 were seen throughout followup. Adverse events included leg pain, vaginal exposure and urinary retention in 1, 2 and 5 patients, respectively.

Conclusions:

The Elevate Anterior and Apical Prolapse Repair System was associated with good anatomical restoration and significant improvements in validated symptom and quality of life indexes through 2 years of assessments. Our experience suggests that the system is a safe, effective surgical procedure in appropriately selected patients. Long-term followup is important, given the FDA (Food and Drug Administration) warning regarding the use of surgical mesh in the repair of pelvic organ prolapse. Ⓐ

Evidence-Based Reference

1. Rapp DE, King AB, Rowe B, et al.: Comprehensive evaluation of anterior elevate system for the treatment of anterior and apical pelvic floor descent: 2-year followup, *J Urol* 191:389–394, 2014. Ⓐ

BASIC INFORMATION

DEFINITION

- *Pemphigus* refers to a group of rare, potentially fatal, chronic, autoimmune blistering diseases of the skin and mucous membranes
- Pemphigus has four main subtypes:
  1. Pemphigus vulgaris (PV) (most common) (Fig. P1-19)
     1. Pemphigus vegetans, a rare clinical variant of PV
  2. Pemphigus foliaceus (PF)
     1. Pemphigus erythematosus, a variant of PF
  3. Paraneoplastic pemphigus
  4. Immunoglobulin (Ig) A pemphigus

SYNONYMS

Pemphigus
Fogo selvagem: endemic pemphigus foliaceus
Senear-Usher syndrome: pemphigus erythematosus

ICD-9CM CODES
694.4 Pemphigus
ICD-10CM CODES
L10.0 Pemphigus vulgaris

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence is approximately one case per 100,000 persons and varies substantially by geographic region.
- More common in Ashkenazi Jews and people of Middle Eastern descent.
- Typically occurs in the fourth and fifth decades of life, although range of ages affected is broad and it may occur in the very young or elderly.
- No gender predilection

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- History:
  1. Multiple oropharyngeal ulcerations and erosions typically occur first, which can then be followed by a more generalized bullous eruption involving the skin within several weeks or months
  2. Blisters are fragile and rupture easily, leaving painful erosions and ulcerations that may be the predominant clinical finding
  3. Pain associated with oral mucosal blistering often results in dysphagia and hoarseness
  4. Not commonly pruritic
- Physical findings:
  1. Anatomic distribution
     a. Oral mucosa
     b. Can also involve the pharynx, larynx, vagina, penis, anus, and conjunctival mucosa
     c. Generalized cutaneous involvement (Figs. P1-20 and P1-21)
  2. Lesion configuration
     a. Any stratified squamous epithelial surfaces can become involved
  3. Lesion morphology
     a. Flaccid bullae and vesicles
     b. Erosion with crusting commonly occurs

FIGURE P1-19 Pemphigus vulgaris with oral lesions and no intact bullae. (Courtesy Department of Dermatology, University of North Carolina at Chapel Hill. From Goldstein BG, Goldstein AO: *Practical dermatology,* ed 2, St Louis, 1997, Mosby.)

FIGURE P1-20 Pemphigus vulgaris; extensive erosions and blisters are present on the shin. (Courtesy R. A. Marsden, M.D., St. George's Hospital, London. From McKee PH et al [eds]: *Pathology of the skin with clinical correlations,* ed 3, St Louis, 2005, Mosby.)

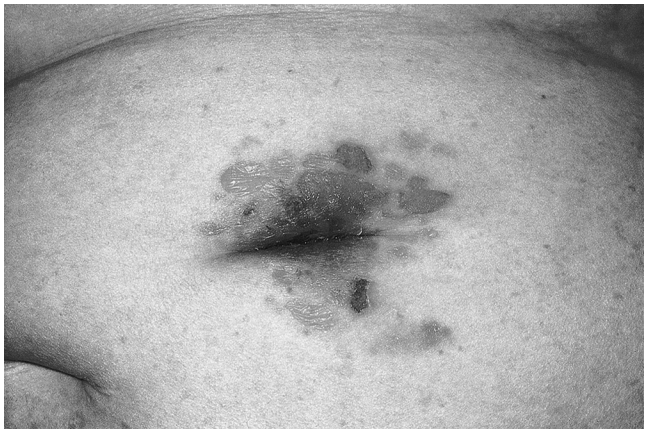


FIGURE P1-21 Pemphigus vulgaris: umbilical lesions showing intact blisters as well as raw erosions. (Courtesy R. A. Marsden, M.D., St. George's Hospital, London. From McKee PH et al [eds]: *Pathology of the skin with clinical correlations,* ed 3, St Louis, 2005, Mosby.)

4. Positive ***Nikolsky sign:*** when the clinician applies lateral pressure to normal-appearing skin at the periphery of active lesions, separation of the superficial epidermis occurs

ETIOLOGY

Autoimmune disease caused by autoantibodies against the cell surface of keratinocytes. The predominant antibody in PV is directed against desmoglein 3; in PF it is directed against desmoglein 1.

Dx DIAGNOSIS

The diagnosis of pemphigus vulgaris should be suspected in patients with painful oral erosions and flaccid bullae or erosions on the skin.

DIFFERENTIAL DIAGNOSIS

- Bullous pemphigoid (Table P1-9)
- Cicatricial pemphigoid
- Behçet's syndrome
- Erythema multiforme
- Hailey-Hailey disease
- Aphthous stomatitis
- Bullous lupus erythematosus
- Drug eruptions
- Dermatitis herpetiformis
- Epidermolysis bullosa acquisita
- IgA pemphigus
- Paraneoplastic pemphigus
- Pemphigus foliaceus

WORKUP

Skin biopsy is diagnostic; specimens should be sent for routine histochemical staining and direct immunofluorescence. Certain laboratory values may also be useful in establishing the diagnosis of pemphigus.

LABORATORY TESTS

- Skin biopsy reveals intraepidermal vesicles, also called *acantholysis* (loss of cell adhesion between the epidermal cells).
- Indirect immunofluorescence may detect circulating autoantibodies.
- Direct immunofluorescence studies of perilesional skin demonstrate IgG directed against keratinocyte surfaces in the epidermis.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Mild soaps and emollients to skin
- Burow's solution may be useful for weeping erosions.
- Soft diet and viscous lidocaine can be used in patients with oral lesions.

ACUTE GENERAL Rx

- For localized disease, topical steroids may be effective.
- For generalized disease, systemic corticosteroids (prednisone) are the mainstay of therapy and often work rapidly to halt blistering.
  1. Initial dose of prednisone is usually 1 mg/kg/day, then tapered over weeks as blistering decreases.
  2. Steroid-sparing immunosuppressive therapies are often initiated simultaneously with prednisone to minimize the side effects of prolonged corticosteroid therapy.

CHRONIC Rx

- Adjuvant therapy such as immunosuppressants, anti-inflammatories, chemotherapeutic agents, and biologics are useful for disease control and to shorten the length of treatment with oral steroids; treatment duration and dosing are determined by clinical response:
  1. Azathioprine 50 to 100 mg/day
  2. Cyclophosphamide 1 to 3 mg/kg/day
  3. Mycophenolate mofetil 500 mg to 2 g daily
- Refractory disease:
  1. IV Ig
  2. Rituximab (anti-CD20 monoclonal antibody)
  3. Plasmapheresis

DISPOSITION

- Before the use of oral corticosteroids, pemphigus was usually a fatal disease with most patients dying within 5 yr of diagnosis.
- Combined corticosteroids and adjuvant therapy have decreased mortality rates to <10%.
- Death generally occurs from sepsis or complications related to medical therapy.

REFERRAL

Dermatology
Otolaryngology

! PEARLS & CONSIDERATIONS

COMMENTS

- PV, unlike bullous pemphigoid, is a disease of middle-aged persons.
- Early diagnosis of pemphigus is important to initiate prompt treatment.
- Oral corticosteroids have many substantial side effects, and patients should be monitored for osteoporosis, hypertension, and diabetes.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pemphigus Vulgaris (Patient Information)

AUTHORS: **JESSICA CORWIN, M.D., M.P.H.** and **KACHIU LEE, B.A.**

TABLE P1-9 Differentiation of Pemphigus Vulgaris and Bullous Pemphigoid

Characteristics	Pemphigus Vulgaris	Bullous Pemphigoid
Age	Usually occurs in middle-aged persons	>60 yr
Site	Oral mucosa, face, chest, groin	Flexural areas, groin, axilla; less often involving mucosal surfaces
Findings	Flaccid bullae and erosions, intraepidermal blisters, IgG autoantibodies against keratinocyte surfaces	Intact bullae, subepidermal blisters, IgG autoantibodies against hemidesmosomal antigens
Treatment	Prednisone 1 mg/kg/day with adjuvant immunosuppressant agents; refractory disease may require intravenous immunoglobulin, plasmapheresis, or rituximab	Prednisone 1 mg/kg/day with adjuvant immunosuppressant therapy; localized disease may be controlled with topical steroids
Prognosis	>90% respond; steroid side effects significant	>90% respond; remissions and recurrences common

SUGGESTED READINGS

Bickle K et al.: Autoimmune bullous dermatoses: a review, *Am Fam Physician* 65(9):2002, 1861.

Dick SE, Werth V: Pemphigus: a treatment update, *Autoimmunity* 39(7):591–599, 2006.

Joly P et al.: A single cycle of rituximab for the treatment of severe pemphigus, *N Engl J Med* 357:545–552, 2007.

Yeh SW et al.: Treatment of pemphigus vulgaris: current and emerging options, *Am J Clin Dermatol* 6(5):327, 2005.

BASIC INFORMATION

DEFINITION

Peptic ulcer disease (PUD) is an ulceration in the stomach or duodenum resulting from an imbalance between mucosal protective factors and various mucosal damaging mechanisms (see "Etiology").

SYNONYMS

PUD
Duodenal ulcer (DU)
Gastric ulcer (GU)

ICD-9CM CODES
536.8 Peptic ulcer disease
531.3 Peptic ulcer, stomach, acute
531.7 Peptic ulcer, stomach, chronic
532.3 Peptic ulcer, duodenum, acute
532.7 Peptic ulcer, duodenum, chronic

ICD-10CM CODES
K25.3 Acute gastric ulcer without hemorrhage or perforation
K25.7 Chronic gastric ulcer without hemorrhage or perforation
K26.3 Acute duodenal ulcer without hemorrhage or perforation
K26.7 Chronic duodenal ulcer without hemorrhage or perforation

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence: 250,000 to 500,000 (200,000 to 400,000 duodenal; 50,000 to 100,000 gastric) annually; duodenal ulcer/gastric ulcer ratio is 4:1.
- Anatomic location: <90% of duodenal ulcers occur in the first portion of the duodenum; gastric ulcers occur most frequently in the lesser curvature near the incisura angularis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination is often unremarkable.
- Patient may have epigastric tenderness, tachycardia, pallor, hypotension (from acute or chronic blood loss), nausea and vomiting (if pyloric channel is obstructed), boardlike abdomen and rebound tenderness (if perforated), and hematemesis or melena (with a bleeding ulcer). Box P1-4 describes key symptoms and signs of peptic ulcer.

ETIOLOGY

Often multifactorial. The following are common mucosal damaging factors:

- *Helicobacter pylori* infection. *H. pylori* is the major cause of PUD. It is found in more than 70% of patients with duodenal ulcers and gastric ulcers in the United States. Rates are much higher (>90%) in other parts of the world. Eradication of *H. pylori* markedly reduces peptic ulcer recurrence.
- Medications (NSAIDs, glucocorticoids). Risk factors for development of NSAID-related ulcers are described in Table P1-10.
- Incompetent pylorus or lower esophageal sphincter
- Bile acids
- Impaired proximal duodenal bicarbonate secretion
- Decreased blood flow to gastric mucosa
- Acid secreted by parietal cells and pepsin secreted as pepsinogen by chief cells
- Cigarette smoking
- Alcohol

TABLE P1-10 Risk Factors for Development of NSAID-Related Ulcers

Definite
Advanced age
History of ulcer
Concomitant corticosteroid therapy
Concomitant anticoagulation therapy
High doses of NSAIDs
Serious systemic disorders
Possible
Concomitant infection with *Helicobacter pylori*
Cigarette smoking
Consumption of alcohol

NSAIDs, Nonsteroidal antiinflammatory drugs.
From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.

BOX P1-4 Key Symptoms and Signs of Peptic Ulcer

Uncomplicated Ulcer
No symptoms ("silent ulcer" in up to 40% of cases)
Epigastric pain
Pain may radiate to the back, thorax, other parts of abdomen (cephalad most likely, caudad least likely)
Pain may be nocturnal (most specific), "painful hunger" relieved by food, or continuous (least specific)
Nausea
Vomiting
Heartburn (mimics or associated with gastroesophageal reflux)

Complicated Ulcer
Acute perforation
Severe abdominal pain
Shock
Abdominal boardlike rigidity (and rebound and other signs of peritoneal irritation)
Free intraperitoneal air
Hemorrhage
Hematemesis and/or melena
Hemodynamic changes, anemia
Previous history of ulcer symptoms (80%)
Gastric outlet obstruction
Satiation, inability to ingest food, eructation
Nausea, vomiting (and related disturbances)
Weight loss

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Gastroesophageal reflux disease
- Cholelithiasis syndrome
- Pancreatitis
- Gastritis
- Nonulcer dyspepsia
- Neoplasm (gastric carcinoma, lymphoma, pancreatic carcinoma)
- Angina pectoris, myocardial infarction, pericarditis
- Dissecting aneurysm
- Other: high small-bowel obstruction, pneumonia, subphrenic abscess, early appendicitis

WORKUP

Comprehensive history and physical exam to exclude other diagnoses. Diagnostic modalities include endoscopy or upper GI series. Endoscopy is preferred.

LABORATORY TESTS

- Routine laboratory evaluation is usually unremarkable.
- Anemia may be present in patients with significant GI bleeding.
- *H. pylori* testing by endoscopic biopsy, urea breath test, stool antigen test (*H. pylori* stool antigen), or specific antibody test is recommended:
  1. Serologic testing for antibodies to *H. pylori* is easy and inexpensive; however, the presence of antibodies demonstrates previous but not necessarily current infection. Antibodies to *H. pylori* can remain elevated for months to years after infection has cleared; therefore antibody levels must be interpreted in light of the patient's symptoms and other test results (e.g., PUD seen on upper GI series).
  2. The urea breath test documents active infection (sensitivity and specificity >90%). The patient ingests a small amount of urea labeled with carbon 13 or carbon 14. If urease is present (produced by the organism), the urea is hydrolyzed and the patient exhales labeled carbon dioxide that is then collected and measured. This test is more expensive and not as readily available. Use of proton pump

inhibitors (PPI) within 2 wk of the urea breath test may interfere with test results. A new card test for ^{14}C urea is available and provides a testing option in primary care settings. It uses a flat breath card that is read by a small analyzer.

3. Histologic evaluation of endoscopic biopsy samples is considered by many the gold standard for accurate diagnosis of *H. pylori* infection. However, detection of *H. pylori* depends on the site and number of biopsy samples, the method of staining, and experience of the pathologist.
4. Stool antigen test is an ELISA that identifies *H. pylori* antigen in a stool specimen through a polyclonal anti–*H. pylori* antibody. It is as accurate as the urea breath test for diagnosis of active infection and follow-up evaluation of patients treated for *H. pylori.* A negative result on the stool antigen test 6 wk after completion of therapy identifies patients in whom eradication of *H. pylori* was successful.

- Additional laboratory evaluation is indicated only in specific cases (e.g., amylase level in suspected pancreatitis, serum gastrin level in suspected Zollinger-Ellison [ZE] syndrome).

IMAGING STUDIES

Conventional upper GI barium studies identify approximately 70% to 80% of PUD; accuracy can be increased to approximately 90% by using double contrast.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Stop smoking; smoking increases the risk of PUD, decreases the healing rate, and increases the frequency of recurrence.
- Avoid NSAIDs and alcohol.
- Special diets have been proved unrelated to ulcer development and healing; however, avoid foods that cause symptoms.

ACUTE GENERAL Rx

Eradication of *H. pylori,* when present, can be accomplished with various regimens:

1. PPI (e.g., omeprazole 20 mg bid or lansoprazole 30 mg bid, esomeprazole 40 mg qd) *plus* clarithromycin 500 mg bid *and* amoxicillin 1000 mg bid for 10 days. This regimen achieves an eradication rate of 80% to 90% and can be used as first-line therapy for patients not allergic to penicillin.
2. PPI bid *plus* amoxicillin 500 mg bid *plus* metronidazole 500 mg bid for 10 days.
3. PPI bid *plus* clarithromycin 500 mg bid *and* metronidazole 500 mg bid for 10 days. This regimen is useful in those with penicillin allergy.
4. A 1-day quadruple therapy may be as effective as a 7-day triple-therapy regimen. The 1-day quadruple-therapy regimen consists of 2 tablets of 262-mg bismuth subsalicylate qid, 1 500-mg metronidazole tablet qid, 2 g of amoxicillin suspension qid, and 2 capsules of 30 mg of lansoprazole.
5. Bismuth compound qid *plus* tetracycline 500 mg qid *and* metronidazole 500 mg qid for 14 days.
6. A combination of levofloxacin 250 mg bid, amoxicillin 1000 mg bid, and a PPI bid for 10 to 14 days can be used as salvage therapy after unsuccessful attempts to eradicate *H. pylori* using other regimens.

A 10-day sequential therapy has been reported to be superior to standard triple therapy for eradication of *H. pylori.* It consists of 5 days of treatment with a PPI and one antibiotic (usually amoxicillin) followed by 5-day treatment with the PPI and two other antibiotics (usually clarithromycin and metronidazole).

PUD patients testing negative for *H. pylori* should be treated with antisecretory agents:

- H_2 receptor antagonists (H_2RAs): cimetidine, ranitidine, famotidine, and nizatidine are all effective; they are usually given in split dose or at nighttime.
- PPIs: can also induce rapid healing; they are usually given 30 min before meals.

Antacids and sucralfate are also effective agents for the treatment and prevention of PUD.

CHRONIC Rx

Maintenance therapy in duodenal ulcer patients is indicated in the following situations:

- Persistent smokers
- Recurrent ulcerations
- Long-term treatment with NSAIDs, glucocorticoids
- Elderly or debilitated patients
- Aggressive or complicated ulcer disease (e.g., perforation, hemorrhage)
- Asymptomatic bleeders

Misoprostol therapy (100 μg qid with food, increased to 200 μg qid if well tolerated) is useful for the prevention of NSAID-induced gastric ulcers in all patients on long-term NSAID therapy; it is contraindicated in women of childbearing age because of its abortifacient properties. PPIs are at least as effective as misoprostol and more effective than H_2 receptor antagonists at healing ulcers and maintaining remission in patients on long-term NSAIDs.

DISPOSITION

- The recurrence rate for untreated PUD is ~60% (>70% in smokers). Treatment decreases the recurrence rate by nearly 30%.
- Patients with recurrent ulcers should be re-treated for an additional 8 wk and then placed on maintenance therapy with H_2RAs, PPIs, sucralfate, or antacids.
- An ulcer is considered refractory to treatment if healing is not evident after 8 wk for duodenal ulcers and 12 wk for gastric ulcers. In these patients maximum acid inhibition (e.g., esomeprazole 40 mg bid) is preferred over continued therapy with standard antiulcer therapy.
- Eradication of *H. pylori* (when present) is indicated in all patients. A negative stool antigen test for *H. pylori* 6 wk after treatment accurately confirms cure of *H. pylori* infection with reasonable sensitivity in initially seropositive healthy subjects.
- Screening for ZE syndrome should also be considered in patients with multiple recurrent ulcers; in patients with ZE, the serum gastrin level is >1000 pg/ml and the basal acid output is usually >15 mEq/hr.
- Surgery for refractory ulcers is now only rarely performed; it consists of highly selective vagotomy for duodenal ulcers or ulcer removal with antrectomy or hemigastrectomy without vagotomy for gastric ulcers.

REFERRAL

- GI referral for patients requiring endoscopy
- Surgical referral for patients with nonhealing ulcers despite appropriate medical therapy

PEARLS & CONSIDERATIONS

COMMENTS

- Patients with gastric ulcers should have repeat endoscopy after 4 to 6 wk of therapy to document healing and test exfoliative cytology for gastric carcinoma.
- After endoscopic treatment of bleeding peptic ulcers, bleeding recurs in up to 20% of patients. PPI administration intravenously by continuous infusion substantially reduces the risk of recurrent bleeding. High-dose IV esomeprazole (80 mg IV bolus followed by 8 mg/hr infusion over 72 hr) given after successful endoscopic therapy to patients with high-risk peptic ulcer bleeding has been reported to reduce recurrent bleeding at 72 hr and to maintain sustained clinical benefits for up to 30 days.
- Among low-dose aspirin recipients who had peptic ulcer bleeding, continuous aspirin therapy may increase the risk for recurrent bleeding; however, mortality was reported higher among those who stopped aspirin therapy and were at risk for cardiovascular events.

EBM EVIDENCE

available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Peptic Ulcer (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Objective:
To determine whether once-daily esomeprazole 40 mg or 20 mg compared with placebo reduces the incidence of peptic ulcers over 26 weeks of treatment in patients taking low-dose acetylsalicylic acid (ASA) and who are at risk for ulcer development.

Design:
Multinational, randomised, blinded, parallel-group, placebo-controlled trial.

Setting:
Cardiology, primary care and gastroenterology centres (n = 240).

Patients:
Helicobacter pylori-negative patients taking daily low-dose ASA (75–325 mg), who fulfilled one or more of the following criteria: age ≥18 years with history of uncomplicated peptic ulcer; age ≥60 years with either stable coronary artery disease, upper gastrointestinal symptoms and five or more gastric/duodenal erosions, or low-dose ASA treatment initiated within 1 month of randomisation; or age ≥65 years. All patients were ulcer-free at study entry.

Interventions:
Once-daily, blinded treatment with esomeprazole 40 mg, 20 mg or placebo for 26 weeks.

Main Outcome Measures:
The primary end point was the occurrence of endoscopy-confirmed peptic ulcer over 26 weeks.

Results:
A total of 2426 patients (52% men; mean age 68 years) were randomised. After 26 weeks, esomeprazole 40 mg and 20 mg significantly reduced the cumulative proportion of patients developing peptic ulcers; 1.5% of esomeprazole 40 mg and 1.1% of esomeprazole 20 mg recipients, compared with 7.4% of placebo recipients, developed peptic ulcers (both $p<0.0001$ vs placebo). Esomeprazole was generally well tolerated.

Conclusions:
Acid-suppressive treatment with once-daily esomeprazole 40 mg or 20 mg reduces the occurrence of peptic ulcers in patients at risk for ulcer development who are taking low-dose ASA. Ⓐ

Evidence-Based Reference

Scheiman JM et al.: Prevention of peptic ulcers with esomeprazole in patients at risk of ulcer development treated with low-dose acetylsalicylic acid: a randomised, controlled trial (OBERON), *Heart* 97:797–802, 2011. Ⓐ

SUGGESTED READINGS

Jafri N et al.: Meta-analysis: sequential therapy appears superior to standard therapy for *Helicobacter pylori* infection in patients naive to treatment, *Ann Intern Med* 148:923–931, 2008.

Sung J et al.: Intravenous esomeprazole for prevention of recurrent peptic ulcer bleeding, *Ann Intern Med* 150:455, 2009.

Sung J et al.: Continuation of low-dose aspirin therapy in peptic ulcer bleeding, *Ann Intern Med* 152:1–9, 2010.

BASIC INFORMATION

DEFINITION

Pericarditis is the inflammation (or infiltration) of the pericardium. Acute pericarditis is a syndrome characterized by typical chest pain, a pathognomonic pericardial friction rub on auscultation, and specific electrocardiogram (ECG) changes.

ICD-9CM CODES
420.91 Pericarditis

ICD-10CM CODES
I30.0 Acute nonspecific idiopathic pericarditis
I30.1 Infectious pericarditis
I30.8 Other forms of acute pericarditis
I30.9 Acute pericarditis, unspecified
I301.0 Chronic adhesive pericarditis
I31.1 Chronic constrictive pericarditis
I31.3 Pericardial effusion (non-inflammatory)
I31.9 Diseases of pericardium, unspecified (tamponade)
I31.2 Hemopericardium

EPIDEMIOLOGY & DEMOGRAPHICS

- The exact incidence of acute pericarditis is not known. However, it is approximately 0.1% of hospitalized patients, and 5% of patients seen in the emergency room for nonacute myocardial infarction chest pain.
- Increased incidence found in males and in adults compared with children.
- The use of thrombolytic agents and early revascularization has greatly reduced the incidence of both early postinfarction pericarditis and Dressler's syndrome.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Severe, constant pain that localizes over the anterior chest and may radiate to the arms and back. As opposed to ischemic pain, the pain is pleuritic and is improved by sitting up and leaning forward. While present in the majority of cases, chest pain may be absent, particularly when uremia or rheumatologic causes are the underlying etiology.
- A pericardial friction rub is virtually pathognomonic of acute pericarditis, although is not present in all patients. When present, it is virtually pathognomonic of acute pericarditis. It is best heard with the patient sitting up and leaning forward and by pressing the diaphragm of the stethoscope firmly against the chest at the lower left sternal border during inspiration. It consists of three short, scratchy sounds, corresponding to a systolic, diastolic, and late diastolic component. In many patients, the rub is not clearly triphasic.
- The physical exam is important in assessing the presence of cardiac tamponade which may occur as a complication of large or rapidly accumulating effusions. Classic tamponade findings include hypotension, jugular venous distention, and muffled heart sounds (Beck's triad). In addition, tachycardia and pulsus paradoxus are usually present.

ETIOLOGY

- Most common causes of pericarditis are idiopathic or viral: 80% to 90% of cases.
- Other infectious agents (bacterial [1% to 2%], tuberculous [4% to 9%], HIV fungal, amebic, toxoplasmosis)
- Collagen-vascular disease (systemic lupus erythematosus, rheumatoid arthritis, scleroderma, vasculitis, dermatomyositis): 3% to 4% of cases.
- Neoplasm (primary or metastatic [breast, lung, leukemia, lymphoma]): 7% to 13% of cases.
- Drug-induced: procainamide, hydralazine, phenytoin, isoniazid, rifampin, doxorubicin, mesalamine, adalimumab.
- Acute myocardial infarction and post-MI (Dressler's syndrome, usually 2 weeks post MI).
- Trauma, including iatrogenic causes (post-pericardiotomy, postpacemaker lead placement, postcatheter ablation, post-CPR).
- Postmediastinal radiation (e.g., patients with Hodgkin's disease).
- Metabolic (hypothyroidism, uremia).
- Leakage of aortic aneurysm into pericardial sac.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Angina pectoris.
- Dissecting aortic aneurysm.
- Pulmonary causes: embolism, infarction, pneumothorax, pneumonia with pleurisy.
- Dissecting aneurysm.
- Gastrointestinal causes: hepatitis, cholecystitis, GERD, hiatal hernia, esophageal rupture.
- Musculoskeletal strain.

WORKUP

Diagnosis is clinical, based on history and physical examination. ECG may help confirm the diagnosis if typical changes are found. The diagnosis of acute pericarditis requires at least two of the following symptoms or signs to be present: typical chest pain, pericardial friction rub, characteristic ECG changes, and the presence of a pericardial effusion. Echocardiogram may diagnose an associated pericardial effusion if present; however, it may be present only in up to 50% to 60% cases of acute pericarditis, and its presence should not be used as a cornerstone of diagnosing pericarditis. Laboratory tests may help elucidate the underlying cause.

LABORATORY TESTS

Laboratory tests will not confirm the diagnosis, but can help determine a specific etiology. Initial blood work should be limited to the following tests:

- Complete blood count with differential.
- Erythrocyte sedimentation rate, C-reactive protein (not specific but may be of value in following the course of the disease and the response to therapy).
- Blood urea nitrogen, creatinine.
- Troponin I (plasma troponins are elevated in 35% to 50% of patients with pericarditis, and indicate involvement of the myocardium, i.e., myopericarditis).

The following tests may be useful when specific etiologies of pericarditis are suspected:

- HIV.
- PPD.
- Antinuclear antibody, rheumatoid factor.

PERICARDIAL SAMPLING

- Pericardiocentesis is indicated in patients with tamponade physiology, in those with purulent pericarditis, when a neoplastic origin is suspected, and in patients with a significant idiopathic pericardial effusion that has not resolved by 3 mo. The fluid should be analyzed for red and white blood cell counts, cytology, glucose, lactate dehydrogenase, protein, pH, triglyceride level, and culture. Polymerase chain reaction assays or elevated levels of adenosine deaminase activity are useful when suspecting tuberculous pericarditis.
- Pericardial biopsy may be helpful in recurrent pericardial effusion if the diagnosis remains elusive. It should also be considered whenever malignancy or tuberculosis is suspected.

IMAGING STUDIES

- Echocardiogram to detect and determine amount of pericardial effusion (present in 50% to 60% of patients) (Fig. P1-22); absence of effusion. Moreover, an echocardiogram will help to rule out cardiac tamponade, suggest a possible etiology of the pericarditis, and also help to assess for any associated acute myocarditis.
- ECG: the changes vary with the evolutionary stage of pericarditis. If there is myocardial involvement, there may be focal ECG changes that mimic territorial ischemia. Patients with acute STEMI, but not those with acute pericarditis, show prolongation of QRS complex and shortening of QT interval in ECG leads with ST-segment elevation.[1] ECG changes in pericarditis are as follows:
  1. Acute phase: PR-segment depression and diffuse ST-segment elevations (particularly evident in the precordial leads), which can be distinguished from acute MI by the lack of reciprocal changes and the absence of Q waves
  2. Intermediate phase: return of PR and ST segments to baseline, and T-wave inversion in leads previously showing ST-segment elevation (Fig. P1-23)
  3. Late phase: resolution of the T-wave changes
- Chest x-ray: done primarily to rule out abnormalities of the mediastinum or lung fields that may cause chest pain.
  Cardiac silhouette may appear enlarged in patients with pericardial effusion if ≥200 ml of fluid has accumulated (Fig. P1-24).

[1]Rossello X et al: New electrocardiographic criteria to differentiate acute pericarditis and mycardial infarction, *Am J Med* 127:223-239, 2014.

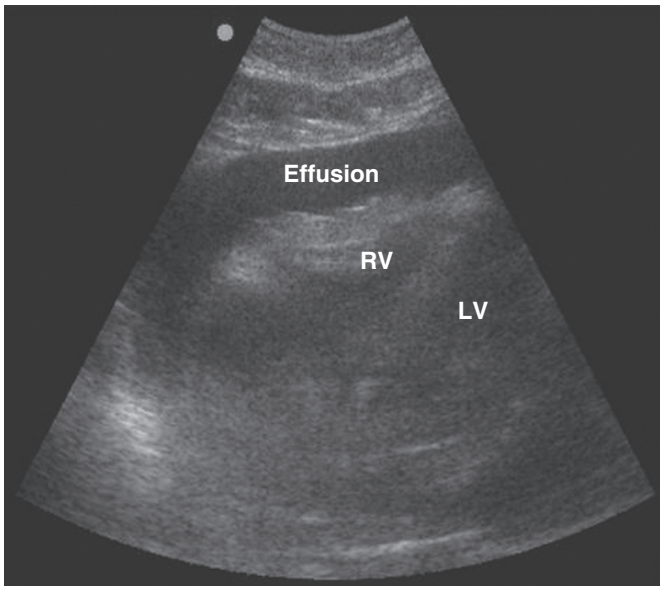


FIGURE P1-22 Bedside ultrasound showing large pericardial effusion. *LV,* Left ventricle; *RV,* right ventricle. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

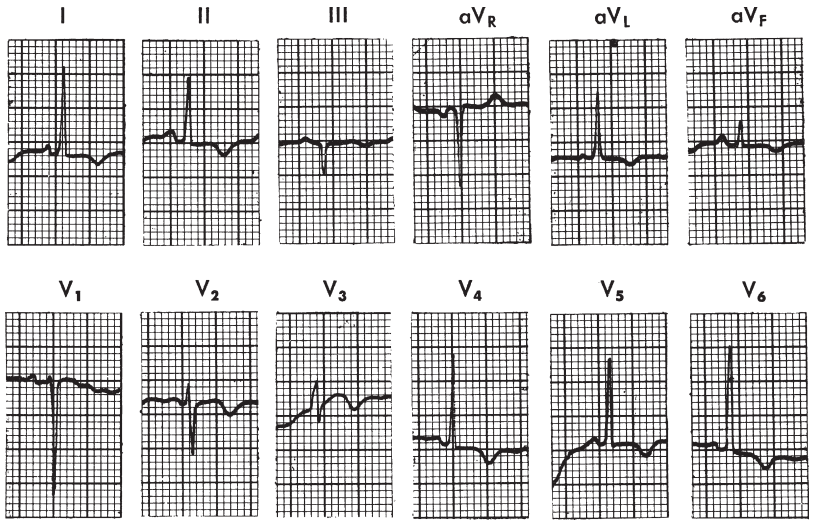


FIGURE P1-23 Pericarditis, evolving pattern. Note the diffuse T-wave inversions in leads I, II, III, aVL, aVF, and V2 to V6. (From Goldberg AL [ed]: *Clinical electrocardiography,* ed 5, St Louis, 1994, Mosby.)

Calcifications around the heart may be seen with constrictive pericarditis.
- MRI (Fig. P1-25) may be useful in patients with constrictive pericarditis and when malignancy is suspected.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Limitation of activity until the pain abates.
- Patient education regarding potential complications (e.g., cardiac tamponade, constrictive pericarditis).

ACUTE GENERAL Rx

- Aspirin 650-1000 mg tid. NSAIDs can be used in place of aspirin (e.g., ibuprofen 600-800 mg tid, indomethacin 50 mg tid). NSAIDs are contraindicated in patients with recent MI and CHF.
- Colchicine 0.5-0.6 mg bid should be used in combination with aspirin/NSAIDs. Several randomized trials (ICAP, COPE, COPPS) as well as a recent meta-analysis have now demonstrated that colchicine is effective in both reducing symptoms and the rates of recurrent pericarditis. Its use is recommended for first episodes but is not currently approved for recurrent disease.
- Use of corticosteroids is controversial. There is evidence of their use being associated with increased recurrence, side effects, and hospitalizations. Current guidelines recommend that systemic steroid therapy be restricted to patients with underlying connective tissue disease, autoimmune disease or uremia pericarditis. One study found that using a lower dose (0.25 to 0.5 mg/kg per day) maintained for 4 weeks and followed by a slow taper had same efficacy and fewer adverse effects than with higher conventional doses (1 mg/kg/day for 2 to 4 weeks).
- Close observation of patients when there is suspicion for cardiac tamponade.
- Avoidance of anticoagulants (increased risk of hemopericardium).

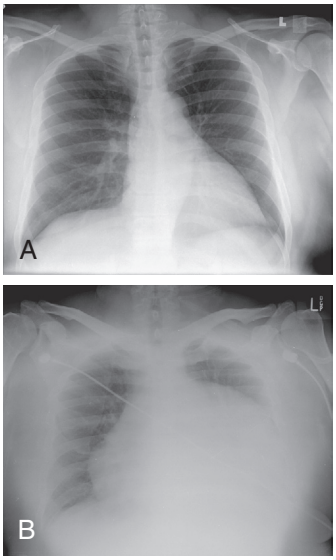


FIGURE P1-24 Chest Xray. A, Patient's chest radiograph 1 year before presentation with cardiac tamponade. **B,** Same patient's chest radiograph on presentation to the emergency department with cardiac tamponade. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

TREATMENT OF UNDERLYING CAUSE

- Bacterial pericarditis: systemic antibiotics and surgical drainage of pericardium
- Collagen vascular disease: prednisone
- Uremic: dialysis

POTENTIAL COMPLICATIONS FROM PERICARDITIS:

1. **Chronic constrictive pericarditis:**
   a. Physical examination: jugular venous distention, Kussmaul's sign (increase in jugular venous distention during inspiration as a result of increased venous pressure), pericardial knock (early diastolic filling sound heard 0.06 to 0.1 sec after S2), clear lungs, tender hepatomegaly, pedal edema, ascites, scrotal edema, and possible anasarca.
   b. Chest radiograph: clear lung fields, normal or slightly enlarged heart, pericardial calcification.
   c. ECG: low-voltage QRS complex.
   d. Echocardiography: may show respiratory inflow variation over the mitral and tricuspid valves (due to variations in the diastolic ventricular pressure gradients with respiration), pericardial thickening or may be normal.
   e. Cardiac catheterization: elevation of right-sided filling pressures: shows a prominent Y descent in the right atrial tracing, a "dip and plateau" tracing of the right ventricular pressure and discordance of right ventricular and left ventricular systolic pressures

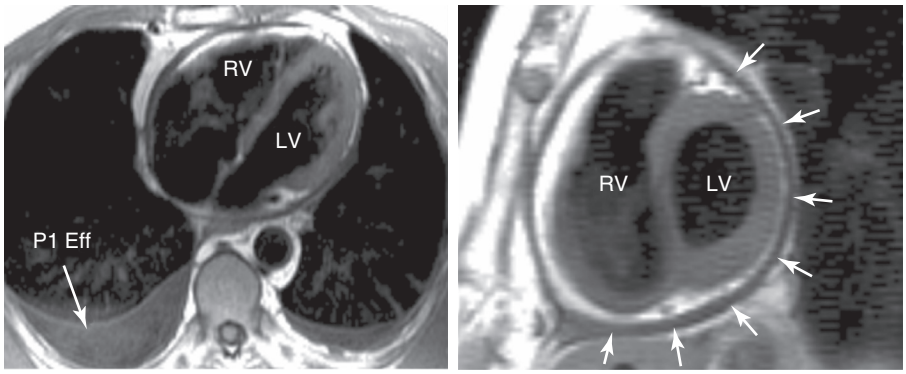


FIGURE P1-25 Cardiovascular magnetic resonance in a patient with constrictive pericarditis. On the *right* is a basal short-axis view of the ventricles showing a thickened pericardium encasing the heart *(arrows).* On the *left* is a transaxial view, again showing the thickened pericardium, particularly over the right heart, but also a pleural effusion *(P1 Eff). LV,* Left ventricle; *RV,* right ventricle. (From Zipes DP et al [eds]: *Braunwald's heart disease,* ed 7, Philadelphia, 2005, Saunders.)

during respiration.

f. Therapy: surgical stripping or removal of both layers of the constricting pericardium.

2. **Cardiac tamponade:** occurs in 5% to 15% of patients with idiopathic pericarditis, but in up to 60% of those with neoplastic, tuberculous, or purulent pericarditis.
   a. Signs and symptoms: dyspnea, orthopnea, interscapular pain.
   b. Physical examination: distended neck veins, distant heart sounds, decreased apical impulse, diaphoresis, tachypnea, tachycardia, Ewart's sign (an area of dullness at the angle of the left scapula caused by compression of the lungs by the pericardial effusion), hypotension, narrowed pulse pressure, or pulsus paradoxus (decrease in systolic blood pressure ≥10 mm Hg during inspiration; most specific sign). Of all the clinical signs, a pulsus paradoxus >10 mm Hg in patients with pericardial effusion is the most specific for tamponade.
   c. Chest x-ray: cardiomegaly ("water-bottle" configuration of the cardiac silhouette may be seen) with clear lungs; may be normal when acute tamponade occurs rapidly in the absence of prior pericardial effusion.
   d. ECG: decreased amplitude of the QRS complex, electrical alternans (occurs more frequently with neoplastic effusions).
   e. Echocardiography: may show diastolic collapse of the right ventricle and/or the right atrium, respiratory inflow variation over the mitral valve and tricuspid valve (due to transmission of respiratory changes in intrathoracic pressure to the ventricles), or paradoxical wall motion may also be seen.
   f. Cardiac catheterization: equalization of pressures within chambers of the heart, elevation of right atrial pressure with a prominent x but no significant y descent.
   g. Therapy: immediate pericardiocentesis, preferably by needle paracentesis with the use of echocardiography, fluoroscopy, or CT In patients with recurrent effusions (e.g., neoplasms), placement of a percutaneous drainage catheter or pericardial window may be necessary.

3. **Effusive-constrictive pericarditis:** Uncommon syndrome characterized by concomitant tamponade caused by tense pericardial effusion and constriction caused by the visceral pericardium.
   a. Signs and symptoms: in addition to features of tamponade and/or constriction, may demonstrate decreased breath sounds (pleural effusions), peripheral edema, ascites, pulsatile hepatomegaly, and cachexia. Kussmaul's sign is typically not present.
   b. Echocardiography: typically not sensitive enough to distinguish effusive-constrictive pericarditis from other types.
   c. Cardiac catheterization: mixed picture with features of constriction and tamponade. Before drainage, Y descent is usually less prominent than expected and right atrial v wave persists. After drainage, may continue to have elevated right atrial and pulmonary wedge pressures.
   d. Therapy: extensive epicardiectomy (with disruption of the visceral layer of pericardium) is the procedure of choice in symptomatic patients.

4. **Myopericarditis**: myocardial injury unrelated to MI. It occurs in up to 15% of patients with pericarditis. ECG reveals concave downward ST-segment elevation and/or deep T wave inversions; cardiac enzymes are positive. May be associated with arrhythmias.

DISPOSITION

- Complete resolution of pain and other signs and symptoms during the initial 3 wk of therapy occurs in 70% to 90% of cases.
- Recurrence in 10% to 15% of patients within the initial 12 mo. The recurrence rate increases up to 50% after a first recurrence.
- Recurrence of large effusion after pericardiocentesis is common in patients with idiopathic chronic pericardial effusion. Pericardiectomy should be considered in these patients.
- Most cases of pericarditis can be treated in the outpatient setting. Indications for hospitalization are fever >38° C, immunosuppressed state, history of trauma, subacute onset, oral anticoagulant therapy, presence of myocarditis (myopericarditis), large pericardial effusion or tamponade, and failure to respond to 1 wk of outpatient treatment.
- In patients with pericardial effusion after cardiac surgery, use of NSAIDs is not recommended because they have not been shown to reduce the size of the effusions or prevent late cardiac tamponade. One randomized trial (COPPS) suggested that prophylactic colchicine may reduce the risk of developing a postpericardiotomy syndrome.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pericarditis (Patient Information)

AUTHOR: **AMANDA C. DORAN, M.D., Ph.D**

EVIDENCE

Abstract[1]

Background:

No preventive pharmacologic strategies have been proven efficacious for the prevention of postoperative effusions after cardiac surgery. Colchicine is safe and efficacious for the prevention of pericarditis. On this basis, we realized a substudy of the COPPS trial to assess the efficacy and safety of colchicine for the prevention of postoperative pericardial and pleural effusions.

Methods:

The COPPS is a multicenter, double-blind, randomized trial, where 360 consecutive patients (mean age 65.7 ± 12.3 years, 66% men), 180 in each treatment arm, were randomized on the third postoperative day to receive placebo or colchicine for 1 month (1.0 mg twice daily for the first day, followed by a maintenance dose of 0.5 mg twice daily in patients ≥70 kg, and halved doses for patients <70 kg). The incidence of postoperative effusions was evaluated in each study group.

Result:

Despite similar baseline features, colchicine significantly reduced the incidence of postoperative pericardial (12.8% versus 22.8%, P = .019, relative risk reduction 43.9%, no. of patients needed to treat 10) and pleural effusions (12.2% versus 25.6%, P = 0.002, relative risk reduction 52.3%, no. of patients needed to treat 8). The rate of side effects (only gastrointestinal intolerance) and drug withdrawal was similar in the study groups with a trend towards an increased rate of both events for colchicine. In multivariable analysis, female gender (hazard ratio 1.76, 95% CI 1.03 to 3.03, P = 0.040) and pleura incision (hazard ratio 2.58, 95% CI 1.53 to 4.53, P <0.001) were risk factors for postoperative effusions.

Conclusions:

Colchicine is safe and efficacious for the primary prevention of postoperative effusions after cardiac surgery. Ⓐ

Evidence-Based Reference

Imazio M, et al.: Colchicine prevents early postoperative pericardial and pleural effusions, *Am Heart J* 162:527–532, 2011. Ⓐ

SUGGESTED READINGS

Alabed M et al.: Colchicine for pericarditis, *Cochrane Database Syst Rev*, 2014.

Imazio M et al.: A randomized trial of colchicine for acute pericarditis, *N Engl J Med* 369:161522–161528, 2013.

Imazio M et al.: Colchicine for recurrent pericarditis, *Ann Intern Med* 155: 409–414, 2011.

Imazio M et al.: Corticosteroids for recurrent pericarditis: high versus low doses: a nonrandomized observation, *Circulation* 118(6):667–671, 2008. Epub Jul 21, 2008.

Imazio M et al.: Indicators of poor prognosis of acute pericarditis, *Circulation* 115:2739–2744, 2007.

Imazio M et al.: A randomized trial of colchicine for acute pericarditis, *N Engl J Med* 369:1522–1528, 2013.

LeWinter MM: Clinical practice. Acute pericarditis, *N Engl J Med* 371:2410-2416, 2014.

Khandaker MH et al.: Pericardiectomy vs medical management in patients with relapsing pericarditis, *Mayo Clin Proc* 87(11):1062–1070, 2012.

Maisch B et al.: Guidelines on the diagnosis and management of pericardial diseases executive summary: the task force on the diagnosis and management of pericardial diseases of the European Society of Cardiology, *Eur Heart J* 25:587, 2004.

Mevrin P et al.: NSAID treatment for postoperative pericardial effusion, *Ann Intern Med* 152:137–143, 2010.

Snyder MJ et al.: Acute pericarditis: Diagnosis and management, *Am Fam Physician* 89(7):553–560, 2014.

BASIC INFORMATION

DEFINITION

Peripheral arterial disease (PAD) refers to atherosclerotic, inflammatory, occlusive, and aneurysmal diseases involving the abdominal aorta and its branch arteries. (We will focus on lower extremity PAD.)

SYNONYMS

PAD
Peripheral vascular disease (PVD)
Arteriosclerosis obliterans
Atherosclerotic occlusive disease
Atherosclerosis of the extremities
Peripheral arterial stenosis
Vaso-occlusive disease of the legs
Chronic critical limb ischemia

ICD-9CM CODES
443.9 Peripheral vascular disease
ICD-10CM CODES
I73.9 Peripheral vascular disease, unspecified
I79 Disorders of arteries, arterioles and capillaries in diseases classified elsewhere

EPIDEMIOLOGY & DEMOGRAPHICS

- Approximately 4.3% to 5.28% of the adult population over the age of 40 has PAD, and the prevalence is nearly equal in men and women. It increases with age, from 5.28% in those aged 40 to 49 yr to 18.83% in those aged 70 to 79 yr. However symptoms of claudication are more likely to be present in males with PAD (50%) vs. women with PAD (25%).
- As per the PARTNERS study, the prevalence of PAD in patients >70 yr or 50-69 yr with history of smoking or diabetes was 29%.
- Risk factors that increase risk of PAD according to a 2013 meta-analysis of 112,027 studied patients include:
- Smoking (odds ratio 2.72)
- Diabetes (odds ratio 1.88)
- Hypertension (odds ratio 1.55)
- Hypercholesterolemia (odds ratio 1.19)
- Black race/ethnicity has greater prevalence according to NHANES data (odds ratio 2.83)
- Patients with newly diagnosed PAD are six times more likely to die within the next 10 yr when compared with patients without PAD.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Peripheral arterial disease may present in a variety of ways:
- 20% to 50% of patients are asymptomatic.
- 10% to 35% of patients present with intermittent claudication (aching pain, cramping, or numbness of the calf induced by exercise, relieved by rest).
- 40% to 50% of patients present with atypical symptoms of claudication involving the calf, thigh, or buttock.
- 1% to 2% of patients may present with critical limb ischemia manifested as tissue loss or rest pain in a limb with nonhealing ulcers, necrotic tissue, or gangrene (Fig. P1-26).
- Diminished pulses and/or cool skin temperature of lower extremities.
- Bruits heard over the distal aorta, iliac, or femoral arteries.
- Changes in skin color, especially on feet (rubor with prolonged capillary refill on dependency or delayed pallor), livedo reticularis.
- Trophic changes of hair loss, brittle nails, and muscle atrophy.
- Weakness, numbness, or a feeling of heaviness in legs.
- Aching or burning in toes and feet during rest and especially while lying flat, which may be a sign of ischemia and more serious PAD.

ETIOLOGY

PAD is primarily the result of atherosclerotic disease and the formation of plaques that consist of a lipid core of cholesterol and inflammatory mediators with a fibrous intravascular covering. Symptoms of claudication are a product of physiologically significant luminal stenoses of the peripheral vessels, limiting blood flow to limb muscles.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Spinal stenosis
- Musculoskeletal disorder
- Lumbar spinal stenosis or nerve root compression (neurogenic or pseudoclaudication)
- Peripheral neuropathy
- Reflex sympathetic dystrophy
- Raynaud's disease
- Compartment syndrome

FIGURE P1-26 Ischemic skin ulcer induced by trauma from shoes. This patient with peripheral arterial occlusive disease suffered severe superficial skin necrosis of several toes because of shoes that were too tight. (From Crawford MH et al [eds]: *Cardiology,* ed 2, St Louis, 2004, Mosby.)

- Deep venous thrombosis
- Popliteal entrapment syndrome
- Direct vascular injury

WORKUP

- Thorough history, including symptoms regarding walking impairment, claudication, ischemic rest pain, or nonhealing wounds in patients ≥70 yr or those ≥50 yr with a history of smoking and/or diabetes:
- Measurement of blood pressure in both arms and notation of asymmetry.
- Palpation and recording of carotid pulses, upstroke, amplitude, and presence of bruits.
- Auscultation and palpation of abdomen for bruits, aortic pulsation, and diameter.
- Palpation of brachial, radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial pulses. Pulse intensity should be recorded as follows: 0, absent; 1+, diminished; 2+, normal; 3+, bounding.
- Auscultation of femoral arteries for the presence of bruits.
- Extremities should be inspected for color, temperature, integrity of the skin, hair loss, and hypertrophic nails.

The most widely used classification schemes are Fontaine's stages and Rutherford's categories.

- Fontaine's staging system is as follows:
  1. I: Asymptomatic
  2. IIa: Mild claudication
  3. IIb: Moderate-severe claudication
  4. III: Ischemic rest pain
  5. IV: Ulceration or gangrene
- Table P1-11 describes the Fontaine classification of peripheral arterial disease.
- Rutherford's categories are as follows:
  1. Grade 0, Category 0: Asymptomatic
  2. Grade I, Category 1: Mild claudication
  3. Grade I, Category 2: Moderate claudication
  4. Grade I, Category 3: Severe claudication
  5. Grade II, Category 4: Ischemic rest pain
  6. Grade III, Category 5: Minor tissue loss
  7. Category IV, Category 6: Major tissue loss
- Measurement of resting ankle-brachial index (ABI) should be performed to establish diagnosis of lower extremity PAD in patients with suspected lower extremity PAD (individuals with one or more of the following exertional leg symptoms: nonhealing wounds, age >65, or age >50 with smoking or diabetes history). ABI should be measured in both legs in all new patients (Fig. P1-27).
- The severity of PAD is based on the ABI at rest and during treadmill exercise (1 to 2 mph, 5 min, or symptom limited).
  1. Noncompressible: >1.3
  2. Normal: 1.00 to 1.29 at rest
  3. Borderline: 0.91 to 0.99 at rest
  4. Mild: ABI at rest 0.71 to 0.90 or ABI during exercise 0.50 to 0.90
  5. Moderate: ABI at rest 0.41 to 0.70 or ABI during exercise 0.20 to 0.50
  6. Severe: ABI at rest <0.40 or ABI during exercise <0.20
- Toe-brachial index should be used in patients suspected of PAD with unreliable ABI due to stiff noncompressible vessels. A TBI of <0.70 is the most frequently recommended threshold

for an abnormal result; however, this has not been as rigorously studied or validated against angiographic and clinical outcomes as the ABI cutoff of ≤0.90.

LABORATORY TESTS

Laboratory tests can help identify risk factors and allow for their modification. These include lipid profile, hemoglobin A_{1C}, homocysteine levels, fibrinogen, D-dimer, and CRP.

PHYSIOLOGIC TESTING AND IMAGING STUDIES

- The diagnosis of PAD can be confirmed by measuring the ABI or toe-brachial index.
- Rest or exercise pulse volume recordings (PVRs) and segmental limb pressures are also useful. PVRs measure volume of limb flow per pulse in different segments of the limb (e.g., thigh, calf, ankle, metatarsal, and toes). They help to assess the location and severity of the lesion with alterations in the pulse volume contour and amplitude indicating proximal arterial obstruction.
- Conventional angiography remains the gold standard, but ultrasonography, computed tomography angiography (CTA), and magnetic resonance angiography (MRA) have largely replaced catheter-based angiography in the initial diagnostic evaluation. CT is 92% sensitive and 91% specific. MRA is 93% to 100% sensitive and 96% to 100% specific for PAD.
- Contrast angiography (Fig. EP1-28) is now reserved for patients with PAD who are being considered for endovascular revascularization and can provide physiologic information such as pressure gradients prior to percutaneous intervention.

TABLE P1-11 Fontaine Classification of Peripheral Artery Disease

Stage	Symptoms
I	Asymptomatic
II	Intermittent claudication
IIa	Pain free, claudication walking >200 m
IIb	Pain free, claudication walking <200 m
III	Rest and nocturnal pain
IV	Necrosis, gangrene

From Bonow RO et al: *Braunwald's heart disease: a textbook of cardiovascular medicine,* ed 9, Philadelphia, 2012, Saunders.

Rx TREATMENT

The treatment goal in patients with PAD is to focus on cardiovascular risk-factor reduction to decrease morbidity and mortality as well as to improve limb-related symptoms. There are also medical and surgical approaches to management of limb-related symptoms.

CHRONIC MEDICAL Rx

LOWERING CARDIOVASCULAR MORBIDITY AND MORTALITY

- Medical therapy for PAD is mainly aimed at decreasing cardiovascular risk; however, smoking cessation may decrease progression of PAD.
- Smoking cessation should be emphasized in patients with PAD at each visit with assistance of behavioral and pharmacologic treatment (Class I).
- Proper foot care, including use of appropriate footwear, chiropody/podiatric medicine, daily foot inspection, skin cleansing, and use of topical moisturizing creams, should be encouraged, and skin lesions and ulcerations should be addressed urgently in all patients with diabetes and lower extremity PAD (Class I).
- Antiplatelet therapy is indicated to reduce risk of myocardial infarction, stroke, and vascular death in individuals with symptomatic PAD with either aspirin (75 to 325 mg) or clopidogrel (75 mg) (Class I) and in asymptomatic patients (Class IIa). No clear benefit has been observed with combination aspirin and clopidogrel therapy.
- Warfarin is not indicated.
- Lipid lowering therapy in patients with lower limb PAD has been shown to help slow disease progression, alleviate symptoms, and improve walking distance. The 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol recommends that patients with atherosclerotic PAD receive moderate- to high-dose statin therapy in order to lower risk of cardiovascular events regardless of baseline cholesterol values. Prior guidelines have recommended goal LDL cholesterol of <100 mg/dL and possibly <70 mg/dL in high-risk patients.
- Management of hypertension with a goal of <140/90 mm Hg or <130/80 mm Hg if the patient has diabetes or chronic renal disease. Ramipril use has been reported to improve walking ability and quality of life in PAD patients with intermittent claudication.
- Aggressive control of blood sugar in diabetic patients with PAD is recommended, although studies have failed to demonstrate a beneficial effect on intensive insulin therapy in lowering risk of PAD.

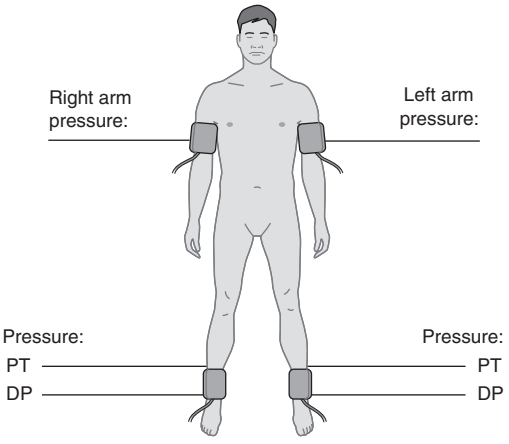
TREATMENT OF CLAUDICATION

- Exercise therapy: Studies have shown that a rigorous exercise-training program may be as beneficial as lower-extremity bypass surgery in symptomatic improvement. Patients should be prescribed exercise for a minimum of 30 to 45 min, in sessions performed at least three times per week for a minimum of 12 wk. Supervised treadmill and resistance training has been shown to be superior to self-directed exercise and improves functional performance measured by treadmill walking and quality of life evaluation.
- Pharmacologic therapy: Firm data showing symptomatic benefit with drug therapy exists only for cilostazol (Pletal) and naftidrofuryl, the latter of which is only available in Europe. Cilostazol 100 mg bid has been shown to increase pain-free and maximal walking distance by 40% to 60% in symptomatic patients with infrainguinal PAD after 12 to 24 wk of therapy, and has been demonstrated to improve ABI.
- Cilostazol is a phosphodiesterase (PDE) inhibitor that reduces platelet aggregation

How to Perform and Calculate the ABI

Partners Program ABI Interpretation

Above 0.90—Normal
0.71–0.90—Mild Obstruction
0.41–0.70—Moderate Obstruction
0.00–0.40—Severe Obstruction



RIGHT ABI **LEFT ABI**

$$\frac{\text{Higher right ankle pressure}}{\text{Higher arm pressure}} = \frac{\text{mm Hg}}{\text{mm Hg}} = \underline{\quad} \qquad \frac{\text{Higher left ankle pressure}}{\text{Higher arm pressure}} = \frac{\text{mm Hg}}{\text{mm Hg}} = \underline{\quad}$$

EXAMPLE

$$\frac{\text{Higher ankle pressure}}{\text{Higher arm pressure}} = \frac{92 \text{ mm Hg}}{164 \text{ mm Hg}} = 0.56$$ See ABI Chart

FIGURE P1-27 Performing pressure measurements and calculating the ankle-brachial index (ABI). To calculate the ABI, systolic pressures are determined in both arms and both ankles with the use of a handheld Doppler instrument. The highest readings for the dorsalis pedis (DP) and posterior tibial (PT) arteries are used to calculate the index. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

and causes arterial vasodilation. It does not prolong bleeding when combined with other antiplatelet agents such as aspirin or clopidogrel. Due to increased mortality seen in studies of other PDE inhibitors used as inotropes (e.g., milrinone), cilostazol is contraindicated in patients with systolic heart failure.

- Pentoxifylline is approved for symptomatic relief of PAD symptoms, but its effects in clinical trials have been mixed with observed magnitudes of benefit that overall are inferior to cilostazol.

REVASCULARIZATION

There is no difference in percutaneous vs. surgical revascularization in iliac and femoropopliteal disease except for the higher morbidity with surgery and greater re-interventions in the percutaneous approach.

- The 2011 ACC/AHA guidelines on PAD have suggested that the following factors be considered prior to revascularization with either percutaneous/endovascular or surgical methods:
  1. Considerations in percutaneous/endovascular treatment:
     1. Should be considered in those who have a vocational or lifestyle-limiting disability due to intermittent claudication when clinical features suggest a reasonable likelihood of symptomatic improvement with endovascular intervention and (a) there has been an inadequate response to exercise or pharmacologic therapy and/or (b) there is a very favorable risk-benefit ratio (e.g., focal aortoiliac occlusive disease).
     2. In TASC (TransAtlantic Inter-Society Consensus) type A iliac and femoropopliteal arterial lesions.
     3. Endovascular therapy is preferred in patients aged 50 yr or younger, because they have a higher risk of graft failure after surgical therapy than older patients.
     4. Endovascular intervention is not indicated as prophylactic therapy in an asymptomatic patient with lower-extremity PAD, or if there is no significant pressure gradient across a stenosis even after augmentation of flow with vasodilators.
     5. Stenting is effective as primary therapy for common iliac artery stenosis and occlusions, and in external iliac artery stenoses and occlusions but not for infra-inguinal disease in the femoral, popliteal, and tibial arteries where it should be reserved for those who fail balloon dilatation.
  2. Considerations in surgical revascularization:
     1. Individuals with claudication symptoms who have a significant functional disability that is vocational or lifestyle limiting. These patients need to also be unresponsive to exercise or pharmacotherapy and should have a reasonable likelihood of symptomatic improvement with an acceptable surgical risk.
     2. Iliac or femoropopliteal disease with long segments; multifocal segments; long segment occlusions; and eccentric, calcified stenosis, which are less amenable to percutaneous interventions.
     3. Surgical intervention is not indicated to prevent progression to limb-threatening ischemia in patients with intermittent claudication as generally claudication does not progress to severe ischemia.
     4. Prior to any surgical therapy, patients should have a preoperative cardiovascular risk evaluation as it is a high-risk surgery and is associated with a higher morbidity compared to percutaneous revascularization.

DISPOSITION

Risk factors for atherosclerosis should be assessed, and appropriate modification instituted. Focus should be placed on smoking cessation, dietary adjustment, and pharmacotherapy for dyslipidemia, hyperglycemia, and hypertension. All patients with PAD should receive aspirin therapy unless contraindicated. Revascularization is performed if the symptoms of PAD do not improve with conservative therapy as discussed previously.

REFERRAL

Consultation with vascular medicine, vascular surgery, or other physicians with expertise in PAD is recommended in patients with rest pain, functional disability from pain, ABI <0.50 at rest, or any physical signs of limb ischemia or gangrene.

PEARLS & CONSIDERATIONS

COMMENTS

- PAD remains underdiagnosed and undertreated.
- Patients with PAD are at markedly higher risk of future coronary, cerebrovascular, and other vascular events.
- Medical treatment is aimed mainly at cardiovascular risk factor modification, except for cilostazol.
- Studies of the natural history of claudication show the relative safety of initial conservative treatment of PAD in the absence of critical limb ischemia.
- When PAD limits a patient's ability to walk and exercise, percutaneous revascularization can be considered.
- Exercise training is an important and often neglected treatment strategy that has proven beneficial in improving functional status, reducing symptoms, and improving quality of life. Exercise capacity alone is the strongest predictor of mortality in patients with PAD.
- Surgical intervention should be considered in patients who meet the criteria for intervention but have lesions that are not amenable to PTA/stenting or in older patients with a low surgical risk. In younger patients, due to the high risk of graft failure and recurrence, surgery should be a last resort.

PREVENTION

Cardiovascular disease is the major cause of death in patients with intermittent claudication. Therefore, the treatment of claudication is directed not only at improving walking distance but also at reducing cardiovascular risk.

PATIENT & FAMILY EDUCATION

The following organizations offer more information about PAD:

- American College of Cardiology (http://www.acc.org)
- Vascular Disease Foundation (http://www.vdf.org)

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Peripheral Arterial Disease (Patient Information)

AUTHORS: **DAVID SUK, M.D.,** and **PRANAV M. PATEL, M.D.**

EVIDENCE

Abstract[1]

Purpose:
Intermittent claudication is a common symptom of peripheral arterial disease. Currently, there is a lack of consensus on the most effective therapies for this problem. We conducted a meta-analysis of randomized trials assessing the efficacy of endovascular therapy (EVT) compared with noninvasive therapies for the treatment of intermittent claudication.
Methods:
Randomized trials comparing the efficacy of EVT and noninvasive therapies, such as medical therapy (MT) and supervised exercise (SVE) in patients with intermittent claudication were identified by a systematic search. Data were pooled, and combined overall effect sizes (standardized differences of mean values) were calculated for a random effect model in terms of ankle-brachial index (ABI) and treadmill walking for initial claudication distance (ICD) and maximum walking distance (MWD). Nine eligible trials (873 participants) were included: two compared EVT and MT alone, four compared EVT and SVE, and three trials compared EVT plus SVE vs SVE alone.
Results:
Heterogeneity between studies was marked. Quantitative data analysis suggested that EVT improved outcomes over MT alone at early follow-up evaluations. Outcomes of EVT plus SVE were better than those of SVE alone in terms of both ABI and treadmill walking at immediate, early, and intermediate follow-up. No substantial differences in outcomes of EVT alone compared with SVE alone were found.
Conclusion:
In patients with intermittent claudication, current evidence supports improved ABI and treadmill walking when EVT is added to MT or SVE during early and intermediate follow-up. There is no evidence that EVT alone provides improved outcome over SVE alone. There is low confidence in these findings for a number of reasons, including the small number of trials, the small size of these studies, the heterogeneity in study design, and the limited use of quality of life tools in assessing outcomes. More consistent data from larger, more homogenous studies, including longer follow-up, are required. Ⓐ

Abstract[2]

Background:
Patients with critical limb ischaemia have a high rate of amputation and mortality. We tested the hypothesis that non-viral 1 fibroblast growth factor (NV1FGF) would improve amputation-free survival.
Methods:
In this phase 3 trial (EFC6145/TAMARIS), 525 patients with critical limb ischaemia unsuitable for revascularisation were enrolled from 171 sites in 30 countries. All had ischaemic ulcer in legs or minor skin gangrene and met haemodynamic criteria (ankle pressure <70 mmHg or a toe pressure <50 mmHg, or both, or a transcutaneous oxygen pressure <30 mmHg on the treated leg). Patients were randomly assigned to either NV1FGF at 0.2 mg/mL or matching placebo (visually identical) in a 1:1 ratio. Randomisation was done with a central interactive voice response system by block size 4 and was stratified by diabetes status and country. Investigators, patients, and study teams were masked to treatment. Patients received eight intramuscular injections of their assigned treatment in the index leg on days 1, 15, 29, and 43. The primary endpoint was time to major amputation or death at 1year analysed by intention to treat with a log-rank test using a multivariate Cox proportional hazard model. This trial is registered with ClinicalTrials.gov, number NCT00566657.
Findings:
259 patients were assigned to NV1FGF and 266 to placebo. All 525 patients were analysed. The mean age was 70 years (range 50–92), 365 (70%) were men, 280 (53%) had diabetes, and 248 (47%) had a history of coronary artery disease. The primary endpoint or components of the primary did not differ between treatment groups, with major amputation or death in 86 patients (33%) in the placebo group, and 96 (36%) in the active group (hazard ratio 1.11, 95% CI 0.83–1.49; p=0.48). No significant safety issues were recorded.
Interpretation:
TAMARIS provided no evidence that NV1FGF is effective in reduction of amputation or death in patients with critical limb ischaemia. Thus, this group of patients remains a major therapeutic challenge for the clinician. Ⓐ

Abstract[3]

Background:
Controversy exists as to the relative merits of surgical and endovascular treatment of femoropoliteal arterial disease.
Methods:
A systematic review of the literature was undertaken to identify studies comparing open surgical and percutaneous transluminal methods for the treatment of femoropopliteal arterial disease.
Outcome
Data were pooled and combined overall effect sizes were calculated using fixed or random effects models.
Results:
Four randomized controlled trials and six observational studies reporting on a total of 2817 patients (1387 open, 1430 endovascular) were included. Endovascular treatment was accompanied by lower 30-day morbidity (odds ratio [OR], 2.93; 95% confidence interval [CI], 1.34-6.41) and higher technical failure (OR, 0.10; 95% CI, 0.05-0.22) than bypass surgery, whereas no differences in 30-day mortality between the two groups were identified (OR, 0.92; 95% CI, 0.55-1.51). Higher primary patency in the surgical treatment arm was found at 1 (OR, 2.42; 95% CI, 1.37-4.28), 2 (OR, 2.03; 95% CI, 1.20-3.45), and 3 (OR, 1.48; 95% CI, 1.12-1.97) years of intervention. Progression to amputation was found to occur more commonly in the endovascular group at the end of the second (OR, 0.60; 95% CI, 0.42-0.86) and third (OR, 0.55; 95% CI, 0.39-0.77) year of intervention. Higher amputation-free and overall survival rates were found in the bypass group at 4 years (OR, 1.31; 95% CI, 1.07-1.61 and OR, 1.29; 95% CI, 1.04-1.61, respectively).
Conclusions:
High-level evidence demonstrating the superiority of one method over the other is lacking. An endovascular-first approach may be advisable in patients with significant comorbidity, whereas for fit patients with a longer-term perspective a bypass procedure may be offered as a first-line interventional treatment. Ⓐ

Abstract[4]

Objectives:
The study investigated the efficacy and safety of a balloon expandable, sirolimus-eluting stent (SES) in patients with symptomatic infrapopliteal arterial disease.
Background:
Results of infrapopliteal interventions using balloon angioplasty and/or bare stents are limited by a relatively high restenosis rate, which could be potentially improved by stabilizing the lesion with a SES.
Methods:
Two hundred patients (total lesion length 27 ± 1 mm) were randomized to infrapopliteal SES stenting or percutaneous transluminal balloon angioplasty (PTA). The primary endpoint was 1-year in-segment binary restenosis by quantitative angiography.
Results:
Ninety-nine and 101 patients (mean age 73.4 years; 64% diabetics) were randomized to SES and PTA, respectively (8 crossover bailout cases to SES). At 1 year, there were lower angiographic restenosis rates (22.4% vs. 41.9%, $P = .019$), greater vessel patency (75.0% vs. 57.1%, $P = .025$), and similar death, repeat revascularization, index-limb amputation rates, and proportions of patients with improved Rutherford class for SES versus PTA.
Conclusions:
SES implantation may offer a promising therapeutic alternative to PTA for treatment of infrapopliteal peripheral arterial disease. Ⓐ

Evidence-Based Reference

Ahimastos AA et al.: A meta-analysis of the outcome of endovascular and non-invasive therapies in the treatment of intermittent claudication, *J Vasc Surg* 54:1511–1521, 2011. Ⓐ

Antoniou GA et al.: A meta-analysis of endovascular versus surgical reconstruction of femoropopliteal arterial disease, *J Vasc Surg* 57:242–253, 2013. Ⓐ

Belch J: on behalf of the TAMARIS Committees and Investigators: Effect of fibroblast growth factor NV1FGF on amputation and death: a randomised placebo-controlled trial of gene therapy in critical limb ischaemia, *Lancet* 377:1929–1937, 2011. Ⓐ

Scheinert D et al.: A prospective randomized multicenter comparison of balloon angioplasty and infrapopliteal stenting with the sirolimus-eluting stent in patients with ischemic peripheral arterial disease: 1-year results from the ACHILLES Trial, *J Am Coll Cardiol* 60:2290–2295, 2012. Ⓐ

Stone NJ, Robinson JG, Lichtenstein AH et al.: 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, *Circulation* 129(25 suppl 2):S1–S45, 2014. Ⓐ

SUGGESTED READINGS

Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA Guideline Recommendations): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guideline, *J Am Coll Cardiol* 61(14):1555–1570, 2013.

Ahimastos AA et al.: Effect of ramipril on walking times and quality of life among patients with peripheral artery disease and intermittent claudication: a randomized trial, *JAMA* 309:453–460, 2013.

Conen D et al.: Smoking, smoking status, and risk for sympathetic peripheral artery disease in women, *Ann Intern Med* 154:719–726, 2011.

Fowkes FG et al.: Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis, *Lancet* 382(9901):1329–1340, 2013.

Ghannam M et al.: Ankle-brachial index as a clinical tool, *Am J Med* 125: 1171–1172, 2012.

Hankey G et al.: Medical treatment of peripheral arterial disease, *JAMA* 295:547, 2006.

Hirsch AT et al.: ACC/AHA Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society for Vascular Medicine and Biology, and the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients with Peripheral Arterial Disease), *J Am Coll Cardiol* 47:1239–1312, 2006. Available at http://www.acc.org/clinical/guidelines/pad/index.pdf.

Høyer C, Sandermann J, Petersen LJ: The toe-brachial index in the diagnosis of peripheral arterial disease, *J Vasc Surg* 58(1):231–238, 2013.

Kiernan TJ: Comprehensive evaluation and medical management of infrainguinal peripheral artery disease: "when to treat, when not to treat", *Tech Vasc Interv Radiol* 13(1):2–10, 2010.

Leeper NJ, Myers J, Zhou M et al.: Exercise capacity is the strongest predictor of mortality in patients with peripheral arterial disease, *J Vasc Surg* 57(3):728–733, 2013.

McDermott MM et al.: Treadmill exercise and resistance training in patients with peripheral arterial disease with and without intermittent claudication: a randomized controlled trial, *JAMA* 301:165, 2009.

Menke J, Larsen J: Meta-analysis: accuracy of contrast-enhanced magnetic resonance angiography for assessing steno-occlusions in peripheral arterial disease, *Ann Intern Med* 153:325–334, 2010.

Met R et al.: Diagnostic performance of computed tomography angiography in peripheral arterial disease, *JAMA* 301(4):415–424, 2009.

Norgren L et al.: Inter-society consensus for the management of peripheral arterial disease (TASC II), *J Vasc Surg* 45:S5, 2007.

Olin JW et al.: Peripheral artery disease: current insight into the disease and its diagnosis and management, *Mayo Clin Proc* 85(7):678–692, 2010.

Rooke TW et al.: 2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, *J Am Coll Cardiol* 58:2020, 2011.

Salhiyyah K, Senanayake E, Abdel-Hadi M, Booth A, Michaels JA: Pentoxifylline for intermittent claudication, *Cochrane Database Syst Rev* 1:CD005262, 2012.

Selvin E, Erlinger TP: Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey 1999-2000, *Circulation* 110(6):738–743, 2004.

Shanmugasundaram M et al.: Peripheral arterial disease—what do we need to know? *Clinical Cardiology* 34(8):478–482, 2011.

Stevens JW, Simpson E, Harnan S et al.: Systematic review of the efficacy of cilostazol, naftidrofuryl oxalate and pentoxifylline for the treatment of intermittent claudication, *Br J Surg* 99(12):1630–1638, 2012.

Sun Z: Diagnostic accuracy of multislice CT angiography in peripheral arterial disease, *J Vasc Interv Radiol* 17(12):1915–1921, 2006.

Vidula H et al.: Biomarkers of inflammation and thrombosis as predictors of near-term mortality in patients with peripheral arterial disease: a cohort study, *Ann Intern Med* 148:85–93, 2008.

The Warfarin Antiplatelet Vascular Evaluation Trial Investigators: Oral anticoagulant and antiplatelet therapy and peripheral arterial disease, *N Engl J Med* 357:217, 2007.

White C: Intermittent claudication, *N Engl J Med* 356:1241–1250, 2007.

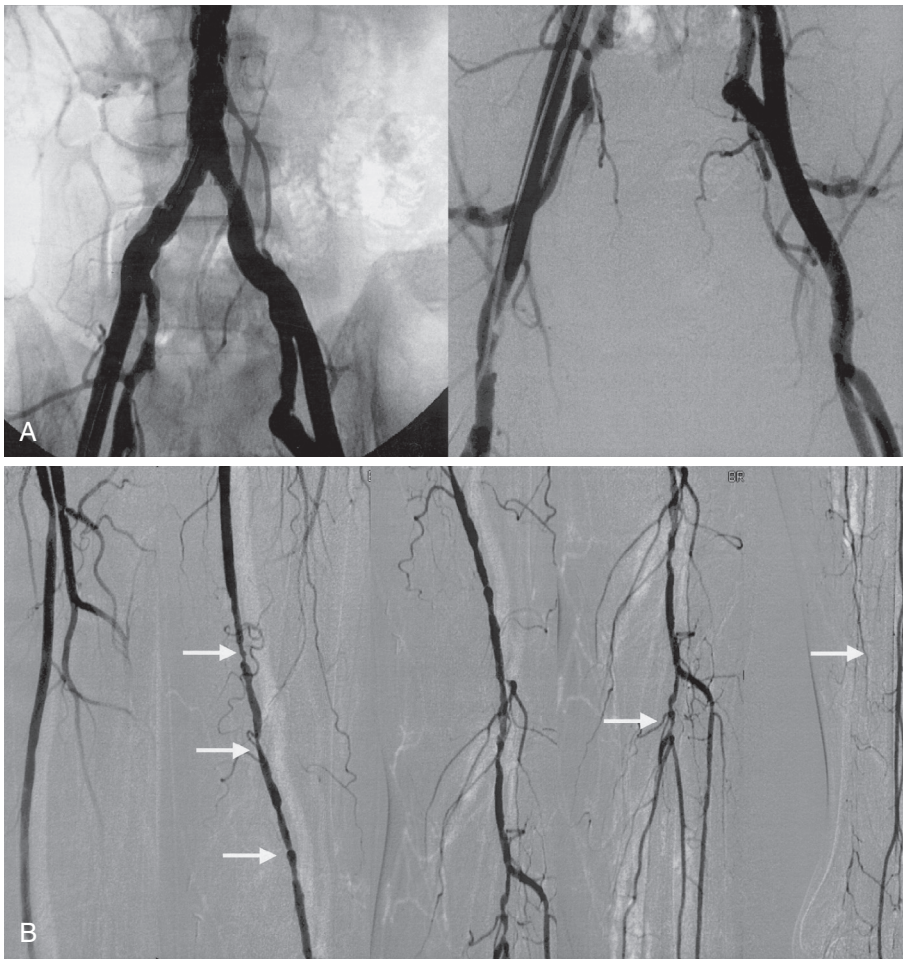


FIGURE EP1-28 Angiogram of a patient with disabling left calf claudication. A, The aorta and bilateral common iliac arteries are patent. **B,** The left superficial femoral artery has multiple stenotic lesions *(arrows).* There is a significant stenosis of the left tibioperoneal trunk and left posterior tibial artery *(arrows).* (From Zipes DP et al [eds]: *Braunwauld's heart disease,* ed 7, Philadelphia, 2005, Saunders.)

BASIC INFORMATION

DEFINITION

Peritonitis refers to the acute onset of severe abdominal pain caused by peritoneal inflammation.

Secondary peritonitis is a localized (abscess) or diffuse peritonitis originating from a defect in abdominal viscus.

SYNONYMS

Acute abdomen
Surgical abdomen

ICD-9CM CODES
567.2 Peritonitis
ICD-10CM CODES
K65.0 Generalized (acute) peritonitis
K65.8 Other peritonitis
K65.9 Peritonitis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

Common presentation as a result of diverse etiologies; for example, 5% to 10% of the population has acute appendicitis at some point in their lives.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute abdominal pain
- Abdominal distention and ascites
- Abdominal rigidity, rebound, and guarding
- Fever, chills
- Exacerbation with movement
- Anorexia, nausea, and vomiting
- Constipation
- Decreased bowel sounds
- Hypotension and tachycardia
- Tachypnea, dyspnea

ETIOLOGY

- Microbiology: most common is gram-negative bacteria (*Escherichia coli, Enterobacter, Klebsiella, Proteus*), gram-positive bacteria (enterococci, streptococci, staphylococci), anaerobic bacteria (*Bacteroides, Clostridium*), and fungi
- Acute perforation peritonitis: gastrointestinal perforation, intestinal ischemia, pelvic peritonitis, and other forms
- Postoperative peritonitis: anastomotic leak, accidental perforation, and devascularization
- Posttraumatic peritonitis: after blunt or penetrating abdominal trauma

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Postoperative: abscess, sepsis, bowel obstruction, injury to internal organs
- Gastrointestinal: perforated viscus, appendicitis, inflammatory bowel disease, infectious colitis, diverticulitis, acute cholecystitis, peptic ulcer perforation, pancreatitis, bowel obstruction
- Gynecologic: ruptured ectopic pregnancy, pelvic inflammatory disease, ruptured hemorrhagic ovarian cyst, ovarian torsion, degenerating leiomyoma
- Urologic: nephrolithiasis, interstitial cystitis
- Miscellaneous: abdominal trauma, penetrating wounds, infections caused by intraperitoneal dialysis

WORKUP

- Acute peritonitis is mainly a clinical diagnosis based on patient history and physical examination.
- Laboratory and imaging studies (see "Laboratory Tests") assist in determining the need for and type of intervention.
- If patient is hemodynamically unstable, immediate diagnostic laparotomy should be performed in lieu of adjuvant diagnostic studies.

LABORATORY TESTS

- Complete blood count: leukocytosis, left shift, anemia
- SMA7: electrolyte imbalances, kidney dysfunction
- Liver function tests: ascites from liver disease, cholelithiasis
- Amylase: pancreatitis
- Blood cultures: bacteremia, sepsis
- Peritoneal cultures: infectious etiology
- Blood gas: respiratory versus metabolic acidosis
- Ascitic fluid analysis: exudate versus transudate
- Urinalysis and culture: urinary tract infection
- Cervical cultures for gonorrhea and *Chlamydia*
- Urine/serum human chorionic gonadotropin

IMAGING STUDIES

- Abdominal series: free air from perforation, small or large bowel dilation from obstruction, identification of fecalith
- Chest x-ray examination: elevated diaphragm, pneumonia
- Pelvic/abdominal ultrasound: abscess formation, abdominal mass, intrauterine versus ectopic pregnancy, identify free fluid suggestive of hemorrhage or ascites
- CT: mass, ascites

TREATMENT

NONPHARMACOLOGIC THERAPY

- IV hydration to correct dehydration, hypovolemia
- Blood transfusion to correct anemia from hemorrhage
- Nasogastric decompression, especially if obstruction is present
- Oxygen: intubation if necessary
- Bed rest

ACUTE GENERAL Rx

- Surgery to correct underlying pathology, such as controlling hemorrhage, correcting perforation, draining abscess
- Broad-spectrum antibiotics to cover both gram-negative aerobic and gram-negative anaerobic bacteria:
  1. Mild-moderate disease: piperacillin-tazobactam 3.375 g IV q6h or 4.5 g IV q8h *or* ticarcillin-clavulanate 3.1 g IV q6h. Alternative agents are ciprofloxacin 400 mg IV q12h or levofloxacin 750 mg IV q24h *plus* metronidazole 1 g IV q12h.
  2. Severe life-threatening disease: imipenem 500 mg IV q6h or meropenem 1 g IV q8h. Alternative agents are ampicillin *plus* metronidazole *plus* ciprofloxacin.
- Pain control: morphine or meperidine as needed (hold until diagnosis confirmed)

DISPOSITION

Depends on etiology of peritonitis, age of patient, coexisting medical disease, and duration of process before presentation

REFERRAL

Surgical consultation is required in all cases of acute peritonitis.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Bosscha K et al.: Surgical management of severe secondary peritonitis, *Br J Surg* 86(11):1371, 1999.

Marshall JC, Innes M: Intensive care management of intra-abdominal infection, *Crit Care Med* 31(8):2228, 2003.

Wittmann DH et al.: Management of secondary peritonitis, *Ann Surg* 224(1):10, 1996.

BASIC INFORMATION

DEFINITION

Pernicious anemia (PA) is an autoimmune disease resulting from antibodies against intrinsic factor and gastric parietal cells.

SYNONYMS

Megaloblastic anemia resulting from vitamin B_{12} deficiency

ICD-9CM CODES
281.0 Pernicious anemia
ICD-10CM CODES
D51 Vitamin B_{12} deficiency anemia due to intrinsic factor deficiency

EPIDEMIOLOGY & DEMOGRAPHICS

- Increased incidence in females and older adults (diagnosis is unusual before age 35 yr)
- The overall prevalence of undiagnosed PA after age 60 yr is 1.9%
- Prevalence is highest in women (2.7%), particularly in black women (4.3%)
- Increased incidence of autoimmune disease (e.g., type 1 diabetes mellitus, Graves disease, Addison disease), *Helicobacter pylori* infection

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Mucosal pallor, glossitis
- Peripheral sensory neuropathy with paresthesias initially and absent reflexes in advanced cases
- Loss of joint position sense, pyramidal or long tract signs
- Possible splenomegaly and mild hepatomegaly
- Generalized weakness and delirium/dementia

ETIOLOGY

- Gastric/antiparietal cell antibodies in >70% of patients; antiintrinsic factor antibodies in >50% of patients
- Atrophic gastric mucosa
- Inborn errors of cobalamin-cofactor synthesis are rare. The cobalamin gene *(cblD)* is localized to human chromosome 2q23.2. Mutations in the gene designated MMADHC (methylmalonic aciduria, cblD type, and homocystinuria) are responsible for the cblD defect in vitamin B_{12} metabolism.
- Fig. EP1-29 illustrates the components and mechanism of cobalamin absorption. An etiopathophysiologic classification of cobalamin deficiency is described in Section II.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Nutritional vitamin B_{12} deficiency
- Malabsorption
- Chronic alcoholism (multifactorial)
- Chronic gastritis related to *H. pylori* infection
- Folic acid deficiency
- Myelodysplasia

WORKUP

- The clinical presentation of PA varies with the stage. Initially, patients may be asymptomatic. In advanced stages patients may have impaired memory, depression, gait disturbances, paresthesias, and reports of generalized weakness.
- Investigation consists primarily of laboratory evaluation. Table P1-12 describes a stepwise approach to the diagnosis of cobalamin and folate deficiency.
- Endoscopy and biopsy for atrophic gastritis may be performed in selected cases.
- Diagnosis is crucial because failure to treat may result in irreversible neurologic deficits.

LABORATORY TESTS

- Complete blood count generally reveals macrocytic anemia and leukopenia with hypersegmented neutrophils (Fig. EP1-30).
- Mean corpuscular volume (MCV) is generally significantly elevated in the advanced stages.
- Reticulocyte count is low to normal.
- Falsely low serum cobalamin levels can occur in patients with severe folate deficiency, in patients using high doses of ascorbic acid, and when cobalamin levels are measured after nuclear medicine studies (radioactivity interferes with cobalamin radioimmunoassay measurement).
- Falsely high normal levels in patients with cobalamin deficiency can occur in severe liver disease or chronic granulocytic leukemia (Table P1-13).
- The absence of anemia or macrocytosis does not exclude the diagnosis of cobalamin deficiency. Anemia is absent in 20% of patients with cobalamin deficiency, and macrocytosis is absent in >30% of patients at the time of diagnosis. It can be blocked by concurrent iron deficiency or anemia of chronic disease and may be masked by thalassemia trait.
- Laboratory tests used for detecting cobalamin deficiency in patients with normal vitamin B_{12} levels include serum and urinary methylmalonic acid (MMA) level (elevated), total homocysteine level (elevated), intrinsic factor antibody (positive). MMA level can also be used to differentiate cobalamin from folate deficiency because most patients with folate deficiency have normal or mild elevations of MMA levels.
- An increased concentration of plasma methylmalonic acid does not predict clinical manifestations of vitamin B_{12} deficiency and should not be used as the only marker for diagnosis of B_{12} deficiency.

TABLE P1-12 Stepwise Approach to the Diagnosis of Cobalamin and Folate Deficiency

Megaloblastic Anemia or Neurologic-Psychiatric Manifestations Consistent with Cobalamin Deficiency *Plus* Test Results On Serum Cobalamin and Serum Folate

Cobalamin* (pg/mL)	Folate† (ng/mL)	Provisional Diagnosis	Proceed With Metabolites?‡
>300	>4	Cobalamin or folate deficiency is unlikely	No
<200	>4	Consistent with cobalamin deficiency	No
200-300	>4	Rule out cobalamin deficiency	Yes
>300	<2	Consistent with folate deficiency	No
<200	<2	Consistent with (1) combined cobalamin plus folate deficiency or (2) isolated folate deficiency	Yes
>300	2-4	Consistent with (1) folate deficiency or (2) an anemia unrelated to vitamin deficiency	Yes

Test Results on Metabolites: Serum Methylmalonic Acid and Total Homocysteine

Methylmalonic Acid (Normal, 70-270 nM)	Total Homocysteine (Normal, 5-14 μM)	Diagnosis
Increased	Increased	Cobalamin deficiency confirmed; folate deficiency still possible (i.e., combined cobalamin plus folate deficiency possible)
Normal	Increased	Folate deficiency is likely
Normal	Normal	Cobalamin and folate deficiency is excluded

*Serum cobalamin levels: abnormally low, less than 200 pg/mL; clinically relevant low-normal range, 200 to 300 pg/mL.
†Serum folate levels: abnormally low, less than 2 ng/mL; clinically relevant low-normal range, 2 to 4 ng/mL.
‡Any frozen-over sample from serum folate/cobalamin determination can be subjected to metabolite tests.
From Hoffman R: *Hematology, basic principles and practice,* 6th ed, Philadelphia, 2013, Saunders.

TABLE P1-13 Serum Cobalamin: False-Positive and False-Negative Test Results

Falsely Low Serum Cobalamin in the Absence of True Cobalamin Deficiency

Folate deficiency (one-third of patients)
Multiple myeloma
TCI deficiency
Megadose vitamin C therapy

Falsely Raised Cobalamin Levels in the Presence of a True Deficiency*

Cobalamin binders (TCI and II) increased (e.g., myeloproliferative states, hepatomas, and fibrolamellar hepatic tumors)
TCII-producing macrophages are activated (e.g., autoimmune diseases, monoblastic leukemias and lymphomas)
Release of cobalamin from hepatocytes (e.g., active liver disease)
High serum anti-IF antibody titer

IF, Intrinsic factor; *TC,* transcobalamin.
*Although a low serum cobalamin level is not synonymous with cobalamin deficiency, 5% of patients with true cobalamin deficiency have low-normal cobalamin levels, a potentially serious problem because the patient's underlying cobalamin deficiency will progress if uncorrected.
From Hoffman R: *Hematology, basic principles and practice,* 6th ed, Philadelphia, 2013, Saunders, 2013.

- Additional laboratory abnormalities can include elevated lactate dehydrogenase, direct hyperbilirubinemia, and decreased haptoglobin.
- Bone marrow aspirate may show giant C-shaped neutrophil bands and megaloblastic normoblasts (Fig. EP1-31).
- Schilling test: No longer available in most laboratories. It was historically used to identify the locus of cobalamin malabsorption and, in some instances such as pernicious anemia or bacterial overgrowth, the cause of cobalamin deficiency.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Avoid folic acid supplementation without proper vitamin B_{12} supplementation. Doses of folic acid greater than 0.1 mg/day may result in hematologic remission in patients with vitamin B_{12} deficiency but will not prevent neurologic manifestations.

ACUTE GENERAL Rx

Traditional therapy of a cobalamin deficiency consists of IM injections of vitamin B_{12} 1000 mcg/wk for the initial 4 to 6 wk followed by 1000 mcg/mo IM indefinitely. In patients who have no nervous system involvement, intranasal cyanocobalamin may be used in place of IM cyanocobalamin when hematologic parameters have returned to normal range. The initial dose of intranasal cyanocobalamin (Nascobal) is 1 spray (500 mcg) in one nostril once per week. Cost generally exceeds $120/mo. Monitor response and increase dose if serum B_{12} levels decline. Consider return to intramuscular vitamin B_{12} supplementation if decline recurs.

CHRONIC Rx

- Parenteral vitamin B_{12} 1000 mcg/mo or intranasal cyanocobalamin 500 mcg/wk (see "Acute General Rx") for the remainder of life.
- Oral cobalamin (1000 to 2000 mcg/day) has been reported as also being effective in mild cases of pernicious anemia because approximately 1% of an oral dose is absorbed by passive diffusion, a pathway that does not require intrinsic factor. Cost for 1 mo of therapy is approximately $5.

DISPOSITION

Anemia generally resolves with appropriate treatment. Neurologic deficits, if present at diagnosis, may be permanent.

REFERRAL

Gastrointestinal referral for endoscopy on diagnosis of PA and surveillance endoscopy every 5 yr to rule out gastric carcinoma.

PEARLS & CONSIDERATIONS

COMMENTS

- Early manifestations of negative cobalamin balance are increased serum methylmalonic acid and total homocysteine levels. This occurs when the total cobalamin in serum is still in the low-normal range.
- Patients must understand that therapy is lifelong. Vitamin B_{12} deficiency that is allowed to progress for longer than 3 months may produce permanent degenerative lesions of the spinal cord.
- Vitamin B_{12} deficiency may suppress signs of polycythemia vera; treatment of B_{12} deficiency may unmask this disorder.
- Blunted or impeded therapeutic response to vitamin B_{12} may be due to concurrent iron or folic acid deficiency, uremia, infection, and use of drugs with bone marrow suppressant properties.
- Self-injection of vitamin B_{12} may be taught in selected patients. Cost of monthly injection is less than $5.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pernicious Anemia (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Coelho D et al.: Gene identification for the cblD defect of vitamin B_{12} metabolism, *N Engl J Med* 358:1454–1464, 2008.

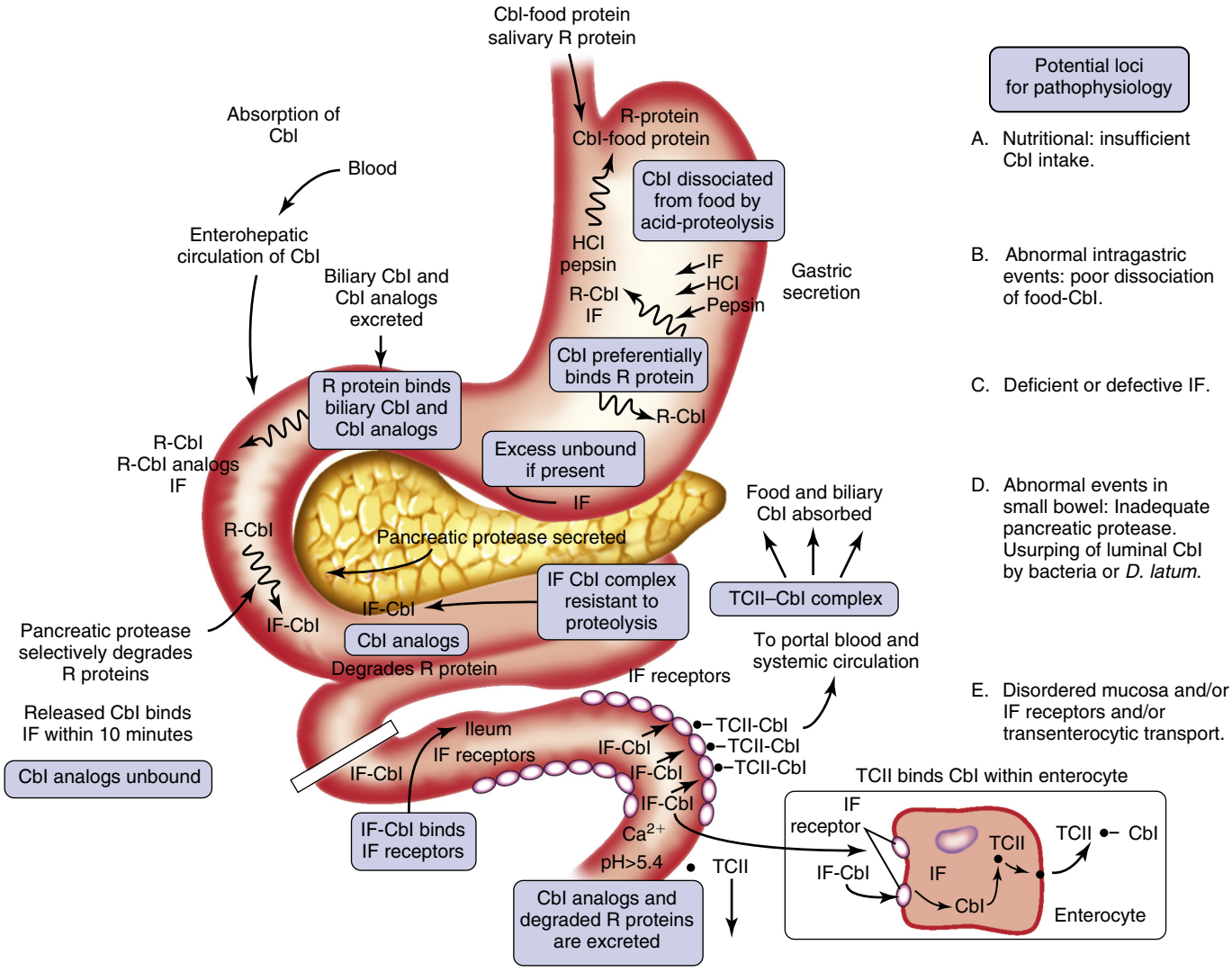


FIGURE EP1-29 Components and mechanism of cobalamin absorption. *Cbl,* Cobalamin; *HCl,* hydrochloric acid; *IF,* intrinsic factor; *R,* protein ligand; *TCII,* transcobalamin II. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 6, Philadelphia, 2013, Elsevier.)

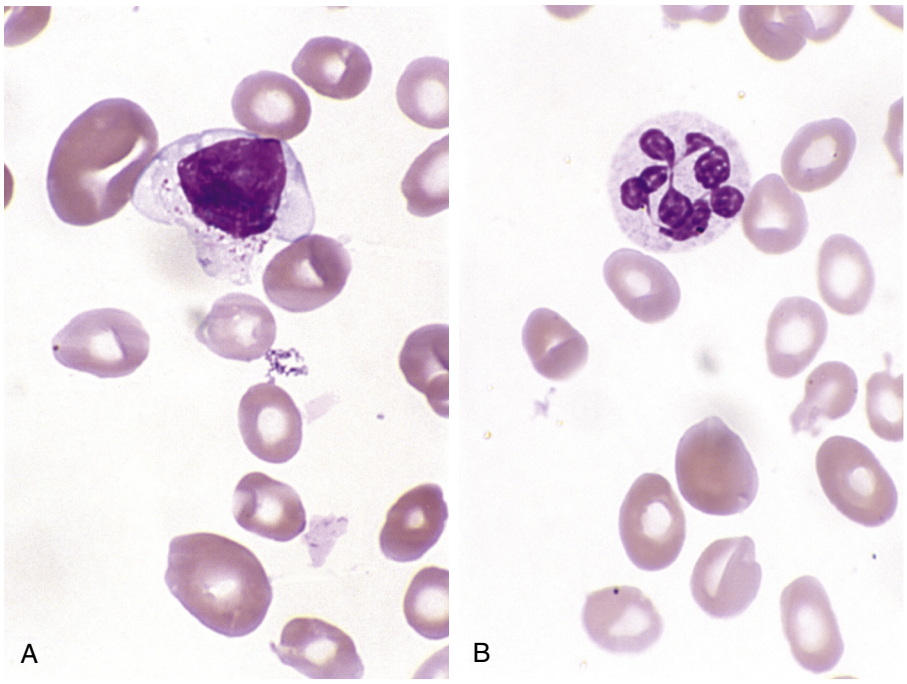


FIGURE EP1-30 Macro-ovalocytes **(A)** and hypersegmented neutrophils **(B)** are typical features of megaloblastic anemia. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

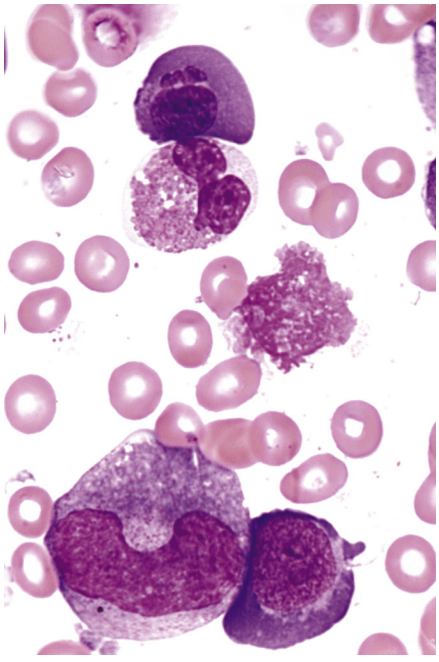


FIGURE EP1-31 Bone marrow aspirate from a patient with cobalamin deficiency illustrates a giant C-shaped neutrophil band and megaloblastic normoblasts. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Pertussis is a prolonged bacterial infection of the upper respiratory tract characterized by paroxysms of an intense cough.

SYNONYMS

Whooping cough

ICD-9CM CODES
033.9 Pertussis
ICD-10CM CODES
A37.90 Whooping cough, unspecified species without pneumonia

EPIDEMIOLOGY

INCIDENCE (IN U.S.): Case reports from 2013 declined to 28,639. This is compared to 48,277 cases reported in 2012, the highest rate reported since 1955 and included 20 deaths, primarily among infants aged <12 months. In 2014, there was a pertussis epidemic in California with nearly 10,000 cases reported (26 cases/100,000). Highest incidence was among infants younger than 1 year (174.6 cases/100,000), and the rate was significantly higher among Hispanic infants.

PEAK INCIDENCE:
- Childhood
- Usually affects children aged <1 yr

PREDOMINANT AGE:
- 50% in children aged <1 yr
- 20% in children aged >15 yr
- Classically an infection of infants and young children, pertussis is often overlooked as a cause of chronic cough in adults. However, a resurgence of pertussis has been observed in recent years, with nearly 50% of all cases identified in adolescents and adults, likely due to waning immunity and decreased effectiveness of acellular vaccines in early childhood compared to older, whole-cell-derived vaccines.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Infection is characterized by 3 phases: catarrhal, paroxysmal, and convalescent
- Catarrhal phase: Usually begins with a 1- to 2-wk prodrome that resembles a common cold. This phase may be mild or absent in adolescents and adults given partial immunity from prior immunization
- After this initial phase, increased production of mucus occurs. Excessive lacrimation and conjunctival infection should heighten the suspicion for pertussis
- Paroxysmal phase: Increased mucus production is followed by an intense, paroxysmal cough, ending with gasps and an inspiratory whoop
- In some children, apnea, cyanosis and anoxia are noted; posttussive gagging and vomiting are characteristic of pertussis
- Cases can be severe and life-threatening in young infants, particularly children <6 months old
- When prolonged, frank exhaustion and even apnea occur. The paroxysmal phase lasts from 2 wk to 2 mo
- Convalescent phase: Lasts over 2 months and is characterized by cough of decreasing severity

ETIOLOGY

Bordetella pertussis, a gram-negative rod which adheres to human cilia and respiratory epithelia

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Croup
- Epiglottitis
- Foreign body aspiration
- Bacterial pneumonia
- Viral pneumonia

WORKUP

Pertussis is often overlooked as a cause of chronic cough, especially in adolescents and adults. The presence of posttussive emesis and/or inspiratory whoop increases the likelihood of pertussis but only modestly. Therefore, clinicians must use their overall impression in pursuing the diagnosis.

- Enzyme-linked immunosorbent assay for detection of antibody to pertussis. Polymerase chain reaction (PCR) is the most sensitive method for rapid detection of pertussis. PCR testing should be used only to confirm a diagnosis in persons with signs and symptoms consistent with pertussis. PCR testing sensitivity declines and is unlikely to be positive after 1 month of infection. PCR testing after 5 days of treatment with antibiotics can cause false-negative results and is generally not recommended
- Blood cultures in hospitalized patients
- Chest x-ray
- Culture of bacteria, usually from nasopharynx by aspiration or by swabbing the posterior nasopharynx with a polyester-tipped, rayon-tipped, or nylon-flocked swab
- Immunofluorescent staining of nasopharyngeal secretions
- Serologic tests for immunoglobulin G (IgG) or A (IgA) are available. A twofold increase between acute and convalescent sera is considered proof of seroconversion. A single elevated IgG or IgA titer is considered diagnostic when no acute serum is available. Can be useful for diagnosis later in illness.

LABORATORY TESTS

Complete blood count, which usually demonstrates marked lymphocytosis:
- Up to 18,000 white blood cells
- 70% to 80% lymphocytes

IMAGING STUDIES

Chest x-ray examination is of value if secondary bacterial pneumonia is suspected.

TREATMENT

ACUTE GENERAL Rx

- Intensive supportive care:
  1. Adequate hydration
  2. Control of secretions
  3. Maintenance of airway
- Antibiotics (Table EP1-14) are indicated even though their ability to alter the course of the disease is controversial.
  1. Azithromycin 500 mg on day 1, followed by 250 mg for days 2 to 5. Erythromycin 50 mg/kg/day for 14 days. Recent literature reports indicate that a 7-day treatment regimen may be as effective as a 14-day course of erythromycin. TMP/SMX 320/1600 mg per day in divided doses can be used in patients with allergy or intolerance to macrolides.
  2. Although unproved, dexamethasone 1 mg/kg/day in four doses for severe, life-threatening paroxysms.
  3. Ceftriaxone 75 mg/kg/day in two doses for broad coverage of secondary bacterial pneumonias.
  4. Close observation of infants <6 months old as risk for apnea is high in this age group.
- Vaccination is successful in preventing the disease: universal vaccination is advised for all children and adults. The Advisory Committee on Immunization Practices (ACIP) updated Tdap recommendations to include a single dose of Tdap vaccine in place of routine Td for adults age 19-64 yr and a single-dose Tdap for adults 65 yr and older who have or will have close contact with an infant (>12 mo). The ACIP also recommends that all pregnant women receive a dose of Tdap with every pregnancy, preferably during weeks 27-36 of gestation.
- Azithromycin, clarithromycin, or erythromycin is recommended for all household contacts and should be given to all persons at high risk of severe disease from pertussis and who were in contact with a pertussis case within 21 days of cough onset: TMP/SMX in two oral doses per day for those intolerant to macrolides.

DISPOSITION

Close attention to accepted vaccination schedules is the best prevention.

REFERRAL

To intensive care setting for life-threatening infections:
- Pulmonologist
- Infectious disease specialist

PEARLS & CONSIDERATIONS

- The diagnosis of pertussis in a young child is easily recognized, but in adults pertussis can be a subtle diagnosis and is often missed. The tip-off is often a persistent, hacking, and productive cough with minor or no fever in a previously healthy person that lasts < 2 wk.
- Approximately 11% of pertussis cases in the pediatric population are attributable to vaccine refusal, dispelling the myth that herd immunity protects children whose parents refuse pertussis vaccine.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pertussis (Patient Information)

AUTHOR: **RUSSELL J. MCCULLOH, M.D.**

SUGGESTED READINGS

Cornia PB et al.: Does this coughing adolescent or adult patient have pertussis? *JAMA* 304(8):890–896, 2010.

Glanz JM et al.: Parental refusal of pertussis vaccination is associated with an increased risk of pertussis infection in children, *Pediatrics* 123:1446, 2009.

Gregory DS: Pertussis: a disease affecting all ages, *Am Fam Physician* 74:420, 2006.

Heininger U, Cherry JD: Pertussis immunization in adolescents and adults—*Bordetella pertussis* epidemiology should guide vaccination recommendations, *Expert Opin Biol Ther* 6(7):685, 2006.

Kline JM et al.: Pertussis: a re-emerging infection, *Am Fam Phys* 88(8):507–514, 2013.

Matthias J, Dusek C, Pritchard PS, Rutledge L, Kinchen P, Lander M: Notes from the field: Outbreak of pertussis in a school and religious community averse to health care and vaccinations —Columbia County, Florida, 2013, *MMWR* 63(30):655, 2014.

Paisley RD et al.: Whooping cough in adults: an update on a reemerging infection, *Am J Med* 125(2):141–143, 2012.

Roehr B: Whooping cough outbreaks hit several U.S. states, *BMJ* 341:4627, 2010.

Schafer S et al.: A community-wide pertussis outbreak, *Arch Intern Med* 166:1317, 2006.

Shapiro ED: Acellular vaccines and resurgence of pertussis, *JAMA* 308:2149–2150, 2012.

Spector TB, Maziarz EK: *Pertussis. Med Clin North Am* 97(4):537–552, 2013. http://dx.doi.org/10.1016/j.mcna.2013.02.004. ix. Epub 2013 Apr 17.

Tivari T et al.: National Immunization Program, CDC. Recommended antimicrobial agents for the treatment and post exposure prophylaxis of pertussis: 2005 CDC guidelines, *MMWR Recomm Rep* 54:1, 2005.

TABLE EP1-14 Recommended Antimicrobial Treatment and Postexposure Prophylaxis for Pertussis, by Age Group

	PRIMARY AGENTS		ALTERNATE AGENT*	
Age Group	**Azithromycin**	**Erythromycin**	**Clarithromycin**	**TMP-SMZ**
>1 mo	Recommended agent. 10 mg/kg/day in a single dose for 5 days (only limited safety data available)	Not preferred Erythromycin is substantially associated with infantile hypertrophic pyloric stenosis Use if azithromycin is unavailable; 40-50 mg/kg/day in 4 divided doses for 14 days	Not recommended (safety data unavailable)	Contraindicated for infants aged >2 mo (risk for kernicterus)
1-5 mo	10 mg/kg/day in a single dose for 5 days	40-50 mg/kg/day in four divided doses for 14 days	15 mg/kg/day in two divided doses for 7 days	Contraindicated at age >2 mo For infants aged ≥2 mo: TMP 8 mg/kg/day plus SMZ 40 mg/kg/day in two divided doses for 14 days
Infants aged ≥6 mo and children	10 mg/kg in a single dose on day 1 (maximum 500 mg), then 5 mg/kg/day (maximum 250 mg) on days 2-5	40-50 mg/kg/day (maximum 2 g/day) in four divided doses for 14 days	15 mg/kg/day in two divided doses (maximum 1 g/day) for 7 days	TMP 8 mg/kg/day plus SMZ 40 mg/kg/day in two divided doses for 14 days
Adolescents and adults	500 mg in a single dose on day 1 then 250 mg/day on days 2-5	2 g/day in four divided doses for 14 days	1 g/day in two divided doses for 7 days	TMP 320 mg/day, SMZ 1600 mg/day in two divided doses for 14 days

*Trimethoprim-sulfamethoxazole (TMP-SMZ) can be used as an alternative agent to macrolides in patients aged ≥2 mo who are allergic to macrolides, who cannot tolerate macrolides, or who are infected with a rare macrolide-resistant strain of *Bordetella pertussis*.

From Centers for Disease Control and Prevention: Recommended antimicrobial agents for treatment and postexposure prophylaxis of pertussis: 2005 CDC guidelines, *MMWR Morbid Mortal Wkly Rep* 54:1-16, 2005.

BASIC INFORMATION

DEFINITION

- A hamartomatous polyp is a benign intestinal growth that may contain all components of the intestinal mucosa. In gastrointestinal polyposis, multiple such polyps coexist within the intestinal tract, and associated manifestations are usually also present.
- Juvenile polyps are benign polyps composed of cystic dilatations of glandular structures within the fibroblastic stroma of the lamina propria. They may cause bleeding or intussusception.
- Commonly recognized syndromes are Peutz-Jeghers syndrome, juvenile polyposis syndrome, Cowden's disease, Bannayan-Ruvalcaba-Riley syndrome, and Cronkhite-Canada syndrome. Other, lesser known inherited hamartomatous polyposis syndromes are hereditary mixed polyposis syndrome, intestinal ganglioneuromatosis and neurofibromatosis (variant of von Recklinghausen's syndrome), Devon family syndrome, basal cell nevus syndrome, and tuberous sclerosis (may involve gastrointestinal tract). Table P1-15 describes general features of some inherited colorectal cancer syndromes.

ICD-9CM CODES
759.6 (Peutz-Jeghers syndrome)
211.3 (Cronkhite-Canada syndrome)
ICD-10CM CODES
D12.6 Colon, unspecified (adenomatosis of colon, hereditary polyposis)

EPIDEMIOLOGY

- Colonic adenomas, the precursors of nearly all colorectal cancers, are found in nearly 40% of patients by age 60 yr.
- 25% of men and 15% of women who undergo colonoscopy are found to have one or more adenomas.
- Detection of any adenoma in patients <60 yr confers an increased risk of colorectal cancer (by a factor of 2.6) in their first-degree relatives.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

PEUTZ-JEGHERS SYNDROME

- Transmission: autosomal dominant with incomplete penetrance
- Disease expression:
  1. Stomach, small and large intestinal hamartomas with bands of smooth muscle in the lamina propria
  2. Pigmented lesions around mouth (lips and buccal mucosa), nose, hands, feet, genitals, and perineal areas
  3. Ovarian tumors
  4. Sertoli cell testicular tumors
  5. Airway polyps
  6. Pancreatic cancer
  7. Breast cancer
  8. Urinary tract polyps
- Cumulative lifetime cancer risk
  1. Colon cancer: 39%
  2. Stomach cancer: 29%
  3. Small intestine cancer: 13%
  4. Pancreatic cancer: 36%
  5. Breast cancer: 54%
  6. Ovarian cancer: 10%
  7. Sertoli cell tumor: 9%
  8. Overall cancer risk: 93%
- Clinical manifestation:
  1. Gastrointestinal, small-bowel obstruction, intussusception, gastrointestinal bleeding
  2. See chapters on relevant malignancies for their signs and symptoms

JUVENILE POLYPOSIS SYNDROME

- Transmission: autosomal dominant
- Disease expression
  1. Solitary juvenile polyps numbering 10 or more in the rectum or throughout the gastrointestinal tract; the polyps are smooth and covered with normal epithelium
  2. Various congenital abnormalities coexist in 20%
- Cumulative cancer risk is increased (may be as high as 50%)
- Clinical manifestation
  1. Intestinal obstruction
  2. Intussusception
  3. Gastrointestinal bleeding

COWDEN'S DISEASE

- Transmission: autosomal dominant, rare
- Disease expression
  1. Juvenile intestinal polyposis
  2. Orocutaneous hamartomas
  3. Fibrocystic breast disease and breast cancer
  4. Goiter and thyroid cancer
  5. Facial tricholemmomas (papules) in 83%
- Cumulative cancer risk
  1. Gastrointestinal: same as general population
  2. Thyroid: 3% to 10%
  3. Breast: 25% to 50%

BANNAYAN-RUVALCABA-RILEY SYNDROME

- Transmission: autosomal dominant, rare
- Disease expression
  1. Juvenile intestinal polyposis
  2. Macrocephaly
  3. Developmental delay
  4. Penile pigmented spots
  5. Cumulative cancer risk unknown

CRONKHITE-CANADA SYNDROME

- Transmission: acquired
- Age of onset: midlife
- Disease expression
  1. Diffuse gastrointestinal juvenile polyposis (50% to 95% of cases)
  2. Chronic diarrhea and protein-losing enteropathy (the entire intestinal mucosa may be inflamed), which leads to abdominal pain, weight loss, and various complications of malnutrition

TABLE P1-15 General Features of the Inherited Colorectal Cancer Syndromes

Syndrome	Polyp Histology	Polyp Distribution	Age of Onset	Risk of Colon Cancer	Genetic Lesion	Clinical Manifestations	Associated Lesions
Familial adenomatous polyposis (Fig. P1-32)	Adenoma	Large intestine, duodenum	16 yr (range, 8-34 yr)	100%	5q (*APC* gene)	Rectal bleeding, abdominal pain, bowel obstruction	Desmoids, CHRPE
Peutz-Jeghers syndrome	Hamartoma	Large and small intestine	First decade	Slightly above average	19p (*STK11* gene)	Possible rectal bleeding, abdominal pain, intussusception	Orocutaneous melanin pigment spots, other tumors
MUTYH-associated polyposis	Adenoma	Large intestine, duodenum	45-50 yr (range, 13-60 yr)	75% (range, 50%-100%)	1p (*MYH* gene)	Rectal bleeding, abdominal pain, bowel obstruction	CHRPE, osteomas
Juvenile polyposis	Hamartoma (rarely adenoma)	Large and small intestine	First decade	≈9%	*PTEN, SMAD4, BMPR1*	Possible rectal bleeding, abdominal pain, intussusception	Pulmonary AVMs
Hereditary nonpolyposis colon cancer	Adenoma	Large intestine	40 yr (range, 18-65 yr)	30%	Mismatch repair genes*	Rectal bleeding, abdominal pain, bowel obstruction	Other tumors (e.g., ovary, uterus, pancreas, stomach)

AVM, Arteriovenous malformation; *CHRPE,* congenital hypertrophy of the retinal pigment epithelium; *MUTYH,* mutY homolog *(Escherichia coli).*
*Including *hMSH2, hMSH3, hMSH6, hMLH1, hPMS1,* and *hPMS2.*
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

3. Dystrophic nails
4. Alopecia
5. Hyperpigmentation

- Cumulative cancer risk: same as the average population

Dx DIAGNOSIS

Diagnosis is suggested in many cases by family history and confirmed by colonoscopy and physical findings described previously.

Rx TREATMENT

GENERAL Rx

Peutz-Jeghers syndrome:

- Colonoscopies with polypectomies
- Screening for breast cancer, testicular cancer, possibly ovarian cancer

Juvenile polyposis syndrome:

- Colonoscopies with polypectomies if few colon polyps
- Total colectomy if numerous polyps
- Esophagogastroscopies and polypectomies

Cowden's disease:

- Rigorous breast cancer screening or prophylactic simple bilateral mastectomy with reconstruction.

Cronkhite-Canada syndrome:

- Progressive malabsorption syndrome is the hallmark of this syndrome, and no specific treatment exists. Enteral or parenteral feeding is the cornerstone of management and can result in remission.

DISPOSITION

- The screening of first-degree relatives of patients with colonic adenomas detected before 60 yr of age is controversial. Some recommend beginning colonoscopic screening at age 40 yr or 10 yr younger than the age at diagnosis of the youngest person in the family with an adenoma.
- Recommended interval between colonoscopies from the U.S. Consensus Guidelines for Colonoscopic Surveillance after Polypectomy are as follows:
  1. 10 yr for small, rectal hyperplastic polyps
  2. 5 to 10 yr for one to two low-risk adenomas (tubular adenomas <1 cm)
  3. 3 yr for low-risk adenomas or any high-risk adenoma (large [≥1 cm] or histologically advanced adenomas [tubulovillous or villous adenomas or villous adenomas and those with high-grade dysplasia])
  4. <3 yr for presence of >10 adenomas
  5. 2 to 6 mo for inadequately removed adenomas

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Peutz-Jeghers Syndrome (Patient Information)
Familial Adenomatous Polyposis and Gardner Syndrome (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

FIGURE P1-32 Familial adenomatous polyposis. This disorder is marked by the development of hundreds of large bowel adenomas, as seen in this segment of large bowel, which is covered with adenomas of various sizes. It usually arises in the second and third decades. (From Skarin AT: *Atlas of diagnostic oncology*, 4th ed, St Louis, 2010, Mosby, 2010.)

SUGGESTED READING

Levine JS, Ahnen DJ: Adenomatous polyps of the colon, *N Engl J Med* 355: 2551–2557, 2006.

BASIC INFORMATION

DEFINITION

Peyronie's disease is an abnormal curvature and shortening of the penis during an erection. This is caused by scarring of the tunica albuginea of the corpora cavernosa.

SYNONYMS

Plastic induration of the penis
Penile fibromatosis

ICD-9CM CODES
607.89 Peyronie's disease
ICD-10CM CODES
N48.6 Induratio penis plastica

EPIDEMIOLOGY & DEMOGRAPHICS

- Peyronie's disease occurs in approximately 1% of men.
- It is commonly seen between the ages of 45 and 60 yr.
- A genetic predisposition has been suggested.
- There are no incidence and prevalence data available in the literature.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Painful erections
- Tenderness over the scar tissue area
- Erectile dysfunction
- Curvature of the erected penis interfering with penetration
- Dupuytren's contracture is a commonly associated finding in patients with Peyronie's disease

ETIOLOGY

- Specific cause is unknown. It is believed that scar tissue forms on either the dorsal or ventral midline surface of the penile shaft. The scar restricts expansion at the involved site, causing the penis to bend or curve in one direction.
- The precipitating factor appears to be trauma from repetitive microvascular injury caused by vigorous sexual intercourse, accidents, or prior surgeries (e.g., transurethral or radical prostatectomy, cystoscopy).

DIAGNOSIS

Diagnosis is based on the clinical findings.

DIFFERENTIAL DIAGNOSIS

- The history differentiates congenital from acquired curvatures of the penis.
- Other causes of erectile dysfunction must be excluded, including metabolic, diabetic, thyroid, and renal causes, in addition to hypogonadism and hyperprolactinemia.

WORKUP

History and physical examination alone will usually establish the diagnosis of Peyronie's disease.

LABORATORY TESTS

There are no specific blood tests to diagnose Peyronie's disease. Electrolytes, blood urea nitrogen, creatinine, glucose, thyroid function tests (thyroid-stimulating hormone, T_3U, T_4), testosterone, and prolactin levels are blood tests to exclude other medical causes of erectile dysfunction.

IMAGING STUDIES

Imaging studies are not specific.

TREATMENT

NONPHARMACOLOGIC THERAPY

A conservative approach of reassurance and observation is taken at first because the disease process may be self-limiting.

ACUTE GENERAL Rx

Although not substantiated by direct randomized, controlled clinical trials, the following treatment modalities have been tried:

- Vitamin E 400 mg bid.
- Paraaminobenzoic acid 12 g/day.
- Colchicine 0.6 mg bid for 2 to 3 wk.
- Fexofenadine 60 mg bid for 3 mo.
- Steroid injection into the scar tissue.
- Collagenase injection into the scar tissue.
- Radiation to the scar tissue area.
- Extracorporeal shockwave therapy (ESWT): Current evidence on the safety, but not the efficacy, of ESWT appears adequate. From comparative studies, the main benefits of ESWT were the alleviation of pain and reduction of angulation of the penis. In one comparative study, 10 of 20 patients receiving ESWT had a decrease in the curvature of at least 30%. Case series evidence also suggested some improvement of sexual performance.
- Other medications that can be helpful include verapamil, tamoxifen, and interferon.

CHRONIC Rx

In patients who have progressed to intractable pain with erection or erectile dysfunction, surgical treatment with excision of the plaque and skin grafting may be indicated.

DISPOSITION

Peyronie's disease evolves slowly and in some cases can resolve on its own. Waiting for 1 yr before proceeding with surgical attempts is recommended.

REFERRAL

A urologic consultation is recommended in patients with progressive symptoms and erectile dysfunction.

PEARLS & CONSIDERATIONS

COMMENTS

- Peyronie's disease is not commonly seen in younger patients because they are able to sustain intracorporeal pressures high enough to stretch the scar tissue, preventing it from deforming the penis during erection.
- Trauma from buckling of the erected penis is thought to be the precipitant cause of scar formation and Peyronie's disease. It is found more often in men who are sexually very active and vigorous, having sexual intercourse daily or almost daily.
- Sexual positions with the woman being on top or thrusting the penis into the anterior vaginal wall are thought to increase the chances of developing Peyronie's disease.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Peyronie's Disease (Patient Information)

AUTHOR: **TANYA ALI, M.D.**

SUGGESTED READINGS

Ralph DJ, Minhas S: The management of Peyronie's disease, *BJU Int* 93(2):208, 2004.

Smith CJ et al.: Peyronie's disease: the epidemiology, aetiology and clinical evaluation of deformity, *BJU Int* 95(6):729, 2005.

Pharyngitis/Tonsillitis (PTG)

BASIC INFORMATION

DEFINITION

Inflammation of the pharynx or tonsils

SYNONYMS

Sore throat
Group A streptococci (GAS)

ICD-9CM CODES
462 Pharyngitis
ICD-10CM CODES
J02.9 Acute pharyngitis, unspecified
J03.0 Acute tonsillitis
J03.9 Acute tonsillitis, unspecified
J04.0 Acute laryngitis

EPIDEMIOLOGY & DEMOGRAPHICS

Acute pharyngitis accounts for 1.3% of outpatient visits to health care providers in the United States.
PEAK INCIDENCE: Late winter/early spring (GAS infections)
PREDOMINANT SEX: Females = males
PREDOMINANT AGE:

- All ages affected
- Streptococcal pharyngitis most common among school-age children (5-15 yr of age). GAS are responsible for 5%-15% of cases of pharyngitis in adults and 20%-30% of cases in children (5-15 yr of age).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pharynx:
  1. May appear normal to severely erythematous
  2. Tonsillar hypertrophy and exudates commonly seen but do not indicate etiology
- Viral infection:
  1. Rhinorrhea
  2. Conjunctivitis
  3. Cough
- Bacterial infection, especially GAS:
  1. High fever
  2. Systemic signs of infection
- Herpes simplex or enterovirus infection: vesicles
- Streptococcal infection:
  1. Rare complications:
     a. Scarlet fever
     b. Rheumatic fever
     c. Acute glomerulonephritis
  2. Extension of infection: tonsillar, parapharyngeal, or retropharyngeal abscess presenting with severe pain, high fever, trismus
- Streptococcal tonsillitis is manifested as acute onset of fever, headache, neck pain, odynophagia, sore throat, otalgia, red tongue with enlargement of papillae, sore throat, red swollen uvula, and tender anterior cervical adenitis.
- Peritonsillar abscess (accumulation of pus between the tonsil and its capsule) is the most common complication of acute tonsillitis. Clinical signs include deformed posterior pharynx, medial displacement of the uvula, trismus, and muffled voice (hot-potato voice).
- Table P1-16 describes seven danger signs in patients with sore throat.

ETIOLOGY

- Viruses:
  1. Respiratory syncytial virus
  2. Influenza A and B
  3. Epstein-Barr virus
  4. Adenovirus
  5. Herpes simplex
- Bacteria:
  1. GAS: *Streptococcus pyogenes.* β-Hemolytic GAS are the most common cause of acute tonsillitis.
  2. *Neisseria gonorrhoeae*
  3. Fusobacterium necrophorum (10% of pharyngitis): highest incidence in patients aged 15 to 30 years
- Other organisms:
  1. *Mycoplasma pneumoniae*
  2. *Chlamydophila pneumoniae*
  3. *Arcanobacterium haemolyticum*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Sore throat associated with granulocytopenia, thyroiditis
- Tonsillar hypertrophy associated with lymphoma
- Section II describes the differential diagnosis of sore throat.

WORKUP

The Centor criteria to identify patients at risk for GAS consists of (1) fever subjective or measured >38.1° C (100.5° F), (2) absence of cough, (3) tonsilar exudates, (4) tender anterior cervical lymphadenopathy. Patients with ≤1 criteria are at low risk and do not need additional testing. The Mclsaac criteria adds 1 point for age 3-14 and subtracts a point for age ≥45 yr.

- Rapid streptococcal antigen test (culture should be performed if rapid test negative)
- Throat swab for culture to exclude *S. pyogenes, N. gonorrhoeae* (requires specific transport medium) in selected cases

LABORATORY TESTS

- Bloodwork is only rarely necessary
- Complete blood count with differential
  1. May help support diagnosis of bacterial infection when diagnosis is unclear
  2. Streptococcal infection suggested by leukocytosis >15,000/mm^3
- Viral cultures, serologic studies rarely needed
- Monospot if diagnosis is unclear

TABLE P1-16 Seven Danger Signs in Patients with Sore Throat

1. Persistence of symptoms longer than 1 wk without improvement
2. Respiratory difficulty, particularly stridor
3. Difficulty in handling secretions
4. Difficulty in swallowing
5. Severe pain in the absence of erythema
6. A palpable mass
7. Blood, even in small amounts, in the pharynx or ear

From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.

IMAGING STUDIES

Seldom indicated. If necessary to distinguish between tonsillitis and peritonsillar abscess, CT or MRI of the neck can be done.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Fluids
- Salt water gargles

ACUTE GENERAL Rx

- Analgesics: aspirin (adults) or acetaminophen or ibuprofen (adults and children)
- If streptococcal infection proven or suspected:
  1. Penicillin V 500 mg PO bid for 10 days or benzathine penicillin 1.2 million U IM once (adults). Children: penicillin V 250 mg bid or tid
  2. Erythromycin 500 mg PO bid or 250 mg qid for 10 days or azithromycin if penicillin allergic
- If gonococcal infection proven or suspected: ceftriaxone 250 mg IM once.
- Amoxicillin 500 mg tid for 10 days is the primary antibiotic treatment of streptococcal tonsillitis. Macrolides or clindamycin can be used in penicillin-allergic patients.
- Treatment of peritonsillar abscess is drainage through needle or incision.

CHRONIC Rx

- Recurrent streptococcal infections are common and may represent reinfection from other household members, including pets.
- There is no conclusive evidence from randomized clinical trials that tonsillectomy is superior to antibiotic therapy for recurrent tonsillitis in adults.
- Tonsillopharyngitis is generally managed in an outpatient setting with follow-up arranged in 1 to 2 wk. Admission to the hospital is indicated for local suppurative complications (peritonsillar abscess; lateral pharyngeal or posterior pharyngeal abscess; impending airway closure; or inability to swallow food, medications, or water).

REFERRAL

- To otolaryngologist:
  1. If peritonsillar or other abscess is suspected
  2. If tonsillar hypertrophy persists

PEARLS & CONSIDERATIONS

COMMENTS

- Antibiotic therapy should be avoided unless bacterial etiology is suspected or proven, especially in adults.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Sore Throat (Patient Information)
Tonsillitis (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Centor RM et al.: The clinical presentation of fusobacterium-positive and streptococcal-positive pharyngitis in a university health clinic, *Ann Intern Med* 162:241–247, 2015.

Cirilli AR: Emergency evaluation and management of the sore throat, *Emerg Med Clin North Am* 31(2):501–515, 2013.

Choby BA: Diagnosis and treatment of streptococcal pharyngitis, *Am Fam Physician* 79(5):383–390, 2009.

Linder JA et al.: Evaluation and treatment of pharyngitis in primary care practice, *Arch Intern Med* 166:1374–1379, 2006.

Patel NN, Patel DN: Acute exudative tonsillitis, *Am J Med* 122:17–20, 2009.

Tewfik TL, Al Garni M: Tonsillopharyngitis: clinical highlights, *J Otolaryngol* 34(Suppl 1):S45, 2005.

Wessels MR: Streptococcal pharyngitis, *N Engl J Med* 364:648–655, 2011.

BASIC INFORMATION

DEFINITION

Pheochromocytomas are catecholamine-producing tumors that originate from chromaffin cells of the adrenergic system. They generally secrete both norepinephrine and epinephrine, but norepinephrine is usually the predominant amine.

SYNONYMS

Paraganglioma

ICD-9CM CODES
194.0 Pheochromocytoma
255.6 Medulloadrenal hyperfunction
ICD-10CM CODES
C74.9 Malignant neoplasm of adrenal gland, unspecified
C75.9 Malignant neoplasm of endocrine gland, unspecified
E27.5 Adrenomedullary hyperfunction

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence: 0.05% of population; peak incidence in 30s and 40s.
- Approximately 25% of patients with apparently sporadic pheochromocytoma may be carriers of mutations.
- Approximately 25% of pheochromocytomas are familial and associated with genetic disorders (Table P1-17). Pheochromocytoma is a feature of two disorders with an autosomal-dominant pattern of inheritance:
  1. Multiple endocrine neoplasia (MEN) type 2
  2. Von Hippel-Lindau disease: angioma of the retina, hemangioblastoma of the central nervous system, renal cell carcinoma, pancreatic cysts, and epididymal cystoadenoma
- Pheochromocytomas occur in 5% of patients with neurofibromatosis type 1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Hypertension: can be sustained (55%) or paroxysmal (45%).
- Headache (80%): usually paroxysmal in nature and described as "pounding" and severe.
- Palpitations (70%): can be present with or without tachycardia.
- Hyperhidrosis (60%): most evident during paroxysmal attacks of hypertension.
- Physical examination may be entirely normal if done in a symptom-free interval; during a paroxysm the patient may demonstrate marked increase in both systolic and diastolic pressure, profuse sweating, visual disturbances (caused by hypertensive retinopathy), dilated pupils (from catecholamine excess), paresthesias in the lower extremities (caused by severe vasoconstriction), tremor, tachycardia.
- Orthostatic hypotension is common among patients with pheochromocytoma due to reduction of blood volume and desensitization of adrenergic receptors by the chronic excess of catecholamines.

ETIOLOGY

- Catecholamine-producing tumors that are usually located in the adrenal medulla.
- Specific mutations of the RET protooncogene cause familial predisposition to pheochromocytoma in MEN 2.
- Mutations in the von Hippel-Lindau tumor suppressor gene (*VHL* gene) cause familial disposition to pheochromocytoma in von Hippel-Lindau disease.
- Recently identified genes for succinate dehydrogenase subunit D *(SDHD)* and succinate dehydrogenase subunit B *(SDHB)* predispose carriers to pheochromocytoma and globus tumors.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Anxiety disorder
- Thyrotoxicosis
- Amphetamine or cocaine abuse
- Carcinoid
- Essential hypertension

WORKUP

Laboratory evaluation and imaging studies to locate the neoplasm (Fig. P1-33). Misdiagnosis of pheochromocytoma is not uncommon. Correct interpretation of biochemical tests and imaging is crucial to a correct diagnosis.

LABORATORY TESTS

- Although there is no consensus on the best test, plasma-free metanephrines have been suggested as the test of first choice for excluding the tumor. Elevated plasma concentrations of normetanephrines or metanephrine have a sensitivity of up to 100%, but the specificity is markedly lower.
- 24-hr urine collection for metanephrines (up to 100% sensitive) will also show increased metanephrines; the accuracy of the 24-hr urinary levels for metanephrines can be improved by indexing urinary metanephrine levels by urine creatinine levels.

TABLE P1-17 Autosomal Dominant Syndromes Associated with Pheochromocytoma and Paraganglioma

Syndrome	Gene	Gene Locus	Protein Product	Protein Function	Gene Mechanism	Typical Tumor Location
SDHD (familial paraganglioma type 1)*	*SDHD*	11q23	SDH D subunit	ATP production	Tumor suppressor	Skull base and neck; occasionally adrenal medulla, mediastinum, abdomen, pelvis
Familial paraganglioma type 2*	*SDHAF2*	11q13.1	Flavination cofactor	ATP production	Tumor suppressor	Skull base and neck; occasionally abdomen and pelvis
SDHC (familial paraganglioma type 3)	*SDHC*	1q21	SDH C subunit	ATP production	Tumor suppressor	Skull base and neck
SDHB (familial paraganglioma type 4)	*SDHB*	1p36.1-35	SDH B subunit	ATP production	Tumor suppressor	Abdomen, pelvis and mediastinum; rarely adrenal medulla, skull base, and neck
MEN1	*MEN1*	11q13	Menin	Transcription regulation	Tumor suppressor	Adrenal medulla
MEN2A and MEN2B	*RET*	10q11.2	RET	Tyrosine kinase receptor	Protooncogene	Adrenal medulla, bilaterally
Neurofibromatosis type 1	*NF1*	17q11.2	Neurofibromin	GTP hydrolysis	Tumor suppressor	Adrenal-periadrenal
von Hippel-Lindau disease	*VHL*	3p25-26	VHL	Transcription elongation suppression	Tumor suppressor	Adrenal medulla, bilaterally; occasionally paraganglioma
Familial pheochromocytoma	*FP/TMEM127*	2q11	Transmembrane protein	Regulation of the mTORC1 signaling complex	Tumor suppressor	Adrenal medulla

ATP, Adenosine triphosphate; *GTP,* guanosine triphosphate; *MEN,* multiple endocrine neoplasia; *SDH,* succinate dehydrogenase.
*Associated with maternal imprinting.
From Melmed S: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders, Elsevier.

IMAGING STUDIES

- Abdominal CT scan (Fig. EP1-34) with and without contrast (88% sensitivity) is useful in locating pheochromocytomas >0.5 inch in diameter (90% to 95% accurate).
- MRI with contrast: pheochromocytomas demonstrate a distinctive MRI appearance (up to 100% sensitivity); MRI may become the diagnostic imaging modality of choice.
- Scintigraphy with 131 or 1-123 I-MIBG (up to 100% sensitivity) (Fig. EP1-34): this norepinephrine analog localizes in adrenergic tissue; it is particularly useful in locating extraadrenal pheochromocytomas.
- 6-[^{18}F]Fluorodopamine positron emission tomography is reserved for cases in which clinical symptoms and signs suggest pheochromocytoma and results of biochemical tests are positive but conventional imaging studies cannot locate the tumor. An alternative approach is to use vena caval sampling for plasma catecholamines and metanephrines.

Rx TREATMENT

GENERAL Rx

Laparoscopic adrenalectomy (surgical resection for both benign and malignant disease):

1. Preoperative stabilization with combination of alpha-adrenergic blocking agents (prazosin, doxazosin, terazosin, or phenoxybenzamine), beta-blocker, and liberal fluid and salt intake starting 10 to 14 days before surgery. Beta-blockers should be avoided until patients receive adequate alpha-adrenergic blockade for several days to avoid hypertensive crisis due to unopposed alpha stimulation. Amlodipine or verapamil can be added to beta-blockers if blood pressure control is still inadequate. Table EP1-18 describes orally administered drugs to treat pheochromocytoma.
2. Hypertensive crisis preoperatively and intraoperatively can be controlled with nitroprusside. Table EP1-19 summarizes intravenously administered drugs used to treat pheochromocytoma.

PEARLS & CONSIDERATIONS

COMMENTS

- Obtaining a detailed family history is important because 25% of pheochromocytomas are familial.
- Screening for pheochromocytoma should be considered in patients with any of the following:
  1. Malignant hypertension
  2. Poor response to antihypertensive therapy
  3. Paradoxical hypertensive response
  4. Hypertension during induction of anesthesia, parturition, surgery, or thyrotropin-releasing hormone testing
  5. Hypertension associated with imipramine or desipramine
  6. Neurofibromatosis (increased incidence of pheochromocytoma)
- All patients with pheochromocytoma should be screened for MEN-2 and von Hippel-Lindau disease with the pentagastrin test, serum parathyroid hormone, ophthalmoscopy, MRI of the brain, CT scan of the kidneys and pancreas, and ultrasonography of the testes.
- In patients with pheochromocytoma, routine analysis for mutations of *RET, VHL, SDHD,* and *SDHB* is indicated to identify pheochromocytoma-associated syndromes.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pheochromocytoma (Patient Information)

AUTHORS: **MARK F. BRADY, M.D., M.P.H., M.M.S.** and **FRED F. FERRI, M.D.**

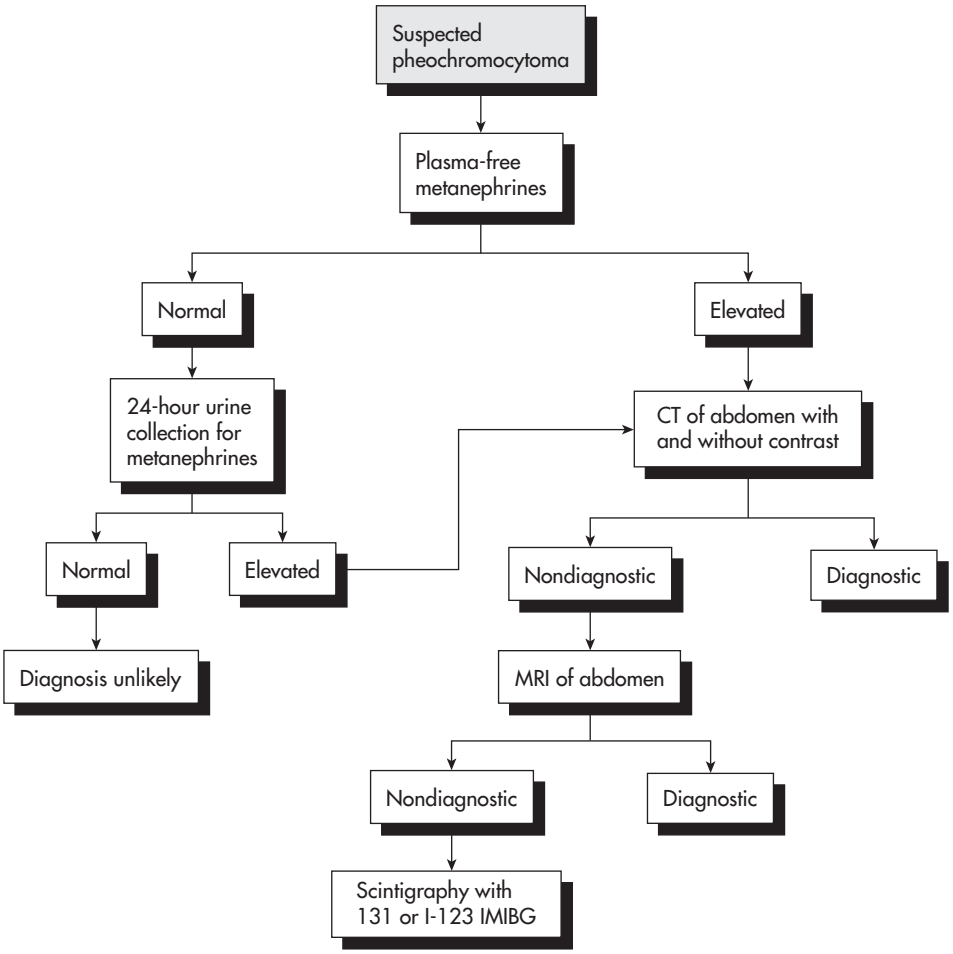


FIGURE P1-33 Pheochromocytoma. *CT,* Computed tomography; *IMIBG,* iodine metaiodobenzyl guanidine; *MRI,* magnetic resonance imaging.

SUGGESTED READINGS

Guller U et al.: Detecting pheochromocytoma: defining the most sensitive test, *Ann Surg* 243:102–107, 2006.

Lenders JW et al.: Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline, *J Clin Endocrinol Metab* 99:1915–1942, 2014.

Manger WM: The protean manifestations of pheochromocytoma, *Horm Metab Res* 41:658–663, 2009.

Mazza A et al.: Anti-hypertensive treatment in pheochromocytoma and paraganglioma: current management and therapeutic features, *Horm Metab Res Jul 2 Epub*, 2003.

Yu R et al.: Diagnosis and treatment of pheochromocytoma in an academic hospital from 1997 to 2007, *Am J Med* 122:85–95, 2009.

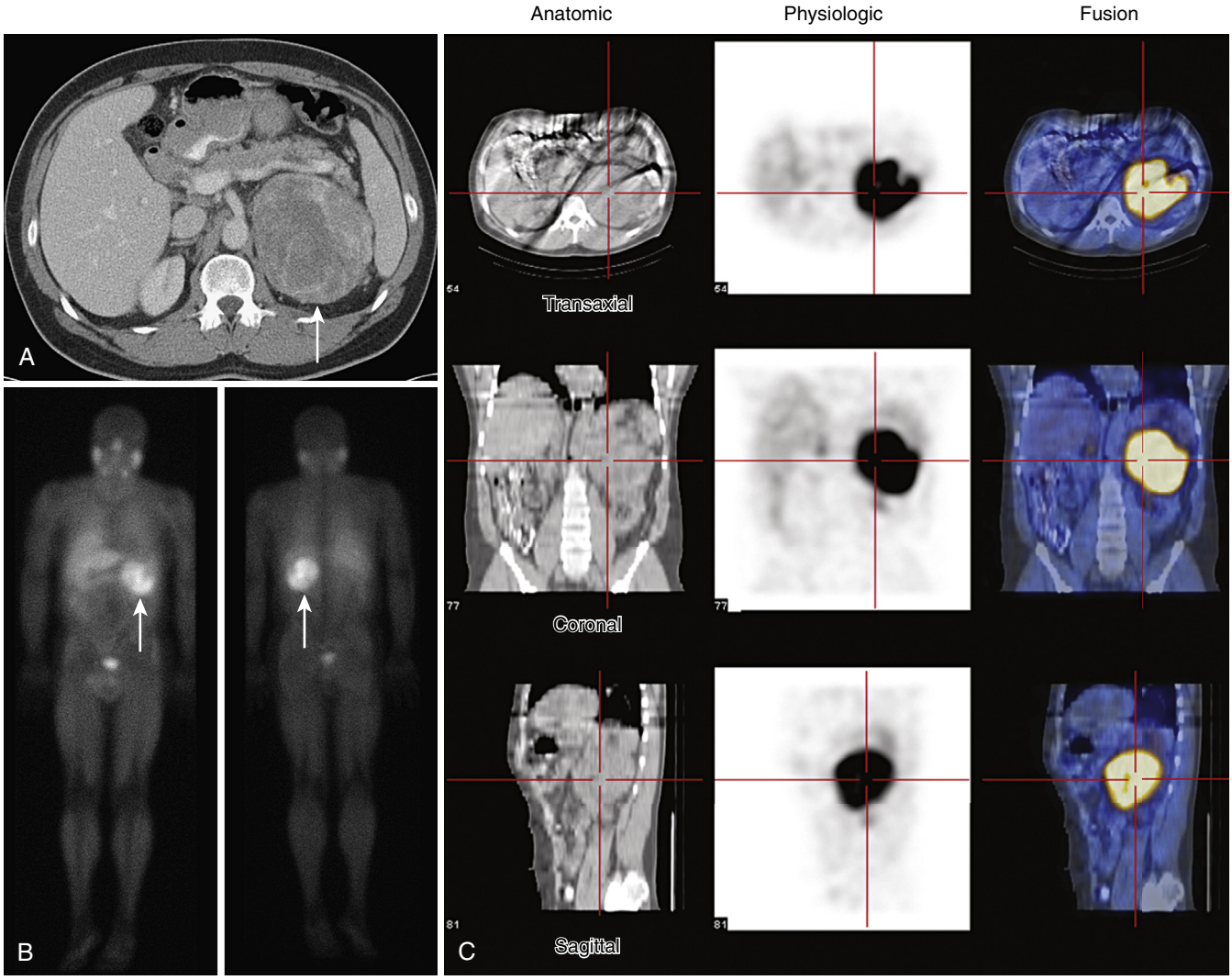


FIGURE EP1-34 Computed tomography (CT) and ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) imaging from a 44-year-old man. He presented with a 9-year history of hypertension and recent onset of head throbbing, chest pressure, and abdominal pain. The 24-hour urine studies were abnormal: norepinephrine, 900 μg (normal, <170); epinephrine, 28 μg (normal, <35); dopamine, 468 μg (normal, <700); and total metanephrines, 17,958 μg (normal, <1000). **A,** Axial CT image with contrast shows a large, partially vascular and partially necrotic left adrenal tumor *(arrow).* **B,** 123I-MIBG whole-body scan shows a large focus of increased radiotracer uptake in the left upper abdomen *(arrow)* that corresponds to the mass seen on the CT image; no other abnormal uptake is seen. **C,** ^{123}I-MIBG and single-photon emission computed tomography (SPECT) fusion CT images correlate with the images seen on CT (anatomic) with those seen on ^{123}I-MIBG (physiologic) in the axial, coronal, and sagittal planes. After α- and β-adrenergic blockade, a 13.5 × 12 × 9-cm, 680-g pheochromocytoma was removed. (From Melmed S: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders, Elsevier.)

TABLE EP1-18 Orally Administered Drugs Used to Treat Pheochromocytoma

Drug	Initial Dosage, mg/day* (Maximum)	Side Effects
α-Adrenergic Blocking Agents		
Phenoxybenzamine	10† (100)†	Postural hypotension, tachycardia, meiosis, nasal congestion, diarrhea, inhibition of ejaculation, fatigue
Prazosin	1 (20)‡	First-dose effect, dizziness, drowsiness, headache, fatigue, palpitations, nausea
Terazosin	1 (20)†	First-dose effect, asthenia, blurred vision, dizziness, nasal congestion, nausea, peripheral edema, palpitations, somnolence
Doxazosin	1 (20)	First-dose effect, orthostasis, peripheral edema, fatigue, somnolence
Combined α- and β-Adrenergic Blocking Agent		
Labetalol	200† (1200)†	Dizziness, fatigue, nausea, nasal congestion, impotence
Calcium Channel Blocker		
Nicardipine sustained-release	30† (120)†	Edema, dizziness, headache, flushing, nausea, dyspepsia
Catecholamine Synthesis Inhibitor		
α-Methyl-ρ-L tyrosine (metyrosine)	1000‡ (4000)‡	Sedation, diarrhea, anxiety, nightmares, crystalluria, galactorrhea, extrapyramidal symptoms

*Given once daily unless otherwise indicated.
†Given in two doses daily.
‡Given in three or four doses daily.
From Melmed S: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders, Elsevier.

TABLE EP1-19 Intravenously Administered Drugs Used to Treat Pheochromocytoma

Agent	Dosage Range
For Hypertension	
Phentolamine	Administer a 1-mg IV test dose, then 2- to 5-mg IV boluses as needed or continuous infusion.
Nitroprusside	IV infusion rates of 2 μg/kg of body weight per minute are suggested as safe. Rates >4 μg/kg per minute may lead to cyanide toxicity within 3 hr. Doses >10 μg/kg per minute are rarely required, and the maximal dose should not exceed 800 μg/min.
Nicardipine	Initiate therapy at 5.0 mg/hr; the IV infusion rate may be increased by 2.5 mg/hr q15 min up to a maximum of 15.0 mg/hr.
For Cardiac Arrhythmia	
Lidocaine	Initiate therapy with an IV bolus of 1-1.5 mg/kg (75-100 mg); additional boluses of 0.5-0.75 mg/kg (25-50 mg) can be given q5-10 min if needed up to a maximum of 3 mg/kg. Loading is followed by maintenance IV infusion of 2-4 mg/min (30-50 μg/kg per minute) adjusted for effect and settings of altered metabolism (e.g., heart failure, liver congestion) and as guided by blood level monitoring.
Esmolol	An initial IV loading dose of 0.5 mg/kg is infused over 1 min, followed by a maintenance infusion of 0.05 mg/kg per minute for the next 4 min. Depending on the desired ventricular response, the maintenance infusion may then be continued at 0.05 mg/kg per minute or increased stepwise (e.g., by 0.1 mg/kg per minute increments to a maximum of 0.2 mg/kg per minute), with each step being maintained for ≥4 min.

From Melmed S: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders, Elsevier.

BASIC INFORMATION

DEFINITION

Specific phobias are anxiety disorders characterized by an excessive, persistent fear elicited by a specific object or situation that is then avoided or tolerated with intense distress. The provoking stimulus may be a specific object, such as an animal or insect; natural environments, such as heights or water; or a specific situation, such as the sight of blood, the receipt of an injection, or being in a tunnel or on a bridge. Social anxiety disorder (formerly named social phobia) is a specific, separately diagnosed disorder characterized by a fear of being embarrassed, humiliated, or rejected in social or performance situations. Agoraphobia also is a separately diagnosed disorder, characterized by an intense anxiety about being in a place or situation from which they would not be able to escape in the event of a panic attack or panic-like symptoms. Such situations include being in enclosed/crowded spaces or being more than a certain distance from home alone. If agoraphobia is present in individuals with panic disorder, both diagnoses are given.

SYNONYMS

Simple phobia (obsolete name for specific phobia)

Phobias named for the provoking stimulus, such as arachnophobia (fear of spiders) and acrophobia (fear of heights)

Specific phobias are codes:
ICD-9CM and DSM-5
300.29 Other isolated specific phobias
ICD-10CM
F40.2xx
Social Phobia:
ICD-9CM and DSM-5
300.23
ICD-10CM
F40.1 Social phobias
F40.2 Specific phobias
F40.8 Other phobic anxiety disorders
F40.9 Phobic anxiety disorder, unspecified
Agoraphobia:
ICD-9CM and DSM-5
300.22
ICD-10CM
F40.00

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: The majority of cases of specific phobia tend to onset prior to age 10; median onset is from ages 7-10.

PREVALENCE (IN U.S.)

- Specific phobias are prevalent in 7% to 9% of the general population (12-month prevalence rate).
- Social anxiety disorder is prevalent in approximately 7% to 13% of the general population.
- Agoraphobia is prevalent in approximately 1.7% of the general population per year.

PREDOMINANT SEX AND AGE

- Females with specific phobias outnumber males 2:1, though rates vary by phobia.
- More women than men are affected with social anxiety disorder (odds ratios ranging from 1.5-2.2).
- Agoraphobia is more prevalent in women than men (2:1).
- Most specific phobias have childhood onset, although it is possible for them to develop at any age.
- Situational phobias tend to have a later age of onset compared to natural environment, animal, or blood-injection phobias.
- Onset of social anxiety disorder usually occurs in the mid-teens, with onset after age 25 being unusual; this disorder is generally lifelong.
- Onset of agoraphobia typically occurs in late adolescence or early adulthood; two thirds of cases onset prior to age 35.

GENETICS: Specific phobia and social anxiety disorder are more common in first-degree relatives.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- When approaching the phobic stimulus, the experience of extreme anxiety is often accompanied by autonomic symptoms such as tachycardia, tremor, and diaphoresis; depersonalization may occur. In blood or injection phobias, symptoms are often followed by a parasympathetic response that can cause vasovagal syncope.
- Specific phobias frequently occur with other anxiety disorders.

ETIOLOGY

There is no clear etiology and likely is a combination of factors including temperamental (e.g., behavioral inhibition, neuroticism), environmental (e.g., negative encounters with the feared stimulus, parental overprotection), and genetic.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Social anxiety disorder is distinguished from specific phobias in that what is feared is humiliation or embarrassment in social interaction or performance situations, rather than fear of a specific object or environment.
- Panic attacks (with or without agoraphobia): anxiety symptoms seen in specific phobia may resemble symptoms of panic attacks, but the stimulus in the specific or social situation is clear, whereas panic attacks do not have a clearly associated provoking stimulus (i.e., they occur unexpectedly in the absence of a trigger).
- Posttraumatic stress disorder (PTSD): anxiety and physiologic arousal associated with specific cues from the traumatic event defining the PTSD may resemble the symptoms induced by a phobia.
- Generalized anxiety disorder (GAD): may be difficult to distinguish from social anxiety disorder, but in social anxiety disorder the focus is fear of embarrassment or humiliation in the presence of other people, whereas GAD has no specific focus for the worry.
- Avoidant personality disorder is often comorbid with social anxiety disorder.
- Psychotic disorders can present with a fear of being in public that arises from delusions.

WORKUP

- History: usually diagnostic. This should include information about other medical disorders, medications, any history of past trauma, and substance abuse. Fig. P1-35 describes a diagnostic decision tree for specific phobias.
- Physical examination: to confirm absence of cardiovascular abnormalities such as arrhythmias or evidence of endocrinologic reasons for hyperarousal such as an enlarged or tender thyroid gland.

LABORATORY TESTS

No specific laboratory tests are indicated.

IMAGING STUDIES

No specific imaging studies are recommended.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cognitive-behavioral therapy (CBT) and exposure-based treatments have been effective for treating specific phobia and social anxiety disorder in controlled trials and are considered an appropriate first-line treatment.
- Behavioral treatments sometimes involve relaxation training, often paired with visualization and progressive desensitization.
- Success rates in treating specific phobias are higher when the phobia is not complicated by other anxiety disorders.

ACUTE GENERAL Rx

- Although benzodiazepines provide rapid relief of anxiety associated with exposure to provoking stimuli, they are associated with adverse effects including somnolence, accidents, abuse, and dependence, and thus are not recommended as a first-line treatment.
- Beta-blockers (e.g., propranolol) have been used to decrease autonomic hyperarousal and tremor associated with performance situations (e.g., before public speaking), but are not recommended for more generalized forms of social anxiety disorder.

CHRONIC Rx

- If the phobic stimulus is rarely encountered, benzodiazepines used on an as-needed basis can be an appropriate long-term treatment; however, there is a risk of abuse and dependence that makes them a less desirable choice for long-term treatment.
- Selective serotonin reuptake inhibitors are the most effective pharmacologic treatment in reducing symptoms and improving function for people with social anxiety disorder.
- Monoamine oxidase inhibitors are also effective for treatment of social anxiety disorder, but are rarely used due to dietary restrictions and adverse effects.

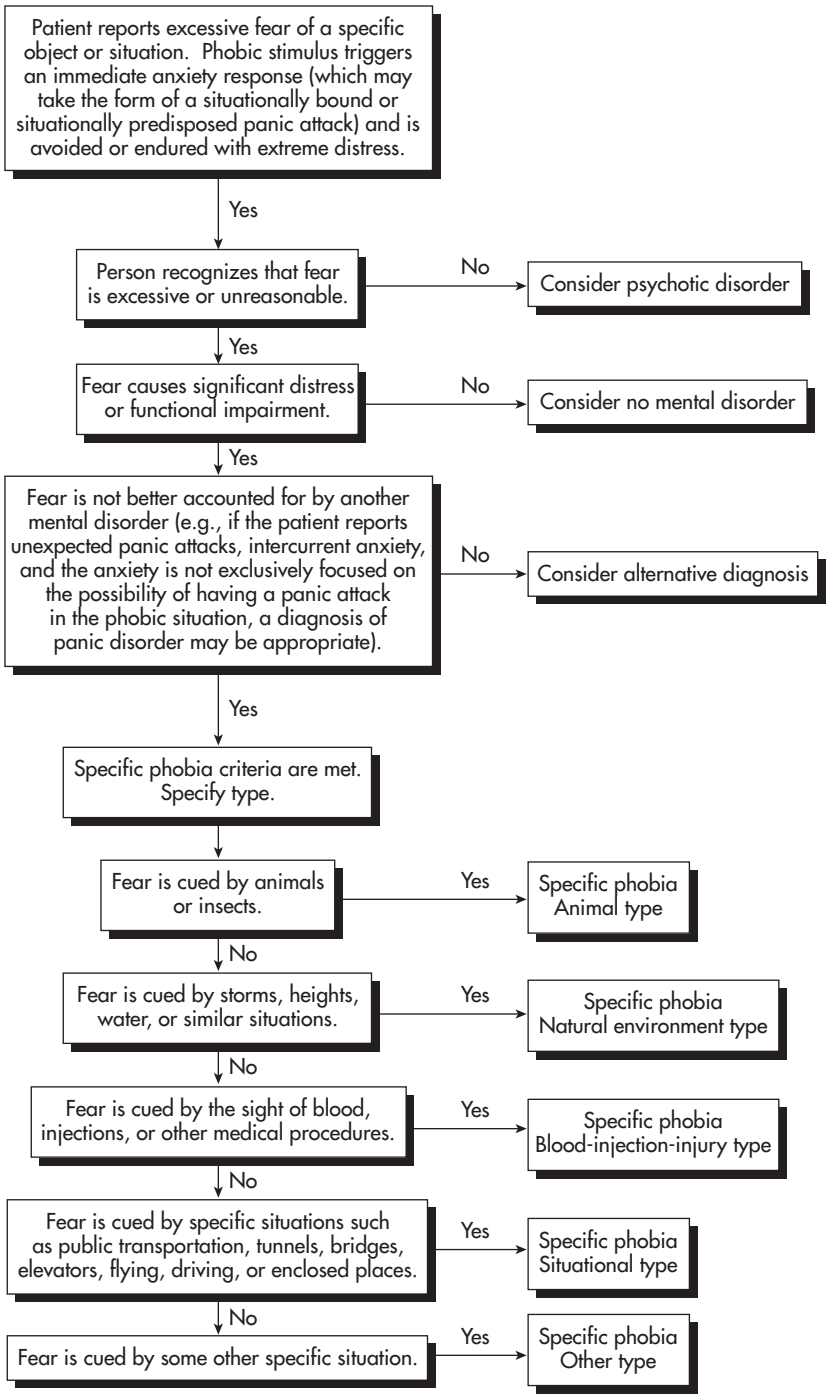


FIGURE P1-35 Specific phobia: diagnostic decision tree. (From Lieberman, K: Social and specific phobias. In Lieberman K. (ed.): *Psychiatry behavioral science and clinical essentials: a companion to Tasman*, Philadelphia, 2000, Saunders, p. 368-378.)

COMPLEMENTARY & ALTERNATIVE MEDICINE

No definitive evidence supports complementary or alternative medicines in the treatment of phobic disorders.

DISPOSITION

Phobic disorders are generally present for life, although outpatient-based treatment may effectively reduce symptoms.

REFERRAL

Recommended for confirmation of diagnosis and for evaluation for psychotherapy and other treatment modalities.

PEARLS & CONSIDERATIONS

People with social anxiety disorder often have low self-esteem and fear being scrutinized by others such that they avoid or are fearful of any situation in which others may assess or evaluate them directly or indirectly. More than half are concurrently affected by another anxiety disorder, and alcohol and other substance dependence is common because these patients often use substances to mask their anxiety.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Phobias (Patient Information)
Panic Disorder, With or Without Agoraphobia (Related Key Topic)
Posttraumatic Stress Disorder (Related Key Topic)
Social Anxiety Disorder (Related Key Topic)

AUTHOR: **KRISTY L. DALRYMPLE, PH.D.**

EVIDENCE

Abstract[1]

Previous studies examining the relationship between specific phobia and major depression have reported mixed findings. The results of some studies have suggested that specific phobia is associated with a higher prevalence of comorbid depression, whereas others have found no association. The purpose of this study was to further examine whether specific phobia is an independent contributor to major depression by using data from the National Comorbidity Survey, a household probability sample of adults (N 55 877) aged 15 to 54 years in the U.S. After adjusting for demographic differences and comorbid mental disorders, multiple logistic regression analyses confirmed that specific phobia remains positively associated with comorbid depression (odds ratio, 1.9; 95% confidence interval, 1.6-2.4). Additional analysis found this relationship to be specific to individuals with a fear of heights, animals, and closed spaces, as well as those endorsing at least two irrational fears. These results suggest that the types and number of fears play an important role in the probability of lifetime depression.

Most of us were surprised and frankly incredulous at the finding from the National Comorbidity Study that "simple" specific phobias were associated with a significant increase in depression in later life. It just seemed that these specific phobias, which we all considered to be minor problems that could be ignored, could not be the specific risk factor that they appear to be for major depression. However, this recent reanalysis suggests that this relationship is there for people with a fear of heights, animals, and closed spaces, and for those who have two or more irrational fears. Like the article by Widom et al, this is a clear childhood identifier for future depressive problems and one that should command more of our attention. Ⓐ

Evidence-Based Reference

Choy Y et al.: Specific phobia and comorbid depression: a closer look at the National Comorbidity Survey data, *Compr Psychiatry* 48:132–136, 2007. Commentary by J.C. Ballenger, M.D. Ⓐ

SUGGESTED READINGS

Anxiety Disorders Association of America. http://www.adaa.org.

Beesdo K et al.: Anxiety and anxiety disorders in children and adolescents: developmental issues and implications for DSM-V, *Psychiatr Clin North Am* 32(3):483–524, 2009.

LeBeau RT et al.: Specific phobia: a review of DSM-IV specific phobia and proposals for DSM-V, *Depress Anxiety* 27(2):148–167, 2010.

Ollendick TH, Davis TE: One-session treatment for specific phobias: a review of Öst's single-session exposure with children and adolescents, *Cog Behav Ther* 42(4):275–283, 2013.

Wolitzky-Taylor KB et al.: Psychological approaches in the treatment of specific phobias: a meta-analysis, *Clin Psychol Rev* 28(6):1021–1037, 2008.

BASIC INFORMATION

DEFINITION

From the Latin words *pilus,* meaning "hair," and *nidus,* meaning "nest."

A *pilonidal sinus* is a short tract that extends from the skin surface and most likely represents a distended hair follicle. It is most commonly found in the intergluteal fold sacrococcygeal region, but it can also occur in the interdigital area, umbilicus, chest wall, and scalp. An *acute pilonidal abscess,* which consists of pus and a wall of edematous fat, results from rupture of an infected follicle into fat. A *chronic pilonidal abscess* results when an infected follicle ruptures directly into surrounding tissues; the wall of a chronic pilonidal abscess consists of fibrous tissue. A *pilonidal cyst* develops from a chronic abscess of long duration as a thin and flat lining of epithelium grows into the cavity from the skin surface.

SYNONYMS

Jeep disease

ICD-9CM CODES
685.1 Pilonidal cyst
ICD-10CM CODES
L05 Pilonidal cyst
L05.0 Pilonidal cyst with abscess
L05.9 Pilonidal cysts without abscess

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 26 cases per 100,000 persons
PREDOMINANT SEX: Males are more commonly affected than females (2.2:1).
AVERAGE AGE OF PRESENTATION: 21 yr
RISK FACTORS:
- Male sex
- Caucasian race
- Family predisposition
- Obesity
- Sedentary lifestyle
- Occupation requiring prolonged sitting
- Local hirsutism
- Poor hygiene
- Increased sweat activity

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- May manifest as asymptomatic pits or pores in the natal cleft (Fig. EP1-36)
- Tenderness after physical activity or prolonged sitting
- Acute pilonidal abscess in 20% of patients with pilonidal disease
- Presents as a hot, tender, fluctuant swelling just lateral to the midline over the sacrum that may exude pus through the midline pit
- Chronic pilonidal abscess in 80% of patients with pilonidal disease
- Acute suppuration, tenderness, swelling, and heat
- Infrequently, systemic reaction: occasionally fever, leukocytosis, and malaise

ETIOLOGY

- Currently believed to be acquired rather than congenital.
- Drilling of hair shed from the perineum or the head into sebaceous or hair follicles in the natal cleft.
- Drilling is facilitated by the friction of the natal cleft.
- Subsequent infection by skin organisms leads to pilonidal abscess.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Perianal abscess arising from the posterior midline crypt
- Hidradenitis suppurativa
- Carbuncle
- Furuncle
- Osteomyelitis
- Anal fistula
- Coccygeal sinus

WORKUP

- Diagnosis is based on history and physical examination.
- Midline pits present behind the anus overlying the sacrum and coccyx.
- Broken hairs are often seen extruding from the midline pits.
- Insert probe in pilonidal sinus in path away from the anus.
- Complicated anal fistula may be angulating posteriorly before passing into a retrorectal abscess, but thorough examination of the anal cavity usually discloses point of origin.

LABORATORY TESTS

Complete blood count

IMAGING STUDIES

CT scan in advanced, recurrent cases

TREATMENT

NONPHARMACOLOGIC THERAPY

Prevention of exacerbations:
1. Local hygiene
2. Avoidance of prolonged sitting position
3. Weight reduction

ACUTE GENERAL Rx

- Procedure of choice for first-episode acute abscess: simple incision and drainage in an outpatient setting. Box EP1-5 describes surgical options for the treatment of pilonidal sinus.
- Cure rate of 76% after 18 mo
- Antibiotics: generally not indicated unless the patient has a medical condition such as rheumatic heart disease or is immunosuppressed

CHRONIC Rx

Elective treatment of pilonidal disease:
1. Minimal surgery:
   a. Remove hair from midline pits and shave buttocks.
   b. May use a fine wire brush with local anesthesia to clear the pits and any lateral openings of granulation tissue and hair.
   c. Keep area clean.
2. Fistulotomy and curettage:
   a. Used when minimal surgery does not control episodes of suppuration
   b. Pass probe to outline the pilonidal sinus and open tract surgically
   c. Curette granulation tissue at the base of the sinus and excise edges of the skin
   d. Keep open granulating wound meticulously clean and allow to heal
   e. If complete healing does not take place, use a skin graft or advancement flap to close the defect
3. Marsupialization:
   a. This is the treatment of choice for chronic pilonidal disease.
   b. Wide excision of the pilonidal area is performed, including all affected skin and subcutaneous tissues down to the presacral fascia.
   c. Wound is left open, allowed to marsupialize, or closed as a primary procedure.
   d. Give antibiotics for 24 hr (particularly those directed against *Staphylococcus* and *Bacteroides* species).
4. Other procedures:
   a. Excision and closure
   b. Excision and skin grafting
   c. Bascom procedure (follicle removal and lateral drainage)
   d. Flaps: *Z*-plasty, V-Y advancement flap, rhomboid flap, gluteus maximus myocutaneous flap

DISPOSITION

- Recurrence rate for excision (most definitive procedure): 1% to 6%
- Incidence of squamous cell carcinoma in a chronic, recurrent pilonidal sinus is rare <1%

REFERRAL

- Emergency department for incision and drainage for an acute abscess
- To a surgeon for elective treatment or management of chronic or recurrent disease

PEARLS & CONSIDERATIONS

COMMENTS

Because of significant associated morbidity, the elective surgical procedures outlined are performed only after the potential risks versus benefits are carefully weighed.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pilonidal Cyst (Patient Information)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Church JM: Pilonidal cyst: cause and treatment, *Dis Colon Rectum* 43(8):1146, 2000.
Hull TL, Wu J: Pilonidal disease, *Surg Clin North Am* 82(6):1169, 2002.

FIGURE EP1-36 Midline pits in the gluteal cleft represent a classic finding of pilonidal disease. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 19, Philadelphia, 2011, Saunders.)

BOX EP1-5 Surgical Options for the Treatment of Pilonidal Sinus

Midline Approach
Sinus excision: open vs. marsupialization vs. closure

Unroofing and Curettage
Asymmetric or oblique excision
Karydakis procedure
Bascom: open vs. closure
Cleft
Flaps
Rhomboid
V-Y advancement
Z-plasty
Gluteal myocutaneous

Others
Phenolization
Vacuum-assisted closure

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

BASIC INFORMATION

DEFINITION

Pinworms are a noninvasive infestation of the intestinal tract by *Enterobius vermicularis,* a helminth of the nematode family. It is a small (1 cm in length), white, thread-like roundworm that typically inhabits the cecum, appendix, and adjacent areas of the ileum and ascending colon.

SYNONYMS

Enterobiasis

ICD-9CM CODES
127.4 Enterobiasis
ICD-10CM CODES
B80 Enterobiasis

EPIDEMIOLOGY & DEMOGRAPHICS

- Most common intestinal nematode; approximately 30,000 cases annually in the United States.
- Worldwide distribution, but most common in temperate climates.
- The prevalence of pinworm infection is lowest in infants and reaches highest infection rate in school-age children (ages 5 to 14 yr).
- Eggs are infective within 6 hr of oviposition and may remain so for 20 days.
- Clusters are found in families, institutionalized persons, and homosexual men.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most infested persons are asymptomatic.
- Perianal itching is the most common reported symptom, with scratching leading to excoriation and sometimes secondary infection.
- Rarely insomnia, irritability, anorexia, and weight loss are described.
- Granulomas have been described in various organs resulting from worms wandering outside the intestines and dying there.

ETIOLOGY & PATHOGENESIS

- *E. vermicularis* is highly prevalent throughout the world, particularly in countries of the temperate zone. Human beings are the only host for this worm. Infestation is by fecal-oral route; ingested eggs hatch in the stomach and the larvae migrate to the colon, where they mature. Gravid female worms containing an average of 10,000 ova migrate to the perianal skin at night, lay their eggs there, and die. The eggs embryonate within 6 hr and cause itching; scratching causes egg deposition under fingernails, from which they can contaminate food or lead to autoreinfection.
- *E. vermicularis* may be transmitted between sexual partners, especially those engaging in oral-anal sex.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Perianal itching related to poor hygiene
- Hemorrhoidal disease and anal fissures
- Perineal yeast/fungal infections
  Section II describes the causes of pruritus ani.

WORKUP

Identification of adult worms or eggs. *E. vermicularis* ova are ovoid but flattened on one side and measure approximately 56 × 27 micrometers (Fig. P1-37). The eggs can be identified on transparent tape placed on the perianal skin on awakening. (NOTE: Five consecutive negative tests rule out the diagnosis.) A single examination detects 50% of infections, three examinations detect 90%, and five examinations detect 99%.

TREATMENT

- Single dose of mebendazole (100 mg) with a repeat dose given after 2 wk results in cure rates of 90% to 100%.
- Single dose of albendazole (400 mg) with a second dose given 2 wk later is also highly effective.
- Pyrantel pamoate (11 mg/kg up to 1 g) can prevent against *E. vermicularis.* It is available as a suspension and has minimal toxicity (mild transient gastrointestinal symptoms, headache, drowsiness). A repeat dose after 2 wk is recommended because of the frequency of reinfection and autoinfection.
- Other infected family members, classmates, or residents of long-term care facilities should be treated at the same time as the index case.

PEARLS & CONSIDERATIONS

- Eosinophilia is not observed in most cases because tissue invasion does not occur.
- Good hand hygiene is the most effective method of prevention.
- Frequent changing of underclothes, bed clothes, and bed sheets is helpful to decrease risk of autoinfection.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pinworms (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

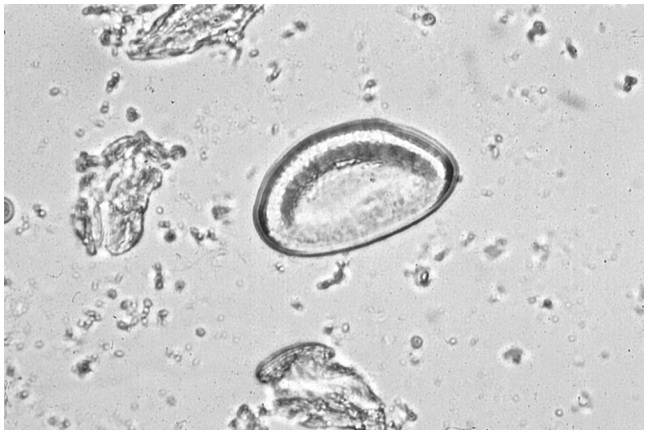


FIGURE P1-37 Enterobius vermicularis embryonated egg. Note larva inside (40 × 10 μm). (From Gorbach SL et al [eds]: *Infectious diseases,* ed 2, Philadelphia, 1998, Saunders.)

SUGGESTED READINGS

Dent AE, Kazura JW: Enterobiasis (Enterobius vermicularis). In Kliegman R et al.: *Nelson textbook of pediatrics*, ed 19, Philadelphia, 2011, Saunders.

Lohiya GS et al.: Epidemiology and control of enterobiasis in a developmental center, *West J Med* 172:305–308, 2000.

BASIC INFORMATION

DEFINITION

Piriformis syndrome is a form of low back pain caused by prolonged or excessive contraction of the piriformis muscle and characterized by pain and instability. The pain is usually present in the hip, groin, buttock, coccyx, and distal part of the lower extremity.

SYNONYMS

- Deep gluteal syndrome
- Pelvic outlet syndrome
- Infrapiriform foramen syndrome

ICD-9CM CODES
956.0 Injury to sciatic nerve
ICD-10CM CODES
S74.00 Injury of sciatic nerve at hip and thigh level

EPIDEMIOLOGY & DEMOGRAPHICS

- Women are affected more than men.
- It occurs in middle-aged patients (mean age of about 38).
- Incidence of piriformis syndrome has been estimated at 2.4 million/yr.
- Female-to-male incidence ratio is 6:1.
- About 6% of patients with sciatica have piriformis syndrome.

PHYSICAL FINDING & CLINICAL PRESENTATION

CLINICAL PRESENTATION: Patients with piriformis syndrome may present the following symptoms:

- Gluteal pain (97.9% of cases) which may:
  1. Be chronic
  2. Radiate to the distal part of the lower extremities
  3. Worsen with squatting or walking
- Rectal pain (worse during defecation)
- Hip movements (especially adduction and internal rotation) cause pain
- Labia majora or scrotal pain
- Dyspareunia in women
- Disturbances of potency in men
- Pain and discomfort on sitting

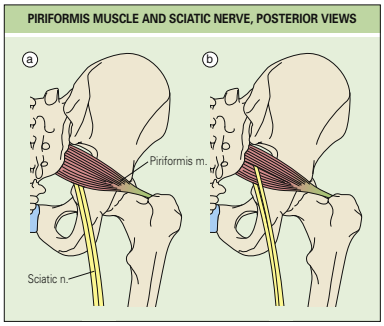


FIGURE EP1-38 Piriformis muscle and sciatic nerve, posterior views. The piriformis muscle arises from the anterior surface of the sacrum and the gluteal surface of the ilium and crosses the greater sciatic foramen to insert onto the superior border of the greater trochanter. **A,** In most instances, the sciatic nerve passes along the anterior surface of the piriformis muscle and exits the pelvis below the piriformis muscle, passing posteriorly along its inferior border. **B,** In some individuals, a portion of the sciatic nerve passes through the piriformis muscle. Other anatomic variants have been described. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

PHYSICAL FINDINGS:

- Piriformis syndrome is a diagnosis of exclusion.
- There are no neurologic deficits in patients with piriformis syndrome.
- There is tenderness over the gluteal area.
- Gluteal atrophy may be present.
- Sacroiliac tenderness.
- Shortening of the limb on the affected side.
- Other signs used in diagnosing piriformis syndrome include:
  1. *Lasègue sign*—Extension of the knee with the hip flexed to 90 degrees produces pain in the vicinity of the greater sciatic notch.
  2. *Pace sign*—Resisted abduction-external rotation of the thigh causes pain and weakness on the affected side.
  3. *Freiberg sign*—With the patient in the supine position, passive internal rotation of the extended thigh causes pain.
  4. Pain in the back when the patients lies with the painful side up and involved leg flexed.

ETIOLOGY

1. Trauma to the buttocks/gluteal region.
2. Spinal stenosis.
3. Anatomic variations of the division of the sciatic nerve.
4. As the sciatic nerve passes through the greater sciatic foramen, it is in close proximity to the piriformis muscle (Fig. EP1-38). Pain results from compression of the sciatic nerve by the piriformis muscle.
5. Laminectomy.
6. Intragluteal injection.
7. Hypertrophy and spasm of the piriformis muscle.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

1. Lumbosacral disc or spine injury
2. Sacroiliac joint injury
3. Hamstring injury
4. Sciatic nerve entrapment
5. Paraspinal muscle spasm
6. Herniated intervertebral disc
7. Unrecognized pelvic fracture
8. Iliac vein thrombosis
9. Postlaminectomy syndrome
10. Undiagnosed nephrolithiasis

WORKUP

Usually involves imaging studies

- Computed tomography scan:
  1. Used to identify spinal stenosis
  2. May show a large mass anterior to the piriformis muscle
- Magnetic resonance imaging:
  1. May show an enlarged piriformis muscle on T_1- or T_2-weighted images
- Electromyogram (EMG):
  1. Normal EMG findings in the gluteus minimus, gluteus medius, and tensor fasciae latae muscles
  2. Abnormal EMG findings in the gluteus maximus and piriformis muscles

TREATMENT

Sciatica due to piriformis syndrome is usually treated conservatively. Treatment modalities include physical therapy, lifestyle modalities, medications, and psychotherapy.

TREATMENT DURING ACUTE PHASE

- Stop offending activities
- Start physical therapy (PT) and occupational therapy treatment
  a) PT
    1. The basic PT treatment is **stretching** and **manual therapy.**
    2. PT modalities are most beneficial when used in conjunction with stretching exercise.
    3. Ultrasound and/or moist heat is recommended before stretching.
    4. Massage of the lumbosacral and gluteal areas reduces muscle tightness and sciatic nerve irritation.
    5. Cold pack and/or electrical stimulation may be applied after exercise.
  b) Occupational therapy. Advise patients to:
    1. Avoid sitting for prolonged periods.
    2. Make frequent stops when driving to get up and stretch.
  c) Surgical intervention. This is considered only when medical treatment fails and symptoms become intractable and/or disabling. Indications for surgical intervention include hematoma, abscess, neoplasm, compression of the nerve by gluteal vein varicosities. Response to surgical treatment is often disappointing. Promising results include:
    1. Piriformis tendon release
    2. Sciatic neurolysis
  d) Other treatment modalities
    - Local injection of anesthetics into trigger points
    - Botulinum toxin injection
    - Nonsteroidal antiinflammatory drugs and opiates
    - Transrectal message

TREATMENT DURING RECOVERY PHASE

- Start gradual strengthening activities for the piriformis and gluteal muscles.
- Continue therapeutic modalities.
- Start light sport-specific activities and functional training if patient is asymptomatic.
- Some athletes may consider changing their footwear to avoid additional stress on the piriformis muscle.

TREATMENT DURING MAINTENANCE PHASE

- Continue performing a home exercise program for increasing flexibility and strength.
- Athletes may increase their training volume as tolerated.
- Compliance to a daily stretching program is crucial to avoid recurrence of this syndrome.

REFERRAL

- Physical therapist: to instruct patients about stretching and pain-relieving maneuvers
- Orthopedic: when diagnosis is in doubt, the patient failed conservative treatment, and surgical evaluation is needed
- Neurologist: for EMG studies

PEARLS & CONSIDERATIONS

COMMENTS

Athletes may return to play when:
1. They are pain free with full range of motion.
2. They have full strength in the affected side.

PREVENTION

To prevent the recurrence of pain:
1. Avoid risk factors.
2. Continue stretching exercises.

SUGGESTED READING

Available at www.expertconsult.com

AUTHOR: **DANIEL K. ASIEDU, M.D., PH.D.**

SUGGESTED READING

Parziale JR et al.: The piriformis syndrome, *Am J Orthop (Belle Mead NJ)* 25: 819–823, 1996.

BASIC INFORMATION

DEFINITION

Pituitary adenoma is a benign neoplasm of the anterior lobe of the pituitary that causes symptoms, either by excess secretion of hormones or by a local mass effect as the tumor impinges on other, nearby structures (e.g., optic chiasm, hypothalamus, pituitary stalk). Pituitary adenomas are classified by their size, function, and features that characterize their appearance. Microadenomas are <10 mm in size, and macroadenomas are ≥10 mm in size.

- *Acromegaly* is the disease state characterized by a pituitary adenoma that secretes growth hormone (GH).
- A *prolactinoma* secretes prolactin (PRL).
- *Cushing's disease* is a disease state of hypersecretion of adrenocorticotropic hormone. (ACTH).
- *Thyrotropin-secreting pituitary adenomas* secrete primarily thyroid-stimulating hormone (TSH).
- *Nonsecretory pituitary adenomas* are those in which the neoplasm is a space-occupying lesion whose secretory products do not cause a specific disease state.

ICD-9CM CODES
253 Pituitary adenoma
ICD-10CM CODES
D35.2 Benign neoplasm of pituitary gland

EPIDEMIOLOGY & DEMOGRAPHICS

CLASSIFICATION (BY HORMONE SECRETED)

- PRL only: 35%.
- No hormone: 30%.
- GH only: 20%.
- PRL and GH: 7%.
- ACTH: 7%.
- Luteinizing hormone (LH), follicle-stimulating hormone (FSH), TSH: 1%.

PREVALENCE/INCIDENCE

- Pituitary adenomas: up to 10% to 15% of all intracranial neoplasms; 3% to 27% at autopsy series.
- Prolactinomas: up to 20% in women with unexplained primary or secondary amenorrhea.
- GH-secreting pituitary adenoma: 50 to 60 cases per 1 million persons.
- Thyrotropin-secreting pituitary adenoma: 2.8% of pituitary adenomas with a slight female/male predominance of 1.7:1
- Corticotropin-secreting pituitary adenomas: female/male predominance of 8:1 but overall rare diagnosis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

PROLACTINOMAS

- Females:
  1. Galactorrhea.
  2. Amenorrhea.
  3. Oligomenorrhea with anovulation.
  4. Infertility.
  5. Estrogen deficiency leading to hirsutism.
  6. Decreased vaginal lubrication.
  7. Osteopenia.
- Males:
  1. Large tumors more common as a result of delayed diagnosis.
  2. Possible impotence, decreased libido, or hypogonadism.
  3. Galactorrhea rare because males lack the estrogen-dependent breast growth and differentiation.

GH-SECRETING PITUITARY ADENOMA: ACROMEGALY

- Coarse facial features.
- Oily skin.
- Prognathism.
- Carpal tunnel syndrome.
- Osteoarthritis.
- History of increased hat, glove, or shoe size.
- Decreased exercise capacity.
- Visual field deficits.
- Diabetes mellitus.

CORTICOTROPIN-SECRETING PITUITARY ADENOMA: CUSHING'S DISEASE

- Usually present when the tumor is small (1 to 2 mm).
- 50% of the tumors <5 mm.
- Other symptoms:
  1. Truncal obesity.
  2. Round facies (moon face).
  3. Dorsocervical fat accumulation (buffalo hump).
  4. Hirsutism.
  5. Acne.
  6. Menstrual disorders.
  7. Hypertension.
  8. Striae.
  9. Bruising.
  10. Thin skin.
  11. Hyperglycemia.

THYROTROPIN-SECRETING PITUITARY ADENOMA

- In males, larger, more invasive, and more rapidly growing tumors that present later in life.
- Other symptoms: thyrotoxicosis, goiter, visual impairment.

NONSECRETORY PITUITARY ADENOMAS (ENDOCRINE INACTIVE PITUITARY ADENOMA)

- Usually large at the time of diagnosis.
- Symptoms:
  1. Bitemporal hemianopsia as a result of compression of the optic chiasm.
  2. Hypopituitarism from compression of the pituitary gland.
  3. Hypogonadism in men and in premenopausal women.
  4. Cranial nerve deficits caused by extension into the cavernous sinus.
  5. Hydrocephalus from extension into the third ventricle, compressing the foramen of Monro.
  6. Diabetes insipidus resulting from compression of the hypothalamus or pituitary stalk (a rare complication).

ETIOLOGY

Benign neoplasms of epithelial origin

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

PROLACTINOMA

- Pregnancy.
- Postpartum puerperium.
- Primary hypothyroidism.
- Breast disease.
- Breast stimulation.
- Drug ingestion (especially phenothiazines, antidepressants, haloperidol, methyldopa, reserpine, opiates, amphetamines, and cimetidine).
- Chronic renal failure.
- Liver disease.
- Polycystic ovarian disease.
- Chest wall disorders.
- Spinal cord lesions.
- Previous cranial irradiation.

ACROMEGALY: Ectopic production of GH-releasing hormone from a carcinoid or other neuroendocrine tumor

CUSHING'S DISEASE

- Diseases that cause ectopic sources of ACTH overproduction (including small-cell carcinoma of the lung, bronchial carcinoid, intestinal carcinoid, pancreatic islet cell tumor, medullary thyroid carcinoma, or pheochromocytoma).
- Adrenal adenomas, adrenal carcinoma.
- Nelson's syndrome.

THYROTROPIN-SECRETING PITUITARY ADENOMAS: Primary hypothyroidism.

NONSECRETORY PITUITARY ADENOMA: Nonneoplastic mass lesions of various etiologies (e.g., infectious, granulomatous).

WORKUP

Screening tests for functional pituitary adenomas are described in Table P1-20.

PROLACTINOMA: First step: measurement of basal PRL levels (practitioners should be aware of discriminatory values in their own institutions).

- Elevated PRL levels are correlated with tumor size.
- Level >200 ng/ml indicates likely prolactinoma, with levels of 100 to 200 ng/ml being equivocal and possibly associated with medications or other sources.
- Basal PRL levels between 20 and 100 suggest a microadenoma as well as other conditions such as psychotropic drug ingestion, recent breast examination, and even a recent meal.
- Basal level <20 ng/ml is usually considered normal. Each laboratory should develop its own normative values, however, and practitioner should refer to these values.
- Threshold level for obtaining imaging such as MRI should be developed by individual providers depending on the level of specificity and sensitivity desired.

ACROMEGALY

- First screening tests are the measurement of the serum insulin-like growth factor I level, postprandial serum GH, and TRH stimulation test.

TABLE P1-20 Screening Tests for Functional Pituitary Adenomas

Disorder	Test	Comments
Acromegaly	IGF1 OGTT with GH obtained at 0, 30, and 60 min.	Interpret IGF1 relative to age- and gender-matched controls.Normal subjects should suppress GH to <1 μg/L.
Prolactinoma	Serum PRL level.	A level >500 μg/L is pathognomonic for macroprolactinoma.If >200 μg/L, prolactinoma is likely.*
Cushing's disease	24-hr UFC Nighttime salivary cortisol Dexamethasone (1 mg) at 11 PM and fasting plasma cortisol measured at 8 AM ACTH assay	Ensure that urine collection is total and accurate by measuring urinary creatinine. Free salivary cortisol reflects circadian rhythm and elevated levels may indicate Cushing's disease. Normal subjects suppress to <1.8 μg/dL. Distinguishes adrenal adenoma from ectopic ACTH or Cushing's disease.
TSH-secreting tumor	TSH measurement Free T_4 by dialysis Total T_3.	If T_4 or T_3 is elevated and TSH is measurable or elevated, a TSH-secreting tumor may be present.

*Risperidol may result in prolactin levels >200 μg/L.
ACTH, Adrenocorticotropic hormone; *GH*, growth hormone; *IGF1*, insulin-like growth factor type 1; *OGTT*, oral glucose tolerance test; *PRL*, prolactin; *T3*, triiodothyronine; *T4*, thyroxine; *TSH*, thyroid-stimulating hormone; *UFC*, urinary free cortisol.
From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

- Follow with an oral glucose tolerance test.
- Failure to suppress serum GH to <2 ng/ml with an oral load of 100 g glucose is considered conclusive.
- A GH-releasing hormone level >300 ng/ml is indicative of an ectopic source of GH.

CUSHING'S DISEASE

- Normal or slightly elevated corticotropin levels ranging from 20 to 200 pg/ml; normal is 10 to 50 pg/ml (normative data should be developed by each institution for its population).
- Level <10 pg/ml usually indicates an autonomously secreting adrenal tumor.
- Level >200 pg/ml suggests an ectopic corticotropin-secreting neoplasm.
- Cushing's disease can be assessed by absence of cortisol suppression with the low-dose dexamethasone test but with the presence of cortisol suppression after the high-dose test. As a method to distinguish Cushing's disease from an ectopic source of ACTH, this test is robust.
- 24-hr urine collection should demonstrate an increased level of cortisol excretion.

THYROTROPIN-SECRETING PITUITARY ADENOMA:

- Highly sensitive thyrotropin assays, which evaluate the presence of thyrotoxicosis, are one way to detect a thyrotropin-secreting tumor.
- Free alpha subunit is secreted by >80% of tumors, with the ratio of the alpha subunit to thyrotropin <1.
- With central resistance to thyroid hormone, ratio is <1 and the sella is normal.
- Laboratory tests show elevated serum levels of both T_3 and T_4.

NONSECRETORY PITUITARY ADENOMA

- Visual field testing.
- Assessment of the pituitary and organ function to determine if there is hypopituitarism or hypersecretion of hormones (even if the effects of hypersecretion are subclinical).
- TRH to provoke secretion of FSH, LH, and LH-beta-subunit; will not elicit response in normal persons.
- Exclusion of Klinefelter's syndrome in patient with longstanding primary hypogonadism, elevated gonadotropin levels, and enlargement of the sella.

IMAGING STUDIES

Study of choice: MRI of the pituitary (Fig. EP1-39) and hypothalamus.

- When evaluating Cushing's disease, small size at the onset of symptoms noted.
- MRI, in this case, only 60% sensitive at best and may yield false-positive results.
- CT scan only when MRI is unavailable or is otherwise contraindicated.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

SURGERY

- Selective transsphenoidal resection of the adenoma (Table P1-21) is the treatment of choice for acromegaly, Cushing's disease, and thyrotropin-secreting pituitary adenomas, all of which tend to be microadenomas at the time of onset of symptoms.
- Macroadenomas, such as the nonsecretory pituitary adenoma, may also be surgically removed, but risk of recurrence is greater with these tumors and adjunctive therapy such as irradiation may also be necessary.
- Bilateral adrenalectomy has been performed in patients with Cushing's disease after failure of other therapies; complications requiring lifelong hormone replacement or Nelson's syndrome (rapid enlargement of pituitary tumor due to adrenal resection) may occur.

RADIOTHERAPY

- Radiotherapy is used primarily as adjuvant treatment. It is reserved for patients who have not responded to surgical treatment and who still have symptoms of the adenoma.
- Used with varying degrees of success in all the different pituitary adenomas.
- Radiotherapy complications include long-term hypopituitarism (40% of patients) and secondary neoplasms (1.5% of patients).

TABLE P1-21 Transsphenoidal Pituitary Surgery

Primary Indications

General

Visual tract or central nervous compression arising from within sella
Relief of compressive hypopituitarism by presenting, residual, or recurrent tumor tissue
Tumor recurrence after surgery or irradiation
Pituitary hemorrhage
Cerebrospinal fluid leak
Resistance to medical therapy
Intolerance of medical therapy
Personal choice
Desire for immediate pregnancy with macroadenoma
Requirement for diagnostic tissue histology

Specific

Acromegaly
Cushing's disease
Clinically nonfunctioning macroadenoma
Prolactinoma
Nelson syndrome
TSH-secreting adenoma

Side Effects

Transient

Diabetes insipidus
Cerebrospinal fluid leak and rhinorrhea
Inappropriate ADH secretion
Arachnoiditis
Meningitis
Postoperative psychosis
Local hematoma
Arterial wall damage
Epistaxis
Local abscess
Pulmonary embolism
Narcolepsy

Permanent (up to 10%)

Diabetes insipidus
Total or partial hypopituitarism
Visual loss
Inappropriate ADH secretion
Vascular occlusion
CNS damage: oculomotor palsy, hemiparesis, encephalopathy
Nasal septum perforation

Surgery-Related Mortality (up to 1%)

Brain, hypothalamic
Vascular damage
Postoperative meningitis
Cerebrospinal fluid leak
Pneumocephalus
Acute cardiopulmonary disease
Anesthesia-related
Seizure

ADH, Antidiuretic hormone; *CNS,* central nervous system; *TSH,* thyroid-stimulating hormone.
From Melmed S et al: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

ACUTE GENERAL Rx

PROLACTINOMA

- Bromocriptine, a dopamine analogue, is generally given orally in divided doses of 1.5 to 10 mg. Cabergoline is given once or twice weekly. It is better tolerated and more effective than bromocriptine for tumor shrinkage but more expensive.

- Side effects include orthostatic hypotension, nausea, and dizziness; avoided by beginning with low-dose therapy.
- Other compounds include pergolide mesylate, a long-acting ergot derivative with dopaminergic properties, as well as other nonergot derivatives.

ACROMEGALY

- Somatostatin analogues: octreotide, lanreotide administered as monthly injections.
- Cabergoline or bromocriptine can also be used. They have modest activity but can be administered orally and are less expensive than somatostatin analogues.
- Pegvisomant can also be used to normalize IGF-1 levels.

CUSHING'S DISEASE

- Ketoconazole, which inhibits the cytochrome P-450 enzymes involved in steroid biosynthesis, is effective in managing mild to moderate disease in daily oral doses of 600 to 1200 mg.
- Metyrapone and aminoglutethimide can be used to control hypersecretion of cortisol but are generally used when preparing a patient for surgery or while waiting for a response to radiotherapy.

THYROTROPIN-SECRETING PITUITARY ADENOMA

- Ablative therapy with either radioactive iodide or surgery is indicated.
- Treatment directed to the thyroid alone may accelerate growth of the pituitary adenoma.
- Octreotide has been shown to be effective in doses similar to those used for acromegaly.

NONSECRETORY PITUITARY ADENOMA

- There is no role for medical therapy at this time.
- Surgery and radiotherapy may be indicated. An algorithm for the management of nonfunctioning pituitary adenomas is described in Fig. P1-40.

CHRONIC Rx

For all pituitary adenomas:

- Careful follow-up is important. Patients undergoing transsphenoidal microsurgical resection should be seen in 4 to 6 wk to ensure that the adenoma has been completely removed and that the endocrine hypersecretion is resolved.

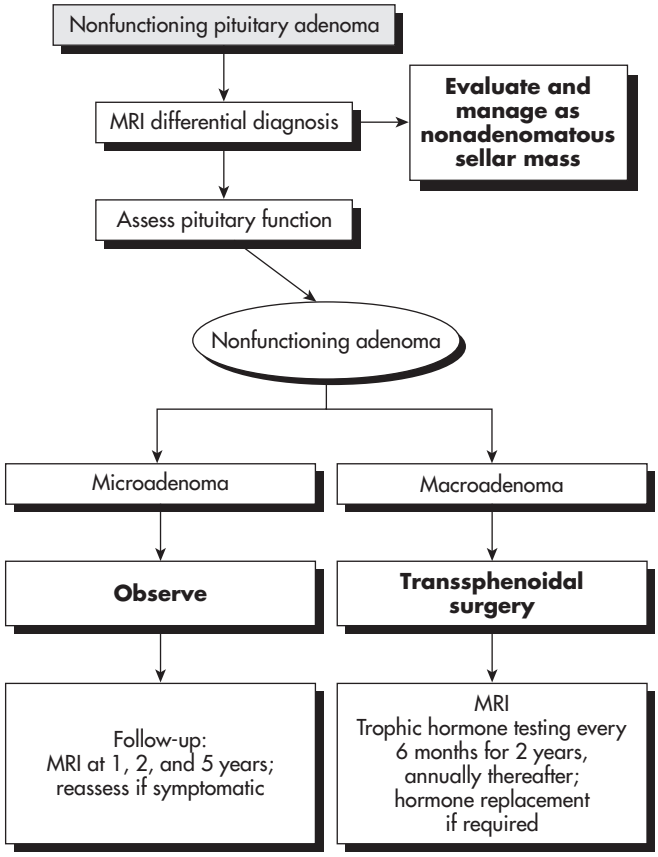


FIGURE P1-40 Management of nonfunctioning pituitary adenomas. Skilled interpretation of magnetic resonance images is crucial to diagnose a nonadenomatous mass such as a meningioma, aneurysm, or other sellar lesion. (From Melmed S et al: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.)

- If there is good clinical response, patient should be monitored yearly for recurrence and to follow the level of the hypersecreted hormone.
- Patients who have undergone irradiation should have close follow-up with backup medical therapy because response to radiotherapy may be delayed; incidence of hypopituitarism also increases with time.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fig. 3-162 Evaluation of suspected pituitary tumor (Algorithm)
Pituitary Adenoma (Patient Information)
Acromegaly (Related Key Topic)
Amenorrhea (Related Key Topic)
Cushing's Disease and Syndrome (Related Key Topic)
Galactorrhea (Related Key Topic)
Prolactinoma (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Davis AK et al.: Pituitary tumors, *Reproduction* 121(3):363, 2001.

Kovacs K et al.: Classification of pituitary adenomas, *J Neurooncol* 54(2):121, 2001.

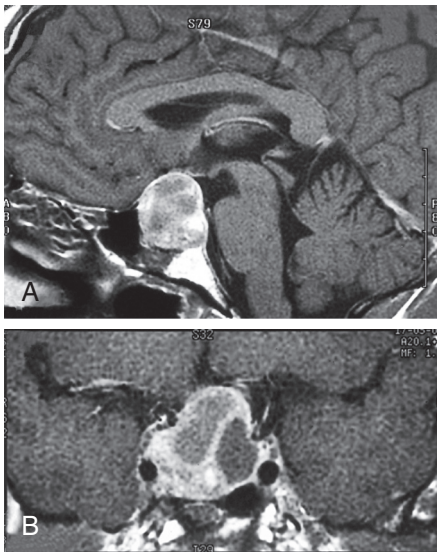


FIGURE EP1-39 Magnetic resonance T1-weighted gadolinium-enhanced image of a pituitary adenoma. A, Sagittal image. **B,** Coronal image. (Courtesy of D. Thomas. From Kanski JJ, Bowling B: *Clinical ophthalmology, a systematic approach,* ed 7, Philadelphia, 2010, Saunders.)

Pityriasis Rosea PTG

BASIC INFORMATION

DEFINITION

Pityriasis is a common self-limiting skin eruption of unknown etiology.

ICD-9CM CODES
696.3 Pityriasis rosea
ICD-10CM CODES
L42 Pityriasis rosea

EPIDEMIOLOGY & DEMOGRAPHICS

- Most cases of pityriasis rosea occur between ages 10 and 35 yr; mean age is 23 yr.
- The incidence of disease is highest in the fall and spring.
- Female/male ratio is 1.5:1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Initial lesion (herald patch), an annular pink patch with trailing scale, precedes the eruption by approximately 1 to 2 wk; typically measures 3 to 6 cm; it is round to oval in appearance and most frequently located on the trunk (Fig. P1-41).
- Eruptive phase follows within 2 wk and peaks after 7 to 14 days.
- Lesions are most frequently located in the lower abdominal area. They have a salmon-pink appearance in whites and a hyperpigmented appearance in blacks.
- Most lesions are 4 to 5 mm in diameter; center has a "cigarette paper" appearance; border has a characteristic ring of scale (collarette).
- Lesions occur in a symmetric distribution and follow the cleavage lines of the trunk (Christmas tree pattern).
- The number of lesions varies from a few to hundreds.
- Most patients are asymptomatic; pruritus is the most common symptom.
- History of recent fatigue, headache, sore throat, and low-grade fever is present in approximately 25% of cases.

ETIOLOGY

Unknown, possibly viral (picornavirus).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Tinea corporis (can be ruled out by potassium hydroxide examination).
- Secondary syphilis (absence of herald patch, positive serologic test for syphilis).
- Psoriasis.
- Nummular eczema.
- Drug eruption: medications that may cause rashes similar to pityriasis rosea include clonidine, captopril, interferon, bismuth, barbiturates, gold, hepatitis B vaccine, and imatinib mesylate.
- Viral exanthem.
- Eczema.
- Lichen planus.
- Tinea versicolor (the lesions are more brown and the borders are not as ovoid).
- Erythema migrans.

WORKUP

Presence of herald lesion and characteristic rash are diagnostic. Skin biopsy is generally reserved for atypical cases.

LABORATORY TESTS

Generally not necessary; serologic test for syphilis if clinically indicated.

TREATMENT

NONPHARMACOLOGIC THERAPY

The disease is self-limited and generally does not require any therapeutic intervention.

ACUTE GENERAL Rx

- Use calamine lotion or oral antihistamines in patients with significant pruritus.
- Use prednisone tapered over 2 wk in patients with severe pruritus.
- Direct sun exposure or use of ultraviolet light within the first week of eruption is beneficial in decreasing the severity of disease.

DISPOSITION

- Spontaneous complete resolution of the rash within 4 to 8 wk.
- Recurrence rare (<2% of cases).

PEARLS & CONSIDERATIONS

COMMENTS

Reassure patient that the disease is not contagious and its course is benign.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pityriasis Rosea (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

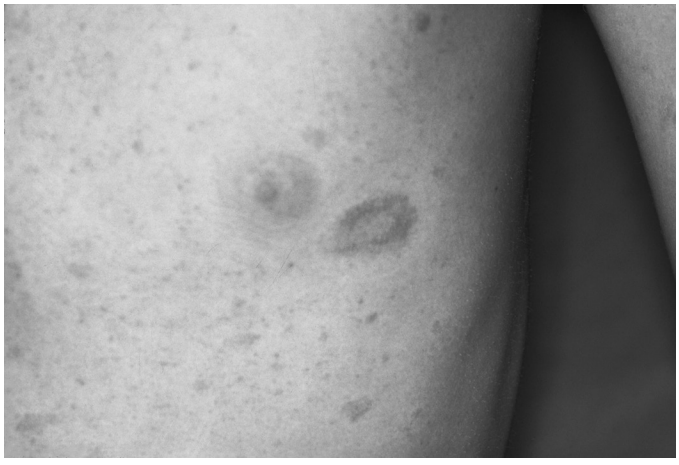


FIGURE P1-41 Herald patch and surrounding pityriasis rosea. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

SUGGESTED READING

Stulberg D, Wolfrey J: Pityriasis rosea, *Am Fam Physician* 69:87, 2004.

BASIC INFORMATION

DEFINITION

Placenta previa is the implantation of the placenta over the internal os. Four degrees of this abnormality (Fig. P1-42) have been traditionally defined; however, the accurate localization of the placental edge in relation to the discrete point of the internal os with transvaginal sonography makes the following terms outmoded:

1. Total placenta previa: the internal os is covered completely.
2. Partial placenta previa: the internal os is partially covered.
3. Marginal placenta previa: the edge of the placenta is at the margin of the internal os.
4. Low-lying placenta: the placenta is implanted in the lower uterine segment and, although its edge does not reach the internal os, is in close proximity to it.

ICD-9CM CODES
641.1 Placenta previa
ICD-10CM CODES
O44 Placenta previa
O44.0 Placenta previa specified as without hemorrhage
O44.1 Placenta previa specified as with hemorrhage

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 0.26% to 0.7% of pregnancies

RISK FACTORS

- Previous cesarean delivery (after one cesarean delivery, the risk is 1% to 4%; after four or more, the risk approaches 10%).
- Multiparity has also been associated with placenta previa.
- Smoking and cocaine use
- Previous myomectomy or Asherman syndrome
- Multiple gestation
- Abnormal or large placenta

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The classic presentation of placenta previa is painless vaginal bleeding, usually in the second or third trimester. Uterine contractions may or may not be present. On physical examination, the uterus is soft and pain free. The fetus is often in breech, transverse lie, or high. Fetal distress is usually not present.

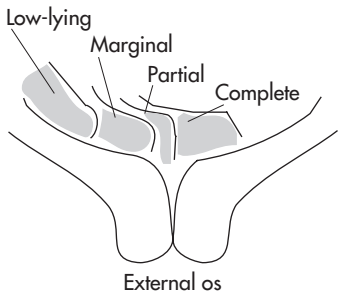


FIGURE P1-42 Depiction of degrees of placenta previa. (From Weissleder R et al: *Primer of diagnostic imaging,* St Louis, 2007, Mosby.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Placenta accreta
- Placenta percreta
- Placenta increta
- Vasa previa
- Abruptio placentae
- Vaginal or cervical trauma
- Labor
- Local malignancy

WORKUP

- Do *not* perform a digital vaginal examination.
- The diagnosis of placenta previa can seldom be firmly established by physical examination alone. A speculum examination in a hospital setting to exclude any local bleeding may be performed.
- This diagnosis should not be dismissed until thorough evaluation, including sonography, has completely excluded its presence.

LABORATORY TESTS

- A complete blood count can be used to monitor hemoglobin and hematocrit.
- A Kleihauer-Betke preparation of maternal blood in all Rh-negative women and Rh-immune globulin when indicated

IMAGING STUDIES

- The simplest and safest method of placental localization is transabdominal sonography with confirmatory imaging by transvaginal ultrasonography (TVS). Transabdominal ultrasound alone is inaccurate in the diagnosis of placenta previa and should be used only as a screening tool. TVS (Fig. EP1-43) has become the gold standard for the diagnosis of placenta previa. It is safe even in the presence of active bleeding. A distance of ≤20 mm from placental edge to interior cervical os is becoming a new criterion for performing term cesarean delivery in women with placenta previa.
- MRI has also been effective in detecting placenta previa, although sonography remains the preferred method.

TREATMENT

NONPHARMACOLOGIC THERAPY

- In preterm pregnancies with no active bleeding, close observation and expectant management are indicated. In those with active bleeding, conservative management, including blood transfusions for severe bleeds, is appropriate. The woman should stay in the hospital for at least 48 hr after the bleeding has stopped.
- Bed rest, preferably in a hospital setting, should be prescribed.

ACUTE GENERAL Rx

- Initial assessment for signs of maternal hemodynamic compromise or hemorrhagic shock; large-bore IV access with crystalloid fluid resuscitation
- Assess fetal status and gestational age by sonogram and continuous fetal heart rate monitoring
- Cross-matched blood should be made available during bleeding episodes; if the hemorrhage is severe, cesarean delivery is indicated despite fetal immaturity
- Tocolytic therapy may be considered in those women in preterm labor, as well as the administration of corticosteroids to enhance fetal lung maturity

CHRONIC Rx

- Cesarean delivery is necessary in nearly all cases of placenta previa.
- Uncontrollable hemorrhage after placental removal should be anticipated as a result of the poorly contractile nature of the lower uterine segment. The need for hysterectomy to control bleeding should be discussed with the patient before delivery.

DISPOSITION

Because of the unpredictable nature of placenta previa, not all women with placenta previa can be treated expectantly.

REFERRAL

Affected women and their families should be aware of all signs and symptoms that would necessitate immediate transport to the hospital. The possibility of hysterectomy should also be discussed early during pregnancy.

PEARLS & CONSIDERATIONS

COMMENTS

Third-trimester measurement of the distance from the placental edge to the internal cervical os by TVS commonly is used to gauge the likelihood of need for cesarean section. The decision to offer women with a placenta that is situated 11 to 20 mm away a trial of labor remains controversial. Recent reports by Vergani et al indicate that more than two thirds of women with a placental edge to cervical os distance of >10 mm fewer than 28 days before delivery can deliver vaginally without increased risk of hemorrhage

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Placenta Previa (Patient Information)
Vaginal Bleeding During Pregnancy (Related Key Topic)

AUTHORS: **SONYA S. ABDEL-RAZEQ, M.D.,** and **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Oppenheimer LW, Farine D: A new classification of placenta previa: measuring progress in obstetrics, *Am J Obstet Gynecol* 201:227, 2009.

Vergani P et al.: Placenta previa: distance to interval os and mode of delivery, *Am J Obstet Gynecol* 201:266, 2009.

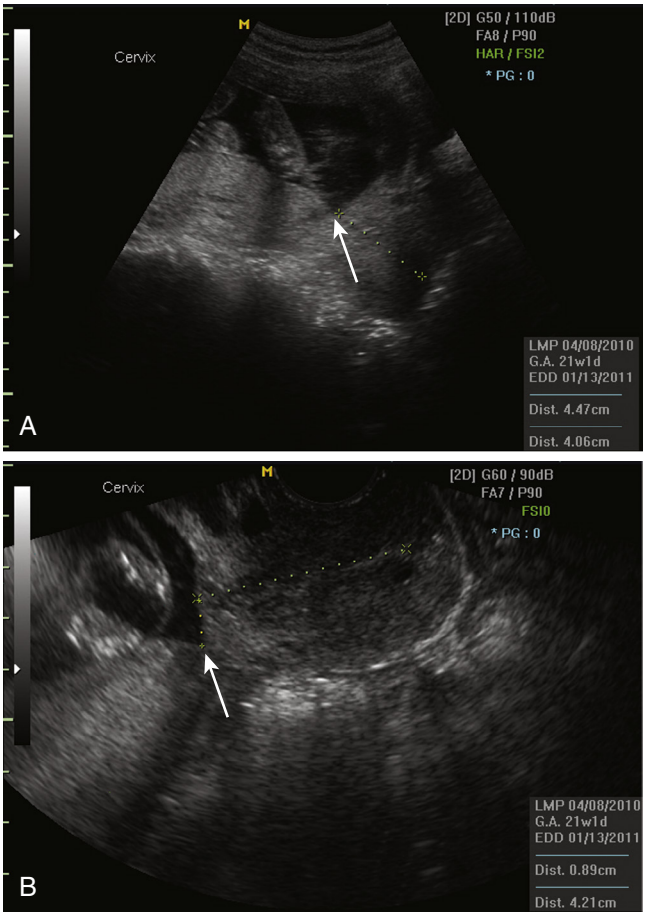


FIGURE EP1-43 Transabdominal and transvaginal ultrasounds of marginal placenta previa. *Arrows* identify placental edge. (Courtesy K. Francois. From Gabbe S.G.: *Obstetrics*, 6th ed, Philadelphia, Saunders, 2012.)

Plantar Fasciitis PTG

BASIC INFORMATION

DEFINITION

The plantar fascia arises from the calcaneal tuberosity and has various attachments as it travels longitudinally, ending at the digital level (Fig. P1-44). It acts as a tension band supporting the medial longitudinal arch of the foot. Plantar fasciitis describes the local inflammation and subsequent pain occurring at the insertion at the medial calcaneal tuberosity or along the course of the fascial band.

SYNONYMS

Heel pain syndrome

ICD-9CM CODES
728.71 Plantar fasciitis
726.73 Calcaneal spur
ICD-10CM CODES
M72.2 Plantar fascial fibromatosis
M77.30 Calcaneal spur, unspecified foot

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Plantar fasciitis affects >1 million persons/yr in the United States and two thirds of patients will seek care from their primary care physician for this condition. It is one of the more common causes of heel pain in adults.
PREDOMINANT SEX: Females slightly greater than males, studies vary.
PREDOMINANT AGE: Commonly middle aged; any age group possible.
RISK FACTORS: Weight gain, obesity (present in 90% of patients), increased activity, change in activity type, prolonged standing, hard surfaces, trauma, certain activities (see "Etiology").

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pain is localized to the heel or along the course of the plantar fascia.
- Pain is greatest upon first steps in the morning and upon standing after rest (poststatic dyskinesia).
- Symptoms may improve throughout the day or with ambulation, but may persist or increase with prolonged standing.
- Pain may be elicited with ankle dorsiflexion and simultaneous subtalar eversion.
- Often exquisitely tender upon palpation of the medial calcaneal tuberosity.
- May have localized or medial heel edema.

ETIOLOGY

- Any factor that increases the tension at the insertion of the fascia on the medial calcaneal tuberosity, creating local inflammation. Evidence suggests that plantar spurs are secondary rather than an etiology; these are an incidental finding in about 30% of asymptomatic patients.
- Achilles/ankle equinus or pseudoequinus.
- Active STJ/rearfoot pronation, such as with calcaneal or forefoot varus.
- A strain of the fascia or dorsiflexory force of the forefoot on the midfoot or vice versa. Example: jumping from a height, sprinting from starting blocks, reaching on a ladder.

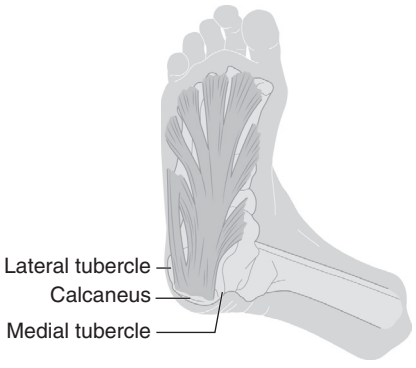


FIGURE P1-44 Plantar view of origin and insertion of plantar fascia. (From Frontera WR: *Essentials of physical medicine and rehabilitation,* ed 2, Philadelphia, 2008, Saunders.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Calcaneal fracture, including traumatic or stress fracture, or bone bruise.
- Tarsal tunnel syndrome.
- Calcaneal osteomyelitis.
- Bone cyst or bone tumor.
- Posterior tibial tendon dysfunction (often misdiagnosed as plantar fasciitis).
- Plantar fascial fibromatosis (thickening/soft tissue mass along the plantar fascial band).
- Systemic cause: gout, Paget's disease of the bone, psoriasis, Reiter's syndrome, etc.
- Plantar fascia rupture.

STUDIES

- Weight-bearing x-rays: rule out tumor or trauma (lateral, oblique, calcaneal axial views).
- MRI/bone scan to rule out stress fracture (takes 2 wk to show on x-ray).
- MRI or ultrasound if suspected plantar fascial fibromatosis.
- May need to rule out tarsal tunnel syndrome with nerve studies.

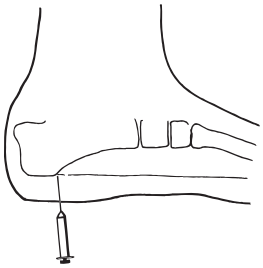


FIGURE P1-45 Injection site for plantar fasciitis. Injection should be through the sole into the area of maximum tenderness. A 25 or 27-gauge needle should be used and the medication injected slowly because some pain may occur. The total volume should be no >1.5 ml. (From Mercier L: *Practical orthopedics*, ed 5, St Louis, 2002, Mosby.)

TREATMENT

- Supportive lace-up sneakers with firm, cushioned sole. Weight loss for obese patients.
- Ice, stretching exercises, NSAIDs, limit activity.
- Low-dye strapping/taping.
- Steroid/local anesthetic injections (Fig. P1-45) via several techniques. Although corticosteroid injection is often used to alleviate pain from plantar fasciitis, evidence supporting this treatment is limited. Trials have shown that pain improvement after steroid injection is slightly faster than placebo and benefits are likely to be short lived.
- Custom orthotics will limit subtalar joint overpronation and other faulty biomechanics.
- Add heel cushion to orthotics if acute pain/inflammation.
- Heel lifts if the etiology is Achilles equinus or pseudoequinus.
- Night splints maintain ankle dorsiflexion overnight.
- Severe cases may require a cast or cast walker for 4 to 6 wk.
- Recalcitrant cases may require surgical endoscopic or open fasciotomy.

DISPOSITION

Cases that are treated sooner and acute cases with sudden onset have a higher likelihood of resolving completely. Chronic, recalcitrant cases may require surgery.

REFERRAL

- For biomechanical exam or surgical consult (podiatric/orthopedic foot/ankle surgeon).
- Physical therapy is often beneficial when first-line therapy fails.

PEARLS & CONSIDERATIONS

COMMENTS

Caution: common, seemingly simple diagnosis. Do not overlook differential diagnosis.

PREVENTION

- Avoid shoes with bendable/flexible soles and shoes without laces/straps.
- Maintain foot/ankle flexibility with stretching exercises.
- Seek treatment at first signs of pain. Faster recovery rate with early diagnosis and treatment.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Plantar Fasciitis (Patient Information)

AUTHOR: **BROOKE E. KEELEY, D.P.M.**

SUGGESTED READINGS

Goff JD, Crawford R: Diagnosis and treatment of plantar fasciitis, *Am Fam Physician* 84(6):676–682, 2011.

Healey K, Chen K: Plantar fasciitis: current diagnostic modalities and treatments, *Clinics Pod Med Surg* 27:3, 2010.

McMillan AM et al.: Ultrasound-guided corticosteroid injection for plantar fasciitis: randomized controlled trial, *BMJ* 344:e3260, 2012.

Thomas JL et al.: The diagnosis and treatment of heel pain: a clinical practice guideline-revision 2010, *J Foot Ankle Surg* 49(3 Suppl):S1, 2010.

Young C: In the clinic: plantar fasciitis, *Ann Intern Med* 156(1), 2012. ITC 1–1.

BASIC INFORMATION

DEFINITION

Pleurisy refers to the inflammation of the parietal pleura. This inflammation results in pleuritic chest pain that is characteristically worsened with respiration or movement.

SYNONYMS

Pleuritis

ICD-9CM CODES
511.0 Pleurisy
ICD-10CM CODES
R09.1 Pleurisy

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: One of the most common causes of pleuritic chest pain is viral pleurisy. However, there are a variety of disorders that may result in pleurisy. Infectious diseases, rheumatologic disorders, thromboembolic events, and trauma may all lead to pleural inflammation. Therefore, the incidence of pleurisy varies in accordance with the underlying etiology.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The defining characteristic of pleurisy is chest pain that worsens with respiration, coughing, or sneezing.
- Pleuritic chest pain is typically described as sharp or stabbing. However, pleuritic chest pain may also be described as dull pain, burning pain, or a "catch" while breathing.
- Movements of the trunk or chest wall may exacerbate pain. Patients with pleurisy may locate the position of minimal discomfort and remain still in that position.
- Dyspnea may be associated with pleurisy.
- Physical exam may be remarkable for a pleural friction rub.
- Decreased breath sounds, rales, or egophony may be appreciated if pneumonia is the underlying etiology of the patient's pleurisy.

ETIOLOGY

- Pleurisy is caused by inflammation of the parietal pleura. The visceral pleura is not innervated by nociceptors. However, injury or inflammation at the periphery of the lung parenchyma often results in inflammation of the overlying parietal pleura. The parietal pleura, which lines the rib cage and the lateral portion of each hemidiaphragm, is innervated by intercostal nerves; therefore pain is localized to the cutaneous distribution of those nerves (over the chest wall). The parietal pleura of the central diaphragm is innervated by fibers that travel with the phrenic nerve; therefore pain associated with inflammation in this area is referred to the ipsilateral shoulder or neck.
- Various underlying etiologies may result in pleurisy, including:
  1. Thromboembolism (pulmonary embolism).
  2. Viral infection (coxsackieviruses, respiratory syncytial virus [RSV], cytomegalovirus [CMV], adenovirus, Epstein-Barr virus [EBV], parainfluenza, influenza).
  3. Bacterial infection (pneumonia or tuberculous pleuritis).
  4. Fungal infection (coccidioidomycosis, histoplasmosis).
  5. Rheumatologic disease (rheumatoid arthritis, systemic lupus erythematosus [SLE]).
  6. Medications.
  7. Malignancy of the lung or pleura.
  8. Trauma (rib fracture).
  9. Hereditary (familial Mediterranean fever, sickle cell disease).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cardiac: myocardial infarction, ischemia, pericarditis.
- Intraabdominal process: pancreatitis, cholecystitis.
- Thromboembolic: pulmonary embolism, infarction of lung parenchyma.
- Traumatic/mechanical: rib fracture or pneumothorax.
- Viral infection: viral infections may lead to epidemic pleurodynia (also known as Bornholm's disease). Implicated viruses include coxsackieviruses, RSV, CMV, adenovirus, EBV, parainfluenza, influenza. Of note, viral pleurisy is a diagnosis of exclusion.
- Bacterial infection: pneumonia or tuberculous pleurisy.
- Fungal infection: coccidioidomycosis, histoplasmosis.
- Rheumatologic disease: rheumatoid arthritis, SLE.
- Medications: drug-induced lupus.
- Hereditary causes: familial Mediterranean fever, sickle cell disease.
- Malignancy: malignancy affecting the lung or pleura.
- Uremia.

WORKUP

- A thorough history and physical exam of all patients presenting with pleuritic chest pain should be taken. The time course of the patient's symptoms can provide valuable diagnostic clues. Acute onset of symptoms is suggestive of traumatic injuries, spontaneous pneumothorax, pulmonary embolism, or myocardial infarction. Subacute onset of symptoms suggests a potential infectious, rheumatologic, or medication-induced cause. Viral pleurisy is often associated with prodromal symptoms of upper respiratory infection. Chronic or recurrent symptoms suggest a potential malignant, tuberculous, or hereditary cause.
- Chest x-ray to evaluate for pneumonia, pneumothorax, or pleural effusion.
- ECG to evaluate for infarction, ischemia, or pericarditis.
- Evaluation for pulmonary embolism should be undertaken if clinical suspicion exists.

LABORATORY TESTS

- Laboratory testing varies based on suspected underlying etiology. Consider CBC, Chem 7, and D-Dimer testing depending on clinical presentation.
- If a pleural effusion is present, diagnostic thoracentesis may provide valuable diagnostic clues to the underlying etiology.

IMAGING STUDIES

- Chest x-ray.
- ECG.
- CT chest in selected patients.

TREATMENT

- Treatment of pleurisy consists of pain control as well as treating the underlying condition.
- NSAIDs are the preferred first-line agent to control pain associated with pleurisy. Human studies have been limited to trials using indomethacin for pain control, although an NSAID class effect is presumed.
- Indomethacin 50 mg orally up to three times a day has been found to be effective in relieving pain and is associated with an improvement in mechanical lung function.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **MARISA E. VAN POZNAK, M.D.**

SUGGESTED READINGS

Kass SM et al.: Pleurisy, *Am Fam Physician* 75(9):1357–1364, 2007.

Kosowsky JM, Kimberly HH: Pleural Disease. In Marx JA, Hockberger RS, Walls RM, editors: *Rosen's Emergency Medicine*, ed 8, Philadelphia, 2014, Saunders, pp 988–996.

Murray JF, Gebhardt GF: Chest pain. In: (editor: Mason RJ; et al.) Murray and Nadel's textbook of respiratory medicine, ed 5 Elsevier: Philadelphia.

Pneumocystis jiroveci (carinii) Pneumonia PTG

BASIC INFORMATION

DEFINITION

Pneumocystis jiroveci pneumonia (PJP) is a serious respiratory infection caused by the fungal pathogen *P. jiroveci* (formerly known as *P. carinii*).

SYNONYMS

PCP
PJP

ICD-9CM CODES
136.3 *Pneumocystis jiroveci (P. carinii)* pneumonia
ICD-10CM CODES
B59 Pneumocystosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):
- Seen primarily in the setting of AIDS.
- Approximately 95% of cases occur in HIV infected individuals with CD4 counts <200/mm^3.
- Also seen in other immunocompromised patients with severe cell-mediated immune deficiency (congenital T-cell deficiency, acute leukemia, lymphoma, bone marrow or organ transplant deficiency).
- Rituximab use has been associated with PJP in HIV-negative patients, most of whom had hematologic cancers.

PEAK INCIDENCE: Age 20 to 40 yr (parallel to AIDS epidemic).
PREDOMINANT SEX: Equal incidence when adjusted for HIV status.
PREDOMINANT AGE:
- 20 to 40 yr

GENETICS: Neonatal infection:
- Most frequent opportunistic infection among HIV-infected children, occurring in approximately 30%.
- Neonatal occurrence unusual.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fever, cough, shortness of breath present in almost all cases. May be subacute or insidious.
- Lungs frequently clear to auscultation, although rales occasionally present.
- Cyanosis and pronounced tachypnea in severe cases.
- Hemoptysis unusual.
- Spontaneous pneumothorax.

ETIOLOGY

- *P. jiroveci* (formerly *P. carinii*) recently reclassified as a fungal organism (previously classified as a protozoan) (Fig. EP1-46).
- Reactivation of dormant infection.
- Extrapulmonary involvement rare but possible.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other opportunistic respiratory infections:
  1. Tuberculosis
  2. Histoplasmosis
  3. Cryptococcosis
- Nonopportunistic infections:
  1. Bacterial pneumonia
  2. Viral pneumonia
  3. Mycoplasmal pneumonia
  4. Legionellosis
- Occurs almost exclusively in the setting of profound depression of cellular immunity.

WORKUP

- Chest x-ray (Fig. EP1-47) or chest CT.
- Arterial blood gases.
- Because *Pneumocystis* cannot be cultured, diagnosis relies on detection of the organism by colorimetric or immunofluorescent stains or PCR.
- Cannot be cultured. Sputum examination for cysts of PJP and to exclude other pathogens.
- Bronchoscopy with bronchoalveolar lavage or lung biopsy for diagnosis if sputum examination is negative or equivocal. Stains such as Gomori methenamine silver stain or toluidine blue O are used to identify the organism.

LABORATORY TESTS

- Arterial blood gas monitoring.
- Elevated lactate dehydrogenase in majority of cases.
- HIV antibody test and CD4 cell count if cause of underlying immune deficiency state is unclear.

IMAGING STUDIES

- CT scan of the chest in selected patients (Fig. EP1-48).
- PJP may appear as diffuse, unilateral, bilateral, or interstitial infiltrates on chest x-ray or CT. Imaging may be normal in up to one quarter of individuals. Pneumothoraces may also occur.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Supplemental oxygen.
- Ventilatory support if needed.
- Prompt thoracotomy if pneumothorax develops.

ACUTE GENERAL Rx

For confirmed or suspected PJP:
- Trimethoprim-sulfamethoxazole (15 to 20 mg/kg trimethoprim and 75 to 100 mg/kg sulfamethoxazole qd) PO or IV per day divided and given q6 to 8h.
- Pentamidine (4 mg/kg IV qd) (severe cases with a contraindication to trimethoprim/sulfamethoxazole).
- Either regimen with prednisone (40 mg PO bid):
  1. If arterial oxygen pressure <70 mm Hg.
  2. If arterial-alveolar oxygen pressure difference >35 mm Hg.
  3. Dose tapered to 20 mg bid after 5 days and 20 mg qd after 10 days.
- Therapy continued for 3 wk.
- Alternative therapies available for patients unable to tolerate conventional therapy:
  1. Dapsone/trimethoprim
  2. Clindamycin/primaquine
  3. Atovaquone

CHRONIC Rx

- After completion of therapy, prophylaxis should be maintained with trimethoprim-sulfamethoxazole (one single-strength tablet PO qd or double-strength three times weekly) until the CD4 cell count is >200 for 3 mo.
- Patients intolerant of this therapy should be treated with dapsone (100 mg PO qd) or atovaquone (1500 mg PO qd).
- Inhaled pentamidine (300 mg monthly by standardized nebulizer) is less effective and is reserved for patients intolerant to other forms of prophylaxis.

DISPOSITION

After completion of therapy, long-term ambulatory follow-up is mandatory to provide secondary prevention of PJP (see "Chronic Rx" above) and management of the underlying immunodeficiency syndrome.

REFERRAL

- To pulmonologist for bronchoscopy if diagnosis cannot be confirmed by sputum examination.
- To an infectious disease specialist if case is severe or difficult to manage.

PEARLS & CONSIDERATIONS

COMMENTS

- All patients, especially those with severe infection or intolerant of conventional therapy, should be followed by a physician experienced in the management of PJP and, if appropriate, in the long-term management of HIV infection or other underlying disease.
- Severe and life-threatening hypoglycemia may occur after 1 or 2 wk after start of IV pentamidine. Monitor closely and advise the patient of symptoms of hypoglycemia.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pneumocystis Pneumonia (Patient Information)

AUTHOR: **PHILIP A. CHAN, M.D., M.S.**

SUGGESTED READINGS

Kovacs JA, Masur H: Evolving health effects of pneumocystis, *JAMA* 301(24):2578–2585, 2009.

Torres HA et al.: Influence of type of cancer and hematopoietic stem cell transplantation on clinical presentation of *Pneumocystis jirovecii* pneumonia in cancer patients, *Eur J Clin Microbiol Infect Dis* 25(6):382, 2006.

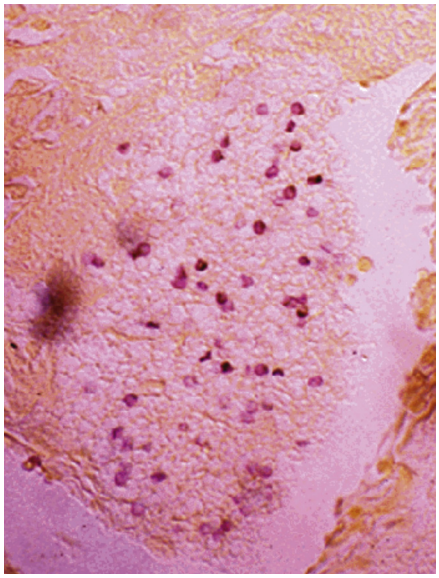


FIGURE EP1-46 Wright-Giemsa stain of *Pneumocystis jiroveci (carinii)* pneumonia. (From Gabbe S.G.: *Obstetrics*, 6th ed, Philadelphia, 2012, Saunders.)

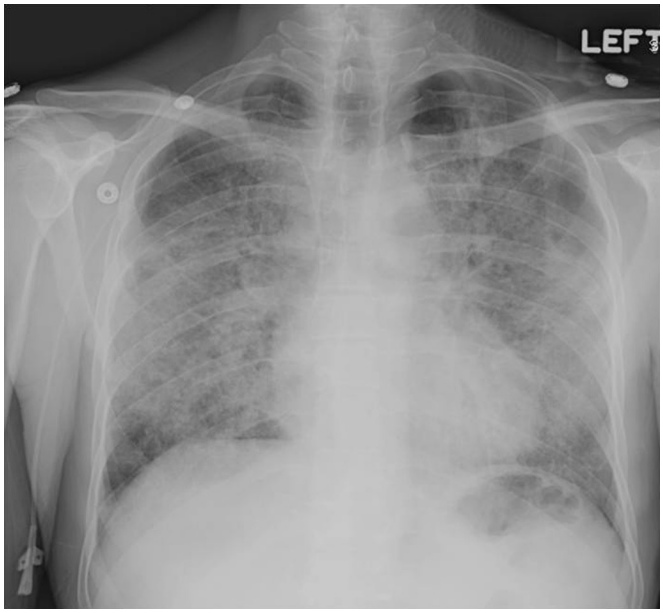


FIGURE EP1-47 Chest radiograph showing diffuse interstitial infiltrate in a patient with *Pneumocystis jiroveci* pneumonia. (From Firestein GS et al [eds]: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

FIGURE EP1-48 Computed tomography scan of the chest demonstrating ground-glass opacity in a patient with *Pneumocystis jiroveci* pneumonia. (From Firestein GS et al [eds]: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

BASIC INFORMATION

DEFINITION

A spontaneous pneumothorax (SP) is defined as the accumulation of air into the pleural space, collapsing the lung without a precipitating event. This can be primary SP (without any obvious underlying lung disease) or secondary SP (with underlying lung disease).

SYNONYMS

Primary spontaneous pneumothorax
Secondary spontaneous pneumothorax

ICD-9CM CODES
512.0S Spontaneous tension pneumothorax
512.8 Other spontaneous pneumothorax
ICD-10CM CODES
J93.83 Other pneumothorax
J93.9 Pneumothorax, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Approximately 20,000 new cases of SP occur each year in the United States.
- SP is more common in men than women (6:1).
- Incidence of primary SP is 7.4 per 100,000 in men and 1.2 per 100,000 in women.
- Incidence of secondary SP is 6.3 per 100,000 in men and 2.0 per 100,000 in women.
- SP is commonly seen in tall, thin young men aged 20 to 40 yr.
- Risk factors include smoking, family history, Marfan's syndrome, homocystinuria, and thoracic endometriosis.
- Anorexia nervosa is thought to be a risk factor due to pulmonary parenchymal consequences of malnutrition.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Sudden onset of pleuritic chest pain (90%), usually at rest, which often becomes dull after a few hours.
- Pain is usually unilateral and can be sharp and agonizing and associated with considerable apprehension.
- Dyspnea (80%), which often resolves within 24 hr, despite persistence of pneumothorax.
- Cough (10%).
- Asymptomatic (5%); may take up to 7 days to come to medical attention.
- Tachycardia.
- Hypoxemia.
- Hypercapnia is rare because the alveolar ventilation is maintained by the contralateral lung.
- Decreased chest excursion on the affected side.
- Diminished breath sounds.
- Subcutaneous emphysema may be present.
- Hyperresonance on percussion.

ETIOLOGY

- In primary SP, rupture of small blebs, usually located near the apex of the upper lobes, is a common cause. The check-valve mechanism is uncommon in this case; therefore, tension pneumothorax rarely occurs.
- In secondary SP, chronic obstructive pulmonary disease is the most common cause, but it can also be associated with pneumonia, bronchogenic carcinoma, mesothelioma, sarcoidosis, tuberculosis, cystic fibrosis, and many other lung diseases (Fig. P1-49).

DIAGNOSIS

Established by the chest x-ray (Fig. P1-50).

DIFFERENTIAL DIAGNOSIS

- Pleurisy.
- Pulmonary embolism.
- Myocardial infarction.
- Pericarditis.
- Asthma.
- Pneumonia.

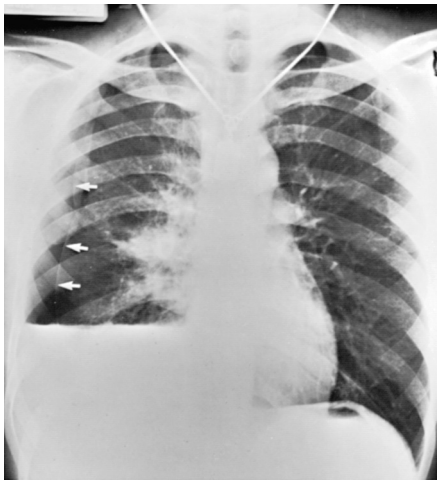


FIGURE P1-50 Chest radiograph shows right hydropneumothorax. Horizontal line in lower right hemithorax is interface between air and liquid in pleural space. *Arrows* point to visceral pleura above level of effusion. There is air in pleural space between visceral pleura and chest wall. (From Weinberg SE et al: *Principles of pulmonary medicine,* ed 5, Philadelphia, 2008, Saunders.)

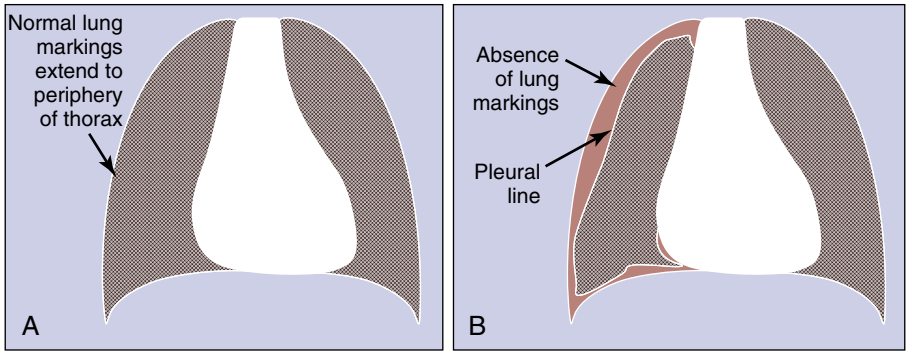


FIGURE P1-49 Pneumothorax. A, Schematic of normal lung. **B,** Schematic of pneumothorax. Pneumothoraces can range in size from tiny to massive. Because of the variability in their size and location, pneumothoraces can be difficult to detect on chest x-ray. For example, a pneumothorax that is anterior or posterior rather than lateral may be hidden on frontal chest x-ray, particularly one taken in the supine position. An upright chest x-ray should be obtained if possible. An expiratory film is thought to be more sensitive, because the lung and thorax decrease in size during expiration, but air trapped in the pleural space remains the same size and thus appears relatively larger. Subtle pneumothoraces may not be visible on chest x-ray. In some cases, subcutaneous air may be the only visible clue to underlying lung injury. CT is extremely sensitive for pneumothorax, although controversy remains over the proper management of pneumothoraces seen only on CT. Ultrasound is also thought to be more sensitive than chest x-ray for detection of pneumothorax, although, again, the management of pneumothorax seen only on ultrasound is uncertain because this is a relatively newly described method of detection. The chest x-ray findings of pneumothorax include a lack of the normal lung markings, which should be visible to the periphery of the chest wall. Sometimes a line marking the boundary of the lung and visceral pleura is visible, although this can be confused with ribs and with the medial margin of the scapula. Depending on the degree of pneumothorax and lung collapse, the lung parenchyma may appear denser than the opposite side. In extreme cases of tension pneumothorax, the pressure exerted by the air in the pleural space may begin to displace other structures, including the diaphragm and mediastinum. In tension pneumothorax, the hyperinflated hemithorax may also have abnormally positioned ribs, with a position more horizontal than usual. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

WORKUP

Includes CXR and, in some inconclusive cases, CT scan of the chest.

LABORATORY TESTS

Arterial blood gases may show hypoxemia and hypocapnia as a result of hyperventilation.

IMAGING STUDIES

- SP is usually confirmed by upright CXR:
  1. A white visceral pleural line. The absence of vessel markings peripheral to this line helps differentiate from mimicking conditions such as an overlying skin fold. A lateral width of 1 cm corresponds to 10% pneumothorax.
  2. The left lateral decubitus position is the most sensitive and the supine position the least sensitive. Inspiratory and expiratory films have equal sensitivities.
  3. As little as 50 ml of air can be detected on upright film.
- Tension pneumothorax (Fig. P1-51) is a medical emergency and should be suspected when the patient is hemodynamically unstable or with contralateral tracheal and mediastinal deviation and ipsilateral flattening or inversion of the diaphragm on the CXR (Fig. EP1-52).
- CT scan can be done in suspected but difficult-to-visualize pneumothoraces, to differentiate from large subpleural bullae or to evaluate for underlying lung pathology, especially in patients with secondary pneumothorax.

Rx TREATMENT

INITIAL MANAGEMENT

- 100% oxygen administration reduces the partial pressure of nitrogen in pleural capillaries, consequently quadrupling the rate of pneumothorax absorption, and should be administered to all patients with pneumothorax.
- Further treatment is based on the size of the pneumothorax.
  1. If the pneumothorax is small (<3 cm between lung and chest wall on CXR), the patient can be treated with observation alone. Repeat imaging should be performed to ensure stability/resorption of the pneumothorax.
  2. If the pneumothorax is >3 cm, or if the patient is symptomatic with chest pain and dyspnea, initial management should focus on removing air from the pleural space. Needle aspiration is the treatment of choice in the clinically stable patient.
- Needle aspiration can be done at the bedside using a large-bore angiocatheter needle or commercially available needle thoracotomy kit. The needle is introduced in the second intercostal space midclavicular line. The catheter is left in place and attached to a three-way stopcock and a large syringe. Air is aspirated until resistance is met or the patient experiences significant coughing. Repeat CXR is done immediately after aspiration and again in 4 to 24 hr to document reexpansion of the lung. If the pneumothorax fails to resolve with aspiration, a chest tube should be placed.
- If there is improvement but not complete resolution of pneumothorax after the aspiration, the catheter can be attached to a Heimlich (one-way) valve to allow further lung expansion. Some stable patients can be discharged home with this device in place if close follow-up monitoring can be obtained. An alternative approach is to perform an autologous blood patch. This involves withdrawal of peripheral blood and infusion into the pleural space through a chest tube.
- Chest tube insertion has been recommended for patients with primary SP who do not respond to simple aspiration and for all patients with secondary SP, recurrent pneumothorax, or tension pneumothorax. Most patients can be managed with small chest tubes (<22 Fr). The chest tube can be connected to a water seal device, with or without suction, and left in position until the pneumothorax has resolved.
- An algorithmic approach to the treatment of primary spontaneous pneumothorax is outlined in Fig. P1-53.

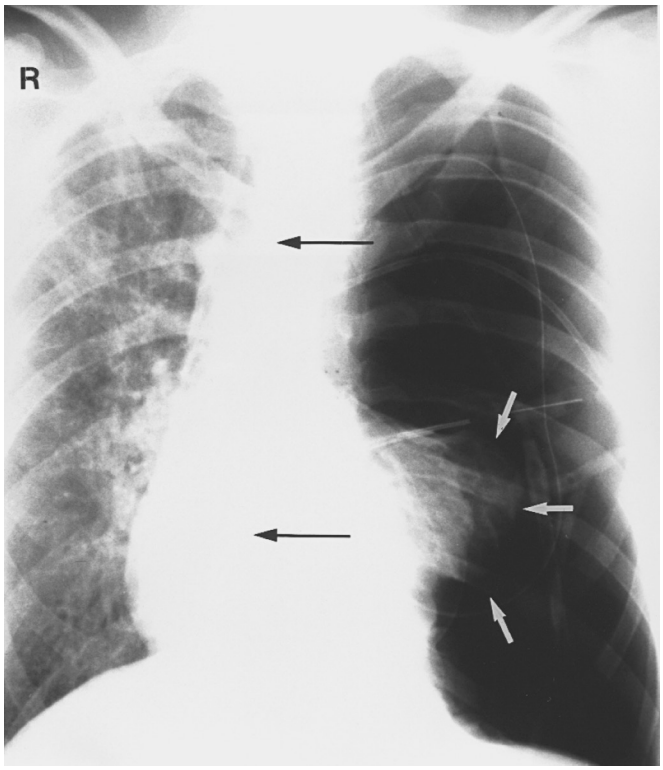


FIGURE P1-51 Tension pneumothorax. On this PA chest radiograph, the left hemithorax is very dark or lucent because the left lung has collapsed completely *(white arrows).* The tension pneumothorax can be identified by the fact that the mediastinal contents, including the heart, are shifted toward the right *(black arrows),* and the left hemidiaphragm is flattened and depressed. (From Mettler FA et al: *Primary care radiology,* Philadelphia, 2000, Elsevier.)

PREVENTION

- Approximately 25% to 50% of patients with primary SP with have a recurrence within 1 yr.
- Multiple techniques have been used to prevent recurrence, including intrapleural instillation of sclerosing agents, pleurectomy, laser abrasion of parietal pleura, and pleural abrasion with dry gauze.
- The current recommended approach is the use of video-assisted thoracoscopy (VATS) with an aim to excise the associated bullae or perform guided pleurodesis or treatment. Most pulmonologists recommend definitive management after the first recurrence. However, high-risk occupations such as divers or pilots should be considered for surgery after their first pneumothorax. Similarly, complex conditions such as patients with persistent bronchopleural fistula suggested by a persistent air leak from the chest tube should also be considered for VATS and early surgical intervention. The overall recurrence rate is estimated at <5% after VATS.
- The recurrence rates for the instillation of sclerosing agents (minocycline 5 mg/kg in 50 ml of normal saline or doxycycline 500 mg in 50 ml of normal saline) are higher than for VATS-guided therapy (<25%). Therefore this mode of therapy should be reserved for patients who are poor surgical candidates.
- Talc has also been used as a sclerosing agent with favorable results; however, concerns persist due to case reports describing acute

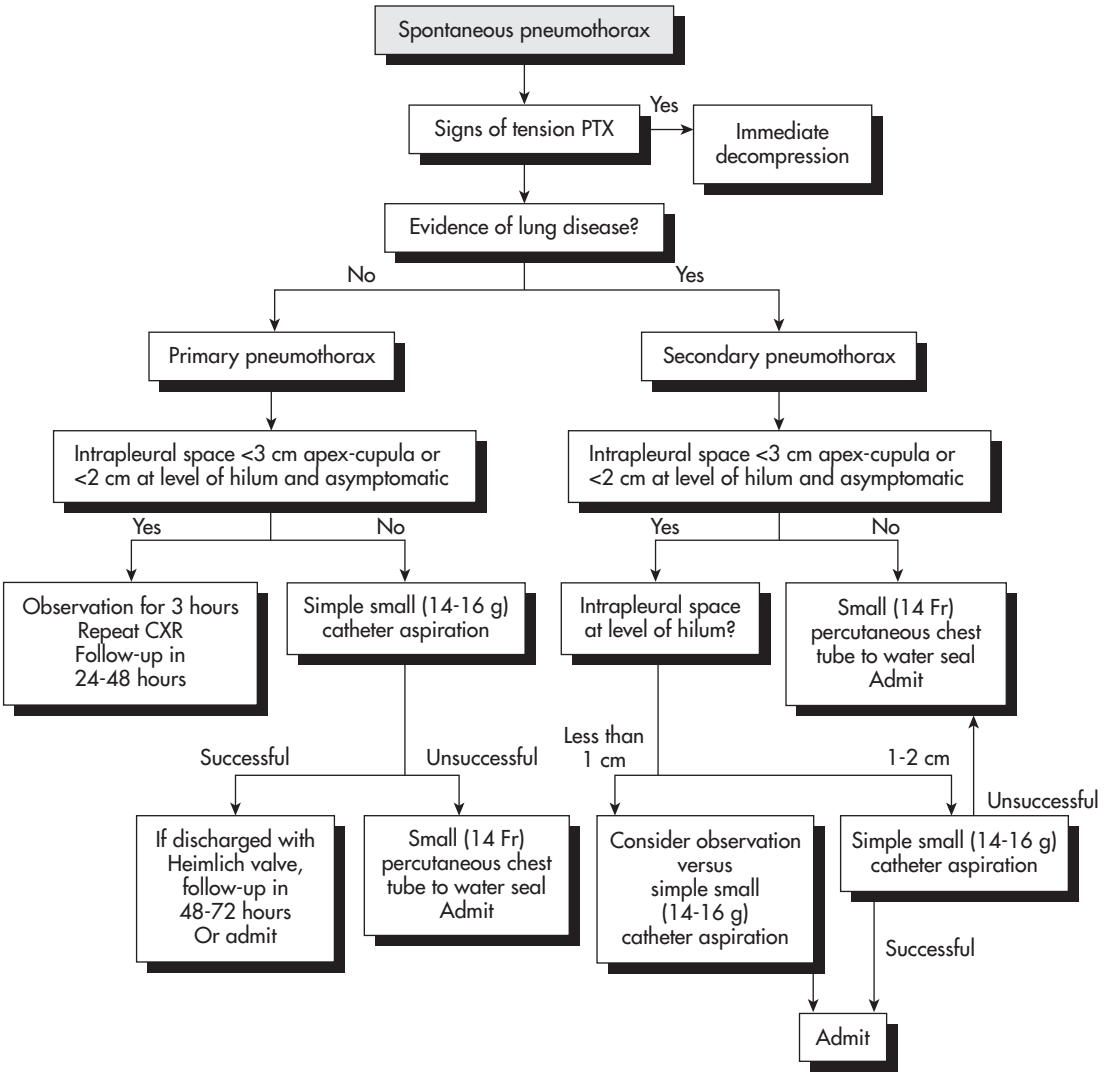


FIGURE P1-53 Algorithmic approach to the treatment of primary spontaneous pneumothorax. *CXR*, Chest radiograph. (From Adams JG et al: *Emergency medicine: clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

respiratory distress syndrome and pleural calcification occurring after use.
- Open thoracotomy is performed in patients who do not respond to VATS or when VATS is not available.

DISPOSITION

- Smoking cessation should be advised.
- Death from primary SP is uncommon. In patients with secondary SP and chronic obstructive pulmonary disease, mortality rates range from 1% to 16%.

REFERRAL

A pulmonary specialist and surgical consultation are recommended.

PEARLS & CONSIDERATIONS

- The rate of pleural air absorption is approximately 1.25% of the volume of the hemithorax per day. Therefore the interval for complete resolution of pneumothorax with observation can be estimated.
- Catamenial pneumothorax is a rare condition characterized by recurrent SP coinciding with the onset of menses. It usually affects the right lung and is believed to be caused by endometriosis with involvement of the diaphragm and/or pleura. It is believed to be hormonally related, and treatment is aimed at endometrial suppression.

COMMENTS

- Patients with AIDS and *Pneumocystis carinii* infection have a high incidence of SP. Treatment typically requires chest tube placement and either thoracoscopy or open thoracotomy.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pneumothorax (Patient Information)

AUTHORS: **JOHANNES STEINER, M.D.,** and **RICHARD REGNANTE, M.D.**

SUGGESTED READINGS

Baumann MH et al.: Management of spontaneous pneumothorax: an American College of Chest Physicians Delphi consensus statement, *Chest* 119(2):590, 2001.

Baumann MH et al.: Pneumothorax, *Respirology* 9(2):137, 2004.

Biffl WL, Narayanan V, Gaudiani JL, Mehler PS: The management of pneumothorax in patients with anorexia nervosa: A case report and review of the literature, *Patient Saf Surg* 4:1, 2010.

Chen F et al.: Position of a chest tube at video-assisted thoracoscopic surgery for spontaneous pneumothorax, *Respiration* 73(3):329, 2006.

Deavanand A et al.: Simple aspiration versus chest tube insertion in the management of primary spontaneous pneumothorax: a systematic review, *Respir Med* 98(7):579, 2004.

Morimoto T et al.: Effects of timing of thoracoscopic surgery for primary spontaneous pneumothorax on prognosis and cost, *Am J Surg* 187(6):767, 2004.

Morse JL, Sadafer B: Acute tension pneumothorax and tension penumoperitoneum in a patient with anorexia nervosa, *J Emerg Med* 38:e13, 2010.

Noppen M et al.: Music: a new cause of primary spontaneous pneumothorax, *Thorax* 59(8):722, 2004.

Sahn SA, Heffner JE: Spontaneous pneumothorax, *N Engl J Med* 342:868, 2000.

Wakai A: Spontaneous pneumothorax, *Clin Evid* 13:2005, 1884.

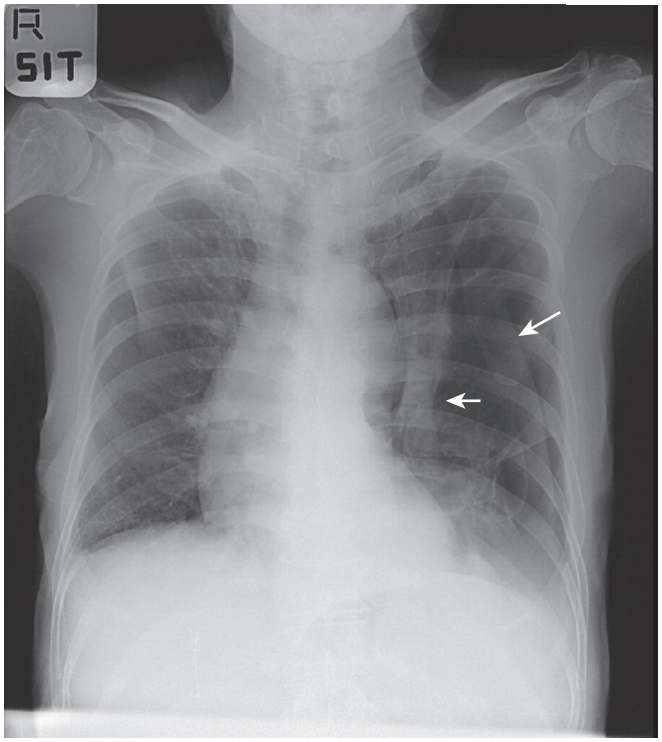


FIGURE EP1-52 Chest radiograph showing left pneumothorax with shift of the mediastinum and trachea to the right side (*white arrows*). The left lung is not completely collapsed, suggesting the presence of a loculated tension pneumothorax. (From Siu Wa Chan, S: Tension pneumothorax managed without immediate needle decompression, *Am J Emerg Med* 36(3):242-245, 2009.

Poison Ivy Dermatitis PTG

BASIC INFORMATION

DEFINITION

Poison ivy dermatitis is a contact dermatitis caused by exposure to urushiol, the oil of plants of the genus *Toxicodendron,* which includes poison ivy, poison oak, and poison sumac.

SYNONYMS

Rhus dermatitis
Toxicodendron dermatitis

ICD-9CM CODES
692.6 Dermatitis due to plant
ICD-10CM CODES
L23.7 Allergic contact dermatitis due to plants, except food

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Affects 10 million to 40 million Americans annually.
PEAK INCIDENCE: More frequent in months when outdoor activity is more common.
PREVALENCE: From 50% to 75% of the adult population is clinically sensitive to these plants. Sensitivity rates are lower in urban areas. (Tolerance is found in 10% to 15% of the population.)
PREDOMINANT SEX AND AGE: Sensitization occurs most commonly between ages 8 and 14 yr. Sensitivity wanes with age, especially with limited exposure and prior mild reactions.
GENETICS: There is believed to be a genetic susceptibility to sensitivity; however, the rash occurs in all ethnicities and skin types.
RISK FACTORS: Firefighters, forestry workers, farmers, and outdoor workers in general as well as those who participate in outdoor recreation. These plants are indigenous to the United States, Canada, and Mexico, and cases are most common in these areas.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients typically present with intense pruritus and rash. The patient may not be aware of exposure to the plant.
- Symptoms typically peak from 1 to 14 days after exposure depending on the degree of exposure and thickness of affected skin.
- Dermatitis may initially present as erythema and may develop into papules, vesicles, and bullae.
- Lesions may be found in the classic linear configuration, typically in exposed areas likely to have been in contact with plants (Fig. EP1-54). Atypical appearance or location of dermatitis is more common with secondary exposure, such as through pets or infected tools or clothing.
- Face and genital involvement may present with significant edema.
- Inhalation of urushiol aerosolized by fire can cause significant respiratory tract inflammation. This can be a particular occupational hazard of forest firefighters.
- Postinflammatory hyperpigmentation may occur, more commonly in dark skin types. This usually resolves with treatment.

ETIOLOGY

- Initial contact with oil of plants in this genus, which is released with damage to plant parts, causes a classic T-lymphocyte–mediated delayed-type allergic reaction.
- Subsequent exposures cause a cell-mediated cytotoxic immune response.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Allergic contact dermatitis from other plants or nonplant substances.
- Irritant contact dermatitis.
- Nummular dermatitis.
- Arthropod reactions, including scabies and bedbug bites.

WORKUP

Typically not needed. Diagnosis is based on characteristic rash and possibly history of exposure.

TREATMENT

Prevention is the most effective treatment.

NONPHARMACOLOGIC THERAPY

- After known exposure, patients should remove contaminated clothing and wash the skin gently with soap and water. Washing after appearance of dermatitis does not prevent further lesions.
- Calamine lotion, cool compresses, baking soda, or colloidal oatmeal baths may provide symptomatic relief.
- Keep nails short and clean to help prevent secondary bacterial infection.
- Exposed clothing, as well as tools, pets, and equipment, should be washed with soap and water to prevent secondary exposure.

ACUTE GENERAL Rx

- Topical steroids generally should be avoided. They may be effective in mild, early cases with erythema and pruritus but no vesiculation.
- Topical antibiotics should be avoided.
- Use of antihistamines for associated pruritus may be effective, but this has not been extensively studied.
- Systemic corticosteroids offer significant relief in moderate to severe *Rhus* dermatitis, including generalized rash or severe facial or genital involvement.
- Effective dosing of oral prednisone is 1 mg/kg/day over 7 to 10 days (maximum 60 mg initial dose), with tapering over an additional 7 to 10 days.
- Inadequate doses or too-rapid tapering of systemic steroids may cause symptom rebound.
- IM treatment with long-acting triamcinolone suspension may be considered for patients intolerant of oral therapy.

CHRONIC Rx

- Recurrence may be caused by repeated exposure to fomites, including contaminated clothing, equipment, or pets.
- Secondary bacterial infection of the skin is the most common complication of *Rhus* dermatitis. Staph and strep are the most common pathogens, but MRSA must be considered.

DISPOSITION

Untreated *Rhus* dermatitis will resolve in 1 to 3 weeks.

REFERRAL

Refer to dermatology if there is diagnostic confusion.

PEARLS & CONSIDERATIONS

PREVENTION

- Patients should be educated regarding identification and avoidance as well as washing to remove the oil after known exposure.
- Total avoidance of the plants may not be practical.
- The use of barrier creams applied before exposure to prevent dermatitis may be of some benefit, particularly in potential occupational (therefore predictable) exposure.
- Products available for postexposure prophylaxis are effective; however, equal efficacy may be obtained from less expensive liquid dishwashing soap.
- Desensitization has not been found to be effective.

PATIENT & FAMILY EDUCATION

- "Leaves of three, let it be," is a helpful reminder for patients.
- Patient education material, including access to photographs of the leaves of these plants in a variety of seasons and conditions, may be useful.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Poison Ivy (Patient Information)
Contact Dermatitis (Related Key Topic)

AUTHOR: **MARGARET TRYFOROS, M.D.**

SUGGESTED READINGS

Gladman AC: Toxicodendron dermatitis: poison ivy, oak, and sumac, *Wilderness Environ Med* 17(2):120, 2006.

McGovern TW et al.: Is it, or isn't it? Poison ivy look-a-likes, *Am J Contact Dermat* 11(2):104, 2000.

FIGURE EP1-54 Allergic contact dermatitis to *Rhus*. A, The classic appearance of allergic contact dermatitis is illustrated in this patient, who came into contact with poison oak. The lesions are linear but not following Blaschko lines. The eruption is microvesicular and extremely pruritic. **B,** *Rhus* dermatitis. Linear bullae are characteristic of an allergic contact dermatitis. (Courtesy O. Dale Collins III. From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

BASIC INFORMATION

DEFINITION

Poliomyelitis is a symptomatic infection caused by poliovirus, which is transmitted by fecal-oral route, and which (on rare occasions) may result in paralysis.

SYNONYMS

Polio
Infantile paralysis

ICD-9CM CODES
045.9 Poliomyelitis
ICD-10CM CODES
A80.9 Acute poliomyelitis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.)

- All cases in the United States and Western Hemisphere are now vaccine associated (because of use of the live-attenuated oral polio vaccine [OPV]).
- Before 1997, there were 6 to 10 cases a year in the United States caused by OPV. Since 2000, only inactivated polio vaccine (IPV) has been used in the United States.

PREDOMINANT AGE: Almost always infants or young children.

GENETICS

NEONATAL INFECTION: Most cases occur in otherwise healthy infants who receive OPV, or their contacts.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Exposure of a nonimmune host to poliovirus usually results in asymptomatic infection.
- A small percentage of individuals may have one of three presentations after an incubation period of 7 to 14 days:
  1. Abortive poliomyelitis: a flulike illness.
     a. Fever.
     b. Malaise.
     c. Headache.
     d. Sore throat.
  2. Nonparalytic poliomyelitis: an aseptic meningitis that correlates with invasion of the CNS.
     a. Headache.
     b. Neck stiffness.
     c. Change in mental status.
  3. Paralytic poliomyelitis.
     a. Most commonly affects the lumbar or bulbar regions.
     b. Following paralysis, a period of variable degrees of recovery, the majority of which occurs in 2 to 6 mo.
     c. Paralysis from involvement of motor neurons in the spinal cord.
     d. Flaccid paralysis without sensory defects.
     e. Postpolio syndrome late sequelae, which may occur many years after the acute illness.
     f. Functional deterioration of muscle groups that had recovered from initial paralysis thought to result from failure of reinnervation, which initially was able to restore function to weakened or paralyzed areas.

ETIOLOGY

- Virus of genus *Enterovirus* (3 serotypes of polio virus [types 1 to 3]).
- Classic endemic and epidemic disease caused by wild-type poliovirus.
- Due to vaccination efforts, there have been no endemic polio cases in the Western Hemisphere since 1991. Only 650 cases occurred worldwide in 2011 with outbreaks of polio recently in Tajikistan, Russia, Kazakhstan, and Congo.
- All cases in the United States currently caused by a live, attenuated virus in the OPV.
  1. Extremely rare complication that occurs in vaccine recipients or their contacts.
  2. Paralysis from lower motor neuron damage caused by viral infection.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Guillain-Barré syndrome.
- CVA.
- Botulism food poisoning.
- Spinal cord compression.
- West Nile virus.
- Other nonpolio enteroviruses (such as enterovirus 71):
  1. Aseptic meningitis.
  2. Paralysis (rare).

WORKUP

- Isolation of virus:
  1. Stool or a rectal swab.
  2. Throat swabs.
  3. Rarely CSF.
- Paired sera for antibody titer determinations for each of the three serotypes, but serologic tests cannot distinguish between wild-type virus and vaccine-virus infection.

LABORATORY TESTS

CSF:

- Aseptic meningitis.
- Elevated WBCs.
- Elevated protein.
- Normal glucose.

IMAGING STUDIES

MRI may show involvement of anterior horn of the spinal cord.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Maintenance of respiration and hydration.
- Early mobilization and exercise once fever subsides.

ACUTE GENERAL Rx

- Aimed at reduction of pain and muscle spasm.
- No agent to alter the course of disease.

CHRONIC Rx

Physical therapy.

DISPOSITION

- In the abortive and nonparalytic forms, complete recovery.
- Paralytic disease:
  1. Variable degrees of recovery.
  2. 80% usually in the first 6 mo following illness.

REFERRAL

Always refer to an infectious disease consultant. Cases should be reported to public health agencies.

PEARLS & CONSIDERATIONS

COMMENTS

- Risk of disease in recipients of OPV is approximately 1 in 2.5 million.
- Use of IPV is not associated with disease:
  1. Does not confer local (mucosal) immunity.
  2. Will not immunize nonvaccinated contacts.
  3. Requires boosters.
  4. Is given by injection.
- To decrease the incidence of vaccine-associated polio, the routine childhood vaccination schedule in the U.S. was changed to immunization with 4 doses of inactivated poliovirus vaccine at 2, 4, and 6 mo through 18 mo and 4 through 6 yr of age. Exclusive use of IPV is now recommended. OPV use is limited to unvaccinated persons with plans for imminent (<4 wk) travel to polio-endemic areas.
- Postpolio syndrome (PPS): consists of new or progressive muscle weakness and disability of unclear etiology decades after development of acute poliomyelitis:

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Alexander LN et al.: Vaccine policy changes and epidemiology of poliomyelitis in the United States, *JAMA* 292(14):1696, 2004.

American Academy of Pediatrics Committee on Infectious Diseases, *Poliovirus. Pediatrics* 128(4):805, 2011.

Howard RS: Poliomyelitis and the postpolio syndrome, *BMJ* 330(7503):1314, 2005.

Senior K et al.: Polio eradication within our grasp? *Lancet Infect Dis* 8(10): 591–592, 2008.

Wiysonge CS et al.: Eradication of poliomyelitis, *Lancet* 366(9492):1163, 2005.

BASIC INFORMATION

DEFINITION

Polyarteritis nodosa (PAN) is a systemic vasculitic syndrome involving medium-sized to small arteries, characterized histologically by necrotizing inflammation of the arterial media and inflammatory cell infiltration. It is not associated with antineutrophil cytoplasmic antibodies (ANCA).

SYNONYMS

Periarteritis nodosa
PAN
Necrotizing arteritis

ICD-9CM CODES
446.0 Polyarteritis nodosa
ICD-10CM CODES
M30.0 Polyarteritis nodosa

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence is 1/100,000 persons annually.
- Increased incidence in patients with hepatitis B surface antigen or hepatitis C virus.
- Male/female ratio of 2:1.
- Can occur in any age group, more commonly between 40 yr and 60 yr.
- No racial predilection is observed.
- Prevalence is 2 to 33/1,000,000.
- Is also associated with hairy cell leukemia.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Typical presentation is subacute in >90% of cases.
- Nausea, vomiting, headache.
- Testicular pain or tenderness.
- Myalgias, weakness, or leg tenderness in 24% to 80% of cases.
- Neuropathy (mononeuritis multiplex), foot drop.
- Cutaneous manifestations like tender nodules, livedo reticularis, palpable purpura, ulceration of digits.
- Abdominal pain after meals, hematemesis, hematochezia, occasionally with diarrhea and gastrointestinal bleeding in severe cases.
- Asymmetric polyarthritis (tending to involve large joints of lower extremities); true synovitis occurs only in a minority of patients.
- Presence of lung vasculitis suggests other causes.
- Fever (PAN is often a cause of fever of unknown origin) can range from intermittent, low-grade fevers to high fevers with chills.
- Chest pain secondary to ischemic infarcts in the coronary arteries, pericarditis, congestive heart failure, and arrhythmias are seen with cardiac involvement.
- Tachycardia is common and often striking.
- Hypertension secondary to renal ischemia, perirenal hematomas.

ETIOLOGY

- Unknown.
- Hepatitis B virus–associated PAN appears to be an immune complex–mediated disease.
- Hepatitis C and hairy cell leukemia are also associated in some cases.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cryoglobulinemia.
- Systemic lupus erythematosus.
- Infections (e.g., subacute bacterial endocarditis, trichinosis, *Rickettsia*).
- Lymphoma.
- Henoch-Schönlein purpura.
- Wegener granulomatosis.
- Microscopic polyangiitis.
- Kawasaki disease.
- Churg-Strauss syndrome.
- Giant cell arteritis.
- Human immunodeficiency virus.

WORKUP

- Laboratory evaluation, arteriography, and biopsy of small or medium-sized arteries can confirm diagnosis. Clinical manifestations are variable and depend on the arteries involved and the organs affected (e.g., kidney involvement occurs in >80% of cases). Table P1-22 summarizes investigations for patients with suspected PAN.
- The presence of any three of the following 10 items allows the diagnosis of PAN with a sensitivity of 82% and a specificity of 86%:
  1. Weight loss >4 kg.
  2. Livedo reticularis.
  3. Testicular pain or tenderness.
  4. Myalgias, weakness, or leg tenderness.
  5. Neuropathy.
  6. Diastolic blood pressure <90 mm Hg.
  7. Elevated blood urea nitrogen (BUN) or creatinine.
  8. Positive test for hepatitis B virus.
  9. Arteriography revealing small or large aneurysms and focal constrictions between dilated segments.

TABLE P1-22 Investigations for Patients with Suspected Polyarteritis Nodosa (PAN)

Test	Supports Diagnosis of PAN	Supports an Alternative Diagnosis	Comment
Elevated C-reactive protein	+		Supports the presence of systemic inflammation
Elevated sedimentation rate	+		Supports the presence of systemic inflammation
Elevated serum creatinine	+/–	+/–	Raised serum creatinine, typically without hematuria or proteinuria on urinalysis, may indicate renal ischemia or infarction. Significant proteinuria or hematuria (especially red cell casts) would suggest glomerular disease, which is *not* a feature of PAN
Abnormal liver function tests	+		May suggest hepatitis, either from HBV or as a result of ischemic hepatitis from PAN affecting the hepatic arteries
Positive HBV serology	+		Seen in HBV PAN
Anemia	+		Due to chronic inflammation or from gastrointestinal blood loss
Positive ANCA		+	A positive ANCA would suggest an alternative type of vasculitis such as granulomatosis with polyangiitis or MPA
Elevated creatine kinase	+/–	+/–	Normal or mildly elevated, despite any muscle involvement
Blood cultures		+	To exclude endocarditis or other infective mimic of vasculitis
Positive HCV serology and cryoglobulins		+	HCV associated with a skin limited manifestation of PAN, but typically it is associated with a small vessel vasculitis related to cryoglobulinemia
Positive rheumatoid factor and ACPA		+	To rule out rheumatoid arthritis, especially in the context of a patient presenting predominantly with arthritis
Positive ANA and anti-dsDNA		+	In patients with clinical features consistent with SLE or other connective tissue disease
HIV positive		+	

ACPA, Anticitrullinated protein antibody; *ANA,* antinuclear antibody; *ANCA,* antineutrophil cytoplasm antibody; *dsDNA,* double-stranded deoxyribonucleic acid; *ESR,* erythrocyte sedimentation rate; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HIV,* human immunodeficiency virus; *MPA,* microscopic polyangiitis; *SLE,* systemic lupus erythematosus.
From Firestein GS et al: *Kelly's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.

10. Biopsy of small or medium-sized artery containing necrotizing inflammatory infiltrate.

LABORATORY TESTS

- Elevated BUN or creatinine, positive test for hepatitis B virus or hepatitis C.
- Elevated erythrocyte sedimentation rate and C-reactive protein, anemia, elevated platelets, eosinophilia, proteinuria, hematuria.
- Biopsy of small or medium-sized artery of symptomatic sites (muscle, nerve) is >90% specific. Biopsy of the gastrocnemius muscle and sural nerve is commonly performed.
- Circumferential or segmental vessel wall involvement with necrotizing mixed cell inflammation with fibrinoid necrosis is characteristic lesion of active PAN.
- Assays for antinuclear antibody and rheumatoid factor are negative; however, low, nonspecific titers may be detected.
- Serum and urine immunofixation electrophoresis for monoclonal gammopathy and human immunodeficiency virus should also be tested for alternative diagnoses.

IMAGING STUDIES

Arteriography can be done in patients with negative biopsies or if there are no symptomatic sites. Mesenteric angiography will reveal aneurysmal dilation of the renal, mesenteric (Fig. P1-55), or hepatic arteries. Less invasive techniques, such as computed tomography (CT) and MRI angiography, also help evaluate the extent and resolution of the disease.

Nerve conduction studies are useful in patients with neuropathy suggesting PAN, helping to evaluate nerves or muscles to biopsy.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Low-sodium diet in hypertensive patients.

ACUTE GENERAL Rx

- Prednisone 1 to 2 mg/kg/day with higher doses initially, then tapering the doses slowly with overall course of average 9 months or longer.

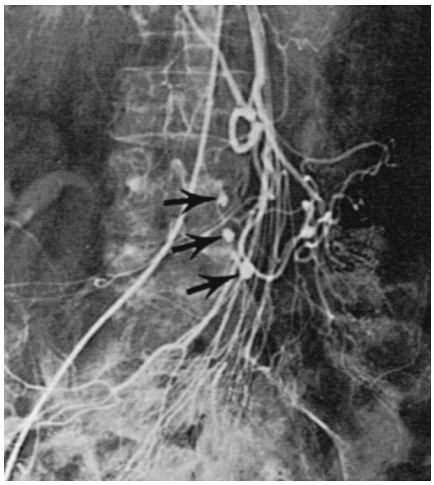


FIGURE P1-55 Superior mesenteric arteriogram in patients with polyarteritis. Several small aneurysms *(arrows)* are present in branches of superior mesenteric artery. (Courtesy Dr. A.W. Stanson. From Harris ED et al: *Kelley's textbook of rheumatology,* ed 7, 2005, Saunders.)

- Patients with isolated cutaneous involvement may be treated with steroids alone or in combination with methotrexate.
- Severe PAN with multiorgan involvement treated with a combination of cyclophosphamide 1.5 to 2 mg/kg per day and glucocorticoids has shown good disease outcomes. Once patient achieves stable remission, transition to a less toxic immunomodulatory therapy such as methotrexate or azathioprine, along with tapering doses of oral prednisone, is indicated for chronic therapy.
- In conditions where the disease is resistant to cyclophosphamide glucocorticoids, pulse steroids for few months then switching to alternate agents such as mycophenolate, azathioprine or methotrexate is tried.
- If hepatitis B is identified, then appropriate antiviral treatment (interferon alpha-2b or lamivudine with or without plasma exchange) is initiated.

CHRONIC Rx

Monitoring for infections and potential complications such as thrombosis, infarction, or organ necrosis. Hypertension in patients with renal involvement in PAN is treated with angiotensin-converting enzyme inhibitor.

DISPOSITION

The 5-yr survival is <20% in untreated patients. Treatment with corticosteroids increases survival to approximately 50%. Use of both corticosteroids and immunosuppressive drugs may increase 5-yr survival to >80%. Poor prognostic signs are severe renal or gastrointestinal involvement. Patients on cyclophosphamide should have regular white cell count monitoring for leukopenia. Cyclophosphamide can cause increased risk of infertility, myelodysplasia, lymphoma, bladder malignancy, and when given in combination of high-dose corticosteroids can predispose patients to infection with *Pneumocystis jiroveci (carinii)* pneumonia. Therefore, close follow-up and PCP prophylaxis are recommended.

REFERRAL

Patients with suspected diagnosis of PAN should be immediately referred to a rheumatologist.

PEARLS & CONSIDERATIONS

- After treatment, patients should be followed up closely for relapse throughout their lifetime.
- Smoking cessation, exercise, and lifestyle modifications should be discussed to decrease vascular complications.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **SYEDA M. SAYEED, M.D.** and **HAROLD A. HALL, M.D.**

SUGGESTED READINGS

Guillevin L et al.: Hepatitis B virus-associated polyarteritis nodosa: clinical characteristics, outcome, and impact of treatment in 115 patients, *Medicine (Baltimore)* 84(5):313, 2005.

Guillevin L et al.: Short-term corticosteroids then lamivudine and plasma exchanges to treat hepatitis B virus-related polyarteritis nodosa, *Arthritis Rheum* 51:482–487, 2004.

Longford CA: Treatment of polyarteritis nodosa, microscopic polyangiitis, and Churg-Strauss syndrome: where do we stand? *Arthritis Rheum* 44:508–512, 2001.

Ribi C et al.: Treatment of polyarteritis nodosa and microscopic polyangiitis without poor-prognosis factors: a prospective randomized study of one hundred twenty-four patients, *Arthritis Rheum* 62(4):1186, 2010.

Stone JH: Polyarteritis nodosa, *JAMA* 288:1632, 2002.

BASIC INFORMATION

DEFINITION

Polycystic kidney disease (PKD) refers to a systemic hereditary disorder characterized by the formation of cysts in the cortex and medulla of both kidneys (Figs. P1-56 and P1-57).

SYNONYMS

Autosomal-dominant polycystic kidney disease (ADPKD)

ICD-9CM CODES
753.1 Polycystic kidney, unspecified type
753.13 Polycystic kidney, autosomal dominant
ICD-10CM CODES
Q61.3 Polycystic kidney, unspecified
Q61.2 Polycystic kidney, adult type

EPIDEMIOLOGY & DEMOGRAPHICS

- Most common inherited cause of kidney disease. Prevalence is 1:400 to 1:1000 live births in the United States.
- Affects all racial groups worldwide.
- Results in kidney failure in the majority of individuals by the fifth to sixth decade.
- ADPKD occurs in one in 1000 persons.
- Usually presents in the third to fourth decades of life and generally leads to end-stage renal disease (ESRD) in the sixth or seventh decade of life.
- ADPKD comprises 5% of the ESRD population in the United States.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Characterized by focal development of renal and extrarenal cysts in an age-dependent manner, resulting in a slow, gradual, and massive kidney enlargement.

Symptoms:

- Pain (60%): acute pain can be associated with renal hemorrhage, passage of stones (20% of patients; usually uric acid or calcium oxalate), and urinary tract infections.
- Palpable flank mass.
- Hypertension: >60% of patients; usually develops before the loss of renal function. Hypertension in ADPKD is associated with increased total kidney volume, activation of the renin-angiotensin-aldosterone system, and progression of kidney disease.
- Headache.
- Nocturia, hematuria.

Renal manifestations:

- Kidney and cyst volumes and renal blood flow (or vascular resistance) are the strongest predictors of renal function decline. Kidney function does not decline in individuals with PKD until kidney size is at least five times greater than normal.
- Morphometric analysis of sequential CT was shown to be sufficiently accurate to monitor rates of renal enlargement in PKD, and MRI-based methods have been developed. Two general groups of kidney volume increase: those with rapid rates (>5% increase in total kidney volume per year) and those with rates of progression <5% per year. Intervals between measurements as short as 6 mo may be adequate to determine an effect of treatment that reduces the rates of volume progression >50% in those with rapidly progressive disease.
- All cysts develop from preexisting renal tubule segments, and only a small portion of the nephrons (1%) undergoes cystic formation.
- Renal failure: in most patients renal function is maintained within normal range, despite relentless growth of cysts, until the fourth to sixth decades of life.
- Nephrolithiasis (20%).
- Urinary tract infection.

Extrarenal manifestations:

- Associated with liver cysts (50% to 70%), pancreatic cysts (10%), splenic cysts (5%), central nervous system arachnoid cysts (5%), and cerebral aneurysms (20%).
- Polycystic liver disease: most common extrarenal manifestation—associated with both PKD1 and non-PKD1 genotypes.
- Vascular manifestations: intracranial aneurysms (occur in approximately 6% of patients with a negative family history of aneurysms and 16% of those with a positive history), thoracic aortic and cervicocephalic artery dissection, and coronary artery aneurysms.
- Increased incidence of diverticular disease and mitral valve prolapse.

ETIOLOGY

- Dominantly inherited heterogenic systemic disease: mutations in *PKD1* (chromosome region 16p13.3; 85% of cases) or *PKD2* (4q21; approximately 15% of cases).
- Polycystin 1 and polycystin 2 are the protein products of PKD1 and PKD2, which interact and coassemble and seem to function together to regulate the morphologic configuration of epithelial cells. Although individuals with PKD1 are clinically indistinguishable from individuals with PKD2, patients with PKD2 have a less severe course of disease with a later mean age of diagnosis, hypertension, and end-stage renal disease (ESRD).
- Disease penetrance is 100%.

DIAGNOSIS

Sonographic imaging or CT scan:

1. In an individual with a family history for the disease, including:
   - Age <30 yr: at least two unilateral or bilateral cysts.
   - 30 to 59 yr: two cysts in each kidney.
   - ≥60 yr: four cysts in each kidney.
2. In the absence of a family history: bilateral renal enlargement or cysts or the presence of multiple bilateral cysts with hepatic cysts together and in the absence of other manifestations suggesting a different renal cyst disease.
   - Genetic testing can be used when the imaging results are equivocal and when a definitive diagnosis is required in a

FIGURE P1-56 Tomogram of autosomal-dominant polycystic kidney disease. Kidney cysts. (From Stein JH [ed]: *Internal medicine*, ed 5, St Louis, 1998, Mosby.)

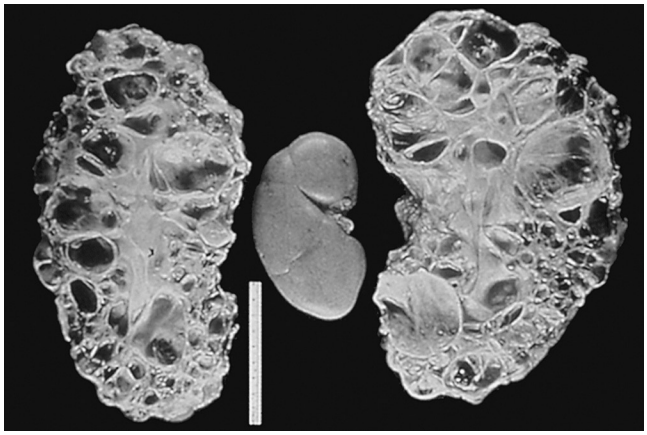


FIGURE P1-57 Markedly enlarged polycystic kidneys from a patient with autosomal-dominant polycystic kidney disease compared with a normal kidney *(middle)*. (From Johnson RJ, Feehally J: *Comprehensive clinical nephrology*, ed 2, St Louis, 2000, Mosby.)

younger individual, such as a potential living related kidney donor.

DIFFERENTIAL DIAGNOSIS

- Simple cysts.
- Autosomal-recessive PKD in children.
- Tuberous sclerosis.
- von Hippel-Lindau syndrome.
- Acquired cystic kidney disease.

LABORATORY TESTS

- Hemoglobin and hematocrit are elevated because of increased secretion of erythropoietin from functioning renal cysts.
- Electrolyte abnormalities commonly seen in any patients with renal insufficiency.
- Blood urea nitrogen and creatinine can be elevated.
- Urinalysis can show microscopic hematuria and proteinuria (seldom >1 g/24 hr). Proteinuria >2 g/day is unusual and suggests the presence of another kidney disease.

IMAGING STUDIES

- A cyst is considered to be present if it measures >2 mm in diameter.
- Abdominal renal ultrasound is the easiest and most cost-efficient test for renal cysts. Renal ultrasound can detect cysts from 1 to 1.5 cm.
- Abdominal CT scan is more sensitive than ultrasound and can detect cysts as small as 0.5 cm.
- Both studies can detect associated hepatic, splenic, and pancreatic cysts.
- MRI is more sensitive than ultrasound and may help distinguish renal cell carcinomas from simple cysts.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Treatment consists of the standard therapies for chronic renal disease, including good blood pressure control and control of hyperlipidemia.
- When conservative measures fail to control the pain, infection, or bleeding, surgical interventions such as cystic decompression by aspiration under ultrasound or CT guidance or laparoscopic or surgical cyst fenestration through lumbotomy or flank incision may be of benefit.
- When above measures fail, nephrectomy should be undertaken in ESRD.
- Combined percutaneous cyst drainage and antibiotic treatment provide the best treatment results for hepatic cyst infection.

ACUTE GENERAL Rx

- Kidney infections should be treated with antibiotics known to penetrate the cyst (fluoroquinolones are good agents because of their lipophilic properties and bactericidal action against gram-negative pathogens).
- Early detection and treatment of hypertension are important because cardiovascular disease is the main cause of death.

CHRONIC Rx

- Treatment of hypertension: as compared with standard blood pressure control, rigorous blood pressure control is associated with a slower increase in total kidney volume, no overall change in the estimated GFR, a greater decline in left ventricular mass index, and greater reduction in urinary albumin excretion.[1]
- Dialysis for end-stage renal failure.
- Pretransplant nephrectomy is reserved for patients with a history of infected cyst or frequent bleeding.
- Renal transplantation is the treatment of choice for ESRD.
- Cyst infections are often difficult to treat. Lipophilic agents penetrate the cysts consistently. If fever persists after 1 to 2 wk of appropriate antimicrobial treatment, percutaneous or surgical drainage of the cysts may be needed. Several months of antibiotic treatment may be needed to eradicate the infection.
- Most cases of polycystic liver disease do not need treatment; patients should avoid estrogens and compounds that promote cyclic adenosine monophosphate accumulation (e.g., caffeine).

DISPOSITION

- Most patients with PKD will progress to renal failure.
- Gross hematuria is usually self-limited.

REFERRAL

- Nephrology consultation.
- Urology can also be consulted in patients with nephrolithiasis, for recurrent episodes of gross hematuria, or for consideration for nephrectomy before transplantation.
- Counseling should be done before PKD genetic testing. Benefits include certainty of diagnosis that could affect family planning, early detection and treatment of disease complications, and selection of genetically unaffected family members for living related donor transplantation. Potential discrimination in terms of insurability and employment associated with a positive diagnosis should be discussed.

[1]Schrier RW et al.: Blood pressure in early autosomal dominant polycystic kidney disease, *N Engl J Med* 371:2255-2266, 2014.

PEARLS & CONSIDERATIONS

- ESRD patients with PKD do better on dialysis than do patients with other causes of ESRD.
- There is no difference in patient survival after transplantation between patients with PKD and other ESRD populations.
- Widespread screening is not indicated. Indications for screening include family history of aneurysm, subarachnoid hemorrhage, previous aneurysm rupture, preparation for major elective surgery, high-risk occupations (airplane pilots), and patient anxiety despite adequate information.
- Kidney and cyst volumes are the strongest predictors of renal function decline.

COMMENTS

- Conservative management is recommended for patients with a small (<7 mm) cerebral aneurysm, particularly in the anterior circulation. Rescreening of patients with a family history of intracranial aneurysm after 5 to 10 yr seems reasonable.
- Trials have shown reduction of total kidney volume and preservation of renal function with long-acting octreotide (two 20 mg IM injections of octreotide LAR every 28 days) in a 3-year follow-up.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Polycystic Kidney Disease (Patient Information)

AUTHOR: **SHAHNAZ PUNJANI, M.D.**

SUGGESTED READINGS

Caroli A et al.: Effect of long-acting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomized, placebo-controlled, multicenter trial, *Lancet* 382:1485–1495, 2013.

Chapman AB: Autosomal dominant polycystic kidney disease: time for a change? *J Am Soc Nephrol* 18(5):1399, 2007.

Grantham J: Volume progression in autosomal dominant polycystic kidney disease: the major factor determining clinical outcomes, *Clin J Am Soc Nephrol* 1(1):148, 2006.

Pei Y: Diagnostic approach in autosomal dominant polycystic kidney disease, *Clin J Am Soc Nephrol* 1(5):1108, 2006.

Rapoport J: Autosomal dominant polycystic kidney disease: pathophysiology and treatment, *Q J Med* 100: 1, 2007.

Serra AL et al.: Sirolimus and kidney growth in autosomal dominant polycystic kidney disease, *N Engl J Med* 363:820–829, 2010.

Srivastava A, Patel N: Autosomal dominant polycystic kidney disease, *Am Fam Physician* 90(5):303–307, 2014.

Torres VE et al.: Autosomal dominant polycystic kidney disease, *Lancet* 369(9569):1287, 2007.

Torres VE et al.: Tolvaptan in patients with autosomal dominant polycystic disease, *N Engl J Med* 367:2407–2418, 2012.

Walz G et al.: Everolimus in patients with autosomal dominant polycystic kidney disease, *N Engl J Med* 363:830–840, 2010.

BASIC INFORMATION

DEFINITION

Polycystic ovary syndrome (PCOS) is characterized by an accumulation of incompletely developed follicles in the ovaries due to anovulation and associated with ovarian androgen production. In its complete form, it is associated with polycystic ovaries, amenorrhea, hirsutism, and obesity. Criteria for PCOS according to published definitions are described in Table P1-23.

SYNONYMS

Stein-Leventhal syndrome
PCOS

ICD-9CM CODES
256.4 Polycystic ovary syndrome
ICD-10CM CODES
E28.2 Polycystic ovarian syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- 6% to 25% of reproductive-age women (most common endocrine disorder in this population).
- Symptoms usually begin around the time of menarche, and the diagnosis is often made during adolescence or young adulthood.
- Increased risk of endometrial and ovarian cancers.
- PCOS is the most common cause of anovulatory infertility

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Oligomenorrhea or amenorrhea.
- Dysfunctional uterine bleeding.
- Infertility.
- Hirsutism.
- Acne, alopecia, acanthosis nigricans (Fig. P1-58).
- Obesity (40% only), predominantly abdominal obesity.
- Insulin resistance (type 2 diabetes mellitus).
- Hypertension.

ETIOLOGY & PATHOGENESIS

Elevated serum luteinizing hormone (LH) concentrations and an increased serum LH/follicle-stimulating hormone (FSH) ratio result either from an increased gonadotropin-releasing hormone hypothalamic secretion or less likely from a primary pituitary abnormality. This results in dysregulation of androgen secretion and increased intraovarian androgen, the effect of which in the ovary is follicular atresia, maturation arrest, polycystic ovaries, and anovulation. Hyperinsulinemia is a contributing factor to ovarian hyperandrogenism, independent of LH excess. A role for insulin growth factor (IGF) receptors has been postulated for the association of PCOS and diabetes. Fig. EP1-59 illustrates the pathologic mechanisms in PCOS.

DIAGNOSIS

The diagnosis of PCOS excludes secondary causes (androgen-producing neoplasm, hyperprolactinemia, adult-onset congenital adrenal hyperplasia).

Clinical:

- The symptoms, signs, and biochemical features of PCOS vary greatly among women and may change over time.
- PCOS is the most common cause of chronic anovulation with estrogen present. A positive progesterone withdrawal test establishes the presence of estrogen. Medroxyprogesterone (Provera) 10 mg qd is administered for 5 days and bleeding occurs if estrogen is present.
- The presence of oligomenorrhea, hirsutism, obesity, and documented polycystic ovaries establishes the diagnosis.

DIFFERENTIAL DIAGNOSIS

Causes of amenorrhea:

- Primary (unusual in PCOS).
  1. Genetic disorder (Turner's syndrome).
  2. Anatomic abnormality (e.g., imperforate hymen).
- Secondary
  1. Pregnancy.
  2. Functional (cause unknown, anorexia nervosa, stress, excessive exercise, hyperthyroidism, less commonly hypothyroidism, adrenal dysfunction, pituitary dysfunction, severe systemic illness, drugs such as oral contraceptives, estrogens, or dopamine agonists).
  3. 1.3. Abnormalities of the genital tract (uterine tumor, endometrial scarring, ovarian tumor).

LABORATORY TESTS

- Glucose tolerance test at the initial presentation and every 2 yr thereafter (rule out diabetes mellitus). Impaired glucose tolerance is very common, occurring in approximately 30% of women with PCOS.
- Fasting lipid panel (rule out dyslipidemia), alanine aminotransferase, aspartate aminotransferase (rule out hepatic steatosis).
- Elevated LH/FSH ratio >2.5.
- Prolactin level elevation in 25%.
- Elevated androgens (testosterone [free and total levels], DHEA-S) (rule out androgen-secreting tumor).
- Other: thyroid-stimulating hormone (rule out hypothyroidism), 17-hydroxyprogesterone (rule out congenital adrenal hyperplasia), 24-hr urine for cortisol and creatinine (rule out Cushing's syndrome).
- TSH

IMAGING STUDIES

Pelvic ultrasound (Fig. P1-60) (or CT scan) reveals the presence of twofold to fivefold ovarian enlargement with a thickened tunica albuginea, thecal hyperplasia, and 20 or more subcapsular follicles from 1 to 15 mm in diameter (Fig. P1-61). It is important to note that having polycystic ovaries alone does not make the diagnosis of PCOS because 20% of women with polycystic ovaries have no symptoms.

TREATMENT

The goal is to interrupt the self-perpetuating abnormal hormone cycle:

- Reduction of ovarian androgen secretion by laparoscopic ovarian wedge resection. Laparoscopic ovarian surgery (laparoscopic

TABLE P1-23 Criteria for Polycystic Ovary Syndrome According to Published Definitions

	NICHD/NIH/1990	Rotterdam 2003	AE-PCOS/2009
Diagnostic criteria	Requires simultaneous presence of: Clinical and/or biochemical hyperandrogenism Menstrual dysfunction	Requires the presence of at least two criteria: Clinical and/or biochemical hyperandrogenism Ovulatory dysfunction PCOM	Requires the presence of: Hyperandrogenism and/or hyperandrogenemia Ovarian dysfunction: oligoovulation or anovulation and/or polycystic ovaries
Exclusion criteria	Congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome, and hyperprolactinemia	Congenital adrenal hyperplasia, androgen-secreting tumors, and Cushing's syndrome	21-hydroxylase-deficient nonclassic adrenal hyperplasia, androgen-secreting neoplasms, androgenic–anabolic drug use or abuse, the hyperandrogenic-insulin resistance-acanthosis nigricans syndrome, thyroid dysfunction, and hyperprolactinemia
Clinical traits	Hirsutism, acne, and alopecia	Hirsutism, acne, and androgenic alopecia	Hirsutism
PCOM	Not included	At least one ovary showing either: Twelve or more follicles of 2-9 mm in diameter Ovarian volume, 10 ml	At least one ovary showing either: Twelve or more follicles of 2-9 mm in diameter Ovarian volume, 10 ml

AE-PCOS, Androgen Excess and PCOS Society; *NICHD/NIH,* National Institute for Child Health and Human Development/National Institutes of Health; *PCOM,* polycystic ovarian morphology.
From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.

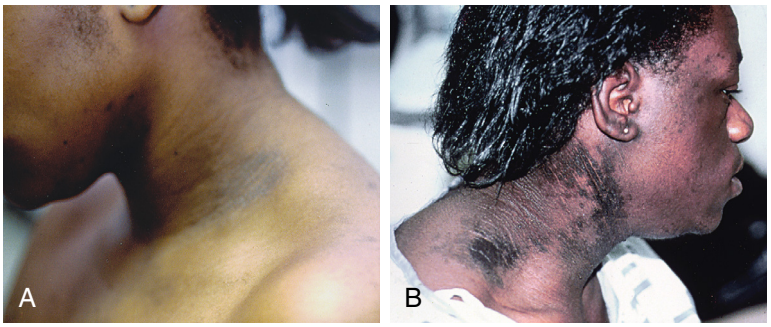


FIGURE P1-58 Acanthosis nigricans. A, Moderate acanthosis nigricans (i.e., darkening and thickening of skin) at the lateral lower fold of the neck. Notice facial hirsutism (sideburns) in the same patient. **B,** Severe acanthosis nigricans in another patient with severe insulin resistance. (**B,** Courtesy of Dr. R. Ann Word, Dallas, Texas. From Melmed S et al: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.)

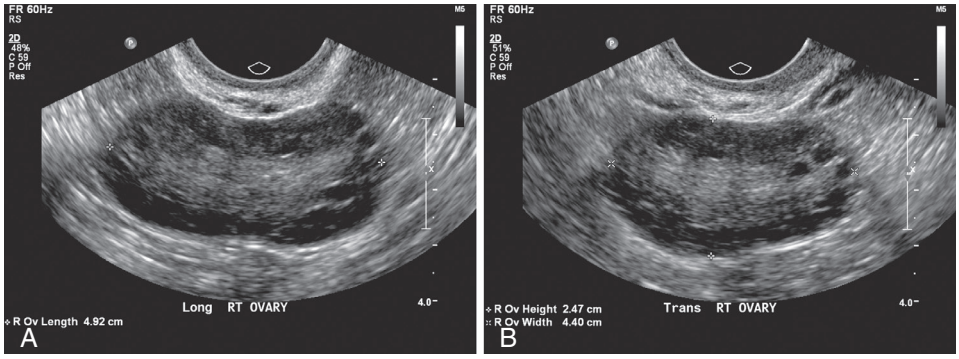


FIGURE P1-60 A, Transvaginal ultrasound in the longitudinal plane showing polycystic ovary morphology. Numerous small follicles surround an echogenic central stroma. **B,** Transvaginal ultrasound in the transverse plane in the same patient. (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.)

ovarian drilling [LOD]) is a useful alternative that does not trigger ovarian hyperstimulation.
- Reduction of ovarian androgen secretion by using oral contraceptives or LH-releasing hormone (LHRH) analogs.
- Weight reduction for all obese women with PCOS. Loss of abdominal fat seems to be crucial to restore ovulation.
- FSH stimulation with clomiphene HMG or pulsatile LHRH.
- Urofollitropin (pure FSH) administration.
- Metformin improves ovulation, insulin sensitivity, and possibly hyperandrogenemia.

Choice of treatment:
- The management of hirsutism without risking pregnancy includes oral contraceptives, glucocorticoids, LHRH analogs, or spironolactone (an antiandrogen). Finasteride and flutamide may be similarly effective in reducing hirsutism as spironolactone.
- Pregnancy can be achieved with clomiphene (alone or with glucocorticoids, human chorionic gonadotropin, or bromocriptine), HMG, urofollitropin, pulsatile LHRH, or ovarian wedge resection. Metformin may also induce ovulation. Recent trials comparing the aromatase inhibitor letrozole to clomiphene for infertility have shown higher live-birth and ovulation among infertile women with PCOS treated with letrozole
- Psychological screening for depression is recommended. Women with PCOS are fourfold more likely to have abnormal depression scores.

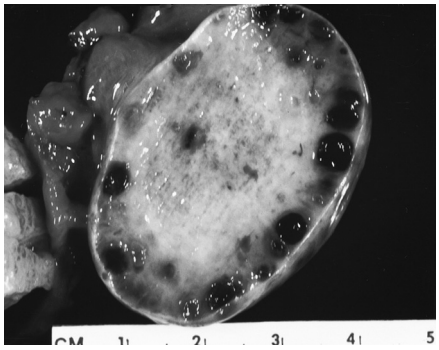


FIGURE P1-61 Sagittal section of a polycystic ovary illustrating large number of follicular cysts and thickened stroma. (From Mishell DR: *Comprehensive gynecology*, ed 3, St Louis, 1997, Mosby.)

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Context:
Polycystic ovary syndrome (PCOS) is a heterogeneous, genetically complex, endocrine disorder of uncertain etiology in women.

Objective:
Our aim was to compare the gene expression profiles in stimulated granulosa cells of PCOS women with and without insulin resistance versus matched controls.

Research Design and Methods:
This study included 12 normal ovulatory women (controls), 12 women with PCOS without evidence for insulin resistance (PCOS non-IR), and 16 women with insulin resistance (PCOS-IR) undergoing in vitro fertilization. Granulosa cell gene expression profiling was accomplished using Affymetrix Human Genome-U133 arrays. Differentially expressed genes were classified according to gene ontology using ingenuity pathway analysis tools. Microarray results for selected genes were confirmed by real-time quantitative PCR.

Results:
A total of 211 genes were differentially expressed in PCOS non-IR and PCOS-IR granulosa cells (fold change ≥1.5; P ≤0.001) versus matched controls. Diabetes mellitus and inflammation genes were significantly increased in PCOS-IR patients. Real-time quantitative PCR confirmed higher expression of NCF2 (2.13-fold), TCF7L2 (1.92-fold), and SERPINA1 (5.35-fold). Increased expression of inflammation genes ITGAX (3.68-fold) and TAB2 (1.86-fold) was confirmed in PCOS non-IR. Different cardiometabolic disease genes were differentially expressed in the two groups. Decreased expression of CAV1 (–3.58-fold) in PCOS non-IR and SPARC (–1.88-fold) in PCOS-IR was confirmed. Differential expression of genes involved in TGF-β signaling (IGF2R, increased; and HAS2, decreased), and oxidative stress (TXNIP, increased) was confirmed in both groups.

Conclusions:
Microarray analysis demonstrated differential expression of genes linked to diabetes mellitus, inflammation, cardiovascular diseases, and infertility in the granulosa cells of PCOS women with and without insulin resistance. Because these dysregulated genes are also involved in oxidative stress, lipid metabolism, and insulin signaling, we hypothesize that these genes may be involved in follicular growth arrest and metabolic disorders associated with the different phenotypes of PCOS. Ⓐ

Abstract[2]

Objective:
The aim was to compare the effects of a traditional therapy (an oral estroprogestagen) to those of a novel treatment (a low-dose combination of generics) in adolescent girls with androgen excess.

Study Design and Methods:
In an open-label trial over 1 yr, 34 adolescents (age, 16 yr; body mass index, 23 kg/m^2) with hyperinsulinemic androgen excess and without pregnancy risk were randomized to receive daily ethinyl estradiol-cyproterone acetate (EE-CA; Diane 35 Diario) or a low-dose combination of pioglitazone 7.5 mg/d, flutamide 62.5 mg/d, and metformin 850 mg/d (PioFluMet). Markers of androgen excess, C-reactive protein, high molecular weight adiponectin, lipids, carotid intima media thickness, body composition (absorptiometry), abdominal fat partitioning (magnetic resonance imaging), and gene expression in longitudinal biopsies of sc adipose tissue at the abdominal level (RT-PCR) were assessed at baseline and after 1 yr.

Results:
EE-CA and low-dose PioFluMet reduced androgen excess comparably, but had divergent effects on C-reactive protein, high molecular weight adiponectin, lipids, carotid intima media thickness, lean mass, abdominal and visceral fat, and on the expression of CD163, leptin, TNF-like weak inducer of apoptosis receptor, and angiopoietin-like protein 4, respectively, related to macrophage activation, fat accretion, inflammation, and lipoprotein metabolism in adipose tissue. All these divergences pointed to a healthier condition on low-dose PioFluMet.

Conclusion:
EE-CA and PioFluMet are similarly effective in reversing androgen excess over 1 yr, but low-dose PioFluMet is superior in reversing inflammatory, metabolic, and cardiovascular anomalies that are often associated with androgen excess. Ⓐ

Abstract[3]

Context:
A previous genome-wide association study in Chinese women with polycystic ovary syndrome (PCOS) identified a region on chromosome 2p16.3 encoding the LH/choriogonadotropin receptor (LHCGR) and FSH receptor (FSHR) genes as a reproducible PCOS susceptibility locus.

Objective:
The objective of the study was to determine the role of the LHCGR and/or FSHR gene in the etiology of PCOS in women of European ancestry.

Design:
This was a genetic association study in a European ancestry cohort of women with PCOS.

Setting:
The study was conducted at an academic medical center.

Participants:
Participants in the study included 905 women with PCOS diagnosed by National Institutes of Health criteria and 956 control women.

Intervention:
We genotyped 94 haplotype-tagging single-nucleotide polymorphisms and two coding single-nucleotide polymorphisms mapping to the coding region of LHCGR and FSHR plus 20 kb upstream and downstream of the genes and test for association in the case control cohort and for association with nine quantitative traits in the women with PCOS.

Results:
We found strong evidence for an association of PCOS with rs7562215 (P =0.0037) an rs10495960 (P =0.0046). Although the marker with the strongest association in the Chinese PCOS genome-wide association study (rs13405728) was not informative in the European populations, we identified and genotyped three markers (rs35960650, rs2956355, and rs7562879) within 5 kb of rs13405728. Of these, rs7562879 was nominally associated with PCOS (P =0.020). The strongest evidence for association mapping to FSHR was observed with rs1922476 (P =0.0053). Furthermore, markers with the FSHR gene region were associated with FSH levels in women with PCOS.

Conclusions:
Fine mapping of the chromosome 2p16.3 Chinese PCOS susceptibility locus in a European ancestry cohort provides evidence for association with two independent loci and PCOS. The gene products LHCGR and FSHR therefore are likely to be important in the etiology of PCOS, regardless of ethnicity. Ⓐ

Abstract[4]

Polycystic Ovary Syndrome

Study Question:
Can we develop an adequate preconception prediction model to identify those women with polycystic ovary syndrome (PCOS) who have an increased risk of developing gestational diabetes mellitus (GDM) during subsequent pregnancy?

Study Answer:
The risk of developing GDM in women with PCOS can be adequately predicted before conception by a prediction model.

What is Known Already:
Women with PCOS are at increased risk of pregnancy complications, especially GDM. GDM has serious short-term and long-term effects on mother and baby.

Study Design, Size, Duration:
This study is a part of a multicentre prospective cohort study, which was conducted between April 2008 and April 2012. A total of 326 women with PCOS were included.

Participants/Materials, Setting, Methods:
Women with PCOS and a wish to conceive were included before conception and followed until 6 weeks after delivery. Maternal, neonatal and

birth complications were reported. A multivariate model was developed to predict the most common pregnancy complication, GDM, by using univariate and multivariate logistic regression of preconception patient characteristics. The area under the curve (AUC) of the receiver-operating characteristic was used to test the performance of the model.

Main Results and the Role of Chance:

A total of 189 women (58%) achieved an ongoing pregnancy (8% multiples) and delivered a live-born neonate. One or two maternal complications occurred in 62 (33%) pregnant women, mainly GDM (n ¼ 41; 22%) and pregnancy-induced hypertension (n = 14; 7%). In children, one or two complications were observed in 49 (26%) of 206 children born, e.g. premature delivery (n = 23; 12%) and small for gestational age (n = 15; 8%). The preconception prediction model for GDM performed well (AUC 0.87, 95% CI 0.81-0.93). First-degree relatives with type 2 diabetes mellitus, serum levels of fasting glucose, fasting insulin, Androstenedione and sex hormone-binding globulin before conception were identified as predictors.

Limitations, Reasons for Cautions:

The prediction model has not yet been externally validated in another group of patients. Also, there were missing data for some of the determinants, which were accounted for by multiple imputation.

Wider Implications of the Findings:

Women with PCOS who achieve a pregnancy have an increased risk of GDM. The prediction model can be used to identify women particularly at risk for GDM who should be monitored closely to enable preventative measures that may reduce the risk of developing GDM and its adverse consequences.

Study Funding/Competing Interest(s):

No external funding was used for the study. M.A.W., S.M.V.V., A.J.G., A.F. and M.P.H.K. have nothing to disclose. C.B.L has received fees and grant support from the following companies (in alphabetic order): Auxogen, European Society of Human Reproduction and Embryology and MSD. J.S.E.L. has received fees and grant support from the following companies (in alphabetic order): Ferring, Gennovum, Merck-Serono, MSD, Organon, Schering Plough, Sharp & Dome and Serono. M.J.C. has received grant support from the following companies (in alphabetic order): Illumina and MSD. B.C.J.M.F. has received fees and grant support from the following companies (in alphabetic order): Ferring, Ova-Science, PregLem SA, Roche and Watson Laboratories.

Trial Registration Number. dNCT00821379 [Clinicaltrials.gov]. Ⓐ

Abstract[5]

Polycystic Ovary Syndrome

Background:

Women with polycystic ovary syndrome (PCOS) have an adverse cardiovascular risk profile and an increased prevalence of nonalcoholic fatty liver disease (NAFLD), which is also associated with an adverse cardiovascular risk profile.

Objective:

To compare the cardiovascular risk profile of women with PCOS alone and women with PCOS and NAFLD.

Design, Setting and Participants:

Twenty-five oligoanovulatory women with PCOS were screened for NAFLD (including liver biopsy if appropriate) and had their cardiovascular risk factors measured which included the inflammatory marker C-reactive protein (CRP), endothelial function {measured using endoPAT 2000 and serum markers [intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), E-selectin and P-selectin]}, clot structure and function [maximum absorbance (MA) and lysis potential (LT)].

Results:

Twelve patients had confirmed PCOS without evidence of NAFLD, and 13 patients had confirmed PCOS with evidence of NAFLD. The PCOS and NAFLD group were heavier (BMI 43.9 ± 2.2 kg.m^2) compared with the PCOS alone group (BMI 37.6 ± 1.4 kg/m^2 P = 0.03). There was no difference in CRP (7.57 ± 0.95 versus 6.59 ± 1.87 mm P = 0.62) or endothelial function (RH-PAT 1.96 ± 0.1 versus 1.74 ± 0.16 P = 0.25), ICAM-1 (221.±.48 versus 250 ± 60 ng/ml P = 0.19), VCAM-1 (2124 ± 78 versus 2314 ± 91 ng/ml P = 0.13), E-selectin (33.9 ± 3.3 versus 39.5 ± 15.5 ng/ml P = 0.31) and P-selectin (101.0 ± 6.6 versus 95.9 ± 10.2 ng/ml P = 0.69). There was no difference in clot formation or lysis.

Conclusion:

The patients with PCOS and NAFLD were heavier compared with patients with PCOS alone. Despite this, we were unable to demonstrate differences in inflammatory markers, endothelial function or clot structure and function, suggesting that severity of steatosis is not the most important determinant of cardiovascular risk in PCOS. Ⓐ

Evidence-Based References

Kaur S et al.: Differential gene expression in granulosa cells from polycystic ovary syndrome patients with and without insulin resistance: identification of susceptibility gene sets through network analysis, *J Clin Endocrinol Metab* 97:E2016–E2021, 2012. Ⓐ

Díaz M et al.: Ethinyl estradiol-cyproterone acetate versus low-dose pioglitazone-flutamide-metformin for adolescent girls with androgen excess: divergent effects on CD163, TWEAK receptor, ANGPTL4, and LEPTIN expression in subcutaneous adipose tissue, *J Clin Endocrinol Metab* 97:3630–3638, 2012. Ⓐ

Mutharasan P et al.: Evidence for chromosome 2p16.3 polycystic ovary syndrome susceptibility locus in affected women of European ancestry, *J Clin Endocrinol Metab* 98:E185–E190, 2013. Ⓐ

De Wilde MA, Veltman-Verhulst SM, Goverde AJ et al.: Preconception predictors of gestational diabetes: a multicenter prospective cohort study on the predominant complication of pregnancy in polycystic ovary syndrome, *Hum Reprod* 29:1327–1336, 2014. Ⓐ

Dawson AJ, Sathyapalan T, Smithson JAJ et al.: A comparison of cardiovascular risk indices in patients with polycystic ovary syndrome with and without coexisting nonalcoholic fatty liver disease, *Clin Endocrinol* 80:843–849, 2014. Ⓐ

Sprung VS, Jones H, Pugh CJ et al.: Endothelial dysfunction in hyperandrogenic polycystic ovary syndrome is not explained by either obesity or ectopic fat deposition, *Clin Sci* 126:67–74, 2014. Ⓐ

Randeva HS, Tan BK, Weickert MO et al.: Cardiometabolic aspects of the polycystic ovary syndrome, *Endocr Rev* 33:812–841, 2012. Ⓐ

Brzozowska MM, Ostapowicz G, Weltman MD: An association between nonalcoholic fatty liver disease and polycystic ovarian syndrome, *J Gastroenterol Hepatol* 24:243–247, 2009. Ⓐ

SUGGESTED READINGS

Cotton D et al.: In the clinic: the polycystic ovary Polycystic Ovary syndrome, *Ann Intern Med ITC*2–11, Feb 2011.

Dokras AS et al.: Increased risk for abnormal depression scores in women with polycystic ovary syndrome: a systematic review and meta-analysis, *Obstet Gynecol* 117:145, 2011.

Legro RS et al.: Letrozole versus clomiphene for infertility in the polycystic ovary syndrome, *N Engl J Med* 371:119–129, 2014.

Nestler JE: Metformin for the treatment of polycystic ovary syndrome, *N Engl J Med* 358:47–54, 2008.

Radosh L: Drug treatment for polycystic ovary syndrome, *Am Fam Physician* 79(8):671–676, 2009.

Setji TL, Brown AJ: Polycystic ovary syndrome: update on diagnosis and treatment, *Am J Med* 127:912–919, 2014.

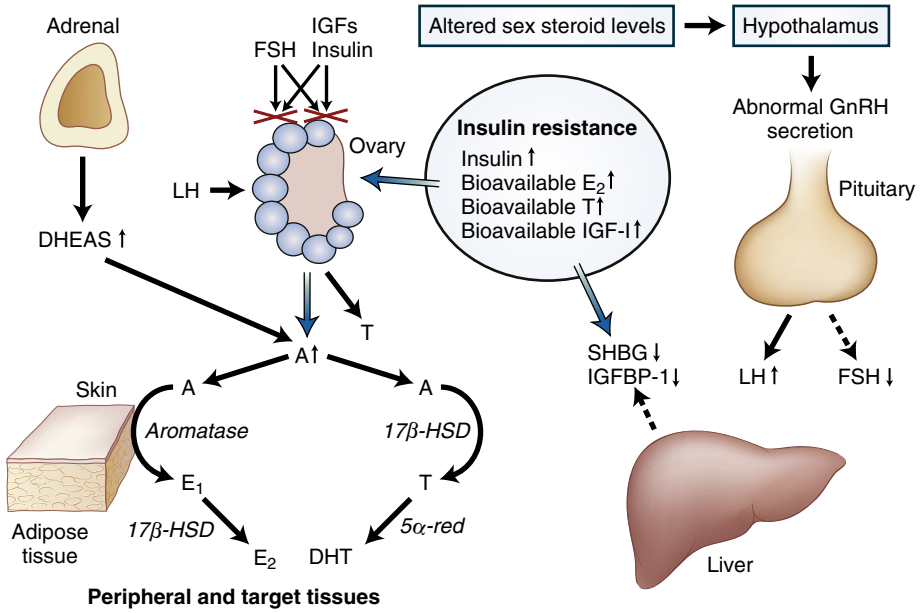


FIGURE EP1-59 Pathologic mechanisms in polycystic ovary syndrome (PCOS). A deficient in vivo response of the ovarian follicle to physiologic quantities of follicle-stimulating hormone (*FSH*), possibly because of an impaired interaction between signaling pathways associated with FSH and insulin-like growth factors (*IGFs*) or insulin, may be an important defect responsible for anovulation in PCOS. Insulin resistance associated with increased circulating and tissue levels of insulin and bioavailable estradiol (E_2), testosterone (*T*), and IGF1 gives rise to abnormal hormone production in a number of tissues. Oversecretion of luteinizing hormone (*LH*) and decreased output of FSH by the pituitary, decreased production of sex hormone–binding globulin (*SHBG*) and IGF-binding protein 1 (*IGFBP-1*) in the liver, increased adrenal secretion of dehydroepiandrosterone sulfate (*DHEAS*), and increased ovarian secretion of androstenedione (*A*) all contribute to the feed-forward cycle that maintains anovulation and androgen excess in PCOS. Excessive amounts of E_2 and T arise primarily from the conversion of A in peripheral and target tissues. T is converted to the potent steroids estradiol or DHT (dihydrotestosterone). Reductive 17β-hydroxysteroid dehydrogenase (17β-HSD) enzyme activity may be conferred by protein products of several genes with overlapping functions; 5α-reductase (5α-red) is encoded by at least two genes, and aromatase is encoded by a single gene. *GnRH*, Gonadotropin-releasing hormone. (From Melmed S et al: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Polycythemia vera is a chronic myeloproliferative disorder that originates from a pluripotent hematopoietic stem cell and is characterized mainly by erythrocytosis (increase in red blood cell [RBC] mass).

SYNONYMS

Primary polycythemia
Vaquez disease

ICD-9CM CODES
238.4 Polycythemia vera
ICD-10CM CODES
D45 Polycythemia vera

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1 case per 100,000 persons. Occurs most commonly in patients aged 50 to 75 years. Mean age at onset is 60 yr; men are affected more often than are women.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Polycythemia vera has a latent, proliferative, and spent phase. The patient generally comes to medical attention because of symptoms associated with increased blood volume and viscosity or impaired platelet function:

- Impaired cerebral circulation resulting in headache, vertigo, blurred vision, dizziness, transient ischemic attack, cerebrovascular accident
- Fatigue, poor exercise tolerance
- Pruritus, particularly after bathing (caused by overproduction of histamine)
- Bleeding: epistaxis, upper gastrointestinal bleeding (increased incidence of peptic ulcer disease)
- Abdominal discomfort from splenomegaly; hepatomegaly may be present
- Hyperuricemia may result in nephrolithiasis and gouty arthritis
- Nearly 20% of patients experience arterial or venous thrombosis as their initial symptom.

The physical examination may reveal:

- Facial plethora, congestion of oral mucosa, ruddy complexion
- Enlargement and tortuosity of retinal veins
- Splenomegaly (found in >75% of patients)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Smoking:

- Polycythemia is caused by increased carboxyhemoglobin, resulting in left shift in the hemoglobin (Hgb) dissociation curve.
- Laboratory evaluation shows increased hematocrit (Hct), RBC mass, erythropoietin level, and carboxyhemoglobin.
- Splenomegaly is not present on physical examination.

Hypoxemia (secondary polycythemia):

- Living for prolonged periods at high altitudes, pulmonary fibrosis, congenital cardiac lesions with right-to-left shunts.
- Laboratory evaluation shows decreased arterial oxygen saturation and elevated erythropoietin level.
- Splenomegaly is not present on physical examination.

Erythropoietin-producing states:

- Renal cell carcinoma, hepatoma, cerebral hemangioma, uterine fibroids, polycystic kidneys.
- The erythropoietin level is elevated in these patients, and the arterial oxygen saturation is normal.
- Splenomegaly may be present with metastatic neoplasms.

Stress polycythemia (Gaisböck's syndrome, relative polycythemia):

- Laboratory evaluation demonstrates normal RBC mass, arterial oxygen saturation, and erythropoietin level; plasma volume is decreased.
- Splenomegaly is not present on physical examination.

Hemoglobinopathies associated with high oxygen affinity:

- An abnormal oxyhemoglobin-dissociation curve (P50) is present.

WORKUP

Recent developments in molecular biology have identified a single, acquired point mutation in the Janus kinase 2 *(JAK2)* gene in the majority of patients with polycythemia vera and other pH-negative myeloproliferative disorders. The *JAK2* mutation is found in >95% of patients with polycythemia vera and can be used for diagnostic purposes. Testing for the *JAK2 V617F* mutation with polymerase chain reaction assay is now available. In patients with high hematocrit (>52% in men or >48% in women) and in the absence of coexisting secondary erythrocytosis, the presence of the *JAK2* mutation is sufficient for the diagnosis of polycythemia vera.

The World Health Organization diagnostic criteria for polycythemia vera are described in Table P1-24.

LABORATORY TESTS

- Elevated RBC count (>6 million/mm^3), elevated Hgb (>18 g/dl in men, >16 g/dl in women), elevated Hct (<54% in men, <49% in women)
- Increased white blood cell count (often with basophilia); thrombocytosis in the majority of patients
- Elevated leukocyte alkaline phosphatase, serum vitamin B_{12}, and uric acid levels
- Low serum erythropoietin level
- Bone marrow aspiration revealing RBC hyperplasia (Fig. EP1-62) and absent iron stores

TREATMENT

NONPHARMACOLOGIC THERAPY

Phlebotomy to keep Hct >45% in men and >42% in women is the mainstay of therapy. Phlebotomy, however, has no effect on the development of myelofibrosis.

ACUTE GENERAL Rx

- Hydroxyurea can be used in conjunction with phlebotomy to decrease the incidence of thrombotic events.
- Interferon-alpha-2b is also effective in controlling RBC values without significant side effects.
- Myelosuppressive therapy with chlorambucil is effective but should not be routinely used because of its leukemogenic potential.
- Box P1-6 describes an algorithm for management of patients with polycythemia vera.
- Recent trials have shown that ruxolitinib, a Janus kinase (JAK) 1 and 2 inhibitor was superior to standard therapy in controlling the hematocrit, reducing the spleen volume and improving symptoms associated with polycythemia vera.

CHRONIC Rx

- Patient education regarding need for lifelong monitoring and treatment.
- Adjunctive therapy: treatment of pruritus with antihistamines, control of significant hyperuricemia with allopurinol, reduction of gastric hyperacidity with antacids of H_2 blockers, low-dose aspirin to treat vasomotor

TABLE P1-24 World Health Organization 2008 Diagnostic Criteria for Polycythemia Vera

Major Criteria

1. Hemoglobin (Hgb) >18.5 g/dl (men), >16.5 (women); *or* Hgb or hematocrit (Hct) >99% reference range for age, sex, or altitude of residence; *or* Hgb >17 g/dl (men), >15 g/dl (women) if associated with a sustained increase of ≥2 g/dl from baseline that cannot be attributed to correction of iron deficiency; *or* elevated red cell mass (>25% above mean normal predicted value)
2. Presence of *JAK2 V617F* or similar mutation

Minor Criteria

1. Bone marrow trilineage myeloproliferation
2. Subnormal serum erythropoietin level
3. Endogenous erythroid colony formation in vitro

Either both major criteria and one minor criterion *or* the first major criterion and two minor criteria must be met for diagnosis of polycythemia vera.

From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.

BOX P1-6 Algorithm for Management of Patients with Polycythemia Vera

Low-risk young patients (age <60 years) and no history of thrombosis, platelet count <1.5 × 10^6 mm^{-3}

Phlebotomy + low-dose aspirin (81 mg/day) to maintain hematocrit lower than 45% in males and lower than 42% in females. Aspirin should not be used in patients with histories of a hemorrhagic episode or with extreme thrombocytosis (>1.5 × 10^6 mm^{-3}) or acquired von Willebrand syndrome.

↓

Thrombosis or hemorrhage
Systemic symptoms
Severe pruritus refractory to histamine antagonists
Painful splenomegaly

↓

Hydroxyurea 15-20 mg/kg (unless younger than 40 years, pregnant, intolerant to hydroxyurea; consider pegylated INF)

↓

Pegylated INF 45 to 180 μg/wk or INF (3 × 10^6 units three times a week; alter dose depending on response and toxicity). Consider the use of pegylated INF, which can be administered once weekly.

↓

If platelet control is inadequate or patient cannot tolerate interferon, one option is the use of anagrelide. However, the use of this drug is controversial. In this case, supplemental phlebotomy is required to maintain hematocrit lower than 45% in males and lower than 42% in females, and the use of hydroxyurea should be considered, especially if patient continues to have thrombotic episodes.

↓

If the patient has increasing splenomegaly, systemic symptoms, or repeated thromboses despite adequate dose of hydroxyurea (2-3 g/day), start busulfan, 4 to 6 mg/day orally for 4 to 8 weeks. It should be mentioned that the sequential use of hydroxyurea and busulfan may be associated with an increased risk of leukemia. Supplemental phlebotomy may be required.

Painful splenomegaly

↓

Splenectomy + continued systemic therapy

↓

High-risk patients (age >60 years), previous thrombosis, platelet count >1.5 × 10^6 mm^{-3}

Phlebotomy to hematocrit of 42% in females and 45% in males
Aspirin (81 mg/day) to be given only in patients with platelet counts <1.5 × 10^6 mm^{-2}
Myelosuppressive therapy with hydroxyurea 30 mg/kg orally for 1 week
Then 15 to 20 mg/kg

↓

If patient continues to have thrombotic episodes and has extreme thrombocytosis or cannot tolerate hydroxyurea

Consider pegylated INF 45 to 180 μg/wk or add busulfan 4-6 mg/d orally for 4 to 8 weeks.

If on busulfan, stop when blood counts are normalized or platelet count is lower than 300,000 mm^{-3}.

Occasional supplemental phlebotomy if hematocrit is >42% in females and greater than 45% in males; when patient relapses (patient is symptomatic), initiate busulfan therapy again at same dose.

Patient age >70 years

Phlebotomy + low-dose aspirin + hydroxyurea

↓

No response or poor compliance

Busulfan 4 to 6 mg/day orally for 4 to 8 weeks. Stop when blood counts are normalized or platelet count is lower than 300,000 mm^{-3}.

(From Hoffman R.: *Hematology, basic principles and practice*, 6th ed, Philadelphia, 2013, Saunders.)

symptoms in patients without bleeding diathesis. Low-dose aspirin can safely prevent thrombotic complications in patients with polycythemia vera and should be given to all patients in absence of contraindications.

DISPOSITION

- The median survival time without treatment is 6 to 18 mo after diagnosis; phlebotomy extends the average survival time to 12 yr.
- Patients with polycythemia vera with a hematocrit <45% have a significantly lower rate of cardiovascular death and major thrombosis than those with hematocrit of 45% to 50%.
- Prognosis is worse in patients >60 yr and those with a history of thrombosis.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Polycythemia Vera (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Campbell PJ, Green AR: The myeloproliferative disorders, *N Engl J Med* 355:2452, 2006.

Marchioli R et al.: Cardiovascular events and intensity of treatment in polycythemia vera, *N Engl J Med* 368:22–33, 2013.

Spivak JL: Narrative review: thrombocytosis, polycythemia vera, and JAK2 mutations: the phenotypic mimicry of chronic myeloproliferation, *Ann Intern Med* 152:300–306, 2010.

Stuart BJ, Vieira AJ: Polycythemia vera, *Am Fam Physician* 69:2139, 2004.

Vannucchi AM, et al: Ruxolitinib versus standard therapy for the treatment of polycythemia vera, *N Engl J Med* 372:426-435, 2015.

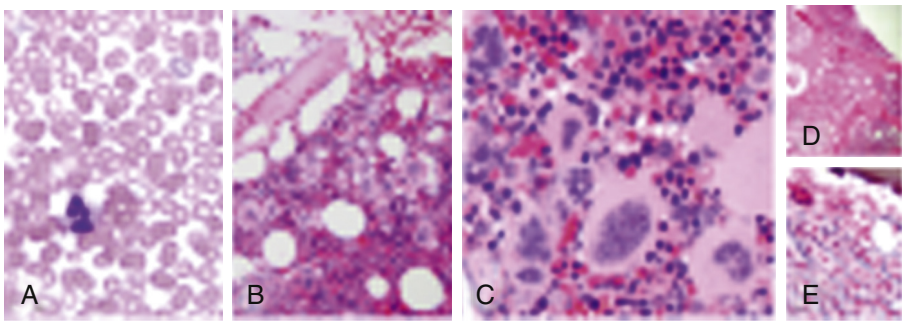


FIGURE EP1-62 A-E, Photomicrograph of bone marrow biopsy obtained from a polycythemia vera patient in myelofibrotic phase demonstrating hypercellularity and increased number of megakaryocytes (×160). (From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

BASIC INFORMATION

DEFINITION

Polymyalgia rheumatica (PMR) is an inflammatory condition characterized by shoulder and pelvic girdle muscle pain and stiffness.

SYNONYMS

Anarthritic rheumatoid syndrome
PMR

ICD-9CM CODES
725.0 Polymyalgia rheumatica
ICD-10CM CODES
M35.3 Polymyalgia rheumatica

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 60 to 80/100,000; rare in African Americans.
PREDOMINANT SEX: Female/male ratio of 2:1.
PREDOMINANT AGE: Age >50 years with greater incidence as age increases.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- In majority of patients, sudden onset of muscle pain and stiffness.
- Neck, shoulders, and arms are most often affected. Pelvic girdle and thigh muscles also involved.
- Patients often note severe pain and stiffness.
- Constitutional symptoms of fatigue, malaise, and loss of appetite may accompany pain and stiffness.
- Physical exam is fairly benign; passive range of motion is typically preserved; may find minimal joint swelling, and strength testing is normal.
- Presence of fever, chills, night sweats, visual disturbances, headaches, or jaw claudication suggests concomitant giant cell arteritis and warrants further evaluation.

ETIOLOGY

Appears to be related to the presence of HLA-D4 haplotypes, which confer susceptibility to activation of the innate immune system leading to inflammation.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

See Box P1-7.

WORKUP

- Elderly patients with PMR symptoms should have initial laboratory evaluation with ESR, CRP, CBC, CPK.
- ESR >40 is seen in majority of patients.
- May have a normocytic, normochromic anemia and thrombocytosis.
- An algorithm for diagnosing polymyalgia rheumatica without giant cell arteritis is described in Fig. P1-63.
- Table P1-25 describes diagnostic criteria for PMR.

TREATMENT

ACUTE GENERAL Rx

- Prednisone 15 to 20 mg/day with dramatic improvement in symptoms typically noted in 24 to 48 hr.
- Initial dose of prednisone maintained for 4 to 8 wk with steroid dose reduced by 20% every month as long as patient remains symptom free. Monitor acute phase reactants (ESR and CRP). When dose reaches 10 mg/day, taper slowly. Flares can be managed by increasing prednisone by 10% to 20%.
- It is prudent to start a proton-pump inhibitor at initiation of therapy given the need for gastric protection in an elderly age group at high risk for GI toxicity.
- Attention should be paid to bone health given most patients are on steroids for 1 to 2 yr. Calcium and vitamin D supplementation should be started early on with possible bisphosphonate use if indicated by bone density measurement.

PEARLS & CONSIDERATIONS

Patients with PMR should be monitored carefully for the development of giant cell arteritis. Patients who have incomplete response to treatment with prednisone or have an evolving pattern of pain and swelling should be reevaluated for the possibility of a different diagnosis.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Polymyalgia Rheumatica (PMR) (Patient Information)
Giant Cell Arteritis (Related Key Topic)
Vasculitis, Systemic (Related Key Topic)

AUTHOR: **NUHA R. SAID, M.D.**

BOX P1-7 Disease Entities with Polymyalgias

Rheumatoid arthritis
Rotator cuff syndrome
Osteoarthritis of shoulder and hip joints
Fibromyalgia
Polymyositis/dermatomyositis
Spondyloarthritis
Systemic lupus erythematosus
Vasculitides
Paraneoplastic myalgias
Infection-associated myalgias
RS3PE (remitting seronegative symmetric synovitis and pitting edema)
Parkinson's disease
Hypothyroidism

From Hochberg M: *Rheumatology,* ed 4, Philadelphia, 2007, Mosby.

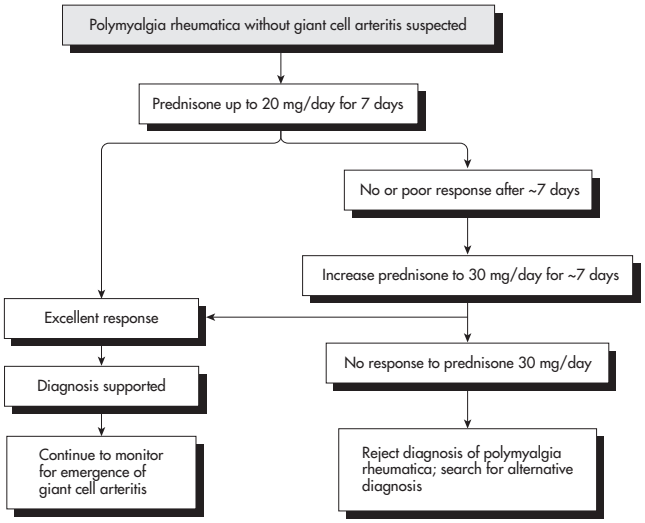


FIGURE P1-63 Algorithm for diagnosing polymyalgia rheumatica without giant cell arteritis. (From Firestein GS et al: *Kelly's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.)

TABLE P1-25 Polymyalgia Rheumatica: Diagnostic Criteria

Chuang et al 1982	Healey 1984
• Age of onset = 50 yr or older • Erythrocyte sedimentation rate >40 mm/h • Bilateral aching and stiffness for =1 mo and involving two of the following areas: neck or torso, shoulders or proximal regions of the arms, and hips or proximal aspects of the thighs • Exclusion of all other diagnoses causing PMR-like symptoms	• Age of onset = 50 yr or older • Erythrocyte sedimentation rate >40 mm/h • Pain persisting for =1 mo and involving two of the following areas: neck, shoulders, and pelvic girdle • Absence of other diseases capable of causing the musculoskeletal symptoms • Morning stiffness lasting >1 hr • Rapid response to prednisone (=20 mg/day)

From Hochberg M: *Rheumatology,* ed 4, Philadelphia, 2007, Mosby.

SUGGESTED READINGS

Bird HA: Criteria for polymyalgia rheumatica: tale without end, *J Rheumatol* 35:188, 2008.

Caylor T, Perkins A, et al.: Recognition and management of polymyalgia rheumatica and giant cell arteritis, *Am Fam Physician* 88(10):676–684, 2013.

Hennell S et al.: Evidence-based management for polymyalgia rheumatica for rheumatology practitioners, nurses and physiotherapists, *Musculoskeletal Care* 5(2):65, 2007.

Hutchings A et al.: Clinical outcomes, quality of life and diagnostic uncertainty in the first year of polymyalgia rheumatica, *Arthritis Rheum* 57(5):803, 2007.

Ntatsaki E, Watts RA: Management of polymyalgia rheumatica, *BMJ* 340:620, 2010.

Salvarani C et al.: Polymyalgia rheumatica and giant-cell arteritis, *Lancet* 372:234, 2008.

Weyand C, Goronzy JJ: Giant-cell arteritis and polymyalgia rheumatica, *N Engl J Med* 371:50–7, 2014.

BASIC INFORMATION

DEFINITION

Polypharmacy is the concomitant use of many different medications ranging from 2 or more to 10 or more drugs. The most common definition is 5 or more prescribed medications for one patient. Polypharmacy is important when the medications are inappropriate without a clear benefit to the patient. Medication errors, adverse drug reactions, drug interactions, hospitalizations, nonadherence, functional decline, and/or increased costs have been associated with polypharmacy.

SYNONYMS

Potentially inappropriate medications (PIMs)

ICD-9CM CODES
Not applicable
ICD-10CM CODES
X71.9 Counseling, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Incidence increases with age and disease burden.
PREVALENCE: One in five Americans receives potentially inappropriate drug therapy, although prevalence may be substantially higher in specific clinical settings.
PREDOMINANT SEX AND AGE:
- Adults aged 65 and older.
- Women.

RISK FACTORS
- Multiple chronic diseases.
- Frequent hospitalizations.
- Multiple providers and pharmacies.

PHYSICAL FINDINGS & CLINICAL PRESENTATION
- Presence of one or more drugs without a clearly defined purpose.
- Presence of therapeutic duplications such as multiple proton pump inhibitors.
- Presence of prescriptions for both generic and brand-name versions of the same drug.
- Unexpected response to drug therapy ranging from lack of efficacy to exaggerated responses.
- Expanded list of new medications for a patient late in life or at the end of life.
- Decreased patient adherence and limited patient understanding of their drug regimen.
- Presence of a "geriatric syndrome" such as falling, excessive sedation and confusion, urinary retention or incontinence, reduced oral intake, and general failure to thrive

ETIOLOGY

- Inadequate communication and coordination between physicians, pharmacists, patients, and caregivers.
- Prescribing cascade (not recognizing new problem as a drug side effect and prescribing a second drug).
- Continuing medications without a review of risks, benefits, and appropriateness.
- Increasing number and marketing of medications.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Misuse, overuse, or underuse of drug therapy.

WORKUP

- Obtain a thorough medication history including prescriptions OTC drugs, dietary supplements, and medications used on a prn basis.
- "Brown bag" approach: visually verify all medication bottles for actual ingredients.
- Although the number of drugs does not necessarily identify inappropriate prescribing, the likelihood of at least one or more inappropriate drugs being present increases when at least five drugs are prescribed.
- Risk assessment tools such as the Drug Burden Index (DBI) can help guide the medication review process. The DBI estimates the use of sedative and anticholinergic medications and their associated physical and cognitive impairments.
- Use standard tools to evaluate drug regimens:
  1. **Beers criteria**: identifies potentially dangerous or ineffective drugs for older adults, such as ketorolac, muscle relaxants, and drugs with strong anticholinergic properties.
  2. STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions) and START (Screening Tool to Alert to Right Treatment) criteria: help detect inappropriate prescribing and underprescribing of clinically indicated medications.
  3. **Medication Appropriateness Index (MAI):** evaluates key elements of appropriate prescribing.
     1. Is there an indication for the drug?
     2. Is the medication effective for the condition?
     3. Is the dose appropriate for the patient and the condition?
     4. Are the directions practical and correct?
     5. Are there clinically significant drug-drug or drug-disease interactions?
     6. Is there unnecessary duplication with other drugs?
     7. Is the duration of therapy appropriate?
     8. Is this drug the least expensive of the equally effective alternatives?
  4. Warfarin and other anticoagulants, antiplatelet agents, insulins and oral hypoglycemic agents, opioids, and digoxin are associated with high rates of adverse drug reactions and hospitalizations; patients requiring these drugs should be monitored closely.

TREATMENT

NONPHARMACOLOGIC THERAPY

Consider nonpharmacologic alternatives to drug therapy.

ACUTE GENERAL Rx

If acute drug-related problems are identified, establish priorities for safely withdrawing/tapering the offending drugs.

CHRONIC Rx

- Always assess the potential risks and benefits from each specific medication, especially in patients with multiple comorbid conditions or limited life expectancy.
- Consideration should be given to the incremental benefit from each drug added to a complex drug regimen. For example, what would be the risk to benefit ratio to a 90-year-old individual from the addition of spironolactone to a regimen consisting of lisinopril, candesartan, and carvedilol for heart failure?

DISPOSITION

Safe discontinuation of inappropriate medications from a regimen may take at least several months.

REFERRAL

Referral to a clinical pharmacist for a comprehensive drug regimen review and potentially to a geriatrician, especially for frail older adults.

PEARLS & CONSIDERATIONS

COMMENTS

The prevention and/or identification of polypharmacy should focus on the appropriateness of the medications for the *individual* person and not simply the number of medications. The decision regarding what is "appropriate" for an individual should consider the patient's own priorities and expected risk and benefit to that individual. In addition, clinical practice guidelines for common chronic diseases rarely acknowledge the presence of concomitant conditions when recommending drug therapies.

PREVENTION

- Multiple systems are needed to prevent inappropriate polypharmacy.
- Consider whether a drug is needed for a new symptom and whether the symptom is actually an unrecognized ADR.
- Nonpharmacologic therapies and lifestyle modifications should be encouraged whenever possible and appropriate.
- Use of electronic health records in which the medication list is updated *regularly* against what the patient is actually taking.
- OTC drugs and dietary supplements should be identified when taking a medication history.
- Medication reconciliation should be performed at least every 6 mo for medically complex older adults, upon every hospital admission, after every hospital discharge, and whenever new drugs are added.
- Counseling at hospital discharge during which the provider ensures patient and caregiver understanding of any medication change. Both written and oral instructions should be provided in the patient's preferred language and at the appropriate literacy level.

- Effective communication between health care professionals is essential, with one prescriber taking overall responsibility for drug therapy.
- Regular evaluation of how frequently "as needed" medications are being used by the patient. For example, the "Rule of 2" for short-acting beta-agonists may identify a need for a change in maintenance therapy.

PATIENT & FAMILY EDUCATION

- An up-to-date list of all drugs taken on a regular or prn basis must be maintained. The list should include all prescription and OTC drugs including eye drops, inhalers, and skin creams. Dietary supplements such as vitamins and herbals should also be on the list. The National Transitions of Care Coalition's "My Medicine List" is an excellent tool for patients (http://www.ntocc.org/Portals/0/PDF/Resources/My_Medicine_list.pdf), as well as My Medication Action Plan (MAP). Patients should bring their list to each physician appointment and ask providers to review all drugs at least once a year.
- After being discharged from the hospital, patients and/or caregivers should compare newly prescribed drugs to their existing drugs. They should ask which drugs should be stopped, which should be continued, and which should be continued but in a different dosage or frequency.
- Patients enrolled in Medicare Part D may be eligible for Medication Therapy Management (MTM) review programs.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **SYDNEY SPRINGER, PHARM.D. CANDIDATE** and **ANNE L. HUME, PHARM.D.**

SUGGESTED READINGS

American Geriatrics Society: American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults, *J Am Geriatr Soc* 60:616–631, 2012.

Gokula M et al.: Tools to reduce polypharmacy, *Clin Geriatr Med* 28:323–341, 2012.

Hitzeman N et al.: Appropriate use of polypharmacy for older patients, *Am Fam Physician* 87(7):483–484, 2013.

Holmes HM: Rational prescribing for patients with a reduced life expectancy, *Clin Pharmacol Ther* 1:103, 2009.

Scott IA et al.: Minimizing inappropriate medications in older populations: a ten-step conceptual framework, *Am J Med* 6:125, 2012.

Steinman MA et al.: Managing medications in clinically complex elders, *JAMA* 304:1592, 2010.

BASIC INFORMATION

DEFINITION

Clinically significant portal hypertension is defined as a portal vein pressure >10 mm Hg, most commonly attributable to liver disease.

SYNONYMS

None

ICD-9CM CODES
572.3 Portal hypertension
ICD-10CM CODES
K76.6 Portal hypertension

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence of portal hypertension is not known.
- Cirrhosis is the most common cause of portal hypertension in the United States.
- Portal hypertension is developed by >90% of patients with cirrhosis.
- Alcoholic and viral liver diseases are the most common causes of cirrhosis and portal hypertension in the United States.
- Schistosomiasis is the main cause of portal hypertension outside the United States.
- Esophageal varices may appear when portal vein pressure rises to >10 mm Hg.
- Variceal hemorrhage is the most serious complication of portal hypertension and may occur when portal pressures rise >12 mm Hg.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Jaundice.
- Ascites (Fig. P1-64).
- Spider angiomata.
- Testicular atrophy.
- Gynecomastia.
- Palmar erythema.

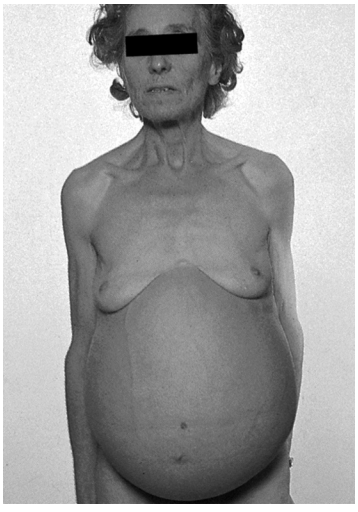


FIGURE P1-64 Ascites secondary to portal hypertension. Note the dilated collateral vein running up the right side of the abdomen. (From Forbes A et al [eds]: *Atlas of clinical gastroenterology,* ed 3, Oxford, 2005, Mosby.)

- Dupuytren's contracture.
- Asterixis (with advanced liver failure).
- Irritability, encephalopathy.
- Splenomegaly.
- Dilated veins in the anterior abdominal wall.
- Venous pattern on the flanks.
- Caput medusae (tortuous collateral veins around the umbilicus).
- Hemorrhoids.
- Hematemesis.
- Melena.
- Pruritus.

ETIOLOGY

Pathophysiologically caused by:

1. Conditions resulting in an increased resistance to flow.
   - Prehepatic (e.g., portal vein thrombosis, splenic vein thrombosis, congenital stenosis).
   - Hepatic (e.g., cirrhosis, alcoholic liver disease, primary biliary cirrhosis, schistosomiasis).
   - Posthepatic (e.g., Budd-Chiari syndrome, constrictive pericarditis, inferior vena cava obstruction, cor pulmonale, tricuspid regurgitation).
2. Conditions leading to increase in portal blood flow.
   - Splanchnic arterial vasodilation accompanying portal hypertension, mediated by local release of nitric oxide.
   - Arterial-portal venous fistulae.

Table P1-26 summarizes the etiology of portal hypertension.

DIAGNOSIS

- The diagnosis of portal hypertension is made on clinical grounds after a comprehensive history and physical examination.
- Noninvasive and invasive procedures confirm diagnosis and determine the severity of portal hypertension.

DIFFERENTIAL DIAGNOSIS

- Ascites from infection, neoplasm, or other inflammatory processes.
- Obesity.
- Abdominal organomegaly.

WORKUP

The workup of portal hypertension includes blood tests and noninvasive imaging studies to determine if the cause of portal hypertension is prehepatic, hepatic, or posthepatic. Ascitic fluid analysis is a key part of the diagnosis.

LABORATORY TESTS

- Complete blood count with platelets.
- Liver function tests with serum albumin.
- Prothrombin and partial thromboplastin times.
- Hepatitis B surface antigen and antibody.
- Hepatitis C antibody.
- In selected cases: iron, total iron-binding capacity, and ferritin; antinuclear antibody, anti–smooth muscle antibodies, antimitochondrial antibody, ceruloplasmin, alpha-1 antitrypsin.
- Ascitic fluid analysis: a serum-ascites albumin gradient ≥1.1 mg/dl suggests portal hypertension. Polymorphonuclear cells ≥250 cells/ml or positive Gram stain or culture suggest complicating spontaneous bacterial peritonitis (SBP).

IMAGING STUDIES

- Duplex-Doppler ultrasound is effective in screening for portal hypertension.
- Less commonly, CT/MRI/MRA scanning (Fig. P1-65) or liver-spleen nuclear medicine scanning can be used if the results from ultrasound are equivocal.
- Upper endoscopy is the most reliable test documenting the presence of esophageal varices.

TREATMENT

The treatment of portal hypertension is complex and involves measures to reduce the hypertension directly, minimize volume overload, correct underlying disorders, and prevent complications (most notably SBP and variceal bleeding).

NONPHARMACOLOGIC THERAPY

Dietary sodium restriction to generally 2000 mg/day forms the basis of therapy to limit fluid overload.

ACUTE GENERAL Rx

- For tense ascites, serial large-volume paracentesis (LVP) is generally recommended. The use of albumin infusion (8 to 10 g/L of ascites fluid removed) during LVP >5 L has been shown to reduce the incidence of postparacentesis circulatory dysfunction, although its use remains somewhat controversial.
- IV diuretics, typically furosemide and spironolactone, are used to achieve natriuresis and net negative salt and water balance. Renal function and serum electrolytes are monitored frequently, with transition to an oral regimen for long-term therapy.
- SBP is treated with IV antibiotics directed against enteric bacteria.
- Acute variceal hemorrhage is treated with crystalloid and blood product resuscitation, IV octreotide, terlipressin/vasopressin or somatostatin, and urgent upper endoscopy, often with sclerotherapy or band ligation. Patients with acute variceal hemorrhage should receive antibiotic prophylaxis against SBP.
- Traditionally, a transjugular intrahepatic portosystemic shunt (TIPS) or surgical shunt placement may be considered in patients not responding to above measures. However, recent data show early TIPS placement improved outcomes in acute variceal hemorrhage.

CHRONIC Rx

- Dietary sodium restriction in combination with diuretics: the typical ratio of furosemide 40 mg to spironolactone 100 mg retains normal serum potassium levels in most patients.
- Nonselective beta-blockers (propranolol and nadolol) in dosages sufficient to reduce the resting heart rate by 25% have been shown

TABLE P1-26 Etiology of Portal Hypertension

Condition	Site of Increased Resistance	FHVP	WHVP	HVPG	SPP	Liver Disease
Cirrhosis	Intrahepatic sinusoidal	Normal	Increased	Increased	Increased	Yes
Alcoholic hepatitis	Intrahepatic sinusoidal	Normal	Increased	Increased	Increased	Yes
Extrahepatic portal, splenic, or mesenteric vein thrombosis	Extrahepatic presinusoidal	Normal	Normal	Normal	Increased	No
Early primary biliary cirrhosis, PSC, sarcoid, schistosomiasis, congestive heart failure, noncirrhotic portal fibrosis, NRH	Intrahepatic presinusoidal	Normal	Normal/?raised	Normal/?raised	Increased	No
Hemochromatosis, peliosis, infiltrative disease, acute fatty liver of pregnancy	Intrahepatic sinusoidal hypertension	Normal	Increased	Increased	Increased	Yes
Veno-occlusive disease, posttransplant rejection	Intrahepatic postsinusoidal hypertension	Normal	?Increased	?Decreased	Increased	Yes
Budd-Chiari syndrome (noncirrhotic)	Extrahepatic postsinusoidal hypertension	Increased	Increased	Normal	Increased	Depends on severity
Constrictive pericarditis, inferior vena cava obstruction, congenital inferior vena cava web, right heart failure	Extrahepatic postsinusoidal hypertension	Increased	Increased	Normal	Increased	Depends on severity

FHVP, Free hepatic venous pressure; *HVPG,* hepatic venous pressure gradient; *SPP,* systolic pulse pressure; *WHVP,* wedged hepatic venous pressure.
From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

FIGURE P1-65 MR angiography showing portal hypertension with collaterals. The shrunken liver and collateral are obvious. (From Forbes A et al [eds]: *Atlas of clinical gastroenterology,* ed 3, St Louis, 2005, Mosby.)

to be effective in primary prophylaxis for first-time variceal bleeding and for preventing recurrent variceal bleeding. Dosages are usually given bid and decreased if heart rate falls to <55 beats/min or systolic blood pressure drops to <90 mm Hg. The addition of a long-acting nitrate (e.g., isosorbide-5-mononitrate) has been shown to improve portal hemodynamics. Findings of a prospective trial of beta-blockers to prevent the formation of varices were negative. The combination of beta-blockade plus endoscopic esophageal variceal banding is superior to either intervention alone.

- Intermittent LVP may be needed in "diuretic resistant" patients.
- Patients with prior SBP merit lifelong antibiotics for secondary prevention.
- Abstinence from alcohol or treatment for hepatitis B or hepatitis C. Vaccination for hepatitis A and B as appropriate.
- Hepatic transplantation is an option in selected patients.

DISPOSITION

- The most common complication associated with portal hypertension is variceal bleeding. The risk of bleeding from varices is approximately 15% at 1 yr.
- Development of the hepatorenal syndrome (HRS) is associated with high near-term mortality. In particular, HRS may complicate SBP, which emphasizes the importance of making the diagnosis of SBP and instituting appropriate prophylaxis.

REFERRAL

Consultation with a gastroenterologist is recommended in all patients with portal hypertension to screen for esophageal varices.

PEARLS & CONSIDERATIONS

Splanchnic arterial vasodilation is increasingly recognized as an important component of the pathophysiology of portal hypertension and ascites. There may be vasodilation in other capillary beds as well; of note, pulmonary arteriolar vasodilation can create a significant shunt fraction and resultant hypoxemia in the absence of chest radiograph or CT chest evidence of parenchymal disease. The diagnosis is suspected when otherwise unexplained hypoxia arises in a patient with cirrhosis, along with platypnea (dyspnea worse when sitting upright) and orthodeoxia (desaturation with upright posture). The diagnosis is confirmed by echocardiography with agitated saline, in which there is delayed appearance of bubbles in the left heart after injection into a peripheral vein.

COMMENTS

Portal hypertension and its complications carry significant morbidity and mortality rates. Emphasize ethanol abstinence, provide vaccinations and prophylactic therapy where indicated, and consider early referral to a specialist for assistance with management and consideration for hepatic transplantation.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **MEL L. ANDERSON, M.D.**

SUGGESTED READINGS

Blei AT: Portal hypertension and its complications, *Curr Opin Gastroenterol* 23(3):275, 2007.

Bosch J et al.: The management of portal hypertension: rational basis, available treatments and future options, *J Hepatol* 48(suppl 1):S68, 2008.

De Francis R: Evolving consensus in portal hypertension. Report of the Baveno IV consensus workshop on methodology of diagnosis and therapy in portal hypertension, *J Hepatol* 43(1):167, 2005.

Garcia-Pagan JC et al.: Early use of TIPS in patients with cirrhosis and variceal bleeding, *N Engl J Med* 362:2370–2379, 2010.

Gines P et al.: Current concepts: management of cirrhosis and ascites, *N Engl J Med* 350:1646, 2004.

Runyon B: Practice Guidelines Committee, American Association for the Study of Liver Diseases (AASLD): management of adult patients with ascites due to cirrhosis, *Hepatology* 3:841, 2004.

Wong CL et al.: Does this patient have bacterial peritonitis or portal hypertension? How do I perform a paracentesis and analyze the results? *JAMA* 299(10):1166, 2008.

Portal Vein Thrombosis

BASIC INFORMATION

DEFINITION

Portal vein thrombosis (PVT) is thrombotic occlusion of the portal vein. The thrombus can also involve segments of the mesenteric veins and/or the splenic vein.

SYNONYMS

Pylethrombosis
PVT

ICD-9CM CODES
452 Portal vein thrombosis
ICD-10CM CODES
I81 Portal vein thrombosis

EPIDEMIOLOGY & DEMOGRAPHICS

Occurs with equal frequency in children (peak age: 6 yr) and adults (peak age: 40 yr)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute PVT may present with sudden onset of fever and abdominal pain (when there is mesenteric extension).
- Upper gastrointestinal hemorrhage (hematemesis and/or melena) caused by esophageal varices.

ETIOLOGY & PATHOPHYSIOLOGY

In children: umbilical sepsis (pathophysiology unknown). In adults:

1. Hypercoagulable states.
   - Antiphospholipid syndrome.
   - Neoplasm (common cause).
   - Paroxysmal nocturnal hemoglobinuria.
   - Myeloproliferative diseases.
   - Oral contraceptives.
   - Polycythemia vera.
   - Pregnancy.
   - Protein S or C deficiency.
   - Sickle cell disease.
   - Thrombocytosis.
2. Inflammatory diseases.
   - Crohn's disease.
   - Pancreatitis.
   - Ulcerative colitis.
3. Complications of medical intervention.
   - Ambulatory dialysis.
   - Chemoembolization.
   - Liver transplantation.
   - Partial hepatectomy.
   - Sclerotherapy.
   - Splenectomy.
   - Transjugular intrahepatic portosystemic shunt.
4. Infections
   - Appendicitis.
   - Diverticulitis.
   - Cholecystitis.
5. Miscellaneous.
   - Cirrhosis (common cause).
   - Bladder cancer.

Pathophysiology: PVT results in portal hypertension, leading to esophageal and gastrointestinal varices. The liver sustained by the hepatic artery maintains normal function.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Causes of upper gastrointestinal hemorrhage and abdominal pain are described in Section II.

WORKUP

- Abdominal ultrasound (Fig. P1-66) or MRI may show the PVT. Abdominal ultrasound color Doppler imaging has a 98% negative predictive value and is considered the imaging modality of choice in diagnosing PVT.
- Determination of underlying cirrhosis of the liver should be the foremost step.
- Esophagogastroscopy shows esophageal varices.

TREATMENT

- Anticoagulation data on thrombolytic therapy are inconclusive. In patients with chronic PVT and concomitant cirrhosis, long-term anticoagulation is generally not recommended.
- Variceal sclerotherapy or banding.
- Surgical mesocaval or splenorenal shunt.
- The roles of thrombolysis and transjugular intrahepatic portosystemic shunt continue to evolve.

REFERRAL

- To surgeon to rule out intestinal infarction.
- To gastroenterologist.

SUGGESTED READINGS

Available at www.expertconsult.com

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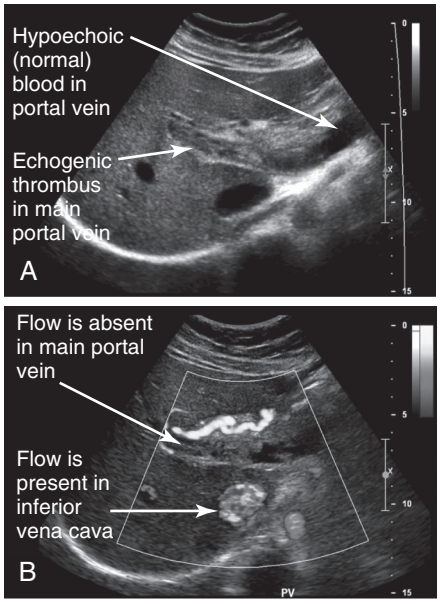

FIGURE P1-66 Portal vein thrombosis: ultrasound. This 22-year-old female, 2 months postpartum, presented with 1 week of right upper quadrant pain. Ultrasound was performed to evaluate for suspected cholecystitis or symptomatic cholelithiasis. Instead, portal vein thrombosis was discovered. The postpartum state is a risk factor for this condition. Hypercoagulable states and inflammatory or neoplastic abdominal conditions, including pancreatitis and abdominal malignancies, also can result in portal vein thrombosis. **A,** Ultrasound gray scale image showing thrombus in the main portal vein. **B,** Doppler ultrasound showing no flow within the portal vein. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

SUGGESTED READING

Parikh S et al.: Portal vein thrombosis, *Am J Med* 123:111–119, 2010.

BASIC INFORMATION

DEFINITION

Postconcussive syndrome (PCS) refers to persistent neurologic, cognitive, and psychological symptoms that result from traumatic brain injury (TBI), usually manifest within 4 weeks of injury and last beyond 3 months. PCS can also follow moderate and severe brain injury, although it is more commonly associated with mild brain injury or concussion. Concussion is an acute trauma-induced alteration of mental function lasting <24 hr, with or without preceding loss of consciousness.

SYNONYMS

PCS
Postconcussion syndrome
Posttraumatic nervous instability or brain injury
Postcontusion syndrome or encephalopathy
Status post commotio cerebri

ICD-9CM CODES
310.2 Postconcussion syndrome
ICD-10CM CODES
F07.81 Postconcussional syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence is approximately 27 cases per 100,000 persons/year.
- From 30% to 80% of patients with mild to moderate brain injury will experience some symptoms of PCS.
- Usually reported in the young, ages 20 to 30 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Usually present without focal neurologic deficits on examination.
- Symptoms start within a few days to weeks after the head injury and usually persist after 3 mo.
- Can be divided into early and late or persistent (>6 mo).
- 15% of patients will have persistent symptoms 1 yr later.
- Symptoms include (at least three of the following after TBI to meet ICD-10 criteria):
  1. Headache (usually of fronto-occipital location and showing characteristics of tension or migraine headache). The International Headache Society suggests that coding and attribution of headaches with characteristics of primary headaches but in the setting of an inciting event should be attributed to the event, unless there was a known history of the headache and the inciting event was seen as aggravating/initiating the preexisting migraine/tension headache.
  2. Fatigue
  3. Dizziness and/or vertigo
  4. Impaired memory
  5. Difficulty in concentrating
  6. Insomnia
  7. Irritability
  8. Lowered tolerance of stress, emotion, or alcohol
- Other associated symptoms: noise sensitivity, neck pain, nondermatomal paresthesias, interference with social role functioning.

ETIOLOGY

- Caused by TBI from events such as falls, motor vehicle accidents, military injuries, and contact sports.
- Postmortem findings reveal diffuse axonal injury as the primary pathologic finding along with small petechial hemorrhages and local edema.
- The primary injury triggers a slew of pathophysiological changes at the cellular level secondary to the axonal stretching and injury, leading to alterations in membrane and intracellular physiology, thereby affecting neurotransmission. These changes are believed to be a factor in determining whether the outcome will be an apparent normal recovery or persistent postconcussion symptoms.
- A psychogenic origin has been suggested by a number of empiric and clinical observations; however, limitations in methodology and differing definitions preclude firm conclusions. Prior history of anxiety is a strong risk factor for occurrence of PCS.

DIAGNOSIS

A careful history, a nonfocal neurologic examination, and normal neurologic testing will usually establish the diagnosis.

DIFFERENTIAL DIAGNOSIS

- Headache (dissection of the vertebral artery, occipital neuralgia)
- Epidural hematoma
- Subdural hematoma
- Skull fracture
- Cervical spine disk disease
- Whiplash
- Cerebrovascular accident
- Depression
- Anxiety

WORKUP

To exclude other causes of neurologic symptoms after TBI:
- Normal results of electroencephalography
- Normal evoked potentials
- Neuropsychological testing, which often reveals difficulties in concentration, memory, language, and executive function

LABORATORY TESTS

Various biomarkers in blood and cerebrospinal fluid and genetic testing have been proposed and studied in patients with TBI, but these tests are not specific and are not routinely used.

IMAGING STUDIES

- There is no imaging modality to diagnose PCS. PCS is primarily a clinical diagnosis.
- 10% of CT scans of the head following mild TBI are abnormal, showing mild subarachnoid hemorrhage, subdural hemorrhage, or contusions.
- MRI of the head after an mTBI is abnormal in 30% of patients with normal CT scans and may show irregular brain contours or old cerebral contusions.
- Recent improvements in imaging modalities, including diffuse tensor imaging (DTI) and susceptibility weighted imaging (SWI) in MRI, functional MRI (fMRI), and metabolic imaging such as magnetic resonance spectroscopy (MRS), positron emission tomography (PET), and single-photon emission computed tomography (SPECT) imaging, appear to be promising in elucidating the underlying pathophysiology of TBI and PCS, although they have not found a major role in clinical practice yet.
- None of the imaging modalities have been able to predict the occurrence of PCS in patients with mild TBI

TREATMENT

Must be recognized as a physiologic and psychological problem and treated accordingly.

GENERAL Rx

- Must be individualized to the patient's particular symptoms.
- Simple and early reassurance is often the major treatment.
- Symptoms are often refractory to treatment
- Supportive care may include the use of nonnarcotic analgesics and antiemetics.
- Pain management.
- Amitriptyline has been widely used for posttraumatic tension-type headaches as well as for nonspecific symptoms such as irritability, dizziness, insomnia, and depression.
- Posttraumatic migraine-type headaches can be treated with a trial of propranolol or amitriptyline alone or in combination.
- Depression can be treated with selective serotonin reuptake inhibitors but may not respond as well when compared with patients without PCS who have depression.
- Some patients may be admitted for severe symptoms; most can be managed as outpatients.
- There may be a role for cognitive behavioral therapy in treating symptoms.

NONPHARMACOLOGIC THERAPY

- Early psychological intervention and cognitive rehabilitation are key for full recovery.
- Physical and occupational therapy.
- Avoidance of alcohol, narcotics, and sleep deprivation.
- Explanation of symptoms and expectations, combined with early follow-up with reassurance, may hasten resolution of symptoms.

DISPOSITION

- Most patients improve after mild TBI without any residual deficits within 3 months.
- Although good improvement is typically seen within the first 6 mo, patients can continue to show improvement for up to 12-18 mo.
- Patients with very severe brain injuries (low Glasgow Coma Scale [GCS] score) and prolonged anterograde amnesia are at increased risk of development of some degree of permanent cognitive and personality disturbance.

- Predictors for the development of persistent PCS include:
  1. Female sex
  2. Ongoing litigation (conflicting studies)
  3. Low socioeconomic status
  4. Prior headaches
  5. Prior TBI
  6. Prior psychiatric illnesses such as anxiety

REFERRAL

Early consultations with psychologists, psychiatrists, neurologists, and rehabilitation specialists in an outpatient setting may be beneficial.

PEARLS & CONSIDERATIONS

- PCS starts within a few days after the injury.
- Recognizing depression and treating pain symptoms early in the course may help prevent the development of persistent PCS (>1 yr).
- The severity of the trauma does not clearly predict the risk of PCS.
- The severity of brain injury is usually documented by initial GCS score, duration of loss of consciousness, and duration of amnesia; however, there is a move toward tests of function, such as neuropsychological testing or fMRI.

COMMENTS

- Attempts to determine how much of a role psychological and/or neurologic factors play in the PCS are important but very difficult.
- No medication at hospital discharge has been proved to change the natural course of the disease.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Post-concussion Syndrome (Patient Information)

AUTHOR: **PRASHANTH KRISHNAMOHAN, M.B.B.S, M.D**

SUGGESTED READINGS

Al Sayegh A et al.: Psychological approaches to treatment of postconcussion syndrome: a systematic review, *J Neurol Neurosurg Psychiatry* 81(10):1128–1134, 2010.

Anderson EE et al.: Mild traumatic brain injuries: a 10-yr follow-up, *J Rehabil Med* 43(4):323–329, 2011.

Bigler ED, Maxwell WL: Neuropathology of mild traumatic brain injury: relationship to neuroimaging findings, *Brain Imaging Behav* 6(2):108–136, 2012.

Evans RW: Persistent posttraumatic headache, postconcussion syndrome, and whiplash injuries: the evidence for a nontraumatic basis with an historical review, *Headache* 50(4):716–724, 2010.

Evans RW: *Postconcussion syndrome.* http://www.uptodate.com. Accessed Aug 29, 2010.

Helmick K et al.: Cognitive rehabilitation for military personnel with mild traumatic brain injury and chronic post-concussional disorder: results of April 2009 consensus conference, *Neuro Rehabil* 26(3):239–255, 2010.

Jotwani V, Harmon KG: Postconcussion syndrome in athletes, *Curr Sports Med Rep* 9(1):21–26, 2010.

McAllister TW, Arciniegas D: Evaluation and treatment of postconcussive symptoms, *Neuro Rehabil* 17(4):265, 2002.

McConnell A, Shubrook J: Concussion care: simple strategies, big payoffs, *J Fam Pract* 58(8):410, 2009.

Obermann M et al.: Post-traumatic headache: is it for real? Crossfire debates on headache: pro, *Headache* 50(4):710–715, 2010.

Wood RL: Post concussional syndrome: all in the minds eye! *J Neurol Neurosurg Psychiatry* 78:552, 2007.

BASIC INFORMATION

DEFINITION

Postpartum hemorrhage (PPH) is classically defined as estimated blood loss >500 ml after a vaginal birth or >1000 ml after a cesarean section. Primary PPH is hemorrhage within the first 24 hr after delivery. Secondary PPH is hemorrhage after 24 hr and within 6-12 wk.

SYNONYMS

Obstetric hemorrhage

ICD-9CM CODES
666 Postpartum hemorrhage
ICD-10CM CODES
072.1 Other immediate postpartum hemorrhage

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 4%-6%
PREDOMINANT SEX AND AGE: Female of reproductive age
RISK FACTORS: Prolonged labor, augmented labor, rapid labor, history of PPH, episiotomy, preeclampsia, multiple gestation, macrosomic infant, operative delivery, chorioamniotis, bleeding dyscrasia, Asian or Hispanic ethnicity

PHYSICAL FINDINGS & CLINICAL PRESENTATION (Table P1-27)

- Bleeding is generally brisk at time of delivery.
- Examination findings include boggy uterus with continued passage of clot or blood with fundal pressure.
- Objective findings can also include hypotension, tachycardia, and oliguria with substantial blood loss.

ETIOLOGY

- Primary: uterine atony (>80%), retained placenta, coagulopathies, lacerations
- Secondary: subinvolution of placental site, retained products, infection, coagulopathies

DIAGNOSIS

WORKUP

- Bladder should be emptied
- Bimanual examination to evaluate for atony; massage if it is present
- Examination to verify that no lacerations are present, including cervical examination with necessary lighting and retractors
- Ultrasonography at bedside to evaluate for retained tissue or clot
- Examination to verify that placenta is intact

LABORATORY TESTS

Significant hemorrhage can lead to disseminated intravascular coagulation (DIC). If DIC is suspected, complete blood count and coagulation panels should be ordered. Similarly, if coagulopathy is suspected, evaluation of clotting factors should be ordered.

IMAGING STUDIES

Ultrasonography can be used to scan for retained products, including clot or placenta. It can be performed to assess the need for more invasive measures, such as instrumentation or a manual sweep.

TREATMENT (Table P1-28, Table P1-29, Box P1-8)

Medical management with uterotonics is generally the first line of treatment:

- Oxytocin (IV, 10-40 units diluted into IV solution, or 10 units IM); often given prophylactically immediately after delivery
- Methergine (IM, 0.2 mg)
- Hemabate (IM, 0.25 mg)
- Misoprostol (800-1000 mcg rectally)

NONPHARMACOLOGIC THERAPY

Secondary management includes the following:

- Packing with gauze, Foley catheter, or tamponade balloon
- Uterine curettage for suspected retained products
- Uterine artery embolization
- Surgical management with laparotomy
  1. Hypogastric artery ligation
  2. Bilateral uterine artery ligation (O'Leary sutures)
  3. B-lynch sutures
  4. Hysterectomy

ACUTE GENERAL Rx

Uterotonics, surgical management, embolization, blood transfusion. Fig. P1-67 outlines the management of postpartum hemorrhage.

CHRONIC Rx

For anemia: ferrous sulfate supplementation to support new red blood cell production

TABLE P1-27 Presentation of Symptoms in Postpartum Hemorrhage

% Blood loss (ml)	Systolic blood pressure (mm Hg)	Signs and symptoms
10-15 (500-1000)	Normal	Tachycardia, palpitations, dizziness
15-25 (1000-1500)	Low-normal	Tachycardia, weakness, diaphoresis
25-35 (1500-2000)	70-80	Restlessness, pallor, oliguria
35-45 (2000-3000)	50-70	Collapse, air hunger, anuria

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

TABLE P1-28 Therapeutic Response to Initial Fluid Resuscitation

Response	Description	Follow-up treatment
Rapid response	<20% of blood volume lost	No additional fluids or blood are needed.
Transient response	20%-40% of blood volume lost; responds to initial fluid bolus but later has worsening vital signs	Continue fluids and consider blood transfusions.
Minimal or no response	Ongoing severe hemorrhage with >40% blood volume lost	Continue aggressive fluid and blood product replacements.

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

TABLE P1-29 Dosing Regimens for Oxytocic Drugs

Drug	Regimens
Oxytocin (Pitocin)	5-unit IV bolus
	Add 20-40 units oxytocin to 1 L of fluids
	10 units intramyometrially
Methylergonovine (Methergine)	0.2 mg IM every 2-4 hr
Ergonovine (Ergotrate Maleate)	100-125 mcg IM or intramyometrially every 2-4 hr
	200-250 mcg IM
	Total dose 1.25 mg
Carboprost (Hemabate)	250 mcg IM or intramyometrially every 15-90 min
	Total dose 2 mg
Misoprostol	800 mcg PR or 800 mcg of sublingual misoprostol

IM, Intramuscular; *IV*, intravenous; *PR*, per rectum.
From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

DISPOSITION

- The patient should be closely watched for at least 24 hr after a postpartum hemorrhage. Laboratory findings should be monitored to follow trends on the Hunt and Hess scale. Vital signs should be monitored for evidence of hemodynamic stability and appropriate response to anemia.
- Morbidity can include shock, acute respiratory distress syndrome, Sheehan's syndrome, and loss of fertility.

REFERRAL

During the course of a postpartum hemorrhage, the anesthesiology department should be notified and adequate nursing should be available. Early considerations should be made to notify obstetricians. If bleeding is brisk or estimated blood loss is considerable, preparation should be made for transfusion of blood products, including drawing blood for typing and notifying the blood bank.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **LEO HAN, M.D.**

BOX P1-8 Blood Product Replacement

Cross-matched blood
Type-specific or "saline cross-matched" blood
Compatible ABO and Rh blood types
Rh-negative blood is preferable.
Warm the blood, if possible, especially if the rate of infusion is >100 ml/min or if the total volume transfused is high; cold blood is associated with an increased incidence of arrhythmias and paradoxical hypotension.
Administer calcium if blood is transfused rapidly at >100 ml/min because of binding of calcium by anticoagulants in banked blood.
Give 6-10 units fresh frozen plasma (FFP) for every 10 units of packed red blood cell transfusions.
Give 10-12 units of platelets if the platelet count decreases to <50 × 109/L.
Cryoprecipitate can be given to replace fibrinogen in addition to the FFP.
Consider 60-120 mcg/kg intravenous bolus injection of recombinant activated factor VII (rFVIIa).

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

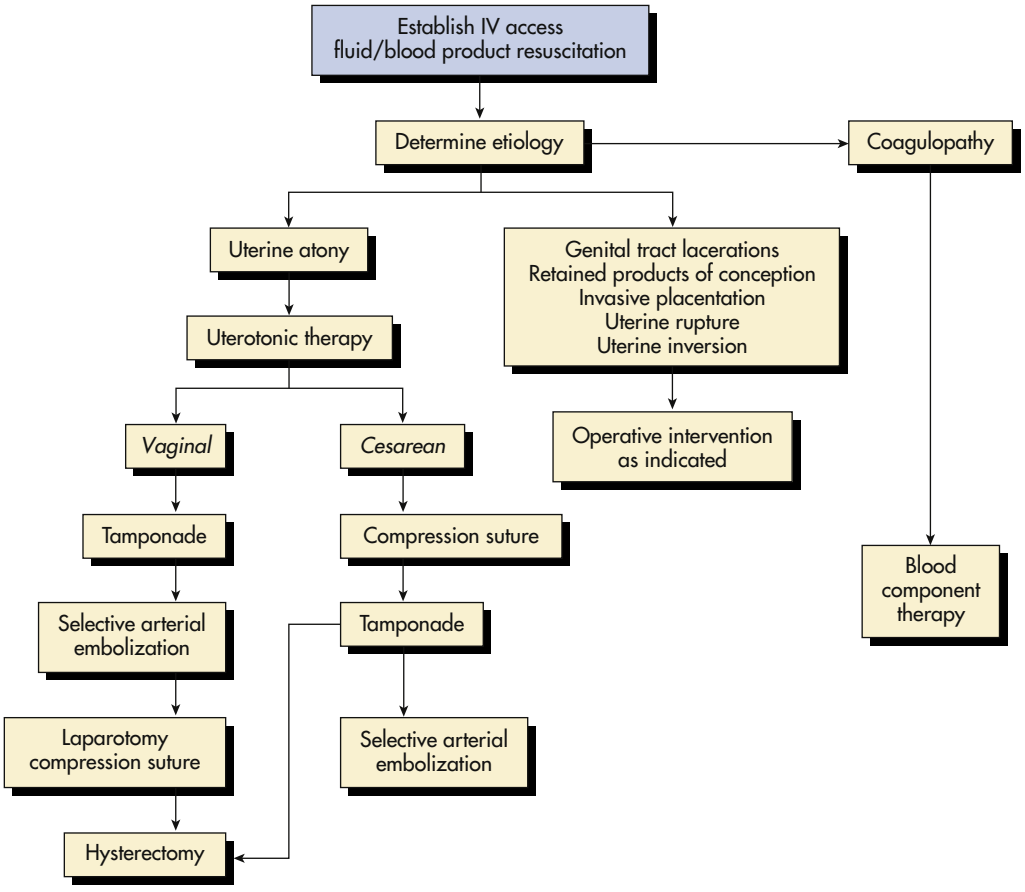

FIGURE P1-67 Management of postpartum hemorrhage. (From Gabbe S.G.: *Obstetrics*, 6th ed, Philadelphia, 2012, Saunders.)

SUGGESTED READINGS

Combs CA et al.: Factors associated with post-partum hemorrhage with vaginal birth, *Obstet Gynecol* 77:69–76, 1991.

Mousa HA, Alfirevic Z: Treatment for primary postpartum haemorrhage, *Cochrane Database Syst Rev* 1:CD003249, 2007.

Postpartum hemorrhage: ACOG Practice Bulletin No. 76, *Obstet Gynecol* 108:1039–1047, 2006.

BASIC INFORMATION

DEFINITION

Postpoliomyelitis syndrome (PPS) is a disorder typically characterized by the gradual onset and slow progression of new weakness, fatigue, and pain in survivors of paralytic poliomyelitis after a period of partial or complete recovery and many years of neurologic stability. The symptoms are persistent and cannot be explained by the presence of other neurologic, medical, or orthopedic conditions.

SYNONYMS

Post-polio syndrome
Progressive postpoliomyelitis muscular atrophy

ICD-9CM CODES
138 Late effects of acute poliomyelitis
ICD-10CM CODES
G14 Post-polio myelitic syndrome
B91 Sequelae of poliomyelitis
Excludes 1: sequelae of poliomyelitis (B91)

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Estimates vary from 22% to 85% of individuals who survive acute poliomyelitis
PEAK INCIDENCE: About 30 to 36 years following acute poliomyelitis, although cases have been reported between 8 and 71 years.
RISK FACTORS:
- Increasing age and greater length of time since the episode of acute poliomyelitis
- Acute poliomyelitis at an older age
- Greater severity of the acute poliomyelitis or chronic deficits after recovery

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The most common clinical features are new weakness (20% to 60%), fatigue (59% to 89%), and pain (38% to 86%).
- The symptoms typically have an insidious onset with gradual progression.
- The new weakness is typically, but not exclusively, in muscles that were previously affected by the acute poliomyelitis.
- Fatigue may be described as general or muscular in nature and is often the most disabling symptom.
- Pain is usually described as severe aching, cramping, or burning localized to the muscles or joints, particularly in areas previously affected by acute poliomyelitis
- Respiratory weakness and sleep-disordered breathing with nocturnal hypoventilation occur less frequently
- Other less common features include fasciculations, dysphagia, dysarthria, and cold intolerance
- Neurologic examination reveals evidence of asymmetric, lower motor neuron weakness with or without musculoskeletal deformities secondary to longstanding polio such as asymmetric limb size, kyphoscoliosis, degenerative joint disease, and joint instability.

ETIOLOGY

The pathophysiologic basis of PPS remains unclear, although there are several proposed mechanisms. The most popular hypothesis is that the reduced population of enlarged motor units after acute poliomyelitis is subject to increased stress and overuse over the course of years. This leads to distal degeneration of the motor units and worsening denervation, causing clinical symptoms.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

PPS is a diagnosis of exclusion. A particular individual's symptoms will determine the differential, but some commonly considered entities:
- Amyotrophic lateral sclerosis (ALS)
- Cervical or lumbosacral radiculopathy
- Acquired demyelinating polyneuropathies
- Myasthenia gravis
- Fibromyalgia
- Chronic fatigue syndrome
- Anemia
- Hypothyroidism
- Arthritis
- Depression
- Normal aging

WORKUP

- A detailed history should confirm a past history of acute poliomyelitis followed by a period of stability prior to emergence of the new symptoms
- A neurologic exam confirms weakness of the lower motor neuron pattern
- Nerve conduction studies and electromyography confirm the presence of denervation and help exclude other potential causes of weakness.
- A sleep study should be strongly considered to evaluate for the presence of sleep-disordered breathing.
- Pulmonary function tests should be strongly considered to evaluate for evidence of respiratory weakness.
- A swallow study should be performed in patients with difficulty swallowing.

LABORATORY TESTS

Complete blood count, electrolytes, and thyroid function tests are conducted to exclude other causes of fatigue. Erythrocyte sedimentation rate is typically normal, and increase in creatinine kinase levels (if any) is nonspecific.

IMAGING STUDIES

Magnetic resonance imaging of the brain and spine can be helpful in excluding other potential causes of weakness.

CRITERIA FOR DIAGNOSING POSTPOLIOMYELITIS SYNDROME

1. Prior episode of poliomyelitis with evidence of residual lower motor neuron loss
2. Duration of acute onset of polio and neurologic and functional stability of 15 or more years
3. Gradual onset of persistent new weakness and abnormal muscle fatigability (lasting 1 year or longer)
4. Exclusion of other conditions mentioned in the previous differential diagnosis section

TREATMENT

There is no specific therapy for PPS. However, a multidisciplinary management program tailored to the patient's presentation can be very helpful in the management of symptoms, resulting in improved functionality and quality of life.
- Most individuals will benefit from physical activity regimens (i.e., nonfatiguing exercise programs) designed by a physical therapist to focus on energy conservation and pacing.
- Orthoses and assistive devices may facilitate ambulation and other activities of daily living as well as reduce the risk of falls.
- Pain can often be controlled with conservative measures such as activity and lifestyle modifications, but analgesic medications may be necessary in some cases. Amitriptyline has been found to help with relief of pain and fatigue in anecdotal cases.
- Trials indicate that drugs such as IVIG and lamotrigine as well as application of static magnetic fields over identified trigger points may be beneficial in treating muscle weakness and pain; however, these treatments warrant further investigation.
- Several studies evaluating the use of pyridostigmine for the treatment of weakness and fatigue in PPS have had conflicting results.
- Studies evaluating amantadine, modafinil, prednisone, and human growth hormone have failed to show any definitive benefit.
- There have been promising initial results with limited studies of lamotrigine and intravenous immunoglobulin, but further trials are needed.

DISPOSITION

- The symptoms of PPS tend to be slowly progressive and may stabilize over the course of years.
- The weakness, fatigue, and pain may result in disability.
- Rarely fatal, but individuals with respiratory weakness and dysphagia are at increased risk and may benefit from early use of noninvasive respiratory support.

REFERRAL

- Neuromuscular specialist can assist in diagnosis and management.
- Physiatry, physical therapy, and occupational therapy for rehabilitation and assistive devices.
- Speech therapy referral is useful in patients with dysarthria or dysphagia.
- Pulmonary consult should be obtained for patients with symptoms or signs of respiratory weakness.
- Orthopedic consult may be necessary for patients requiring surgical correction of joint deformities.

- A mental health professional can assist with management of depression and other psychosocial issues.

PEARLS & CONSIDERATIONS

COMMENTS

- A diagnosis of PPS should only be made after a thorough evaluation for other potential causes of the patient's symptoms has been completed.
- Due to the high incidence of PPS among the large number of poliomyelitis survivors, PPS is the most common motor neuron disease worldwide.
- For patients with PPS who need to undergo surgical procedures, shorter-acting anesthetic agents should be used due to these patients' impaired baseline respiratory status and their potentially increased sensitivity to anesthetic and nondepolarizing neuromuscular blocking agents.

PATIENT & FAMILY EDUCATION

Website: http://www.mayoclinic.com/health/post-polio-syndrome/DS00494

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **DIVYA SINGHAL, M.D.**

SUGGESTED READINGS

Amato AA, Russell JA: Neuromuscular disorders. McGraw-Hill: New York.

Gonzalez H et al.: Management of postpolio syndrome, *Lancet Neurol* 9:634–642, 2010.

Jubelt B, Drucker J: Poliomyelitis and the post-polio syndrome. In Younger D, editor: *Motor disorders*. Lippincott Williams & Wilkins: Philadelphia, p. 381.

Koopman FS et al.: Treatment for post-polio syndrome (Review), *Cochrane Database Syst Rev* 16(2):CD007818, 2011.

Trojan DA et al.: Post-poliomyelitis syndrome, *Muscle Nerve* 31:6–19, 2005.

BASIC INFORMATION

DEFINITION

Posttraumatic stress disorder (PTSD) develops in some people after witnessing or experiencing a traumatic event that involves actual or threatened injury to self or others. Symptoms continue longer than a month after the event or have delayed onset and include: intrusive thoughts, nightmares, avoidance of things associated with the trauma, hypervigilance, and negative changes in mood and cognition. These symptoms cause distress and a decline in function. People with PTSD may feel numb or irritable or may be easily startled or frightened and sometimes isolate themselves from others.

SYNONYMS (HISTORICAL)

Soldier's heart
Effort syndrome
Shell shock
Irritable heart
Traumatic necrosis
Survivor syndrome
Concentration camp syndrome
PTSD

ICD-9CM and DSM-5 CODES
309.81
ICD-10CM CODES
F43.1 Post-traumatic stress disorder

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Fewer than 10% of individuals who have experienced a traumatic event will develop PTSD.

PREVALENCE (IN U.S.)

- One of the most common psychiatric disorders; estimated lifetime prevalence 7.8% to 12.3%.
- Prevalence among high-risk populations (e.g., combat veterans or victims of violent crimes) up to 58%.
- Psychiatric comorbidity is common (depression, anxiety disorder, or substance use)
- Factors most associated with development are previous traumatic experience and subsequent life stress and perceived lack of social support
- Twice as many women as men are affected (prevalence 10% to 14% for women and 5% to 6% for men). More than 50% of cases in women are related to sexual assault.

PREDOMINANT AGE: No predisposing age factors.

GENETICS: Twin studies have demonstrated genetic vulnerability related to combat.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Core symptom clusters include intrusion, avoidance, negative mood and cognition, hyperarousal, and sometimes dissociative symptoms. Individuals present with different variations of these symptoms. Symptoms must occur for >1 month and result in significant distress and functional impairment.

Key PTSD symptoms:

1. Distressing memories or dreams of the event. Note: Children older than 6 may express this symptom in repetitive play.
2. Flashbacks.
3. Intense distress after reminders of the event.
4. Avoidance due to trauma-related thoughts or feelings.
5. Persistent negative trauma-related emotions.
6. Feeling detached.
7. Aggressive or reckless behavior.
8. Hypervigilance.
9. Problems with concentration or sleep.
10. Depersonalization.

ETIOLOGY

- Interpersonal violence is more likely to cause PTSD than events such as motor vehicle accidents or natural disasters.
- Severity of physical injury is a weaker predictor of PTSD than the psychological distress; stress duration is the most important factor.
- Proposed mechanisms include activation of the amygdala, disruption of prefrontal cortex modulation of the amygdala, and excessive stress-induced HPA and alpha-1 receptor activation.

DIAGNOSIS

Diagnosis is made when the stressor is consistent with DSM-5 definition (follows), and the individual experiences symptoms of re-experiencing, avoidance, negative mood and cognition, and arousal and reactivity as defined under "Clinical Presentation." The symptoms must be present for >one month, must cause impairment in functioning, and must not be attributable to substance use or other medical conditions. Subtypes meet specified criteria and in addition have dissociative symptoms or delayed onset (meeting full criteria at least six months after the event.)

Definition of Stressor

Exposure to death, threatened death, actual or threatened serious injury, or actual or threatened sexual violence, as follows: (1 required)

1. Directly experiencing the event.
2. Witnessing the event occur to others.
3. Indirectly, by learning that a close relative or close friend was exposed to trauma. If the event involved actual or threatened death, it must have been violent or accidental.
4. Repeated or extreme indirect exposure to aversive details of the event(s), usually in the course of professional duties (e.g., first responders collecting body parts; professionals repeatedly exposed to details of child abuse). This does not include indirect nonprofessional exposure through electronic media, television, movies, or pictures, unless the exposure is work related.

DIFFERENTIAL DIAGNOSIS

- Adjustment disorders: precipitating stress is less catastrophic and psychological reaction is less specific.
- Acute stress disorder: duration of symptoms from 48 hr to 4 wk after trauma.

Anxiety disorder and obsessive-compulsive disorder

- Major depressive disorder.
- Personality disorders.
- Dissociative disorders
- Conversion disorder (functional neurological symptom disorder).
- Psychotic disorder.
- Traumatic brain injury.

WORKUP

- Among self-report questionnaires and structured diagnostic instruments, the best validated is the Posttraumatic Diagnostic Scale.
- Laboratory and imaging are not clinically useful.
- Primary care PTSD (PC-PTSD) screen recommended by the Veterans Administration. "Yes" answers to three of four of the questions is a positive screen:
  In your life, have you ever had any experience that was so frightening, horrible, or upsetting that, in the past month, you:
  Have had nightmares about it or thought about it when you did not want to?
  Tried hard not to think about it or went out of your way to avoid situations that reminded you of it?
  Were constantly on guard, watchful, or easily startled?
  Felt numb or detached from others, activities, or your surroundings?

TREATMENT

- Talk therapy, either psychodynamic or CBT with sensitivity to pacing, readiness, containment, and dissociation, can decrease symptom intensity and frequency. Prolonged exposure (PE), a type of CBT that includes education on stress response, breathing training, and prolonged recounting of the event including sensory details, was found to be more effective than standard CBT in female veterans. There is some controversy regarding appropriateness of exposure therapy for all patients, particularly those with "complex PTSD" from multiple lifetime traumatic events, and the potential for "retraumatization."
- Group therapy is helpful, particularly for combat veterans.
- Eye movement desensitization reprocessing (EMDR) has shown efficacy in controlled trials.

MEDICATIONS

There is no definitive cure for PTSD, and individuals have varying responses to different medications. Sertraline and paroxetine, both SSRIs, are the only FDA-approved medications for PTSD. Other medication use is off-label with differing levels of evidence to support use. Medications are used to target symptoms and the physiologic changes associated with PTSD.

- SSRIs, SNRIs: sertraline, paroxetine, fluoxetine, venlafaxine.

- Other antidepressants: mirtazapine, nefazodone.
- Mood stabilizers: topiramate has been shown to be effective in some studies. Other mood stabilizers are sometimes used off-label to target individual patient symptoms, such as severe irritability, anxiety, aggression, or depression.
- Guanfacine may be helpful in treating arousal symptoms.
- Prazosin may decrease distressing dreams and improve sleep quality.
- Atypical antipsychotics have had mixed results in clinical trials. Risperidone been shown to be effective in some studies. Other antipsychotics are sometimes used off-label to target individual patient symptoms such as paranoia, extreme anxiety, or angry outbursts.

ACUTE GENERAL Rx

- Immediate postincident debriefing may worsen outcome.
- A brief course of benzodiazepines may be helpful acutely but has not been shown to decrease development of core symptoms.
- Beta-adrenergic blockers may be helpful if given within hours after the trauma to disrupt the physiologic stress response.
- Sedating antidepressants or sleep aids may be helpful for initial insomnia.

COMPLEMENTARY & ALTERNATIVE APPROACHES

Acupuncture has been shown to be effective in decreasing symptoms of PTSD.

DISPOSITION

- Recovery rates are highest in the first 12 mo after onset.
- Average duration of symptoms is 36 mo for those who undergo treatment and 64 mo for those never treated.
- 50% chance of remission at 2 yr; 50% have chronic symptoms.
- Predictors of chronic course include previous trauma, premorbid psychiatric function, panic reaction at time of event, prolonged terror, or dissociation at time of event.

REFERRAL

Because early intervention improves outcome, refer to psychiatry as soon as diagnosis made.

PEARLS & CONSIDERATIONS

- PTSD can be associated with suicidal ideation and attempts.
- PTSD can be associated with aggressive and violent behavior.
- Traumatic medical experiences such as being in the ICU, or a myocardial infarction, or an emergent cesarean section can cause PTSD.
- Individuals with PTSD are 80% more likely to have a comorbid psychiatric disorder, including substance abuse.
- Among combat veterans of recent wars, there is a 41% co-occurrence with mild TBI.
- PTSD may vary culturally and present as culturally specific syndromes and idioms of distress.
- Treatment can be effective even if it begins years after the traumatic event occurred.
- PTSD is increasingly being conceived of as a stress-induced fear-circuitry disorder of the limbic system.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Posttraumatic Stress Disorder (PTSD) (Patient Information)

AUTHORS: **KAILA COMPTON, M.D., Ph.D.** and **ALISON C. MAY, M.D.**

SUGGESTED READINGS

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, *DSM-5*, May 7, 2013. 5th Edition.

Bastien DL: Pharmacological treatment of combat-induced PTSD: a literature review, *Br J Nurs* 219(5):318–321, Mar 11-24, 2010.

Bisson JI: Post-traumatic stress disorder, *BMJ* 334:789–793, 2007.

Breslau N et al.: Previous exposure to trauma and PTSD effects of subsequent trauma: results from the Detroit area study of trauma, *Am J Psychiatry* 156: 902, 1999.

Crumlish N, O'Rourke K: A systematic review of treatments for post-traumatic stress disorder among refugees and asylum-seekers, *J Nerv Ment Dis* 198(4):237–251, Apr 2010.

Davydow DS et al.: Posttraumatic stress disorder in generalized intensive care unit survivors: a systematic review, *Gen Hosp Psychiaty* 30:421, 2008.

Edmundson D et al.: Posttraumatic stress prevalence and risk of recurrence in acute coronary syndrome patients: a meta-analytic review, *PLoS One* 7:e38915, 2012.

Forbes D et al.: Australian guidelines for the treatment of adults with acute stress disorder and post-traumatic stress disorder, *Aust N Z J Psychiatry* 41(8):637–648, 2007.

Heim C, Nemeroff CB: Neurobiology of posttraumatic stress disorder, *CNS Spectr* 14(1):13–24, 2009. Suppl 1.

Jonas DE et al. Psychological and Pharmacological Treatments for Adults With Posttraumatic Stress Disorder (PTSD) [Internet]. Agency for Healthcare Research and Quality: Rockville, MD.

Karl A et al.: A meta-analysis of structural brain abnormalities in PTSD, *Neurosci Biobehav Rev* 30:1004, 2006.

Kubzansky LD et al.: Prospective study of posttraumatic stress disorder symptoms and coronary heart disease in the normative aging study, *Arch Gen Psychiatry* 64:109–116, 2007.

National Center for PTSD (NCPTSD), United States Department of Veterans Affairs: Available at http://www.ptsd.va.gov. Accessed September 2013.

Schottenbauer MA et al.: Contributions of psychodynamic approaches to treatment of PTSD and trauma: a review of the empirical treatment and psychopathology literature, *Psychiatry* 71(1):13–34, 2008.

Watts BV et al.: Meta-analysis of the efficacy of treatments for posttraumatic stress disorder, *J Clin Psychiatry* 74(6):e541–e550, 2013.

BASIC INFORMATION

DEFINITION

Postural orthostatic tachycardia syndrome (POTS), an under-recognized autonomic disorder, is defined as a form of orthostatic intolerance in which an exaggerated increase in heart rate (HR; >30 beats per min or an increase to 120 beats per min within 5 min of standing or tilt up) occurs during standing, without orthostatic hypotension. Symptoms occur while standing and are relieved by recumbency. It is often misdiagnosed as panic or anxiety disorders. These symptoms may be profoundly exacerbated by simple activities such as walking or even eating and thus can be very disabling.

SYNONYMS

Orthostatic intolerance
Orthostatic tachycardia
POTS Postural tachycardia syndrome

ICD-9CM CODES
337.9
ICD-10CM CODES
G90.9 Disorder of the autonomic nervous system, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Unknown.
PREVALENCE: Estimated to be 5-10× more common than orthostatic hypotension; ~500,000 patients in the United States (25% are disabled and unable to work).
PREDOMINANT SEX AND AGE: Female/male ratio of 5:1. Mean age is 30 years old (most commonly between 15-50 years old).
GENETICS: Possible links with mutations in a norepinephrine transporter have been identified. They result in decreased norepinephrine clearance, causing excessive sympathetic activation.
RISK FACTORS
- Female sex.
- Preceding viral infection or systemic illness (up to 50% of cases).
- Deconditioning and prolonged bed rest.
- Medications (e.g., vasodilators, diuretics, antidepressants, anxiolytic agents).
- Predisposition to hypovolemia.
- Autoimmune disorders (e.g., multiple sclerosis).
- Excessive sympathetic states (e.g., sepsis, trauma, surgery).
- Underlying autonomic neuropathy such as in advanced diabetic states.
- Chronic fatigue syndrome (40% have POTS).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms vary, are due to orthostasis (with cerebral hypoperfusion) or sympathetic overreaction, and commonly include:
- Palpitations, especially with standing and may have constant tachycardia up to >160 beats/min while standing.
- Blurred vision.
- Anxiety.
- Fatigue upon standing.
- Tremulousness.
- Dizziness, lightheadedness, presyncope, and syncope.
- Intolerance to exercise or heat and constantly feeling cold.
- Nausea.
- Cyclic nature (e.g., worsening with intravascular volume changes during menstrual cycle).

Physical findings are mostly the orthostatic hemodynamic changes and may include a reduced pulse pressure with marked beat-to-beat variability of both pulse pressure and HR. Flack sign is the difficulty in palpating a radial pulse with continued standing or Valsalva maneuver. There may be venous prominence with continued standing resulting in blueness and swelling of the feet.
- 10% of dysautonomic POTS may progress to paroxysmal atrial fibrillation.
- Recent studies suggest a link between dysautonomic POTS and joint hypermobility syndrome.

ETIOLOGY

Heterogenous etiologies, which overlap in different types of POTS:
- Hypovolemic POTS: Decreased effective intravascular volume, with peripheral and splanchnic venous pooling that worsen with standing. Most patients do not have reduced plasma volume or red cell mass.
- Neuropathic or dysautonomic POTS: Patchy sympathetic denervation of lower extremities and kidneys resulting in orthostatic venous pooling and relative hypovolemia with failure of the peripheral vasculature to vasoconstrict properly upon standing.
- Hyperadrenergic or beta hypersensitivity POTS: High orthostatic plasma norepinephrine levels (≥600 pg/ml); prominent symptoms are of sympathetic over-activation.
- These patients may even have significant orthostatic hypertension. An underlying genetic disorder may be a possible cause.
- Deconditioned POTS: Venous pooling in lower extremities due to weak leg "muscle pump"; fibromyalgia-type symptoms with anxiety, exercise intolerance, and prominent fatigue.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Orthostatic hypotension.
- Inappropriate sinus tachycardia.
- Dehydration.
- Medication side effects.
- Other forms of autonomic neuropathies.
- Other forms of central dysautonomias.
- Deconditioning.
- Anxiety and panic attacks

WORKUP

- Full autonomic system review to evaluate for autonomic neuropathies.
- Orthostatic vital signs.
- Tilt table testing is diagnostic. Continuous monitoring of HR and BP for at least 10 min. Findings during head-up tilt include:
  1. Increase in HR of ≥30 beats/min (HR usually ≥120 beats/min).
  2. Absence of drop in BP.
  3. Orthostatic intolerance symptoms (see earlier).
  4. Plasma catecholamines should be measured supine and after standing for 15 minutes. In 50% of patients standing, norepinephrine level ≥600 pg/ml, signifying a hyperadrenergic response.
  5. 24-hour urine sodium of <100 mEq signifies a hypovolemic state.
- Iron studies and complete blood count to evaluate for anemia.

LABORATORY TESTS

Include serum norepinephrine and 24-hour urine sodium to rule out hyperadrenergic and hypovolemic states.

IMAGING STUDIES

None unless otherwise indicated.

TREATMENT

Education about the pathophysiology of POTS and aggravating and alleviating factors can help patients better handle the condition. Suspected medications should be discontinued. ~40% to 90% of patients respond to a combination of nonpharmacotherapy and pharmacotherapy (mostly β-blockers, then SSRIs, bupropion, pharmacologic volume expanders, or α-1 agonists).

NONPHARMACOLOGIC THERAPY

Cornerstone of therapy is increasing vascular tone and effective intravascular volume with preventing of venous pooling.
- Some measures, such as contracting muscles below the waist for 30 seconds and wearing abdominal binders or a support hose, can reduce venous capacitance and increase total peripheral resistance.
- Drinking two 8-oz glasses of water sequentially can result in sympathetically mediated pressor response lasting for 1 to 2 hr.
- Hypovolemic patients usually improve with increasing fluid (2 L/day) and sodium intake (10 to 20 g of salt).
- All patients (especially deconditioned ones) can benefit from an exercise training program (aerobic with lower extremity strengthening).
- Atrio-ventricular node ablation and pacemaker implantation can be considered for recurrent syncope refractory to all other therapies.

ACUTE GENERAL Rx

Volume expansion with 1 L of normal saline over 1 to 3 hours.

CHRONIC Rx

- β-blockers (propranolol and atenolol) for neuropathic (allow for unopposed α-receptor-mediated vasoconstriction) and hyperadrenergic POTS (block β1 receptors in heart).
- SSRIs for neuropathic and hyperadrenergic POTS (decrease the central production of serotonin).

- Volume expanders (fludrocortisone and oral vasopressin) for hypovolemic and neuropathic POTS.
- Midodrine for neuropathic POTS.
- Central sympatholytic agents (clonidine and methyldopa) for hyperadrenergic POTS.
- Erythropoietin for refractory neuropathic POTS (increases sensitivity to angiotension II).
- Recent data shows that the acetylcholinesterase inhibitor pyridostigmine may be an effective agent.

DISPOSITION
Can usually be managed in an outpatient setting.

REFERRAL
Cardiology as needed.

PEARLS & CONSIDERATIONS

COMMENTS
This syndrome is still not well understood and current therapies may not be effective. Because of its debilitating nature and its recurrent symptoms, patients often feel discouraged and may need psychological support.

PREVENTION
None except therapies above.

SUGGESTED READINGS
Available at www.expertconsult.com

AUTHORS: **PHILLIP RUISI D.O** and **ARAVIND RAO KOKKIRALA, M.D.**

SUGGESTED READINGS

Arnold AC et al.: Low-dose propranolol and exercise capacity in postural tachycardia syndrome: a randomized study, *Neurology* 80:1927, 2013.

Benarroch EE: Postural tachycardia syndrome: a heterogeneous and multifactorial disorder, *Mayo Clin Proc* 87(12):1214–1225, 2012.

Blomström-Lundqvist C et al.: ACC/AHA/ESC guidelines for patients with supraventricular arrhythmias, *J Am Coll Cardiol* 42(8):1493–1531, 2003.

Carew S et al.: A review of postural orthostatic tachycardia syndrome, *Europace* 11(1):18–25, 2009.

Kimpinski K et al.: A prospective, 1 year follow-up study of postural tachycardia syndrome, *Mayo Clin Proc* 87(8):746–752, 2012.

Medow MS et al.: The postural tachycardia syndrome, *Cardiol Rev* 15(2):67–75, 2007.

Ojha A et al.: Comorbidities in pediatric patients with postural tachycardia syndrome, *J Pediatr* 158:20, 2011.

Thanavaro JL et al.: Postural orthostatic tachycardia syndrome: diagnosis and treatment, *Heart Lung* 40(6):554–560, 2011.

BASIC INFORMATION

DEFINITION

Precocious puberty is defined as sexual development occurring before age 8 yr in females and 9 yr in males.

SYNONYMS

Pubertas praecox

ICD-9CM CODES
259.1 Precocious puberty
ICD-10CM CODES
E30.1 Precocious puberty

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Estimated to be between 1 in 5000 to 1 in 10,000.
PREDOMINANT SEX: Females are affected more often than males for the idiopathic variant; for other causes, dependent on the underlying etiology.
GENETICS: The genetics for some of the etiologies of precocious puberty is known. Deficiency of *MKRN3* causes central precocious puberty in humans.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- In females: breast development, pubic hair development, accelerated growth, menarche.
- In males: increase in testicular volume and penile length, pubic hair development, accelerated growth, muscular development, acne, change in voice, penile erections.

ETIOLOGY

- Idiopathic or true: diagnosis of exclusion.
- Central nervous system (CNS) pathology: tumors, hydrocephalus, ventricular cysts, benign lesions.
- Severe hypothyroidism.
- Posttraumatic head injury.
- Genetic disorders: neurofibromatosis, tuberous sclerosis, McCune-Albright syndrome, congenital adrenal hyperplasia.
- Gonadal tumors.
- Nongonadal tumors: hepatoblastoma.
- Exposure to exogenous sex steroids.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Most common diagnoses to consider: premature thelarche and premature adrenarche.
- Gonadotropin hormone-releasing hormone (GnRH)-dependent precocious puberty: idiopathic, CNS tumors, hypothalamic hamartomas, neurofibromatosis, tuberous sclerosis, hydrocephalus, status after acute head injury, ventricular cysts, status after CNS infection.
- GnRH-independent precocious puberty: congenital adrenal hyperplasia, adrenocortical tumors (males), McCune-Albright syndrome (females), gonadal tumors, ectopic human chorionic gonadotropin (hCG)-secreting tumors (chorioblastoma, hepatoblastoma), exposure to exogenous sex steroids, severe hypothyroidism.
- Table P1-30 summarizes the differential diagnosis of sexual precocity.

WORKUP

Thorough history and physical examination are essential to determine if the patient has true precocious puberty. Particular attention should be paid to growth, development, order of appearance of the secondary sexual characteristics, pubertal development in family members, medications, neurologic symptoms, Tanner staging, abdominal and neurologic examination. Flowcharts for diagnosing sexual precocity in females and males are shown in Figs. P1-68 and P1-69.

LABORATORY TESTS

- GnRH testing will help determine if dependent or independent cause.
- Sex hormone studies: luteinizing hormone, follicle-stimulating hormone, hCG, testosterone (males), estrogen (females). Levels of sex steroids should be determined in the morning, with use of assays that have detection limits adapted to pediatric values. In girls, serum estradiol levels are highly variable and have a rather low sensitivity for the diagnosis of precocious puberty.
- T_4, thyroid-stimulating hormone.

IMAGING STUDIES

- CT scan or MRI of the brain to evaluate for CNS pathology.
- Consideration of pelvic ultrasound in female patients to evaluate for ovarian cysts or tumors.
- Abdominal imaging with CT scan if intraabdominal pathology suspected.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Good communication with the parents is essential to care.
- Psychological support for the child may be needed with regard to self-image and problems with peer acceptance.

ACUTE GENERAL Rx

There is no acute therapy for precocious puberty.

CHRONIC Rx

Therapy depends on the etiology of precocious puberty. For the treatment of central or gonadotropin-dependent precocious puberty depot GnRH agonists (leuprorelin, leuprolide, triptorelin, goserelin, histrelin, buserelin) are effective.

- Leuprolide is given 0.25 to 0.3 mg/kg with a 7.5 mg minimum IM every 4 wk. Local side effects include pain, erythema, and inflammatory reactions. Other side effects include headaches and menopausal-like symptoms (asthenia, hot flashes).
- For other CNS lesions and extragonadal tumors, therapy is dependent on the type of lesion, location of the lesion, and the overall prognosis of the underlying problem.
- For severe hypothyroidism, treatment with thyroid hormone will result in regression of the sexual development. The child will subsequently undergo appropriate pubertal development later in life.
- For familial male gonadotropin-independent precocious puberty, the androgen-synthesis inhibitor ketoconazole can be used at doses of 600 mg/day divided tid, or a combination of the aromatase inhibitor testolactone and spironolactone can be used.

DISPOSITION

- For true precocious puberty and some CNS lesions, long-term outcome is usually very good. When drug therapy is instituted, it is continued until a time when further pubertal development is appropriate. It is then discontinued, allowing the child to progress through puberty.
- For other cases, long-term outcomes depend on the prognosis of the underlying cause.

REFERRAL

- Initial workup can be instituted by the primary care provider.
- Referral to an endocrinologist is indicated for most children because they will need long-term management, monitoring, and treatment.
- Attention to the emotional needs of the child is important.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Precocious Puberty (Patient Information)

AUTHOR: **RUBEN ALVERO, M.D.**

TABLE P1-30 Differential Diagnosis of Sexual Precocity

	Plasma Gonadotropins	LH Response to GnRH	Serum Sex Steroid Concentration	Gonadal Size	Miscellaneous
Gonadotropin-Dependent					
True precocious puberty	Prominent LH pulses (premature reactivation of GnRH pulse generator)	Pubertal LH response initially during sleep	Pubertal values of testosterone or estradiol	Normal pubertal testicular enlargement or ovarian and uterine enlargement	MRI of brain to rule out CNS tumor or other abnormality; skeletal survey for McCune-Albright syndrome (by US)
Incomplete Sexual Precocity (Pituitary Gonadotropin-Independent)					
MALES					
Chorionic gonadotropin-secreting tumor in males	High hCG, low LH	Prepubertal LH response	Pubertal value of testosterone	Slight to moderate uniform enlargement of testes	Hepatomegaly suggests hepatoblastoma; CT scan of brain if chorionic gonadotropin-secreting CNS tumor suspected
Leydig cell tumor in males	Suppressed	No LH response	Very high testosterone	Irregular, asymmetric enlargement of testes	
Familial testotoxicosis	Suppressed	No LH response	Pubertal values of testosterone	Testes symmetric and >2.5 cm but smaller than expected for pubertal development; spermatogenesis occurs	Familial; probably sex-limited, autosomal dominant trait
Virilizing congenital adrenal hyperplasia	Prepubertal	Prepubertal LH response	Elevated 17-OHP in CYP21 deficiency or elevated 11-deoxycortisol in CYP11B1 deficiency	Testes prepubertal	Autosomal recessive, may be congenital or late-onset form, may have salt loss in CYP21 deficiency or hypertension in CYP11B1 deficiency
Virilizing adrenal tumor	Prepubertal	Prepubertal LH response	High DHEAS and androstenedione values	Testes prepubertal	CT, MRI, or US of abdomen
Premature adrenarche	Prepubertal	Prepubertal LH response	Prepubertal testosterone, DHEAS, or urinary 17-ketosteroid values appropriate for pubic hair stage 2	Testes prepubertal	Onset usually after 6 yr of age; more frequent in CNS-injured children
FEMALES					
Granulosa cell tumor (follicular cysts may present similarly)	Suppressed	Prepubertal LH response	Very high estradiol	Ovarian enlargement on physical examination, CT, or US	Tumors often palpable on physical examination
Follicular cyst	Suppressed	Prepubertal LH response	Prepubertal to very high estradiol	Ovarian enlargement on physical examination, CT, or US	Single or recurrent episodes of menses and/or breast development; exclude McCune-Albright syndrome
Feminizing adrenal tumor	Suppressed	Prepubertal LH response	High estradiol and DHEAS values	Ovaries prepubertal	Unilateral adrenal mass
Premature thelarche	Prepubertal	Prepubertal LH, pubertal	Prepubertal or early estradiol response	Ovaries prepubertal	Onset usually before 3 yr of age
Premature adrenarche	Prepubertal	Prepubertal LH response	Prepubertal estradiol; DHEAS or urinary 17-ketosteroid values appropriate for pubic hair stage 2	Ovaries prepubertal	Onset usually after 6 yr of age; more frequent in brain-injured children
Late-onset virilizing congenital adrenal hyperplasia	Prepubertal	Prepubertal LH response	Elevated 17-OHP in basal or corticotropin-stimulated state	Ovaries prepubertal	Autosomal recessive
IN BOTH SEXES					
McCune-Albright syndrome	Suppressed	Suppressed	Sex steroid pubertal or higher	Ovarian (on US); slight testicular enlargement	Skeletal survey for polyostotic fibrous dysplasia and skin examination for café au lait spots
Primary hypothyroidism	LH prepubertal; FSH may be slightly elevated	Prepubertal FSH may be increased	Estradiol may be pubertal	Testicular enlargement; ovaries cystic	TSH and prolactin elevated; T_4 low

CNS, Central nervous system; *CT*, computed tomography; *CYP*, P450 cytochrome isoenzyme; *DHEAS*, dehydroepiandrosterone sulfate; *GnRH*, gonadotropin-releasing hormone; *hCG*, human chorionic gonadotropin; *LH*, luteinizing hormone; *MRI*, magnetic resonance imaging; *17-OHP*, 17-hydroxyprogesterone; T_4, thyroxine; *TSH*, thyrotropin; *US*, ultrasonography.

From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams Textbook of Endocrinology,* ed 12, 2011, Philadelphia, Saunders, Elsevier Inc.

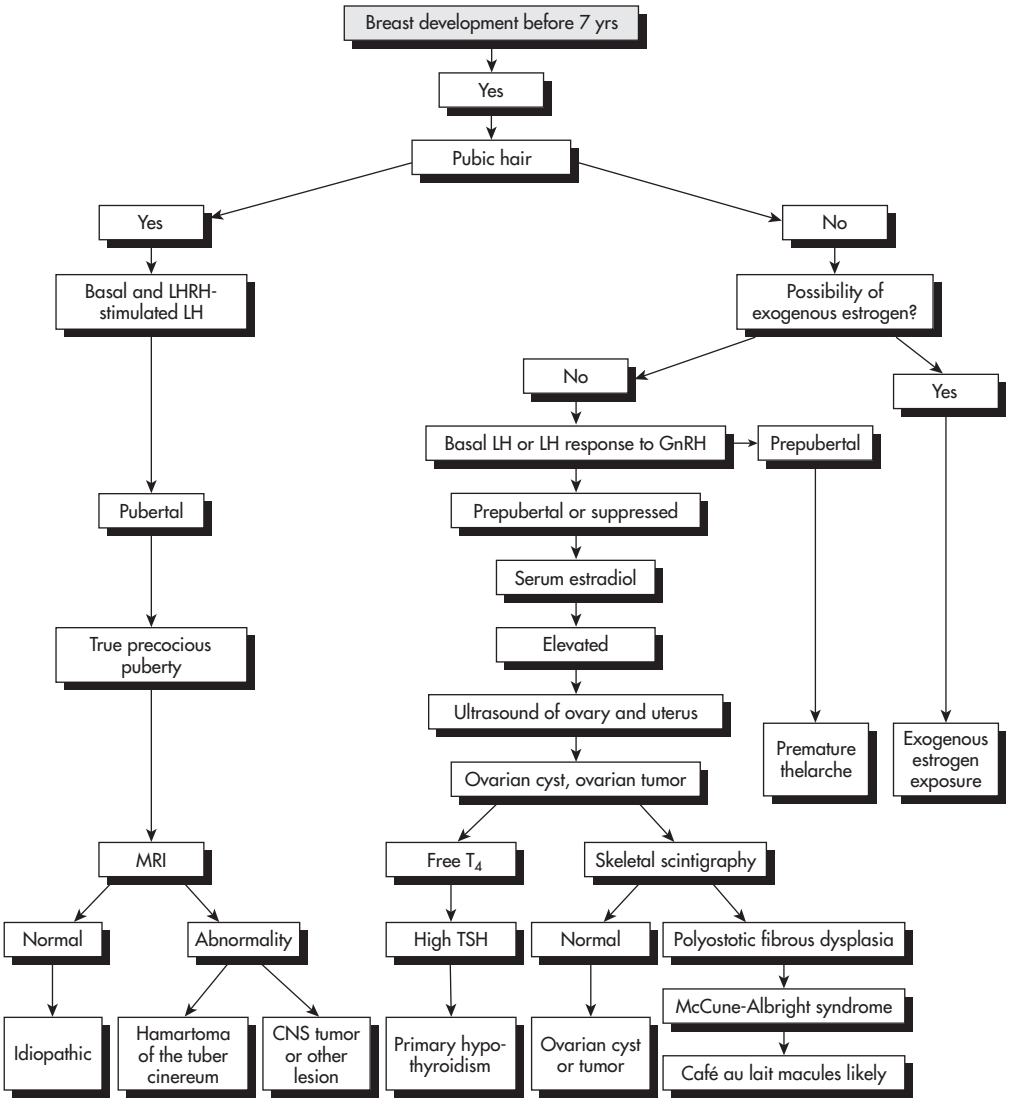

FIGURE P1-68 Flowchart for diagnosing sexual precocity in girls. *CNS*, Central nervous system; *FSH*, follicle-stimulating hormone; *LH*, luteinizing hormone; T_4, thyroxine; *TSH*, thyroid-stimulating hormone. (From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology*, ed 3, Philadelphia, 2011, Saunders.)

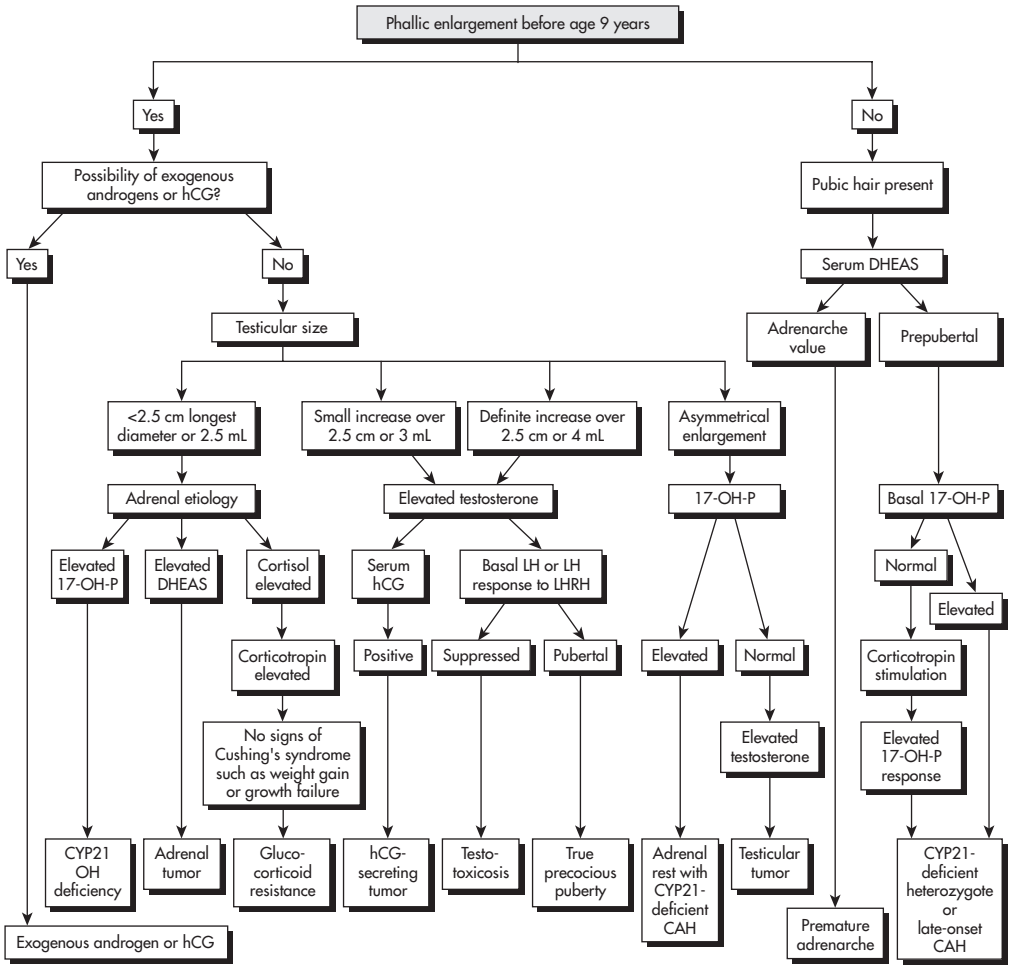

FIGURE P1-69 Flowchart for diagnosing sexual precocity in a phenotypic male. *CAH*, Congenital adrenal hyperplasia; *DHEAS*, dehydroepiandrosterone sulfate; *hCG*, human chorionic gonadotropin; *17-OH-P*, 17-hydroxyprogesterone. (From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.)

SUGGESTED READINGS

Abreau AP: Central precocious puberty caused by mutations in the imprinted gene. MKRN3, *N Engl J Med* 368:2469–2479, 2013.

Carel JC, Leger J: Precocious puberty, *N Engl J Med* 358:2366, 2008.

BASIC INFORMATION

DEFINITION

Preeclampsia involves the triad of hypertension, proteinuria, and edema that develops after the twentieth week of gestation. Mild preeclampsia is defined as a blood pressure of >140/90 mm Hg. Severe preeclampsia (Table P1-31) is associated with a blood pressure <160/110 mm Hg, proteinuria <5 g in a 24-hr urine collection, oliguria (>400 ml/24 hr), cerebral or visual disturbances, epigastric pain, pulmonary edema, thrombocytopenia, hepatic dysfunction, or severe intrauterine growth restriction. Criteria for atypical preeclampsia are described in Box P1-9. Table P1-32 differentiates preeclampsia from chronic hypertension.

SYNONYMS

Pregnancy-induced hypertension
Toxemia of pregnancy

ICD-9CM CODES
642.6 Preeclampsia
ICD-10CM CODES
O14.0 Moderate pre-eclampsia
O14.1 Severe pre-eclampsia
O14.9 Pre-eclampsia, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 0% to 14% in primigravidas, 5.7% to 7.3% in multigravidas
RISK FACTORS: Increased incidence and severity with multiple gestations or renal or collagen-vascular diseases. Extremes of reproductive age, <20 or >35 yr, obesity, African American race, thrombophilia, previous preeclampsia.
GENETICS: Positive correlation with maternal and paternal family history

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Preeclampsia typically presents with hypertension, peripheral edema, and proteinuria, most commonly in the third semester of pregnancy.
- Generalized swelling or nondependent edema, possibly manifested by rapid weight gain (>4 lb/wk) even in the absence of edema
- Auscultation of pulmonary rales
- Right upper quadrant pain (HELLP syndrome [hemolysis, elevated liver enzymes, and low platelet count] or subcapsular liver hematoma)
- Hyperreflexia or clonus
- Vaginal bleeding (placental abruption)
- Acute or chronic fetal compromise manifested by intrauterine growth restriction or fetal tachycardia with late decelerations, respectively
- Wide range of symptoms attributable to multiorgan system dysfunction, involving hepatic, hematologic, renal, pulmonary, and central nervous systems
- Possibility of severe disease despite "normal" blood pressure readings, so a high index of suspicion must be maintained in high-risk situations

ETIOLOGY

- Exact etiology or toxic substance is unknown
- Theories:
  1. Imbalance between thromboxane A_2 (vasoconstrictor and platelet aggregator) and prostacyclin (vasodilator)
  2. Abnormal trophoblastic invasion of spiral arteries
  3. Increased sensitivity to angiotensin II by the muscular walls of the arteries
  4. Excess circulating soluble fms-like tyrosine kinase 1 (*sFlt1*), which binds placental growth factor (PlGF) and vascular endothelial growth factor (VEGF), may have a pathogenic role
- Potential secondary effects of the metabolic, inflammatory endothelial alternatives in preeclampsia are described in Table P1-33.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute fatty liver of pregnancy
- Appendicitis

TABLE P1-31 Criteria for the Diagnosis of Severe Preeclampsia

In patients with preeclampsia, **severe preeclampsia** can be diagnosed if any one of the following criteria is present:

Blood pressure
≥160 mm Hg systolic or ≥110 mm Hg diastolic on two separate occasions at least 6 hours apart
Proteinuria
Random urine protein-creatinine ratio ≥5 mg/ml (500 mg/mmol) *or* proteinuria ≥5 g/24 h
Oliguria <500 ml in 24 hours
Cerebral or visual disturbances such as cerebrovascular accident, seizures, or visual loss
Pulmonary edema
Epigastric or right upper quadrant pain
Hepatocellular injury (serum transaminases at least twice normal)
Serum lactate dehydrogenase: >600 IU/L
Thrombocytopenia <100,000
Fetal growth restriction (birth weight less than 10th percentile for the gestational age)

From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

BOX P1-9 Criteria for Atypical Preeclampsia

Gestational hypertension plus one or more of the following:
Symptoms of preeclampsia
Hemolysis
Thrombocytopenia (<100,000/mm^3)
Elevated liver enzymes: two times the upper limit of the normal value for aspartate transaminase (AST) and alanine transaminase (ALT)
Gestational proteinuria plus one or more of the following:
- Symptoms of preeclampsia
- Hemolysis
- Thrombocytopenia
- Elevated liver enzymes
- Early signs and symptoms of preeclampsia-eclampsia at <20 weeks
- Late postpartum preeclampsia-eclampsia (>48 hours postpartum)

(From Gabbe S.G.: *Obstetrics*, 6th ed, Philadelphia, 2012 Saunders.)

TABLE P1-32 Differences between Preeclampsia and Chronic Hypertension

Feature	Preeclampsia	Chronic Hypertension
Age (yr)	Young (<20)	Older (>30)
Parity	Primigravida	Multigravida
Onset	After 20 wk of pregnancy	Before 20 wk of pregnancy
Weight gain and edema	Sudden	Gradual
Systolic blood pressure	<160 mm Hg	>160 mm Hg
Funduscopic findings	Spasm, edema	Arteriovenous nicking, exudates
Left ventricular hypertrophy	Rare	More common
Proteinuria	Present	Absent
Plasma uric acid	Increased	Normal
Blood pressure after delivery	Normal	Elevated

From Zipes DP et al (eds): *Braunwald's heart disease,* ed 7, Philadelphia, 2005, Saunders.

- Diabetic ketoacidosis
- Gallbladder disease
- Gastroenteritis
- Glomerulonephritis
- Hemolytic-uremic syndrome
- Hepatic encephalopathy
- Hyperemesis gravidarum
- Idiopathic thrombocytopenia
- Thrombotic thrombocytopenic purpura
- Nephrolithiasis
- Pyelonephritis
- Peptic ulcer disease
- Systemic lupus erythematosus
- Viral hepatitis

WORKUP

- Two blood pressure measurements with the patient in lateral recumbent position 6 hr apart, with an absolute pressure >140/90 mm Hg or an increase of 30 mm Hg systolic or 15 mm Hg diastolic from baseline, an increase in the mean arterial pressure (MAP) of 20 mm Hg, or an absolute MAP >105 mm Hg
- Evaluation for proteinuria as defined by >0.1 g/L on urine dipstick or >300 mg protein on a 24-hr urine collection
- Evaluation of fetal status for evidence of intrauterine growth restriction, oligohydramnios, alteration in umbilical or uterine artery Doppler flow, or acute compromise, such as abruption
- Because of the insidious nature of the disease with potential for multiple organ involvement, as well as its prevalence, complete evaluation for preeclampsia in any pregnant patient presenting with central nervous system derangement or gastrointestinal symptoms after 20 wk of gestation
- Evaluation for associated conditions such as disseminated intravascular coagulation, hepatic dysfunction, or subcapsular hematoma
- Fig. P1-70 outlines a management plan for patients with severe preeclampsia

LABORATORY TESTS

- High-risk patients: baseline assessment of renal function (24-hr urine collection for protein and creatinine clearance), platelets, blood urea nitrogen, creatinine, liver function tests (LFTs), and uric acid should be obtained at the first prenatal visit.
- Complete blood count (hemoglobin, hematocrit, platelets) may show signs of volume contraction or HELLP syndrome.
- LFTs (aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase) are useful in evaluation for HELLP syndrome or to exclude important differentials.
- Hyperuricemia or increased creatinine may indicate decreasing renal function.
- Prothrombin time, partial thromboplastin time, and fibrinogen should be checked to rule out disseminated intravascular coagulation.
- Peripheral smear may demonstrate microangiopathic hemolytic anemia.
- Complement levels can be used to differentiate from an acute exacerbation of a collagen-vascular disease.
- Increased levels of *sFlt1* and reduced levels of PlGF predict subsequent development of preeclampsia.

IMAGING STUDIES

- CT scan of head if atypical presentation of eclampsia, possibility of intracerebral bleed, or prolonged postictal state
- Sonogram of fetus to evaluate for intrauterine growth restriction (Fig. P1-71), amniotic fluid, placenta
- Sonogram of maternal liver if suspect subcapsular hematoma

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Bed rest in left lateral decubitus position

TABLE P1-33 Potential Secondary Effects of the Metabolic, Inflammatory Endothelial Alternatives in Preeclampsia

CVS	Increased peripheral resistance leading to hypertension Increased vascular permeability and reduced maternal plasma volume
Lungs	Laryngeal and pulmonary edema
Renal	Glomerular damage leading to proteinuria, hypoproteinemia, and reduced oncotic pressure, which further exacerbates the hypovolemia. May develop acute renal failure ± cortical necrosis
Clotting	Hypercoagulability, with increased fibrin formation and increased fibrinolysis, i.e., disseminated intravascular coagulation
Liver	HELLP syndrome Hepatic rupture
CNS	Thrombosis and fibrinoid necrosis of the cerebral arterioles Eclampsia (convulsions), cerebral hemorrhage, and cerebral edema
Fetus	Impaired uteroplacental circulation, potentially leading to FGR, hypoxemia, and intrauterine death

CVS, Cardiovascular system; *CNS,* central nervous system; *FGR,* fetal growth restriction; *HELLP,* hemolysis, elevated liver enzymes, low platelets.

From Drife J, Magowan B: *Clinical obstetrics and gynecology,* Philadelphia, 2004, Saunders.

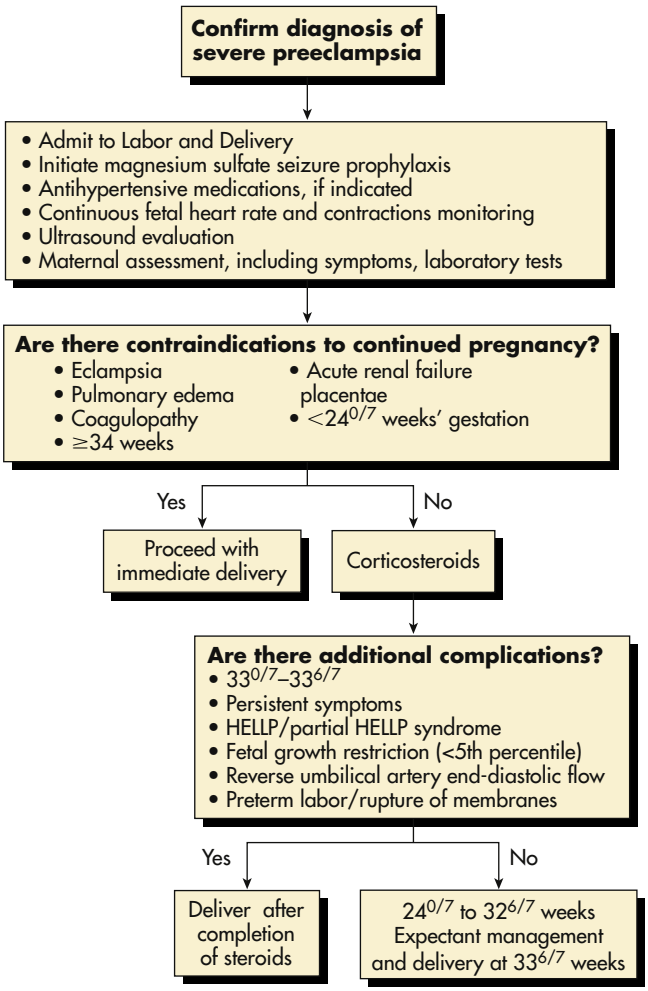

FIGURE P1-70 Management plan for patients with severe preeclampsia. (From Gabbe S.G.: *Obstetrics,* 6th ed, Philadelphia, 2012 Saunders.)

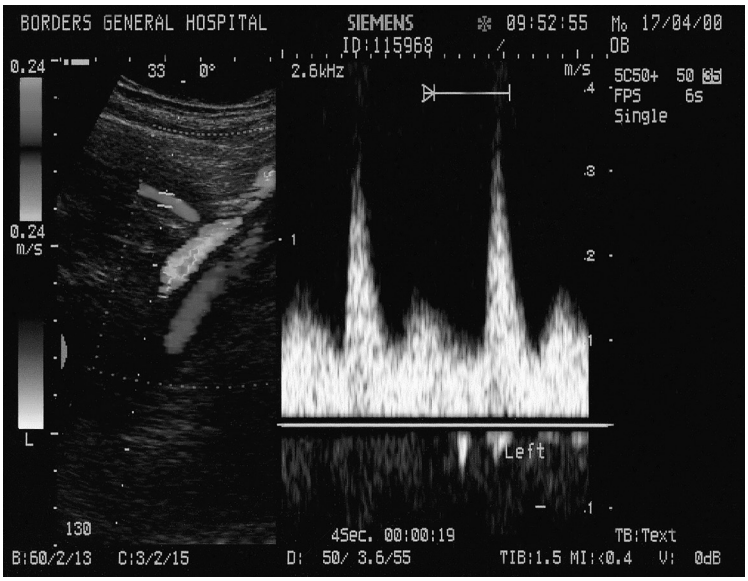

FIGURE P1-71 Uterine artery Doppler notching at 24 wk is predictive of preeclampsia and intrauterine growth restriction in high-risk mothers. (From Drife J, Magowan B: *Clinical obstetrics and gynecology,* Philadelphia, 2004, Saunders.)

ACUTE GENERAL Rx

Delivery is the treatment of choice and the only cure for the disease. This must be taken in the context of the gestational age of the fetus, severity of the preeclampsia, and the likelihood of a successful induction and reliability of patient.

- Administer magnesium sulfate 6 g IV loading dose, with 2 to 3 g maintenance or phenytoin at 10 to 15 mg/kg loading dose, then 200 mg IV q8h starting 12 hr after loading dose.
- Hydralazine 10 mg IV, labetalol hydrochloride 20 to 40 mg IV, nifedipine 20 mg SL can be used for acute blood pressure control.
- Continuous fetal monitoring is needed.
- Epidural is anesthesia of choice for pain management in labor or cesarean section.
- All patients undergoing induction of labor should receive antiseizure medications regardless of severity of disease.

CHRONIC Rx

- Mild preeclampsia <37 wk: close observation for worsening maternal or fetal condition, with delivery at >37 wk with favorable cervix or at 40 wk regardless of cervical status.
- Severe preeclampsia: delivery in the presence of maternal or fetal compromise, labor, or >34 wk; at 28 to 34 wk consider steroids with close monitoring, and at <24 wk consider termination of pregnancy.
- Methyldopa is drug of choice for long-term blood pressure control during pregnancy.

DISPOSITION

Preeclampsia is a progressive and unpredictable disease process; a course of expectancy should be managed with caution. Up to 20% of patients who have seizures are normotensive.

REFERRAL

Obstetric management is indicated because of the insidious nature of the disease, with transfer of all cases <34 wk to a facility with a level three nursery.

PEARLS & CONSIDERATIONS

COMMENTS

- Low-dose aspirin beginning as early as the second trimester, decreases the risk of preeclampsia, preterm birth, and intrauterine growth retardation in women who are at high risk of preeclampsia. The American College of Obstetricians and Gynecologists (ACOG) recommends low-dose aspirin beginning in the late first trimester for women with a history of early-onset preeclampsia and preterm delivery at <34 weeks' gestation or preeclampsia in more than one prior pregnancy. The U.S. Preventive Services Task Force (USPSTF) recommends the use of low-dose aspirin (81 mg/day) as preventive medication after 12 weeks of gestation in women who are at high risk for preeclampsia.
- Calcium supplementation 1500 mg qd should also be considered in high-risk patients beginning after first trimester to decrease the risk of recurrence.
- Although the absolute risk of end-stage renal disease (ESRD) in women who have had preeclampsia is low, preeclampsia is a marker for an increased risk of subsequent ESRD.
- The development of preeclampsia may be one of the earliest identifiable risk markers for potential future cardiovascular disease in women. It has been shown that women who develop preeclampsia have a higher incidence of cardiovascular risk factors including components of the metabolic syndrome within 1 yr of delivery.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Preeclampsia (Patient Information)
Eclampsia (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Henderson JT et al.: Low-dose aspirin for prevention of morbidity and mortality from preeclampsia: A systematic evidence reviewed for the U.S. Preventive Services Task Force, *Ann Intern Med* 160:695–703, 2014.

Lain KY, Roberts JM: Contemporary concepts of the pathogenesis and management of preeclampsia, *JAMA* 287:3183, 2002.

LeFevre ML: Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement, *Ann Intern Med* 161:819–826, 2014.

Levine RJ et al.: Circulating angiogenic factors and risk of preeclampsia, *N Engl J Med* 350:672, 2004.

Smith GN et al.: A history of preeclampsia identifies women who have underlying cardiovascular risk factors, *Am J Obstet Gynecol* 200:58, 2009.

BASIC INFORMATION

DEFINITION

Premature labor is defined as regular contractions that result in cervical dilation or effacement prior to 37 wk gestation.

SYNONYMS

Preterm labor

ICD-9CM CODES
644.0
ICD-10CM CODES
O60.0 Preterm labor without delivery
O60.1 Preterm spontaneous labor with preterm delivery
O60.2 Preterm spontaneous labor with term delivery

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The incidence of preterm births in the U.S. has increased over the past two decades from 9.5% in 1981 to 12.7% in 2006. Between 40% and 45% of these births follow spontaneous preterm labor; either the remaining preterm births result from preterm premature rupture of membranes (PPROM), or they occur secondary to maternal or fetal indications.
PREDOMINANT SEX AND AGE: Pregnant women at the extremes of reproductive age (<17 yr and >35 yr) are at greatest risk.
GENETICS: A genetic component has been suggested. Women with sisters who have had preterm births and women with grandparents who were born preterm may be at increased risk for having preterm deliveries themselves. Single-nucleotide polymorphisms have also been associated with preterm labor.
RISK FACTORS: Risk factors for premature labor include a prior preterm delivery, intrauterine infection, systemic or genital tract infections, interpregnancy interval (<6 mo), short cervical length (<25 to 30 mm), low pre-pregnancy BMI (<19.8 kg/m^2), age <17 yr or >35 yr, a history of elective pregnancy termination, history of prior stillbirth, African-American ethnicity, vaginal bleeding, polyhydramnios or oligohydramnios, multiple gestation, structural abnormalities of the uterus, history of cervical cone biopsy or loop electrocautery excision, in vitro fertilization or ovulation induction, tobacco use, heavy alcohol consumption, cocaine use, heroin use, and psychological or social stress.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Presenting symptoms include increased pelvic pressure, abdominal cramping or contractions, increased vaginal discharge, vaginal spotting, or leakage of fluid.

ETIOLOGY

Causes of premature labor are varied and often difficult to determine. Premature labor may be secondary to infection, systemic illness, trauma, anatomic abnormalities (i.e., uterine anomaly such as lateral fusion defects like unicornuate or bicornuate uterus), or a combination of factors. It is thought that cervical ripening is the most common first step to premature labor or delivery. Subsequently, decidual-membrane activation occurs, as do contractions (Box P1-10).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

The differential should include premature labor, preterm rupture of membranes, preterm contractions (contractions prior to 37 wk gestation that do not result in cervical change), and abdominal pain or cramping secondary to other medical conditions. There are many conditions that may cause preterm contractions or premature labor. These include:

- Infection
  1. Chorioamnionitis
  2. Genital tract infections, including bacterial vaginosis, gonorrhea, chlamydia
  3. Urinary tract infections, including pyelonephritis, cystitis, or asymptomatic bacteruria
  4. Gastroenteritis
- Trauma
- Placental abruption
- Illicit drug use
- Preterm premature rupture of membranes
- Appendicitis
- Nephrolithiasis
- Pancreatitis
- Cholelithiasis

WORKUP

- History and physical exam to rule out trauma, abuse, other causes of abdominal pain, and infection
- Fetal heart rate monitoring and tocometry to determine fetal status and contraction frequency
- Speculum exam to visually assess the cervix and assess for rupture of membranes, bleeding, infection, or advanced cervical dilation
  1. If the patient is <35 wk gestation, a Fetal Fibronectin (FFN) test should be collected prior to performing a digital exam or transvaginal ultrasound. A FFN test can help predict preterm delivery if the patient has a cervical length on transvaginal ultrasound of <30 mm
- Digital exam to determine cervical dilation and effacement, and fetal station

LABORATORY TESTS

- CBC
- Urine analysis and culture
- Urine toxicology screen
- Collect tests for GBS, gonorrhea, and *Chlamydia*
- Perform a wet prep for yeast, bacterial vaginosis, and *Trichomonas*
- Fetal fibronectin
- Consider PT, PTT, INR, CMP, amylase, and lipase
- Amniocentesis may be performed if an intraamniotic infection is suspected

IMAGING STUDIES

A formal ultrasound is indicated to determine estimated fetal weight, fetal presentation, amniotic fluid volume, placental location and appearance, and cervical length.

TREATMENT

Patients with premature labor should be delivered promptly when an intraamniotic infection

BOX P1-10 Factors Linked to Preterm Labor

Demographic and Psychosocial
Extremes of age (>40 yr, teenagers)
Lower socioeconomic status
Tobacco use
Cocaine abuse
Prolonged standing (occupation)
Psychosocial stressors
Reproductive and Gynecologic
Prior preterm delivery
Diethylstilbestrol exposure
Multiple gestations
Anatomic endometrial cavity anomalies
Cervical incompetence
Low pregnancy weight gain
First-trimester vaginal bleeding
Placental abruption or previa
Surgical
Prior reproductive organ surgery
Prior paraendometrial surgery other than genitourinary (appendectomy)
Infectious
Urinary tract infections
Nonuterine infections
Genital tract infections (bacterial vaginosis)

(From Marx J.A. et al: *Rosen's emergency medicine: concepts and clinical practice,* 7th ed, Philadelphia, 2010, Elsevier.)

is suspected or when they have cervical dilation >5 cm, a persistently nonreassuring fetal heart rate tracing, intrauterine growth restriction, or vaginal bleeding concerning for placental abruption.

NONPHARMACOLOGIC THERAPY

- Smoking cessation
- Bedrest, activity restriction, and pelvic rest are often recommended, but there are insufficient data to support this practice.

ACUTE GENERAL Rx

- Antenatal administration of corticosteroids between 24 wk and 33 6/7 wk gestation is recommended for women at risk of preterm delivery to prevent neonatal respiratory distress syndrome and decrease the incidence of intraventricular hemorrhage and necrotizing enterocolitis.
- Numerous tocolytic agents have been used in an attempt to inhibit contractions (Box P1-11). Although efficacy is unclear, they can be utilized during an observation period in an effort to prolong gestation for administration of steroids or to transfer the mother to a facility capable of caring for preterm infants. This, of course, assumes there are no maternal or fetal medical contraindications to use of tocolytic drugs and no indications for rapid delivery. The most commonly used tocolytics are beta-mimetics (terbutaline), magnesium sulfate, calcium channel blockers (nifedipine), or prostaglandin synthetase inhibitors (indomethacin, ketorolac, sulindac).
- Routine antibiotic use has failed to show benefit in the absence of a known infection. But all mothers in preterm labor (without a documented negative group B strep culture) should be given antibiotics to prevent neonatal infection.

CHRONIC Rx

- Patients with a history of prior spontaneous preterm birth may be candidates for prophylactic use of 17 alpha-hydroxyprogesterone caproate between 16 wk and 36 wk gestation.
- Patients with a history of preterm birth and short cervix may also be candidates for prophylactic or rescue cerclage.
- There is no evidence supporting the use of maintenance tocolytic therapy

BOX P1-11 Commonly Used Tocolytic Agents

Magnesium sulfate
- 4–6 g IV bolus over 30 min
- 2–4 g/hr IV infusion

Terbutaline
- 5–10 mg PO q4–6 h
- 0.25–0.5 mg SC q 30 min–6 h
- 10–80 μg/min IV

Ritodrine*
- 10 mg PO q2–4 h
- 5–10 mg IM q2–4 h
- 50–350 μg/min IV

Isoxsuprine
- 20 mg PO q4–6 h
- 0.05–0.5 mg/min IV

*Ritodrine is currently discontinued in the United States.
IV, Intravenously; *PO*, orally; *SC*, subcutaneously.
(From Marx J.A. et al: *Rosen's emergency medicine: concepts and clinical practice,* 7th ed, Philadelphia, 2010, Elsevier.)

REFERRAL

- Women who present in preterm labor should be referred to an obstetrician and transferred to a facility with a neonatal intensive care unit.
- For women who present for prenatal care with a history of preterm delivery, early referral to an obstetrician is also recommended

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Abruptio Placentae (Related Key Topic)
Breech Birth (Related Key Topic)

AUTHOR: **LAUREN MAY, M.D.**

EVIDENCE

Abstract[1]

Objective:

To assess short- and long-term outcomes of pregnant women with very early rupture of membranes randomized to serial amnioinfusion or expectant management, and to collect data to inform a larger, more definitive clinical trial.

Methods:

This was a prospective non-blinded randomized controlled trial with randomization stratified for pregnancies in which the membranes ruptured between 16 + 0 and 19 + 6 weeks' gestation and 20 + 0 and 23 + 6 weeks' gestation to minimize the risk of random imbalance in gestational age distribution between randomized groups. Intention-to-treat analysis was used. The study was conducted in four UK hospital-based fetal medicine units (Liverpool Women's NHS Trust, St Mary's Hospital Manchester, Birmingham Women's NHS Foundation Trust and Wirral University Hospitals Trust). The participants were women with confirmed preterm prelabor rupture of membranes at 16 + 0 to 24 + 0 weeks' gestation. Women with multiple pregnancy, fetal abnormality or obstetric indication for immediate delivery were excluded. Participants were randomly allocated to either serial weekly transabdominal amnioinfusions if the deepest pool of amniotic fluid was < 2 cm or expectant management until 37 weeks' gestation. Short-term maternal, pregnancy and neonatal and long-term outcomes for the child were studied. Long-term respiratory morbidity was assessed using validated respiratory questionnaires at 6, 12 and 18 months of age and infant lung function test at around 12 months of age. Neurodevelopment was assessed using the Bayley Scales of Infant Development, second edition (BSID-II) at corrected age of 2 years.

Results:

Fifty-eight women were randomized to the study. Two babies were excluded from the analysis because of termination of pregnancy for lethal anomaly, leaving 56 participants (28 assigned to serial amnioinfusion and 28 to expectant management) recruited between 2002 and 2009. There was no significant difference in perinatal mortality (19/28 vs 19/28; relative risk (RR) 1.0 (95% CI, 0.70-1.43)) and maternal or neonatal morbidity. The overall chance of surviving without long-term respiratory or neurodevelopmental disability was 4/56 (7.1%); 4/28 (14.3%) in the amnioinfusion group and 0/28 in the expectant group (RR 9.0 (95% CI, 0.51-159.70)).

Conclusions:

This pilot study found no major differences in maternal, perinatal or pregnancy outcomes. The study was not designed to show a difference between the groups and the number of survivors was too small to draw any conclusions about long-term outcomes. It does, however, signal that a larger definitive study to evaluate amnioinfusion for improvement in healthy survival is needed. The pilot suggests that, with appropriate funding, such a study is feasible. Ⓐ

Evidence-Based References

Roberts D, Vause S, Martin W, et al.: Amnioinfusion in very early preterm prelabor rupture of membranes (AMIPROM): pregnancy, neonatal and maternal outcomes in a randomized controlled pilot study, *Ultrasound Obstet Gynecol* 43:490–499, 2014. Ⓐ

Porat S, Amsalem H, Shah PS, Murphy KE: Transabdominal amnioinfusion for preterm premature rupture of membranes: a systematic review and metaanalysis of randomized and observational studies, *Am J Obstet Gynecol* 207:393, 2012. e1-393.e11 Ⓐ

Van Teeffelen S, Pajkrt E, Willekes C, Van Kuijk SM, Mol BW: Transabdominal amnioinfusion for improving fetal outcomes after oligohydramnios secondary to preterm prelabour rupture of membranes before 26 weeks, *Cochrane Database Syst Rev* 8:CD009952, 2013. Ⓐ

Hofmeyr GJ, Essilfie-Appiah G, Lawrie TA: Amnioinfusion for preterm premature rupture of membranes, *Cochrane Database Syst Rev* 12:CD000942, 2011. Ⓐ

Roberts D, Vause S, Martin W, et al.: Amnioinfusion in preterm premature rupture of membranes (AMIPROM): a randomised controlled trial of amnioinfusion versus expectant management in very early preterm premature rupture of membranesda pilot study, *Health Technol Assess* 18:1–135, 2014. Ⓐ

SUGGESTED READINGS

ACOG Practice Bulletin No 31: American College of Obstetricians and Gynecologists: Assessment of risk factors for preterm birth, *Obstet Gynecol* 98:709–716, 2001.

ACOG Practice Bulletin No. 43: American College of Obstetricians and Gynecologists: Management of preterm labor, *Obstet Gynecol* 101:1039–1047, 2003.

Committee Opinion No 445: American College of Obstetricians and Gynecologists: Antibiotics for preterm labor, *Obstet Gynecol* 114:1159–1160, 2009.

Goldenberg RL et al.: Epidemiology and causes of preterm birth, *Lancet* 371:75–84, 2008.

Goldenberg RL et al.: Prevention of premature birth, *N Engl J Med* 339:313–320, 1998.

Goldenberg RL et al.: The management of preterm labor, *Obstet Gynecol* 100:1020–1037, 2002.

Gomez R et al.: Cervicovaginal fibronectin improves the prediction of preterm delivery based on sonographic cervical length in patients with preterm uterine contractions and intact membranes, *Am J Obstet Gynecol* 192:350–359, 2005.

Guinn DA et al.: Management options in women with preterm uterine contractions: a randomized clinical trial, *Am J Obstet Gynecol* 177:814–818, 1997.

Iams JD et al.: Care for women with prior preterm birth, *Am J Obstet Gynecol* 203:89–100, 2010.

Iams JD et al.: Primary, secondary, and tertiary interventions to reduce the morbidity and mortality of preterm birth, *Lancet* 371:164–175, 2008.

Martin JA et al.: Preterm births–United States 2007, *MMWR Surveill Summ* (60 Suppl)78–79, 2011.

Mercer BM et al.: Preterm labor and preterm premature rupture of the membranes: diagnosis and management, *Infect Dis Clin North Am* 11:177–201, 1997.

BASIC INFORMATION

DEFINITION

Premature rupture of membranes (PROM) is defined as rupture of membranes at term before the onset of labor.

SYNONYM(S)

Preterm premature rupture of membranes (prior to 37 weeks)
PROM

ICD-9CM CODES
658.1 Premature rupture of membranes
ICD-10CM CODES
042 Premature rupture of membranes

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Affects approximately 8% of all pregnancies.
RISK FACTORS: Intraamniotic infection, low socioeconomic status, second and third trimester bleeding, low body mass index, nutritional deficiencies, connective tissue disorders, maternal cigarette use, cervical conization or cerclage, short cervix, pulmonary disease in pregnancy, uterine overdistension, amniocentesis, prior history of PROM, prior history of preterm delivery.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients will classically present complaining of leakage or gush of fluid from the vagina. Patients may also present with contractions and vaginal bleeding. Additional symptoms can include fever, chills or abdominal pain if there is concurrent infection. Ultrasound will often demonstrate oligohydramnios.

ETIOLOGY

- Premature rupture of membranes at term may occur due to physiologic changes in addition to uterine contractions causing shearing forces. Although there are many risk factors for PROM, it often occurs in the absence of any known risk factor.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Differential diagnosis includes leakage of urine or vaginal discharge.

WORK-UP

- Sterile speculum examination demonstrating pooling of fluid in posterior fornix, visualization of fluid coming out of the cervix during Valsalva maneuver, basic vaginal pH, and characteristic ferning pattern of vaginal fluid that is dried on a microscope.
- Care should be taken to avoid any procedure that may introduce infection, so digital examination should be avoided unless patient is in active labor or delivery is imminently planned. This is of particular importance in preterm PROM.
- Fig. P1-72 shows initial assessment and management of women with premature rupture of the membranes

LABORATORY TEST(S)

- pH test: sample vaginal fluid from posterior fornix. Normal vaginal pH is 4.5-6.0. pH of amniotic fluid is 7.1-7.3. False positive test can occur in presence of blood or semen, antiseptic of bacterial vaginosis.
- Microscopy: visualization of ferning of vaginal fluid allowed to dry on the microscope slide. False positive test can occur if cervical mucus is sampled.
- Commercially available tests: AmniSure and other tests are available and demonstrate good sensitivity and specificity; however, per the American College of Obstetrics and Gynecology, these should be considered ancillary to standard evaluation.

IMAGING STUDIES

- Abdominal ultrasound: evaluation of amniotic fluid volume either by maximum vertical pocket or amniotic fluid index. Oligohydramnios or low fluid volume in itself should not be considered diagnostic of PROM.
- Amniotic fluid dye test: This is considered the gold standard in diagnosis of PROM, used in clinical scenario of suspected preterm PROM with equivocal testing. Indigo carmine dye is injected via ultrasound guidance into the amniotic sac, and diagnosis made if blue dye passes into vagina.

TREATMENT

NONPHARMACOLOGIC THERAPY

- All patients with PROM should have prompt evaluation of gestational age, fetal well-being via NST monitoring, and fetal presentation. In a patient with evidence of intraamniotic infection or fetal distress, prompt delivery is recommended. Close monitoring and consideration of delivery is recommended if there is concern for placental abruption.
- Collect swab for evaluation of GBS status.

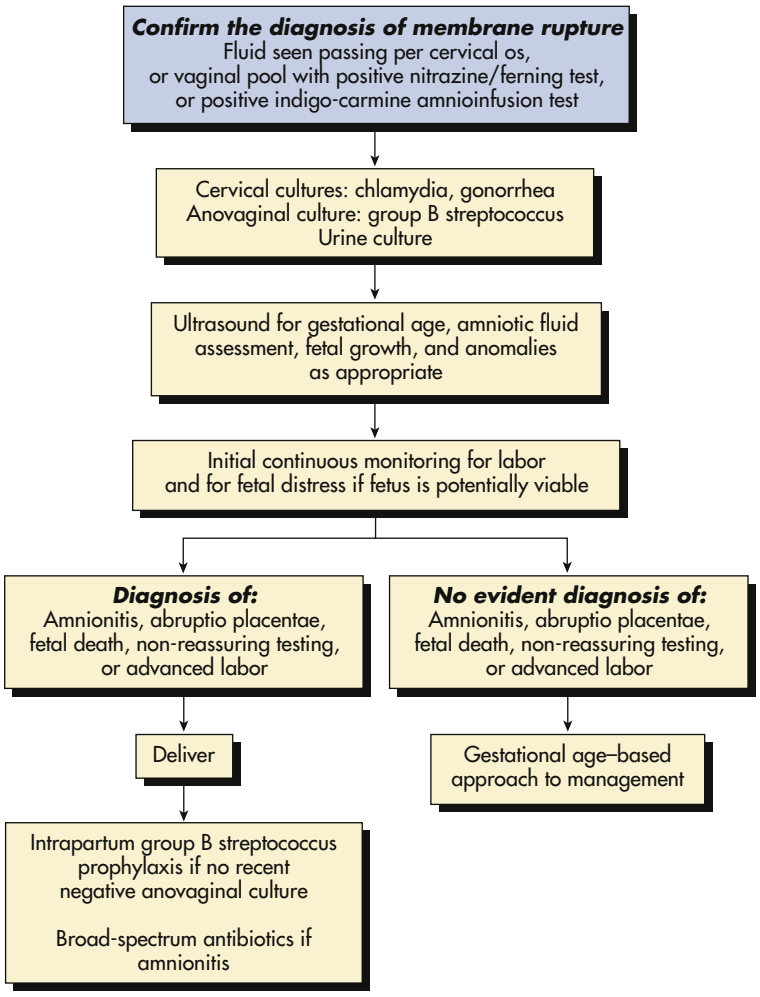

FIGURE P1-72 Initial assessment and management of women with preterm premature rupture of the membranes. (From Mercer BM: Preterm premature rupture of the membranes: diagnosis and management. *Clin Perinatol* 31:765, 2004.)

ACUTE GENERAL Rx

Term PROM:

- Any patient diagnosed with PROM at term should proceed toward delivery. Induction of labor has been shown to decrease time to delivery, risk of chorioamnionitis, endometritis, and NICU admissions, with no increase in rate of operative delivery.
- A period of expectant management can be offered in select patients who decline induction and have been appropriately counseled.
- Routine induction agents may be used. The most researched agents for induction in setting of PROM include oxytocin and prostaglandins. Oxytocin has been shown to be associated with lower rates of chorioamnionitis.
- GBS prophylaxis should be provided in GBS positive individuals or individuals with GBS unknown status and concurrent risk factors

Preterm PROM:

- 34 weeks or above: Clinician should proceed toward delivery as in term patients
- 24 to 34 weeks:
  - Administration of betamethasone for fetal lung maturity
  - Administration of prophylactic antibiotics to prolong latency period, consisting of 7-day course of parenteral and oral therapy. Current guidelines recommend ampicillin or amoxicillin and erythromycin.
  - Expectant management until 34 weeks, unless fetal lung maturity is demonstrated between 32-34 weeks.
  - Magnesium sulfate administration if delivery is imminent and <32 weeks
  - GBS prophylaxis in setting of GBS unknown /GBS positive if delivery is expected.

CHRONIC Rx

- Hospitalization with expectant management is recommended for all patients with preterm PROM. Ongoing maternal and fetal surveillance in a hospital setting allows for quick recognition of infection, labor, or fetal compromise secondary to cord compression.

DISPOSITION

- Most women with preterm PROM will proceed to deliver within one week despite medical interventions. Latency period is generally longer when PROM occurs at an earlier gestational age.
- Clinical chorioamnionitis develops in 13-16% of preterm PROM. This risk is increased with earlier PROM as well as with an increase in the number of digital vaginal examinations.
- Complications of preterm PROM are related mostly to complications of prematurity, and decrease with increasing gestational age at time of delivery. The most common complications include respiratory distress, neonatal infection, intraventricular hemorrhage, and necrotizing enterocolitis.
- There is a 1-2% risk of antenatal demise in the setting of preterm PROM

REFERRAL

- Consultation with an Ob-Gyn is recommended in the setting of preterm PROM.

PEARLS & CONSIDERATIONS

PREVENTION

- Patients with a history of preterm delivery (with or without PROM) may benefit from administration of progesterone supplementation in future singleton pregnancy starting at 16 to 24 weeks to prevent preterm delivery.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Premature Labor (Related Key Topic)
Abruptio Placentae (Related Key Topic)

AUTHOR: **CLAIRE SCHULTZ, M.D.**

SUGGESTED READINGS

Dare MR, Middleton P, Crowther CA, Flenady VJ, Varatharaju B: Planned early birth versus expectant management (waiting) for prelabour rupture of membranes at term (37 weeks or more), *Cochrane Database Syst Rev* (1):CD005302, 2006 Jan 25.

Premature Rupture of Membranes: ACOG Practice Bulletin, *Clinical Management Guidelines for Obstetrician-Gynecologists* 139, Oct 2013.

BASIC INFORMATION

DEFINITION

The *Diagnostic and Statistical Manual of Mental Disorders,* 5th edition, requires as criteria for definition of premenstrual dysphoric disorder (PMDD) the presence of five or more of the following symptoms in most menstrual cycles for the past year.

- The symptoms should be present most of the time during the last week of the luteal phase, with remission beginning within a few days after the onset of the follicular phase, and absent during the week after menses. One or more of the following symptoms must be present:
  1. Marked depressed mood, feeling of hopelessness, or self-deprecating thoughts.
  1. Marked anxiety, tension, feeling of being "keyed up" or "on edge".
  2. Marked affective lability (e.g., feeling suddenly sad or tearful or increased sensitivity to rejection).
  3. Persistent and marked anger or irritability or increased interpersonal conflicts.
- One (or more) of the following symptoms must additionally be present to reach a total of 5 symptoms when combined with symptoms 1-4 noted above:
  4. Decreased interest in usual activities (e.g., work, school, friends, hobbies).
  5. Subjective sense of difficulty in concentrating.
  6. Lethargy, easy fatigability, or marked lack of energy.
  7. Marked change in appetite, overeating, or specific food cravings.
  8. Hypersomnia or insomnia.
  9. A subjective sense of being overwhelmed or out of control.
  10. Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of "bloating," or weight gain.
- The disturbance markedly interferes with work or school or with usual social activities and relationships with others (e.g., avoidance of social activities, decreased production and efficiency at work or school).
- The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder (although it may be superimposed on any of these disorders).
- The first three criteria must be confirmed by prospective daily ratings during at least two consecutive symptomatic cycles (diagnosis may be made provisionally before such confirmation).
- The symptoms are not attributable to the physiologic effects of a substance (e.g., a drug of abuse, a medication, other treatment) or another medical condition (e.g., hyperthyroidism).

NOTE: In menstruating women, the luteal phase corresponds to the period between ovulation and the onset of menses, and the follicular phase begins with menses. In nonmenstruating women (e.g., women who have had a hysterectomy), determination of the timing of the luteal and follicular phases may require measurement of circulating reproductive hormones.

ICD-9CM CODES
625.4 Premenstrual dysphoric syndrome
ICD-10CM CODES
N94.3 Premenstrual tension syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- PMDD affects 3% to 5% of women of reproductive age.
- Genetic factors play a significant role (increased incidence in monozygotic twins and in women whose mothers had PMDD).
- 30% to 76% of women with PMDD have a lifetime history of depression.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination may be completely normal.
- Depressed mood, tachycardia, sweating from comorbid disorders (e.g., panic disorder, major depression) may be present.
- Symptoms occur during the last half of the menstrual cycle (the luteal phase) and are absent from the first day of menstruation until ovulation (follicular phase).

ETIOLOGY

- Unknown. Serotonin deficiency and altered sensitivity in serotoninergic system in response to phasic hormone fluctuations in the menstrual cycle are believed to play a role.
- Progesterone appears to be the main precipitating factor in PMDD symptoms, but estrogen may also provoke symptoms.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Premenstrual syndrome.
- Dysthymic syndrome.
- Personality disorder.
- Panic disorder.
- Major depressive disorder.
- Hyperthyroidism.
- Polycystic ovarian syndrome.
- Drug or alcohol abuse.
- Irritable bowel syndrome.
- Endometriosis.

WORKUP

- Diagnosis is based on obtaining a detailed history and ruling out the presence of physical or psychiatric disorders. No objective diagnostic tests exist.
- The diagnosis should be confirmed by using a symptom checklist prospectively for two consecutive menstrual cycles. Commonly used diagnostic instruments include the Calendar of Premenstrual Experiences and the Premenstrual Syndrome Diary.

LABORATORY TESTS

- None are usually necessary.
- A serum thyroid-stimulating hormone test to exclude thyroid problems, complete blood count to rule out anemia, and a chemistry profile to assess electrolytes may be ordered if diagnosis is unclear.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Reduction in intake of caffeine, refined sugars, or sodium may be helpful in some patients.
- Increased aerobic exercise, smoking cessation, alcohol restriction, and regular sleep are often beneficial.
- Stress reduction and management will decrease severity of symptoms.

GENERAL Rx

- Selective serotonin reuptake inhibitors are useful for the treatment of PMDD. Commonly used agents and initial doses are fluoxetine 10 mg qd, sertraline 50 mg qd, paroxetine 10 mg qd, and citalopram 20 mg qd. Many patients will require titration to significantly higher doses to achieve therapeutic benefit. These medications can be administered continuously during the menstrual cycle or only when the patients experience symptoms. Luteal phase or intermittent administration involves initiating medication at the time of ovulation and stopping it at the beginning of menses.
- Other useful agents are benzodiazepines (alprazolam 0.25 mg tid prn) and the tricyclic antidepressant clomipramine (25 mg qd as starting dose).
- Gonadotropin-releasing hormone (GnRH) agonists are effective in treating patients with PMDD. The accelerated bone loss and vasomotor symptoms associated with long-term use of a GnRH agonist will require add-back therapy. Hormonal intervention with monthly intramuscular injections of leuprolide has been reported effective in some patients; however, it should be reserved only for patients unresponsive to first- and second-line agents.
- Nutritional supplementation (vitamin B_6 up to 100 mg/day, vitamin E up to 600 IU/day, calcium carbonate up to 1200 mg/day, and magnesium up to 500 mg/day) are also commonly used for symptom reduction in some patients with limited results.
- Ovariectomy may be considered in severe refractory cases.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

American Psychiatric Association. Desk reference to the diagnostic criteria from DSM-5. American Psychiatric Association: Arlington, VA.

Biggs WS, DeMuth RH: Premenstrual syndrome and premenstrual dysphoric disorder, *Am Fam Physician* 84(8):918–924, 2011.

Segebladh B et al.: Evaluation of different add-back estradiol and progesterone treatments to gonadotropin-releasing hormone against treatment in patients with premenstrual dysphoric disorder, *Am J Obstet Gynecol* 201(139):e1–e8, 2009.

BASIC INFORMATION

DEFINITION

Premenstrual syndrome (PMS) is a cyclic recurrence during the luteal phase of the menstrual cycle of somatic, affective, and behavioral disturbances that are of sufficient severity to affect interpersonal relationships adversely or interfere with normal activities.

SYNONYMS

PMS

ICD-9CM CODES
625.4 Premenstrual tension syndromes
ICD-10CM CODES
N94.3 Premenstrual tension syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- PMS is believed to be extremely prevalent, intermittently affecting approximately one third of all premenopausal women.
- Severe cases occur in approximately 2% to 10% of women with PMS.
- Those seeking treatment for PMS are usually in their 30s or 40s.
- The natural history of PMS has not been clearly elucidated.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Diverse and potentially disabling symptoms. Table P1-34 summarizes common symptoms of cyclic PMS.
- Associated with >150 psychological, physical, and behavioral symptoms
- Most frequent reason for seeking treatment: emotional symptoms
- Most common emotional symptoms: depression, irritability, anxiety, labile moods, anger, crying easily, sadness, extreme sensitivity, nervous tension
- Most common physical symptoms: headache, bloating, cramps, breast tenderness, migraines, fatigue, weight gain, aches and pains, palpitations
- Most common behavior symptom: food cravings
- Other behavioral symptoms: increased appetite, increased alcohol intake, decreased motivation, decreased efficiency, avoidance of activities, staying home, sleep changes, libido changes, forgetfulness, decreased concentration

ETIOLOGY

- Etiology remains obscure.
- Because of the multifactorial, multiorgan nature of PMS, a single etiologic cause is unlikely.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- A diagnosis of exclusion, so other medical or psychological disorders should be ruled out.
- Most common disorders: depression or anxiety, thyroid disease.

WORKUP

- History
- Physical examination
- Laboratory studies to rule out alternative diagnosis
- If no alternative diagnosis confirms diagnosis of PMS, basal body temperature charting is used to determine if the patient is ovulating:
  1. If she is not ovulating, it is not PMS.
  2. If she is ovulating, symptoms should be charted for at least two cycles to determine if the symptoms occur in the luteal phase.
  3. If symptoms are not occurring in the luteal phase, it is not PMS and further investigation is needed.
     a. If symptoms occur in the follicular phase, patient has premenstrual exacerbation of another condition.
     b. If symptoms do not occur in the follicular phase, diagnosis of PMS is confirmed.

LABORATORY TESTS

- None available to specifically confirm the diagnosis of PMS
- Thyroid function tests to rule out thyroid disease

TREATMENT

NONPHARMACOLOGIC THERAPY

- Individualization of the treatment plan to maximize therapeutic response. Fig. P1-73 describes a summary of treatment approaches to PMS.
- Psychosocial intervention:
  1. Education
  2. Stress management
  3. Environmental changes
  4. Adequate rest and sleep
  5. Regular exercise
- Nutritional recommendations:
  1. Regularly eaten, well-balanced meals
  2. Adequate amounts of protein, fiber, and complex carbohydrates; low fat
  3. Avoidance of foods that are high in salt and simple sugars; may promote water retention, weight gain, and physical discomfort
  4. Avoidance of caffeine-containing beverages; stimulant effects of caffeine may worsen tension, irritability, and insomnia
  5. Avoidance of alcohol and illicit drugs; may worsen emotional lability
  6. Calcium supplementation (1000 mg/day for women 19 to 50 yr, 1300 mg/day for girls 14 to 18 yr) to reduce the physical and emotional symptoms
  7. Magnesium (360 mg/day) to reduce water retention and the negative effect associated with PMS
  8. Pyridoxine (vitamin B_6) 50 mg bid to improve depression, fatigue, irritability, and natural diuretic ability; neurotoxicity observed at higher dosages

ACUTE GENERAL Rx

Suppression of ovulation:
- Oral contraceptives: one pill per day
- Progestin-only oral contraceptive: one pill per day
- Oral micronized progesterone: 100 mg every morning and 200 mg every evening on days 17 through 28 of menstrual cycle
- Progestin suppository: 200 to 400 mg bid on days 17 through 28 of menstrual cycle
- Oral contraceptive containing drospirenone/ethinyl estradiol: very effective in decreasing physical symptoms
- Medroxyprogesterone: 150 mg IM q3mo
- Levonorgestrel implants: surgical insertion every 5 yr
- Transdermal estradiol: one or two 100-μg patches every 3 days
- Danazol: 100 to 200 mg/day (ovulation not suppressed at this dose); has significant side-effect profile
- Gonadotropin-releasing hormone (GnRH) agonists: daily by intranasal spray or monthly by depot injection; profound hypoestrogenism, concerns for osteoporosis and vasomotor symptoms

TABLE P1-34 Common Symptoms of Cyclic Premenstrual Syndrome

Somatic Symptoms	
Abdominal bloating	Constipation or diarrhea
Acne	Headache
Alcohol intolerance	Peripheral edema
Breast engorgement and tenderness	Weight gain
Clumsiness	
Emotional and Mental Symptoms	
Anxiety	Insomnia
Change in libido	Irritability
Depression	Lethargy
Fatigue	Mood swings
Food cravings (especially salt and sugar)	Panic attacks
Hostility	Paranoia
Inability to concentrate	Violence toward self and others
Increased appetite	Withdrawal from others

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

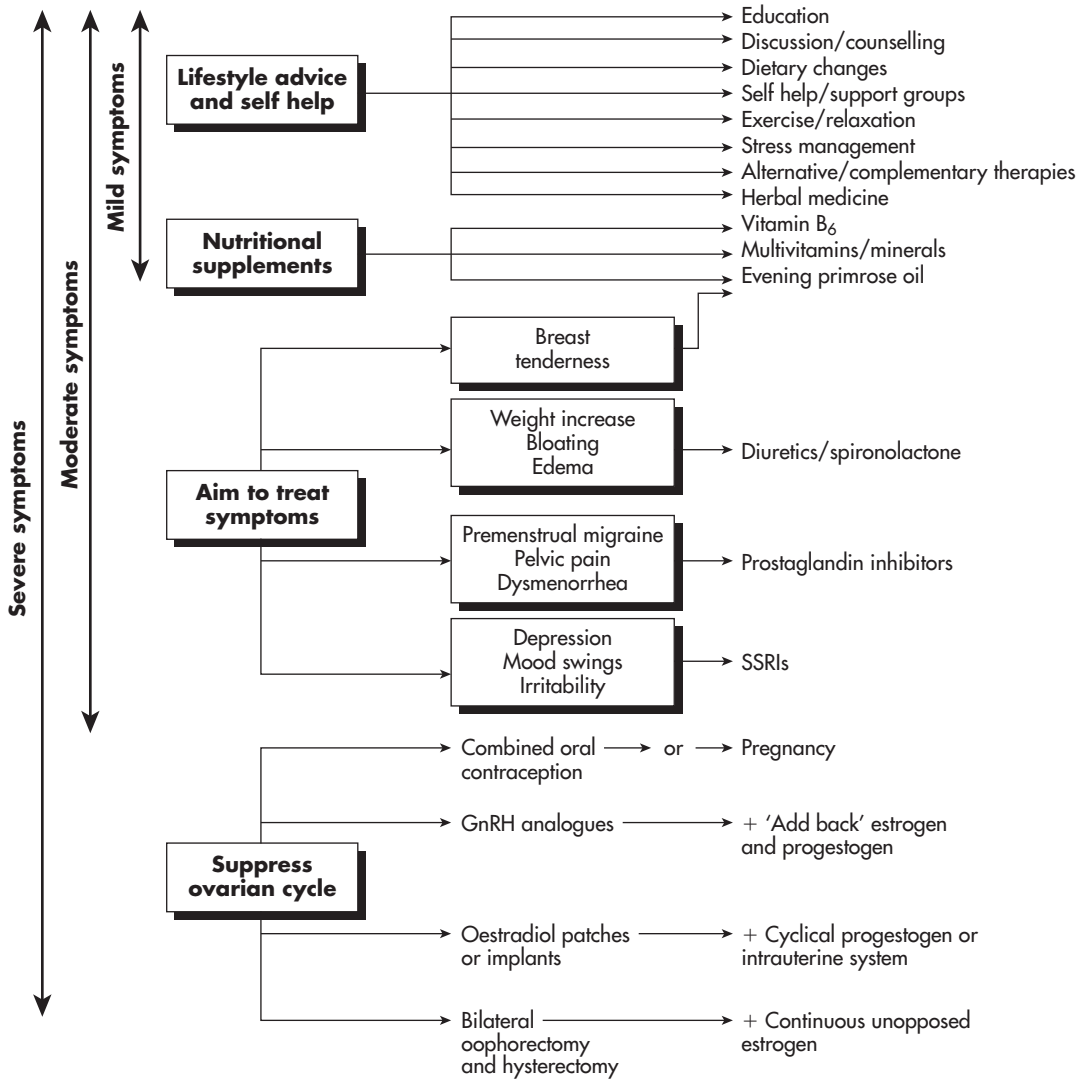

FIGURE P1-73 Summary of treatment approaches to PMS. (Modified from Andrews G: Premenstrual syndrome. In Andrews G. (ed): *Women's sexual health*, Oxford, 2005, Elsevier.)

Suppression of physical symptoms:
- Spironolactone: 25 to 50 mg bid on days 14 through 28 of menstrual cycle
- Mefenamic acid
  1. For fluid retention: 250 mg tid on days 24 through 28 of cycle
  2. For pain: 500 mg tid on days 19 through 28 of cycle
- Bromocriptine: 5 mg/day on days 10 through 26 of cycle
- Danazol: 200 mg/day on days 19 through 28 of cycle
- Naproxen: 550 mg bid on days 17 through 28 of cycle, Naprosyn-500 mg bid on days 17 through 28 of cycle

Suppression of psychological symptoms:
- Nortriptyline: 50 to 125 mg/day
- Fluoxetine: 20 mg/day or 90 mg weekly (this medication has indications for premenstrual dysphoric disorder)
- Buspirone: 10 mg bid or tid on days 16 through 28 of cycle, then taper drug
- Alprazolam: 25 mg tid on days 16 through 28 of cycle, then taper drug
- Clonidine: 0.1 mg bid
- Naltrexone: 0.25 mg/day on days 9 through 18 of cycle
- Atenolol: 50 mg/day
- Paroxetine: 20 mg/day
- Sertraline: 50 to 100 mg/day
- Nefazodone: initial dosage 100 mg bid; after 1 wk increase to 150 mg bid
- Propranolol: 20 to 40 mg bid
- Verapamil: 100 to 320 mg qd

CHRONIC Rx

- Therapy is largely trial and error, with the goal of providing effective treatment with the safest and most simple therapy. Provider should initially attempt to ameliorate the most pronounced symptom(s).
- For severe intractable PMS: bilateral oophorectomy; give trial of GnRH therapy or danazol before surgery (bilateral oophorectomy should be exceedingly rare).
- Estrogen replacement therapy recommended postoperatively to reduce the risk of osteoporosis, heart disease, and genitourinary atrophy.

DISPOSITION

Improved symptoms in 90% of women over time

REFERRAL

- For counseling with a psychologist or psychiatrist if underlying psychiatric disorder is discovered (cognitive-behavioral therapy)
- To a gynecologist if surgical therapy is contemplated

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Premenstrual Syndrome (Patient Information)
Dysmenorrhea (Related Key Topic)
Premenstrual Dysphoric Disorder (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.,** and **GEORGE T. DANAKAS, M.D.**

SUGGESTED READINGS

Biggs WS, DeMuth RH: Premenstrual syndrome and premenstrual dysphoric disorder, *Am Fam Physician* 84(8):918–924, 2011.

Brown C: A new monophasic oral contraceptive containing drospirenone: effect on premenstrual symptoms, *J Reprod Med* 47(1):14, 2002.

Miner C, Brown E: Weekly luteal-phase dosing with enteric-coated fluoxetine 90 mg in premenstrual dysphoric disorder: a randomized, double blind, placebo-controlled clinical trial, *Clin Ther* 24(3):417, 2002.

Pearlstein T: Selective serotonin reuptake inhibitors for premenstrual dysphoric disorder: the emerging gold standard, *Drugs* 62(13):2002, 1869.

Wyatt K: Premenstrual syndrome, *Clin Evid* 7:338, 2002.

BASIC INFORMATION

DEFINITION

Preoperative evaluation is the clinical risk evaluation for patients undergoing surgery. It is an overall assessment of patient's health and surgery's risk. The goal of the assessment is not to "clear" the patient for the surgery, because there is always some level of risk, but to provide accurate preoperative risk stratification and implement possible risk reduction strategies. Preoperative evaluation should also include functional assessment and determine social support. It also provides an opportunity for discussion and helps to alleviate patient's anxiety before surgery.

SYNONYMS

Preoperative evaluation and risk reduction
Risk reduction in patients undergoing invasive procedures
Preoperative clearance

ICD-9CM CODES
ICD-V72.81–ICD-V72.84
ICD-10CM CODES
Z01.810 Encounter for preprocedural cardiovascular examination
Z01.811 Encounter for preprocedural respiratory examination
Z01.818 Encounter for other preprocedural examination
Z01.812 Encounter for preprocedural laboratory examination

EPIDEMIOLOGY & DEMOGRAPHICS

The number of outpatient surgical procedures performed in the United States has been gradually expanding over the years. By the end of 2010, outpatient procedures accounted for more than 50% of all surgeries compared with less than 33% in 2000. (U.S. Surgical Procedure Volumes Report #A626, February 2012).

Some studies have shown the benefits of preoperative testing while others have shown no added benefit. Lack of added benefit has been particularly true for otherwise healthy individuals: the prevalence of significant unrecognized disease and the predictive value of tests are both low for this population–leading to an excess of false-positive tests.

In a trial of 1061 ambulatory surgical patients randomly assigned to preoperative testing or no testing, there was no difference in perioperative adverse events or events within 30 days of the surgery (Chung F et al., 2009).

Certain risk factors do exist that may be helpful: The nature and extent of surgery appear to play a role, as do increasing age, exercise capacity, and certain medications. Additionally, patients with certain pre-existing conditions such as diabetes may benefit from adjustments to their insulin preoperatively, for instance. The primary care physician may be best suited to adjust medications. Box P1-12 describes stratification of risk of common noncardiac surgical procedures.

Preoperative evaluation offers an excellent opportunity to reach out to patients about other preventive, screening, and routine health care issues as well. The primary care physician is uniquely poised to provide an accurate assessment and risk stratification of patients and to develop care plans for follow-up. This information can then be used to help surgeons counsel patients and guide patients' decision making.

PEAK INCIDENCE: When there are adverse consequences from surgery, cardiovascular complications account for the majority of morbidity and mortality in patients. Perioperative MIs (PMI) is one of the most important predictors of short- and long-term morbidity and mortality associated with surgery. The highest incidence of PMI is in the first 3 to 5 days after surgery.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The history, physical, and other studies need to assess the risks for myocardial infarction, arrhythmias, heart failure, endocarditis, stroke, venous thrombosis and pulmonary embolism, prolonged mechanical ventilation and respiratory failure, hemorrhage, diabetic acidosis, renal or hepatic failure, and infection.

WORKUP (Fig. P1-74)

HISTORY: A thorough medical history is the most valuable tool. Assess the urgency of the surgical procedure. A conversation with the surgical team is helpful for urgent and emergent procedures.

Some standard screening questionnaires have been adapted to help identify patients who would benefit from formal preoperative evaluation.

- Age is important to consider because age is often associated with an increasing number of comorbidities, which are in turn associated with an increase in perioperative risk.
- All patients should be asked about their exercise capacity before surgery. One way to assess functional capacity is in metabolic equivalents (METS) (*Circulation,* 2009) (Table P1-35). Studies have shown that those who have a low exercise capacity have twice as much risk for postoperative complications compared to those who have high exercise capacity.
- Evaluate for evidence of active cardiac conditions: unstable angina, recent MI (<30 days), significant arrhythmia, decompensated CHF, and severe valvular disease.
- Other medical conditions and risk factors:
  - Stable CAD, compensated CHF, HTN
  - Chronic lung diseases
  - Obstructive sleep apnea (preoperative screening [STOP-Bang, Berlin scores] in all patients)
  - Other medical comorbidities: CVA, diabetes mellitus (DM), CKD, liver diseases
  - Personal or family history of anesthetic complications
  - Personal or family history of hypercoagulable states or bleeding disorders
  - Medications such as anticoagulants, antiplatelets, NSAIDs, and oral hypoglycemic agents
  - Smoking
  - Alcohol
    - Obesity
    - Pregnancy
- Consider further testing based on above risk factors. The decision to order preoperative tests should be guided by the patient's clinical history, comorbidities, and physical examination findings. Cardiac evaluation algorithm for noncardiac surgery is described later (Fleisher et al, 2007).

In August 2014, The American College of Cardiology and American Heart Associated (ACC/AHA) updated their guidelines.[1] These new guidelines classify the urgency of surgery in 4 categories:

- Emergency (necessary within 6 hours)
- Urgent (necessary within 6-24 hours)
- Time-sensitive (can delay 1-6 weeks)
- Elective (can delay up to 1 year)

Surgical risk based on surgical and patient characteristics is either low (<1% risk of major adverse cardiac events) or high (≥1% risk of major adverse cardiac events). The intermediate risk category has been eliminated. Examples of high risk procedures include vascular surgery, orthopedic surgery, intraperitoneal and intrathoracic surgery, head and neck surgery, and

BOX P1-12 Stratification of Risk of Common Noncardiac Surgical Procedures

High risk (>5%)	Emergent and urgent major operations, especially in the elderly
	Aortic and noncarotid major vascular surgery
	Surgery associated with large fluid status change or blood loss
Intermediate risk (1%-5%)	Head and neck surgery
	Carotid endarterectomy surgery
	Major thoracic surgery
	Major abdominal surgery
	Orthopedic surgery
	Prostate surgery
Low risk (<1%)	Eye and skin surgery
	Endoscopy
	Breast
	Ambulatory procedure

[1] Fleisher LA et al: 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American HeartAssociation Task Force on practice guidelines, *J Am Coll Cardiol* 64:e77-e137, 2014.

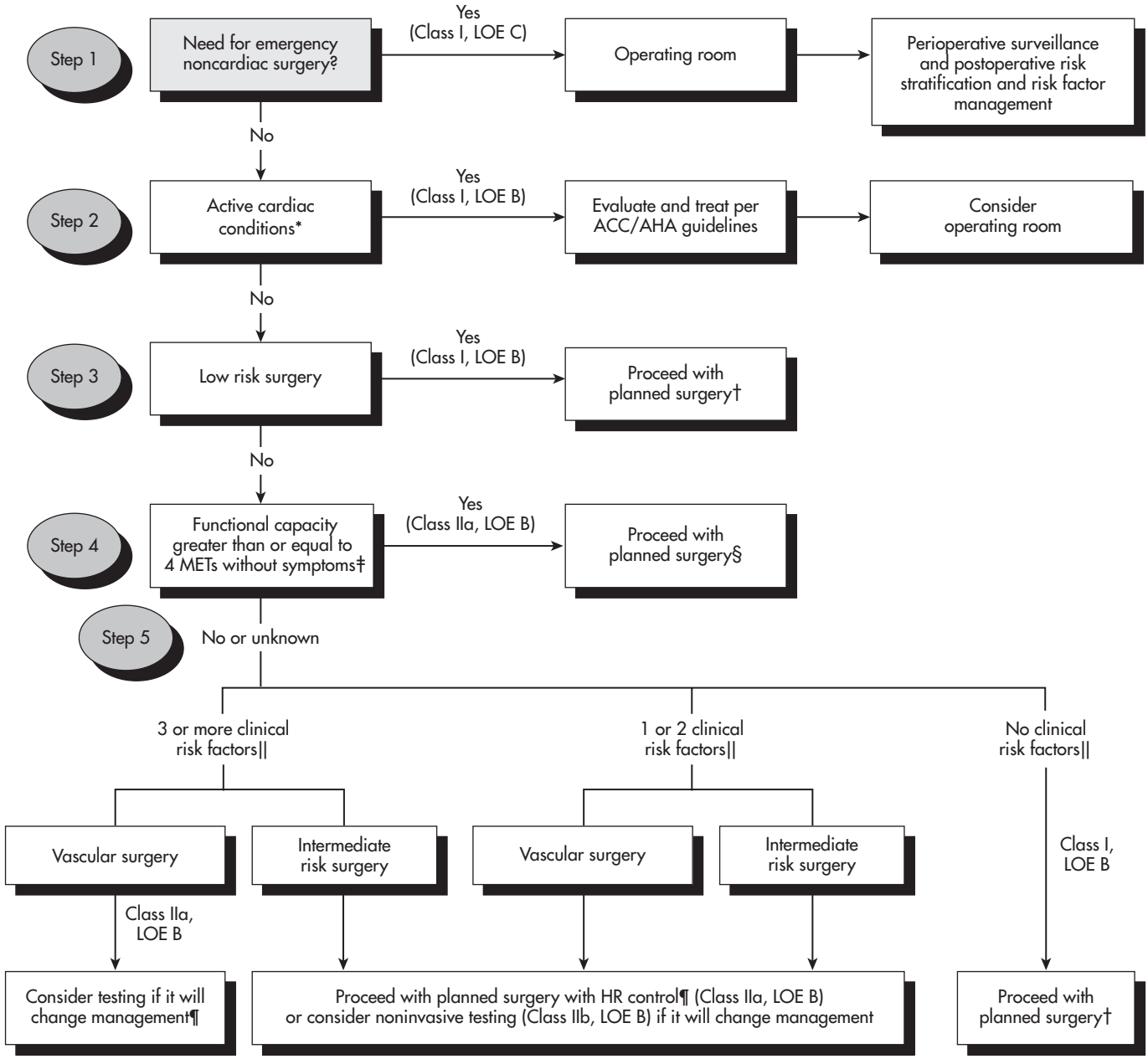

FIGURE P1-74 Stepwise approach to preoperative cardiac assessment. Cardiac evaluation and care algorithm for noncardiac surgery based on active clinical conditions, known cardiovascular disease, or cardiac risk factors for patients 50 years of age or older. (Adapted from Fleisher LA et al: ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery, *Circulation* 116: e418-e500, 2007.)

TABLE P1-35 Functional Capacity (Metabolic Equivalents)

<4 METS	4-10 METS	>10 METS
Daily living activities	Heavy housework	Strenuous exercise
Walking (2 mph)	Walking up a hill	Skiing
Walk 1-2 blocks	Walking (4 mph)	Tennis (single)
	Cycling	
	Golf	
	Tennis (double)	

(1 MET: energy expenditure of 70-kg man sitting quietly)

Adapted from Fleisher LA et al: ACC/AHA 2007 Guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery, *Circulation* 116:e418-e500, 2007.

prostate surgery. Ambulatory surgery, endoscopic procedures, and cataract surgery are considered low risk. The Revised Cardiac Risk Index (RCRI) is based on the following 6 factors, each worth a point: high risk surgery, ischemic heart disease, heart failure, stroke or TIA, diabetes requiring insulin, and renal insufficiency (serum creatinine >2.0 mg/dL). A patient with a RCRI score 0 to 1 is considered to be at low risk; a value of 2 or above is high risk.

PHYSICAL EXAMINATION

- Vital signs: blood pressure, heart rate and rhythm, rate and ease of respirations, and temperature.
- Cardiovascular exam. Auscultate heart to check for heart murmurs, pathologic heart sounds, and ventricular systolic or diastolic dysfunction.
- Respiratory exam. Auscultate lungs for crackles, wheezes, decreased breath sounds.
- Vascular exam. Examine for carotid, abdominal, and femoral bruits.
- Integumentary exam. Check for evidence of venous stasis in lower extremities, petechiae, and unusual bruises.
- Mental status. Conduct a mini-mental exam.

LABORATORY TESTS & IMAGING STUDIES

- Determine the patient's age, height, weight.
- Routine laboratory studies are not necessary unless there is a specific medical indication. (*Anesthesiology,* 2002). Testing need not be repeated if results are recently available, unless there has been a change in clinical status.
  - Low-risk procedures do not require routine basic metabolic panel, blood glucose, liver function, hemostasis evaluation, or a urine analysis.
  - For intermediate- and high-risk procedures as well as in the setting of diabetes, cardiac, or renal disease, obtain a complete blood count.
  - A CBC is recommended for all patients older than age 65 undergoing major surgery as well as anyone undergoing a surgery with expected large amounts of blood loss.
  - Fasting glucose is recommended for all patients age >45 yr. Coagulation studies are only needed for patients with personal or family history of bleeding or thrombophilia and for those taking anticoagulants.
  - Urine hCG is recommended for all women of childbearing age.
- Electrocardiogram: routine ECG is not recommended. The 2007 ACC/AHA guidelines do recommend resting 12 leads ECG for patients with:
  - At least one clinical risk factor for those who are undergoing vascular surgery (class I, level of evidence (LOE) B)
  - Known cardiovascular disease, peripheral arterial disease, and cerebrovascular disease for patients scheduled for intermediate-risk surgery (class I, LOE C)
  - No clinical risk factors for patients scheduled to undergo vascular surgery (class IIa, LOE B)
  - At least one clinical risk factor for patients who are undergoing intermediate-risk surgery (class IIb LOE B)
- Echocardiography: indicated only if new signs and symptoms of CHF or new cardiac murmurs on physical examination.
- Exercise or pharmacologic stress testing: only indicated for evaluation of the potentially high-risk patients: for patients scheduled to undergo vascular surgery with 3 or more clinical risk factors and poor functional capacity (<4 METS) if it will change management (class IIa) (Fleisher et al, 2007).
- Chest x-ray: routine CXR is not recommended. It is indicated for patients >50 years of age undergoing high-risk procedures (American College of Physicians [ACP] recommendations) and patients with new respiratory symptoms, suspected congestive heart failure, or valvular heart disease.
- Pulmonary function tests: It is only recommended for patients undergoing lung resection surgery but can be considered in:
  - Patients with COPD or asthma, only if clinical evaluation cannot determine if they are at their best baseline.
  - Patients with dyspnea or exercise intolerance that remains unexplained after clinical evaluation.
- Arterial blood gas: should be obtained only when clinically significant (to determine if lung disease is compensated).

Rx TREATMENT

- Beta blockers: While routine administration of perioperative beta-blockers was advocated for many years, conflicting evidence currently exists regarding their efficacy. While confirming a decrease in cardiac events with aggressive preoperative beta-blockade, the POISE trial (extended-release metoprolol beginning on the day of surgery) showed an increase in mortality and stroke risk (*Lancet*, 2008). On the other hand, DECREASE IV (fluvastatin + bisoprolol) demonstrated a cardioprotective effect of perioperative beta-blocker use without increased incidence in perioperative stroke or mortality (Dunkelgrun M et al, 2009). For now, the only class I indication for perioperative beta-blockers is the continuation of a beta-blocker in patients who are already taking it. In addition, several class IIa recommendations exist for patients with CAD and multiple clinical risk factors who are undergoing intermediate to high-risk surgery and especially vascular surgery. In these situations, beta-blockers should be started at least 1 wk before surgery with careful dose titration to avoid frank bradycardia or hypotension.
- Statins: decrease cardiovascular events in patients undergoing vascular surgery (*N Engl J Med,* 2009).
- Aspirin: continuation of aspirin should be considered in patients who were previously taking aspirin (Class IIa, LOE B). For surgeries where increased bleeding could result in significant morbidity (e.g., neurosurgery) or when the risk of stopping aspirin is minimal, aspirin should be stopped 7 days or more before surgery. Aspirin can be restarted on the first postoperative day as long as adequate hemostasis has been achieved.
- Adenosine diphosphate (ADP) antagonists (ticlopidine, clopidogrel, prasugrel): in patients with recently placed stents, elective surgical procedures should be delayed (minimum 3 wk for bare metal stents [BMS] and 3 mo for drug-eluting stents [DES]) while the patient is undergoing dual antiplatelet therapy. For procedures that must be performed, continuation of aspirin therapy is recommended. A short-term discontinuation of anti-ADP therapy while aspirin is continued may be relatively safe (*Circulation,* 2009).
- Anticoagulation therapy: patients taking warfarin who have a high risk of thromboembolism should be bridged with low-molecular-weight heparin (LMWH) (with the last dose 24 h before surgery) or unfractionated heparin (UFH) (with drip stopped 4 hr before surgery). Resumption of bridging therapy within 24 hr is safe for minor procedures but is associated with unacceptable, high bleeding rates in patients undergoing major surgery (Dunn et al, 2007). Therefore, it is recommended to wait 48 to 72 hr postoperatively to resume bridging therapy in patients who had major surgery. Another alternative regimen is to resume warfarin 12 to 24 hr postoperatively without any bridging therapy (Douketis et al, 2008).
- NSAIDs: NSAID therapy is almost never necessary, and it should be stopped before surgery (5-10 days prior).
- Pacemakers and defibrillators: consultation with an electrophysiologist is recommended. Pacemaker should be reprogrammed to an asynchronous mode (VOO, DOO), and defibrillation function must be set off to avoid unintentional discharge during surgery (electrocauterization).
- Smoking: smoking cessation is recommended at least 8 wk before surgery.
- Chronic obstructive pulmonary disease (COPD): COPD therapy should be optimized. Steroids and maximal bronchodilator therapy are reasonable for patients who are not at their best baseline.
- Hypertension: SBP <180 mm Hg and DBP <110 mm Hg are generally considered acceptable. In case of elective surgery, though, it is better to postpone it to allow for better BP control.
- Diabetes mellitus:
  - Type I DM: scheduled basal insulin should be given the night before surgery or the morning of surgery. Continuous insulin infusion with glucose infusions might be necessary during prolonged procedures.
  - In type II DM with oral therapy: short-acting sulfonylureas and other oral agents should be held the same day. Metformin and long-acting sulfonylureas should be held one day prior, and metformin should

be kept on hold for 48 hr postoperatively. Short-acting insulin sliding scale should be used for blood glucose control meanwhile.
  - In insulin-dependent type II DM: 50% to 100% of the basal insulin should be given depending on whether the patient will be able to eat postoperatively. During major procedures, patients may need an insulin drip and D5% infusion.
  - Currently, a blood glucose level <180 mg/dl postoperatively is considered appropriate. Aggressive blood glucose control (81-108 mg/dl vs. <180 mg/dl) showed a slight increase in risks in both surgical and medical critical care patients. (NICE-SUGAR Study Investigators, 2009).
- Liver disease: nonoperative alternative should be strongly recommended in patients with advanced cirrhosis. If surgery is deemed necessary, optimize preoperative status: correct coagulopathy, thrombocytopenia, volume status, electrolytes, ascites, and encephalopathy.
- End-stage renal disease: achieve euvolemia and correct electrolytes. Patients receiving hemodialysis should undergo dialysis the day before surgery. In patients with a prior history of uremic bleeding, desmopressin administration should be considered.
- Corticosteroid management and adrenal insufficiency: in patients taking exogenous steroids, continuation of the same steroid regimen is reasonable. In those with chronic adrenal insufficiency, steroid supplementation is generally recommended with the dose titrated to the level of stress of the surgical procedure.

PEARLS & CONSIDERATIONS

COMMENTS

Although most individuals will not require any significant preoperative testing, certain conditions will require further workup.

- Ischemic heart disease
  - If patient has angina, determine frequency, precipitating factors, response to rest and nitroglycerin
  - If patient has had prior cardiac catheterizations or coronary revascularizations, obtain previous records
- Dysrhythmias and pacemakers
  - Examine current and prior ECGs for high-grade atrioventricular block, symptomatic ventricular arrhythmias, and supraventricular tachycardias at uncontrolled rates.
  - If patient has a pacemaker, establish the type and mode, date of implantation, and when it was last interrogated.
- Valvular and congenital heart disease
  - Look for signs of severe valvular heart disease on last echocardiographic evaluations.
- Cerebrovascular disease
  - Inquire about prior carotid artery ultrasounds
- Venous thromboembolism
  - Determine results of studies for thrombophilia (factor V Leiden mutation, lupus anticoagulant, antithrombin III, protein C or S).
- Tools for cardiac risk assessment:
  - http://www.statcoder.com
  - http://www.infopoems.com

PATIENT & FAMILY EDUCATION

Advise patients that their preoperative evaluation visit with their PCP is another opportunity for them to bring up concerns or get questions answered about their upcoming procedure.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

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EVIDENCE

Abstract[1]

Background:

The 2007 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines on Perioperative Cardiac Evaluation and Care for Noncardiac Surgery is the accepted standard for perioperative cardiac evaluation. Anesthesiology training programs are required to teach these algorithms. We estimated the percentage of residents nationwide who correctly applied suggested testing algorithms from the ACC/AHA guidelines when they evaluated simulated patients in common clinical scenarios.

Methods:

Anesthesiology resident volunteers at 24 training programs were presented with 6 scenarios characterized by surgical procedure, patient's risk factors, and patient's functional capacity. Scenarios and 5 possible recommendations per scenario were both presented in randomized orders. Senior anesthesiologists at 24 different United States training programs along with the first author of the 2007 ACC/AHA guidelines validated the appropriate recommendation to this web-based survey before distribution.

Results:

The 548 resident participants, representing 12% of anesthesiology trainees in the United States, included 48 PGY-1s (preliminary year before anesthesia training), 166 Clinical Anesthesia Year 1 (CA-1) residents, 161 CA-2s, and 173 CA-3s. For patients with an active cardiac condition, the upper 95% confidence bound for the percent of residents who recommended evaluations consistent with the guidelines was 78%. However, for the remaining 5 scenarios, the upper 95% confidence bound for the percent of residents with an appropriate recommendation was 46%.

Conclusions:

The results show that fewer than half of anesthesiology residents nationwide correctly demonstrate the approach considered the standard of care for preoperative cardiac evaluation. Further study is necessary to elucidate the correct intervention(s), such as use of decision support tools, increased clarity of guidelines for routine use, adjustment in educational programs, and/or greater familiarity of responsible faculty with the material. Ⓐ

Evidence-Based Reference

Vigoda MM et al.: 2007 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines on perioperative cardiac evaluation are usually incorrectly applied by anesthesiology residents evaluating simulated patients, *Anesth Analg* 112:940–949, 2011. Ⓐ

SUGGESTED READINGS

Chung F et al.: Elimination of preoperative testing in ambulatory surgery, *Anesth Analg* 108:467–475, 2009.

Douketis JD et al.: *The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practices Guidelines*, 8th Edition, 2008. Chest 133: 299S–339S.

Dunkelgrun et al.: Bisoprolol and fluvastatin for the reduction of perioperative cardiac mortality and myocardial infarction in intermediate-risk patients undergoing noncardiovascular surgery: a randomized controlled trial (DECREASE-IV), *Ann Surg* 249:921–926, 2009.

Dunn AS, Spyropoulos AC, Turpie AG: Bridging therapy in patients on long-term oral anticoagulants who require surgery: the Prospective Perio-operative Enoxaparin Cohort Trial (PROSPECT), *J Thromb Haemost* 5:2211–2218, 2007.

Feely MA et al.: Preoperative testing before noncardiac surgery: guidelines and recommendations, *Am Fam Physician* 87(6):414–418, 2013.

Fleisher LA et al.: ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery, *Circulation* 116:e418–e500, 2007.

Fleisher LA et al.: 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, *Circulation* 120:e169, 2009.

Fleisher LA et al.: 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines, *J Am Coll Cardiol* 64:e77–e137, 2014.

Holt NF: Perioperative cardiac risk reduction, *Am Fam Physician* 85:239–246, 2012.

LeBlond R et al. DeGowin's diagnostic examination. ed 9, McGraw-Hill: New York.

NICE-SUGAR Study Investigators et al.: Intensive versus conventional glucose control in critically ill patients, *N Engl J Med* 360:1283–1297, 2009.

Poldermans D et al.: Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: the Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-Cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anesthesiology (ESA), *Eur J Anaesthesiol* 27:92–137, 2010.

Practice advisory for preanesthesia evaluation: a report by the American Society of Anesthesiologists Task Force on Preanesthesia Evaluation, *Anesthesiology* 96:485, 2002.

Shammash JB, Kimmel SE, Morgan JP: *Estimation of cardiac risk prior to noncardiac surgery,* last updated Nov 20, 2013 Available at http://www.uptodate.com.

Smetena GW: Evaluation of preoperative pulmonary risk. Available at http://www.uptodate.com.

Smetana GW: Preoperative medical evaluation of the healthy patients. Available at http://www.uptodate.com.

BASIC INFORMATION

DEFINITION

Pressure ulcers are soft tissue lesions resulting from compression, shearing forces, friction, and moisture that usually occur over bony prominences and external surfaces over an extended period of time.

SYNONYMS

Decubitus ulcers
Pressure sores
Bedsores
Decubiti

ICD-9CM CODES
707.0 Pressure ulcer, unspecified site
ICD-10CM CODES
L89 Pressure ulcers
Subcategories of codes determined by stage and location of ulcer
L89.153 Example: Stage 3 ulcer of sacral area

EPIDEMIOLOGY & DEMOGRAPHICS

- Pressure ulcers affect 3 million adults in the United States.
- The estimated cost of treating each case of pressure ulcers ranges from $37,800 to $70,000.
- Occurs in all health care settings from hospitals to nursing homes and even at home. Incidence approaches as many as 40% of affected individuals. Prevalence has declined among all nursing home residents over the past decade. It is highest in institutions with lower staffing levels of certified nurses and nursing assistants, reflecting emphasis on health care resources more than medical decision making.
- Associated with decreased quality of life and significant morbidity and mortality. One-year mortality rate approaches 40%.
- Pain occurs in two thirds of patients with stage II or greater pressure ulcers.
- Complicated by cellulitis, osteomyelitis, abscesses, and sepsis.

CLINICAL PRESENTATION

The National Pressure Ulcer Advisory Panel in 2007 has outlined the staging system of pressure ulcers as follows:

Stage I: Nonblanchable erythema of intact skin usually over a bony prominence or boggy, mushy feeling of skin

Stage II: Partial-thickness skin loss involving the epidermis, dermis, or both. May also present as an intact or ruptured serum-filled blister.

Stage III: Full-thickness skin loss involving damage or necrosis of subcutaneous tissue that may extend down to, but not through, underlying fascia or muscle. There may be undermining and tunneling.

Stage IV: Full-thickness skin loss with exposed muscle, bone, or supporting structures (e.g., tendons, joint capsule). Sloughing or eschar may be present. These ulcers often include undermining and tunneling (Fig. P1-75).

Deep tissue injury: Purple or maroon localized area of discolored, intact skin or blood-filled blister due to damage of underlying tissue from pressure and/or shear.

Unstageable: Full-thickness tissue loss with the base of the ulcer covered by slough or eschar on the wound bed.

Only pressure ulcers are classified by stage.

ETIOLOGY

Pressure ulcers are soft tissue injuries caused by constant, unrelieved pressure in tissues overlying bony prominences. The four main external factors include pressure, shearing forces, friction, and moisture. Host factors include immobility, incontinence, malnutrition, compromised skin perfusion, and concurrent medical illnesses. A number of neurologic and nonneurologic diseases may contribute, lead to, or exacerbate the development of pressure ulcers. However, further studies need to be performed to identify whether these are independent predictors.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Venous insufficiency ulcers
- Arterio-occlusive ulcers
- Diabetic ulcers
- Skin cancer
- Cellulitis
- Kennedy ulcers (rapidly progressing unpreventable ulcers that occur at the end of life)

WORKUP

Evaluate ulcer characteristics, including its stage, appearance, location, and size (documented on a clock face, with the patient's head at 12 o'clock and feet at 6 o'clock). For stages III and IV, describe the wound bed (epithelialization, granulation tissue, necrotic tissue, eschar); presence of exudates, including type and amount; depth and wound edges (undermining, sinus tracts, tunneling, or fistulas); signs of infection (purulent drainage, odor, surrounding cellulitis); and pain. In addition, pressure ulcer risk factors and causes should be reassessed.

LABORATORY TESTS

- Directed at identifying cause of risk factors or any complications arising from the pressure ulcer (e.g., abscess or osteomyelitis).
- Cultures of wound bed are not believed to be helpful and should be avoided. Deep tissue biopsy is the gold standard if a culture is indicated.
- Markers for malnutrition include prealbumin, albumin, transferrin, lymphocyte count, and total cholesterol level.
- Complete blood count if systemic infection is suspected.

IMAGING STUDIES

- Ultrasound not proven to be effective.
- Plain radiographs, MRI, and bone scan may help identify osteomyelitis when clinically suspected.
- A comparison study of 44 patients scheduled for open biopsy did not show MRI to have superior diagnostic benefit over plain radiography.

PREVENTION & TREATMENT

- Identify high-risk patients using standardized risk assessment scales (e.g., Braden, Norton, and Waterlow scales).
- Routine skin inspection and good skin care for high-risk patients.
- Minimize prolonged skin exposure to moisture, urine, or stool.
- Treat dry, cracking skin.
- Use repositioning and pressure-reducing devices (e.g., foam mattresses, low–air loss beds, pillows, or foam wedges when in bed or in a chair).
  - Patient repositioning (based on individual tissue tolerance):
    A recent multicenter trial demonstrated no difference in pressure ulcer formation in high-risk nursing home patients turned at 2-, 3-, and 4-hour intervals when on a high-density foam mattress.
  - Bed surface

Air-fluidized beds

a. Two RCTs found that use of air-fluidized beds contributed to the healing of a greater number of ulcers after 15 days compared with standard care.

FIGURE P1-75 Natural debridement of pressure injury at 2 weeks. (From Tallis R, Fillit H: *Brockelhurst's textbook of geriatric medicine and gerontology*, ed 6, London, 2003, Churchill Livingstone.)

b. Systematic review revealed no differences in rate of pressure ulcer healing with use of either alternating-pressure mattresses or low–air loss beds compared with standard care.

Pressure-relieving overlays

a. One RCT demonstrated that a viscoelastic pad on the operating table significantly reduced incidence of postoperative pressure ulcers compared with a standard operating table.

Foam alternatives

a. Forty-one RCTs demonstrated that patients lying on standard hospital mattresses are more likely to develop pressure ulcers than those patients lying on higher specification foam mattresses.

- Use adequate support surfaces while in bed or in a chair to prevent "bottoming out" (defined as less than 1 inch between patient and support surface; measured by putting hand under support surface and feeling thickness to patient).
- Recent systematic review of pressure ulcer prevention strategies showed poor methodology in most studies. Use of support surfaces, repositioning, optimized nutrition, and sacral skin moisturizing was most appropriate.
  - The 2010 consensus statement from the National Pressure Ulcer Advisory Panel said that not all pressure ulcers are avoidable because there are patient situations where pressure cannot be relieved and perfusion cannot be improved.

NONPHARMACOLOGIC THERAPY

- Should be cleaned at each dressing change; necrotic tissue should be debrided quickly because it delays wound healing (except for heel ulcers).
- Wound irrigation should not exceed 15 psi and is best done with an 18-gauge angiocatheter.
- No single dressing or product is superior; should be used to keep ulcer bed moist and protect it from urine/stool. Silver dressings (which are felt to be antimicrobial), topical phenytoin, and growth factors should be limited to difficult-to-heal wounds, chronic ulcers, and extensive burns given their extra cost and limited scientific validation.
- Avoid agents that are cytotoxic to epithelial cells (e.g., iodine, iodophor, sodium hypochlorite, hydrogen peroxide, acetic acid, alcohol).
- Reduce pressure by using foam mattress, dynamic support surface (e.g., low–air loss bed), and frequent repositioning (e.g., q2h or, in cases of poor perfusion, more frequently).
- Hyperbaric oxygen, ultrasound, ultraviolet, electromagnetic therapy, and low-energy radiation either are ineffective or have not been extensively evaluated for efficacy.
- Negative pressure devices (Vac devices) may help in wounds that have significant drainage. They also may improve healing by promoting angiogenesis, improving tissue perfusion, and decreasing bacterial count. Calcium alginate and foam dressings may also be beneficial for such wounds.
- Although correcting poor nutrition has been shown to be beneficial, a recent large investigation demonstrated that feeding tube insertion did not prevent or heal pressure ulcers, but increased the risk for developing a pressure ulcer.
- Minimize or promptly remove urinary and/or fecal contamination.
- Use a standardized assessment tool to monitor wound healing on weekly basis. Examples of monitoring scales include the Pressure Sore Status Tool (PSST) and Pressure Ulcer Scale for Healing (PUSH) in addition to the NPUAP staging system.
- No RCTs have compared debridement versus without debridement in the treatment of pressure ulcers.
- Thirty-two RCTs have compared different debridement agents, but there is insufficient evidence to promote the use of one particular agent.
- One RCT demonstrated ulcers treated with collagenase healed significantly more quickly than those treated with hydrocolloid.
- One RCT comparing honey-treated dressing with dressing soaked with saline showed faster healing times with the honey-treated group.
- A meta-analysis and one RCT found significant benefit in rates of healing with use of hydrocolloid dressings versus traditional saline gauze dressings but not over other forms such as hydrogels, foam dressings, or collagenase.
- No benefit was found with nutritional and vitamin supplements, artificial nutrition, or ultrasound therapy.

ACUTE GENERAL Rx

- Management of pressure ulcers is contingent on the stage of the ulcer.
- The cornerstone of therapy involves use of appropriate wound dressings, pressure-relieving devices, treatment of infection, debridement, and surgical consultation when appropriate.
- Adjunctive therapies such as electrical stimulation, negative pressure wound therapy, therapeutic ultrasound, hyperbaric oxygen, topical oxygen, and application of growth factors to the wound are being investigated.
- Pain medications are necessary because pressure ulcers are often painful. One study found that excruciating pain was more prevalent in nursing home residents with pressure ulcers.

CHRONIC Rx

- Continue vigilance with pressure reduction because pressure ulcers can recur with minimal trauma.
- Consider radiologic evaluation for infected ulcer bed, occult osteomyelitis, or abscess.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Vitamin C, zinc, and multivitamin supplements may be of benefit to optimize nutrition.

DISPOSITION

- When systematic risk assessments are done and preventive measures are followed, most pressure ulcers can be prevented. Most ulcers heal when appropriate management strategies are followed.
- Stage IV ulcers in high-risk patients (e.g., paraplegics) can take months or years to heal.

REFERRAL

- Physical and occupational therapists to improve bed and chair mobility.
- Wounds with necrotic tissue need referral to persons trained in sharp debridement.
- To plastic surgeons for operative repair for large stage III or IV ulcers that do not respond to optimal care.
- To a specialty wound center for nonhealing ulcers.

PEARLS & CONSIDERATIONS

COMMENTS

- Up to 10% of older persons will have a pressure ulcer.
- Because 70% of pressure ulcers occur in older persons, the approach should be similar to other multifactorial geriatric syndromes with a multidisciplinary team approach. Identify and reduce all modifiable risk factors for pressure ulcers.
- Treat the pain associated with pressure ulcers.
- Proper skin care, use of support surfaces, mobilization, and attention to nutrition are key for prevention and treatment.
- Clinical studies have not revealed if any one dressing product is superior.
- Nonhealing ulcers require assessment for debridement, infection, abscess, and/or referral to a wound center.

PATIENT & FAMILY EDUCATION

- Educate patient and family members on the risk factors for pressure ulcers.
- Encourage mobility and adequate nutritional intake and avoid bed rest.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Bed Sores (Patient Information)

AUTHORS: **RACHEL ROACH, M.S.N., A.P.R.N.-B.C.**, **NOEL S. C. JAVIER, M.D.**, and **CLARISSE DEXTER, R.N.P., W.C.C.**

SUGGESTED READINGS

Antokal S et al: National Pressure Ulcers Advisory Panel: Friction induced skin injuries. Are they pressure ulcers? White paper 11/20/2012. Available at www.npuap.org/wp-content/upload/2012/01/NPUAP-friction-white-paper.pdf.

Bergstrom N et al.: Turning for ulcer reduction: a multisite randomized clinical trial in nursing homes, *J Am Geriatr Soc* 61(10):1705–1713, 2013.

Black J et al.: National Pressure Ulcer Advisory Panel's updated pressure ulcer staging system, *Dermatol Nurs* 19(4):343, 2007.

Bluestein D, Javaheri A: Pressure ulcers: prevention, evaluation, and management, *Am Fam Physician* 78(10):1186–1194, 2008.

Chou R et al.: Pressure ulcer risk assessment and prevention, a systematic comparative effectiveness review, *Ann Intern Med* 159:28–38, 2013.

Heyneman A et al.: A systematic review of the use of hydrocolloids in the treatment of pressure ulcers, *J Clin Nurs* 17(9):1164, 2008.

Larson D et al.: Is there a simple, definitive, and cost-effective way to diagnose osteomyelitis in the pressure ulcer patient? *Plast Reconstr Surg* 127:670, 2011.

Li Y et al.: Association of race and sites of care with pressure ulcers in high-risk nursing home residents, *JAMA* 306:179, 2011.

Lyder C: Pressure ulcer prevention and management, *JAMA* 289(2):223, 2003.

National Pressure Ulcer Advisory Panel 9 (NPUAP): Pressure Ulcer Scale for Healing (PUSH), PUSH tool version 3.0. Available at http://www.npuap.org/PDF/push3.pdf.

Qaseem A, et al: Rick assessment and prevention of pressure ulcers: A clinical practice guideline from the American College of Physicians, *Ann Intern Med* 162:359–369, 2015.

Qaseem A, et al: Treatment of pressure ulcers: A clinical practice guideline from the American College of Physicians, *Ann Intern Med* 162:370–379, 2015.

Reddy M et al.: Preventing pressure ulcers: a systematic review, *JAMA* 296(8):974, 2006.

Reddy M et al.: Treatment of pressure ulcers: a systematic review, *JAMA* 300(22):2647–2662, 2008.

Sibbald RG et al.: Pressure ulcer staging revisited: superficial skin changes and deep pressure ulcer framework, *Adv Skin Wound Care* 24:571, 2011.

Teno JM et al.: Feeding tubes and the prevention or healing of pressure ulcers, *Arch Intern Med* 172(9):697–701, 2012.

Teno JM et al.: Daily pain that was excruciating at some time in the previous week: prevalence, characteristics, and outcomes in nursing home residents, *J Am Geriatr Soc* 52:762–767, 2004.

Wang C et al.: Hyperbaric oxygen for treating wounds: a systematic review of the literature, *Arch Surg* 138:272, 2003.

Weheida SM et al.: Comparing the effects of two dressings on healing of low grade pressure ulcers, *J Med Res Inst* 12:259–278, 1991.

White-Chu F et al.: Pressure ulcers in long term care, *Clin Geriatric Med* 27:241–258, 2011.

BASIC INFORMATION

DEFINITION

Priapism is the persistent, usually painful erection associated or unassociated with sexual stimulation. There are two major forms: low-flow (veno-occlusive) priapism and high-flow priapism (associated with increased arterial inflow without increased venous outflow resistance).

ICD-9CM CODES
607.3 Priapism
ICD-10CM CODES
N48.30 Priapism, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Peak incidence is seen from ages 5 to 10 yr and 20 to 50 yr.
- In the younger group, priapism is often associated with sickle cell disease or neoplasm. In the older group it is often caused by pharmacologic agents.
- Low-flow (veno-occlusive priapism [type I]) is much more common than high-flow (type II).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- In idiopathic priapism the initial erection is associated with prolonged sexual excitement. Previous transient episodes are frequently reported. The erection involves the corpora cavernosa alone. Detumescence does not occur spontaneously.
- In secondary priapism, sexual excitement need not be involved. Otherwise the clinical picture is the same as in idiopathic priapism.
- Table P1-36 compares normal erection and priapism.

ETIOLOGY

Idiopathic: prolonged sexual arousal
Secondary or associated causes:
- Sickle cell disease
- Diabetes
- Leukemia (especially chronic myelogenous leukemia)
- Solid tumor (malignant) penile infiltration
- Spinal cord injury
- Perineal or penile trauma
- Iatrogenic
- Total parenteral nutrition, which includes a fat emulsion
- Hyperosmolar IV contrast
- Spinal or general anesthesia
- Anticoagulant therapy
- Phenothiazines
- Trazodone
- Intracorporeal injection therapy for impotence
- Phosphodiesterase type 5 inhibitors (e.g., sildenafil [Viagra], tadalafil [Cialis], vardenafil [Levitra])

PATHOPHYSIOLOGY

- Low-flow priapism: prolonged erection leads to edema of the cavernosal trabeculae, resulting in a sequence of stasis, thrombosis, venous occlusion, fibrosis, scarring, and possibly impotence.
- High-flow priapism: cavernosal artery rupture leading to an arteriocavernous fistula.

DIAGNOSIS

WORKUP

None if the associated underlying causes are known to be present. Otherwise they should be ruled out. Low-flow priapism can be distinguished from high-flow priapism by obtaining a corporeal blood gas value. A P_{O_2} <30 mm Hg, P_{CO_2} >60 mm Hg, and a pH <7.25 are consistent with low-flow priapism. High-flow priapism can be confirmed by a perineal Doppler ultrasound or arteriography (useful to identify arterial-lacunar fistula).

TREATMENT

Goal: achieve detumescence with preservation of potency.

1. Medical therapies:
   - Ice packs
   - Ice water enemas
   - Hot water enemas
   - Pressure dressing
   - Sedatives
   - Analgesics
   - Antispasmodic/anticholinergic drugs
   - Estrogens
   - Anticoagulants
   - Procaine
   - Amyl nitrite
   - Local or general anesthesia
   - Ketamine (1 mg/lb)
2. In the patient with sickle cell disease: intravenous hydration, alkalinization, transfusion or exchange transfusion, oxygen.
3. Corporeal irrigation with normal saline may be used for low-flow priapism. The midshaft of the penis can be injected with a small-gauge butterfly needle and irrigated with 10 to 20 ml of normal saline, followed by an intracorporeal injection of an alpha-adrenergic agonist every 5 min until detumescence. Commonly used intracavernous vasoconstrictor agents are epinephrine (10 to 20 mcg), phenylephrine (250 to 500 mcg), and ephedrine (50 to 100 mg). It is mandatory to monitor the patient's blood pressure and pulse when using alpha-adrenergic agonists.
4. Surgery:
   - Cavernospongiosum shunt
   - Glans-cavernosum shunt
   - Cavernosaphenous shunt
   - In the less common situation of high-flow priapism (diagnosed by the finding of bright red arterial blood on aspiration), arterial embolization or surgical ligation is recommended.

PROGNOSIS

Impotence is associated with the duration of priapism, with 36 hr being an important threshold.

REFERRAL

To urologist

EVIDENCE

Available at www.expertconsult.com

RELATED CONTENT

Priapism (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

TABLE P1-36 Comparison of Normal Erection and Priapism

Factor	Normal Erection	Priapism
Portion of penis involved	Corpora cavernosa and corpus spongiosum and glans	Corpora cavernosa
Cause	Vasodilatation of penile arteries	Obstruction of venous outflow Disturbance of neuroarterial mechanism (imbalance between it and adrenergic activity) Increased viscosity
Sexual desire	Present	Absent
Pain	Absent	Present
Duration	Minutes to hours	Hours to days

From Nseyo UO (ed): *Urology for primary care physicians,* Philadelphia, 1999, Saunders.

EVIDENCE

Abstract[1]

Context:

Priapism is defined as a penile erection that persists beyond or is unrelated to sexual interest or stimulation. It can be classified into ischaemic (low flow), arterial (high flow), or stuttering (recurrent or intermittent).

Objective:

To provide guidelines on the diagnosis and treatment of priapism.

Evidence Acquisition: Systematic literature search on the epidemiology, diagnosis, and treatment of priapism. Articles with highest evidence available were selected to form the basis of these recommendations.

Evidence Synthesis:

Ischaemic priapism is usually idiopathic and the most common form. Arterial priapism usually occurs after blunt perineal trauma. History is the mainstay of diagnosis and helps determine the pathogenesis. Laboratory testing is used to support clinical findings. Ischaemic priapism is an emergency condition. Intervention should start within 4-6 h, including decompression of the corpora cavernosa by aspiration and intracavernous injection of sympathomimetic drugs (e.g. phenylephrine). Surgical treatment is recommended for failed conservative management, although the best procedure is unclear. Immediate implantation of a prosthesis should be considered for long-lasting priapism. Arterial priapism is not an emergency. Selective embolization is the suggested treatment modality and has high success rates. Stuttering priapism is poorly understood and the main therapeutic goal is the prevention of future episodes. This may be achieved pharmacologically, but data on efficacy are limited.

Conclusions:

These guidelines summarise current information on priapism. The extended version is available on the European Association of Urology Website (www.uroweb.org/guidelines/).

Patient Summary:

Priapism is a persistent, often painful, penile erection lasting more than 4 h unrelated to sexual stimulation. It is more common in patients with sickle cell disease. This article represents the shortened EAU priapism guidelines, based on a systematic literature review. Cases of priapism are classified into ischaemic (low flow), arterial (high flow), or stuttering (recurrent). Treatment for ischaemic priapism must be prompt in order to avoid the risk of permanent erectile dysfunction. This is not the case for arterial priapism. Ⓐ

Evidence-Based Reference

Salonia A, Eardley I, Giuliano F, et al.: European Association of Urology guidelines on priapism, *Eur Urol* 65:480–489, 2014. Ⓐ

BASIC INFORMATION

DEFINITION

Primary biliary cirrhosis (PBC) is a chronic, variably progressive cholestatic liver disease most often affecting women and characterized by destruction of the small intrahepatic bile ducts leading to portal inflammation, fibrosis, cirrhosis, and ultimately, liver failure.

SYNONYMS

Biliary cirrhosis
Nonsuppurative destructive cholangitis
Autoimmune cholangiopathy

ICD-9CM CODES
571.6 Biliary cirrhosis
ICD-10CM CODES
K74.3 Primary biliary cirrhosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:

- PBC affects all races and accounts for 0.6% to 2% of deaths from cirrhosis worldwide.
- Annual incidence rates range from 0.7 to 49 cases per million.

PREVALENCE: Prevalence is greatest in the U.K., Scandinavia, Canada, and the U.S., and varies tremendously by geographic areas, ranging from 6.7 to 402 cases per million. Disease burden seems to be increasing, which may be a result of better detection rather than true rise in disease incidence.

PREDOMINANT SEX: Female to male ratio of up to 10:1.

PREDOMINANT AGE: Onset typically occurs between the ages of 30 and 65 yr, and it is uncommon before age 25 yr.

PREDOMINANT RACE: Predominantly Caucasian but can be seen in other races.

GENETICS

- Although there are no clearly identified genetic factors associated with PBC, there is a clear familial occurrence. Prevalence among first-degree relatives is 5% to 6%, and 1% to 6% of all patients have at least one affected family member. The concordance rate among monozygotic twins is 63%.
- Up to 84% of patients with PBC have at least one other autoimmune disorder, such as thyroiditis, Sjögren's syndrome, rheumatoid arthritis, Raynaud's phenomenon, or scleroderma. A variant form of PBC exists as an overlap syndrome with autoimmune hepatitis (AIH).
- PBC is closely associated with a greater risk of hepatocellular carcinoma as well as an overall greater risk of cancer.

ETIOLOGY

- Although the cause of PBC remains unknown, it is believed to require both a genetic susceptibility as well as an environmental trigger, ultimately leading to the modification of mitochondrial proteins triggering a persistent T lymphocyte–mediated attack on intralobular bile duct epithelial cells.
- PBC is associated with the DRB1*08 family of alleles, but there is a great deal of variation among ethnicities.
- Possible environmental triggers include cigarette smoking, urinary tract infections, reproductive hormone replacement, nail polish, and toxic waste sites (particularly exposure to halogenated hydrocarbons), as well as xenobiotics in animal models of PBC.
- Recent studies have identified a group of autoantigens collectively known as the "M2 subtype" of autoantigens that play a major role in the early pathogenesis of PBC. These are peptides within the mitochondrial membrane that share structural homology. The enzyme complex subunit (PDC-E2) is one of the key autoantigens in this group. Patients with PBC have a tenfold increased concentration of cytotoxic $CD8^+$ lymphocytes recognizing this peptide in their livers compared with their blood, and most antimitochondrial antibodies (AMAs), which are the serologic hallmark of this disease, react to the PDC-E2 subunit. In addition, bile duct epithelial cells handle PDC-E2 in a unique way that exposes them to immune-mediated attack by PDC-E2–oriented cytotoxic T cells. Future therapies may be specific immunomodulation directed at these peptides.
- In addition to the T lymphocyte–mediated direct destruction of small bile ducts, secondary damage to hepatocytes results from the chronic accumulation of bile acids.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Clinical stages:

- Asymptomatic
- Symptomatic
- Cirrhotic
- Hepatic failure

Symptoms:

- 50% to 60% of patients may be asymptomatic; 40% to 100% of these patients will develop symptoms, and nearly 25% of symptomatic patients at diagnosis will progress to liver failure within 10 yr without treatment.
- Fatigue (78% of patients) and pruritus (20% to 70% of patients) are the usual presenting symptoms.
- Pruritus is worse at night, under constricting, coarse garments; in association with dry skin; and in hot, humid weather. The cause is unknown; it is no longer believed to be a result of the retention of bile acids in skin. Pruritus may first occur during pregnancy but is distinguished from pruritus of pregnancy because it persists into the postpartum period and beyond.
- Other common symptoms include jaundice, unexplained right upper quadrant pain (10%), manifestations of portal hypertension, sicca symptoms, and scleroderma-like lesions.
- Musculoskeletal complaints caused by inflammatory arthropathy in 40% to 70% of patients: 5% to 10% experience development of chronic rheumatoid arthritis and 10% experience development of "arthritis of PBC."
- Steatorrhea may be seen in advanced disease.

Physical:

- Variable: Results depend on stage of disease at time of presentation; patients at the early stage may be completely unaffected.
- Excoriations may be present.
- Hepatomegaly (70%) and splenomegaly (initially 35%) may be present in more advanced disease.
- Xanthomas and jaundice appear in advanced disease. Kayser-Fleischer rings are rare and result from copper retention. Hyperpigmentation of the skin due to melanin deposition may be present.
- Late physical findings mirror those of cirrhosis: spider nevi, temporal and proximal limb wasting, ascites, and edema.

DIAGNOSIS

The diagnosis of PBC can be established when two of the following three criteria are met.

- Positive serum AMA, titer >1:40
- Biochemical evidence of cholestasis (mainly alkaline phosphatase elevation)
- Characteristic liver histology: nonsuppurative destructive cholangitis and destruction of interlobular bile ducts

DIFFERENTIAL DIAGNOSIS

- Drug-induced cholestasis
- PBC-AIH overlap syndrome: reported in almost 10% of adults with AIH or PBC; transition from stable PBC to AIH and vice versa also seen
- Other etiologies of chronic liver disease and cirrhosis, such as alcoholic cirrhosis, chronic viral hepatitis, primary sclerosing cholangitis, AIH, sarcoidosis, chemical/toxin-induced cirrhosis, other hereditary or familial disorders (e.g., cystic fibrosis, α-1-antitrypsin deficiency)
- Biliary obstruction

WORKUP

History, physical examination, laboratory evaluation, liver biopsy

LABORATORY TESTS

- AMAs found in 95% of patients with PBC and are 98% specific.
- Antinuclear antibodies (ANAs) and AMAs found in approximately 50% of patients. In approximately 5% of patients, AMAs are absent or present only in low titer (AMA-negative PBC). Nearly all of these patients have ANA or AMAs, or both.
- Cholestatic pattern of liver biochemical markers, that is, markedly increased alkaline phosphatase (of hepatic origin).
- γ-Glutamyl transpeptidase is increased.
- Serum IgM levels are increased (lower in AMA-negative PBC).
- Bilirubin level is normal early; increases with disease progression (direct and indirect) in 60% of patients. Increased serum bilirubin level is a poor prognostic sign.
- Aminotransferase level may be normal and, if increased, is rarely more than five times the upper limit of normal.

- Markedly increased serum lipids in more than 50% of patients. Total cholesterol may exceed 1000 mg/dl. No increased risk for death from atherosclerosis seen, possibly because of high levels of LP-X, an anti-atherogenic low-density lipoprotein particle, very-high-density lipoprotein levels, and low serum levels of lipoprotein(a).
- Percutaneous liver biopsy confirms or rules out the diagnosis, allows staging, but is not essential in order to initiate medical therapy in patients with typical liver chemistry and positive AMA test.
- Histology is not uniform, so histologic stage is based on the most advanced lesion present.
  1. Stage I: Lymphocytic infiltration of the epithelial cells of the small bile ducts with granuloma-like lesions, limited to portal triads (bridging fibrosis)
  2. Stage II: Extension of inflammatory cells to periportal parenchyma, invasion by foamy macrophages, and development of biliary piecemeal necrosis
  3. Stage III: Fibrous septa link portal triads
  4. Stage IV: Frank cirrhosis; hyaline deposits and accumulation of stainable copper are also seen

IMAGING STUDIES

If history, physical examination, blood tests, and liver biopsy are all consistent with PBC, neither imaging nor cholangiography is necessary (Fig. EP1-76).

PROGNOSIS

- Median survival was 10 yr but may be getting longer with earlier diagnosis and initiation of treatment.
- Mean time of progression from stage I or II disease to cirrhosis with no medical treatment is 4 to 6 yr.
- Neither presence nor total titer level of AMAs predicts survival, disease progression, or response to therapy.
- Prognostic laboratory measures: Serum bilirubin is most important.
- Response to ursodiol therapy can be prognostic: Patients with a decrease in alkaline phosphatase level of at least 40% or to the reference range after 1 yr of treatment with ursodeoxycholic acid (UDCA) may have a prognosis similar to an age-matched healthy population. Similarly, the Mayo Risk score, a predictor of short-term survival probability (http://www.mayoclinic.org/gi-rst/mayomodel1.html), can also reliably predict life expectancy when calculated after 6 mo of ursodiol therapy.
- Poorer prognosis exists with jaundice, advanced histologic stage, advanced age, edema, coagulopathy, and ascites.

Rx TREATMENT

- Treatment is according to the clinical stage of the disease.
- Asymptomatic stage: Follow bilirubin every 3 mo. Once liver function test results become abnormal, begin UDCA at 13 to 15 mg/kg/day in a twice-daily divided dose regardless of histologic stage. Side effects may include weight gain of approximately 5 lbs during the first 1 to 2 yr and, less commonly, thinning of hair and loose stools. Watch for interactions with cholestyramine and other bile-acid sequestrants, as well as antacids, which may interfere with UDCA absorption. Efficacy is best if started during stage I or II disease but should be started at any stage of disease. Lifelong therapy is currently recommended, but benefits are still observed if therapy is interrupted and restarted.
- Treatment also includes treatment of associated conditions such as pruritus, osteoporosis, increased low-density lipoprotein level, and any eventual complications of cirrhosis.
- 20% of patients will not respond to medical therapy and will proceed to liver transplantation, which is the only definitive treatment for this disease.

ACUTE GENERAL Rx

- Symptomatic stage: Goals of treatment are resolution of pruritus, decrease of alkaline phosphatase levels, and delay of progression to liver failure.
- Ursodiol can significantly improve bilirubin and alkaline phosphatase levels, prolong survival without liver transplantation, and delay progression of liver fibrosis and development of portal hypertension.
- The addition of colchicine, methotrexate, or bezafibrate has not been found to be of benefit to mortality or time to liver transplantation in controlled trials.
- Prednisone, azathioprine, penicillamine, and cyclosporine are no longer used because of limited efficacy and significant toxicity.
- For the pruritus of PBC, cholestyramine resin (4 g/dose; maximum, 16 g/day) reduces pruritus in most patients but must be given at least 2 to 4 hr apart from ursodiol to avoid reducing the efficacy of that drug. Antihistamines at bedtime help nighttime symptoms. Rifampin (150 to 300 mg bid) or oral opiate antagonists such as naltrexone (50 mg daily) can be used for pruritus refractory to bile acid sequestrants. Intractable pruritus can be an indication for liver transplantation.

CHRONIC Rx

- Liver function tests should be checked every 3 to 6 mo.
- Management of sicca syndrome: Artificial tears can be used initially for dry eyes. Saliva substitutes can be used for xerostomia and dysphagia; pilocarpine or cevimeline for refractory cases. Moisturizers can be given for vaginal dryness.
- Treatment/Prevention of osteopenia/osteoporosis: Patients with PBC should be provided 1000 to 1500 mg calcium and 1000 IU of vitamin D daily in the diet and as supplements if needed. Bone densitometry should be done every 2 to 4 yr. Alendronate (70 mg weekly) should be considered if patients are osteopenic in the absence of acid reflux or known varices.
- Hyperlipidemia is common in patients with cholestatic liver disease. Statins are safe in patients who may need treatment even if liver chemistry is abnormal.
- Vitamin A, K, and E deficiencies can be clinically important in advanced cases and respond to oral replacement.
- Upper endoscopy to assess for varices should be done every 2 to 3 yr in patients with cirrhosis or Mayo risk score >4.1. Nonselective beta-blockers or endoscopic banding can be considered for prevention of variceal hemorrhage.
- Regular screening for hepatocellular carcinoma with ultrasound and α-fetoprotein every 6 to 12 mo is recommended for patients with cirrhosis.
- Liver transplantation is the only effective treatment for patients with liver failure. Indications for transplantation include hepatic decompensation (ascites, encephalopathy, jaundice), hepatocellular carcinoma fulfilling Milan criteria (see "Hepatocellular Carcinoma"), and intractable pruritus.
- The outcome of liver transplantation for patients with PBC is more favorable than that of nearly all other liver disease categories. The survival rates are 85% to 90% and 80% to 85% at 1 and 5 yr, respectively. Although recurrent disease may develop in 20% to 25% of patients after liver transplantation over 10 yr, patient and graft survival is usually not affected.

DISPOSITION

Definitive treatment requires liver transplantation; survival is 7 to 16 yr depending on symptoms at time of diagnosis.

REFERRAL

Gastroenterology and/or hepatology for treatment, evaluation for liver transplantation, and management of portal hypertension

PEARLS & CONSIDERATIONS

- AMA is the serologic hallmark of PBC.
- The prototypical patient with PBC is a middle-aged, Caucasian woman reporting fatigue and pruritus.
- Ursodiol should be started as soon as liver biochemical markers begin to increase and is most effective when started early in the course of the disease.
- Associated illnesses must be detected and treated.
- Liver transplantation is the only effective treatment for PBC with end-stage liver failure.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Primary Biliary Cirrhosis (PBC) (Patient Information)

AUTHORS: **MICHAEL ENGELS, M.D.**, **JEANETTE G. SMITH, M.D.**, and **KITTICHAI PROMRAT, M.D.**

SUGGESTED READINGS

Hirschfield GM et al.: Primary biliary cirrhosis associated with HLA, IL12A, and IL12RB2 variants, *N Engl J Med* 360:2544–2555, 2009.

Lindor K: Ursodeoxycholic acid for the treatment of primary biliary cirrhosis, *N Engl J Med* 357:1524–1529, 2007.

Lindor KD et al.: American Association for Study of Liver Diseases: primary biliary cirrhosis, *Hepatology* 50(1):291–308, 2009.

Selmi C et al.: Primary biliary cirrhosis, *Lancet* 377:1600–1609, 2011.

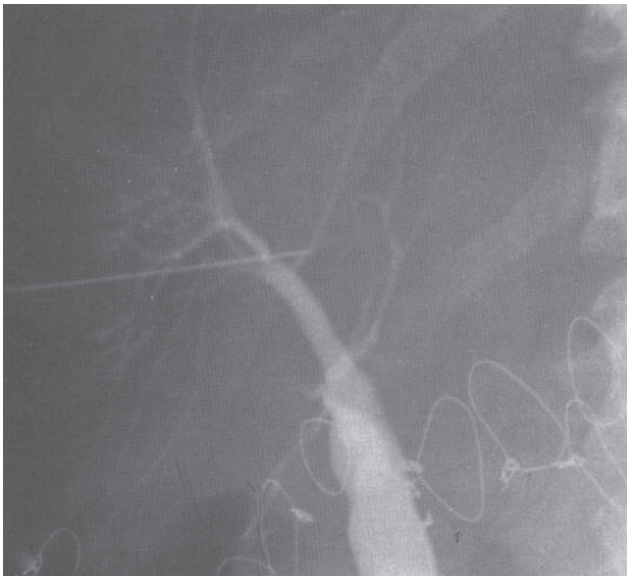

FIGURE EP1-76 Primary biliary cirrhosis demonstrated by endoscopic retrograde cholangiopancreatography. (From Berk RN, Ferrucci Jr JT, Leopold GR: *Radiology of the gallbladder and bile ducts: diagnosis and intervention,* Philadelphia, 1983, Saunders.)

Primary immunodeficiency diseases (PIDDs) are a collection of >200 rare disorders involving the absence or malfunction of integral parts of the immune system. The etiologies of PIDDs are not communicable in the infectious sense, but vertically transmissible via transfer of inherited genetic defects. Although some defects affect a single part of the immune system, others cause multicomponent breakdown of combined innate and cellular immune responses and suggest the interplay of epigenetic influences. To be considered a PIDD, the cause must not be secondary to another disease, drug/chemical, or environmental exposure. Primary immunodeficiency disease onset may occur at birth, as most do, or at any subsequent developmental stage and may affect anyone with only specific regard to gender or ethnicity. Predominant antibody deficiencies can be found in Table P1-37.

SYNONYMS

PID
PIDD
PI

ICD-9CM CODES
279.3 Unspecified immunity deficiency
279.2 Combined immunity deficiency
288.x
334.8
ICD-10CM CODES
D84.9 Immunodeficiency, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

Overall about 1:500 are born with and 1:1200 currently live with a PIDD, these numbers generally exclude the milder forms of immunodeficiency (e.g. IgA deficiency). The predilection for age and gender varies according to the specific disorder.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The history, signs, and symptoms depend on the precise genetic disorder. Recurrent, persistent, or unusual infections, as well as developmental delay or congenital anomalies, are among the most common attributes present when considering a primary immunodeficiency as a potential diagnosis.

ETIOLOGY

- Inherited

Dx DIAGNOSIS

The International Union of Immunological Societies (IUSIS) PID expert committee has set forth a PID classification system that is updated every other year. The PIDDs are grouped into 8 categories, based on the primary mechanism of each disease. Due to the complexity of the classification system in clarifying a PID case and the reasoning that most PIDs will present in nonimmunological fields of medicine, a phenotype-based algorithmic approach highlighting the clinical and biological characteristics of a particular PID has been synthesized to aid in diagnosis.

- Combined T-cell and B-cell immunodeficiencies
- Well-defined syndromes with immunodeficiency
- Predominantly antibody deficiencies
- Disease of immune dysregulation
- Congenital defects of phagocyte number, function, or both
- Defects of innate immunity
- Auto-inflammatory disorders
- Complement deficiencies

DIFFERENTIAL DIAGNOSIS

- Secondary immunodeficiency, primary infections

WORK-UP

• A thorough history detailing the type, location, and frequency of the infections, as well as any physical exam findings that may indicate recurrent or persistent infections (e.g., scarred tympanic membranes) is essential in the initial characterization of the suspect immunodeficiency.

LABORATORY TESTS

- Screening Tests
  - Complete blood count with a manual differential: the most important test upon initial evaluation is whether lymphocyte, neutrophil, or platelet counts are normal.
  - Quantitative immunoglobulin levels (IgG, IgA, IgM, IgE): The specimen should be processed at a CLIA (Clinical Laboratories Improvement Act)-approved laboratory and be evaluated within the context of the patient's age and clinical presentation.
  - Vaccine responsive antibody quantification: Important to the evaluation of an antibody deficiency disorder is evaluating whether there are truly low serum immunoglobulin responses to both polysaccharide- and protein-based vaccines.
  - Any further investigation should defer to an immunologist for guidance based on history, symptoms, and clinical presentation and may involve a more precise analysis of immunoglobulin subtypes, T and B lymphocytic subsets, cell surface markers, complement levels, and gene sequencing.

Rx TREATMENT

Treatment depends highly on the specific immunodeficiency and should always include primary treatment and prophylaxis of the offending infectious agents. Education on the necessary precautions to minimize potential infections is crucial. A systematic consideration of the appropriate vaccinations is key to avoid any unnecessary infections or complications. Specific PIDDs carry the risk of malignancies and require regular screenings.

See Section III for algorithmic approaches to primary immunodeficiency disease.

NONPHARMACOLOGIC THERAPY

Surgical intervention may be necessary for specific congenital malformations and possibly if malignancy is identified. In the case of a severe combined immune deficiency, patient bone marrow transplantation may be a therapeutic option.

PATIENT/FAMILY EDUCATION

- Due to the nature of primary immunodeficiencies, affecting both the patient and family members, genetic counseling is key to comprehensive patient care. Although immunologists are well versed in the genetic inheritance of the PIDDs, referral to a genetic counselor is often advised.

SUGGESTED READINGS

Available at www.expertconsult.com

Author: **KEVIN V. PLUMLEY, M.D., M.P.H.,** and **STEVEN M. SEPE, M.D., Ph.D.**

TABLE P1-37 Predominant Antibody Deficiencies

	Disease	Mode of Inheritance/Genetic Locus	Clinical Features
Severe reduction in all serum immunoglobulin isotypes with absent B cells	Bruton tyrosine kinase deficiency	XL/Xq21.3-22	Severe bacterial infections (especially of the respiratory tract), absent lymphoid tissue
	μ heavy chain deficiency	AR/14q32.3	Severe bacterial infections
	λ5 deficiency	AR/22q11.21	Severe bacterial infections
	Igα deficiency	AR/19q13.2	Severe bacterial infections
	Igβ deficiency	AR/17q23	Severe bacterial infections
	BLNK deficiency	AR/10q23.2	Severe bacterial infections
	Thymoma with immunodeficiency (Good syndrome)	None	Recurrent infection with encapsulated bacteria and diarrhea, autoimmune phenomena
	Myelodysplasia	Variable/monosomy 7, trisomy 8, dyskeratosis congenita	Recurrent infections and pancytopenia
Severe reduction in at least two serum immunoglobulin isotypes with low or normal B-cell numbers	Common variable immunodeficiency syndromes TACI alterations BAFFR alterations MSH5 alterations	≈10% with family history AR or AD AD and AR/17p11.2 AR/22q13 Unk/6p22.1-p21.3	Recurrent respiratory tract infections leading to chronic sinusitis, hearing loss, bronchiectasis, autoimmune disease, lymphoproliferation, malignancy (especially non-Hodgkin lymphoma and gastric carcinoma)
	ICOS deficiency	AR/2q33	Recurrent infections
	CD19 deficiency	AR/16p11.2	Recurrent infections
	X-linked lymphoproliferative disease (mutation in SH2 domain protein 1A)	XL/Xq25-q26	Fulminant infection with EBV, lymphoma, dysgammaglobulinemia
Severe reduction in serum IgG and IgA with increased IgM and normal B-cell numbers (disorders of immunoglobulin class switching)	CD40 ligand deficiency	XL/Xq26.3-Xq27.1	Recurrent infections with bacteria and opportunistic pathogens, neutropenia, autoimmune disease
	CD40 deficiency	AR/20q11-20q13.2	Recurrent infections with bacteria and opportunistic pathogens, neutropenia, autoimmune disease
	NF-κB essential modulator (*NEMO*) hypomorphic mutations	XL/Xq28	Recurrent infections with bacteria and opportunistic pathogens, neutropenia, autoimmune disease
	AID deficiency	AR/12p13	Recurrent bacterial infections and diarrhea, marked enlargement of lymphoid organs
	UNG deficiency	AR/12q23-q24.1	Recurrent bacterial infections and diarrhea, marked enlargement of lymphoid organs
Isotype or light-chain deficiencies with normal B-cell numbers	Ig heavy-chain deficiency	AR/14q32	Most patients are healthy
	κ-chain deficiency	AR/2p11.2	Most patients are healthy
	Isolated IgG subclass deficiency	Variable/unknown	Most patients are healthy
	IgA deficiency associated with IgG subclass deficiency	Variable/unknown	Most patients are healthy
	Selective IgA deficiency	Variable/unknown	Most patients asymptomatic, but increased prevalence of infections, autoimmune disease, atopy, and celiac disease
Specific antibody deficiency with normal immunoglobulin level and B-cell number	Inability to make antibodies to specific antigens	Variable/unknown	Recurrent sinopulmonary infection, bronchiectasis, diarrhea, autoimmune disease
Transient hypogammaglobulinemia of infancy	IgG and IgA deficiency	Variable/unknown	More likely to be male (60%–80%), mild infections and diarrhea, atopy

AID, Activation-induced cytidine deaminase; *BAFF-R,* B cell–activating factor receptor; *BLNK,* B linker; *EBV,* Epstein-Barr virus; *ICOS,* inducible T-cell costimulator; *Igα,* immunoglobulin-associated α; *Igβ,* immunoglobulin-associated β; *λ5,* immunoglobulin lambda-like polypeptide; *MSH5,* mutS homolog 5; *NF-κB,* nuclear factor kappa-B; *TACI,* transmembrane activator and CAML-interactor; *UNG,* uracil DNA glycosylase.

(From Hoffman R: *Hematology, basic principles and practice*, 6th ed, Philadelphia, 2013, Saunders.)

SUGGESTED READINGS

Lim MS, Elenitoba-Johnson KS: "The Molecular Pathology of Primary Immunodeficiencies", *The Journal of molecular diagnostics : JMD* 6(2):59–83, 2004. http://dx.doi.org/10.1016/S1525-1578(10)60493-X. PMC 1867474. PMID 15096561.

Boyle JM, Buckley RH: "Population prevalence of diagnosed primary immunodeficiency diseases in the United States", *J. Clin. Immunol* 27(5):497–502, 2007. http://dx.doi.org/10.1007/s10875-007-9103-1. PMID 17577648.

Bousfiha et al.: A phenotypic approach for IUIS PID Classification and Diagnosis: Guidelines for Clinicians at the Bedside, *J Clin Immunol* 33(6):1078–1087, 2014. PMID 23657403.

Notarangelo LD: "Primary Immunodeficiencies", *J Allergy Clin Immunol* 2010:125, 2010. S182-94: PMID 20042228.

Pravaneh et al.: "Primary Immunodeficiencies: A Rapidly Evolving Story", *J Allergy Clin Immunol* 2013(131):314–323, 2013. PMID 23374262.

Buckley et al.: *"Diagnostic & Clinical Care Guidelines for Primary Immunodeficiency Diseases" Immune Deficiency Foundation 2009*, 2009.

BASIC INFORMATION

DEFINITION

Primary myelofibrosis (PMF) is a clonal stem cell disorder characterized by chronic myeloproliferation, atypical megakaryocytic hyperplasia, bone marrow fibrosis (Figs. EP1-77 and P1-78) and extramedullary hematopoiesis in the spleen. PMF is a myeloproliferative neoplasm; however, it does not include patients who present with myelofibrosis with an associated antecedent diagnosis.

ICD-9CM CODES
238.76 Primary myelofibrosis
ICD-10CM CODES
C94.4 Acute panmyelosis with myelofibrosis
D47.1 Chronic myeloproliferative disease

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): ~0.21 per 100,000
PREDOMINANT SEX AND AGE:
- No sex association
- Median age of diagnosis is ~67 years of age

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fatigue
- Symptoms related to splenomegaly: abdominal fullness, early satiety
- Acute left upper quadrant pain with the development of spontaneous splenic infarction
- Due to extramedullary hematopoiesis: hepatomegaly and portal hypertension, lymphadenopathy, ascites, or pleural effusions
- Infection
- Skeletal changes
- Leukemic transformation
  1. Incidence 3.9% to 20%
  2. Within the first 10 yr of diagnosis
  3. >20% blasts in the bone marrow or extramedullary leukemic deposits
- Table P1-38 summarizes symptoms and physical findings of patients with primary myelofibrosis detected at diagnosis
- Thrombohemorrhagic events

ETIOLOGY

- Clonal disorder of multipotent hematopoietic progenitors arising from the hematopoietic stem cell compartment
- Single mutation in Janus family of cytoplasmic nonreceptor tyrosine kinase (JAK)–2, which is a guanine-to-thymine mutation resulting in a substitution of valine to phenylalanine codon 617 within the pseudokinase domain (JH2) of JAK2 (JAK2V617F)
- JAK2 mutation results in autoinhibition and constitutive JAK2 activity
- Present in 40% to 50% of PMF patients
- Alternative alleles: somatic mutations at codon 515 of the thrombopoietin receptor gene MPL (three different substitutions—W515L (leucine), W515K (lysine), or W515A (alanine)—present in 10% of JAK2V617F-negative patients
- Table P1-39 describes genetic lesions identified in patients with primary myelofibrosis

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Myelofibrosis in the setting of preexisting PV or ET (MPN)
- Chronic myelogenous leukemia
- Myelodysplastic syndrome with marrow fibrosis
- Acute myelofibrosis of acute megakaryocytic leukemia
- Marrow fibrosis associated with hairy cell leukemia, lymphoma, and multiple myeloma
- Nonhematologic disorders with bone marrow fibrosis: solid tumor metastases to the bone marrow, autoimmune disorders, and secondary hyperparathyroidism with vitamin D deficiency

WORKUP

- WHO criteria for PMF (3 major, 2 minor; Box P1-13)

TABLE P1-38 Summary of Symptoms and Physical Findings of Patients With Primary Myelofibrosis Detected at Diagnosis

Symptom or Finding	Incidence (%)
Asymptomatic	16-30
Fatigue	47-71
Fever	5-15
Weight loss	7-39
Night sweats	6-21
Symptoms due to enlarged spleen	11-48
Bleeding	5-20
Gout or renal stones	6-13
Pallor	60
Petechiae or ecchymoses	15-20
Splenomegaly	89-99
Hepatomegaly	39-70
Peripheral edema	13
Evidence of portal hypertension	2-6
Lymphadenopathy	1-10
Jaundice	0-4

(From Hoffman R: *Hematology, basic principles and practice*, ed 6, Philadelphia, 2013, Saunders.)

LABORATORY TESTS

- Anemia (hemoglobin <10g/dl)
- Platelet count and white blood cell count vary widely
- Peripheral blood smear: nucleated red blood cells, granulocyte precursors, and teardrop-shaped erythrocytes (leukoerythroblastosis)
- Bone marrow is fibrotic, megakaryocytic dysplasia
- Presence of JAK2V617F mutation

TREATMENT

Risk factors are based on Dynamic International Prognostic Scoring System plus (DIPSS-plus).
- Age >65 years
- Hemoglobin <10 g/dl
- Leukocyte count >25 × 10^9/L
- Circulating blasts >1%
- Presence of constitutional symptoms
- Red cell transfusion need
- Platelet <100 × 10^9/L
- Unfavorable karyotype (complex or presence of +8, –7/7q–, i(17q), inv(3), –5/5q–, 12p–, or 11q23 rearrangement)

Scoring: low (0 risk factors); intermediate 1 (1 risk factor); intermediate 2 (2 or 3 risk factors), and high (>4 risk factors). Figure P1-78 illustrates a risk-adapted therapy in primary myelofibrosis.

LOW AND INTERMEDIATE 1 RISK

- Asymptomatic - observation
- Conventional drug therapy if symptomatic (response rates to each of the following agents is ~15%-25%):
  1. Anemia – thalidomide and prednisone
  2. Patients who are not transplant candidates–an androgen preparation or danazol or erythropoiesis-stimulating agent
  3. Patients with a 5q deletion–lenalidomide
  4. Treatment failure with thalidomide, danazol, or androgens–lenalidomide
  5. Symptomatic splenomegaly–hydroxyurea

INTERMEDIATE 2 AND HIGH RISK

- Palliative options:
  1. Conventional drug therapy (see above)
  2. Splenectomy – hydroxyurea refractory splenomegaly
  3. Radiotherapy - hydroxyurea refractory splenomegaly
  4. Experimental drug therapy
  5. JAK2 inhibitor ATP mimetics
  6. Interferon-alpha
- Curative options:
  1. Allogeneic stem cell transplant (5-year disease-free survival 33% and treatment-related mortality 35%-50%)

DISPOSITION:
Median survival between 3.5 and 5 years based on above DIPSS-plus scoring system
Median survival based on genomic analysis:
- CALR mutated 17.7 yr; JAK2 mutated 9.2 yr; MPL mutated 9.1 yr; triple-negative 3.2 yr.

PEARLS & CONSIDERATIONS

- PMF is a clonal stem cell disorder.
- Significant proportion of PMF patients have JAK2V617F or MPL mutations.
- The only curative treatment is autologous stem cell transplant.

SUGGESTED READINGS

Available at www.expertconsult.com

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TABLE P1-39 Acquired Genetic Lesions Identified in Patients With Primary Myelofibrosis

Gene	Location	Mutation	Frequency
Janus kinase 2 (JAK2)	9p24 exon 14	JAK2V617F	65%
	9p24 exon 12		Infrequent
Ten-eleven translocation 2 (TET2)	4q24		17%
Enhancer of zeste homolog 2 (EZH2)	7q36.1		13%
Myeloproliferative leukemia virus (MPL)	1p34 exon 10	MPLW515L/K	5%-10%
Casitas B-lineage lymphoma (CBL)	11q23.3	Exons 8 and 9	6%
Isocitrate dehydrogenase (IDH 1 and 2)	2q33.3/15q26.1		4%
Ikaros family zinc finger 1 (IKZF1)	7p12		Infrequent
Additional sex Combs-like 1 (ASXL1)	20q11.1		Infrequent

(From Hoffman R: *Hematology, basic principles and practice*, ed 6, Philadelphia, 2013, Saunders.)

BOX P1-13 Diagnostic Criteria for Primary Myelofibrosis

WHO Diagnostic Criteria for PMF Requires Meeting All 3 Major Criteria and ≥2 Minor Criteria Outlined

Major Criteria

1. Megakaryocyte proliferation, including small-to-large megakaryocytes, with aberrant nuclear/cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering accompanied by either reticulin and/or collagen fibrosis, or in the absence of reticulin fibrosis (i.e., prefibrotic PMF), the megakaryocyte changes must be accompanied by increased marrow cellularity, granulocytic proliferation, and often decreased erythropoiesis
2. Not meeting WHO criteria for chronic myelogenous leukemia, polycythemia vera, myelodysplastic syndromes, or other myeloid neoplasm
3. Demonstration of JAK2V617F or other clonal marker or no evidence of reactive marrow fibrosis

Minor Criteria

1. Leukoerythroblastosis
2. Increased serum lactate dehydrogenase
3. Anemia
4. Palpable splenomegaly

International Working Group for Myeloproliferative Neoplasms Research and Treatment Criteria for Post–Polycythemia Vera/Essential Thrombocythemia (post-PV/ET) Myelofibrosis Requires Meeting Both Major Criteria and ≥2 Minor Criteria

Major Criteria

1. Documentation of a previous diagnosis of PV or ET as defined by the WHO criteria
2. Bone marrow fibrosis grade 2-3 (on 0-3 scale) or grade 3-4 (on 0-4 scale)*

Minor Criteria

1. A leukoerythroblastic peripheral blood picture (for both PV and ET)
2. Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly (for both PV and ET)
3. Development of ≥1 of 3 constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5° C) (for both PV and ET)
4. Anemia or sustained loss of requirement for phlebotomy in the absence of cytoreductive therapy (for PV)
5. Anemia and a decrease of hemoglobin level ≥2 g/dl from baseline (for ET)
6. Increased serum lactate dehydrogenase (for ET)

*Grade 2-3 according to the European classification: diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain) or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain). Grade 3-4 according to the standard classification: diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis.

From Tefferi A: How I treat myelofibrosis, *Blood* 117:3494-3504, 2011.

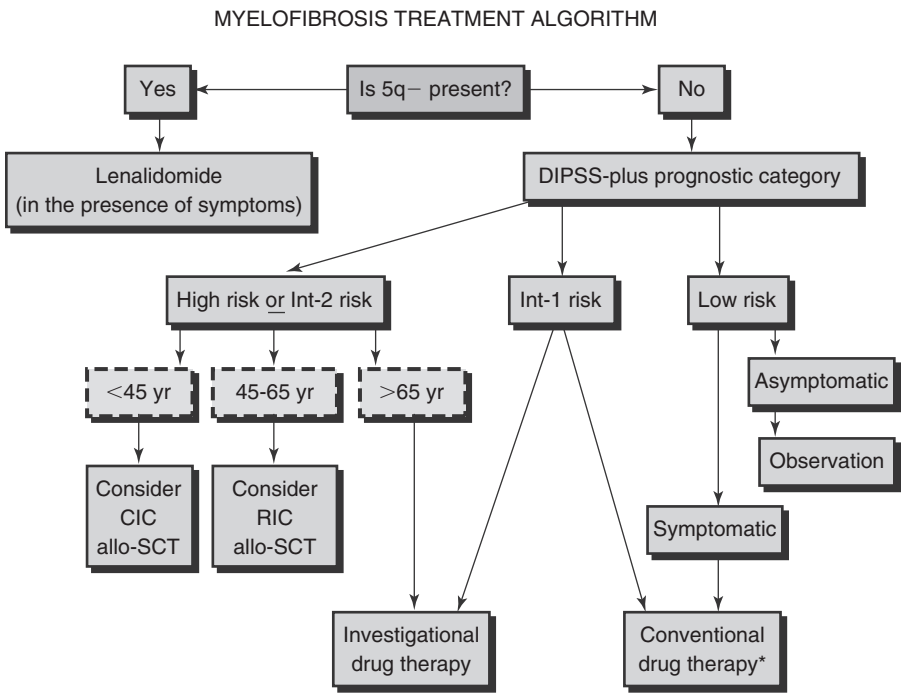

FIGURE P1-78 Risk-adapted therapy in primary myelofibrosis. *Conventional drug therapy includes erythropoiesis-stimulating agents, androgens, danazol, corticosteroids, thalidomide, lenalidomide, hydroxyurea, and cladribine. *allo-SCT,* Allogeneic stem cell transplantation; *DIPSS-plus,* Dynamic International Prognostic Scoring System plus prognostic model for primary myelofibrosis; *CIC,* conventional-intensity conditioning; *Int,* intermediate; *RIC,* reduced-intensity conditioning. (From Tefferi A: How I treat myelofibrosis, *Blood* 117(13):3494-3504, 2011.)

SUGGESTED READINGS

Abdel-Wahab O, Levine R: Primary myelofibrosis: update on definition, pathogenesis, and treatment, *Annu Rev Med* 60:233–245, 2009.

Cervantes F et al.: Myelofibrosis with myeloid metaplasia in young individuals: disease characteristics, prognostic factors and identification of risk groups, *Br J Haematol* 102(3):684, 1998.

Harrison C et al.: JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis, *N Engl J Med* 366:787–798, 2012.

Mesa R et al.: Population-based incidence and survival figures in essential thrombocythemia and agnogenic myeloid metaplasia: an Olmsted County Study, 1976-1995, *Am J Hematol* 61(1):10–15, 1999.

Savona M: Are we altering the natural history of primary myelofibrosis?, *Leukemia Research*, 2014. EPUB ahead of print.

Rumi E et al.: Clinical Effect of driver mutations of JAK2, CALR, or MPL in primary myelofibrosis, *Blood*, 2014. July. EPUB ahead of print.

Tefferi A et al.: CALR vs JAK2 vs MPL-mutated or triple-negative myelofibrosis: clinical, cytogenetic and molecular comparisons, *Leukemia* 28(7):1472–1477, 2014 July.

Tefferi A: Primary myelofibrosis: 2013 update on diagnosis, risk-stratification, and management, *Am J Hematol* 88:142–150, 2013.

Tefferi A: How I treat myelofibrosis, *Blood* 117(13):3494–3504, 2011.

Vardiman J et al.: The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes, *Blood* 114(5):937, 2009.

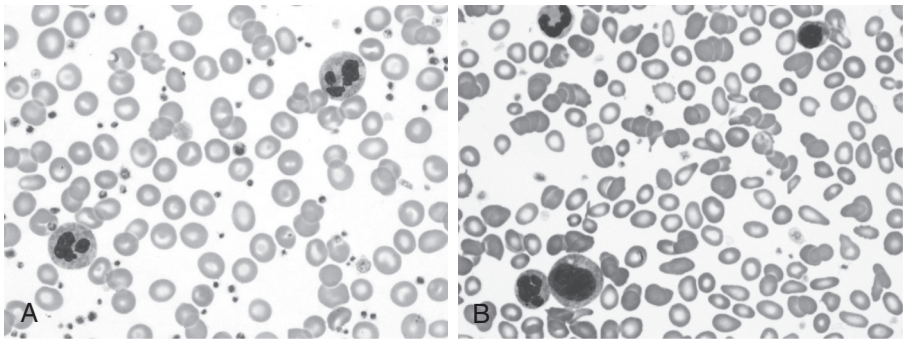

FIGURE EP1-77 A Blood smears from prefibrotic and fibrotic stages of primary myelofibrosis. A, This smear from the prefibrotic stage shows neutrophilia and thrombocytosis but minimal red cell changes. **B,** This smear from the fibrotic stage shows leukoerythroblastosis with marked red cell abnormalities, including many teardrop forms. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

Primary Ovarian Insufficiency

BASIC INFORMATION

DEFINITION

- Woman younger than 40 yr of age with amenorrhea, oligomenorrhea, or dysfunctional uterine bleeding for 4 mo or more along with follicle stimulating hormone (FSH) levels in the menopausal range meet diagnostic criteria for primary ovarian insufficiency.
- Menopause younger than the age of 40 yr.

SYNONYMS

Hypergonadotropic hypogonadism
Premature ovarian failure
Premature menopause
Gonadal dysgenesis

ICD-9CM CODES
256.31 Premature menopause
ICD-10CM CODES
E28.3 Primary ovarian failure
E28.9 Ovarian dysfunction, unspecified
E28.310 Symptomatic premature menopause

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Affects 1% to 4% of the female population in the U.S.
PREDOMINANT AGE: 1:250 incident cases by age 35 and 1:100 by age 40

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The most common presentation is disturbance in menstrual pattern due to intermittent ovarian function.
- Between 5% and 30% of affected women have another affected female relative.
- Between 10% and 30% of affected women already have a concurrent autoimmune condition, the most common of which is hypothyroidism.
- Symptoms of estrogen deficiency include hot flashes, night sweat, poor concentration, drying of the vagina, and infertility.
- Physical exam may reveal stigmata of an autoimmune condition such as vitiligo, thyroid enlargement, or Turner's syndrome (webbed neck, short stature, and high-arched palate).

ETIOLOGY (see Table P1-40)

Idiopathic in 95% of cases

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Pregnancy
- Causes of secondary amenorrhea include eating disorder, exercise, drugs, sarcoidosis, polycystic ovarian disease, hypothalamic amenorrhea, hyperprolactinemia/prolactinoma, and Cushing's disease.

WORKUP

- After pregnancy is ruled out, the initial evaluation should include the measurement of serum prolactin, FSH, and thyrotropin (TSH) levels.
- If the FSH level is in the menopausal range (>40 uIU/ml by radioimmunoassay), the test should be repeated in 1 month along with a serum estradiol measurement to confirm the diagnosis of primary ovarian insufficiency.

LABORATORY TESTS

Once a diagnosis of premature ovarian failure is made, other evaluations include:

- Autoimmune disorders, adrenal insufficiency (seen in 3% of cases): serum anti-adrenal and anti-21 hydroxylase antibodies should be measured.
- Hypothyroidism: serum TSH, T_4, and anti-TPO antibodies
- All cases should be screened for osteoporosis by DXA for bone mineral density.
- A karyotype analysis should be performed for all patients to look for chromosomal defects including Turner's variant or deletions of the X chromosome.
- Permutations for the fragile X syndrome (*FMR1* gene) should be checked for as well.

IMAGING STUDIES

Pelvic ultrasound has no proven benefit in the management of these patients.

TREATMENT

NONPHARMACOLOGIC THERAPY

Counseling or patient support group should be offered to all women with low self-esteem and depression due to the psychological scar left by the diagnosis.

ACUTE GENERAL Rx

- Physiologic estrogen and progestin replacement is reasonable in the cases of young women until they reach the age of natural menopause.
- A dose of 100 mcg of estradiol per day, administered by transdermal patch, achieves average estradiol level observed in normal menstruating women and effectively treats symptoms.

TABLE P1-40 Mechanisms and Causes of Primary Ovarian Insufficiency

Accelerated Follicular Depletion
Genetic: Turner's syndrome, fragile X premutations, galactosemia
Toxic: Chemotherapy, radiation, infections such as mumps or cytomegalovirus
Autoimmune: Polyglandular failure, hypothyroidism, Addison's disease, vitiligo, myasthenia gravis
Abnormal Follicular Stimulation
Gonadotropin receptor function: follicle stimulating hormone/luteinizing hormone receptor mutation
Enzyme defects: Aromatase deficiency
Luteinized follicles

- Cyclic medroxyprogesterone at a dose of 10 mg per day for 12 days each month is the preferred progestin to provide protection against endometrial cancer.
- Pregnancy may occur while a woman is taking estrogen and progesterone therapy and the therapy should be stopped immediately if the pregnancy test is found to be positive.

CHRONIC Rx

- Intake of 1200 mg of elemental calcium and 800 units of vitamin D_3 per day should be encouraged to prevent bone loss. A serum 25-hydroxyvitamin D level of 30 ng per ml or higher should be maintained.
- Patients with positive tests for adrenal antibodies should be evaluated annually for adrenal insufficiency by corticotropin stimulation test.
- Patients who wish to avoid pregnancy should use a barrier method or an IUD.
- Options for parenthood include adoption, foster parenthood, egg donation, and embryo donation.

DISPOSITION

Women with the known diagnosis should be encouraged to maintain a lifestyle that optimizes bone and cardiovascular health, including regular weight-bearing exercises, adequate intake of calcium (1200 mg daily) and vitamin D (800 IU daily), healthy diet to prevent obesity, and screening for cardiovascular risk factors.

REFERRAL

Referral to gynecologist and reproductive endocrinologist may be helpful in patients who decide to pursue parenthood.

PEARLS & CONSIDERATIONS

COMMENTS

- Common etiologies should be ruled out, including chromosomal abnormalities, fragile X premutations, and autoimmune causes.
- Management directed at symptom resolution and bone protection primarily, but should include psychosocial support for women facing this devastating diagnosis.

PREVENTION

Early diagnosis of primary ovarian insufficiency important for osteoporosis prevention and possibly prevention of coronary artery disease.

PATIENT & FAMILY EDUCATION

www.pofsupport.org
poi.nichd.nih.gov

SUGGESTED READINGS

Available at www.expertconsult.com

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SUGGESTED READINGS

The International Premature Ovarian Failure Association: homepage. www.pofsupport.org. Accessed April 25, 2013.

Nelson L et al.: Primary ovarian insufficiency, *N Engl J Med* 360:606–614, 2009.

Welt CK: Primary ovarian insufficiency: a more accurate term for premature ovarian failure, *Clin Endocrinol (Oxf)* 68:499–509, 2008.

BASIC INFORMATION

DEFINITION

Primary sclerosing cholangitis (PSC) is a chronic progressive cholestatic liver disease characterized by segmental fibrosing and inflammation of intrahepatic and extrahepatic bile ducts complicated by recurrent cholangitis, cholangiocarcinoma (CCA), cirrhosis, and portal hypertension.

SYNONYMS

Chronic obliterative cholangitis
Fibrosing cholangitis
Stenosing cholangitis
PSC

ICD-9CM CODES
567.1 Cholangitis
ICD-10CM CODES
K83.0 Cholangitis
K83.0 Disease of biliary tract, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- The incidence and prevalence of PSC are 0.9 to 1.3 cases and 8.5 to 16.2 cases per 100,000 population, respectively.
- About 65% of patients with PSC are men
- Mean age of presentation is 30 to 40 yr.
- 60% to 80% of patients with PSC also have inflammatory bowel disease (IBD). 4% of patients with ulcerative colitis (UC) will develop PSC. PSC is an independent risk factor for developing colon cancer in patients with IBD.
- PSC can coexist with other autoimmune liver disease. Autoimmune hepatitis (AIH) and PSC overlap syndrome can be seen in young adults and children.
- Cholangiocarcinoma is present in 1% to 2% of PSC patients at diagnosis. The lifetime risk is 5% to 10%.
- The median survival from time of diagnosis is 10 to 15 yr without liver transplantation.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most patients are asymptomatic (15% to 40%) at the time of diagnosis with normal physical findings.
- More than 75% of asymptomatic patients develop symptoms, the most common of which are pruritus (70%) and fatigue (70%). Physical findings of symptomatic patients may reveal jaundice, skin excoriation and hyperpigmentation from scratching, hepatosplenomegaly, and xanthelasma. Other symptoms include abdominal discomfort, steatorrhea, jaundice, and weight loss, which are concerning for advanced PSC, sepsis or mechanical obstruction (i.e., cholangitis), and malignancy (i.e., cholangiocarcinoma).
- Patients can also present with advanced liver disease and decompensated cirrhosis (i.e., ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and variceal hemorrhage) or hepatic failure. Physical findings in these patients may reveal a shrunken nodular liver and evidence of portal hypertension.
- Physical findings of symptomatic patients may reveal jaundice, skin excoriation and hyperpigmentation from scratching due to pruritus, hepatosplenomegaly, and xanthelasma. In patients with cirrhosis, physical findings may reveal a shrunken nodular liver and evidence of portal hypertension.

ETIOLOGY

- The cause of PSC is unknown, but mechanisms include genetic factors, bile acid toxicity, environmental gut microbiota translocation, and gut liver lymphocyte homing mechanisms.
- Genetic and immunologic factors are supported by reports of familial occurrence of this disorder and increased frequency of HLA B8 and DR3. Genome-wide association studies have discovered novel loci associated with PSC, but the functional aspects of these genes are still unknown.
- Portosystemic inflammation caused by translocation of the gut microbiota is an increasing area of research. The close association with UC and PSC may be secondary to gut-activated T lymphocytes in IBD causing portal inflammation because of overlapping adhesion molecules in the gut and liver.

DIAGNOSIS

Diagnosis is based on characteristic cholangiographic findings in combination with clinical, biochemical, and in some cases histologic features. Table P1-41 describes staging of PSC.

DIFFERENTIAL DIAGNOSIS

- Choledocholithiasis
- Surgical biliary trauma
- Recurrent pyogenic cholangitis
- Ischemic cholangitis
- Cholangiocarcinoma
- IgG4-associated cholangitis (IAC)
- Intraarterial chemotherapy
- Diffuse intrahepatic metastasis
- Histiocytosis X

TABLE P1-41 Staging of Primary Sclerosing Cholangitis

Stage	Description
I—Portal	Portal edema, inflammation, ductal proliferation; abnormalities do not extend beyond the limiting plate
II—Periportal	Periportal fibrosis with or without inflammation extending beyond the limiting plate
III—Septal	Septal fibrosis, bridging necrosis, or both
IV—Cirrhotic	Biliary cirrhosis

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

WORKUP

History, physical examination, laboratory evaluation, imaging studies, and possible liver biopsy

LABORATORY TESTS

- Serum biochemical tests usually indicate cholestasis with predominant elevation in the serum alkaline phosphatase (three to ten times the upper limit of normal); however, this value can vary and be normal during the disease course. Serum aminotransferase levels are elevated in the majority of patients (two to three times the upper limits of normal). Serum bilirubin is usually normal at the time of diagnosis unless patient has advanced stricturing disease.
- A wide range of autoantibodies can be detected in patients with PSC; however, they are nonspecific for PSC, including the perinuclear antineutrophil cytoplasmic antibody (pANCA). Autoantibodies such as antinuclear antibody (ANA), anti-smooth muscle antibody (ASMA), and serum IgG levels are useful in the diagnosis of PSC-AIH overlap syndrome and IAC with autoimmune pancreatitis. In particular, elevated levels of IgG4 are found in 10-20% of PSC patients, with a subset of these patients displaying features of autoimmune pancreatitis. These patients may have normalization of liver function tests with corticosteroid therapy.

IMAGING STUDIES

- Cholangiography is considered to be the gold standard for the diagnosis of PSC. Characteristic findings reveal segmental fibrosis of bile ducts with saccular dilatation of normal intervening areas resulting in a "beads-on-a-string" appearance (Fig. P1-79).

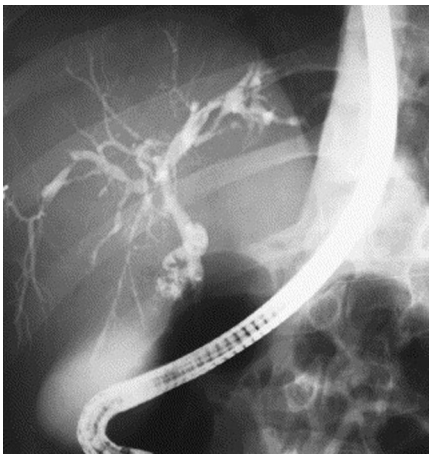

FIGURE P1-79 A 29-year-old male patient who was diagnosed with PSC 5 years previously. Both the intra- and extrahepatic bile ducts are involved at cholangiography. (From Parlak E et al: An endoscopic finding in patients with primary sclerosing cholangitis: retraction of the main duodenal papilla into the duodenum wall, *Gastrointest Endosc* 65[3]:535, 2007.)

- Magnetic resonance cholangiopancreatography (MRCP) has an overall diagnostic accuracy rate of 90%. It is the first imaging modality of choice when PSC is suspected because endoscopic retrograde cholangiopancreatography (ERCP) can be associated with serious complications (i.e., pancreatitis and cholangitis).
- Liver biopsy is not necessary for the diagnosis of PSC in patients with typical cholangiographic findings, except for small duct PSC. Biopsies are subject to sample variation, and the typical onion skin–type periductal fibrosis finding is rare. Liver biopsy may help in the diagnosis of PSC-AIH overlap syndrome, small-duct PSC (normal cholangiogram), or IAC.

Rx TREATMENT

- No medical therapy has been proved to be effective in halting the disease progression of PSC.
- Ursodeoxycholic acid (UDCA) has not shown benefit in randomized controlled trials. Although biochemical improvement has been seen with UCDA, there has been no proven benefit on survival, and in one trial, high-dose UCDA (28-30 mg/kg/day) was associated with colorectal dysplasia. Therefore high-dose UDCA is not universally recommended as medical therapy in patients with PSC. A trial of medium- or low-dose UDCA to measure biochemical and symptomatic response may be warranted in selected patients.
- Management of PSC patients is aimed at symptom relief and management of complications from PSC (i.e., obstruction/strictures).
- The use of corticosteroids and other immunosuppressive agents is not recommended in patients with PSC alone; however, it is recommended in patients with PSC-AIH overlap syndrome.
- Use of tumor necrosis factor inhibitors has been ineffective in PSC. Other monoclonal antibody therapies targeting lymphocyte trafficking, tyrosine kinase signaling, and liver fibrosis are being studied.

ACUTE GENERAL Rx

- Bile acid sequestrants (i.e., cholestyramine 16 g/day) are the preferred choice for the initial management of pruritus. Alternative agents for pruritus refractory to bile acid sequestrants include rifampicin 150 to 300 mg twice daily, naltrexone 50 mg daily, and sertraline 75 to 100 mg daily.
- Patients who present with increasing serum bilirubin and/or worsening pruritus, progressive bile duct dilatation on imaging studies, or cholangitis need to be evaluated for dominant strictures with imaging. A dominant stricture is a stenosis ≤1.5 mm in the common bile duct or ≥1 mm in the hepatic duct
- ERCP with brushings, cytology, and fluorescent in situ hybridization (FISH) is recommended to evaluate dominant strictures for cholangiocarcinoma. Once malignancy is excluded, balloon dilatation with or without stenting is recommended to treat symptoms. If ERCP is unsuccessful, percutaneous cholangiopancreatography with stenting should be considered.
- In noncirrhotic patients with dominant strictures refractory to endoscopic or percutaneous management, surgery should be considered, although this may complicate future liver transplantation surgery.
- Antibiotic usage is recommended in patients with dominant strictures/obstructions both acutely and for long-term prophylaxis in patients with recurrent cholangitis.

CHRONIC Rx

- Avoidance of alcohol and vaccination against hepatitis A and B are advised.
- Patients with PSC are at risk for osteoporosis and osteopenia. At time of diagnosis a DEXA scan is recommended and should be repeated in 2 to 3 yr. Calcium (1000 to 1500 mg) and vitamin D 600-800 IU daily are recommended for patients with osteopenia and the addition of bisphosphonate is recommended in patients with osteoporosis.
- Patients with newly diagnosed PSC should have a full colonoscopy with biopsies to exclude concurrent IBD and for surveillance of colorectal cancer. In patients with IBD, continued surveillance colonoscopy with biopsies at 1- to 2-yr intervals is recommended. In patients without IBD, a suggested 5-yr surveillance interval has been recommended due to an increased risk of colorectal cancer.
- Cholangiocarcinoma development is common in PSC. PSC patients with biochemical or symptomatic deterioration should be evaluated for CCA. Surveillance for CCA with annual MRCP and CA19-9 has been recommended by some authorities. Abnormal values should prompt further investigation of dominant strictures with ERCP. Although CA19-9 may detect CCA, even high levels (>129 U/mL) may lack specificity since one-third of patients did not have CCA after 30 months of follow up. These differences may in part be due to genotypic differences in *FUT2/3* alleles that affect expression of CA19-9.
- Annual transabdominal ultrasound is recommended due to the increased risk of gallbladder malignancy. If masses are detected, cholecystectomy should be performed.
- Patients with cirrhosis are recommended to have gastroesophageal variceal and hepatocellular carcinoma (HCC) surveillance at regular intervals.
- Annual surveillance for cholangiocarcinoma with MRCP or ultrasound and CA 19-9 testing can be considered.
- In cases of HCC and CCA, depending on underlying liver disease, resection versus liver transplantation would be required.

DISPOSITION

Liver transplantation is the only effective treatment for patients with end-stage liver disease, portal hypertension, liver failure, and recurrent or intractable bacterial cholangitis. Survival is excellent, with 90% and 80% survival rates at 1 and 5 yr, respectively. The recurrence of PSC after transplant is reportedly 5% to 20%.

REFERRAL

Gastroenterology and/or hepatology for treatment of PSC, management of its complications, surveillance of associated malignancy, and evaluation for liver transplantation.

PEARLS & CONSIDERATIONS

- Management of PSC targets symptom relief, complications of PSC, cirrhosis, early carcinoma detection, and timely referral for liver transplantation.
- UDCA is not universally recommended for treatment of PSC.
- Patients are at increased risk for the development of colorectal cancer, gallbladder cancer, and cholangiocarcinoma and need surveillance.
- In patients with cirrhosis, surveillance for gastroesophageal varices and HCC is recommended.
- Liver transplant remains the only definitive therapy for complications of PSC.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Ulcerative Colitis (Related Key Topic)

AUTHORS: **CHARLES WANG, M.D.**, and **AMANDA PRESSMAN, M.D.**

SUGGESTED READINGS

Chapman R et al.: Diagnosis and management of primary sclerosing cholangitis, *Hepatology* 51(2):660–678, 2010.

Culver EL, Chapman RW: Systematic review: management options for primary sclerosing cholangitis and its variant forms–IgG4-associated cholangitis and overlap with autoimmune hepatitis, *Aliment Pharm Therap* 33(12):1273–1291, 2011.

Eaton EJ et al.: Pathogenesis of primary sclerosing cholangitis and advances in diagnosis and management, *Gastroenterology* 145(3):521–536, 2013.

Jayant A et al.: Primary sclerosing cholangitis, *Inflamm Bowel Dis* 11(1):62–72, 2005.

Karlsen TH et al.: Update on primary sclerosing cholangitis, *J Hepatol* 59(3):572–581, 2013.

Mendes FD et al.: Primary sclerosing cholangitis, *Clin Liver Dis* 8:195–211, 2004.

Razumilava N et al.: Cancer surveillance in patients with primary sclerosing cholangitis, *Hepatology* 54(5):1842–1852, 2011.

Wannhoff A et al.: FUT2 and FUT3 genotype determines CA19-9 cut-off values for detection of cholangiocarcinoma in patients with primary sclerosing cholangitis, *J Hepatol* 59(6):1278–1284, 2013.

BASIC INFORMATION

DEFINITION

Progressive multifocal leukoencephalopathy (PML) is an uncommon and often fatal subacute demyelinating disease of the white matter, caused by reactivation of the JC virus (JCV) infection in an immunocompromised individual. JCV was isolated in 1971 and is named for the initials of the first patient from whose brain it was isolated.

ICD-9CM CODES
046.3 Progressive multifocal leukoencephalopathy
ICD-10CM CODES
A81.2 Progressive multifocal leukoencephalopathy

EPIDEMIOLOGY & DEMOGRAPHICS

RISK FACTORS: Typically seen in patients with profound immunosuppression and impaired cell-mediated immunity. These include patients with AIDS, lymphoproliferative disorders, chronic infections such as tuberculosis, and, more recently, patients on immunosuppressive or immunomodulating medications such as natalizumab, rituximab, efalizumab, brentuximab-vedotin, and mycophenolate mofetil.

INCIDENCE & PREVALANCE:

- Two population groups—HIV and natalizumab-treated patients—have seen a significant increase in PML.
- HIV: a 50-fold increase in PML cases was reported with HIV epidemic. 3% to 5% patients with HIV will develop PML. PML is an AIDS-defining illness. Highly active retroviral therapy (HAART) has led to some decline in PML cases.
- Incidence of PML in natalizumab-treated patients 3 to 4/1000 patients and depends on treatment duration.
- Seroepidemiologic studies have shown that asymptomatic primary infection with JCV occurs at an early age, and by adult life 30% to 90% of the population is seropositive.

PREDOMINANT SEX & AGE: Males and females are equally affected. There is no specific age distribution.

GENETICS: Unknown

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Subacute neurologic deficits are common; can also present acutely as a stroke mimic.
- The clinical course spans weeks to months leading to severe disability and death.
- PML lesions usually involve cerebral hemispheres; cerebellum and brainstem involvement may be seen in AIDS. Multifocal asymmetric white matter involvement is common; rarely there can be gray matter involvement including cerebellar granular cells.
- Non–AIDS-associated PML: early lesions involve occipital subcortical white matter and cause visual-field deficits (homonymous hemianopia) or cortical blindness. Motor weakness and altered mentation may be seen, while headache, seizures, and extrapyramidal syndromes are rare.
- AIDS-related PML: motor weakness is more common. Abnormalities of speech, cognition, gait, sensation, and visual impairment may also be seen.
- Natalizumab-associated PML: frontal lobe is commonly involved, leading to cognitive impairment, neurobehavioral changes, motor disorders, language disorders, and visual defects.
- Immune reconstitution inflammatory syndrome (IRIS): a paradoxical clinical deterioration that occurs during immunologic recovery in previously immunocompromised patients, such as antiretroviral therapy–treated HIV-seropositive patients, or cessation of immunomodulating treatment, such as natalizumab. An increase in the number or size of lesions on neuroimaging with contrast enhancement of brain lesions and brain edema may be seen.

ETIOLOGY & PATHOGENESIS

- JCV infection may be acquired through respiratory tissue or oropharyngeal route; seroconversion usually occurs in childhood.
- A cytotoxic-specific response against JCV acts as a containing mechanism for PML. Immunosuppression leads to development of PML either as primary infection of the CNS following immunosuppression or reactivation of a dormant infection. The virus produces lytic infection of the oligodendrocytes and causes demyelination. Neuronal infection does not usually occur except in granule cell neurons of the cerebellum.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Multiple sclerosis.
- Acute disseminated encephalomyelitis.
- Vasculitis.
- HIV encephalitis.
- Mitochondrial encephalopathies (e.g., MELAS).
- Posterior reversible encephalopathy syndrome.

WORKUP

- Diagnosis is based on compatible clinical presentation, MRI brain features, and detection of JCV in CSF.
- Brain biopsy is the gold standard and demonstrates a triad of histopathologic findings—demyelination, bizarre astrocytes, and enlarged oligodendrocytic nuclei.

LABORATORY TESTS

- CSF examination: usually normal; may show mild lymphocytic pleocytosis (20 to 25 leukocytes/ml) and elevated protein (usually <65 mg/dl).
- CSF PCR for JCV has a sensitivity of 95% and specificity of 99% using ultrasensitive PCR techniques, but may be lower depending on the techniques used.

IMAGING STUDIES

- MRI brain is the neuroimaging of choice and shows demyelinating lesions that are hyperintense on T2 and FLAIR sequences, hypointense on T1, and may enhance with gadolinium.
- CT head may show subcortical hypodensities with faint contrast enhancement.
- MR spectroscopy will demonstrate features of demyelination—decreased N-acetyl acetate, increased choline, and increased lactate.

TREATMENT

There is no specific treatment for PML. Treatment is aimed at reversal of the underlying causes of immunosuppression.

NONPHARMACOLOGIC THERAPY

Plasma exchange and immunoadsorption for natalizumab-treated patients to rapidly reduce blood levels of natalizumab and hasten restoration of immune function.

ACUTE GENERAL Rx

- HIV-positive patients: antiretroviral therapy should be optimized.
- HIV-negative patients: immunosuppressive medication should be discontinued; plasma exchange may be considered for natalizumab-treated patients.
- IRIS: treatment with steroids should be considered.

CHRONIC Rx

No specific pharmacologic therapy exists for chronic treatment.

DISPOSITION

Of all HIV-related cerebral disorders, PML probably has the worst prognosis. Pre-AIDS era survival was 6 months. With HAART, incidence and prognosis of PML has improved. A lower CSF JCV load and better CD4 counts have better prognoses. Natalizumab-treated patients have worse prognoses seen with longer time to diagnosis, presence of widespread disease, and brainstem involvement.

REFERRAL

Refer to neurology if patients have neurologic deficits of uncertain etiology, especially in the setting of AIDS or immunosuppression.

PEARLS & CONSIDERATIONS

COMMENTS

PML is a fatal opportunistic cerebral infection that should be considered in all immunosuppressed individuals presenting with neurologic deficits and demyelinating cerebral lesions. Early referral to a center with neurologic expertise, especially neuroimmunology or neuroinfectious diseases, should be considered.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **PADMAJA SUDHAKAR, M.B.B.S.,** and **SACHIN KEDAR, M.B.B.S., M.D.**

SUGGESTED READINGS

Berger JR: The clinical features of PML, *Cleve Clin J Med* 2(78 Suppl):S8–S12, 2011.

Sahraian MA et al.: Progressive multifocal leukoencephalopathy: a review of the neuroimaging features and differential diagnosis, *Eur J Neurol* 19(8):1060–1069, 2012.

BASIC INFORMATION

DEFINITION

Progressive supranuclear palsy (PSP) is an atypical parkinsonian syndrome characterized by supranuclear gaze impairment, prominent and early postural instability with falls, axial greater than appendicular rigidity, and poor or absent response to levodopa.

SYNONYMS

Steele-Richardson-Olszewski syndrome
Progressive supranuclear ophthalmoplegia

ICD-9CM CODES
333.0 Other degenerative diseases of the basal ganglia
ICD-10CM CODES
G23.1 Progressive supranuclear ophthalmoplegia
G23.9 Degenerative disease of basal ganglia, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 1.1 per 100,000 (5.3 per 100,000 over age 50)
PREVALENCE: 4.9 per 100,000 (6.4 per 100,000 age-adjusted)
PREDOMINANT SEX AND AGE: Slight male predominance; mean age onset 63 yr, very uncommon for onset <50 yr
GENETICS: Familial cases have been reported only rarely. The vast majority of cases are sporadic.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Tremorless parkinsonism is the general clinical presentation, and differentiation from idiopathic Parkinson's disease can be challenging early in the disease course. However, there are certain symptoms that can serve as "red flags" to consider PSP:

- Early postural instability and retropulsion leads to frequent falls; falls within the first year of onset of symptoms is typically the rule.
- Supranuclear gaze palsy is often preceded by slowing of vertical saccades; square wave jerks can be present; blepharospasm is common.
- Dystonia of the frontalis and procerus muscles gives the PSP patient a "surprised" or "frightened" expression as opposed to the hypomimia of Parkinson's disease (Fig. P1-80).
- Speech is typically strained, spastic, hypernasal, with a low-pitched dysarthria.
- Pseudobulbar affect and "emotional incontinence" can be seen, with easy crying or laughter.
- Early cognitive impairment, most commonly with apathy, disinhibition, and anxiety.

ETIOLOGY

PSP is caused by neuronal degeneration of nuclei in the midbrain and basal ganglia, as a result of abnormal tau protein accumulation, most commonly in astrocyte inclusions and neurofibrillary tangles.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Parkinson's disease: responds more robustly to levodopa, progression much slower, and lacks "red flag" symptoms above.
- Corticobasal degeneration: also a tauopathy like PSP, but characterized by parkinsonism with prominent asymmetric dystonia, cortical sensory signs such as astereognosis, typically progressing to apraxia and sometimes an "alien hand" syndrome.
- Multiple system atrophy: distinguished by autonomic involvement such as orthostatic hypotension, cerebellar ataxia, and inspiratory stridor.
- Dementia with Lewy bodies: dementia coincident with parkinsonism, fluctuating mental status, visual hallucinations often preceding onset of dopaminergic treatment.

WORKUP

- PSP is a clinical diagnosis, best made by a neurologist familiar with the disorder such as a movement disorders specialist.
- A robust response to a trial of levodopa may help to lead consideration away from PSP.
- MRI scan (see below) can be helpful.

LABORATORY TESTS

There are no diagnostic laboratory tests.

IMAGING STUDIES

- Dorsal midbrain atrophy is commonly seen on MRI.
- Dopamine transporter imaging (DaTScan with [^{123}I]β-CIT SPECT) shows reduced uptake in PSP and is therefore not useful in differentiating PSP from Parkinson's disease or other causes of parkinsonism.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Physical therapy, in particular focusing on fall prevention, is essential for avoiding the morbidity associated with frequent falls. Assistive devices such as a walker or wheelchair should be encouraged.
- Dysphagia is a common finding and should be monitored for closely in conjunction with a speech therapist.
- Prisms may be helpful in some patients for the eye movement abnormalities that can result in misalignment and diplopia; however, benefits, if noted, tend to be short-lived as the disease progresses.

FIGURE P1-80 A patient with progressive supranuclear palsy with staring expression, frontalis overactivity, and retrocolitis. She is wearing a neck sling for a fractured wrist sustained in a fall. (From Burn D, Lees A: Progressive supranuclear palsy: where are we now? *Lancet Neurol* 1:359, 2002.)

CHRONIC Rx

- Although classically felt to be unresponsive to levodopa, there is often a transient response to this medication and it can be useful. The poor response to levodopa is most likely due to the loss of postsynaptic dopamine receptors.
- Anticholinergic medications should be avoided.
- Blepharospasm can be effectively treated with botulinum toxin injections.

DISPOSITION

Median latency from symptom onset to wheelchair-bound state is 5 yr and to death is 7 yr.

REFERRAL

Referral to a general neurologist or movement disorders center is appropriate.

PEARLS & CONSIDERATIONS

COMMENTS

Consider PSP in a parkinsonian patient with the onset of falls within 1 yr of diagnosis, vertical eye movement abnormalities, early cognitive impairment, pseudobulbar affect, frontonasal dystonia, or poor response to levodopa.

PATIENT & FAMILY EDUCATION

Patient and caregiver information and resources can be found at www.wemove.org (a comprehensive movement disorders website) as well as the Society for Progressive Supranuclear Palsy at www.curepsp.org.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **ANDREW DUKER, M.D.**

SUGGESTED READINGS

Colosimo C et al.: Fifty years of progressive supranuclear palsy, *J Neurol Neurosurg Psychiatry* 85:938–944, 2014.

Houghton DL, Litvan I: Unraveling progressive supranuclear palsy: from the bedside back to the bench, *Parkinsonism Relat Disord* 13:S341–S346, 2007.

Litvan I et al.: Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome), *Neurology* 47:1–9, 1996.

Williams DR et al.: Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism, *Brain* 128:1247–1258, 2005.

BASIC INFORMATION

DEFINITION

Prolactinomas are monoclonal tumors that secrete prolactin.

ICD-9CM CODES
253.1 Forbes-Albright syndrome
ICD-10CM CODES
D35.2 Benign neoplasm of pituitary gland
E22.8 Other hyperfunction of pituitary gland

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Most common pituitary tumor; nearly 30% of all pituitary adenomas secrete enough prolactin to cause hyperprolactinemia.
PREDOMINANT SEX: Microadenomas are more common in women; macroadenomas are found more frequently in men.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Men: decreased facial and body hair, infertility, small testicles; may also have decreased libido, erectile dysfunction, and delayed puberty (caused by decreased testosterone as a result of inhibition of gonadotropin secretion).
- Women: physical examination may be normal; history may reveal amenorrhea, galactorrhea (Fig. EP1-81), oligomenorrhea, and anovulation.
- Both sexes: visual field defects and headache may occur depending on size of tumor and its expansion.

ETIOLOGY

Prolactin-secreting pituitary adenomas: microadenomas (<10 mm diameter) or macroadenomas (>10 mm diameter). No risk factors have been identified for sporadic prolactinomas. Rarely prolactinomas can be part of multiple endocrine neoplasia (MEN) type 1 syndrome.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Secretion of prolactin is under tonic inhibitory control by hypothalamic dopamine. Hyperprolactinemia may be caused by the following:

- Drugs: risperidone, phenothiazines, methyldopa, reserpine, monoamine oxidase inhibitors, androgens, progesterone, cimetidine, tricyclic antidepressants, haloperidol, meprobamate, chlordiazepoxide, estrogens, narcotics, metoclopramide, verapamil, amoxapine, cocaine, oral contraceptives
- Hepatic cirrhosis, renal failure, primary hypothyroidism
- Ectopic prolactin-secreting tumors (hypernephroma, bronchogenic carcinoma)
- Infiltrating diseases of the pituitary (sarcoidosis, histiocytosis)
- Head trauma, chest wall injury, spinal cord injury
- Polycystic ovary disease, pregnancy, nipple stimulation
- Idiopathic hyperprolactinemia, stress, exercise

WORKUP

- The diagnosis of prolactinoma is established by demonstration of an elevated serum prolactin level (after exclusion of other causes of hyperprolactinemia) and radiographic evidence of a pituitary adenoma.
  1. Normal mean prolactin levels are 8 ng/ml in women and 5 ng/ml in men.
  2. Levels >300 ng/ml are virtually diagnostic of prolactinomas.
  3. Prolactin levels can vary with time of day, stress, sleep cycle, and meals. More accurate measurements can be obtained 2 to 3 hr after awakening, preprandially, and when patient is not distressed.
  4. Serial measurements are recommended in patients with mild prolactin elevations.
- TSH, free T_4, BUN, Creat, ALT, AST are useful tests. Pregnancy test in all women of childbearing age.
- All patients with prolactinomas should undergo visual field testing. Serial evaluation is recommended, particularly during pregnancy in patients with macroadenomas.

IMAGING STUDIES

- MRI with gadolinium enhancement is the procedure of choice in the radiographic evaluation of pituitary disease.
- In absence of MRI, a radiographic diagnosis is best accomplished with a high-resolution CT scanner and special coronal cuts through the pituitary region.

TREATMENT

NONPHARMACOLOGIC THERAPY

Pregnancy and breastfeeding should be avoided because they can encourage tumor growth.

ACUTE GENERAL Rx

- Management of prolactinomas depends on their size and encroachment on the optic chiasm and other vital structures, the presence or absence of gonadal dysfunction, and the patient's desires regarding fertility. Fig. P1-82 describes a management algorithm for prolactinomas.
- Medical therapy is preferred when fertility is an important consideration.
  1. Bromocriptine: initial dose is 0.625 mg at bedtime for the first week. After 1 wk, add morning dose of 1.25 mg. Gradually increase dose by 1.25 mg/wk until dose of 5 to 10 mg/day is achieved. Bromocriptine decreases size of the tumor and generally lowers the prolactin level into the normal range when the initial serum prolactin is <500 ng/ml. Side effects of bromocriptine are nausea, constipation, dizziness, and nasal stuffiness. Bromocriptine appears to be safe during pregnancy.
  2. Cabergoline is a longer-acting dopamine agonist that is more expensive but may be more effective and better tolerated than bromocriptine; initial dose is 0.25 mg twice weekly.
- Transsphenoidal resection: option in an infertile patient who cannot tolerate bromocriptine or cabergoline or when medical therapy is ineffective. The success rate depends on the location of the tumor (entirely intrasellar), experience of the neurosurgeon, and size of the tumor (<10 mm in diameter); the recurrence rate may reach 80% within 5 yr. Possible complications of transsphenoidal surgery vary with experience and skill of the neurosurgeon and tumor anatomy and include transient diabetes insipidus, hypopituitarism, cerebrospinal fluid rhinorrhea, and infections (meningitis, wound infection).
- Pituitary irradiation is useful as adjunctive therapy of macroadenomas (>10 mm in diameter) and in patients with persistent hypersecretion after surgery. Potential complications include cranial nerve damage, radionecrosis, and cognitive abnormalities.
- Stereotactic radiosurgery (gamma knife) has become popular as a modality in the treatment of prolactinomas. A high dose of ionizing radiation is delivered to the tumor through multiple ports. Its advantage is minimal irradiation to surrounding tissues. Proximity of the tumor to the optic chiasm limits this therapeutic modality.

CHRONIC Rx

- Patients on medical therapy require periodic measurement of prolactin levels. An attempt to reduce the dose of bromocriptine or cabergoline can be made after the prolactin level has been normal for 2 yr. An MRI scan of the pituitary should be obtained to rule out tumor enlargement within 6 mo of initiation of tapering regimen.
- Evaluation and monitoring of pituitary function are recommended after transsphenoidal surgery.

DISPOSITION

- Transsphenoidal surgery will result in a cure in nearly 50% to 75% of patients with microadenomas and 10% to 20% of patients with macroadenomas.
- Nearly 20% of microprolactinomas resolve during long-term dopamine agonist treatment.

PEARLS & CONSIDERATIONS

COMMENTS

- Patients must be monitored for several years after surgery because up to 50% of microadenomas and nearly 90% of macroadenomas can recur.
- Pituitary microadenomas are found in 10.9% of autopsies, and 44% of these microadenomas are prolactinomas.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Prolactinoma (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

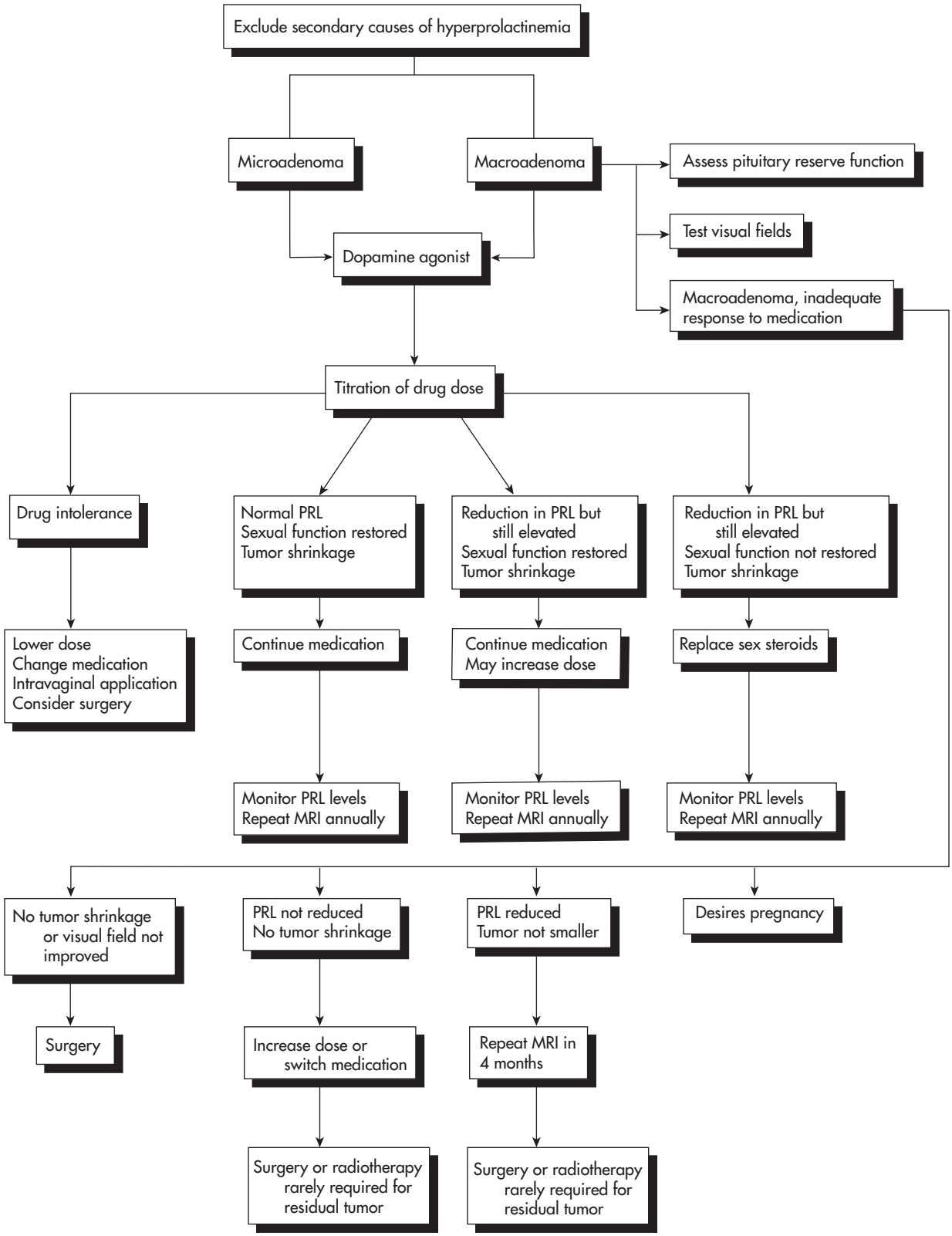

FIGURE P1-82 Prolactinoma management. After secondary causes of hyperprolactinemia have been excluded, subsequent management decisions are based on clinical imaging and biochemical criteria. *MRI,* Magnetic resonance imaging; *PRL,* prolactin. (Modified from Larsen PR et al: *Williams textbook of endocrinology,* ed 11, Philadelphia, 2008, Saunders.)

EVIDENCE

Abstract[1]

Context:
Prolactinoma is the most frequent pituitary tumour among women of child-bearing age. Only a few studies have addressed the outcome of prolactinoma after pregnancy.

Objective:
To study remission, defined as prolactin normalization without medical treatment, after pregnancy and lactation in women with prolactinoma.

Patients and Methods:
A retrospective study conducted in 2 Belgian academic centres including 73 patients (54 microprolactinomas and 19 macroprolactinomas) with 104 pregnancies continuing beyond first trimester. Dopamine agonists were stopped in early pregnancy in all treated cases. Prolactin level and adenoma size at pituitary magnetic resonance imaging (MRI) were recorded before pregnancy and throughout follow-up.

Results:
Thirty of 73 women (41%) were in remission after a median follow-up of 22 months after delivery or cessation of lactation. Adenoma size at diagnosis was smaller in women in remission (5 vs 8 mm). There was a nonsignificant higher rate of remission for microprolactinomas than for macroprolactinoma (46% vs 26%). The first pituitary MRI after pregnancy and lactation showed no tumour and a decreased adenoma size in 23% and 39% of women, respectively. MRI normalization was associated with remission. The number of pregnancies per woman as well as breastfeeding and its duration did not influence remission rate.

Conclusion:
More than 40% of women with previous diagnosis of prolactinoma have normal PRL level without medical treatment for a median follow-up of 22 months after pregnancy and lactation. The likelihood of remission is associated with a smaller initial adenoma size and normalization of pituitary MRI after pregnancy. Ⓐ

Abstract[2]

Context:
Concern exists in the literature that the long-term use of ergot-derived dopamine agonist drugs for the treatment of hyperprolactinemia may be associated with clinically significant valvular heart disease.

Objective:
The aim of the study was to determine the prevalence of valvular heart abnormalities in patients taking dopamine agonists as treatment for lactotrope pituitary tumors and to explore any associations with the cumulative dose of drug used.

Design:
A cross-sectional echocardiographic study was performed in a large group of patients who were receiving dopamine agonist therapy for hyperprolactinemia. Studies were performed in accordance with the British Society of Echocardiography minimum dataset for a standard adult transthoracic echocardiogram. Poisson regression was used to calculate relative risks according to quartiles of dopamine agonist cumulative dose using the lowest cumulative dose quartile as the reference group.

Setting:
Twenty-eight centers of secondary/tertiary endocrine care across the United Kingdom participated in the study.

Results:
Data from 747 patients (251 males; median age, 42 y; interquartile range [IQR], 34e52 y) were collected. A total of 601 patients had taken cabergoline alone; 36 had been treated with bromocriptine alone; and 110 had received both drugs at some stage. The median cumulative dose for cabergoline was 152 mg (IQR, 50e348 mg), and for bromocriptine it was 7815 mg (IQR, 1764e20 477 mg). A total of 28 cases of moderate valvular stenosis or regurgitation were observed in 24 (3.2%) patients. No associations were observed between cumulative doses of dopamine agonist used and the age-corrected prevalence of any valvular abnormality.

Conclusion:
This large UK cross-sectional study does not support a clinically concerning association between the use of dopamine agonists for the treatment of hyperprolactinemia and cardiac valvulopathy. Ⓐ

Evidence-Based References

Domingue M-E, Devuyst F, Alexopoulou O, et al.: Outcome of prolactinoma after pregnancy and lactation: a study on 73 patients, *Clin Endocrinol* 80:642–648, 2014. Ⓑ

Drake WM: on behalf of the UK Dopamine Agonist Valvulopathy Group: A cross-sectional study of the prevalence of cardiac valvular abnormalities in hyperprolactinemic patients treated with ergot-derived dopamine agonists, *J Clin Endocrinol Metab* 99:90–96, 2014. Ⓑ

Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G: Valvular heart disease and the use of dopamine agonists for Parkinson's disease, *N Engl J Med* 356:39–46, 2007. Ⓐ

Schade R, Andersohn F, Suissa S, HaverkampW Garbe E: Dopamine agonists and the risk of cardiac-valve regurgitation, *N Engl J Med* 356:29–38, 2007. Ⓐ

Steffensen C, Maegbaek ML, Laurberg P, et al.: Heart valve disease among patients with hyperprolactinemia: a nationwide population-based cohort study, *J Clin Endocrinol Metab* 97:1629–1634, 2012. Ⓐ

SUGGESTED READINGS

Klibansku A: Prolactinomas, *N Engl J Med* 362:1219–1226, 2010.

Leung A, Pacaud D: Diagnosis and management of galactorrhea, *Am Fam Physician* 70:543, 2004.

Schlechte JA: Prolactinoma, *N Engl J Med* 349:2035, 2003.

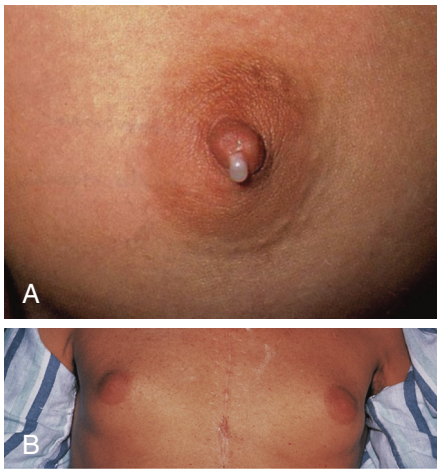

FIGURE EP1-81 Effects of prolactinoma. A, Galactorrhea in a female. **B,** Gynecomastia in a male. (**A** from Bouloux PM: *Clinical medicine assessment questions in color,* St Louis, 1993, Wolfe. **B** from Mir MA: *Atlas of clinical diagnosis,* Edinburgh, 2003, Saunders.)

Pronator Syndrome

BASIC INFORMATION

DEFINITION

Pronator syndrome is a form of compression neuropathy of the median nerve in the proximal forearm caused primarily by the pronator teres muscle (Fig. P1-83). Occasionally, only the anterior interosseus motor branch is affected, sometimes causing a specific separate clinical presentation.

SYNONYMS

Kiloh-Nevin syndrome (anterior interosseus syndrome)

ICD-9CM CODES
354.1 Median nerve entrapment
354.9 Mononeuritis of upper limb
ICD-10CM CODES
G56.10 Other lesions of median nerve, unspecified upper limb
G56.90 Unspecified mononeuropathy of unspecified upper limb

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT SEX: Males are affected more often than females.

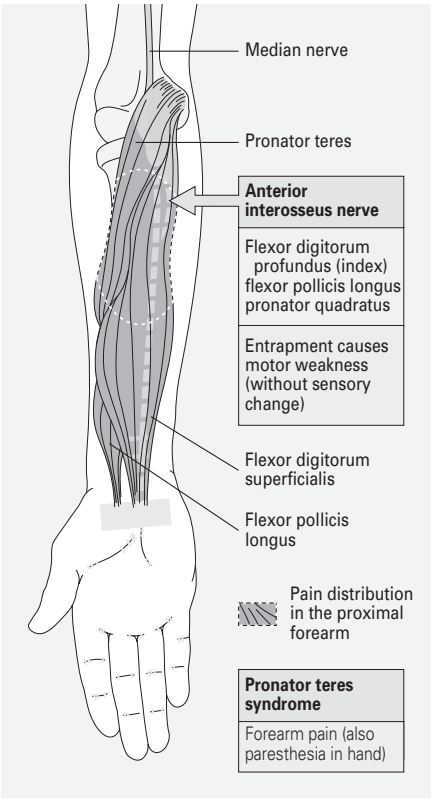

FIGURE P1-83 Forearm entrapment regions. The median nerve may be compressed at several locations in the forearm, most commonly as it traverses the pronator teres muscle. The anterior interosseus branch of the median nerve is solely motor, thus entrapment produces no sensory deficit. (From Hochberg MC et al [eds]: *Rheumatology,* ed 3, St Louis, 2003, Mosby.)

INCIDENCE: Rare (comprises <1% of median nerve entrapment disorders); most common in dominant arm.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Forearm discomfort and fatigue, often resulting from repetitive pronation.
- Insidious onset.
- Nocturnal paresthesias are not typical.
- Vague numbness in hand, primarily in thumb and index finger, may be present.
- Tenderness and enlargement of the pronator teres may be present.
- Tinel's sign may be positive at the site of compression.
- Although there are no reliable provocative tests, painful paresthesias may occasionally be elicited with forced pronation of the forearm against resistance.
- Motor impairment is rare.

Anterior interosseus nerve syndrome:

- Forearm pain and weakness.
- Patient may be unable to form a circle when trying to pinch the index finger and thumb because of the inability to flex distal phalanges of thumb and index finger.
- Sensation to the hand is not affected.

ETIOLOGY

- Localized anatomic compression.
- Trauma.
- Traumatic cutdown or phlebotomy.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Carpal tunnel syndrome.
- Cervical disc syndrome with radiculopathy.
- Tendon rupture.
- Tendinitis.

WORKUP

- Electrodiagnostic studies may be helpful; they are indicated if symptoms persist >4 to 6 wk or if motor weakness is suspected.
- Plain radiography to rule out bony abnormalities causing compression.

TREATMENT

- Rest, bracing of forearm, sling.
- Stretching exercises, physical therapy.
- Nonsteroidal anti-inflammatory drugs.

DISPOSITION

Patients whose symptoms are mainly subjective often respond to nonsurgical management. Motor deficits may not be reversible despite surgery.

REFERRAL

Surgical referral in cases of failed medical management or when motor weakness is present.

PEARLS & CONSIDERATIONS

COMMENTS

Prognosis for recovery is good. When indicated, surgical intervention is most effective if the diagnosis can be firmly established by objective testing.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Bridgeman C et al.: Clinical and electrophysiological presentation of pronator syndrome, *Electromyogr Clin Neurophysiol* 47(2):89, 2007.

Cain EL et al.: Elbow injuries in throwing athletes: a current concepts review, *Am J Sports Med* 31(4):621, 2003.

Neal S, Fields KB: Peripheral nerve entrapment and injury in the upper extremity, *Am Fam Physician* 81(2):147, 2010.

Rehak DC: Pronator syndrome, *Clin Sports Med* 20(3):531, 2001.

Sellards R, Kuebrich C: The elbow: diagnosis and treatment of common injuries, *Prim Care* 32(1):1, 2005.

Tsai P, Steinberg DR: Median and radial nerve compression about the elbow, *Instr Course Lect* 57:177, 2008.

BASIC INFORMATION

DEFINITION & CLASSIFICATION

Prostate cancer is a neoplasm involving the prostate. Various classifications have been developed to evaluate malignancy potential and prognosis.

- The degree of malignancy varies with the stage:
  1. Stage A: Confined to the prostate, no nodule palpable.
  2. Stage B: Palpable nodule confined to the gland.
  3. Stage C: Local extension.
  4. Stage D: Regional lymph nodes or distant metastases.
- In the Gleason classification, two histologic patterns are independently assigned numbers 1 to 5 (best to least differentiated). These numbers are added to give a total tumor score between 2 and 10. Prognosis is best for highly differentiated tumors (e.g., Gleason score 2 to 4) compared with most poorly differentiated tumors (Gleason score 7 to 10).
- Another commonly used classification is the Tumor-Node-Metastasis (TNM) classification of prostate cancer.

ICD-9CM CODES
185 Malignant neoplasm of prostate
ICD-10CM CODES
C61 Malignant neoplasm of prostate

EPIDEMIOLOGY & DEMOGRAPHICS

- Prostate cancer has surpassed lung cancer as the most common nonskin cancer in men.
- In the United States nearly 200,000 cases are diagnosed yearly, and nearly 30,000 males die from prostate cancer each year (second leading cause of death from cancer in U.S. men).
- Incidence of prostate cancer increases with age: uncommon <50 yr; 80% of new cases are diagnosed in patients aged ≥65 yr. Widespread PSA testing has doubled the incidence of prostate cancer and the lifetime risk for prostate cancer to approximately 16%. Prostate cancer is also diagnosed earlier, and the incidence of clinically "silent" T1 tumors has increased from 17% in 1989 to 48% in 2001 since the advent of PSA screening.
- Average age at time of diagnosis is 72 yr.
- Blacks in the United States have the highest incidence of prostate cancer in the world (one in every nine males).
- Incidence is low in Asians.
- Approximately 9% of all prostate cancers may be familial. Obesity is a risk factor for prostate cancer. High-fat, low-fiber diet increases risk. High insulin levels may also increase the risk of prostate cancer. Dietary supplementation with vitamin E has been reported to significantly increase the risk of prostate cancer among healthy men. Linkage studies have implicated chromosome 17p21-22 as a possible location of a prostate-cancer susceptibility gene. Germline mutations in *HOXB13* are associated with a significantly increased risk of hereditary prostate cancer.
- Mortality rates of prostate cancer have declined substantially in the past 15 yr from 34% in 1990 to <20% currently.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Generally silent disease until it reaches advanced stages.
- Bone pain and pathologic fractures may be initial symptoms of prostate cancer.
- Local growth can cause symptoms of outflow obstruction.
- Digital rectal examination (DRE) may reveal an area of increased firmness; 10% of patients will have a negative DRE.
- Prostate may be hard, fixed, with extension of tumor to the seminal vesicles in advanced stages.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Benign prostatic hypertrophy
- Prostatitis
- Prostate stones

LABORATORY TESTS

- Fig. EP1-84 describes the assessment and treatment of patients with prostate cancer suspected on the grounds of a DRE and PSA. Measurement of prostate-specific antigen (PSA) is controversial in early diagnosis of prostate cancer. PSA screening is associated with psychological harm, and its potential benefits remain uncertain. In asymptomatic men with no history of prostate cancer, screening using PSA does not reduce all-cause mortality or death from prostate cancer. Normal PSA is found in >20% of patients with prostate cancer, whereas only 20% of men with PSA levels between 4 ng/ml and 10 ng/ml have prostate cancer. Most guidelines encourage a shared decision-making approach between patient and physician regarding PSA testing. Available evidence favors clinician discussion of the pros and cons of PSA screening with average-risk men aged 65 to 69 yr. Only men who express a definite preference for screening should have PSA testing. Rather than widespread annual PSA screening, a reasonable approach may be to focus on high-risk men (those with PSA levels ≥2 ng/ml at age 60). The American Cancer Society recommends offering the PSA test and DRE yearly to men aged ≥50 yr who have a life expectancy of at least 10 yr. Earlier testing, starting at age 40 to 45 yr, is recommended for men at high risk (e.g., blacks, men with family history of prostate cancer). An isolated elevation in PSA level should be confirmed several weeks later before proceeding with further testing, including prostate biopsy. Screening for prostate cancer in men aged ≥75 yr is controversial and generally not recommended. The American College of Physicians (ACP) recommends that clinicians should not screen for prostate cancer using the PSA in average-risk men under age 50, men over age 69, or men with a life expectancy of <10 to 15 yr. The U.S. Preventive Services Task Force (USPSTF) recommends against PSA-based screening for prostate cancer in all age groups. According to the USPSTF:
  - The magnitude of harms from screening (e.g., falsely high PSA levels, psychological effects, unnecessary biopsies, overdiagnosis of indolent tumors) is "at least small."
  - The magnitude of treatment-associated harms (i.e., adverse effects of surgery, radiation, and hormonal therapy) is "at least moderate."
  - The 10-yr mortality benefit of PSA-based prostate cancer screening is "small to none."
  - The overall balance of benefits and harms results in "moderate certainty that PSA-based screening has no net benefit."
- Free PSA: the use of serum free PSA for prostate screening has been proposed by some urologists as a means to decrease unwarranted biopsies without missing a significant number of prostate cancers. This approach is based on the higher free PSA in men with benign prostatic hyperplasia and the higher protein-bound PSA levels in men with prostate cancer. For example, in men with total PSA levels of 4 to 10 ng/ml, the cancer probability is 0.25, but if the percentage of free PSA is ≤17%, the probability of cancer increases to 0.45.
- PSA velocity: the rate of increase of serum PSA over time (PSA velocity) can aid in the diagnosis of prostate cancer. A yearly PSA velocity >0.75 ng/ml increases the likelihood of later malignancy when total PSA is still within normal range. Proper interpretation of PSA velocity requires at least three PSA measurements over an 18-month period because most PSA variations are physiologic. Recent trials have cast a doubt on the value of PSA velocity by showing that adding PSA velocity as a trigger for biopsy did not improve predictive accuracy beyond that of using PSA threshold values alone.
- Age-adjusted PSA: there is evidence that the current threshold of 4.0 ng/ml is inadequate for younger men, because in a recent study 22% of men with PSA levels between 2.6 and 4.0 were found to have prostate cancer. The concept of age-related cutoffs remains controversial. Lowering the upper limit of normal for PSA would improve sensitivity but decrease specificity.
- Prostatic acid phosphatase can be used for evaluation of nonlocalized disease.
- Prostate cancer gene 3 *(PCA3)* is overexpressed in prostate cancer cell, and high levels are suggestive of prostate cancer. Measurement of *PCA3* in urine specimens collected after digital exams is helpful to make decisions about prostate biopsy in men with elevated PSA.
- Transrectal biopsy and fine-needle aspiration of prostate can confirm the diagnosis. Indications for biopsy include an abnormal

PSA level, an abnormal DRE, or a previous biopsy specimen that showed prostatic intraepithelial neoplasia or prostatic atypia. The number of cores taken is patient specific, typically including a minimum of 10 cores. Prostate volume negatively affects cancer detection rate (23% in glands >50 cm^3, 38% in glands <50 cm^3).

IMAGING STUDIES

- Bone scan is useful to evaluate bone metastasis (present or eventually develops in almost 80% of patients). However, according to the American Urological Association (AUA), the routine use of bone scanning is not required for staging of prostate cancer in asymptomatic men with clinically localized cancer if the PSA level is ≤20 ng/ml.
- CT scan, MRI, and transrectal ultrasonography may be useful in selected patients to assess extent of prostate cancer. High-resolution MRI with magnetic nanoparticles has been used for the detection of small and otherwise undetectable lymph node metastases in patients with prostate cancer. However, according to the AUA, transrectal ultrasonography adds little to the combination of PSA and DRE. Similarly, CT and MRI imaging are generally not indicated for cancer staging in men with clinically localized cancer and PSA <25 ng/ml. With regard to pelvic lymph node dissection in staging, the AUA states that it may not be required in patients with PSA levels <10 ng/ml and when PSA level is <20 ng/ml and the Gleason score is <6.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Watchful waiting is reasonable in selected patients with early-stage (T-IA) and projected life expectancy <10 yr or in patients with focal and moderately differentiated carcinoma.

ACUTE GENERAL Rx

- Therapeutic approach varies with the following:
  1. Stage of the tumor.
  2. Patient's life expectancy.
  3. General medical condition.
  4. Patient's treatment preference (e.g., patient may be opposed to orchiectomy).
- The optimal treatment of clinically localized prostate cancer is unclear. It's important to remember that all forms of treatment have potential adverse effects. Management requires careful consideration of the potential benefits and harms of intervention, the patient's age, health status, and individual preferences.
  1. Radical prostatectomy is generally performed in patients with localized prostate cancer and life expectancy >10 yr. Radical prostatectomy reduces disease-specific mortality, overall mortality, and the risks of metastasis and local progression. The absolute reduction in the risk of death after 10 yr is small, but the reductions in the risks of metastasis and local tumor progression are substantial. Postoperative complications of radical prostatectomy include urinary incontinence (10% to 20% depending on degree of neurovascular bundle and urethral preservation, patient age, and correct mucosal apposition) and erectile dysfunction (percentage >50% and varies with patient age, preoperative erectile dysfunction, stage of tumor at time of surgery, and preservation of neurovascular bundle). Lower complication rates occur in hospitals that perform a large number of prostatectomies. Fewer men will have postsurgical erectile dysfunction after unilateral or bilateral nerve-sparing surgery. In men undergoing prostatectomy, robotic-assisted laparoscopic surgery represents an alternative to open retropubic radical prostatectomy. Despite advertisements that suggest that there are fewer complications after robotic surgery, recent data show that sexual dysfunction occurs postoperatively in about 88% of patients who have undergone robotic-assisted or conventional prostatectomy and that incontinence problems are more prevalent (33%) with robotic surgery than with open retropubic radical prostatectomy (RPP) (27%). Recent trials have shown that prostatectomy is preferred over "watchful waiting" in patients with localized prostate cancer detected by PSA if the PSA level is >10 ng/ml. In this subgroup, the 10-year mortality is 48.4% with prostatectomy versus 61.6% with watchful waiting. In men who have low-risk disease (PSA level <10 mcg/L, stage <T2a, Gleason score ≤3 + 3), and <6% risk for prostate cancer–specific death at 15 yr, watchful waiting (WW) and active surveillance (AS) are reasonable and underutilized options.
  2. Radiation therapy (external-beam irradiation or brachytherapy with implantation of radioactive pellets [iodine-125 or palladium-103 seeds] into the prostate gland) represents an alternative in patients with localized prostate cancer, especially poor surgical candidates or patients with a high-grade malignancy. The efficacy of brachytherapy is comparable to external radiation. In patients receiving external-beam radiation, a total dose of 79.2 Gy (high dose) compared with a total dose of 70.2 Gy (conventional dose) has been reported to lower the risk of recurrence without increased risk of morbidity and mortality. Newer radiation treatments such as intensity-modulated radiation therapy (IMRT) and proton therapy are becoming increasingly popular and replacing the older technique of conformal radiation therapy over the past 10 years. Trials have shown that among patients with nonmetastatic prostate cancer, the use of IMRT compared with conformal therapy is associated with less gastrointestinal morbidity and fewer hip fractures but more erectile dysfunction; IMRT compared with proton therapy is associated with less GI morbidity. Patients with localized prostate cancer and high risk for extraprostatic disease and disease recurrence (e.g., Gleason score ≤7 with multiple positive biopsy cores and clinical stage T1b-T2b) may benefit (increased overall survival) with the addition of 6 mo of androgen suppression therapy to radiation therapy.
  3. Watchful waiting is reasonable in patients who are too old or too ill to survive longer than 10 yr. If the cancer progresses to the point where it becomes symptomatic, palliation can be attempted with several methods. Conservative management is also reasonable for patients with Gleason score of 2 to 4 because these patients do not have a shortened life expectancy and treatment is associated with long-term side effects. Watchful waiting also appears to be safe in older men with less-aggressive disease. Individual preferences play a central role in the decision whether to treat or to pursue active surveillance.
- Patients with advanced disease and projected life expectancy <10 yr are candidates for radiation therapy and hormonal therapy (diethylstilbestrol, luteinizing hormone–releasing hormone analogs, antiandrogens, bilateral orchiectomy).
- Recommended treatment of patients with regional metastatic prostate cancer with projected life expectancy ≥10 yr includes radiation therapy and hormonal therapy.
- Prostate cancer is an androgen-receptor-dependent disease, and the blocking of androgen-receptor signaling is an effective treatment modality. Androgen deprivation therapy (ADT) is the mainstay of treatment for metastatic prostate cancer. Adverse effects of ADT include decreased libido, impotence, hot flashes, osteopenia with increased fracture risk, metabolic alterations, and changes in mood and cognition. Adjuvant treatment with luteinizing hormone-releasing hormone (LHRH) agonists (goserelin, leuprolide, or triptorelin) plus antiandrogens (flutamide, bicalutamide, or nilutamide), when started simultaneously with external-beam radiation, improves local control and survival in patients with locally advanced prostate cancer. Pamidronate inhibits osteoclast-mediated bone resorption and prevents bone loss in the hip and lumbar spine in men receiving treatment for prostate cancer. Gonadotropin-releasing hormone (GnRH) receptor antagonists can be used for rapid medical castration of men with advanced prostate cancer. Degarelix is an injectable GnRH agonist useful to suppress testosterone in patients with prostate cancer who are not good candidates for LHRH agonists and refuse surgical castration. Assessment of bone density and treatment with once-weekly oral alendronate can prevent and improve the bone loss that occurs in men receiving ADT for prostate cancer.

- Docetaxel plus prednisone or docetaxel plus estramustine can be used in metastatic hormone–refractory prostate cancer. Newer treatments for hormone-refractory prostate cancer (castration-resistant cancer) include immunotherapy with sipuleucel and cabazitaxel, a microtubule inhibitor that interferes with cell mitosis and replication. Both agents can prolong survival but adverse effects can be severe and both agents are very expensive. Abiraterone is an oral agent that blocks biosynthesis of androgens by inhibiting CYP17, an enzyme required for androgen biosynthesis. It has been FDA approved for oral treatment, in combination with prednisone, of metastatic castration-resistant prostate cancer in patients previously treated with docetaxel.
- Enzalutamide is a newer nonsteroidal antiandrogen. Trials have shown it to be highly effective in extending survival in patients with metastatic castration-resistant prostate cancer. It can be used sequentially with other agents such as docetaxel, abiraterone, cabazitaxel, and immunotherapy. Radium-223, an alpha emitter, selectively targets bone metastases and has been found effective in improving survival in men with castration-resistant prostate cancer and bone metastases.

CHRONIC Rx

- Patients should be monitored at 3- to 6-mo intervals with clinical examination and PSA for the first year, then every 6 mo for the second year, then yearly if stable. For patients who have undergone radical prostatectomy, a rising PSA level suggests evidence of residual or recurrent prostate cancer. Salvage radiotherapy may potentially cure patients with disease recurrence after radical prostatectomy.
- Chest radiography and bone scan should be performed yearly or sooner if patient develops symptoms.

DISPOSITION

- Prognosis varies with the stage of the disease and the Gleason classification (see "Definition"). For patients between ages 65 and 69 yr at diagnosis and a Gleason score of 2 to 4, the probability of dying from prostate cancer 15 yr after diagnosis is 0.06 and that of dying from other causes is 0.56. If the Gleason score is 7 to 10, the probability of dying from prostate cancer increases to 0.72 and from other causes varies from 0.25 to 0.36.
- The ploidy of the tumor also has prognostic value; prognosis is better with diploid tumor cells and worse with aneuploid tumor cells.
- For grade 1 tumors, the extended 10-yr, disease-specific survival is similar for patients with prostatectomy (94%), radiotherapy (90%), and conservative management (93%); survival rate is better with surgery than with radiotherapy or conservative management in patients with grade 2 or 3 localized prostate cancer.
- Expression of the gene *EZH2* has been identified as an important factor in the determination of the aggressiveness of prostate cancer. A recent study revealed that expression of the *EZH2* gene may be a better predictor of clinical failure than Gleason score, tumor stage, or surgical margin status. Testing for *EZH2* protein in prostate cancer tissue may be useful to determine prognosis and direct treatment.
- Preoperative PSA level and PSA velocity have prognostic significance. Men whose PSA level increases by >2.0 mcg/ml during the year before the diagnosis of cancer may have a relatively high risk of death from prostate cancer despite undergoing radical prostatectomy.
- Extraprostatic disease is detected at radical prostatectomy in 38% to 52% of patients and is associated with a risk of disease recurrence, progression, and death. In these patients, adjuvant radiotherapy results in significantly reduced risk of PSA relapse and disease recurrence; however, the improvements in metastases-free survival and overall survival are not statistically significant.
- The Prostate Cancer Prevention trial revealed that the use of 5-alpha-reductase inhibitors lowers the incidence of prostate cancer but also increases the incidence of high-grade tumors (Gleason score >7). It is possible that these agents delay diagnosis of prostate cancer by lowering PSA levels and decreasing prostate size. The trade-off inherent in using 5-alpha-reductase inhibitors for prostate cancer prevention is risk of one additional high-grade cancer in order to avert three or four lower-grade cancers. Based on these results, the FDA's Oncologic Drugs Advisory Committee concluded that finasteride and dutasteride do not have a favorable risk-benefit profile for chemoprevention of prostate cancer in healthy men.
- Patients undergoing prostatectomy are more likely to have urinary incontinence than those undergoing radiotherapy at 2 years and 5 years. However, at 15 years there are no significant relative differences in disease-specific functional outcomes among men undergoing prostatectomy or radiotherapy.

EVIDENCE

available at www.expertconsult.com

SUGGESTED READINGS

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RELATED CONTENT

Prostate Cancer (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Background:
The purpose of this analysis was to compare long-term urinary, bowel, and sexual function after radical prostatectomy or external-beam radiation therapy.

Methods:
The Prostate Cancer Outcomes Study (PCOS) enrolled 3533 men in whom prostate cancer had been diagnosed in 1994 or 1995. The current cohort comprised 1655 men in whom localized prostate cancer had been diagnosed between the ages of 55 and 74 years and who had undergone either surgery (1164 men) or radiotherapy (491 men). Functional status was assessed at baseline and at 2, 5, and 15 years after diagnosis. We used multivariable propensity scoring to compare functional outcomes according to treatment.

Results:
Patients undergoing prostatectomy were more likely to have urinary incontinence than were those undergoing radiotherapy at 2 years (odds ratio, 6.22; 95% confidence interval [CI], 1.92 to 20.29) and 5 years (odds ratio, 5.10; 95% CI, 2.29 to 11.36). However, no significant between-group difference in the odds of urinary incontinence was noted at 15 years. Similarly, although patients undergoing prostatectomy were more likely to have erectile dysfunction at 2 years (odds ratio, 3.46; 95% CI, 1.93 to 6.17) and 5 years (odds ratio, 1.96; 95% CI, 1.05 to 3.63), no significant between-group difference was noted at 15 years. Patients undergoing prostatectomy were less likely to have bowel urgency at 2 years (odds ratio, 0.39; 95% CI, 0.22 to 0.68) and 5 years (odds ratio, 0.47; 95% CI, 0.26 to 0.84), again with no significant between-group difference in the odds of bowel urgency at 15 years.

Conclusions:
At 15 years, no significant relative differences in disease-specific functional outcomes were observed among men undergoing prostatectomy or radiotherapy. Nonetheless, men treated for localized prostate cancer commonly had declines in all functional domains during 15 years of follow-up. (Funded by the National Cancer Institute.) Ⓐ

Abstract[2]

Watchful Waiting/Outcomes

Purpose:
Active surveillance is becoming an increasingly common management strategy for low grade prostate cancer and involves repeat prostate biopsies over time. It has been hypothesized that serial biopsies can lead to reduced erectile function in patients on active surveillance and we explored this hypothesis in a longitudinally followed cohort.

Materials and Methods:
We identified 342 men on active surveillance whose first biopsy occurred between 2000 and 2009.We investigated erectile function using patient reported outcomes, namely the 6 erectile function questions from the IIEF-6 (International Index of Erectile Function). We estimated the change in erectile function with time using locally weighted scatterplot smoothing.

Results:
The median (IQR) patient age in this cohort was 64 years (58e68). Median follow-up on active surveillance was 3.5 years (2.3e5.0) and the median number of biopsies was 5 (3e6). During the first 4 years on active surveillance erectile function decreased 1.0 point per year (95% CI 0.2, 1.7) on the IIEF-6 (scale 1 to 30). When stratified by comorbidities or number of biopsies we see an almost identical decrease in erectile function with time. The use of phosphodiesterase-5 inhibitors increased from 5% to 27% from baseline to year 5 on active surveillance.

Conclusions:
In this longitudinally followed active surveillance cohort we observed a small decrease in erectile function and an increase in the use of phosphodiesterase-5 inhibitors with time. While we cannot separate out the effect of multiple biopsies from that of the natural aging process on erectile function in this observational study, our data suggest that active surveillance related biopsies do not have a large impact on erectile function. Ⓐ

Abstract[3]

Natural History/Outcomes

Background:
The authors investigated the prevalence of pretreatment urinary, sexual, hormonal, and bowel dysfunction in a contemporary, population-based prostate cancer cohort. They also explored the associations between baseline function and age, comorbidity, and timing of baseline survey completion with respect to treatment.

Methods:
The Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR) study is a population-based, prospective cohort study that enrolled 3691 men with incident prostate cancer during 2011 and 2012. Pretreatment function was ascertained using the Expanded Prostate Cancer Index-26 (EPIC-26). Data were stratified by age, comorbidity, and timing of baseline survey completion with respect to treatment. Unadjusted and multivariable linear regression analyses were performed to evaluate the relations between exposures and pretreatment function.

Results:
After applying exclusion criteria, the study cohort comprised 3072 men. A strikingly high proportion of men reported inability to obtain erections satisfactory for intercourse (45%) and some degree of urinary incontinence (17%) at baseline. Sexual function was particularly age-sensitive, with patients aged ≤60 years reporting summary scores in excess of 30 points higher than patients aged ≥75 years ($P < 0.001$). Compared with the healthiest men, highly comorbid patients reported less favorable function in each domain, including urinary incontinence (summary score, 89.5 versus 74.1; $P < 0.001$) and sexual function (summary score, 70.8 versus 32.9; $P < 0.001$). Although statistically significant differences in summary scores were identified between patients who completed the baseline questionnaire before treatment (52%) versus after treatment (48%), the absolute differences were small (range, 1 to 3 points).

Conclusions:
Patients with newly diagnosed prostate cancer exhibit a wide distribution of pretreatment function. The current data may be used to redefine the population "at risk" for treatment-related harms. Ⓐ

Abstract[4]

Erectile dysfunction (ED) is a major adverse effect of radical prostatectomy (RP). We conducted a randomized controlled trial to examine the efficacy of aerobic training (AT) compared with usual care (UC) on ED prevalence in 50 men ($n = 25$ per group) after RP. AT consisted of five walking sessions per week at 55% to 100% of peak oxygen uptake (VO-2peak) for 30 to 60 min per session following a nonlinear prescription. The primary outcome was change in the prevalence of ED, as measured by the International Index of Erectile Function (IIEF), from baseline to 6 mo. Secondary outcomes were brachial artery flow-mediated dilation (FMD), VO2peak, cardiovascular (CV) risk profile (eg, lipid profile, body composition), and patient-reported outcomes (PROs). The prevalence of ED (IIEF score ≤21) decreased by 20% in the AT group and by 24% in the UC group (difference: p=0.406). There were no significant between-group differences in any erectile function subscale ($p > 0.05$). Significant between-group differences were observed for changes in FMD and VO-2peak, favoring AT. There were no group differences in other markers of CV risk profile or PROs. In summary, nonlinear AT does not improve ED in men with localized prostate cancer in the acute period following RP.

Trial Registration:
Clinicaltrials.gov identifier NCT00620932. Ⓐ

Abstract[5]

Radiation therapy

Importance:
Tadalafil is used to treat erectile dysfunction after prostate cancer treatment, but its role as a preventive agent is undefined.

Objectives:
To determine primarily whether tadalafil preserved erectile function in men treated with radiotherapy for prostate cancer, and secondarily to determine whether participant- or partner-reported overall sexual function and sexual and marital satisfaction were affected.

Design, Setting, and Participants:
Stratified, placebo-controlled, double-blind, parallel-group study with 1:1 randomization at 76 community-based and tertiary medical sites in the United States and Canada. A patient group of 242 participants with intact erectile function scheduled to receive radiotherapy for prostate cancer were recruited between November 2009 and February 2012 with follow-up through March 2013.
Interventions:
A group of 121 participants were assigned 5 mg of tadalafil daily and 121 were assigned placebo for 24 weeks starting with external radiotherapy (63%) or brachytherapy (37%). Participant-reported International Index of Erectile Function response before radiotherapy and at weeks 2 and 4, between weeks 20 and 24, between weeks 28 and 30, and 1 year thereafter. Participants and partners could respond also to the Sexual Adjustment Questionnaire and to the Locke Marital Adjustment Test before radiotherapy, between weeks 20 and 24 and weeks 28 and 30, and at 1 year.
Main Outcomes and Measures:
Primary outcome was off-drug spontaneous erectile function 28 to 30 weeks after radiotherapy started. Secondary end points were spontaneous erection at 1 year; overall sexual function and satisfaction; marital adjustment; and partner-reported satisfaction and marital adjustment at 28 to 30 weeks and 1 year, predictors of tadalafil response; and adverse events.
Results:
Among 221 evaluable participants, 80 (79%; 95% CI, 70% to 88%) assigned to receive tadalafil retained erectile function between weeks 28 and 30 compared with 61 (74%; 95% CI, 63% to 85%) assigned to receive placebo ($P = 0.49$); an absolute difference of 5% (95% CI, –9% to 19%). A significant difference was also not observed at 1 year (72%; 95% CI, 60% to 84% versus 71%; 95% CI, 59% to 84%; $P = 0.93$). Tadalafil was not associated with significantly improved overall sexual function or satisfaction; a significant difference was not observed in any domain subscale. Partners of men assigned tadalafil noted no significant effect on sexual satisfaction, and marital adjustment was not significantly improved in participants or partners.
Conclusions and Relevance:
Among men undergoing radiotherapy for prostate cancer, daily use of tadalafil compared with placebo did not result in improved erectile function. These findings do not support daily use of tadalafil to prevent erectile dysfunction in these patients.
Trial Registration:
clinicaltrials.gov Identifier: NCT00931528. Ⓐ

Abstract[6]

Diagnostics
Background:
Conventional biopsy fails to detect the presence of some prostate cancers (PCas). Men with a prior negative biopsy but persistently elevated prostate-specific antigen (PSA) pose a diagnostic dilemma, as some harbor elusive cancer.
Objective:
To determine whether use of magnetic resonance ultrasound (MR-US) fusion biopsy results in improved detection of PCa compared with repeat conventional biopsy.
Design, Setting, and Participants:
In a consecutive-case series, 105 subjects with prior negative biopsy and elevated PSA values underwent multiparametric magnetic resonance imaging (MRI) and fusion biopsy in an outpatient setting.
Intervention:
Suspicious areas on multiparametric MRI were delineated and graded by a radiologist; MR-US fusion biopsy was performed by a urologist using the Artemis device; targeted and systematic biopsies were obtained regardless of MRI result.
Outcome Measurements and Statistical Analysis:
Detection rates of all PCa and clinically significant PCa (Gleason ≥3 + 4 or Gleason 6 with maximal cancer core length ≥4 mm) were determined. The yield of targeted biopsy was compared with systematic biopsy. The ability of an MRI grading system to predict clinically significant cancer was investigated. Stepwise multivariate logistic regression analysis was performed to determine predictors of significant cancer on biopsy.
Results and Limitations:
Fusion biopsy revealed PCa in 36 of 105 men (34%; 95% confidence interval [CI], 25 to 45). Seventy-two percent of men with PCa had clinically significant disease; 21 of 23 men (91%) with PCa on targeted biopsy had significant cancer compared with 15 of 28 (54%) with systematic biopsy. Degree of suspicion on MRI was the most powerful predictor of significant cancer on multivariate analysis. Twelve of 14 (86%) subjects with a highly suspicious MRI target were diagnosed with clinically significant cancer.
Conclusions:
MR-US fusion biopsy provides improved detection of PCa in men with prior negative biopsies and elevated PSA values. Most cancers found were clinically significant. Ⓐ

Abstract[7]

Screening
Background:
The chance that a prostate cancer detected by screening is overdiagnosed (ie, it would not have been detected in the absence of screening) can vary widely depending on patient age and tumor characteristics. The purpose of this study is to use age, Gleason score, and prostate-specific antigen (PSA) level to help inform patients with screen-detected prostate cancers about the chances their cancers were overdiagnosed.
Methods:
A computer microsimulation model of prostate cancer natural history was used to generate virtual life histories in the presence and absence of PSA screening, including an indicator of whether screen-detected cancers are overdiagnosed. A logistic regression model was fit to non-metastatic patients diagnosed by screening with PSA <10 ng/mL, and a nomogram was created to predict the individualized risk of overdiagnosis given age, Gleason score, and PSA at diagnosis.
Results:
The calibrated microsimulation model closely reproduces observed incidence trends in the Surveillance, Epidemiology, and End Results registries by age, stage, and Gleason score. The fitted logistic regression predicts risks of overdiagnosis among PSA-detected patients with an area under the curve of 0.75. Chances of overdiagnosis range from 2.9% to 88.1%.
Conclusions:
The chances of overdiagnosis vary considerably by age, Gleason score, and PSA at diagnosis. The overdiagnosis nomogram presents tailored estimates of these risks based on patient and tumor information known at diagnosis and can be used to inform decisions about treating PSA-detected prostate cancers. Ⓐ

Evidence-Based References

Resnick, et al.: Long-term functional outcomes after treatment for localized prostate cancer, *N Engl J Med* 368:368–445, 2013. Ⓐ

Braun K, Ahallal Y, Sjoberg DD, et al.: Effect of repeated prostate biopsies on erectile function in men on active surveillance for prostate cancer, *J Urol* 191:744–749, 2014. Ⓐ

Resnick MJ, Barocas DA, Morgans AK, et al.: Contemporary prevalence of pretreatment urinary, sexual, hormonal, and bowel dysfunction: defining the population at risk for harms of prostate cancer treatment, *Cancer* 120:1263–1271, 2014. Ⓑ

Jones LW, Hornsby WE, Freedland SJ, et al.: Effects of nonlinear aerobic training on erectile dysfunction and cardiovascular function following radical prostatectomy for clinically localized prostate cancer, *Eur Urol* 65:852–855, 2014. Ⓐ

Pisansky TM, Pugh SL, Greenberg R, et al.: Tadalafil for prevention of erectile dysfunction after radiotherapy for prostate cancer: The Radiation Therapy Oncology Group [0831] Randomized Clinical Trial, *JAMA* 311:1300–1307, 2014. Ⓐ

Sonn GA, Chang E, Natarajan S, et al.: Value of targeted prostate biopsy using magnetic resonance ultrasound fusion in men with prior negative biopsy and elevated prostate-specific antigen, *Eur Urol* 65:809–815, 2014. Ⓑ

Gulati R, Inoue LYT, Gore J, et al.: Individualized estimates of overdiagnosis in screen-detected prostate cancer, *J Natl Cancer Inst* 106:djt367, 2014. Ⓑ

Esposito K, Giugliano, Di Palo C, et al.: Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial, *JAMA* 291:2978–2984, 2004. Ⓐ

SUGGESTED READINGS

Andriole GL et al.: Effect of dutasteride on the risk of prostate cancer, *N Engl J Med* 362:1192–1202, 2010.

Bannoro R et al.: Comparative evaluation of radiation treatments for clinically localized prostate cancer: an updated systematic review, *Ann Intern Med* 15S:171–178, 2011.

Barry MJ et al.: Adverse effects of robotic-assisted laparoscopic versus open retropubic radical prostatectomy among a nationwide random sample of Medicare-age men, *J Clin Oncol* 30:513, 2012.

Bill-Axelson A et al.: Radical prostatectomy versus watchful waiting in early prostate cancer, *N Engl J Med* 370:932–942, 2014.

Carlsson S et al.: Influence of blood prostate specific antigen levels at age 60 on benefits and harms of prostate screenings: Population based cohort study, *BMJ* 348:2296, 2014.

Crawford ED et al.: Diagnostic performance of *PCA3* to detect prostate cancer in men with increased prostate specific antigen: a prospective study of 1,962 cases, *J Urol* 188:1726–1731, 2012.

Dahabreh IJ et al.: Active surveillance in men with localized prostate cancer, *Ann Intern Med* 156:582–590, 2012.

D'Amico AV et al.: Androgen suppression and radiation vs radiation alone for prostate cancer, *JAMA* 299(3):289, 2008.

Djulbegovic M et al.: Screening for prostate cancer: systematic review and meta-analysis of randomized controlled trials, *BMJ* 341:c4543, 2010.

Ewing CM et al.: Germline mutations in HOXB13 and prostate-cancer risk, *N Engl J Med* 366:141–149, 2012.

Ganz PA et al.: NIH state of the science conference: role of active surveillance in the management of men with localized prostate cancer, *Ann Intern Med* 156:591–595, 2012.

Gittleman M et al.: A 1-year, open label, randomized phase II dose finding study of degarelix for the treatment of prostate cancer in North America, *J Urol* 18:1986, 2008.

Greenspan S et al.: Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer, *Ann Intern Med* 146:416, 2007.

Hayes JH et al.: Active surveillance compared with initial treatment for men with low-risk prostate cancer, *JAMA* 304(21):2373–2380, 2010.

Hoffman RM et al.: Health outcomes in older men with localized prostate cancer: results from the prostate cancer outcomes study, *Am J Med* 119:418, 2006.

Hoffman RM: Screening for prostate cancer, *N Engl J Med* 365:2011, 2013.

Hu JC et al.: Comparative effectiveness of minimally invasive vs. open radical prostatectomy, *JAMA* 302(14):1557–1564, 2009.

Jones CU et al.: Radiotherapy and short-term androgen deprivation for localized prostate cancer, *N Engl J Med* 365:107–118, 2011.

Kantoff PW et al.: Sipuleucel-T immunotherapy for castration-resistant prostate cancer, *N Engl J Med* 363:411–422, 2010.

Klein EA et al.: Vitamin E and the risk of prostate cancer, *JAMA* 306(14):1549–1556, 2011.

Lin K et al.: Benefits and harms of prostate-specific antigen screening for prostate cancer: an evidence update from the U.S. Preventive Services Task Force, *Ann Intern Med* 149:192–199, 2008.

Moyer VA: on behalf of the US Preventive Services Task Force: Screening for prostate cancer: US Preventive Services Task Force recommendation statement, *Ann Intern Med* 157:120–134, 2012.

Resnick MJ et al.: Long-term functional outcomes after treatment of localized prostate cancer, *N Engl J Med* 368:436–445, 2013.

Sanda MG et al.: Quality of life and satisfaction with outcome among prostate cancer survivors, *N Engl J Med* 358:1250–1261, 2008.

Scher HI et al.: Increased survival with enzalutamide in prostate cancer after chemotherapy, *N Engl J Med* 367:1187–1197, 2012.

Shappley III WV et al.: Prospective study of determinants and outcomes of deferred treatment or watchful waiting among men with prostate cancer in a nationwide cohort, *J Clin Oncol* 20(27):4980, Oct 2009.

Sharifi N et al.: Androgen deprivation therapy for prostate cancer, *JAMA* 294:238–244, 2005.

Sheets NC et al.: Intensity-modulated radiation therapy, proton therapy, or conformal radiation therapy and morbidity and disease control in localized prostate cancer, *JAMA* 307(15):1611–1620, 2012.

Smith MR et al.: Denosumab in men receiving androgen-deprivation therapy for prostate cancer, *N Engl J Med* 361:745–755, 2009.

Theoret MR et al.: The risks and benefits of 5 alpha-reductase inhibitors for prostate cancer prevention, *N Engl J Med* 365:97–99, 2011.

Thompson IM et al.: Adjuvant radiotherapy for pathologically advanced prostate cancer, *JAMA* 296:2329, 2006.

Vockers AJ et al.: An empirical evaluation of guidelines on PSA velocity in prostate cancer detection, *J Natl Cancer Inst* 103:462, 2011.

Vogelzang NJ, Enzalutamide: a major advance in the treatment of metastatic prostate cancer, *N Engl J Med* 367:13, 2012.

Walczak J, Carducci M: Prostate cancer: a practical approach to current management of recurrent disease, *Mayo Clin Proc* 82(2):243, 2007.

Walsh PC et al.: Localized prostate cancer, *N Engl J Med* 357:26, 2007.

Wilt TJ et al.: Systematic review: comparative effectiveness and harms of treatments for clinically localized prostate cancer, *Ann Intern Med* 148:435–448, 2008.

Wilt TJ et al.: Radical prostatectomy versus observation for localized prostate cancer, *N Engl J Med* 367:203, 2012.

Wilt TJ, Dahm P: PSA screening for prostate cancer: Achieve more for patients and payers by doing less, *BMJ* 348:2559, 2014.

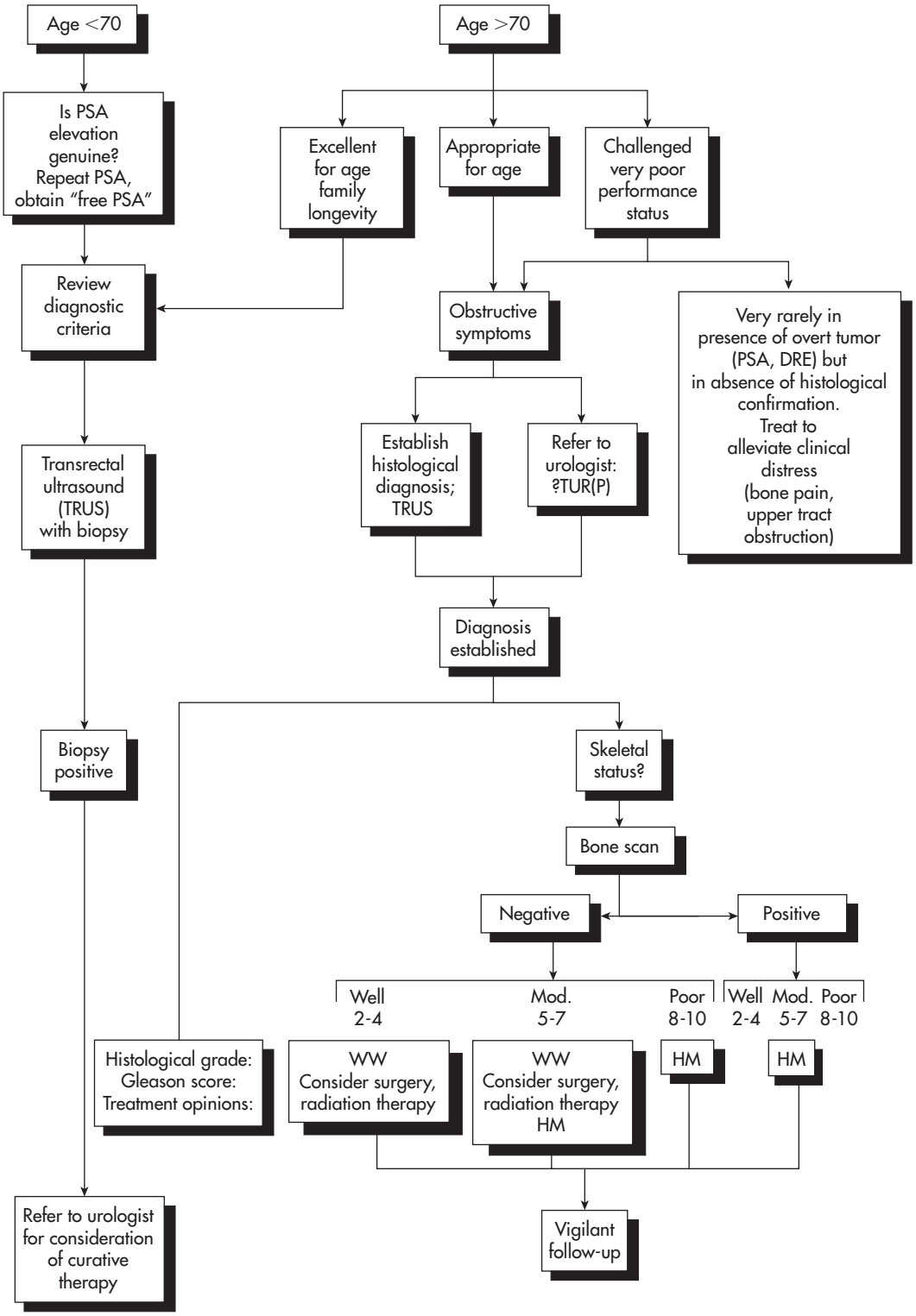

FIGURE EP1-84 Assessment and treatment of a patient with prostate cancer suspected on the grounds of a digital rectal examination (*DRE*) and prostate-specific antigen (*PSA*). *HM*, Hormonal manipulation; *TUR(P)*, transurethral resection (prostate); *WW*, watchful waiting. (Modified from Tallis RC, Fillit HM [eds]: *Brocklehurst's textbook of geriatric medicine and gerontology*, ed 6, London, 2003, Churchill Livingstone.)

BASIC INFORMATION

DEFINITION

Prostatitis refers to inflammation of the prostate gland. There are four major categories:

1. Acute bacterial prostatitis (type I).
2. Chronic bacterial prostatitis (type II).
3. Chronic prostatitis/pelvic pain syndrome (CP/CPPS) (type III): subdivided into type IIIA (inflammatory) and IIIB (noninflammatory).
4. Asymptomatic inflammatory prostatitis (type IV).

ICD-9CM CODES
601.0 Prostatitis (acute)
601.1 Prostatitis (chronic)
ICD-10CM CODES
N41.0 Acute prostatitis
N41.1 Chronic prostatitis

EPIDEMIOLOGY & DEMOGRAPHICS

- 50% of men will have symptoms of prostatitis in their lifetime.
- Prostatitis accounts for >8% of visits to urologists and 1% of visits to primary care physicians.
- The prevalence of chronic bacterial prostatitis is 5% to 10%.
- CP/CPPS is the most common of the clinically defined prostatitis syndromes, with prevalence ranging from 9% to 12% of men.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

1. Acute bacterial prostatitis:
   - Sudden or rapidly progressive onset of:
     - Dysuria.
     - Frequency.
     - Urgency.
     - Nocturia.
     - Perineal pain that may radiate to the back, rectum, or penis.
   - Hematuria or a purulent urethral discharge may occur.
   - Occasionally urinary retention complicates the course.
   - Fever, chills, and signs of sepsis can also be part of the clinical picture.
   - On rectal examination the prostate is typically tender.
2. Chronic bacterial prostatitis:
   - Characterized by positive culture of expressed prostatic secretions. May cause symptoms such as suprapubic, low back, or perineal pain; mild urgency, frequency, and dysuria with urination; and possibly recurrent urinary tract infections.
   - May be asymptomatic when the infection is confined to the prostate.
   - May present as an increase in severity of baseline symptoms of benign prostatic hypertrophy (BPH).
   - When cystitis is also present, urinary frequency, urgency, and burning may be reported.
   - Hematuria may be a presenting complaint.
   - In elderly men, new onset of urinary incontinence may be noted.
3. CP/CPPS:
   - Presents similarly with pain in the pelvic region lasting >3 mo. Symptoms also can include pain in the suprapubic region, low back, penis, testes, or scrotum.
   - The symptoms can be of variable severity and may include lower urinary tract symptoms, sexual dysfunction, and reduced quality of life.

ETIOLOGY

1. Acute bacterial prostatitis:
   - Acute, usually gram-negative infection of the prostate gland. *E. coli* is the most commonly isolated organism.
     - Generally associated with cystitis.
     - Results from the ascent of bacteria into the urethra.
   - Occasionally the route of infection is hematogenous or a lymphatogenous spread of rectal bacteria.
   - Consider *Neisseria gonorrhoeae* or *Chlamydia trachomatis* in young patients (age <35 yr) with risk of sexually transmitted disease (STD).
2. Chronic bacterial prostatitis:
   - Often asymptomatic. *E. coli* is the most commonly isolated organism.
   - Exacerbation of symptoms of BPH caused by the same mechanism as in acute bacterial prostatitis.
3. CP/CPPS:
   - Type IIIA: refers to symptoms of prostatic inflammation associated with the presence of white blood cells in prostatic secretions with no identifiable bacterial organism.
   - *Chlamydia* infection may be etiologically implicated in some cases.
   - Type IIIB: refers to symptoms of prostatic inflammation with no or few white blood cells in the prostatic secretion.
   - Its cause is unknown. Spasm in the bladder neck or urethra may be responsible for the symptoms.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- BPH with lower urinary tract symptoms
- Prostate cancer

WORKUP

- Rectal examination:
  1. Tender prostate most suggestive of acute bacterial prostatitis.
  2. Enlarged prostate common in chronic bacterial prostatitis.
  3. Normal prostate is consistent with chronic bacterial prostatitis and CP/CPPS.
- Expression of prostatic secretions by prostate massage is contraindicated in acute bacterial prostatitis but is appropriate in the other three situations.

LABORATORY TESTS

- Urinalysis.
- Urine culture and sensitivity.
- Bacterial localization studies can be performed but are cumbersome and impractical in most clinical settings.
- Cell count and culture of expressed prostatic secretions.
- Prostate-specific antigen (PSA) is not used to diagnose prostatitis and is not recommended unless a nodule is present on digital examination. A rapid rise over baseline should raise the possibility of prostatitis even in the absence of symptoms. In such cases, a follow-up PSA after treatment of prostatitis is appropriate.
- Complete blood count and blood cultures if fever, chills, or signs of sepsis exist.

TREATMENT

1. Acute bacterial prostatitis:
   - Uncomplicated (with risk of STD, age <35 yr): ceftriaxone 250 mg IM × 1 dose *or* cefixime 400 mg PO × 1 *then* doxycycline 100 mg bid × 10 days.
   - Uncomplicated with low risk of STD: levofloxacin 500 mg qd or ciprofloxacin 500 mg bid × 10-14 days.
2. Chronic bacterial prostatitis:
   - First-line choice is a quinolone (ciprofloxacin or levofloxacin) for 4 wk.
   - Trimethoprim-sulfamethoxazole (TMP-SMX) is second-line choice for 1-3 mo if the organism is sensitive. Tissue penetration for TMP-SMX is not as good as quinolones, and there is evidence of increasing uropathogenic resistance.
3. CP/CPPS:
   - No specific treatment. A brief course of NSAIDs may be tried until urine localization cultures are completed. Alfuzosin may reduce symptoms in men who have not received prior therapy with an alpha-blocker.
   - Recent trials have shown modest improvement with quinolones (possibly secondary to their anti-inflammatory and analgesic effects), but antibiotics are not generally effective and should be avoided in patients who are afebrile and have normal urinalysis results.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Prostatitis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Anothaisintawee T et al.: Management of chronic prostatitis/chronic pelvic pain syndrome, *JAMA* 305(1):78–86, 2011.

Nickel JC et al.: Alfuzosin and symptoms of chronic prostatitis-chronic pelvic pain syndrome, *N Engl J Med* 359(25):2663–2673, 2008.

Shoskes DA et al.: Phenotypically directed multimodal therapy for chronic prostatitis/chronic pain syndrome, *Urology* 75(6):1249–1253, 2010.

BASIC INFORMATION

DEFINITION

Pruritus ani refers to an intense chronic itching of the anus and perianal skin.

ICD-9CM CODES
698.0 Pruritus ani
ICD-10CM CODES
L29.0 Pruritus ani

EPIDEMIOLOGY & DEMOGRAPHICS

- Any age can be affected.
- Occurs in 1% to 5% of the population.
- Male/female predominance of 4:1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Anal itching.
- Anal fissures.
- Hemorrhoids.
- Excoriations.
- Pinworms.
- Fecal incontinence.

ETIOLOGY

Anorectal diseases and fecal contamination:
- Diarrhea.
- Anal incontinence.
- Hemorrhoids.
- Fissures.
- Fistulae.
- Rectal prolapse.
- Malignancy: Bowen's disease, epidermoid cancer, perianal Paget's disease.

Infections:
- Fungal: candidiasis, dermatophytes.
- Parasitic: pinworms, scabies.
- Bacterial: *Staphylococcus aureus,* erythrasma.
- Lymphogranuloma venereum.
- Granuloma inguinale.
- Chancroid.
- Molluscum contagiosum.
- Trichomoniasis.
- Venereal: herpes, gonococcal syphilis, human papillomavirus.

Local irritants:
- Moisture, obesity, excessive perspiration.
- Soaps, hygiene products.
- Toilet paper: perfumed, dyed.
- Underwear: irritating fabrics, detergents.
- Anal creams, suppositories.
- Dietary: coffee, beer, acidic foods.
- Drugs: mineral oil, ascorbic acid, hydrocortisone sodium succinate, quinine, colchicine.

Dermatologic diseases:
- Psoriasis.
- Atopic dermatitis.
- Seborrheic dermatitis.

Section II also describes the various causes of pruritus ani.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Allergies.
- Anxiety.
- Dermatologic conditions.
- Infections.
- Parasites.
- Diabetes mellitus.
- Chronic liver disease.
- Neoplasia.
- Proctalgia fugax.

WORKUP

- Detailed history regarding bowel habits, hygiene, use of perfumed products, and medical history.
- Inspection of perianal area.
- Possible biopsy to exclude neoplasia.
- Microscopic inspection of scrapings.
- Colposcopy of perineum.

LABORATORY TESTS

- Chemistry profile.
- Urinalysis.
- Cultures.
- Stool for ova and parasites.
- Tape test.
- Glucose tolerance test, if necessary.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of tight, nonbreathable clothing and underclothing.
- Discontinuation or curtailment of coffee, beer, citrus fruits, tomatoes, chocolate, and tea. Dietary modification is frequently recommended, although its effectiveness has not been established.
- Cleansing of anal area after bowel movements with a premoistened pad or tissue and avoidance of perfumes and dyes present in toilet paper and soaps.
- Avoidance of excessive perspiration.
- Aggressive management of fecal leakage or incontinence to avoid soiling of perianal skin.

ACUTE GENERAL Rx

- Minimization of frequent loose stools with antidiarrheals and fiber agents if appropriate.
- Use of a 1% hydrocortisone cream sparingly bid during the acute phase of pruritus ani but not for >2 wk to avoid atrophy.
- Protective ointments such as zinc oxide may be helpful.
- Treatment of predisposing factors, such as parasites, diabetes, liver disease, hemorrhoids, and other infections.

CHRONIC Rx

- Possible complications: excoriation and secondary bacterial infection; must be treated aggressively.
- Longstanding, intractable pruritus ani: good response to intracutaneous injections of methylene blue and other agents, steroid injection.

DISPOSITION

- Usually good results with total resolution of symptoms.
- In some, persistent and recurrent symptoms.

REFERRAL

To colorectal specialist if conservative measures fail or if patient experiences rectal bleeding or change in bowel movements.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Anal Itching (Patient Information)
Hemorrhoids (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READING

Heard S: Pruritus ani, *Aust Fam Physician* 33(7):511, 2004.

BASIC INFORMATION

DEFINITION

Pruritus vulvae refers to intense itching of the female external genitalia.

SYNONYMS

Vulvodynia

ICD-9CM CODES
698.1 Pruritus of genital organs
ICD-10CM CODES
L29.2 Pruritus vulvae
L29.3 Anogenital pruritus, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- A female disorder that can affect women at any age.
- Young girls: infection is usually causative.
- Postmenopausal women: frequently affected because of hypoestrogenic state.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Constant, intense itching or burning of the vulva.

ETIOLOGY

- Approximately 50% are caused by monilial infection or trichomoniasis.
- Other infectious causes are herpes simplex, condylomata acuminata, and molluscum contagiosum.
- Other causes:
  1. Infestations with scabies, pediculosis pubis, and pinworms.
  2. Dermatoses such as hypertrophic dystrophy, lichen sclerosus, lichen planus, and psoriasis.
  3. Neoplasms such as Bowen's disease, Paget's disease, and squamous cell carcinoma.
  4. Allergic or chemical dermatitis caused by dyes in clothing or toilet paper, detergents, contraceptive gels, vaginal medications, douches, or soaps.
  5. Vulvar or vaginal atrophy.
- Severe pruritus is probably caused by degeneration and inflammation of terminal nerve fibers.
- Most intense itching occurs with hyperplastic lesions.
- Children typically (75%) have nonspecific pruritus, lichen sclerosus, bacterial infections, yeast infection, or pinworm infestation.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Vulvitis.
- Vaginitis.
- Lichen sclerosus.
- Squamous cell hyperplasia.
- Pinworms.
- Vulvar cancer.
- Syringoma of the vulva.

WORKUP

- Inspection of vulva, vagina, and perianal area for infection, fissures, ulcerations, induration, or thick plaques.
- Must rule out trichomoniasis, candidiasis, bacterial vaginosis, allergy, vitamin deficiencies, diabetes. Fig. P1-85 describes a diagnostic approach to the diagnosis of vulvar pruritus.

LABORATORY TESTS

- Wet prep of saline and potassium hydroxide of vaginal discharge.
- Tape test to look for pinworms.
- Vaginal cultures.
- Biopsy when needed (punch biopsy commonly used).

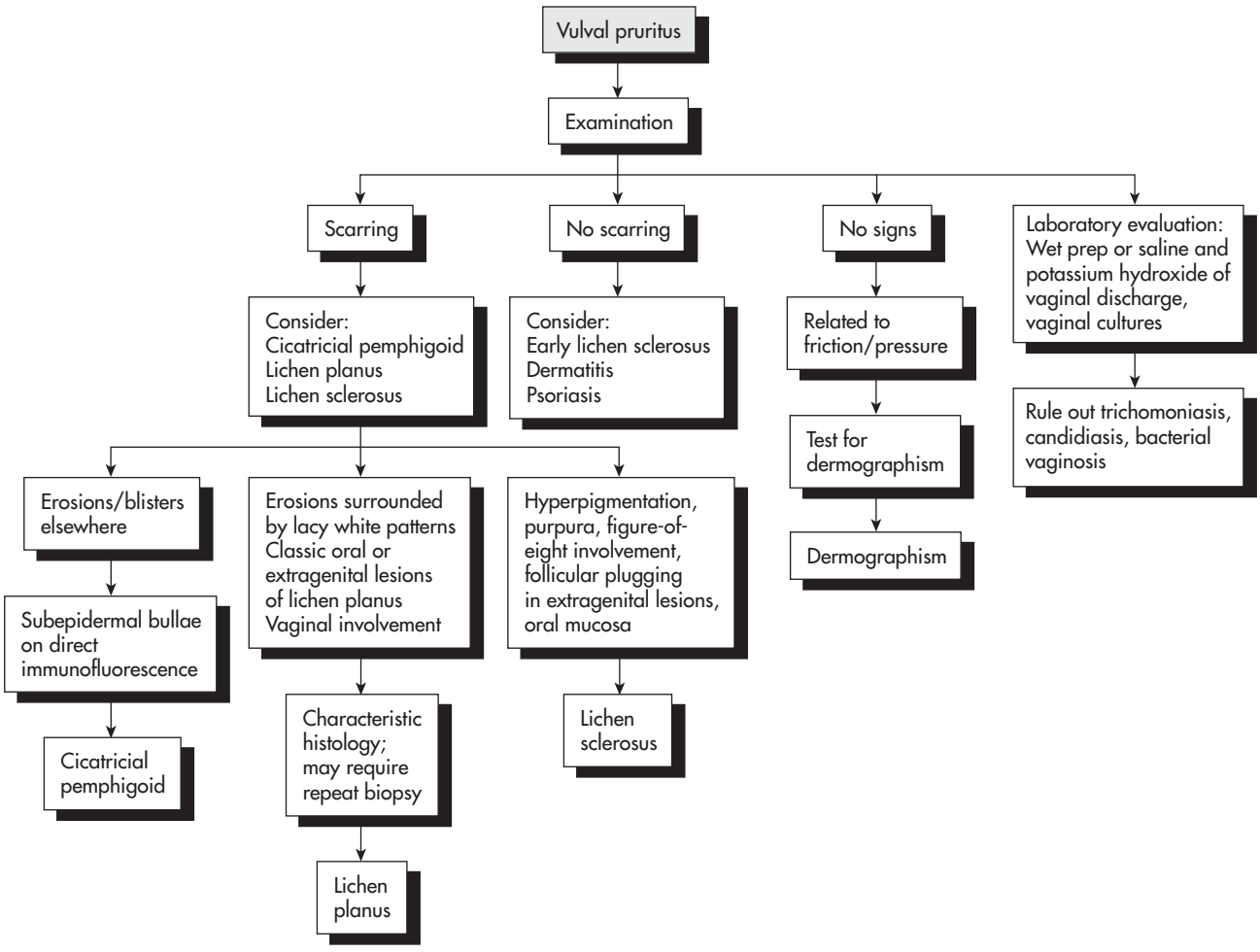

FIGURE P1-85 Diagnosis of vulvar pruritus. (Modified from Bolognia JL et al [eds]: *Dermatology,* ed 2, St Louis, 2008, Mosby.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Keep vulva clean and dry.
- Wear white cotton panties.
- Avoid perfumes and body creams over vulvar area because they can cause irritation.
- Reduce stress.
- Apply wet dressings with aluminum acetate (Burow's) solution frequently.
- Avoid coffee and caffeine-containing beverages, chocolate, and tomatoes.
- Sitz baths may be helpful.

ACUTE GENERAL Rx

Need to treat underlying problem:

- Yeast infection: any of the vaginal creams or difluconazole 150-mg one-time dose.
- Trichomoniasis or *Gardnerella vaginalis:* metronidazole 500 mg or 375 mg PO bid for 7 days.
- Urinary tract infection: treatment of specific organism.
- Estrogen replacement therapy if atrophy is the cause of pruritus.
- Pinworms: mebendazole 100 mg 1 tablet at diagnosis and repeated in 1 to 2 wk; also treat other members in family aged >2 yr.
- Squamous cell hyperplasia: local application of corticosteroids.
  1. One of the high- or medium-potency corticosteroids (0.025% or 0.01% fluocinolone acetonide or 0.01% triamcinolone acetonide) can be used to relieve itching.
  2. Rub into vulva bid or tid for 4 to 6 wk.
  3. Once itching is controlled, fluorinated steroid can be discontinued and patient can be switched to hydrocortisone preparation.
- Lichen sclerosus: topical 2% testosterone in petrolatum massaged into the vulvar tissue. bid or tid; clobetasol propionate gel 0.05% tid for 5 days is effective.
- Treatment with immune response modifiers.

CHRONIC Rx

- If not relieved by topical measures: intradermal injection of triamcinolone (10 mg/ml diluted 2:1 saline); 0.1 ml of the suspension injected at 1-cm intervals and tissue gently massaged.
- If symptoms still uncontrollable: SC injection of absolute alcohol 0.1 ml at 1-cm intervals.

DISPOSITION

Usually controlled with conservative measures and topical steroids.

REFERRAL

To a gynecologist for further workup if conservative measures do not give relief.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Vaginitis, Estrogen-Deficient (Related Key Topic)
Vaginitis, Fungal (Related Key Topic)
Vaginitis, Prepubescent (Related Key Topic)
Vaginitis, Trichomonas (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READING

Boardman LA et al.: Recurrent vulvar itching, *Obstet Gynecol* 105(6):1451, 2005.
Welch B et al.: Vulval itch, *Aust Fam Physician* 33(7):505, 2004.

BASIC INFORMATION

DEFINITION

Psittacosis is a systemic infection caused by the bacterium *Chlamydophila psittaci* (formerly known as *Chlamydia psittaci*) and is predominantly transmitted by birds.

SYNONYMS

Ornithosis
Parrot pneumonia

ICD-9CM CODES
073.9 Psittacosis
ICD-10CM
A70 Chlamydia psittaci infections

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.)

- Between 2000 and 2009 there were between 8 and 25 cases a year but only 4 cases in 2010.
- True incidence possibly higher because infections may be subclinical.
- Highest incidence among pet owners and people working with birds.

PEAK INCIDENCE: Age 30 to 60 yr.
PREVALENCE (IN U.S.):

- Low among humans.
- More than 130 avian species serve as hosts of the bacterium and between 5% to 8% of birds carry the organism, including poultry, seagulls, and geese.
- Most human infections are from birds of the order Psittaformes, which includes cockatiels, parrots, cockatoos, and budgerigars.

PREDOMINANT SEX: Equal sex distribution.
PREDOMINANT AGE: More common in adults.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Incubation period of 5 to 15 days.
- Subclinical infection.
- Onset abrupt or insidious.
- Most common symptoms:
  1. Fever.
  2. Myalgias.
  3. Chills.
  4. Cough.
- Most common clinical syndrome: atypical pneumonia with fever, headache, dry cough, and a chest radiograph more dramatically abnormal than the physical examination.
- Ranges from mild disease to respiratory failure and death, although this is extremely unusual.
- Other clinical presentations:
  1. Mononucleosis-like syndrome.
  2. Typhoidal form.
- Most frequent physical findings:
  1. Fever.
  2. Pharyngeal erythema.
  3. Rales.
  4. Hepatomegaly.
- Less common findings:
  1. Somnolence.
  2. Confusion.
  3. Relative bradycardia.
  4. Pleural rub.
  5. Adenopathy.
  6. Splenomegaly.
  7. Horder's spots (pink blanching maculopapular rash).
- Besides the lungs, other specific end-organ involvement:
  1. Pericarditis.
  2. Myocarditis.
  3. Endocarditis.
  4. Hepatitis
  5. Joints.
  6. Kidneys (glomerulonephritis).
  7. Central nervous system.

ETIOLOGY

- *C. psittaci* is an obligate intracellular bacterium.
- Infection is usually spread by the respiratory route from infected birds, by direct contact or aerosolization of dried feces or bird feather dust, and rarely from a bite.
- There is a history of exposure to birds in 85% of patients, mostly with birds as pets.
- Strains from turkeys and psittacine birds are most virulent for human beings.
- Cows, goats, and sheep are occasionally implicated.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- *Legionella*.
- *Mycoplasma*.
- *Chlamydophila pneumoniae*.
- Viral respiratory infections.
- Typhoid fever.
- Viral hepatitis.
- Aseptic meningitis.
- Mononucleosis.

WORKUP

- Complete blood count, renal and liver function tests.
- *Chlamydophila* serology.
- Chest x-ray.
- Special immunostaining of respiratory secretions.

LABORATORY TESTS

- White blood count is normal or slightly elevated.
- ESR and C-reactive protein are generally elevated.
- Mild liver function abnormalities are common (50%).
- Blood cultures are almost always negative.
- Studies on respiratory secretions:
  1. Direct immunofluorescent antibody of respiratory secretions with monoclonal antibodies to chlamydial antigens.
  2. *Chlamydophila* lipopolysaccharide antigen by enzyme immunoassay.
  3. Polymerase chain reaction.
- Serologic studies:
  1. Complement-fixing antibodies (CF).
  2. Microimmunofluorescence antibody test (MIF).
  3. Possible false-negative results and cross-reaction with other chlamydial species with both techniques.

IMAGING STUDIES

- Chest x-ray is abnormal in 50% to 90% with a variety of patterns.
- Pleural effusions are common.

TREATMENT

NONPHARMACOLOGIC THERAPY

Oxygen supplementation as needed.

ACUTE GENERAL Rx

- Doxycycline (100 mg PO bid) for 10 to 14 days after fever declines *or*
- Tetracycline (500 mg PO qid).
- Macrolides such as erythromycin or azithromycin are considered second-line agents in adults but first-line agents in children.
- Quinolones such as ciprofloxacin and moxifloxacin are effective in vitro, but more studies are needed for clinical use.

CHRONIC Rx

In the rare cases of endocarditis, combination of heart valve replacement and prolonged antibiotic course may be the treatment of choice.

DISPOSITION

- Mortality rate is low (0.7%).
- Poor prognostic factors:
  1. Advanced age.
  2. Leukopenia.
  3. Severe hypoxemia.
  4. Renal failure.
  5. Confusion.
  6. Multilobe pulmonary involvement.
- Possible reinfection.

REFERRAL

- To infectious disease expert:
  1. Complicated atypical pneumonia or other end-organ involvement.
  2. Suspicion of an outbreak.
- To pulmonologist for diagnostic bronchoscopy.

PEARLS & CONSIDERATIONS

COMMENTS

- Hospitalized patients do not require specific isolation precautions.
- Any confirmed or suspected case of psittacosis should be reported to public health authorities.
- Recent evidence indicates that *C. psittaci* may be associated with induction of a rare form of lymphoma found in the ocular adnexa; case reports have described regression of ocular lymphoma with antibiotic treatment for *C. psittaci*.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Cunha BA: The atypical pneumonias: clinical diagnosis and importance, *Clin Microbiol Infect* 3:12, 2006.

Ferreri AJ et al.: Regression of ocular adnexal lymphoma after *Chlamydia psittaci*-eradicating antibiotic therapy, *J Clin Oncol* 23(22):5067, 2005.

Smith KA et al.: Compendium of measures to control *Chlamydophila psittaci* (formerly *Chlamydia psittaci*) infection among humans (psittacosis) and pet birds, 2005, *J Am Vet Med Assoc* 226(4):532, 2005.

Stewardson AJ, Grayson MK: Psittacosis, *Infect Dis Clin North Am* 24(1):7–25, 2010.

Vargas RL et al.: Is there an association between ocular adnexal lymphoma and infection with *Chlamydia psittaci?* The University of Rochester experience, *Leuk Res* 30(5):547, 2006.

BASIC INFORMATION

DEFINITION

Psoriasis is a chronic skin disorder characterized by excessive proliferation of keratinocytes, resulting in the formation of thickened scaly plaques, itching, and inflammatory changes of the epidermis and dermis. The various forms of psoriasis include guttate, pustular, and arthritis variants.

ICD-9CM CODES
696.0 Psoriasis, arthritis, arthropathic
696.1 Psoriasis, any type except arthropathic
ICD-10CM CODES
L40 Psoriasis
L40.4 Guttate psoriasis
L40.1 Generalized pustular psoriasis
L40.8 Other psoriasis
L40.9 Psoriasis unspecified
L40.54 Psoriatic juvenile arthropathy
L40.0 Psoriasis vulgaris

EPIDEMIOLOGY & DEMOGRAPHICS

- Psoriasis affects 1% to 3% of the world's population. Most patients have limited psoriasis involving <5% of their body surface.
- There is a strong association between psoriasis and human leukocyte antigens (HLAs) B13, B17, and B27 (pustular psoriasis).
- Peak age of onset is bimodal (adolescents and at age 60 yr).
- Men and women are affected equally.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Approximately 85% of patients with psoriasis have mild-to-moderate disease.
- The primary psoriatic lesion is an erythematous papule topped by a loosely adherent scale. Scraping the scale results in several bleeding points ***(Auspitz sign)***.
- Chronic plaque psoriasis generally manifests with symmetric, sharply demarcated, erythematous, silver-scaled patches affecting primarily the intergluteal folds, elbows, scalp, fingernails, toenails, and knees (Fig. P1-86). This form accounts for 80% of psoriasis cases.
- Psoriasis can also develop at the site of any physical trauma (sunburn, scratching). This is known as Koebner's phenomenon.
- Nail involvement is common (pitting of the nail plate), resulting in hyperkeratosis, onychodystrophy with onycholysis.
- Pruritus is variable; soreness and bleeding may occur.
- Joint involvement can result in sacroiliitis and spondylitis.
- Guttate psoriasis is generally preceded by streptococcal pharyngitis and manifests with multiple droplike lesions on the extremities and the trunk.
- Adverse effect on psychological and social functioning, with affected persons often feeling stigmatized.

ETIOLOGY

- Unknown, but there is a strong genetic component and high heritability. There are at least nine chromosomal loci with linkage to psoriasis. These loci are called psoriasis susceptibility 1 through 9 (PSORS1-PSORS9). PSORS1 locus in the major histocompatibility complex (MHC) region on chromosome 6 is considered the most important susceptibility locus and is believed to account for 35% to 50% of the heritability of the disease.
- Familial clustering (genetic transmission with a dominant mode with variable penetrants).
- One third of persons affected have a positive family history.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Contact dermatitis.
- Atopic dermatitis.
- Stasis dermatitis.
- Tinea.
- Nummular dermatitis.
- Candidiasis.
- Mycosis fungoides.
- Cutaneous systemic lupus erythematosus.
- Secondary and tertiary syphilis.
- Drug eruption.

WORKUP

- Diagnosis is clinical. Blood work is rarely needed.
- Skin biopsy is rarely necessary.

LABORATORY TESTS

Generally not necessary for diagnosis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Sunbathing generally leads to improvement.
- Eliminate triggering factors (e.g., stress, certain medications [e.g., lithium, beta-blockers, antimalarials]).
- Patients with psoriasis benefit from a daily bath in warm water followed by application of a cream or ointment moisturizer. Regular use of an emollient moisturizer limits evaporation of water from the skin and allows the stratum corneum to rehydrate itself.

GENERAL Rx

Therapeutic options vary according to the extent of disease. Approximately 70% to 80% of all patients can be treated adequately with topical therapy.

- Patients with limited disease (<20% of the body) can be treated with the following:
  1. Topical steroids: disadvantages are brief remissions, expense, and decreased effect with continued use. Salicylic acid can be compounded by pharmacist in concentrations of 2% to 10% and used in combination with a corticosteroid to decrease the amount of scale.
  2. Calcipotriene: a vitamin D analogue effective for moderate plaque psoriasis. Adults should comb the hair, apply solution to the lesions, and rub it in, avoiding uninvolved skin. Disadvantages include its cost and potential burning and skin irritation. It should not be used concurrently with salicylic acid because calcipotriene is inactivated by the acidic nature of salicylic acid. Taclonex ointment is a combination of calcipotriene and the high-potency corticosteroid betamethasone dipropionate. It is well tolerated and more effective than either agent used alone but also much more expensive.
  3. Tar products (Estar, LCD, Psorigel) can be used overnight and are most effective when combined with ultraviolet B (UVB) light (Goeckerman regimen).
  4. Anthralin: useful for chronic plaques; can result in purple-brown staining; best used with UVB light.
  5. Retinoids such as tazarotene 0.05%, 0.1% cream or gel, are effective in thinning plaques but are expensive and can cause irritation.
  6. Other useful measures include tape or occlusive dressing, UVB and lubricating agents, and interlesional steroids.
- Therapeutic options for persons with generalized disease (affecting >20% of the body) and for those with inadequate response to topical agents:
  1. UVB light exposure three times a week: this therapy does not require administration of a systemic drug (unlike psoralen plus ultraviolet A [PUVA]), but to be effective, it requires removal of scale with keratolytic agents and emollients.
  2. Oral PUVA administered two to three times weekly is effective for generalized disease. It is often considered in patients for whom narrow-band UVB therapy is ineffective. However, many PUVA treatments are required, necessitating frequent office visits, and it may be associated with phototoxicity, such as erythema and blistering, and increased risk of skin cancer.
- Systemic treatments include methotrexate 25 mg/wk for severe psoriasis. Etretinate (a synthetic retinoid) is most effective for palmar-plantar pustular psoriasis. Dose is 0.5 to 1 mg/kg/day. It can cause liver enzyme and lipid abnormalities and is teratogenic.
- Cyclosporine is also effective in severe psoriasis; however, relapses are common.
- Chronic plaque psoriasis may be treated with alefacept, a recombinant protein that selectively targets T lymphocytes. Treatment with alefacept for 12 wk (0.025, 0.075, or 0.150 mg/kg of body weight IV weekly) may result in significant improvement. Some patients also demonstrate a sustained clinical response after the cessation of treatment. This medication is very expensive (a 12-wk course can cost >$8000).
- TNF inhibitors: Treatment with etanercept, a tumor necrosis factor (TNF) antagonist, for

24 wk can also lead to a reduction in severity of plaque psoriasis. Efalizumab, a humanized monoclonal antibody that inhibits the activation of T cells, has also been reported to produce significant improvement in plaque psoriasis treatment period. Adalimumab—a fully human, anti-TNF-alpha monoclonal antibody—has been reported to be effective for joint and skin manifestations of psoriasis.

- Newer biologic agents in patients with moderate to severe plaque psoriasis are ustekinumab (an interleukin-12 and interleukin-23 blocker), brodalumab and secukinumab anti–interleukin-17 receptor antibodies, and briakinumab, a monoclonal antibody against the p40 molecule shared by interleukin-12 and interleukin-23, which is overexpressed in psoriatic skin lesions. Trials have shown efficacy in the treatment of moderate-to-severe psoriasis.

FIGURE P1-86 Clinical phenotypes in psoriasis: plaque psoriasis (psoriasis vulgaris). A, At extensor surface of elbow and on scalp (**B**). **C,** Genital psoriasis. **D,** Inframammary and umbilical flexural psoriasis. **E,** Guttate psoriasis in a father and child. **F,** Erythrodermic psoriasis on the trunk and upper limbs. **G,** Pustular psoriasis on the foot. **H,** The Koebner phenomenon on a surgical abdominal wound. (From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

DISPOSITION

The course of psoriasis is chronic, and the disease may be refractory to treatment.

REFERRAL

- Dermatology referral is recommended in all patients with generalized disease.
- Hospital admission may be necessary for severe diffuse or poorly responsive psoriasis. The Goeckerman regimen combines daily application of tar with UVB exposure and can result in prolonged remissions.

PEARLS & CONSIDERATIONS

COMMENTS

Psoriasis is more emotionally than physically disabling for most patients. Counseling may be indicated, particularly when it affects younger patients.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Psoriasis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Psoriasis is a common, chronic, inflammatory, multisystem disease with predominantly skin and joint manifestations affecting approximately 2% of the population. In the first five parts of the American Academy of Dermatology Psoriasis Guidelines of Care, we have presented evidence supporting the use of topical treatments, phototherapy, traditional systemic agents, and biological therapies for patients with psoriasis and psoriatic arthritis. In this sixth and final section of the Psoriasis Guidelines of Care, we will present cases to illustrate how to practically use these guidelines in specific clinical scenarios. We will describe the approach to treating patients with psoriasis across the entire spectrum of this fascinating disease from mild to moderate to severe, with and without psoriatic arthritis, based on the five guidelines published before. Although specific therapeutic recommendations are given for each of the cases presented, it is important that treatment be tailored to meet individual patient needs. In addition, we will update the prior five guidelines and address gaps in research and care that currently exist, while making suggestions for further studies that could be performed to help address these limitations in our knowledge base. Ⓐ

Evidence-Based Reference

Menter A et al.: Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 6. Guidelines of care for the treatment of psoriasis and psoriatic arthritis: case-based presentations and evidence-based conclusions, *J Am Acad Dermatol* 65:137–174, 2011. Ⓐ

SUGGESTED READINGS

Griffiths C, Barker J: Pathogenesis and clinical features of psoriasis, *Lancet* 370:263, 2007.

Griffiths C et al.: Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis, *N Engl J Med* 362:118–128, 2010.

Langley RG et al.: Secukinumab in plaque psoriasis, results of two phase 3 trials, *N Engl J Med* 371:326–338, 2014.

Luba KM, Stulberg DL: Chronic plaque psoriasis, *Am Fam Physician* 73:636, 2006.

Menter A, Griffiths C: Current and future management of psoriasis, *Lancet* 370:272, 2007.

Neigle N, McBane S: Psoriasis, *Am Fam Phys* 87(9):626–633, 2013.

Paller AS et al.: Etanercept treatment for children and adolescents with plaque psoriasis, *N Engl J Med* 358(3), 2008.

Papp KA et al.: Brodalumab, an anti-interleukin 17 receptor antibody for psoriasis, *N Engl J Med* 366:1181–1189, 2012.

Reich K et al.: A 52-week trial comparing briakinumab with methotrexate in patients with psoriasis, *N Engl J Med* 365:1586–1596, 2011.

Schon MP, Boehncke WH: Psoriasis, *N Engl J Med* 353:2005, 1899.

Stern RS: Psoralen and ultraviolet A light therapy for psoriasis, *N Engl J Med* 357:682, 2007.

Psoriatic Arthritis ALG PTG

BASIC INFORMATION

DEFINITION

Psoriatic arthritis is an inflammatory arthropathy occurring in association with skin psoriasis and generally in the absence of rheumatoid factor (RF). It is often included in a class of disorders called the *seronegative spondyloarthropathies,* a family of diseases characterized by inflammation of the spine, peripheral joints, and enthesial sites (sites of insertion of tendon into bone). Classifications of psoriatic arthritis are described in Table P1-42.

ICD-9CM CODES
696.0 Psoriatic arthritis
ICD-10CM CODES
L40.5+ Arthropathic psoriasis
L40.54 Psoriatic juvenile arthropathy

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 0.1% to 0.2% overall, variable estimates of 7% to 30% of patients with psoriasis (psoriasis incidence varies by population but overall estimated prevalence of 1% to 2% of general population)
PREDOMINANT SEX: Equal male/female distribution of 1:1.
PREDOMINANT AGE: Symptom onset generally age 30 to 55 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Variably arthritis, dactylitis, spondylitis, and enthesitis occur in the setting of known psoriasis although joint symptoms may predate skin psoriasis in ~15% of patients.
  - Arthritis is inflammatory in nature, commonly characterized by prolonged morning stiffness, joint erythema, warmth, or swelling including joint effusions.
- Distribution of joint involvement follows five classically described patterns (Box P1-14).
- Often more than one classical pattern will occur simultaneously and patterns can evolve over time in an individual patient. Subtypes of psoriatic arthritis are described in Box P1-14.
- Dactylitis refers to diffuse swelling of a digit, either finger or toe, which is typically the result of inflammation in both small joints of the digit as well as associated tenosynovitis of digital tendons. Dactylitis is common in psoriatic arthritis and occurs in approximately 30% to 40% of patients during the course of disease.
- Enthesitis commonly occurs at the Achilles tendon insertion into the calcaneus as well as the insertion of the plantar fascia. Findings on physical exam may include swelling and tenderness.
- Dystrophic changes of the nails (pitting, onycholysis) may occur in association with joint inflammation in involved digits.
- Spondyloarthritis may include sacroiliitis as well as inflammation of the axial spine, but is generally less likely to cause contiguous fusion to the extent seen in ankylosing spondylitis.

ETIOLOGY

Unknown.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rheumatoid arthritis.
- Erosive osteoarthritis.
- Crystal arthritis including gout and pseudogout.
- Other seronegative spondyloarthropathies, including reactive arthritis, enteropathic arthritis, and ankylosing spondylitis.
- The differential diagnosis of spondyloarthropathies is described in Section III.

WORKUP

- Diagnosis generally made on clinical grounds based on history, exam, and radiographic findings given lack of specific lab findings. An algorithm for the diagnosis of psoriatic arthritis is described in Fig. P1-87.
- Early diagnosis may be difficult to establish when the arthritis develops before skin lesions appear.

LABORATORY TESTS

- No specific/diagnostic lab tests.
- Acute phase reactants such as ESR and CRP may be elevated although less commonly than in patients with rheumatoid arthritis.
- Anemia of chronic disease may be seen.
- RF, while generally negative, can be present in >10% of patients.
- *HLA B27* is significantly more common in patients with axial inflammation (note that *HLA B27* positivity is present in up to 8% of general population).
- Arthrocentesis of active joint generally demonstrates inflammatory synovial fluid and absence of crystals.

IMAGING STUDIES

- Radiographic findings (Fig. P1-88) of involved joints may include soft tissue swelling, joint space narrowing, subluxation, erosive changes, and new bone formation such as periostitis and fusion.
- Severe digital erosive change with adjacent heterotopic bone formation may give rise to "pencil in cup" deformity seen in arthritis mutilans.

BOX P1-14 Subtypes of Psoriatic Arthritis

Distal interphalangeal joint–predominant arthritis (10%) (Fig. P1-89).
Symmetric polyarthritis–predominant arthritis (5% to 20%).
Asymmetric oligoarthritis or monoarthritis (70% to 80%).
Axial disease–predominant (spondylitis and/or sacroiliitis) (5% to 20%).
Arthritis mutilans (rare).

From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

TABLE P1-42 Classifications of Psoriatic Arthritis

	CLASSIFICATION CRITERIA FOR PSORIATIC ARTHRITIS (CASPAR)*		
Moll and Wright	**Points**	**Category**	**Description**
Presence of psoriasis and: An inflammatory arthritis (peripheral arthritis and/or sacroiliitis or spondylitis) The (usual) absence of serologic tests for rheumatoid factor	2	Current psoriasis or personal or family history of psoriasis	Psoriatic skin or scalp disease confirmed by dermatologist or rheumatologist; history of psoriasis from patient, family physician, dermatologist, rheumatologist, or other qualified practitioner; patient-reported history of psoriasis in first- or second-degree relative
	1	Psoriatic nail dystrophy on current physical examination	Includes onycholysis, pitting, and hyperkeratosis
	1	Negative for rheumatoid factor	Enzyme-linked immunosorbent assay or nephelometry preferred (no latex) using local laboratory reference range
	1	Current dactylitis or history of dactylitis documented by a rheumatologist	Swelling of entire digit
	1	Radiographic evidence of juxta-articular new bone formation	Ill-defined ossification near joint margins excluding osteophyte formation on plain radiographs of hand or foot

*Psoriatic arthritis is diagnosed when ≥3 points are assigned in the presence of inflammatory articular disease (joint, spine, or entheseal).
From Hochberg MC et al: Rheumatology, ed 5, St Louis, 2011, Mosby.

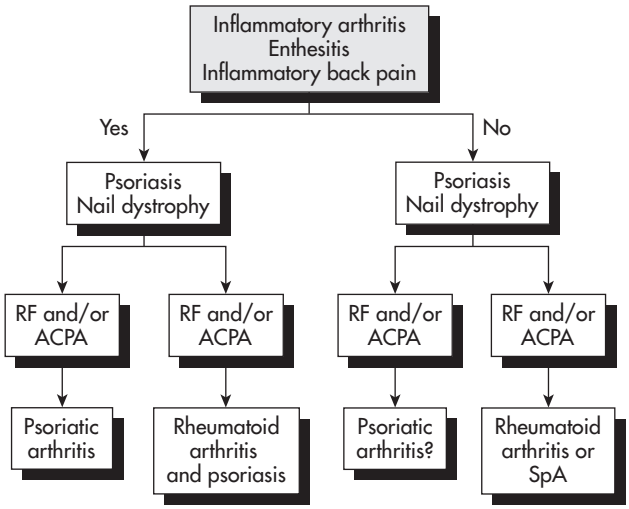

FIGURE P1-87 Algorithm to be used in the diagnosis of individual patients presenting with possible psoriatic arthritis. Some patients may present with typical articular manifestations of psoriatic arthritis, but in the absence of skin or nail disease. They can be diagnosed as having definite psoriatic arthritis only when psoriasis subsequently develops. *ACPA,* Anticitrullinated protein antibody; *RF,* rheumatoid factor; *SpA,* spondyloarthropathy. (Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

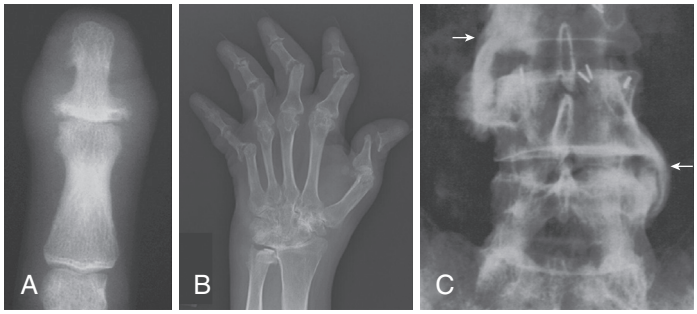

FIGURE P1-88 Psoriatic arthritis (x-ray). A, Distal interphalangeal joint with classic radiographic findings, including soft tissue swelling, bone erosions with accompanying bone proliferation, and lack of osteoporosis. **B,** Arthritis mutilans resulting from psoriatic arthritis with destructive changes and joint deformity of the hand and pancompartmental ankylosis of the wrist. **C,** Psoriatic spondylitis. Thick asymmetric paravertebral ossifications (*arrows*), which are characteristic of psoriatic spondylitis and reactive arthritis. (From Resnick D, Niwayama G: *Diagnosis of bone and joint disorders,* Philadelphia, 1988, WB Saunders.)

FIGURE P1-89 The hands of a woman with symmetric polyarthritis. Initially, this was indistinguishable from rheumatoid disease, but note the distal interphalangeal joint involvement, which is uncommon in rheumatoid arthritis, as well as the skin psoriasis. (From Klippel J et al [eds]: *Primary care rheumatology,* London, 1999, Mosby.)

- Findings in patients with spondylitis may include sacroiliitis and development of vertebral syndesmophytes that often bridge adjacent vertebral bodies.
- Musculoskeletal ultrasound may be helpful in the evaluation of an inflamed enthesis or joint.
- MRI may be helpful in the evaluation of sacroiliitis or spinal involvement.

Rx TREATMENT

ACUTE GENERAL Rx

- NSAIDs may be used for mild symptoms or limited involvement.
- Intraarticular corticosteroid injections can be used as adjunctive therapy in involved joints.

CHRONIC Rx

The choice of therapeutic agents in psoriatic arthritis depends on the types of clinical manifestations by an individual patient as not all agents are effective for all types of clinical manifestations. For example, inflammation at the enthesis and spine are not responsive to traditional oral disease modifying agents such as methotrexate or leflunomide but are responsive to tumor necrosis factor (TNF) blocking agents such as infliximab, adalimumab, and etanercept.

- NSAIDs may be used for mild or limited disease
- In patients with several sites of active peripheral joint disease, elevated acute phase reactants, or with evidence of erosive changes on imaging, traditional DMARDs such as methotrexate, sulfasalazine, and leflunomide should be considered early in disease.
- In patients with peripheral arthritis who fail to respond to traditional DMARD therapy, additional therapy with a tumor necrosis factor (TNF) inhibitor should be considered. Current FDA approved TNF inhibitors for psoriatic arthritis include etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol.
- In patients with predominant axial disease not responsive to NSAIDs, anti-TNF therapy should be considered for initial disease-modifying therapy.
- Enthesitis and dactylitis are poorly responsive to oral DMARD therapy but like spondylitis will often respond to anti-TNF therapy.
- Ustekinumab, a human IgG monoclonal antibody that binds to the p40 subunit of interleukin-12 and -23 and is responsible for T-helper-17 inflammatory cell suppression effectively treats psoriasis and psoriatic arthritis and is FDA approved as an alternative biologic treatment for psoriatic arthritis.[i] Recent trials involving brodalumab, an Ant-IL17RA monoclonal antibody, in psoriatic arthritis have shown significantly improved response rates.
- New targeted therapeutics have recently been demonstrated to be effective in psoriatic arthritis and approved for use in psoriatic arthritis. These include ustakinumab which is a biologic targeted inhibitor of IL12/23 previously found to be effective in psoriasis. Another agent recently approved is apremilast, which is an oral phosphodiesterase 4 (PDE 4) inhibitor that has been demonstrated to be effective in psoriatic arthritis.

REFERRAL

Rheumatology for confirmation of diagnosis and management.

PEARLS & CONSIDERATIONS

- Patients frequently have a positive family history of psoriasis or psoriatic arthritis.
- Severity of skin psoriasis and activity of inflammatory arthritis are frequently discordant.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Psoriatic Arthritis (Patient Information).

AUTHOR: **HARALD A. HALL, M.D.**

SUGGESTED READING

McInnes IB et al.: Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of phase 3, multicenter, double-blind, placebo-controlled PSUMMIT 1 trial, *Lancet* 382:780–789, 2013.

Mease PJ et al.: Brodalumab, an Anti-IL17RA monoclonal antibody in psoriatic arthritis, *N Engl J Med* 370:2295–2306, 2014.

Ritchlin CT et al.: Treatment recommendations for psoriatic arthritis, *Ann Rheum Dis* 68:1387, 2009.

BASIC INFORMATION

DEFINITION

Psychosis is a state in which external reality is distorted by delusions and/or hallucinations (a delusion is a fixed false idiosyncratic belief; a hallucination is a false auditory, visual, olfactory, tactile, or taste perception).

SYNONYMS

Psychosis is a key finding in many mental illnesses, such as brief psychotic disorder, delusional disorder, schizoaffective disorder, schizophrenia, schizophreniform disorder, or shared psychotic disorder. Psychosis can also present as part of the evolution of a mood disorder (depression and bipolar disorder), a sign of an underlying medical condition, or a manifestation of a toxic state, i.e., abuse of substances or withdrawal state.

ICD-10CM CODES

F09 Unspecified organic or symptomatic mental disorder.
F10.5 Psychotic disorder due to psychoactive substance use
F05 Delirium not induced by alcohol and other psychoactive substances.
F06.0 Organic hallucinosis.
F32.3 Major depressive disorder, single episode, severe with psychotic features.
F30.2 and F31.2 Manic episode with psychosis and bipolar affective disorder with psychosis.

EPIDEMIOLOGY & DEMOGRAPHICS

One-year prevalence: 4.5 per 1000. The (demographics of) psychosis depends on the underlying disorder.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

History:

- Past and current medical history important to identify potential medical etiologies.
- Medication use.
- Use of illicit substances or alcohol.
- Identification of functional and social impairment.
- Behavior that is odd or unpredictable; patient may be acting based on misinterpretation of their reality or false perceptions (delusions or hallucinations).

Examination:

- Examine for symptoms of:
  - Mood disorder: delusions or hallucinations are usually congruent with the mood (e.g., auditory hallucinations in a depressed patient may tell the patient what a terrible person he is).
  - Altered or disorganized thought pattern: usually reflected in disorganized speech (including word salad, thought blocking, rhyming, clang associations).
  - Lack of insight into problems
  - Signs of Parkinson's disease, dementia.

ETIOLOGY

- Involves an interaction among:
  1. Dopaminergic overactivity (particularly in the mesolimbic, nigrostriatal, and mesocortical systems).
  2. Environmental, social, or childhood factors.
  3. Genetic predisposition.

DIAGNOSIS

WORKUP

- Evaluate for potential confounding factors. Fig. P1-90 describes an algorithmic approach to evaluation of the psychotic patient.
- Underlying mental disorder: schizophrenia, major depression, brief psychotic disorder, delusional disorder, schizoaffective disorder, schizophreniform disorder.
- Underlying personality disorder: borderline, paranoid, schizoid, schizotypal.
- Underlying medical conditions: infections ranging from UTIs to HIV/AIDS, Parkinson's disease, Huntington's disease, leprosy, malaria, sarcoidosis, systemic lupus erythematosus, prion disease, hypoglycemia, postpartum state, cerebrovascular event, temporal lobe epilepsy, brain neoplasm.
- Medications: systemic steroids, anticonvulsants, antiparkinsonian medications, some chemotherapy, scopolamine.
- Underlying dementia: Alzheimer's disease, Lewy body dementia, vascular dementia.
- Illicit drugs (usually with chronic use; can be caused by intoxication or withdrawal): LSD, PCP, cocaine, gamma-hydroxybutyrate (GHB; withdrawal), alcohol, amphetamines, marijuana. New substances of abuse (e.g., "bath salts", synthetic cannabinoids) may not be detected by current toxicology panels.
- Traumatic brain injury.
- Intensive care unit stay: hypoxia, decreased cardiac output, infection, medications, sleep deprivation, alteration of diurnal cycle, sensory deprivation or overload, pain.
- Emotional stress.

LABORATORY TESTS

Consider checking chemistry panel (calcium), complete blood count, UA, liver function tests, cortisol, HIV, rapid plasma reagin, thyroid-stimulating hormone, toxicology screen, lumbar puncture (LP).

IMAGING STUDIES

Consider chest x-ray (rule out sarcoid), electroencephalography, head CT or MRI.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cognitive-behavioral therapy.
- Social and behavioral skills training.
- Training for self-management of disease.
- Aforementioned strategies favored over psychoanalytic techniques given the relative inability for abstract thought and lack of insight in psychotic patients.
- Family intervention, including education and strategies to reduce emotional expression.
- Counseling for substance abuse.

ACUTE GENERAL Rx

- Antipsychotics, such as haloperidol and consider combining with anticholinergics like benztropine to reduce side effects if such arise; low doses should control first episode. Use with caution in elderly patients because adverse effects limit effectiveness. Second-generation antipsychotics are also useful starting with low doses. Newer formulations are available in rapid injectable form or oral disintegrating tablets.
- Benzodiazepines if agitation is severe.
- Discontinue offending medication if present.

CHRONIC Rx

Second-generation antipsychotics may reduce the incidence of tardive dyskinesia but may increase incidence of metabolic disorders compared with first-generation antipsychotics. Multicenter trials showed similar efficacy between first and second generation. Consider economic, including insurance formulary, factors when selecting a maintenance regimen.

DISPOSITION

Prognosis varies according to etiology of psychosis. In general, the more severe and longer the psychotic episode, the worse the prognosis.

REFERRAL

Patient should be admitted for acute stabilization if actively psychotic to prevent harm to self and others as well as ensure administration of medications.

PEARLS & CONSIDERATIONS

- Delusions and/or hallucinations are hallmarks of psychosis.
- Rule out medical or drug causes of psychosis.
- Antipsychotics are the mainstay of acute and chronic treatment.
- Consider alternatives to antipsychotics in elderly or intellectually disabled patients (see "Nonpharmacologic Therapy").

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Psychosis (Patient Information)
Delirium (Related Key Topic)

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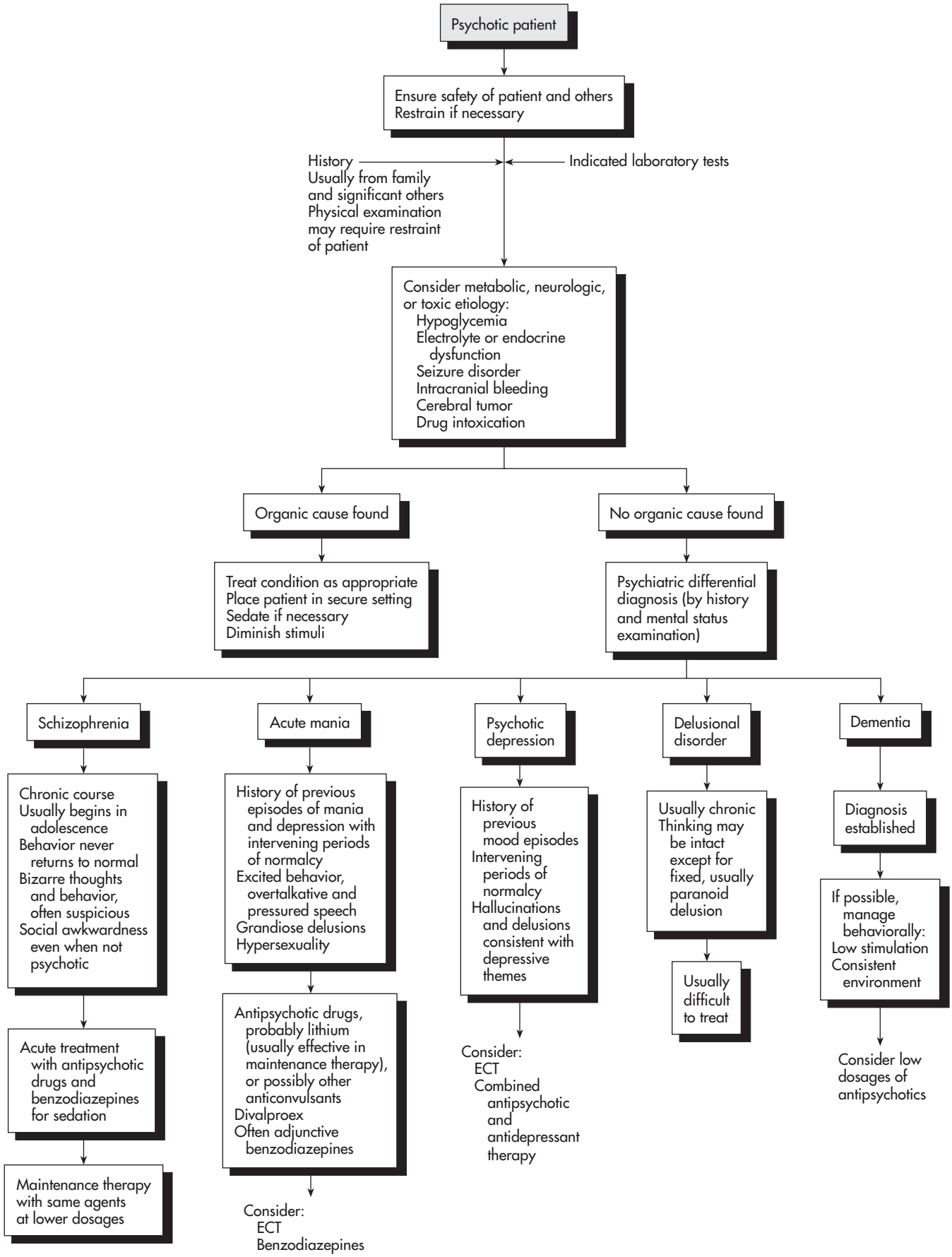

FIGURE P1-90 Evaluation of psychotic patient. *ECT,* Electroconvulsive therapy. (Modified from Greene HL et al [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

EVIDENCE

Abstract[1]

Objective:
Using longitudinal and prospective measures of trauma during childhood, the authors assessed the risk of developing psychotic symptoms associated with maltreatment, bullying, and accidents in a nationally representative U.K. cohort of young twins.

Method:
Data were from the Environmental Risk Longitudinal Twin Study, which follows 2232 twin children and their families. Mothers were interviewed during home visits when children were ages 5, 7, 10, and 12 on whether the children had experienced maltreatment by an adult, bullying by peers, or involvement in an accident. At age 12, children were asked about bullying experiences and psychotic symptoms. Children's reports of psychotic symptoms were verified by clinicians.

Results:
Children who experienced maltreatment by an adult (relative risk = 3.16, 95% CI = 1.92–5.19) or bullying by peers (relative risk = 2.47, 95% CI = 1.74–3.52) were more likely to report psychotic symptoms at age 12 than were children who did not experience such traumatic events. The higher risk for psychotic symptoms was observed whether these events occurred early in life or later in childhood. The risk associated with childhood trauma remained significant in analyses controlling for children's gender, socioeconomic deprivation, and IQ; for children's early symptoms of internalizing or externalizing problems; and for children's genetic liability to developing psychosis. In contrast, the risk associated with accidents was small (relative risk=1.47, 95% CI=1.02–2.13) and inconsistent across ages.

Conclusions:
Trauma characterized by intention to harm is associated with children's reports of psychotic symptoms. Clinicians working with children who report early symptoms of psychosis should inquire about traumatic events such as maltreatment and bullying. Ⓐ

Abstract[2]

Context:
People experiencing possible prodromal symptoms of psychosis have a very high risk of developing the disorder, but it is not possible to predict, on the basis of their presenting clinical features, which individuals will subsequently become psychotic. Recent neuroimaging studies suggest that there are volumetric differences between individuals at ultra-high risk (UHR) for psychosis who later develop psychotic disorder and those who do not. However, the samples examined to date have been small, and the findings have been inconsistent.

Objective:
To assess brain structure in individuals at UHR for psychosis in a larger and more representative sample than in previous studies by combining magnetic resonance imaging data from 5 different scanning sites.

Design:
Case-control study.

Setting:
Multisite.

Participants:
A total of 182 individuals at UHR and 167 healthy controls. Participants were observed clinically for a mean of 2 years. Forty-eight individuals (26.4%) in the UHR group developed psychosis and 134 did not.

Main Outcome Measures:
Magnetic resonance images were acquired from each participant. Group differences in gray matter volume were examined using optimized voxel-based morphometry.

Results:
The UHR group as a whole had less gray matter volume than did controls in the frontal regions bilaterally. The UHR subgroup who later developed psychosis had less gray matter volume in the left parahippocampal cortex than did the UHR subgroup who did not.

Conclusions:
Individuals at high risk for psychosis show alterations in regional gray matter volume regardless of whether they subsequently develop the disorder. In the UHR population, reduced left parahippocampal volume was specifically associated with the later onset of psychosis. Alterations in this region may, thus, be crucial to the expression of illness. Identifying abnormalities that specifically predate the onset of psychosis informs the development of clinical investigations designed to predict which individuals at high risk will subsequently develop the disorder. Ⓐ

Abstract[3]

Objective:
To examine the influence of cannabis use on long-term outcome in patients with a first psychotic episode, comparing patients who have never used cannabis with (a) those who used cannabis before the first episode, but stopped using it during follow-up and (b) those who used cannabis both before the first episode and during follow-up.

Methods:
Patients were studied following their first admission for psychosis. They were interviewed at years 1, 3, and 5. At follow-up after 8 years, functional outcome and alcohol and drug abuse were recorded. Patients were classified according to cannabis use: 25 had cannabis use before their first psychotic episode and continuous use during follow-up (CU), 27 had cannabis use before their first episode, but stopped its use during follow-up (CUS), and 40 never used cannabis (NU).

Results:
The 3 groups did not differ significantly in symptoms or functional outcome at baseline or during short-term follow-up. The CUS group exhibited better long-term functional outcome compared with the other 2 groups and had fewer negative symptoms than the CU group, after adjusting for potential confounders. For the CUS group, the effect size was 1.26 (95% confidence interval [CI] = 0.65 to 1.86) for functional outcome and −0.72 (95% CI = −1.27 to −0.14) for negative symptoms. All patients experienced improvements in positive symptoms during long-term follow-up.

Conclusion:
Cannabis has a deleterious effect, but stopping use after the first psychotic episode contributes to a clear improvement in outcome. The positive effects of stopping cannabis use can be seen more clearly in the long term. Ⓐ

Abstract[4]

Background:
During the last decades we have seen a new focus on early treatment of psychosis. Several reviews have shown that duration of untreated psychosis (DUP) is correlated to better outcome. However, it is still unknown whether early treatment will lead to a better long-term outcome. This study reports the effects of reducing DUP on 5-year course and outcome.

Method:
During 1997–2000 a total of 281 consecutive patients aged >17 years with first episode non-affective psychosis were recruited, of which 192 participated in the 5-year follow-up. A comprehensive early detection (ED) programme with public information campaigns and low-threshold psychosis detection teams was established in one healthcare area (ED-area), but not in a comparable area (no-ED area). Both areas ran equivalent treatment programmes during the first 2 years and need-adapted treatment thereafter.

Results:
At the start of treatment, ED-patients had shorter DUP and less symptoms than no-ED-patients. There were no significant differences in treatment (psychotherapy and medication) for the 5 years. Mixed-effects modelling showed better scores for the ED group on the Positive and Negative Syndrome Scale negative, depressive and cognitive factors and for global assessment of functioning for social functioning at 5-year follow-up. The ED group also had more contacts with friends. Regression analysis did not find that these differences could be explained by confounders.

Conclusions:
Early treatment had positive effects on clinical and functional status at 5-year follow-up in first episode psychosis. Ⓐ

Abstract[5]

Context:
A number of studies have found that the use of cannabis and other psychoactive substances is associated with an earlier onset of psychotic illness.
Objective:
To establish the extent to which use of cannabis, alcohol, and other psychoactive substances affects the age at onset of psychosis by meta-analysis.
Data Sources:
Peer-reviewed publications in English reporting age at onset of psychotic illness in substance-using and non–substance-using groups were located using searches of CINAHL, EMBASE, MEDLINE, PsycINFO, and ISI Web of Science.
Study Selection:
Studies in English comparing the age at onset of psychosis in cohorts of patients who use substances with age at onset of psychosis in non–substance-using patients. The searches yielded 443 articles, from which 83 studies met the inclusion criteria.
Data Extraction:
Information on study design, study population, and effect size were extracted independently by 2 of us.
Data Synthesis:
Meta-analysis found that the age at onset of psychosis for cannabis users was 2.70 years younger (standardized mean difference = −0.414) than for nonusers; for those with broadly defined substance use, the age at onset of psychosis was 2.00 years younger (standardized mean difference = −0.315) than for nonusers. Alcohol use was not associated with a significantly earlier age at onset of psychosis. Differences in the proportion of cannabis users in the substance-using group made a significant contribution to the heterogeneity in the effect sizes between studies, confirming an association between cannabis use and earlier mean age at onset of psychotic illness.
Conclusions:
The results of meta-analysis provide evidence for a relationship between cannabis use and earlier onset of psychotic illness, and they support the hypothesis that cannabis use plays a causal role in the development of psychosis in some patients. The results suggest the need for renewed warnings about the potentially harmful effects of cannabis. Ⓐ

Evidence-Based References

Arseneault L et al.: Childhood trauma and children's emerging psychotic symptoms: a genetically sensitive longitudinal cohort study, *Am J Psychiatry* 168:65–72, 2011. Ⓐ.

Mechelli A et al.: Neuroanatomical abnormalities that predate the onset of psychosis: a multicenter study, *Arch Gen Psychiatry* 68:489–495, 2011. Ⓐ.

González-Pinto A et al.: Cannabis and first-episode psychosis: different long-term outcomes depending on continued or discontinued use, *Schizophr Bull* 37:631–639, 2011. Ⓐ.

Larsen TK et al.: Early detection of psychosis: positive effects on 5-year outcome, *Psychol Med* 41:1461–1469, 2011. Ⓐ.

Large M et al.: Cannabis use and earlier onset of psychosis: a systematic meta-analysis, *Arch Gen Psychiatry* 68:555–561, 2011. Ⓐ.

SUGGESTED READINGS

Bertelsen M et al.: Five-year follow-up of a randomized multicenter trial of intensive early intervention vs standard treatment for patients with a first episode of psychotic illness: the OPUS trial, *Gen Psychiatry* 65(7):762, 2008.

Hackman DT et al.: Prescription drug monitoring program inquiry in psychiatric assessment: detection of high rates of opioid prescribing to a dual diagnosis population, *J Clin Psychiatry* 75(7):750–756, 2014.

Leentjens AF et al.: Delirium: An evidence-based medicine (EBM) monograph for psychosomatic medicine practice, commissioned by the Academy of Psychosomatic Medicine (APM) and the European Association of Consultation Liaison Psychiatry and Psychosomatics (EACLPP), *J Psychosom Res* 73(2):149–152, 2012.

Moreno C et al.: Psychotic symptoms are associated with physical health problems independently of a mental disorder diagnosis: results from the WHO World Health Survey, *World Psychiatry* 12(3):251–257, 2012.

Tyrer P et al.: Risperidone, haloperidol, and placebo in the treatment of aggressive challenging behaviour in patients with intellectual disability: a randomised controlled trial, *Lancet* 371:57, 2008.

Wainwright LD et al.: What do relatives experience when supporting someone in early psychosis? *Psychol Psychother*, 2014.

BASIC INFORMATION

DEFINITION

Pulmonary hypertension (PH) is defined as the presence of an abnormally elevated pulmonary arterial pressure. A mean pulmonary artery pressure (PAP) >25 mm Hg at rest or pulmonary artery systolic pressure >35 mm Hg is considered abnormal. Pulmonary arterial hypertension (PAH) is a syndrome with various causes and is defined as pulmonary hypertension with a normal pulmonary capillary wedge pressure, left atrial pressure, or left ventricular end diastolic pressure ≤5 mm Hg, and a pulmonary vascular resistance >3 Wood units on right heart catheterization. Idiopathic pulmonary arterial hypertension (IPAH) is diagnosed when PAH is present without any apparent cause. It is a highly morbid disease characterized by progressive obliteration of precapillary arterioles. Pulmonary hypertension from lung disease is covered under the separate topic Cor Pulmonale.

SYNONYMS

Idiopathic pulmonary arterial hypertension (IPAH)
Secondary pulmonary arterial hypertension (PAH)
Group I Pulmonary Hypertension

ICD-9CM CODES
416.0 Primary pulmonary hypertension
416.8 Secondary pulmonary hypertension
ICD-10CM CODES
I27.0 Primary pulmonary hypertension
I27.2 Other secondary pulmonary hypertension

EPIDEMIOLOGY & DEMOGRAPHICS

- IPAH is rare, occurring in one to two cases per 1 million people per year, with an overall prevalence estimated at 1300 per 1 million.
- IPAH is more common in women than men (3:1), usually presenting in the third to fourth decades of life.
- In adults the most common cause of pulmonary hypertension is lung disease.
- IPAH incidence ranges from 1-2 per million per year, and prevalence is 0.1-0.2% of all post mortem examinations.
- Prevalence of secondary PAH could range from 8-12% in cases of scleroderma, 0.5% of HIV, 23-53% of mixed connective tissue disorders, and 1-4% cases of systemic lupus erythromatosus.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Insidious, may go undetected for years.
- Exertional dyspnea most common presenting symptom (60%).
- Fatigue and weakness.
- Syncope, classically exertion-related or after a warm shower with peripheral vasodilation.
- Chest pain.
- Hoarse voice from compression of recurrent laryngeal nerve by an enlarged pulmonary artery (Ortner's syndrome).
- Loud P2 component of the second heart sound and paradoxical splitting of second heart sound.
- Right-sided S4.
- Jugular venous distention.
- Abdominal distention and ascites.
- Prominent parasternal (right ventricular [RV]) impulse.
- Holosystolic tricuspid regurgitation murmur heard best along the left fourth parasternal line that increases in intensity with inspiration.
- Peripheral edema.

ETIOLOGY

- The etiology of IPAH is unknown. Most cases are sporadic, but there is a 6% to 12% familial incidence.
- PH is associated with several known risk factors: connective tissue disorders, portal hypertension and liver cirrhosis, appetite-suppressant drugs (fenfluramine), hemoglobinopathies, and infections including schistosomiasis and HIV disease. It is estimated that 10% of patients with hemoglobinopathies and 0.5% of patients with HIV infection develop moderate to severe PH. Schistosomiasis, sickle cell disease, and HIV disease may be the most common causes of PH worldwide, although pulmonary venous hypertension from left ventricular failure and PH related to COPD are more common causes of PH in developed nations.
- Several genetic abnormalities have been associated with the familial form of IPAH, many of which are mutations in the genes that code for members of the tumor growth factor-beta family of receptors (BMPR-II, ALK-1, endoglin) on chromosome 2q33. A recent study[1] has identified the association of a novel gene, *KCNK3,* with familial and idiopathic pulmonary arterial hypertension.
- Familial PAH is an autosomal-dominant disease with variable penetrance, affecting only about 10% to 20% of carriers.
- Several factors play a role in the pathogenesis of PAH, including a genetic predisposition, endothelial cell dysfunction, abnormalities in vasomotor control, thrombotic obliteration of the vascular lumen, and vascular remodeling through cell proliferation and matrix production.
- SSRI use in late pregnancy is associated with increased persistent PH in newborns.
- The updated clinical classification of PAH is described in Table P1-43.

DIAGNOSIS

- PAH is a hemodynamic diagnosis involving the detection of elevated pressure in the pulmonary arteries and elevated pulmonary vascular resistance in the pulmonary vascular bed, occurring in the absence of significant pulmonary venous hypertension; characterization of this abnormality determines its etiology.
- Right-sided heart catheterization must be performed in all patients suspected of having PAH to establish the diagnosis and to assess

[1]Ma L et al: A novel channelopathy in pulmonary arterial hypertension, *N Engl J Med* 369:351-361, 2013.

TABLE P1-43 Updated Clinical Classification of Pulmonary Hypertension

Group 1
Pulmonary arterial hypertension
Idiopathic pulmonary arterial hypertension
Heritable
BMPR2
ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
Unknown
Drug- and toxin-induced
Associated with:
Connective tissue diseases
HIV infection
Portal hypertension
Congenital heart diseases
Schistosomiasis
Chronic hemolytic anemia
Persistent pulmonary hypertension of the newborn
Pulmonary veno-occlusive disease with left to right shunts and/or pulmonary capillary hemangiomatosis
Group 2
Pulmonary hypertension owing to left heart disease
Systolic dysfunction
Diastolic dysfunction
Valvular disease
Group 3
Pulmonary hypertension owing to lung diseases and/or hypoxia
Chronic obstructive pulmonary disease
Interstitial lung disease
Other pulmonary diseases with mixed restrictive and obstructive pattern
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental abnormalities
Group 4
Chronic thromboembolic pulmonary hypertension
Group 5
Pulmonary hypertension with unclear multifactorial mechanisms
Hematologic disorders: myeloproliferative disorders, splenectomy
Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
Metabolic disorders: glycogen storage disease, Gaucher's disease, thyroid disorders
Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK1, Activin receptor-like kinase type 1; *BMPR2,* bone morphogenetic protein receptor type 2; *HIV,* human immunodeficiency virus.
From Simonneau G et al: Updated clinical classification of pulmonary hypertension, *J Am Coll Cardiol* 54:S43-S54, 2009.

pulmonary hemodynamics and acute vasoreactivity response testing.
- IPAH is a diagnosis that rests on the detection of PH with exclusion of known causes of high pulmonary arterial pressure.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is as listed under "Etiology."

EVALUATION

- Consists of establishing the diagnosis and etiology.
- Echocardiography with Doppler technique can provide a noninvasive but limited estimation of systolic PAP. Common findings include tricuspid regurgitation, right heart enlargement, abnormal movement of septum and, rarely, pericardial effusion. However, the diagnosis of PH cannot be established by echocardiography alone, as echocardiography can overestimate or underestimate PAP.
- ECG shows RV enlargement, strain pattern, and right axis deviation.
- Chest radiograph (Fig. EP1-91) shows enlarged central pulmonary arteries and right heart enlargement. Chest radiography is abnormal in 90% of patients at diagnosis.
- A normal chest radiograph does not rule out the diagnosis. High-resolution computed tomography (CT) (Fig. EP1-92) can assist in the evaluation for emphysema or interstitial lung disease. Ventilation-perfusion lung scan has high sensitivity for chronic thromboembolic disease. The diagnosis should be confirmed by pulmonary angiography, which has high specificity.
- Pulmonary function tests may show obstructive (airway disease) and/or restrictive disease (parenchymal disease) depending on etiology. Diffusion capacity of carbon monoxide in the lung is reduced due to pulmonary vascular destruction in PAH.
- In asymptomatic patients the severity of a pulmonary arterial hypertension (PAH) patient's disease should be evaluated in a systematic and consistent manner, using a combination of World Health Organization (WHO) functional class (FC), exercise capacity, echocardiographic, laboratory, and hemodynamic variables in order to inform therapeutic decisions.
- Symptomatic patients with PAH, in the absence of contraindications, should undergo acute vasoreactivity testing using a short-acting agent at a center with experience in the performance and interpretation of vasoreactivity testing.
- Right heart catheterization is required to assess pulmonary hemodynamics, exclude shunts and left heart disease, and perform acute vasoreactivity response testing.
- Screening for the presence of PAH with Doppler echocardiography is warranted in individuals with a known predisposing genetic mutation or first-degree relative with IPAH, connective tissue diseases (especially scleroderma), congenital heart disease with left-to-right shunt, or portal hypertension undergoing evaluation for orthotopic liver transplantation.
- Determining the degree of functional impairment, as assessed by the WHO functional classification system (Classes I-IV) and the 6-min walk test (6MWT), is a useful way to monitor disease progression and assess response to treatment.

LABORATORY TESTS

- Complete blood count is usually normal in PAH but may show secondary polycythemia.
- Arterial blood gases show low PO_2 and oxygen saturation.
- Overnight oximetry and/or sleep study to rule out sleep apnea or hypopnea.
- Other blood tests: antinuclear antibody (ANA), antineutrophil cytoplasmic antibodies (ANCA), anti-Scl-70, anticentromere, ribonucleoprotein antibody levels, and rheumatoid factor (RF) to screen for underlying connective tissue disease, HIV serology, liver function tests, and antiphospholipid antibodies.
- Brain natriuretic peptide (BNP) level can provide prognostic information, with elevation in BNP level being associated with increased mortality.
- Ventilation-perfusion lung scan has high sensitivity for chronic thromboembolic PAH. The diagnosis should be confirmed by pulmonary angiography, which has high specificity.

Rx TREATMENT

- Most of the evidence in management of PAH is limited to IPAH. There is some evidence in treatment of PAH associated with connective tissue disease, especially scleroderma, and congenital heart disease. The recommendations for treating PAH associated with other causes are limited to case studies and expert opinions.
- There is some evidence for the use of advanced therapies for sarcoidosis-associated PH. The heterogeneity of sarcoid-associated PH complicates the interpretation.

NONPHARMACOLOGIC THERAPY

- Oxygen therapy to improve alveolar oxygen flow in both idiopathic and secondary PH. Goal oxygen saturation >90%.
- Avoidance of vigorous exercise and pregnancy.

GENERAL TREATMENT

1. Diuretics (e.g., furosemide 40 to 80 mg qd) improve dyspnea by reducing preload and peripheral edema. Avoid excessive diuresis in patients who are preload dependent.
2. Digoxin 0.25 mg qd has been used in patients with IPAH with inconclusive benefits.
3. Oral anticoagulation with warfarin is recommended especially for IPAH, as per a 1984 retrospective study by Fuster et al that showed improved long-term survival. This practice is supported by the high incidence of antemortem clots found in autopsy in the small pulmonary arteries and arterioles of patients with IPAH. Recommended goal for INR is lower at 1.5 to 2.5.

CHRONIC Rx

- Acute vasoreactivity response testing should be done in all patients at the time of right heart catheterization. Epoprostenol, adenosine, or nitric oxide is generally used to assess the response. A positive response is a fall in mean PAP of >10 mm Hg to a value of <40 mm Hg, with increased or unchanged cardiac output. Fewer than 10% of patients are responders in IPAH.
- The positive responders may benefit from treatment with calcium channel blockers (diltiazem, amlodipine, or nifedipine). Verapamil is not recommended because of its negative inotropic effects. All patients should be reassessed in 6 to 8 wk to demonstrate sustained benefit from the calcium channel blocker.
- Calcium channel blockers (CCBs) should not be used empirically to treat PAH in the absence of demonstrated acute vasoreactivity.
- Prostanoids (epoprostenol, treprostinil, iloprost, and beraprost) act as potent vasodilators of pulmonary arteries and inhibitors of platelet aggregation. Ideal for class IV patients.
  1. Epoprostenol: IV formulation with very short half-life. Requires long-term IV access with associated risks of infection and thrombosis. Rapid tachyphylaxis, and therefore dose escalation, is seen. Common side effects include jaw pain, abdominal cramping, and diarrhea. Limited evidence exists for use in secondary PAH patients.
  2. Treprostinil: IV and SQ formulation with longer half-life. Main disadvantage is pain at SQ pump site (no long-term evidence for IV formulation). Treprostinil is also available as a nebulized inhaled solution.
  3. Iloprost: aerosolized formulation with short half-life requiring 6 to 8 treatments/day.
  4. Beraprost: PO formulation. Not approved in the United States.
- Endothelin receptor antagonists (ERAs):
  1. Bosentan (nonselective endothelin A and B receptor blocker): oral pulmonary vasodilator, requires monthly liver function tests, often response delay by weeks. Thus, it is not an ideal starting therapy for WHO class IV patients. It is effective in class II and III patients.
  2. Sitaxsentan and ambrisentan (selective endothelin A receptor blockers).
- Macitentan: Recently FDA approved. Recommended dose is 10 mg/day. Cost of 1 month of treatment is >$6000.
- Phosphodiesterase (PDE-5) inhibitors (sildenafil and tadalafil): act by increasing concentration of nitric oxide. Sildenafil is administered as 20 mg PO tid up to 80 mg PO tid. Tadalafil dose is 40 mg once daily. Highly effective in WHO class II patients, both in IPAH and scleroderma-associated PAH.
- Guanylate cyclase (sGC) stimulators: Riociguat was recently FDA approved.

Caveats to treatment depending on WHO class of symptoms are as follows:

- For treatment-naive PAH patients with WHO functional class II or III symptoms who are not candidates for, or who have failed CCB

therapy, monotherapy should be initiated with a currently approved endothelin receptor antagonist (ERA), phosphodiesterase-5 (PDE5) inhibitor, or the soluble guanylate cyclase stimulator riociguat.
- For treatment-naive PAH patients with WHO functional Class III symptoms who have evidence of rapid progression of their disease, or other markers of a poor clinical prognosis, consideration of initial treatment with a parenteral prostanoid is advised.
- For treatment-naive PAH patients in WHO class IV who are unable or do not desire to manage parenteral prostanoid therapy, treatment with an inhaled prostanoid in combination with an ERA is advised.
- For treatment-naive PAH patients in WHO class IV who are unable or do not desire to manage parenteral prostanoid therapy, we advise treatment with an inhaled prostanoid in combination with an ERA.
- For WHO class III or IV PAH patients with unacceptable clinical status despite established PAH-specific monotherapy, we advise addition of a second class of PAH therapy to improve exercise capacity. Such patients are ideally evaluated at centers with expertise in the evaluation and treatment of complex patients with PAH.
- Combination therapies: considered when there is no improvement or deterioration on monotherapy.
- Bosentan + inhaled iloprost (STEP trial) showed some benefit over monotherapy.
- IV epoprostenol + oral bosentan (BREATH-2 trial) did not show much difference.
- IV epoprostenol + oral sildenafil (PACES trial) showed benefit over monotherapy.
- Lung transplantation and heart-lung transplantation are other options in patients with end-stage class IV disease. Atrial septostomy may be performed as a bridge to transplant. The defect can be closed at the time of transplantation.
- Atrial septostomy is recommended for individuals with a room air SaO_2 >90% who have severe right-sided heart failure (with refractory ascites) despite maximal diuretic therapy, or who have signs of impaired systemic blood flow (such as syncope) from reduced left heart filling.
- Lung transplant recipients with IPAH had survival rates of 73% at 1 yr, 55% at 3 yr, and 45% at 5 yr.

TREATMENT OF SECONDARY PAH:
- Directed toward cause. Some situations merit mention.
- PAH with uncorrected congenital heart disease: Eisenmenger's syndrome. Medical treatment generally ineffective. Heart-lung transplantation required in most patients. PH may persist after surgical correction of congenital heart disease, and pulmonary vasodilators can be effective therapies in this patient population.
- PAH with scleroderma: selective pulmonary vasodilators are effective.
- PAH with lung disease or hypoxia: oxygen therapy, for hypoxemia, CPAP (for OSA), control of primary disease process.
- PAH with chronic thromboembolic disease: may consider pulmonary vasodilators after anticoagulation and pulmonary thromboendarterectomy (or if thromboendarterectomy is not an option) if continued symptoms and elevation in PVR and transpulmonary gradient.
- PAH with HIV: control of viral load by antiretroviral therapy.

FOLLOW-UP

Regular follow-up at 3-mo intervals with clinical assessment: WHO class and 6MWT, 6 to 12 mo objective assessment of RV function by ECG and cardiac catheterization studies.

DISPOSITION

- The 6MWT is predictive of survival in patients with idiopathic PAH. A baseline 6MWT ˂250 m is associated with a 50% risk of death at 2 yr. Drop in O_2 saturation >10% during the test increases mortality risk 2.9 times over a median follow-up of 26 mo.
- A BNP level ≥350 pg/ml at baseline evaluation is associated with a 25% risk of death at 2 yr.
- WHO class II and III patients with PAH have a mean survival of 3.5 yr.
- WHO class IV patients have a mean survival of 6 mo.
- As per the REVEAL (Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management) risk score, poor prognostic signs include:
  1. Signs of RV failure.
  2. WHO functional class III or IV.
  3. Walk a distance of <165 meters in 6-min walk test.
  4. Peak VO2 <15 ml/min/kg in cardiopulmonary testing.
  5. Elevated BNP levels >180 pg/ml.
  6. Presence of pericardial effusion.
  7. TAPSE [tricuspid annular plane systolic excursion] <2 cm on echo of right ventricle.
  8. Right atrial pressure >20 mm Hg or pulmonary vascular resistance of >32 Wood units on right heart catheterization.
  9. Increased heart rate >92 or BP <109 mm Hg.
  10. Male gender >60 years of age.
  11. Concomitant renal dysfunction with estimated glomerular filtration rate ≤30/mL/min/m.
  12. Diffusion capacity of lung for carbon monoxide (DLCO) <33%.

REFERRAL

If the diagnosis of IPAH is suspected, a consultation with a pulmonary specialist is recommended. Secondary causes of PH may require disease-specific consultations.

PEARLS & CONSIDERATIONS

- The exertional dyspnea of PAH is typically described by patients as being relentlessly progressive over several months to a year, often out of proportion to, or in the absence of, underlying heart or lung disease.
- Over 20% of patients in the Registry to Evaluate Early and Long-term PAH Disease Management had symptoms for more than 2 years before PAH was recognized. Consideration of the diagnosis of PAH in the differential diagnosis of unexplained dyspnea, especially in younger individuals, is essential.
- Chest x-ray may reveal evidence of interstitial fluid or fibrosis within the lungs in cases of secondary PH. IPAH is not associated with infiltrates on chest radiograph.

COMMENTS

- RV systolic pressure (RVSP) as estimated by echocardiography is not a good indicator of the presence of PAH because RVSP increases with age and body mass index. Athletically conditioned men also have a higher resting RVSP. Thus, these measurements can be misleading.
- Abrupt development of pulmonary edema during acute vasodilator testing suggests pulmonary venoocclusive disease or pulmonary capillary hemangiomatosis and is a contraindication to long-term vasodilator treatment.
- In advanced PAH, heart rate increase is the main compensatory mechanism and reflects increased sympathetic tone. A higher heart rate at rest is an important marker of prognosis and should be assessed at frequent intervals after initiation of treatment for PAH.

FUTURE DIRECTIONS

- Serotonin receptor modulators, platelet-derived growth factor, and Rho kinase inhibitors.
- Gene analysis to identify genes that determine individual disease susceptibility and help identify targeted therapy.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pulmonary Hypertension (Patient Information)

AUTHOR: **RABIA ARSHAD, M.D.**

EVIDENCE

Abstract[1]

Background:

For almost 30 years, anticoagulation has been recommended for patients with idiopathic pulmonary arterial hypertension (IPAH). Supporting evidence, however, is limited, and it is unclear whether this recommendation is still justified in the modern management era and whether it should be extended to patients with other forms of pulmonary arterial hypertension (PAH).

Methods and Results:

We analyzed data from Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA), an ongoing European pulmonary hypertension registry. Survival rates of patients with IPAH and other forms of PAH were compared by the use of anticoagulation. The sample consisted of 1283 consecutively enrolled patients with newly diagnosed PAH. Anticoagulation was used in 66% of 800 patients with IPAH and in 43% of 483 patients with other forms of PAH. In patients with IPAH, there was a significantly better 3-year survival ($P = 0.006$) in patients on anticoagulation compared with patients who never received anticoagulation, albeit the patients in the anticoagulation group had more severe disease at baseline. The survival difference at 3 years remained statistically significant ($P = 0.017$) in a matched-pair analysis of $n = 336$ IPAH patients. The beneficial effect of anticoagulation on survival of IPAH patients was confirmed by Cox multivariable regression analysis (hazard ratio, 0.79; 95% confidence interval, 0.66 to 0.94). In contrast, the use of anticoagulants was not associated with a survival benefit in patients with other forms of PAH.

Conclusions:

The present data suggest that the use of anticoagulation is associated with a survival benefit in patients with IPAH, supporting current treatment recommendations. The evidence remains inconclusive for other forms of PAH.

Clinical Trial Registration:

URL: http://www.clinicaltrials.gov. Unique identifier: NCT01347216. Ⓐ

Evidence-Based Reference

Olsson KM, Delcroix M, Ghofrani HA et al.: Anticoagulation and survival in pulmonary arterial hypertension: Results from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA), *Circulation* 129:57–65, 2014. Ⓐ

SUGGESTED READINGS

Archer S, Michelakis E: Phosphodiesterase type 5 inhibitors for pulmonary arterial hypertension, *N Engl J Med* 361:1864–1871, 2009.

Barnett CF et al.: Pulmonary hypertension, an increasingly recognized complication of hereditary hemolytic anemias and HIV infection, *JAMA* 299(3):324–331, 2008.

Brown LM et al.: Delay in recognition of pulmonary arterial hypertension: factors identified from the REVEAL Registry, *Chest* 140(1):19, 2011.

Chin K, Rubin J: Pulmonary artery hypertension, *J Am Coll Cardiol* 51:1527, 2008.

Fritz JS et al.: Baseline and follow-up six minute walk distance and BNP predict 2-year mortality in pulmonary arterial hypertension, *Chest* 143(2):315–323, 2013.

Galie N et al.: Guidelines for the diagnosis and treatment of pulmonary hypertension: The task force for the diagnosis and treatment of pulmonary hypertension of the European societies of cardiology and the European respiratory society, endorsed by the international society of heart and lung transplantation, *Eur J Heart* 30:2493–2537, 2009.

Ghofrani HA et al.: Future perspectives for the treatment of pulmonary arterial hypertension, *J Am Coll Cardiol* 54(1 suppl):S108, 2009.

Henkins IR et al.: Relation of heart rate to prognosis in patients with idiopathic pulmonary arterial hypertension, *Am J Cardiol* 103:1451–1456, 2009.

Hoeper MM et al.: Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension, *J Am Coll Cardiol* 54(1 suppl):S85, 2009.

Kieler H et al.: SSRI during pregnancy and risk of persistent pulmonary hypertension in the newborn: population based cohort study from the five Nordic countries, *BMJ* 344:d8012, 2012.

Lee SH, Rubin LJ: Current treatment strategies for pulmonary arterial hypertension, *J Intern Med* 258(3):199, 2005.

McLaughlin VV et al.: Prognosis of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines, *Chest* 126(suppl 1):S78, 2004.

Poms AD: The REVEAL registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension, *Chest* 141(2):354–362, 2012.

Pulido T et al.: Macitentan and morbidity and mortality in pulmonary arterial hypertension, *N Engl J Med* 369:809–818, 2013.

Rubin LJ, Badesch DB: Evaluation and management of the patient with pulmonary arterial hypertension, *Ann Intern Med* 143:282, 2005.

Simonneau G et al.: Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension, *Ann Intern Med* 149:521–530, 2008.

Simonneau G et al.: Updated clinical classification of pulmonary hypertension, *J Am Coll Cardiol* 54(1 Suppl):543–554, 2009.

Stringham R, Shah NR: Pulmonary arterial hypertension: an update on diagnosis and treatment, *Am Fam Physician* 82(4):370–377, 2010.

Taichman DB et al.: Pharmocologic therapy for pulmonary arterial hypertension in adults : CHEST Guidelines and Expert Panel Report, *CHEST* 146(2):449–475, 2014.

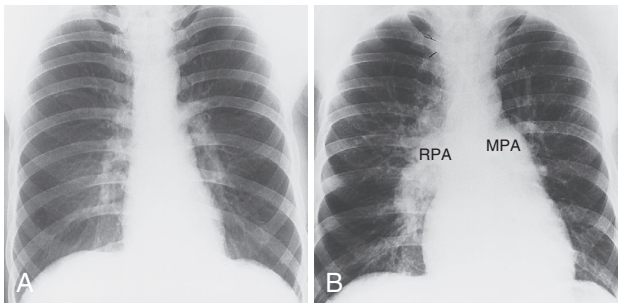

FIGURE EP1-91 Progressive pulmonary arterial hypertension. This patient initially presented with a relatively normal chest radiograph **(A).** However, several years later **(B)** there is increasing heart size and marked dilation of the main pulmonary artery *(MPA)* and right pulmonary artery *(RPA).* Rapid tapering of the arteries as they proceed peripherally is suggestive of pulmonary hypertension and is sometimes referred to as pruning. (From Mettler FA [ed]: *Primary care radiology,* Philadelphia, 2000, Saunders.)

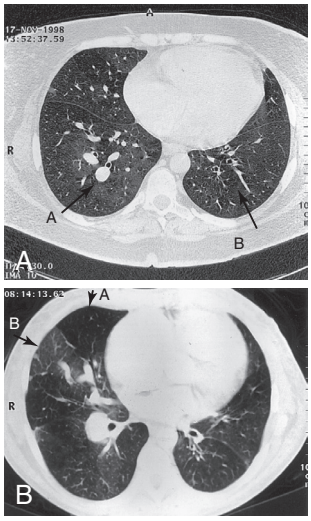

FIGURE EP1-92 Chest computed tomographic scans in a patient with chronic thromboembolic pulmonary hypertension. A, Helical scan with contrast medium enhancement of the pulmonary vasculature shows a marked disparity in vessel size between the involved vessels *(A),* which are enlarged from thrombus, and the uninvolved vessels *(B).* **B,** Non-contrast-enhanced high-resolution scan illustrates a marked mosaic pattern manifest by differences in density of regions of the lung parenchyma reflecting the perfused areas *(B)* and the nonperfused areas *(A),* also consistent with underlying thromboembolic disease. (From Zipes DP et al [eds]: *Braunwauld's heart disease,* ed 7, Philadelphia, 2005, Saunders.)

BASIC INFORMATION

DEFINITION

Acute cardiogenic pulmonary edema (ACPE) is a life-threatening condition that may occur when there is elevated left ventricular (LV) filling pressure related to systolic or diastolic LV dysfunction.

SYNONYMS

Cardiogenic pulmonary edema
Acute cardiogenic pulmonary edema
ACPE
Acute heart failure [AHF] with pulmonary edema

ICD-9CM CODES
428.1 Acute pulmonary edema with heart disease
ICD-10CM CODES
I50.1 Left ventricular failure

EPIDEMIOLOGY & DEMOGRAPHICS

- Leading cause of hospitalization (6.5 million hospital days in the United States each year).
- In-hospital mortality rate is 10% to 20%, particularly when associated with acute MI.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Dyspnea (exertional, paroxysmal nocturnal dyspnea, orthopnea, or at rest).
- Cough and wheezing.
- Diaphoresis, perioral and peripheral cyanosis.
- Pink, frothy sputum.
- Moist, bilateral pulmonary rales are the most common findings and noted in up to 87% of the patients.
- Increased pulmonary second sound, S_3 gallop. S3 gallop is present in up to one-third of the patients and correlates well with the degree of LV systolic dysfunction and BNP levels..
- Hypertension (unless in cardiogenic shock and hypotensive).
- Tachycardia.
- Bulging neck veins with elevated jugular venous pressure and positive hepatojugular reflex.
- Altered mental status or drowsiness due to hypoperfusion.
- Peripheral edema.

ETIOLOGY

Increased pulmonary capillary pressure attributable to:

- Acute myocardial infarction.
- Exacerbation of chronic congestive heart failure due to poor dietary or medical compliance, use of concomitant nonsteroidal anti-inflammatory drugs, calcium antagonists such as verapamil and diltiazem, excessive alcohol consumption, anemia or inadequately treated hypertension.
- Valvular regurgitation (e.g., mitral regurgitation).
- Ventricular septal defect.
- Severe myocardial ischemia.
- Mitral stenosis.
- Other: cardiac tamponade, endocarditis, myocarditis, arrhythmias, cardiomyopathy, hypertensive crisis, endocrine abnormalities such as thyrotoxicosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Noncardiogenic pulmonary edema (see Fig. P1-93).
- Pulmonary embolism.
- Exacerbation of asthma.
- Exacerbation of chronic obstructive pulmonary disease.
- Sarcoidosis.
- Pulmonary fibrosis.
- Lymphangitic carcinomatosis.
- Pulmonary fibrosis.
- Viral pneumonitis and other pulmonary infections.

LABORATORY TESTS

- Arterial blood gases (ABGs): respiratory and metabolic acidosis, decreased Pa_{O_2}, increased Pa_{CO_2}, low pH. (NOTE: The patient may initially show respiratory alkalosis as a result of hyperventilation in attempts to maintain Pa_{O_2}.)
- Measurement of plasma brain natriuretic peptide (elevated). The Breathing Not Properly [BNP] Multinational Study demonstrated that elevated BNP levels are able to distinguish dyspnea caused by heart failure from those caused by pulmonary disease. The BASEL study with nt-pro-BNP demonstrated similar results in patients presenting with acute dyspnea.
- Cardiac biomarkers: troponin I levels to evaluate for possible acute myocardial infarction.
- Basic chemistries: hyponatremia is common in chronic heart failure; evaluate renal function.

IMAGING STUDIES

- ECG:
  1. May have evidence of ischemia, arrhythmias, or LV hypertrophy (often seen in diastolic dysfunction).
- Chest x-ray (Fig. P1-94):
  1. Pulmonary congestion with Kerley B lines; fluffy perihilar infiltrates in the early stages; bilateral interstitial alveolar infiltrates.
  2. Pleural effusions.
  3. Enlarged cardiac silhouette.
- Echocardiogram:
  1. Useful to evaluate valvular abnormalities, diastolic versus systolic dysfunction.
  2. Can help differentiate cardiogenic versus noncardiogenic pulmonary edema.
  3. Can also estimate pulmonary capillary wedge pressure using E/E' ratio, where E = early diastolic transmitral blood flow velocity and E' = early diastolic mitral annular tissue velocity.
- Right heart catheterization (RHC): May be used in selected patients such as those in shock or unclear hemodynamics. RHC in pulmonary edema will show increased pulmonary artery diastolic pressure and pulmonary capillary wedge pressure (PCWP) generally ≥25 mm Hg; low mixed venous oxyhemoglobin saturation. In the ESCAPE trial, use of RHC did not significantly affect in-hospital or 6 mo mortality or days of hospitalization compared with clinical assessment alone and was related to more adverse events.

Signs	Cardiac	Renal	Lung Injury
Heart size	Enlarged	Normal	Normal
Blood flow	Inverted	Balanced	Normal
Kerley lines	Common	Common	Absent
Edema	Basilar	Central: butterfly	Diffuse
Air bronchograms	Not common	Not common	Very common
Pleural effusions	Very common	Common	Not common

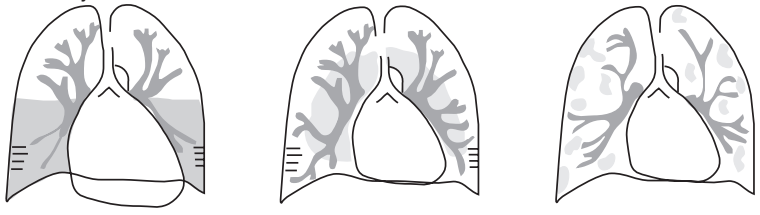

FIGURE P1-93 Types of pulmonary edema. (From Weissleder R et al: *Primer of diagnostic imaging,* St Louis, 2007, Mosby.)

Rx TREATMENT

ACUTE GENERAL Rx

All the following steps can be performed concomitantly:

- 100% oxygen by face mask. Noninvasive ventilation (continuous positive airway pressure [CPAP]) or bilevel noninvasive positive-pressure ventilation [NPPV]) reduces dyspnea and corrects metabolic abnormalities more rapidly than does standard oxygen therapy, and may reduce the need for endotracheal intubation. Both CPAP and bilevel NPPV systems can improve oxygenation and lower carbon dioxide tensions. Monitor ABGs; if marked hypoxemia or severe respiratory acidosis, intubate the patient and place on a mechanical ventilator. Positive pressure ventilation (invasive or noninvasive) decreases preload and afterload and reduces the work of breathing, while positive end expiratory pressure improves oxygenation.
- Pharmacologic preload reducers:
  1. Furosemide: 1 mg/kg IV bolus (typically 40 to 100 mg) to rapidly establish diuresis and decrease venous return through its venodilator action; may double the dose in 30 min if no effect. As per the DOSE trial (NEJM March 3, 2011), among patients with acute decompensated heart failure, there were no significant differences in patient global assessment of symptoms or in the change in renal function when diuretic therapy was administered by bolus as compared with continuous infusion or at a high dose as compared with a low dose
  2. Nitrates: particularly useful if the patient has concomitant chest pain or is hypertensive.
     a. Nitroglycerin: 150 to 600 mcg SL or nitroglycerin spray may be given immediately on arrival and repeated multiple times if the patient remains symptomatic and blood pressure remains stable.
     b. 2% nitroglycerin ointment: 1 to 3 inches out of the tube applied continuously; absorption may be erratic.
     c. IV nitroglycerin: 100 mg in 500 ml of D_5W solution; start at 6 mcg/min (2 ml/hr).
  3. Morphine: 2 to 4 mg IV, SC, or IM; may repeat q15min prn. It decreases venous return, anxiety, and systemic vascular resistance (naloxone should be available at bedside to reverse the effects of morphine if respiratory depression occurs). However, potential adverse effects of morphine administration may outweigh these physiologic benefits, and the role of morphine in treatment of ACPE has recently been questioned.
- Vasodilator therapy:
  1. Angiotensin-converting enzyme (ACE) inhibitors: captopril 25 mg PO tablet can be used for SL administration (placing a drop or two of water on the tablet and placing it under the tongue helps dissolve it); onset of action is <10 min, peak effect can be reached in 30 min. ACE inhibitors can also be given IV (e.g., enalapril at 1 mg IV given q2h prn).
  2. Nitroprusside: useful for afterload reduction in hypertensive patients with decreased cardiac index (CI).
     a. Increases the CI and decreases LV filling pressure.
     b. Nitroprusside use in patients with acute myocardial infarction is controversial because it may increase ischemia by decreasing blood flow to the myocardium.
  3. Nesiritide (recombinant human BNP) causes potent vasodilation in the venous and arterial vessels, including coronary vasculature, produces significant reduction in venous and ventricular filling pressures, and mildly increases cardiac output. However, its high cost and potential safety concerns, including increased mortality, have limited its use.
  4. Seralaxin, an experimental drug, which is a recombinant form of relaxin-2, increases production of NO and binds to endothelial B receptor on endothelial cells causing vasodilation, may have a future role in the treatment of acute heart failure.
- Inotropes:
  1. Dopamine and dobutamine: parenteral inotropic agent of choice in severe cases of cardiogenic pulmonary edema. It can be administered at a dosage of 2.5 to 10 mcg/kg/min IV.
  2. IV phosphodiesterase inhibitors (amrinone, milrinone, and enoximone [available only in Europe]) may be useful in refractory cases. Milrinone may be associated with increased hypotension and new atrial arrhythmias with increased mortality in patients with ischemia HF and should be used with caution.
- Levosimendan is a novel agent that increases myocardial contractility and produces peripheral vasodilation through calcium sensitization. In clinical trials such as REVIVE-II and SURVIVE, levosimendan has been shown to significantly increase cardiac output, reduce PCWP and afterload, and improve dyspnea compared with standard care. It has, however, been associated with increased atrial fibrillation and hypotension.
- Potential future therapies: Istaroxime, natriuretic peptides, adenosine antagonists, vasopressin antagonists, endothelin antagonists.
- Mechanical support:
  1. Intra-arterial balloon pump (IABP): decreases afterload
  2. Ultrafiltration/aquapheresis

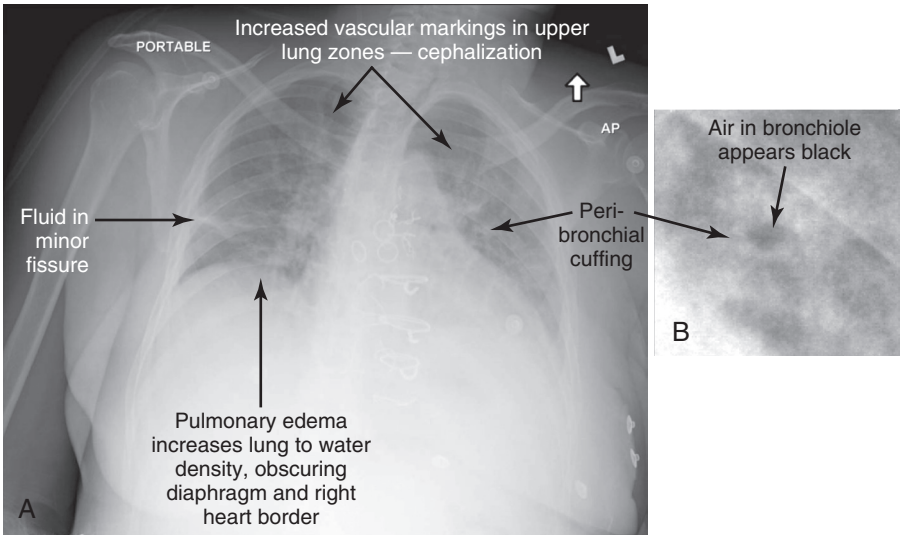

FIGURE P1-94 Pulmonary edema. A, Anterior-posterior chest x-ray. **B,** Close-up from **A.** This 53-year-old female with end-stage renal disease missed dialysis and presented to the emergency department. Her examination demonstrated bilateral rales. Her x-ray shows mild cardiomegaly, bilateral interstitial opacities, and cephalization of the pulmonary vascular markings. The minor fissure appears thickened. These findings are consistent with pulmonary edema. In addition, peribronchial cuffing is present. As discussed elsewhere, this is a nonspecific thickening of the bronchial wall that can occur from edema in the setting of heart failure, asthma, viral illness, or even infections such as pertussis. The thickened wall appears white, whereas the air-filled bronchiole appears black and has a circular short-axis cross section. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

PEARLS & CONSIDERATIONS

COMMENTS

Accumulated evidence still favors the use of noninvasive ventilation, especially CPAP, in patients with ACPE, especially as this therapy reduces dyspnea and helps correct metabolic abnormalities more rapidly than standard oxygen therapy. The role of morphine in the treatment of ACPE has come into question. Also refer to section on Heart Failure.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **MARC PAUL WAASE, M.D., Ph.D**

EVIDENCE

Abstract[1]

Purpose:

Continuous positive airway pressure (CPAP) is a useful treatment for patients with acute cardiogenic pulmonary edema (CPE). However, its usefulness in the out-of-hospital setting has been poorly investigated and only by small and single-centre studies. We designed a multicenter randomised study to assess the benefit of CPAP initiated out of hospital.

Methods:

A total of 207 patients with CPE were randomly allocated by emergency mobile medical units to receive either standard treatment alone or standard treatment plus CPAP. CPAP was maintained after admission to the intensive care unit (ICU). Inclusion criteria were orthopnoea, respiratory rate >25 breaths/min, pulse oximetry <90% in room air and diffuse crackles. The primary end point was assessed during the first 48 h and combined: death, presence of intubation criteria, persistence of either all inclusion criteria or circulatory failure at the second hour or their reappearance before 48 h. Absence of all criteria defined successful treatment.

Results:

CPAP was used for 60 min [40, 65] (median [Q1, Q3]) in the pre-hospital setting and 120 min [60, 242] in ICU and was well tolerated in all patients. Treatment was successful in 79% of patients in the CPAP group and 63% in the control group ($p = 0.01$), especially for persistence of inclusion criteria after 2 h (12 versus 26%) and for intubation criteria (4 versus 14%). CPAP was beneficial irrespective of the initial $PaCO_2$ or left ventricular ejection fraction.

Conclusion:

Immediate use of CPAP in out-of-hospital treatment of CPE and until CPE resolves after admission significantly improves early outcome compared with medical treatment alone. Ⓐ

Evidence-Based Reference

Ducros L: CPAP for acute cardiogenic pulmonary oedema from out-of-hospital to cardiac intensive care unit: a randomised multicentre study, *Intensive Care Med* 37:1501–1509, 2011. Ⓐ

SUGGESTED READINGS

Acute Decompensated Heart Failure National Registry (ADHERE): *Am Coll Cardiol* 46(1):57–64, 2005. http://dx.doi.org/10.1016/j.jacc.2005.03.051.

Ennezat PV et al.: Recent therapeutic trials on fluid removal and vasodilation in acute heart failure, *Eur Heart J Cardiovasc Care Nov*, 2014.

Gray A et al.: Non-invasive ventilation in acute cardiogenic pulmonary edema, *N Engl J Med* 359:142, 2008.

Ware LB, Matthay MA: Acute pulmonary edema, *N Engl J Med* 353:2788, 2005.

Weng CL et al.: Meta-analysis: noninvasive ventilation in acute cardiogenic pulmonary edema, *Ann Intern Med* 152:590–600, 2010.

BASIC INFORMATION

DEFINITION

Pulmonary embolism (PE) refers to the lodging of a thrombus or other embolic material from a distant site in the pulmonary circulation. A classification of acute pulmonary embolism is described in Table P1-44.

SYNONYMS

Pulmonary thromboembolism
PE

ICD-9CM CODES
415.1 Pulmonary embolism and infarction
ICD-10CM CODES
I26 Pulmonary embolism
I26.0 Pulmonary embolism with acute cor pulmonale

EPIDEMIOLOGY & DEMOGRAPHICS

- 650,000 cases of PE occur in the United States each year (increased incidence in women and with advanced age); annually, as many as 300,000 people in the United States die from acute PE, and the diagnosis is often not made until after autopsy. The incidence of PE is increasing with the increasing use of spiral CT scans, with a lower severity of illness and lower mortality, suggesting the increase is caused by earlier diagnosis.
- More than 90% of pulmonary emboli originate in the deep venous system of the lower extremities.
- Pulmonary thromboembolism is associated with >200,000 hospitalizations and nearly 30,000 deaths each yr in the United States.
- 8% to 10% of victims of PE die within the first hr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most common symptom: dyspnea (82% to 85%).
- Tachypnea (30% to 60%).
- Chest pain: may be nonpleuritic or pleuritic (infarction) (40% to 49%).
- Syncope (massive PE) (10% to 14%).
- Fever, diaphoresis, apprehension.
- Hemoptysis (2%).
- Evidence of DVT may be present (e.g., swelling and tenderness of extremities).
- Cardiac examination may reveal: tachycardia (23%), increased pulmonic component of S2, murmur of tricuspid insufficiency, right ventricular heave, right-sided S3.
- Pulmonary examination: may demonstrate rales, localized wheezing, friction rub.

ETIOLOGY

- Thrombus, fat, or other foreign material
- Risk factors for PE:
  1. Prolonged immobilization, reduced mobility.
  2. Postoperative state, major surgery.
  3. Trauma to lower extremities, immobilizer, or cast.
  4. Estrogen-containing birth control pills, hormone replacement therapy.
  5. Prior history of DVT or PE.
  6. CHF.
  7. Pregnancy and early puerperium.
  8. Visceral cancer (lung, pancreas, alimentary and genitourinary tracts).
  9. Spinal cord injury.
  10. Advanced age.
  11. Obesity.
  12. Hematologic disease (e.g., factor V Leiden mutation, antithrombin III deficiency, protein C deficiency, protein S deficiency, lupus anticoagulant, polycythemia vera, dysfibrinogenemia, paroxysmal nocturnal hemoglobinuria, acquired protein C resistance without factor V Leiden, G20210A prothrombin mutation).
  13. COPD, diabetes mellitus, acute medical illness.
  14. Prolonged air travel.
  15. Central venous catheterization.
  16. Autoimmune diseases (SLE, IBD, RA).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Myocardial infarction.
- Pericarditis.
- Pneumonia.
- Pneumothorax.
- Chest wall pain.
- GI abnormalities (e.g., peptic ulcer, esophageal rupture, gastriti.
- CHF
- Pleuritis.
- Anxiety disorder with hyperventilation.
- Pericardial tamponade.
- Dissection of aorta.
- Asthma.

WORKUP

- Clinical assessment alone is insufficient to diagnose or rule out PE. It is also important to remember that no single noninvasive test has both high sensitivity and high specificity for PE. Consequently, in addition to clinical assessment, most patients require an imaging test to diagnose PE. Figs. P1-95 and P1-96 are diagnostic algorithms for suspected PE. The Wells prediction rules can be used to estimate the probability of PE. Each of the following findings is assigned a score:
  1. Clinical signs/symptoms of deep vein thrombosis (score = 3.0).
  2. No alternate diagnosis as likely or more likely than PE (score = 3.0).
  3. Heart rate >100/min (score = 1.5).
  4. Immobilization or surgery in last 4 weeks (score = 1.5).
  5. Previous history of DVT or PE (score = 1.5).
  6. Hemoptysis (score = 1.0).
  7. Cancer actively treated within last 6 months (score = 1.0).
- The probability of PE is high if total score is >6, moderate if 2-6; and low if <2.
- The modified Wells score divides PE as likely (>4 points) or unlikely (<4 points).
- A low clinical probability of PE in association with a normal plasma D-dimer measurement essentially rules out PE, and further imaging is not needed. If clinical probability is intermediate or high, and/or the D-dimer measurement is abnormal, further workup with imaging is needed.
- Spiral chest CT with contrast (see Fig. P1-97) is an excellent diagnostic modality (83% sensitivity and 96% specificity).
- V/Q scan is reserved for patients with clinically significant contrast allergies or renal insufficiency.
- Pulmonary angiogram (gold standard) can confirm the diagnosis, but is rarely used.
- Serial compressive duplex ultrasonography of lower extremities can be used in patients with "low-probability" lung scan and high clinical suspicion (see "Imaging Studies"). It is useful if positive; negative results do not exclude PE.

LABORATORY TESTS

- ABGs may reveal hypoxemia and respiratory alkalosis (decreased Pa_{O_2} and Pa_{CO_2} and increased pH); normal results do not rule out PE.
- Alveolar-arteriolar (A-a) oxygen gradient, a measure of the difference in oxygen concentration between alveoli and arterial blood, may be elevated. However, a normal A-a gradient does not rule out PE.
- Plasma D-dimer measurement: D-dimer assays by ELISA detect the presence of plasmin-mediated degradation products of fibrin that contain cross-linked D fragments

TABLE P1-44 Classification of Acute Pulmonary Embolism

Classification	Presentation	Therapy
Massive PE	Systolic blood pressure <90 mm Hg or poor tissue perfusion or multisystem organ failure plus right or left main pulmonary artery thrombus or "high clot burden"	Thrombolysis or embolectomy or inferior vena caval filter plus anticoagulation
Submassive PE	Hemodynamically stable but moderate or severe right ventricular dysfunction or enlargement	Addition of thrombolysis, embolectomy, or filter remains controversial
Small to moderate PE	Normal hemodynamics and normal right ventricular size and function	Anticoagulation

From Bonow RO et al: *Heart disease,* ed 9, Philadelphia, 2012 ,Saunders.

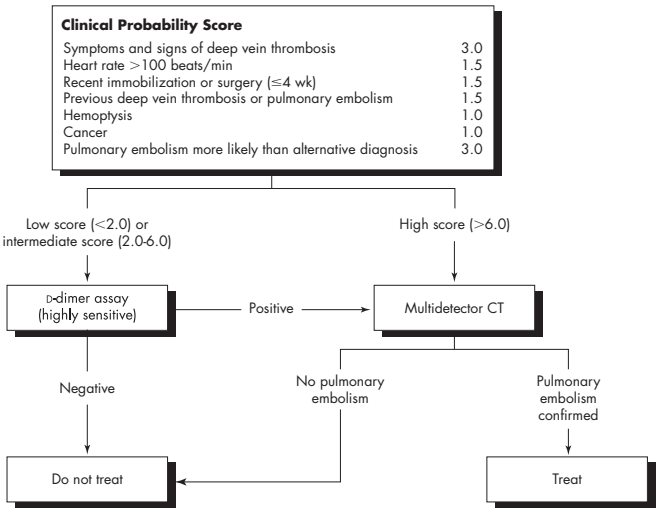

FIGURE P1-95 Diagnostic algorithm for suspected pulmonary embolism in a patient without hypotension or shock. This assessment of clinical probability is based on the Wells score (which has a range of 0 to 12.5, with higher scores indicating higher clinical probability). The revised Geneva score may be used as an alternative. If a moderately sensitive latex-derived D-dimer assay is used instead of the highly sensitive enzyme-linked immunosorbent D-dimer assay, pulmonary embolism can be ruled out only in patients with a low clinical probability. Alternatively, the Wells score can be dichotomized, classifying pulmonary embolism as unlikely (≤4.0) or likely (>4.0). For patients in whom pulmonary embolism is considered unlikely, either a highly sensitive or a moderately sensitive D-dimer assay can be used to rule out the diagnosis without need for further testing. If multidetector CT pulmonary angiography, with or without venography, is negative in a patient with a high clinical probability, the possibility of a false negative result should be considered and further testing performed to rule outpulmonary embolism. Options include serial venous ultrasonography, ventilation-perfusion lung scanning, and pulmonary angiography. If a multidetector CT scan shows only subsegmental defects in a patient with a low clinical probability, the possibility of a false positive result should be considered, and further testing (e.g., venous ultrasonography) should be performed to confirm the diagnosis. This may also apply to patients with an intermediate clinical probability, although the need for further tests is less well established for these patients. (From Konstantinides S: Acute pulmonary embolism, *N Engl J Med* 359:2804-2813, 2008.)

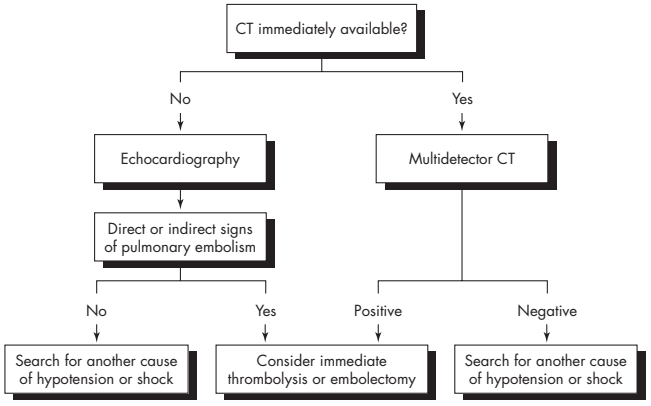

FIGURE P1-96 Emergency diagnostic workup for suspected pulmonary embolism in a patient with hypotension or shock. A direct sign of pulmonary embolism on a transthoracic or transesophageal echocardiogram is the presence of thrombi in the right atrium, right ventricle, or pulmonary artery. Thrombi may protrude into the left atrium through a patent foramen ovale. Indirect signs include right ventricular dysfunction (identified by the finding of dilation, free-wall hypokinesia, or paradoxical septal wall motion); a systolic pressure gradient between the right ventricle and the right atrium of more than 30 mm Hg; and a pulmonary arterial flow acceleration time of less than 80 msec. When direct or indirect signs of pulmonary embolism are present, immediate treatment (without further diagnostic tests) is justified, particularly if CT angiography is still not available and arterial hypotension or shock persists. Adapted from the 2008 Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology. Since validation of diagnostic algorithms in prospective trials excluded hemodynamically unstable patients, these recommendations reflect expert opinion. (From Konstantinides S: Acute pulmonary embolism, *N Engl J Med* 359:2804-2813, 2008.)

in the whole blood or plasma. A normal plasma D-dimer level is useful to exclude PE in patients with a low pretest probability of PE. However, it cannot be used to "rule in" the diagnosis because it increases with many other disorders (e.g., metastatic cancer, trauma, sepsis, postoperative state). Plasma D-dimer can also be used in conjunction with lower-extremity compression ultrasonography in patients with indeterminate V/Q and spiral CT scans. Absence of DVT and presence of a normal D-dimer level in these settings generally rules out clinically significant PE.

- Elevated cardiac troponin levels also occur in patients with PE because of right ventricular dilation and myocardial injury; therefore, PE should be considered in the differential diagnosis of all patients presenting with chest pain or dyspnea and elevated cardiac troponin levels.
- Elevated serum BNP levels in patients with acute PE may reflect RV overload.
- ECG is abnormal in 85% of patients with acute PE. Frequent abnormalities are sinus tachycardia; nonspecific ST-segment or T-wave changes; S-1, Q-3, T-3 pattern (10% of patients); S-1, S-2, S-3 pattern; T-wave inversion in V_1 to V_6; acute RBBB; new-onset atrial fibrillation; ST segment depression in lead II; right ventricular strain. A right ventricular strain pattern on ECG in patients with PE and normal blood pressure is associated with adverse short-term outcome and adds incremental prognostic value to echocardiographic evidence of right ventricular function.

IMAGING STUDIES

- Chest x-ray may be normal; suggestive findings include elevated diaphragm, pleural effusion, dilation of pulmonary artery, infiltrate or consolidation, abrupt vessel cut-off, oligemia distal to the PE (**Westermark sign**), or atelectasis. A wedge-shaped consolidation in the middle and lower lobes is suggestive of a pulmonary infarction and is known as "**Hampton's hump.**"
- CT angiography is an accurate, noninvasive tool in the diagnosis of PE at the main, lobar, and segmental pulmonary artery levels. A major advantage of CT angiography over standard pulmonary angiography is its ability to diagnose intrathoracic disease other than PE that may account for the patient's clinical picture. It is also less invasive, less costly, and more widely available. Its major shortcoming is its poor sensitivity for subsegmental emboli.
- V/Q Lung scan (in patient with normal chest x-ray examination): This test must be interpreted within the pretest probability of having a PE.
  1. A normal lung scan rules out PE.
  2. A ventilation-perfusion mismatch is suggestive of PE, and a lung scan interpretation of high probability is confirmatory (Fig. EP1-98).
  3. If the clinical suspicion of PE is high and the lung scan is interpreted as low probability, moderate probability, or indeterminate,

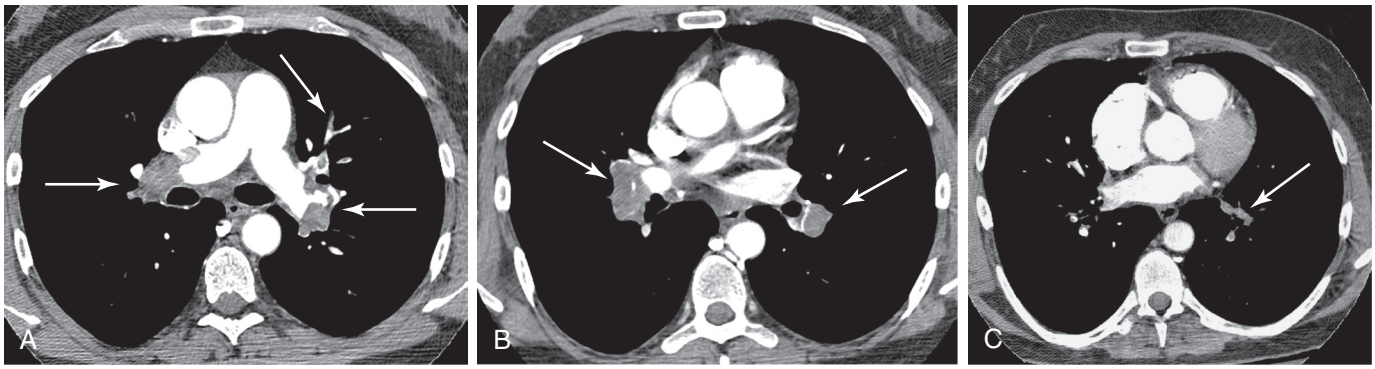

FIGURE P1-97 A 46-year-old woman presented with acute shortness of breath and hypoxia. Chest radiograph was normal. **A,** Chest computed tomography shows a low-attenuation filling defect in left and right main pulmonary arteries *(arrows)* and left upper lobe segmental artery *(arrow),* representing massive pulmonary embolism. Emboli extend to left and right interlobar arteries (*arrows),* as well as a left lower lobe segmental artery *(arrow),* seen in **B** and **C,** respectively. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

a pulmonary arteriogram is diagnostic; a positive arteriogram confirms diagnosis; a positive compressive duplex ultrasonography for DVT obviates the need for an arteriogram, because treatment with IV anticoagulants is indicated in these patients; the overall sensitivity of compressive ultrasonography for DVT in patients with PE is 29%, specificity 97%; adding ultrasonography in patients with a nondiagnostic lung scan prevents 9% of angiographies; however, this improvement in efficacy is achieved at the cost of unnecessary anticoagulant therapy in 26% of patients who have false-positive ultrasonography results.

- Angiography: pulmonary angiography is the historic gold standard; however, it is invasive, expensive, and not readily available in some clinical settings. False-positive pulmonary angiograms may result from mediastinal disorders such as radiation fibrosis and tumors.
- Gadolinium-enhanced magnetic resonance angiography (MRA/MRV) of the pulmonary arteries has a moderate sensitivity and high specificity for the diagnosis of PE at experienced centers, but obtaining acceptable images is technically challenging and should only be performed if other imaging tests are contraindicated.
- Echocardiography: useful for identifying patients with PE who may have poor prognosis. Moderate or severe hypokinesis, persistent pulmonary hypertension, patent foramen ovale, and free-floating right heart thrombus are markers for increased risk of death or recurrent thrombosis. Such patients should be considered for thrombolysis or embolectomy.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Correction of risk factors (see "Etiology") to prevent future PE.

ACUTE GENERAL Rx

Patients with acute PE should be initially stratified according to risk (Table P1-44) so that higher-risk therapies (e.g., thrombolysis, embolectomy) are offered to patients with the greatest chance of benefit.

- Anticoagulants are recommended as initial therapy in patients with small to moderate PE.
- Anticoagulant drugs for initial treatment of PE are described in Table EP1-45. Unfractionated heparin (UFH) (IV or subcutaneous), subcutaneous low-molecular-weight heparin (LMWH), or subcutaneous fondaparinux is recommended for the initial treatment for at least 5 days. If IV unfractionated heparin is used, a bolus dose (80 U/kg) followed by a weight-based (18 U/kg/hr) continuous infusion to achieve therapeutic anti-factor Xa (or aPTT) levels should be used. LMWH and fondaparinux should be avoided in patients with severe renal failure.
- Oral rivaroxaban, a factor Xa inhibitor (15 mg bid for 3 wk, then 20 mg/d), has been studied as a treatment for DVT and for PE, without prior parenteral therapy. For both DVT and PE, treatment with rivaroxaban alone was noninferior to treatment with LMWH followed by a vitamin K antagonist with regard to the endpoint of recurrent venous thromboembolism. Use of rivaroxaban should be avoided in patients with severe renal failure.
- Dabigatran, a direct thrombin inhibitor (150 mg twice a day), has been recently approved for the treatment of PE from data assembled from the RECOVER, REMEDYSM, and RESONATE trials. Dabigatran met its noninferiority efficacy endpoints with improved safety margins (bleeding) compared to warfarin. All trial recipients received heparin bridge to start their anticoagulation.
- Apixaban, a Factor Xa inhibitor (10 mg twice a day for a week, followed by 5 mg twice a day), was recently approved for the treatment of acute PE based on the data in the AMPLIFY and AMPLIFY-EXT trials, in which apixaban met its noninferiority mark in terms of efficacy and improved safety compared to warfarin.
- Thrombolytic agents (urokinase, tPA, streptokinase): provide rapid resolution of clots with increased risk of major bleeding (up to 3% incidence of intracranial hemorrhage); thrombolytic agent are the treatment of choice in patients with massive PE who are hemodynamically unstable and with no contraindication to their use. The use of thrombolytic agent in the treatment of hemodynamically stable patients with acute submassive PE remains controversial, although there is some evidence that half dose tPA has some efficacy. Use of the thrombolytic agents alteplase (100 mg IV over 2-hr period) in normotensive patients with moderate or severe right ventricular dysfunction identified by ECG has been advocated by some physicians. Use of alteplase in conjunction with heparin has been shown to improve the clinical course of stable patients who have acute submassive PE without internal bleeding, mainly by reducing need for subsequent thrombolytic use. Additional studies are needed to confirm these findings before recommending routine use of this therapeutic approach. The Pulmonary Embolism Thrombolysis (PEITHO) trial revealed that in patients with intermediate risk of pulmonary embolism, fibrinolytic therapy prevented hemodynamic compensation but increased the risk of major hemorrhage and stroke.
- Long-term treatment for PE not associated with malignancy can be carried out with warfarin therapy or rivaroxaban.
- For PE associated with malignancy, LMWH is recommended for long-term therapy.
- For PE occurring in the setting of a reversible risk factor, anticoagulation should be continued for 3 mo. For patients with an unprovoked PE, longer-term anticoagulation should be considered, and indefinite long-term anticoagulation should be used in patients with recurrent unprovoked PE. Important factors to consider in the decision to extend anticoagulation include the patient's risk of bleeding and patient preferences after an informed discussion of risks and benefits.
- If thrombolytics and anticoagulants are contraindicated (e.g., GI bleeding, recent CNS surgery, recent trauma) or if the patient continues to have recurrent PE despite anticoagulation therapy, vena caval interruption is indicated by transvenous placement of an inferior vena caval filter.

- IVC filters are also strongly associated with reduced in-hospital fatality rate in stable patients who received thrombolytic therapy. It seems prudent to consider a vena cava filter in patients with PE who are receiving thrombolytic therapy.
- Acute pulmonary artery surgical embolectomy or catheter-based thrombectomy may be indicated in a patient with massive PE who cannot receive thrombolytic therapy. Pulmonary embolectomy is also recommended for those whose critical status does not allow sufficient time for thrombolytic therapy to be effective and for those who remain unstable after receiving fibrinolysis.

CHRONIC Rx

- Elimination of risk factors (see "Etiology").
- Patients with unprovoked DVT/PE have a high rate of recurrent VTE. Longer durations of chronic anticoagulation after unprovoked DVT/PE result in lower rates of recurrent DVT/PE while on anticoagulation, but benefits are lost once anticoagulation is halted. The use of indefinite anticoagulation in selected individuals with apparently unprovoked DVT/PE must be weighed against ongoing bleeding risk and other factors.
- A recent study demonstrated that aspirin (100 mg daily) is superior to placebo in preventing recurrence of venous thromboembolism in patients with a first-ever unprovoked venous thromboembolism (VTE) who had already completed 6 to 18 months of oral anticoagulation. This suggests that aspirin could be offered as an alternative to oral anticoagulants for prevention of recurrent VTE in patients who refuse to or cannot continue oral anticoagulant therapy but who have a high risk of recurrent VTE.
- Trials involving extending the treatment time of the novel oral anticoagulants (rivaroxaban, dabigatran, and apixaban) all showed superior efficacy and reduced morbidity compared to placebo as well as similar rate of major bleeding (though increased all bleeding).

DISPOSITION

- Mortality can be reduced to <10% by rapid and effective treatment. Stratification of risk of death associated with PE and severity-adjusted treatment is described in Table EP1-46.
- Mortality from recurrent pulmonary emboli is 8% with effective treatment and >30% in patients with untreated pulmonary emboli.

PEARLS & CONSIDERATIONS

COMMENTS

- Use of clinical prediction rules in association with D-dimer testing may reduce the use of unnecessary imaging in patients in whom PE is unlikely.
- Massive PE (PE associated with hypotension, shock, or circulatory arrest) remains the clearest situation in which thrombolytics should be employed. Submassive PE (PE associated with right ventricular dysfunction or injury but without hypotension) remains an area of controversy with regards to thrombolytic use.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pulmonary Embolism (PE) (Patient Information)
Deep Vein Thrombosis (Related Key Topic)
Hypercoagulable State (Related Key Topic)

AUTHOR: **BARRY FINE, M.D., Ph.D**

EVIDENCE

Abstract[1]

Background:
In haemodynamically stable patients with acute symptomatic pulmonary embolism (PE), studies have not evaluated the usefulness of combining the measurement of cardiac troponin, transthoracic echocardiogram (TTE), and lower extremity complete compression ultrasound (CCUS) testing for predicting the risk of PE-related death.

Methods:
The study assessed the ability of three diagnostic tests (cardiac troponin I (cTnI), echocardiogram, and CCUS) to prognosticate the primary outcome of PE-related mortality during 30 days of follow-up after a diagnosis of PE by objective testing.

Results:
Of 591 normotensive patients diagnosed with PE, the primary outcome occurred in 37 patients (6.3%; 95% CI 4.3% to 8.2%). Patients with right ventricular dysfunction (RVD) by TTE and concomitant deep vein thrombosis (DVT) by CCUS had a PE-related mortality of 19.6%, compared with 17.1% of patients with elevated cTnI and concomitant DVT and 15.2% of patients with elevated cTnI and RVD. The use of any two-test strategy had a higher specificity and positive predictive value compared with the use of any test by itself. A combined three-test strategy did not further improve prognostication. For a subgroup analysis of high-risk patients, according to the pulmonary embolism severity index (classes IV and V), positive predictive values of the two-test strategies for PE-related mortality were 25.0%, 24.4% and 20.7%, respectively.

Conclusions:
In haemodynamically stable patients with acute symptomatic PE, a combination of echocardiography (or troponin testing) and CCUS improved prognostication compared with the use of any test by itself for the identification of those at high risk of PE-related death. Ⓐ

Abstract[2]

Background:
The most effective agent for prophylaxis against venous thromboembolic disease after total joint arthroplasty (TJA) remains unknown. The paucity of literature comparing different methods of pulmonary embolism (PE) prophylaxis and fear of litigation make it difficult for surgeons to abandon the use of aggressive chemical prophylaxis.

Questions/Purposes:
We compared the (1) overall frequency of symptomatic PE, (2) risk of symptomatic PE after propensity matching that adjusted for potentially confounding variables, and (3) other complications and length of stay before and after propensity matching in patients undergoing TJA at our institution who received either aspirin or warfarin prophylaxis.

Methods:
A total of 28,923 patients underwent TJA between January 2000 and June 2012 at our institution, had either aspirin (325 mg twice daily; 2800 patients) or warfarin prophylaxis (26,123 patients), and were registered in our institutional electronic database. The incidence of symptomatic PE, symptomatic deep vein thrombosis (DVT), hematoma formation, infection, wound complications, and mortality up to 90 days postoperatively was collected from the database. We performed multivariate analysis and 3:1 and 5:1 propensity score matching for comorbid and demographic variables.

Results:
The overall symptomatic PE rate was lower ($p < 0.001$) in patients receiving aspirin (0.14%) than in the patients receiving warfarin (1.07%). This difference did not change after matching. The aspirin group also had significantly fewer symptomatic DVTs and wound-related problems and shorter hospital stays, which did not change after matching.

Conclusions:
After publication of the American Academy of Orthopaedic Surgeons' guidelines, some surgeons have utilized aspirin as thromboprophylaxis after TJA. Based on our findings from a large institutional database, aspirin offers suitable prophylaxis against symptomatic PE in selected patients. Ⓐ

Evidence-Based References

Jiménez D et al.: Combinations of prognostic tools for identification of high-risk normotensive patients with acute symptomatic pulmonary embolism, *Thorax* 66:75–81, 2011. Ⓐ

Raphael IJ, Tischler EH, Huang R et al.: Aspirin: An alternative for pulmonary embolism prophylaxis after arthroplasty?, *Clin Orthop Relat Res* 472:482–488, 2014. Ⓑ

SUGGESTED READINGS

Agnelli G, Becattini C: Acute pulmonary embolism, *N Engl J Med* 363:266–274, 2010.

Aujesky D et al.: Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomized, non-inferiority trial, *Lancet* 378:41, 2011.

Chagnon I et al.: Comparison of two clinical prediction rules and implicit assessment among patients with suspected pulmonary embolism, *Am J Med* 113(4):269–275, 2002.

DeMonaco NA et al.: Pulmonary embolism incidence is increasing with use of spiral computed tomography, *Am J Med* 121:611–617, 2008.

Douketis JD et al.: The risk for fatal pulmonary embolism after discontinuing anticoagulant therapy for venous thromboembolism, *N Engl J Med* 147:766–774, 2008.

Konstantinides S: Acute pulmonary embolism, *N Engl J Med* 359:2806, 2008.

Meyer G et al.: Fibrinolysis for patients with intermediate-risk pulmonary embolism, *N Engl J Med* 370:1402–1411, 2014.

Qaseem A et al.: Current diagnosis of venous thromboembolism in primary care: a clinical practice guideline from the American Academy of Family Physicians and the American College of Physicians, *Ann Intern Med* 146:454, 2007.

Sareyyupoglu B et al.: A more aggressive approach to emergency embolectomy for acute pulmonary embolism, *Mayo Clin Proc* 85(9):785–790, 2010.

Sharifi M et al.: Moderate pulmonary embolism treated with thrombolytics (MOPETT), *Am J Cardiol* 111(2):273, 2013.

Spurzem JR, Geraci SA: Outpatient management of patients following pulmonary embolism, *Am J Med* 123:987–990, 2010.

Stein PD et al.: Challenges in the diagnosis of acute pulmonary embolism, *Am J Med* 121:565–571, 2008.

Tapson VF: Acute pulmononary embolism, *N Engl J Med* 358:1037–1052, 2008.

The Van Gogh Investigators: Idraparinux versus standard therapy for venous thromboembolic disease, *N Engl J Med* 357:1094, 2007.

Torbicki A et al.: Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology, *Eur Heart J* 29(18):2276–2315, 2008.

Vanni S et al.: Prognostic value of ECG among patients with acute pulmonary embolism and normal blood pressure, *Am J Med* 122:257–264, 2009.

Zoller B et al.: Risk of pulmonary embolism in patients with autoimmune disorders: a nationwide follow-up study from Sweden, *Lancet* 379:244–249, 2012.

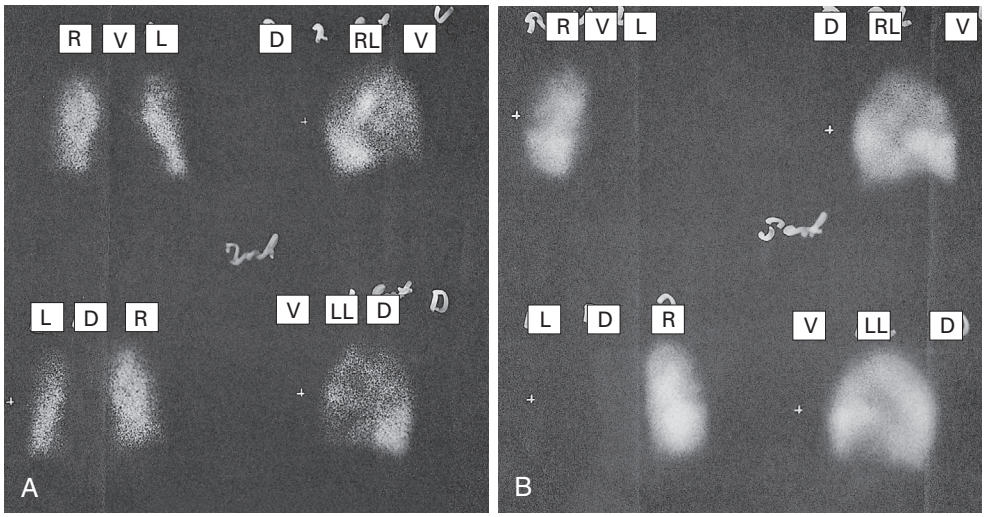

FIGURE EP1-98 Ventilation-perfusion lung scan in massive pulmonary embolism. A, A normal pattern on the ventilation scan. **B,** The complete disappearance of the entire left lung from the perfusion scan indicates proximal occlusion of the left pulmonary artery. *D,* Dorsal; *L,* left; *LL,* left lobe; *R,* right; *RL,* right lobe; *V,* ventral. (From Crawford MH et al [eds]: *Cardiology*, ed 2, St Louis, 2004, Mosby.)

TABLE EP1-45 Anticoagulant Drugs for Initial Treatment of Pulmonary Embolism*

Drug	Dose	Remarks
Unfractionated heparin (intravenous infusion)†	80 IU/kg of body weight as an intravenous bolus, followed by continuous infusion at the rate of 18 IU/kg/hr.	Adjust infusion rate to maintain aPTT between 1.5 and 2.5 times control, corresponding to therapeutic heparin levels (0.3 to 0.7 IU/ml by factor Xa inhibition)‡; monitor platelet count at baseline and every other day from day 4 to day 14 or until heparin is stopped; investigate for heparin-induced thrombocytopenia if platelet count falls by ≥50% or a thrombotic event occurs.
Low-molecular-weight heparins (subcutaneous injection)§		Low-molecular-weight heparins have not been tested in patients with arterial hypotension or shock and thus are not recommended for such patients; monitoring of anti–factor Xa levels may be helpful in patients at increased risk for bleeding, particularly those with moderate or severe renal impairment; the need for monitoring anti–factor Xa levels in pregnant women remains controversial; monitor platelet count at baseline and every 2-4 days from day 4 to day 14 or until heparin is stopped.¶
Enoxaparin	1.0 mg/kg every 12 hr or 1.5 mg/kg once daily‖	If creatinine clearance is <30 ml/min, reduce enoxaparin dose to 1 mg/kg once daily; consider unfractionated heparin infusion as an alternative.
Tinzaparin	175 U/kg once daily	
Fondaparinux§	5 mg (body weight, <50 kg); 7.5 mg (body weight, 50-100 kg); or 10 mg (body weight, >100 kg), administered once daily.	This drug is contraindicated in patients with severe renal impairment (creatinine clearance, <30 ml/min); no routine platelet monitoring is necessary.

*The abbreviation aPTT denotes activated partial thromboplastin time.
†Unfractionated heparin is the preferred treatment in patients with severe renal dysfunction (creatinine clearance, <30 ml per minute), since it is not eliminated by the kidneys, and in patients with an increased risk of bleeding (i.e., those with congenital or acquired bleeding diathesis, active ulcerative or angiodysplastic gastrointestinal disease, recent hemorrhagic stroke, recent brain, spinal, or ophthalmologic surgery, diabetic retinopathy, or bacterial endocarditis), owing to its short half-life and reversible anticoagulant effects.
‡It is recommended that the treatment dose be adjusted on the basis of standardized nomograms such as that proposed by Raschke et al.
§Tinzaparin and fondaparinux are explicitly approved for the treatment of acute pulmonary embolism. Enoxaparin is approved for the treatment of deep vein thrombosis with or without pulmonary embolism.
¶This recommendation applies to postoperative patients and to medical or obstetrical patients who have received unfractionated heparin within the past 100 days. For medical or obstetrical patients who have received only low-molecular-weight heparin, some authorities recommend no routine monitoring of platelet counts.
‖Once-daily injection of enoxaparin at a dose of 1.5 mg per kilogram is approved for inpatient treatment of pulmonary embolism in the United States and in some, but not all, European countries.
From Konstantinides S: Acute pulmonary embolism, *N Engl J Med* 359:2804-2813, 2008.

TABLE EP1-46 Stratification of Risk of Death Associated with Pulmonary Embolism and Severity-Adjusted Treatment*

	RISK FACTOR			
Early Risk of Death	**Shock or Hypotension (on Clinical Examination)**	**Right Ventricular Dysfunction (on Echocardiography or Multidetector CT)**	**Myocardial Injury (on Cardiac Troponin Testing)**	**Recommended Treatment**
High	Present	Present†	NA‡	Unfractionated heparin plus thrombolysis or embolectomy
Intermediate§	Absent	Present	Present	Low-molecular-weight heparin or fondaparinux; as a rule, no early thrombolysis; monitor clinical status and right ventricular function
Low	Absent	Absent	Absent	Low-molecular-weight heparin or fondaparinux; consider outpatient treatment

*Adapted with modifications from the 2008 Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology. NA denotes not applicable.
†If RV function is normal on echocardiography, or if a CT scan shows no RV dilatation in a patient with hemodynamic compromise and clinically suspected pulmonary embolism, an alternative diagnosis should be sought.
‡Troponin test results do not influence risk assessment or treatment in hemodynamically compromised patients with acute pulmonary embolism.
§Although it has been suggested that normotensive patients with both RV dysfunction and myocardial injury have a higher risk of death than those with only one of these risk factors, there is currently no definitive proof that they should receive more aggressive treatment.
From Konstantinides S: Acute pulmonary embolism, *N Engl J Med* 359:2804-2813, 2008.

BASIC INFORMATION

DEFINITION

Pulseless electrical activity (PEA) is defined as the presence of organized electrical activity without sufficient mechanical contraction of the heart to produce a palpable pulse or measurable blood pressure.

SYNONYMS

Electromechanical dissociation (EMD)

ICD-9CM CODES
427.5 Cardiac arrest
ICD-10CM CODES
I46.9 Cardiac arrest, cause unspecified
I49.9 Cardiac arrhythmia, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Accounts for about 35% of cardiac arrest cases.
- Increasingly recognized as the cause of sudden cardiac death in patients with implantable cardioverter-defibrillators.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

PRIMARY PEA:
- Organized electrical activity (not VT/VF).
- No detectable pulse.

SECONDARY PEA: As in primary PEA and may also have:
- Bradycardia: drug overdose.
- Tachycardia: hypovolemia, massive PE.
- Decreased jugular venous pressure (JVP): hypovolemia.
- Elevated JVP and no pulse with CPR: cardiac tamponade, massive PE, tension pneumothorax.
- Absent unilateral breath sounds and tracheal deviation: tension pneumothorax.
- Cyanosis: hypoxia.

ETIOLOGY

PRIMARY PEA: Myocardial electromechanical uncoupling secondary to advanced heart muscle disease.

SECONDARY PEA: Because of changes in the loading conditions of the heart, ischemia, myocardial depressants
- Massive MI.
- Massive PE.
- Hypovolemia.
- Cardiac tamponade.
- Tension pneumothorax.
- Hypoxia.
- Hypothermia.
- Acidosis.
- Hyperkalemia/hypokalemia.
- Drug overdose: β-blockers, calcium channel blockers, digoxin, tricyclic antidepressants, benzodiazepines, opioids.

DIAGNOSIS

WORKUP

- Stabilizing patient and workup to establish etiology should proceed simultaneously.
- History, physical examination, laboratory tests, imaging studies.

LABORATORY TESTS

- CBC, potassium, magnesium, CK-MB, troponin, toxicology screen.
- Arterial blood gas.
- ECG (Fig. P1-99):
  Low voltage: tamponade.
  Right heart strain: PE, pneumothorax.
  Arrhythmias: MI, metabolic abnormalities, drug effects.
  ST changes, Q waves: MI.

IMAGING STUDIES

- Chest radiograph: rule out pneumothorax, aortic dissection.
- Chest CT/pulmonary arteriogram: rule out PE.
- Echocardiogram: rule out tamponade, ischemia (LV contractility, wall motion), valve dysfunction, tumors, and clots. May help diagnose aortic dissection and PE and assess intravascular volume status.
- Abdominal radiograph: rule out ruptured abdominal aortic aneurysm.

TREATMENT

Identifying and treating a reversible cause is critical.

Physiologic parameters can help monitor quality of CPR and detect the return of spontaneous circulation (ROSC). Suggested methods include quantitative waveform capnography (if intubated), arterial relaxation "diastolic" pressure (if arterial catheter in place), or central venous oxygen saturation (if central venous catheter in superior vena cava).

NONPHARMACOLOGIC THERAPY

- Activate emergency response service.
- Begin CPR; ensure high quality, minimize interruptions. Perform CPR for 2 min between pauses to assess rhythm and circulation.
- Attach cardiac monitor/defibrillator.
- Obtain IV/intraosseous (IO) access.
- Consider advanced airway placement.
- Confirm absence of blood flow with Doppler ultrasound, arterial line, or bedside echocardiogram.

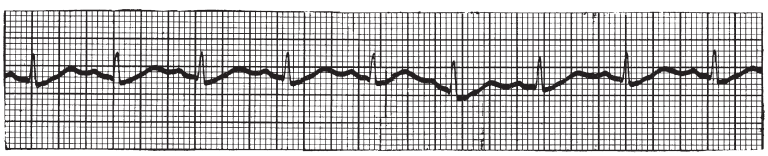

FIGURE P1-99 Sinus rhythm with pulseless electrical activity (PEA). Although the ECG showed sinus rhythm, the patient had no pulse or blood pressure. In this case the PEA was a result of depressed myocardial function after a cardiac arrest. (From Goldberg AL: *Clinical electrocardiography,* ed 5, St Louis, 1994, Mosby.)

ACUTE GENERAL Rx

- Treat specific cause if known.
- Give 100% oxygen.
- Epinephrine 1 mg IV push/IO, q3 to 5min; vasopressin 40 U IV/IO may be used to replace the first or second dose of epinephrine.
- Give normal saline (20 ml) bolus after peripheral IV administration of medication to improve its distribution.
- Medication can be given via endotracheal tube if IV/IO access cannot be obtained; IV/IO routes preferred because they provide more predictable drug delivery and pharmacologic effects. Give 2 to 2.5× the IV dose in 10 ml of sterile water.
- If rhythm changes to VF or pulseless VT.
  1. Defibrillate.
  2. For refractory VF or pulseless VT consider amiodarone.
- If achieve ROSC, initiate postcardiac arrest care.

DISPOSITION

Of hospitalized patients who develop PEA, <15% survive to discharge. Survival rates much lower in patients with prehospital PEA. Survivors often have poor neurologic outcomes.

REFERRAL

As needed for underlying condition.

PEARLS & CONSIDERATIONS

- 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care recommend the use of epinephrine in PEA resuscitation. New data suggest that epinephrine use may be associated with worse neurologic outcomes and increased long-term mortality. Recent study suggests that the use of steroids in resuscitation and for postresuscitation shock improved neurologic outcomes and survival to hospital discharge.
- Termination of resuscitation guidelines exist for out-of-hospital cardiac arrest. Similar guidelines for in-hospital cardiac arrest are not available; termination of resuscitation is based on multiple patient factors.
- Therapeutic hypothermia (32° to 34° C for 12 to 24 hr) may improve neurologic outcomes and reduce mortality in comatose cardiac arrest survivors. Recent study suggests target temperature of 36° C may be equally effective.
- Prognosis may be guided by testing, but no single exam finding or test is definitive. Delay testing for at least 24 hr after ROSC. Available tests include median nerve somatosensory-evoked potentials, EEG, or corneal and pupillary reflexes. Prognostication is more difficult in patients treated with hypothermia; wait >72 hr before attempting to predict outcome.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **SUDEEP KUAR AULAKH, M.D.**

SUGGESTED READINGS

Hagihara A et al.: Prehospital epinephrine use and survival among patients with out-of-hospital cardiac arrest, *JAMA* 307:1161, 2012.

Lundbye JB et al.: Therapeutic hypothermia is associated with improved neurologic outcome and survival in cardiac arrest survivors of non-shockable rhythms, *Resuscitation* 83:202, 2012.

Meaney PA et al.: Rhythms and outcomes of adult in-hospital cardiac arrest, *Crit Care Med* 38:101, 2010.

Mentzelopoulos SD et al.: Vasopressin, steroids, and epinephrine and neurologically favorable survival after in-hospital cardiac arrest: a randomized clinical trial, *JAMA* 310:270, 2013.

Miller C et al.: Towards evidence based emergency medicine: best BETs from the Manchester Royal Infirmary. BET 1: the use of adrenaline and long-term survival in cardiopulmonary resuscitation following cardiac arrest, *Emerg Med J* 30:249, 2013.

Morrison LJ et al.: Part 3: ethics: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, *Circulation* 122(suppl 3):S665, 2010.

Nielsen N et al.: Targeted temperature management at 33°C versus 36°C after cardiac arrest, *N Engl J Med* 369:2197, 2013.

Morrison LJ et al.: Strategies for improving survival after in-hospital cardiac arrest in the United States: 2013 consensus recommendations: a consensus statement from the American Heart Association, *Circulation* 127:1538, 2013.

Neumar RW et al.: Part 8: adult advanced cardiovascular life support: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, *Circulation* 122(suppl 3):S729, 2010.

Peberdy MA et al.: Part 9: post-cardiac arrest care: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, *Circulation* 122(Suppl 3):S768, 2010.

BASIC INFORMATION

DEFINITION

Pure red cell aplasia is characterized by a triad of severe anemia, reticulocytopenia (<1%), and the absence of erythroid precursors in the bone marrow. All other cell lineages (namely, myeloid precursors and megakaryocytes) are normal. Tables EP1-47 and EP1-48 describe classifications of pure red cell aplasia.

SYNONYMS

Congenital hypoplastic anemia
Joseph-Blackfan-Diamond syndrome
Acquired red cell aplasia

ICD-9CM CODES
284.01 Constitutional red cell aplasia
284.81 Red cell aplasia (acquired) (adult) (with thymoma)
ICD-10CM CODES
D61.01 Constitutional (pure) red blood cell aplasia
D60.0 Chronic acquired pure red cell aplasia

EPIDEMIOLOGY & DEMOGRAPHICS

- The frequency of this disease has been underestimated mainly due to self-limiting nature of most of the cases.
- Rare disease (WHO classification).

PREDOMINANT SEX AND AGE: The male to female ratio is 2:1 for pure red cell aplasia with thymoma. However, immune-mediated cases are seen more commonly in females.
GENETICS: Mutation in the gene RPS19 located at 19q13.2 has been seen in 25% of congenital hypoplastic anemia patients.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Anemia is the primary problem in pure red cell aplasia.
- Patients with severe anemia can present with fatigue, pallor, tachycardia, and dyspnea.
- Congenital hypoplastic anemia is usually associated with physical findings of short stature, abnormal thumbs, and mental retardation.
- Other stigmata of underlying illnesses such as splenomegaly, enlarged parotid glands, lymphadenopathy, leg ulcers, and thymomas should be looked for.
- Physical findings related to complications from therapy including iron overload secondary to transfusion therapy; corticosteroid therapy and immunotherapy may be seen as well.

ETIOLOGY (Table EP1-49)

- Congenital: usually sporadic caused by injury to stem cells in utero.
- Acquired:
  1. Acute, self-limited (usually secondary to drugs, chemicals [Table EP1-50], and viral infections).
  2. Chronic (with underlying thymomas, autoimmune disorders, and immunocompromised states).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Pure red cell aplasia.
  1. Bone marrow findings: normal cellularity except diminished RBC precursors.
  2. Peripheral blood: anemia only.
  3. Cytogenetics: negative.
- Myelodysplastic syndrome.
  1. Bone marrow findings: hypercellular.
  2. Peripheral blood: pancytopenia with cellular dysplasia.
  3. Cytogenetics: positive (5q deletion).
- Aplastic anemia
  1. Bone marrow findings: hypocellular.
  2. Peripheral blood: pancytopenia.
  3. Cytogenetics: negative.

WORKUP

A search should always be made for the underlying condition. Fig. EP1-100 is a diagnostic algorithm for pure red cell aplasia.

LABORATORY TESTS

- CBC with peripheral smear: normocytic, normochromic anemia.
- Reticulocyte count: diminished (<1% or <10,000/μL).
- Bone marrow biopsy is essential to make this diagnosis and rule out other causes: normocellular marrow with normal myeloid precursors and megakaryocytes but absent erythroid precursors.
- Viral titers, if clinically indicated.
- Antinuclear antibody testing.
- Chest x-ray or chest CT should be ordered in all cases to rule out underlying thymoma.

TREATMENT

- Treatment of the underlying cause.
- Red cell transfusions for symptomatic anemia.

NONPHARMACOLOGIC THERAPY

- Treatment of underlying cause includes cessation of the offending drug. Viral infections usually resolve spontaneously in 2 to 3 wk.
- About 10% to 15% of patients have thymomas. Surgical resection results in amelioration of anemia in 30% of cases.

ACUTE GENERAL Rx

- Packed red cell transfusion is indicated for symptomatic anemia.
- A vast majority of patients have a protracted remitting and relapsing course, requiring long-term support of anemia with blood transfusions and long-term treatment with immunosuppressive agents.

CHRONIC Rx

- In refractory and relapsed cases, immunosuppressive therapy usually with prednisone or in combination with cyclosporine or cyclophosphamide or antithymocyte globulin (ATG) should be considered. This should always be done in consultation with a hematologist.
- Immunocompromised hosts with pure red cell aplasia secondary to parvovirus infection may not improve spontaneously and often benefit from high-dose intravenous immunoglobulin (IVIG) therapy.
- Certain cases of thymomas with pure red cell aplasia that do not respond to surgery may respond to somatostatin analogs (e.g., octreotide) in combination with prednisone.
- In patients with pure cell aplasia caused by anti-erythropoietin antibodies, stopping erythropoietin therapy and transfusing RBCs can help to correct severe anemia.

DISPOSITION

- Acute self-limited pure red cell aplasia has an excellent prognosis.
- The mortality rate is low in most of the acquired chronic cases but may have significant morbidity related to the underlying condition and complication of therapy.
- Patients with congenital red cell aplasia undergo remission in 15% to 25% of cases

TABLE EP1-47 Classification of Pure Red Cell Aplasia

Acute Transient Anemia
- Idiopathic: transient erythroblastopenia of childhood
- Viral infection: parvovirus B19, hepatitis, Epstein-Barr virus
- Drugs*: azathioprine, cephalothin, chloramphenicol, dapsone, diphenylhydantoin, isoniazid, procainamide

Chronic Anemia
- Constitutional: Diamond-Blackfan anemia
- T-cell mediated: thymoma, T-cell large granular lymphocytic leukemia, chronic lymphocytic leukemia, myelodysplastic syndrome
- Immunoglobulin G autoantibody mediated: systemic autoimmune disorders (rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, myasthenia gravis)
- Insufficient antibody production: acquired immunodeficiency syndrome with parvovirus, pregnancy, organ transplantation
- ABO-incompatible stem cell transplants
- Erythropoietin therapy in patients with chronic renal disease (due to anti-EPO Ab formation)
- Anti-erythropoietin antibody due to recombinant human erythropoietin therapy

*Drug list is not all-inclusive.
From Jaffe ES et al: *Hematopathology*, Philadelphia, 2011, Saunders.

TABLE EP1-48 Classification of Pure Red Cell Aplasia

Congenital (DBA)		
Primary	Autoimmune	
	Idiopathic	
Secondary	Thymoma	
	Hematologic malignancies	CLL
		T-LCL/chronic NK-LGL leukemia
		Myeloma
		NHL
		MDS
		ALL
	Solid tumors	Renal cell carcinoma
		Thyroid cancer
		Various adenocarcinomas
	Infections	Parvovirus B19
		EBV, mumps
		HIV, HTLV-1
		CMV
		Viral hepatitis (Hep A, Hep C)
		Leishmaniasis
		Gram+ systemic infections, e.g., staphylococcemia
		Meningococcemia
	Autoimmune conditions	SLE
		RA
		Sjögren's syndrome
		Mixed connective tissue disease
		Autoimmune hepatitis
		Anti-Epo antibodies
		ABO-incompatible BMT
		Minor incompatibility
	Drugs and chemicals	
	Pregnancy	
	Severe nutritional deficiencies	
	Renal failure	

ALL, Acute lymphoblastic leukemia; *BMT*, bone marrow transplantation; *CLL*, chronic lymphocytic leukemia; *CMV*, cytomegalovirus; *DBA*, Diamond-Blackfan anemia; *EBV*, Epstein-Barr virus; *HTLV-1*, human T-lymphotrophic virus; *MDS*, myelodysplastic syndrome; *NHL*, non-Hodgkin lymphoma; *NK-LGL*, natural killer large granular lymphocyte; *RA*, refractory anemia; *SLE*, systemic lupus erythematosus; *T-LGL*, T-cell large granular lymphocyte.
From Hoffman R et al: *Hematology, basic principles and practice*, ed 5, Philadelphia, 2009, Churchill Livingstone.

TABLE EP1-49 Causes of Acquired Red Cell Aplasia

Drugs	Viruses
Procainamide	Parvovirus B19
Phenytoin	Mumps
Sulfonamides	Hepatitis
Zidovudine	Infectious mononucleosis (Epstein-Barr virus)
Azathioprine	Atypical *Mycoplasma*
Chloramphenicol	
Isoniazid	
Recombinant erythropoietin therapy/anti-EPO antibodies	
Malignancies	**Autoimmune Conditions**
Thymomas (5%)	Systemic lupus erythematosus
Chronic lymphocytic leukemia, chronic myeloid leukemia	Rheumatoid disease
Hodgkin's disease	Autoimmune hemolytic anemia
Large granular lymphocyte leukemia	
Immunocompromised States	**Others**
Human immunodeficiency virus	Pregnancy
Human T-lymphotrophic virus type 1	ABO-incompatible hematopoietic cell transplantation
Idiopathic	

and may not need treatment again, or may relapse after reaching adulthood.

REFERRAL

All patients should be referred to a hematologist for complete workup, diagnosis, initiation of appropriate treatments, and monitoring of the response to therapy.

PEARLS & CONSIDERATIONS

COMMENTS

- Rare diagnosis.
- Most cases self-limiting.

PREVENTION

Medications implicated as the cause of pure red cell aplasia should be avoided.

PATIENT & FAMILY EDUCATION

- The consequences of iron overload and secondary hemosiderosis from repeated transfusion therapy should be explained to patients.
- The possibility of the transmission of infections with transfusions and immunotherapy should be discussed with patients.
- Long-term use of corticosteroids, immunomodulators can result in significant adverse effects that should be explained to patients.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **PRIYA BANSAL, M.D., M.P.H.**

TABLE EP1-50 Drugs and Chemicals Implicated in Pure Red Cell Aplasia

Alemtuzumab	Isoniazid
Allopurinol	Lamivudine
α-Methyldopa	Linezolid
Aminopyrine	Maloprim
Azathioprine	Penicillin
Benzene	Phenylbutazone
Carbamazepine	Phenytoin
Cephalothin	Procainamide
Chloramphenicol	Ribavirin
Chlorpropamide	Rifampicin
Cladribine	Sulfasalazine
Cotrimoxazole	Sulfathiazole
D-Penicillin amine	Sulindac
Erythropoietin	Tacrolimus
Estrogens	Mycophenolate mofetil
Fludarabine	Thiamphenicol
FK506	Ticlopidine
Gold	Valproic acid
Halothane	Zidovudine
Interferon-α	

From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

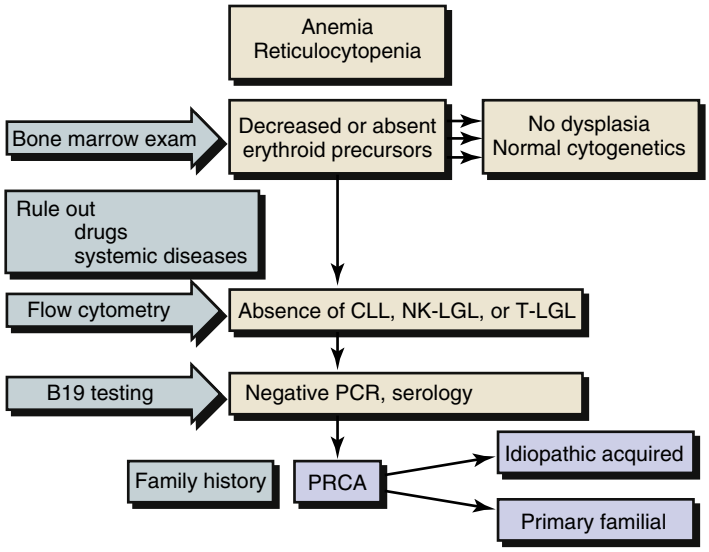

FIGURE EP1-100 Diagnostic algorithm for pure red cell aplasia *(PRCA).* *CLL,* Chronic lymphocytic leukemia; *NK-LGL,* natural killer cell large granular lymphocyte; *PCR,* polymerase chain reaction; *T-LGL,* T cell large granular lymphocyte. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

SUGGESTED READINGS

Macdougall IC et al.: A peptide-based erythropoietin-receptor agonist for pure red cell aplasia, *N Engl J Med* 361:1848–1855, 2011.

Sawada K et al.: Acquired pure red cell aplasia: updated review of treatment, *Br J Haematol* 142(4):505–514, 2008.

BASIC INFORMATION

DEFINITION

Pyelonephritis is an infection, usually bacterial in origin, of the upper urinary tract.

SYNONYMS

Acute pyelonephritis
Pyonephrosis
Renal carbuncle
Lobar nephronia
Acute bacterial nephritis

ICD-9CM CODES

590.81 Pyelonephritis
599.0 Urinary tract infection
595.9 Cystitis

ICD-10CM CODES

N10 Acute tubulo-interstitial nephritis
N11 Chronic tubulo-interstitial nephritis
N11.0 Nonobstructive reflux-associated chronic pyelonephritis
N11.1 Chronic obstructive pyelonephritis
N11.8 Other chronic tubulo-interstitial nephritis
N11.9 Chronic tubulo-interstitial nephritis, unspecified
N12 Tubulo-interstitial nephritis, not specified as acute or chronic

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Extremely common.
PREDOMINANT SEX: Female.
PREDOMINANT AGE:

- Sexually active years in women.
- Usually age >50 yr in men.

GENETICS: Congenital urologic structural disorders may predispose to infections at an early age.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fever, rigors, chills.
- Flank pain.
- Dysuria.
- Polyuria.
- Hematuria.
- Toxic feeling and appearance.
- Nausea and vomiting.
- Headache.
- Diarrhea.
- Physical examination notable.
  1. Costovertebral angle tenderness.
  2. Exquisite flank pain.

ETIOLOGY

- Gram-negative bacilli such as *Escherichia coli* and *Klebsiella* spp. in more than 95% of cases.
- Other, more unusual gram-negative organisms, especially if instrumentation of the urinary system has occurred.
- Resistant gram-negative organisms or even fungi in hospitalized patients with indwelling catheters.
- Gram-positive organisms such as enterococci.
- *Staphylococcus aureus:* presence in urine indicates hematogenous origin.
- Viruses: rarely, but these are usually limited to the lower tract.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Nephrolithiasis.
- Appendicitis.
- Ovarian cyst torsion or rupture.
- Acute glomerulonephritis.
- Pelvic inflammatory disease.
- Endometritis.
- Other causes of acute abdomen.
- Perinephric abscess.
- Hydronephrosis.

WORKUP

- No workup usually indicated in sexually active women.
- Poorly responding infections, especially with azotemia and frank bacteremia.
- Renal sonogram or CT scan (Fig. P1-101) to assess for underlying urologic pathology such as hydronephrosis.
- Urologic imaging studies in all young men and boys.
- Prostate assessment in older men.

LABORATORY TESTS

- Complete blood count with differential.
- Renal panel.
- Blood cultures.
- Gram stain of urine, urinalysis, and urine cultures

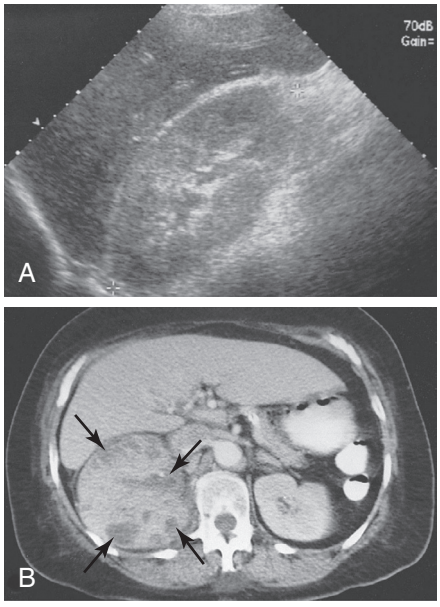

FIGURE P1-101 Acute pyelonephritis. A, Ultrasound image demonstrates an enlarged echogenic kidney. Bipolar length of kidney is 12.9 cm. **B,** CT scan with contrast enhancement obtained 24 hours later demonstrates multiple nonenhancing abscesses *(arrows).* (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

- Urgent renal sonography if obstruction or closed space infection suspected.
- CT scans may better define the extent of collections of pus and can identify emphysematous pyelonephritis.
- Helical CT scans excellent to detect calculi.

TREATMENT

ACUTE GENERAL Rx

- Hospitalization for:
  1. Toxic patients.
  2. Complicated infections.
  3. Diabetes.
  4. Suspected bacteremia.
- Keep patients well hydrated.
- IV fluids are indicated for those unable to take adequate amounts of liquids.
- Give antipyretics such as acetaminophen when necessary.
- Antibiotic therapy should be initiated after cultures are obtained and guided by the results of culture and sensitivity testing.
  1. Oral quinolones such as ciprofloxacin (500 mg PO bid usually for 10 to 14 days) or Levaquin (500 or 750 mg for 10 to 14 days) are typically used for stable patients who can tolerate oral medications with sensitive pathogens. The optimum duration of therapy for acute pyelonephritis is unclear. Recent trials have shown that a short course (7 days) is not inferior to a 14-day course in women with uncomplicated pyelonephritis.
  2. IV antibiotic options for more toxic patients pending cultures include ceftriaxone (1 to 2 g q day), IV cipro (400 mg q12h) or IV Levaquin (500 to 750 mg IV q day), piperacillin/tazobactam (3.375 g IV q6h) or carbapenems such as meropenem or imipenem (500 mg IV q6-8h).
  3. Ceftazidime 1 to 2 g IV 8h, piperacillin/tazobactam, and carbapenems are best choices for *Pseudomonas*. There is increasing resistance of *Pseudomonas* to ciprofloxacin.
  4. Aminoglycosides such as gentamicin (2 mg/kg IV load followed by 1 mg/kg IV q8h-12h adjusted for renal function) added, but nephrotoxicity possible, especially in diabetics with azotemia.
  5. Vancomycin 1 g IV q12h or linezolid 600 mg IV or PO q12h to cover gram-positive cocci such as enterococci or staphylococci. Daptomycin 4 to 6 mg/kg IV q day is another alternative.
  6. Ampicillin 1 to 2 g IV q4 to 6h to cover ampicillin-sensitive enterococci +/– an aminoglycoside for synergy.
- Prompt drainage with nephrostomy tube placement for obstruction.
- Surgical drainage of large collections of pus to control infection.
- Diabetic patients, as well as those with indwelling catheters, are especially prone to complicated infections and abscess formation.

CHRONIC Rx

- Repair underlying structural problems, especially when renal function is compromised.

1. Reflux.
2. Obstruction.
3. Nephrolithiasis should be considered.

- Patients with diabetes mellitus and indwelling urinary catheters are at particular risk of severe and complicated infections.
- When possible, remove catheters.

DISPOSITION

Most patients with uncomplicated pyelonephritis are now treated as outpatients or in short hospitalizations. Indications to admit a patient with pyelonephritis include pregnancy, suspected urinary obstruction, suspected renal abscess or perinephric abscess, bacterial sepsis, diabetes or other immunocompromised states, recurrent or refractory pyelonephritis, or infection with an unusual or antibiotic-resistant microorganism.

REFERRAL

- To a surgeon for correction of underlying urologic problems (e.g., reflux and hydronephrosis).
- To a pediatrician for detection of reflux to avoid recurrent urinary tract infection and loss of renal function.
- To an internist for aggressive metabolic and urologic evaluation for patients with nephrolithiasis.

PEARLS & CONSIDERATIONS

Pyelonephritis is a systemic illness and may be a source of bacteremia and sepsis, especially if accompanied by urinary obstruction. Workup for abscess, obstruction, papillary necrosis, and other local complications of pyelonephritis should be initiated if the patient is septic, if patient does not respond to antibiotic therapy after 72 hr of treatment, or if infection is accompanied by worsening renal function.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pyelonephritis (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Bloomfield P et al.: Antibiotics for acute pyelonephritis in children, *Cochrane Database Syst Rev* 1:CD003772, 2005.

Eliakim-Raz N et al.: Duration of antibiotic treatment for acute pyelonephritis and septic urinary tract infection—7 days or less versus longer treatment: systematic review and meta-analysis of randomized controlled trials, *J Antimicrob Chemother* 68(10):2183–2191, 2013.

Gupta K et al.: International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in woman: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases, *Clin Infect Dis* 52(5):e103–e120, 2011.

Hill JB et al.: Acute pyelonephritis in pregnancy, *Obstet Gynecol* 105(1):18, 2005.

Sandberg T et al.: Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised open-label and double-blind, placebo-controlled, non-inferiority trial, *Lancet* 9840:484–490, 2012.

Scholes D et al.: Risk factors associated with acute pyelonephritis in healthy women, *Ann Intern Med* 142(1):20, 2005.

BASIC INFORMATION

DEFINITION

Pyoderma gangrenosum (PG) is a rare, noninfectious neutrophilic dermatosis that presents as an inflammatory skin disease characterized by a papule or pustule that progresses to a painful ulcer with violaceous overhanging borders and a purulent base. In contrast to its name, PG is neither an infectious nor gangrenous condition.

SYNONYMS

PG
Classic pyoderma gangrenosum
Atypical pyoderma gangrenosum
Peristomal pyoderma gangrenosum

ICD-9CM CODES
686.01 Pyoderma gangrenosum
ICD-10CM CODES
L88 Pyoderma gangrenosum

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 10 cases per million people per year.
PREDOMINANT AGE: Most common in young and middle-aged adults, with an average age of onset between 40 and 60 years. Children can be affected.
PREDOMINANT SEX: Women are more frequently affected.
GENETICS: Familial cases of PG have been reported. PAPA syndrome is an autosomal dominant disorder linked to a mutation on chromosome 15q and characterized by pyogenic sterile arthritis, PG, and acne.
RISK FACTORS: Autoimmune diseases, particularly ulcerative colitis, Crohn's disease, and rheumatoid arthritis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Typically presents first as an inflammatory papule, pustule, vesicle, or nodule that rapidly and painfully progresses to an ulcer or erosion with tissue necrosis and enlargement of the area. The ulcer or erosion is surrounded by a violaceous border with a surrounding erythema (Fig. EP1-102). Level of the pain is greater than expected based upon the appearance of the ulcer. Fever may be present.

FIGURE EP1-102 Pyoderma gangrenosum. Note undermined hemorrhagic borders. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

- Classic PG is commonly found on the lower extremities.
- Atypical PG occurs more frequently in the upper extremities, head, and neck. Atypical PG lesions begin as pustules and become plaques that may be studded with pustules.
- Peristomal PG lesions appear similarly to classic PG lesions; however, they occur around surgically created stomas such as in Crohn's disease surgery.
- PG might also involve the genital area or might rarely affect extracutaneous sites (liver, lungs, intestines, cornea, heart, bones, CNS).
- As many as 30% of lesions occur via pathergy. Pathergy is the abnormal development of skin lesions at the sites of injury, including minor injuries. Pathergy-induced PG lesions can be misdiagnosed as cellulitis. Surgery can also induce pathergy.
- Some patients only present with a single episode of PG, while others can have multiple episodes or a chronic relapsing course.
- Approximately 50% of PG sufferers have an underlying systemic disease, including inflammatory bowel disease, myeloproliferative diseases, hematologic disorders (most frequently IgA monoclonal gammopathy), or inflammatory arthritis, pulmonary diseases, SLE, thyroid diseases, solid organ cancers, viral and autoimmune hepatitis, sarcoidosis, and major depression.

ETIOLOGY

Neutrophilic infiltration causing cutaneous damage seems to be a major part of the underlying mechanism. Abnormalities in neutrophil function, genetic variations, and dysregulation of the innate immune system are the primary factors causing PG.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

PG is often misdiagnosed due to its rareness, its similar appearance to other lesions, and a general lack of awareness of its existence.
- Cellulitis.
- Vascular occlusion disorders.
- Fungal infection.
- Brown recluse spider bite.
- Primary systemic vasculitides such as polyarteritis nodosa and granulomatosis with polyangiitis.
- Malignancies such as squamous cell carcinoma, cutaneous lymphoma, and metastatic carcinoma.
- Sporotrichosis.
- Angiocentric T cell lymphoma.
- Cryoglobulinemia.
- Drugs.
- Livedoid vasculopathy.
- Antiphospholipid syndrome.
- Erythema nodosum.

WORKUP

PG is a diagnosis of exclusion. Workup should include biopsy of lesions and evaluation for associated underlying illness such as inflammatory bowel disease, arthritis, or malignancy. History, particularly as to the timing and progression of the lesions and inciting injury, is particularly important, as well as the physical appearance and localization of the lesions.

LABORATORY TESTS

Skin biopsy is not diagnostic in itself because the findings are nonspecific. However, it may be helpful in excluding other diseases. Histopathologic findings show sterile dermal neutrophilia with or without mixed inflammation or lymphocytic vasculitis. Giant cells or leukocytoclastic vasculitis might be found. Other appropriate testing include rheumatologic lab work, hepatitis panel, or colonoscopy to evaluate for inflammatory arthritis, hepatitis, paraproteinemia, or inflammatory bowel disease (IBD). Tissue cultures should also be performed to rule out bacterial or fungal causes. Direct immunofluorescence studies might show deposition of IgM, C3, and fibrin in vessel walls.

IMAGING STUDIES

Consider colonoscopy and/or CT to evaluate for IBD. Chest radiography to evaluate for the presence of extracutaneous involvement and for possible infection before the initiation of immunosuppressive therapy.

TREATMENT

The major treatment modalities revolve around wound care for the ulcers themselves, as well as either topical or systemic therapy.

NONPHARMACOLOGIC THERAPY

Surgery or aggressive debridement should be avoided in PG lesions because the surgery can cause pathergy and worsen the lesions. When needed, grafting should be performed concurrently with systemic immune-modulating therapy to prevent worsening of the lesions.

ACUTE GENERAL Rx

Care may include one or more of the following:
- Topical wound care and moist healing.
- Topical high-potency steroids (e.g., clobetasol).
- Topical immune modulators (e.g., tacrolimus).
- Systemic glucocorticoids (e.g., prednisone).
- Systemic immune modulators (e.g., cyclosporine).
- Antibiotics—only in cases of superinfection and if used with one of above.
- Infliximab in patients with Crohn's disease.
- Dapsone or colchicine have shown some benefit.
- Second-line treatment includes immunomodulatory drugs (thalidomide, azathioprine, mycophenolate mofetil, methotrexate, IV immune globulin).

CHRONIC Rx

Similar to above except for longer durations or in pulse therapy.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Not relevant.

DISPOSITION

Can be treated in both inpatient and outpatient settings depending on severity and therapeutic modalities.

REFERRAL

- Dermatology.
- Rheumatology.
- Gastroenterology, especially in cases of IBD-related PG.
- Hematology.

PEARLS & CONSIDERATIONS

COMMENTS

PG is a diagnosis of exclusion that should only be made after other diseases in the differential have been ruled out and the patient has been evaluated for the associated diseases seen in >50% of cases.

PATIENT & FAMILY EDUCATION

Support for PG can often be found in the support groups for associated diseases, particularly Crohn's disease, ulcerative colitis, erythema nodosum, and rheumatoid arthritis.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **CATHERINE ELIAS NAJEM, M.D.**

SUGGESTED READINGS

Brooklyn TN et al.: Infliximab for the treatment of pyoderma gangrenosum: a randomized double blind, placebo controlled trial, *Gut* 55(4):505–509, 2006.

Callen JP, Jackson JM: Pyoderma gangrenosum: an update, *Rheum Dis Clin North Am* 33(4):787–802, 2007.

Ephgrave K: Extra-intestinal manifestations of Crohn's disease, *Surg Clin North Am* 87(3):673–680, 2007.

Habif T: Pyoderma gangrenosum. In: (editor: Habif T.) Clinical dermatology. Mosby: Edinburgh.

Nico MM et al.: Pyostomatitis vegetans and its relation to inflammatory bowel disease, pyoderma gangrenosum, pyodermatitis vegetans, and pemphigus, *J Oral Pathol Med* 41:584, 2012.

Powell F.C: Hackett B.C.; Wallach D. Pyoderma gangrenosum. In: (editor: Goldsmith L.A et al.) ed 8 Fitzpatrick's dermatology in general medicine. Vol. 1 McGraw-Hill Companies, Inc:New York, p. 371.

Preiswerk B et al.: From a pimple to a crater, *Lancet* 13(9791):636, 378, 2011.

Reichrath J et al.: Treatment recommendations for pyoderma gangrenosum: an evidence-based review of the literature based on more than 350 patients, *J Am Acad Dermatol* 53(285):273–283, 2009.

Weedon D: The vasculopathic reaction pattern. In: Weedon's Skin Pathology. Elsevier Limited, p. 195.

Wollina U: Pyoderma gangrenosum—a review, *Orphanet J Rare Dis* 2(19), 2007.

Pyogenic Granuloma

BASIC INFORMATION

DEFINITION

Pyogenic granuloma is a benign vascular lesion of the skin and mucous membranes. The lesions are caused by capillary proliferation, generally the result of trauma.

SYNONYMS

Granuloma pyogenicum
Tumor of pregnancy
Eruptive hemangioma
Lobular capillary hemangioma
Granulation tissue–type hemangioma

ICD-9CM CODES
686.1 Pyogenic granuloma
ICD-10CM CODES
L98.0 Pyogenic granuloma

EPIDEMIOLOGY & DEMOGRAPHICS

- Common in children and young adults. Also found more frequently in pregnant women.
- Equally prevalent in males and females, with no racial or familial predisposition.
- Caused by trauma or surgery.
- Gingival lesions occur more frequently during pregnancy.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Small (<1 cm), yellow to red, dome-shaped lesions.
- May have surrounding scale at base (Fig. P1-103).
- Most commonly found on the head, neck, and extremities.
- Often found on the gingiva during pregnancy (called *epulis*).
- Extremely friable, can easily ulcerate, and may bleed profusely with minor trauma.

ETIOLOGY

Trauma causing focal capillary growth. These lesions are neither infectious in etiology nor granulomatous in histology.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Amelanotic melanoma.
- Bacillary angiomatosis.
- Glomus tumor.
- Hemangioma.
- Irritated nevus.
- Wart.
- Kaposi's sarcoma.

WORKUP

Diagnosis is based on clinical history and appearance. Generally begins with trauma followed by the development of an erythematous papule. The lesion tends to bleed easily and develops over several days to weeks.

LABORATORY TESTS

Pathologic examination should be performed after excision to rule out melanoma.

TREATMENT

ACUTE GENERAL Rx

- Excision: using 1% lidocaine for anesthesia, shave or curette at base and border. Follow with electrocauterization or cryotherapy.
- Pulsed-dye laser is also a safe and effective treatment modality.
- Pregnancy epulis generally resolves spontaneously after childbirth.

REFERRAL

Dermatology referral recommended if lesion recurs or multiple satellite lesions occur after excision.

PEARLS & CONSIDERATIONS

COMMENTS

- Removal of entire lesion is essential because lesions may recur at the site of residual tissue.
- Patients and parents should be alerted to the possibility of recurrence after removal.
- Multiple satellite lesions occasionally develop near a primary pyogenic granuloma, usually after destruction of that lesion.

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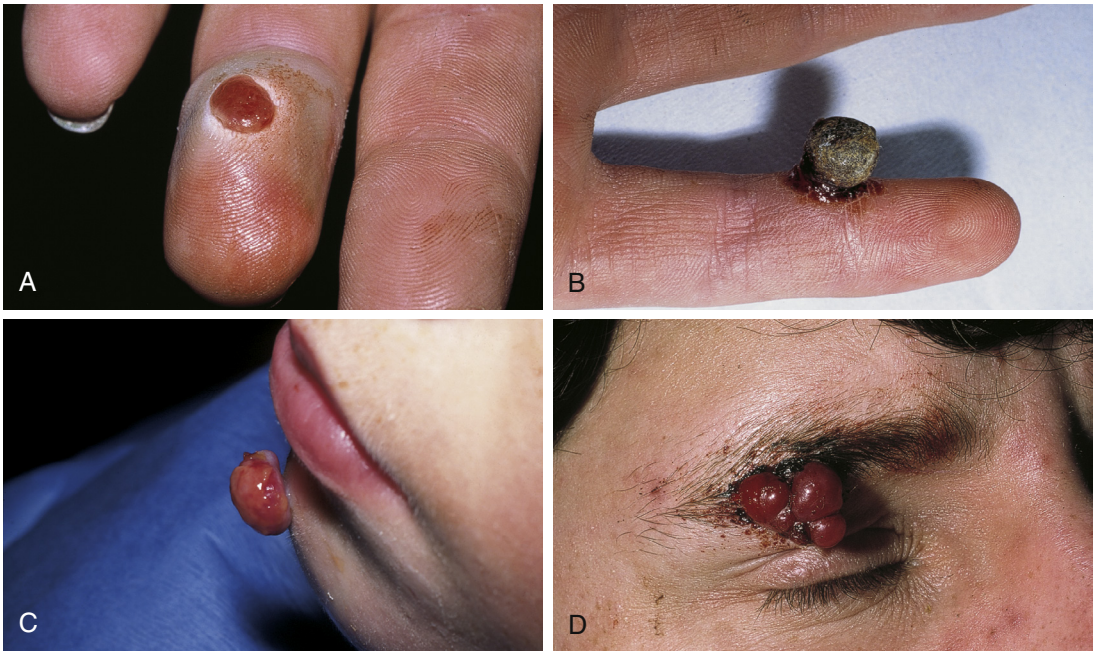


FIGURE P1-103 Pyogenic granuloma. A, This is the classic appearance of a red, friable nodule growing rapidly on the finger. There is often a portion that extends under the skin laterally. **B,** Pyogenic granuloma on the finger. This lesion is more dry and crusted. **C,** Pyogenic granuloma on the chin of an adult. The fingers, lip, palms, soles, and face are typical sites. **D,** Pyogenic granuloma of the eyebrow. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

BASIC INFORMATION

DEFINITION

Q fever is a systemic febrile illness caused by *Coxiella burnetii* that may be acute or chronic.

SYNONYMS

C. burnetii infection

ICD-9CM CODES
083.0 Q fever
ICD-10CM CODES
A78 Q fever

EPIDEMIOLOGY & DEMOGRAPHICS

- *C. burnetii* is found worldwide. Fig. EQ1-1 illustrates distribution in the United States in 2010.
- Common animal reservoirs are cattle, sheep, and goats.
- Pets such as cats, rabbits, pigeons are also reservoirs.
- A parturient cat caused an outbreak in Nova Scotia just by delivering in the same room as a card game.
- Most cases are found in individuals who have direct contact with infected animals (e.g., farmers, veterinarians) or who are exposed to contaminated animal urine, feces, milk, or placental tissues.
- Q fever is seen more often in men than in women (ratio of 3:1).
- Its incidence in the U.S. is increasing, with more than 30 cases recently reported in U.S. military personnel recently deployed to Iraq and Afghanistan.
  - One hundred sixty seven cases in 2008.
- *C. burnetii* is a Centers for Disease Control and Prevention (CDC) class B bioterrorism agent.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute Q fever presentation:
  Fever
  Pneumonia
  Hepatitis
  Meningoencephalitis
- Chronic Q fever presentation (duration of infection >6 months):
  Endocarditis
  Hepatitis
- Most common clinical symptoms:
  Chills
  Sweats
  Nausea
  Vomiting
  Cough, nonproductive
  Headache
  Fatigue
- Most frequent physical findings:
  Fever
  Inspiratory rales
  Purpuric rash
  Hepatomegaly
  Splenomegaly
- Infected pregnant women may be asymptomatic acutely, yet fetal wastage may occur.

ETIOLOGY

- Q fever is caused by the Proteobacteria *C. burnetii*.
- *C. burnetii* is a gram-negative coccobacillus transmitted from arthropods to animals to human beings.
- The disease is acquired most often by inhalation of aerosols. In the lungs, it proliferates in macrophages and then gains access to the bloodstream, producing a transient bacteremia. Thereafter it can invade many organs, most commonly the lungs and liver.
- There is an incubation period of 3 to 30 days before systemic symptoms manifest.

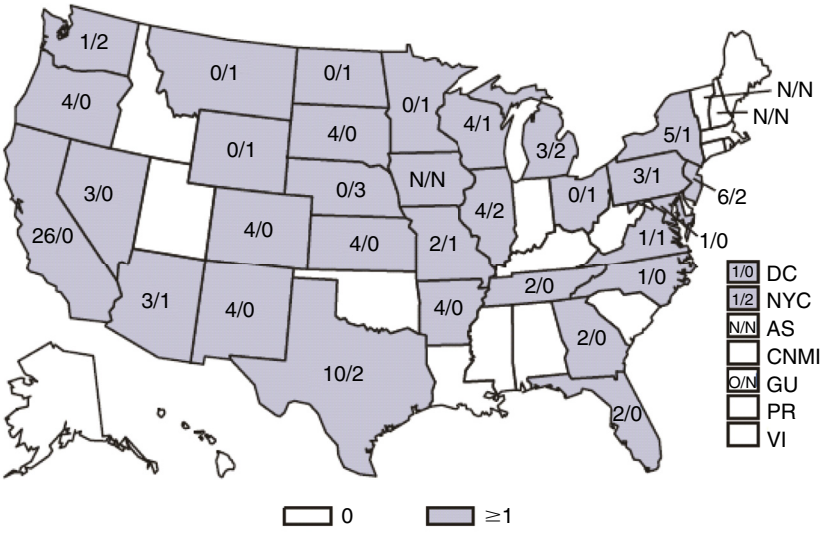


FIGURE EQ1-1 Q Fever, acute and chronic. Number of reported cases: United States and U.S. territories, 2010. (From Centers for Disease Control and Prevention: Summary of notifiable diseases—United States, 2010, *MMWR Morb Mortal Wkly Rep* 59:1-111, 2012.)

- Persons with abnormal heart valves, prosthetic valves, and endovascular grafts are at high risk of progression to chronic Q fever. This includes individuals with bicuspid aortic valves.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Q fever can have various presentations and must be in the differential diagnosis of fever, hepatitis, pneumonia, endocarditis, and meningitis. Situations that should prompt serologic testing for Q fever are described in Table EQ1-1.

WORKUP

- Complete blood count (CBC), erythrocyte sedimentation rate (ESR), and liver function tests
- Urinalysis
- Serology
- Chest x-ray

TABLE EQ1-1 Situations That Should Prompt Serologic Testing for Q Fever

Acute Q Fever (Phase II Antigen and IgG ≥200 and IgM ≥50)
Fever in a patient in contact with ungulates
Unexplained prolonged fever (>7 days)
Granulomatous hepatitis
Fever and thrombocytopenia
Meningoencephalitis
Myocarditis
Erythema nodosum
Fever during pregnancy
Fever in a patient in contact with a parturient pet
Unexplained atypical pneumonia
Fever and an increase in transaminases (2-5 times the normal level)
Aseptic meningitis
Guillain-Barré syndrome
Pericarditis
Spontaneous abortion
Chronic Q Fever (Phase I Antigen and IgG ≥800 and IgA ≥100)
Blood culture–negative endocarditis
Patient with a valvulopathy and unexplained fever
Weight loss
Fatigue
Increased erythrocyte sedimentation rate
Increased transaminases
Thrombocytopenia
Patient with unusually rapid degradation of a prosthetic valve
Fever in a patient with a vascular aneurysm or prosthesis
Aseptic osteomyelitis
Chronic pericarditis
Multiple spontaneous abortions

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

LABORATORY TESTS

In acute Q fever:
- CBC and white blood cell count are usually normal.
- Thrombocytopenia can occur (25%).
- Elevation of hepatic transaminases (two to three times the normal range) may be seen.
- Antibody detection by immunofluorescence assay is the most commonly used method because of its high sensitivity and specificity. Complement fixation (CF) shows a fourfold rise in titer between acute and convalescent samples.
- Polymerase chain reaction is desirable in early disease.
- Testing has been approved by the FDA and can be obtained from the CDC through the state health department.

In chronic Q fever (almost always endocarditis):
- ESR is elevated.
- Anemia is present.
- Microscopic hematuria
- Blood cultures are almost always negative.
- MIF (microimmunofluorescence) titer of >1:800 to phase I antigen is diagnostic.

IMAGING STUDIES

- Chest x-ray is abnormal, showing segmental lobe consolidation.
- Pleural effusions (35%)
- Transthoracic echocardiogram after the diagnosis of acute Q fever can be used to stratify risk of progression to endocarditis.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Oxygen as needed in patients with pneumonia

ACUTE GENERAL Rx

- Acute Q fever can be treated with doxycycline (100 mg bid) for 14 to 21 days *or*
- Clarithromycin is the macrolide of choice for acute infection given intolerance of doxycycline.
- Ofloxacin 200 mg PO q8h or ciprofloxacin 875 mg PO bid for 14 to 21 days
- Hydroxychloroquine plus doxycycline for endocarditis associated with Q fever
- Fluoroquinolones are recommended for suspected meningoencephalitis.
- Pregnant women may be treated with trimethoprim-sulfamethoxazole.

CHRONIC Rx

- Chronic Q fever is treated with a combination of two antibiotics, doxycycline 100 mg bid and rifampin 900 mg qd *or*
- Doxycycline 100 mg bid and ofloxacin 200 mg PO q8h *or* Cipro 875 mg PO bid
- Doxycycline 100 mg bid and hydroxychloroquine 200 mg PO tid is the preferred therapy.
- Duration of treatment: 2 to 3 yr, at minimum 18 months
- Consider prophylactic treatment for exposed individuals with preexistent high-risk cardiac lesions.

DISPOSITION

- Patients with acute Q fever respond well with antibiotics, with deaths rarely reported.
- Mortality rate in chronic Q fever endocarditis is high (24%). Many patients will need valve replacement surgery.

REFERRAL

Referral to an infectious disease expert is recommended in any cases of suspected acute or chronic Q fever.

REPORTING

Q fever has been a reportable disease in the U.S. since 1999. The CDC must be notified of cases.

PEARLS & CONSIDERATIONS

COMMENTS

- An acellular (CMR) vaccine is available in the U.S. However, vaccines that are available in other countries such as Australia have been more thoroughly studied.
- Infected patients do not require specific isolation precautions.
- Q fever derived its name in 1935 from Derrick, who was suspicious of a new disease during a series of acute febrile illnesses in abattoir workers of Queensland, Australia, justifying the name of Q fever (for "query").

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **PATRICIA CRISTOFARO, M.D.**

SUGGESTED READINGS

Anderson A et al.: Diagnosis and management of Q fever–United States 2013: recommendations from the CDC and the Q Fever Working Group, *MMWR* 62:1, 2013.

Bjork A et al.: First reported multi-state human Q fever outbreak in the United States, 2011, *Vector borne Zoonotic Dis*, 2013. In press.

Carcopino X et al.: Managing Q fever during pregnancy: the benefits of long-term cotrimoxazole therapy, *Clin Infect Dis* 45:548, 2007.

Centers for Disease Control and Prevention: Notes from the field: Q fever outbreak associated with goat farms—Washington and Montana, 2011, *MMWR* 60:1393, 2011.

Denman J, Woods M: Acute Q fever in pregnancy: report and literature review, *Intern Med J* 39(7):479–481, 2009.

Frankel D et al.: Q fever in France, 1985-2009, *Emerg Infect Dis* 17:350, 2011.

Ghigo E et al.: Intracellular life of Coxiella burnetii in macrophages, *Ann NY Acad Sci* 1166:55–66, May 2009.

Hartzell JD et al.: Q fever: epidemiology, diagnosis, and treatment, *Mayo Clin Proc* 83(5):574, 2008.

Healy B et al.: The value of follow-up after acute Q fever infection, *J Infect* 52(4):e109, 2006.

Karakousis PC et al.: Chronic Q fever in the US, *J Clin Microbiol* 44:2283, 2006.

Marrie TJ: Q fever pneumonia, *Infect Dis Clin North Am* 24(1):27–41, 2010.

McQuiston JH et al.: National surveillance and the epidemiology of human Q-fever in the United States, 1978-2004, *Am J Trop Med Hyg* 75(1), 2006.

Milazzo A et al.: Q fever vaccine uptake in South Australian meat processors prior to the introduction of the National Q Fever Management Program, *Commun Dis Intell* 29(4):400, 2005.

Oren I et al.: An outbreak of Q fever in an urban area in Israel, *Eur J Clin Microbiol Infect Dis* 24(5):338, 2005.

Raoult D et al.: Natural history and pathophysiology of Q fever, *Lancet Infect Dis* 5(4):219, 2005.

Rolain JM, Raoult D: Molecular detection of Coxiella burnetii in blood and sera during Q fever, *QJM* 98(8):615, 2005.

Tissot-Dupont H et al.: Role of sex, age, previous valve lesion, and pregnancy in the clinical expression and outcome of Q fever after a large outbreak, *Clin Infect Dis* 44:232, 2007.

Wagner-Wiening C et al.: Serological diagnosis and follow-up of asymptomatic and acute Q fever infections, *Int J Med Microbiol* 40:294, 2006.

Wegdam-Blans MC et al.: Chronic Q fever: review of the literature and a proposal for new diagnostic criteria, *J Infect* 64:247–259, 2012.

BASIC INFORMATION

DEFINITION

Rabies is a fatal zoonotic illness caused by the rabies virus and transmitted to human beings by the bite of an infected animal.

SYNONYMS

Hydrophobia

ICD-9CM CODES
071 Rabies
ICD-10CM CODES
A82.9 Rabies, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Approximately two cases annually. 45 cases from 1995 to 2009.
PREDOMINANT SEX: Men are more commonly affected (70% of cases)
PREDOMINANT AGE: <16 yr and <55 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Incubation period of 10 to 90 days
  1. Shorter incubation period with bites on the face. In domestic animals the incubation period is generally 3 to 12 weeks but can range from several days to months, rarely exceeding 6 months
  2. Longer if extremities involved
- Prodrome
  1. Fever
  2. Headache
  3. Malaise
  4. Pain or anesthesia at exposure site
  5. Sore throat
  6. Gastrointestinal symptoms
  7. Psychiatric symptoms
- Acute neurologic period, with objective evidence of central nervous system involvement
  1. Extreme hyperactivity and bizarre behavior alternating with periods of relative calm
  2. Hallucinations, disorientation
  3. Seizures
  4. Paralysis
  5. Fear, pain, and spasm of the pharynx and larynx caused by drinking
  6. Coma, death

ETIOLOGY

- Rabies virus: bullet-shaped virus that belongs to Rhaboviridae family, genus *Lyssavirus*
- Cases in the United States are associated with:
  1. Bats
  2. Raccoons
  3. Foxes
  4. Skunks
- Small rodents (squirrels, mice, rats, chipmunks) and lagomorphs such as rabbits almost never have rabies and in the United States have never been a source of transmission of rabies to humans.
- In 35 of the 45 cases occurring in the United States from 1995 to 2009, exposure to bats was felt to be the source albeit many did not have a clinically evident bite or scratch.
- Imported cases are usually associated with dogs.
- Unusual acquisition:
  1. By organ transplantation: kidney, liver, arterial segment
  2. By aerosol transmission in laboratory workers and spelunkers

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Delirium tremens
- Tetanus
- Hysteria
- Psychiatric disorders
- Other viral encephalitides
- Guillain-Barré syndrome
- Poliomyelitis

WORKUP

- The direct fluorescent antibody (DFA) test is the gold standard for rabies diagnosis. Animals submitted for rabies testing should be euthanized in a way that maintains the integrity of the brain
- Negri bodies are eosinophilic cytoplasmic inclusions found in neurons. They are the best-known histologic feature of rabies
- The national case definition for animal rabies requires laboratory confirmation by either:
  1. A positive DFA test (preferably performed on CNS tissue); or
  2. Isolation of rabies virus (in cell culture or in a laboratory animal)
- Figure R1-1 describes an approach to assessing rabies exposure and initiating post-exposure prophylaxis (PEP) in the United States.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Isolation of the patient to prevent transmission to others
- Supportive therapy

ACUTE GENERAL Rx

- No known beneficial therapy. A case report from 2005 describes a 15-yr-old girl who survived rabies and had been treated with a combination of ketamine, midazolam, ribavirin, and amantadine. It is known as the Milwaukee protocol. The protocol has been unsuccessful in subsequent reports and is considered investigative.
- Emphasis is placed on prophylaxis of potentially exposed individuals after an exposure:
  1. Thorough wound cleansing and irrigation of the wound with soap and water as soon as possible. If available, a virucidal agent (e.g., povidone-iodine solution) should be used to irrigate the wounds.
  2. Active and passive immunization is most effective when used within 72 hr of exposure.
- Vaccinations: The CDC has recently recommended reducing the number of vaccine doses for postexposure prophylaxis. Current recommendations for rabies postexposure prophylaxis are as follows:
  1. Human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) 1 ml IM (deltoid area) 1 each on days 0, 3, 7, and 14 in patients not previously vaccinated. In patients previously vaccinated administer HDCV or PCECV 1 ml IM (deltoid area) 1 each on days 0 and 3. Human rabies hyperimmune globulin (RIG) 20 IU/kg body weight should be administered to persons not previously vaccinated. If anatomically feasible, the full dose should be infiltrated into the wound; any remaining volume should be given IM at a site separate from vaccine administration.
- Preexposure prophylaxis with HDCV or RVA (1 ml IM on days 0, 7, and 21 or 28) in individuals at high risk for acquisition:
  1. Veterinarians
  2. Laboratory workers working with rabies virus
  3. Spelunkers
  4. Visitors to endemic areas

DISPOSITION

Virtually always fatal. Rabies has one of the highest case/fatality ratios of any infectious disease.

REFERRAL

- To infectious disease consultant
- To local health authorities

PEARLS & CONSIDERATIONS

COMMENTS

- Most cases in the United States are caused by:
  1. Bat bites, often after minimal contact and inapparent exposure to infected bat saliva
  2. Dog bites occurring outside the United States
- Rare cases can be transmitted by mucous membrane contact of aerosolized virus (caves, laboratory-acquired cases).

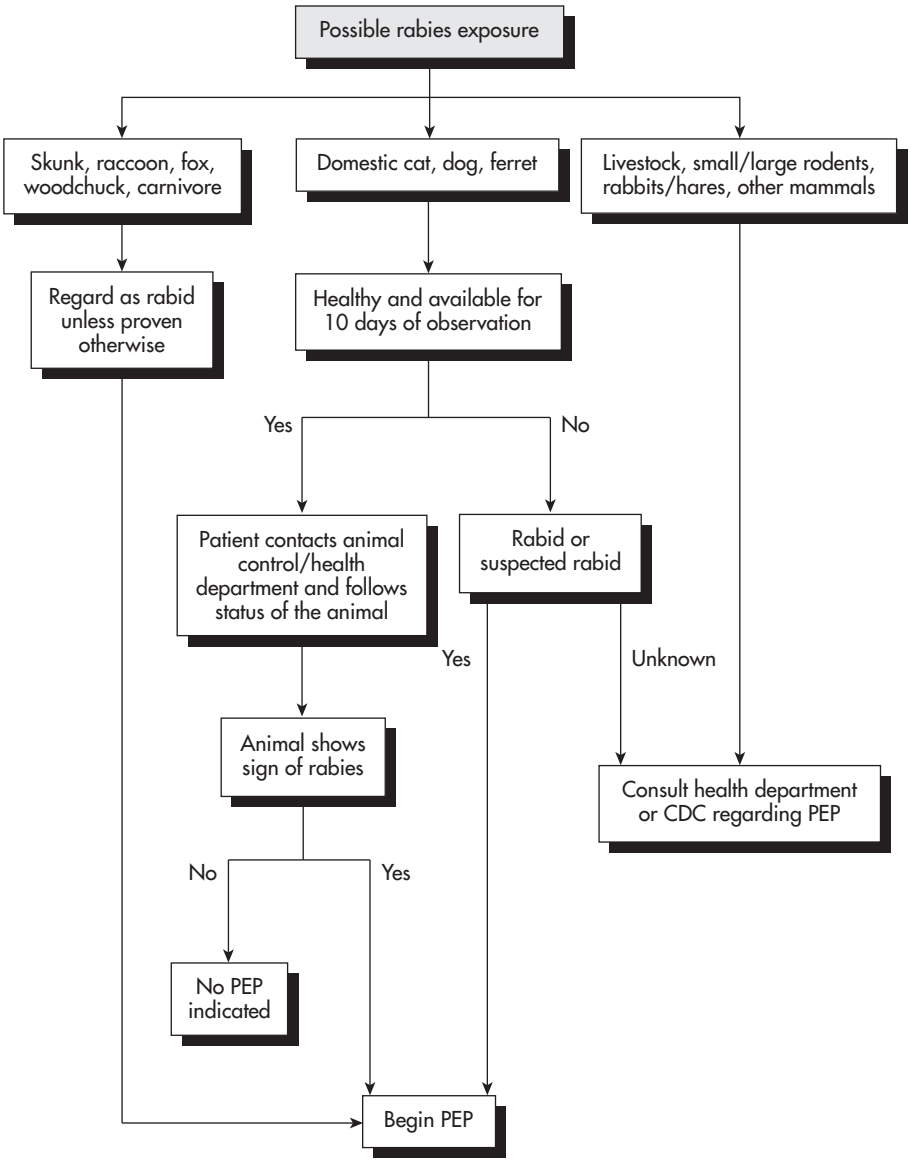
SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Rabies (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**



ALL WOUND EXPOSURES
Copious irrigation of wound and treatment with virucidal agent, such as povidine-iodine.

These recommendations are in accordance with CDC recommendations for exposures in the United States. Exposures outside the United States should be managed in consultation with the CDC.

FIGURE R1-1 Approach to assessing rabies exposure and initiating postexposure prophylaxis (PEP) in the United States. CDC, Centers for Disease Control and Prevention. (Adams JG et al: *Emergency Medicine, Clinical Essentials,* 2nd ed, Philadelphia, Elsevier, 2013.)

SUGGESTED READINGS

Hemachudha T, Wilde H: Survival after treatment of rabies, *N Engl J Med* 353(10):1068, 2005.

National Association of State Public Health Veterinarians, Inc: Compendium of animal rabies prevention and control, 2011, *MMWR Recomm Rep* 60(RR-6): 1–17, 2011.

Nigg AJ, Walker PL: Overview, prevention, and treatment of rabies, *Pharmacotherapy* 29(10):1182–1195, 2009.

Srinivasan A et al.: Transmission of rabies virus from an organ donor to four transplant recipients, *N Engl J Med* 352:1103, 2005.

Willoughby RE et al.: Survival after treatment of rabies with induction of coma, *N Engl J Med* 352:2508–2514, 2005.

BASIC INFORMATION

DEFINITION

Radiation is the emission of energy as electromagnetic waves or moving subatomic particles. It can be natural or man-made. Natural radiation can come from a cosmic source, such as the sun, or a terrestrial source, such as naturally occurring radionuclides. Man-made radiation can come from nuclear reactors and x-ray machines. Radiation with the potential for human tissue injury can either be ionizing or nonionizing radiation. Ionizing radiation can cause a direct effect with its interactions on cellular molecules such as DNA bases, proteins, and cellular membranes, or by indirectly affecting these molecules by influencing other molecules, primarily water, to generate free radicals. Examples of ionizing radiation include x-rays, gamma rays, and photons. Nonionizing radiation causes damage to biological tissues and aforementioned cellular components through the transfer of thermal (heat) energy. Examples of nonionizing radiation include microwave heating and sun exposure.

UNITS OF RADIATION

- Roentgen (R): unit of exposure in air.
- Radiation absorbed dose (rad): amount of radiation absorbed in a material; 100 rad =1 gray (Gy).
- Roentgen equivalent man (rem): amount of radiation biologic damage; 100 rem = 1 Sievert (Sv). It takes into account differential sensitivity among tissues (quality factor) (Table ER1-1).
- Lethal dose of radiation (LD 50): amount of radiation associated with death in 50% of those similarly exposed.

SYNONYMS

For large exposures (deterministic, or nonstochastic, effects of radiation):
Acute radiation syndrome
Radiation sickness
Chronic low-dose exposures produce stochastic effects. This has no common synonyms.

ICD-9CM CODES
990 Radiation exposure
ICD-10CM CODES
W88 Exposure to ionizing radiation
T66 Unspecified effects of radiation

EPIDEMIOLOGY & DEMOGRAPHICS

- High-dose radiation doses are limited to nuclear disasters.
- Epidemiology of cumulative low-level radiation is not well understood and is based on the following two dose-dependent theories:
  1. Stochastic effects of radiation exposure: there is a probability of damage-increased effect with dose, but there is no dose threshold and severity is not dose related.
  2. Deterministic effects: severity of damage is dose related but with a threshold below which there is no negative outcome.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Low-level radiation: Low-level radiation over time may present clinically with various malignancies that may be at increased incidence compared with background rates of malignancies, but there remains much controversy.
- Exposure to radiation from medical imaging tests has been implicated in secondary cancer; the rate of cancer has been found to be dose dependent and exposure increases incremental risk.
- Occupational radiation exposure has been associated with cancer risk, both non-CLL leukemia and other cancers. Occupational exposure has been implicated to cause cataracts in medical professionals who get exposure in a dose-dependent relationship.
- The clinical course of acute radiation syndrome depends on absorbed radiation dose and distribution. Although all tissues composed of short-lived cells are affected by radiation, the most sensitive of cells in adults include:
  - Crypt cells in the intestines
  - Hematopoietic cells in the bone marrow
  - Spermatocytes in the testis
- Acute radiation syndrome: Effects of acute radiation exposure are better studied based on previous nuclear disasters and are summarized in Table ER1-2. Radiation sickness

TABLE ER1-2 Dose Estimates for Common Life and Medical Activities

Activity	Dose Estimate
Natural background and man-made radiation (annual average dose equivalent, including radon)	360 mrem
Diagnostic chest x-ray	6-10 mrem
Flight from Los Angeles to Paris	800 mrem
Barium enema	5 mrem
Smoking 1.5 packs per day for 1 year	16,000 mrem = 16 rem
Heart catheterization	45,000 mrad = 45 rad = 0.45 Gy
Mild acute radiation syndrome	200 rad = 2 Gy
LD_{50} for acute whole body irradiation	450 rad = 4.5 Gy
Occupational limit for a radiation worker	5 rem = 0.05 Sv
Limit of a member of the public	0.1 rem = 0.001 Sv = 1 mSv

Gy, Gray; *LD50,* median lethal dose; *mrad,* millirad; *mrem,* millirem; *mSv,* millisievert; *rad,* radiation absorbed dose; *rem,* roentgen equivalent man; *Sv,* sievert.
Modified from Goans RE: Medical management of radiation incidents. In Shannon MW et al (eds): *Haddad and Winchester's clinical management of poisoning and drug overdose,* ed 4, Philadelphia, 2007, Saunders.

TABLE ER1-1 Symptoms, Therapy, and Prognosis of Whole Body Ionizing Radiation Injury

	0-1 SV	1-2 SV	2-6 SV	6-10 SV	10-20 SV	>50 SV
Therapeutic needs	None	Observation	Specific treatment	Possible treatment	Palliative	Palliative
Vomiting	None	5%-50%	>3 Gy, 100%	100%	100%	100%
Time to nausea, vomiting	—	3 hr	2 hr	1 hr	30 min	<30 min
Main locus of injury	None	Lymphocytes	Bone marrow	Bone marrow	Small bowel	Brain
Symptoms and signs	—	Moderate leukopenia, epilation	Leukopenia, hemorrhage, epilation	Leukopenia, hemorrhage, epilation	Diarrhea, fever, electrolyte imbalance	Ataxia, coma, convulsions
Critical period	—	—	4-6 wk	4-6 wk	5-14 days	1-4 hr
Therapy	Reassurance	Observation	Transfusion of granulocytes, platelets	Transfusion, antibiotics, bone marrow transplantation	Fluids and salts, possible bone marrow transplantation	Palliative
Prognosis	Excellent	Excellent	Guarded	Guarded	Poor	Hopeless
Lethality	0	0	0%-80%	80%-100%	100%	100%
Time of death	—	—	2 mo	1-2 mo	2 wk	1-2 days
Cause of death	—	—	Infection, hemorrhage	Hemorrhage, infection, pneumonitis	Enteritis, infection	Cerebral edema

Modified from Phillips TL: Radiation injury. In Wyngaarden JB et al (eds): *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.

symptoms are most apparent with doses >1 Gy delivered at a high dose rate.

1. Stage 1 (prodromal phase): flulike syndrome with anorexia, apathy, nausea, vomiting, diarrhea, fever, tachycardia, and/or headache, usually occurring within 48 to 72 hours.
2. Stage 2 (latent phase): a short period characterized by improvement in symptoms, lasting for several days to a month. Duration is inversely related to dose of radiation received and may be absent at severe doses of 10 Gy or greater.
3. Stage 3 (manifest illness phase): if the person survives this stage, recovery is likely.
    1. Hematopoietic syndrome: effects can occur with exposure >1 Gy and include pancytopenia, increased infection risk, and bleeding disorders.
    2. GI syndrome: radiation induces loss of intestinal crypts, resulting in abdominal pain, nausea, vomiting, anorexia, and diarrhea.
    3. Central nervous system: symptoms occur with a very high level of acute radiation (>5 Gy) and include ataxia, confusion, and coma.
4. Stage 4: Death or recovery, lasting weeks to months. Radiation exposure of greater than 5 Gy results in a high risk of death. No individual has survived doses of greater than 10 Gy of exposure. If patients survive, they will need lifelong follow-up because of the potential for unusual infections, organ dysfunction, and carcinogenesis.
    1. Radiation "burn": Prolonged exposure from fluoroscopy can lead to acute radiodermatitis presenting as red patches but over a few weeks can lead to tissue necrosis.

PROGNOSIS

ACUTE RADIATION SYNDROME

- Exposure <1 Gy: almost certain survival
- Exposure 1 to 2 Gy: 90% survival with medical care
- Exposure 2 to 3.5 Gy: probable survival with medical care
- Exposure 3.5 to 5.5 Gy: 50% survival with medical care
- Exposure 5.5 to 10 Gy: probable death
- Exposure >10 Gy: certain death

CHRONIC LOW-DOSE EXPOSURE: excess cancer not detected below 100 mSv

DIAGNOSIS

ACUTE RADIATION SYNDROME

- Diagnosis usually accompanies a nuclear disaster and therefore suspicion is already very high.
- Workup can include measuring radiation levels at site. Estimation of exposure may be accomplished using tools such as the METREPOL (Medical Treatment Protocols for Radiation Accident) clinical grading system, which is useful for prognosis.
- Laboratory studies: in the acute setting, CBC, brain imaging

CHRONIC LOW-DOSE EXPOSURE: Currently impossible to determine whether a subsequently diagnosed malignancy is radiation induced. Workup is for underlying malignancy evaluation.

ETIOLOGY

ACUTE RADIATION SYNDROME: usually nuclear disaster

CHRONIC LOW-DOSE EXPOSURE: The average annual dose to residents of the U.S. is approximately 3.6 mSv.

- Cosmic: positive-charged ions that interact with atmosphere to create secondary radiation
- Terrestrial: radon, potassium-40, thorium, and uranium
- Man-made: medical radiation including x-rays, CT scans, PET scans, nuclear stress tests, nuclear weapon fallout, fluoroscopy, and smoking

TREATMENT

- For all accidental radiation contamination, such as nuclear medicine materials, the following decontamination steps are considered mandatory:
    1. Perform at site of exposure unless there is continued radiation exposure.
    2. Remove all clothing (and treat as radioactive waste). Providers should use strict isolation precautions, including donning of gown, mask, cap, double gloves, and shoe covers, when evaluating and treating contaminated patients.
    3. Wash patient with mild soap (neutral pH) and tepid water. Dispose of contaminated water as radioactive waste.
    4. Scrub any open wound.
    5. Depending on the situation, the regional emergency response system should be called for additional measures such as evacuation.
- Management of acute radiation syndrome:
    1. Establish IV access.
    2. Monitor physiologic signs.
    3. Manage the airway.
    4. Manage burns.
    5. Identify and treat other injuries.
    6. Provide analgesia.
    7. Give antiemetics (e.g., ondansetron).
    8. Manage bleeding and transfuse if necessary.
    9. Diagnose and treat sepsis. Administration of antibiotics reduces the mortality rate. In nonneutropenic patients, use of antibiotics should be reserved for obvious foci of infection secondary to extensive burns, penetrating wounds, and/or abdominal/visceral trauma.
    10. Confirm initial dose estimate using chromosome aberration cytogenetic bioassay when possible.
    11. Thyroid protection should be considered with exposure to radioactive iodine exposure (e.g., nuclear reactor incident, atomic blast). Prevention of significant uptake is achieved with administration of potassium iodide (KI) within 6 hours of exposure. Repeat doses (every 24 hours) of KI can be administered if radioactive iodine exposure is expected for more than 24 hours.
    12. Consider colony-stimulating factors (CSFs). In any adult with whole-body or significant partial body exposure >3 Gy, treatment with CSFs should be rapidly initiated (e.g., G-CSF or filgrastim, 5 mcg/kg of body weight per day). CSFs may be withdrawn when the absolute neutrophil count reaches a level greater than 1.0×10^9 after recovery from the nadir.
    13. Consider stem cell transplantation in people with exposure dose of 7 to 10 Gy who do not have significant burns or other major organ toxicity and who have an appropriate donor.
    14. Provide counseling; 75% of individuals exposed to nuclear weapon detonations exhibit some form of psychological symptoms, ranging from insomnia to difficulty concentrating and social withdrawal.
- Chronic low-dose exposures: Treatment of radiation-induced organ damage would not differ significantly from non–radiation-induced cancers, cataracts, or skin lesions.
- Late sequelae of radiation exposure include cardiac manifestations such as restrictive cardiomyopathy, constrictive pericarditis and coronary artery disease. Those at high risk are patients with a radiation exposure of >35 Gy to the heart and usually manifests after 10 years of radiation exposure.

PEARLS & CONSIDERATIONS

COMMENTS

- It is difficult to make a link between exposure to chronic low-level radiation and a specific malignancy in an individual.
- Positioning patients for fluoroscopy procedures and monitoring amount of x-ray radiation are very important to prevent radiation burns.
- Humans are consistently exposed to background/naturally occurring radiation.
- Ionizing radiation from medical imaging procedures is not negligible. Since the early 1980s, the per capita dose of radiation from medical imaging has increased by a factor of nearly 6. Radiation exposure from imaging at current rates is predicted to be responsible for 2% of future cancers.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **DILBAHAR S. MOHAR, M.D.** and **PRANAV M. PATEL, M.D.**

EVIDENCE

Abstract[1]

Context:

People being exposed to potentially harmful amounts of radioactive iodine need prophylaxis to prevent high radiation-absorbed doses to the thyroid.

Objective:

Parameters determining the individual protective effect of a pharmacologic intervention were investigated.

Design and Participants:

Biokinetics of ^{123}I was evaluated in 27 healthy volunteers (aged 22–46 yr, median 25 yr, in total 48 assessments) twice in a baseline measurement of the undisturbed kinetics and in an intervention assessment 48 h later.

Interventions:

Seven regimens using single doses of potassium iodide (KI) or sodium perchlorate (SP) at different times relative to exposure were compared: 100 mg KI (–24, 2, 8, 24 h), 100 mg SP (2 h), or 1 g SP (2, 8 h).

Main Outcome Measures:

Different drugs and dosages and the influence of individual parameters of iodine kinetics should be tested.

Results:

Mean dose reductions for interventions at –24, 2, 8, and 24 h relative to the activity incorporation were 88.7, 59.7, 25.4, and 2.8%, respectively. One gram SP was equally effective as 100 mg KI; residual uptake was observed after 100 mg SP. The individual dose reduction decreased exponentially with the effective half-life of the activity in the blood. Kinetics in subjects older than 40 yr was as assumed in official guidelines for the prophylaxis after nuclear accidents but was faster in younger participants.

Conclusions:

Data on the efficacy of thyroid blocking used in the guidelines are adequate for older people but not for young individuals with their typically faster kinetics. SP may be used for thyroid blocking as alternative for individuals with iodine hypersensitivity. Ⓐ

Evidence-Based Reference

Hänscheid H et al.: Facing the nuclear threat: thyroid blocking revisited, *J Clin Endocrinol Metab* 96:3511, 2011. Ⓐ

SUGGESTED READINGS

Bashore T et al.: American College of Cardiology/Society for Cardiac Angiography and Interventions clinical expert consensus document on cardiac catheterization laboratory standards: a report of the American College of Cardiology, *JACC* 37(8), 2001.

Berkey FJ: Managing the adverse effects of radiation therapy, *Am Fam Physician* 82(4):381–388, 2010.

Christodouleas JP et al.: Short-term and long-term health risks of nuclear-power-plant accidents, *N Engl J Med* 364:2334, 2011.

Dörr H, Meineke V: Acute radiation syndrome caused by accidental radiation exposure - therapeutic principles, *BMC Medicine* 126(9), 2011.

Fazel R et al.: Exposure to low-dose ionizing radiation from medical imaging procedures, *N Engl J Med* 361:849, 2009.

Health Physics Society. Health Physics Society fact sheet. http://www.hps.org/documents/meddiagimaging.pdf. Accessed September 28, 2009.

Mettler FA et al.: Major radiation exposure–what to expect and how to respond, *N Engl J Med* 346:1554, 2002.

Muirhead CR et al.: Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers, *Br J Cancer* 100:206–212, 2009.

National Research Council. Health risks from exposure to low level ionizing radiation, BEIR VII. National Academies Press: Washington, DC.

Neriishi K et al.: Postoperative cataract cases among atomic bomb survivors: radiation dose response and threshold, *Radiation Res* 168:404, 2007.

Smith-Blindman R et al.: Use of diagnostic imaging studies and associated radiation exposure for patients enrolled in large integrated health care systems, 1996-2010, *JAMA* 307:2400, 2012.

Sodickson A et al.: Recurrent CT, Cumulative Radiation Exposure, and Associated Radiation-induced Cancer Risks from CT of Adults, *Radiology* 251:175–184, 2009.

US Department of Health and Human Services: *Population Monitoring in Radiation Emergencies: A guide for state and local health planners*, 2nd ed . Available at. http://www.bt.cdc.gov/radiation/pdf/population-monitoring-guide.pdf, 2014 (Accessed September 20, 2014).

Wagner LK et al.: Potential biological effects following high x-ray dose interventional procedures, *J Vasc Interv Rad* 5:71, 1994.

Waselenko JK et al.: Medical management of the acute radiation syndrome, *Ann Intern Med* 140:1037, 2004.

BASIC INFORMATION

DEFINITION

Ramsay Hunt syndrome is a localized herpes zoster infection involving the seventh nerve and geniculate ganglia, resulting in hearing loss, vertigo, and facial nerve palsy.

SYNONYMS

Herpes zoster oticus
Geniculate herpes
Herpetic geniculate ganglionitis

ICD-9CM CODES
053.11 Ramsay Hunt syndrome
ICD-10CM CODES
B02.21 Postherpetic geniculate ganglionitis

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT SEX: Equal sex distribution
PREDOMINANT AGE:
- Increasingly common with advancing age
- Rare in childhood

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Characteristic vesicles:
  1. On pinna
  2. In external auditory canal (Fig. R1-2)
  3. In distribution of the facial nerve and, occasionally, adjacent cranial nerves
- Facial paralysis on the involved side

FIGURE R1-2 Herpes zoster of the geniculate ganglion resulting in vesicles on the ear (as shown here) and tympanic membrane occurs in Ramsay Hunt syndrome. Both seventh and eighth cranial nerve functions may be affected. (From White GM, Cox NH [eds]: *Diseases of the skin: color atlas and text,* ed 2, St Louis, 2006, Mosby.)

ETIOLOGY

Reactivation of dormant infection with varicella-zoster virus after primary varicella

DIAGNOSIS

- Usually made by recognition of the clinical features detailed previously
- Viral culture and/or microscopic examination of specimens taken from active vesicles

DIFFERENTIAL DIAGNOSIS

- Herpes simplex
- External otitis
- Impetigo
- Enteroviral infection
- Bell's palsy of other etiologies
- Acoustic neuroma (before appearance of skin lesions)

The differential diagnosis of headache and facial pain is described in Section II.

WORKUP

If the diagnosis is in doubt, confirm varicella-zoster virus infection.

LABORATORY TESTS

- Generally not necessary
- Viral culture of specimens of vesicular fluid and scrapings of the vesicle base
- Tzanck preparation, which may reveal multinucleated giant cells
- Direct immunofluorescent staining of scrapings

IMAGING STUDIES

MRI may demonstrate enhancement of the facial and vestibulocochlear nerves before appearance of vesicles.

TREATMENT

ACUTE GENERAL Rx

- Use of corticosteroids is controversial.
- Acyclovir (800 mg PO five times qd for 10 days), famciclovir (500 mg tid for 7 days), or valacyclovir (1 g q8h for 7 days) may hasten healing.
- Use of prednisone (60 mg PO qd for 7 days or on a tapering regimen, 40 mg PO for 2 days, 30 mg for 7 days, followed by tapering course) is recommended by some authors but its use remains controversial.
- Analgesics should be used as indicated.

CHRONIC Rx

- Duloxetine and amitriptyline are effective in postherpetic pain.
- Other agents for postherpetic pain include gabapentin and pregabalin.
- Narcotic analgesics may occasionally be necessary.

DISPOSITION

Recurrences are unusual.

REFERRAL

To otolaryngologist: patients with persistent facial paralysis for potential surgical decompression of the facial nerve

PEARLS & CONSIDERATIONS

COMMENTS

Immunodeficiency states, particularly HIV infection, should be considered in:
- Younger patients
- Severe cases
- Patients with a history of specific risk behavior

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Ramsay Hunt Syndrome (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Diaz GA et al.: A case of Ramsay Hunt-like syndrome caused by herpes simplex virus type 2, *Clin Infect Dis* 40(10):1545, 2005.

Kinishi M et al.: Acyclovir improves recovery rate of facial nerve palsy in Ramsay Hunt syndrome, *Auris Nasus Larynx* 28(3):223, 2001.

Verm AM et al.: Necrotizing herpetic retinopathy associated with Ramsay Hunt syndrome, *Arch Ophthalmol* 120(7):989, 2002.

BASIC INFORMATION

DEFINITION

Raynaud's phenomenon (RP) is a vasospastic disorder that causes an exaggerated response to cold temperatures and/or emotional stress, resulting in episodic digital ischemia. It presents as a cold-induced, symmetric, sharply demarcated white or blue discoloration of the distal fingers or toes, followed by erythema at a variable time after rewarming.

SYNONYMS

Primary Raynaud's phenomenon or Raynaud's disease
Secondary Raynaud's phenomenon

ICD-9CM CODES
443.0 Raynaud's syndrome, Raynaud's disease, Raynaud's phenomenon (secondary)
ICD-10CM CODES
I73.0 Raynaud's syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- RP is classified clinically into primary or secondary forms and affects approximately 3% to 5% of the general population, 15% of children younger than 12 yr, and less than 1% of adults older than 60 yr.
- Occurs more commonly in colder climates.
- Primary RP usually occurs between the ages of 12 and 25 yr.
- It is more likely to affect women than men (4:1).
- 5% to 15% of patients with primary Raynaud's phenomenon develop a secondary cause later in the course of the disease (mostly a connective tissue disorder).
- Secondary RP tends to begin after age 35 to 40 yr.
- Secondary RP occurs in more than 90% of patients with scleroderma and in approximately 30% of patients with systemic lupus erythematosus or Sjögren's syndrome.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The typical manifestation of RP is the biphasic color response of the digits to cold exposure and rewarming, which may or may not be accompanied by pain. RP most often affects the hand (Fig. R1-3).
  1. White (pallor) or blue (cyanotic) discoloration of the digit(s) resulting from vasospasm on cold or vibration exposure.
  2. Red (rubor) with or without pain and paresthesia when vasospasm resolves and blood returns to the digit.
- Color changes can sometimes be induced by placing the hand in an ice bath, although this is not recommended as a diagnostic maneuver because responses may be inconsistent even in patients with definite RP.
- Color changes are well delineated, symmetric, and usually bilateral, involving the fingers and toes. The index, middle, and ring fingers are commonly involved and the thumb infrequently; however, if the thumb is involved, that suggests secondary causes of RP.
- Fingertips are most often involved, but feet, ears, nose, tongue, and nipples can also be affected.
- Patients with RP may exhibit a violaceous or reticular pattern of skin of arms and legs, sometimes with regular, unbroken circles (livedo reticularis).
- Duration of attacks can range from seconds to hours and averages 15 to 20 min.
- Chronic skin changes resulting from repeated attacks may include skin thickening and brittle nails. Ulcerations and, rarely, gangrene may occur.
- Physical examination should also include examination for symptoms associated with autoimmune disease, such as fever, rash, arthritis, dry eyes, dry mouth, myalgias, or cardiopulmonary abnormalities.

ETIOLOGY

- Primary RP can also be called idiopathic Raynaud's phenomenon, primary Raynaud's syndrome, or Raynaud's disease. It occurs in the absence of any associated disease.
- With primary RP, the possibility that another first-degree family member is affected is reported as approximately 25%.
- Secondary RP is associated with an underlying pathologic condition or disorder, use of certain drugs, or related occupation. Secondary RP is associated with:
  1. CREST syndrome (calcinosis, RP, esophageal involvement, sclerodactyly, and telangiectasia)
  2. Scleroderma, Sjögren's syndrome, mixed connective tissue disease, polymyositis, and dermatomyositis
  3. Primary pulmonary hypertension
  4. Systemic lupus erythematosus, arteritis
  5. Rheumatoid arthritis
  6. Thromboangiitis obliterans (Buerger's disease)
  7. Drugs (beta-blockers, ergotamine, methysergide, vinblastine, bleomycin, oral contraceptives, nicotine, clonidine, cocaine, caffeine, vinyl chloride, tegafur, interferon alfa, interferon beta)
  8. Hematologic disorders (polycythemia, cryoglobulinemia, cold agglutinins, paraproteinemia, cryofibrinogenemia)
  9. Carpal tunnel syndrome
  10. Use of tools that vibrate
  11. Endocrine disorders (hypothyroidism, carcinoid syndrome, pheochromocytoma, metabolic syndrome)
  12. Estrogen replacement therapy without progesterone
  13. Hypercoagulable states, protein C, protein S, antithrombin III deficiency, factor V Leiden deficiency, and antiphospholipid syndrome
  14. Poliomyelitis is a rare cause
  15. Primary biliary cirrhosis
  16. Vasospastic disorders (migraines, Prinzmetal angina)
  17. Malignancies (angiocentric lymphoma, ovarian cancer)

FIGURE R1-3 Raynaud's phenomenon. Sharply demarcated cyanosis of the fingers with proximal venular congestion (livedo reticularis) is seen. (From Klippel J et al [eds]: *Primary care rheumatology,* London, 1999, Mosby.)

DIAGNOSIS

Clinical criteria:
- Definite RP: repeated episodes of biphasic color change on cold exposure
- Possible RP: Uniphasic color changes plus numbness or paresthesia on cold exposure
- No RP: No color change on cold exposure

The suggested criteria for primary RP are:
- Symmetric attacks
- Absence of tissue necrosis, ulceration, gangrene, or peripheral vascular disease
- Absence of a secondary cause on the basis of a patient's history and general physical examination
- Negative nail-fold capillary examination
- Negative test for antinuclear antibody (ANA)
- Normal erythrocyte sedimentation rate (ESR)

Secondary RP is suggested by the following findings:
- Onset of symptoms after age 30 yr
- Male gender
- Episodes that are painful, asymmetric, or associated with ischemic skin lesions
- Clinical features suggestive of a connective-tissue disease
- Elevated specific autoantibody tests and ESR
- Evidence of microvascular disease on microscopy of nail-fold capillaries

DIFFERENTIAL DIAGNOSIS

- Neurogenic thoracic outlet syndrome or carpal tunnel syndrome
- Frostbite or cold weather injury
- Medication reaction (ergotamine, chemotherapeutic agents)
- Atherosclerosis, thromboembolic disease
- Buerger's disease, embolic disease
- Acrocyanosis
- Livedo reticularis
- Injury from repetitive motion

WORKUP

- Fig. R1-4 describes an approach to diagnosis of Raynaud's phenomenon. Once the diagnosis of RP is established, differentiating primary from secondary is helpful in treatment and prognosis.

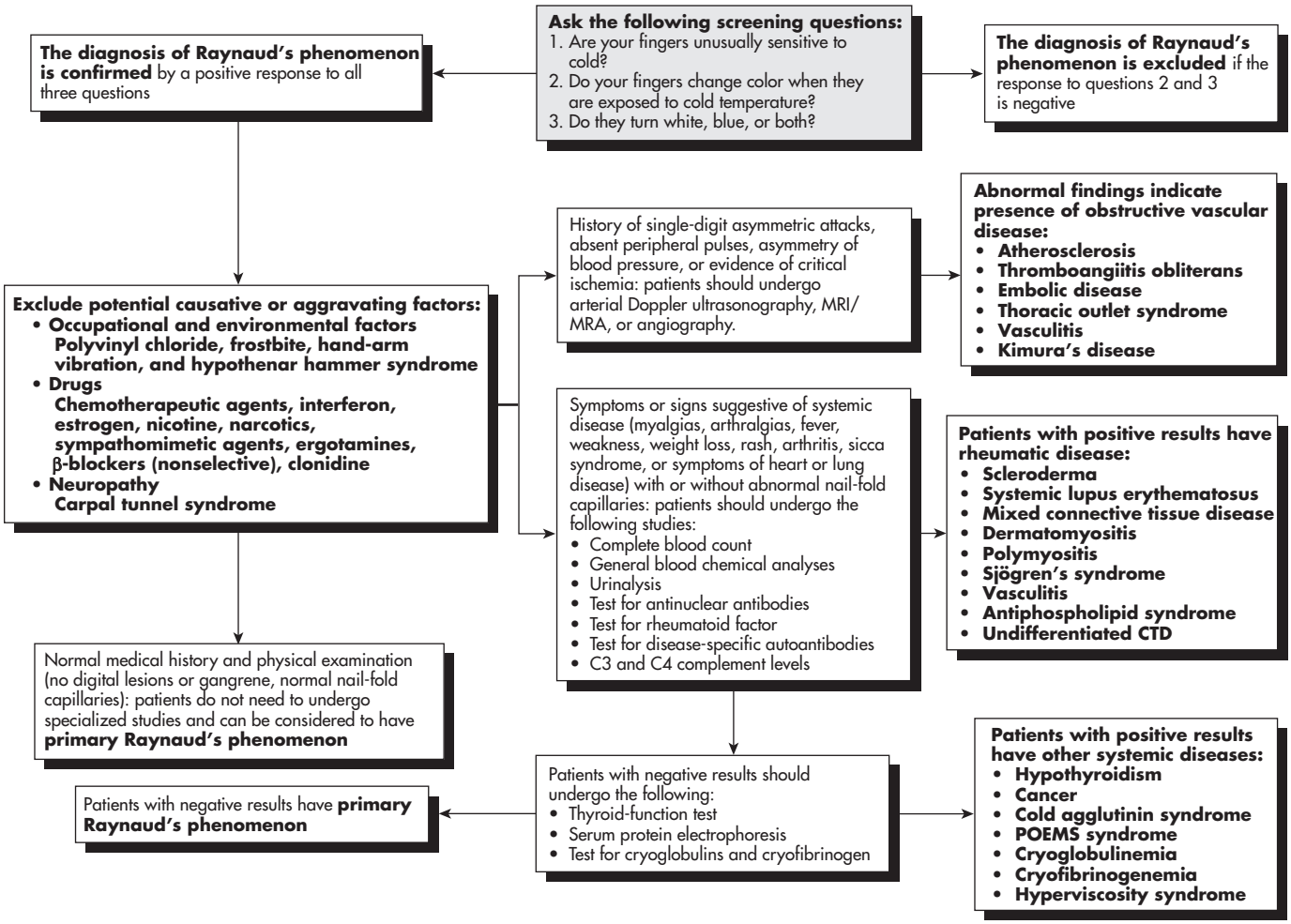


FIGURE R1-4 Approach to diagnosis of Raynaud's phenomenon. CTD, Connective tissue disease: MRA, magnetic resonance angiography: MRI, magnetic resonance imaging: POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. (From Firestein GS et al [eds]: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

- Patients who are younger when their symptoms occur, have a normal history and physical examination and normal nail-fold capillaries, and have no history of digital ischemic lesions can be considered as having primary RP. These patients can be monitored clinically without any further testing.
- If a secondary cause of RP is suspected, appropriate laboratory testing is recommended (see "Laboratory Tests"). Secondary RP has associated abnormal nail-fold microscopy.

LABORATORY TESTS

- CBC, serum electrolytes, blood urea nitrogen, creatinine, ESR, ANAs, VDRL antibody test, rheumatoid factor, and urinalysis should be included in the initial evaluation.
- If the history, physical examination, and initial laboratory tests suggest a possible secondary cause, specific serologic testing (e.g., anticentromere antibodies, anti-Scl 70, cryoglobulins, complement testing, and serum protein electrophoresis) may be indicated.
- Noninvasive vascular testing includes finger systolic blood pressures, segmental blood pressure measurements, cold recovery time (measure vasoconstrictor and vasodilator responses of finger to cold), fingertip thermography, and laser Doppler with thermal challenge (measures relative change in skin blood flow with ambient warming).

IMAGING STUDIES

- The diagnosis of RP should not be made on the basis of laboratory tests, and imaging studies should not replace a good history and physical examination.
- Duplex ultrasound can image the palmar arch and digital arteries for patency.
- Magnetic resonance angiography is useful for imaging larger arteries.
- Contrast angiography is the gold standard for arterial imaging.
- Nail-fold capillary microscopy can differentiate primary from secondary RP.
- Videomicroscopy and thermography are also useful for diagnosis of RP.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoid drugs that may precipitate RP (see "Etiology").
- Avoid cold exposure and sudden temperature shifts. Use warm gloves, hats, and garments during the winter months or before going into cold environments (e.g., air-conditioned rooms).
- Avoid stressful situations, and use relaxation techniques in preventing RP attacks.

ACUTE GENERAL Rx

- Acute measures to terminate an attack include rotating the arms in a windmill pattern, placing the hands under warm water or in a warm body fold such as the axilla, and the swing-arm maneuver.
- Medications are indicated in the treatment of RP if there are signs of critical ischemia or if the quality of life of the patient is affected to the degree that activities of normal living are no longer possible and preventive techniques do not work.

CHRONIC Rx

- Dihydropyridine calcium channel blockers (e.g., nifedipine, amlodipine, felodipine, nisoldipine, isradipine) are the most effective pharmacologic treatment for RP and are the drugs of choice.

- Nifedipine is most often prescribed at a dose of 10 to 20 mg 30 min before cold exposure. If symptoms occur with long duration, nifedipine XL 30 to 180 mg PO qd is often effective.
- Some potential therapeutic options include direct vasodilators such as nitroprusside, hydralazine, papaverine, minoxidil, niacin, and griseofulvin. Topical 1% nitroglycerin or topical l-arginine, ethyl nicotinate, hexyl nicotinate, thurfyl salicylate may also be useful, particularly if low blood pressure is a concern.
- Phosphodiesterase inhibitors (cilostazol, pentoxifylline, and sildenafil), angiotensin 2 receptor antagonists (losartan), and selective serotonin reuptake inhibitors (fluoxetine) have been used with some limited success.
- Alpha receptor antagonists such as prazosin and phenoxybenzamine have shown some effectiveness in treating RP.
- The prostaglandins, including inhaled iloprost, IV epoprostenol, alprostadil, and tadalafil, may be promising in severe RP. However, additional experience and controlled studies are needed.
- Antioxidants like zinc gluconate have been used to decrease tissue damage.
- *N*-Acetylcysteine and probucol have been shown to lead to improvement in RP.
- Anticoagulation with IV unfractionated heparin or subcutaneous low-molecular-weight heparin and addition of aspirin can be considered during the acute phase of a severe ischemic event. Aspirin (81 mg/day) therapy can be considered in all patients with secondary RP with a history of ischemic ulcers or thrombotic events; however, caution should be exercised because aspirin can theoretically worsen vasospasm by the inhibition of prostacyclin. Long-term anticoagulation with heparin or warfarin is not recommended unless there is evidence of a hypercoagulable state.
- Bypass surgery can be performed for severe RP associated with reconstructible arterial occlusive disease.
- Sympathectomy is available for unreconstructible occlusive disease or pure vasospastic disease refractory to medical treatment.
- Microsurgical revascularization of the hand and digital reconstruction may improve digital vascular perfusion and heal digital ulcers when proximal arterial occlusion is associated with digital vasospasm.
- Ischemic digital lesions should be treated with topical antibiotics and daily cleansing with soap and water. Digits that progress to dry gangrene should be permitted to undergo autoamputation. Surgical amputation is limited for intractable pain or deep tissue infection.

DISPOSITION

The prognosis of patients with RP depends on the etiology.

- Primary RP is fairly benign, usually remaining stable and controlled with nonpharmacologic medical treatment.
- Remission of primary RP can occur spontaneously.
- Patients with secondary RP, specifically those with scleroderma, CREST syndrome, or thromboangiitis obliterans, may develop severe ischemic digits with ulceration, gangrene, and autoamputation.

REFERRAL

- Rheumatology consult is indicated if secondary collagen vascular disease is diagnosed.
- Vascular surgery consult is indicated if ulcers, gangrene, or threatened digit loss is noted.

PEARLS & CONSIDERATIONS

- Most patients with RP can be managed by a primary care provider.
- It is important to differentiate primary from secondary forms. Secondary forms may become manifest as far out as 10 yr from the diagnosis of RP. It is important to take immediate action during an attack, and patients are encouraged to:
  1. Keep warm
  2. Not use tobacco products
  3. Avoid aggravating medications
  4. Control stress
  5. Exercise
  6. Follow up with a physician

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Raynaud's Phenomenon (Patient Information)

AUTHORS: **SYEDA M. SAYEED, M.D.,** and **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Bakst R et al.: Raynaud's phenomenon: pathogenesis and management, *J Am Acad Dermatol* 59(4):633–653, 2008.

Cook JP et al.: Mechanisms of Raynaud's disease, *Vasc Med* 10:297–307, 2005.

Henness S, Wigley FM: Current drug therapy for scleroderma and secondary Raynaud's phenomenon: evidence-based review, *Curr Opin Rheumatol* 19(6):611, 2007.

Wigley FM: Raynaud's phenomenon, *N Engl J Med* 347:1001–1008, 2002.

BASIC INFORMATION

DEFINITION

Rectal prolapse is an often socially disabling condition characterized by the circumferential protrusion of part or all layers of the rectum beyond the anus. The two main types of rectal prolapse include: (1) partial prolapse including the anal or rectal mucosa only, and (2) complete (full-thickness) prolapse involving all layers of the rectum (Fig. R1-5). A third and less common type is prolapse of the rectal wall that does not protrude through the anus known as an occult prolapse or rectal intussusception.

SYNONYMS

Procidentia
Rectal intussusception

ICD-9CM CODES
569.1 Rectal prolapse
ICD-10CM CODES
K62.3 Rectal prolapse
K62.2 Anal prolapse

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Unknown in general population. In children with cystic fibrosis it approaches 20%.
PEAK INCIDENCE: Women after the fifth decade represent between 80% and 90% of patients with rectal prolapse. Incidence increases with each decade in female patients until the seventh decade.
PREVALENCE: N/A
PREDOMINANT SEX AND AGE: Rectal prolapse occurs at the extremes of age, with an equal sex distribution in children. In adults, females predominate by a ratio of nine to one.
GENETICS: N/A
RISK FACTORS: Cystic fibrosis, hemorrhoids, laxity of the pelvic fascia/muscles due to prior pelvic surgery or obstetric trauma, anal sphincter dysfunction, chronic constipation, and increasing age

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most patients detect a mass, usually after defecation or strenuous activity. Later in the course, patients may develop prolapse with activities such as standing or walking.
- In children, the prolapse usually appears as a painless, maroon-colored mass associated with mucous or blood
- Anal sphincter weakness associated with rectal prolapse may cause fecal incontinence
- Other common symptoms include rectal bleeding, a change in bowel habits, incomplete evacuation or tenesmus, and a mucous discharge with bowel movements.
- Differentiating between mucosal and complete prolapse can be helpful yet challenging. Mucosal prolapse usually occurs distal to the dentate line, extending only a few centimeters beyond the anus. Complete prolapse may extend up to 15 cm and will usually have a normal-appearing anus as compared to mucosal prolapse, in which the anal edges appear everted.

ETIOLOGY

- Rectal prolapse usually occurs secondary to a deficient pelvic floor which leads to rectal herniation
- Multiple conflicting theories exist for the etiology of rectal prolapse including: (1) a redundant sigmoid colon lying deep within the pelvis, (2) an intussusception due to poor anorectal tone, (3) injury to the pudendal nerves from repeated stretching of the pelvic floor, and (4) abnormal fixation of the rectum.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rectal cancer, hemorrhoids, rectal polyps, intussusception

WORKUP

- General principles of evaluation include a thorough physical examination including digital rectal examination, imaging studies to evaluate various etiologies, and surgical consultation for repair

LABORATORY TESTS

- In general, patients with rectal prolapse do not need laboratory testing if they are appear well or are mostly asymptomatic.
- A hemoglobin/hematocrit may be obtained if there is concern for significant bleeding. A metabolic panel may be obtained if there is concern for electrolyte abnormalities.
- All patients that require surgical intervention will need preoperative laboratory testing.

IMAGING STUDIES

- Screening evaluation of the colon with colonoscopy or a barium enema is recommended in most adult patients after reduction or repair of rectal prolapse.
- Additional studies such as cinedefecography, anorectal manometry, electromyography, and colonic transit studies may be considered in the evaluation of patients with rectal prolapse.

TREATMENT

- Operative intervention is the mainstay of treatment for rectal prolapse with over 100 different procedures described. Goals of surgical treatment include control of the prolapse, restoring continence, and preventing constipation.
- The choice of operative repair takes into account many factors including: coexisting slow transit constipation, postoperative rectal compliance, pelvic floor denervation, the possibility of postoperative sexual dysfunction in men, age, cardiac and pulmonary risk factors, prior abdominal surgeries or pelvic irradiation, and overall immune function.
- Given that many patients with rectal prolapse carry high operative risk given age and concomitant disease, nonoperative treatment is appealing but only temporary.

NONPHARMACOLOGIC THERAPY

- Abdominal procedures such as suture rectopexy with sigmoid resection and/or subtotal colectomy yield better results in young, healthy patients and are associated with lower recurrence rates.
- Perineal procedures such as perineal rectosigmoidectomy with levatorplasty have a higher rate of recurrence and functional abnormality, yet carry a lower surgical risk and are thus reserved for high risk, older surgical patients.

ACUTE GENERAL Rx

- Manual reduction can be attempted after appropriate analgesia or sedation. In children, the protruding mucosa proximal to the anorectal ring is replaced by applying slow and steady pressure to the prolapsed segment.
- In adults, manual reduction is more challenging and may take several minutes. The thumbs are placed over the prolapsed segment medially and the fingers grasp the outer walls laterally. Continuous, steady pressure starting with the thumbs followed by rolling of the fingers can aid in reduction.
- After reduction, a digital rectal examination should be performed on all patients to ensure that the reduction is complete, and to evaluate for mass or polyps. Gauze with a lubricant jelly can be placed over the anus and taped in place after reduction.
- Patients with severe rectal prolapse that cannot be reduced or have ischemia/gangrene of the prolapsed segment will require emergency surgical consultation and hospitalization.
- Granulated sugar applied for 15 minutes to a swollen prolapsed segment has been used to reduce edema before attempting manual reduction.

CHRONIC Rx

- Patients with edematous rectal walls, venous engorgement, thrombosis, ulcerations, strangulation, or ischemia will likely not be candidates

FIGURE R1-5 Prolapse of the rectum. (Courtesy of Gershon Effron, MD, Sinai Hospital of Baltimore. From Seidel HM, et al: *Mosby's Guide to Physical Examination,* ed 4, St. Louis, 1999, Mosby.)

for manual reduction and will require more urgent surgical referral.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

- N/A

DISPOSITION

- Patients with reducible and nonischemic rectal prolapse without significant bleeding can be referred for outpatient surgical consultation and intervention.
- Patients with ischemic or nonreducible segments associated with gangrene or severe bleeding will need to be hospitalized.

REFERRAL

- Patients with rectal prolapse will require colorectal surgical consultation. Many patients will also require referral to a gastroenterologist for screening colonoscopy.

PEARLS & CONSIDERATIONS

COMMENTS

- Rectal prolapse is a relatively rare yet socially debilitating condition that appears at the extremes of age
- Manual reduction is the mainstay of initial treatment after appropriate analgesia or sedation
- Surgical referral is warranted for all patients and emergent referral should be made for all patients with ischemic, gangrene, or nonreducible prolapsed segments.

PREVENTION

- Avoiding chronic constipation

AUTHOR: **STEVEN ROUGAS, M.D., M.S.**

SUGGESTED READINGS

Burgess BE: Anorectal disorders. In Tintinalli JE, Stapczynski J, Ma O, Cline DM, Cydulka RK, Gourgiotis S, Baratsis S, editors: *Rectal prolapse*, Int J Colorectal Dis, 22. 2007, pp 231–243.

Meckler GT, editor: *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 7 e, New York, 2011, McGraw-Hill.

BASIC INFORMATION

DEFINITION

Reiter's syndrome is one of the seronegative spondyloarthropathies, so called because serum rheumatoid factor is not present in these forms of inflammatory arthritis. There is an international consensus that the term *reactive arthritis* (ReA) should replace the name "Reiter's syndrome" to describe this constellation of signs and symptoms. Unfortunately, the original name is still associated with the syndrome. Reiter's syndrome is an asymmetric polyarthritis that affects mainly the lower extremities and is associated with one or more of the following:

- Urethritis
- Cervicitis
- Dysentery
- Inflammatory eye disease
- Mucocutaneous lesions

SYNONYMS

Reiter's disease
Reactive arthritis
Seronegative spondyloarthropathy

ICD-9CM CODES
099.3 Reiter's syndrome
ICD-10CM CODES
M02.30 Reiter's disease, unspecified site

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 0.0035% annually of men ≤50 yr
PEAK INCIDENCE: Most common in the third decade
PREDOMINANT SEX: Male
PREDOMINANT AGE: 20 to 40 yr
GENETICS: Familial disposition: strongly associated with HLA-B27 (63% to 96%)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Polyarthritis
  1. Affecting the knee and ankle
  2. Commonly asymmetric
- Heel pain and Achilles tendinitis, especially at the insertion of the Achilles tendon
- Plantar fasciitis
- Large effusions
- Dactylitis, or "sausage toe"
- Urethritis
- Uveitis or conjunctivitis; uveitis can progress to blindness without treatment
- Keratoderma blennorrhagicum, circinate balanitis
  1. Hyperkeratotic lesions on soles of the feet (Fig. ER1-6), toes, penis (Fig. ER1-7), hands
  2. Closely resembles psoriasis
- Aortic regurgitation similar to that seen in ankylosing spondylitis

ETIOLOGY

- Epidemic Reiter's syndrome after outbreaks of dysentery has been well described.
- Genetically susceptible HLA-B27 individuals are at risk for developing Reiter's syndrome after infection with certain pathogens:
  1. *Salmonella*
  2. *Shigella*
  3. *Yersinia enterocolitica*
  4. *Chlamydia trachomatis*
- Symptom complex indistinguishable from Reiter's syndrome has been described in association with HIV infection.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Ankylosing spondylitis
- Psoriatic arthritis
- Rheumatoid arthritis
- Gonococcal arthritis-tenosynovitis
- Rheumatic fever

WORKUP

- X-ray examination of affected joints
- Synovial fluid examination and culture
- Careful examination of eyes and skin
- Cultures for gonococcus (urethral, cervical, stool)

LABORATORY TESTS

- Elevated but nonspecific erythrocyte sedimentation rate
- No specific laboratory tests to diagnose Reiter's syndrome
- Do not use HLA-B27 testing as a diagnostic tool

IMAGING STUDIES

Plain radiographs:

- Juxtaarticular osteopenia of affected joints
- Erosions and joint space narrowing in more advanced disease
- Periostitis and reactive new bone formation at the insertions of the Achilles tendon and the plantar fascia
- Sacroiliitis:
  1. Unilateral or bilateral
  2. Indistinguishable from ankylosing spondylitis
- Vertebral bridging osteophytes

TREATMENT

NONPHARMACOLOGIC THERAPY

Physical therapy to maintain range of motion of the spine and other joints

ACUTE GENERAL Rx

- Flares treated with nonsteroidal anti-inflammatory drugs such as indomethacin (25 to 50 mg PO tid).
- Enteric or urethral infection should be treated with appropriate antibiotic coverage.
- Uveitis should be treated with steroid eye drops in consultation with an ophthalmologist.
- Achilles tendinitis and plantar fasciitis should be treated with injections of methylprednisolone (40 to 80 mg).
- Sulfasalazine (2 to 3 g PO tid) may be effective.
- Careful monitoring for the following is essential:
  1. Gastrointestinal toxicity
  2. Hypersensitivity
  3. Bone marrow suppression
- Persistent and uncontrolled disease should be managed with cytotoxic drugs (methotrexate, azathioprine) in consultation with a rheumatologist.

CHRONIC Rx

Chronic disease is best managed by a team approach with the collaboration of a rheumatologist or other experienced physician and physical therapist.

DISPOSITION

- Recurrences are frequent, even with treatment.
- Long-term sequelae:
  1. Persistent polyarthritis
  2. Chronic back pain
  3. Heel pain
  4. Progressive iridocyclitis
  5. Aortic regurgitation

REFERRAL

- To ophthalmologist if uveitis is suspected
- To rheumatologist if arthritis and tendinitis fail to improve rapidly after a course of nonsteroidal anti-inflammatory drugs

PEARLS & CONSIDERATIONS

COMMENTS

- Infection with HIV is associated with particularly severe cases of Reiter's syndrome.
- HIV testing is recommended, especially if risk factors such as unprotected sexual activity or IV drug use are identified.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Reiter's Syndrome (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Eapen BR: A new insight into the pathogenesis of Reiter's syndrome using bioinformatics tools, *Int J Dermatol* 42(3):242, 2003.

Hannu T: Reactive arthritis, *Best Pract Res Clin Rheumatol* 25(3):347–357, 2011.

Klecker RJ, Weissman BN: Imaging features of psoriatic arthritis and Reiter's syndrome, *Semin Musculoskelet Radiol* 7(2):115, 2003.

Neumann S et al.: Reiter's syndrome as a manifestation of an immune reconstitution syndrome in an HIV-infected patient: successful treatment with doxycycline, *Clin Infect Dis* 36(12):1628, 2003.

Petersel DL, Sigal LH: Reactive arthritis, *Infect Dis Clin North Am* 19(4):863–883, 2005.

Schneider JM et al.: Reiter's syndrome, *Cutis* 71(3):198, 2003.

FIGURE ER1-6 Reiter's syndrome. A and **B,** Examples of lesions on the soles; these annular lesions are typical of keratoderma blennorrhagicum. (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

FIGURE ER1-7 Reiter's syndrome. Circinate balanitis, with urethral discharge. (Courtesy Dr. B. Stanley. From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

BASIC INFORMATION

DEFINITION

Renal artery stenosis (RAS) is the progressive narrowing of the renal artery, which is most commonly due to atherosclerosis or fibromuscular dysplasia (FMD). RAS is an important, potentially reversible cause of hypertension ischemic nephropathy, and destabilizing cardiac syndromes. RAS increases the risk of acute renal artery occlusion, which usually results from cardiac emboli, vascular emboli, or in situ thrombosis.

SYNONYMS

Acute:
- Renal artery thrombosis
- Renal artery embolism

Chronic:
- Renovascular hypertension

ICD-9CM CODES
440.1 Renal artery stenosis
405.01 Renovascular hypertension, secondary
447.9 Renal artery hyperplasia

ICD-10CM CODES
I70.1 Atherosclerosis of renal artery
I15.0 Renovascular hypertension
I77.9 Disorder of arteries and arterioles, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Chronic RAS:
  1. Atherosclerotic RAS (ARAS) accounts for about 90% of chronic RAS. True prevalence is unknown.
     a. General population autopsy studies show prevalence of 4% and 2% to 5% in hypertensive patients.
     b. In the general population >65 yr of age, the prevalence is 6.8% (5.5% of women, 9.1% of men, 6.7% of African Americans, and 6.9% of Caucasians). Of those with ARAS, 12% had bilateral disease.
     c. In patients with malignant hypertension, the prevalence is 43% in Caucasians and 7% in African Americans. In patients with mild hypertension, the prevalence is <1%.
     d. In patients with peripheral artery disease, the prevalence is 22% to 59%.
  2. FMD accounts for approximately 10% of chronic RAS. It is typically seen in women (81%) aged <50 yr. 26% have bilateral disease.
     - Acute renal artery occlusion:
       1. Epidemiology depends on the underlying cause. The incidence on autopsy study was 1.4%.

ETIOLOGY

RAS and thrombosis:
- Atherosclerosis: risk factors for atherosclerosis include family history, smoking, diabetes, hypertension, and hyperlipidemia. Typically involves the ostium and proximal third of the main renal artery. Patients with ARAS are often older and have multiple cardiovascular risk factors and systemic atherosclerosis.
- Fibromuscular dysplasia (FMD) (Fig. R1-8): etiology unknown. Classified into three categories based on the layer of arterial wall affected: medial (>90%), intimal (<10%), adventitial (<1%). Typically involves the distal main renal artery and intrarenal branches. FMD is largely a disease of the young and healthy with few risk factors.
- Extrinsic compression (e.g., neoplasm)
- Neurofibromatosis and fibrous bands
- Vasculitides, including autoimmune (Takayasu's syndrome, antiphospholipid syndrome), infectious (syphilis)
- Renal artery aneurysm
- Hypercoagulable state
- Complication of renal transplantation (role of cyclosporine)

Renal artery embolism (cardiac conditions contribute 90%):
- Left ventricular thrombus (may be the result of myocardial infarction or other cardiomyopathy)
- Atrial fibrillation
- Endocarditis
- Paradoxical emboli from deep vein thrombosis in patient with atrioventricular or ventricular septal defect
- Atheromatous plaques (cholesterol emboli)

PATHOGENESIS

- Pathogenesis of fibromuscular dysplasia is unknown.
- The pathogenesis of hypertension is related to the neurohormonal cascade resulting from renal ischemia. The macula densa of the kidney senses a decreased systemic blood pressure caused by the reduced blood flow through the stenotic artery leading to a decrease in the glomerular filtration rate. Renal hypoperfusion or ischemia produces an increase in plasma renin that stimulates the conversion of angiotensin I to angiotensin II, causing vasoconstriction and aldosterone secretion, sodium retention, and potassium wasting. Hypertension results and can be self-sustaining, even in the case of unilateral RAS, because of hypertensive damage to the contralateral kidney.

NATURAL HISTORY

- RAS caused by fibromuscular dysplasia generally does not progress. Fibromuscular dysplasia RAS responds well to angioplasty with long-term patency of the lesion typically observed.
- RAS associated with atherosclerosis is progressive and confers a poor prognosis. Of patients with >60% stenosis, 5% progress to total occlusion in 1 yr and 11% progress in 2 yr.
- An increased pulse pressure (PP), defined as systolic minus diastolic blood pressure, has been implicated in the development and progression of small-vessel disease and has been shown to reflect more advanced renal disease. It can help identify patients who are less likely to benefit from percutaneous interventions.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Progressive RAS:
- Majority of patients with RAS are asymptomatic.

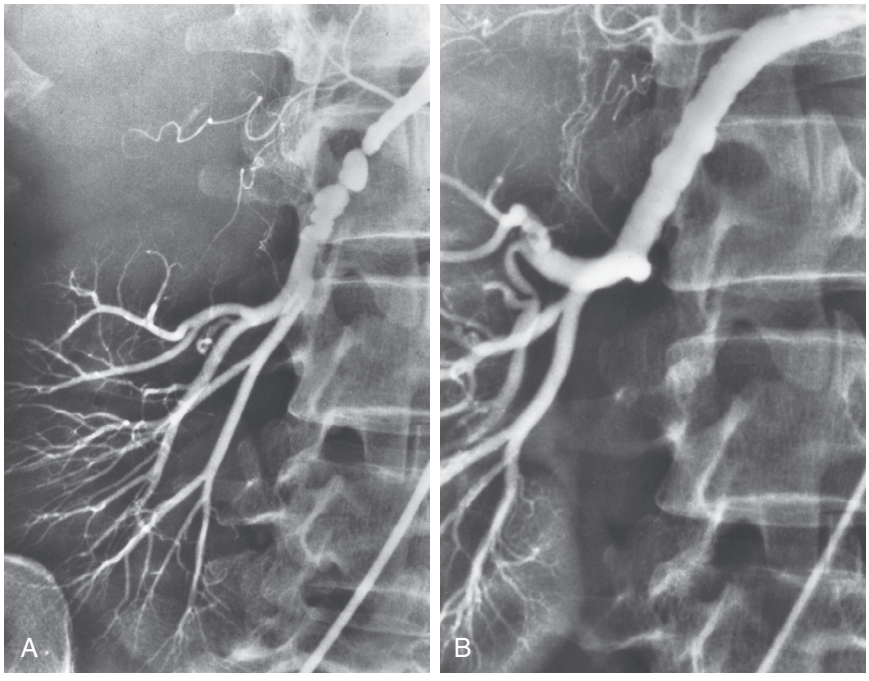


FIGURE R1-8 Fibromuscular dysplasia. A, Selective renal arteriogram illustrating the beaded appearance of fibromuscular dysplasia with multiple webs characteristic of medial fibroplasia in a 39-yr-old woman. **B,** Selective injection of the same renal artery after technically successful percutaneous transluminal renal angioplasty. (Courtesy Michael McKusick, M.D., Mayo Clinic, Rochester, Minnesota. From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

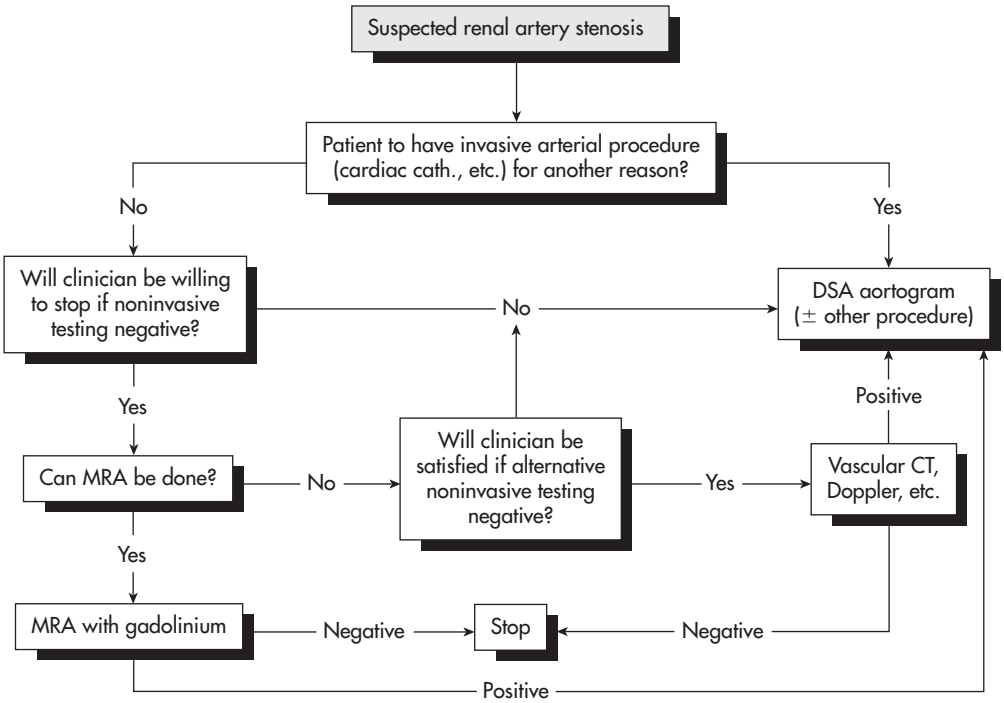


FIGURE R1-9 Approach to the anatomic evaluation of renal artery stenosis. Once stenosis is suspected, if the patient is to have another invasive arterial procedure, noninvasive imaging is deferred and a low-volume digital subtraction aortogram *(DSA)* is done at the time of that procedure. In other cases, the clinician should assess whether a negative noninvasive test would be sufficient evidence to acquit the renal arteries. If so, noninvasive testing should be performed. If not, consideration should be given to DSA and selective angiography. *Cath,* Catherization; *CT,* computed tomography; *MRA,* magnetic resonance angiography. (From Zipes DP et al [eds]: *Braunwald's heart disease,* ed 7, Philadelphia, 2005, Saunders.)

- Fibromuscular dysplasia: new-onset hypertension at age <50 yr or hypertension in any patient without family history or risk factors
- Atherosclerotic renal artery disease: new-onset hypertension at age >55 yr, with risk factors for or evidence of atherosclerotic disease
- Uncontrolled hypertension refractory to three or more medications including a diuretic
- Abdominal bruit (40% of cases)
- Chronic kidney disease
- Hypertensive retinopathy
- Pulmonary edema in a hypertensive patient
- Hypokalemia
- Acute kidney injury (AKI) after the administration of an ACE inhibitor (ACEI) has previously been considered a marker for bilateral RAS but is neither sensitive nor specific.

Acute renal artery occlusion:

- Flank or abdominal pain
- Fever
- Nausea and/or vomiting
- Leukocytosis
- Hematuria (microscopic or gross)
- Elevated aspartate aminotransferase, lactate dehydrogenase, and alkaline phosphatase
- Oliguric renal failure if occlusion is bilateral; normal or near-normal renal function in unilateral occlusion
- Cholesterol or septic emboli: depending on distribution of emboli, patients may have multisystem manifestations such as visual disturbance, painful distal extremities, abdominal pain, signs of organ or limb ischemia; laboratory findings include eosinophiluria, proteinuria, AKI, elevated erythrocyte sedimentation rate

DIAGNOSIS

SCREENING

American College of Cardiology and American Heart Association (ACC/AHA) guidelines for identifying patients who should be screened for RAS:

- Onset of hypertension at age <30 yr or severe hypertension at age >55 yr
- Clinical findings that suggest secondary hypertension as opposed to essential hypertension in the absence of another more likely cause of secondary hypertension such as pheochromocytoma
- Malignant hypertension: hypertension with coexistent evidence of acute end-organ damage (acute renal failure, acute decompensated heart failure, new visual or neurologic disturbance, and/or advanced retinopathy)
- Accelerated hypertension: sudden and persistent worsening of previously controlled hypertension
- Resistant hypertension: full doses of a three-drug regimen that includes a diuretic
- Sudden unexplained pulmonary edema
- New azotemia or acute renal failure after ACEI or angiotensin receptor blockers (ARBs)
- Unexplained atrophic kidney or variation in size of both kidneys by >1.5 cm, smaller kidney likely affected by RAS

LABORATORY TESTS

- Basic chemistry, including sodium, potassium, blood urea nitrogen, and creatinine
- Glomerular filtration rate
- Urinalysis and urine cultures
- Electrocardiogram to evaluate for atrial fibrillation and signs of coronary artery disease/myocardial infarction
- Hypercoagulable workup in setting of thrombosis or embolic disease

IMAGING STUDIES

- Duplex Doppler ultrasonography, CT angiography, and magnetic resonance angiography (MRA) are effective diagnostic screening methods. The choice of imaging modality will depend on the availability of the diagnostic tool, the experience and local accuracy of each modality, and patient characteristics, including body size, renal function, contrast allergy, and presence of prior stents. Fig. R1-9 describes an approach to the anatomic evaluation of RAS. An approach to the angiographic evaluation and treatment of RAS is described in Fig. ER1-10.
- Duplex Doppler ultrasonography is safe and inexpensive. When compared with angiography, duplex ultrasound has a sensitivity of 84% to 98% and a specificity of 62% to 99% for detecting RAS. An end-diastolic velocity of >150 cm/sec predicts severe RAS (>80% stenosis). Peak systolic velocity >285 cm/sec, renal/aorta ratio >3.5, and/or renal resistive index >0.15 correlated

with RAS >60%. Duplex Doppler ultrasonography may also be used to measure the renal dimensions. US is a good surveillance test to monitor stent patency after intervention. Limitations include operator-dependent imaging, patient body habitus, and poor visualization of accessory renal arteries.

- MRA (Fig. R1-11) provides good visualization of both main and accessory renal arteries. The test has high sensitivity (90%-100%) and a specificity of 76% to 94%. Limitations include the associated risk of nephrogenic systemic fibrosis with gadolinium infusion, high cost, inability to image within a previously placed metallic stent, and lack of widespread availability.
- CT angiography is fast and effective. When compared with angiography, CT has a sensitivity of 59% to 96% and a specificity of 82% to 99%. CT has good spatial resolution and can detect restenosis through metal stents but requires radiation exposure and infusion of potentially nephrotoxic iodinated contrast.
- IV digital subtraction catheter angiography (88% sensitivity, 90% specificity) is the gold standard for anatomic diagnosis of RAS. It is not a first-line screening tool but is recommended after a positive noninvasive test, or for patients with high clinical suspicion but inconclusive noninvasive tests. Renal fractional flow reserve (FFR) at the time of catheter angiography can be used to assess severity of RAS using maximal vasodilatation. A systolic gradient of at least 21 mm Hg or renal fractional flow reserve of <0.90 can be considered hemodynamically significant. This modality should be reserved for patients with a high likelihood of intervention.

Rx TREATMENT

ACUTE GENERAL Rx

Acute renal artery thrombosis:

- Thrombolytic therapy
- Anticoagulation
- Revascularization (endovascular therapy or surgery). Endovascular renal artery stenting is favored over surgery, and has shown better clinical results when compared with balloon angioplasty (without stenting) in ARAS. Balloon angioplasty with bailout stent placement if necessary is recommended for FMD. Primary open revascularization with vascular reconstruction can be considered selectively for patients with complex disease that extends into segmental arteries, small renal arteries, or early primary branching of the main renal artery.
- Acute blood pressure control with IV antihypertensives

CHRONIC Rx

Renal artery thrombosis/emboli: anticoagulation based upon underlying condition. If the patient has atrial fibrillation with therapeutic INR, consider INR 2.5 to 3.5.

Cholesterol emboli:

- Supportive care

RAS:

- Because of the activation of the renin-angiotensin-aldosterone system in RAS, ACEI/ARBs are recommended and well tolerated (92%) for the treatment of renovascular hypertension. Renal function should be monitored carefully when initiating or titrating these medications, particularly in patients with bilateral RAS (78% tolerability) or unilateral stenosis with solitary kidney, so as to avoid precipitating AKI.
- Beta-blockers and calcium channel blockers are recommended for the treatment of hypertension in patients with RAS of all types.
- Antiplatelet therapy and statin therapy in patients with atherosclerotic RAS.
- Percutaneous intervention or surgical revascularization should be reserved for patients whose blood pressure control with medication is difficult and for patients with progressive disease. The ACC/AHA guidelines for clinical indications of renal artery revascularization in the presence of significant stenosis include:
  1. Accelerated, resistant, or malignant hypertension (class IIa)
  2. Hypertension with unilateral small kidney (class IIa)
  3. Hypertension with intolerance to medication (class IIa)
  4. Treatment of cardiac destabilization syndromes such as unexplained heart failure exacerbations or episodes of flash pulmonary edema (class I), and refractory or unstable angina (class IIa)
  5. Progressive chronic kidney disease with bilateral RAS or RAS associated with a solitary functioning kidney (class IIa)
- Randomized control trials (e.g., DRASTIC, ASTRAL, and CORAL) have shown no benefit to percutaneous therapy when compared with medical therapy, with endpoints of blood pressure control, renal function, and cardiovascular events. However, these trials did have several inherent limitations.
  1. The DRASTIC trial was a small angioplasty-only trial that showed no difference in blood pressure but did show decrease in daily doses of antihypertensive drugs and number of drugs in the intervention group.
  2. The ASTRAL trial was a moderate-sized trial of stenting versus medication in moderate RAS that showed no difference in blood pressure control or the number of antihypertensives but had increased risks associated with intervention.
  3. CORAL is a large prospective multicenter trial comparing stenting versus medication in severe RAS (>60% stenosis); this study confirms that in patients with atherosclerotic renal-artery stenosis and hypertension, clinical outcomes are not improved by stenting, and renal artery stenting is futile in those patients.

DISPOSITION & REFERRAL

- Patients with uncontrolled hypertension on multiple agents should be referred for management by a specialist.
- Decision for percutaneous intervention for atherosclerotic RAS requires weighing the risks and benefits in detail and should be reserved for selected patients until further data are available.

PEARLS & CONSIDERATIONS

- Symptoms for acute renal artery occlusion are nonspecific and can be confused with nephrolithiasis and pyelonephritis among other causes. Evaluation with LDH and liver enzymes can be very helpful. LDH four times the normal range without significant transaminitis is consistent with renal infarction.
- Renal artery stenting currently requires more data to address its utility in both unilateral and bilateral RAS.
- The modality for the type of imaging should depend on the expertise of the institution.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Renal Artery Stenosis (Patient Information)
Hypertension (Related Key Topic)

AUTHORS: **CHRIS W. PAN, M.D., M.B.A., M.S.**, and **PRANAV M. PATEL, M.D.**

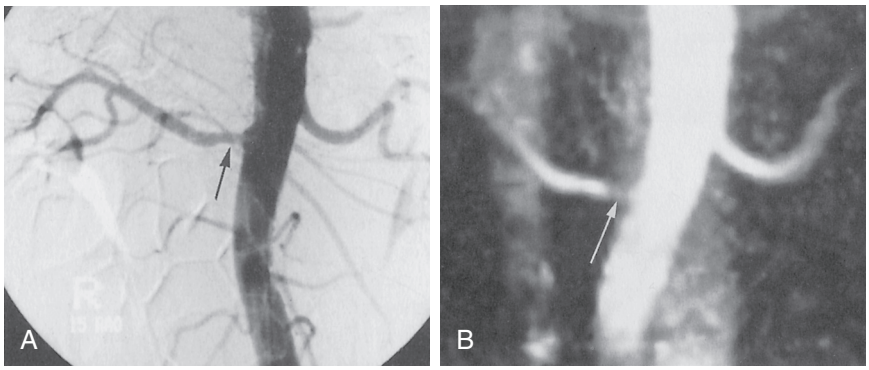


FIGURE R1-11 Renal arteriograms. A, Conventional renal digital subtraction (DSA) showing mild renal stenosis *(arrows)* on the right. **B,** Magnetic resonance angiogram (MRA) of the same patient. The stenosed segment *(arrows)* is clearly seen in this coronal projection. (Courtesy Dr. W. Gedroyc. From Souhami RL, Moxham J: *Textbook of medicine,* ed 4, London, 2002, Churchill Livingstone.)

SUGGESTED READINGS

Investigators Astral: Revascularization versus medical therapy for renal-artery stenosis, *N Engl J Med* 361:1953–1962, 2009.

Bax L et al.: Stent placement in patients with atherosclerotic renal artery stenosis and impaired renal function: a randomized trial, *Ann Intern Med* 150(12):840–848, 2009.

Cooper CJ et al.: Stenting and medical therapy for atherosclerotic renal-artery stenosis, *N Engl J Med* 370:13–22, 2014.

de Leeuw PW et al.: Treatment of athrosclerotic renal artery stenosis: time for a new approach, *JAMA* 309:663–664, 2013.

Dieter RS et al.: Usefulness of wide pulse pressure as a predictor of poor outcome after renal artery angioplasty and stenting, *Am J Cardiol* 104:732–734, 2009.

Dworkin LD, Cooper CJ: Renal artery stenosis, *N Engl J Med* 361:1972–1978, 2009.

Hansen KJ et al.: Prevalence of renovascular disease in the elderly: a population-based study, *J Vasc Surg* 36(3):443–451, 2002.

Hirsch AT et al.: ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): executive summary a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients with Peripheral Arterial Disease) endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation, *J Am Coll Cardiol* 47(6):1239–1312, 2006.

Kapar N et al.: Physiological assessment of renal artery stenosis: comparisons of resting and hyperemic renal pressure measurements, *Catheter Cardiovac Interv* 76(5):726–732, 2010.

Lao D et al.: Atherosclerotic renal artery stenosis, diagnosis and treatment, *Mayo Clin Proc* 86(7):649–657, 2011.

Regnante RA et al.: Renal artery stenosis: clinical and therapeutic implications, *Med Health Rhode Island* 91(10):315, 2008.

Safian RD, Madder RD: Refining the approach to renal artery stenosis, *JACC Cardiovasc Interv* 2(3):161–174, 2009.

Seddon M: Atherosclerotic renal artery stenosis: review of pathophysiology, clinical trial evidence, and management strategies, *Can J Cardiol* 27:468–480, 2011.

Slovut DP, Olin JW: Fibromuscular dysplasia, *N Engl J Med* 350:1862, 2004.

Sung WH et al.: Endovascular and open revascularization for nonatherosclerotic renal artery disease, *Arch Surg* 145(9):832–839, 2010.

Trinquart L et al.: Efficacy of revascularization for renal artery stenosis caused by fibromuscular dysplasia: a systematic review and meta-analysis, *Hypertension* 56:525–532, 2010.

Weber BR et al.: Renal artery stenosis: epidemiology and treatment, *Int J Nephrol Renovasc Dis* 7:169–181, May 13 2014.

White CJ et al.: Indications for renal arteriography at the time of coronary arteriography: a science advisory from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology, and the Councils on Cardiovascular Radiology and Intervention and on Kidney in Cardiovascular Disease, *Circulation* 114:1892, 2006.

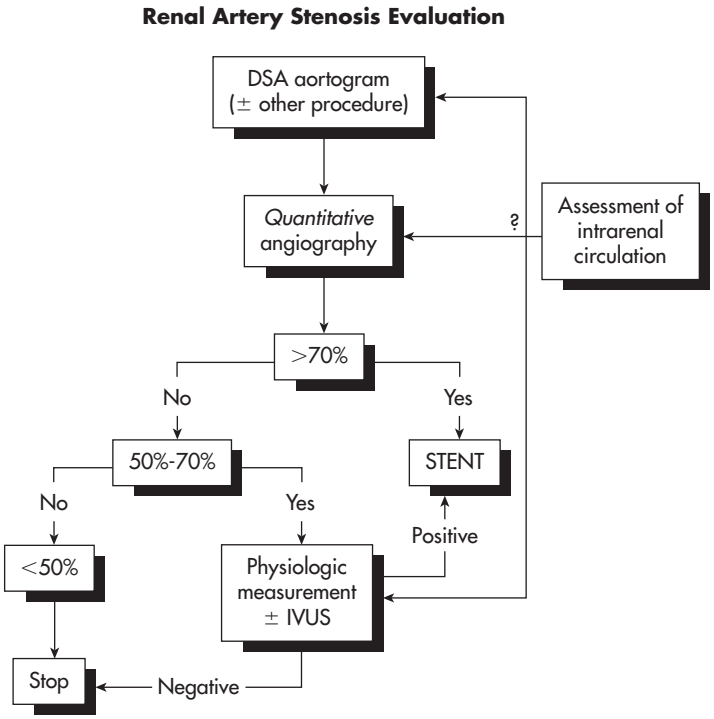


FIGURE ER1-10 Approach to the angiographic evaluation and treatment of renal artery stenosis. Once a digital subtraction aortogram *(DSA)* is performed, confirming the presence of renovascular disease, quantitative angiography, and objective evaluation of the severity of stenosis should be performed. Very severe (>70% diameter stenosis) lesions are subjected to revascularization, and mild lesions (<50% diameter stenosis) are not. It is believed that the intermediate lesion should be assessed with physiologic evaluation and/or an additional anatomic documentation of severity, such as intravascular ultrasound *(IVUS).* The absence of tranlesional flow acceleration or a pressure gradient should mitigate the desire to intervene. (From Zipes DP et al [eds]: *Braunwald's heart disease,* ed 7, Philadelphia, 2005, Saunders.)

BASIC INFORMATION

DEFINITION

Renal cell carcinoma is a primary adenocarcinoma originating in the renal parenchyma from the malignant transformation of proximal renal tubular epithelial cells. Most renal cell cancers are of clear cell type. Papillary tumors comprise 15% of renal cancers, and chromophobe tumors make up 10%.

SYNONYMS

Hypernephroma
Clear cell carcinoma of the kidney
Grawitz tumor
Renal cell adenocarcinoma (RCA)

ICD-9CM CODES
189.0 Adenocarcinoma of kidney
189.1 (Renal pelvis)
ICD-10CM CODES
C64.9 Malignant neoplasm of kidney, except renal pelvis
C65.9 Malignant neoplasm of renal pelvis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Approximately one in 10,000 persons annually (3% of all adult malignancies). In the United States, renal cancer is the seventh leading malignant condition among men and twelfth among women. Two percent of cases of renal cancer are associated with inherited syndromes.
PREDOMINANT SEX: Male/female ratio of 2:1.
PREDOMINANT AGE: Peaks at age 50 to 70 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The classic presentation of RCA includes the triad of flank pain, hematuria, and a palpable abdominal mass. This now represents an unusual presentation. Current presenting findings in RCA patients now include:

Hematuria	50% to 60%
Elevated erythrocyte sedimentation rate	50% to 60%
Abdominal mass	25% to 45%
Anemia	20% to 40%
Flank pain	35% to 40%
Hypertension	20% to 40%
Weight loss	30% to 35%
Fever	5% to 15%
Hepatic dysfunction	10% to 15%
Classic triad (hematuria, abdominal mass, flank pain)	5% to 10%
Hypercalcemia	3% to 6%
Erythrocytosis	3% to 4%
Varicocele	2% to 3%

ETIOLOGY

Hereditary forms:
- Familial renal carcinoma.
- Renal carcinoma associated with Von Hippel-Lindau disease.
- Hereditary papillary renal cell carcinoma.

Risk factors:
- Cigarette smoking.
- Obesity.
- Use of diuretics.
- Phenacetin-containing analgesics.
- Asbestos exposure.
- Gasoline and other petroleum products.
- Lead.
- Cadmium.
- Thorotrast.
- Role of the *VHL* gene on chromosome 3.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Transitional cell carcinomas of the renal pelvis (8% of all renal cancers).
- Wilms' tumor.
- Other rare primary renal carcinomas and sarcomas.
- Renal cysts.
- All causes of hematuria (see Section II).
- Retroperitoneal tumors.

WORKUP

Laboratory tests and imaging studies.

LABORATORY TESTS

- Urinalysis: hematuria.
- Complete blood count: anemia or erythrocytosis.
- Nonmetastatic hepatic dysfunction with elevated alkaline phosphatase, prolonged prothrombin time, and hypoalbuminemia.
- Hypercalcemia (caused by parathyroid-related protein).
- Other: elevated ferritin, elevated insulin and glucagon levels, elevated alpha-fetoprotein, and elevated beta–human chorionic gonadotropin.
- Recent reports indicate that urine AQP1 and ADFP concentrations quantified by Western blot appear to be sensitive and specific biomarkers of kidney cancers of proximal tubule origin and may be useful to diagnose an imaged renal mass and screen for kidney cancer at an early stage. Additional investigations are under way to determine if these tests should become standard tumor markers in the investigation of renal masses.

IMAGING STUDIES

Nearly 50% of renal cancers are now detected because a renal mass is incidentally detected on radiographic evaluation.
- Renal ultrasound.
- Abdominal CT scan with contrast (Fig. R1-12 and Fig. R1-13); CT-guided biopsy is generally not necessary for diagnosis of solid masses >4 cm (high likelihood of cancer).
- MRI.
- Renal arteriogram.
- Intravenous pyelography.

STAGING

See Table R1-3.

COMMON SITES OF METASTASES

Lung	50% to 60%
Bone	30% to 40%
Regional nodes	15% to 30%
Main renal vein	15% to 20%
Perirenal fat	10% to 20%
Adrenal (ipsilateral)	10% to 15%
Vena cava	10% to 15%
Brain	10% to 15%
Adjacent organs (colon, pancreas)	10%
Kidney (contralateral)	2%

TREATMENT

- Surgery

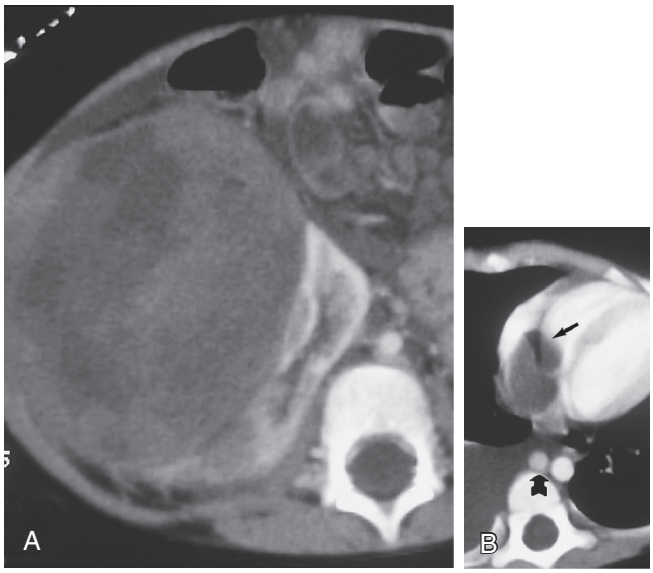


FIGURE R1-12 Renal cell carcinoma. Ultrasound demonstrates a 17-mm hyperreflective mass in the left kidney with posterior shadowing. (From Grainger RG et al [eds]: *Grainger & Allison's diagnostic radiology,* ed 4, London, 2001, Harcourt.)

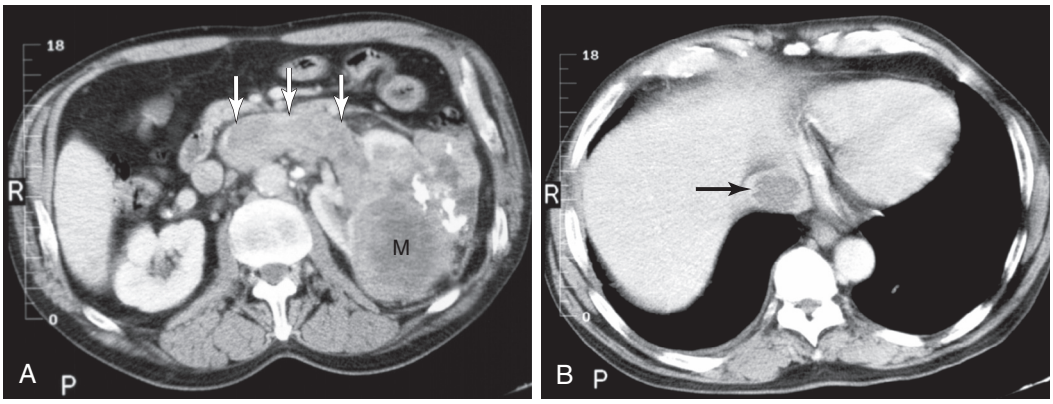


FIGURE R1-13 Renal cell carcinoma. In this patient, the computed tomography scan at the midportion of the kidneys (*A*) demonstrates a large left renal mass (*M*) that extends into the renal vein and into the inferior vena cava (*arrows*). An image at the level of the base of the heart shows that the tumor thrombus (*arrow*) extends into the right atrium. (From Mettler FA Jr: *Essentials of radiology,* 3 ed, 2014, Saunders.)

TABLE R1-3 Comparison of Conventional and TNM Staging Classification of Renal Cell Carcinomas

Robson Stage	T	N	M
I: Tumor confined by capsule	T_1 (tumor ≤2.5 cm) T_2 (tumor >2.5 cm, limited to kidney)		
II: Tumor extension to perirenal fat or ipsilateral adrenal but confined by Gerota's fascia	T_3a (tumor invades adrenal gland or perinephric fat but not beyond Gerota's fascia)		
IIIa: Renal vein or inferior vena caval involvement	T_3b (renal vein or caval involvement below diaphragm)	N_0 (nodes negative)	M_0 (no distant metastases)
IIIb: Lymphatic involvement	T_{1-4}	N_1 (single lymph node ≤2 cm) N_2 (single node 2 to 5 cm, or multiple) N_3 (single or multiple nodes >5 cm)	T_3c (caval involvement above nodes <5 cm)
IIIc: Combination of IIIa and IIIb	$T_{3, 4}$		
IVa: Spread to contiguous	T_4 (tumor extends beyond organs except ipsilateral adrenal Gerota's fascia)		
IVb: Distant metastases	T_{1-4}		M_1 (distant metastases)

1. Surgical nephrectomy (open procedure or laparoscopic approach) is the only effective management for stages I, II, and some stage III tumors. Although radical nephrectomy had long been the standard treatment, retrospective studies have shown that partial rather than radical nephrectomy is associated with improved survival and is appropriate for patients with renal cell neoplasms <4 cm that are not adjacent to renal pelvis.
2. Various forms of partial nephrectomy may be available for patients with bilateral cancers or with a solitary kidney.
3. The role of nephrectomy in patients with metastatic renal cell carcinoma is controversial and should probably be reserved for patients who have a solitary metastasis amenable to surgical resection. However, there are data showing that nephrectomy before immunotherapy improves survival in patients with metastatic renal cell cancer compared with immunotherapy alone.

- Angioinfarction (for palliation).
- Radiotherapy (for palliation).
- Chemotherapy: In patients with unresectable disease, inhibitors of vascular endothelial growth factor (VEGF) such as the antivascular endothelial growth factor antibody bevacizumab, mTOR kinase inhibitors such as everolimus and temsirolimus, and the tyrosine kinase inhibitors axitinib, sunitinib, pazopanib, and sorafenib can be used as first-line therapy.
- Hormonal therapy (high-dose progesterone may achieve a 15% to 20% response rate).
- Immunotherapy: interleukin-2 may achieve a 15% to 30% response rate; alpha-, beta-, and gamma-interferons are somewhat less effective and now used less frequently.

PROGNOSIS

Prognosis of surgically treated patients:

TNM Stage	5-yr Survival (%)
I	95
II	88
III (renal vein or vena cava)	50 to 60
III (nodal involvement)	15 to 25
IV	5 to 20

REFERRAL

To urologist
To oncologist if metastatic

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Kidney Cancer (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Cohen HT, McGovern FJ: Renal cell carcinoma, *N Engl J Med* 35:2477, 2005.

Curti BD: Renal cell carcinoma, *JAMA* 292:97, 2004.

Flanigan RC et al.: Nephrectomy followed by interferon alpha-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer, *N Engl J Med* 345:1655, 2002.

Hudes G et al.: Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma, *N Engl J Med* 356:2271, 2007.

Morrissey J et al.: Urinary biomarkers for the early diagnosis of kidney cancer, *Mayo Clin Proc* 85(5):413–421, 2010.

Motzer RJ et al.: Sunitinib in patients with metastatic renal cell carcinoma, *JAMA* 295:2516, 2006.

Motzer RJ et al.: Sunitinib versus interferon alfa in metastatic renal-cell carcinoma, *N Engl J Med* 356:115, 2007.

Tan HJ et al.: Long-term survival following partial vs radical nephrectomy among older patients with early-stage kidney cancer, *JAMA* 307(15):1629–1635, 2012.

Yang CJ: A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer, *N Engl J Med* 349:427, 2003.

BASIC INFORMATION

DEFINITION

Renal tubular acidosis (RTA) is a disorder characterized by the inability to excrete H^+ or inadequate generation of new HCO_3-. RTA syndromes are summarized in Table ER1-4. Factors differentiating types of RTA are described in Table R1-5. Four main types of RTA are described in the medical literature:

- Type I (classic, distal RTA): abnormality in distal hydrogen secretion, resulting in hypokalemic hyperchloremic metabolic acidosis.
- Type II (proximal RTA): decreased proximal bicarbonate reabsorption, resulting in hypokalemic hyperchloremic metabolic acidosis.
- Type III (RTA of glomerular insufficiency): normokalemic hyperchloremic metabolic acidosis as a result of impaired ability to generate sufficient NH_3 in the setting of decreased glomerular filtration rate (<30 ml/min). This type of RTA is described in older textbooks and is considered by many not to be a distinct entity.
- Type IV (hyporeninemic hypoaldosteronemic RTA): aldosterone deficiency or antagonism, resulting in decreased distal acidification and decreased distal sodium reabsorption with subsequent hyperkalemic hyperchloremic acidosis.

SYNONYMS

RTA

ICD-9CM CODES
588.8 Renal tubular acidosis
ICD-10CM CODES
N25.89 Other disorders resulting from impaired renal tubular function

EPIDEMIOLOGY & DEMOGRAPHICS

RTA type IV affects mostly adults, whereas RTA types I and II are more frequent in children.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Examination may be normal.
- Poor skin turgor may be present from dehydration.
- Muscle weakness and muscle aches from hypokalemia may occur.
- Low back pain and bone pain may be present in patients with abnormalities of calcium metabolism (RTA II).
- There is failure to thrive in children (RTA II).

ETIOLOGY

- Type I RTA: autoimmune disorders, primary biliary cirrhosis and other liver diseases, medications (amphotericin, nonsteroidals), systemic lupus erythematosus, Sjögren's syndrome, genetic disorders (Ehlers-Danlos syndrome, Marfan syndrome, hereditary elliptocytosis), toxins (toluene), disorders with nephrocalcinosis (hyperparathyroidism, vitamin D intoxication, idiopathic hypercalciuria), tubulointerstitial disease (obstructive uropathy, renal transplantation).
- Type II RTA: Fanconi's syndrome, primary hyperparathyroidism, multiple myeloma, medications (acetazolamide).
- Type IV RTA: diabetes mellitus, sickle cell disease, Addison's disease, urinary obstruction.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Diarrhea with significant bicarbonate loss.
- Other causes of metabolic acidosis.
- Respiratory acidosis.

WORKUP

Detection of hyperchloremic metabolic acidosis with arterial blood gases (ABGs) and serum electrolytes and evaluation of potential causes (see "Etiology"). Fig. ER1-14 describes an approach to the patient with RTA.

LABORATORY TESTS

- ABGs reveal metabolic acidosis; serum potassium is low in RTA types I and II, normal in type III, and high in type IV.
- Minimal urine pH is >5.5 in RTA type I and <5.5 in types II, III, and IV.
- Urinary anion gap is 0 or positive in all types of RTA.
- Additional useful studies include serum calcium level and urine calcium.
- Anion gap is normal.
- Parathyroid hormone measurement is useful in patients suspected of primary hyperparathyroidism (may be associated with type II RTA).

IMAGING STUDIES

- Plain abdominal radiography is useful to evaluate for nephrocalcinosis.
- Renal sonogram can be used to evaluate renal size or presence of stones.
- Intravenous pyelogram in patients with nephrocalcinosis or nephrolithiasis.

TREATMENT

ACUTE GENERAL Rx

- Types I and II are treated with oral sodium bicarbonate (1 to 2 mEq/kg/day in RTA I, 2 to 4 mEq/kg/day in RTA type II) titrated to correct acidosis.
- Potassium supplementation is needed in hypokalemic patients.
- Type IV RTA can be treated with furosemide to lower elevated potassium levels and sodium bicarbonate to correct significant acidosis. Fludrocortisone 100 to 300 mg/day can be used to correct mineralocorticoid deficiency.

CHRONIC Rx

- Frequent monitoring of potassium levels in RTA type IV.
- Monitoring for bone disease in RTA type II.
- Monitoring for nephrocalcinosis and nephrolithiasis in RTA type I.

DISPOSITION

- Prognosis varies with the presence of associated conditions (see "Etiology").
- Untreated distal RTA may result in hypercalcemia, hyperphosphaturia, nephrolithiasis, and nephrocalcinosis.

PEARLS & CONSIDERATIONS

COMMENTS

Patient education material can be obtained from the National Kidney and Urologic Diseases Information Clearinghouse, Box NKUDIC, Bethesda, MD 20893.

AUTHOR: **FRED F. FERRI, M.D.**

TABLE R1-5 Factors Differentiating Type 1, Type 2, and Type 4 Renal Tubular Acidosis (RTA)

	Type 1 RTA	Type 2 RTA	Type 4 RTA
Serum K^+	Low	Low	High
Renal function	Normal or near normal	Normal or near normal	Stage 3, 4, or 5 chronic kidney disease
Urine pH during acidosis	High	Low	Low or high
Serum HCO_3- (mmol/L)	10-20	16-18	16-22
Urine pCO_2 (mm Hg)	<40	<40	>70
Urine citrate	Low	High	Low
Fanconi syndrome	No	May be present	No

From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

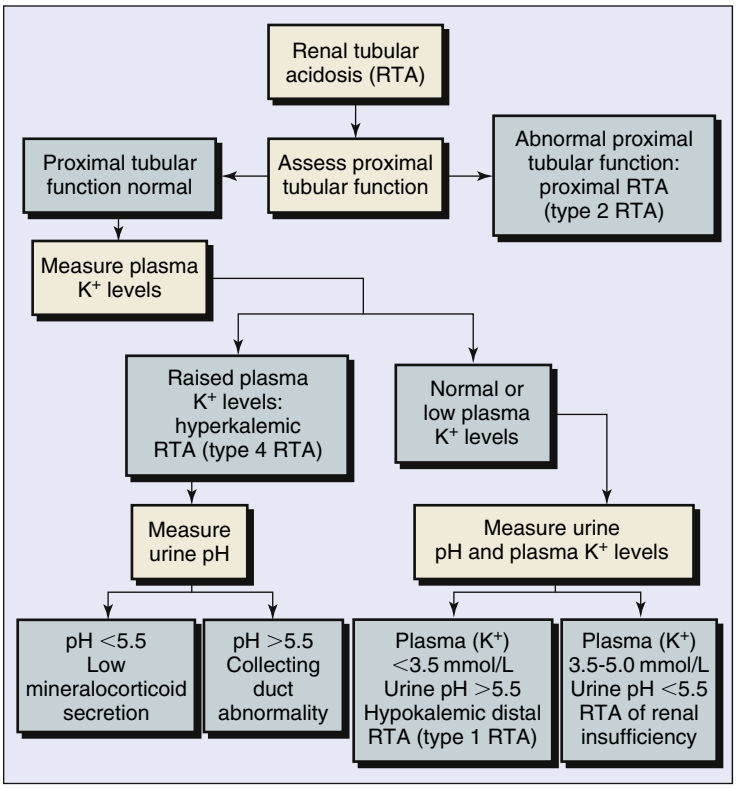


FIGURE ER1-14 Approach to the patient with renal tubular acidosis. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

TABLE ER1-4 Renal Tubular Acidosis Syndromes

Type	Locus	Defect
Proximal	S_1-S_3	↓ HCO_3– threshold
Hyperkalemic	CCD principal cell	↓ V_M (–) leading to ↓ H^+ secretion
Gradient limited	OMCD intercalated cells	Three specific defects in H^+ secretion

CCD, Cortical collecting duct; *OMCD,* outer medullary collecting duct; *S,* segment; *V_M (–),* negative transepithelial voltage in the OMCD.

From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.

Renal Vein Thrombosis

BASIC INFORMATION

DEFINITION

Renal vein thrombosis is the thrombotic occlusion of one or both renal veins.

ICD-9CM CODES
453.3 Renal vein thrombosis
ICD-10CM CODES
I82.3 Embolism and thrombosis of renal vein

EPIDEMIOLOGY & DEMOGRAPHICS

- Incidence unknown; probably an underdiagnosed condition.
- May occur at any age with no gender preference.
- Epidemiology tied to the underlying cause.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Acute bilateral renal vein thrombosis:
- Back and bilateral flank pain.
- Acute renal failure.

Acute unilateral renal vein thrombosis:
- Flank pain.
- Decline in renal function.
- Hematuria.
- Increase in the amount of proteinuria if associated with nephrotic syndrome.

Chronic unilateral renal vein thrombosis:
- May be silent.
- Pulmonary emboli and hemolysis.
- Back pain.
- Deep vein thrombosis in lower extremities.
- Edema.
- Glycosuria.
- Hyperchloremic acidosis.
- Left varicocele (if the left renal vein is thrombosed).
- Dilated abdominal veins.

ETIOLOGY & PATHOGENESIS

- Extrinsic compression by a tumor or retroperitoneal mass.
- Invasion of the renal vein or inferior vena cava by tumor (almost always renal cell cancer).
- Trauma.
- Hypercoagulable states.
- Dehydration.
- Glomerulopathies (membranous glomerulonephritis, crescentic glomerulonephritis, systemic lupus erythematosus, amyloidosis) especially in the presence of nephrotic syndrome when the serum albumin is <2 g/dl.

NOTE: For unknown reasons, diabetic nephropathy is not commonly associated with renal vein thrombosis even if the nephrotic syndrome is present.

A controversy has existed regarding whether the renal vein thrombosis association with nephrotic syndrome is a complication of nephrotic syndrome or whether renal vein thrombosis occurring in the setting of increased renal vein pressure (e.g., with congestive heart failure, constrictive pericarditis, or extrinsic compression) can independently cause proteinuria. Current evidence is that renal vein thrombosis does not cause nephrotic syndrome.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

The diagnosis of renal vein thrombosis does not include any differential consideration. The differential diagnosis is that of proteinuria. Renal vein thrombosis should be considered if proteinuria worsens or if renal function worsens in a patient with glomerulonephritis. Renal vein thrombosis should also be considered in patients with pulmonary emboli and no lower-extremity deep vein thrombosis.

WORKUP

Clinical suspicion (see "Differential Diagnosis") and imaging studies.

IMAGING STUDIES

- Abdominal ultrasound.
- Abdominal MRI or CT with contrast (Fig. R1-15).
- Renal arteriography (delayed films during venous phase).
- Selective renal vein venography (inferior venacavogram images should be obtained before advancing the catheter in the vena cava because clots, if present, could be dislodged).
- Renal biopsy may be indicated if evidence of nephritis is present (e.g., active urinary sediment).

TREATMENT

- Anticoagulation in acute renal vein thrombosis to prevent pulmonary emboli and in attempt to improve renal function and decrease proteinuria.
- Thrombolytic therapy or surgical thrombectomy has also been reported to be effective
- The value of anticoagulation in chronic renal vein thrombosis is dubious except in nephrotic patients with membranous glomerulonephritis with profound hypoalbuminemia where prolonged prophylactic anticoagulation may be of benefit even if renal vein thrombosis has not been documented.

PROGNOSIS

Probable worsening of the underlying glomerulonephritis by acute renal vein thrombosis; the effect of chronic renal vein thrombosis is unclear.

AUTHOR: **FRED F. FERRI, M.D.**

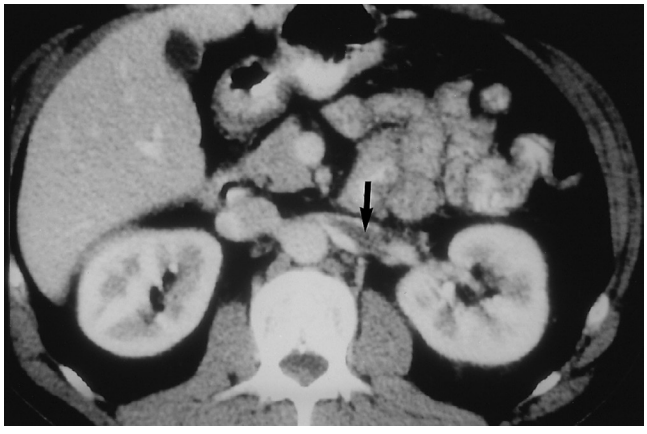


FIGURE R1-15 Renal vein thrombus in a patient with nephritic syndrome. Contrast medium–enhanced CT at the level of the renal vein shows thrombus in the left renal vein (arrow). (From Grainger R.G.; et al. [eds]: *Grainger & Allison's diagnostic radiology,* ed 4, Philadelphia, 2001, Churchill Livingstone.)

BASIC INFORMATION

DEFINITION

Respiratory syncytial virus (RSV) is an RNA virus that tends to form syncytia in tissue culture. RSV causes repeated acute respiratory tract infections in people of all ages. It is highly contagious and is the leading cause of severe lower respiratory tract infections in infants and young children, while it usually manifests as upper respiratory infections, bronchiolitis, or tracheobronchitis in older children and adults.

SYNONYMS

RSV

ICD-9CM CODES
079.6 Respiratory syncytial virus
ICD-10-CM CODES
B97.4 Respiratory syncytial virus as the cause of diseases classified elsewhere

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Humans are the only source of infection. There are 64 million infections worldwide annually, resulting in 160,000 deaths; it is associated with 120,000 U.S. pediatric hospitalizations annually and millions worldwide.
PEAK INCIDENCE: In nontropical areas of the Northern Hemisphere, seasonal outbreaks usually occur November to April, with a peak in January or February; in nontropical areas of the Southern Hemisphere, May to September, with a peak in May, June, or July. In the tropics, seasonal outbreaks usually occur during the rainy season. Incubation ranges from 2 to 8 days; although 4 to 6 days is most common.
PREVALENCE: Nearly everyone is infected by age 2, with reinfections occurring at all ages.
PREDOMINANT SEX AND AGE: Male sex may predispose to more severe respiratory disease in RSV infection. Age predominance in infancy and the elderly.
GENETICS: Severe disease is associated with polymorphisms in various interleukins and CCR5.
RISK FACTORS: For children, risk factors include attending daycare or school and inpatient hospitalization. Severe disease is seen primarily in infants and young children (especially those born before 35 wk of gestation); the elderly; and in patients with cardiac, pulmonary, or immune system dysfunction.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Physical findings include fever, tachypnea, prolonged expiration, wheezes and rales, cough, rhinorrhea, coryza, conjunctivitis, and otitis media. Clinical presentation can include pneumonia and bronchiolitis.

ETIOLOGY

Humans are the only known reservoir. Transmission is by large respiratory droplets via close contact or contaminated surfaces, where it can survive for several hours. The CDC recommends hand washing, gowns, and gloves to prevent nosocomial infection, which is especially common on pediatric wards. However, the CDC does not recommend excluding children with respiratory illnesses who are well enough to attend school or daycare, as RSV is often spread during early stages of illness.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Influenza, parainfluenza, and adenovirus

WORKUP

- History with a focus on upper and lower respiratory symptoms, fever, and (in infants) apnea.
- Focused physical exam including temperature and pulse oximetry, as well as lung and HEENT exam.

LABORATORY TESTS

Nasopharyngeal specimens can be analyzed using rapid diagnostic assays, such as immunofluorescent and enzyme immunoassay techniques for detection of viral antigen and are generally reliable in infants and young children. Virus isolation is also possible, but requires 1 to 5 days and accuracy may vary. Serologic testing (serum antibodies) is less useful because it is unreliable in infants and is confounded in other patients due to repeated infections.

IMAGING STUDIES

Chest x-ray for suspected pneumonia, but not routinely in suspected bronchiolitis

TREATMENT

NONPHARMACOLOGIC THERAPY

Early diagnosis and isolation techniques are important in limiting spread of RSV infections.

ACUTE GENERAL Rx

Primary treatment is predominantly supportive in nature. May include hydration, clinical assessment of respiratory status, measurement of oxygen saturation, supplemental oxygen, bronchodilators, suction of the upper airway, nebulized hypertonic saline, and, if required, intubation and mechanical ventilation.

- Mild disease: symptomatic treatment and supportive therapy.
- Severe disease may require oxygen therapy, bronchodilators, hospitalization, intubation, and mechanical ventilation. The use of corticosteroids remains controversial, especially in infants, and is not recommended by the American Academy of Pediatrics.
- Ribavirin is not recommended for routine use but may be indicated in specific situations, such as for treatment of severe lower respiratory tract RSV infections in pediatric and adult patient populations with additional underlying compromising conditions such as chronic lung conditions, prematurity, BPD, congenital heart disease, immunodeficiency, immunosuppression, or organ transplantation. It may also be used in selected patients with documented, potentially life-threatening RSV. Updated eligibility criteria for treatment may change, and updates should be sought from the American Academy of Pediatrics Red Book in its print or online version. Further studies are needed. New research in the field of RNA interference based agents has shown promising results for the treatment of acute RSV infection but is still in phase II trials.

REFERRAL

To pulmonology and infectious disease specialists for severe disease or when use of ribavarin is considered; hospitalization for those with respiratory compromise.

PEARLS & CONSIDERATIONS

PREVENTION

Primary prevention is through avoidance of transmission through hand washing, proper procedures to avoid spread in health care facilities, and diagnosis of suspected cases.

No benefit has been found from the use of RSV prophylaxis IVIG or RSV immune globulin (IG) monoclonal antibody, and RSV-IVIG is no longer available. Palivizumab, a humanized mouse monoclonal antibody, may be used in certain infants and children to reduce the risk of lower tract disease, in those with chronic lung disease of prematurity, history of preterm birth, or with congenital heart disease. Updated eligibility criteria for prophylaxis may change, and consultation with pulmonary or infectious disease specialists is recommended.

PATIENT & FAMILY EDUCATION

Hand washing with soap and water for 15-20 seconds, covering mouths and noses when coughing or sneezing, avoid sharing cups and eating utensils with those whom may be infected, and refrain from kissing loved ones possibly infected may all aid in preventing future infection.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **JONATHAN P. CLARKE, M.D.,** and **STEVEN BUSSELEN, M.D.**

SUGGESTED READINGS

American Academy of Pediatrics: Committee on Infectious Diseases: Policy statements–Modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections, *Pediatrics 124*:1694, 2009.

American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis: Clinical Practice Guideline: Diagnosis and management of bronchiolitis, *Pediatrics* 118:1774–1793, 2006.

American Academy of Pediatrics: Respiratory syncytial virus. In Pickering LK (ed): Red book: 2012 report of the Committee on Infectious Diseases, ed 29, Elk Grove Village, IL, American Academy of Pediatrics, pp 609–618.

Centers for Disease Control: www.cdc.gov

Meissner HC, et al.: Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections, *Pediatrics* 112:1447–1452, 2003.

World Health Organization. Homepage. www.who.int. Accessed April 30, 2013.

BASIC INFORMATION

DEFINITION

Restless legs syndrome (RLS) is an awake phenomenon consisting of an urge to move legs, usually associated with feeling of discomfort in legs.

SYNONYMS

RLS
Wittmaack-Ekbom syndrome

ICD-9CM CODES
333.94 Restless leg syndrome
ICD-10CM CODES
G25.81 Restless legs syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Average prevalence rate is 1% to 29%. Prevalence estimates in Europe are around 10%, and 0.1% to 12% in East Asian population.
PEAK PREVALENCE: 10% in persons aged 30 to 79 and 19% in persons aged 80 or above.
PREDOMINANT SEX: Early-onset RLS is more common in females, with 2:1 female/male ratio.
PREDOMINANT AGE: Prevalence of RLS increases with age, and it is more commonly seen in elderly population.
GENETICS: Genetic basis of RLS has been reported, particularly in early-onset RLS.
- Autosomal dominant disorder
- Common among first-degree relatives
- RLS associated with certain sequences in chromosome 6p,12q, 14q, 9p, 20p, 2p, 16p

RISK FACTORS: Diabetes mellitus (most consistent risk factor for RLS), iron deficiency anemia (IDA), end-stage renal disease (ESRD) requiring hemodialysis, pregnancy, rheumatoid arthritis, Parkinson's disease, neuropathy, and myelopathy

CLASSIFICATION

- Primary RLS is without any obvious cause, with no associated disorder.
- Secondary RLS results from other medical conditions; the most frequently found associations are pregnancy, IDA, ESRD, and Parkinson disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Wide spectrum of severity of clinical manifestations has been reported in RLS.
- Most common symptom is unpleasant sensations in legs ("dysesthesias"), reported as discomfort or "creepy-crawling" sensations, mostly bilateral. Arms are occasionally involved.
- There is an extreme urge to move legs and relief is sustained as long as the movement continues.
- Symptoms are worse at night or evening. Best sleep is usually early in the morning.

ETIOLOGY

The exact etiology remains unknown. Pharmacologic, pathologic, physiologic, and imaging studies have implicated dopaminergic pathways, brain iron metabolism, and endogenous opioid pathways.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Periodic limb movement disorder (PLMD)
- Nocturnal leg cramps
- Painful peripheral neuropathy
- Akathisia
- Positional discomfort
- Volitional movements, foot tapping, leg rocking

WORKUP

- Diagnosis of RLS is based on established clinical criteria (Table R1-6) and normal neurologic examination.
- Testing is done to determine possible cause of secondary RLS.
- Polysomnography to document periodic limb movements during sleep
- Leg activity monitors to determine limb movements during sleep but they are unable to distinguish periodic limb movements from periodic movements associated with sleep apnea.
- Nerve conduction studies and electromyography for associated peripheral neuropathy

LABORATORY TESTS

- Iron status: serum ferritin, total iron binding capacity, percent saturation
- CBC for anemia in case of iron deficiency
- Metabolic panel: blood urea nitrogen and serum creatinine for renal insufficiency

IMAGING STUDIES

No imaging studies are required for diagnosis for RLS.

TREATMENT

Treatment options for RLS include:
- Dopaminergic agents, levodopa, and dopamine agonists help to ameliorate RLS symptoms, decrease periodic limb movements, and improve sleep. Dopamine agonists, pramipexole and ropinirole, are first-line agents in the treatment of RLS.
- Anticonvulsants, such as gabapentin, have been shown to be effective in multiple studies. A recent trial has shown that pregabalin is also effective and well tolerated for RLS.[1] Limited case reports reveal use of lamotrigine, Gabitril, and topiramate in patients who are intolerant to other agents.
- Opiates, mostly methadone, are generally reserved as last line of treatment.
- Iron replacement should be started in case of iron deficiency.

NONPHARMACOLOGIC THERAPY

- Avoidance of caffeine, alcohol, nicotine, and medications that exacerbate RLS
- Physical and mental activity
- Good sleep hygiene

ACUTE GENERAL Rx

Once the diagnosis of RLS is considered based on clinical criteria as mentioned in Table R1-6 and causes impairment of quality of life, a dopamine agonist (bromocriptine, pramipexole, or ropinirole) should be started at low dose and then gradually tapered depending on tolerance. Dopaminergic medications have the potential to cause iatrogenic worsening (augmentation) of RLS with long-term treatment.

REFERRAL

Refer to neurologist if diagnosis is uncertain or an underlying disorder is suspected.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Restless Legs Syndrome (Patient Information)

AUTHOR: **FARIHA ZAHEER, M.D.**

TABLE R1-6 Diagnostic Criteria for Restless Legs Syndrome

Minimal Criteria

1. Desire to move the legs usually associated with paresthesias.
2. Motor restlessness, as characterized by floor pacing, leg rubbing, stretching, and flexing.
3. Worse at rest, with relief by activity.
4. Worse at night.

Additional Criteria

1. Sleep disturbances, as difficulty in sleep onset and maintaining sleep, daytime fatigue, or somnolence.
2. Involuntary movements, as periodic limb or leg movements in sleep and periodic or aperiodic limb movements while awake.
3. Neurologic examination is normal in idiopathic restless legs syndrome.
4. Clinical course may begin at any age but most severe in middle and older age.
5. Family history suggests autosomal dominant mode of inheritance in 1/3 of the cases.

From Stiansy K et al: Clinical symptomatology and treatment of restless leg syndrome and periodic limb movement disorder, *Sleep Med Rev* 6(4):253-265, 2002.

[1]Allen RP et al: Comparison of pregabalin with pramipexole for restless legs syndrome, *N Engl J Med* 370: 621-631, 2014.

SUGGESTED READINGS

Lesage S, Hening WA: The restless legs syndrome and periodic limb movement disorder: a review of management, *Semin Neurol* 24(3):249–259, 2004.

Natarajan R: Review of periodic limb movement and restless leg syndrome, *J Postgrad Medicine* 56(2):157–162, 2010.

Salas RE et al.: Update in restless leg syndrome, *Curr Opinion Neurol* 23:401–406, 2010.

Winter AC et al.: Vascular risk factors, cardiovascular disease, and restless legs syndrome in men, *Am J Med* 126:228–235, 2013.

Winter AC et al.: Vascular risk factors, cardiovascular disease, and restless legs syndrome in women, *Am J Med* 126:220–227, 2013.

BASIC INFORMATION

DEFINITION

Retinal detachment is the separation of the neurosensory retina (NSR) from the retinal pigment epithelium (RPE). This results in the accumulation of subretinal fluid (SRF) in the potential space between the NSR and the RPE. The main types of retinal detachment are rhegmatogenous (caused by retinal tear or break), tractional, exudative, and combined types.

ICD-9CM CODES
361 Retinal detachment and defects
ICD-10CM CODES
H33 Retinal detachment and breaks
H33.2 Serous retinal detachment
H33.5 Other retinal detachments
H33.0 Retinal detachment with retinal break

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.)
- 0.02% of the population
- Particularly common in patients with high myopia of 5 diopters or more

PEAK INCIDENCE: Incidence increases with increasing age or increasing myopia.
PREVALENCE (IN U.S.): Busy ophthalmologists may see one or two acute retinal detachments per month.
PREDOMINANT AGE
- Congenital in younger patients.
- Trauma in patients aged 30 to 40 yr and older.
- High myopia is an important risk factor.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Elevation of retina and vessels associated with tears in the retina (Figs. R1-16 and R1-17), fluid, and/or hemorrhage beneath the retina and changes in the vitreous.
- Reports of flashing lights and floaters.
- After a variable period of time, the patient notices a relative peripheral visual field defect that may progress to involve central vision.

ETIOLOGY

- Trauma.
- Tears in the retina.
- Vitreous detachment.
- Uveitis.
- Tumors.
- Scleritis.
- Inflammatory disease.
- Diabetes.
- Collagen-vascular disease.
- Vascular abnormalities.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Degenerative retinoschisis.
- Uveal effusion syndrome.
- Choroidal detachment.
- Hemorrhage.
- Tumors.

WORKUP

- Full eye examination.
- Visual fields.
- Ultrasonography to show the retinal detachment or tumors beneath it.
- Medical workup only when inflammation or systemic disease considered.

LABORATORY TESTS

Usually not necessary.

IMAGING STUDIES

B scan ultrasonography (US) of the eye.

TREATMENT

NONPHARMACOLOGIC THERAPY

Immediate surgery. The three principal methods for reattachment of the retina in patients with primary retinal detachment are scleral buckling, vitrectomy, and pneumatic retinopexy. There is a paucity of randomized trials comparing these procedures and the choice remains subjective. Some data suggest that vitrectomy may be preferable for detachment in pseudophakic eyes, whereas primary detachment in phakic eyes with complexity exceeding the original indications for rheumatic retinopexy may be treated with scleral buckling or vitrectomy.

ACUTE GENERAL Rx

- Early surgery to repair the detachment.
- Treatment of the underlying disorder.

CHRONIC Rx

Occasionally, steroids or other treatment of underlying disease is indicated.

DISPOSITION

- Immediately refer to an ophthalmologist.
- Early intervention improves outcomes.

REFERRAL

Immediately.

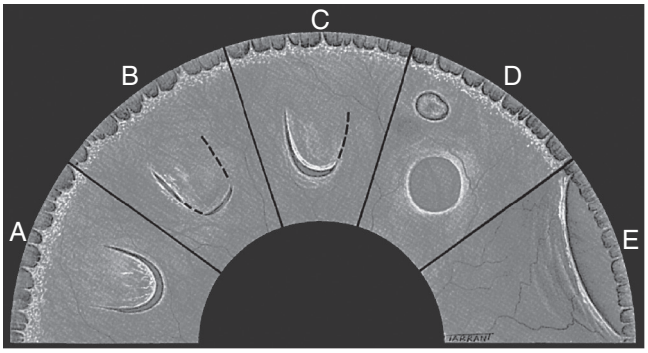


FIGURE R1-16 Retinal tears. A, Complete U-shaped; **B,** linear; **C,** L-shaped; **D,** operculated; **E,** dialysis. (From Kanski JJ, Bowling B. *Clinical ophthalmology: a systematic approach,* ed 7, Philadelphia, 2010, Saunders.)

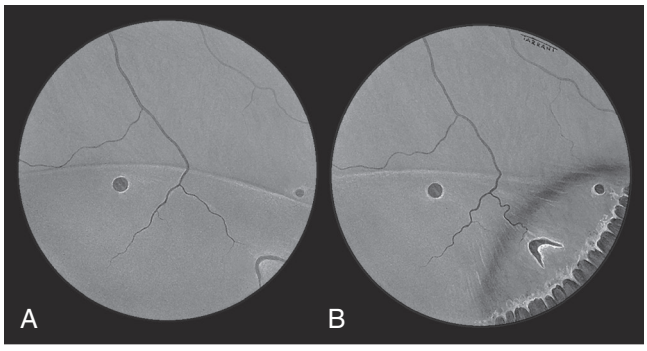


FIGURE R1-17 Appearance of retinal breaks in detached retina. A, Without scleral indentation; **B,** with indentation. (From Kanski JJ, Bowling B. *Clinical ophthalmology: a systematic approach,* ed 7, Philadelphia, 2010, Saunders.)

PEARLS & CONSIDERATIONS

COMMENTS

If treated early, most patients will recover a substantial portion of their vision.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **R. SCOTT HOFFMAN, M.D.**

SUGGESTED READINGS

Carpineto P et al.: Retinal detachment prophylaxis, *Ophthalmology* 109(2):217, 2002.

D'amico DJ: Primary retinal detachment, *N Engl J Med* 359:2346–2354, 2008.

Etminan M et al.: Oral fluoroquinolones and the risk of retinal detachment, *JAMA* 307(13):1416–1419, 2013.

Kanski JJ, Bowling B. Clinical ophthalmology: a systematic approach, ed 7, Saunders: Philadelphia.

Yazici B et al.: Prediction of visual outcome after retinal detachment surgery using the Lotmar visometer, *Br J Ophthalmol* 86(3):278, 2002.

BASIC INFORMATION

DEFINITION

In a retinal hemorrhage, blood accumulates in or on the surface of the retina, in the subretinal space, or in the vitreous cavity. Generally, these hemorrhages are abnormal and causes should be sought (see "Etiology").

SYNONYMS

Retinal hemorrhage, vitreous hemorrhage
Subretinal or preretinal hemorrhages
Splinter hemorrhage, dot and blot hemorrhages
Roth spots (small white centered blood, traditionally associated with endocarditis)

ICD-9CM CODES
362.81 Retinal hemorrhage
ICD-10CM CODES
H35.60 Retinal hemorrhage, unspecified eye

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Busy ophthalmologists see one or two cases a month.
PEAK INCIDENCE

- In children: associated primarily with trauma and hematologic disorders (must consider shaken baby syndrome), rare retinal vascular diseases of children (Coat's, Eale's disease).
- Associated with trauma, diabetes, vascular disease (hypertensive retinopathy, retinal vascular occlusions, sickle cell disease, anemia), macular degeneration, altitude changes (mountain climbing).

PREDOMINANT AGE: Usually vascular disease in older patients.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Hemorrhage within the retina or subretinal area (Fig. R1-18).
- Evidence of retinal tears, tumors, and inflammation; macular degeneration, drugs, diabetes.

ETIOLOGY

- Diabetes.
- Hypertension.
- Trauma.
- Inflammation.
- Tumors.
- Subretinal neovascularization.
- Associated with diabetes and aging.
- Rapid changes in altitude (mountain climbing or scuba diving).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Evaluate patients for local and systemic diseases.
- Trauma in children or adults
- Venous or arterial occlusion associated with atherosclerotic or heart disease may cause retinal hemorrhage.
- Rule out malignant melanoma, trauma, hypertensive cardiovascular disease.
  1. Section II describes the differential diagnosis of acute painless loss of vision.

WORKUP

Complete general physical examination, evaluate for trauma; look for systemic diseases and medication etiologies.

LABORATORY TESTS

- Minimum: complete blood count, erythrocyte sedimentation rate, complete blood chemistries.
- Visual field testing.

IMAGING STUDIES

- Usually not necessary.
- Trauma: skull radiographs or head CT (evaluate for fractures).
- Ultrasound.
- Fluorescein angiography (evaluate retinal vascular diseases and macular degeneration).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Laser or treatment of underlying disorder.
- Treat medical problems (age-related macular degeneration, etc.).

ACUTE GENERAL Rx

- Laser treatment may be indicated for certain retinal diseases.
- Treatment may be indicated with wet macular degeneration (intravitreal injection).
- Treat underlying disease.
- Repair any damage from trauma.

CHRONIC Rx

- Vitamin therapy: high in zinc and antioxidants for macular degeneration.
- Treatment will differ depending on various causes of bleeding.
- Encourage adequate control of underlying medical disorders.

DISPOSITION

If present, hemorrhage in the retina is generally considered abnormal; refer to ophthalmologist for evaluation.

REFERRAL

Immediate referral to an ophthalmologist, especially if there is a significant change in vision; early treatment significantly affects outcome.

PEARLS & CONSIDERATIONS

COMMENTS

- Vision may return substantially.
- Complete recovery of vision depends on cause.
- Chronic situations have poor prognosis.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Diabetic Retinopathy (Patient Information)

AUTHOR: **R. SCOTT HOFFMAN, M.D.**

FIGURE R1-18 Fronds of neovascularization on the disc are present in this right eye. Temporally, two cotton-wool spots have adjacent intraretinal hemorrhage and preretinal hemorrhage. Native retinal arteries are narrowed and show evidence of sclerosis. (From Palay D [ed]: *Ophthalmology for the primary care physician*, St Louis, 1997, Mosby.)

SUGGESTED READINGS

Duncan BB et al.: Hypertensive retinopathy and incident coronary heart disease in high risk men, *Br J Ophthalmol* 86(9):1002, 2002.

Gardner HB: Retinal hemorrhages in children, *Ophthalmology* 110(9):1863, 2003.

Kanski JJ, Bowling B: Clinical ophthalmology: a systematic approach. ed 7, Saunders: Philadelphia.

Lauritzen DB, Weiter JJ: Management of subretinal hemorrhage, *Int Ophthalmol Clin* 42(3):87, 2002.

Schloff S et al.: Retinal findings in children with intracranial hemorrhage, *Ophthalmology* 109(8):1472, 2002.

BASIC INFORMATION

DEFINITION

Retinitis pigmentosa (RP) refers to a clinically and genetically diverse group of diffuse retinal dystrophies initially predominantly affecting the rod photoreceptor cells with subsequent degeneration of cones (rod-cone dystrophy).

ICD-9CM CODES
362.74 Retinitis pigmentosa, pigmentary retinal dystrophy
ICD-10CM CODES
H35.5 Hereditary retinal dystrophy

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE:
- Recessive incidence: in the 20s
- Dominant form: in the 40s

PREVALENCE (IN U.S.): One in 5000 persons. It is the most commonly encountered hereditary fundus dystrophy.
PREDOMINANT SEX: Depends on inheritance.
PREDOMINANT AGE: The age of onset, rate of progression, eventual vision loss, and associated ocular features are frequently related to the mode of inheritance.
GENETICS:
- 19% dominant.
- 19% recessive.
- 8% X-linked.
- 46% not known to be genetically related (mutations).
- 8% undetermined cause.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Deposition of retinal pigment in midperiphery and centrally in the retina (Fig. ER1-19) with a pale optic nerve and narrowing of blood vessels (Fig. R1-20).
- Possible cataracts and macular edema.
- Decrease in night vision and peripheral vision. Patients typically lose night vision to a greater extent than they lose day vision, and they lose peripheral vision before losing central vision.

ETIOLOGY

RP may occur as an isolated sporadic disorder, or may be inherited as AD, AR, or XL. Many cases are due to mutation of the rhodopsin gene. XL is the least common but most severe form, and may result in complete blindness by the third or fourth decade.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Syphilis.
- Old inflammatory scars.
- Old hemorrhage.
- Diabetes.
- Toxic retinopathies (phenothiazines, chloroquine).

WORKUP

- Electrophysiologic studies.
- Dark adaptation studies.
- Visual fields.

LABORATORY TESTS

- Usually not necessary.
- VDRL (syphilis), glucose (selected patients).

IMAGING STUDIES

- Usually not necessary.
- Rate of decline of vision for different groups cannot be accurately determined; decline rates are fastest in patients with mutations.

TREATMENT

CHRONIC Rx

- No proven effective therapy.
- Correction of biochemical abnormalities. Some success has been reported with subretinal gene therapy in which patients with mutations in the gene encoding RPE65 were treated with delivery under the retina of a normal RPE65 gene by intraocular injection.
- Nutritional supplements: sometimes vitamin E or vitamin A may be helpful.
- In patients with advanced disease, treatment options may include attempts to regenerate photoreceptors by transplantation or genetic manipulation of nonphotoreceptor retinal cell types.

DISPOSITION

Disease may be either mild or severe, but if the patient is expected to progress to total blindness, counseling and early education are important.

REFERRAL

To ophthalmologist to confirm diagnosis.

PEARLS & CONSIDERATIONS

COMMENTS

- Patient education material can be obtained from the Retinitis Pigmentosa Foundation Fighting Blindness, 1401 Mt. Royal Avenue, 4th Floor, Baltimore, MD 21217.
- Research in fetal retinal pigment transplantation and computer chip implantation is ongoing.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Retinitis Pigmentosa (Patient Information)

AUTHOR: **R. SCOTT HOFFMAN, M.D.**

FIGURE R1-20 Retinitis pigmentosa. (From Behrman R.E. [ed]: *Nelson textbook of pediatrics,* Philadelphia, 2005, Saunders.)

SUGGESTED READINGS

Chow AY et al.: The artificial silicon retina microchip for the treatment of vision loss from retinitis pigmentosa, *Arch Ophthalmol* 122(4):460, 2004.

Jacobson SG, Cideciyan AV: Treatment possibilities for retinitis pigmentosa, *N Engl J Med* 363:17, 2010.

Kanski JJ, Bowling B: Clinical ophthalmology: a systematic approach. ed 7, Saunders: Philadelphia.

Radtke ND et al.: Vision change after sheet transplant of fetal retina with retinal pigment epithelium to a patient with retinitis pigmentosa, *Arch Ophthalmol* 122(8):1159, 2004.

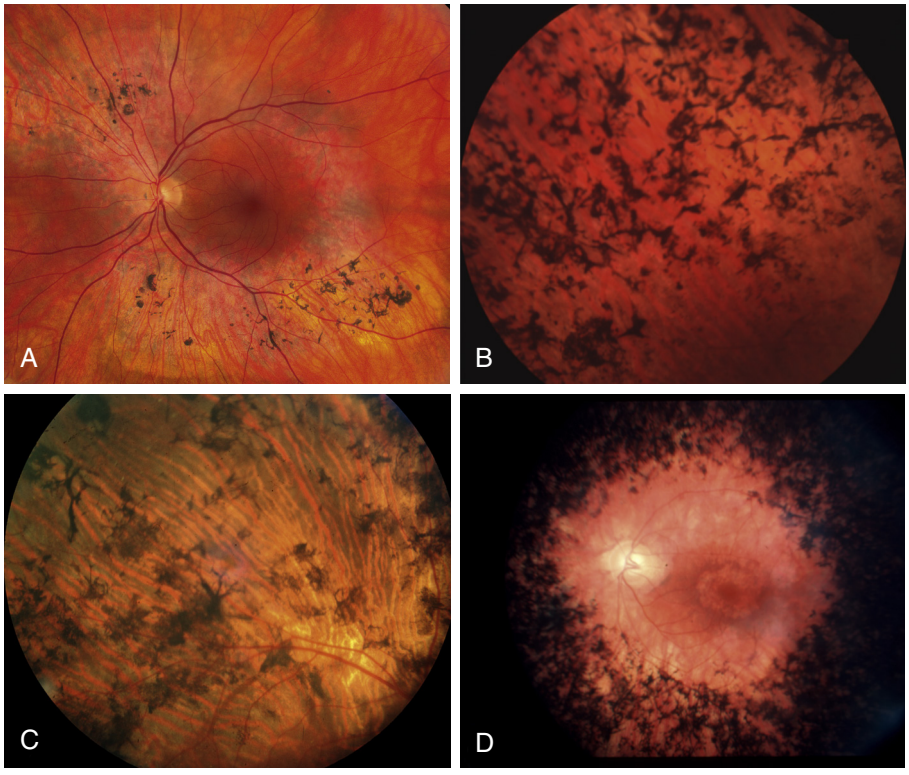


FIGURE ER1-19 Progression of retinitis pigmentosa. A, Early changes. **B,** Advanced changes. **C,** Unmasking of choroidal vessels. **D,** End-stage disease. (**A** courtesy P. Saine; from Kanski J.J.; Bowling B. *Clinical ophthalmology: a systematic approach,* ed 7, Philadelphia, 2010, Saunders.)

BASIC INFORMATION

DEFINITION

Retinoblastoma is an inherited, highly malignant congenital neoplasm arising from the neural layers of the retina.

ICD-9CM CODES

190.5 Retinoblastoma, malignant neoplasm of eyes, retina

ICD-10CM CODES

C69.20 Malignant neoplasm of unspecified retina

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Retinoblastoma affects 1 in 15,000 children, with ~300 children newly diagnosed each year in the United States. It is the most common primary intraocular malignancy of childhood.

PEAK INCIDENCE:

- 6 to 13 mo. Mean age at diagnosis is 12 mo for bilateral tumors and 24 mo for unilateral tumors.
- 72% diagnosed by age 3 yr.
- 90% diagnosed by age 4 yr.

PREDOMINANT AGE: 8 mo.

GENETICS:

- Gene mutation or an autosomal-dominant gene with 80% to 95% penetration.
- 5% mutations.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Leukocoria (white reflex or white pupil) (Fig. R1-21).
- White elevated retinal masses.
- Strabismus.
- Glaucoma.
- Uveitis.
- Vitreous masses and opacity.

ETIOLOGY

The retinoblastoma gene is a tumor suppressor gene located on the long arm of chromosome 13 at region 14 that codes for the RB protein. Of all retinoblastomas, ~60% are attributable to somatic, nonhereditary mutations.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Examination of eye.

- Strabismus.
- Retinal detachment.
- Uveitis.
- Other tumors.
- Glaucoma.
- Coats' disease (pathologic telangiectatic retinal vessels that leak and lead to accumulation of subretinal fluid and lipid).
- Endophthalmitis.
- Cataract.
- Infectious.

WORKUP

Diagnosis is by ophthalmologic examination. An awake examination to determine if the patient can fixate and extent of eye mobility should be done. Examination should also include visual acuity, papillary examination, extraocular movements, slit-lamp examination for evidence of iris neovascularization, hyphema or hypopyon, indirect ophthalmoscopy with 360 degrees of scleral depression, and fundus photographs documenting all lesions. Ophthalmologic examination is followed by ultrasonography of the eye and MRI of the orbits and brain to exclude extraocular extension and trilateral retinoblastoma.

CLASSIFICATION

Retinoblastoma is separated into intraocular and extraocular disease. The Reese-Ellsworth classification system became outdated as chemoreduction strategies became widely used for salvage therapy and a new international classification system for intraocular retinoblastoma was formulated in 2003, which more accurately reflects response to standardized chemotherapy regimen used in conjunction with focal consolidative therapy. The international classification system is subdivided into group A (small), group B (medium), group C (confined, medium), group D (diffuse, large), and group E (enucleation, advanced).

IMAGING STUDIES

- MRI: may show calcifications in retina.
- Ultrasonography: good delineation of mass.

TREATMENT

Usually treated by a multidisciplinary team consisting of a pediatrician, an ophthalmologist, a pediatric oncologist, and pediatric radiation oncologist. Treatment depends on location and stage of tumor when diagnosed:

- Chemotherapy for larger tumors usually with carboplatin, etoposide, and vincristine. The goal of chemotherapy is to reduce the tumor volume for focal therapy with cryotherapy, laser, thermotherapy, or plaque brachytherapy.
- Radioactive plaque brachytherapy with iodine 125 or ruthenium 106 plaques and cryotherapy.
- Surgical enucleation of the eye.
- Radiation and chemotherapy.

DISPOSITION

Overall there is a high cure rate (93% 5-yr survival in the United States) for retinoblastoma. Group A tumors generally have good visual and survival prognosis with focal consolidative therapy alone, groups B and C are treated with chemotherapy and focal therapy with good results (vision salvage rates up to 93%), group D patients often eventually require enucleation despite treatment.

REFERRAL

- To ophthalmologist, pediatric oncologist, and pediatric radiation oncologist.
- Prospective parents with a family history of retinoblastoma should be referred for genetic counseling. Genetic testing should be carried out for most retinoblastoma patients unless it is declined.

PEARLS & CONSIDERATIONS

COMMENTS

- High incidence of second tumor in survivors compared with general population.
- High incidence of lung cancer, bladder cancer, and other epithelial cancers.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Retinoblastoma (Patient Information)

AUTHOR: **R. SCOTT HOFFMAN, M.D.**

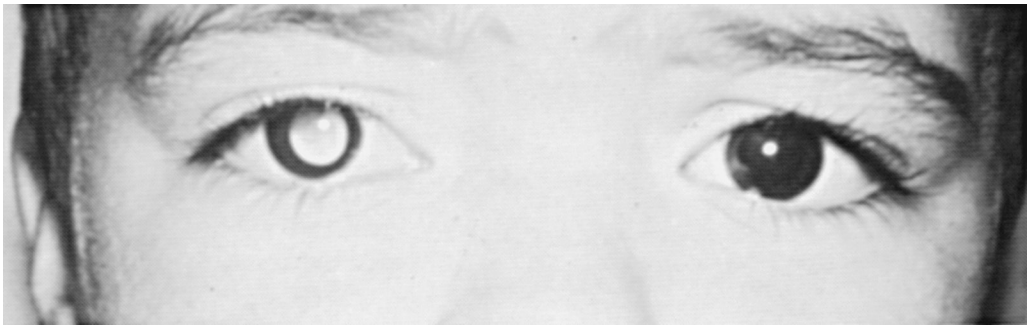


FIGURE R1-21 Leukocoria. White papillary reflex in a child with retinoblastoma. (From Behrman RE [ed]: *Nelson textbook of pediatrics,* Philadelphia, 2005, Saunders.)

SUGGESTED READINGS

Brichand B et al.: Combined chemotherapy and local treatment in the management of intraocular retinoblastoma, *Med Pediatr Oncol* 38(6):411, 2002.

Butros LJ et al.: Delayed diagnosis of retinoblastoma analysis of degree, cause, and potential consequences, *Pediatrics* 109(3):E45, 2002.

De Potter P: Current treatment of retinoblastoma, *Curr Opin Ophthalmol* 13(5):331, 2002.

Lee V et al.: Globe conserving treatment of the only eye in bilateral retinoblastoma, *Br J Ophthalmol* 87(11):1374, 2003.

Linn Murphree A et al.: Intraocular retinoblastoma: the case for a new group classification, *Ophthalmol Clin North Am* 18:41–53, 2005. vii.

Linn P, O'Brien JM: Frontiers in the management of retinoblastoma, *Am J Ophthalmol* 148:192–198, 2009.

Melamud A et al.: Retinoblastoma, Am *Fam Physician* 73:1039–1044, 2006.

Schouten-Van Meeteren AY et al.: Overview: chemotherapy for retinoblastoma: an expanding area of clinical research, *Med Pediatr Oncol* 38(6):428, 2002.

Shields CL et al.: The International Classification of retinoblastoma predicts chemoreduction success, *Ophthalmology* 113:2276–2280, 2006.

Sussman DA et al.: Comparison of retinoblastoma reduction for chemotherapy vs external beam radiotherapy, *Arch Ophthalmol* 121(7):979, 2003.

BASIC INFORMATION

DEFINITION

Retroperitoneal fibrosis (RPF) is a rare syndrome hallmarked by chronic inflammation and development of extensive fibrosis in the retroperitoneum, resulting in entrapment and obstruction of retroperitoneal structures such as the aorta, kidneys, and ureters.

SYNONYMS

Ormond's disease (Idiopathic retroperitoneal fibrosis)
RPF

ICD-9CM CODES
593.4 Other ureteric obstruction
ICD-10CM CODES
N13.8 Other obstructive and reflux uropathy

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: RPF is a rare disease. True incidence is not known. Estimated annual incidence ranges from 1:200,000 to 1:500,000.
PEAK INCIDENCE: Peak incidence is in adults 40 to 60 years old. Mean age of onset is 54 to 60 yr.
PREDOMINANT SEX AND AGE: Occurs predominantly in men. Male-to-female ratio is approximately 2:1.
RACE: All races appear to be equally affected.
RISK FACTORS: Radiation exposure, malignancy, TB, medications (methysergide, ergotamine, B-blockers, phenacetin).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

CLINICAL PRESENTATION

- Early symptoms are vague and not specific.
- It can take 4 to 6 mo, even up to a year, from the time symptoms start until a concrete diagnosis is made.
- Dull, noncolicky pain in the lower back, flank, lower abdomen, and scrotum in 92% of cases.
- Other uncommon symptoms include:
  - Fever.
  - Malaise.
  - Weight loss.
  - Anorexia.
  - Vomiting.
- Rare presentations include:
  - Lower extremity edema—due to venous or lymphatic involvement.
  - Macroscopic hematoma—as a result of arterial encasement.
  - Intermittent claudication.
  - Phlebitis.
  - Deep vein thrombosis (DVT)/pulmonary embolism.
  - Raynaud's phenomenon.
- Also associated with:
  - Ulcerative colitis.
  - Crohn's disease.
  - Sclerosing cholangitis.

PHYSICAL FINDINGS

- Hypertension (HTN) is found in about 50% of cases. Obstruction of the urinary tract will lead to renin release with subsequent development of HTN. Obstructive nephropathy will also cause volume-dependent HTN.
- Other physical findings on exam include:
  1. Abdominal or pelvic pain.
  2. Lower extremity edema.
  3. Thrombosis.
  4. Ascites.
  5. Intestinal obstruction.
  6. Jaundice.
  7. Spinal cord compression.
  8. Scoliosis.
  9. Hydrocele.

ETIOLOGY

- Idiopathic in most cases (60% to 70%). Rule out other possible causes before labeling as idiopathic.
- Atherosclerosis: can lead to inflammatory periaortitis (fibrosis developed in response to leakage of ceroid from atheroma into periaortic tissues).
- Inflammation or trauma/injury of the retroperitoneal space.
  1. Abdominal/pelvic/retroperitoneal surgery.
- Intraabdominal inflammatory process—diverticulitis, ulcerative colitis, pancreatitis.
- Injury—radiation therapy, contrast extravasation.
- Connective tissue and autoimmune diseases: several of these diseases have been implicated, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), scleroderma, recurrent polychondritis, immune-complex glomerulonephritis, systemic vasculitis (Wegener's granulomatosis, Takayasu's disease, Henoch-Schonlein purpura, PAN).
- Drug-induced: well-documented for methysergide, also beta-blockers, antihypertensives (alpha-methyldopa), analgesics.
- Malignancy: Account for about 8% of cases. Usually metastatic from breast, lung, GI tract bladder, prostate, sarcoma, lymphoma, cervix, urinary tract).
- Exposure to asbestos and tobacco smoke results in strong risk factors for idiopathic RPF. Coexposure to asbestos and smoke has a multiplicative effect on risk compared with single exposure.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Retroperitoneal lymphoma.
- Sclerosing mesenteritis.
- Desmoid-type fibromatosis.
- Inflammatory myofibroblastic tumor.
- Hemorrhage.
- Amyloidosis.
- Infection.

WORKUP

Definite diagnosis is established by laparoscopic biopsy, computed tomography (CT) scan, or ultrasonographic guided percutaneous needle biopsy. Workup usually also involves:

- Measuring markers of inflammatory disease.
- Measuring indicators of renal function disorder.
- Radiography.
- Biopsy.

LABORATORY TESTS

- Increase in erythrocyte sedimentation rate (ESR): almost always present.
- Elevated C-reactive protein (CRP). CRP and ESR both lack sensitivity and specificity for the diagnosis of RPF.
- Serum creatinine is variably raised: present in 50% to 75% of patients.
- Anemia (normochromic, normocytic).
- Mild thrombocytosis.
- Polyclonal hypergammaglobinemia.
- Antinuclear antibody (ANA) (positive in 5% to 60% of patients).
- Alkaline phosphatase.
- Microscopic hematuria (very rarely).

IMAGING STUDIES

- Radiographic imaging usually provides a tentative diagnosis.
- Contrast enhanced CT scan is the preferred imaging method (Fig. ER1-22).

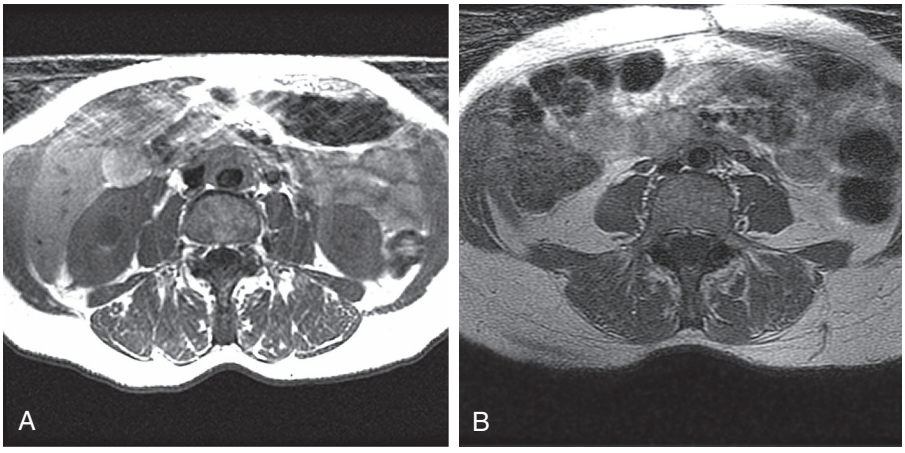


FIGURE ER1-22 Retroperitoneal fibrosis. A, At the time of presentation for back pain, the patient had extensive fibrosis in the retroperitoneum, as seen in this computed tomographic image. The fibrosis encases the paravertebral muscles. **B,** After several months of corticosteroid therapy (1 mg/kg/day prednisone), the patient's fibrosis improved significantly. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

- Other methods available:
  1. Magnetic resonance imaging (MRI).
  2. Nuclear medicine (using gallium scintigraphy).
  3. Sonography.
  4. Intravenous urography (shows the classic triad: *delay of contrast material, unilateral or bilateral hydro-ureteronephrosis,* and *medial deviation of the middle third of the ureter*).

BIOPSY

- Diagnosis may be confirmed by histology and immunochemistry.
- Laparoscopic biopsy is safe, less invasive, and cost effective.
- CT- and US-guided biopsy can be used.

Rx TREATMENT

PRINCIPLES OF TREATMENT

- The goals of treatment are:
- Identify and remove/discontinue the use of any inciting or suspected drug.
- Suppress the inflammatory process.
- Preserve renal function.
- Exclude malignancy.
- Relieve symptoms.
- Initial treatment depends on the stage and level of renal impairment.
- A combination of surgical and nonsurgical approaches is needed.

NONPHARMACOLOGIC THERAPY

Surgery is used as a second–line treatment option after failed medical treatment—or in patients with contraindications/unwillingness to use of long-term immunosuppression medications.

Surgical methods include:

- Relieving the ureteral obstruction by percutaneous nephrostomy, retrograde ureteric catheterization, or ureteric J stents.
- Open biopsy.
- Ureterolysis (to free the ureter) is effective in 90% of patients but is associated with high morbidity (~60%). Laparoscopic ureterolysis allows shorter hospital stays.
- Omentoplasty (wrapping of the ureters in the omentum).

ACUTE GENERAL Rx/ CHRONIC Rx

The aim of pharmacologic treatment is to reduce morbidity and prevent complications. Immunosuppressives and/or hormones are used.

- Immunosuppression:
  - Corticosteroids.
  - Azathioprine with or without corticosteroids.
  - Cyclophosphamide with or without corticosteroids.
  - Mycophenolate mofetil with or without corticosteroids.
  - Cyclosporin.
- Hormonal:
  - Tamoxifen.
  - Medroxyprogesterone acetate.
  - Progesterone.

DISPOSITION

- Follow-up is mandatory. Long-term follow-up is needed because stenosis can recur many years later.
- Watch out for postobstruction physiologic diuresis, especially of sodium or urea. This is usually self-limiting. Fluid and electrolyte replacement is needed.
- Serial CT scan (3- to 6-mo intervals) needed to follow response to treatment.
- Check ESR, C-reactive protein (CRP), and serum creatinine every 4-6 weeks to assess response to treatment.
- Provide early referral for nephrology follow-up.
- Prognosis is good for nonmalignant RPF.
- Prognosis is poor for malignant RPF.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **DANIEL K. ASIEDU, M.D., PH.D.**

SUGGESTED READINGS

Biyani CS et al: Retroperitoneal fibrosis, *Medscape Reference Drugs, Diseases & Procedures* Available at: emedicine.medscape.com/article/458501-followup #a2649. Accessed September 2012.

Goldoni M et al.: Asbestos and smoking as risk factors for idiopathic retroperitoneal fibrosis, *Ann Intern Med* 161:181–188, 2014.

Scheel PJ et al.: Combined prednisone and mycophenolate mofetil treatment for retroperitoneal fibrosis, *Ann Intern Med* 154:31, 2011.

Van Bommel EFH: Retroperitoneal fibrosis, *Netherlands J Med* 60(6):231, 2002.

Vivas I et al.: Retroperitoneal fibrosis: typical and atypical manifestations, *Br J Radiol* 73:214, 2000.

BASIC INFORMATION

DEFINITION

- Reye's syndrome is a postinfectious triad consisting of encephalopathy, fatty liver degeneration, and transaminase elevation.

ICD-9CM CODES
331.81 Reye's syndrome
ICD-10CM CODES
G93.7 Reye's syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- During the 1970s, 300 to 600 cases were being reported yearly in the United States.
- Since the mid-1980s, after the understanding that aspirin is associated with Reye's syndrome, the yearly count has fallen to <20 cases.
- Seasonal relation with influenza and varicella outbreaks.
- Age: rare in persons aged >18 yr; peak age (in the United States) is 6 to 8 yr.
- Case-fatality rate: 25% to 50%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Shortly after recovery from a viral infection (flu or chickenpox), an afebrile child begins to vomit intractably. Hepatomegaly is often present. The vomiting can lead to dehydration. Occasionally, symptoms of hypoglycemia are present. After 2 days symptoms of encephalopathy dominate the clinical picture (lethargy, confusion, stupor, coma, seizures, decorticate or decerebrate posture) (Table ER1-7).

ETIOLOGY

- Temporal association with influenza and varicella infection.
- Epidemiologic association with aspirin or other salicylate use to treat the viral infection.
- Possible association with aflatoxin and pesticides.
- Pathology.
  - Liver: no inflammation; the striking finding is panlobular microvesicular hepatocyte infiltration on light microscopy and mitochondrial injury on electron microscopy.
  - Brain: no inflammation but cerebral edema and anoxic degeneration.
  - Pathogenesis: not fully understood but mitochondrial dysfunction is clearly center stage.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Inborn errors of metabolism (e.g., carnitine deficiency, ornithine transcarbamylase deficiency).
- Salicylate or amiodarone intoxication.
- Jamaican vomiting sickness.
- Hepatic encephalopathy of any cause.
- Table ER1-8 describes diseases that present a clinical or pathologic picture resembling Reye's syndrome.

TABLE ER1-8 Diseases That Present a Clinical or Pathologic Picture Resembling Reye's Syndrome

Metabolic disease
Organic aciduria
Disorders of oxidative phosphorylation
Urea cycle defects (carbamoyl phosphate synthetase, ornithine transcarbamylase)
Defects in fatty acid oxidation metabolism
Acyl-CoA dehydrogenase deficiencies
Systemic carnitine deficiency
Hepatic carnitine palmitoyltransferase deficiency
3-OH, 3-methylglutaryl-CoA lyase deficiency
Fructosemia
Central nervous system infections or intoxications (meningitis), encephalitis, toxic encephalopathy
Hemorrhagic shock with encephalopathy
Drug or toxin ingestion (salicylate, valproate)

CoA, Coenzyme A.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

TABLE ER1-7 Clinical Staging of Reye's Syndrome

Grade	Symptoms at Time of Admission
I	Usually quiet, **lethargic** and sleepy, vomiting, laboratory evidence of liver dysfunction
II	Deep lethargy, **confusion,** delirium, combative, hyperventilation, hyperreflexic
III	Obtunded, **light coma,** seizures, decorticate rigidity, intact pupillary light reaction
IV	Seizures, deepening coma, **decerebrate rigidity,** loss of oculocephalic reflexes, fixed pupils
V	Coma, loss of deep tendon reflexes, respiratory arrest, fixed dilated pupils, **flaccidity/decerebrate** intermittent isoelectric electroencephalogram

From Behrman RE: *Nelson textbook of pediatrics,* ed 17, Philadelphia, 2005, Saunders.

WORKUP

According to the Centers for Disease Control and Prevention (CDC) case definition, the following conditions must be met for consideration as a Reye's syndrome case:

1. Acute noninflammatory encephalopathy documented by:
   - Alteration in the level of consciousness and, if available, a record of cerebrospinal fluid containing ≤8 leukocytes per mm3 or
   - Histologic specimen demonstrating cerebral edema without perivascular or meningeal inflammation.
2. Hepatopathy documented either by a liver biopsy or autopsy considered to be diagnostic of Reye's syndrome or by a threefold or greater rise in the levels of serum aspartate aminotransferase, serum alanine aminotransferase, or serum ammonia and
3. No more reasonable explanation for the cerebral and hepatic abnormalities.

LABORATORY TESTS

- Elevated transaminase (alanine aminotransferase and aspartate aminotransferase).
- Elevated ammonia level.
- Occasional elevation of creatine phosphokinase, lactate dehydrogenase, and bilirubin and prolongation of prothrombin time.
- Occasional hypoglycemia (in patients <4 yr).
- Cerebrospinal fluid is normal or contains <8 white blood cells per milliliter.
- Rarely a liver biopsy is indicated (in infants or in recurrent cases).

TREATMENT

- Supportive.
- Mannitol, glycerol, or hyperventilation for cerebral edema if present.
- Interferon-alfa (experimental).
- Prevention.
  1. Influenza vaccine.
  2. Varicella vaccine.
  3. Avoidance of aspirin in children, especially during influenza and varicella outbreaks.

AUTHOR: **FRED F. FERRI, M.D.**

BASIC INFORMATION

DEFINITION

Rh incompatibility occurs when an absence of the D antigen on maternal red blood cells (RBCs) and its presence on fetal RBCs cause risk of isoimmunization.

ICD-9CM CODES
656.1 Rh incompatibility

ICD-10CM CODES
O36.0910 Maternal care for other rhesus isoimmunization, first trimester, not applicable or unspecified
T80.4 Rh incompatibility reaction
T80.4 Unspecified complication following infusion, transfusion, and therapeutic injection

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE

- The absence of the D antigen (Rh – blood type) occurs in 15% of whites, 8% of blacks, and virtually no Asians or Native Americans. If the father's blood type is not known, the chance that an Rh – pregnant woman is bearing an Rh + fetus is approximately 60%.
- Of those pregnancies complicated by Rh incompatibility, the risk of maternal isoimmunization to the D antigen is approximately 8% for each ABO-compatible pregnancy if no prophylaxis is given.
- Maternal-fetal ABO incompatibility is somewhat protective against Rh isoimmunization.

GENETICS: Five major loci determine Rh status: C, D, E, c, e. The presence of the D antigen results in an Rh + individual. Its absence results in an Rh – individual. Of Rh + fathers, 45% are homozygotes, and 55% are heterozygotes. For homozygous Rh + fathers, the probability of an Rh + offspring is 100%. The probability for heterozygotes is approximately 50%.

RISK FACTORS

- Antepartum: fetal-to-maternal transfusion.
- Intrapartum: fetal-to-maternal transfusion, spontaneous abortion, ectopic pregnancy, abruptio placentae, abdominal trauma, chorionic villus sampling, amniocentesis, percutaneous umbilical blood sampling (PUBS), external cephalic version, manual removal of the placenta, therapeutic abortion, autologous blood product administration.

ETIOLOGY

The initial response to D antigen exposure is production of immunoglobulin (Ig) M (molecular weight 900,000) that does not cross the placenta. With a repeated exposure, IgG (MW 160,000) is produced. IgG can cross the placenta and enter the fetal circulation, producing hemolysis in the fetus. This may produce erythroblastosis fetalis or hemolytic disease in the newborn, resulting in antepartum or neonatal death or neurologic damage to the fetus because of hyperbilirubinemia and kernicterus.

DIAGNOSIS

LABORATORY TESTS

ABO and Rh blood type and an antibody screen as part of the initial prenatal profile.

- If antibody screen negative:
  1. Repeat antibody screen at 28 wk gestation.
  2. Obtain neonatal blood type after delivery.
  3. If Rh incompatibility is confirmed by the neonatal blood type, a Kleihauer-Betke or rosette test should be performed to determine the amount of fetomaternal transfusion in the following high-risk circumstances: abruptio placentae, placenta previa, cesarean delivery, intrauterine manipulation, manual removal of the placenta.
- If anti-D antibody screen is positive:
  1. Maternal indirect Coombs test is needed to determine antibody titer.
  2. Determine paternal Rh status and zygosity.
  3. If father is heterozygous, PUBS or amniotic fluid is needed to determine fetal Rh status.

IMAGING STUDIES

Ultrasound evaluation can diagnose hydrops fetalis, but it cannot predict it.

TREATMENT

PREVENTION OF D ISOIMMUNIZATION

- 50 mcg of D immunoglobulin: after spontaneous or induced abortion or ectopic pregnancy <13 wk gestation.
- 300 mcg of D immunoglobulin (protects against 30 ml of fetal blood).
  1. After spontaneous or induced abortion >13 wk gestation, amniocentesis, chorionic villous sampling, PUBS, external cephalic version, or other intrauterine manipulation.
  2. As antepartum prophylaxis at 28 wk gestation. Maternal anti-D prophylaxis does not cause hemolysis in the fetus or newborn.
  3. At delivery if the neonate is D- or Du-positive.
  4. If Kleihauer-Betke or rosette test confirms >30 ml of fetal red blood in maternal circulation, additional D immunoglobulin is indicated. Confirm adequacy of therapy by a maternal indirect Coombs test 48 to 72 hr after Rh immune globulin is given.

MANAGEMENT OF D ISOIMMUNIZED PREGNANCIES

- Serial amniocentesis for assessment of OD_{450} after 25 wk gestation with interpretation of the Delta OD_{450} according to criteria established by Liley.
- PUBS if ultrasonographic evidence of hydrops, rising zone II Delta OD_{450} values on amniocentesis, or maternal history of a severely affected child.
- Intrauterine exchange transfusion if severe anemia is documented remote from term.
- Initiation of steroids for lung maturation at 28 wk in severely affected pregnancies with delivery at lung maturity.
- Delivery as soon as lung maturation is achieved in mild to moderately affected pregnancies.

Fig. R1-23 shows an algorithm for clinical management of a patient with red cell sensitization in the first affected pregnancy and Fig. R1-24 shows an algorithm for clinical management of a patient with red cell sensitization and a previously affected fetus or infant.

DISPOSITION

Survival of nonhydropic infants is 90%. Of infants with hydrops, 82% survive.

REFERRAL

Refer all Rh isoimmunized pregnancies to a tertiary care center before 18 to 20 wk gestation.

SUGGESTED READING

Available at www.expertconsult.com

AUTHOR: **LAUREL M. WHITE, M.D.**

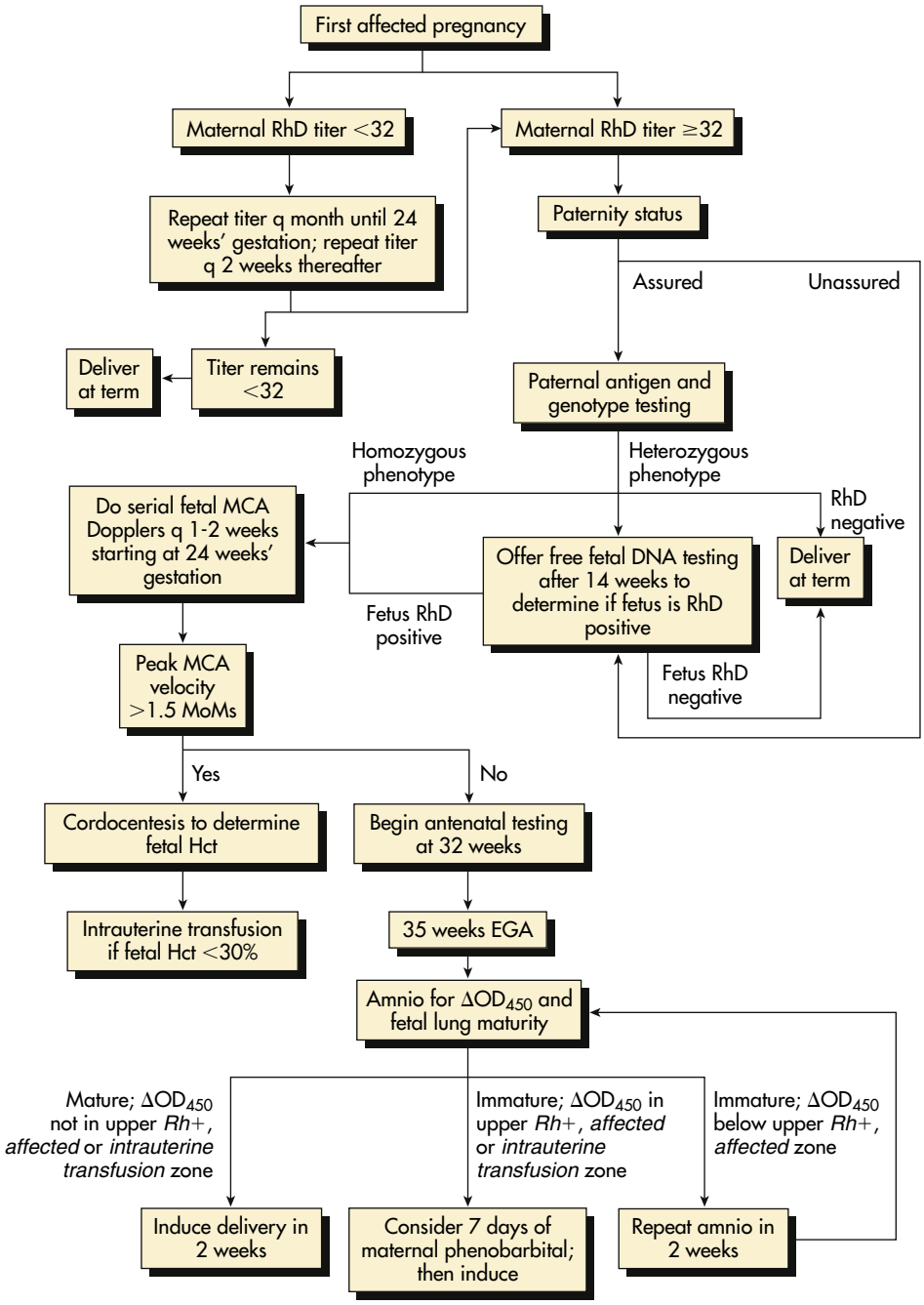


FIGURE R1-23 Algorithm for clinical management of a patient with red cell sensitization in the first affected pregnancy.

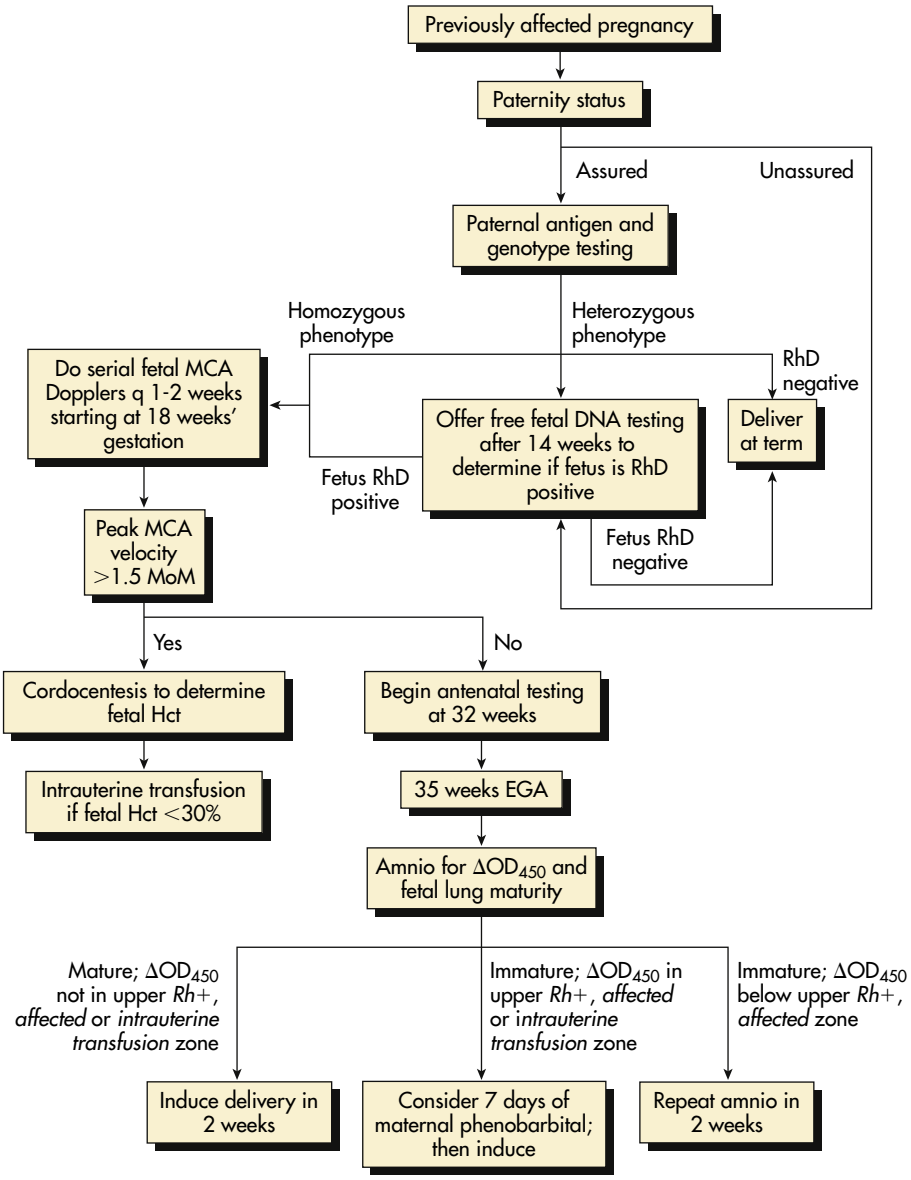


FIGURE R1-24 Algorithm for clinical management of a patient with red cell sensitization and a previously affected fetus or infant. (From Gabbe SG; *Obstetrics,* 6 ed, Philadelphia, 2012, Saunders.)

SUGGESTED READING

Maayan-Metzger A et al.: Maternal anti-D prophylaxis during pregnancy does not cause neonatal hemolysis, *Arch Dis Child* 84:60, 2001.

BASIC INFORMATION

DEFINITION

Rhabdomyolysis is the dissolution or disintegration of muscle, which causes membrane lysis and leakage of muscle constituents, resulting in the excretion of myoglobin in the urine. In general CK levels in excess of 5× normal and the presence of myoglobinuria with the appropriate clinical presentation (see below) are sufficient criteria for the diagnosis of rhabdomyolysis. Renal damage can occur as a result of tubular obstruction by myoglobin as well as hypovolemia.

ICD-9CM CODES
728.89 Rhabdomyolysis
ICD-10CM CODES
M62.9 Disorder of muscle, unspecified
T79.6 Traumatic ischemia of muscle
M62.89 Other specified disorders of muscle

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT AGE: Rare in children. Increased risk in advanced age (>80 yr).
MORTALITY RATE: 8%.
ONSET: The average length of time on statin therapy before rhabdomyolysis is 1 yr. Average time for onset of rhabdomyolysis after addition of fibrate to statin therapy is 32 days.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Variable muscle tenderness. Rhabdomyolysis apart from statin use presents with muscle symptoms only 50% of the time.
- Weakness.
- Muscular rigidity.
- Fever.
- Altered consciousness.
- Muscle swelling.
- Malaise, fatigue. In statin-induced rhabdomyolysis, fatigue (74%) is nearly as common as muscle pain (88%).
- Dark urine: myoglobinuria may cause the urine to be reddish-brown.

ETIOLOGY

- Exertion (exercise-induced). Genetic mutations associated with exertional rhabdomyolysis are described in Table R1-9.
- Electrical injury.
- Drug-induced (statins, combination of statins with fibrates, or erythromycin, simvastatin and amiodarone, amphetamines, haloperidol).
- Compartment syndrome.
- Multiple trauma.
- Malignant hyperthermia.
- Limb ischemia.
- Reperfusion after revascularization procedures for ischemia.
- Extensive surgical (spinal) dissection, bariatric surgery.
- Tourniquet ischemia.
- Prolonged static positioning during surgery.
- Infectious and inflammatory myositis.
- Metabolic myopathies.
- Hypovolemia and urinary acidification are important precipitating causes in the development of acute renal failure.
- Sickle cell trait is a predisposing condition.
- Hypothyroidism.
- Alcoholism.
- Seizures.
- Table R1-10 summarizes the various causes of rhabdomyolysis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- "Creatine Kinase Elevation" in Section IV describes a clinical algorithm for the evaluation of creatine phosphokinase (CPK) elevation.

LABORATORY TESTS

- Screening for myoglobinuria with a simple urine dipstick test using orthotoluidine or benzidine. Myoglobinuria does not occur in the absence of rhabdomyolysis; therefore, when present, it is the best marker and diagnostic cornerstone of rhabdomyolysis.
- Blood urea nitrogen, creatinine.

TABLE R1-9 Genetic Mutations Associated with Exertional Rhabdomyolysis

Gene	
Ryanodine receptor 1	*RyR1*
Myoadenylate deaminase	*AMPDA1*
Carnitine palmitoyltransferase II	*CPT2*
Myophosphorylase	*PYGM*
Phosphofructokinase	*PFKM*
Phosphorylase *b* kinase	*PHKA1*
Very long chain acyl coenzyme-A dehydrogenase	*ACAD9*
Phosphoglycerate mutase	*PGAMM*
Phosphoglycerate kinase	*PGK1*
Lactate dehydrogenase	*LDHA*
Cytochrome *c* oxidase	*COX I, II,* and *III*
Cytochrome *b* (complex III)	*CYTB*
Mitochondrial tRNA	*Mt-tRNA*
β-Sarcoglycan	*SGCB*

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

- Increased CK: CK levels typically peak 2 to 5 days after the initial insult (Fig. R1-25). Levels above 15,000 U/L are more likely to be associated with renal injury.
- Hyperkalemia.
- Hypocalcemia: due to influx and deposition of of Ca^{2+} in damaged muscle tissue. Hypercalcemia may follow resolution of rhabdomyolysis with subsequent release of calcium back into the circulation.
- Hyperphosphatemia.
- Elevations in serum myoglobin precede the rise in CK, but it is rapidly eliminated, making this test a less reliable marker of muscle injury.
- Pigmented granular casts.
- Hyperuricemia.
- Anion gap metabolic acidosis may be present due to the release of organic acids from damaged muscle.
- Box R1-1 summarizes laboratory abnormalities observed with rhabdomyolysis.

TREATMENT

ACUTE GENERAL Rx

- Early, aggressive, high-volume IV fluid replacement. Fluid repletion reduces the accumulation of toxic intracellular contents caused by the rapid breakdown of muscle and subsequent renal damage. Fig. R1-26 describes a treatment algorithm for rhabdomyolysis.

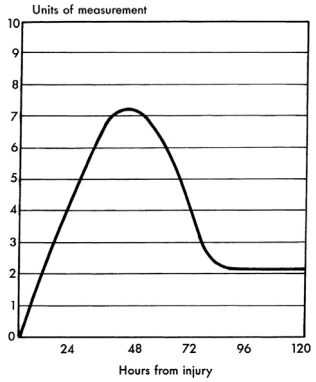


FIGURE R1-25 Typical creatine kinase elimination curve. (From Rosen P [ed]: *Emergency medicine,* ed 4, St Louis, 1998, Mosby.)

TABLE R1-10 Causes of Rhabdomyolysis

Muscle injury/ischemia	Trauma, pressure necrosis, electric shock, burns, acute vascular disease
Myofiber exhaustion	Seizures, excessive exercise, heat exhaustion
Toxins	Alcohol, cocaine, heroin, amphetamines, Ecstasy, phencyclidine, snakebite
Drugs	Statins, fibrates, zidovudine, neuroleptic malignant syndrome, azathioprine, theophylline, lithium, diuretics
Electrolyte disorders	Hypophosphatemia, hypokalemia, excess water shifts (hyperosmolality)
Infections	Viral (influenza, HIV, Coxsackievirus, Epstein-Barr virus), bacterial *(Legionella, Francisella, Streptococcus pneumoniae, Salmonella, Staphylococcus aureus)*
Familial	McArdle's disease, carnitine palmitoyl transferase deficiency, malignant hyperthermia
Other	Hypothyroidism, polymyositis, dermatomyositis

From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

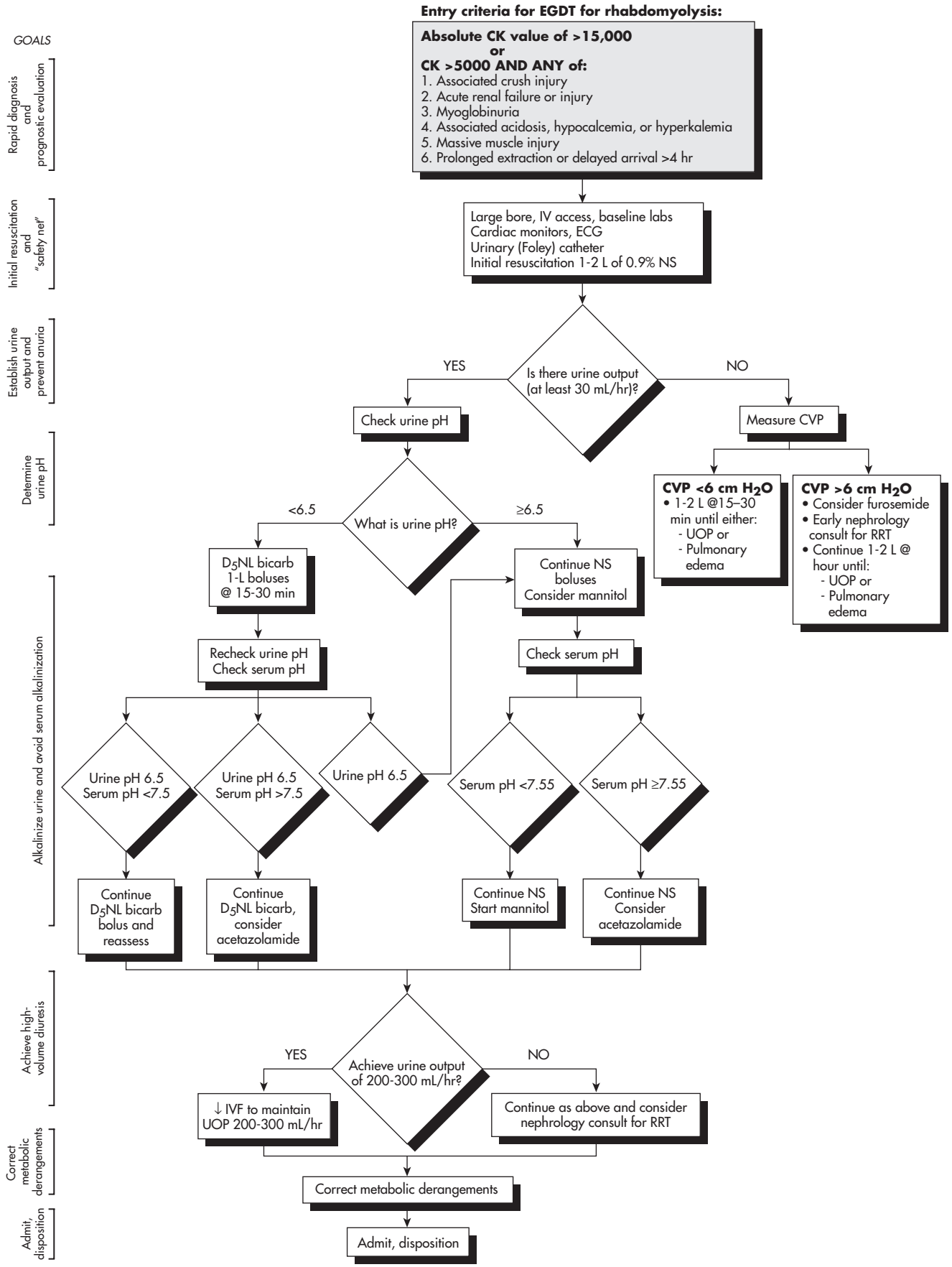


FIGURE R1-26 Early goal-directed therapy for rhabdomyolysis. *CK*, Creatine kinase; *CVP*, central venous pressure; *D5NL bicarb*, 5% dextrose in normal sodium bicarbonate solution; *EGDT*, early goal-directed therapy; *IV*, intravenous; *IVF*, intravenous fluid; *NS*, normal saline; *RRT*, renal replacement therapy; *UOP*, urinary output. (From Adams JG et al: Emergency Medicine, Clinical Essentials, 2nd ed, Philadelphia, Elsevier 2013.)

BOX R1-1 Laboratory Abnormalities Observed with Rhabdomyolysis

Potassium
Elevated
Risk for acute kidney injury

Bicarbonate
Decreased (20 mEq/L)
Metabolic acidosis

Uric Acid
Elevated (>7 mg/dL)
Marker of acute renal failure

Sodium
Usually normal
Can decrease with mannitol therapy
Use serum osmolarity values as a guide

Phosphate
Elevated
Risk for precipitation of calcium phosphate
May need phosphate binders if phosphate >7 mg/dL

Creatine Kinase
Elevated
Associated with creatine kinase level of 15 to 75,000

Blood Urea Nitrogen
Elevated (>20 mg/dL)

Creatinine
Elevated

Calcium
Initially low, sometimes markedly so
Rebound phase may demonstrate hypercalcemia

Liver Function Tests
Sometimes elevated
Serum aspartate transaminase, lactate dehydrogenase, aldolase, muscle enzyme levels elevated

Troponin
Normal
Suspect myocardial damage as a cause (or effect) if elevated
Seven percent false-positive rate for troponin I

Anion Gap
Sometimes elevated
May be predictive of acute renal failure

Prothrombin Time, Partial Thromboplastin Time, D-Dimer
Disseminated intravascular coagulation in up to 30% of severe cases
Associated with higher mortality

(From Adams J.G.; et al. *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

- Initiate volume repletion with normal saline at a rate of 200 to 1000 ml/hour depending on the setting and severity. Consider treatment with mannitol (up to 200 g/day and cumulative dose up to 800 g) to induce diuresis to prevent acute renal failure. Typically a 20% mannitol infusion at a dose of 0.5 g/kg is given over a 15-min period followed by an infusion at 0.1 g/kg/hr. Fluids should be administered at a rate that results in a urine output of 200 ml/hr until CK levels begin to decrease. Check for plasma osmolality and plasma osmolal gap. Discontinue mannitol if diuresis (>20 ml/hr) is not established. Maintain volume repletion until myoglobinuria is cleared (negative urine dipstick for blood).
- Monitor serum potassium frequently. Correct electrolyte imbalances. Correct hypocalcemia only if symptomatic or if severe hyperkalemia occurs.
- Treatment of electrolyte imbalances.
- Alkalinization of urine (to maintain urine pH between 6 and 7 and keep serum pH at 7.50) is controversial but appears helpful in research models when administered early in the course of rhabdomyolysis. Urine alkalinization may trap myoglobin, thereby preventing toxic myoglobin precipitation, and lowers lipid peroxidation, reactive oxygen species formation, and myoglobin-induced vasoconstriction.
- Fasciotomy is indicated in compartment syndrome for preservation of muscle and nerve function. Fasciotomy can lead to rapid decompression of compartment syndrome.

DISPOSITION

Early diagnosis and management are necessary to avoid renal failure, which occurs in 30% of cases. Rhabdomyolysis accounts for 7% to 10% of all cases of acute kidney injury.

REFERRAL

Renal consultation.

PEARLS & CONSIDERATIONS

COMMENTS

- Statin-induced rhabdomyolysis is 12 times more frequent when statins are combined with fibrates compared with statin monotherapy.
- Short-term high-dose corticosteroids (500 to 1000 mg of methylprednisolone) have been successfully used in the treatment of alcohol-induced rhabdomyolysis unresponsive to fluid repletion and may be reasonable in cases of severe rhabdomyolysis refractory to conventional treatment. Corticosteroids block the response of neutrophils to damage tissues and inhibit the chemotaxis of monocytes and neutrophils to sites of inflammation. It has been hypothesized that corticosteroid administration may help diminish the inflammatory exacerbation of muscle damage.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Rhabdomyolysis (Patient Information)
Statin-Induced Muscle Syndromes (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Background:
Intoxication due to quail consumption is rarely seen. Such a toxicologic syndrome (also called coturnism) occurs during the migration of quails from north to south, when they consume hemlock seeds. The clinical symptoms and laboratory results are indicative of acute rhabdomyolysis.

Objectives:
Acute rhabdomyolysis has a wide range of etiologies. Coturnism is a rare cause of acute rhabdomyolysis that can be lethal due to renal failure and shock. To avoid severe complications, coturnism may be considered if the history is appropriate.

Case Report:
We report four cases of coturnism from quail consumption; the patients were admitted with some combination of symptoms including muscle tenderness, extremity pain, nausea, and vomiting. They were treated with vigorous isotonic crystalloid hydration and urine alkalinization. Consequently, the laboratory results returned to normal ranges and the clinical symptoms disappeared.

Conclusion:
Although coturnism is a rarely seen toxicologic syndrome that causes rhabdomyolysis, we present this case to increase awareness that it may present with symptoms of muscle tenderness, extremity pain, nausea, and vomiting after quail consumption. Ⓐ

Evidence-Based Reference

Korkmaz I et al.: Quail consumption can be harmful, *J Emerg Med* 41:499–502, 2011. Ⓐ

SUGGESTED READINGS

Ahn SC: Neuromuscular complications of statins, *Phys Med Rehabil Clin North Am* 19:47, 2008.

Alsheikh-Ali AA et al.: Effect of the magnitude of lipid lowering on risk of elevated liver enzymes, rhabdomyolysis, and cancer: insights from large randomized statin trials, *J Am Coll Cardiol* 50(5):409, 2007.

Antons KA et al.: Clinical perspectives of statin-induced rhabdomyolysis, *Am J Med* 119:400–409, 2006.

Antoon JW, Chakraborti C: Corticosteroids in the treatment of alcohol-induced rhabdomyolysis, *Mayo Clin Proc* 86(10):1005–1007, 2011.

Bosch X et al.: Rhabdomyolysis and acute kidney injury, *N Engl J Med* 361:62–72, 2009.

Chatzizisis YS et al.: Risk factors and drug interactions predisposing to statin-induced myopathy: implications for risk assessment prevention and treatment, *Drug Saf* 38(3):171, 2010.

Ettinger JE et al.: Rhabdomyolysis: diagnosis and treatment in bariatric surgery, *Obes Surg* 17(4):525, 2007.

Finsterer J et al.: Severe rhabdomyolysis after excessive bodybuilding, *J Sports Med Phys Fitness* 47:502, 2007.

Joy TR, Hegele RA: Narrative review: statin-related myopathy, *Ann Intern Med* 150:858–868, 2009.

Klopstock T: Drug-induced myopathies, *Curr Opin Neurol* 21:590, 2008.

BASIC INFORMATION

DEFINITION

Rheumatic fever is a multisystem inflammatory disease that occurs in the genetically susceptible host 2 to 4 wk after a pharyngeal infection with group A streptococci.

SYNONYMS

Acute rheumatic fever
Rheumatic carditis

ICD-9CM CODES
390; 716.9 Rheumatic fever
ICD-10CM CODES
I00 Rheumatic fever without heart involvement
I01 Rheumatic fever with heart involvement
I01.0 Acute rheumatic pericarditis
I01.1 Acute rheumatic endocarditis
I01.2 Acute rheumatic myocarditis
I01.8 Other acute rheumatic heart disease
I01.9 Acute rheumatic heart disease, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):
- 0.1% to 3% in patients with untreated streptococcal pharyngitis.
- Higher incidence of streptococcal pharyngitis with:
  1. Crowding.
  2. Poverty.
  3. Young age.

PREDOMINANT AGE:
- Age 5 to 15 yr for first attack, rare before the age of 3.
- Possible relapses later.

PEAK INCIDENCE: School-age children.
GENETICS: Familial disposition: predisposition to the disease is likely to be genetically determined.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute streptococcal pharyngitis, which may be subclinical and not reported by the patient.
- After latent period of 2 to 4 wk (average, 19 days), acute rheumatic attack.
- Patient is febrile, with a migratory polyarthritis of knees, ankles, wrists, elbows; typically severe for 1 wk, remits by 3 to 4 wk.
- Carditis.
  1. New heart murmur.
     a. Mitral regurgitation.
     b. Aortic insufficiency.
     c. Diastolic mitral murmur
  2. Cardiomegaly.
  3. CHF.
  4. Pericardial friction rub or effusion.
- Rarely, pancarditis is severe and fatal.
- Subcutaneous nodules can be palpated over extensor tendon surfaces or bony prominences, such as the skull.
- Chorea (Sydenham's chorea) is characterized by rapid involuntary movements affecting all muscles.
  1. Muscular weakness.
  2. Emotional lability.
  3. Rarely seen after adolescence and almost never in adult males.
- Erythema marginatum.
  1. Evanescent, pink, well-demarcated spreading to trunk and proximal extremities.
  2. Not specific.
- Arthralgias (joint pain without swelling).
- Abdominal pain.

ETIOLOGY

- Group A streptococci not recovered from tissue lesions.
- It does not occur in the absence of a streptococcal antibody response.
- Immunologic cross-reactivity between certain streptococcal antigens and human tissue antigens suggests an autoimmune cause.
- Both initial attacks and recurrences can be completely prevented by prompt treatment of streptococcal pharyngitis with penicillin.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rheumatoid arthritis.
- Juvenile rheumatoid arthritis (Still's disease).
- Bacterial endocarditis.
- Systemic lupus.
- Viral infections.
- Poststreptococcal reactive arthritis: severe arthritis but no carditis.

WORKUP

- "Jones Criteria (revised) for Guidance in the Diagnosis of Rheumatic Fever."
- One major and two minor criteria if supported by evidence of an antecedent group A streptococcal infection.
- Major criteria
  1. Carditis and valvulitis.
  2. Migratory arthritis (predominantly involving large joints).
  3. Central nervous system involvement (e.g., chorea).
  4. Erythema marginatum.
  5. Subcutaneous nodules.
- Minor criteria
  1. Fever.
  2. Arthralgia.
  3. Increased acute-phase reactants.
     a. ESR.
     b. C-reactive protein.
     c. Leukocytosis.
- Prolonged P-R interval

LABORATORY TESTS

- Throat cultures are usually negative at presentation of clinical manifestations of rheumatic fever.
- Streptococcal antibody tests are more useful in establishing the diagnosis.
  1. Peak at the beginning of the attack.
  2. Can document a recent streptococcal infection.
- ASO (antistreptolysin O) titers peak:
  1. 4 to 5 wk after the actual streptococcal throat infection.
  2. Which coincides during the second or third wk of rheumatic fever illness.
- Anti-DNase B (Streptozyme) can be detected for 6 to 9 mo following infection and can be tested for if ASO titer negative.
- Other antistreptococcal antibody tests include: streptokinase and antihyaluronidase.
- High-titer streptococcal antibodies:
  1. Are supportive of diagnosis, but not proof.
  2. Should be interpreted in the context of clinical criteria.

IMAGING STUDIES

- Chest x-ray to assess heart size.
- Echocardiogram:
  1. To evaluate murmurs.
  2. To rule out pericardial effusion.

TREATMENT

ACUTE GENERAL Rx

- Course of penicillin to eradicate throat carriage of group A streptococci.
- Arthralgia or arthritis without carditis: aspirin 90 to 100 mg/kg/day for 2 wk, followed by 60 to 70 mg/kg/day for the subsequent 4 to 6 wk if needed.
- Carditis and heart failure:
  1. Prednisone 40 to 60 mg/day.
  2. IV corticosteroids, such as methylprednisolone, 10 to 40 mg/day for severe carditis.

CHRONIC Rx

Secondary prevention (prevention of recurrences):
- Monthly treatment with benzathine penicillin 1.2 million U IM or penicillin V: 250 mg orally bid.
- Erythromycin in patients with penicillin allergy: 250 mg bid or sulfadiazine orally at 0.5 g once a day for patients <27 kg and 1.0 g daily for patients >27 kg.

Duration of prophylaxis (American Heart Association recommendations):
- Rheumatic fever without carditis: 5 yr or until 21 yr of age, whichever is longer.
- Rheumatic fever with carditis but without residual heart disease (no clinical or echocardiographic evidence of persistent valvular disease): 10 yr or until 21 yr of age, whichever is longer.
- Rheumatic fever with carditis and residual heart disease (clinical or echocardiographic evidence of persistent valvular disease): 10 yr or until 40 yr of age, whichever is longer, sometimes lifelong prophylaxis.

DISPOSITION

- Damage of heart valves because of fibrosis.
  1. Late sequela of recurrent attacks.
  2. Frequent cause of valvular heart disease in developing countries.
- May progress to heart failure

REFERRAL

To cardiologist for management of severe carditis.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Rheumatic Fever (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Gerber MA et al.: Prevention of rheumatic fever and diagnosis and treatment of acute streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease committee of the Council on Cardiovascular disease in the young, *Circulation* 119:1541–1551, 2009.

Jaggi P: Rheumatic fever and postgroup A streptococcal arthritis, *Pediatr Infect Dis J* 30(5):424–425, 2011.

Kaplan EL: Pathogenesis of acute rheumatic fever and rheumatic heart disease: evasive after half a century of clinical, epidemiological, and laboratory investigation, *Heart* 91(1):3, 2005.

Robertson KA et al.: Antibiotics for the primary prevention of acute rheumatic fever: a meta-analysis, *BMC Cardiovasc Disor* 5(1):11, 2005.

Sharland M et al.: Antibiotic prescribing in general practice and hospital admissions for peritonsillar abscess, mastoiditis, and rheumatic fever in children: time trend analysis, *BMJ* 331(7512):328, 2005.

Vijayalakshmi IB et al.: The role of echocardiography in diagnosing carditis in the setting of acute rheumatic fever, *Cardiol Young* 15(6):583, 2005.

Walker K, Wilmshurst J: Acute rheumatic fever, *Lancet* 366(9494):1354, 2005.

BASIC INFORMATION

DEFINITION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by inflammatory polyarthritis, which affects peripheral joints, especially the small joints of the hands and feet. Chronic untreated inflammation may lead to joint erosions and joint destruction.

ICD-9CM CODES
714.0 Rheumatoid arthritis
ICD-10CM CODES
M06.9 Rheumatoid arthritis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Annual incidence in northern Europe and the United States 0.15 to 0.60 per 1000.
PEAK INCIDENCE: Steadily increases with age until the mid-70s.
PREVALENCE: 0.5% to 1.0% of the worldwide population.
PREDOMINANT SEX AND AGE: Male/female ratio of 1:2; prevalence increases with age.
GENETICS: Genetic factors account for >50% of risk of disease. RA is polygenic; identified genetic associations include *HLA-DRB1, PTPN22,* and *PADI4.*
RISK FACTORS: Female sex, age, tobacco use, silica exposure, obesity.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Initial presentation:
- A>6 wk of pain, swelling, warmth in one or more peripheral joints, frequently with symmetric joint involvement involving wrists, hands, and/or feet, and often associated with >1 hr of morning stiffness.
- Most common joints involved include metacarpophalangeal (MCP), proximal interphalangeal (PIP), wrists, metatarsophalangeal (MTP), and ankles.
- Also elbows, shoulders, hips, and knees.
- Distal interphalangeal (DIP) joints are spared.
- Sacroiliac and vertebral joints are spared except for C1 to C2.

Chronic longstanding disease:
- "Swan-neck" (DIP flexion and PIP hyperextension) and "boutonniere" PIP flexion and DIP hyperextension) deformities (Fig. R1-27), as well as MCP subluxation resulting in ulnar drift (Fig. R1-28).
- C1-C2 (atlantoaxial) inflammation can lead to odontoid erosion and transverse ligament laxity, resulting in atlantoaxial subluxation and cord compression.
- Joint damage of wrists, elbows, shoulders, hips, and knees can lead to severe osteoarthritis, necessitating joint surgery and/or replacement.

Extraarticular manifestations:
- Secondary Sjögren's syndrome (~35%): immune-mediated inflammation of lacrimal and salivary glands resulting in dry mouth and eyes (sicca syndrome).
- Rheumatoid nodules (25%): on extensor surfaces and pressure points, in rheumatoid factor positive (RF+) disease. Histopathology demonstrates palisading histiocytes surrounding fibrinoid necrosis.
- Normocytic normochromic anemia.
- Felty's syndrome: RA with splenomegaly and leukopenia.
- Pulmonary disease
  - Pleural disease (effusions, pleuritis).
  - Interstitial lung disease (up to 10% clinically significant).
- Vasculitis.
- Cardiac disease
  - Pericarditis.
  - An ↑ risk of cardiovascular disease.
- Ocular disease
  - Keratoconjunctivitis sicca (dry eye, without dry mouth/secondary Sjögren's) (10%).
  - Episcleritis, scleritis.
- Amyloidosis: longstanding RA. Can affect heart, kidney, liver, spleen, intestines, and skin.

ETIOLOGY

Unknown. It is likely that a combination of genetic and environmental factors leads to aberrant immune activation and inflammatory response in the joint. Stages of disease development presumably include:
- Initiation of immune response (trigger unknown, but environmental exposures such as tobacco and silica have been implicated).
- Perpetuation of inflammatory response, with migration of inflammatory cells into joint space, activation of macrophage-like and fibroblast-like synoviocytes, and development of "synovial pannus," a thickened synovial membrane.
- The pannus releases proinflammatory cytokines (TNF-α, IL-1, IL-6, IL-8), as well as proteases, which erode cartilage and bone.
- Many of the new "biologic" disease-modifying antirheumatic drugs (DMARDs) are engineered to target these cytokines.

DIAGNOSIS

The American College of Rheumatology and the European League Against Rheumatism have developed new classification criteria for RA. Four variables constitute the new criteria:
1. The number and size of involved joints (score 0 to 5, with higher scores for a larger number of small joints affected).
2. Results of rheumatoid factor (RF) and anti-citrullinated protein antibody testing (score 0 to 3, with more points for a high positive RF or anti-CCP).
3. Abnormal sedimentation rate or elevated C-reactive protein (1 point).
4. Symptom duration >6 wk (1 point).

Scores ≥6 points are considered to have "definite RA." Maximum score is 10 points.

DIFFERENTIAL DIAGNOSIS

- Infections: parvovirus B19, hepatitis B, hepatitis C, poststreptococcal reactive arthritis, acute rheumatic fever.
- Systemic lupus erythematosus.
- Seronegative spondyloarthropathies.
- Calcium pyrophosphate deposition (CPPD or "pseudo-RA").
- Polymyalgia rheumatica.
- Hemochromatosis.
- Scleroderma.
- Osteoarthritis (see Table R1-11).

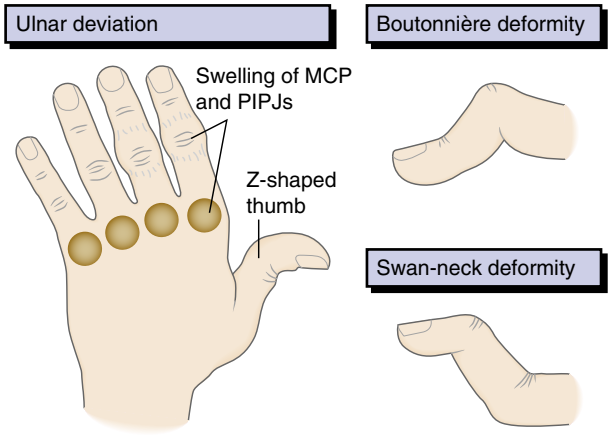


FIGURE R1-27 Characteristic hand deformities in rheumatoid arthritis. *MCP,* Metacarpophalanges; *PIPJs,* proximal interphalangeal joints. (From Ballinger A.; *Kumar & Clark's essentials of clinical medicine,* ed 6, Edinburgh, 2012, Saunders.)

FIGURE R1-28 Rheumatoid arthritis. Hand of a 60-year-old man with seropositive rheumatoid arthritis. There are fixed deformities and gross rheumatoid nodules. (From Canoso J.J.; *Rheumatology in primary care,* Philadelphia, 1997, Saunders.)

TABLE R1-11 Factors Useful for Differentiating Early Rheumatoid Arthritis from Osteoarthritis

	Rheumatoid Arthritis	Osteoarthritis
Age at onset	Childhood and adults, peak incidence in 50s	Increases with age
Predisposing factors	Susceptibility epitopes (HLA-DR4, HLA-DR1)	Trauma
	PTPN22, PADI4 polymorphisms, and others	Congenital abnormalities (e.g., shallow acetabulum)
	Smoking	
Early symptoms	Morning stiffness	Pain increases through the day and with use
Joints involved	Metacarpophalangeal joints, wrists, proximal interphalangeal joints most often; distal interphalangeal joints almost never	Distal interphalangeal joints (Heberden's nodes), weight-bearing joints (hips, knees)
Physical findings	Soft tissue swelling, warmth	Bony osteophytes, minimal soft tissue swelling early
Radiologic findings	Periarticular osteopenia, marginal erosions	Subchondral sclerosis, osteophytes
Laboratory findings	Increased C-reactive protein, rheumatoid factor, anticitrullinated protein antibody, anemia, leukocytosis	Normal

From Firestein G.S.; et al. [eds]: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.

LABORATORY TESTS

- RF. An immunoglobulin directed against the Fc region of the IgG.
- Sensitivity ~60%.
- Specificity ~80%. False positives are seen with hepatitis C, subacute bacterial endocarditis, sarcoidosis, malignancy, Sjögren's, SLE, increasing age.
- Anti-cyclic citrullinated peptide (anti-CCP) antibodies. More specific than RF for RA (up to 95% to 98%). Sensitivity similar to RF. The presence of either RF or anti-CCP ("seropositive RA") is associated with more severe RA.
- An ↑ Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)
- An ↑ CBC with differential: possible mild anemia and leukocytosis
- Synovial fluid: inflammatory, with >2000 PMNs.

IMAGING STUDIES

Plain radiography:

- Earlier changes include soft tissue swelling, joint space narrowing, and periarticular osteopenia.
- Later changes include periarticular erosions, especially in MCPs, PIPs, MTPs, and wrist. This reflects cartilage and bone destruction secondary to pannus (Fig. R1-29).
- MRI and musculoskeletal ultrasound are more sensitive for detecting erosive disease and joint effusion/synovitis.

FIGURE R1-29 Rheumatoid arthritis. A, Periarticular osteopenia and marginal erosions in metacarpophalangeal joints and a proximal interphalangeal *(arrows).* **B,** In the same patient, marginal erosions at metatarsal heads. (From Canoso J.J.; *Rheumatology in primary care,* Philadelphia, 1997, Saunders.)

Rx TREATMENT

Early identification and treatment of RA with DMARDs are crucial. More than half of patients have radiographic joint damage within 2 yr of disease onset, but early aggressive treatment (with DMARDs) is associated with less damage. Fig. R1-30 describes the American College of Rheumatology recommendations for treatment of rheumatoid arthritis.

ACUTE GENERAL Rx

- NSAIDs: Sometimes used initially to relieve pain and mild inflammation, or used later in the disease course for additional control of mild pain. NSAIDs are NOT disease modifying.
- Corticosteroids: oral or intraarticular, frequently used initially to reduce inflammation rapidly until oral DMARD treatments take effect. They may also be used during acute flares or in low doses for additional control of inflammation. They have many side effects, including but not limited to weight gain, increased risk of diabetes, osteoporosis, and avascular necrosis.

CHRONIC Rx

DMARDs: Can be classified into "nonbiologic" and "biologic" treatments.

Nonbiologic DMARDs: commonly used agents are methotrexate (MTX), hydroxychloroquine (HCQ), sulfasalazine (SSZ), and leflunomide. Most of these are associated with potential toxicity and require close monitoring. They are also slow-acting drugs that require >8 wk to become fully effective.

MTX is the most commonly used DMARD worldwide for the treatment of RA.

"Triple therapy"—MTX, HCQ, and SSZ are superior to MTX alone.

Biologic DMARDs: newer biologically engineered therapies, which target cytokines and cells involved in the RA inflammatory response. Major side effects include an increased risk of severe infection, most notably reactivation of tuberculosis with anti-TNF agents. A negative PPD is a prerequisite to initiate therapy. Biologic DMARDs are most effective when used in combination with a nonbiologic DMARD, usually MTX.

Tumor necrosis factor α inhibitors (TNFI). Includes infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab.

Abatacept (CTLA-4Ig). A recombinant protein that prevents costimulatory binding of antigen presenting cell to T cell, preventing T cell activation.

Tocilizumab (anti–IL-6). A monoclonal antibody against the IL-6 receptor.

Tofacitinib (JAK3 inhibitor). Inhibits the JAK-STAT intracellular signaling pathway, thus preventing the production of inflammatory mediators. The first oral biologic DMARD.

Rituximab (anti-CD20). A monoclonal antibody against CD20 antigen on B lymphocytes.

DISPOSITION

- Remissions and exacerbations are common, but condition is chronically progressive in the majority of cases.
- Joint degeneration and deformity often lead to disability. Joint replacement is indicated for patients with severe joint damage whose symptoms are poorly controlled by medical management.
- Early and aggressive diagnosis and treatment are crucial in preventing or slowing joint destruction.

REFERRAL

- Early referral to rheumatologist.
- Orthopedic consultation for corrective surgery.

PEARLS & CONSIDERATIONS

RA sometimes develops acutely in the postpartum patient; conversely, many patients with RA will experience remission during pregnancy.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Rheumatoid Arthritis (Patient Information)

AUTHOR: **KERRI BATRA, M.D.**

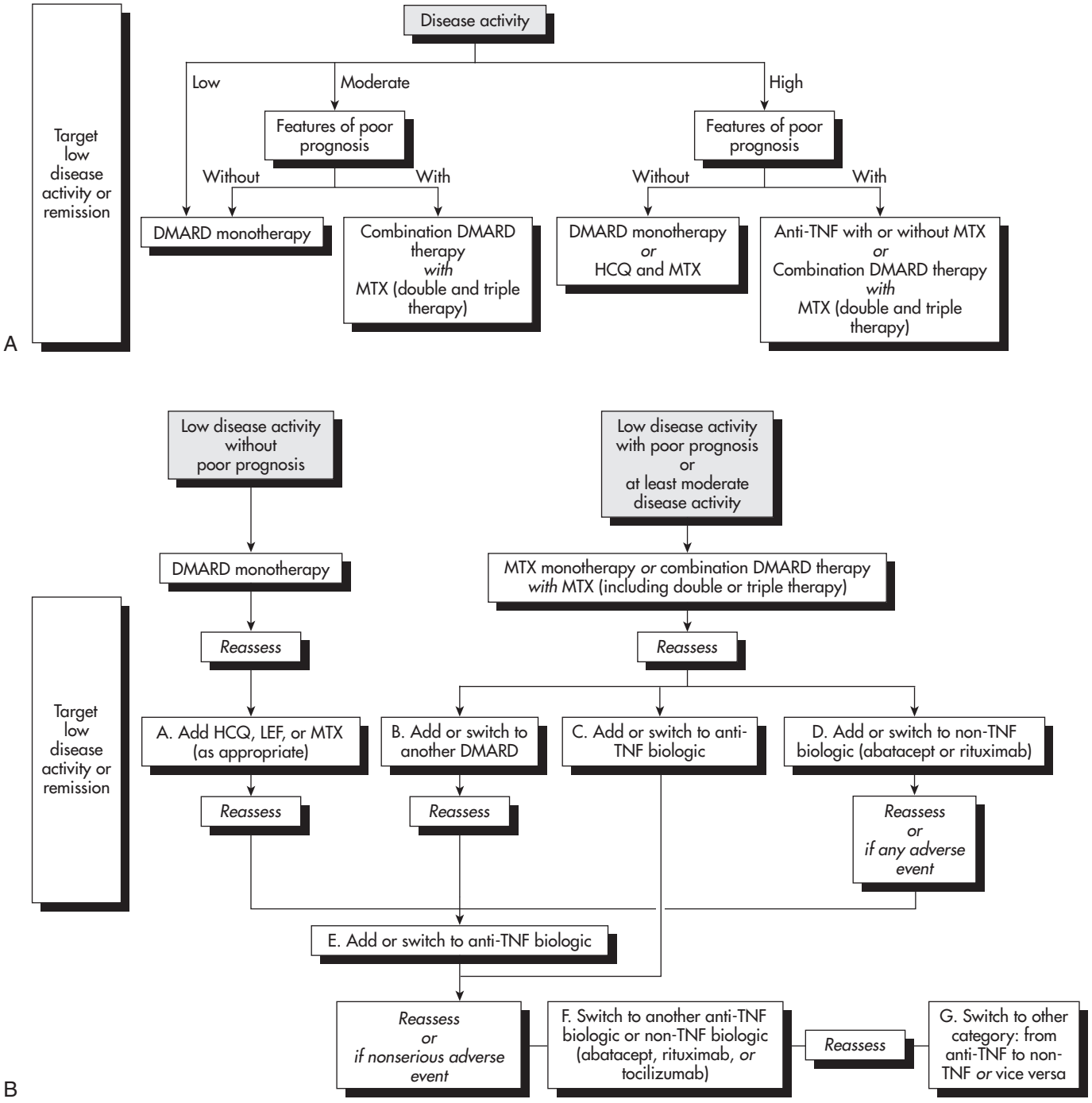


FIGURE R1-30 American College of Rheumatology recommendations for treatment of rheumatoid arthritis. A, Early disease. **B**, Established disease. *DMARD*, Disease-modifying antirheumatic drug; *HCQ*, hydroxychloroquine; *LEF*, leflunomide; *MTX*, methotrexate; *TNF*, tumor necrosis factor. (From Firestein G.S.; et al. [eds]: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

EVIDENCE

Abstract[1]

We searched databases for controlled clinical studies and performed a meta-analysis on the effectiveness of yoga interventions on pain and associated disability. Five randomized studies reported single-blinding and had a higher methodological quality; 7 studies were randomized but not blinded and had moderate quality; and 4 nonrandomized studies had low quality. In 6 studies, yoga was used to treat patients with back pain; in 2 studies to treat rheumatoid arthritis; in 2 studies to treat patients with headache/migraine; and 6 studies enrolled individuals for other indications. All studies reported positive effects in favor of the yoga interventions. With respect to pain, a random effect meta-analysis estimated the overall treatment effect at SMD=–0.74 (CI: –0.97; –0.52, P<.0001), and an overall treatment effect at SMD=–0.79 (CI: –1.02; –0.56, P<0.0001) for pain-related disability. Despite some limitations, there is evidence that yoga may be useful for several pain-associated disorders. Moreover, there are hints that even short-term interventions might be effective. Nevertheless, large-scale further studies have to identify which patients may benefit from the respective interventions. Ⓐ

Evidence-Based Reference

Büssing A et al.: Effects of yoga interventions on pain and pain-associated disability: a meta-analysis, *J Pain* 13:1–9, 2012. Ⓐ

SUGGESTED READINGS

Aletaha D et al.: Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism Collaborative Initiative, *Arthritis Rheum* 62:2569, 2010.

Bakker MF et al.: Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis, *Ann Intern Med* 156:329–339, 2012.

Donahue KE et al.: Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis, *Ann Intern Med* 148:124, 2008.

Finckh A et al.: Treatment of very early rheumatoid arthritis with symptomatic therapy, disease-modifying antirheumatic drugs, or biologic agents, *Ann Intern Med* 151:612–621, 2009.

Goekoop-Ruiterman JP et al.: Comparison of treatment strategies in early rheumatoid arthritis, *Ann Intern Med* 146:406–415, 2007.

Heiberg MS et al.: The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis: results from a longitudinal, observational, multicenter study, *Arthritis Rheum* 59:234, 2008.

McInnes IB, Schett G: The pathogenesis of rheumatoid arthritis, *N Engl J Med* 365:2205, 2011.

Nishimura K et al.: Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis, *Ann Intern Med* 146:797–808, 2007.

O'Dell JR et al.: Therapies for active rheumatoid arthritis after methotrexate failure, *N Engl J Med* 369:307–318, 2013.

Papp SR et al.: The rheumatoid wrist, *J Am Acad Orthop Surg* 14:65, 2006.

Sfikakis PP: The first decade of biologic TNF antagonists in practice: lessons learned, unresolved issues, and future directions, *Curr Dir Autoimmun* 11:180, 2010.

Shmerling RH: Testing for anti-cyclic citrullinated peptide antibodies: is it time to set this genie free? *Arch Intern Med* 169(1):9–14, 2009.

Smolen J et al.: New therapies for treatment of rheumatoid arthritis, *Lancet* 370:1861–1874, 2007.

Sokka T: Quantitative assessment of rheumatoid arthritis in standard clinical care: turning clinical care into clinical science, *Best Pract Res Clin Rheumatol* 21(4):653, 2007.

Sokka T et al.: Remission and rheumatoid arthritis: data on patients receiving usual care in twenty-four countries, *Arthritis Rheum* 58:2642, 2008.

Wasserman AM: Diagnosis and management of rheumatoid arthritis, *Am Fam Physician* 84(11):1245, 2011.

BASIC INFORMATION

DEFINITION

Rickets is a result of deficient mineralization of osteoid matrix before closure of epiphyseal plate causing softening and weakening of bones in infants and children. The mineralization impairment may be secondary to abnormal calcium, phosphorus, or vitamin D metabolism leading to accumulation of osteoid before epiphyseal closure, compromising bone stability at sites of rapid bone growth. When this occurs in adulthood after epiphyseal closure, it is referred to as osteomalacia. Renal osteodystrophy is a term used to describe a similar condition in patients with chronic kidney disease. Certain forms of the disorder may respond only to high doses of vitamin D and are referred to as vitamin D–resistant rickets (VDRR), which are also known as hereditary vitamin D-dependent rickets.

ICD-9CM CODES

268.0 Active rickets
268.1 Late effect rickets
275.3 Vitamin D–resistant rickets, familial hypophosphatemia
588.0 Renal rickets (renal osteodystrophy)
268.2 Osteomalacia

ICD-10CM CODES

E55.0 Rickets, active
E83.30 Disorder of phosphorus metabolism, unspecified
N25.0 Renal osteodystrophy
M83.9 Adult osteomalacia, unspecified

RISK FACTORS

- Children ages 6 to 24 months.
- Premature infants.
- Residents of northern latitudes with inadequate sunlight exposure.
- Solely breastfed infants.
- Darker skin pigmentation.
- Use of anticonvulsants.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The classic clinical presentation of children with rickets includes the following:

- Apathy, muscle weakness, delayed growth.
- Skeletal pain and swollen joints.
- Protuberant abdomen due to muscle hypotonia.
- Widened sutures, delayed closure of fontanelles, and frontal bossing of head.
- Craniotabes (softening of skull bones).
- Delayed eruption and poorly mineralized teeth.
- Bowing deformity of lower extremities, specifically femur and tibia (Fig ER1-31).
- Rachitic rosary (enlargement and prominence of the rib head at the costochondral junctions).
- Harrison's groove (indentation of the lower ribs).
- Pathologic fractures.

The less pronounced clinical presentation of adults with osteomalacia includes the following:

- Skeletal pain and bone tenderness.
- Muscle hypotonia and proximal muscle weakness.
- Pathologic fractures and decreased bone density.
- Gait disturbances.

ETIOLOGY

The most common cause of rickets and osteomalacia is vitamin D deficiency. Vitamin D and PTH play an important role in calcium homeostasis. This may arise from various conditions, including inadequate dietary intake, malabsoption, chronic parenteral nutrition and the additional risk factors listed previously. Malabsorption that causes inefficient mineralization is observed in such diseases as cystic fibrosis, celiac disease, and many chronic illnesses. Vitamin D is required for adequate calcium absorption in the GI tract. Low vitamin D leads to a reduced intestinal absorption of calcium causing a compensatory increase in PTH and resorption of bone, leading to increased alkaline phosphatase levels.

Other causes specifically include vitamin D–dependent rickets (type I & II), VDRR, also known as hereditary hypophosphatemic rickets.

- VDRR type I results from abnormalities in the gene coding for 25 (OH)D3-1-alpha-hydroxylase, and type II results from defective vitamin D receptors.
- Chronic renal failure can produce bone mineralization deficiency due to electrolyte abnormalities causing hypocalcemia and renal osteodystrophy (renal rickets). This results in decreased excretion of phosphate, therefore elevating serum phosphorus, along with elevated parathyroid hormone (PTH) and low levels of 1,25-OH vitamin D.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Osteoporosis.
- Hyperparathyroidism.
- Hyperthyroidism.
- Hypophosphatasia.
- Skeletal dysplasia.

WORKUP

Rickets is a clinical diagnosis. It is often challenging to determine the exact etiology; however, clinical, biochemical, and radiologic findings can be useful.

A thorough dietary and medication history for children is important. Bone biopsy is generally not performed; however, it is the diagnostic gold standard.

LABORATORY TESTS

- Requires a high degree of interest because many of the conditions are so similar that only a complicated laboratory evaluation may establish the diagnosis. Children may present solely with an elevated alkaline phosphate level and characteristic physical findings.
- Blood testing would include serum calcium, inorganic phosphorus (Pi), alkaline phosphate, PTH, 25-OH vitamin D, creatinine, and liver enzymes.

IMAGING STUDIES

- In rickets, characteristic radiologic findings include irregular epiphyseal-metaphyseal junctions with widening and flaring of the epiphyses of long bones, causing bowing.
- Pseudofractures (Looser zones) and narrow radiolucent lines may be seen as a result of microfractures at high stress points or at the location of entry of blood vessels into the bone and are observed in severe rickets and osteomalacia.

TREATMENT

- Treatment is dependent on the underlying etiology; however, high doses of vitamin D resolves most deficiencies. Nutritional deficiency of vitamin D is rare now with the amount of vitamin D present in milk.
- VDRR type I is treated with both vitamin D and phosphate replacement. The earliest biochemical change after initiation of treatment is an increase in the level of phosphorus followed by a rise in calcium level. Serum calcium, phosphorus, alkaline phosphatase, calcidiol levels and urine calcium and phosphorus levels should be obtained within 2 weeks of initiation of therapy and at periodic intervals thereafter. The treatment of type II is more complex and requires the expertise of an endocrinologist and/or nephrologists.
- Familial hypophosphatemic rickets is treated with calcitriol and oral phosphorus.

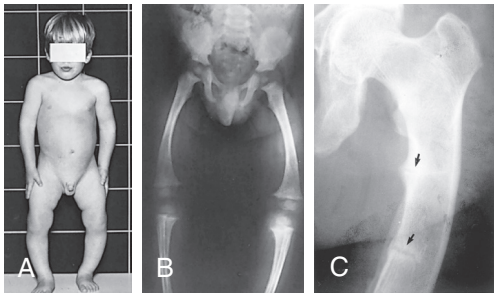


FIGURE ER1-31 **A,** A typical example of rickets. Note the bowing of the femurs and tibiae, which may result from vitamin D deficiency, phosphate deficiency, or other causes. **B,** A skeletal radiograph of a child with rickets. Note that the weight-bearing bones of the lower extremities are bowed and that the epiphyses are open, mottled, and overgrown. **C,** Looser zones or pseudofractures that are characteristic of osteomalacia or rickets. Because the epiphyses are closed, the patient is an adult. This radiograph is diagnostic of osteomalacia. (From Stewart A: Metabolic bone diseases. In Andreoli T.E.; et al. [eds]: *Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.)

- Oral phosphorus alone is the treatment of choice for hereditary hypophosphatemic rickets with hypercalciuria.

REFERRAL

- Because of the complex nature of many of these disorders, a qualified endocrinologist and nephrologist should be consulted for treatment.
- Orthopedic consultation may be required for some cases of bowlegs or spinal deformities, which may require specific bracing for long-term growth of the bones. Corrective surgery may be necessary if the deformity is very severe.
- Surgical care is also indicated for slipped capital femoral epiphysis, which is fairly common in renal rickets.

SUGGESTED READINGS

Goodman SB et al.: The effects of medications on bone, *J Am Acad Orthop Surg* 15(8):450, 2007.

McKay CP, Portale A: Emerging topics in pediatric bone and mineral disorders. 2008, *Semin Nephrol* 29:370, 2009.

Nield LS et al.: Rickets: not a disease of the past, *Am Fam Physician* 74:619, 2006.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Vitamin D Deficiency (Patient Information)

AUTHOR: **STEPHANIE A. CURRY, M.D.**

BASIC INFORMATION

DEFINITION

Rocky Mountain spotted fever (RMSF) is a life-threatening, tick-borne febrile illness caused by infection with *Rickettsia rickettsii.* The infection occurs when *R. rickettsii* in the salivary glands of a vector tick is transmitted into the dermis, spreading and replicating in the cytoplasm of endothelial cells and eliciting widespread vasculitis and end-organ damage.

ICD-9CM CODES
082.0 Rocky Mountain spotted fever
ICD-10CM CODES
A77.0 Spotted fever due to Rickettsia rickettsii

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 0.18 to 0.32 cases per 100,000 person-years
PREVALENCE: Most prevalent in the Southeast, followed by the South Central states, but seen anywhere (Fig. R1-32). It has recently been reported in eastern Arizona, with common brown dog ticks *(Rhipicephalus sanguineus)* implicated as a vector of *R. rickettsii.*
PREDOMINANT SEX: Affects both genders equally.
PREDOMINANT AGE: Occurs at any age, but more likely in children ages 5 to 14 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Incubation: 2 to 14 days
- First symptoms: fever, headache, malaise, myalgias

Common History, Signs, or Symptoms	%
Tick bite	65
Fever	100
Rash	90
Rash on palms and soles (Fig. R1-33)	80
Headache	90
Myalgia	75
Nausea or vomiting	60
Abdominal pain	40
Conjunctivitis	30
Edema	20
Pneumonitis	15
Any severe neurologic complication (including stupor, delirium, seizures, ataxia, papilledema, focal neurologic deficits, and coma)	30

- Rash:
  - Appears during first 3 days in 50%; by day 5, 80% have it. No rash in 10%.
  - Initial appearance: blanching erythematous macules on wrists and ankles that then spread to trunk, palms, and soles (Fig. R1-34).
  - Lesions may evolve into papules and eventually become nonblanching (petechiae or palpable purpura).
- Gastrointestinal symptoms:
  - Nausea, vomiting, and abdominal pain are common.
  - Occasionally may mimic an "acute abdomen" (e.g., appendicitis, cholecystitis).
  - Mild hepatitis.
- Cardiopulmonary involvement:
  - Interstitial pneumonitis.
  - Myocarditis.
- Renal problems:
  - Prerenal azotemia.
  - Interstitial nephritis.
  - Glomerulonephritis.
- Neurologic involvement:
  - Encephalitis (confusion, lethargy, delirium).
  - Ataxia.
  - Convulsion.
  - Cranial nerve palsy.
  - Speech impediment.
  - Hemiparesis or paraparesis.
  - Spasticity.
- Fulminant RMSF:
  1. Early, widespread vascular necrosis leading to multisystem illness and death.

ETIOLOGY & PATHOGENESIS

- Infectious agent: *R. rickettsii* (an intracellular bacterium).
- Vector: dog tick and wood tick (vertical transmission exists in ticks, but horizontal transmission involving rodents represents an important reservoir for the agent). In the United States *R. rickettsii* is transmitted mainly by the American dog tick *(Dermacentor variabilis)* and the Rocky Mountain wood tick *(D. andersoni).*
- Pathogenesis: the spread of *R. rickettsii* is hematogenous with attachment to the vascular endothelium, causing a vasculitis. The manifestations of this illness are caused by increased vascular permeability.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Influenza A, enteroviral infection, typhoid fever, leptospirosis, infectious mononucleosis, viral hepatitis, sepsis, ehrlichiosis, gastroenteritis, acute abdomen, bronchitis, pneumonia, meningococcemia, disseminated gonococcal infection, secondary syphilis, bacterial endocarditis, toxic shock syndrome, scarlet fever, rheumatic fever, measles, rubella, typhus, rickettsialpox, Lyme disease, drug hypersensitivity reactions, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, Kawasaki disease, immune complex vasculitis, connective tissue disorders.

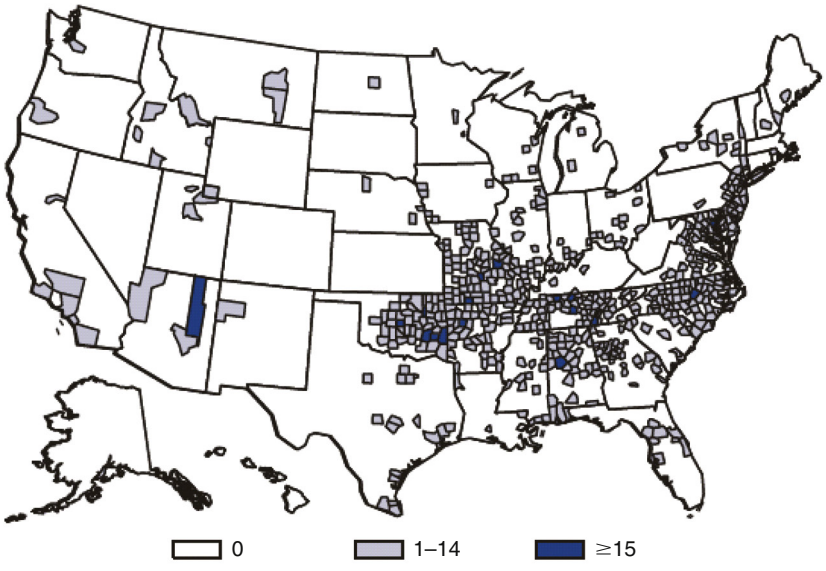


FIGURE R1-32 Spotted fever rickettsiosis. Number of reported cases, by county, United States, 2010. (From Centers for Disease Control and Prevention: Summary of notifiable diseases—United States, 2010, *MMWR Morb Mortal Wkly Rep* 59[53]:1-111, 2012.)

FIGURE R1-33 Palmar rash associated with Rocky Mountain spotted fever. (From Walker DH, Raoult D: *Rickettsia rickettsii* and other spotted fever group rickettsiae [Rocky Mountain spotted fever and other spotted fevers]. In Mandell GL et al [eds]: *Principles and practice of infectious diseases,* ed 5, New York, 2000, Churchill Livingstone.)

FIGURE R1-34 Late appearance of rash: Rocky Mountain spotted fever manifesting on lower extremity. (Courtesy of Theodore Woodward, MD.) (From Marx JA et al: *Rosen's emergency medicine: concepts and clinical practice,* 7 ed, Philadelphia, 2010, Elsevier.)

WORKUP

Consider RMSF in any patient with an acute febrile illness with headache and myalgia, especially with an associated history of tick exposure. Absence of rash does not rule out the diagnosis. Box R1-2 shows the diagnostic criteria for Rocky Mountain spotted fever.

LABORATORY TESTS

Routine Tests	%
White cell count	
<10,000/mm^3	72
>10% bands	69
Platelet count	
<150,000/mm^3	52
<99,000/mm^3	32
Serum sodium value <132 mEq/L	56
Aspartate aminotransferase ≥2× normal	62
Alanine aminotransferase ≥2× normal	39
Bilirubin value >1.4 mg/dl	30
Cerebrospinal fluid	
Opening pressure ≥250 mm H_2O	14
Glucose value ≤50 mg/dl	8
Protein value ≥50 mg/dl	35
White cell count ≥5/mm^3	38
Mononuclear cell predominance	46
Polymorphonuclear cell predominance	50

- Etiologic tests:
  1. Antibody titers to *R. rickettsii* (by indirect fluorescent antibody test). The diagnosis of RMSF requires a fourfold increase 2 wk apart and thus is not helpful in the care of the patients despite a sensitivity and specificity of near 100%.
  2. The only test that can provide a timely diagnosis is the immunohistologic demonstration of *R. rickettsii* in skin biopsy specimens.

BOX R1-2 Diagnostic Criteria for Rocky Mountain Spotted Fever

Laboratory Criteria

- Serologic evidence of a significant change in serum antibody titer reactive with *Rickettsia rickettsii* antigens between paired serum specimens, as measured by a standardized assay conducted in a commercial, state, or reference laboratory.
- Demonstration of *R. rickettsii* antigen in a clinical specimen by immunohistochemical methods.
- Detection of *R. rickettsii* DNA in a clinical specimen by the polymerase chain reaction (PCR) assay.
- Isolation of *R. rickettsii* from a clinical specimen in cell culture.

For confirmed cases, a significant change in titer must be determined by the testing laboratory; examples of commonly used measures of significant change include, but are not limited to, a fourfold or greater change in antibody titer as determined by indirect immunofluorescent antibody (IFA) assay or an equivalent change in optical density measured by enzyme-linked immunosorbent assay (EIA or ELISA).

Case Classification (CDC Case Definition, 2004)

Confirmed: The patient has a clinically compatible illness that is laboratory confirmed.
Probable: The patient has a clinically compatible illness and serologic evidence of antibody reactive with *R. rickettsii* in a single serum sample at a titer considered indicative of current or past infection (cutoff titers are determined by individual laboratories).

CDC, Centers for Disease Control and Prevention.
From Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis—United States. *MMWR Recomm Rep* 55(RR-4):18, 2006.
From Marx JA et al: *Rosen's emergency medicine: concepts and clinical practice,* 7 ed, Philadelphia, 2010, Elsevier.)

Rx TREATMENT

- Oral or IV doxycycline, 200 mg/day in 2 divided doses for 7 days or for 2 days after defervescence.
- Chloramphenicol, 50 mg/kg/day in 4 divided doses; chloramphenicol may be preferred during pregnancy because of the effects of doxycycline on fetal bones and teeth; therapy continued for at least 2 days after defervescence.

PROGNOSIS

Fatality rate: 1% to 4% (five times greater if treatment is initiated after day 5 of illness, which is more likely in the absence of rash and during seasonal nonpeak tick activity). Long-term sequelae seen in patients who recover from severe RMSF: paraparesis, hearing loss; peripheral neuropathy; bladder and bowel incontinence; cerebellar, vestibular, and motor dysfunction; language disorders; limb amputation; and scrotal pain after cutaneous necrosis.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Rocky Mountain Spotted Fever (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Demma LJ et al.: Rocky Mountain spotted fever from an unexpected tick vector in Arizona, *N Engl J Med* 353:587, 2005.

Masters EJ: Rocky Mountain spotted fever, *Arch Intern Med* 163:769, 2003.

BASIC INFORMATION

DEFINITION

Rosacea is a chronic skin disorder characterized by papules and pustules affecting the face and often associated with flushing and erythema.

SYNONYMS

Acne rosacea

ICD-9CM CODES
695.3 Rosacea
ICD-10CM CODES
L71 Rosacea
L71.9 Rosacea unspecified
L71.1 Rhinophyma
L71.8 Other rosacea
L71.0 Perioral dermatitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Rosacea occurs in 1 in 20 Americans.
- Onset often between ages 30 and 50 yr
- More common in people of Celtic origin; however, this disease may be overlooked in nonwhites because skin pigmentation results in atypical presentation.
- Female/male ratio of 3:1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Facial erythema, presence of papules, pustules, and telangiectasia.
- Excessive facial warmth and redness are the predominant presenting symptoms.
- Itching is generally absent.
- Comedones are absent (unlike acne).
- Women are more likely to show symptoms on the chin and cheeks, whereas in men the nose is commonly involved.
- Ocular findings (mild dryness and irritation with blepharitis, conjunctival injection, burning, stinging, tearing, eyelid inflammation, swelling, and redness) are present in 50% of patients.

Rosacea can be classified into four major subtypes:

1. Erythematotelangiectatic (vascular): erythema in central part of face, telangiectasia, flushing.
2. Papulopustular (inflammatory): presence of dome-shaped erythematous papules and small pustules, in addition to facial erythema, flushing, and telangiectasia.
3. Phymatosis (Fig. ER1-35): presence of thickened skin with prominent pores that may affect the nose (rhinophyma), chin (gnathophyma), forehead (metophyma), eyelids (blepharophyma), and ears (otophyma).
4. Ocular: conjunctival injection, sensation of foreign body in the eye, telangiectasia and erythema of lid margins, scaling.

ETIOLOGY

- Unknown but believed to involve the vasculature.
- Hot drinks, alcohol, and sun exposure may accentuate the erythema by causing vasodilation of the skin.
- Flare-ups may also result from reactions to medications (e.g., simvastatin, angiotensin-converting enzyme inhibitors, vasodilators, fluorinated corticosteroids), stress, extreme heat or cold, wind, humidity, strenuous exercise, spicy drinks, menstruation.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Drug eruption.
- Acne vulgaris.
- Contact dermatitis.
- Systemic lupus erythematosus.
- Carcinoid flush.
- Idiopathic facial flushing.
- Seborrheic dermatitis.
- Facial sarcoidosis.
- Photodermatitis.
- Mastocytosis.
- Perioral dermatitis.
- Granulomas of the skin.

WORKUP

Diagnosis is based on clinical findings. Distinguishing features between acne and rosacea are the presence of telangiectasia and deep diffuse erythema and absence of comedones in rosacea.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoid alcohol, excessive sun exposure, and hot drinks of any type.
- Use of mild, nondrying soap is recommended; local skin irritants should be avoided.
- Reassure patient that rosacea is completely unrelated to poor hygiene.
- Vascular laser surgery is effective for telangiectasia.
- Surgical options are available for rhinophyma.

GENERAL Rx

- Several classes of drugs are used in treatment of rosacea, including the metronidazole family, the tetracycline family, and azelaic acid.
- Vascular rosacea: topical therapy with metronidazole aqueous gel (MetroGel) applied bid is effective as initial therapy for mild cases. A new 1% formulation of metronidazole (Noritate) applied daily may improve patient compliance. Clindamycin lotion (Cleocin), sulfacetamide, or erythromycin 2% solution may also be effective. Brimonidine (Mirvaso) is a selective alpha$_2$-adrenergic receptor agonist recently FDA-approved as a gel preparation for topical treatment of adults with persistent facial erythema of rosacea.
- Pustular and ocular rosacea: systemic antibiotics (doxycycline 100 mg qd or tetracycline 250 mg qid until symptoms diminish, then taper off). Minocycline 50 to 100 mg qd should be used only in resistant cases because this medication is expensive. Oral metronidazole (200 mg qd to bid) for 4 to 6 wk is also effective.
- Isotretinoin (Accutane) 0.5 to 1 mg/kg/day in two divided doses for 15 to 20 wk can be used for refractory papular and pustular rosacea; use of retinoids may, however, worsen erythema and telangiectasis.
- Laser treatment is an option for progressive telangiectasias or rhinophyma.
- Erythema and flushing may respond to low-dose clonidine (0.05 mg bid).
- Treatment of phymatous rosacea: oral tetracyclines, oral isotretinoin, ablative/pulsed dye laser therapy, electrosurgery.
- Treatment of ocular rosacea: topical or oral tetracyclines, artificial tears, and/or lid cleansing for eyelid hygiene.

DISPOSITION

- Rosacea is often resistant to initial treatment and recurrent. Periods of remission and relapse are common.
- The progression of rosacea is variable. Typical stages include:
  1. Facial flushing.
  2. Erythema and/or edema and ocular symptoms.
  3. Papules and pustules.
  4. Rhinophyma.

PEARLS & CONSIDERATIONS

COMMENTS

- The course of the disease is typically chronic, with remissions and relapses.
- Patients with resistant cases may have *Demodex folliculorum* mite infestation or tinea infection (diagnosis can be confirmed with potassium hydroxide examination); the role of *D. folliculorum* in rosacea is unclear. These mites can sometimes be found in large numbers in the lesions; however, their numbers do not generally decline with treatment.
- Rosacea can result in emotional and social stigmas, especially because many people associate rosacea and rhinophyma with alcohol abuse.
- Early consultation with an ophthalmologist is recommended in patients with suspected ocular involvement.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Rosacea (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Background:
Rosacea is a chronic dermatosis that is usually confined to the face. A pulsed dye laser (PDL) system has been proven to be effective in treating rosacea-associated erythema and telangiectasias. Niacin is a cutaneous vasodilator that can increase the chromophore through increased blood flow.

Objectives:
We hypothesized that increased blood flow by pretreatment with topical niacin could enhance the effect of PDL in the treatment of rosacea.

Methods:
Eighteen Korean patients with rosacea were recruited. Three sessions of 585-nm PDL using a subpurpuragenic dose with and without pretreatment with niacin cream were performed on randomly assigned half-faces at 3-week intervals. Erythema was assessed objectively by a polarization colour imaging system, and evaluations were also made by three blinded dermatologists. Patient satisfaction was evaluated using a 10-point visual analogue scale.

Results:
Fifteen patients completed this study. All patients showed an improvement in erythema after three sessions of PDL treatment both with and without niacin pretreatment ($P = 0.023$ and $P = 0.009$, respectively). There was no significant difference in the improvement of objective erythema between the two sides. However, based on physician assessment the overall clinical improvement on the niacin side was significantly higher ($P = 0.005$), and patient satisfaction was also higher on the niacin-pretreated side ($P = 0.007$). There were no remarkable side-effects, with the exception of transient erythema and edema.

Conclusions:
Pretreatment with topical niacin safely enhanced the effect of 585-nm PDL treatment of rosacea-associated erythema in Koreans. Application of niacin can be helpful in overcoming the relatively lower effect of subpurpuragenic PDL in dark-skinned Asians. Ⓐ

Evidence-Based Reference

Kim TG et al.: Enhancing effect of pretreatment with topical niacin in the treatment of rosacea-associated erythema by 585-nm pulsed dye laser in Koreans: a randomized, prospective, split-face trial, *Br J Dermatol* 164:573–579, 2011. Ⓐ

SUGGESTED READINGS

Goldgar C et al.: Treatment options for acne rosacea, *Am Fam Physician* 80(5):461–468, 2009.

Powell FC, Rosacea: *N Engl J Med* 352:793, 2005.

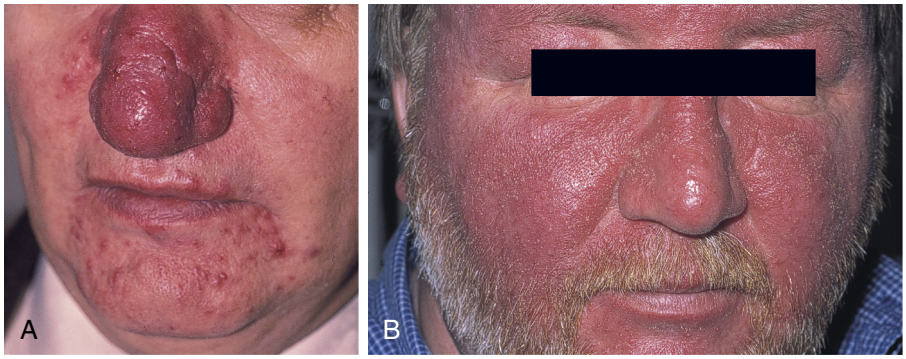


FIGURE ER1-35 Severe rosacea. A, Note the scattered papules on the face and the confluent involvement of the nose. Alcohol ingestion is not related to this appearance. **B,** Note the severe inflammation with confluent redness and significant edema. (From White G.M.; Cox N.H.; [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

BASIC INFORMATION

DEFINITION

Roseola is a benign viral illness found in infants and characterized by high fevers that last 3 or 4 days, followed by defervescence and development of a macular or maculopapular rash.

SYNONYMS

Exanthem subitum.
Sixth disease.
Roseola infantum.
Pseudorubella.
Human herpesvirus 6 (HHV-6), human herpesvirus 7 (HHV-7).

ICD-9CM CODES
057.8 Roseola
ICD-10CM CODES
B08.2 Exanthema subitum (sixth disease)

EPIDEMIOLOGY & DEMOGRAPHICS

- Nearly one third of all infants develop roseola before the age of 2 yr.
- Peak prevalence is between 7 and 13 mo.
- More than 90% of children older than 2 yr of age are seropositive for the virus causing roseola.
- Roseola is spread from person to person. It is not known how it is spread, but it must be very efficiently spread and presumably via the respiratory tract.
- There is no predilection for gender or time of year.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Typically the child develops a high fever, usually up to 104° F (40° C), that lasts for 3 to 5 days.
- Fever may be associated with a runny nose, irritability, and fatigue.
- A rash appears within 48 hr of defervescence; it begins on the neck or trunk and then spreads to the extremities, and persists for a few hours to 2 days.
- Faint pink maculopapular rash that blanches when palpated (Fig. ER1-36) and generally nonpruritic.
- Other common findings: cervical and/or occipital adenopathy, erythematous tympanic membranes, anorexia.
- Nagayama spots: red papules on the soft palate or base of the uvula.
- Seizures.
- Less common: febrile seizures (≤6% of cases), cough, diarrhea, aseptic meningitis.

ETIOLOGY

- Roseola is usually caused by human herpesvirus-6 (HHV-6) in the great majority of cases but other causes include human herpesvirus-7, enteroviruses, adenoviruses, and parainfluenza virus type 1. A small percentage of children may have primary infection with HHV-7.
- The incubation period is between 5 and 15 days.

DIAGNOSIS

The diagnosis of roseola is usually made by the clinical presentation as stated previously. It can be confirmed serologically by indirect immunofluorescence assays, ELISA, neutralization assays, and immunoblot. Viral culture is the gold standard to document active viral replication but is expensive, time consuming, and available only in research laboratories.

DIFFERENTIAL DIAGNOSIS

- Rubeola (measles).
- Rubella.
- Fifth disease (erythema infectiosum) caused by parvovirus B19.
- Enteroviral infections.
- Drug eruption.
- Mononucleosis.
- All causes of fever (e.g., otitis media, pneumonia, and urinary tract infection).
- Meningitis.

WORKUP

- If unsure of the diagnosis of roseola in a febrile infant, a fever workup is done to rule out other infectious causes.
- The decision to proceed with a fever workup is a clinical judgment call.

LABORATORY TESTS

- CBC with differential usually shows relative neutropenia and mild atypical lymphocytosis.
- Erythrocyte sedimentation rate (ESR), blood cultures as indicated.
- Urinalysis and urine cultures.
- Stool cultures if diarrhea is present.
- Lumbar puncture if needed to rule out meningitis in patients with mental status changes.
- Commercial assays can be used to detect HHV-6-specific IgG antibody responses but IgM assays are not always reliable for acute infection.

IMAGING STUDIES

Chest x-ray to rule out pneumonia.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive care.
- Maintain hydration by drinking clear fluids: water, fruit juice, lemonade, and so forth.
- Sponge bathe with lukewarm water if febrile.

ACUTE GENERAL Rx

- Acetaminophen 10 to 15 mg/kg per dose at 4-hr intervals for fever.
- Ibuprofen 5 to 10 mg/kg per dose at 6-hr intervals (maximal dose 600 mg).

CHRONIC Rx

Roseola is a viral disease that is short lasting; chronic treatment is usually not an issue.

DISPOSITION

- Roseola is generally a benign, self-limited disease that usually lasts approximately 1 wk.
- Complications, although rare, can occur and include:
  1. Febrile seizures.
  2. Meningitis.
  3. Encephalitis.
  4. Pneumonitis.
  5. Hepatitis.

REFERRAL

Subspecialty consultation is made with the appropriate discipline if any of the previously mentioned complications occur (e.g., neurology for seizures).

PEARLS & CONSIDERATIONS

COMMENTS

- A child with fever and rash should be excluded from day care.
- HHV-6 is named accordingly because it is the sixth herpesvirus discovered after herpes simplex 1 (HSV-1), HSV-2, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and varicella-zoster virus (VZV).
- Roseola is called sixth disease because it represents the sixth childhood "exanthem"; the other five are measles, scarlet fever, rubella, Dukes disease, and erythema infectiosum.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Roseola (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Caserta MT et al.: Human herpesvirus 6, *Clin Infect Dis* 33(6):829, 2001.
Ward KN: The natural history and laboratory diagnosis of human herpesviruses-6 and -7 infections in the immunocompetent, *J Clin Virol* 32(3):183, 2005.
Zerr DM et al.: A population-based study of primary human herpesvirus 6 infection, *N Engl J Med* 352(8):768, 2005.

FIGURE ER1-36 Roseola infantum. Erythematous, blanching macules, and papules **(A)** in an infant who had high fever for 3 days preceding development of the rash. On closer inspection **(B),** some lesions reveal a subtle peripheral halo of vasoconstriction. (From Paller A.S.; Mancinin A.J.; [eds]: *Hurwitz clinical pediatric dermatology,* ed 3, Philadelphia, 2006, Saunders.)

BASIC INFORMATION

DEFINITION

- Rotator cuff disease is a spectrum of afflictions involving the four rotator cuff muscles of the shoulder: supraspinatus, infraspinatus, teres minor, and subscapularis.
- It consists of subacromial bursitis, rotator cuff tendinopathy, and partial- or full-thickness muscle or tendon tear.

SYNONYMS

Rotator cuff syndrome
Shoulder impingement syndrome
Painful arc syndrome
Supraspinatus syndrome

ICD-9CM CODES	
726.10	Rotator cuff syndrome
727.61	Rotator cuff rupture
ICD-10CM CODES	
M75.1	Rotator cuff syndrome
M75.100	Unspecified rotator cuff tear or rupture of unspecified shoulder, not specified as traumatic

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: 5% to 10% of the population. Shoulder pain is the third most frequent musculoskeletal reason to present to primary care and accounts for up to 10% of all referrals to physical therapists.
PREDOMINANT SEX: Males more than females.
PREDOMINANT AGE: >40 yr.
RISK FACTORS: Repetitive overhead activity, advanced age, obesity, smoking, trauma, sporting activities.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Lateral shoulder pain with overhead activity.
- Pain at night when lying on the shoulder.
- Muscle weakness indicates a tear.
- Atrophy and sunken appearance of the scapular muscles with longstanding disease.
- Tenderness over the affected muscle or under the acromion (Fig. R1-37).
- Useful clinical tests:
- ***Hawkins-Kennedy sign:*** shoulder and elbow are flexed at 90 degrees; shoulder pain is elicited with passive internal rotation (Fig. R1-38, *A*).
- ***Painful arc sign:*** pain with active abduction of the shoulder between 70% to 120%.
- ***Drop arc sign:*** failure to smoothly control shoulder adduction.
- Painful resisted external rotation and forced passive full-forward flexion (Fig. R1-38, *B, C*).
- The combination of Hawkins-Kennedy sign, the painful arc sign, and weakness in external rotation yields the best probability (95%) for any degree of impingement.
- The combination of drop arm sign, painful arc sign, and weakness in external rotation accurately predicts full-thickness tears (91%).
- A recent study revealed that a positive painful arc test result and a positive external rotation resistance test result are the most accurate findings for detecting rotator cuff disease, whereas the presence of a positive lag test (external or internal rotation) result is most accurate for diagnosis of a full-thickness rotator cuff tear.
- A subacromial lidocaine injection can be used to distinguish weakness from rotator cuff tendinopathy and true tears—normal strength after injection indicates tendinopathy.

ETIOLOGY

A combination of tendon overload, microvascular compromise, and compression by surrounding structures.

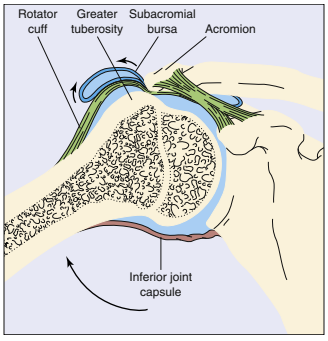


FIGURE R1-37 Impingement of the rotator cuff and subacromial bursa. Mechanism of impingement of the rotator cuff and subacromial bursa between the humeral head and overlying coracoacromial arch. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bicipital tendinitis, labrum tears, adhesive capsulitis, glenohumeral osteoarthritis, acromioclavicular injury, subscapular bursitis, avascular necrosis. Table R1-12 describes the differential diagnosis of shoulder pain.
- Neurologic and visceral etiologies need to be ruled out.

IMAGING STUDIES

- Plain radiography: not routinely needed; can reveal tendon calcifications and migration of humeral head, indicating a large tear.
- Ultrasonography: accurate tool for initial evaluation, but has limitations; partial tears are difficult to identify; highly operator-dependent.
- MRI is the test of choice for shoulder soft tissue lesions.

TREATMENT

ACUTE GENERAL Rx

- Ice and rest without overhead activity.
- Physical therapy.
- NSAIDs for 7 to 10 days, then as needed.
- Subacromial glucocorticoid injections can be used in patients with severe pain and without suspected tears.
- Surgery is reserved for healthy patients with acute full-thickness tears or with chronic partial tears who fail conservative management.

DISPOSITION

Return to work or sport should be gradual and is based upon the ability to exhibit full ROM and appropriate strength without discomfort.

REFERRAL

- To physical therapy
- Orthopedic consultation should be obtained in patients with a clinically significant rotator cuff tear and in patients who fail to improve with medical management.

PEARLS & CONSIDERATIONS

COMMENTS

- Supraspinatus is the most commonly injured muscle.

FIGURE R1-38 Impingement tests. A, Forced passive internal rotation. **B,** Resisted external rotation. **C,** Forced passive full forward flexion. (From Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.)

TABLE R1-12 Differential Diagnosis of Shoulder Pain: Clinical and Radiographic Features of Common Causes of Shoulder Pain

Diagnosis	Age	Type of Onset	Location of Pain	Night Pain	Active Range of Motion	Passive Range of Motion	Impingement Signs	Radiation of Pain	Paresthesia	Weakness	Instability	Radiographic Changes	Special Features
Rotator cuff tendinitis	Any	Acute or chronic	Deltoid region	+	↓↓ Guarding	Normal	+++	–	–	Only due to pain	Look for	In chronic cases	Painful arc of abduction
Rotator cuff tears (chronic)	>40 yr	Often chronic	Deltoid region	++	↓↓↓	Normal (may ↓ later)	++	–	–	++	–	+	Wasting of cuff muscles
Bicipital tendinitis	Any	Overuse	Anterior	–	↓ Guarding	Normal	+	Occasionally into biceps	–	Only due to pain	Look for	None	Special examination tests
Calcific tendinitis	30-60 yr	Acute	Point of shoulder	++	↓↓↓ Guarding	Normal except for pain	+++	–	–	Only due to pain	–	++	Tenderness ++
Capsulitis (“frozen shoulder”)	>40 yr	Insidious	Deep in shoulder	++	↓↓	↓↓	+	–	–	–	–	–	Global range of motion ↓
Acromioclavicular joint	Any	Acute or chronic	Over joint	Lying on side	Ø Full elevation	Normal	–	–	–	–	–	In chronic cases	Local tenderness
Osteoarthrosis of glenohumeral joint	>40 yr	Insidious	Deep in shoulder	++	↓↓	↓↓	–	–	–	May be mild	–	+++	Crepitus
Glenohumeral instability	Usually <25 yr	Episodic	Anterior or posterior	–	Only apprehension	Only apprehension	Possible	–	+ With acute episodes	+ With acute episodes	+++	Often	Stress tests
Cervical spondylosis	>40 yr	Insidious	Suprascapular	Often	Normal	Normal	–	++	+++	+	–	In cervical spine	Pain with neck movement
Thoracic outlet syndrome	Any	Usually with activity	Neck, shoulder, arm	–	Normal	Normal	–	++	++	++	–	–	Special examination tests

From Hochberg MC et al: *Rheumatology,* ed 5, Philadelphia, 2011, Mosby.

- Rotator cuff tears can be asymptomatic.
- Identification of partial tears remains a clinical challenge and imaging is often needed.
- It is important to differentiate tears from tendinopathy because they require different management.
- Most patients respond to conservative management.
- Untreated, longstanding rotator cuff tendinopathy can cause significant loss in range of motion and adhesive capsulitis.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Rotator Cuff Pain (Patient Information)
Rotator Cuff Tear (Patient Information)
Rotator Cuff Tendinitis (Patient Information)
Rotator Cuff Tendinosis (Patient Information)
Bursitis (Related Key Topic)

AUTHOR: **DAN A. CRISTESCU, M.D.**

EVIDENCE

Abstract[1]

Objectives:
Treatment for degenerative rotator cuff disease of the shoulder includes physiotherapy. Dynamic humeral centering (DHC) aims at preventing subacromial impingement, which contributes to the disease. The goal of this study was to assess the effectiveness of DHC.

Method:
A group of 69 patients with shoulder pain and impingement syndrome were prospectively included in a single-center randomized trial with a 12-month follow-up. Patients and assessor were blinded to the study hypothesis and treatment, respectively. DHC and nonspecific mobilization as control were performed for 6 weeks, in 15 supervised individual outpatient sessions, and patients performed daily home exercises. The planned primary outcome was the Constant score including subscores for pain, activity, mobility and strength at 3 months. Secondary outcomes were the Constant score and subscores at 12 months, and medication use for pain at 3 and 12 months.

Results:
The DHC group did not differ from the control group in the total Constant score at 3 months. However, the DHC group showed a higher Constant subscore for pain (12.2 [SD 2.8] versus 9.9 [2.9], least square means difference 2.1, 95% CI 0.7 to 3.5, p = 0.004). At 3 months, the DHC group also showed a higher rate of no medication use (96.7% versus 71%, proportional difference 25.7, 95% CI 3.7 to 51.9, p = 0.012). There was no other intergroup difference.

Conclusions:
There was no difference in the total Constant score between DHC and controls. However, pain was improved at 3 months after DHC. The differences found in subscores for pain should be explored in future studies. Trial registration clinicaltrials.gov Identifier: NCT 01022775. Ⓐ

Abstract[2]

Purpose:
The purpose of this meta-analysis was to critically assess whether there are differences in clinical outcomes between single-row and double-row rotator cuff repair in prospective randomized Level I studies.

Methods:
Using Medline, Scopus, Scirus, CINAHL (Cumulative Index to Nursing and Allied Health Literature), and the Cochrane Library, as well as a hand search, we searched for randomized prospective trials comparing single-row and double-row rotator cuff repair. The functional outcome scores included the American Shoulder and Elbow Surgeons shoulder scale, the Constant shoulder score, and the University of California, Los Angeles shoulder rating scale. A test of heterogeneity was performed to determine whether there was a difference across the included studies.

Results:
Five studies met our inclusion criteria. A test of heterogeneity showed no difference across these studies. The functional American Shoulder and Elbow Surgeons; Constant; and University of California, Los Angeles outcomes scores showed no difference between single- and double-row rotator cuff repair.

Conclusions:
We found no significant differences in clinical outcomes between single-row and double-row rotator cuff repair in a meta-analysis of Level I studies.

Level of Evidence:
Level I, meta-analysis of Level I randomized controlled studies. Ⓐ

Abstract[3]

Purpose
The purpose of this study was to compare clinical outcomes in the first postoperative year of patients with full-thickness small to medium-sized tears undergoing all-arthroscopic (AA) versus mini-open (MO) rotator cuff repair.

Methods:
One hundred patients were randomized to either AA or MO rotator cuff repair at the time of surgery on an intention-to-treat basis. Patients were evaluated before and 6, 12, 26, and 52 weeks after surgery using the Disabilities of the Arm, Shoulder, and Hand (DASH) score as a primary outcome score and the Constant Murley score, visual analog scale (VAS) pain/impairment score, and measurement of active forward flexion/external rotation as secondary outcome measures. Ultrasound evaluation was used to assess structural integrity of the repair 1 year postoperatively.

Results:
Forty-seven patients were analyzed in the AA group and 48 in the MO group. Five patients were lost to follow-up. Mean age was 57.2 (SD 8.0) years in the AA group and 57.8 (SD 7.9) years in the MO group. Primary and secondary outcome measures significantly improved in both groups postoperatively. Overall mean primary and secondary postoperative outcome scores did not statistically significantly differ between the treatment groups (DASH between-group mean difference: -3.4; 95% confidence interval [CI], -10.2 to 3.4; P = 0.317). However, at the 6-week follow-up, DASH score, VAS pain and impairment, and active forward flexion were significantly more improved in the AA group than in the MO group. A retear was seen in 8 patients (17%) in the AA group and 6 patients (13%) in the MO group. Five patients in the AA group (11%) and 6 patients (13%) in the MO group developed adhesive capsulitis.

Conclusions:
Functional outcome, pain, range of motion, and complications do not significantly differ between patients treated with all-arthroscopic repair and those treated with mini-open repair in the first year after surgery. Patients do attain the benefits of treatment somewhat sooner (6 weeks) with the arthroscopic procedure.

Level of Evidence:
Level II, randomized controlled trial without postoperative blinding. Ⓐ

Evidence-Based References

Beaudreuil J et al.: Assessment of dynamic humeral centering in shoulder pain with impingement syndrome: a randomised clinical trial, *Ann Rheum Dis* 70:1613–1618, 2011. Ⓐ

Sheibani-Rad S et al.: Arthroscopic single-row versus double-row rotator cuff repair: a metaanalysis of the randomized clinical trials, *Arthroscopy* 29: 343–348, 2013. Ⓐ

Van der Zwaal P et al.: Clinical outcome in all-arthroscopic versus mini-open rotator cuff repair in small to medium-sized tears: a randomized controlled trial in 100 patients with 1-year follow-up, *Arthroscopy* 29:266–273, 2013. Ⓐ

SUGGESTED READINGS

Cools AM et al.: Screening the athlete's shoulder for impingement symptoms: a clinical reasoning algorithm for early detection of shoulder pathology, *Br J Sports Med* 42:628, 2008.

Hermans J et al.: Does this patient with shoulder pain have rotator cuff disease? The rational clinical examination systematic review, *JAMA* 310(8):837–847, 2013.

Kim HM et al.: Shoulder strength in asymptomatic individuals with intact compared with torn rotator cuffs, *J Bone Joint Surg Am* 91:289, 2009.

Koester MC et al.: The efficacy of subacromial corticosteroid injection in the treatment of rotator cuff disease: a systematic review, *J Am Acad Orthop Surg* 15:3, 2007.

Maman E et al.: Outcome of nonoperative treatment of symptomatic rotator cuff tears monitored by magnetic resonance imaging, *J Bone Joint Surg* 91:2009, 1898.

Matsen FA: Rotator cuff failure, *N Engl J Med* 358:2138, 2008.

Park HB et al.: Diagnostic accuracy of clinical tests for the different degrees of subacromial impingement syndrome, *J Bone Joint Surg Am* 87:1446, 2005.

Seida JC et al.: Systematic review: nonoperative and operative treatments for rotator cuff tears, *Ann Intern Med* 153:246–255, 2010.

Silverstein BA et al.: Natural course of nontraumatic rotator cuff tendinitis and shoulder symptoms in a working population, *Scand J Work Environ Health* 32:99, 2006.

Whittle S, Buchbinder R: In the clinic. Rotator cuff disease, *Ann Intern Med* 162:ITC1-15, 2015.

Wolff AB et al.: Partial-thickness rotator cuff tears, *J Am Acad Orthop Surg* 14:715, 2006.

BASIC INFORMATION

DEFINITION

Rubella is a mild illness caused by the rubella virus that can cause severe congenital problems by in vitro transmission to a fetus when a pregnant woman becomes infected.

SYNONYMS

German measles

ICD-9CM CODES
056.9 Rubella
771.0 (Congenital)
V04.3 (Vaccination)
ICD-10CM CODES
B06.9 Rubella without complication
B06 Rubella
B06.8 Rubella with other complications
P35.0 Congenital rubella syndrome
Z23 Encounter for immunization

EPIDEMIOLOGY & DEMOGRAPHICS

- Before vaccination (i.e., before 1969):
  - 28 reported cases per 100,000 person-years, eight of which were in persons >15 yr
  - Four cases of congenital rubella syndrome per 100,000 live births
- After mass vaccination (i.e., after 1980) most cases have occurred in unimmunized people, with <1 case per 100,000 person-years (acquired and congenital) (Fig. ER1-39).
- Currently, 10% to 20% of childbearing-age women are susceptible.
- The highest risk of developing long-term complications of congenital infection exists during the first trimester of gestation; both risk of congenital infection and long-term complications drop during the second trimester, and although the risk of congenital infection increases during the third trimester, there is no risk of long-term complication at that point.

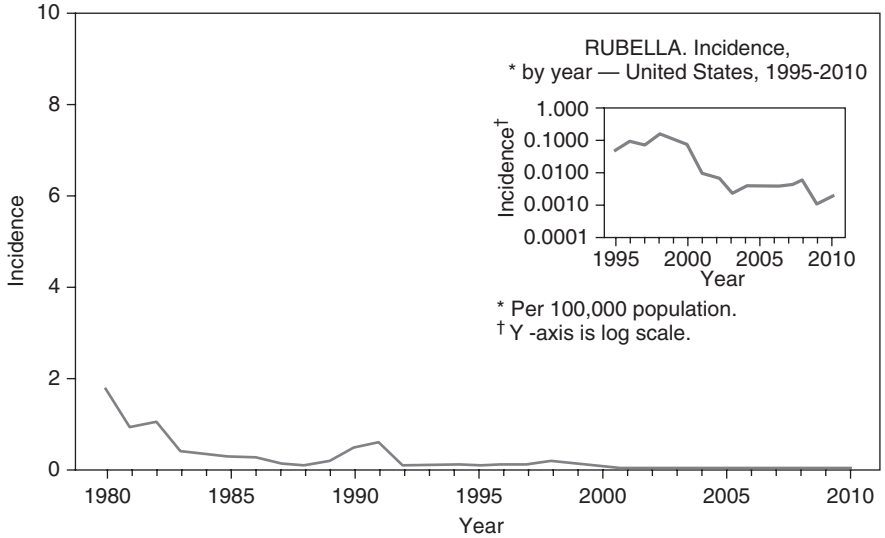


FIGURE ER1-39 Rubella. Incidence, by year—United States, 1980-2010. (From Centers for Disease Control and Prevention: Summary of notifiable diseases—United States, 2010, *MMWR Morb Mortal Wkly Rep* 59:1-111, 2012.)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

1. Acquired infection:
   - Incubation: 14 to 21 days.
   - Prodrome: 1 to 5 days; low-grade fever, headache, malaise, anorexia, mild conjunctivitis, coryza, pharyngitis, cough, and cervical, suboccipital, and postauricular lymphadenopathy.
   - Rash: 1 to 5 days.
2. Enanthema: palatal macules.
3. Exanthema (rash): blotchy eruption beginning on face and neck (Fig. ER1-40) and then spreading to trunk and limbs.
   - Occasional splenomegaly and hepatitis (during rash).
   - Complications: arthritis (15%, mostly in adult women), thrombocytopenia, myocarditis, optic neuritis, encephalitis (all < 0.1%).

FIGURE ER1-40 Rash of rubella. (From Kliegman R.M.; et al. *Nelson textbook of pediatrics.* ed 19, Philadelphia, Saunders, 2011.)

4. Congenital infection (see Table ER1-13):
   - Deafness: 85%.
   - Intrauterine growth retardation: 70%.
   - Cataracts: 35%.
   - Retinopathy: 35%.
   - Patent ductus arteriosus: 30%.
   - Pulmonary artery hypoplasia: 25%.
   - In utero death: 20%.
   - Mental retardation: 10% to 20%.
   - Meningoencephalitis: 10% to 20%.
   - Behavior disorder: 10% to 20%.
   - Hepatosplenomegaly: 10% to 20%.
   - Bone radiolucencies: 10% to 20%.
   - Diabetes mellitus (type 1): 10% to 20% by age 35 yr.
   - Other congenital heart defects: 2% to 5%.

ETIOLOGY & PATHOGENESIS

1. Acquired infection:
   - Viral portal of entry is upper respiratory tract.
   - Viral replication occurs in lymph nodes, then hematogenous dissemination occurs to many organs, including placenta if present.
   - Immune complexes may be cause of rash and arthritis.

TABLE ER1-13 Pathologic Findings in Congenital Rubella Syndrome

System	Pathologic
Cardiovascular	Patent ductus arteriosus Pulmonary artery stenosis Ventriculoseptal defect Myocarditis
Central nervous system	Chronic meningitis Parenchymal necrosis Vasculitis with calcification
Eye	Microphthalmia Cataract Iridocyclitis Ciliary body necrosis Glaucoma Retinopathy
Ear	Cochlear hemorrhage Endothelial necrosis
Lung	Chronic mononuclear interstitial pneumonitis
Liver	Hepatic giant cell transformation Fibrosis Lobular disarray Bile stasis
Kidney	Interstitial nephritis
Adrenal gland	Cortical cytomegaly
Bone	Malformed osteoid Poor mineralization of osteoid Thinning cartilage
Spleen, lymph node	Extramedullary hematopoiesis
Thymus	Histiocytic reaction Absence of germinal centers
Skin	Erythropoiesis in dermis

From Kliegman R.M.; et al. *Nelson textbook of pediatrics,* ed 19, Philadelphia, Saunders, 2011.

2. Congenital infection:
   - Fetus is infected by the placenta during maternal-acquired infection.
   - Cellular damage in the fetus results from cytolysis of fetal cells, mostly by fetal vasculitis or from immune-mediated inflammation and damage.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

1. Acquired rubella syndrome:
   - Other viral infections by enteroviruses, adenoviruses, human parvovirus B-19, measles.
   - Scarlet fever.
   - Allergic reaction.
   - Kawasaki disease.
2. Congenital rubella syndrome:
   - Congenital syphilis, toxoplasmosis, herpes simplex, cytomegalovirus, and enterovirus can cause a similar set of problems.

WORKUP

1. Acquired infection:
   - Serologic test (hemagglutination inhibition, neutralization tests, complement fixation tests, passive agglutination, enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA]).
   - Immunoglobulin (Ig) M antibodies (by EIA) are detected early: second to fourth week.
   - IgG antibodies (by ELISA) can be measured as acute phase (7 days after rash onset) and convalescent phase (14 days later).
2. Congenital infection:
   - Viral culture (from nasopharynx).
   - Serologic studies: IgM antirubella virus detection by EIA is the method of choice (after the newborn is age 5 mo).

IMMUNIZATION

- Four existing vaccines provide persisting immunity in 92% of vaccines. Indications:
  1. All children ≥12 mo (as part of the measles-mumps-rubella [MMR] vaccine).
  2. Postpubertal women.
- Vaccinate if not known to be immunized (advise not to become pregnant within 3 mo of vaccination).
- Premarital serologic screening for rubella immunity.
- Prenatal or antepartum serologic screening for rubella.
- Vaccinate susceptible women postpartum.
- Serologic screening for female workers likely to be exposed to rubella (e.g., teachers, child care employees, health care workers).

Contraindications:
- Pregnancy.
- Recent receipt of immune globulin or blood transfusion (2 wk before to 3 mo after).
- Immunodeficiency (except AIDS).

Adverse reactions:
- Fever, rash, or lymphadenopathy: 5% to 15%.
- Arthralgias: 0.5% in children; 25% in adult women.
- Transient peripheral neuropathy (rare).

Rx TREATMENT

- No known effective antiviral therapy.
- Management of specific congenital problems as appropriate.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Rubella (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Madsen KM et al.: A population-based study of measles, mumps, and rubella vaccination and autism, *N Engl J Med* 347(19):1477, 2002.

U.S. Department of Health: Control and prevention of rubella: evaluation and management of suspected outbreaks, rubella in pregnant women, and surveillance for congenital rubella syndrome, *MMWR* 50(RR-12):1, 2001.

BASIC INFORMATION

DEFINITION

Salivary gland neoplasms are benign or malignant tumors of a salivary gland (parotid, submandibular, or sublingual).

SYNONYMS

These tumors are often named according to their histologic type (see "Diagnosis").

ICD-9CM CODES
142.9 Salivary gland neoplasm
142.0 (Parotid)
142.1 (Submandibular)
142.2 (Sublingual)

ICD-10CM CODES
C08.9 Malignant neoplasm of major salivary gland, unspecified
C07 Malignant neoplasm of parotid gland
C08.0 Malignant neoplasm of submandibular gland
C08.1 Malignant neoplasm of sublingual gland

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: One to two cases per 100,000 person-years (1% of all head and neck tumors).
DISTRIBUTION:
- Parotid gland, 85% (80% are benign).
- Submandibular gland, 10% (55% are benign).
- Sublingual and minor glands, 5% (35% are benign).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Parotid gland:
  1. Painless swelling overlying the masseter muscle (under the temporomandibular joint).
  2. Pain.
  3. Facial nerve palsy.
  4. Cervical lymph nodes.
  5. Mass in oral cavity.
- Submandibular gland: swelling under anterior portion of the mandible.
- Sublingual gland: intraoral swelling under the tongue, medial to the mandible.

DIAGNOSIS

PATHOLOGY

HISTORY

Benign Tumors
- Mixed tumor (usually parotid).
- Adenolymphoma (Warthin's tumor).
- Pleomorphic adenoma.
- Capillary hemangioma, lymphangioma (in children).
- Intraductal papilloma.
- Other (e.g., myoepithelioma, canalicular adenoma, basal cell adenoma).

MALIGNANT TUMORS

- Mucoepidermoid carcinoma (most common malignant tumor of the parotid gland).
- Adenoid cystic carcinoma.
- Adenocarcinoma.
- Malignant mixed tumor.
- Squamous cell carcinoma.
- Other.

STAGE (TNM):

T_0	No evidence of primary tumor
T_1	Tumor <2 cm
T_2	Tumor 2 to 4 cm
T_3	Tumor 4 to 6 cm
T_4	Tumor >6 cm

All subdivided into
- Without local extension.
- With local extension.

N_0	No lymph node metastasis
N_1	Single ipsilateral node <3 cm
N_2	Ipsilateral, contralateral, or bilateral node <6 cm
N_3	Any node >6 cm
M_0	No distant metastasis
M_1	Distant metastasis

Stage I	T_{1a} or $_{2a}N_0M_0$
Stage II	$T_{1b,2b,3a}$ N_0M_0
Stage III	$T_{3b,4a}$ N_0M_0 or any T except $_{4b}N_1M_0$
Stage IV	T_{4b} any N any M or any T $N_{2,3}M_0$ or any T, any N_1M_1

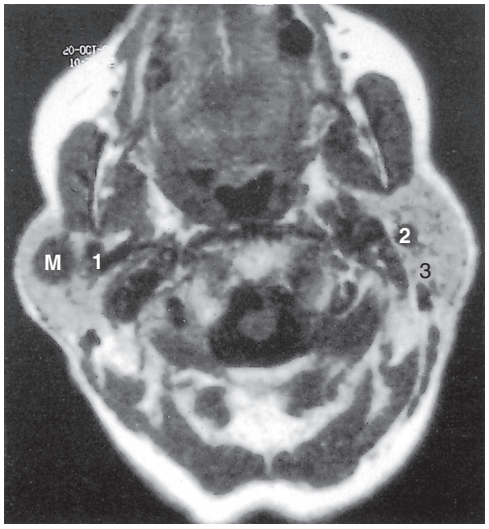


FIGURE S1-1 Pleomorphic Adenoma of Parotid Gland. Pleomorphic adenoma in the right parotid (M) is a well-defined, low-signal intensity mass on the axial T_1-weighted MRI. Note displacement of the retromandibular vein (1) medially by the mass compared with the normal left retromandibular vein (2). The left facial nerve (3) branching through the normal left parotid is seen. (From Skarin AT: *Atlas of diagnostic oncology,* 4 ed, St Louis, 2010, Mosby.)

WORKUP

- Fine-needle aspiration. The sensitivity, specificity, and accuracy of parotid gland aspirates are approximately 92%, 100%, and 98%, respectively.
- Imaging by CT scan or MRI (Fig. S1-1).
- Open biopsy (rarely indicated).

TREATMENT

Malignant tumors:
- Surgery is the mainstay of treatment; gland resection and neck dissection if lymph nodes are involved.
- A lateral lobectomy with preservation of facial nerve should be considered for tumors confined to the superficial lobe of the parotid gland. Gross tumor should not be left in situ, but if the facial nerve is able to be preserved by "peeling" tumor off the nerve, it should be attempted, followed by radiation therapy for microscopic disease.
- Postoperative radiation is indicated for high-grade malignancies demonstrating extraglandular disease, perineural invasion, direct invasion of surrounding tissues, or regional metastases.
- Chemotherapy.
  Benign tumors: surgery for tumor resection.

PROGNOSIS OF MALIGNANT TUMORS

Five-year survival rates:
- Mucoepidermoid carcinoma: 75% to 95%.
- Adenoid cystic carcinoma: 40% to 80%.
- Adenocarcinoma: 20% to 75%.
- Malignant mixed tumor: 35% to 75%.
- Squamous cell carcinoma: 25% to 60%.

PEARLS & CONSIDERATIONS

COMMENTS

Salivary gland neoplasms most often present as slow-growing, well-circumscribed masses. Pain, rapid growth, nerve weakness, fixation to skin or underlying muscle, and paresthesias usually are indicative of malignancy.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READING

Available at www.expertconsult.com

RELATED CONTENT

Salivary Gland Tumors (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READING

Stewart CJ et al.: Fine needle aspiration cytology of salivary gland: a review of 341 cases, *Diagn Cytopathol* 22:139, 2000.

BASIC INFORMATION

DEFINITION

Salmonellosis is an infection caused by one of several serotypes of a gram-negative bacillus of the genus *Salmonella.* Current *Salmonella* nomenclature is described in Table S1-1.

SYNONYMS

Typhoid fever
Paratyphoid fever
Enteric fever

ICD-9CM CODES
003.0 Salmonellosis
ICD-10CM CODES
A02.0 *Salmonella* enteritis
A02.1 *Salmonella* sepsis
A02.2 Localized *Salmonella* infections
A02.8 Other specified *Salmonella* infections
A0.9 *Salmonella* infection, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.)

- Epidemiologically, the clinical syndromes are divided into those that cause a typhoidal type of infection (systemic illness with fever and abdominal pain) such as *Salmonella typhi* and those that do not: nontyphoidal *Salmonella* infections (gastroenteritis) such as *S. enteritidis, S. newport,* and *S. typhimurium.*
- Estimated 1 million cases/yr of nontyphoidal salmonellosis in the United States.
- Approximately 500 cases of *Salmonella typhi* infection reported each yr. In 2009 contaminated peanut butter and peanut products caused a nationwide *Salmonella typhimurium* outbreak in 46 states, affecting more than 700 individuals.
- Largest outbreak: 200,000 people who ingested contaminated milk.

PEAK INCIDENCE: Summer and fall.

PREDOMINANT AGE

- <20 yr old.
- >70 yr old.
- Highest rates of infection in infants, especially neonates.

GENETICS

Neonatal infection.

- Highly susceptible to infection with nontyphoidal *Salmonella*.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Infections
  1. Localized to GI tract (gastroenteritis).
  2. Systemic (typhoid fever).
  3. Localized outside of GI tract.
- Gastroenteritis
  1. Incubation period: 12 to 48 hr.
  2. Nausea, vomiting.
  3. Diarrhea, abdominal cramps.
  4. Fever.
  5. Bacteremia: occurs mostly in the immunocompromised host or those with underlying conditions, including HIV infection.
  6. Self-limited illness lasting 3 or 4 days.
  7. Colonization of GI tract persistent for months, especially in those treated with antibiotics.
- Typhoid fever.
  1. Incubation period of few days to several wk.
  2. Prolonged fever, often with a stepwise-increasing temperature pattern.
  3. Myalgias.
  4. Headache, cough, sore throat.
  5. Malaise, anorexia.
  6. Abdominal pain.
  7. Hepatosplenomegaly.
  8. Diarrhea or constipation early in the course of illness.
  9. Rose spots (faint, maculopapular, blanching lesions) sometimes seen on chest or abdomen.
- Untreated disease
  1. Fever lasting 1 to 2 mo.
  2. Main complication: GI bleeding caused by perforation from ulceration of Peyer's patches in the ileum.
  3. Rare complications:
     a. Mental status changes.
     b. Shock.
  4. Relapse rate of approximately 10%.
- Infections outside GI tract
  1. Can occur in virtually any location.
  2. Usually occur in patients with underlying diseases.
  3. Endocarditis, endovascular infections are caused by seeding of atherosclerotic plaques or aneurysms.
  4. Hepatic or splenic abscesses in patients with underlying disease in these organs.
  5. Urinary tract infections in patients with renal TB or schistosomiasis.
  6. *Salmonellae* are a frequent cause of gram-negative meningitis in neonates.
  7. Osteomyelitis in children with hemoglobinopathies (particularly sickle cell disease).

ETIOLOGY

- More than 2000 serotypes of *Salmonella* exist, but only a few cause disease in humans. Host factors and conditions predisposing to the development of systemic disease with nontyphoidal *Salmonella* strains are described in Table S1-2.
- Raw produce is an increasingly recognized vehicle for salmonellosis. In 2008 there was a large outbreak of *Salmonella* Saintpaul involving 1500 persons, of whom 21% were hospitalized and 2 died. It was due to contaminated jalapeno and serrano peppers. More recently outbreaks of human *Salmonella* infections have been increasingly associated with contact with live poultry.
- Some found only in humans are the cause of enteric fever.
  1. *S. typhi.*
  2. *S. paratyphi.*
- Some responsible for gastroenteritis and frequently isolated from raw meat and poultry and uncooked or undercooked eggs.
  1. *S. typhimurium.*
  2. S. enteritidis.
- *S. choleraesuis* is a prototype organism that causes extraintestinal nontyphoidal disease.
- Transmission generally via ingestion of contaminated food or drink.
- Outbreaks of gastroenteritis related to contaminated poultry, meat, and dairy products are common.
- Typhoid fever is a systemic illness caused by serotypes exclusive to humans.
  1. Acquisition by ingestion of food or water contaminated by other humans
  2. Most cases in the United States are:
     a. Acquired during foreign travel
     b. Acquired by ingestion of food prepared by chronic carriers, many of whom have acquired the organism outside of the United States.

TABLE S1-1 *Salmonella* Nomenclature

Traditional Usage	Formal Name	CDC Designation
S. typhi	*S. enterica** subsp. enterica ser. Typhi	*S.* ser. Typhi
S. dublin	*S. enterica* subsp. enterica ser. Dublin	*S.* ser. Dublin
S. typhimurium	*S. enterica* subsp. enterica ser. Typhimurium	*S.* ser. Typhimurium
S. choleraesuis	*S. enterica* subsp. enterica ser. Choleraesuis	*S.* ser. Choleraesuis
S. marina	*S. enterica* subsp. houtenae ser. Marina	*S.* ser. Marina

CDC, Centers for Disease Control and Prevention; *ser.,* serovar; *subsp.,* subspecies.
*Some authorities prefer *S. choleraesuis* or *S. enteritidis* rather than *S. enterica* to describe the species.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

TABLE S1-2 Host Factors and Conditions Predisposing to the Development of Systemic Disease with Nontyphoidal *Salmonella* Strains

Neonates and young infants (≤3 mo of age)
HIV/AIDS
Other immunodeficiencies and chronic granulomatous disease
Immunosuppressive and corticosteroid therapies
Malignancies, especially leukemia and lymphoma
Hemolytic anemia, including sickle cell disease, malaria, and bartonellosis
Collagen vascular disease
Inflammatory bowel disease
Achlorhydria or use of antacid medications
Impaired intestinal motility
Schistosomiasis, malaria
Malnutrition

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other causes of prolonged fever:
  1. Malaria.
  2. TB.
  3. Brucellosis.
  4. Amebic liver abscess.
- Other causes of gastroenteritis:
  1. Bacterial: *Shigella, Yersinia, Campylobacter* spp.
  2. Viral: Norwalk virus, rotavirus.
  3. Parasitic: *Entamoeba histolytica, Giardia lamblia.*
  4. Toxic: enterotoxigenic *E. coli, Clostridium difficile.*

WORKUP

- Typhoid fever
  1. Cultures of blood, stool, urine; repeat if initially negative.
  2. Blood cultures are more likely to be positive early in the course of illness.
  3. Stool and urine cultures are more commonly positive in the second and third wk of illness.
  4. Highest yield with bone marrow biopsy cultures: 90% positive.
  5. Serology using Widal's test is helpful in retrospect, showing a fourfold increase in convalescent titers.
- Gastroenteritis: stool cultures.
- Extraintestinal localized infection:
  1. Blood cultures.
  2. Cultures from the site of infection.

LABORATORY TESTS

- Neutropenia is common.
- Transaminitis is possible.
- Culture to grow organism: blood, body fluids, biopsy specimens.

IMAGING STUDIES

- Not routinely indicated.
- Radiographs of bone may be suggestive of osteomyelitis (particularly in patients with sickle cell disease and bone infarctions).
- CT scan or sonogram of abdomen:
  1. May reveal hepatic or splenic abscesses or pleural involvement.
  2. May reveal aortic aneurysm.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Adequate hydration and electrolyte replacement in people with diarrhea.

ACUTE GENERAL Rx

- Typhoid fever:
  1. Levofloxacin 750 mg PO/IV q24h or ciprofloxacin 500 mg PO bid or 400 mg IV bid for 7 to 10 days. Should not be used as first line in patients from South Asia due to resistance unless known to be susceptible.
  2. Ceftriaxone 2 g IV qd for 7 to 14 days or cefixime (20-30 mg/kg/day orally divided into q12h dosing for 7 to 14 days).
  3. Another alternative agent: azithromycin (1 g orally then 500 mg daily for 5 to 7 days)
  4. Children: see Table S1-3. In general, quinolones are avoided in children unless a multidrug-resistant strain is involved due to concerns of possible cartilage damage. Another alternative for children: azithromycin (10 to 20 mg/kg to 1 g maximum once daily for 5 to 7 days)
  5. If tests show susceptibility, can also use amoxicillin or Bactrim in adults and children.
  6. Dexamethasone 3 mg IV initially, followed by 1 mg IV q6h for eight doses for patients with shock or mental status changes.
- Gastroenteritis:
  1. Usually not indicated for gastroenteritis alone because this illness usually self-limited.
  2. Treatment may prolong the carrier state and is discouraged for healthy patients <50 yr of age who have relatively mild disease.
  3. Prophylactic treatment for patients who are at high risk of developing complications from bacteremia (see Table S1-3).
     a. Neonates.
     b. Patients with hemoglobinopathies.
     c. Patients with atherosclerosis.
     d. Patients with aneurysms.
     e. Patients with prosthetic devices.
     f. Immunocompromised patients.

CHRONIC Rx

- Carrier states are possible in those with typhoid fever.
- More common in people >60 yr of age and in people with gallstones.
- Usual site of colonization is the gallbladder.
- Treatment should be considered for those with persistently positive stool cultures and for food handlers.
- Suggested regimens for eradication of carrier state:
  1. Ciprofloxacin 500 mg PO bid for 4 wk.
  2. SMX/TMP 1 to 2 DS tabs PO bid for 6 wk (if susceptible).
  3. Amoxicillin 2 g PO q8h for 6 wk (if susceptible).
- Cholecystectomy may be required in carriers with gallstones who fail medical therapy, but this is rarely indicated for nontyphoidal salmonellosis currently.
- Prolonged course of oral therapy or lifetime suppression for patients with AIDS who have chronic infection.

DISPOSITION

- Typhoid fever
  1. Treated patients usually respond to therapy; small percentage of chronic carriers.
  2. Untreated patients may have serious complications.
- Gastroenteritis
  1. Usually self-limited.
  2. May be recurrent or persistent in AIDS patients.

REFERRAL

- If gastroenteritis is persistent or recurrent.
- If there is evidence of extraintestinal infection, typhoid fever, or chronic carriers.

TABLE S1-3 Treatment of *Salmonella* Gastroenteritis

Organism and Indication	Dose and Duration of Treatment
Salmonella infections in infants <3 mo of age or immunocompromised persons (in addition to appropriate treatment for underlying disorder)	Cefotaxime 100-200 mg/kg/day every 6 hr for 5-14 days *or* Ceftriaxone 75 mg/kg/day once daily for 7 days *or* Ampicillin 100 mg/kg/day every 6 hr for 7 days *or* Cefixime 15 mg/kg/day for 7-10 days

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

PEARLS & CONSIDERATIONS

COMMENTS

- Quinolones should not be used in children or pregnant women.
- Infections should be reported to local health departments.
- Recent outbreaks in the United States have been traced back to raw tomatoes, peanut butter, pet turtles, and frozen pot pies.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Salmonellosis (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

EVIDENCE

Abstract[1]

Background:

Raw produce is an increasingly recognized vehicle for salmonellosis. We investigated a nationwide outbreak that occurred in the United States in 2008.

Methods:

We defined a case as diarrhea in a person with laboratory-confirmed infection with the outbreak strain of *Salmonella enterica* serotype Saintpaul. Epidemiologic, traceback, and environmental studies were conducted.

Results:

Among the 1500 case subjects, 21% were hospitalized, and 2 died. In three case–control studies of cases not linked to restaurant clusters, illness was significantly associated with eating raw tomatoes (matched odds ratio, 5.6; 95% confidence interval [CI], 1.6 to 30.3); eating at a Mexican-style restaurant (matched odds ratio, 4.6; 95% CI, 2.1 to ∞) and eating Pico de Gallo salsa (matched odds ratio, 4.0; 95% CI, 1.5 to 17.8), corn tortillas (matched odds ratio, 2.3; 95% CI, 1.2 to 5.0), or salsa (matched odds ratio, 2.1; 95% CI, 1.1 to 3.9); and having a raw jalapeño pepper in the household (matched odds ratio, 2.9; 95% CI, 1.2 to 7.6). In nine analyses of clusters associated with restaurants or events, jalapeño peppers were implicated in all three clusters with implicated ingredients, and jalapeño or serrano peppers were an ingredient in an implicated item in the other three clusters. Raw tomatoes were an ingredient in an implicated item in three clusters. The outbreak strain was identified in jalapeño peppers collected in Texas and in agricultural water and serrano peppers on a Mexican farm. Tomato trace-backs did not converge on a source.

Conclusions:

Although an epidemiologic association with raw tomatoes was identified early in this investigation, subsequent epidemiologic and microbiologic evidence implicated jalapeño and serrano peppers. This outbreak highlights the importance of preventing raw-produce contamination. Ⓐ

Evidence-Based Reference

Behravesh CB et al.: Salmonella Saintpaul Outbreak Investigation Team: 2008 outbreak of Salmonella Saintpaul infections associated with raw produce, *N Engl J Med* 364:918–927, 2011. Ⓐ

SUGGESTED READINGS

Behravesh CB et al.: 2008 outbreak of Salmonella Saintpaul infections associated with raw produce, *N Engl J Med* 364:918–927, 2011.

Cavallaro E et al.: Salmonella typhimurium infections associated with peanut products, *N Engl J Med* 365:601–610, 2011.

Centers for Disease Control and Prevention: Salmonellosis associated with pet turtles—Wisconsin and Wyoming, *MMWR Morb Mortal Wkly Rep* 54(9):223, 2004. 2005.

Crump JA, Mintz ED: Global trends in typhoid and paratyphoid fever, *Clin Infect Dis* 50(2):241–246, 2010.

DuPont HL: Acute infectious diarrhea in immunocompetent adults, *N Engl J Med* 370:1532–1540, 2014.

DuPont HL: Bacterial diarrhea, *N Engl J Med* 361:1560, 2009.

Gaffga NH: Outbreak of salmonellosis linked to live poultry from a mail-order hatchery, *N Engl J Med* 366:2065–2073, 2012.

BASIC INFORMATION

DEFINITION

Sarcoidosis is a chronic multisystem granulomatous disease characterized histologically by the presence of nonspecific, noncaseating granulomas.

SYNONYMS

Boeck's sarcoid

ICD-9CM CODES
135.0 Sarcoidosis
ICD-10CM CODES
D86 Sarcoidosis
D86.0 Sarcoidosis of lung
D86.1 Sarcoidosis of lymph nodes
D86.2 Sarcoidosis of lung with sarcoidosis of lymph nodes
D86.3 Sarcoidosis of skin
D86.8 Sarcoidosis of other and combined sites
D86.9 Sarcoidosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Incidence is 11 in 100,000 in whites and 35 in 100,000 in blacks; presents most commonly in the winter and early spring.
PREDOMINANT SEX: Increased incidence in females.
PREDOMINANT AGE: 20 to 40 yr.
GENETICS: Familial clustering has been described. Having a first-degree relative with sarcoidosis increases the risk for disease fivefold.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical manifestations often vary with the stage of the disease and degree of organ involvement. Patients may be asymptomatic, but a chest radiograph may demonstrate findings consistent with sarcoidosis (see "Imaging Studies"). Nearly 50% of patients with sarcoidosis are diagnosed by incidental findings on chest radiograph. Thoracic involvement occurs in >90% of patients with sarcoidosis.
- Frequent manifestations:
  1. Pulmonary manifestations: dry, nonproductive cough; dyspnea; chest discomfort.
  2. Constitutional symptoms: fatigue, weight loss, anorexia, malaise.
  3. Visual disturbances: blurred vision, ocular discomfort, conjunctivitis, iritis, uveitis (65% of patients).
  4. Dermatologic manifestations (30% of patients): erythema nodosum (10% of patients), macules, papules, subcutaneous nodules, hyperpigmentation, lupus pernio (indurated violaceous lesions on the nose, lips, ears, and cheeks that can erode into underlying cartilage and bone) (Fig. ES1-2).
  5. Myocardial disturbances, arrhythmias, cardiomyopathy. Cardiac sarcoidosis is much more common than clinically appreciated and is found in up to 25% of patients in the United States.
  6. Splenomegaly, hepatomegaly.
  7. Rheumatologic manifestations: arthralgias have been reported in up to 40% of patients.
  8. Neurologic and other manifestations: cranial nerve palsies, diabetes insipidus, meningeal involvement, parotid enlargement, hypothalamic and pituitary lesions, peripheral adenopathy. Neurosarcoidosis is detected in up to 25% of patients and can occur in the absence of apparent disease elsewhere.

ETIOLOGY

Unknown. A cardinal feature of sarcoidosis is the presence of CD4+ T cells that interact with antigen-presenting cells to initiate the formation and maintenance of granulomas. Multiple lines of evidence suggest that sarcoidosis may result from the interaction of multiple genes with environmental exposures or infection.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Tuberculosis.
- Lymphoma.
- Hodgkin's disease.
- Metastases.
- Pneumoconioses.
- Enlarged pulmonary arteries.
- Infectious mononucleosis.
- Lymphangitic carcinomatosis.
- Idiopathic hemosiderosis.
- Alveolar cell carcinoma.
- Pulmonary eosinophilia.
- Hypersensitivity pneumonitis.
- Fibrosing alveolitis.
- Collagen disorders.
- Parasitic infection.

Section II describes the differential diagnosis of granulomatous lung disease and a classification of granulomatous disorders.

WORKUP

- No pathognomonic diagnostic test exists for sarcoidosis, so the diagnosis remains one of exclusion. Workup is aimed at excluding critical organ involvement, determining extent and severity of disease, and excluding other disease. The presence of noncaseating granulomas does not establish the diagnosis, because conditions such as tuberculosis and malignancies, among others, can cause granulomas. A complete neurologic and ophthalmologic examination is mandatory. A complete occupational and environmental exposure history is recommended.
- Initial laboratory evaluation should include complete blood count, serum chemistries (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes, blood urea nitrogen, creatinine, serum calcium), urinalysis, 24-hour urinary excretion of calcium, CRP, ESR, and tuberculin skin test.
- Chest radiograph and ECG should also be obtained in all patients with sarcoidosis.
- Pulmonary function testing: spirometry, diffusion capacity of carbon monoxide–single breath.
- Biopsy should be done on accessible tissues suspected of sarcoid involvement (conjunctiva, skin, lymph nodes); bronchoscopy with transbronchial biopsy (85% diagnostic yield) is often performed in patients without any readily accessible site. Endobronchial ultrasound-guided fine-needle aspiration of intrathoracic lymph nodes also has high diagnostic yield and makes use of mediastinoscopy mostly unnecessary. Among patients with suspected Stage I/II pulmonary sarcoidosis undergoing tissue confirmation, the use of endosonographic nodal aspiration compared with bronchoscopic biopsy resulted in greater diagnostic yield.

LABORATORY TESTS

Laboratory abnormalities:
- Hypergammaglobulinemia, anemia, leukopenia may be present.
- Liver function test abnormalities are common.
- Hypercalcemia (11% of patients), hypercalciuria (40% of patients; attributable to increased gastrointestinal absorption, abnormal vitamin D metabolism, and increased calcitriol production by sarcoid granuloma).
- Angiotensin-converting enzyme: elevated in approximately 60% of patients with sarcoidosis; nonspecific and generally not useful as a diagnostic tool and in following the course of the disease.

IMAGING STUDIES

- Chest radiograph (Fig. S1-3): adenopathy of the hilar and paratracheal nodes is a frequent finding. Parenchymal changes may also be present, depending on the stage of the disease (stage 0, normal radiograph; stage I, bilateral hilar adenopathy; stage II, stage I plus pulmonary infiltrate; stage III, pulmonary infiltrate without adenopathy; stage IV, advanced fibrosis with evidence of "honeycombing," hilar retraction, bullae, cysts, and emphysema).
- Pulmonary function tests (spirometry and diffusing capacity of the lung for carbon dioxide): may be normal or may reveal a restrictive ventilatory defect with reduced forced vital capacity, reduced DLCO, or both.
- For patients without apparent lung involvement, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) is useful in identifying sites for diagnostic biopsy.
- CT imaging is generally unnecessary for most patients with sarcoidosis. It is indicated when the chest radiograph is atypical for sarcoidosis or if the patient has hemoptysis.
- FDG-PET and MRI with gadolinium are useful in patients with suspected cardiac and neurologic involvement.
- Gallium-67 scan: represents an older testing modality. It will localize in areas of granulomatous infiltrates; however, it is not specific and not necessary. The "panda" sign (localization in the lacrimal and salivary glands, giving a "panda" appearance to the face) is suggestive of sarcoidosis.

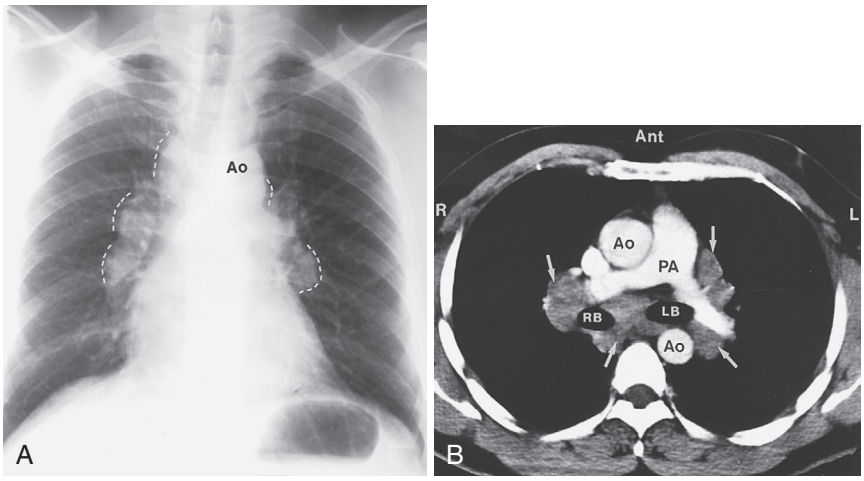


FIGURE S1-3 Sarcoid. Marked lymphadenopathy *(dotted lines)* is seen in the region of both hila in the right paratracheal region **(A).** The transverse contrast-enhanced CT scan of the upper chest **(B)** clearly shows the ascending and descending aorta *(Ao)* as well as the pulmonary artery *(PA)* and superior vena cava. The right and left mainstem bronchus area is also seen. The arrows indicate the extensive lymphadenopathy. *LB,* Left bronchus; *RB,* right bronchus. (From Mettler FA [ed]: *Primary care radiology,* Philadelphia, 2000, Saunders.)

TABLE S1-4 Indications for Use of Corticosteroids in Sarcoidosis

Disorder	Treatment
Iridocyclitis	Corticosteroid eye drops; local subconjunctival deposit of cortisone
Posterior uveitis	Oral prednisone
Pulmonary involvement	Steroids rarely recommended for stage I; typically used if infiltrate remains static or worsens over 3-mo period or the patient is symptomatic
Upper airway obstruction	Rare indication for intravenous steroids
Lupus pernio	Oral prednisone shrinks the disfiguring lesions
Hypercalcemia	Responds well to corticosteroids
Cardiac involvement	Corticosteroids usually recommended if patient has arrhythmias or conduction disturbances
Central nervous system involvement	Response is best in patients with acute symptoms
Lacrimal/salivary gland involvement	Corticosteroids recommended for disordered function, not gland swelling
Bone cysts	Corticosteroids recommended if symptomatic

From Andreoli TE (ed): *Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.

Rx TREATMENT

GENERAL Rx

- Many patients with sarcoidosis will not require any treatment. In general, treatment should be instituted when organ function is threatened. Corticosteroids (Table S1-4) are the mainstay of therapy when treatment is required (e.g., prednisone 40 mg qd for 8 to 12 wk with gradual tapering of the dose to 10 mg qod over 8 to 12 mo); corticosteroids should be considered in patients with severe symptoms (e.g., dyspnea, chest pain); hypercalcemia; ocular, central nervous system, or cardiac involvement; or progressive pulmonary disease. Patients with interstitial lung disease benefit from oral steroid therapy for 6 to 24 mo.
- A lack of benefit from steroid therapy may be due to the presence of irreversible fibrotic disease. Patients with progressive disease refractory to corticosteroids may be treated with methotrexate 7.5 to 15 mg once per week or another immunosuppressant such as azathioprine or mycophenolate mofetil.
- Hydroxychloroquine is effective for chronic disfiguring skin lesions, hypercalcemia, and neurologic involvement.
- Nonsteroidal antiinflammatory drugs are useful for musculoskeletal symptoms and erythema nodosum.
- Pulmonary rehabilitation in patients with significant respiratory insufficiency. Consider liver and lung transplantation in patients unresponsive to conventional treatment.

DISPOSITION

- The majority of patients with sarcoidosis have spontaneous remission within 2 yr and do not require treatment. Their course can be followed by periodic clinical evaluation, chest radiographs, and pulmonary function tests.
- Blacks have increased rates of pulmonary involvement, a worse long-term prognosis, and more frequent relapses.
- Up to one third of patients have unrelenting disease, leading to clinically significant organ impairment. Adverse prognostic factors in sarcoidosis include age of onset >40 yr, cardiac involvement, neurosarcoidosis, progressive pulmonary fibrosis, chronic hypercalcemia, chronic uveitis, involvement of nasal mucosa, nephrocalcinosis, and presence of cystic bone lesions and lupus pernio.

REFERRAL

Ophthalmologic examination is indicated in all patients with suspected sarcoidosis because ocular findings (iridocyclitis, uveitis, conjunctivitis, and keratopathy) are found in ≥25% of documented cases.

PEARLS & CONSIDERATIONS

COMMENTS

- Serial spirometry and measurement of DLCO can be useful in following response to therapy and disease progression.
- Approximately 15% to 20% of patients with lung involvement advance to irreversible lung impairment (bronchiectasis, cavitation, progressive fibrosis, pneumothorax, and respiratory failure). Death from pulmonary failure occurs in 5% to 7% of patients with sarcoidosis.
- Newer treatment approaches are aimed at targeting mechanisms involving CD4 type 1 helper T cells.
- The diagnosis of sarcoidosis should be reconsidered in the presence of atypical manifestations or persistent/progressive disease despite appropriate therapy.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Sarcoidosis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

FIGURE ES1-2 Sarcoidosis. A, Erythema nodosum. **B,** Bilateral hilar lymphadenopathy. **C,** Seventh nerve palsy. **D,** Lupus pernio. **E,** Lacrimal gland enlargement. (**D** courtesy M.A. Mir. From Mir MA: *Atlas of clinical diagnosis,* Philadelphia, 2003, Saunders.)

SUGGESTED READINGS

Iannuzzi MC, Fontana JR: Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics, *JAMA* 305(4):391–399, 2011.

Iannuzzi MC et al.: Sarcoidosis, *N Engl J Med* 357:2153, 2007.

Judson MA: The management of sarcoidosis by the primary care physician, *Am J Med* 120:2153, 2007.

Spagnolo P et al.: Sarcoidosis: challenging diagnostic aspects of an old disease, *Am J Med* 125:118–125, 2012.

BASIC INFORMATION

DEFINITION

Sarcomas are heterogenous groups of malignant tumors of connective tissue. They show a wide range of differentiation—blood vessels (angiosarcoma), fat tissue (liposarcoma), bone (osteosarcoma). Sarcomas occur in soft tissues and bones, but are more common in soft tissues. They affect virtually all tissues, but 75% occur in the limbs. Sarcomas of bone are extremely rare. There are three histiogenic types: osteosarcoma, Ewing's sarcoma, and chondrosarcoma.

ICD-9CM CODES

171.0 Malignant neoplasm of connective and other soft tissue of head, face, and neck (depends on type)

ICD-10CM CODES

C40 Malignant neoplasm of bone and articular cartilage of limbs

C41 Malignant neoplasm of bone and articular cartilage of other unspecified sites

C22.3 Angiosarcoma of liver

C49.9 Malignant neoplasm of connective and soft tissue, unspecified

C49.0 Malignant neoplasm of connective and soft tissue of head, face, and neck

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Soft tissue sarcoma: 30 cases per million per annum.

Sarcoma of bone: 8 cases per million per annum.

Soft tissue sarcoma can occur at any age.

- In the United States there are 7800 new cases per year.
- Incidence increases with age.
- Average age of diagnosis is 57 yr.
- Men and women are affected equally.
- Soft tissue sarcomas represent <1% of all newly diagnosed malignancies.

Sarcomas of bone represent 0.2% of all new cancers.

- About 2600 new cases in the United States each year.

Osteosarcoma and Ewing's sarcoma (the two most common bone tumors) occur predominantly during childhood and adolescence.

GENETICS

See "Etiology."

Physical Findings & Clinical Presentation

- Bone sarcomas. Clinical presentation usually includes:
  - Pain—at rest or at night.
  - Swelling or mass at the site.
  - Pathologic fractures.
- Soft tissue sarcomas:
  Present with painless mass (usually >5 cm). Mass grows slowly for months or years.

ETIOLOGY

- Most sarcomas arise sporadically.
- Genetic predispositions:
  1. Familial retinoblastoma (mutation of the *RBI* gene at 13q14) predisposes to osteosarcoma.
  2. Neurofibromatosis type 1 (mutation of *NF1* gene at 17q11) predisposes to malignant peripheral nerve sheath tumor.
  3. Diaphyseal aclasis (an autosomal inherited condition) is associated with increased risk of peripheral chondrosarcoma.
- Environmental causes:
  1. Previous radiotherapy (e.g., for cervical or breast cancer): predisposes to sarcoma 4 yr or so later.
  2. Chronic lymphedema: associated with the development of angiosarcoma.
  3. Exposure to chemicals (e.g., dioxins, phenoxyacetic herbicides, vinyl chloride).
  4. Viruses (e.g., human herpesvirus 8 causes Kaposi's sarcoma).
  5. Foreign body (shrapnel, medical implants)

DIAGNOSIS

WORKUP

- Soft tissue sarcoma: any unexplained superficial soft tissue mass >5 cm or deep-seated soft tissue mass should be regarded as malignant until proven otherwise.
- Bone sarcoma: patients with unexplained bone pain, persistent bone tenderness, or nonmechanical bone pain (especially when it disturbs sleep or rest) have bone cancer until proven otherwise.
- Patients with suspected spontaneous fracture or recurrence of the fracture with minor trauma should be considered as having bone cancer.
- Referral to a sarcoma treatment center of all patients with a suspected sarcoma is recommended.

IMAGING STUDIES

- A chest spiral CT scan is compulsory for staging purposes. Chest spiral CT helps detect lung metastasis, since metastasis through blood to the lungs is the principal form of spread.
- Staging aids in estimating prognosis, survival, and plan management.
- The American Joint Committee on Cancer (AJCC) and International Union Against Cancer (IUCC) are widely used for staging classification.
- Soft tissue sarcoma.
- Magnetic resonance imaging (MRI) is the initial imaging modality of choice, especially for soft tissue sarcoma of the extremities, trunk, and head and neck. CT with IV contrast is also useful for diagnosis.
- Ultrasound is used to help differentiate between benign and suspicious lesions.
- Bone sarcoma
- Radiograph (Fig. S1-4) is the initial imaging of choice. It helps to rule out bone tumor, shows calcification, and reveals bone erosions. Fig. S1-5 Summarizes radiographic features that may help differentiate benign from malignant lesions.
- A multidisciplinary approach is essential. The team should include radiologist, surgeons, pathologist, medical oncologist, and radiation therapists.

BIOPSY

- In nearly all cases a biopsy is needed to establish a tissue diagnosis.
- Multiple core needle biopsies are usually done.
- An excisional biopsy may be used for superficial lesions <5 cm.
- In carefully selected cases an open biopsy may be done (rarely used because of its high complication rate).
- For difficult to palpate or necrotic soft sarcomas, ultrasound or computed tomography (CT)–guided biopsies are performed.
- Biopsy results are interpreted collaboratively by the specialist sarcoma pathologist, surgeon, and radiologist together.

HISTOLOGIC DIAGNOSIS

- Treatment planning is guided by a histologic diagnosis.
- Histologic diagnosis is made according to the World Health Organization (WHO) classification.

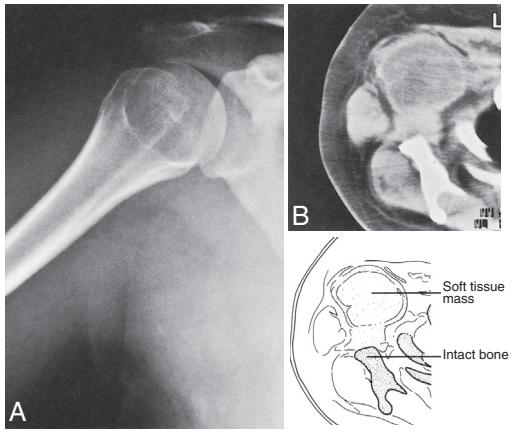
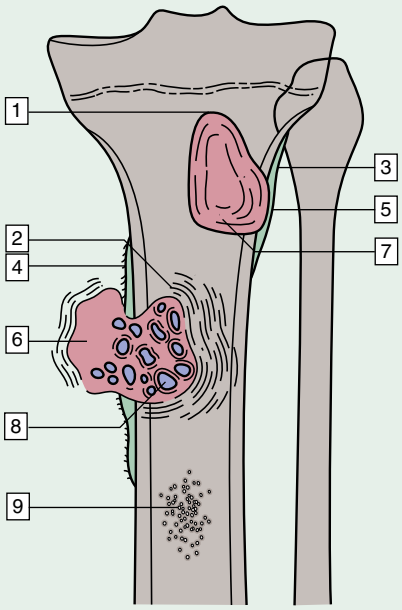


FIGURE S1-4 Fibrosarcoma. A, Anteroposterior plain film of the shoulder of a 40-year-old woman with a history of an enlarging mass in the right axilla shows an ill-defined mass adjacent to the lateral border of the scapula. **B,** CT section with contrast enhancement shows the extent of the mass and the lack of bone involvement. The tumor proved to be a fibrosarcoma. (From Skarin AT: *Atlas of diagnostic oncology,* ed 3, St Louis, 2003, Mosby.)



Feature	Benign (slow-growing process)	Malignant (aggressive process)
Border	1. Sharply outlined, sclerotic (narrow zone of transition)	2. Poorly defined (wide zone of transition)
Periosteal reaction	3. Solid, uninterrupted	4. Interrupted (sunburst, Codman triangle)
Soft tissue extension/mass	5. Absent or contained by shell of periosteal new bone	6. Frank extension through destroyed periosteum
Type of bone destruction	7. Geographic: uniformly destroyed area with sharply defined border	8. "Moth-eaten" (likely malignant): destroyed areas with ragged borders
		9. Permeative (aggressive/malignant): ill-defined destruction spreading through marrow space

FIGURE S1-5 Benign versus malignant bone lesions. The radiographic features illustrated may help differentiate benign from malignant lesions. (From Bullough PG, Vigorita VJ: *Atlas of orthopedic pathology.* Baltimore/New York, 1984, University Park Press/Gower Medical Publishing, in Skarin AT: *Atlas of Diagnostic Oncology,* 4 ed, St Louis, 2010, Mosby, 2010.)

- WHO has defined >50 histologic subtypes of soft tissue sarcoma.
- Newer methods such as immunocytochemistry and cytogenetics can aid diagnosis. They identify tumor lineage.

Rx TREATMENT

Treatment depends on the extent of the disease and falls into several groups.

Acute General Rx

- Tumors treated by surgery: for example, in most adults soft tissue sarcoma and sarcoma of bone are not sensitive to chemotherapy.
  1. Surgery must be done by surgeon trained to treat this disease.
  2. Wide excision with negative margins is the standard surgical procedure.
  3. For bone sarcomas amputation has been the standard procedure. Recent advances permit the avoidance of amputation with limb-sparing surgery followed by reconstruction by endoprosthetic replacement.
- Chemotherapy followed by local therapy: for example, osteosarcoma.
  1. Early chemotherapy to reduce disseminated micrometastasis and tumor size.
- Follow-up of bone sarcoma after treatment includes:
  - Periodic monitoring with radiographs and other imaging modalities.
  - CT scan of the chest.
  - Bone scan.
- Follow-up of soft tissue sarcoma (extremities):
  - Physical exam detects 97% of recurrence.
  - Physical exam is done every 3-6 mo for 3 yr, then every 6 mo for the next 2 yr for stage II and III cancers, then annually.
  - Imaging.
- Stage I: CXR every 6-12 mo.
- Stages II and III: image the primary site with MRI or CT.
- Chest x-ray or chest CT every 3 to 6 mo for 5 yr, then annually.

REFERRAL

- Because sarcomas are relatively uncommon yet comprise a wide variety of different entities, evaluation by oncology teams who have expertise in the field is recommended.
- Treatment and follow-up guidelines have been published by the National Comprehensive Cancer Network (www.nccn.org).

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **DANIEL K. ASIEDU, M.D., PH.D.**

SUGGESTED READINGS

Casali PG, Blay J-Y: Soft tissue sarcoma: ESMO clinical practice guidelines for diagnosis, treatment and follow up, *Ann Oncol* 21(Suppl 5):v198–v203, 2010.

Rosier RN, Bukata SV: Sarcomas of bone. In Chang AE et al, editor: *Oncology: an evidence-based approach*. Springer: New York.

Sinha S, Peach AHS: Diagnosis and management of soft tissue sarcoma, *Br Med J* 341:c7170, 2011.

Skubitz KM, D'Adamo DR: Sarcoma, *Mayo Clin Proc* 82(11):1409–1432, 2007.

Windham TC, Sondak VK: Soft tissue sarcoma. In Chang AE et al, editor: *Oncology: an evidence-based approach*. Springer: New York.

BASIC INFORMATION

DEFINITION

Scabies is a contagious disease caused by the mite *Sarcoptes scabiei.*

ICD-9CM CODES
133.0 Scabies
ICD-10CM CODES
B86 Scabies

EPIDEMIOLOGY & DEMOGRAPHICS

- Scabies is generally acquired by sleeping with or in the bedding of infested individuals.
- It is generally associated with poor living conditions and is also common in hospitals and nursing homes.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Primary lesions are caused when the female mite burrows within the stratum corneum, laying eggs within the tract she leaves behind; burrows (linear or serpiginous tracts, see Fig. S1-6) end with a minute papule or vesicle.
- Primary lesions are most commonly found in the web spaces of the hands, wrists, buttocks, scrotum, penis, breasts, axillae, and knees. They are often confused with eczema (Fig. S1-7).
- Secondary lesions result from scratching or infection.
- Intense pruritus, especially nocturnal, is common; it is caused by an acquired sensitivity to the mite or fecal pellets and is usually noted 1 to 4 wk after the primary infestation.
- Examination of the skin may reveal burrows, tiny vesicles, excoriations, inflammatory papules.
- Widespread and crusted lesions (Norwegian or crusted scabies) may be seen in elderly and immunocompromised patients (Fig. ES1-8). Pruritus may be mild or absent due to impaired host immune response.

ETIOLOGY

- Human scabies is caused by the mite *S. scabiei,* var. *hominis* (Fig. S1-9). After impregnation on the skin surface, the gravid female burrows in the stratum corneum within 30 min and gradually extends the tract along the boundary with the stratum granulosum depositing 10 to 25 oval eggs in a 4- to 5-wk period. The eggs hatch in 3 to 5 days, and larvae move to the skin surface and mature in 2 to 3 wk, resuming the cycle.
- Clinical manifestations result from a delayed type IV hypersensitivity reaction to the mete, eggs, saliva, or scybala.

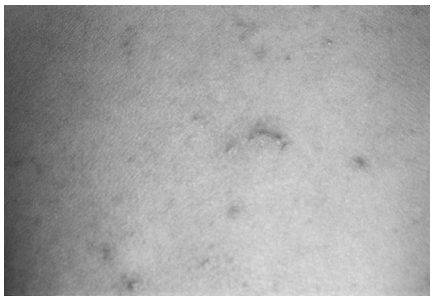


FIGURE S1-6 Classic scabies burrow. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Pediculosis.
- Atopic dermatitis.
- Flea bites.
- Seborrheic dermatitis.
- Dermatitis herpetiformis.
- Contact dermatitis.
- Nummular eczema.
- Syphilis.
- Other insect infestation.

WORKUP

Diagnosis is made on the clinical presentation and on the demonstration of mites, eggs, or mite feces.

LABORATORY TESTS

- Microscopic demonstration of the organism, feces, or eggs: a drop of mineral oil may be placed over the suspected lesion before removal; the scrapings are transferred directly to a glass slide; a drop of potassium hydroxide is added and a cover slip is applied.
- Skin biopsy is rarely necessary to make the diagnosis.

FIGURE S1-7 Scabies in an infant. Diffuse pruritic, eczematous lesions on an infant are often confused with eczema. (From White GM, Cox NH [eds]: *Diseases of the skin: a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

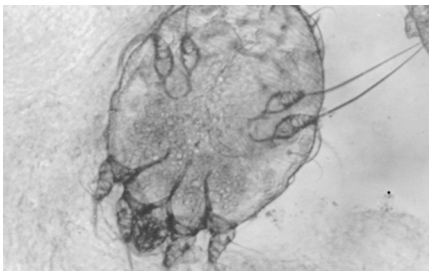


FIGURE S1-9 Scabies organism in a wet mount preparation. (From Mandell GL: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, ed 5, New York, 2000, Churchill Livingstone.)

TREATMENT

NONPHARMACOLOGIC THERAPY

Clothing, underwear, and towels used in the 48 hr before treatment must be laundered.

ACUTE GENERAL Rx

- Permethrin 5% cream (Elimite) is usually effective with one treatment; it should be massaged into the skin from head to soles of feet and applied under fingernails and toenails (it's best if applied in the evening and left overnight to maximize exposure); remove 8 to 14 hr later by washing. Repeat in 1 to 2 wk. Permethrin is safe for children >2 mo old.
- A single dose (150 to 200 μg/kg in 6-mg tablets) of ivermectin, an antihelmintic agent, is also effective for the treatment of scabies. It is the best treatment for generalized crusted scabies. Three to seven doses of ivermectin given on days 1, 2, 8, 9, 15, 22, and 28 may be needed for crusted scabies.
- Pruritus generally abates 24 to 48 hr after treatment but can last up to 2 wk; oral antihistamines are effective in decreasing postscabietic pruritus.
- Topical corticosteroid creams may hasten the resolution of secondary eczematous dermatitis.
- If the patient is a resident of an extended care facility, it is important to educate the patients, staff, family, and frequent visitors about scabies and the need to have full cooperation in treatment. Scabicide should be applied to all patients, staff, and frequent visitors, whether symptomatic or not; symptomatic family members of staff and visitors should also receive treatment.

DISPOSITION

Refractory cases usually are seen with immunocompromised hosts or patients with underlying skin diseases. ***Norwegian scabies*** refers to a highly contagious variant often found in institutions caring for physically and mentally disabled individuals.

PEARLS & CONSIDERATIONS

COMMENTS

- Lindane is potentially neurotoxic and should not be used on infants or pregnant women (permethrin is safe and effective in these situations).
- Sexual partners should be notified and treated.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Scabies (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Currie BJ, McCarthy JS: Permethrin and ivermectin for scabies, *N Engl J Med* 362:717, 2010.

Markova A et al: In the clinic: Common cutaneous parasites, *Ann Intern Med, Spt* 2014.

FIGURE ES1-8 Norwegian scabies. (From Swartz, MH: *Textbook of physical diagnosis,* 7 ed, Philadelphia, 2014, Saunders, 2014.)

BASIC INFORMATION

DEFINITION

Scarlet fever is a rash involving the skin and tongue and complicating streptococcal group A pharyngitis.

SYNONYMS

Scarlatina
SF

ICD-9CM CODES
034.1 Scarlet fever
ICD-10CM CODES
A38 Scarlet fever
A38.9 Scarlet fever, uncomplicated

EPIDEMIOLOGY & DEMOGRAPHICS

- Same as streptococcal pharyngitis; namely, children ages 5 to 15 yr. May also complicate impetigo.
- Most common in cooler climates during the late fall, winter, and early spring.
- Most cases follow tonsillitis or pharyngitis; however, it has also been reported after wounds ("surgical scarlet fever"), burns, and pelvic or puerperal infections.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Diffuse erythema, beginning on face and spreading to neck, back, chest, rest of trunk, and extremities (Fig. S1-10*A*). Most intense on inner aspects of arms and thighs.
- Erythema blanches, but nonblanching petechiae may be present or produced by a tourniquet.
- Strawberry or raspberry tongue (Fig. S1-10*B, C*).
- Rash lasts approximately 1 wk and then desquamates.
- Febrile illness with headache, malaise, anorexia, and pharyngitis begins after a 2 to 4 day incubation period.
- Scarlatinal rash begins 1 or 2 days after the onset of pharyngitis.

ETIOLOGY

Caused by group A beta-hemolytic *Streptococcus* infection, which produces one of three erythrogenic toxins (NOTE: *Some streptococcal species have the ability to cause both scarlet fever and rheumatic fever*).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Viral exanthems (covered in Section II).
- Kawasaki disease.
- Toxic shock syndrome.
- Drug rashes.

See differential diagnosis of "Pharyngitis" in Section I.

WORKUP

- Identification of group A *Streptococcus* by throat culture.
- Streptolysin O antibody titers.

TREATMENT

- Penicillin 250 mg PO qid for 10 days or erythromycin 250 mg PO qid for 10 days in penicillin-allergic patients. A clinical response can be expected in 24 to 48 hr.
- Benzathine penicillin 1 to 2 million U IM once; may be used for a patient who cannot swallow pills.

COMPLICATIONS (RARE)

- Peritonsillar abscess.
- Mastoiditis.
- Otitis media.
- Pneumonia.
- Sepsis and distant foci of infection.
- Acute rheumatic fever.
- Inability to swallow liquids or upper airway obstruction requiring hospitalization.

NOTE: Failure to respond to penicillin should raise doubt about the diagnosis because *Streptococcus* may be carried in the pharynx without causing infection.

PEARLS & CONSIDERATIONS

COMMENTS

Patients with antibodies against the toxin are spared the rash but still develop other symptoms of the infection (e.g., sore throat).

RELATED CONTENT

Scarlet Fever (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

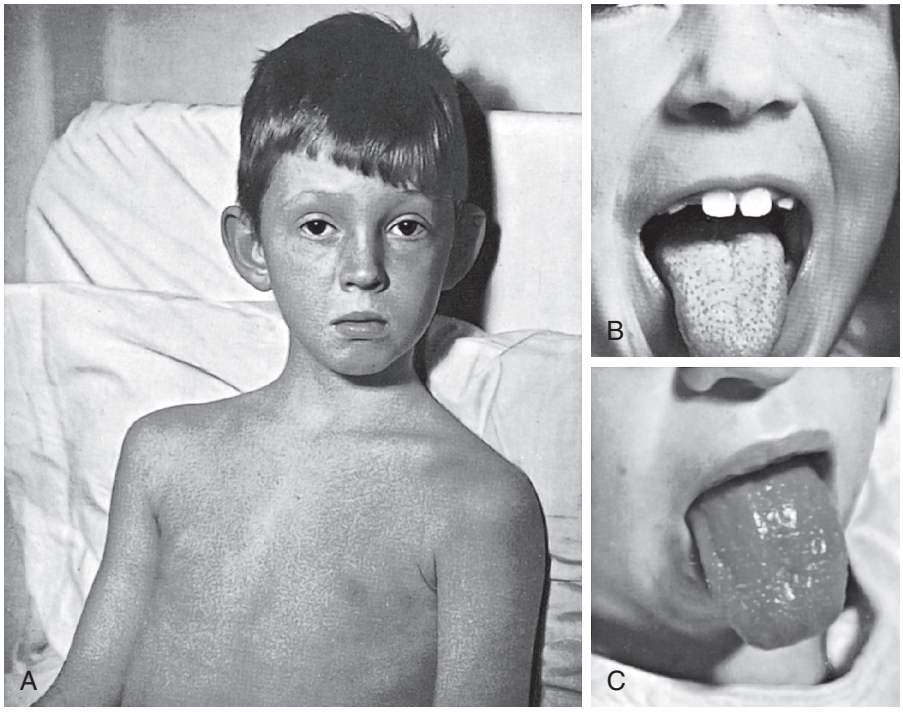


FIGURE S1-10 Scarlet fever. A, Punctate, erythematous rash (2nd day). **B,** White strawberry tongue (1st day). **C,** Red, strawberry tongue (3rd day). (Courtesy Dr. Franklin H. Top, Professor and Head of the Department of Hygiene and Preventive Medicine, State University of Iowa, College of Medicine, Iowa City, IA; and Parke, Davis & Company's Therapeutic Notes. From Gershon AA et al: *Krugman's infectious diseases of children*, ed 11, Philadelphia, 2004, Mosby.)

BASIC INFORMATION

DEFINITION

Schistosomiasis is caused by infection with parasite blood flukes known as schistosomes. Their life cycle is illustrated in Fig. ES1-11.

SYNONYMS

Bilharziasis
Urinary schistosomiasis
Hepatosplenic schistosomiasis
Swimmer's itch
Katayama fever
Snail fever

ICD-9CM CODES

120.0 Schistosomiasis due to *Schistosoma haematobium*
120.1 Schistosomiasis due to *Schistosoma mansoni*
120.2 Schistosomiasis due to *Schistosoma japonicum*
120.3 Cutaneous schistosomiasis
120.8 Other specified schistosomiasis
120.9 Schistosomiasis unspecified

ICD-10CM CODES

B65 Schistososmiasis (bilharziasis)
B65.0 Schistosomiasis due to *Schistosoma haematobium*
B65.1 Schistosomiasis due to *Schistosoma mansoni*
B65.2 Schistosomiasis due to *Schistosoma japonicum*
B65.8 Other schistosomiasis
B65.9 Schistosomiasis, unspecified

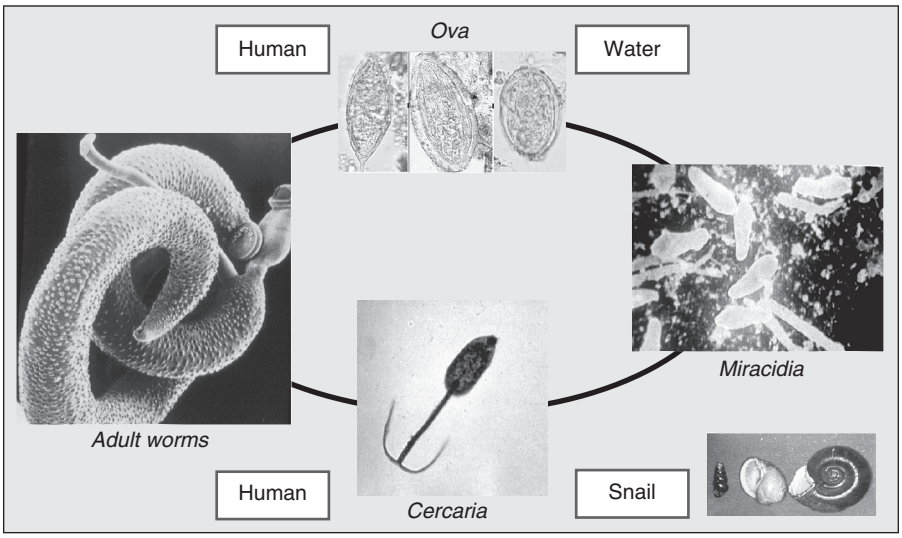


FIGURE ES1-11 Life cycle of schistosomes. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

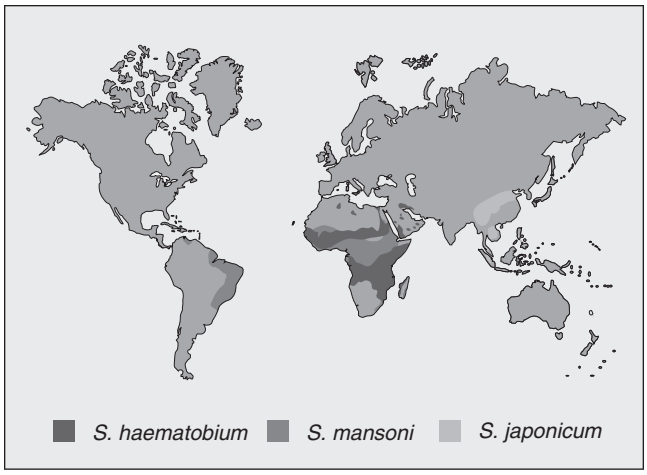


FIGURE ES1-12 World map showing the geographic distribution of the main pathogenic schistosomes. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE

- Worldwide >230 million people, 20 million people with severe disease, and >200,000 deaths annually. In the United States, it is estimated to exceed 400,000 people.
- Geographic distribution of schistosomiasis (see Fig. ES1-12) is confined to an area between 36° north and 34° south latitude, where fresh water temperatures average 25° to 30° C, and where freshwater snail (intermediate host) habitats are located.

PREVALENCE: The greatest cercarial exposure usually occurs in boys ages 5 to 10 yr.

DISTRIBUTION

- *Schistosoma mansoni* in tropical and subtropical areas of sub-Saharan Africa, the Middle East, South America, and the Caribbean.
- *S. haematobium* in North Africa, sub-Saharan Africa, the Middle East, and India.
- *S. japonicum* in Asia, particularly in China, the Philippines, Thailand, and Indonesia.
- *S. intercalatum* in Cameroon and the Democratic Republic of the Congo.
- *S. mekongi* in Mekong River (Laos and Cambodia).

ETIOLOGY & PATHOGENESIS

- Human infections are caused by five main schistosome species (three major ones and two less common): *S. mansoni, S. haematobium, S. japonicum, S. mekongi,* and *S. intercalatum*.
- Acquisition of disease via contact with fresh water containing infectious free-living cercarial larvae that penetrate intact skin and transform into schistosomulae.
- Once inside humans, they ultimately reach, depending on the species, the venules of the target organs and develop into adult worms. Male and female worms mate continuously at this point.
- Adult worms are 1 to 3 cm in length and live 3 to 7 years. Females lay eggs that on contact with fresh water become miracidium larvae that then enter freshwater snails (an intermediate host). The miracidia develop further and exit the snail in water as cercarial larvae that will enter humans as the definitive host.
- The eggs produced by adult worms are released into the bloodstream and can invade local tissue. This tissue insult induces a granulomatous reaction that involves T-helper-2 cytokines, eosinophils, and macrophages. These granulomas contain the egg and the proteolytic enzymes it releases to prevent tissue necrosis.
- In the United States, most cases are acquired during foreign travel or appear in immigrants.
- Human disease is primarily associated with the host's granulomatous response to eggs retained in the tissue.
- Incubation period is typically 2 to 12 weeks for acute illness, but chronic infection can remain asymptomatic for years.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

ACUTE SYMPTOMS

- Swimmer's itch: initial penetration of the skin by cercariae. Most commonly seen with *S. japonicum* infection
- Katayama fever: systemic hypersensitivity reaction to migrating parasites early in infection.

CHRONIC SYMPTOMS

- Failure to thrive in children from regions where schistosomiasis is endemic.

- Intestinal schistosomiasis
  1. Abdominal pain.
  2. Poor appetite.
  3. Bloody diarrhea.
  4. Iron-deficiency anemia.
  5. Intestinal polyp.
  6. Bowel ulcer and strictures.
- Hepatic schistosomiasis
  1. Hepatomegaly.
  2. Splenomegaly.
  3. Portal hypertension.
  4. Esophageal varices.
  5. Ascites.
- Urinary schistosomiasis.
  1. Hematuria (micro- or macroscopic).
  2. Dysuria.
  3. Urinary frequency.
  4. Fibrosis of bladder and ureters.
  5. Squamous cell cancer of bladder.
  6. Proteinuria.
  7. Nephrotic syndrome.

COMPLICATIONS

- Neurologic complications.
  1. Granuloma of spinal cord or brain.
  2. Transverse myelitis.
  3. Epilepsy or focal neurologic deficit.
- Pulmonary complications.
  1. Granulomatous pulmonary endarteritis.
  2. Pulmonary hypertension.
  3. Cor pulmonale.
- Other complications include tubal obstruction and infertility.
- Recurrent bacteremia and recurrent UTI.
- Significant systemic associations: malnutrition, impaired growth.

Comorbidities

- HIV: schistosomiasis may increase the risk of HIV infection.
- Hepatitis B and C: people who have coinfection appear to have more severe disease.
- Malaria: possible protective effect of schistosomiasis on malaria infection.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Amebiasis.
- Bacillary dysentery.
- Bowel polyp.
- Prostatic disease.
- Genitourinary tract cancer.
- Bacterial infections of the urinary tract.

WORKUP

- Microscopy in urine or stool.
- Tissue biopsy (rectal, ideally under direct visualization).
- Serology
- CBC.
- LFT.
- US of abdomen, including bladder.
- CT scan of abdomen.

LABORATORY TESTS

- CBC shows eosinophilia, anemia, thrombocytopenia.
- LFT with mild increase in alkaline phosphatase and GGT.
- Microscopy: stool and urine.
- Serology: ELISA for detecting both schistosomal antibodies and antigen.
- Rectal biopsy or bladder mucosal biopsy.

IMAGING STUDIES

- An x-ray of the abdomen shows "fetal head" calcification.
- Sonography can detect thickened bladder wall, hydronephrosis and hydroureter, and bladder polyps or calcification. It can also detect thickened fibrosed portal tracts.
- Esophagoscopy documents esophageal varices.
- Liver biopsy may also demonstrate granuloma and periportal fibrosis (also called Symmer's pipestem fibrosis).
- Cystoscopy should be considered in cases of persistent urinary symptoms as there is risk of bladder cancer, even in pediatric cases.

Rx TREATMENT

- Oral antihistamines can relieve symptoms of swimmer's itch (reaction from skin penetration of cercariae after water exposure). Regardless, dermatologic symptoms resolve gradually.
- Drug of choice is praziquantel 40 mg/kg of body weight PO in one or two doses. *S. japonicum* and *S. mekongi* require a dose of 60 mg/kg divided in three doses.
- Any pregnant or lactating women with evidence of schistosomiasis should receive treatment with praziquantel. In pregnant women, praziquantel administration is preferred after the first trimester.
- Alternatives: oxamniquine 15 mg/kg PO once or 20 mg/kg PO daily for 3 days for recalcitrant infections of *S. mansoni* and metrifonate for urinary schistosomiasis but currently not available.
- Oral steroids are indicated with Katayama fever and central nervous system involvement.

DISPOSITION

Treated patients usually respond to therapy. Definitive cure has occurred only when there is total disappearance of viable eggs from the excreta for a total of 6 mo after treatment. Patients may excrete nonviable eggs for months to years after effective therapy and may require examination to confirm nonviability early after initial treatment.

REFERRAL

- To an infectious disease specialist knowledgeable in parasitology and geographic medicine for treatment and follow-up.
- To a gastroenterologist for sclerotherapy of bleeding esophageal varices, if needed in advanced hepatosplenic schistosomiasis.
- To a urologist for management and follow-up of urinary complications of *S. haematobium* infection of the genitourinary tract.

! PEARLS & CONSIDERATIONS

COMMENTS

Prevention:

- Chemotherapy with yearly praziquantel.
  1. Mass.
  2. Targeted population.
- Snail control
  1. Molluscicide (historically not effective).
  2. Environmental modification.
  3. Biologic control.
- Reduction of water contact and contamination.
  1. Provision of domestic water supplies.
  2. Provision for sanitary disposal of excreta.
- Vaccines are in development.
- Improved living standards.

Screening:

- Travelers and refugees from endemic areas and that have been exposed to fresh water.
  1. Serology.
  2. Urine and stool microspcopy.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **RUSSELL J. MCCULLOH, M.D.** and **SANET TORRES-TORRES, M.D.**

SUGGESTED READINGS

Clerinx J, van Gompel A: Schistosomiasis in travelers and migrants, *Travel Med Infect Dis* 9(1):6–24, 2011.

Colley DG, Bustinduy AL, Evan Secor W et al.: Human schistosomiasis, *Lancet* 383:2253–2264, 2014.

Colley DG, Evan Secor W: Immunology of human schistosomiasis. Parasite Immunol, *Epub*, 2013. http://dx.doi.org/10.1111/pim.12087. Nov 4.

Ekpo UF et al.: Schistosomiasis in infants and pre-school-aged children in sub-Saharan Africa: implication for control, *Parasitology* 139(7):835–841, 2012.

Gray DJ et al.: Diagnosis and management of schistosomiasis, *BMJ* 342, 2011. 10.1136/bmj.d2651. d2651.

Siddiqui AA et al.: Schistosomiasis vaccines, *Hum Vaccin* 7, 2011. 10.4161/hv.7.11.17017. Epub 2011 Nov 1.

Steinmann P et al.: Schistosomiasis and water resources development: systematic review, meta-analysis, and estimates of people at risk, *Lancet Infect Dis* 6(7):411, 2006.

Vennervald BJ et al.: Morbidity in schistosomiasis: an update, *Curr Opin Infect Dis* 17(5):439, 2004.

Wu W, Huang Y: Application of praziquantel in schistosomiasis japonica control strategies in China, *Parasitol Res* 112(3):909–915, 2013.

BASIC INFORMATION

DEFINITION

Schizophrenia is a disorder that causes significant distortions in thinking, perception, speech, and behavior. Characteristics include psychosis, apathy, social withdrawal, and cognitive impairment, which result in significant social impairment.

SYNONYMS

Dementia praecox

ICD-9CM and DSM-5 CODES
295.90 Schizophrenia, unspecified type
ICD-10CM CODES
F20 Schizophrenia
F20.0 Paranoid schizophrenia
F20.1 Hebephrenic schizophrenia
F20.2 Catatonic schizophrenia
F20.3 Undifferentiated schizophrenia
F20.5 Residual schizophrenia
F20.6 Simple schizophrenia
F20.8 Other schizophrenia
F20.9 Schizophrenia, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 0.2 per 1000.
PREVALENCE: 0.5%; lifetime prevalence risk, 0.4%.
PREDOMINANT SEX: Males have a more severe illness with earlier onset. Prevalence in males approximately 1.4 times higher.
PREDOMINANT AGE:
- Age of onset of psychotic symptoms is the early 20s for males and the late 20s for females.
- Age of onset of negative symptoms is usually earlier (i.e., the mid-teenage years).

PEAK INCIDENCE: Between ages of 16 and 30 yr.
GENETICS
- Genetics accounts for 70% of risk; the remaining 30% associated with other factors such as urban environments, migration, or cannabis use.
- First-degree relatives have a 10 times greater chance of becoming schizophrenic.
- Discordant rates among identical twins are higher than expected with the simple inheritance pattern.
- Associations with several chromosomes have been described, but none has been replicated.
- Evidence exists that triplet nucleotide repeat expansion (e.g., such as that seen with Huntington's disease) may play a role in the inheritance of the disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Schizophrenia is best defined as a dementing illness that begins early in life and that progresses slowly throughout the lifetime.
- Frequent structural brain imaging findings include the enlargement of the ventricular system, a loss of brain volume and cortical gray matter, and an alteration of the white matter tracts.
- The initial "negative" symptoms of adolescence (prodromal phase)—cognitive decline, social withdrawal and awkwardness, loss of motivation and pleasure, and loss of emotional expressiveness—begin after a period of normal development.
- During early adulthood, positive symptoms of psychosis and thought disturbance occur; psychotic symptoms then wax and wane throughout life. Treatment ameliorates positive symptoms, but generally does little for negative ones.
- The condition is also accompanied by cognitive impairment, including problems with attention and concentration, psychomotor speed, learning, memory, and executive functions (e.g., abstract thinking, problem solving, planning).
- Social and occupational dysfunction can be profound.

ETIOLOGY

- The basic determination of whether this is a degenerative or developmental condition has not been made.
- The major hypothesis is that abnormality of the mesocortical pathways produces the hypofrontality and the negative symptoms. This occurs along with a compensatory hyperactivation of the mesolimbic pathways, which produces the positive symptoms of psychosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Schizophrenia is diagnosed when an individual has experienced at least 6 mo (1 mo if using ICD-10 criteria) of hallucinations, delusions, thought disorders, catatonia, or negative symptoms (e.g., avolition, anhedonia, social isolation, affective flattening).
- Any medical condition, medicine, or substance that can affect brain homeostasis can cause psychosis; this is distinguished from schizophrenia by a relatively brief course and an alteration in mental status that suggests an underlying delirium.
- Other neurologic conditions that have psychosis as the initial presentation (e.g., Huntington's disease) need to be ruled out.
- Mood disorders with psychosis: these are indistinguishable from schizophrenia cross-sectionally but have a longitudinal course that includes full recovery.
- Delusional disorder involves nonbizarre delusions and lacks the thought disturbance, hallucinations, and negative symptoms of schizophrenia.
- Autism in the adult has an early age of onset and lacks significant hallucinations or delusions.

WORKUP

- History and physical examination to help determine whether the psychosis is primary or secondary.
- Neurologic examination to uncover the soft neurologic signs (e.g., clumsiness, cortical thumb, loss of fine motor movements) that are common with schizophrenia.

LABORATORY TESTS

- No laboratory tests are specific.
- Laboratory examinations (e.g., chemistry profile, blood count, sedimentation rate, toxicology screen, urinalysis) are geared toward excluding a primary medical condition or toxic state. Note that new common drugs of abuse may not be detectable with regular screening tests.

IMAGING STUDIES

- CT or MRI of the brain during the initial workup; repeated if the course of the illness varies from what is expected.
- EEG may reveal slowing when psychosis is the result of an encephalopathy. Findings can be similar as a result of common medication use for treatment of psychosis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Significant social support is required by most schizophrenic patients, but available support services are grossly inadequate. Schizophrenic patients constitute nearly one third of all homeless individuals. They usually require help with basic social, occupational, and interaction skills.
- Family stress can precipitate relapse and re-hospitalization. Family interventions can reduce morbidity.
- Cognitive behavioral therapy can reduce the severity of both psychotic and negative symptoms.
- Illness management training for patients can increase medication adherence and reduce symptom distress.
- Integrated treatment that includes assertive community treatment, family involvement programs, and social skills training reduces the severity of both psychotic and negative symptoms, reduces comorbid substance misuse, reduces hospital days, increases adherence to treatment, and increases satisfaction with treatment.

ACUTE GENERAL Rx

- Acute psychosis is usually adequately controlled with antipsychotic agents.
- Few differences in effectiveness exist between first-generation antipsychotics (e.g., haloperidol, perphenazine, fluphenazine, chlorpromazine) and second-generation antipsychotics (e.g., risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, clozapine, lurasidone) for nonrefractory patients. First-generation antipsychotics are slightly more likely than second-generation antipsychotics to cause a parkinsonian state and eventual tardive dyskinesia (rate of tardive dyskinesia, 15% to 30%). Antiparkinsonian drugs (e.g., benztropine, amantadine) are used to ameliorate the parkinsonism. Risperidone has been shown to be superior to haloperidol for the prevention of acute psychotic relapse.
- Sedatives (i.e., benzodiazepines and, to a lesser degree, barbiturates) can be used transiently if a patient is in an agitated state.

CHRONIC Rx

- Relapse prevention is a major goal of treatment. Noncompliance is common and leads to high relapse rates. Antipsychotic agents usually must be continued at the same doses that controlled psychosis. For noncompliant patients, long-acting injectable preparations given biweekly or monthly can be used.
- Most patients frequently switch among antipsychotics; there is considerable individual variability with regard to antipsychotic response and vulnerability to specific adverse effects.
- Clozapine is more effective than other agents for treatment-refractory patients. However, it requires monitoring to prevent life-threatening adverse effects. Olanzapine may also be more effective than less expensive first-generation drugs but has substantial adverse metabolic effects. Lurasidone is a newer second-generation antipsychotic that appears to be better tolerated, but longer-term studies are needed.
- Neurocognitive improvement associated with antipsychotic treatment among patients with schizophrenia is small and does not differ between first-generation and second-generation antipsychotics.
- Antiparkinsonian agents may also need to be continued for the long term.
- Tardive dyskinesia (i.e., choreoathetoid movements of the muscles of tongue and face and occasionally of other muscle groups) can occur in as many as 30% of patients with the long-term use of neuroleptics.
- The negative symptoms of schizophrenia can resemble depression. In addition, depressive disorders may occur in schizophrenic patients. Antidepressant treatment of the negative symptoms is usually not effective. However, antidepressants can improve the symptoms of a comorbid depressive episode.
- Mood stabilizers (e.g., lithium, valproate, carbamazepine) are of little use unless the patient has a comorbid impulse control disorder.
- Substance abuse is a major problem for more than a third of schizophrenic patients. More than half of these patients smoke cigarettes. Unfortunately, these individuals do poorly in traditional substance abuse treatment programs. Specialized "dual-diagnosis" programs with highly structured aftercare are required.
- Specific antipsychotic medications have been associated with weight gain (i.e., olanzapine and clozapine) and QT prolongation. Hyperlipidemia and diabetes mellitus are associated with second-generation antipsychotics, and hyperprolactinemia is associated with first-generation antipsychotics. (Risperidone, a second-generation antipsychotic, can also produce hyperprolactinemia.) Clozapine is associated with agranulocytosis. Metabolic status and weight should be screened before the start of treatment and at regular intervals.
- Patients with schizophrenia have a higher lifetime incidence of suicide, with 20% attempting on one or more occasions and 5% to 6% completing suicide. Comorbid use of substances and hopelessness are associated risk factors. Clozapine has shown the ability to decrease the incidence of suicidal attempts in schizophrenia patients.
- Several 1st and 2nd generation antipsychotics are available in long-acting injectable preparations that may be helpful in addressing issues of poor compliance or difficulty when treatment needs to be supervised

DISPOSITION

- The positive symptoms of as many as 20% to 30% of schizophrenic patients do not respond to available treatments. A much higher fraction of patients experience relapse as a result of poor compliance.
- Negative symptoms are responsible for the 50% to 70% of patients in whom deterioration in occupational and social function continues.
- Approximately 10% of schizophrenic patients will complete suicide.
- The course of the illness is most strongly predicted by the level of social development attained at the onset of psychosis.
- Schizophrenic patients die 12 to 15 years sooner than the average population, mostly as a result of physical causes related to a lack of access to health care or as a result of health risk factors (e.g., smoking, obesity).

REFERRAL

- If hospitalization is required.
- If patient is noncompliant.
- If patient is resistant to treatment.

PEARLS & CONSIDERATIONS

- Rule out delirium caused by medical conditions, medications, or substance abuse before diagnosing an individual's psychotic behavior as schizophrenia.
- All antipsychotic medications have high discontinuation rates in chronic schizophrenia treatment. Olanzapine and clozapine may be more effective than other antipsychotics for chronic treatment, but they have significant side effects.
- Significant social support is required for most patients with schizophrenia. Nonpharmacologic therapy should be used in conjunction with pharmacotherapy.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Schizophrenia (Patient Information)

AUTHORS: **ARNALDO A. BERGES, M.D., RICHARD J. GOLDBERG, M.D., M.S.,** and **MICHAEL K. ONG, M.D., PH.D.**

EVIDENCE

Abstract[1]

Objective:
Cognitive remediation therapy for schizophrenia was developed to treat cognitive problems that affect functioning, but the treatment effects may depend on the type of trial methodology adopted. The present meta-analysis will determine the effects of treatment and whether study method or potential moderators influence the estimates.

Method:
Electronic databases were searched up to June 2009 using variants of the key words "cognitive," "training," "remediation," "clinical trial," and "schizophrenia." Key researchers were contacted to ensure that all studies meeting the criteria were included. This produced 109 reports of 40 studies in which ≥70% of participants had a diagnosis of schizophrenia, all of whom received standard care. There was a comparison group and allocation procedure in these studies. Data were available to calculate effect sizes on cognition and/or functioning. Data were independently extracted by two reviewers with excellent reliability. Methodological moderators were extracted through the Clinical Trials Assessment Measure and verified by authors in 94% of cases.

Results:
The meta-analysis (2,104 participants) yielded durable effects on global cognition and functioning. The symptom effect was small and disappeared at follow-up assessment. No treatment element (remediation approach, duration, computer use, etc.) was associated with cognitive outcome. Cognitive remediation therapy was more effective when patients were clinically stable. Significantly stronger effects on functioning were found when cognitive remediation therapy was provided together with other psychiatric rehabilitation, and a much larger effect was present when a strategic approach was adopted together with adjunctive rehabilitation. Despite variability in methodological rigor, this did not moderate any of the therapy effects, and even in the most rigorous studies there were similar small-to-moderate effects.

Conclusions:
Cognitive remediation benefits people with schizophrenia, and when combined with psychiatric rehabilitation, this benefit generalizes to functioning, relative to rehabilitation alone. These benefits cannot be attributed to poor study methods. Ⓐ

Abstract[2]

Background:
Long-acting injectable risperidone, a second-generation antipsychotic agent, may improve adherence to treatment and outcomes in schizophrenia, but it has not been tested in a long-term randomized trial involving patients with unstable disease.

Methods:
We randomly assigned patients in the Veterans Affairs (VA) system who had schizophrenia or schizoaffective disorder and who had been hospitalized within the previous 2 years or were at imminent risk for hospitalization to 25 to 50 mg of long-acting injectable risperidone every two weeks or to a psychiatrist's choice of an oral antipsychotic. All patients were followed for up to 2 years. The primary end point was hospitalization in a VA or non-VA psychiatric hospital. Symptoms, quality of life, and functioning were assessed in blinded videoconference interviews.

Results:
Of 369 participants, 40% were hospitalized at randomization, 55% were hospitalized within the previous 2 years, and 5% were at risk for hospitalization. The rate of hospitalization after randomization was not significantly lower among patients who received long-acting injectable risperidone than among those who received oral antipsychotics (39% after 10.8 months vs. 45% after 11.3 months; hazard ratio, 0.87; 95% confidence interval, 0.63 to 1.20). Psychiatric symptoms, quality of life, scores on the Personal and Social Performance scale of global functioning, and neurologic side effects were not significantly improved with long-acting injectable risperidone as compared with control treatments. Patients who received long-acting injectable risperidone reported more adverse events at the injection site and more extrapyramidal symptoms.

Conclusions:
Long-acting injectable risperidone was not superior to a psychiatrist's choice of oral treatment in patients with schizophrenia and schizoaffective disorder who were hospitalized or at high risk for hospitalization, and it was associated with more local injection-site and extrapyramidal adverse effects. (Supported by the VA Cooperative Studies Program and Ortho-McNeil Janssen Scientific Affairs; ClinicalTrials.gov number, NCT00132314.) Ⓐ

Evidence-Based References

Wykes T et al.: A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes, *Am J Psychiatry* 168:472–485, 2011. Ⓐ

Rosenheck SA et al.: for the CSP555 Research Group: Long-acting risperidone and oral antipsychotics in unstable schizophrenia, *N Engl J Med* 364:842–851, 2011. Ⓐ

SUGGESTED READINGS

Barbui C et al.: Does the addition of a second antipsychotic drug improve clozapine treatment? *Schizophr Bull* 35(2):458–468, 2009.

Hackman DT et al.: Prescription drug monitoring program inquiry in psychiatric assessment: detection of high rates of opioid prescribing to a dual diagnosis population, *J Clin Psychiatry* 75(7):750–756, 2014.

Ray WA et al.: Atypical antipsychotic drugs and the risk of sudden cardiac death, *N Engl J Med* 360:225–235, 2009.

Rosenheck RA et al.: Long-acting risperidone and oral antipsychotics in unstable schizophrenia, *N Engl J Med* 364:842–851, 2011.

Sin J, Norman I: Psychoeducational interventions for family members of people with schizophrenia: a mixed-method systematic review, *J Clin Psychiatry* 74(12):e1145–e1162, 2014.

Van Os J et al.: Schizophrenia, *Lancet* 374:635, 2009.

BASIC INFORMATION

DEFINITION

Scleritis is inflammation of the sclera (the fibrous layer of the eye underlying the conjunctiva and episclera). It is characterized by edema and cellular infiltration of the entire thickness of the sclera.

Classification of immune:

1. Anterior nonnecrotizing scleritis: can be subdivided into diffuse or nodular.
2. Anterior necrotizing scleritis with inflammation: can be subdivided into vasoocclusive, granulomatous, or surgically induced. Aggressive form of scleritis. Average age of onset is 60 yr. Bilateral in 60% of patients.
3. Scleromalacia perforans: typically affects elderly women with longstanding rheumatoid arthritis.
4. Posterior scleritis: involves the deeper tissues of the eye and is potentially blinding. Age of onset is often under 40 yr. Bilateral in 35% of cases.

SYNONYMS

Anterior scleritis
Diffuse nodular, necrotizing scleritis
Scleromalacia perforans
Scleral melt syndrome

ICD-9CM CODES
379.0 Scleritis and episcleritis
ICD-10CM CODES
H15.0 Scleritis
H15.1 Episcleritis

EPIDEMIOLOGY & DEMOGRAPHICS

PEAK INCIDENCE: Increases with increasing age.
INCIDENCE (IN U.S.): Busy ophthalmologists may see one or two cases a year
PREVALENCE (IN U.S.): Relatively rare.
PREDOMINANT SEX: 61% women.
PREDOMINANT AGE: 52 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Deep, boring (dull) eye pain that may awaken patient from sleep.
- Photophobia.
- Tearing.
- Painful eye movements.
- Globe is tender to touch.
- Conjunctival injection (Fig. S1-13).
- Thinning of the sclera.
- An underlying systemic autoimmune disease is found in >50% of patients. Most common rheumatic problem is rheumatoid arthritis. Most patients with systemic disease are diagnosed before development of scleritis.

ETIOLOGY

- Inflammatory (seen with rheumatoid arthritis, granulomatosis with polyangiitis [Wegener granulomatosis], relapsing polychondritis, polyarteritis nodosa), lupus, sarcoidosis.
- Allergic.
- Infectious scleritis (herpes zoster, tuberculosis, Lyme disease, syphilis, *Pseudomonas aeruginosa, Nocardia,* leprosy) is uncommon, accounting for 4% to 18% of cases
- Approximately 50% of patients with scleritis have an underlying systemic disease (vasculitis, infectious disease).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Most common causes are rheumatoid arthritis and other collagen-vascular diseases.

- Occasionally there are allergic, infectious, or traumatic causes.
- Conjunctivitis, iritis, and episcleritis should be considered in the differential diagnosis. Patients with episcleritis generally have less pain and vision is unaffected.

WORKUP

- Eye examination.
- Visual field examination.
- Workup for autoimmune disease (e.g., vasculitis, collagen vascular diseases)

LABORATORY TESTS

Rheumatoid factor, antinuclear antibody, erythrocyte sedimentation rate, ANCA (c-ANCA, p-ANCA), antiphospholipid antibodies, may be useful for underlying etiology.

IMAGING STUDIES

Usually not necessary; CT scan of orbit may be useful in selected patients for collagen vascular disease or vasculitis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Bandage lenses.
- Surgery if thinning of the sclera is severe to prevent eye rupture.

ACUTE GENERAL Rx

Immunotherapy:

- Steroids (topical, periocular, and systemic).
- Cycloplegic drops.
- Nonsteroidal antiinflammatory drugs (topical and systemic); systemic more effective than topical.
- Cytotoxic agents (cyclophosphamide, azathioprine, mycophenolate mofetil, methotrexate).
- Immune modulators (cyclosporin, tacrolimus).
- Specific antibodies (infliximab, rituximab).

CHRONIC Rx

- Systemic corticosteroids can be given for the underlying disease.
- Local steroids may be helpful.
- Control underlying disease.

DISPOSITION

Urgent referral to ophthalmologist because this disorder can be a sight-threatening condition.

REFERRAL

If not referred to an ophthalmologist early, patients may develop uveitis and other complications.

PEARLS & CONSIDERATIONS

COMMENTS

An ominous diagnosis because these patients often have other severe underlying debilitating disease processes.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **R. SCOTT HOFFMAN, M.D.**

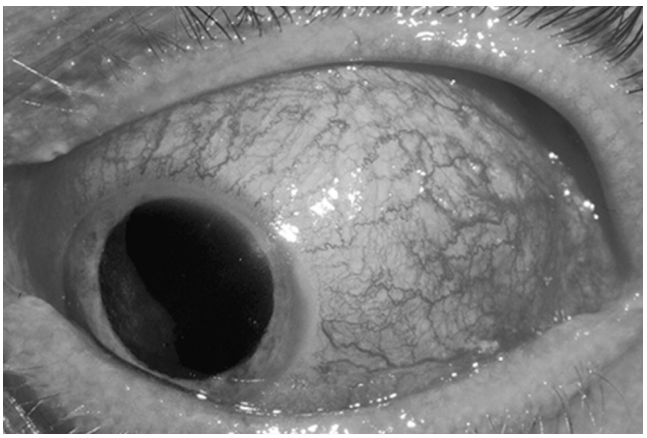


FIGURE S1-13 In diffuse anterior scleritis, widespread injection of the conjunctival and deep episcleral vessels occurs. (From Palay D [ed]: *Ophthalmology for the primary care physician,* St Louis, 1997, Mosby.)

SUGGESTED READINGS

Akpek EK et al.: Evaluation of patients with scleritis for systemic disease, *Ophthalmology* 111(3):501, 2004.

Bhat P et al.: Chronic herpes simplex scleritis: characterization of 9 cases of an underrecognized clinical entity, *Am J Ophthalmol* 148:779–788, 2009.

Etminan M et al.: Inflammatory ocular adverse events with the use of oral bisphosphonates: a retrospective cohort study, *CMAJ* 184:E431, 2012.

Kanski JJ, Bowling B: *Clinical ophthalmology: a systematic approach*, ed 7, Saunders: Philadelphia.

Paresio CG et al.: Systemic disorders associated with episcleritis and scleritis, *Curr Opin Ophthalmol* 12(6):471, 2001.

Sainz de la Maza M et al.: Ocular characteristics and disease associations in scleritis: associated peripheral keratopathy, *Arch Ophthalmol* 120(1):15, 2002.

Thorne JE et al.: Severe scleritis and urticarial lesions, *Am J Ophthalmol* 134(6):932, 2002.

BASIC INFORMATION

DEFINITION

Scleroderma (systemic sclerosis [SSc]) is a connective tissue disorder that is characterized by thickening and fibrosis of the skin and variably severe involvement of diverse internal organs. It can be subdivided into two major subgroups: (1) limited cutaneous SSc (lcSSc), which involves mainly the face, neck, arms, and hands; and (2) diffuse cutaneous SSc (dcSSc), which affects the skin in a more generalized distribution including the entire extremities, face, neck, and trunk. Both subgroups typically have characteristic internal organ involvement. Table S1-5 compares localized scleroderma and SSc. A classification of scleroderma is described in Box S1-1.

BOX S1-1 Classification of Scleroderma

I. Localized scleroderma
  A. Morphea
  B. Linear scleroderma
  C. Scleroderma en coup de sabre
II. Systemic sclerosis
  A. Limited cutaneous systemic sclerosis
  B. Diffuse cutaneous systemic sclerosis

From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

SYNONYMS

Systemic sclerosis

Morphea applies to localized scleroderma that affects only the skin

Scleredema is a disease of the skin that is distinct from scleroderma

ICD-9CM CODES
710.1 Scleroderma
701.0 Morphea

ICD-10CM CODES
M34.0 Progressive systemic sclerosis
L94.0 Localized scleroderma (morphea)
L94.1 Linear scleroderma

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: There are 2.3 to 22.8 cases per 1 million persons per yr, but many mild cases go unrecognized.

PREVALENCE: 50 to 300 cases per 1 million persons.

PREDOMINANT SEX: Female/male ratio of 4:1.

PREDOMINANT AGE: 30 to 50 yr.

DISTRIBUTION: Worldwide.

TABLE S1-5 Comparison of Localized Scleroderma and Systemic Sclerosis

Feature	Localized Scleroderma/ Morphea	Systemic Sclerosis
Skin findings	Patches or linear distribution of thickened skin	Sclerodactyly ± proximal skin thickening
Raynaud's phenomenon	Absent	Present
Digital ischemic changes	Absent	Usually present (digital pitting scars or ulcers, loss of fingerpad substance)
Internal organ disease	Absent	Present
Antinuclear antibody	Positive in ≥50% of cases	Positive in ≥85% of cases
Scleroderma-specific autoantibodies*	Negative	Positive in 60% of cases
Biopsy—histologic findings	Dermal fibrosis	Dermal fibrosis

*Scleroderma-specific antibodies include antibodies to centromere, topoisomerase-1 (Scl 70), and RNA polymerase III.
From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

FIGURE S1-17 Digital gangrene on the fingertips of a patient with scleroderma. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

PHYSICAL FINDINGS

1. Skin
   - Tightening of the skin begins on the hands and then progresses to the forearms, face, and neck; the skin is shiny, taut, and sometimes red, with a loss of creases and hair. Skin involvement in scleroderma is subdivided into "limited" and "diffuse" cutaneous forms (Fig. ES1-14). Fig ES1-15 illustrates the method used to semi-quantify skin thickness in scleroderma.
   - Later, skin tightening may limit movement by causing flexion contractures of the fingers, wrists, and elbows. Perioral skin tightening (Fig. ES1-16) results in decreased oral aperture, furrowing around the lips, and dry membranes.
   - Pigmentary changes may occur.
   - Skin atrophy and digital gangrene of fingertips (Fig. S1-17) occurs during later stages.
2. Musculoskeletal.
   - Joint pain and swelling
   - Symmetric inflammatory arthritis.
   - Myopathy.
3. Gastrointestinal involvement.
   - Esophageal dysmotility with heartburn, dysphagia, and odynophagia.
   - Delayed gastric emptying.
   - Small-bowel dysmotility with abdominal cramps and diarrhea.
   - Colon dysmotility with constipation.
   - Primary biliary cirrhosis (see "Primary Biliary Cirrhosis" in Section I).
4. Pulmonary manifestations
   - Pulmonary fibrosis with symptoms of dyspnea and nonproductive cough as well as fine inspiratory crackles on examination.
   - Pulmonary hypertension.
5. Cardiac involvement.
   - Myocardial fibrosis that leads to congestive heart failure.
6. Renal involvement.
   - Malignant hypertension
   - Rapidly progressive renal failure.
7. Other organ involvement.
   - Hypothyroidism.
   - Erectile dysfunction.
   - Sjögren's syndrome.
   - Entrapment neuropathies.
8. CREST syndrome (term now replaced by lcSSc).
   - Calcinosis, Raynaud's syndrome, Esophageal dysmotility, Sclerodactyly (Fig. S1-18). Telangiectasias—with CREST syndrome, scleroderma is limited to the distal extremities. This acronym is now considered obsolete by many because it does not accurately reflect the burden of internal organ involvement.

CLINICAL PRESENTATION

- Raynaud's phenomenon: initial complaint in 70% of patients (NOTE: The prevalence of Raynaud's phenomenon is 5% to 10% in the general population; most cases do not progress to scleroderma).
- Finger or hand swelling that is sometimes associated with carpal tunnel syndrome.

- Arthralgias/arthritis.
- Internal organ involvement.

ETIOLOGY

The etiology of this condition is unknown. Genetic profiles show clustering of different alleles according to the subtype of SSc. There is abnormal selection of fibroblasts and aberrant control of connective tissue synthesis by fibroblasts and other cells. Although there are characteristic autoantibodies detected, it is not clear that they directly participate in the pathogenesis of the disease.

- Extracellular connective tissue activation.
- Frequent immunologic abnormalities including autoantibodies.
- Inflammation in the early stages of disease.
- Vasoconstriction.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

DERMATOLOGIC

- Scleredema.
- Amyloidosis.
- Porphyria cutanea tarda.
- Eosinophilic fasciitis.
- Reflex sympathetic dystrophy.
- Nephrogenic systemic fibrosis.

SYSTEMIC

- Idiopathic pulmonary fibrosis.
- Primary pulmonary hypertension.
- Primary biliary cirrhosis.
- Cardiomyopathies.
- Gastrointestinal dysmotility problems.
- Systemic lupus erythematosus and overlap syndromes.

WORKUP

Laboratory tests and imaging studies.

LABORATORY TESTS

- Antinuclear antibodies (homogeneous, speckled, or nucleolar patterns).
- Negative antibody to native DNA.
- Negative antismooth muscle antibody.
- Autoantibodies against ribonucleoprotein positive in 20% of patients.
- Rheumatoid factor positive in 20% of patients.
- Anticentromere antibodies in one third of patients with lcSSc.
- Positive extractable nuclear antibody to Scl-70 in 40% of patients with dcSSc.
- Routine biochemistry tests may indicate specific organ involvement (e.g., liver, kidney, muscle).

FIGURE S1-18 Sclerodactyly in a patient with systemic sclerosis. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

IMAGING AND OTHER STUDIES

1. Arthritis: joint radiographs.
2. Gastrointestinal.
   - Endoscopy (diagnostic procedure of choice; may be therapeutic).
   - Cine-esophagography (in rare circumstances).
   - Barium swallow (occasionally indicated).
   - Esophageal manometry (almost never necessary).
3. Pulmonary.
   - Chest x-ray.
   - Pulmonary function tests (especially single-breath diffusion capacity for CO).
   - Chest computed tomography (CT) scan.
   - Bronchoscopy with biopsy.
   - Gallium lung scan.
   - Bronchoalveolar lavage.
4. Heart.
   - ECG.
   - Ambulatory (Holter) ECG monitoring.
   - Echocardiography.
   - Cardiac catheterization.
5. Kidney: renal biopsy.
6. Skin: skin biopsy.

Rx TREATMENT

1. Fig. S1-19 illustrates management strategies in SSc. No disease-modifying therapy available. Immunosuppressive agents used in individual patients. Prednisone should be used with extreme caution, especially in doses >20 mg/day. Table S1-6 summarizes current recommendations for treatment of scleroderma.
2. Raynaud's syndrome:
   - Calcium channel blockers (i.e., long-acting dihydropyridines).
   - Peripheral α1-adrenergic blockers.
   - Angiotensin II receptor blockers.
   - Pentoxifylline.
   - Phosphodiesterase inhibitors.
   - Stellate ganglionic blockades.
   - Digital sympathectomy.
3. Arthralgias: nonsteroidal anti-inflammatory drugs.
4. Skin: for extensive skin fibrosis, immunomodulatory drugs have been used such as methotrexate, mycophenolate mofetil, and cyclophosphamide, but have not been proved to be beneficial.
5. Esophageal reflux.
   - H_2-receptor blockers.
   - Proton pump inhibitors.
6. Pulmonary hypertension and fibrosis.
   - Oxygen.
   - Diuretics (with caution).
   - Endothelin-1 receptor inhibitors (bosentan, ambrisentan).
   - Sildenafil, tadalafil.
   - Prostacyclin analogues (epoprostenol, iloprost, treprostinil).
   - Lung transplantation.
   - Cyclophosphamide chemotherapy for symptomatic scleroderma-related interstitial lung disease.
7. Renal involvement.
   - Angiotensin-converting enzyme inhibitors.
   - Dialysis.
   - Renal transplantation.

REFERRAL

Rheumatology consultation.

! PEARLS & CONSIDERATIONS

COMMENTS

- Plasmacytoid dendritic cells have been implicated in the pathogenesis of systemic sclerosis. CXCL4 is the predominant protein secreted by plasmacytoid dendritic cells in systemic sclerosis and could be used as a biomarker in systemic sclerosis. Plasma levels of CXCL4 are elevated in patients with systemic sclerosis and correlated with the presence and progression of complications, such as long fibrosis and pulmonary arterial hypertension.
- A recent trial of autologous hematopoietic stem cell therapy (HSCT) versus monthly cyclophosphamide in patients with early diffuse cutaneous systemic sclerosis showed better long-term event-free survival and overall survival at a median follow-up of approximately 6 years and clinically meaningful improvements in objective and patient reported outcome measures at 2 years with HSCT. However, there was greater treatment-related mortality.

RELATED CONTENT

Scleroderma (Patient Information)

AUTHOR: **EDWARD V. LALLY, M.D.**

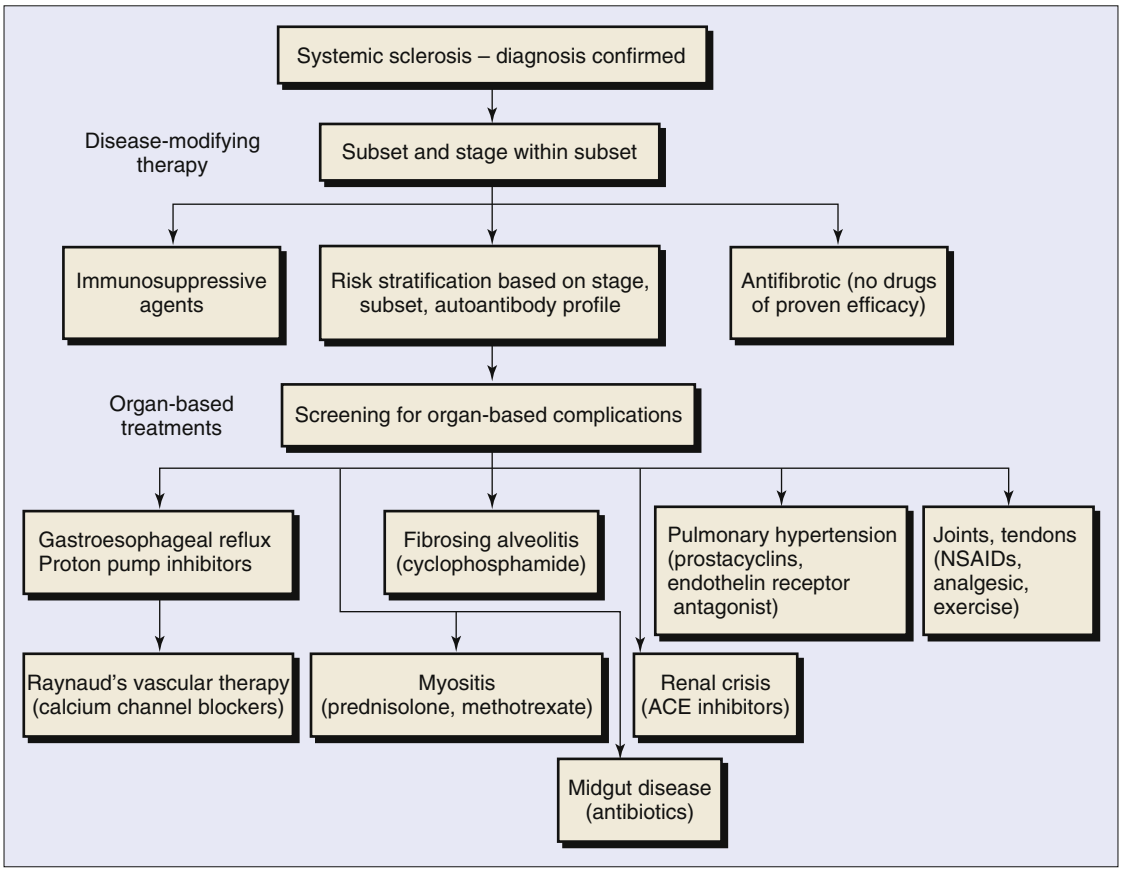


FIGURE S1-19 Management strategies in systemic sclerosis. *NSAIDs,* Nonsteroidal anti-inflammatory drugs. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

TABLE S1-6 Current Recommendations for Treatment of Scleroderma

Manifestation	Primary Therapy	Alternative/Second-Line Therapy
Raynaud's phenomenon	Vasodilators (CCB) Antiplatelet	PDE5 inhibitors, prostacyclin, endothelin antagonists
Hypertensive renal disease	ACE inhibitors	ARBs, CCB, prostacyclin, renal transplant (wait at least 24 mo)
GI involvement	**Upper GI** Dental/periodontal care, lifestyle modifications, proton pump inhibitors, prokinetics	EGD to treat stenosis and/or GAVE
	Lower GI Probiotics, rotational antibiotics	Total parenteral nutrition
Skin	Mycophenolate mofetil, cyclophosphamide	IVIG, ATG, research trial (severe cases)
Interstitial lung disease	Cyclophosphamide, mycophenolate mofetil, azathioprine	Research trial
Pulmonary arterial hypertension	PDE5 inhibitors, endothelin antagonists, prostacyclin	Combination therapy, atrioseptostomy, lung transplant, research trial
Cardiac involvement	Heart failure therapy, diuretics, CCB	Immunosuppression (myocardial inflammation)
Joints	Prednisone, methotrexate, TNF inhibitors	IVIG (if contractures and rubs are present), PT/OT
Muscles	Prednisone, methotrexate, azathioprine	IVIG
Psychosocial	Antidepressants, pain control, sleep control	Support group

ACE, Angiotensin-converting enzyme; *ARBs*, angiotensin receptor blockers; *ATG,* antithymocyte globulin; *CCB,* calcium channel blockers; *EGD,* esophagogastroduodenoscopy; *GAVE,* gastric antral vascular ectasia; *GI,* gastrointestinal; *HSCT,* hematopoietic stem cell transplantation; *IVIG,* intravenous immunoglobulin; *PDE5,* phosphodiesterase-5 inhibitor; *PT/OT,* physical therapy/occupational therapy; *TNF,* tumor necrosis factor.
From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.

SUGGESTED READINGS

Gabrielli A et al.: Scleroderma, *N Engl J Med* 360:1989–2003, 2009.
Herrick AL et al.: Observational study of treatment outcome in early diffuse cutaneous systemic sclerosis, *J Rheumatol* 37:116, 2010.
Khanna D Georges GE, Couriel DR: Autologous hematopoietic stem cell therapy in severe systemic sclerosis, Ready for Clinical Practice? *JAMA* 311, 2014. 2485–2485.
Van Laar JM et al.: Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial, *JAMA*, 2014. http://dx.doi.org/1001/JAMA. 6368.
Van Bon L et al.: Proteome-wide analysis and CXCL4 as a biomarker in systemic sclerosis, *N Engl J Med* 370:433–443, 2014.

FIGURE ES1-14 Skin involvement in scleroderma is subdivided into "limited" and "diffuse" cutaneous forms. A, Sclerodactyly in limited cutaneous disease. **B,** Truncal changes in diffuse cutaneous disease. **C,** Inflammatory signs in early active skin disease. **D,** Finger contracture in the chronic fibrotic phase of skin involvement in scleroderma. (From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

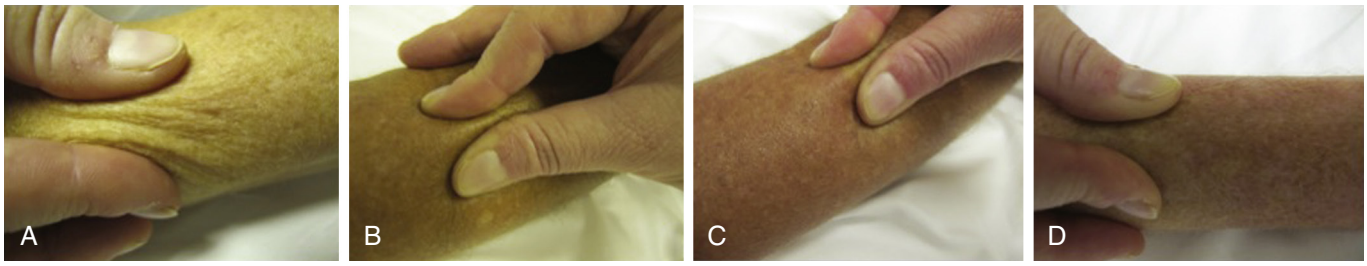


FIGURE ES1-15 Method used to semi-quantify skin thickness in scleroderma. The modified Rodnan skin score is obtained by clinical palpation of 17 different body areas (fingers, hands, forearms, upper arms, chest, abdomen, thighs, lower legs, and feet) and subjective averaging of the thickness of each specific site: 0 = normal **(A)**; 1 = mild **(B)**; 2 = moderate **(C)**; and 3 = severe **(D)**. The maximum score is 51. (From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

FIGURE ES1-16 Oral manifestations. A, Perioral skin tightening with decreased oral aperture, furrowing around the lips, and dry membranes. **B,** Periodontal disease with regression of gum and loosening of teeth. **C** and **D,** Telangiectasias on lips and tongue. (From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

BASIC INFORMATION

DEFINITION

Scoliosis is a lateral curvature of the spine in the upright position, usually 10 degrees or greater. Scoliosis may be classified as either structural (fixed, nonflexible) or nonstructural (flexible, correctable).

ICD-9CM CODES

737.30 Idiopathic scoliosis
737.39 Paralytic scoliosis
754.2 Congenital scoliosis
737.43 Associated with neurofibromatosis

ICD-10CM CODES

M41 Scoliosis
M41.0 Infantile idiopathic scoliosis
M41.1 Juvenile idiopathic scoliosis
M41.3 Thoracogenic scoliosis
M41.20 Other idiopathic scoliosis, site unspecified
M41.80 Other forms of scoliosis, site unspecified
Q67.5 Congenital deformity of spine
M41.40 Neuromuscular scoliosis, site unspecified

EPIDEMIOLOGY & DEMOGRAPHICS (IDIOPATHIC FORM)

PREDOMINANT SEX: The incidence of scoliosis is the same in males and females; however, females have up to a 10-fold greater risk of curve progression.

PREVALENCE: Four cases per 1000 persons. Idiopathic scoliosis is present in 2% to 4% of adolescents.

PREDOMINANT AGE

- Onset variable.
- Most curves found in adolescents (age ≥11 yr).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Record patient age (in years plus months) and height.
- Perform neurologic examination to rule out neuromuscular disease.
- Inspect the shoulders and iliac crests to determine if they are level.
- Palpate the spinous processes to determine their alignment.
- Have the patient bend forward symmetrically at the waist with the arms hanging free (Adams' position); observe from the back or front to detect abnormal spine rotation (Fig. S1-20).

ETIOLOGY

- 90% unknown, usually referred to as *idiopathic* (genetic).
- Congenital spine deformity.
- Neuromuscular disease.
- Leg-length inequality.
- Local inflammation or infection.
- Acute pain (disk disease).
- Chronic degenerative disk disease with asymmetric disk narrowing.

Curves of an idiopathic nature or those accompanying congenital deformity or neuromuscular disease are associated with structural changes. The nonstructural types (leg-length discrepancy, inflammation, or acute pain) disappear when the offending disorder is corrected.

DIAGNOSIS

WORKUP

- Curvatures associated with congenital spine abnormalities, neuromuscular disease, and other less common forms of scoliosis can usually be identified by history or associated radiographic or physical findings.
- The diagnosis of scoliosis is suspected on the basis of physical examination and confirmed by radiography performed while the patient is in a standing position. Physical examination with the Adams' forward bend test and scoliometer measurement can identify scoliosis and the radiologic testing for Cobb angle measurement can confirm the diagnosis. The Risser grade measures ossification. It consists of 5 grades ranging from 25% ossification in grade 1 to fusion of ossified epiphysis to the iliac wing in grade 5. Scoliosis screening is described in Fig. S1-21.

IMAGING STUDIES

- Diagnosis of idiopathic scoliosis is confirmed by a standing roentgenogram of the spine.
- Severity of the curve is measured in degrees, usually by the Cobb method (Fig. S1-22).
- MRI is usually not indicated unless there is pain, a neurologic deficit, or a left thoracic curve (which is often associated with an underlying spinal disorder).

TREATMENT

ACUTE GENERAL Rx

- Treatment or correction of cause if curve is nonstructural.
- Early detection is key in treating genetic curve.
- Regular observation for curves <20 degrees.
- Bracing for idiopathic curves of 25 to 45 degrees in patients with an immature skeleton to prevent progression.
- Surgery for idiopathic curves >45 degrees in patients with an immature skeleton.

DISPOSITION

- The larger the curve at detection, the greater the chance of progression.
- Progression is more common in young children who are beginning their growth spurt.
- Curves in females are more likely to progress.
- Curves <20 degrees will improve spontaneously >50% of the time.
- Failure to diagnose and treat these curves may allow progressive deformity, pain, and cardiopulmonary compromise to develop.
- Spinal deformities >50 degrees in adults may progress and eventually become painful.
- There is no difference in the rate of back pain in the general population and patients with adolescent idiopathic scoliosis.

REFERRAL

For orthopedic consultation if structural curve is present.

PEARLS & CONSIDERATIONS

COMMENTS

- Congenital scoliosis has a high incidence of cardiac and urinary tract abnormalities.
- Bracing is not intended to completely straighten the idiopathic curve. It may improve the curvature, but is mainly used to stabilize and prevent progression.
- The initial Cobb angle magnitude (≥25 degrees) is the most important predictor of long-term curve progression.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Scoliosis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

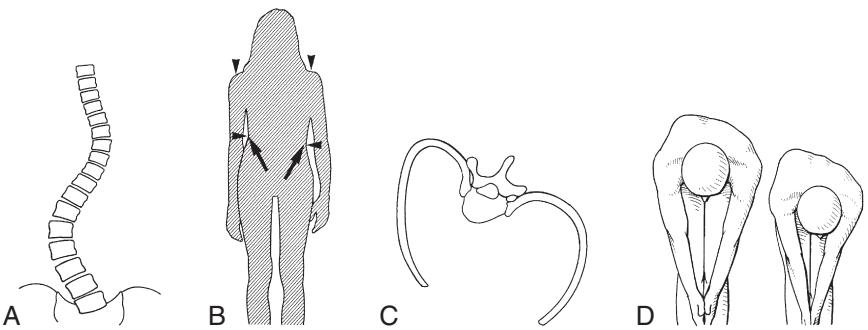
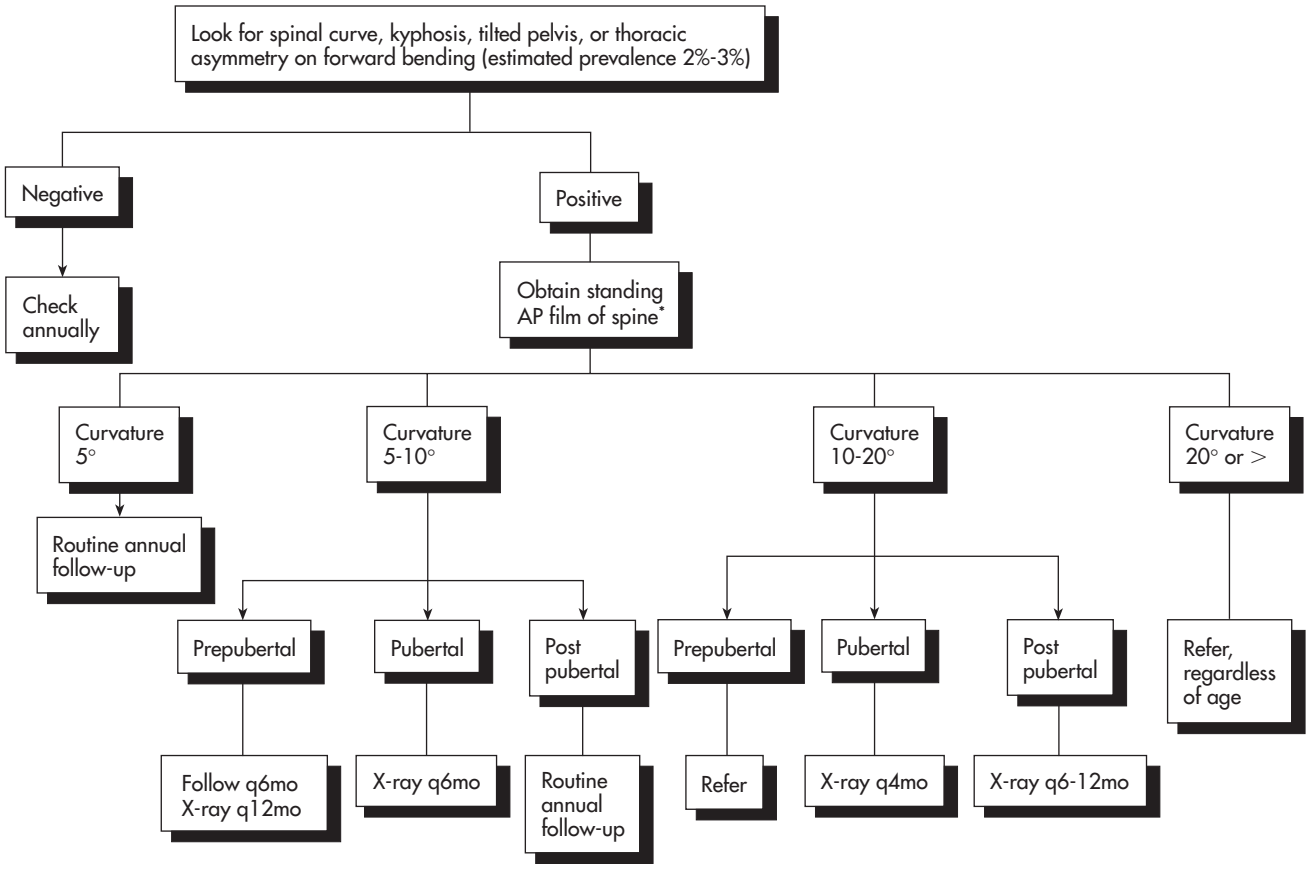


FIGURE S1-20 Structural changes in idiopathic scoliosis. A, As curvature increases, alterations in body configuration develop in both the primary and compensatory curve regions. **B,** Asymmetries of shoulder height, waistline, and the elbow-to-flank distance are common findings. **C,** Vertebral rotation and associated posterior displacement of the ribs on the convex side of the curve are responsible for the characteristic deformity of the chest wall in scoliosis patients. **D,** In the school screening examination for scoliosis, the patient bends forward at the waist. Rib asymmetry of even a small degree is obvious. (From Scoles PV: Spinal deformity in childhood and adolescence. In Behrman RE, Vaughn VC III [eds]: *Nelson textbook of pediatrics*, ed 5, Philadelphia, 1989, Saunders.)



*Cobb method of angle measurement.

1. Find the lowest vertebra whose bottom tilts toward concavity of curve.
2. Erect a perpendicular line from extension of bottom surface.
3. Find highest vertebra as in #1 and erect perpendicular from extension of top surface.
4. Measure intersecting angle = angle of scoliosis.

FIGURE S1-21 Scoliosis screening and follow-up. *AP,* Anteroposterior. (From Driscoll C [ed]: *The family practice desk reference,* ed 3, St Louis, 1996, Mosby.)

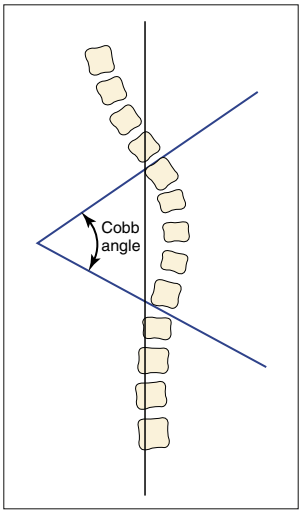


FIGURE S1-22 Cobb angle. This is measured using the superior and inferior end plates of the most tilted vertebrae at the end of each curve. (From Tschudy MM, Arcara KM: *The Harriet Lane handbook,* ed 19, Philadelphia, 2012, Mosby.)

SUGGESTED READINGS

Davids JR et al.: Indications for magnetic resonance imaging in presumed adolescent idiopathic scoliosis, *J Bone Joint Surg Am* 86A:2187, 2004.

Fernandes P, Weinstein SL: Natural history of early onset scoliosis, *J Bone Joint Surg Am* 89A(suppl 1):21, 2007.

Gillingham BL et al.: Early onset idiopathic scoliosis, *J Am Acad Orthop Surg* 14:101, 2006.

Helenius I et al.: Long-term health-related quality of life after surgery for adolescent idiopathic scoliosis and spondylolisthesis, *J Bone Joint Surg Am* 90A:1231, 2008.

Horne JP, Flannery R, Usman S: Adolescent idiopathic scoliosis: diagnosis and management, *Am Fam Phys* 89(3):193–198, 2014.

Hresko MT: Idiopathic scoliosis in adolescents, *N Engl J Med* 368:834–841, 2013.

Lenke LG, Dobbs MB: Management of juvenile idiopathic scoliosis, *J Bone Joint Surg Am* 89A(suppl 1):55, 2007.

Richards BS, Vitale MG: Screening for idiopathic scoliosis in adolescents, *J Bone Joint Surg Am* 90A:195, 2008.

Sanders JO et al.: Predicting scoliosis progression from skeletal maturity: a simplified classification during adolescence, *J Bone Joint Surg Am* 90A:540, 2008.

Sengupta DK, Webb JK: Scoliosis, the current concepts, *Indian J Orthop* 44(1):5, 2010.

Ugwonali OF et al.: Effect of bracing on the quality of life of adolescents with idiopathic scoliosis, *Spine J* 4:254, 2004.

Weinstein JL et al.: Effects of bracing in adolescents with idiopathic scoliosis, *N Engl J Med* 369:1512–1521, 2013.

BASIC INFORMATION

DEFINITION

Recurrent depressive episodes during autumn and winter alternating with nondepressive episodes during spring and summer. Patients with seasonal affective disorder (SAD) have experienced two episodes of major depression in the past 2 yr that demonstrate the temporal seasonal relations and have had no nonseasonal episodes over this period.

SYNONYMS

SAD
Seasonal depression
Winter depression
Wintertime blues

ICD-9CM and DSM-5 CODES

296.30 Major depressive affective disorder, recurrent episode, unspecified degree

ICD-10CM CODES

F33 Recurrent depressive disorder
F33.0 Recurrent depressive disorder, current episode, mild
F33.1 Recurrent depressive disorder, moderate
F33.2 Recurrent depressive disorder, severe without psychotic symptoms
F33.3 Recurrent depressive disorder, severe with psychotic symptoms
F33.4 Recurrent depressive disorder, currently in remission
F33.9 Recurrent depressive disorder, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Climate, genetic vulnerability, and sociocultural factors all play a role. The risk of seasonal mood swings is clearly associated with northern latitudes. The prevalence of SAD is estimated to be 0.5% to 1.5% in northern European populations, but up to 10% to 20% of these populations report milder, recurrent episodes consistent with subsyndromal SAD. In the United States, it is estimated that about 5% of the population experiences SAD.
- As with other depressive disorders, women are affected disproportionately.
- Younger age, as well as greater familiarity with SAD, is associated with increased prevalence.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The symptoms of SAD can be identical to those of other depressive episodes, but tend to include features associated with atypical major depression, including low energy, irritability, weight gain, and overeating. The onset of neurovegetative symptoms often precedes the onset of cognitive and affective symptoms.
- Average duration is 5 mo, generally beginning in November.

ETIOLOGY

- Explanations focus on diathesis-stress models. An interaction between biologic and cognitive-affective factors appears to contribute to SAD. Retinal sensitivity anomalies and emotional reactivity to light stimuli, genetic variables predisposing to seasonal shift in sleep patterns in response to shorter photoperiod, circadian rhythm disturbance, and irregularities in melatonin and melatonin-serotonin interaction have been identified as potential risk factors. Shorter photoperiod and decrease in sunlight are hypothesized to be the triggers.
- Several neurotransmitters implicated, including dopamine, serotonin, and norepinephrine.
- Cognitive risk factors include elevated rumination and negative cognitions related to the winter season and its impact on one's mood.
- Low activity and exercise levels, which are also implicated in nonseasonal depression, have been shown in some studies to characterize SAD.

DIAGNOSIS

Diagnostic workup similar to that for major depression.

DIFFERENTIAL DIAGNOSIS

- Major depressive disorder.
- Minor depression or adjustment disorder.
- Bipolar affective disorder.
- Evaluate for substance use (especially alcohol).
- Medical illness or medications that may contribute to depression (e.g., endocrine disorders, neurologic disease).

WORKUP

- As with major depression, consider medical etiologies and rule out as indicated by the presenting signs and symptoms. Consider endocrine evaluation, especially thyroid function; sleep studies and a toxicology screen might be considered.
- Structured Interview Guide for the Hamilton Depression Rating Scale–Seasonal Affective Disorders Version (SIGH-SAD) used in research settings.
- In patients with major depressive disorder treated longitudinally, the routine use of depression scales to monitor outcome can help identify seasonal fluctuations of symptoms.

LABORATORY TESTS

As directed by presenting symptoms.

IMAGING STUDIES

Generally not indicated.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Phototherapy presupposes that artificial light at a similar strength to natural sunlight will prevent the biologic changes that mediate SAD.
- Many studies have demonstrated efficacy of light therapy in individuals with SAD. Recent studies indicate that light therapy may also be efficacious, with various subtypes of depression, including both melancholic and atypical, and for individuals with nonseasonal depression.
- Light therapy may be used as a first-line treatment; choice of light therapy versus medication or psychotherapy depends on various factors, however, including severity of symptoms and suicidality, prior response to medication or light therapy, feasibility, and patient preference.
- Some studies showing retinal sensitivity anomalies in SAD normalize following phototherapy.
- Phototherapy tends to use 2500 to 10,000 lux delivered by a commercial light box or a portable head-mounted unit. Phototherapy is recommended to begin within 2 wk of the start of symptoms and continue through the winter months. Patients are instructed to sit ~18 in from the light box for 30 min up to several hours once or twice per day for a minimum of 1 wk.
- A recent meta-analysis demonstrated efficacy of high-density negative ions in reducing depressive severity, although further research is needed to determine whether efficacy is comparable to light therapy.
- Small trials have demonstrated the efficacy of cognitive-behavioral therapy tailored specifically for SAD, either alone or with possible additive effects to light therapy. CBT for SAD appears to operate through distinct mechanisms than light therapy (e.g., reducing rumination and negative SAD-related cognitions). Patients with elevated cognitive symptoms of depression may benefit from CBT or combined CBT with light therapy over light therapy alone, but further research is needed.

PHARMACOLOGIC THERAPY

Bupropion effective in preventing recurrence.

ACUTE GENERAL Rx

Necessary if patient is suicidal.

CHRONIC Rx

- Growing support for use of SSRIs for SAD (e.g., fluoxetine, sertraline), although more research is needed.
- Preliminary studies demonstrated efficacy of novel antidepressants that act on melatonin (i.e., agomelatine), but further research is needed.

DISPOSITION

Psychiatric referral may be helpful to confirm diagnosis. Recommended for high-risk and suicidal patients.

REFERRAL

For active suicidal ideation, psychosis, symptoms suggestive of bipolar disorder.

PEARLS & CONSIDERATIONS

Patients with SAD may present with a complaint of overeating, particularly food high in carbohydrates.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Seasonal Affective Disorder (SAD) (Patient Information)

AUTHORS: **MARK ZIMMERMAN, M.D.,** and **CATHERINE D'AVANZATO, PH.D.**

SUGGESTED READINGS

Golden RN et al.: The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence, *Am J Psychiatry* 162(4):656, 2005.

Kurlansik SL, Ibay AD: Seasonal affective disorder, *Am Fam Physician* 86(11):1037–1041, 2012.

Lurie SJ et al.: Seasonal affective disorder, *Am Fam Physician* 74(9):1521–1524, 2006.

Rohan KJ et al.: A randomized controlled trial of cognitive-behavioral therapy, light therapy, and their combination for seasonal affective disorder, *J Consult Clin Psychol* 75(3):489, 2007.

Westrin A, Lam RW: Seasonal affective disorder: a clinical update, *Ann Clin Psychiatry* 19(4):239, 2007.

Seborrheic Dermatitis (SD) PTG

BASIC INFORMATION

DEFINITION

Seborrheic dermatitis (SD) is a common, inflammatory skin condition characterized by a mild to severe rash with scaling and erythema that occurs in areas of the skin rich in sebaceous glands.

SYNONYMS

SD
Dandruff
Cradle cap (Fig. S1-23)
Sebopsoriasis
Seborrheic eczema
Pityriasis capitis
Seborrhea

ICD-9CM CODES
690.10 Seborrheic dermatitis
ICD-10CM CODES
L21.9 Seborrheic dermatitis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Affects 3% to 5% of otherwise healthy adults.
PREDOMINANT SEX AND AGE: Can occur from infancy through old age, with peak incidence in adolescents and young adults and increasing again after age 50 yr. More common in men than women.
RISK FACTORS: More common in patients with HIV/AIDS, Parkinson's disease, other neurologic disorders, mood disorders, chronic alcoholic pancreatitis, hepatitis, cancer, and genetic disorders (e.g., Down syndrome). Occurs more often during winter season.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Mild, greasy scaling of the scalp and nasolabial folds (Fig. S1-24), postauricular skin, beard area, eyebrows, trunk, and sometimes the central face. Blepharitis, otitis externa, and coexisting acne vulgaris or pityriasis may also be present. Itching and stinging of lesions can occur. Increased occurrence during times of stress or sleep deprivation.

ETIOLOGY

Actual etiology is unknown but has been linked to hormone levels, fungal infections, altered immune function, nutritional deficits, and neurogenic factors. Fungal infections of the *Malassezia* species have been associated with SD, and the skin changes are thought to result from an inflammatory response to malassezia yeast.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Atopic dermatitis.
- Candidiasis.
- Dermatophytosis.
- Impetigo.
- Psoriasis.
- Rosacea.
- Systemic lupus erythematosus.
- Tinea infection.
- Contact dermatitis.
- Nummular dermatitis.

WORKUP

- Diagnosis usually based on clinical identification of lesions.
- Skin biopsies can be performed, if warranted, to distinguish SD from similar disorders

LABORATORY TESTS

Microscopic examination with special stains can be used to determine if yeast cells are present in keratinocytes.

FIGURE S1-24 Seborrheic dermatitis. (From Swartz MH: *Textbook of physical diagnosis,* ed 7, Philadelphia, 2014, Saunders, 2014.)

FIGURE S1-23 Cradle cap in an infant. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Patient education that SD is a chronic condition and treatment is aimed at resolving lesions but does not prevent recurrence.
- General recommendations: wash skin regularly, soften and remove scales, and apply moisturizing emollients after washing.
- Scale removal can be accomplished through the application of mineral or olive oil and removed with a comb or brush after 1 hr.

ACUTE GENERAL Rx

- Topical steroids: can be in the form of shampoos, creams, or ointments. Can be used alone or in more severe SD with antifungals.
- Antifungals (e.g., Nizoral, selenium sulfide, ketoconazole [the most evidence for effectiveness among antifungals], ciclopirox, fluconazole). Reserve oral antifungal therapy for patients with widespread SD or SD that is refractory to topical therapy. Itraconazole 200 mg/day for 7 days is a sample oral regimen.
- Calcineurin inhibitors (e.g., tacrolimus ointment, pimecrolimus cream): good when face and ears are affected.
- Keratolytics (e.g., tar, salicylic acid, zinc pyrithione).
- Treatment of any secondary bacterial infection with oral antibiotics.

CHRONIC Rx

Recalcitrant SD: topical azole combined with desonide regimen (limit use to 2 wk), pimecrolimus cream.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Tea tree oil (melaleuca oil).

REFERRAL

Consider referral to dermatology for recalcitrant cases or uncertain diagnosis

PEARLS & CONSIDERATIONS

- Use a combination of topical steroids and antifungal cream for severe SD.
- Limit use of steroids to 2-wk course of treatment due to risk of cutaneous atrophy and telangiectasias.
- SD of the scalp can be treated with an antifungal (e.g., 2% ketoconazole) or keratolytic shampoo. Limit use of antifungal shampoos to twice a week to prevent drying of the scalp. Alternate the use of antifungal shampoos with a moisturizing shampoo.
- In patients with widespread SD, consider testing for HIV infection.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **ANNGENE G. ANTHONY, M.D., M.P.H.**

SUGGESTED READINGS

Clark GW et al.: Diagnosis and treatment of seborrheic dermatitis, *Am Fam Physician* 91(3):185–190, 2015.

Finnish Medical Society Duodecim. Seborrhoeic dermatitis. In: EBM Guidelines. Evidence-based medicine. Wiley Interscience: Helsinki, Finland.

Gupta AK et al.: Seborrheic dermatitis, *J Eur Acad Dermatol Venereol* 18:13–26, 2004.

Naldi L, Rebora A: Seborrheic dermatitis, *N Engl J Med* 360:387–396, 2009.

National Institute for Health and Care Excellence: *Clinical knowledge summaries: seborrhoeic dermatitis.* www.cks.nhs.uk/seborrhoeic_dermatitis, 2011 (Accessed 2011).

Schwartz RA et al.: Seborrheic dermatitis: an overview, *Am Fam Physician* 74:125–130, 2006.

BASIC INFORMATION

DEFINITION

Sepsis is an exaggerated inflammatory response to an infectious stimulus. It is generally caused by generalized bacterial or fungal infection and characterized by evidence of infection, fever or hypothermia, hypotension, and evidence of end-organ compromise.

SYNONYMS

Septicemia
Sepsis syndrome
Severe sepsis
Systemic inflammatory response syndrome
Septic shock

ICD-9CM CODES
038.9 Sepsis
038.40 Sepsis, gram-negative bacteremia
038.1 Sepsis, *Staphylococcus*
ICD-10CM CODES
A41.9 Sepsis, unspecified organism
A41.50 Gram-negative sepsis, unspecified
A41.2 Sepsis due to unspecified *Staphylococcus*

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.)
- Exact incidence is unknown.
- Approximately 750,000 cases of severe sepsis occur among hospitalized patients each year in the United States.
- Complicates a minority of bacteremia cases and may occur in the absence of documented bacteremia.

PREDOMINANT SEX: Males slightly more commonly affected than females.

PREDOMINANT AGE
- Neonatal period.
- Patients >65 yr of age account for 60% of all cases of severe sepsis.

GENETICS
- Familial disposition: a great variety of congenital immunodeficiency states and other inherited disorders may predispose to septicemia.
- Neonatal infection: incidence is high in neonatal period.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fever or hypothermia.
- Hypotension.
- Tachycardia.
- Tachypnea.
- Altered mental status.
- Bleeding diathesis.
- Skin rashes.
- Symptoms that reflect primary site of infection: urinary tract, GI tract, CNS, respiratory tract.
- Table S1-7 describes some clinical signs and symptoms of sepsis.

ETIOLOGY

- Disseminated infection with a great variety of bacteria:
  A. Gram-negative bacteria.
     1. *Escherichia coli.*
     2. *Klebsiella* spp.
     3. *Pseudomonas aeruginosa.*
     4. *Proteus* spp.
     5. *Neisseria meningitides.*
  B. Gram-positive bacteria.
     1. *Staphylococcus aureus* (including MRSA).
     2. *Streptococcus* spp.
     3. *Enterococcus* spp.
- Less common infections:
  1. Fungal.
  2. Viral.
  3. Rickettsial.
  4. Parasitic.
- Sepsis is a complex dysregulation of both inflammation and coagulation. There is activation of coagulation, inflammatory cytokines, complement, and kinin cascades with release of a variety of vasoactive endogenous mediators.
- Predisposing host factors:
  1. General medical condition.
  2. Extremes of age.
  3. Immunosuppressive therapy.
  4. Recent surgery.
  5. Granulocytopenia.
  6. Hyposplenism.
  7. Diabetes.
  8. Instrumentation.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cardiogenic shock.
- Acute pancreatitis.
- Pulmonary embolism.
- Systemic vasculitis.
- Toxic ingestion.
- Exposure-induced hypothermia.
- Fulminant hepatic failure.
- Collagen-vascular diseases.

WORKUP

- Evaluation should focus on identifying a specific pathogen and localizing the site of primary infection. Fig. ES1-25 illustrates workup following results of blood cultures.
- Hemodynamic, metabolic, coagulation disorders should be carefully characterized.
- Intensive monitoring, including the use of central venous catheters.

LABORATORY TESTS

- Cultures of blood and examination and culture of sputum, urine, wound drainage, stool, and CSF, depending on the presenting signs and symptoms for each patient.
- CBC with differential, coagulation profile.
- Routine chemistries, LFTs.
- ABGs, lactic acid level; procalcitonin might be useful as a general marker of infection/sepsis.
- Urinalysis.

IMAGING STUDIES

- Chest x-ray examination.
- Other radiographic and radioisotope procedures according to suspected site of primary infection.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Tissue oxygenation: mixed venous oxygen saturation maintained >70% if possible; early mechanical ventilation with low title volume (6 ml/kg predicted body weight) to protect lung parenchyma from overstretching and "volutrauma."
- Focal infection should be drained if possible, and potentially infected catheters should be removed.

ACUTE GENERAL Rx

- Blood pressure support, rapid IV fluid resuscitation and vasopressors, if needed, with the goal of reestablishing a mean arterial blood pressure >65 mm Hg; reduction in blood lactate and improved mixed venous oxygen saturation >70% within 6 hr of recognition of septic shock is associated with improved survival. If possible, measure vena cava oxygen saturation ($ScvO_2$) to assess adequacy of resuscitation. If the $ScvO_2$ is <70%, consider

TABLE S1-7 Clinical Signs and Symptoms of Sepsis

Infection	General	Inflammatory	Hemodynamic	Tissue Perfusion
Documented or suspected	Temperature >38°C or <36°C Heart rate >90 beats/min Respiratory rate ≥20 breaths/min Altered mental status Hyperglycemia Third spacing of fluid	WBC count <4000 or >12,000 cells/mcL or ≥10% bands	Hypotension: systolic blood pressure <90 mm Hg MAP <70 mm Hg SV_{O_2} >70 CI >3.5 L/min/m^2	Hypoxemia: (Pao_2/Fio_2 <300) Acute oliguria (urine output <0.5 ml/kg/hr) Coagulopathy Abnormal liver function tests Platelet count <100,000 cells/μL Lactic acidosis Skin mottling

CI, Cardiac index; *MAP,* mean arterial pressure; *SVo_2,* mixed venous oxygen saturation; *WBC,* white blood cell.
From Cameron, JL, Cameron AM: *Current surgical therapy*, ed 10, Philadelphia, 2011, Saunders.

TABLE S1-8 Initial Antibiotic Recommendations for Septic Patients*

Empiric coverage	Vancomycin 15 mg/kg q12h plus either piperacillin-tazobactam† 3.375 g IV q6h or imipenem 0.5 g IV q6h or meropenem 1.0 g IV q8h with or without an aminoglycoside (e.g., tobramycin 5 mg/kg IV q24).‡
Community-acquired pneumonia	Ceftriaxone 1 g IV q24h plus azithromycin 500 mg IV q24h or a fluoroquinolone (e.g., moxifloxacin 400 mg IV q24h or levofloxacin 750 mg IV q24h).§
Community-acquired urosepsis	Ciprofloxacin 400 mg IV q24h or ampicillin 2 g IV q6h plus gentamicin 5 mg/kg IV q24h.
Meningitis	Vancomycin 500-750 mg IV q6h plus ceftriaxone 2 g IV q12h plus dexamethasone 0.15 mg/kg IV q6h × 2-4 days preferably before antibiotics; add ampicillin 2 g IV q4h if *Listeria* is suspected.
Nosocomial pneumonia	Vancomycin 15 mg/kg q12h plus either piperacillin-tazobactam 4.5 g IV q6h or imipenem 0.5 g IV q6h or meropenem 1 g IV q8h or cefepime 2 g IV q12h plus either an aminoglycoside (e.g., amikacin 15 mg/kg IV q24h or tobramycin 7 mg/kg IV q24h) or levofloxacin 750 mg IV q24h. Some authorities would substitute linezolid 600 mg IV q12h for vancomycin if methicillin-resistant *Staphylococcus aureus* is of significant concern or known to be the cause.
Neutropenia	Cefepime 2 g IV q8h; add vancomycin 15 mg/kg IV q12h if a central line is present and infection is a concern. Add antifungal coverage with liposomal amphotericin B 3-5 mg/kg q24h or caspofungin 70 mg IV × 1 then 50 mg IV q24h if fever persists $5 days. If invasive aspergillosis is highly suspected or proven, voriconazole 6 mg/kg IV q12h × 2 then 4 mg/kg IV q12h should be used.
Cellulitis and skin infections	Vancomycin 15 mg/kg IV q12h. Add piperacillin-tazobactam 4.5 g IV q6h in diabetics or immunocompromised patients. If necrotizing fasciitis is suspected, add clindamycin 900 mg IV; surgical debridement is crucial.

*Assumes normal renal function; dose adjustments required with impaired creatinine clearance.
†Substitute aztreonam 2 g IV q8h if penicillin allergic.
‡Monitor drug levels of aminoglycosides (i.e., peak and trough).
§Use ceftriaxone and azithromycin if the patient is admitted to the intensive care unit.
From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.

packed red blood cell transfusion to achieve Hct >30%. Start inotropic agents (dobutamine) if $ScvO_2$ is <70% despite transfusion and adequate fluid resuscitation.

1. IV hydration; crystalloids are as effective as colloids as resuscitation fluids, give 30 ml/kg IV if fluid depletion is suspected. Most patients need 4 to 6 L of fluid in the first 6 hours. Trials have shown that resuscitation with balanced crystalloids or albumin compared with other fluids seems to be associated with reduced mortality and that albumin replacement in addition to crystalloids alone does not improve the rate of survival at 28 and 90 days.
2. Therapy with vasopressors (e.g., norepinephrine, epinephrine, vasopressin) if mean arterial blood pressure of >65 mm Hg cannot be maintained by hydration alone. A recent trial comparing low-dose vasopressin with norepinephrine revealed that low-dose vasopressin did not reduce mortality rates as compared with norepinephrine among patients with septic shock who were treated with catecholamine vasopressors.

- Correction of acidosis by improving the tissue perfusion, not by giving bicarbonate
  1. Mechanical ventilation as needed.
- Antibiotics
  1. Directed at the most likely sources of infection. Table S1-8 describes initial antibiotic recommendations for septic patients.
  2. Should generally provide broad coverage of gram-positive and gram-negative bacteria (or fungi if clinically indicated).
  3. Antibiotics should be administered within 1 hr of the diagnosis of septic shock—this is a medical emergency.
  4. The role of corticosteroids in the acute management of septicemia has long been debated. Previous trials had shown that corticosteroid therapy improved hemodynamic outcomes in patients with severe septic shock. Patients with relative adrenal insufficiency may benefit from low-dose therapy with hydrocortisone (200 mg IV by continuous infusion for 7 days). Recent trials, however, revealed that hydrocortisone did not improve survival or reversal of shock, either overall or in patients who did not have a response to corticotropin, although hydrocortisone hastened reversal of shock in patients in whom shock was reversed. Until definitive data are available, the decision to administer corticosteroids for septic shock should be based on the individual patient's severity of illness versus risk of corticosteroid administration. The corticotropin (ACTH) stimulation test is not helpful and should not be used to determine the need for corticosteroid in these patients.
- Blood transfusion: A lower hemoglobin threshold is preferred. Trials have shown that among patients with septic shock, mortality at 90 days and rates of ischemic events and use of life support is similar among those assigned to blood transfusion at a higher hemoglobin threshold (hemoglobin level of 9 g/dL or less) and those assigned to blood transfusion at a lower threshold (hemoglobin level of 7 g/dL or less).

CHRONIC Rx

- Adjust antibiotic therapy on the basis of culture results.
- In general, continue antibiotic therapy for a minimum of 7 to 10 days.
- If hyperglycemia develops during treatment start continuous insulin IV infusion, maintain blood glucose in the 110-180 mg/dl level, and avoid insulin-induced hypoglycemia.

DISPOSITION

All patients with sepsis should be hospitalized and given access to intensive monitoring and nursing care.

REFERRAL

- To infectious diseases expert.
- To physician experienced in critical care.

PEARLS & CONSIDERATIONS

COMMENTS

- Mortality rises quickly if antibiotic therapy is not instituted promptly (preferably within 1 hr of onset of shock) and metabolic derangements are not treated aggressively.
- Human recombinant activated protein C (drotrecogin alfa activated) was taken off the market as a treatment for sepsis after follow up studies showed no added benefit to standard sepsis care.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **STEVEN M. OPAL, M.D.**

EVIDENCE

Abstract[1]

Objective:

To evaluate the effects of single-dose etomidate on the adrenal axis and mortality in patients with severe sepsis and septic shock.

Design:

A systematic review of randomized controlled trials and observational studies with meta-analysis.

Setting:

Literature search of EMBASE, Medline, Cochrane Database, and Evidence-Based Medical Reviews.

Subjects:

Sepsis patients who received etomidate for rapid sequence intubation.

Interventions:

None.

Measurements and Main Results:

We conducted a systematic review of randomized controlled trials and observational studies with meta-analysis assessing the effects of etomidate on adrenal insufficiency and all-cause mortality published between January 1950 and February 2012. We only examined studies including septic patients. All-cause mortality served as our primary end point, whereas the prevalence of adrenal insufficiency was our secondary end point. Adrenal insufficiency was determined using a cosyntropin stimulation test in all studies. We used a random effects model for analysis; heterogeneity was assessed with the I2 statistic. Publication bias was evaluated with Begg's test. Five studies were identified that assessed mortality in those who received etomidate. A total of 865 subjects were included. Subjects who received etomidate were more likely to die (pooled relative risk 1.20; 95% confidence interval 1.02-1.42; Q statistic, 4.20; I2 statistic, 4.9%). Seven studies addressed the development of adrenal suppression associated with the administration of etomidate; 1303 subjects were included. Etomidate administration increased the likelihood of developing adrenal insufficiency (pooled relative risk 1.33; 95% confidence interval 1.22-1.46; Q statistic, 10.7; I2 statistic, 43.9%).

Conclusions:

Administration of etomidate for rapid sequence intubation is associated with higher rates of adrenal insufficiency and mortality in patients with sepsis. Ⓐ

Evidence-Based Reference

Chan CM et al.: Etomidate is associated with mortality and adrenal insufficiency in sepsis: a meta-analysis, *Crit Care Med* 40:2945–2953, 2012. Ⓐ

SUGGESTED READINGS

Angus D, van der Poll T: Severe sepsis and septic shock, *N Engl J Med* 369: 840–851, 2013.

Caironi P et al.: Albumin replacement in patients with severe sepsis or septic shock, *N Engl J Med* 370:1412–1421, 2014.

Cawcutt KA, Peters SG: Severe sepsis and septic shock: clinical overview and update on management, *Mayo Clin Proc* 89(11):1572–1578, 2015.

Dellinger RP et al.: Surviving Sepsis Campaign: international guidelines for the management of severe sepsis and septic shock, *Crit Care Med* 41(2):580–637, 2013.

Holst L et al.: Lower versus higher hemoglobin threshold for transfusion in septic shock, *N Engl J Med* 371:1381–1391, 2014.

Kumar A et al.: Early combination antimicrobial therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis, *Crit Care Med* 38:1773–1785, 2010.

The NICE-SUGAR Study Investigators: Intensive versus conventional glucose control in critically ill patients, *N Engl J Med* 360(13):1283–1297, 2009.

Ranieri VM et al.: Drotecogin alfa (activated) in adults with septic shock, *N Engl J Med* 366(22):2055–2064, 2012.

Rochwerg B et al.: Fluid resuscitation in sepsis, a systematic review and network meta-analysis, *Ann Inter Med* 161:347–355, 2014.

Russell J et al.: Vasopressin versus norepinephrine infusion in patients with septic shock, *N Engl J Med* 358:877–887, 2008.

Sprung CL et al.: Hydrocortisone therapy for patients with septic shock, *N Engl J Med* 358:111–124, 2008.

Vincent JL, Opal SM, Marshall J, Tracey K: Definitions for sepsis: Time for a change, *Lancet* 381:774–775, 2013.

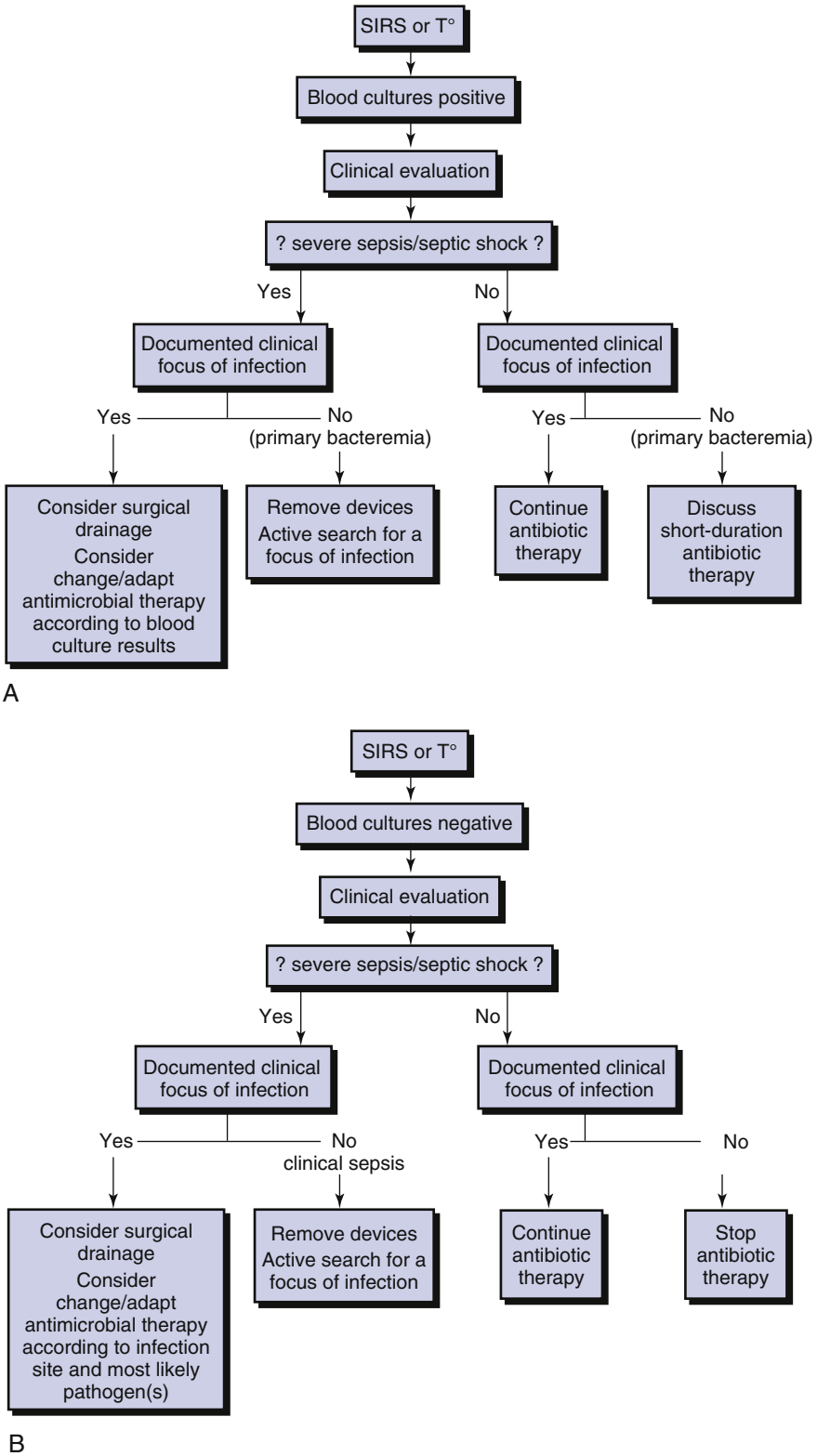


FIGURE ES1-25 Workup following results of blood cultures. A, Evaluation of a patient treated for suspected acute bacteremia in the presence of a positive blood culture at 48 to 72 hr. **B,** Evaluation of a patient treated for suspected acute bacteremia in the presence of a negative blood culture at 48 to 72 hr. *SIRS,* Systemic inflammatory response syndrome; *T* °, >100.4° F (38° C). (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Septic arthritis is a highly destructive form of joint disease most often caused by hematogenous spread of organisms from a distant site of infection. Direct penetration of the joint as a result of trauma or surgery and spread from adjacent osteomyelitis may also cause bacterial arthritis. Any joint in the body may be affected.

SYNONYMS

Infectious arthritis
Bacterial arthritis
Pyogenic arthritis

ICD-9CM CODES
711 Pyogenic arthritis, site unspecified
ICD-10CM CODES
M00.9 Pyogenic arthritis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Unknown.
PREVALENCE (IN U.S.): Unknown.
PREDOMINANT SEX: Gonococcal arthritis in females.
PREDOMINANT AGE: Gonococcal arthritis in sexually active adults.
PEAK INCIDENCE:
- Gonococcal arthritis: young adults.
- Other bacterial causes: all ages.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Hallmark: acute onset of monoarticular joint pain, erythema, heat, and immobility.
- Limited range of motion of the joint.
- Effusion, with varying degrees of erythema and increased warmth around the joint.
- Single joint affected in 80% to 90% of cases of nongonococcal arthritis.
- Gonococcal dermatitis-arthritis syndrome.
  1. Typical pattern is a migratory polyarthritis or tenosynovitis.
  2. Small pustules on the trunk or extremities.
- Febrile patient at presentation.
- Most commonly affected joints in adult: knee and hip, but any joint may be involved; in children: hip.

ETIOLOGY

- Bacteria spread from another locus of infection.
  1. Highly vascular synovium is invaded by hematogenously spread bacteria.
  2. WBC enzymes cause necrosis of synovium, cartilage, and bone.
  3. Extensive joint destruction is rapid if infection is not treated with appropriate IV antibiotics and drainage of necrotic material.
- Predisposing factors: rheumatoid arthritis, prosthetic joints, advanced age, immunodeficiency (HIV, DM, immunosuppressive drugs), sexual activity (gonococcal arthritis), skin infections, cutaneous ulcers (contiguous spread), recent joint surgery, recent intraarticular infection. Fig. ES1-26 illustrates routes by which bacteria can reach the joint.
- The most common nongonococcal organisms are staphylococci (40%), streptococci (28%), and gram-negative bacilli (19%). Less common are mycobacteria (8%), gram-negative cocci (3%), anaerobes (1%), and gram-positive bacilli (1%).
- Staphylococci (*S. aureus* and coagulase-negative staphylococcal species) account for >50% of prosthetic-hip and prosthetic-knee infections. *S. aureus* is very common in patients with rheumatoid arthritis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Gout.
- Pseudogout.
- Trauma.
- Hemarthrosis.
- Rheumatic fever.
- Adult or juvenile rheumatoid arthritis.
- Spondyloarthropathies such as reactive arthritis (Reiter's syndrome).
- Osteomyelitis.
- Viral arthritides.
- Septic bursitis.
- Lyme disease caused by *Borrelia burgdorferi.*

WORKUP

- Joint aspiration, Gram stain, and culture of the synovial fluid. Fig. ES1-27 describes an algorithm for synovial fluid analysis in septic arthritis.
- Immediate arthrocentesis before other studies are undertaken or antibiotics instituted. Synovial fluid should be evaluated at bedside and then sent for lab evaluation.

LABORATORY TESTS

- Joint fluid analysis.
  1. Synovial fluid leukocyte count is usually elevated >50,000 cells/mm^3 with > 80% polymorphonuclear cells.
  2. Counts are highly variable, with similar findings in gout, pseudogout, or rheumatoid arthritis. Lower WBC counts can occur in joint replacement, disseminated gonococcal disease, and peripheral leukopenia.
  3. Synovial fluid glucose or protein is not helpful because results are not specific for septic arthritis. The differential diagnosis of synovial fluid abnormalities is described in Section IV.
  4. PCR testing: useful for detection of uncommon organisms (e.g., Lyme disease).
  5. Crystal analysis: septic arthritis can coexist with crystal arthropathy; therefore, the presence of crystals does not preclude a diagnosis of septic arthritis.
- Blood cultures: positive in 25% to 50% of patients with septic arthritis.
- Culture of possible extraarticular sources of infection.
- Elevated peripheral WBC count, ESR (nonspecific), C-reactive protein (CRP) (nonspecific). When elevated, ESR and CRP may be useful to monitor therapeutic response.
- If gonococcus is suspected, perform nucleic acid amplification tests (NAATs) on synovial fluid.

IMAGING STUDIES

- Radiograph of the affected joint (Fig. ES1-28): useful to rule out osteomyelitis, fractures, chondrocalcinosis, or inflammatory arthritis.
- MRI: findings that suggest an acute intraarticular infection include the combination of bony erosions with marrow edema.
- CT scan: useful for early diagnosis of infections of the spine, hips, and sternoclavicular and sacroiliac joints.
- Ultrasound: can be useful for detecting effusions in joints that are more difficult to examine (e.g., hip).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Affected joints aspirated daily to remove necrotic material and to follow serial WBC counts and cultures.
- If no resolution with IV antibiotics and closed drainage: open debridement and lavage, particularly in nongonococcal infections.
- Prevention of contractures:
  - After acute stage of inflammation, range-of-motion exercises of the affected joint.
  - Physical therapy helpful.

ACUTE GENERAL Rx

- IV antibiotics immediately after joint aspiration and Gram stain of the synovial fluid. Empiric antibiotic therapy is based on organism found on Gram stain of synovial fluid:
  - Gram-positive cocci: vancomycin.
  - Gram-negative cocci: ceftriaxone.
  - Gram-negative rods: ceftazidime, cefepime, piperacillin-tazobactam. Aztreonam or fluoroquinolones can be used in patients with allergy to penicillin or cephalosporins.
  - Negative Gram stain: vancomycin plus either ceftazidime or a carbapenem such as meropenem or ertapenem.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Septic Arthritis (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

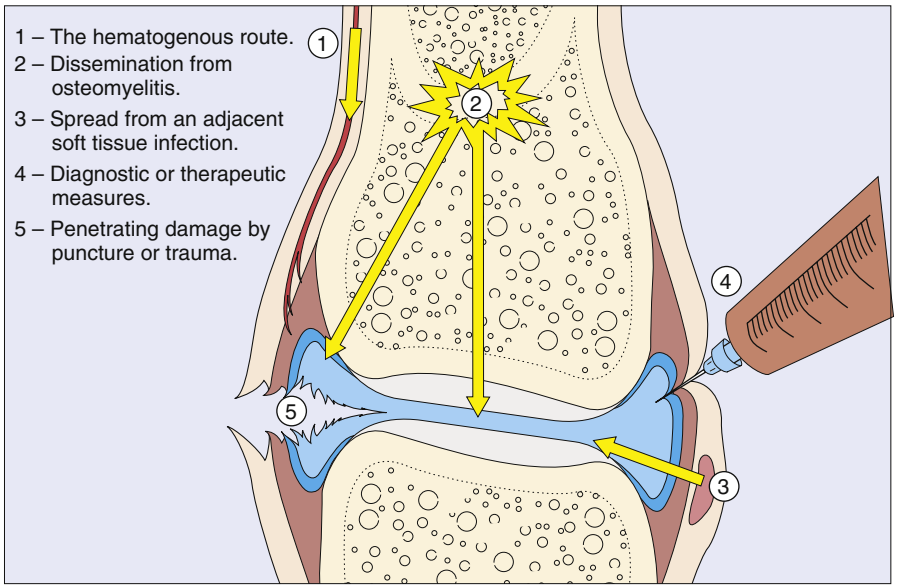


FIGURE ES1-26 Routes by which bacteria can reach the joint. (From Hochberg MC et al: *Rheumatology,* ed 5, St. Louis, Mosby, 2011.)

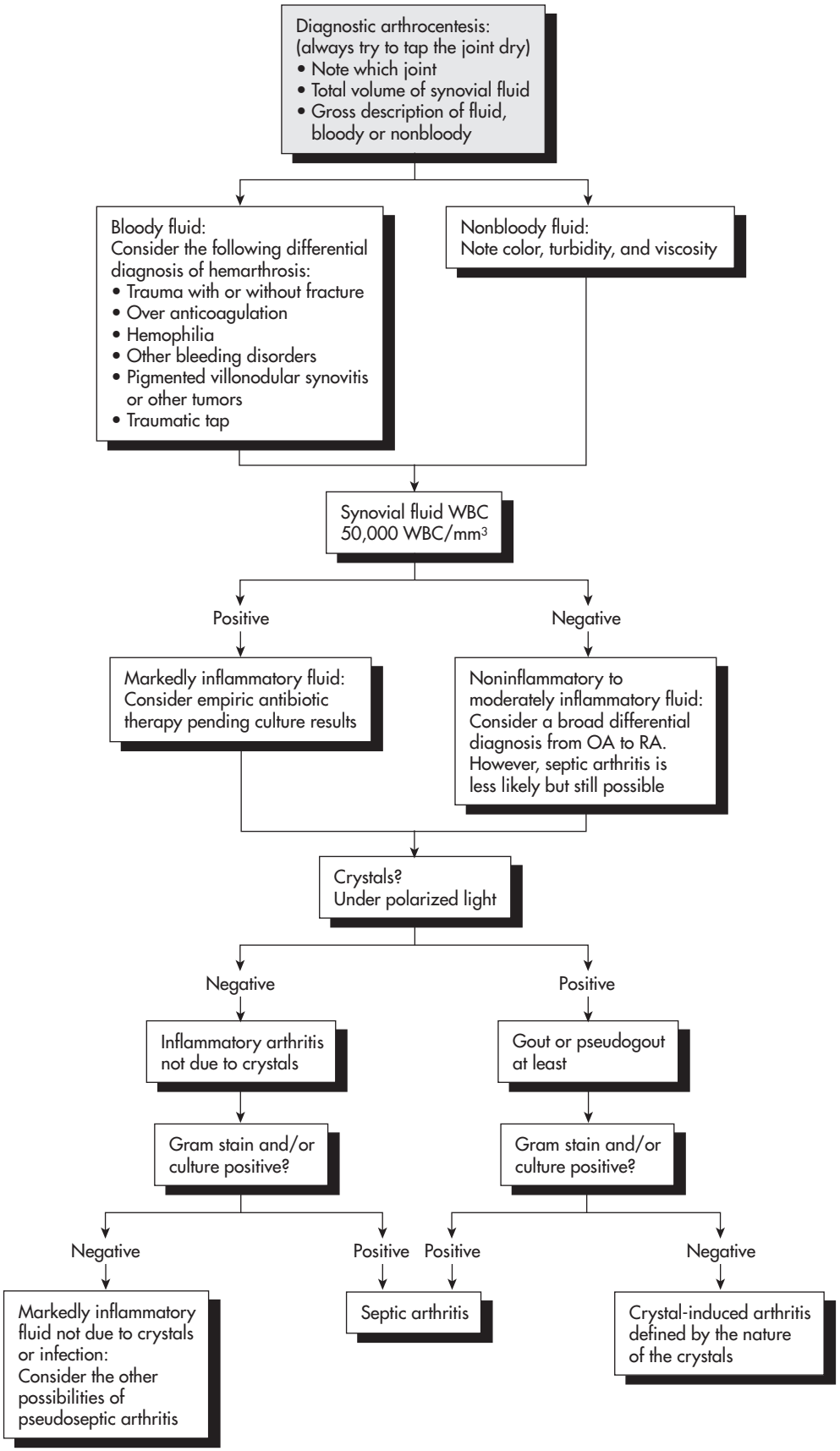


FIGURE ES1-27 Algorithm for synovial fluid analysis in septic arthritis. *OA,* Osteoarthritis; *RA,* rheumatoid arthritis; *WBC,* white blood cell count. (From Harris ED et al [eds]: *Kelley's textbook of rheumatology,* ed 7, Philadelphia, 2005, Saunders.)

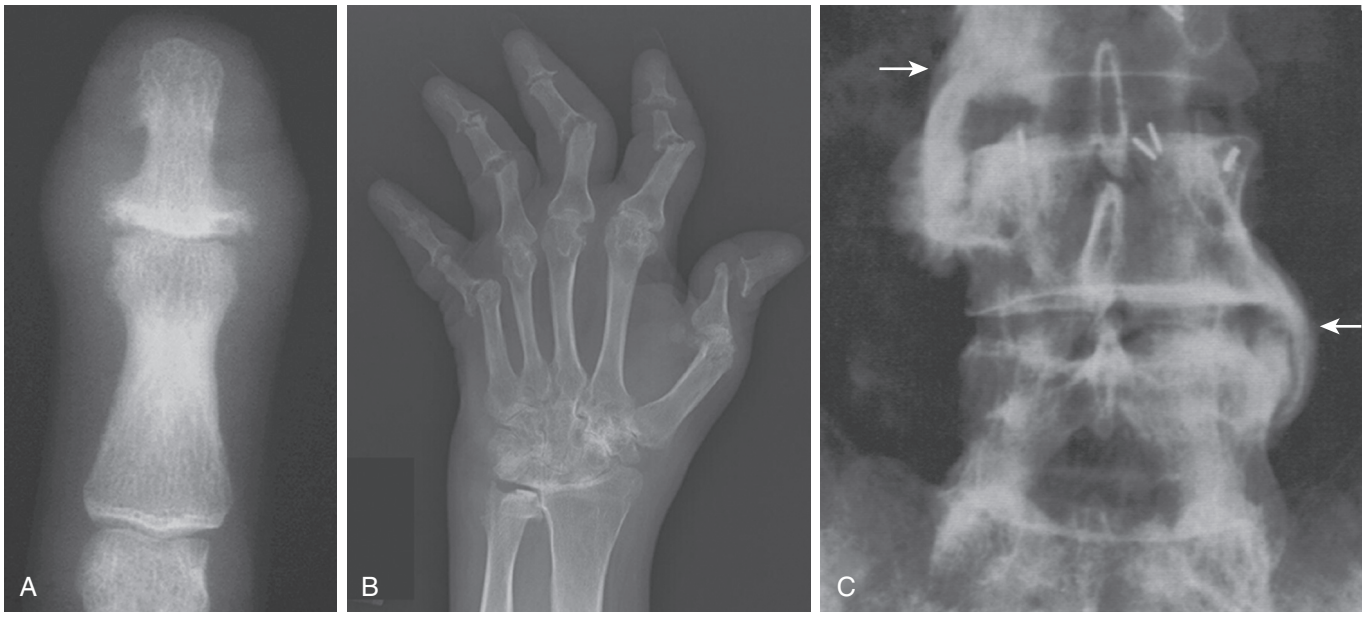


FIGURE ES1-28 Septic arthritis (x-ray and magnetic resonance imaging [MRI]). A, X-ray in anteroposterior view of sacroiliac joints shows destruction of the right sacroiliac joint as part of septic arthritis *(arrows).* **B,** In another patient, short tau inversion recovery (STIR) coronal MRI through sacroiliac joints shows erosive changes in the right sacroiliac joint with extensive bone marrow edema. **C** and **D,** Tuberculous spondylitis. **C,** X-ray of the lumbar spine in lateral view shows disk space narrowing at the L3-L4 level with destructive changes involving the superior end plate of the L4 vertebral body *(arrow).* **D,** Coronal STIR MRI of the lumbar spine of the same patient confirms focal destruction of the L4 vertebral body *(arrow).* Enlargement of both psoas muscles (P) with increased signal is noted, owing to paraspinal extension of the infection. (From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

SUGGESTED READINGS

DelPozo JL, Patel R: Infection associated with prosthetic joints, *N Engl J Med* 361:787–794, 2009.

Horowitz DL et al.: Approach to septic arthritis, *Am Fam Physician* 84(6):653–660, 2011.

Margaretten ME: Does this adult patient have septic arthritis? *JAMA* 297:1478–1488, 2007.

Ross JJ: Septic arthritis, *Infect Dis Clin North Am* 19:799–817, 2005.

Yagupsky P: Differentiation between septic arthritis and transient synovitis of the hip in children, *J Bone Joint Surg Am* 87(2):459, 2005.

BASIC INFORMATION

DEFINITION

Serotonin syndrome (SS) refers to a group of symptoms resulting from increased activity of serotonin (5-hydroxytryptamine) in the CNS. SS is a drug-induced disorder that is classically characterized by a change in mental status and alteration in neuromuscular activity and autonomic function.

SYNONYMS

SS
Hyperserotonemia
Serotonergic syndrome
Serotonin toxicity

ICD-9CM CODES

333.99 Syndrome serotonin

ICD-10CM CODES

Y49	Adverse effects due to psychotropic drugs
Y49.0	Adverse effects due to tricyclic and tetracyclic antidepressants
Y49.1	Adverse effects due to monoamine-oxidase-inhibitor antidepressants
Y49.2	Adverse effects due to other and unspecified antidepressants
Y49.3	Adverse effects due to phenothiazine antipsychotics and neuroleptics
G25.89	Other specified extrapyramidal and movement disorders

EPIDEMIOLOGY & DEMOGRAPHICS

- The incidence of SS is not known.
- SS is seen in all age groups, from neonates to elderly.
- SS classically occurs in patients receiving two or more serotonergic drugs, but it can also occur with monotherapy—selective serotonin reuptake inhibitor (SSRI) monotherapy has an incidence of 0.5 to 0.9 cases of SS per 1000 patient-mo. Although there is an FDA alert, it has been argued that there is a lack of sufficient evidence showing that SSRIs and triptans cause serious SS.
- Concomitant use of an SSRI with a monoamine oxidase inhibitor (MAOI) poses the greatest risk of developing SS.
- Combination of SSRIs with other serotonergic drugs (e.g., tryptophan, illicit drugs like cocaine and MDMA, "Ecstasy") or drugs with serotonergic properties (e.g., lithium, meperidine, triptans, linezolid) may also lead to SS.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Findings of clonus with hyperreflexia in the setting of recent (<5 wk) use of serotonergic agents strongly suggest the diagnosis of SS.
- Symptoms can manifest within minutes to hours after starting a new psychopharmacologic treatment, increasing the dose of a serotonergic drug, or administering a second serotonergic drug.
- Clonus (inducible, spontaneous, and ocular) is the key finding in establishing a diagnosis of SS.
- Other pertinent findings include:
  - Confusion, agitation, hypomania.
  - Fever >38° C (100° F), tachycardia, and tachypnea.
  - Nausea, vomiting, abdominal pain, and diaphoresis.
  - Diarrhea, tremors, shivering, and seizures.
  - Hyperreflexia and muscle rigidity.

ETIOLOGY

- Hyperstimulation of the brain stem and spinal cord serotonin receptors leading to the neuromuscular and autonomic symptoms.
- Psychopharmacologic drugs—in particular, fluoxetine and sertraline co-administered with MAOI (e.g., tranylcypromine and phenelzine)—have been cited in the literature as a common cause of SS. Triptans (serotonin-receptor agonists used in the treatment of migraines) may also precipitate the SS when used in combination with SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs).

BOX S1-2 Classes of Medications That Produce Serotonin Syndrome in Psychiatric Patients

Selective serotonin reuptake inhibitors
Monoamine oxidase inhibitors
Atypical antipsychotics
Heterocyclic antidepressants
Trazodone
Dual-uptake inhibitors
Psychostimulants
Buspirone
Mood stabilizers
Analgesics
Antiemetics
Cough suppressants
Dietary supplements

From Goldman L, Schafer AI: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Saunders.

Box S1-2 describes classes of medications that produce SS in psychiatric patients.

DIAGNOSIS

- The diagnosis of SS is made on clinical grounds. There are no specific laboratory tests for SS. A high index of suspicion along with a detailed medication history is the mainstay of diagnosis.
- Diagnostic criteria: most accurate is Hunter Serotonin Toxicity Criteria (sensitivity 84%, specificity 97%, confirmation by toxicologist). Sternbach's diagnostic criteria (Table S1-9) is also commonly used.
- To fulfill Hunter criteria a patient must have consumed a serotonergic drug and have one of the following:
  1. Spontaneous clonus.
  2. Inducible clonus plus agitation or diaphoresis.
  3. Ocular clonus plus agitation or diaphoresis.
  4. Tremor and hyperreflexia.
  5. Temperature >38° C (100° F) plus hypertonia plus ocular clonus or inducible clonus.

DIFFERENTIAL DIAGNOSIS

- Neuroleptic malignant syndrome (NMS), substance abuse (e.g., cocaine, amphetamines), anticholinergic toxicity, thyroid storm, infection (e.g., meningitis, encephalitis), alcohol and opioid withdrawal.
- Classic features in differentiation of NMS from SS are that SS develops over 24 hr, involves neuromuscular hyperactivity, and begins to resolve within 24 hr with appropriate therapy, whereas NMS develops gradually over days to weeks, involves sluggish neuromuscular response, and resolves over an average period of 1 wk to 10 days.

TABLE S1-9 Criteria to Determine Serotonin Syndrome and Toxicity

Sternbach's diagnostic criteria for serotonin syndrome	1. Recent addition or increase of proserotonergic medication 2. At least three of the following: • Agitation • Ataxia • Diaphoresis • Diarrhea • Hyperreflexia • Hyperthermia • Mental status changes • Myoclonus • Shivering • Tremor 3. Neuroleptic agent not added or dose increased before the onset of symptoms 4. Diagnosis of infections, withdrawal, and other poisoning or metabolic disruptions excluded
Hunter's criteria for serotonin toxicity (context of serotonergic medications)	1. If patient has spontaneous clonus, serotonin toxicity present 2. If no spontaneous clonus, one of the following needed for a diagnosis of serotonin toxicity: • Inducible clonus *and* agitation *or* diaphoresis • Ocular clonus *and* agitation *or* diaphoresis • Tremor *and* hyperreflexia • Temperature >38° C *and* ocular clonus *or* inducible clonus

From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

WORKUP

- Because SS is a clinical diagnosis, there is no laboratory test that confirms the diagnosis, and serum serotonin concentration does not correlate with clinical picture. Other causes are described in "Differential Diagnosis." Thus, all patients should have blood tests and diagnostic imaging studies to rule out infectious, toxic, and metabolic causes.
- Additional laboratory tests are performed to exclude complicating features of SS (e.g., renal failure secondary to rhabdomyolysis).

LABORATORY TESTS

- CBC with differential to rule out sepsis.
- Electrolytes, BUN, and creatinine to rule out acidosis and renal failure.
- Blood and urine toxicology screen.
- Thyroid function tests.
- Creatine-phosphokinase (CPK) with isoenzymes.
- Urine and blood cultures.
- ECG because ventricular rhythm disturbance is a potentially fatal complication.

IMAGING STUDIES

Imaging studies are not specific in the diagnosis of SS and are only ordered to exclude other causes with similar clinical presentations as SS.

Rx TREATMENT

- Once a diagnosis of SS is established, appropriate consultation with a medical toxicologist, clinical pharmacologist, and/or poison control center should be sought.
- Management includes:
  - Discontinue use of all potential precipitating drugs.
  - Provide supportive management.
  - Control agitation.
  - Administer serotonin antagonists.
  - Control autonomic instability.
  - Control hyperthermia.
  - Reassess the need to resume the use of the serotonergic agent once the symptoms have resolved.

NONPHARMACOLOGIC THERAPY

- Discontinuation of the drug is the mainstay of therapy.
- Treatment is supportive: maintaining oxygenation and blood pressure and monitoring respiratory status. Hypotensive patients may require both IV fluids and vasopressor therapy.
- Patients who are severely hyperthermic with temperatures >41° C (106° F) should be given IV sedation, paralyzed, and intubated. Cooling blankets can be used for patients with mild to moderate hyperthermia. There is no role for acetaminophen here.
- Intubation is recommended for patients unable to protect their airways as a result of mental status changes or seizures.

ACUTE GENERAL Rx

- Benzodiazepines for control of agitation are preferred to physical restraints.
  1. Lorazepam 1 to 2 mg IV every 30 min has been used effectively in treating agitation, muscle rigidity, myoclonus, and seizure complications.
  2. Diazepam is an alternative choice.
- Blood pressure management with short-acting agents such as esmolol and nitroprusside.
- Serotonin antagonists should be titrated to clinical effectiveness in patients for whom nonpharmacologic therapy and benzodiazepines are not achieving adequate response, although substantial and rigorous data are lacking.
  1. Cyproheptadine 4 mg tablet or 2 mg/5 ml syrup is given 12 mg initially followed by 2 mg every 2 hr until therapeutic response is achieved in adults (up to 32 mg/day); children ages 7 to 14 should receive 4 mg every 6 hr (up to 16 mg/day), children ages 2 to 6 should receive 2 mg every 6 hr (up to 12 mg/day), and children younger than 2 yr should receive a maximum of 0.25 mg/kg/day as 0.06 mg/kg every 6 hr.
  2. Atypical antipsychotic agents with serotonin antagonist properties (e.g., olanzapine 10 mg SL) have been tried with some success.
  3. Chlorpromazine 50 to 100 mg IM may be considered in severe cases.

CHRONIC Rx

For patients not requiring hospital admission, cyproheptadine and lorazepam can be given in an oral dose on a prn basis with close follow-up.

DISPOSITION

- SS is a potentially life-threatening condition if not recognized early, although it does exist on a spectrum.
- Prompt diagnosis and withdrawal of the medication result in improvement of symptoms within 24 hr.
- Seizures, rhabdomyolysis, hyperthermia, ventricular arrhythmia, respiratory arrest, and coma are all complicating features of SS.

REFERRAL

All cases of SS secondary to psychotropic medications should be referred to a psychiatrist.

PREVENTION

Modify prescription practices by avoiding multidrug regimens.

PEARLS & CONSIDERATIONS

The combined use of SSRIs and MAOIs is contraindicated.

COMMENTS

- The use of SSRIs and other serotonergic agents is not an absolute contraindication; however, prompt withdrawal of the medication is recommended if any symptoms suggesting SS occur.
- SS is usually found in patients being treated for depression, bipolar disorders, obsessive-compulsive disorder, attention-deficit disorder, and Parkinson's disease.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **MARK F. BRADY, M.D., M.P.H., M.M.S.**

SUGGESTED READINGS

Ables AZ, Nagubilli R: Prevention, recognition, and management of serotonin syndrome, *Am Fam Physician* 181(9):1139–1142, 2010.

Boyer EW, Shannon M: The serotonin syndrome, *N Engl J Med* 352:1112–1120, 2005.

Dunkley EJ et al.: The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity, *QJM* 96:635, 2003.

Evans RW et al.: The FDA alert on serotonin syndrome with the use of triptans combined with selective serotonin reuptake inhibitors: American Headache Society position paper, *Headache* 50(6):1089–1099, 2010.

Gillman PK: Triptans, serotonin agonists, and serotonin syndrome (serotonin toxicity): a review, *Headache* 50(2):264–272, 2010.

Sclar DA et al.: Concomitant triptan and SSRI or SNRI use: a risk for serotonin syndrome, *Headache* 48:126–129, 2008.

BASIC INFORMATION

DEFINITION

Severe acute respiratory syndrome (SARS) is a respiratory illness caused by a coronavirus called SARS-associated coronavirus (SARS-CoV).

CLINICAL CRITERIA:

A. Asymptomatic or mild respiratory illness
B. Moderate respiratory illness
   1. Temperature of >100.4° F (>38° C)* *and*
   2. One or more clinical findings of respiratory illness (e.g., cough, shortness of breath, difficulty breathing, hypoxia)
C. Severe respiratory illness
   1. Temperature of >100.4° F (>38° C) *and*
   2. One or more clinical findings of respiratory illness (e.g., cough, shortness of breath, difficulty breathing, hypoxia) *and*
      a. Radiographic evidence of pneumonia, *or*
      b. Respiratory distress syndrome, *or*
      c. Autopsy findings consistent with pneumonia or respiratory distress syndrome without an identifiable cause

EPIDEMIOLOGIC CRITERIA

- Travel (including transit in an airport) within 10 days of onset of symptoms to an area with current or previously documented or suspected community transmission of SARS, *or*
- Close contact† within 10 days of onset of symptoms with a person known or suspected to have SARS.
- The Chinese horseshoe bat, which is a healthy carrier of SARS, has been identified as the reservoir of the virus in nature. The spread of the virus was facilitated by people eating bats or using bat feces in traditional medicine for asthma, kidney ailments, and general malaise.

Laboratory criteria:

- Confirmed:
  1. Detection of antibody to SARS-CoV in a serum sample, *or*
  2. Detection of SARS-CoV RNA by reverse-transcription polymerase chain reaction (PCR) confirmed by a second PCR assay by using a second aliquot of the specimen and a different set of PCR primers, *or*
  3. Isolation of SARS-CoV
- Negative:
  1. Absence of antibody to SARS-CoV in a convalescent-phase serum sample obtained >28 days after symptom onset
- Undetermined:
  1. Laboratory testing either not performed or incomplete

Case classification‡:

- Probable case: meets the clinical criteria for severe respiratory illness of unknown etiology and epidemiologic criteria for exposure; laboratory criteria confirmed or undetermined.
- Suspect case: meets the clinical criteria for moderate respiratory illness of unknown etiology and epidemiologic criteria for exposure; laboratory criteria confirmed or undetermined.

Exclusion criteria: a case may be excluded as a suspect or probable SARS case if:

- An alternative diagnosis can fully explain the illness.
- The case has a convalescent-phase serum sample (i.e., obtained >28 days after symptom onset) that is negative for antibody to SARS-CoV.
- The case was reported on the basis of contact with an index case that was subsequently excluded as a case of SARS, provided other possible epidemiologic exposure criteria are not present.

SYNONYMS

SARS

ICD-9CM CODES
Not available
ICD-10CM CODES
J12.81 Pneumonia due to SARS-associated coronavirus

EPIDEMIOLOGY & DEMOGRAPHICS

- The disease was first recognized in Asia in February 2003 and spread to >24 countries in North and South America, Europe, and Asia over the next several months, affecting >8000 patients and resulting in >750 deaths. In July 2003, cases were no longer being reported, and SARS outbreaks worldwide were considered contained.
- Most reported cases of SARS in the United States were attributed to exposure through foreign travel to countries with community transmission of SARS, with only limited secondary spread to close contacts such as family members and health care workers.
- Incubation period is 2 to 10 days.
- Evidence of airborne transmission of the SARS virus and laboratory-acquired SARS have now been documented.

PHYSICAL FINDINGS & CLINICAL PRESENTATION§

- Early manifestations: fever, myalgias, and headache. Fever is often high and associated with chills or rigors. Fever may be absent in elderly patients.
- Dry, nonproductive cough occurs within 2 to 4 days of onset of fever.
- Diarrhea may occur in up to 25% of cases.
- Dyspnea and hypoxemia follow the cough and may require intubation in nearly 20% of patients.
- A biphasic course of illness may occur with initial improvement followed by subsequent deterioration in some patients.

ETIOLOGY

SARS-associated coronavirus.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- *Legionella* pneumonia.
- Influenza A and B.
- Respiratory syncytial virus.
- Acute respiratory distress syndrome (ARDS).

WORKUP

Initial diagnostic testing for suspected SARS patients should include chest radiograph, pulse oximetry, blood cultures, sputum Gram stain and culture, and testing for viral respiratory pathogens, notably influenza A and B and respiratory syncytial virus. A specimen for *Legionella* and pneumococcal urinary antigen testing should also be considered.

LABORATORY TESTS

When to test for SARS:

- In the absence of documented SARS transmission, diagnostic testing for SARS-associated coronavirus (SARS-CoV) should *not* be considered unless the clinician and health department have a high index of suspicion for SARS (e.g., a hospitalized pneumonia patient has a possible SARS exposure during travel and no other explanation for the patient's pneumonia).

*A measured documented temperature of >100.4° F (>38° C) is preferred. However, clinical judgment should be used when evaluating patients for whom a measured temperature of >100.4° F (>38° C) has not been documented. Factors that might be considered include patient self-report of fever, use of antipyretics, presence of immunocompromising conditions or therapies, lack of access to health care, and inability to obtain a measured temperature. Reporting authorities should consider these factors when classifying patients who do not strictly meet the clinical criteria for this case definition.

†Close contact is defined as having cared for or lived with a person known to have SARS or having a high likelihood of direct contact with respiratory secretions and/or body fluids of a patient known to have SARS. Examples of close contact include kissing or embracing, sharing eating or drinking utensils, close conversation (<3 ft), physical examination, and any other direct physical contact between persons. Close contact does not include activities such as walking by a person or sitting across a waiting room or office for a brief period.

‡The last date for illness onset is 10 days (i.e., one incubation period) after removal of a CDC travel alert. The case patient's travel should have occurred on or before the last date the travel alert was in place.

Assays for the laboratory diagnosis of SARS-CoV infection include enzyme-linked immunosorbent assay, indirect fluorescent-antibody assay, and reverse-transcription PCR assays of appropriately collected clinical specimens. Absence of SARS-CoV antibody from serum obtained <28 days after illness onset, a negative PCR test, or a negative viral culture does not exclude SARS-CoV infection and is not considered a definitive laboratory result. In these instances a convalescent serum sample obtained >28 days after illness is needed to determine infection with SARS-CoV.

§Asymptomatic SARS-CoV infection or clinical manifestations other than respiratory illness might be identified as more is learned about SARS-CoV infection.

- Respiratory specimens should be collected as soon as possible in the course of the illness. The likelihood of recovering most viruses diminishes markedly >72 hours after symptom onset.
- Three types of specimens may be collected for viral or bacterial isolation and PCR. These include (1) nasopharyngeal wash/aspirates, (2) nasopharyngeal swabs, or (3) oropharyngeal swabs. Nasopharyngeal aspirates are the specimen of choice for detection of respiratory viruses and are the preferred collection method among children aged <2 yr.
- Laboratory testing on initial evaluation should also include CBC with differential, platelet count, liver enzymes, LDH, and CPK. Common laboratory abnormalities in SARS include thrombocytopenia, lymphopenia, elevated LDH, and elevated CPK, ALT, AST.

IMAGING STUDIES

- Chest x-ray: patchy focal infiltrates or consolidation with peripheral distribution.
- Chest x-ray may be normal in up to 25% of patients.
- Pleural effusions generally are not present.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive care.
- Nearly 25% of cases will require ventilator assistance.
- Nutritional support.

ACUTE GENERAL Rx

- There is no specific treatment currently available for SARS.
- Broad-spectrum antibiotics (quinolone or macrolide) are generally started pending laboratory testing.
- Use of corticosteroids (methylprednisolone 40 mg bid or doses up to 2 mg/kg/day) is controversial, but may be beneficial in patients with significant hypoxemia and progressive pulmonary infiltrates.
- In a preliminary, uncontrolled study of patients with SARS, use of interferon alfacon-1 plus corticosteroids was beneficial.

DISPOSITION

- Case-fatality rate is 3% to 12%.
- Mortality rate is higher in elderly and immunocompromised patients and lower in pediatric age group.

REFERRAL

- Infectious disease consultation and pulmonary consultation are recommended in all cases.
- Notification of State Department of Health is mandatory.

PEARLS & CONSIDERATIONS

COMMENTS

- Persons who may have been exposed to SARS should be vigilant for fever (i.e., measure temperature twice daily) and respiratory symptoms over the 10 days after exposure. During this time, in the absence of both fever and respiratory symptoms, persons who may have been exposed to SARS patients need not limit their activities outside the home and should not be excluded from work, school, out-of-home child care, church, or other public areas.
- Exposed persons should notify their health care provider immediately if fever or respiratory symptoms develop.
- Symptomatic persons exposed to SARS should follow the following infection control precautions:
  1. If fever or respiratory symptoms develop, the person should limit interactions outside the home and not go to work, school, out-of-home child care, church, or other public areas. In addition, the person should use infection control precautions in the home to minimize the risk for transmission, and continue to measure temperature twice daily.
  2. If symptoms improve or resolve within 72 hr after first symptom onset, the person may be allowed, after consultation with local public health authorities, to return to work, school, out-of-home child care, church, or other public areas, and infection control precautions can be discontinued.
  3. For persons who meet or progress to meet the case definition for suspected SARS (e.g., develop fever and respiratory symptoms), infection control precautions should be continued until 10 days after the resolution of fever, provided respiratory symptoms are absent or improving.
  4. If the illness does not progress to meet the case definition, but the individual has persistent fever or unresolving respiratory symptoms, infection control precautions should be continued for an additional 72 hr, at the end of which time a clinical evaluation should be performed. If the illness progresses to meet the case definition, infection control precautions should be continued as described earlier. If case definition criteria are not met, infection control precautions can be discontinued after consultation with local public health authorities and the evaluating clinician.
- Persons who meet or progress to meet the case definition for suspected SARS (e.g., develop fever and respiratory symptoms) or whose illness does not meet the case definition, but who have persistent fever or unresolving respiratory symptoms over the 72 hr after onset of symptoms, should be tested for SARS coronavirus infection.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Lim PL et al.: Laboratory-acquired SARS, *N Engl J Med* 350:1740, 2004.

Poutanen SM et al.: Identification of severe acute respiratory syndrome in Canada, *N Engl J Med* 348:20, 2004.

Yu IT et al.: Evidence of airborne transmission of SARS virus, *N Engl J Med* 350:1731, 2004.

BASIC INFORMATION

DEFINITION

Sexual assault is any sexual act performed by one person on another without consent, resulting from the use of force, the threat of force or from the victim's inability to give consent.

SYNONYMS

Rape

ICD-9CM CODES
E960.1 Rape
ICD-10CM CODES
Y05 Sexual assault by bodily force

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 17.6% of women, 3% of men
PEAK INCIDENCE: As high as 25%
PREVALENCE (IN U.S.): 17.7 million women, 2.8 million men
PREDOMINANT SEX AND AGE: Female, age 16-24
RISK FACTORS: Alcohol/drug consumption, prior history of being sexually/physically abused, multiple sexual partners, involvement in sex work, poverty, incarceration/institutionalization, mental retardation

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Extragenital trauma: 70%: bruises, abrasions, erythema on thigh, arms, face, neck
- Anogenital trauma: 27%: injury to breasts, external genitalia, vagina, anus, rectum
- Physical findings more likely if examined within 72 hr of event, if event occurred outdoors, and if perpetrator was unknown

DIAGNOSIS

WORKUP

- History
  - Circumstances of assault: date, time, location
  - Physical description of perpetrator
  - Areas of trauma, specifically details of oral, vaginal, anorectal contact, or penetration
  - Condom use
  - Ejaculation: presence or absence
  - Presence of bleeding in victim or perpetrator
  - Recent consensual sexual activity
  - Showering, bathing, changing of clothes since event
- Physical examination
  - Ideally performed by individual trained to perform sexual assault examinations, i.e., SANE (Sexual Assault Nurse Evaluation) providers: www.sane-sart.com
  - Physical exam can take 3-6 hr to complete
  - Components
    - Physical examination of entire body
    - Forensic evidence collection
    - STD evaluation and treatment
    - Pregnancy risk evaluation
    - Care of injuries
  - General physical exam components
    - Documentation of any physical trauma, including photographs
    - Colposcopy: may reveal areas of minor genital trauma
    - Wood's light: to reveal foreign debris or semen
  - Forensic evaluation: not required, but should be offered; written informed consent needed
    - Commercially made specimen collection kits available: once completed, kits need to be sealed and handled according to kit instructions
    - U.S.: States required to provide free specimen collection
    - Samples of blood, saliva, mucosal swabs: buccal/vaginal/rectal, fingernail scrapings/clippings, hair specimens
    - Clothing: if unchanged since event
- Box S1-3 summarizes potential specimens to be gathered for forensic evidence collection.
- Fig. S1-29 describes an algorithm for emergency department management of patients after sexual assault.

LABORATORY TESTS

- Pregnancy test (if applicable)
- STD testing
  - GC/CT: recommended for all, may be excluded if individual elects for prophylactic treatment
  - Wet mount or vaginal swab for *Trichomonas*
  - Baseline HIV/hepatitis/syphilis testing: individual basis
    - Retest for HIV/syphilis at 6 wk, 3 mo, and 6 mo from incident

IMAGING STUDIES

Use of imaging studies as dictated by other injuries sustained for diagnosis/treatment of fractures, soft tissue, and other traumatic injuries

TREATMENT

NONPHARMACOLOGIC THERAPY

Acute crisis counseling: to support mental health needs of victim in immediate post-assault period

ACUTE GENERAL Rx

- Sexually transmitted infections
  - Empiric treatment recommended secondary to poor follow-up rates
  - Gonorrhea: ceftriaxone 250 mg IM *or* cefixime 400 mg PO
  - *Chlamydia:* azithromycin 1 g (single dose) *or* doxycycline 100 mg bid × 7 days
  - Trichomoniasis: metronidazole 2 g PO (single dose)
- Hepatitis B
  - If perpetrator known to be infected: HBIG + Hep B vaccination
  - If perpetrator disease status unknown: Hep B vaccination alone
  - If victim has already been vaccinated with documented immunity: no treatment necessary
- HIV
  - Use of antiretrovirals after sexual assault is controversial.
  - Overall risk of acquiring HIV is unknown but higher in certain situations.
    - Male-on-male rapists
    - Assault occurring in area with high local prevalence

BOX S1-3 Potential Specimens to Be Gathered for Forensic Evidence Collection

Clothing
- Each article of clothing should be packaged in separate paper bags to avoid cross-contamination
- If the patient has changed her clothing, only underwear should be collected

Known blood sample
- Crime laboratory assesses for the secretor status and blood type of the patient

Toxicology testing (urine and blood)
- For use in cases in which drug-facilitated sexual assault is suspected
- Collect for evaluation less than 72 to 96 hr after the assault (the time varies by crime laboratory)

Oral swabs and smears
- Collect for evaluation up to 24 hr after the assault

Head hair combings
Fingernail scrapings
Foreign material collection
Swabs of bite marks or areas where the assailant's mouth touched the patient
Pubic hair combings
External genital swabs
Vaginal swabs and smears
- Cervical sampling should be considered for evaluation between 96 and 120 hr after the assault

Perianal swabs
Anorectal swabs and smears
- Collect for evaluation up to 24 hr after the assault

Forensic photography
- Three views per injury, one with a ruler for scale

From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

- Multiple assailants
- Anal sexual assault
- Presence of trauma, bleeding, or genital lesions in either victim/assailant

- Antiretroviral drugs should be offered in all situations.
- Ideally, antiretrovirals are initiated within 4 hr; should not start if >72 hr.

- Pregnancy
  - Pregnancy risk is estimated to be 5% per rape in women age 12-45.
  - Emergency contraception should be offered in all cases.
    - Levonorgestrel: 0.75 mg q12h for two doses or 1.5 mg single dose
    - Yuzpe regimen: 100 mcg ethinyl estradiol + 0.5 mg levonorgestrel, repeated in 12 hr
    - Ulipristal (selective progesterone receptor modulator): preferred method when >72 hr from assault
  1. Antiemetics: EC + antibiotics for STD prophylaxis commonly causes nausea.

CHRONIC Rx

- No chronic prescriptions
- Long-term psychiatric counseling may be needed.

REFERRAL

Mental health professional

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Chlamydia Genital Infections (Related Key Topic)
Contraception (Related Key Topic)
Gonorrhea (Related Key Topic)
Syphilis (Related Key Topic)

AUTHOR: **SARAH L. CHISHOLM, M.D.**

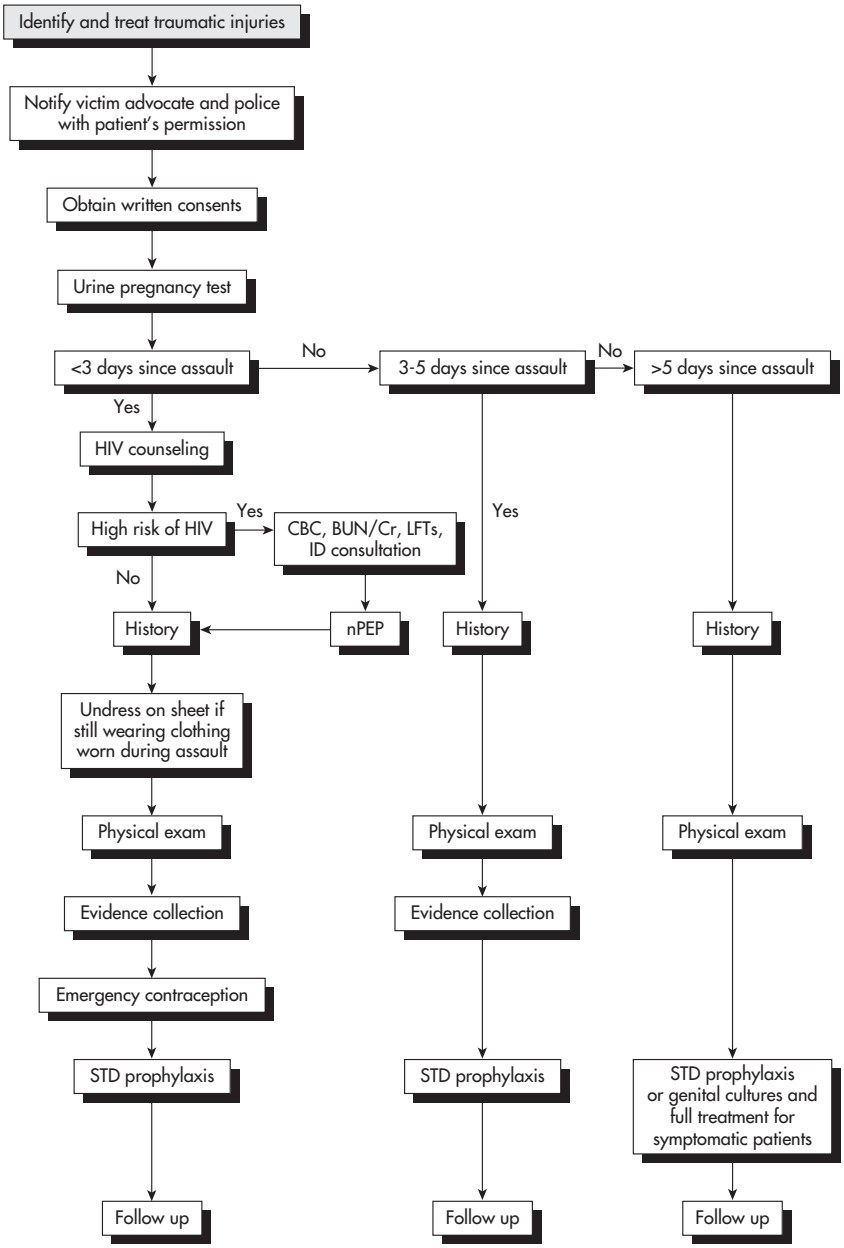


FIGURE S1-29 Emergency department management of patients after sexual assault. *BUN*, Blood urea nitrogen; *CBC*, complete blood count; *Cr*, creatinine; *HIV*, human immunodeficiency virus; *LFTs*, liver function tests; *nPEP*, nonoccupational postexposure prophylaxis; *STD*, sexually transmitted disease. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

SUGGESTED READINGS

American College of Obstetricians and Gynecologists: Committee on Health Care for Underserved Women: Committee opinion no. 499: sexual assault, *Obstet Gynecol* 118(2 Pt 1):396–399, 2011.

Bates CK et al. Evaluation and management of adult sexual assault victims. Available at www.uptodate.com. Accessed June 22, 2012.

Fisher BS et al. The sexual victimization of college women. Department of Justice, National Institute of Justice, Publication No. NCJ 182369: Washington, DC.

Fong C: Post-exposure prophylaxis for HIV infection after sexual assault: when is it indicated? *Emerg Med J* 18:242–245, 2001.

Ledray LE: SANE development and operation guide. Sexual Assault Resource Service, *J Emerg Nurs* 24(2):197–198, 1998.

Tjaden P, Thoennes N: Extent, nature, and consequences of rape victimization: findings from the National Violence Against Women survey, *Department of Justice*, 2006. Available at www.ncjrs.gov/pdffiles1/nij/210346.pdf. Accessed July 22, 2012.

Workowski KA, Berman S: Sexually transmitted disease treatment guidelines 2010, *MMWR Recomm Rep* 59(RR-12):1–110, 2010.

BASIC INFORMATION

DEFINITION

A sexual dysfunction in a woman is any disorder that interferes with female sexuality and that causes marked distress to that person. These disorders are generally categorized into four types:

1. Hypoactive sexual desire disorder (most common)
2. Sexual arousal disorder
3. Orgasmic disorders
4. Sexual pain disorders (including dyspareunia, vaginismus, and vulvodynia)

Female sexual dysfunction is also further categorized as lifelong (primary) or acquired (secondary), situational (e.g., current partner) or generalized (all partners and settings).

SYNONYMS

Female sexual dysfunction

ICD-9CM CODES
302.70 Decreased libido
302.72 Disorders of arousal
302.73 Orgasmic disorders
ICD-10CM CODES
R37 Sexual dysfunction, unspecified
F52.31 Female orgasmic disorder

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: According to the National Health and Social Life Survey, in 1999, ~20% to 50% of women reported some form of sexual dysfunction during their lifetimes. One third of women reported a decrease in sexual interest, and one fourth reported an inability to achieve orgasm.

PREVALENCE: A more recent survey of women 18 yr of age and older found an age-adjusted prevalence of any sexual problem to be ~43%.

PREDOMINANT AGE: Sexually related personal distress was more common in middle-aged women (aged 45 to 64) than in younger or older women.

RISK FACTORS

- Correlates of distressing sexual problems include poor self-assessed health, low education level, depression, anxiety, thyroid conditions, and urinary incontinence.
- Obesity and overweight body status have been associated with lower sexual satisfaction and desire.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- History:
  - Important to obtain the patient's definition of the dysfunction, including its onset and duration; to determine whether the dysfunction is situational or global; and to determine whether more than one dysfunction exists and the interrelationship among the dysfunctions
  - Related medical and gynecologic conditions (including prior gynecologic surgery)
  - Psychosocial factors, including sexual abuse, sexual orientation, depression and anxiety, status of current relationships and sexual activity, personal and family beliefs about sexuality
  - Current medications including OTC and herbal preparations, alcohol, tobacco and drug use, and birth control method
- Physical examination:
  - The gynecologic examination can aid in identifying signs of decreased estrogen and androgen levels, infection, endometriosis, pelvic floor dysfunction, and systemic disease
  - Other body systems as indicated (e.g., cardiovascular, thyroid)

ETIOLOGY

- Chronic medical conditions (e.g., diabetes, coronary vascular disease, arthritis, urinary incontinence)
- Medication induced (e.g., antihypertensives, selective serotonin reuptake inhibitors [SSRIs])
- Gynecologic conditions (e.g., cystitis, posthysterectomy, gynecologic cancers, breast cancer [femininity/self-image issues; chemotherapy effects], postpregnancy, postmenopausal)
- Psychosocial (e.g., religion, taboos, identity conflicts, guilt, relationship problems, abuse, rape, life stressors)
- Fig. S1-30 illustrates the four phases of the human sexual response as postulated by Masters and Johnson.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Depression
- Psychosocial stressors
- Medical disease (e.g., thyroid dysfunction)

LABORATORY TESTS

- Cervical cultures and vaginal swabs for infectious disease
- Pap smear
- Appropriate laboratory tests if comorbid or chronic disease is suspected

IMAGING STUDIES

Appropriate imaging studies if comorbid or chronic disease is suspected

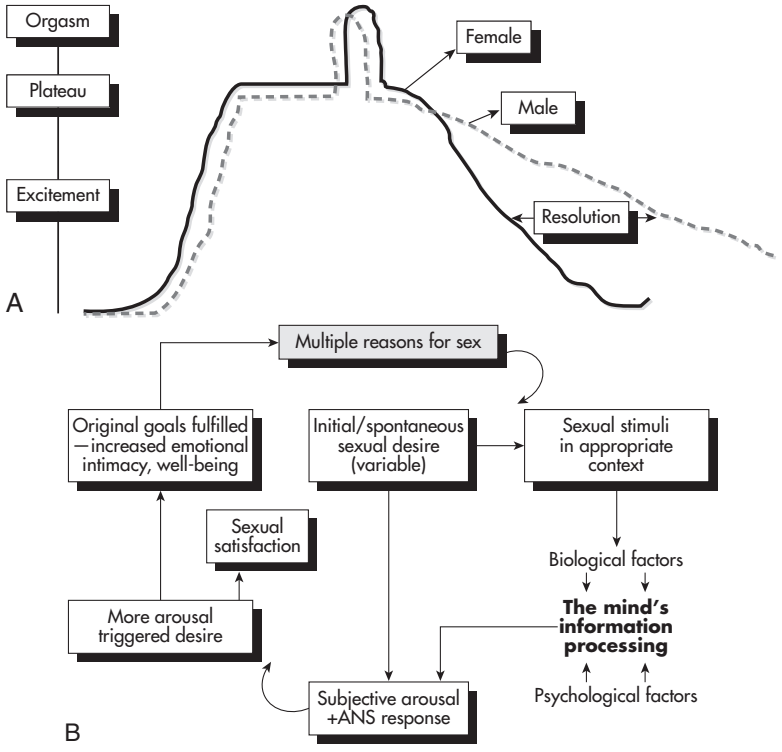


FIGURE S1-30 A, The four phases of the human sexual response cycle as postulated by Masters and Johnson. Because the resolution phase is prolonged considerably in men, men can experience refractoriness to further stimulation for varying lengths of time before they can achieve another orgasm. As discussed in the text, understanding of the human sex response cycle has evolved substantially since the publication of this work. **B,** The circular human response cycle of overlapping phases. It is increasingly recognized that the human sexual response involves much more complexity, circularity, and flexibility than is reflected in Masters and Johnson's original model. "Desire" may or may not be present initially; it can be triggered during the experience. Arousal and desire overlap. Multiple psychologic and biologic factors influence the information processing of sexual stimuli. Underlying this processing may be the individual's unique tendency for excitation versus inhibition. *ANS,* autonomic nervous system. (From Melmed S: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Education including a discussion of normal sexual behavior
- Stress management
- Activities to enhance stimulation and eliminate routine
- Distraction techniques
- Noncoital behavior
- Position changes (e.g., female astride)
- Lubricants (e.g., nonpetroleum based). There are several over-the-counter lubricants and massage oils, some of which are hypoallergenic, that can be safely applied to female genitalia

ACUTE GENERAL Rx

NSAIDs before intercourse for sexual pain disorders

CHRONIC Rx

- Treat underlying medical, gynecologic, or psychological conditions.
- Reduce comorbidities, including weight loss.
- Increase physical activity (associated with increased satisfaction and sexual engagement).
- For medication-induced conditions, decrease dose or change medication.
- For postmenopausal women or those with hypoestrogenism, try estrogen replacement therapy with or without progesterone.
- For postmenopausal vaginal and/or vulvar atrophy, ospemifene has been associated with improved sexual function.
- Testosterone therapy (controversial): results show increase in satisfying sexual activity and sexual desire. Must weigh risks vs. benefits of use.
- Sildenafil (evidence from RCTs for use in patients with neurodegenerative disease and antidepressant-induced FSD after traditional therapy has failed). Data are conflicting. Phosphodiesterase inhibitors may increase blood flow to the genitalia but generally appear to have little benefit in treating arousal disorders.
- Bupropion 300 to 400 mg/day was shown to increase sexual arousal and orgasm completion in a recent trial. In addition, adjunctive treatment with bupropion significantly improved key aspects of sexual function in women with SSRI-induced sexual dysfunction.
- Behavioral therapy (e.g., cognitive-behavioral therapy to reduce anxiety).
- Table S1-10 summarizes investigational pharmacotherapy for women's sexual dysfunctions.

REFERRAL

- Gynecologic referral for conditions that may be amenable to surgical therapy
- Psychological referral for conditions (e.g., depression, abuse) that may benefit from counseling or psychotherapy
- Social services referrals for active abuse issues

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Female Sexual Dysfunction (Patient Information)

AUTHOR: **ANNGENE G. ANTHONY, M.D., M.P.H.**

TABLE S1-10 Investigational Pharmacotherapy for Women's Sexual Dysfunctions

Sexual Dysfunction	Mechanisms of Dysfunction	Drug Type	Off-Label and Investigational Drugs	Comments
Sexual interest/desire disorder	Loss of brain's arousability to sexual stimuli	Drugs with specific serotonin receptor subtype or agonist/antagonist profile	Flibanserin: 5-HT1A agonist and 5-HT2A antagonist, weak partial D_4 agonist	RCTs (discontinued in 2010)
Subjective arousal disorder		Melanocortin agonists	Bremelanotide: synthetic peptide, α-MSH analog agonist at MC1R, MC3R, MC4R	Small RCT showed benefit for women's arousal disorder with in-home use of nasal drug 45 min before sex. Sponsor has discontinued trials.
Combined arousal disorder		Dopamine agonists	Bupropion	One small 4-mo study in nondepressed premenopausal women showed increased arousability and sexual response, no increase in initial desire.
Genital arousal disorder: Estrogen deplete	Loss of genital vasocongestion in response to sexual stimulation	To provide local substrate for estrogen and testosterone intracrine synthesis	Local vaginal DHEA	Phase 3 RCT showed increased maturation of vaginal epithelium, lower pH, and sexual benefit in all domains of response from local vaginal DHEA for 12 wk.
		Selective tissue estrogenic activity regulator with androgenic and progestogenic properties	Tibolone	RCT of dysfunctional women showed tibolone marginally superior to 50 μg/140 μg combined transdermal estradiol/norethisterone. Major problem is distinguishing the subgroup of women with genital arousal disorder who have reduced genital vasocongestion. Small RCTs in diabetes and MS showed only modest benefit from sildenafil.
Genital arousal disorder despite estrogen replete	Loss of genital vasocongestion in response to sexual stimulation	To enhance the action of NO–PDEIs	Sildenafil, tadalafil, vardenafil	
Serotoninergic antidepressant–associated orgasmic disorder	Former orgasmic response absent or extremely delayed	PDEIs	Sildenafil	8-wk RCT with very strict entry criteria showed benefit from 50-100 mg sildenafil.

D4, Dopamine 4 receptor; *DHEA,* dehydroepiandrosterone; *5-HT,* serotonin; *ISSWSH,* International Society for the Study of Women's Sexual Health; *MC1R,* melanocortin-1 receptor; *MS,* multiple sclerosis; *MSH,* melanocyte-stimulating hormone; *NO,* nitric oxide; *PDEIs,* phosphodiesterase inhibitors; *RCTs,* randomized controlled trials.

From Melmed S: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

EVIDENCE

Abstract[1]

Introduction:

Erectile dysfunction (ED) impacts both members of the couple. Female partners of men with ED are more likely to report reduced sexual quality of life than women whose partners do not have ED.

Aim:

To assess vardenafil efficacy in men with ED and determine the effects of treatment on their female partner's sexual quality of life.

Methods:

Study participants comprised men aged 18–64 years with ED and their female partners. Eligible men had ED of ≥6 months' duration and a female partner who was motivated to support their ED treatment. Eligible women had a total Female Sexual Function Index score >23.55, indicating absence of significant sexual dysfunction. Following a 4-week screening period, men were randomized to treatment with vardenafil 10 mg or placebo, which could be titrated to 20 or 5 mg after 4 weeks.

Main Outcomes Measures:

Primary efficacy variables were question 3 of the Sexual Encounter Profile questionnaire (SEP3) and the quality-of-life domain of the modified Sexual Life Quality Questionnaire (mSLQQ-QOL).

Results:

The intent-to-treat population included 343 couples, with 168 and 175 men receiving vardenafil or placebo, respectively. Vardenafil treatment significantly improved both erection maintenance and the female partners' sexual quality of life. Least squares (LS) mean SEP3 overall success rates after 12 weeks of treatment were 9.5 (baseline) vs. 67.2 (week 12) and 12.4 (baseline) vs. 24.2 (week 12) in the vardenafil and placebo groups, respectively ($P<0.0001$). In female partners, LS mean mSLQQ-QOL scores were 28.8 (baseline) vs. 68.2 (last observation carried forward [LOCF]) in the vardenafil group and 24.6 (baseline) vs. 40.5 (LOCF) in the placebo group ($P<0.0001$).

Conclusions:

Vardenafil treatment of men with ED improved both their erectile function and the sexual quality of life of their female partners. Ⓐ

Evidence-Based Reference

Martin-Morales A et al.: Improvement in sexual quality of life of the female partner following vardenafil treatment of men with erectile dysfunction: a randomized, double-blind, placebo-controlled study, *J Sex Med* 8(10):2831–2840, 2011. Ⓐ

SUGGESTED READINGS

Basson R et al.: Report of the International Consensus Development Conference on Female Sexual Dysfunction: definitions and classifications, *J Urol* 163(3):888–893, 2000.

Brown D et al.: Assessing the clinical effectiveness of sildenafil for the treatment of female sexual dysfunction, *Ann Pharmacother* 43(7):1275–1285, 2009.

Constantine G et al.: Female sexual function improved with ospemifene in postmenopausal women with vulvar and vaginal atrophy: results of a randomized, placebo-controlled trial, *Climateric Sept* 25:1–7, 2014. [Epub ahead of print].

Esposito K et al.: Lifestyle/dietary recommendations for erectile dysfunction and female sexual dysfunction, *Urol Clin North Am* 38(3):293–301, 2011.

Frank JE et al.: Diagnosis and treatment of female sexual dysfunction, *Am Fam Physician* 77(5):635–642, 2008.

Jordan R et al.: Developing treatments for female sexual dysfunction, *Clin Pharmacol Ther* 89(1):137–141, 2011.

Laumann EO et al.: Sexual dysfunction in the United States: prevalence and predictors, *JAMA* 281:537–544, 1999.

Safarinejad MR: Reversal of SSRI-induced female sexual dysfunction by adjunctive bupropion in menstruating women: a double-blind, placebo-controlled and randomized study, *J Psychopharmacol* 25(3):370–378, 2011.

Segraves RT et al.: Bupropion sustained release for the treatment of hypoactive sexual desire disorder in premenopausal women, *J Clin Psychopharmacol* 24:339, 2004.

Shifren JL et al.: Sexual problems and distress in United States women: prevalence and correlates, *Obstet Gynecol* 112(5):970–978, 2008.

BASIC INFORMATION

DEFINITION

Shaken baby syndrome is a potentially life-threatening and severe form of abuse in which an infant or child is violently shaken. Intracranial injury is caused by rapid acceleration and rotation of the cranium (sometimes associated with impact on a solid object which leads to rapid angular deceleration). The classic injury pattern associated with shaking includes diffuse subdural hemorrhage, retinal hemorrhages, and diffuse brain injury (Fig. ES1-31). The diagnosis is often difficult to make because the clinical manifestations are nonspecific, perpetrators are unlikely to report a history of trauma, and there may be little to no external signs of injury.

SYNONYMS

Shaken infant syndrome
Abusive head trauma
Nonaccidental head injury

ICD-9CM CODES
995.55 Shaken infant syndrome
ICD-10CM CODES
T74.1 Physical abuse
T74.4 Shaken infant syndrome, initial encounter

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Most common cause of death or serious neurologic injury resulting from child abuse. It is specific to infancy, when children have unique anatomic features. A population-based study conducted in the United States showed an incidence of abusive head trauma in children <2 yr of 17 per 100,000 persons with a higher incidence in the first year of life compared to the second. Population-based studies in Europe show similar incidence in the first yr.
PEAK INCIDENCE: Shaken babies are typically younger than 1 yr; with median age of 4 mo.

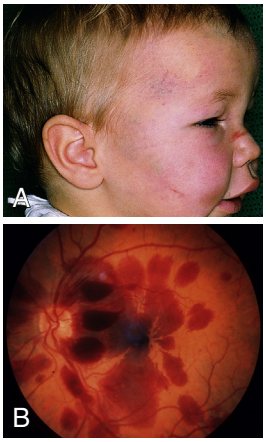


FIGURE ES1-31 Shaken baby syndrome. A, Facial bruising. **B,** Fundus hemorrhages involving different levels. (Courtesy R. Bates. From Kanski JJ, Bowling B: *Clinical ophthalmology, a systematic approach,* ed 7, Philadelphia, 2010, Saunders.)

PREVALENCE: ~25% of clinically diagnosed babies with shaken baby syndrome die, and ~80% of the remaining suffer lifelong neurologic damage.
PREDOMINANT SEX: About 60% of identified victims of shaking injury are male. Children of families who live at or below the poverty level are at an increased risk for these injuries as well as any type of child abuse.
RISK FACTORS: History of abuse, history of domestic violence, low socioeconomic status, perinatal illness, incessant crying, and family dysfunction. The perpetrators in 65%-90% of cases are males and are most commonly the father.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

In several retrospective series, no history of a traumatic event was offered in 64%-97% of cases. One study of 364 children with shaken baby syndrome found that 40% had no signs of external injury on initial evaluation. Majority will have an abnormal neurologic examination. Generally present with nonspecific symptoms (i.e., seizures, failure to thrive, vomiting associated with lethargy or drowsiness, decreased feeding, hypothermia, bradycardia, hypertension or hypotension, respiratory irregularities, apnea, coma or death). Retinal and cranial hemorrhages and brain injury are hallmarks of the syndrome. Other signs of abuse such as skull fractures, occult fractures (particularly of ribs and long bone diaphysis), abdominal injury and hearing loss, may be present.

ETIOLOGY

Angular deceleration forces cause primary parenchymal injury including traumatic axonal injury. Neuropathology and imaging techniques have established the cause of brain injury as hypoxic ischemic encephalopathy.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Head trauma from other etiology vs. infection vs. bleeding disorder vs. other etiology

WORKUP

Imaging of the brain, skeletal survey

LABORATORY TESTS

CBC, chemistry, coagulation study, lumbar puncture if meningitis is considered

IMAGING STUDIES

Initial study of unenhanced CT scan and skeletal survey. MRI should be done as follow up in patients with abnormal CT findings and is indicated for infants who are asymptomatic but require neuroimaging after finding noncranial injuries.

TREATMENT

Treatment focused on targeting specific injuries and also on prevention of future injuries.

NONPHARMACOLOGIC THERAPY

Admission to a hospital for observation.

ACUTE GENERAL Rx

Supportive care and interventions as dictated by the clinical, laboratory, and imaging findings

CHRONIC Rx

Counseling, working with the child's school to optimize academic development

REFERRAL

Neurologist and neurosurgery (if needed)

PEARLS & CONSIDERATIONS

PREVENTION

The National Center on Shaken Baby Syndrome offers a prevention program. Additionally, researchers like Harvey Karp have suggested ideas.

PATIENT & FAMILY EDUCATION

Shaken baby syndrome can result in lifelong, irreversible injuries. Prevention is a key component. Infants crying most commonly leads to shaking. Therefore the National Center on Shaken Baby Syndrome offers a prevention program, the **Period of Purple Crying,** which seeks to help parents and other caregivers understand crying in normal infants. By defining and describing the sometimes inconsolable infant crying that can sometimes cause stress, anger, and frustration in parents and caregivers, the program hopes to educate and empower people to prevent abusive head trauma.

Another method that may help is one suggested by author Dr. Harvey Karp's "five S's":

1. Shushing: use "white noise" or rhythmic sounds that mimic the constant whir of noise in the womb.
2. Side/stomach positioning: place the baby on the left side to help digestion.
3. Sucking: let the baby breast-feed or bottle-feed, or give the baby a pacifier or finger to suck on.
4. Swaddling: wrap the baby up snugly in a blanket to help him or her feel more secure.
5. Swinging gently: rock in a chair, use an infant swing, or take a car ride to help duplicate the constant motion the baby felt in the womb.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **PRIYA SARIN GUPTA, M.D, M.P.H., LEANNA R. GARBUS, OMS III**, and **POOJA VERMA, M.D.**

SUGGESTED READINGS

Fujiwara T et al.: Effectiveness of educational materials designed to change knowledge and behavior about crying and shaken baby syndrome: a replication of a randomized controlled trial in Japan, *Child Abuse Negl* 36(9):613–620, 2012.

Kliegman RM et al.: Nelson textbook of pediatrics. ed 19 Saunders: Philadelphia.

Kulvichit K: Circumpapillary retinal ridge in the shaken-baby syndrome, *N Engl J Med* 351(19):2021, 2004.

National Center on Shaken Baby Syndrome: homepage. Available at: http://dontshake.org. Accessed March 27, 2013.

BASIC INFORMATION

DEFINITION

Sheehan's syndrome is a state of hypopituitarism resulting from an infarct of the pituitary secondary to postpartum hemorrhage or shock, causing partial or complete loss of the anterior pituitary hormones (adrenocorticotropic hormone [ACTH], follicle-stimulating hormone [FSH], luteinizing hormone [LH], growth hormone [GH], prolactin [PRL], thyroid-stimulating hormone [TSH]) and their target organ functions.

ICD-9CM CODES
253.2 Sheehan's syndrome
ICD-10CM CODES
E23.0 Hypopituitarism

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: One case in 10,000 deliveries (perhaps more rare in the United States).
PREDOMINANT SEX: Affects only females.
RISK FACTORS:
- Hypovolemic shock.
- Type 1 (insulin-dependent) diabetes mellitus (secondary to microvascular disease).
- Sickle cell anemia (secondary to occlusion of the small vessels in the pituitary).

ONSET OF SYMPTOMS: Presentation is subacute with progressive hypopituitarism, inability to lactate (due to prolactin deficiency), and amenorrhea. Average delay of 5 to 7 yr between onset of symptoms and diagnosis of disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Failure of lactation.
- Infertility.
- Failure to resume menses after delivery.
- Failure to regrow shaved pubic or axillary hair.
- Skin depigmentation (including areola).
- Rapid breast involution.
- Superinvolution of the uterus.
- Hypothyroidism.
- Adrenal cortical insufficiency.
- Diabetes insipidus (rare).

ETIOLOGY

- Compromise of the blood supply to the low-pressure pituitary sinusoidal system may occur with postpartum hemorrhage or shock, resulting in pituitary infarct and/or necrosis.
- It is hypothesized that locally released factors may mediate vascular spasm of the pituitary blood supply.
- Severity of postpartum hemorrhage does not always correlate with the presence of Sheehan's syndrome.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Chronic infections.
- HIV.
- Sarcoidosis.
- Amyloidosis.
- Rheumatoid disease.
- Hemochromatosis.
- Metastatic carcinoma.
- Lymphocytic hypophysitis.

WORKUP

- Target gland deficiency should be investigated by measuring levels of ACTH, FSH, LH, TSH (which may be normal or low), and T_4. Cortisol and estradiol (which may be low) should also be measured.
- Provocative testing of pituitary hormone reserves (e.g., metyrapone test, insulin tolerance test, and cosyntropin test): normal, subnormal, or delayed responses may suggest the presence of islands of pituitary cells that no longer have the support of the hypothalamic-portal circulation.
- Measurement of insulin-like growth factor-I to screen for GH deficiency: subnormal levels suggest decreased GH.
- Impaired prolactin response to TRH or dopamine antagonist stimulation is frequently found.
- During pregnancy, adjustments must be made in interpreting both hormone levels and responses to various stimuli because of normal physiologic changes.

IMAGING STUDIES

- Study of choice: MRI of the pituitary.
  1. Sella turcica partially or totally empty.
  2. Rules out mass lesion.
- CT scan of the pituitary when MRI is unavailable or contraindicated.

TREATMENT

ACUTE GENERAL Rx

- Acute form can be lethal, presenting with hypotension, tachycardia, failure to lactate, and hypoglycemia.
- A high degree of suspicion is required with any woman who has undergone postpartum hemorrhage and shock.
- IV corticosteroids and fluid replacement should be given initially.
- Diagnosis is confirmed with a full endocrinologic workup.
- Thyroid hormone is replaced as levo-thyroxine.

CHRONIC Rx

- With late-onset disease (symptoms of general hypopituitarism, such as oligomenorrhea or amenorrhea, vaginal atrophic changes, and loss of libido): a full endocrinologic workup and replacement of the appropriate hormones are needed.
- With symptoms of adrenal insufficiency: corticosteroids should be given.
  1. A maintenance dose of cortisone acetate or prednisone may be given.
  2. Because adrenal production of cortisol is not entirely dependent on ACTH, replacement of mineralocorticoids is rarely necessary.
  3. Stress doses of glucocorticoids should be administered during surgery or during labor and delivery.

DISPOSITION

- Patients who receive early diagnosis and adequate hormonal replacement may expect favorable outcomes, including subsequent pregnancy.
- Central adrenal insufficiency is the primary cause of mortality in Sheehan's syndrome.

REFERRAL

Patients should have yearly examinations by an endocrinologist.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hypopituitarism (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READING

Kovacs K: Sheehan's syndrome, *Lancet* 361(9356):520, 2003.

BASIC INFORMATION

DEFINITION

Shigellosis is an inflammatory disease of the bowel caused by one of several species of *Shigella.* It is the third most common cause of diarrhea in the United States after *Salmonella* and *Campylobacter* and the most common cause of bacillary dysentery in the United States.

SYNONYMS

Bacillary dysentery

ICD-9CM CODES
004.9 Shigellosis
ICD-10CM CODES
A03.9 Shigellosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 6.59 cases per 100,000 population with approximately 450,000 cases/yr
PREDOMINANT SEX: Male homosexuals at increased risk.
PREDOMINANT AGE: Shigellosis predominantly affects children with 28 cases per 100,000 population in children <4 yr old and 25.67 cases per 100,000 population in children aged 4 to 11.
PEAK INCIDENCE: Summer.
GENETICS: Neonatal infection: rare but severe.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Possibly asymptomatic, but incubation period can range from 1 to 7 days with an average of 3 days.
- Mild illness that is usually self-limited, resolving in a few days.
- High fever.
- Watery diarrhea.Dysentery (abdominal cramps, tenesmus, and numerous, small-volume stools with blood, mucus, and pus).
- Descending intestinal tract illness, reflecting infection of small bowel first and then the colon.
- Severe disease is more common in children and elderly and outside of the United States.
- Complications of severe illness:
  1. Seizures.
  2. Megacolon.
  3. Intestinal perforation.
  4. Death.
- Extraintestinal manifestations are rare.
- Bacteremia is more common in children; in adults it has been described in patients with AIDS, the elderly, and diabetics.
- Hemolytic-uremic syndrome (HUS): can be caused by *S. dysenteriae* 1.
- Reactive arthritis, sometimes as part of Reiter's syndrome following *S. flexneri* infection.

ETIOLOGY

- *Shigella:* gram-negative rod bacteria that are less susceptible to stomach acid and thus as few as 10 to 100 bacteria can cause disease. The bacteria invade colonic tissue and cause inflammation.
  1. *S. flexneri.*
  2. *S. dysenteriae.*
  3. *S. sonnei.*
  4. *S. boydii.*
- *S. sonnei* is the most commonly isolated species in the United States (over 75% of cases), and it usually causes a mild watery diarrhea.
- Direct person-to-person transmission is thought to be the most common route. Outbreaks among men who have sex with men have occurred because of direct or indirect oral-anal contact.
- Contaminated food or water may transmit disease.
- Outbreaks have occurred in day care centers, a community wading pool frequented by toddlers, and residential institutions.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- May mimic other bacterial gastroenteritis, such as *Clostridium difficile, Salmonella, Campylobacter,* and *Yersinia.*
- Dysentery can also be caused by *Entamoeba histolytica.*
- Bloody diarrhea may resemble disease caused by invasive *E. coli* (IEC).
- Hemolytic-uremic syndrome caused by enterohemorrhagic *E. coli* (O157:H7).

LABORATORY TESTS

- The diagnosis is established by bacterial stool culture.
- Stool should be cultured from fresh samples, because the yield is increased by processing the specimen soon after passage. The best yield is from the mucoid part of the stool.
- Serology is available but rarely useful.
- Polymerase chain reaction (PCR) is available but due to cost used mainly for outbreak investigations.
- Fecal leukocyte preparation may show WBCs.
- Total WBCs may be low, normal, or high. Leukemoid reactions can occur in children.

IMAGING STUDIES

Abdominal radiographs may suggest megacolon or perforation in rare, severe cases.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Adequate hydration.
- Electrolyte replacement.

ACUTE GENERAL Rx

Antibiotics:
- To shorten course of illness.
- To limit transmission of illness.
- For adults: Pending susceptibilities, ciprofloxacin 750 mg PO bid for 3 days or levofloxacin 500 to 750 mg q day for 3 days should be used. An alternative is azithromycin 500 mg q day for 3 days.
- For children: IV ceftriaxone (50 mg/kg/day) for 5 days in cases of severe disease. For oral therapy, can use cefixime: 8 mg/kg/day as single daily dose or divided q12h for 5 days *or* azithromycin: 10 mg/kg/day in a single daily dose for 3 days. A short course of an oral quinolone can also be used safely although they are not approved for children.

DISPOSITION

- Most disease is self-limited.
- Severe illness may be fatal.

REFERRAL

For severe illness or complications.

PEARLS & CONSIDERATIONS

COMMENTS

- Shigella is one cause of "gay bowel syndrome."
- Illness is worsened by agents that decrease intestinal motility.
- Food handlers, child care providers, and health care workers should have a negative stool culture documented following treatment.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Shigellosis (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Ashkenazi S: Shigella infections in children: new insights, *Semin Pediatr Infect Dis* 15(4):246, 2004.

DuPont HL: Acute infectious diarrhea in immunocompetent adults, *N Engl J Med* 370:1532–1540, 2014.

Ekdahl K, Andersson Y: The epidemiology of travel-associated shigellosis—regional risks, seasonality and serogroups, *J Infect* 51(3):222, 2005.

Niyogi SK: Shigellosis, *J Microbiol* 43(2):133–143, 2005.

Taylor DN et al.: Rifaximin, a nonabsorbed oral antibiotic, prevents shigellosis after experimental challenge, *Clin Infect Dis* 42(9):1283, 2006.

BASIC INFORMATION

DEFINITION

Short bowel syndrome (SBS) is a malabsorption syndrome that results from extensive small intestinal resection or congenital causes (Table S1-11).

SYNONYMS

Short bowel
SBS

ICD-9CM CODES
579.3 (Postsurgical malabsorption)
ICD-10CM CODES
K91.2 Postsurgical malabsorption, not elsewhere classified

EPIDEMIOLOGY & DEMOGRAPHICS

- Parallels Crohn's disease (see "Crohn's Disease" in Section I), which is the most common cause of the syndrome in adults.
- In children, two thirds of short bowels are related to congenital abnormalities (intestinal atresia, gastroschisis, volvulus, aganglionosis) and one third are related to necrotizing enterocolitis.
- Prevalence: 10,000 to 20,000 cases are estimated to exist in the United States.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Diarrhea and steatorrhea
- Weight loss
- Anemia related to iron or vitamin B_{12} absorption
- Bleeding diathesis related to vitamin K malabsorption
- Osteoporosis/osteomalacia related to vitamin D and calcium malabsorption
- Hyponatremia, hypokalemia
- Hypovolemia
- Other macronutrient or micronutrient deficiency states

TABLE S1-11 Causes of Short Bowel Syndrome

Congenital
Congenital short bowel syndrome
Multiple atresias
Gastroschisis
Bowel resection
Necrotizing enterocolitis
Volvulus with or without malrotation
Long-segment Hirschsprung disease
Meconium peritonitis
Crohn's disease
Trauma

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

ETIOLOGY

- Extensive bowel resection for treatment of the conditions mentioned previously (see "Epidemiology").
- Congenital (Table S1-11).

The human intestine is 3 to 8 m in length. Removal of up to half of the small intestine produces no disruption in nutrient absorption, and most patients can maintain nutritional balance on oral feeding if they have more than 100 cm (3 ft) of jejunum. Similarly, 100 cm of intact jejunum can maintain a normal water, sodium, and potassium balance under normal circumstances. The presence of an intact colon can compensate for some small intestine loss.

Site-specific functions:

- Calcium, magnesium, phosphorus, iron, and vitamins are absorbed in the duodenum and proximal jejunum.
- Vitamin B_{12} and bile acids are absorbed in the ileum. The resection of more than 60 cm of ileum results in vitamin B_{12} malabsorption. The loss of more than 100 cm results in fat malabsorption (from the loss of bile acids).
- The loss of gastrointestinal endocrine hormones can affect intestinal motility.
- Intestinal bacterial overgrowth may also occur, especially if the ileocecal valve is lost.

DIAGNOSIS

Presence of macronutrient and/or micronutrient loss in a patient with a known history of bowel resection

DIFFERENTIAL DIAGNOSIS

Because the history of significant bowel resection is typically known, there is no differential diagnosis. If that history is not known, all causes of weight loss, malabsorption, and diarrhea must be considered.

TABLE S1-12 Management Strategies for Short Bowel Syndrome

1. Acute phase
   a. Treat postoperative complications
   b. Maintain full support via the parenteral route
   c. Initiate low-rate trophic enteral feeds
   d. Document amount and site of remaining bowel and underlying disease
2. Early adaptation (up to 1 yr postsurgery)
   a. Increase enteral nutrition to tolerance; supplement with glutamine
   b. Achieve permanent parenteral access, if indicated
   c. Maximize antiperistaltic agents
   d. Octreotide for high-output ostomy or fistula
   e. Dietary counseling
   f. Clinical trials of trophic growth factors
3. Long-term adaptation (>1 yr postsurgery)
   a. Recruit bypassed bowel
   b. Bowel-lengthening procedure (Bianchi or STEP)
   c. Monitor for development of TPN-associated complications, and refer for transplant before recurrent sepsis, thrombosis, or end-stage liver disease

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

TREATMENT

Extensive small bowel resection with colectomy (<100 cm of jejunum)

- Rx: long-term total parenteral nutrition (TPN). Some patients can switch to oral intake after 1 to 2 yr of TPN. In jejunostomy patients, excessive fluid loss can be reduced with H_2 blockers, proton pump inhibitors, or octreotide. Micronutrients are supplemented.

Extensive small bowel resection with partial colectomy (usually patients with Crohn's disease)

- Rx: oral intake alone is possible in all patients with >100 cm of jejunum. In addition to vitamin B_{12} deficiency, these patients often have diarrhea. Consider lactose malabsorption and bacterial overgrowth treated, respectively, with lactose restriction and antibiotics (tetracycline 250 mg tid or metronidazole 500 mg tid for 2 wk). Nonspecific antidiarrheal agents may also be indicated (e.g., Imodium or codeine). The patient must be monitored for micronutrient losses.
- Table S1-12 summarizes management strategies for SBS. Intestinal transplantation is performed mostly in children at selective centers.
- FDA-approved medications for SBS in patients receiving nutritional support are:
  1. Recombinant growth hormone somatropin (Zorbtive): effective in increasing weight and reducing parenteral nutrition volume. These effects do not persist when the drug is stopped.
  2. Teduglutide (Gattex), a recombinant DNA analog of glucagon-like peptide-2. It promotes mucosal growth in the small bowel through stimulation of crypt cell proliferation and inhibition of enterocyte apoptosis. This drug may have to be continued indefinitely for effects to persist.

COMPLICATIONS

- Oxalate kidney stones
- Cholesterol gallstones
- D-Lactic acidosis

PROGNOSIS

- Directly dependent on the extent of the bowel resection and in the case of Crohn's disease by the underlying illness
- Whether the colon remains in continuity with the small bowel is an important factor in the patient's ability to adapt after significant small bowel resection.

EVIDENCE

Available at www.expertconsult.com

RELATED CONTENT

Short Bowel Syndrome (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Background and Aims:
Teduglutide, a GLP-2 analogue, may restore intestinal structural and functional integrity by promoting repair and growth of the mucosa and reducing gastric emptying and secretion, thereby increasing fluid and nutrient absorption in patients with short bowel syndrome (SBS). This 24-week placebo-controlled study evaluated the ability of teduglutide to reduce parenteral support in patients with SBS with intestinal failure.

Methods:
In 83 patients randomised to receive subcutaneous teduglutide 0.10 mg/kg/day (n=32), 0.05 mg/kg/day (n=35) or placebo (n=16) once daily, parenteral fluids were reduced at 4-week intervals if intestinal fluid absorption (48 h urine volumes) increased ≥10%. Responders were subjects who demonstrated reductions of ≥20% in parenteral volumes from baseline at weeks 20 and 24. The primary efficacy end point, a graded response score (GRS), took into account higher levels and earlier onset of response, leading to longer duration of response. The intensity of the response was defined as a reduction from baseline in parenteral volume (from 20% to 100%), and the duration of the response was considered the response at weeks 16, 20 and 24. The results were tested according to a step-down procedure starting with the 0.10 mg/kg/day dose.

Results:
Using the GRS criteria, teduglutide in a dose of 0.10 mg/kg/day did not have a statistically significant effect compared with placebo (8/32 vs 1/16, p=0.16), while teduglutide in a dose of 0.05 mg/kg/day had a significant effect (16/35, p=0.007). Since parenteral volume reductions were equal (353±475 and 354±334 ml/day), the trend towards higher baseline parenteral volume (1816±1008 vs 1374±639 ml/day, p=0.11) in the 0.10 mg/kg/day group compared with the 0.05 mg/kg/day group may have accounted for this discrepancy. Three teduglutide-treated patients were completely weaned off parenteral support. Serious adverse events were distributed similarly between active treatment groups and placebo. Villus height, plasma citrulline concentration and lean body mass were significantly increased with teduglutide compared with placebo.

Conclusions:
Teduglutide was safe, well tolerated, intestinotrophic and suggested pro-absorptive effects facilitating reductions in parenteral support in patients with SBS with intestinal failure.ClinicalTrials.gov number: NCT00172185. Ⓐ

Abstract[2]

Background & Aims:
Teduglutide, a glucagon-like peptide 2 analogue, might restore intestinal structural and functional integrity by promoting growth of the mucosa and reducing gastric emptying and secretion. These factors could increase fluid and nutrient absorption in patients with short bowel syndrome with intestinal failure (SBS-IF). We performed a prospective study to determine whether teduglutide reduces parenteral support in patients with SBS-IF.

Methods:
We performed a 24-week study of patients with SBS-IF who were given subcutaneous teduglutide (0.05 mg/kg/d; n = 43) or placebo (n = 43) once daily. Parenteral support was reduced if 48-hour urine volumes exceeded baseline values by ≥10%. The primary efficacy end point was number of responders (patients with >20% reduction in parenteral support volume from baseline at weeks 20 and 24).

Results:
There were significantly more responders in the teduglutide group (27/43 [63%]) than the placebo group (13/43 [30%]; $P = .002$). At week 24, the mean reduction in parenteral support volume in the teduglutide group was 4.4 ± 3.8 L/wk (baseline 12.9 ± 7.8 L/wk) compared with 2.3±2.7 L/wk (baseline 13.2 ± 7.4 L/wk) in the placebo group ($P < .001$). The percentage of patients with a 1-day or more reduction in the weekly need for parenteral support was greater in the teduglutide group (21/39 [54%]) than in the placebo group (9/39 [23%]; $P = .005$). Teduglutide increased plasma concentrations of citrulline, a biomarker of mucosal mass. The distribution of treatment-emergent adverse events that led to study discontinuation was similar between patients given teduglutide (n = 2) and placebo (n = 3).

Conclusions:
Twenty-four weeks of teduglutide treatment was generally well tolerated in patients with SBS-IF. Treatment with teduglutide reduced volumes and numbers of days of parenteral support for patients with SBS-IF; ClinicalTrials.gov Number, NCT00798967. Ⓐ

Evidence-Based Reference

Jeppesen PB et al.: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome, *Gut* 60:902–914, 2011. Ⓐ

Jeppesen PB et al.: Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure, *Gastroenterology* 143:1473–1481, 2012. e3 Ⓐ

DEFINITION

Short QT syndrome (SQTS) is a genetically inherited disorder of cardiac repolarization characterized by a severely shortened QT interval on the ECG, leading to atrial and ventricular arrhythmias and sudden cardiac death in affected individuals. This is a primary electrical disorder and patients have structurally normal hearts.

SYNONYMS

SQTS

ICD 9CM CODES
426.89 Other specified conduction disorders
ICD 10CM CODES
I45.89 Other specified conduction disorders

EPIDEMIOLOGY AND DEMOGRAPHICS

- Unknown; disease described for the first time only in 2000 (Gussak et al., 2000)
- This is primarily because, while there is near-unanimity on what constitutes the upper limit of a normal QT interval, no such consensus exists about the lower limit. In most (but not all) cases of the SQTS, the QT or QTc (corrected QT interval) has been <360 msec; however, there are many individuals with that QT interval who are clinically unaffected. Consequently, the incidence and prevalence is unknown, especially given the extremely small number of individuals diagnosed with the syndrome.
- Genetics: the disease is genetically heterogeneous and transmitted in an autosomal dominant fashion. So far, six variants have been identified. Three represent gain of function mutations, and three represent loss of function mutations. SQT1 is the most common variant described, due to a mutation in the cardiac ion channel KCNH2(HERG).

PHYSICAL FINDINGS AND CLINICAL PRESENTATION:

- Seen across all age groups, though most patients are children or young adults.
- Syncope and cardiac arrest are the most common presenting features. Syncope is likely due to ventricular arrhythmias. Sudden death can happen with exercise as well as at rest. Cardiac arrest is often the first manifestation of the disease with a peak incidence in the first year of life.
- Atrial fibrillation and flutter are well described as being part of the syndrome.
- A significant percentage of patients are asymptomatic

ETIOLOGY

- Cardiac repolarization abnormality
- Genetic channelopathy transmitted via autosomal dominant mode, caused by missense mutations on genes (six identified so far)
- Mutations cause an increase in net outward current from either a reduction in inward depolarizing currents INa or ICa or augmentation of outward repolarizing currents I to, I K1, I K-ATP, I ACh, I Kr or I Ks. The resultant shortening of the action potential causes a shortening of the effective refractory period, with subsequent increased susceptibility of both atrial and ventricular muscle to premature depolarizations that lead to AF and VF.
- Acquired causes—see "Differential Diagnosis"

Dx DIAGNOSIS

- The differential diagnosis of a short QT includes various conditions such as hyperkalemia, hypercalcemia, acidosis, digitalis toxicity, effect of acetylcholine or epinephrine, sinus tachycardia, or hyperthermia. All these are possible causes of an acquired short QT interval that must be ruled out before a diagnosis of SQTS can be entertained.
- It must be remembered that merely having a short QT on the surface ECG does not confer a diagnosis of SQTS. The clinical history, including family history and genetic testing, are included in the criterion necessary to establish a diagnosis of SQTS, and are invaluable in making the diagnosis (Table S1-13).

WORK-UP

- Evaluation of any survivor of sudden death starts with a detailed history and physical examination, with particular emphasis on family history. Many patients with SQTS have unexplained syncope or palpitations prior to resuscitated sudden death. Atrial fibrillation is common in SQTS patients and a family history of lone AF should also be sought, in addition to resuscitated VF arrest.
- Physical examination is mostly normal in patients with SQTS.
- ECG findings in SQTS include not only an abnormally short QT interval (usually <360 msec), but usually also a short or even absent ST interval, with the T-wave appearing to emanate directly from the S-wave. T-waves are usually any combination of tall, narrow, and symmetric, with a prolonged Tpeak-Tend ratio (Fig. S1-32). Another feature to look for is the lack of adaptation of the QT interval to the heart rate (diminished rate dependence) as a result of which the corrected QT interval can be misleading; therefore, QT measurement on resting ECG in SQTS is more accurate with heart rate as close to 60 as possible.
- Echocardiogram and cardiac MRI should be performed to confirm a lack of structural heart disease.
- Holter recordings and stress tests can document a lack of variation of the QT interval in relation to the RR cycle; this is an important aspect of establishing the diagnosis. The QT interval shortens only slightly with increasing heart rates, so the QT and QTc values approach normal levels during faster heart rates. The QT fails to lengthen at slower heart rates.
- At electrophysiology study, the atrial and ventricular refractory periods are usually very short (140-200 msec at a CL of 400-600 msec). Sustained atrial fibrillation or flutter with rapid ventricular rates are often induced with programmed stimulation in the atrium. The inducibility of VF in SQTS patients at EPS is about 60%. EPS has a role in adding to the diagnosis by demonstrating short A and V refractory periods (also seen in other channelopathies such as Brugada syndrome), but given its low sensitivity it cannot be used for risk stratification.

TABLE S1-13 SQTS Diagnostic Criteria

	Points
QT_c, msec	
<370	1
<350	2
<330	3
Jpoint-Tpeak interval <120 msec	1
Clinical history	
History of sudden cardiac arrest	2
Documented polymorphic VT or VF	2
Unexplained syncope	1
Atrial fibrillation	1
Family history	
First- or second-degree relative with high-probability SQTS	2
First- or second-degree relative with autopsy-negative sudden cardiac death	1
Sudden infant death syndrome	1
Genotype	
Genotype positive	2
Mutation of undetermined significance in a culprit gene	1

VF, ventricular fibrillation; *VT*, ventricular tachycardia.
A minimum of 1 point must be obtained in the electrocardiographic section in order to obtain additional points.
High-probability SQTS: ≥4 points; intermediate-probability SQTS; 3 points, low-probability SQTS: ≤2 points. Electrocardiogram: must be recorded in the absence of modifiers known to shorten the QT. Jpoint-Tpeak interval must be measured in the precordial lead with the greatest amplitude T-wave. Clinical history: events must occur in the absence of an identifiable etiology, including structural heart disease. Points can only be received for 1 of cardiac arrest, documented polymorphic VT, or unexplained syncope. Family history: points can only be received once in this section.
Adapted from Gollob MH, Redpath CJ, Roberts JD: The short QT syndrome: proposed diagnostic criteria, *J Am Coll Cardiol* 57(7):802-812, 2011. http://dx.doi.org/10.1016/j.jacc.2010.09.048)

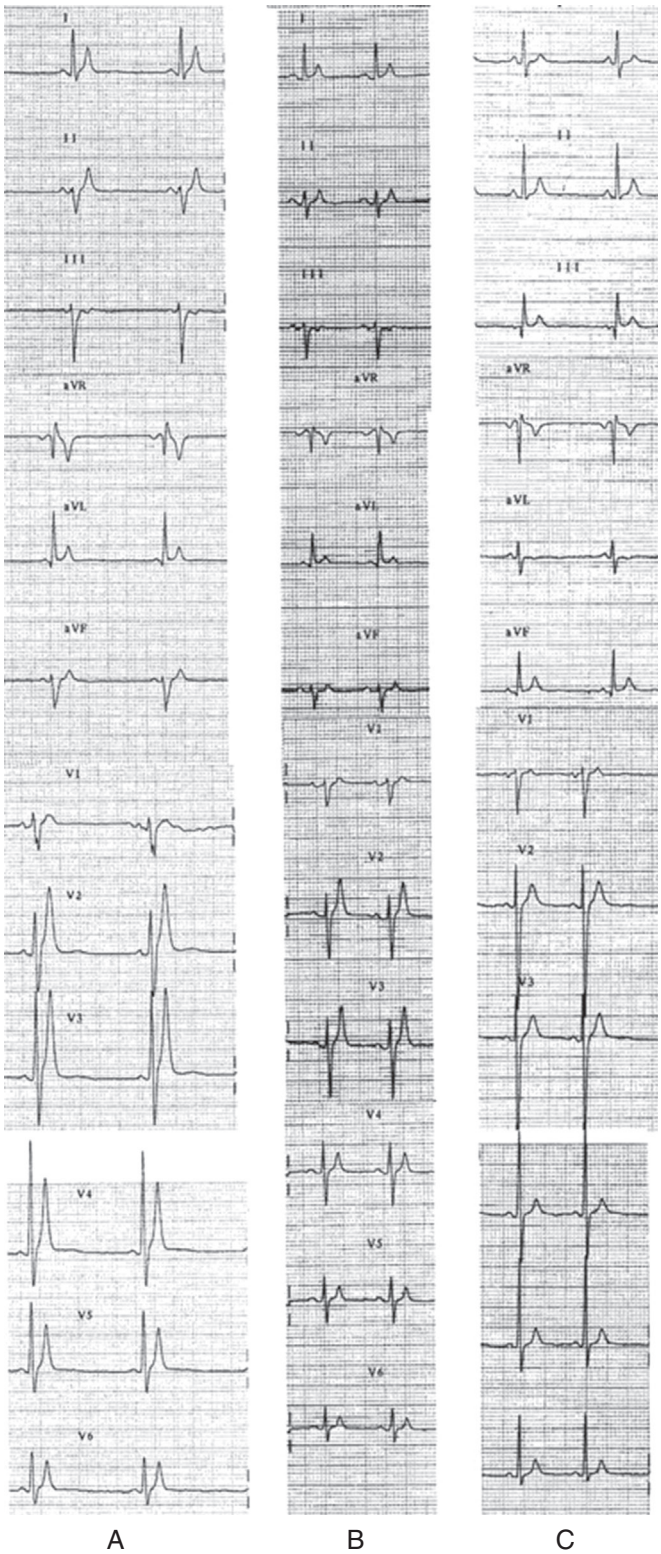


FIGURE S1-32 Twelve-lead ECG (25 mm/s paper speed) of family 1 patients. A, Patient 1 (IV, 3): sinus rhythm, heart rate 52 beats per minute (bpm); left-axis deviation, QT 280 msec. **B,** Patient 2 (IV, 2): sinus rhythm, heart rate 96 bpm; left-axis deviation, QT 220 msec. **C,** Patient 3 (V, 1): sinus rhythm with mean heart rate 92 bpm, QT 260 msec. (Adapted with permission from Gaita F et al: Short QT syndrome: a familial cause of death, *Circulation* 108:965-970, 2003.)

LABORATORY TESTS

Genetic testing is recommended for all patients in whom a diagnosis of SQTS is suspected. This is especially true if they have a clinical or family history of syncope or sudden death.

Rx TREATMENT

- There is no significant clinical data on how to approach patients with an isolated short QT interval but no family or clinical history or genotype criterion (low and intermediate probability of SQTS). Risk stratification of these patients is not possible at this time; however, they should be referred to an electrophysiologist with expertise on this topic for comprehensive testing, including genetic testing.
- Patients with QT <330 msec and one criterion from clinical/family history or genetic testing fall in the high probability category of SQTS and hence a higher risk subgroup for sudden cardiac death. An ICD implant is recommended in this group for secondary and possibly also primary prevention against sudden cardiac death.
- SQTS is a highly lethal disease and survivors of cardiac arrest are at high risk for subsequent events. ICD implantation is strongly recommended in this group.
- A peculiar issue in patients with SQTS implanted with an ICD is double counting of peaked T-waves that are closely coupled to the QRS complex. This often leads to inappropriate ICD shocks. Most ICDs have programming modifications that can be turned on to get around this problem.
- Pharmacologic therapy is usually only advised in patients with multiple and frequent appropriate ICD shocks.
- However, they may be the mainstay of therapy in patients in whom an ICD cannot be implanted for various reasons, including in children in whom technical challenges are significant.
- While many drugs, such as flecainide, sotalol, ibutilide, hydroquinone, and amiodarone, have been used in an attempt to increase the QT interval, most of the available data favor hydroquinidine as the drug of choice across all forms of the SQTS.

REFERRAL

Consultation with an electrophysiologist is strongly recommended if SQTS is suspected.

PEARLS AND CONSIDERATIONS

- SQTS is a rare genetic syndrome causing arrhythmias and sudden death.
- Should be suspected in patients with QT interval <360 msec presenting with syncope, sudden cardiac death, or atrial fibrillation and a family history of the same.

AUTHOR: **JOYDEEP GHOSH, M.D.**

SUGGESTED READINGS

Gaita F, Giustetto C: Mazzanti A. Short QT syndromes, *Card Electrophysiol Clin* 2:551–558, 2010.

Garberoglio L et al.: Is acquired short QT due to digitalis intoxication responsible for malignant ventricular arrhythmias? *J Electrocardiol* 40:43–46, 2007.

Gollob MH, Redpath CJ, Roberts JD: The short QT syndrome: proposed diagnostic criteria, *J Am Coll Cardiol* 57:802–812, 2011.

Gussak I et al.: Idiopathic short QT interval: a new clinical syndrome? *Cardiology* 94:99–102, 2000.

Mazzanti A, Kanthan A, Monteforte N et al.: Novel insight into the natural history of short Qt syndrome, *J Am Coll Cardiol* 63:1300–1308, 2014.

Patel C, Yan G, Antzelevitch C: Short QT syndrome: from bench to bedside, *Circulation* 3:401–408, 2010.

Schimpf R et al.: Congenital short QT syndrome and implantable cardioverter defibrillator treatment: inherent risk for inappropriate shock delivery, *J Cardiovasc Electrophysiol* 14:1273–1277, 2003.

Gaita F et al.: Short QT syndrome: pharmacological treatment, *J Am Coll Cardiol* 43:1494–1499, 2004.

BASIC INFORMATION

DEFINITION

Sialadenitis is an inflammation of the salivary glands.

ICD-9CM CODES
527.2 Sialadenitis
ICD-10CM CODES
K11.20 Sialadenitis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

Parotid or submandibular glands are most frequently affected (Fig. S1-33).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Pain and swelling of the affected salivary gland.
- Increased pain with meals.
- Erythema and localized tenderness at the duct opening.
- Massage may express purulent discharge from duct orifice.
- Induration and pitting of the skin, with involvement of the masseteric and submandibular spatial planes in severe cases.

ETIOLOGY

- Ductal obstruction is generally from a mucus plug caused by stasis of saliva with increased viscosity with subsequent stasis and infection.
- Acute suppurative sialadenitis is a bacterial infection of the salivary gland. Most frequent infecting organisms are *Staphylococcus aureus* (50% to 90% of cases), streptococcal species, *Hemophilus influenzae, Pseudomonas, Enterobacter, Klebsiella, Enterococcus, Proteus,* and *Candida* spp.
- Sjögren's syndrome, diabetes mellitus, hypothyroidism, renal failure, trauma, radiation therapy, chemotherapy, dehydration, and chronic illness are predisposing factors.
- Mumps is the most common cause of nonsuppurative acute sialadenitis. Majority of cases (>80%) occur in children younger than 15 years.

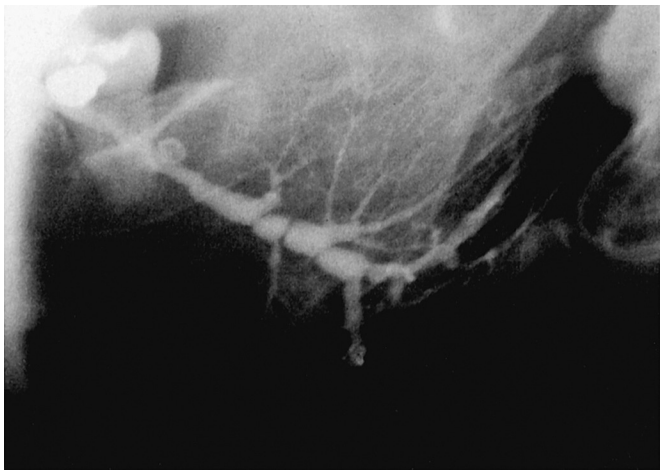


FIGURE S1-33 Sialogram of patient with chronic sialadenitis showing sausage link–like patterns and massive duct dilation. (From Blitzer CE et al: Sialadenitis. In Johnson JT, Yu VL [eds]: *Infectious diseases and antimicrobial therapy of the ears, nose, and throat,* Philadelphia, 1997, Saunders.)

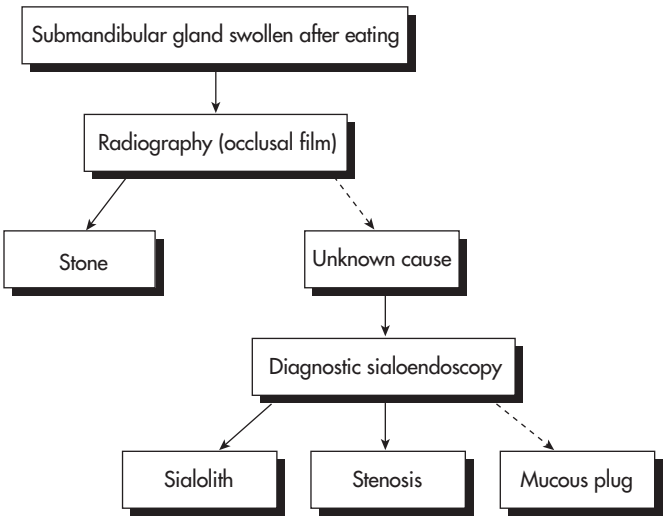


FIGURE S1-34 Diagnostic algorithm. (From C.-Q. Yu et al.; Selective management of obstructive submandibular sialadenitis; Br J Oral Maxillofacial Surg 46(1) 46–49 (2008).)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Salivary gland neoplasm.
- Ductal stricture.
- Sialolithiasis.
- Decreased salivary secretion as a result of medications (e.g., amitriptyline, diphenhydramine, anticholinergics).

WORKUP

- Generally not necessary. Fig. S1-34 describes a diagnostic algorithm.
- Ultrasound or CT scan in patients not responding to medical treatment.

LABORATORY TESTS

- Generally not indicated.
- Complete blood count with differential to possibly reveal leukocytosis with left shift.

IMAGING STUDIES

- Ultrasound or CT scan may be needed in patients not responding to medical therapy.
- Sialography should not be performed during the acute phase.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Massage of the gland: may express pus and relieve some of the pressure.
- Rehydration.
- Warm compresses.
- Oral cavity irrigations.
- Administration of sialagogues such as lemon drops or vitamin C lozenges.

ACUTE GENERAL Rx

- Amoxicillin-clavulanate 500 to 875 mg or cefuroxime 250 to 500 mg bid should be given for 10 days. Clindamycin is an alternative choice in patients allergic to penicillin.
- IV antibiotics (e.g., cefoxitin, nafcillin) can be given in severe cases.

DISPOSITION

Complete recovery unless the patient has underlying obstruction (e.g., ductal stricture, tumor, or stone)

REFERRAL

- To ear-nose-throat specialist for nonresolving cases despite appropriate antibiotic therapy.
- For salivary gland incision and drainage, which may be necessary in resistant cases.

PEARLS & CONSIDERATIONS

COMMENTS

Prevention of dehydration will decrease the risk of sialadenitis.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Salivary Gland Inflammation (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Maresh A et al.: Sialoendoscopy in the diagnosis and treatment of obstructive sialadenitis, *Laryngoscope* 121(3):495–500, 2011.

Wilson KF et al.: Salivary gland disorders, *Am Fam Physician* 89(11):882–888, 2014.

BASIC INFORMATION

DEFINITION

Sialolithiasis is the existence of hardened intraluminal deposits in the ductal system of a salivary gland.

SYNONYMS

Salivary gland stone
Salivary calculus

ICD-9CM CODES
527.5 Sialolithiasis
ICD-10CM CODES
K11.5 Sialolithiasis

EPIDEMIOLOGY & DEMOGRAPHICS

Affects patients mostly in the fifth to eighth decades and occurs most commonly in the submandibular gland (80%); only 14% are located in a parotid gland.

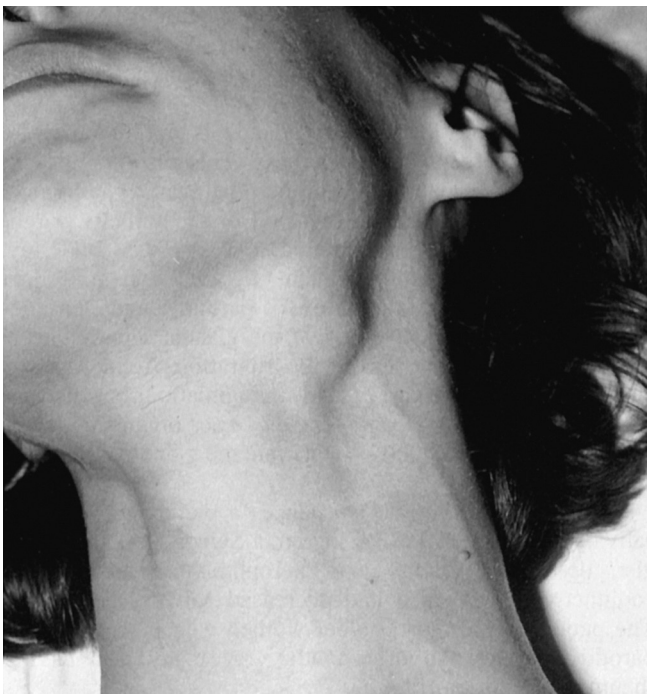


FIGURE S1-35 Patient with large calculus and obstruction of the left submandibular gland. (From Blitzer CE et al: Sialadenitis. In Johnson JT, Yu VL [eds]: *Infectious diseases and antimicrobial therapy of the ears, nose, and throat,* Philadelphia, 1997, Saunders.)

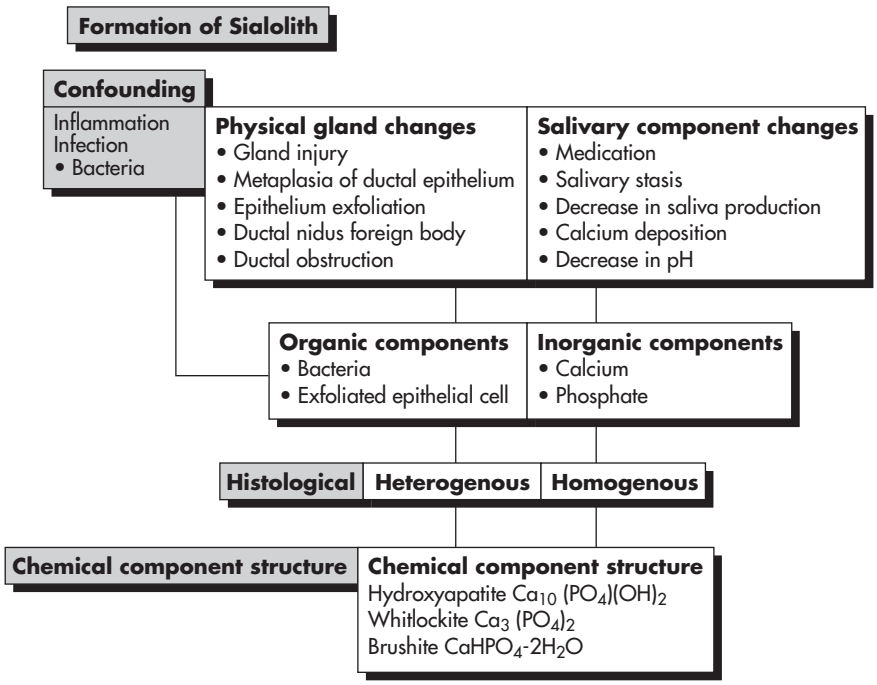


FIGURE S1-36 Algorithm of clinical findings and pathogenesis of sialolithiasis. (From Lee L.T. and Wong Y.K. Sialolithiasis in minor salivary glands. J Oral Maxillofac Surg 2010.)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms: colicky postprandial pain and swelling of a salivary gland. Tends to have a remitting/relapsing course.
- Signs: swelling and tenderness of a salivary gland. The stone may be felt by palpation of the floor of the mouth (Fig. S1-35).

ETIOLOGY

- The cause is unknown. Contributing factors include saliva stagnation, sialadenitis (inflammation of a salivary gland), ductal inflammation, or injury (Fig. S1-36).
- Salivary calculus composition is mainly calcium phosphate and carbonate, often combined with small proportions of magnesium, zinc, ammonium salts, and organic materials or debris.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Lymphadenitis.
- Salivary gland tumor.
- Salivary gland bacterial (*Staphylococcus* or *Streptococcus*), viral (mumps), or fungal infection (sialadenitis).
- Noninfectious salivary gland inflammation (e.g., Sjögren's syndrome, sarcoidosis, lymphoma).
- Salivary duct stricture.
- Dental abscess.

IMAGING STUDIES

- Ultrasonography and non–contrast-enhanced computed tomography are useful in detecting the stone.
- Sialography.

TREATMENT

- Warm soaks to area.
- Antibiotics if associated bacterial sialadenitis is present.
- Bland diet; avoid citrus fruit and spices.
- The surgical approach depends on the location of the stone. Submandibular stones can usually be excised intraorally under local anesthesia. Manual stone extraction sometimes associated with incisional enlargement of the ductal orifice. Sialendescopy with a semirigid endoscope is preferred to open surgery. Stones in the parotid duct may require parotidectomy.
- Surgical salivary gland removal may be necessary for retained hilar calculi.

REFERRAL

To otorhinolaryngologist.

RELATED CONTENT

Salivary Gland Stones (Patient Information)

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Maresh A et al.: Sialoendoscopy in the diagnosis and treatment of obstructive sialadenitis, *Laryngoscope* 121(3):495–500, 2011.

Wilson KF et al.: Salivary gland disorders, *Am Fam Physician* 89(11):882–888, 2014.

BASIC INFORMATION

DEFINITION

Sickle cell disease is a hemoglobinopathy characterized by the production of hemoglobin S caused by substitution of the amino acid valine for glutamic acid in the sixth position of the gamma-globin chain. When exposed to lower oxygen tension, red blood cells (RBCs) assume a sickle shape, resulting in stasis of RBCs in capillaries. Painful crises are caused by ischemic tissue injury resulting from obstruction of blood flow produced by sickled erythrocytes. Vasoocclusive crises are the main reason for hospital admission of children with sickle cell disease.

SYNONYMS

Sickle cell anemia
SCA
SCD
Hemoglobin S disease

ICD-9CM CODES
286.60 Sickle cell anemia
ICD-10CM CODES
D57.1 Sickle-cell disease without crisis
D57.2 Double heterozygous sickling disorders
D57.3 Sickle-cell trait
D57.8 Other sickle-cell disorders

EPIDEMIOLOGY & DEMOGRAPHICS

- Sickle cell hemoglobin S is transmitted by an autosomal-recessive gene. In African Americans, the incidence of sickle cell anemia at birth is 1 in 600 and the incidence of all genotypes of sickle cell disease is 1 in 300.
- Sickle cell trait occurs in approximately 300 million people worldwide, with the highest prevalence of approximately 30% to 40% in sub-Saharan Africa. In the United States, it is found in nearly 10% of black Americans.
- It is estimated that 2000 babies are born with sickle cell disease in the United States each year.
- There is no predominant sex.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical examination is variable depending on the degree of anemia and presence of acute vasoocclusive syndromes or neurologic, cardiovascular, genitourinary, and musculoskeletal complications. Pain in adults with sickle cell disease is the rule rather than the exception and is far more prevalent and severe than reported in older large-scale surveys.
- There is no clinical laboratory finding that is pathognomonic of painful crisis of sickle cell disease. The diagnosis of a painful episode is made solely on the basis of the medical therapy and physical examination.
- Bones are the most common site of pain. Dactylitis, or hand-foot syndrome (acute, painful swelling of the hands and feet), is the first manifestation of sickle cell disease in many infants. Irritability and refusal to walk are other common symptoms. After infancy, musculoskeletal pain can be symmetric, asymmetric, or migratory, and it may or may not be associated with swelling, low-grade fever, redness, or warmth.
- In both children and adults, sickle vasoocclusive episodes are difficult to distinguish from osteomyelitis, septic arthritis, synovitis, rheumatic fever, or gout.
- When abdominal or visceral pain is present, care should be taken to exclude sequestration syndromes (spleen, liver) or the possibility of an acute condition such as appendicitis, pancreatitis, cholecystitis, urinary tract infection, pelvic inflammatory disease, or malignancy.
- Pneumonia develops during the course of 20% of painful events and can present as chest and abdominal pain. In adults chest pain may be a result of vasoocclusion in the ribs and often precedes a pulmonary event. The lower back is also a frequent site of painful crisis in adults.
- The acute chest syndrome manifests with chest pain, fever, wheezing, tachypnea, and cough. Chest radiograph may reveal pulmonary infiltrates. Common causes include infection (*Mycoplasma, Chlamydia,* viruses), infarction, and fat embolism.
- Musculoskeletal and skin abnormalities seen in sickle cell anemia include leg ulcers (particularly on the malleoli) and limb-girdle deformities caused by avascular necrosis of the femoral and humeral heads. Osteonecrosis of the heads of the femur and humerus is found in nearly 50% of adults with sickle cell disease.
- Endocrine abnormalities include delayed sexual maturation and late physical maturation, especially evident in boys.
- Neurologic abnormalities on examination may include seizures and altered mental status. Strokes occur in about 10% of children and adults with sickle cell anemia and approximately 35% of children with sickle cell anemia have cerebrovascular disease.
- Infections, particularly involving *Salmonella, Mycoplasma,* and *Streptococcus,* are relatively common.
- Severe splenomegaly as a result of sequestration often occurs in children before splenic atrophy.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Thalassemia
- Iron-deficiency anemia, leukemia
- The differential diagnosis of patients presenting with a painful crisis is discussed in "Physical Findings"

WORKUP

- Screening of all newborns regardless of racial background is performed in the United States. Screening can be performed with sodium metabisulfite reduction test (Sickledex test).
- Hemoglobin electrophoresis will also confirm the diagnosis and is useful to identify hemoglobin variants such as fetal hemoglobin and hemoglobin A_2.
- Sickle cell disease encompasses genotypes associated with hemolysis and vasoocclusive crisis. Hemoglobin electrophoresis results, mean corpuscular volume, erythrocyte morphology, and degree of anemia can be used to differentiate among the sickle cell syndromes.
- For prenatal diagnosis, initial step is identification of parenteral globin gene mutation by DNA-based testing. If positive, then DNA-based testing of chorionic villus sampling or amniotic fluid cells is performed.

LABORATORY TESTS

- Anemia (resulting from chronic hemolysis), reticulocytosis, leukocytosis, and thrombocytosis are common.
- Elevations of bilirubin and lactate dehydrogenase are also common.
- Peripheral blood smear may reveal sickle cells, target cells, poikilocytosis, and hypochromia (Fig. S1-37).
- Elevated blood urea nitrogen and creatinine may be present in patients with progressive renal insufficiency.
- Urinalysis may reveal hematuria and proteinuria.

IMAGING STUDIES

- Chest x-ray is useful in patients presenting with chest syndrome. Cardiomegaly may be present on chest x-ray.
- MRI or bone scan is useful to rule out osteomyelitis (usually the result of *Salmonella*).
- CT scan or MRI of brain is often needed in patients with neurologic complications such as transient ischemic attack, cerebrovascular accident, seizures, or altered mental status.
- Transcranial Doppler ultrasonography (TCD) is a useful commodity to identify children with sickle cell anemia who are at risk for stroke. There should be an annual screening starting at age 2 until age 16. Patients determined to be at risk (transcranial Doppler velocity ≥200 cm/s) should be enrolled in long-term transfusion programs. These are

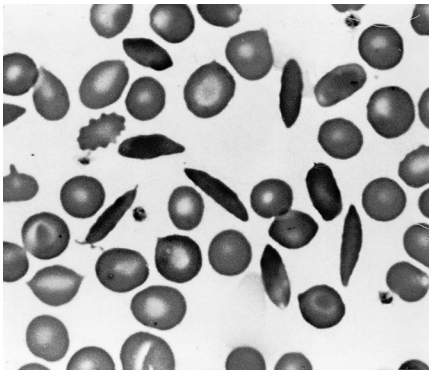


FIGURE S1-37 Photomicrograph of peripheral blood smear with sickle cells, typical of sickle cell anemia. (From Andreoli TE [ed]: *Cecil essentials of medicine,* ed 4, Philadelphia, 1997, Saunders.)

effective in reducing risk of stroke by >90%. In adults magnetic resonance angiography (MRA) can be used instead of TCD to identify those at risk for stroke.

- Doppler echocardiography may be helpful in diagnosing pulmonary hypertension but has a low positive predictive value. Screening for vasculopathy is done by estimating the tricuspid regurgitant jet velocity (TRV). Elevated values are predictive of early mortality. The prevalence of pulmonary hypertension when right heart catheterization is performed is approximately 6% in adults with sickle cell disease.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Patients should be instructed to avoid conditions that may precipitate sickling crisis, such as hypoxia, infections, acidosis, and dehydration.
- Maintain adequate hydration (PO or IV).
- Correct hypoxia.

ACUTE GENERAL Rx

- Aggressively diagnose and treat suspected infections (*Salmonella* osteomyelitis and pneumococcal infections occur more often in patients with sickle cell anemia because of splenic infarcts and atrophy). Combination therapy with a cephalosporin and erythromycin plus incentive spirometry and bronchodilators is useful in patients with acute chest syndrome.
- Provide pain relief during the vasoocclusive crisis. The fear of creating or perpetuating addiction or being deceived by patients often causes physicians to prescribe subtherapeutic dosages of opioids. However, available evidence suggests that the prevalence of drug addiction among patients with sickle cell anemia is no higher than in the overall U.S. population. Medications should be administered on a fixed time schedule with a dosing interval that does not extend beyond the duration of the desired pharmacologic effect.
  1. Meperidine is contraindicated in patients with renal dysfunction or central nervous system disease because its metabolite, normeperidine (which is excreted by the kidneys), can cause seizures.
  2. Narcotics (e.g., morphine 0.1 mg/kg IV q3-4h or 0.3 mg/kg PO q4h) should be given on a fixed schedule (not prn for pain), with rescue dosing for breakthrough pain as needed.
  3. Except when contraindications exist, concomitant use of nonsteroidal anti-inflammatory drugs should be standard treatment.
  4. Nurses should be instructed not to give narcotics if the patient is heavily sedated or respirations are depressed.
  5. When the patient shows signs of improvement, narcotic drugs should be tapered gradually to prevent withdrawal syndrome. It is advisable to observe the patient on oral pain relief medications for 12 to 24 hr before discharge from the hospital.
  6. Analgesic medications should be used in combination with psychological, behavioral, and physical modalities in the management of sickle cell disease.
     - Incentive spirometry is recommended in patients hospitalized for a vasoocclusive crisis.
- Aggressively diagnose and treat any potential complications (e.g., septic necrosis of the femoral head, priapism, bony infarcts, and acute chest syndrome).
- Overall strategies for the management of acute chest syndrome are described in Table S1-14.
- Hydroxyurea (15 mg/kg body weight per day in patients with normal creatinine clearance) increases hemoglobin F levels and reduces the incidence of vasoocclusive complications. It is generally well tolerated. Side effects consist primarily of mild, reversible neutropenia. Hydroxyurea therapy is strongly recommended for adults with three or more vasoocclusive crises during any 12-month period, with SCD pain or chronic anemia interfering with daily activities, or with severe or recurrent episodes of acute chest syndrome. It should be avoided in patients with existing leukopenia, thrombocytopenia, or severe hypoplastic anemia. It is indicated for adults with sickle cell anemia who have moderate to severe disease, typically those with three or more acute painful crises or episodes of the acute chest syndrome in the previous year.
- Replace folic acid (1 mg PO qd) due to loss from increased utilization of folic acid stores due to chronic hemolysis. Sickle cell patients also often have mineral and vitamin deficiencies (calcium, zinc, and vitamins A, C, D, and E) and may need vitamin and nutritional supplementation.

TABLE S1-14 Overall Strategies for the Management of Acute Chest Syndrome

Prevention

Incentive spirometry and periodic ambulation in patients admitted for vasoocclusive crises, surgery, or febrile episodes
Watchful waiting in any hospitalized child or adult with sickle cell disease (pulse oximetry monitoring and frequent respiratory assessments)
Avoidance of overhydration
Intense education and optimum care of patients who have sickle cell anemia and asthma

Diagnostic Testing and Laboratory Monitoring

Blood cultures
Nasopharyngeal samples for viral culture (respiratory syncytial virus, influenza)
Blood counts every day and appropriate chemistries
Continuous pulse oximetry
Chest radiographs

Treatment

Blood transfusion (simple or exchange)
Supplemental O_2 for drop in pulse oximetry by 4% over baseline, or values <90%
Empirical antibiotics (cephalosporin and macrolide)
Continued respiratory therapy (incentive spirometry and chest physiotherapy as necessary)
Bronchodilators and steroids for patients with asthma
Optimum pain control and fluid management

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

CHRONIC Rx

- Guidelines for prompt management of fever, infections, pain, and specific complications should be reviewed.
- Genetic counseling is recommended in all cases.
- Silent cerebral infarcts are the most common neurologic injury in children with sickle cell anemia and are associated with the recurrence of an infarct (stroke or silent cerebral infarct) and impaired cognition. A recent trial revealed that regular blood-transfusion therapy significantly reduced the incidence of cerebral infarct in children with sickle cell anemia. Additional research is required before these results can be translated into medical practice to develop a balance between stroke prevention and avoidance of unnecessary transfusions. Exchange transfusions may be necessary for patients with acute neurologic signs, in aplastic crisis, or undergoing surgery. The target hemoglobin level is 10 to 11 g/dl (hematocrit 30%). Transfusing to a higher Hb/Hct should be avoided due to associated hyperviscosity if there is a substantial portion of HbS in the blood. Indications for transfusion in sickle cell disease are described in Table S1-15. Iron overload due to blood transfusions (transfusional hemosiderosis) can be treated with chelating agents (deferoxamine [SC infusion], deferasirox [PO], and deferiprone [PO]).
- Angiotensin-converting enzyme inhibitor therapy is recommended for microalbuminuria in adults with SCD.
- Children and adults with proliferative sickle cell retinopathy should be referred to specialists for consideration of laser photocoagulation.
- Allogeneic stem cell transplantation can be curative in young patients with symptomatic sickle cell disease; however, the death rate from the procedure is nearly 10%, the marrow recipients are likely to be infertile, and there is an undefined risk of chemotherapy-induced malignancy. Myeloablative stem cell transplantation is generally limited to children under age 16 with severe disease.
- Penicillin V 125 mg PO bid should be administered by age 2 mo and increased to 250 mg bid by age 3 yr. Penicillin prophylaxis can be discontinued after age 5 yr except in children who have had splenectomy.
- Table S1-16 summarizes disease-modifying treatments to consider.

REFERRAL

- Hospitalization is generally recommended for most crises and complications.
- Psychosocial counseling and support structures should be developed.

TABLE S1-15 Indications for Transfusion in Sickle Cell Disease

	Duration	Consensus	Method	Goal*
Stroke, acute	Single	+	Ex	HbS < 30%
Stroke, ongoing care	Chronic	+	Either	HbS < 30%
High-velocity transcranial Doppler	Chronic	+	Either	HbS < 30%
ACS, initial episode	Single	+	Dir > Ex	Hgb 10
ACS, recurrent	6-12 mo	+	Either	
Pulmonary hypertension	Chronic	+	Either	
Multiorgan failure	Single	+	Ex	
Major surgery	Single	+	Dir	Hgb 10
Acute anemia	Single	+	Dir	
Recurrent spleen sequestration	Chronic	+		
Sepsis/meningitis	Single	+	Dir	
Severe chronic pain	6-12 mo	+		
Congestive heart failure	Chronic	+		
Silent infarct with abnormal neuropsychology	Chronic	–		
Pregnancy		–		
Anemia/renal failure	Chronic	–		
Leg ulcers	6-12 mo	–		
Severe growth delay		–		
Severe eye disease		–		
Priapism		–		

ACS, Acute chest syndrome; *Dir,* direct; *Ex,* exchange; *Hb,* hemoglobin type; *Hgb,* hemoglobin concentration; +, consensus reached; –, consensus not reached.
*Goal of transfusion if a consensus has been reached.
From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.

Table S1-16 Disease-Modifying Treatments to Consider*

Robust clinical data	Penicillin prophylaxis
	Streptococcus pneumoniae vaccination
	Hydroxyurea
	Chronic exchange transfusion
	Iron chelation for chronic iron overload†
Limited clinical data	Folate supplementation‡
	Haemophilus influenzae vaccination
	Influenza vaccination
	Erythropoietin
	Phlebotomy
Experimental	Hb F reactivation with decitabine, histone deacetylase inhibitors, or imids
	Erythropoietin for chronic relative reticulocytopenia
	Nutritional supplements and antioxidants (e.g., glutamine, zinc, multivitamins)
	N-acetylcysteine

Hb F, Fetal hemoglobin.
*See text for specific indications and limitations.
†Best data from thalassemia patient experience.
‡Risks minimal (however, can mask vitamin B_{12} deficiency). Therefore, it is generally done.
From Hoffman R: Hematology, basic principles and practice, 6th ed, Philadelphia, 2013, Saunders.

- At least yearly evaluation by a hematologist competent in sickle cell anemia is recommended in all patients with sickle cell anemia.
- Patients with pulmonary hypertension should follow up with a cardiologist and a pulmonologist.

PEARLS & CONSIDERATIONS

COMMENTS

- Pain in adults with sickle cell disease is the rule rather than the exception and needs to be treated appropriately.
- Patients and their families should receive genetic counseling and should be made aware of the difference between sickle cell trait and sickle cell disease.
- Regular immunizations and pneumococcal vaccination are recommended. The prophylactic administration of penicillin soon after birth and the timely administration of pneumococcal and *Haemophilus influenzae* type b vaccines have resulted in a significant decline in the incidence of these infections. The heptavalent conjugated pneumococcal vaccine (Prevan) should be administered from 2 mo of age. The 23-valent unconjugated pneumococcal vaccine is given from age 2 yr and can be boosted once 3 yr later. Influenza vaccination can be given after 6 mo of age.
- Patients should be instructed on a well-balanced diet and appropriate folic acid supplementation.
- The presence of dactylitis, Hb 7, or leukocytosis in the absence of infection during the first 2 yr of life indicates a higher risk of severe sickle cell disease later in life.
- Among patients with sickle cell disease, acute chest syndrome is commonly precipitated by fat embolism and infection, especially community-acquired pneumonia. Among older patients and those with neurologic symptoms, the syndrome often progresses to respiratory failure.
- Poloxamer 188, a nonionic surfactant with hemorheologic and antithrombotic properties, has been reported to produce a significant but relatively small decrease in the duration of painful episodes and an increase in the proportion of patients who achieved resolution of the symptoms. A more significant effect was observed in patients who received concomitant hydroxyurea.
- Pulmonary hypertension is a complication of chronic hemolysis and is associated with a high risk of death. It can be detected by Doppler echocardiography in more than 30% of adult patients with sickle cell disease. Cardiac catheterization will confirm the diagnosis. It is resistant to hydroxyurea therapy.
- Neurocognitive brain dysfunction is common in sickle cell disease. Trials have shown that compared with healthy controls, adults with sickle cell disease have a poorer cognitive performance, which is associated with anemia and age.
- Among patients with sickle cell disease hospitalized with vasoocclusive pain crisis, the use of inhaled nitric oxide compared with placebo did not improve time to crisis resolution.
- The average life span of individuals with sickle cell trait is similar to that of the general population. However, it is associated with a higher incidence of renal medullary cancer.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Sickle Cell Anemia (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Brawley OW et al.: National Institute of Health Consensus Development Conference Statement: hydroxyurea treatment for sickle cell disease, *Ann Intern Med* 148:932–938, 2008.

DeBraun MR et al.: Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia, *N Engl J Med* 371:699–710, 2014.

Gladwin MT, Vichinski EP: Pulmonary complications of sickle cell disease, *N Engl J Med* 359:2254–2265, 2008.

Gladwin MT et al.: Nitric oxide for inhalation in the acute treatment of sickle cell pain crisis, *JAMA* 305(9):893–902, 2011.

Lanzkron S et al.: Systematic review: hydroxyurea for the treatment of adults with sickle cell disease, *Ann Intern Med* 148:939–955, 2008.

Parent F et al.: A hemodynamic study of pulmonary hypertension in sickle cell disease, *N Engl J Med* 365:44–53, 2011.

Platt OS: Hydroxyurea for the treatment of sickle cell anemia, *N Engl J Med* 358:1362–1369, 2008.

Rogovik AL et al.: Admission and length of stay due to painful vasoocclusive crisis in children, *Am J Emergency Med* 27:797–801, 2009.

Steinberg MH: In the clinic. Sickle cell disease, *Ann Intern Med* 155(5), 2011. ITC3:1–15.

Tsaras G et al.: Complications associated with sickle cell trait: a brief narrative review, *Am J Med* 122:507–512, 2009.

Vichinsky EP et al.: Neuropsychological dysfunction and neuroimaging abnormalities in neurologically intact adults with sickle cell anemia, *JAMA* 303(18):1823–1831, 2010.

Yawn BP et al.: Management of sickle cell disease, Summary of the 2014 evidence-based report by Expert Panel Members, *JAMA* 312(10):1033–1048, 2014.

BASIC INFORMATION

DEFINITION

Sinus node dysfunction is a group of cardiac rhythm disturbances characterized by abnormalities of the sinus node, including (1) chronic, inappropriate bradycardia; (2) sinus pauses, arrest, or exit block; (3) sinoatrial exit block; and (4) alternating sinus bradycardia with paroxysmal supraventricular tachyarrhythmias known as tachycardia-bradycardia syndrome. When sinus node dysfunction is associated with symptoms, it is called sick sinus syndrome (SSS).

SYNONYMS

Sinus pause
Sinus arrest
Tachycardia-bradycardia syndrome
Sinoatrial exit block
SSS
Bradycardia-tachycardia syndrome

ICD-9CM CODES
427.81 Sick sinus syndrome
ICD-10CM CODES
I49.5 Sick sinus syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- In children: associated with congenital and acquired heart disease, particularly after cardiac surgery.
- In adults: it is primarily a disease of the elderly secondary to idiopathic degenerative disease. A recent population study has suggested that white race, increased BMI, prolonged baseline QRS or right bundle branch block, HTN, or other cardiovascular diseases are associated with increased incidence of sick sinus syndrome.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Light-headedness, syncope, presyncope, palpitations. Other manifestations include dyspnea on exertion and worsening angina.
- Physical examination may be normal or reveal abnormalities (e.g., heart murmurs or gallop sounds) associated with the underlying heart disease.

ETIOLOGY

- Sinus node fibrosis is the primary etiology, which may also affect the atrioventricular node, the His bundle, or its branches.
- In addition, acute coronary syndromes, diseases of the SA nodal artery, inflammatory and infiltrative diseases such as hemochromatosis, amyloidosis, collagen vascular diseases (SLE and scleroderma), epicardial and pericardial diseases, medications (beta-blockers, calcium channel blockers, methyldopa, cimetidine, clonidine, lithium and antiarrhythmics), trauma following cardiac surgery, hypothyroidism, hypothermia, hypoxia, sepsis, muscular dystrophies (myotonic dystrophy, Friedreich ataxia), infectious etiologies such as Lyme disease, increased intracranial pressure.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bradycardia: atrioventricular block
- Tachycardia: atrial fibrillation
- Atrial flutter
- Paroxysmal atrial tachycardia
- Sinus tachycardia

WORKUP

- ECG (Fig. S1-38)
- Ambulatory cardiac rhythm monitoring
- 24-hour ambulatory ECG (Holter) with diary to correlate symptoms to findings
- Event recorder or a loop recorder if symptoms are less frequent
- Exercise stress testing to evaluate the severity of chronotropic incompetence
- Electrophysiologic testing, including sinus nodal recovery time and sinoatrial conduction time

TREATMENT

- Permanent pacemaker placement is primarily indicated if bradycardia is symptomatic. Indications for permanent pacemaker in sinus node dysfunction are described in Table S1-17.
- In tachycardia-bradycardia syndrome, drug treatment is indicated for tachycardia, primarily with AV node blocking agents after placement of the permanent pacemaker.

REFERRAL

To cardiologist

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **AMANDA C. DORAN, M.D., Ph.D.**

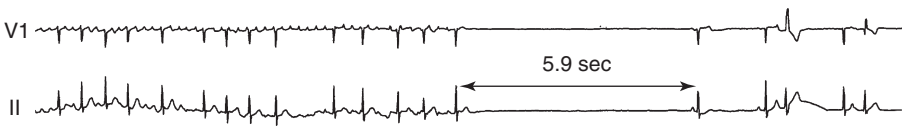


FIGURE S1-38 Tachycardia-bradycardia syndrome. Two surface ECG leads show atrial fibrillation that spontaneously terminates followed by a 5.9-second pause before sinus rhythm resumes. The patient became light-headed during this period. (From Issa Z et al: *Clinical arrhythmology and electrophysiology,* ed 2, Philadelphia, 2012, Saunders.)

TABLE S1-17 Indications for Permanent Pacing in Sinus Node Dysfunction

Class	Indications
I	• Sinus node dysfunction with documented symptomatic bradycardia or sinus pauses • Symptomatic sinus bradycardia that is iatrogenic and will occur as a consequence of essential long-term therapy of a type and dose of drugs for which there are no acceptable alternatives. • Symptomatic chronotropic incompetence.
IIa	• Sinus node dysfunction, occurring spontaneously or as a result of necessary drug therapy, with a heart rate of less than 40 beats/min when a clear association between significant symptoms consistent with bradycardia has not been documented. • Unexplained syncope when sinus abnormalities are observed or provoked with electrophysiologic study.
IIb	• A chronic heart rate of less than 40 beats/min, while awake, in the minimally symptomatic patient.
III	• Sinus node dysfunction in asymptomatic patients, including those in whom substantial sinus bradycardia (heart rate of less than 40 beats/min) is a consequence of long-term drug treatment. • Sinus node dysfunction in which symptoms suggestive of bradycardia are clearly documented as not associated with a slow heart rate. • Symptomatic bradycardia associated with non-essential drug therapy.

ACC, American College of Cardiology; *AHA*, American Heart Association; *HRA*, Heart Rhythm Society.
Adapted from ACC/AHA/HRS 2008 revised guidelines.

SUGGESTED READINGS

Epstein AE et al: ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: executive summary, *Heart Rhythm* 5:934–955, 2008.

Jensen PN et al: Incidence of and risk factors for sick sinus syndrome in the general population, *J Am Coll Cardiol* 64(6):531–538, 2014.

Semelka M et al: Sick sinus syndrome: a review, *Am Fam Physician* 87(10):691–696, 2013.

BASIC INFORMATION

DEFINITION

Sideroblastic anemia is a heterogeneous group of blood disorders whose two distinctive features are ring sideroblasts in the bone marrow (abnormal erythroblasts with excessive iron accumulation in the mitochondria) and impaired heme biosynthesis. They are classified as hereditary, acquired, and reversible.

SYNONYMS

Hereditary sideroblastic anemias
Acquired idiopathic sideroblastic anemia (AISA)
Reversible sideroblastic anemias

ICD-9CM CODES
285.0 Sideroblastic anemia
ICD-10CM CODES
D64.0 Hereditary sideroblastic anemia
D64.1 Secondary sideroblastic anemia due to disease
D64.3 Other sideroblastic anemias

EPIDEMIOLOGY & DEMOGRAPHICS

- Sex-linked; primarily affects males.
- AISA affects middle-aged and older adults.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The symptoms for sideroblastic anemia are the same for any anemia and iron overload:

- Fatigue, weakness, palpitations, shortness of breath, headaches, and irritability.
- Physical findings may include pallor, tachycardia, hepatosplenomegaly, S3 gallop, jugular vein distention, and rales.

ETIOLOGY

- The hereditary forms can be X-linked, autosomal dominant or autosomal recessive.
- Acquired forms may be associated with chemotherapy or irradiation.
- Refractory anemia with ringed sideroblast develops as a subtype of myelodysplasia.
- Reversible sideroblastic anemia can be caused by alcohol, isoniazid, pyrazinamide, cycloserine, chloramphenicol, or copper deficiency.
- A classification of sideroblastic anemias is described in Table ES1-18.

DIAGNOSIS

The principal feature is indolent and progressive mild anemia that develops insidiously in a middle-aged or elderly patient with normal or increased MCV and a blood smear showing a population of hypochromic RBCs. Symptoms of iron overload may lead to discovery of the underlying disorder. The history and clinical findings, together with typical laboratory findings, usually permit accurate diagnosis of each type of sideroblastic anemia. The molecular defects can be identified in several hereditary forms and in some patients with AISA.

TABLE ES1-18 Classification of Sideroblastic Anemias

HEREDITARY (NONSYNDROMIC)
X-linked
Autosomal dominant or recessive
ACQUIRED
Idiopathic acquired* (refractory anemia with ring sideroblasts)
Associated with previous chemotherapy, irradiation, or in transition myelodysplasia or myeloproliferative diseases
DRUGS
Alcohol
Isoniazid
Chloramphenicol
Other drugs
RARE CAUSES
Erythropoietic protoporphyria
Copper deficiency or zinc overload
Hypothermia
HEREDITARY (SYNDROMIC)
X-linked sideroblastic anemia with ring sideroblasts and cerebellar ataxia
Myopathy, lactic acidosis and sideroblastic anemia
Pearson syndrome
Thiamine-responsive megaloblastic anemia

*Trial of pyridoxine indicated.
From Hoffman R: *Hematology, basic principles and practice,* 6th ed, Philadelphia, 2013, Saunders.

DIFFERENTIAL DIAGNOSIS

- Sideroblastic anemia must be differentiated from other causes of microcytic hypochromic anemia: iron deficiency anemia, thalassemia, anemia of chronic disease, and lead poisoning.
- Tissue iron overload from sideroblastic anemia may act similar to hereditary hemochromatosis with liver cirrhosis, diabetes, congestive heart failure, or cardiac arrhythmias.

WORKUP

Laboratory evaluation: CBC, iron studies, free erythrocyte protoporphyrin level, MRI, bone marrow aspiration, and liver biopsy.

LABORATORY TESTS

- Hypochromic microcytic anemia for the hereditary type and normo- or macrocytic anemia for AISA.
- High serum iron levels, low transferrin along with increased transferrin saturation and high serum ferritin.
- Peripheral smear: dimorphic large and small cells (Fig. ES1-39) revealing Pappenheimer bodies or siderocytes when stained for iron.
- Bone marrow shows increased iron stores (Fig. ES1-40) and the classic ringed sideroblasts not seen in normal bone marrow tissue (Fig. ES1-41). The ringed sideroblasts represent iron storage in the mitochondria of normoblasts.
- In transfusion-dependent anemias, monitoring of ferritin and transferrin saturation levels is recommended despite minimal transfusion needs to avoid iron overload.
- Features of ineffective erythropoiesis like increase in indirect bilirubin concentration, decrease in haptoglobin, increase in LDH, and normal or increase in reticulocyte number is seen.

TREATMENT

Treatment is directed at controlling symptoms of anemia and preventing organ damage from iron overload.

NONPHARMACOLOGIC THERAPY

Avoid alcohol

ACUTE GENERAL Rx

- A trial of pyridoxine (100 to 200 mg) is indicated for all patients with hereditary sideroblastic anemia.
- 25% to 50% may show full or partial response to pyridoxine.
- Patients who do not respond will need to be treated with blood transfusion.
- Chelation therapy is needed for patients with transfusion-dependent anemia to prevent complications of iron overload.
- Erythropoietin and granulocyte colony-stimulating factor may show some success in treating MDS-associated refractory anemia with ringed sideroblast.
- Secondary sideroblastic anemia caused by medication can be reversed by withdrawing the medication and administering vitamin B_6 (50 to 200 mg/day).

CHRONIC Rx

- Organ dysfunction resulting from iron overload will require periodic phlebotomy to keep serum ferritin level <300 ng/ml.
- Iron chelating therapy for patients with moderately severe anemia in those who require regular red cell transfusion: deferoxamine continuous infusion or the oral agent deferasirox (EXJADE).
- Splenectomy should be avoided at all costs.

DISPOSITION

In patients with anemia alone, life expectancy is normal. In patients dependent on blood transfusions, morbidity from iron overload can be expected. There are two types of AISA:

1. Pure sideroblastic anemia: with dysplasia confined to the erythroid cell lineage; survival similar to age-matched controls; no incidence of leukemic transformation.
2. Refractory anemia with ringed sideroblasts: dysplastic features involving the red cell lineage, granulopoiesis, and/or megakaryopoiesis; approximately 5% will develop acute leukemia. Erythropoietin and granulocyte colony-stimulating factor therapy do not change survival.

REFERRAL

- Hematology.
- Families with severe forms of hereditary sideroblastic anemia should receive genetic counseling.

PEARLS & CONSIDERATIONS

- Sideroblastic anemia can be thought of as an iron-loading anemia secondary to defective heme synthesis.
- A predisposition to leukemia evolution has not been observed in patients with hereditary forms.
- Symptoms rather than an absolute hemoglobin level or hematocrit should guide transfusion therapy.

COMMENTS

Vitamin B_6, or pyridoxal phosphate, is a required cofactor in heme synthesis, and drugs such as isoniazid, cycloserine, and pyrazinamide can inhibit its function.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fig. 3-12 Algorithm for Diagnosis of Anemias (Algorithm)

AUTHOR: **BILAL H. NAQVI, M.D.**

SUGGESTED READINGS

Alcindor T, Bridges KR: Sideroblastic anemias, *Br J Hematol* 116(4):733, 2002.
Bottomley SS: Congenital sideroblastic anemias, *Curr Hematol Rep* 5(1):41, 2006.

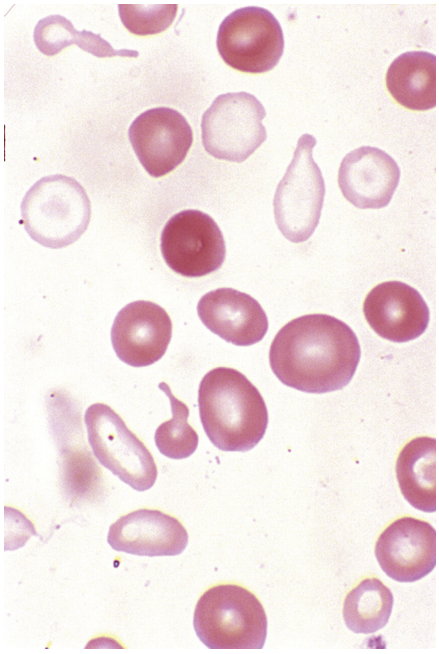


FIGURE ES1-39 Pyridoxine-responsive sideroblastic anemia showing a dimorphic population of normochromic normocytic red cells and hypochromic microcytes. Hypochromic teardrop forms are common in sideroblastic anemia. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

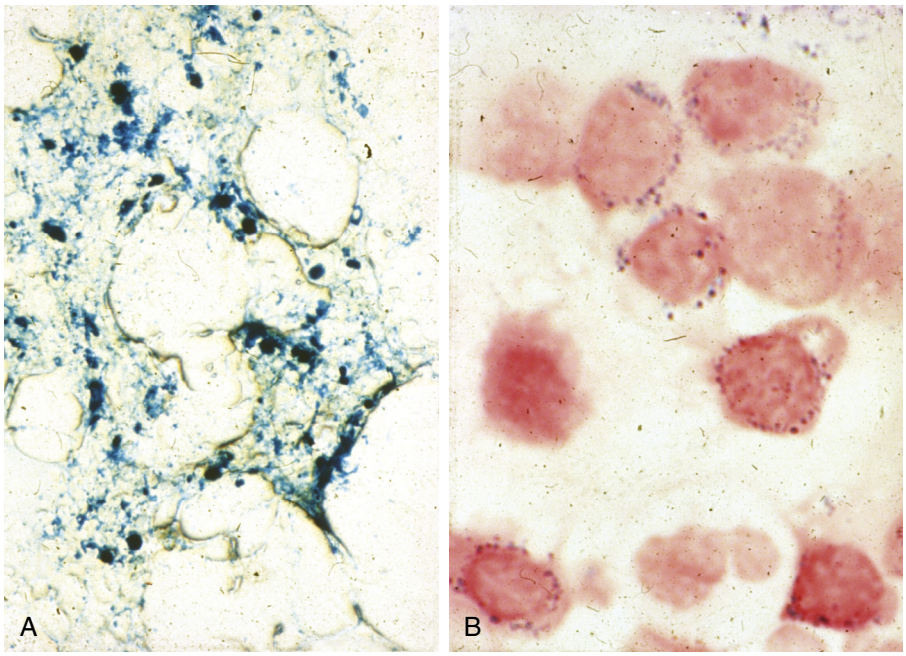


FIGURE ES1-40 Increased iron stores **(A)** and numerous ring sideroblasts **(B)** are the diagnostic hallmarks of all forms of sideroblastic anemia. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

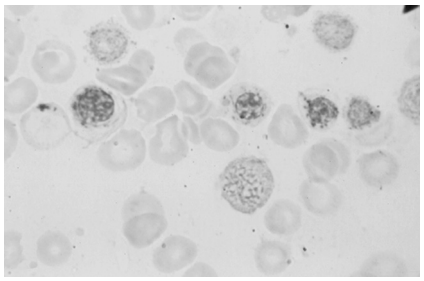


FIGURE ES1-41 Prussian blue iron stain of the bone marrow shows ringed sideroblasts. (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

BASIC INFORMATION

DEFINITION

Silicosis is a lung disease attributable to the inhalation of silica (silicon dioxide) in crystalline form (quartz) or in cristobalite or tridymite forms.

SYNONYMS

Pneumoconiosis caused by silica

ICD-9CM CODES
502 Silicosis, occupational
ICD-10CM CODES
J62.8 Pneumoconiosis due to other dust containing silica

EPIDEMIOLOGY & DEMOGRAPHICS

- Occupational disease affecting men and women involved in gathering, milling, processing, or using silica-containing rock or sand. Jobs that can lead to silicosis are described in Box S1-4.
- An estimated 1 million Americans are exposed.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Dyspnea
- Cough
- Wheezing
- Abnormal chest radiograph in an asymptomatic person

ETIOLOGY

- Silica particles are ingested by alveolar macrophages, which in turn release oxidants causing cell injury and cell death, attract fibroblasts, and activate lymphocytes, increasing immunoglobulins in the alveolar space.
- Hyperplasia of alveolar epithelial cells occurs.
- Collagen accumulates in the interstitium.
- Neutrophils also accumulate and secrete proteolytic enzymes, which leads to tissue destruction and emphysema.
- Silica dust may be carcinogenic (not proven).
- Exposure to silicosis predisposes to tuberculosis.
- Some patients develop rheumatoid silicotic pulmonary nodules and may have arthritic symptoms of rheumatoid arthritis (Caplan's syndrome). Scleroderma has also been associated with silicosis.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other pneumoconiosis, berylliosis, hard metal disease, asbestosis
- Sarcoidosis
- Tuberculosis
- Interstitial lung disease
- Hypersensitivity pneumonitis
- Lung cancer
- Langerhans' cell granulomatosis (histiocytosis X)
- Granulomatous pulmonary vasculitis

WORKUP

- History of occupational exposure
- Chest radiograph (Fig. S1-42)

Chronic silicosis:
- Most common clinical presentation. Onset is after decades of repeated exposure.
- Characteristic finding: small, rounded lung parenchymal opacities
- Hilar lymphadenopathy with "eggshell" calcifications
- Pleural plaques (uncommon)

Accelerated silicosis (progressive massive fibrosis):
- Develops <10 years after initial exposure.
- Large parenchymal lesions resulting from coalesced small nodules
- Higher risk for progressive massive fibrosis

Acute silicosis:
- Develops several weeks to <5 years after silica exposure.
- Ground-glass appearance of the lung fields
- Chest CT scan
- Pulmonary function tests
- Combination of obstructive and restrictive changes with or without reduction in diffusing capacity
- Bronchoscopy with lung biopsy in uncertain cases

COURSE

Chronic silicosis:
- May not progress with absence of further exposure
- Accelerated silicosis: progressive respiratory failure and cor pulmonale

Acute silicosis:
- Fatal course from respiratory failure over several months to a few years

TREATMENT

- Treatment is symptomatic (supplemental O_2 for hypoxemia, bronchodilators, antibiotics for infections).
- Prevention (industrial hygiene)
- Treatment of associated tuberculosis if present
- Supportive measures (oxygen, bronchodilators)
- Consider lung transplant for patients who develop chronic respiratory failure.

RELATED CONTENT

Silicosis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

BOX S1-4 Jobs That Can Lead to Silicosis

Mining: surface or underground mining (tunneling)
Milling: ground silica for abrasives and filler
Quarrying
Sandblasting (e.g., of buildings, preparing steel for painting)
Pottery; ceramic or clay work
Grinding, polishing using silica wheels
Stone work
Foundry work: grinding, molding, chipping
Refractory brick work
Glass making: to polish and as an abrasive
Boiler work: cleaning boilers
Manufacture of abrasives

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

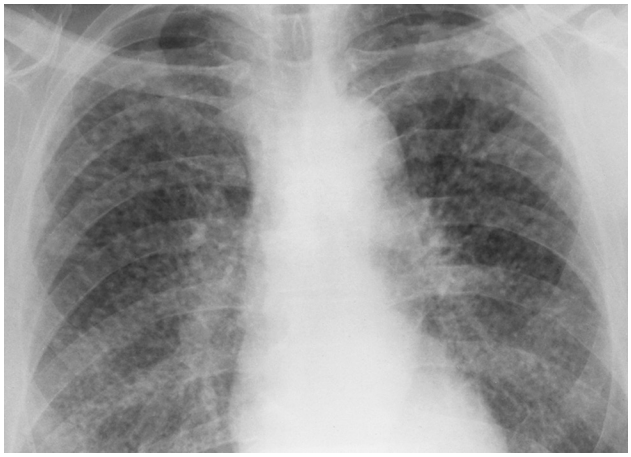


FIGURE S1-42 Simple silicosis. There are multiple small (2- to 4-mm) nodules distributed throughout the lungs, with an upper lobe predominance. (From McLoud TC: *Thoracic radiology: the requisites,* St Louis, 1998, Mosby.)

BASIC INFORMATION

DEFINITION

Cavernous sinus thrombosis (CST) is a late complication of facial or paranasal sinus infection, resulting in thrombosis of the cavernous sinus and inflammation of its surrounding anatomic structures, including cranial nerves III, IV, V (ophthalmic and maxillary branch), and VI, and the internal carotid artery.

SYNONYMS

Cavernous sinus thrombosis (CST)
Intracranial venous sinus thrombosis or thrombophlebitis
Dural sinus thrombosis

ICD-9CM CODES
325 Phlebitis and thrombophlebitis of intracranial venous sinuses
ICD-10CM CODES
G08 Intracranial and intraspinal phlebitis and thrombophlebitis

EPIDEMIOLOGY & DEMOGRAPHICS

- CST is rare in the postantibiotic era.
- Before antibiotics the mortality rate was 80% to 100%.
- With antibiotics and early diagnosis, mortality rates have fallen to ~20%.
- Reported morbidity rates have also declined from between 50% and 70% to only 22% with advances in imaging modalities and aggressive medical care.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Can be either an acute and fulminant disease or an indolent and subacute presentation.
- Septic cases of CST commonly present with high-grade fever (picket fence pattern) and signs of sepsis.
- Headache, although not specific, is the most common presenting symptom and may precede fever and periorbital edema by several days. Elderly patients, however, may only demonstrate alteration in mental status without antecedent headache. The triad of unilateral or bilateral progressive chemosis, periorbital edema, and proptosis with headache is a classical presentation in patients with CST. These signs and symptoms are related to the anatomic structures affected within the cavernous sinus, notably cranial nerves III to VI, as well as impaired venous drainage from the orbit and eye.

Other common signs and symptoms include:

- Ptosis.
- Cranial nerve palsies (III, IV, V, VI).
  1. Sixth nerve palsy is the most common (abducens nerve is located medially in the cavernous sinus and is surrounded by blood, making it more susceptible to inflammatory changes).
  2. Hypoesthesia or hyperesthesia of the ophthalmic and maxillary branch of the fifth nerve is common. Periorbital sensory loss and impaired corneal reflex may be noted.
- Papilledema, retinal hemorrhages, and decreased visual acuity progressing to blindness may occur from venous congestion within the retina.
- Pupil may be dilated and sluggishly reactive.
- Headache with nuchal rigidity and changes in mental status may occur if the infection spreads intracranially to the meninges and brain parenchyma.
- Infection can spread to the contralateral cavernous sinus through the intercavernous sinuses within 24 to 48 hr of initial presentation.
- Patients may also develop signs and symptoms of pituitary insufficiency.

ETIOLOGY

- CST most commonly results from contiguous spread of an infection from the sinuses (sphenoid, ethmoid, or frontal) or the medial third of the face (areas around the eyes and nose that drain to the ophthalmic vein). Nasal furuncles are the most common facial infection to produce this complication. Less-common primary sites of infection include dental abscess, tonsils, soft palate, middle ear, or orbit (orbital cellulitis).
- CST also can result from hematogenous spread of infection to the cavernous sinus by the superior and inferior ophthalmic veins or through the lateral and sigmoid sinuses. It can spread in a retrograde direction depending on the pressure gradients, because the dural sinuses are valveless.
- *Staphylococcus aureus* is the most commonly identified pathogen, found in 60% to 70% of the cases.
- *Streptococcus* is the second leading cause.
- Gram-negative rods and anaerobes may also lead to CST.
- Rarely, *Aspergillus fumigatus* and mucormycosis cause CST.
- Risk factors for dural sinus thrombosis include venous hypercoagulable disorders, infections (see above), trauma, malignancies, systemic inflammatory disorders, pregnancy, and dehydration.

DIAGNOSIS

- The diagnosis of CST is made by clinical suspicion and confirmed by appropriate imaging studies.
- Proptosis, ptosis, chemosis, and cranial nerve palsy beginning in one eye and progressing to the other eye establish the diagnosis.

DIFFERENTIAL DIAGNOSIS

- Orbital or periorbital cellulitis.
- Internal carotid artery aneurysm or fistula.
- Cerebrovascular disease.
- Migraine headache.
- Allergic blepharitis.
- Thyroid ophthalmopathy.
- Orbital neoplasm.
- Meningitis.
- Epidural and subdural infections.
- Epidural and subdural hematoma.
- Subarachnoid hemorrhage.
- Acute angle-closure glaucoma.
- Trauma.

WORKUP

CST is a clinical diagnosis, with laboratory tests and imaging studies confirming the clinical impression.

LABORATORY TESTS

- Complete blood count, erythrocyte sedimentation rate, blood cultures, and sinus cultures help establish and identify an infectious primary source. Metabolic panel to look for electrolyte imbalances in cases of suspected pituitary involvement (DI/SIADH).
- Lumbar puncture (LP) helps to distinguish CST from more localized processes (e.g., sinusitis, orbital cellulitis). LP reveals inflammatory cells in 75% of cases. In half of these cases, the cerebrospinal fluid profile is typical for a parameningeal focus (high white blood cells with polymorphonuclear and/or mononuclear cells, normal glucose, normal protein, culture negative), and in one third may be similar to that of a bacterial meningitis.

IMAGING STUDIES

- MRI with gadolinium, including magnetic resonance angiography and magnetic resonance venogram (Fig. S1-43), is more sensitive than CT scan and is the imaging study of choice to diagnose CST. Findings may include deformity of the internal carotid artery within the cavernous sinus and an obvious signal hyperintensity within thrombosed vascular sinuses.
- Noncontrast CT scan of the head and orbits may demonstrate increased density in the region of the cavernous sinus but has relatively low sensitivity. Contrast-enhanced CT scan may reveal underlying sinusitis, thickening of the superior ophthalmic vein, and irregular filling defects within the cavernous sinus; however, findings may be normal early in the disease course.

TREATMENT

NONPHARMACOLOGIC THERAPY

Recognizing the primary source of infection (i.e., facial cellulitis, middle ear, and sinus infections) and treating the primary source expeditiously is the best way to prevent CST.

ACUTE GENERAL Rx

- Appropriate therapy should take into account the primary source of infection as well as possible associated complications such as brain abscess, meningitis, or subdural empyema.
- Broad-spectrum intravenous antibiotics are used as empiric therapy until a definite pathogen is found. Treatment should include vancomycin to cover hospital or community-acquired methicillin-resistant *Staphylococcus*

aureus or resistant *Streptococcus pneumoniae* plus a third- or fourth-generation cephalosporin:
1. Vancomycin (1 g q12h with normal renal function) plus either ceftriaxone (2 g q12h) or cefepime (2 g q8 to 12h).
2. Metronidazole 500 mg IV q6h should be added if anaerobic bacterial infection is suspected (dental or sinus infection).

- Most experts recommend anticoagulation with heparin after the diagnosis is confirmed, unless surgical intervention is planned or there is evidence of an expanding hematoma. Cerebral infarction or intracranial hemorrhage should first be ruled out before initiating heparin therapy. Early heparinization has been suggested in patients with unilateral CST to prevent clot propagation. Coumadin therapy should be avoided in the acute phase of the illness, but should ultimately be instituted to achieve an INR of 2 to 3 and continued until the infection, symptoms, and signs of CST have resolved or significantly improved. Retrospective case reports and case series have demonstrated a favorable outcome in terms of decreased mortality in the anticoagulated patients.
- Steroid therapy is also controversial but may prove helpful in reducing cranial nerve dysfunction or when progression to pituitary insufficiency occurs. Corticosteroids should only be instituted after appropriate antibiotic coverage. Dexamethasone 10 mg q6h is the treatment of choice.
- Emergent surgical drainage with sphenoidotomy is indicated if the primary site of infection is believed to be the sphenoid sinus.

CHRONIC Rx

- Patients with CST are usually treated with prolonged courses (3 to 4 wk) of IV antibiotics. If there is evidence of complications such as intracranial suppuration, 6 to 8 wk of total therapy may be warranted.
- All patients should be monitored for signs of complicated infection, continued sepsis, or septic emboli while antibiotic therapy is being administered. Relapse of septic CST can occur after an initial improvement weeks after stopping antibiotic treatment.

DISPOSITION

- CST can be a life-threatening, rapidly progressive infectious disease with high morbidity and mortality rates (30%) despite antibiotic use. Morbidity and mortality rates are increased in cases of sphenoid sinus infection.
- Complications of untreated CST include extension of thrombus to other dural sinuses, carotid thrombosis with concomitant strokes, subdural empyema, brain abscess, or meningitis. Septic embolization may also occur to the lungs, resulting in acute respiratory distress syndrome, pulmonary abscess, empyema, and pneumothorax.
- Thirty percent of treated patients develop long-term sequelae, including cranial nerve palsies, blindness, pituitary insufficiency, and hemiparesis.

REFERRAL

If suspected, CST should be considered a medical emergency. Depending on source of infection, appropriate consultation should be made (i.e., ear-nose-throat, ophthalmology, and infectious disease).

PEARLS & CONSIDERATIONS

COMMENTS

CST is a medical emergency and should be suspected with progressing chemosis, proptosis, and cranial neuropathy in a patient with headaches with or without fever.

The anatomy of the cavernous sinus explains the clinical findings: CS lies just above and lateral to the sphenoid sinus and drains the middle portion of the face by the superior and inferior ophthalmic veins; cranial nerves III, IV, V, and VI pass alongside or through the cavernous sinus.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Cavernous Sinus Thrombosis (Patient Information)

AUTHOR: **PRASHANTH KRISHNAMOHAN, M.B.B.S., M.D.**

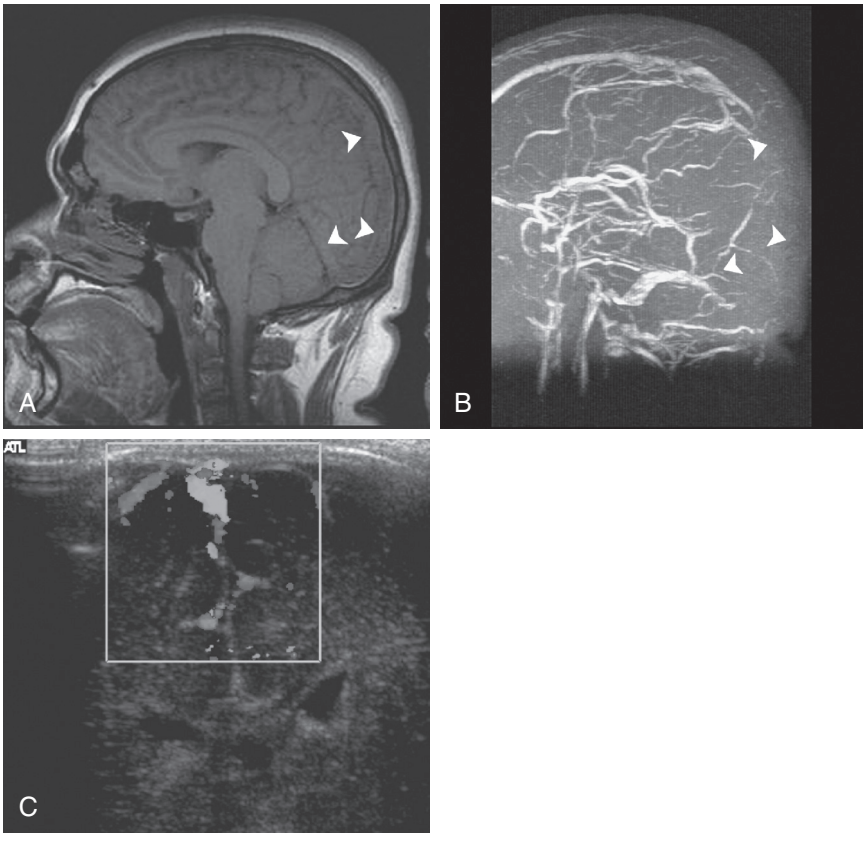


FIGURE S1-43 Superior sagittal sinus (SSS) thrombosis on magnetic resonance venogram (MRV). Sagittal T1 magnetic resonance imaging **(A)** shows intermediate signal intensity in sagittal and straight sinuses *(arrowheads).* No flow is seen on MRV **(B)** in these vessels *(arrowheads),* which is consistent with thrombosis. Color Doppler evacuation **(C)** of the SSS in another 6-mo-old patient with suspected thrombosis demonstrated a patent SSS with normal draining cortical veins. (From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.)

SUGGESTED READINGS

Agayev A, Yilmaz S: Images in clinical medicine: cavernous sinus thrombosis, *N Engl J Med* 359(21):2266, 2008.

Bhatia K, Jones NS: Septic cavernous sinus thrombosis secondary to sinusitis: are anticoagulants indicated? A review of the literature, *J Laryngol Otol* 116:667, 2002.

Coutinho JM et al.: Unfractionated or low-molecular weight heparin for the treatment of cerebral venous thrombosis, *Stroke* 41:2575–2580, 2010.

Desa V, Green R: Cavernous sinus thrombosis: current therapy, *J Oral Maxillofac Surg* 70:2085–2091, 2012.

Ferro JM et al.: Cerebral vein and dural sinus thrombosis in elderly patients, *Stroke* 36:2005, 1927.

Hoshino CH et al.: Septic cavernous sinus thrombosis complicated by narrowing of the internal carotid artery, subarachnoid abscess and multiple pulmonary septic emboli, *Intern Med* 46:317, 2007.

Leach JL et al.: Imaging of cerebral venous thrombosis: current techniques, spectrum of findings, and diagnostic pitfalls, *Radiographics* 26:S19–41, 2006.

Liu C et al.: Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicilin-resistant Staphylococcus aureus infections in adults and children, *Clin Infect Dis* 52:e18–e55, 2011.

Southwick FS. Septic dural sinus thrombosis. Available from: http://www.uptodate.com. Accessed August 29, 2011.

Southwick FS et al.: Septic thrombosis of the dural venous sinuses, *Medicine* 65:82–106, 1986.

Stam J: Thrombosis of the cerebral veins and sinuses, *N Engl J Med* 352(17):1791–1798, 2005.

BASIC INFORMATION

DEFINITION

Sinusitis is inflammation of the mucous membranes lining one or more of the paranasal sinuses. The various presentations are:

- Acute sinusitis: infection lasting <4 wk, with complete resolution of symptoms.
- Subacute infection: lasts from 4 to 12 wk, with complete resolution of symptoms.
- Recurrent acute infection: episodes of acute infection lasting <30 days, with resolution of symptoms, which recur at intervals at least 10 days apart.
- Chronic sinusitis: inflammation lasting >12 wk, with persistent upper respiratory symptoms.
- Acute bacterial sinusitis superimposed on chronic sinusitis: new symptoms that occur in patients with residual symptoms from prior infection(s). With treatment, the new symptoms resolve but the residual ones do not.

SYNONYMS

Rhinosinusitis: sinusitis is almost always accompanied by inflammation of the nasal mucosa; thus it is now the preferred term.

ICD-9CM CODES
473.9 Sinusitis (accessory) (nasal) (hyperplastic) (nonpurulent) (purulent) (chronic)
461.9 Acute sinusitis
ICD-10CM CODES
J32.9 Chronic sinusitis, unspecified
J01.90 Acute sinusitis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Seems to correlate with the incidence of upper respiratory tract infections and higher in women than men; 30 million cases a year in the United States.

PEAK INCIDENCE:

- Fall, winter, spring: September through March
- In adults: greatest incidence between 45 and 74 years of age
- Approximately 6% to 7% of children presenting with respiratory symptoms have acute sinusitis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients often give a history of a recent upper respiratory illness with some improvement, then a relapse.
- Mucopurulent secretions in the nasal passage:
  1. Purulent nasal and postnasal discharge lasting 7 to 10 days
  2. Facial tightness, pressure, or pain
  3. Nasal obstruction
  4. Headache
  5. Decreased sense of smell
  6. Purulent pharyngeal secretions, brought up with cough, often worse at night
- Erythema, swelling, and tenderness over the infected sinus in a small proportion of patients:
  1. Diagnosis cannot be excluded by the absence of such findings.
  2. These findings are not common, and do not correlate with number of positive sinus aspirates.
- Intermittent low-grade fever in about half of adults with acute bacterial sinusitis.
- Toothache is a common complaint when the maxillary sinus is involved.
- Periorbital cellulitis and excessive tearing with ethmoid sinusitis:
  1. Orbital extension of infection: chemosis, proptosis, impaired extraocular movements
- Characteristics of acute sinusitis in children with upper respiratory tract infections:
  1. Persistence of symptoms
  2. Cough
  3. Bad breath
- Symptoms of chronic sinusitis (may or may not be present):
  1. Nasal or postnasal discharge
  2. Fever
  3. Facial pain or pressure
  4. Headache
- Nosocomial sinusitis is typically seen in patients with nasogastric tubes or nasotracheal intubation.

ETIOLOGY

- Each of the four paranasal sinuses is connected to the nasal cavity by narrow tubes (ostia), 1 to 3 mm in diameter; these drain directly into the nose through the turbinates. The sinuses are lined with a ciliated mucous membrane (mucoperiosteum).
- Acute viral infection:
  1. Infection with the common cold or influenza
  2. Mucosal edema and sinus inflammation
  3. Decreased drainage of thick secretions/obstruction of the sinus ostia
  4. Subsequent entrapment of bacteria
     a. Multiplication of bacteria
     b. Secondary bacterial infection
- Other predisposing factors:
  1. Tumors
  2. Polyps
  3. Foreign bodies
  4. Congenital choanal atresia
  5. Other entities that cause obstruction of sinus drainage
  6. Allergies
  7. Asthma
- Dental infections lead to maxillary sinusitis.
- Viruses recovered alone or in combination with bacteria (in 16% of cases):
  1. Rhinovirus
  2. Coronavirus
  3. Adenovirus
  4. Parainfluenza virus
  5. Respiratory syncytial virus
- The principal bacterial pathogens in sinusitis are *Streptococcus pneumoniae*, nontypable *Haemophilus influenzae,* and *Moraxella catarrhalis*.
- In the remainder of cases *Streptococcus pyogenes, Staphylococcus aureus,* beta-hemolytic streptococci, and mixed anaerobic infections (*Peptostreptococcus, Fusobacterium, Bacteroides, Prevotella* spp.) are found.
- Infection is polymicrobial in about one third of cases.
- Anaerobic infections are seen more often in cases of chronic sinusitis and in cases associated with dental infection; anaerobes are unlikely pathogens in sinusitis in children.
- Fungal pathogens are isolated with increasing frequency in immunocompromised patients but remain uncommon pathogens in the paranasal sinuses. Fungal pathogens include: *Phaeohyphomycosis, Aspergillus, Pseudallescheria, Sporothrix,* and *Zygomycetes* spp.
- Nosocomial infections: occur in patients with nasogastric tubes, nasotracheal intubation, cystic fibrosis, and immunocompromised state.
  1. *S. aureus* (including MRSA)
  2. *Pseudomonas aeruginosa*
  3. *Klebsiella pneumoniae*
  4. *Enterobacter* spp.
  5. *Proteus mirabilis*
- Organisms typically isolated in chronic sinusitis:
  1. *S. aureus*
  2. *S. pneumoniae*
  3. *H. influenzae*
  4. *P. aeruginosa*
  5. *Anaerobes*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Temporomandibular joint disease
- Migraine headache
- Cluster headache
- Dental infection
- Trigeminal neuralgia
- Allergic rhinitis
- Drugs (cocaine, decongestant overuse)
- Gastroesophageal reflux disease
- Wegener granulomatosis
- Cystic fibrosis

WORKUP

- The diagnosis is generally based on clinical signs and symptoms (purulent rhinorrhea and facial pain). Radiologic tests and cultures are not recommended initially and should be considered only when treatment is ineffective and sinusitis persists.
- In the normal healthy host, the paranasal sinuses should be sterile. Although the contiguous structures are colonized with bacteria and likely contaminate the sinuses, the mucociliary lining functions to remove these bacteria.
- Gold standard for diagnosis: recovery of bacteria in high-density $\geq 10^4$ colony-forming units/ml from a paranasal sinus, in the setting of a patient with history of upper respiratory infection and symptoms persisting for 7 to 10 days. Sinus aspiration is the best method for obtaining cultures; however, it must be

performed by an otorhinolaryngologist and is not practical for the primary care practitioner. Therefore, most diagnoses are based on the clinical history and presentation, possibly supported by radiologic evaluations.

1. Standard four-view sinus radiographs
   a. Complete opacification and air-fluid levels are most specific findings (average 85% and 80%, respectively)
   b. Mucosal thickening has low specificity (40% to 50%)
   c. Absence of all three of the previous findings has estimated sensitivity of 90%
   d. Overall, standard radiographs are of limited use in diagnosis, although negative films are strong evidence against the diagnosis
2. CT scans:
   a. Much more sensitive than plain radiographs in detecting acute changes and disease in the sinuses
   b. Recommended for patients requiring surgical intervention, including sinus aspiration; it is a useful adjunct to guide therapy
3. Transillumination:
   a. Used for diagnosis of frontal and maxillary sinusitis
   b. Place transilluminator in the mouth or against cheek to assess maxillary sinuses, under medial aspect of the supraorbital ridge to assess frontal sinuses
   c. Absence of light transmission indicates that sinus is filled with fluid
   d. Dullness (decreased light transmission) is less helpful in diagnosing infection
4. Endoscopy:
   a. Used to visualize secretions coming from the ostia of infected sinuses
   b. Culture collection via endoscopy often contaminated by nasal flora; not nearly as good as sinus puncture
5. Sinus puncture:
   a. Gold standard for collecting sinus cultures
   b. Generally reserved for treatment failures, suspected intracranial extension, and nosocomial sinusitis

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

To help promote sinus drainage:

- Air humidification with vaporizers (for steam) or humidifiers (for a cool mist)
- Application of hot, wet towel over the face
- Sipping hot beverages
- Hydration

ACUTE GENERAL Rx

- Sinus drainage:
  1. Nasal vasoconstrictors, such as phenylephrine nose drops, 0.25% or 0.5%
  2. Topical decongestants should not be used for more than a few days because of the risk of rebound congestion
  3. Systemic decongestants
  4. Nasal or systemic corticosteroids, such as nasal beclomethasone, short-course oral prednisone
  5. Nasal irrigation, with hypertonic or normal saline (saline may act as a mild vasoconstrictor of nasal blood flow)
  6. Use of antihistamines has no proven benefit, and the drying effect on the mucous membranes may cause crusting, which blocks the ostia, thus interfering with sinus drainage
- Analgesics, antipyretics

Antimicrobial therapy:

- Most cases of acute sinusitis have a viral cause and will resolve within 2 wk without antibiotics.
- Current treatment recommendations favor symptomatic treatment for those with mild symptoms. Physicians grossly overprescribe antibiotics for presumed bacterial sinusitis despite a much higher prevalence of viral infections.
- Antibiotics should not be prescribed for mild to moderate sinusitis within the first week of illness. They should be reserved for those with severe symptoms who meet the criteria for diagnosis of sinusitis.
- Antibiotic therapy is usually empiric, targeting the common pathogens:
  1. First-line antibiotics in children include amoxicillin or amoxicillin/clavulanate. For adults amoxicillin/clavulanate or doxycycline is first-line agent, with quinolones (levofloxacin or moxifloxacin) reserved as second-line agents unless patient is penicillin allergic.
  2. Second-line antibiotics include the newer macrolides: clarithromycin, and oral cephalosporins: cefuroxime axetil, cefprozil, cefaclor, loracarbef, but high rate of resistance of *S. pneumoniae* is a concern with these agents as is *H. influenzae* resistance with TMP-SMX and azithromycin such that they should no longer be used as first-line agents.
  3. For patients with uncomplicated acute sinusitis, the less expensive first-line agents appear to be as effective as the costlier second-line agents.
- Hospitalization and IV antibiotics may be required for more severe infection and those with suspected intracranial complications. Broader-spectrum antibiotic coverage may be indicated in severe cases, to cover for MRSA, *Pseudomonas*, and fungal pathogens.
- Duration of therapy generally 5 to 7 days in adults rather than 10 to 14 days as recommended in the past.

  Optimal duration of treatment in children varies from 10 to 28 days.

Surgery:

- Surgical drainage indicated
  1. If intracranial or orbital complications suspected
  2. Many cases of frontal and sphenoid sinusitis
  3. Chronic sinusitis recalcitrant to medical therapy
- Surgical debridement imperative in the treatment of fungal sinusitis

Complications:

- Untreated, sinusitis may lead to a number of serious, life-threatening complications.
- Intracranial complications include meningitis, brain abscess, and epidural and subdural empyema.
- Intracranial sequelae are more common with frontal and ethmoid infections.
- Extracranial complications include orbital cellulitis, blindness, orbital abscess, osteomyelitis.
- Extracranial sequelae are more commonly seen with ethmoid sinusitis.

CHRONIC Rx

- Broad-spectrum antibiotics that cover both aerobes and anaerobes
- Duration of therapy not clearly established: range 3 to 6 wk
- Adjunctive therapy: one or more of the various options listed previously
- Surgical intervention may be necessary in nonresponders

DISPOSITION

Appropriate diagnosis and treatment are necessary to avoid the various sequelae that can occur without proper therapy.

REFERRAL

- To infectious disease specialist if failure to respond to initial therapy
- To otorhinolaryngologist for:
  1. Failure to respond to therapy
  2. Suspected fungal infection
  3. Suspected intracranial or orbital complications

PEARLS & CONSIDERATIONS

- Recurrent sinusitis is usually related to anatomic defects, poor drainage, or immunocompromised states; such patients deserve a thorough workup by an ENT specialist and/or an infectious disease specialist.
- Nosocomial sinusitis from obstruction by nasotracheal or nasogastric tubes is not uncommon and can be difficult to recognize in patients in the critical care units.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Sinusitis (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

AAP Guideline on diagnosis and management of acute bacterial sinusitis in children 1 to 18 years of age, *Pediatrics*, 2013.

Cherry WB, Li J: Chronic rhinosinusitis in adults, *Am J Med* 121:185–189, 2008.

DeMuri GP, Wald ER: Acute bacterial sinusitis in children, *N Engl J Med* 367: 1128–1134, 2012.

Garbutt J et al.: Amoxicillin for acute rhinosinusitis, *JAMA* 307(7):686, 2012.

Rosenfeld RM, et al.: Clinical practice guideline: adult sinusitis, *Otolaryngol Head Neck Surg* 137(3 Suppl):S1–S31, 2007.

Smith SR et al.: Treatment of mild to moderate sinusitis, *Arch Intern Med* 172(6):510–513, 2012.

Taxy JB: Paranasal fungal sinusitis: contributions of histopathology to diagnosis: a report of 60 cases and literature review, *Am J Surg Pathol* 30(6):713, 2006.

Turner BJ et al.: In the clinic: acute sinusitis, *Ann Intern Med ITC* 13–31, 2010.

Williamson I et al.: Antibiotics and topical nasal steroid for treatment of acute maxillary sinusitis, *JAMA* 298(1):2487–2496, 2007.

BASIC INFORMATION

DEFINITION

Sjögren's syndrome (SS) is an autoimmune disorder that targets exocrine glands. It is characterized by lymphocytic and plasma cell infiltration and destruction of salivary and lacrimal glands with subsequent diminished lacrimal and salivary gland secretions. It can occur in both primary and secondary forms.

- Primary: dry mouth (xerostomia) and dry eyes (xerophthalmia) develop as isolated entities.
- Secondary: associated with other autoimmune connective tissue diseases.

SYNONYMS

Sicca syndrome
Sicca complex

ICD-9CM CODES
710.2 Sjögren's syndrome
ICD-10CM CODES
M35.00 Sicca syndrome, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 3.9 per 100,000
PREVALENCE: Prevalence is 0.3% to 0.6% of population; secondary SS is also common and can affect up to 15% of patients with systemic lupus erythematosus (SLE) and nearly 25% of rheumatoid arthritis (RA) and scleroderma patients.
PREDOMINANT SEX: Female/male ratio of approximately 9:1
PREDOMINANT AGE: Peak incidence is in the fourth and fifth decade, but SS can occur in all ages.
RISK FACTOR: Seen in all races/ethnicities, but more common in Caucasians.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Diagnosis of SS is based on the presence of at least two of three objective diagnostic tests below:
  1. Positive serum levels of anti-SS-A/Ro and/or anti-SS-B/La or a positive rheumatoid factor and antinuclear antibody (ANA) titer of at least 1:320
  2. Salivary gland biopsy exhibiting focal sites of inflammation. One or more sites of inflammation per 4 mm^2 is considered to be positive.
  3. Keratoconjunctivitis sicca with ocular staining score of three or more (the dissipation rate of a specialized dye that is applied to the tear film that bathes the surface of the eye; a score of three or more is considered to be positive).
- Dry mouth with dry lips (cheilosis), erythema of tongue (Fig. S1-44) and other mucosal surfaces, carious teeth
- Dry eyes (conjunctival injection, corneal ulceration, blurred vision, decreased luster, enlargement of lacrimal glands, and irregularity of the corneal light reflex)
- Possible salivary gland enlargement and dysfunction, with subsequent difficulty in chewing and swallowing food and in speaking without frequent water intake, thickened saliva, and burning sensation in mouth
- Leukocytoclastic vasculitis may be present.
- Skin ulceration, photosensitivity, and allergic drug eruptions
- Extraglandular involvement occurs in 50% of patients. There are multiple systemic manifestations associated with SS, which include the following:
  - Dyspareunia can occur secondary to vaginal dryness
  - Pulmonary involvement includes interstitial lung disease, chronic obstructive pulmonary disease, lymphocytic interstitial pneumonitis, fibrosis, and xerotrachea
  - Gastrointestinal conditions such as esophageal dysmotility, hepatitis, and pancreatitis can occur
  - Renal manifestations include renal tubular acidosis, Fanconi syndrome, and interstitial nephritis
  - Neurologic involvement including peripheral neuropathy and trigeminal neuropathy
  - Musculoskeletal symptoms including arthralgias and polymyopathy
  - Hematologic conditions such as lymphoma and leukopenia. Nearly 5% of patients develop B-cell lymphoma.
  - RA and other connective tissue diseases are present in secondary SS.
  - Hypothyroidism may be observed in patients with SS.

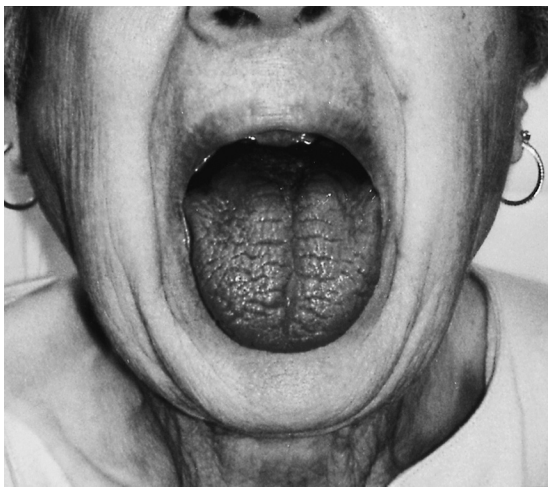


FIGURE S1-44 "Crocodile tongue" in a patient with Sjögren's syndrome. (From Noble J: *Primary care medicine*, ed 3, St Louis, 2001, Mosby.)

ETIOLOGY

Autoimmune disorder of unclear etiology. It is associated with certain HLA-DQ alleles. It has been postulated that viral agents (e.g., hepatitis C) may trigger the clinical presentation.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Medication-related dryness (e.g., anticholinergics, antihistamines)
- Age-related exocrine gland dysfunction
- Mouth breathing
- Anxiety
- HIV infection
- Hepatitis C infection
- Diabetes mellitus
- Chronic sialadenitis
- Acromegaly
- Hyperlipidemia
- Graft-versus-host disease
- Other: sarcoidosis, primary salivary hypofunction, radiation injury, amyloidosis
- IgG4-related disease
- Ocular herpetic lesions, blepharitis, corneal abrasions
- An algorithm for the diagnosis of SS is provided in Fig. S1-45.

WORKUP

Workup involves ocular and oral examination and laboratory and radiographic testing to demonstrate the following criteria for diagnosis of primary and secondary SS.

PRIMARY

- Symptoms and objective signs of ocular dryness:
  1. Schirmer's test (Fig. S1-46): <8 mm wetting per 5 min
  2. Positive rose bengal or fluorescein staining of cornea and conjunctiva to demonstrate keratoconjunctivitis sicca
  3. Tear breakup time and tear osmolality measured after instillation of fluorescein
- Symptoms and objective signs of dry mouth:
  1. Decreased parotid flow using Lashley cups or other methods
  2. Abnormal biopsy result of minor salivary gland (focus score >2 based on average of four assessable lobules)
  3. Assessment of rate of saliva production in which collection of ≤1.5 ml after two expectorations 15 min apart is considered positive
- Evidence of systemic autoimmune disorder:
  1. Elevated rheumatoid factor (70%-90% of patients)
  2. Elevated titer of ANA >1:320 (80% of patients)
  3. Presence of anti-SS-A (Ro) (>60% of patients) or anti-SS-B (La) antibodies (40% of patients)

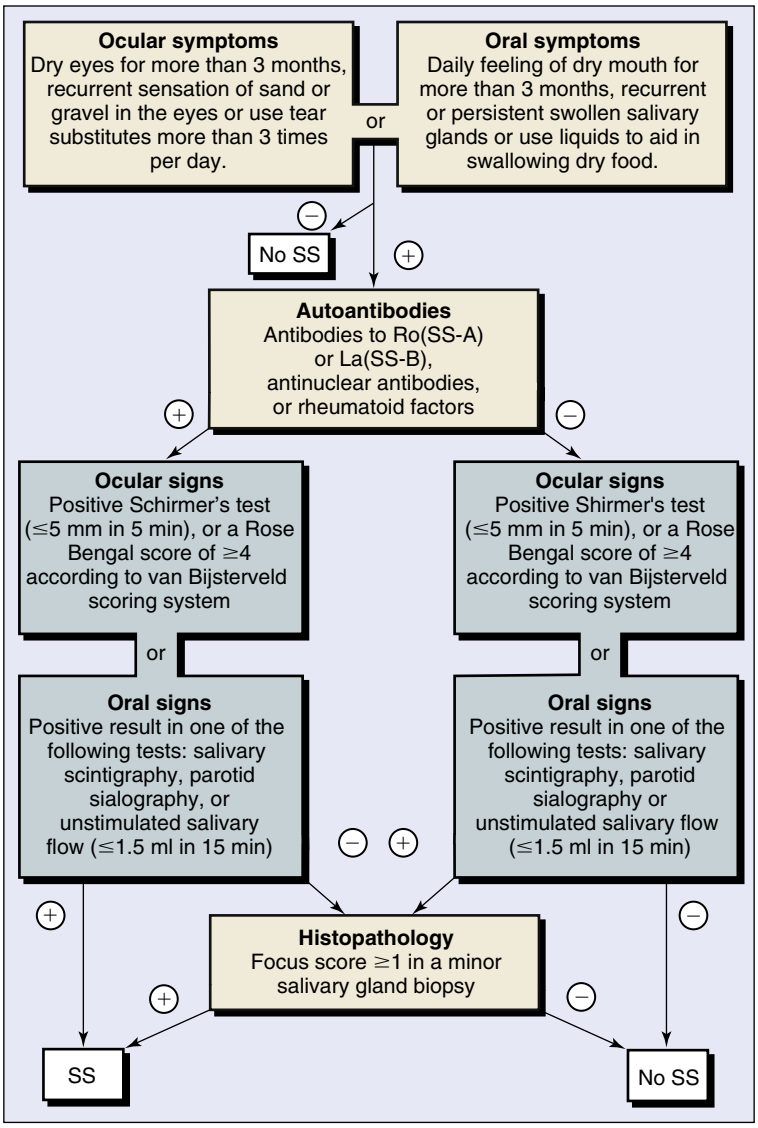


FIGURE S1-45 Suggested algorithm for the diagnosis of Sjögren's syndrome. Exclusion criteria include hepatitis C or human immunodeficiency virus infection, sarcoidosis, graft-versus-host disease, preexisting lymphoma, previous head or neck irradiation, and use of anticholinergic drugs. (From Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.)

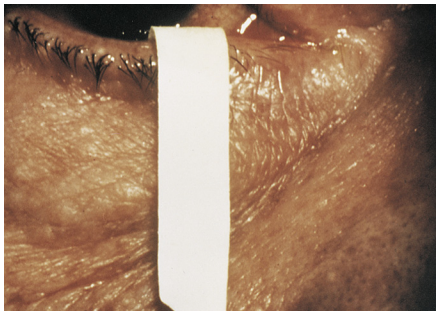


FIGURE S1-46 Schirmer test in a patient with Sjögren's syndrome. Wetting of less than 5 mm/5 min of the filter paper strip is shown. (From Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.)

SECONDARY

- Characteristic signs and symptoms of SS
- Clinical features sufficient to allow a diagnosis of RA, SLE, polymyositis, or scleroderma

LABORATORY TESTS

- Positive ANA (80% of patients) with autoantibodies anti-SS-A and anti-SS-B may be present.
- Additional laboratory abnormalities may include elevated erythrocyte sedimentation rate, anemia (normochromic, normocytic), abnormal liver function studies, elevated serum beta$_2$ microglobulin levels, rheumatoid factor, hypergammaglobulinemia, antibodies to double–stranded DNA in cases with proteinuria, serum C3 and C4, and cryoglobulins (30% of patients).
- A definite diagnosis of SS can be made with a salivary gland biopsy.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Adequate fluid replacement. Ameliorate skin dryness by gently blotting dry after bathing, leaving a small amount of moisture, and then applying a moisturizer.
- Increased environmental moisture by using humidifiers
- Proper oral hygiene (daily topical fluoride use, antimicrobial mouth rinses, and stabilization of oral cavity pH) to reduce the incidence of caries.
- Sugar-free chewing gum and sour lemon lozenges to stimulate salivary secretion.
- Periodic dental and ophthalmologic evaluations to screen for complications

GENERAL Rx

- Use artificial tears frequently.
- The muscarinic agonist pilocarpine (5 mg PO qid) is useful to improve dryness. A cyclosporine 0.05% ophthalmic emulsion (Restasis) may also be useful for dry eyes.
- Cevimeline (Evoxac), a cholinergic agent with muscarinic agonist activity, 30 mg PO tid is effective for the treatment of dry mouth in patients with SS.
- Hydroxychloroquine alone or in conjunction with methotrexate may be useful for arthralgias and cutaneous manifestations.
- Oral cyclosporine only improves the symptoms of subjective dryness.
- Rituximab (RTX) has shown some improvement in oral dry mouth symptoms although its utility is not yet fully established.
- Propionic acid gel can be used for vaginal dryness.
- Systemic manifestations are treated according to symptoms and complications.
- Cyclophosphamide, azathioprine, and mycophenolate mofetil are generally reserved for life-threatening extraglandular manifestations.
- Fig. ES1-47 describes a treatment algorithm for Sjögren's syndrome.

REFERRAL

- Rheumatology referral is generally indicated.
- Referral should be made to an oncologist when lymphoma is suspected.

PEARLS & CONSIDERATIONS

COMMENTS

- Unusual presentations of SS may occur in association with polymyalgia rheumatica, chronic fatigue syndrome, fever of unknown origin, and inflammatory myositis.
- The most serious complication of primary SS is the development of non-Hodgkin's lymphoma and other lymphoproliferative disorders, which occur at a 44-fold increased rate as compared to age-matched controls.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Sjögren's Syndrome (Patient Information)

AUTHORS: **SYEDA M. SAYEED, M.D.** and **HARALD A. HALL, M.D.**

SUGGESTED READINGS

Kruszka P, O'Brian RJ: Diagnosis and management of Sjögren syndrome, *Am Fam Physician* 79(6):465–470, 2009.

Ng WF, Bowman SJ: Biological therapies in primary Sjögren's syndrome, *Expert Opin Biol Ther J* 11(7):921–936, 2011.

Papas AS et al.: Successful treatment of dry mouth and dry eye symptoms in Sjögren's syndrome patients with oral pilocarpine: a randomized, placebo-controlled, dose-adjustment study, *J Clin Rheumatol* 10:169–177, 2004.

Shiboski SC et al.: American College of Rheumatology classification criteria for Sjögren's syndrome: a data-driven, expert consensus approach in the Sjögren's International Collaborative Clinical Alliance cohort, *Arthritis Care Res (Hoboken)* 64:475–487, 2012.

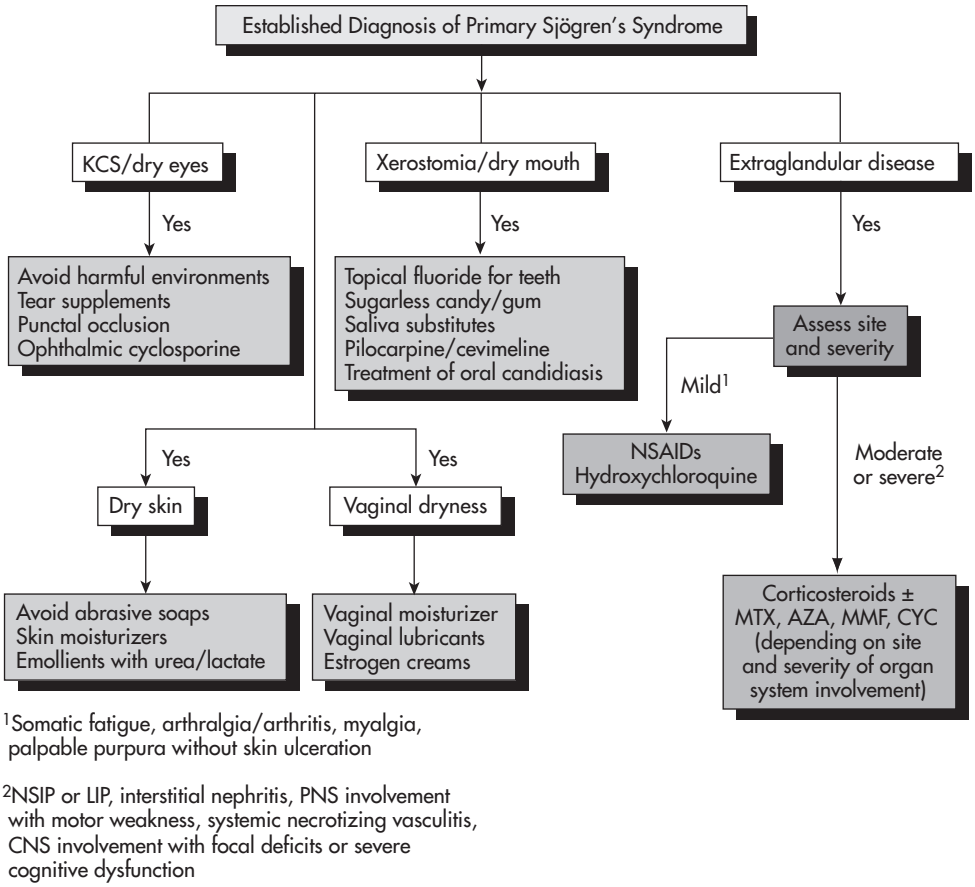


FIGURE ES1-47 Treatment algorithm for Sjögren's syndrome. The treatment of Sjögren's syndrome usually requires a multidisciplinary approach involving rheumatologists, ophthalmologists, dentists/oral surgeons, otolaryngologists, and other subspecialists, depending on the extent of extraglandular disease. In all cases, it is prudent to minimize the use of medications that can exacerbate the symptoms of dryness, such as antihistamines, antidepressants, muscle relaxers, and other drugs with anticholinergic properties. The treatment of extraglandular disease is individualized according to the site and severity of organ system involvement. The approaches indicated in the algorithm for the treatment of extraglandular disease are not supported by evidence from randomized, controlled trials, but rather from expert opinion based on retrospective case series and clinical experience. *AZA,* Azathioprine; *CNS,* central nervous system; *CYC,* cyclophosphamide; *KCS,* keratoconjunctivitis sicca; *LIP,* lymphocytic interstitial pneumonitis; *MMF,* mycophenolate mofetil; *MTX,* methotrexate; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *NSIP,* nonspecific interstitial pneumonitis; *PNS,* peripheral nervous system. (From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

BASIC INFORMATION

DEFINITION

The *International Classification of Sleep Disorders, Second Edition*, classifies sleep-disordered breathing disorders into three categories: central sleep apnea syndrome, obstructive sleep apnea (OSA), and sleep-related hypoventilation/hypoxic syndromes. The American Academy of Sleep Disorders defines OSA as repetitive episodes of upper airway obstruction that occur during sleep and that are typically associated with oxyhemoglobin desaturations.

SYNONYMS

Sleep apnea syndrome
Sleep-disordered breathing
Obstructive sleep apnea syndrome
Obstructive sleep apnea–hypopnea syndrome
OSA

ICD-9CM CODES

327.2	Organic sleep apnea
327.21	Organic sleep apnea, unspecified
327.23	Obstructive sleep apnea (adult) (pediatric)

ICD-10CM CODES

G47.30	Sleep apnea, unspecified
G47.31	Primary central sleep apnea
G47.33	Obstructive sleep apnea (adult) (pediatric)

EPIDEMIOLOGY & DEMOGRAPHICS

OSA is a common disease in the U.S. Data from the Wisconsin Cohort Study indicated that the prevalence of OSA in people between the ages of 30 and 60 yr is 9%-24% for men and 4%-9% for women. The estimated prevalence of OSA is 4% for men and 2% for women. The prevalence of OSA increases from 18-45 years of age, with a plateau occurring at 55-65 years of age. The prevalence is higher in obese and hypertensive patients. ~2% of children have OSA, which develops more commonly between the ages of 2-8 yr when adenotonsillar size is largest relative to upper airway. Risk factors include obesity and craniofacial and upper airway soft tissue abnormalities, retrognathia, and potential risk factors include heredity, current tobacco smoking, nasal congestion, and diabetes.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Nocturnal symptoms, including nocturia and angina pectoris
- Snoring that can be loud, habitual, and bothersome to others
- Witnessed apneas that often interrupt snoring and end with a snort
- Gasping, choking, or smothering sensations that arouse the patient from sleep
- Restless sleep associated with frequent arousals
- Daytime symptoms:
  - Nonrestorative sleep
  - Not feeling refreshed upon awakening
  - Morning headache
  - Dry mouth or throat upon awakening
  - Excessive daytime sleepiness, typically during quiet activities
  - Daytime fatigue or tiredness
  - Problems with memory, concentration, and cognitive function, especially with executive functioning
  - Easily angered, short tempered, and inattentive
  - Hyperactivity in children
  - Symptoms of fibromyalgia
- Systemic hypertension (HTN)
- Obesity (body mass index >30 kg/m^2)
- History of insulin resistance or type 2 diabetes mellitus
- Mood swings, irritability, anxiety, depression
- Decreased libido and impotence
- Neck circumference of >43 cm (17 in) in men and >37 cm (15 in) in women
- Erythematous oropharynx because of snoring.
- Adenotonsillar hypertrophy, excessive soft tissue, high-arched hard palate, pendulous uvula, prominent tongue, large degree of overjet, and retrognathia or micrognathia can be present.
- Narrowing of lateral airway walls is independent predictor of OSA in men but not women.
- Craniofacial skeletal abnormalities can lead to OSA, particularly among children and nonobese adults.
- A positive family history increases an individual's risk with each additional close family member with OSA.

ETIOLOGY

- Narrowing of upper airway as a result of obesity or increased peripharyngeal fat deposition, retrognathia and/or micrognathia, adenotonsillar hypertrophy, macroglossia, or neuromuscular weakness
- Upper airway muscular weakness as a result of neuromuscular disorders, primary CNS disorders (e.g., stroke), or metabolic disorders
- Other diseases associated with the development of OSA (e.g., hypothyroidism, acromegaly)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Anemia
- Anxiety or panic disorder
- Behaviorally induced insufficient sleep syndrome
- Cardiac or heart disease
- Central sleep apnea
- Circadian rhythm disorder
- Depression
- Drug or alcohol abuse
- Gastroesophageal reflux
- Hypothyroidism
- Idiopathic hypersomnia with long or short sleep time
- Inadequate sleep hygiene
- Insomnia
- Medication effect
- Narcolepsy
- Nocturnal asthma
- Nocturnal gastroesophageal reflux
- Nocturnal seizures
- Obesity-hypoventilation syndrome (i.e., Pickwickian syndrome)
- Parasomnias
- Parkinson's disease
- Periodic limb movement disorder
- Primary snoring
- Pulmonary or lung disease
- Restless legs syndrome
- Shift work sleep disorder
- Sleep fragmentation (multiple causes)

WORKUP

- Evaluation should include questions about snoring, witnessed apneas, gasping or choking episodes, restless sleep, and excessive daytime sleepiness.
- Mood swings and personality changes should be addressed.
- Job performance and difficulty driving or previous motor vehicle accidents related to excessive daytime sleepiness should be discussed.
- Additional concerns include morning dry mouth/throat, morning headaches, alcohol intake, weight gain, mood or personality changes.
- A thorough drug history should include muscle relaxants and sedatives.
- A family history should target any family members with OSA.
- Physical exam is frequently normal in patients with OSA except for the presence of obesity, enlarged neck circumference, and HTN.
- OSA is confirmed by nocturnal polysomnography (PSG), which is the gold standard for diagnosis. The PSG (Fig. S1-48) should be performed during the patient's typical sleeping hours; it should include all stages of sleep as well as sleep in the supine position.
- The severity of the OSA is determined by the apnea-hypopnea index (AHI), which is derived from the total number of apneas and hypopneas divided by the total sleep time.
- Recommended severity cutoff levels for the AHI in adult patients are as follows:
  1. Mild: 5-15 episodes/hr (with symptoms)
  2. Moderate: 15 to 30 episodes per hr
  3. Severe: >30 episodes per hr
- Criteria for the treatment of mild OSA often require symptoms, including excessive daytime sleepiness, cardiovascular disease, HTN, and mood swings.
- In-home respiratory monitoring may be effective alternative to PSG for evaluation of OSA.

LABORATORY TESTS

- Arterial blood gas testing should be performed if a patient has suspected pulmonary HTN or cor pulmonale to rule out daytime hypoxemia or hypercapnia.
- Thyroid-stimulating hormone level should be obtained if hypothyroidism is suspected.
- Fasting glucose level is recommended because OSA increases the risk of developing diabetes independent of other risk factors.

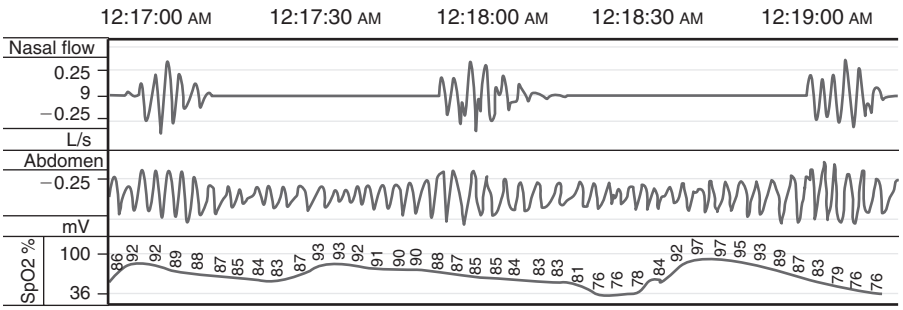


FIGURE S1-48 Polysomnographic tracing of a patient with obstructive sleep apnea during 2 minutes of non–rapid eye movement sleep. Displayed are airflow in the upper airway ("nasal flow"), recorded with a nasal pressure transducer, respiratory effort ("abdomen"), recorded by inductance plethysmography; and oxygen saturation of hemoglobin (SpO_2) recorded with pulse oximetry. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

- CBC is helpful to look for anemia; iron studies if anemia is detected and ferritin level if concomitant RLS is present.
- Pulmonary function testing if pulmonary disorder is suspected or to assess severity of neuromuscular disease, if present.
- ECG or echocardiogram is indicated if a cardiac disorder (e.g., arrhythmia, pulmonary HTN) is suspected.

IMAGING STUDIES

- Plain radiography of the neck can be helpful to assess the soft tissues of patients with suspected anatomic abnormalities.
- Chest x-ray if pulmonary disease is suspected.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Behavioral modifications:
  - Weight loss in overweight and obese patients. Weight loss is effective for reducing the severity of OSA, and if significant, it may potentially allow some patients to discontinue continuous positive airway pressure (CPAP) therapy.
  - Weight loss with bariatric surgery may improve OSA in some patients, but its definitive role remains unclear. In a recent trial in obese patients with OSA, the use of bariatric surgery compared with conventional weight loss therapy did not result in a statistically greater reduction in AHI despite major differences in weight loss.
  - Exercise without weight loss may improve OSA.
  - Avoid alcohol for 4-6 hr before bedtime.
  - Avoid muscle relaxants and sedating medications.
  - Sleep hygiene training.
  - Avoid or eliminate supine sleeping positions.
  - Avoid medications that may worsen OSA.
- Medical treatment:
  - CPAP is the primary therapy for OSA. It delivers a constant airway pressure that acts as a pneumatic splint that relieves the upper airway obstruction.
  - Other methods of delivering positive pressure include:
    - Bilevel positive airway pressure (BiPAP), which delivers a preset inspiratory and expiratory airway pressure.
    - Autotitrating positive airway pressure (APAP), which increases or decreases the level of pressure in response to change in airflow, a vibratory snore, or change in circuit pressure.
    - Adaptive servoventilation provides a varying amount of inspiratory pressure superimposed on a low level of CPAP.
    - Oral appliance constructed by a reputable and qualified dentist may be effective for the treatment of mild OSA in certain patients, especially those with retrognathia. Mandibular advancement devices (MADs) are a good alternative to CPAP in patients who are unable to tolerate CPAP. Trials have shown that although CPAP is more effective than MADs in reducing AHI (4.5 vs 11 events/h, respectively), self-reported adherence with use of MADs is higher (6.5 vs 5.2h/night for CPAP use).There was no overall difference between MADs and CPAP with respect to improvement in blood pressure, daytime sleepiness, or quality of life.
    - Optimal treatment of allergic rhinitis is needed; nasal irrigation with saline followed by nasal corticosteroids is often helpful.
    - Symptoms of excessive daytime sleepiness may linger and require further investigation or medical therapy.
    - Patients should be considered for surgery if multiple attempts at CPAP therapy have failed and if an oral appliance is not an option. If the patient opts for surgery, ensure that it is performed by a reputable and qualified otolaryngologist and is based on the location of airway collapse.
- Surgical treatment
  - Adenotonsillectomy is often curative for children with OSA.
  - Nasal septoplasty should be considered for patients with nasoseptal deformities.
  - Uvulopalatopharyngoplasty, which involves resection of the uvula and the soft palate, is effective for a small number of patients. However, predicting which patients will benefit is difficult.
  - Tracheostomy is typically reserved for patients with very severe OSA who failed medical therapy or who have cor pulmonale.

DISPOSITION

- The short-term prognosis for excessive daytime sleepiness and snoring is good to excellent with the regular use of nasal CPAP, but no studies have been performed to address the long-term effects in a large population of patients.
- Residual symptoms of excessive daytime sleepiness can occur in some patients with OSA despite regular CPAP use. This has led the FDA to approve modafinil for the management of residual sleepiness.

REFERRAL

- Highly trained sleep specialists with expertise in caring for patients with OSA are recommended, especially for complex cases.
- Surgical referral to otolaryngology should be considered for children with adenotonsillar hypertrophy and for adults who are unresponsive to weight loss and CPAP therapy.
- Referral to a qualified dentist for treatment with an oral appliance may be useful for certain patients with mild OSA.

PEARLS & CONSIDERATIONS

- OSA is a common disorder that is underrecognized and underdiagnosed, so the identification of risk factors is crucial for making the correct diagnosis.
- The prevalence of OSA increases among women after menopause.
- The degree of adenotonsillar hypertrophy does not correlate with the presence of OSA in children.
- A 10% weight loss can decrease the AHI of a patient with OSA by as much as 50%.
- The single most effective therapy for OSA is nasal CPAP.
- Patients with OSA are more vulnerable than healthy persons to the effects of alcohol consumption and sleep restriction with regard to various driving performance variables.
- OSA is a risk factor for HTN. In patients with untreated HTN and OSA, the use of CPAP results in small but statistically significant reductions in blood pressure.
- OSA may also be an independent risk factor for peptic ulcer bleeding.
- Ethnic differences may exist for some populations, with South Asians having a higher prevalence and risk for cardiovascular side effects.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Sleep Apnea (Patient Information)

AUTHOR: **DON HAYES, JR., M.D., M.S.**

EVIDENCE

Abstract[1]

Study Objectives:
To evaluate the efficacy of a 12-week exercise training program for reducing obstructive sleep apnea (OSA) severity and improving sleep quality, and to explore possible mechanisms by which exercise may reduce OSA severity.
Design:
Randomized controlled trial.
Setting:
Clinical exercise physiology center, sleep laboratory.
Participants:
Forty-three sedentary and overweight/obese adults aged 18-55 years with at least moderate-severity untreated OSA (screening apnea-hypopnea index [AHI] ≥15).
Interventions:
Participants randomized to exercise training (n=27) met 4 times/week for 12 weeks and performed 150 min/week of moderate intensity aerobic activity, followed by resistance training twice/week. Participants randomized to a stretching control (n=16) met twice weekly for 12 weeks to perform low-intensity exercises designed to increase whole-body flexibility.
Measurements and Results:
OSA severity was assessed with one night of laboratory polysomnography (PSG) before and following the 12-week intervention. Measures of sleep quality included PSG, actigraphy (7-10 days), and the Pittsburgh Sleep Quality Index. Compared with stretching, exercise resulted in a significant AHI reduction (exercise: 32.2±5.6 to 24.6±4.4, stretching: 24.4±5.6 to 28.9±6.4; P<0.01) as well as significant changes in oxygen desaturation index (ODI; P=0.03) and stage N3 sleep (P=0.03). Reductions in AHI and ODI were achieved without a significant decrease in body weight. Improvements in actigraphic sleep and subjective sleep quality were also noted following exercise compared with stretching.
Conclusions:
Exercise training had moderate treatment efficacy for the reduction of AHI in sedentary overweight/obese adults, which suggests that exercise may be beneficial for the management of OSA beyond simply facilitating weight loss.
Trial Registration:
Clinicaltrials.gov identification number NCT00956423. Ⓐ

Abstract[2]

Study Objective:
To determine the neurocognitive effects of continuous positive airway pressure (CPAP) therapy on patients with obstructive sleep apnea (OSA).
Design, Setting, and Participants:
The Apnea Positive Pressure Long-term Efficacy Study (APPLES) was a 6-month, randomized, double-blind, 2-arm, sham-controlled, multicenter trial conducted at 5 U.S. university, hospital, or private practices. Of 1,516 participants enrolled, 1,105 were randomized, and 1,098 participants diagnosed with OSA contributed to the analysis of the primary outcome measures.
Intervention:
Active or sham CPAP.
Measurements:
Three neurocognitive variables, each representing a neurocognitive domain: Pathfinder Number Test-Total Time (attention and psychomotor function [A/P]), Buschke Selective Reminding Test-Sum Recall (learning and memory [L/M]), and Sustained Working Memory Test-Overall Mid-Day Score (executive and frontal-lobe function [E/F]).
Results:
The primary neurocognitive analyses showed a difference between groups for only the E/F variable at the 2 month CPAP visit, but no difference at the 6 month CPAP visit or for the A/P or L/M variables at either the 2 or 6 month visits. When stratified by measures of OSA severity (AHI or oxygen saturation parameters), the primary E/F variable and one secondary E/F neurocognitive variable revealed transient differences between study arms for those with the most severe OSA. Participants in the active CPAP group had a significantly greater ability to remain awake whether measured subjectively by the Epworth Sleepiness Scale or objectively by the maintenance of wakefulness test.
Conclusions:
CPAP treatment improved both subjectively and objectively measured sleepiness, especially in individuals with severe OSA (AHI >30). CPAP use resulted in mild, transient improvement in the most sensitive measures of executive and frontal-lobe function for those with severe disease, which suggests the existence of a complex OSA-neurocognitive relationship. Clinical Trial Information: Registered at clinicaltrials.gov. Identifier: NCT00051363. Ⓐ

Abstract[3]

Rationale:
Twenty-eight percent of people with mild to moderate obstructive sleep apnea experience daytime sleepiness, which interferes with daily functioning. It remains unclear whether treatment with continuous positive airway pressure improves daytime function in these patients.
Objectives:
To evaluate the efficacy of continuous positive airway pressure treatment to improve functional status in sleepy patients with mild and moderate obstructive sleep apnea.
Methods:
Patients with self-reported daytime sleepiness (Epworth Sleepiness Scale score > 10) and an apnea-hypopnea index with 3% desaturation and from 5 to 30 events per hour were randomized to 8 weeks of active or sham continuous positive airway pressure treatment. After the 8-week intervention, participants in the sham arm received 8 weeks of active continuous positive airway pressure treatment.
Measurements and Main Results:
The total score on the Functional Outcomes of Sleep Questionnaire was the primary outcome measure. The adjusted mean change in the total score after the first 8-week intervention was 0.89 for the active group (n = 113) and -0.06 for the placebo group (n = 110) ($P = .006$). The group difference in mean change corresponded to an effect size of 0.41 (95% confidence interval, 0.14-0.67). The mean (SD) improvement in Functional Outcomes of Sleep Questionnaire Total score from the beginning to the end of the crossover phase (n = 91) was 1.73 ± 2.50 (t[90] = 6.59; $P < .00001$) with an effect size of 0.69.
Conclusions:
Continuous positive airway pressure treatment improves the functional outcome of sleepy patients with mild and moderate obstructive sleep apnea. Ⓐ

Evidence-Based Reference

Kline CE et al.: The effect of exercise training on obstructive sleep apnea and sleep quality: a randomized controlled trial, *Sleep* 34:1631–1640, 2011. Ⓐ

Kushida CA et al.: Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: the Apnea Positive Pressure Long-Term Efficacy Study (APPLES), *Sleep* 35:1593–1602, 2012. Ⓐ

Weaver TE et al.: Continuous positive airway pressure treatment of sleepy patients with milder obstructive sleep apnea: results of the CPAP Apnea Trial North American Program (CATNAP) Randomized Clinical Trial, *Am J Respir Crit Care Med* 186:677–683, 2012. Ⓐ

SUGGESTED READINGS

Basner RC: Continuous positive airway pressure for obstructive sleep apnea, *N Engl J Med* 356(17):1751–1758, 2007.

Bhattacharjee R et al.: Adenotonsillectomy outcomes in treatment of obstructive sleep apnea in children: a multicenter retrospective study, *Am J Respir Crit Care Med* 182(5):676–683, 2010.

Botros N et al.: Obstructive sleep apnea as a risk factor for type 2 diabetes, *Am J Med* 122(12):1122–1127, 2009.

Campos-Rodriguez F et al.: Mortality in obstructive sleep apnea-hypopnea patients treated with positive airway pressure, *Chest* 128(2):624–633, 2005.

Campos-Rodriguez F et al.: Cardiovascular mortality in women without continuous positive airway pressure treatment, *Ann Intern Med* 156:115–122, 2012.

Capdevila OS et al.: Pediatric obstructive sleep apnea: complications, management, and long-term outcomes, *Proc Am Thorac Soc* 5(2):274–282, 2008.

Caples SM et al.: Surgical modifications of the upper airway for obstructive sleep apnea in adults: a systematic review and meta-analysis, *Sleep* 33(10):1396–1407, 2010.

Chan AS et al.: Non-positive airway pressure modalities: mandibular advancement devices/positional therapy, *Proc Am Thorac Soc* 5(2):179–184, 2008.

Dixon SB et al.: Surgical vs conventional therapy for weight loss treatment of obstructive sleep apnea: a randomized controlled trial, *JAMA* 308(11): 1142–1149, 2012.

Duran-Cantolla J et al.: CPAP as treatment for systemic hypertension in people with obstructive sleep apnea: randomized controlled trial, *BMJ* 341:c5991, 2010.

Friedman M et al.: Updated systematic review of tonsillectomy and adenoidectomy for treatment of pediatric obstructive sleep apnea/hypopnea syndrome, *Otolaryngol Head Neck Surg* 140(6):800–808, 2009.

Golbin JM et al.: Obstructive sleep apnea, cardiovascular disease, and pulmonary hypertension, *Proc Am Thorac Soc* 5(2):200–206, 2008.

Greenburg DL et al.: Effects of surgical weight loss on measures of obstructive sleep apnea: a meta-analysis, *Am J Med* 122(6):535–542, 2009.

Kline CE et al.: The effect of exercise training on obstructive sleep apnea and sleep quality: a randomized controlled trial, *Sleep* 34(12):1631–1640, 2011.

Marcus CL et al.: A randomized trial of adenotonsillectomy for childhood sleep apnea, *N Engl J Med* 368:236602376, 2013 .

Myers KA et al.: Does this patient have obstructive sleep apnea? The rational clinical examination systematic review, *JAMA* 310(7):731–741, 2013.

Phillips CL et al.: Health outcomes of continuous positive airway pressure versus orsl appliance treatment for obstructive sleep apnea: a randomized controlled trial, *Am J Resp Crit Care Med* 187:879–887, 2013.

Qaseem A et al.: Diagnosis of obstructive sleep apnea in adults: A clinical practice guideline from the American College of Physicians, Ann Intern Med 161:210–220, 2014.

Qaseem A.: et al. Management of obstructive sleep apnea in adults: a clinical practice guideline from the American College of Physicians, *Ann Int Med* 159:471–483, 2013.

Qureshi A et al.: Medical treatment of obstructive sleep apnea, *Semin Respir Crit Care Med* 26(1):96–108, 2005.

Sharma SK et al.: CPAP for the metabolic syndrome in patients with obstructive sleep apnea, *N Engl J Med* 365(24):2277–2286, 2011.

Shiao TH et al.: Sleep apnea and risk of peptic ulcer bleeding: a nationwide population-based study, *Am J Med* 126:249–255, 2013.

Tonelli de Oliveira AC et al.: Diagnosis of obstructive sleep apnea syndrome and its outcomes with home portable monitoring, *Chest* 135(2):330–336, 2009.

Vakulin A et al.: Effects of alcohol and sleep restriction on simulated driving performance in untreated patients with obstructive sleep apnea, *Ann Intern Med* 151:447–455, 2009.

Won CH et al.: Surgical treatment of obstructive sleep apnea: upper airway and maxillomandibular surgery, *Proc Am Thorac Soc* 5(2):193–199, 2008.

Young T et al.: Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort, *Sleep* 31(8):1071–1078, 2008.

Slipped Capital Femoral Epiphysis (SCFE) PTG

BASIC INFORMATION

DEFINITION

Slipped capital femoral epiphysis (SCFE) is a pediatric abnormality defined as displacement of the capital femoral epiphysis (femoral head) posteriorly on the metaphysis (femoral neck) at the level of the physis (growth plate)

- Commonly unilateral but can present with bilateral hip involvement
- Classified as stable or unstable
- Stable SCFE: slipped capital femoral epiphysis in a child who is able to walk with minimal or no symptoms
- Unstable SCFE: slipped capital femoral epiphysis resulting in a child who cannot walk or who cannot walk without crutches and is associated with severe pain of acute onset

SYNONYMS

Slipped capital femoral epiphysis, nontraumatic
Slipped upper femoral epiphysis
Slipped upper femoral epiphysis, nontraumatic

ICD-10CM CODES
732.2 Nontraumatic slipped upper femoral epiphysis
ICD-10CM CODES
M93.003 Unspecified slipped upper femoral epiphysis (nontraumatic), unspecified hip

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Reported incidence in male children is 13.35 cases per 100,000 children, and reported incidence in female children is 8.07 cases per 100,000 children.
PEAK INCIDENCE: Average age at diagnosis is 13.5 yr for boys and 12.0 yr for girls.
PREVALENCE: 10.8 cases per 100,000 children
PREDOMINANT SEX: More common in boys than girls
GENETICS: More commonly seen in blacks and Hispanic populations; no strong evidence of genetic predisposition
RISK FACTORS: Obesity by far the greatest risk factor

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The slip occurs at the weakest part of the physeal plate and results in the head being displaced from the metaphysis.
- Typical presentation of pain in the knee, hip, groin, thigh, or all; external rotation of the extremity and limp are commonly seen. Few patients present with painless limp; <10% report inciting trauma; even fewer complain of severe hip pain and inability to bear weight.
- Important physical exam findings include limited range of motion of the affected hip on internal rotation; involved hip typically will go into obligatory external rotation if passively flexed up to 90 degrees.
- Patients with unstable SCFE are unable to bear weight, their leg is in external rotation, and any hip motion is painful.

ETIOLOGY

- Multifactorial
- The slip itself usually occurs during the preadolescent growth spurt.
- 25%-40% are bilateral slips.
- Obesity: of children diagnosed with SCFE, 63% are at the 90th percentile for weight or higher.
- Growth surges: varying levels of hormonal activity associated with the adolescent growth spurt may also contribute to the causes of SCFE.
- Endocrine disorders: related endocrine disorders include hypothyroidism, growth hormone supplementation, hypogonadism, and panhypopituitarism; consider an endocrinopathy in SCFE with unusual presentations, including patients who are younger than 8 yr, older than 15 yr, or underweight.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Apophyseal avulsion fracture
- Avascular necrosis
- Hip apophysitis
- Transient synovitis
- Stress fracture
- Septic arthritis
- Osteomyelitis
- Legg-Calvé-Perthes disease
- Adductor muscle strain (groin pull)

WORKUP

- Diagnosis is based on physical exam and radiologic findings.
- Laboratory testing can be done to look for secondary causes.

LABORATORY TESTS

Check renal, endocrine, growth hormone, thyroid function tests in patients <10 yr of age and body weight <50th percentile or less.

IMAGING STUDIES

- Plain radiographs are sensitive and specific to make the diagnosis of SCFE.
- B/L hip x-rays: both AP and frog-leg lateral views should be done; 60% of patients have bilateral hip involvement at presentation.
- The frog-leg lateral view is more sensitive.
- Physical blurring of the epiphysis or widening can be seen.
- Bone scans may be helpful in predicting prognosis; "cold spots" on technetium bone scan in acute SCFE may represent ischemia and/or avascular necrosis.

TREATMENT

- Once diagnosis is confirmed, the patient should be placed on non–weight-bearing crutches or in a wheelchair and quickly referred to an orthopedic surgeon for surgical management.
- The initial goals of treatment are to prevent slip progression and avoid complications.
- A recent open-label observational trial suggested a potential role for intravenous bisphosphonates as adjunctive therapy for acute SCFE that has been operatively fixed but had "cold spots" on bone scan indicating ischemia or necrosis; rationale for bisphosphonate use was to decrease necrotic bone resorption and allow for revascularization.

NONPHARMACOLOGIC THERAPY

- The standard treatment of SCFE is surgery.
- The standard surgical procedure of stable SCFE is in situ fixation with a single screw.
- For unstable SCFE, treatment goals are similar to those of stable SCFE with in situ fixation, but there is controversy as to the specifics of treatment, including timing of surgery, value of reduction, and whether traction should be used.
- Prophylactic treatment of the contralateral hip in SCFE is controversial and not recommended in most patients.
- Prophylactic pinning may be indicated in high-risk patients such as those with obesity or an endocrine disorder.

DISPOSITION

- SCFE is a common preadolescent disorder with little short-term morbidity and rare long-term sequelae if diagnosed and treated before the development of a severe deformity.
- The two most feared complications of SCFE are osteonecrosis/avascular necrosis and chondrolysis.
- Osteonecrosis/avascular necrosis: occurs in up to 60% of unstable SCFE; factors associated include overreduction of unstable SCFE, reduction of stable SCFE, pin penetration of posterior quadrant, and multiplicity of pin; often leads to advanced and early degenerative osteoarthritis.
- Chondrolysis: acute dissolution of articular cartilage in association with rapid progressive joint stiffness and pain; usually as a complication of surgery but can occur in untreated SCFE as well; incidence has decreased to 1%-2% with improvement in surgical techniques.

PEARLS & CONSIDERATIONS

- Physicians should consider SCFE when a child between the ages of 10-15 yr presents with limping and groin, hip, thigh, or knee pain.
- Physical exam usually shows decreased internal rotation of the hip and obligatory external rotation.
- Radiography to rule out SCFE should include anteroposterior lateral views of the hips (frog-lateral views for stable SCFE; cross-table views for unstable SCFE).
- The standard treatment of stable SCFE is in situ fixation with a single screw.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **WAFFIYAH AFRIDI, M.D.**

SUGGESTED READINGS

Gholve PA: Slipped capital femoral epiphysis update, *Curr Opin Pediatr* 21(1):39–45, 2009.

Görtz S et al. The hip. In: (editor: Hochberg MC et al.) *Rheumatology,* ed 5, Mosby, St Louis.

Loder RT: Controversies in slipped capital femoral epiphysis, *Orthop Clin North Am* 37:211–221, 2006.

Peck D: Slipped capital femoral epiphysis: diagnosis and management, *Am Fam Physician* 82(3):258–262, 2010.

Ramachandaran M et al.: Intravenous bisphosphonate therapy for traumatic osteonecrosis of the femoral heads in adolescents, *J Bone Joine Surg Am* 89:1727–1734, 2007.

BASIC INFORMATION

DEFINITION

- Mechanical obstruction means the blockage of the intestinal lumen, preventing the passage of luminal contents through the gut tube.
- This may be either:
  a) Simple obstruction: in which the lumen may be *partially* or *completely blocked* but with intact intestinal blood flow
  b) Strangulated obstruction
    1. This is a surgical emergency.
    2. Usually the obstruction is complete, blood flow to the obstructed segment is cut off, and tissue necrosis and gangrene may occur.

ICD 9CM CODES

560.9 Unspecified intestinal obstruction
560.1 Paralytic ileus
560.31 Gallstone ileus
560.8 Other specified intestinal obstruction
560 Intestinal obstruction

ICD-10CM CODES

K56.6 Other and unspecified intestinal obstruction
K56.9 Ileus, unspecified
K56.5 Intestinal adhesions (bands) with obstruction
K56.4 Other impaction of intestine
K56.3 Gallstone ileus
K56.2 Volvulus
K5.1 Intussusception
K56 Paralytic ileus and intestinal obstruction

EPIDEMIOLOGY & DEMOGRAPHICS

- The most frequently encountered surgical disorder of the small intestines is mechanical small bowel obstruction (SBO).
- 75% of all cases of small bowel obstruction are due to intraabdominal adhesion related to prior abdominal surgery.

PREDOMINANT SEX AND AGE: None

PHYSICAL FINDINGS & CLINICAL PRESENTATION

PHYSICAL FINDINGS: These may include:

- Abdominal distention
- Hyperactive bowel sounds (an early occurrence)
- Hypoactive bowel sounds (late finding)
- Hernia
- Rectal examination may reveal
  1. Blood (suggestive of neoplasm or strangulation)
  2. Masses

CLINICAL PRESENTATION: There are four key symptoms: abdominal pain, vomiting, distention, and constipation

- Abdominal pain
  1. Often crampy; intermittent
  2. Constant pain (that is, change in pain's character) signifies serious complication
- Nausea
- Vomiting (bilious vomiting seen in proximal obstructions)
- Diarrhea (early finding)
- Constipation (a late finding)
- Fever and/or tachycardia (these late findings may be seen with strangulation or intestinal ischemia)

ETIOLOGY

- Postoperative adhesions (may cause acute obstruction usually within one mo of surgery; or chronic obstructions can occur years later)
- Incarcerated inguinal hernia
- Malignant tumor
- IBD
- Gallstone ileus
- Stricture
- Cystic fibrosis
- Volvulus
- In children consider pyloric stenosis, intussusception, congenital atresia

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Cholangitis
- Cholecystitis
- Gastroenteritis
- Inflammatory bowel disease
- Endometriosis
- Mesenteric ischemia
- Pancreatitis
- Ovarian torsion

WORKUP

- During the initial evaluation of patients with suspected SBO, the primary objectives are to gauge the degree of metabolic derangement and volume depletion and to assess the need for and expediency of surgery. As with many surgical conditions, determining the correct diagnosis and management strategy hinges on a focused yet thorough history and physical examination.

LABORATORY TESTS

- Laboratory abnormalities are not diagnostic of bowel obstruction but instead may indicate complications of obstruction. Essential laboratory tests include:
  1. Basic metabolic panel
  2. CBC: hemoconcentration, leukocytosis
  3. Urinalysis
  4. Serum amylase: may be elevated
  5. LDH
  6. Hepatic panel
  7. Type and cross-match

IMAGING STUDIES

- Initial radiographic evaluation begins with plain x-ray films of the abdomen (supine and erect) and an upright chest radiograph. An upright chest radiograph is of paramount importance to inspect for pneumoperitoneum and also for evidence of aspiration in a patient with a history of vomiting. A supine and upright plain abdominal x-ray in patients with suspected small bowel obstruction may show:
  1. Ladder-like pattern of dilated small bowel loops with air-fluid levels (Fig. S1-49) indicating small bowel obstruction
  2. Accumulation of air and fluid proximal and clearance of fluid and air distal to the post of obstruction
- Enteroclysis (a fluoroscopic x-ray of the small intestine) is useful in detecting obstruction and can distinguish partial from complete blockage and adhesions from metastases.
- CT scan is the study of choice if the patient has fever, tachycardia, abdominal pain, and leukocytosis. It can reveal the etiology of the obstruction: abscess, inflammatory process, extra-luminal pathology, and/or metastases.
- CT can elucidate the cause, such as the presence of a mass (Fig. S1-50) or a hernia with subsequent obstruction (Fig. S1-51). In addition, CT has high sensitivity for detecting strangulation and pneumoperitoneum indicative of a perforation and is particularly useful

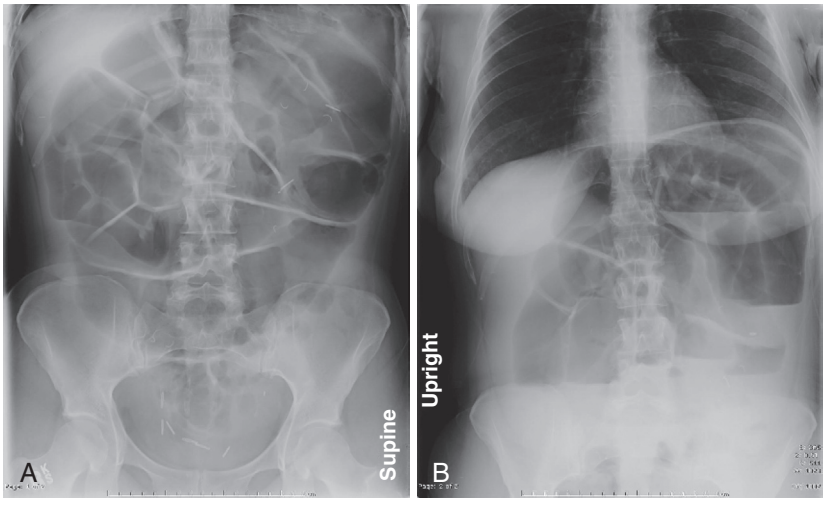


FIGURE S1-49 A, Supine film showing dilated loops of small bowel in a patient with small bowel obstruction. **B,** Upright abdominal film revealing multiple air-fluid levels and small bowel dilation, consistent with a diagnosis of small bowel obstruction. (From Marx J: *Rosen's emergency medicine: concepts and clinical practice*, ed 6, Philadelphia, 2006, Saunders.)

FIGURE S1-50 CT scan of small bowel volvulus with notable mesenteric torsion. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 10, Philadelphia, 2011, Saunders.)

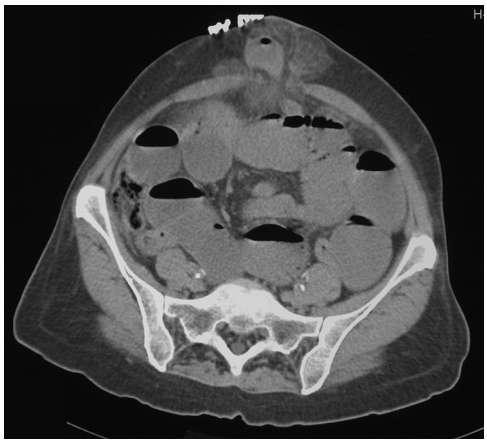


FIGURE S1-51 CT scan of complete small bowel obstruction due to incisional hernia. (From Cameron IL, Cameron AM: *Current surgical therapy*, ed 10, Philadelphia, 2011, Saunders.)

FIGURE S1-52 Coronal image of CT scan showing mass in proximal small bowel with decompressed loops of small bowel distal to obstruction. (From Cameron JL, Cameron AM: *Current surgical therapy*, ed 10, Philadelphia, 2011, Saunders.)

in the early postoperative setting to rule out ischemia, intraabdominal abscess, or morbidity as the underlying cause. It is also useful in patients with a history of malignancy to differentiate potentially recurrent disease from adhesions (Fig. S1-52).

- CT enterography, in which intraluminal distention is achieved with administration of large volumes of oral contrast such as water-methylcellulose solution, can be useful. This modality is most often used to diagnose patients with Crohn's disease–related strictures, and its benefit is high-resolution imaging of the bowel wall; however, it is impractical in the patient with gastrointestinal (GI) distress who is nauseated and vomiting.

Rx TREATMENT

EMERGENCY ROOM CARE

- Vigorous fluid resuscitation and correction of electrolyte disorders underpin the initial therapeutic goals of both nonoperative and preoperative management strategies. Placing a Foley catheter to measure urinary output, establishing adequate intravenous access, and reassessing hemodynamic and electrolyte status are all essential in the initial management.
- Initial treatment consists of:
  1. Designate the patients nothing by mouth ("NPO")
  2. Fluid resuscitation (with isotonic Ringer's or normal saline solution)
  3. Bowel decompression (via nasogastric [NG] tube placement): a standard NG tube provides symptomatic relief, prevents added gas and fluid accumulation proximally, and enables the serial assessment of antegrade fluid movement.
  4. Pain management
  5. Antiemetic administration
  6. Surgical consultation: must be done early
  7. Antibiotic administration

NONSURGICAL INPATIENT CARE

- Continue NG suction.
- Provide adequate fluid.

Patients with low-grade partial SBOs are prone to spontaneous resolution with conservative interventions such as bowel rest, NG decompression, and appropriate fluid resuscitation. For partial or simple obstructions resolution usually occurs within 72 hr.

SURGICAL CARE

More than 25% of inpatients admitted because of SBO will require an operation. Patients with complete or high-grade partial SBO are most likely to need surgery, with less than 20% successfully managed nonoperatively. Surgery is indicated in:

- Strangulated obstruction (which is a surgical emergency)
- Simple complete obstruction: after failed nonoperative care

AUTHOR: **DANIEL K. ASIEDU, M.D., PH.D.**

SUGGESTED READINGS

Foster NM et al.: Small bowel obstruction: a population-based appraisal, *J Am Coll Surg* 203(170), 2006.

Way LW, Doherty GM: Obstruction of the small intestine. In: *Current surgical diagnosis & treatment*. Lange Medical Books/McGraw-Hill: New York, pp. 683–687.

BASIC INFORMATION

DEFINITION

Smallpox infection is caused by the variola virus, a DNA virus member of the genus *Orthopoxvirus.* It is a human virus with no known nonhuman reservoir of disease. Natural infection occurs after implantation of the virus on the oropharyngeal or respiratory mucosa.

ICD-9CM CODES

050.9 Smallpox NOS
V01.3 Smallpox exposure
050.0 Smallpox, hemorrhagic (pustular)
050.1 Variola minor (alastrim)
050.0 Variola major

ICD-10CM CODES

B03 Smallpox
Z20.89 Contact with and (suspected) exposure to other communicable diseases

EPIDEMIOLOGY & DEMOGRAPHICS

- Smallpox infection was eliminated from the world in 1977. The last cases of smallpox, from laboratory exposure, occurred in 1978. The threat of bioterrorism has brought on renewed interest in the smallpox virus.
- Routine vaccination against smallpox ended in 1972.
- Smallpox is spread from person to person by infected saliva droplets in face-to-face contact with the ill person. Criteria for the suspicion of smallpox in patients with acute generalized vesicular or pustular rash are described in Box ES1-5. Categorization of risk of smallpox from clinical criteria is described in Box ES1-6.
- Persons with smallpox are most infectious during the first week of illness, when the largest amount of virus is present in saliva; however, some risk of transmission lasts until all scabs have fallen off.
- The incubation period is approximately 12 days (range, 7 to 17 days) after exposure.
- Contaminated clothing or bed linens can also spread the virus. Special precautions need to be taken to ensure that all bedding and clothing of patients are cleaned appropriately with bleach and hot water. Disinfectants such as bleach and quaternary ammonia can be used for cleaning contaminated surfaces.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Initial symptoms include high fever, fatigue, and headaches and backaches. A characteristic rash, most prominent on the face, arms, and legs, follows in 2 to 3 days (Fig. ES1-53).
- The rash starts with flat red lesions that evolve at the same rate. The rash follows a centrifugal pattern.
- Lesions are firm to the touch, domed, or umbilicated. They become pus filled and begin to crust early in the second week.
- Scabs develop and then separate and fall off after approximately 3 to 4 wk. Depigmentation persists at the base of the skin lesions for 3 to 6 mo after illness. Scarring is usually most extensive on the face.
- Associated with the rash may be fever, headache, generalized malaise, vomiting, and colicky abdominal pain.
- Variola major may produce a rapidly fatal toxemia in some patients.
- Complications of smallpox include dehydration, pneumonia, blepharitis, conjunctivitis, and corneal ulcerations.

ETIOLOGY

Smallpox is caused by the variola virus. There are at least two strains of the virus, the most virulent known as *variola major* and a less virulent strain known as *variola minor* (alastrim).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rash from other viral illnesses (e.g., hemorrhagic chickenpox, measles, Coxsackievirus)
- Abdominal pain may mimic appendicitis
- Meningococcemia
- Insect bites
- Impetigo
- Dermatitis herpetiformis
- Pemphigus
- Papular urticaria

WORKUP & LABORATORY TESTS

- Laboratory examination requires high-containment (BL-4) facilities.
- Electron microscopy of vesicular scrapings can be used to distinguish poxvirus particles from varicella-zoster virus or herpes simplex. To obtain vesicular or pustular fluid it may be necessary to open lesions with the blunt edge of a scalpel. A cotton swab may be used to collect the fluid.
- In the absence of electron microscopy, light microscopy can be used to visualize variola viral particles (Guarnieri bodies) after Giemsa staining.
- Polymerase chain reaction techniques and restriction fragment-length polymorphisms can rapidly identify variola.

IMAGING STUDIES

Chest radiograph in patients with suspected pneumonia

TREATMENT

NONPHARMACOLOGIC THERAPY

- Supportive therapy
- IV hydration in severe cases
- A suspect case of smallpox should be placed in strict respiratory and contact isolation

ACUTE GENERAL Rx

- There is no proven treatment for smallpox. Vaccination administered within 3 to 4 days may prevent or significantly ameliorate subsequent illness. Vaccinia immune globulin can be used for treatment of vaccine complications and for administration with vaccine to those for whom vaccine is otherwise contraindicated.

BOX ES1-5 Criteria for Suspicion of Smallpox in Patients with Acute Generalized Vesicular or Pustular Rash

- Febrile prodrome:
  1. >101° F, 1-4 days before rash onset
  2. With headache, backache, or abdominal pain
- Firm, deep-seated, well-circumscribed vesicles/pustules
- Lesions in the same stage of development in any one area of the body

Minor Smallpox Criteria

- Centrifugal distribution
- First lesions in the pharynx, oral mucosa
- Patient appears "toxic"
- Slow evolution of the rash:
  1. 1-2 days each stage: macule, papule, vesicle
- Lesions on palms and soles

From Vincent JL et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, Saunders.

BOX ES1-6 Categorization of Risk of Smallpox from Clinical Criteria

High Risk of Smallpox

- Febrile prodrome *and*
- Classic smallpox lesion *and*
- Lesions in the same stage of development

Moderate Risk of Smallpox

- Febrile prodrome *and* one other *major* smallpox criterion *or*
- Febrile prodrome *and* four or more minor smallpox criteria

Low Risk of Smallpox

- No febrile prodrome or
- Febrile prodrome *and* fewer than four minor smallpox criteria

From Vincent JL et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, Saunders.

FIGURE ES1-53 Appearance of the rash of smallpox on days 6 to 7. All the lesions are in the same stage of development. (From Gorbach SL: *Infectious diseases,* ed 2, Philadelphia, 1998, Saunders.)

- Patients can benefit from supportive therapy (e.g., IV fluids, acetaminophen for pain or fever).
- Antibiotics are indicated only if secondary bacterial infections occur. Penicillinase-resistant antimicrobial agents should be used if smallpox lesions are secondarily infected.
- Topical idoxuridine should be considered for corneal lesions.

DISPOSITION

- The mortality rate for variola major is 20% to 50%. Variola minor has a mortality rate of 1%.
- After severe smallpox, pitted lesions (most commonly on the face) are seen in up to 80% of survivors.
- Panophthalmitis and blindness from viral keratitis or secondary eye infection occur in 1% of patients.
- Arthritis caused by viral infection of the metaphysis of growing bones occurs in 2% of children.

REFERRAL

ID consultation and notification of local health authorities is mandatory in all cases of smallpox.

PEARLS & CONSIDERATIONS

- The smallpox virus is fragile; in the event of an aerosol release, all viruses will be inactivated or dissipated within 1 to 2 days. Buildings exposed to the initial aerosol release of the virus do not need to be decontaminated. By the time the first cases are identified, typically 2 wk after release, the virus in the building will be gone. Infected patients, however, will be capable of spreading the virus and possibly contaminating surfaces while they are sick. Standard hospital-grade disinfectants such as quaternary ammonias are effective in killing the virus on surfaces and should be used for disinfecting hospitalized patients' rooms or other contaminated surfaces. In the hospital setting, patients' linens should be autoclaved or washed in hot water with bleach added. Infectious waste should be placed in biohazard bags and autoclaved before incineration.
- Symptomatic patients with suspected or confirmed smallpox are capable of spreading the virus. Patients should be placed in medical isolation to avoid spread of the virus. In addition, people who have come into close contact with smallpox patients should be vaccinated immediately and closely watched for symptoms of smallpox.

COMMENTS

- In people exposed to smallpox, the vaccine can lessen the severity of or even prevent illness if given within 4 days of exposure.
- The vaccine against smallpox contains another live virus called *vaccinia.* The vaccine does not contain smallpox virus. Smallpox vaccination produces a skin lesion that is infectious. Vaccine virus in the skin lesion can be transferred to others if the skin lesion is touched directly or if the bandage is handled casually with ungloved hands. The vaccination site is infectious until the scab falls off, approximately 21 days after vaccination.
- Primary vaccination confers full immunity to smallpox in more than 95% of persons for up to 10 yr.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Breman JG, Henderson DA: Diagnosis and management of smallpox, *N Engl J Med* 346:1300, 2002.

Frey SE et al.: Clinical responses to undiluted and diluted smallpox vaccine, *N Engl J Med* 346:1265, 2002.

Henderson DA et al.: Smallpox as a biological weapon, *JAMA* 281:2127, 1999.

Kim M et al.: Responding to suspected smallpox cases in the Los Angeles County from 2002 to 2006: identifying areas for education, *Am J Emergency Med* 27:55–62, 2009.

BASIC INFORMATION

DEFINITION

Social anxiety disorder (SAD) is a persistent and intense fear of being embarrassed, humiliated, or negatively evaluated in social situations. SAD commonly presents as excessive anxiety or fear in situations involving social interactions (e.g., conversing with one or a group of other individuals, with sexually attractive others, with authority figures), performance situations (e.g., public speaking, acting/performing in front of an audience), or situations in which one is being observed (e.g., while eating). Individuals with SAD fear that they will behave in these situations in ways that will cause them to be embarrassed or that others will judge them negatively. Many individuals also fear that they will show anxiety symptoms that will be observed by others. The anxiety must persist in these situations for at least 6 mo, and for children it must occur with peers and not just with adults. The anxiety often results in avoidance of these situations, thus leading to significant occupational, academic, and/or social impairment as well as marked distress. A specifier of "performance only" should be given when the fears are confined to speaking or performing in public.

SYNONYMS

Social phobia
SAD

ICD-9CM and DSM-5 CODES
300.23 Social phobia
ICD-10CM CODES
F93.2 Social anxiety disorder of childhood
F40.1 Social phobias
F40.9 Phobic anxiety disorder, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Ranges from 4 to 5 to 9/1000 person-yrs; cumulative incidence of 11.0% in first three decades of life
PEAK INCIDENCE: Highest standardized incidence rates per person-yr between 10 and 19 yr of age
PREVALENCE (IN U.S.): Lifetime prevalence of 12% in epidemiologic samples, and 12-month prevalence of 7%; point prevalence of up to 30% in outpatient clinical settings
PREDOMINANT SEX: More common in women than in men (odds ratio of 1.5 to 2.2) in epidemiologic samples; rates are equivalent or slightly higher in males in clinical settings
PREDOMINANT AGE: Mean age at onset ~16 yr of age; median age at onset, 13 yr of age; onset rarely occurs after age 25, with 75% having an onset between 8 and 15 yr of age
GENETICS:
- Heritability ranges from 20% to 50%.
- 15% to 26% risk of SAD among first-degree relatives of those with SAD.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Physical symptoms during social interactions such as heart palpitations, sweating, shaking, and/or blushing, which may take the form of a panic attack.
- Fear that others will observe these physical symptoms in social situations and negatively judge them; fears that they will "say something stupid," make a mistake, or offend others also are common.
- Report being "shy" most of their lives.
- Comorbid psychiatric disorders (e.g., major depression, other anxiety disorders) and substance abuse (e.g., alcohol/cannabis) are common.
- Few seek treatment specifically for SAD, and instead initially seek treatment for other psychiatric disorders (e.g., major depression, other anxiety disorders).
- The onset of SAD often precedes that of the other comorbid psychiatric conditions.

ETIOLOGY

- There is no clear etiology and likely is a combination of multiple factors.
- Research has examined developmental psychology factors (e.g., lack of modeling of socialization by parents), temperamental factors (e.g., behavioral inhibition), and occurrence of prior traumatic social experiences (e.g., significant teasing by peers, being embarrassed or humiliated in a social or performance situation).
- The risk of SAD also may be increased with family history.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other anxiety disorders (e.g., panic disorder with agoraphobia).
- As a consequence of mood disorders (e.g., avoidance of social situations associated with major depression).
- Pervasive developmental disorder (e.g., autism spectrum disorder).
- Personality disorders (e.g., schizoid personality disorder); however, in the case of avoidant personality disorder, both may be diagnosed.
- Anxiety associated with medical conditions such as stuttering or Parkinson's disease.

WORKUP

- Psychiatric history is required for a diagnosis.
- Screening measures may improve detection of SAD as it is a chronic, disabling condition for which many individuals do not seek treatment.
- Physical examination may be useful in ruling out other explanations for physical symptoms that are present, and to rule out presence of social anxiety due to a medical condition.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Cognitive-behavior therapy (CBT)
- Acceptance and Commitment Therapy (ACT)
- Interpersonal Psychotherapy (IPT)
- Exposure therapy
- Social skills training

PHARMACOLOGIC THERAPY

- SSRIs/SNRIs
- Benzodiazepines (less favored)
- MAOIs (less favored)
- Beta-blockers (e.g., propranolol, atenolol: for performance-related anxiety)

ACUTE GENERAL Rx

- SAD is a chronic condition; therefore acute treatment is rarely indicated.
- However, benzodiazepines or beta-blockers may be prescribed on an as-needed basis for acute performance anxiety. Caution should be taken when prescribing benzodiazepines due to the possibility of dependence or misuse and high incidence of relapse following discontinuation, and long-term use of these medications generally is discouraged.
- Beta-blockers may also be prescribed on an as-needed basis, particularly for physical symptoms experienced during performance situations. However, evidence does not support its use for more generalized forms of SAD.

CHRONIC Rx

- CBT is effective and an appropriate first-line treatment.
- SSRIs/SNRIs (e.g., paroxetine, sertraline, venlafaxine) are also effective in the treatment of SAD and are a first-line pharmacologic treatment.
- MAOIs previously were considered gold standard treatment for SAD, but currently are less favorable due to side effects and dietary restrictions.
- Combination treatment of SSRI/SNRI and CBT is effective for SAD; however, some research has suggested that CBT alone may result in greater long-term benefit compared to combination treatment.

DISPOSITION

- SAD is a chronic condition, typically unremitting without treatment.
- Treatment may significantly improve SAD, although symptoms and impairment may continue to be present for some individuals following treatment.

REFERRAL

- If comorbid psychiatric conditions are present
- If the symptoms do not improve upon treatment or response to treatment is not optimal

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Anxiety (Generalized Anxiety Disorder) (Related Key Topic)

AUTHOR: **KRISTY L. DALRYMPLE, PH.D.**

EVIDENCE

Abstract[1]

Context:
Cognitive therapy (CT) focuses on the modification of biased information processing and dysfunctional beliefs of social anxiety disorder (SAD). Interpersonal psychotherapy (IPT) aims to change problematic interpersonal behavior patterns that may have an important role in the maintenance of SAD. No direct comparisons of the treatments for SAD in an outpatient setting exist.

Objective:
To compare the efficacy of CT, IPT, and a waiting-list control (WLC) condition.

Design:
Randomized controlled trial.

Setting:
Two academic outpatient treatment sites.

Patients:
Of 254 potential participants screened, 117 had a primary diagnosis of SAD and were eligible for randomization; 106 participants completed the treatment or waiting phase.

Interventions:
Treatment comprised 16 individual sessions of either CT or IPT and 1 booster session. Twenty weeks after randomization, posttreatment assessment was conducted and participants in the WLC received 1 of the treatments.

Main Outcome Measures:
The primary outcome was treatment response on the Clinical Global Impression Improvement Scale as assessed by independent masked evaluators. The secondary outcome measures were independent assessor ratings using the Liebowitz Social Anxiety Scale, the Hamilton Rating Scale for Depression, and patient self-ratings of SAD symptoms.

Results:
At the posttreatment assessment, response rates were 65.8% for CT, 42.1% for IPT, and 7.3% for WLC. Regarding response rates and Liebowitz Social Anxiety Scale scores, CT performed significantly better than did IPT, and both treatments were superior to WLC. At 1-year follow-up, the differences between CT and IPT were largely maintained, with significantly higher response rates in the CT vs the IPT group (68.4% vs 31.6%) and better outcomes on the Liebowitz Social Anxiety Scale. No significant treatment×site interactions were noted.

Conclusions:
Cognitive therapy and IPT led to considerable improvements that were maintained 1 year after treatment; CT was more efficacious than was IPT in reducing social phobia symptoms. Ⓐ

Evidence-Based Reference

Stangier U et al.: Cognitive therapy vs. interpersonal psychotherapy in social anxiety disorder: a randomized controlled trial, *Arch Gen Psychiatry* 68:692–700, 2011. Ⓐ

SUGGESTED READINGS

Acarturk C et al.: Psychological treatment of social anxiety disorder: a meta-analysis, *Psychol Med* 39:241–254, 2009.

Aderka IM et al.: Functional impairment in social anxiety disorder, *J Anxiety Disord* 26:393–400, 2012.

Blanco C et al.: A placebo-controlled trial of phenelzine, cognitive behavioral group therapy, and their combination for social anxiety disorder, *Arch Gen Psychiatry* 67:286–295, 2010.

Blanco C et al.: Predictors of persistence of social anxiety disorder: a national study, *J Psychiatr Res* 45:1557–1563, 2011.

Canton J et al.: Optimal treatment of social phobia: systematic review and meta-analysis, *Neuropsychiatr Dis Treat* 8:203–215, 2012.

Furukawa TA et al.: Cognitive-behavioral therapy modifies the naturalistic course of social anxiety disorder: findings from an ABA design study in routine clinical practices, *Psychiatry Clin Neurosci* 67:139–147, 2013.

Jorstad-Stein EC, Heimberg RG: Social phobia: an update on treatment, *Psychiatr Clin North Am* 32:641–663, 2009.

Stuhldreher N et al.: The costs of social anxiety disorder: the role of symptom severity and comorbidities, *J Affect Disord* 165:87–97, 2014.

BASIC INFORMATION

DEFINITION

Somatization disorder has been replaced in DSM-5 with the diagnostic term *somatic symptom disorder*. In this condition one or more somatic symptoms are distressing or disruptive of daily life. There is often disproportionate thoughts about the seriousness of one's symptoms, persistent anxiety about one's health, and excessive time and energy devoted to the symptoms. There is often a pattern of recurring multiple somatic complaints that begin before the age of 30 yr and persist over several years. Patients complain of multiple symptoms but persistent pain is common. DSM-5 drops the term "unexplained by a medical condition" from the criteria.

SYNONYMS

Briquet's syndrome
Nonorganic physical symptoms
Medically unexplained symptoms
Functional somatic symptoms
Somatic symptom disorder

ICD-9CM and DSM-5 CODES
300.82 Undifferentiated somatoform disorder
ICD-10CM CODES
F45.0 Somatization disorder
F45.1 Undifferentiated somatoform disease

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE (IN U.S.): Lifetime rates of 0.25% to 2% in women, ≤0.2% in men
PEAK INCIDENCE: Typically before age 25 yr
PREDOMINANT SEX: Women are more commonly affected in the United States (10:1 ratio)
PREDOMINANT AGE: Onset occurs before age 30 yr and usually in adolescence.
GENETICS: In males, there is a high risk of associated substance abuse or antisocial personality disorder.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Onset is characteristically in the teens; course is marked by frequent, often unexplained, and frequently disabling pain symptoms and physical complaints.
- Patient frequently undergoes multiple procedures and seeks treatment from multiple physicians. Symptom focus rotates periodically with new physicians sought for new complaints.
- Patient often has a comorbid psychiatric disorder, most commonly generalized anxiety, panic disorder, or depression.

ETIOLOGY

- Believed to be the physical expression of psychological distress; there appears to be a biologic predisposition.
- May be more common in individuals without sufficient verbal or intellectual capacity to communicate psychological distress, individuals with alexithymia (inability to describe emotional states), or individuals from cultural backgrounds that consider emotional distress as an undesirable quality.
- Some aspects of somatic symptom disorder possibly learned from somatizing parents.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Psychological factors affecting other medical conditions (ICD-10 F45.1, DMS-5 316): psychological or behavioral factors adversely affect the medical condition in various ways, such as influencing the course of the medical condition or interfering with treatment.
- Conversion disorder: an alteration or loss of voluntary motor or sensory function without demonstrable physical cause and related to a psychological stress or a conflict. Findings provide evidence of incompatibility between the symptom and recognized neurologic or medical conditions (ICD-9 code 300.11).
- Factitious disorder (e.g., Munchausen's syndrome) and malingering: the psychologic basis of the complaints in somatization disorder is not conscious as in factitious disorder, in which the goal is to be in the patient role, and malingering, in which symptoms are also produced consciously but for some secondary gain like a monetary award in litigation or opioids.

WORKUP

- Rule out a general medical condition.
- If somatization is suspected on the basis of a history of repeated, multiple, unexplained complaints, restraint in ordering tests is recommended.

LABORATORY TESTS

No specific laboratory tests are required.

IMAGING STUDIES

No specific imaging studies are required.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Legitimize patient's complaints.
- Minimize diagnostic investigation and symptomatic treatment. Only do invasive testing or procedures when there are clear-cut signs, not just symptom reports.
- Set attainable treatment goals. Patients may benefit from realizing that even though they cannot be cured, they will be cared for. This may help reassure them that they will continue to have a relationship with the caregiver.
- Treat coexisting psychiatric conditions such as depression and anxiety.

ACUTE GENERAL Rx

- At each visit do a brief physical examination focusing on the area of complaint.
- Gently praise increased functioning rather than focusing on symptoms.
- Explore recent life events and ask how the patient is handling these.
- Convey empathy with the patient's suffering and psychosocial difficulties.
- No specific pharmacologic therapy has been clearly proven effective, although a number of agents, including gabapentin and St. John's wort, have been useful in some studies.

CHRONIC Rx

- Provide one primary care practitioner to manage care.
- Avoid confronting the patient regarding the psychological origin of symptoms.
- Ensure follow-up visits at regular intervals (e.g., 2- to 4-wk intervals that are not symptom contingent; maintain the regularity even if the symptoms improve so that the patient does not need new symptoms to continue the relationship).
- Avoid invasive or expensive diagnostic procedures unless there are clear signs of new illness, not just symptoms.
- Diagnose and treat mood or anxiety disorders.
- Cognitive behavior therapy groups have been helpful for patients with unexplained somatic symptoms and can dramatically improve functioning.

DISPOSITION

A chronic condition with frequent exacerbations

REFERRAL

If the patient is open to discussing psychological issues, a referral for psychotherapy can be made.

PEARLS & CONSIDERATIONS

Patients with somatization disorder respond best to establishing a regular, working relationship with a primary care provider. Avoiding confrontations about the origins of symptoms, investigating symptoms when related to actual signs of disease, and gently investigating concurrent stressors will help avoid most of the common problems with this population.

Patients with subsyndromal symptoms (i.e., failing to meet the full criteria but having three or more medically unexplained symptoms) may be just as challenging and chronic. They warrant similar approaches as utilized for the full syndrome.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Somatization Disorder (Patient Information)

AUTHOR: **STUART J. EISENDRATH, M.D.**

SUGGESTED READINGS

Jackson JL, Kroenke K: Prevalence, impact, and prognosis of multisomatoform disorder in primary care: a 5-year follow-up study, *Psychosom Med* 70(4):430–434, 2008.

Katsamanis M et al.: Psychophysiologic treatment for patients with medically unexplained symptoms: a randomized controlled trial, *Psychosomatics* 52(3):218–229, 2011.

Mayou R: Is the DSM-5 chapter on somatic symptom disorder any better than DSM-IV somatoform disorder? *Br J Psychiatry* 204(6):418–419, 2014.

Rief W: Isaac M: The future of somatoform disorders: somatic symptom disorder, bodily distress disorder or functional syndromes? *Curr Opin Psychiatry* 27(5):315–319, 2014.

Smits FT et al.: Epidemiology of frequent attenders: a 3-year historic cohort study comparing attendance, morbidity and prescriptions of one-year and persistent frequent attenders, *BMC Public Health* 9:36, 2009.

BASIC INFORMATION

DEFINITION

Spasticity is an exaggerated tone that displays a velocity-dependent increase in resistance of muscles to a passive stretch stimulus.

SYNONYMS

Hypertonicity

ICD-9CM CODES

782.85 Spasm of muscle
342.1, 343.0-344.9 Spastic paralysis
781.0 Abnormal involuntary movements/Spasms NOS
781.2 Abnormality of gait/spastic
342.1 Spastic hemiplegia
344.0-344.9 Spastic paralysis specified as noncongenital or noninfantile
343 Infantile cerebral palsy/spastic infantile paralysis

ICD-10CM CODES

M62.838 Other muscle spasm
G81.10 Spastic hemiplegia affecting unspecified side
R25.0 Abnormal head movements
R26.0 Ataxic gait
G81.10 Spastic hemiplegia affecting unspecified side
G83.9 Paralytic syndrome, unspecified
G80.9 Cerebral palsy, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Spasticity affects between 47% and 70% of people with multiple sclerosis, 32% to 36% of those with spinal cord injury, approximately 20% of those with stroke, more than 90% with cerebral palsy, and approximately 50% of patients with traumatic brain injury.

PREDOMINANT SEX AND AGE: Spasticity is not affected by sex, race, or age group, nor is it more prevalent in any of those groups.

RISK FACTORS: Multiple sclerosis, stroke, spinal cord injury, cerebral palsy, traumatic brain injury

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patient may present with impaired gait, impaired limb function, decreased mobility, or discomfort due to increased muscle tone.
- While increased tone may preserve strength in the affected muscles, function may be impaired, especially fine motor. Examine active and passive motion, reflexes, and functions:
  1. Strength may be normal or decreased. Isometric strength is typically greater than concentric strength.
  2. Tone may be variably increased to passive range of motion (modified Ashworth scale; see Table S1-19).
  3. Reflexes are typically brisk.
  4. Patient may have accompanying extensor plantar signs, clonus, or spontaneous flexor spasms.
  5. Function may be impaired or enhanced due to increased tone.

TABLE S1-19 Modified Ashworth Scale

0	No increase in muscle tone
1	Slight increase in muscle tone, manifested by a catch and release or by minimal resistance at the end range of motion when the part is moved in flexion or extension/abduction or adduction
1+	Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of motion
2	More marked increase in muscle tone through most of the range of motion, but the affected part is easily moved
3	Considerable increase in muscle tone, passive movement is difficult
4	Affected part is rigid in flexion or extension (abduction or adduction)

From Stein J: Spasticity. In Frontera WR et al (eds): *Essentials of physical medicine and rehabilitation,* ed 2, Philadelphia, 2008, Saunders.

ETIOLOGY

Upper motor neuron injury, most commonly due to multiple sclerosis, stroke, spinal cord injury, cerebral palsy, traumatic brain injury

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Rigidity, clonus, dystonia, dyskinesia, myotonia, tetanus, muscle contracture, cramps

WORKUP

- A diagnosis is established clinically.
- Investigate reversible exacerbating causes of spasticity: underlying infection, bladder distention, bowel impaction, fracture, pain.

LABORATORY TESTS

Urinalysis, complete blood count, metabolic panel

IMAGING STUDIES

Chest x-ray, abdominal x-ray series, bladder ultrasound

TREATMENT

First treat reversible causes of spasticity (see "Workup"), then proceed to physical and pharmacologic therapeutics. Lastly, consider surgical intervention in severe, refractory cases.

NONPHARMACOLOGIC THERAPY

- Physical therapeutics include range of motion and muscle stretching, serial casting or orthotics, muscle cooling, electrical stimulation.
- Surgical procedures include tenotomy, tendon lengthening, and tendon transfers. More invasive surgical interventions include peripheral neurectomy, myelotomy, and rhizotomy.

ACUTE GENERAL Rx

- Oral medications: baclofen, tizanidine, diazepam, dantrolene (Table ES1-20)
- Other interventions: intrathecal baclofen, botulinum toxin intramuscular injections, chemical nerve blocks (with bupivacaine, phenol, or ethyl alcohol)

COMPLEMENTARY & ALTERNATIVE MEDICINE

EMG biofeedback

DISPOSITION

Typically nonprogressive, but medications may lose efficacy after long duration of use. Drug holidays (with use of alternate spasmolytic) may be beneficial.

REFERRAL

- Physicians: neurologist or physiatrist with expertise in botulinum toxin injection and/or intrathecal spasmolytic therapy is recommended when oral medications are ineffective or not tolerated.
- Physical and occupational therapy

PEARLS & CONSIDERATIONS

- Assess whether the spasms recently increased in severity or intensity (as would occur with reversible exacerbating causes).
- Consider whether patient's tone is beneficial or detrimental to patient's functionality or overall health status.
- Spasticity may assist posture and mobility, as well as maintain muscle mass and bone mineralization, reduce dependent edema, and prevent deep venous thromboses.
- Spasticity may impair patient's functionality, interfere with activities of daily living, interfere with sleep, and cause discomfort.
- Monitor liver function with dantrolene and tizanidine, as these drugs may cause hepatotoxicity.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **SACHIN KEDAR, M.B.B.S., M.D.**

SUGGESTED READINGS

Bovend'Eerdt T et al.: The effects of stretching in spasticity: a systematic review, *Arch Phys Med Rehabil* 89(7):1395–1406, 2008.

Gupta A et al.: Non-traumatic spinal cord lesions: epidemiology, complications, neurological and functional outcome of rehabilitation, *Spinal Cord* 47:307–311, 2009.

Little J.; Massagli T. Spasticity and associated abnormalities of muscle tone. In: (editors: Delisa J.; Gans B.) Rehabilitation medicine: principles and practice. ed 3 Lippincott-Raven: Philadelphia.

New P et al.: Nontraumatic spinal cord injury: demographic characteristics and complications, *Arch Phys Med Rehabil* 83(7):996–1001, 2002.

Stein J. Spasticity. In: (editor: Frontera W.R.; et al.) Essentials of physical medicine and rehabilitation. ed 2 Saunders: Philadelphia.

Wedekind C, Lippert-Gruner M: Long-term outcome in severe traumatic brain injury is significantly influenced by brainstem involvement, *Brain Inj* 19: 681–684, 2005.

Wichers MJ et al.: Clinical presentation, associated disorders and aetiological moments in cerebral palsy: a Dutch population-based study, *Disabil Rehabil* 27:583–589, 2005.

TABLE ES1-20 Commonly Used Oral Spasmolytic Medications

Medication	Mechanism of Action	Starting Dose	Maximum Dose	Common Side Effects	Considerations†
Baclofen	GABA-B agonist	5 mg tid	20 mg qid*	Sedation, rare hepatotoxicity	Cognitive impairment
Diazepam	GABA-A agonist	2 mg bid	10 mg qid	Sedation, dependence or tolerance	History of substance abuse, cognitive impairment
Tizanidine	Alpha-2 agonist	2 mg tid	12 mg tid	Sedation, hypotension, hepatotoxicity	Cognitive impairment
Dantrolene	Blocks Ca^{2+} release from sarcoplasmic reticulum	25 mg daily	100 mg qid	Weakness, hepatotoxicity	Liver disease

*Approved by the U.S. Food and Drug Administration only up to 80 mg/day, but many clinicians exceed this in patients who tolerate this medication well but do not respond to smaller doses.
†Baclofen, diazepam, and tizanidine are centrally acting and may exacerbate cognitive impairment. Dantrolene acts peripherally; however, it has the rare but fatal side effect of hepatotoxicity.
Modified from Stein J: Spasticity. In Frontera WR et al (eds): *Essentials of physical medicine and rehabilitation,* ed 2, Philadelphia, 2008, Saunders.

BASIC INFORMATION

DEFINITION

Spina bifida refers to a group of neural tube disorders that involve the spinal column and include spina bifida occulta and spina bifida cystica (Fig. ES1-54). Anencephaly and cranium bifidum (i.e., encephalocele) are also classified as neural tube disorders.

Spina bifida occulta is a midline defect of closure of the posterior vertebral arches and laminae and usually involves the L5-S1 area of the spinal cord.

Spina bifida cystica includes both meningocele and myelomeningocele. Meningocele is a midline defect in which meninges herniate through the posterior vertebral arch defect with a normal spinal cord in a normal position in the spinal canal; this condition makes up about 5% of cases of spina bifida cystica. Myelomeningocele is the most severe form of disease in the spectrum of spina bifida. The meninges, fragments of bone and cartilage, and the spinal cord herniate through the vertebral arches or the skin; this condition makes up about 95% of cases. The majority of these defects (~75%) are located in the lumbosacral area (Figs. ES1-55 and ES1-56).

SYNONYMS

Dysraphism
Meningomyelocele
Neural tube disorders

ICD-9CM CODES
756.17 Spina bifida occulta
741.9 Meningocele/myelomeningocele (without mention of hydrocephalus)

ICD-10CM CODES
Q76.0 Spina bifida occulta
Q05.8 Sacral spina bifida without hydrocephalus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:
- Spina bifida occulta: 10% of the general pediatric population
- Spina bifida cystica: 0.15% of Caucasians, 0.04% of African Americans
- Highest in Ireland and lowest in Japan
- Influenced by season, economic status, maternal age, heat exposure, and a mother who has had other children with neural tube defects

PREVALENCE: About 12 infants are born daily with spina bifida or anencephaly.
PREDOMINANT SEX: Females are affected more frequently than males.
RISK FACTORS:
- Nutritional deficiency (specifically folate)
- Prior children with neural tube defects (risk increases 1.5% to 2%)
- If two prior children had spinal column defects, the risk increases 6% to 10%.

GENETICS: Unknown

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Spina bifida occulta:
  1. Most patients are asymptomatic and have a normal neurologic examination.
  2. In some cases, patients may have a patch of hair, a lipoma, skin discoloration, or a dermal sinus overlying the defect.
  3. The condition is occasionally associated with syringomyelia, diastematomyelia, and a tethered cord.
- Meningocele:
  1. Patients typically have a normal neurologic examination; however, lesions may be accompanied by tethering, syringomyelia, or diastematomyelia.
  2. Constipation or bladder dysfunction can develop as a result of an enlargement of the lesion.
- Myelomeningocele:
  1. The lesion can be completely exposed, or it may have a skinlike membrane that covers it.
  2. The extent of the neurologic deficits depends on the level of the lesion:
     1. Thoracolumbar: hypertonic bladder with normal anal tone
     2. Below L2: flaccid tone; areflexic paraparesis; sensory loss in L3-L4 dermatomes; bladder and bowel incontinence; and poor anal sphincter tone, which can result in rectal prolapse

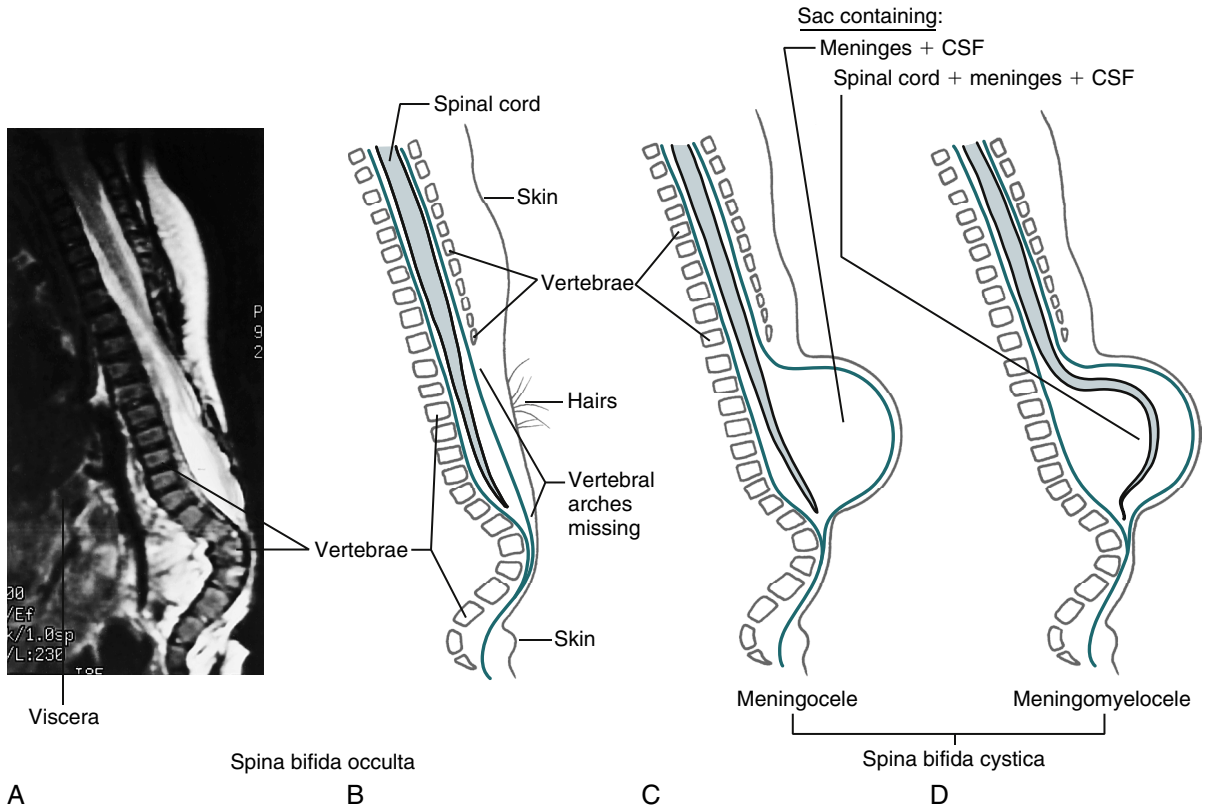


FIGURE ES1-54 Sagittal views of spina bifida malformations. Magnetic resonance image **(A)** and corresponding views showing spina bifida occulta **(A, B)** and spina bifida cystica (**C,** meningocele; **D**, meningomyelocele). *CSF,* Cerebrospinal fluid. (From Haines DE: *Fundamental neuroscience for basic and clinical applications,* ed 3, Philadelphia, 2006, Churchill Livingstone.)

3. Below S3: motor deficits are absent; bladder and anal sphincter paralysis with saddle anesthesia

2. Joint deformities include contractures, hip dislocations, scoliosis, clubfoot, and rocker-bottom foot.
3. Hydrocephalus with Chiari type II malformations occurs in up to 90% of lumbosacral myelomeningoceles, and it is seen in more than half of cases at birth.
4. Tethered cord disease manifests with a loss of motor function, spasticity with contractures, rapid progression of scoliosis with bent posture, back pain, and changes in urodynamics.
5. The condition is associated with disorders of cell migration that cause brain malformations, including heterotopia and schizencephaly.
6. With this disease, there may also be multiorgan developmental disease (e.g., renal agenesis/anomalies, duodenal atresia, cardiac malformations, tracheoesophageal fistulas).

ETIOLOGY

- The posterior neuropore closes at about 26 to 28 days of gestation, which is typically before the mother has knowledge of the pregnancy. The failure of the closure results in any of the neural tube disorders, with the severity being dependent on the stage of development at closure (i.e., earlier in development results in spina bifida cystica vs. spina bifida occulta).
- The cause of the failure to close is unknown, but it is thought to be multifactorial and to involve genetic defects, environmental toxins, and folate deficiency.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Isolated to this group of disorders

WORKUP

- Spina bifida occulta: none, unless foot deformities, neurogenic bladder, or neurologic deficits develop, which would be concerning for spinal cord pathology
- Spina bifida cystica: mostly includes imaging studies

LABORATORY TESTS

None

IMAGING STUDIES

- Ultrasound of affected areas
- MRI of head and spine
- Computed tomography is a quicker study and would not require sedation; however, this method exposes the patient to radiation and therefore should be minimized.

Rx TREATMENT

- Spina bifida occulta: if asymptomatic with normal examination, none
- Meningocele: none
- Myelomeningocele: antiepileptic medications, if warranted

NONPHARMACOLOGIC THERAPY

- Spina bifida occulta: there is no nonpharmacologic therapy used for this condition, unless the patient develops neurologic disease that is suggestive of underlying spinal cord disease.
- Meningocele: most of these defects are covered by skin, so there is minimal risk of infection. If the patient has a normal examination with full-thickness skin, surgery can be delayed. However, if cerebrospinal fluid begins to leak or if the skin is thin, then immediate surgical correction is warranted.
- Myelomeningocele: initial sac closure with a ventriculoperitoneal shunt is usually performed during the first 48 hr of life.
- The in utero closure of spinal lesions has been successful in a few centers, but there is a lack of evidence to support this procedure. The theory is that early closure possibly results in less severe motor disease, joint deformities, and sensory loss.

CHRONIC Rx

- Involves a multidisciplinary approach that includes primary care, neurology, urology, orthopedic surgery, neurosurgery, and physical and occupational therapy
- Bladder catheterization to ensure complete emptying of urinary bladder and minimization of renal scarring
- Urodynamic evaluations
- Bowel training with stool softeners and enemas (an appendicostomy may be placed for antegrade enemas, if warranted.)
- The goal is to prevent the further loss of function and to maximize ambulation:
  1. Close monitoring via physical examination for further worsening of clubfoot, spasticity, sensory loss as a result of possible shunt malfunction, or tethering of cord, which would warrant neurosurgical intervention
  2. Orthotics
  3. Physical and occupational therapy
- Frequent skin examinations to monitor for decubitus ulcer formation

DISPOSITION

- 70% of patients have normal intelligence; this is affected by episodes of meningitis and encephalitis
- Higher incidence of learning disorders and seizures as compared with the general population, which is likely related to brain malformations

FIGURE ES1-55 Lumbosacral myelomeningocele covered by an epithelialized membrane. (From Kliegman RM [ed]: *Nelson textbook of pediatrics,* ed 18, Philadelphia, 2007, Saunders.)

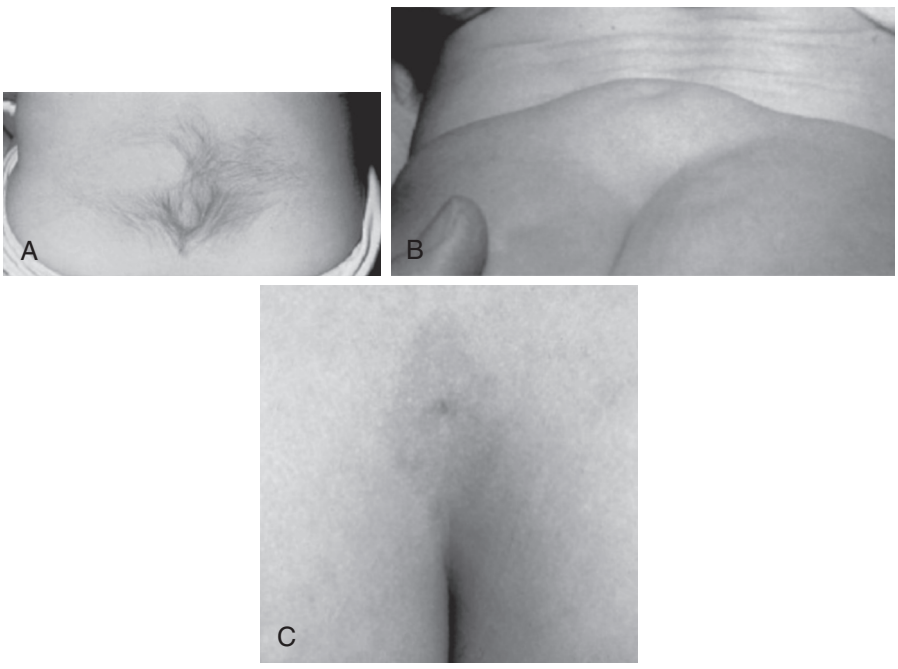


FIGURE ES1-56 Examples of cutaneous malformations associated with spina bifida occulta. A, Tuft of hair. **B,** Sacral lipoma. **C,** Sinus tract that communicates with a dermoid tumor. (From Zitelli BJ, Davis HW [eds]: *Atlas of pediatric physical diagnosis,* ed 5, Philadelphia, 2007, Saunders.)

PEARLS & CONSIDERATIONS

PREVENTION

All women of childbearing age should take a daily multivitamin for folate supplementation (0.4 mg/day), because more than half of pregnancies are unplanned, and the greatest benefit is seen when supplements are taken for about 1 mo before conception. In addition, women who are taking valproic acid, carbamazepine, methotrexate, sulfamethoxazole/trimethoprim, and other medications that affect folate metabolism probably need a higher dose (e.g., 1 mg/day).

PATIENT & FAMILY EDUCATION

Spina Bifida Family Support and Spina Bifida Central have websites where families can share their experiences and information about their children.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Meningomyelocele (Related Key Topic)

AUTHOR: **DONITA DILLON LIGHTNER, M.D.**

EVIDENCE

Abstract[1]

Background:

Prenatal repair of myelomeningocele, the most common form of spina bifida, may result in better neurologic function than repair deferred until after delivery. We compared outcomes of in utero repair with standard postnatal repair.

Methods:

We randomly assigned eligible women to undergo either prenatal surgery before 26 weeks of gestation or standard postnatal repair. One primary outcome was a composite of fetal or neonatal death or the need for placement of a cerebrospinal fluid shunt by the age of 12 months. Another primary outcome at 30 months was a composite of mental development and motor function.

Results:

The trial was stopped for efficacy of prenatal surgery after the recruitment of 183 of a planned 200 patients. This report is based on results in 158 patients whose children were evaluated at 12 months. The first primary outcome occurred in 68% of the infants in the prenatal-surgery group and in 98% of those in the postnatal-surgery group (relative risk, 0.70; 97.7% confidence interval [CI], 0.58 to 0.84; P<0.001). Actual rates of shunt placement were 40% in the prenatal-surgery group and 82% in the postnatal-surgery group (relative risk, 0.48; 97.7% CI, 0.36 to 0.64; P<0.001). Prenatal surgery also resulted in improvement in the composite score for mental development and motor function at 30 months (P = 0.007) and in improvement in several secondary outcomes, including hindbrain herniation by 12 months and ambulation by 30 months. However, prenatal surgery was associated with an increased risk of preterm delivery and uterine dehiscence at delivery.

Conclusions:

Prenatal surgery for myelomeningocele reduced the need for shunting and improved motor outcomes at 30 months but was associated with maternal and fetal risks. (Funded by the National Institutes of Health; ClinicalTrials.gov number, NCT00060606.) Ⓐ

Evidence-Based Reference

Adzick NS for the MOMS Investigators: A randomized trial of prenatal versus postnatal repair of myelomeningocele, *N Engl J Med* 364:993–1004, 2011. Ⓐ

SUGGESTED READINGS

Kliegman RM: Meningocele. In Kliegman RM editor: *Nelson textbook of pediatrics*, ed 18, Saunders, p 592.3.

Kliegman RM: Myelomeningocele. In Kliegman RM editor: *Nelson textbook of pediatrics,* ed 18, Saunders, p 592.4.

Kliegman RM: Spina bifida occulta. In Kliegman RM editor: *Nelson textbook of pediatrics,* ed 18, Saunders, p 592.2.

Menkes JH et al: Neuroembryology, genetic programming, and malformations of the nervous system. In Menkes JH editor: *Child neurology,* ed 7, Lippincott Williams & Wilkins: Philadelphia, pp 287–299.

Rowe DE, Jadhav AL: Care of the adolescent with spina bifida, *Pediatr Clin North Am* 55:1359–1374, 2008.

Sarwark JF: Common orthopedic problems II: spina bifida, *Pediatr Clin North Am* 43:1151–1158, 1996.

Spinal Cord Compression PTG

BASIC INFORMATION

DEFINITION

Spinal cord compression is the neurologic loss of function due to compression of the spinal cord or cauda equina in the spinal canal. Fig. S1-57 illustrates a schematic demarcation of levels of principal dermatomes shown as distinct segments. Lesions may be complete or incomplete and develop gradually or acutely. Incomplete lesions often present as distinct syndromes, as follows:

- Central cord syndrome
- Anterior cord syndrome
- Brown-Séquard syndrome
- Conus medullaris syndrome
- Cauda equina syndrome

ICD-9CM CODES
344.89 Brown-Séquard syndrome
344.60 Cauda equina syndrome
336.8 Conus medullaris syndrome
Other lesions listed by site
ICD-10CM CODES
G83.81 Brown-Séquard syndrome
G83.4 Cauda equina syndrome
G95.81 Conus medullaris syndrome
Other lesions listed by site

EPIDEMIOLOGY

Spinal cord injury (SCI) occurs more commonly in males with a mean age of 38 years. Alcohol plays a role in at least 25% of SCI.
INCIDENCE: 11,000 new cases/yr
PREVALENCE: 171,000 persons
COST (IN U.S.): >$5 billion/yr
RISK FACTORS: Underlying spinal disease can predispose to SCI:

- Cervical spondylosis
- Atlantoaxial instability
- Congenital conditions (tethered cord)
- Osteoporosis
- Ankylosing spondylitis or RA of the spine

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Clinical features reflect the amount of spinal cord involvement:

- Motor loss and sensory abnormalities
- Babinski testing usually positive
- Clonus
- Gradual compression, often manifested by progressive difficulty walking, clonus with weight bearing, and involuntary spasm; development of sensory symptoms; bladder dysfunction (late)
- ***Central cord syndrome:*** results in a variable quadriparesis. It is described as a motor impairment greater in upper than lower extremities, bladder dysfunction, and variable degree of sensory loss below the injury level. It occurs after mild trauma in the setting of preexisting cervical spondylosis and results in variable quadriplegia.
- ***Anterior cord syndrome:*** affects the anterior or ventral 2/3 of the spinal cord, sparing the dorsal columns. It is often caused by a vascular injury to the anterior spinal artery. It results in motor, pain, and temperature loss below the lesion.
- ***Brown-Séquard syndrome:***
  1. Spinal cord syndrome caused by injury to either half of the spinal cord and resulting in the loss of motor function, position, vibration, and light touch on the affected side
  2. Pain and temperature sense loss on the opposite side
- ***Conus medullaris syndrome:*** results in variable motor loss in the lower extremities with loss of bowel and bladder function
- ***Cauda equina syndrome:*** typical low back pain, weakness in both lower extremities, saddle anesthesia, and loss of voluntary bladder and bowel control

ETIOLOGY

- Trauma. Most SCIs result from high-speed motor vehicle accidents, falls, sports injuries, or violence.
- Tumor
- Infection
- Inflammatory processes
- Degenerative disk conditions with spinal stenosis
- Acute disk herniation
- Cystic abnormalities
- Ankylosing spondylitis
- Table S1-21 summarizes physical examination findings associated with vertebral fractures and spinal cord injuries

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

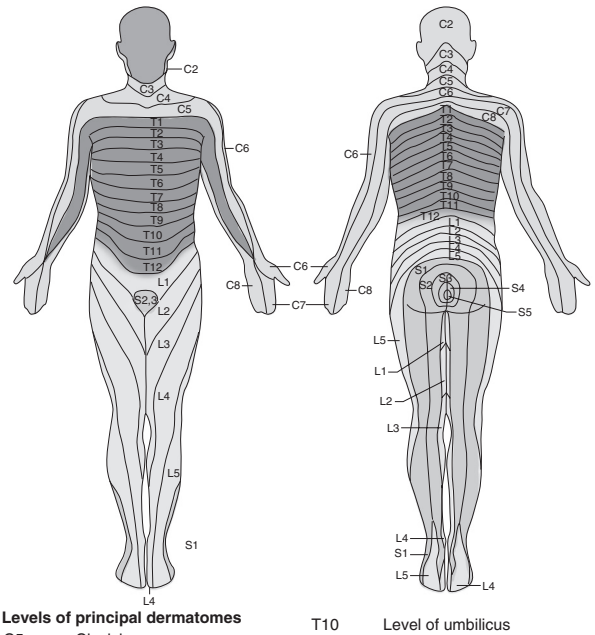
- See "Etiology."
- Section II describes the differential diagnosis of paraplegia.

WORKUP

- Spinal cord compression: requires an immediate referral for radiographic and neurologic assessment.
- Mental status evaluation and CNS function should be included as SCI might be associated with head injury.
- The primary assessment of a patient with SCI follows the ABCD prioritization scheme.
- With respect to airway management, suspected SCI dictates in-line immobilization of the spine at all times, so hyperextension of the neck is contraindicated. A jaw thrust must be used to open the airway, and required intubation must be done with the head/neck in a neutral position.
- Techniques to minimize spine movement include the use of log-roll movements and a back board for transfer and placement of a rigid cervical collar.
- Lab results are usually unremarkable unless underlying infectious or inflammatory causes are associated.

IMAGING STUDIES

- Depend on the suspected etiology
- Neurologic signs and symptoms of SCI in the setting of normal plain x-rays should warrant further imaging studies.



Levels of principal dermatomes

C5	Clavicles
C5,6,7	Lateral parts of upper limbs
C8, T1	Medial sides of upper limbs
C6	Thumb
C6,7,8	Hand
C8	Ring and little fingers
T4	Level of nipples
T10	Level of umbilicus
T12	Inguinal or groin regions
L1,2,3,4	Anterior and inner surfaces of lower limbs
L4,5 S1	Foot
L4	Medial side of great toe
S1,2, L5	Posterior and outer surfaces of lower limbs
S1	Lateral margin of foot and little toe
S2,3,4	Perineum

FIGURE S1-57 Schematic demarcation of levels of principal dermatomes shown as distinct segments. There is actually considerable overlap between any two adjacent dermatomes. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2011, Saunders.)

TABLE S1-21 Physical Examination Findings Associated with Vertebral Fractures and Spinal Cord Injuries

Injury	Physical Examination Area	Associated Findings
Vertebral fracture	Spine	Tenderness of the neck and/or back. Examine the entire spine because vertebral fractures may occur in multiples.
	Neurologic	See spinal cord injury below.
	Chest	*Thoracic spine fractures:* check for chest tenderness, unequal breath sounds, and arrhythmia, which are suggestive of an associated intrathoracic injury or myocardial contusion.
	Abdomen/pelvis	*Thoracolumbar and lumbar spine fractures:* check for abdominal or pelvic tenderness. For instance, up to 50% of patients with a transverse process fracture and 33% of patients with a Chance fracture have concurrent intraabdominal pathology. A transverse area of ecchymosis on the lower abdominal wall (seat belt sign) increases the chance of an abdominopelvic injury.
	Extremity	*Thoracolumbar and lumbar spine fractures*: check for calcaneal tenderness because 10% of calcaneal fractures are associated with a low thoracic or lumbar fracture. Mechanistically, these areas are fractured as a result of axial loading.
Spinal cord injury	Neurologic, motor (anterior column)	Assess motor function on a scale of 0 to 5. The *motor level* is defined as the most caudal segment with at least 3/5 strength. Injuries to the first eight cervical segments result in tetraplegia (previously known as quadriplegia); lesions below the T1 level result in paraplegia.
	Neurologic, sensory (spinothalamic tract)	Assess sensory function via pinprick and light touch on the following scale: 0 = absent; 1 = impaired; 2 = normal. The *sensory level* is defined as the most caudal segment of the spinal cord with normal sensory function. The highest intact sensory level should be marked on the patient's spine to monitor for progression.
	Neurologic, sensory (dorsal column)	Assess vibratory sensory function on a scale of 0 to 2 by using a tuning fork over bony prominences. Assess position sense (proprioception) by flexing and extending the great toe.
	Neurology, deep tendon reflex	On a scale of 0 to 4, assess the deep tendon reflexes in the upper (biceps, triceps) and lower (patellar, Achilles) extremities.
	Anogenital	Assess rectal tone, sacral sensation, signs of urinary or fecal retention or incontinence, and priapism. Also check the anogenital reflexes: an *anal wink* (S2-S4) is present if the anal sphincter contracts in response to stroking the perianal skin area. The *bulbocavernosus reflex* (S3-S4) is elicited by squeezing the glans penis or clitoris (or pulling on an inserted Foley catheter), which results in reflexive contraction of the anal sphincter.
	Head-to-toe examination	A spinal cord injury may mask a patient's ability to perceive and localize pain. Imaging of high-risk areas, such as the abdomen, and areas of bruising or swelling may be required to exclude occult injuries.

From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

- Complete set of cervical x-rays should include anteroposterior, lateral, and open-mouth odontoid views.
- After initial resuscitative efforts, fine-cut helical CT scan with coronal and sagittal reconstructions have supplanted plain radiographs in most trauma centers as an initial evaluation in detecting spine fractures.
- MRI provides a detailed image of the spinal ligaments, intervertebral discs, and paraspinal soft tissues and is very sensitive for detecting epidural hematoma (Fig. S1-58).

Rx TREATMENT

- Urgent surgical decompression is usually indicated as soon as the etiology is established.
- Corticosteroids: The administration of methylprednisolone reduces the amount of secondary injury that occurs after SCI and has become an important tool in the treatment of SCI by improving outcomes. Corticosteroids should not be used in patients with associated traumatic brain injury and penetrating injuries since they might increase mortality.

DISPOSITION

Important indicators regarding prognosis:

- The greater the distal motor and sensory sparing, the greater the expected recovery.
- When a plateau of recovery is reached, no further improvement is expected.
- Rapid improvement is associated with better long-term recovery. Patients with acute traumatic SCI need monitoring in the ICU and evaluation for potential life-threatening complications, including cardiovascular instability and respiratory failure.
- Prophylaxis against DVT and PE should always be provided.

REFERRAL

Immediate referral for radiographic and neurologic evaluation and treatment in all suspected cases of spinal cord compression

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Spinal Stenosis (Patient Information)

AUTHOR: **CATHERINE ELIAS NAJEM, M.D.**

FIGURE S1-58 Magnetic resonance image demonstrating compression of the thecal sac *(arrows).* (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

SUGGESTED READINGS

Baines MJ: Spinal cord compression—a personal and palliative care perspective, *Clin Oncol (R Coll Radiol)* 14(2):135, 2002.

Banerjee R et al.: Spinal epidural hematoma induced by leukemia, *Orthopedics* 27:864, 2004.

Benjamin R: Neurologic complications of prostate cancer, *Am Fam Physician* 65(9):2002, 1834.

Berrand T, Samant R: Palliative radiotherapy knowledge among community family physicians and nurses, *J Cancer Educ* 23:156, 2008.

Buchner M, Schiltenwolf M: Cauda equina syndrome caused by intervertebral lumbar disc prolapse: mid-term results of 22 patients and literature review, *Orthopedics* 25:727, 2002.

Carlson GD et al.: Sustained spinal cord compression. Part I: time-dependent effect on long-term pathophysiology, *J Bone Joint Surg* 85:86, 2003.

Carlson GD et al.: Sustained spinal cord compression. Part II: effect of methylprednisolone on regional blood flow and recovery of somatosensory evoked potentials, *J Bone Joint Surg* 85:95, 2003.

Casey AT et al.: Rheumatoid arthritis of the cervical spine: current techniques for management, *Orthop Clin North Am* 33(2):291, 2002.

Jagas M et al.: Vertebroplasty with methacrylate bone cement and radiotherapy in the treatment of spinal metastases with epidural spinal cord compression, *Orthop Traumatol Rehabil* 7(5):491, 2005.

Kadanka Z et al.: Approaches to spondylotic cervical myelopathy: conservative versus surgical in a 3-year follow-up study, *Spine* 27(20):2205, 2002.

Lada R. Metastatic spinal cord compression. In: (editor: Vecht C.) Handbook of clinical neurology, Part 3. 69 Elsevier: Amsterdam, p. 167.

Malcolm GP: Surgical disorders of the cervical spine: presentation and management of common disorders, *J Neurosurg Psychiatry* 73(suppl 1):134, 2002.

Matsunaga S et al.: Trauma-induced myelopathy in patients with ossification of the posterior longitudinal ligament, *J Neurosurg* 97(2 suppl):172, 2002.

Mohanty SP, Venkatram N: Does neurological recovery in thoracolumbar and lumbar burst fractures depend on the extent of canal compromise? *Spinal Cord* 40(6):295, 2002.

Nowak DD et al.: Central cord syndrome, *J Am Acad Orthop Surg* 17:756, 2009.

Rades D et al.: Do bladder cancer patients with metastatic spinal cord compression benefit from radiotherapy alone? *Urology* 69(6):1081, 2007.

Shimomura T et al.: Prognostic factors for deterioration of patients with cervical spondylotic myelopathy after nonsurgical treatment, *Spine* 32:2474, 2007.

Sorar M et al.: Cervical compression myelopathy: is fusion the main prognostic indicator? *J Neurosurg Spine* 6(6):531, 2007.

Tosteson A et al.: Surgical treatment of spinal stenosis with and without degenerative spondylolisthesis: cost-effectiveness after 2 years, *Ann Intern Med* 149:845–853, 2008.

Venkitaraman R et al.: Outcome of early detection and radiotherapy for occult spinal cord compression, *Radiother Oncol* 85:469, 2007.

Vitarbo EA, Levi AD: Spinal cord injury. In: (editor: Vincent JL et al.) Textbook of critical care. ed 6, Saunders: Philadelphia.

Yagi M et al.: Long-term surgical outcome and risk factors in patients with cervical myelopathy and a change in signal intensity of intramedullary spinal cord on magnetic resonance imaging, *J Neurosurg Spine* 12:59, 2010.

Spinal Epidural Abscess ALG EBM

BASIC INFORMATION

DEFINITION

A spinal epidural abscess (SEA) is a focal suppurative infection occurring in the spinal epidural space.

ICD-9CM CODES
324.1 Spinal epidural abscess
ICD-10CM CODES
G06.1 Intraspinal abscess and granuloma

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.)
- 2 to 25 cases/100,000 hospitalized patients/yr
- May be increasing over the past 3 decades

PREDOMINANT AGE

- Median age of onset approximately 50 yr (35 yr in intravenous drug users)
- Peak incidence in seventh and eighth decades of life

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The presentation of SEA can be nonspecific.
- Fever, malaise, and back pain are the most consistent early symptoms.
- Pain is often focal. It may initially be mild but can progress to become severe.
- As the disease progresses, root pain can occur, followed by motor weakness, sensory changes, bladder and bowel dysfunction, and paralysis.
- Physical findings may be limited to fever or spinal tenderness.
- The evolution to neurologic deficits can occur as quickly as a few hours, or over weeks to months.
- Once paralysis occurs, it may quickly become irreversible without the appropriate intervention.

ETIOLOGY

- Pyogenic bacteria account for the majority of cases in the United States. Immigrants from TB-endemic areas may present with tuberculous SEAs. Fungi and parasites can also cause this condition. The most common causative organism is *Staphylococcus aureus.* Gram-negative bacilli and anaerobes may be seen if the infection has a urinary or GI source.
- Most posterior SEAs are thought to originate from distant focus (e.g., skin and soft tissue infections), while anterior SEAs are commonly associated with diskitis or vertebral osteomyelitis. No source was found in approximately one third of cases.
- Associated predisposing conditions include diabetes mellitus, alcoholism, cancer, AIDS, and chronic renal failure, or following epidural anesthesia, spinal surgery or trauma, or IV drug use. No predisposing condition is found in approximately 20% of patients.
- Damage to the spinal cord can be caused by direct compression of the spinal cord, vascular compromise, bacterial toxins, and inflammation.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Herniated disk
- Vertebral osteomyelitis and diskitis
- Metastatic tumors
- Meningitis

LABORATORY TESTS

- WBC may be normal or elevated.
- ESR is usually elevated over 30 mm/hr.
- Blood cultures are positive in approximately 60% of patients with SEA.
- CSF cultures are positive in 19%, but lumbar puncture is unnecessary, and may be contraindicated.
- Once imaging is done, CT-guided aspiration or open biopsy should be done to determine causative organism. Abscess content culture is positive in 90% of patients.

IMAGING STUDIES

- MRI with gadolinium is the imaging modality of choice (Fig. S1-59); CT scan with contrast may show the abscess (Fig. S1-60) but is less sensitive than MRI.
- CT with myelography is more sensitive for cord compression.

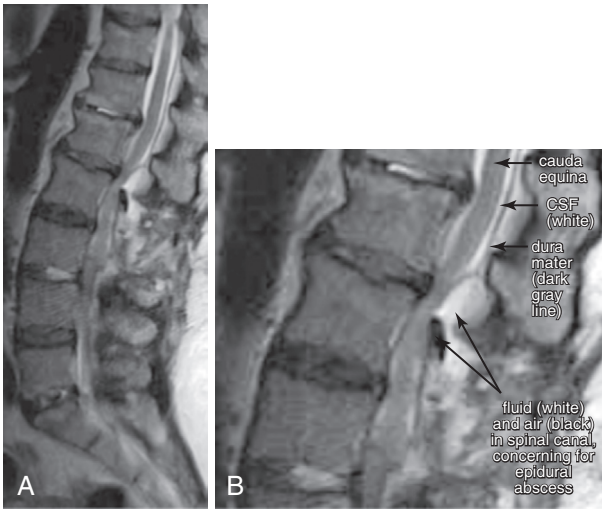


FIGURE S1-59 Same patient as in Fig. S1-60, in whom noncontrast computed tomography showed air in the spinal canal, concerning for epidural abscess. Magnetic resonance imaging (MRI) of the lumbar spine without contrast was performed, as the patient was in acute renal failure. **A,** This T_2-weighted sagittal MR image provides useful information even without gadolinium contrast. **B,** Close-up. On T_2-weighted MRI sequences, fluid including cerebrospinal fluid *(CSF)* appears white. Fat-containing tissues such as bone marrow and the spinal cord or cauda equina appear dark gray. Calcified bone appears nearly black due to an absence of resonating protons. Air appears completely black for the same reason. The midline sagittal image shows the cauda equina to be impinged upon by an epidural fluid collection containing air—an epidural abscess. The dura mater is visible as a thin, dark gray line parallel to the spinal cord. It is indented in the region of the epidural abscess. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

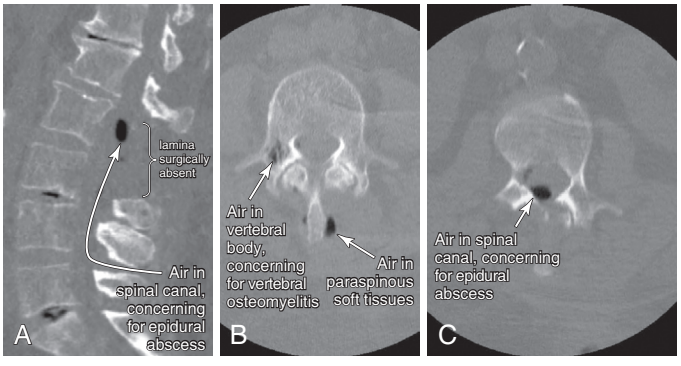


FIGURE S1-60 This 67-year-old female presented with delirium and fever. Three months prior, she had undergone lumbar laminectomy, and her wound had been treated with a wound VAC dressing. Magnetic resonance imaging was not initially available, so noncontrast computed tomography (CT) was performed. Noncontrast CT is excellent at delineating air, which appears black on bone windows. **A,** The midsagittal view demonstrates air *(black)* in the spinal canal at the L2 and L3 levels. On the axial views **(B, C),** air is visible in the spinal canal, in paraspinal soft tissues, and within the vertebral body. These findings are concerning for a paraspinal infection that has developed into an epidural abscess with vertebral osteomyelitis. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Surgical decompression is the mainstay of treatment. Decompression within the first 24 hr has been related to an improved prognosis.
- Nonsurgical treatment is effective in some patients, but failure rate may be excessive. This approach should not be considered and should only be attempted in the absence of signs of compressive myelopathy and with very careful follow-up.

ACUTE GENERAL Rx

- In addition to surgery, antibiotics directed at the most likely organism should be initiated. Fig. S1-61 describes an algorithm for the management of patients with SEA.
- If the organism is unknown, broad coverage against staphylococci, streptococci, and gram-negative bacilli should be initiated. Empiric antimicrobial therapy typically includes vancomycin plus an antipseudomonal cephalosporin or carbapenem. The regimen can be adjusted according to culture results. Therapy should continue for at least 4 to 6 wk.

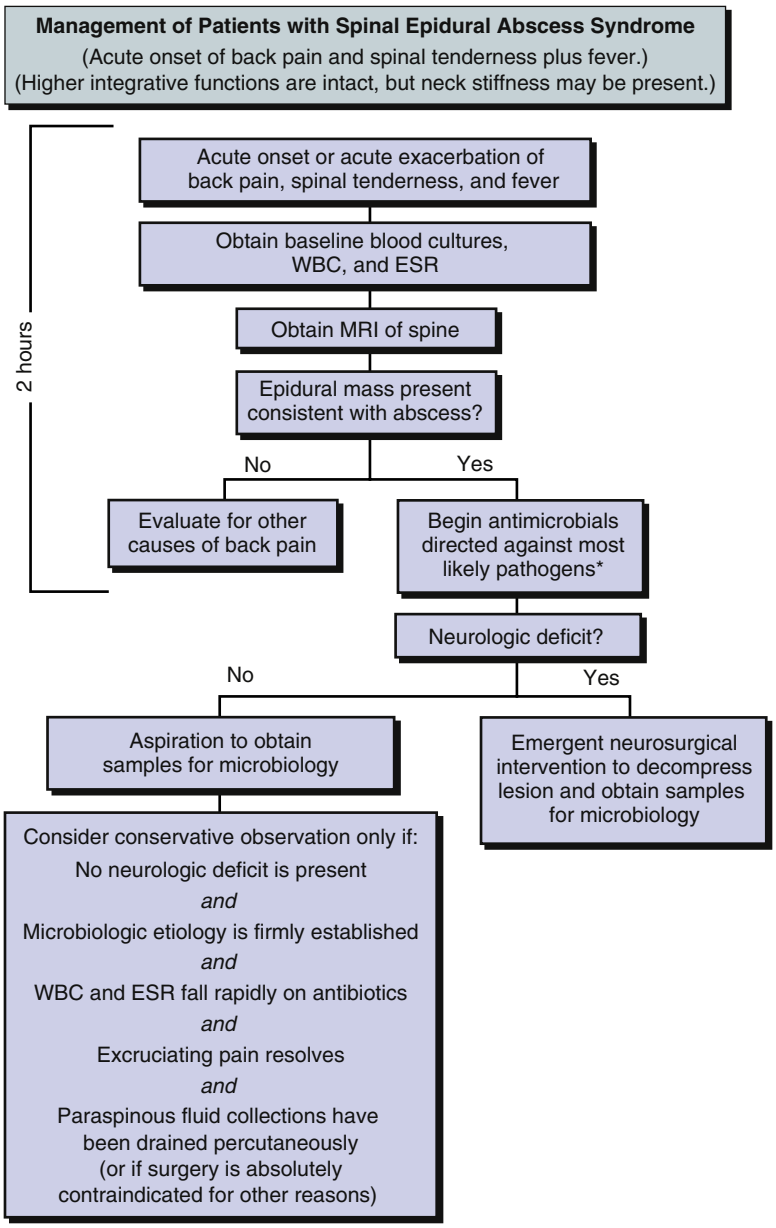


FIGURE S1-61 Algorithm for the management of patients with spinal epidural abscess syndrome. If magnetic resonance imaging *(MRI)* cannot be performed, myelography, high-contrast computed tomography (CT), or CT-myelography may be an acceptable alternative to localize an epidural abscess. *If abscess drainage can be performed promptly, antimicrobial drugs may be withheld until specimens for microbial analysis are obtained. *ESR,* Erythrocyte sedimentation rate; *WBC,* white blood cell. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

CHRONIC Rx

Neurologic deficits may remain despite aggressive treatment.

DISPOSITION

Irreversible paralysis and death can occur in up to 25% of patients.

REFERRAL

All cases should be referred to a neurosurgeon and an infectious disease specialist.

PEARLS & CONSIDERATIONS

- It is critically important to recognize this process early; the prognosis is generally excellent if treatment is initiated while symptoms are localized and before evidence of myelopathy develops.
- The likelihood of success postsurgery is low in patients who have developed complete paralysis for longer than 36 hours.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

EVIDENCE

Abstract[1]

Background Context:
Spinal epidural abscess (SEA) is a rare, serious and increasingly frequent diagnosis. Ideal management (medical vs. surgical) remains controversial.

Purpose:
The purpose of this study is to assess the impact of risk factors, organisms, location and extent of SEA on neurologic outcome after medical management or surgery in combination with medical management.

Study Design:
Retrospective electronic medical record (EMR) review.

Patient Sample:
We included 128 consecutive, spontaneous SEA cases from a single tertiary medical center, from January 2005 to September 2011. There were 79 males and 49 females with a mean age of 52.9 years (range, 22–83).

Outcome Measures:
Patient demographics, presenting complaints, radiographic features, pre/post-treatment neurologic status (ASIA motor score [MS] 0–100), treatment (medical vs. surgical) and clinical follow up were recorded. Neurologic status was determined before treatment and at last available clinical encounter. Imaging studies reviewed the location/extent of pathology.

Methods:
Inclusion criteria were a diagnosis of a bacterial SEA based on radiographs and/or intraoperative findings, age greater than 18 years, and adequate EMR. Exclusion criteria were postinterventional infections, Pott's disease, isolated discitis/osteomyelitis, treatment initiated at an outside facility, and imaging suggestive of a SEA but negative intraoperative findings/cultures.

Results:
The mean follow-up was 241 days. The presenting chief complaint was site-specific pain (100%), subjective fevers (50%), and weakness (47%). In this cohort, 54.7% had lumbar, 39.1% thoracic, 35.9% cervical, and 23.4% sacral involvement spanning an average of 3.85 disc levels. There were 36% ventral, 41% dorsal, and 23% circumferential infections. Risk factors included a history of IV drug abuse (39.1%), diabetes mellitus (21.9%), and no risk factors (22.7%). Pathogens were methicillin-sensitive *Staphylococcus aureus* (40%) and methicillin-resistant *S. aureus* (30%). Location, SEA extent, and pathogen did not impact MS recovery. Fifty-one patients were treated with antibiotics alone (group 1), 77 with surgery and antibiotics (group 2). Within group 1, 21 patients (41%) failed medical management (progressive MS loss or worsening pain) requiring delayed surgery (group 3). Irrespective of treatment, MS improved by 3.37 points. Thirty patients had successful medical management (MS: pretreatment, 96.5; post-treatment, 96.8). Twenty-one patients failed medical therapy (41%; MS: pretreatment, 99.86, decreasing to 76.2 [mean change, –23.67 points], postoperative improvement to 85.0; net deterioration, –14.86 points). This is significantly worse than the mean improvement of immediate surgery (group 2; MS: pretreatment, 80.32; post-treatment, 89.84; recovery, 9.52 points). Diabetes mellitus, C-reactive protein greater than 115, white blood count greater than 12.5, and positive blood cultures predict medical failure: None of four parameters, 8.3% failure; one parameter, 35.4% failure; two parameters, 40.2% failure; and three or more parameters, 76.9% failure.

Conclusion:
Early surgery improves neurologic outcomes compared with surgical treatment delayed by a trial of medical management. More than 41% of patients treated medically failed management and required surgical decompression. Diabetes, C-reactive protein greater than 115, white blood count greater than 12.5, and bacteremia predict failure of medical management. If a SEA is to be treated medically, great caution and vigilance must be maintained. Otherwise, early surgical decompression, irrigation, and debridement should be the mainstay of treatment. Ⓐ

Evidence-Based References

Patel AR, Alton TB, Bransford RJ, et al.: Spinal epidural abscesses: risk factors, medical versus surgical management, a retrospective review of 128 cases, *Spine J* 14:326–330, 2014. Ⓐ

Darouiche RO: Spinal epidural abscess, *N Engl J Med* 355:2012–2020, 2006. Ⓐ

SUGGESTED READINGS

Curry WT et al.: Spinal epidural abscess: clinical presentation, management, and outcome, *Surg Neurol* 63(4):364, 2005.

Moriya M et al.: Successful management of cervical spinal epidural abscess without surgery, *Intern Med* 44(10):1110, 2005.

Savage K et al.: Spinal epidural abscess: early clinical outcome in patients treated medically, *Clin Orthop Relat Res* 439:56, 2005.

Torgovnick J et al.: Spinal epidural abscess: clinical presentation, management and outcome, *Surg Neurol* 63:364, 2005.

Spinal Stenosis, Lumbar PTG

BASIC INFORMATION

DEFINITION

Spinal stenosis is the pathologic condition caused by the compressing or narrowing of the spinal canal, nerve root canal, or intervertebral foramina at the lumbar region.

SYNONYMS

Central spinal stenosis
Lateral spinal stenosis
Spondylosis

ICD-9CM CODES
724.02 Spinal stenosis lumbar, lumbosacral
ICD-10CM CODES
M48.06 Spinal stenosis, lumbar region

EPIDEMIOLOGY & DEMOGRAPHICS

More common between 50 and 60 yr of age

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms caused by direct mechanical compression or indirect vascular compression of the nerve roots or the cauda equina.
- Neurogenic claudication: leg, buttock, or back pain precipitated by walking and relieved by sitting.
- Pain may radiate down to ankles and is associated with numbness, tingling, and weakness.
- Taking a flexed posture reduces symptoms because it increases the available space in the lumbar spinal canal.
- Decreased lumbar extension.
- Normal peripheral pulses.
- Positive Romberg's sign (decreased proprioception).
- Wide-based gait.
- Reduced knee and ankle reflex.
- Urine incontinence.

ETIOLOGY

Spinal stenosis may be primary or secondary (Fig. S1-62)

- Primary stenosis (congenital or developmental narrowing)
  1. Idiopathic
  2. Achondroplasia
  3. Morquio-Ullrich syndrome
- Secondary stenosis (acquired)
  1. Degenerative (hypertrophy of the articular processes, disk degeneration, ligamentum flavum hypertrophy, spondylolisthesis)
  2. Fracture/trauma
  3. Postoperative (postlaminectomy)
  4. Paget's disease
  5. Ankylosing spondylitis
  6. Tumors
  7. Acromegaly

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Osteoarthritis of the knee or hip
- Acute cauda equina syndrome, resulting from compression by epidural abscess or tumors
- Pain and weakness caused by multiple myeloma or osteomyelitis
- Intermittent claudication—peripheral vascular disease
- Peripheral neuropathy such as that caused by a herniated nucleus pulposus
- Scoliosis or spondylolisthesis
- Rheumatoid diseases: ankylosing spondylitis, Reiter's syndrome, fibromyalgia
- Table S1-22 compares clinical features of spinal stenosis, peripheral vascular disease, and disk disease.

WORKUP

History, physical examination, and specific imaging studies

IMAGING STUDIES

- Lumbar spine film sensitivity 66%, specificity 93%.
- Ultrasound of the spinal canal has also been used.
- CT scan of the lumbosacral spine: sensitivity (75% to 85%), specificity (80%).
- MRI of the lumbosacral spine (Fig. S1-63): sensitivity (80% to 90%), specificity (95%).
- Myelogram: sensitivity (77%), specificity (72%). Absolute stenosis is defined as the anterior-posterior (AP) diameter of the spinal canal <10 mm. Relative stenosis: 10 to 12 mm AP diameter.
- Electromyography (EMG) and nerve conduction velocity (NCV) are additional studies particularly useful in differentiating peripheral neuropathy from lumbar spinal stenosis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Physiotherapy
- Lumbar corsets
- Back exercises
- Abdominal muscle strengthening
- Aquatic exercises

ACUTE GENERAL Rx

- Surgery is indicated in patients with significant compression of nerve roots as determined by MRI or CT and incapacitating symptoms limiting activities of daily living or bladder and bowel incontinence.
- Surgical procedures include decompressive laminectomy, arthrodesis, hemilaminectomy, and medial facetectomy.

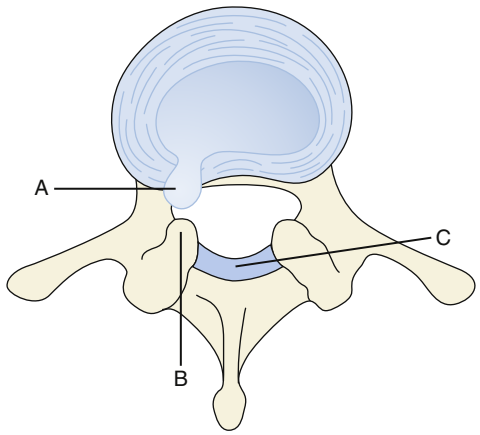


FIGURE S1-62 Spinal stenosis secondary to a combination of disk herniation *(A),* facet joint hypertrophy *(B),* and hypertrophy of the ligamentum flavum *(C).* (From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

TABLE S1-22 Comparative Clinical Features of Spinal Stenosis, Peripheral Vascular Disease, and Disc Disease

Feature	Spinal Stenosis	Disc Prolapse	Peripheral Vascular Disease
Reduced straight leg raise	Rarely	Usually	No
Neurologic deficit	Sometimes	Often	No
Leg pain on walking	Yes	Usually	Yes
Leg pain on sitting	No	Yes	No
Pain relief on standing still	No	No	Yes
Pain relief on sitting	Yes	No	Yes
Numbness/paresthesia	Yes	Yes	Sometimes

From Carr A, Hamilton W: *Orthopedics in primary care,* ed 2, Philadelphia, 2005, Butterworth-Heinemann.

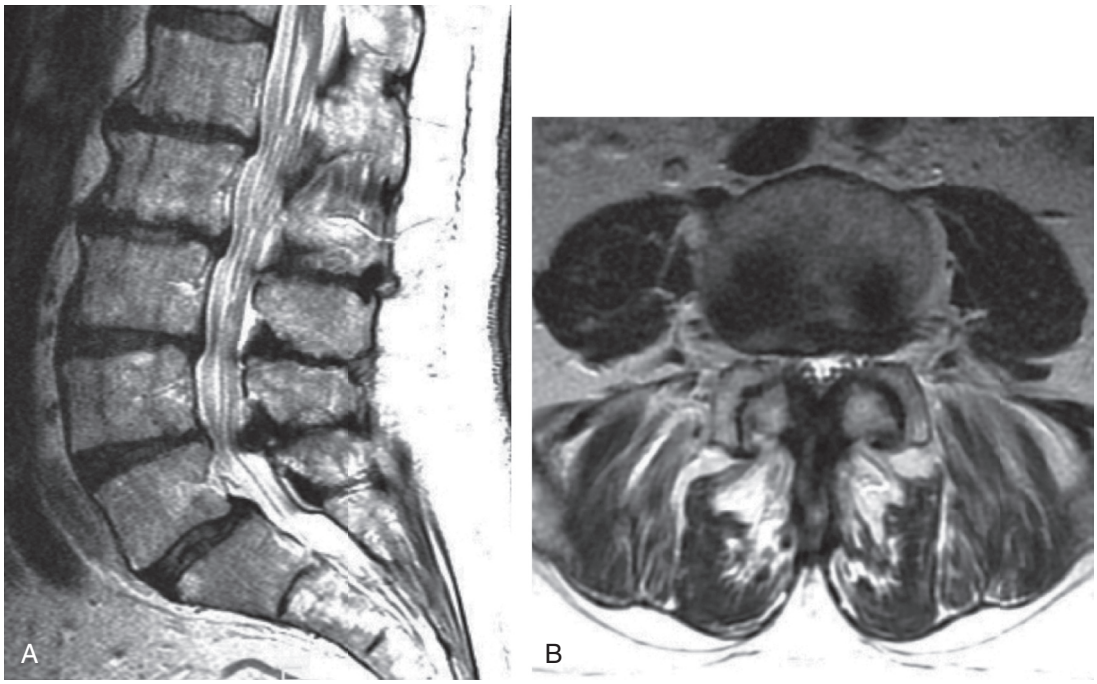


FIGURE S1-63 Degenerative spinal stenosis. A, The sagittal T2-weighted magnetic resonance image shows decreased anteroposterior diameter of the neural canal at the L4-5 level due to redundancy of the ligamentum flavum. **B,** The axial image through the L4-5 disk shows decreased cross-sectional area of the thecal sac from hypertrophic changes of the facet joints posterolateral to the thecal sac. (Courtesy Dr. John Crues, University of California, San Diego.)

- Lumbar interspinous process decompression using X-STOP device: a titanium oval spacer placed between the two adjacent spinous processes of the affected level; provides an unloading distractive force to the stenotic middle column part of the motion segment.

CHRONIC Rx

- Conservative therapy with NSAIDs (ibuprofen 800 mg PO tid, naproxen 500 mg PO bid) may be tried for symptomatic relief in addition to acetaminophen 1 g PO qid.
- Epidural glucocorticoid injections are widely used to treat symptoms of lumbar spinal stenosis; however, rigorous data are lacking regarding the effectiveness and safety of these injections. A recent trial revealed that in the treatment of lumbar spinal stenosis, epidural injection of glucocorticoids plus lidocaine offered minimal or no short-term benefit as compared with epidural injection of lidocaine alone.

DISPOSITION

- Approximately 20% of patients having surgery require repeat surgery within 10 yr. Nearly one third of these patients continue to experience pain.
- The natural history of spinal stenosis is one of slow progression. Although not very common, cord compression with resultant bowel and bladder incontinence and paresis can occur.
- Operative treatment is more effective in reducing pain and disability than nonoperative treatment.

REFERRAL

- Patients who have spinal stenosis should be referred to an orthopedic surgeon specializing in back surgery or to a neurosurgeon.
- Pain clinic referrals should be made if surgery is contraindicated or if the patient does not want surgery.

PEARLS & CONSIDERATIONS

COMMENTS

- Approximately one third of patients have coexisting peripheral vascular disease.
- The severity of cauda equina constriction is directly related to the walking ability and the pain intensity in the legs and back.
- Spinal stenosis is also a cause of chronic low back pain in the young.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Spinal Stenosis (Patient Information)

AUTHOR: **JORGE A. VILLAFUERTE, M.D.**

SUGGESTED READINGS

de Graaf I et al.: Diagnosis of lumbar spinal stenosis: a systematic review of the accuracy of diagnostic tests, *Spine* 31(10):1168–1176, 2006.

Fu YS et al.: Long-term outcomes of two different decompressive techniques for lumbar spinal stenosis, *Spine* 33(5):514–518, 2008.

Friedly JL et al.: A randomized trial of epidural glucocorticoid injections for spinal stenosis, *N Engl J Med* 371:11–21, 2014.

Malmivaara A et al.: (for the Finnish Lumbar Spinal Research Group): Surgical or nonoperative treatment for lumbar spinal stenosis? A randomized controlled trial, *Spine* 32(1):1–8, 2007.

Pua Y-H et al.: Treadmill walking with body weight support is no more effective than cycling when added to an exercise program for lumbar spinal stenosis: a randomised controlled trial, *Aust J Physiother* 53(2):83–89, 2007.

Spengler DM: Surgery reduced pain at two years but did not differ from nonsurgical treatment for physical function in lumbar spinal stenosis, *J Bone Joint Surg Am* 90(11):2553, 2008.

Tosteson A et al.: Surgical treatment of spinal stenosis with and without degenerative spondylolisthesis: cost-effectiveness after 2 years, *Ann Intern Med* 149:845–853, 2008.

Weinstein JN et al.: Surgical versus non-surgical therapy for lumbar spinal stenosis, *N Engl J Med* 358:794–810, 2008.

BASIC INFORMATION

DEFINITION

The spinocerebellar ataxias (SCAs) are a heterogeneous group of autosomal dominantly inherited genetic conditions that cause progressive ataxia and other neurologic symptoms.

SYNONYMS

Autosomal-dominant cerebellar ataxia (ADCA)
Machado-Joseph disease (eponym for SCA3; this may be the most common SCA)

ICD-9CM CODES
334.2 Primary cerebellar degeneration
ICD-10CM CODES
G11.9 Hereditary ataxia, unspecified
G11.8 Other hereditary ataxias

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: The prevalence of the condition is approximately 3 persons per 100,000. The most common SCAs are 1, 2, 3, 6, and 7.
PREDOMINANT SEX: SCA demonstrates no gender preference.
PREDOMINANT AGE: The age of onset is often during the 30s or 40s. However, this can be highly variable, even within family groups; SCAs can occur anytime from childhood to late adulthood.
GENETICS: All SCAs are inherited in an autosomal dominant fashion; however, reduced penetrance can be present.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Chronically progressive ataxia is the predominant symptom of all of the SCAs. It typically presents as a combination of balance and gait difficulty, limb incoordination, nystagmus, and dysarthria.
- More than 36 different genetic subtypes of SCA have been described to date. Although certain clinical characteristics are common to specific SCA subtypes, there is significant overlap among and variability within these conditions, so making a diagnosis on the basis of the clinical presentation alone can be challenging and sometimes impossible without genetic testing. Some of the more common SCAs and their possible distinguishing features in addition to ataxia include the following:
  1. SCA1 can be characterized by nystagmus, spasticity, and neuropathy.
  2. SCA2 can be characterized by slow saccades, gaze palsy, neuropathy, and sometimes parkinsonism or dementia.
  3. SCA3, which is also known as Machado-Joseph disease (Fig. S1-64), can be characterized by neuropathy, amyotrophy, parkinsonism, and dystonia.
  4. SCA6 is generally felt to be a pure cerebellar syndrome with ataxia and nystagmus (gaze evoked and downbeat) as well as a frequently later age of onset.
  5. SCA7 is characterized by dementia, vision loss caused by a pigmentary maculopathy, and spasticity.
  6. Knowledge in this area is constantly expanding and being updated. Online sources of information (e.g., Online Mendelian Inheritance in Man [http://www.ncbi.nlm.nih.gov/omim]) can be invaluable for tracking new developments.

ETIOLOGY

Several of the SCAs are the result of polyglutamine CAG repeat expansions; this causes the accumulation of mutant proteins inside neurons, which is thought to cause dysfunction and cell death. Higher numbers of repeats are correlated with an earlier onset of symptoms, and anticipation may be present. Other types of repeat expansions and point mutations have been found with several SCAs; for others, the affected gene has not been identified.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Structural cerebellar abnormality: includes cerebellar tumor, inflammation (e.g., multiple sclerosis), stroke, or hemorrhage; the time course for these causes is typically more acute or subacute than chronic.
- Endocrine dysfunction: hypothyroidism or hypoparathyroidism can uncommonly cause ataxia.
- Alcoholic cerebellar degeneration: caused by heavy alcohol use; gait ataxia predominates.
- Other toxin-induced ataxias: antiepileptic medications, lithium, and chemotherapeutic agents.
- Creutzfeldt-Jakob disease: rapidly progressive ataxia, dementia, and myoclonus.
- Paraneoplastic cerebellar degeneration: found in association with primary malignancies (e.g., small cell lung cancer, breast cancer); subacute-onset ataxia that progresses rapidly.
- Celiac disease: gluten-sensitive enteropathy with malabsorption may be associated with ataxia; autoantibodies such as antigliadin or antiendomysial antibodies are typically present.
- Multiple system atrophy: cerebellar variant of this disorder causes ataxia; there is typically associated parkinsonism with some degree of autonomic dysfunction (e.g., orthostatic hypotension, urinary incontinence).
- Friedreich's ataxia: autosomal recessive inheritance, generally younger age of onset (i.e., mean 15 yr of age), lower limb areflexia, and posterior column dysfunction.
- Ataxia associated with vitamin E deficiency: can be an autosomal recessive disorder or acquired; clinically resembles Friedreich's ataxia, with areflexia and loss of position sense.
- Ataxia telangiectasia: autosomal recessive inheritance, childhood onset, oculocutaneous telangiectases, and immunodeficiency.
- Wilson's disease: can cause hepatic dysfunction and a variety of movement disorders, including ataxia; particularly important to screen for this in patients who are young at onset because it is treatable
- Dentatorubral-pallidoluysian atrophy: autosomal dominant like SCA but typically has ataxia with associated choreoathetosis, myoclonus, epilepsy, and dementia.
- Fragile X–associated tremor/ataxia syndrome: premutation of the fragile X mutation gene; more common among males than females; late onset of ataxia (i.e., >50 yr), tremor, and sometimes parkinsonism; MRI often shows T2 hyperintensity in the middle cerebellar peduncle.
- Box S1-7 shows the classification of the various causes of ataxia.

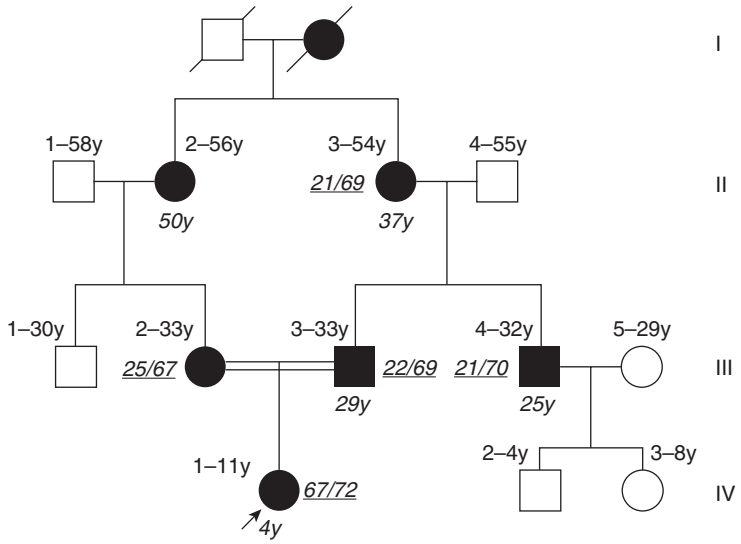


FIGURE S1-64 Family pedigree of proband (IV-1). Age at onset of spinocerebellar ataxia type 3 symptoms is given beneath symbols (*italics*). Above symbols the actual age of the members of the family are given. If tested, the number of CAG repeat units of the *ATXN3* allele pair is also given (*underscored italics*). (From Daniel R. Carvalho et al.: *Homozygosity enhances severity in spinocerebellar ataxia type 3; Pediatric neurology*, Volume 38, Issue 4, April 2008, pp. 296–299.)

BOX S1-7 Classification of Ataxia

Congenital Ataxias

Hereditary Ataxias

Autosomal Recessive Ataxias
- Friedreich's ataxia
- Ataxia–telangiectasia
- Ataxia with oculomotor apraxia type 1
- Ataxia with oculomotor apraxia type 2
- Autosomal recessive spastic ataxia of Charlevoix-Saguenay
- Abetalipoproteinemia
- Ataxia with isolated vitamin E deficiency
- Refsum's disease
- Cerebrotendinous xanthomatosis
- Marinesco-Sjögren syndrome
- Autosomal recessive ataxia with known gene locus
- Early-onset cerebellar ataxia

X-Linked Ataxias
- Fragile X tremor ataxia syndrome

Autosomal Dominant Ataxias
- Spinocerebellar ataxias
- Dentatorubral-pallidoluysian atrophy
- Episodic ataxias

Nonhereditary Degenerative Ataxias
- Multiple system atrophy, cerebellar type
- Sporadic adult-onset ataxia of unknown etiology

Acquired Ataxias
- Alcoholic cerebellar degeneration
- Ataxia as a result of other toxic causes (e.g., antiepileptic medications, lithium, solvents)
- Paraneoplastic cerebellar degeneration
- Other immune-mediated ataxias (e.g., gluten ataxia, ataxia associated with anti-glutamic acid decarboxylase antibodies)
- Acquired vitamin E deficiency
- Hypothyroidism
- Ataxia as a result of physical causes (e.g., heat stroke, hyperthermia)

From Goetz CG: *Textbook of clinical neurology*, ed 3, Philadelphia, 2007, Saunders.

LABORATORY TESTS

- Rule out acquired causes of ataxia, depending on the clinical scenario, with thyroid studies, toxicology screening, and the determination of the vitamin E level or presence of paraneoplastic antibodies.
- Screen for Wilson's disease with ceruloplasmin and, if indicated, a 24-hour urinary copper determination.
- Genetic testing is commercially available for many but not all of the SCAs.

IMAGING STUDIES

- MRI of the brain should be performed to exclude structural abnormalities.
- Cerebellar or brain stem atrophy can be seen with several of the SCA subtypes.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Speech therapy for dysarthria and dysphagia.
- Physical therapy.
- Occupational therapy.

CHRONIC Rx

Treatment is symptomatic and supportive. In some cases, parkinsonism can respond to levodopa. Clonazepam can be helpful if tremor is prominent. Spasticity can be treated with baclofen or tizanidine. Dystonia may benefit from botulinum toxin injections.

DISPOSITION

All SCA disorders are progressive, although the speed is variable from subtype to subtype and from patient to patient. On average, patients become wheelchair bound 15 yr after the onset of ataxia, and death can occur after 20 to 25 yr.

REFERRAL

Referral to a general neurologist or to a movement disorders center is appropriate.

PEARLS & CONSIDERATIONS

COMMENTS

- Genetic testing can have consequences for both the patient and the family. These issues should be discussed during the informed consent process. Patients who desire asymptomatic testing as a result of a relevant family history should undergo genetic counseling before testing.
- In symptomatic patients with a family history of dominantly inherited ataxia, the diagnostic process is relatively straightforward. Genetic testing that is directed toward likely mutations by phenotype and ethnic origin should be the first step rather than an extensive workup for other causes.

PATIENT & FAMILY EDUCATION

Patient educational materials as well as contact information for support and advocacy groups are available on the website of the National Ataxia Foundation: http://www.ataxia.org.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **ANDREW DUKER, M.D.**

SUGGESTED READINGS

Bird TD. Hereditary ataxia overview. Available at http://www.ncbi.nlm.nih.gov/books/NBK1138/. Accessed March 28, 2013.

Klockgether T: The clinical diagnosis of autosomal dominant spinocerebellar ataxias, *Cerebellum* 7:101–105, 2008.

Neuromuscular Disease Center: Ataxias: classification. Available at http://neuromuscular.wustl.edu/ataxia/aindex.html.

Verbeek DS, van de Warrenburg BPC: Genetics of the dominant ataxias, *Semin Neurol* 31:461–469, 2011.

Spontaneous Bacterial Peritonitis

BASIC INFORMATION

DEFINITION

Spontaneous bacterial peritonitis (SBP) is an inflammatory reaction of the peritoneum secondary to the presence of bacteria or other microorganisms. More specifically, SBP is defined as an ascitic fluid infection without an evident intraabdominal surgically treatable source occurring primarily in patients with advanced cirrhosis of the liver.

SYNONYMS

Primary peritonitis
SBP

ICD-9CM CODES
567.2 Peritonitis
ICD-10CM CODES
K65.2 Spontaneous bacterial peritonitis

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: The prevalence of SBP in cirrhotic patients admitted to the hospital has been estimated at 10% to 30%.
PREDOMINANT SEX: Males affected more often than females.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute fever with accompanying abdominal pain/ascites, nausea, vomiting, diarrhea.
- In cirrhotic patients, presentation may be subtle with a low-grade temperature (100° F) with or without abdominal abnormalities.
- In patients with ascites, a heightened degree of awareness is necessary for detection
- Jaundice and encephalopathy.
- Deterioration of mental status and/or renal function.

ETIOLOGY

- *Escherichia coli.*
- *Klebsiella pneumoniae.*
- *Streptococcus pneumoniae.*
- *Streptococcus* and *Enterococcus* spp.
- *Staphylococcus aureus.*
- Anaerobic pathogens: *Bacteroides, Clostridium* organisms.
- Other: fungal, mycobacterial, viral.

DIAGNOSIS

The diagnosis of SBP is established by a positive ascitic fluid bacterial culture and an elevated ascitic fluid absolute polymorphonuclear leukocyte count (≥250 cells/mm^3).

DIFFERENTIAL DIAGNOSIS

- Appendicitis (in children).
- Perforated peptic ulcer.
- Secondary bacterial peritonitis.
- Peritoneal abscess.
- Splenic, hepatic, or pancreatic abscess.
- Cholecystitis.
- Cholangitis.

WORKUP

Paracentesis and ascitic fluid analysis will confirm diagnosis (see "Laboratory Tests").

LABORATORY TESTS

Ascitic fluid analysis reveals the following:

- Cell count with an absolute polymorphonuclear cell count >250/mm^3.
- Presence of bacteria on Gram stain.
- pH <7.31.
- Lactic acid >32 mg/dl.
- Protein <1 g/dl.
- Glucose >50 mg/dl.
- Lactate dehydrogenase <225 mU/ml.
- Positive culture of peritoneal fluid.
- Measurement of the serum/ascites/albumin gradient: The serum/ascites/albumin gradient indirectly measures portal pressure. The albumin concentration of ascitic fluid and serum must be obtained on the same day. The ascitic fluid value is subtracted from the serum value to obtain the gradient. If the difference (not a ratio) is >1.1 g/dl, the patient has portal hypertension, with 97% accuracy. If the difference is <1.1 g/dl, portal hypertension is not present. The majority of patients with SBP have portal hypertension as a result of cirrhosis.

IMAGING STUDIES

- Abdominal ultrasound: if there is clinical difficulty in performing paracentesis.
- CT scan: to rule out secondary peritonitis (if indicated) and to exclude abscess, mass.

TREATMENT

ACUTE GENERAL Rx

- Cefotaxime (2 g IV q8h) or ceftriaxone (2 g IV q24h) or ticarcillin-clavulanate or piperacillin-tazobactam. Continue therapy for 7 days. Repeat diagnostic paracentesis can be done at day 2. Repeat paracentesis at 48 hr will demonstrate a significant decrease in polymorphonuclear count in patients with SBP. If ascites PMN count decreases by at least 25% at day 2, IV therapy can be switched to PO (levofloxacin 250 mg PO bid) to complete 7 days of therapy.
- IV albumin (1 g/kg of body weight) if BUN >30 mg/dL, bilirubin >4 mg/dL; repeat at day 3 if renal dysfunction persists.

PROPHYLAXIS

- Ciprofloxacin 500 mg PO qd or levofloxacin 250 mg PO qd.
- Alternative therapy: TMP-SMX one double-strength tablet PO qd.
- Prophylaxis should be continued until disappearance of ascites or until liver transplantation.

DISPOSITION

- The overall mortality rate from an episode of SBP is 20%, and following an episode, the 1-year mortality rate approaches 70%.

REFERRAL

- To a gastroenterologist for management of ascites and prevention of recurrent SBP.
- To an infectious disease specialist for management of difficult-to-treat infections, antibiotic-resistant bacterial infections, or antibiotic drug intolerance.

PEARLS & CONSIDERATIONS

COMMENTS

- Renal failure is a major cause of morbidity in cirrhotic patients with SBP. The use of IV albumin (1.5 g/kg at the time of diagnosis and 1 g/kg on day 3) may lower the rate of renal failure and mortality in patients with SBP.
- The criteria for the diagnosis of SBP require that abdominal paracentesis be performed and ascitic fluid be analyzed before a diagnosis of SBP can be made.
- Culturing ascitic fluid as if it were blood (with bedside inoculation of at least 10 ml of ascitic fluid directly into blood culture bottles at the bedside) has been shown to significantly increase the culture positivity of the ascitic fluid in the 80% to 100% range.
- Avoid therapeutic paracenteses during active infection.
- Positive blood cultures in an individual with ascites require exclusion of a peritoneal source by paracentesis.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Gonzalez-Suarez B et al.: Pharmacologic treatment of portal hypertension in the prevention of community-acquired spontaneous bacterial peritonitis, *Eur J Gastroenterol Hepatol* 18(1):49, 2006.

Koulaouzidis A et al.: Spontaneous bacterial peritonitis, *World J Gastroenterol* 15:1042–0, 2009.

Narula N et al.: Should albumin be used in all patients with spontaneous bacterial peritonitis? *Can J Gastroenterol* 25(7):373–376, 2011.

Runyon BA: Early events in spontaneous bacterial peritonitis, *Gut* 53(6):782, 2004.

Wiest R et al.: Spontaneous bacterial peritonitis: recent guidelines and beyond, *Gut* 61(2):297–310, 2012.

Wong CL et al.: Does this patient have bacterial peritonitis or portal hypertension? How do I perform a paracentesis and analyze the results? *JAMA* 299(10):1166, 2008.

BASIC INFORMATION

DEFINITION

Spontaneous miscarriage is fetal loss before week 20 of pregnancy, calculated from the patient's last menstrual period or the delivery of a fetus weighing <500 g. Early loss is before menstrual week 12, whereas late loss refers to losses from weeks 12 to 20.

Miscarriage can also be classified as incomplete (partial passage of fetal tissue through partially dilated cervix), complete (spontaneous passage of all fetal tissue), threatened (uterine bleeding without cervical dilation or passage of tissue), inevitable (bleeding with cervical dilation without passage of fetal tissue), or missed abortion (intrauterine fetal demise without passage of tissue).

Recurrent miscarriage involves three or more spontaneous pregnancy losses before week 20 although most providers will perform an evaluation for recurrent spontaneous abortion after two losses. The definition is somewhat variable depending on the source.

SYNONYMS

Spontaneous abortion

ICD-9CM CODES
634.0 Spontaneous abortion
ICD-10CM CODES
O03.9 Complete or unspecified spontaneous abortion without complication

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 5%-20% of clinically recognized pregnancies; 80% of miscarriages occur in the first trimester. Recurrent miscarriage occurs in <1% of couples attempting to have children.

GENETICS

- Distribution of abnormal karyotypes: autosomal trisomy (50%), monosomy 45,X (20%), triploidy (15%), tetraploidy (10%), structural chromosomal abnormalities (5%).
- With two or more spontaneous miscarriages, a karyotype can be performed on the products of conception to evaluate for aneuploidy, which may be associated with a balanced translocation in one of the parents, and which has a substantially increased risk for abortion (depending on the actual type of translocation), and, if the pregnancy is carried to term, has a 3% to 5% risk for an unbalanced karyotype. In patients with habitual abortion, evaluation for anatomic defects such as uterine septum and for antiphospholipid syndrome (lupus anticoagulant, beta 2 glycoprotein IgG/IgM and anticardiolipin antibody) IgG/IgM should also be obtained.

RISK FACTORS

Vaginal bleeding, especially >3 d, carries with it a 15%-20% chance of miscarriage. Diabetes should be controlled to reduce risk.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Profuse bleeding and cramping have a higher association with miscarriage than bleeding without cramping, which is more consistent with a threatened miscarriage.
- Cervical dilation with history or finding of fetal tissue at cervical os may be present.
- In cases of missed abortion, uterine size may be smaller than menstrual dating, in contrast to molar gestation, where size may be greater than dates.

ETIOLOGY

- In a general overview the etiology can be classified in terms of maternal (environmental) and fetal (genetic) factors, with the majority of miscarriages being related to genetic or chromosomal causes.
- Causes: uterine anomalies (unicornuate uterus risk, 50%; bicornuate or septate uterus risk, 25%-30%); incompetent cervix (iatrogenic or congenital, associated with 20% of mid-trimester losses); diethylstilbestrol exposure in utero (T-shaped uterus); submucous leiomyomas; intrauterine adhesions or synechiae; luteal phase or progesterone deficiency; autoimmune disease such as anticardiolipin antibodies; uncontrolled diabetes mellitus. Rare or controversial causes include HLA associations between mother and father; infections such as tuberculosis, *Chlamydia,* and *Ureaplasma;* smoking and alcohol use; irradiation; and environmental toxins. Most of the literature is observational in nature, which may skew risk factor data.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Normal pregnancy
- Hydatidiform molar gestation
- Ectopic pregnancy
- Dysfunctional uterine bleeding
- Pathologic endometrial or cervical lesions

WORKUP

- All patients with bleeding in the first trimester should have an evaluation for possible ectopic pregnancy.
- If there are three early, prior pregnancy losses, a workup and treatment for recurrent miscarriage should begin before next conception. If there is a strong history for second-trimester loss, consideration for cerclage should be given if the history is consistent with incompetent cervix (e.g., painless cervical dilation).
- Most providers will initiate an evaluation for couples who have had 2 previous losses.
- One unexplained fetal loss beyond 10 wk or 1 birth before 34 wk because of preeclampsia should prompt an evaluation for antiphospholipid syndrome.

LABORATORY TESTS

- Type and antibody screen are used to evaluate the need for Rh immune globulin.
- During the preconception period in patients with habitual abortion, hemoglobin A_{1c}, anticardiolipin antibody, lupus anticoagulant, prothrombin gene 20210A, karyotyping, and anatomic evaluation to assess for uterine septum. With increasing age, oocyte quality is a factor and some practitioners will perform day 3 of the menstrual cycle FSH and antimüllerian hormone to assess for diminished ovarian reserve.
- Progesterone level <5 mg/dl suggests nonviable gestation vs. >25 mg/dl, which suggests a good prognosis.

IMAGING STUDIES

Transvaginal sonogram (preferably) can be used with menstrual dating and serum quantitative human chorionic gonadotropin to document pregnancy location, fetal heart presence, gestational sac size, and adnexal pathology.

TREATMENT

NONPHARMACOLOGIC THERAPY

Depending on the patient's clinical status, desire to continue the pregnancy, and certainty of the diagnosis, expectant management can be considered. In pregnancies <6 wk or >14 wk, complete expulsion of fetal tissue usually occurs and surgical intervention such as D&C can be avoided.

ACUTE GENERAL Rx

- Incomplete miscarriage between 6 and 14 wk can be associated with great blood loss; these patients should undergo D&C.
- In cases of missed abortion, if fetal demise has occurred >6 wk before or gestational age is >14 wk, there is an increased risk of hypofibrinogenemia with disseminated intravascular coagulation. Thus D&C or manual vacuum aspiration should be performed early in the disease course. Consider use of misoprostol (Cytotec) 200 mg PO q6h as an alternative approach if patient desires a less invasive approach.
- Rh-negative patients should be given RhoGAM 50 mcg IM to prevent Rh isoimmunization.

PEARLS & CONSIDERATIONS

Spontaneous pregnancy loss is recommended as a replacement for the term *abortion* and to acknowledge the emotional aspects of losing a pregnancy.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Miscarriage (Patient Information)

AUTHOR: **RUBEN ALVERO, M.D.,** and **SCOTT J. ZUCCALA, D.O.**

SUGGESTED READINGS

Branch DW et al.: Recurrent miscarriage, *N Engl J Med* 363:1740–1747, 2010.

Griebel CP et al.: Management of spontaneous abortion, *Am Fam Physician* 72:1243, 2005.

BASIC INFORMATION

DEFINITION

Sporotrichosis is a granulomatous disease caused by the dimorphic fungus *Sporothrix schenckii.*

SYNONYMS

Lymphocutaneous sporotrichosis
Cutaneous sporotrichosis
Pulmonary sporotrichosis

ICD-9CM CODES
117.1 Sporotrichosis
ICD-10CM CODES
B42.1 Lymphocutaneous sporotrichosis
B42.7 Disseminated sporotrichosis
B42.8 Other forms of sporotrichosis
B42.9 Sporotrichosis, unspecified
B42.0 Pulmonary sporotrichosis

EPIDEMIOLOGY & DEMOGRAPHICS

PREDOMINANT SEX: The most common form, lymphocutaneous sporotrichosis, occurs equally in both sexes. Males predominate in both pulmonary and osteoarticular sporotrichosis.
PREDOMINANT AGE: Generally, lymphocutaneous sporotrichosis occurs in people 35 yr of age or younger, and pulmonary sporotrichosis occurs in people between the ages of 30 and 60 yr, often alcoholic men with COPD.
GENETICS: Neonatal infection: at least one case of transmission from the cheek lesions of the mother to the skin of the infant has been reported.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Cutaneous disease
  1. Arises at the site of inoculation, often the site of soil exposure
  2. Initial lesion usually located on the distal part of an extremity (Fig. ES1-65), although any area may be affected, including the face
  3. Variable incubation period of approximately 3 wk once introduced into the skin
  4. Granulomatous reaction provoked
  5. Lesion becomes papulonodular, erythematous, elastic, variable in size
  6. Subsequently, nodule becomes fluctuant, undergoes central necrosis, breaks down, discharges mucoid pus from which fungus may be isolated
  7. Indolent ulcer with raised erythematous or violaceous borders
  8. Secondary lesions:
     a. Develop along superficial lymphatic channels
     b. Evolve in the same manner as the primary lesion, with subsequent inflammation, induration, and suppuration
- Fixed, or plaque form
  1. Erythematous verrucous, ulcerated, or crusted lesions
  2. Does not spread locally
  3. Does not involve lymphatic vessels
  4. Rarely undergoes spontaneous resolution
  5. More often persists for years without systemic symptoms and within a setting of normal laboratory examinations
- Osteoarticular involvement
  1. Most common extracutaneous form
  2. Usually presents as monoarticular arthritis
  3. Left untreated, may progress to:
     a. Synovitis
     b. Osteitis
     c. Periostitis
     d. All involving elbows, knees, wrists, and ankles
  4. Joint inflamed
     a. Associated with an effusion
     b. Painful on motion
- Early pulmonary disease
  1. Usually associated with a paucity of clinical findings
     a. Low-grade fever
     b. Cough
     c. Fatigue
     d. Malaise
     e. Weight loss
  2. Untreated
     a. Cavitary pulmonary disease
     b. Frank pulmonary dysfunction
  3. Meningitis uncommon
     a. Except perhaps in the immunocompromised patient
     b. Presents with few signs or symptoms of neurologic involvement, usually headache
  4. Few reported cases
     a. Infection of the ocular adnexa
     b. Endophthalmitis without antecedent trauma
     c. Infection of the testes and epididymis

FIGURE ES1-65 Sporotrichosis of the fifth finger in a gardener. Three nodular lesions are visible on the hand and arm. (From Mandell GL et al: *Principles and practice of infectious diseases,* ed 7, Philadelphia, 2010, Saunders.)

ETIOLOGY

- *Sporothrix schenckii*
  1. Global in distribution
  2. Often isolated from soil, plants, and plant products
  3. Majority of case reports from tropical and subtropical regions of the Americas
- Occupational or recreational exposure
  1. Hay
  2. Straw
  3. Sphagnum moss
  4. Timber
  5. Thorny plants (e.g., roses and barberry bushes)
- Animal contact
  1. Armadillos
  2. Cats
  3. Squirrels
- Human-to-human transmission
- Tattooing

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Fixed, or plaque, sporotrichosis
  1. Bacterial pyoderma
  2. Foreign body granuloma
  3. Tularemia
  4. Anthrax
  5. Other mycoses: blastomycosis, chromoblastomycosis
- Lymphocutaneous sporotrichosis
  1. *Nocardia brasiliensis*
  2. *Leishmania braziliensis*
  3. Atypical mycobacterial disease: *M. marinum, M. kansasii*
- Pulmonary sporotrichosis
  1. Pulmonary TB
  2. Histoplasmosis
  3. Coccidioidomycosis
- Osteoarticular sporotrichosis
  1. Pigmented villonodular synovitis
  2. Gout
  3. Rheumatoid arthritis
  4. Infection with *M. tuberculosis*
  5. Atypical mycobacteria: *M. marinum, M. kansasii, M. avium-intracellulare*
- Meningitis
  1. Histoplasmosis
  2. Cryptococcosis
  3. TB

WORKUP

- The diagnosis should be considered in individuals who are occupationally exposed to soil, decaying plant matter, and thorny plants (gardeners, horticulturists, farmers) who present with chronic nonhealing ulcers or lesions with or without associated arthritis or pulmonary symptoms.
- Diagnosis is made by culture:
  1. Pus
  2. Joint fluid
  3. Sputum
  4. Blood
  5. Skin biopsy
- Isolation of the fungus from any site is considered diagnostic of infection.
- Saprophytic colonization of the respiratory tract has been described.
- A positive blood culture may indicate infection in an immunocompromised host.
- Increasingly sensitive laboratory culturing systems may detect the fungus in the normal host.
- Biopsy specimens are diagnostic if characteristic cigar-shaped, round, oval, or budding yeast forms are seen.

- Despite special staining, the yeast may remain difficult to detect unless multiple sections are examined.
- No standard method of serologic testing is available.
- Previously described techniques have been hampered by the presence of antibody in the absence of infection.

LABORATORY TESTS

- CBCs and serum chemistries are generally normal.
- Elevated ESR is seen with extracutaneous disease.
- CSF analysis in meningeal disease reveals:
  1. Lymphocytic pleocytosis
  2. Elevated protein
  3. Hypoglycorrhachia
- Nested polymerase chain reaction (PCR) assay represents a future clinical modality to rapidly detect *Sporothrix schenckii.*

IMAGING STUDIES

- Chest x-ray examination: unilateral or bilateral upper lobe cavitary or noncavitary lesions
- Radiographic findings of affected joints:
  1. Loss of articular cartilage
  2. Periosteal reaction
  3. Periarticular osteopenia
  4. Cystic changes

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Local heat and prevention of bacterial superinfection in cutaneous or plaque form. This treatment is important for pregnant women as azoles are teratogenic.

ACUTE GENERAL Rx

CUTANEOUS AND LYMPHOCUTANEOUS SPOROTRICHOSIS

- Itraconazole at doses of 200 mg/day is the drug of choice and should be given for 2 to 4 wk after the lesions have resolved.
- Alternative treatment: use saturated solution of potassium iodide (SSKI) 5 to 10 drops PO tid or 1.5 ml PO tid, gradually increasing to 40 to 50 drops PO tid or 3 ml PO tid after meals.
- Maximum tolerated dose should be continued until cutaneous lesions have resolved, approximately 6 to 12 wk.
- Adjunctive therapy with heat is useful and occasionally curative.
- Side effects of SSKI:
  1. Nausea
  2. Anorexia
  3. Diarrhea
  4. Parotid or lacrimal gland hypertrophy
  5. Acneiform rash

DEEP-SEATED MYCOSES (E.G., OSTEOARTICULAR, NONCAVITARY PULMONARY DISEASE)

- Itraconazole
  1. Appropriate initial chemotherapy
  2. Less toxic than amphotericin B
  3. Better tolerated than ketoconazole
  4. 200 mg PO bid for 1 to 2 yr with continued lifelong suppressive therapy in selected patients
  5. Absence of relapses from 40 to 68 mo has been documented when at least 200 mg/day administered for 24 mo
  6. Insufficient data for use in disseminated disease (e.g., fungemia and meningitis)
  7. Drug levels should be monitored to assess absorption.
- Parenteral amphotericin B, total course of 2 to 2.5 g or more, results in cure in approximately two thirds of cases. Lipid Am B 3 to 5 mg/kg/day is also recommended and less toxic.
  1. Relapses are common.
  2. Amphotericin B-resistant isolates of *Sporothrix schenckii* have been reported.
  3. Remains the drug of choice for severely ill patients with disseminated disease.
  4. In cavitary pulmonary disease, given perioperatively as an adjunct to surgical resection.
  5. When patient is improved, can continue treatment with itraconazole 200 mg PO bid.
  6. Treat for at least 12 mo.
  7. Fluconazole
  8. Less effective than itraconazole
  9. The latest IDSA guidelines recommend fluconazole only as an alternative treatment for lymphocutaneous disease
  10. Requires daily doses of 400 mg/day for lymphocutaneous disease and 800 mg/day for visceral or osteoarticular disease

CHRONIC Rx

For lymphocutaneous and visceral disease, therapy with itraconazole 200 mg/day for periods of 24 mo or greater. *Sporothrix* is resistant to voriconazole. It is sensitive in vitro to posaconazole, but existing data are very limited at present.

DISPOSITION

- Prognosis for cutaneous disease is good.
- Prognosis is less satisfactory for extracutaneous disease, especially if associated with abnormal immunologic states or other underlying systemic diseases.

REFERRAL

- To surgeon; with an established diagnosis of pulmonary sporotrichosis, cavitary lesions require resection of involved tissue and possible pretreatment with amphotericin
- To infectious disease physician

PEARLS & CONSIDERATIONS

COMMENTS

- In patients with underlying immunosuppression (e.g., hematologic malignancy or infection with HIV), progression of the initial infection may develop into multifocal extracutaneous sporotrichosis.
- In this subset of patients, dissemination of cutaneous lesions is accompanied by hematogenous spread to lungs, bone, mucous membranes, CNS.
- Osteoarticular and pulmonary manifestations predominate with the development of polyarticular arthritis and osteolytic bone lesions.
- In the absence of therapy, the infection is ultimately fatal.
- Patients with underlying immunosuppressive states should be carefully evaluated even when presenting with single cutaneous lesions.
- Diagnostic modalities should include:
  1. Radiographic examination of chest
  2. Technetium pyrophosphate bone scan
  3. Culture of synovial fluid, blood, skin lesion(s)
- In patients with AIDS, itraconazole appears to be the drug of choice, although meningitis and pulmonary disease may warrant the use of amphotericin B.
- In patients with AIDS, lifetime suppressive therapy with itraconazole should follow initial therapy because of the potential for relapse and dissemination. Treatment may be terminated when CD4 counts exceed 200.
- Disseminated cases have been reported with the use of TNF-alpha inhibitors.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **PATRICIA CRISTOFARO, M.D.**

SUGGESTED READINGS

Bernardes-Engermann AR et al.: Development of an enzyme-linked immunosorbent assay for the serodiagnosis of several clinical forms of sporotrichosis, *Med Mycol* 43(6):487, 2005.

Bunce PE et al.: Disseminated sporotrichosis in a patient with hairy cell leukemia treated with Ampho B and posaconazole, *Med Mycol* 50:197, 2012.

Da Rosa AC et al.: Epidemiology of sporotrichosis; a study of 304 cases in Brazil, *J Am Acad Dermatol* 52(3 Pt 1):451, 2005.

De Lima Barros MB et al.: Treatment of cutaneous sporotrichosis with itraconazole-study of 645 patients, *Clin Infect Dis* 52:e200, 2011.

Freitas DF et al.: Sporotrichosis in HIV-infected patients: report of 21 cases of endemic sporotrichosis in Rio de Janeiro, *Med Mycol* 50:170, 2012.

Gottlieb GS et al.: Disseminated sporotrichosis associated with treatment with immunosuppressants and tumor necrosis factor-alpha antagonists, *Clin Infect Dis* 37(6):838, 2003.

Kauffman CA: Sporotrichosis, *Clin Infect Dis* 29(2):231, 1999.

Kauffman CA et al.: Clinical practice guidelines for the management of sporotrichosis: 2007 update by the Infectious Diseases Society of America, *Clin Infect Dis* 45(10):1255, 2007.

Neyra E et al.: Epidemiology of human sporotrichosis investigated by amplified fragment length polymorphism, *J Clin Microbiol* 43(3):1348, 2005.

Schubach AO et al.: Epidemic cat-transmitted sporotrichosis, *N Engl J Med* 353(11):1185, 2005.

Tiwari A et al.: Primary pulmonary sporotrichosis: case report and review of the literature, *Infect Dis Clin Pract* 20:25, 2012.

Xue S et al.: Oral potassium iodide for the treatment of sporotrichosis, *Cochrane Database Syst Rev* (4):CD006136, Oct 7, 2009.

Squamous Cell Carcinoma EBM PTG

BASIC INFORMATION

DEFINITION

Squamous cell carcinoma (SCC) is a malignant tumor of the skin arising in the epithelium.

SYNONYMS

SCC
Skin cancer

ICD-9CM CODES
173.9 Skin neoplasm, site unspecified
ICD-10CM CODES
C44.5 Malignant neoplasm of skin of trunk
C44.4 Malignant neoplasm of skin of scalp and neck
D04 Carcinoma in situ of skin
C44.9 Malignant neoplasm of skin, unspecified
C44.0 Malignant neoplasm of skin of lip
C44.2 Malignant neoplasm of skin of ear and external auricular canal
C44.3 Malignant neoplasm of skin of other and unspecified parts of skin

EPIDEMIOLOGY & DEMOGRAPHICS

- SCC is the second most common cutaneous malignancy, comprising 20% of all cases of nonmelanoma skin cancer.
- Incidence is highest in lower latitudes (e.g., southern Unites States, Australia).
- Male/female ratio is 2:1.
- Incidence increases with age and sun exposure.
- Average age at diagnosis is 66 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- SCC commonly affects the scalp, neck region, back of hands, superior surface of the pinna, and the lip (Fig. S1-66).
- The lesion may have a scaly, erythematous macule or plaque.
- Telangiectasia, central ulceration may also be present (Fig. S1-67).
- Most SCCs present as exophytic lesions that grow over a period of months.
- Although most SCCs are relatively slow growing and nonaggressive, some (2%-5%) can exhibit rapid growth and metastases. Aggressive tumors are more common in immunocompromised patients and when arising from scars, burns, or prior injury (Marjolin's ulcer). Presence of SCC on ears, lips, or size >2 cm are high-risk features of SCC.

ETIOLOGY

Risk factors include ultraviolet B radiation, immunosuppression (kidney transplant recipients have a threefold increased risk), arsenic exposure, HPV infection, and tobacco abuse.

FIGURE S1-66 Squamous cell carcinoma of the lip. The lower lip **(A)** is a relatively commonly affected site. Smoking is a risk factor for this site, and the prognosis is poorer compared to similar-sized lesions at other sun-exposed sites. Treatment is usually by wedge excision or with radiotherapy. By contrast, the upper lip margin **(B)** is a relatively uncommon site. The chronic trauma from the patient's only three teeth may have been relevant. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

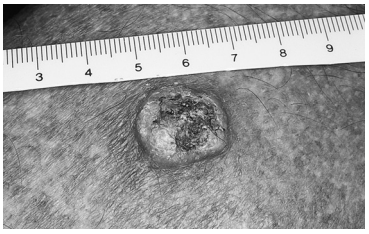


FIGURE S1-67 Squamous cell carcinoma. Nodular hyperkeratotic lesion with central erosion. (From Noble J et al: *Textbook of primary care medicine,* ed 3, St Louis, 2001, Mosby.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Keratoacanthomas
- Actinic keratosis
- Amelanotic melanoma
- Basal cell carcinoma
- Benign tumors
- Healing traumatic wounds
- Spindle cell tumors
- Warts

WORKUP

Diagnosis is made by full-thickness skin biopsy (incisional or excisional).

TREATMENT

ACUTE GENERAL Rx

- Electrodesiccation and curettage for small SCCs (<2 cm in diameter), superficial tumors, and lesions located in extremity and trunk.
- Tumors thinner than 4 mm can be managed by simple local removal.
- Lesions between 4 and 8 mm thick or those with deep dermal invasion should be excised.
- Tumors penetrating the dermis can be treated with several modalities, including excision and Mohs' surgery, radiation therapy, and chemotherapy. Mohs' surgery is commonly used for lesions on the face.
- Metastatic SCC can be treated with cryotherapy and combination of chemotherapy using 13-*cis*-retinoic acid and interferon-alpha 2A.

DISPOSITION

- Survival is related to size, location, degree of differentiation, immunologic status of the patient, depth of invasion, and presence of metastases. Risk factors for metastasis include lesions on the lip or ear, increasing lesion depth, and poor cell differentiation.
- Patients whose tumors penetrate through the dermis or exceed 8 mm in thickness are at risk of tumor recurrence.
- The most common metastatic locations are regional lymph nodes, liver, and lung.
- Tumors on the scalp, forehead, ears, nose, and lips also carry a higher risk.
- SCCs originating in the lip and pinna metastasize in 10% to 20% of cases.
- Five-year survival for metastatic SCC is 34%.

REFERRAL

Oncology referral for metastatic SCC

PEARLS & CONSIDERATIONS

COMMENTS

SCC arising in areas of prior radiation, thermal injury, and areas of chronic ulcers or chronic draining sinuses are more aggressive and have a higher frequency of metastasis than those originating in actinic damaged skin.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Squamous Cell Carcinoma (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Background:
Despite the fact that ultraviolet (UV) light exposure is the most important risk factor for cutaneous squamous cell carcinoma (SCC) there is an ongoing debate concerning the relationship between cumulative work-related UV exposure and SCC occurrence.

Objectives:
To analyse comprehensively the relationship between work-related UV exposure and SCC risk.

Methods:
We conducted a systematic electronic literature search in PubMed (up to 5 May 2010) supplemented by a hand search, which identified 18 relevant studies that were included in the review. Data abstraction and study quality assessment was done independently by two reviewers. Maximally adjusted odds ratios (ORs) and corresponding 95% confidence intervals (CIs) of all included studies were pooled in a random-effects meta-analysis. Sensitivity analysis included meta-regression on study-specific covariates to explore the robustness of the results and to identify sources of heterogeneity between studies. Eighteen studies (six cohort studies, 12 case–control studies) met the eligibility criteria and were included in the systematic review.

Results:
Sixteen studies (89%) found an increased risk of SCC in individuals with occupational UV light exposure compared with individuals without occupational UV light exposure, reaching statistical significance in 12 studies. Two studies found no association between occupational UV light exposure and SCC occurrence. The pooled OR (95% CI) was 1.77 (1·40–2·22) and did not differ significantly between cohort studies [OR (95% CI): 1.68 (1.08–2.63)] and case–control studies [OR (95% CI): 1.77 (1.37–2.30)]. Meta-regression analyses suggested an increasing strength of the association between occupational UV light exposure and SCC risk with decreasing latitude.

Conclusions:
In summary, there is consistent epidemiological evidence for a positive association between occupational UV light exposure and SCC risk. Ⓐ

Evidence-Based Reference

Schmitt J et al.: Occupational ultraviolet light exposure increases the risk for the development of cutaneous squamous cell carcinoma: a systematic review and meta-analysis, *Br J Dermatol* 164:291–307, 2011. Ⓐ

SUGGESTED READING

Stulberg DL et al.: Diagnosis and treatment of basal cell and squamous cell carcinomas, *Am Fam Physician* 70:1481, 2004.

BASIC INFORMATION

DEFINITION

Statin-induced muscle syndromes (SIMS) include myopathy, myalgia, myositis, and rhabdomyolysis. Definitions for these syndromes are inconsistent in the medical literature.

- Myopathy: a general term defined as any disease of muscles.
- Myalgia: muscle weakness or pain without serum creatinine kinase elevation.
- Myositis: muscle weakness or pain with an increased serum creatinine kinase level.
- Rhabdomyolysis: muscle weakness or pain and a marked serum creatinine kinase level usually greater than 10 times the upper limit of normal and serum creatinine elevation as well as signs of brown urine and elevated urine myoglobin. A rare immune-mediated necrotizing myopathy (IMNM) has also been associated with the use of statins with symptoms persisting after discontinuation of the drug. This condition presents with symmetric proximal arm and leg weakness and severe elevations of muscle enzymes.

SYNONYMS

Statin-induced myopathies
Statin-induced myositis
Statin-induced myalgias
Statin-induced rhabdomyolysis

ICD-9CM CODES
729.1 Myalgia and myositis
728.8 Rhabdomyolysis
359.4 Toxic myopathy
359.9 Myopathy, unspecified
359.81 Critical illness myopathy
359.89 Other myopathies
ICD-10CM CODES
M60.9 Myositis, unspecified
M62.82 Rhabdomyolysis
G72.2 Myopathy due to other toxic agents
G72.9 Myopathy, unspecified
G72.81 Critical illness myopathy
G72.89 Other specified myopathies

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Risk of statin-induced rhabdomyolysis is 1.2 per 10,000 persons/yr. Rhabdomyolysis risk of death is 0.15 deaths per 1 million prescriptions. SIMS most commonly occur in people aged 51 to 75, which may reflect the pattern of statin use.
PEAK INCIDENCE: Patients on high-dose statins have a 0.9% incidence of statin-induced rhabdomyolysis.
PREVALENCE: The prevalence of statin-induced myalgias is about 1% to 5%, similar to placebo in clinical trials, although observational studies have suggested a prevalence of 10% or higher. Statins may cause elevated transaminases (ALT, AST) at a prevalence of 0.5% to 2.0% and rhabdomyolysis ~0.08%.
PREDOMINANT SEX AND AGE: The mean age of hospitalized patients with statin-induced myopathy or rhabdomyolysis was 64 yr. Slightly more common in women (56%).
GENETICS: Interpatient variability exists in the activity of the *CYP3A4* gene for the metabolism of simvastatin, atorvastatin, and lovastatin. Homozygous carriers of CYP2D6 (poor metabolizers) had a higher rate of discontinuation of simvastatin due to muscle syndromes compared with the CYP2D6 wild-type genotype; patients taking atorvastatin and having a muscle event were more likely to have the CYP2D6*4 allele. SLCO1B1 polymorphisms encode for the organic anion transport of statins into the liver cells. Some data exist on deficiencies in ubiquinone (coenzyme Q10) in patients with a mutation in the *COQ2* gene.
RISK FACTORS: Small body frame; age over 80 yr; women, particularly frail elderly women; patients taking multiple drugs, especially gemfibrozil, niacin, cyclosporine, itraconazole, ketoconazole, erythromycin, clarithromycin, verapamil, amiodarone; renal or liver impairment; pharmacogenetic variability; hypothyroidism; excessive alcohol intake; vigorous exercise; severe infections; excessive grapefruit juice ingestion; inherited defects of muscle metabolism such as carnitine palmityl transferase II deficiency, McArdle's disease, and myoadenylate deaminase deficiency; acquired myopathies such as postpoliomyelitis syndrome; lipophilic statins (simvastatin, atorvastatin, lovastatin); multiple conditions such as diabetes; and drugs of abuse (amphetamines, heroin, cocaine, phencyclidine).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Myopathy can occur at any time, although it is more common within the first 4 weeks of therapy.
- Proximal generalized muscle aches, body aches, and pains, and may be mild or severe.
- Dark-colored urine
- Muscle cramps, spasms, tenderness, or stiffness
- Unusually tired or weak
- Nocturnal cramping
- Tendon pain

ETIOLOGY

- History of current statin use
- May be explained by one of three deficiencies of end products of the 3-hydroxy-3-methylglutaryl-coA reductase pathway: cell signaling and apoptosis, mitochondrial function and ubiquinone concentrations, and cholesterol concentrations and cell membrane integrity.
- The risk may be enhanced by drug interactions that interfere with hepatic metabolism and gut wall transport of interacting medications and by pharmacodynamic effects.
- Underlying metabolic muscle disorder may predispose a patient to develop myopathy.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Bursitis, tendinitis, radiculopathy, osteoarthritis, muscle strain, myofascial pain, hypothyroidism, proton-pump inhibitor-induced polymyositis, viral illness, polymyositis, and polymyalgia rheumatica

WORKUP

Workup consists of a thorough history, including exercise history, urine color, medication history, and physical exam to palpate tenderness and obtain blood tests to evaluate muscle and kidney damage.

LABORATORY TESTS

If severe myopathy or rhabdomyolysis is suspected:

- Elevated CPK, positive serum myoglobin, elevated BUN, serum creatinine, AST, ALT, LDH, and potassium
- Urine creatinine, positive casts, and hemoglobin in urine with absence of red blood cells
- Consider electrocardiogram and assessment of calcium, phosphate, and uric acid.

If mild to moderate myopathy is suspected:

- Monitor TSH and CPK levels; CPK may only be elevated when sudden severe myopathy occurs.
- If the patient has brown or dark urine or elevated CPK, monitor BUN and serum creatinine.

IMAGING STUDIES

- Not recommended

TREATMENT

Nonpharmacologic Therapy

- Treatment of rhabdomyolysis is generally supportive in nature (see "Rhabdomyolysis" topic).

ACUTE GENERAL Rx

- Stop statin therapy immediately if muscle symptoms occur. Check history, potential drug-drug interactions, CPK, TSH, renal function, hepatic function, and urinalysis.
- If patients have suspected rhabdomyolysis, they should be hospitalized and treated with supportive therapy and monitoring of complications.
- If CPK <10× the upper limit of normal without symptoms, continue statin therapy at the same or lower dosage
- If CPK <10× the upper limit of normal with intolerable symptoms, discontinue statin.
- If CPK >10× the upper limit of normal, discontinue statin.

Box S1-8 describes recommendations of the National Lipid Association Statin Safety Assessment Task Force regarding statin and muscle safety.

CHRONIC Rx

- After stopping the statin and symptom or CPK resolution, which may take up to 4 months, consider the same statin at a lower dosage or a different statin at an equivalent or lower dosage.
- When restarting therapy, consider statins such as low-dose rosuvastatin; pravastatin; and alternate-day dosing of rosuvastatin or atorvastatin.
- If patient had rhabdomyolysis secondary to statin therapy, consider nonstatin treatments.

- If the patient develops myopathy after a second trial of therapy, statin treatment should be permanently discontinued and nonstatin cholesterol-lowering therapy initiated.
- For IMNM, immunosuppressive therapy with prednisone and at least one agent have been used.

COMPLEMENTARY & ALTERNATIVE MEDICINE

- The effect of coenzyme Q10 on reducing or preventing SIMS remains controversial. Given its safety, coenzyme Q10 can be recommended if the actions listed under "Chronic Rx" are insufficient to continue the use of the statin and if the muscle symptoms have been limited to myalgias. Use coenzyme Q10 with caution in patients taking warfarin, as its anticoagulant effect may be decreased.
- Observational studies have suggested an association between vitamin D deficiency and statin-induced myopathy. Data are conflicting. The effects of supplementing vitamin D in patients with statin myopathy are limited and cannot be recommended unless a vitamin D deficiency is present.

DISPOSITION

- Usually resolves within 1 wk up to 4 mo after discontinuing statin therapy.
- Once the patient has a full recovery, an alternative statin can be tried.
- Statins should not be restarted in IMNM.

REFERRAL

- If rhabdomyolysis is suspected, immediate referral for hospitalization is suggested.

PEARLS & CONSIDERATIONS

COMMENTS

SIMS are usually mild and will resolve within a few wk after discontinuing statin therapy. However, such syndromes may progress to rhabdomyolysis.

PREVENTION

- Follow the 2013 AHA/ACC treatment guidelines to achieve the appropriate percent reduction in LDL cholesterol and limit the concomitant use of fibrates with statins.
- Discontinue statin therapy prior to and during surgical procedures.
- If patient requires a short-term therapy with an interacting medication such as an azole antifungal, temporarily discontinue statin therapy until interacting therapy is completed.
- If statin–fibric acid therapy is warranted, fenofibrate is preferred over gemfibrozil to decrease risk of myopathy.
- Baseline liver function testing before initiation of statin therapy and only if clinically indicated thereafter

PATIENT & FAMILY EDUCATION

- Inform patients to promptly report muscle weakness, unexpected muscle pain, or brownish urine.
- Ensure that the pharmacist and/or primary care physician checks for drug-drug interactions with every new prescription, including those from dentists and physicians from other specialties.
- Coenzyme Q10 may lessen milder muscle symptoms from statins, but patients should inform their physician and pharmacist if they decide to use this supplement.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Rhabdomyolysis (Related Key Topic)

AUTHORS: **LISA COHEN, PHARM.D.,** and **ANNE L. HUME, PHARM.D.**

BOX S1-8 Recommendations to Health Care Professionals Regarding Statin and Muscle Safety

- Whenever muscle symptoms or an increased CK level is encountered in patients receiving statin therapy, health professionals should attempt to rule out other causes, because these are most likely to explain the findings. Other common causes include increased physical activity, trauma, falls, accidents, seizure, shaking chills, hypothyroidism, infections, carbon monoxide poisoning, polymyositis, dermatomyositis, alcohol abuse, and drug abuse (cocaine, amphetamines, heroin, or PCP).
- Obtaining a pretreatment, baseline CK level can be considered in patients who are at high risk of experiencing muscle toxicity (e.g., older patients or those combining a statin with an agent known to increase myotoxicity), but this is not routinely necessary in other patients.
- It is unnecessary to measure CK levels in asymptomatic patients during the course of statin therapy, because marked, clinically important CK elevations are rare and are usually related to physical exertion or other causes.
- Patients receiving statin therapy should be counseled about the increased risk of muscle symptoms, particularly if initiation of vigorous, sustained endurance exercise or a surgical operation is being contemplated; they should be advised to report such muscle symptoms to a health professional.
- Creatine kinase measurements should be obtained in symptomatic patients to help gauge the severity of muscle damage and facilitate decision of whether to continue therapy or alter doses.
- In patients who develop intolerable muscle symptoms with or without CK elevation and for whom other etiologies have been ruled out, the statin should be discontinued. Once symptoms disappear, the same or different statin at the same or a lower dose can be restarted to test the reproducibility of symptoms. Recurrence of symptoms with multiple statins and doses requires initiation of other lipid-altering therapy.
- In patients who develop tolerable muscle symptoms or have no symptoms but have a CK level <10 × ULN, statin therapy may be continued at the same or reduced doses and symptoms may be used as the clinical guide to stop or continue therapy.
- In patients who develop rhabdomyolysis (CK >10,000 IU/L or >10 × ULN with an elevation in serum creatinine or need for intravenous hydration therapy), statin therapy should be stopped. Intravenous hydration therapy in a hospital should be instituted if indicated for patients experiencing rhabdomyolysis. Once patients recover, risk vs. benefit of statin therapy should be carefully reconsidered.

CK, Creatine kinase; *PCP,* phencyclidine; *ULN,* upper limit of normal.
From McKenney JM et al: Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force, *Am J Cardiol* 97(suppl 8A):89C-94C, 2006.

SUGGESTED READINGS

Antons KA et al.: Clinical perspectives of statin-induced rhabdomyolysis, *Am J Med* 119:400, 2006.

Bitzur R et al.: Intolerance to statins: mechanisms and management, *Diabetes Care* 36(Suppl 2), 2014.

Chatzizisis YS et al.: Risk factors and drug interactions predisposing to statin-induced myopathy, *Drug Safety* 330:171, 2010.

Eckel RH: Approach to the patient who is intolerant of statin therapy, *J Clin Endocrinol Metab* 95:2015–2022, 2010.

Fernandez G et al.: Statin myopathy: a common dilemma not reflected in clinical trials, *Clev Clin J Med* 78:393, 2011.

Gupta A et al.: The relationship of vitamin D deficiency to statin myopathy, *Atherosclerosis* 215:23, 2011.

Lasker SS, Chowdhury TA: Myalgia while taking statins, *BMJ* 345:e5348, 2012.

McKenney JM et al.: Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force, *Am J Cardiol* 97((Suppl) 89), 2006.

Mohassel P, Mammen AL: Statin-associated autoimmune myopathy and anti-HMGCR autoantibodies, *Muscle Nerve* 48(4):477–483, 2013. 10.1002/mus.23854.

Norata GD et al.: Statins and skeletal muscle toxicity: from clinical trials to everyday practice, *Pharmacol Res* 88C:107–113, 2014.

Pasternak RC et al.: ACC/AHA/NHLBI clinical advisory on the use and safety of statins, *JACC* 40:567, 2002.

Patel AM: Statin toxicity from macrolide antibiotic coprescription, *Ann Int Med* 158:868–876, 2013.

Wyman M et al.: Coenzyme Q10: a therapy for hypertension and statin-induced myalgias? *Cleve Clin J Med* 77:435, 2010.

BASIC INFORMATION

DEFINITION

Status epilepticus is a medical neurologic emergency. It is historically defined as 30 min of continuous seizure activity or two or more seizures without full recovery of consciousness between seizures. However, in practice a continuous seizure that lasts >5 min should be treated as status epilepticus.

SYNONYMS

Convulsive status epilepticus
Nonconvulsive status epilepticus

ICD-9CM CODES
345.3 Grand mal status
ICD-10CM CODES
G41 Status epilepticus
G40.301 Generalized idiopathic epilepsy and epileptic syndromes, not intractable, with status epilepticus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 40 to 100 cases per 100,000 persons
PEAK INCIDENCE: It is most common among children younger than 1 yr and adults older than 60 yr.
PREDOMINANT SEX AND AGE: No gender preference

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients can present with repetitive tonic clonic movements of the body (convulsive status epilepticus); other patients are comatose and nonresponsive (nonconvulsive status epilepticus).
- Patients may also present with lethargy, intermittent confusion, and involuntary movements.

ETIOLOGY

- Status epilepticus can be the result of an acute neurologic injury, such as stroke, meningitis, etc.
- In patients with epilepsy, abrupt discontinuation of antiepileptic drugs can result in status epilepticus.
- See Table S1-23 for causes of status epilepticus.

TABLE S1-23 Causes of Status Epilepticus

- Stroke (ischemic/hemorrhagic)
- CNS infections
- Traumatic head injury
- CNS toxicity: certain medications, drugs, ethanol
- Brain tumors or other mass lesions
- Metabolic disturbances: hypoglycemia, hyponatremia
- Abrupt discontinuation of antiepileptic drugs in patient with epilepsy
- Cryptogenic

CNS, Central nervous system.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Convulsive syncope
- Encephalopathies: metabolic, infectious, toxic, etc.
- Nonepileptic spells

WORKUP

- ABCs
- ICU admission
- Emergent electroencephalogram (EEG)
- Continuous video EEG in refractory cases
- Investigation of the patient with status epilepticus is summarized in Box S1-9.

LABORATORY TESTS

- Routine blood workup (CBC, CMP, glucose, electrolytes)
- Urine drug screen
- Lumbar puncture and CSF analysis in patients with suspected meningitis

IMAGING STUDIES

- Immediate CT scan of the head
- MRI of the brain should be performed once the patient is in a stable condition.

TREATMENT

- Patients with continuous seizure activity over 3 min need intravenous lorazepam 0.1 mg/kg at 2 mg/min (or diazepam 0.2 mg/kg at 5 mg/min only when lorazepam is not available).
- Lorazepam is followed by intravenous fosphenytoin 20 mg/kg (PE) at a rate not greater than 150 mg/min.
- An alternate to fosphenytoin is phenytoin 20 mg/kg IV at up to 50 mg/min as tolerated. Vital signs should be monitored during the infusion.
- If seizures continue, intravenous phenobarbital, midazolam, or propofol is an alternative. Other agents used include intravenous valproic acid and intravenous levetiracetam.
- Results of recent trials comparing intramuscular midazolam vs. intravenous lorazepam for prehospital status epilepticus show that IM midazolam may be as good as lorazepam, with successful termination of seizures in 73% of patients in the IM midazolam group vs. 63% in the IV lorazepam group. This difference was attributed to the more rapid administration of the IM medication (1.2 min vs. 4.8 min with the IV route).

BOX S1-9 Investigation of the Patient with Status Epilepticus

To Be Performed in All Patients with Status Epilepticus
Serum glucose, electrolytes, calcium, magnesium
Blood gas, serum osmolality
Toxicology screen (serum and urine)
Antiepileptic drug levels
Complete blood count (RBC, differential WBC, platelet count)
Liver enzymes, serum ammonium
Blood culture
Lumbar puncture, including:
1. Opening pressure
2. Cell count, Gram stain, smear for acid-fast bacilli
3. Viral and bacterial cultures
4. PCR for herpesvirus

EEG, preferably continuous monitoring with video
1. To monitor for subtle or subclinical seizures
2. To guide antiepileptic drug therapy
3. To localize the epileptogenic brain region (focal slowing or epileptiform activity)

To Be Considered in Patients with Status Epilepticus
Structural neuroimaging (CT, MRI)
1. To diagnose acute infarction, hemorrhage, vascular malformation, encephalitis, abscess, neurocysticercosis, neoplasm
2. In nonlesional cases, may localize the epileptogenic zone by evidence of focal edema in the affected cortical region
3. To assess the degree of cerebral edema and diagnose impending uncal or transtentorial herniation
4. MR angiography may identify CNS vasculitis, especially in medium or large vessel disease

Functional neuroimaging (PET, SPECT)
1. In nonlesional cases, may identify the epileptogenic zone

Cerebral angiography
1. To identify small vessel CNS vasculitis, which may not be visible on MR angiography

Rheumatologic workup for vasculitides
ESR, C-reactive protein, rheumatoid factor, serum complement levels, antineutrophil cytoplasmic antibodies

Brain biopsy
1. To diagnose cerebral vasculitis (granulomatous compared with nongranulomatous)
2. To identify malformations of cortical development

CNS, Central nervous system; *CT,* computed tomography; *EEG,* electroencephalography; *ESR,* erythrocyte sedimentation rate; *MRI,* magnetic resonance imaging; *PCR,* polymerase chain reaction; *PET,* positron emission tomography; *RBC,* red blood cell; *SPECT,* single-photon emission computed tomography; *WBC,* white blood cell.
From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.

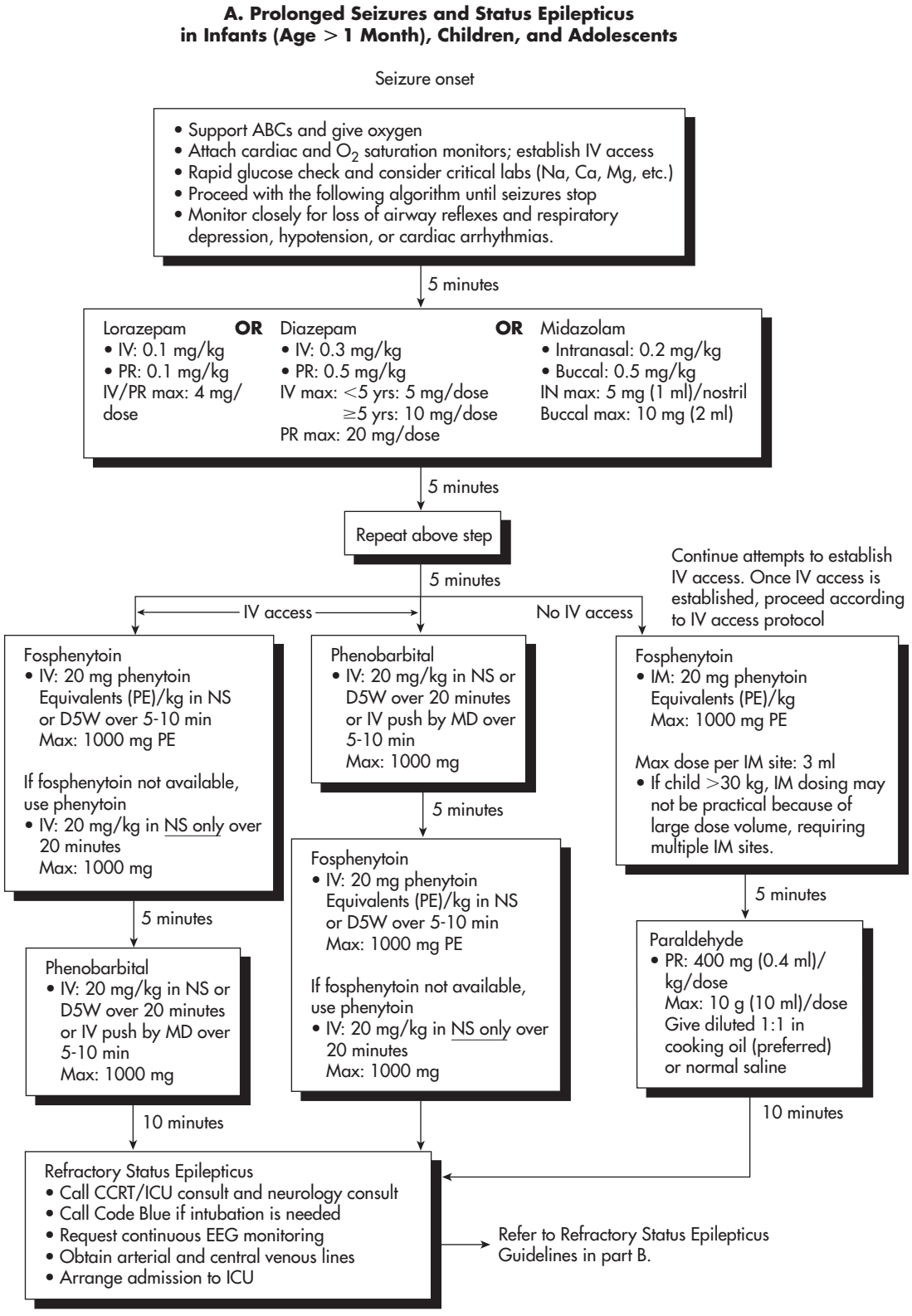


FIGURE S1-68 Guidelines for the treatment of prolonged seizures and status epilepticus in infants (age >1 month), children, and adolescents. (From The Hospital for Sick Children, Toronto, Canada. In Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.)

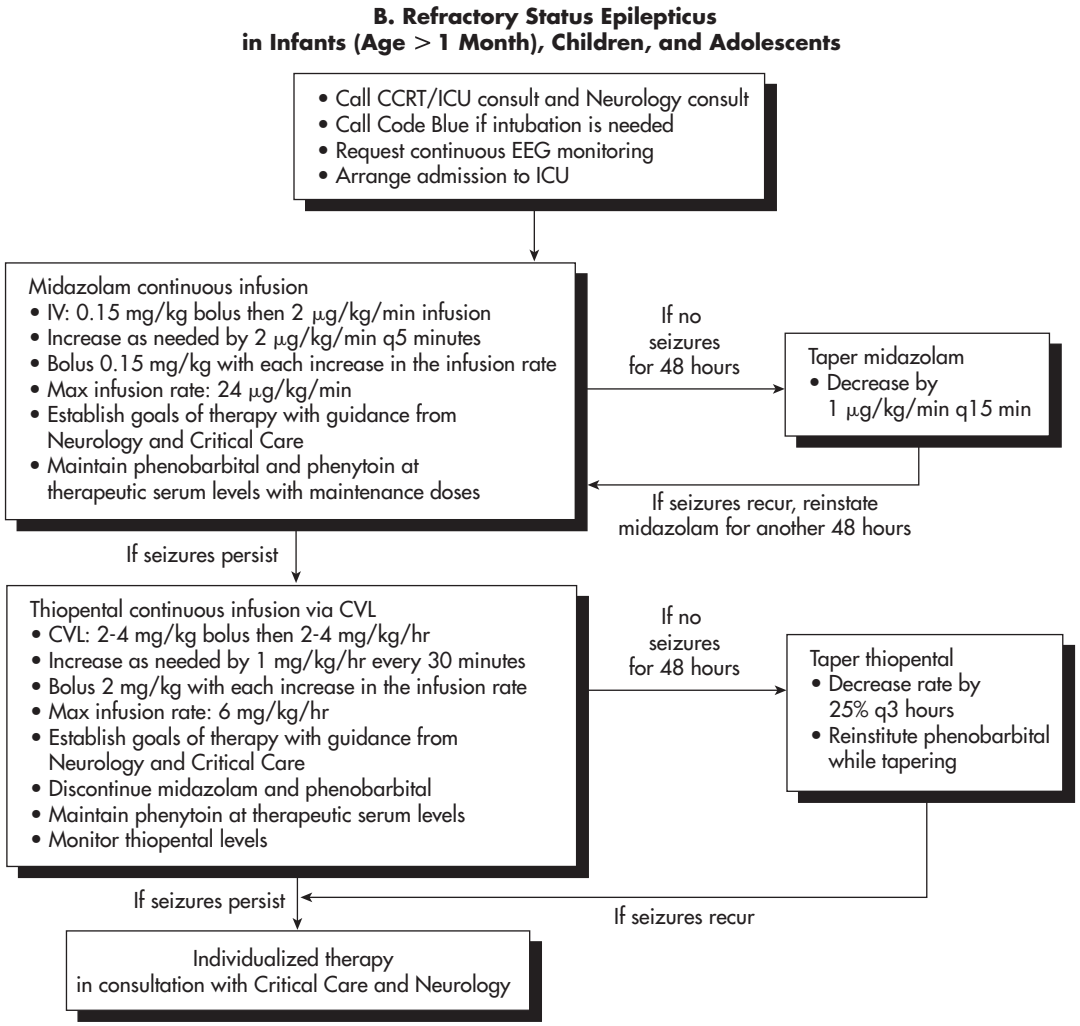


FIGURE S1-68 (Continued)

- Fig. S1-68 describes guidelines for the treatment of prolonged seizures and status epilepticus in infants (>1 mo), children, and adolescents and refractory status epilepticus.

NONPHARMACOLOGIC THERAPY

None

GENERAL Rx

It is important to find out the etiology of the status epilepticus (e.g., metabolic disturbance, infection). The appropriate treatment/understanding of the underlying cause of the status epilepticus will impact successful treatment.

CHRONIC Rx

- Chronic treatment of status epilepticus depends on underlying etiology.
- Patient with status epilepticus due to epilepsy will need chronic treatment.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Not applicable

DISPOSITION

- Response to treatment depends on the etiology of the status epilepticus.
- When there is no CNS injury as a cause or result of the status epilepticus, the prognosis is good.
- No driving until seizure freedom in accordance with local laws and regulations.

REFERRAL

Status epilepticus is a neurologic emergency; therefore immediate neurologic consultation is warranted.

PEARLS & CONSIDERATIONS

COMMENTS

- Status epilepticus is a medical emergency that carries a high risk of mortality. Mortality among patients who present in status epilepticus is 15% to 22%. Among those who survive, functional ability will decline in 25% of cases.
- Continuous video EEG is crucial in the treatment of these patients because some of them may not be clinically seizing (convulsing) but electrographically they may still have subclinical repetitive seizures or subclinical status epilepticus.

PREVENTION

Medication compliance is crucial in patients with epilepsy.

PATIENT & FAMILY EDUCATION

- Patients with epilepsy have normal lives.
- The goal of treatment is no seizures and no side effects to medications.
- Patient education and information can be obtained at the Epilepsy Foundation: www.epilepsyfoundation.org
- Pregnant women with epilepsy should visit the Antiepileptic Drug Pregnancy Registry website for information and assistance: www2.massgeneral.org/aed
- Patients with ongoing seizures are forbidden from driving; check state regulations and laws regarding driving and epilepsy.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **PATRICIO SEBASTIAN ESPINOSA, M.D., M.P.H.**

EVIDENCE

A 54-year-old woman was transferred to a university hospital for severe sepsis and multiorgan failure. A complex partial seizure was noted and she was placed on continuous electroencephalography (EEG). During EEG monitoring she developed generalized convulsive status epilepticus. After consultation with family it was decided not to escalate treatment due to her overall medical condition. She proceeded sequentially through the five stages of status epilepticus, described by Treiman et al. (1990) over 22 h and 30 min and then developed electrocerebral silence. This case is significant in that it is the first report of a single individual experiencing all five stages of status epilepticus displayed on a continuous EEG. The case further demonstrates the rapid progression of status epilepticus and exemplifies the need for prompt treatment. Ⓐ

Evidence-Based Reference

Pender RA, Losey TE: A rapid course through the five electrographic stages of status epilepticus, *Epilepsia* 53:e193–e195, 2012. Ⓐ

SUGGESTED READINGS

Continuum (Minneap Minn) 16(3 Epilepsy), 2010.

Hirsh LJ: Intramuscular vs. intravenous benzodiazepines for prehospital treatment of status epilepticus, *N Engl J Med* 366:659–661, 2012.

Milligan TA et al.: Frequency and patterns of MRI abnormalities due to status epilepticus, *Seizure* 18(2):104–108, 2009.

Silbergleit R et al.: Intramuscular vs. intravenous therapy for prehospital status epilepticus, *N Engl J Med* 366:591, 2012.

Treiman DM et al.: A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group, *N Engl J Med* 339(12):792–798, 1998.

Wyllie E et al.: The treatment of epilepsy: principles & practice. ed 4 Lippincott Williams & Wilkins: Philadelphia.

Stevens-Johnson Syndrome PTG

BASIC INFORMATION

DEFINITION

Stevens-Johnson syndrome (SJS) is a rare, severe vesiculobullous form of erythema multiforme (EM) affecting the skin, mouth, eyes, and genitalia. SJS is defined as affecting <10% of body surface area (BSA). When it affects 10%-30% of BSA, it is known as SJS–toxic epidermal necrolysis (TEN) overlap syndrome. TEN affects >30% of BSA.

SYNONYMS

SJS
Herpes iris
Febrile mucocutaneous syndrome

ICD-9CM CODES
695.1 Stevens-Johnson syndrome
ICD-10CM CODES
L51.1 Stevens-Johnson syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- SJS affects predominantly children and young adults.
- Male/female ratio is 2:1.
- Prevalence: 1:100,000 for SJS and 1:1,000,000 for TEN

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The cutaneous eruption generally occurs within 8 wk of drug initiation and is generally preceded by vague, nonspecific symptoms of low-grade fever and fatigue occurring 1 to 14 days before the skin lesions. Cough is often present. Fever may be high during the active stages.
- Enlarging red-purple macules or papules and bullae generally occur on the conjunctiva, mucous membranes of the mouth (Fig. S1-69), nares, and genital regions.
- Corneal ulcerations may result in blindness.
- Ulcerative stomatitis results in hemorrhagic crusting.
- Nikolsky sign (shearing off of epidermis with pressure on skin) can be present.
- Flat, atypical target lesions or purpuric maculae may be distributed on the trunk or be widespread (Fig. S1-70).
- The pain from oral lesions may compromise fluid intake and result in dehydration.
- Thick, mucopurulent sputum and oral lesions may interfere with breathing.

ETIOLOGY

- Drugs (e.g., phenytoin, sulfonamides, lamotrigine, sertraline, NSAIDs, tramadol, allopurinol, β-lactam antibiotics, phenobarbital) are the most common cause.
- Upper respiratory tract infections (e.g., *Mycoplasma pneumoniae*) and HSV infections have also been implicated.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Toxic erythema (drugs or infection)
- Pemphigus
- Pemphigoid
- Urticaria
- Hemorrhagic fevers
- Serum sickness
- *Staphylococcus* scalded-skin syndrome
- Behçet's syndrome

WORKUP

- Diagnosis is generally based on clinical presentation and characteristic appearance of the lesions.
- Skin biopsy is generally reserved for when classic lesions are absent and diagnosis is uncertain. Biopsy reveals epidermal necrolysis but cannot distinguish between SJS, TEN, and EM.

LABORATORY TESTS

CBC with differential, cultures in cases of suspected infection.

IMAGING STUDIES

Chest x-rays may show patchy changes in patients with pulmonary involvement.

FIGURE S1-69 Lip changes found in Stevens-Johnson syndrome associated with *Mycoplasma pneumoniae* infection. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

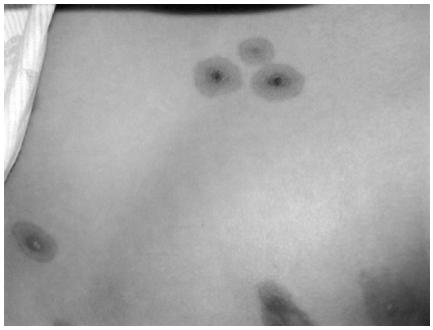


FIGURE S1-70 Classic erythema multiforme skin lesions found in Stevens-Johnson syndrome associated with *Mycoplasma pneumoniae* infection. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Withdrawal of any potential drug precipitants
- Careful skin nursing to prevent secondary infection

ACUTE GENERAL Rx

- Treatment of associated conditions (e.g., acyclovir for HSV infection, azithromycin for *Mycoplasma* infection)
- Antihistamines for pruritus
- Treatment of the cutaneous blisters with cool, wet Burow's compresses
- Relief of oral symptoms by frequent rinsing with lidocaine (Xylocaine Viscous)
- Liquid or soft diet with plenty of fluids to ensure proper hydration
- Treatment of secondary infections with antibiotics
- Corticosteroids: use remains controversial; should be used only in severe cases early in the disease; when used, prednisone 20 to 30 mg bid until new lesions no longer appear, then rapidly tapered
- Topical steroids: may use to treat papules and plaques; however, should not be applied to eroded areas
- Vitamin A: may be used for lacrimal hyposecretion
- Consider IVIG in severe cases.

DISPOSITION

- Prognosis varies with severity of disease. It is generally good in patients with limited disease; however, mortality rate may approach 10% in patients with extensive involvement. A severity of illness score known as SCORETEN that incorporates increased glucose level (>252 mg/dL), increased BUN (>28 mg/dL), electrolytes (serum bicarbonate <20 mEq/L), age (>40 yr), immunosuppression (presence of cancer), involvement >10% of BSA, and increased heart rate (>120 beats/min) can be used to calculate mortality risk.
- Oral lesions may continue for several months.
- Scarring and corneal abnormalities may occur in 20% of patients.

REFERRAL

- Hospital admission in a unit used for burn care is recommended in severe cases.
- Urethral involvement may necessitate catheterization.
- Ocular involvement should be monitored by an ophthalmologist.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Stevens-Johnson Syndrome (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READING

Wetter DA, Camilleri MJ: Clinical, etiologic, and histopathologic features of Stevens-Johnson during an 8-year period at Mayo Clinic, *Mayo Clin Proc* 85(2):131–138, 2010.

BASIC INFORMATION

DEFINITION

Stomatitis is inflammation involving the oral mucous membranes. Mucositis is inflammation and ulceration of the mucous membranes. It is most commonly seen in the mouth but can occur anywhere in the GI, genitourinary (GU), or respiratory tract. It is most often due to side effects of chemotherapy or radiation therapy (Fig. ES1-71) in cancer patients.

SYNONYMS

Heterogeneous grouping of unrelated illnesses, each with its own designation(s)

ICD-9CM CODES
528.0 Stomatitis
054.2 (herpetic)
528.2 (aphthous)
112.0 (monilial)

ICD-10CM CODES
K12 Stomatitis and related lesions
K12.1 Other forms of stomatitis
K12.3 Oral mucositis (ulcerative)
K13.0 Other and unspecified lesions of oral mucosa
K12.0 Recurrent oral aphthae
B37.0 Candidal stomatitis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

WHITE LESIONS

- Candidiasis (thrush).
- Caused by yeast infection *(Candida albicans).*
- Examination: white, curdlike material (Fig. ES1-72) that when wiped off leaves a raw bleeding surface.
- Epidemiology: seen in the very young and the very old, those with immunodeficiency (AIDS, cancer), persons with diabetes, and patients treated with antibacterial agents.
- Other.
  1. Leukoedema: filmy opalescent-appearing mucosa, which can be reverted to normal appearance by stretching. This condition is benign.
  2. White sponge nevus: thick, white corrugated folds involving the buccal mucosa. Appears in childhood as an autosomal dominant trait. Benign condition.
  3. Darier's disease (keratosis follicularis): white papules on the gingivae, alveolar mucosa, and dorsal tongue. Skin lesions also present (erythematous papules). Inherited as an autosomal dominant trait.
  4. Chemical injury: white sloughing mucosa.
  5. Nicotine stomatitis: whitened palate with red papules.
  6. Lichen planus: linear, reticular, slightly raised striae on buccal mucosa. Skin is involved by pruritic violaceous papules on forearms and inner thighs.
  7. Discoid lupus erythematosus: lesion resembles lichen planus.
  8. Leukoplakia: white lesions that cannot be scraped off; 20% are premalignant epithelial dysplasia or squamous cell carcinoma.
  9. Hairy leukoplakia: shaggy white surface that cannot be wiped off; seen in HIV infection, caused by Epstein-Barr virus.

RED LESIONS

- Candidiasis may present with red lesions instead of the more frequent white. Median rhomboid glossitis is a chronic variant.
- Benign migratory glossitis (geographic tongue): area of atrophic depapillated mucosa surrounded by a keratotic border. Benign lesion, no treatment required.
- Hemangiomas.
- Histoplasmosis: ill-defined, irregular patch with a granulomatous surface, sometimes ulcerated.
- Allergy.
- Anemia: atrophic reddened glossal mucosa seen with pernicious anemia.
- Erythroplakia: red patch usually caused by epithelial dysplasia or squamous cell carcinoma.
- Burning tongue (glossopyrosis): normal examination; sometimes associated with denture trauma, anemia, diabetes, vitamin B_{12} deficiency, psychogenic problems.

DARK LESIONS (BROWN, BLUE, BLACK)

- Coated tongue: accumulation of keratin; harmless condition that can be treated by scraping.
- Melanotic lesions: freckles, lentigines, lentigo, melanoma, Peutz-Jeghers syndrome, Addison's disease.
- Varices.
- Kaposi's sarcoma: red or purple macules that enlarge to form tumors; seen in patients with AIDS.

RAISED LESIONS

- Papilloma.
- Verruca vulgaris.
- Condyloma acuminatum.
- Fibroma.
- Epulis.
- Pyogenic granuloma.
- Mucocele.
- Retention cyst.

BLISTERS

- Primary herpetic gingivostomatitis.
- Caused by herpes simplex virus type 1 or, less frequently, type 2.
- Course: day 1: malaise, fever, headache, sore throat, cervical lymphadenopathy; days 2 and 3: appearance of vesicles that develop into painful ulcers of 2 to 4 mm in diameter; duration of up to 2 wk.
- Recurrent intraoral herpes: rare; recurrences typically involve only the keratinized epithelium (lips).
- Pemphigus and pemphigoid.
- Hand-foot-mouth disease: caused by coxsackievirus group A.
- Erythema multiforme.
- Herpangina: caused by echovirus.
- Traumatic ulcer.
- Primary syphilis.
- Perlèche (or angular cheilitis).
- Recurrent aphthous stomatitis (canker sores): most common oral mucosa lesion; may be associated with many systemic diseases.
- Behçet's syndrome (aphthous ulcers, uveitis, genital ulcerations, arthritis, and aseptic meningitis).
- Reiter's syndrome (conjunctivitis, urethritis, and arthritis with occasional oral ulcerations).
- Unknown cause.

Course: solitary or multiple painful ulcers may develop simultaneously and heal over 10 to 14 days. The size of the lesions and the frequency of recurrences are variable.

DIAGNOSIS

WORKUP

- White lesions: candidiasis (thrush) diagnosis: ovoid yeast and hyphae seen in scrapings treated with KOH culture.
- Blisters:
  1. Exfoliative cytology.
  2. Viral culture.
  3. Immunofluorescence for herpes antigen.

TREATMENT

White lesions: candidiasis (thrush) treatment:

- Topical with nystatin or clotrimazole.
- Systemic with ketoconazole or fluconazole.

Blisters:

- Supportive.
- Consider acyclovir.

Recurrent intraoral herpes/aphthous ulcerations: topical corticosteroids (dexamethasone ointment applied to the identified ulcer tid) or systemic steroids for severe cases.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Stomatitis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Amir J et al.: Treatment of herpes simplex gingivostomatitis with acyclovir in children: a randomized double blind placebo controlled study, *BMJ* 314:1997, 1800.

Khandwala A et al.: 5% amlexanox oral paste, a new treatment for recurrent minor aphthous ulcers. Clinical demonstration of acceleration of healing and resolution of pain, *Oral Surg Oral Med Oral Pathol* 83:222, 1997.

Liu C et al.: Efficacy and safety of dexamethasone ointment on recurrent aphthous ulceration, *Am J Med* 125:292–310, 2012.

FIGURE ES1-71 Oral mucositis caused by radiation therapy. (From Keefe ZDM, Logan R: Oral complications of cancer and its treatment. In Walsh TD et al [eds]: *Palliative medicine,* Philadelphia, 2008, Saunders.)

FIGURE ES1-72 Stomatitis and mucositis. **A,** Marked stomatitis in a patient receiving methotrexate. **B,** Aphthous stomatitis related to severe granulocytopenia after chemotherapy. The ulcers may be due to herpes simplex or other infection. **C,** Mucositis in a patient receiving combination chemotherapy for head and neck cancer. **D,** Marked ulcer of the tongue in a 32-year-old man receiving induction chemotherapy for acute leukemia. **E,** Mucositis of the tongue due to *Monilia* infection (thrush) in a patient receiving corticosteroids for brain metastases. **F,** Marked oral mucositis due to mixed infection in a patient receiving chemotherapy for acute leukemia. (From Skarin AT: *Atlas of diagnostic oncology,* 4 ed, St Louis, 2010, Mosby.)

BASIC INFORMATION

DEFINITION

Strabismus is a condition of the eyes in which the visual axes of the eyes are not straight in the primary position or in which the eyes do not follow each other in the different positions of gaze.

SYNONYMS

Esotropia
Exotropia
Restrictive eye movement

ICD-9CM CODES
378.9 Strabismus
ICD-10CM CODES
H50.9 Strabismus, unspecified
H50.0 Convergent concomitant strabismus
H50.1 Divergent concomitant strabismus
H50.2 Vertical strabismus
H50.3 Intermittent heterotropia
H50.4 Other and unspecified heterotropia
H50.0 Heterophoria
H50.6 Mechanical strabismus
H50.8 Other specified strabismus
H51.9 Unspecified disorder of binocular movement

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 2% of all children
PEAK INCIDENCE: Childhood
PREDOMINANT SEX: None
PREDOMINANT AGE: Birth to age 5 yr
GENETICS:
None known

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Conjugate gaze loss in both eyes with the eyes focusing independently
- Amblyopia (a decrease in best-corrected visual acuity in an otherwise structurally healthy eye) may occur with untreated strabismus.

ETIOLOGY

- Many cases are congenital.
- Accommodative cases occur later with focusing.
- Rarely, there is neurologic disease or severe refractive errors.
- Hereditary form is common, with hyperopia (far-sightedness) the most common.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Measuring eye position and movement
- Vision testing
- Refractive errors
- Central nervous system (CNS) tumors
- Orbital tumors
- Brain and CNS dysfunction

WORKUP

- Eye examination. Fig. ES1-73 illustrates diagnostic tests that help differentiate between common causes of strabismus. Strabismus is classified according to the type and magnitude of misalignment. Esotropia refers to an inward deviation of the nonfixing eye and exotropia to the outward deviation of the nonfixing eye. Hypertropia is a vertical deviation in which the nonfixing eye is higher, and hypotropia is a vertical deviation in which the nonfixing eye is lower.
- Measurement of deviation: the ***Hirschberg test*** (Fig. S1-74) gives a rough estimate of the angle of a manifest strabismus and is especially useful in young or uncooperative patients or when fixation in the deviating eye is poor.
- Visual field
- MRI to rule out tumors that develop later with no apparent cause

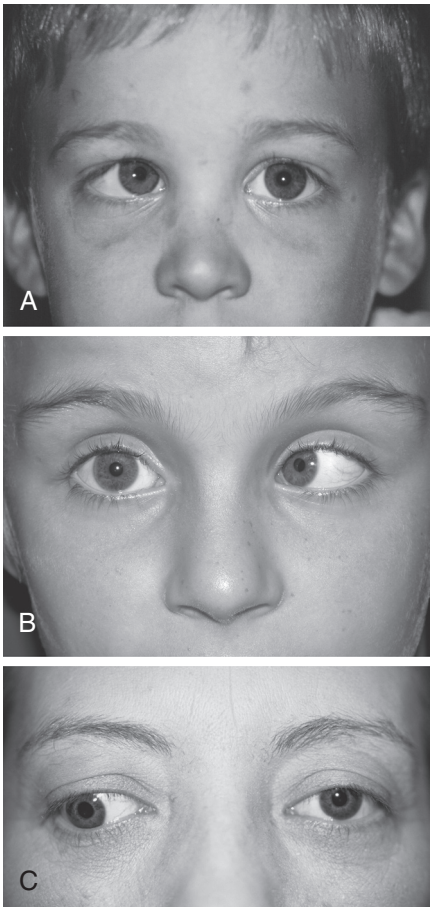


FIGURE S1-74 Hirschberg test. A, The right corneal reflex is near the temporal border of the pupil, indicating an angle of about 15°. **B,** The left corneal reflex is at the limbus, indicating an angle of about 45°. **C,** The right corneal reflex is at the limbus in a divergent squint. (**A** courtesy J. Yanguela. From Kanski JJ, Bowling B: *Clinical ophthalmology, a systematic approach,* ed 7, Philadelphia, 2010, Saunders.)

LABORATORY TESTS

Generally not needed

IMAGING STUDIES

Necessary only if other neurologic findings are found

TREATMENT

NONPHARMACOLOGIC THERAPY

- Glasses
- Patching: best between age 3 and 7 yr; vision most improved by 3 to 6 mo
- Prisms
- Atropine: same as patching most of the time, although patching may give better results in resistant cases

CHRONIC Rx

- Glasses
- Alternate eye patching
- Surgery
- Prisms

DISPOSITION

- The earlier the condition is treated, the more likely the child will have normal vision in both eyes.
- After age 7 yr, visual loss is usually permanent from amblyopia.

REFERRAL

- Early for full rehabilitation of eye cosmetically and functionally
- To an ophthalmologist for management (usually)

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Strabismus (Patient Information)

AUTHOR: **R. SCOTT HOFFMAN, M.D.**

SUGGESTED READING

Donahue SP: Pediatric strabismus, *N Engl J Med* 356:1040, 2007.

FIGURE ES1-73 Diagnostic tests that help differentiate between common causes of strabismus. (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 23, Philadelphia, 2008, Saunders.)

BASIC INFORMATION

DEFINITION

Ischemic stroke is the sudden onset of a focal neurologic deficit as a result of ischemia. Acute ischemic stroke may be defined as relating to the first few days after onset of neurologic symptoms. However, the purpose of this chapter is to help the provider make decisions regarding the acute stroke patient within the first several hours of symptoms; this is the crucial time for definitive treatment interventions.

SYNONYMS

Stroke
Brain attack
Cerebrovascular accident (this is a nonspecific term and should not be used.)

ICD-9CM CODES

494.31	Ischemic stroke
436	Acute stroke

ICD-10CM CODES

I63	Cerebral infarction
I63.3	Cerebral infarction due to thrombosis of cerebral arteries
I63.4	Cerebral infarction due to embolism of cerebral arteries
I63.5	Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
I63.6	Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
I63.8	Other cerebral infarction
I63.9	Cerebral infarction, unspecified
I67.89	Other cerebrovascular disease

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE

- ~800,000 new or recurrent strokes occur each year in the U.S.
- Stroke is the number three cause of death (130,000 deaths every year) and the leading cause of long-term disability in the U.S.

PREVALENCE: There are ~4.5 million stroke survivors in the U.S.

RISK FACTORS: Hypertension, dyslipidemia, diabetes mellitus, and smoking are the four major risk factors. Other risk factors include atrial fibrillation, mechanical heart valve, patent foramen ovale, recent myocardial infarction, carotid stenosis, hypercoagulable states, subclinical atrial tachyarrhythmias without clinical atrial fibrillation, sickle cell disease, and obesity.

GENETICS: Multifactorial

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Clinical presentation varies with the artery and region of CNS affected. Following are some common syndromic presentations. Please note that this list is not comprehensive and that all findings for a particular syndrome may not be listed here.

- Large- to medium-sized arteries:
  1. Left middle cerebral artery: right face, arm, and leg weakness and sensory loss with aphasia (expressive, receptive, or both); possible hemianopia
  2. Right middle cerebral artery: left face, arm, and leg weakness and sensory loss with hemineglect; possible hemianopia
  3. Basilar artery: typically an acute loss of consciousness preceded by vertigo, nausea, vomiting, and diplopia; quadriparesis or quadriplegia may be seen, including "locked-in" syndrome
  4. Posterior cerebral artery: unilateral hemianopia; blindness with anosognosia (Anton syndrome) if bilateral
  5. Anterior cerebral artery: unilateral leg weakness and sensory loss
  6. Cerebellum: ataxia (typically of the limbs), often with vertigo, nausea, and vomiting
- Small arteries (common lacunar syndromes)
  1. Lateral medullary (Wallenberg's) syndrome
  2. Posterior limb internal capsule

ETIOLOGY

Etiologies include atherosclerosis, cardioembolism, artery-to-artery embolism, small-vessel lipohyalinosis, arteritis, arterial dissection, and vasospasm.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of acute ischemic stroke includes hemorrhagic stroke (intracerebral hemorrhage), seizure with postictal paralysis, migraine with hemiparesis, syncope, hypoglycemia, hypertensive encephalopathy, and conversion disorder.

LABORATORY TESTS

- Immediate (Box S1-10): CBC, metabolic panel that includes blood glucose and renal function, PT/INR, aPTT, troponin I, and urinalysis. Blood glucose is the only test required before initiation of IV tPA.
- National Institutes of Health Stroke Scale: a brief, focused neurologic examination aimed at providing a numeric estimate of the severity of stroke; can be performed by any health care provider trained in its use; may increase the likelihood of the correct assessment of stroke
- ECG and telemetry monitoring
- Echocardiogram to look for potential cardiogenic source of embolism, infective endocarditis and intracardiac shunts

IMAGING STUDIES

- Immediate (Fig. S1-75): computed tomography (CT) of the head without contrast to rule out hemorrhage.
- MRI of the brain with stroke protocol to assess the extent of stroke (because CT typically will not show an ischemic stroke for several hours), but it is rarely needed in the hyperacute setting to determine reperfusion strategy, although some newer techniques like diffusion and perfusion MR are being utilized for this purpose at some centers.
- Several other neuroimaging studies are useful during the early stages of acute stroke to assess whether there is a thrombus that is amenable to intervention (Table S1-24).

Cross reference: see "Transient Ischemic Attack" for general workup, which is identical to that for ischemic stroke.

TREATMENT

NONPHARMACOLOGIC THERAPY

GENERAL CONSIDERATIONS

- Airway and breathing should be maintained.
- Supplemental oxygen should be provided to keep the oxygen saturation at ≥92%.
- Pneumatic compression devices or pharmacologic means should be applied to help prevent deep venous thromboses.
- Avoid any and all oral intake until swallowing is clearly unimpaired; this helps to avoid aspiration pneumonia.
- Early mobilization for rehabilitation is desirable.

BOX S1-10 Immediate Diagnostic Studies: Evaluation of a Patient with Suspected Acute Ischemic Stroke

All Patients	Selected Patients
Noncontrast brain computed tomographic scan (magnetic resonance imaging, if available)	Hepatic function tests
Blood glucose level*	Toxicology screen
Serum electrolyte and renal function tests	Blood alcohol level
Electrocardiography	Pregnancy test
Markers of cardiac ischemia	Arterial blood gas tests (if hypoxia is suspected)
Complete blood count, including platelet count†	Chest radiography (if lung disease is suspected)
Prothrombin time/international normalized ratio†	Lumbar puncture (if subarachnoid hemorrhage is suspected and computed tomography scan is negative for blood)
Activated partial thromboplastin time*	Electroencephalogram (if seizures are suspected)
Oxygen saturation	

*Only test recommended before initiation of IV rtPA
†Although it is desirable to know the results of these tests before giving a patient tissue plasminogen activator, thrombolytic therapy should not be delayed while awaiting the results unless (1) there is clinical suspicion of a bleeding abnormality or thrombocytopenia; (2) the patient has received heparin or warfarin; or (3) the patient's use of anticoagulants is not known.
From Christensen H et al: Abnormalities on ECG and telemetry predict stroke outcome at 3 months, *J Neurol Sci* 234:99-103, 2005.

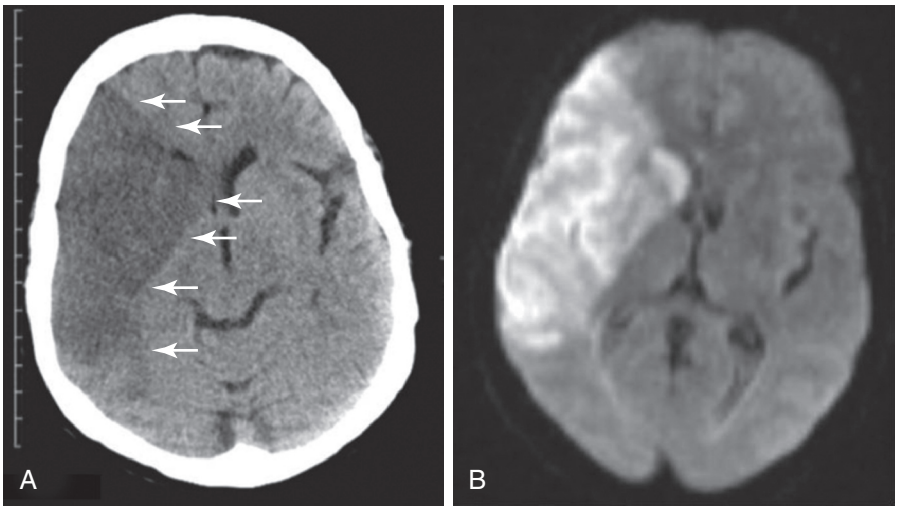


FIGURE S1-75 Large right middle cerebral artery infarct on an unenhanced computed tomographic scan **(A)** and a diffusion-weighted magnetic resonance image **(B)**. There is a mass effect, and this patient is at risk for cerebral herniation syndromes.

TABLE S1-24 Imaging Modalities for Stroke

Imaging Modality	Advantage	Disadvantage
Cerebral catheter angiography	• Allows for the definitive assessment of cerebral circulation (gold standard) • Allows for the deployment of intra-arterial thrombolysis and thrombectomy devices if a thrombus is found • Allows for the assessment of collateral circulation	• Invasive (significant risks) • High cost • Not available at all facilities
Doppler studies	• Noninvasive • May be performed at the patient's bedside	• Can be limited by the patient's body habitus • Operator dependent
Magnetic resonance angiography	• Excellent view of the large arteries of the neck and brain • No contrast material needed	• Cannot be performed in patients who are critically ill, who are unable to tolerate supine positioning, who have a pacemaker or other ferromagnetic hardware, or who are claustrophobic
Magnetic resonance perfusion	• Assesses cerebral hemodynamics • May show ischemic penumbra (i.e., the area of the brain that may be saved by timely intervention)	• Not commonly available • Not well standardized
CT angiography	• Excellent view of the large arteries of the neck and brain • Similar to magnetic resonance angiography with regard to resolution	• Requires intravenous contrast
CT perfusion	• Assesses cerebral hemodynamics • May show ischemic penumbra (i.e., the area of the brain that may be saved by timely intervention)	• Challenging to interpret in some cases • Not routinely available at many facilities • Requires intravenous contrast

- Consider neurosurgical intervention for craniectomy in select cases. Typical cases in which craniectomy may be performed include cerebellar ischemia with compression of the brain stem and/or the fourth ventricle as well as large right middle cerebral artery ischemia. Available evidence suggests that it may be better to perform early hemicraniectomy (<48 hr) to achieve better outcomes. Decompressive hemicraniectomy has shown good benefit in terms of mortality but not much benefit in terms of disability and functional outcomes.

ACUTE GENERAL Rx

INTRAVENOUS THROMBOLYSIS

- IV TPA is the only medical therapy approved by the U.S. FDA for the treatment of acute ischemic stroke. Clinical trials involving tenecteplase, a genetically engineered mutant TPA, have shown significantly better reperfusion and clinical outcomes than alteplase in patients with stroke who were selected on the basis of CT perfusion imaging but is still not approved for routine clinical use.
- The time window for administration is within 3 hr of symptom onset.
- There are strict criteria for the administration of IV TPA (see Box S1-11).
- The protocol is weight based, with 90 mg being the maximum allowable dose.
- The risk of brain hemorrhage with IV TPA is about 5% in stroke patients.
- Recent data suggest that IV TPA can be administered safely and with benefit in select patients up to 4.5 hours after symptom onset. There are additional exclusion criteria if IV TPA is given beyond the 3-hr window.

IMMEDIATE CATHETER CEREBRAL ANGIOGRAPHY FOR ENDOVASCULAR INTERVENTION

(Figs. S1-76 and S1-77): Methods available:

- The Merci clot retrieval system is approved by the U.S. FDA for use up to 8 hr after the onset of symptoms.
- The Penumbra System is also available at some centers. More recently, 2 other mechanical revascularization devices, namely the Solitaire FR (flow restoration) and Trevo, have been approved by the FDA. These devices showed better recanalization rates with fewer complications compared to the Merci device. A recent trial comparing endovascular thrombectomy with the solitaire FR (flow restoration) stent retriever and alteplase therapy revealed that in patients with ischemic stroke with a proximal cerebral arterial occlusion and salvageable tissue on CT perfusion imaging, early thrombectomy with the solitaire FR stent retriever improved reperfusion, early neurologic recovery, and functional outcome.*
- Intraarterial tissue plasminogen activator (TPA) is used routinely for up to 6 hr after the onset of symptoms, although it is not approved by the U.S. FDA for this purpose.

Pearls and caveats:

- Multimodal therapy (i.e., thrombectomy and intraarterial TPA) is sometimes performed.
- Endovascular treatment may be performed for select cases in which intravenous (IV) TPA has failed to recanalize an occluded artery.
- Endovascular intervention may be an option for cases in which there are systemic contraindications to IV TPA.
- Endovascular intervention is useful only for large, accessible thrombi. Therefore, if a stroke patient is a candidate for IV TPA, then he or she should probably receive IV TPA.
- One can reasonably expect an endovascular recanalization rate of 60% in appropri-

*Campbell BCV et al.: Endovascular therapy for ischemic stroke with perfusion-imaging selection, *N Engl J Med* 372:1009-1018, 2015.

BOX S1-11 Three-Hour Criteria for Tissue Plasminogen Activator (Alteplase [Activase]) Use in Patients with Thromboembolic Stroke

Criteria for considering TPA as a treatment option:
- Clinical presentation consistent with an ischemic stroke with clearly demonstrable neurological deficits
- Noncontrast CT head without evidence of hemorrhage
- Time since onset of symptoms (or last known normal if time of onset not known) clearly <3 hr (3-4.5 hr with additional exclusion criteria) before TPA administration would begin
- Age ≥18 years

Criteria for excluding TPA as a treatment option:
- Absolute exclusion criteria:
- Historic and clinical findings suggestive of subarachnoid hemorrhage, even if CT scan is normal
  1. Sudden, severe headache, often with a loss of consciousness at onset
  2. Vomiting
- Active internal bleeding, increased risk of bleeding, or known bleeding diathesis, including those resulting from:
  1. Recent use of warfarin with an INR of ≥1.7
  2. Use of heparin within 48 hr with a prolonged aPTT
  3. Current use of direct thrombin inhibitors or factor Xa inhibitors
  4. Platelet count of <100,000/mm^3
  5. History of intracranial hemorrhage
  6. Known intracranial neoplasm, arteriovenous malformation or aneurysm
  7. Arterial puncture at a noncompressible site within the past 7 days
- Stroke, intracranial surgery, or head trauma within the previous 3 mo
- Systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg that does not decrease below that range with treatment
- Blood glucose <50 mg/dl or >400 mg/dl
- CT findings:
  1. Evidence of intracranial hemorrhage
  2. Hypodensity or effacement of the sulci in one third of the territory of the middle cerebral artery

Relative exclusion criteria:
- Major surgery or serious trauma within the preceding 14 days
- Acute myocardial infarction (recent within the previous 3 months) or post–myocardial infarction pericarditis
- GI or GU bleeding within the past 21 days
- Seizure at stroke onset
- Rapidly improving neurologic signs or Isolated mild neurologic deficits
- Patient who is pregnant or lactating

Additional exclusion criteria for administering IV tPA in the 3-4.5 hour window
- Age > 80 years
- High stroke scale on presentation (NIHSS > 25)
- Current use of oral anticoagulants regardless of INR

Prior history of stroke and diabetes mellitus

aPTT, Activated partial thromboplastin time; *CT,* computed tomography; *GI,* gastrointestinal; *GU,* genitourinary; *INR,* international normalized ratio; *TPA,* tissue plasminogen activator.
Modified from Rakel RE [ed]: *Principles of family practice,* ed 6, Philadelphia, 2002, Saunders.

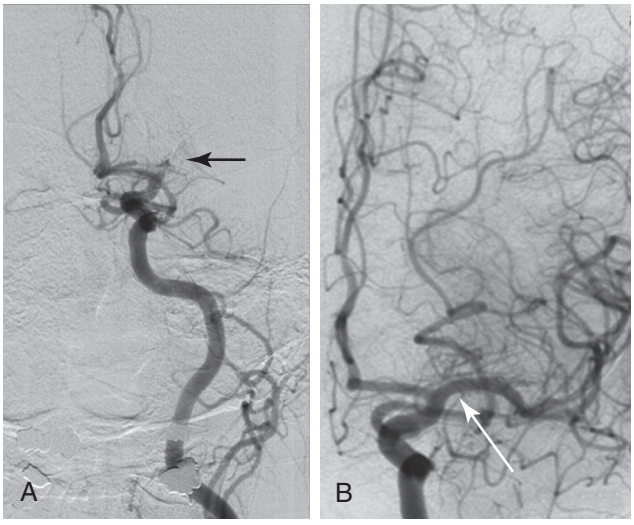


FIGURE S1-76 A, A catheter angiogram showing left middle cerebral artery occlusion, which caused severe stroke symptoms for several hours. **B,** The artery was opened with the Merci clot retrieval system, and this resulted in normal flow.

ate patients when used alone. Combining the Solitaire device with other endovascular approaches has shown recanalization rates close to 88% in recent studies (Solitaire).
- Complications can ensue from the endovascular procedure itself, including an intracerebral hemorrhage rate that is similar to that associated with IV TPA.
- Endovascular intervention is typically available only at select large stroke centers.
- Some practitioners are making use of perfusion imaging (i.e., CT perfusion and magnetic resonance perfusion) to assess whether there is salvageable brain tissue before performing the procedure. In some cases, this may lead to a dramatic expansion of traditional time windows; this practice is currently being studied in clinical trials.
- Fever: Fever is harmful during acute stroke. Ascertaining and addressing the cause while lowering an elevated temperature is strongly advised.

HYPERTENSION: Elevated blood pressure is common during acute stroke, and it often subsides without specific therapy. In general, hypertension is not treated acutely unless it is extremely high (e.g., >220 mm Hg systolic blood pressure); there is evidence of organ damage caused by the hypertension; or thrombolysis is being considered, in which case the blood pressure needs to come down (if it can be safely accomplished) to <185/110 mm Hg. It is risky to severely decrease blood pressure in the presence of acute ischemic stroke as it can cause an extension of the stroke into the ischemic penumbra. A 15% to 25% decrease over the first 24 hours is recommended.

HYPOTENSION: The presence of systemic hypotension in acute ischemic stroke portends a poor outcome. The cause should be sought, and volume depletion should be corrected with normal saline. Cardiac arrhythmias should be treated. Induced hypertension with vasopressor agents may be useful for select cases with an ischemic penumbra that is at risk, but caution is strongly advised.

HYPOGLYCEMIA: Hypoglycemia can mimic stroke. Prompt assessment of serum glucose level and replacement as necessary are important.

HYPERGLYCEMIA: The presence of hyperglycemia worsens ischemic stroke outcome. Hyperglycemia should be managed aggressively.

ANTIPLATELET THERAPY: Oral or feeding tube administration of aspirin (325 mg/day) within 48 hours of stroke onset is advised to decrease the likelihood of a repeat ischemic stroke. Other oral antiplatelet regimens approved for secondary stroke prophylaxis (e.g., clopidogrel, aspirin plus extended-release dipyridamole) will also suffice and may be superior in the long term. In patients with acute ischemic stroke and atrial fibrillation, full dose anticoagulation with heparin infusion or low molecular weight heparin should be avoided in the acute setting, as this could potentially harm the patient by causing symptomatic intracranial hemorrhage

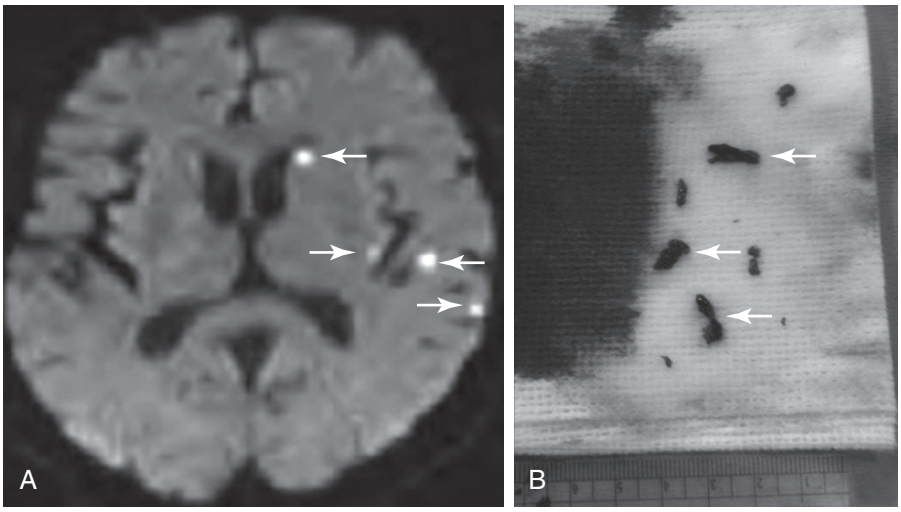


FIGURE S1-77 A, A diffusion-weighted magnetic resonance image of the same patient as shown in previous figure, this time showing only mild left cerebral ischemia after intervention. The patient was clinically normal. **B,** Thrombi removed from the middle cerebral artery with the use of the Merci clot retrieval system.

and there is very little evidence to suggest any benefit.

DISPOSITION

Patients with acute ischemic stroke should be cared for in a stroke unit or an intensive care unit. Nurses with skills in stroke care and telemetry monitoring should be routine. Once the patient is stable and the workup is complete, rehabilitation should be arranged.

REFERRAL

Patients with acute ischemic stroke should be transported to a hospital in which providers are skilled in stroke care. Depending on the severity and duration of symptoms, the patient may qualify for immediate endovascular intervention at a comprehensive stroke center, even if he or she is not a candidate for IV TPA. If complications from brain edema develop, further evaluation by a neurosurgeon may be helpful during the acute phase.

PEARLS & CONSIDERATIONS

PREVENTION

- The prevention of acute ischemic stroke depends on the aggressive management of risk factors in individual patients.
- Cross reference: stroke, secondary prevention
- Paroxysmal atrial fibrillation is common in patients with cryptogenic stroke. A recent study found that noninvasive ambulatory ECG monitoring for 30 days significantly improved the detection of atrial fibrillation by a factor of >5 and nearly doubled the rate of anticoagulant treatment compared to the standard practice of short duration ECG monitoring

PATIENT & FAMILY EDUCATION

Patients and families need to be taught about ways to reduce the risk for recurrent stroke, including lifestyle modifications. Education about rehabilitation goals, when appropriate, should also be accomplished.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Fig. E3-197 Algorithm for the emergency evaluation of a patient with suspected stroke (Algorithm)

Stroke (Patient Information)

AUTHORS: **PRASHANTH KRISHNAMOHAN, M.B.B.S., M.D.,** and **MICHAEL R. DOBBS, M.D.**

EVIDENCE

Abstract[1]

Background and Purpose:

In ischemic stroke, MR perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI) mismatch represents tissue at risk for infarction. Infarct growth should only take place in the presence of mismatch, although there have been reports of this occurring. We hypothesized that this observation may be attributable to the presence of undetected "hidden mismatch," which may become obvious when coregistration techniques are used.

Methods:

MR PWI/DWI was performed within 48 hours of stroke onset and a final T2-weighted image at ≈3 months. Volumetric-subtraction mismatch volume was defined as PWI minus DWI volume and infarct growth was defined as T2 minus DWI volume. Coregistration mismatch volume was PWI not overlapped by DWI. Mismatch salvage was the proportion of coregistered mismatch tissue that had not progressed to infarction.

Results:

Thirty-four patients were studied with MR at a median of 4.9 hours (interquartile range, 2.9–21.1 hours). With the volumetric-subtraction technique, 5 patients (14.7%; 95% CI, 0.05%–0.31%) had infarct growth exceeding mismatch volume, 11 patients (32.0%) had no mismatch and, among these, 3 (27.3%) had infarct growth (median volume, 2.2 mL; interquartile range, 1.0–6.5 mL). All patients had mismatch volume identified by coregistration method that was greater than infarct growth volume. The proportion of this volume salvaged was 77.7% (interquartile range, 63.0%–98.9%).

Conclusions:

The illogical finding of infarct growth volume being greater than the presence of mismatch volume can be explained by the presence of "hidden mismatch," which may be detected by coregistration methods. Ⓐ

Evidence-Based Reference

Ma HK et al.: The hidden mismatch: an explanation for infarct growth without perfusion-weighted imaging/diffusion-weighted imaging mismatch in patients with acute ischemic stroke, *Stroke* 42:662–668, 2011. Ⓐ

SUGGESTED READINGS

Adams HP Jr et al.: Guidelines for the early management of adults with ischemic stroke, *Stroke* 38(5):1655–1711, 2007.

Baker WL et al.: Neurothrombectomy devices for the treatment of acute ischemic stroke: state of the evidence, *Ann Intern Med* 154:243–252, 2011.

Broderick JP et al.: Endovascular therapy after intravenous t-PA versus t-PA alone for stroke, *N Engl J Med* 368:893–903, 2013.

Bushnell C: McCullough: Stroke prevention in women: Synopsis of the 2014 American Heart Association/American Stroke Association Guideline, *Ann Intern Med* 160:853–857, 2014.

Ciccone A et al.: Endovascular treatment for acute ischemic stroke, *N Engl J Med* 368:904–913, 2013.

Gladstone DJ et al.: Atrial fibrillation in patients with cryptogenic stroke, *N Engl J Med* 370:2467–2477, 2014.

Healey JS et al.: Subclinical atrial fibrillation and the risk of stroke, *N Engl J Med* 366:120–129, 2012.

Juttler G et al.: Hemicraniotomy in older patients with extensive middle-cerebral-artery stroke, *N Engl J Med* 370:1091–1100, 2014.

Parsons M et al.: A randomized trial of tenecteplase vs. alteplase for acute ischemic stroke, *N Engl J Med* 366:1099, 2012.

Solitaire FR: Thrombectomy for acute ischemic stroke: retrospective multicenter analysis of early postmarket experience after FDA approval.

Wechsler LR: Intravenous thrombolytic therapy for acute ischemic stroke, *N Engl J Med* 364:2138–2146, 2011.

BASIC INFORMATION

DEFINITION

Hemorrhagic stroke is the sudden onset of a focal neurologic deficit caused by hemorrhage into or around the brain.

SYNONYMS

Intracerebral hemorrhage (ICH)
Intracranial hemorrhage
Cerebrovascular attack (This is a nonspecific term and should not be used.)
The term *subarachnoid hemorrhage* refers to a specific location for hemorrhage, which commonly occurs as a result of a ruptured aneurysm. Please see "Subarachnoid Hemorrhage" for additional information.

ICD-9CM CODES
431 Intracerebral hemorrhage
432.9 Unspecified intracranial hemorrhage
ICD-10CM CODES
I61 Intracerebral hemorrhage
I61.0 Intracerebral hemorrhage in hemisphere, subcortical
I61.1 Intracerebral hemorrhage in hemisphere, cortical
I61.2 Intracerebral hemorrhage in hemisphere, unspecified
I61.3 Intracerebral hemorrhage in brainstem
I61.4 Intracerebral hemorrhage in cerebellum
I61.5 Intracerebral hemorrhage, intraventricular
I61.6 Intracerebral hemorrhage, multiple localized
I61.9 Nontraumatic intracerebral hemorrhage, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: There are approximately 800-1000 new or recurrent strokes per year in the United States, of which ~10% to 15% are hemorrhagic.
RISK FACTORS:
- Hypertension
- Anticoagulant use
- Thrombolysis
- Alcoholism
- Illicit drug use (e.g., cocaine)
- Cerebral amyloid angiopathy

GENETICS: Multifactorial

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The presentation varies with the region of the brain that is affected. The following are common locations for hemorrhage:
- Basal ganglia
- Cerebellum
- Pons
- Lobar (i.e., amyloid angiopathy)
- The ICH score is a widely used grading scale for risk stratification. Parameters used to calculate the ICH score include Glascow Coma Score (GCS) (0 to 2 points) at presentation, patient age ≥ 80 (1 point), ICH volume ≥ 30 mL (1 point), presence of intraventricular blood (1 point), and infratentorial origin of blood. (1 point). Scores range from 0 to 6 with a score of 0 conferring 0% mortality and a score of 6 with estimated 100% mortality.

ETIOLOGY

- Rupture of vessels
- Aneurysm
- Arteriovenous malformation
- Brain tumor
- Amyloid angiopathy

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Ischemic stroke
- Seizure with postictal paralysis
- Syncope
- Migraine with hemiparesis
- Conversion disorder

LABORATORY TESTS

- CBC, metabolic panel including blood glucose and renal function, PT/INR, aPTT, urinalysis, and toxicology screens
- ECG and telemetry monitoring

IMAGING STUDIES

- Immediate: CT scanning of the head without contrast is highly sensitive for hemorrhage (Fig. S1-78).
- CT or MR angiogram to rule out an underlying vascular malformation. CT spot sign on the CTA has been shown to be a reliable early predictor of hematoma expansion.
- MRI of the brain with a gradient echo sequence is also highly sensitive for hemorrhage, including intracerebral microhemorrhages that may not be visible with computed tomography scanning. MRI may also help to identify underlying brain tumors or vascular malformations, especially if the bleeding occurs at atypical sites.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Urgent neurosurgical evaluation is needed in many cases either for evacuation of the hematoma or for relieving raised intracranial pressure by procedures such as EVD placement or decompressive surgeries.
- Surgery should be performed promptly for cases of cerebellar hemorrhage of >3 cm when the patient is deteriorating clinically, showing brain stem edema or hydrocephalus.
- Surgery for lobar or deep brain clots may be considered for select cases, although the level of evidence for efficacy is not high.
- Recent innovative surgical techniques, such as instillation of thrombolytic agents for intraventricular hemorrhage and minimally invasive surgery for hematoma evacuation, appear to be promising, although there are no large randomized controlled trials yet to prove that they are beneficial.
- Pneumatic compression devices should be applied to help prevent deep venous thrombosis. Chemical DVT prophylaxis can be started after 48 to 72 hours in most situations once the bleed has been determined to be stable
- Early mobilization for rehabilitation is desirable.

ACUTE GENERAL Rx

- Hypertension (Box S1-12): Blood pressure should be quickly lowered by 15% and then gradually and safely brought to the individual patient's target range. In theory, this may diminish the expansion of the hematoma. More aggressive control of SBP to 140 or less in the acute setting has been shown to be safe, although it did not improve outcomes in terms of mortality or major disability significantly in clinical trials. Evidence suggests that a more sustained BP control with continuous IV medications might be more beneficial

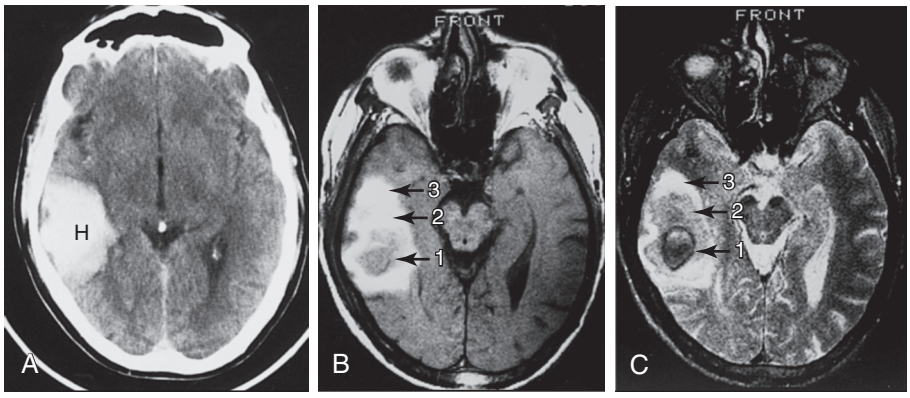


FIGURE S1-78 Hemorrhage. Axial CT image **(A)** demonstrates a large area of acute hemorrhage *(H)* in right temporal lobe. T_1-weighted **(B)** and T_2-weighted **(C)** MRI scans demonstrate the hemorrhage in various stages of breakdown. Center of lesion is dark on T_1- and T_2-weighted images, indicating oxyhemoglobin *(1)*. Intermediate zone is bright on T_1-weighted image and gray on T_2-weighted image, indicating intracellular methemoglobin *(2)*. Outer rim is bright on both T_1- and T_2-weighted images, indicating extracellular methemoglobin *(3)*. (From Vincent JL et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, Saunders.)

BOX S1-12 Suggested Recommended Guidelines for the Treatment of Elevated Blood Pressure in Patients with Spontaneous Intracerebral Hemorrhage

1. SBP of >200 mm Hg or MAP of >150 mm Hg: Consider the aggressive reduction of BP with continuous intravenous infusion, with BP monitoring every 5 min.
2. SBP of >180 mm Hg or MAP of >130 mm Hg with evidence or suspicion of elevated ICP: Consider ICP monitor and reducing BP with intermittent or continuous intravenous medications to keep cerebral perfusion pressure >60 to 80 mm Hg.
3. SBP of >180 mm Hg or MAP of >130 mm Hg without evidence or suspicion of elevated ICP: Consider a modest reduction of BP (e.g., MAP of 110 mm Hg or target blood pressure of 160/90 mm Hg) with intermittent or continuous intravenous medications, and clinically reexamine the patient every 15 min.

BP, Blood pressure; *ICP,* intracranial pressure; *MAP,* mean arterial pressure; *SBP,* systolic blood pressure.
Modified from Broderick J et al: Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update, *Stroke* 38:2001-2023, 2007.

than using intermittent medications resulting in significant BP variability.
- Hyperglycemia: a high blood glucose level predicts a worse outcome. Markedly elevated glucose levels should be lowered to <200 mg/dL.
- Seizures: if seizures occur, they should be treated aggressively, including with intravenous medications, if needed.
- Elevated intracranial pressure: this condition should be treated with a graded approach, which may include the elevation of the head of the bed, analgesia/sedation, hyperventilation, and osmotic therapy. In patients clinically suspected to have elevated ICP, invasive monitoring of the ICP may be required. If conservative treatment fails to control ICP, EVD placement or other decompressive procedures like craniotomy need to be pursued.
- Antipyretics should be administered for fever in addition to searching for a cause of the fever.
- Protamine sulfate is used to treat cases of heparin-induced intracerebral hemorrhage.
- Prothrombin concentrate complex (PCC) is now recommended for reversal of warfarin-associated ICH. Vitamin K and FFP may also be used as adjuncts. Routine use of recombinant factor VII concentrates are not recommended due to insufficient evidence and concern for increased risk of thromboembolic events.
- Recommendations for thrombolytic-associated intracerebral hemorrhage treatment include the consideration of the infusion of platelets and cryoprecipitate.
- Early hematoma expansion has been associated with a poor outcome. Hemostatic therapy such as recombinant factor VII concentrates has not been shown to improve outcomes despite reducing hematoma expansion. Efforts are under way to identify patients at high risk of early hematoma expansion by using clinical and radiographic information to determine who may benefit from more aggressive hemostatic intervention.

DISPOSITION

For large hemorrhages or unstable patients, immediate referral to a stroke center

REFERRAL

Patients with hemorrhagic stroke should be transported to a hospital where providers are skilled in the treatment of stroke and cerebrovascular diseases including the availability of neurosurgery services and neurocritical care. Depending on the severity and duration of symptoms, the patient may require neurosurgical intervention.

PEARLS & CONSIDERATIONS

- Outcomes are inversely correlated with hemorrhage size.
- Specific reversal agents may be useful for warfarin-, heparin-, or thrombolysis-associated hemorrhage.
- No procoagulant medications have yet been shown to be safe and effective for the mitigation of spontaneous intracerebral hemorrhage in placebo-controlled trials.

PREVENTION

- Prevention depends on the aggressive management of risk factors in individual patients, including hypertension, smoking, alcohol use, and cocaine use.
- Newer oral anticoagulants (NOACs) dabigatran, apixaban, rivaroxaban are uniformly associated with an overall reduced risk of iatrogenic intracerebral hemorrhage (ICH) when used for stroke prevention in atrial fibrillation. Any of the currently available NOACs can be considered first line for patients at high risk for ICH.[1]

PATIENT & FAMILY EDUCATION

Patients and families need to understand that most patients will not soon achieve functional independence and that rehabilitation will be a long process. Education about avoiding antithrombotic agents should be stressed as appropriate for individual circumstances.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Stroke (Patient Information)

AUTHORS: **MICHAEL R. DOBBS, M.D.,** and **PRASHANTH KRISHNAMOHAN, M.B.B.S., M.D.**

[1] Chatterjee S et al.: New oral anticoagulants and the risk of intracranial hemorrhage: traditional and Bayesian meta-analysis and mixed treatment comparison of randomized trials of new oral anticoagulants in atrial fibrillation, *JAMA Neurol* 70(12):1486-1490, 2013.

SUGGESTED READINGS

Anderson CS, Heeley E, Huang Y, et al.: Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage, *N Engl J Med* 368:2355–2365, 2013.

Chatterjee S et al.: New oral anticoagulants and the risk of intracranial hemorrhage: traditional and Bayesian meta-analysis and mixed treatment comparison of randomized trials of new oral anticoagulants in atrial fibrillation, *JAMA Neurol* 70(12):1486-1490, 2013.

Morgenstern LB, Hemphill JC, Anderson C, et al.: Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association, *Stroke* 41:2108–2129, 2010.

Demchuk AM et al.: Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study, *Lancet Neurol* 11:307–314, 2012.

Hemphill JC 3rd et al.: The ICH score: a simple, reliable grading scale for intracerebral hemorrhage, *Stroke* 32:891–897, 2012.

Mayer SA, Brun NC, Begtrup K et al.: Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage, *N Engl J Med* 358:2127–2137, 2008.

Morgenstern LB, Hemphill JC, Anderson C, et al.: Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association, *Stroke* 41:2108–2129, 2010.

BASIC INFORMATION

DEFINITION

Secondary prevention of stroke involves preventing the recurrence of a cerebral vascular ischemic or hemorrhagic stroke after a primary event.

SYNONYMS

Brain attack
Stroke
Cerebral thrombosis
Cerebral hemorrhage
Brain infarct

ICD-9CM CODES
433 Precerebral vessel occlusion
434 Cerebral vessel thrombosis or occlusion
ICD-10CM CODES
I65.2 Occlusion and stenosis of carotid artery
I65.0 Occlusion and stenosis of vertebral artery
I65.9 Occlusion and stenosis of unspecified precerebral artery
I66 Occlusion and stenosis of cerebral artery, not resulting in cerebral infarction
I65.1 Occlusion and stenosis of basilar artery

EPIDEMIOLOGY

Stroke is the third leading cause of death in the U.S. Each year, there are a total of 800,000 strokes, of which approximately 200,000 are recurrent strokes. Thus, secondary prevention of ischemic stroke remains good treatment strategy. Secondary prevention is specifically targeted toward modifiable risk factors.

RISK FACTORS: Age is the most important nonmodifiable risk factor. Modifiable risk factors include hypertension, hyperlipidemia, cigarette smoking, excessive alcohol consumption, physical inactivity, obesity (i.e., a body mass index of >25 kg/m^2), and diabetes mellitus.

GENETICS: Multifactorial

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Stroke can have a varied presentation. Typically, the individual has a sudden definable loss of motor, sensory, visual, or cognitive functions that have a clear time of onset and that are noticed by others or by the individuals themselves.
- Physical findings such as weakness and/or numbness in one limb or on one side of the body, facial droop, visual field loss, or the inability to understand or communicate with others raises one's suspicion of a stroke event.

ETIOLOGY

- Strokes are broadly divided into ischemic or hemorrhagic (i.e., intraparenchymal or subarachnoid hemorrhage)
- Ischemic strokes can be caused by large-vessel atherosclerosis, cardioembolism such as in atrial fibrillation or cardiomyopathy, or small vessel disease such as lacunar stroke. Rare causes such as recreational drug use (e.g., cocaine abuse); arterial dissection; and hypercoagulable states need to be considered when ischemic stroke occurs in younger individuals.
- The most common cause of intracerebral hemorrhage is uncontrolled hypertension. Spontaneous rupture of a brain aneurysm causes subarachnoid hemorrhage.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Seizure and postictal states
- Complicated migraine
- Hypoglycemia
- Brain tumor
- Somatization disorder

WORKUP

- Blood glucose level at the bedside or in the office
- aPTT, PT/INR, CBC, and CMP
- Fasting lipid panel
- Hypercoagulability tests for young stroke patients with no obvious risk factors

IMAGING STUDIES

- Computed tomography scanning of the head without contrast can differentiate between ischemic and hemorrhagic stroke. MRI of the brain is a more specific test.
- Carotid ultrasound and transcranial Doppler are used to detect large-vessel atherosclerosis. Magnetic resonance and computed tomography angiography are good alternatives.
- Echocardiogram and ECG can be used to detect a cardioembolic source.

TREATMENT

The secondary prevention of stroke is targeted toward modifiable risk factors. These include lifestyle modifications such as appropriate diet, exercise, weight loss, and smoking cessation, and risk factor modification as listed below. All patients with noncardioembolic ischemic stroke or transient ischemic attack (TIA) should be on aspirin (50 to 325 mg/day), a combination of aspirin and extended-release dipyridamole, or clopidogrel. A consultation with a neurologist should be considered for young stroke patients and for patients with no obvious cause or with stroke from unusual causes (e.g., hypercoagulable states, dissections).

PREVENTING STROKE IN SPECIFIC CONDITIONS

1. Cardioembolic strokes as a result of atrial fibrillation have two first-line drug therapies: warfarin and dabigatran. Warfarin remains a first-line therapy with an international normalized ratio (INR) between 2.0 and 3.0. Dabigatran has equal efficacy as warfarin without the need for routine monitoring of INR. Dabigatran is approved by the U.S. Food and Drug Administration at a dosing regimen of 150 mg twice a day. For patients with contraindications to anticoagulants, aspirin (325 mg/day) is recommended. The Active-A trial suggested that a combination of aspirin and clopidogrel is slightly better than aspirin alone for those unable to tolerate warfarin.
2. Cardioembolic strokes as a result of a prosthetic metallic valve: anticoagulant therapy with warfarin is recommended with a goal INR between 2.5 and 3.5.
3. Strokes as a result of large-vessel atherosclerosis (i.e., symptomatic carotid stenosis): for patients with recent TIA or ischemic stroke within the last 6 months and ipsilateral severe (70% to 99%) carotid artery stenosis, carotid endarterectomy (CEA) performed by a surgeon is recommended and results in a perioperative morbidity and mortality rate of <6%. For patients with recent TIA or ischemic stroke and ipsilateral moderate (50% to 69%) carotid stenosis, CEA is recommended. When the degree of stenosis is <50%, there is no indication for CEA. Carotid stenting is not indicated except for cases in which surgery is high risk. Current trials are comparing carotid enterectomy versus carotid stenting. As of 2013, the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) has shown no inferiority of stenting versus endarterectomy, and stenting may favor younger patients or those at higher surgical risk for complications.
4. Symptomatic intracranial atherosclerosis: treatment with aspirin has proven effective and just as efficacious as warfarin in both the WASID and WARSS studies. The utility of angioplasty and stenting in patients with symptomatic intracranial atherosclerosis is available at several stroke centers but remains investigational (Fig. S1-79). In April 2011 the NINDS stopped enrollment into the symptomatic intracranial artery stenosis stenting trial (SAMMPRIS).
5. Patent foramen ovale (PFO): the American Academy of Neurology recommends medical therapy for stroke patients with PFO. Trials are under way to evaluate if endovascular PFO closure reduces the risk of recurrent transient ischemic attacks or strokes.
6. Intracerebral hemorrhage: for immediate management, please refer to the chapter on intracerebral hemorrhage. Antiplatelet agents should be held for 3 to 4 weeks and can be restarted if there is a compelling indication such as nonvalvular atrial fibrillation. The American Stroke Association/American Heart Association 2010 guideline recommends avoiding long-term anticoagulation (e.g., warfarin, heparin) after spontaneous lobar intracerebral hemorrhage, but antiplatelet therapy (e.g., aspirin, clopidogrel, Aggrenox) may be considered in all cases of intracerebral hemorrhage where there is a definite indication. Consider a neurology consultation in these cases.

PREVENTING LONG-TERM COMPLICATIONS AFTER A STROKE

Evaluation by a physical, occupational, and speech therapist will reduce the long-term disability that can follow a stroke event. The American Stroke Association 2010 guideline

recommends a multidisciplinary approach to rehabilitation. Studies have shown an improved survival and recovery. Home-based rehabilitation can be considered after discussion with the rehabilitation specialist.

RISK FACTOR MODIFICATION

1. Hypertension: antihypertensive treatment is recommended for both the prevention of recurrent stroke and the prevention of other vascular events in persons who have had an ischemic stroke or a TIA. Absolute target blood pressure level and reduction are uncertain and should be individualized. Blood pressure should be lowered gradually over a period of months to prevent cerebral hypoperfusion and extension of stroke. Lifestyle modifications as listed above should be included as part of a comprehensive antihypertension treatment plan.
2. Diabetes: the goal for the hemoglobin A_{1c} level should be <7%. For type 2 diabetics, diet and exercise can prove very beneficial. Type 1 diabetics can also benefit from diet and compliance with their insulin regimen. Uncontrolled hyperglycemia can lead to acceleration of both intracranial and extracranial arteriosclerosis. Always consider consulting a diabetic educator.
3. Hyperlipidemia: for patients with ischemic stroke or TIA with elevated cholesterol levels, statin agents are recommended. The target goals for cholesterol lowering are an LDL-C level of <100 mg/dl and an LDL-C level of <70 mg/dl for very high-risk persons with multiple risk factors (e.g., both coronary artery disease and diabetes).
4. Cigarette smoking: absolute cessation is required. Try to offer pharmacologic therapy or counseling services to the patient. Secondhand tobacco exposure is just as dangerous, so inquire about secondhand exposure.
5. Obesity: weight reduction may be considered for all overweight ischemic stroke and TIA patients to maintain the goal of a body mass index of between 18.5 and 24.9 kg/m^2 and a waist circumference of <35 in for women and <40 in for men.
6. Excessive alcohol consumption: patients with ischemic stroke or TIA who are heavy drinkers should eliminate or reduce their consumption of alcohol. Light to moderate levels of no more than two drinks per day for men and one drink per day for nonpregnant women may be considered.

DISPOSITION

Secondary stroke prevention is a multifaceted approach of lifestyle modification and pharmacologic intervention that is aimed at preventing or limiting disability.

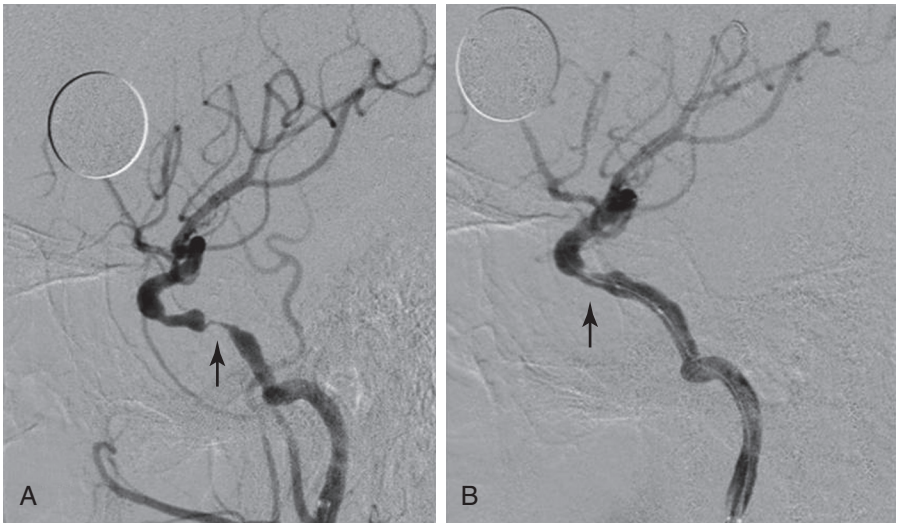


FIGURE S1-79 A, Intracranial high-grade symptomatic stenosis. **B,** This patient failed aggressive medical therapy and responded only to angioplasty and stenting.

REFERRAL

For complicated recurrent strokes, a referral to a neurologist who specializes in stroke is recommended.

PEARLS & CONSIDERATIONS

The modification of risk factors is the best preventive measure for stroke. Lifestyle modification is a very important aspect of secondary stroke prevention. Always consider the patient's ability to afford the therapy and prescribed follow-up tests. Experience teaches us that patients sometimes will not let us know about their ability to afford therapies unless we inquire.

PREVENTION

Prevention is the goal of treatment, and compliance is the most important factor. Review risk factor reduction and pharmacologic therapy as previously discussed.

PATIENT/FAMILY EDUCATION

More information can be obtained from the following sources:

- American Heart Association, National Center, 7272 Greenville Avenue, Dallas, TX 75231
- American Stroke Association, 1-888-4-STROKE or 1-888-478-7653
- H.O.P.E. for Stroke, 250 Duck Pond Drive, Wantagh, NY 11793, 516-804-8495

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Stroke (Patient Information)
Transient Ischemic Attack (Related Key Topic)

AUTHOR: **NAWAZ HACK, M.D.**

EVIDENCE

Abstract[1]

Context:
Cardiovascular disease (CVD) risk increases beginning at systolic blood pressure levels of 115 mmHg. Use of antihypertensive medications among patients with a history of CVD or diabetes and without hypertension has been debated.
Objective:
To evaluate the effect of antihypertensive treatment on secondary prevention of CVD events and all-cause mortality among persons without clinically defined hypertension.
Data Sources:
Meta-analysis with systematic search of MEDLINE (1950 to week 3 of January 2011), EMBASE, and the Cochrane Collaboration Central Register of Controlled Clinical Trials and manual examination of references in selected articles and studies.
Study Selection:
From 874 potentially relevant publications, 25 trials that fulfilled the predetermined inclusion and exclusion criteria were included in the meta-analysis.
Data Extraction:
Information on participant characteristics, trial design and duration, treatment drug, dose, control, and clinical events were extracted using a standardized protocol. Outcomes included stroke, myocardial infarction (MI), congestive heart failure (CHF), composite CVD outcomes, CVD mortality, and all-cause mortality.
Results:
Compared with controls, participants receiving antihypertensive medications had a pooled relative risk of 0.77 (95% confidence interval [CI], 0.61 to 0.98) for stroke, 0.80 (95% CI, 0.69 to 0.93) for MI, 0.71 (95% CI, 0.65 to 0.77) for CHF, 0.85 (95% CI, 0.80 to 0.90) for composite CVD events, 0.83 (95% CI, 0.69 to 0.99) for CVD mortality, and 0.87 (95% CI, 0.80 to 0.95) for all-cause mortality from random-effects models. The corresponding absolute risk reductions per 1000 persons were −7.7 (95% CI, −15.2 to −0.3) for stroke, −13.3 (95% CI, −28.4 to 1.7) for MI, −43.6 (95% CI, −65.2 to −22.0) for CHF events, −27.1 (95% CI, −40.3 to −13.9) for composite CVD events, −15.4 (95% CI, −32.5 to 1.7) for CVD mortality, and −13.7 (95% CI, −24.6 to −2.8) for all-cause mortality. Results did not differ according to trial characteristics or subgroups defined by clinical history.
Conclusions:
Among patients with clinical history of CVD but without hypertension, antihypertensive treatment was associated with decreased risk of stroke, CHF, composite CVD events, and all-cause mortality. Additional randomized trial data are necessary to assess these outcomes in patients without CVD clinical recommendations. Ⓐ

Abstract[2]

Background:
Vitamin K antagonists are highly effective in preventing stroke in patients with atrial fibrillation but have several limitations. Apixaban is a novel oral direct factor Xa inhibitor that has been shown to reduce the risk of stroke in a similar population in comparison with aspirin.
Methods:
In this randomized, double-blind trial, we compared apixaban (at a dose of 5 mg twice daily) with warfarin (target international normalized ratio, 2.0 to 3.0) in 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke. The primary outcome was ischemic or hemorrhagic stroke or systemic embolism. The trial was designed to test for noninferiority, with key secondary objectives of testing for superiority with respect to the primary outcome and to the rates of major bleeding and death from any cause.
Results:
The median duration of follow-up was 1.8 years. The rate of the primary outcome was 1.27% per year in the apixaban group, as compared with 1.60% per year in the warfarin group (hazard ratio with apixaban, 0.79; 95% confidence interval [CI], 0.66 to 0.95; P<0.001 for noninferiority; P=0.01 for superiority). The rate of major bleeding was 2.13% per year in the apixaban group, as compared with 3.09% per year in the warfarin group (hazard ratio, 0.69; 95% CI, 0.60 to 0.80; P<0.001), and the rates of death from any cause were 3.52% and 3.94%, respectively (hazard ratio, 0.89; 95% CI, 0.80 to 0.99; P=0.047). The rate of hemorrhagic stroke was 0.24% per year in the apixaban group, as compared with 0.47% per year in the warfarin group (hazard ratio, 0.51; 95% CI, 0.35 to 0.75; P<0.001), and the rate of ischemic or uncertain type of stroke was 0.97% per year in the apixaban group and 1.05% per year in the warfarin group (hazard ratio, 0.92; 95% CI, 0.74 to 1.13; P=0.42).
Conclusions:
In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality. (Funded by Bristol-Myers Squibb and Pfizer; ARISTOTLE ClinicalTrials.gov number, NCT00412984.) Ⓐ

Abstract[3]

For the secondary prevention of stroke of arterial origin, aspirin is the most widely studied and prescribed agent the world over. Cilostazol is both an antiplatelet and vasodilating agent. This agent has been used mainly in Asian populations with noncardioembolic stroke and no clinically evident cardiac disease. Ⓐ

Evidence-Based References

Thompson AM et al.: Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: a meta-analysis, *JAMA* 305:913–922, 2011. Ⓐ

Granger: CG for the ARISTOTLE Committees and Investigators: Apixaban versus warfarin in patients with atrial fibrillation, *N Engl J Med* 365:981–992, 2011. Ⓐ

Kamal AK et al.: Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin, *Stroke* 42:e-382–e-384, 2011. Ⓐ

SUGGESTED READINGS

Furie KL: Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association, *Stroke* 42:227–276, 2011.

Spence JD: Secondary stroke prevention, *Nature Rev Neurol* 6:477–486, 2010.

Vermeer SE, et al.: Silent brain infarcts: a systemic review, *Lancet Neurol* 6:611, 2007.

BASIC INFORMATION

DEFINITION

Sturge-Weber syndrome (SWS) is a sporadic congenital disorder characterized by a dermal capillary malformation (port-wine stain) occurring in association with vascular malformations of the leptomeninges and the eye.

Sturge first described a patient with epilepsy, a facial capillary malformation, and buphthalmos in 1879. Parkes Weber better characterized the pattern and distribution of the characteristic intracranial calcifications. The complete syndrome generally includes the triad of facial dermal capillary malformation (port-wine stain), ipsilateral central nervous system (CNS) vascular malformation (leptomeningeal angiomatosis), and vascular malformation of the choroid of the eye associated with glaucoma. Partial forms have been reported.

SYNONYMS

Sturge (-Weber) (-Dimitri) disease or syndrome
Encephalocutaneous angiomatosis SWS

ICD-9CM CODES
759.6 Other congenital hamartoses not elsewhere classified
ICD-10CM CODES
Q85.8 Other phakomatoses, not elsewhere classified

EPIDEMIOLOGY & DEMOGRAPHICS

SWS is not a heritable disorder; thus recurrence is unlikely.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

SWS is characterized by a facial angioma (port-wine stain) and an associated leptomeningeal angioma. These vascular malformations are associated with specific ocular and neurologic abnormalities.

CUTANEOUS MANIFESTATIONS

- Cutaneous port-wine stain is the most common type of vascular malformation, occurring in 0.3% of newborns (Fig. ES1-80*A*). However, only a small number of children with port-wine stains have SWS.
- In SWS, the port-wine stain typically is present on the forehead and upper eyelid, primarily in the distribution of the first or second division of the trigeminal nerve. Extension of the skin lesion to both sides of the face and the trunk and extremities is common.
- The distribution of the cutaneous angioma influences the risk of an associated leptomeningeal angioma. Leptomeningeal angioma occurs in approximately 90% of cases when the port-wine stain involves both the upper and lower eyelids compared with 10% when only one eyelid is affected.
- The skin lesion usually is obvious at birth. However, its appearance changes with age and its size increases as the patient grows. In the newborn, the lesion is flat and usually light pink in color. It typically darkens with age to a deep red, port-wine appearance and vascular ectasias develop (Fig. ES1-80*B*). The vascular ectasias produce nodularity and superficial blebbing, which lead to overgrowth of the underlying soft tissues and sometimes the bone.
- It may extend to mucosal surfaces with concomitant gingival hypertrophy, which may be even further accentuated in patients being treated with phenytoin for seizures. Some patients exhibit accelerated eruption of teeth.

LEPTOMENINGEAL ANGIOMA

- Leptomeningeal angioma occurs in 10% to 20% of cases when a typical facial lesion is present. The intracerebral lesion usually occurs on the same side as the port-wine stain. Leptomeningeal angiomatosis seldom occurs without an accompanying facial angioma.
- The parietal and occipital areas are affected most commonly, although any portion of the cerebrum can be involved.
- The pathologic appearance of the leptomeninges includes thickening and discoloration caused by the increased vascularity. The angiomatous tissue typically fills the subarachnoid space in the sulci, and large, tortuous venous structures drain superficially or into the deep venous system. The underlying parenchyma may be atrophic and contain multiple calcific granular deposits. The intraparenchymal calcification may result from chronic tissue hypoxia caused by venous stasis.

OCULAR MANIFESTATIONS:

- Ocular features of SWS include glaucoma and vascular malformations of the conjunctiva, episclera, choroid, and retina.
- The predominant ocular abnormality is glaucoma (increased intraocular pressure), which occurs in 30% to 70% of affected patients. The risk of glaucoma is highest in the first decade. Congenital glaucoma is seen in approximately one half of patients with SWS and presents in newborns with enlargement of the globe *(buphthalmos).* Patients occasionally develop glaucoma as adults. Thus continued vigilance is needed, even in patients with initially normal intraocular pressure.
- Angioma of the choroid occurs in 30% to 40% of patients with SWS and can lead to increased intraocular pressure. These lesions may be diffuse or localized within the retina.
- Episcleral and conjunctival lesions include anomalous vessels or true angiomata. These may be caused by increased venous pressure in the eye.
- Weber originally noted heterochromia of the iris. The more deeply pigmented iris usually is ipsilateral to the facial angioma. The pigmentation is caused by aggregated melanocytic hamartomata on the anterior surface of the iris.

NEUROLOGIC FEATURES

- The neurologic features of SWS are progressive and include seizures, focal neurologic deficits, and mental retardation. These disorders occur with variable severity. A small proportion of patients have no neurologic abnormalities.
- The reasons for neurologic progression are uncertain. A possible mechanism is hypoxic-ischemic injury to tissue adjacent to the leptomeningeal angioma. Other proposed mechanisms are venous occlusion and increased venous pressure.

SEIZURES:

1. Seizures occur in 80% of patients with SWS and are more common with bilateral than unilateral port-wine stains. Seizures may develop at any age, although they usually start in early childhood.
2. Seizures are often the first symptom to appear. Initially, seizures are typically focal but often become generalized tonic clonic. Less often, infantile spasms or myoclonic or atonic seizures are seen. The occurrence of seizures, the age at onset, and the response to treatment affect prognosis. Onset before age 1 yr and poor response to anticonvulsant therapy are associated with a greater likelihood of cognitive impairment.
   - Hemiparesis: often develops acutely in conjunction with the onset of seizures. The deficit occurs contralateral to the facial and intracranial lesions. The affected extremity usually does not grow at a normal rate, resulting in hemiatrophy. Some

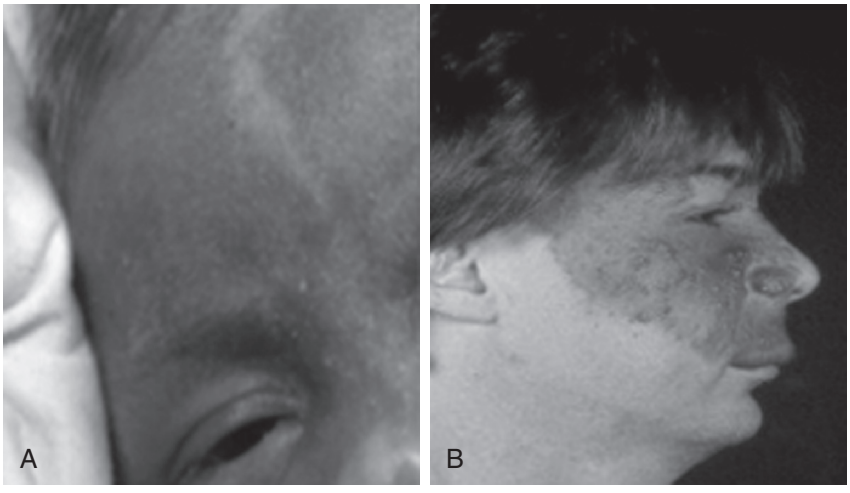


FIGURE ES1-80 Port-wine stain at different stages.

affected children have progressive loss of motor function or have a series of stroke-like events.
- Mental retardation: children with SWS typically develop normally for several months after birth, then manifest developmental delay. However, impairment can be obvious soon after birth, especially in infants with extensive brain involvement. Cognitive function is poorest in patients with bilateral intracerebral lesions. In one report, only 8% of patients with bilateral leptomeningeal angiomata were intellectually normal.
- Behavior problems: are more common in SWS patients than in their unaffected siblings. Higher risk for psychological problems is associated with poorer cognitive function and frequent seizures. However, behavior problems can occur in patients with normal intelligence.
- Other deficits: many patients have visual field defects, typically homonymous hemianopia. This is from the involvement of the leptomeningeal angioma with one or both occipital lobes or optic tracts. Hydrocephalus also may occur. This disorder is believed to result from increased venous pressure caused by thrombosis of the deep venous channels or extensive arteriovenous anastomoses.

ETIOLOGY

The Sturge-Weber syndrome and port-wine stains are caused by a somatic activating mutation in *GNAQ*.[1]

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Klippel-Trenaunay-Weber syndrome (extensive capillary angiomata associated with dysplastic veins involving the limbs and trunk, often with hypertrophy of the affected extremity)
- Von Hippel-Lindau disease (associated with capillary retinal angiomata in contrast to cavernous angiomata seen in SWS)

WORKUP

SWS should be suspected in all patients with facial capillary malformations involving the trigeminal dermatome. At-risk infants should undergo careful physical examination to determine the extent of the malformation.

IMAGING STUDIES

- Most children with facial port-wine stains without an intracranial lesion would be expected to develop normally. Therefore performing neuroimaging studies is helpful to provide prognostic information.
- Plain radiographs of the skull may detect intracranial calcifications, revealing the classic "tram line" appearance, but calcifications are often not present before age 2 yr. Newer radiographic techniques have made plain films obsolete.
- The preferred technique is MRI with gadolinium contrast, which demonstrates the presence of the leptomeningeal angioma and the extent of involvement with brain structures (Fig. ES1-81).
- If MRI is not readily available, cranial CT reliably identifies brain calcification and provides some anatomic information.
- In some cases leptomeningeal involvement may not be detected by neuroimaging during infancy and only becomes apparent later. There is no absolute way to exclude intracerebral lesions during the first year after birth.

Rx TREATMENT

No specific treatment exists for SWS. The cutaneous, ocular, and neurologic manifestations are treated with mixed success.

ACUTE GENERAL & CHRONIC Rx

Port-wine stain:
- Port-wine stains can be treated by selective photothermolysis with a pulsed-dye laser. Treatment can be further optimized for individual patients so that blanching of the lesion can be accomplished in the fewest possible sessions.
- The response of facial port-wine stains to laser treatment depends on the location and size of the lesion and the patient's age. The greatest decrease in size occurs in the smallest lesions and in the youngest children (<1 yr). The greater success in the youngest patients may reflect treatment before the development of ectasias.
- Complications of laser therapy include scarring and transient hyperpigmentation. Retinal injury can occur if the eyes are not shielded properly.

Glaucoma:
- The development of new medications has improved the medical management of glaucoma in SWS. However, topical treatment often is ineffective in normalizing intraocular pressure. In these cases, the surgical treatment depends on the etiology of the glaucoma.

Seizures:
- Management of seizures in SWS often is difficult. The success of controlling seizures with anticonvulsant medication is variable and unpredictable. Carbamazepine is the recommended antiepileptic of choice. In refractory cases, hemispherectomy or more limited surgical resection of epileptogenic tissue may be beneficial, although risks often outweigh benefits.

REFERRAL

- Initial ophthalmologic evaluation should be performed in the neonatal period because of the risk of congenital glaucoma.
- If the first complete ophthalmologic evaluation is normal, it should be repeated frequently (some authors have suggested quarterly evaluations) for the first 2 yr of life.
- If the examination results remain normal, the vision should be reevaluated at least annually throughout the patient's lifetime.
- Periodic evaluation by a pediatric neurologist is an essential component of the management of SWS.

PEARLS & CONSIDERATIONS

COMMENTS

- The prognosis for SWS depends on the extent of the leptomeningeal angioma and its effect on the perfusion of the cerebral cortex as well as the severity of ocular involvement.
- Prognosis also is affected by the age of onset of seizures and whether they can be controlled.
- Neurologic function may deteriorate with age. As a result, approximately half of affected adults are impaired, including those who initially were normal.

[1]Shirley MD et al: Sturge-Weber syndrome and port-wine stains caused by somatic mutation in GNAQ, *N Engl J Med* 368:1971-1979, 2013.

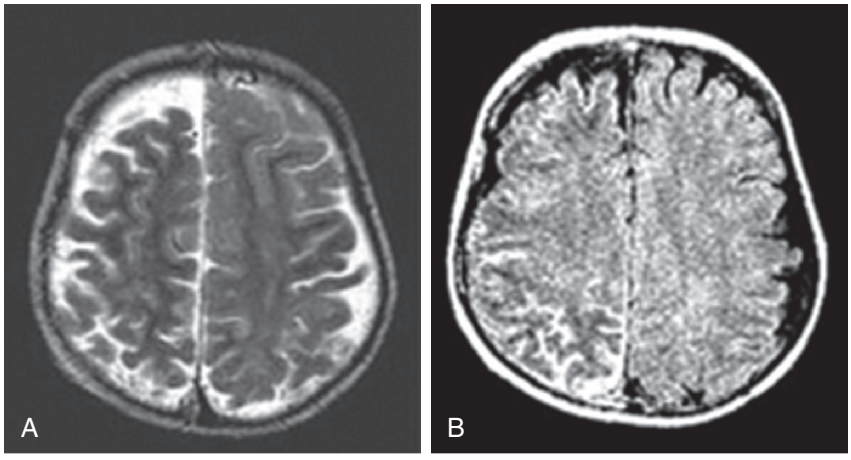


FIGURE ES1-81 Axial magnetic resonance image of child with Sturge-Weber syndrome demonstrating atrophy of the left hemisphere and contrast enhancement of the surface of the left hemisphere particularly prominent over the occipital lobe.

PATIENT & FAMILY EDUCATION

The Sturge-Weber Foundation is an active support group for patients and families (http://www.sturge-weber.com).

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **RUBY K. SATPATHY, M.D.**

SUGGESTED READINGS

Garzon MC et al.: Vascular malformations. Part II: associated syndromes, *J Am Acad Dermatol* 56(4):541, 2007.

Nathan N, Thaller SR: Sturge-Weber syndrome and associated congenital vascular disorders: a review, *J Craniofac Surg* 17(4):724, 2006.

BASIC INFORMATION

DEFINITION

Stuttering is a problem of speech fluency, usually starting in early childhood. Stuttered speech is broken by repetitions, prolongations or abnormal stoppages of sounds, syllables, or words.

SYNONYMS

Childhood-Onset Fluency Disorder

ICD-9CM and DSM-5 CODES
315.35 Childhood onset fluency disorder
ICD-10CM CODES
F80.81 Stuttering

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Approximately 5% of children have stuttered 6 months or more. About 1% of the population is affected by stuttering at any given time.
PREDOMINANT SEX AND AGE: During childhood, twice as many boys stutter as girls. More girls than boys outgrow stuttering, which results in four times as many men stuttering as women.
GENETICS: Studies show higher rates of stuttering within families of those who stutter and a higher concordance for stuttering in identical twins compared to fraternal twins.
RISK FACTORS: Presence of other speech or language disorder, family history of stuttering, onset after 3.5 years of age, male sex, and stuttering over 6 months in duration.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Stuttering usually presents between the ages of 2 and 5, when normal language development begins and children are transitioning from using simple phrases to more complex sentences. Stuttered speech is characterized by at least one of the following: repetitions (for for for example), prolongations (ffffffor example), interjections, broken words, audible or silent blocking, and circumlocutions (word substitutions to bypass difficult words).
- If stuttering is left untreated, it can lead to significant impairment in academic, social, and occupational spheres. Affected individuals show fear and embarrassment around speech and may avoid speaking in some situations. Compensatory maladaptive behaviors may also develop such as eyelid closing, involuntary movements, and some physical tension around the mouth during speech.
- Differentiating stuttering from normal developmental dysfluency is important. Normal dysfluency occurs in many children, is self-limited, and does not need treatment. It is characterized by occasional stuttering events (once every 10 sentences) and brief stuttering events (<0.5 second). The child does not seem concerned about the dysfluency and the disrupted speech tends to come and go based on whether the child is tired, excited, or talking about new or complex topics. Stuttering, in comparison, is defined by more frequent (>3% to 10% of speech) and longer stuttering events (>0.5 second). Also, the repetitions are greater in number ("for for for for for example" as opposed to "for for for example") and the prolongations are longer ("Forrrrrrrrrrrrrrrr example" as opposed to "Forrrrr example").

ETIOLOGY

- Findings in twin studies consistently demonstrate strong phenotype inheritance in identical twins.
- Researchers at present are utilizing genome-wide association study (GWAS) and functional genome-wide association study (fGWAS) techniques to better understand specific genetic variations that are associated with stuttering. One research group found that susceptibility to nonsyndromic stuttering is associated with variations in genes governing lysosomal metabolism. Another group found that variations in genes which govern zinc and glucose mitigated neurological functions are associated with stuttering. Findings from both research groups have not been confirmed or replicated by other groups.
- Stuttering might be related to abnormal elevations of cerebral dopamine activity.
- Brain imaging studies show distinct differences in sensorimotor integration centers in the brains of those who stutter compared to controls.
- Although parents do not cause their child's stuttering, a critical, impatient, or interrupting speech environment can lead to worsening stuttered speech.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Stuttering is classified as neurogenic, psychogenic, or developmental. Neurogenic stuttering can result from traumatic brain injuries (TBIs) or cerebrovascular accidents. Psychogenic stuttering is usually preceded by an emotional stressor. Those affected by psychogenic stuttering are usually not overly concerned about the dysfluency and their stuttering does not improve when singing or when reciting something in a chorus, as is the case in developmental stuttering. Developmental stuttering, known simply as stuttering, is the most common form and usually presents in the preschool years.

WORKUP

- The clinical interview should include assessment of symptoms (onset, context, quality, frequency, duration, etc.) and impact on academic, social, or occupational spheres. A developmental history and family history of stuttering should be obtained, as well as assessing for family discord or recent emotional stressors. One should also try to assess parental response to the child's stuttering (intrusive/critical/anxious vs. accepting/patient/calm).
- A full physical exam should be conducted with special attention to the mental status exam and neurologic exam.
- No laboratory tests or imaging studies are indicated unless neurogenic stuttering is suspected.
- Evaluation by an audiologist for a formal hearing assessment to rule out hearing loss or discrimination disorder may be beneficial in some cases.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Typically, the treatment of choice for stuttering is Speech and Language Therapy (SALT). Medications are not a first-line treatment.
- SALT consists of the following treatment modalities: fluency-shaping mechanisms, stuttering modification, delayed auditory feedback devices, and the Lidcombe approach (parental use of operant conditioning techniques).
- The above therapies help the child reduce fear about stuttering and produce speech more easily. The child is helped to speak slower and without increased physical tension and struggle. Families are encouraged to create an atmosphere of acceptance and calm for their child to speak and to model slower speech.

ACUTE GENERAL Rx

- There have been no large-scale pharmacologic treatment trials for stuttering. Smaller-scale trials and case studies have been conducted with a variety of agents, including clonidine, antipsychotics, and GABA-A partial agonists. Clonidine was found to be ineffective in reducing speech dysfluency. Weaker studies involving antipsychotic medications have found some positive effects, but almost all of these studies have serious methodologic problems and the associated side-effect profile makes using these agents for the long-term treatment of stuttering prohibitive. In some instances (e.g., a TBI patient with resulting neurogenic stuttering and psychosis), an antipsychotic might work well. A recent double-blind, randomized, placebo-controlled study of the GABA-A partial agonist pagoclone showed a modest reduction in speech dysfluency in adults.
- Case reports of deep brain stimulation of the ventral intermediate nucleus of the thalamus have shown some reduction in speech dysfluency in adults with severe stuttering.

DISPOSITION

Although the natural rate of recovery from stuttering is thought to be as high as 88%, evidence shows that the best treatment results occur when children are referred early.

REFERRAL

Those with severe stuttering should be referred immediately to a speech-language pathologist for further evaluation and treatment. Those with mild stuttering should be referred if stuttering continues for longer than 6 wk or if there is significant concern by the parent or child.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **JAMISON ROGERS, M.D.**

SUGGESTED READINGS

Boyd A et al.: Pharmacological agents for developmental stuttering in children and adolescents, *J Clin Psychopharmacol* 31(6):740–744, 2011.

Catalano G et al.: Olanzipine for the treatment of acquired neurogenic stuttering, *J Psychiatr Pract* 15(6):484–488, 2009.

Craig A et al.: Epidemiology of stuttering in the community across the entire life span, *J Speech Lang Hear Res* 45(6):1097–1105, 2002.

Guitar B et al. The child who stutters: to the pediatrician. ed 4 Stuttering Foundation of America: Memphis, TN.

Kang C et al.: Mutations in the lysosomal enzyme-targeting pathway and persistent stuttering, *N Engl J Med* 362:677, 2010.

Kraft SJ et al.: A novel approach to the identification of stuttering genes, Presented at the 7th World Congress of Fluency Disorders Tours, France, 2012.

Maguire GA et al.: Alleviating stuttering with pharmacological interventions, *Expert Opin Pharmacother* 5:1565–1571, 2004.

Maguire GA et al.: Alleviation of developmental stuttering following deep brain stimulation of the ventral intermediate nucleus of the thalamus, *Am J Psychiatry* 69(7):759–760, 2012.

Mansson H: Childhood stuttering: incidence and development, *J Fluency Disord* 25:47–57, 2000.

Prasse JE et al.: Stuttering: an overview, *Am Fam Physician* 77(9):1271–1276, 2008.

Suresh R et al.: New complexities in the genetics of stuttering: significant sex-specific linkage signals, *Am J Hum Genet* 78:554–563, 2006.

Yairi E: et ak:Epideniology of stuttering: 21st century advances, *J Fluency Disord* 38:66–87, 2013.

BASIC INFORMATION

DEFINITION

Subarachnoid hemorrhage (SAH) is defined as hemorrhage into the subarachnoid space. Box S1-13 describes the Hunt and Hess clinical classification of SAH.

SYNONYMS

Subarachnoid bleed

ICD-9CM CODES
430 Subarachnoid hemorrhage
ICD-10CM CODES
I60 Subarachnoid hemorrhage
I60.1 Subarachnoid hemorrhage from middle cerebral artery
I60.2 Subarachnoid hemorrhage from anterior communicating artery
I60.3 Subarachnoid hemorrhage from posterior communicating artery
I60.4 Subarachnoid hemorrhage from basilar artery
I60.5 Subarachnoid hemorrhage from vertebral artery
I60.7 Subarachnoid hemorrhage from intracranial artery, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: ~6 to 8 cases/100,000 persons per yr
PREDOMINANT SEX: Women aged >55 yr were found to have a 25% greater risk of developing SAH compared with men of the same age.
PREDOMINANT AGE: The mean age at onset is 55 yr.
PEAK INCIDENCE: Most aneurysmal SAH occurs in people who are between the ages of 55 and 60 yr.
GENETICS:
- First-degree relatives have a 5 to 12 times greater risk of developing SAH compared with the general population.
- Autosomal dominant polycystic kidney disease is known to be associated with cerebral aneurysms in 8% of cases; screening is recommended in families with this condition in which one family member has experienced a ruptured aneurysm.

RISK FACTORS: Although genetics seem to play a factor in SAH, lifestyle factors are more important for determining overall risk. These risk factors include smoking, hypertension, oral contraception, pregnancy, and amphetamine/cocaine use.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The primary symptom is a sudden, severe headache in 97% of cases. This is classically described as the "worst headache of my life" and also called a thunderclap headache. This headache may be associated with nausea/vomiting, neck pain, seizure, or loss of consciousness.
- 30% to 60% of patients report a history of sentinel bleeds with short-lasting headaches during the weeks before the hemorrhage.
- Altered mental status and coma may result from the direct effect (hemorrhagic mass effect), but more likely is the result of acutely increased intracranial pressure.
- A posterior communication aneurysm may cause third cranial nerve palsy.
- Table ES1-25 describes the World Federation of Neurologic Surgeons clinical classification of SAH.

ETIOLOGY

- Trauma is the most common cause of SAH; a ruptured aneurysm is the most common cause of spontaneous SAH (75%-80% of spontaneous SAH).
- Idiopathic SAH, also known as angiogram-negative SAH, accounts for 5% to 20% of spontaneous SAH. In these cases, no angiographic cause of the hemorrhage is found.
- Other causes of spontaneous SAH include arteriovenous malformations, bleeding into preexisting tumors, vasculitis, and cerebral artery dissection.
- Cocaine abuse, sickle cell anemia, coagulopathies, and pituitary apoplexy can also result in SAH.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Intracerebral hemorrhage as a result of trauma, tumors, and stroke with hemorrhagic conversion
- Other causes: thunderclap headaches such as idiopathic thunderclap headache, migraine headache, sexual headache, cough headache, exertional headache, secondary causes including, but not limited to, pituitary apoplexy or acute hydrocephalus

WORKUP

- Computed tomography (CT) of the head: shows hemorrhage in more than 95% of cases, especially during the acute phase (i.e., 24 to 48 hr) after the onset of bleeding. Box S1-14 describes the Fisher grade of SAH on initial CT. About 3%-5% of SAH may be missed on initial CT of the head.
- Lumbar puncture should be performed in all cases of suspected SAH with "normal CT of the head." The following suggest SAH:
  1. An RBC count of more than 100,000/m^3 in tubes 1 and 4.
  2. Presence of xanthochromia or bilirubin in the cerebrospinal fluid.
- CT angiogram or a cerebral angiogram is imperative for determining the origin of the SAH. Angiography may also be extremely useful, because it offers a therapeutic modality via the coil embolization of the aneurysm.

LABORATORY TESTS

- Basic laboratory values, including CBC, chemistry panel, prothrombin time, partial thromboplastin time, and platelet count
- Serum troponin and sodium levels are important to guide management; elevated troponins indicate cardiac ischemia and a poor outcome. Troponin may be elevated in acute SAH, but often reflects a sympathetic side effect on the myocardium rather than an ischemic myocardial infarction.
- Sodium levels should be monitored frequently and patients should be at least normonatremic. Patients with SAH are prone to developing cerebral salt wasting, resulting in hyponatremia.

BOX S1-13 Hunt and Hess Clinical Classification of Subarachnoid Hemorrhage

I	Asymptomatic or mild headache and neck stiffness
II	Moderate to severe headache and neck stiffness ± cranial nerve palsy
III	Mild focal deficit, lethargy, or confusion
IV	Stupor, moderate to severe hemiparesis
V	Deep coma, extensor posturing

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

BOX S1-14 Fisher Grade of Subarachnoid Hemorrhage on Initial Computed Tomography

1	No blood detected
2	Diffuse or vertical layers <1 mm thick
3	Localized subarachnoid clot and/or vertical layers ≥1 mm thick
4	Intraparenchymal or intraventricular clot with diffuse or no SAH
Modified Fisher CT Rating Scale	
1	Minimal or diffuse thin SAH without IVH
2	Minimal or thin SAH with IVH
3	Thick cisternal clot without IVH
4	Thick cisternal clot with IVH

CT, Computed tomography; *IVH,* intraventricular hemorrhage; *SAH,* subarachnoid hemorrhage.
From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

IMAGING STUDIES

- High-resolution CT scanning (Fig. S1-82) correctly identifies more than 95% of SAH cases, with blood appearing hyperdense in the subarachnoid spaces.
- Cerebral angiography is the gold standard for diagnosis.
- MRI is not a good imaging modality during the acute phase; however, its sensitivity increases after 4 to 7 days.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Patients with a depressed level of consciousness may need to be intubated and mechanically ventilated in an intensive care unit setting.
- A lumbar drain or a ventriculostomy is required for patients who develop hydrocephalus and increased intracranial pressure. It is also recommended for patients with Hunt and Hess grade 3 or higher.

ACUTE GENERAL Rx

- Critical care management: initial management strategies are geared toward stabilizing the patient and preventing rehemorrhage and hydrocephalus.
- Blood pressure control: tight blood pressure control is paramount, before securing the aneurysm to protect against rerupture. This can be done with the use of antihypertensive infusions (e.g., labetalol 5 to 10 mg IV over 2 minutes. Double the dose every 5 minutes to a max cumulative dose of 300 mg. Start infusion [0.5 to 2 mg/min] once systolic target is achieved.) or as-needed medications. A systolic blood pressure of 120 to 150 mm Hg is recommended. Placement of arterial line is recommended.
- Pain control: using short-acting and less-sedating medications (e.g., codeine, low-dose morphine).
- Seizures occur in about 3% of patients during the acute phase; use of prophylactic antiepileptics is controversial.
- Vasospasm: cerebral vasospasm is a dreaded complication leading to cerebral ischemia, disability, and death after SAH. It typically develops around day 4 to 14 (but may occur up to day 21) after the hemorrhage and reaches a peak on day 6 to 8. Treatment strategies include:
  1. "Triple H" therapy—*H*ypertension, *H*ypervolemia, and *H*emodilution—was originally described to maintain cerebral perfusion. However, its efficacy has been questioned in treating vasospasm. Rather, current medical therapy for vasospasm focuses upon hypertension, with typical mean arterial pressure goals of 90-100, and euvolemia instead of hypervolemia, as the latter was found to lead to significant cardiopulmonary and hemodynamic complications.
  2. Nimodipine: has been shown to improve outcomes if it is administered between days 4 and 21 after the hemorrhage, even if it does not significantly reduce the amount of vasospasm detected on angiography.
- In cases of aneurysmal SAH, treatment of the aneurysm is paramount, and focuses upon occlusion/exclusion of the aneurysm to prevent rebleeding. The most common treatment methods are:
  1. Microsurgical clipping: performed through a craniotomy by placing a clip around the neck of the aneurysm.
  2. Endovascular coiling: performed via intra-arterial angiography; it consists of deploying platinum coils inside the aneurysm to cause thrombosis of the aneurysmal sac.

CHRONIC Rx

- Management of reversible risk factors mentioned above (smoking, hypertension).
- Management of neurologic disability through physical therapy and rehabilitation.

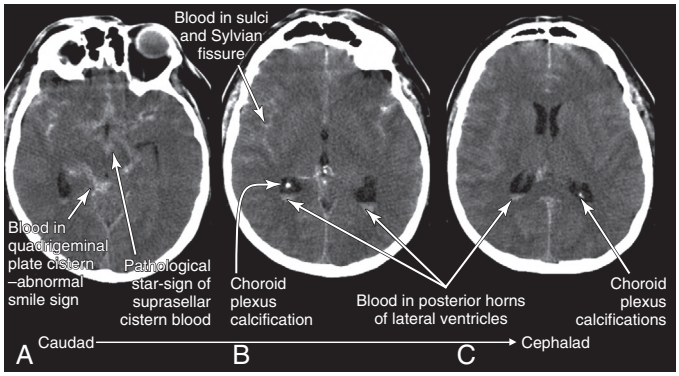


FIGURE S1-82 Subarachnoid hemorrhage (SAH), noncontrast CT, brain windows. Acute SAH appears white on noncontrast computed tomography (CT) brain windows. **A** through **C,** nonconsecutive axial slices, progressing from caudad to cephalad. In this case of diffuse SAH, note the presence of subarachnoid blood filling the sulci, as well as extending into the cisterns, Sylvian fissures, and even lateral ventricles. In **A,** blood *(white)* fills the suprasellar cistern. This star-shaped structure is normally filled with CSF *(black).* The quadrigeminal plate cistern is normally a smile-shaped black crescent, filled with CSF, but in this case is filled with blood. Extremely bright calcifications in the choroid plexus of the posterior horns of the lateral ventricles are common, normal findings—do not mistake these for hemorrhage. Note their similarity in density to bone of the calvarium. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

DISPOSITION

- SAH is often associated with a poor outcome with a death rate between 30% and 40%; 10% to 15% of patients die before they reach the hospital.
- Almost half of those who survive hospitalization have cognitive impairments that affect their lifestyles.

REFERRAL

Patients should be managed in a cerebrovascular center that maintains capacity to perform open surgical and endovascular procedures, with a critical care unit experienced in caring for neurosurgical patients.

PEARLS & CONSIDERATIONS

COMMENTS

- "Thunderclap" headaches should be considered SAH till proven otherwise and evaluated by CT of the head with/without LP.
- All SAH should be managed in a critical care setting (preferably neurocritical care unit) with neurosurgical care available.
- Measures to prevent rebleeding include adequate control of blood pressure and aneurysm treatment with the use of coiling or clipping.
- A recent multicenter cohort study[1] revealed that among patients presenting to the emergency department with acute nontraumatic headache that reached maximal intensity within 2 hr and who had normal neurologic findings, the Ottawa SAH rule was highly sensitive for identifying subarachnoid hemorrhage. Additional evaluation in implementation studies is required before this rule is applied in routine clinical care.

PREVENTION

Controlling some of the modifiable risk factors, including smoking and blood pressure, may help to decrease the risk of aneurysmal rupture.

PATIENT & FAMILY EDUCATION

- SAH is a devastating condition, with most survivors developing significant cognitive deficits. A good support system and an adequate physical and cognitive rehabilitation program may prove useful to survivors.
- Screening may be useful for patients with two or three first-degree relatives with SAH.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **WISSAM S. Z. ASFAHANI, M.D.**, and **JUSTIN F. FRASER, M.D.**

[1]Perry JJ et al: Clinical decision rules to rule out subarachnoid hemorrhage for acute headache, *JAMA* 310(12):1248-1255, 2013.

EVIDENCE

Abstract[1]

Purpose:
The aim of this guideline is to present current and comprehensive recommendations for the diagnosis and treatment of aneurysmal subarachnoid hemorrhage (aSAH).

Methods:
A formal literature search of MEDLINE (November 1, 2006, through May 1, 2010) was performed. Data were synthesized with the use of evidence tables. Writing group members met by teleconference to discuss data-derived recommendations. The American Heart Association Stroke Council's Levels of Evidence grading algorithm was used to grade each recommendation. The guideline draft was reviewed by 7 expert peer reviewers and by the members of the Stroke Council Leadership and Manuscript Oversight Committees. It is intended that this guideline be fully updated every 3 years.

Results:
Evidence-based guidelines are presented for the care of patients presenting with aSAH. The focus of the guideline was subdivided into incidence, risk factors, prevention, natural history and outcome, diagnosis, prevention of rebleeding, surgical and endovascular repair of ruptured aneurysms, systems of care, anesthetic management during repair, management of vasospasm and delayed cerebral ischemia, management of hydrocephalus, management of seizures, and management of medical complications.

Conclusions:
aSAH is a serious medical condition in which outcome can be dramatically impacted by early, aggressive, expert care. The guidelines offer a framework for goal-directed treatment of the patient with aSAH. Ⓐ

Abstract[2]

Objective:
To measure the sensitivity of modern third-generation computed tomography in emergency patients being evaluated for possible subarachnoid haemorrhage, especially when carried out within six hours of headache onset.

Design:
Prospective cohort study.

Setting:
11 tertiary care emergency departments across Canada, 2000-9.

Participants:
Neurologically intact adults with a new acute headache peaking in intensity within one hour of onset in whom a computed tomography was ordered by the treating physician to rule out subarachnoid haemorrhage.

Main Outcome Measures:
Subarachnoid haemorrhage was defined by any of subarachnoid blood on computed tomography, xanthochromia in cerebrospinal fluid, or any red blood cells in final tube of cerebrospinal fluid collected with positive results on cerebral angiography.

Results:
Of the 3132 patients enrolled (mean age 45.1, 2571 (82.1%) with worst headache ever), 240 had subarachnoid haemorrhage (7.7%). The sensitivity of computed tomography overall for subarachnoid haemorrhage was 92.9% (95% confidence interval 89.0% to 95.5%), the specificity was 100% (99.9% to 100%), the negative predictive value was 99.4% (99.1% to 99.6%), and the positive predictive value was 100% (98.3% to 100%). For the 953 patients scanned within six hours of headache onset, all 121 patients with subarachnoid haemorrhage were identified by computed tomography, yielding a sensitivity of 100% (97.0% to 100.0%), specificity of 100% (99.5% to 100%), negative predictive value of 100% (99.5% to 100%), and positive predictive value of 100% (96.9% to 100%).

Conclusion:
Modern third-generation computed tomography is extremely sensitive in identifying subarachnoid haemorrhage when it is carried out within six hours of headache onset and interpreted by a qualified radiologist. Ⓐ

Abstract[3]

Background:
In patients with aneurysmal subarachnoid hemorrhage (SAH), preliminary results indicate that the amplitude of the single intracranial pressure (ICP) wave is a better predictor of the early clinical state and 6-month outcome than the mean ICP.

Objective:
To perform a randomized and blinded single-center trial comparing the effect of mean ICP vs mean ICP wave amplitude (MWA)-guided intensive care management on early clinical state and outcome in patients with aneurysmal SAH.

Methods:
Patients were randomized to 2 different types of ICP management: maintenance of mean ICP less than 20 mmHg and MWA less than 5 mmHg. Early clinical state was assessed daily using the Glasgow Coma Scale. The primary efficacy variable was 12-month outcome in terms of the Rankin Stroke Score.

Results:
Ninety-seven patients were included in the study. There were no significant differences in treatment between the 2 groups apart from a larger volume of cerebrospinal fluid drained during week 1 in the MWA group. There was a tendency toward higher Glasgow Coma Scale scores in the MWA group during weeks 1 ($P = .08$) and 2 ($P = .07$). Outcome in terms of Rankin Stroke Score at 12 months was significantly better in the MWA group ($P<.05$).

Conclusions:
This randomized and blinded trial disclosed a significant better primary efficacy variable (Rankin Stroke Score after 12 months) in the MWA patient group. We suggest that proactive intensive care management with MWA-tailored cerebrospinal fluid drainage during the first week improves aneurysmal SAH outcome. Ⓐ

Evidence-Based References

[1] Connolly ES Jr et al.: Guidelines for the management of aneurysmal subarachnoid hemorrhage: a guideline for healthcare professiionals from the American Heart Association/American Stroke Association, *Stroke* 43(6):1711–1737, 2012. Ⓐ

[2] Perry JJ et al.: Sensitivity of computed tomography performed within six hours of onset of headache for diagnosis of subarachnoid haemorrhage: prospective cohort study, *BMJ 343 d4277*, 2011. Ⓐ

[3] Eide PK et al.: A randomized and blinded single-center trial comparing the effect of intracranial pressure and intracranial pressure wave amplitude-guided intensive care management on early clinical state and 12-month outcome in patients with aneurysmal subarachnoid hemorrhage, *Neurosurgery* 89:1105–1115, 2011. Ⓐ

SUGGESTED READINGS

Edlow JA: Diagnosis of subarachnoid hemorrhage, *Neurocrit Care* 2(2):99, 2005.

Rinkel GJE et al.: Calcium antagonists for aneurysmal subarachnoid haemorrhage, *Cochrane Database Syst Rev* 1:CD000277, 2005.

Rinkel GJE et al.: Circulatory volume expansion therapy for aneurysmal subarachnoid haemorrhage, *Cochrane Database Syst Rev* 4:CD000483, 2004.

Van der Schaaf I et al.: Endovascular coiling versus neurosurgical clipping for patients with aneurysmal subarachnoid haemorrhage, *Cochrane Database Syst Rev* 4:CD003085, 2005.

Van Gijn J et al.: Subarachnoid hemorrhage, *Lancet* 369:306–318, 2007.

TABLE ES1-25 World Federation of Neurologic Surgeons Clinical Classification of Subarachnoid Hemorrhage

Grade	Glasgow Coma Scale	Motor Deficits
I	15	Absent
II	13-14	Absent
III	13-14	Present
IV	7-12	Present or absent
V	3-6	Present or absent

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

Subclavian Steal Syndrome

BASIC INFORMATION

DEFINITION

Subclavian steal syndrome is an occlusion or severe stenosis of the proximal subclavian artery leading to decreased antegrade flow or retrograde flow in the ipsilateral vertebral artery and neurologic symptoms referable to the posterior circulation.

SYNONYMS

Proximal subclavian (or innominate) artery stenosis or occlusion

ICD-9CM CODES
435.2 Subclavian steal syndrome
ICD-10CM CODES
G45.8 Other transient cerebral ischemic attacks and related syndromes

EPIDEMIOLOGY & DEMOGRAPHICS

- Similar to that of other manifestations of atherosclerosis (coronary artery disease, cerebrovascular disease, or peripheral vascular disease)
- Affects middle-aged persons (men somewhat younger than women on average) with arteriosclerotic risk factors, including family history, smoking, diabetes mellitus, hyperlipidemia, hypertension, and sedentary lifestyle

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms:
- Many patients are asymptomatic.
- Upper-extremity ischemic symptoms: fatigue, exercise-related aching, coolness, numbness of the involved upper extremity.
- Neurologic symptoms are reported by 25% of patients with known unilateral subclavian steal. These include brief spells of:
  1. Vertigo
  2. Diplopia
  3. Decreased vision
  4. Oscillopsia
  5. Gait unsteadiness

These spells are only occasionally provoked by exercising the ischemic upper extremity (classic subclavian steal). Left subclavian steal is more common than right, but the latter is more serious.
- Posterior circulation stroke related to subclavian steal is rare.
- Innominate artery stenosis can cause decreased right carotid artery flow and cerebrovascular symptoms of the anterior cerebral circulation, but this is uncommon.

Physical findings:
- Delayed and smaller volume pulse (wrist or antecubital) in the affected upper extremity
- Lower blood pressure in the affected upper extremity
- Supraclavicular bruit

NOTE: Inflating a blood pressure cuff will increase the bruit if it originates from a vertebral artery stenosis and decrease the bruit if it originates from a subclavian artery stenosis.

ETIOLOGY & PATHOGENESIS

Etiology:
- Atherosclerosis
- Arteritis (Takayasu's disease and temporal arteritis)
- Embolism to the subclavian or innominate artery
- Cervical rib
- Long-term use of a crutch
- Occupational (baseball pitchers and cricket bowlers)

Pathogenesis: the vertebral artery originates from the subclavian artery. For subclavian steal to occur, the occlusion must be proximal to the takeoff of the vertebral artery. On the right side, only a small distance separates the bifurcation of the innominate artery and the takeoff of the vertebral artery, explaining why the condition occurs less commonly on the right side. Occlusion of the innominate artery must affect right carotid artery flow.

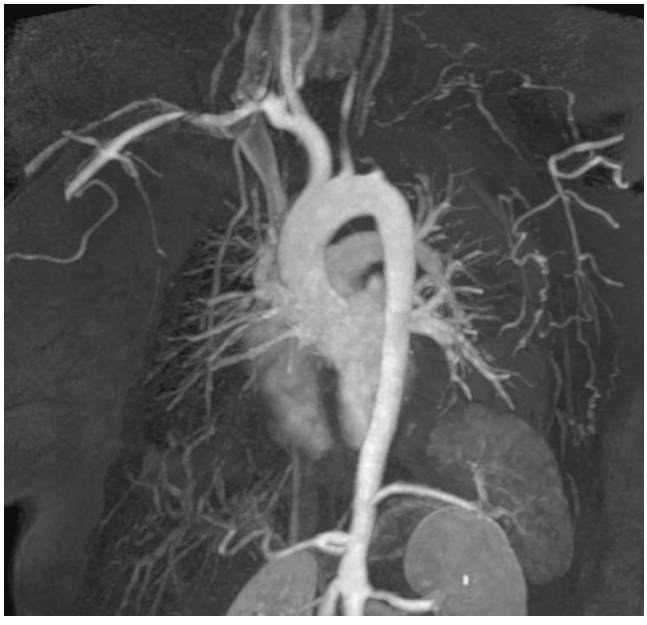


FIGURE S1-83 Magnetic resonance arteriogram demonstrating diffuse moderate stenosis of the proximal left common carotid and proximal occlusion of the left subclavian artery coming off the aortic arch with development of an extensive collateral network. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

DIAGNOSIS

The carotid arteries should be evaluated at least noninvasively in all cases.

DIFFERENTIAL DIAGNOSIS

- Posterior circulation transient ischemic attack or stroke
- Upper-extremity ischemia
  1. Distal subclavian artery stenosis or occlusion
  2. Raynaud's syndrome
  3. Thoracic outlet syndrome

WORKUP

- Noninvasive upper-extremity arterial flow studies
- Doppler sonography of the vertebral, subclavian, and innominate arteries
- Arteriography, magnetic resonance arteriogram (Fig. S1-83)

TREATMENT

- In most patients the disease is benign and requires no treatment other than atherosclerosis risk factor modification and aspirin. Symptoms tend to improve over time as collateral circulation develops.
- Vascular surgical reconstruction requires a thoracotomy; it may be indicated in innominate artery stenosis or when upper-extremity ischemia is incapacitating.

AUTHOR: **FRED F. FERRI, M.D.**

BASIC INFORMATION

DEFINITION

A subdural hematoma (SDH) is a collection of blood or blood products between the arachnoidal (superficial) layer of the brain and the dura or meningeal layer of the brain. Subdural hematomas can be acute (ASDH) or chronic (CSDH).

SYNONYMS

Subdural hemorrhage

ICD-9CM CODES
852.10 Subdural hematoma
ICD-10CM CODES
S06.5 Traumatic subdural hemorrhage

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE
- The exact incidence of ASDH is unknown, but it is very common in trauma patients.
- CSDH is most common in the elderly with an incidence of 1.72 to 13.1 per 100,000.
- Patients on warfarin have a reported incidence between 21% and 36%.

PREVALENCE: Unknown

PREDOMINANT AGE AND SEX
- Patients with cerebral atrophy such as the elderly (>70 yr) and alcoholic populations
- Infant population (e.g., shaken baby)

RISK FACTORS
- Trauma and antithrombotic therapy are the most common risk factors for ASDH and CSDH.
- Brain atrophy secondary to advanced age and alcoholism are common risk factors, especially with the coagulopathy seen in chronic alcoholics.
- Intracranial hypotension associated with CSF shunts or leaks is uncommon but important.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Symptoms vary on the basis of acuity, size, and location. Acute traumatic SDHs are often seen in comatose patients. When associated with a midline shift (i.e., >5 mm), they can cause signs of cerebral herniation (e.g., ipsilateral pupil dilation, contralateral weakness) requiring prompt surgical evacuation.
- Patients with CSDH may present with diverse nonspecific symptoms such as headaches, confusion, aphasia, hemiparesis, TIA-like symptoms, and seizures.

ETIOLOGY

SDH is usually the result of shearing and tearing of a bridging vein between the brain parenchyma and the dura mater. Other causes of bleeding into the subdural space include contusion, extension of parenchymal hemorrhage, rarely other vascular abnormalities (e.g., AV malformation, aneurysm, dural AV fistula).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Other causes of subdural collections, such as hygromas, abscesses, and tumor infiltrations

WORKUP

- Clinical assessment: patient history, including medications with anticoagulant properties, alcohol abuse, trauma, cancer, and recent bacterial infections
- Physical examination, including alertness, pupil and facial symmetry, and motor weakness (i.e., pronator drift)
- Noncontrast CT scan of the head

LABORATORY TESTS

Assessment of the patient's coagulation status including CBC with platelet count, prothrombin time, partial thromboplastin time and liver function test (especially with a history of alcoholism or liver failure)

IMAGING STUDIES

CT scan of the head (Fig. S1-84): demonstrates the classic crescentic collection between the brain and inner table. For comatose and trauma patients, include a cervical spine CT scan. ASDH is usually hyperdense, whereas a CSDH is usually hypodense on noncontrast CT. Contrast is only needed if there are concerns about tumor or infection.

TREATMENT

- Correction of underlying coagulopathy, if present (e.g., Coumadin reversal)
- The majority of SDH can be managed without surgery in awake patients with normal neurologic examinations.

NONPHARMACOLOGIC THERAPY

Surgical treatment is indicated in:
- All ASDHs measuring >10 mm in thickness with a midline shift >5 mm on CT scan should be evacuated.
- CSDH with a mass effect, a clear change in the neurologic examination from baseline, or enlargement of the hematoma size, evacuation via craniotomy or burr hole should be considered.

DISPOSITION

Depending on the size and location of the SDH and the examination of the patient, observation can range from the ICU to outpatient management. When observation of the patient is considered, clinical examinations should be serially performed. Patient baseline and follow-up clinical examinations are more important than CT scan findings.

REFERRAL

Neurosurgical and operative consultation should be made available.

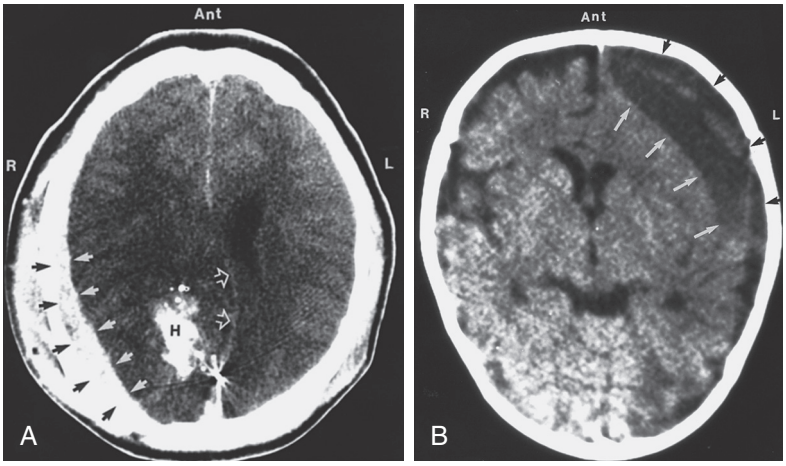


FIGURE S1-84 A, Noncontrast CT scan of an acute subdural hematoma shows a crescentic area of increased density in the right posterior parietal region between the brain and the skull *(black and white arrows).* An area of intraparenchymal hemorrhage *(H)* is also seen. **B,** A chronic subdural hematoma for a different patient is shown. There is an area of decreased density in the left frontoparietal region *(arrows)* that effaces the sulci, compresses the anterior horn of the left lateral ventricle, and shifts the midline somewhat to the right. (From Mettler FA [ed]: *Primary care radiology,* Philadelphia, 2000, Saunders.)

PEARLS & CONSIDERATIONS

COMMENTS

- Many elderly patients have small CSDHs or hygromas. Unless these are associated with seizures or clinical or radiographic progression, they are usually not emergent. The important thing is to recognize the cause (e.g., medication, fall risk).
- Recurrence after surgical management for CSDH is common.
- SDHs in elderly patients can have a mixed hyperdense and hypodense appearance on noncontrast CT scan; this is suggestive of acute and chronic components.

PATIENT & FAMILY EDUCATION

Individuals with SDHs are at higher risk for seizure, so surveillance is important.

RELATED CONTENT

Subdural Hematoma (Patient Information)

AUTHOR: **WISSAM S. Z. ASFAHANI, M.D**.

BASIC INFORMATION

DEFINITION

CDC defines suicide and suicidal behavior as:

- Suicide

Death caused by self-directed injurious behavior with any intent to die as a result of the behavior.

- Suicide attempt

A nonfatal self-directed potentially injurious behavior with any intent to die as a result of the behavior. A suicide attempt may or may not result in injury.

- Suicidal ideation

Thinking about, considering, or planning for suicide.

SYNONYMS

Self-murder

ICD-9CM CODES
Categorized by method
ICD-10CM CODES

X70	Intentional self-harm by hanging, strangulation and suffocation
X71	Intentional self-harm by drowning and submersion
X72	Intentional self-harm by handgun discharge
X75	Intentional self-harm by explosive material
X76	Intentional self-harm by smoke, fire and flames
X78	Intentional self-harm by sharp object
X81	Intentional self-harm by jumping or lying before moving object
X83	Intentional self-harm by other specific means
X64	Intentional self-poisoning by an exposure to other and unspecified drugs, medicaments, and biological substances

EPIDEMIOLOGY & DEMOGRAPHICS

Suicide was the tenth leading cause of death for all ages in 2010. There were 38,364 suicides in 2010 in the United States—an average of 105 each day.

SUICIDE RESULTS IN AN ESTIMATED $34.6 BILLION IN COMBINED MEDICAL AND WORK LOSS COSTS

Analysis report indicates that the annual age adjusted suicide rate among persons aged 35-64 increased 28.4% from 13.7 per 100, 000 population in 1999 to 17.6 in 2010 (CDC, 2014).

Mortality (CDC, 2009 data)

All suicides

- Number of deaths: 36,891 (2009, CDC)
- Deaths per 100,000 population: 11.5
- Cause of death rank: 10th leading cause of death in 2009

Firearm suicides

- Number of deaths: 17,352
- Deaths per 100,000 population: 5.8

Suffocation suicides

- Number of deaths: 8161
- Deaths per 100,000 population: 2.7

Poisoning suicides

- Number of deaths: 6358
- Deaths per 100,000 population: 2.1

Suicidal deaths are only part of the problem. More people survive suicide attempts than actually die. They are often seriously injured and need medical care.

AGE-RELATED DATA

- Incidence of suicide increases with age (13.1 cases/100,000 persons ages 15 to 24 yr, 16.9 cases/100,000 persons ages 65 to 74 yr, and 23.5 cases/100,000 persons ages 75 to 84 yr)
- During 2002 to 2006, the greatest percentage of suicides occurred by firearm among all race/ethnicity groups for persons ages 65 yr and older. Except for Asian/Pacific Islanders, suffocation accounted for the highest percentage of suicides among those 65 yr and older (52.6%).

GENDER DIFFERENCES

- Women attempt suicide about two to three times as often as men.
- Males succeed at taking their own lives at nearly four times the rate of females and represent 79% of all U.S. suicides.
- Suicide is the seventh leading cause of death for males and sixteenth leading cause for females.
- Firearms are the most common method of suicide among males (56%).
- Poisoning is the most common method in women (40.3%).

ENVIRONMENTAL FACTORS

- Suicide rates traditionally decrease in times of war and increase in times of economic crises.
- After adjusting for age, suicide rates are highest in the western and northwestern regions of the United States.

MARITAL STATUS: Suicide rates are highest among the divorced, separated, and widowed and lowest among the married.

SUBSTANCE USE: CDC data: 33.3% of suicides tested positive for alcohol and 16.4% for opiates.

RISK FACTORS (Table ES1-26)

- Previous suicide attempt(s).
- History of depression or other mental illness (bipolar, psychosis, PTSD, and others).
- Anxiety.
- Alcohol or drug abuse.
- Family history of suicide or violence.
- Physical illness. Patients who have recently received a cancer diagnosis have increased risk of suicide.
- Feeling alone.
- Individuals with a mental or substance use disorder account for >90% of suicides.
- Access to firearms is associated with risk for completed suicide
- The concurrence of more than one condition (e.g., depression and alcohol abuse) greatly increases the risk.
- Hopelessness is a strong predictor of suicide potential.
- Rates are higher in developing countries.
- Rates vary by occupation, ethnicity, and employment status.

PROTECTIVE FACTORS (CDC)

- Effective clinical care for mental, physical, and substance abuse disorders
- Easy access to a variety of clinical interventions and support for help seeking

TABLE ES1-26 Suicide and Risk Factors: A Summary

Primary Diagnosis	Demographics	Personality Factors	Comorbidities	Social Factors	Other Factors
Bipolar	Male	Borderline	Substance abuse	Divorced	Means available
Schizophrenia	Older age	Narcissistic	Panic disorder	Widower	History of child abuse
Major depressive disorder	White race	Antisocial	Anxiety	Lives alone	Few reasons to live
Dysthymia	Homosexuality	Conduct disorder	Axis III dx	Isolated	Lots of adverse events
Adjustment disorder	History of attempt	Impulsive		Money worries	Change in grades
Conduct disorder	Family history			Other losses	Change in friends
Psychosis	Suicidal ideas			No religion	Giving things away
	Hopeless				Guns in the home
	Helpless				

From Sadock BJ et al: *Kaplan & Sadock's comprehensive textbook of psychiatry,* ed 9, Philadelphia, 2009, Wolters Kluwer Health/Lippincott Williams & Wilkins.

- Family and community support (connectedness). Men who are socially well-integrated have a more than two-fold reduced risk for suicide.
- Support from ongoing medical and mental health care relationships
- Skills in problem solving, conflict resolution, and nonviolent ways of handling disputes
- Cultural and religious beliefs that discourage suicide and support instincts for self-preservation

SUICIDAL BEHAVIOR

- All suicidal behavior should be taken seriously, as a failed attempt may lead to a completed suicide in the future.
- Nearly half of suicides are preceded by an attempt that does not end in death.
- Those with a history of attempts are 23 times more likely to eventually end their own lives than those without.
- A suicidal gesture does not have death as a goal, but can serve as a dramatic way of alerting others to some type of ongoing distress.
- Risky behaviors such as speeding or disregarding traffic laws, or abusing drugs, are considered parasuicide when the person shows total disregard for whether the actions might result in his or her death.
- Unsuccessful suicide attempts may also result from miscalculations in the plan. These people are at high risk for attempting suicide again.

EVALUATION

- The provider must directly inquire into the presence of suicidal ideation. Approximately one half to two thirds of individuals who commit suicide visit physicians within 1 mo of taking their lives.
- Explicit suicidal intent, hopelessness, and a well-formulated plan indicate high risk. Clinicians can use the mnemonic SAL: Is the method **s**pecific? Is it **a**vailable? Is it **l**ethal?
- The concurrence of multiple psychiatric problems, substance abuse, and multiple physical problems increases the risk.
- Covert suicidal ideation occurs in patients primarily with multiple vague physical complaints, depression, anxiety, or substance abuse.
- Primary care-feasible screening tools might help to identify some adults at increased risk for suicide but have limited ability to detect suicide risk in adolescents. Psychotherapy may reduce suicide attempts in some high-risk adults, but effective interventions for high-risk adolescents are not yet proven.

ACUTE INTERVENTIONS

- Place patient in a safe environment (usually hospitalization in a psychiatric unit or a medical unit with continuous observation).
- Emergency medical stabilization and clearance as required, related to severity and lethality of attempt, age, comorbid medical issues, and overall clinical presentation.

ACUTE PSYCHOPHARMACOLOGIC INTERVENTIONS

- Benzodiazepines may be useful in reducing extreme anxiety and dysphoria in an acutely suicidal patient; however, these agents should not be prescribed until the means of the suicidal attempt are known (not a benzodiazepine overdose) and patient is medically stable (i.e., respiratory system, vital signs, cognitive functioning are stable).
- Antipsychotics (typicals or atypicals) can be used if psychosis is present (e.g., voices telling patient to hurt self) and to manage acute agitation.
- If indicated, mood stabilizers and antidepressants can be started in the acute setting but may have up to a 2-wk latency period. However, awareness of increased risk of suicidal thoughts/behavior with these medications in some populations is required.

THERAPY

- Long-term: psychotherapy aimed at factors that underlie the decision to pursue suicide or at the risk factors contributing to suicidal behavior
- Substance abuse treatment (e.g., Alcoholics Anonymous, Narcotics Anonymous) when substance use disorder is present
- Therapy should be aimed at the underlying condition (e.g., antidepressants for depression, anxiolytics or antidepressants for anxiety, substance abuse treatment, or psychotherapy for chronic low self-esteem, hopelessness).
- In elderly, loneliness and medical disability are major reasons for suicide and therefore major targets for intervention.
- Involvement of family members, spouse, loved one, caregivers if possible for therapy and management.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **ALI KAZIM, M.D.**

EVIDENCE

Abstract[1]

Objective:

The authors assessed whether clinical and psychosocial factors in depressed adolescents at baseline predict suicide attempts and nonsuicidal self-injury over 28 weeks of follow-up.

Method:

Participants were 164 adolescents with major depressive disorder taking part in the Adolescent Depression Antidepressants and Psychotherapy Trial (ADAPT). Clinical symptoms, family function, quality of current personal friendships, and suicidal and nonsuicidal self-harm were assessed at baseline. Suicidal and nonsuicidal self-harm thoughts and behaviors were assessed during 28 weeks of follow-up.

Results:

High suicidality, non-suicidal self-injury, and poor family function at entry were significant independent predictors of suicide attempts over the 28 weeks of follow-up. Non-suicidal self-injury over the follow-up period was independently predicted by non-suicidal self-injury, hopelessness, anxiety disorder, and being younger and female at entry.

Conclusions:

Both suicidal and nonsuicidal self-harm persisted in depressed adolescents receiving treatment in the ADAPT study. A history of nonsuicidal self-injury prior to treatment is a clinical marker for subsequent suicide attempts and should be as carefully assessed in depressed youths as current suicidal intent and behavior. Ⓐ

Evidence-Based Reference

Wilkinson P et al.: Clinical and psychosocial predictors of suicide attempts and nonsuicidal self-injury in the Adolescent Depression Antidepressants and Psychotherapy Trial (ADAPT), *Am J Psychiatry* 168:495–501, 2011. Ⓐ

SUGGESTED READINGS

Adams SM et al.: Pharmacologic management of adult depression, *Am Fam Physician* 77(6):785, 2008.

American Association of Suicidology, website. www.suicidology.org.

Anglemyer A et al.: The accessibility of firearms and risk for suicide and homicide victimization among household members, *Ann Int Med* 160:101–110, 2014.

CDC Morbidity and Mortality Weekly Report: *CDC; National Center for Injury prevention and Control, Division of Violence Prevention*, August 2014.

Centers for Disease Control and Prevention (CDC). Web Based Injury Statistics Query and Reporting System (WISQARS). National Center for Injury Prevention and Control: Atlanta, GA.

Fang F et al.: Suicide and cardiovascular death after a cancer diagnosis, *N Engl J Med* 366:1310–1318, 2012.

Feldman MD et al.: Let's not talk about it: suicide inquiry in primary care, *Ann Fam Med* 5(5):412, 2007.

Forsuicidesurvivors.com website

Goldman SJ et al.: Suicide attempt in young people: a signal for long-term health care and social needs, *JAMA Psychiatry* 71(2):119-127, 2014.

Hawton K, van Heeringen K: *Suicide. Lancet* 373(9672):1372–1381, 2009.

Horowitz L et al.: Ask suicide-screening questions to everyone in medical settings: the asq'em quality improvement project, *Psychosomatics* 54(3):239–247, 2013.

Horowitz L et al.: Ask suicide-screening questions (ASQ), a brief instrument for the Pediatric Emergency Department, *Arch Pediatr Adolesc Med* 166(12):1170–1176, 2012.

McDowell AK et al.: Practical suicide-risk management for the busy primary care physician, *Mayo Clin Proc* 86(8):792–800, 2011.

Norris D, Clark M: Evaluation and treatment of the suicidal patient, *Am Fam Physician* 85(6):602–605, 2012.

O'Connor E et al.: Screening for and treatment of suicide risk relevant to primary care: a systematic review for the U.S. Preventive Services Task Force, *Ann Int Med* 158:741–754, 2013.

Sadock BJ et al.: Kaplan & Sadock's comprehensive textbook of psychiatry, ed 9, Wolters KluwerHealth/Lippincott Williams & Wilkins: Philadelphia.

Tsai A, et al.: Social integration and suicide mortality among men: 24-year cohort study of U.S. Health Professionals, *Ann Intern Med* 161:85–95, 2014.

BASIC INFORMATION

DEFINITION

Superior vena cava (SVC) syndrome is a set of symptoms that results when a mediastinal mass compresses the SVC or the veins that drain into it, resulting in obstruction of blood flow from the head, neck, upper torso, or extremities to the right atrium.

ICD-9CM CODES
453.2 Vena cava thrombosis
ICD-10CM CODES
I87.1 Compression of vein

EPIDEMIOLOGY & DEMOGRAPHICS

- SVC syndrome occurs in 15,000 persons in the United States every year.
- More than 50% of patients present with SVC at the initial manifestation of a previously undiagnosed malignancy.
- Mirrors lung cancer (especially small cell carcinoma) and lymphoma (see "Lung Neoplasm" and "Lymphoma" in Section I).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The pathophysiology of the syndrome involves the increased pressure in the venous system draining into the SVC, producing edema of the head, neck, and upper extremities. Symptoms develop over a period of 2 wk in one third of patients and include:

- Shortness of breath
- Chest pain
- Cough
- Dysphagia, hoarseness, stridor
- Headache
- Syncope
- Visual trouble

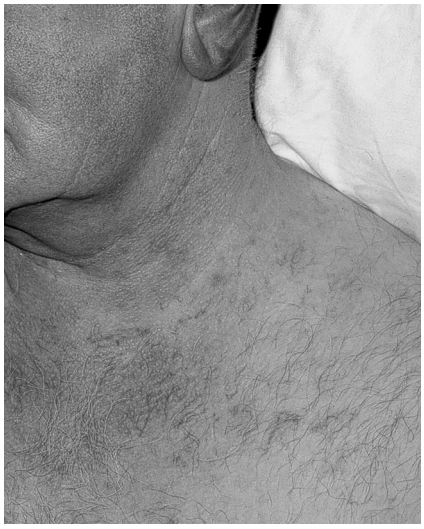


FIGURE S1-85 Superior vena cava obstruction causing dilated veins and plethora of the upper trunk and neck in a patient with bronchial carcinoma. Patients with superior vena cava obstruction are occasionally referred to dermatologists with suspected contact allergy (eyelid swelling) or angioedema (facial or hand swelling). (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text*, ed 2, St Louis, 2006, Mosby.)

Signs:

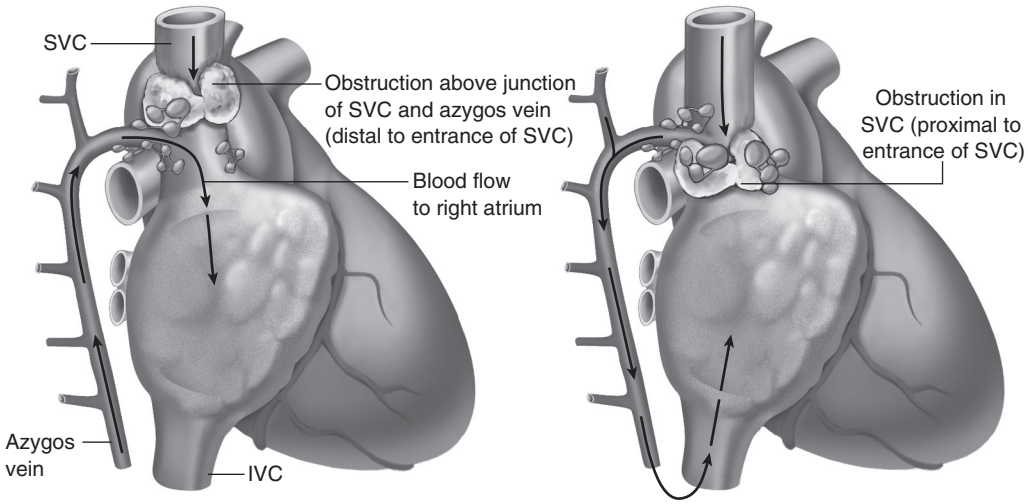
- Chest wall vein distention (Fig. S1-85)
- Neck vein distention
- Facial edema, facial plethora
- Upper-extremity swelling
- Cyanosis

ETIOLOGY

- Lung cancer (65% of all cases, of which half are small cell lung cancer)
- Lymphoma (15%)
- Thymoma
- Tuberculosis
- Goiter
- Aortic aneurysm (arteriosclerotic or syphilitic)
- SVC thrombosis
  1. Primary: associated with a central venous catheter
  2. Secondary: as a complication of SVC syndrome associated with one of the abovementioned causes
- Inflammatory process, fibrosing mediastinitis
- Fig. S1-86 illustrates the anatomy of superior vena cava syndrome. Table S1-27 summarizes common malignancies associated with SVC syndrome in adults.

DIAGNOSIS

CT scan of the chest with contrast (Fig. S1-87) is the most useful diagnostic study. MRI is usually adequate to establish the diagnosis of SVC obstruction and to assist in the differential diagnosis of probable cause.



Manifestations of supra-azygos SVC obstruction

- Distended arm and neck veins
- Edema of neck, face, and arms
- Congested mucous membranes (mouth)
- Dilated, tortuous vessels on upper chest and back

A

Manifestations of infra-azygos SVC obstruction

- More severe symptoms but all of the features for obstruction distal to entrance of SVC
- Dilation of collateral vessels on anterior and posterior abdominal wall with downward blood flow into IVC, then back to heart

B

FIGURE S1-86 Anatomy of superior vena cava (SVC) syndrome. Lymph nodes may obstruct blood return above the entrance of the azygos vein **(A)**, resulting in edema of the face, neck, and arms and distended veins in the neck and arms and over the upper chest. Obstruction below the return of the azygos vein **(B)** results in retrograde flow through the azygos through collateral veins to the inferior vena cava (IVC), with all the symptoms and signs in **A** plus dilation of the veins over the abdomen as well. (Modified from Skatin AT (ed): *Atlas of diagnostic oncology,* ed 3, Philadelphia, 2003, Elsevier.)

TABLE S1-27 Malignancies Associated with Superior Vena Cava (SVC) Syndrome in Adults*

Neoplastic Diagnosis	Percentage of SVC	Percentage of Disease-Associated SVC
Lung cancer, stage 3B or 4:	48-81	
Small cell lung cancer		15-45
Squamous cell cancer		20-25
Adenocarcinoma		5-25
Large cell carcinoma		4-30
Lymphoma:	2-21	
Diffuse large cell lymphoma		64
Lymphoblastic lymphoma		33
Breast cancer	11	

*Include lung cancer, lymphomas, and metastases from other solid tumors. 75% to 85% of patients with SVC have neoplastic disease.

From Zipes DP et al (eds): *Braunwald's heart disease,* ed 7, Philadelphia, 2005, Saunders.

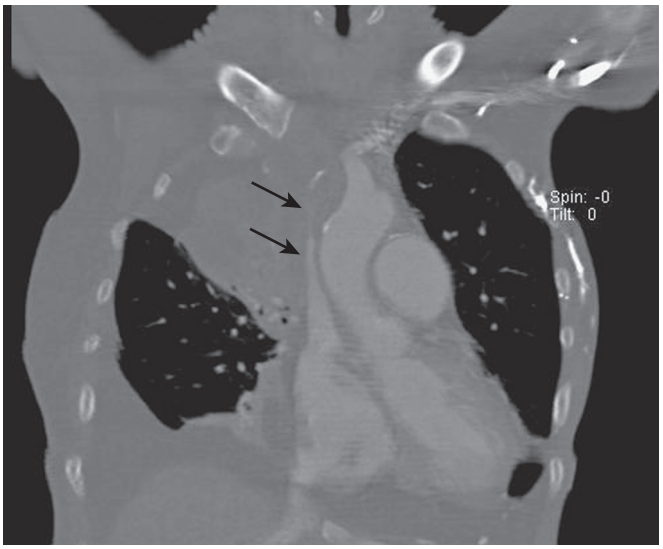


FIGURE S1-87 Computed tomography scan showing blockage of the superior vena cava *(arrows).* (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

DIFFERENTIAL DIAGNOSIS

The syndrome is characteristic enough to exclude other diagnoses. The differential diagnosis concerns the underlying etiologies listed above.

WORKUP

- Chest radiograph (mediastinal widening, pleural effusion)
- Chest CT with contrast or MRI (in patient who cannot tolerate contrast medium)
- Venography: warranted only when an intervention (e.g., stent or surgery) is planned
- Percutaneous needle biopsy or mediastinoscopy are usually the initial diagnostic modalities used to establish a histologic diagnosis

Rx TREATMENT

- Although invasive procedures such as mediastinoscopy are associated with higher than usual risk of bleeding, a tissue diagnosis is usually needed before commencing therapy.
- Management is guided by the severity of the symptoms and the underlying etiology.
- Emergency empiric radiation is indicated in critical situations such as respiratory failure or central nervous system signs associated with increased intracranial pressure.
- Treatment of the underlying malignancy:
  1. Radiotherapy: the majority of tumors causing SVC syndrome are sensitive to radiotherapy
  2. Systemic chemotherapy
- Anticoagulant or fibrinolytic therapy in patients who do not respond to cancer treatment within a week or if an obstructing thrombus has been documented.
- Loop diuretics are often used, but their effect is limited.
- Upright positioning and fluid restriction until collateral channels develop and allow for clinical regression are useful modalities for SVC syndrome secondary to benign disease.
- Steroids (dexamethasone 4 mg q6h) may be useful in reducing the tumor burden in lymphoma and thymoma.
- Percutaneous self-expandable stents that can be placed under local anesthesia with radiologic manipulation are useful in the treatment of SVC syndrome to bypass the obstruction, especially in cases associated with malignant tumors.
- Surgical bypass grafting is infrequently used to treat SVC syndrome.

REFERRAL

To a thoracic surgeon, pulmonary specialist, or oncologist

AUTHOR: **FRED F. FERRI, M.D.**

BASIC INFORMATION

DEFINITION

Supraventricular tachycardia (SVT) is a group of tachyarrhythmias that originate from within or above the atrioventricular (AV) node and are characterized by sudden onset and abrupt termination. They include AV nodal reentrant tachycardia (AVNRT), AV reentrant tachycardia (AVRT), atrial fibrillation, atrial flutter, sinus tachycardia, and atrial tachycardia.

SYNONYMS

SVT
Paroxysmal Supraventricular tachycardia (SVT)

ICD-9CM CODES
427.0 Paroxysmal atrial tachycardia
ICD-10CM CODES
I47.1 Supraventricular tachycardia

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients may be either symptomatic or asymptomatic.
- Patient may be aware of "fast" heartbeat (palpitations) or have presyncope, syncope, or chest pain.
- Hemodynamic status during arrhythmia may vary and can depend on the patient's comorbidities and presence of underlying structural heart disease.

ETIOLOGY

- AVNRT—Dual electrical pathways within or near the AV node.
- AVRT (Wolff-Parkinson-White syndrome)—accessory pathway mediated, either orthodromic (antegrade through the AV node and retrograde through the accessory pathway) or antidromic (antegrade through the accessory pathway and retrograde through the AV node).
- Atrial fibrillation and atrial flutter are covered in separate topics.
- Paroxysmal atrial tachycardia and multifocal atrial tachycardia—abnormal automaticity of atrial tissue or triggered activity.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Other arrhythmias that present with narrow complex tachycardia like PSVT are:
1. Fascicular VT.
2. Junctional tachycardias.
3. Artifact such as with Parkinson's.

PSVT can be broad complex as well, and the features to distinguish it from ventricular tachycardia are outlined in Table S1-28.

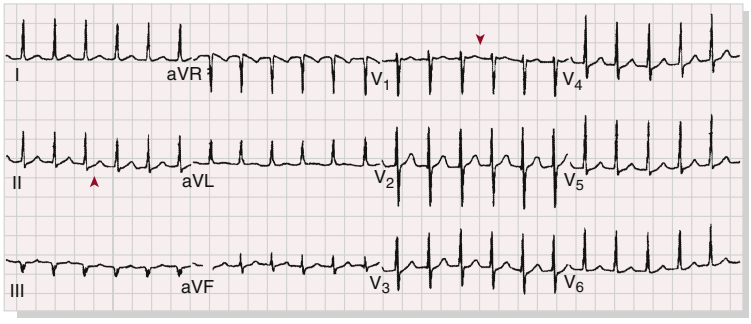
WORKUP

- Electrocardiography.
- Shows a rate >100 beats/min.
- P waves may or may not be seen (the presence of P waves depends on the relation of atrial to ventricular depolarization). P wave morphology can be useful in discriminating rhythms. P waves with a similar axis to the sinus node can be atrial tachycardias and sinus tachycardias. P waves with retrograde depolarization of the atria (seen as inverted in the inferior leads) can be seen in AVNRT, AVRT, and atrial tachycardia. Sawtooth P waves are indicative of classical counterclockwise typical type I flutter, and an absence of P waves with irregular R-R intervals points to atrial fibrillation. Variable (>3) morphologies of P wave are suggestive of multifocal atrial tachycardia.
- Wide QRS complex (>0.12 sec) with initial slurring (delta wave) during sinus rhythm and short PR (<0.12 sec) is characteristic of WPW syndrome.
- QRS complex during SVT is usually narrow; however, may be widened because of intrinsic conduction disease, myocardial disease, or rate-related bundle branch block. It may also be widened if the patient has antidromic AVRT.
- Pseudo r and pseudo S waves may be seen in atrioventricular nodal tachycardia (Fig. S1-88).
- Fig. S1-89 illustrates the differential diagnosis of different types of SVT based on timing of atrial activity (RP and PR intervals).
- Holter or event monitor to document the arrhythmias if they are paroxysmal.

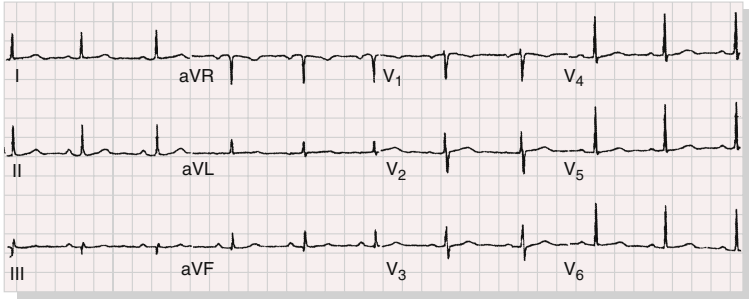
TABLE S1-28 Features That May Differentiate Ventricular Tachycardia from Supraventricular Tachycardia with Aberrancy

Helpful Features	Implications
Positive QRS concordance	Diagnostic of VT
Presence of AV dissociation, capture beats, or fusion beats	Diagnostic of VT
Atypical RBBB (monophasic R, QR, RS, or triphasic QRS in V_1; R:S ratio < 1, QS or QR, monophasic R in V_6)	Suggests VT
Atypical LBBB (R >30 min or R to S [nadir or notch] >60 min in V_1 or V_2; R:S ratio < 1, QS or QR in V_6)	Suggests VT
Shift of axis from baseline	Suggests VT
History of CAD	Suggests VT
QRS during tachycardia identical to QRS during sinus rhythm	Suggests SVT
Termination with adenosine	Suggests SVT

AV, Atrioventricular; *CAD,* coronary artery disease; *LBBB,* left bundle branch block; *RBBB,* right bundle branch block; *SVT,* supraventricular tachycardia; *VT,* ventricular tachycardia.
From Andreoli TG et al (eds): *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.



A



B

FIGURE S1-88 Twelve-lead electrocardiogram of atrioventricular nodal reentrant tachycardia. A, During tachycardia a pseudo-r wave is seen in lead V_1 *(arrowhead),* and pseudo-S waves *(arrowhead)* are seen in leads II, III, and aVF. **B,** These waves become more obvious when compared with the QRS complexes during sinus rhythm. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

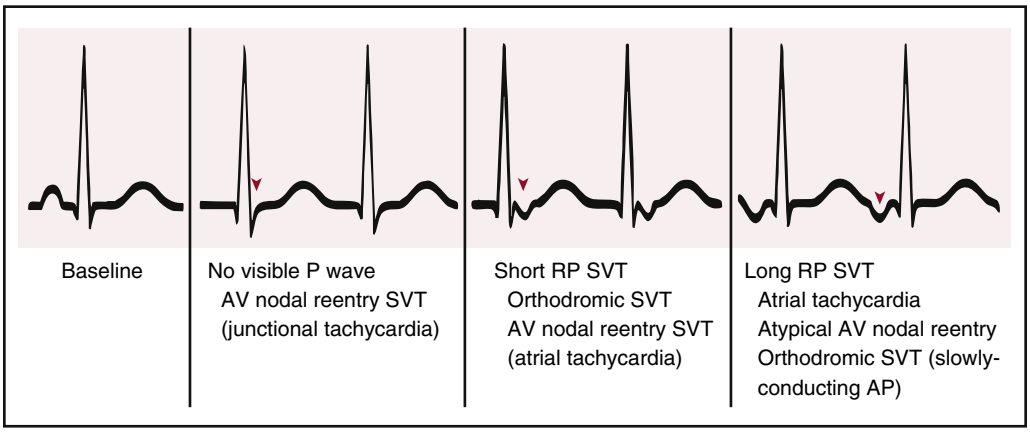


FIGURE S1-89 Differential diagnosis of different types of supraventricular tachycardia (SVT) based on timing of atrial activity (RP and PR intervals). Left, normal beat. Different types of tachycardia are listed below the representative electrocardiographic patterns that they can produce, categorized by P wave position relative to the QRS complex. *Red arrowhead* shows the location of the P wave in each example. *AV*, Atrioventricular; *AP*, accessory pathway. (From Bonow RO et al: *Braunwald's heart disease: a textbook of cardiovascular medicine,* Philadelphia, 2012, Saunders.)

- Echocardiography is appropriate to assess for the presence of underlying structural heart disease.
- Laboratory workup including thyroid function tests, electrolytes, etc.
- Evaluation for obstructive sleep apnea, lung disease, drugs such as theophylline, etc., which may be triggers.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Valsalva maneuver in the supine position is the most effective way to terminate most types of SVT; carotid sinus massage (after excluding occlusive carotid disease) is also commonly used to elicit vagal efferent impulses. These are effective in terminating AVRT, AVNRT, and some types of atrial tachycardia but only transiently slow down AV conduction in case of sinus tachycardia, atrial flutter, and atrial fibrillation without terminating the actual tachycardia.
- Synchronized DC shock is used if patient shows signs of hemodynamic instability.
- Table S1-28 describes useful features to differentiate ventricular tachycardia from SVT with aberrancy.

ACUTE GENERAL Rx

- Adenosine is useful for treatment of orthodromic AVRT and AVNRT and can uncover the underlying rhythm in paroxysmal atrial tachycardia; it is the first choice of therapy for treatment of almost all episodes of SVT unresponsive to vagal maneuvers. The dose is 12 mg given as a rapid IV bolus; tachycardia is usually terminated within a few seconds. If necessary, may repeat with 12 mg IV bolus. Contraindications are second or third degree atrioventricular block, WPW with atrial fibrillation, sick sinus syndrome, and chronic use of drugs such as dipyridamole, theophylline, or aminophylline and heart transplant. Adenosine may cause bronchospasm in asthmatics.
- Verapamil 5 to 10 mg IV is given over 5 min; if no effect, may repeat in 30 min.
  1. Verapamil should be used cautiously in patients with SVT associated with hypotension.
  2. Slow injection of calcium chloride (10 ml of a 10% solution given over 5 to 8 min before verapamil administration) decreases the hypotensive effect without compromising its antiarrhythmic effect.
- Repeat carotid massage after IV verapamil if SVT persists.
- Metoprolol (IV 5 mg/2 min up to 15 mg) or esmolol (500 μg/kg IV bolus, then 50 μg/kg/min) may be effective in the treatment of SVT.
- IV digoxin (0.75 to 1 mg slow IV loading in increments of 0.25 mg over several hours) if other agents are not effective.
  1. Repeat carotid massage 30 min later; if not successful, give additional 0.25 mg IV digoxin and repeat carotid sinus massage 1 hr later.
  2. Digoxin, beta-blockers, and calcium-channel blockers should be avoided in patients with pre-excitation syndrome to avoid increased conduction through the accessory pathway.

DISPOSITION

Most patients respond well with resolution of the paroxysmal atrial tachycardia upon treatment (see "Acute General Rx"). Some patients may need chronic AV blocking agents for recurrence.

REFERRAL

Radiofrequency ablation (RFA) is the procedure of choice in symptomatic patients who are refractory to medical therapy especially in AVRT, AVNRT, and atrial flutter. RFA has high efficacy rates (single procedure success is 93.2%), low all-cause mortality (0.1%), and low adverse events (2.9%). Despite high reported success rates, RFA appears to be underused in clinical practice.

PEARLS & CONSIDERATIONS

COMMENTS

Accessory pathways occur in 0.1% to 0.3% of the general population.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **BARRY FINE, M.D., PH.D.**

SUGGESTED READINGS

Blomstrom-Lundqvist C et al.: ACC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias—executive summary, *J Am Coll Cardiol* 42(8):1493, 2003.

Colucci RA et al.: Common types of supraventricular tachycardia: diagnosis and management, *Am Fam Physician* 82(8):942–952, 2010.

Fox DJ et al.: Supraventricular tachycardia: diagnosis and management, *Mayo Clin Proc* 83(12):1400, 2008.

Marine JE: Catheter ablation therapy for supraventricular arrhythmias, *JAMA* 298(3):2768, 2007.

Spector P et al.: Meta-analysis of ablation of atrial flutter and supraventricular tachycardia, *Am J Cardiol* 104(671), 2009.

BASIC INFORMATION

DEFINITION

Syncope is the transient loss of consciousness with spontaneous recovery that results from an acute global reduction in cerebral blood flow. There are 3 major types: neurally mediated, orthostatic, and cardiac. Syncope is a symptom, and the goal is to distinguish lethal causes from benign causes of transient loss of consciousness.

ICD-9CM CODES
780.2 Syncope
ICD-10CM CODES
R55 Syncope and collapse

EPIDEMIOLOGY & DEMOGRAPHICS

- Syncope accounts for 3% to 5% of emergency department visits.
- 30% of the adult population will experience at least one syncopal episode during their lifetimes.
- Incidence of syncope is highest in elderly men and young women.
- 15% of children and adolescents experience syncope; less than 5% have cardiac causes.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Blood pressure: if low, consider orthostatic hypotension; if unequal in both arms (difference >20 mm Hg), consider subclavian steal or dissecting aneurysm. (NOTE: Blood pressure [BP] and heart rate should be recorded in the supine and standing positions, waiting at least 5 minutes between each position.) If there is a drop in BP but no change in heart rate (HR), the patient may be taking a beta-blocker or may have an autonomic neuropathy.
- Pulse: if patient has tachycardia, bradycardia, or irregular rhythm, consider arrhythmia.
- Heart: if there are murmurs present, consider syncope attributable to left ventricular outflow obstruction (aortic stenosis or idiopathic hypertrophic subaortic stenosis); if there are jugular venous distention and distal heart sounds, consider cardiac tamponade.
- Carotid sinus pressure: can be diagnostic if it reproduces symptoms and other causes are excluded; a pause >3 sec or a systolic BP drop >50 mm Hg without symptoms or <30 mm Hg with symptoms when sinus pressure is applied separately on each side for <5 sec is considered abnormal. This test should be avoided in patients with carotid bruits or cerebrovascular disease. ECG monitoring, IV access, and bedside atropine should be available when carotid sinus pressure is applied.

ETIOLOGY

- Neurally mediated syncope: most common type, accounting for two-thirds of cases. It includes vasovagal, situational, carotid hypersensitivity, and postexertional syncope.
  1. Psychophysiologic (emotional upset, panic disorders, hysteria, hyperventilation)
  2. Visceral reflex (micturition, defecation, food ingestion, coughing, ventricular contraction, glossopharyngeal neuralgia)
  3. Carotid sinus pressure
  4. Reduction of venous return caused by Valsalva maneuver
- Orthostatic hypotension (10% of cases)
  1. Hypovolemia
  2. Vasodilator medications
  3. Autonomic neuropathy (diabetes, amyloid, Parkinson's disease, multisystem atrophy)
  4. Pheochromocytoma
  5. Carcinoid syndrome
- Cardiac (10% to 20%)
  1. Reduced cardiac output
     a. Left ventricular outflow obstruction (aortic stenosis, hypertrophic cardiomyopathy)
     b. Obstruction to pulmonary flow (pulmonary embolism, pulmonic stenosis, primary pulmonary hypertension)
     c. Myocardial infarct with pump failure
     d. Cardiac tamponade
     e. Mitral stenosis
     f. Reduction of venous return (atrial myxoma, valve thrombus)
     g. Beta-blocker therapy
  2. Arrhythmias or asystole
     a. Extreme tachycardia (>160 to 180 beats/min)
     b. Severe bradycardia (<30 to 40 beats/min)
     c. Sick sinus syndrome
     d. Atrioventricular block (second or third degree)
     e. Ventricular tachycardia or fibrillation
     f. Long QT syndrome
     g. Pacemaker malfunction
     h. Psychotropic medications and beta-blockers

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

1. Seizure (see "Workup")
2. Vertebrobasilar transient ischemic attack (TIA) usually manifests as diplopia, vertigo, or ataxia but not loss of consciousness. Isolated episodes of transient loss of consciousness (TLOC) without accompanying neurologic symptoms are unlikely to be TIAs.
3. Recreational drugs or alcohol.
4. Functional causes, such as stress and somatoform disorders.
5. Sleep disorders, such as sleep attacks and narcolepsy, are also in the differential for TLOC.
6. Head trauma.

WORKUP

The history is crucial to diagnosing the cause of syncope and may suggest a diagnosis that can be evaluated with directed testing. History is also important to determine other etiologies for TLOC, such as seizure. Fig. ES1-90 describes an algorithm for syncope evaluation.

- Sudden LOC: consider cardiac arrhythmias.
- Gradual LOC: consider orthostatic hypotension, vasodepressor syncope, hypoglycemia.
- History of aura before LOC or prolonged confusion (>1 min), amnesia, or lethargy after LOC suggests seizure rather than syncope.
- Patient's activity at the time of syncope:
  1. Micturition, coughing, defecation: consider syncope caused by decreased venous return.
  2. Turning head or while shaving: consider carotid sinus syndrome.
  3. Physical exertion in a patient with murmur: consider aortic stenosis.
  4. Arm exercise: consider subclavian steal syndrome.
  5. Assuming an upright position: consider orthostatic hypotension.
- Associated events:
  1. Chest pain: consider myocardial infarction, pulmonary embolism.
  2. Palpitations: consider arrhythmias.
  3. Incontinence (urine or fecal) and tongue biting are associated with seizure or syncope.
  4. Brief, transient shaking after LOC may represent myoclonus from global cerebral hypoperfusion and not seizures. However, sustained tonic/clonic muscle action is more suggestive of seizure.
  5. Focal neurologic symptoms or signs point to a neurologic event such as a seizure with residual deficits (e.g., Todd's paralysis) or cerebral ischemic injury.
  6. Psychologic stress: syncope may be vasovagal.
- Review current medications, particularly antihypertensive and psychotropic drugs.
- All patients presenting with syncope require electrocardiography, orthostatic vital signs, and QT interval monitoring.

LABORATORY TESTS

Routine blood tests rarely yield diagnostically useful information and should be done only if they are specifically suggested by the results of the history and physical examination. Box ES1-15 describes possibly useful tests. The following are commonly ordered tests:

- Pregnancy test in women of childbearing age
- Complete blood count to look for anemia and signs of infection
- Electrolytes, blood urea nitrogen, creatinine, magnesium, and calcium to look for electrolyte abnormalities and evaluate fluid status
- Serum glucose level
- Cardiac troponins, especially if the patient gives a history of chest pain before the syncopal episode
- Drug and alcohol levels with suspected toxicity

IMAGING STUDIES

- ECG to rule out arrhythmias; may be diagnostic in 5% to 10% of patients.
- Echocardiography.
- If seizure is suspected, CT scan and/or MRI of the head and electroencephalogram may be useful.
- If head trauma or neurologic signs on examination, CT or MRI may be helpful.
- If arrhythmias are suspected, a 24-hr Holter monitor or admission to a telemetry unit is

appropriate. In general, Holter monitoring is rarely useful, revealing a cause for syncope in <3% of cases. Loop recorders that can be activated after syncopal episode to retrieve information about the cardiac rhythm during the preceding 4 min add considerable diagnostic yield in patients with unexplained syncope.

- Implantable cardiac monitors that function as permanent loop recorders or implantable cardioverter-defibrillators, which are placed subcutaneously in the pectoral region with the patient under local anesthesia, are useful in patients with cardiac syncope.
- Electrophysiologic studies may be indicated in patients with structural heart disease and/or recurrent syncope.

TILT-TABLE TESTING

- Useful to support a diagnosis of neurally mediated syncope. Patients age >50 yr should have stress testing before tilt-table testing. Positive results would preclude tilt-table testing.
- Indicated in patients with recurrent episodes of unexplained syncope as well as patients in high-risk occupations (e.g., pilots, bus drivers) (Fig. S1-91). The test is also useful for identifying patients with prominent bradycardic response who may benefit from implantation of a permanent pacemaker. The test is contraindicated in patients with recent stroke, MI, and severe coronary or carotid disease.
- It is performed by keeping the patient strapped in an upright posture on a tilt table with footboard support. The angle of the tilt table varies from 60 to 80 degrees. The duration of upright posture during tilt-table testing varies from 25 to 45 min.
- The hallmark of neurally mediated syncope is severe hypotension associated with a paradoxic bradycardia triggered by a specific stimulus. The diagnosis of neurally mediated syncope is likely if upright tilt testing reproduces these hemodynamic changes in <15 min and causes presyncope or syncope.

PSYCHIATRIC EVALUATION

- May be indicated in young patients without heart disease who have frequently recurring transient loss of consciousness and other somatic symptoms.
- Generalized anxiety disorder, pain disorder, and major depression predispose patients to neurally mediated reactions and may result in syncope.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Ensure proper hydration; consider compression stockings and salt tablets in appropriate patients.
- Eliminate medications that may induce hypotension.

ACUTE GENERAL Rx

- Varies with the underlying etiology of syncope (e.g., pacemaker in patients with syncope resulting from complete heart block).
- Syncope caused by orthostatic hypotension is treated with volume replacement in patients with intravascular volume depletion. Also consider midodrine to promote venous return by adrenergic-mediated vasoconstriction and Florinef for its mineralocorticoid effects to increase intravascular volume.

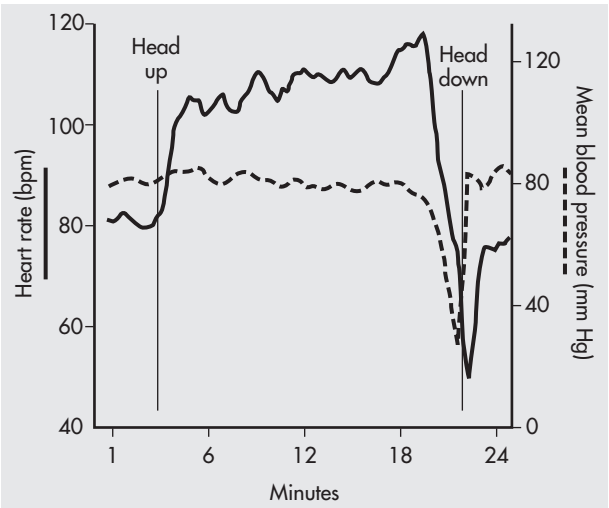


FIGURE S1-91 Head-up tilt test performed on an 18-year-old woman with a history of syncope associated with pain, preceded by a prodrome of dizziness, graying vision, and diaphoresis. A similar prodrome preceded syncope during the test. Note the precipitous and nearly simultaneous decline of heart rate and blood pressure after an initial rise in heart rate. Vital signs returned to normal rapidly after the head was lowered. (Courtesy Robert F. Sprung, University of Utah. In Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, Saunders.)

DISPOSITION

Prognosis varies with the age of the patient and the etiology of the syncope. In general:

- Benign prognosis (very low 1-yr morbidity rate) in patients:
  1. Age <30 yr and having noncardiac syncope
  2. Age <70 yr and having vasovagal or psychogenic syncope or syncope of unknown cause
- Poor prognosis (high mortality and morbidity rates) in patients with cardiac syncope, with presenting systolic BP <90 mm Hg.
- Patients with the following risk factors have a higher 1-yr mortality rate: abnormal ECG, history of ventricular arrhythmia, history of congestive heart failure.

REFERRAL

Hospital admission in elderly patients without prior history of syncope or unknown etiology of their syncope and in any patients suspected of having cardiac syncope, with presenting systolic BP <90 mm Hg.

PEARLS & CONSIDERATIONS

COMMENTS

- Section III, "Palpitations, Dizziness, and/or Syncope," describes an algorithmic approach to the patient.
- The etiology of syncope is identified in <50% of cases during the initial evaluation.
- A thorough history and physical examination are the most productive means of establishing a diagnosis in patients with syncope.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Syncope (Patient Information)

AUTHOR: **TZU-CHING (TEDDY) WU, M.D.**

EVIDENCE

Abstract[1]

Background:

There is a relative paucity of studies investigating the mechanisms of syncope among heart failure patients with implantable cardioverter-defibrillators, and it is controversial whether nonarrhythmogenic syncope is associated with increased mortality.

Methods and Results:

The Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy (MADIT-RIT) randomized 1500 patients to 3 different implantable cardioverter-defibrillator programming arms: (1) Conventional programming with therapy for ventricular tachycardia $170 bpm; (2) high-rate cutoff with therapy for ventricular tachycardia $200 bpm and a monitoring zone at 170 to 199 bpm, and (3) prolonged 60-second delay with a monitoring zone before therapy. Syncope was a prespecified safety end point that was adjudicated independently. Multivariable Cox models were used to identify risk factors associated with syncope and to analyze subsequent risk of mortality. During follow-up, 64 of 1500 patients (4.3%) had syncope. The incidence of syncope was similar across the 3 treatment arms. Prognostic factors for all-cause syncope included the presence of ischemic cardiomyopathy (hazard ratio [HR], 2.48; 95% confidence interval [CI], 1.42-4.34; P = 0.002), previous ventricular arrhythmias (HR, 2.99; 95% CI, 1.18-7.59; P = 0.021), left ventricular ejection fraction #25% (HR, 1.65; 95% CI, 0.98-2.77; P = 0.059), and younger age (by 10 years; HR, 1.25; 95% CI, 1.00-1.52; P = 0.046). Syncope was associated with increased risk of death regardless of its cause (arrhythmogenic syncope: HR, 4.51; 95% CI, 1.39-14.64, P = 0.012; nonarrhythmogenic syncope: HR, 2.97; 95% CI, 1.07-8.28, P = 0.038).

Conclusions:

Innovative programming of implantable cardioverterdefibrillators with therapy for ventricular tachycardia >200 bpm or a long delay is not associated with increased risk of arrhythmogenic or all-cause syncope, and syncope caused by slow ventricular tachycardias (<200 bpm) is a rare event. The clinical risk factors associated with syncope are related to increased cardiovascular risk profile, and syncope is associated with increased mortality irrespective of the cause.

Clinical Trial Registration: http://www.clinicaltrials.gov. Unique identifier: NCT00947310. Ⓐ

Evidence-Based Reference

1. Ruwald MH, Okumura K, Kimura T, et al.: Syncope in High-Risk Cardiomyopathy Patients With Implantable Defibrillators: Frequency, Risk Factors, Mechanisms, and Association With Mortality: Results From the Multicenter Automatic Defibrillator Implantation TrialeReduce Inappropriate Therapy (MADIT-RIT) Study, *Circulation* 129:545–552, 2014. Ⓐ

SUGGESTED READINGS

Brignole M et al.: Guidelines on management (diagnosis and treatment) of syncope 2004, *Europace* 6:467, 2004.

Chen LY et al.: Management of syncope in adults: an update, *Mayo Clin Proc* 83(11):1280–1293, 2008.

Fenton AM et al.: Vasovagal syncope, *Ann Intern Med* 133:722, 2000.

Gauer RL: Evaluation of syncope, *Am Fam Physician* 84(6):640–650, 2011.

Grubb BP: Neurocardiogenic syncope, *N Engl J Med* 352:1002–1010, 2005.

Hanna EB: Syncope: Etiology and diagnostic approach, *Cleveland Clin J Med* 81:755–766, 2014.

Kapoor WN: Syncope, *N Engl J Med* 343:2000, 1856.

Menozzi C et al.: Mechanism of syncope in patients with heart disease and negative electrophysiologic test, *Circulation* 105:2741, 2002.

Tretter JT, Kavey RE: Distinguishing cardiac syncope from vasovagal syncope in a referral population, *J Pediatr* 163(6):1618–1623, 2013.

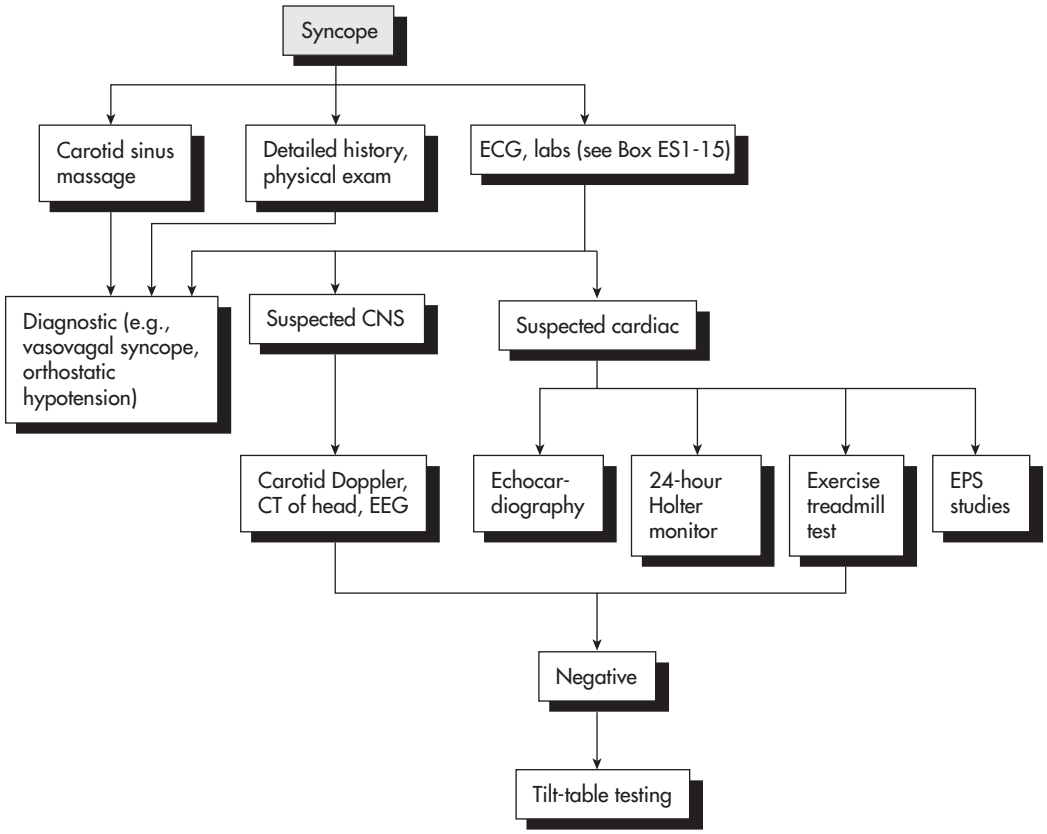


FIGURE ES1-90 Syncope evaluation. *CNS,* Central nervous system; *CT,* computed tomography; *ECG,* electrocardiograph; *EEG,* electroencephalograph; *EPS,* electrophysiologic. (From Ferri FF: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging*, ed 3, Philadelphia, 2014, Mosby.)

BOX ES1-15 Syncope

Diagnostic Imaging

Best Test

None; diagnostic imaging should be guided by history and physical exam

Ancillary Tests

Echocardiography is useful in patients with a heart murmur to r/o aortic stenosis, hypertrophic cardiomyopathy, or atrial myxoma
If seizure is suspected, CT of head and EEG are indicated
Spiral CT of chest or ventilation/perfusion scan if PE is suspected

Lab Evaluation

Best Test

None

Ancillary Tests

Routine blood tests rarely yield diagnostically useful information and should be done only when specifically suggested by history and physical exam
Serum pregnancy test should be considered in women of childbearing age
CBC, electrolytes, BUN, creatinine
Serum calcium, magnesium
ABGs
ECG
Cardiac troponins, CK isoenzymes if history of chest pain before syncope
Toxicology screen in selected patients
Cardiac stress test
Electrophysiologic (EPS) studies

ABG, Arterial blood gas; *BUN,* blood urea nitrogen; *CBC,* complete blood count; *CT,* computed tomography; *ECG,* electrocardiograph; *EEG,* electroencephalograph. From Ferri FF: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 3, Philadelphia, 2014, Mosby.

Syndrome of Inappropriate Antidiuresis PTG

BASIC INFORMATION

DEFINITION

Syndrome of inappropriate antidiuresis (SIAD) is a syndrome characterized by excessive secretion of antidiuretic hormone (ADH) in absence of normal osmotic or physiologic stimuli (increased serum osmolarity, decreased plasma volume, hypotension).

SYNONYMS

SIAD
SIADH
Syndrome of inappropriate antidiuretic hormone secretion
Syndrome of inappropriate ADH release
Inappropriate secretion of antidiuretic hormone

ICD-9CM CODES
276.9 Inappropriate secretion of antidiuretic hormone
ICD-10CM CODES
E22 Syndrome of inappropriate secretion of antidiuretic hormone

EPIDEMIOLOGY & DEMOGRAPHICS

SIAD is the most frequent cause of hyponatremia. Nearly 50% of hyponatremia detected in the hospital setting is caused by SIAD.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The patient is generally normovolemic or slightly hypervolemic; edema is absent.
- Delirium, lethargy, and seizures may be present if the hyponatremia is severe or of rapid onset.
- Manifestations of the underlying disease may be evident (e.g., fever from an infectious process or headaches and visual field defects from an intracranial mass).
- Diminished reflexes and extensor plantar responses may occur with severe hyponatremia.

ETIOLOGY

- Neoplasm: lung, oropharynx, stomach, duodenum, pancreas, brain, thymus, bladder, prostate, endometrium, mesothelioma, lymphoma, Ewing's sarcoma
- Pulmonary disorders: pneumonia, aspergillosis, pulmonary abscess, TB, bronchiectasis, emphysema, cystic fibrosis, status asthmaticus, respiratory failure associated with positive-pressure breathing
- Intracranial pathology: trauma, neoplasms, infections (meningitis, encephalitis, brain abscess), hemorrhage, hydrocephalus, MS, Guillain-Barré syndrome
- Postoperative period: surgical stress, ventilators with positive pressure, anesthetic agents
- Drugs: nicotine, chlorpropamide, thiazide diuretics, vasopressin, desmopressin, oxytocin, chemotherapeutic agents (vincristine, vinblastine, cyclophosphamide), carbamazepine, phenothiazines, MAO inhibitors, tricyclic antidepressants, narcotics, nicotine, clofibrate, haloperidol, SSRIs, NSAIDs
- Other: acute intermittent porphyria, myxedema, psychosis, delirium tremens, ACTH deficiency (hypopituitarism), general anesthesia, endurance exercise
- Table S1-29 summarizes common etiologies of the syndrome of inappropriate antidiuretic hormone secretion.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hyponatremia associated with hypervolemia (congestive heart failure, cirrhosis, nephrotic syndrome)
- Factitious hyponatremia (hyperglycemia, abnormal proteins, hyperlipidemia)
- Hyponatremia associated with hypovolemia (e.g., burns, GI fluid loss)

WORKUP

- Demonstration through laboratory evaluation (see "Laboratory Tests") of excessive secretion of ADH in absence of appropriate osmotic or physiologic stimuli (abnormal result on test of water load, elevated plasma arginine vasopressin levels despite the presence of hypotonicity and clinical euvolemia)
- Demonstration of normal thyroid, adrenal, and cardiac function
- No recent or concurrent use of diuretics
- Failure to correct hyponatremia after 0.9% saline infusion
- Correction of hyponatremia through fluid restriction
- Diagnostic criteria for SIADH are described in Table S1-30

LABORATORY TESTS

- Hyponatremia
- Decreased effective osmolality (<275 mOsm/kg of water)
- Urine osmolality >100 mOsm/kg of water during hypotonicity
- Urinary osmolarity > serum osmolarity
- Urinary sodium usually >40 mEq/L with normal dietary salt intake
- Normal BUN, creatinine (indicative of normal renal function and absence of dehydration), normal TSH
- Decreased uric acid

IMAGING STUDIES

Chest radiograph to rule out neoplasm or infectious process

TREATMENT

NONPHARMACOLOGIC THERAPY

Fluid restriction to 500 to 800 ml/day with close monitoring of levels of urinary and plasma electrolytes. Adequate intake of dietary protein and salt should be encouraged.

ACUTE GENERAL Rx

- In emergency situations (seizures, coma) SIAD can be treated with combination of:
  1. Hypertonic saline solution (slow infusion of 250 ml of 3% NaCl). Infuse 3% saline

TABLE S1-29 Common Etiologies of the Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

Tumors
Pulmonary/mediastinal (bronchogenic carcinoma, mesothelioma, thymoma)
Nonchest (duodenal carcinoma, pancreatic carcinoma, ureteral/prostate carcinoma, uterine carcinoma, nasopharyngeal carcinoma, leukemia)
Central Nervous System Disorders
Mass lesions (tumors, brain abscesses, subdural hematoma)
Inflammatory diseases (encephalitis, meningitis, systemic lupus erythematosus, acute intermittent porphyria, multiple sclerosis)
Degenerative/demyelinative diseases (Guillain-Barré syndrome, spinal cord lesions)
Miscellaneous (subarachnoid hemorrhage, head trauma, acute psychosis, delirium tremens, pituitary stalk section, transsphenoidal adenomectomy, hydrocephalus)
Drug-Related
Stimulated release of AVP (nicotine, phenothiazines, tricyclics)
Direct renal effects and/or potentiation of AVP antidiuretic effects (dDAVP, oxytocin, prostaglandin synthesis inhibitors)
Mixed or uncertain actions (ACE inhibitors, carbamazepine and oxcarbazepine, chlorpropamide, clofibrate, clozapine, cyclophosphamide, 3,4-methylenedioxymethamphetamine ["Ecstasy"], omeprazole; serotonin reuptake inhibitors, vincristine)
Pulmonary
Infections (tuberculosis, acute bacterial and viral pneumonia, aspergillosis, empyema)
Mechanical/ventilatory causes (acute respiratory failure, COPD, positive-pressure ventilation)
Other Causes
Acquired immunodeficiency syndrome (AIDS) and AIDS-related complex
Prolonged strenuous exercise (marathon, triathlon, ultramarathon, hot-weather hiking)
Senile atrophy
Idiopathic

ACE, Angiotensin-converting enzyme; *AVP,* arginine vasopressin; *COPD,* chronic obstructive pulmonary disease; *dDAVP,* desmopressin.
From Melmed S: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

(513 mmol/L) at a rate of 1 to 2 ml/kg of body weight per hour to increase the serum sodium level by 1 to 2 mmol/L/hr.

2. Furosemide, 20 to 40 mg IV. This combination increases the serum sodium by causing diuresis of urine that is more dilute than plasma and prevents extracellular fluid volume expansion.

- The rapidity of correction varies depending on the degree of hyponatremia and if the hyponatremia is acute or chronic; generally the serum sodium should be corrected only halfway to normal in the initial 24 hr. A prudent approach is to increase serum sodium by <0.5 mEq/L/hr and limit the total increase to 8 to 12 mmol/L during the first 24 hr.

TABLE S1-30 Diagnostic Criteria for the Syndrome of Inappropriate Antidiuretic Hormone Release

Essential Diagnostic Criteria
Decreased extracellular fluid effective osmolality (<270 mOsm/kg H_2O)
Inappropriate urinary concentration (>100 mOsm/kg H_2O)
Clinical euvolemia
Elevated urinary Na^+ concentration under conditions of normal salt and water intake
Absence of adrenal, thyroid, pituitary, or renal insufficiency or diuretic use
Supplemental Criteria
Abnormal water-load test (inability to excrete at least 90% of a 20-ml/kg water load in 4 hours and/or failure to dilute urine osmolality to <100 mOsm/kg)
Plasma vasopressin level inappropriately elevated relative to the plasma osmolality
No significant correction of plasma Na^+ level with volume expansion, but improvement after fluid restriction

From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

- Close monitoring of the rate of correction (every 2 to 3 hr) is recommended to avoid overcorrection. In patients with hyponatremia of chronic duration, correction of serum sodium level by >12 mmol/L over a period of 24 hr increases the risk of osmotic demyelination.
- Conivaptan (20 to 40 mg/day IV) or tolvaptan (15 mg/day PO initially) are selective arginine-vasopressin (AVP) antagonists useful in selected hospitalized patients with moderate-to-severe hypervolemic and euvolemic hyponatremia. Their direct antagonism of the renal V_2 receptors increases urine water excretion, resulting in an increase in free water clearance (aquaresis). With these agents there is a significant increase in serum sodium concentration in as early as 8 hours and the change is maintained for several days. Potential problems associated with these agents are risk of osmotic demyelination if serum sodium levels are corrected too rapidly and are infusion-site reactions (50% of patients) with conivaptan.

CHRONIC Rx

- Depending on the underlying etiology, fluid restriction may be needed indefinitely. Monthly monitoring of electrolytes is recommended in patients with chronic SIAD.
- Demeclocycline 300 to 600 mg PO bid reduces urinary osmolality and increases serum sodium levels. It may be useful in patients with chronic SIAD (e.g., secondary to neoplasm) but use with caution in patients with hepatic disease; its side effects include nephrogenic diabetes insipidus (DI) and photosensitivity. This medication is also very expensive.
- Successful treatment of chronic nephrogenic SIAD with urea to induce osmotic diuresis has been reported in children and adults. However, oral intake of urea (30 g/day) is generally poorly tolerated.

DISPOSITION

- Prognosis varies depending on the cause. Generally, prognosis is benign when SIAD is caused by an infectious process.
- Morbidity and mortality are high (>40%) when serum sodium concentration is <110 mEq/L.

REFERRAL

Hospital admission depending on severity of symptoms and degree of hyponatremia

PEARLS & CONSIDERATIONS

COMMENTS

- Use of hypertonic (3%) saline is contraindicated in patients with CHF, nephrotic syndrome, or cirrhosis.
- Too rapid correction of hyponatremia can cause demyelination and permanent central nervous system damage. When considering the use of vasopressor receptor antagonists, their perceived short-term benefits of improving serum sodium need to be weighed against the risks involved with overcorrection of hyponatremia.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Syndrome of Inappropriate Secretion of Antidiuretic Hormone (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READING

Ellison DH, Berl T: The syndrome of inappropriate antidiuresis, *N Engl J Med* 356:2064–2072, 2007.

BASIC INFORMATION

DEFINITION

Syphilis is a systemic sexually transmitted treponemal disease, with acute and chronic manifestations, characterized by primary skin lesions; secondary eruption involving skin and mucous membranes; long periods of latency; and late lesions of the skin, bone, viscera, central nervous system, and cardiovascular system.

SYNONYMS

Lues

ICD-9CM CODES
097.9 Syphilis, acquired unspecified
ICD-10CM CODES
A51.0 Primary genital syphilis
A51.1 Primary anal syphilis
A51.2 Primary syphilis of other sites
A51.3 Secondary syphilis of skin and mucous membranes
A51.4 Other secondary syphilis
A51.5 Early syphilis, unspecified
A52 Late syphilis
A52.0 Cardiovascular syphilis
A52.1 Symptomatic neurosyphilis
A52.3 Asymptomatic neurosyphilis
A52.3 Neurosyphilis, unspecified
A53.9 Syphilis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Widespread, primarily involving ages 20 to 35 yr. Racial differences in incidence are related to social factors. Usually more prevalent in urban areas. Estimated annual incidence of more than 55,000 cases in the United States. Rates reached historic lows in the United States in 2000 but began increasing among males in 2001 and increase has continued. Rates are disproportionately higher among black and Hispanic men who have sex with men (MSM) compared with white MSM and among young MSM.
- Communicability is indefinite and variable. Communicable during primary, secondary, and latent mucocutaneous lesions in up to first 4 yr of latency. Most probable congenital transmission occurs in early maternal syphilis. Adequate penicillin treatment ends infectivity within 24 to 48 hr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

PRIMARY SYPHILIS: Characteristic lesion is a painless chancre on genitalia, mouth, or anus (Fig. S1-92); atypical primary lesions may occur. Usually appears 3 wk after exposure and may spontaneously involute.

SECONDARY SYPHILIS

- Localized or diffuse mucocutaneous lesions and generalized lymphadenopathy. Common to have constitutional symptoms, flulike symptoms. May begin approximately 4 to 6 wk after appearance of primary lesion. Manifestations may resolve in 1 wk to 12 mo.
- 60% to 80% of patients have maculopapular lesions on their palms and soles.
- Condylomata lata intertriginous papules form at areas of friction and moisture, such as the vulva.
- 21% to 58% have mucocutaneous or mucosal lesions (pharyngitis, tonsillitis, "mucous patch" lesion on oral and genital mucosa).

EARLY LATENT (≤1 YR): Generally asymptomatic

LATE LATENT (>1 YR)

- Characterized by gummas (nodular, ulcerative lesions) that can involve the skin, mucous membranes, skeletal system, and viscera.
- Manifestations of cardiovascular syphilis include aortitis, aneurysm, or aortic regurgitation.
- Neurosyphilis may be asymptomatic or symptomatic. Tabes dorsalis, meningovascular syphilis, general paralysis, or insanity may occur. Iritis, choroidoretinitis, and leukoplakia may also occur.

ETIOLOGY

- *Treponema pallidum,* a spirochete
- Spread by sexual intercourse or by intrauterine transfer

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other genitoulcerative diseases such as herpes, chancroid (see Section II)
- See Section III for a clinical algorithm for the evaluation of genital ulcer disease

WORKUP

Confirmation is primarily through laboratory diagnosis. An algorithm for interpretation of reactive serologic tests for syphilis is described in Fig. ES1-93.

LABORATORY TESTS

- Dark-field microscopy of fluid from lesion to look for treponeme is the definitive method for diagnosis of early syphilis.
- Serologic testing, both nontreponemal (VDRL, RPR) and treponemal (FTA, MHA). Many labs now screen patients for syphilis with automated treponemal antibody immunoassays and then confirm positive results with nontreponemal tests. The use of only one type of serologic test is insufficient for diagnosis because each type of test has limitations, including the possibility of false-positive test results in persons without syphilis. False-positive nontreponemal test results can be associated with various medical conditions unrelated to syphilis, including autoimmune conditions, older age, and injection-drug use; therefore, persons with a reactive nontreponemal test should receive a treponemal test to confirm the diagnosis of syphilis. Positive results on both treponemal and nontreponemal testing indicate new untreated syphilis. When the nontreponemal test is negative despite a positive screen, an additional treponemal screen may be helpful. Trials have shown that two positive treponemal screens help identify a population with likely prior or current syphilis, and treatment of these patients may be justifiable.

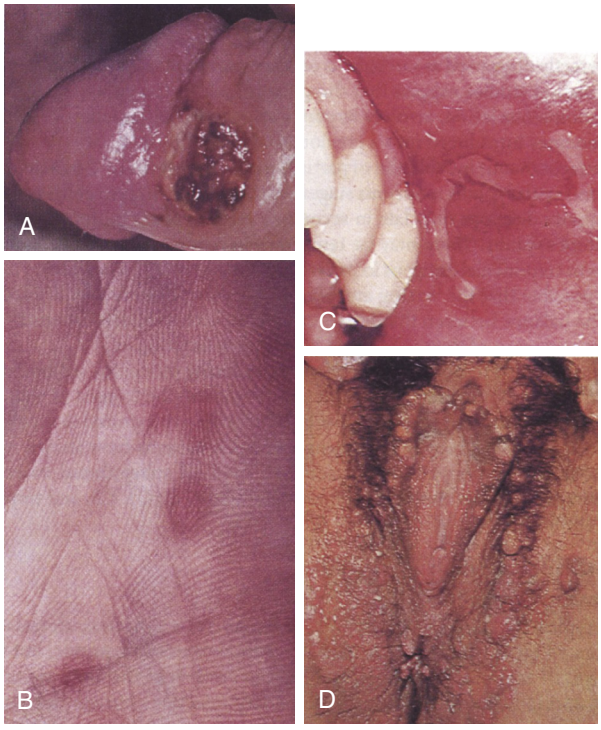


FIGURE S1-92 Syphilis lesions. A, Chancre in primary syphilis. **B,** Palmar lesions of a coppery color in secondary syphilis. **C,** Mucous patch in secondary syphilis. **D,** Condylomata lata in secondary syphilis. (**A, C,** and **D** from Forbes CD, Jackson WF: *Color atlas and text of clinical medicine,* ed 3, London, 2003, Mosby. **B** from Habif TP et al: *Skin disease: diagnosis and treatment,* St Louis, 2001, Mosby.)

- In patients with neurosyphilis, serologic criteria for response to therapy is a fourfold or greater decrease in VDRL titer over 6 to 12 months.
- Lumbar puncture (LP) for cerebrospinal fluid VDRL (CSF-VDRL) in patients with evidence of latent syphilis. When reactive in the absence of substantial contamination of CSF with blood, it is considered diagnostic of neurosyphilis. The Centers for Disease Control and Prevention indications for LP are neurologic symptoms, treatment failure, any eye or ear involvement, or evidence of active syphilis (aortitis, gumma, iritis).
- HIV testing in all patients.

Rx TREATMENT

ACUTE GENERAL Rx

- Early (primary, secondary, early latent): penicillin G benzathine 2.4 million U IM × 1 *or* azithromycin 2 g PO × 1 dose
- Late (late latent, cardiovascular, gumma): penicillin G benzathine 2.4 million U IM q wk × 3 wk or doxycycline 100 mg PO bid × 4 wk
- Neurosyphilis: aqueous crystalline penicillin G 18 to 24 million U/day, administered as 3 to 4 million U IV q4h × 10 to 14 days or procaine penicillin 2.4 million U IM/day plus probenecid 500 mg PO qid, both for 10 to 14 days
- Congenital syphilis: aqueous crystalline penicillin G 50,000 U/kg/dose IV q12h × first 7 days of life and q8h after that for total of 10 days or procaine penicillin G 50,000 U/kg/dose IM/day × 10 days
- Penicillin-allergic patients with primary or secondary syphilis: doxycycline 100 mg PO bid × 14 days, or tetracycline 500 mg PO qid × 14 days, or ceftriaxone 1 g IM or IV qd × 10 to 14 days. A recent large study has shown that a single oral dose of azithromycin (2 g administered as 4 500-mg tablets) can be curative in patients with early syphilis
- Latent syphilis in penicillin-allergic patient: doxycycline 100 mg PO bid or tetracycline 500 mg qid for 28 days
- Tetracyclines are contraindicated in pregnancy. If pregnant and penicillin allergic, must be desensitized prior to treatment

DISPOSITION

- Repeat quantitative nontreponemal tests at 3, 6, and 12 mo. Pregnancy requires monthly tests until delivery.
- If a fourfold increase in titer occurs, if initial high titer fails to drop by fourfold within a year, or signs persist, retreatment may be indicated. Use treatment regimen for late syphilis.
- Pregnant women without a fourfold drop in titer in a 3-mo period need to be retreated.
- Cases should be reported to local or state health department for referral, follow-up, and partner notification.

REFERRAL

- Pregnant and possible congenital syphilis
- Pregnant and allergic to penicillin, with need to be desensitized
- Late latent syphilis with serious central nervous system, cardiovascular, or other organ system compromise

PEARLS & CONSIDERATIONS

- Jarisch-Herxheimer reaction (fever, myalgia, tachycardia, hypotension) may occur within 24 hr of treatment.
- One third of untreated patients develop central nervous system and/or cardiovascular sequelae.
- Up to 80% of those treated during late stages remain seropositive indefinitely.
- Treponemal tests remain positive even after adequate therapy.
- Male circumcision does not decrease the incidence of syphilis (unlike HIV, HSV-2, and HPV infection).
- Partner notification and treatment:
  1. Persons who are exposed within 90 days preceding the diagnosis of primary, secondary, or early latent syphilis in a sex partner might be infected even if seronegative; therefore, such persons should be treated presumptively.
  2. Persons who were exposed ≥90 days before the diagnosis of syphilis in a sex partner should be treated presumptively if serologic test results are not available immediately and the opportunity for follow-up is uncertain.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Syphilis (Patient Information)
Tabes Dorsalis (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Centers for Disease Control and Prevention. 2010: sexually transmitted diseases treatment guidelines, *MMWR Recomm Rep* 59(RR-12), 2010.

Clement M et al.: Treatment of syphilis: a systematic review, *JAMA* 312(18):1905–1917, 2014.

Hook III EW et al.: A phase III equivalence trial of azithromycin versus benzathine penicillin for treatment of early syphilis, *J Infect Dis* 201:1729, 2010.

Park IU et al.: Screening for syphilis with the treponemal immunoassay: analysis of discordant serology results and implications for clinical management, *J Infect Dis* 204:1297, 2011.

Roett MA et al.: Diagnosis and management of genital ulcers, *Am Fam Physician* 85(3):254–262, 2012.

Su JT et al.: Primary and secondary syphilis among black and Hispanic men who have sex with men: case report data from 27 states, *Ann Intern Med* 155:145–151, 2011.

Tobian AA et al.: Male circumcision for the prevention of HSV-2 and HPV infections and syphilis, *N Engl J Med* 360:1298–1309, 2009.

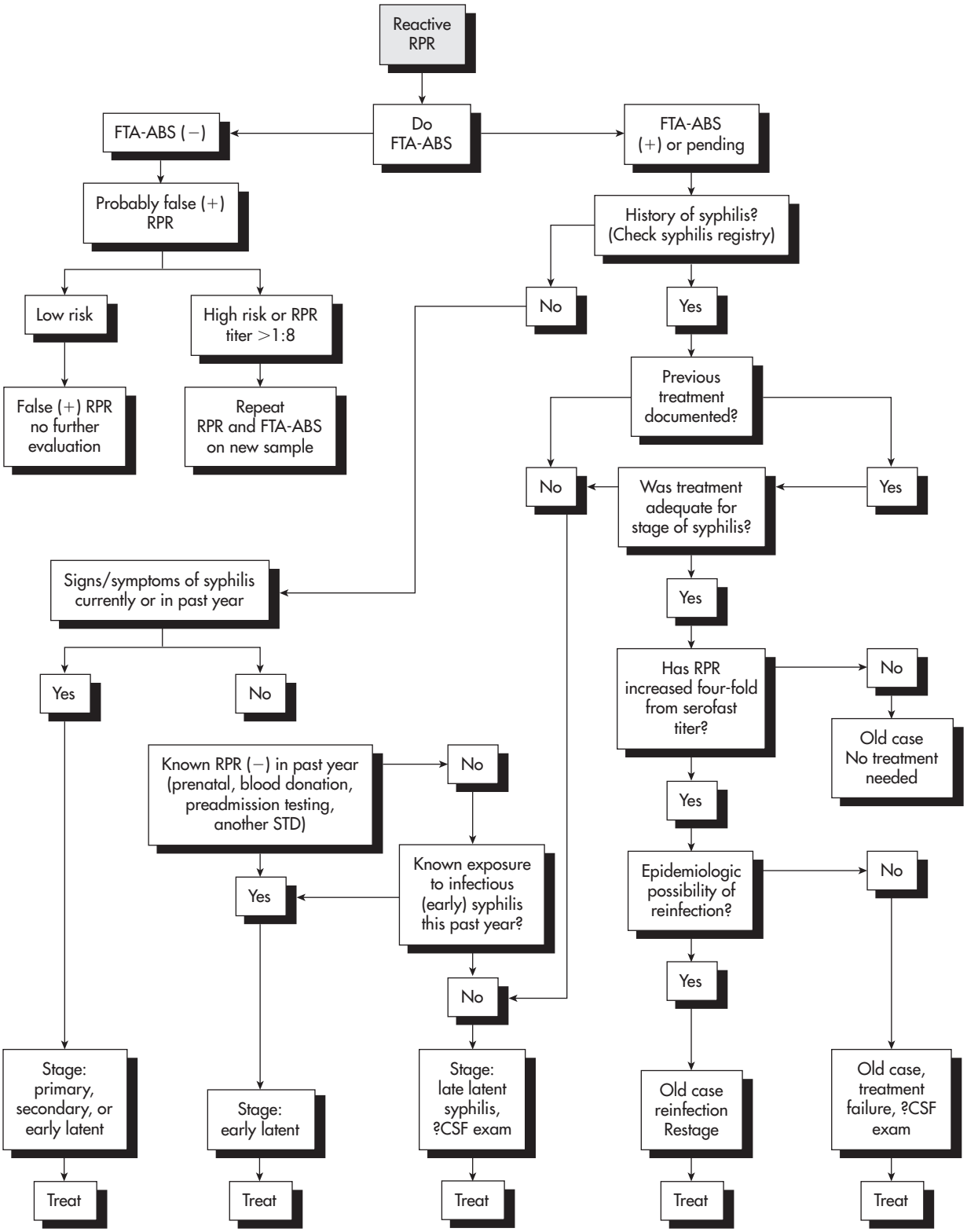


FIGURE ES1-93 Interpretation of reactive serologic tests for syphilis. *CSF,* Cerebrospinal fluid; *FTA-ABS,* fluorescent treponemal antibody absorption; *RPR,* rapid plasma reagent; *STD,* sexually transmitted disease. (From Habif TA: *Clinical dermatology,* ed 4, St Louis, 2004, Mosby.)

BASIC INFORMATION

DEFINITION

Syringomyelia is a condition characterized by the formation of fluid-filled tubular cavities within the cervical spinal cord, sometimes involving the medulla oblongata, in which case it will be called syringobulbia.

SYNONYMS

Syrinx

ICD-9CM CODES
336.0 Syringomyelia
ICD-10CM CODES
G95.0 Syringomyelia and syringobulbia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE

- A rare condition
- No accurate figures for the incidence of syringomyelia
- Incidence of posttraumatic syringomyelia is between 1.9% and 4.5%

PREVALENCE

- A prevalence of 7 per 100,000 has been suggested
- About 40% to 75% of patients with Chiari malformation have syringomyelia, while in 90% of patients with syringomyelia it is associated with Chiari malformation.

PREDOMINANT SEX AND AGE

- Symptoms commonly begin in late adolescence or early adulthood
- Both sexes are equally affected

RISK FACTORS

- Spinal cord anomalies like spina bifida and Chiari malformations
- Base of skull anomalies like achondroplasia
- Spinal cord trauma, including birth trauma
- Intra- or extramedullary spinal tumors
- Multiple sclerosis plaques in the spine
- Spinal arteriovenous malformations
- History of meningitis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Onset is usually insidious, often asymptomatic until the third or fourth decade.
- Cervical spine is the most commonly affected area.
  1. Neuropathic joints (Fig. ES1-94), intrinsic hand atrophy, hand and/or arm weakness, and sensory loss
  2. Painless burns or other injuries in the hand
  3. Neck, back, arm, and/or leg pain
  4. Loss of pain and temperature sensation in upper extremities, but tactile sense is preserved.
  5. Sharp testing elicits no pain, but patient often perceives the sharpness of the object.
  6. A Charcot joint in the shoulder or elbow may develop.
  7. Impaired walking, toe walking in children
  8. Bowel disturbances such as constipation, and bladder disturbances, such as incontinence
- Loss of upper limb reflexes
- Hyperreflexia is present in the lower extremity.
  1. Cape-like sensory loss
  2. Ataxia
- Scoliosis is common, especially in children.
- Nystagmus and Horner's syndrome may also occur.
- Hemangiomas or midline tuft of hair may also indicate underlying spine deformities

ETIOLOGY

- Cause is unknown, but is believed to result from obstruction of the outlet of the fourth ventricle, often associated with a Chiari I malformation, which causes fluid to be diverted down the central cord.
- A history of birth trauma often exists.
- Previous history of intramedullary tumors or meningitis might predispose to syrinx formation.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Amyotrophic lateral sclerosis/motor neuron disease
- Multiple sclerosis
- Spinal cord tumor
- Transverse myelitis
- Tabes dorsalis
- Vitamin B_{12} deficiency
- Copper deficiency
- Progressive spinal muscular atrophy

IMAGING STUDIES

- Plain radiographs usually reveal widening of the bony canal in the region of involvement.
- Bony anomalies are often present at the base of the skull and at the C1-C2 spinal segments.
- MRI (Fig. ES1-95) of the spine is the gold standard study of choice. Gadolinium contrast is necessary to rule out spinal tumors.
- CT myelography is an alternative test if MRI is contraindicated

TREATMENT

- No medical treatment is available.
- Decompressive laminectomy of C1 and C2.
- Syringostomy
- Insertion of a syringoperitoneal or syringopleural shunt

DISPOSITION

- The condition is slowly progressive in most cases but the course of the disease may be quite variable, ranging from death in a few months to slow incapacitation over several years; progression may halt at any time.
- Surgical intervention leads to improvement in neurologic findings in 30% of patients.
- Physical and occupational therapies prevent further loss of function.

REFERRAL

Neurology and neurosurgery referral when diagnosis is suspected

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Syringomyelia (Patient Information)

AUTHOR: **CATHERINE ELIAS NAJEM, M.D.**

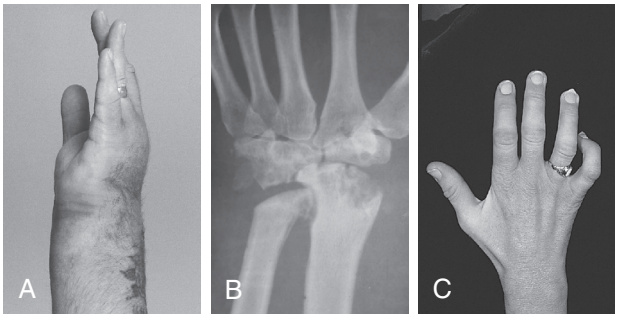


FIGURE ES1-94 Syringomyelia. A, A neuropathic wrist joint in a patient with mild syringomyelia. Note the swelling and deformity of the joint. **B,** Radiograph showing the gross destruction of the proximal carpal row with attrition and simplification of the bony margins. Residual fragments of bone and considerable soft tissue swelling can also be seen. **C,** Wasting of the intrinsic muscle of the hand and "claw" deformity. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2001, Mosby.)

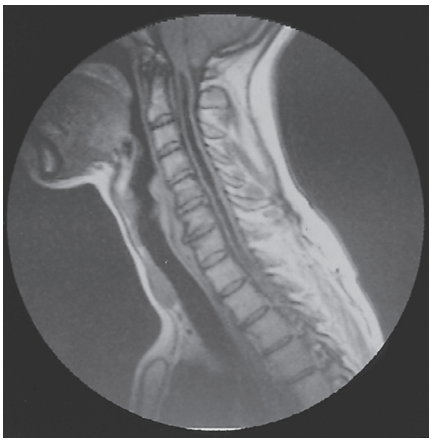


FIGURE ES1-95 Magnetic resonance imaging of cervical spine in syringomyelia, showing the fluid-filled syrinx in the center of the spinal cord. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

SUGGESTED READINGS

Akhtar OH, Rowe DE: Syringomyelia-associated scoliosis with and without the Chiari I malformation, *J Am Acad Orthop Surg* 16:407, 2008.

Chu WC et al.: A detailed morphologic and functional magnetic resonance imaging study of the craniocervical junction in adolescent idiopathic scoliosis, *Spine* 32(15):1667, 2007.

Di Lorenzo N, Cacciola F: Adult syringomyelia. Classification, pathogenesis and therapeutic approaches, *J Neurosurg Sci* 49:65–72, 2005.

Fernandez AA et al.: Malformations of the craniocervical junction (Chiari type I and syringomyelia: classification, diagnosis, and treatment), *BMC Musculoskelet Disord* 10(Suppl 1):51, 2009.

Heiss JD et al.: Pathophysiology of persistent syringomyelia after decompressive craniocervical surgery. Clinical article, *J Neurosurg Spine* 13:729–742, 2010.

Klekamp J: The pathophysiology of syringomyelia: historical overview and current concepts, *Acta Neurochir* 144(7):649, 2002.

Magge SN et al.: Idiopathic syrinx in the pediatric population: a combined center experience, *J Neurosurg Pediatr* 7:30–36, 2011.

Mallucci C, Brodbelt A: The enigma of syringomyelia, *Br J Neurosurg* 21:423, 2007.

Riente L et al.: Neuropathic shoulder arthropathy associated with syringomyelia and Arnold-Chiari malformation (type I), *J Rheumatol* 29(3):638, 2002.

Wang R et al.: Atypical syringomyelia without cavity in a patient with Chiari malformation and hydrocephalus, *Spine* 32(16):467, 2007.

BASIC INFORMATION

DEFINITION

Systemic lupus erythematosus (SLE) is a chronic, multisystemic disease characterized by production of autoantibodies and protean clinical manifestations.

SYNONYMS

SLE

ICD-9CM CODES

710.0 Systemic lupus erythematosus

ICD-10CM CODES

M32 Systemic lupus erythematosus
M32.0 Drug-induced systemic lupus erythematosus
M32.1+ Systemic lupus erythematosus with organ or system involvement
M32.8 Other forms of systemic lupus erythematosus
M32.9 Systemic lupus erythematosus, unspecified
M32.10 Systemic lupus erythematosus, organ or system involvement unspecified

TABLE S1-31 Potential Clinical Manifestations of Systemic Lupus Erythematosus

Target Organ	Potential Clinical Manifestations
Constitutional	Fatigue, anorexia, weight loss, fever, lymphadenopathy
Musculoskeletal	Arthritis, myositis, arthralgias, myalgias, avascular necrosis, osteoporosis
Skin	Malar rash, discoid rash, photosensitive rash, cutaneous vasculitis, livedo reticularis, periungual capillary abnormalities, Raynaud's phenomenon, alopecia, oral and nasal ulcers
Renal	Hypertension, proteinuria, hematuria, edema, nephrotic syndrome, renal failure
Cardiovascular	Pericarditis, myocarditis, conduction system abnormalities, Libman-Sacks endocarditis
Neurologic	Seizures, psychosis, cerebritis, stroke, transverse myelitis, depression, cognitive impairment, headaches, pseudotumor, peripheral neuropathy, chorea, optic neuritis, cranial nerve palsies
Pulmonary	Pleuritis, interstitial lung disease, pulmonary hemorrhage, pulmonary hypertension, pulmonary embolism
Hematologic	Immune-mediated cytopenias (hemolytic anemia, thrombocytopenia or leukopenia), anemia of chronic inflammation, hypercoagulability, thrombocytopenic thrombotic microangiopathy
Gastroenterology	Hepatosplenomegaly, pancreatitis, vasculitis affecting bowel, protein-losing enteropathy
Ocular	Retinal vasculitis, scleritis, episcleritis, papilledema

Modified from Kliegman RM et al: *Nelson textbook of pediatrics*, ed 19, Philadelphia, 2011, Saunders.

FIGURE S1-96 Acute cutaneous lupus erythematosus (LE) (systemic LE). The classic butterfly rash occurs in 10% to 50% of patients with acute LE. (From Habif TP: *Clinical dermatology: a color guide to diagnosis and therapy,* ed 3, St Louis, 1996, Mosby.)

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 20 to 70 cases per 100,000 persons. Certain ethnic groups, including those of African, Hispanic, or Asian ancestry, are at an increased risk of developing the disorder.
PREDOMINANT SEX: Female/male ratio is 9:1.
PREDOMINANT AGE: Predominant age ranges from 20 to 45 yr (childbearing age).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Constitutional: unexplained fever, fatigue, malaise (see Table S1-31)
- Skin: malar rash sparing nasolabial folds (acute cutaneous lupus) (Fig. S1-96); annular or papulosquamous rash (subacute cutaneous lupus) (Fig. S1-97); raised erythematous patches with subsequent edematous plaques and adherent scales (discoid cutaneous lupus) (Fig. S1-98); alopecia, nasal, or oropharyngeal ulcerations; Raynaud's phenomenon; petechiae, palpable purpura, skin ulceration, or digital ischemia (vasculitis); livedo reticularis or livedo racemosa (secondary antiphospholipid antibody syndrome)
- Musculoskeletal: arthritis (tenderness, swelling, effusion) typically affecting peripheral joints; myositis
- Cardiac: pericardial rub (pericarditis), heart murmur (Libman-Sacks endocarditis and other valvular heart disease), congestive heart failure (myocarditis), premature atherosclerotic heart disease
- Pulmonary: pleuritis, pneumonitis, diffuse alveolar hemorrhage
- Gastrointestinal: abdominal pain, intestinal vasculitis, ascites
- Neurologic: headache, psychosis, seizure, acute confusional states, peripheral or cranial neuropathy, transverse myelitis, cerebral vascular accident, chronic cognitive impairment
- Hematologic: anemia (hemolytic, anemia chronic disease, aplastic anemia), thrombocytopenia, leukopenia, lymphadenopathy, secondary antiphospholipid antibody syndrome
- Renal: acute renal failure, proteinuria, nephritic syndrome, nephrotic syndrome

ETIOLOGY

Exact etiology and pathogenesis are uncertain. Genetic susceptibility to lupus is likely inherited as a polygenic trait. Multiple genetic linkages including 1q23, 2q35-37, 6p21-11, and 12q24 show strong associations with SLE. Environmental factors such as ultraviolet light exposure and Epstein-Barr virus infection may have a triggering role. Autoantibodies can be present years before the diagnosis of SLE. Evidence supports the improper processing of nuclear proteins and nucleic acid from cell death. Impairments in neutrophil cell death via a process termed NET-osis (nuclear extracellular trap) contribute to the accumulation of nuclear debris. This, in turn, can lead to the presentation of self-nuclear material to plasmacytoid dendritic cells. Plasmacytoid dendritic cells propagate antibody and immune complex production via a type I interferon-dependent mechanism.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rheumatologic disorder
- Rheumatoid arthritis, mixed connective tissue disease, systemic vasculitis
- Neoplastic disorder
- Hematologic malignancy, paraneoplastic syndrome
- Systemic infection
- Other: thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, primary antiphospholipid antibody syndrome

WORKUP

The diagnosis of SLE is suspected when any four or more of the following 1997 American College of Rheumatology (ACR) criteria (sensitivity 86%, specificity 93%) are present. The more inclusive 2012 Systemic Lupus International Collaborating Clinics (SLICC) Classification Criteria (sensitivity 94%, specificity 92%) is also a validated clinical tool for the diagnosis of SLE.

1997 ACR Criteria

- Malar rash
- Discoid rash
- Photosensitivity (recurrence of unusual skin rash in sun-exposed areas)
- Oral or nasopharyngeal painless ulceration, observed by physician
- Arthritis, nonerosive
- Serositis (pleuritis, pericarditis)
- Renal disorder (persistent proteinuria >0.5 g/day, or ≥3+ on dipstick if quantitation not performed; cellular casts)
- Neurologic disorder (seizures, psychosis [in absence of offending drugs or metabolic derangement])
- Hematologic disorder:
  1. Hemolytic anemia with reticulocytosis
  2. Leukopenia (<4000/mm^3 total on two or more occasions)
  3. Lymphopenia (<1500/mm^3 on two or more occasions)
  4. Thrombocytopenia (<100,000/mm^3 in the absence of offending drugs)
- Immunologic disorder:
  1. Anti–double-stranded DNA antibody (anti-dsDNA)
  2. Anti-Smith antibody (anti-Sm)
  3. Antiphospholipid antibodies (anticardiolipin IgM or IgG, lupus anticoagulant, anti-beta-2 glycoprotein IgM or IgG, or false-positive fluorescent treponemal antibody absorption test or *Treponema pallidum* immobilization for 6 months)
- Antinuclear antibody (ANA): an abnormal titer of ANA by immunofluorescence or equivalent assay at any time in the absence of drugs known to be associated with drug-induced lupus syndrome

2012 SLICC Criteria

SLE can be diagnosed if:

I. Biopsy proven nephritis with either ANA or anti-dsDNA antibodies

or

II. Patient satisfies four clinical criteria, requiring at least one clinical and at least one immunologic criterion

Clinical Criteria

1. Acute cutaneous lupus (Malar rash, bullous lupus, toxic epidermal necrolysis, photosensitive lupus rash, maculopapular lupus, subacute cutaneous lupus)
2. Chronic cutaneous lupus (Discoid, hypertrophic verrucous, panniculitis, mucosal lupus, lupus tumidus, chilblains lupus, lichen planus)
3. Oral ulcers or nasal ulcers
4. Nonscarring alopecia
5. Synovitis (more than two joints or inflammatory arthralgia of more than two joints)

FIGURE S1-97 Subacute cutaneous lupus. (From Hochberg MC et al: *Rheumatology*, ed 4, St Louis, 2008, Mosby.)

FIGURE S1-98 Discoid lupus erythematosus. (From Firestein GS et al: *Kelley's textbook of rheumatology,* ed 8, Philadelphia, 2008, Saunders.)

TABLE S1-32 Autoantibodies and Clinical Significance in Systemic Lupus Erythematosus (SLE)

Autoantibody	Prevalence in SLE	Clinical Significance
Antinuclear Antibody		
Anti-dsDNA	60%	95% specificity for SLE; fluctuates with disease activity; associated with glomerulonephritis
Anti-Smith	20%-30%	99% specificity for SLE; associated with anti-U1RNP antibodies
Anti-U1RNP	30%	Antibody associated with mixed connective tissue disease and lower frequency of glomerulonephritis
Anti-Ro/SSA	30%	Associated with Sjögren's syndrome, photosensitivity, SCLE, neonatal lupus, congenital heart block
Anti-La/SSB	20%	Associated with Sjögren's syndrome, SCLE, neonatal lupus, congenital heart block, anti-Ro/SSA
Antihistone	70%	Also associated with drug-induced lupus
Antiphospholipid	30%	Associated with arterial and venous thrombosis, pregnancy morbidity

SCLE, Subacute cutaneous lupus erythematosus.

From Firestein GS et al: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.

6. Serositis (pleurisy for more than 1 day, pericardial pain for more than 1 day)
7. Renal (> 500 mg proteinuria/24 hours) or RBC casts)
8. Neurologic (seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, acute confusional state)
9. Hemolytic anemia
10. Lymphopenia (<1000/mm^3 at least once)
11. Thrombocytopenia (<100,000/mm^3 at least once)

Immunologic Criteria

1. ANA
2. Anti-dsDNA (>2× laboratory reference range)
3. Anti-Smith
4. Antiphospholipid antibodies (Lupus anticoagulant, RPR, anti-cardiolipin IgA, IgG, IgM, anti-β2 glycoprotein IgA, IgG, IgM)
5. Low complements
6. Direct Coombs test in the absence of hemolytic anemia

LABORATORY TESTS

Suggested initial laboratory evaluation of suspected SLE:

- Complete blood count with differential, blood urea nitrogen and serum creatinine, urinalysis, ESR, PT, PTT, complements (C3, C4, CH50)
- ANA

Consider additional laboratory testing:

- Anti-dsDNA, anti-Smith, anti-SSA, anti-SSB, anti-RNP antibodies. Table S1-32 summarizes autoantibodies and clinical significance in SLE.
- Lupus anticoagulant, RPR, anticardiolipin antibodies, anti-beta-2 glycoprotein antibodies especially in patients with thrombotic events or recurrent miscarriages
- Random spot urine protein to urine creatinine ratio, 24-hour urine protein collection if proteinuria
- Direct Coombs

IMAGING STUDIES

- Chest x-ray for evaluation of pulmonary involvement (pleural effusion, pulmonary infiltrates)
- Electrocardiogram for chest pain
- Echocardiogram if murmur, evidence of new or unexplained congestive heart failure, or suspected pericarditis

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Patients with SLE should avoid sunlight and use high-SPF sunscreen.
- Screening and counseling for modifiable cardiovascular risk factors like cigarette cessation are necessary for the prevention of atherosclerotic disease.
- Counseling for pregnancy planning should be performed for patients of childbearing age.
- Calcium carbonate and vitamin D_3 supplementation for prevention of early osteoporosis.

GENERAL Rx

- Limited and defined courses of corticosteroids are useful for a variety of SLE symptoms. Steroid courses should be restricted to acute or subacute control of symptoms, due to an associated increased cardiovascular risk and long term use of corticosteroids.
- Immunosuppressive drugs such as methotrexate or azathioprine are used as steroid-sparing drugs. Indications for immunosuppressive therapy in SLE are described in Tables S1-33 and S1-34.
- Joint pain and mild serositis are generally well controlled with nonsteroidal anti-inflammatory drugs or low-dose corticosteroids. Hydroxychloroquine and methotrexate are also effective for arthritis. Leflunomide, rituximab, or anti-TNF agents may be considered for difficult arthritis.
- Cutaneous manifestations
  1. Topical or intradermal corticosteroids are helpful for individual discoid lesions, especially in the scalp.
  2. Hydroxychloroquine is efficacious. A combination of quinacrine and hydroxychloroquine or chloroquine could be considered for refractory skin disease.
- Hematologic manifestations
  1. Corticosteroids are first-line therapy.

TABLE S1-33 Indications for Immunosuppressive Therapy in Systemic Lupus Erythematosus

General Indications
Involvement of major organs or extensive involvement of nonmajor organs (skin) refractory to other agents, or both
Failure to respond to or inability to taper corticosteroids to acceptable doses for long-term use
Specific Organ Involvement
Renal
Proliferative or membranous nephritis (nephritic or nephritic syndrome), or both
Hematologic
Severe thrombocytopenia (platelets <20,000/mm^3)
Thrombotic thrombocytopenic purpura–like syndrome
Severe hemolytic or aplastic anemia, or immune neutropenia not responding to glucocorticoids
Pulmonary
Lupus pneumonitis or alveolar hemorrhage, or both
Cardiac
Myocarditis with depressed left ventricular function, pericarditis with impending tamponade
Gastrointestinal
Abdominal vasculitis
Nervous system
Transverse myelitis, cerebritis, optic neuritis, psychosis refractory to corticosteroids, mononeuritis multiplex, severe peripheral neuropathy

From Firestein GS et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.

TABLE S1-34 Recommended Immunosuppressive Therapy for Major Organ Involvement in Systemic Lupus Erythematosus

Disease Severity	Induction Therapy	Maintenance Therapy
Mild	High-dose GC (0.5-1 mg/kg/day prednisone ×4-6 wk, tapered to 0.125 mg/kg every other day within 3 mo) alone or in combination with AZA (1-2 mg/kg/day)	Low-dose GC (prednisone ≤0.125 mg/kg on alternative days) alone or with AZA (1-2 mg/kg/day)
	If no remission within 3 mo, treat as moderately severe	Consider further gradual tapering at the end of each year of remission
Moderate	MMF (2 g/day) (or AZA) with GC as above; if no remission after the first 6-12 mo, treat as severe	MMF tapered to 1.5 g/day for 6-12 mo and then to 1 g/day; consider further tapering at the end of each year in remission Alternative: AZA (1-2 mg/kg/day)
Severe	Pulse IV-CYC alone or in combination with pulse IV-MP for the first 6 mo (background GC 0.5 mg/kg/day for 4 wk, then taper)	Quarterly pulses of IV-CYC for at least 1 year beyond remission
	If no response, consider adding RTX or switch to MMF	Alternative: AZA (1-2 mg/kg/day), MMF (1-2 g/day)

AZA, Azathioprine; *CYC,* cyclophosphamide; *GC,* glucocorticoid; *IV,* intravenous; *MMF,* mycophenolate mofetil; *MP,* methylprednisolone; *RTX,* rituximab.

From Firestein GS et al: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.

TABLE S1-35 Severity of Lupus Nephritis*

Proliferative Disease	
Mild	Type III without severe histologic features (e.g., crescents, fibrinoid necrosis); low chronicity index (i.e., ≤3); normal renal function; nonnephrotic-range proteinuria
Moderately severe	Mild disease as defined above with partial or no response after the initial induction therapy or delayed remission (>12 months), or Focal proliferative nephritis with adverse histologic features or reproducible increase of at least 30% in serum creatinine levels, or Diffuse proliferative nephritis (class IV) without adverse histologic features
Severe	Moderately severe as defined above but not remitting after 6 to 12 months of therapy, or Proliferative disease with impaired renal function and fibrinoid necrosis or crescents in >25% of glomeruli, or Mixed membranous and proliferative nephritis, or Proliferative nephritis with high chronicity alone or in combination with high activity (chronicity index >4 or chronicity index >3 and activity index >10), or Rapidly progressive glomerulonephritis (doubling of serum creatinine within 2 to 3 months)
Membranous Nephropathy	
Mild	Nonnephrotic-range proteinuria with normal renal function
Moderate	Nephrotic-range proteinuria with normal renal function at presentation
Severe	Nephrotic-range proteinuria with impaired renal function at presentation (at least 30% increase in serum creatinine)

*Concomitant therapy with corticosteroids or other immunosuppressive drugs may modify urinary sediment and/or histologic findings and should be taken into consideration.

From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

2. Azathioprine can be used for thrombocytopenia or hemolytic anemia.
3. Intravenous immunoglobulin or rituximab may be considered for severe leukopenia, autoimmune hemolytic anemia, or autoimmune thrombocytopenia.

- Central nervous system manifestations.
  1. Headaches are treated symptomatically.
  2. Anticonvulsants and antipsychotics may be indicated.
  3. Standard therapy for other neuropsychiatric SLE symptoms is not established.
- Renal disease (Class III, IV, V lupus nephritis; see Table S1-35)
  1. The use of high doses of intravenous cyclophosphamide with corticosteroids given at monthly intervals is more effective in preserving renal function than is treatment with glucocorticoids alone.
  2. Increasingly, mycophenolate mofetil (maximum of 3000 mg daily in divided doses) has become the induction treatment of choice due to its improved tolerability and better fertility profile. Studies show that patients treated with mycophenolate mofetil as induction therapy had similar renal and nonrenal outcomes as compared to high-dose intravenous cyclophosphamide.
- Mycophenolate mofetil or azathioprine is used for maintenance therapy.
- Severe nonrenal organ disease
  1. Evidence from systematic randomized controlled trials for nonrenal lupus treatment is comparatively limited.
  2. High-dose intravenous cyclophosphamide is used as induction treatment. Azathioprine or mycophenolate mofetil may be used as maintenance drugs.
  3. Intravenous immunoglobulin may be considered in severe disease when concomitant infection is present.
  4. Plasmapheresis may be considered in critical situations, but efficacy is not proved in controlled trials and infectious complication is a substantial consideration.
- New therapy
  1. Rituximab: randomized controlled trials for rituximab as an adjunct induction agent were negative in terms of both renal and nonrenal outcomes. Other clinical trials have shown an improvement in certain SLE parameters with rituximab.
  2. Belimumab: in March 2011, the U.S. Food and Drug Administration approved belimumab for treatment of active SLE in adults. When used in addition to standard therapy, patients on belimumab showed increased efficacy compared to placebo based on a newly defined clinical benchmark. A majority of study patients had primary dermatologic or joint disease. Patients with CNS or serious kidney disease were excluded. Belimumab-treated patients had a reduced time to disease flare and lower glucocorticoid exposure.

DISPOSITION

- Most patients with SLE experience remissions and exacerbations.
- Five-year survival rate has improved to over 90% in patients with newly diagnosed SLE since the advent of potent immunosuppressive therapy. The 15-year survival rate is now 85%.
- African Americans, Asian Americans, and Hispanic Americans in general have a worse prognosis.
- The leading cause of death in SLE patients in developed countries is premature atherosclerosis.
- The quality of life for SLE patients is poor due to fatigue, chronic pain, and cognitive impairment.

REFERRAL

- Rheumatology consultation for all patients with SLE
- Hematology consultation for patients with significant hematologic abnormalities (e.g., severe hemolytic anemia or thrombocytopenia)
- Nephrology consultation in patients with significant renal involvement
- Dermatology consultation for patients with unexplained or unusual skin rash
- Cardiology consultation for patients with lupus carditis, arrhythmias

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Systemic Lupus Erythematosus (Patient Information)

AUTHOR: **SAMUEL H. POON, M.D.**

EVIDENCE

Abstract[1]

Objective:

We sought to assess if the exclusive use of a broad-spectrum sunscreen can prevent skin lesions in patients with different subtypes of cutaneous lupus erythematosus (CLE) induced by ultraviolet (UV) irradiation under standardized conditions.

Methods:

A total of 25 patients with a medical history of photosensitive CLE were included in this monocentric, randomized, vehicle-controlled, double-blind, intraindividual study. The test product and its vehicle were applied 15 minutes before UVA and UVB irradiation of uninvolved skin areas on the upper aspect of the back in a random order, and standardized phototesting was performed daily for 3 consecutive days.

Results:

Characteristic skin lesions were induced by UVA and UVB irradiation in 16 patients with CLE in the untreated area, and 14 patients showed a positive test result in the vehicle-treated area. In contrast, no eruptions compatible with CLE were observed in the sunscreen-treated area in any of the 25 patients. This resulted in significant differences ($P<.001$) between UV-irradiated sunscreen-treated versus vehicle-treated areas, and between UV-irradiated sunscreen-treated versus untreated areas. Furthermore, a significant difference ($P<.05$) was observed concerning the age of disease onset and the patient history of photosensitivity. Patients who were younger than 40 years at onset of CLE reported photosensitivity significantly more often than patients with a higher age of disease onset. None of the patients showed any adverse events from application of the test product or the vehicle.

Limitations:

Data resulting from standardized experimental phototesting might not be transferable to a clinical setting.

Conclusion:

These results indicate clearly that the use of a highly protective broad-spectrum sunscreen can prevent skin lesions in photosensitive patients with different subtypes of CLE. Ⓐ

Evidence-Based Reference

Kuhn A et al.: Photoprotective effects of a broad-spectrum sunscreen in ultraviolet-induced cutaneous lupus erythematosus: a randomized, vehicle-controlled, double-blind study, *J Am Acad Dermatol* 64:37–48, 2011. Ⓐ

SUGGESTED READINGS

Bosch X: Systemic lupus erythematosus and the neutrophil, *N Engl J Med* 365:758–760, 2011.

D'Cruz DP et al.: Systemic lupus erythematosus, *Lancet* 369:587, 2007.

Fine DM: Pharmacologic therapy of lupus nephritis, *JAMA* 293:3053, 2005.

Furie R et al.: A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus, *Arthritis Rheum* 63:3918–3930, 2011.

Navarra SV et al.: Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial, *Lancet* 377:1721–1731, 2011.

Tsokos GC: Systemic lupus erythematosus, *N Engl J Med* 365:2110–2121, 2011.

BASIC INFORMATION

DEFINITION

Tabes dorsalis is a form of tertiary neurosyphilis affecting the dorsal columns of the spinal cord and peripheral nerves, characterized by paroxysmal pain, particularly in the abdomen and legs; sensory ataxia; normal strength; autonomic dysfunction; and Argyll Robertson pupils.

SYNONYMS

Posterior spinal sclerosis
Tabetic neurosyphilis
Syphilitic myeloneuropathy

ICD-9CM CODES
094.0 Tabes dorsalis, ataxia, locomotor
ICD-10CM CODES
A52.11 Tabes dorsalis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Rare, but increasing with HIV/AIDS
PEAK INCIDENCE: 15 to 20 yr after initial infection
PREVALENCE (IN U.S.): Rare; more common with HIV/AIDS epidemic. Ten percent of untreated patients with syphilis develop neurosyphilis, 2% to 5% of whom may develop tabes dorsalis. Relative prevalence of tabes dorsalis is reduced compared with the preantibiotic era. This may be the only clinical manifestation of neurosyphilis that has been altered during the antibiotic era.
PREDOMINANT SEX: Male

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Argyll Robertson pupils are common. The pupil reacts poorly to light but well to accommodation (light-near dissociation)

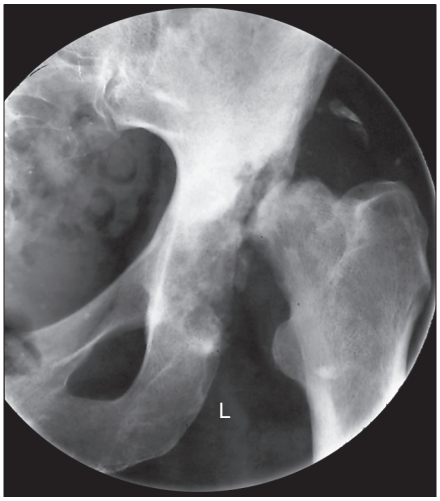


FIGURE ET1-1 Neuropathic hip secondary to tabes dorsalis. (Courtesy Dr. I. Watt. From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

- Loss of position and vibration at ankles (wide-based gait, inability to walk in the dark, sensory ataxia)
- Loss of deep pain sensation, resulting in deep foot ulcers
- Degenerative joint disease (Fig. ET1-1), especially in knees, caused by severe neuropathy (Charcot joints)
- Normal strength with areflexia in the legs
- Lightning pains in the legs
- Severe intermittent visceral pains, such as gastrointestinal and laryngeal (visceral crises)
- Autonomic dysfunction (urinary and fecal incontinence)

ETIOLOGY

Infectious *(Treponema pallidum).* Neurosyphilis occurs as a consequence of treponemal penetration of the blood-brain barrier.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Vitamin B_{12} deficiency (subacute combined degeneration of the spinal cord)
- Vitamin E deficiency
- Chronic nitrous oxide abuse
- Spinal cord neoplasm (involving conus medullaris)
- Lyme disease

WORKUP

Thorough neurologic history and examination

LABORATORY TESTS

- Lumbar puncture for elevated Venereal Disease Research Laboratory (VDRL) and fluorescent treponemal antigen-antibody test (FTA-ABS) titers: false-positive cerebrospinal fluid (CSF) VDRL titers may occur with traumatic tap. CSF mononuclear pleocytosis (>5 white cells/μL; commonly >20) with increased protein supports the diagnosis.
- Serum VDRL test: results may be normal in 25% to 30% of patients. Serum microhemagglutination: *Treponema pallidum* (MHA-TP) or FTA-ABS is necessary if clinical suspicion is high.
- False-positive serum VDRL may occur in Lyme disease, nonvenereal treponematoses, genital herpes simplex, pregnancy, systemic lupus erythematosus, alcoholic cirrhosis, scleroderma, and mixed connective tissue disease.
- Persons who are HIV positive are at increased risk of developing neurosyphilis. A new development in the detection of neurosyphilis in patients who are HIV positive is the use of the B cell chemoattractant chemokine (CXC motif) ligand 13 as a CSF marker.

IMAGING STUDIES

Not necessary if diagnosis confirmed clinically and serologically

TREATMENT

ACUTE GENERAL Rx

- Aqueous penicillin G 3 million to 4 million U IV q4h for 10 to 14 days or penicillin G 18-24 million units per day as continuous infusion.
- If patient is penicillin allergic, either desensitize to penicillin or obtain an infectious disease (ID) consultation.
- Many of the symptoms—degenerative neuropathic joint disease, lightning pains—persist after treatment.

CHRONIC Rx

- Physical therapy
- Analgesics, carbamazepine, gabapentin, or steroids may help lightning pain
- Supportive care (wheelchair, toileting issues, etc.)

DISPOSITION

- Close follow-up required. Repeat lumbar puncture is recommended every 6 mo until CSF pleocytosis normalizes. If pleocytosis does not normalize in 6 mo or CSF is still abnormal in 2 yr, repeat treatment. Serologic criterion for response to therapy is a fourfold or greater decrease in VDRL titer over 6-12 mo.
- Further indication for retreatment: if there is a fourfold increase in titers or a failure of titers >1:32 to decrease at least fourfold by 6-12 mo.

REFERRAL

- Joint replacement in moderate cases
- ID consult for patients with penicillin allergy

PEARLS & CONSIDERATIONS

COMMENTS

Diagnosis should be considered in all patients with a progressive neuropsychiatric disorder with signs of spinal cord dysfunction and peripheral neuropathy.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Syphilis (Related Key Topic)

AUTHOR: **SACHIN KEDAR, M.B.B.S., M.D.**

SUGGESTED READINGS

Centers for Disease Control and Prevention: 2010 sexually transmitted diseases treatment guidelines, *MMWR Morb Mortal Wkly Rep* 59(RR-12):1–110, 2010.

Conde-Sendin MA et al.: Current clinical spectrum of neurosyphilis in immunocompetent patients, *Eur Neurol* 52:29, 2004.

Marra CM et al.: CXCL13 as a cerebrospinal fluid marker for neurosyphilis in HIV-infected patients with syphilis, *Sex Transm Dis* 37(5):283–287, 2010.

Mattei PL et al.: Syphilis: a reemerging infection, *Am Fam Phys* 86(5):433–440, 2012.

Timmermans M, Carr J: Neurosyphilis in the modern era, *J Neurol Neurosurg Psychiatry* 75:1727, 2004.

BASIC INFORMATION

DEFINITION

Takayasu's arteritis is a chronic idiopathic systemic granulomatous large-vessel vasculitis that primarily affects the aorta and its main branches. It often presents as a pulseless disease caused by widespread arterial stenosis.

SYNONYMS

Pulseless disease
Aortitis syndrome
Aortic arch arteritis
Nonspecific aortoarteritis

ICD-9CM CODES
446.7 Takayasu disease or syndrome
ICD-10CM CODES
M31.4 Aortic arch syndrome [Takayasu]

EPIDEMIOLOGY & DEMOGRAPHICS

Takayasu's arteritis is the third most common childhood vasculitis worldwide, although it is relatively uncommon in Europe and North America. Most cases have been reported in Japan, China, India, and Mexico. There is typically a considerable delay to diagnosis in Western populations as opposed to Asian countries, owing in large part to the increased incidence in Asia.

INCIDENCE: Incidence in the United States is 2.6/1 million persons.

PREDOMINANT SEX AND AGE: The female/male ratio is 8:1. The age of onset is usually between 10 and 40 yr of age, with three quarters of patients presenting between the age of 10 and 20 years old.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Takayasu's arteritis is typically divided into systemic and occlusive stages, with the occlusive stage characterized by ischemia and symptoms from arterial occlusion. Table T1-1 summarizes common symptoms and signs in Takayasu's arteritis.
- The systemic stage of Takayasu's arteritis manifests as nonspecific inflammatory symptoms, including the following:
  1. Low-grade fever
  2. Malaise
  3. Weight loss
  4. Fatigue
  5. Arthralgia and myalgia
  6. Carotidynia
- The occlusive stage of Takayasu's arteritis may progress to stenosis or aneurysm of the aorta and its primary branches, and may manifest as a variety of clinical signs and symptoms, such as:
  1. Arm or leg claudication, weakness, and numbness
  2. Amaurosis fugax, diplopia, headache, orthostasis, vertigo, or syncope
  3. Angina or myocardial infarction
  4. Vascular bruits of the carotid artery, subclavian artery, and aorta
  5. Discrepancy of blood pressures between the upper extremities, typically of ≥10 mm Hg
  6. Diminished or absent pulses, ischemic ulcerations, or gangrene in advanced disease
  7. Hypertension
  8. Retinopathy
  9. Aortic insufficiency as a result of aortic root dilatation and aneurysm formation
  10. Weakness of the arterial walls may give rise to localized aneurysms/dissection.

ETIOLOGY

- The cause of Takayasu's arteritis is poorly understood. Cell-mediated mechanisms are thought to be important to the pathogenesis. Positive associations with HLA-B52, HLA-B39, and HLA-B67 have been identified, suggesting an immunogenetic component.
- Infiltration by inflammatory cells (lymphocytes, macrophages, and multinucleated giant cells) into the vasa vasorum and media of the large elastic arteries (Fig. ET1-2) leads to production of matrix metalloproteinases (MMP), which cause destruction of elastic fibers in the arterial wall, neovascularization, and other inflammatory changes. An intermediate stage, driven in part by TNF-alpha, leads to mucopolysaccharide deposition and proliferation of fibroblasts and smooth muscle cells causing intimal hypertrophy. With chronic disease, inflammatory lesions progress to either thick fibrotic calcified narrowings (≥90% of cases) or aneurysms if fibrosis is insufficient and the arterial wall is instead thinned and dilated (≥25% of cases).
- Infection, in particular, tuberculosis, has been implicated in the pathogenesis of Takayasu's disease with several studies reporting an increased incidence of caseating granulomas in Takayasu patients. Additional immunologic studies lend support to a pathogenic role of CD4 and CD8 T-cells in this patient population.

DIAGNOSIS

Diagnostic criteria for Takayasu's arteritis were established by the American College of Rheumatology in 1990. A diagnosis is made if at least three of the six criteria are present; this results in a sensitivity of 91% and specificity of 98%. The criteria are:

- Age of disease onset <40 yr
- Claudication of the extremities
- Decreased brachial artery pulse
- Systolic blood pressure difference ≥10 mm Hg between left and right arms
- Bruit over one or both of the subclavian arteries or the abdominal aorta

TABLE T1-1 Common Symptoms and Signs (%) in Takayasu's Arteritis

	STUDY					
Symptom/Sign	**Japan (n = 52)**	**India (n = 106)**	**China (n = 530)**	**Korea (n = 129)**	**USA (n = 60)**	**Mexico (n = 107)**
Fatigue/constitutional	27%	—	—	34%	43%	78%
Weight loss	—	9%	—	11%	20%	22%
Musculoskeletal	6%	5%	—	—	53%	53%
Claudication	13%	—	25%	21%	90%	29%
Headache	31%	44%	—	60%	42%	57%
Visual changes	6%	12%	10%	20%	30%	8%
Syncope/dizziness	40%	26%	14%	36%	35%	13%
Palpitations	23%	19%	—	23%	10%	43%
Dyspnea	21%	26%	11%	42%	—	72%
Carotidynia	21%	—	—	2%	32%	—
Hypertension	33%	77%	60%	40%	35%	72%
Bruit	—	35%	58%	37%	80%	94%
Decreased pulses	62%	—	37%	55%	60%	96%
Asymmetric blood pressure	—	—	—	—	47%	—

From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

TABLE T1-2 Pathologic Characteristics of Selected Forms of Vasculitis

	Takayasu's Arteritis	Polyarteritis Nodosa	Wegener's Granulomatosis	Churg-Strauss Syndrome	Henoch-Schönlein Purpura	Cutaneous Leukocytoclastic Angiitis
Vessels involved	Elastic (large) or muscle (medium-sized) arteries	Medium-sized and small muscle arteries	Small arteries and veins; sometimes medium-sized vessels	Small arteries and veins; sometimes medium-sized vessels	Capillaries, venules, arterioles	Capillaries, venules, arterioles
Organ involvement	Aorta, aortic arch and major branches, pulmonary arteries	Skin, peripheral nerve, gastrointestinal tract, other viscera	Upper respiratory tract, lungs, kidneys, skin, eyes	Upper respiratory tract, lungs, heart, peripheral nerves	Skin, joints, gastrointestinal tract, kidneys	Skin, joints
Type of vasculitis and inflammatory cells	Granulomatous with some giant cells; fibrosis in chronic stages	Necrotizing, with mixed cellular infiltrate	Necrotizing or granulomatous (or both); mixed cellular infiltrate plus occasional eosinophils	Necrotizing or granulomatous (or both); prominent eosinophils and other mixed infiltrate	Leukocytoclastic, with some lymphocytes and variable eosinophils; IgA deposits in affected tissues	Leukocytoclastic, with occasional eosinophils

From Goldman L, Schafer AI: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Saunders.

- Abnormal arteriogram, not related to arteriosclerosis or fibromuscular dysplasia

DIFFERENTIAL DIAGNOSIS

Table T1-2 describes pathologic characteristics of selected forms of vasculitis. Other causes of inflammatory arteritis must be excluded:

- Temporal arteritis (giant cell arteritis)
- Syphilis
- Tuberculosis
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Buerger's disease
- Behçet's disease
- Cogan's syndrome
- Kawasaki disease
- Spondyloarthropathies

WORKUP

Any young patient with findings of absent pulses and loud bruits merits a workup for Takayasu's arteritis. The workup generally includes blood testing to look for signs of inflammation as well as imaging studies. An angiogram continues to be the diagnostic gold standard; however, due to advances in noninvasive vascular imaging, modalities such as magnetic resonance and computed tomography angiography (MRA and CTA), ultrasound, and FDG-PET are commonly used for diagnosis as well as in serial monitoring of disease activity.

LABORATORY TESTS

- Erythrocyte sedimentation rate (ESR) and serum C-reactive protein levels are usually elevated, but can be normal even in the setting of active vasculitis.
- A CBC may reveal a normal or elevated white blood cell count as well as anemia.
- Immunologic studies may include elevated immunoglobulins (IgG and IgA) and complement components (C3 and C4).
- Hypercoagulation and increase in platelet aggregation
- Recent studies have attempted to establish a link between elevated levels of various interleukins and other inflammatory markers and active disease.

IMAGING STUDIES

- Imaging of the entire aorta and major branch vessels using angiography, CTA or MRA
- CTA can detect changes in the vessel wall and provide an accurate representation of luminal diameters.
- Cardiovascular magnetic resonance (CMR) provides information on vessel lumen and wall thickening, cardiac morphology and function, and myocardial tissue characterization.
- Angiography (Fig. T1-3) can show the narrowing of the aorta and its branches, aneurysm formation, poststenotic dilation, and the development of any collateral circulation. Angiographic findings are classified into five types:
  1. Type I: lesions that involve only branches of the aortic arch
  2. Type IIa: lesions that involve the ascending aorta, the aortic arch, and its branches
  3. Type IIb: lesions from IIa plus the thoracic descending aorta
  4. Type III: lesions that involve the thoracic descending aorta, abdominal aorta, and/or renal arteries
  5. Type IV: lesions that involve the abdominal aorta and/or renal arteries
  6. Type V: lesions that involve the entire aorta and its branches
- Chest radiography: pathologic changes of the aorta are often visible, with areas of alternating stenosis and dilation seen. Segmental calcification outlining areas of aortic narrowing is characteristic of Takayasu's disease.
- Ultrasound: carotid, thoracic, and abdominal ultrasound are useful adjunctive imaging studies to diagnose the occlusive disease that results from Takayasu's arteritis. The addition of Doppler is helpful to assess blood flow and absent pulses.
- Positron emission tomography using radioisotope fluorodeoxyglucose (FDG-PET) as a marker for tissue with high glucose uptake has shown promising results in terms of specificity and sensitivity.

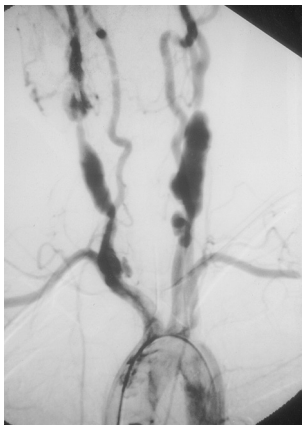


FIGURE T1-3 Angiogram of a child with Takayasu's arteritis that shows massive bilateral carotid dilation, stenosis, and poststenotic dilation. (From Behrman RE: *Nelson textbook of pediatrics*, ed 16, Philadelphia, 2000, Saunders.)

Rx TREATMENT

- To date there have been no controlled clinical trials evaluating the efficacy or safety of different agents in the acute or chronic treatment of Takayasu's arteritis.

ACUTE GENERAL Rx

- High-dose glucocorticoids are first-line therapy for suppressing systemic symptoms and stopping disease progression. Prednisone (40 to 60 mg PO daily or 1 mg/kg/day) can be used for 3 months or intravenous steroids can be administered initially.
- Patients are monitored for symptoms and the ESR is followed. Attempts to taper prednisone can be made with resolution of constitutional symptoms, significant decline in the ESR and C-reactive protein levels, and in accordance with imaging studies.

- The majority of patients require a second agent to achieve and sustain remission with steroid dose reduction. Commonly used second-line agents include methotrexate, azathioprine, and cyclophosphamide.
- Strong observational evidence supports use of TNF-α inhibitors in treating patients refractory to initial therapies and in those patients unable to taper steroids. Limited experience with other biologic agents, including the IL-6 inhibitor tocilizumab and the B-cell inhibitor rituximab, has shown promising results in certain patient groups.

CHRONIC Rx

Patients with Takayasu's arteritis are monitored closely for signs of relapse and disease complications with clinical assessment, inflammatory biomarkers (e.g., ESR and CRP), and imaging.

Multiple indexes exist for the assessment of disease activity, including the NIH criteria for active disease, the Disease Extent Index-Takayasu (DEI-Tak), and the Indian Takayasu's Arteritis Score (ITAS).

- Treatment of hypertension in these patients can be difficult, especially since typically there is concurrent glucocorticoid therapy and there is the potential for renovascular hypertension. Special monitoring should be employed when using ACE inhibitors due to the high frequency of renal artery stenosis in this population.
- Percutaneous angioplasty or bypass grafts should be considered for irreversible arterial stenoses with severe ischemia (cardiac or cerebral), severe hypertension in renal artery stenosis, or aneurysmal enlargement with risk of rupture. Five-year arterial complication rate after surgical or endovascular revascularization is 44%; the likelihood of complications increases sevenfold when inflammation is present at the time of revascularization.
- There have been positive data regarding drug-eluting stents, and in particular sirolimus-covered stents, likely related to the synergistic effect of its antiproliferative and immunosuppressive properties.
- Studies of coronary artery angioplasty and stenting in this population are limited, due to a high frequency of coronary lesions that are near the ostia; a large number of these patients have surgical interventions as opposed to percutaneous interventions.
- Aortic regurgitation may require valve replacement or repair by surgery, although the need to manipulate friable tissue can lead to complications such as valvular detachment after replacement.

DISPOSITION

- Immunosuppressant therapy may achieve clinical remission.
- No studies have proved that treatment results in regression of stenosis, although there are limited case reports describing the return of pulses with treatment.
- With the addition of a second agent for patients with treatment resistance or relapse, 50% remission has been seen.
- Quality of life is comparable to that of patients with rheumatoid arthritis or ankylosing spondylitis.
- Mortality results are mixed, with high rates in reports from Asia and lower rates in studies performed in the United States (2%). In the absence of major complications (MI, stroke, severe HTN, heart failure, aneurysm), 5-year survival rates reach 95%. In the presence of major complications, 5-year survival is 50% to 70%.
- Death can occur suddenly from a ruptured aneurysm, a myocardial infarction, or a cerebrovascular accident.

REFERRAL

Whenever the diagnosis of vasculitis is suspected, a rheumatology consultation is appropriate. Vascular surgery and cardiology consultations are recommended for any evidence of carotid, peripheral, or coronary artery disease or if a large abdominal aneurysm is found.

PEARLS & CONSIDERATIONS

With long-term glucocorticoid use, consider measures to protect against bone loss. Bisphosphonates have been studied prospectively with corticosteroid use in this fashion; remember to ensure adequate dietary calcium and vitamin D intake as well.

COMMENTS

The long-term prognosis of patients with treated Takayasu's disease varies by geography, and 10-yr survival ranges from 80% to 96%.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Vasculitis (Related Key Topic)

AUTHORS: **DAVID SUK, M.D.,** and **PRANAV M. PATEL, M.D.**

SUGGESTED READINGS

Arend WP et al.: American College of Rheumatology 1990 Criteria for the classification of Takayasu's arteritis, *Arthritis Rheum* 33:1129, 1990.

Chatterjee S et al.: Clinical diagnosis and management of large vessel vasculitis: takayasu arteritis, *Curr Cardiol Rep* 16(7):1–10, 2014.

Clifford A, Hoffman G: Recent advances in the medical management of Takayasu arteritis: an update on use of biologic therapies, *Current Opinion in Rheumatology* 26(1):7–15, 2014, January 2014.

Hahn-Kover K et al.: Diagnosis of Takayasu arteritis, *J Clin Rheumatol* 11(3):170, 2005.

Kissin EY et al.: Diagnostic imaging in Takayasu arteritis, *Curr Opin Rheumatol* 16:31, 2004.

Maksimowicz-McKinnon K et al.: Takayasu arteritis: what is the long term prognosis? *Rheum Dic Clin North Am* 33:777, 2007.

Mason JC: Takayasu arteritis—advances in diagnosis and management, *Nat Rev Rheumatol* 6(7):406–415, 2010.

Matsuura K et al.: Surgical treatment of aortic regurgitation due to Takayasu arteritis: long-term morbidity and mortality, *Circulation* 112:3707, 2005.

O'Connor TE et al.: Role of inflammatory markers in Takayasu arteritis disease monitoring, *BMC Neurology* 14(1):62, 2014.

Saadoun D et al.: Retrospective analysis of surgery versus endovascular intervention in Takayasu arteritis: a multicenter experience, *Circulation* 125:813–819, 2012.

Seko Y: Giant cell and Takayasu arteritis, *Curr Opin Rheumatol* 19:39, 2007.

Weyend CM, Goronzy JJ: Mechanisms of disease: medium and large vessel vasculitis, *N Engl J Med* 349:160, 2003.

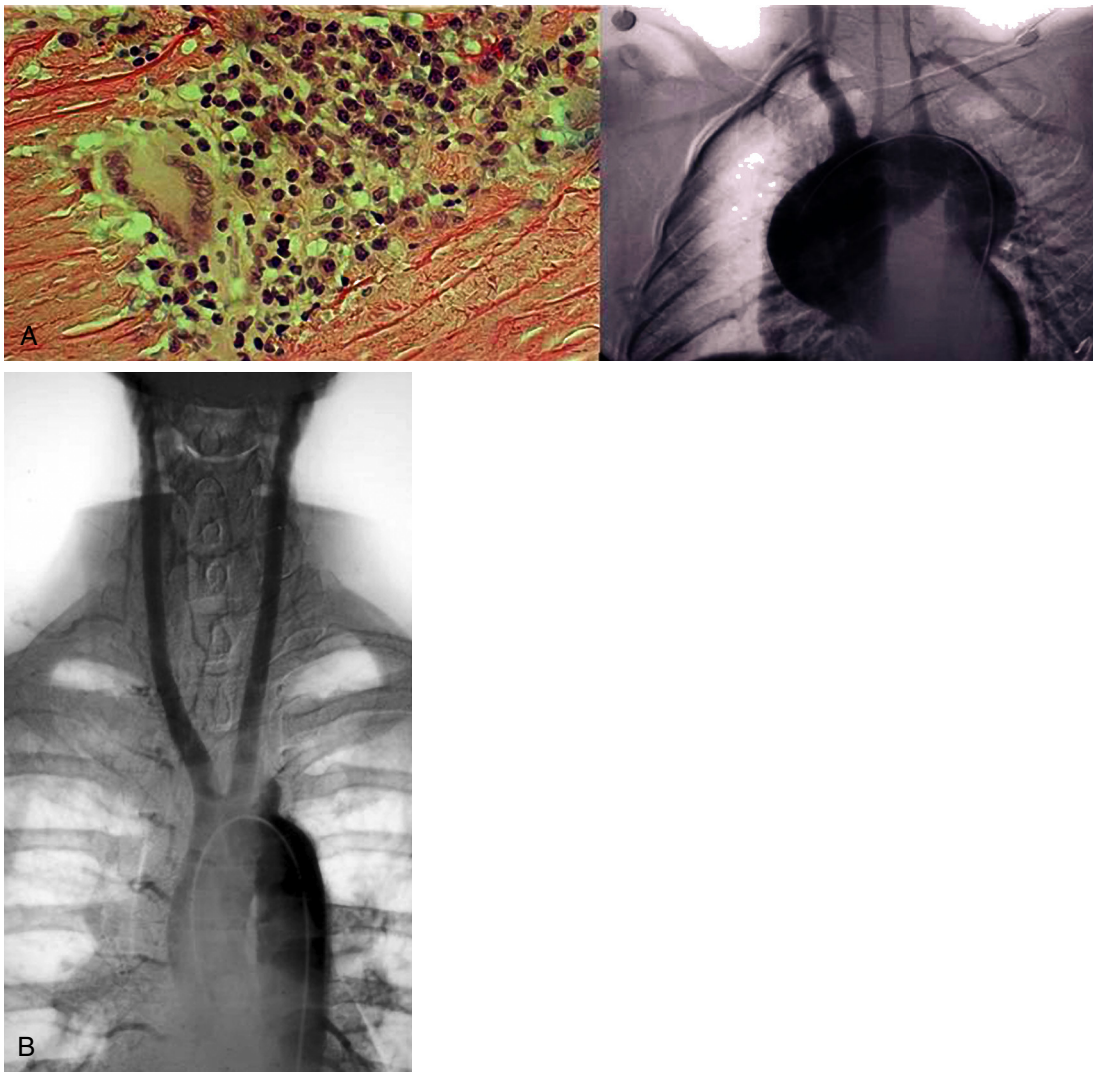


FIGURE ET1-2 Takayasu disease. A, Takayasu arteritis. Granulomatous inflammation and medial destruction (left) has led to marked aortic root dilation (right) in a 17-year-old female high school student who developed symptoms of congestive heart failure and exertional angina. She also had diffuse narrowing of the left common carotid artery and irregular dilation of the innominate artery. (Hematoxylin-eosin stain; magnification ×40.) **B,** Occlusion of both subclavian arteries led to leg pressures being the only reliable measure of central aortic pressure. (Bonow RO et al: *Heart Disease*, ed 9, Philadelphia, 2012, Saunders.)

BASIC INFORMATION

DEFINITION

Takotsubo cardiomyopathy, also known as stress cardiomyopathy (SC), is a syndrome characterized by transient systolic dysfunction and ballooning of the apical and/or mid segments of the left ventricle (LV) that mimics acute myocardial infarction (MI) but in the absence of obstructive coronary artery disease with acute ECG changes including ST segment elevation or depression, in the absence of recent head trauma, intracranial hemorrhage, pheochromocytoma, myocarditis, or hypertrophic cardiomyopathy. Typically, but not always, it is preceded by severe illness or intense emotional, physical, or psychological stress. Initially described in the 1990s in Japan, on left ventriculography this irreversible cardiomyopathy has a distinctive shape similar to a *tako-tsubo* pot with a narrow neck and round bottom, used by fishermen to trap octopi.

SYNONYMS

Stress cardiomyopathy (SC)
Left ventricular apical ballooning syndrome (LVABS)
Broken heart syndrome

ICD-9CM CODES
429.83 Takotsubo syndrome
ICD-10CM CODES
I51.81 Takotsubo syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Uncertain, although increasingly reported. The recurrence rate is 11.4% over 4 yr after initial presentation. Occurs mostly in summer; fewest cases in winter.
PREVALENCE: Studies suggest that it comprises 0.7% to 2.5% of cases presenting with acute coronary syndrome (ACS).
PREDOMINANT SEX AND AGE: Postmenopausal women (90%) are predominantly affected.
RISK FACTORS: Frequently, but not always, triggered by severe medical illness or intense emotional or physical stress (death of loved ones, domestic abuse, fierce arguments, financial hardships, etc.)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acute substernal chest pain, dyspnea, syncope, shock, electrocardiographic (ECG) changes, or elevated cardiac biomarkers; similar to an acute MI.
- Heart failure, a frequent complication (30%) of takotsubo, is seen mostly in patients with other comorbidities and poor functional class. Recovery of function within a few days or weeks after admission is typical. In one experimental study, resolution was described as immediate after injection of adenosine.
- Overall prognosis is benign, but even short-term LV dysfunction can lead to thromboembolic phenomena. Anticoagulation is recommended for certain patients.

ETIOLOGY

Not well understood. Hypotheses include excessive catecholamine release, coronary artery spasm, and/or microvascular disease. Unknown why women are more commonly affected or why the apex and/or mid cavity are affected. Fig. T1-4 depicts the interplay among triggers, pathogenic factors, and predisposing factors in SC.
Several mechanisms have been advocated for acute and reversible coronary microvascular dysfunction:

- Acute microvascular spasm.
- Excessive sympathetic stimulation may induce myocardial metabolic impairment and stunning. Neurogenic stunned myocardium caused by an acute cardiac autonomic dysfunction.
- Coronary artery disease with aborted myocardial infarction. Transient coronary occlusion by a fast-dissolving clot. Spontaneous reperfusion
- Occurrence in postmenopausal women may support the hypothesis of stress-mediated vasoconstriction enhanced by estrogen depletion
- Studies have documented elevated plasma norepinephrine and epinephrine levels in Takotsubo cardiomyopathy.
- Increased serum concentrations of catecholamines have been shown to generate direct myocyte injury. Oxidation of catecholamines results in the formation of highly toxic substances and free radicals, causing intracellular calcium overload and myocardial cell damage. The typical histologic signs of catecholamine toxicity, which are described as focal, mononuclear, inflammatory areas of fibrotic response and characteristic contraction bands, are also reported to be present in takotsubo cardiomyopathy.
- Several studies have indicated that beta-adrenoceptor stimulation is associated with alteration in gene expression of Ca^{2+}-regulatory proteins, which are crucial for contractile function.
- More recently, catecholamine disorder of glucose metabolism has been suggested on the basis of decreased left ventricular apical ^{18}F fluorodeoxyglucose uptake on positron emission scanning.
- Increased beta-adrenoreceptors in the apex and increased surface area of the apex due to trabeculations have also been proposed. Overexpression of beta-adrenoreceptors in response to supraphysiologic doses of epinephrine in mice models has been shown to have negative inotropic effects, possibly due to the intracellular signal trafficking switch from Gs protein to Gi protein.

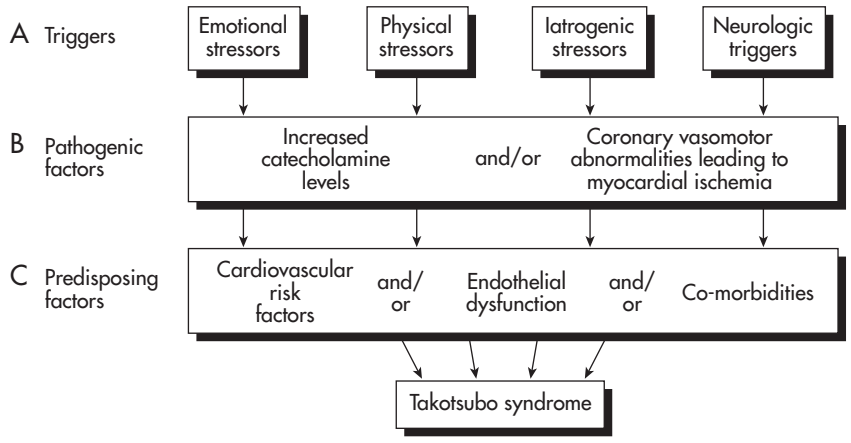


FIGURE T1-4 The interplay among triggers, pathogenic factors, and predisposing factors in Takotsubo disease. (From Pelliccia F, et al: Takotsubo syndrome (stress cardiomyopathy): an intriguing clinical condition in search of its identity, *Am J Med* 127:699-704, 2014.)

DIAGNOSIS

Mayo Clinic proposed criteria (2008) for diagnosis of SC: All 4 criteria required to make diagnosis.

- Transient hypokinesis, akinesis, or dyskinesis in the left ventricular mid segments with or without apical involvement (Fig. T1-5); regional wall motion abnormalities (RWMA) that extend beyond a single epicardial vascular distribution; and frequently, but not always, a stressful trigger.
- Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture.
- New ECG abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponins. Ogura and associates reported that the absence of reciprocal changes, the absence of abnormal Q wave, and the sum of ST-segment elevation in leads V4–6 more than the sum of ST-segment elevation in leads V1-3 identified takotsubo cardiomyopathy with a high sensitivity and specificity. Kosuge and associates recently reported that the combination of the presence of ST-segment depression in lead aVR and the absence of ST-segment elevation in lead V1 also showed a high sensitivity and specificity for diagnosing takotsubo cardiomyopathy. Q-T dispersion is more common in Takotsubo.
- Absence of pheochromocytoma or myocarditis.

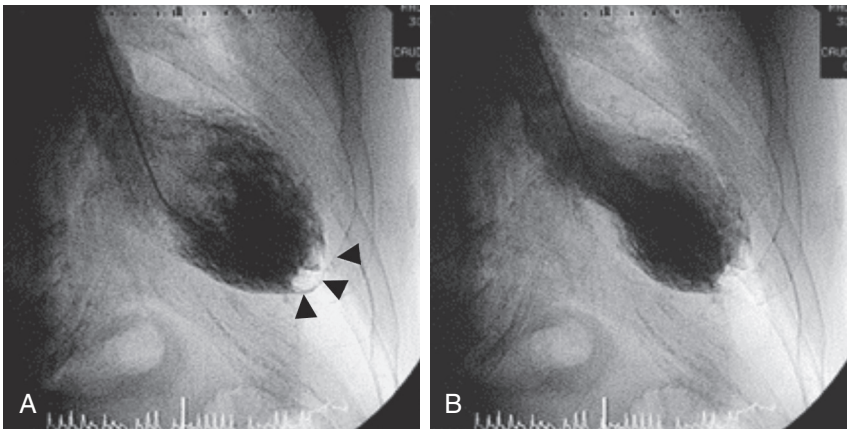


FIGURE T1-5 **A** and **B,** Left ventriculogram showing apical ballooning characteristic of stress-induced cardiomyopathy. (From Mitsuma W et al: *JACC* 51(1): cover, 2008.)

- An inverted takotsubo pattern—mid ventricular ballooning with sparing of the basal and apical segments—atypical variant.
- The RWMA of the right ventricle is present in 30% of patients who tend to develop CHF and who have a poor outcome.

DIFFERENTIAL DIAGNOSIS

- Acute MI
- Cardiac syndrome X
- Prinzmetal's angina
- Myocarditis
- Cocaine abuse

WORK-UP

- This should be suspected in postmenopausal women who present with ACS after intense stress.
- Cardiology consult should be immediately obtained
- Significant CAD should be ruled out as an etiology of the cardiomyopathy, usually by coronary catheterization.

LABORATORY TESTS

- Cardiac biomarkers are often elevated, but typically less than MI. Beta natriuretic peptide (BNP) levels are also commonly elevated.
- Histopathologic findings include interstitial infiltrates of mononuclear lymphocytes and macrophages with fibrosis and contraction band necrosis. These findings are different from coagulation necrosis seen in typical atherosclerotic epicardial artery occlusion and myocardial infarction.

IMAGING STUDIES

- Typically diagnosed in the catheterization lab during left ventriculography, although echocardiography (ECHO) can also show the characteristic apical ballooning. Contrast ECHO is quite useful to exclude apical thrombus. Cardiovascular MRI at the time of initial clinical presentation may provide relevant functional and tissue information that might aid in the establishment of the diagnosis of SC.
- Cardiac magnetic imaging (CMR) features helpful in diagnosis: absence of late gadolinium enhancement (LGE) in contrast to MI and consistent with myocardial viability.

COMPLICATIONS

- Approximately 20% include cardiogenic shock, heart failure, arrhythmias, intraventricular thrombus formation (incidence 2.5%), acute clinically significant mitral regurgitation, LV outflow tract (LVOT) obstruction, free wall rupture, and even death. An LV apical thrombus carries a great risk of cerebrovascular accident and distant embolization during the recovery phase.
- Risk score to predict likelihood of acute HF based on three variables: age >70 years, presence of physical stressor, and LV ejection fraction <40%.
- Prognosis is worse for males.
- Although overall prognosis is good, arrhythmic risk is increasingly being recognized. Vulnerable populations include patients with a QTc >500 msec.

Rx TREATMENT

There are no randomized data or established consensus. In most cases, supportive care is sufficient without specific therapy, due to a favorable prognosis. Standard treatment for systolic dysfunction including beta blockers, ACE inhibitors, and diuretics for volume overload. Patients who are in shock should get urgent ECHO to determine presence of LVOT obstruction.

NONPHARMACOLOGIC THERAPY

Patients in shock without significant LVOT obstruction may benefit from an intraaortic balloon pump (IABP).

ACUTE GENERAL Rx

- Patients who are hemodynamically stable should be started on a beta-blocker, ACE inhibitor, and diuretic if needed.
- Patients who are in shock and with significant LVOT obstruction may benefit from cautious fluid resuscitation (if no significant pulmonary congestion), and use of beta-blockers (can improve hemodynamics by resolution of the obstruction). The use of IABP in this case is controversial due to the potential worsening of LVOT obstruction.
- Patients with systolic anterior motion (SAM) of the anterior mitral valve leaflet or LVOT obstruction should not be exposed to inotropic agents even if they are in shock.

CHRONIC Rx

- Continued medical therapy and repeat ECHO (in 4 to 6 wk) to ensure normalization of systolic function (most patients normalize by this time).
- Duration of medical therapy is debatable. A period of 3-6 mo has been suggested.
- Three months of anticoagulation is suggested if an intraventricular thrombus is detected.
- Recently published data could not find the protective effect of β-blockers in preventing the occurrence or recurrence of SC.

DISPOSITION

Carries a favorable prognosis compared to STEMI or NSTEMI; in-hospital mortality is approximately 2%.

REFERRAL

Follow-up with a cardiologist is suggested.

PEARLS & CONSIDERATIONS

COMMENTS

The term *takotsubo* is the Japanese name for an octopus trap (*tako-tsubo*), which has a similar shape of the LV in systole during a left ventriculogram (see Fig. T1-5).

PREVENTION

Minimizing stress may reduce incidence but no data to support this.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **RABIA ARSHAD, M.D.**

SUGGESTED READINGS

Abisse SA et al.: Takotsubo cardiomyopathy, *Rhode Island Med J* 2:23–27, 2014.

Eitel I et al.: Clinical characteristics and cardiovascular magnetic resonance findings in stress (Takotsubo) cardiomyopathy, *JAMA* 306(3):277–286, 2011.

Elesber AA et al.: Transient cardiac apical ballooning syndrome: prevalence and clinical implications of right ventricular involvement, *J Am Coll Cardiol* 47(5):1082–1083, 2006.

Gianni M et al.: Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review, *Eur Heart J* 27(13):1523–1529, 2006.

Golabchi A et al.: Takotsubo cardiomyopathy or broken heart syndrome: a review article, *J Res Med Sci* 16(3):340–345, 2011.

Haghi D et al.: Incidence and clinical significance of left ventricular thrombus in takotsubo cardiomyopathy assessed with echocardiography, *QJM* 101(5):381–386, 2008.

Haghi D et al.: Right ventricular involvement in Takotsubo cardiomyopathy, *Eur Heart J* 27(20):2433–2439, 2006.

Hurst RT et al.: Transient midventricular ballooning syndrome: a new variant, *J Am Coll Cardiol* 48(3):579–583, 2006.

Kosuge M et al.: Simple and accurate electrocardiographic criteria to differentiate takotsubo cardiomyopathy from anterior acute myocardial infarction, *J Am Coll Cardiol* 55(22):2514–2516, 2010.

Lee JW et al.: Stress-induced cardiomyopathy: the role of echocardiography, *J Cardiovasc Ultrasound* 19(1):7–12, 2011.

Movahed MR et al.: Review: transient left ventricular apical ballooning, broken heart syndrome, ampulla cardiomyopathy, atypical apical ballooning, or Tako-Tsubo cardiomyopathy, *Cardiovasc Revasc Med* 8(4):289–292, 2007.

Nef HM: Tako-tsubo cardiomyopathy (apical ballooning), *Heart* 93(10):1309–1315, 2007.

Ogura R et al.: Specific findings of the standard 12-lead ECG in patients with "Takotsubo" cardiomyopathy: comparison with the findings of acute anterior myocardial infarction, *Circ J* 67:687–690, 2003.

Pelliccia F et al.: Takotsubo syndrome (stress cardiomyopathy): An intriguing clinical condition in search of its identity, *Am J Med* 127:699–704, 2014.

Prasad A et al.: Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction, *Am Heart J* 155(3):408–417, 2008.

Rotondi et al.: Takotsubo cardiomyopathy and arrhythmic risk, *Eur Rev Med Pharmacol Sci* 17(1):105–111, 2013.

Singh K et al.: Meta analysis of clinical correlates of acute mortality in Takotsubo cardiomyopathy, *Am J Cardiol* 419:1420–1428, 2014.

Zeb M et al.: Takotsubo cardiomyopathy: a possible metabolic disorder, *Heart Metab* 6(2):36–40, 2014.

BASIC INFORMATION

DEFINITION

Four species of adult tapeworm (cestodes) may infect humans as the definitive host: *Taenia saginata* (beef tapeworm), *Taenia solium* (pork tapeworm), *Diphyllobothrium latum* (fish tapeworm), and *Hymenolepis nana.* In addition, several tapeworms (*T. solium, T. crassiceps, T. multiceps*) can infect human tissue in their larval form, resulting in cysticercosis, and others infect in their intermediate forms, resulting in hydatid disease (see "Echinococcosis" in Section I)

SYNONYMS

Cysticercosis (larval infection by *T. solium*)

ICD-9CM CODES
123.9 Tapeworm infestation
ICD-10CM CODES
B68.0 *Taenia solium* taeniasis
B68.1 *Taenia saginata* taeniasis
B68.9 Taeniasis unspecified
B70.0 Diphyllobothriasis
B71.9 Cestode infection, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.):
- Diagnosed primarily in immigrants, particularly those from Latin America and Southeast Asia
- Varies widely by country of origin and dietary practices

PREVALENCE (IN U.S.):
- *T. saginata:* <0.1%
- *D. latum:* <0.05%
- *T. solium:* <0.1%
- *H. nana:* sporadic, often in setting of outbreak

PREDOMINANT SEX: Equal sex distribution

PREDOMINANT AGE:
- *T. saginata, T. solium, D. latum:* 20 to 39 yr of age
- *H. nana* in setting of institution outbreaks: children

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Adult worms
1. Attach to bowel mucosa via suckers, hooks, or grooves depending on species
2. Feed and grow, producing digestive/body/reproductive segments called proglottids
3. Cause minimal or no symptoms or sequelae but occasionally can cause nausea, anorexia, or epigastric pain.

Cysticercosis: larval infection by *T. solium*
1. Mass lesions of brain (neurocysticercosis), soft tissue, viscera
2. Neurocysticercosis may cause seizures, hydrocephalus (due to ventricle obstruction)

Prolonged infection with *D. latum*
1. Vitamin B_{12} deficiency
2. Megaloblastic anemia

ETIOLOGY

TAPEWORM:
- Adult worms consist of a head, neck, and hundreds or thousands of proglottids. Each proglottid contains male and female reproductive organs, including eggs.
- Adult worm resides in small or large bowel; proglottids and eggs are passed in stool.
- *T. saginata* may produce up to 100,000 eggs/proglottid and *T. solium* up to 50,000 eggs/proglottid.
- Eggs are ingested by the animal intermediate host.
- Eggs hatch into larvae.
- Larvae perforate the host intestinal wall and disseminate into skeletal muscle, brain, viscera.
- Develop into cysticerci (scolex inside a cyst) over several weeks
- Humans eat infected beef *(T. saginata),* pork *(T. solium),* or fish *(D. latum).*
- Larval scolex attaches to intestinal wall and mature into adults within the GI lumen.
- *H. nana* infection is acquired by ingesting eggs in human or rodent feces.

CYSTICERCOSIS:
- Humans ingest eggs of *T. solium* in food contaminated with human feces that contain the eggs.
- Eggs hatch into larvae in gut and cross intestinal wall.
- Larvae disseminate widely through tissues (particularly soft tissue and CNS) forming cystic lesions containing either viable or nonviable larvae.

DIAGNOSIS

WORKUP

- Stool examination for eggs or proglottids (tapeworm)
  1. Eggs of *Taenia* spp. cannot be differentiated by microscopy, but the species can be identified through examination of the proglottids in stool.
  2. Eggs of *Taenia* spp. are round and measure 30 to 40 micrometers.
- Cerebral CT scan (neurocysticercosis)
- Serum antibody (neurocysticercosis) with high sensitivity with multiple cysts (94%) but low with a single cyst or calcified cysts (as low as 28%)
- CBC may show eosinophilia

IMAGING STUDIES

- Tapeworm: incidental finding on upper GI series
- Neurocysticercosis:
  1. Cerebral cysts are readily demonstrated by CT scan or MRI.
  2. Calcified lesions are an incidental finding.

TREATMENT

ACUTE GENERAL Rx

- All adults and children with intestinal tapeworm infections should be treated with a single oral dose of praziquantel.
  1. *T. solium:* 5-10 mg/kg
  2. *T. saginata:* 5-10 mg/kg
  3. *D. latum:* 5-10 mg/kg
  4. *H. nana:* 25 mg/kg and a repeat dose 7-10 days later if heavy infection
- Praziquantel acts by causing changes in the teguments of the worms, allowing increased permeability to calcium ions, which then accumulate inside worm and cause paralysis.
- Repeat stool screening at 1 and 3 mo to confirm cure.
- Can use purgatives adjunctively to hasten clearance of deceased worms from intestine
- An alternative therapy to praziquantel for tapeworm infections is niclosamide, 2 g PO once for adults and 1 g for children 11-34 kg and 1.5 g for children over 34 kg.
- Therapy that may be considered for symptomatic cysticercosis:
  1. May regress spontaneously (i.e., no treatment)
  2. Surgery, especially in cases of ventricular obstruction (neurocysticercosis)
  3. Albendazole 10-15 mg/kg/day PO divided in two doses for 8 days
  4. Praziquantel 50-100 mg/kg/day PO for 15-30 days divided in three doses
  5. Use of steroids in neurocysticercosis may reduce CNS inflammation and increase levels of albendazole in CNS.
- Therapy contraindicated with:
  1. Ocular infections
  2. Cerebral infections in which local inflammation caused by destruction of the parasite may cause significant damage
- Adjunctive antiepileptics may be necessary for neurocysticercosis

CHRONIC Rx

- Retreatment if required
- Avoidance of undercooked pork, meat, or fish
- Cysticercosis: proper hand washing, proper disposal of human waste

DISPOSITION

- Neurologic follow-up for patients with neurocysticercosis
- Ophthalmologic follow-up for patients with ocular involvement

REFERRAL

Patients treated for neurocysticercosis should be evaluated by a physician experienced in managing this infection, if possible.

PEARLS & CONSIDERATIONS

COMMENTS

T. solium is the most dangerous of the tapeworms because of the potential for cysticercosis by means of autoinfection.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Tapeworm Infection (Patient Information)
Cysticercosis (Related Key Topic)

AUTHORS: **RUSSELL J. McCULLOH, M.D.**

SUGGESTED READINGS

Brunetti E, White AC Jr: Cestode infestations: hydatid disease and cysticercosis, *Infect Dis Clin North Am* 2692:421–435, 2012.

Buyuk Y et al.: Non-ruptured hydatid cyst can lead to death by spread of cyst content into bloodstream: an autopsy case, *Eur J Gastroenterol Hepatol* 17(6):671, 2005.

DeGiorgio C et al.: Sero-prevalence of *Taenia solium* cysticercosis and *Taenia solium* taeniasis in California, *USA. Acta Neurol Scand* 111(2):84, 2005.

Del Brutto OH: Neurocysticercosis: a review, *Sci World J* 2012:159821, 2012.

Flisser A et al.: Short report: evaluation of a self-detection tool for tapeworm carriers for use in public health, *Am J Trop Med Hyg* 72(5):510, 2005.

Infanger M et al.: Surgical and medical management of rare echinococcosis of the extremities: pre- and postoperative long-term chemotherapy, *Scand J Infect Dis* 37(11):954, 2005.

Neumayr A et al.: Justified concern or exaggerated fear: the risk of anaphylaxis in percutaneous treatment of cystic echinococcosis: a systematic literature review, *Jun5 PLoS Negl Trop Dis* 6:e1154, 2011.

BASIC INFORMATION

DEFINITION

Tardive dyskinesia (TD) is a syndrome of involuntary movements associated with the long-term use of antipsychotic medication, particularly first-generation antipsychotics. Patients exhibit rapid, repetitive, stereotypic movements that mostly involve the oral, lingual, trunk, and limb areas.

SYNONYMS

Orofacial dyskinesia
Tardive syndrome
TD

ICD-9CM and DSM-5 CODES
333.72 Acute dystonia due to drugs
ICD-10CM CODES
G24.0 Neuroleptic-induced tardive dyskinesia

EPIDEMIOLOGY & DEMOGRAPHICS

- The disorder is caused by dopamine-blocking antipsychotics (e.g., haloperidol) and antiemetics (e.g., metoclopramide, prochlorperazine, and promethazine).
- With first-generation antipsychotics, at least 20% of patients are affected with TD, and ~5% are expected to develop TD with each year of antipsychotic treatment.
- The incidence of TD is declining with the increased use of second-generation antipsychotics. ~0.5% to 1% of all adults develop TD yearly while taking these medications.
- Risk increases with the duration of antipsychotic treatment, in female and in elderly patients, in patients with brain damage or dementia, with concurrent anticholinergic use, and in patients with nonschizophrenia diagnoses.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- TD is classically described as a chronic condition of insidious onset, but symptoms are variable over time and may even improve despite continued antipsychotic therapy.
- The condition typically appears with the reduction or withdrawal of the antipsychotic medications.
- TD classically involves stereotypic movements of the mouth and tongue, including lip smacking and puckering, tongue twisting and protrusion, and facial grimacing.
- TD may also involve slow, writhing movements of the trunk or choreoathetotic movements of the fingers and toes.
- The involuntary mouth movements associated with TD may be suppressed by voluntary actions (e.g., putting food in the mouth, talking).
- Variants of TD with similar treatment include tardive dystonia (e.g., torticollis, blepharospasm), tardive myoclonus, tardive akathisia, and tardive tics.

ETIOLOGY

TD is caused by chronic exposure to dopamine receptor antagonists that is thought to result in the upregulation of dopamine receptors in the basal ganglia as well as damage to striatal cholinergic neurons. Dysfunction of striatal GABAergic interneurons has also been implicated. Recently, it has been proposed that dopamine receptor hypersensitivity and neurodegenerative changes might cause altered synaptic plasticity of excitatory synapses onto striatal interneurons, resulting in an imbalance between the direct and indirect basal ganglia pathways.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acute extrapyramidal symptoms (e.g., short-term withdrawal dyskinesias, parkinsonism, akathisia)
- Basal ganglia movement disorders (e.g., Huntington's chorea, Tourette's syndrome, levodopa-induced dyskinesia in Parkinson's disease, Wilson's disease)
- Autoimmune diseases (Sydenham's chorea, multiple sclerosis)
- Other causes of neurologic damage (e.g., lead or mercury toxicity, HIV, neurosyphilis, head injury, neurodegeneration from illicit substances)
- Mannerisms associated with disorganized type or catatonic type schizophrenia
- Hyperthyroidism-induced choreoathetosis
- Edentulous dyskinesias and improperly fitted dentures
- Rabbit syndrome (a rare variant of extrapyramidal symptoms with rapid vertical orofacial movements without tongue involvement); may respond to anticholinergic agents

WORKUP

TD is a diagnosis of exclusion, with emphasis on a complete neuropsychiatric and medication history and a thorough physical examination.

IMAGING STUDIES

Standard brain imaging is normal in patients with TD.

TREATMENT

ACUTE GENERAL Rx

- Treatment is predicated on prevention: limit the indications for antipsychotics; use the lowest effective dose; discontinue the drugs, when feasible; and monitor patients frequently. Anticholinergic medications may worsen symptoms.
- Switch to second-generation antipsychotics, if possible.

CHRONIC Rx

- If continued antipsychotic treatment is needed, switching to clozapine or quetiapine is the preferred initial treatment.
- For mild to moderate TD, clonazepam, vitamin B6, amantadine, propranolol, levetiracetam and gingko biloba may be helpful, although controlled trial evidence remains weak.
- For severe or persistent TD, tetrabenazine, a centrally acting synaptic dopamine depleter, is becoming a first-line treatment option.
- For disabling TD, deep brain stimulation of the subthalamic nucleus or internal globus pallidus seems to provide significant symptom reduction without exacerbation of psychiatric symptoms.
- TD is potentially irreversible in nearly two thirds of patients; thus, patients undergoing long-term treatment with dopamine receptor–blocking medications require frequent monitoring and aggressive management at the onset of TD symptoms.

REFERRAL

Movement disorder specialist consultation if symptoms are severe

PEARLS & CONSIDERATIONS

- First-generation antipsychotics should be resumed to treat TD in the absence of active psychosis only as a last resort for persistent, disabling, and treatment-resistant TD.
- Avoid the use of anticholinergic medications (e.g., benztropine), which may exacerbate TD symptoms.
- A worsening of the overall psychopathology in patients with schizophrenia is longitudinally associated with the emergence of TD and suggestive of a worse prognosis.
- Recent evidence suggests increased overall mortality among patients with TD, which highlights the need for referral for more aggressive specialized interventions.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Tardive Dyskinesia (Patient Information)

AUTHOR: **JOHN A. GRAY, M.D., PH.D.**

SUGGESTED READINGS

Chen JJ et al.: Tetrabenazine for the treatment of hyperkinetic movement disorders: a review of the literature, *Clin Ther* 34(7):1487–1504, 2012.

Cloud LJ et al.: Tardive dyskinesia: therapeutic options for an increasingly common disorder, *Neurotherapeutics* 11:166–176, 2014.

Loonen AJM, Ivanova SA: New insights into the mechanism of drug-induced dyskinesia, *CNS Spectr* 18:15–20, 2013.

Rana AQ et al.: New and emerging treatments for symptomatic tardive dyskinesia, *Drug Des Devel Ther* 7:1329–1340, 2013.

BASIC INFORMATION

DEFINITION

Tarsal tunnel syndrome is the most common compressive neuropathy in the foot and ankle. The syndrome is secondary to a pathologic, structural, or biomechanical factor that causes compression of the posterior tibial nerve or its branches (medial calcaneal, medial plantar, lateral plantar branches), within or distal to the tarsal canal (Fig. T1-6).

ICD-9CM CODES
355.5 Tarsal tunnel syndrome
ICD-10CM CODES
G57.50 Tarsal tunnel syndrome, unspecified lower limb

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Most common entrapment neuropathy in the foot/ankle
PREDOMINANT SEX: Relatively equal

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms can vary widely in location and nature. One or many symptoms can occur.
- Common presentations: medial ankle pain, localized heel pain, distal numbness/shooting pain, and generalized foot/ankle pain that keeps the patient awake at night
- Percussion over the porta pedis resulting in Tinel's sign (distal radiation of symptoms)
- Valleix phenomenon (producing proximal symptomatology) is consistent with tarsal tunnel syndrome.
- In cases of mechanical etiology, holding the foot in a dorsiflexed and everted subtalar joint position may reproduce symptoms.
- Look for: localized edema, varicosities, palpable soft tissue masses, biomechanical abnormalities, and signs of trauma.
- Loss of motor function and permanent loss of sensation are extremely rare.

ETIOLOGY

- Inflammatory (adjacent tendonitis, recent ankle trauma)
- Compressive pathology (ganglion cyst, lipoma, varicosities)
- Structural (osseous): exostosis, severe arthritis, fracture of rearfoot/ankle
- Biomechanical: abnormal calcaneal eversion or inversion, subtalar joint pronation
- Systemic causes of neuropathy: diabetes, hypothyroidism, Reiter's syndrome, and more

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Plantar fasciitis
- Calcaneal fracture/other osseous trauma.
- Ankle sprain/strain or chronic ST injury. Posterior tibial tendonitis often overlooked
- Systemic causes of peripheral neuropathy: diabetes, hypothyroidism, Reiter's syndrome
- Radiculopathy
- Peripheral vascular disease

DIAGNOSTIC STUDIES

- X-rays: rule out trauma, bone tumor, structural deformity.
- Biomechanical exam.
- MRI: look for soft tissue mass, edema, trauma.
- EMG/nerve conduction studies support clinical diagnosis, but false negatives are common.
- Local diagnostic injections: evaluate local versus proximal source of neuropathy.

TREATMENT

- First line: rest, ice, limit aggravating activity
- Address shoegear problems: in structural cases, tight shoegear will exacerbate symptoms, while in functional cases symptoms may be aggravated by loose/unstable rearfoot fit.
- Nonsteroidal anti-inflammatory drugs
- Biomechanical: custom orthotics for optimal biomechanical function/stabilization. Heel lifts assist by promoting ankle plantar flexion, supinating the foot, and reducing pressure within the tarsal tunnel.
- Ankle bracing if ankle instability present and contributing factor
- Physical therapy (iontophoresis, other therapeutic modalities, strength/flexibility work)
- Local steroid injection
- If persistent, offloading with cast or cast walker may yield resolution in 3 to 6 wk
- Surgical: release of retinaculum, mass excision, etc.

DISPOSITION

Can yield lifelong, chronic pain with unknown specific etiology or can follow a limited course once causative factor resolved (mechanical, healed ankle sprain, soft tissue mass resection, etc.).

REFERRAL

- Physical therapy for various treatment modalities
- Podiatric or foot/ankle orthopedic surgeon for biomechanical evaluation, orthotic treatment, diagnostic/therapeutic injection, and surgery if necessary

PEARLS & CONSIDERATIONS

- Be sure to rule out etiologies such as calcaneal fracture and bone or soft tissue tumor.
- Differentiation from plantar fasciitis is often difficult, yet the initial therapy can be identical (refer to "Plantar Fasciitis").

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Tarsal Tunnel Syndrome (Patient Information)

AUTHOR: **BROOKE E. KEELEY, D.P.M.**

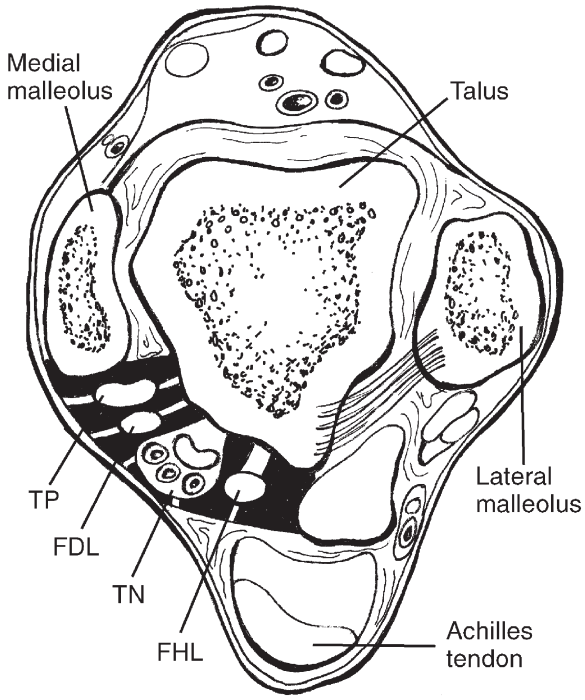


FIGURE T1-6 Anatomy of tarsal tunnel syndrome. Transverse view of ankle. Tendons and neurovascular elements are included in individual fibrous septa that connect periosteum with the deep fascia. *FDL,* Flexor digitorum longus; *FHL,* flexor hallucis longus tendon; *TN,* tibial nerve (single contour), posterior tibial artery, veins; *TP,* tibialis posterior tendon. (From Canoso J: *Rheumatology in primary care,* Philadelphia, 1997, Saunders.)

SUGGESTED READINGS

McCluskey LF, Webb LB: Compression and entrapment neuropathies of the lower extremity, *Clin Podiatr Med Surg* 16(1), 1999.

Thomas JL et al.: The diagnosis and treatment of heel pain: a clinical practice guideline—revision 2010, *J Foot Ankle Surg* 49(3 suppl):1–19, 2005.

Willis JD: A non-neurologist's guide to understanding the EMG/NCV report, *Clin Podiatr Med Surg* 16(1), 1999.

Temporomandibular Joint Syndrome ALG PTG

BASIC INFORMATION

DEFINITION

Temporomandibular joint (TMJ) syndrome refers to a group of disorders leading to symptoms of the TMJ. Temporomandibular joint disorders (TMD) can be classified as intra-articular (within the joint) or extra-articular (involving the surrounding musculature).

SYNONYMS

Temporomandibular dysfunction
Painful temporomandibular joint
TMJ
Temporomandibular disorders (TMD)

ICD-9CM CODES
524.60 Temporomandibular joint pain-dysfunction syndrome
ICD-10CM CODES
N26.60 Temporomandibular joint disorder, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- 15% of the population have TMJ disorders.
- Females are affected more often than males (4:1 ratio).
- Occurs between the second and fourth decades of life.
- Usually unilateral, affecting either side with equal frequency.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Often unilateral pain in the muscles of mastication, usually described as a "dull" ache
- Otalgia
- Odontalgia
- Headaches (frontal, temporal, retro-orbital)
- Tinnitus
- Dizziness
- Clicking or popping sounds with movement of the TMJ
- Joint locking
- Application of mild anterior pressure with a finger placed posteriorly to each tragus may result in tenderness, clicking, or crepitus.
- Limited range of motion of the TMJ
- Symptoms usually appear in association with a stressful life event

ETIOLOGY

- Multifactorial, encompassing local anatomic anomalies to systemic disease processes
- Myofascial pain-dysfunction syndrome: the most common cause of TMJ syndrome and results from teeth grinding and clenching the jaw (bruxism)
- Internal TMJ derangement: abnormal connection of the articular disk to the mandibular condyle
- Degenerative joint disease
- Rheumatoid arthritis
- Gouty arthritis
- Pseudogout
- Ankylosing spondylitis
- Trauma
- Prior surgery (orthodontic, intraarticular steroid injection)
- Tumors

DIAGNOSIS

Can be made based on history and physical examination in most cases.

DIFFERENTIAL DIAGNOSIS

Includes the list provided above. Myofascial pain-dysfunction syndrome, internal TMJ derangement, and degenerative joint disease represent >90% of all causes of TMJ syndrome. Others not mentioned include dental problems such as dental caries, loss of posterior teeth support, and Eagle's syndrome (stylohyoid syndrome, carotidynia, and trigeminal neuralgia). Alternative diagnoses such as otitis, mastoiditis, salivary gland disorders, migraine headache, sinusitis, posthepatic neuralgia, trigeminal neuralgia, glossopharyngeal neuralgia, and giant cell arteritis should always be excluded.

WORKUP

The diagnosis is based largely on history and physical examination findings. Radiographic imaging evaluation is used to exclude anatomic or systemic causes of disease when conservative management has failed.

LABORATORY TESTS

Laboratory examination is not very helpful.

IMAGING STUDIES

- Plain radiographs: the most common views are the panoramic, transorbital, and transpharyngeal in both opened and closed positions.
- Arthrography is helpful in looking for meniscus involvement but is seldom performed anymore.
- CT scan is highly accurate in diagnosing meniscal and osseous derangements of the TMJ.
- MRI is the procedure of choice and has replaced arthrography in cases of disabling pain or if locking occurs. It is used to determine disc position and morphology along with degenerative bony changes.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Soft diet to rest the muscles of mastication
- Heat 15 to 20 min four to six times per day
- Massage of the masseter and temporalis muscles
- Formed splints or bite appliances to reduce compression of retrodiscal tissue (Fig. ET1-7)
- Range-of-motion exercises
- Cognitive-behavioral therapy and biofeedback have been shown to reduce pain.
- Acupuncture

ACUTE GENERAL Rx

- Nonsteroidal anti-inflammatory drugs: ibuprofen 800 PO mg tid PRN, naproxen 500 mg PO bid prn, titrated to relieve symptoms
- Muscle relaxants at bedtime: diazepam 2.5 to 5 mg PO tid PRN or amitriptyline 5 to 100 mg PO qd PRN
- In degenerative joint disease of the TMJ, intraarticular steroid injection can be tried
- Botulism toxin injections into the masticatory muscles
- Arthrocentesis with joint lavage and lysis of adhesions (Fig. ET1-8)
- In patients with pain and clicking in the TMJ that is unresponsive to nonsurgical treatment, the disc should be repositioned arthroscopically or by open surgery (discoplasty) (see "Chronic Rx")

CHRONIC Rx

- Most of the above treatments are used for myofascial pain-dysfunction syndrome; however, they can be applied to other causes of TMJ syndrome. Surgery is usually a measure of last resort in patients who do not respond to nonpharmacologic and acute general treatment.
- Surgical procedures include:
  1. Meniscoplasty
  2. Meniscectomy
  3. Subcondylar osteotomy
  4. TMJ reconstruction

DISPOSITION

The course depends on the underlying etiology; however, less than 5% of adults with temporomandibular symptoms develop chronic symptoms.

REFERRAL

All patients with TMJ syndrome refractory to conservative nonpharmacologic and acute therapy should be referred to a periodontist, oral maxillofacial surgeon, or ear-nose-throat surgeon.

PEARLS & CONSIDERATIONS

Patients with rheumatoid arthritis involving the TMJ usually have bilateral involvement.

COMMENTS

Frequently, emotional stress initiates the myofascial pain-dysfunction, which accounts for 85% of all cases of TMJ syndrome.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Temporomandibular Joint (TMJ) Syndrome (Patient Information)

AUTHORS: **RYAN W. ZUZEK, M.D.** and **DOUGLAS BURTT, M.D.**

SUGGESTED READINGS

Buescher JJ: Temporomandibular joint disorders, *Am Fam Physician* 76:1477, 2007.

Dimitroulis G: The role of surgery in the management of disorders of the temporomandibular joint: a critical review of the literature. Part 1, *Int J Oral Maxillofac Surg* 34(2):107, 2005.

Dimitroulis G: The role of surgery in the management of disorders of the temporomandibular joint: a critical review of the literature. Part 2, *Int J Oral Maxillofac Surg* 34(3):231, 2005.

Gauer RL, Semidey MJ: Diagnosis and treatment of temporomandibular disorders, *Am Fam Physician* 91(6):378–386, 2015.

Herb K et al.: Temporomandibular joint pain and dysfunction, *Curr Pain Headache Rep* 10(6):408, 2006.

Scrivani S et al.: Temporomandibular disorders, *N Engl J Med* 359:2693–2705, 2008.

Sommer OJ et al.: Cross-sectional and functional imaging of the temporomandibular joint: radiology, pathology, and basic biomechanics of the jaw, *Radiographics* 23(6):e14, 2003.

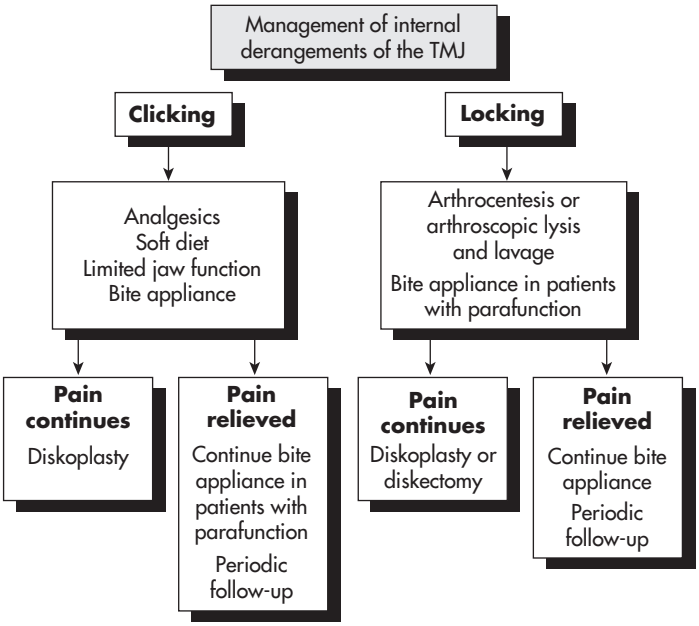


FIGURE ET1-7 Management of internal derangements of the temporomandibular joint (TMJ). Patients with painful clicking or locking are treated medically initially, whereas patients with locking require surgical intervention. (From Firestein GS et al: *Kelley's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.)

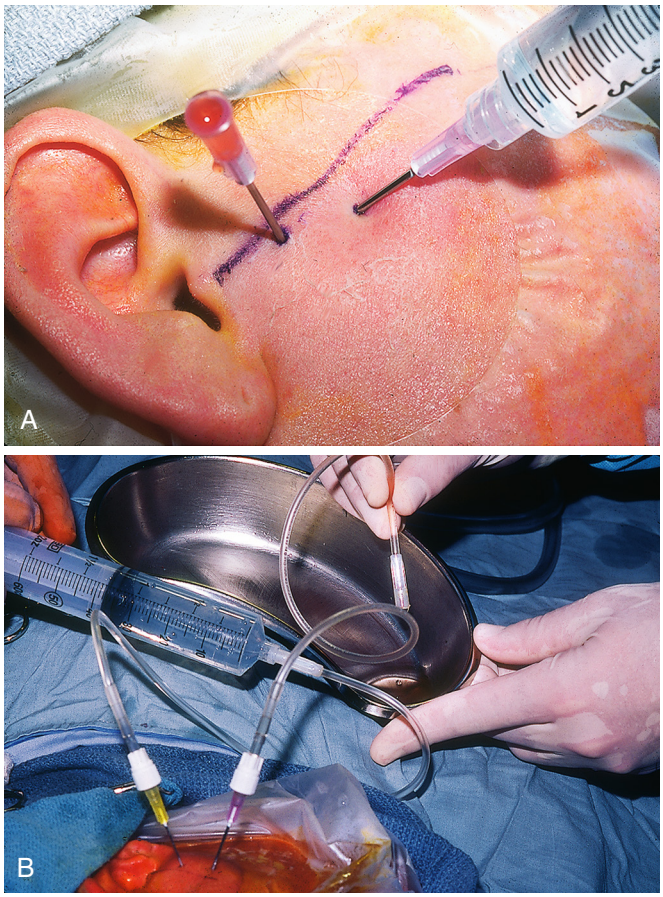


FIGURE ET1-8 **A**, Hypodermic needles inserted into the upper joint space to allow lavage of the joint. **B**, Joint being irrigated with lactated Ringer's solution. (From Firestein GS et al: *Kelley's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.)

BASIC INFORMATION

DEFINITION

Tension-type headaches (TTH) are recurrent headaches lasting 30 min to 7 days without nausea or vomiting and with at least two of the following characteristics: pressing or tightening quality (nonthrobbing), mild or moderate intensity, bilateral, and not aggravated by routine physical activity.

SYNONYMS

Muscle contraction headache
Tension headache
Stress headache
Essential headache
TTH

ICD-9CM CODES
307.81 Tension headache
ICD-10CM CODES
G44.209 Tension-type headache, unspecified, not intractable

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Most common type of headache; as high as 70% of all headaches presenting to primary care physician
PEAK INCIDENCE: Occurs at all ages
PREVALENCE (IN U.S.): Males: 63%/yr; females: 86%/yr
PREDOMINANT SEX: Females are affected more often than males

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Pressure or "bandlike" tightness all around the head; may be worse at the vertex. Cervical, paracervical, and trapezius muscle spasm and/or tenderness on palpation may be present. Scalp tenderness or hypersensitivity to pain also occurs. Symptoms suggestive of migraine are usually not present (e.g., throbbing pain, nausea/vomiting, visual complaints, aura). Either one symptom of photo- or phonophobia does not exclude the diagnosis of TTH.

ETIOLOGY

- Unclear; little data to support postulated muscle contraction component. More likely a multifactorial disorder with several possible concurrent pathophysiologic mechanisms.
- No recent data to support the long-standing belief that these headaches arise from stress or other psychological factors. However, components of stress, sleep deprivation, hunger, and eyestrain may exacerbate symptoms. Stress and poor coping mechanisms may initiate and propagate pain (via activation of second messengers in downstream pain substrates). In episodic TTH, peripheral mechanisms are predominant, whereas central mechanisms are involved in chronic TTH.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Migraine (would expect associated symptoms; see topic "Headache, Migraine")
- Cervical spine disease
- Intracranial mass (may present with focal neurologic signs, seizures, or headache awakening patient from sleep)
- Idiopathic intracranial hypertension (found more often in obese women of childbearing age, may have papilledema, visual loss, or diplopia)
- Rebound headache from overuse of analgesics
- Secondary headache (e.g., temporomandibular joint syndrome, thyrotoxicosis, polycythemia, drug side effects)
- Migraine and TTH may often coexist and may be difficult to differentiate (suggest headache calendar).
- Section II describes the differential diagnosis of headaches.

WORKUP

- Thorough history and physical examination for any new-onset headache
- Neuroimaging should be performed when unexplained neurologic findings are present on examination or in cases of atypical new-onset sudden and severe headaches.

LABORATORY TESTS

- No routine tests
- Erythrocyte sedimentation rate in elderly patients suspected of having temporal arteritis

IMAGING STUDIES

CT scan and/or MRI may be used to exclude intracranial pathology. MRI is better for imaging the posterior fossa. Contrast should be used if mass lesion is suspected.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Electromyography (EMG) biofeedback has a documented effect, whereas cognitive-behavioral therapy and relaxation training are most likely effective (especially in adolescents and children).
- Physical therapy (including stretching exercises, massage, and ultrasound) and acupuncture may be effective, but there is no robust scientific evidence for efficacy.
- Schultz-type autogenic training (relaxation technique based on passive concentration and body awareness of specific sensations), transcutaneous electrical nerve stimulation, heat

ACUTE GENERAL Rx

Nonnarcotic analgesics (first choice) and combination analgesics containing caffeine (second choice) with limited frequency to prevent drug-induced and/or rebound headache

CHRONIC Rx

- Tricyclic antidepressants (e.g., amitriptyline 10 to 150 mg hs) (first choice); mirtazapine and venlafaxine (second choice); treatment may be limited by side effects.
- Avoid narcotics, limit NSAIDs, consider indomethacin; if related to cervical muscle spasm, may consider trial of muscle relaxants (e.g., Skelaxin 400 to 800 mg tid)
- Botulinum toxin A has been FDA approved for prophylactic treatment of chronic daily headaches. Trials have shown a small-to-modest benefit for chronic headaches but are not associated with fewer tension-type headaches per month.

DISPOSITION

May not respond fully to treatment

REFERRAL

If uncertain about diagnosis or unexplained focal neurologic findings on examination

PEARLS & CONSIDERATIONS

It is imperative to avoid overuse of caffeine- and barbiturate-containing medications because of the risk of rebound headaches.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Tension Headache (Patient Information)

AUTHOR: **RICHARD S. ISAACSON, M.D.**

SUGGESTED READINGS

Bendtsen L et al.: EFNS guideline on the treatment of tension-type headache: report of an EFNS task force, *Eur J Neurol* 17:1318, 2010.

Bendtsen L, Jensen R: Mirtazapine is effective in the prophylactic treatment of chronic tension-type headache, *Neurology* 62:1706, 2004.

Bronfort G et al.: Non-invasive physical treatments for chronic/recurrent headache, *Cochrane Database Syst Rev* 3:CD001878, 2004.

Chen Y: Advances in the pathophysiology of tension-type headache: from stress to central sensitization, *Curr Pain Headache Rep* 13:6, 2009.

Goadsby P: Headache (chronic tension-type), *BMJ* 12:2004, 1808.

Headache Classification Committee of the International Headache Society. The international classification of headache disorders, *Cephalalgia* 24:1, 2004.

Holroyd KA et al.: Management of chronic tension-type headache with tricyclic anti-depressant medication, stress management therapy, and their combination: a randomized controlled trial, *JAMA* 285(17):2208, 2001.

Jackson JL et al.: Botulinum toxin A for prophylactic treatment of migraine and tension headaches in adults, *JAMA* 307(16):1736–1745, 2012.

Lipton RB et al.: Classification of primary headaches, *Neurology* 63:427, 2004.

Millea P, Brodie J: Tension-type headache, *Am Fam Physician* 66:797, 2002.

Silberstein SD, Rosenberg J: Multispecialty consensus on diagnosis and treatment of headache, *Neurology* 54:1553, 2000.

Zsombok T et al.: Effect of autogenic training on drug consumption in patients with primary headache: an 8-month follow-up study, *Headache* 43:251, 2003.

BASIC INFORMATION

DEFINITION

Testicular neoplasms are primary cancers originating in a testis.

SYNONYMS

Testis tumor
Testicular neoplasms

ICD-9CM CODES
186.9 Testicular neoplasm
M906/3 (seminoma)
M9101/3 (embryonal carcinoma or teratoma)
M9100/3 (choriocarcinoma)
ICD-10CM CODES
C62.1 Malignant neoplasm of unspecified descended testis
C62.0 Malignant neoplasm of undescended testis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 5.4 cases per 100,000 men annually. White men have the highest incidence at 6.3 cases/100,000 men. Testicular cancer is the most common cancer diagnosis in men between 15 and 35 yr. The incidence has been gradually increasing since 1975.
PREVALENCE: 1% to 2% of all cancers in males.
PREDOMINANT AGE: Can occur in any age but most common in young adults; average age for embryonal cell carcinoma: 30 yr; average age for seminoma: 36 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Testicular cancer typically presents as a painless mass in the testis. Any mass within the testicle should be considered cancer until proven otherwise. It may be found by the patient, who brings it to the attention of a physician, or it may be found by a physician on a routine examination.
- Symptoms other than scrotal or testicular swelling are typically absent unless the cancer has metastasized (10% of patients at diagnosis). Occasionally a patient may report scrotal fullness or heaviness. About 10% of patients present with acute pain. Back pain secondary to enlarged retroperitoneal lymph nodes can occur. Gynecomastia from tumors that secrete beta-human chorionic gonadotropin (hCG) is found in 5% of men with testicular cancer.
- Testicular palpation should be performed with two hands. Transillumination may distinguish a solid mass (e.g., cancer) and a fluid-filled lesion (e.g., hydrocele or spermatocele). The mass is nontender; indeed, it is less sensitive than a normal testicle.

ETIOLOGY, CLASSIFICATION, & PATHOLOGY

- Cryptorchidism (undescended testes) is a major risk factor even if corrected by orchiopexy; however, treatment of undescended testis before puberty decreases the risk of testicular cancer from fivefold to twofold. Other risk factors are family history (risk is 8 to 10 times as high in a brother of a person with testicular cancer), genetic disorders (Down's syndrome, testicular dysgenesis syndrome), Klinefelter's syndrome, infertility, tobacco use, and white race (risk is highest among whites and lowest among blacks).
- Classification: testicular cancers can be classified as pure seminomas or nonseminomatous germ cell tumors (embryonic carcinoma, choriocarcinoma, yolk sac carcinoma, teratoma).
- Pathology: germ cell tumors account for >95% of testicular cancers.

Cell Type	Frequency (%)
Seminoma	42
Embryonal cell carcinoma	26
Teratocarcinoma	26
Teratoma	5
Choriocarcinoma	1

- Other rare types:
  - Yolk sac carcinoma.
  - Mixed germ cell tumors.
  - Carcinoid tumor.
  - Sertoli cell tumors.
  - Leydig cell tumors.
  - Lymphoma.
  - Metastatic cancer to the testes.
- TNM staging system for testicular cancer
  - T_0: No apparent primary.
  - T_1: Testis only (excludes rete testis).
  - T_2: Beyond the tunica albuginea.
  - T_3: Rete testis or epididymal involvement.
  - T_4: Spermatic cord.
    1. Spermatic cord.
    2. Scrotum.
- N_0: No nodal involvement.
- N_1: Ipsilateral regional nodal involvement.
- N_2: Contralateral or bilateral abdominal or groin nodes.
- N_3: Palpable abdominal nodes or fixed groin nodes.
- N_4: Juxtaregional nodes.
- M_0: No distant metastases.
- M_1: Distant metastases present.

The clinical stages consist of stage I, with tumor confined to the testis; stage II, with positive regional lymph nodes; and stage III, with metastases. Figure T1-9 shows the clinical staging of testicular cancer.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Spermatocele.
- Varicocele.
- Hydrocele.
- Epididymitis/orchitis.
- Epidermoid cyst of the testicle.
- Epididymis tumors.
- Inguinal hernia.
- Hematocele or testicular rupture.
- Torsion of testicular appendage.
- Skin cancer.

WORKUP

Physical examination, laboratory tests, and imaging studies (see Section III, "Testicular Mass"). A radical inguinal orchiectomy is diagnostic and therapeutic. Immunohistochemical analysis is used to determine the histologic composition of the tumor. Staging involves CT of chest, abdomen, and pelvis and measurement of beta subunit of human chorionic gonadotropins (β-hCG), alpha-fetoprotein, and lactate dehydrogenase.

LABORATORY TESTS

- Serum hCG.
- Serum alpha-fetoprotein (AFP): elevated in nonseminoma tumors.
  One or both of these tumor markers will be elevated in 70% of cases of testicular cancer.
- Serum lactate dehydrogenase (LDH) level: elevated with rapid turnover of malignant cells.
- Testicular biopsy contraindicated.

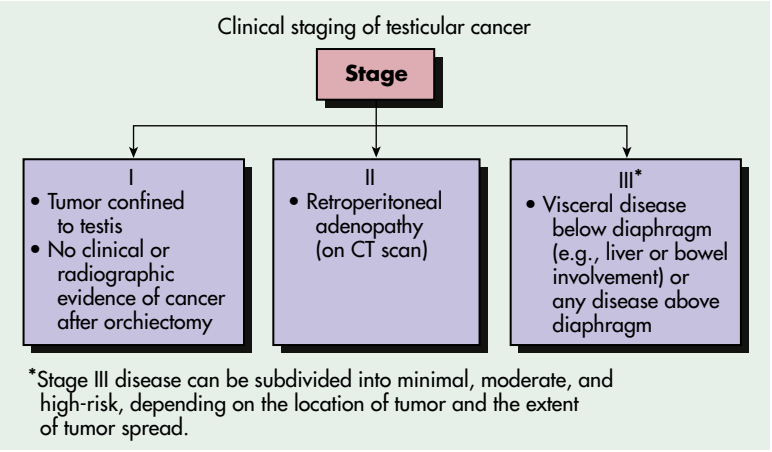


FIGURE T1-9 Clinical Staging of Testicular Cancer. The AJCC TNM staging system is less commonly used, because it is based upon histologic evaluation of the orchidectomy specimen and retroperitoneal periaortic lymph node dissection. Because the latter may not be performed in every patient, the clinical staging system is generally more practical. (From Skarin AT. *Atlas of diagnostic oncology,* ed 4, St Louis, 2010, Mosby.)

IMAGING STUDIES

- Testicular ultrasound.
- CT scan of chest, pelvis, and abdomen.
- MRI of the brain in patients with neurologic symptoms.
- PET scan is not recommended (frequent false positives).

Rx TREATMENT

- Seminoma
  1. Stage I: Most patients with clinical stage 1 are cured with orchiectomy. Radical orchiectomy plus one cycle of single agent carboplatin chemotherapy or radiation therapy (RT) to the paraaortic lymph nodes was the standard of treatment for many years but has been eliminated in many instances and most patients are treated with active surveillance post orchiectomy. More relapses are associated with surveillance (20% vs. 4% with radiotherapy or chemotherapy), but long-term survival approaches 100% irrespective of initial option chosen.[1]
  2. Stage IIA or IIB: RT or cisplatin-based chemotherapy (e.g., cisplatin, bleomycin, etoposide).
- Nonseminoma
  1. Stage IA: radical orchiectomy plus nerve sparing retroperitoneal lymph node dissection (RPLND).
  2. Stage IB: Same as stage IA plus two cycles of chemotherapy (bleomycin, etoposide, and cisplatin [BEP]).
  3. Advanced stages: cisplatin-based chemotherapy or RPLND.
- Posttreatment surveillance for testicular cancer survivors (annually).
  1. Fertility assessment.
  2. Physical examination and skin examination (increased risk of dysplastic nevi).
  3. Testicular examination (3% to 4% risk of second testicular cancer).
  4. Serum tumor markers (hCG, AFP).
  5. Abdominal and pelvic CT every 3 to 4 months for 2 years, every 6 to 12 months in third and fourth year, and annually thereafter.

DISPOSITION

- The overall cure for testicular cancer is >95% (80% for metastatic disease). Patients with pure seminomas have a better prognosis. Prognosis can be determined by criteria established by the International Germ Cell Consensus Criteria (Table T1-3). Because treatment produces favorable outcomes even in advanced stages, the U.S. Preventive Services Task Force recommends against screening asymptomatic men for testicular cancer.
- Therapeutic radiation and chemotherapy are risk factors for cancers of thyroid, lymphoma, kidney, pancreas, stomach, and leukemia.

[1] Hanna NH, Einhorn LH: Testicular cancer, discoveries and updates, *N Engl J Med* 371:2005-2016, 2014.

TABLE T1-3 International Germ Cell Consensus Criteria for Testicular Cancer

Nonseminoma	Seminoma
Good Prognosis	
Testis/retroperitoneal primary	Any primary site
And	*And*
No nonpulmonary visceral metastases	No nonpulmonary visceral metastases
And	*And*
Good markers—all of • AFP < 1000 ng/mL and • hCG < 5000 IU/L (1000 ng/mL) and • LDH < 1.5 × upper limit of normal	Normal AFP, any hCG, any LDH
58% of nonseminomas	90% of seminomas
5-year PFS 89%	5-year PFS 82%
5-year survival 92%	5-year survival 86%
Intermediate Prognosis	
Testis/retroperitoneal primary	Any primary site
And	*And*
No nonpulmonary visceral metastases	Nonpulmonary visceral metastases
And	*And*
Intermediate markers—any of • AFP ≥ 1000 and ≤ 10,000 ng/mL or • hCG ≥ 5000 IU/L and ≤ 50,000 IU/L or • LDH ≥ 1.5 × normal and ≤ 10 × normal	Normal AFP, any hCG, any LDH
28% of nonseminomas	10% of seminomas
5-year PFS 75%	5-year PFS 67%
5-year survival 80%	5-year survival 72%
Poor Prognosis	
Mediastinal primary	No patients classified as
Or	poor prognosis
Nonpulmonary visceral metastases	
Or	
Poor markers—any of • AFP > 10,000 ng/mL or • hCG > 50,000 IU/L (10,000 ng/mL) or • LDH > 10 × upper limit of normal	
16% of nonseminomas	
5-year PFS 41%	
5-year survival 48%	

AFP, α-fetoprotein; *hCG,* human chorionic gonadotrophin; *LDH,* lactate dehydrogenase; *PFS,* progression-free survival.
From Skarin AT. *Atlas of diagnostic oncology,* ed 4, St Louis, 2010, Mosby.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Testicular Cancer (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Purpose:

To evaluate the prevalence of testicular microlithiasis (TM) in children who have undergone scrotal ultrasonography (US) and their association with testicular tumors.

Materials and Methods:

This HIPAA-compliant study with waiver of informed consent was approved by the institutional review board. From 2003 to 2012, all patients with scrotal US and report mentioning calcifications or microlithiasis and all patients with testicular tumors from pathology database were identified. US studies were evaluated for the type of TM (classic ≥5 microliths or limited <5 microliths in a single view) and change in follow-up studies if available. Medical charts were reviewed for US indication, underlying medical conditions, and pathologic abnormalities, when available. Fisher exact test was used to analyze the association of testicular tumors and TM.

Results:

A total of 3370 boys had scrotal US, 83 (2%) of whom had TM or microcalcifications in the report. TM was usually bilateral (n = 62, 75%) and classic (n = 59, 71%) type. TM was significantly less common in those younger than 2 years of age than in older age groups (0.1% versus 3.1%, $P < 0.0001$). The most common indication for US was scrotal pain (40 of 83 patients, 48%), and the most common associated medical condition was cryptorchidism (nine of 83 patients, 11%). Testicular tumor was significantly more likely in boys with TM (12% versus 0.3%, $P < 0.01$). Five (83%) of six patients with premalignant or benign tumors had a premalignant condition (cryptochydism in two and Peutz-Jeghers syndrome in three). Four patients with TM had malignant testicular tumors, all diagnosed after the age of 16 years.

Conclusion:

TM has a prevalence of 2% in boys who undergo scrotal US. It is most commonly bilateral, classic type, and stable at follow-up studies. There is a significant association of TM and testicular tumors. Malignant tumors were seen only in adolescent boys. Ⓐ

Evidence-Based Reference

Cooper M, Kaefer M, Fan R, et al.: Testicular microlithiasis in children and associated testicular cancer, *Radiology* 270:857–863, 2014. Ⓐ

SUGGESTED READINGS

Feldman DR et al.: Medical treatment of advanced testicular cancer, *JAMA* 299(6):672–684, 2008.

Lin K, Sharangpani R: Screening for testicular cancer: an evidence review for the U.S. Preventive Services Task Force, *Ann Intern Med* 153:396–399, 2010.

Petterson A et al.: Age at surgery for undescended testis and risk of testicular cancer, *N Engl J Med* 356:1835, 2007.

Shaw J: Diagnosis and treatment of testicular cancer, *Am Fam Physician* 77(4):469–474, 2008.

Testicular Torsion PTG

BASIC INFORMATION

DEFINITION

Testicular torsion is a twisting of the spermatic cord leading to cessation of testicular blood flow, ischemia, and infarction if left untreated.

SYNONYMS

Spermatic cord torsion

ICD-9CM CODES
608.2 Testicular torsion
ICD-10CM CODES
N44.03 Torsion of testis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Affects one in 4000 males aged <25 yr
PREDOMINANT AGE: Two thirds of all cases occur between the ages of 12 and 18 yr, but may occur at any age, including antenatally.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Typical sequence is sudden onset of hemiscrotal pain, then swelling, nausea, and vomiting without fever or urinary symptoms.
- Physical examination may reveal a tender firm testis, high-riding testis, horizontal lie of testis, absent cremasteric reflex, and no pain with elevation of testis. Absence of the cremasteric reflex (stroking or pinching the medial thigh normally causes contraction of the cremaster muscle and elevation of the testis) is the most sensitive physical finding.
- Painless testicular swelling occurs in 10%.
- One out of three patients reports previous episodes of spontaneously remitting scrotal pain.
- In the neonate, testicular torsion should be presumed in patients with a painless, discolored hemiscrotal swelling.
- In rare cases, torsion may involve an undescended testicle. In such situations an empty hemiscrotum is palpated together with a tender lump in the inguinal area.

ETIOLOGY

- There are two types of testicular torsion: extravaginal, caused by nonadherence of the tunica vaginalis to the dartos layer, and intravaginal, caused by malrotation of the spermatic cord with the tunica vaginalis. Intravaginal torsion accounts for 90% of cases.
- Torsion usually occurs in the absence of any precipitating events. Trauma accounts for <10% of cases.

DIAGNOSIS

Diagnosis is made mainly by clinical suspicion (Table ET1-4). Color Doppler ultrasound evaluation or a nuclear testicular scan (Fig. ET1-10) may help with the diagnosis. Ultrasonography will show absent or decreased blood flow; scintigraphy reveals decreased perfusion on symptomatic side.

DIFFERENTIAL DIAGNOSIS

See Fig. T1-11.

- Torsion of the testicular appendages (appendix testis)
- Testicular tumor
- Epididymitis
- Incarcerated inguinoscrotal hernia
- Orchitis
- Spermatocele
- Hydrocele, varicocele

WORKUP

The diagnosis is usually based on history and physical examination.

IMAGING STUDIES

- Radionuclide scrotal scanning (technetium-99m): cold testicle
- Doppler ultrasonic stethoscope (Doppler flowmetry)

TREATMENT

Surgical derotation of the spermatic cord followed by bilateral testicular fixation with nonabsorbable sutures. If the affected testis is nonviable, orchiectomy of the affected testis and orchiopexy of the contralateral side are performed. Attempts at manual detorsion should not delay surgical consultation.

PROGNOSIS

- The degree of ischemia depends on the duration of torsion and the degree of rotation of the spermatic cord.
- There is an 80% testicular salvage rate if detorsion occurs within 12 hr of onset.
- After 24 hr, irreversible testicular infarction is expected.
- Because the contralateral testes can be affected (immunologic process), when treatment is delayed and return of blood flow does not occur after detorsion, some recommend orchiectomy of the infarcted testicle.

REFERRAL

To urologist

PEARLS & CONSIDERATIONS

- Manual detorsion by external rotation of the testis toward the thigh can be attempted for adolescent intravaginal torsion if an operating facility is not readily available.
- Extravaginal torsion is diagnosed in the newborn. Intravaginal torsion can occur at any age but is usually diagnosed in males ages 12 to 18 yr.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Testicular Torsion (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

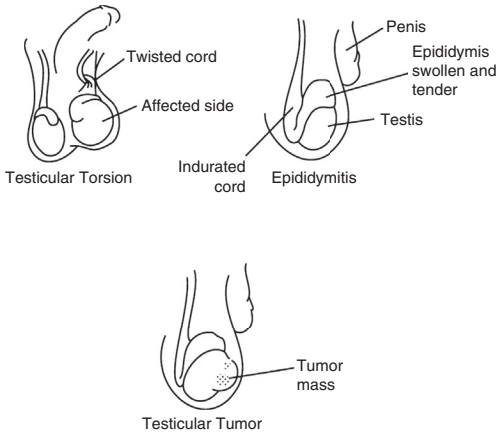


FIGURE T1-11 Physical findings in acute scrotum. *Upper left*, Testicular torsion. *Upper right*, Epididymitis. *Lower*, Testicular tumor. Scrotal examination, which begins with palpation of the scrotal contents, should be performed in the following order: (1) testes, (2) epididymides, (3) spermatic cord structures, and (4) inguinal ring. (From Nseyo U, Weinman E, Lamm DL: *Urology for primary care physicians*, Philadelphia, 1999, WB Saunders.)

SUGGESTED READING

Ringdahl E, Teague L: Testicular torsion, *Am Fam Physician* 74:1739, 2006.

TABLE ET1-4 Differentiation of Testicular Torsion, Epididymitis, and Appendage Torsion

	Testicular Torsion	Epididymitis*	Appendage Torsion
Historical Features			
Age	Peak incidence in neonatal and adolescent groups but may occur at any age	Primarily adolescents and adults but may occur at any age	Typically prepubertal boys
Risk factors	Undescended testicle (neonate), rapid increase in testicular size (adolescent), failure of previous orchiopexy	Sexual activity or promiscuity, GU anomalies, GU instrumentation	Presence of appendages
Pain onset	Sudden	Gradual	Gradual or sudden
Previous episodes of similar pain	Possible (spontaneous detorsion)	Unlikely	Occasional
History of trauma	Possible	Possible	Possible
Nausea, vomiting	More likely	Less likely	Less likely
Dysuria	Less likely	More likely	Less likely
Physical Findings			
Fever	Less likely	More likely, particularly with advanced disease (epididymoorchitis)	Less likely
Location of swelling and tenderness	Testicle, progressing to diffuse hemiscrotal involvement	Epididymis, progressing to diffuse hemiscrotal involvement	Localized to head of affected testicle or epididymis
Cremasteric reflex	Testicular torsion less likely if present	May be present or absent	May be present or absent
Testicle position	High-riding testicle, transverse alignment	Normal position, vertical alignment	Normal position, vertical alignment
Pyuria	Less likely	More likely	Less likely

GU, Genitourinary.
*Including epididymoorchitis.
From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

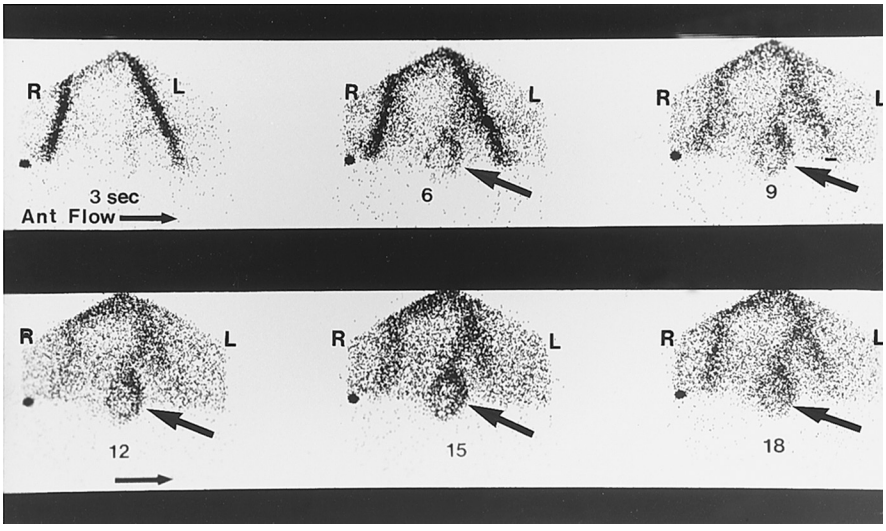


FIGURE ET1-10 Testicular torsion. Evaluation of blood flow to the testicle has been done by giving an intravenous bolus of radioactive material. The right and left iliac vessels are clearly identified, and sequential images are obtained every 3 sec. Here, increased flow is seen to the rim of the left testicle *(arrows),* and there is no blood flow centrally. This is the appearance of a testicular torsion in which the torsion has been present for more than approximately 24 hr. (From Mettler FA [ed]: *Primary care radiology,* Philadelphia, 2000, Saunders.)

BASIC INFORMATION

DEFINITION

Tetanus is a life-threatening illness manifested by muscle rigidity and spasms; it is caused by a neurotoxin (tetanospasmin) produced by *Clostridium tetani.*

SYNONYMS

Lockjaw
Generalized tetanus
Neonatal tetanus
Cephalic tetanus
Localized tetanus

ICD-9CM CODES
037 Tetanus
ICD-10CM CODES
A35 Other tetanus
A34 Obstetrical tetanus

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): 233 cases between 2001 and 2008, or 0.10 cases/millon. Overall case fatality was 13.2%, but 31.3% for people over 65.
INCIDENCE (WORLDWIDE): About 1 million cases of tetanus are reported worldwide annually, suggesting a global incidence of about 18 per 100,000 persons per year and an estimated 300,000 to 500,000 deaths per year. Tetanus is an expected complication when disasters strike in developing countries where tetanus immunization coverage is low.
PREDOMINANT AGE: >60 yr of age
GENETICS: Neonatal infection:
- Rare in the United States
- Among the leading causes of neonatal mortality in many parts of the world (caused by infection of the umbilical cord stump)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Trismus ("lockjaw")
- Risus sardonicus (peculiar grin), characteristic grimace that results from contraction of the facial muscles (Fig. T1-12)

FIGURE T1-12 Facial muscle involvement in tetanus, producing characteristic **"**risus sardonicus." (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

- Generalized muscle spasms causing severe pain and, at times, respiratory compromise and death
- Rigid abdominal muscles, flexed arms, and extended legs (Fig. T1-13)
- Autonomic dysfunction several days after onset of illness
- Leading cause of death: fluctuations in heart rate and blood pressure
- Usually, absence of fever
- Localized tetanus
  1. Rigidity of muscles near the injury
  2. Weakness as a result of lower motor neuron injury
  3. May be self-limited and resolve spontaneously
  4. More often progresses to generalized tetanus
  5. Cephalic tetanus:
     a. May occur with head injuries or chronic otitis with localized ear or mastoid infection with *C. tetani*
     b. Can manifest as cranial nerve dysfunction

ETIOLOGY

- *C. tetani* is a gram-positive, spore-forming bacillus (Fig. T1-14) that resides primarily in the soil.
- Majority of cases are caused by punctures and lacerations (Fig. T1-15).
- Toxin is elaborated from organisms in a contaminated wound.
- Local symptoms are caused by inhibition of neurotransmitter at presynaptic sites.
  1. Over the next 2 to 14 days, the toxin travels up the neurons to the CNS, where it acts on inhibitory neurons to prevent neurotransmitter release.
  2. Unopposed motor activity results in tonic contractions of muscles.

FIGURE T1-13 Neonatal tetanus. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Strychnine poisoning
- Dystonic reaction caused by neuroleptic agents
- Local infection (dental or masseter muscle) causing trismus
- Severe hypocalcemia
- Hysteria

WORKUP

- Positive wound culture is not helpful in diagnosis.
- Isolation of organism is possible in patients without the illness.

LABORATORY TESTS

- Usually, normal blood counts and chemistries
- Toxicology of serum and urine to rule out strychnine poisoning

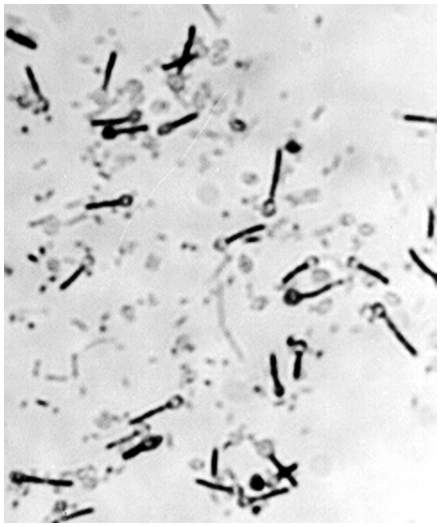


FIGURE T1-14 ***Clostridium tetani:*** **a gram-positive bacillus with terminal spores.** (Courtesy J. Campbell, Oxford University Clinical Research Unit, Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam. From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

FIGURE T1-15 Lacerations to the feet are the most common focus of *Clostridium tetani* infection. Note clawing of toes secondary to increased tone in surrounding muscles. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Monitoring in a hospital ICU: keep surroundings dark and quiet
- Intubation or tracheostomy for severe laryngospasm
- Prompt irrigation and debridement of wound to eliminate spores and necrotic tissue that can favor germination

ACUTE GENERAL Rx

- Passive immunization with Human tetanus immunoglobulin (HTIG) 500 U as soon as possible via IM injection in thigh or deltoid muscle. Some studies recommend 3000 to 6000 U for generalized tetanus.
- Tetanus toxoid (Td) 0.5 ml by IM injection at a different site. Redose later for a total of 3 doses spaced at least 2 weeks apart to elicit active immunization
- Antibiotics alone may fail without adequate debridement. Metronidazole 500 mg IV q6h to 8 h, or penicillin G 2 to 4 million U IV q4h to q6h for 7 to 10 days, or doxycycline 100 mg IV q12h.
- IV diazepam 10 to 30 mg to control muscle spasms. Alternative agents are midazolam, baclofen, magnesium sulfate, propofol, dantrolene, barbiturates, and chlorpromazine
- Neuromuscular blockade if necessary with pancuronium or vecuronium
- Beta-blockers (e.g., labetalol: 0.25 to 1 mg/min) to control sympathetic hyperactivity

CHRONIC Rx

- Supportive care. Beta-blockers (labetalol), magnesium sulfate, and morphine (0.5 to 1.0 mg/kg/h continuous infusion) can improve autonomic dysfunction
- Possible mechanical ventilation. Consider tracheostomy. If ventilator support is not available, benzodiazepines are the preferred agent to manage respiratory failure
- Minimal external stimuli
- Control of heart rate and blood pressure:
  1. Labetalol for sympathetic hyperactivity
  2. Pacemaker for sustained bradycardia
- Physical therapy once spasms subside

DISPOSITION

Full recovery over weeks to months if complications can be avoided

REFERRAL

- To emergency department
- To infectious disease specialist

PEARLS & CONSIDERATIONS

COMMENTS

- Illness is preventable. Table T1-5 describes tetanus prophylaxis in routine wound management.
- Boosters of Td should be given every 10 yr to maintain immune status.
- Passive as well as active immunization (HTIG and Td) should be given for patients with tetanus-prone wounds who have not been adequately immunized in the previous 5 yr.
- A recent U.S. study showed that only 72% of people older than 6 yr had protective levels of antibody.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Tetanus (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

TABLE T1-5 Tetanus Prophylaxis in Routine Wound Management

History of Absorbed Tetanus Toxoid	CLEAN, MINOR WOUNDS		OTHER WOUNDS*	
	Tdap or Td†	TIG‡	Tdap or Td†	TIG‡
Uncertain, or <3 doses	Yes	No	Yes	Yes
3 or more doses	No§	No	No‖	No

DT, Diphtheria and tetanus toxoid vaccine; *DTaP,* combined diphtheria toxoid–tetanus toxoid–acellular pertussis vaccine; *Td,* tetanus toxoid and reduced diphtheria toxoid vaccine; *Tdap,* tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine; *TIG,* tetanus immune globulin.

*Such as, but not limited to, wounds contaminated with dirt, feces, and saliva; puncture wounds; avulsions; wounds resulting from missiles, crushing, burns, and frostbite.

†For children <7 yr of age, DTaP is preferred to tetanus toxoid alone if <3 doses of DTaP have been previously given. If pertussis vaccine is contraindicated, DT is given. For persons ≥7 yr of age, Td (or Tdap for adolescents 11 to 18 yr of age) is preferred to tetanus toxoid alone. Tdap is preferred to Td for adolescents 11 to 18 yr of age who have never received Tdap. Td is preferred to tetanus toxoid for adolescents who received Tdap previously or when Tdap is not available.

‡TIG should be administered for tetanus-prone wounds in HIV-infected patients regardless of the history of tetanus immunizations.

§Yes, if ≥10 yr since the last tetanus toxoid–containing vaccine dose.

‖Yes, if ≥5 yr since the last tetanus toxoid–containing vaccine dose. (More frequent boosters are not needed and can accentuate adverse events.)

Adapted from the Centers for Disease Control and Prevention: Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines. Recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR Morbid Mortal Wkly Rep* 55:1–43, 2006.

SUGGESTED READINGS

Afshar M et al.: Narrative review: tetanus—a health threat after natural disasters in developing countries, *Ann Intern Med* 154:329–335, 2011.

Aronoff DM: *Clostridium novyi*, *sordelli*, and *tetani*: mechanisms of disease, *Anaerobe* 24:98–101, 2013.

Ataro P, Mushatt D, Ahsan S: Tetanus: a review, *South Med J* 104(8):613–617, 2011.

Demicheli V et al.: Vaccines for women to prevent neonatal tetanus, *Cochrane Database Syst Rev* 4:CD002959, 2005.

Rao KN et al.: Structural analysis of the catalytic domain of tetanus neurotoxin, *Toxicon* 45(7):929, 2005.

Rhee P et al.: Tetanus and trauma: a review and recommendations, *J Trauma* 58(5):1082, 2005.

BASIC INFORMATION

DEFINITION

Tetralogy of Fallot (TOF) is a congenital heart deformity that consists of the following four features (Fig. T1-16):

1. Malalignment ventricular septal defect (VSD).
2. Infundibular stenosis and/or pulmonary valve stenosis that leads to the obstruction of the right ventricular (RV) outflow tract.
3. An aorta that overrides the VSD by <50% of its diameter with rightward conal deviation.
4. Concentric RV hypertrophy.

SYNONYMS

TOF

ICD-9CM CODES
745.2 Tetralogy of Fallot
ICD-10CM CODES
Q21.3 Tetralogy of Fallot

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE

- TOF is the most common cyanotic congenital heart defect.
- TOF accounts for nearly 7% to 10% of all cases of congenital heart disease.
- Occurs in approximately 3.9/10,000 live births in the United States.
- It is the most common cyanotic malformation to reach adulthood without reparative surgery.

PREDOMINANT SEX: Slightly higher incidence in males than females.
GENETICS: Genetic influence is suspected.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Of the four major features of TOF, infundibular and pulmonary stenosis that lead to RV outflow tract obstruction and the presence of a VSD are the defects that result in abnormal intracardiac circulation and lead to clinical manifestations:
  - Right-to-left shunting and hypoxemia.
  - Decreased pulmonary blood flow.
  - Altered RV hemodynamics.
- The aforementioned pathophysiology results in common manifestations of TOF, including the following:
- Low birth weight and growth rate.
- Dyspnea on exertion.
- The child assuming a squatting position after exercise to increase systemic vascular resistance, thereby decreasing right-to-left shunting.
  - Cyanosis of the nail beds and lips.
  - Digital clubbing.
  - Palpable RV impulse.
  - Systolic thrill along the left sternal border.
  - Single second heart sound comprised of aortic component only.
  - A grade 3 to 5 crescendo/decrescendo systolic murmur is heard along the left mid to upper sternal border with posterior radiation.
- In TOF with pulmonary atresia, murmur is softened/absent and the patient is deeply cyanotic.
- Paroxysmal episodes of worsening cyanosis and rapid and deep breathing ("tet" spells) may occur with when there is transient increase in right ventricular outflow tract obstruction.
- "Tet" spells, and sometimes syncope may be noticed after feeding and defecation.
- The degree of RV outflow obstruction determines the age and symptoms at presentation. In neonates with severe obstruction, profound cyanosis may result from insufficient pulmonary blood flow. Cases with mild to moderate obstruction and adequate pulmonary flow ("pink tet") may be diagnosed while patient is being evaluated for murmur or heart failure.
- After repair, patients may have a low-pitched diastolic murmur at the pulmonic area that is consistent with pulmonary regurgitation or occasionally a pansystolic murmur that is consistent with a VSD patch leak. If the patient only has a palliative shunt, a continuous murmur may be heard over the chest on the side of the shunt.
- Fig T1-17 shows the pathophysiologic mechanisms of a hypoxic (tet) spell.

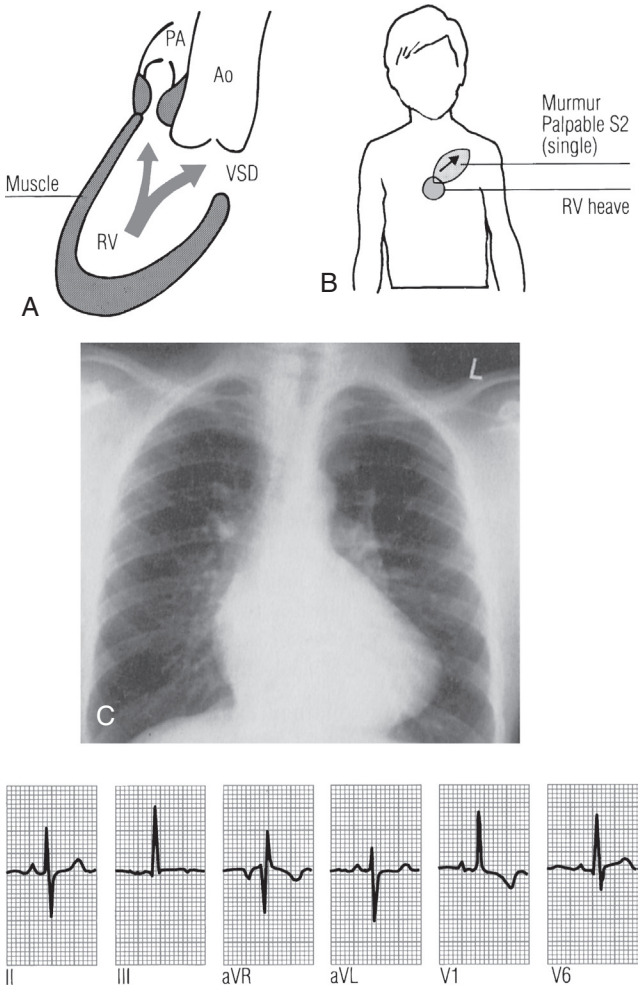


FIGURE T1-16 Features of Fallot tetralogy. A, Diagram of abnormality. *Ao,* Aorta; *PA,* pulmonary artery; *VSD,* ventricular septal defect. **B,** Physical signs. **C,** Chest x-ray showing right ventricular hypertrophy, typical "coeur en sabot." **D,** ECG showing right atrial and ventricular hypertrophy and right axis deviation. (From Souhami RL, Moxham J: *Textbook of medicine,* ed 4, London, 2002, Churchill Livingstone.)

ETIOLOGY

TOF results from the abnormal septation of the embryologic conotruncus and is associated with some genetic disorders, but the exact molecular mechanism leading to the defect is unknown.

DIAGNOSIS

- The diagnosis of TOF is suspected in any neonate, infant, or child who presents with cyanosis and a heart murmur (see "Physical Findings & Clinical Presentation").
- TOF is associated with other cardiac defects:
  - Persistent foramen ovale/atrial septal defect.
  - Pulmonary artery anomalies.
  - Right aortic arch.
  - Left superior vena cava to coronary sinus.
  - Additional VSDs.
  - Coronary artery anomalies.
  - Aortic valve regurgitation.
- Associated anomalies and syndromes include the following:
  - DiGeorge.
  - De Lange.

- Goldenhar.
- Klippel-Feil.
- VACTERL.
- CHARGE.
- Pierre Robin.
- Trisomies 21, 13, and 18.
- Fetal alcohol.
- Alagille.
- MTHFR polymorphism.

DIFFERENTIAL DIAGNOSIS

- Asthma.
- Isolated VSD.
- Pulmonary atresia.
- Patent ductus arteriosus.
- Aortic stenosis.
- Pneumothorax.

WORKUP

- Detailed history and physical examination, including pulse oximetry.
- Echocardiogram, chest radiograph, 12-lead ECG, and routine laboratory tests.

LABORATORY TESTS

- Pulse oximetry to determine oxygenation.
- The CBC shows polycythemia from long-standing hypoxemia.
- Arterial blood gas levels show hypoxemia, normal pH, and pCO_2 (carbon dioxide levels).
- ECG commonly demonstrates right axis deviation, RV hypertrophy, and right atrial enlargement.
- Exercise testing may help to evaluate functional capacity and exertional arrhythmias.

IMAGING STUDIES

- Chest radiography reveals a boot-shaped heart that is commonly described as *coeur en sabot;* a prominent RV with decreased pulmonary vascularity; and a heart size that is usually normal. However, in patients with increased aortopulmonary collateral blood flow or with associated large patent ductus arteriosus, the heart size is increased with increased pulmonary vascularity.
- Echocardiography demonstrates VSD(s), anatomy and severity of right ventricular outflow tract obstruction, aortic arch anatomy, coronary anatomy and other associated anomalies.
- Cardiac catheterization and angiography help to determine hemodynamics, the severity of right-to-left shunting, the localization of the VSD, coronary artery anatomy, right ventricular outflow obstruction, pulmonary artery stenosis, and assessment of aortopulmonary collaterals. However, it is infrequently required when the diagnosis is clear from noninvasive testing.
- Cardiac MRI can used for the localization of a residual VSD after prior surgery, the anatomic assessment of the RV outflow tract, the assessment of RV volumes and function, the quantification of degree of pulmonary regurgitation, and the detection of RV myocardial fibrosis. Magnetic resonance angiography (MRA) can be a noninvasive alternative to cardiac catheterization for the evaluation of pulmonary vascular anatomy and the ascending aorta.

Multislice spiral computed tomography may occasionally be used for diagnosis, and may be helpful during the planning of the repair procedure when the anatomy is unusual or complex. Its use in children may be limited by the risks associated with radiation exposure. It can also be used to make assessments that are similar to those usually made by MRI for patients who are unable to undergo MRI (such as those with permanent pacemakers).

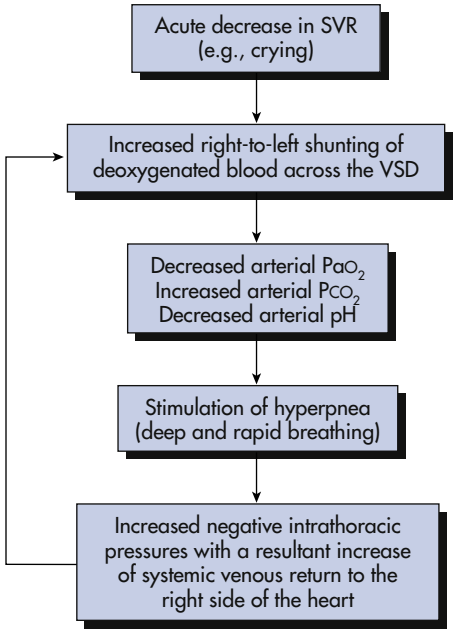


FIGURE T1-17 Pathophysiologic mechanisms of a hypoxic (tet) spell. *SVR,* Systematic vascular resistance; *VSD,* ventricular septal defect. (From Marx et al: *Rosen's emergency medicine: concepts and clinical practice,* 7 ed, 2010, Elsevier.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Oxygen.
- Prostaglandins at time of birth to keep a patent ductus and to maintain ductal flow to the lungs.
- Knee-chest position during hypoxemic spells to help reduce venous return and to increase systemic vascular resistance, thereby decreasing right-to-left shunting.

ACUTE GENERAL Rx

- The acute treatment of any infant or child with TOF who is cyanotic with respiratory distress is aimed at increasing systemic vascular resistance and decreasing right-to-left shunting (e.g., phenylephrine 0.1 to 0.5 mcg/kg/min intravenously to increase systemic vascular resistance, and oxygen and morphine to decrease pulmonary vascular resistance).
- Intravenous sodium bicarbonate for metabolic acidosis and, if more is necessary, respiratory support with intubation and sedation are required to control respiratory distress in cyanotic spells.
- Intravenous b-blockers (e.g., propranolol 0.15 to 0.25 mg/kg via slow intravenous push) are used to decrease RV outflow tract contractility.
- Emergent complete surgical repair or subclavian artery to pulmonary artery shunt (Blalock-Taussig shunt) is required if all of the above treatments fail.

CHRONIC Rx

- Palliative surgery includes procedures to increase pulmonary blood flow, thus improving oxygen saturation and allowing for pulmonary artery growth. Examples of palliative procedures include the modified Blalock-Taussig shunt, in which a Gore-Tex tube is used to create a connection between the subclavian artery and the pulmonary artery; the Waterston shunt, which attaches the ascending aorta to the right pulmonary artery; and the Potts shunt, which attaches the descending aorta to the left pulmonary artery (the latter two operations are no longer performed as they tended to lead to unpredictable pulmonary blood flow). These are generally performed in patients who are not candidates for complete surgical repair due to prematurity, hypoplastic pulmonary arteries, and/or coexistent cardiac anomalies.
- Complete surgical repair has good success and involves closing the VSD with a Dacron patch and relieving the RV outflow tract obstruction by resection of the infundibular stenosis, patch augmentation of the RV outflow, or the placement of a transannular patch. Frequently this is done before the age of 3 to 4 months but can be done in the neonatal period if the anatomy is suitable. Following surgical repair most patients have dramatic improvement in symptoms and are generally able to lead a relatively normal life.

- Postoperative issues include the following:
  1. Residual pulmonic regurgitation.
  2. Progressive RV dilation and dysfunction from pulmonary regurgitation leading to need for pulmonary valve replacement.
  3. Residual RV outflow tract obstruction.
  4. Branch pulmonary artery stenosis or hypoplasia.
  5. Sustained ventricular tachycardia.
  6. Sudden cardiac death.
  7. Atrioventricular block, atrial flutter, and atrial fibrillation.
  8. Progressive aortic regurgitation.
  9. Syndromal associations.

DISPOSITION

- In the current era, almost all patients with TOF have either palliative or complete surgical repair before they reach adulthood.
- <3% of patients with TOF survive to 40 yr without surgery.
- Survival after successful complete operative repair of TOF is excellent (35-yr survival rate for patients after TOF repair is 85%).

Adults who underwent palliative surgery during childhood can present with cyanosis and clubbing, polycythemia, and pulmonary hypertension where there is excessive pulmonary blood flow.

- Pulmonary regurgitation, residual pulmonary stenosis, and tricuspid regurgitation are the most common long-term sequelae in adults who underwent repair in childhood.
- Current guidelines and studies support pulmonary valve replacement with a bioprosthesis if the RV diastolic volume by cardiac MRI is >150 mL/m^2, RV systolic volume >80 mL/m^2, if there is evidence of RV dysfunction (RVEF <47%) or concomitant moderate or worse tricuspid regurgitation.
- Conduction disturbances; aortic root dilatation and aortic regurgitation are less common long-term issues. Aortic dissection is extremely rare in patients with TOF.
- Ventricular arrhythmia can lead to sudden cardiac death in 8.3% of surgically repaired patients by the age of 35 yr. Monomorphic ventricular tachycardia is likely the result of a reentry circuit from RV scar caused by the surgery.
- A prolonged QRS duration on the preoperative ECG predicts an increased risk of postoperative supraventricular or ventricular arrhythmia. Prolongation of the QRS beyond 180 msec identifies patients who are at increased risk of ventricular tachycardia after surgery.
- Patients with signs or symptoms of arrhythmia may need to undergo invasive electrophysiologic testing and may require mapping and/or ablation of arrhythmias, antiarrhythmic medications, or the placement of an implantable cardiac defibrillator.
- Reduced exercise capacity is frequently the result of chronic pulmonary regurgitation or residual RV outflow tract obstruction.
- Patients with left ventricular dysfunction may benefit with angiotensin-converting enzyme inhibitors, diuretics, and digoxin.
- Women with repaired TOF should be assessed by a cardiologist before considering pregnancy to determine if pulmonic valve replacement is needed first, though many will tolerate pregnancy and delivery well.
- The offspring of patients with TOF are more likely than the general population to have congenital heart anomalies.
- Selected patients with normal RV pressures and function without evidence of residual shunt and without atrial or ventricular tachyarrhythmia are eligible to participate in competitive sports.

REFERRAL

- Infants and children with cyanotic heart disease should be referred to a pediatric cardiologist for further diagnostic evaluation. After being diagnosed with TOF, patients should be referred to centers with experience in palliative and complete surgical repair.
- Adult patients with repaired TOF should be comanaged with a cardiologist who specializes in adults with congenital heart disease on at least an annual basis.

PEARLS & CONSIDERATIONS

- TOF was first described by the French physician Etienne Fallot in 1888.
- The first palliative surgical treatment for TOF was performed by Dr. Alfred Blalock at Johns Hopkins University in 1945 (i.e., the Blalock-Taussig shunt).
- The first surgical repair for TOF was performed by Dr. C. Walton Lillehei at the University of Minnesota in 1954.

COMMENTS

The severity of RV outflow tract obstruction is the primary determinant of clinical symptoms and outcomes.

- There is a 3% increased risk of congenital heart disease in the children of parents with TOF.
- Unrepaired TOF requires subacute bacterial endocarditis prophylaxis before any dental work or nonsterile surgical procedures (e.g., surgery of the bowel or bladder).
- Children with TOF are at risk for neurodevelopmental delay when they reach school age.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Tetralogy of Fallot (Patient Information)

AUTHOR: **JONATHAN GINNS, M.D.**

SUGGESTED READINGS

Al-Habib HF et al.: Contemporary patterns of management of tetralogy of Fallot: data from the Society of Thoracic Surgeons Database, *Ann Thorac Surg* 90(3):813–819, 2010. discussion 819–820.

Apitz C et al.: Tetralogy of Fallot, *Lancet* 374:1462–1470, 2009.

Graham TP Jr et al.: Task Force 2: congenital heart disease, *J Am Coll Cardiol* 45(8):1326, 2005.

Jonas RA: Early primary repair of tetralogy of Fallot, *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 12:39–47, 2009.

Malhotra SP, Hanley FL: Surgical management of pulmonary atresia with ventricular septal defect and major aortopulmonary collaterals: a protocol-based approach, *Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu* 12:145–151, 2009.

Shinebourne E et al.: Tetralogy of Fallot: from fetus to adult, *Heart* 92(9):1353, 2006.

Verheugt C et al.: Long-term prognosis of congenital heart defects: a systematic review, *Int J Cardiol* 131(1):25–32, 2008.

Warnes CA: The adult with congenital heart disease: born to be bad? *J Am Coll Cardiol* 46(1):1, 2005.

BASIC INFORMATION

DEFINITION

Thalassemias are a heterogeneous group of disorders of hemoglobin synthesis that have in common a deficient synthesis of one or more of the polypeptide chains of the normal human hemoglobin, resulting in a quantitative abnormality of the hemoglobin thus produced. Table T1-6 describes the various thalassemias. There are no qualitative changes such as those encountered in the hemoglobinopathies (e.g., sickle cell disease).

SYNONYMS

Mediterranean anemia
Cooley's anemia

ICD-9CM CODES
282.4 Thalassemia
ICD-10CM CODES
D56 Thalassemia
D56.0 Alpha thalassemia
D56.1 Beta thalassemia
D56.2 Delta-beta thalassemia
D56.3 Thalassemia trait
D56.4 Hereditary persistence of fetal hemoglobin (HPFH)
D56.8 Other thalassemias
D56.9 Thalassemia, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Thalassemia is among the most common genetic disorders worldwide. Approximately 4.83% of the world's population carry globin variants, including 1.67% of the population that are heterozygous for alpha-thalassemia and beta-thalassemia.
- The highest concentration of alpha-thalassemia is found in Southeast Asia and the African west coast. For example, the prevalence is 5% to 10% in Thailand. It is also common among blacks, with a prevalence of approximately 5%.
- The worldwide prevalence of beta-thalassemia is approximately 3%; in certain regions of Italy and Greece the prevalence reaches 15% to 30%. This high prevalence can be found in Americans of Italian or Greek descent.
- The distribution of thalassemia in Europe and Africa parallels that of malaria, suggesting that thalassemic persons are more resistant to the parasite, thus permitting evolutionary survival advantage.

CLASSIFICATION

Beta-thalassemia:
- Beta (+) thalassemia (suboptimal beta-globin synthesis)
- Beta (o) thalassemia (total absence of beta-globin synthesis)
- Delta-beta-thalassemia (total absence of both delta-globin and beta-globin synthesis)
- Lepore hemoglobin (synthesis of small amounts of fused delta-beta-globin and total absence of delta- and beta-globin)
- Hereditary persistence of fetal hemoglobin (HPHF) (increased hemoglobin F synthesis and reduced or absence of delta- and beta-globin)

Alpha-thalassemia:
- Silent carrier (three alpha-globin genes present)
- Alpha-thalassemia trait (two alpha-globin genes present)
- Hemoglobin H disease (one alpha-globin gene present)
- Hydrops fetalis (no alpha-globin gene)
- Hemoglobin constant sprint (elongated alpha-globin chain)

Thalassemic hemoglobinopathies:
- Hb Terre Haute, Hb Quong Sze, HbE, Hb Knossos

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Beta-thalassemia:
- Heterozygous beta-thalassemia (thalassemia minor): no or mild anemia, microcytosis and hypochromia, mild hemolysis manifested by slight reticulocytosis and splenomegaly

TABLE T1-6 The thalassemias

Thalassemia	Globin Genotype	Features	Expression	Hemoglobin Analysis
α-Thalassemia				
1 gene deletion	-,α/α,α	Normal	Normal	Newborn: Bart's 1%-2%
2 gene deletion trait	-,α/-,α -, -/α,α	Microcytosis, mild hypochromasia	Normal, mild anemia	Newborn: Bart's: 5%-10%
3 gene deletion hemoglobin H	-,-/-,α	Microcytosis, hypochromic	Mild anemia, transfusions not required	Newborn: Bart's: 20%-30%
2 gene deletion 1 Constant Spring	-,-/α,$\alpha^{\text{Constant Spring}}$	Microcytosis, hypochromic	Moderate to severe anemia, transfusion, splenectomy	2%-3% Constant Spring, 10%-15% hemoglobin H
4 gene deletion	-,-/-,-	Anisocytosis, poikilocytosis	Hydrops fetalis	Newborn: 89%-90% Bart's with Gower 1 and 2 and Portland
Nondeletional	α,α/α,α^{variant}	Microcytosis, mild anemia	Normal	1%-2% variant hemoglobin
β-Thalassemia				
β^0 or β^+ heterozygote: trait	β^0/A, β^+/A	Variable microcytosis	Normal	Elevated A_2, variable elevation of F
β^0-Thalassemia	β^0/β^0, β^+/β^0, E/β^0	Microcytosis, nucleated RBC	Transfusion dependent	F 98% and A_2 2% E 30%-40%
β^+-Thalassemia severe	β^+/β^+	Microcytosis, nucleated RBC	Transfusion dependent/thalassemia intermedia	F 70%-95%, A_2 2%, trace A
Silent	β^+/A	Microcytosis	Normal with only microcytosis	A_2 3.3%-3.5%
β^+/β^+	Hypochromic, microcytic	Mild to moderate anemia	A_2 2%-5%, F 10%-30%	
Dominant (rare)	B^0/A	Microcytosis, abnormal RBCs	Moderately severe anemia, splenomegaly	Elevated F and A_2
d-Thalassemia	A/A	Normal	Normal	A_2 absent
$(d\beta)^0$-Thalassemia	$(d\beta)^0$/A	Hypochromic	Mild anemia	F 5%-20%
$(d\beta)^+$-Thalassemia Lepore	β^{Lepore}/A	Microcytosis	Mild anemia	Lepore 8%-20%
Lepore	$\beta^{\text{Lepore}}/\beta^{\text{Lepore}}$	Microcytic, hypochromic	Thalassemia intermedia	F 80%, Lepore 20%
γdβ-Thalassemia	$(\Upsilon^{A}d\beta)^0$/A	Microcytosis, microcytic, hypochromic	Moderate anemia, splenomegaly, homozygote: thalassemia intermedia	Decreased F and A_2 compared with db-thalassemia
ϒ-Thalassemia	$(\Upsilon^{A}\Upsilon^{G})^0$/A	Microcytosis	Insignificant unless homozygote	Decreased F
Hereditary Persistence of Fetal Hemoglobin				
Deletional	A/A	Microcytic	Mild anemia	F 100% homozygotes
Nondeletional	A/A	Normal	Normal	F 20%-40%

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

- Homozygous beta-thalassemia (thalassemia major): intense hemolytic anemia; transfusion dependency; bone deformities (skull and long bones); hepatomegaly; splenomegaly; iron overload leading to cardiomyopathy, diabetes mellitus, and hypogonadism; growth retardation; pigment gallstones; susceptibility to infection
- Thalassemia intermedia caused by combination of beta- and alpha-thalassemia or beta-thalassemia and Hb Lepore: resembles thalassemia major but is milder

Alpha-thalassemia:

- Silent carrier: no symptoms.
- Alpha-thalassemia trait: microcytosis only.
- Hemoglobin H disease: moderately severe hemolysis with microcytosis and splenomegaly.
- The loss of all four alpha-globin genes is incompatible with life (stillbirth of hydropic fetus). NOTE: Pregnancies with hydrops fetalis are associated with a high incidence of toxemia.

ETIOLOGY

- Beta-thalassemia: it is caused by more than 200 point mutations and, rarely, by deletions. The reduction of beta-globin synthesis results in redundant alpha-globin chains (Heinz bodies), which are cytotoxic and cause intramedullary hemolysis and ineffective erythropoiesis. The pathophysiology of beta-thalassemia is illustrated in Fig. ET1-18. Fetal hemoglobin may be increased.
- Alpha-thalassemia: several mutations can result in insufficient amounts of alpha-globin available for combination with non–alpha-globins.

Dx DIAGNOSIS

LABORATORY TESTS

Beta-thalassemia:

- Microcytosis (mean cell volume: 55 to 80 fL)
- Normal red blood cell (RBC) distribution width index (RDW)
- Smear: nucleated RBCs, anisocytosis, poikilocytosis, polychromatophilia, Pappenheimer and Howell-Jolly bodies
- Hemoglobin electrophoresis: absent or reduced hemoglobin A, increased fetal hemoglobin, variable increase in the amount of hemoglobin A_2
- Markers of hemolysis: elevated indirect bilirubin and lactate dehydrogenase, decreased haptoglobin

Alpha-thalassemia:

- Microcytosis in the absence of iron deficiency
- Hemoglobin electrophoresis normal except for the presence of hemoglobin H in hemoglobin H disease (Table T1-7)

Rx TREATMENT

- Thalassemia minor: no treatment, but avoid iron administration for incorrect diagnosis of iron deficiency.
- Beta-thalassemia major (and hemoglobin H disease):
  1. Transfusion therapy: Guidelines for transfusion therapy recommend administration of 10 to 15 mL/kg of RBC every 2 to 4 weeks to maintain the pretransfusion hemoglobin level above 9 to 10.5 g/dl. Use of leukoreduced RBCs that have been stored for less than 7 to 10 days is preferred. Use of first-degree relatives as blood donors should be avoided.
  2. Chelation therapy: Transfusion hemosiderosis is the major cause of late morbidity and mortality in patients with thalassemia major. Each unit of packed RBCs contains approximately 250 mg of iron. Chelation of iron can be accomplished with desferrioxamine (by IV or subcutaneous administration, 8 to 12 hr nightly, 5 to 6 days a week at a dose of 2 to 6 g/day with a portable infusion pump). Deferiprone, an oral chelating agent, can be used as a second-line treatment of iron overload caused by blood transfusions (transfusional hemosiderosis).
  3. Splenectomy for hypersplenism if present.
  4. Bone marrow transplantation. Although hematopoietic stem cell transplantation is the only curative approach for thalassemia, it has been limited by the high cost and scarcity of human leukocyte antigen–matched donors. Before transplantation, it is necessary to administer myeloablative regimens to eradicate the endogenous thalassemic bone marrow. Commonly used agents are hydroxyurea, azathioprine, fludarabine, busulfan, and cyclophosphamide.
  5. Hydroxyurea may increase the level of hemoglobin F.

! PEARLS & CONSIDERATIONS

- Polymerase chain reaction can be used to detect point mutations or deletions in chorionic villous samples, enabling first-trimester, DNA-based testing for thalassemia.
- Preimplantation genetic diagnosis can be extended to human leukocyte antigen typing on embryonic biopsies, allowing the selection of an embryo that is not affected by thalassemia and that may also serve as a stem cell donor for a previously affected child within the same family.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **FRED F. FERRI, M.D.**

TABLE T1-7 Distinguishing Laboratory Features of α- and β-Thalassemias

Diagnosis*	BCB Prep†	HbA_2‡	HbF	HbH	Hb Barts in Newborn§
Normal	–	nl	nl	nl	–
α-Thalassemia	+	nl	nl	nl or ↑	+
β-Thalassemia	–	nl or ↑	nl or ↑	nl	–

Hb, Hemoglobin type; *nl,* normal; ↑, increased; –, negative; +, positive.

Can be negative for a one α-globin deletion (silent carrier), for compound heterozygotes with combined α- and β-thalassemia, and other hemoglobinopathies (e.g., HbE or HbS). Table shows typical results; exceptions occur.

*All forms of α -or β-thalassemia are pooled; specific results will vary.

†Brilliant cresyl blue (*BCB*) or inclusion body prep. Results vary by lab, but this can be done semiquantitatively. This can be negative when a one α-globin deletion (silent carrier) is present. This assay is unreliable in the presence of other hemoglobins (e.g., HbS or HbE). This can be negative when α- and β-thalassemia are simultaneously present.

‡HbA_2 results vary depending on laboratory method.

§Hb Barts increases with the degree of α-thalassemia.

From Fuhrman: *pediatric critical care,* ed 4. Philadelphia, 2010, Elsevier)

SUGGESTED READINGS

Piel FB, Weatherall DJ: The α-thalassemias, *N Engl J Med* 371:1908–1916, 2014.
Round D, Rachmilewitz E: Beta thalassemia, *N Engl J Med 353* 1135, 2005.

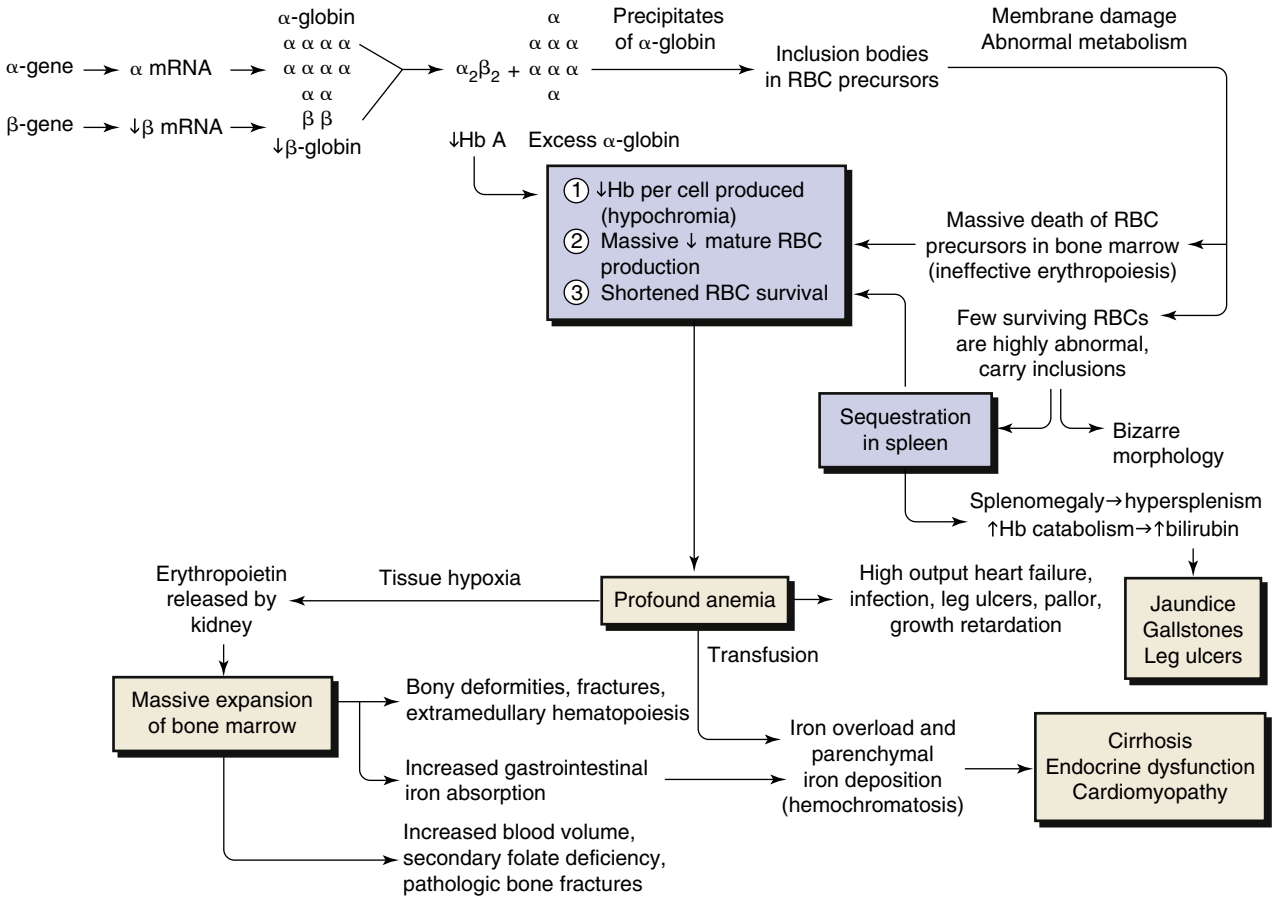


FIGURE ET1-18 Pathophysiology of severe forms of β-thalassemia. The diagram outlines the pathogenesis of clinical abnormalities resulting from the primary defect in β-globin chain synthesis. *RBC,* Red blood cell. (From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

Thoracic Outlet Syndrome PTG

BASIC INFORMATION

DEFINITION

Thoracic outlet syndrome (TOS) describes a condition producing upper extremity symptoms believed to result from neurovascular compression at the thoracic outlet (Fig. T1-19). Three types are described on the basis of point of compression: (1) cervical rib and scalenus syndrome, in which abnormal scalene muscles or the presence of a cervical rib may cause compression; (2) costoclavicular syndrome, in which compression may occur under the clavicle; and (3) hyperabduction syndrome, in which compression may occur in the subcoracoid area. The compression occurs in three anatomical structures–arteries, veins, and nerves.

- Neurogenic TOS: Caused by compression of brachial nerve plexus
- Arterial TOS: Caused by subclavian artery compression
- Venous TOS: Caused by compression of subclavian vein

ICD-9CM CODES
353.0 Thoracic outlet syndrome
ICD-10CM CODES
G54.0 Brachial plexus disorders

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Varies from source to source; presence of cervical ribs in 0.5% to 1% of population (50% bilateral), but most are asymptomatic
PREDOMINANT SEX: Females affected more often than males (ratio of 3.5:1)
PREDOMINANT AGE: Rare in those aged <20 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms and signs are related to the degree of involvement of each of the various structures at the level of the first rib.
- True venous or arterial involvement is not common.
- Diagnosis is most often used in the consideration of neural pain affecting the arm, which suggests involvement of the brachial plexus.
  1. Arterial compression: pallor, paresthesias, diminished pulses, coolness, Raynaud's phenomenon, digital gangrene, supraclavicular bruit or mass, and stroke
  2. Venous compression: edema and pain; thrombosis causing superficial venous dilation in the shoulder area
  3. Neurologic compression: Pain and or paresthesia of neck, shoulder region, arm or hand, depending on the root involved with difficulty. Intrinsic weakness and diminished sensation on examination
  4. Possible supraclavicular tenderness
  5. Provocative tests (Adson's, Wright's): may reproduce pain but are of disputed usefulness

ETIOLOGY

- Congenital cervical rib or fibrous extension of cervical rib (Fig. T1-20)
- Abnormal scalene muscle insertion
- Drooping of shoulder girdle from generalized hypotonia or trauma
- Narrowed costoclavicular interval as a result of downward and backward pressure on shoulder (sometimes seen in individuals who carry heavy backpacks), poor posturing, pregnancy
- Acute venous thrombosis with exercise (effort thrombosis)
- Bony abnormalities of first rib
- Abnormal fibromuscular bands
- Malunion of clavicle fracture

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Carpal tunnel syndrome
- Cervical radiculopathy
- Brachial neuritis
- Ulnar nerve compression (cubital tunnel syndrome)
- Complex regional pain syndrome
- Superior sulcus tumor

WORKUP

Fig. T1-21 describes a diagnostic algorithm for thoracic outlet syndrome. Except for venous or arterial pathology, no ancillary diagnostic tests are reliable for diagnostic confirmation.

IMAGING STUDIES

- Electromyography, nerve conduction velocity studies to rule out carpal tunnel syndrome, cervical radiculopathy
- Ultrasound for initial evaluation for arterial or venous thoracic outlet syndrome
- Cervical spine radiographs to rule out cervical disk disease
- Chest radiograph to rule out lung tumor
- Computed tomography (CT) for detailed anatomical relationship of vascular structure to surrounding muscles and bones

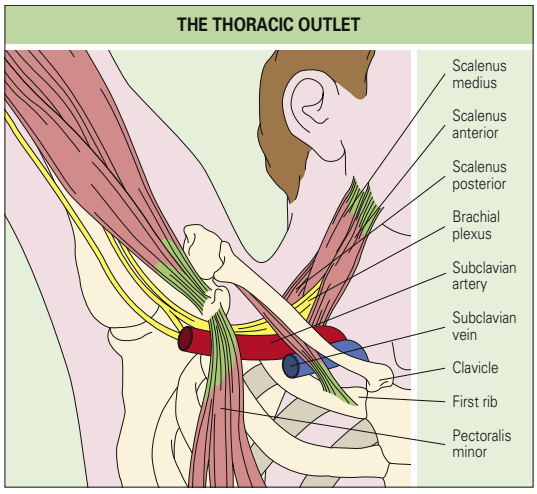


FIGURE T1-19 The thoracic outlet. Three narrow channels of the outlet include the scalene triangle, the costoclavicular passage, and the pectoralis minor attachment at the coracoid process. (Hochberg MC et al: *Rheumatology*, ed 5, St Louis, 2011, Mosby.)

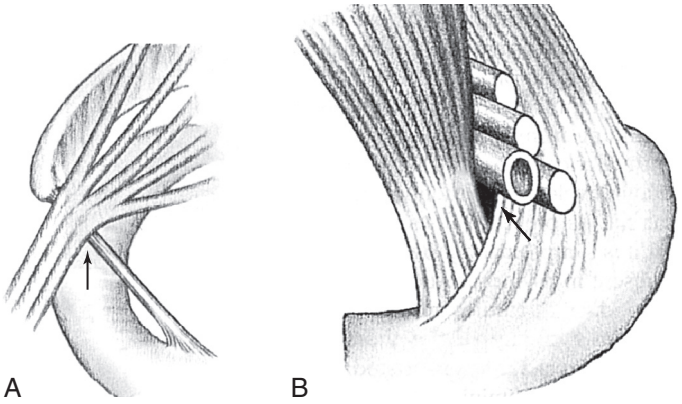


FIGURE T1-20 A, Compression caused by a cervical rib *(arrow).* **B,** Abnormal scalene muscle insertions that may cause compression at the cervicobrachial region *(arrow).* (From Mercier LR: *Practical orthopedics,* ed 5, St Louis, 2000, Mosby.)

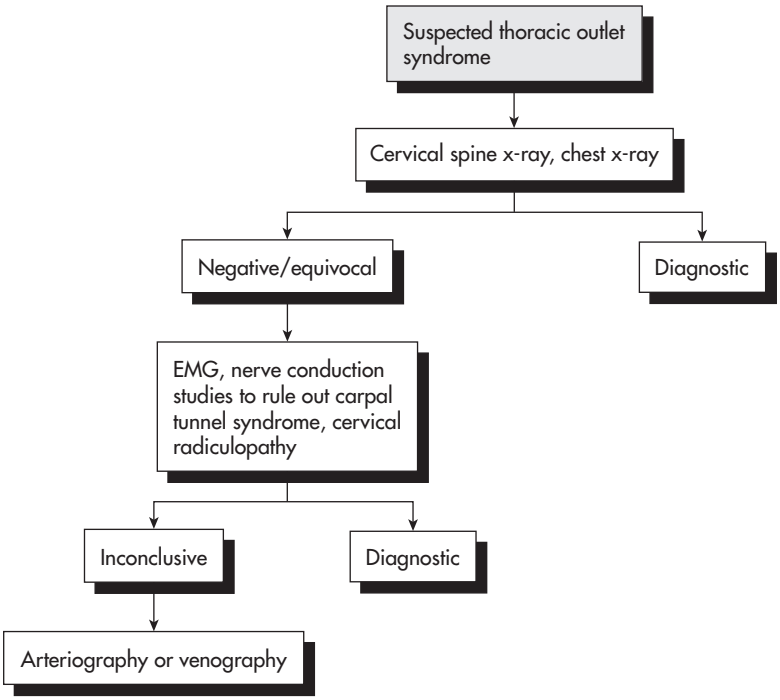


FIGURE T1-21 Thoracic outlet syndrome. *EMG,* Electromyogram.

- Contrast-enhanced magnetic angiography can be very useful in assessing vessel imaging while using provocative arm positions.
- Arteriography or venography can be used for dynamic studies while performing upper extremity maneuvers and also performing thrombolysis if needed.

Rx TREATMENT

ACUTE GENERAL Rx

- Sling for pain relief
- Physical therapy modalities plus shoulder girdle–strengthening exercises
- Postural reeducation
- Nonsteroidal anti-inflammatory drugs
- Muscle relaxants

CHRONIC Rx

- Surgical treatment is indicated:
- After failure of physical therapy
- TOS with complications like thrombosis, aneurysms
- Neurologic compressions
- Sympathetic cervical rib
- Surgical options include:
- Thoracic outlet decompression
- Cervical rib resection
- Thoracic sympathetectomy
- Vascular repair
- Catheter-directed thrombolysis

DISPOSITION

- Nonsurgical treatment: often successful for patients with pain as the primary symptom
- Complications of surgical treatment include transient dysesthesia, venous injury, arterial injuries, or brachial plexus injuries.

REFERRAL

For vascular surgery consultation when venous or arterial impairment is present

PEARLS & CONSIDERATIONS

COMMENTS

- True thoracic outlet syndrome is probably an uncommon condition.
- Diagnosis is often used to describe a wide variety of clinical symptoms.
- Considerable disagreement exists regarding the frequency of this disorder.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Thoracic Outlet Syndrome (Patient Information)

AUTHOR: **SYEDA M. SAYEED, M.D.**

SUGGESTED READINGS

Arthur LG et al.: Pediatric thoracic outlet syndrome: a disorder with serious vascular complications, *J Pediatr Surg* 43:1089, 2008.

Campbell WW, Landau ME: Controversial entrapment neuropathies, *Neurosurg Clin North Am* 19:597, 2008.

Malas FU et al.: Etiologic factors in thoracic outlet syndrome, *Orthopedics* 30(6):425, 2007.

Monica JT et al.: Thoracic outlet syndrome with subclavian artery thrombosis undetectable by magnetic resonance angiography, *J Bone Joint Surg Am* 89:1589, 2007.

Nichols AW: Diagnosis and management of thoracic outlet syndrome, *Curr Sports Med Rep* 8:240, 2009.

Sadat U et al.: Diagnosis of thoracic outlet syndrome: an overview, *Br J Hosp Med* 69:260, 2008.

Sanders RJ et al.: Diagnosis of thoracic outlet syndrome, *J Vasc Surg* 46:601, 2007.

Urschel HC, Kourlis H: Thoracic outlet syndrome: a 50-year experience at Baylor University Medical Center, *Proc (Bayl Univ Med Cent)* 20(2):125, 2007.

Wehbe MA, Leinberry CF: Current trends in treatment of thoracic outlet syndrome, *Hand Clin* 20:119, 2004.

BASIC INFORMATION

DEFINITION

Thromboangiitis obliterans (TAO, Buerger's disease) is an uncommon nonatherosclerotic segmental, inflammatory occlusive disease that affects small and medium-sized arteries and veins of the extremities. TAO is an inflammatory disease; however, in contrast with all the major forms of arteritis, fibrinoid necrosis of the arterial wall is not observed, and the vascular wall is preserved. This feature distinguishes TAO from other types of systemic vasculitis and from atherosclerosis, in which there is usually disruption of the internal elastic lamina and media. TAO is characterized by a highly cellular and inflammatory occlusive thrombus.

SYNONYMS

Buerger's disease
Presenile gangrene
TAO

ICD-9CM CODES
443.1 Thromboangiitis obliterans (Buerger's disease)
ICD-10CM CODES
I73.1 Thromboangiitis obliterans (Buerger's disease)

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: The prevalence of TAO varies by population studied, but overall trends show a decline. It is most common in the Mediterranean, Asia, and the Middle East, probably because of a higher rate of tobacco use.

- In the Mayo Clinic annual registration per 100,000, the prevalence decreased from 104.3 in 1947 to 13.5 in 1987.
- Among patients with peripheral artery disease, the prevalence of TAO was 0.5% to 5.6% in Western Europe.
- As a percent of all cases of peripheral artery disease, the prevalence was highest in India (45 to 63%), followed by Korea (40%), the former Yugoslavia (38%), and Japan (32%).
- Commonly reported very high prevalence among Ashkenazi Jews is incorrect.

PREDOMINANT SEX AND AGE: TAO affects predominantly males (70%-91%) between the ages of 40 and 45. Almost all patients are cigarette smokers or use smokeless tobacco and marijuana. There has been a recent increase among females that is attributed to increased smoking.

RISK FACTORS:

- Smoking, other atherosclerotic risk factors commonly absent
- Male sex
- Studies have suggested increased prevalence in women from 11% to 23%, unclear if this is related to cigarette usage.
- Age <45
- Periodontal infection (may be a confounder although pathogens have been found in occluded arteries of patients)
- Mediterranean, Middle Eastern, or Asian descent

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most common presentation: young man, less than 40 to 45 years old, tobacco use and signs of lower limb ischemia.
- Most common symptoms: intermittent claudication, superficial thrombophlebitis, digital ischemia, distal digital ulcerations, paresthesias from ischemic neuropathy, and Raynaud's phenomenon, which may occur in up to 40% of those affected and be asymmetric.
- Advanced disease may present with rest pain as the first symptom, and then necrosis, ulceration, and gangrene.
- Superficial thrombophlebitis, migratory pattern of tender nodules, helps distinguish TAO from other vasculitides.
- The predominance of distal limb involvement including upper and lower extremities helps distinguish TAO from peripheral artery disease. The lower extremities are involved in nearly all cases, while the upper extremities are involved in 40% to 50%. The disease rarely affects the vessels proximal to the popliteal artery.
- Commonly, two or more extremities involved, rarely affects the vessels proximal to the popliteal artery
  1. 72% with lower-extremity ischemic ulcerations
  2. 40% to 50% with upper extremities involved
- Rare atypical clinical manifestations can involve other vessels, including the abdomen, coronaries, and renal and cerebral vasculature. With more advanced disease, larger arteries can be affected and multiorgan involvement, while rare, has been reported.
- Rest pain generally occurs on the forefoot and is continuous; patients may therefore sleep with their legs dangling downward.
- There can be evidence of prolonged capillary refill with dependent rubor.
- Although nonspecific, a positive Allen's test in a young smoker with digital ischemia can be suggestive of the disease.

ETIOLOGY

- The etiology of TAO remains unclear; however, a multifactorial mechanism has been proposed that involves a combination of genetic susceptibility, tobacco exposure, and immune and coagulable responses.
- Inherited and acquired prothrombotic factors as well as particular HLA antigens have been linked to TAO.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Limb ischemia as a result of emboli or atherosclerotic occlusive disease
- Acquired or inherited hypercoagulable state
- Autoimmune disorders
- Acrocyanosis
- Carpal tunnel syndrome
- CREST syndrome (i.e., calcinosis cutis, Raynaud's phenomenon, esophageal motility disorder, sclerodactyly, and telangiectasia)
- Diabetes mellitus
- Repetitive vibratory equipment use
- Hypothenar hammer syndrome
- Ergotamine intoxication
- Polyarteritis nodosa
- Disseminated intravascular coagulation
- Cannabis arteritis
- Peripheral neuropathy

CLINICAL CRITERIA

A clinical diagnosis can be established when all five criteria are met (most widely accepted, but not validated):

- Age <50 yr
- Current or recent history of tobacco use
- Infra-popliteal or occlusive disease (objectively noted on vascular testing)
- Upper limb involvement or phlebitis migrans
- Absence of atherosclerotic risk factors other than smoking, exclusion of autoimmune disease, thrombophilia, diabetes, and proximal embolic sources
- Other diagnostic criteria have been proposed by Papa et al, Mills and Porter, and Shionoya clinical criteria.

WORKUP

- TAO is a predominantly clinical diagnosis that can be suspected in patients who meet the above clinical criteria. However, the diagnosis of TAO is more a function of ruling out other, more common entities that may produce similar clinical symptoms. Biopsy provides a definitive diagnosis, but subcutaneous nodules are not always present.
- A positive Allen's test at the wrist of a young smoker is suggestive of TAO.

LABORATORY TESTS

- The primary goal of laboratory testing in patients with suspected TAO is to exclude alternative diagnoses.
- Markers of inflammation and auto-antibodies are usually absent:
  1. CRP and ESR, normal in patients with TAO and not normal in the majority of vasculitides.
  2. Lupus anticoagulant and anticardiolipin antibodies are detected in some patients but may also indicate an isolated thrombophilia.
  3. Anti-endothelial antibodies have been described in Buerger disease.
- Biopsy is required for definitive diagnosis and is helpful in atypical presentations; but it is rarely needed.
  1. May show highly cellular thrombus in medium sized arteries and superficial veins followed by organization and recanalization.
  2. Segmental obliteration of involved arteries but the internal elastic membrane of vessel walls remains intact.

IMAGING STUDIES

- Ankle brachial index if lower extremity signs or symptoms, wrist-brachial index for upper extremity signs of symptoms with digit pressures should be performed.
- Duplex ultrasonography has been demonstrated to show corkscrew collaterals in patients with TAO.
- Computed tomographic angiography (CTA), magnetic resonance angiography (MRA), or invasive catheter-based contrast angiography may be performed to identify distribution of vascular involvement and show normal proximal arteries and extent of disease.
- Echocardiography may be indicated in certain cases when acute distal arterial occlusion caused by cardiac thromboembolism is suspected.
- Angiography, gold standard for diagnosis, findings in TAO are described in Box ET1-1, and Fig. ET1-22 shows an angiogram of a patient with TAO. (Martorell Sign: Corkscrew Collaterals, sensitive but not specific for TAO.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Smoking cessation is essential to preventing further episodes of TAO by halting the progression of disease, whereas other therapies are palliative. An increased rate of limb amputation due to progression of disease has been demonstrated in patients who continue tobacco use. The disease may be activated by smoking as little as one or two cigarettes a day.

ACUTE GENERAL Rx

- Discontinuation of tobacco use is the definitive therapy for TAO. Pharmacotherapy and smoking cessation groups should be offered to patients. Transdermal nicotine patches and nicotine chewing gum should be avoided because they may keep the disease active.

BOX ET1-1 Angiographic Findings in Thromboangiitis Obliterans (Buerger Disease)

- Involvement of small- and medium-sized vessels; palmar, plantar, tibial, peroneal, radial, and ulnar arteries; and digital arteries of fingers and toes
- Normal extremity arteries proximal to the popliteal and distal brachial levels
- Absence of proximal atherosclerosis and vascular calcification
- No source of thrombus
- Abrupt transition from a normal and smooth proximal artery to an area of occlusion
- Symmetric and segmental arterial involvement
- Tortuous "corkscrew" collaterals are suggestive, but not pathognomonic, of Buerger disease

From Cameron JL, Cameron AM: *Current surgical therapy*, ed 10, Philadelphia, 2011, Saunders.

- Patients should be treated with antiplatelet agents as well as walking exercises.
- Patient with critical limb ischemia should be hospitalized.
- Therapeutic options have been limited to vasodilators, prostaglandin analogs (vasodilator and platelet aggregation inhibitor), intermittent pneumatic compression, spinal cord stimulation, and peripheral periarterial sympathectomy:
  1. Treatment of patients in the acute phase of TAO with the prostanoid vasodilator iloprost (intravenous only, as oral therapy has no significant clinical effect) has been associated with reduced rest pain, greater healing of ischemic ulcers, and a two thirds reduction in the amputation rate.
  2. IV alprostadil alphadex, another prostanoid, was compared to aspirin in a small prospective trial in patients with TAO and critical limb ischemia, which showed improved ulcer healing and pain reduction at 21 and 28 days.
  3. Other vasodilators (α-blockers, calcium channel blockers, and sildenafil) may be helpful but have not been studied in prospective clinical trials.
- Pneumatic compression has been used to augment perfusion to the lower extremities in patients with severe claudication or critical limb ischemia who are not revascularization candidates.
- Epidural spinal cord stimulation has been shown to improve regional perfusion.
- Peripheral periarterial sympathectomy may be considered for patients with refractory pain and digital ischemia (Box ET1-2).

CHRONIC Rx

- Surgical revascularization is usually not feasible because of the distal and diffuse nature of the disease but may be considered in patients with critical limb ischemia and suitable distal target vessels.
- Venous graft bypasses have an approximately 40% to 60% failure rate at 5 to 10 yr follow-up, and are lower in those who continue to smoke.
- Other invasive therapies include sympathectomy or spinal cord stimulation for pain control.

EXPERIMENTAL THERAPIES

- Intramuscularly administered vascular endothelial growth factor has shown improved ischemic ulcer healing and reduced ischemic rest pain in patients with critical limb ischemia in the short-term.
- Intramuscular transplantation of autologous bone-marrow mononuclear cells showed improvements in leg pain, ulcer size, and pain-free walking distance at 2 yr.

BOX ET1-2 Treatment Options in Thromboangiitis Obliterans (Buerger Disease)

- Cessation of tobacco products
- Local wound care
- Arterial reconstruction with vein graft
- Prostaglandin analog iloprost or treprostinil sodium
- Cilostazol
- Hyperbaric oxygen therapy
- Calcium channel blockers (e.g., amlodipine or nifedipine for vasospasm)
- Intermittent pneumatic compression pump
- Implantable spinal cord stimulator
- Therapeutic angiogenesis
- Amputation

From Cameron JL, Cameron AM: *Current surgical therapy*, ed 10, Philadelphia, 2011, Saunders.

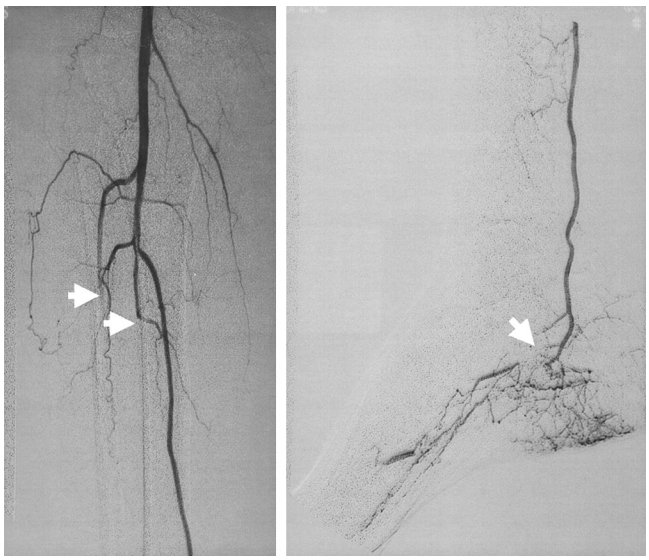


FIGURE ET1-22 Angiogram of a young woman with thromboangiitis obliterans. The *left panel* demonstrates occlusion of the anterior tibial and peroneal arteries *(arrows).* The *right panel* demonstrates an occlusion of the distal portion of the posterior tibial artery *(arrow)* with bridging collateral vessels. (From Zipes DP et al [eds]: *Braunwald's heart disease*, ed 8, Philadelphia, 2008, Saunders.)

- Immunoabsorption therapy has shown improved leg pain, healing of ischemic ulcerations at up to 6 months.
- Other pharmacological therapies being studied include bosentan (endothelin receptor antagonist) and cilostazol (phosphodiesterase inhibitor).

DISPOSITION

- Periods of exacerbation and remission are characteristic of TAO. The disease typically intensifies at the age of 30 to 40 and then symptoms diminish. Patients aged 60 yr or older rarely have recurrence of symptoms.
- The risk of major amputation was 11% at 5 yr, 21% at 10 yr, and 23% at 20 yr. Risk of amputation was eliminated by 8 yr after smoking cessation.

REFERRAL

Smoking cessation counseling, rheumatology consultation, and vascular surgery consultation are recommended for any young smoker with claudication and ischemic ulcers, especially if both the upper and lower extremities are involved.

PEARLS & CONSIDERATIONS

COMMENTS

- The pathogenesis of the disease is still poorly understood but smoking plays a key role.
- A multifactorial mechanism has been proposed that involves a combination of genetic susceptibility, tobacco exposure, and immune and coagulable responses.
- The diagnosis is predominantly clinical; however, the criteria are somewhat controversial. Biopsy of subcutaneous nodules can also be useful but is not necessary for a diagnosis.
- No diagnostic criteria are fully accepted by international circles.
- Discontinuation of tobacco use is the definitive therapy for TAO.

PATIENT/FAMILY EDUCATION

Patients with TAO must be warned about tobacco use and secondhand passive smoke. Information for patients can be obtained from the following organizations:

- Vascular Disease Foundation (http://www.vdf.org)
- Mayo Foundation for Medical Education and Research (http://www.mayoclinic.com)

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Thromboangiitis Obliterans (Buerger's Disease) (Patient Information)

AUTHORS: **AARON F. JOLLY, M.D.,** and **PRANAV M. PATEL, M.D.**

SUGGESTED READINGS

Fujii Y, Sogo J, Hidaka T, et al.: Color Doppler flows of corkscrew collaters in thromboangiitis obliterans (Buerger's disease) using color duplex ultrasonography, *J Am Coll Cardiol* 57:2539, 2011.

Malecki R et al.: Thromboangiitis obliterans in the 21st century: a new face of disease, *Atherosclerosis* 206:328–334, 2009.

Olin JW et al.: Thromboangiitis obliterans (Buerger's disease), *Curr Opin Rheumatol* 18(1):18, 2006.

The European TAO Study Group: Oral iloprost in the treatment of thromboangiitis obliterans (Buerger's disease): a double-blind, randomised, placebo-controlled trial, *Eur J Vasc Endovasc Surg* 15:300, 1998.

Piazza G et al.: Thromboangiitis obliterans, *Circulation* 121:1858–1861, 2010.

Puéchal X et al.: Thromboangiitis obliterans or Buerger's disease: challenges for the rheumatologist, *Rheumatology* 46(2):192, 2007.

Vijayakumar A, Tiwari R: Kumar Prabhuswamy V. Thromboangiitis obliterans (Buerger's disease)—current practices, *Int J Inflamm* 2013, 2013. http://dx.doi.org/10.1155/2013/156905.

BASIC INFORMATION

DEFINITION

Thrombocytosis is defined by an elevated platelet count (>450,000/mm^3) in peripheral blood. It is caused by overproduction of platelets (reactive thrombocytosis), or it may be caused by clonal expansion of megakaryocytes (clonal thrombocytosis). Reactive thrombocytosis is driven by excessive cytokines induced by various stimuli, such as trauma or inflammation. The latter is defined as chronic myeloproliferative disorders (CMPD), of which four subgroups are well characterized: chronic myelogenous leukemia (CML), polycythemia vera (PV), primary myelofibrosis (PMF), and essential thrombocythemia (ET). In addition, platelet count can be spuriously elevated in some conditions (see differential diagnosis). Extreme thrombocytosis is defined as platelet count >1 million/ml.

SYNONYMS

Thrombocythemia

ICD-9CM CODES

289.9 Unspecified diseases of blood and blood-forming organs
238.71 Essential thrombocytosis

ICD-10CM CODES

D47.3 Essential (hemorrhagic) thrombocythemia
D75.9 Disease of blood and blood-forming organs, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

Reactive thrombocytosis is much more frequent than clonal thrombocytosis (70% vs. 22% in one series).
Epidemiology for essential thrombocythemia:
INCIDENCE: 2.5 cases/100,000 population/yr
PREVALENCE: Estimated as 24 cases/100,000 population
PREDOMINANT SEX AND AGE: The median age at diagnosis is 60 yr. Female/male ratio is 2:1.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Regardless of the cause, a high platelet count may be associated with vasomotor symptoms such as headache, visual disturbances, dizziness, atypical chest pain, acral dysesthesia, and erythromelalgia.
- Thrombotic and bleeding complications can occur.
- Symptoms and complications are much more likely to occur in association with autonomous thrombocytosis than reactive thrombocytosis.
- The degree of thrombocytosis does not predict the likelihood of autonomous thrombocytosis, and does not generally correlate to the risk of thrombosis.
- Splenomegaly is common with CMPD.
- Coexistent leukocytosis and erythrocytosis are common with CML and PV.
- Disease transformation from ET to PV, PMF, and acute myeloid leukemia (AML) is uncommon.

ETIOLOGY

- Etiology is unclear in essential thrombocythemia.
- Abnormality in Jak2-STAT pathway may play a role in pathogenesis of CMPD.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Spurious thrombocytosis
  - Mixed cryoglobulinemia
  - Circulating cytoplasmic fragments in patients with leukemia, lymphoma, or severe hemolysis or burns can be counted as platelets
- Reactive thrombocytosis
  - Benign hematologic disorders
  - Acute hemorrhage, iron deficiency anemia, hemolytic anemia
  - Chronic infection, such as tuberculosis
  - Acute and chronic inflammatory disorders
  - Rheumatologic disorders
  - Inflammatory bowel disease
  - Celiac disease
  - Functional and surgical asplenia
  - Tissue damage
  - Trauma, thermal burn
  - Myocardial infarction
  - Acute pancreatitis
  - Recent surgery
  - Renal failure, nephrotic syndrome
  - Exercise
  - Medications, such as vincristine, epinephrine
- Clonal thrombocytosis
  - CML
  - PV
  - PMF
  - Myelodysplastic syndrome (5q-syndrome)
  - AML with inv(3), t(3;3)
  - Essential thrombocytosis (Box T1-3)

WORKUP

- Comprehensive history and physical examination to exclude many of the common causes of reactive thrombocytosis: history and physical examination suggestive of acute blood loss, iron deficiency, acute or chronic infection/inflammation, medication use, asplenia, malignancy, and trauma should be looked for. Fig. ET1-23 describes a diagnostic algorithm for thrombocytosis. The diagnosis of ET requires platelet counts >600 x 109/L on two separate occasions >4 weeks apart, absence of Philadelphia chromosome, and exclusion of secondary causes of thrombocytosis.
- Repeat CBC with peripheral blood smear and bone marrow biopsy (Figs. T1-24 and ET1-25) to exclude spurious thrombocytosis.

LABORATORY TESTS

- CBC with peripheral blood smear: Howell-Jolly bodies and target cells are present in patients with asplenia; nucleated RBC, teardrop RBC and WBC precursors in patients with PMF
- Serum ferritin level: low ferritin level suggests iron deficiency
- Serum C-reactive protein (CRP), ESR, and plasma fibrinogen: nonspecific markers of infection or inflammation
- Philadelphia chromosome or BCR-ABL rearrangement: positive in CML
- Serum erythropoietin assay: low to normal in PV and ET
- JAK2 mutation analysis: PV and ET; JAK2 mutation is found in 95% to 99% of patient with PV, in 40% to 60% of patients with PMF, and in about 50% of patients with ET
- MPL and CALR mutation analysis: Frequency is reported as 4% and 15% to 32%, respectively in ET
- Bone marrow chromosome analysis: 5q-syndrome and other myelodysplastic syndrome, CML

BOX T1-3 World Health Organization Diagnostic Criteria for Essential Thrombocythemia

Diagnosis requires that all of the following criteria be met:

- Sustained platelet count ≥450 × 10^9/L[a]
- Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes; no significant increase or left shift of neutrophil granulopoiesis or erythropoiesis
- Failure to meet the WHO criteria for polycythemia vera,[b] primary myelofibrosis,[c] BCR-ABL1–positive chronic myelogenous leukemia,[d] myelodysplastic syndrome,[e] or other myeloid neoplasms
- Demonstration of JAK2 V617F or other clonal marker; or, in the absence of JAK2 V617F, no evidence of reactive thrombocytosis[f]

[a]Sustained during the workup process.
[b]Requires the failure of iron replacement therapy to increase the hemoglobin level to the polycythemia vera range in the presence of decreased serum ferritin. Exclusion of polycythemia vera is based on hemoglobin and hematocrit levels; red cell mass measurement is not required.
[c]Requires the absence of relevant reticulin fibrosis, collagen fibrosis, peripheral blood leukoerythroblastosis, or markedly hypercellular marrow accompanied by megakaryocyte morphology typical for primary myelofibrosis—small to large megakaryocytes with an aberrant nuclear-to-cytoplasmic ratio and hyperchromatic, bulbous, or irregularly folded nuclei and dense clustering.
[d]Requires the absence of BCR-ABL1.
[e]Requires the absence of dyserythropoiesis and dysgranulopoiesis.
[f]Causes of reactive thrombocytosis include iron deficiency, splenectomy, surgery, infection, inflammation, connective tissue disease, metastatic cancer, and lymphoproliferative disorders. However, the presence of a condition associated with reactive thrombocytosis does not exclude the possibility of essential thrombocythemia if other criteria are met.
From Swerdlow SH et al (eds): *WHO classification of tumours of haematopoietic and lymphoid tissues,* Lyon, France, 2008, IARC Press.

- Bone marrow exam in ET may show clusters of abnormal megakaryocytes and increased reticulin fibrosis (see Fig. ET1-25).

Rx TREATMENT

Treatment for ET will be addressed in this chapter. Reactive thrombocytosis has been rarely associated with thrombosis or bleeding and generally does not require specific therapy.

ACUTE GENERAL Rx

- Vasomotor symptoms easily manageable with low-dose aspirin (<100 mg/day)
- Bleeding
  1. Discontinue any platelet antiaggregating agent, such as aspirin or nonsteroidal anti-inflammatory agents.
  2. Evaluate for disseminated intravascular coagulopathy and coagulation factor deficiency. Acquired factor V deficiency is occasionally present in association with autonomous thrombocytosis. In that case, treat with fresh frozen plasma infusion.
  3. In case of extreme thrombocytosis, acquired von Willebrand disease may occur. Immediate platelet apheresis with definitive therapy with a platelet-lowering agent is essential in this instance.
- Thrombosis
  1. Arterial or venous thrombosis occurs in 20% to 30% of patients.
  2. If the platelet count is >800,000/mm^3, platelet apheresis coupled with a platelet-lowering agent should be considered with the goal of platelet count <400,000/mm^3.
  3. Initial workup should include additional thrombophilic diseases, such as proteins C and S abnormality, antithrombin, anticardiolipin antibody, mutations of factor V and II, and plasma homocysteine.
  4. Anticoagulant therapy for 3 to 9 mo based on the presence or absence of additional thrombophilic defects.

CHRONIC Rx

Treatment strategies for ET are based on the presence or absence of risk factors for thrombosis. Smoking cessation and obesity management should be discussed with all patients with ET. In low-risk patients (age <60 yr, no history of thrombosis or hemorrhage, platelet count <1 million/mL), observation may be adequate. Treatment with low-dose aspirin is indicated in low-risk patients with vasomotor symptoms or with other indications for aspirin use. The cytoreductive therapy along with low-dose aspirin therapy is indicated in high-risk patients (age >60 yr and/or with previous history of thrombosis).

- Low-dose aspirin (81 mg/day) may be safe and effective in preventing vascular events. It is also effective in preventing recurrent vascular events in high-risk patients and in treating the vasomotor symptoms.
- Cytoreductive therapy
  1. Hydroxyurea (HU) versus anagrelide: HU plus aspirin is suggested to be safer and more effective than anagrelide plus aspirin in regard to thrombosis, bleeding, and transformation to PMF at 5 yr in a randomized trial. Monitor liver function tests and the degree of neutropenia or anemia with HU therapy.
  2. The incidence of leukemic conversion in patients with ET treated with HU alone is reported as <1%. Interferon alpha may be effective for controlling platelet count in patients failing treatment with HU.

DISPOSITION

Although long survival is expected in patients with ET, it is inferior to the sex- and age-matched U.S. population.

An International Prognostic Score for Essential thrombocythemia (IPSET) was proposed by International Working Group on Myelofibrosis Research and Treatment based on age, WBC count, and history of thromboembolism at diagnosis.

REFERRAL

Refer to hematologist/oncologist when platelet count is consistently elevated >450,000/mm3 without causes for reactive thrombocytosis.

PEARLS & CONSIDERATIONS

COMMENTS

- Some patients with clinically apparent ET have Philadelphia chromosome or BCR-ABL rearrangement, even in the absence of other features of CML. It is suggested that it should be tested in all ET patients due to its potential therapeutic implications.
- The risk of bleeding with aspirin use in patients with ET is increased when the platelet count is >1 million/ml.

PATIENT & FAMILY EDUCATION

Smoking cessation is encouraged in both patients with ET and reactive thrombocytosis.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **ETSUKO AOKI, M.D., PH.D.**

SUGGESTED READINGS

Alvarez-Larran A et al.: Observation versus antiplatelet therapy as primary prophylaxis for thrombosis in low-risk essential thrombocythemia, *Blood* 116:1205, 2010.

Harrison CN et al.: Guideline for investigation and management of adults and children presenting with a thrombocytosis, *Br J Haematol* 149:352, 2010.

Passamonti F et al.: A prognostic model to predict survival in 867 World Health Organization-defined essential thrombocythemia at diagnosis, *Blood* 120:1197, 2012.

Tefferi A et al.: Personalized management of essential thrombocythemia-application of recent evidence to clinical practice, *Leukemia* 27:617, 2013.

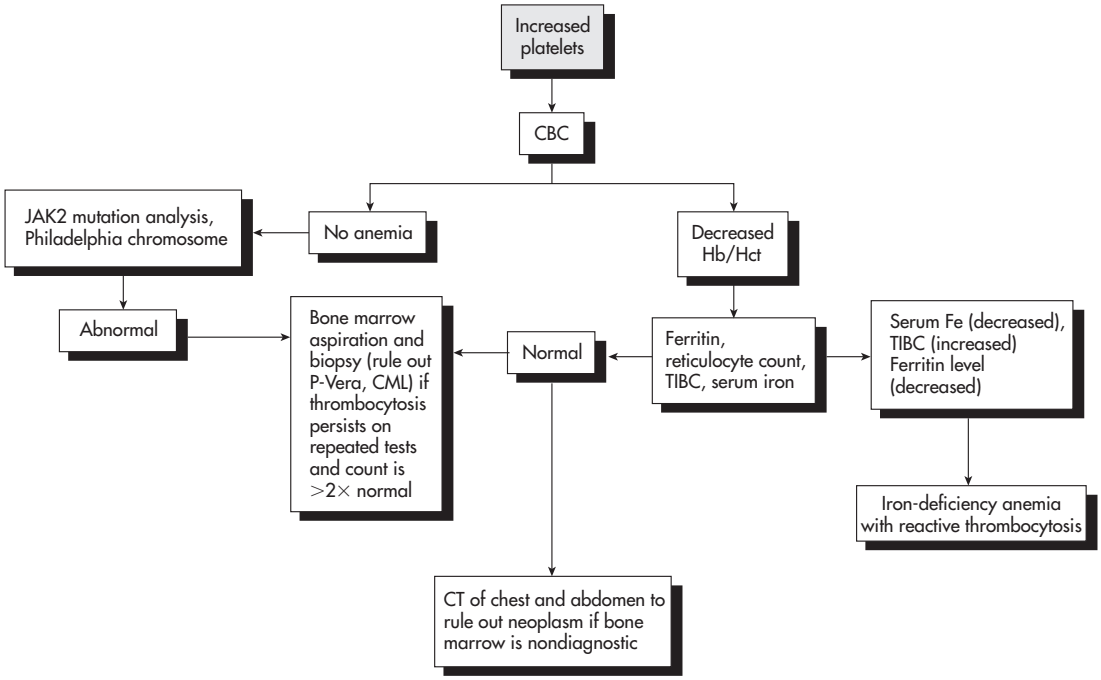


FIGURE ET1-23 Thrombocytosis diagnosis. *CBC,* Complete blood count; *CML,* chronic myelogenous leukemia; *CT,* computed tomography; *Fe, iron; Hb/Hct,* hemoglobin /hematocrit; *TIBC,* total iron-binding capacity. (Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

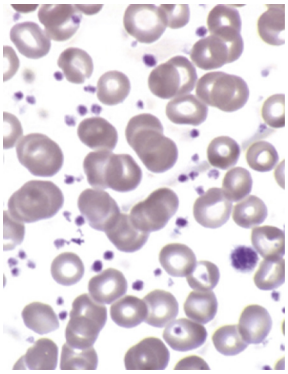


FIGURE ET1-24 Essential thrombocythemia: peripheral blood smear. The peripheral blood smear in ET shows a marked thrombocytosis with anisocytosis (varying sizes) of the platelets. (From Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

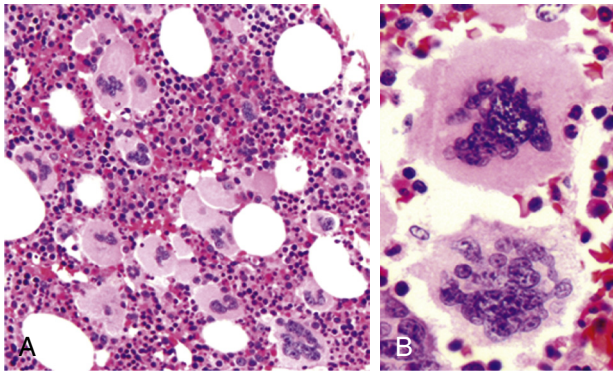


FIGURE ET1-25 Essential thrombocythemia: bone marrow biopsy. The bone marrow **(A)** is hypercellular and exhibits a marked proliferation of large and giant megakaryocytes in loose clusters with other hematopoietic elements in the background. The large megakaryocytes **(B)** tend to be extensively lobulated. (From Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

Thrombophlebitis, Superficial Venous PTG

BASIC INFORMATION

DEFINITION

Superficial venous thrombophlebitis (SVT) is an inflammation of a vein with subsequent secondary thrombus formation. SVT most frequently involves superficial veins of the leg, but any superficial vein can be affected. SVT has been reported to occur in 125,000 people in the United States per year; however, the actual incidence is likely far greater. SVT is not always a benign condition. SVT should be regarded as the superficial venous manifestation of a systemic process known as venous thromboembolism (DVT, PE).

SYNONYMS

SVT
Superficial phlebitis
Superficial suppurative thrombophlebitis
Suppurative thrombophlebitis

ICD-9CM CODES
451.0 Thrombophlebitis, superficial
ICD-10CM CODES
I80.00 Phlebitis and thrombophlebitis of superficial vessels of unspecified lower extremity

EPIDEMIOLOGY & DEMOGRAPHICS

- Approximately 30% to 45% of patients diagnosed with SVT are men with an average age of 54 yr.
- Approximately 55% to 70% of patients diagnosed with SVT are women with an average age of 58 yr.
- The overall recurrence of SVT is 18% over an average observation period of 15 mo, equally involving varicose and nonvaricose veins.
- The lifetime incidence of SVT in those with untreated varicose veins has been estimated at 25% to 50%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Subcutaneous vein is palpable as a tender cord or "wormlike" mass with increased warmth and erythema.
- Induration, redness, and tenderness are localized along the course of the vein. This linear appearance rather than circular appearance is useful to distinguish thrombophlebitis from other conditions (cellulitis, erythema nodosum).
- There is some swelling of the overlying skin and subcutaneous tissue but without generalized edema of the limb.
- Low-grade fever may be present.

ETIOLOGY

- In the lower extremity, 70% of SVT occurs in patients with varicose veins, with the great saphenous vein being most commonly involved (60% to 80%).
- Intravenous catheters and infusion of caustic drugs are the most common cause of upper extremity SVT.
- Malignancy
- Pregnancy/puerperium
- Hypercoagulable states
- Previous
- DVT/SVT
- OCP (oral contraceptive pill)/HRT (hormone replacement therapy)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Lymphangitis
- Cellulitis
- Erythema nodosum
- Panniculitis
- Acute lipodermatosclerosis

WORKUP

The clinical investigation includes not only the local findings but also the presence of varicose veins with or without the stigmata of chronic venous insufficiency. Today, duplex ultrasound is the most important additional diagnostic tool.

IMAGING STUDIES

- Duplex ultrasound offers the advantage of being inexpensive, noninvasive, and repeatable for follow-up examination.
- Ultrasonography confirms the diagnosis, shows the location of the thrombus and its location regarding the saphenofemoral and/or saphenopopliteal junctions.
- Ultrasound examination of patients with SVT has revealed that a concomitant DVT can exist in 15% to 20%.
- In up to 25% of these patients, the DVT may not be contiguous with the SVT and may be found in the contralateral leg.
- Therefore bilateral duplex exam is recommended in all cases of SVT that involve the main trunk of the great saphenous vein (GSV) or small saphenous vein (SSV).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Warm, moist compresses
- Do not restrict activity. Immediate mobilization with walking exercises.

ACUTE GENERAL Rx

- Treatment guidelines for SVT are not well established because of the lack of controlled clinical trials. In general, the primary goal of management should be to prevent thrombus extension and the risk of venous thromboembolism. All other therapy is directed at patient comfort.
- In patients with migratory SVT, recurrent SVT, or SVT without varicose veins, the underlying condition should be investigated and treatment directed accordingly.
- The most common cause of upper extremity SVT is an intravenous catheter. Treatment starts with removal of the cannula and application of warm compresses. The resultant lump may persist for months. No anticoagulant therapy is required.
- In patients with lower extremity SVT in a varicose vein branch, control of pain with analgesics and the use of gradient compression stockings are usually sufficient. Patients are encouraged to continue their usual daily activities.
- Many investigators favor systemic anticoagulation when there is superficial thrombosis of 5 cm or more in length, the thrombus is within 1 cm of the saphenous junctions, or more than 5 cm of the saphenous trunk is involved, as shown by duplex ultrasonography.
- The 2012 American College of Chest Physicians guidelines recommend the use of fondaparinux (1 mg/kg/day) for 45 days over no anticoagulation in patients with lower extremity SVT within 1 cm of the saphenofemoral or saphenopopliteal junction.
- In the case of patients with varicose veins secondary to saphenous vein reflux, a catheter vein ablation procedure should be performed only after the acute SVT episode is over in order to avoid the thromboembolic complications induced by such procedures.

DISPOSITION

Clinical improvement within 10 to 14 days

REFERRAL

Referral to vascular surgeon or phlebologist with vascular lab

PEARLS & CONSIDERATIONS

SUPERFICIAL SUPPURATIVE THROMBOPHLEBITIS

- Superficial suppurative thrombophlebitis is associated with an intravenous catheter or multiple puncture sites secondary to IV drug abuse and is located primarily in the upper extremity.
- Clinical presentation is similar to that of nonsuppurative SVT but with associated fever, leukocytosis, and/or septicemia.
- Most cases of intravenous catheter sepsis are not complicated by suppurative thrombophlebitis; local IV catheter site infections occur in about 7% of cases and septicemia is found in only 1 of every 400 IV catheterizations.
- The incidence of peripheral vein suppurative thrombophlebitis is highest in patients with specific risk factors such as burns, steroids, and IV drug abuse.
- Treatment consists of antibiotics with adequate coverage of gram-negative rods and *Staphylococcus aureus,* including MRSA. Initial empirical treatment is with IV vancomycin 1 g q12h *plus* ceftriaxone 1 g IV q24h. Alternative regimen consists of daptomycin 6 mg/kg IV q 12h *plus* ceftriaxone 1 g IV q24h.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Thrombophlebitis (Patient Information)

AUTHOR: **FRANK G. FORT, M.D.**

SUGGESTED READINGS

Chirinos JA et al.: Septic thrombophlebitis: diagnosis and management, *Am J Cardiovasc Drugs* 6(1):9–14, 2006.

Decousus H et al.: Fondaparinux for the treatment of superficial-vein thrombosis in the legs, *N Engl J Med* 363:1222–1232, 2010.

DiNisio M et al.: Treatment for superficial thrombophlebitis of the leg, CD004982 *Cochrane Database Syst Rev* 2, 2007.

DiNisio M, Middeldorp S: Treatment of lower extremity superficial thrombophlebitis, *JAMA* 311:729, 2014.

Quenet S et al.: STENOX Group. Factors predictive of venous thrombotic complications in patients with isolated superficial vein thrombosis, *J Vasc Surg* 38:944–949, 2003.

BASIC INFORMATION

DEFINITION

Thrombotic thrombocytopenic purpura (TTP) is a rare disorder characterized by thrombocytopenia (often accompanied by purpura) and microangiopathic hemolytic anemia; neurologic impairment, renal dysfunction, and fever may also be present.

SYNONYMS

TTP

ICD-9CM CODES
446.6 Thrombotic thrombocytopenic purpura
ICD-10CM CODES
M31.1 Thrombotic microangiopathy

EPIDEMIOLOGY & DEMOGRAPHICS

- TTP primarily affects females aged between 18 and 50 yr.
- The incidence of acquired TTP in adults is 2.9 cases per million per year. Incidence in children is 0.1 cases per million per year. There is increased incidence in HIV/AIDS and during pregnancy.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The disease often begins as a flulike illness ultimately followed by clinical and laboratory abnormalities.
- Most patients present with nonspecific constitutional symptoms (weakness, nausea, abdominal pain, vomiting).
- Purpura (secondary to thrombocytopenia).
- Jaundice, pallor (from hemolysis).
- Mucosal bleeding.
- Fever.
- Fluctuating levels of consciousness (caused by thrombotic occlusion of the cerebral vessels). However, one third of patients have no neurologic abnormalities.
- Renal failure and neurologic events are usually end-stage features.

ETIOLOGY

- Acquired TTP is an autoimmune disorder caused by autoantibody inhibition of ADAMTS13 activity. Hereditary TTP (also called Upshaw-Schulman syndrome) is caused by homozygous or compound heterozygous ADAMTS13 mutations.
- Many drugs, including clopidogrel, penicillin, antineoplastic agents (gemcitabine, mitomycin C, cyclosporine) oral contraceptives, quinine, and ticlopidine, have been associated with TTP. Other precipitating causes include infectious agents, pregnancy, malignancies, allogeneic bone marrow transplantation, and neurologic disorders.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Disseminated intravascular coagulation (DIC)
- Malignant hypertension
- Vasculitis
- Eclampsia or preeclampsia
- Hemolytic-uremic syndrome (typically encountered in children, often after a viral infection)
- Gastroenteritis as a result of a serotoxin-producing serotype of *Escherichia coli*
- Medications: clopidogrel, ticlopidine, penicillin, antineoplastic chemotherapeutic agents, oral contraceptives

WORKUP

- A comprehensive history, physical examination, and laboratory evaluation usually confirm the diagnosis. Fig. T1-26 is an algorithm for diagnosis of TTP.

LABORATORY TESTS

- Severe anemia and thrombocytopenia (platelet count <50,000 or >50% reduction from previous counts). Peripheral blood smear (Fig. ET1-27) reveals numerous red cell fragments (schistocytes).
- Elevated blood urea nitrogen and creatinine.
- Evidence of hemolysis: elevated reticulocyte count, indirect bilirubin, lactate dehydrogenase, decreased haptoglobin.
- Urinalysis: hematuria (red blood cells [RBCs] and RBC casts in urine sediment) and proteinuria.
- Peripheral smear: severely fragmented RBCs (schistocytes). More than 4% RBC fragments in the peripheral blood.
- No laboratory evidence of DIC (normal fibrin degradation product, fibrinogen).
- The diagnosis of hereditary TTP requires documentation of ADAMTS13 deficiency and an absence of ADAMTS13 autoantibody inhibitor, and confirmation requires documentation of ADAMTS13 mutations. Diagnostic criteria for acquired TTP are the presence of microangiopathic hemolytic anemia and thrombocytopenia without another apparent cause. An ADAMTS13 level indicating less than 10% of normal activity supports the clinical diagnosis of acquired TTP.

TREATMENT

ACUTE GENERAL Rx

- Discontinue potential offending agents. Initiate ADAMTS13 replacement by plasma infusion in patients with hereditary TTP.
- The American Association of Blood Banks, the American Society for Apheresis, and the British Committee for Standards in Haematology recommend daily plasma exchange with replacement of 1.0 to 1.5 times the predicted plasma volume of the patient as standard therapy for TTP. The British guidelines recommend that plasma exchange therapy be continued for a minimum of 2 days after the platelet count returns to normal (>150,000 cells/m^3).
- High-dose plasma infusion (25 ml/kg/day) may be useful only if plasma exchange cannot be promptly started and for patients with very severe or refractory disease between plasma exchange sessions. High-dose plasma infusions can cause volume overload in patients with renal insufficiency.
- Patients with hereditary TTP who experience severe plasma allergic reactions have been effectively treated with plasma-derived factor VIII concentrate that contains ADAMTS13.
- Corticosteroids (prednisone 1 to 2 mg/kg/day) may be effective alone in patients with mild disease or may be administered concomitantly with plasmapheresis plus plasma exchange with fresh frozen plasma.
- The monoclonal antibody rituximab has also been used for treatment of TTP.
- Platelet transfusions are contraindicated except in severely thrombocytopenic patients with documented bleeding or those who are facing surgery or other invasive procedures in the setting of severe thrombocytopenia.
- Use of antiplatelet agents (acetylsalicylic acid, dipyridamole) is controversial.
- Splenectomy is performed in refractory cases.
- Dialysis is rarely required.

CHRONIC Rx

- Relapsing TTP may be treated with plasma exchange.
- Remission of chronic TTP that is unresponsive to conventional therapy has been reported after treatment with cyclophosphamide and the monoclonal antibody rituximab.
- Splenectomy done while the patients are in remission has been used in some centers to decrease the frequency of relapse in TTP.

DISPOSITION

- Survival of patients with TTP currently exceeds 80% with plasma exchange therapy.
- Relapse occurs in 20% to 40% of patients who have TTP in remission.

REFERRAL

Surgical referral for splenectomy in selected patients (see "Acute General Rx" and "Chronic Rx").

PEARLS & CONSIDERATIONS

COMMENTS

The diagnosis of TTP/hemolytic-uremic syndrome should be considered in pregnant women with vague neurologic, gastrointestinal, or renal symptoms in either the obstetric triage or emergency department areas.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hemolytic Uremic Syndrome (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

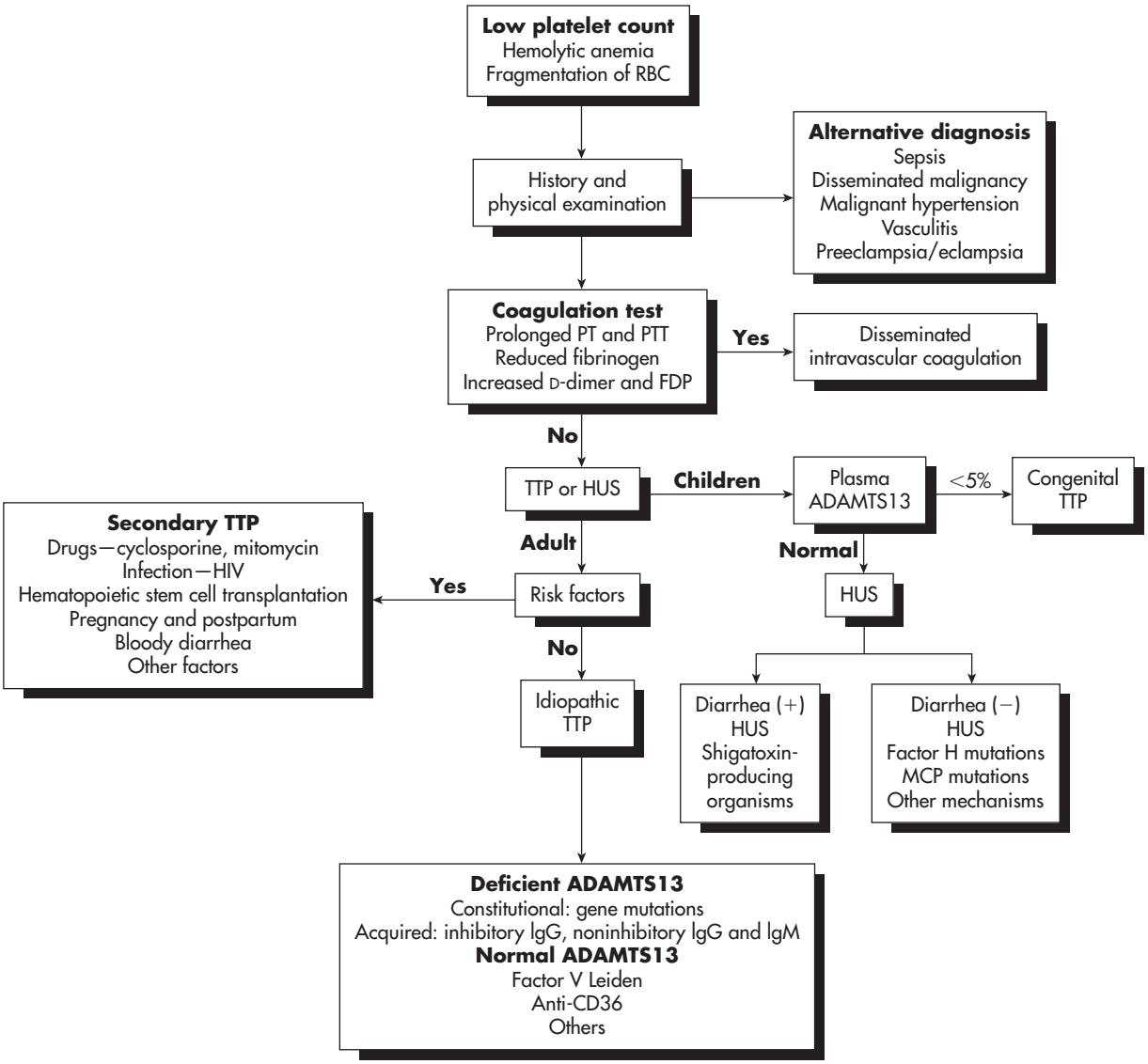


FIGURE T1-26 Algorithm for diagnosis of thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS). *MCP,* Membrane cofactor protein; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *RBC,* red blood cell. (From Young NS et al [eds]: *Clinical hematology,* St Louis, 2006, Mosby.)

SUGGESTED READINGS

Crowther MA, George JN: Thrombotic thrombocytopenic purpura: 2008 update, *Cleve Clin J Med* 75:369, 2008.

George JN: Thrombotic thrombocytopenic purpura, *N Engl J Med* 354:1927, 2006.

George JN, Nester CM: Syndromes of thrombotic microangiopathy, *N Engl J Med* 371:654–666, 2014.

Naik S, Mahoney DH: Successful treatment of congenital TTP with a novel approach using plasma-derived factor VIII, *J Pediatr Hematol Oncol* 35:551–553, 2013.

Stella CL et al.: The diagnostic dilemma of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome in the obstetric triage and emergency department: lessons from 4 tertiary hospitals, *Am J Obstet Gynecol* 200:381.e1–381.e6, 2009.

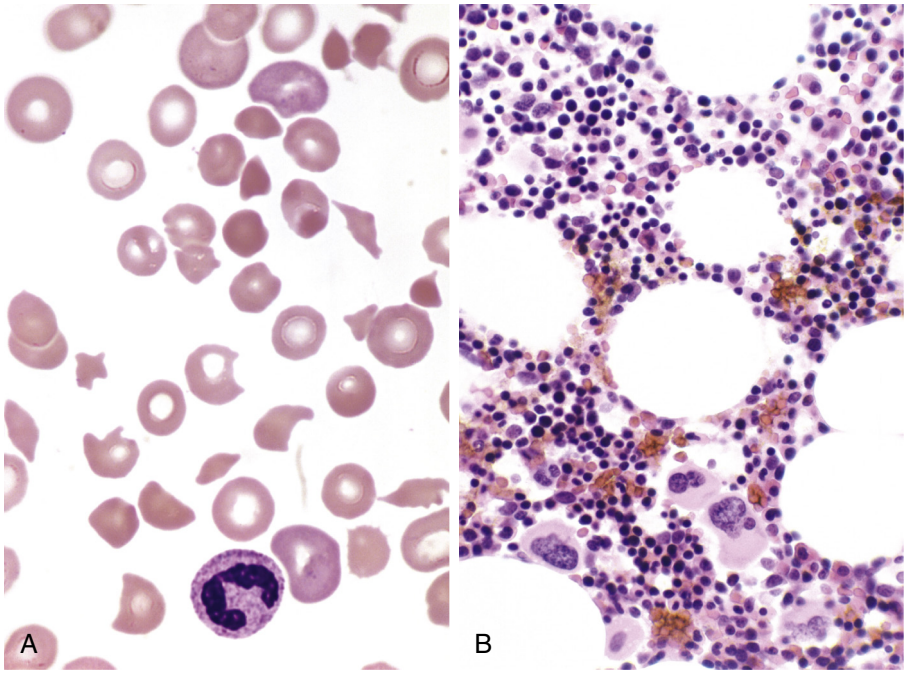


FIGURE ET1-27 A, Peripheral blood smear of thrombotic thrombocytopenic purpura. Numerous red cell fragments (schistocytes) are present. No platelets are seen in this field. **B,** The bone marrow trephine biopsy section demonstrates increased numbers of megakaryocytes. (From Jaffe ES et al: *Hematopathology,* Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Thyroid carcinoma is a primary neoplasm of the thyroid. There are four major types of thyroid carcinoma: papillary, follicular, anaplastic, and medullary.

SYNONYMS

Papillary carcinoma of thyroid
Follicular carcinoma of thyroid
Anaplastic carcinoma of thyroid
Medullary carcinoma of thyroid

ICD-9CM CODES
193 Malignant neoplasm of thyroid
ICD-10CM CODES
C73 Malignant neoplasm of thyroid gland

EPIDEMIOLOGY & DEMOGRAPHICS

- Thyroid cancer is the most common endocrine cancer, with over 48,000 new cases in the United States and approximately 1100 deaths.
- Female/male ratio is 3:1.
- Median age at diagnosis: 45 to 50 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Presence of thyroid nodule
- Hoarseness and cervical lymphadenopathy
- Painless swelling in the region of the thyroid

ETIOLOGY

- Risk factors: prior neck irradiation
- Multiple endocrine neoplasia II (medullary carcinoma)
- Inherited syndromes associated with thyroid cancer are described in Table T1-8
- GLP-1 receptor agonists for the treatment of type 2 DM (e.g., exenatide, albiglutide) can increase the risk of medullary thyroid carcinoma (MTC)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Multinodular goiter
- Lymphocytic thyroiditis
- Ectopic thyroid

TABLE T1-8 Inherited Syndromes Associated with Thyroid Cancer

Multiple endocrine neoplasia (MEN) 2A and 2B
Isolated familial medullary thyroid cancer
Gardner syndrome
Familial adenomatous polyposis
Carney complex
Cowden syndrome
Familial nonmedullary thyroid cancer

From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.

WORKUP

The workup of thyroid carcinoma includes laboratory evaluation and diagnostic imaging. However, diagnosis is confirmed with fine-needle aspiration or surgical biopsy. The characteristics of thyroid carcinoma vary with the type:

- Papillary carcinoma (85%):
  1. Most frequently occurs in women during second or third decades
  2. Histologically, psammoma bodies (calcific bodies present in papillary projections) are pathognomonic; found in 35% to 45% of papillary thyroid carcinomas
  3. Majority are not papillary lesions but mixed papillary follicular carcinomas
  4. Spread is by lymphatics and by local invasion
- Follicular carcinoma (10%):
  1. More aggressive than papillary carcinoma
  2. Incidence increases with age
  3. Tends to metastasize hematogenously to bone, producing pathologic fractures
  4. Tends to concentrate iodine (useful for radiation therapy)
- Anaplastic carcinoma (1%):
  1. Very aggressive neoplasm
  2. Two major histologic types: small cell (less aggressive, 5-yr survival approximately 20%) and giant cell (death usually within 6 mo of diagnosis)
- MTC (4%):
  1. Unifocal lesion: found sporadically in elderly patients
  2. Bilateral lesions: associated with pheochromocytoma and hyperparathyroidism; this combination is known as MEN-II and is inherited as an autosomal-dominant disorder

LABORATORY TESTS

- Thyroid function studies are generally normal. Thyroid-stimulating hormone (TSH), T4, and serum thyroglobulin levels should be obtained before thyroidectomy in patients with confirmed thyroid carcinoma. Serum thyroglobulin levels can be useful postoperatively to monitor recurrence of thyroid carcinoma (Fig. ET1-28).
- Increased plasma calcitonin assay in patients with medullary carcinoma (tumors produce thyrocalcitonin). RET proto-oncogene sequencing and measurement of plasma free metanephrine and normetanephrine levels to rule out coexistent pheochromocytoma are recommended in all patients with medullary thyroid cancer.
- Fine-needle aspiration biopsy is the best method to assess a thyroid nodule (see "Thyroid Nodule" in Section I).

IMAGING STUDIES (Fig. ET1-29)

- Thyroid ultrasound can detect solitary solid nodules that have a high risk of malignancy. However, a negative ultrasound does not exclude diagnosis of thyroid carcinoma.
- Thyroid scanning with iodine-123 or technetium-99m can identify hypofunctioning (cold) nodules, which are more likely to be malignant. However, warm nodules can also be malignant.

STAGING

- Stage I: thyroid cancer of any size without distal spread in patient under age 45. In patients 45 years or older, tumor size ≤2 cm without local invasion or positive cervical lymph nodes
- Stage II: distal spread in patient younger than 45 years. In patients 45 years or older, tumors >2 cm but <4 cm without local invasion or positive cervical lymph nodes
- Stage III: tumors >4 cm in patient over 45 years of age
- Stage IV: distal spread in patient over 45 years of age

TREATMENT

ACUTE GENERAL Rx

- Papillary carcinoma:
  1. Total thyroidectomy is indicated if the patient has:
     a. Extrapyramidal extension of carcinoma
     b. Papillary carcinoma limited to thyroid but a positive history of irradiation to the neck
     c. Lesion >2 cm
  2. Lobectomy with isthmectomy may be considered in patients with intrathyroid papillary carcinoma <2 cm and no history of neck or head irradiation; surgery should be followed with suppressive therapy with thyroid hormone because these tumors are TSH responsive. The accepted practice is to suppress serum TSH concentrations to <0.1 microunit/ml in patients with persistent disease, suppression to 0.1-0.5 microunit/ml in patients who are disease free but are at high risk of recurrence, and a goal TSH level of 0.3-2.0 microunits/ml in patients who are disease free and have a low risk of recurrence.
  3. Radioiodine ablation reduces rates of death and recurrence (Table T1-9). Radioiodine is administered for stages III and IV disease.
- Follicular carcinoma:
  1. Total thyroidectomy followed by TSH suppression, as previously noted
  2. Radiotherapy with iodine-131 followed by thyroid suppression therapy with triiodothyronine is useful in patients with metastasis (Table T1-9)
- Anaplastic carcinoma:
  1. At diagnosis, this neoplasm is rarely operable; palliative surgery is indicated for extremely large tumor compressing the trachea.
  2. Management is usually restricted to radiation therapy or chemotherapy (combination of doxorubicin, cisplatin, and other antineoplastic agents) (Table T1-9); these measures rarely provide significant palliation.
- Medullary carcinoma:
  1. Thyroidectomy should be performed, followed by TSH suppression.
  2. Vandetanib, an oral tyrosine kinase inhibitor, was recently FDA-approved for treatment of symptomatic or progressive,

unresectable, locally advanced or metastatic medullary thyroid cancer. It is not recommended for treatment of asymptomatic or less aggressive disease due to its many serious side effects.

3. Patients and their families should be screened for pheochromocytoma and hyperparathyroidism.

DISPOSITION

Prognosis varies with the type of thyroid carcinoma: 5-yr survival approaches 80% for follicular carcinoma and is approximately 5% with anaplastic carcinoma (see Table T1-10).

PEARLS & CONSIDERATIONS

COMMENTS

- Family members of patients with medullary carcinoma should be screened; DNA analysis for the detection of mutations in the *RET* gene structure permits the identification of *MEN IIA* gene carriers.
- Motesanib, an oral inhibitor of vascular endothelial growth factor (VEGF) receptors, has been reported effective in inducing partial responses in patients with advanced or metastatic differentiated thyroid cancer that is progressive.
- While there is little controversy regarding the benefit of radioactive iodine in iodine-avid advanced-stage well-differentiated thyroid cancer, the indications for radioactive iodine following total thyroidectomy in patients with very low risk disease is controversial. Proponents argue that its use may destroy microscopic metastases while opponents counter that the risk of secondary cancer due to radioactive iodine is not warranted in patients whose prognosis is typically excellent.
- Metastatic thyroid cancers that are refractory to radioiodine (iodine-131) are associated with a poor prognosis. Recent trials have shown that the selective mitogen-activated protein kinase (MAPK) pathway antagonist selumetinib produces clinically meaningful increases in iodine uptake and retention in some patients with thyroid cancer that is refractory to radioiodine. In recent phase 2 trials, lenvatinib has also shown significant improvements in progression-free survival and response rate among patients with iodine-131 refractory thyroid cancer.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Thyroid Cancer (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

TABLE T1-9 Indications for Iodine-131 Treatment in Patients with Papillary, Follicular, or Hürthle Cell Thyroid Carcinoma after Initial Definitive Near-Total Thyroidectomy

No Indication

Adult patients at very low risk for cause-specific mortality or relapse: complete surgical resection, favorable histology, and limited extent of disease (e.g., PTC patients with MACIS scores <6; patients with tumor size <1 cm, N0, and M0).

Definite Indications

Distant metastasis at diagnosis

Incomplete tumor resection

Complete tumor resection but high risk for mortality or recurrence (e.g., PTC patients with MACIS scores ≥6 and pTNM stage II/III FTC or HCC)

Probable Indications

Incomplete surgery (less than near-total thyroidectomy, no lymph node dissection)

PTC or FTC in a child younger than 16 yr

If PTC, tall cell or columnar cell variant and diffuse sclerosing variant

If FTC, widely invasive or poorly differentiated tumor

Bulky nodal metastases

FTC, Follicular thyroid carcinoma; *HCC,* Hürthle cell carcinoma; *MACIS,* scoring system based on metastasis, age, completeness of resection, invasion, and size; *PTC,* papillary thyroid carcinoma; *pTNM,* pathologic tumor-node-metastasis classification.

From Melmed S et al (eds): *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

TABLE T1-10 Characteristics of Thyroid Cancers

Type of Cancer	Percentage of Thyroid Cancers	Age of Onset (Yr)	Treatment	Prognosis
Papillary	88	40-80	Thyroidectomy, followed by radioactive iodine ablation and TSH suppression	Good
Follicular	10	45-80	Thyroidectomy, followed by radioactive iodine ablation and TSH suppression	Fair to good
Medullary	3-4	20-50	Thyroidectomy and central compartment lymph node dissection and TSH suppression	Fair
Anaplastic	1	50-80	Isthmusectomy followed by palliative x-ray treatment	Poor
Lymphoma	<1	25-70	X-ray therapy and/or chemotherapy	Fair

From Andreoli TE et al: *Andreoli and Carpenter's Cecil essentials of medicine,* ed 8, Philadelphia, 2010, Saunders.

EVIDENCE

Abstract[1]

Purpose:
To use objective and subjective voice function analysis to compare outcomes in patients who had undergone conventional open thyroidectomy or robotic thyroidectomy.

Methods:
The study involved 88 consecutive patients who underwent thyroid surgery between May 2009 and December 2009; 46 patients underwent a conventional open thyroidectomy, and 42 underwent a robotic thyroidectomy. Auditory perceptual evaluation was used to make subjective assessments of voice function, and videolaryngostroboscopy, acoustic voice analysis with aerodynamic study, electroglottography, and voice range profile were used to make objective assessments. Each assessment was made before surgery and at 1 week and 3 months after surgery.

Results:
The conventional open and robotic thyroidectomy groups were similar in terms of age, gender ratio, and disease profile. We found that 18 (20.5%) of the 88 patients showed some level of voice dysfunction at 1 week after surgery; that the dysfunction resolved by 3 months after surgery in all cases; and that it was not permanent according to postoperative videolaryngostroboscopy. The conventional open and robotic thyroidectomy groups were found to have similar levels of dysfunction at 1 week after surgery, except for jitter, which was greater in the robotic group. For both groups, any such dysfunction spontaneously resolved by 3 months after surgery, and there were no significant differences between the groups in terms of any voice function parameter.

Conclusions:
Voice dysfunction was present after both open and robotic thyroidectomy (without any evident laryngeal nerve injury). However, function subsequently normalized to preoperative levels at 3 months after surgery in both groups. Voice function outcomes after robotic thyroidectomy are similar to those after conventional open thyroidectomy. Ⓐ

Abstract[2]

Background:
The objectives of this study were to evaluate a screening method for detecting postoperative vocal cord palsy and lower-pitched voice and to identify how a prethyroidectomy laryngeal disorder affects posthyroidectomy voice change by using our subjective voice questionnaire.

Methods:
We examined 300 consecutive patients scheduled to undergo thyroidectomies between November 2010 and August 2011. Laryngoscopic examination, thyroidectomy-related voice questionnaire (TVQ) administration, and acoustic and perceptual analyses were performed preoperatively and 2 weeks after thyroidectomy.

Results:
Ninety-eight (32.6%) patients had a preoperative laryngeal disorder. Postoperatively, 31 (10.3%) patients had vocal cord palsy, and 54 (18%) had a lower-pitched voice 2 weeks after thyroidectomy. Postoperative TVQs classified 25 (8.4%) patients as normal and 275 (91.6%) patients as abnormal, including 79 (26.3%) mild, 131 (43.6%) moderate, and 65 (21.6%) severe cases. Of the patients with vocal cord palsy, 80.6% belonged to the severe group, and 92.6% of patients with lower-pitched voices belonged to the moderate and severe groups. Fundamental frequency and speaking fundamental frequency were decreased significantly in women. The most efficient TVQ cutoff values for detecting postthyroidectomy vocal cord palsy and postoperative lower-pitched voice were 35 (87.1% sensitivity, 79.9% specificity) and 25 (75.9% sensitivity, 56.5% specificity), respectively. Total TVQ scores increased more in the nonlaryngeal than in the laryngeal disorder group.

Conclusions:
During the early postoperative period, 28.3% of patients had vocal cord palsy or lower-pitched voices, which could be evaluated using a simple questionnaire. Therefore early postoperative voice evaluation is important. Patients with nonlaryngeal disorders may be more sensitive than those with laryngeal disorders to laryngeal symptoms. Ⓐ

Evidence-Based References

Lee J, et al.: Postoperative functional voice changes after conventional open or robotic thyroidectomy: a prospective trial, *Ann Surg Oncol* 19:2963–2970, 2012. Ⓐ

Chun BJ, et al.: Early postoperative vocal function evaluation after thyroidectomy using thyroidectomy related voice questionnaire, *World J Surg* 36:2503–2508, 2012. Ⓐ

SUGGESTED READINGS

Haymart MR et al.: Use of radioactive iodine for thyroid cancer, *JAMA* 306(7): 721–728, 2011.

Ho AL et al.: Selumitinib-enhanced radioiodine uptake in advanced thyroid cancer, *N Engl J Med* 368:623–632, 2013.

Lin JH et al.: The role of neck ultrasonography in thyroid cancer, *Am J Otolaryngol* 30:324–326, 2009.

Mallick U et al.: Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer, *N Engl J Med* 366:1674–1685, 2012.

Schlumberger M et al.: Lenvatinib versus placebo in radioactive-refractory thyroid cancer, *N Engl J Med* 372:621–630, 2015.

Sherman SI et al.: Motesanib diphosphate in progressive differentiated thyroid cancer, *N Engl J Med* 359:31, 2008.

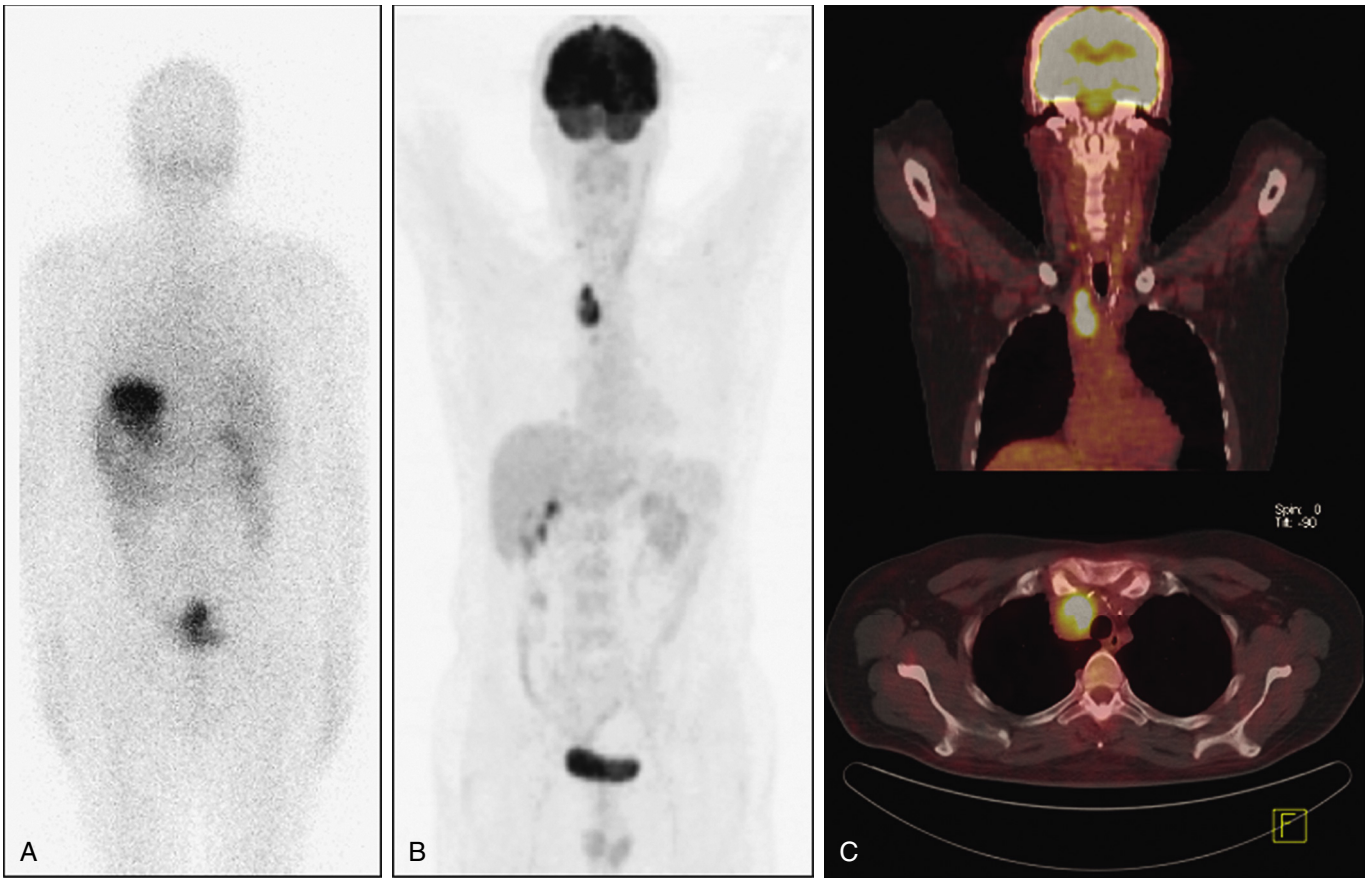


FIGURE ET1-28 This patient was being monitored for a papillary thyroid carcinoma treated by total thyroidectomy and postoperative radioiodine. The serum thyroglobulin level was 45 ng/ml during levothyroxine suppressive treatment. **A,** A total-body scan was performed 3 days after administration of 100 mCi (3.7 GBq). There is no visible uptake in the neck and thorax. Notice the accumulation of radioiodine in the stomach, colon, and bladder. **B,** Positron emission tomography scan using [18F]-fluorodeoxyglucose (18FDG) with maximal intensity projection demonstrates significant uptake in the upper mediastinum. **C,** In fusion images of 18FDG-PET and CT scans, axial and coronal slices localized the FDG uptake in the right paratracheal mediastinum, corresponding to a lymph node metastasis that was subsequently excised. Serum thyroglobulin became undetectable during thyroid hormone treatment. (From Melmed S et al [eds]: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.)

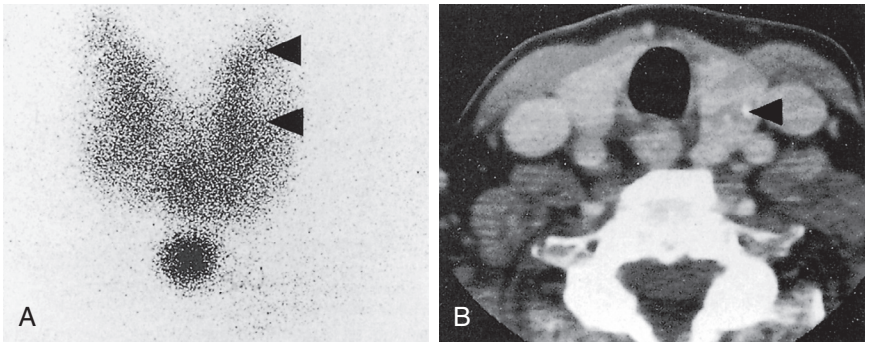


FIGURE ET1-29 Papillary adenocarcinoma. A 74-year-old woman presented with a thyroid nodule. **A,** An ^{123}I thyroid scan (anterior view) demonstrates a "cold" nodule *(arrows)* in the upper portion of the left thyroid lobe. The "hot" spot below the thyroid is a suprasternal marker. **B,** An axial CT scan demonstrates an irregular density within the left thyroid lobe at the level of the lesion seen on the radionuclide scan. The lesion contains a single area of calcification *(arrow)* and is not sharply demarcated from normal thyroid tissue. At operation, there proved to be extracapsular extension. (From Skarin AT: *Atlas of diagnostic oncology,* ed 3, St Louis, 2003, Mosby.)

BASIC INFORMATION

DEFINITION

A thyroid nodule is an abnormality found on physical examination of the thyroid gland; nodules can be benign (70%) or malignant.

ICD-9CM CODES
241.0 Nodule, thyroid.
ICD-10CM CODES
E04.1 Nontoxic single thyroid nodule.
E05.2 Thyrotoxicosis with toxic single thyroid nodule.

EPIDEMIOLOGY & DEMOGRAPHICS

- Palpable thyroid nodules occur in 4% to 7% of the population.
- Thyroid nodules can be found in 50% of autopsies; however, only one in 10 is palpable.
- Malignancy is present in 5% to 15% of all thyroid nodules and in 7% to 9% of palpable nodules.
- Incidence of thyroid nodules increases after 45 yr. They are found more frequently in women.
- History of prior head and neck irradiation increases the risk of thyroid cancer.
- Increased likelihood that nodule is malignant: nodule increasing in size or >3 cm, regional lymphadenopathy, fixation to adjacent tissues, age <40 yr, symptoms of local invasion (dysphagia, hoarseness, neck pain, male sex, family history of thyroid cancer or polyposis [Gardner syndrome]), rapid growth during levothyroxine therapy, microcalcification within the nodule, and high intranodular vascular flow.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Palpable, firm, and nontender nodule in the thyroid area should prompt suspicion of carcinoma. Signs of metastasis are regional lymphadenopathy and inspiratory stridor.
- Signs and symptoms of thyrotoxicosis can be found in functioning nodules.

ETIOLOGY

- History of prior head and neck irradiation.
- Family history of pheochromocytoma, carcinoma of the thyroid, and hyperparathyroidism (medullary carcinoma of the thyroid is a component of MEN-II).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Thyroid carcinoma.
- Multinodular goiter.
- Thyroglossal duct cyst.
- Epidermoid cyst.
- Laryngocele.
- Nonthyroid neck neoplasm.
- Branchial cleft cyst.

WORKUP

- Fine-needle aspiration (FNA) biopsy is the best diagnostic study; the accuracy can be >90%, but it is directly related to the level of experience of the physician and the cytopathologist interpreting the aspirate. FNA is not routinely recommended for thyroid nodules <1 cm in diameter unless there are significant risk factors (see above).
- FNA biopsy is less reliable with thyroid cystic lesions; surgical excision should be considered for most thyroid cysts not abolished by aspiration.
- A diagnostic approach to thyroid nodule is described in Fig. T1-30. Preoperative, ultrasonically guided FNA accurately classifies 62% to 85% of thyroid nodules as benign; however, 15% to 30% of aspirations yield indeterminate cytologic findings. Table T1-11 describes the probability of malignancy at histology based on FNA biopsy cytology.

LABORATORY TESTS

- Serum TSH should be obtained in all patients with thyroid nodules. If suppressed, obtain free T4 and free T3 and thyroid scan to rule out "hot nodule," indicative of hyperthyroid adenoma. Less than 1% of hyperfunctioning nodules are malignant.
- Thyroid-stimulating hormone (TSH), T4, and serum thyroglobulin levels should be obtained before thyroidectomy in patients with confirmed thyroid carcinoma on FNA biopsy.
- Serum calcitonin at random or after pentagastrin stimulation is useful when suspecting medullary carcinoma of the thyroid and in anyone with a family history of medullary thyroid carcinoma.
- Serum thyroid autoantibodies (see "Thyroiditis" in Section I) are useful in patients with multinodular goiter and when suspecting thyroiditis.
- Molecular analysis of thyroid tissue for the presence of BRAF and RAS mutations and for RET/PTC and PAX8-PPAR gamma 1 gene rearrangements can be used as a diagnostic tool, since 60% to 70% of thyroid cancers harbor at least one genetic mutation. The gene expression classifier profile can be used to identify a subpopulation of patients with a low likelihood of cancer, thereby avoiding unnecessary surgery in patients with indeterminate FNA. The gene expression classifier test has a high negative predictive value for cytologically indeterminate nodules (95% for an atypical or follicular lesion of undetermined significance, 94% for a follicular neoplasm, and 85% for a lesion suggestive of cancer).

IMAGING STUDIES

- Thyroid ultrasound (Fig. ET1-31) is useful to evaluate the size of the thyroid and the number, composition (solid versus cystic), and dimensions of the thyroid nodule; solid thyroid nodules have a higher incidence of malignancy, but cystic nodules can also be malignant. The three characteristics on thyroid ultrasound most predictive of cancer are nodules >2 cm, microcalcifications, and entirely solid nodules.
- Thyroid scan can be performed with technetium-99m pertechnetate, iodine-123, or iodine-131. Iodine isotopes are preferred because up to 35% of nodules that appear functioning on pertechnetate scanning may appear nonfunctioning on radioiodine scanning. A thyroid scan:
  1. Classifies nodules as hyperfunctioning (hot), normally functioning (warm), or nonfunctioning (cold); cold nodules have a higher incidence of malignancy.
  2. Scan has difficulty evaluating nodules near the thyroid isthmus or at the periphery of the gland.
  3. Normal tissue over a nonfunctioning nodule might mask the nodule as "warm" or normally functioning.
- Both thyroid scan and ultrasound provide information about the risk of malignant neoplasia based on the characteristics of the thyroid nodule, but their value in the initial evaluation of a thyroid nodule is limited because neither provides a definite tissue diagnosis.

TREATMENT

GENERAL Rx

- Evaluation of results of FNA:
  1. Normal cells: may repeat biopsy during present evaluation or reevaluate patient after 3 to 6 mo of suppressive therapy (L-thyroxine, prescribed in doses to suppress the TSH level to 0.1 to 0.5).
     a. Failure to regress indicates increased likelihood of malignancy.
     b. Reliance on repeat FNA biopsy is preferable to routine surgery for nodules not responding to thyroxine.
- Indeterminate: use of gene expression classifier profile. If suspicious, perform surgery; if benign, monitor with subsequent repeat FNA and gene expression classifier profile.
- Malignant cells: surgery.

DISPOSITION

Variable with results of FNA biopsy.

REFERRAL

Surgical referral for FNA biopsy.

PEARLS & CONSIDERATIONS

COMMENTS

- Most solid, benign nodules grow; therefore an increase in nodule volume alone is not a reliable predictor of malignancy.
- Surgery is indicated in hard or fixed nodule, presence of dysphagia or hoarseness, and rapidly growing solid masses regardless of "benign" results on FNA.
- Suppressive therapy of malignant thyroid nodules postoperatively with thyroxine is indicated. The use of suppressive therapy for benign solitary nodules is controversial.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Thyroid Nodule (Patient Information)
Thyroiditis (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

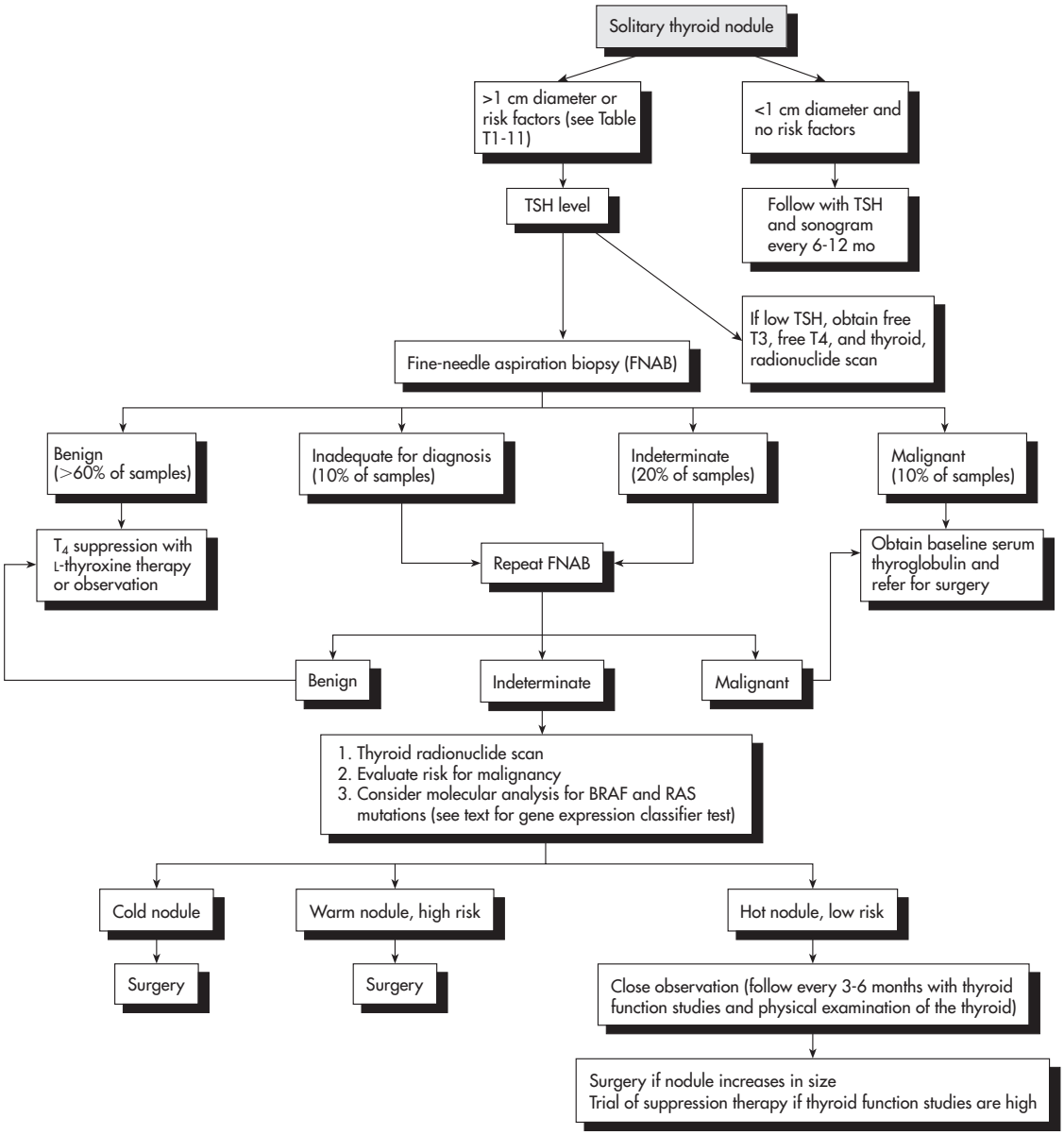


FIGURE T1-30 Diagnostic algorithm for thyroid nodule. (From Ferri, F: Ferri's Best Test, 3rd ed, Philadelphia, Elsevier, 2014.)

TABLE T1-11 Clinical and Ultrasound Findings in Favor of Malignant Thyroid Nodules

Clinical Features	Ultrasound Findings
History	**Higher Suspicion**
Young age (<20 yr) or older age (>60 yr)	Hypoechoic lesions
Male gender	Irregular margins
Neck irradiation during childhood or adolescence	Presence of microcalcifications
Rapid growth	Absence of halo
Recent changes in speaking, breathing, or swallowing	Internal or central blood flow
Family history of thyroid malignancy or MEN2	
Physical Examination	**Low Suspicion**
Firm and irregular consistency of nodule	Echo-free (cystic) lesion
Fixation to underlying or overlying tissues	Spongiform lesion
Vocal cord paralysis	
Regional lymphadenopathy	

From Melmed S, Polonsky KS, Larsen PR, et al: *Williams Textbook of Endocrinology,* ed 12, Philadelphia, 2011, Elsevier.

SUGGESTED READINGS

Alexander EK et al.: Pre-operative diagnosis of benign thyroid nodules with indeterminate cytology, *N Engl J Med* 367:705–715, 2012.

Castro MR, Gharib H: Continuing controversies in the management of thyroid nodules, *Ann Intern Med* 142:926, 2005.

Durante C et al.: The natural history of benign thyroid nodules, *JAMA* 313(9): 926–935, 2015.

Lin JH et al.: The role of ultrasonography in thyroid cancer, *Am J Otolaryngol* 30:324–326, 2009.

Shetty SK et al.: Significance of incidental thyroid lesions detected on CT: correlation among CT, sonography, pathology. *Am J Roentgenol* 187:1349, 2006.

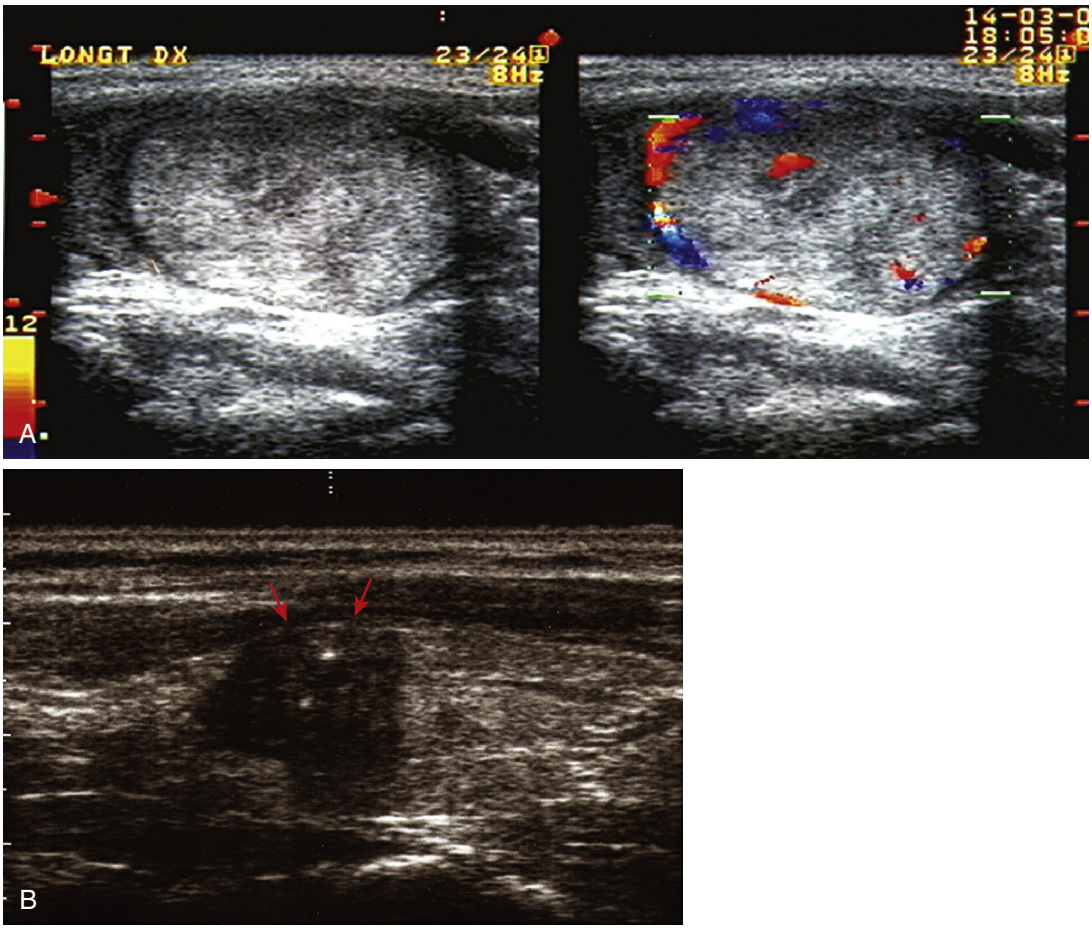


FIGURE ET1-31 Conventional and color flow Doppler ultrasonography. A, Benign lesion. Sonogram shows well-defined, oval, hyperechoic nodule with perinodular and slight intranodular blood flow. **B,** Malignant lesion. Sonogram shows a nodule with inhomogeneous hypoechoic aspect, microcalcifications, irregular borders, and invasion of the thyroid capsule (arrows). (From Melmed S, Polonsky KS, Larsen PR, et al: Williams Textbook of Endocrinology, ed 12, Philadelphia; 2011, Elsevier.)

BASIC INFORMATION

DEFINITION

Thyroiditis is an inflammatory disease of the thyroid. It is a multifaceted disease with various etiologies, different clinical characteristics (depending on the stage), and distinct histopathology. Thyroiditis can be subdivided into three common types (Hashimoto's, painful, and painless) and two rare forms (suppurative and Riedel's). To add to the confusion, there are various synonyms for each form, and there is no internationally accepted classification of autoimmune thyroid disease.

SYNONYMS

Hashimoto's thyroiditis: chronic lymphocytic thyroiditis, chronic autoimmune thyroiditis, lymphadenoid goiter

Painful subacute thyroiditis: subacute thyroiditis, giant cell thyroiditis, de Quervain's thyroiditis, subacute granulomatous thyroiditis, pseudogranulomatous thyroiditis

Painless postpartum thyroiditis: subacute lymphocytic thyroiditis, postpartum thyroiditis

Painless sporadic thyroiditis: silent sporadic thyroiditis, subacute lymphocytic thyroiditis

Suppurative thyroiditis: acute suppurative thyroiditis, bacterial thyroiditis, microbial inflammatory thyroiditis, pyogenic thyroiditis

Riedel's thyroiditis: fibrous thyroiditis

ICD-9CM CODES

245.2 Hashimoto's thyroiditis
245.1 Subacute thyroiditis
245.9 Silent thyroiditis
245.0 Suppurative thyroiditis
245.3 Riedel's thyroiditis

ICD-10CM CODES

E06.3 Autoimmune thyroiditis
E06.1 Subacute thyroiditis
E06.9 Thyroiditis, unspecified
E06.0 Acute thyroiditis
E06.5 Other chronic thyroiditis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Hashimoto's: patients may have signs of hyperthyroidism (tachycardia, diaphoresis, palpitations, weight loss) or hypothyroidism (fatigue, weight gain, delayed reflexes) depending on the stage of the disease. Usually there is diffuse, firm enlargement of the thyroid gland; the gland may also be of normal size (atrophic form with clinically manifested hypothyroidism).
- Painful subacute: exquisitely tender, enlarged thyroid, fever; signs of hyperthyroidism are initially present; signs of hypothyroidism can subsequently develop.
- Painless thyroiditis: clinical features are similar to subacute thyroiditis except for the absence of tenderness of the thyroid gland.
- Suppurative: patient is febrile with severe neck pain, focal tenderness of the involved portion of the thyroid, erythema of the overlying skin.
- Riedel's: slowly enlarging hard mass in the anterior neck; often mistaken for thyroid cancer; signs of hypothyroidism occur in advanced stages.

ETIOLOGY

- Hashimoto's: autoimmune disorder that begins with the activation of CD4 (helper) T-lymphocytes specific for thyroid antigens. The etiologic factor for the activation of these cells is unknown.
- Painful subacute: possibly postviral; usually follows a respiratory illness not considered to be a form of autoimmune thyroiditis
- Painless thyroiditis: frequently occurs postpartum
- Suppurative: infectious etiology, generally bacterial, although fungi and parasites have also been implicated; often occurs in immunocompromised hosts or after a penetrating neck injury
- Riedel's: fibrous infiltration of the thyroid; etiology unknown
- Drug induced: lithium, interferon-alfa, amiodarone, interleukin-2

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- The hyperthyroid phase of Hashimoto's, subacute, and silent thyroiditis can be mistaken for Graves' disease.
- Riedel's thyroiditis can be mistaken for carcinoma of the thyroid.
- Painful subacute thyroiditis can be mistaken for infections of the oropharynx and trachea or for suppurative thyroiditis.
- Factitious hyperthyroidism can mimic silent thyroiditis.

WORKUP

- The diagnostic workup includes laboratory and radiologic evaluation to rule out other conditions that may mimic thyroiditis (see above) and differentiate the various forms of thyroiditis.
- The patient's medical history may be helpful in differentiating the various types of thyroiditis (e.g., presentation after childbirth is suggestive of silent [postpartum, painless] thyroiditis; occurrence after a viral respiratory infection suggests subacute thyroiditis; history of penetrating injury to the neck indicates suppurative thyroiditis) (Table ET1-12).

LABORATORY TESTS

- Thyroid-stimulating hormone, free T_4: may be normal or indicative of hypothyroidism or hyperthyroidism depending on the stage of the thyroiditis.
- White blood cell (WBC) with differential: increased WBC with left shift occurs with subacute and suppurative thyroiditis.
- Antimicrosomal antibodies: detected in >90% of patients with Hashimoto's thyroiditis and 50% to 80% of patients with silent thyroiditis.
- Serum thyroglobulin levels are elevated in patients with subacute and silent thyroiditis; this test is nonspecific but may be useful in monitoring the course of subacute thyroiditis and distinguishing silent thyroiditis from factitious hyperthyroidism (low or absent serum thyroglobulin level).

IMAGING STUDIES

Twenty-four–hour radioactive iodine uptake (RAIU) is useful to distinguish Graves' disease (increased RAIU) from thyroiditis (normal or low RAIU). Table ET1-13 summarizes factors that influence 24-hr thyroid iodide uptake.

TREATMENT

ACUTE GENERAL Rx

- Treat hypothyroid phase with levothyroxine 25 to 50 mcg/day initially and monitor serum thyroid-stimulating hormone initially every 6 to 8 wk.
- Control symptoms of hyperthyroidism with beta-blockers (e.g., propranolol 20 to 40 mg PO q6h).
- Control pain in patients with subacute thyroiditis with nonsteroidal anti-inflammatory drugs. Prednisone 20 to 40 mg qd may be used if nonsteroidals are insufficient, but it should be gradually tapered off over several weeks.
- Use IV antibiotics and drain abscess (if present) in patients with suppurative thyroiditis.

DISPOSITION

- Hashimoto's thyroiditis: long-term prognosis is favorable; most patients recover their thyroid function.
- Painful subacute thyroiditis: permanent hypothyroidism occurs in 10% of patients.
- Painless thyroiditis: 6% of patients have permanent hypothyroidism.
- Suppurative thyroiditis: there is usually full recovery after treatment.
- Riedel's thyroiditis: hypothyroidism occurs when fibrous infiltration involves the entire thyroid.

REFERRAL

Surgical referral in patients with compression of adjacent neck structures and in some patients with suppurative thyroiditis

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Thyroiditis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Context:
The incidence of postpartum thyroiditis (PPT) varies widely in the literature. Limited data exist concerning the hormonal status of women with PPT at the end of the first postpartum year.

Objective:
Our aim was to conduct a large prospective study of the incidence and clinical course of PPT.

Design:
A total of 4394 women were screened for thyroid function and thyroid autoantibodies at 6 and 12 months postpartum. Women were classified as being at high or low risk of having thyroid disease before any thyroid testing.

Setting:
The study was conducted at two ambulatory clinics in southern Italy, an area of mild iodine deficiency.

Patients:
A total of 4394 pregnant women were studied.

Intervention:
There was no intervention.

Main Outcome Measures:
We measured incidence, clinical presentation, and course of postpartum thyroiditis.

Results:
The incidence of postpartum thyroiditis was 3.9% (169 of 4384). Women classified as being at high risk for thyroid disease had a higher incidence of PPT than women classified as low risk (11.1 *vs.* 1.9%; odds ratio, 6.69; 95% confidence interval, 4.63, 9.68). Eighty-two percent of the 169 women with PPT had a hypothyroid phase during the first postpartum year. At the end of the first postpartum year, 54% of the 169 women had persistent hypothyroidism.

Conclusions:
One of every 25 women in southern Italy developed PPT. Women at high risk for thyroid disease have an increased rate of PPT. The high rate of permanent hypothyroidism at 1 yr should result in a reevaluation of the widely held belief that most women with PPT are euthyroid at the end of the first postpartum year. Ⓐ

Evidence-Based Reference

Stagnaro-Green A et al.: High rate of persistent hypothyroidism in a large-scale prospective study of postpartum thyroiditis in southern Italy, *J Clin Edocrinol Metab* 96:652–657, 2011. Ⓐ

SUGGESTED READINGS

Bindra A, Braunstein GD: Thyroiditis, *Am Fam Physician* 73:1769, 2006.
Pearce EN et al.: Thyroiditis, *N Engl J Med* 348:2646, 2003.

TABLE ET1-13 Factors that Influence 24-Hour Thyroid Iodide Uptake

Factors That Increase Uptake
Increased Hormone Synthesis
Hyperthyroidism
Response to glandular hormone depletion
Recovery from thyroid suppression
Recovery from subacute thyroiditis
Antithyroid agents
Excessive hormone losses
Nephrotic syndrome
Chronic diarrheal states
Soybean ingestion
Normal Hormone Synthesis
Iodine deficiency
Dietary insufficiency
Excessive loss (dehalogenase defect, pregnancy)
Hormone biosynthetic defects
Factors That Decrease Uptake
Decreased Hormone Synthesis
Primary hypofunction
Primary hypothyroidism
Antithyroid agents
Hormone biosynthetic defects
Hashimoto's disease
Subacute thyroiditis
Secondary hypofunction
Exogenous thyroid hormones
Not Reflecting Decreased Hormone Synthesis
Increased availability of iodine
Diet or drugs
Cardiac or renal insufficiency
Increased hormone release
Very severe hyperthyroidism (rare)

From Melmed S, Polonsky KS, Larsen PR, et al: *Williams Textbook of Endocrinology,* ed 12, 2011, Elsevier.

TABLE ET1-12 Human Iodothyronine Selenodeiodinases

Parameter	Type 1 (Outer and Inner Ring)	Type 2 (Outer Ring)	Type 3 (Inner Ring)
Physiologic role	rT_3 and T_3S degradation; source of plasma T_3 in thyrotoxic patients	Provide intracellular T_3 in specific tissues, a source of plasma T_3	Inactivate T_3 and T_4
Tissue location	Liver, kidney, thyroid, pituitary(?); not CNS	CNS, pituitary, BAT, placenta, thyroid, skeletal muscle, heart	Placenta, CNS, hemangiomas, fetal or adult liver, skeletal muscle
Subcellular location	Plasma membrane	Endoplasmic reticulum	Plasma membrane
Preferred substrates (position deiodinated)	rT_3 (5′), T_3S	T_4, rT_3 (5′)	T_3, T_4
K_m	rT_3, 10^{-7}; T_4, 10^{-6}	10^{-9}	10^{-9}
Susceptibility to PTU	High	Absent	Absent
Response to increased T_4	↑	↓	↑

BAT, Brown adipose tissue; *CNS,* central nervous system; K_m, Michaelis-Menten constant; *PTU,* 6-n propylthiouracil; rT_3, reverse triiodothyronine; T_3, triiodothyronine; T_3S, T_3SO_4; T_4, thyroxine.
From Melmed: *Williams textbook of endocrinology,* ed 12, Philadelphia, 2011, Saunders.

BASIC INFORMATION

DEFINITION

Thyrotoxic storm is the abrupt and severe exacerbation of thyrotoxicosis. It is an acute, life-threatening complication of hyperthyroidism.

ICD-9CM CODES
242.9 Thyrotoxic storm
ICD-10CM CODES
E05.5 Thyroid crisis or storm

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Tremor, tachycardia/tachyarrhythmias, fever (as high as 105.8° F)
- Sweating, diarrhea, vasodilation
- Lid lag, lid retraction, proptosis
- Altered mental status (psychosis, coma, seizures)
- Goiter
- Other: evidence of precipitating factors (infection, trauma), CHF, hepatosplenomegaly, jaundice

ETIOLOGY

- Precipitating factors: surgery, infection, myocardial infarction or cardiac disease, diabetic ketoacidosis, labor, iodinated IV contrast agents, radioactive iodine therapy
- Inadequate therapy in a hyperthyroid patient

DIAGNOSIS

The clinical presentation is variable. The patient may present with the following signs and symptoms:

- Fever
- Marked anxiety and agitation, psychosis
- Hyperhidrosis, heat intolerance
- Marked weakness and muscle wasting
- Tachyarrhythmias, palpitations
- Diarrhea, nausea, vomiting
- Elderly patients may have a combination of tachycardia, congestive heart failure (CHF), and mental status changes

DIFFERENTIAL DIAGNOSIS

- Psychiatric disorders
- Alcohol or other drug withdrawal
- Pheochromocytoma
- Metastatic neoplasm

WORKUP

- Laboratory evaluation to confirm hyperthyroidism (elevated free T4, decreased thyroid-stimulating hormone [TSH])
- Evaluation for precipitating factors (e.g., ECG and cardiac enzymes in suspected MI, blood and urine cultures to rule out sepsis)
- Elimination of disorders noted in the differential diagnosis (e.g., psychiatric history, evidence of drug and alcohol abuse)

LABORATORY TESTS

- Free T_4, TSH
- Complete blood count with differential
- Blood and urine cultures
- Glucose
- Liver enzymes
- Blood urea nitrogen, creatinine
- Serum calcium
- Creatine phosphokinase

IMAGING STUDIES

Chest x-ray to exclude infectious process, neoplasm, CHF in suspected cases

TREATMENT

NONPHARMACOLOGIC THERAPY

- Nutritional care: replace fluid deficit aggressively (daily fluid requirement may reach 6 L); use solutions containing glucose and add multivitamins to the hydrating solution.
- Monitor for fluid overload and CHF in the elderly and in those with underlying cardiovascular or renal disease.
- Treat significant hyperthermia with cooling blankets.

ACUTE GENERAL Rx

- Inhibition of thyroid hormone synthesis:
  1. Administer propylthiouracil (PTU) 800 mg initially (PO or by nasogastric tube)/PR, then 200 to 300 mg PO/PR q6h.
  2. If the patient is allergic to PTU, use methimazole 80 to 100 mg (PO or by nasogastric tube) /PR followed by 40 mg PO/PR q8h. Methimazole can also be administered IV 60 to 120 mg daily, divided doses.
- Inhibition of stored thyroid hormone release from the gland:
  1. Sodium Iodide 1 g IV over 24 hours or potassium iodide (oral) 5 drops 4 times/day (super-saturated potassium iodide). It is important to administer PTU or methimazole 1 hr *before* the iodide to prevent the oxidation of iodide to iodine and its incorporation in the synthesis of additional thyroid hormone.
  2. Corticosteroids: dexamethasone 1-2 mg IV q6h or hydrocortisone 100 mg IV q6h for approximately 48 hr is useful to inhibit thyroid hormone release, impair peripheral conversion of T_3 from T_4, and provide additional adrenocortical hormone to correct deficiency (if present).
- Suppression of peripheral effects of thyroid hormone:
  1. Beta-adrenergic blockers: administer propranolol 60 to 80 mg every 4 hours. Propranolol may also be given IV 1 mg/min for 2 to 10 min under continuous ECG and blood pressure monitoring. Beta-adrenergic blockers must be used with caution in patients with severe CHF or bronchospasm. Cardioselective beta-blockers (e.g., esmolol 500 mg IV over 1 min, then 50 to 100 mg/kg/min or metoprolol 5 to 10 mg IV every 2 to 4 hours) may be more appropriate for patients with bronchospasm, but these patients must be closely monitored for exacerbation of bronchospasm because these agents lose their cardioselectivity at high doses. The calcium channel blocker diltiazem can also be given to reduce the heart rate. Dose is 0.25 mg/kg over 2 min, then infusion of 10 mg/min. Oral dose is 60 to 90 mg every 6 to 8 hours.
- Control of fever with acetaminophen 325 to 650 mg q4h; avoidance of aspirin because it displaces thyroid hormone from its binding protein
- Consider digitalization of patients with CHF and atrial fibrillation (these patients may require higher than usual digoxin doses)
- Treatment of any precipitating factors (e.g., antibiotics if infection is strongly suspected)

DISPOSITION

Patients with thyrotoxic crisis should be treated and appropriately monitored in the ICU.

REFERRAL

Endocrinology referral is appropriate in patients with thyrotoxic crisis.

PEARLS & CONSIDERATIONS

COMMENTS

If the diagnosis is strongly suspected, therapy should be started immediately without waiting for laboratory confirmation.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Graves' Disease (Related Key Topic)
Hyperthyroidism (Related Key Topic)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READING

McDermott MT: In the clinic. Hyperthyroidism, *Ann Intern Med ITC 1–14 July* 3, 2012.

BASIC INFORMATION

DEFINITION

Tinea capitis is a dermatophyte infection of hair shaft and follicles of the scalp, eyebrows, and eyelashes. It is a form of superficial mycosis. Etiologic agents are fungal species of the genera *Microsporum* and *Trichophyton*.

SYNONYMS

Ringworm of the scalp, ringworm of the head, gray patch tinea capitis, black dot tinea capitis, tinea tonsurans, herpes tonsurans, kerion, favus

ICD-9CM CODES
110.0 Tinea capitis
ICD-10CM CODES
B35.0 Tinea barbae and tinea capitis

EPIDEMIOLOGY & DEMOGRAPHICS

Tinea capitis primarily affects prepubertal children with peak age between 3 and 7 yr old. Adult cases are rare, possibly because of the fungistatic effect of the sebum found in older persons. Urban living, large family size, low socioeconomic status, and crowded living conditions may contribute to an increased incidence of tinea capitis. The elderly and immunocompromised individuals have an increased risk of infection. The incidence of the disease varies worldwide; however, it has is relatively low in the United States. It is reportedly widespread in parts of central and South America, India, and Africa.

In the United States, peak incidence occurs in school-aged children of low socioeconomic status, with African-American male children accounting for the greatest proportion of cases. About 3% to 8% of American children are affected, and 34% of household contacts are asymptomatic carriers.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Classic triad of scalp scaling, alopecia, and cervical adenopathy
- Most forms of tinea capitis begin with one or few round patches of scale or alopecia.
- Primary lesions include plaques, papules, pustules, or nodules on the scalp (usually occipital region).
- Secondary lesions include scales, alopecia (usually reversible), erythema, exudates, and edema.
- Scalp pruritus may be present.
- Fever, pain, and lymphadenopathy (commonly postcervical) may occur with inflammatory lesions.
- Different clinical patterns of tinea capitis have been described:
  1. Gray patch: Lesions are scaly and well demarcated. The hairs within the patch break off a few millimeters above the scalp. One or several lesions may be present; sometimes the lesions join to form larger ones.
  2. Black dot: Early lesions with erythema and scaling patch are easily overlooked until areas of alopecia develop. Hairs within the patches break at the surface of the scalp, leaving behind a pattern of swollen black dots.
  3. Kerion (Fig. T1-32): inflamed, exudative, pustular, boggy, tender nodules exhibiting marked edema, and hair loss seen in severe tinea capitis. Caused by immune response to the fungus. May lead to some scarring.
  4. Favus: production of scutula (hair matted together with dermatophyte hyphae and keratin debris), characterized by yellow cup-shaped crusts around hair shafts. A fetid odor may be present.

ETIOLOGY

Although fungi of the *Microsporum* or *Trichophyton* genera cause most cases of tinea capitis, causative species vary between geographical areas and across time. *T. tonsurans* is the predominant cause of tinea capitis, present in more than 90% of cases in North and Central America. *Microsporum canis, M. audouinii,* and *Trichophyton mentagrophytes* are less common. The most common causative species for black dot tinea capitis is *T. tonsurans*, while gray patch tinea capitis tends to be caused by *M. andouinii* and *M. canis.* Infection of the hair shaft is preceded by invasion of the stratum corneum of the scalp. Transmision of *T. tonsurans* occurs from person-to-person via infected persons or asymptomatic carriers, fallen infected hairs, animal vectors, and fomites. *M. audouinii* is commonly spread by dogs and cats. Infectious fungal particles may remain viable for many months. Even though the organism remains viable on combs, hairbrushes, and other fomites for long periods of time, the role of fomites in spreading the infection may vary in different geographic areas.

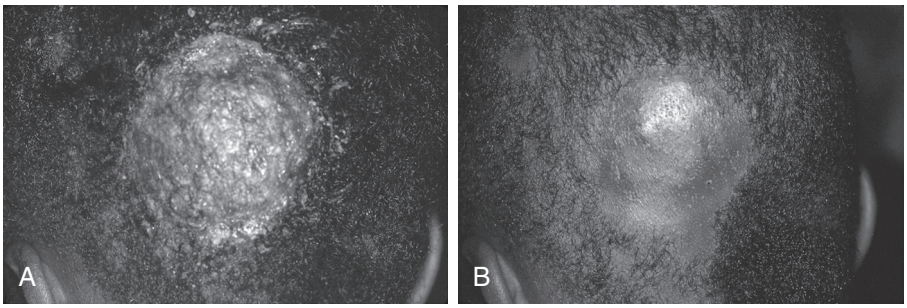


FIGURE T1-32 A, Kerion. Boggy granulomatous mass of the scalp. **B,** Scarring after kerion. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Seborrheic dermatitis and psoriasis may be confused with tineacapitis. Other conditions that resemble tinea capitis include alopecia areata, impetigo, pediculosis, trichotillomania, traction alopecia, folliculitis, pseudopelade, seborrhea/atopic dermatitis, psoriasis, carbuncles, pyoderma, lichen ruber planus, lupus erythematosus should also be considered in the differential. Table T1-14 highlights distinctive features of conditions that may be confused for tinea capitis.

WORKUP

- KOH testing of hair shaft extracted from the lesion, not the scale, because the *T. tonsurans* spores attach to or reside inside hair shafts and will rarely be found in the scales.
- Wood's ultraviolet light fluoresces blue-green on hair shafts for Microsporum infections but will fail to identify *T. tonsurans.*
- Fungal culture of hairs and scales on fungal medium such as Sabouraud's agar may be used to confirm the diagnosis, especially if uncertain.
- Histology of biopsies with fungal staining in cases where mycology tests are negative because of treatment initiation.

TREATMENT

- Griseofulvin is the gold standard FDA-approved treatment. It is less costly than other drug options and has an excellent long-term safety profile. Micronized and ultramicronized preparations are absorbed better, and side effects are infrequent, especially when administered with fatty meals. Periodic monitoring of hematologic, liver, and renal function may be indicated, especially in prolonged treatment over 8 wk.

  Children: Griseofulvin is approved for children older than 2 yr of age: microsize griseofulvin 10 to 25 mg/kg PO per day in one single dose or two divided doses (maximum, 1 g/day; for tinea capitis, higher doses [20-25 mg/kg/day] have been recommended) or ultramicrosize griseofulvin, 5 to 15 mg/kg PO per day (maximum, 750 mg/day), in one single dose or two divided doses. Optimally, griseofulvin is given after a meal containing fat (e.g., peanut butter or ice cream). Recommended treatment length is 6 to 8 wk and should be continued 2 wk beyond clinical resolution (until hair regrowth occurs). Some children may require higher doses to achieve clinical cure.

  Adults and elderly persons: microsize griseofulvin 500 mg PO per day in one single dose or divided doses. The other option is

TABLE T1-14 Differential Diagnosis of Tinea Capitis

Disorder	Differentiating Features
Psoriasis	Red skin with thick, uniform, silvery scale, sharply demarcated; often psoriasis at other body sites also
Dermatitis	Main possibility is seborrheic dermatitis: usually more diffuse and has uniform fine scaling, rather than localized areas; doesn't typically cause alopecia or significant inflammation. May also be present on the face, especially the nasolabial fold, or as otitis externa. Atopic dermatitis is generally diffuse on scalp and almost inevitably present at other sites, but may coexist with tinea capitis, especially in children.
Pityriasis amiantacea	Thick sheets of asbestos-like scale, very adherent, generally a solitary patch. This may occur in various dermatoses.
Lichen simplex	Usually nape of neck; cobblestoned or lichenified skin thickening, with broken hairs that are not coated with scale
Alopecia areata	Usually not inflamed (may be mildly so), not scaly, usually sharply defined. "Exclamation mark" hairs occur but are not coated with fungus; "cadaverized" hairs especially cause difficulty, as they mimic black dot alopecia.
Scarring alopecias	Examples: discoid lupus erythematosus, lichen planus of scalp; cause perifollicular inflammation around intact hairs; usually associated with lesions at other sites also. Dissecting cellulitis of scalp is also in this differential.
Bacterial infections	Impetigo causes crusting but little inflammation, and hairs are intact; carbuncle is deeper and very tender but may be in the differential of kerion
Trichotillomania	Broken hairs of unequal length, but hair shafts themselves and the scalp are normal
Damage from hairdressing processes	Usually clear from the timescale
Neoplasm	May be in the differential of kerion; usually slower-growing and mainly on elderly, balding scalp, whereas kerion is in children or young adults with previously intact hair

From White GM, Cox NH (eds): *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.

ultramicrosize griseofulvin 375 mg PO per day in one single dose or divided doses. Recommended treatment length is 4 to 6 weeks.

- New alternative treatments: oral terbinafine, itraconazole, or fluconazole are comparable in efficacy and safety to griseofulvin, with possibly shorter treatment and better patient compliance. Preferred when resistant or when an allergy to griseofulvin is of concern. Monitoring of CBC, liver function tests, and renal function may be indicated.
  1. Terbinafine—4-wk course of therapy as effective as with griseofulvin. Dosages are 67.5 mg/day for patients weighing <20 kg; 125 mg/day for patients weighing 20 to 40 kg; and 250 mg for patients weighing >40 kg.
  2. Itraconazole—3.5 mg/kg daily for 4 to 6 wk or pulse therapy of 5 mg/kg daily for 1 wk each month for 2 to 3 mo (not approved for children)
  3. Fluconazole—the only oral antifungal agent approved for children <2 yr, 6 mg/kg/day for 6 wk in children (3 to 6 wk in adults) or 8 mg/kg weekly for 8 to 12 wk (cap at 150 mg weekly for adults)
- The adjuvant use of antifungal shampoos may be recommended for all patients and household contacts. Shampoo like selenium sulfide 2.5% used for 5 min or ketoconazole shampoo used 2 to 3 times/wk can help prevent infection or eradicate asymptomatic carrier state by inhibiting fungal growth.
- Severe inflammatory kerion can be managed with additional prednisone 40 mg daily (1 mg/kg/day in children) and tapering over 2 wk.
- Prompt treatment is indicated, as is examination of siblings and other household contacts for evidence of tinea capitis.
- Recommend follow-up visit every 2 to 4 wk with Wood's light, microscopic study, and fungal culture. A mycologic documented cure is the goal of treatment.
- Pets that are infected or asymptomatic carriers should be treated.
- Children receiving treatment for tinea capitis may attend school once they start therapy with griseofulvin or other effective systemic agent.

PEARLS & CONSIDERATIONS

- Systemic antifungal therapy is required for tinea capitis because topical antifungal medications are not effective.
- Shaving of the head, haircuts, or wearing a cap or scarf during treatment is unnecessary.
- Sharing of combs, hair ribbons, and hairbrushes should be discouraged.

COMMENTS

- Confirming the diagnosis of tinea capitis with a laboratory specimen is important because misdiagnosis will result in delay or improper treatment.
- Patients and their families should look for sources of infections and disinfect contaminated objects such as combs, brushes, towels, and headgear. Avoid sharing personal hygiene utensils.
- Culture of hairs and scalp dander facilitates carrier identification and prevention.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Tinea Capitis (Patient Information)

AUTHORS: **PRIYA SARIN GUPTA, M.D., M.P.H., NADINE MBUYI, M.D.,** and **ALVARO M. RIVERA, M.D.**

SUGGESTED READINGS

American Academy of Pediatrics. Red book online. http://intl-aapredbook.aappublications.org. Accessed May 2, 2013.

Gilbert DN et al.: *The Sanford guide to antimicrobial therapy*, Hyde Park, VT, 2007, Antimicrobial Therapy.

Goldstein AO et al.: Dermatophyte (tinea) infections, *UpToDate Online* 17.3, 2009.

Gupta AK, Drummond-Main C: Meta-analysis of randomized, controlled trials comparing particular doses of griseofulvin and terbinafine for the treatment of tinea capitis, *Pediatr Dermatol* 30:1–6, 2013.

Mohrenschlager M et al.: Pediatric tinea capitis: recognition and management, *Am J Clin Dermatol* 6(4):203–213, 2005.

Roberts BJ, Friedlander SF: Tinea capitis: a treatment update, *Pediatr Ann* 34(3):191–200, 2005.

Seebacher C et al.: Tinea capitis: ringworm of the scalp, *Mycoses* 50(3):218–226, 2007.

Shy R: Tinea corporis and tinea capitis, *Pediatr Rev* 28(5):164–174, 2007.

Trovato MJ et al.: Tinea capitis: current concepts in clinical practice, *Cutis* 77(2):93–99, 2006.

Tinea Corporis PTG

BASIC INFORMATION

DEFINITION

Tinea corporis is a dermatophyte fungal infection caused by the genera *Trichophyton* or *Microsporum.*

SYNONYMS

Ringworm
Body ringworm
Tinea circinata

ICD-9CM CODES
110.5 Tinea corporis
ICD-10CM CODES
B35.4 Tinea corporis

EPIDEMIOLOGY & DEMOGRAPHICS

- The disease is more common in warm climates.
- There is no predominant age or sex.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Typically appears as single or multiple annular lesions with an advancing scaly border (Fig. T1-33); the margin is slightly raised, reddened, and may be pustular.
- The central area becomes hypopigmented and less scaly as the active border progresses outward (Fig. T1-34).
- The trunk and legs are primarily involved.
- Pruritus is variable.
- It is important to remember that recent topical corticosteroid use can significantly alter the appearance of the lesions.

ETIOLOGY

Trichophyton rubrum is the most common pathogen.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Pityriasis rosea
- Erythema multiforme
- Psoriasis
- Cutaneous systemic lupus erythematosus
- Secondary syphilis
- Nummular eczema
- Eczema
- Granuloma annulare
- Lyme disease
- Tinea versicolor
- Contact dermatitis

WORKUP

Diagnosis is usually made on clinical grounds. It can be confirmed by direct visualization under the microscope of a small fragment of the scale using wet mount preparation and potassium hydroxide solution; dermatophytes appear as translucent branching filaments (hyphae) with lines of separation appearing at irregular intervals.

LABORATORY TESTS

- Microscopic examination of hyphae
- Mycotic culture is usually not necessary.
- Biopsy is indicated only when the diagnosis is uncertain and the patient has not responded to treatment.

TREATMENT

NONPHARMACOLOGIC THERAPY

Affected areas should be kept clean and dry.

ACUTE GENERAL Rx

- Various creams are effective; the application area should include normal skin approximately 2 cm beyond the affected area:
  1. Butenafine cream applied qd for 14 days
  2. Terbinafine cream applied bid for 14 days
- Systemic therapy is reserved for severe cases and is usually given up to 4 wk; commonly used agents:
  1. Fluconazole, 200 mg qd
  2. Terbinafine, 250 mg qd

DISPOSITION

Majority of cases resolve without sequelae within 3 to 4 wk of therapy.

REFERRAL

Dermatology referral in patients with persistent or recurrent infections

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Ringworm (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

FIGURE T1-33 Tinea corporis. (Courtesy of David Effron, MD.)

FIGURE T1-34 Annular lesion (tinea corporis). Note raised erythematous, scaling border and central clearing. (From Noble J et al: *Textbook of primary care medicine,* ed 3, St Louis, 2001, Mosby.)

SUGGESTED READINGS

Andrews MD, Burns M: Common tinea infections in children, *Am Fam Physician* 77(10):1415–1420, 2008.

Hainer BL: Dermatophyte infections, *Am Fam Physician* 67:101, 2003.

Weinstein A, Berman B: Topical treatment of common superficial tinea infections, *Am Fam Physician* 65:2095, 2002.

BASIC INFORMATION

DEFINITION

Tinea cruris is a dermatophyte infection of the groin.

SYNONYMS

Jock itch
Groin ringworm

ICD-9CM CODES
110.3 Tinea cruris
ICD-10CM CODES
B35.6 Tinea cruris

EPIDEMIOLOGY & DEMOGRAPHICS

- Most common during the summer in adolescent and young adult males.
- Males are affected more frequently than females; however, it has become more common in postpubertal females who are overweight or who often wear tight jeans or pantyhose.
- The infection often coexists with tinea pedis.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Erythematous plaques have a half-moon shape and a scaling border.
- The acute inflammation tends to move down the inner thigh and usually spares the scrotum; in severe cases the fungus may spread onto the buttocks.
- Itching may be severe.
- Red papules and pustules may be present.
- An important diagnostic sign is the advancing well-defined border with a tendency toward central clearing (Fig. T1-35).

ETIOLOGY

- Dermatophytes of the genera *Trichophyton, Epidermophyton,* and *Microsporum. T. rubrum* and *E. floccosum* are the most common infecting agents.
- Transmission from direct contact (e.g., infected persons, animals). The patient's feet should be evaluated as a source of infection because tinea cruris is often associated with tinea pedis.

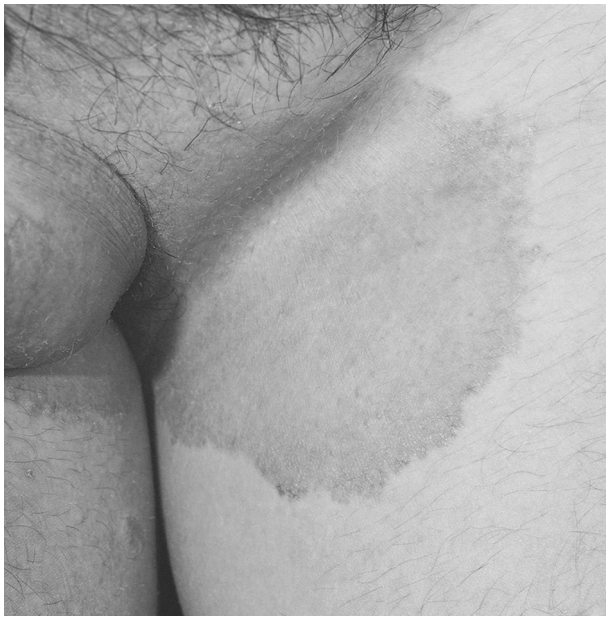


FIGURE T1-35 Tinea cruris. A half-moon–shaped plaque has a well-defined, scaling border. (From Habif TB: *Clinical dermatology: a color guide to diagnosis and therapy*, ed 3, St Louis, 1996, Mosby.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Candidal intertrigo
- Psoriasis
- Seborrheic dermatitis
- Erythrasma
- Contact dermatitis
- Tinea versicolor

WORKUP

Diagnosis is based on clinical presentation and demonstration of hyphae microscopically using potassium hydroxide.

LABORATORY TESTS

- Microscopic examination
- Cultures are generally not necessary.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Keep infected area clean and dry.
- Boxer shorts are preferred to briefs.

ACUTE GENERAL Rx

- Various topical antifungal agents are available:
  1. Butenafine cream, applied qd × 14 days
  2. Terbinafine cream, applied bid × 14 days
- Drying powders (e.g., miconazole nitrate) may be useful in patients with excessive perspiration.
- Oral antifungal therapy is generally reserved for cases unresponsive to topical agents or can be used along with topical agents in severe cases. Effective medications are fluconazole 200 mg qd × 10 days and terbinafine 250 mg qd × 30 days.

DISPOSITION

Most cases respond promptly to therapy with complete resolution within 2 to 3 wk.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Tinea Cruris (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Andrews MD, Burns M: Common tinea infections in children, *Am Fam Physician* 77(10):1415–1420, 2008.

Hainer BL: Dermatophyte infections, *Am Fam Physician* 67:101, 2003.

Tinea Pedis PTG

BASIC INFORMATION

DEFINITION

Tinea pedis is a dermatophyte infection of the feet.

SYNONYMS

Athlete's foot

ICD-9CM CODES
110.4 Tinea pedis
ICD-10CM CODES
B35.3 Tinea pedis

EPIDEMIOLOGY & DEMOGRAPHICS

- Most common dermatophyte infection
- Increased incidence in hot humid weather; occlusive footwear is a contributing factor
- Occurrence is rare before adolescence
- More common in adult males

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Typical presentation is variable and ranges from erythematous scaling plaques (Fig. T1-36) and isolated blisters to interdigital maceration.
- The infection usually starts in the interdigital spaces of the foot. Most infections are found in the toe webs or on the soles.
- Fourth or fifth toes are most commonly involved.
- Pruritus is common and is most intense after removal of shoes and socks.
- Infection with *Trichophyton rubrum* often manifests with a "moccasin" distribution affecting the soles and lateral feet.

FIGURE T1-36 Tinea pedis. (From Goldstein BG, Goldstein AO: *Practical dermatology,* ed 2, St Louis, 1997, Mosby.)

ETIOLOGY

Dermatophyte infection caused by *T. rubrum, Trichophyton mentagrophytes,* or less commonly *Epidermophyton floccosum*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Contact dermatitis
- Toe web infection (bacterial or candidal infection)
- Eczema
- Psoriasis
- Keratolysis exfoliativa
- Juvenile plantar dermatosis

WORKUP

- Diagnosis is usually made by clinical observation.
- Laboratory testing, when performed, generally consists of a simple potassium hydroxide preparation with mycologic examination under a light microscope to confirm the presence of dermatophytes.

LABORATORY TESTS

- Microscopic examination of a scale or the roof of a blister with 10% KOH under low or medium power will reveal hyphae.
- Mycologic culture is rarely indicated in the diagnosis of tinea pedis.
- Biopsy is reserved for when the diagnosis remains in question after testing or failure to respond to treatment.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Keep infected area clean and dry. Aerate feet by using sandals when possible.
- Use 100% cotton socks rather than nylon socks to reduce moisture.
- Areas likely to become infected should be dried completely before being covered with clothes.

ACUTE GENERAL Rx

- Benzylamines: butenafine HCl 1% cream applied bid for 1 wk or qd for 4 wk is effective in interdigital tinea pedis.
- Allylamines: terbinafine cream applied bid × 14 days, or naftifine 1% cream applied qd or naftifine gel applied bid for 4 wk produces a significantly high cure rate.
- Imidazoles: econazole, ketoconazole, miconazole, luliconazole, and clotrimazole cream are also effective agents. Clotrimazole 1% cream is an over-the-counter treatment. It should be applied to affected and surrounding area bid for up to 4 wk.
- Ciclopirox and tolnaftate are other antifungal agents available in cream, suspension, or gel. Tolnaftate is also available as a lotion, spray, or powder.
- When using topical preparations, the application area should include normal skin approximately 2 cm beyond the affected area.
- Areas of maceration can be treated with Burow's solution soaks for 10 to 20 min bid followed by foot elevation.
- Oral agents (fluconazole 150 mg once per week for 4 wk) can be used in combination with topical agents in resistant cases.

PEARLS & CONSIDERATIONS

- Combination therapy of antifungal and corticosteroid (clotrimazole/betamethasone [Lotrisone]) should only be used when the diagnosis of fungal infection is confirmed and inflammation is a significant issue.
- Nystatin is not effective and should not be used.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Athlete's Foot (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READING

Andrews MD, Burns M: Common tinea infections in children, *Am Fam Physician* 77(10):1415, 2008.

BASIC INFORMATION

DEFINITION

Tinea versicolor is a fungal infection of the skin caused by the yeast *Pityrosporum orbiculare (Malassezia furfur).*

SYNONYMS

Pityriasis versicolor

ICD-9CM CODES
111.0 Tinea versicolor
ICD-10CM CODES
B36.0 Pityriasis versicolor

EPIDEMIOLOGY & DEMOGRAPHICS

- Increased incidence in adolescence and young adulthood
- More common during the summer (hypopigmented lesions are more evident when the skin is tanned)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most lesions begin as multiple small, circular macules of various colors (Fig. T1-37).
- The macules may be darker or lighter than the surrounding normal skin and will scale with scraping.
- Most frequent site of distribution is trunk.
- Facial lesions are more common in children (forehead is most common facial site).
- Eruption is generally of insidious onset and asymptomatic.
- Lesions may be hyperpigmented in blacks.
- Lesions may be inconspicuous in fair-complexioned individuals, especially during the winter.
- Most patients become aware of the eruption when the involved areas do not tan (Fig. T1-38).

ETIOLOGY

The infection is caused by the lipophilic yeast *P. orbiculare* (round form) and *P. ovale* (oval form), which are normal inhabitants of the skin flora. Factors that favor proliferation are pregnancy, malnutrition, immunosuppression, oral contraceptives, and excess heat and humidity.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Vitiligo
- Pityriasis alba
- Secondary syphilis
- Pityriasis rosea
- Seborrheic dermatitis
- Postinflammatory hyperpigmentation or hypopigmentation

WORKUP

Diagnosis is based on clinical appearance; identification of hyphae and budding spores ("spaghetti and meatballs" appearance) with microscopy confirms diagnosis.

FIGURE T1-37 Tinea versicolor. (Courtesy David Effron, M.D.)

FIGURE T1-38 The classic presentation of tinea versicolor with white, oval, or circular patches on tan skin. (From Habif TB: *Clinical dermatology: a color guide to diagnosis and therapy,* ed 3, St Louis, 1996, Mosby.)

LABORATORY TESTS

Microscopic examination with potassium hydroxide confirms diagnosis.

TREATMENT

NONPHARMACOLOGIC THERAPY

Sunlight accelerates repigmentation of hypopigmented areas.

ACUTE GENERAL Rx

- Topical treatment: selenium sulfide 2.5% suspension (Selsun or Exsel) applied daily for 30 min for 7 consecutive days results in a cure rate of 80% to 90%.
- Antifungal topical agents (e.g., miconazole, ciclopirox, clotrimazole) are also effective.
- Oral treatment can be given along with topical agents but is generally reserved for resistant cases. Effective agents are ketoconazole 200 mg qd for 5 days, or single 400-mg dose (cure rate >80%), fluconazole 400 mg given as a single dose (cure rate >70% at 3 wk after treatment), or itraconazole 200 mg/day for 5 days.

DISPOSITION

The prognosis is good, with eradication of the fungus usually occurring within 3 to 4 wk of treatment; however, recurrence is common.

PEARLS & CONSIDERATIONS

COMMENTS

Patients should be informed that the hypopigmented areas will not disappear immediately after treatment and that several months may be necessary for the hypopigmented areas to regain their pigmentation.

RELATED CONTENT

Tinea Versicolor (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

Tinnitus ALG EBM PTG

BASIC INFORMATION

DEFINITION

Tinnitus is a perceived sound in the absence of acoustic stimulus external to the head. It may be unilateral, bilateral, or lateral dominant. It is commonly described as a ringing, buzzing, roaring, hissing, whistling, humming, cricket-like, or pulsing sound. It is frequently a symptom associated with hearing loss, Meniere's disease, acoustic neuroma, drug toxicity, depression, or an autoimmune inner ear disease. The sound may be internal and perceived only by the patient, called subjective or tonal tinnitus, or it may be heard by both the patient and the examiner, called objective or nontonal tinnitus.

SYNONYMS

Ringing in the ear(s)

ICD-9CM CODES
388.3 Tinnitus
388.30 Tinnitus, unspecified
388.31 Subjective tinnitus
388.32 Objective tinnitus

ICD-10CM CODES
H93.1 Tinnitus
H93.2 Other abnormal auditory perceptions

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE

- The American Tinnitus Association reports 50 million Americans have tinnitus for >6 mo.
- Prevalence increases with age, peaking for persons aged 65-74 years.
- Prevalence in the United States based on National Health Interview Survey (NHIS) in 1996:
  1. 2.98% all ages
  2. 0.26% for persons <18 yr old
  3. 1.6% for persons aged 18-44 yr
  4. 5.96% for persons aged 45-64 yr: 7.7% males, 4.3% females
  5. 9.6% for persons aged 65-74 yr: 12% males, 7.7% females
  6. 7.6% for persons >75 yr old: 11.4% males, 5.3% females
  7. 2:1 South/Northeast regions
- Up to 18% of people in industrialized societies are mildly affected by chronic tinnitus, and 0.5% report tinnitus having a severe effect on their daily life.

PREDOMINANT SEX AND AGE: Persons most affected are male, caucasian, elderly, persons with hearing impairment, persons living in southern United States. For military veterans, tinnitus is the third most common service-related disability

RISK FACTORS: Any condition causing hearing loss or damage to the auditory system can produce tinnitus. Cochlear damage from exposure to noise is the most common cause. Exposure to ototoxic drugs is also important.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- History should focus on exposure to loud noises, evidence of hearing loss, ototoxic drugs.
- Patient should be screened for depression.
- Patient who complains of sound in ear may also complain of ear pain or fullness.
- Objective tinnitus is pulsatile and coincides with patient's pulse.
- Physical examination should focus on HEENT, neck, and neurologic exam.
- May be no significant physical findings.

ETIOLOGY

- The mechanism behind tinnitus is poorly understood. It may originate at any point along the auditory pathway. Causes of tinnitus include injured cochlear hair cells, spontaneous activity in auditory nerve fibers, hyperactivity in the auditory nuclei in the brain stem, or a reduction in the suppressive activity of the central auditory cortex.
- Medications implicated in causing tinnitus include: salicylates, NSAIDs, aminoglycosides, loop diuretics, valproate, quinine, chemotherapeutic agents, cisplatin, vincristine, heavy metals such as lead.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Subjective/tonal tinnitus:
  1. Otologic: tympanic membrane disorder, inner ear disorder (hair cells, organ of Corti), Meniere's disease
  2. Ototoxic medications
  3. Neurologic: multiple sclerosis, head trauma, cochlear nerve lesion, acoustic schwannoma, neurofibroma, meningioma
  4. Metabolic: thyroid disorder, hyperlipidemia (leading to plaque formation), vitamin B_{12} deficiency
  5. Psychogenic: depression, anxiety, fibromyalgia
  6. Infectious: otitis media, Lyme disease, meningitis, syphilis
- Objective/nontonal tinnitus:
  1. Vascular: arterial bruit, venous hum, arteriovenous malformation, vascular tumors
  2. Neurologic: contraction of muscles of the eustachian tube, contraction of the stapedius muscle, contraction of the tensor tympani muscles, or a palatal myoclonus, glomus jugulare tumor
  3. Conductive: patulous (wide-open) eustachian tube

WORKUP

- Audiometry, tympanometry
- Electronystagmography to evaluate for Meniere's disease
- Box ET1-4 describes useful diagnostic tests. An algorithm for tinnitus evaluation is described in Fig. ET1-39.

LABORATORY TESTS

Evaluate for metabolic abnormalities: TSH, CBC, B_{12}, lipid panel.

IMAGING STUDIES

- CT/MRI: to evaluate for subjective tinnitus
- MRI/MRA: to evaluate objective tinnitus

TREATMENT

NONPHARMACOLOGIC THERAPY

It is best to avoid exposure to excessive noise, ototoxic agents, and to wear protective equipment in noisy environments, or mask the tinnitus through amplification of normal sounds with a hearing aid. Habituation techniques such as tinnitus retraining therapy may help. Cognitive behavioral therapy helps patients cope with tinnitus distress through biofeedback.

ACUTE GENERAL Rx

- If the tinnitus is severe enough to cause suicidal symptoms, immediate referral to a psychiatrist and an otolaryngologist is recommended to minimize the time to diagnosis and optimize treatment.
- Patients with persistent symptoms or tinnitus accompanied by visual changes or headache should be evaluated for tumors such as acoustic neuroma.

CHRONIC Rx

There is insufficient evidence to support the use of any medication, vitamin, or nutritional supplement to treat tinnitus.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Possibly effective: acupuncture, relaxation therapy, hypnosis (based on systematic review)

DISPOSITION

Clinical course is variable. About 20% to 25% of patients with chronic tinnitus consider it a significant problem. Individualized tinnitus management programs can be beneficial in most patients.

PEARLS & CONSIDERATIONS

PREVENTION

- Avoid loud, chronic noise and ototoxic drugs.
- Higher caffeine intake is associated with a lower risk of incident tinnitus in women.

PATIENT & FAMILY EDUCATION

- American Tinnitus Association: 800-634-8978, http://www.ata.org

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Tinnitus (Patient Information)

AUTHORS: **VICKY H. BHAGAT, M.D., M.P.H.** and **DAWN HOGAN, M.D.**

EVIDENCE

Abstract[1]

Objectives/Hypothesis:
To evaluate the existing level of evidence for tinnitus management strategies identified in the UK Department of Health's Good Practice Guideline.

Study Design:
Systematic review of peer-reviewed literature and meta-analyses.

Methods:
Searches were conducted in PubMed, Cambridge Scientific Abstracts, Web of Science, and EMBASE (earliest to August 2010), supplemented by hand searches in October 2010. Only randomized controlled trials that used validated questionnaire measures of symptoms (i.e., measures of tinnitus distress, anxiety, depression) were included.

Results:
Twenty-eight randomized controlled trials met our inclusion criteria, most of which provide moderate levels of evidence for the effects they reported. Levels of evidence were generally limited by the lack of blinding, lack of power calculations, and incomplete data reporting in these studies. Only studies examining cognitive behavioral therapy were numerous and similar enough to perform meta-analysis, from which the efficacy of cognitive behavioral therapy (moderate effect size) appears to be reasonably established. Antidepressants were the only drug class to show any evidence of potential benefit.

Conclusions:
The efficacy of most interventions for tinnitus benefit remains to be demonstrated conclusively. In particular, high-level assessment of the benefit derived from those interventions most commonly used in practice, namely hearing aids, maskers, and tinnitus retraining therapy needs to be performed. Ⓐ

Evidence-Based Reference

Hoare DJ et al.: Systematic review and meta-analysis of randomized controlled trials examining tinnitus management, *Laryngoscope* 121:1555–1564, 2011. Ⓐ

SUGGESTED READINGS

Baguley DM: Hyperacusis, *J R Soc Med* 96(12):582, 2003.

Folmer RL et al.: Tinnitus: questions to reveal the cause, answers to provide relief, *J Fam Pract* 53(7):532–540, 2004.

Glicksman JT et al.: A prospective study of caffeine intake and risk of incident tinnitus, *Am J Med* 127:739–743, 2014.

Henry JA et al.: General review of tinnitus: prevalence, mechanisms, effects, and management, *J Speech Lang Hear Res* 48(5):1204–1235, 2005.

Lockwood AH et al.: Tinnitus, *N Engl J Med* 347(12):904–910, 2002.

McFerran DJ, Phillips JS: Tinnitus, *J Laryngol Otol* 121(3):201–208, 2007.

Patterson MB, Balough BJ: Review of pharmacological therapy, *Int Tinnitus J* 12(2):149–159, 2006.

Ropper AH, Samuels MA. Deafness, dizziness, and disorders of equilibrium. In: (editors: Ropper AH, Samuels MA. Adams and Victor's principles of neurology. ed 9 McGraw-Hill: New York.

Savage J, Waddell A: Tinnitus, *Clin Evid (Online)*, 2012. pii 0506.

Weinberger B et al. Mental status and neurological examination in older adults. In: (editor: Halter JB et al. Hazzard's geriatric medicine and gerontology. ed 6 McGraw-Hill: New York.

Weissman JL, Hirsch BE: Imaging of tinnitus: a review, *Radiology* 216(2):342–349, 2000.

BOX ET1-4 Tinnitus

Diagnostic Imaging	Lab Evaluation
Best Tests	***Best Test***
None	None
Ancillary Tests	***Ancillary Tests***
Carotid Doppler ultrasound	CBC
MRI of brain and auditory canals	Lipid panel
Brain MRA	TSH

CBC, Complete blood count; *MRA,* magnetic resonance angiography; *MRI,* magnetic resonance imaging.
From Ferri FF: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging*, ed 2, Philadelphia, 2009, Mosby.

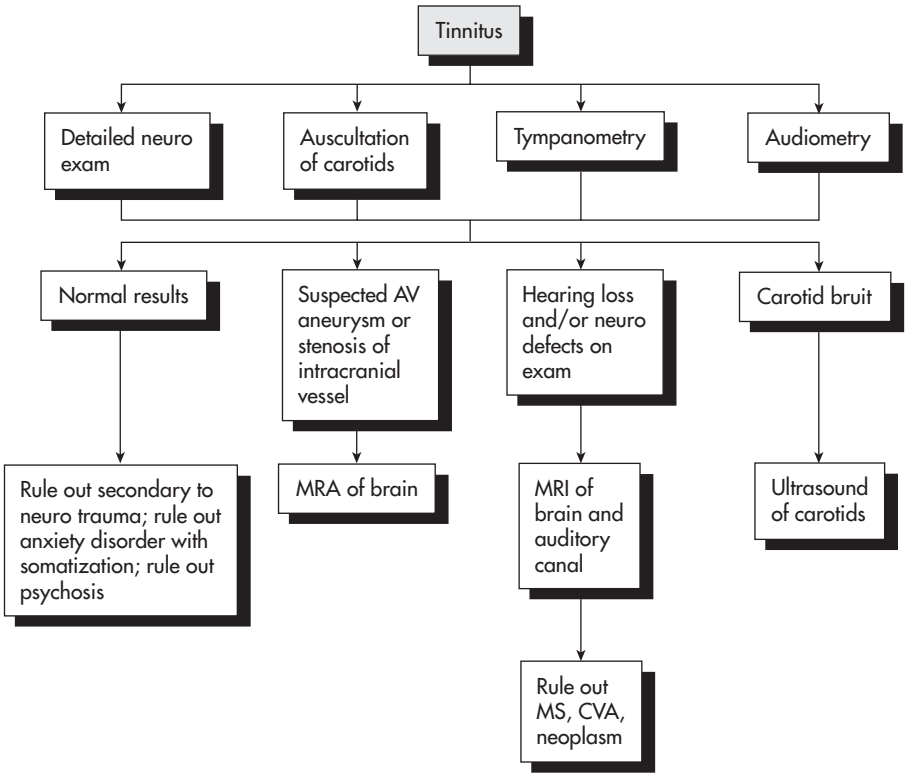


FIGURE ET1-39 Tinnitus evaluation. *AV,* Atrioventricular; *CVA,* cerebrovascular accident; *MRA,* magnetic resonance angiography; *MRI,* magnetic resonance imaging; *MS,* multiple sclerosis. (From Ferri FF: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging*, ed 3, Philadelphia, 2014, Elsevier.)

BASIC INFORMATION

DEFINITION

The term *Torsade de Pointes* (TdP) refers to a polymorphic ventricular tachycardia (VT) associated with a prolonged QT interval and electrocardiographically characterized by QRS complexes of changing amplitude that appear to twist around the isoelectric line, hence the name *Torsade de Pointes*, or "twisting of the points" (Fig. T1-40).

The torsades can be typical when initiated following short-long-short coupling intervals or can be the rarer short-coupled variant initiated by normal short coupling. Typical features of TdP include a markedly prolonged QT interval >500 msec in the beats preceding the onset of the arrhythmia, a polymorphic VT with a ventricular rate of 160 to 250 beats per minute, irregular RR intervals, and a cycling of the QRS axis through 180 degrees every 5 to 20 beats. The TdP typically starts with premature ventricular contractions (PVCs) discharging during the termination of the long T-wave and precipitate successive bursts of VT with the typical twisting appearance of progressive changes in QRS contour and amplitude. It maybe repetitive, nonsustained, or sustained, and may degenerate into ventricular fibrillation.

SYNONYM(S)

Torsades
TdP

ICD-9CM CODES
429.1 Ventricular tachycardia
ICD-10-CM CODE(S)
I47.2 Ventricular tachycardia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: In congenital long QT syndromes (LQTS), TdP may occur in up to 6% cases at rest and 9% of cases during an exercise test. Among drug-induced causes of TdP, the incidence may vary between <1% in cases of antibiotics and antipsychotics to 2% to 4% when caused by class III anti-arrhythmics such as sotalol, ibutilide, and dofetilide. The incidence during intracranial events such as subarachnoid hemorrhage may be as high as 8% if associated with hypokalemia.

PREDOMINANT SEX AND AGE: Women, perhaps due to a longer baseline QT interval, are at greater risk for torsades than men.

GENETICS: If the torsades is due to underlying congenital LQTS, two patterns of inheritance have been identified: the more common autosomal-dominant Romano-Ward and Timothy syndromes, and the much rarer autosomal recessive cases. The latter are usually more severe, often but not always involving consanguineous marriages, and are often associated with congenital deafness (the Jervell Lange-Nielsen syndrome). Mutations in 8 genes have been identified.

RISK FACTORS: TdP in patients with congenital LQTS is often initiated by an external trigger (Table T1-15). Triggers can include exercise, noise, emotion, sudden waking from sleep by an alarm clock, telephone ringing, thunder, swimming, or diving. TdP in LQT1 patients is usually triggered by exercise and swimming, and noise; LQT2 by emotion, pregnancy, or noise; and LQT3 when at rest or asleep. Risk factors for drug-induced TdP are outlined in Table T1-16. Drug-induced TdP is equally common in the hospital setting versus that caused by outpatient drugs, and the risk factors for developing TdP in hospitalized patients are outlined in Table T1-17.

PATHOPHYSIOLOGY

- The electrophysiological mechanisms responsible for torsades are not clearly understood. Most data suggest that early afterdepolarization is responsible for the initiation of torsades. Perpetuation may be caused by transmural entry, triggered activity, or abnormal automaticity. A distinct group of cells called the M cells, located in the mid-myocardium, have prolonged repolarization and may play a role in the genesis of TdP.
- Drugs with the potential to cause TdP most frequently inhibit the rapid potassium channels and result in prolongation of the action potential duration, producing a prolonged QT on ECG.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical features depend on whether the TdP is caused by acquired or congenital long QT syndrome. Congenital LQTS patients may have certain specific triggers, such as noise, exercise, and emotions (see "Risk Factors").
- Symptoms of the tachycardia itself include palpitations, syncope, presyncope, seizures, and sudden cardiac death (SCD).
- Patients resuscitated from SCD have an especially ominous prognosis, with a relative risk of 12.9 of experiencing another cardiac arrest.

ETIOLOGY

The etiology or triggers of TdP may be congenital or acquired causes of QT prolongation (see Table T1-15). For a comprehensive list of drugs that can cause or have the potential to cause Torsade de Pointes, see "Patient/Family Education."

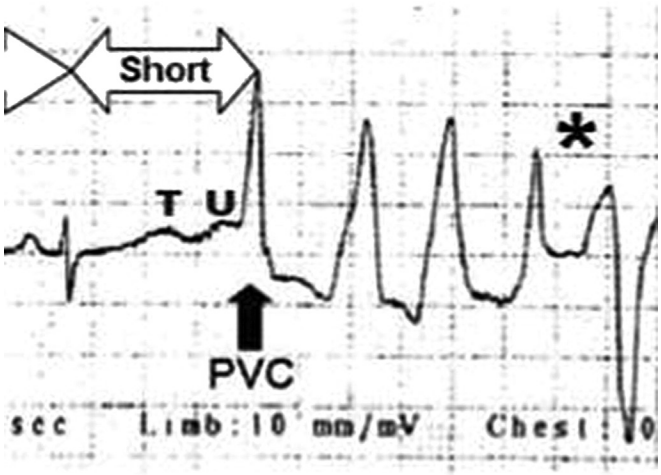


FIGURE T1-40 Onset of TdP during the recording of a standard 12-lead ECG in a young male with a history of drug addiction treated with chronic methadone therapy who presented to a hospital emergency department after ingesting an overdose of prescription and over-the-counter drugs from his parent's drug cabinet. Classic ECG features evident in this rhythm strip include a prolonged QT interval with distorted T-U complex, initiation of the arrhythmia after a short-long-short cycle sequence by a PVC that falls near the peak of the distorted T-U complex, "warm-up" phenomenon with initial R-R cycles longer than subsequent cycles, and abrupt switching of QRS morphology from predominantly positive to predominantly negative complexes (asterisk). (From Drew BJ et al: Prevention of Torsade de Pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation, *J Am Coll Cardiol* 55;934-947, 2010.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Other causes of broad complex tachycardia such as:

- Polymorphic VT.
- Wolff-Parkinson-White (WPW) syndrome with atrial fibrillation.
- SVT with aberrancy.
- ECG artifact.

WORKUP

- ECG and telemetry are the mainstay of diagnosing TdP as they detect the arrhythmia, the preceding prolonged QT interval, and the long-short cycles that trigger it.
- Determination and treatment of the etiology of TdP (see Table T1-15) is key.

LABORATORY TESTS

- Electrolytes.
- Thyroid function tests.
- Genetic studies if suspicion of congenital LQT syndrome.
- Troponin to rule out myocardial infarction.

IMAGING STUDIES

- Echocardiography to rule out structural heart disease as a cause of VT.

TABLE T1-15 Causes and Triggers of Torsade de Pointes

Congenital	
	• Romano-Ward syndrome [autosomal dominant]
	• Jervell Lange-Nielsen syndrome [autosomal recessive]
	• LQTS channelopathies
Acquired	
Metabolic syndromes	
	• Hypokalemia
	• Hypocalcemia
	• Hypomagnesemia
	• Starvation
	• Anorexia nervosa
	• Liquid protein diets
	• Hypothyroidism
Bradyarrhythmias	
	• Sinus node dysfunction
	• Second- or third-degree AV block
Antiarrhythmic drugs	
	• Quinidine
	• Procainamide
	• Disopyramide
	• Amiodarone and dronedarone
	• Sotalol
	• Dofetilide, ibutilide, azimilide
Antimicrobial drugs	
	• Erythromycin, clarithromycin, azithromycin
	• Pentamidine
	• Azole antifungals like voriconazole
	• Fluoroquinolones such as levofloxacin & moxifloxacin
	• Chloroquine
Antihistaminics	
	• Terfenadine
	• Astemizole
Psychiatric drugs	
	• Phenothiazines
	• Thioridazine
	• Tricyclic antidepressants
	• Haloperidol
	• Risperidone
	• Selective serotonin reuptake inhibitors
Antineoplastic agents	
	• Tyrosine kinase inhibitors such as sunitinib, dasatinib
	• Vorinostat
	• Arsenic
Gastric motility agents	
	• Cisapride, domperidone
Opioid dependence drugs	
	• Methadone
Other factors	
	• Myocardial ischemia
	• Hypothermia
	• Intracranial disease
	• HIV infection
	• Connective tissue disease with anti-Ro/SSA antibodies
	• Periodic paralysis (Andersen syndrome)
	• Cocaine

TABLE T1-16 Risk Factors for Drug-Induced Torsade de Pointes

- Congenital long QT
- Female gender
- Electrolyte abnormalities (hypokalemia, hypomagnesemia, hypocalcemia)
- Diuretic use
- Bradycardia
- Cardiac hypertrophy
- Myocardial fibrosis
- Congestive heart failure
- Renal and liver insufficiency
- Coadministration of drugs blocking P450 isoenzyme CYP3A4
- High doses or rapid intravenous infusion of the drug
- Baseline electrocardiographic abnormalities (prolonged QT, T-wave lability)

From Gowda RM et al: Torsades de Pointes: the clinical considerations, *Int J Cardiol* 96(1):1-6, 2004.

TABLE T1-17 Risk Factors for Torsade de Pointes in Hospitalized Patients

- Clinically recognizable risk factors
- QTc >500 msec
- LQT2-type repolarization: notching
- Use of QT-prolonging drugs
- Concurrent use of more than one QT-prolonging drug
- Rapid infusion by intravenous route
- Heart disease
- Congestive heart failure
- Myocardial infarction
- Advanced age
- Female sex
- Hypokalemia
- Hypomagnesemia
- Hypocalcemia
- Treatment with diuretics
- Impaired hepatic drug metabolism
- Bradycardia
- Sinus bradycardia, heart block, incomplete heart block with pauses
- Premature complexes leading to short-long-short cycles
- Multiple clinically recognizable risk factors
- Clinically silent risk factors
- Occult (latent) congenital LQTS
- Genetic polymorphisms

From Drew B.J.; et al. Prevention of Torsade de Pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation, *Circulation* 121(8):1047, 2010.

- Stress test to rule out myocardial ischemia. Stress ECG may sometimes unmask underlying long QT syndromes and related TdP.
- CT scan of the head if intracranial disease is suspected.
- Fig. T1-41 shows Torsades de Pointes in a teenage patient with long QT syndrome.

Rx TREATMENT

The cornerstone of treatment comprises intravenous magnesium, overdrive pacing, and isoproterenol. Withdrawal of causative drugs and correction of underlying causes such as electrolyte imbalances, hypothermia, ischemia, and so on is also key

NONPHARMACOLOGIC THERAPY

- Withdrawal of any offending drugs and correction of electrolyte abnormalities are recommended in patients presenting with Torsades de Pointes (Class I recommendation).
- Temporary atrial or ventricular overdrive pacing is a Class I recommendation for all causes of TdP if intravenous magnesium fails.
- Acute and long-term pacing is recommended for patients presenting with TdP due to heart block and symptomatic bradycardia (Class 1) or those with recurrent pause-dependent torsades (Class IIa).
- Active internal and external rewarming if hypothermia is the etiology.
- If TdP degenerates into ventricular fibrillation, defibrillation and advanced cardiac life support protocol should be followed.

ACUTE GENERAL Rx

- Intravenous magnesium sulfate 1-2 g given over 1-2 min is first-line therapy for patients

FIGURE T1-41 Torsades de Pointes in a teenage patient with long QT syndrome. This arrhythmia is associated with no pulse and results in syncope. It often terminates spontaneously, but otherwise rapidly degenerates to ventricular fibrillation. (From Fuhrman: *Pediatric critical care,* ed 4, 2010, Elsevier.)

who present with LQTS and few episodes of Torsades de Pointes (Class IIa). Magnesium is not likely to be effective in patients with a normal QT interval
- Isoproterenol is reasonable as temporary treatment in patients with acute disease who present with recurrent pause-dependent TdP and who do not have congenital LQTS (Class IIa).
- Beta-blockade combined with pacing is reasonable acute therapy for patients who present with TdP and sinus bradycardia (Class IIa).
- Potassium repletion to 4.5 to 5 mmol/L may be considered for patients who present with torsades de points (Class IIb).
- Intravenous lidocaine, oral mexiletine, or phenytoin may be considered in patients who present with LQT3 and Torsade de Pointes (Class IIb).

CHRONIC Rx

- TdP resulting from congenital LQTS is treated with beta-blockade, pacing, and implantable cardioverter-defibrillator (ICD) in high-risk cases. For patients who continue to have syncope despite maximal drug therapy, cervicalthoracic sympathectomy may be considered.
- Long-term pacing is recommended for patients presenting with TdP due to heart block and symptomatic bradycardia.
- Avoid use of QT-prolonging drugs.
- Lifestyle modification in case of congenital LQTS.
- In patients with eating disorders, nutritional rehabilitation will correct the QT prolongation over the long term (3 to 18 mo).
- Psychiatric evaluation of patients with drug overdose and eating disorders.

DISPOSITION

Patients with TdP should be monitored in an intensive care setting.

REFERRAL

Patients should have an urgent cardiology consultation.

PEARLS & CONSIDERATIONS

COMMENTS

- Identification of the etiology for TdP is key in diagnosis, management, and prognosis of this condition.
- Drugs associated with TdP vary greatly in their risk for arrhythmia; an updated list can be found at www.qtdrugs.org. The risk-benefit ratio should be assessed for each individual to determine whether the potential therapeutic benefit of a drug outweighs the risk for TdP.
- Risk factors for drug-induced TdP include older age, female sex, heart disease, electrolyte disorders (especially hypokalemia and hypomagnesemia), renal or hepatic dysfunction, bradycardia or rhythms with long pauses, treatment with more than one QT-prolonging drug, and genetic predisposition.
- After initiation of a drug associated with TdP, ECG signs indicative of risk for arrhythmia include an increase in QTc from predrug baseline of >60 msec, marked QTc interval prolongation >500 msec, T-U wave distortion that becomes more exaggerated in the beat after a pause, visible T-wave alternans, new-onset ventricular ectopy, and couplets and nonsustained polymorphic ventricular tachycardia initiated in the beat after a pause.

PREVENTION

The 2011 AHA/ACC scientific statement on prevention of TdP suggests a strategy of documenting the QTc interval before and at least every 8 to 12 hr after the initiation, increased dose, or overdose of QT-prolonging drugs. If QTc prolongation is observed, documentation of more frequent measurements is recommended. The duration of QTc monitoring depends upon the duration of treatment with the QT-prolonging drug and the drug half-life.

PATIENT/FAMILY EDUCATION

- Patients should be educated about avoiding use of QT-prolonging drugs. A complete list of these drugs can be found at www.qtdrugs.org or at http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm.
- First-degree relatives of all patients with congenital LQTS should undergo genetic testing.
- Congenital LQTS patients should avoid certain specific triggers (e.g., swimming and exercise in LQTS 1 and LQTS 2 and acoustic stimuli in LQTS 2).
- It is recommended that all patients affected by LQTS avoid competitive sports activity.

RELATED TOPICS

Long QT Syndrome (Related Key Topic)

AUTHOR: **GAGAN SAHNI, M.D.**

SUGGESTED READINGS

Drew BJ et al.: Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation, *Circulation* 121(8):1047, 2010.

Oppenheimer SM et al.: Cerebrogenic cardiac arrhythmias. Cerebral electrocardiographic influences and their role in sudden death, *Arch Neurol* 47(5):513, 1990.

Zipes DP et al.: ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines, *J Am Coll Cardiol* 4(5):e247, 2006.

BASIC INFORMATION

DEFINITION

Torticollis is a contraction or contracture of the muscles of the neck that causes the head to be tilted to one side. It is usually accompanied by rotation of the chin to the opposite side with flexion (Fig. T1-42). Usually it is a symptom of some underlying disorder. This term is often used incorrectly in cases when the torticollis may simply be positional.

SYNONYMS

Twisted neck
"Wry neck"
Spasmodic torticollis

ICD-9CM CODES

723.5 Spastic (intermittent) torticollis
754.1 Congenital muscular (sternocleidomastoid)
333.83 Spasmodic

ICD-10CM CODES

M43.6 Torticollis
Q68.0 Congenital deformity of sternocleidomastoid muscle
G24.3 Spasmodic torticollis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Congenital muscular torticollis:
  1. Palpable soft tissue "mass" in the sternocleidomastoid shortly after birth
  2. Mass gradually subsides, leaving a shortened, contracted sternocleidomastoid muscle
  3. Head characteristically tilted toward the side of the mass and rotated in the opposite direction
  4. Facial asymmetry and other secondary changes persisting into adulthood
- Spasmodic torticollis:
  1. "Spasms" in the cervical musculature; may be bilateral and uncontrollable
  2. Head often tilted toward the affected side
- Findings in other cases depend on etiology

ETIOLOGY

Torticollis has been found to have more than 50 different causes:

- Localized fibrous shortening of unknown cause involving the sternocleidomastoid, leading to the condition termed *congenital muscular torticollis*
- Spasmodic torticollis: of uncertain etiology, possibly a variant of dystonia musculorum deformans
- Infection, specifically pharyngitis, tonsillitis, retropharyngeal abscess
- Miscellaneous rare causes: congenital musculoskeletal deformities, trauma, inflammation from rheumatoid arthritis, vestibular disturbances, posterior fossa tumor, syringomyelia, neuritis of spinal accessory nerve, and drug reactions

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Usually involves separating each disorder from the others
- Acquired positional disorders (e.g., ocular disturbances, acute disk herniation)

WORKUP

- Workup depends on the clinical situation.
- Laboratory studies are usually not helpful unless infection or rheumatoid disease is suspected.
- Section II describes a differential diagnosis for the evaluation and therapy of neck pain.
- Any child with a gradually increasing torticollis should have a complete eye examination.

IMAGING STUDIES

- Plain radiographs in cases of trauma or to rule out congenital abnormalities
- MRI in appropriate cases
- Electrodiagnostic studies: only rarely indicated to rule out neurologic causes

TREATMENT

- Congenital muscular torticollis: gentle stretching exercises carried out by the parent
- Spasmodic torticollis: physical therapy, psychotherapy, cervical braces, biofeedback, and pain control
- Focal dystonia responds well to injections of botulinum toxin type A or B.
- Other forms: treated according to etiology

DISPOSITION

- Most patients with congenital muscular torticollis respond well to conservative treatment.
- Spasmodic torticollis is often resistant to normal conservative treatment.
- Prognosis of other forms of torticollis depends on etiology.

REFERRAL

- Torticollis often requires a multidisciplinary approach unless the etiology is obvious.
- Children usually do not require any specific studies; however, an orthopedic consultation is recommended.
- Fixed deformity in the child; may need orthopedic referral for surgical release.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Torticollis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

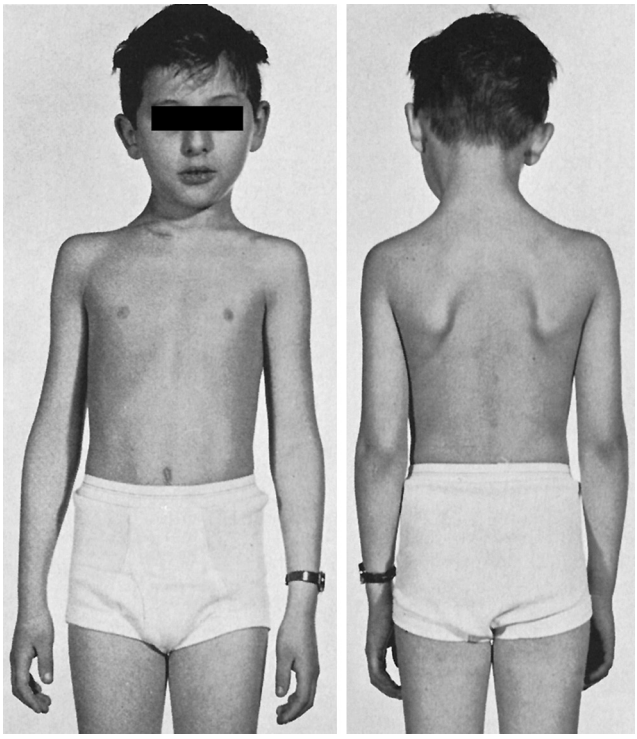


FIGURE T1-42 Torticollis. In this child, the right sternocleidomastoid muscle is contracted. (From Brinker MR, Miller MD: *Fundamentals of orthopaedics,* Philadelphia, 1999, Saunders.)

SUGGESTED READINGS

Crowner BE: Cervical dystonia: disease profile and clinical management, *Phys Ther* 87:1511, 2007.

Ferreira JJ et al.: The management of cervical dystonia, *Expert Opin Pharmacother* 8(2):129, 2007.

Hosalkar HS et al.: Congenital osseous anomalies of the upper cervical spine, *J Bone Joint Surg Am* 90A:337, 2008.

Papadimitriou NG et al.: Acute torticollis after isolated stress fracture of the first rib in a child, *J Bone Joint Surg Am* 87A:2537, 2005.

Parikh SN et al.: Magnetic resonance imaging in the evaluation of infantile torticollis, *Orthopedics* 27:509, 2004.

Sankar WN et al.: Orthopedic conditions in the newborn, *J Am Acad Orthop Surg* 17:112, 2009.

Slawek J et al.: Factors affecting the health-related quality of life of patients with cervical dystonia and the impact of botulinum toxin type A injections, *Funct Neurol* 22(2):95, 2007.

BASIC INFORMATION

DEFINITION

Tics are sudden, brief, intermittent involuntary or semi-voluntary movements (motor tics) or sounds (phonic or vocal tics) that mimic fragments of normal behavior.

Tourette's syndrome (TS) is an inherited neuropsychiatric disorder characterized by motor, vocal, and phonic tics that change during the course of illness. Onset is typically before age 18 (new-onset tics can occasionally occur after age 18 yr, but for DSM-IV criteria of TS, they must begin before this age).

SYNONYMS

Gilles de la Tourette syndrome
TS
Tourette's disorder

ICD-9CM CODES
307.23 Gilles de la Tourette disorder
ICD-10CM CODES
F95.2 Combined vocal and multiple motor tic disorder [de la Tourette]

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE (IN U.S.): Unknown; estimates range from 0.7% to 5%.
PREDOMINANT SEX: Approximate male/female ratio of 3:1.
PREDOMINANT AGE: Typical age of onset is between 2 and 15 yr (mean 5 to 7 yr).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Neurologic examination is normal.
- Vocal and/or phonic tics could be simple (clearing of throat, sniffing, grunting or sucking sounds) or complex (repetitive short phrases, e.g., "you bet," swearing [coprolalia]).
- Motor tics can be simple (e.g., blinking, grimacing, head jerking) or complex (e.g., gesturing). Tics wax, wane, and change over time. Often they can be suppressed for short periods. Commonly they are preceded by an urge to perform the tic.
- TS is often associated with a variety of behavioral symptoms, most commonly attention deficit hyperactivity disorder (ADHD) and obsessive-compulsive disorder (OCD).

TS can be diagnosed using the DSM-5 criteria as follows:

1. Both multiple motor and one or more vocal tics must be present at some time during the illness, although not necessarily concurrent.
2. The tics may wax and wane in frequency but have persisted for >1 year since first tic onset.
3. Age at onset is <18 yr.
4. Disturbance is not attributable to the direct physiologic effects of a substance (e.g., stimulants) or a general medical condition (e.g., Huntington's disease or postviral encephalitis).

ETIOLOGY

Exact pathogenesis is unknown. Genetic predisposition is likely as there is a strong family history of OCD or TS in patients with tics, and twin studies provide evidence for the importance of genetic factors. Recent analysis of linkage in a two-generation pedigree has led to the identification of a mutation in the HDC gene encoding l-histidine decarboxylase, the rate-limiting enzyme in histamine biosynthesis, pointing to a role for histaminergic neurotransmission in the mechanism and modulation of Tourette's syndrome and tics (Fig. T1-43). Immunologic dysfunction is being explored in the pathogenesis of this complex disorder.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Sydenham's chorea: occurs after infection with group A *Streptococcus.*
- PANDAS: pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection.
- Sporadic tic disorders: tend to be motor or vocal but not both.
- Head trauma.
- Drug intoxication: many drugs are known to induce or exacerbate tic disorder, including methylphenidate, amphetamines, pemoline, anticholinergics, and antihistamines.
- Postinfectious encephalitis.

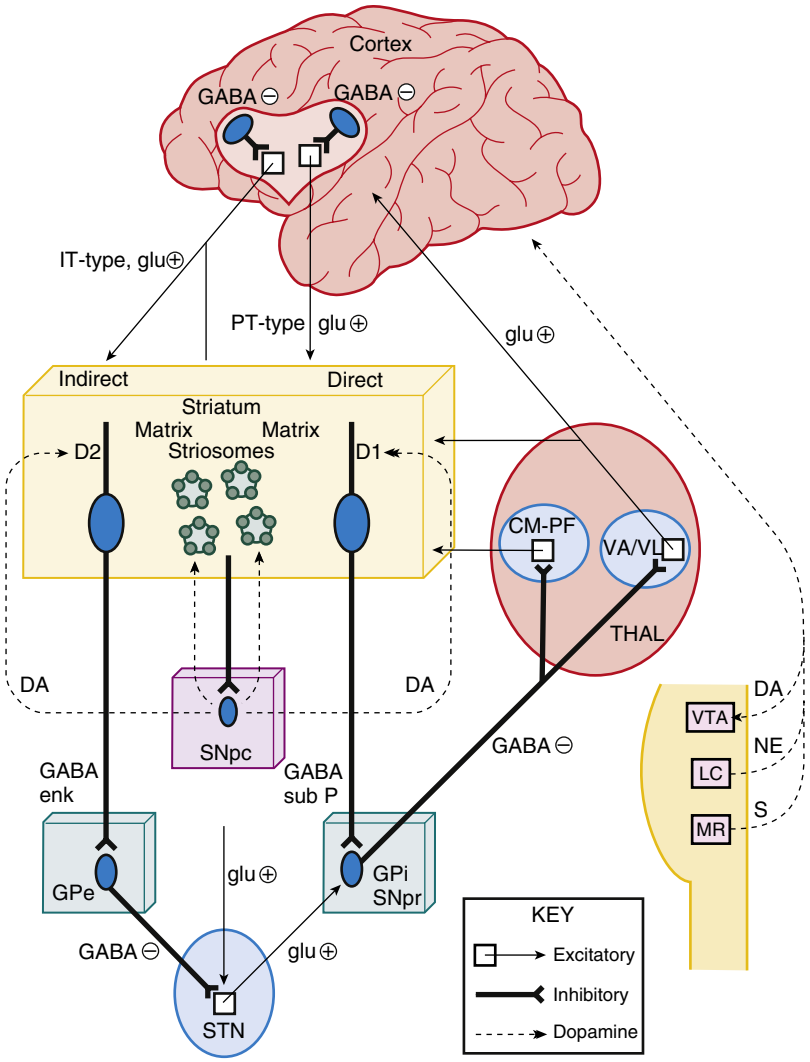


FIGURE T1-43 The cortico-striatal-thalamo-cortical pathway and ascending cortical inputs. Hypothesized abnormalities have included disorders of excess excitation or diminished inhibition, disruptions in frontal cortex, striatum, or striosomes, and abnormalities of various synaptic neurotransmitters. *CM-PF,* Centromedian-parafascicular complex; *DA,* dopamine; *enk,* enkephalins; *GABA,* gamma-aminobutyric acid; *glu,* glutamate; *GPe,* globus pallidus externa; *GPi,* globus pallidus interna; *IT,* intra telencephalic; *LC,* locus coeruleus; *MR,* median raphe; *NE,* norepinephrine; *PT,* pyramidal tract; *S,* serotonin; *SNpc,* substantia nigra pars compacta; *SNpr,* substantia nigra pars reticulata; *STN,* subthalamic nucleus; *sub P,* substance P; *THAL,* thalamus; *VA/VL,* ventral anterior/ve ntral lateral nuclei; *VTA,* ventral tegmental area. (From Harris K and Singer HS. Tic disorders: Neural circuits, neurochemistry, and neuroimmunology. *J Child Neurology* 2006;21:678–689.)

- Inherited disorders: Huntington's disease, Hallervorden-Spatz disease, and neuroacanthocytosis. All these conditions should have other observed abnormalities on neurologic examination.

WORKUP

Clinical observation and history to confirm diagnosis.

LABORATORY TESTS

No definitive laboratory tests.

IMAGING STUDIES

CT scan and MRI of brain are normal and unnecessary in the absence of abnormal neurologic examination.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

Multidisciplinary: education of parents, teachers, psychologists, and school nurses is essential. Cognitive behavioral therapy termed habit-reversal treatment is efficacious in suppressing tics.

ACUTE GENERAL Rx

Dopamine-blocking agents may be used to reduce severity of tics acutely (e.g., haloperidol 0.25 mg PO qhs initially). There are risks of side effects, such as acute dystonic reactions.

CHRONIC Rx

Tics only require treatment when they interfere with psychosocial, educational, and occupational functioning of a person.

TICS:

- Alpha-2 agonists like clonidine and guanfacine are used for treatment of motor tics and are considered by some experts as first-line medications because of their favorable adverse effect profile. However, they are more beneficial for treatment of behavioral symptoms and should be preferred for patients with predominant psychiatric problems.
- Haloperidol and pimozide are the only neuroleptics that are approved by U.S. FDA for the treatment of tics in TS. Pimozide is started as 0.5 to 1.0 mg at night and increased every 5 to 7 days to therapeutic dose of 2 to 8 mg. Haloperidol is started as 0.25 to 0.5 mg and can be increased to 1 to 4 mg depending on response and side effects. Use of neuroleptics carries a small but significant risk of tardive dyskinesia.
- Tetrabenazine: dopamine-depleting agent can be used effectively in TS patients for control of tics. It does not cause many of the typical side effects of the neuroleptics but is not readily available. Severe depression may occur with use of this medication.
- Dopamine agonists: a few small, open-label studies have found that ropinirole and pramipexole in low doses may be effective in reducing tic severity.
- Botulinum toxin local injection is effective for focal tics like eye blinking and neck and shoulder tics. The benefits are temporary, lasting 3 to 6 mo.
- Surgical treatment with deep brain stimulation has also been reported effective in some patients with disabling tics that are refractory to medications.

ADHD: Stimulants (dextroamphetamine, methylphenidate) are useful for symptoms of ADHD but may exacerbate tics in 25% of patients, but should be used if troublesome behavioral symptoms persist.

OCD: Selective serotonin reuptake inhibitors, such as fluoxetine, are the most effective.

DISPOSITION

- In the later teen years, intensity and frequency of tics typically diminish.
- One third of patients will achieve significant remission, although complete, lifelong remission is rare.
- One third will have mild, persistent, but "non-impairing" tics.

REFERRAL

To a neurologist to confirm initial diagnosis and for treatment in difficult cases.

PEARLS & CONSIDERATIONS

- Tics do not need treatment unless they interfere with an individual's ability to function.
- Greater improvement in symptom severity among children with Tourette's and chronic tic disorder has been reported with a comprehensive behavioral intervention compared with supportive therapy and education.
- An important part of treatment is appropriate evaluation and therapy of coexisting conditions (e.g., ADHD, OCD).
- Deep brain stimulation (DBS) has shown some promising results as an alternative therapy in patients with medically refractory disease.

COMMENTS

Patient education may be obtained from the Tourette's Syndrome Association, 4240 Bell Blvd., Bayside, NY 11361-2864; 800-237-0717 or 718-224-2999; http://www.tsa-usa.org.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Tourette's Syndrome (Patient Information)

AUTHOR: **FARIHA ZAHEER, M.D.**

SUGGESTED READINGS

Ercan-Sencicek AG et al.: l-Histidine decarboxylase and Tourette's syndrome, *N Engl J Med* 362:1901–1908, 2010.

Hartmann A et al.: Pharmacological treatment of Gilles de la Tourette syndrome, *Neurosci Biobehav Rev*, 2009. pii: S0149–7634(12)00181-9, [Epub ahead of print].

Kenney C et al.: Tourette's syndrome, *Am Fam Physician* 77(5):651, 2008.

Kurlan R: Tourette's syndrome, *N Engl J Med* 363:2332–2338, 2010.

Marcus D, Kurlan R: Tics and its disorders, *Neurol Clin* 19(3):735–758, 2001.

Piacentini J et al.: Behavior therapy for children with Tourette disorder, *JAMA* 303(19):1929–1937, 2010.

Pringsheim T: Tics, *Curr Opin Neurol* 16:523–527, 2003.

Sandor P: Pharmacological management of tics in patients with TS, *J Psychosom Res* 55:41–48, 2003.

Savica R et al.: Deep brain stimulation in Tourette syndrome: a description of 3 patients with excellent outcome, *Mayo Clin Proc* 87(1):59–62, 2012.

BASIC INFORMATION

DEFINITION

Toxic epidermal necrolysis (TEN) is a rare, acute, life-threatening mucocutaneous disease that is characterized by whole epidermal keratinocyte death resulting in dermal-epidermal separation of more than 30% body surface area (BSA). TEN and Steven-Johnson Syndrome (SJS) were initially described as separate entities, but are now considered to be variants of the same spectrum of disease, with similar clinical, histopathologic, and pathogenic features. SJS involves less than 10% BSA, SJS-TEN overlap involves 10–30% BSA, and TEN involves more than 30% BSA. TEN and SJS are caused by a hypersensitivity reaction to medications.

SYNONYMS

Lyell's syndrome

ICD-9CM CODES
695.15 Toxic epidermal necrolysis
ICD-10CM CODES
L51.2 Toxic epidermal necrolysis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE:
Annual incidence is two to seven cases per million per year
PREDOMINANT SEX AND AGE:
Women/men ratio 1.5:1
GENETICS: Some ethnic groups are more susceptible to developing TEN to certain medications when having specific human leukocyte antigen (HLA) alleles: e.g., to carbamazepine in Asians and East Indians with HLA-B*1502 and Europeans with HLA-A*3101, or to allopurinol in Han Chinese with HLA-B*5801.
RISK FACTORS: Slow acetylator genotypes, immunosuppression, and concomitant administrations of radiotherapy and anticonvulsants increase the risk for TEN.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The lesions in TEN are dynamic and follow a sequence of changes characterized below.

- *Early*: Fever, stinging eyes, pain upon swallowing may precede cutaneous manifestations by 2 to 7 days.
- *Later*: Generalized, dusky red, purpuric macules of irregular size and shape, with tendency to coalesce. Nikolsky sign positive (top layers of the skin slip away from the lower layers when slightly rubbed), detachment of large sheets of necrotic epidermis, extreme skin pain, mucosal involvement, anxiety, and asthenia. As the necrotic epidermis detaches from the underlying dermis, flaccid blisters form. The blisters can be extended sideways by slight pressure with a finger as more necrotic epidermis is displaced laterally (Asboe–Hansen sign). TEN patients resemble burn victims clinically, as well as in morbidity and mortality.
- *Resolution*: Scarring may develop when healing (joint contractures, eye complications, strictures of esophagus, anus, vagina, urethra).

ETIOLOGY

Exfoliation of the epidermis is due to extensive keratinocyte apoptosis. Several mechanisms have been postulated to explain the keratinocyte apoptosis. These include drug- or cytotoxic T-cell–mediated expression of FasL, perforin, granulysin, and granzyme B by keratinocytes.

Medications most commonly associated with the development of TEN are shown in Table T1-18. Medications other than those listed in Table T1-18 have been classified to carry a lower risk, a doubtful risk, or being without evidence for a risk to induce TEN (see references).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Steven-Johnson syndrome +SJS/TEN overlap
- Erythema multiforme-major (mostly postinfectious)
- Staphylococcal scalded skin syndrome
- Generalized fixed drug eruptions
- Paraneoplastic pemphigus
- Drug-induced linear IgA bullous dermatosis

WORKUP

Identification of TEN is based on the clinical findings of epidermal detachment of more than 30% BSA, mucous membrane involvement, and full-thickness epidermal necrolysis, as described by pathology. A complete medication history should be taken including a time line outlining when new medications were started before the onset of the clinical symptoms. TEN most commonly occurs between 1 and 4 weeks after starting a new drug, but can occur at any time. Risk assessment should be done by using the SCORTEN mortality prognostic indicator (see Table T1-19). Workup for the patient is similar to burn patients.

TABLE T1-18 Medications Most Commonly Causing TEN

Allopurinol	Cotrimoxazole
Sulfa-drugs	Aminopenicillins
Carbamazepine	Cephalosporins
Phenobarbital	Quinolones
Phenytoin	Minocycline
Phenylbutazone	Trimethoprim-Sulfamethoxazol
Lamotrigine	Amithiozone (thioacetazone)
Nevirapine	Antiretroviral drugs, especially NNRTIs
Oxicam NSAIDS	
Thiacetazone	

LABORATORY TESTS

In addition to the skin biopsy, no specific laboratory test is available to diagnose TEN. Standard chemistry to monitor electrolyte and fluid balance and organ function (e.g., serum urea, bicarbonate, glucose; see Table T1-19) should be monitored as in burn patients.

IMAGING STUDIES

N/A

TREATMENT

Withdrawing the offending drug reduces the risk of death by 30% per day and is the single most important measure in the management of TEN.

NONPHARMACOLOGIC THERAPY

- *Symptomatic treatment:*
  - SCORTEN > 1: transfer to intensive care unit / burn unit
  - Fluid replacement
  - Peripheral venous access (preferably in non-involved areas)
  - Increased environmental temperature (30°C)
  - Air-fluidized bed
  - Early nutritional support through nasogastric tube
  - Aseptic procedures, frequent culturing of skin, blood, urine specimens
  - No prophylactic antibiotics
  - Prophylactic anticoagulation
  - Nonadhesive wound dressings, porcine xenografts, human allografts, autologous skin grafts, skin substitutes
  - Daily ophthalmologic exam/consultation; artificial tears, antibiotic eyedrops every 2 hours; early mechanical disruption of synechia
  - Regular mouth washes with antiseptic/antifungal solutions

ACUTE GENERAL Rx

There is no consensus for the optimal pharmacologic treatment of TEN.

- High dose steroids may be effective in the initial course of the disease, but probably increase mortality later on due to infectious complications (sepsis).

TABLE T1-19 SCORTEN Mortality Prognostic Indicator

Prognostic Factor	Points	SCORTEN	Mortality (%)
Age >40 yrs	1	0-1	3.2
Heart rate >120 bpm	1	2	12.1
Cancer/hematologic malignancy	1	3	35.8
BSA involved more than 10% on day 1	1	4	58.3
Serum urea level >28 mg/dL	1	>5	90
Serum bicarbonate level <20 mEq/L	1		
Serum glucose level >252 mg/dL	1		

- Administration of high dose IVIg over 3-4 days may reduce TEN associated mortality (e.g., by blocking Fas-FasL interaction).
- Other agents that may also be effective in the treatment of TEN include cyclosporine, cyclophosphamide, plasmapheresis, and N-acetylcysteine.

DISPOSITION

Late withdrawal of the causative drug is associated with a less favorable outcome/increased mortality. If he/she survives, the patient may suffer debilitating and disfiguring scars and contractures, requiring extensive physical therapy and/or surgical interventions.

PEARLS & CONSIDERATIONS

COMMENTS

Early recognition and prompt discontinuation of the culprit drug saves lives.

PREVENTION

In order to prevent recurrences, it is of pivotal importance that patients are never again exposed to the drug that caused TEN. This also includes chemically related medications. Avoiding any drugs that have caused less severe drug reactions in the past is important for primary prevention of TEN.

RELATED CONTENT

Erythema Multiforme-Major (Related Key Topic)
Steven-Johnson Syndrome (Related Key Topic)

DRUG REACTIONS

Third-Degree Burns

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHORS: **GANARY DABIRI, M.D., Ph.D.,** and **THOMAS M. RÜNGER, M.D., Ph.D.**

SUGGESTED READINGS

Bastuji-Garin S et al: SCORTEN: A severity-of-illness score for toxic epidermal necrolysis, *J Invest Dermatol* 115:49, 2000.

Schwartz RA et al: CME: Toxic epidermal necrolysis Part 1, *J Am Acad Dermatol* 69:173.e1–13, 2012.

Schwartz RA et al: CME: Toxic epidermal necrolysis Part 2, *J Am Acad Dermatol* 69:187.e1–16, 2012.

Trent JT et al: Use of SCORTEN to accurately predict mortality in patients with toxic epidermal necrolysis in the United States, *Arch Dermatol* 140:890, 2004.

Villano JH, Lovell EO: Mixed signals: toxic epidermal necrolysis, *Am J Med* 128(3):254–256, 2015.

BASIC INFORMATION

DEFINITION

Toxic megacolon is a rare but severe complication of colonic inflammation, usually inflammatory bowel disease (IBD). It is characterized by total or segmental nonobstructive colonic distension (>6 cm) associated with systemic toxicity of inflammatory or infectious etiology.

SYNONYMS

Toxic dilatation of the colon

ICD-9-CM CODES
564.7 Megacolon other than Hirschsprung's
ICD 10-CM CODES
K59.3 Megacolon, not elsewhere classified
A04.7 Megacolon due to *Clostridium difficile*

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Varies depending on etiology. Incidence in patients with ulcerative colitis (UC) is between 7% and 10% and approximately 1% and 5% in patients with Crohn's. *Clostridium difficile* infections may be complicated by toxic megacolon in up to 3% of cases.
PEAK INCIDENCE: N/A
PREVALENCE: N/A
PREDOMINANT SEX AND AGE: With increasing rates of *Clostridium difficile (C. diff)* infections due to overuse of antibiotics and hypervirulent strains, patients aged 65 and older are at higher risk for developing toxic megacolon as a result of *C. diff* infection.
GENETICS: There are no known genetic factors that predispose patients to developing toxic megacolon associated with an inflammatory or infectious etiology.
RISK FACTORS: Major risk factors include inflammatory, infectious, and ischemic conditions of the colon, especially in individuals who are immunocompromised. Other risk factors include hypokalemia, use of narcotics or antidiarrheal agents, pregnancy, and recent instrumentation (such as colonoscopy).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with toxic megacolon usually appear severely ill. Clinical symptoms are similar to those of IBD and acute colitis and may include abdominal pain, diarrhea (usually bloody), and vomiting.
- Physical exam findings may include a distended, tender, and tympanic abdomen with reduced or absent bowel sounds. The patient may also present with signs of shock such as fever, tachycardia, mental status changes, and hypovolemia.
- Laboratory findings may include leukocytosis, anemia, and electrolyte abnormalities such as hypokalemia and hypoalbuminemia.

ETIOLOGY

- Most common etiologies are inflammatory conditions such as UC, Crohn's, and Behcet's disease.
- Infectious etiologies such as *C. diff, Salmonella, Shigella, E. coli,* cytomegalovirus, and *Entamoeba* can also be complicated by toxic megacolon.
- Other less common etiologies include ischemic colitis, malignancy such as lymphoma, and Kaposi's sarcoma. In general, toxic megacolon is more likely to complicate pancolitis than segmental colitis (Box T1-5).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Ischemic colitis, Crohn's disease, ulcerative colitis

WORKUP

- General principles of workup include physical examination to evaluate for an acute abdomen condition, laboratory testing to detect electrolyte abnormalities, and plain radiography to evaluate for colonic dilatation.
- Clinical criteria for toxic megacolon, proposed by Jalan et al in 1969, are still used. A diagnosis can be made if radiographic evidence of colonic distention > 6 cm is present with at least three of the following: fever > 38°C, heart rate > 120, leukocytosis > 10.5, or anemia. In addition, at least one of the following must also be present: dehydration, altered level of consciousness, electrolyte abnormalities, or hypotension.

LABORATORY TESTS

- Initial testing should include a CBC, full chemistry panel, lactic acid, coagulation panel, liver function panel, and a type and screen

IMAGING STUDIES

- All patients should initially receive a plain abdominal radiograph to assess for colonic dilatation. Common findings include mucosal irregularity, loss of haustrations, "thumb printing" due to bowel wall edema, and thickening of the colonic wall with a continuous segment of air-filled colon > 6 cm in diameter. The transverse or right colon is usually the most dilated segment seen.
- Computed tomography (CT) has been increasingly used to assess disease extent and for surgical planning. It can also be helpful when differentiating between the various etiologies of toxic megacolon and to assess for complications such as intraabdominal hemorrhage or abscess.

BOX T1-5 Disorders Associated With Toxic Megacolon

Inflammatory bowel disease
- Ulcerative colitis
- Crohn's disease

Infectious colitis
- *Salmonella*, *Shigella*, amoebic colitis
- *Clostridium difficile*
- Cytomegalovirus colitis
- HIV infection

Cancer chemotherapy
Ischemia

HIV, Human immunodeficiency virus.
From Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

TREATMENT

Treatment includes both medical and surgical options. Principles of initial management include treating the underlying cause and managing symptoms of shock with early surgical and gastroenterology consultation.

NONPHARMACOLOGIC THERAPY

- Surgery may be required in up to 50% of patients with toxic megacolon who do not show clinical improvement within 24 to 48 hours. The preferred first-line surgical treatment is subtotal colectomy with an end ileostomy. Other options include total proctocolectomy or colon decompression via the Turnbull method.
- Timing of surgical treatment is still controversial, with many advocating for aggressive medical treatment and observation before surgical intervention. Definitive indications for early surgical treatment include perforation, persistent colonic hemorrhage, or rapid clinical deterioration.

ACUTE GENERAL Rx

- Medications that impact colonic motility such as anticholinergics, opioids, and antidiarrheal agents should be discontinued and avoided.
- Electrolyte abnormalities, dehydration, and anemia are common clinical findings and should be addressed early. Fluid resuscitation with an isotonic solution (normal saline or lactated Ringer's) and correction of electrolyte disturbances (especially hypokalemia) can help prevent worsening atony of the colonic wall. Patients with anemia from colonic hemorrhage should receive blood transfusion.
- Patients with systemic signs of infection or a suspected infectious etiology should receive broad-spectrum antibiotics. Infections due to *C. diff* should be treated with vancomycin (oral or rectal) or metronidazole (oral or IV). Toxic megacolon due to cytomegalovirus should be treated with ganciclovir IV.
- Patients with inflammatory etiologies such as UC or Crohn's should receive high-dose IV steroids, either hydrocortisone 100 mg IV or methylprednisolone 60 mg IV. Steroids should not be used in patients with a confirmed infectious etiology.
- There are no data to currently support empiric treatment of toxic megacolon due to IBD with cyclosporine or infliximab. These treatment options should be reserved for

patients who are not steroid responsive, and should be limited to one attempt at clinical improvement so as not to delay surgical intervention.

CHRONIC Rx

- Patients with IBD will need continued treatment for the underlying disease process once the acute processes associated with toxic megacolon have resolved.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

- N/A

DISPOSITION

- All patients with toxic megacolon will require admission, possibly to the intensive care unit depending on their clinical presentation.

REFERRAL

- Surgical consultation in all cases.
- All patients with toxic megacolon due to newly diagnosed IBD who are discharged from the hospital should be referred to a gastroenterologist for continued treatment.

PEARLS & CONSIDERATIONS

COMMENTS

- Early recognition and treatment of toxic megacolon is critical given the associated high morbidity and mortality.
- Anticholinergic medications, antidiarrheal agents, and opioids can precipitate or worsen toxic megacolon.
- Management includes medical and surgical treatment with in-patient hospitalization and treatment of the underlying cause.

PREVENTION

- Prevention focuses on treatment of underlying causes of colitis to prevent complications such as toxic megacolon.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Crohn's Disease (Related Key Topic)
Clostridium Difficile Infection (Related Key Topic)
Small Bowel Obstruction (Related Key Topic)
Ulcerative Colitis (Related Key Term)

AUTHOR: **STEVEN ROUGAS, M.D., M.S.**

SUGGESTED READINGS

Autenrieth DM, Baumgart DC: Toxic megacolon, *Inflamm Bowel Dis* 18:584–591, 2012.

Strong SA: Management of acute colitis and toxic megacolon, *Clin Colon Rectal Surg* 23:274–284, 2010.

Kman NE, Werman HA: Disorders presenting primarily with diarrhea. In Tintinalli JE, Stapczynski J, Ma O, Cline DM, Cydulka RK, Meckler GD,T, editors: *Tintinalli's emergency medicine: a comprehensive study guide*, ed 7, New York, 2011, McGraw-Hill.

BASIC INFORMATION

DEFINITION

Toxic shock syndrome (TSS) is an acute febrile illness resulting in multiple organ system dysfunction caused most commonly by a bacterial exotoxin. Disease characteristics also include hypotension, vomiting, myalgia, watery diarrhea, vascular collapse, and an erythematous sunburnlike cutaneous rash that desquamates during recovery.

SYNONYMS

TSS

ICD-9CM CODES
040.89 Toxic shock syndrome
ICD-10CM CODES
A48.3 Toxic shock syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- Case reported incidence peak: 14 cases per 100,000 menstruating women annually in 1980; has since fallen to one case per 100,000 persons
- Occurs most commonly between ages 10 and 30 yr in healthy, young, menstruating white females
- Case fatality ratio of 3%

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fever (>38.0° C)
- Diffuse macular erythrodermatous rash that involves both skin and mucous membranes, resembles sunburn, and also involves the palms and soles. The rash then desquamates 1 to 2 wk after disease onset in survivors
- Orthostatic hypotension
- Gastrointestinal symptoms: vomiting, diarrhea, abdominal tenderness
- Constitutional symptoms: myalgia, headache, photophobia, rigors, altered sensorium, conjunctivitis, arthralgia
- Respiratory symptoms: dysphagia, pharyngeal hyperemia, strawberry tongue
- Genitourinary symptoms: vaginal discharge, vaginal hyperemia, adnexal tenderness
- End-organ failure
- Severe hypotension and acute renal failure
- Hepatic failure
- Cardiovascular symptoms: disseminated intravascular coagulation, pulmonary edema, acute respiratory distress syndrome (ARDS), endomyocarditis, heart block

ETIOLOGY

- Menstruation-associated TSS: 45% of cases associated with tampons, diaphragm, or vaginal sponge use.
- Non–menstruation-associated TSS: 55% of cases associated with puerperal sepsis, post–cesarean section endometritis, mastitis, sinusitis, wound or skin infection, septorhinoplasty, pelvic inflammatory disease, respiratory infections following influenza, enterocolitis, and burns.
- Causative agent: *Staphylococcus aureus* infection of a susceptible individual (10% of population lacking sufficient levels of antitoxin antibodies), which liberates the disease mediator TSST-1 (exotoxin). While most cases are caused by methicillin-susceptible *S. aureus* (MSSA), cases of TSS from methicillin-resistant *S. aureus* (MRSA) have occurred, particularly those due to the more virulent community-associated MRSA strains.
- *S. aureus* exotoxins are superantigens that can activate large numbers of T cells (up to 20% at one time) resulting in a massive cytokine production: interleukin (Il-1), Il-2, TNF, and interferon gamma that then mediate the signs and symptoms of the disease.
- Other causative agents: coagulase-negative streptococci producing enterotoxins B or C, and exotoxin A–producing group A beta-hemolytic streptococci.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Staphylococcal food poisoning
- Septic shock
- Mucocutaneous lymph node syndrome
- Scarlet fever
- Rocky Mountain spotted fever
- Meningococcemia
- Toxic epidermal necrolysis
- Kawasaki syndrome
- Leptospirosis
- Legionnaires' disease
- Hemolytic-uremic syndrome
- Stevens-Johnson syndrome
- Scalded skin syndrome
- Erythema multiforme
- Acute rheumatic fever

WORKUP

Broad-spectrum syndrome with multiorgan system involvement and variable but acute clinical presentation, including the following:

- Fever (>38° C)
- Classic desquamating rash (1 to 2 wk)
- Hypotension/orthostatic systolic blood pressure ≤90 mm Hg
- Syncope
- Negative throat and cerebrospinal fluid cultures
- Negative serologic test for Rocky Mountain spotted fever, rubeola, and leptospirosis
- Clinical involvement of three or more of the following:
  - Cardiopulmonary: ARDS, pulmonary edema, endomyocarditis, second- or third-degree atrioventricular block
  - Central nervous system: altered sensorium without focal neurologic findings
  - Hematologic: thrombocytopenia (platelets <100,000)
  - Liver: elevated liver function test results
  - Renal: >5 cells/high-power field, negative urine cultures, azotemia, and increased creatinine (double normal)
  - Mucous membrane involvement: vagina, oropharynx, conjunctiva
  - Musculoskeletal: myalgia, creatine phosphokinase twice normal
  - Gastrointestinal: vomiting, diarrhea

LABORATORY TESTS

- Pan culture (cervix and vagina, throat, nasal passages, urine, blood, cerebrospinal fluid, wound) for *Staphylococcus, Streptococcus* (Table T1-20), and other pathogenic organisms
- Electrolytes to detect hypokalemia, hyponatremia
- Complete blood count with differential and clotting profile for anemia (normocytic or normochromic), thrombocytopenia, leukocytosis, coagulopathy, and bacteremia
- Chemistry profile to detect decreased protein, increased aspartate aminotransferase, increased alanine aminotransferase, hypocalcemia, elevated blood urea nitrogen and creatinine, hypophosphatemia, increased lactate dehydrogenase, increased creatine phosphokinase
- Urinalysis to detect white blood cells (>5 cells/high-power field), proteinemia, microhematuria
- Arterial blood gases to assess respiratory function and acid-base status
- Serologic tests considered for Rocky Mountain spotted fever, rubeola, and leptospirosis

TABLE T1-20 Staphylococcal versus Streptococcal Toxic Shock Syndrome

Feature	Staphylococcal	Streptococcal
Age	Primarily 15-35 yr	Primarily 20-50 yr
Gender	Higher frequency in women	Men and women equally affected
Severe pain	Rare	Common
Hypotension	100%	100%
Erythroderma rash	Very common	Less common
Renal failure	Common	Common
Bacteremia	Low frequency	60%
Tissue necrosis	Rare	Common
Predisposing factors	Tampons, surgery	Cuts, burns, varicella
Thrombocytopenia	Common	Common
Mortality rate	<3%	30%-70%

From Mandell GL et al: *Principles and practice in infectious diseases,* ed 7, Philadelphia, 2008, Churchill Livingstone.

IMAGING STUDIES

- Chest x-ray examination to evaluate pulmonary edema
- ECG to evaluate arrhythmia
- Sonography, CT scan, or MRI considered if pelvic abscess or tubo-ovarian abscess suspected

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- For optimal outcome: high index of suspicion and early and aggressive supportive management in an ICU setting
- Aggressive fluid resuscitation (maintenance of circulating volume, cardiac output, systolic blood pressure)
- Thorough search for a localized infection or nidus: incision and drainage, debridement, removal of tampon or vaginal sponge
- Central hemodynamic monitoring, Swan-Ganz catheter, and arterial line for surveillance of hemodynamic status and response to therapy
- Foley catheter to monitor hourly urine output
- Possible military antishock trousers as temporary measure
- Acute ventilator management if severe respiratory compromise
- Renal dialysis for severe renal impairment
- Surgical intervention for indicated conditions (i.e., ruptured tubo-ovarian abscess, wound abscess, mastitis)

ACUTE GENERAL Rx

- Isotonic crystalloid (normal saline solution) for volume replacement following "7-3" rule (refers to the response in millimeters of mercury [mm Hg] of the pulmonary artery wedge pressure to volume replacement).
- Electrolyte replacement (K^+, C^+)
- Packed red blood cells, coagulation factor replacement, fresh frozen plasma to treat anemia or dilation and curettage.
- Vasopressor therapy for hypotension refractory to fluid volume replacement (e.g., dopamine beginning at 2 to 5 μg/kg/min)
- Steroids have been used but are not generally recommended due to lack of evidence of benefit.
- It is not clear whether antibiotics alter the course of acute TSS. Most authors recommend that patients receive 10 to 14 days of combination antibiotic therapy. In staphylococcal TSS, effective agents are clindamycin (900 mg IV every 8 hr in adults or 25 to 40 mg/kg per day in children) plus vancomycin (adults: 30 mg/kg per day IV in two divided doses; children: 40 mg/kg per day IV in four divided doses). Oxacillin or nafcillin sodium (2 g IV every 4 hr in adults; children: 100 to 150 mg/kg per 24 hr divided in four doses) can be used instead of vancomycin if TSS due to MSSA. An alternative to vancomycin is linezolid.
- In streptococcal TSS, effective agents are penicillin G 24 million units/day in divided doses *plus* clindamycin 900 mg IV q8h. Alternative agents are ceftriaxone 2 g IV q24h *plus* clindamycin 900 mg IV q8h.
- Broad-spectrum antibiotic including gram-negative coverage added if concurrent sepsis suspected with TSS.
- Intravenous immune globulin (IVIG): while no controlled trials exist, most authors recommend IVIG (400 mg/kg in a single dose administered over several hours) in severe cases of TSS that are not responding to fluids or vasopressors. It may neutralize superantigen and decrease tissue damage.
- Tetracycline added if considering Rocky Mountain spotted fever.

CHRONIC Rx

- Severely ill patient: may require prolonged hospitalization and supportive management with gradual recovery and/or sequelae from severe end-organ involvement (ARDS or renal failure requiring dialysis)
- Majority of patients: complete recovery
- Early-onset complications (within 2 wk):
  - Skin desquamation
  - Impaired digit sensation
  - Denuded tongue
  - Vocal cord paralysis
  - Acute tubular necrosis
  - ARDS
- Late-onset complications (after 8 wk):
  - Nail splitting and loss
  - Alopecia
  - Central nervous system sequelae
  - Renal impairment
  - Cardiac dysfunction
- Recurrent TSS:
  - More common in menstruation-related cases.
  - Less common in patients treated with beta-lactamase–resistant antistaphylococcal antibiotics.
  - Patients with history of TSS: if suspect signs and symptoms occur, have high index of suspicion and low threshold for evaluation and treatment.
  - Screen for nasal carriage of *S. aureus* in patients with *S. aureus* TSS and treat with mupirocin in those with positive cultures.

PREVENTION

- Avoidance of tampons or use of low-absorbency tampons only (<4 hr in situ) and alternate with napkins
- Education for patients concerning signs and symptoms of TSS
- Avoidance of tampons for patients with history of TSS

DISPOSITION

- Complete recovery for most patients
- Long-term management of early- and late-onset complications for minority of patients

REFERRAL

- For multidisciplinary management, involving primary physician, gynecologist, internist, infectious disease specialist, and other supportive care specialists
- To tertiary-level hospital

PEARLS & CONSIDERATIONS

COMMENTS

Patient information is available from American College of Gynecologists and Obstetricians.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Toxic Shock Syndrome (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Issa NC et al.: Staphylococcal toxic shock syndrome: suspicion and prevention are keys to control, *Postgrad Med* 110(4):55, 2001.

Lappin E, Ferguson AJ: Gram-positive toxic shock syndromes, *Lancet Infect Dis* 9(5):281–290, 2009.

BASIC INFORMATION

DEFINITION

Toxoplasmosis is an infection caused by the protozoal parasite *Toxoplasma gondii.*

ICD-9CM CODES
130.9 Toxoplasmosis
ICD-10CM CODES
B58.9 Toxoplasmosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.)
- 3% to >50% of healthy adults (seroprevalence)
- Increases with age
- Increases with certain activities
  1. Slaughterhouse workers
  2. Cat owners
- Increases with certain geographic locations: high prevalence of cats

PREDOMINANT SEX: Equal gender distribution
PREDOMINANT AGE
- Infancy (congenital infection)
- Prevalence increases with age

PEAK INCIDENCE: Temperate climates
GENETICS: Congenital infection: 400 to 4000 cases/yr in the United States.
- Incidence and severity vary with the trimester of gestation during which the mother acquired infection.
  1. 10% to 25% (first trimester)
  2. 30% to 54% (second trimester)
  3. 60% to 65% (third trimester)
- Congenital infection occurring in the first trimester is the most severe.
- 89% to 100% of infections in the third trimester are asymptomatic.
- Risk to the fetus is not correlated with symptoms in the mother.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Acquired (immunocompetent host)
  1. 80% to 90% asymptomatic
  2. Adenopathy (usually cervical)
  3. Fever
  4. Myalgias
  5. Malaise
  6. Sore throat
  7. Maculopapular rash
  8. Hepatosplenomegaly
  9. Chorioretinitis rare
- Acquired (in patients with AIDS, CD4 count <100)
  1. 89% of symptomatic cases
     a. Encephalitis
     b. Intracerebral mass lesions
  2. Pneumonitis
  3. Chorioretinitis
  4. Other end organ
- Acquired (immunocompromised patients)
  1. Encephalitis
  2. Myocarditis (especially in heart transplant patients)
  3. Pneumonitis
- Ocular infection in the immunocompetent host
  1. Congenital infection
  2. Blurred vision
  3. Photophobia
  4. Pain
  5. Loss of central vision if macula involved
  6. Focal necrotizing retinitis
  7. Typically presents in second or third decade
- Congenital
  1. Results from acute infection acquired by the mother within 6 to 8 wk before conception or during gestation
  2. Usually, asymptomatic mother
  3. No sign of disease
  4. Chorioretinitis
  5. Blindness
  6. Epilepsy
  7. Psychomotor or mental retardation
  8. Intracranial calcifications
  9. Hydrocephalus
  10. Microcephaly
  11. Encephalitis
  12. Anemia
  13. Thrombocytopenia
  14. Hepatosplenomegaly
  15. Lymphadenopathy
  16. Jaundice
  17. Rash
  18. Pneumonitis
  19. Most infected infants are asymptomatic at birth

ETIOLOGY

- *Toxoplasma gondii*
  1. Ubiquitous intracellular protozoan
  2. Present worldwide
  3. Cat is definitive host (Fig. ET1-44)
- Human infection
  1. Ingestion of oocysts shed by cats in soil, litter boxes, vegetables
  2. Ingestion of inadequately cooked meat containing tissue cysts
  3. Vertical transmission

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Lymphadenopathy
  1. Infectious mononucleosis
  2. Cytomegalovirus (CMV) mononucleosis
  3. Cat-scratch disease
  4. Sarcoidosis
  5. Tuberculosis
  6. Lymphoma
  7. Metastatic cancer
- Cerebral mass lesions in immunocompromised host
  1. Lymphoma
  2. Tuberculosis
  3. Bacterial abscess
- Pneumonitis in immunocompromised host
  1. *Pneumocystis jirovecii (carinii)* pneumonia
  2. Tuberculosis
  3. Fungal infection
- Chorioretinitis
  1. Syphilis
  2. Tuberculosis
  3. Histoplasmosis (competent host)
  4. CMV
  5. Syphilis
  6. Herpes simplex
  7. Fungal infection
  8. Tuberculosis (AIDS patient)
- Myocarditis
  1. Organ rejection in heart transplant recipients
- Congenital infection
  1. Rubella
  2. CMV
  3. Herpes simplex
  4. Syphilis
  5. Listeriosis
  6. Erythroblastosis fetalis
  7. Sepsis

WORKUP

- Acute infection, immunocompetent host
  1. CBC
  2. *Toxoplasma* serology (IgG, IgM) in serial blood specimens 3 wk apart
  3. Lymph node biopsy if diagnosis uncertain
- Immunocompromised host
  1. CNS symptoms
     a. Cerebral CT scan or MRI if CNS symptoms present
     b. Spinal tap, if safe
     c. Brain biopsy if no response to empiric therapy
  2. Ocular symptoms
     a. Funduscopic examination
     b. Serologic studies
     c. Rarely, vitreous tap
  3. Pulmonary symptoms
     a. Chest x-ray examination
     b. Bronchoalveolar lavage
     c. Transbronchial or open-lung biopsy
  4. Myocarditis
     a. Cardiac enzymes
     b. Electrocardiogram
     c. Endomyocardial biopsy for definitive diagnosis
- Toxoplasmosis in pregnancy
  1. Initial maternal screening with IgM and IgG
     a. If negative, mother at risk of acute infection and should be retested monthly
     b. If both IgG and IgM positive, obtain IgA and IgE ELISA, AC/HS test
     c. IgA and IgE ELISA, AC/HS test elevated in acute infection
     d. Ig high for 1 yr or more
     e. IgG repeated 3 to 4 wk later to determine if titer is stable
  2. Acute maternal infection not excluded or documented
     a. Fetal blood sampling (for culture, Ig, IgA, IgE)
     b. Amniotic fluid polymerase chain reaction (PCR)
  3. Fetal ultrasound every other wk if maternal infection documented
- Congenital toxoplasmosis
  1. Placental histology
  2. Specific IgM or IgA in infant's blood

LABORATORY TESTS

- Antibody studies
  1. More than one test necessary to establish diagnosis of acute toxoplasmosis
  2. IgM antibody
     a. Appears 5 days into infection
     b. Peaks at 2 wk

   c. Falls to low level or disappears within 2 mo
   d. May persist at low levels for 1 yr or more
3. Antibody not measurable
   a. Ocular toxoplasmosis
   b. Reactivation
   c. Immunocompromised hosts
4. IgA ELISA, IgE ELISA, and IgE ASAGA
   a. More sensitive tests
   b. Disappear more rapidly than Ig, establishing diagnosis of acute infection
5. IgG antibody
   a. Appears 1 to 2 wk after infection
   b. Peaks at 6 to 8 wk
   c. Gradually declines over months to years

IMAGING STUDIES

- Chest x-ray if pulmonary involvement suspected
- Cerebral CT scan (Fig. T1-45) or MRI if encephalitis suspected

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Selected cases of ocular infection
  1. Photocoagulation
  2. Vitrectomy
  3. Lentectomy
- Selected cases of congenital cerebral infection
  1. Ventricular shunting

ACUTE GENERAL Rx

- Acute infection, immunocompetent host
  1. No treatment, unless severe and persistent symptoms or vital organ damage
- Acute infection, immunocompromised host, non-AIDS
  1. Treat even if asymptomatic

FIGURE T1-45 Toxoplasmic encephalitis in person who has AIDS. A cranial CT scan shows bilateral contrast-enhanced ring lesions with peripheral edema and mass effect. (From Cohen J, Powderly WG: *Infectious diseases,* ed 2, St Louis, 2004, Mosby.)

   2. Duration
      a. Until 4 to 6 wk after resolution of all signs and symptoms
      b. Usually 6 mo or longer
- Reactivated infection, immunocompromised host, non-AIDS
  1. Treat if symptomatic
- Acute or reactivated infection, AIDS
  1. Treat in all cases
  2. Induction course
     a. 3 to 6 wk.
     b. Maintenance therapy continued for life; consider discontinuation of suppressive therapy if the patient has a good response to antiretroviral therapy and if the CD4 count remains >200 cells/mm^3 for more than 3 mo.
  3. Empiric therapy
     a. AIDS with positive IgG
     b. Multiple ring-enhancing lesions on cerebral CT scan or MRI
     c. Response seen by day 7 in 71% and day 14 in 91%
- Ocular infection
  1. Treat in all cases
  2. Therapy continued for 1 mo or longer if needed
  3. Response seen in 70% within 10 days
  4. Retreat as needed
  5. Steroids may be indicated in patients with signs or symptoms of increased intracranial pressure
  6. Surgical treatment in selected cases
- Treatment regimens
  1. Pyrimethamine 200 mg loading dose once PO, then 50 mg (<60 kg) to 75 mg (>60 kg) q day; plus
  2. Leucovorin 10 to 20 mg PO qid, plus
  3. Sulfadiazine 1 (<60 kg) to 1.5 g (>60 kg) PO q6h

Other treatment options (if sulfa hypersensitivity or allergy is present): pyrimethamine 50 to 75 mg/day PO with leucovorin 10 to 20 mg/day PO and either (1) clindamycin 600 mg q6h PO or IV (up to 1200 mg IV) q6h, or (2) clarithromycin 1 g PO bid, or (3) dapsone 100 mg/day PO, or (4) atovaquone 750 mg PO q6h.

- Acute infection in pregnancy
  1. Treat immediately
  2. Risk of fetal infection reduced by 60% with treatment
     a. First trimester
        i. Spiramycin 3 g PO qid in two to four divided doses
        ii. Sulfadiazine 4 g PO qid in four divided doses
     b. Second and third trimester
        i. Sulfadiazine as previously described, *plus*
        ii. Pyrimethamine 25 mg PO qid, *plus*
        iii. Leucovorin 5 to 15 mg PO qid
        iv. Spiramycin as previously described
- Congenital infection
  1. Sulfadiazine 50 mg/kg PO bid, *plus*
  2. Pyrimethamine 2 mg/kg PO for 2 days, then 1 mg/kg PO, three times weekly, *plus*
  3. Leucovorin 5 to 20 mg PO three times weekly
  4. Minimum duration of treatment: 12 mo

CHRONIC Rx

Maintenance therapy in AIDS patients because of the high risk (80%) of relapse
1. Pyrimethamine 25 mg PO qid
2. Sulfadiazine 500 mg PO qid
3. Leucovorin 10 to 20 mg PO qid

DISPOSITION

- Prognosis
  1. Excellent in the immunocompetent host
  2. Good in ocular infection (although relapses are common)
- Treatment of acute infection in pregnancy
  1. Reduces incidence and severity of congenital toxoplasmosis
- Treatment of congenital infection
  1. Improvement in intellectual function
  2. Regression of retinal lesions
- AIDS
  1. 70% to 95% response to therapy

REFERRAL

- To infectious disease expert:
  1. Immunocompromised hosts
  2. Pregnant women
  3. Difficulty in making a diagnosis or deciding on treatment
- To pediatric infectious disease expert:
  1. Congenital infection
- To obstetrician:
  1. Pregnant seronegative mother
  2. Acute seroconversion
- To ophthalmologist:
  1. Congenital infection
  2. Any case of ocular infection

PEARLS & CONSIDERATIONS

COMMENTS

- Prevention of toxoplasmosis is most important in seronegative pregnant women and immunocompromised hosts.
- Patient instructions:
  1. Cook meat to 66° C.
  2. Cook eggs.
  3. Do not drink unpasteurized milk.
  4. Wash hands thoroughly after handling raw meat.
  5. Wash kitchen surfaces that come in contact with raw meat.
  6. Wash fruits and vegetables.
  7. Avoid contact with materials potentially contaminated with cat feces.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Toxoplasmosis (Patient Information)

AUTHOR: **PHILIP A. CHAN, M.D., M.S.**

SUGGESTED READINGS

Boyer KM et al.: Risk factors for *Toxoplasma gondii* infection in mothers of infants with congenital toxoplasmosis: implications for prenatal management and screening, *Am J Obstet Gynecol* 192(2):564, 2005.

Kaye A: Toxoplasmosis: diagnosis, treatment, and prevention in congenitally exposed infants, *J Pediatr Health Care* 25(6):355–364, 2011.

Kravetz JD, Federman DG: Prevention of toxoplasmosis in pregnancy: knowledge of risk factors, *Infect Dis Obstet Gynecol* 13(3):161, 2005.

Montoya JG, Remington JS: Management of *Toxoplasma gondii* infection during pregnancy, *Clin Infect Dis* 47(4):554–566, 2008.

Soheilian M et al.: Prospective randomized trial of trimethoprim/sulfamethoxazole versus pyrimethamine and sulfadiazine in the treatment of ocular toxoplasmosis, *Ophthalmology* 112(11):1876, 2005.

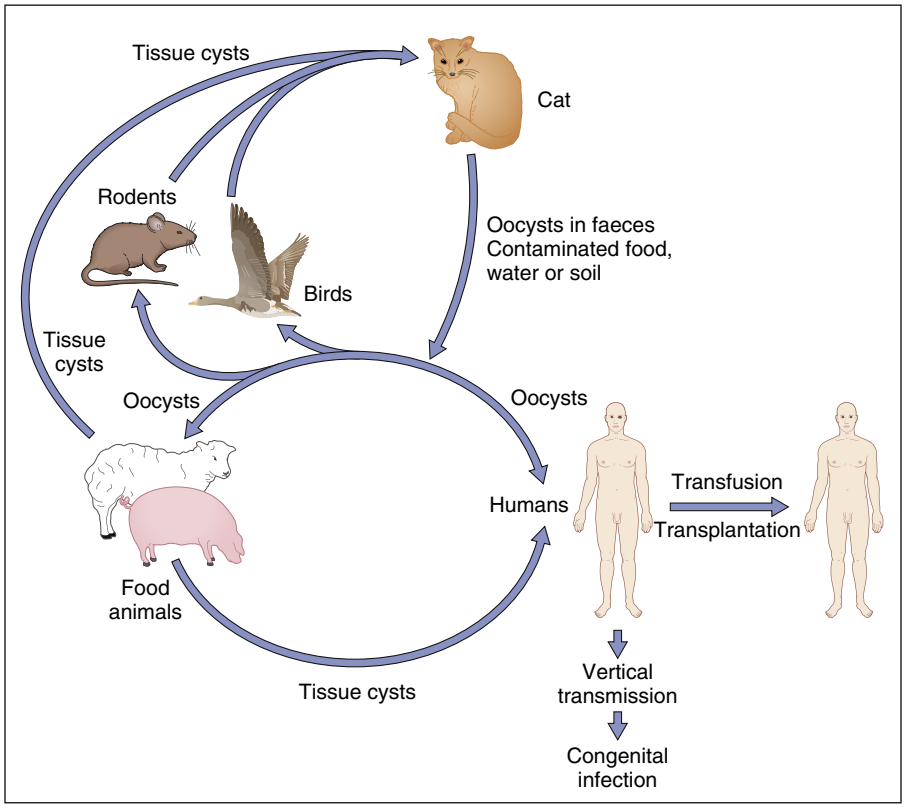


FIGURE ET1-44 Life cycle of *Toxoplasma gondii*. (From Kanski JJ, Bowling B: *Clinical ophthalmology, a systematic approach,* ed 7, Philadelphia, 2010, Saunders.)

BASIC INFORMATION

DEFINITION

Bacterial tracheitis is an acute infectious disease affecting the trachea and large conducting airways. Tracheal inflammation may be caused by a large number of inhaled stimuli, but bacterial infection is a life-threatening illness associated with purulent secretions and subglottic edema.

SYNONYMS

Bacterial tracheobronchitis
Pseudomembranous croup
Membranous laryngotracheobronchitis

ICD-9CM CODES
464.10 Tracheitis
ICD-10CM CODES
J04.1 Acute tracheitis
J04.10 Acute tracheitis without obstruction

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.)
- Uncommon
- May be the most common cause of acute upper airway obstruction requiring admission to pediatric ICUs

PEAK INCIDENCE: Three fourths of cases reported in winter
PREDOMINANT SEX: Boys > girls in one series
PREDOMINANT AGE
- 1 mo to 8 yr
- Almost all <13 yr (most <3 yr)

GENETICS
- Down syndrome is a possible predisposing factor.
- Congenital infection: some cases have been found in those with anatomic abnormalities of the upper airways.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Croupy or "brassy" cough
- Inspiratory stridor (frequent)
- Wheezing (unusual)
- Fever (often >102° F)
- Thick, purulent secretions expectorated
  1. Minority of patients expectorate "ricelike" pellets.
  2. Most patients are unable to mobilize secretions.
     a. Become inspissated
     b. Form pseudomembranes

ETIOLOGY

- *Staphylococcus aureus*
- *Haemophilus influenzae*
- Beta-Hemolytic streptococcal infection
- Secondary to viral infections of the respiratory tract
  1. Primary influenza
  2. Respiratory syncytial virus
  3. Parainfluenza
- Many cases follow measles
  1. Especially when accompanied by chest radiographic infiltrates
  2. Sometimes fatal outcome
  3. Associated with prolonged endotracheal intubation

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Viral croup
- Epiglottitis
- Diphtheria
- Necrotizing herpes simplex infection in the elderly
- Cytomegalovirus in immunocompromised patients
- Invasive aspergillosis in immunocompromised patients

WORKUP

DIRECT LARYNGOSCOPY
1. Typical secretions
   a. May form pseudomembranes
   b. Airway obstruction
2. Normal epiglottis rules out epiglottitis
3. Possible subglottic edema

LABORATORY TESTS

- WBC is sometimes elevated.
- On differential, left shift is almost universal.
- Gram stain and culture of tracheal secretions confirm diagnosis.
- Blood cultures are positive in a minority.

IMAGING STUDIES

- Lateral x-ray examination of neck
  1. Normal epiglottis
  2. Vague density or a "dripping candle" appearance of tracheal mucosa
     a. Secretions
     b. Pseudomembranes
- Chest radiograms
  1. Not diagnostic
  2. Should not be performed on patients in acute respiratory distress, because severe or fatal upper airway obstruction can develop suddenly
- Pneumonic infiltrates frequent
- Atelectasis: unusual but can lead to lobar collapse

TREATMENT

NONPHARMACOLOGIC THERAPY

- Aggressive maintenance of a patent airway
  1. Laryngoscopy or bronchoscopy used diagnostically and therapeutically to strip away pseudomembranes
  2. Voluminous and tenacious secretions suctioned from the underlying friable mucosa
     a. May extend from between the vocal cords to the main carina
     b. Larger channels of rigid instruments for more effective suctioning
- Prevention of complete large airway obstruction
  1. Nasotracheal intubation
  2. Humidification of inspired gas
  3. Frequent saline instillation and suctioning
  4. Intubation with general anesthesia, performed in the operating room, is preferred by some
- Ventilatory support necessary with initial management in ICU

ACUTE GENERAL Rx

- Antibiotic therapy: start immediately, generally continued for 1 to 2 wk
- Initial therapy directed against *H. influenzae* and *S. aureus* (e.g., ceftriaxone and vancomycin)
- Oral therapy is usually sufficient after 5 or 6 days of IV administration

DISPOSITION

- Most patients are extubated in 5 to 6 days after initiating antibiotic therapy.
- Anoxic encephalopathy is reported in 7% of survivors.

REFERRAL

Suspected diagnosis

PEARLS & CONSIDERATIONS

COMMENTS

- Infants are at increased risk of airway obstruction because of the small airway dimension.
- Presence of pneumonia and a staphylococcal cause are thought to worsen prognosis.
- Reported complications: toxic shock syndrome, persistent postextubation stridor, pneumothorax, and volutrauma

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Croup (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Gaugler C et al.: Neonatal necrotizing tracheobronchitis: three case reports, *J Perinatol* 24(4):259, 2004.

Graf J, Stein F: Tracheitis in pediatric patients, *Semin Pediatr Infect Dis* 17(1): 11–13, 2006.

Salamone FN et al.: Bacterial tracheitis reexamined: is there a less severe manifestation? *Otolaryngol Head Neck Surg* 131(6):871, 2004.

Tebruegge M et al.: Bacterial tracheitis: a multi-centre perspective, *Scan J Infect Dis* 41(8):548–557, 2009.

BASIC INFORMATION

DEFINITION

Acute hemolytic transfusion reaction (AHTR) is acute intravascular hemolysis caused by mismatches in the ABO system. It is caused by complement-fixing immunoglobulin (Ig) and IgG antibodies to group A and B red blood cells. Hemolytic transfusion reactions can also be caused by minor antigen systems; however, they are usually less severe. In delayed serologic transfusion reactions, hemolysis with hemoglobinemia is unusual; in delayed reactions the only manifestations may be the development of a newly positive Coombs test and fever. The clinical severity of an ABO-incompatible blood transfusion is significantly influenced by the degree of complement activation and cytokine stimulation. In an extravascular hemolytic transfusion reaction, complement is either not fixed at all or is fixed only to C3b. This presentation is commonly associated with Rh antibodies, but can be seen with any number of non–ABO antigen–antibody complexes.

SYNONYMS

AHTR
Acute hemolytic transfusion reaction

ICD-9CM CODES
999.8 Other transfusion reaction
ICD-10CM CODES
T80.9 Unspecified complication following infusion, transfusion and therapeutic injection
T80.3 ABO incompatibility reaction
T80.4 Rh incompatibility reaction
T80.8 Other complications following infusion, transfusion, and therapeutic injection

EPIDEMIOLOGY & DEMOGRAPHICS

- Acute intravascular hemolysis occurs in one to five per 50,000 transfusions.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Hypotension
- Pain at the infusion site
- Fever, tachycardia, chest pain, dyspnea, dizziness, bronchospasm
- Lower back pain due to ischemic muscle pain or vasospasm rather than kidney pain from developing renal failure
- Severe reactions often occur in surgical patients under anesthesia who are unable to give any warning signs.
- Table T1-21 summarizes signs and symptoms of acute adverse reactions to blood transfusion
- Patients with acute extravascular hemolytic transfusion reactions typically do not present as a clinical emergency. In most cases presentation is with a low-grade fever from the generation of IL-1 or other proinflammatory cytokines. Hemoglobinuria and hemoglobinemia are rarely present unless the amount of incompatible blood infused is excessive.

ETIOLOGY

Most fatal hemolytic reactions are caused by clerical errors and mislabeled specimens.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bacterial contamination of blood
- Hemoglobinopathies

WORKUP

The transfusion must be stopped immediately. The blood bank must be notified, and the donor transfusion bag must be returned to the blood bank along with a freshly drawn posttransfusion specimen.

LABORATORY TESTS

- The direct antiglobulin test (DAT) usually becomes positive in an immune hemolytic reaction (if tested before all the incompatible RBCs are destroyed). Preparation of an antibody eluate is necessary to identify the offending antibody.
- Analyze urine for hemoglobinuria (wine-colored urine), observe plasma for hemoglobinemia (pink plasma).
- Labs: Decreased hematocrit and serum haptoglobin (haptoglobin low to 0 mg/dL). Elevated BUN, creatinine, LDH, bilirubin.
- Monitor coagulation status (PT, aPTT, fibrinogen).

TREATMENT

NONPHARMACOLOGIC THERAPY

- Stop transfusion immediately. Test anticoagulated blood from the recipient for the presence of free hemoglobin in the plasma.
- Monitor vital signs closely, and maintain IV access with a suitable crystalloid or colloid solution.
- Maintain an adequate airway.

ACUTE GENERAL Rx

- Treatment is supportive and consists of fluid resuscitation, vasopressor support, and mannitol.
- Vigorous IV hydration (0.9% NaCl or some other suitable crystalloid solution) to maintain urine flow at >100 ml/hr until hypotension is corrected and hemoglobinuria clears. IV furosemide may be necessary to maintain adequate renal flow.
- The addition of mannitol may prevent renal damage (controversial). Mannitol, if chosen, must be used with caution; if acute tubular necrosis occurs before mannitol infusion, pulmonary edema may occur as a result of the acute increase in intravascular volume secondary to fluid expansion.
- Monitor for the presence of disseminated intravascular coagulation. PT, aPTT, and fibrinogen levels should be closely monitored.
- If sepsis is suspected, culture as appropriate.

DISPOSITION

Mortality rate exceeds 50% in severe transfusion reactions.

PEARLS & CONSIDERATIONS

COMMENTS

Hemolysis caused by minor antigen systems is generally less severe and may be delayed 5 to 10 days after transfusion.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **FRED F. FERRI, M.D.**

TABLE T1-21 Signs and Symptoms of Acute Adverse Reactions to Blood Transfusion

Reaction	Fever	Chills/ Rigors	Nausea/ Vomiting	Chest Discomfort/ Pain	Facial Flushing	Wheezing/ Dyspnea	Back/ Lumbar Pain	Discomfort at Infusion Site	Hypotension
Acute hemolytic	X	X	X	X	X	X	X	X	X
Febrile nonhemolytic	X	X		X	X				
Nonimmune hemolysis									
Acute lung injury	X			X		X			X
Allergic									
Massive transfusion complications									
Anaphylaxis	X	X	X	X	X	X	X	X	X
Passive cytokine infusion	X	X	X			X			
Hypervolemia						X			
Bacterial sepsis	X	X	X				X	X	X
Air embolus				X		X			

From Goldman L, Bennett JC [eds]: *Cecil's textbook of medicine,* ed 22, Philadelphia, 2004, Saunders.

SUGGESTED READING

Sharma S et al.: Transfusion of blood and blood products: indications and complications, *Am Fam Physician* 83(6):719–724, 2011.

BASIC INFORMATION

DEFINITION

Transient ischemic attack (TIA) is a transient episode of neurologic dysfunction caused by focal brain, spinal cord, or retinal ischemia without acute infarction on MRI. TIA symptoms typically resolve within 60 min and almost always within 24 hr.

SYNONYMS

TIA
Amaurosis fugax
"Mini-stroke"
Pre-stroke

ICD-9CM CODES
435.9 Unspecified transient cerebral ischemia
ICD-10CM CODES
G45.9 Transient cerebral ischemic attack, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 49 to 83 cases per 100,000 persons annually
PEAK INCIDENCE: After age 60 yr
PREVALENCE: 200,000 to 500,000 persons in the United States. The annual risk of stroke after a TIA or minor stroke is 3% to 4% approximately.
PREDOMINANT SEX AND RACE: Males > females; African American > Caucasian
RISK FACTORS: Same as for ischemic stroke

PHYSICAL FINDINGS & CLINICAL PRESENTATION

TIAs often present with ipsilateral transient monocular blindness (amaurosis fugax), contralateral numbness or weakness, contralateral homonymous hemianopsia, and/or aphasia.

ETIOLOGY

Embolic (cardioembolism in 10% to 15%), large vessel atherothrombotic disease (20% to 25%), lacunar disease, hypoperfusion, hypercoagulable state, arteritis

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Seizures, hypoglycemia, complicated migraine, intracranial hemorrhage, mass lesion, vestibular disease, Bell's palsy, meningitis, multiple sclerosis, subdural hematoma, brain abscess, cervical or lumbar spine disease, conversion disorder

WORKUP

Given the high risk of stroke within the first 48 hr following TIA (up to 10%), hospital admission for workup is advised. Fig T1-46 describes a TIA algorithm. The American Heart Association recommends that the ABCD2 score be used in the evaluation of TIA. It consists of 1 point for age ≥60 years, 1 point for BP ≥140 mm Hg systolic or ≥90 mm Hg diastolic, clinical features (2 points for unilateral weakness, 1 point for speech impairment), duration of TIA (2 points for duration ≥60 min, 1 point for duration 10-59 min), presence of diabetes mellitus (1 point). According to the guidelines, it is reasonable to hospitalize patients with TIA if they present within 72 hours and have an ABCD2 score ≥3. There is some debate about the usefulness of this scale since it fails to account for changes seen on echocardiogram, carotid Dopplers, or ECG that may place the patient at more imminent risk of stroke (carotid stenosis, Afib, cardiac thrombus, etc). Alternatives to this scoring system are being investigated.

LABORATORY TESTS

Complete blood count, basic metabolic panel, prothrombin time, activated partial thromboplastin time, sedimentation rate, fasting lipid panel, serum glucose and hemoglobin A_{1c} (to detect latent diabetes mellitus)

IMAGING STUDIES

- CT scan should be obtained to exclude hemorrhage; MRI with diffusion weighting if immediately available.
- Imaging of the vessels should be obtained via magnetic resonance angiography (MRA), computed tomography angiography (CTA), or carotid Doppler/transcranial Doppler (CD/TCD).
  1. If symptoms are referable to the posterior circulation, MRA or CTA should be obtained in lieu of CD/TCD.
  2. Transthoracic echocardiogram should be obtained.
  3. An echocardiogram with bubble should be obtained in all patients younger than 50 yr with TIA symptoms.
- Electrocardiogram should be obtained to exclude the presence of arrhythmias, namely atrial fibrillation.

At least 24 hr of heart rhythm monitoring should be accomplished to screen for arrhythmia. Many stroke centers now utilize prolonged ambulatory cardiac rhythm monitoring over several weeks to months to identify paroxysmal atrial fibrillation in select patients when there is a high index of clinical suspicion.

- Paroxysmal atrial fibrillation is common in patients with TIA. A recent study found that noninvasive ambulatory ECG monitoring for 30 days significantly improved the detection of atrial fibrillation by a factor of more than five and nearly doubled the rate of anticoagulant treatment as compared with the standard practice of short duration ECG monitoring.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Carotid endarterectomy or carotid stenting should be considered for patients found to have carotid stenosis as the cause for TIA. Please refer to "Carotid Stenosis" chapter for more information.
- The practice of intracranial angioplasty and stenting has largely declined following the publication of negative results from clinical trials and is only used in select patients who fail maximal medical management with aggressive platelet inhibition, strict risk factor control such as hyperlipidemia, hypertension, diabetes mellitus, weight loss, treatment of sleep apnea and smoking cessation among others.

ACUTE GENERAL Rx

- In the absence of contraindications, patients who are identified to have atrial fibrillation should be considered for anticoagulation with intravenous heparin (or therapeutic lovenox) along with warfarin until target INR between 2.0 and 3.0 is achieved.
- Although no compelling evidence exists for the use of heparin in the acute treatment of TIAs without cardioembolic source, patients who develop recurrent symptoms within the same vascular territory that increase in duration, severity, and/or frequency (crescendo TIA/stuttering TIA) may benefit from its use pending cardiac and vascular imaging and identification of a possible source.

CHRONIC Rx

- Chronic therapy should be aimed at modifying the four major risk factors: hypertension, dyslipidemia, diabetes mellitus, and smoking cessation.
- Antiplatelet therapy should be used to reduce the risk of recurrent TIAs or subsequent stroke. Three antiplatelet agents are commonly used in stroke prevention: aspirin, aspirin/dipyridamole, and clopidogrel. All are reasonable choices but practitioners should consider their individual patient's comorbidities when selecting an antiplatelet agent.
- Dose-adjusted warfarin (INR 2.0 to 3.0) is indicated for prevention of future strokes in atrial fibrillation patients. The direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors apixaban and rivaroxaban have been approved as alternative treatments to warfarin for stroke prevention in atrial fibrillation.

PEARLS & CONSIDERATIONS

- Despite complete symptom resolution, 20% to 50% of patients clinically suspected to have suffered a TIA have evidence of acute tissue infarction on MRI.
- Dual antiplatelet therapy in acute TIA and minor stroke is being evaluated. A recent trial revealed that among patients with TIA or minor stroke who can be treated within 24 hr after the onset of symptoms, the combination of clopidogrel and aspirin is superior to aspirin alone for reducing the risk of stroke in the first 90 days and does not increase the risk of hemorrhage.

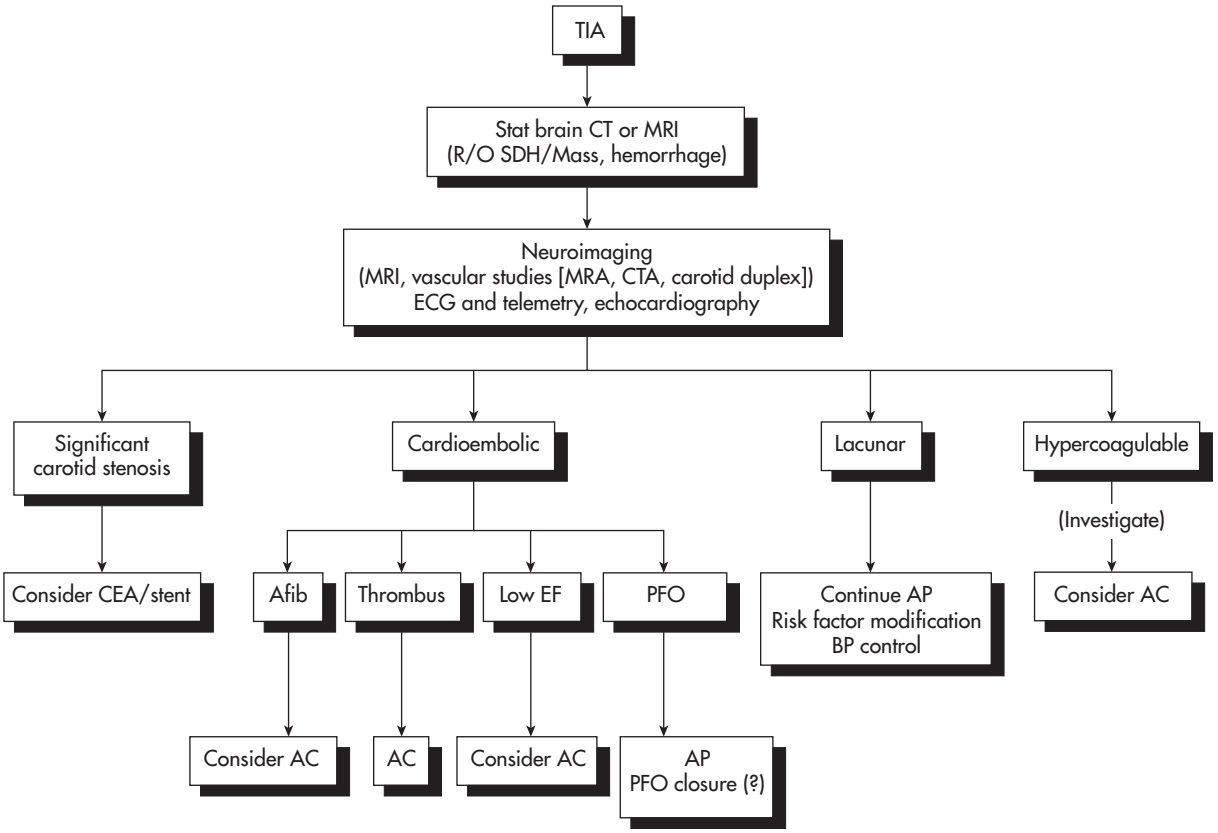


FIGURE T1-46 Transient ischemic attack *(TIA).* *AC,* Anticoagulation; *AP,* antiplatelet; *ASA,* aspirin; *BP,* blood pressure; *CEA,* carotid endarterectomy; *CTA,* CT angiography; *EF,* ejection fraction; *MRA,* magnetic resonance angiography; *PFO,* patent foramen ovale; *SDH,* subdural hematoma.

PREVENTION

A healthy lifestyle and management of cardiovascular risk factors should be encouraged.

PATIENT/FAMILY EDUCATION

Patients should be counseled on the early signs of stroke symptoms and instructed to promptly seek medical attention if they develop symptoms concerning for stroke. Patients should be encouraged to pursue a healthy lifestyle to include exercise and smoking cessation. In addition, patients should take an active role in controlling blood pressure and blood glucose. Further educational materials can be found online at http://www.strokecenter.org/.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Transient Ischemic Attack (TIA) (Patient Information)

AUTHOR: **PRASHANTH KRISHNAMOHAN, M.B.B.S., M.D.**

SUGGESTED READINGS

Davis SM, Donnan CA: Secondary prevention after ischemic stroke or transient ischemic attack, *N Engl J Med* 366:1814–1822, 2012.

Easton JD et al.: Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Council; Council of Cardiovascular Surgery and Anesthesia; Council of Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease, *Stroke* 40:2276–2293, 2009.

Kernan WN et al.: Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association, *Stroke* 45:2160–2236, 2014.

Giles MF, Rothwell PM: Systematic review and pooled analysis of published and unpublished validations of the ABCD and ABCD^2 transient ischemic attack risk scores, *Stroke* 41(4):667–673, 2010.

Gladstone DJ et al.: Atrial fibrillation in patients with cryptogenic stroke, *N Engl J Med* 370:2467–2477, 2014.

Mohr JP et al. Long-term medical management of ischemic stroke and transient ischemic attack due to arterial disease. In: (editor: Mohr J.P.) Stroke: pathophysiology, diagnosis, and management. Sudlow & Warlow: Philadelphia, pp. 1129–1150.

Wang Y et al.: Clopidogrel with aspirin in acute minor stroke or transient ischemic attack, *N Engl J Med* 369:11–19, 2013.

BASIC INFORMATION

DEFINITION

Demyelination in a transverse region of the spinal cord due to an inflammatory process that leads to sensory and motor changes below the lesion. The pathologic hallmark of transverse myelitis is the presence of focal collections of lymphocytes and monocytes with varying degrees of demyelination, axonal injury, and astroglial and microglial activation within the spinal cord.

SYNONYMS

None

ICD-9CM CODES

341.2 Acute (transverse) myelitis
323.82 Other causes of myelitis, transverse myelitis NOS
341.2 Acute (transverse) myelitis

ICD-10CM CODES

G37.3 Acute transverse myelitis in demyelinating disease of central nervous system
G04.89 Other myelitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Annual incidence ranges from 1.3 to 8 cases per million. The incidence increases to 24.6 cases per million annually if acquired demyelination causes such as multiple sclerosis (MS) are included.
PREVALENCE: Unknown
PREDOMINANT SEX: None
GENETICS: No genetic predisposition has been shown.
PEAK INCIDENCE: Bimodal peak in the incidence between 10 to 19 yr and 30 to 39 yr
RISK FACTORS: Infection, vaccination

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The clinical signs are caused by an interruption in ascending and descending neuroanatomic pathways in the transverse plane of the spinal cord, and a resulting sensory level is characteristic of transverse myelitis.
- Rapid onset of symmetric or asymmetric paraparesis or paraplegia of the lower extremities over a few days, ascending paresthesia, trunk sensory level, back pain, sphincter dysfunction, and positive Babinski with upgoing toes bilaterally. The arms may also be involved but less than the legs in most cases.
- One third to one half of patients present with localizing back pain.
- There is progression to nadir of clinical deficits between 4 hr and 21 days after symptom onset.
- Urinary incontinence or retention, GI disturbances (incontinence or constipation), and sexual dysfunction are common.

ETIOLOGY

- Demyelination due to the body's immune response to infection, post-vaccination, multiple sclerosis, or idiopathic (15% to 30% of cases).
- An autoantibody to aquaporin 4 has been identified in transverse myelitis secondary to NMO.
- About 50% of patients have had a recent upper respiratory infection.
- Epstein-Barr virus and cytomegalovirus are most common viral infections.
- Hepatitis B, varicella, enterovirus, rhinovirus, mycoplasma, syphilis, measles, Lyme disease are less common.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- MS
- Neuromyelitis optica (NMO)
- Tumor of spinal cord
- Herniated or slipped discs
- Spinal stenosis
- Abscess
- Vascular malformation

WORKUP

- Transverse myelitis should be suspected in patients with a history of rapid (hours to days) onset of motor weakness and sensory abnormalities with bladder or bowel dysfunction that is referable to the spinal cord. The dysfunction is bilateral (not necessarily symmetric) and there is a clearly defined sensory (dermatomal) level.
- Lumbar puncture looking for oligoclonal bands for MS or infection.
- Magnetic resonance imaging (MRI) of brain and MRI of spine at level of suspected involvement (Fig. ET1-47).
- Computed tomography (CT) if MRI is unavailable; may use myelography with CT.

LABORATORY TESTS

- ANA, hepatitis B serology, Lyme disease titer, VDRL
- Cerebrospinal fluid (CSF) may show increased protein/normal protein, lymphocytes, and normal glucose.
- Serum NMO-IgG to evaluate for neuromyelitis optica.

IMAGING STUDIES

- MRI shows demyelinating lesion on T_2 with contrast enhancement.
- Chest and joint radiology
- CT or PET scan as indicated by history and examination

TREATMENT

Corticosteroids are the first-line treatment for transverse myelitis; IVIG and plasma exchange can be considered in intractable cases, although there is no evidence-based medicine for use of corticosteroids, plasma exchange, or IVIG. A referral to a neurologist is recommended for treatment.

NONPHARMACOLOGIC THERAPY

- Physical therapy
- Respiratory and oropharyngeal support

ACUTE GENERAL Rx

- High-dose IV corticosteroid (e.g., methylprednisolone 1000 mg/day for 3 to 5 days)
- Rescue therapy with plasma exchange may be helpful in patients who do not respond to corticosteroids
- Combination therapy with plasmapheresis and immunosuppressive agents (e.g., cyclophosphamide) may also be effective
- Naproxen, ibuprofen for pain

CHRONIC Rx

- Baclofen, tizanidine, or some other muscle relaxant for muscle spasms
- Gabapentin for pain
- Low-molecular-weight heparin for DVT prophylaxis in patients with immobility

DISPOSITION

- One third of patients with transverse myelitis will have complete recovery, one third will have fair recovery, and one third have permanent disability and do not recover. Recurrence or relapse is possible.
- Patients who need further care including urinary retention may need home nursing assistance. Some patients may benefit from a rehabilitation, either inpatient or outpatient.

REFERRAL

- Consider physical therapy.
- Consider occupational therapy.
- Consider rehab services.
- Consider psychiatric consultation (high incidence of long-term mood and anxiety disorders).

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **SHARLISA WALLER HUTSON, M.D.**

SUGGESTED READINGS

Frohman EM, Wingerchuk DM: Transverse myelitis, *N Engl J Med* 363:564, 2010.

Kaplin AI et al.: Diagnosis and management of acute myelopathies, *Neurologist* 11:2–18, 2005.

National Institute of Neurological Disorders and Stroke. National Institutes of Health: *Transverse myelitis fact sheet*. available at www.ninds.nih.gov/disorders/transversemyelitis/detail_transversemyelitis.htm.

Ropper AH, Samuels MA: *Adams and Victor's principles of neurology*, chapters 36 and 44, New York: McGraw-Hill.

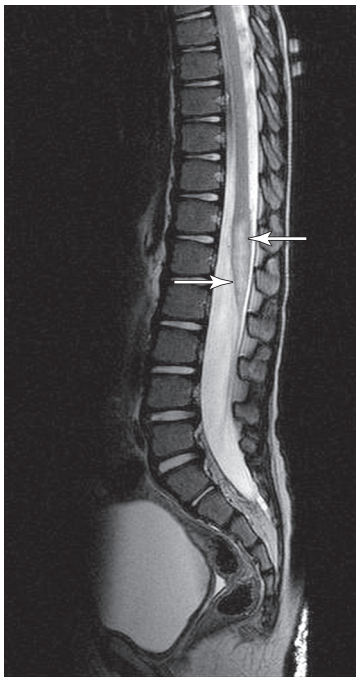


FIGURE ET1-47 Patient with clinical picture of transverse myelitis. Sagittal T_2-weighted MRI of the distal cord shows central T_2 hyperintensity within the conus medullaris *(arrows)* in this case of ADEM. An acute spinal cord infarct also could have this imaging appearance. (From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.)

Hippocrates: 'No head injury is too severe to be despaired of, nor too trivial to be ignored'

BASIC INFORMATION

DEFINITION

Impact to the head resulting in varying levels of cellular and macroscopic changes, detected with clinical examination supplemented by imaging studies. Maas et al have proposed this definition: "brain damage resulting from external forces, as a consequence of direct impact, rapid acceleration or deceleration, a penetrating object (e.g., gunshot) or blast waves from an explosion. The nature, intensity, direction, and duration of these forces determine the pattern and extent of damage."

SYNONYMS

TBI
Head injury
Concussion
Intracranial contusion

ICD-9CM CODES
854.00 Intracranial injury of other and unspecified nature without open intracranial wound with state of consciousness unspecified
ICD-10CM CODES
S06.9X0A Intracranial injury

EPIDEMIOLOGY & DEMOGRAPHICS

Traumatic brain injury is a worldwide leading cause of mortality in young individuals. Urbanization and increasing use of motor vehicles has led to an overall increase in TBI, especially in high income and developing countries.
INCIDENCE: Globally, more than 10 million people suffer TBI resulting in mortality or requiring hospitalization each year.[4] By the year 2020, it is projected that TBI will surpass many diseases as the major cause of death and disability worldwide. It has been estimated that TBI accounts for 9% of global mortality and is a threat to health in every country in the world. The financial burden of TBI has been estimated to be greater than $60 billion per year in the United States alone.
PREVALENCE: The prevalence of TBI in the United States has been estimated at approximately 5.3 million. In the European Union with 330 million inhabitants, approximately 7,775,000 new TBI cases occur each year.
PEAK INCIDENCE: Approximate incidence in the US per CDC data is 103/100,000 population. In the European Union, this is estimated to be at 235/100,000.
PREDOMINANT SEX AND AGE: TBI occurs more frequently in young adults, particularly males 15 to 25 years of age, and has a high cost to society because of life years lost as a result of death and disability.
GENETICS: Work on the genetic basis and the susceptibility it affords in traumatic brain injury is being currently studied. The most recognized association between a genetic polymorphism and outcome involves the apolipoprotein E (apo E) gene. The ε4 allele has been associated with poorer outcome after TBI. The same isoform is associated with Alzheimer's and increased deposition of amyloid beta lipoprotein after TBI. TBI and apo E ε4 synergistically are also associated with a 10-fold increased risk for Alzheimer's as well as larger intracerebral hematomas and greater ischemia after TBI.
RISK FACTORS: N/A.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

TBI patients can present with a spectrum of clinical symptoms including nausea, vomiting, headache, seizures, altered mental status, and/or coma. Stigmata of trauma, including bruises, scalp lacerations, periorbital or mastoid ecchymosis suggesting skull base fractures are telltale signs of possible underlying traumatic brain injury. The spectrum of TBI is most commonly assessed using the Glasgow Coma Scale (GCS), which ranges from 3 to 15 and utilizes eye, motor, and verbal exams (Table T1-22).

ETIOLOGY

Etiology, in most cases is impact related. Mechanical falls, motor vehicle accidents, and assaults resulting in direct or indirect trauma to the head from acceleration and rotational forces results in brain injury.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of traumatic brain injury is quite limited; however, there are several considerations and diagnoses, which are considered as a possibility within the realm of TBI. These are enumerated in the imaging section.

WORKUP

TBI workup is always a part of the advanced trauma life support (ATLS) protocol. Primary and secondary survey followed by imaging studies constitutes the standardized approach to TBI. Focused TBI workup includes:

- History: including timing of injury, duration of loss of consciousness if applicable, seizures if any, comorbidities, use of anticoagulants and antiplatelet agents (requires reversal in the event of intracranial blood on imaging).
- Neurological examination: Glasgow Coma Scale, cranial nerves, motor/sensory exam.
- CT imaging of the head if there is a significant history of impact to the head, polytrauma, positive loss of consciousness, or stigmata of trauma to the head.

LABORATORY TESTS

Basic labs including CBC, basic metabolic panel, prothrombin time, activated partial thromboplastin time, urinary drug screen. Upcoming tests for platelet function analysis for unknown antiplatelet use are also being performed for early reversal with platelet replacement.

IMAGING STUDIES (Table T1-23)

CT imaging of the forms the current cornerstone of imaging modalities for head trauma. Usually in addition to a plain CT of the head (Fig. T1-48), CTA head/neck and CT of the spine is helpful if arterial or C-spine injury is suspected, respectively. Other imaging modalities such as MRI can be helpful in certain situations, but are typically

TABLE T1-22 Glasgow Coma Scale (GCS)

Adult		Infant
Eye Opening	**E**	**Eye Opening**
Spontaneous	4	Spontaneous
To speech	3	To speech
To pain	2	To pain
No response	1	No response
Best Motor Response	**M**	**Best Motor Response**
Obeys verbal command	6	Normal movements
Localizes to pain	5	Localizes to pain
Withdraws to pain	4	Withdraws to pain
Flexion (decorticate)	3	Flexion (decorticate)
Extension (decerebrate)	2	Extension (decerebrate)
No response	1	No response
Best Verbal Response	**E**	**Best Verbal Response**
Oriented speech	5	Coos, babbles
Disoriented speech	4	Cries but consolable
Inappropriate words	3	Persistently irritable
Incomprehensible sounds	2	Grunts to pain/restless
No response	1	No response

Mild TBI: GCS 13-15, Moderate TBI: GCS 9-12, Severe TBI GCS 8 or less
GCS can range from 3 to 15. If intubated, then verbal component is replaced by 'T'. Best possible score if intubated is 10T, and worse is 3T.
In obtunded patients, pain stimulus can be central or peripheral. In patients with suspected spinal cord injury and paralysis, central stimulus to elicit facial grimace can be used to assess motor and eye component.

TABLE T1-23 Comparison of Head Imaging Modalities

	Computed Tomography Scans	Magnetic Resonance Imaging	Angiography	Skull Radiography
Advantages	Fast Patient accessible for monitoring Defines acute hemorrhages, mass effects, bone injuries, hydrocephalus, intraventricular blood, edema	Defines contusions and pericontusion edema, posttraumatic ischemic infarction, brainstem injuries	Helps localize acute traumatic lesions Defines vascular injuries, injuries to venous sinuses Detects mass effects	Readily available May help screen some patients for further imaging studies
Disadvantages	Artifacts arise from patient's movement, foreign bodies Streak artifacts may obscure brainstem or posterior fossa	Slow Patients not easily accessible for monitoring Does not define most acute hemorrhagic lesions Not useful for bone injuries	Does not define nature of acute lesion Does not detect infratentorial masses	Does not indicate presence or absence of intracranial injury
Indications	Acute severe head trauma Acute moderate head trauma Suspected depressed skull fracture High-risk minor head trauma Suspected child abuse in minor head trauma Deteriorating neurologic status	Persistent symptoms with postconcussive syndrome Suspected post-traumatic ischemic infarction Suspected contusions not seen on CT scan	Suspected vascular injury CT scan not available	CT scan may not be done Penetrating head trauma

CT, Computed tomography.
From Marx: *Rosen's emergency medicine: concepts and clinical practice,* J.A. Marx, R.S. Hockberger, R.M. Walls, et al. (eds.) 7 ed, 2010, Elsevier.

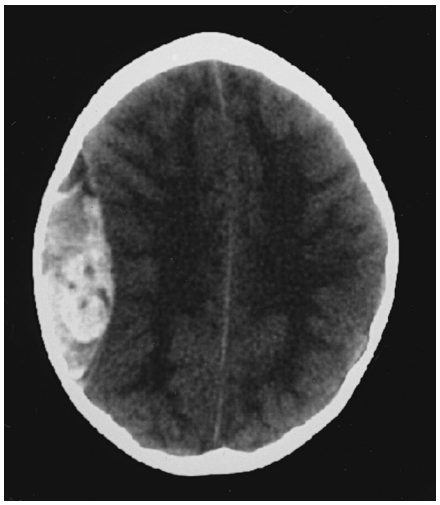


FIGURE T1-48 Non–contrast-enhanced computed tomography scan of acute epidural hematoma at the level of right midconvexity. There is an associated mass effect and moderate midline shift. (From Marx: *Rosen's emergency medicine: concepts and clinical practice,* J.A. Marx, R.S. Hockberger, R.M. Walls, et al. (eds.) 7 ed, 2010, Elsevier.)

adjuncts in the acute setting to CT-guided management. Canadian CT head rules are a useful guide and based on risk factors[11]:

HIGH-RISK
1. Failure to reach GCS of 15 within 2 hours
2. Suspected open or any signs of basal skull fracture
3. More than two episodes of vomiting
4. Age older than 65

LOW RISK
1. Dangerous mechanism of injury or polytrauma
2. Loss of consciousness lasting >30 minutes

Pathologies that can be identified with imaging are noted below:

- Primary extraaxial: epidural, subdural, subarachnoid and intraventricular hemorrhage
- Primary intraaxial: axonal injury, cortical contusion, intracerebral hemorrhage, encephalomalacia (from prior TBI or vascular insult)
- Vascular injury: dissection, traumatic carotid-cavernous fistula (CCF), dural arteriovenous fistula (DVA), pseudoaneurysm formation
- Secondary acute injury: diffuse cerebral swelling/dysautoregulation (seen more commonly in children from posttraumatic hyperemia), infarction, infection from penetrating trauma, brain herniation from mass lesion or cerebral edema
- Secondary chronic injury: hydrocephalus (posttraumatic due to disruption of normal CSF absorption pathways), encephalomalacia, CSF leak (from skull base fractures, manifests as otorrhea or rhinorrhea, leptomeningeal cyst (seen most commonly in infants, skull fracture resulting in underlying dural injury)

Rx TREATMENT

Prevention of secondary injury is the primary goal of prehospital and early in-hospital management. Most common mechanisms of secondary injury are either intracranial (ICP, hematoma) or systemic (hypoxia, hypovolemia, hypotension). Early categorization of head trauma patients according to the severity (based on GCS) and transport to facilities equipped with personnel and technology to deal with issues pertaining to head trauma has improved the overall management of head injury patients and prevention of secondary injury. Airway, breathing, and circulation, however, still remain the most important parameters to be stabilized which directly or indirectly can effect GCS and overall outcome. Trauma guidelines suggest intubation should be performed in any patient with a GCS of 8 or less to prevent hypoxemia and hypercapnia. Intravenous fluid resuscitation should also be started early to prevent hypovolemia resulting in hypotension which has been shown to double the mortality. Transfer and care in a Level I trauma center has shown to be associated with better outcomes.

Details of in-hospital management including critical care and surgical intervention is beyond the scope of this text. Some important points are summarized below.

1. ATLS protocol (airway, breathing, circulation, disability, exposure)
2. Ventilatory support
3. Optimization of oxygenation, ventilation and fluid status
4. CT head to evaluate for mass lesion (hematoma) or cerebral edema which may necessitate surgical intervention or ICP monitor placement. ATLS guidelines recommend maximum 30 minutes between initial assessment and CT head.
5. In case of severe TBI (GCS 8 or less) or moderate TBI (GCS 8 to 13) with unreliable neurological exam, patients should be admitted to the intensive care unit for frequent neurological checks.
6. ICP monitor placement for GCS 8 or less to closely monitor intracranial pressure. ICP monitors are of various kinds; most commonly used: external ventricular drain, intraparenchymal pressure monitor, bolt device with brain tissue oxygen pressure monitoring with fiberoptic pressure monitor. Recent research has also supported the use of brain tissue oxygen monitoring for severe TBI patients.
7. Surgical decompression may involve evacuation of hematoma (epidural, subdural, intraparenchymal contusion) through craniotomy alone (replacement of bone after completion of operation) versus decompressive craniectomy (complete removal of bone without replacement) in certain cases where cerebral edema is out of proportion to the presence of mass lesion.
8. Avoiding electrolyte imbalance, especially hyponatremia which may contribute to cerebral edema and increase intracranial pressure.

BOX T1-6 Indications for Acute Seizure Prophylaxis in Severe Head Trauma

Depressed skull fracture
Paralyzed and intubated patient
Seizure at the time of injury
Seizure at emergency department presentation
Penetrating brain injury
Severe head injury (Glasgow Coma Scale score ≤8)
Acute subdural hematoma
Acute epidural hematoma
Acute intracranial hemorrhage
Prior history of seizures

Marx, JA et al: *Rosen's emergency medicine: concepts and clinical practice*, 7th ed. Philadelphia, 2010, Elsevier.

9. Elevation of head of bed to allow better venous drainage, in an attempt to reduce intracranial pressure.
10. ICP management, which may include: surgical hematoma evacuation, administration of hyperosmotic fluids to reduce edema, pharmacologic sedation and paralysis, pentobarbital-induced coma, and surgical decompression of the brain.
11. Prevention of seizures in the acute setting. The most commonly used and studied drug is phenytoin. Indications for acute seizure prophylaxis in severe head trauma are described in Box T1-6.
12. DVT prophylaxis is recommended in almost all patients on hospital day 1. SCDs for immobile or bed bound patients to prevent DVTs.
13. Early initiation of parentral nutrition.

CHRONIC Rx

- Patients suffering from TBI are shown to benefit from neurocognitive occupational and physical therapy. The Glasgow Outcome Scale is a comprehensive measure of severity and eventual outcome of brain injury. Posttraumatic amnesia, age, length of coma, GCS score within the first 24 hours, imaging study scales are some of the factors that affect outcome and dictate long-term prognosis.
- Chronic treatment addresses several sequelae of TBI, including (but not limited to): dysautonomia, agitation, sleep disturbance, posttraumatic epilepsy, spasticity, dsyphagia, syndrome of the trephined, posttraumatic hydrocephalus, apathy, fecal/urinary incontinence, headache, and neuropathic pain syndromes.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Currently, there are no proven drugs that improve outcomes after TBI. Several pro-drugs are being experimented on, with the hopes to have a single TBI cocktail that would enhance repair at the cellular and molecular pathway level. Neurostimulants such as amantadine, bromocriptine, amphetamine and methylphenidate are used in the rehabilitation phase with anecdotal data, but good RTCs are lacking in this area.

DISPOSITION

Depending on severity of head injury, patients may require admission to a rehabilitation facility or discharge to home with outpatient neurocognitive therapy.

REFERRAL

Early transfer to a Level 1 Trauma Center with Neurosurgical personnel, if high risk findings are noted on clinical exam or CT head, is associated with better outcomes.

PEARLS & CONSIDERATIONS

TBI is major healthcare issue. Guidelines have been developed to address TBI in a timely and effective fashion. Clinical acumen and judgment, however, is irreplaceable and should be exercised for better patient care and outcomes. Early recognition of high-risk patients, early imaging and early evaluation at a Level 1 Trauma Center by a specialist is associated with good outcomes. The goal of healthcare providers in the field or in the community is to identify patients who need this attention.

PATIENT/FAMILY EDUCATION

Brain Injury Association of America http://www.biausa.org/
Brain Injury Resource Center http://www.headinjury.com/linktbisup.htm

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Concussion (Related Key Topic)

AUTHORS: **FARHAN A. MIRZA, M.B.B.S.,** and **JUSTIN F. FRASER, M.D.**

SUGGESTED READINGS

Demetriades D, Martin M, Salim A et al.: Relationship between American College of Surgeons trauma center designation and mortality in patients with severe trauma (injury severity score > 15), *J Am Coll Surg* 202:212–215, 2006.

Hyder AA, Wunderlich CA, Puvanachandra P et al.: The impact of traumatic brain injuries: a global perspective, *NeuroRehabilitation* 22:341–353, 2007.

Langlois J, Rutland-Brown W, Thomas K: *Traumatic brain injury in the United States: Emergency department visits, hospitalizations, and deaths*, Atlanta, 2006, Centers for Disease Control and Prevention, National Center for Injury Prevention and Control.

Liaquat I, Dunn LT, Nicoll JA et al.: Effect of apolipoprotein E genotype on hematoma volume after trauma, *J Neurosurg* 96:90–96, 2002.

Lopez AD, Murray CC: The global burden of disease, 1990–2020, *Nat Med* 4:1241–1243, 1998.

Maas AI, Stocchetti N, Bullock R: Moderate and severe traumatic brain injury in adults, *Lancet Neurol* 7:728–741, 2008.

Mackenzie EJ, Rivara FP, Jurkovich GJ et al.: The National Study on Costs and Outcomes of Trauma, *J Trauma* 63(Suppl 6):S54–S67, 2007.

Mayeux R, Ottman R, Maestre G et al.: Synergistic effects of traumatic head injury and apolipoprotein ε 4 in patients with Alzheimer's disease, *Neurology* 45:555–557, 1995.

Stiell IG, Wells GA, Vandemheen K et al.: The Canadian CT head rule for patients with minor head injury, *Lancet* 357:1391–1396, 2001.

Tagliaferri F, Compagnone C, Korsic M et al.: A systematic review of brain injury epidemiology in Europe, *Acta Neurochir (Wien)* 148:255–268, 2006.

Teasdale GM, Nicoll JAR, Murray G et al.: Association of apolipoprotein E polymorphism with outcome after head injury, *Lancet* 350:1069–1071, 1997.

World Health Statistics: *Global Health Statistics, 2007*, ed 3, Geneva, 2007, World Health Organization. Available at. http://www.who.int/whosis/en/.

Zhou W, Xu D, Peng X et al.: Meta-analysis of APOE4 allele and outcome after traumatic brain injury, *J Neurotrauma* 25:279–290, 2008.

BASIC INFORMATION

DEFINITION

Trichinosis is an infection by one of various species of the nematode parasite *Trichinella.*

SYNONYMS

Trichinella spiralis muscle infection
Trichinellosis

ICD-9CM CODES
124 Trichinosis
ICD-10CM CODES
B75 Trichinellosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.)

- About 20 cases per year in the US between 2008 and 2010
- Most cases occur outside the United States worldwide.

GENETICS: Congenital infection:

- Abrupt delivery of stillbirths in infected pregnant women
- Vertical infection of the fetus

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms:
  1. Incubation period is usually 7 to 30 days and may vary widely depending on the time from ingestion of contaminated meat and on worm burden.
  2. Mild infections can be subclinical.
- Enteral phase:
  1. Correlates with penetration of ingested larvae into the intestinal mucosa
  2. May last from 2 to 6 wk
  3. Mild, transient diarrhea and nausea
  4. Abdominal pain
  5. Diarrhea or constipation
  6. Vomiting
  7. Malaise
  8. Low-grade fevers
- Migratory or parenteral phase:
  1. In the intestine, maturation and mating
  2. Newborn larvae
     a. Penetrate into lymphatic and blood vessels
     b. Migrate to muscles, where they penetrate into muscle cells, enlarge, coil, and develop a cyst wall
  3. Patients may present with:
     a. Fever
     b. Myalgias
     c. Periorbital or facial edema
     d. Headache
     e. Skin rash, splinter hemorrhages under fingernails
     f. Other symptoms caused by the penetration of tissues by the newborn migrating larvae
  4. Peak in symptoms 2 to 3 wk after infection, then slowly subside
- Severe complications:
  1. Brain damage by granulomatous inflammation or occlusion of arteries
  2. Myocarditis with arrhythmias
  3. Respiratory myositis due to diaphragmatic involvement

ETIOLOGY

- *Trichinella* is a parasitic intracellular round worm. Larvae of *trichinella* species invade columnar epithelium cells of villi of the small intestine and develop into adult worms (Fig. ET1-49).
- It is one of the most ubiquitous parasites in the world and may be found in virtually all warm-blooded animals. Most infections are due to *T. spiralis.*
- Humans are incidental hosts and infections in humans occur by the ingestion of contaminated animal meat that is raw or partially cooked and contains viable cysts.
- Most cases are now related to the consumption of poorly processed pork or wild game (bear, wild boar, cougar, and walrus).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Different presentations have different differential diagnoses.
- Early illness may resemble gastroenteritis.
- Later symptoms may be confused with:
  1. Measles
  2. Dermatomyositis
  3. Glomerulonephritis

WORKUP

- Antibody assay of serum is usually positive by approximately 2 to 4 wk after infection and can remain positive for years.
- Muscle biopsy is used to detect the larva in muscle tissue if diagnosis unclear; best done by placing the tissue between two slides.

LABORATORY TESTS

- CBC: leukocytosis with prominent eosinophilia (20% to 90%)
- ESR: usually normal
- Elevation of muscle enzymes common (i.e., CPK, LDH, aldolase)
- Serology: antibodies detected by ELISA and Western blot but not useful in early disease
- Muscle biopsy to look for larvae directly. Biopsy is best done in symptomatic muscles and near insertion of a tendon

IMAGING STUDIES

Soft-tissue radiographs may show calcified cyst walls.

TREATMENT

NONPHARMACOLOGIC THERAPY

Bed rest for myalgias

ACUTE GENERAL Rx

- Most infections are self-limited and do not require specific treatment
- Albendazole: 400 mg twice a day for 10 to 14 days
- Mebendazole: 200 to 400 mg tid for 3 days then 400 to 500 mg tid for 10 days
- Steroids in critically ill patients
- Salicylates to decrease muscle discomfort

DISPOSITION

- Most symptoms subside over time.
- Reports of long-term sequelae:
  1. Myalgias
  2. Headaches
- Occasionally, death occurs.

REFERRAL

Diagnosis uncertain

PEARLS & CONSIDERATIONS

COMMENTS

- Prevention by thorough cooking of meats to at least 77° C.
- Inadequate to smoke, cure, or dry meats.

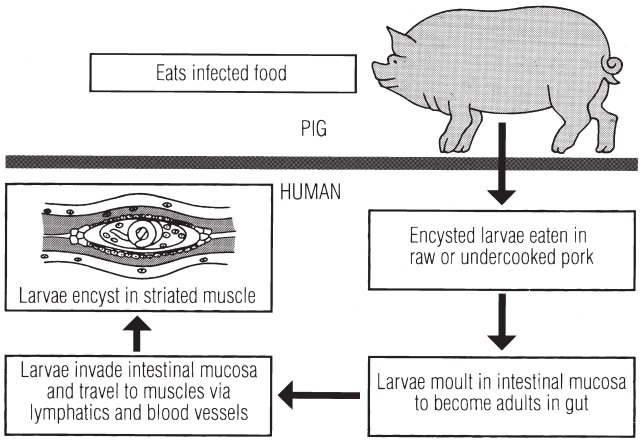


FIGURE ET1-49 Lifecycle of *Trichinella spiralis.* (From Souhami RL, Moxham J: *Textbook of medicine,* ed 4, London, 2002, Churchill Livingstone.)

- Freezing at –15° C for 3 wk will kill *T. spiralis* larvae in pork.
- *T. nativa* is a freeze-resistant species that remains viable after freezing, even for months or years; it has been associated with infection from ingestion of bear meat.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Trichinosis (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Centers for Disease Control and Prevention (CDC): Trichinellosis associated with bear meat—New York and Tennessee, MMWR, *Morb Mortal Wkly Rep* 53(27):606, 2004.

Gottstein B et al.: Epidemiology, diagnosis, treatment, and control of trichinellosis, *Clin Microbiol Rev* 22(1):127–145, 2009.

Moller LN et al.: Outbreak of trichinellosis associated with consumption of game meat in West Greenland, *Vet Parasitol* 132(1–2): 131, 2005.

Murrell KD, Pozio E: Worldwide occurrence and impact of human trichinellosis, 1986-2009, *Emerg Infect Dis* 17(12):2194–2202, 2011.

Piergili-Fioretti D et al.: Re-evaluation of patients involved in a trichinellosis outbreak caused by *Trichinella britovi* 15 years after infection, *Vet Parasitol* 132(1–2):119, 2005.

BASIC INFORMATION

DEFINITION

Tricuspid regurgitation (TR) refers to an abnormal retrograde flow of blood from the right ventricle to the right atrium (Fig. ET1-50)

SYNONYMS

Tricuspid insufficiency
Tricuspid incompetence

ICD-9CM CODES
397.0 Diseases of the tricuspid valve
424.2 Tricuspid valve disorders, specified as non-rheumatic

ICD-10CM CODES
I07.1 Tricuspid insufficiency
I07.2 Tricuspid stenosis with insufficiency
I07.8 Other tricuspid valve diseases
I07.9 Tricuspid valve disease, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- In the adult population, the most important cause of TR is usually functional rather than structural, secondary to the dilation of the right ventricle and of the tricuspid annulus.
- In adolescents and young adults, most cases of TR are the result of congenital cardiac abnormalities.
- In patients with rheumatic heart disease, TR rarely occurs alone; it is usually associated with mitral or aortic valve disease.
- A small degree (i.e., trace to mild) of TR is present in approximately 70% of normal adults. On echocardiography, this "normal" degree of regurgitation is localized to a small region adjacent to valve closure, it often does not extend throughout systole, and it has a low signal strength.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Isolated TR can cause nonspecific symptoms (e.g., exercise intolerance).
- Signs and symptoms in the presence of TR are usually the result of an underlying cause.
- Signs and symptoms may be caused by accompanying right-sided heart failure (e.g., jugular venous distention, peripheral edema, parasternal lift, ascites, hepatomegaly, right-sided S_3).
- A lower-left parasternal holosystolic murmur may be found; the murmur becomes louder during inspiration (Carvallo's sign) and during maneuvers that increase venous return such as squatting, leg lifts, and isotonic exercises.
- Prominent V waves in the jugular venous waveform can occur analogous to prominent V-waves in the Swan-Ganz catheter pressure waveform in the setting of significant MR.
- Severe TR may produce systolic propulsion of the eyeballs, pulsatile varicose veins, a venous systolic thrill and murmur in the neck, a mid-diastolic murmur in severe regurgitation, and systolic hepatic pulsation.
- Atrial fibrillation or flutter is common as a result of right atrial enlargement secondary to elevated right atrial pressure.

ETIOLOGY

- Tricuspid valve dysfunction can occur with structurally normal (functional TR) or abnormal valves (structural TR)
- Functional TR involves conditions that lead to the dilation of the tricuspid annulus or right ventricular enlargement, including the following:
  1. Any cause of pulmonary hypertension (e.g., chronic obstructive pulmonary disease, pulmonary embolism, restrictive lung disease, collagen vascular disease, primary pulmonary hypertension, left to right shunts [i.e., ASD, VSD, anomalous pulmonary venous return])
  2. Left-sided heart failure that leads to right-sided heart failure (this is the most common cause of right sided heart failure)
  3. Dilated cardiomyopathy
  4. Right ventricular infarction
- Structural TR involves conditions directly affecting the tricuspid valve apparatus, including the following:
  1. Rheumatic heart disease
  2. Congenital conditions (e.g., Ebstein's anomaly—apical displacement of tricuspid valve, tricuspid atresia, cleft valve associated with atrioventricular canal malformations—primum ASD)
  3. Endocarditis, either bacterial (particularly related to intravenous drug use) or marantic (e.g., systemic lupus erythematosus, rheumatoid arthritis, and adenocarcinoma)
  4. Tricuspid valve prolapse or chordae rupture
  5. Carcinoid syndrome—can also lead to tricuspid stenosis
  6. Marfan's syndrome
  7. Iatrogenic damage to the valve (e.g., pacemaker, implantable cardioverter-defibrillator, endomyocardial biopsy, anorectic drugs)
  8. External trauma (e.g., deceleration injury)
  9. Right atrial myxoma
  10. Collagen vascular diseases
  11. Radiation injury
  12. Endomyocardial fibrosis (important cause in tropical Africa)
  13. Metastatic cardiac tumors such as renal cell carcinoma, etc.

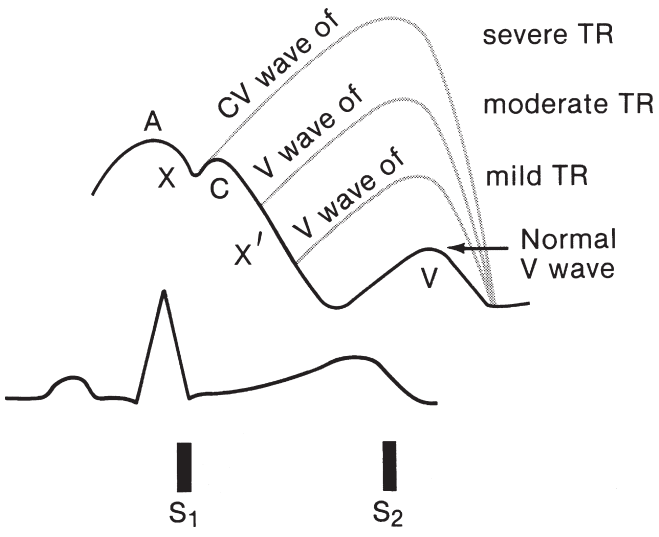


FIGURE ET1-50 The jugular venous pulse in tricuspid regurgitation. The jugular venous pulse wave normally drops during ventricular systole. As tricuspid regurgitation becomes more severe, the CV wave becomes more obvious during ventricular systole. (From Conn R: *Current diagnosis,* ed 9, Philadelphia, 1997, Saunders.)

DIAGNOSIS

The diagnosis of TR is made noninvasively by physical examination and imaging techniques (e.g., echocardiography) and invasively by right-sided heart catheterization in selected cases.

DIFFERENTIAL DIAGNOSIS

On the basis of heart auscultation, the diagnosis of TR may be confused with other causes of systolic murmurs, such as mitral regurgitation, aortic stenosis, pulmonary stenosis, ventricular septal defect, and hypertrophic cardiomyopathy.

WORKUP

Any patient suspected of having significant TR should undergo the following:
- Chest x-ray
- ECG
- Echocardiogram (confirmatory)
- Right-sided cardiac heart catheterization (in selected cases)
- CMR (in selected cases)

LABORATORY TESTS

ECG may show evidence of the following:
- Right atrial enlargement (e.g., P-wave amplitude in leads II or III or aVF of >2.5 mV)

- Right ventricular enlargement or hypertrophy (e.g., R:S ratio >1 in V_1, R >7 mm in V_1, or R wave in V_1+, S wave in V_5, or V_6 >10.5 mm)
- Right axis deviation—mean QRS axis between 100 and 270 degrees
- Atrial fibrillation

IMAGING STUDIES

- A chest x-ray may show the following:
  1. Evidence of chronic obstructive pulmonary disease (e.g., flattened diaphragms, barrel chest, dilated pulmonary arteries, increased retrosternal air space) or restrictive lung disease
  2. Enlarged right atrium
  3. Enlarged right ventricle
  4. Enlarged/prominent pulmonary arteries
- An echocardiogram (either transthoracic or transesophageal) will do the following:
  1. Assess tricuspid valve structure and motion, measure annular size, and identify other cardiac abnormalities. Transesophageal echocardiogram is not typically needed since the tricuspid valve is an anterior structure easily assessed on transthoracic echocardiogram.
  2. Estimate the severity of TR (vena contracta width >0.7 cm and systolic flow reversal in hepatic veins)
  3. Estimate the pulmonary artery pressure
  4. Exclude vegetation, mass, or prolapse
  5. Assess left and right ventricular function
- CMR (cardiovascular magnetic resonance)
  1. If echocardiographic evaluation is poor
  2. Quantitative measurements of TR volume
  3. RV volumes
  4. Ejection fraction
- Right-sided cardiac heart catheterization shows the following:
  1. Elevated right atrial and right ventricular systolic and end-diastolic pressures
  2. Large V waves

Rx TREATMENT

The treatment of TR is usually directed at the underlying cause.

NONPHARMACOLOGIC THERAPY

Oxygen therapy is beneficial for patients with functional TR caused by underlying pulmonary hypertension provoked by alveolar hypoxia.

ACUTE GENERAL Rx

- Functional TR caused by left-sided heart failure is treated in the standard way with preload reduction, afterload reduction, or inotropic therapy in the setting of a low cardiac output state (see "Congestive Heart Failure").
- The reversal of pulmonary hypertension with vasodilators or pulmonary thromboendarterectomy has been shown to reverse functional TR.
- Structural TR treatment depends on the underlying cause of heart disease.

CHRONIC Rx

- The 2006 American College of Cardiology/American Heart Association Guidelines Pertaining to the Surgical Management of Tricuspid Valve Disease/Regurgitation include the following:
  1. Class I: Tricuspid valve repair is beneficial for severe TR in patients with mitral valve (MV) disease that requires MV surgery. **B**
  2. Class IIa: Tricuspid valve replacement or annuloplasty is reasonable for a symptomatic patient with severe primary TR and for severe TR as a result of diseased or abnormal tricuspid valve leaflets that are not amenable to annuloplasty or repair. **C**
  3. Class IIb: Tricuspid annuloplasty may be considered for less-than-severe TR in patients who are undergoing MV surgery when there is pulmonary hypertension or tricuspid annular dilatation (usually >21 mm/m^2 body surface area [BSA]). **C**
  4. Class III: Tricuspid valve replacement or annuloplasty is not indicated for asymptomatic patients with TR whose pulmonary artery pressure is <60 mm Hg in the presence of a normal MV or for those with mild TR. **C**
- Patients with severe TR of any cause have poor long-term outcomes as a result of right ventricular dysfunction or systemic venous congestion.
- During recent years, annuloplasty has become an established surgical approach to significant TR. A recent study showed that tricuspid valve (TV) repair with an annuloplasty ring results in improved long-term outcomes.
- When the valve leaflets themselves are diseased, abnormal, or destroyed, valve replacement with a low-profile mechanical valve or bioprosthesis is often necessary. A bioprosthesis is almost always used.
- A biologic prosthesis is preferred because of the high rate of thromboembolic complications that occur with mechanical prostheses in the tricuspid position.
- In patients with TR due to refractory endocarditis, such as in intravenous drug users, total excision of the diseased valve is done to eradicate the endocarditis without immediate replacement of the valve to avoid reinfection, and antibiotics are resumed. Initially, most patients tolerate the loss of the tricuspid valve without any difficulty. However, RV dysfunction usually occurs subsequently, and therefore, a bioprosthetic valve may be inserted 6-9 mo after valve excision and control of infection.

DISPOSITION

- Regardless of the cause, a greater-than-mild degree of TR is associated with decreased survival.
- Clinically insignificant TR can be detected by color Doppler imaging in many normal people. This is not an indication for either routine follow-up or prophylaxis against bacterial endocarditis.
- Isolated TR should not pose a significant problem during pregnancy, although greater care may be necessary for protection from diuretic-induced hypoperfusion.
- Isolated TR with normal right ventricular function does not preclude an individual's involvement in competitive sports.

REFERRAL

For patients with significant symptomatic TR, a cardiology consultation is recommended.

PEARLS & CONSIDERATIONS

- TR that results from tricuspid valve prolapse is often associated with concurrent MV prolapse.
- Secondary TR commonly occurs in combination with left-sided valvular heart disease. It often does not improve, despite correction of the left-sided valve dysfunction.
- Functional tricuspid insufficiency, if left uncorrected, carries serious long-term consequences.
- Antibiotic prophylaxis for dental, gastrointestinal, or genitourinary procedures is no longer recommended for patients with only structural tricuspid valve abnormalities.
- Tricuspid annuloplasty at the time of MV surgery results in improved functional capacity without any increase in perioperative morbidity or mortality.
- If a donor heart develops TR after cardiac transplantation, tricuspid valve replacement with a biologic prosthesis is a safe, durable, and effective method of treating TR after transplantation. This allows for future endomyocardial biopsies to be performed. Mechanical valves should be avoided.
- In TR due to endocarditis in intravenous drug users, the diseased tricuspid valve is commonly excised without immediate replacement of the valve, and interval TV replacement is done 6-9 mo after the endocarditis has been completely treated with antibiotics to avoid re-infection of the bioprosthesis.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Tricuspid Regurgitation (Patient Information)

AUTHORS: **PHILLIP RUISI D.O.** and **ARAVIND RAO KOKKIRALA, M.D.**

SUGGESTED READINGS

Bonow RO et al.: 2008 Focused update incorporated into ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease), *Circulation* 118:e523–e661, 2008.

Raman SV et al.: Tricuspid valve disease: tricuspid valve complex perspective, *Curr Probl Cardiol* 27:97–144, 2002.

Rogers JH et al.: The tricuspid valve: current perspective and evolving management of tricuspid regurgitation, *Circulation* 119:2718–2725, 2009.

Singh SK et al.: Midterm outcomes of tricuspid valve repair versus replacement for organic tricuspid disease, *Ann Thorac Surg* 82:1735–1741, 2006.

Song H: Percutaneous mitral valvuloplasty versus surgical treatment in mitral stenosis with severe tricuspid regurgitation, *Circulation* 116:1246–1250, 2007.

Trichon BH, O'Connor CM: Secondary mitral and tricuspid regurgitation accompanying left ventricular systolic function: is it important, and how is it treated? *Am Heart J* 144(3):373–376, 2002.

BASIC INFORMATION

DEFINITION

Tricuspid stenosis (TS) is an uncommon valvular pathology that is caused by the narrowing of the tricuspid valve orifice, which results in the restriction of right atrial emptying. TS is most often rheumatic in origin, and it often presents with a combination of regurgitation and stenosis.

SYNONYMS

Tricuspid valve stenosis
TS

ICD-9CM CODES
397.0 Disease of the tricuspid valve
ICD-10CM CODES
I07.0 Tricuspid stenosis

EPIDEMIOLOGY & DEMOGRAPHICS

- TS is most commonly caused by rheumatic heart disease, and it almost always occurs with associated mitral or aortic valve disease. In rheumatic heart disease, mitral and aortic valve involvement are much more common than tricuspid valve involvement.
- Other causes of TS include congenital atresia or stenosis of the valve, right atrial or metastatic tumors, carcinoid syndrome (although tricuspid regurgitation is a more common presentation in this disease state), or bacterial endocarditis that involves an infected pacemaker lead or prosthetic valve.
- Antibiotic therapy has made rheumatic heart disease and TS in the United States very rare.
- TS is present at autopsy in 15% of patients with rheumatic heart disease, but it is clinically significant in only 5%.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Obstruction to tricuspid flow limits cardiac output and leads to elevated mean right atrial pressures very easily even with a gradient as small as 5 mm Hg.
- As a result, most patients with significant TS have systemic venous congestion, jugular venous distention, ascites, and peripheral edema.
- Symptoms and physical examination findings usually depend on the presence and severity of concomitant mitral or aortic valve disease.
- Symptoms of right heart failure include fatigue, right upper quadrant abdominal pain (from hepatic congestion), ascites, hepatomegaly, peripheral edema, and clear lungs.
- Jugular venous distention, a prominent a wave that can sometimes approach the level of the right ventricular systolic pressure, slow rate of y descent that is barely appreciated, and palpable hepatic pulsations are noted during sinus rhythm.
- A right atrial pulsation may be palpated to the right of the sternum, and a diastolic thrill that increases with inspiration may be felt over the left sternal edge.
- An opening snap and a low-frequency diastolic murmur are best heard along the left sternal border of the fourth intercostal space. The murmur is softer, high-pitched, and shorter in duration as compared to mitral stenosis. The murmur is augmented by inspiration (i.e., Carvallo's sign), leg raises, isotonic exercise, and squatting (all maneuvers that increase venous return to the right side of the heart).

ETIOLOGY

- Rheumatic heart disease results in the scarring of the valve leaflets starting at the leaflet tips, shortening of the chordae tendineae, and fusion of the commissures, thereby leading to the immobility of the valve leaflets and the narrowing of the tricuspid valve orifice.
- Other causes are congenital, infectious (e.g., endocarditis), metabolic, and enzymatic abnormalities (e.g., carcinoid syndrome, Whipple's disease, Fabry's disease); right atrial or metastatic tumors; and, rarely, scarring and adhesions as a result of complications of pacemaker placement.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Congenital tricuspid atresia or stenosis, as can be seen in Noonan's syndrome (autosomal dominant disorder characterized by congenital heart defects, typically pulmonary valve stenosis and ASDs)
- Right heart diastolic dysfunction: endomyocardial fibrosis or constrictive pericarditis, restrictive cardiomyopathies (however, restrictive cardiomyopathy and constrictive pericarditis demonstrate a steep y wave descent in the right atrial pressure tracings)
- Extrinsic compression of the right ventricle: severe pectum excavatum, massive ascites, pleural effusion, pericardial effusion, or tumor
- Obstruction of right atrial emptying: right atrial myxoma (although myxomas are typically found in the left atrium), metastatic tumor, right atrial thrombi, or tricuspid valve vegetation (particularly in association with a permanent pacemaker lead)

WORKUP

- Echocardiography is the diagnostic test of choice to evaluate the tricuspid valve.
- ECG is recommended to look for atrial arrhythmias, atrial fibrillation, or atrial flutter as a result of an enlarged right atrium. ECG in tricuspid stenosis may show tall atrial P waves more than 2.5 mm in the inferior leads with no right ventricular hypertrophy.
- Chest x-ray, which can demonstrate enlargement of the right atrium and IVC.
- Right heart catheterization is an option when echocardiography cannot be used to make a definitive diagnosis. Right heart catheterization can demonstrate prominent a wave and slow rate of Y descent.

IMAGING STUDIES

- Echocardiography reveals thickening and shortening of the tricuspid valve leaflets, restricted movement of the leaflets and the leaflet tips, a reduction in the diameter of the annulus, and diastolic doming of the valve. Evidence of right atrial enlargement and dilated IVC is present in most cases. For severe TS the mean gradient is typically more than 5 mm Hg. Transesophageal echocardiography is typically not of use since the tricuspid valve is an anterior structure and is easily visualized via transthoracic echocardiogram.
- Doppler echocardiography or cardiac catheterization demonstrates a reduced tricuspid valve area (characterized as severe when <1 cm^2) and a diastolic pressure gradient across the tricuspid valve (normal gradient, <1 mm Hg, and TS can be diagnosed with a mean pressure gradient as low as 2 mm Hg).
- Chest radiography may reveal an enlarged right atrium and a reduced pulmonary blood volume from decreased right ventricular cardiac output.

TREATMENT

NONPHARMACOLOGIC THERAPY

Salt and fluid restriction is essential to decrease peripheral edema.

ACUTE GENERAL Rx

- Assess and treat the underlying cause of the valvular pathology.
- Treat bacterial endocarditis with antibiotics.
- Treat right atrial thrombus obstructing RV inflow with systemic anticoagulation (typically seen with dialysis catheters).
- Treat right atrial myxoma obstructing RV inflow with surgical resection.
- Manage right atrial volume overload with loop diuretics.
- Prescribe rate-controlling atrioventricular nodal blocking agents and anticoagulants for patients with atrial arrhythmias (atrial fibrillation and atrial flutter).

CHRONIC Rx

- Symptoms of systemic venous hypertension and congestion can be controlled with diuretics and angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, along with generalized salt and fluid restriction.
- Balloon valvuloplasty or dilation of the stenosed tricuspid valve has been shown to be effective, especially in patients with transvalvular pressure gradients 3 mm Hg and above, along with valve areas less than 1.5 cm^2. Patients with clinical evidence of systemic venous hypertension and congestion should be considered for valvotomy. However, tricuspid regurgitation that is characterized as more than mild is generally considered a contraindication to valvotomy because this can further worsen the tricuspid regurgitation. Tumor masses, vegetations, and thrombi are also contraindications to valvotomy.

- Surgery for TS is usually recommended when the valve is not treatable by balloon valvuloplasty and the mean diastolic gradient across the tricuspid valve is >5 mm Hg.
- Isolated tricuspid valve replacement surgery is not rare, but it is recommended for severe symptomatic TS. It is typically performed in the setting of concomitant mitral or aortic valve surgery.
- Surgical procedures for TS include commissurotomy and tricuspid valve replacement, and are typically avoided if valvotomy can be performed because of the relatively high postoperative morbidity and mortality rates.
- Tricuspid valve replacement is usually done with a large bioprosthesis, which is preferred to a mechanical prosthesis because of the high risk of thrombosis and the longer durability of bioprosthetic valve in the tricuspid position as opposed to the mitral or aortic positions.

DISPOSITION

The natural course of severe TS is not well known.

REFERRAL

TS may be difficult to diagnose, so consultation with a cardiologist is recommended.

PEARLS & CONSIDERATIONS

- Rheumatic heart disease accounts for >90% of stenotic tricuspid valves.
- Rheumatic TS almost always occurs in association with mitral valve disease and sometimes with aortic valve disease.
- The majority of cases present with tricuspid regurgitation or a combination of regurgitation and stenosis.

COMMENTS

Tricuspid valve replacement carries a 30-day operative morbidity and mortality rate of 5% to 7% in addition to a high risk of right heart thrombus formation. Therefore, surgical procedures are reserved for patients who are not candidates for balloon dilation techniques. Unlike patients with mitral stenosis, patients with TS typically do not report dyspnea, orthopnea, or paroxysmal nocturnal dyspnea symptoms.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Tricuspid Stenosis (Patient Information)

AUTHORS: **PHILLIP RUISI, D.O.**, and **ARAVIND RAO KOKKIRALA, M.D.**

SUGGESTED READINGS

AHA/ACC Guidelines for the management of patients with valvular heart disease, *Circulation* 129:e521–e643, 2014.

Block PC, Bonhoeffer P: Percutaneous approaches to valvular heart disease, *Curr Cardiol Rep* 7(2):108–113, 2005.

Mehra MR et al.: Difficult cases in heart failure: isolated tricuspid stenosis and heart failure: a focus on carcinoid heart disease, *Congest Heart Fail* 9(5):294, 2003.

Raman SV et al.: Tricuspid valve disease: tricuspid valve complex perspective, *Curr Probl Cardiol* 27(3):103, 2002.

Zaibag AM et al.: Percutaneous balloon valvuloplasty in tricuspid stenosis, *Br Heart J* 57:51–53, 1987.

BASIC INFORMATION

DEFINITION

Tricyclic antidepressants (TCAs) are secondary or tertiary amines that have variable abilities to inhibit reuptake of neurotransmitters (norepinephrine, dopamine, and serotonin) and to be anticholinergic, antihistaminic, and sedating. These properties are important to consider when prescribing these agents and when managing an intentional or accidental overdose.

SYNONYMS

Tricyclic antidepressant intoxication or poisoning
TCA OD

ICD-9CM CODES
969.0 Poisoning by antidepressant drugs
ICD-10CM CODES
T43.0 Poisoning by tricyclic and tetracyclic antidepressants

EPIDEMIOLOGY & DEMOGRAPHICS

- TCAs are one of the most common causes of death from prescription drug overdose in the United States.
- Available TCAs: amitriptyline, imipramine, desipramine, nortriptyline, doxepin, amoxapine, clomipramine, protriptyline, and others.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Cardiovascular:
- Intraventricular conduction delay (QRS prolongation).
- Sinus tachycardia.
- Atrioventricular block.
- Prolongation of the QT interval.
- Ventricular tachycardia.
- Wide complex tachycardia without P waves.
- Refractory hypotension (the most common cause of death from TCA overdose).
- Late arrhythmias or sudden death (in addition to the arrhythmias, which occur during the first 24 to 48 hr; late problems can occur up to 5 days after the overdose).
- Fig. ET1-51 illustrates a common ECG rhythm abnormality in tricyclic overdose.

Central nervous system:
- Coma.
- Delirium.
- Myoclonus.
- Seizures.

Other:
- Hyperthermia.
- Ileus.
- Urinary retention.
- Rhabdomyolysis.
- Kidney failure.
- Pulmonary complications (e.g., aspiration pneumonitis).
- Life-threatening overdose exists with the ingestion of >1 g of a TCA. Among patients who reach a hospital, most deaths occur within the first 24 hr; lack of initial symptoms can be deceptive.

ETIOLOGY AND PATHOGENESIS

- Mechanisms of TCA cardiovascular toxicity (Table ET1-24).
- CNS toxicity:
  1. Cholinergic blockade is believed to cause hyperthermia, ileus, urinary retention, pupillary dilation, delirium, and coma.
  2. The mechanism of myoclonus and seizures is not fully understood.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Cardiotoxicity from TCA can be confused with intoxication by drugs that cause QRS prolongation. These include class Ia antiarrhythmic agents (disopyramide, procainamide, quinidine), class Ic antiarrhythmic agents (encainide, flecainide, propafenone), cocaine, propranolol, quinine, chloroquine, neuroleptics, propoxyphene, and digoxin. Other causes of QRS prolongation include hyperkalemia, ischemic heart disease, cardiomyopathy, and cardiac conduction system dysfunction.

WORKUP

- Clinical presentation.
- Knowledge of the overdose.
- Although serum drug levels do not correlate well with toxicity, TCA concentration >1 mcg/ml can be life threatening; TCA concentration >3 mcg/ml is often fatal.
- Baseline complete blood count, prothrombin time, blood urea nitrogen, creatinine, and electrolytes.

TREATMENT

ACUTE GENERAL Rx

1. Initial measures:
   - Hospitalization with cardiac monitoring as well as monitoring of vital signs and temperature.
   - Initiate IV access.
   - Administer activated charcoal with sorbitol.
   - Large-bore tube gastric lavage is of unproven benefit.
   - Ipecac is contraindicated.
   - 12-Lead ECG.
   - If no evidence of cardiotoxicity has been noted during the first 6 hr of observation, further monitoring is not necessary; if there is evidence of cardiotoxicity, monitoring should continue for 24 hr after all signs of toxicity have resolved.

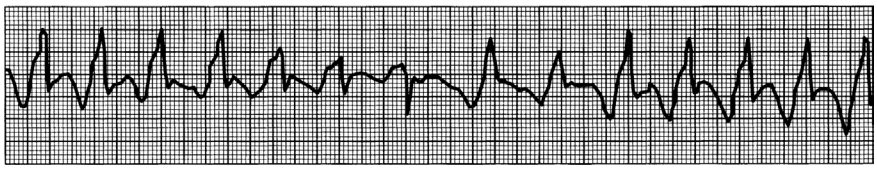


FIGURE ET1-51 Rhythm ECG in tricyclic overdose. (From Souhami RL, Moxham J: *Textbook of medicine,* ed 4, London, 2002, Churchill Livingstone.)

TABLE ET1-24 Mechanism of Tricyclic Antidepressant Cardiovascular Toxicity

Toxic Effect	Mechanism
Conduction Delays, Arrhythmias	
QRS prolongation atrioventricular block	Cardiac sodium channel → slowed depolarization in atrioventricular node, His-Purkinje fibers, and ventricular myocardium.
Sinus tachycardia	Cholinergic blockade, inhibition of norepinephrine reuptake.
Ventricular tachycardia	
Monomorphic	Cardiac sodium channel inhibition → reentry.
Torsades de pointes	Cardiac potassium channel inhibition → prolonged repolarization.
Ventricular bradycardia	Impaired cardiac automaticity.
Hypotension	
Vasodilation	Vascular alpha-adrenergic receptor blockade.
Decreased cardiac contractility	Cardiac sodium channel inhibition → impaired excitation-contraction coupling.

TABLE ET1-25 Treatment of Complications of Tricyclic Antidepressant Toxicity

Toxic Effect	Treatment
Cardiovascular	
QRS prolongation	Hypertonic $NaHCO_3$ if QRS prolongation is marked or progressing; not clear if treatment is needed in the absence of hypotension or arrhythmias.
Hypotension	Intravascular volume expansion, $NaHCO_3$ Vasopressors (norepinephrine) or inotropic agents (dopamine.) Correct hyperthermia, acidosis, seizures. Consider mechanical support.
Ventricular tachycardia	$NaHCO_3$, lidocaine, overdrive pacing. Correct hypotension, hypothermia, acidosis, seizures.
Torsades de pointes	Overdrive pacing.
Ventricular bradycardia	Chronotropic agent (epinephrine), pacemaker.
Sinus tachycardia	Treatment rarely needed.
Atrioventricular block type II second or third degree	Pacemaker.
Hypertension	Rapidly titratable antihypertensive agent (nitroprusside).
Central Nervous System	
Delirium	Restraints, benzodiazepine. Neuromuscular blockade for hyperthermia, acidosis.
Seizures	Benzodiazepine. Neuromuscular blockade for hyperthermia, acidosis.
Coma	Intubation, ventilation if needed.
Other	
Hyperthermia	Control seizures, agitation. Cooling measures.
Acidosis	$NaHCO_3$ Correct hypotension, hypoventilation

SUGGESTED READING

Glauser J: Tricyclic antidepressant poisoning, *Cleve Clin J Med* 67:704, 2000.

2. See Table ET1-25 for treatment of specific complications of TCA toxicity.
3. Hemodialysis is not effective.
4. When the patient is medically stable, psychiatric evaluation should be obtained.
5. An algorithm for treatment of tricyclic antidepressant overdoses is described in Fig. ET1-52.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **FRED F. FERRI, M.D.**

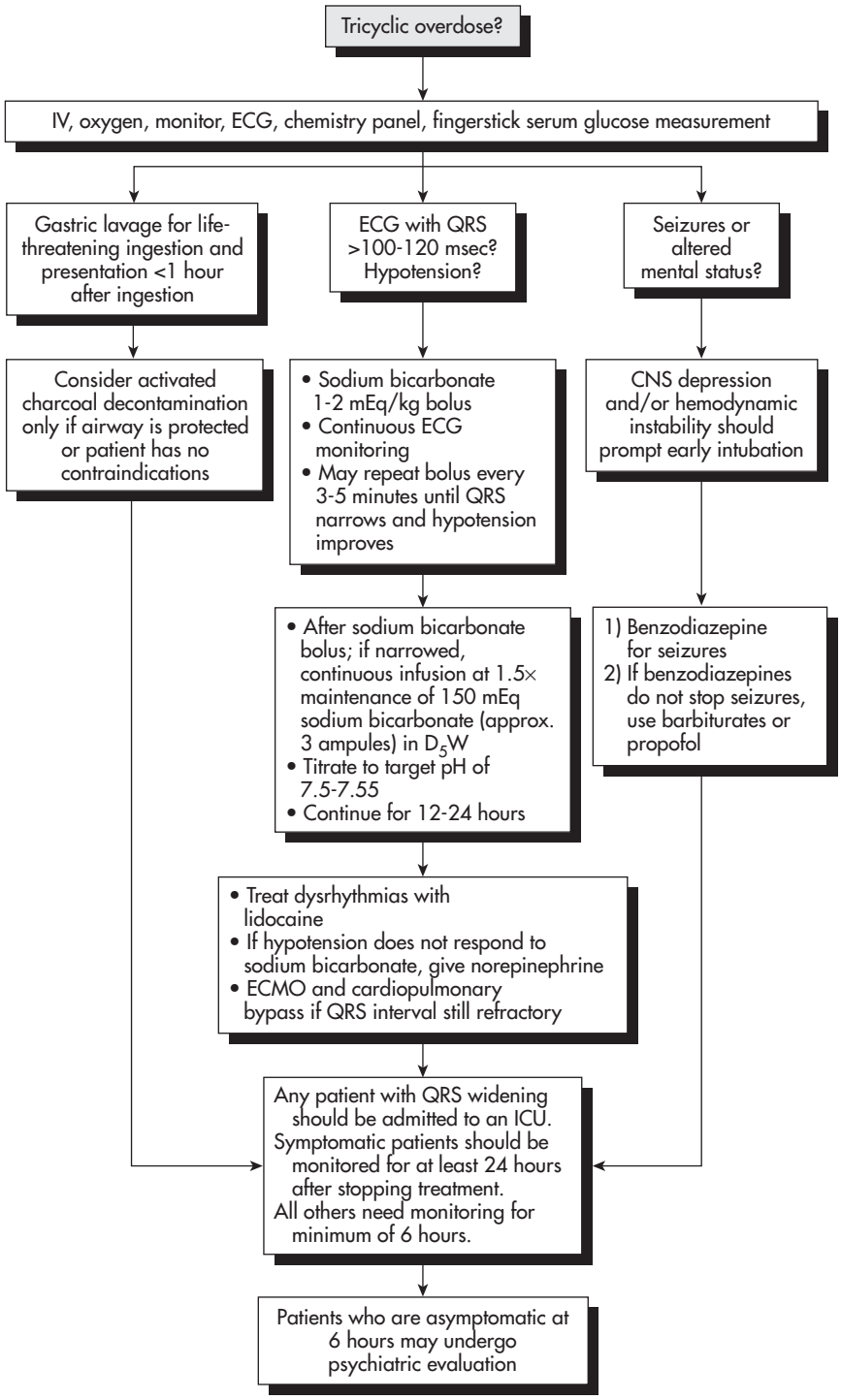


FIGURE ET1-52 Algorithm for treatment of tricyclic antidepressant overdoses. *CNS*, central nervous system; *D5W*, 5% dextrose in water; *ECG*, electrocardiogram; *ECMO*, extracorporeal membrane oxygenation; *ICU*, intensive care unit; *IV*, intravenous. (From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

Trigeminal Neuralgia PTG

BASIC INFORMATION

DEFINITION

Trigeminal neuralgia is an intense, usually unilateral, paroxysmal, stabbing pain in the sensory distribution of the fifth cranial nerve.

SYNONYMS

Tic douloureux ("painful tics/spasms")

ICD-9CM CODES
350.1 Trigeminal neuralgia
ICD-10CM CODES
G50.0 Trigeminal neuralgia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 4 per 100,000
PEAK INCIDENCE: Incidence increases with age and peaks at 67 yr; onset in 90% of patients is after age 40.
PREVALENCE: 155 in 1 million
PREDOMINANT SEX AND AGE: Male/female ratio is 1:1.5.
RISK FACTORS: Most cases are idiopathic; age and multiple sclerosis are risk factors.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients present with paroxysmal, unilateral facial pain that is usually described as shock-like, stabbing, or electric (Fig. T1-53).
- Pain can be spontaneous or triggered by touch, an air current, or activities such as shaving, eating, or brushing teeth.
- In severe cases, facial spasms can accompany the pain.
- Pain is usually described in distribution of the second (V2-maxillary) and third (V3-mandibular) divisions of the trigeminal nerve.
- The pain seldom lasts more than a few seconds to a minute.
- There is usually no sensory or motor loss.

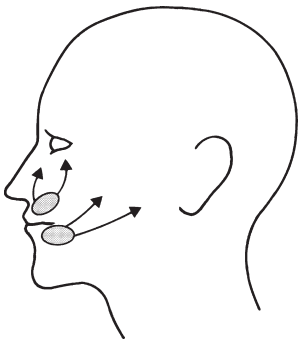


FIGURE T1-53 Trigeminal neuralgia. The two most common sites of origin and radiation of pain are shown: mouth-ear and nose-orbit. Pain usually starts in the region of the encircled area and radiates in the directions shown. (From Souhami RL, Moxham J: *Textbook of medicine,* ed 4, London, 2002, Churchill Livingstone.)

ETIOLOGY

- Idiopathic or "classical": cause usually unknown, likely an aberrant artery or vein compressing cranial nerve V at or near the pons
- Secondary: accounts for up to 15% of cases; caused by nonvascular lesions such as a demyelinating plaque from multiple sclerosis, or compression from a tumor near the pons.
- Box T1-7 summarizes causes of trigeminal neuralgia

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Trigeminal neuropathy
- Primary stabbing headache
- Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT)
- Postherpetic neuralgia
- Glossopharyngeal neuralgia
- Dental pain

WORKUP

Trigeminal neuralgia is a clinical diagnosis (see above).

IMAGING STUDIES

Neuroimaging (MRI) should be considered in young patients (<40 years) with atypical symptoms (sensory loss, bilateral symptoms).

TREATMENT

PHARMCOLOGIC Rx

- Carbamazepine 400 to 800 mg, 2 to 3 times daily divided dosing is the recommended initial treatment. This can be titrated to pain relief by 100 to 200 mg every 3 days to a maximum of 1200 mg divided bid or tid.
- Oxcarbazepine can be used if carbamazepine is not tolerated due to side effects. Other medications include baclofen, phenytoin, gabapentin, clonazepam, lamotrigine, and levetiracetam.
- Drug combinations can be tried when one medication is partially effective before proceeding with secondary intervention.
- Spontaneous remissions may be seen in trigeminal neuralgia, and therefore periodic medication tapers should be considered if the patient is pain free.
- In the elderly population, caution should be used when initiating and titrating the above medications. Caution and extensive counseling should also be used in women of childbearing age when initiating treatment with antiseizure medications.

NONPHARMACOLOGIC THERAPY

Patients with refractory pain eventually need secondary intervention such as microvascular decompression, selective nerve fiber destruction (rhizotomy), glycerol injection, thermal lesioning, chemical ablation, or gamma knife radiosurgery. Microvascular decompression is the only available nondestructive procedure, and is effective in 75% of patients, with observed long-term benefits.

DISPOSITION

- Most patients are responsive to initial pharmacologic treatment. Spontaneous remission is possible.
- Medical management is eventually ineffective in 30% to 50% of patients.

REFERRAL

Referral to a neurologist is appropriate if there is uncertainty about diagnosis or if symptoms are refractory to conservative management.

BOX T1-7 Causes of Trigeminal Neuralgia

Classical
Neurovascular compression by an artery or vein
Symptomatic
Saccular aneurysm
Arteriovenous malformation
Tumors/mass-lesions at cerebellopontine angle
- Vestibular schwannoma
- Meningioma
- Epidermoid

Primary demyelinating disorders
- Multiple sclerosis
- Charcot-Marie-Tooth disease (rare)

Infiltrative disorders
- Trigeminal amyloidoma

Nondemyelinating lesions
- Small infarct or angioma in the brainstem

Familial

Modified from Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.

PEARLS & CONSIDERATIONS

In a young patient with trigeminal neuralgia, secondary causes such as multiple sclerosis should be considered, and an MRI of the head obtained. In secondary disease, initial therapy should address underlying secondary causes.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Trigeminal Neuralgia (Patient Information)

AUTHOR: **JONATHAN H. SMITH, M.D.**

SUGGESTED READINGS

Barker 2nd FG et al.: The long-term outcome of microvascular decompression for trigeminal neuralgia, *NEJM* 334(17):1077–1083, 1996.

Gronseth G: Practice parameter: the diagnostic evaluation and treatment of trigeminal neuralgia (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the European Federation of Neurological Societies, *Neurology* 71(15):1183, 2008.

Katusic S et al.: Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945-1984, *Ann Neurol* 27(1):89–95, 1990.

Lambert M: AAN and EFNS guideline on diagnosing and treating trigeminal neuralgia, *Am Fam Physician* 79(11):1291, 2008.

BASIC INFORMATION

DEFINITION

Trigger finger, or digital stenosing tenosynovitis, refers to an inflammatory process of the digital flexor tendon sheath that can lead to nodule formation of the flexor tendon. These changes lead to pain and difficulty or inability to extend the digit due to inability of the flexor tendon to glide through the A1 pulley.

SYNONYMS

Digital stenosing tenosynovitis

ICD-9CM CODES
727.03 Trigger finger (acquired).
ICD-10CM CODES
M65.30 Trigger finger, unspecified finger

EPIDEMIOLOGY & DEMOGRAPHICS

In adults, the middle finger is most often affected (Fig. T1-54). In children, the thumb is most often affected.
PREDOMINANT SEX AND AGE: Female/male ratio of 4:1. Trigger finger can be found in all age groups but is commonly found in patients aged >45 yr.
RISK FACTOR: Repetitive use occupations, such as meat cutters, seamstresses, tailors, and dentists.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Tenosynovitis of the flexor tendon always precedes the mechanical symptoms of triggering, resulting in pain over the flexor tendon with palpation, passive stretching, or resisting flexion isometrically.
- A palpable tender nodule is noted at palmar aspect of the metacarpophalangeal (MCP) joint of the affected digit.

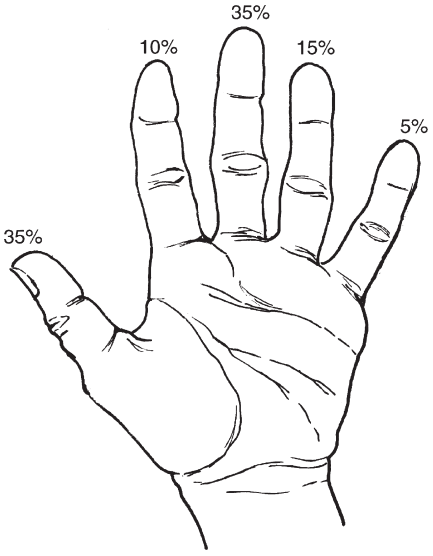


FIGURE T1-54 Trigger finger. Frequency of trigger finger according to digit in adults. In children, virtually all cases occur in the thumb. (From Canoso J: *Rheumatology in primary care,* Philadelphia, 1997, Saunders.)

- Painful triggering or snapping with flexion of the affected digit.
- Locking or loss of active digital extension.
- The digit can be fixed in flexion (trapped or incarcerated).
- Usually affects one digit. If more digits are involved, a systemic cause is most likely present (e.g., diabetes, rheumatoid arthritis).

ETIOLOGY

Trigger finger is described as being primary or secondary:
- Primary (idiopathic).
- Secondary.
  1. Diabetes.
  2. Rheumatoid arthritis.
  3. Hypothyroidism.
  4. Histiocytosis.
  5. Amyloidosis.
  6. Gout.

DIAGNOSIS

Clinical history and physical examination

DIFFERENTIAL DIAGNOSIS

- Dupuytren's contracture.
- De Quervain's tenosynovitis.
- Acute digital tenosynovitis.
- Proliferative tenosynovitis.
- Ulnar collateral ligament injury (gamekeeper's thumb).
- Carpal tunnel syndrome.
- Flexor tendon rupture.
- MCP osteoarthritis.

WORKUP

Pursued if a secondary cause is suspected.

LABORATORY TESTS

- Complete blood count with differential.
- Electrolytes, blood urea nitrogen, creatinine.
- Blood glucose, Hb_{A1c}.
- Thyroid function tests.
- Rheumatoid factor/anti-CCP antibody.
- Uric acid.

IMAGING STUDIES

- Radiograph studies are not helpful unless a secondary cause has affected other organs (e.g., rheumatoid lung).

FIGURE T1-55 Injection into the palm for trigger finger. (From Carr A, Hamilton W: *Orthopedics in primary care,* ed 2, Philadelphia, 2005, Saunders.)

- Musculoskeletal ultrasonography can be useful in characterizing the lesion and guiding treatment.

TREATMENT

The goals of treatment are to reduce swelling and inflammation in the flexor tendon sheath and allow smooth movement of the tendon under the A1 pulley of the MCP joint.

NONPHARMACOLOGIC THERAPY

- Ice, splinting or buddy taping to the adjacent finger for 4 to 6 wk.
- Preventive measures include the use of gloves and damping tape to widen grips.
- Physiotherapy with stretching and heat.

ACUTE GENERAL Rx

- In idiopathic trigger finger, different steroid preparations with local anesthetics are used if patients have not responded to conservative treatment (Fig. T1-55).
- If symptoms do not resolve in 6 wk, a repeat injection can be tried.
- Pain control.

CHRONIC Rx

- Surgical release is indicated in patients with refractory symptoms (e.g., locked digits) despite nonpharmacologic and acute treatment.
- Surgery is also indicated in patients with recurrent symptoms despite two steroid injections.

DISPOSITION

- After steroid injection, symptoms usually resolve in 3 to 5 days, and locking resolves in 60% of the cases in 2 to 3 wk.
- If symptoms recur, a repeat steroid injection improves the symptoms in ≥80% of patients.
- Diabetic patients do not have the same success rate with steroid injections as the idiopathic group.

REFERRAL

If steroid injection therapy is considered, a rheumatology or hand surgery consult is requested.

PEARLS & CONSIDERATIONS

COMMENTS

If more than one digit is involved, a workup for a secondary systemic cause is in order.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Trigger Finger (Patient Information)

AUTHORS: **RYAN W. ZUZEK, M.D.,** **PAUL GORDON, M.D.**, and **DANIEL E. MENDEZ-ALLWOOD, M.D.**

SUGGESTED READINGS

Akhtar S et al.: Management and referral for trigger finger/thumb, *BMJ* 331(7507):30, 2005.

Mol M et al.: Resolution and recurrence rates of idiopathic trigger finger after corticosteroid injection, *Hand* 8(2):183–190, 2013.

Ryzewicz M, Wolf J: Trigger digits: principles, management and complications, *J Hand Surg* 31(1):135, 2006.

Saldana MJ: Trigger digits: diagnosis and treatment, *J Am Acad Orthop Surg* 9(4):246, 2001.

Wang J et al.: Percutaneous release, open surgery, or corticosteroid injection, which is the best treatment method for trigger digits? *Clin Orthop Relat Res* 471(6):1879–1886, 2013.

Trochanteric Bursitis PTG

BASIC INFORMATION

DEFINITION

Trochanteric bursitis reflects inflammation or irritation of the bursa or bursae located at the insertion of the gluteal muscles at the greater trochanter of the femur (Fig. T1-56).

SYNONYMS

Greater trochanteric pain syndrome
Greater trochanteric bursitis

ICD-9CM CODES
726.5 Bursitis trochanteric area
726.5 Enthesopathy of hip region (Bursitis of hip, Trochanteric tendinitis)
ICD-10CM CODES
M70.60 Trochanteric bursitis, unspecified hip

EPIDEMIOLOGY & DEMOGRAPHICS

- Trochanteric bursitis can be associated with other conditions, including osteoarthritis of the hip, lumbar spinal degenerative joint disease, and rheumatoid arthritis.
- Incidence peaks between the fourth and sixth decades of life but can occur at any age.
- Occurs in females more often than males (ratio of 4:1).
- Bilateral prevalence in females is 6.6% and in males is 1.9%.
- Unilateral prevalence in females is 15.0%, whereas in males is 8.5%.
- Prevalence is 3200/100,000.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Lateral hip pain is the most common symptom, though the hip joint itself is not involved. The pain is chronic, intermittent, and located over the outer lateral hip and thigh.
- Bursal swelling may be present.
- Pain is precipitated with prolonged lying or standing on the affected side.
- Walking, climbing, and running exacerbate the pain.
- Point tenderness over the greater trochanter is noted.
- Pain is reproduced with resisted hip abduction.

FIGURE T1-56 Typical location of pain in trochanteric bursitis syndrome. This is also a frequent pain radiation site for lumbar spine lesion, various nerve compression syndromes, and hip disease, particularly in osteonecrosis of the femoral head. (From Canoso JJ: *Rheumatology in primary care,* Philadelphia, 1997, Saunders.)

ETIOLOGY

- The specific cause of trochanteric bursitis is not known, although repetitive high-intensity use of the tensor fasciae and gluteus medius over the outer femur, trauma, infection (tuberculosis and bacterial), and crystal deposition can precipitate the disease.
- Trochanteric bursitis can occur when other conditions such as osteoarthritis of the knee and hip, sacroiliac joint disorders, leg length discrepancy, ankle sprain, and bunions of the feet cause changes in the patient's gait, placing varus stress on the hip joint.
- It can also occur as a complication resulting from arthroscopic surgery of the hip (estimated 1.4% of cases).

DIAGNOSIS

A detailed physical examination and clinical presentation usually make the diagnosis of trochanteric bursitis. X-ray images are helpful adjunctive studies used to exclude other conditions either associated with or mimicking trochanteric bursitis.

DIFFERENTIAL DIAGNOSIS

- Osteoarthritis of the hip
- Osteonecrosis of the hip
- Stress fracture of the hip
- Osteoarthritis of the lumbar spine
- Meralgia paresthetica
- Iliotibial band syndrome
- Fibromyalgia
- Iliopsoas bursitis
- Trochanteric tendonitis
- Trauma
- Osteomyelitis
- Tuberculosis of the greater trochanter
- Metastatic bone disease
- Septic arthritis
- Gluteal medius tendon tears

WORKUP

A workup is indicated if suspected associated conditions exist; otherwise treatment can be started on clinical grounds alone.

LABORATORY TESTS

Generally not indicated in clear cases.

IMAGING STUDIES

- Standing anterior to posterior pelvic x-rays and specific views of hip and back are used to evaluate associated symptoms such as leg length discrepancy, lumbar spondylosis, and sacroiliac joint diseases causing the bursitis. Sometimes calcifications may be seen around the greater trochanter in the areas of bursal development.
- Bone scan is usually not necessary.
- CT and MRI may show bursitis but are usually not warranted unless suspect associated conditions that would affect treatment decisions. MRI shows increased signal in bursitis.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Physical therapy and iliotibial band stretching exercises can reduce irritation of the trochanteric bursa area.
- Heat application prior to exercising
- Ultrasound therapy
- Rest
- Treat gait disturbance by knee brace, shoe lift, ankle supports, foot orthotics for the specific underlying conditions

ACUTE GENERAL Rx

- NSAIDs for pain relief: ibuprofen 800 mg PO tid or naproxen 500 mg PO bid for the initial 4 wk
- Using US to enhance absorption of topical corticosteroids percutaneously (phonophoresis)
- Corticosteroid injection
- Regional anesthetic block can be used as a treatment and may also help differentiate from referred pain.

CHRONIC Rx

Although rarely done, surgical removal of the bursa or with also lengthening of iliotibial band with bursectomy is possible for patients with refractory symptoms or infection.

DISPOSITION

- Most patients respond to NSAIDs and/or nonpharmacologic therapy.
- Steroid injection: ~70% of patients respond after first injection and >90% respond to two injections.
- 25% of patients receiving steroid injection may develop a relapse.

REFERRAL

A rheumatology or orthopedics referral is made if steroid injection therapy is needed or if the etiology is believed to be infectious.

PEARLS & CONSIDERATIONS

Patients with trochanteric bursitis will commonly report "hip" pain. The physical examination readily distinguishes true hip pain from trochanteric bursitis. Relief of pain with local corticosteroid injection is helpful in differentiating trochanteric bursitis from referred pain.

COMMENTS

- The absence of pain with flexion and extension differentiates trochanteric bursitis from degenerative joint disease of the hip.
- Localization of pain over the lateral hip and thigh differentiates trochanteric bursitis from meralgia paresthetica located over the anterolateral thigh and osteoarthritis located over the inner thigh groin area.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Trochanteric Bursitis(Patient Information)

AUTHORS: **SYEDA M. SAYEED, M.D.** and **UZMA NASIR, M.D.**

SUGGESTED READINGS

Adkins SB, Figler RA: Hip pain in athletes, *Am Fam Physician* 61(7):2109, 2000.

Canoso JJ: Hip pain. In Canoso JJ, Kersey R (eds): *Rheumatology in primary care.* Philadelphia, Saunders.

Cardone DA, Tallia AF: Diagnostic and therapeutic injection of the hip and knee, *Am Fam Physician* 67:2147, 2003.

Lievense A et al.: Prognosis of trochanteric pain in primary care, *Br J Gen Pract* 55:199–204, 2005.

Lustenberger DP et al.: Efficacy of treatment of trochanteric bursitis:a systemic review, *Clin J Sport Med* 21:447, 2011.

Martin RL, Sekika JK: The interrater reliability of 4 clinical tests used to assess individuals with musculoskeletal hip pain, *J Orthop Sports Phys Ther* 38(2):71, 2008.

Rifat SF, Moeller JL: Injection and aspiration techniques for the primary care physician, *Compr Ther* 28(4):222–229, 2002.

Sayed-Noor AS et al.: Distal lengthening of ilio-tibial band by Z-plasty for treating refractory greater trochanteric pain after total hip arthroplasty (Pedersen-Noor operation), *Arch Orthop Trauma Surg* 129:597–602, 2009.

Segal NA et al.: Multicenter Osteoarthritis Study Group: Greater trochanteric pain syndrome: epidemiology and associated factors, *Arch Phys Med Rehabil* 88(8):988, 2007.

Strauss EJ et al.: Greater trochanteric pain syndrome, *Sports Med Arthrosc* 18:113–119, 2010.

BASIC INFORMATION

DEFINITION

Tropical sprue is a malabsorption syndrome occurring primarily in tropical regions, including Puerto Rico, India, and Southeast Asia.

SYNONYMS

Postinfectious tropical malabsorption
"Tropical enteropathy," referring to a subclinical form of tropical sprue

ICD-9CM CODES
579.1 Tropical sprue
ICD-10CM CODES
K90.1 Tropical sprue

EPIDEMIOLOGY & DEMOGRAPHICS

- Tropical sprue is endemic in tropical regions of Venezuela, Colombia, the Middle East, the Far East, the Caribbean (Puerto Rico, Haiti, Dominican Republic, Cuba), and India.
- The disease affects mainly adults, although it has been reported in all age groups.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The classic clinical features of tropical sprue are nonspecific and simply reflect the symptom of malabsorption. Onset is generally not insidious, and most patients can pinpoint when their disorder began.
- Diffuse, nonspecific abdominal tenderness and distention. Abdominal pain is crampy in nature.
- Low-grade fever.
- Glossitis, cheilosis, hyperkeratosis, hyperpigmentation.
- Diarrhea, often with mucus and foul-smelling stools from fat malabsorption.
- Nausea, which leads to decreased appetite and decreased oral intake.
- Lactose intolerance often develops early in the course of tropical sprue.

ETIOLOGY

- Unknown. There is a strong presumption that it is caused by an enteric infection, perhaps in individuals predisposed by some nutritional deficiency.
- Associated with overgrowth of predominantly coliform bacteria in the small intestine.

DIAGNOSIS

The clinical features of tropical sprue include anorexia, diarrhea, weight loss, abdominal pain, and steatorrhea; these symptoms can develop in expatriates even several months after returning to temperate regions.

DIFFERENTIAL DIAGNOSIS

- Celiac disease
- Parasitic infestation
- Inflammatory bowel disease
- Other causes of malabsorption (e.g., Whipple's disease)
- Lymphoma
- Pancreatic tumor
- Intestinal tuberculosis
- Microsporidia-associated HIV enteropathy

WORKUP

Diagnostic workup includes a comprehensive history (especially travel history), physical examination, laboratory evidence of malabsorption (see below), and jejunal biopsy; the biopsy results are nonspecific, with blunting, atrophy, and even disappearance of the villi and subepithelial lymphocytic infiltration. Partial villus atrophy distinguishes tropical sprue histologically from celiac sprue, which reveals flattened mucosa.

LABORATORY TESTS

- Megaloblastic anemia (>50% of cases)
- Vitamin B_{12} deficiency, folate deficiency
- Abnormal D-xylose absorption (72-hr fecal fat determination or serum carotene concentration)
- Stool examination to exclude *Giardia* spp.

IMAGING STUDIES

Gastrointestinal series with small-bowel follow-through may reveal coarsening of the jejunal folds.

TREATMENT

NONPHARMACOLOGIC THERAPY

Monitoring of weight and calorie intake

ACUTE GENERAL Rx

- Folic acid therapy (5 mg bid for 2 wk followed by a maintenance dose of 1 mg tid) will improve anemia and malabsorption in more than two thirds of patients.
- Tetracycline 250 mg qid for 4 to 6 wk in individuals who have returned to temperate zones, up to 6 mo in patients in endemic areas; ampicillin 500 mg bid for at least 4 wk in patients intolerant to tetracycline.
- Correction of vitamin B_{12} deficiency: vitamin B_{12} 1000 mcg IM weekly for 4 wk, then monthly for 3 to 6 mo.
- Correction of other nutritional deficiencies (e.g., calcium, iron).

DISPOSITION

Complete recovery with appropriate therapy

REFERRAL

Gastrointestinal referral for jejunal biopsy

PEARLS & CONSIDERATIONS

COMMENTS

- Tropical sprue should be considered in any patient who presents with chronic diarrhea, weight loss, and malabsorption, especially if there is significant travel and exposure history.
- Important factors in the medical history in addition to travel history are use of medications that may predispose to a small-bowel overgrowth, HIV exposure (increased risk of chronic diarrhea), and any surgical procedure that may predispose to blind loop syndrome.
- Most of the functional changes in tropical sprue may be related to small-bowel mucosal damage; however, there is also dysfunctional hormonal regulation of the gut (increased enteroglucagon and motilin levels, decreased postprandial insulin and gastric inhibitory peptide), and decreased ability of the colon to absorb water.
- Even with prolonged therapy relapses can occur; however, some may be attributable to reexposure to an infecting organism rather than relapsing disease.

AUTHOR: **FRED F. FERRI, M.D.**

BASIC INFORMATION

DEFINITION

Miliary tuberculosis (TB) is an infection of disseminated hematogenous disease, caused by the bacterium *Mycobacterium tuberculosis* (Mtb), and is often characterized as resembling millet seeds on pathologic or radiologic examination. Extrapulmonary disease may occur in virtually every organ site.

SYNONYMS

Disseminated TB

ICD-9CM CODES
018.94 Miliary tuberculosis
ICD-10CM CODES
A19.9 Miliary tuberculosis, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): >38% of AIDS patients with TB have disseminated disease, often with concurrent pulmonary and extrapulmonary active sites. (See "Tuberculosis, Pulmonary" in Section I.)

PREVALENCE (IN U.S.)

- Undetermined
- Highest prevalence
  1. AIDS patients
  2. Minorities
  3. Children
  4. Foreign-born persons
  5. Elderly

PREDOMINANT SEX

- No specific predilection
- Male predominance in AIDS, shelters, and prisons reflected in disproportionate male TB incidence

PREDOMINANT AGE: Predominantly among 24 to 45 yrs

PEAK INCIDENCE: HIV-positive patients, regardless of age

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- See also "Etiology"
- Common symptoms
  1. High intermittent fever (93%)
  2. Night sweats (79%)
  3. Weight loss (85%)
  4. Dyspnea (64%)
  5. Cough (82%)
- Symptoms referable to individual organ systems may predominate
  1. Meninges
  2. Pericardium
  3. Liver
  4. Kidney
  5. Bone
  6. GI tract
  7. Lymph nodes
  8. Serous spaces
     a. Pleural
     b. Pericardial
     c. Peritoneal
     d. Joint
  9. Skin
  10. Lung: cough, shortness of breath
- Adrenal insufficiency possible, caused by infection of adrenal gland
- Pancytopenia
  1. With fever and weight loss *or*
  2. Without other localizing symptoms or signs *or*
  3. With only splenomegaly
- TB hepatitis
  1. Tender liver
  2. Obstructive enzymes (alkaline phosphatase) elevated out of proportion to minimal hepatocellular enzymes (SGOT, SGPT) and bilirubin
- TB meningitis
  1. Gradual-onset headache
  2. Minimal meningeal signs
  3. Malaise
  4. Low-grade fever (may be absent)
  5. Sudden stupor or coma
  6. Cranial nerve VI palsy
- TB pericarditis
  1. Effusions resembling TB pleurisy
  2. Cardiac tamponade
- Skeletal TB
  1. Large joint arthritis (with effusions resembling TB pericarditis)
  2. Bone lesions (especially ribs)
  3. Pott's disease
     a. TB spondylitis, especially of lower thoracic spine
     b. Paraspinous TB abscess
     c. Possible psoas abscess
     d. Frequent cord compression (often relieved by steroids)
- Genitourinary TB
  1. Renal TB
     a. Papillary necrosis
     b. Destruction of renal pelvis
     c. Strictures of upper third of ureters
     d. Hematuria
     e. Pyuria with misleading bacterial cultures
     f. Preserved renal function
  2. TB orchitis or epididymitis
     a. Scrotal mass
     b. Draining abscess
  3. Chronic prostatic TB
- GI TB
  1. Diarrhea
  2. Pain
  3. Obstruction
  4. Bleeding
  5. Especially common with AIDS
  6. Bowel lesions
     a. Circumferential ulcers
     b. Short strictures
     c. Calcified granulomas
     d. TB mesenteric caseous adenitis
     e. Abscess, but rare fistula formation
     f. Often difficult to distinguish from granulomatous bowel disease (Crohn's disease)
- TB peritonitis
  1. Fluid resembles TB pleurisy
  2. PPD often negative
  3. Tender abdomen
  4. Doughy peritoneal consistency, often with ascites
  5. Peritoneal biopsy indicated for diagnosis
- TB lymphadenitis (scrofula)
  1. May involve all node groups
  2. Common adenopathies
     a. Cervical
     b. Supraclavicular
     c. Axillary
     d. Retroperitoneal
  3. Biopsy generally needed for diagnosis
  4. Surgical resection of nodes may be necessary
  5. Especially common with AIDS
- Cutaneous TB
  1. Skin infection from autoinoculation or dissemination
  2. Nodules or abscesses
  3. Tuberculids (possibly allergic reactions)
  4. Erythema nodosum
- Miscellaneous presentations
  1. TB laryngitis
  2. TB otitis
  3. Ocular TB
     a. Choroidal tubercles
     b. Iritis
     c. Uveitis
     d. Episcleritis
  4. Adrenal TB
  5. Breast TB

ETIOLOGY

- See also "Pulmonary Tuberculosis" in Section I.
- Mtb, a slow-growing, aerobic, non–spore forming, nonmotile acid-fast bacillus
- Humans are the only reservoir for Mtb.
- Pathogenesis:
  1. Acid-fast bacilli (AFB) (Mtb) are ingested by macrophages in alveoli, then transported to regional lymph nodes where spread is contained.
  2. Some AFB reach the bloodstream and disseminate widely.
  3. Immediate active disseminated disease may ensue or a latent period may develop.
  4. During latent period, T-cell immune mechanisms contain infection in granulomas until later reactivation occurs as a result of immunosuppression or other undefined factors in conjunction with reactivated pulmonary TB or alone.
- Miliary TB may occur as a consequence of the following:
  1. Primary infection: inability to contain primary infection leads to a hematogenous spread and progressive disseminated disease.
  2. In late chronic TB and in those with advanced age or poor immunity, a continuous seeding of the blood may develop and lead to disseminated disease.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Widespread sites of possible dissemination associated with myriad differential diagnostic possibilities:

- Lymphoma
- Typhoid fever

- Brucellosis
- Other tumors
- Collagen-vascular disease

WORKUP

- Prompt evaluation is essential
- Sputum for AFB stain and culture and chest x-ray
- High-resolution CT is more sensitive for miliary TB than CXR
- PPD, which may be negative in immunocompromised patients
- Fluid analysis and mycobacterial culture wherever available
  1. Sputum
  2. Blood: particularly helpful in patients with AIDS
  3. Urine
  4. CSF
  5. Pleural
  6. Pericardial
  7. Peritoneal
  8. Gastric aspirates
- Biopsy of any involved tissue is advisable to make immediate diagnosis
  1. Transbronchial biopsy preferred and easily accessible
  2. Bone marrow
  3. Lymph node
  4. Scrotal mass if present
  5. Any other involved site
  6. Positive granuloma or AFB on biopsy specimen is diagnostic
- Imaging studies as needed

LABORATORY TESTS

- Culture and fluid analysis as described previously
- Smear-negative sputum often is positive weeks later on culture
- CBC is usually normal
- ESR is usually elevated

IMAGING STUDIES

- Chest x-ray examination (may or may not be positive) (see "Tuberculosis, Pulmonary" in Section I)
- CT scan or MRI of brain and spinal cord (Fig. T1-57)
  1. Tuberculoma
  2. Basilar arachnoiditis
- Barium studies of bowel

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Bed rest during acute phase of treatment
- High-calorie, high-protein diet to reverse malnutrition and enhance immune response to TB
- Isolation in negative-pressure rooms with high-volume air replacement and circulation (with health care provider wearing proper protective 0.5- to 1-micron filter respirators)
  1. Until three consecutive sputum AFB smears are negative, if pulmonary disease coexists
  2. Isolation not required for closed-space TB infections

ACUTE GENERAL Rx

- See "Tuberculosis, Pulmonary" in Section I.
- Therapy should be initiated immediately. Do not wait for definitive diagnosis.
- More rapid response to chemotherapy by disseminated TB foci than cavitary pulmonary TB.
- Treatment for 6 mo with INH plus rifampin plus PZA.
  1. Treatment for 12 mo often required for bone and renal TB.
  2. Prolonged treatment often required for CNS and pericardial.
  3. Prolonged treatment often required for all disseminated TB in infants.
- Compliance (rigid adherence to treatment regimen) is the chief determinant of success.
  1. Supervised directly observed therapy (DOT) is recommended for all patients.
  2. Supervised DOT is mandatory for unreliable patients.
- Steroids are often helpful additions in fulminant miliary disease with the hypoxemia and DIC.

CHRONIC Rx

- Generally not indicated beyond treatment described previously
- Prolonged treatment supervised by infectious disease expert required in a few complicated infections caused by resistant organisms

DISPOSITION

- Monthly follow-up by physician experienced in TB treatment
- Confirm sensitivity testing, and alter treatment appropriately (see "Tuberculosis, Pulmonary" in Section I)

REFERRAL

- To infectious disease expert for:
  1. HIV-positive patient
  2. Patient with suspected drug-resistant TB
  3. Patient previously treated for TB
  4. Patient whose fever has not decreased and sputum (if positive) has not converted to negative in 2 to 4 wk
  5. Patients with overwhelming pulmonary or extrapulmonary TB
- To pulmonary, orthopedic, or GI physicians for examinations or biopsy

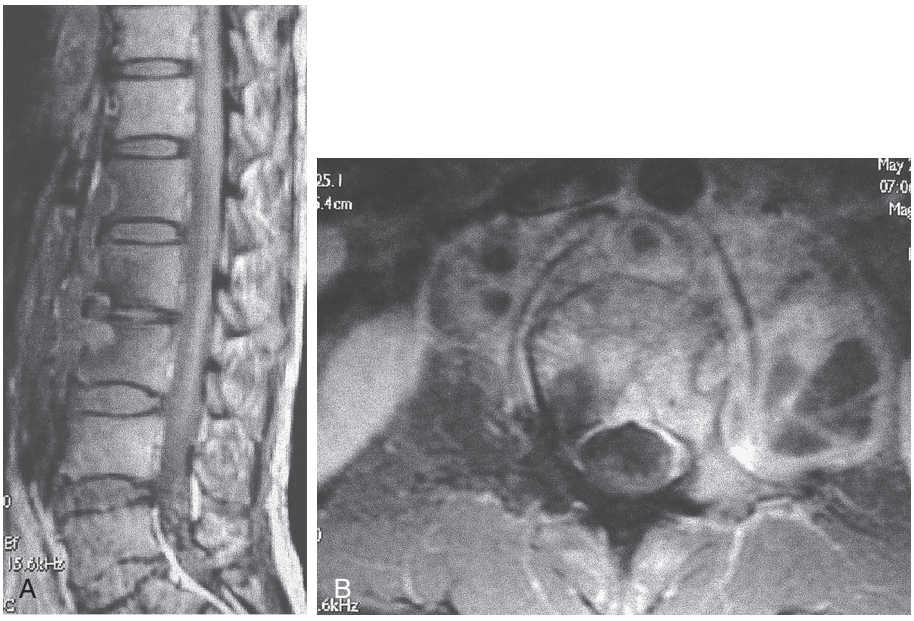


FIGURE T1-57 A and **B,** Magnetic resonance images of tuberculous spinal osteomyelitis with scalloping of the vertebrae (tuberculous caries) and paraspinal "cold" abscesses. (From Grainger RG, Allison D: *Grainger & Allison's diagnostic radiology, a textbook of medical imaging,* ed 4, London, 2001, Churchill Livingstone.)

PEARLS & CONSIDERATIONS

COMMENTS

- Consider acute TB in critically ill patients with enigmatic acute respiratory distress syndrome, shock, or DIC.
- All contacts (especially close household contacts and infants) should be properly tested for PPD conversions >3 mo following exposure.
- Those with positive PPD should be evaluated for active TB and properly treated or given prophylaxis.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Tuberculosis, Pulmonary (Related Key Topic)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

American Thoracic Society: CDC and the Infectious Disease Society of America: Controlling tuberculosis in the United States, *MMWR Morb Mortal Wkly Rep* 54(RR-12):1, 2005.

Golden MP, Vikram HR: Extrapulmonary tuberculosis: an overview, *Am Fam Physician* 72(9):1761, 2005.

Jacob JT et al.: Acute forms of tuberculosis in adults, *Am J Med* 122:12–17, 2009.

Maher D et al.: Tuberculosis deaths in countries with high HIV prevalence: what is their use as an indicator in tuberculosis programme monitoring and epidemiological surveillance? *Int J Tuberc Lung Dis* 9(2):123, 2005.

Matsushima T: Miliary tuberculosis or disseminated tuberculosis, *Intern Med* 44(7):687, 2005.

Mitnick CD et al.: Comprehensive treatment of extensively drug-resistant tuberculosis, *N Engl J Med* 369:563–574, 2008.

Miyoshi I et al.: Miliary tuberculosis not affecting the lungs but complicated by acute respiratory distress syndrome, *Intern Med* 44(6):622, 2005.

Sharma SK et al.: Miliary tuberculosis: new insights into an old disease, *Lancet Infect Dis* 5(7):415, 2005.

Torgersen J et al.: Molecular epidemiology of pleural and other extrapulmonary tuberculosis: a Maryland state review, *Clin Infect Dis* 42(10):1375, 2006.

BASIC INFORMATION

DEFINITION

Pulmonary tuberculosis (TB) is an infection of the lung and, occasionally, surrounding structures, caused by the bacterium *Mycobacterium tuberculosis* (Mtb). Multidrug-resistant (MDR) TB is defined as disease caused by strains of Mtb that are at least resistant to treatment with isoniazid and rifampin; extensively drug-resistant (XDR) TB refers to disease caused by MDR strains that are also resistant to treatment with any fluoroquinolone and any of the injectable drugs used in the treatment of second-line anti-TB drugs.

SYNONYMS

TB

ICD-9CM CODES
011.9 Pulmonary tuberculosis
ICD-10CM CODES
A15.0 Tuberculosis of lung

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (WORLDWIDE): In 2012 there were:
- 8.6 million new cases of active tuberculosis; 13% involved coinfection with HIV
- 1.4 million deaths from TB, including 430,000 among HIV-infected patients; 310,000 incident cases of multidrug-resistant TB

Sub-Saharan Africa has the highest rates of active TB per capita.

Absolute number of cases is highest in Asia, with India and China having the greatest burden of disease globally.

INCIDENCE (IN U.S.)
- In 2012, there were 9,945 cases of TB in the United States for a rate of 3.2 cases/100,000 persons—the lowest reported rate since recording began in 1953 and a 5.4% decline in cases from 2011.
- >90% of new cases each yr from reactivated prior infections
- 9% newly infected
- Only 10% of patients with purified protein derivative (PPD) conversions (higher [8%/yr] in HIV-positive patients) will develop TB, most within 1 to 2 yr
- Two thirds of all new cases in racial and ethnic minorities
- 80% of new cases in children in racial and ethnic minorities
- Occurs most frequently in geographic areas and among populations with highest AIDS prevalence
  1. Urban blacks and Hispanics between 25 and 45 yr old
  2. Poor, crowded urban communities
- Nearly 36% of new cases from new immigrants
- In 2012 in the United States, 1.1% of cases were MDR TB which is a decline from 8.2% in 2008.

PREVALENCE (IN U.S.)
- Estimated 10 million people infected
- Varies widely among population groups

PREDOMINANT SEX
- No specific predilection
- Male predominance in AIDS, shelters, and prisons reflected in disproportionate male incidence

PREDOMINANT AGE
- 24 to 45 yr old
- Childhood cases common among minorities
- Nursing home outbreaks among elderly

PEAK INCIDENCE
- Infancy
- Teenage years
- Pregnancy
- Elderly
- HIV-positive patients, regardless of age, at highest risk

GENETICS
- Populations with widespread low native resistance have been intensely infected when initially exposed to TB.
- Following elimination of those with least native resistance, incidence and prevalence of TB tend to decline.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- See "Etiology"
- Primary pulmonary TB infection generally asymptomatic
- Reactivation pulmonary TB
  1. Fever
  2. Night sweats
  3. Cough
  4. Hemoptysis
  5. Scanty nonpurulent sputum
  6. Weight loss
- Progressive primary pulmonary TB disease: same as reactivation pulmonary TB
- TB pleurisy
  1. Pleuritic chest pain
  2. Fever
  3. Shortness of breath
- Rare massive, suffocating, fatal hemoptysis secondary to erosion of pulmonary artery within a cavity (Rasmussen's aneurysm)
- Chest examination
  1. Not specific
  2. Usually underestimates extent of disease
  3. Rales accentuated following a cough (posttussive rales)

ETIOLOGY

- Mtb, a slow-growing, aerobic, non-spore-forming, nonmotile bacillus, with a lipid-rich cell wall:
  1. Lacks pigment
  2. Produces niacin
  3. Reduces nitrate
  4. Produces heat-labile catalase
  5. Mtb staining, acid-fast and acid-alcohol fast by Ziehl-Neelsen method, appearing as red, slightly bent, beaded rods 2 to 4 microns long (acid-fast bacilli [AFB]), against a blue background
  6. Polymerase chain reaction (PCR) to detect <10 organisms/ml in sputum (compared with the requisite 10,000 organisms/ml for AFB smear detection)
  7. Culture
     a. Growth on solid media (Löwenstein-Jensen; Middlebrook 7H11) in 2 to 6 wk
     b. Growth in liquid media (BACTEC, using a radioactive carbon source for early growth detection) often in 9 to 16 days
     c. Enhanced in a 5% to 10% carbon dioxide atmosphere
  8. DNA fingerprinting (based on restriction fragment length polymorphism [RFLP])
     a. Facilitates immediate identification of Mtb strains in early growing cultures
     b. False negatives possible if growth suboptimal
  9. Humans are the only reservoir for Mtb
  10. Transmission
      a. Facilitated by close exposure to high-velocity cough (unprotected by proper mask or respirators) from patient with AFB-positive sputum and cavitary lesions, producing aerosolized droplets containing AFB, which are inhaled directly into alveoli
      b. Occurs within prisons, nursing homes, and hospitals
- Pathogenesis
  1. AFB (Mtb) ingested by macrophages in alveoli, then transported to regional lymph nodes, where spread is contained
  2. Some AFB may reach bloodstream and disseminate widely
  3. Primary TB (asymptomatic, minimal pneumonitis in lower or midlung fields, with hilar lymphadenopathy) essentially an intracellular infection, with multiplication of organisms continuing for 2 to 12 wk after primary exposure, until cell-mediated hypersensitivity (detected by positive skin test reaction to tuberculin PPD) matures, with subsequent containment of infection
  4. Local and disseminated AFB thus contained by T-cell-mediated immune responses
     a. Recruitment of monocytes
     b. Transformation of lymphocytes with secretion of lymphokines
     c. Activation of macrophages and histiocytes
     d. Organization into granulomas, where organisms may survive within macrophages (Langhans' giant cells), but within which multiplication essentially ceases (95%) and from which spread is prohibited
  5. Progressive primary pulmonary disease
     a. May immediately follow the asymptomatic phase
     b. Necrotizing pulmonary infiltrates
     c. Tuberculous bronchopneumonia
     d. Endobronchial TB
     e. Interstitial TB
     f. Widespread miliary lung lesions
  6. Postprimary TB pleurisy with pleural effusion
     a. Develops after early primary infection, although often before conversion to positive PPD

   b. Results from pleural seeding from a peripheral lung lesion or rupture of lymph node into pleural space
   c. May produce a large (sometimes hemorrhagic) exudative effusion (with polymorphonuclear cells early, rapidly replaced by lymphocytes), frequently without pulmonary infiltrates
   d. Generally resolves without treatment
   e. Portends a high risk of subsequent clinical disease, and therefore must be diagnosed and treated early (pleural biopsy and culture) to prevent future catastrophic TB illness
   f. May result in disseminated extrapulmonary infection
7. Reactivation pulmonary TB
   a. Occurs months to years following primary TB
   b. Preferentially involves the apical posterior segments of the upper lobes and superior segments of the lower lobes
   c. Associated with necrosis and cavitation of involved lung, hemoptysis, chronic fever, night sweats, weight loss
   d. Spread within lung occurs via cough and inhalation
8. Reinfection TB
   a. May mimic reactivation TB
   b. Ruptured caseous foci and cavities, which may produce endobronchial spread
9. Mtb in both progressive primary and reactivation pulmonary TB
   a. Intracellular (macrophage) lesions (undergoing slow multiplication)
   b. Closed caseous lesions (undergoing slow multiplication)
   c. Extracellular, open cavities (undergoing rapid multiplication)
   d. INH and rifampin are cidal in all three sites
   e. Pyrazinamide (PZA) especially active within acidic macrophage environment
   f. Extrapulmonary reactivation disease also possible
10. Rapid local progression and dissemination in infants with devastating illness before PPD conversion occurs
11. Most symptoms (fever, weight loss, anorexia) and tissue destruction (caseous necrosis) from cytokines and cell-mediated immune responses
12. Mtb has no important endotoxins or exotoxins
13. Granuloma formation related to tumor necrosis factor (TNF) secreted by activated macrophages

DX DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Necrotizing pneumonia (anaerobic, gram-negative)
- Histoplasmosis
- Coccidioidomycosis
- Melioidosis
- Interstitial lung diseases (rarely)
- Cancer
- Sarcoidosis
- Silicosis
- Rare pneumonias
  1. *Rhodococcus equi* (cavitation)
  2. *Bacillus cereus* (50% hemoptysis)
  3. *Eikenella corrodens* (cavitation)

WORKUP

- Sputum for AFB stains
- Chest x-ray (Fig. ET1-58)
- PPD (tuberculin skin test [TST])
  1. Recent conversion from negative to positive within 3 mo of exposure is highly suggestive of recent infection.
  2. Single positive PPD is not helpful diagnostically.
  3. Negative PPD never rules out acute TB.
  4. Be certain that positive PPD does not reflect "booster phenomenon" (prior positive PPD may become negative after several yr and return to positive only after second repeated PPD; repeat second PPD within 1 wk), which thus may mimic skin test conversion.
  5. Positive PPD reaction is determined as follows:
     a. Induration after 72 hr of intradermal injection of 0.1 ml of 5 TU-PPD
     b. 5-mm induration if HIV-positive (or other severe immunosuppressed state affecting cellular immune function), close contact of active TB, fibrotic chest lesions
     c. 10-mm induration if in high–medical risk groups (immunosuppressive disease or therapy, renal failure, gastrectomy, silicosis, diabetes), foreign-born high-risk group (Southeast Asia, Latin America, Africa, India), low socioeconomic groups, IV drug addict, prisoner, healthcare worker
     d. 15-mm induration if low risk
  6. Anergy antigen testing (using mumps, *Candida,* tetanus toxoid) may identify patients who are truly anergic to PPD and these antigens, but results are often confusing. Not recommended.
  7. Patients with TB may be selectively anergic only to PPD.
  8. Positive PPD indicates prior infection but does not itself confirm active disease.
- Interferon gamma release assays (IGRAs): diagnostic test for latent TB infection, known as the quantaferon test (QFT-G). This is a blood test that measures interferon response to specific Mtb antigens. The test is FDA approved and is available in inpatient and outpatient labs and state health departments. It may assist in distinguishing true positive reactions, from individuals with latent TB, from PPD reactions related to nontuberculous mycobacteria; prior BCG vaccination; or difficult-to-interpret skin test results from people with dermatologic conditions or immediate allergic reactions to PPD. The diagnostic utility of the test as a replacement or supplement to the standard PPD is not yet fully determined. When IGRA is used for routine screening, positive results should be repeated routinely due to a high rate of false-positive results. The enzyme-linked immunospot assay (Elispot plus) incorporating a novel antigen, RV3879c, when used in combination with tuberculin testing, has been reported to enable rapid exclusion of active infection in patients with moderate to high pretest probability of TB. Other IGRAs now available for detection of TB using blood include QFT-GIT and the T-spot TB test.
- The Xpert MTB/RIF is an automated molecular test for *Mycobacterium tuberculosis* (MTB) and resistance to rifampin (RIF) that provides sensitive detection of TB and rifampin resistance directly from untreated sputum in less than 2 hr with minimal hands-on time.

LABORATORY TESTS

- Sputum for AFB stains and culture
  1. Induced sputum if patient not coughing productively
- Sputum from bronchoscopy if high suspicion of TB with negative expectorated induced sputum for AFB
  1. Positive AFB smear is essential before or shortly after treatment to ensure subsequent growth for definitive diagnosis and sensitivity testing
  2. Consider lung biopsy if sputum negative, especially if infiltrates are predominantly interstitial
- AFB stain-negative sputum may grow Mtb subsequently
- Gastric aspirates reliable, especially in HIV-negative patients
- CBC
  1. Variable values
     a. WBCs: low, normal, or elevated (including leukemoid reaction: >50,000)
     b. Normocytic, normochromic anemia often
  2. Rarely helpful diagnostically
- ESR usually elevated
- Thoracentesis
  1. Exudative effusion
     a. Elevated protein
     b. Decreased glucose
     c. Elevated WBCs (polymorphonuclear leukocytes early, replaced later by lymphocytes)
     d. May be hemorrhagic
  2. Pleural fluid usually AFB-negative
  3. Pleural biopsy often diagnostic—may need to be repeated for diagnosis
  4. Culture pleural biopsy tissue for AFB
- Bone marrow biopsy is often diagnostic in difficult-to-diagnose cases, especially miliary TB

IMAGING STUDIES

- Chest x-ray
  1. Primary infection reflected by calcified peripheral lung nodule with calcified hilar lymph node

2. Reactivation pulmonary TB
   a. Necrosis
   b. Cavitation (especially on apical lordotic views)
   c. Fibrosis and hilar retraction
   d. Bronchopneumonia
   e. Interstitial infiltrates
   f. Miliary pattern
   g. Many of previous findings may also accompany progressive primary TB
3. TB pleurisy
   a. Pleural effusion, often rapidly accumulating and massive
4. TB activity not established by single chest x-ray examination
5. Serial chest x-ray examinations are excellent indicators of progression or regression

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Increased rest during acute phase of treatment
- High-calorie, high-protein diet to reverse malnutrition and enhance immune response to TB
- Isolation in negative-pressure rooms with high-volume air replacement and circulation, with health care provider wearing proper protective 0.5- to 1-micron filter respirators, until three consecutive sputum AFB smears are negative

ACUTE GENERAL Rx

- Compliance (rigid adherence to treatment regimen) chief determinant of success.
  1. Supervised directly observed therapy (DOT) recommended for all patients and mandatory for unreliable patients
- Preferred adult regimen: DOT.
  1. Isoniazid (INH) 15 mg/kg (max 900 mg), rifampin 600 mg, ethambutol (EMB) 30 mg/kg (max 2500 mg), and pyrazinamide (PZA) (2 g [<50 kg]; 2.5 g [51 to 74 kg]; 3 g [>75 kg]) thrice weekly for 6 mo
  2. Alternative, more complicated DOT regimens
- Rifapentine, a rifampin derivative with a much longer serum half-life, was shown to be as effective when administered weekly (with weekly isoniazid) as conventional regimens for drug-sensitive pulmonary TB in non–HIV-infected patients.
- Short-course daily therapy: adult.
  1. HIV-negative patient: 6 mo total therapy (2 mo INH 300 mg, rifampin 600 mg, and EMB 15 mg/kg [max 2500 mg]) and PZA (1.5 g [<50 kg]; 2 g [51 to 74 kg]; 2.5 g [>75 kg]) daily and until smear negative and sensitivity confirmed; then INH and rifampin daily for 4 mo
  2. HIV-positive patient: 9 mo total therapy (2 mo INH, rifampin, EMB, and PZA daily until smear negative and sensitivity confirmed; then INH and rifampin qid for 7 mo)
  3. Continue treatment at least 3 mo following conversion to negative cultures
- Drug resistance (often multiple drug resistance TB [MDRTB]) increased by:
  1. Prior treatment
  2. Acquisition of TB in developing countries
  3. Homelessness, incarceration
  4. AIDS, IVDA
  5. Known contact with MDRTB
- Never add single drug to failing regimen.
- Never treat TB with fewer than two to three drugs or two to three new additional drugs.
- Other medications used in MDR or XDRTB include: moxifloxacin, cycloserine, aminoglycosides such as amikacin or kanamycin, clarithromycin, PAS, and ethionamide.
- Bedaquiline, a diarylquinoline antimycobacterial, was FDA-approved in 2013 for treatment of MDR-TB. Recommended dose is 400 mg once daily for 2 wk, followed by 200 mg 3×/wk for weeks 3 to 24. Bedaquiline is administered in combination with ≥3 drugs to which it is susceptible.
- Monitor for clinical toxicity (especially hepatitis).
  1. Patient and physician awareness that anorexia, nausea, right upper quadrant pain, and unexplained malaise require immediate cessation of treatment
  2. Evaluation of liver function testing
     a. Minimal SGOT/SGPT elevations without symptoms generally transient and not clinically significant
- Preventive treatment for PPD conversion only (infection without disease).
  1. Must be certain that chest x-ray examination is negative and patient has no symptoms of TB
  2. Most important groups:
     a. HIV-positive and other severely immunocompromised patients
     b. Close contact with active TB
     c. Recent converter
     d. Old TB on chest x-ray examination
     e. IV drug addict
     f. Medical risk factor
     g. High-risk foreign country
     h. Homeless
  3. The traditional preventive therapy for persons with latent M. tuberculosis consists of INH 300 mg daily for 9 to 12 mo; at least 12 mo if HIV-positive patient. The CDC has issued recommendations for a new regimen consisting of isoniazid and rifapentine administered once a week for 12 weeks as directly observed therapy. Studies have demonstrated that this regimen is as effective as 9 months of isoniazid therapy for preventing tuberculosis. Patients who should not receive this regimen include children younger than 2 years, persons with HIV infection taking antiretroviral therapy, pregnant women or those who may become pregnant during the course of treatment, and patients who have latent *M. tuberculosis* infection that is presumed to be resistant to isoniazid or rifampin.
- Infants generally given prophylaxis immediately if recent contact with active TB (even if infant PPD negative), then retested with PPD in 3 mo (continuing INH if PPD becomes positive and stopping INH if PPD remains negative).
- Chronic, stable PPD (several yr) given INH prophylaxis generally only if patient is <35 yr old.
  1. INH toxicity may outweigh benefit
  2. Individualize decision
- Preventive therapy for suspected INH-resistant organisms is unclear.

CHRONIC Rx

- Generally not indicated beyond treatment described previously
- Prolonged treatment, supervised by infectious disease expert, in a few very complicated infections caused by resistant organisms

DISPOSITION

- Monthly follow-up by physician experienced in TB treatment
- Confirm sensitivity testing and alter treatment appropriately
- Frequent sputum samples until culture is negative
- Confirm chest x-ray regression at 2 to 3 mo

REFERRAL

- To infectious disease expert for:
  1. HIV-positive patient
  2. Patient with suspected drug-resistant TB
  3. Patients previously treated for TB
  4. Patients whose fever has not decreased and sputum has not converted to negative in 2 to 4 wk
  5. Patients with overwhelming pulmonary or extrapulmonary TB
- To pulmonologist for bronchoscopy or pleural biopsy

PEARLS & CONSIDERATIONS

COMMENTS

- All contacts (especially close household contacts and infants) should be properly tested for PPD conversions during 3 mo following exposure.
- Those with positive PPD should be evaluated for active TB and properly treated or given prophylaxis.
- Previous treatment is a common risk factor for XDR and MDR TB.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Tuberculosis (TB) (Patient Information)
Tuberculosis, Miliary (Related Key Topic)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

American Thoracic Society: CDC, and the Infectious Diseases Society of America: Controlling tuberculosis in the United States, *MMWR Morb Mortal Wkly Rep* 54(RR-12):1, 2005.

Boehme EC et al.: Rapid molecular detection of tuberculosis and rifampin resistance, *N Engl J Med* 363:1005–1015, 2010.

Centers for Disease Control and Prevention: Updated guidelines for using interferon gamma release assays to detect mycobacterium tuberculosis infection—United States, 2010, *MMWR Morb Mortal Wkly Rep* 59(RR-5), 2010.

Centers for Disease Control and Prevention: Recommendations for use of an isoniazid-rifapontine regimen with direct observation to treat latent Mycobacterium tuberculosis infection, *MMWR Morb Mortal Wkly Rep* 60(48):1650–1653, 2011.

Horsburgh CR, Rubin EJ: Clinical practice: latent tuberculosis infection in the United States, *N Engl J Med* 364(15):1441–1448, 2011.

Jacob JT et al.: Acute forms of tuberculosis in adults, *Am J Med* 122:12–17, 2009.

Kwan CK, Ernst JD: HIV and tuberculosis: a deadly human syndemic, *Clin Microbiol Rev* 24(2):351–376, 2011.

Loddenkemper R et al.: To repeat or not to repeat—that is the question! Serial testing of health-care workers for TB infection, *Chest* 142:10, 2012.

Nathanson E et al.: MDR tuberculosis—critical steps for prevention and control, *N Engl J Med* 363:1050–1058, 2010.

Perez-Velez CM, Marais BJ: Tuberculosis in children, *N Engl J Med* 367:348–361, 2012.

Reves R, Schluger NW: Update in tuberculoisis and nontuberculous mycobactwerial infections 2013, *Am J Repir Crit Care Med* 189(8):894–898, 2014.

Sia IG, Wieland ML: Current concepts in the management of tuberculosis, *Mayo Clin Proc* 86(4):348–361, 2011.

Sterling TR et al.: Three months of rifapontine and isoniazid for latent tuberculosis infection, *N Engl J Med* 365:2155–2156, 2011.

Wilson ML: Recent advances in the laboratory detection of Mycobacterium tuberculosis complex and drug resistance, *Clin Infect Dis* 52(11):1350–1355, 2011.

Zumla AI et al.: New antituberculosis drugs,regimens,and adjunct therapies:needs, advances, and future prospects, *Lancet Infect Dis Apr* 14(4):327–340, 2014.

Zumla A et al.: Tuberculosis, *N Engl J Med* 368:745–755, 2013.

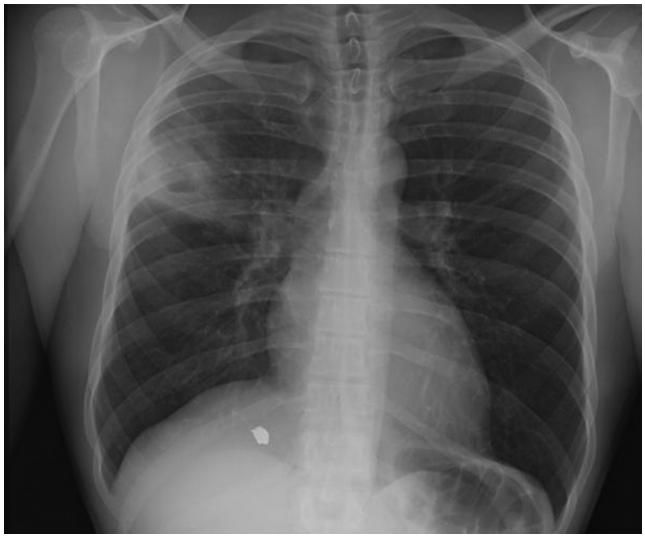


FIGURE ET1-58 Miliary pattern in tuberculosis consists of numerous nodules of uniform size. (From Grainger RG et al [eds]: *Grainger & Allison's diagnostic radiology,* ed 4, Philadelphia, 2001, Churchill Livingstone.)

BASIC INFORMATION

DEFINITION

Tuberous sclerosis (TS) is an inherited neurocutaneous disorder that is characterized by pleomorphic features involving many organ systems, including multiple benign neoplasms (hamartomas) of the brain, kidney, and skin.

SYNONYMS

TS
TSC
Tuberous sclerosic complex

ICD-9CM CODES
759.5 Tuberous sclerosis
ICD-10CM CODES
Q85.1 Tuberous sclerosis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: TS has an estimated incidence of 1 case per 6000 live births. Thus, it is the second most common neurocutaneous syndrome after neurofibromatosis.
PREVALENCE: The disorder affects about 1 in 10,000 persons in the general population.
PREDOMINANT SEX: TS has no predilection for gender or race.
GENETICS

- TS is an autosomal dominant disorder with almost complete penetrance but a wide range of clinical severity. However, only one third of cases are familial. The apparently nonfamilial cases can represent either spontaneous mutations or mosaicism.
- Genetic research has identified two TS genes. One is located on chromosome 9 (*TSC1* gene) and the other on chromosome 16 (*TSC2* gene). About 68% of cases occur as a result of new gene mutations. Because of the genetic transmission and new mutations, antenatal diagnosis is difficult.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Dermatologic manifestations may be the only clues the family physician has to the diagnosis of the disorder, which is also marked by childhood seizures and mental retardation (Figs. ET1-59 through ET1-61).

FIGURE ET1-59 Hypomelanotic macules ("ash leaf" spots).

- The diagnostic criteria for TS were recently revised at a consensus conference. Major and minor features are listed in Table ET1-26.
- The classic diagnostic triad of seizures, mental retardation, and facial angiofibromas (Vogt's triad) occurs in less than 50% of patients with TS.
- All of the clinical features of TS may not be apparent in the first yr of life. Thus, a child is often initially diagnosed with possible or probable TS and the diagnosis of definite TS is made after additional features are identified.
- Dermatologic manifestations: a careful skin examination of patients at risk for TS continues to be the easiest and most accessible method of establishing the diagnosis (Table ET1-27).
- Neurologic manifestations: these are the leading cause of morbidity and mortality in patients with TS. Brain hamartomas in the form of cortical tubers, subependymal nodules, and subependymal giant cell astrocytomas are often responsible for intractable seizures, most commonly as infantile spasms. Approximately 90% to 96% of TS patients suffer from seizures. Approximately 85% of patients have their first epileptic episode in the first 2 yr of life. Behavioral and cognitive dysfunction, including autism and mental retardation, can be seen in 40% to 50% of patients.
- Renal and pulmonary manifestations are strongly associated with TS.
- Angiomyolipoma is the most common renal lesion found in TS patients. Clinically evident pulmonary involvement in TS patients is relatively rare, with an estimated incidence of 1% to 6%. The most common lesion is lymphangiomyomatosis (LAM), a progressive cystic lung disease with progressive dyspnea and spontaneous pneumothorax in a childbearing woman.
- Cardiovascular manifestations: these are often the earliest diagnostic findings in patients with TS. Rhabdomyoma is the most common primary cardiac tumor in infants and children. Its incidence in TS patients ranges between 47% and 60%. In fact, 80% to 95% of patients with cardiac rhabdomyomas have TS.
- The most common ocular findings in TS are retinal hamartomas, appearing in 40% to 50% of patients.

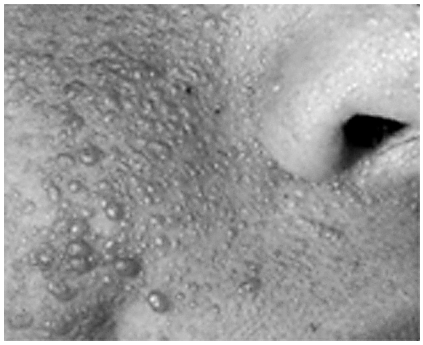


FIGURE ET1-60 Facial angiofibromas.

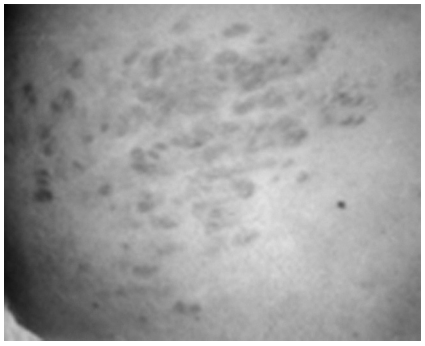


FIGURE ET1-61 Shagreen patches.

ETIOLOGY

TS is an autosomal dominant disorder.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Cutaneous manifestations:

- Nevus anemicus
- Nevus depigmentosus (nevus achromicus)
- Vitiligo

WORKUP

- The dermatologic manifestations of TS are helpful in diagnosing this disorder. When TS

TABLE ET1-26 Revised Diagnostic Criteria for Tuberous Sclerosis Complex (TSC)

Major Features

1. Facial angiofibromas or forehead plaque
2. Nontraumatic ungual or periungual fibroma
3. Hypomelanotic macule (3 or more)
4. Shagreen patch (connective tissue nevus)
5. Multiple retinal nodular hamartomas
6. Cortical tuber
7. Subependymal nodule
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma, single or multiple
10. Lymphangiomyomatosis
11. Renal angiomyolipoma

Minor Features

1. Multiple, randomly distributed pits in dental enamel
2. Hamartomatous rectal polyps
3. Bone cysts
4. Cerebral white matter radial migration lines
5. Gingival fibromas
6. Nonrenal hamartomas
7. Retinal achromic patch
8. "Confetti" skin lesions
9. Multiple renal cysts

Definite TSC: either two major features or one major feature plus two minor features.
Probable TSC: one major plus one minor feature. Possible TSC: either one major feature or two or more minor features.

has been inherited in the autosomal dominant form, dermatologic signs are almost universally present in one of the patient's parents.
- No specific prenatal laboratory test is available.
- Early recognition of TS is vital because prompt implementation of the recommended diagnostic evaluation (neuroimaging studies, EEG, ECG, renal ultrasonography, and chest CT) may prevent serious clinical consequences.
- Some findings in TS complex (TSC), notably renal angiomyolipomas and pulmonary lymphangioleiomyomatosis (LAM) emerge later, placing adults with undiagnosed TSC at increased risk for morbidity and mortality.

LABORATORY TESTS

- Molecular genetic testing: in recent years, molecular genetic testing for TS has become clinically available. Such testing identifies mutations in the *TSC1* and *TSC2* genes by one of several methods, most commonly polymerase chain reaction (PCR) amplification of individual exons, followed by DNA sequencing on DNA obtained from a patient's blood sample.
- DNA testing for TS is potentially useful in several settings:
  1. First, it can be helpful in confirming a clinical diagnosis of TS, especially in young patients in whom many clinical signs and symptoms have yet to develop.
  2. Second, in many families with a history of TS in which there is a sporadic case of TS in a new child, genetic testing can provide reassurance to parents, children, and other family members that they do not carry the TS gene mutation.
  3. Third, DNA testing is useful for prenatal diagnosis.

Rx TREATMENT

The management of TSC is presently symptomatic.

NONPHARMACOLOGIC THERAPY

Genetic counseling should be offered to families with affected members, even though accurate counseling remains difficult because of the variability of gene expression.

ACUTE GENERAL Rx & CHRONIC Rx

- Treatment methods currently available for patients with disfiguring facial angiofibromas include cryosurgery, curettage, dermabrasion, chemical peeling, excision, and laser therapy.
- Some patients have been treated successfully with antiepileptic medications; unfortunately, there are multiple cases of intractable seizure in which medical treatment is ineffective. In some cases of intractable epilepsy, neurosurgical intervention becomes a lifesaving option.
- In such drug-resistant cases of TS, the early administration of vigabatrin (γ-vinyl-gamma aminobutyric acid), a selective irreversible inhibitor of GABA-transaminase, has been proved to result in 80% to 100% cessation rates of infantile spasms. Vigabatrin is marketed in many European countries, but remains unavailable in the United States and has not been approved by the FDA.
- Embolization and/or renal sparing surgery are treatment options for renal angiomyolipomas.
- Oophorectomy, medroxyprogesterone, and tamoxifen have been advocated for patients with LAM, but therapeutic benefit is unclear. Lung transplantation is reserved for patients with end-stage LAM.
- Most rhabdomyomas tend to regress with increasing age, although tumor growth has been documented in some at puberty. Surgery is recommended only for life-threatening situations, such as hemodynamic compromise.
- Oral rapamycin or sirolimus therapy can induce regression of brain astrocytomas associated with TS. Ongoing therapeutic trials with rapamycin in lymphangioleiomyomatosis appear promising.
- Neurosurgical resection is the standard treatment for subependymal giant-cell astrocytomas in patients with the TSC. Trials with everolimus, which inhibits the mammalian target of rapamycin, a protein regulated by gene products involved in the TSC, have shown marked reduction in volume of subependymal giant-cell astrocytomas and seizure frequency.

REFERRAL

A multidisciplinary team including genetics, neurology, ophthalmology, nephrology, dermatology, neurosurgery, and plastic surgery should evaluate children suspected of having TS.

PEARLS & CONSIDERATIONS

PREVENTION

It is speculated that if one could establish the prenatal diagnosis of TS and begin using rapamycin early, one might prevent the development of TS manifestations.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Tuberous Sclerosis (Patient Information)

AUTHOR: **RUBY K. SATPATHY, M.D.**

TABLE ET1-27 Cutaneous Manifestations Associated with Tuberous Sclerosis Complex

Cutaneous Lesions	Descriptions	Age of Onset	Prevalence	Diagnostic Classification
Hypomelanotic macules ("ash leaf" spots) or Fitzpatrick patches	Leaf-shaped or polygonal white spots enhanced by Wood's lamp examination	Earliest cutaneous lesion; usually present at birth or infancy on buttocks	97.2%	Major
Facial angiofibromas	Red to pink papules with a smooth surface, symmetrically distributed over the centrofacial areas, sparing the upper lips	Second to fifth yr of life; become more prominent with age	74.5%	Major
Shagreen patches	Slightly elevated patch or plaque, usually found on the dorsal body surfaces, especially the lumbosacral area; its rough surface resembles an orange peel; represents a connective tissue nevus, sometimes called collagenoma	Rare during infancy; tend to increase in size and number with age	48.1%	Major
Molluscum pendulum	Multiple soft pedunculated skin growths on neck; rarely in axilla or groin	More common during first decade of life; rare during infancy	22.6%	Minor
Forehead fibrous plaque	Yellowish-brown or skin-colored plaques of variable size and shape, usually located on the forehead or scalp	Common at any age and can be seen at birth or early infancy	18.9%	Major
Periungual fibromas	Skin-colored or reddish nodules seen on the lateral nail groove, nail plate, or along the proximal nail folds; more commonly found on the toes than on the fingers	Present at puberty or soon after; become more common with age	15.1%	Major
"Confetti-like" macules	Multiple 1-2 mm white spots symmetrically distributed over extremities	Second decade or adulthood	2.8%	Minor

SUGGESTED READINGS

Bissler JJ et al.: Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis, *N Engl J Med* 358:140–151, 2008.

Crino PB et al.: The tuberous sclerosis complex, *N Engl J Med* 355:1345–1356, 2006.

Hurst JS, Wilcoski S: Recognizing an index case of tuberous sclerosis, *Am Fam Physician* 61(3):703–708, 2001.

Krueger DA et al.: Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis, *N Engl J Med* 363:1801–1811, 2010.

Schwartz RA: Tuberous sclerosis complex: advances in diagnosis, genetics, and management, *J Am Acad Dermatol* 57(2):189–202, 2007.

Seibert D et al.: Recognition of tuberous sclerosis in adult women: delayed presentation with life-threatening consequences, *Ann Intern Med* 154:806–813, 2011.

BASIC INFORMATION

DEFINITION

Tularemia is a zoonosis caused by the small, facultative gram-negative intracellular coccobacillus *Francisella tularensis.* Clinical manifestations range from asymptomatic illness to septic shock and death.

SYNONYMS

Rabbit fever
Deerfly fever
O'Hara's disease

ICD-9CM CODES
021.9 Tularemia
ICD-10CM CODES
A21.9 Tularemia, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Overall incidence in the United States is about 120 cases/year with the highest reported incidence found in South Dakota, Arkansas, Missouri, and Oklahoma (Fig. ET1-62). It is also found in Canada, Mexico, European countries, Turkey, Israel, China, and Japan.
PREDOMINANT SEX: Male
PREDOMINANT AGE: Occurs at any age but is most common in 5- to 9-year-olds and in men >55 years of age.
PEAK INCIDENCE: June through August and in December

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Physical findings:
- Incubation period is 3 to 5 days but may range from 1 to 21 days.
- Most common initial signs and symptoms:
  1. Fever
  2. Chills
  3. Headache
  4. Malaise
  5. Anorexia
  6. Fatigue
  7. Cough
  8. Myalgias
  9. Chest discomfort
  10. Vomiting
  11. Abdominal pain
  12. Diarrhea
  13. Conjunctivitis
  14. Lymphadenitis

Clinical presentation:
- Ulceroglandular and glandular: account for 75% to 80% of cases. Fever and a single erythematous papuloulcerative lesion with a central eschar accompanied by tender lymphadenopathy (Fig. ET1-63). Overall mortality for this form of tularemia is generally low (<2%).
- Oculoglandular: accounts for 1% to 2% of cases. Painful inflamed conjunctiva with numerous yellowish nodules and pinpoint ulcers. Purulent conjunctivitis with regional lymphadenopathy. Corneal perforation may occur.
- Oropharyngeal and gastrointestinal: account for 1% to 4% of cases. Acute, exudative, or membranous pharyngitis associated with cervical lymphadenopathy. Ulcerative intestinal lesion associated with mesenteric lymphadenopathy, diarrhea, abdominal pain, nausea, vomiting, and GI bleeding.
- Pulmonary: occurs often in the elderly and has a higher mortality. Symptoms include nonproductive cough, dyspnea, or pleuritic chest pain.
- Typhoidal: 10% of all cases of tularemia, usually following ingestion of viable *F. tularensis* bacteria. Rare in United States. Symptoms include high continuous fever, signs of endotoxemia, abdominal pain, and severe headache. Mortality can approach 30%.

COMPLICATIONS

1. Intravascular coagulation
2. Renal failure
3. Rhabdomyolysis
4. Jaundice
5. Hepatitis
6. Meningitis
7. Encephalitis
8. Pericarditis
9. Peritonitis
10. Osteomyelitis
11. Splenic rupture
12. Thrombophlebitis
13. Myositis and sepsis

ETIOLOGY

- Caused by infection with *F. tularensis.*
- Two main biovars of *F. tularensis:* type A and type B. Type A produces severe disease in humans. Type B produces milder subclinical infection.
- Transmitted by ticks, tabanid flies, and mosquitoes. Also acquired by inhalation and ingestion.
- Cases also occur after exposure to animals (wild rabbit, squirrels, birds, sheep, beavers, muskrats, and domestic dogs and cats) or animal products.
- Laboratory acquisition is possible.
- Pathogenesis: after inoculation into the skin the organism multiplies locally within 2 to 5 days, then it produces erythematous tender or pruritic papule. The papule rapidly enlarges and forms an ulcer with a black base. The bacteria actively inhibit the protective host response by inducing anti-inflammatory cytokines and spread to the regional lymph nodes producing lymphadenopathy, and with bacteremia may spread to distant organs.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rickettsial infections
- Meningococcal infections
- Cat-scratch disease
- Infectious mononucleosis
- Atypical pneumonia
- Group A strep pharyngitis
- Typhoid fever
- Fungal infection—sporotrichosis
- Anthrax
- Plague
- Bacterial skin infections

WORKUP

- CBC
- Chest x-ray
- Cultures of blood, lymph node, pleural fluid, wounds, sputum, and gastric aspirate
- Antigen detection in urine
- Polymerase chain reaction (PCR)
- Serology

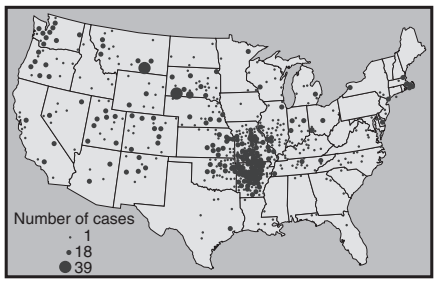


FIGURE ET1-62 Reported cases of tularemia in the United States from 1990 to 2000, based on 1347 patients reporting county of residence in the continental United States. Alaska reported 10 cases in four counties during 1990-2000. The circle size is proportional to the number of cases, ranging from 1 to 39 cases. (From the Centers for Disease Control and Prevention: Tularemia—United States, 1990-2000, *MMWR Morb Mortal Wkly Rep* 51:181-184, 2002.)

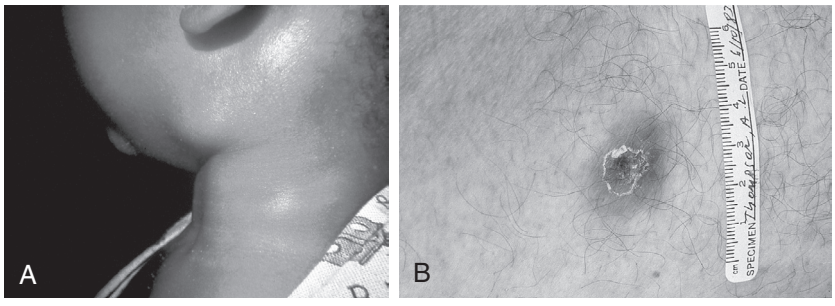


FIGURE ET1-63 Examples of primary lesions seen in ulceroglandular tularemia. A, Large cervical and submandibular lymph nodes in a young child; an ulcer was found under the hairline on her forehead at the site of a tick bite. **B,** Papule undergoing central necrosis with desquamation on the thigh of a middle-aged man. (**A** courtesy Dr. Joseph A. Bocchini, Louisiana State University Health Sciences Center, Shreveport, LA. **B** from Mandell GL et al: *Principles and practice of infectious diseases,* ed 6, Philadelphia, 2005, Churchill Livingstone.)

LABORATORY TESTS

- WBC count and ESR normal or elevated.
- Rarely seen on Gram-stained smears or tissue biopsies; a tiny gram-negative bacillus.
- Antibodies to *F. tularensis* demonstrated by tube agglutination, microagglutination, hemagglutination, and ELISA; definitive serologic diagnosis requires a fourfold or greater rise in titer between acute and convalescent specimens.
- PCR to facilitate early diagnosis.

IMAGING STUDIES

Chest x-ray examination to show bilateral patchy infiltrate, lobar parenchymal infiltrate, cavitary lesion, pleural effusion, or emphysema

Rx TREATMENT

ACUTE GENERAL Rx

- Immediate therapy to limit extent of acute illness and complication.
- Streptomycin 15 mg/kg IV q12h (daily dose should not exceed 2 g) or gentamicin 5 mg/kg/day in 2 or 3 divided doses for 10 days.
- Doxycycline 100 mg IV or PO bid.
- Ciprofloxacin 400 mg IV or 750 mg PO bid for 14-21 days.
- Combination antibiotics required for tularemic meningitis—chloramphenicol plus streptomycin.
- Surgical therapies are limited to drainage of abscessed lymph nodes and chest tube drainage of empyemas.

PROGNOSIS

The mortality rate of severe untreated infection (tularemic pneumonia and typhoidal tularemia) can be as high as 30%. Overall mortality associated with tularemia is 2% to 4% with appropriate treatment. Lifelong immunity usually follows tularemia.

DISPOSITION

Follow up as outpatient

PREVENTION

- Educate the public in the handling of sick or dead animals.
- Use insect repellents.
- Remove ticks promptly.
- Drink only potable water.
- Adequately cook wild meats.
- Tularemia vaccine has been developed but is not commercially available in the United States; however, it is available from the Centers for Disease Control and Prevention (CDC). Vaccination of high-risk individuals working with large quantities of cultured organism is recommended.
- Avoid skinning wild animals, especially rabbits; wear gloves while handling animal carcasses.
- Do not use wells or other water that is contaminated by dead animals.
- Hospitalized patients with tularemia do not need special isolation (no person-to-person transmission). Standard universal precautions for contaminated secretion are adequate when handling drainage from wounds.
- Laboratory personnel should be notified of potential danger of growing this organism in the laboratory and generation of an infectious aerosol from dried culture media.

REFERRAL

- For consultation with infectious diseases specialist in suspected cases.
- A cluster of tularemia cases, particularly in an urban area or nonendemic regions, should prompt concern over the possibility of bioterrorism; the local public health authorities should be contacted immediately to investigate the possibility of deliberate release of tularemia as a weapon of terror.

PEARLS & CONSIDERATIONS

- Alert the microbiology laboratory to the possibility of tularemia; this is a major biohazard in the laboratory.
- Do not use doxycycline or tetracycline in children or pregnant women.
- Because of its highly contagious nature with low inoculums, tularemia is considered an agent that could be used by terrorists. It is classified as a category A critical biologic agent by the CDC.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **STEVEN M. OPAL, M.D.**

SUGGESTED READINGS

Centers for Disease Control and Prevention: Tularemia transmitted by insect bites—Wyoming, 2001-2003, *MMWR Morb Mortal Wkly Rep* 54(7):170, 2005.

Centers for Disease Control and Prevention: Tularemia-United States, 2001-2010, *MMWR Morb Mortal Wkly Rep* 62(47):963–966, 2013.

Feldman KA et al.: An outbreak of primary pneumonic tularemia on Martha's Vineyard, *N Engl J Med* 345(22):1601–1606, 2001.

Meagher KE, Decker CF: Other tick-borne illnesses: tularemia, Colorado tick fever, tick paralysis, *DM* 58(6):370–376, 2012.

Schmitt P et al.: A novel screening ELISA and a confirmatory Western blot useful for diagnosis and epidemiological studies of tularemia, *Epidemiol Infect* 133(4):759–766, 2005.

Sharma N et al.: Detection of Francisella tularenesis-specific antibodies in patients with tularemia by a novel competitive enzyme-linked immune-sorbent assay, *Clin Vaccine Immunol* 20:9–16, 2013.

Staples JE et al.: Epidemiologic and molecular analysis of human tularemia, United States, 1964-2004, *Emerg Infect Dis* 12(7):1113, 2006.

BASIC INFORMATION

DEFINITION

- Tumor lysis syndrome (TLS) is a potentially deadly constellation of metabolic derangements that can occur in tumors before or after starting cancer treatment. It is one of the major oncological emergencies.
- It usually occurs in patients with bulky, rapidly proliferating, and treatment-responsive tumors.
- It is associated with acute leukemias, high-grade non-Hodgkin's lymphoma, solid tumors, and hematologic cancers.
- Tumor lysis syndrome occurs when large numbers of cancer cells are destroyed either spontaneously or during cancer treatment. The result is the release of large amounts of intracellular ions and other metabolic products into the blood. This leads to:
  1. Hyperkalemia
  2. Hypocalcemia
  3. Hyperphosphatemia
  4. Hyperuricemia
  5. Acute renal failure

  Cairo and Bishop classification of TLS:

1. **Laboratory TLS** is defined by the presence of at least 2 of the following biochemical variables (hyperkalemia, hypocalcemia, hyperphosphatemia, hyperuricemia) within 3 days before or 7 days after initiation of chemotherapy despite adequate hydration and the use of uric acid lowering agents. Laboratory TLS is clinically silent.
2. **Clinical** TLS occurs when at least one of the clinical complications such as seizure, acute renal failure, cardiac dysrhythmias occur and it is not believed to be due to chemotherapy.

ICD-9CM CODES
277.88 Other specified disorders of metabolism
ICD-10CM CODES
E88.3 Tumor lysis syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Unknown, but it is the most common disease-related emergency encountered by physicians caring for children or adults with hematologic cancers. The incidence depends on cancer mass (the greater the mass, the greater the content released at cell death), patient characteristic (for example preexisting renal insufficiency, dehydration, hypotension), and supportive care.

PREVALENCE:
- Varies
- Increased frequency is associated with bulky, aggressive, and treatment-sensitive tumors.

PREDOMINANT SEX AND AGE:
- No sex predilection exists.
- Occurs in all age groups. The elderly are more susceptible because of impaired renal function with age.

GENETICS: No known racial predilection

RISK FACTORS: Risk factors for developing tumor lysis syndrome include:
- Bulky tumor and large tumor burden, as in:
  1. Acute leukemias with elevated WBC count
  2. Large, bulky, rapidly proliferating solid tumors
  3. High-grade lymphomas
- Tumors sensitive to treatment
- Dehydration
- Hypotension
- Exogenous potassium, phosphate
- CHF
- Exposure to nephrotoxic substances
- Baseline renal insufficiency
- Older patients (due to these patients having a lower glomerular filtration rate)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

CLINICAL PRESENTATION: Patients may present with a number of symptoms either before starting chemotherapy or commonly within 3 days after initiating cytotoxic treatment. Common symptoms include:
- Nausea
- Vomiting
- Edema
- Shortness of breath (from fluid overload or CHF)
- Lethargy/weakness
- Seizure
- Syncope
- Muscle cramps
- Tetany

PHYSICAL FINDINGS: Physical findings usually reflect the effects of specific metabolic derangement. Patients with tumor lysis syndrome present with hyperkalemia, hyperuremia, hypocalcemia, and hyperphosphatemia.
- Hyperkalemia causes:
  - Weakness
  - Paresthesia
  - Paralysis
  - ECG changes
  - Cardiac arrhythmias
  - Cardiac arrest
- Hyperuremia:
  - Weakness
  - Malaise
  - Vomiting
  - Pruritus
  - Restless legs
  - Ecchymoses
  - Hiccups
  - Paresthesia
  - Pericarditis
  - Dyspnea
  - Hypertension
- Hypocalcemia:
  - Paresthesia
  - Tetany
  - Bronchospasm
  - Heart block
  - Muscle twitching
- Hyperphosphatemia:
  - Oliguria
  - Anuria
  - Renal failure

ETIOLOGY

- Can occur spontaneously or after initiation of therapy in patients with:
  - Acute leukemias
  - Bulky solid tumors
  - High-grade lymphomas
- Administration of certain agents:
  - Paclitaxel
  - Hydroxyurea
  - Etoposide
  - Fludarabine
- It has been reported in some cancer patients who received:
  - Intrathecal administration of chemotherapy
  - Rare causes: pregnancy, fever, some patients under general anesthesia

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

See "Acute Kidney Injury" topic in Section I.

LABORATORY TESTS

- Monitor BUN, creatinine phosphate, potassium, calcium, uric acid, LDH in high-risk patients before and up to 72 hr after initiating therapy. If evidence of tumor lysis syndrome develops, check these at least twice a day.
- Closely monitor urine output (for signs of oliguria).
- Perform frequent ECG or continuous cardiac monitoring to look for lethal arrhythmia (that can be caused by K or Ca abnormalities).

TREATMENT

GENERAL PRINCIPLES

- It is very important to identify high-risk patients (by assessing the extent of tumor burden, renal function, and pathologic findings) in order to initiate prophylactic measures before starting treatment. Delay in doing this may lead to life-threatening conditions.
- Optimal treatment involves preservation of renal function. It also includes the prevention of cardiac dysrhythmias and neuromuscular irritability.
- In patients with pretreatment tumor lysis syndrome:
  1. Correct all metabolic derangement before starting cancer treatment, if possible.
- Careful and frequent laboratory and clinical monitoring. Check:
  - Baseline ECG/continuous cardiac monitoring
  - Renal/fluid status by checking vital signs, daily weights, fluid intake/output
  - For high-risk patients and those with overt tumor lysis syndrome, check the following at least twice daily:
    - Basic metabolic panel
    - Calcium
    - Uric acid
    - Phosphate
    - LDH

TREATMENT OPTIONS (PREVENTIVE MEASURES) FOR HIGH-RISK PATIENTS WITHOUT TUMOR LYSIS SYNDROME

- **Hydration:** prevent volume depletion and help correct electrolyte derangement
  - Start 24-48 hr before initiating cancer treatment and continue for up to 72 hr after treatment.
  - May use D_5W plus 2 amps of $NaCO_3$.
- **Control of hyperuricemia:** use allopurinol or rasburicase.
  - Allopurinol (xanthine oxidase inhibitor prevents the conversion of xanthine and hypoxanthine to uric acid)
    - Give 600 mg/day PO or IV for prophylaxis and 600 to 900 mg/day PO or IV to treat tumor lysis syndrome.
  - Rasburicase (recombinant urate oxidase) is used when uric acid levels cannot be lowered by standard procedures.
  - Given IV or IM at dosages from 50 to 100 U/kg/day for 1 to 5 days.
    - Do not give together with allopurinol.
    - Alkalization is not necessary.
    - Contraindicated in glucose-6-phosphate dehydrogenase deficiency and pregnancy.
- Diuretics: indicated for well-hydrated patients with poor/inadequate diuresis.
  1. Furosemide may be used in well-hydrated patients with elevated potassium or in patients with fluid overload.

TREATMENT OF PATIENTS WITH TUMOR LYSIS SYNDROME

- Principles:
  - General and preventive measures as mentioned in General Principles and Treatment Options
  - Aggressively treating electrolyte disturbances to prevent cardiac dysrhythmias and neuromuscular irritability.
  - Treat renal failure if above fail
- Treating electrolyte disturbances:
  - Hyperuricemia: as outlined above
  - Hyperkalemia:
    - Restrict dietary potassium
    - Stop potassium in IV fluid
    - IV infusion of glucose and insulin (to move K to intracellular space)
    - IV gluconate (cardioprotective effect)
    - PO potassium-exchange resins
    - If above measures fail, then immediate dialysis is needed
  - Hyperphosphatemia
    - Decrease dietary intake
    - IV glucose plus insulin
    - Oral phosphate binders
  - Hypocalcemia
    - Treat only if symptomatic (e.g., neuromuscular irritability as in positive Chvostek or Trousseau sign).
    - Calcium gluconate only when symptomatic.
    - Calcitrol can be used only if serum phosphate level is normal.

TREAT RENAL FAILURE

- Consider early dialysis if above methods fail.
- Dialysis prevents life-threatening complications and irreversible renal failure.
- Hemodialysis is the preferred procedure.

REFERRAL

- Nephrology
- Critical care

PEARLS & CONSIDERATIONS

COMMENTS

- High-risk patients should have prophylactic measures 24-48 hr before starting cytotoxic drugs. Low-intensity initial therapy is also recommended in patients at high-risk for tumor lysis syndrome.
- Prophylactic measures include:
  - IV hydration
  - Administration of allopurinol
  - Urinary alkalization
- Monitor blood chemistry and fluid status.
- Complications of tumor lysis syndrome include:
  - Uremia
  - Renal failure
  - Electrolyte disturbances
  - Cardiac arrhythmia
  - Pulmonary edema secondary to aggressive hydration
  - Metabolic alkalosis from IV bicarbonate administration

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **DANIEL K. ASIEDU, M.D., PH.D.**

SUGGESTED READINGS

De Angelo DJ: Metabolic emergencies in oncology. In: Chang AE, et al. (eds) *Oncology: an evidence-based approach.* New York: Springer.

Howard SC: The tumor lysis syndrome, *N Engl J Med* 364:1844–1854, 2011.

BASIC INFORMATION

DEFINITION

Turner syndrome is a pattern of malformation characterized by short stature, ovarian hypofunction, loose nuchal skin, and cubitus valgus, as described by Turner in 1938. An associated 45,X chromosome constitution was recognized by Ford et al in 1959.

ICD-9CM CODES
758.6 Syndrome, Turner
ICD-10CM CODES
Q96.9 Turner's syndrome, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

One case in every 2500 to 5000 live female births

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Turner phenotype is recognizable at any point on the developmental spectrum.
- In spontaneous abortions it is the most common sex chromosome abnormality detected (45,X chromosome constitution) and accounts for 20% of such cases.
- In fetuses, it is suspected when ultrasonographic manifestations such as thickening of the nuchal folds, frank nuchal cystic hygromas, or mild shortness of the femur at mid-trimester are identified.

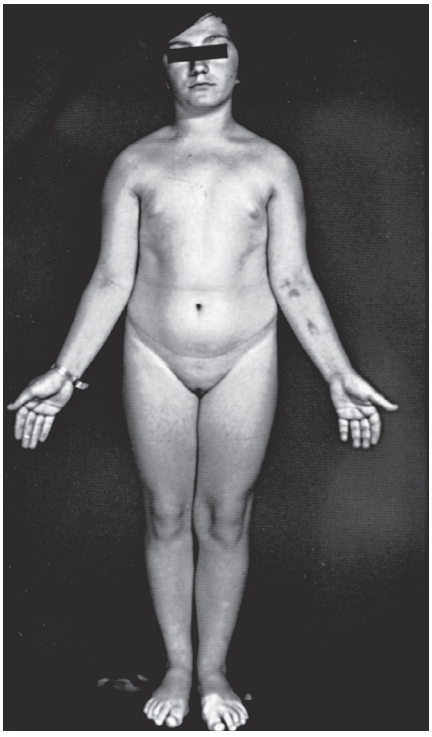


FIGURE ET1-64 Turner syndrome in a 15-year-old girl exhibiting failure of sexual maturation, short stature, cubitus valgus, and goiter. There is no webbing of the neck. Karyotyping revealed 45,X/46,XX chromosome complement. (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

- In infants:
  1. At birth may display loose nuchal skin (pterygium colli) and edema on the dorsa of hands and feet
  2. Canthal folds reflecting midface hypoplasia and redundant skin in the periorbital region
  3. Nipples appearing widely spaced (interthelial distance greater than one fourth the chest circumference)
  4. Heart and cardiovascular system: murmur of aortic stenosis or bicuspid aortic valve or diminished femoral pulses suggestive of aortic coarctation
  5. Renal ultrasonography: renal ectopia such as pelvic kidney or horseshoe kidneys
- In older children:
  1. Slow linear growth
  2. Short stature (Fig. ET1-64): may be improved with growth hormone therapy. Combining childhood ultra low-dose estrogen with growth hormone may improve growth and provide other potential benefits associated with early initiation of estrogen replacement
  3. Delayed or absent menses: secondary sex characteristics possibly normalized with estrogen replacement therapy
  4. Intelligence is often normal, but delays in spatial perception or visual-motor integration are commonly observed; frank mental retardation is rare

ETIOLOGY

- Abnormal phenotype caused by absence of the second sex chromosome, whether X or Y
- 45,X chromosome constitution in approximately 50% of affected individuals
- Other chromosome aberrations (40% of cases): isochromosome Xq (46,X,i[Xq]) or mosaicism (XX/X)
- With deletions involving the short (or "p") arm of the X chromosome: short stature but little ovarian hypofunction
- Deletions involving Xq13-q27: ovarian failure
- Usually a deficiency of paternal contribution of sex chromosome, reflecting paternal nondisjunction

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Noonan syndrome (PTPN11 mutation), an autosomally dominant inherited disorder also characterized by loose nuchal skin, midface hypoplasia, canthal folds, and stenotic cardiac valvular defects and affecting males and females equally; also have normal chromosome constitutions
- Other conditions in the differential diagnosis of loose skin, whether or not associated with edema:
  1. Fetal hydantoin syndrome (loose nuchal skin, midface hypoplasia, distal digital hypoplasia)
  2. Disorders of chromosome constitution (trisomy 21, tetrasomy 12p mosaicism)
  3. Congenital lymphedema (Milroy edema)

WORKUP

- Giemsa banded karyotype to confirm clinical diagnosis
- Cardiologic consultation for evaluation for cardiac valvular abnormalities or aortic coarctation
- Renal ultrasonography once diagnosis is established
- Endocrine evaluations in older patients with short stature or amenorrhea
- Psychometrics to document known or suspected learning disabilities

LABORATORY TESTS

- As noted, routine Giemsa banded karyotype on peripheral lymphocytes is the gold standard to confirm the clinical impression in all suspected cases of Turner syndrome
- Important to exclude the presence of Y chromosome in mosaics
- Recognition of associated medical problems, such as hypergonadotropic hypogonadism or autoimmune thyroiditis, prompting periodic evaluation of these potential areas

IMAGING STUDIES

- Echocardiogram
- Renal ultrasonography
- Abdominal ultrasonography for evaluation of ovarian and uterine size and morphology
- MRI of brain (especially in cases with known or suspected neurologic impairment)
- Radiographs (for evaluation of carpal/metacarpal abnormalities, radioulnar synostosis)
- Bone age (for evaluation of short stature)

TREATMENT

Recognition of the multisystem involvement of Turner syndrome necessitates multiple medical specialists working in concert with the primary care provider to maximize and improve outcome while minimizing unnecessary or redundant testing.

NONPHARMACOLOGIC THERAPY

General medical care guided by normal medical standards with special attention paid to identifying such age-related problems as developmental delays, learning disabilities, slow growth, or amenorrhea.

ACUTE GENERAL Rx

Specific treatment geared to the specific medical problem (e.g., cardiac or renal dysfunction)

CHRONIC Rx

- Estrogen-replacement therapy in early adolescents
- Some benefit from recombinant human growth hormone therapy

REFERRAL

- To geneticist: clinical diagnosis, differential diagnosis, recurrence risk counseling, cytogenetic tests

- To endocrinologist (pediatric): evaluation of short stature, estrogen or growth hormone replacement therapy
- To cardiologist: for cardiac valvular abnormalities or aortic coarctation

PEARLS & CONSIDERATIONS

COMMENTS

- Although newer studies are optimistic regarding outcomes, previous reports suffered from retrospective observations, case reports, and ascertainment bias, contributing to a generally poor interaction between physician and patient.
- Affected individuals and families often benefit from the contemporary experiences and expertise of members of genetic support groups. The Turner Syndrome Society of the United States (800-365-9944; http://www.turnersyndrome.org) and the Alliance of Genetic Support Groups (800-336-4363 or 202-966-5557; http://geneticalliance.org) are valuable resources.
- A Turner syndrome diagnosis should be considered in all girls with short stature or primary amenorrhea.
- Almost all women with Turner syndrome are infertile, although some conceive with assisted reproduction.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Turner's Syndrome (Patient Information)

AUTHORS: **LAURA M. ANDOLINA, M.S.,** and **RUBEN ALVERO, M.D.**

EVIDENCE

Abstract[1]

Objective:
To examine the effect of oxandrolone and the timing of pubertal induction on final height in girls with Turner's syndrome receiving a standard dose of growth hormone.
Design:
Randomised, double blind, placebo controlled trial.
Setting:
36 paediatric endocrinology departments in UK hospitals.
Participants:
Girls with Turner's syndrome aged 7-13 years at recruitment, receiving recombinant growth hormone therapy (10 mg/m^2/week).
Interventions:
Participants were randomised to oxandrolone (0.05 mg/kg/day, maximum 2.5 mg/day) or placebo from 9 years of age. Those with evidence of ovarian failure at 12 years were further randomised to oral ethinylestradiol (year 1, 2 μg daily; year 2, 4 μg daily; year 3, 4 months each of 6, 8, and 10 μg daily) or placebo; participants who received placebo and those recruited after the age of 12.25 years started ethinylestradiol at age 14.
Main Outcome Measure:
Final height.
Results:
106 participants were recruited, of whom 14 withdrew and 82/92 reached final height. Both oxandrolone and late pubertal induction increased final height: by 4.6 (95% confidence interval 1.9 to 7.2) cm (P = 0.001, n = 82) for oxandrolone and 3.8 (0.0 to 7.5) cm (P = 0.05, n = 48) for late pubertal induction with ethinylestradiol. In the 48 children who were randomised twice, the effects on final height (compared with placebo and early induction of puberty) of oxandrolone alone, late induction alone, and oxandrolone plus late induction were similar, averaging 7.1 (3.4 to 10.8) cm (P < 0.001). No cases of virilization were reported.
Conclusion:
Oxandrolone had a positive effect on final height in girls with Turner's syndrome treated with growth hormone, as did late pubertal induction with ethinylestradiol at age 14 years. However, these effects were not additive, so using both had no advantage. Oxandrolone could, therefore, be offered as an alternative to late pubertal induction for increasing final height in Turner's syndrome. A

Abstract[2]

Background:
Short stature and ovarian failure are characteristic features of Turner's syndrome. Although recombinant human growth hormone is commonly used to treat the short stature associated with this syndrome, a randomized, placebo-controlled trial is needed to document whether such treatment increases adult height. Furthermore, it is not known whether childhood estrogen replacement combined with growth hormone therapy provides additional benefit. We examined the independent and combined effects of growth hormone and early, ultra-low-dose estrogen on adult height in girls with Turner's syndrome.
Methods:
In this double-blind, placebo-controlled trial, we randomly assigned 149 girls, 5.0 to 12.5 years of age, to four groups: double placebo (placebo injection plus childhood oral placebo, 39 patients), estrogen alone (placebo injection plus childhood oral low-dose estrogen, 40), growth hormone alone (growth hormone injection plus childhood oral placebo, 35), and growth hormone–estrogen (growth hormone injection plus childhood oral low-dose estrogen, 35). The dose of growth hormone was 0.1 mg per kilogram of body weight three times per week. The doses of ethinyl estradiol (or placebo) were adjusted for chronologic age and pubertal status. At the first visit after the age of 12.0 years, patients in all treatment groups received escalating doses of ethinyl estradiol. Growth hormone injections were terminated when adult height was reached.
Results:
The mean standard-deviation scores for adult height, attained at an average age of 17.0±1.0 years, after an average study period of 7.2±2.5 years were −2.81±0.85, −3.39±0.74, −2.29±1.10, and −2.10±1.02 for the double-placebo, estrogen-alone, growth hormone–alone, and growth hormone–estrogen groups, respectively (P < 0.001). The overall effect of growth hormone treatment (vs. placebo) on adult height was a 0.78±0.13 increase in the height standard-deviation score (5.0 cm) (P < 0.001); adult height was greater in the growth hormone–estrogen group than in the growth hormone–alone group, by 0.32±0.17 standard-deviation score (2.1 cm) (P = 0.059), suggesting a modest synergy between childhood low-dose ethinyl estradiol and growth hormone.
Conclusions:
Our study shows that growth hormone treatment increases adult height in patients with Turner's syndrome. In addition, the data suggest that combining childhood ultra-low-dose estrogen with growth hormone may improve growth and provide other potential benefits associated with early initiation of estrogen replacement. (Funded by the National Institute of Child Health and Human Development and Eli Lilly; ClinicalTrials.gov number, NCT00001221.) A

Evidence-Based References

Gault EJ et al.: Effect of oxandrolone and timing of pubertal induction on final height in Turner's syndrome: randomised, double blind, placebo controlled trial, *BMJ 342 d1980*, 2011. A

Ross JL et al.: Growth hormone plus childhood low-dose estrogen in Turner's syndrome, *N Engl J Med* 364:1230–1242, 2011. A

SUGGESTED READINGS

Conniff C: Turner's syndrome, *Adolesc Med* 13(2):359, 2002.

Elsheikh M et al.: Turner's syndrome in adulthood, *Endocr Rev* 23(1):120, 2002.

Ross JL et al.: Growth hormone plus childhood low-dose estrogen in Turner's syndrome, *N Engl J Med* 364:1230–1242, 2011.

BASIC INFORMATION

DEFINITION

Typhoid fever is a systemic infection caused by *Salmonella typhi.*

SYNONYMS

Typhoid
Enteric fever

ICD-9CM CODES
002.0 Typhoid fever
ICD-10CM CODES
A01.00 Typhoid fever, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Approximately 400 cases of *S. typhi* infections are reported annually in the United States (Fig. ET1-65). Over three quarters of the cases reported in the United States are now associated with foreign travel (most from Asia, Africa, and Central America).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Incubation period of a few days to several wk.
- Usual manifestations:
  1. Prolonged fever
  2. Myalgias
  3. Headache
  4. Cough
  5. Sore throat
  6. Malaise
  7. Anorexia, at times with abdominal pain and hepatosplenomegaly
  8. Diarrhea or constipation may occur early in the course of illness
  9. Rose spots, which are faint, maculopapular, blanching lesions, may sometimes be seen on the chest or abdomen
- In the untreated patient, fever may last 1 to 2 mo. The main complication of untreated disease is GI bleeding as a result of perforation from ulceration of Peyer's patches in the ileum. Mental status changes and shock are rare complications. The relapse rate is approximately 10%.

ETIOLOGY

- *Salmonella typhi*
- *S. paratyphi* causes a similar illness in humans.
- *S. typhi* or *S. paratyphi* found only in humans
- Acquisition of disease by ingestion of food or water contaminated by other humans
- In the United States most cases are acquired either during foreign travel or by ingestion of food prepared by chronic carriers, many of whom acquired the organism outside of the United States.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Malaria
- Tuberculosis
- Brucellosis
- Amebic liver abscess

WORKUP

- Blood, stool, and urine cultures are helpful.
- Cultures should be repeated if initially negative.
- Blood cultures are more likely to be positive early in the course of illness.
- Stool and urine cultures are more commonly positive in the second and third wk of illness.
- Bone marrow biopsy cultures are 90% positive, although this procedure is usually not necessary.
- Serology using Widal test is helpful in retrospect, showing a fourfold increase in convalescent titers. Rapid and specific *S. typhi* IgM antibody test kits are becoming available that can assist in a rapid diagnosis during acute illness.

LABORATORY TESTS

- Neutropenia is common.
- Transaminitis is possible.
- Culture:
  1. Blood
  2. Body fluids
  3. Biopsy specimens

TREATMENT

ACUTE GENERAL Rx

- If not acquired in Asia: ciprofloxacin 400 mg IV q12h or levofloxacin 750 mg PO/IV q24h for 7-10 days
- If acquired in Asia: ceftriaxone 2 g IV daily for 7-14 days
- Dexamethasone, 3 mg/kg IV initially, followed by 1 mg/kg IV q6h for 8 doses for patients with septic shock or typhoid meningitis with antibiotic therapy

CHRONIC Rx

- Carrier states possible
- More common in age >60 yr and in people with gallstones
- Usual site of colonization: gallbladder
- Treatment in those with persistently positive stool cultures and in food handlers
- Suggested regimens for eradication of carrier state
  1. Ciprofloxacin 500 mg PO bid for 4 wk
  2. SMX/TMP 1 to 2 tabs PO bid for 6 wk (if susceptible)
  3. Amoxicillin, 2 g PO q8h for 6 wk (if susceptible)
- Cholecystectomy possibly required in carriers with gallstones who fail medical therapy

DISPOSITION

- Treated patients usually respond to therapy, with a small percentage becoming chronic carriers.
- The relapse rate is approximately 10%.
- Untreated patients may have serious complications.

REFERRAL

- Failure of therapy
- Chronic carrier

PEARLS & CONSIDERATIONS

COMMENTS

- Oral and parenteral vaccines are available for travelers to areas of high risk.
- Vaccines are about 70% effective and well tolerated but are infrequently used.
- Immunity wanes after several yr.
- Parenteral polysaccharide-based vaccine preparations have improved and are better tolerated than the old whole cell vaccine preparation.
- Infection with antimicrobial-resistant *S. typhi* strains among U.S. patients with typhoid fever is associated with travel to the Indian subcontinent, and an increasing proportion of these infections are due to *S. typhi* strains with decreased susceptibility to fluoroquinolones and beta-lactam antibiotics.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Typhoid Fever (Patient Information)

AUTHOR: **STEVEN M. OPAL, M.D.**

SUGGESTED READINGS

Anusha R et al.: Comparison of the Enterocheck WB rapid antigen test with blood culture methods for the diagnosis of typhoid fever, *Ann Trop Paediatr* 31(3):231–234, 2011.

Crump JA, Mintz ED: Global trends in typhoid and paratyphoid fever, *Clin Infect Dis* 50(2):241–246, 2010.

de Jong HK, Parry CM, van der Poll T, Wiersinga WJ: Host-pathogen interaction in invasive Salmonellosis, *PLoS Pathog* 8(10):e1002933, 2012.

Huang DB, DuPont HL: Problem pathogens: extra-intestinal complications of *Salmonella enterica* serotype Typhi infection, *Lancet Infect Dis* 5(6):341, 2005.

Lynch MF et al.: Typhoid fever in the United States, 1999-2006, *JAMA* 302(8): 859–865, 2009.

Neil KP et al.: A large outbreak of typhoid fever associated with a high rate of intestinal perforation in the Kasese district of Uganda 2008-9, *Clin Infect Dis* 54:1091–1099, 2012.

Steinberg EB et al.: Typhoid fever in travelers: who should be targeted for prevention? *Clin Infect Dis* 39(2):186, 2004.

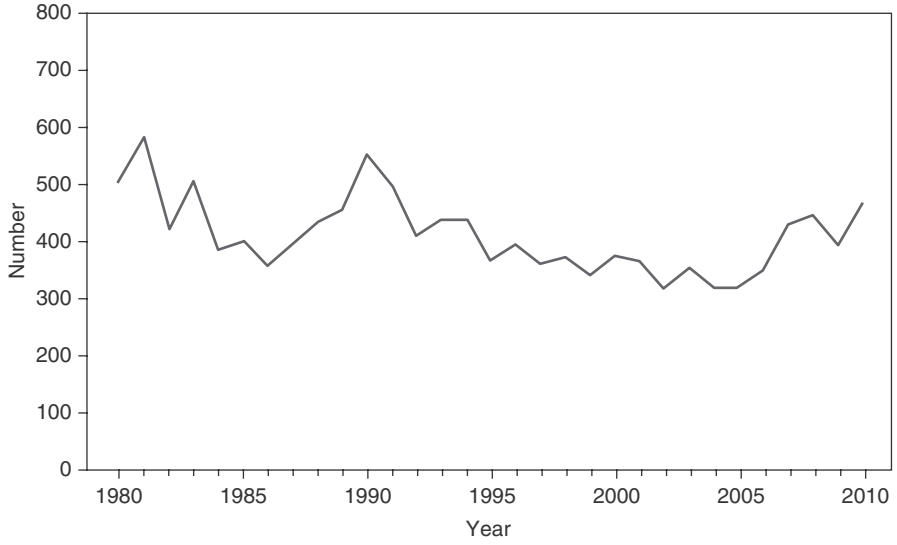


FIGURE ET1-65 Typhoid fever. Number of reported cases, by year—United States, 1980-2010. (From Centers for Disease Control and Prevention: Summary of notifiable diseases—United States, 2010, *MMWR Morb Mortal Wkly Rep* 59[53]:1-111, 2012.)

Ulcerative Colitis EBM PTG

BASIC INFORMATION

DEFINITION

Ulcerative colitis (UC) is an idiopathic, remitting and relapsing, chronic inflammatory bowel disease that starts in the rectum and extends proximally.

SYNONYMS

UC
Inflammatory bowel disease (IBD)
Idiopathic proctocolitis
Pancolitis

ICD-9CM CODES
556.9 Ulcerative colitis
ICD-10CM Codes
K51.0 Ulcerative pancolitis
K51.2 Ulcerative proctitis
K51.3 Ulcerative rectosigmoiditis
K51.5 Left-sided colitis
K51.8 Other ulcerative colitis
K51.90 Ulcerative colitis, unspecified, without complications

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The incidence of UC is 9 to 12 cases per 100,000 persons per year in the U.S.; worldwide, the estimated incidence ranges from 1.2 to 20.3 cases per 100,000 person-years and its prevalence ranges from 7.6 to 246.0 per 100,000 persons. It is most common between ages 15 and 40 yr, with a second peak between 50 and 80 yr. The disease affects men and women at similar rates. Infection with nontyphoid salmonella or campylobacter is associated with an 8-10 time higher risk of developing ulcerative colitis in the following year. Worldwide UC is more common than Crohn's disease.

PREVALENCE: The prevalence of UC is 7.6 to 246.0 cases per 100,000 per year. Higher prevalence in Ashkenazi Jewish descendants.

GEOGRAPHIC DISTRIBUTION: The highest incidence and prevalence of IBD are seen in northern Europe and North America, and the lowest in continental Asia.

GENETICS:

- Both specific and nonspecific gene variants are associated with UC.
- There are 47 loci associated with UC, of which 19 are specific for UC and 28 are shared with Crohn's disease.
- Abnormalities in humoral and cellular adaptive immunity are also found in UC.

ETIOLOGY AND PATHOGENESIS

Accumulating evidence suggests that it may result from an inappropriate inflammatory response to environmental triggers and immune dysregulation involving CD4+ T-cell Th2 response in a genetically susceptible host.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients with UC often present with acute onset of bloody diarrhea accompanied by tenesmus, fever, and dehydration. At presentation 40% of adults have proctitis, 40% have left-sided colitis, and 20% have pancolitis.
- Abdominal distention and tenderness may indicate the presence of complications such as toxic megacolon.
- The onset of symptoms is typically acute and is generally followed by periods of spontaneous remission and frequent relapses.
- Fever, evidence of dehydration may be present during the acute flare-up.
- Evidence of extraintestinal manifestations may be present in nearly 25% of patients: liver disease, sclerosing cholangitis, iritis, uveitis, episcleritis, arthritis, erythema nodosum, pyoderma gangrenosum, aphthous stomatitis.

TABLE U1-1 Comparison of Crohn's Disease and Ulcerative Colitis

Feature	Crohn's Disease	Ulcerative Colitis
Rectal bleeding	Sometimes	Common
Diarrhea, mucus, pus	Variable	Common
Abdominal pain	Common	Variable
Abdominal mass	Common	Not present
Growth failure	Common	Variable
Perianal disease	Common	Rare
Rectal involvement	Occasional	Universal
Pyoderma gangrenosum	Rare	Present
Erythema nodosum	Common	Less common
Mouth ulceration	Common	Rare
Thrombosis	Less common	Present
Colonic disease	50%-75%	100%
Ileal disease	Common	None except backwash ileitis
Stomach-esophageal disease	More common	Chronic gastritis can be seen
Strictures	Common	Rare
Fissures	Common	Rare
Fistulas	Common	Rare
Toxic megacolon	None	Present
Sclerosing cholangitis	Less common	Present
Risk for cancer	Increased	Greatly increased
Discontinuous (skip) lesions	Common	Not present
Transmural involvement	Common	Unusual
Crypt abscesses	Less common	Common
Granulomas	Common	None
Linear ulcerations	Uncommon	Common

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Crohn's disease (Table U1-1)
- Bacterial infections (Table U1-2)
  1. Acute: *Campylobacter, Yersinia, Salmonella, Shigella, Chlamydia, Escherichia coli, Clostridium difficile,* gonococcal proctitis
  2. Chronic: Whipple's disease, tuberculosis, enterocolitis
- Irritable bowel syndrome
- Protozoal and parasitic infections (amebiasis, giardiasis, cryptosporidiosis)
- Neoplasm (intestinal lymphoma, carcinoma of colon)
- Ischemic bowel disease
- Diverticulitis
- Celiac sprue, lymphocytic or collagenous colitis, radiation enteritis, endometriosis
- Solitary rectal ulcer
- Acute self-limited colitis
- Medication (NSAIDs, chemotherapy)

WORKUP

An accurate diagnosis of UC should define the extent and severity of inflammation. Diagnostic workup includes:

- Comprehensive history, physical examination
- Laboratory tests (see "Laboratory Tests")
- Colonoscopy to establish the presence of mucosal inflammation; typical endoscopic findings in UC are areas of continuous friable mucosa; diffuse, uniform erythema replacing the usual mucosal vascular pattern; and pseudopolyps. The transition from abnormal to normal tissue tends to be abrupt. Rectal involvement is invariably present if the disease is active. Pathologic findings suggestive of UC include crypt abscesses and atrophy, mucin depletion, basal plasmacytosis, basal lymphoid aggregates, increased lamina propria cellularity, and Paneth cell metaplasia.

LABORATORY TESTS

- Anemia and high erythrocyte sedimentation rate (in severe colitis) are common but normal levels do not rule out the disorder.
- Potassium, magnesium, calcium, and albumin may be decreased.
- Antineutrophil cytoplasmic antibodies (ANCA) with a perinuclear staining pattern (pANCA) can be found in >45% of patients; there is an

TABLE U1-2 Infectious Agents Mimicking Inflammatory Bowel Disease

Agent	Manifestations	Diagnosis	Comments
Bacterial			
Campylobacter jejuni	Acute diarrhea, fever, fecal blood, and leukocytes	Culture	Common in adolescents, may relapse
Yersinia enterocolitica	Acute → chronic diarrhea, right lower quadrant pain, mesenteric adenitis-pseudoappendicitis, fecal blood, and leukocytes Extraintestinal manifestations, mimics Crohn's disease	Culture	Common in adolescents as fever of unknown origin, weight loss, abdominal pain
Clostridium difficile	Postantibiotic onset, watery → bloody diarrhea, pseudomembrane on sigmoidoscopy	Cytotoxin assay	May be nosocomial Toxic megacolon possible
Escherichia coli O157:H7	Colitis, fecal blood, abdominal pain	Culture and typing	Hemolytic-uremic syndrome
Salmonella	Watery → bloody diarrhea, food borne, fecal leukocytes, fever, pain, cramps	Culture	Usually acute
Shigella	Watery → bloody diarrhea, fecal leukocytes, fever, pain, cramps	Culture	Dysentery symptoms
Edwardsiella tarda	Bloody diarrhea, cramps	Culture	Ulceration on endoscopy
Aeromonas hydrophila	Cramps, diarrhea, fecal blood	Culture	May be chronic Contaminated drinking water
Plesiomonas	Diarrhea, cramps	Culture	Shellfish source
Tuberculosis	Rarely bovine, now *Mycobacterium tuberculosis* Ileocecal area, fistula formation	Culture, purified protein derivative, biopsy	Can mimic Crohn's disease
Parasites			
Entamoeba histolytica	Acute bloody diarrhea and liver abscess, colic	Trophozoite in stool, colonic mucosal flask ulceration, serologic tests	Travel to endemic area
Giardia lamblia	Foul-smelling, watery diarrhea, cramps, flatulence, weight loss; no colonic involvement	"Owl"-like trophozoite and cysts in stool; rarely duodenal intubation	May be chronic
AIDS-Associated Enteropathy			
Cryptosporidium	Chronic diarrhea, weight loss	Stool microscopy	Mucosal findings not like inflammatory bowel disease
Isospora belli	As in *Cryptosporidium*		Tropical location
Cytomegalovirus	Colonic ulceration, pain, bloody diarrhea	Culture, biopsy	More common when on immunosuppressive medications

From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

increased frequency in treatment-resistant left-sided colitis, suggesting a possible association between these antibodies and a relative resistance to medical therapy in patients with UC.

- Calprotectin is a protein that is measured in feces as a marker of intestinal mucosa leukocyte activity that may be useful for screening of patients with suspected IBD. Trials have shown that based on a pretest probability of IBD of 32% in adults, an abnormal fecal calprotectin test would increase the posttest probability to 91% and a normal result would reduce the probability to 3%.
- Fecal lactoferrin is also a sensitive marker of intestinal inflammation.
- Stool examinations for ova and parasites, stool culture, and testing for *Clostridium difficile* toxin and *E. coli* O157:H7 may be useful to eliminate other causes of diarrhea in selected patients with risk factors.

IMAGING STUDIES

Image studies (plain radiography, CT scan [Fig. U1-1]) are generally reserved for suspected complications such as perforation of bowel or toxic megacolon.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Correct nutritional deficiencies; total parenteral nutrition with bowel rest may be necessary in severe cases. Folate supplementation may reduce the incidence of dysplasia and cancer in chronic UC.
- Avoid oral feedings during acute exacerbation to decrease colonic activity; a low-roughage diet may be helpful in early relapse.
- Psychotherapy is useful in most patients. Referral to self-help groups is also important because of the chronicity of the disease and the young age of the patients.

ACUTE GENERAL Rx

The therapeutic options vary with the degree of disease (mild, severe, fulminant) and areas of involvement (distal, extensive).

- Mild disease can be treated with 5-aminosalicylate agents (mesalamine, olsalazine, balsalazide, sulfasalazine). It can be administered as an enema (40 mg once daily at bedtime for 3 to 6 wk) or suppository (500 mg bid) for patients with distal colonic disease. Oral forms in which the 5-acetyl salicylic acid is in a slow-release or pH-dependent matrix (Pentasa 1 g qid, Asacol 800 mg PO tid) can deliver therapeutic concentrations to the more proximal small bowel or distal ileum. Olsalazine can be useful for maintenance of remission of UC in patients intolerant to sulfasalazine. Usual dose is 500 mg bid taken with food. Balsalazide is indicated for mild to moderately active UC. Usual dose is three 750-mg capsules tid. Probiotics may also be helpful in inducing remission in mild-to-moderate UC.
- Mild-to-moderate UC is often treated with a combination of rectal and oral 5-aminosalicylate. Refractory patients are candidates for oral glucocorticoids or immunosuppressive agents (e.g., cyclosporine).
- Severe disease usually responds to oral corticosteroids (e.g., prednisone 40 to 60 mg/day); the FDA has recently approved an extended-release formulation of the corticosteroid budesonide for induction of remission in mild to moderate ulcerative colitis. Corticosteroid suppositories or enemas are

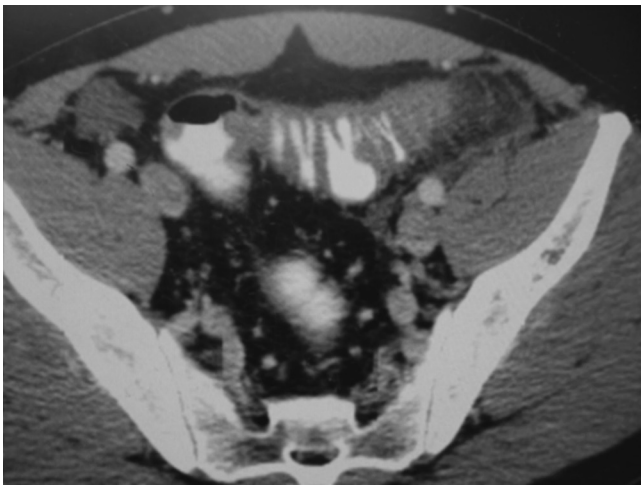


FIGURE U1-1 Computed tomography scan showing colonic wall thickening in a patient with ulcerative colitis. (From Adams JG, et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

also useful for distal colitis. The immunosuppressant azathioprine also provides effective long-term treatment for Crohn's disease.

- Biological agents are emerging treatment options for the management of ulcerative colitis. Infliximab, a chimeric monoclonal antibody, has been shown to be effective in patients who have not responded to corticosteroid therapy. Newer TNF inhibitors include adalimumab (ADA), golimumab, and vedolizumab for treatment of moderate-to-severe ulcerative colitis. Head-to-head trials of these biologic agents are necessary to establish the best therapeutic option.
- Fulminant disease generally requires hospital admission and parenteral corticosteroids (e.g., IV hydrocortisone 100 mg q6h). When bowel movements have returned to normal and the patient is able to eat normally, oral prednisone is resumed. IV cyclosporine can also be used in severe refractory cases; renal toxicity is a potential complication.
- Surgery is indicated in patients who do not respond to intensive medical therapy. Proctocolectomy is usually curative in these patients and also eliminates the high risk of developing adenocarcinoma of the colon (10% to 20% of patients develop it after 10 yr with the disease). Total proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the procedure of choice for most patients who require elective surgery, since it preserves anal sphincter function. Continent ileostomy is an alternative procedure.

CHRONIC Rx

- Colonoscopic surveillance and multiple biopsies should be instituted approximately 10 yr after diagnosis because of the increased risk of colon carcinoma.
- Erythropoietin is useful in patients with anemia refractory to treatment with iron and vitamins.
- In patients on long-term steroid therapy, periodic bone density scans are recommended to screen for glucocorticoid-induced osteoporosis.

DISPOSITION

- The natural history of the disease is one of remission and episodic flares.
- The clinical course is variable. ~66% of patients will achieve clinical remission with medical therapy, and nearly 80% of treatment-compliant patients maintain remission. 15% to 20% of patients eventually require colectomy. Pouchitis is the most common long-term complication of IPAA (up to 40% of patients). >75% of patients treated medically will experience relapse.

REFERRAL

- Gastrointestinal consultation for initial diagnostic sigmoidoscopy/colonoscopy in suspected cases
- Surgical referral for patients with severe disease unresponsive to medical therapy

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Ulcerative Colitis (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Objective:
The aim of this study was to assess the efficacy and safety of adalimumab (ADA), a recombinant human monoclonal antibody against tumour necrosis factor α (TNF), for the induction of clinical remission in anti-TNF naïve patients with moderately to severely active ulcerative colitis.

Methods:
This 8-week, multicentre, randomised, double-blind, placebo-controlled study (NCT00385736), conducted at 94 centres in North America and Europe, enrolled ambulatory adult patients with Mayo score of ≥6 points and endoscopic subscore of ≥2 points despite treatment with corticosteroids and/or immunosuppressants. Under the original study protocol, 186 patients were randomised (1:1) to subcutaneous treatment with ADA160/80 (160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6) or placebo. Subsequently, at the request of European regulatory authorities, the protocol was amended to include a second induction group (ADA80/40: 80 mg at week 0, 40 mg at weeks 2, 4 and 6). The primary efficacy endpoint was clinical remission (Mayo score ≤2 with no individual subscore >1) at week 8, assessed in 390 patients randomised (1:1:1) to ADA160/80, ADA80/40, or placebo. Safety was assessed in all enrolled patients. Patients, study site personnel, investigators, and the sponsor were blinded to treatment assignment.

Results:
At week 8, 18.5% of patients in the ADA160/80 group (p=0.031 vs placebo) and 10.0% in the ADA80/40 group (p=0.833 vs placebo) were in remission, compared with 9.2% in the placebo group. Serious adverse events occurred in 7.6%, 3.8% and 4.0% of patients in the placebo, ADA80/40, and ADA160/80 groups, respectively. There were two malignancies in the placebo group, none in the ADA groups. There were no cases of tuberculosis and no deaths.

Conclusions:
ADA160/80 was safe and effective for induction of clinical remission in patients with moderately to severely active ulcerative colitis failing treatment with corticosteroids and/or immunosuppressants. Ⓐ

Abstract[2]

Background:
Recent studies have focused on the importance of mucosal healing in ulcerative colitis (UC). However, it was still unclear whether higher doses of delayed-release mesalazine (mesalamine) could provide additional benefit.

Aim:
To examine how two doses of delayed-release mesalazine (4.8 g/day and 2.4 g/day) from ASCEND I and II compare in their relative ability to heal colonic mucosa over time.

Methods:
Primary data from two prospective 6-week, double-blind, randomised studies in patients with mildly to moderately active UC were pooled and analysed retrospectively. The mucosal healing analysis focuses on moderately active UC patients (n =391), comprising a majority of patients (84%). Additional analyses examined the relationship between mucosal healing and dose, clinical response to therapy and patient quality of life (Inflammatory Bowel Disease Questionnaire, IBDQ).

Results:
At week 3, mucosal healing (endoscopy subscore of 0 or 1) was achieved in 65% of moderately active UC patients on 4.8 g/day and 58% of patients on 2.4 g/day (P=0.219). At week 6, this increased to 80% for 4.8 g/day and 68% for 2.4 g/day (P=0.012). Healing rates with the higher dose were also greater across all extents of disease and in patients with prior steroid use. At 6 weeks, clinical response to therapy and mucosal healing were found to be well correlated (kappa=0.694). Likewise, the change in IBDQ at week 6 showed a significant relationship with mucosal healing (P<0.0001).

Conclusion:
Mucosal healing rates in UC achieved at 6 weeks were statistically significantly higher with delayed-release mesalazine at 4.8 g/day vs. 2.4g/day (Clinicaltrials.gov: NCT00577473, NCT00073021). Ⓐ

Evidence-Based References

Reinisch W, et al.: Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial, *Gut* 60:780–787, 2011. Ⓐ

Lichtenstein GR, et al.: Randomised clinical trial: delayed-release oral masalazine 4.8 g/day vs. 2.4 g/day in endoscopic mucosal healing—ASCEND I and II combined analysis, *Aliment Pharmacol Ther* 33:672–678, 2011. Ⓐ

SUGGESTED READINGS

Abraham C, Cho J: Inflammatory bowel disease, *N Engl J Med* 361:2066–2078, 2009.

Adams MA, Bornemann PH: Ulcerative colitis, *Am Fam Physician* 87(10):699–705, 2013.

Danese S, Fiocchi C: Ulcerative colitis, *N Engl J Med* 365:1713–1725, 2011.

Danese S et al.: Biological agents for moderately active ulcerative colitis, a systematic review and network meta-analysis, *Ann Intern Med* 160:704–711, 2014.

Feuerstein JD, Cheifetz AS: Ulcerative colitis: epidemiology, diagnosis, and management, *Mayo Clin Proc* 89(11):1553–1563, 2014.

Gisbert JP et al.: Comparative effectiveness of azathioprine in Crohn's disease and ulcerative colitis: prospective, long-term, follow-up study of 394 patients, *Aliment Pharmacol Ther* 28:228–238, 2008.

Langan RC et al.: Ulcerative colitis: diagnosis and treatment, *Am Fam Physician* 76:1323–1330, 2007.

Sanborn WJ et al.: Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis, *N Engl J Med* 367:616–624, 2012.

Van Rheenen PF et al.: Fecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis, *BMJ* 341:c3369, 2010.

BASIC INFORMATION

DEFINITION

Urinary tract infection (UTI) is a term that encompasses a broad range of clinical entities that have in common a positive urine culture. A conventional threshold is growth of >100,000 colony-forming units per milliliter from a midstream-catch urine sample. In symptomatic patients, a smaller number of bacteria (between 100 and 10,000 colony-forming units per milliliter of midstream urine) is recognized as an infection.

SYNONYMS

UTI

ICD-9CM CODES
595.0 Acute cystitis
595.3 Trigonitis
595.2 Chronic cystitis
590.1 Acute pyelonephritis
590.0 Chronic pyelonephritis
590.8 Nonspecific pyelonephritis

ICD-10CM Codes
N30.00 Acute cystitis without hematuria
N30.30 Trigonitis without hematuria
N30.20 Other chronic cystitis without hematuria
N39.0 Urinary tract infection, site not specified

CLASSIFICATION

- Uncomplicated UTI: occurs in a normal urinary tract and resolves rapidly with conventional antimicrobials.
- Complicated UTI: occurs in patients with coexisting pathology (strictures, stones, comorbidities [diabetes mellitus, multiple sclerosis, spinal cord injuries]).
- First infection: the first documented UTI; tends to be uncomplicated and is easily treated.
- Unresolved bacteriuria: UTI in which the urinary tract is not sterilized during therapy. Main causes are bacterial resistance, patient noncompliance with medication, mixed bacterial infection, rapid reinfection, azotemia, infected stones, Münchausen syndrome, and papillary necrosis.
- Bacterial persistence: UTI in which the urine cultures become sterile during therapy, but a persistent source of infection from a site within the urinary tract that was excluded from the high urinary concentrations gives rise to reinfection by the same organism. Causes include infected stone, chronic bacterial prostatitis, atrophic infected kidney, vesicovaginal or enterovesical fistulas, obstructive uropathy, infected pyelocaliceal diverticula, infected ureteral stump after nephrectomy, infected necrotic papillae from papillary necrosis, infected urachal cysts, infected medullary sponge kidney, urethral diverticula, and foreign bodies.
- Reinfection: UTI in which a new infection occurs with new pathogens at variable intervals after a previous infection has been eradicated.
- Relapse: the less common form of recurrent infection; occurs within 2 wk of treatment when the same organism reappears in the same site as the previous infection. Relapsing infections of the urinary tract most commonly occur in pyelonephritis, kidney obstruction from a stone, and prostatitis.

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE

- UTI is the most common bacterial infection encountered in the ambulatory care setting in the U.S. The self-reported annual incidence of UTI in women is 12%, and by age 32 half of all women report having had at least one UTI.
- In neonates: more common in boys as a result of anatomic abnormalities such as posterior urethral valves.
- In preschool children: more common in girls (4.5% vs. 0.5% for boys).
- In adulthood: more common in women, with a 1% to 3% prevalence in nonpregnant women. Table U1-3 describes factors modulating risk for acute uncomplicated UTIs in women. In pregnancy at 12 wk, the incidence of asymptomatic bacteriuria is similar to nonpregnant women, at 2% to 10%. However, 25%-30% of pregnant women with untreated asymptomatic bacteriuria develop acute pyelonephritis, especially in the second and third trimesters, and have a pyelonephritic recurrence rate of 10%. In adults aged ≥65 yr, at least 10% of men and 20% of women have bacteriuria.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- UTI presentation is inconsistent and cannot be relied on to diagnose UTI accurately or to localize the site of infection. Patients report:
  1. Urinary frequency, urgency
  2. Dysuria
  3. Urge incontinence
  4. Suprapubic pain
  5. Gross or microscopic hematuria
- When negative cultures are associated with significant pyuria, vaginal discharge, or hematuria, infections with *Chlamydia trachomatis, Neisseria gonorrhoeae,* and *Trichomonas vaginalis* should be considered.
- Acute pyelonephritis presents with fever, flank or abdominal pain, chills, malaise, vomiting, and diarrhea. It is these systemic symptoms that distinguish pyelonephritis from cystitis. Complications of acute pyelonephritis are renal abscess, perinephric abscess, emphysematous pyelonephritis, and pyonephrosis.

ETIOLOGY & PATHOGENESIS

- Four major pathways:
  1. Ascending from the urethra
  2. Lymphatic
  3. Hematogenous
  4. Direct extension from another organ system
- Other risk factors: neurologic diseases, renal failure, diabetes, anatomic abnormalities, bladder outlet obstruction, urethral stricture, vesicoureteral reflux, fistula, urinary diversion, megacystis, infected stones, age, pregnancy, instrumentation, poor patient compliance, poor hygiene, infrequent voiding, diaphragm contraceptives, tampon use, douches, and catheters.
- Catheters: all patients who require a long-term Foley catheter eventually develop significant levels of bacteriuria. Treatment is reserved for individuals who become symptomatic (leukocytosis, fever, chills, malaise, loss of appetite, etc.) Using prophylactic antibiotics to treat patients who have chronic catheters is to be discouraged because of the risk of acquiring bacteria resistant to antibiotic therapy.
- Once bacteria reach the urinary tract, three factors determine whether the infection occurs (Box EU1-1). These factors also determine the anatomic level of the UTI:
  1. Virulence of the microorganism
  2. Inoculum size
  3. Adequacy of the host defense mechanisms
- Urinary pathogens: in 95% of UTIs the infecting organism is a member of the Enterobacteriaceae, enterococci, or, in young women, *Staphylococcus saprophyticus. Escherichia coli* is the most common pathogen (85% of UTI cases). In contrast, the organisms that commonly colonize the distal urethra and skin of both men and women and the vagina of women are *Staphylococcus epidermidis,* diphtheroids, lactobacilli, *Gardnerella vaginalis,* and a variety of anaerobes that rarely cause UTIs. In general, the isolation of two or

TABLE U1-3 Factors Modulating Risk for Acute Uncomplicated Urinary Tract Infections in Women

Host Determinants	Uropathogen Determinants
Behavioral: sexual intercourse, use of spermicidal products, recent antimicrobial use, suboptimal voiding habits	*Escherichia coli* virulence determinants: P, S, Dr, and type I fimbriae; hemolysin; aerobactin; serum resistance
Genetic: innate and adaptive immune response, enhanced epithelial cell adherence, antibacterial factors in urine and bladder mucosa, nonsecretor of ABO blood group antigens, P_1 blood group phenotype, reduced CXCR1 expression, previous history of recurrent cystitis	
Biologic: estrogen deficiency in postmenopausal women, micturition	

From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

more bacterial species from a urine culture signifies a contaminated specimen unless the patient is being managed with an indwelling catheter or urinary diversion or has a chronic complicated infection.
- Defense mechanisms against cystitis: low pH and high osmolarity, mucopolysaccharide glycosaminoglycan protective layer, normal bladder that empties completely and has no incontinence, and the presence of estrogen.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Interstitial cystitis
- Vaginitis
- Urethritis (gonococcal, nongonococcal, *Trichomonas*)
- Frequency-urgency syndrome, prostatitis (acute and chronic)
- Obstructive uropathy
- Infected stones
- Fistulas
- Papillary necrosis
- Vesicoureteral reflux
- Irritation

LABORATORY TESTS

- Urinalysis with microscopic evaluation of clean-catch urine for bacteria and pyuria. The presence of ≥10 leukocytes/μl of unspun urine from a midstream catch indicates UTI. If urine dipsticks are used, the presence of positive nitrite and positive leukocyte esterase is indicative of UTI in a symptomatic patient.
- Urine culture and sensitivity are useful in complicated UTIs but generally not needed in uncomplicated UTIs.
- Complete blood count with differential (shows leukocytosis)
- Antibody-coated bacteria are seen with pyelonephritis

IMAGING STUDIES

- Warranted only if renal infection or genitourinary abnormality is suspected
- KUB (kidneys, ureter, and bladder); voiding cystourethrogram; renal sonogram; intravenous pyelogram; CT scan; nuclear scan
- Specialty examination: cystoscopy with occasional retrograde pyelography to rule out obstructive uropathy; stenting the obstruction possibly required

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Hot sitz baths, anticholinergics, urinary analgesics
- For pyelonephritis: bed rest, analgesics, antipyretics, and IV hydration

ACUTE GENERAL Rx

- Conventional therapy of 7 days; short-term therapy of 3 or 5 days (Fig. EU1-2).
- Agents of choice: nitrofurantoin, fluoroquinolones, trimethoprim plus sulfonamide (TMP-SMX), amoxicillin/clavulanate, and cephalosporins. Drug resistance needs to be considered when choosing antibiotic therapy. Currently, in the U.S., fluoroquinolone resistance exceeds 20% and TMP-SMX resistance 40% in some regions, but resistance is much lower for nitrofurantoin.
- For pyelonephritis: hospitalization until afebrile and stable, then at home by home care agency with IV antibiotic composed of aminoglycoside plus cephalosporin for 1 wk followed by oral agents (based on sensitivity) for 2 wk. Moderate forms of pyelonephritis may be successfully treated with fluoroquinolone therapy for 21 days without requiring hospitalization. Most important, complicating factors such as obstructive uropathy or infected stones must be identified and treated.
- A urinary analgesic (e.g., phenazopyridine) can also be used along with antibiotics in patients with significant dysuria.

PEARLS & CONSIDERATIONS

COMMENTS

- Asymptomatic bacteriuria: occurs in both anatomically normal and abnormal urinary tracts. This can clear spontaneously, persist, or lead to symptomatic kidney infection. Treatment is recommended in patients with vesicoureteral reflux, stones, obstructive uropathy, parenchymal renal disease, or diabetes mellitus and in pregnant or immunocompromised patients.
- Pregnancy: 25% to 30% of pregnant women with asymptomatic untreated bacteriuria develop pyelonephritis. This is associated with prematurity and low-birth-weight infants. Confirmed significant bacteriuria should be treated with an aminopenicillin and cephalosporin.
- Recurrent UTI: caused by an unresolved infection, vaginal colonization of the originally infecting organism, or reinfection with a new strain. Management of recurrent UTI includes continuous antibiotic prophylaxis, intermittent self-treatment, and postcoital prophylaxis. Prophylaxis is recommended for women who have two or more symptomatic UTIs over a 6-mo period or three or more episodes over a 12-mo period.
1. Changes after menopause: lower levels of lactobacilli, decreased estrogen, senile atrophy of the genitalia, and loss of bladder elasticity (compliance).
2. Biologic factors altering defense systems: the presence of sialosyl galactosyl globoside on the surface of the kidney acts as a powerful receptor for *Escherichia coli* and increases the risk for UTI; the presence of the blood group P_1 causes increased binding of *E. coli* that is resistant to normal infection-fighting mechanisms in the body. It is believed that some individuals are deficient in a compound called human beta-defensin-1, a naturally occurring antibiotic that fights *E. coli* within the urinary tract.
3. Cranberry juice is often used as a remedy for the prevention of UTIs; however, randomized placebo-controlled trials have shown that it is no better than placebo for preventing UTIs.

RESISTANCE

- Because of the overuse of antibiotics, organisms once sensitive to a number of antimicrobial agents are now increasingly resistant, making effective management of UTI and pyelonephritis more difficult and potentially more dangerous. Most important has been the increasing resistance to trimethoprim plus sulfamethoxazole (TMP-SMX), the current primary care provider drug of choice for acute uncomplicated UTI in women.
- When choosing a treatment regimen, physicians should consider such factors as:
  1. In vitro susceptibility
  2. Adverse effects
  3. Cost effectiveness
  4. Resistance rates in their respective communities

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Urinary Tract Infection (Patient Information)
Urinary Tract Infection (Child) (Patient Information)
Pyelonephritis (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.,** and **PHILIP J. ALIOTTA, M.D.**

EVIDENCE

Abstract[1]

Background:

A number of observational studies and a few small or open randomized clinical trials suggest that the American cranberry may decrease incidence of recurring urinary tract infection (UTI).

Methods:

We conducted a double-blind, placebo-controlled trial of the effects of cranberry on risk of recurring UTI among 319 college women presenting with an acute UTI. Participants were followed up until a second UTI or for 6 months, whichever came first. A UTI was defined on the basis of the combination of symptoms and a urine culture positive for a known uropathogen. The study was designed to detect a 2-fold difference between treated and placebo groups, as was detected in unblinded trials. We assumed 30% of participants would experience a UTI during the follow-up period.

Results:

Overall, the recurrence rate was 16.9% (95% confidence interval, 12.8%–21.0%), and the distribution of the recurrences was similar between study groups, with the active cranberry group presenting a slightly higher recurrence rate (20.0% vs 14.0%). The presence of urinary symptoms at 3 days, 1–2 weeks, and at ≥1 month was similar between study groups, with overall no marked differences.

Conclusions:

Among otherwise healthy college women with an acute UTI, those drinking 8 oz of 27% cranberry juice twice daily did not experience a decrease in the 6-month incidence of a second UTI, compared with those drinking a placebo. Ⓐ

Evidence-Based Reference

Barbosa-Cesnik C et al.: Cranberry juice fails to prevent recurrent urinary tract infection: results from a randomized placebo-controlled trial, *Clin Infect Dis* 52:23–30, 2011. Ⓐ

SUGGESTED READINGS

Barbosa-Cesnik C et al.: Cranberry juice fails to prevent recurrent urinary tract infection: results from a randomized placebo-controlled trial, *Clin Infect Dis* 52:23, 2011.

Gupta K, Trautner B: In the clinic: urinary tract infection, *Ann Intern Med* 156(5):ITC3–1, 2012.

Hooton TM: Uncomplicated urinary tract infection, *N Engl J Med* 366:1028, 2012.

Kodner CM, Gupton TEK: Recurrent urinary tract infections in women: diagnosis and management, *Am Fam Physician* 82(6):638–643, 2010.

McKinnell JA et al.: Nitrofurantoin compares favorably to recommended agents as empirical treatment of uncomplicated urinary tract infections in a decision and cost analysis, *Mayo Clin Proc* 86:840, 2011.

BOX EU1-1 Bacterial Factors

- The size of the inoculum
- The virulence of the infecting organism:
- Virulence factors:
  - P-fimbriae facilitate the adherence of bacteria to biologic surfaces.
  - K-antigens facilitate adherence and protect the organisms from the host-immune response.
  - O-antigens are an important source of the systemic reactions, such as fever and shock, that occur with bacterial infections.
  - H-antigens are associated with flagella and are related to bacterial locomotion.
  - Hemolysin may potentiate tissue damage and facilitate local bacterial growth.
  - Urease alkalinizes the urine and facilitates stone formation, thus potentiating infection.
- Biofilms harbor bacteria on prosthetic devices and may be a source of recurrent infections.
- The presence of sialosyl galactosyl globoside on the surface of kidney cells. This compound is a highly powerful receptor for Escherichia coli bacteria.
- Women with a deficiency in human beta-defensin-1 are at greater risk for urinary tract infection.
- Adequacy of host defense mechanisms

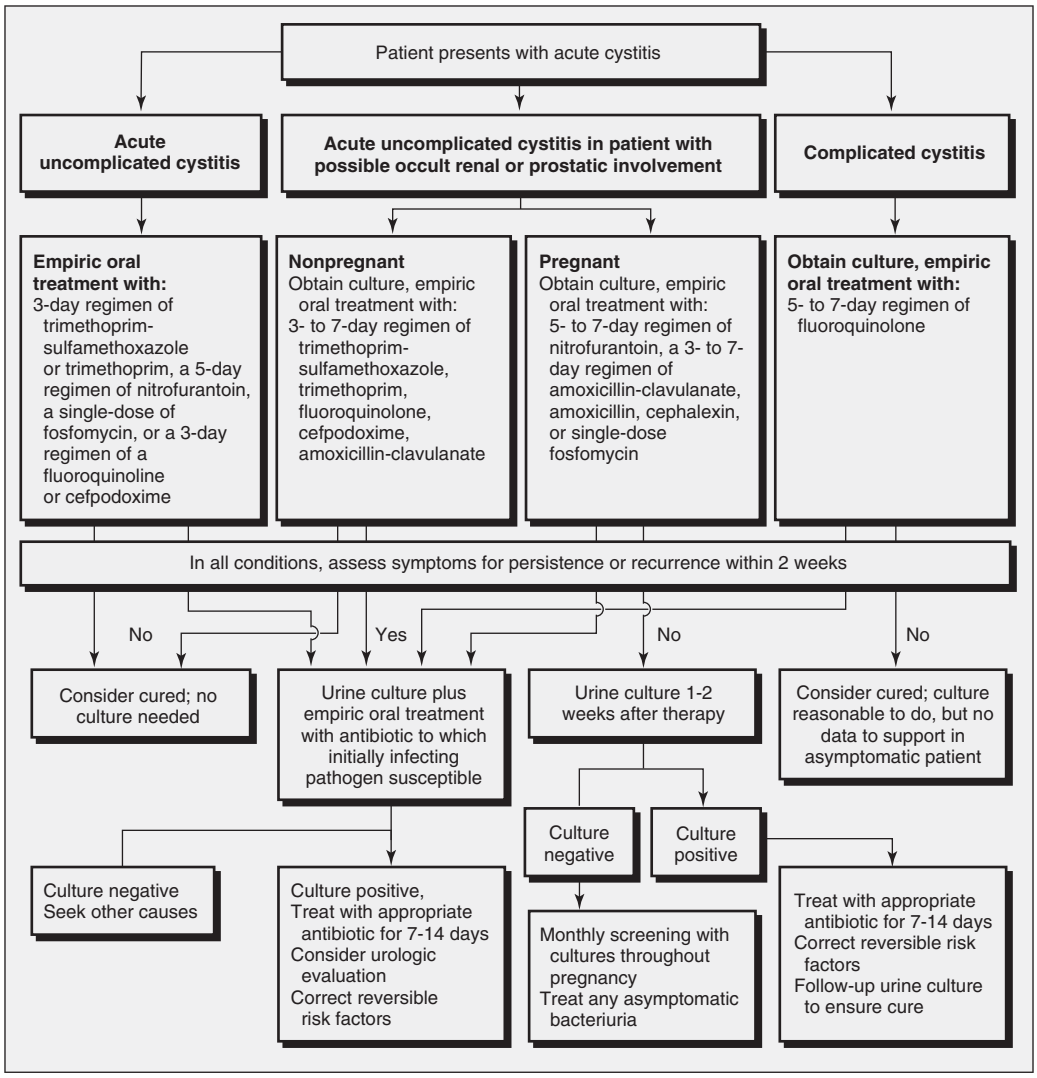


FIGURE EU1-2 Algorithm for management of acute cystitis. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

BASIC INFORMATION

DEFINITION

Urolithiasis is the presence of calculi within the urinary tract. The five major types of urinary stones are calcium oxalate (>50%), calcium phosphate (10% to 20%), uric acid (7%), struvite (7%), and cystine (3%) (Table U1-4).

SYNONYMS

Kidney stones
Renal colic
Nephrolithiasis

ICD-9CM CODES
592.9 Urinary calculus
ICD-10CM Codes
N20.9 Urinary calculus, unspecified
N20.0 Calculus of kidney
N20.1 Calculus of ureter
N20.2 Calculus of kidney with calculus of ureter
N21.0 Calculus in bladder
N21.1 Calculus in urethra
N21.9 Calculus of lower urinary tract, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- In the U.S., the lifetime prevalence of nephrolithiasis is 13% in men and 7% in women, annually.
- Between 1% and 1.7% of emergency department visits (1 to 2 million visits annually) are accounted for by a primary diagnosis of renal colic or renal calculus.
- The incidence of symptomatic nephrolithiasis is greatest during the summer as a result of increased humidity and temperatures with a concomitant increased risk of dehydration and concentrated urine.
- Calcium oxalate or mixed calcium oxalate/calcium phosphate stones account for nearly 70% of uroliths. Supersaturation, often expressed as the ratio of urinary calcium oxalate or calcium phosphate concentration to its solubility, is the driving force in stone formation. At levels above 1, crystals can nucleate and grow, promoting stone formation.

TABLE U1-4 Stone Composition and Relative Occurrence

Stone Composition	Occurrence (%)
Calcium-containing stones	
Ca oxalate	60
Mixed Ca oxalate/hydroxyapatite	20
Brushite	2
Non–calcium containing stones	
Uric acid	7
Magnesium ammonium phosphate (struvite)	7
Cystine	1-3 (10% of stones in children)
Xanthine	<1
Medication-related stones	<1

From Lipshultz LI et al: *Urology and the primary care practitioner,* ed 3, Philadelphia, 2008, Elsevier.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Stones may be asymptomatic, or they may cause the following signs and symptoms as a result of obstruction:

- Sudden onset of flank tenderness
- Nausea and vomiting
- The patient being in constant movement in an attempt to lessen the pain. (Patients with an acute abdomen are usually still because movement exacerbates the pain.)
- Pain that is referred to the testes or labium by the progression of stone down the urinary ureter
- Fever and chills that accompany the acute colic if there is superimposed infection
- Pain that may radiate anteriorly over to the abdomen and result in intestinal ileus

ETIOLOGY

- Supersaturation, often expressed as the ratio of urinary calcium oxalate or calcium phosphate concentration to its solubility, is the driving force in calcium kidney stone formation
- Increased absorption of calcium in the small bowel: type I absorptive hypercalciuria (i.e., independent of calcium intake)
- Idiopathic hypercalciuria nephrolithiasis. (This is the most common diagnosis for patients with calcium stones; the diagnosis is made only if there is no hypercalcemia and no known cause of the hypercalciuria.)
- Increased vitamin D synthesis (e.g., as a result of renal phosphate loss: type III absorptive hypercalciuria)
- Renal tubular malfunction with inadequate reabsorption of calcium and resulting hypercalciuria
- Heterozygous mutations in the NPT2a gene that result in hypophosphatemia and urinary phosphate loss
- Hyperparathyroidism with resulting hypercalcemia
- Elevated uric acid level (e.g., metabolic defects, dietary excess) (Box EU1-2)
- Chronic diarrhea (e.g., inflammatory bowel disease) with increased oxalate absorption
- Type I (distal tubule) renal tubular acidosis (>1% of calcium stones)
- Long-term hydrochlorothiazide treatment
- Chronic infections with urease-producing organisms (e.g., *Proteus, Providencia, Pseudomonas, Klebsiella*). (Struvite, or magnesium ammonium phosphate crystals, is produced when the urinary tract is colonized by bacteria, thus producing elevated concentrations of ammonia [Box EU1-3])
- Abnormal excretion of cystine
- Chemotherapy for malignancies
- Estrogen supplements

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Urinary tract infection
- Pyelonephritis
- Diverticulitis
- Pelvic inflammatory disease
- Ovarian pathology
- Factitious (i.e., in drug addicts)
- Appendicitis
- Small-bowel obstruction
- Ectopic pregnancy

The differential diagnosis of obstructive uropathy is described in Section II.

WORKUP

- Fig. EU1-3 describes an algorithm for evaluation of suspected renal colic.
- Stone analysis should be performed on recovered stones.
- A clinical algorithm for the evaluation of nephrolithiasis is described in Fig. EU1-4.
- Box U1-4 describes events in the medical history that may be significant with regard to urolithiasis.

BOX U1-4 Components of the Medical History That Are Significant for Urolithiasis

- Diseases associated with disturbances of calcium metabolism: primary hyperparathyroidism, Wilson's disease, medullary sponge kidney, osteoporosis, immobilization, sarcoidosis, osteolytic metastases, plasmacytoma, neuroendocrine tumors, Paget's disease
- Dietary history: purine gluttony, calcium excess, milk alkali, oxalate excess, sodium excess, low citrus fruit intake
- Medications: uricosurics, diuretics, analgesics, vitamins C and D, antacids (especially phosphorus-binding agents), acetazolamide, calcium channel blockers, triamterene, estrogens, theophylline, protease inhibitors (indinavir), sulfonamides
- Diseases associated with disturbances of oxalate metabolism: primary hyperoxaluria types I and II, Crohn's disease, ulcerative colitis, intestinal bypass surgery (especially jejunoileal bypass), ileal resection
- Diseases associated with disturbances of purine metabolism
- Intrinsic metabolic disorders: anemia, neoplastic disorders (especially leukemias), intoxication, myocardial infarction, irradiation, cytotoxic chemotherapy
- Enzyme deficiency: primary gout, Lesch-Nyhan syndrome
- Altered excretion: renal insufficiency, metabolic acidosis
- Infectious history: organisms (particularly *Proteus* and *Klebsiella*), febrile, upper tract involvement, and dates (if hospitalized)

Modified from Nseyo UO (ed): *Urology for primary care physicians,* Philadelphia, 1999, Saunders.

LABORATORY TESTS

- Urinalysis: Hematuria may be present; however, its absence does not exclude urinary stones. The evaluation of the urinary pH is of value for the identification of the type of stone: a pH of >7.5 is associated with struvite stones, whereas a pH of <5 generally is seen with uric acid or cystine stones. A low serum bicarbonate concentration with a urine pH of ≥6 is suggestive of renal tubular acidosis.
- Urine culture and sensitivity results should be obtained for all patients.
- Serum chemistries should include calcium, electrolytes, phosphate, and uric acid.
- Additional tests: 24-hr urine collection for calcium, uric acid, phosphate, oxalate, and citrate excretion is generally reserved for patients with recurrent stones.

IMAGING STUDIES

- Common diagnostic modalities for renal colic are summarized in Table U1-5. There is a lack of consensus whether the initial imaging method for patients with suspected nephrolithiasis should be CT or ultrasonography.
- Renal sonogram (Fig. U1-5): A recent comparative study revealed that initial sonography is associated with lower cumulative radiation exposure than initial CT, without significant differences in high-risk diagnoses with complications, serious adverse events, pain scores, return emergency department visits, or hospitalizations. On the basis of this study, it is reasonable to use ultrasonography as the initial imaging modality in suspected nephrolithiasis. Accuracy of sonography in detecting distal ureteral stones can be high but is variable with size of the calculus and expertise of the technician and radiologist.
- Unenhanced (noncontrast) helical computed tomography scanning can be used to visualize the calculus (Fig. EU1-6), which is identified by the "rim sign" or "halo" that represents the edematous ureteral wall around the stone. The test is fast and accurate (sensitivity nearly 100%; specificity, 94% to 96%), and it can be used to readily identify all stone types in all locations.

TABLE U1-5 Common Diagnostic Imaging Modalities for Renal Colic

Modality	Information Provided	Radiation Dose	Contrast	Approximate Cost	Time
CT	Renal stones, including size and position of stones and evidence of obstruction Alternative diagnoses, such as AAA, appendicitis, and free air	4-10 mSv	No	$750-$1000	Less than 5 min to perform, 30 min for interpretation
CT with IV contrast	Same as noncontrast CT Delineation of renal mass lesions Additional information about vascular dissections and mesenteric ischemia	4-10 mSv	Yes	$750-$1000	Less than 5 min, after delay to measure creatinine
CT with IV and oral contrast	Same as CT with IV contrast Potentially improved diagnosis of bowel abnormalities	4-10 mSv	Yes	$750-$1000	Less than 5 min, after delay of approximately 2 hr to ingest oral contrast
Intravenous urogram	Structural and functional information about obstruction Rarely, identification of other pathology, such as AAA	1.5 mSv	Yes	$350	Approximately 75 min
X-ray	Possible identification of stone, but not useful for hydronephrosis or most other pathology	0.5-1 mSv	No	$250	Less than 5 min
Ultrasound	Identification of hydronephrosis or hydroureter Possible identification of stone Used to assess for AAA or biliary disease	No	No	$150	Approximately 15-30 min—bedside ultrasound is quicker

CT, Computed tomography; *IV,* intravenous.

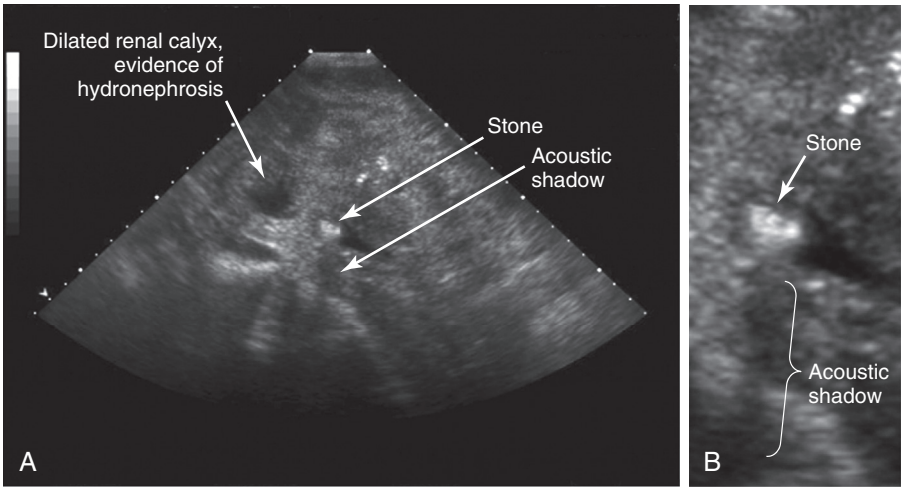


FIGURE U1-5 Ultrasound of renal stone. Ultrasound can be used to assess for renal stones and complications such as hydronephrosis. Stones can be difficult to detect, whereas hydronephrosis is usually readily observed. Because stones are dense, they reflect sound and prevent its through transmission. As a result, stones are echogenic (bright) on ultrasound, and cast an acoustic shadow (black). **A,** Short-axis view of kidney. **B,** Close-up. (From Broder JS: *Diagnostic imaging for the emergency physician*, Philadelphia, 2011, Saunders.)

- Plain films of the abdomen can identify radiopaque stones (e.g., calcium, uric acid) of ≥5 mm in diameter.
- Intravenous pyelography demonstrates the size and location of the stone as well as the degree of obstruction. However, this modality is now rarely used and has largely been replaced by computed tomography.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- An increase in water or other fluid intake is recommended; in fact, a doubling of previous fluid intake should occur unless the patient has a history of congestive heart failure or fluid overload. Generally, patients at increased risk for the development of stones should increase their fluid intake to >2 L/day (68 oz/day) to maintain a urine volume of >2 L/day.
- Normal dietary calcium intake is recommended. If one does not consume enough calcium, less is available to bind to dietary oxalate; as a result, more oxalate reaches the colon, is absorbed into the bloodstream, and excreted as calcium oxalate, thus setting the stage for calcium urolithiasis.
- Sodium restriction to decrease calcium excretion and decreased protein intake to 1 g/kg/day to decrease uric acid, calcium, and oxalate excretion should be considered.
- Increasing the amount of bran in the diet may decrease bowel transit time with an increased binding of calcium and a subsequent decrease in urinary calcium.

ACUTE GENERAL Rx

- Pain control: ketorolac (60 mg intramuscularly) can be used for moderate pain. However, the use of narcotics is generally indicated because of the severity of pain.
- Specific therapy is tailored to the stone type:
  1. Uric acid calculi: control of hyperuricosuria with allopurinol 100 to 300 mg/day; increase urinary pH with potassium citrate 10-mEq tablets tid. Alkalinization of the urine may help prevent uric acid stones and cystine stones.
  2. Calcium stones:
     1. Hydrochlorothiazide 25 to 50 mg qd in patients with type I absorptive hypercalciuria
     2. Decrease bowel absorption of calcium with cellulose phosphate 10 g/day in patients with type I absorptive hypercalciuria
     3. Orthophosphates to inhibit vitamin B synthesis in patients with type III absorptive hypercalciuria
     4. Potassium citrate supplementation for patients with hypocitraturic calcium nephrolithiasis
     5. Purine dietary restrictions or allopurinol for patients with hyperuricosuric calcium nephrolithiasis
     6. Paradoxically, calcium restriction is not warranted for patients who have had calcium stones and may even be harmful
  3. Struvite stones:
     1. Most of these stones are large and cause obstruction and bleeding.
     2. Extracorporeal shock wave lithotripsy (ESWL) and percutaneous nephrolithotomy are generally necessary. Percutaneous nephrolithotomy is very effective for large stones in the kidney and is especially indicated for struvite stones.
     3. The prolonged use of antibiotics directed against the predominant urinary tract organism may be beneficial to prevent recurrence.
  4. Cystine stones: hydration and alkalinization of the urine to pH >6.5; penicillamine and tiopronin can be used to reduce the formation of cystine; captopril is also beneficial and causes fewer side effects.
- Possibly useful medications to help with the passage of distal ureteral stones of <10 mm in diameter are tamsulosin (alpha-adrenergic antagonist) and nifedipine (calcium channel blocker used for ureteral dilatation and relaxation). Side effects may include dizziness with tamsulosin and hypotension with nifedipine.
- Administer antibiotics if fever or pyuria (>5 to 20 leukocytes/high-power field) is present.
- Surgical treatment for patients with severe pain that is unresponsive to medication and patients with persistent fever or nausea or significant impediment of urine flow:
  1. Ureteroscopic stone extraction. Indications for percutaneous nephrolithotomy are described in Table EU1-6.
  2. ESWL for most renal stones. In 2011 the European Association of Urology recommended shock wave lithotripsy as first-line therapy for non-lower pole renal calculi <2 cm in diameter and for lower pole renal calculi <1 cm in diameter. Several types of lithotripters are in clinical use and differ from one another primarily in the way they generate shock waves. Contraindications to shock wave lithotripsy include pregnancy, active UTI, coagulopathies, and distal obstruction. Spinal or orthopedic deformities and morbid obesity may also preclude lithotripsy due to inability to properly position patient or inadequate visualization of the stone.
- Fig. EU1-7 describes the management of ureteral stones.
- In 1997, the American Urological Association issued the following guidelines for the treatment of ureteral stones:
  1. Proximal ureteral stones <1 cm in diameter: the options are ESWL, percutaneous nephroureterolithotomy, and ureteroscopy.
  2. Proximal ureteral stones >1 cm in diameter: the options are ESWL, percutaneous nephroureterolithotomy, and ureteroscopy. The placement of a ureteral stent should be considered if the stone is causing high-grade obstruction.
  3. Distal ureteral stones <1 cm in diameter: most of these stones pass spontaneously. ESWL and ureteroscopy are two accepted modes of therapy.
  4. Distal ureteral stones >1 cm in diameter: the options are watchful waiting, ESWL, and ureteroscopy (after stone fragmentation).

Fig. EU1-7 describes an approach to the management of ureteral calculi.

CHRONIC Rx

The maintenance of proper hydration and dietary restrictions (see "Acute General Rx")

DISPOSITION

- >50% of patients will pass the stone within 48 hr.
- Stones will recur in approximately 50% of patients within 5 yr if no medical treatment is provided.

REFERRAL

A urology referral should be undertaken for patients with complicated or recurrent urolithiasis. Most patients with small uncomplicated ureteral or renal calculi can be followed up as outpatients, whereas patients with persistent vomiting, suspected urinary tract infection, pain that is unresponsive to oral analgesics, or obstructing calculus associated with a solitary kidney should be admitted.

PEARLS & CONSIDERATIONS

COMMENTS

- The early identification and aggressive treatment of urinary tract infections is indicated for all patients with struvite stones.
- The alkalinization of urine (i.e., getting to a pH of >7.5 with the use of penicillamine) is useful for patients with recurrent cystine stones.
- Stones <5 mm in diameter often pass spontaneously whereas stones >10 mm generally do not.
- An algorithmic approach to the management of ureteral calculi is described in Fig. EU1-7.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Kidney Stones (Patient Information)
Urinary Tract Infection (Patient Information)

AUTHORS: **PHILIP J. ALIOTTA, M.D., M.S.H.A.**, and **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Borghi L et al.: Comparison of two diets for the prevention of recurrent stones in idiopathic hypercalciuria, *N Engl J Med* 346:77, 2002.

Fink HA et al.: Medical management to prevent recurrent nephrolithiasis in adults: a systematic review for an American College of Physicians clinical guideline, *Ann Intern Med* 158:535–543, 2013.

Frassetto L, Kohlstadt I: Treatment and prevention of kidney stones: an update, *Am Fam Physician* 84(11):1234–1242, 2011.

Moesbergen TC et al.: Distal ureteral calculi: US follow-up, *Radiology* 260:575, 2011.

Pearle M: Shock-wave lithotripsy for renal calculi, *N Engl J Med* 367:50–57, 2012.

Pietrow PK, Karellas ME: Medical management of common urinary calculi, *Am Fam Physician* 74:86, 2006.

Prie D et al.: Nephrolithiasis and osteoporosis associated with hypophosphatemia caused by mutations in the type 2a sodium-phosphate cotransporter, *N Engl J Med* 347:983, 2002.

Smith-Bindman R et al.: Ultrasonography versus computed tomography for suspected nephrolithiasis, *N Engl J Med* 371:1100–1110, 2014.

Worcester EM, Coe FL: Calcium kidney stones, *N Engl J Med* 363:954–963, 2010.

Worster A et al.: The accuracy of noncontrast helical computed tomography versus intravenous pyelography in the diagnosis of suspected acute urolithiasis: a meta-analysis, *Ann Intern Med* 40:280, 2002.

TABLE EU1-6 Indications for Percutaneous Nephrolithotomy

Indicator	Description	Treatment
Stone size	>3 cm or staghorn	
Composition*	Struvite stones	Complete removal necessary to eliminate infection and minimize stone recurrence
	Calcium oxalate monohydrate stones	Difficult to pulverize by ESWL
	Cystine stones	Difficult to pulverize by ESWL
Stone position	Lower pole stones	Fragments less easily evacuated from dependent lower pole calyces, especially if collecting system dilated
Anatomic abnormalities	PUJ obstruction; calyceal diverticula	Prevent passage of fragments after ESWL
Patient characteristics	Morbid obesity; ureteral obstruction	Stone cannot be placed in focal point of ESWL machine

ESWL is the first choice for stone intervention, except in those circumstances that may favor PCNL.
ESWL, Extracorporeal shock wave lithotripsy; *PCNL,* percutaneous nephrolithotomy; *PUJ,* pelviureteral junction.
*Stone composition can be defined with certainty only by direct stone analysis, but advances in imaging may ultimately provide a means to accurately assess stone composition in situ before treatment, thus allowing the urologist to select the treatment most likely to be successful.
From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

BOX EU1-2 Uric Acid Stones

Low urine pH (≤5.5)
High animal protein diet
Diarrhea
Insulin resistance (high body mass index, metabolic syndrome, type 2 diabetes)

Low Urine Volume
Inadequate fluid intake
Excessive extrarenal fluid losses
Diarrhea
Insensible losses (e.g., perspiration)

Hyperuricosuria
Excessive dietary purine intake
Hyperuricemia
- Gout
- Intracellular-to-extracellular uric acid shift
  - Myeloproliferative disorders
  - Tumor lysis syndrome
- Inborn errors of metabolism
  - Lesch-Nyhan syndrome
  - Glucose-6-phosphatase deficiency

From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

BOX EU1-3 Factors Associated with Struvite Stone Formation

Urease-producing bacteria*:
- *Proteus*
- *Haemophilus*
- *Yersinia* species
- *Staphylococcus epidermidis*
- *Pseudomonas*
- *Klebsiella*
- *Serratia*
- *Citrobacter*
- *Ureaplasma*

Elevated urinary pH

From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

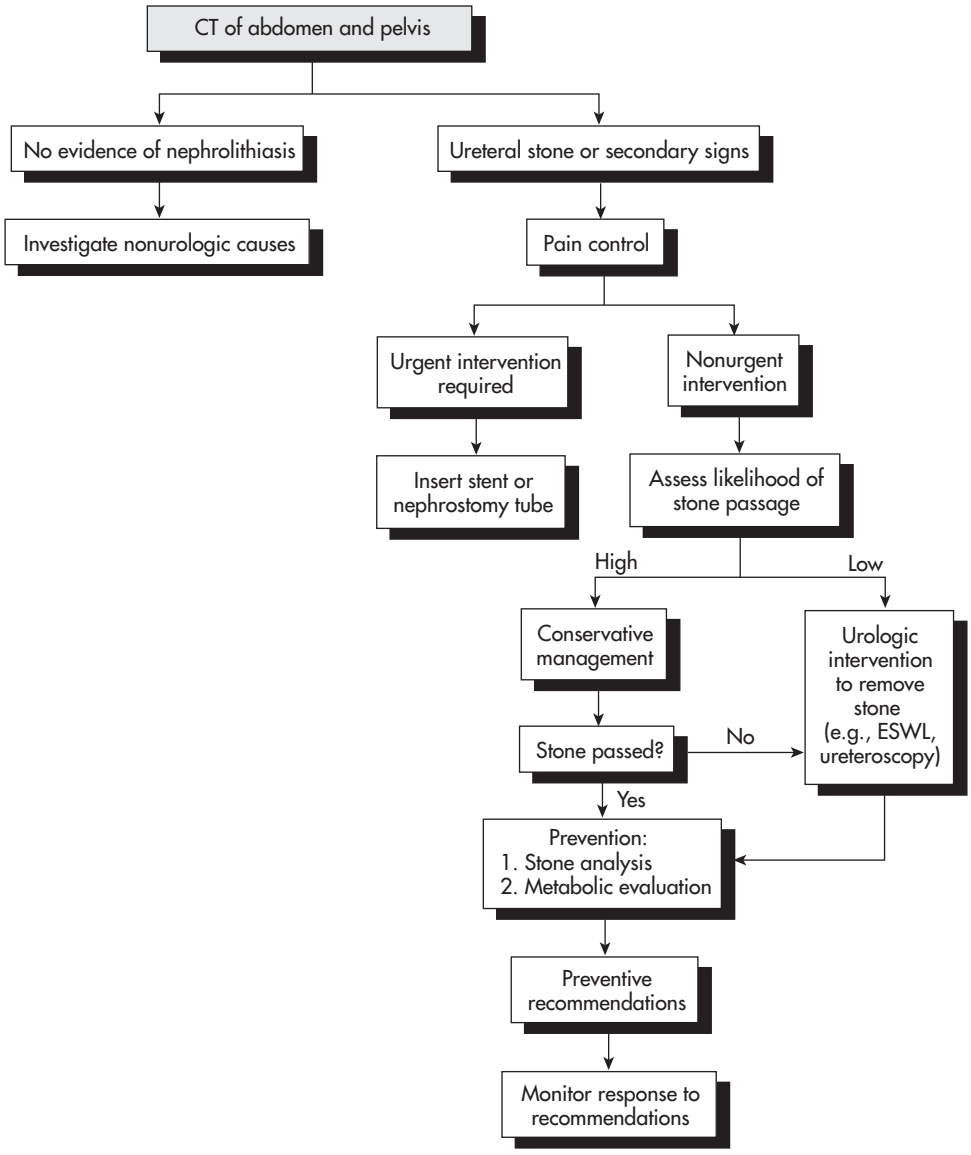


FIGURE EU1-3 Algorithm for evaluation of suspected renal colic. *ESWL,* Extracorporeal shock wave lithotripsy. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

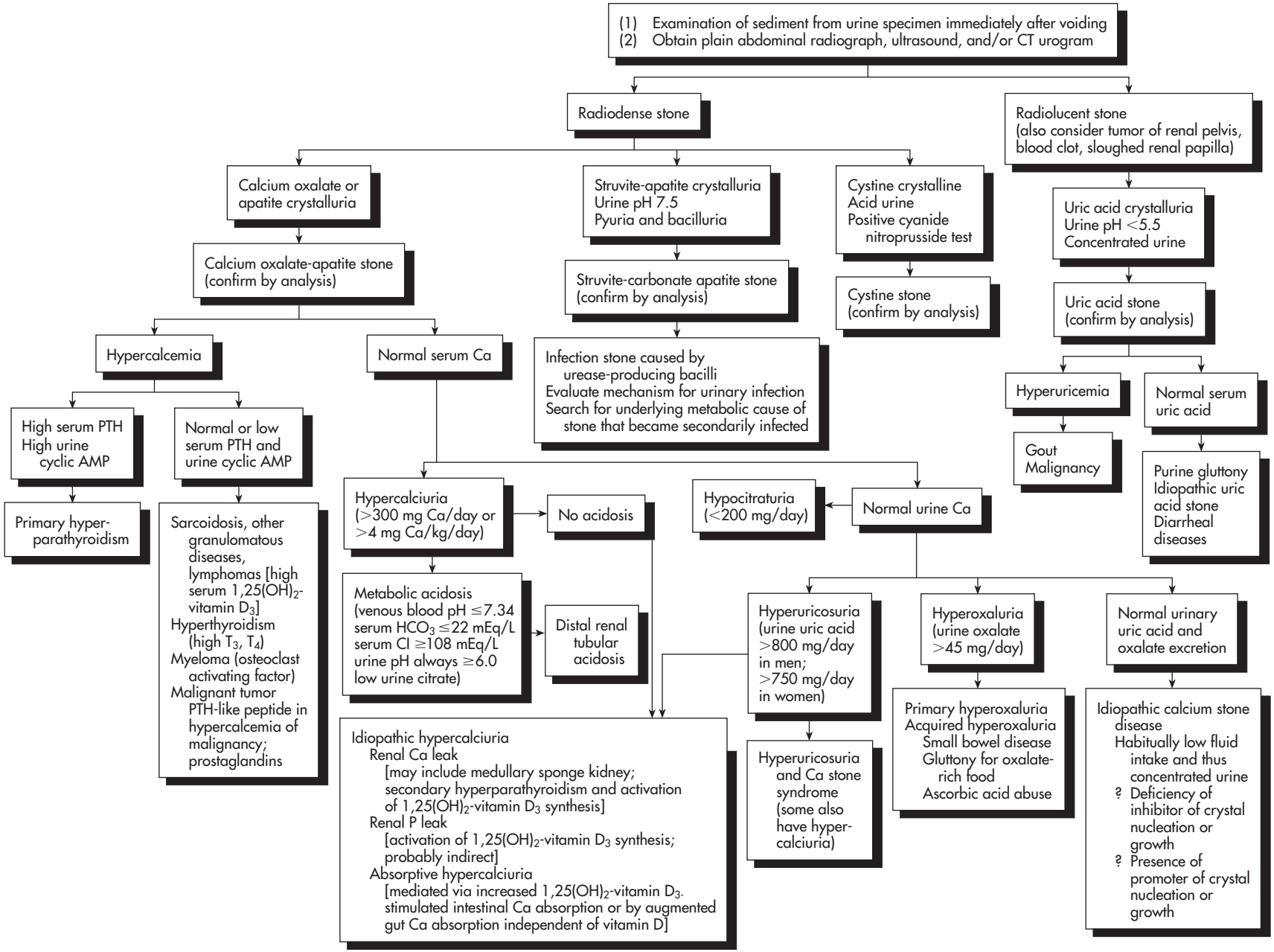


FIGURE EU1-4 Evaluation of patients with suspected nephrolithiasis (flank pain, ureteral colic, hematuria, fever). *AMP,* Adenosine monophosphate; *CT,* computed tomography; *PTH,* parathyroid hormone. (Modified from Stein JH [ed]: *Internal medicine,* ed 5, St Louis, 1998, Mosby.)

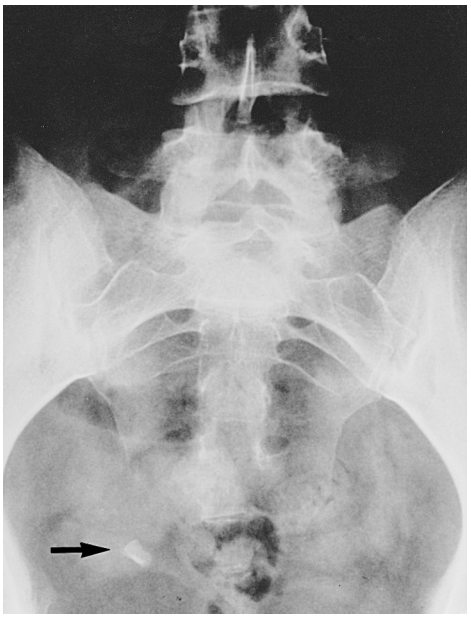


FIGURE EU1-6 Kidney, ureter, and bladder (KUB) radiograph in a patient presenting with hematuria shows a radiopaque shadow *(arrow)* along the course of the distal right ureter that proved to be a calculus. (From Nseyo U, Weinman E, Lamm DL: *Urology for primary care physicians,* Philadelphia, 1999, WB Saunders.)

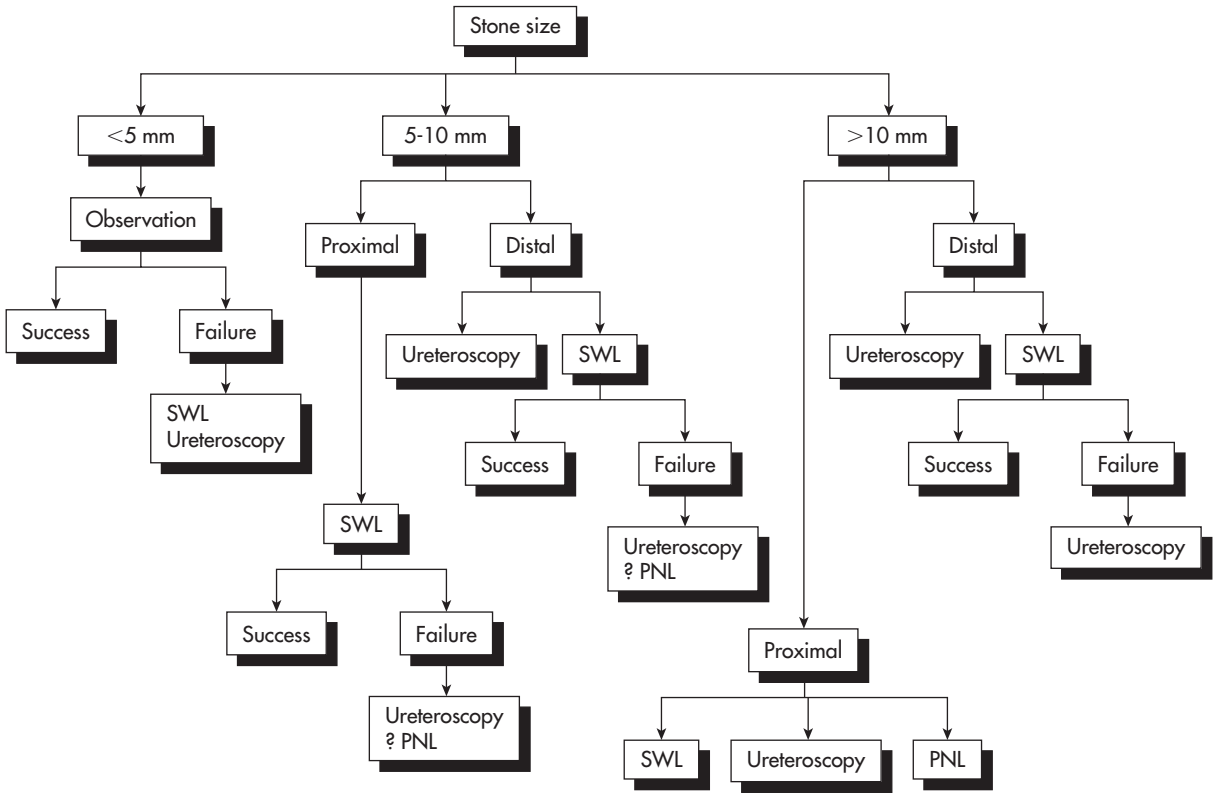


FIGURE EU1-7 Management of urinary calculi. *PNL,* Percutaneous nephrostolithotomy; *SWL,* shock wave lithotripsy. (From Noble J: *Primary care medicine,* ed 3, St Louis, 2001, Mosby.)

BASIC INFORMATION

DEFINITION

Urticaria is a pruritic rash involving the epidermis and the upper portions of the dermis caused by localized capillary vasodilation and followed by transudation of protein-rich fluid in the surrounding tissue and manifesting clinically with the presence of hives. Urticaria is classified according to its chronicity into acute (<6-wk duration) and chronic (>6-wk duration).

SYNONYMS

Hives
Wheals

ICD-9CM CODES
708.8 Other unspecified urticaria
ICD-10CM CODES
L50.0 Allergic urticaria
L50.1 Idiopathic urticaria
L50.2 Urticaria due to cold and heat
L50.8 Other urticaria
L50.9 Urticaria, unspecified
L50.6 Contact urticaria

EPIDEMIOLOGY & DEMOGRAPHICS

- 15% to 20% of the population will have one episode of hives during their lifetime.
- Incidence is increased in atopic patients.
- The etiology of chronic urticaria (hives lasting >6 wk) is determined in only 5% to 20% of cases.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Presence of elevated, erythematous, or white nonpitting plaques that change in size and shape over time; they generally last a few hours and disappear without a trace.
- Annular configuration with central pallor (Fig. EU1-8).
- Angioedema occurs in approximately 40% of cases of urticaria and is caused by mast cell mediator release in the subcutaneous tissue and deep dermis.

ETIOLOGY

- Foods (e.g., shellfish, eggs, strawberries, nuts)
- Drugs (e.g., penicillin, aspirin, sulfonamides)
- Systemic diseases (e.g., systemic lupus erythematosus, serum sickness, autoimmune thyroid disease, polycythemia vera)
- Food additives (e.g., salicylates, benzoates, sulfites)
- Infections (viral infections, fungal infections, chronic bacterial infections); viral upper respiratory infections are the predominant cause
- Physical stimuli (e.g., pressure urticaria, exercise-induced, solar urticaria, cold urticaria)
- Inhalants (e.g., mold spores, animal dander, pollens)
- Contact (nonimmunologic) urticaria (e.g., caterpillars, plants)
- Other: hereditary angioedema, urticaria pigmentosa, pregnancy, cryoglobulinemia, hair bleaches, chemicals, saliva, cosmetics, perfumes, pemphigoid, emotional stress, malignancy (lymphomas, endocrine tumors)
- Idiopathic urticaria is diagnosed in 50% of patients with chronic urticaria.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Erythema multiforme
- Erythema marginatum
- Erythema infectiosum
- Urticarial vasculitis
- Herpes gestationis
- Drug eruption
- Multiple insect bites
- Bullous pemphigoid

WORKUP

- It is useful to determine whether hives are acute or chronic; a medical history focused on various etiologic factors is necessary before embarking on extensive laboratory testing.
- Most cases of acute urticaria resolve spontaneously and diagnostic testing is not required. However, in patients with acute urticaria it is crucial to rule out anaphylaxis.
- A diagnostic approach to chronic urticaria is described in Fig. EU1-9.

LABORATORY TESTS

- Complete blood count with differential.
- Stool for ova and parasites in patients with chronic urticaria and suspected parasitic infestations.
- Skin testing with allergic extracts and screening for dermatographism by attempting to elicit a wheal after application of linear skin pressure should be performed only after withholding antihistamines for 36 to 72 hr to prevent false-negative results.
- Antinuclear antibody, erythrocyte sedimentation rate, thyroid-stimulating hormone, antithyroid antibodies, *Helicobacter pylori* serology, liver function tests, and eosinophil count are indicated only in patients with chronic urticaria. However, even with extensive testing, the cause of chronic urticaria is rarely established.
- Measurement of C4 may be helpful in patients who present with angioedema alone. In these patients, C1 inhibitor deficiency should be considered.
- Skin biopsy is helpful in patients with fever, arthralgias, and elevated erythrocyte sedimentation rate. Histologic evidence of leukocytoclasia (neutrophilic infiltration with fragmentation of nuclei) is indicative of urticarial vasculitis.
- When food allergy is suspected in acute urticaria, testing can be performed using skin prick, immunoCAP, and radioallergosorbent testing.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Remove suspected etiologic agents (e.g., stop aspirin and all nonessential drugs), and restrict diet (e.g., elimination of tomatoes, nuts, eggs, shellfish).
- Elimination of yeast should be attempted in patients with chronic urticaria (*Candida albicans* sensitivity may be a factor in patients with chronic urticaria).

ACUTE GENERAL Rx

- Oral antihistamines: use of nonsedating antihistamines (e.g., loratadine 10 mg qd, cetirizine 10 mg qd, fexofenadine 180 mg qd, levocetirizine 5 mg qd) is preferred over first-generation antihistamines (e.g., hydroxyzine, diphenhydramine).
- Doxepin (a tricyclic antidepressant that blocks both H_1 and H_2 receptors) 25 to 75 mg qhs may be effective in patients with chronic urticaria.
- Oral corticosteroids should be reserved for refractory cases (e.g., prednisone 20 mg qd or 20 mg bid).
- H_2 receptor antagonists (cimetidine, ranitidine, famotidine) can be added to H_1 antagonists in refractory cases.

CHRONIC Rx

- Use of nonsedating antihistamines, doxepin, and/or oral corticosteroids (see "Acute General Rx").
- Low dose of the immunosuppressant cyclosporine (2.5 to 3 mg/kg body weight/day) has been shown to be effective and corticosteroid sparing in chronic urticaria. Algorithms for the evaluation and management of chronic urticaria are described in Figs. EU1-10 and EU1-11, respectively.
- Omalizumab, a monoclonal antibody that inactivates free IgE and down-regulates surface IgE receptors, has been shown effective in trials for refractory chronic urticaria. It is, however, expensive and not currently FDA approved for this indication.
- There are insufficient data to support use of leukotriene antagonists (zafirlukast, montelukast) in patients with chronic urticaria.

DISPOSITION

- Most cases of urticaria resolve within 6 wk.
- Only 25% of patients with a history of chronic urticaria are completely cured after 5 yr.

PEARLS & CONSIDERATIONS

COMMENTS

Local treatment (e.g., starch baths or oatmeal baths) may be helpful in selected patients; however, local treatment is generally not rewarding.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Hives (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

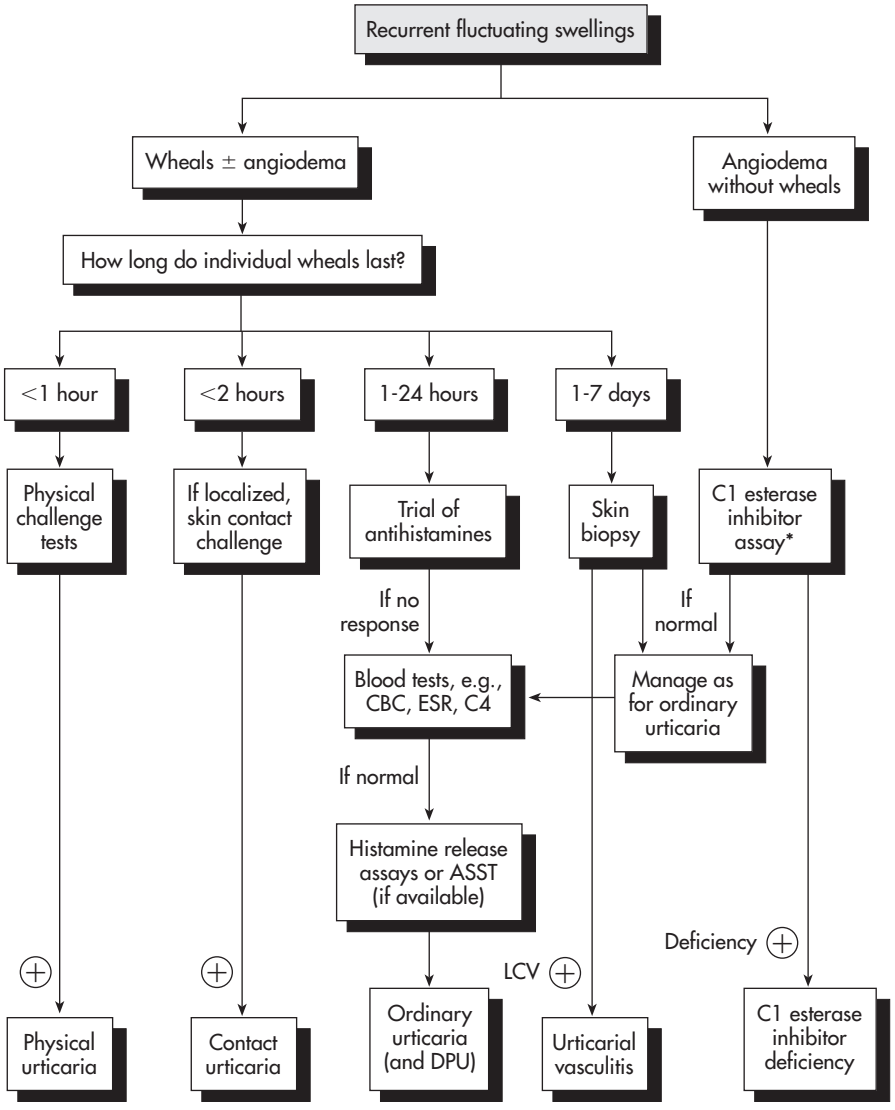
SUGGESTED READINGS

Komarow HD, Metcalfe DD: Office-based management of urticaria, *Am J Med* 121:379, 2008.

Maurer M et al.: Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria, *N Engl J Med* 368:924–935, 2013.

Tarbox JA et al.: Utility of routine laboratory testing in management of chronic urticaria/angioedema, *Ann Allergy Asthma Immunol* 107:239, 2011.

FIGURE EU1-8 Wheal (urticaria). Note central clearing, giving annular configuration. (From Noble J et al: *Textbook of primary care medicine,* ed 3, St Louis, 2001, Mosby.)



*Amount and function.

FIGURE EU1-9 Approach to the diagnosis of chronic urticaria. *ASST,* Autologous serum skin test; *CBC,* complete blood count; *DPU,* delayed pressure urticaria; *ESR,* erythrocyte sedimentation rate. (From Bolognia JL et al: *Dermatology,* St Louis, 2003, Mosby.)

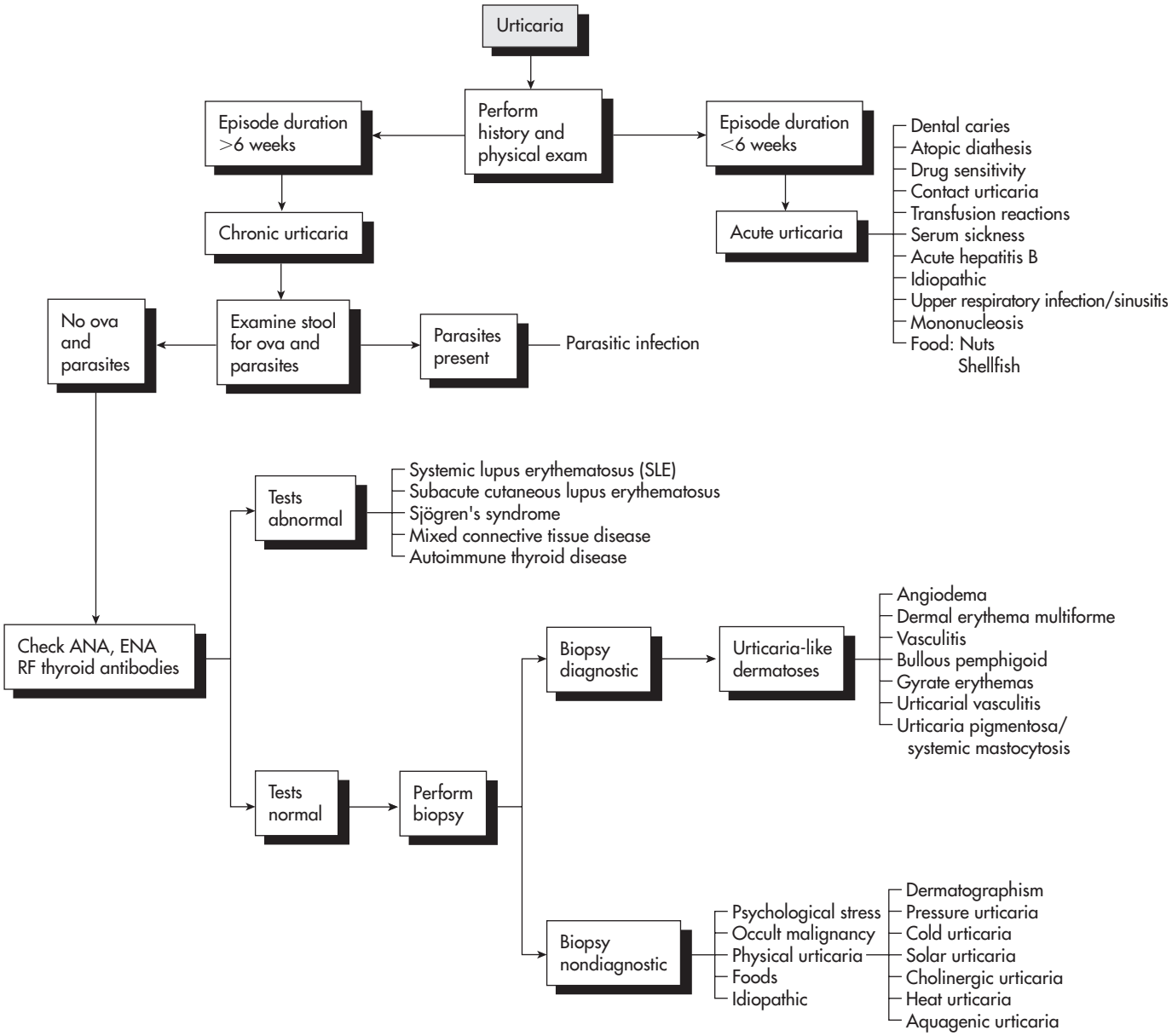


FIGURE EU1-10 Evaluation of urticaria. *ANA,* Antibody to nuclear antigens; *ENA,* extractable nuclear antigens; *RF,* rheumatoid factor. (From Healy PM, Jacobson EJ: *Common medical diagnoses,* ed 3, Philadelphia, 2000, Saunders.)

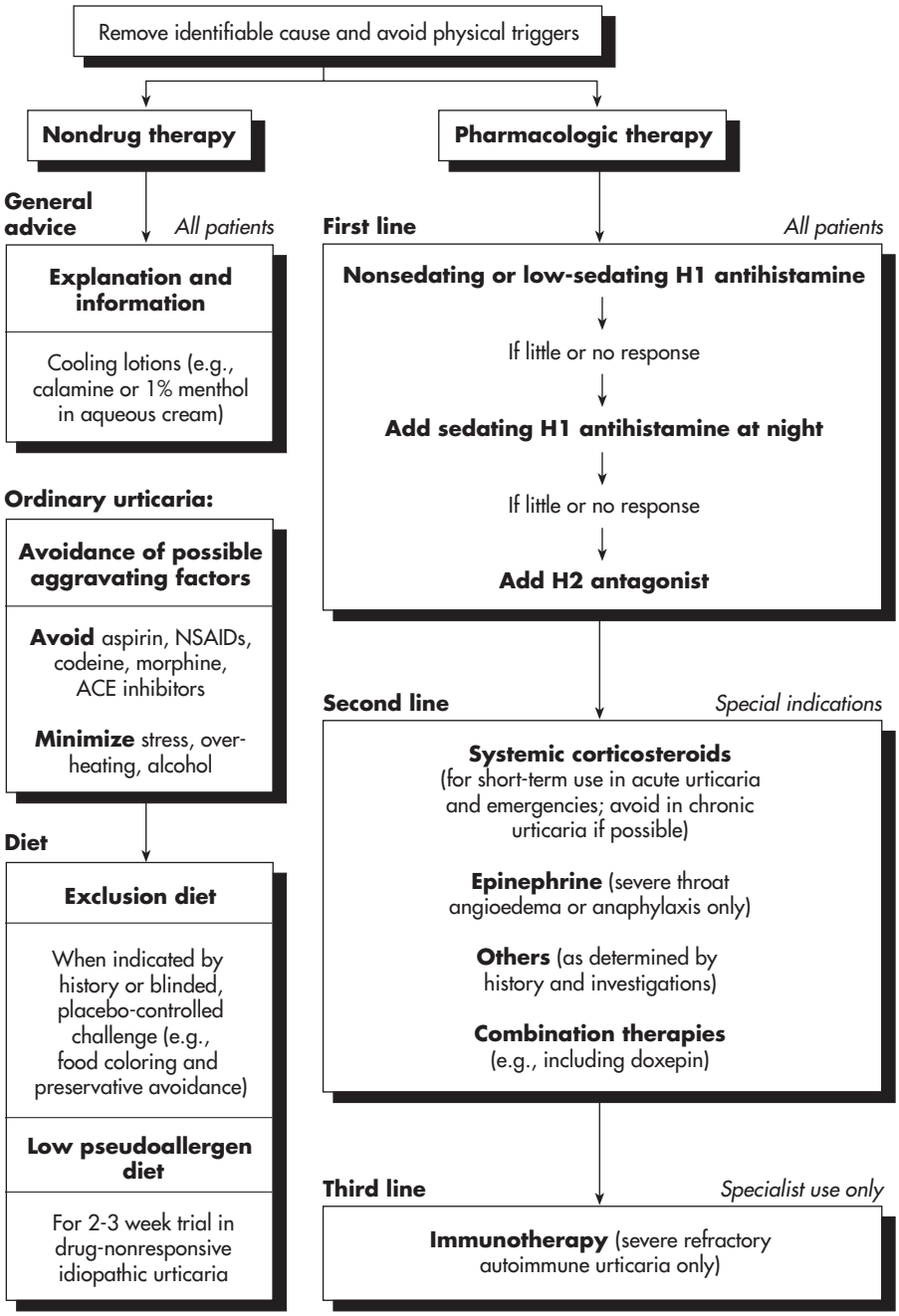


FIGURE EU1-11 Management of ordinary and physical chronic urticaria. *ACE,* Angiotensin-converting enzyme; *NSAIDs,* nonsteroidal anti-inflammatory drugs. (From Bolognia JL et al: *Dermatology,* ed 2, St Louis, 2008, Mosby.)

BASIC INFORMATION

DEFINITION

Uterine fibroids are benign tumors of muscle cell origin. They are discrete nodular tumors that vary in size and number and that may be found as subserosal, intramural, or submucosal masses. They can also be located in the cervix, broad ligament, or on a stalk (pedunculated) (Fig. U1-12). They can also be parasitic, acquiring a blood supply from a nonuterine source.

SYNONYMS

Uterine leiomyomas
Uterine myomas

ICD-9CM CODES
218.9 Leiomyomas, fibroids
ICD-10CM CODES
D25.9 Leiomyoma of uterus, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Estimated prevalence of 20% to 40% of reproductive age women
- The most common benign uterine tumor
- More common in black women than white women
- Asymptomatic fibroids may be present in 40% to 50% of women aged >40 yr
- May occur singly but are often multiple
- Less than half of all fibroids are estimated to produce symptoms
- Frequently diagnosed incidentally on pelvic examination
- There is increased familial incidence
- Potential to enlarge during pregnancy as well as regress after menopause
- Symptomatic fibroids are the primary indication for approximately 30% of all hysterectomies
- Approximately 200,000 hysterectomies, 30,000 myomectomies, and thousands of selective uterine-artery embolizations and high-intensity focused ultrasound procedures are performed annually in the United States to remove or destroy uterine fibroids.[1]

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Enlarged, irregular uterus on pelvic examination
- Presenting symptoms:
  1. Menorrhagia (most common)
  2. Chronic pelvic pain (dysmenorrhea, dyspareunia, pelvic pressure)
  3. Acute pain (torsion of pedunculated fibroid, infarction, and degeneration)
  4. Urinary symptoms (frequency from bladder pressure, partial ureteral obstruction, complete ureteral obstruction)
  5. Rectosigmoid compression with constipation or intestinal obstruction
  6. Prolapse through cervix of pedunculated submucosal tumor
  7. Venous stasis of lower extremities
  8. Polycythemia
  9. Ascites

ETIOLOGY

Incompletely understood. It is suggested that fibroids arise from an original single smooth muscle cell in the myometrium. Each individual fibroid is monoclonal (all the cells are derived from one progenitor myocyte). Malignant degeneration of preexisting leiomyoma is extremely uncommon (<0.5%).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Leiomyosarcoma, ovarian mass (neoplastic, nonneoplastic, endometrioma), inflammatory mass, pregnancy

WORKUP

- Complete pelvic examination, rectovaginal examination
- Estimation of size of mass in centimeters and location of fibroids
- Endometrial sampling may be indicated (biopsy or dilation and curettage) when abnormal bleeding and pelvic mass are present
- If urinary symptoms are prominent, cystometry, cystoscopy to rule out bladder lesions, intravenous pyelogram to rule out impingement on urinary system

LABORATORY TESTS

- Pregnancy test
- Pap smear
- Complete blood count, erythrocyte sedimentation rate
- Fecal occult blood

IMAGING STUDIES

- Pelvic ultrasound (Fig. U1-13) is useful as a primary diagnostic modality. Transvaginal ultrasound commonly has higher diagnostic accuracy.
- MRI scan is helpful in planning treatment if malignancy is strongly suspected. Also important to localize fibroids, especially if myomectomy is contemplated. Size, number, and location of fibroids are also important if a minimally invasive myomectomy is considered.
- Saline infusion sonography is helpful in determining location and degree of intrusion into uterine cavity. Important if hysteroscopic resection is contemplated. Typically at least 50% of the fibroid must be intracavitary for a hysteroscopic approach to be successful.
- Hysteroscopy may provide direct evidence of intrauterine pathology or submucosal leiomyoma that distorts uterine cavity, and surgical resection may be performed during the same procedure.

[1]Bulun SE: Uterine fibroids, *N Engl J Med* 369: 1344-1355, 2013.

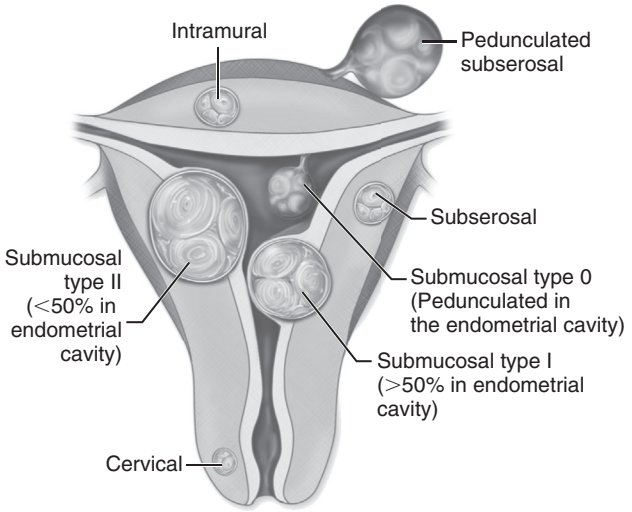


FIGURE U1-12 Drawing of uterus in the coronal plane, illustrating possible location of uterine leiomyomas. (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.)

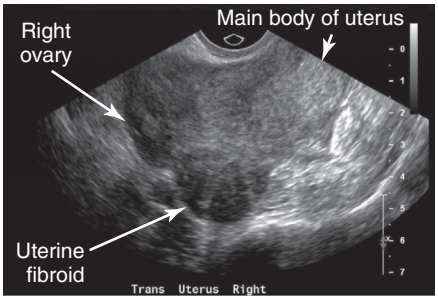


FIGURE U1-13 Fibroid uterus: endovaginal ultrasound. Ultrasound is the primary modality used for evaluation of uterine fibroids (leiomyomas). Typical features include a well-circumscribed appearance. Fibroids may be hypoechoic or hyperechoic relative to the uterus. They may be exophytic or intramural, or they may project into the uterine cavity. Malignant uterine tumors may invade adjacent structures, whereas a fibroid is contained within the uterine serosa. Uterine tumors, both benign and malignant, can show central necrosis, which usually appears hypoechoic with ultrasound. In this 38-year-old woman, the fibroid is exophytic. The right ovary lies adjacent and is difficult to distinguish in this case. (From Broder JS: *Diagnostic imaging for the emergency physician,* Philadelphia, 2011, Saunders.)

Rx TREATMENT

Management should be based on primary symptoms and may include observation with close follow-up, temporizing surgical therapies, embolization, medical management, or definitive surgical procedures. Treatment is generally indicated only when symptoms are present and are severe enough to be unacceptable to the patient.

NONSURGICAL Rx

- Patient observation and follow-up with periodic repeat pelvic examinations to ensure that tumors are not growing rapidly.
- Gonadotropin-releasing hormone (GnRH) agonist use results in 40% to 60% reduction in uterine volume. Hyperestrogenism, reversible bone loss, and hot flushes are associated with use. Limit to short-term use and consider low-dose hormonal replacement to minimize hypoestrogenic effects.
- Regrowth occurs in approximately 50% of women treated within a few months after cessation.
- Indications for GnRH:
  1. Fertility preservation in women with large myomas before attempting conception or preoperative myectomy treatment
  2. Anemia treatment to normalize hemoglobin before surgery
  3. Women approaching menopause to avoid surgery
  4. Preoperative for large myomas to make vaginal hysterectomy, hysteroscopic resection/ablation, or laparoscopic destruction more feasible
  5. Women with medical contraindications for surgery
  6. Personal or medical indications for delaying surgery
- Use of GnRH agonists may alter the consistency of the fibroid, making myomectomy more challenging.
- Progestational agents may also result in decrease in uterine size and amenorrhea, allowing iron therapy to treat anemia with limited success. Ulipristal acetate is a selective progesterone-receptor modulator that acts on progesterone receptors in myometrial and endometrial tissue and inhibits ovulation without causing large effects on estradiol levels or antiglucocorticoid activity. Recent trials have shown that treatment with ulipristal acetate for 13 wk effectively controlled excessive bleeding due to uterine fibroids and reduced the size of the fibroids.
- Other drugs used and under investigation:
  1. Danazol: androgen and multienzyme inhibitor of steroidogenesis
  2. Mifepristone: antiprogestogen shown to reduce the fibroid volume by 40% to 50% with amenorrhea
  3. Raloxifene: selective estrogen receptor modulator, either alone or with a GnRHa, shown to reduce the fibroid volume 70% up to 1 yr but only in postmenopausal women
  4. Fadrozole: aromatase inhibitor reported to have produced a 71% reduction in volume

SURGICAL Rx

- Indications
  1. Abnormal uterine bleeding with anemia refractory to hormonal therapy
  2. Chronic pain with severe dysmenorrhea, dyspareunia, or lower abdominal pressure/pain
  3. Acute pain, torsion, or prolapsing submucosal fibroid
  4. Urinary symptoms or signs such as hydronephrosis
  5. Rapid uterine enlargement premenopausal or any growth after menopause
  6. Infertility or recurrent pregnancy loss with submucous leiomyoma as only finding
  7. Enlarged uterus with compression symptoms or discomfort
- Procedures
  1. Hysterectomy (definitive procedure): Nearly 15% of women with uterine fibroids and a mean age of 45 yr require hysterectomy
  2. Abdominal myomectomy (to preserve fertility or due to patient preference)
  3. Vaginal myomectomy for prolapsed pedunculated submucous fibroid
  4. Hysteroscopic resection
  5. Laparoscopic/robotic myomectomy
  6. Uterine artery embolization (UAE): safe and effective short-term alternative to surgery, but its less invasive nature should be balanced against a higher rate for treatment failure or complications at 5 yr (32%) versus the surgery group (4%). Age 40 years and under at embolization and history of previous myomectomy are significant predictors of embolization failure. If patient wishes to preserve future fertility, UAE should not be performed.

COMPLICATIONS

- Red degeneration
- Leiomyosarcoma (<0.1%). Recent concern has been voiced by the FDA regarding the use of morcellation in minimally invasive surgery due to the possibility of spreading malignancy in the peritoneal cavity.

REFERRAL

Consultation with gynecologic oncologist if suspicion of malignancy

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Uterine Fibroids (Patient Information)
Dysfunctional Uterine Bleeding (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

DeWaay DJ, et al.: Natural history of uterine polyps and leiomyomata, *Obstet Gynecol* 100:3, 2002.

Donnez J, et al.: Ulipristal acetate vs. placebo for fibroid treatment before surgery, *N Engl J Med* 366:409–420, 2012.

Goodwin SC, Spies JB: Uterine fibroid embolization, *N Engl J Med* 361(7): 690–697, 2009.

Moss JG, et al.: Randomized comparison of uterine artery embolization (UAE) with surgical treatment in patients with symptomatic uterine fibroids (REST trial): 5-yr results, *BJOG* 118:936–944, 2011.

Olive DL, et al.: Non-surgical management of leiomyoma, *Curr Opin Obstet Gynecol* 16(3):239, 2004.

Prapas Y, et al.: Laparoscopy vs laparoscopically assisted myomectomy in the management of uterine myomas: a prospective study, *Am J Obstet Gynecol* 200:144, 2009.

Tropeano G, et al.: Incidence and risk factors for clinical failure of uterine leiomyoma embolization, *Obstet Gynecol* 120:269, 2012.

BASIC INFORMATION

DEFINITION

Uterine malignancy includes tumors from the endometrium and sarcomas. Uterine sarcoma is an abnormal proliferation of cells originating from the mesenchymal, or connective tissue, elements of the uterine wall (myometrium).

SYNONYMS

Leiomyosarcomas
Endometrial stromal sarcoma
Malignant mixed Müllerian tumors
Adenosarcomas

ICD-9CM CODES

182.0	Malignant neoplasm of body of uterus (corpus uteri), except isthmus
182.1	Malignant neoplasm of body of uterus, isthmus
182.8	Malignant neoplasm of body of uterus, other specified sites of body of uterus

ICD-10CM CODES

C54.1	Malignant neoplasm of endometrium
C54.0	Malignant neoplasm of isthmus uteri
C54.8	Malignant neoplasm of overlapping sites of corpus uteri

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 17.1 cases per 1 million females. Endometrial cancer remains the most common gynecologic malignancy in the U.S.
PREVALENCE: Uterine sarcoma accounts for 4.3% of all cancers of the uterine corpus and is the most lethal gynecologic malignancy.
MEAN AGE AT DIAGNOSIS: 52 yr
RISK FACTORS: Box U1-5 describes risk factors for uterine sarcoma

BOX U1-5 Risk Factors for Uterine Sarcoma

Nulliparity
Obesity
History of pelvic radiation
Exposure to tamoxifen

From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Abnormal vaginal bleeding is the most common symptom
- May also present as pelvic pain or pressure and pelvic mass on examination
- May appear as tumor protruding through the cervix
- Vaginal discharge may also be a presenting symptom
- Rapidly enlarging uterus or pelvic mass

ETIOLOGY

- The exact etiology is unknown.
- Prior pelvic radiation is a risk factor for sarcoma.
- Black women may be at higher risk.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Leiomyoma

WORKUP

Diagnosis is made histologically by biopsy for abnormal bleeding.

BOX U1-6 Uterine Sarcoma Prognostic Factors

Tumor stage
Tumor grade
Tumor size
Patient age
Vascular space involvement
Mitotic count
Residual disease at surgery
Adjuvant chemotherapy

From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.

BOX U1-7 Uterine Sarcoma: Key Points

The disease mainly affects postmenopausal women.
Most patients present early with postmenopausal bleeding.
The primary treatment is hysterectomy.
Adjuvant radiotherapy to the pelvis is used if poor prognosis features in stage 1 or if spread has occurred beyond the corpus.

From Greer IA et al: *Mosby's color atlas and text of obstetrics and gynecology*, London, 2001, Harcourt.

LABORATORY TESTS

Chest radiography, CT scans, and MRI are used to evaluate metastatic lesions.

IMAGING STUDIES

- Chest x-ray is usually done as routine preoperative testing.
- CT scans (Fig. EU1-15) and MRI are useful for assessing tumor spread once diagnosis is made.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Surgical excision is the mainstay of treatment.
- Grade and stage of tumor affect prognosis.
- The benefit of adjuvant radiotherapy in stage I endometrial adenocarcinoma to improve pelvic disease control and improve survival remains controversial despite several phase 3 trials.
- Chemotherapeutic agents have produced only partial and short-term responses.

DISPOSITION

- Survival varies with each type of sarcoma but is generally very poor. Box U1-6 describes uterine prognostic factors.
- Five-year survival for leiomyosarcoma ranges from 48% for stage I to 0% for stage IV.
- Five-year survival for malignant mixed mesodermal tumor ranges from 36% for stage I to 6% for stage IV.

REFERRAL

Uterine sarcoma should be managed by a gynecologic oncologist and radiation oncologist. Key points in the management of uterine sarcoma are described in Box U1-7.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Uterine Cancer (Patient Information)
Endometrial Cancer (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Elima Y et al.: Para-aortic lymph node metastasis in relation to serum CA 125 levels and nuclear grade in endometrial carcinoma, *Acta Obstet Gynecol Scand* 81(5):458, 2002.

Lee CM et al.: Frequency and effect of adjuvant radiation therapy among women with stage I endometrial adenocarcinoma, *JAMA* 295:389, 2006.

Pitson G et al.: Stage II endometrial carcinoma: prognostic factors and risk classification in 170 patients, *Int J Radiat Oncol Biol Phys* 53(4):862, 2002.

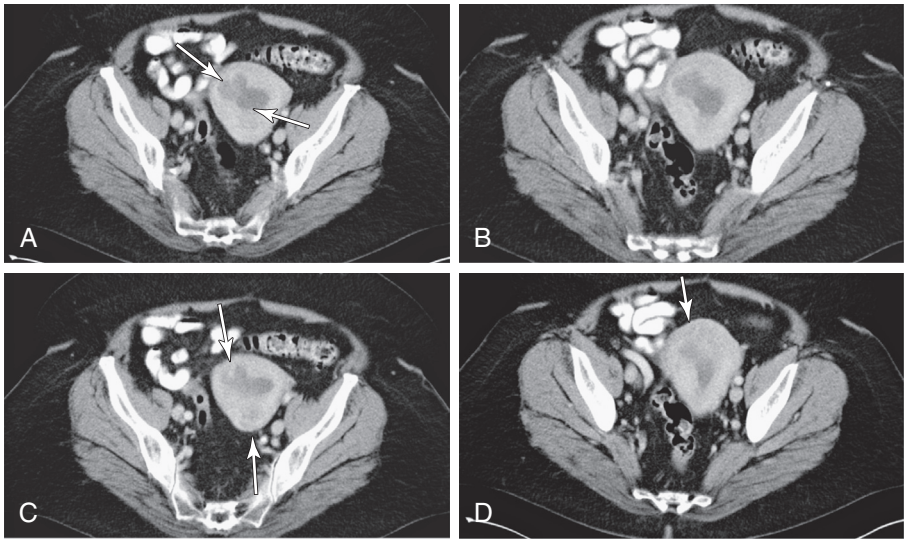


FIGURE EU1-15 A 50-year-old patient with uterine sarcoma. A, Axial contrast-enhanced computed tomographic (CT) image. Low-attenuation lobulated and infiltrating soft tissue fills the endometrial canal *(arrows),* extending into the myometrium. **B,** Axial contrast-enhanced CT image showing same as **A.** Low-attenuation lobulated and infiltrating soft tissue fills the endometrial canal, extending into the myometrium. **C,** Axial contrast-enhanced CT image. Low-attenuation lobulated and infiltrating soft tissue fills the endometrial canal. Subtle myometrial invasion is seen anterior and posterior *(arrows).* **D,** Axial contrast-enhanced CT image. Low-attenuation lobulated and infiltrating soft tissue fills the endometrial canal *(arrow)* showing same. Subtle myometrial invasion is seen fundally. (From Fielding JR et al: *Gynecologic imaging,* Philadelphia, 2011, Saunders.)

BASIC INFORMATION

DEFINITION

Uveitis is inflammation of the uveal tract, including the iris, ciliary body, and choroid. It may also involve other contiguous structures such as the sclera, cornea, retina, and vitreous humor (Fig. U1-14).

SYNONYMS

Anterior uveitis (iritis, iridocyclitis)
Intermediate uveitis (pars planitis)
Posterior uveitis (choroiditis)
Acute or chronic uveitis
Granulomatous or nongranulomatous uveitis

ICD-9CM CODES
364.3 Unspecified iridocyclitis, uveitis
ICD-10CM CODES
H20.0 Acute and subacute iridocyclitis
H20.1 Chronic iridocyclitis
20.8 Other iridocyclitis
H20.9 Unspecified iridocyclitis

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.): Common; busy ophthalmologist will see two or more cases per week.
PEAK INCIDENCE: Middle age or older.
PREVALENCE (IN U.S.): 17 cases per 100,000 persons
PREDOMINANT SEX: None
PREDOMINANT AGE: 38 yr. Although uveitis is less common in children than adults, it is believed to be more severe with an increased risk for vision-threatening complications.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Symptoms of uveitis depend on the site of involvement and whether process is acute or insidious:
  1. Acute anterior uveitis: pain and photophobia. Vision may not be affected initially.
  2. Posterior uveitis: floaters, hazy vision. Involvement of the retina may produce blind spots or flashing lights.
  3. Insidious anterior uveitis: symptoms may not be present until scarring cataracts and loss of vision occur.
- Photophobia
- Blurred visual acuity
- Irregular pupil
- Hazy cornea
- Abnormal cells and flare in anterior chamber or vitreous humor ("flare cells") noted with slit lamp examination
- Retinal hemorrhage, vascular sheathing
- Conjunctival injection
- Ciliary flush
- Keratitic precipitates (white precipitates on the posterior surface of the cornea)
- Hazy vitreous
- Retinal inflammation
- Iris nodules

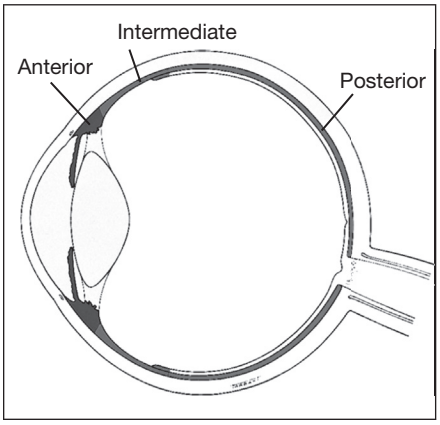


FIGURE U1-14 Anatomic classification of uveitis. (From Kanski JJ, Bowling B: *Clinical ophthalmology, a systematic approach,* ed 7, Philadelphia, 2010, Saunders.)

ETIOLOGY

- Infections: herpes simplex virus, cytomegalovirus, toxoplasmosis, tuberculosis, syphilis, HIV
- Systemic disorders (autoimmunity): sarcoidosis, Behçet's syndrome, HLA-B27–associated diseases (e.g., ankylosing spondylitis, psoriatic arthritis), inflammatory bowel disease, juvenile idiopathic arthritis (Fig. EU1-15)
- Idiopathic (>50% of patients)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Glaucoma
- Conjunctivitis
- Retinal detachment
- Retinopathy
- Keratitis
- Scleritis
- Episcleritis
- Masquerading syndromes: lymphoma, uveal melanoma, metastases (breast, lung, renal), leukemia, retinitis pigmentosa, retinoblastoma

WORKUP

- Comprehensive eye examination including slit lamp exam, dilated ophthalmoscopy

LABORATORY TESTS

- Complete blood count
- Laboratory tests for specific inflammatory causes cited previously in "Workup" (e.g., antinuclear antibody, erythrocyte sedimentation rate, syphilis (VDRL), HLA-B27, purified protein derivative, Lyme titer, angiotensin converting enzyme [ACE])

IMAGING STUDIES

- Chest radiograph in suspected sarcoidosis, tuberculosis, histoplasmosis
- Sacroiliac radiograph in suspected ankylosing spondylitis

TREATMENT

ACUTE GENERAL Rx

- Corticosteroids are the mainstay of therapy for noninfectious causes. The route and dosage of medication depends on the location of inflammation, the severity, and the presence of systemic disease. Cycloplegic drops (cyclopentolate, homatropine BID to QID) and topical steroids (prednisone acetate 1% 1 gtt qh during day, prn at night until favorable response, then q4 to 6h); avoid topical corticosteroids in infectious uveitis. Periocular corticosteroid injections can be used for posterior disease; they have the advantage of achieving high intraocular levels of steroids without the systemic side effects of oral corticosteroids.
- Antibiotics for bacterial infections and antiviral agents, when infection is suspected, should be started to prevent retinal damage.
- Systemic steroids if appropriate for the underlying disease. Systemic corticosteroid therapy is generally reserved for patients with systemic disorders and those with bilateral disease that is refractory to local medication or those with major ocular disability or retinitis.
- Antimetabolites when indicated. Immunosuppressive medications used in steroid-dependent or refractory uveitis include methotrexate, sulfasalazine, azathioprine, cyclosporine, and tacrolimus. These medications can have significant toxicity and should be prescribed only by physicians experienced with their use.
- High-dose IV daclizumab has been reported as effective in reducing active inflammation in active juvenile idiopathic arthritis (JIA)-associated anterior uveitis. Additional trials are needed to better assess efficacy and safety.

REFERRAL

Urgent referral to ophthalmologist for diagnosis and treatment

PEARLS & CONSIDERATIONS

COMMENTS

Chronic anterior uveitis is the most common form of intraocular inflammation in children. JIA is the most common cause.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **R. SCOTT HOFFMAN, M.D.**

SUGGESTED READINGS

Etminan M et al.: Inflammatory ocular adverse events with the use of oral bisphosphonates: a retrospective cohort study, *CMAJ* 184:E431, 2012.

Hajj-Ali RA et al.: Uveitis in the internist's office: are a patient's eye symptoms serious? *Cleve Clin J Med* 72:329–339, 2005.

Holland GN et al.: Chronic anterior uveitis in children: clinical characteristics and complications, *Am J Ophthalmol* 147:667–678, 2009.

Kadayifcilar S et al.: Uveitis in childhood, *J Pediatr Ophthalmol Strabismus* 40(6):335, 2003.

Sen HN et al.: High-dose daclizumab for treatment of juvenile idiopathic arthritis-associated active anterior uveitis, *Am J Ophthalmol* 148:696–703, 2009.

FIGURE EU1-15 Chronic anterior uveitis associated with oligoarticular and polyarticular rheumatoid factor–negative juvenile idiopathic arthritis, demonstrating posterior synechiae and absence of significant sclera inflammation. (From Firestein GS, Budd RC, Gabriel SE, et al: *Kelly's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

BASIC INFORMATION

DEFINITION

Bleeding per vagina at any time during pregnancy must be regarded as abnormal and is associated with an increased likelihood of pregnancy complications.

SYNONYMS

Hemorrhage

ICD-9CM CODES

634.9 Spontaneous abortion
640.0 Threatened abortion
641.1 Placenta previa
641.2 Placental abruption

ICD-10CM CODES

O03.9 Complete or unspecified spontaneous abortion
O44.10 Placenta previa with hemorrhage, unspecified trimester
O45.8X9 Other premature separation of placenta, unspecified trimester

EPIDEMIOLOGY & DEMOGRAPHICS

- Common in U.S.; 20% to 25% of patients have vaginal spotting/bleeding in first trimester; of those, miscarriage occurs in 50%.
- Occurs in women of childbearing age.
- Between 1% and 2% of all pregnancies in the U.S. are ectopic.
- After one ectopic pregnancy, the chance of another is 7% to 15%.
- Ectopic pregnancy is the leading cause of maternal mortality in the first trimester.
- Average reported frequency for placental abruption is about 1 in 150 deliveries (0.3%).
- Incidence of placenta previa is 1 in 200 deliveries (0.5%).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Bleeding: ranges from scant to life-threatening with hemodynamic instability
- Color: brown to bright red
- Can be painless or painful (cramps, back pain, severe abdominal pain)
- Fetal compromise: ranges from none to fetal demise

ETIOLOGY

- Influenced by gestational age
- Vaginal
- Cervical
- Uterine

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Any gestational age:
  1. Cervical lesions: polyps, decidual reaction, neoplasia
  2. Vaginal trauma
  3. Cervicitis/vulvovaginitis
  4. Postcoital trauma
  5. Bleeding dyscrasias
- Gestation <20 wk:
  1. Spontaneous abortion
  2. Presence of intrauterine device
  3. Ectopic pregnancy
  4. Molar pregnancy
  5. Implantation bleeding
  6. Low-lying placenta
- Gestation >20 wk:
  1. Molar pregnancy
  2. Placenta previa
  3. Placental abruption
  4. Vasa previa
  5. Marginal separation of the placenta
  6. Bloody show at term
  7. Preterm labor
- Section II describes the differential diagnosis of vaginal bleeding in pregnancy.

WORKUP

- Gestation <20 wk (Section III, "Bleeding, Early Pregnancy"):
  1. Pelvic examination
  2. Laparoscopy
  3. Laparotomy
  4. Ultrasound to verify viable intrauterine pregnancy
- Gestation >20 wk:
  1. Ultrasound to locate placenta before pelvic examination
  2. If placenta previa, no speculum or bimanual examination
  3. If preterm labor, appropriate evaluation done

LABORATORY TESTS

- Urine pregnancy test: if positive, get quantitative beta human chorionic gonadotropin (βhCG). The following are typical although not entirely exclusive patterns:
  1. Early pregnancy: follow serially every 48 hr
  2. Normal pregnancy: βhCG doubles approximately every 48 hr
  3. Spontaneous abortion: βhCG level will fall
  4. Ectopic pregnancy: βhCG level will rise inappropriately (less than expected; threshold increase over 48 hours should be ≥66%)
  5. Molar pregnancy: βhCG level is higher than expected for gestational age
- CBC
- Blood type and screen (Rh-negative patients need RhoGAM)
- Coagulation profile (useful in missed abortion and abruption)
- Cervical cultures/wet mount
- Pap smear for cervical malignancy; caution with biopsy, because cervix can bleed extensively

IMAGING STUDIES

Ultrasound:

- 5 to 6 wk: gestational sac (transvaginally); βhCG >1500 mIU/ml is discriminatory level for seeing a singleton gestation
- 6 to 7 wk: fetal cardiac activity
- Molar pregnancy: characteristic cluster of cysts
- Location of placenta
- Degree of placental separation: difficult to assess
- Evidence of subchorionic hemorrhage

TREATMENT

NONPHARMACOLOGIC THERAPY

- Pelvic rest: no coitus, douching, or tampons
- Bed rest, if >20 wk
- Counseling: genetic, bereavement

ACUTE GENERAL Rx

- Hemodynamic stabilization
- Emergency D&C, laparotomy, or cesarean section as necessary

CHRONIC Rx

Depends on diagnosis

DISPOSITION

Depends on diagnosis

REFERRAL

- If patient is unstable and needs emergency OB/GYN management and/or surgery
- If patient has diagnosis of ectopic or molar pregnancy, because immediate surgical treatment or medical intervention is indicated
- Perinatal consultation for high-risk pregnancy

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Abruptio Placentae (Related Key Topic)
Cervical Insufficiency (Related Key Topic)
Ectopic Pregnancy (Related Key Topic)
Molar Pregnancy (Related Key Topic)
Placenta Previa (Related Key Topic)
Sheehan's Syndrome (Related Key Topic)
Spontaneous Miscarriage (Related Key Topic)

AUTHORS: **RUBEN ALVERO, M.D.,** and **GEORGE T. DANAKAS, M.D.**

SUGGESTED READINGS

Coppola PT, Coppola M: Vaginal bleeding in the first 20 weeks of pregnancy, *Emerg Med Clin North Am* 21(3):667, 2003.

BASIC INFORMATION

DEFINITION

An abnormal passageway between the vagina and another epithelialized surface (Fig. V1-1)

SYNONYMS

Vaginal sinus

ICD-9CM CODES
619 Fistula involving female genital tract
ICD-10CM CODES
N82 Fistulae involving the female genital tract

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: After benign hysterectomy: <1% (0.08%-0.26%); after radical hysterectomy: 1%-4%. Incidence is difficult to estimate in developing countries because of lack of medical care and medical follow-up after obstetric care.
PREVALENCE: Rare in the developed world from obstetric complications, but in developing countries the best estimate of prevalence is as high as 124 in 100,000.
RISK FACTORS: *In developing countries*

- Obstetric trauma
- Prolonged labor
- Cephalopelvic disproportion causing ischemia and necrosis of the tissue between the fetal head and maternal pubic bone

In developed countries

- Fistula resulting from obstetric trauma are primarily related to vaginal lacerations, for which the risk factors include:
  - Primiparity
  - Midline episiotomies
  - Increasing birth weights
  - Use of vaginal forceps
- Abdominal hysterectomy, especially with the following:
  - Extensive bladder dissection
  - Iatrogenic injury of the bowel or bladder
  - Prolonged operating times
  - Large blood loss
  - Large volume uterus
  - Coexisting pelvic adhesions distorting the normal pelvic anatomy

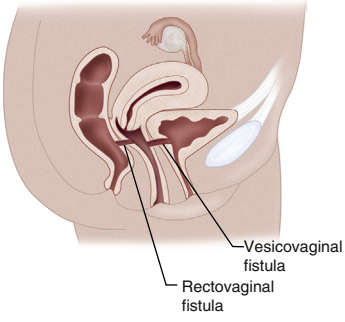


FIGURE V1-1 The two most common types of vaginal fistulas are vesicovaginal and rectovaginal. (From Fielding JR et al: *Gynecologic imaging*, Philadelphia, 2011, Saunders.)

- Invasive cancer
- Pelvic radiation, reported to be dependent on dosimetry
- Chronic inflammatory disease
  - Crohn disease
  - Diverticulitis
- Pelvic infection

`Tuberculosis

- Syphilis
- Lymphogranuloma venereum
- Trauma
- Previous pelvic surgery
- Diabetes mellitus
- Age >50, likely as a result of poor tissue quality from menopausal estrogen deficiency, although some studies have refuted this.
- Tobacco usage
- Foreign bodies

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Flatus, stool, or urine per vagina
- Frequent urinary tract infections
- Mucopurulent malodorous discharge per vagina
- Dyspareunia
- Perineal pain
- Recurrent vaginal infections

ETIOLOGY

- Obstetric
  1. Incompletely repaired or unidentified vaginal lacerations
  2. Prolonged pressure between the fetal head and the maternal pubic bone, causing tissue necrosis
- Gynecologic
  1. Poor-quality tissue with prolonged healing as a result of estrogen deficiency, infection, malignancy, or prior radiation therapy

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Rectal or urinary incontinence
- Pelvic inflammatory disease
- Vaginal infection
- Vaginal fistula
  1. Vesicovaginal
  2. Urethrovaginal
  3. Ureterovaginal
  4. Rectovaginal
- Urinary tract infection

WORKUP

- Thorough history and physical exam, specifically, questioning about Crohn disease symptomology; constitutional symptoms such as weight loss and fatigue, with malignancy in mind
- Obtaining of past medical records specific to obstetric and surgical procedures
- Evaluation of patient's rectal and urinary continence
- Physical exam, looking for extraintestinal signs consistent with Crohn disease; lymphadenopathy; inspection of perineum and perianal area for evidence of abscess, obvious fistula, or scarring; pelvic exam including lighted speculum exam for any vulvar, vaginal, or cervical anomaly, excluding PID
- Biopsy of fistula tract

LABORATORY TEST(S)

- Urinalysis
- Urine culture
- Complete blood count
- Administration of IV indigo carmine (if seen vaginally, diagnostic of vesicovaginal fistula)

IMAGING STUDIES

- Proctoscopy for suspected rectovaginal fistula
- Vaginogram (Fig. V1-2)
- Cystoscopy
- CT of the abdomen and pelvis to exclude malignancy (especially in women with no history of obstetric trauma, previous fistula, IBD, or known pelvic malignancy) (Fig. V1-2)
- Endoanal ultrasound, with or without hydrogen peroxide contrast injected into the suspected fistula tract
- Magnetic resonance imaging
- Intravenous urogram
- Retrograde ureteropyelography

TREATMENT

NONPHARMACOLOGIC THERAPY

- Surgical repair, with multiple documented approaches
  1. Transvaginal
  2. Perineal
  3. Abdominal
  4. Laparoscopic
  5. Robot assisted
  6. Transrectal
- If vesicovaginal identified early
  1. Prolonged urinary catheter placement, greater than 3 weeks

ACUTE GENERAL Rx

- Treatment of urinary or vaginal infection
- Estrogen replacement therapy, local vs. systemic if no contraindications
- Surgical repair of fistula with subsequent pelvic rest for 4-6 wk
- Minimizing Valsalva maneuvers

CHRONIC Rx

- If initial surgical management fails, repeat operations tailored to the cause of the fistula would be indicated, such as advancement flaps, sphincteroplasty, coloanal anastomosis (for rectovaginal fistula), gracilis flap.

DISPOSITION

- Cure rates after surgical repair vary in the literature, especially with the type of fistula repaired. With early intervention, estimated cure rates are between 84%-100% in developed countries.

REFERRAL

- If there is concern for vaginal fistula, the patient should be managed by a surgeon

familiar with fistula surgery for repair and follow-up. Consider consulting with a urologist, colorectal surgeon, gynecologic oncologist, or urogynecologist.

PEARLS & CONSIDERATIONS

PREVENTION

- Prompt repair of obstetric lacerations
- Screen patients most at risk before surgery
- Avoid urologic complications in surgery (e.g., injury to bladder or ureters)
- Cystoscopy with complicated hysterectomy dissections

SUGGESTED READINGS

Available online at www.expertconsult.com

AUTHOR: **AMBER N. FONTENOT FERRISS, M.D.**

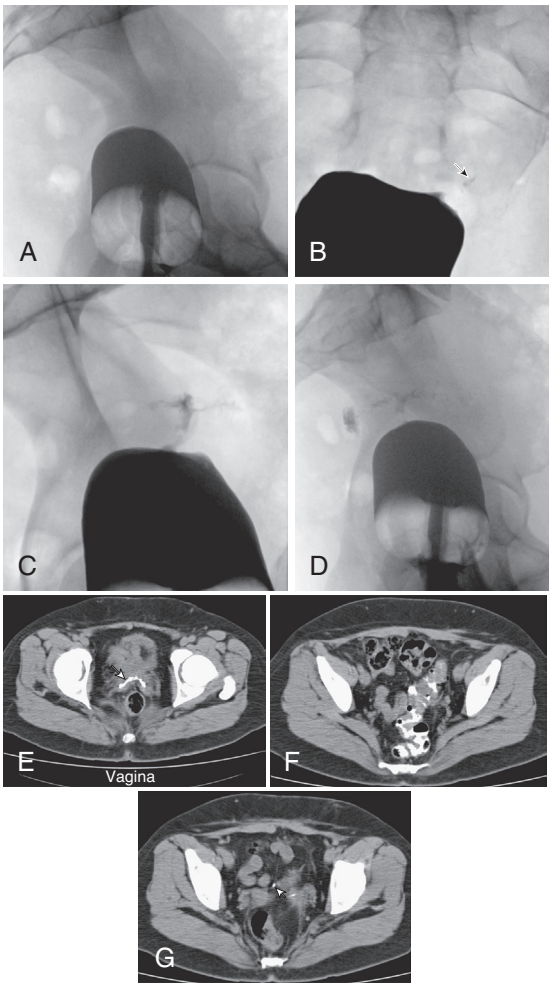


FIGURE V1-2 A 44-year-old woman with gas and stool per vaginum 1 year after hysterectomy. Vaginal fistula was treated medically. **A,** Vaginogram, patient in left lateral position. **B,** Vaginogram, patient supine. The left apical vaginal fistula has just started to fill with contrast agent (*arrow*). **C,** Contrast agent is extending horizontally, likely in a loop of bowel. **D,** Vaginogram, patient in left lateral position, demonstrates small fistula to a loop of bowel, likely the rectosigmoid colon based on its relationship to the sacrum. **E,** Unenhanced computed tomographic (CT) scan of the pelvis immediately after the vaginogram demonstrates residual contrast agent in the vagina (*arrow*). **F,** CT scan confirms contrast agent from the vagina in the rectosigmoid colon. **G,** CT scan demonstrates 3 mm diameter short fistula to the rectosigmoid (*arrow*). (From Fielding JR et al: *Gynecologic imaging*, Philadelphia, 2011, Saunders.)

SUGGESTED READINGS

Champagne BJ, et al.: Rectovaginal fistula, *Surg Clin North Am* 90:69–82, 2010.

DeRidder D: An update on surgery for vesicovaginal and urethrovaginal fistulae, *Curr Opin Urol* 21:297–300, 2011.

DeRidder D: Vesicovaginal fistula: a major healthcare problem, *Curr Opin Urol* 19:358–361, 2009.

Forsgren C, et al.: Risk of pelvic organ fistula in patients undergoing hysterectomy, *Curr Opin Obstet Gynecol* 22:404–407, 2010.

Goh J, et al.: Classification of female genito-urinary tract fistula: a comprehensive review, *Int Urogynecol J* 20:605–610, 2009.

MacRae HM, et al.: Treatment of rectovaginal fistulas that has failed previous repair attempts, *Dis Colon Rectum* 38:921–925, 1995.

Vaginal Malignancy PTG

BASIC INFORMATION

DEFINITION

Vaginal malignancy is an abnormal proliferation of vaginal epithelium demonstrating malignant cells below the basement membrane.

SYNONYMS

Squamous cell carcinoma of the vagina
Adenocarcinoma of the vagina
Melanoma of the vagina
Sarcoma of the vagina
Endodermal sinus tumor

ICD-9CM CODES
184.0 Vagina, vaginal neoplasm
ICD-10CM CODES
C52 Malignant neoplasm of vagina

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 0.42 cases per 100,000 persons
PREVALENCE: Vaginal cancer is the second rarest gynecologic cancer. It comprises 2% of malignancies of the female genital tract.
MEAN AGE AT DIAGNOSIS: Predominantly a disease of menopause. Mean age at diagnosis is 60 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Majority of cases are asymptomatic
- Postmenopausal vaginal bleeding and/or vaginal discharge are the most common symptoms
- May also present as pelvic pain or pressure, dyspareunia, dysuria, malodor, or postcoital bleeding
- May present as a vaginal lesion or abnormal Pap smear

ETIOLOGY

- The exact etiology is unknown.
- Vaginal intraepithelial neoplasia is believed to be a precursor for squamous cell carcinoma of the vagina.
- Long-term pessary use has been associated with vaginal malignancy.
- Prior pelvic radiation may be a risk factor.
- Clear-cell adenocarcinoma may be related to in utero diethylstilbestrol exposure (DES). Treatment of pregnant women with DES ended in the early 1970s, and it is anticipated that this spike in clear cell tumors will abate in the future.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Extension from other primary carcinoma more common than primary vaginal cancer
- Vaginitis

WORKUP

- Diagnosis is made histologically by biopsy.
- Colposcopy and biopsy should follow suspicious Pap smear.
- Cystoscopy, proctosigmoidoscopy, chest radiography, IV urography, and barium enema may be used for clinical staging.
- CT scan (Fig. V1-3), FDG, PET scan, and MRI are used to evaluate spread.
- Staging I to IV (Fig. V1-4).

IMAGING STUDIES

- Chest radiography, IV urography, and barium enema are used for staging.
- CT scan and MRI are good for assessing tumor spread.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Radiation therapy is the mainstay of treatment.
- Stage I tumors that are small and confined to the posterior, upper third of the vagina may be treated with radical surgery.
- Other stages require a whole-pelvis, interstitial, and/or intracavitary radiation therapy.
- Chemotherapy is used in conjunction with radiotherapy in rare select cases.

DISPOSITION

Five-year survival ranges from 80% for stage I to 17% for stage IV.

REFERRAL

Vaginal cancer should be managed by a gynecologic oncologist and radiation oncologist.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Vaginal Cancer (Patient Information)

AUTHOR: **RUBEN ALVERO, M.D.**

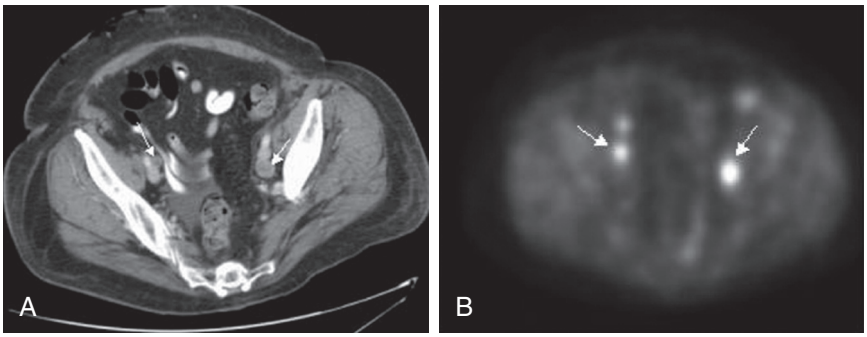


FIGURE V1-3 Vaginal cancer with lymphadenopathy. A, CT of pelvis showing mildly enlarged external iliac nodes suggestive of metastases *(arrows).* **B,** Axial FDG PET scan showing hypermetabolic nodes as hyperintense spots confirming metastases. (From Abeloff MD: *Clinical oncology,* ed 3, Philadelphia, 2004, Churchill Livingstone.)

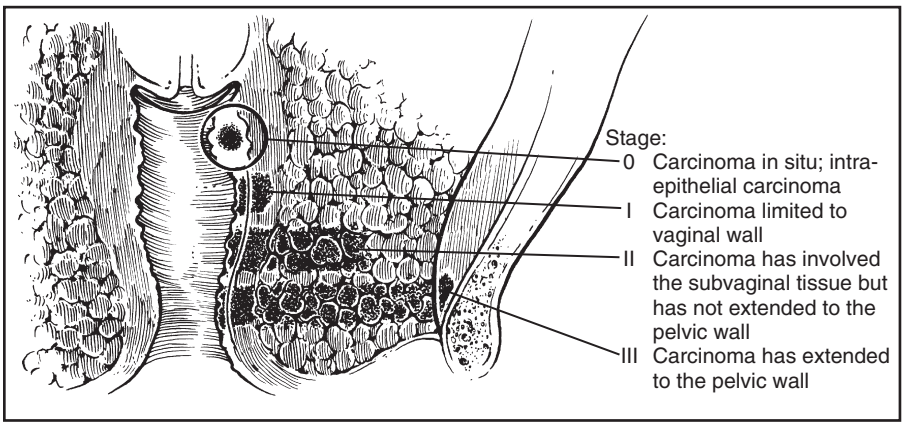


FIGURE V1-4 Staging system for vaginal cancer. Metastatic disease that involves the bladder or rectum is stage IV-a. Metastatic disease beyond the pelvis is stage IV-b. (From Copeland LJ: *Textbook of gynecology,* ed 2, Philadelphia, 2000, Saunders.)

SUGGESTED READING

Kim H et al.: Case report: magnetic resonance imaging of vaginal malignant melanoma, *J Comput Assist Tomogr* 27(3):357, 2003.

BASIC INFORMATION

DEFINITION

Vaginismus refers to the involuntary spasm of the vaginal, introital, and/or levator ani muscles, preventing penetration or causing painful intercourse.

ICD-9CM CODES
300.11 Hysterical vaginismus
306.51 Psychogenic or functional vaginismus
625.1 Reflex vaginismus

ICD-10CM CODES
N94.1 Vaginismus
F52.5 Non-organic vaginismus
F52.5 Vaginismus not due to a substance or known physiological condition

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: Estimated at 11.7% to 42% of women presenting to sexual dysfunction clinics.
PREVALENCE: Affects approximately 1 in 200 women.
PREDOMINANT SEX: Affects only females.
RISK FACTORS: Any previous sexual trauma, including incest or rape.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fear of pain with coitus.
- Dyspareunia.
- Orgasmic dysfunction.

ETIOLOGY

- Learned conditioned response (Fig. V1-5) to real or imagined painful vaginal experience (e.g., traumatic speculum examination, incest, rape).
- Vaginitis.
- Pelvic inflammatory disease.
- Endometriosis.
- Anatomic anomalies.
- Atrophic vaginitis.
- Mucosal tears.
- Inadequate lubrication.
- Focal vulvitis.
- Painful hymenal tags.
- Scarring secondary to episiotomy.
- Skin disorders.
- Topical allergies.
- Postherpetic neuralgia.

DIAGNOSIS

WORKUP

- Thorough history (including sexual history).
- Careful pelvic examination.
- Behavioral therapy.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Deconditioning the response by systematic self-administered progressive dilation techniques using fingers or dilators.
- Behavioral and/or psychosexual therapy

ACUTE GENERAL Rx

- Botulinum toxin therapy given locally has been shown to relieve the perineal muscle spasms associated with vaginismus, allowing resumption of intercourse.
  1. Acts by preventing neuromuscular transmission, causing muscle weakness.
  2. Considered experimental treatment for vaginismus at this time.
- Cause should be determined by history and explained to the patient so that she understands the mechanics of the muscle spasms.
- Patient must be motivated to desire painless vaginal insertion for such reasons as pleasurable coitus, tampon insertion, or gynecologic examination.
- Patient (and her partner) must be willing to patiently undergo the process of systematic desensitization and counseling.

DISPOSITION

A high percentage of successfully treated patients.

REFERRAL

To a gynecologist or sex therapist.

PEARLS & CONSIDERATIONS

COMMENTS

- May uncover early sexual abuse or an aversion to sexuality in general.
- American Association of Sex Educators, Counselors and Therapists, 11 Dupont Circle, NW, Washington, DC, 20036
- Sex Information and Education Council of the United States (SIECUS), 90 John St., New York, NY 10038

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Dyspareunia (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

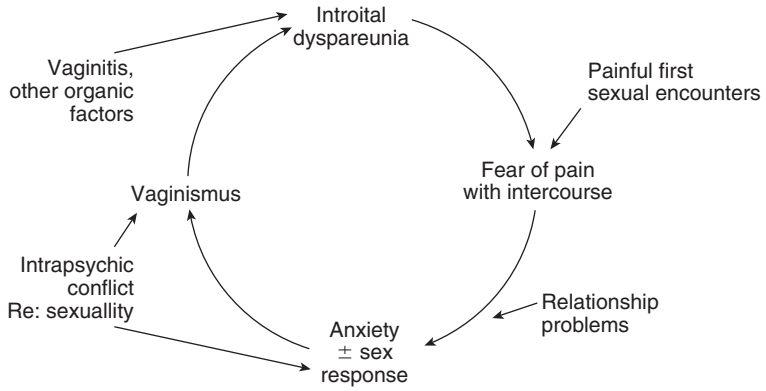


FIGURE V1-5 Dyspareunia and vaginismus cycle. (From Lentz G.M.: *Emotional aspects of gynecology sexual dysfunction, eating disorders, substance abuse, depression, grief, loss; comprehensive gynecology*, St Louis, 2007, Mosby.)

SUGGESTED READINGS

Heim LJ: Evaluation and differential diagnosis of dyspareunia, *Am Fam Physician* 63(8):1535, 2001.

McGuire H, Hawton K: Interventions for vaginismus, *Cochrane Database Syst Rev* 1:CD001760, 2003.

Vaginitis, Estrogen-Deficient

BASIC INFORMATION

DEFINITION

Estrogen-deficient vulvovaginitis is the irritation and/or inflammation of the vulva and vagina because of progressive thinning and atrophic changes secondary to estrogen deficiency (Fig. V1-6).

SYNONYMS

Atrophic vaginitis
Vulvovaginal atrophy

ICD-9CM CODES
616.10 Vulvovaginitis
ICD-10CM CODES
N95.2 Post-menopausal atrophic vaginitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Seen most often in postmenopausal women
- Average age of menopause is 52 yr
- Up to half of postmenopausal women are symptomatic, but a quarter of these will not seek treatment

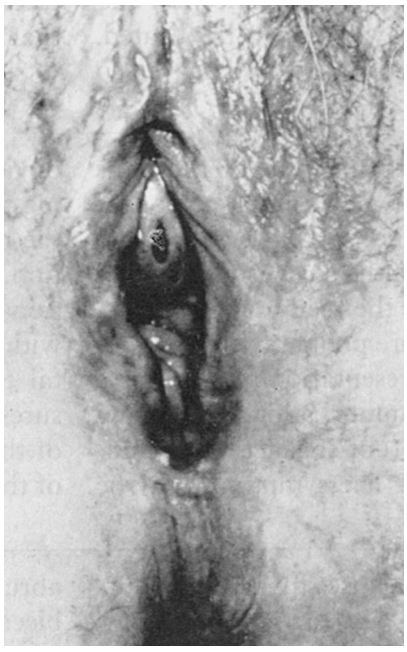


FIGURE V1-6 Advanced postmenopausal atrophy of the vulva in a 72-year-old woman. (From Symonds EM, Macpherson MBA: *Color atlas of obstetrics and gynecology,* St Louis, 1994, Mosby.)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Thinning of pubic hair, labia minora and majora
- Decreased secretions from the vestibular glands, with vaginal dryness
- Regression of subcutaneous fat
- Vulvar and vaginal itching
- Dyspareunia
- Dysuria and urinary frequency
- Vaginal spotting

ETIOLOGY

- Estrogen deficiency. Estrogen is essential to maintaining the urogenital environment. Postmenopausal thinning of the vaginal epithelium and increase in subepithelial connective tissue result in loss of rugal folds and elasticity. Reduced blood flow also contributes to a decline in vaginal secretions.
- Smoking and use of antiestrogen medications (e.g., aromatase inhibitors) increase the risk of vulvovaginal atrophy.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infectious vulvovaginitis
- Squamous cell hyperplasia
- Lichen sclerosus
- Vulvar malignancy
- Vaginal malignancy
- Cervical and endometrial malignancy
- Irritant contact dermatitis

WORKUP

- Pelvic examination
- Speculum examination
- Pap smear
- Possible endometrial biopsy if bleeding

LABORATORY TESTS

FSH and estradiol: generally after menopause, estradiol <15 pg/ml and FSH >40 mIU/ml (diagnosis of menopause usually made on a clinical basis and does not usually require FSH and/or estradiol testing)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of contact irritants such as scented soaps and feminine hygiene products
- Avoidance of synthetic undergarments, tight-fitting clothing

GENERAL Rx

- Regular use of vaginal moisturizers (e.g., Replens) can decrease vaginal itching and irritation.
- Use of water or silicone-based personal lubricants (e.g., Astroglide) during intercourse is useful to reduce dyspareunia.
- Conjugated estrogen vaginal cream intravaginally. Estradiol vaginal cream (0.625 mg estrogen/gram).
  2 to 4 g/day × 2 wk then
  1 to 2 g/day × 2 wk then
  1 to 2 g × 2-3 days/wk
- Vagifem (estradiol vaginal tablets) 25 mg inserted intravaginally daily for 2 wk then twice weekly. May take up to 12 wk to feel the full benefits of the medication.
- Conjugated estrogen vaginal cream: 2 to 4 g qd (3 wk on, 1 wk off) for 3 to 5 mo.
- Hormone replacement therapy (HRT): use ultra-low doses. Estrogen use should be reviewed every 3 to 6 mo, with an attempt to taper or discontinue its use.
- Estraderm patch 0.05 mg × 2 per week.
- If uterus present:
  1. Estrogen + 2.5 mg PO Provera qd *or*
  2. Estrogen + 5 to 10 mg PO Provera × 14 days each mo

DISPOSITION

The symptoms should be improved with the therapy. Caution for vaginal bleeding if uterus present.

REFERRAL

To obstetrician/gynecologist if vaginal bleeding

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pruritus Vulvae (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Hainer BL, Gibson MV: Vaginitis: diagnosis and treatment, *Am Fam Physician* 83(7):807–815, 2011.

Hohenhaus MH: Vulvovaginal atrophy: a common and commonly overlooked problem, *Medicine and Health Rhode Island* 94:138–140, 2011.

BASIC INFORMATION

DEFINITION

Fungal vulvovaginitis is the inflammation of vulva and vagina caused by *Candida* spp.

SYNONYMS

Candidiasis, vulvovaginal
Monilial vulvovaginitis
Vulvovaginal candidiasis
VVC

ICD-9CM CODES
112.1 Vulvovaginitis, monilial
ICD-10CM CODES
B37.3 Candidiasis of vulva and vagina

EPIDEMIOLOGY & DEMOGRAPHICS

- Second most common cause of vaginal infection
- 75% of women will have at least one episode during their childbearing years, and ~40% to 50% of these will have a second attack.
- No symptoms in 20% to 40% of women who have positive cultures

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Intense vulvar and vaginal pruritus
- Edema and erythema of vulva
- Thick, curd-like vaginal discharge ("cottage cheese" discharge)
- Adherent, dry, white, curdy patches attached to vaginal mucosa

ETIOLOGY

- *Candida albicans* is responsible for 80% to 95% of vaginal fungal infections.
- *Candida tropicalis* and *Torulopsis glabrata (Candida glabrata)* are the most common nonalbicans *Candida* species that can induce vaginitis.

PREDISPOSING HOST FACTORS

- Pregnancy
- Oral contraceptives (high-estrogen)
- Diabetes mellitus
- Antibiotics
- Immunosuppression (e.g., HIV)
- Tight, poorly ventilated, nylon underclothing, with increased local perineal moisture and temperature

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bacterial vaginosis
- *Trichomonas* vaginitis
- Atrophic vaginitis

Section II describes the differential diagnosis of vaginal discharges and infections.

WORKUP

- Pelvic examination
- Speculum examination
- Hyphae or budding spores on 10% KOH preparation (positive in 50% to 70% of individuals with yeast infection)
- Normal vaginal pH

Section III, "Vaginal Discharge," describes the evaluation of discharge.

LABORATORY TESTS

Culture, especially recurrence for identification

TREATMENT

ACUTE GENERAL Rx

- Cure rate of the various azole derivatives 85% to 90%; little evidence of superiority of one azole agent over another
- No significant differences in persistent symptoms with oral or vaginal treatment
- Fluconazole 150 mg PO × 1 is preferred treatment
- Cure rate of polyene cream, and suppositories: 75% to 80%
- Miconazole 200-mg suppository, one suppository × 3 days or 2% vaginal cream, one applicatorful intravaginally qhs × 7
- Clotrimazole 200-mg vaginal tablet, one tablet intravaginally qhs × 3 or 100-mg vaginal tablet one tablet intravaginally qhs × 7, or 1% vaginal cream intravaginally qhs × 7
- Butoconazole 2% cream one applicator intravaginally qhs × 3
- Terconazole 80-mg suppository or 0.8% vaginal cream, one suppository or one applicator intravaginally qhs × 3 or 0.4% vaginal cream, one applicator intravaginally qhs × 7
- Gynecazole-1 vaginal cream, one applicator intravaginally × 1
- Tioconazole 6.5% ointment (Vagi-stat), one applicator intravaginally × 1
- In pregnant patient, treat with 7-day course of topical imidazole.

CHRONIC Rx (FOUR OR MORE SYMPTOMATIC EPISODES ANNUALLY)

- Resistance or recurrence
  1. 14- to 21-day course of 7-day regimens mentioned in "Acute General Rx" above
  2. Fluconazole 150 mg PO × 2, 3 days apart
  3. Ketoconazole 200 mg PO bid × 5 to 14 days
  4. Itraconazole 200 mg PO qd × 3 days
  5. Boric acid 600-mg capsule intravaginally bid × 14 days
- Prophylactic regimens
  1. Clotrimazole one 500-mg vaginal tablet each month
  2. Ketoconazole 200 mg PO bid × 5 days each month
  3. Fluconazole 150 mg PO × 1 each month
  4. Miconazole 100-mg vaginal tablet × 2 weekly

DISPOSITION

- If symptoms do not resolve completely with treatment, or if they recur within a 2- to 3-mo period, further evaluation is indicated.
- Reexamination and possibly culture are necessary.
- Positive culture in absence of symptoms should not lead to treatment. Approximately 30% of women harbor *Candida* spp. and other species in the vagina.

REFERRAL

To obstetrician/gynecologist for recurrence

PEARLS & CONSIDERATIONS

COMMENTS

- No evidence that treating a woman's male sexual partner significantly improves woman's infection or reduces her rate of relapse.
- Many *Candida albicans* strains produce hyaluronidase, which is an enzyme that degrades hyaluronan. Elevated hyaluronan levels in vaginal secretions are associated with increased itching, burning, and discharge in women with recurrent vulvovaginal candidiasis.
- Twenty percent of cases of recurrent vulvovaginal candidiasis are due to *Candida* species other than *C. albicans.*

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Candidiasis (Patient Information)
Vaginal Yeast Infection (Patient Information)
Pruritus Vulvae (Related Key Topic)
Vaginitis, Prepubescent (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Lev-Sagie A, et al.: Hyaluronan in vaginal secretions: association with recurrent vulvovaginal candidiasis, *Am J Obstet Gynecol* 201:206, 2009.

Vaginitis, Prepubescent

BASIC INFORMATION

DEFINITION

Prepubescent vulvovaginitis is an inflammatory condition of the vulva and vagina.

ICD-9CM CODES
616.10 Vulvovaginitis
ICD-10CM CODES
N76.0 Acute vaginitis
N76.1 Subacute and chronic vaginitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Most common gynecologic problem of the premenarchal female.
- Prepubertal girl is susceptible to irritation and trauma because of the absence of protective hair and labial fat pads and the lack of estrogenization with atrophic vaginal mucosa.
- Symptoms of vulvovaginitis and introital irritation and discharge account for 80% to 90% of gynecologic visits.
- Nonspecific etiology in approximately 75% of children with vulvovaginitis.
- Majority of vulvovaginitis in children involves a primary irritation of the vulva with secondary involvement of the lower third of the vagina.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Vulvar pain, dysuria, pruritus
1. Discharge is not a primary symptom.
2. If present, vaginal discharge may be foul smelling or bloody.

ETIOLOGY

- Infections
  1. Bacterial
  2. Protozoal
  3. Mycotic
  4. Viral
- Endocrine disorders
- Labial adhesions
- Poor hygiene
- Sexual abuse
- Allergic substance
- Trauma
- Foreign body
- Masturbation
- Constipation

Section II describes the differential diagnosis of vaginal discharge in prepubertal girls.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Physiologic leukorrhea
- Foreign body
- Bacterial vaginosis
- Gonorrhea
- Fungal vulvovaginitis
- *Trichomonas* vulvovaginitis
- Sexual abuse
- Pinworms

WORKUP

- Pelvic, genital examination
- Speculum examination
- Rectal examination
- Vaginoscopy if considering a foreign body
- KOH and normal saline preparation of discharge
- Knee-chest position for examination may be easier for the child to tolerate during an examination

Section III, "Vaginal Discharge," describes the evaluation of discharge.

LABORATORY TESTS

- Urinalysis to rule out urinary tract infection and diabetes
- Cultures including sexually transmitted diseases

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoid tight clothing
- Perineal hygiene
- Avoid irritant chemicals
- Reassurance

ACUTE GENERAL Rx

- Group A beta *Streptococcus* and *Streptococcus pneumoniae:* penicillin V potassium 125 to 250 mg PO qid × 10 days
- *Chlamydia trachomatis:* azithromycin 1 g PO single dose
- *Neisseria gonorrhoeae:* ceftriaxone 250 mg IM × 1 day
  1. Children >8 yr should also be given doxycycline 100 mg bid PO × 7 days
- *Staphylococcus aureus:* amoxicillin-clavulanate 20 to 40 mg/kg/day PO × 7 to 10 days
- *Haemophilus influenzae:* amoxicillin 20 to 40 mg/kg/day PO × 7 days
- *Trichomonas:* metronidazole 125 mg (15 mg/kg/day) tid PO × 7 to 10 days
- Pinworms: mebendazole 100-mg tablet chewable, repeat in 2 wk
- Labial agglutination: spontaneous resolution or topical estrogen cream for 7 to 10 days. High degree of efficacy with topical estrogen hormone.

CHRONIC Rx

See "Referral."

DISPOSITION

Further education:
- Young child: hygiene
- Adolescent: pregnancy prevention and safe sexual practices

REFERRAL

- To obstetrician/gynecologist
- To pediatrician

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Pruritus Vulvae (Related Key Topic)
Vaginitis, Fungal (Related Key Topic)
Vaginitis, *Trichomonas* (Related Key Topic)
Vaginosis, Bacterial (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

SUGGESTED READINGS

Van Neer PA, Korver CR: Constipation presenting as recurrent vulvovaginitis in prepubertal children, *J Am Acad Dermatol* 43(4):718, 2000.

BASIC INFORMATION

DEFINITION

Trichomonas vulvovaginitis is the inflammation of vulva and vagina caused by *Trichomonas* spp.

SYNONYMS

Trichomonas vaginalis
Trichomoniasis
TV

ICD-9CM CODES
131.01 Vulvovaginitis, trichomonal
ICD-10CM CODES
A59.01 Trichomonal vulvovaginitis

EPIDEMIOLOGY & DEMOGRAPHICS

- Acquired through sexual contact
- Diagnosed in
  - 50% to 75% of prostitutes
  - 5% to 15% of women visiting gynecology clinics
  - 7% to 32% of women in sexually transmitted disease (STD) clinics
  - 5% of women in family planning clinics

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Profuse, yellow, malodorous vaginal discharge and severe vaginal itching
- Vulvar itching
- Dysuria
- Dyspareunia
- Intense erythema of the vaginal mucosa
- Cervical petechiae ("strawberry cervix")
- Asymptomatic in ~50% of women and 90% of men

ETIOLOGY

Single-cell protozoan *Trichomonas vaginalis*

RISK FACTORS

- Multiple sexual partners
- History of previous STDs

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS (Table V1-1)

- Bacterial vaginosis
- Fungal vulvovaginitis
- Cervicitis
- Atrophic vulvovaginitis

WORKUP

- Pelvic examination
- Speculum examination
- Mobile trichomonads seen on normal saline preparation (Fig. V1-7): 70% sensitivity
- Elevated pH (>5) of vaginal discharge
- Culture is considered the traditional gold standard laboratory test for diagnosis of TV.
- Nucleic acid amplification tests (NAATs) have been developed that combine excellent performance characteristics with a more rapid turnaround time compared with culture.
- APTIMA assays utilize target capture and transcription-mediated amplification (TMA) to selectively purify, amplify, and detect species-specific 16 S ribosomal RNA. APTIMA *Trichomonas vaginalis* transcription-mediated amplification may be a better laboratory test than culture based on sensitivity and time frame for results.

LABORATORY TESTS

- Culture (modified Diamond media): 90% sensitivity
- Direct enzyme immunoassay
- Fluorescein-conjugated monoclonal antibody test
- Pap test 40% detected

TREATMENT

NONPHARMACOLOGIC THERAPY

Condom use

ACUTE GENERAL Rx

Metronidazole 2 g PO × 1 *or* Tindamax (tinidazole) single 2-g oral dose in both sexes. Treatment of the sexual partner is essential to prevent reinfection.

CHRONIC Rx

- Metronidazole gel: less likely to achieve therapeutic levels; therefore not recommended.
- Metronidazole (retreat): 500 mg PO bid × 7 days.
- Treatment of recurrences: metronidazole 2 g PO qd × 3 to 5 days.
- Allergy, intolerance, or adverse reactions: alternatives to metronidazole are not available. Patients who are allergic to metronidazole can be managed by desensitization.
- Pregnancy:
  1. Associated with adverse outcomes (i.e., premature rupture of membranes)
  2. Metronidazole 2 g PO × 1 day

DISPOSITION

Trichomonas infection is considered an STD; therefore treatment of the sexual partner is necessary.

REFERRAL

To obstetrician/gynecologist for recurrence and pregnancy

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Trichomoniasis (Patient Information)
Pruritus Vulvae (Related Key Topic)

AUTHOR: **RUBEN ALVERO, M.D.**

TABLE V1-1 Differential Diagnosis of Vaginitis

Characteristics of Vaginal Discharge	*C. albicans* Vaginitis	*T. vaginalis* Vaginitis	Bacterial Vaginosis
pH	4.5	>5.0	>5.0
White curd	Usually	No	No
Odor with KOH	No	Yes	Yes
Clue cells	No	No	Usually
Motile trichomonads	No	Usually	No
Yeast cells	Yes	No	No

From Goldman L, Ausiello D (eds): *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, Saunders.

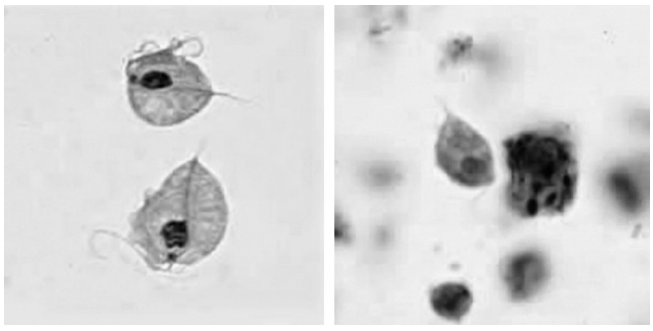


FIGURE V1-7 ***Trichomonas vaginalis*** **trophozoites stained with Giemsa** ***(left)*** **and iron hematoxylin** ***(right).*** (From the Centers for Disease Control and Prevention: *Laboratory identification of parasites of public health concern, Trichomoniasis.* www.dpd.cdc.gov/dpdx/HTML/ImageLibrary/Trichomoniasis_il.htm. Accessed August 30, 2010.)

SUGGESTED READINGS

Nye MB et al.: Comparison of APTIMA *Trichomonas vaginalis* transcription-mediated amplification to wet mount microscopy, culture, and PCR for diagnosis of trichomoniasis in men and women, *Am J Obstet Gynecol* 200:188, 2009.

Workowski KA, Levine WC: Sexually transmitted diseases treatment guidelines, *MMWR Morb Mortal Wkly Rep* 55:11, 2006.

Vancomycin-Resistant *Enterococcus* (VRE)

BASIC INFORMATION

DEFINITION

Enterococci are gram-positive, facultative, anaerobic organisms usually oval in shape and can be seen as single cells, pairs, or chains. Vancomycin-resistant *Enterococcus* (VRE) are enterococci that have become resistant to vancomycin and several antibiotics normally used to treat enterococcal infections.

SYNONYMS

VRE

ICD-9CM CODES
V09.8 Infection with microorganisms resistant to other specified drugs
ICD-10CM CODES
Z16.39 Resistance to other specified antimicrobial drug

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: VRE may be associated with the use of specific classes of antibiotics.
PEAK INCIDENCE: VRE was first reported in Europe in 1986, and there has been a steady rise in the incidence of enterococcal strains resistant to vancomycin. In 2007, 80% of *E. faecium* isolates and 7% of *E. faecalis* isolates were resistant to vancomycin.
PREVALENCE: 80% of *E. faecium* are VRE; 69% of *E. faecalis* are VRE.
RISK FACTORS

- Prior antimicrobial therapy, especially vancomycin
- Prolonged hospitalization
- Chronic medical conditions, renal failure
- Invasive devices
- ICU stay
- Colonization: VRE colonize the gastrointestinal tract; can be found on skin or perirectal swab culture or stool culture

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Patients may be asymptomatic and have gastrointestinal colonization; it can be associated with diarrhea. In hospitalized patients, infection is associated with colonization and can cause wound infections, bacteremia, abscesses (intra-abdominal), and, rarely, pneumonia and urinary tract infections.

ETIOLOGY

- Enterococci are primarily found in the human digestive tract and female genital tract, where they make up a significant portion of the normal bacterial population in healthy people. Enterococci can cause urinary tract, wound, bloodstream, heart valve, and brain infections. In the great majority of cases, VRE infections occur in hospitalized patients who have compromised immune systems. Most cases of VRE are caused by the *E. faecium* strains that have acquired resistance when they came in contact with other bacteria and shared genetic information.
- VRE is most commonly transmitted from one patient to another by health care workers whose hands have become contaminated inadvertently with feces or fluids of a person carrying the organism. VRE are not airborne but can survive on surfaces for several weeks.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other bacterial pathogens in blood, wounds, or urine
- Once colonized, increased incidence to become infected

LABORATORY TESTS

- VRE rectal culture
- VRE stool culture
- Blood, urine, and wound cultures

TREATMENT

- For rectal or stool colonization, therapy is not recommended
- Therapy is complicated by the fact that strains exhibit inherent resistance to many commonly used antibiotics.
- More than 80% of vancomycin-resistant *E. faecium* strains are also resistant to ampicillin.
- In symptomatic patients, if VRE strains are known to be susceptible, potential therapeutic agents include
  1. Linezolid: 600 mg IV or PO q12h
  2. Daptomycin: 4 mg/kg/day IV
  3. Quinupristin-dalfopristin (Synercid) only effective for *E. faecium* strains with no activity for *E. faecalis* strains: 7.5 mg/kg q8-12h. Can cause severe myalgias and arthralgias and venous irritation that often requires use of a central line, which has limited the use of this antibiotic.

REFERRAL

To infectious disease specialist

PEARLS & CONSIDERATIONS

COMMENTS

- Incidence increases with comorbidity and hospitalization.
- The number of patients already colonized with VRE in a defined geographic area (colonization pressure) is the most significant factor for predicting new acquisition of VRE.
- An association between VRE colonization and *Clostridium difficile* infection has been reported in patients with hematologic malignancies.

PREVENTION

Hand hygiene–isolation techniques, cleaning contaminated objects or surfaces, gowns and gloves, antibiotic management (prudent vancomycin use), surveillance

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

SUGGESTED READINGS

Courvalin P: Vancomycin resistance in gram positive cocci, *Clin Infect Dis* 42(Suppl 1):525–534, 2006.

Cunha BA: Antimicrobial therapy of multidrug-resistant *Streptococcus pneumoniae*, vancomycin-resistant enterococci, and methicillin-resistant *Staphylococcus aureus*, *Med Clin North Am* 90(60):1165–1182, 2006.

National Institute of Allergy and Infectious Diseases. *Antimicrobial (drug) resistance: vancomycin-resistant enterococci* (VRE). www3.niaid.nih.gov/topics/antimicrobialresistance/examples/vre/transmission.htm.

BASIC INFORMATION

DEFINITION

Varicella is a viral illness that is characterized by the acute onset of a generalized vesicular rash and fever.

SYNONYMS

Chickenpox

ICD-9CM CODES
052.9 Varicella
ICD-10CM CODES
B01.9 Varicella without complication
B01.0+ Varicella meningitis (G02.0)
B01.1+ Varicella encephalitis (G05.1)
B01.2+ Varicella pneumonia (J17.1)
B01.8 Varicella with other complications

EPIDEMIOLOGY & DEMOGRAPHICS

- Varicella is extremely contagious. More than 90% of unvaccinated contacts become infected.
- The incubation period of chickenpox ranges from 9 to 21 days.
- The peak incidence is during the springtime.
- The predominant age is 5 to 10 yr.
- The infectious period begins 2 days before the onset of clinical symptoms and lasts until all of the lesions have crusted.
- Most patients will have lifelong immunity after an attack of chickenpox; protection from the virus after a varicella vaccine is approximately 6 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Findings vary with the clinical course. Initial symptoms consist of fever, chills, backache, generalized malaise, and headache.
- Symptoms are generally more severe in adults.
- Initial lesions generally occur on the trunk (centripetal distribution) and occasionally on the face; these lesions consist primarily of 3 to 4 mm red papules with an irregular outline and a clear vesicle (Fig. V1-8) on the surface (i.e., the appearance of dewdrops on a rose petal).

FIGURE V1-8 Chickenpox. (From Swartz, MH: *Textbook of physical diagnosis,* 7 ed, Philadelphia, 2014, Saunders.)

- Intense pruritus generally accompanies the initial stage.
- New lesion development generally ceases by the fourth day, with subsequent crusting by the sixth day.
- Lesions generally spread to the face and the extremities (i.e., centrifugal spread).
- Patients generally present with lesions that are in different stages at the same time.
- Crusts generally fall off within 5 to 14 days.
- The fever is usually highest during the eruption of the vesicles; the patient's temperature generally returns to normal after the disappearance of vesicles.
- Signs of potential complications (e.g., bacterial skin infections, neurologic complications, pneumonia, hepatitis) may be present on physical examination.
- Mild constitutional symptoms (e.g., anorexia, myalgias, headaches, restlessness) may be present; these are most common among adults.
- Excoriations may be present if scratching is prominent.

ETIOLOGY

Varicella-zoster virus is a human herpes virus III that can manifest with either varicella or herpes zoster (i.e., shingles, which is a reactivation of varicella).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other viral infection.
- Impetigo.
- Scabies.
- Drug rash.
- Urticaria.
- Dermatitis herpetiformis.
- Smallpox.

WORKUP

The diagnosis is usually made on the basis of the patient's history and clinical presentation.

LABORATORY TESTS

- Laboratory evaluation is generally not necessary.
- The CBC may reveal leukopenia and thrombocytopenia.
- Serum varicella titers (i.e., a significant rise in the serum varicella immunoglobulin G antibody level), skin biopsies, or Tzanck smears are used only when diagnosis is in question.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Use antipruritic lotions for symptomatic relief.
- Avoid scratching to prevent excoriations and superficial skin infections.
- Use a mild soap for bathing.
- Hands should be washed often.

ACUTE GENERAL Rx

- Use acetaminophen for fever and myalgias; aspirin should be avoided because of the associated increased risk of Reye's syndrome.
- Oral acyclovir (20 mg/kg qid for 5 days) initiated at the earliest sign (i.e., within 24 hr of illness) is useful for healthy, nonpregnant individuals 13 yr old or older to decrease the duration and severity of signs and symptoms. Immunocompromised hosts should be treated with intravenous acyclovir 500 mg/m^2 or 10 mg/kg q8h for 7 to 10 days.
- Varicella is most contagious from 2 days before to a few days after the onset of the rash. Varicella vaccine is available for children and adults; protection lasts at least 6 yr. Healthy, nonimmune adults and children exposed to varicella-zoster virus should receive prophylaxis with live attenuated varicella vaccine (Varivax). Patients with HIV or other immunocompromised patients should not receive the live attenuated vaccine.
- Exposed patients with contraindications to varicella vaccine can be treated with varicella-zoster immunoglobulin (VariZIG), which effectively prevents varicella in susceptible individuals. The dose is 12.5 U/kg IM up to a maximum of 625 U. VariZIG must be administered as early as possible after presumed exposure (i.e., within 10 days) for postexposure prophylaxis of varicella.
- Pruritus from chickenpox can be controlled with antihistamines (e.g., hydroxyzine 25 mg q6h) and oral antipruritic lotions (e.g., calamine).
- Oral antibiotics are not routinely indicated and should be used only in patients with secondary infection and infected lesions; the most common infective organisms are *Streptococcus* sp. and *Staphylococcus* sp.

DISPOSITION

- The course is generally benign in immunocompetent adults and children.
- Infants who develop chickenpox are incapable of controlling the infection and should be given varicella-zoster immunoglobulin or gamma globulin if VariZIG is not available.

PEARLS & CONSIDERATIONS

COMMENTS

- VariZIG can be obtained from the nearest regional Red Cross Blood Center or the Centers for Disease Control and Prevention in Atlanta.
- Varicella immunization is recommended for all who have not had chickenpox; the dosage for adults and adolescents (>13 yr old) is two 0.5 ml doses 4 to 8 wk apart.

EVIDENCE

Available at www.expertconsult.com

RELATED CONTENT

Chickenpox (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Background:

Because of ongoing outbreaks of varicella, a second dose of varicella vaccine was added to the routine immunization schedule for children in June 2006 by the Centers for Disease Control and Prevention.

Methods:

We assessed the effectiveness of 2 doses of varicella vaccine in a case-control study by identifying children ≥4 years of age with varicella confirmed by polymerase chain reaction assay and up to 2 controls matched by age and pediatric practice. Effectiveness was calculated using exact conditional logistic regression.

Results:

From July 2006 to January 2010, of the 71 case subjects and 140 matched controls enrolled, no cases (0%) versus 22 controls (15.7%) had received 2 doses of varicella vaccine, 66 cases (93.0%) versus 117 controls (83.6%) had received 1 dose, and 5 cases (7.0%) versus 1 control (0.7%) did not receive varicella vaccine ($P<0.001$). The effectiveness of 2 doses of the vaccine was 98.3% (95% confidence level [CI]: 83.5% to 100%; $P<0.001$). The matched odds ratio for 2 doses versus 1 dose of the vaccine was 0.053 (95% CI: 0.002 to 0.320; $P<0.001$).

Conclusion:

The effectiveness of 2 doses of varicella vaccine in the first 2.5 years after recommendation of a routine second dose of the vaccine for children is excellent. Odds of developing varicella were 95% lower for children who received 2 doses compared with 1 dose of varicella vaccine. Ⓐ

Evidence-Based Reference

Shapiro ED: Effectiveness of 2 doses of varicella vaccine in children, *J Infect Dis* 203:312–315, 2011. Ⓐ

Varicocele EBM PTG

BASIC INFORMATION

DEFINITION

A varicocele is a dilation of the testicular vein and pampiniform plexus within the scrotum.

SYNONYMS

Sometimes referred to as "bag of worms" (Fig. V1-9)

ICD-9CM CODES
456.4 Scrotal varices
ICD-10CM CODES
I86.1 Scrotal varices

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: A varicocele is present in up to 20% of all males. It occurs in approximately 40% of infertile men. However, only 10% to 15% of males with varicoceles have fertility problems.
RISK FACTORS: There are no reliable data on epidemiologic risk factors for varicocele, such as a family history or environmental exposures.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- While most varicoceles are painless, patients may complain of dull, aching pain that is relieved with lying down. They may also complain of testicular atrophy, one testicle being heavier than the other, a swollen testicle, or decreased fertility.
- Patients may report a mass lying posterior to and above the testis. When the patient is supine, dilation of the veins is generally decreased. Dilation and tortuosity of the veins are increased when the patient is upright and when the patient performs a Valsalva maneuver.
- The majority of cases (90%) occur more commonly on the left side because the left spermatic vein enters the left renal vein at a 90-degree angle, whereas the right testicular vein drains directly into the vena cava. Bilateral varicoceles occur in 33% of patients. A unilateral right-sided varicocele is very rare and should raise suspicion for an underlying disease causing obstruction of the vena cava.
- Physical examination reveals a soft scrotal mass that increases in size when standing and is typically described as a "bag of worms."
- Varicoceles can be graded based on physical exam. Grade one is small and is palpable only with Valsalva maneuver. Grade two is moderate and nonvisible on inspection but is palpable on standing. Grade three is large and visible on gross inspection.

ETIOLOGY

Varicoceles are caused by dysfunction of the valves in the spermatic vein, which allows pooling of blood in the pampiniform plexus.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hydrocele
- Spermatocele
- Epididymal orchitis
- Testicular tumor
- Table EV1-2 describes the differential diagnosis of pediatric scrotal masses and pain.

WORKUP

Patient should undergo a testicular exam in the upright and supine position.

LABORATORY TESTS

- Laboratory evaluation is generally not indicated
- Semen analysis may be performed if a varicocele is detected and the patient is infertile.

IMAGING

Usually varicoceles are diagnosed clinically. However, if there is suspicion for underlying malignancy, ultrasound may be used.

TREATMENT

There are no clear guidelines or solid evidence for treatment. Once a varicocele is identified, providers must document bilateral testicular size at regular intervals. Older men who do not want children and are asymptomatic can be treated conservatively. Surgical treatment is indicated for young men with retarded growth of a testis or abnormal sperm counts who want children.

MEDICAL MANAGEMENT

- NSAIDs are beneficial for pain relief.
- Scrotal support can reduce the feeling of "heaviness."

SURGERY

- Should surgery be advisable, varicocelectomy is performed by ligation of the veins of the pampiniform plexus through an inguinal incision or by ligating the internal spermatic vein in the retroperitoneum. This is generally performed as an ambulatory surgery.
- Although surgery will reverse abnormal sperm counts, it will not necessarily reverse infertility.
- Postoperatively the involved testis typically returns to its original size within 1 to 2 yr.
- The success rate of surgical repair is close to 98%; that of percutaneous repair is significantly lower.
- Sclerotherapy represents a less invasive option but is less effective in symptom reduction.

PEARLS & CONSIDERATIONS

- A varicocele in a 10-year-old boy or on the right side may be indicative of an abdominal or retroperitoneal mass. Ultrasound should be performed.
- The sudden occurrence of a left-sided varicocele in an older man indicates occlusion of the spermatic vein and should prompt evaluation for a renal tumor.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Varicocele (Patient Information)

AUTHORS: **EMILY VAN KIRK, M.D.,** and **ANDREW CARAGANIS, M.D.**

FIGURE V1-9 Varicocele. (From Swartz MH: *Textbook of physical diagnosis,* ed 5, Philadelphia, 2006, Saunders.)

EVIDENCE

Abstract[1]

Background:
Randomized controlled trials (RCTs) addressing varicocele treatment are scarce and have conflicting outcomes.

Objective:
To determine whether varicocele treatment is superior or inferior to no treatment in male infertility from an evidence-based perspective.

Design, Setting, and Participants:
A prospective, nonmasked, parallel-group RCT with a one-to-one concealed-to-random allocation was conducted at the authors' institution from February 2006 to October 2009. Married men 20-39 yr of age who had experienced infertility ≥1 yr, had palpable varicoceles, and with at least one impaired semen parameter (sperm concentration <20 million/ml, progressive motility <50%, or normal morphology <30%) were eligible. Exclusions included subclinical or recurrent varicoceles, normal semen parameters, and azoospermia. Sample size analysis suggested 68 participants per arm.

Intervention:
Participants were randomly allocated to observation (the control arm [CA]) or subinguinal microsurgical varicocelectomy (the treatment arm [TA]). Semen analyses were obtained at baseline (three analyses) and at follow-up months 3, 6, 9, and 12. The mean of each sperm parameter at baseline and follow-ups was determined.

Measurements:
We measured the spontaneous pregnancy rate (the primary outcome), changes from baseline in mean semen parameters, and the occurrence of adverse events (AE—the secondary outcomes) during 12-mo follow-up; $p<0.05$ was considered significant.

Results and Limitations:
Analysis included 145 participants (CA: n = 72; TA: n = 73), with a mean age plus or minus standard deviation of 29.3±5.7 in the CA and 28.4±5.7 in the TA (p = 0.34). Baseline characteristics in both arms were comparable. Spontaneous pregnancy was achieved in 13.9% (CA) versus 32.9% (TA), with an odds ratio (OR) of 3.04 (95% confidence interval [CI], 1.33–6.95) and a number needed to treat (NNT) of 5.27 patients (95% CI, 1.55–8.99). In CA within-arm analysis, none of semen parameters revealed significant changes from baseline (sperm concentration [p = 0.18], progressive motility [p = 0.29], and normal morphology [p = 0.05]). Conversely, in TA within-arm analysis, the mean of all semen parameters improved significantly in follow-up versus baseline ($p<0.0001$). In between-arm analysis, all semen parameters improved significantly in the TA versus CA ($p<0.0001$). No AEs were reported.

Conclusions:
Our RCT provided level 1b evidence of the superiority of varicocelectomy over observation in infertile men with palpable varicoceles and impaired semen quality, with increased odds of spontaneous pregnancy and improvements in semen characteristics within 1-yr of follow-up. Ⓐ

Evidence-Based Reference

Abdel-Meguid TA: Does varicocele repair improve male infertility? An evidence-based perspective from a randomized, controlled trial, *Eur Urol* 59:455–461, 2011. Ⓐ

SUGGESTED READINGS

Behrman RE et al. Nelson textbook of pediatrics, ed 16, Saunders: Philadelphia.
Diamond DA: Adolescent varicocele, *Curr Opin Urol* 17(4):263, 2007.
Nseyo UO et al. Urology for primary care physicians. Saunders: Philadelphia.
Will MA et al. The great debate: varicocele treatment and impact on fertility, *Fertil Steril* 95(3):841–852, 2011. Epub 2011 Jan 26.

TABLE EV1-2 Age-Based Differential Diagnosis of Pediatric Scrotal Masses and Pain

Diagnosis	Age at Onset	Pain	Position of Testes, Tenderness	Systemic Symptoms	Comment
Testicular torsion*	All ages; peak onset at 12-18 yr	60% sudden onset; diffuse tenderness	High-riding horizontal lie	Vomiting common; dysuria and fever uncommon	
Testicular appendix torsion	Prepuberty; average age 10 yr	Acute or gradual; focal tenderness	Normal lie; blue dot	Vomiting, dysuria, and fever uncommon	
Epididymoorchitis	>16 yr	Gradual; posterior tenderness	Normal lie	Vomiting uncommon; dysuria and fever common	Adolescent etiology: STD
Hydrocele	Most common during first year of life	Painless	Normal lie	None	Usually resolves by age 12 mo
Inguinal hernia (incarcerated hernia, strangulated hernia*)	Most common during first year of life	Pain with incarceration or strangulation	Normal lie	Vomiting, abdominal pain with incarceration or strangulation	Occurs 10 times more frequently in males than in females; right-sided more common
Varicocele	10-15 yr	Painless, mild discomfort, "pressure or fullness"	Normal lie	None	Associated with infertility; right-sided varicocele should prompt evaluation for tumor causing IVC compression
Testicular tumor	Rare; most occur in patients <30 yr	Painless	Normal lie, nontender mass	None unless advanced tumor	

*Emergency condition.
IVC, Inferior vena cava; *STD*, sexually transmitted disease.
From Adams JG et al: *Emergency medicine: clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

BASIC INFORMATION

DEFINITION

Veins in the leg are soft, thin-walled tubes that return blood back to the heart. This is accomplished by the presence of one-way valves and the action of the calf pump. Superficial venous insufficiency develops when venous return is impaired by valvular incompetence, obstruction, or calf muscle pump failure.

Varicose veins, the most common clinical manifestation of chronic venous disease, are bulging (>3 mm in diameter), tortuous conduits (Fig. V1-10). Reticular veins, often called "feeder veins," are bluish subdermal veins about 1 to 3 mm in diameter that give rise to telangiectasia. Spider veins or telangiectasias are very small (≤1 mm in diameter) thread veins found commonly in clusters on the surface of the skin.

SYNONYMS

Chronic venous disorder

ICD-9CM CODES
454.9 Varicose veins
454.8 Varicose veins with symptoms
ICD-10CM CODES
I83.90 Asymptomatic varicose veins of unspecified lower extremity
I83.899 Varicose veins of unspecified lower extremities with other complications

EPIDEMIOLOGY

PREVALENCE: One large U.S. cohort study found the biannual incidence of varicose veins was 3% in women and 2% in men.

The prevalence of varicose veins in Western populations was estimated in one study to be about 25% to 30% in women and 10% to 20% in men.

RISK FACTORS
Gender: female
Genetics: family history of varicose veins
Increasing age
Multiple pregnancies

SYMPTOMS AND PHYSICAL FINDINGS

Leg complaints consistent with chronic venous disease include aching, heaviness, subjective swelling, cramps, itching, tingling, and pain. These symptoms can be exacerbated by menses, heat, and prolonged standing.

CLINICAL PRESENTATION

- Chronic vein disease is the result of the introduction of high pressures into a normal low-pressure superficial venous system.
- This increased pressure or venous hypertension causes superficial veins to distend to such a degree that vein valves fail to close, causing reflux and pooling of blood in surface veins.
- Manifested clinically by two syndromes:
  1. Junctional: failure of the terminal valve at the intersection between the saphenous vein trunks and the deep system. If the great saphenous vein is involved, large varicose veins are found mainly above medial knee or calf. When the small saphenous vein is involved, large varicose veins are found in posterior knee or calf area. If the anterior accessory of great saphenous vein is involved, large varicose veins are found mainly in anterior or lateral thigh.
  2. Perforator: failure of valves located in perforating vein. Large varicose veins are found most commonly in medial calf and proximal thigh region.

CLASSIFICATION

Chronic venous disease can now be classified using the Clinical-Etiology-Anatomy-Pathophysiology (CEAP) criteria to allow a precise description of the type of venous disease being discussed and provide an orderly framework for decision making (Table V1-3).

ETIOLOGY

- The underlying etiology of varicose veins remains uncertain.
- Important structural changes that occur: failure of vein valve function and vein wall dilation from fragmentation of the muscle layer.

COMPLICATIONS

- Superficial venous thrombophlebitis (SVT): a very common disorder with an incidence of 125,000 new cases per year in the U.S. The most frequent predisposing risk factors are varicose veins. The clinical findings include the presence of erythema, tenderness, and a palpable cord. Pain, increased warmth, and swelling are also present. Diagnosis is made by ultrasonography, which is useful to identify associated deep vein thrombosis that can occur in approximately 15% of patients. The location of the SVT determines the course of treatment; if the proximal great saphenous vein (GSV) is involved, a 1-mo course of low-molecular-weight heparin plus compression stockings has been found to be more effective than vein ligation. If SVT involves branch varicosities, treatment is usually symptomatic (control of pain).
- Bleeding is a more common complication than traditionally suspected. It is associated with thin-walled ectatic veins known as "blue blebs" that are found predominantly in the medial lower calf and ankle region. The best emergency treatment consists of pressure wrapping and not suture ligation, which results in delayed healing of the bleeding site. Sclerotherapy of these veins is the definitive treatment to prevent further bleeding.
- Dermal pathology of prolonged chronic venous disease (CEAP classes 4, 5, and 6).
  1. Varicose eczema: see "Venous Ulcers" section.
  2. Atrophie blanche: see "Venous Ulcers" section.
  3. Lipodermosclerosis: see "Venous Ulcers" section.
  4. Venous stasis ulcer: see "Venous Ulcers" section.

FIGURE V1-10 Varicose veins. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Other conditions that cause leg pain:
- Stress fracture
- Arthritis hip/knee joint
- Gout
- Degenerative disk disease of lower back
- Intermittent claudication secondary to peripheral arterial disease (PAD)
- Medications such as allopurinol and statins

TABLE V1-3 CEAP Classification of Chronic Venous Disease

C: Clinical
C_0: no visible or palpable signs of venous disease
C_1: telangiectasias or reticular veins
C_2: varicose veins
C_3: edema
C_4: pigmentation or eczema
C_5: healed venous ulcer
C_6: active venous ulcer

E: Etiology
c: congenital
p: primary
s: secondary or post thrombotic
n: no venous cause identified

A: Anatomy
s: superficial veins
p: perforator veins
d: deep veins
n: no venous location identified

P: Pathophysiology
r: reflux
o: obstruction
r,o: reflux and obstruction
n: no venous pathophysiology identified

Other conditions that cause leg swelling:
- Cellulitis
- Soft tissue injury to leg/ankle/foot
- Obesity
- Diabetes
- Advancing age
- Medications such as calcium channel blockers, steroids, MAO inhibitors, and tricyclics

WORKUP

The diagnosis of chronic venous disorders is predominantly clinical. Initial evaluation consists of a thorough history and physical exam with classification of disease according to the CEAP criteria.

LABORATORY TESTS

Laboratory tests are not useful in patients with varicose veins.

IMAGING STUDIES

Duplex ultrasonography:
- Gold-standard imaging modality for the diagnosis, prognostic evaluation, pretreatment mapping, and posttreatment assessment of therapeutic intervention.
- Duplex ultrasound is used to identify and quantify points of valvular reflux within the superficial venous system.
- Assessment of valvular reflux is done with patient in the upright position, which physiologically approximates the condition in which valvular reflux occurs.
- Reverse flow of greater than 0.5 sec after distal compression is considered abnormal.

Other tests:
- Air plethysmography: may be useful in patients who have reflux in both superficial and deep venous systems or in patients with an unusual presentation of leg pain.
- Venography: has been largely replaced by duplex ultrasonography but still retains a critical role in the evaluation of chronic venous insufficiency prior to venous reconstruction.

Rx TREATMENT

CONSERVATIVE THERAPY

- Aerobic exercise regularly for 30 min a day.
- Elevate legs above heart level to reduce swelling.
- Flex ankles frequently at work and during air travel or long car travel.
- Maintain proper weight.
- Graduated compression stockings (below knee) to alleviate symptoms in patients who are not candidates or do not desire to undergo treatment of their varicose veins.

SCLEROTHERAPY

- Small- to medium-sized varicose veins such as spider veins and reticular varices in the absence of reflux in saphenous trunks are best treated with liquid sclerotherapy.
- The three principal sclerosants used in the U.S. are hypertonic saline, sodium tetradecylsulfate, and the newly FDA-approved solution, polidocanol.
- These agents are injected into vessels using 27-gauge or 30-gauge needles at concentrations of 23.4%, 0.1%, or 0.5%, respectively, causing injury to the endothelium with the resultant disappearance of the vein over period of time (usually 8 to 12 wk).

AMBULATORY PHLEBECTOMY

- A procedure in which large varicose vein branches are removed with special hook instruments through a small puncture—incisions are made with an 18-gauge needle or No. 11 blade
- Performed safely under local anesthesia in an office setting and offers excellent cosmetic results and relief of symptoms
- Most commonly performed in conjunction with endovenous ablation procedures

ENDOVENOUS ABLATION

- Ablation of diseased saphenous vein trunks, large incompetent tributaries, or perforating veins can be achieved by using:
  1. Radiofrequency energy
  2. Laser energy
  3. Ultrasound-guided foam sclerotherapy.
- The first two accomplish thermal injury to the vein in situ via an intraluminal catheter or bare-tipped laser wire. Chemical ablation uses a solution (polidocanol or sodium tetradecylsulfate) that is injected directly into the vein in the form of foam.
- Endovenous ablation can be performed in an office setting using local anesthesia. Patients can return to their normal daily activities immediately.
- The efficacy of these endovenous ablation procedures has been borne out by numerous published reports with occlusion rates over 95% and reflux free rates over 5-yr follow-up of 86%. A recent trial comparing ultrasound-guided foam sclerotherapy and endovenous laser ablation revealed that quality of life measures were generally similar among the study groups, with the exception of a slightly worse disease-specific quality of life in the foam group than in the surgery group. Both treatments had similar efficacy, but complications were less frequent after laser treatment and ablation rates were lower after foam treatment.

DISPOSITION

- It is important that the physician educate the patient to understand that varicose veins are a chronic and progressive disease.
- Any treatment is at best palliative, as patients in time will develop varicose veins in other areas.

REFERRAL

To either a phlebologist, preferably board certified by the newly created American Board of Phlebology, or a residency-trained vascular surgeon

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Varicose Veins (Patient Information)

AUTHOR: **FRANK G. FORT, M.D.**

SUGGESTED READINGS

Bergen JJ et al.: Chronic venous disease, *N Engl J Med* 355:488–498, 2006.

Brittenden J et al.: A randomized trial comparing treatments for varicose veins, *N Engl J Med* 371:1218–1227, 2014.

Kouri B: Current evaluation and treatment of lower extremity varicose veins, *Am J Med* 122:513–515, 2009.

Lurie F et al.: Prospective randomised study of endovenous radiofrequency obliteration (Closure®) versus ligation and vein stripping (EVOLVeS): two-year follow-up, *Eur J Vasc Endovasc Surg* 29(1):67–73, 2005.

Nijsten T et al.: Minimally invasive techniques in the treatment of saphenous varicose veins, *J Am Acad Dermatol* 60:110–119, 2009.

BASIC INFORMATION

DEFINITION

Vasculitis refers generically to inflammation occurring within the walls of blood vessels. Blood vessel inflammation can result in either perforation of affected vessels with hemorrhage into adjacent structures or thrombosis with subsequent ischemia and infarction of supplied tissues. Vasculitis can occur as a primary process or secondary to another connective tissue disease, infection, or drug exposure. The systemic vasculitides are a heterogeneous group of disorders (Table EV1-4) characterized by blood vessel inflammation affecting vessels of varying size and location resulting in a wide range of clinical manifestations dictated largely by which vessels are affected (Fig. EV1-11). They are traditionally classified according to the size of the blood vessels predominantly affected (Table V1-5). Several of these are covered in individual chapters including chapters on granulomatosis with polyangiitis (GPA), polyarteritis nodosa (PAN), giant cell arteritis (GCA), Takayasu's arteritis, and Henoch-Schönlein purpura (HSP). Severity varies between and within specific vasculitides from a relatively benign, self-limited process to severe, life-threatening multisystem organ involvement with significant morbidity and mortality.

TABLE V1-5 Classification Scheme of Vasculitides According to Size of Predominant Blood Vessels Involved

Primary vasculitides
Predominantly large vessel vasculitides
Takayasu's arteritis
Giant cell arteritis (temporal arteritis)
Cogan's syndrome
Behçet's disease*
Predominantly medium-sized vessel vasculitides
Polyarteritis nodosa
Cutaneous polyarteritis nodosa
Buerger's disease
Kawasaki disease
Primary angiitis of the central nervous system
Predominantly small vessel vasculitides
Immune complex mediated
Goodpasture's disease (anti–glomerular basement membrane disease)†
Cutaneous leukocytoclastic angiitis ("hypersensitivity vasculitis")
Henoch-Schönlein purpura
Hypocomplementemic urticarial vasculitis
Essential cryoglobulinemia‡
Erythema elevatum diutinum
ANCA-associated disorders§
Wegener's granulomatosis‡
Microscopic polyangiitis‡
Churg-Strauss syndrome‡
Renal-limited vasculitis
Secondary forms of vasculitis
Miscellaneous small vessel vasculitides
Connective tissue disorders‡ (rheumatoid vasculitis, lupus erythematosus, Sjögren's syndrome, inflammatory myopathies)
Inflammatory bowel disease
Paraneoplastic
Infection
Drug-induced vasculitis: ANCA-associated, other

ANCA, Antineutrophil cytoplasmic antibody.
*May involve small, medium-sized, and large blood vessels.
†Immune complexes formed in situ, in contrast to other forms of immune complex–mediated vasculitis.
‡Frequent overlap of small and medium-sized blood vessel involvement.
§Not all forms of these disorders are always associated with ANCA.
From Firestein G et al: *Kelley's textbook of rheumatology,* ed 8, Philadelphia, 2008, Saunders.

SYNONYMS

None

ICD-9CM CODES
446.0 Polyarteritis nodosa
446.1 Kawasaki disease
446.4 Wegener's granulomatosis, Churg-Strauss syndrome
446.5 Giant cell arteritis
446.7 Takayasu's arteritis

ICD-10CM CODES
M30.0 Polyarteritis nodosa
M30.3 Mucocutaneous lymph node syndrome [Kawasaki]
M31.30 Wegener's granulomatosis without renal involvement
M31.6 Other giant cell arteritis
M31.4 Aortic arch syndrome [Takayasu]

EPIDEMIOLOGY & DEMOGRAPHICS

- The epidemiology and demographics of the various vasculitides vary by the individual disease and where applicable are covered under the relevant disease chapters.
- The most common form of systemic vasculitis in the United States is giant cell arteritis, with an approximate incidence of 170 cases per 1 million per year in individuals older than 50 years.
- Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis is significantly less common with aggregate incidence estimated at approximately 20 per million in the U.S.
- Age distribution can demonstrate significant variability between the vasculitides as demonstrated by the fact that GCA generally does not occur before age 50, while 90% of cases of HSP occur in the pediatric population and 80% of patients with Kawasaki disease are under age 5.
- While genetics clearly plays a role in disease susceptibility, familial cases of vasculitis are rare.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical presentation often includes nonspecific constitutional symptoms including fever, malaise, headache, and weight loss.
- Signs and symptoms are generally dictated by the tropism of involved vessels.
- Skin manifestations of vasculitis include petechiae, palpable purpura (Fig. V1-12), subcutaneous nodules, livedo reticularis, ulcerations, and digital ischemia.
- Kidney involvement of medium-sized and large vessel vasculitis is often in the form of renovascular hypertension, as opposed to glomerulonephritis in small vessel vasculitis.
- Pulmonary small vessel involvement can cause alveolar hemorrhage, which can present with cough, dyspnea, and alveolar hemorrhage.
- Mononeuritis multiplex is the characteristic finding of vasculitis affecting the vasa nervorum of the peripheral nervous system.
- Gastrointestinal involvement of the mesenteric vasculature can cause postprandial pain, bleeding, and perforation.
- Arthritis, while nonspecific, can be present.
- Significant clinical variability exists between the various vasculitides, although overlapping symptoms may be seen.

ETIOLOGY

Most forms of systemic vasculitis are of unknown etiology. Cryoglobulinemic vasculitis is often secondary to hepatitis C infection, and cutaneous leukocytoclastic vasculitis can often be related to a drug exposure.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Infective endocarditis
- Atrial myxoma

FIGURE V1-12 Leukocytoclastic vasculitis, palpable purpura. (From James W et al: *Andrews' diseases of the skin, clinical dermatology,* ed 10, Philadelphia, 2005, Saunders.)

TABLE V1-6 Differential Diagnostic Features of Selected Forms of Small Vessel Vasculitis

Features	Microscopic Polyangiitis	Wegener's Granulomatosis	Churg-Strauss Syndrome	Henoch-Schönlein Purpura	Cryoglobulinemic Vasculitis
Vasculitic signs and symptoms	+	+	+	+	+
IgA-dominant immune deposits	–	–	–	+	–
Cryoglobulins in blood and vessels	–	–	–	–	–
Antineutrophil cytoplasmic antibodies in blood	+	+	+	–	–
Necrotizing granulomas	–	+	+	–	–
Asthma and eosinophils	–	–	+	–	–

From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

- Cholesterol emboli
- Malignancy

WORKUP

- The diagnosis of most forms of systemic vasculitis relies on the history and physical examination as well as supportive laboratory testing. Table V1-6 describes differential diagnostic features of selected forms of small vessel vasculitis.
- Tissue biopsy is important in establishing an accurate diagnosis; biopsy sites should target affected tissues.
- Imaging such as mesenteric angiography in the setting of PAN affecting the mesenteric vasculature can be supportive and can at times obviate the need for tissue biopsy.

LABORATORY TESTS

- Generic laboratory markers of systemic inflammation include an elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and an anemia of chronic disease.
- ANCA targeting myeloperoxidase (MPO) and proteinase 3 (PR3) are frequently found in several small vessel vasculitides, including GPA (Wegener's), microscopic polyangiitis (MPA), and Churg-Strauss syndrome (CSS).
- Hepatitis C antibodies and rheumatoid factor are often present in cryoglobulinemic vasculitis.
- Urinalysis in patients with glomerulonephritis due to small vessel ANCA-associated vasculitis will generally demonstrate hematuria with an active urinary sediment with red blood cell casts and proteinuria without significant immune deposits (pauci-immune) on biopsy.

IMAGING STUDIES

- Angiography can demonstrate vascular narrowing and aneurysm formation in suspected medium-size and large vessel vasculitis.
- Pulmonary and sinus CT scans can demonstrate active pulmonary and upper airway disease in ANCA-associated vasculitis.

Rx TREATMENT

Treatment of vasculitis depends on the specific type of vasculitis and is tailored to the severity of disease activity.

ACUTE GENERAL Rx

- Systemic corticosteroids are generally required to gain initial control of active disease although mild cases of drug-induced cutaneous leukocytoclastic vasculitis can often be treated with NSAIDs and cessation of the offending medication.
- GCA, HSP, and vasculitis limited to the skin including cutaneous PAN can often be managed without further immunosuppression.
- Major organ-threatening disease in systemic vasculitis has traditionally been treated with oral or intravenous cyclophosphamide.
- Studies have demonstrated noninferiority of rituximab compared to cyclophosphamide in ANCA-associated vasculitis with major organ involvement and it is approved for this use.
- Rituximab with prednisone has also recently been shown to be effective in the treatment of relapsing flares of disease activity in ANCA-associated vasculitis.
- Less severe disease such as granulomatosis with polyangiitis limited to the upper airways can be managed with methotrexate rather than cyclophosphamide.
- The goal of acute therapy is to induce remission of disease activity and is generally continued for 1 to 2 months once this is achieved, at which point chronic therapy is used to prevent disease relapse.

CHRONIC Rx

- The goal of chronic therapy is to prevent disease relapse and minimize medication side effects.
- Steroids are gradually tapered as allowed by disease activity.
- Immunomodulatory agents such as methotrexate or azathioprine are commonly used for maintenance therapy in place of cyclophosphamide to reduce side effects.
- Cryoglobulinemic vasculitis due to chronic hepatitis C will often improve with treatment of the underlying viral infection.
- Rituximab may also be an appropriate remission maintenance agent in ANCA-associated vasculitis, although frequency of dosing and duration of therapy are not yet well characterized.

DISPOSITION

Varies widely among the various vasculitides

REFERRAL

Systemic vasculitis care is generally coordinated by a rheumatologist. Renal, pulmonary, neurologic, and gastrointestinal consultation is often needed when vasculitis involves these organ systems. Isolated cutaneous leukocytoclastic vasculitis is often managed by dermatology.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Churg-Strauss Syndrome (Related Key Topic)
Cogan's Syndrome (Related Key Topic)
Giant Cell Arteritis (Related Key Topic)
Granulomatosis with Polyangiitis (Related Key Topic)
Henoch-Schönlein Purpura (Related Key Topic)
Kawasaki Disease (Related Key Topic)
Polyarteritis Nodosa (Related Key Topic)
Takayasu's Arteritis (Related Key Topic)

AUTHOR: **HARALD A. HALL, M.D.**

SUGGESTED READINGS

Lyons PA et al.: Genetically distinct subsets within ANCA-associated vasculitis, *N Engl J Med* 367:214–223, 2012.
Sharma P et al.: Systemic vasculitis, *Am Fam Physician* 83(5):556–565, 2011.
Specks U et al.: Efficacy of remission-induction regimens for ANCA-associated vasculitis, *N Engl J Med* 369:417–427, 2013.
Stone JH et al.: Rituximab versus cyclophosphamide for ANCA-associated vasculitis, *N Engl J Med* 363:211–220, 2010.

TABLE EV1-4 Comparing the Vasculitides

Disease	Pathophysiology	Classic Features	Testing	Treatment
Temporal arteritis	Mononuclear cell infiltration and giant cell formation	Headache Scalp tenderness Visual disturbance	ESR CRP Biopsy	Prednisone
Takayasu arteritis	Mononuclear cell infiltration and giant cell formation	Visual disturbance, chest pain, abdominal pain, differences in extremity blood pressure and pulses	Angiography	Prednisone Surgical or angiographic intervention
Polyarteritis nodosa	Polymorphonuclear infiltration	Fever, hypertension, myalgias, abdominal pain, hematuria, CHF, GI bleeding, orchitis	ESR, CRP Biopsy Angiography	Prednisone plus cyclophosphamide
Kawasaki disease	Polymorphonuclear infiltration	5-day fever, conjunctivitis, oral lesions, rash, red palms and soles, edema, cervical lymphadenopathy	ESR, CRP Leukocytosis Thrombocytosis Echocardiography	Aspirin plus IV gamma globulin
Wegener granulomatosis	Granuloma formation secondary to aggregating neutrophils	Upper and lower respiratory symptoms, renal insufficiency, skin lesions, visual disturbance	ESR CRP c-ANCA	Cyclophosphamide plus prednisone
Churg-Strauss syndrome	Eosinophilic infiltration Allergic granulomas	Allergic rhinitis Nasal polyps Asthma	Leukocytosis Eosinophilia ESR, CRP Biopsy	Prednisone with or without cyclophosphamide
Henoch-Schönlein purpura	IgA complex deposition	Palpable purpura, arthralgias, GI disturbances, glomerulonephritis	Leukocytosis Eosinophilia Ig A elevation Skin biopsy	Usually self-limited Prednisone if necessary
Cryoglobulinemic vasculitis	Cold precipitable monoclonal or polyclonal immunoglobulins	Palpable purpura, glomerulonephritis, myalgias, weakness, peripheral neuropathy	Low complement levels Hepatitis C Renal biopsy	Interferon alfa plus ribavirin
Cutaneous leukocytoclastic vasculitis	Neutrophilic infiltration Mononuclear and eosinophilic infiltration	Palpable purpura, macules, vesicles, bullae, urticaria	Skin biopsy	Prednisone
Behçet syndrome	Polymorphonuclear infiltration	Recurrent oral aphthous ulcers, genital ulcers, skin lesions, visual disturbance	ESR, CRP Leukocytosis Oral mucosa autoantibodies	Topical glucocorticoids Prednisone

c-ANCA, Cytoplasmic antineutrophil cytoplasmic antibody; *CHF*, congestive heart failure; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *GI*, gastrointestinal; *IgA*, immunoglobulin A; *IV*, intravenous.
From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

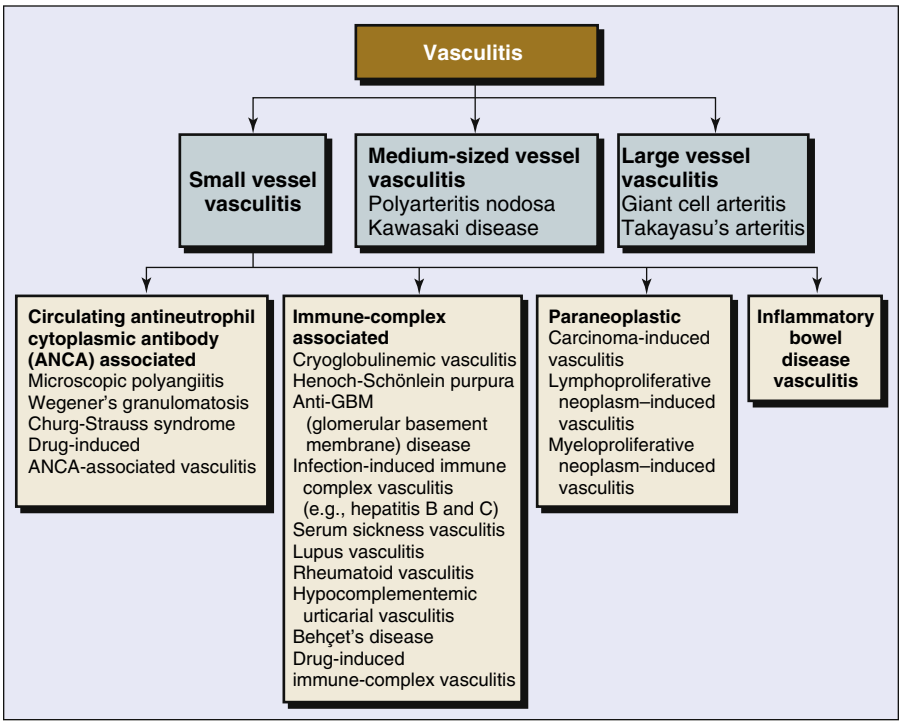


FIGURE EV1-11 The major categories of noninfectious vasculitis. Not included are vasculitides that are known to be caused by direct invasion of vessel walls by infectious pathogens, such as rickettsial vasculitis and neisserial vasculitis. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

BASIC INFORMATION

DEFINITION

The spectrum of chronic venous disease (CVD) ranges from varicose veins to leg edema and skin manifestations consisting of hyperpigmentation, eczema, lipodermatosclerosis, and venous ulcer. These latter venous specific skin changes constitute an advanced form of CVD known as chronic venous insufficiency (CVI).

SYNONYMS

Stasis dermatitis
Post-thrombotic syndrome (PTS)

ICD-9CM CODES
454.1 Varicose veins of lower extremities with inflammation

ICD-10CM CODES
I87.2 Venous insufficiency (chronic) (peripheral)
I87.8 Other specified disorders of veins
I87.9 Disorder of vein, unspecified
I83.10 Varicose veins of unspecified lower extremity with inflammation

EPIDEMIOLOGY & DEMOGRAPHICS

- From 10% to 35% of adults in the United States have some form of CVI.
- Venous ulcers are the complication of CVI that results in the greatest morbidity and affects 4% of people over the age of 65.
- The population-based costs to the U.S. government for CVI treatment and venous ulcer care have been estimated at >$1 billion a year.
- In addition, 4.6 million workdays per year are lost to chronic venous-related diseases.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

The spectrum of cutaneous changes of CVI in the affected leg include:

- Varicose eczema: the most common and earliest sign, this involves the skin above the medial ankle and consists of pruritic, red, and scaly eczematous patches and plaques (Fig. V1-13).
- Hyperpigmentation: caused by the breakdown of red blood cells and leads to hemosiderin deposition and dark staining of the skin (Fig. V1-14).
- Atrophie blanche: usually presents as hypopigmented white patches with focal red punctate dots or telangiectasia surrounded by hyperpigmentation. Skin in this condition is avascular and prone to ulceration (Fig. V1-15).
- Lipodermatosclerosis: a chronic, brawny induration of the skin and underlying fat that usually involves the skin from medial malleolus up to the lower border of the calf. Progression of the disease leads to an "inverted champagne bottle" appearance. The induration and lack of perfusion of the skin in this area make it susceptible to ulcer formation (Fig. V1-16).

ETIOLOGY

- CVI occurs as a result of sustained venous hypertension in the leg, which can be caused by the following:
  1. Primary: vein valve failure with reflux in the superficial venous system or perforating veins (most common cause of CVI).
  2. Secondary: post-thrombotic syndrome in which a deep vein thrombosis causes outflow obstruction or
  3. Combination of the two above processes.
- This sustained elevation in venous pressure or venous hypertension results in pathologic effects in the skin and subcutaneous tissues such as edema, eczema, hyperpigmentation, fibrosis, and ultimately venous ulceration.

DIAGNOSIS

The diagnosis and evaluation of CVI are directed primarily by a detailed history and physical examination.

DIFFERENTIAL DIAGNOSIS

- Contact dermatitis.
- Atopic dermatitis.
- Cellulitis.
- Dermatophyte infection.
- Pretibial myxedema.
- Nummular eczema.
- Xerosis.
- Asteatotic eczema.

WORKUP

The primary goal is to identify the cause of sustained venous hypertension. Fig. V1-17 describes the evaluation and management of chronic venous insufficiency.

LABORATORY TESTS

Generally not indicated

IMAGING STUDIES

- Evaluation of the patient is performed in the standing position with duplex ultrasonography to identify reflux in the superficial, deep,

FIGURE V1-13 Varicose eczema.

FIGURE V1-14 Hyperpigmentation.

FIGURE V1-15 Atrophie blanche.

FIGURE V1-16 Lipodermosclerosis.

and perforating veins as well as obstruction of the deep veins.
- No exam of a leg with CVI is complete without palpation of pulses and/or determination of ankle-brachial index (ABI).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Leg elevation above heart level for 30 min 3 to 4 times a day.
- Weight reduction because obesity is a risk factor for DVT and CVI.
- Walking exercises to improve calf function.
- Physical therapy to improve ankle joint mobility.
- For weeping skin lesions, wet-to-dry dressing changes.

ACUTE GENERAL Rx

- The fundamental role of compression in the treatment of CVI is well recognized and has been validated by randomized controlled trials (RCTs).
- The beneficial effects of gradient compression stockings (decrease in edema and control of discomfort) are due to their effect on microvascular hemodynamics and Starling forces.
- Below-knee compression stocking with a gradient of at least 20 to 30 mm Hg will control edema, alleviate pain, and improve the quality of life in CVI patients.
- Compression stockings are contraindicated in patients with an ABI of <0.6.
- Some patients (acute lipodermatosclerosis) may benefit from nonelastic compression with the Unna gel paste gauze boot to alleviate their symptoms and acute increase in their swelling. The Unna boot is changed once a week.
- Topical corticosteroid creams or ointments (e.g., triamcinolone 0.12% bid) may be used to help reduce inflammation and itching. Steroids should never be applied to ulcer.
- Antibiotics should only be used when treating a clinically apparent, culture-proved infection. Most secondary infections are the result of *Staphylococcus* or *Streptococcus* organisms.
- Diuretics have no role in the treatment of CVI-related edema.

CHRONIC Rx

- While conservative care is fundamental, patients with CVI should be considered for correction of their underlying venous hypertension.
- The majority of patients with CVI have superficial vein or perforator vein reflux as their underlying pathology and would benefit from the newer vein ablation procedures listed below.
  1. Endovenous ablation of superficial (saphenous) or perforator vein reflux.
  2. RF ablation with VNUS closure.
  3. Endovenous laser therapy (EVLT).
  4. Ultrasound-guided foam sclerotherapy.

COMPLEMENTARY & ALTERNATIVE MEDICINE

Several groups of drugs have been evaluated in the treatment of CVI, including coumarins, flavonoids, and saponosides (horse chestnut extracts). These drugs have venoactive properties and are widely used in Europe but are not approved for use in the United States. The precise mechanism of action is not known. Horse chestnut seed extract has been found, in the short term, to be as effective as compression stockings in reducing pain and edema, but long-term efficacy has not been established.

REFERRAL

- Phlebology.
- Vascular surgery.
- Indications for referral.
  - Skin and subcutaneous changes consistent with CVI.
  - Associated peripheral arterial insufficiency (PAD).
  - Longstanding varicose vein disease.
  - Consideration for vein ablation procedure.

PEARLS & CONSIDERATIONS

COMMENTS

- Inflammatory skin changes from CVI are irreversible. The goal of therapy is to eliminate venous hypertension and prevent progression.
- Venous ulcers are often an end-stage manifestation of CVI. Refer to section on "Venous Ulcers" for more information.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Stasis Dermatitis (Patient Information)

AUTHOR: **FRANK G. FORT, M.D.**

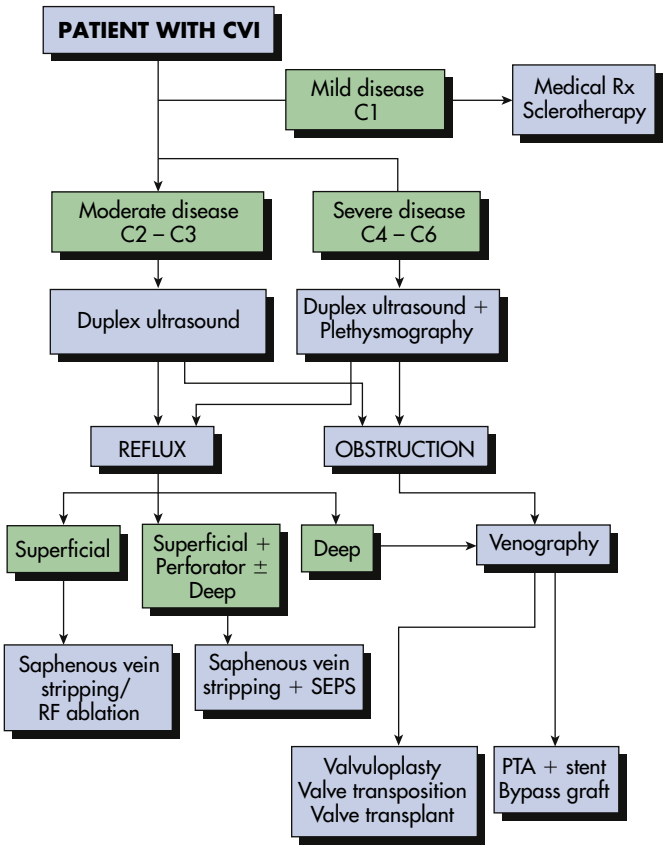


FIGURE V1-17 Evaluation and management of chronic venous insufficiency. (From Cameron JA: *Current surgical therapy "varicose veins",* Philadelphia, 2004, Saunders.)

EVIDENCE

Abstract[1]

Background:
The present randomized double-blind multicenter study was designed to assess the efficacy of a progressive compressive stocking (new concept with maximal pressure at calf), compared with a degressive compressive stocking graded 30 mm Hg, evaluating the improvement of lower leg symptoms of chronic venous insufficiency (CVI) in ambulatory patients with moderate to severe chronic venous disease.

Methods:
Both gender outpatients presenting symptomatic moderate to severe CVI were eligible for treatment with compressive stockings. Patients were randomly assigned to receive either degressive compressive stockings (30 mm Hg at ankle, 21 mm Hg at upper calf) or progressive compressive stockings (10 mm Hg at ankle, 23 mm Hg at upper calf). The primary outcome, evaluated after 3 months, was a composite success outcome, including improvement of pain or heavy legs without onset of either ulcer, deep or superficial vein thrombosis of the lower limbs, or pulmonary embolism. The ease of application of the compressive stockings reported by patients was one of secondary outcome.

Results:
Overall, 401 patients (199 in the progressive compressive stocking group and 202 in the degressive compressive stocking group) were randomized by 44 angiologists in France. Among them, 66% were classified in the C3 CEAP category. The rate of success was significantly higher in the progressive compressive stocking group compared to the degressive compressive stocking group (70.0% versus 59.6%; relative risk, 1.18; 95% confidence interval, 1.02 to 1.37; $P = 0.03$). This was mainly due to more frequent symptom improvement in the progressive compressive stocking group. The compressive stockings were considered easy to apply by 81.3% of patients in the progressive compressive stocking group versus 49.7% of patients in the degressive compressive stocking group ($P < 0.0001$). The rate of related serious adverse events was low and similar in both groups.

Conclusions:
This trial has demonstrated that progressive compressive stockings are more effective than usual degressive compressive stockings in the improvement of pain and lower leg symptoms in patients with CVI. Moreover, progressive compressive stockings were easier to apply, raising no safety concern at 3 months. Ⓐ

Abstract[2]

Background:
Apart from compression therapy, physical therapy has scarcely been evaluated in the treatment of chronic venous disorders (CVDs). Spa treatment is a popular way to administer physical therapy for CVDs in France, but its efficacy has not yet been assessed in a large trial. The objective was to assess the efficacy of spa therapy for patients with advanced CVD (CEAP clinical classes C4-C5).

Methods:
This was a single-blind (treatment concealed to the investigators) randomized, multicenter, controlled trial (French spa resorts). Inclusion criteria were primary or post-thrombotic CVD with skin changes but no active ulcer (C4a, C4b, or C5). The treated group had the usual 3-week spa treatment course soon after randomization; the control group had spa treatment after the 1-year comparison period. All patients continued their usual medical care including wearing compression stockings. Treatment consisted of four balneotherapy sessions per day for 6 days a week. Follow-up was performed at 6, 12 and 18 months by independent blinded investigators. The main outcome criterion was the incidence of leg ulcers at 12 months. Secondary criteria were a modified version of the Venous Clinical Severity Score, a visual analog scale for leg symptoms, and the Chronic Venous Insufficiency Questionnaire 2 and EuroQol 5D quality-of-life autoquestionnaires.

Results:
Four hundred twenty-five subjects were enrolled: 214 in the treatment group (Spa) and 211 in the control group (Ctr); they were similar at baseline regarding their demographic characteristics, the severity of the CVD, and the outcome variables. At 1 year, the incidence of leg ulcers was not statistically different (Spa: +9.3%; 95% confidence interval [CI], +5.6 - +14.3; Ctr: +6.1%; 95% CI, +3.2 - +10.4), whereas the Venous Clinical Severity Score improved significantly in the treatment group (Spa: −1.2; 95% CI, −1.6 - −0.8; Ctr: −0.6; 95% CI, −1.0 - −0.2; $P = .04$). A significant difference favoring spa treatment was found regarding symptoms after 1 year (Spa: −0.03; 95% CI, −0.57 - +0.51; Ctr: +0.87; 95% CI,+0.46 - +1.26; $P = .009$). EuroQol 5D improved in the treatment group (Spa: +0.01; 95% CI, −0.02 - +0.04) while it worsened (Ctr: −0.07; 95% CI, −0.10 - −0.04) in the control group ($P < .001$). A similar pattern was found for the Chronic Venous Insufficiency Questionnaire 2 scale (Spa: −2.0; 95% CI, −4.4 - +0.4; Ctr: +2.4; 95% CI, +0.2 - +4.7; $P = .008$). The control patients showed similar improvements in clinical severity, symptoms, and quality of life after their own spa treatment (day 547).

Conclusions:
In this study, the incidence of leg ulcers was not reduced after a 3-week spa therapy course. Nevertheless, our study demonstrates that spa therapy provides a significant and substantial improvement in clinical status, symptoms, and quality of life of patients with advanced venous insufficiency for at least 1 year. Ⓐ

Evidence-Based References

1. Couzan S, Leizorovicz A, Laporte S et al.: A randomized double-blind trial of upward progressive versus degressive compressive stockings in patients with moderate to severe chronic venous insufficiency, *J Vasc Surg* 56:1344–1350, 2012. Ⓐ
2. Carpentier PH, Blaise S, Satger B, et al: A multicenter randomized controlled trial evaluating balneotherapy in patients with advanced chronic venous insufficiency, *J Vasc Surg* 59:447–454.e1, 2014. Ⓐ

SUGGESTED READINGS

Bergan JJ et al.: Chronic venous disease, *N Engl J Med* 355(5):488, 2006.

Eberhardt RT: Chronic venous insufficiency, *Circulation* 111:2398, 2005.

Raffetto JD: Dermal pathology, cellular biology and inflammation in chronic venous disease, *Thromb Res* 123(Suppl 4):566–571, 2009.

BASIC INFORMATION

DEFINITION

Venous ulcers are defined as chronic defects of the skin that fail to heal spontaneously and persist for longer than 4 weeks. Venous ulcers account for about 70% of all lower extremity ulcerations. They are usually located in the "gaiter" region and can be accompanied by varicose veins, edema, hyperpigmentation, and lipodermatosclerosis. Venous ulceration develops in patients as a result of sustained venous hypertension.

SYNONYMS

Stasis ulcers

ICD-9CM CODES	
459.81	Peripheral venous insufficiency
707.1	Ulcer of the lower limb (calf: 2, ankle: 3)
ICD-10CM CODES	
I87.2	Venous insufficiency (chronic) (peripheral)
L97.909	Non-pressure chronic ulcer of unspecified part of unspecified lower leg with unspecified severity

EPIDEMIOLOGY & DEMOGRAPHICS

In industrialized nations, up to 1.5% of the population will suffer from venous ulcers. In patients ≥65 yr, the incidence increases to 4%. In the United States, >500,000 people suffer from stasis ulcers.

RISK FACTORS

- Obesity.
- Increasing age.
- Family history of chronic venous insufficiency.
- History of deep venous thromboembolism.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Venous ulcers are most commonly located in the lower leg just above the ankle (gaiter region). They are a partial-thickness, irregularly shaped wound with well-defined borders with granulation tissue and fibrin present in the ulcer base (Fig. V1-18). Venous ulcers are relatively painless and are surrounded by brown-stained skin and/or dry, itchy, and reddened skin. In about 50% of patients, there are visible varicose veins in an aching, swollen leg.

ETIOLOGY

The exact mechanism of the role of venous hypertension in the etiology of venous ulcers is not certain. Hemodynamic forces such as venous hypertension, circulatory stasis, and modified conditions of shear stress appear to play an important role in an inflammatory reaction accompanied by leukocyte activation that clinically leads to fibrosclerotic remodeling of the skin and then to ulceration.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Arterial ulcer.
- Neurotrophic ulcers (located predominantly in the foot).
- Vasculitis.
- Pyoderma gangrenosum.
- Ulcerated skin tumors like basal cell or squamous cell carcinoma (Marjolin's ulcer).
- Rheumatoid arthritis.

WORKUP

- The history and clinical signs and symptoms of leg ulcers are often misleading and may not differentiate venous ulcers from other leg ulcers; about 30% of leg ulcers are not of venous origin.
- Measurement of the ankle-brachial index (ABI) is essential in excluding peripheral arterial disease (PAD), which can be present in 20% of patients and is required before starting compression therapy. Arterial insufficiency is suggested by an ABI <0.9.
- Patients with lower-extremity ulcers should also be evaluated for diabetes.
- Coagulation defects have been found in 40% of patients with leg ulcers. This finding suggests that many patients with leg ulcers have a known or suspected history of deep venous thrombosis and a thrombophilia workup is indicated.
- If vasculitis is suspected, a biopsy of the edge of the ulcer can confirm the diagnosis.
- Any wound that has failed to improve after therapy of 4 wk should have a biopsy to rule out malignancy.

IMAGING STUDIES

- Evaluation of patients with venous leg ulcer should include duplex sonography to identify reflux in the superficial, deep, and perforating veins as well as possible obstruction of the deep veins.
- If the ulcer appears to be infected, consider tissue for culture, plain x-ray films, and bone scan to evaluate for osteomyelitis.

FIGURE V1-18 Stasis ulcer. Any ulcer in this location with surrounding edema, redness, and scale is typical of a stasis ulcer. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Fig. V1-19 describes an algorithm for the treatment of venous ulcers.
- Surgical debridement to remove all nonviable material can be accomplished in the office setting with the use of a topical Xylocaine gel. Debridement produces the release of growth factors that allow the development of healthy granulation tissue and the initiation of the healing process.
- The first-line treatment of ulcers includes below-knee compression stockings to improve venous return to the heart, thereby decreasing edema, inflammation, and tissue ischemia (used only if the ABI is between 0.6 and 0.85 because compression can cause limb ischemia).
- There is Level A evidence that graduated compression stockings alone can lead to healing of a venous ulcer. The stockings should be worn during the day and removed at night.
- Regular, brisk walking 30 min a day, five times a week is recommended.
- Elevate leg above heart level and raise the foot of bed with 3-in blocks to reduce edema.
- Role of surgery: in a randomized controlled trial, endovenous catheter ablation of superficial reflux showed no improvement in the healing rate of ulcers but did demonstrate a reduction of ulcer recurrence from 28% to 12% at 12 mo.

ACUTE GENERAL Rx

- Dressings are used under compression stockings to provide a clean, moist environment to promote healing.
- Modern, more complex dressings have been developed and include occlusive and semiocclusive dressings, classified according to their physical composition and ability to control wound drainage.
- Semiocclusive dressings have varying ability to absorb wound drainage. Some examples of this type are hydrocolloids (DuoDerm), hydrogels (Duoderm hydrogel), foam dressings (Allevyn), and alginates.
- Biologic wound dressings (Apligraf) and tissue-engineered products (Oasis) have been developed, and these products can either directly provide growth factors or indirectly stimulate growth factors in the ulcer bed.
- Pentoxifylline (800 mg tid) has been shown to be an effective adjuvant to compression therapy as reported in a meta-analysis of nine clinical trials.
- Skin grafting should be considered for large or refractory ulcers as long as the wound is clean and there is healthy granulation tissue.

- Published randomized clinical trials on the value of the different types of dressings in the management of leg ulcers have not shown effects on ulcer healing. Despite the lack of evidence to support their use, modern dressings remain a part of the standard of care. Decisions regarding their use should be based on local cost of the dressings and the physician's clinical experience.
- Trials involving the use of weekly, low-dose, high-frequency ultrasound for hard-to-heal venous leg ulcers do not support adding therapeutic ultrasound to standard care for venous leg ulcers.

DISPOSITION

The overall prognosis for this condition is poor; the healing rate depends on the initial size of the ulcer. Although 65% to 70% of venous ulcers are healed within 6 mo, the 5-yr recurrence rate of healed venous ulcers can be as high as 40%. Maintenance of lifelong compression therapy is recommended.

REFERRAL

All patients should be evaluated weekly during the first month of therapy. Nonhealing ulcers with little to no improvement should also be referred to a wound care clinic.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **FRANK G. FORT, M.D.**

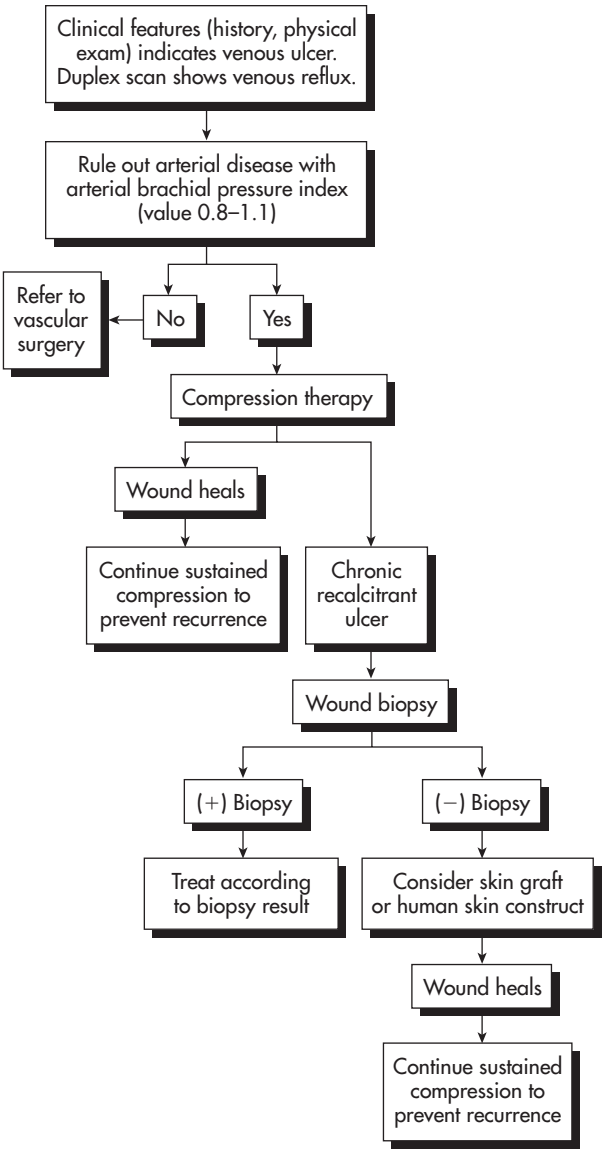


FIGURE V1-19 Scheme for treatment of venous ulcer. (From *Venous Stasis Ulcers; Conn's Current Therapy,* St Louis 2008; Elsevier.)

EVIDENCE

Abstract[1]

Background:
To assess the clinical effectiveness of weekly delivery of low-dose, high-frequency therapeutic ultrasound in conjunction with standard care for hard to heal venous leg ulcers.

Design:
Multicentre, pragmatic, two arm randomised controlled trial.

Setting:
Community and district nurse led services, community leg ulcer clinics, and hospital outpatient leg ulcer clinics in 12 urban and rural settings (11 in the United Kingdom and one in the Republic of Ireland).

Participants:
337 patients with at least one venous leg ulcer of >6 months' duration or >5 cm2 area and an ankle brachial pressure index of ≥0.8.

Interventions:
Weekly administration of low-dose, high-frequency ultrasound therapy (0.5W/cm^2, 1MHz, pulsed pattern of 1:4) for up to 12 weeks plus standard care compared with standard care alone.

Main Outcome Measures:
Primary outcome was time to healing of the largest eligible leg ulcer. Secondary outcomes were proportion of patients healed by 12 months, percentage and absolute change in ulcer size, proportion of time participants were ulcer-free, health related quality of life, and adverse events.

Results:
The two groups showed no significant difference in the time to healing of the reference leg ulcer (log rank test, P = 0.61). After adjustment for baseline ulcer area, baseline ulcer duration, use of compression bandaging, and study centre, there was still no evidence of a difference in time to healing (hazard ratio 0.99 (95% confidence interval 0.70 to 1.40), P = 0.97). The median time to healing of the reference leg ulcer was inestimable. There was no significant difference between groups in the proportion of participants with all ulcers healed by 12 months (72/168 in ultrasound group v 78/169 in standard care group, P = 0.39 for Fisher's exact test) nor in the change in ulcer size at four weeks by treatment group (model estimate 0.05 (95% CI −0.09 to 0.19)). There was no difference in time to complete healing of all ulcers (log rank test, P = 0.61), with median time to healing of 328 days (95% CI 235 to inestimable) with standard care and 365 days (224 days to inestimable) with ultrasound. There was no evidence of a difference in rates of recurrence of healed ulcers (17/31 with ultrasound v 14/31 with standard care, P = 0.68 for Fisher's exact test). There was no difference between the two groups in health-related quality of life, both for the physical component score (model estimate 0.69 (−1.79 to 3.08)) and the mental component score (model estimate −0.93 (−3.30 to 1.44)), but there were significantly more adverse events in the ultrasound group (model estimate 0.30 (0.01 to 0.60)). There was a significant relation between time to ulcer healing and baseline ulcer area (hazard ratio 0.64 (0.55 to 0.75)) and baseline ulcer duration (hazard ratio 0.59 (0.50 to 0.71)), with larger and older ulcers taking longer to heal. In addition, those centres with high recruitment rates had the highest healing rates.

Conclusions:
Low-dose, high-frequency ultrasound administered weekly for 12 weeks during dressing changes in addition to standard care did not increase ulcer healing rates, affect quality of life, or reduce ulcer recurrence. Ⓐ

Evidence-Based Reference

Watson JM: on behalf of the VenUS III Team. Use of weekly, low dose, high frequency ultrasound for hard to heal venous leg ulcers: the VenUS III randomised controlled trial, *BMJ* 342:d1092, 2011. Ⓐ

SUGGESTED READINGS

Beebe-Dimmer JL et al.: The epidemiology of chronic venous insufficiency and varicose veins, *Ann Epidemiol* 15:175–184, 2005.

Collins L, Seraj S: Diagnosis and treatment of venous ulcers, *Am Fam Physician* 81(8):989–996, 2010.

Goldman MP, Fronek A: The Alexander House Group: consensus paper on venous leg ulcer, *J Dermatol Surg Oncol* 18:592–602, 1992.

O'Donnell TF Jr: Venous ulcers: what really works and what does not; based on level I evidence, *Vascular* 13:513–516, 2005.

Raju S, Neglen P: Chronic venous insufficiency and varicose veins, *N Engl J Med* 360:2319–2327, 2009.

Simon DA et al.: Management of venous leg ulcers, *BMJ* 328:1358–1362, 2004.

Watson JM et al.: Use of weekly, low-dose, high-frequency ultrasound for hard to heal venous ulcers: the VenUS III randomized controlled trial, *BMJ* 342:d1092, 2011.

BASIC INFORMATION

DEFINITION

- *Ventricular septal defect* (VSD) refers to an abnormal communication through the septum that separates the right and left ventricles of the heart.
- VSDs may be large or small, single or multiple.
- VSDs are located at various anatomic regions of the septum and classified as follows:
  - Membranous (75% to 80%): This is the most common type of defect, and it extends into the membranous portion of the interventricular septum. The septal leaflet of the tricuspid valve may become adherent and form a "pouch" of the septum that can limit the left-to-right shunting and lead to self-closure.
  - Muscular or trabecular (5% to 20%): This defect is entirely surrounded by muscular tissue. Spontaneous closure is common.
  - Canal or inlet (8%): This defect commonly lies beneath the septal leaflet of the tricuspid valve; associated with Down syndrome.
  - Subarterial, outlet, infundibular, or supracristal (5% to 7%): This is the least common type of defect. It is usually found beneath the aortic valve, and it may lead to aortic regurgitation. High prevalence in Asian population.

SYNONYMS

VSD

ICD-9CM CODES
745.4 Ventricular septal defect
ICD-10 CODES
Q21.0 Ventricular septal defect

EPIDEMIOLOGY & DEMOGRAPHICS

- VSDs are one of the most common congenital heart abnormalities, accounting for 30% of all congenital cardiac defects.
- VSD accounts for ~25% of all congenital heart defects in children and for approximately 10% of defects in adults (the decrease is a result of spontaneous closure that occurs by adulthood).
- The prevalence of VSD is 3 to 3.5 infants per 1000 live births and 0.5/1000 adults.
- VSD is found with equal frequency among both males and females.
- VSD may be associated with the following conditions:
  - Atrial septal defect (35%)
  - Patent ductus arteriosus (22%)
  - Coarctation of the aorta (17%)
  - Subvalvular aortic stenosis (4%)
  - Subpulmonic stenosis, usually associated with progressive aortic regurgitation caused by prolapse of the aortic cusp through the defect
- Multiple VSDs are more prevalent among patients with tetralogy of Fallot and double-outlet right ventricular defects.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Clinical presentation depends on the direction and volume of the VSD shunt, which is dictated by the size of the defect and the ratio of the pulmonary vascular resistance. Fig. V1-20 illustrates the physiology of VSD.
  - Defects of ≤25% of the aortic annulus diameter are small defects. These typically involve small left-to-right shunts, no left ventricular volume overload, and no pulmonary artery hypertension (PAH).
  - Defects that are 25% to 75% of aortic annulus diameter are considered to be moderate in size. Small to moderate left-to-right shunting, mild to moderate left ventricular volume overload, and mild or no pulmonary artery hypertension are seen. Patients may have symptoms of congestive heart failure that may improve with medical therapy or with age as the defect decreases in size relative to increasing body size.
  - Defects of ≥75% of the aortic annulus diameter usually have moderate to large left-to-right shunting, left ventricular volume overload, and pulmonary artery hypertension. These patients usually have a history of congestive heart failure, or they may possibly develop right-to-left shunting in the setting of Eisenmenger's syndrome during late childhood, adolescence, or young adulthood.
- Infants may be asymptomatic at birth because of elevated pulmonary artery resistance. During the first few weeks of life, pulmonary arterial resistance decreases, thereby allowing for more left-to-right shunting through the VSD. This results in a subsequent increase in flow into the lungs, the left atrium, and the left ventricle, which can potentially cause left ventricular volume overload. Tachypnea, failure to thrive, and congestive heart failure may then ensue.
- In adults with VSD, the shunt is left to right in the absence of pulmonary stenosis and pulmonary hypertension. Patients typically manifest symptoms of left-sided heart failure from left ventricular volume overload (e.g., shortness of breath, orthopnea, dyspnea on exertion).
- A spectrum of physical findings may be seen, including the following:
  - Machinelike holosystolic murmur that is heard best along the left sternal border
  - Murmur becomes shorter as right heart pressures increase
  - Systolic thrill
  - Mid-diastolic rumble heard at the apex
  - S_3 heart sound
  - Rales
- With the development of pulmonary hypertension, the following occur:
  - An augmented pulmonic component of the S_2 heart sound
  - Cyanosis, clubbing, right ventricular heave, and signs of right heart failure (i.e., as seen with Eisenmenger's complex, with a reversal of the shunt in a right-to-left direction)

ETIOLOGY

- VSD is usually congenital but can be acquired.
- Acquired VSD may result from postsurgical residual leak, trauma, or myocardial infarction.
- Postinfarct ventricular septal defect (PIVSD) typically occurs 1 to 5 days after the event in 0.2% of patients in the current fibrinolytic, primary angioplasty era.

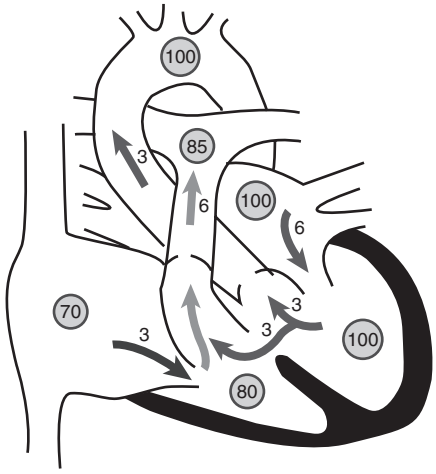


FIGURE V1-20 Physiology of a large ventricular septal defect (VSD). Circled numbers represent oxygen saturation values. The numbers next to the arrows represent volumes of blood flow (in L/min/m^2). This illustration shows a hypothetical patient with a pulmonary-to-systemic blood flow ratio (Qp:Qs) of 2:1. Desaturated blood enters the right atrium from the vena cava at a volume of 3 L/min/m^2 and flows across the tricuspid valve. An additional 3 L of blood shunts left to right across the VSD, the result being an increase in oxygen saturation in the right ventricle. Six liters of blood is ejected into the lungs. Pulmonary arterial saturation may be further increased because of incomplete mixing at right ventricular level. Six liters returns to the left atrium, crosses the mitral valve, and causes a mid-diastolic flow rumble. Three liters of this volume shunts left to right across the VSD, and 3 L is ejected into the ascending aorta (normal cardiac output). (From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.)

Dx DIAGNOSIS

The diagnosis of VSD can be suspected during a physical examination. Imaging studies—particularly transthoracic echocardiography with color Doppler—establish the diagnosis.

DIFFERENTIAL DIAGNOSIS

On the basis of the physical examination alone, the diagnosis of VSD may be confused with other causes of systolic murmurs, such as mitral regurgitation, tricuspid regurgitation, aortic stenosis, pulmonary stenosis, and hypertrophic cardiomyopathy.

WORKUP

Any person who is suspected of having a VSD should undergo an ECG, a chest radiograph, and an echocardiogram.

LABORATORY TESTS

- Laboratory tests are not specific but may offer insight into the severity of the disease.
- The CBC may show polycythemia, especially in patients with Eisenmenger's complex.
- Arterial blood gas results may demonstrate hypoxemia.

IMAGING STUDIES

- ECG findings vary in accordance with the size of the VSD and depending on whether pulmonary hypertension is present. With large VSDs with pulmonary hypertension, right-axis deviation is seen, along with evidence of right ventricular hypertrophy.
- Chest x-ray findings in patients with VSD include the following:
  - Cardiomegaly that results from left ventricular volume overload that directly relates to the magnitude of the shunt
  - The enlargement of the proximal pulmonary arteries along with the redistribution and pruning of the distal pulmonary vessels as a result of sustained pulmonary hypertension (Fig. V1-21*A*)
- Echocardiography is the imaging modality of choice for the diagnosis of VSD:
  - Two-dimensional echocardiography and color Doppler display the size and location of the VSD (Fig. V1-21*B*), the chamber sizes, ventricular function, the presence of aortic valve prolapse or regurgitation, outflow tract obstruction, and the presence of tricuspid regurgitation.
  - Continuous-wave Doppler approximates the gradient between the left and right ventricles and estimates the pulmonary artery pressure.
  - The magnitude of the shunt can be determined by the calculation of the pulmonary-to-systemic flow ratio with the use of echocardiography.
- Heart catheterization is primarily indicated to assess operability of VSD patients with PAH based on their pulmonary vascular resistance (PVR), and in patients in whom the noninvasive testing was inconclusive, and further information, such as quantification of shunting and assessment of pulmonary pressures, is required.
- Ventriculography may help to locate the VSD:
  - MRI and computed tomography scanning can be useful to assess the pulmonary artery, the pulmonary vein, and the aortic anatomy and to confirm the anatomy of unusual VSDs (e.g., inlet or apical defects) that are not seen well with echocardiography.

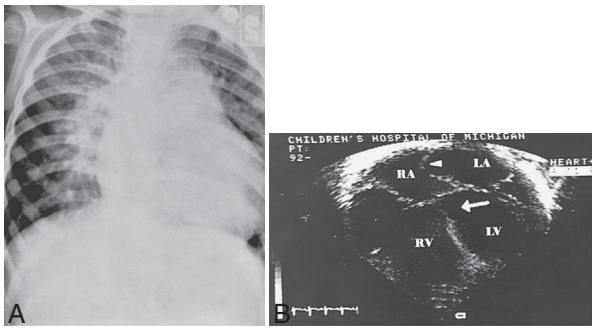


FIGURE V1-21 A, Chest roentgenogram of a child with a large ventricular septal defect, large pulmonary blood flow, and pulmonary hypertension but only mild elevation of peripheral vascular resistance. This is reflected in the evidence of left and right ventricular enlargement, the enlargement of the main pulmonary artery, and a marked increase in pulmonary blood flow. **B,** Apical four-chamber echocardiographic view of ventricular septal defect *(large arrow).* The small arrow points to the interatrial septum. *LA,* Left atrium; *LV,* left ventricle; *RA,* right atrium; *RV,* right ventricle. (**A** from Pacifico AD et al: Surgical treatment of ventricular septal defect. In Sabiston DC Jr, Spencer FC [eds]: *Surgery of the chest,* ed 5, Philadelphia, 1990, Saunders. **B** courtesy of Richard Humes, M.D., Children's Hospital of Michigan, Detroit.)

Rx TREATMENT

The decision to close a VSD depends on the type, size, and shunt severity as well as the patient's pulmonary vascular resistance, functional capacity, and associated valvular abnormalities.

NONPHARMACOLOGIC THERAPY

- Young children and adults with a small, asymptomatic VSD with a large left-to-right ventricular pressure gradient, a pulmonary-to-systemic blood flow ratio of less than 1.5:1, and no evidence of pulmonary hypertension can be observed (i.e., restrictive defect).
- Oxygen for hypoxemia and a low-salt diet are recommended for patients with congestive heart failure.

ACUTE GENERAL & CHRONIC Rx

Closure of the VSD is indicated for the following patients:

- Infants with congestive heart failure. Unrestrictive VSDs require surgical intervention within the first 2 yr of life to prevent pulmonary hypertension.
- Children between the ages of 1 and 6 yr with persistent VSD and a pulmonary-to-systemic blood flow ratio (Qp/Qs) of >2:1
- Adults with a Qp/Qs of ≥2 and clinical evidence of left ventricular volume overload (class I):
  - Positive history of infective endocarditis (IE) (class I)
  - Adults with a Qp/Qs of >1.5 with pulmonary artery pressure that is less than two thirds of the systemic pressure and pulmonary vascular resistance that is less than two thirds of the systemic vascular resistance (class IIa)
  - Adults with a Qp/Qs of >1.5 in the presence of left ventricular systolic or diastolic failure (class IIa)
  - Surgical closure is not indicated for VSD with severe irreversible PAH with high PVR.
  - Although the exact PVR at which a child with VSD and pulmonary arterial hypertension is considered inoperable has not been determined, the consensus is that a PVR of <4 wood units is considered optimal. PVR between 4-8 wood units is considered on a case-by-case basis. There are no definitive guidelines on the use of vasoreactivity as a preoperative predictor, though >20% decrease in PVR during vasodilator testing is considered a positive response.

Surgical closure with Dacron or Gore-Tex patches or primary surgical closure has long been the gold standard of therapy. It has low operative mortality (<2%) at experienced centers. However, surgery still carries a small risk of complete heart block (CHB), postpericardiotomy syndrome, wound infection, and neurologic sequelae related to cardiopulmonary bypass. Over the last two decades, the transcatheter approach to VSD closure has improved considerably and is becoming an increasingly accepted modality of treatment for appropriately selected patients. Some studies have shown similar success rates for both surgical and percutaneous closures, and there are significantly fewer complications, days in the hospital, and blood transfusions after percutaneous closures.

Catheter-based closure in muscular VSD may be considered, especially if the VSD is remote from the tricuspid valve and the aorta, if the VSD is associated with severe left-sided heart chamber enlargement, or if there is PAH (class IIb). Device closure is indicated in residual defects after prior attempts at surgical closure, restrictive VSDs with either a significant left-to-right shunt (Qp/Qs >1.5:1) or hx of IE, trauma, or iatrogenic artifacts after surgical replacement of the aortic valve.

Surgery still remains the treatment of choice in patients with large defects, coexistent

congenital anomalies requiring surgical correction, and defects with close proximity to the aortic valve. Sub-pulmonic VSDs may require surgery due to the increased risk of aortic valve prolapse. Perimembranous VSD with more than trivial aortic regurgitation should be referred to surgery. PIVSDs usually carry a high mortality rate, and surgical closure remains the gold standard in the acute setting or for large (>15 mm) septal ruptures. In the subacute or chronic setting, small or medium PIVSD (<15 mm) can be treated with percutaneous closure with comparable mortality to surgery. VSDs post myocardial infarction generally arise within 1 wk of the acute event. Surgical management within 10 d has better outcomes than waiting for cardiac stabilization.

DISPOSITION

- The natural history of an isolated VSD depends on the type of defect, its size, and any associated abnormalities.
- ~75% to 80% of small VSDs close spontaneously by the time the patient reaches the age of 10 yr.
- Only 10% to 15% of large VSDs will close spontaneously.
- Large VSDs that are left untreated may lead to arrhythmias, congestive heart failure, pulmonary hypertension, and Eisenmenger's complex.
- Eisenmenger's complex carries a poor prognosis, with most patients dying before the age of 40 yr.
- Issues to monitor in adults with unrepaired or repaired and catheter-closed VSDs include the following:
  1. Development of aortic regurgitation
  2. Assessment of associated coronary artery disease
  3. Development of tricuspid regurgitation
  4. Assessment of the degree of left-to-right shunting (in unrepaired or residual VSD after repair)
  5. Ventricular dysfunction
  6. Assessment of pulmonary pressure
  7. Development of subpulmonary stenosis (usually as a result of a double-chambered right ventricle)
  8. Development of discrete subaortic stenosis
  9. Development of arrhythmia or heart block
  10. Thromboembolic complications
  11. Infective endocarditis
- After closure, late survival is excellent when ventricular function is normal. Pulmonary artery hypertension may improve, progress, or remain the same. Late operations may be required for tricuspid or aortic regurgitation.

REFERRAL

All infants and children diagnosed with VSD should be referred to a pediatric cardiologist. Adults with VSD should be referred to an adult cardiologist. Cardiothoracic surgeons who have experience with congenital heart disease surgery should be consulted if surgery is indicated.

FOLLOW-UP

- Adults with no residual VSD, no associated lesions, and normal pulmonary artery pressure do not require continued follow-up at a regional adult congenital heart disease (ACHD) center except on referral from the patient's cardiologist or physician.
- Adults with VSD with residual heart failure, shunts, PAH, AR, or RV outflow tract (RVOT) or LV outflow tract (LVOT) obstruction should be seen at least annually at an ACHD regional center (level of evidence: C).
- Adults with a small residual VSD and no other lesions should be seen every 3 to 5 yr at an ACHD regional center (level of evidence: C).
- Adults with device closure of a VSD should be followed up every 1 to 2 yr at an ACHD center depending on the location of the VSD and other factors.
- Patients who develop bifascicular block or transient trifascicular block after VSD closure are at risk in later years for the development of complete heart block and should be followed up yearly by history and ECG and have periodic ambulatory monitoring and/or exercise testing.

PEARLS & CONSIDERATIONS

COMMENTS

- A loud murmur does not imply a large VSD. Small, hemodynamically insignificant VSDs can cause loud murmurs.
- In patients with Eisenmenger's complex, the right-to-left shunting across the VSD is usually not associated with an audible murmur.
- The risk of patients with unrepaired VSD developing infective endocarditis is 4%. The risk is higher if aortic insufficiency is present.
- For patients with endocarditis, routine antibiotic prophylaxis for dental or surgical procedures is no longer indicated for isolated VSDs, except in the following circumstances:
  1. In the presence of complex congenital heart disease with cyanosis
  2. In the presence of a residual VSD after surgical closure
  3. During the first 6 mo after surgical patch or percutaneous transcatheter closure
- Any patient with a newly diagnosed murmur or hemodynamic compromise after a myocardial infarction should undergo evaluation for possible VSD.
- Pregnancy with a VSD is generally well tolerated in women with small VSDs, no pulmonary artery hypertension, and no associated lesions. Women with large shunts may experience arrhythmias, ventricular dysfunction, and the progression of pulmonary hypertension.
  1. Maternal use of valproic acid and phenytoin has also been suggested to cause structural defects.
- Women with VSDs and severe pulmonary artery hypertension or Eisenmenger's physiology should be counseled against pregnancy because of associated excessive maternal and fetal mortality.
  1. Small perimembranous VSDs (without left heart dilatation) and corrected VSDs have a good prognosis during pregnancy, when LV function is preserved. Prepregnancy evaluation of the presence of a (residual) defect, cardiac dimensions, and an estimation of pulmonary pressures is recommended. Pre-eclampsia may occur more often than in the normal population. Usually follow-up twice during pregnancy is sufficient, and spontaneous vaginal delivery is appropriate.
- Minimally invasive periventricular device closure of VSD without cardiopulmonary bypass under guidance of transesophageal echocardiography is a promising technique, but it needs long-term follow-up.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Ventricular Septal Defect (VSD) (Patient Information)

AUTHOR: **RABIA ARSHAD, M.D.**

SUGGESTED READINGS

Attia R et al.: Which patients might be suitable for a septal occluder device closure of postinfarction ventricular septal rupture rather than immediate surgery? *Interact Cardiovasc Thorac Surg* 11:626–629, 2010.

Butera G et al.: Percutaneous closure of ventricular septal defects. State of the art, *J Cardiovasc Med* 8(1):39–45, 2007.

Lopes AA et al.: Repair of Congenital Heart Disease with associated Pulmonary Hypertension in children, *Pulm Circ* 4(2):330–341, 2014.

Minette MS, Sahn DJ: Ventricular septal defects, *Circulation* 114(20):2190, 2006.

Penny DJ et al.: Ventricular septal defect, *Lancet* 9771(377):1103–1112, 2011.

Rosario MD et al.: Role of percutaneous interventions in adult congenital heart disease, *J Invasive Cardiol* 20(12):671–679, 2008.

Warnes CA et al.: ACC/AHA 2008 guidelines for the management of adults with congenital heart disease, *J Am Coll Cardiol* 52(23):e143–e263, 2008.

Wilson W et al.: Prevention of infective endocarditis, *Guidelines from the American Heart Association, Circulation* 115:739, 2007.

Zheng Q et al.: A comparative study: early results and complications of percutaneous and surgical closure of ventricular septal defect, *Cardiology* 114(4):238–243, 2009.

BASIC INFORMATION

DEFINITION

Ventricular tachycardia (VT) can be classified based on time (duration) or morphology.

Nonsustained ventricular tachycardia (NSVT) is defined as beats originating from the ventricle, lasting from 3 to 30 seconds or for <30 seconds, at a rate >100/min.

Sustained ventricular tachycardia is defined as above but lasts >30 seconds or produces symptoms in the patient and/or requires early intervention due to hemodynamic embarrassment.

Ventricular tachycardia can be monomorphic or polymorphic (see Fig. V1-22), and the etiology, significance and treatment of these two types of VT are different.

SYNONYMS

- Nonsustained paroxysmal ventricular tachycardia (NSVT)
- Sustained ventricular tachycardia
- Ventricular tachycardia (VT)
- Ventricular tachycardia, monomorphic
- Ventricular tachycardia, nonsustained
- Ventricular tachycardia, paroxysmal
- Ventricular tachycardia, polymorphic
- Ventricular tachycardia, sustained

ICD-9CM CODES
427.1 Ventricular tachycardia
ICD-10CM CODES
I47.2 Ventricular tachycardia

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: The actual incidence and prevalence of VT in the general population is unknown. VT, especially NSVT, can be seen in both structurally normal and abnormal hearts, although it is far more common in the latter. In apparently healthy, asymptomatic individuals, the incidence is estimated at 0% to 3% (1).

For details on incidence of NSVT in various cardiac conditions, please refer to Table V1-7.

RISK FACTORS: The presence of structural heart disease is a strong risk factor for VT, but there are multiple, specific types of VT seen in patients without any structural heart disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Patients may be asymptomatic, or they may present with any combination of palpitations, dizziness, syncope, chest pain, shortness of breath, seizures. or even cardiac arrest.
- History of structural heart disease, especially coronary artery disease and a prior myocardial infarction, is a strong predictor of VT. Patents may also have a history of pacemaker or defibrillator implantation. A family history of sudden death must also be sought.
- Physical findings of AV dissociation may be seen by the astute observer. These include cannon A waves in the neck and variability in intensity of heart sounds. The patient may also present physical findings of congestive heart failure including an S3 gallop, pedal edema, or crackles at the lung bases.

Fig. EV1-23 shows initiation and termination of VT by means of programmed ventricular stimulation.

TABLE V1-7 Reported Prevalence of Nonsustained Ventricular Tachycardia in Different Cardiac Conditions

CONDITION	PREVALENCE
Apparently healthy individuals	0-3%
Non-ST ACS (2 to 9 days after admission)	18-25%
Acute MI (early phase)	45-75%
Reperfused acute MI (later than 1 week)	7-13%
Heart failure (LVEF <30-40%)	30-80%
DCM	40-50%
HCM	25-80%
Significant valve disease	≤25%
Hypertension	8%
Hypertension and left ventricular hypertrophy	12%-28%

DCM, Dilated cardiomyopathy; *HCM*, hypertrophic cardiomyopathy; *LVEF*, left ventricular ejection fraction; *MI*, myocardial infarction; *Non-ST ACS*, non–ST-segment elevation acute coronary syndrome.
From Saksena S et al.: *Electrophysiological disorders of the heart,* ed 2, Philadelphia, Elsevier (Table 43-1).

ETIOLOGY

Sustained monomorphic VT is mostly caused by re-entry around a scar in the ventricular wall. The scar is most commonly the result of an old myocardial infarction, but arrhythmogenic RV cardiomyopathy (ARVC), nonischemic dilated cardiomyopathy, sarcoidosis, Chagas disease, tuberculosis, surgical incisions for repair of congenital heart disease and ventricular volume reduction surgery can all cause scars in the myocardium. Fibrosis in the scar creates areas of anatomical conduction block, and fibrosis between surviving myocytes reduces cell-to-cell coupling, thereby distorting the path of propagation and causing areas of slow conduction, which promotes re-entry.

Monomorphic VT can also be seen in patients without any evidence of structural heart disease (idiopathic VT). This subgroup represents 10% of all patients with VT and includes RVOT VT and fascicular VT.

Polymorphic VT is usually the result of active myocardial ischemia, electrolyte abnormalities (hypokalemia, hypomagnesemia) or genetic conditions such as LQTS, BRS, and CPVT. It may also be seen in HCM, various types of nonischemic cardiomyopathy and idiopathic VF. The mechanisms are poorly understood but likely involve an initiating trigger that interacts with multiple rotors in the substrate to maintain the arrhythmia.

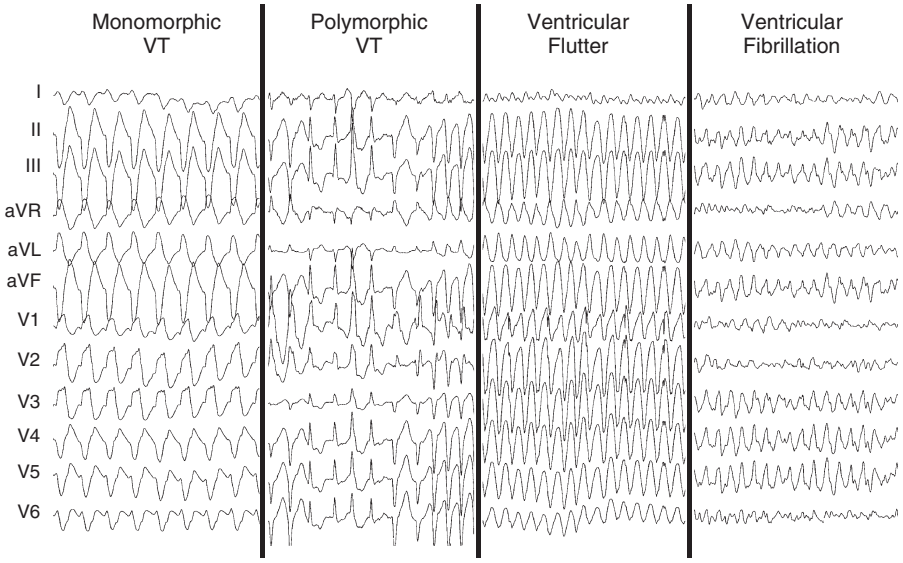


FIGURE V1-22 Surface ECG of different types of VT. (From Issa, Miller, Zipes [eds]; *Clinical Arhrhythmology and Electrophysiology,* ed 1, p. 405, Figure 18-1, Philadelphia, Saunders, Elsevier.)

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of an ECG suspicious of VT includes:

- SVT with aberrancy, either with a preexisting bundle branch block or a rate-related bundle branch block
- SVT in a patient taking anti-arrhythmic drugs, e.g., IA or IC agents
- Antidromic tachycardia from ventricular preexcitation
- Ventricular paced rhythms
- ECG artifact

The following ECG characteristics strongly favor VT as opposed to SVT: NW axis, QRS width >160 ms, AV dissociation, fusion beats, and

capture beats. The last three are highly specific for VT.

WORKUP

- Lab testing should especially focus on checking K and Mg levels.
- A full 12-lead ECG of the tachycardia should always be obtained, whenever possible, and compared to the ECG in sinus rhythm if there is any uncertainty about the diagnosis.
- This should be followed by an echocardiogram and ischemia evaluation with diagnostic coronary angiography and/or nuclear stress testing. An MRI of the heart is indicated if these tests are unable to establish the cause of the arrhythmia.

LABORATORY TESTS

- Potassium, magnesium
- Genetic testing should be reserved for specific situations, i.e., when there is a concern for genetically mediated conditions such as HCM, CPVT, or BRS

IMAGING STUDIES

An echocardiogram and ischemia evaluation with diagnostic coronary angiography and/or nuclear stress testing is recommended to rule out structural heart disease and ischemia. An MRI of the heart is indicated if these tests are unable to establish the cause of the arrhythmia, to rule out cardiomyopathies such as cardiac sarcoidosis, amyloid, LV noncompaction, arrhythmogenic right ventricular dysplasia, etc.

Rx TREATMENT

ACUTE GENERAL Rx

Patients with VT may become hemodynamically unstable very quickly. In such situations emergency synchronized cardioversion (or defibrillation for polymorphic rhythms) is needed. Those who subsequently become pulseless or unresponsive should be managed as per standard ACLS resuscitation protocols.

If the patient is hemodynamically stable, either IV amiodarone, lidocaine (especially if there is a suspicion of ongoing ischemia) or procainamide may be used. In the case of a patient with sustained monomorphic VT and a known structurally normal heart, IV beta blockers or calcium blockers may be used. It must be remembered that use of all these agents may be associated with hemodynamic deterioration and an external defibrillator must be made available at all times.

Electrolyte supplementation is essential if hypokalemia or hypomagnesemia is detected.

CHRONIC Rx

An implantable cardioverter-defibrillator (ICD) is indicated for all cases of monomorphic VT (in the absence of a successful ablation that eliminates all VT, which is usually possible only in patients with normal LVEF and stable VT), since it indicates the presence of a scar and risk of subsequent arrhythmias. For polymorphic VT, a reversible cause such as ischemia or electrolyte disturbances can sometimes be found, and an ICD may not be appropriate under these circumstances.

Chronic therapy with antiarrhythmic medications such as amiodarone, mexiletine or sotalol may be needed even after ICD implantation if the patient presents with multiple appropriate shocks. VT ablation, particularly if performed early after first appropriate ICD discharge, is also very effective in preventing further ICD discharges and is associated with improved acute and long-term outcomes.

DISPOSITION

Patients with sustained VT, either monomorphic or polymorphic, should always be managed in an intensive care unit due to the risk of degeneration to a hemodynamically unstable rhythm. An electrophysiologist must be consulted.

REFERRAL

All patients with VT or NSVT should be referred to a cardiologist or a cardiac electrophysiologist.

PEARLS & CONSIDERATIONS

COMMENTS

- Use of antiarrhythmic drugs especially IC agents to treat NSVT is associated with increased mortality (CAST trial), while beta blockers have been shown to be helpful.
- In patients with coronary disease, NSVT has not been shown to have an adverse significance if LVEF is >40%. If the EF is below 40%, the MUSTT trial showed a benefit of EP-guided ICD therapy over antiarrhythmic agents such as mexiletine, propafenone, sotalol, or amiodarone. Patients with LVEF <35% are candidates for prophylactic ICD implantation based on the MADIT II and SCDHeFt trials.
- In hypertrophic cardiomyopathy, NSVT does seem to confer an increased risk of sudden death, especially if symptomatic, prolonged, or repetitive.
- There are certain conditions in which NSVT does not seem to have an adverse significance and does not predict sudden cardiac death. These include nonischemic dilated cardiomyopathy, mitral valve prolapse, mitral regurgitation, and absence of structural heart disease.

PATIENT/FAMILY EDUCATION

Patients with familial or genetic causes of ventricular tachycardia, should have family screening of first degree relatives.

RELATED TOPICS

Arrhythmogenic Right Ventricular Dysplasia (Related Key Topic)
Brugada Syndrome (Related Key Topic)
Long QT Syndrome (Related Key Topic)
Torsades de Pointes (Related Key Topic)

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **JOYDEEP GHOSH, M.D.**

SUGGESTED READINGS

Bardy G, Lee K, Mark D, et al.: Amiodarone or an implantable cardioverter defibrillator for congestive heart failure, *N Engl J Med* 352:225–237, 2005.

Bunch TJ, Weiss JP, Crandall BG, et al.: Patients treated with catheter ablation for ventricular tachycardia after an ICD shock have lower long term rates of death and heart failure hospitalization than do patients treated with medical management only, *Heart Rhythm* 11(4):533–540, 2014.

Buxton A, Lee K, DiCarlo L, et al.: Electrophysiologic testing to identify patients with coronary artery disease who are at risk for sudden death, *N Engl J Med* 342:1937–1945, 2000.

Echt DS, Liebson PR, Mitchell B, et al.: Mortality and morbidity in patients receiving encainide, flecainide or placebo – The Cardiac Arrhythmia Suppression Trial, *N Engl J Med* 324:781–788, 1991.

Issa, Miller, Zipes: Clinical Arrhythmology and Electrophysiology – Postinfarction sustained monomorphic ventricular tachycardia.

Moss A, Zareba W, Hall J, et al.: Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction, *N Engl J Med* 346:877–883, 2002.

Saksena S, Camm AJ, Boyden PA, Dorian P, Goldschlager N, Vetter VL, Zareba W: *Electrophysiological disorders of the heart*, ed 2, Philadelphia, Elsevier.

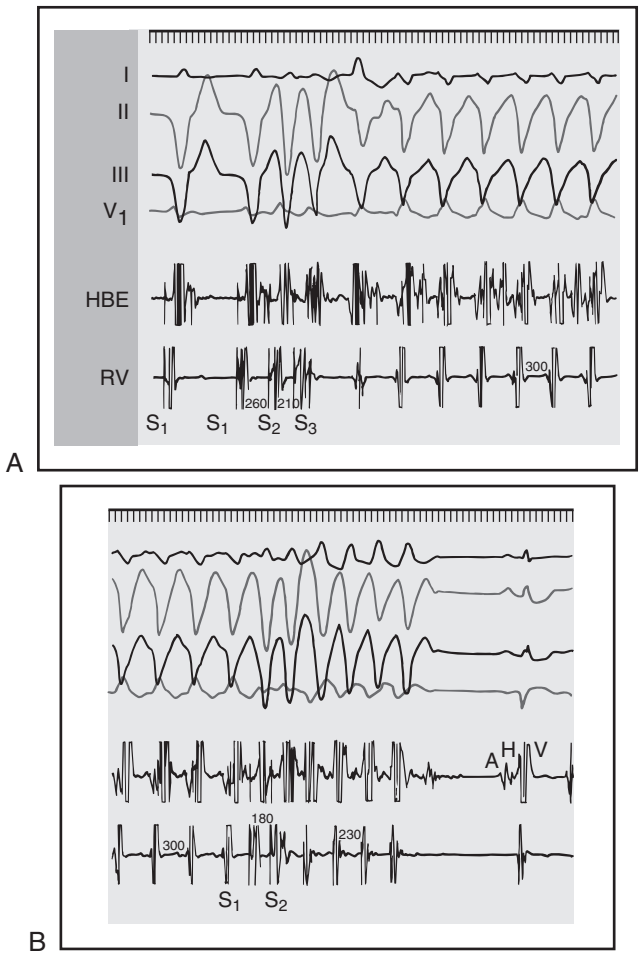


FIGURE EV1-23 Initiation and termination of VT by means of programmed ventricular stimulation. The last two ventricular paced beats at a cycle length of 600 milliseconds are shown in **(A)**. A premature stimulus (S_2) at an S_1–S_2 interval of 260 milliseconds and another premature stimulus (S_3) at a cycle length of 210 milliseconds initiate a sustained monomorphic VT at a cycle length of 300 milliseconds. **B,** Two premature ventricular stimuli (S_1–S_2) create an unstable VT that persists for several beats at a shorter cycle length (230 milliseconds) and then terminates, followed by sinus rhythm. *HBE*, His bundle electrogram; *RV*, right ventricle. (From Bonow R.O. et al: *Heart Disease,* ed 9. Philadelphia, 2012, Saunders.)

BASIC INFORMATION

DEFINITION

Vertebral compression fractures (VCFs) are defined as fractures of spinal vertebrae in which a bony surface is driven toward another bony surface. These fractures are classified as radiographic reductions in vertebral body height of more than 15%.

SYNONYMS

Thoracolumbar vertebral compression fractures
Osteoporotic fractures

ICD-9CM CODES

805.8	Compression fracture, spine
805.4N	Compression fracture, lumbar vertebra
805.2	Compression fracture, thoracic vertebra
733.13	Pathologic vertebral compression fracture; vertebral collapse; collapse of vertebra

ICD-10 CODES

M80.0	Post-menopausal osteoporosis with pathologic fracture
M80.4	Drug-induced osteoporosis with pathological fracture
M80.5	Idiopathic osteoporosis with pathological fracture
M80.8	Other osteoporosis with pathological fracture
M80.9	Unspecified osteoporosis with pathological fracture
S32.009A	Unspecified fracture of unspecified lumbar vertebra, initial encounter for closed fracture
S22.009A	Unspecified fracture of unspecified thoracic vertebra, initial encounter for closed fracture

EPIDEMIOLOGY & DEMOGRAPHICS

~700,000 VCFs occur in the United States each year, and they affect up to 25% of postmenopausal women. The prevalence increases with age, reaching a peak of 40% to 50% among women aged >80 yr. Compression fractures are also a major concern among men, although their rates of VCF are lower.

RISK FACTORS

- Modifiable: tobacco or alcohol use, osteoporosis, estrogen deficiency (i.e., early menopause, bilateral ovariectomy, premenopausal amenorrhea for >1 yr), frailty, impaired vision, abusive situations, inadequate physical activity, low body mass index, and dietary deficiency of vitamin D or calcium
- Nonmodifiable: advanced age, female gender, dementia, Caucasian, history of fractures in adulthood and among first-degree relatives, and falls

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Asymptomatic: Most VCFs are asymptomatic, except for height loss or kyphosis (i.e., dowager's hump [Fig. V1-24]), which is often a sign of multiple VCFs and height loss of >6 cm has a sensitivity/specificity of 94% and 30%, respectively, for VCF.
- Symptomatic: When symptomatic, VCFs usually present as acute back pain after activity (e.g., bending, lifting) or coughing; neck strain and radicular rib pain may also be present.

ETIOLOGY

- VCFs take place when the combination of bending and the axial load on the spine exceed the strength of the vertebral body.
- The primary etiology of VCF is osteoporosis, though a pathologic fracture from an underlying malignancy, typically metastatic disease, must be ruled out.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Osteoporosis
- Malignancy, most often metastases
- Hyperparathyroidism
- Osteomalacia
- Granulomatous diseases (e.g., tuberculosis)
- Hematologic/oncologic diseases (e.g., multiple myeloma, primary bone malignancy)

WORKUP

- Only one third of VCFs are diagnosed. Guidelines for patient selection for vertebral fractural assessment are described in Box V1-1.
- VCFs can be clinically suspected from the history and physical alone, though they are often diagnosed incidentally by imaging performed for another indication.
- There may or may not be a specific injury or a remembered event that led to the VCF.

LABORATORY TESTS

Tests to rule out infection or cancer may be helpful, such as a CBC, an erythrocyte sedimentation rate, an alkaline phosphatase level, and a C-reactive protein level; these tests can be reserved for individuals for whom there is clinical suspicion.

IMAGING STUDIES

- Plain frontal and lateral radiographs (x-rays) are the initial imaging method (Fig. V1-24) and may be sufficient, particularly when no neurologic abnormalities are present. MRI and computed tomography (CT) scans may be uncomfortable or painful for the patient, especially during the acute phase.
- Although CT scans are not routinely necessary for the diagnosis, they can be helpful for visualizing fractures that are not seen on plain films, for evaluating the integrity of the posterior vertebral wall, for ruling out other causes of back pain, for detecting spinal canal narrowing, and for assessing instability.
- MRI may be useful when spinal cord compression is suspected, if neurologic symptoms are present, or to distinguish malignancy from osteoporosis (e.g., in patients <55 yr with VCF after minimal or no trauma).

FIGURE V1-24 Dowager's hump. A, Marked thoracic kyphosis due to multiple osteoporotic fractures in an elderly woman with corresponding radiograph (**B**). (From Hochberg MC et al [eds]: *Rheumatology,* ed 3, St Louis, 2003, Mosby.)

- Bone density studies may be helpful to determine the severity of osteoporosis, which is a key risk factor for future fractures.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Physical therapy
- External back braces: Frequently recommended to relieve pain and improve mobility, however, controlled trials have not shown any effect in patients with vertebral compression fractures.
- Exercise programs: Getting active as soon as possible is extremely important for both short- and long-term recovery.

ACUTE GENERAL Rx

- Analgesics are first line for pain control, including acetaminophen and opioids (oral or parenteral), and pain can be expected to diminish over 4 to 6 wk.
- Nonsteroidal anti-inflammatory drugs are helpful but must be used with caution among elderly patients or when contraindicated.
- Muscle relaxants should be used judiciously because they have significant side effects, particularly in the elderly.
- Intranasal calcitonin (200 units once daily, alternating nostrils) has been shown in some small trials to hasten relief from pain when used as an adjunct to oral analgesics, and a 2- to 4-wk course may be useful for patients who do not achieve adequate control with oral analgesics alone.
- Early mobilization with physical therapy is important for recovery and prevention of subsequent fractures.
- The efficacy of vertebroplasty versus kyphoplasty versus conservative treatment remains controversial.
- Percutaneous vertebroplasty involves the injection of acrylic bone cement into the affected vertebral body in an effort to stabilize the fracture and reduce pain, whereas in kyphoplasty, a high-pressure inflatable bone tamp or balloon is expanded within the body of the affected vertebra to restore prefracture vertebral height before the injection of bone cement. These two procedures were thought to be helpful in patients who did not respond to conservative therapy; however, further studies showed them to be no more effective than sham procedures (Buchbinder et al., 2009; Kallmes et al., 2009). Nonetheless, Klazen et al. (2010) demonstrated in an open-label prospective randomized trial that for the subgroup of patients with acute osteoporotic VCFs fractures and persistent pain, percutaneous vertebroplasty may provide immediate pain relief, sustained for at least a year, which may be significantly greater than that achieved with conservative treatment. Zampiri (2011) showed in a nonrandomized cohort study that elderly patients who underwent kyphoplasty were more likely to be discharged home. McCullough et al. (2013) analyzed Medicare claims of patients with VCF treated with kyphoplasty or vertebroplasty compared with medical management and found no difference in mortality or major medical outcomes but decreased health care utilization in the conservatively managed group. These procedures are still in their infancy, and more answers should be forthcoming as to their efficacy, as well as questions regarding the amount of time that conservative therapy alone should be pursued and which procedure, if any, should be advised. Most current guidelines recommend 4 to 6 wk of medical therapy before pursuing surgical intervention in neurologically intact VCF.

CHRONIC Rx

Osteoporosis should be treated with the reduction of risk factors (e.g., smoking, alcohol), diet, exercise, calcium and vitamin D supplements, and with medications used to treat osteoporosis (e.g., bisphosphonates).

REFERRAL

Referral is indicated for neurologic abnormalities, unremitting pain, instability, continued disability, or when the investigation of the cause of the fracture reveals serious underlying pathology.

BOX V1-1 2007 ISCD Guidelines for Patient Selection for Vertebral Fractural Assessment

- Postmenopausal women with low bone mass (osteopenia) by BMD criteria, *plus* any one of the following: age >70 yr, historical height loss >4 cm (1.6 in), or prospective height loss >2 cm (0.8 in), self-reported vertebral fracture (not previously documented)
- Two or more of the following: age 60 to 69 yr, self-reported prior non-vertebral fracture, historical height loss of 2 to 4 cm, or chronic systemic diseases associated with increased risk of vertebral fractures (e.g., moderate to severe COPD or COAD, seropositive rheumatoid arthritis, Crohn's disease)
- Men with low bone mass (osteopenia) by BMD criteria, *plus* any one of the following: age >80 yr, historical height loss >6 cm (2.4 in), prospective height loss >3 cm (1.2 in), self-reported vertebral fracture (not previously documented)
- Two or more of the following: age 70 to 79 yr, self-reported prior non-vertebral fracture, historical height loss of 3 to 6 cm, on pharmacologic androgen deprivation therapy or following orchiectomy, chronic systemic diseases associated with increased risk of vertebral fractures (e.g., moderate to severe COPD or COAD, seropositive rheumatoid arthritis, Crohn's disease)
- Women or men on chronic glucocorticoid therapy (equivalent to 5 mg or more of prednisone daily for 3 mo or longer)
- Postmenopausal women or men with osteoporosis by BMD criteria, if documentation of one or more vertebral fractures will alter clinical management

BMD, Bone mineral density; *COAD,* chronic obstructive airways disease; *COPD,* chronic obstructive pulmonary disease; *ISCD,* International Society for Clinical Densitometry.
Reproduced with permission from the International Society for Clinical Densitometry.
From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.

PEARLS & CONSIDERATIONS

Prevention of osteoporosis and conservative therapy remain the mainstays of treatment.

COMMENTS

- VCFs should be suspected in anyone aged >50 yr with the acute onset of low back pain. There are many opportunities for diagnosis and treatment that are easy to miss, especially for males.
- Solitary vertebral fractures higher than T7 are unusual and should raise suspicion for other pathologic causes.
- Diagnosing and treating osteoporosis reduce the incidence of VCFs.
- Getting people with VCF physically active as soon as possible will be efficacious both acutely and in the long term.
- In general, VCF will be best managed through a partnership of the patient, the primary care physician, an orthopedist, a physical therapist, a dietitian, and a social worker.

PREVENTION

Reducing the effects of modifiable risk factors is key.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **THOMAS J.T. ANDERSON, M.D.**

EVIDENCE

Abstract[1]

Object:

Osteoporotic vertebral compression fractures (VCFs) are a major cause of increased morbidity in older patients. This randomized controlled trial compared the efficacy of percutaneous vertebroplasty (PV) versus optimal medical therapy (OMT) in controlling pain and improving the quality of life (QOL) in patients with VCFs. Efficacy was measured as the incidence of new vertebral fractures after PV, restoration of vertebral body height (VBH), and correction of deformity.

Methods:

Of 105 patients with acute osteoporotic VCFs, 82 were eligible for participation: 40 patients underwent PV and 42 received OMT. Primary outcomes were control of pain and improvement in QOL before treatment, and these were measured at 1 week and at 2, 6, 12, 24, and 36 months after the beginning of the treatment. Radiologic evaluation to measure VBH and sagittal index was performed before and after treatment in both groups and after 36 months of follow-up.

Results:

The authors found a statistically significant improvement in pain in the PV group compared with the OMT group at 1 week (difference –3.1, 95% CI –3.72 to –2.28; $p<0.001$). The QOL improved significantly in the PV group (difference –14, 95% CI –15 to –12.82; $p<0.028$). One week after PV, the average VBH restoration was 8 mm and the correction of deformity was 8°. The incidence of new fractures in the OMT group (13.3%) was higher than in the PV group (2.2%; $p<0.01$).

Conclusions:

The PV group had statistically significant improvements in visual analog scale and QOL scores maintained over 24 months, improved VBH maintained over 36 months, and fewer adjacent-level fractures compared with the OMT group.Ⓐ

Evidence-Based Reference

Farrokhi MR et al.: Randomized controlled trial of percutaneous vertebroplasty versus optimal medical management for the relief of pain and disability in acute osteoporotic vertebral compression fractures, *J Neurosurg Spine* 14:561–569, 2011. Ⓐ

SUGGESTED READINGS

Asenjo J-F, Rossel F: Vertebroplasty and kyphoplasty: new evidence adds heat to the debate, *Curr Opin Anaesthesiol* 25(5):577–583, 2012.

Brunton S et al.: Vertebral compression fractures in primary care: recommendations from a consensus panel, *J Fam Pract* 54(9):781–788, 2005.

Buchbinder R et al.: A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures, *N Engl J Med* 361:557–568, 2009.

Ensrud KE, Schousboe JT: Vertebral fractures, *N Engl J Med* 364:1634–1642, 2011.

Freedman BA et al.: Osteoporosis and vertebral compression fractures—continued missed opportunities, *Spine J* 8:756–762, 2008.

Kallmes DF et al.: A randomized trial of vertebroplasty for osteoporotic spinal fractures, *N Engl J Med* 361:569–579, 2009.

Klazen CA et al.: Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): an open-label randomised trial, *Lancet* 376:1085–1092, 2010.

McCullough et al.: Major medical outcomes with spinal augmentation vs conservative therapy, Intern Med ePub *JAMA*, 2013 Jul 8. PMID 23836009.

Wong CC et al.: Vertebral compression fractures: a review of current management and multimodal therapy, *J Multidiscip Healthc* 6:205–214, 2013.

Old JL, Calvert M: Vertebral compression fractures in the elderly, *Am Fam Physician* 69:111–116, 2004.

Zampini JM et al.: Comparison of 5766 vertebral compression fractures treated with or without kyphoplasty, *Clin Orthop Relat Res* 468(7):1773–1780, 2010.

Vestibular Neuronitis

BASIC INFORMATION

DEFINITION

Vestibular neuronitis is a syndrome of sudden-onset dysfunction of the peripheral vestibular system, often severe, with prolonged vertigo, nausea, and vomiting.

SYNONYMS

Vestibular neuritis
Acute neuritis
Neurolabyrinthitis
Vestibular neuropathy

ICD-9CM CODES
078.81 Vestibular neuronitis
386.12 Neuronitis, vestibular
ICD-10CM CODES
H81.2 Vestibular neuronitis
H81.8 Other disorders of vestibular function
H81.9 Disorder of vestibular function, unspecified
H81.23 Vestibular neuronitis, bilateral

EPIDEMIOLOGY & DEMOGRAPHICS

Vestibular neuritis is the second most common cause of peripheral vestibular vertigo with an incidence of about 3.5:100,000 population. Although etiology remains uncertain, thought to result from selective inflammation of the vestibular nerve, the etiology is presumed to be viral. Viral origin is supported by the fact that it occurs in epidemics, may affect several family members, and occurs more commonly in spring and early summer. The male-to-female ratio is nearly 1:1. There is selective damage to the superior part of the vestibular labyrinth, supplied by the superior vestibular portion of the eighth cranial nerve.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Course: develops, acutely, over period of hours and resolves over periods of days or weeks, although long-term sequelae may occur, such as residual imbalance and nonspecific dizziness persisting for months. Symptoms include vertigo, spontaneous peripheral nystagmus, positive head-thrust test, and imbalance. Patient reports intense sensation of rotation and difficulty standing and walking and tends to veer toward affected side; autonomic symptoms occur with pallor, sweating, nausea, and vomiting.

ETIOLOGY

Etiology remains uncertain. It is thought to be viral, or secondary to a post-viral inflammatory disorder, in origin, possibly due to herpes zoster, reactivation of herpes simplex, or other viruses, but evidence is circumstantial.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Labyrinthitis: similar symptoms of vertigo, with the addition of unilateral hearing loss
- Labyrinthine infarction
- Acoustic neuroma
- Perilymph fistula
- Brain stem and cerebellar infarction
- Migraine-associated vertigo
- Meniere disease
- Multiple sclerosis

WORKUP

- Patient may fall toward affected side when attempting ambulation or during Romberg tests.
- Hallpike maneuver: checking for nystagmus and asking about recreation of vertigo symptoms
- Head-thrust test: grasp patient's head, apply brief small-amplitude rapid head turn, first to one side and then the other; patient fixates on examiner's nose: positive test is lack of corrective eye movements ("saccades") on affected side. A postive test supports the diagnosis of vestibular neuronitis.
- Laboratory testing and imaging are generally not indicated but may help rule out other etiologies

LABORATORY TESTS

- Electronystagmography (ENG): a battery of eye movement tests that may provide an objective assessment of the vestibular and oculomotor systems and may help localize the lesion's site
- Audiogram: normal

IMAGING STUDIES

Brain imaging: CT or MRI—normal

TREATMENT

NONPHARMACOLOGIC THERAPY

Vestibular exercises, when tolerated, will accelerate recovery.

ACUTE GENERAL Rx

Most treatments are empirical and related to symptoms. Further studies are needed.

- Corticosteroids: corticosteroids are often prescribed, although a recent Cochrane Review finds that there is insufficient evidence for administration. Some studies have shown that glucocorticoids administered within 3 days after onset of vestibular neuronitis may improve long-time recovery of vestibular function and reduce the length of hospital stay and may improve the caloric extent and recovery of canal paresis.
- Antihistamines: e.g., meclizine, dimenhydrinate, promethazine
- Anticholinergics: scopolamine
- Antiemetics: droperidol, prochlorperazine
- Benzodiazepines: e.g., diazepam, valium, lorazepam
- Valacyclovir, either alone or in combination, is likely ineffective in treating vestibular neuronitis.

CHRONIC Rx

- Vestibular rehabilitation exercises
- Anti-GABA agents
- Antihistamines

DISPOSITION

Most patients can be treated as outpatients, but inpatient care may be required in cases where vomiting is uncontrollable. If dehydrated because of severe vomiting, sufferers may require brief parenteral therapy.

REFERRAL

- ENT: if diagnosis uncertain, and if these patients are at risk for benign paroxysmal positional vertigo (BPPV) subsequently; also if symptoms linger
- Neurology: if question of central origin or migraine

PEARLS & CONSIDERATIONS

COMMENTS

- Diagnosis unlikely to be vestibular neuronitis if hearing is impaired or other neurologic signs and symptoms are present.
- Although patients may recover from dramatic acute symptoms, subtle vestibular deficits may linger for prolonged period, if not indefinitely (i.e., residual imbalance and nonspecific dizziness).
- Program of vestibular habituation head movement exercises can reduce imbalance symptoms.

PATIENT & FAMILY EDUCATION

Vestibular Disorders Association: http://www.vestibular.org

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **ROCCO J. RICHARDS, M.D.**

SUGGESTED READINGS

Baloh RW: Vestibular neuritis, *N Engl J Med* 348:1027–1032, 2003.

Cohen HS, Kimball KT: Decreased ataxia and improved balance after vestibular rehabilitation, *Otolaryngol Head Neck Surg* 130(4):418–425, 2004.

Fishman JM et al.: Corticosteroids for the treatment of idiopathic acute vestibular dysfunction (vestibular neuritis), *Cochrane Database Syst Rev* 11(5):CD008607, 2011.

Goudakos JK et al.: Corticosteroids in the treatment of vestibular neuritis: a systematic review and meta-analysis, *Otol Neurotol* 31(2):183–189, 2010.

Karlberg ML, Magnusson M: Treatment of acute vestibular neuronitis with glucocorticoids, *Otol Neurotol* 32(7):1140–1143, 2011.

Strupp M et al.: Methylprednisolone, valacyclovir or the combination for vestibular neuritis, *N Engl J Med* 351(4):354–361, 2004.

BASIC INFORMATION

DEFINITION

Viral meningitis is an acute febrile illness with signs and symptoms of meningeal irritation, usually with a lymphocytic pleocytosis of the cerebrospinal fluid (CSF) and negative CSF bacterial stains and cultures.

SYNONYMS

Aseptic meningitis

ICD-9CM CODES
047.8 Meningitis, aseptic
ICD-10CM CODES
A87.8 Other viral meningitis
A87.9 Viral meningitis, unspecified
A87.2 Lymphocytic choriomeningitis

EPIDEMIOLOGY & DEMOGRAPHICS (Table V1-8)

INCIDENCE (IN U.S.): 11 cases/100,000 persons. Leads to 26,000 to 42,000 hospitalizations a year.
PREDOMINANT SEX: Male = female
GENETICS: Those with abnormal humoral immunity and agammaglobulinemia have associated difficulty with viral clearance.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Fever
- Headache
- Nuchal rigidity
- Photophobia
- Myalgias
- Vomiting
- Rash

ETIOLOGY

- Enterovirus: 85% to 95% of all cases. Most common are coxsackie viruses and echoviruses
- Parechoviruses
- Mumps virus
- Measles
- Arboviruses from mosquitoes: EEE, West Nile, St Louis
- Herpes: HSV-1, HSV-2, VZV, HHV-6, and HHV-7
- Acute HIV
- Lymphocytic choriomeningitis virus
- Adenovirus
- CMV and EBV
- Other arthropod-borne viruses: Powassan virus
- Influenza A and B virus

DIAGNOSIS

The diagnostic approach is similar to that for bacterial meningitis (see "Meningitis, Bacterial"); the foremost need is to rule out bacterial meningitis with CSF evaluation. Presentation may be similar to that of meningitis with bacterial involvement.

DIFFERENTIAL DIAGNOSIS

- Bacterial meningitis
- Meningitis secondary to Lyme disease, TB, syphilis, amebiasis, leptospirosis
- Rickettsial illnesses: Rocky Mountain spotted fever
- Migraine headache
- Medications
- SLE
- Acute mononucleosis/Epstein-Barr virus
- Seizures
- Carcinomatous meningitis

WORKUP

CSF examination:

- Usually shows pleocytosis
- Lymphocytic predominance (neutrophils in early stages)
- Opening pressure: 200 to 250 mm Hg
- WBC: 100 to 1000 mm^3
- Increased CSF protein
- Decreased or normal CSF glucose
- Negative Gram stain, cultures, CIE, latex agglutination
- Viral cultures or serologic testing may be diagnostic
- Polymerase chain reaction for HSV, West Nile, or enterovirus (which could shorten duration of antibiotic treatment and hospitalization if bacterial meningitis was suspected)

LABORATORY TESTS

CBC with differential, blood culturing, and CSF examination (see "Workup")

IMAGING STUDIES

CT scan or MRI: if cerebral edema, focal neurologic findings develop

TREATMENT

No specific antiviral therapy for most viruses. Treatment is supportive unless HSV is detected, which would be treated with IV acyclovir: 10 mg/kg q8h in adults for 14-21 days. Up to 20 mg/kg q8h in children >12 yr.

DISPOSITION

Viral meningitis is almost always an uncomplicated illness that will resolve; however, relapsing headache, myalgia, and weakness may occur for 2 to 3 wk after onset of symptoms.

PEARLS & CONSIDERATIONS

- Enteroviruses are the most common cause of viral meningitis and are transmitted by fecal-oral route and less commonly by the respiratory route. They are more common in summer and fall months. From 2000 to 2005, the most common serotypes were coxsackie viruses A9, B5, and B1 and echoviruses 6, 9, 13, 18, and 30.
- Herpes simplex type 2 (HSV-2) can be a cause of a primary episode of meningitis and also be a cause of recurrent episodes of lymphocytic meningitis. HSV-2 meningitis presents most often without a history of genital herpes or genital symptoms. Recurrent aseptic meningitis also known as Mollaret's disease is predominantly caused by HSV-2 infection.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Meningitis (Patient Information)

AUTHOR: **GLENN G. FORT, M.D., M.P.H.**

TABLE V1-8 Epidemiology of Acute Viral Meningitis

EPIDEMIOLOGIC FACTORS*				
Season	**Patient's Age (yr)**	**Patient's Sex**	**Risk Factor**	**Suggested Viral Agent**
Summer-fall	Infant	—	Infected mother	Coxsackievirus B
	1-15	—	Swimming pools, closed communities	Enteroviruses
			Geographic area: California, southeastern United States	California serogroup virus
Winter	1-15	—	School exposure	Varicella virus, measles virus
		Male/female 3:1		Mumps virus
	16-21	—	College exposure	Measles virus
		Male/female 3:1		Mumps virus
		—		Epstein-Barr virus (mononucleosis)
	Any	—	Mice, rats, hamsters	Lymphocytic choriomeningitis virus
	Adults	—	Varicella-zoster	Varicella-zoster virus
Any	Any	—	Immunocompromise	Adenovirus
		—	Acquired immunodeficiency syndrome	Human immunodeficiency virus

*Epidemiologic factors are suggestive but should not be used to exclude diagnoses in individual cases.
From Gorbach SI: *Infectious diseases,* ed 2, Philadelphia, 1998, Saunders.

SUGGESTED READINGS

Big C et al.: Viral infections of the central nervous system: a case-based review, *Clin Med Res* 7:142–146, 2009.

Ellerin TB et al.: Recurrent meningitis of unknown etiology, *Lancet* 363(9423):1772, 2004.

Landry M et al.: Herpes simplex type-2 meningitis: presentation and lack of standardized therapy, *Am J Med* 122:688–691, 2009.

BASIC INFORMATION

DEFINITION

Viral pneumonia is infection of the pulmonary parenchyma caused by any of a large number of viral agents. The most important viruses are discussed.

SYNONYMS

Nonbacterial pneumonia
Atypical pneumonia

ICD-9CM CODES
480.8 Viral pneumonia
487.0 Viral pneumonia due to influenza
ICD-10CM CODES
J12.9 Viral pneumonia, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE (IN U.S.)

- Influenza virus:
  1. 10% to 20% of population in temperate zones infected during 1-2 mo epidemics occurring yearly during winter months.
  2. Up to 50% infected during pandemics.
  3. Pneumonia develops in small percentage of infected persons.
- Incidence of other important viral pneumonias is not known precisely.

PEAK INCIDENCE

- Influenza:
  1. Winter months for influenza A
  2. Year round for influenza B
  3. Peak of pneumonia seen weeks into the outbreak of infection
- Respiratory syncytial virus (RSV) and parainfluenza virus:
  1. Winter and spring
- Adenovirus:
  1. Endemic (miliary)
- Varicella:
  1. Spring in temperate zones
- Measles:
  1. Year round
- Cytomegalovirus (CMV):
  1. Year round

PREVALENCE (IN U.S.)

- Often related to immune status of the population or presence of an epidemic
- Normal hosts (estimates):
  1. 86% of cases of pneumonia resulting in hospitalization in American adults
  2. 16% of pediatric pneumonias managed as outpatients
  3. 49% of hospitalized infants with pneumonia
- Important problem in hosts with impaired immunity

PREDOMINANT SEX

- None generally
- Male sex may predispose to more severe respiratory disease in RSV infection

PREDOMINANT AGE

- Influenza:
  1. Overall incidence greatest at age 5 yr
  2. Lower with increasing age
  3. The most serious sequelae in those with chronic medical illnesses, especially cardiopulmonary disease
  4. Hospitalizations greatest in infants and adults aged >64 yr
- RSV and parainfluenza virus:
  1. Young children (as the major cause of pneumonia)
  2. Occurs throughout life
- Adenoviruses:
  1. Young children
  2. Adults, primarily military recruits
- Varicella:
  1. Approximately 16% of adults (not infected in childhood) who contract chickenpox
  2. Acute varicella during pregnancy more likely to be complicated by severe pneumonia
  3. 90% of reported varicella pneumonia cases are in adults (highest incidence ages 20 to 60 yr)
- Measles:
  1. Young adults and older children who received a single vaccination (5% failure rate)
  2. Measles during pregnancy more likely to be complicated by pneumonia
  3. Underlying cardiopulmonary diseases and immunosuppression predispose to serious pneumonia complicating measles
  4. Before availability of measles vaccine, 90% of pneumonias in those <10 yr
  5. Currently more than one third of U.S. patients >14 yr
  6. 3% to 50% of measles cases are complicated by pneumonia
- CMV:
  1. Neonatal through adult
  2. Immunosuppression is key predisposing factor

GENETICS: Familial disposition:

- Close contact, not genetics, is important in acquisition
- Congenital anomalies and immunosuppression worsen course of RSV pneumonia

Congenital infection:

- CMV is the most common intrauterine infection in the U.S.
- Pneumonia occurs occasionally in infants with symptomatic congenital infection.

Neonatal infection:

- Severe RSV pneumonia
- Adenovirus pneumonia
  1. 5% to 20% mortality rate
  2. Can lead to residual restrictive or obstructive functional abnormalities
- "Varicella neonatorum"
  1. Disseminated visceral disease including pneumonia
  2. May develop in neonates whose mothers develop peripartum chickenpox
- CMV pneumonia
  1. Generally fatal
  2. Associated with severe cerebral damage in this population

PHYSICAL FINDINGS & CLINICAL PRESENTATION

1. Influenza:
   - Fever, cough, or sore throat (referred to as influenza-like illness [ILI])
   - Uncomfortable or lethargic appearance
   - Prominent dry cough (rarely hemoptysis)
   - Flushed integument and erythematous mucous membranes
   - Rales or rhonchi
2. RSV and parainfluenza:
   - Fever
   - Tachypnea
   - Prolonged expiration
   - Wheezes and rales
3. Adenoviruses:
   - Hoarseness
   - Pharyngitis
   - Tachypnea
   - Cervical adenitis
4. Measles:
   - Conjunctivitis
   - Rhinorrhea
   - Koplik's spots (white lesions on the buccal mucosa)
   - Exanthem (maculopapular rash that starts on the head, then moves down to rest of body)
   - Pneumonitis
     a. May occur as a complication in 3% to 4% of adolescents and young adults
     b. Coincident with rash
     c. May also develop after apparent recovery from measles
   - Fever
   - Dry cough
5. Varicella:
   - Fever
   - Maculopapular or vesicular rash (all lesions at the same stage)
     a. Becomes encrusted
     b. Pneumonia typical 1 to 6 days after rash appears
     c. Pneumonia (Fig. EV1-25) accompanied by cough and occasionally hemoptysis
   - Few auscultatory abnormalities noted on examination of the lungs
6. CMV:
   - Fever
   - Paroxysmal cough
   - Occasional hemoptysis
   - Diffuse adenopathy when pneumonia occurs after transfusion

ETIOLOGY

Viral infection can lead to pneumonia in both immunocompetent and immunocompromised hosts.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Bacterial pneumonia, which frequently complicates (i.e., can follow or be simultaneous with) viral pneumonia
- Other causes of atypical pneumonia:
  1. *Mycoplasma* spp.
  2. *Chlamydia* spp.
  3. *Coxiella* spp.
  4. Legionnaires' disease
- Acute respiratory distress syndrome (ARDS)
- Physical findings and associated hypoxemia confused with pulmonary emboli

WORKUP

- Information about the current prevalent strain of influenza virus can be obtained from local health departments or from the Centers for Disease Control and Prevention.
- Influenza and other viruses may be cultured from respiratory secretions during the initial few days of the illness (special media and techniques necessary).
- Respiratory viral panels that use PCR-based assays to test for a variety of viruses are extremely sensitive and are becoming the test of choice.
- Rapid flu tests have a 50% sensitivity in diagnosing influenza (a negative test does not mean the patient does not have influenza).
- Measles and adenovirus pneumonia are usually diagnosed clinically and can be confirmed with serology.
- CMV may be grown in culture or PCR amplified from bronchoalveolar lavage samples. An algorithm for the workup and management of suspected severe influenza pneumonia in the critical care unit is described in Fig. EV1-26. Open lung biopsy is required for a definite diagnosis of CMV pneumonia.

LABORATORY TESTS:

- Sputum Gram stain (usually produced in scanty amounts) typically shows few polymorphonuclear leukocytes and few bacteria.
- White blood cell count may vary from leukopenic to modest elevation, usually without a leftward shift.
- Disseminated intravascular coagulation occasionally complicates adenovirus type 7 pneumonia.
- Multinucleated giant cells on Tzanck preparation of an unroofed vesicular lesion are useful in diagnosing varicella in a patient with an infiltrate (also found in herpes simplex).
- Severe immunosuppression is associated with symptomatic CMV pneumonia (usually reactivation of latent infection or in previously seronegative recipients from the donor).
- Hypoxemia may be profound.
- Cultures may be helpful in identifying superinfecting bacterial pathogens.
- When they occur, parapneumonic pleural effusions are exudative.

IMAGING STUDIES

- Chest radiographs may demonstrate a spectrum of findings from ill-defined, patchy, or generalized interstitial infiltrates, which can be associated with ARDS.
- A localized dense alveolar infiltrate suggests a superimposed bacterial pneumonia.
- Small calcified nodules may develop as a radiographic residual of varicella pneumonia.

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

General:

- Measures to diminish person-to-person transmission
- Modified bed rest
- Maintenance of adequate hydration
- Possible ventilatory support for severe pneumonia or ARDS

Influenza:

- Yearly prophylactic strain-specific influenza vaccination (only subvirion vaccine should be used in children <13 yr) can be given to prevent infection.
- Live, attenuated influenza vaccines administered by nose drops as effective as injected inactivated viral vaccines.

RSV:

- Isolation techniques are important in limiting spread of RSV infections.
- Immunoglobulins with a high RSV-neutralizing antibody titer are beneficial in treatment.

Adenoviruses:

- Intestinal inoculation of respiratory adenoviruses has been used to successfully immunize military recruits.
- Although they produce no disease in recipients, the viruses may be shed chronically and may infect others at a later date.
- These vaccines are not available for civilian populations.

Varicella:

- Live, attenuated varicella vaccine has been successfully used in clinical trials.
- Varicella-zoster immune globulin should be administered within 4 days of exposure to prevent or modify the disease in susceptible persons.
- Nonimmunized persons exposed to varicella are potentially infectious between 10 and 21 days after exposure.

Measles:

- Effective measles vaccine is available:
  1. The vaccine should be administered at age 15 mo.
  2. A second dose should be administered at the time of school entry.
- Live, attenuated vaccine or gamma-globulin can prevent measles in unvaccinated persons if administered early after exposure.
- Vitamin A given PO for 2 days reduces morbidity and mortality rates from measles in exposed children.

Severe acute respiratory syndrome (SARS)-associated coronaviruses:

- No vaccine currently available.
- Supportive care: ribavirin ineffective, use of steroids or interferon-alpha of unclear value.

ACUTE GENERAL Rx

- **General:** Administer appropriate antibiotics for bacterial superinfections.
- **Influenza:**
  1. Amantadine and rimantadine for influenza A (not active against influenza B). Early use can speed recovery from small airways dysfunction, but whether it influences the development or course of pneumonia is uncertain.
  2. The neuraminidase inhibitors oseltamivir and zanamivir are effective if given in the first 48 hours of symptoms of influenza; their efficacy in established influenza pneumonia is unclear.
  3. Aerosolized ribavirin or amantadine may have a role in severe influenza pneumonia but have not been approved for this indication.
- **RSV and parainfluenza:**
  1. Ribavirin aerosol is effective for severe RSV pneumonia.
  2. There is no approved antiviral therapy for parainfluenza virus pneumonia.
- **Adenoviruses:** no effective agent; some case reports of cidofovir use but unproved.
- **Varicella:**
  1. Varicella pneumonia can be treated with IV acyclovir.
  2. Adults who develop chickenpox should be considered for acyclovir treatment, which may prevent the development of pneumonia.
- **Measles:** no effective antimeasles agent.
- **CMV:**
  1. Acyclovir can prevent CMV infection in renal transplant recipients.
  2. Ganciclovir and foscarnet, with or without CMV hyperimmune globulin, show promise in the treatment of serious CMV infection, including pneumonia, in compromised hosts.

DISPOSITION

- Supportive therapy is useful.
- Death is possible during acute illness.
- Residual functional abnormalities may be persistent or develop into or predispose to chronic respiratory diseases in later life.
- Morbidity and mortality rates after most viral pneumonias are increased by bacterial superinfection.

REFERRAL

- Uncertainty about the diagnosis in a compromised host.
- Symptoms or findings are progressive.
- Severe respiratory compromise, diffuse infiltrates, or the development of ARDS.

! PEARLS & CONSIDERATIONS

COMMENTS

- Influenza spreads by close contact and by small droplets transmitted by cough.
- RSV is effectively transmitted by fomites and by direct contact (little by aerosol).
- Varicella is transmitted by direct contact or by aerosol.
- Of the three major forms of parainfluenza viruses (types 1 to 3), type 3 is the most common cause of viral pneumonia; types 1 and 2 primarily cause laryngotracheitis.
- Recent evidence indicates that a newly discovered virus known as metapneumovirus is a common cause of upper respiratory infections worldwide; this virus can cause pneumonia.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Viral Pneumonia (Patient Information)

AUTHOR: **PHILIP A. CHAN, M.D., M.S.**

SUGGESTED READINGS

Cheng VC et al.: Medical treatment of viral pneumonia including SARS in immunocompetent adults, *J Infect* 49(4):262, 2004.

Falsey AR, Walsh EE: Viral pneumonia in older adults, *Clin Infect Dis* 42(4):518, 2006.

Hohenthal U et al.: Measurement of complement receptor 1 on neutrophils in bacterial and viral pneumonia, *BMC Infect Dis* 6:11, 2006.

Luyt CE et al.: Viral infections in the ICU, *Curr Opin Care* 14(5):605, 2008.

Michelow IC et al.: Epidemiology and clinical characteristics of community-acquired pneumonia in hospitalized children, *Pediatrics* 113(4):701, 2004.

Moreno L et al.: Development and validation of a clinical prediction rule to distinguish bacterial from viral pneumonia in children, *Pediatr Pulmonol* 41(4):331, 2006.

Tsolia MN et al.: Etiology of community-acquired pneumonia in hospitalized school-age children: evidence for high prevalence of viral infections, *Clin Infect Dis* 39(5):681, 2004.

Werno AM et al.: Human metapneumovirus in children with bronchiolitis or pneumonia in New Zealand, *J Paediatr Child Health* 40(9-10):549, 2004.

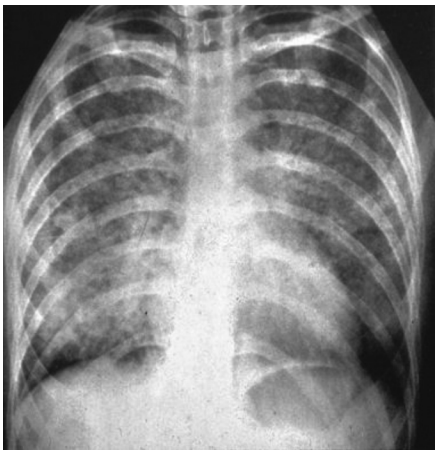


FIGURE EV1-25 This chest radiograph demonstrates bilateral nodular and interstitial pneumonia characteristic of varicella pneumonia. The patient, a 27-year-old gravida 6, para 2, abortus 3 woman, was exposed to varicella infection in her two children. Characteristic skin vesicles of varicella occurred several days before the development of pulmonary symptoms. She required endotracheal intubation and mechanical ventilation for 6 days. She was treated with intravenous acyclovir and ceftazidime for possible superimposed infection. The patient recovered fully and delivered a healthy infant at term. (From Gabbe S.G.: *Obstetrics*, 6th ed, Philadelphia, 2012, Saunders.)

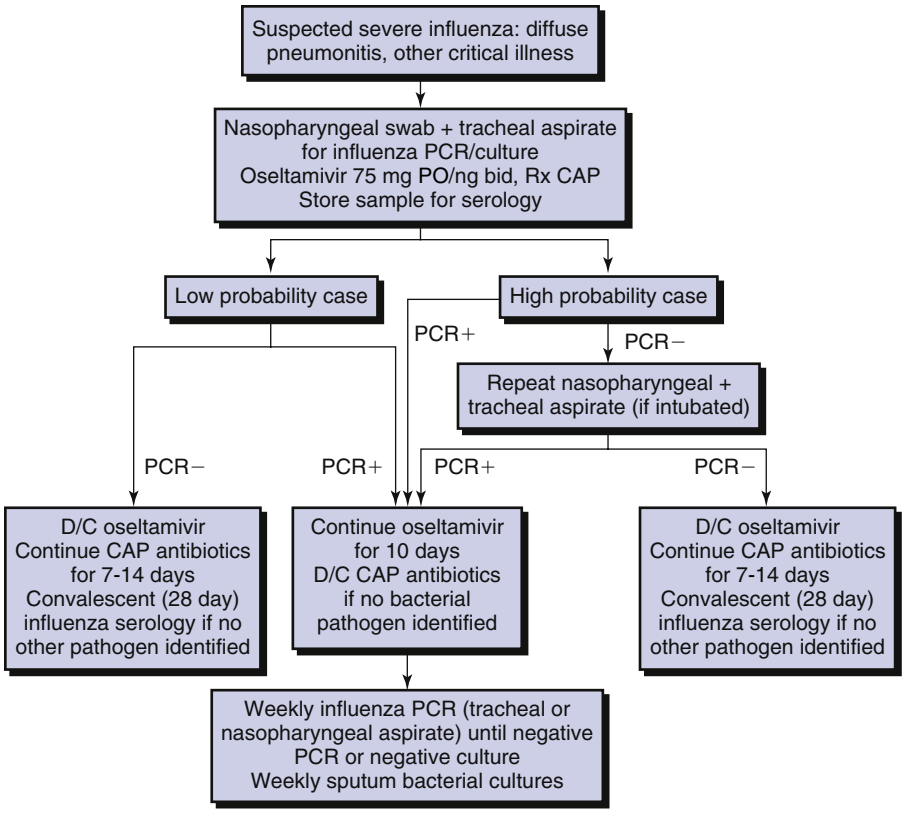


FIGURE EV1-26 Suggested algorithm in the workup and management of suspected severe influenza pneumonia in the critical care unit. *CAP,* Community-acquired pneumonia; *D/C,* discontinue; *PCR,* polymerase chain reaction. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

Vitamin Deficiency (Hypovitaminosis)

BASIC INFORMATION

DEFINITION

Vitamins are organic compounds that cannot be synthesized by humans but are required as nutrients in minute amounts. Vitamins have several different functions: They may regulate cell growth and differentiation, as catalysts, as antioxidants, and as co-enzymes. Vitamins are classified as either fat soluble (vitamins A, D, E, K) or water soluble (B group of vitamins and C). Deficiency of most vitamins is rare in Western countries. Certain groups may be prone to vitamin deficiency, and these are discussed here. Vitamin D deficiency is discussed in a separate topic.

SYNONYMS

Vitamin A: retinol
Vitamin E: alpha tocopherol
Vitamin K: phytonadione or menadiol
Vitamin B_1: thiamine
Vitamin B_2: riboflavin
Niacin: vitamin B_3; nicotinic acid
Vitamin B_5: pantothenic acid
Vitamin B_6: pyridoxine; pyridoxal phosphate
Folic acid: vitamin B_9; folate
Vitamin B_{12}: cyanocobalamin
Vitamin C: ascorbic acid

ICD-9CM CODES

264.8 Vitamin A deficiency
269.1 Vitamin E deficiency
260.0 Vitamin K deficiency
265.1 Vitamin B_1 deficiency
266.0 Vitamin B_2 deficiency
265.2 Niacin deficiency
266.1 Pyridoxine deficiency
266.2 Folic acid deficiency
266.2 Cyanocobalamin deficiency
267 Ascorbic acid deficiency

ICD-10CM CODES

E50 Vitamin A deficiency
E51 Thiamine deficiency
E53 Deficiency of other B group vitamins
E55 Vitamin D deficiency
E56 Other vitamin deficiencies
E56.0 Deficiency of vitamin E
E56.1 Deficiency of vitamin K
E53.0 Riboflavin deficiency
E52 Niacin deficiency [pellagra]
E53.1 Pyridoxine deficiency
E53.8 Deficiency of other specified B group vitamins
E54 Ascorbic acid deficiency

EPIDEMIOLOGY & DEMOGRAPHICS

Deficiency can occur in all age groups but is most common in the elderly.

Vitamin A deficiency: Affects 250 million preschool children worldwide.

Vitamin K deficiency: Varies by geographic regions; no race predilection; affects both sexes equally. Encountered often in infants.

Vitamin B_1 (thiamine) deficiency: Incidence is unknown; no sex, race, or age predilection.

Vitamin B_5 (pantothenic acid) deficiency: Rare, as it is present in all foods.

Vitamin B_{12} (cobalamin) deficiency: Relatively common. Occurs in all age groups but more common in the elderly.

Vitamin B_9 (folic acid) deficiency: Mandatory fortification started in 1998. Prevalence before fortification 16% and after 0.5%. Neural tube defect associated with low maternal folate status during pregnancy. Pregnant women and the elderly are at greatest risk of folic acid deficiency.

Vitamin C (ascorbic acid) deficiency: Smokers and low-income persons are at increased risk.

Fig. V1-27 shows environmental and nutritional factors in disease.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- **Vitamin A:** xerophthalmia; xerosis of the cornea; keratomalacia; Bitot's spots (abnormal squamous cell proliferation and keratinization of the conjunctiva); nyctalopia (poor adaptation to darkness)/night blindness; poor bone growth; dry skin and hair; follicular hyperkeratosis (due to blockage of hair follicles by keratin); pruritus; broken fingernails
- **Vitamin K:** clinical manifestation usually occurs if hypoprothrombinemia is present. Major symptom is bleeding to minor trauma. Also can show easy bruisability, epistaxis, hematoma, gum bleeding
- **Vitamin E:** nerve dysfunction (ataxia; hyporeflexia, peripheral neuropathy); bone weakness.
- **Vitamin B_1 (thiamine)**:
  - Nervous system (dry beriberi): peripheral neuropathy, Wernicke encephalopathy, Korsakoff syndrome.
  - Cardiovascular (wet beriberi): edema, chest pain, increased heart rate (HR), lowered blood pressure (BP).
  - Gastrointestinal (GI): anorexia; constipation.
- **Vitamin B_2 (riboflavin)**:
  - Cheilosis (chapping and fissure of the lip)
  - Glossitis (sore red tongue)
  - Oily, scaly rashes on nasolabial folds, eyelids, scrotum, labia majoris
  - Red itchy eyes
  - Anemia
  - Peripheral neuropathy
- **Vitamin B_3 (niacin)**:
  - Pellagra (4 *D*s—diarrhea, dermatitis, dementia, and ultimately death).
  - Hyperpigmentation of sun-exposed skin.
  - "Raw beef" swollen and painful tongue.
- **Vitamin B_6**: seborrheic dermatitis; glossitis, cheilosis, impaired proprioception; sensory ataxia, seizure.
- **Vitamin B_{12}**: Neurologic symptoms including peripheral neuropathy, ataxia, paresthesia; subacute degeneration of the spinal cord (demyelination of the dorsal column). Patients may also have dementia, depression, and weakness. Glossitis and GI symptoms such as nausea, vomiting, and anorexia are also common.
- **Vitamin B_9 (folic acid)**:
  - Patchy hyperpigmentation of skin (especially between fingers and toes) and mucous membranes
  - Moderate fever (temp <102° F) despite the absence of infection
  - Neural tube defect
  - Angular stomatitis
  - Red, beefy, smooth, and shiny tongue.
- **Vitamin C**: scurvy (poor wound healing, petechiae, follicular hyperkeratosis, fatigue, bleeding gums, weight loss).

ETIOLOGY

- Fat-soluble vitamins (vitamins A, D, E, K):
  1. Decreased ingestion, malnutrition, eating disorders.
  2. Diseases that affect fat absorption decrease the absorption of fat-soluble vitamins—for example, cystic fibrosis, celiac sprue, inflammatory bowel disease, cholestasis, hepatobiliary disease, small bowel surgery.
  3. Change in vitamin metabolism:
     - Alcoholism
     - Drugs such as cholestyramine, warfarin, anticonvulsants, antibiotics (e.g., cephalosporins)
     - Chronic kidney disease
  4. Increased risk in:
     - Vegans
     - Recent immigrants
     - Refugees
     - Toddlers/preschoolers living below the poverty line
- Water-soluble vitamins (the B group of vitamins and vitamin C)—there are several etiologic factors, including:
  - Inadequate intake
  - Decreased absorption
  - Alcoholism
  - Pregnancy/lactation
  - Peritoneal dialysis
  - Medications (e.g., isoniazid, phenothiazines, tricyclic antidepressants)
  - Malabsorption
  - Low income
  - Advanced age
- Vitamin B_{12} deficiency—caused by:
  - Insufficient dietary intake, as in strict vegans
  - Decreased absorption secondary to intrinsic factor deficiency, decreased intrinsic factor secretion, gastric atrophy, gastrectomy
  - Terminal ileum disease such as celiac disease, enteritis, tropical sprue
- Folic acid deficiency—increased needs can lead to deficiency (e.g., pregnancy, lactation, malignancy).
- Derangement of folate metabolism by:
  - Medication (e.g., methotrexate)
  - Disease (e.g., hypothyroidism)
  - Increased excretion: as seen in alcoholics

DIAGNOSIS

WORKUP/LABORATORY TESTS

- General initial laboratory tests include:
  - Complete blood cell count (CBC).
    Liver function tests (LFTs).

Vitamin	Function	Consequences of deficiency
A	Retinal function, epithelial growth control	Night blindness, keratomalacia, xerophthalmia
B_1 (thiamine)	Co-enzyme	Beri beri, Wernicke's encephalopathy
B_2 (riboflavin)	Co-enzyme	Dermatitis, glossitis, keratitis, neuropathy, confusion
B_6 (pyridoxine)	Co-enzyme	Neuropathy
B_{12} (cobalamin)	Nucleic acid synthesis	Megaloblastic anemia Subacute combined degeneration of spinal cord
Niacin	Co-enzyme NAD, NADP	Pellagra (diarrhea, dermatitis, and dementia)
Folate	Co-enzyme in nucleic acid synthesis	Megaloblastic anemia, villous atrophy of gut
Vitamin C	Co-factor in hydroxylation	Scurvy
Vitamin D	Calcium and phosphate absorption	Rickets (childhood) Osteomalacia (adults)
Vitamin E	Antioxidant	Spinocerebellar degeneration
Vitamin K	Co-factor for coagulation factor synthesis	Bleeding due to coagulation defects

FIGURE V1-27 Environmental and nutritional factors in disease. (From Stevens, Alan, MBBS, FRCPath - Core Pathology, 139-150 © 2009 © 2009, Elsevier Limited. All rights reserved.)

Basic metabolic panel (BMP).
Albumin.
- Measurement of serum levels of the specific vitamin in question.

- Specific tests may be considered in the following cases:
  - Vitamin A:
  - Serum retinal level (best test, a direct measure, expensive)
    Retinol binding protein (easier to perform, less expensive)
    Dark-adaptation threshold test.
  1. Vitamin K:
     Prothrombin time/partial thromboplastin time (PT/PTT).
     Prothrombin.
     Des-gamma-carboxy prothrombin (most sensitive test).
  2. Niacin: urine-*N*-methylnicotinamide (level <0.8 mg/day indicates niacin deficiency).
  3. Vitamin B_{12}:
     Serum vitamin B_{12} <100 pg/ml is diagnostic of vitamin B_{12} deficiency.
     Serum methylmalonic acid, which is elevated in B_{12} deficiency.
     Antiparietal antibody.
     Intrinsic factor antibody is decreased.
     Blood smear shows macrocytosis and hypersegmentation of megaloblasts.
     CBC shows increased mean corpuscle volume (MCV).
     Megaloblastic anemia.
  4. Folic acid:
     Check serum folate level
     Additional testing includes checking for serum homocysteine level, which will be elevated.
     Red cell folate level shows chronic folate status.

Rx TREATMENT

Most of the vitamins are available over the counter individually or in different multivitamin formulations.
Specific vitamins:
Vitamin A deficiency: treat with oral supplementation 10,000 IU daily.
- Consume vitamin A–rich foods such as liver, beef, carrots, oranges, mangoes.
- 5 servings of fruit and vegetables give enough carotenoids for a day.

Vitamin K deficiency: treatment depends on the severity of bleeding, administered subcutaneously (SQ) or intramuscularly (IM).
Vitamin B_1 (thiamine) deficiency: give intramuscular thiamine 50 mg for several days.
- If B_1 deficiency is suspected and patient needs intravenous glucose, give thiamine first before intravenous glucose. This prevents the development of Korsakoff psychosis.

Vitamin B_{12} deficiency: give 1000 mcg IM daily for 7 days, then once a week for 1 month, then once a month indefinitely.
- A potential option is oral supplementation.

Folic acid deficiency: daily requirement is 400 to 1000 mcg (1 mg) daily.
- Centers for Disease Control and Prevention (CDC) recommend that women of childbearing age take 400 mcg of folic acid daily.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Anemia, Pernicious (Related Key Topic)
Rickets (Related Key Topic)
Vitamin D Deficiency (Related Key Topic)
Wernicke Syndrome (Related Key Topic)

AUTHOR: **DANIEL K. ASIEDU, M.D., PH.D.**

SUGGESTED READINGS

Jan A, Chow RD: Management of vitamin B_{12} deficiency: what is the role of oral therapy? *Clin Geriatr* 19(3):37–40, 2011.

Schleicher RL et al.: Serum vitamin C and the prevalence of vitamin C deficiency in the United States: 2003-2004 National Health and Nutrition Examination Survey (NHANES), *Am J Clin Nutr* 90:1252–1263, 2009.

Vitamin D Deficiency EBM PTG

BASIC INFORMATION

- Vitamin D is a hormone and a steroid and, by definition, not a vitamin. There are two forms of vitamin D: vitamin D_2 and vitamin D_3.
- Vitamin D_2 is mainly found in some plant foods.
- Vitamin D_3 is produced in skin exposed to ultraviolet (UV) B radiation from sunlight (Fig. V1-28). Gloson, Whistler, and DeBoot independently described rickets in the mid-seventeenth century. Sniadecki first reported the association of rickets with inadequate exposure to sunlight in 1822.
- The major functions of vitamin D include:
  - Increasing calcium and phosphorus absorption from the small intestines.
  - Promoting the maturation of osteoclast to resorb calcium from bones.

DEFINITION

Vitamin D deficiency is characterized by impaired bone mineralization. It is classified as a serum 25-hydroxyvitamin D (25[OH]D) level of <20 ng/ml (50 nmol/L).

The consequences of vitamin D deficiency include:

- Bone disease (rickets, osteoporosis, low bone mass.
- May impair reproductive success.
- Decrease the ability to combat infection (especially TB, influenza, viral infection).
- May induce or worsen autoimmune disorders.
- May increase the incidence of death due to heart disease, IBD, fracture, and cancer of the breast, colon, and prostate.

SYNONYMS

The sunshine vitamin
The antirachitic factor
Cholecalciferol

ICD-9CM CODES
268.9 Vitamin D deficiency unspecified
ICD-10CM CODES
E55.9 Vitamin D deficiency, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE

- Worldwide deficiency and insufficiency affect about 1 billion people.
- Children and young adults: 40% to 50% of preadolescent Caucasian girls, and Hispanic and African American adolescents, are vitamin D deficient.

PEAK INCIDENCE: In the United States, 40% to 100% of the elderly are vitamin D deficient.

PREVALENCE: 42% of African American girls and women 15 to 49 yr old have 25(OH)D levels <20 ng/dl.

PREDOMINANT SEX AND AGE

- Decreased skin production of vitamin D with age.
- Increased prevalence among darker-skinned individuals

RISK FACTORS

1. Age (due to decreased ability to produce D_3)
2. Sunshine-deficient areas (geographic location, living in higher latitudes)
3. Dark-skinned individuals (melanin competes with vitamin D_3 precursors for UV photons and thus decreases pre-D_3 formation)
4. Obese individuals
5. Institutionalized individuals
6. Pregnant and lactating women
7. Use of sunscreen (sun radiation that causes skin cancer also produces pre-vitamin D_3 in skin)
8. Patients on certain medications that antagonize vitamin D action (phenobarbital, phenytoin)
9. Intestinal resection
10. Severe chronic liver diseases (such as cirrhosis)
11. Kidney disease (e.g., nephritic syndrome)
12. Sarcoidosis and lymphomas (increased catabolism of 25[OH]D to 1,25[OH]2D)
13. Intestinal malabsorption disease (caused by celiac sprue, cystic fibrosis, Whipple's disease)

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Rickets—seen in children; caused by defective mineralization in the skeleton (Fig. V1-29).
  - Bowing of the legs.
  - Leg bone pain.
  - Delayed growth.

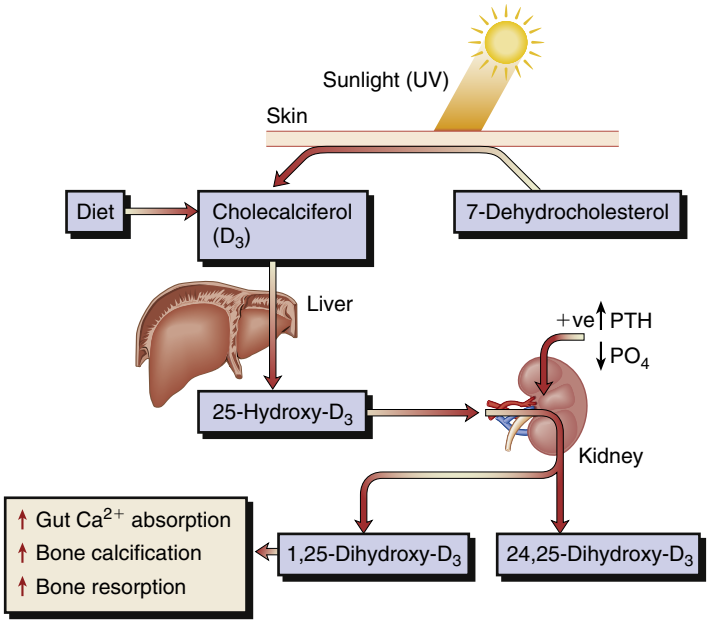


FIGURE V1-28 The metabolism and actions of vitamin D. The primary source of vitamin D in humans is photoactivation in the skin of 7-dehydrocholesterol to cholecalciferol, which is then converted first in the liver to 25-hydroxyvitamin D and subsequently in the kidney to the much more active form, 1,25-dihydroxycholecalciferol ($1,25[OH]_2,D_3$). Regulation of the latter step is by PTH, phosphate, and feedback inhibition by $1,25(OH)_2,D_3$. This step can also occur in lymphomatous and sarcoid tissue, resulting in the hypercalcemia that may complicate these diseases. (From Ballinger A: *Kumar & Clark's essentials of clinical medicine,* ed 6, Edinburgh, 2012, Saunders.)

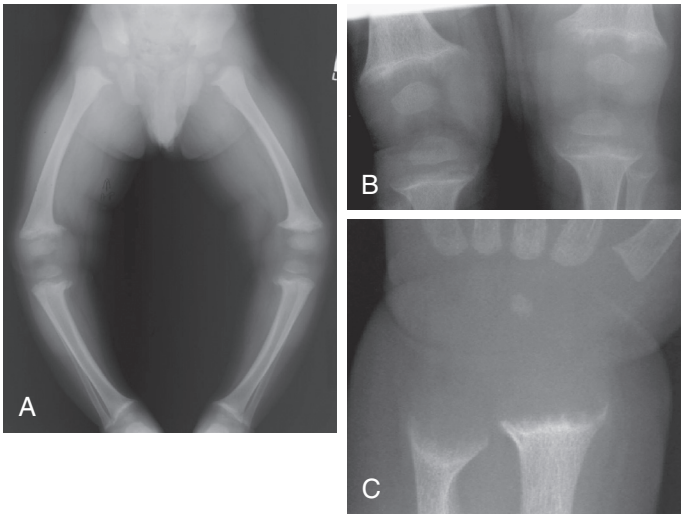


FIGURE V1-29 Radiographs of a child with vitamin D–deficiency rickets demonstrating bowing of the femurs and tibias **(A)** and widened, frayed, demineralized epiphyseal plates **(B** and **C).** (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

- Seizure due to hypocalcemia.
- Osteomalacia—seen in adults.
  - Periosteal bone pain (best detected by putting a firm pressure on tibia or sternal bones).
  - Proximal muscle weakness.
  - Chronic muscle aches/pain.
- Fracture with very minimal trauma (brittle and easily broken bones).
- Severe hypocalcemia—especially in late vitamin D deficiency leading to seizure tetany.
- Hypophosphatemia.
- Neuromuscular.
- Paresthesia.
- Tetany.
- Muscle cramps.

ETIOLOGY

- Inadequate exposure to sunlight, such as:
  - During winter.
  - In nursing home and health care institution residents.
  - With excessive use of sunscreen.
- Medications:
  - Individuals on certain medications, such as phenobarbital, phenytoin, and rifampin (antagonize vitamin D action/increase vitamin D catabolism).
- Diseases and disease states:
  - Diseases causing vitamin D malabsorption:
    Cystic fibrosis.
    Whipple's disease.
    Celiac sprue.
  - Diseases increasing vitamin D catabolism:
    Lymphoma.
    Sarcoidosis.
  - Intestinal resection
  - Decreased 25(OH)D production:
    Kidney disease.
    Liver cirrhosis.

Dx DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Arthritis.
- Fibromyalgia.

WORKUP

- Population-wide screening for vitamin D deficiency is not recommended because evidence to support this practice is lacking.
- Screening is needed for individuals at risk (osteoporosis, history of falls, obese persons, pregnant and lactating women, diseases causing vitamin D malabsorption, African Americans). Workup involves blood and urine tests as well as radiography, as outlined in the next section.

LABORATORY TESTS

- Serum 25(OH)D: this is the best test to determine vitamin D status.
- Parathyroid hormone (PTH): increased levels in vitamin D insufficiency. It is a marker of vitamin D insufficiency.
- Increased (serum or bone) alkaline phosphatase.
- Decreased 24-hour urine calcium (patient should not be on a thiazide).

IMAGING STUDIES

- Radiographs may show:
  - Pseudofractures of the pelvis, femur, metatarsals.
  - Nontraumatic fractures.
- Bone density:
  - Decreased bone mineral density (osteopenia or osteoporosis).

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Natural sources of vitamin D. These include:
  1. Exposure to sunlight. A mild sunburn is equivalent to consuming 10,000-25,000 IU of dietary vitamin D.
  2. Dietary sources are not enough to meet daily requirements. Oily fish such as salmon, cod, and mackerel are rich sources of vitamin D_3.
- Foods fortified with vitamin D.
  1. Mainly fortified dairy products.
  2. Fortified orange juice.

ACUTE GENERAL Rx

- Treating deficiency (general population):
  - 50,000 IU of vitamin D every week for 8 weeks, or
  - 6000 IU daily to achieve a serum level of 25(OH)D of at least 30 ng/ml.
- Maintenance measures after treatment (general population): 1500 to 2000 IU daily.
- Treating deficiency (obese patients, patients with malabsorption syndromes, or those taking certain medications, as indicated earlier).
  - 6000 to 10,000 IU daily.
- Maintenance measures after treatment (obese patients, patients with malabsorption syndromes, or those taking certain medications, as indicated earlier):
  - 3000 to 6000 IU daily.
- After treating deficiency, recheck 25(OH)D in 12 to 14 weeks.

REFERRAL

Referral to an endocrinologist is recommended if there is no response to treatment.

PREVENTION

- Food fortification with vitamin D_2 or vitamin D_3.
- Adequate sun exposure.
- Vitamin D supplementation (per the Endocrine Society):
  - Infants (age range 1 to 12 mo) require at least 400 IU/day of vitamin D.
  - Children (age range 1 to 18 yr) require 600 IU/day of vitamin D.
  - Adult supplementation (adults 19 to 70 yr): 600 IU of vitamin D daily
  - Adult supplementation (persons ≥70 yr): 800 IU of vitamin D daily
  - Exceptions: pregnant or lactating women, obese persons, and patients on antiseizure medications, steroids, antifungals, and AIDS medications should be given 2 × to 3 × more vitamin D.
- Screening: recommended only for individuals at high risk for vitamin D deficiency such as blacks and Hispanics, obese individuals (BMI >30 kg/m^2), patients with osteoporosis, the elderly, and patients with certain chronic diseases (see "Risk Factors"). According to the U.S. Preventive Services Task Force (USPSTF), current evidence is insufficient to assess the balance of benefits and harms of screening for vitamin D deficiency in asymptomatic adults.

! PEARLS & CONSIDERATIONS

- In the United States, vitamin D supplements are available by prescription as vitamin D_2 (ergocalciferol) or over the counter as vitamin D_3 (cholecalciferol, usually in 400 to 1000 IU doses). Both vitamin D_2 and vitamin D_3 are acceptable as supplements. On average, oral vitamin D_3 raises blood levels more than does vitamin D_2.
- Upper limit of maintenance tolerability in healthy adults is 4000 IU a day. More than 4000 IU of vitamin D daily in nondeficient individuals increases the risk of harm. High-level supplements (>10,000 IU daily) are associated with kidney and tissue damage.
- Vitamin D supplementation is recommended for fall prevention. High-dose vitamin D supplementation (≥800 IU daily) has been shown to be favorable in the prevention of hip fracture and any nonvertebral fracture in persons 65 years of age or older.
- Prescribing more than the recommended daily amount to improve quality of life or prevent cardiovascular disease or death is not advised.
- Trials have shown that low vitamin D levels are associated with depressive symptoms, especially in persons with a history of depression. These findings suggest that vitamin D levels may be useful in patients with a history of depression.
- Vitamin D supplementation, administered with calcium, has been shown to lower the risk for falling and improve muscle strength in the elderly, especially in older vitamin D–deficient women who are at high baseline risk for falling.
- The treatment of vitamin D insufficiency in asymptomatic persons might reduce mortality risk in institutionalized elderly persons and risks for falls but not fractures.
- Recent data suggest that vitamin D deficiency is associated with the risk of developing certain cancers (including breast, colon, and prostate).
- Vitamin D deficiency is associated with some autoimmune diseases (types 1 and 2 diabetes, metabolic syndrome, multiple sclerosis).

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Vitamin D Deficiency (Patient Information)

AUTHOR: **DANIEL K. ASIEDU, M.D., PH.D.**

EVIDENCE

Abstract[1]

Objectives:
To examine the association between 25-hydroxyvitamin D (25(OH)D) and physical function in adults of advanced age.
Design:
Cross-sectional and longitudinal analysis of physical function over 3 years of follow-up in the Cardiovascular Health Study All Stars.
Setting:
Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Allegheny County, Pennsylvania.
Participants:
Community-dwelling adults aged 77 to 100 (N = 988).
Measurements:
Serum 25-hydroxyvitamin D 25(OH)D), Short Physical Performance Battery (SPPB), and grip and knee extensor strength assessed at baseline. Mobility disability (difficulty walking half a mile or up 10 steps) and activities of daily living (ADLs) disability were assessed at baseline and every 6 months over 3 years of follow-up.
Results:
Almost one third (30.8%) of participants were deficient in 25(OH)D (<20ng/mL). SPPB scores were lower in those with deficient 25(OH)D (mean (standard error) 6.53 (0.24)) than in those with sufficient 25(OH)D (≥30ng/mL) (7.15 (0.25)) after adjusting for sociodemographic characteristics, season, health behaviors, and chronic conditions (P = .006). Grip strength adjusted for body size was also lower in those with deficient 25(OH)D than in those with sufficient 25(OH)D (24.7 (0.6)kg versus 26.0 (0.6)kg, P = .02). Participants with deficient 25(OH)D were more likely to have prevalent mobility (OR = 1.44, 95% confidence interval (CI)) = 0.96–2.14) and ADL disability (OR = 1.51, 95% CI = 1.01–2.25) at baseline than those with sufficient 25(OH)D. Furthermore, participants with deficient 25(OH)D were at greater risk of incident mobility disability over 3 years of follow-up (hazard ratio = 1.56, 95% CI = 1.06–2.30).
Conclusion:
Vitamin D deficiency was common and was associated with poorer physical performance, lower muscle strength, and prevalent mobility and ADL disability in community-dwelling older adults. Moreover, vitamin D deficiency predicted incident mobility disability. Ⓐ

Abstract[2]

Objective:
To determine the effectiveness of vitamin D supplementation for improving bone mineral density in children and adolescents and if effects vary with factors such as vitamin D dose and vitamin D status.
Design:
Systematic review and meta-analysis.
Data Sources:
Cochrane Central Register of Controlled Trials, Medline (1966 to present), Embase (1980 to present), CINAHL (1982 to present), AMED (1985 to present), and ISI Web of Science (1945 to present), last updated on 9 August 2009, and hand searching of conference abstracts from key journals.
Study Selection:
Placebo-controlled randomised controlled trials of vitamin D supplementation for at least three months in healthy children and adolescents (aged 1 month to <20 years) with bone density outcomes. Two authors independently assessed references for inclusion and study quality and extracted data.
Data Synthesis:
Standardised mean differences of the percentage change from baseline in bone mineral density of the forearm, hip, and lumbar spine and total body bone mineral content in treatment and control groups. Subgroup analyses were carried out by sex, pubertal stage, dose of vitamin D, and baseline serum vitamin D concentration. Compliance and allocation concealment were also considered as possible sources of heterogeneity.
Results:
From 1653 potential references, six studies, totalling 343 participants receiving placebo and 541 receiving vitamin D, contributed data to meta-analyses. Vitamin D supplementation had no statistically significant effects on total body bone mineral content or on bone mineral density of the hip or forearm. There was a trend to a small effect on lumbar spine bone mineral density (standardised mean difference 0.15, 95% confidence interval −0.01 to 0.31; P = 0.07). Effects were similar in studies of participants with high compared with low serum vitamin D levels, although there was a trend towards a larger effect with low vitamin D for total body bone mineral content (P = 0.09 for difference). In studies with low serum vitamin D, significant effects on total body bone mineral content and lumbar spine bone mineral density were roughly equivalent to a 2.6% and 1.7% percentage point greater change from baseline in the supplemented group.
Conclusions:
It is unlikely that vitamin D supplements are beneficial in children and adolescents with normal vitamin D levels. The planned subgroup analyses by baseline serum vitamin D level suggest that vitamin D supplementation of deficient children and adolescents could result in clinically useful improvements, particularly in lumbar spine bone mineral density and total body bone mineral content, but this requires confirmation. Ⓐ

Abstract[3]

Purpose:
The purpose of the study was to examine the relation between serum 25-hydroxyvitamin D (25(OH)D) levels and muscle strength in 419 healthy men and women over a broad age range (20 to 76 yr).
Methods:
Isometric and isokinetic strength of the arms and legs was measured using computerized dynamometry, and its relation to vitamin D was tested in multivariate models controlling for age, gender, resting HR, systolic blood pressure, diastolic blood pressure, body mass index, maximal oxygen uptake (VO_{2max}), physical activity counts, and season of vitamin D measurement.
Results:
Vitamin D was significantly associated with arm and leg muscle strength when controlling for age and gender. When controlling for other covariates listed previously, vitamin D remained directly related to both isometric and isokinetic arm strength but only to isometric leg strength.
Conclusion:
These data suggest that there may be a differential effect of vitamin D on upper and lower body strength. The mechanism for this difference remains unclear but could be related to differences in androgenic effects or to differences in vitamin D receptor expression. Our study supports a direct relation between vitamin D and muscle strength and suggests that vitamin D supplementation be evaluated to determine whether it is an effective therapy to preserve muscle strength in adults. Ⓐ

Evidence-Based References

Houston DK et al.: Serum 25-hydroxyvitamin D and physical function in older adults: the Cardiovascular Health Study All Stars, *J Am Geriatr Soc* 59:1793–1801, 2011. Ⓐ

Winzenberg T et al.: Effects of vitamin D supplementation on bone density in healthy children: systematic review and meta-analysis, *BMJ* 342:c7254, 2011. Ⓐ

Grimaldi AS et al.: 25(OH) Vitamin D is associated with greater muscle strength in healthy men and women, *Med Sci Sports Ecerc* 45:157–162, 2013. Ⓐ

SUGGESTED READINGS

Bischoff-Ferrari HA et al.: A pooled analysis of vitamin D dose requirements for fracture prevention, *N Engl J Med* 367:40–48, 2012.

Heaney RP et al.: Vitamin D_3 is more potent than vitamin D_2 in humans, *J Clin Endocrinol Metab* 96:E447, 2011.

Hoang MT et al.: Association between low serum 25-hydroxyvitamin D and depression in a large sample of healthy adults: the Cooper Center longitudinal study, *Mayo Clin Proc* 86(11):1050–1055, 2011.

Holick MF: Vitamin D deficiency, *N Engl J Med* 357(3):266, 2007.

Holick MF et al.: Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline, *J Clin Endocrinol Metab* 10, 2011. 1210/jc.2011-0385.

Institute of Medicine. Dietary reference intakes for calcium and vitamin D. (website) www.iom.edu/vitamind. Accessed May 8, 2011.

Kennel KA et al.: Vitamin D deficiency in adults: when to test and how to treat, *Mayo Clin Proc* 85(8):752, 2010.

La Blanc ES, et al, on behalf of the U.S. Preventive Services Task Force: Screening for vitamin D deficiency: A systemic review for the U.S. Preventive Task Force, *Ann Intern Med* 162:109–122, 2015.

La Blanc ES, on behalf of the U.S. Preventive Services Task Force: Screening for vitamin D deficiency in adults: U.S. Preventive Task Force recommendation statement, *Ann Intern Med* 162:133–140, 2015.

McGreevy C, Williams D: New insights about vitamin D and cardiovascular disease, *Ann Intern Med* 155:820, 2011.

Murad MH et al.: The effect of vitamin D on falls: a systematic review and meta-analysis, *J Clin Endocrinol Metab* 96:2997, 2011.

Rosen CJ: Vitamin D insufficiency, *N Engl J Med* 364:248, 2011.

Thacher TD et al.: Vitamin D insufficiency, *Mayo Clin Proc* 86(1):50, 2011.

BASIC INFORMATION

DEFINITION

Vitiligo is the acquired loss of epidermal pigmentation that is characterized histologically by the absence of epidermal melanocytes. There are two major forms: nonsegmental (generalized) vitiligo, which accounts for >80% of cases, and segmental vitiligo, which accounts for 30% of childhood cases.

ICD-9CM CODES
709.1 Vitiligo
ICD-10CM CODES
L80 Vitiligo

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: Vitiligo affects 0.5% to 1% of the population; it is the most common depigmenting disorder.
PREDOMINANT AGE: Vitiligo can begin at any age, but the age at onset is <20 yr for half of patients.
GENETICS: A positive family history is present in 25% to 30% of patients, and both sexes are equally affected. There are no differences in the rates of occurrence with regard to skin type or race.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Hypopigmented and depigmented lesions (Fig. V1-30) favor sun-exposed regions, intertriginous areas, genitalia, and sites over bony prominences (i.e., nonsegmental or type A vitiligo).
- Areas around the body orifices are also frequently involved.
- The lesions tend to be symmetric.
- Occasionally the lesions are linear or pseudodermatomal (i.e., segmental or type B vitiligo).
- Vitiligo lesions may occur at trauma sites (i.e., Koebner's phenomenon).
- The hair in affected areas may be white.
- The margins of the lesions are usually well demarcated; when a ring of hyperpigmentation is seen, the term *trichrome vitiligo* is used.

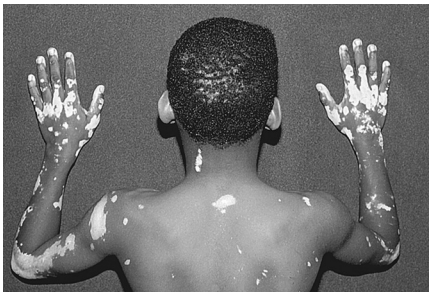


FIGURE V1-30 Multiple, sharply demarcated, symmetric, depigmented areas of vitiligo. (From Behrman RE: *Nelson textbook of pediatrics,* Philadelphia, 2006, Saunders.)

- The term *marginal inflammatory vitiligo* is used to describe lesions with raised borders.
- Initially the disease is limited, but the lesions tend to become more extensive over time.
- Type B vitiligo is more common among children.
- Vitiligo may begin around pigmented nevi and produce a halo (i.e., Sutton's nevus); in such cases, the central nevus often regresses and disappears over time.

ETIOLOGY & PATHOGENESIS

- Three pathophysiologic theories:
  1. Autoimmune theory (i.e., autoantibodies against melanocytes)
  2. Neural theory (i.e., neurochemical mediators selectively destroy melanocytes)
  3. Self-destructive process in which melanocytes fail to protect themselves against cytotoxic melanin precursors
- Although vitiligo is considered to be an acquired disease, 25% to 30% of cases are familial. The mode of transmission is unknown; the condition seems to be polygenic or autosomal dominant with incomplete penetrance and variable expression.
- Associated disorders:
  - Alopecia areata
  - Type 1 diabetes mellitus
  - Adrenal insufficiency
  - Hyperthyroidism and hypothyroidism
  - Mucocutaneous candidiasis
  - Pernicious anemia
  - Polyglandular autoimmune syndromes
  - Melanoma

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Acquired hypopigmentation disorders:
  - Chemical-induced (e.g., chloroquine, imatinib, phenolic-catecholic derivatives [e.g., adhesives, deodorants, latex gloves, lacquer resins, varnish, soap antioxidants, insecticides, printing ink, paints, motor oil additives, disinfectants])
  - Halo nevus
  - Idiopathic guttate hypomelanosis
  - Leprosy
  - Leukoderma associated with melanoma
  - Pityriasis alba
  - Postinflammatory hypopigmentation
  - Tinea versicolor
  - Vogt-Koyanagi syndrome (i.e., vitiligo, uveitis, and deafness)
  - Melasma
  - Mycosis fungoides
- Congenital hypopigmentation disorders:
  - Albinism, partial (piebaldism)
  - Albinism, total
  - Nevus anemicus
  - Nevus depigmentosus
  - Tuberous sclerosis
  - Ito's hypomelanosis

WORKUP

- Inquire about a personal and family history of autoimmune disease.
- Perform a physical examination.
- A Wood's light examination may enhance the lesions of light-skinned individuals.

TREATMENT

Treatment is indicated primarily for cosmetic purposes when depigmentation causes emotional or social distress. Depigmentation is more noticeable among patients with darker complexions.

- Cosmetic masking agents (e.g., Dermablend, Covermark) or stains (e.g., DY-O-Derm, Vitadye)
- Sunless tanning lotions (e.g., dihydroxyacetone)
- Repigmentation (This is achieved by the activation and migration of melanocytes from hair follicles; therefore, skin with little or no hair responds poorly to treatment.)
- Narrow-band ultraviolet B radiation (This is the preferred treatment for nonsegmental vitiligo. It is given twice weekly [not on successive days] during sessions that last from 5 to 10 min. The best results are achieved on the face, trunk, and limbs.)
- Psoralens and sunlight (e.g., PUVAsol)
- Topical mid-potency steroids (e.g., triamcinolone 0.1% or desonide 0.05% cream qd for 3 to 4 mo)
- Topical calcineurin inhibitors for face and neck lesions
- Intralesional steroid injection
- Systemic steroids (e.g., betamethasone 5 mg qd on two consecutive days per wk for 2 to 4 mo)
- Total depigmentation in cases of extensive vitiligo with 20% monobenzyl ether or hydroquinone (This is a permanent procedure, and patients will require lifelong protection from sun exposure.)
- Topical immunomodulators (e.g., tacrolimus, pimecrolimus) (These substances can also induce the repigmentation of vitiliginous skin lesions. However, their potential for systemic immunosuppression or for increasing the risk of skin cancer or other malignancies remains to be defined.)
- Calcipotriol, which is a synthetic analog of vitamin D_3 (This has also been used in combination with ultraviolet light or clobetasol, with limited results.)
- Surgical techniques

EVIDENCE

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SUGGESTED READING

Available at www.expertconsult.com

RELATED CONTENT

Vitiligo (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Background:
Both clobetasol propionate 0.05% (CP 0.05%) and tacrolimus 0.1% (T 0.1%) ointments have been shown to be efficacious and safe in treating vitiligo in the pediatric population.

Objectives:
To assess efficacy and safety of these two therapies compared with each other and with placebo.

Methods:
In this prospective study, children aged 2–16 years with vitiligo, stratified into 'facial' (n = 55) and 'nonfacial' (n = 45) groups, were randomized into three arms: CP 0.05% ointment (n = 30), T 0.1% ointment (n = 31) and placebo (n = 29) for 6 months. Successful repigmentation, defined as > 50% improvement, was evaluated by comparing photographs taken at baseline and at 2, 4 and 6 months.

Results:
In the facial group, 58% of the CP 0.05% group responded successfully compared with 58% of the T 0.1% group, and in the nonfacial group, 39% of the CP 0·05% group responded compared with 23% of the T 0.1% group (P>0.05). There was a significant difference in response between the CP 0.05% group vs. placebo (P<0.0001) and the T 0.1% group vs. placebo (P=0.0004). Spontaneous repigmentation was evaluated as 2.4%. No significant clinical adverse events were noted in any group.

Conclusions:
Both CP 0.05% and T 0.1% ointments offer similar benefit in paediatric vitiligo, both facial and nonfacial. The facial lesions responded faster than the nonfacial ones. Ⓐ

Abstract[2]

Background:
Vitiligo is the most frequent depigmentation disorder of the skin and is cosmetically and psychologically devastating. A recently updated Cochrane systematic review 'Interventions for vitiligo' showed that the research evidence for treatment of vitiligo is poor, making it difficult to make firm recommendations for clinical practice.

Objectives:
To stimulate and steer future research in the field of vitiligo treatment, by identifying the 10 most important research areas for patients and clinicians.

Methods:
A vitiligo priority setting partnership was established including patients, healthcare professionals and researchers with an interest in vitiligo. Vitiligo treatment uncertainties were gathered from patients and clinicians, and then prioritized in a transparent process, using a methodology advocated by the James Lind Alliance.

Results:
In total, 660 treatment uncertainties were submitted by 461 participants. These were reduced to a list of the 23 most popular topics through an online/paper voting process. The 23 were then prioritized at a face-to-face workshop in London. The final list of the top 10 treatment uncertainties included interventions such as systemic immunosuppressants, topical treatments, light therapy, melanocyte-stimulating hormone analogues, gene therapy, and the impact of psychological interventions on the quality of life of patients with vitiligo.

Conclusions:
The top 10 research areas for the treatment of vitiligo provide guidance for researchers and funding bodies, to ensure that future research answers questions that are important both to clinicians and to patients. Ⓐ

Evidence-Based References

Ho N et al.: A double-blind, randomized, placebo-controlled trial of topical tacrolimus 0.1% vs. clobetasol propionate 0.05% in childhood vitiligo, *Br J Dermatol* 165:626–632, 2011. Ⓐ

Eleftheriadou V et al.: Future research into the treatment of vitiligo: where should our priorities lie? Results of the vitiligo priority setting partnership, *Br J Dermatol* 164:530–536, 2011. Ⓐ

SUGGESTED READINGS

Tareb A, Picardo M: Vitiligo, *N Engl J Med* 360:160–169, 2009.

BASIC INFORMATION

DEFINITION

Von Hippel-Lindau disease (VHL) is a rare, autosomal-dominant, inherited disorder that is characterized by the formation of hemangioblastomas, cysts, and malignancies that involve multiple organ systems.

SYNONYMS

Hippel-Lindau syndrome
Cerebelloretinal hemangioblastomatosis
Retinocerebellar angiomatosis
VHL

ICD-9CM CODES
759.6 von Hippel-Lindau disease
ICD-10CM CODES
Q85.8 Other phakomatoses, not elsewhere classified

EPIDEMIOLOGY & DEMOGRAPHICS

- The incidence of VHL is 1 case/36,000 live births.
- The mean age at the onset of clinical manifestations is 26 yr, but the disease can present from infancy until the seventh decade of life.
- In the U.S., approximately 6000 to 7000 people have VHL.
- Affected individuals are at risk for the development of renal cell carcinoma (RCC), pheochromocytoma, pancreatic islet cell tumor, endolymphatic sac tumor, and hemangioblastomas of the cerebellum and the retina.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- There are two clinical types of VHL:
  1. Type 1 has no pheochromocytoma
  2. Type 2 has pheochromocytoma:
     1. Type 2A: hemangioblastoma in the central nervous system (CNS) with no RCC
     2. Type 2B: RCC and other tumors
     3. Type 2C: only pheochromocytoma; associated with Chuvash polycythemia
- Retinal angiomas (60% prevalence):
  1. Usually occurs by age 25 yr with both VHL type 1 and VHL type 2
  2. Often multifocal and bilateral
  3. Detached retina
  4. Glaucoma
  5. Blindness
- CNS hemangioblastomas (70% prevalence):
  1. Cerebellum and spinal cord are the most common sites, followed by the medulla
  2. Usually multiple; mean age at diagnosis is 25 yr; found with VHL types 1, 2A, and 2B
  3. Headache, ataxia, slurred speech, nystagmus, vertigo, nausea, and vomiting
- Renal cysts (approximately 60% prevalence) and clear cell RCC (approximately 25% to 45% prevalence):
  1. Usually occur by the age of 40 yr
  2. May be asymptomatic or cause abdominal and flank pain
  3. RCC is bilateral in 75% of patients
- Pancreatic cysts:
  1. Usually asymptomatic
  2. Large cysts can cause biliary obstructive symptoms
  3. Diarrhea and diabetes may develop if enough of the pancreas is replaced by cysts
- Pheochromocytoma (7% to 18% prevalence):
  1. Found with VHL types 2A, 2B, and 2C
  2. Bilateral in 50% to 80% of cases
  3. Hypertension, palpitations, sweating, and headache
  4. Commonly occurs with pancreatic islet cell tumors
- Papillary cystadenoma of the epididymis (25% to 60% of men with VHL):
  1. Palpable scrotal mass
  2. May be unilateral or bilateral
- Papillary cystadenoma of the broad ligaments (unknown prevalence):
  1. Usually asymptomatic
  2. Reported symptoms include pain, dyspareunia, and menorrhagia
- Endolymphatic sac tumors of the middle ear (approximately 15% prevalence):
  1. Vertigo
  2. Hearing loss
  3. Facial paralysis

ETIOLOGY

VHL is primarily caused by a mutation of the von Hippel-Lindau gene, which is located on the short arm of chromosome 3. The VHL gene codes for a cytoplasmic protein that functions in tumor suppression.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Table EV1-9 compares genetic diseases associated with the development of pancreatic or gut endocrine tumors.

WORKUP

- A clinical diagnosis is established in the presence of a positive family history plus a single CNS hemangioblastoma or a visceral lesion (e.g., RCC, pheochromocytoma, pancreatic cysts or tumors).
- If no clear family history is present, two or more hemangioblastomas or one hemangioblastoma with a visceral lesion is required to make the diagnosis.
- Genetic screening is up to 100% sensitive and specific although in the 20% of patients with de novo VHL mutations, the test may be falsely negative as a result of somatic mosaicism.
- Screening family members is essential for the early detection of VHL disease.

WORKUP

Screening laboratory values and ophthalmoscopic, genetic, and imaging studies to look for sites of involvement

LABORATORY TESTS

- CBC may reveal erythrocytosis that requires periodic phlebotomies
- Electrolytes and renal function tests
- Urine for norepinephrine, epinephrine, and vanillylmandelic acid to look for pheochromocytoma
- Genetic studies: complete sequencing of coding region, Southern blot, and fluorescent in situ hybridization

IMAGING STUDIES

- Indirect and direct ophthalmoscopy, fluorescein angiography, and tonometry are used to screen for retinal angiomas and glaucoma.
- Computed tomographic scanning of the abdomen is used for the screening, detection, and monitoring of patients with renal cysts or tumors, pheochromocytomas, and pancreatic cysts or tumors:
  1. Renal cysts grow an average of 0.5 cm/yr.
  2. Renal tumors grow an average of 1.5 cm/yr.
  3. Computed tomography scans are performed every 6 mo for the first 2 yr and every year for life in patients who have had surgery for RCC.
- MRI with gadolinium (Fig. EV1-31) is used for the screening and evaluation of CNS and spinal cord hemangioblastomas, endolymphatic sac tumors, and pheochromocytomas.
- Angiography may be performed before CNS surgery.

TREATMENT

NONPHARMACOLOGIC THERAPY

Genetic counseling

TABLE EV1-9 Genetic Diseases Associated with the Development of Pancreatic or Gut Endocrine Tumors

Gene	Disease	Phenotype
Menin	Multiple endocrine neoplasia type 1	Parathyroid, pituitary, and pancreatic endocrine tumors
VHL	von Hippel-Lindau disease	Pancreatic endocrine tumors, hemangiomas, and multiple neoplasms
NF-1	Neurofibromatosis	Neurofibromas and pheochromocytomas
TSC1/2	Tuberous sclerosis	Pancreatic endocrine tumors and hamartomas

From Larsen PR et al: *Williams textbook of endocrinology*, ed 10, Philadelphia, 2003, Saunders.

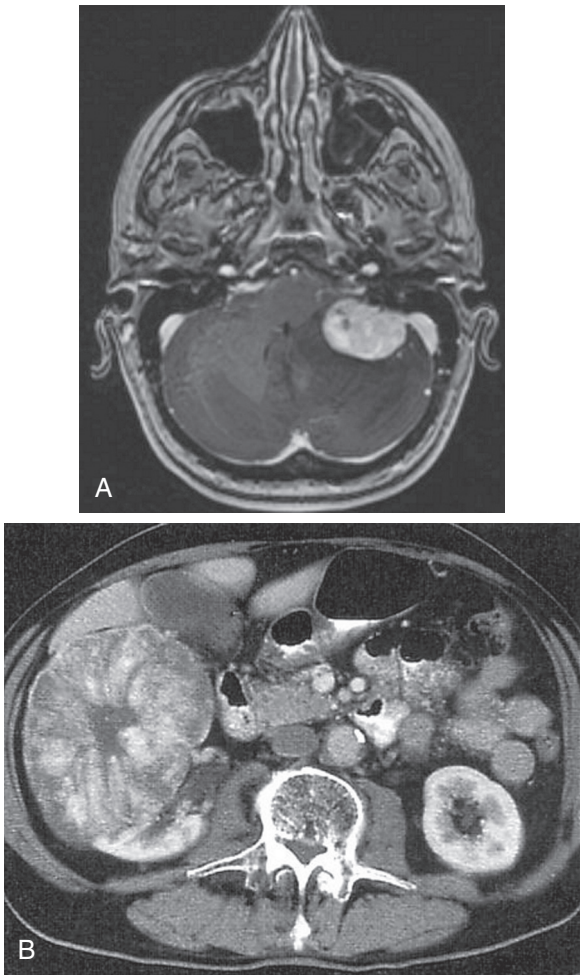

FIGURE EV1-31 Tumors in von Hippel-Lindau syndrome. A, Axial MR shows a cerebellar hemangioma. **B,** Axial CT of the abdomen shows a renal carcinoma. (From Forbes CD, Jackson WF: *Atlas and text of clinical medicine,* 2003, Mosby.)

TABLE EV1-10 Management of Different Manifestations of von Hippel-Lindau Disease

Tumor	Treatment	Screening
Retinal angiomas	If small, laser photocoagulation/cryotherapy; in severe cases, the removal of the affected eye	Retinal examinations once per year soon after birth
Central nervous system hemangioblastomas	Surgical resection for symptomatic patients or large tumors; gamma knife if difficult to remove from primary site	MRI for patients >10 yr once per year
Renal cysts/carcinomas	For tumors <3 cm in diameter, observation; for one tumor >3 cm in diameter, remove all tumors by enucleation or partial nephrectomy; percutaneous radiofrequency ablation and cryosurgery are also performed; surgical resection is not recommended for any cyst without a tumor inside of it; nephrectomy is indicated for patients with end-stage renal disease who require dialysis because of the malignancy potential	CT/MRI scan once yearly; if the patient has relatives with the condition, he or she is checked once per year with CT before the age of 20 yr
Pancreatic cysts	Partial resection of the pancreas, depending on the site of the cyst	
Pheochromocytomas	Preferable to remove only the tumor itself and thus to conserve adrenal function	CT scan once per year for patients <10 yr old

CT, Computed tomography; *MRI,* magnetic resonance imaging.

ACUTE GENERAL Rx

- Laser photocoagulation and cryotherapy are used for patients with retinal angiomas to prevent blindness (Table EV1-10).
- For cerebellar hemangioblastomas, treatment is surgical. External-beam radiation and stereotactic radiosurgery can also be performed.
- For renal tumors, surgery is delayed until one of the renal tumors reaches 3 cm in diameter. Nephron-sparing surgery is the preferred approach.
- Pancreatic islet cell tumors usually require surgical removal.
- Adrenalectomy is performed for pheochromocytoma.
- Antiangiogenic therapy has been shown to improve the survival of patients with RCC, with studies ongoing to assess combination therapy.

CHRONIC Rx

- Dialysis has been delayed for many patients with the use of nephron-sparing surgery.
- Renal transplantation is usually delayed for 1 yr after bilateral nephrectomy for renal tumors to ensure that no metastases have occurred.

DISPOSITION

The median life expectancy of patients with this condition is 49 yr.

REFERRAL

Geneticist, neurosurgeon, urologist, nephrologist, ophthalmologist, otolaryngologist, neurologist, endocrinologist, and radiation oncologist referrals should be considered.

PEARLS & CONSIDERATIONS

- The most common cause of death in patients with VHL is RCC.
- More information for patients can be obtained from the von Hippel-Lindau Family Alliance (http://vhl.org).

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **MARK F. BRADY, M.D., M.P.H., M.M.S.**

SUGGESTED READINGS

Butman JA et al.: Neurologic manifestations of von Hippel-Lindau disease, *JAMA* 300(11):1334–1342, 2008.

Kim JJ et al.: von Hippel-Lindau syndrome, *Adv Exp Med Biol* 685:228–249, 2009.

Lonser RR et al.: von Hippel-Lindau disease, *Lancet* 361:2059, 2003.

Maher ER et al.: von Hippel-Lindau disease: a clinical and scientific review, *Eur J Hum Genet* 19(6):617–623, 2011.

Meister M et al.: Radiological evaluation, management, and surveillance of renal masses in von Hippel-Lindau disease, *Clin Radiol* 64(6):589, 2009.

Shuin T et al.: von Hippel-Lindau disease: molecular pathological basis, clinical criteria, genetic testing, clinical features of tumors and treatment, *Jpn J Clin Oncol* 36(6):337, 2006.

BASIC INFORMATION

DEFINITION

Von Willebrand's disease is a congenital disorder of hemostasis characterized by defective or deficient Von Willebrand factor (vWF). There are several subtypes of Von Willebrand's disease. The most common type (80% of cases) is type I, which is caused by a quantitative decrease in vWF; type IIA and type IIB are results of qualitative protein abnormalities; and type III is a rare, autosomal recessive disorder characterized by a near-complete quantitative deficiency of vWF. Acquired Von Willebrand's disease is a rare disorder that usually occurs in elderly patients and usually presents with mucocutaneous bleeding abnormalities and no clinically meaningful family history. It is often accompanied by a hematoproliferative or autoimmune disorder. Successful treatment of the associated illness can reverse the clinical and laboratory manifestations.

SYNONYMS

Pseudohemophilia
vWD

ICD-9CM CODES
286.4 Von Willebrand's disease
ICD-10CM CODES
D68.0 Von Willebrand's disease

EPIDEMIOLOGY & DEMOGRAPHICS

- Autosomal-dominant disorder.
- Most common inherited bleeding disorder.
- Prevalence is 1% to 2% in general population, according to screening studies; estimates based on referral for symptoms of bleeding suggest a prevalence of 30 to 100 cases per million.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Generally normal physical examination.
- Mucosal bleeding (gingival bleeding, epistaxis) and gastrointestinal bleeding may occur.
- Easy bruising.
- Postpartum bleeding, bleeding after surgery or dental extraction, menorrhagia.

ETIOLOGY

Quantitative or qualitative deficiency of vWF (see "Definition").

DIAGNOSIS

The diagnosis of Von Willebrand's disease generally requires two criteria: (1) a personal history, family history, or physical evidence of mucocutaneous bleeding and (2) a qualitative or quantitative decrease in functional activity of Von Willebrand's disease. The American Society of Hematology states that a definitive diagnosis of vWD may be made if vWF antigen levels are <30 IU/dl. It also describes a gray zone of 30 to 50 IU/dl, designated as "low vWF."

DIFFERENTIAL DIAGNOSIS

Platelet function disorders, clotting factor deficiencies.

WORKUP

- Laboratory evaluation (see "Laboratory Tests").
- Initial testing includes partial thromboplastin time (increased), platelet count (normal), and bleeding time (prolonged).
- Subsequent tests include vWF level (decreased), factor VIII:C (decreased), and ristocetin agglutination (increased in type IIB) (Table V1-11).

LABORATORY TESTS

- Decreased factor VIII coagulant activity.
- Decreased vWF antigen or ristocetin cofactor.
- Normal platelet number and morphology.
- Prolonged bleeding time.
- Normal platelet aggregation studies.
- Type IIA Von Willebrand's disease can be distinguished from type I by absence of ristocetin cofactor activity and abnormal multimer.
- Type IIB Von Willebrand's disease is distinguished from type I by abnormal multimer.

TREATMENT

NONPHARMACOLOGIC THERAPY

- Avoidance of aspirin and other nonsteroidal anti-inflammatory drugs.
- Evaluation for likelihood of bleeding (with measurement of bleeding time) before surgical procedures. When a patient undergoes surgery or receives repeated therapeutic doses of concentrates, factor VIII activity should be assayed every 12 hr on the day a dose is administered and every 24 hr thereafter.

GENERAL Rx

- The mainstay of treatment in Von Willebrand's disease is the replacement of the deficient protein at the time of spontaneous bleeding or before invasive procedures are performed.
- Desmopressin acetate (DDAVP) is useful to release stored vWF from endothelial cells. It is used to cover minor procedures and traumatic bleeding in mild type I Von Willebrand's disease. Dose is 0.3 mcg/kg in 100 ml of normal saline solution IV infused >20 min. DDAVP is also available as a nasal spray (dose of 150 mcg spray administered to each nostril) as a preparation for minor surgery and management of minor bleeding episodes. DDAVP is not effective in type IIA Von Willebrand's disease and is potentially dangerous in type IIB (increased risk of bleeding and thrombocytopenia).
- In patients with severe disease, replacement therapy in the form of cryoprecipitate is the method of choice. The standard dose is 1 bag of cryoprecipitate per 10 kg of body weight.
- Factor VIII concentrate rich in vWF (Humate-P) is useful to correct bleeding abnormalities in type IIA, IIB, and type III Von Willebrand's disease without alloantibodies. Alloantibodies that inactivate vWF and form circulating immune complexes develop in 15% of patients with type III Von Willebrand's disease who have received multiple transfusions. In these patients, recombinant factor VIII is preferred because autoantibodies can elicit life-threatening anaphylactic reactions because of complement activation by immune complexes.
- Life-threatening hemorrhage unresponsive to therapy with cryoprecipitate or factor VIII concentrate may require transfusion of normal platelets.
- Fig. V1-32 summarizes the approach to the management of VWD.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Von Willebrand's Disease (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

TABLE V1-11 Genetic and Laboratory Findings in Von Willebrand's Disease

Parameter Type	BT	VIII-C	vW-Ag	R-Cof	RIPA	Multimer Structure	Mode of Inheritance
I (classic)	P	R	R	R	R	Normal	AD
II							
A	P	N/R	N/R	R	R	Abnormal	AD
B	P	N/R	N/R	N/R	I	Abnormal	AD
III	P	R	R	R	R	Variable	AR

AD, Autosomal dominant; *AR,* autosomal recessive; *BT,* bleeding time; *I,* increased; *N/R,* normal or reduced; *P,* prolonged; *R,* reduced; *R-Cof,* ristocetin cofactor; *RIPA,* ristocetin-induced platelet aggregation (agglutination); *vW-Ag,* Von Willebrand antigen (protein); *VIII-C,* factor VIII coagulant activity.
From Behrman RE: *Nelson textbook of pediatrics,* ed 17, Philadelphia, 2004, Saunders.

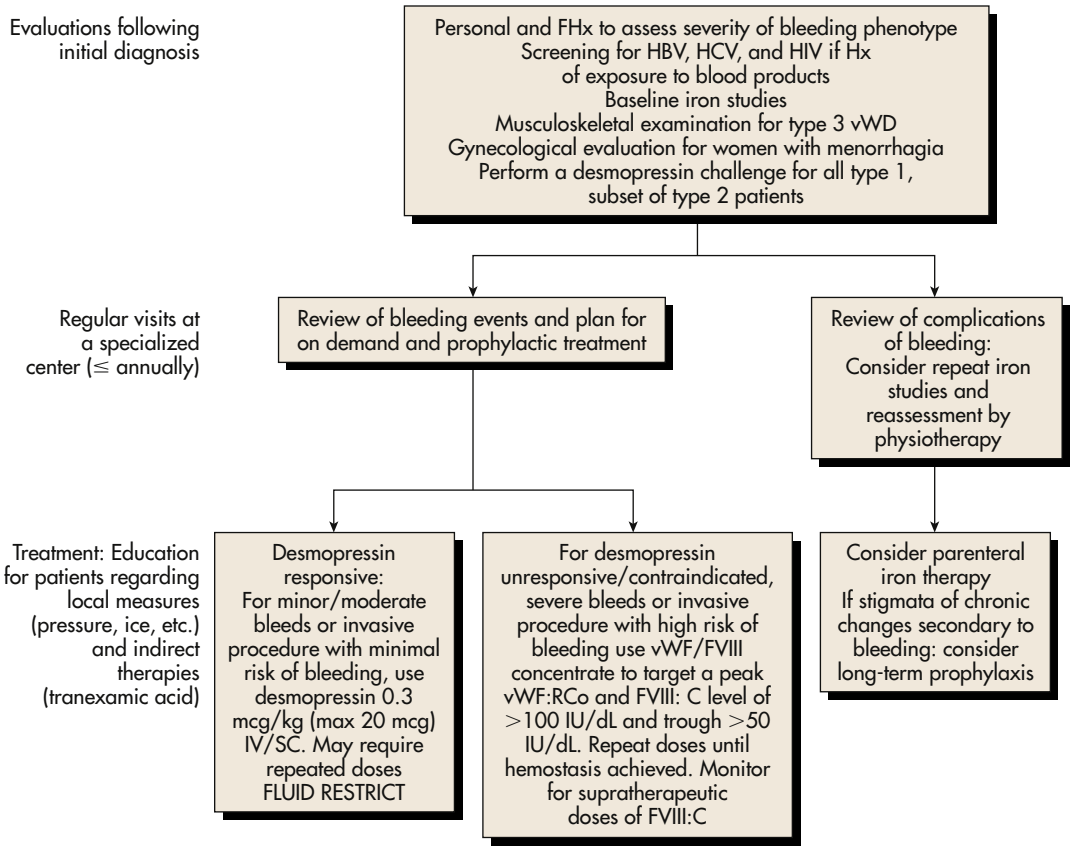

FIGURE V1-32 Approach to the management of Von Willebrand's disease. (From Hoffman R: *Hematology, basic principles and practice,* ed 6, Philadelphia, 2013, Saunders.)

SUGGESTED READINGS

Crownover B et al.: Diagnosing Von Willebrand's disease, *Am Fam Physician* 81(12):1415–1418, 2010.

Hoffman R et al.: *Hematology, basic principles and practice*, ed 6, Philadelphia, 2013, Saunders.

James AH et al.: Von Willebrand's disease and other bleeding disorders in women: consensus on diagnosis and management from an international expert panel, *Am J Gynecol* 201(12):el–8, 2009.

Mannucci PM: Treatment of Von Willebrand's disease, *N Engl J Med* 351:683, 2004.

BASIC INFORMATION

DEFINITION

Vulvar cancer is an abnormal cell proliferation arising on the vulva and exhibiting malignant potential. The majority of vulvar cancers are of squamous cell origin; however, other types include adenocarcinoma, basal cell carcinoma, sarcoma, and melanoma.

SYNONYMS

Squamous cell carcinoma of the vulva (90%)
Basal cell carcinoma of the vulva
Adenocarcinoma of the vulva
Melanoma of the vulva
Bartholin gland carcinoma
Verrucous carcinoma of the vulva
Vulvar sarcoma

ICD-9CM CODES
184.4 Vulvar neoplasm
ICD-10CM CODES
C51.9 Malignant neoplasm of vulva, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

INCIDENCE: 2.2 cases per 100,000 persons
PREVALENCE: Vulvar cancer is uncommon. It comprises 4% of malignancies of the female genital tract. It is the fourth most common gynecologic malignancy.
MEAN AGE AT DIAGNOSIS: Predominantly a disease of menopause. Mean age at diagnosis is 65 yr.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Vulvar pruritus or pain is present.
- May produce a malodorous discharge or present as bleeding.
- Raised lesion that may have fleshy (Fig. V1-33), ulcerated, leukoplakic, or warty appearance; may have multifocal lesions.
- Lesions are usually located on labia majora but may be seen on labia minora, clitoris, and perineum.
- The lymph nodes of groin may be palpable.

ETIOLOGY

- The exact etiology is unknown.
- Vulvar intraepithelial neoplasia has been reported in 20% to 30% of invasive squamous cell carcinoma of the vulva, but the malignant potential is unknown.
- Human papillomavirus is found in 30% to 50% of vulvar carcinoma, but its exact role is unclear.
- Chronic pruritus, wetness, industrial wastes, arsenicals, hygienic agents, and vulvar dystrophies have been implicated as causative agents.
- Vulvar cancer in younger women is more directly dependent on HPV infection, vulvar dysplasia, and tobacco use.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Lymphogranuloma inguinale
- Tuberculosis
- Vulvar dystrophies
- Vulvar atrophy
- Paget's disease

WORKUP

- Diagnosis is made histologically by biopsy
- Thorough examination of the lesion and assessment of spread. Table V1-12 describes FIGO staging of vulvar cancer
- Possible colposcopy of adjacent areas
- Cytologic smear of vagina and cervix
- Cystoscopy and proctosigmoidoscopy may be necessary

IMAGING STUDIES

- Chest radiography
- CT scan and MRI for assessing local tumor spread

TREATMENT

NONPHARMACOLOGIC THERAPY

- Treatment is individualized depending on the stage of the tumor. Fig. V1-34 describes a treatment algorithm for management of patients with vulvar cancer.
- Stage I tumors with <1 mm stromal invasion are treated with complete local excision without groin node dissection. Imiquimod 5% cream, a topical immune response modulator, is also effective in the treatment of vulvar intraepithelial neoplasia.

FIGURE V1-33 Squamous cell carcinoma of the vulva. (From White GM, Cox NH [eds]: *Diseases of the skin, a color atlas and text,* ed 2, St Louis, 2006, Mosby.)

TABLE V1-12 FIGO Staging of Vulval Cancer

Stage I	Tumor confined to the vulva—2 cm or less in diameter. Nodes are not involved.
	A. Lesions less than 1 mm depth invasion
	B. Other lesions less than 2 cm in diameter
Stage II	Tumor confined to the vulva—more than 2 cm in diameter. Nodes are not involved.
Stage III	Tumor of any size with: Adjacent spread to the lower urethra and/or the vagina, the perineum and the anus, and/or unilateral lymph node involvement.
Stage IV	Tumor of any size with bilateral groin lymph node involvement:
	A. Infiltrating the bladder mucosa or the rectal mucosa, or both, including the upper part of the urethral mucosa
	B. Fixed to the bone or other distant metastases. Fixed or ulcerated nodes in either one or both groins.

From Symonds EM, Symonds IM: *Essential obstetrics and gynecology,* ed 4, London, 2004, Churchill Livingstone.

- Stage I tumors with >1 mm stromal invasion are treated with complete local excision with groin node dissection.
- Stage II tumors require radical vulvectomy with bilateral groin node dissection.
- Advanced-stage disease may require the addition of radiation and chemotherapy to the surgical regimen.
- Fig. V1-34 describes a treatment algorithm for management of vulvar cancer.

DISPOSITION

Five-year survival ranges from 90% for stage I to 15% for stage IV.

REFERRAL

Vulvar cancer should be managed by a gynecologic oncologist and radiation oncologist.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Vulvar Cancer (Patient Information)

AUTHOR: **RUBEN ALVERO, M.D.**

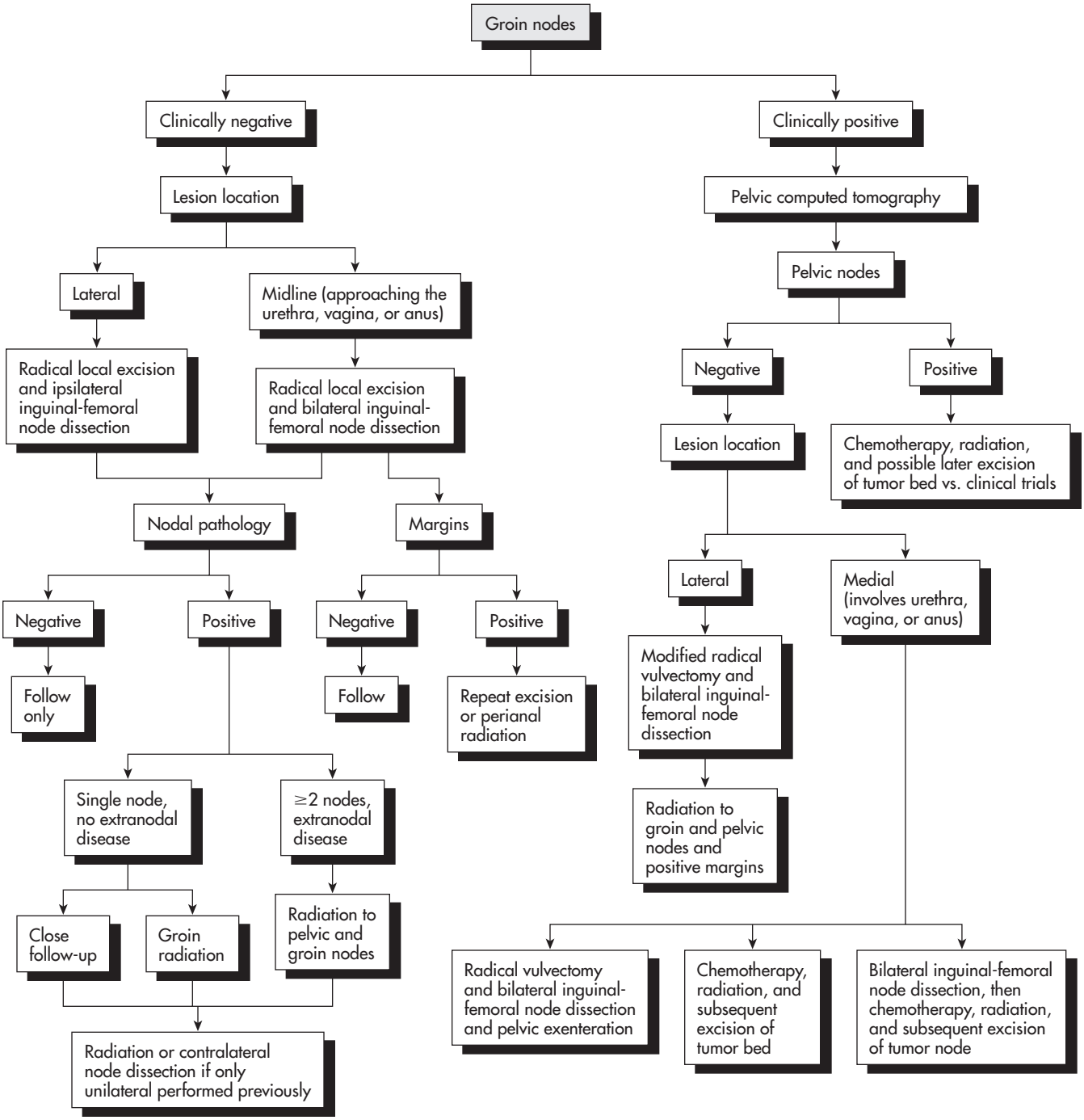

FIGURE V1-34 Treatment algorithm for management of patients with vulvar cancer. (From Copeland LJ: *Textbook of gynecology,* ed 2, Philadelphia, 2000, Saunders.)

SUGGESTED READINGS

Lanneau GS et al.: Vulvar cancer in younger women: demographic features and outcome evaluation, *Am J Obstet Gynecol* 200:645, 2009.

Van Seters M et al.: Treatment of vulvar intraepithelial neoplasia with topical imiquimod, *N Engl J Med* 358:1465–1473, 2008.

BASIC INFORMATION

DEFINITION

Waldenström's macroglobulinemia (WM) is a plasma cell dyscrasia (B-cell malignancy) characterized by lymphoplasmacytic infiltration in the bone marrow (BM) or lymphatic tissue and a monoclonal immunoglobulin M protein (IgM) in the serum.

SYNONYMS

WM
Monoclonal macroglobulinemia
Lymphoplasmacytic lymphoma

ICD-9CM CODES
273.3 Waldenström's macroglobulinemia
ICD-10CM CODES
C88.0 Waldenström macroglobulinemia

EPIDEMIOLOGY & DEMOGRAPHICS

- Accounts for 2% of all hematologic cancers
- 1500 people diagnosed every year in the United States
- Overall incidence: 3.4 per million person-yr in men, 1.7 per million person-yr in women
- Median age approximately 63 yr
- More common among men than women and among whites than blacks

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Headache, dizziness, vertigo, deafness, and seizures (hyperviscosity syndrome)
- Easy bleeding (e.g., epistaxis). The most common symptoms are oronasal bleeding and visual disturbances caused by retinal bleeding.
- Weakness
- Fatigue
- Weight loss
- Pallor
- Retinal vein link-sausage shaped (Fig. W1-1)

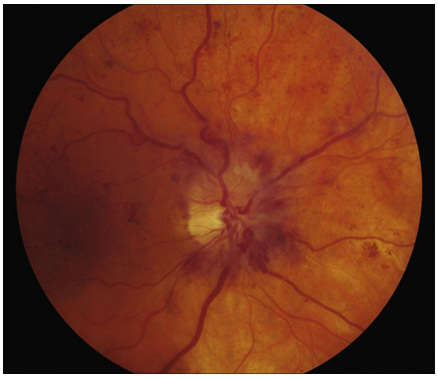

FIGURE W1-1 Hyperviscosity syndrome. Right eye retinal image in a patient with Waldenström's macroglobulinemia and hyperviscosity syndrome showing sausaging (focal venular dilations), intraretinal hemorrhages, microaneurysms, and peripapillary cotton wool spots and disc swelling (papilledema). (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2011, Saunders.)

- Lymphadenopathy (15%)
- Hepatomegaly (20%)
- Most commonly encountered neurologic presentation is symmetric polyneuropathy (5%)
- Splenomegaly (15%)
- Purpura (Fig. W1-2)
- Fever and night sweats

ETIOLOGY

- WM is an IgM-secreting lymphoplasmacytic lymphoma (LPL). The underlying mutation in this disorder has not been delineated.
- Multiple reports suggest familial clustering, which indicates a genetic predisposition. In one study, chromosomal deletions in 6q21–22.1 were confirmed in 42% of WM patients, regardless of family history. In another study, the strongest evidence of linkage was found on chromosomes 1q and 4q.
- The main risk factor for development of WM is having IgM monoclonal gammopathy of unknown significance (MGUS).
- Radiation exposure, occupational chemicals, viral infection, and chronic inflammatory stimulation have been suggested, but there is insufficient evidence to substantiate these hypotheses.
- There is a twofold to threefold increased risk of WM in people with a personal history of autoimmune diseases with autoantibodies. There is also increased risk with HIV, hepatitis, and rickettsiosis.

DIAGNOSIS

The diagnosis of WM is usually established by laboratory blood tests and by BM biopsy. Diagnosis requires demonstration of lymphoplasmacytic lymphoma comprising ≥10% of the BM cellularity and the presence of an IgM M protein. MYD88 L265P is a commonly recurring mutation in WM that can be useful in differentiating it and non-IgM lymphoplasmacytic lymphoma (LPL) from B-cell disorders that have some of the same features.

DIFFERENTIAL DIAGNOSIS

- MGUS
- Multiple myeloma
- Chronic lymphocytic leukemia
- Hairy-cell leukemia
- B-cell lymphoma subtypes
- Smoldering macroglobulinemia

FIGURE W1-2 Nonpalpable purpura of hyperglobulinemic purpura of Waldenström's hypergammaglobulinemia. (From Hochberg MC et al: *Rheumatology,* ed 5, St Louis, 2011, Mosby.)

WORKUP

In any patient suspected of having WM, specific blood tests (CBC, erythrocyte sedimentation rate [ESR], serum or urine protein electrophoresis [SPEP or UPEP, respectively], IgM level, beta 2-microglobulin, serum viscosity) should be ordered. BM biopsy confirms the diagnosis.

LABORATORY TESTS

- CBC with differential:
  1. Anemia is a common finding, with a median hemoglobin value of approximately 10 g/dl. WBC count is usually normal; thrombocytopenia can occur.
  2. Peripheral smear may reveal "stacked coin" rouleaux formations and malignant lymphoid cells in terminal patients.
- Elevated ESR.
- SPEP: homogeneous M spike (monoclonal gammopathy).
- Immunoelectrophoresis: confirms IgM responsible for the M spike. Table W1-1 describes physicochemical and immunologic properties of the monoclonal IgM protein in WM.
- Urine immunoelectrophoresis: monoclonal light chains are usually kappa chains. Bence Jones protein can be seen, but is not the typical finding in WM.
- IgM levels are high, generally >3 g/dl.
- Beta 2-microglobulin: elevated in 55%; high levels are associated with poor prognosis.
- Serum viscosity: symptoms usually occur when the serum viscosity is four times the viscosity of normal serum; classic feature although present in only 15% of cases.
- Cryoglobulins, rheumatoid factor, or cold agglutinins may be present.
- BM biopsy: BM reveals infiltration by a lymphoplasmacytic cell population constituted by small lymphocytes with evidence of plasmacytoid and plasma cell differentiation. The BM infiltration should be confirmed by immunophenotypic studies (flow cytometry or immunohistochemistry) showing the following profile: sIgM+CD19+CD20+CD22+CD79+.

IMAGING STUDIES

- Chest x-ray can be obtained to rule out pulmonary involvement.
- MRI of the spine in conjunction with CT of the abdomen and pelvis is useful in evaluating disease status in WM. BM involvement can be documented by MRI studies of the spine in >90% of patients, and CT of the abdomen and pelvis can demonstrate enlarged nodes.

TREATMENT

- Because of the incurable nature of WM, the aim of treatment is to relieve symptoms and reduce the risk of organ damage. Initiation of therapy should not be based on the IgM levels because this may not correlate with either disease burden or symptomatic status. Patients with smoldering or asymptomatic WM and preserved hematologic function should be observed without therapy. Initiation

TABLE W1-1 Physicochemical and Immunologic Properties of Monoclonal Immunoglobulin Protein in Waldenström's Macroglobulinemia

Properties of Monoclonal Immunoglobulin Protein	Diagnostic Condition	Clinical Manifestations
Pentameric structure	Hyperviscosity	Headaches, blurred vision, epistaxis, retinal hemorrhages, leg cramps, impaired mentation, and intracranial hemorrhage
Prescription on cooling	Cryoglobulinemia (type I)	Raynaud's phenomenon, acrocyanosis, ulcers, purpura, and cold urticaria
Autoantibody activity to myelin-associated glycoprotein, ganglioside M1, and sulfatide moieties on peripheral nerve sheaths	Peripheral neuropathies	Sensorimotor neuropathies, painful neuropathies, ataxic gait, and bilateral foot drop
Autoantibody activity to immunoglobulin G	Cryoglobulinemia (type II)	Purpura, arthralgias, renal failure, and sensorimotor neuropathies
Autoantibody activity to red blood cell antigens	Cold agglutinins	Hemolytic anemia, Raynaud's phenomenon, acrocyanosis, and livedo reticularis
Tissue deposition as amorphous aggregates	Organ dysfunction	Skin: bullous skin disease, papules, and Schnitzler syndrome Gastrointestinal: diarrhea, malabsorption, and bleeding Kidney: proteinuria and renal failure (light-chain component)
Tissue deposition as amyloid fibrils (light-chain fibrils commonly the largest component)	Organ dysfunction	Fatigue, weight loss, edema, periorbital purpura, hepatomegaly, macroglossia, and organ dysfunction of the involved organs: heart, kidney, liver, and peripheral sensory and autonomic nerves

From Hoffman R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

of therapy is appropriate for patients with constitutional symptoms. Considerations for the initiation of treatment include the following: significant adenopathy or organomegaly, symptomatic hyperviscosity, severe neuropathy, amyloidosis, cryoglobulinemia, cold-agglutinin disease, hemoglobin concentration <10 g/dL, or evidence of disease transformation.
- Treatment is directed at both hyperviscosity and the lymphoproliferative disorder itself.

NONPHARMACOLOGIC THERAPY

Asymptomatic patients do not require treatment, and these patients should be monitored periodically for the onset of symptoms or changes in blood tests (e.g., worsening anemia, thrombocytopenia, rising IgM, and serum viscosity).

ACUTE GENERAL Rx

- Treatment of the lymphoproliferative disorder includes single or combination therapy; although guidance has been suggested in the Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) Guidelines, there is no universally agreed upon standard of care:
1. Rituximab, a monoclonal anti-CD20 antibody, can be used in symptomatic patients with modest hematologic compromise, IgM-related neuropathy, or hemolytic anemia unresponsive to corticosteroids.
2. Plasmapheresis should be initial treatment in patients with symptoms of hyperviscosity.
3. DRC regimen (dexamethasone, rituximab, cyclophosphamide) in patients with severe constitutional symptoms, symptomatic bulky disease, hyperviscosity, or profound hematologic compromise.
4. The combination of the proteasome inhibitor bortezomib, dexamethasone, and rituximab (BDR) has also shown a favorable response and remission rate.

CHRONIC Rx

- Rituximab is often used in maintenance therapy.
- Refractory patients can be retried on original therapy if length of response from initial therapy is >2 yr. If the response from the initial therapy was <2 yr, alternative first-line agents such as fludarabine or cladribine can be used.
- Other treatment options: interferon alpha, thalidomide, and autologous stem cell transplantation.

DISPOSITION

- The onset of WM is slow and insidious. Most patients die from progression of the disease with hyperviscosity, hemorrhage, and infection, or from congestive heart failure.
- Some patients develop acute myelogenous leukemia, immunoblastic sarcoma, or chronic myelogenous leukemia as a preterminal event.
- Median survival in patients with WM is about 4 to 5 yr.
- ~10% of patients will achieve complete remission, with prognosis being more favorable (median survival 11 yr).
- A staging system using serum beta 2-microglobulin concentration, hemoglobin concentration, and serum IgM concentration before treatment provides insight into prognosis and survival.
- Other factors can negatively affect the survival: age >65, male gender, the presence of organomegaly, and the presence of cytopenias.

REFERRAL

If WM is suspected, a hematology consultation is helpful in guiding future workup, treatment, and monitoring. Autologous stem cell transplantation should be considered in all eligible patients with relapsed disease.

PEARLS & CONSIDERATIONS

COMMENTS

- WM was first described in 1944 by the Swedish physician Jan Gösta Waldenström.
- Amyloidosis is rare, occurring in 5% of patients with WM.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **MARK F. BRADY, M.D., M.P.H., M.M.S.**

SUGGESTED READINGS

Ansell SM et al.: Diagnosis and management of Waldenström macroglobulinemia: Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) guidelines, *Mayo Clin Proc* 85(9):824–833, 2010.

Dimopoulos MA et al.: Update on treatment recommendations from the Fourth International Workshop on Waldenström's Macroglobulinemia, *J Clin Oncol* 27(1):120–126, 2009.

Fonseca R, Hayman S: Waldenström macroglobulinaemia, *Br J Haematol* 138: 700, 2007.

Gertz MA: Waldenström macroglobulinemia: 2011 update on diagnosis, risk stratification, and management, *Am J Hematol* 86(5):411–416, 2011.

Hoffman R et al.: *Hematology, basic principles and practice*, ed 6, Philadelphia, 2013, Saunders.

Koshiol J et al.: Chronic immune stimulation and subsequent Waldenström macroglobulinemia, *Arch Intern Med* 168(17):1903–1909, 2008.

Kyriakou C et al.: High-dose therapy and autologous stem-cell transplantation in Waldenström macroglobulinemia: the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation, *J Clin Oncol* 28(13):2227–2232, 2010.

Rourke M et al.: Review of clinical trials conducted in Waldenström macroglobulinemia and recommendations for reporting clinical trial responses in these patients, *Leuk Lymphoma* 51(10):1779–1792, 2010.

Stone MJ, Pascual V: Pathophysiology of Waldenström's macroglobulinemia, *Haematologica* 95(3):359–364, 2010.

Treon SP et al.: MYD88 L265P somatic mutation in Waldenström's macroglobulinemia, *N Engl J Med* 367:826–833, 2012.

Vijay A, Gertz MA: Waldenström macroglobulinemia, *Blood* 109(12):5096, 2007.

BASIC INFORMATION

DEFINITION

Warts are benign epidermal lesions caused by human papillomavirus (HPV).

SYNONYMS

Verruca vulgaris (common warts)
Verruca plana (flat warts)
Condyloma acuminatum (venereal warts)
Verruca plantaris (plantar warts)
Mosaic warts (cluster of many warts)
HPV infection

ICD-9CM CODES
078.10 Viral warts
078.19 Venereal wart (external genital organs)
ICD10CM CODES
B07.9 Viral wart, unspecified
B07.8 Other viral warts

EPIDEMIOLOGY & DEMOGRAPHICS

- Risk factors include use of communal showers, occupational handling of meat, and immunosuppression. Common warts occur most frequently in children and young adults.
- Anogenital warts are most common in young, sexually active patients. Genital warts are the most common viral sexually transmitted disease in the United States, with up to 79 million Americans carrying the causative virus, and 14 million persons are newly infected each year in the U.S.
- Persistent infection with oncogenic HPV types can cause cervical cancer in women as well as other anogenital and oropharyngeal cancers in women and men. 66% of cervical cancers, 55% of vaginal cancers, 79% of anal cancers, and 62% of oropharyngeal cancers are attributable to HPV types 16 or 18.
- Common warts are longer lasting and more frequent in immunocompromised patients (e.g., lymphoma, AIDS, immunosuppressive drugs).
- Plantar warts occur most frequently at points of maximal pressure (over the heads of the metatarsal bones or on the heels).

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Common warts (Fig. EW1-3) have an initial appearance of a flesh-colored papule with a rough surface; they subsequently develop a hyperkeratotic appearance with black dots on the surface (thrombosed capillaries). They may be single or multiple and are most common on the hands.
- Warts obscure normal skin lines (important diagnostic feature). Cylindrical projections from the wart may become fused, forming a mosaic pattern.
- Flat warts generally are pink or light yellow, slightly elevated, and often found on the forehead, back of hands, mouth, and beard area. They often occur in lines corresponding to trauma (e.g., a scratch), are often misdiagnosed (particularly when present on the face), and are inappropriately treated with topical corticosteroids.
- Filiform warts have a fingerlike appearance with various projections; they are generally found near the mouth, beard, or periorbital and paranasal regions.
- Plantar warts are slightly raised and have a roughened surface; they may cause pain when walking; as they involute, small hemorrhages (caused by thrombosed capillaries) may be noted.
- Genital warts (Fig. EW1-4) are generally pale pink with several projections and a broad base. They may coalesce in the perineal area to form masses with a cauliflower-like appearance. Intraanal warts occur predominantly in patients who have had receptive anal intercourse, in contrast with perianal warts (Fig. W1-5), which may occur in men and women without a history of anal sex.
- Genital warts on the cervical epithelium can produce subclinical changes that may be noted on Pap smear or colposcopy.

ETIOLOGY

- HPV infection; >150 types of viral DNA have been identified. Transmission of warts is by direct contact. Approximately 40 different types of HPV are transmitted through sexual contact.
- Genital warts: 90% are caused by HPV types 6 or 11. HPV types 16, 18, 31, 33, and 35 are found occasionally in visible genital warts (usually as coinfections with HPV 6 or 11) and can be associated with foci of high-grade, intraepithelial neoplasia, particularly in persons who are infected with HIV infection. In addition to warts on genital areas, HPV types 6 and 11 have been associated with conjunctival, nasal, oral, and laryngeal warts.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Molluscum contagiosum
- Condyloma latum
- Acrochordon (skin tags) or seborrheic keratosis
- Epidermal nevi
- Hypertrophic actinic keratosis
- Squamous cell carcinomas
- Acquired digital fibrokeratoma
- Varicella-zoster virus in patients with AIDS
- Recurrent infantile digital fibroma
- Plantar corns (may be mistaken for plantar warts)

WORKUP

- Diagnosis is generally based on clinical findings.
- Suspect lesions should be biopsied.
- The application of 3% to 5% acetic acid, which causes skin color to turn white, has been used by some providers to detect HPV-infected genital mucosa. However, acetic acid application is not a specific test for HPV infection. Therefore, the routine use of this procedure for screening to detect mucosal changes attributed to HPV infection is not recommended.

LABORATORY TESTS

- Screening for cervical cancer with cytology, which is performed by either Pap smear or liquid-based cytology. Screening guidelines recommend starting screening at age 21. Annual cytology is recommended until at least three normal cytology results are obtained.
- Colposcopy with biopsy is recommended in patients with cervical squamous cell changes.

FIGURE W1-5 Common warts of the hand in a mother and perianal condylomata acuminata in her son. (From Meneghini CL, Bonifaz E: *An atlas of pediatric dermatology,* Chicago, 1986, Year Book Medical Publishers.)

Rx TREATMENT

NONPHARMACOLOGIC THERAPY

- Importance of use of condoms to reduce transmission of genital warts should be emphasized.
- Watchful waiting is an acceptable option in the treatment of nongenital cutaneous warts because many warts will disappear without intervention over time. However, many patients often request treatment because of social stigma or discomfort.
- Plantar warts that are not painful do not need treatment.
- Factors that influence selection of treatment include wart size, wart number, anatomic site of the wart, wart morphology, patient preference, cost of treatment, convenience, adverse effects, and provider experience. Factors that might affect response to therapy include the presence of immunosuppression and compliance with therapy.

GENERAL Rx

- Common warts:
  1. Application of topical salicylic acid 17%. Soak area for 5 min in warm water and dry. Apply thin layer once or twice daily for up to 12 wk, avoiding normal skin. Bandage.
  2. Liquid nitrogen and electrocautery are also common methods of removal. Cure rates for cryotherapy are 50% to 70% after three to four treatments.
  3. Blunt dissection can be used in large lesions or resistant lesions.
  4. Duct tape occlusion is also effective for treating common warts. It is cut to cover warts and left in place for 6 days. It is removed after 6 days and the warts are soaked in water and then filed with pumice stones. New tape is applied 12 hr later. This treatment can be repeated until warts resolve.
  5. Recalcitrant warts can be treated with injection of *Candida* or mumps skin antigen into the wart every 3 to 4 wk for up to three treatments, photodynamic therapy with aminolevulinic acid, pulsed dye laser, and intralesional bleomycin.
- Filiform warts: surgical removal is necessary.
- Flat warts: generally more difficult to treat.
  1. Tretinoin cream applied at bedtime over the involved area for several weeks may be effective.
  2. Application of liquid nitrogen.
  3. Electrocautery.
  4. 5-Fluorouracil cream applied once or twice a day for 3 to 5 wk is also effective. Persistent hyperpigmentation may occur after Efudex use.
- Plantar warts:
  1. Salicylic acid therapy (e.g., Occlusal-HP). Soak wart in warm water for 5 min, remove loose tissue, dry. Apply to area, allow to dry, reapply. Use once or twice daily; maximum 12 wk. Use of 40% salicylic acid plasters (Mediplast) is also a safe, nonscarring treatment; it is particularly useful in treating mosaic warts covering a large area.
  2. Blunt dissection is also a fast and effective treatment modality.
  3. Laser therapy can be used for plantar warts and recurrent warts; however, it leaves open wounds that require 4 to 6 wk to fill with granulation tissue.
  4. Interlesional bleomycin is also effective but generally used when all other treatments fail.
- Genital warts:
  1. Can be effectively treated with 20% podophyllin resin in compound tincture of benzoin applied with a cotton tip applicator by the treating physician and allowed to air dry. The treatment can be repeated weekly if necessary.
  2. Podofilox (Condylox 0.5% gel) is available for application by the patient. Local adverse effects include pain, burning, and inflammation at the site.
  3. Cryosurgery with liquid nitrogen delivered with a probe or as a spray is effective for treating smaller genital warts.
  4. Carbon dioxide laser can also be used for treating primary or recurrent genital warts (cure rate >90%).
  5. Imiquimod cream, 5%, is a patient-applied immune response modifier effective in the treatment of external genital and perianal warts (complete clearing of genital warts in >70% of females and >30% of males in 4 to 16 wk). Sexual contact should be avoided while the cream is on the skin. It is applied 3 times per wk before normal sleeping hours and is left on the skin for 6 to 10 hr.
  6. Sinecatechins (Veregen), a botanical drug product, is also effective for treatment of external genital and perianal warts. Formulation is a 15% ointment applied to affected area tid for up to 16 wk.
- Application of trichloroacetic acid or bichloracetic acid 80% to 90% is also effective for external genital warts. A small amount should be applied only to warts and allowed to dry, at which time a white "frosting" develops. This treatment can be repeated weekly if necessary.

DISPOSITION

- Warts can be effectively treated with the previous modalities with complete resolution in the majority of patients; however, the recurrence rate is high.
- Cervical carcinomas and precancerous lesions in women are associated with genital papillomavirus infection.
- Squamous cell anal cancer is also associated with a history of genital warts.

REFERRAL

- Dermatology referral for warts resistant to conservative therapy
- Surgical referral in selected cases
- Sexually transmitted disease counseling for patients with anogenital warts

PEARLS & CONSIDERATIONS

COMMENTS

- Subungual and periungual warts are generally more resistant to treatment. Dermatology referral for cryosurgery is recommended in resistant cases.
- Examination of sex partners is not necessary for the management of genital warts because no data indicate that reinfection plays a role.

PREVENTION

- Two HPV vaccines are licensed in the United States. Both are composed of type-specific HPVL1 protein, the major capsid protein of HPV. Expression of the L1 protein using recombinant DNA technology produces noninfectious virus-like particles (VLPs). Quadrivalent HPV vaccine (HPV4) contains four HPV type-specific prepared from the L1 proteins of HPV 6, 11, 16, and 18. Bivalent HPV vaccine (HPV2) contains two HPV type-specific VLPs prepared from the L1 proteins of HPV 16 and 18. Both vaccines are administered in a 3-dose series. ACIP recommends routine vaccination with HPV4 or HPV2 for females aged 11 to 12 years and HPV4 for males aged 11 to 12 years. Vaccination is also recommended for females aged 13 to 26 years and for males aged 13 through 21 years who were not vaccinated previously. Males aged 22 through 26 may be vaccinated. ACIP recommends vaccination of men who have sex with men and immunocompromised persons (including those with infection) through age 26 years if not previously vaccinated.
- Male circumcision decreases heterosexual transmission of HPV.

EBM EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Warts (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

EVIDENCE

Abstract[1]

Background:

Infection with human papillomavirus (HPV) and diseases caused by HPV are common in boys and men. We report on the safety of a quadrivalent vaccine (active against HPV types 6, 11, 16, and 18) and on its efficacy in preventing the development of external genital lesions and anogenital HPV infection in boys and men.

Methods:

We enrolled 4065 healthy boys and men 16 to 26 years of age, from 18 countries in a randomized, placebo-controlled, double-blind trial. The primary efficacy objective was to show that the quadrivalent HPV vaccine reduced the incidence of external genital lesions related to HPV-6, 11, 16, or 18. Efficacy analyses were conducted in a per-protocol population, in which subjects received all three vaccinations and were negative for relevant HPV types at enrollment, and in an intention-to-treat population, in which subjects received vaccine or placebo, regardless of baseline HPV status.

Results:

In the intention-to-treat population, 36 external genital lesions were seen in the vaccine group as compared with 89 in the placebo group, for an observed efficacy of 60.2% (95% confidence interval [CI], 40.8 to 73.8); the efficacy was 65.5% (95% CI, 45.8 to 78.6) for lesions related to HPV-6, 11, 16, or 18. In the per-protocol population, efficacy against lesions related to HPV-6, 11, 16, or 18 was 90.4% (95% CI, 69.2 to 98.1). Efficacy with respect to persistent infection with HPV-6, 11, 16, or 18 and detection of related DNA at any time was 47.8% (95% CI, 36.0 to 57.6) and 27.1% (95% CI, 16.6 to 36.3), respectively, in the intention-to-treat population and 85.6% (97.5% CI, 73.4 to 92.9) and 44.7% (95% CI, 31.5 to 55.6) in the per-protocol population. Injection-site pain was significantly more frequent among subjects receiving quadrivalent HPV vaccine than among those receiving placebo (57% vs. 51%, $P<0.001$).

Conclusions:

Quadrivalent HPV vaccine prevents infection with HPV-6, 11, 16, and 18 and the development of related external genital lesions in males 16 to 26 years of age. (Funded by Merck and others; ClinicalTrials.gov number, NCT00090285.) Ⓐ

Evidence-Based Reference

Giuliano AR: Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males, *N Engl J Med* 364(5):401–411, 2011. Ⓐ

SUGGESTED READINGS

Bacelieri R, Johnson SM: Cutaneous warts: an evidence-based approach to therapy, *Am Fam Physician* 72:647, 2005.

Centers for Disease Control and Prevention: Sexually transmitted diseases treatment guidelines, 2010, *MMWR Morb Mortal Wkly Rep* 59(RR-12), 2010.

Giuliano AR et al.: Efficacy of quadrivalent HPV vaccine against HPV infection and disease in males, *N Engl J Med* 364:401–411, 2011.

Huang CM: Human papillomavirus and vaccination, *Mayo Clin Proc* 83(6):701, 2008.

Karnes JB, Usatine RP: Management of external genital warts, *Am Fam Phys* 90(5):312–318, 2014.

Markowitz L: Human papillomavirus vaccination. Recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 63(5), August 29, 2014.

Mulhem E, Pinelis S: Treatment of nongenital cutaneous warts, *Am Fam Physician* 84(3):288–293, 2011.

FIGURE EW1-3 Common warts of the left hand and the chest wall. (From Meneghini CL, Bonifaz E: *An atlas of pediatric dermatology,* Chicago, 1986, Year Book Medical Publishers.)

FIGURE EW1-4 Vulvovaginal human papillomavirus infection. (From Cohen J, Powderly WG: *Infectious* diseases, ed 2, Philadelphia, 2004, Mosby.)

BASIC INFORMATION

DEFINITION

Wernicke syndrome is an acute neuropsychiatric disorder characterized by the classic triad of ophthalmoplegia, ataxia, and disturbances of mental activity or consciousness due to a deficiency of thiamine often associated with chronic alcoholism.

SYNONYMS

Wernicke encephalopathy (WE)
Gayet-Wernicke encephalopathy
Cerebral beriberi
Wernicke's superior hemorrhagic polioencephalitis

ICD-9CM CODES

265.1 Wernicke's encephalopathy, disease, or syndrome (superior hemorrhagic polioencephalitis)
294.0 Wernicke-Korsakoff's syndrome or psychosis, non-alcoholic
291.1 Wernicke-Korsakoff's syndrome or psychosis, alcoholic

ICD-10CM CODES

E51.2 Wernicke encephalopathy
E51.8 Other manifestations of thiamine deficiency
F04 Amnestic disorder due to known physiological condition
F10.96 Alcohol use, unspecified with alcohol-induced persisting amnestic disorder

EPIDEMIOLOGY & DEMOGRAPHICS

- A higher prevalence of WE noted on autopsy studies (0.8% to 2.8%) compared to clinical studies (0.04% to 0.13%)
  - WE lesions on autopsy of alcohol abusers: 12.5%
  - WE lesions on autopsy patients with alcohol-related deaths: 29% to 59%

PREDOMINANT SEX AND AGE

- Male-to-female ratio of 1.7 to 1
- Estimated mortality: 17%

GENETICS

- Biochemical studies in fibroblasts from patients with WE show thiamine-dependent enzyme, transketolase, to have a decreased affinity for thiamine pyrophosphate.
- Thiamine deficiency causes wet (cardiovascular) beriberi more commonly in the Asian population and dry beriberi (polyneuropathy and WE) in the European population.

RISK FACTORS:

- Alcohol abuse/misuse
- Diet
  - Malnutrition/unbalanced nutrition/infant formulas
  - Intravenous hyperalimentation without thiamine supplementation
  - Magnesium depletion–cofactor required by enzymes: transketolase and thiamine pyrophosphokinase
- Gastrointestinal disorders including recurrent vomiting or chronic diarrhea such as hyperemesis gravidarum
- Gastrointestinal surgical procedures (gastrointestinal resection) that cause malabsorption secondary to reduced surface area of gastric and duodenal mucosa such as bariatric surgery
- Systemic cancers
  - Most common underlying disorder onset for WE in children
  - Consumption of thiamine by fast-growing neoplastic cells
- Chemical compounds/drugs or chemotherapeutic treatments
- Systemic diseases
  - Peritoneal or hemodialysis
  - HIV/AIDS
  - Prolonged infectious febrile disease
  - Hypermetabolic states
  - Thyrotoxicosis

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- WE is a clinical diagnosis with a classic triad of ophthalmoplegia, ataxia, and disturbances of mental activity or consciousness—although this triad is only seen in 16% of all patients.
- Eye movement abnormalities include nystagmus, external rectus palsies, and reduced conjugate gaze.
- Ophthalmoscopic findings include swelling of the optic discs and retinal hemorrhages.
- Clinical suspicion must remain high in patients with risk factors listed above, especially in the setting of poor nutrition.
- Diagnosis is confirmed by improvement of neurologic signs after administration of parenteral thiamine.
- Labs and radiologic studies may aid diagnosis, but these should not delay a trial of parenteral administration of thiamine.

ETIOLOGY

- The biologically active form of vitamin B_1, thiamine pyrophosphate (TP), a coenzyme for several important biochemical pathways involved in energy production, lipid metabolism, and production of amino acids and glucose-derived neurotransmitters.
- Body's reserve for thiamine is sufficient for 18 days.
- Malnutrition for 2 to 3 wk or a diet disproportionately high in carbohydrates and low in thiamine intake can lead to an impaired function of enzymes requiring TP.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Other acute encephalopathies (Table EW1-2)
- Paramedian thalamic infarction
- Ventriculoencephalitis, paraneoplastic encephalitis, herpes simplex encephalitis
- Miller-Fisher syndrome
- Primary cerebral lymphoma
- Multiple sclerosis, Behcet's disease, Leigh's disease
- Variant Creutzfeldt-Jakob disease

WORKUP

- WE is a clinical diagnosis based on the triad of features listed above.
- Laboratory tests and radiologic studies as listed below may be obtained to confirm diagnosis.

LABORATORY TESTS

- Blood thiamine concentration.
- Functional measurement of erythrocyte thiamine transketolase (ETKA) before and after administration of parenteral thiamine. A diagnosis may be confirmed if ETKA is low followed by a 25% increase after thiamine supplementation.
- High-performance liquid chromatography for assessment of thiamine, thiamine mono- and di-phosphate in human erythrocytes.
- Serum magnesium concentration (depletion of magnesium may mimic features of WE).

IMAGING STUDIES

MRI of brain may show bilaterally symmetric increase in T2 signal at the paraventricular regions of the thalamus and mammillary bodies. Other areas include hypothalamus, periaqueductal region, floor of the fourth ventricle, and midline cerebellum.

TREATMENT

ACUTE GENERAL Rx

- Treatment should be initiated in all patients with clinical suspicion of WE. Thiamine supplementation should precede glucose administration in all patients at risk for WE.
- Alcoholics with WE: treat with 500 mg of thiamine hydrochloride (dissolved in 100 ml of normal saline) infused intravenously over 30 min, 3 times daily for 2 to 3 days.

TABLE EW1-2 Acute and Subacute Presentation of Nutritional Deficiency Syndromes

Syndrome	Clinical Setting
Wernicke-Korsakoff syndrome	Administration of intravenous glucose to a thiamine-deficient alcoholic patient
Wernicke-Korsakoff syndrome	Intractable vomiting due to hyperemesis gravidarum or gastroplasty
Postgastroplasty neuropathy	Intractable vomiting and severe weight loss in patients following weight reduction surgical procedures
Vitamin B_{12} myeloneuropathy	Nitrous oxide administration in cobalamin-deficient patients
Central pontine myelinolysis	Sudden change in tissue osmolarity in critically ill patients or alcoholics

From Goetz CG: *Textbook of clinical neurology*, ed 3, Philadelphia, 2007, Saunders.

- If a response is observed, continue with 250 mg of thiamine hydrochloride intravenously or intramuscularly daily until clinical improvement ceases.
- Nonalcoholics with WE: treat with 200 mg of thiamine hydrochloride (dissolved in 100 ml of normal saline) infused intravenously over 30 min, 3 times daily for 2 to 3 days.
- Parenteral side effects may include generalized pruritus, transient local irritation, or rarely, anaphylactic or anaphylactoid reactions.
- Parenteral magnesium must be infused concurrently with thiamine.

CHRONIC Rx

Recommended oral dose after treatment for WE: thiamine 30 to 100 mg twice daily

DISPOSITION

- If prompt treatment with thiamine is not administered during the potential reversible stages of WE, Korsakoff's syndrome may develop consisting of a typical pattern of memory loss emerging after the acute global confusional state of WE resolves.
- Approximately 80% who survive WE develop Korsakoff's syndrome.

REFERRAL

In cases of altered mental status, ophthalmoplegia or ataxia of gait, consider neurology consultation. Treatment should be initiated as soon as WE is suspected.

PEARLS & CONSIDERATIONS

COMMENTS

- WE should be suspected in all patients with poor nutrition.
- WE is a clinical diagnosis composed of a triad of confusion, ataxia, and ophthalmoplegia.
- Thiamine infusion should be initiated upon clinical suspicion of WE.
- Thiamine infusion should precede infusion of fluids with glucose in all patients with poor nutrition or clinical suspicion of WE.

PREVENTION

- Prophylactic treatment for patient with severe alcohol withdrawal, poor nourishment, or signs of malnutrition: thiamine 250 mg intramuscular daily for 3 to 5 days.
- In individuals susceptible to WE, 100 mg of intravenous thiamine should precede any glucose infusion.
- Recommended daily dose of thiamine for an average, healthy adult: 1.4 mg or 0.5 mg per 1000 kcal of carbohydrates consumed.
- Higher dose recommended for children, in critically ill conditions, and during pregnancy and lactation.

PATIENT & FAMILY EDUCATION

In cases of known alcohol abuse or severe illness, the patient and family should be counseled on the importance of proper nutrition, including vitamin supplementation.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Alcoholism (Related Key Topic)
Korsakoff's Psychosis (Related Key Topic)
Vitamin Deficiency (Related Key Topic)

AUTHOR: **D. BRANDON BURTIS, D.O.**

SUGGESTED READINGS

Al-Fahad T et al.: Very early onset Wernicke's encephalopathy after gastric bypass, *Obes Surg* 16:671–672, 2006.

Chiossi G et al.: Hyperemesis gravidarum complicated by Wernicke's encephalopathy: background, case report and review of the literature, *Obstet Gynecol Surv* 61:255–268, 2006.

Chung SP et al.: Magnetic resonance imaging as a diagnostic adjunct to Wernicke's encephalopathy in the ED, *Am J Emerg Med* 21:497–502, 2003.

Cook CC: Prevention and treatment of Wernicke-Korsakoff syndrome, *Alcohol Alcohol Suppl* 35:19–20, 2000.

McLean J, Manchip S: Wernicke's encephalopathy induced by magnesium depletion, *Lancet* 353:1768, 1999.

Merkin-Zaborsky H et al.: Thiamine-responsive acute neurological disorders in nonalcoholic patients, *Eur Neurol* 45:34–37, 2001.

Sechi G et al.: Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management, *Lancet Neurol* 6:442, 2007.

Thomson AD: Mechanisms of vitamin deficiency in chronic alcohol misusers and the development of Wernicke-Korsakoff syndrome, *Alcohol Alcohol Suppl* 35:2–7, 2000.

Thomson AD, Marshall EJ: The natural history and pathophysiology of Wernicke's encephalopathy and Korsakoff 's psychosis, *Alcohol Alcohol* 41:151–158, 2006.

Thomson AD et al.: The Royal College of Physicians report on alcohol: guidelines for managing Wernicke's encephalopathy in the accident and emergency department, *Alcohol Alcohol Suppl* 37:513–521, 2002.

Vasconcelos MM et al.: Early diagnosis of pediatric Wernicke's encephalopathy, *Pediatr Neurol* 20:289–294, 1999.

Weidauer S et al.: MR findings and clinical presentation, *Eur Radiol* 13:1001–1009, 2003.

BASIC INFORMATION

DEFINITION

West Nile virus (WNV) infection is an illness affecting the central nervous system (CNS) caused by the mosquito-borne WNV.

SYNONYMS

West Nile virus fever
West Nile virus encephalitis
Neuroinvasive West Nile virus infection
Nonneuroinvasive West Nile virus infection

ICD-9CM CODES
066.4 West Nile virus infection
ICD-10CM CODES
A92.30 West Nile virus infection, unspecified

EPIDEMIOLOGY & DEMOGRAPHICS

- Before 1999, WNV infection was confined to areas in the Middle East, with occasional outbreaks in Europe. The infection began being diagnosed in the Western Hemisphere in 1999. First seen in the northeast and mid-Atlantic states, WNV virus infection has spread steadily each year to new regions of the U.S., with a general westward migration pattern. In 2003, a record number of cases were reported from the U.S., with over 9000 cases reported, resulting in several hundred deaths. Most deaths occur in elderly patients with WNV encephalitis. In 2003, Illinois, Ohio, Michigan, and Louisiana were hardest hit. Since 2004 the incidence of WNV infection waxed and waned as it spread to the western states. Human cases of WNV infection have now been reported across all the contiguous continental U.S. (sparing only Hawaii and Alaska). Since 1999, an estimated 780,000 cases of WNV infection have occurred in the US, with 16,196 cases of neuroinvasive disease and 1549 deaths attributable to WNV. The overall mortality rate from reported cases of symptomatic patients with WNV is about 4%. The virus has now become the most prevalent, reportable, arthropod-borne form of viral encephalitis in North America and is likely to remain for decades to come.
- The virus is carried by a number of species of birds, as well as horses and several other animals. It is transmitted to humans through the bite of an infected mosquito. For this reason, WNV infection is seen primarily from mid-summer to mid-autumn, the period of maximum mosquito intensity.
- The majority of severe cases have been reported among individuals >50 yr of age. There is no gender predilection. Certain HLA haplotypes appear to predispose to severe disease (e.g., HLA-A68 and HLA-C08).
- Person-to-person transmission is fortunately rare but has been reported to occur by blood transfusion, organ transplantation, breast-feeding, and perhaps perinatal transmission; the blood supply is now routinely tested by nucleic acid testing methods to reduce the risk of transmission-acquired WNV in the U.S.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Less than 20% of infected individuals develop symptomatic disease. The initial phase of illness is nonspecific, with abrupt onset of fever (West Nile fever) accompanied by malaise, eye pain, anorexia, headache, and, occasionally, rash and lymphadenopathy. Less commonly, myocarditis, hepatitis, or pancreatitis may occur.
- Encephalitis is the most common neurologic manifestation of West Nile virus infection. Aseptic meningitis may also occur.
- In approximately 1 in 150 cases, especially among elderly patients, severe neurologic sequelae will occur (West Nile neuroinvasive disease [WNND]). Most common among these are ataxia, cranial nerve palsies, optic neuritis, seizures, myelitis, and polyradiculitis.

ETIOLOGY

The WNV is a member of the flavivirus group, along with the yellow fever, dengue, St. Louis, and Japanese encephalitis viruses. It has a large reservoir in nature, infecting many species of birds, as well as certain mammals, and is spread to humans primarily by the bite of an infected *Culex* mosquito or other various species of mosquito with a peak incidence in the late summer and early fall. Neurologic disease is caused by direct invasion of the CNS.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Meningitis or encephalitis caused by more common viruses (e.g., enteroviruses, herpes simplex)
- Bacterial meningitis
- Vasculitis
- Fungal meningitis (e.g., cryptococcal infection)
- Tuberculous meningitis

LABORATORY TESTS

- CBC, electrolytes (hyponatremia common)
- Spinal tap and CSF examination: typically demonstrates lymphocytic pleocytosis with normal level of glucose and elevated level of protein
- CSF WNV IgM antibody level: detection in symptomatic patients is diagnostic of West Nile neuronivasive disease. The antibody can be detected within 9 days of fever onset and can persist for several months. There can be rare false-positive results in people recently vaccinated against Japanese encephalitis or yellow fever viruses.

IMAGING STUDIES

MRI of the brain to exclude mass lesions and cerebral edema

TREATMENT

NONPHARMACOLOGIC THERAPY

Hospitalization, IV hydration, ventilator support may be necessary.

ACUTE GENERAL Rx

No specific therapy has been established in clinical trials. Ribavirin and interferon alfa-2b have been shown to have in vitro activity against the virus. IV immunoglobulin (IVIG) from convalescent patient plasma is under study but no controlled trials have been reported as yet.

CHRONIC Rx

Chronic rehabilitation therapy usually necessary for patients with severe neurologic impairment. Mental status defects following WNV neuroinvasive disease appear to be more common and severe than initially recognized.

DISPOSITION

Chronic rehabilitation as needed following recovery from acute infection. Physical and mental outcome measures seem to normalize within approximately 1 yr in patients with WNV. The presence of preexisting comorbid conditions is associated with longer recovery.

REFERRAL

- Infectious disease consultant
- Public health authorities

PEARLS & CONSIDERATIONS

COMMENTS

- Diagnosis requires a high index of suspicion, because disease course may be nonspecific and may mimic other, more common disorders.
- Specific laboratory diagnostic studies are available only through public-health laboratories.

EVIDENCE

Available at www.expertconsult.com

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

West Nile Virus Infection (Patient Information)

AUTHOR: **STEVEN M. OPAL, M.D.**

EVIDENCE

Abstract[1]

Background:

ChimeriVax-WN02 is a live, attenuated chimeric vaccine for protection against West Nile virus. This Phase II, randomized, double-blind, placebo–controlled, multicenter study assessed the immunogenicity, viremia, and safety of the ChimeriVax-WN02 vaccine.

Methods:

The 2-part study included adults in general good health. In part 1, subjects aged 18–40 years were randomized to 1 of 4 treatment groups: ChimeriVax-WN02 3.7×10^5 plaque-forming units (PFU), 3.7×10^4 PFU, 3.7×10^3 PFU, or placebo. In part 2, subjects aged 41–64 and ≥65 years were randomized to receive ChimeriVax-WN02 3.7×10^5 PFU or placebo.

Results:

In both part 1 and part 2, seroconversion was achieved at day 28 by >96% of subjects in active treatment groups. In part 1, neutralizing antibody titers at day 28 were higher and viremia levels lower with the highest dose, whereas the adverse event profile was similar between the dose groups. In part 2, antibody titers and viremia levels were higher in subjects aged ≥65 years, and more subjects in the 41–64 years cohort experienced adverse events.

Conclusions:

The ChimeriVax-WN02 vaccine was highly immunogenic in younger adults and the elderly, and it was well tolerated at all dose levels and in all age groups investigated. ClinicalTrials.gov identifier: NCT00442169. Ⓐ

Evidence-Based Reference

Biedenbender R et al.: Phase II, randomized, double-blind, placebo-controlled, multicenter study to investigate the immunogenicity and safety of a West Nile virus vaccine in healthy adults, *J Infect Dis* 203:75–84, 2011. Ⓐ

SUGGESTED READINGS

Carson PJ et al.: Long-term clinical and neuropsychological outcomes of West Nile virus infection, *Clin Infect Dis* 43(6):723, 2006.

Centers for Disease Control and Prevention: West Nile virus disease and other arboviral diseases—United States, 2010, *MMWR Morb Mortal Wkly Rep* 63(24):521–526, 2014.

Gottfried K et al.: Clinical description and follow-up investigation of human West Nile Virus cases, *South Med J* 98(6):603–606, 2005.

Higgs S et al.: Nonviremic transmission of West Nile virus, *Proc Natl Acad Sci USA* 102(25):8871–8874, 2005.

Kilpatrick AM: Globalization, land use, and the invasion of West Nile virus, *Science* 334(6054):323–327, 2011.

Lanteri MC et al.: Association between HLA class I and class II alleles and the outcome of West Nile virus infection: an exploratory study, *PLoS One* 6(8):e22948, 2011.

Loeb M et al.: Prognosis after West Nile virus infection, *Ann Intern Med* 149:232–241, 2008.

Petersen LR et al.: West nile virus: Review of the literature, *JAMA* 310:308–315, 2013.

Stramer SL et al.: West Nile virus among blood donors in the United States, 2003 and 2004, *N Engl J Med* 353(5):451–459, 2005.

BASIC INFORMATION

DEFINITION

Whiplash refers to a hyperextension injury to the neck, often the result of being struck from behind by a fast-moving vehicle.

SYNONYMS

Acceleration flexion-extension neck injury

ICD-9CM CODES
847.0 Whiplash injury or syndrome
ICD-10CM CODES
S13.4 Sprain and strain of cervical spine

EPIDEMIOLOGY & DEMOGRAPHICS

- Whiplash occurs in more than 1 million people each year.
- Most injuries (40%) are the result of rear-end motor vehicle accidents.
- Whiplash occurs at all ages, in both sexes, and at all socioeconomic levels.
- Incidence is 4 per 1000 persons and is higher in women than men.
- Nearly 50% of patients with whiplash seek legal advice.
- Whiplash is also seen in shaken baby syndrome.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most present with a history of being involved in a motor vehicle accident and being rear-ended by another vehicle
- Pain not present initially but usually develops hr to a few days later
- Neck tightness and stiffness
- Occipital headache
- Shoulder, arm, and back pain
- Numbness in the arms
- Tinnitus
- Temporomandibular joint (TMJ) pain
- Dysphagia (retropharyngeal hematoma)
- Decreased range of motion of the neck
- Depressive symptoms

ETIOLOGY

- The mechanism of injury is the result of the sudden acceleration of the body forward, forcing the neck to hyperextend backward, causing injury to ligaments, muscles, bone, and/or intervertebral disk. At the end of the accident the head is thrust forward in a flexion position, sometimes causing injury to the cervical spine: C5-C6-C7.
- Motor vehicle accidents, trauma from falls, contact sports, physical abuse, and altercations are all possible causes of whiplash.
- The incidence of whiplash injury following polytrauma is low.
- Low-velocity crashes constitute a major cause of whiplash injury.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Osteoarthritis
- Cervical disk disease
- Fibrositis
- Neuritis
- Torticollis
- Spinal cord tumor
- TMJ syndrome
- Tension headache
- Migraine headache

WORKUP

Any patient who presents with symptoms of whiplash and musculoskeletal or neurologic signs merits a workup to exclude cervical spine fractures or herniated disk disease.

LABORATORY TESTS

Laboratory studies are not helpful.

IMAGING STUDIES

- Plain C-spine films (anteroposterior, lateral, and odontoid views)
- Flexion/extension x-rays
- CT scan to exclude fracture
- MRI as alternative or in addition to CT in selected cases

TREATMENT

NONPHARMACOLOGIC THERAPY

- Soft cervical collar for no longer than 72 hr
- Moist heat 15 to 20 min four to six times per day.
- Continue with usual activities.

ACUTE GENERAL Rx

- Analgesics
  1. NSAIDS
  2. Acetaminophen up to a maximum of 1 g tid
- Muscle relaxants (short-term use)

CHRONIC Rx

NSAIDs and Tylenol can be used on a long-term basis, as needed.

DISPOSITION

- Most patients recover from the acute whiplash injury within weeks.
- Factors associated with persistent and severe whiplash injuries are described in Table W1-3.
- 20% to 40% may develop chronic whiplash syndrome (symptoms of headache, neck pain, and psychiatric complaints that persist for 6 mo).
- Older age, female gender, lawyer involvement, and work status (employed at time of entry to the clinic) were found to be prognostic factors associated with a negative outcome.

TABLE W1-3 Factors Associated with Persistent and Severe Whiplash Injuries

Severe Whiplash Injury
High-speed injury
Intense and rapid onset of pain
Severe restriction of movement at presentation
Abnormal neurology
Bony injuries
Persistent Whiplash Injury
High-speed injury
Intense and rapid onset of pain
Severe restriction of movement at presentation
Abnormal neurology
Bony injuries
Increasing age
Upper limb paresthesias
Cervical spondylosis

From Carr A, Hamilton W: *Orthopedics in primary care,* ed 2, Philadelphia, 2005, Saunders.

REFERRAL

Orthopedic, physical therapy

PEARLS & CONSIDERATIONS

- Nearly one third of all personal injury cases involve cervical injuries.
- There is no dose-response relationship between trauma severity and incidence of whiplash injury.

COMMENTS

The entity of chronic whiplash syndrome remains elusive. Some authorities argue that financial motivation is a factor leading to persistent neck symptoms. Other studies do not substantiate this, showing a true chronic injury to the soft tissues of the neck.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Whiplash (Patient Information)

AUTHOR: **JORGE A. VILLAFUERTE, M.D.**

SUGGESTED READINGS

Carroll LJ et al.: Frequency, timing and course of depressive symptomatology after whiplash, *Spine* 31(16):E551–E556, 2006.

Dufton JA et al.: Prognostic factors associated with minimal improvement following acute whiplash-associated disorders, *Spine* 31(20):E759–E765, 2006.

Giannoudis PV et al.: Incidence and outcome of whiplash injury after multiple trauma, *Spine* 32(7):776–781, 2007.

Rodriquez AA et al.: Whiplash: pathophysiology, diagnosis, treatment, and prognosis, *Muscle Nerve* 29(6):768, 2004.

Sterner Y, Gerdle B: Acute and chronic whiplash disorders—a review, *J Rehabil Med* 36(5):193, 2004.

BASIC INFORMATION

DEFINITION

Whipple's disease is a multisystem illness characterized by malabsorption and its consequences, lymphadenopathy, arthritis, cardiac involvement, ocular symptoms, and neurologic problems; it is caused by the gram-positive bacillus *Tropheryma whippelii.*

SYNONYMS

Intestinal lipodystrophy (name used by Whipple in 1907)

ICD-9CM CODES
040.2 Whipple's disease
ICD-10CM CODES
K90.81 Whipple's disease

EPIDEMIOLOGY & DEMOGRAPHICS

- Uncommon illness (only about 1000 cases have been reported to date)
- Peak age: 30 to 60 yr; mean age at diagnosis 50 yr
- More frequent in men than women and in Caucasians
- Specific environmental factors have not been associated with Whipple's disease

PHYSICAL FINDINGS & CLINICAL PRESENTATION

PHYSICAL FINDINGS

- Abdominal distention, sometimes with tenderness and less commonly fullness or mass, which represents enlarged mesenteric lymph nodes
- Signs of weight loss, cachexia
- Clubbing
- Lymphadenopathy
- Inflamed joints
- Heart murmur or rub
- Sensory loss or motor weakness related to peripheral neuropathy
- Abnormal mental status examination
- Pallor

CLINICAL PRESENTATION

Whipple's disease is characterized by two stages: a prodromal stage and a much later steady-state stage. The prodromal stage is marked by protean symptoms and chronic arthralgias and arthritis. The steady-state stage, which follows the prodromal stage by an average time of 6 yr, is manifested by weight loss, diarrhea, or both. When the disease presents with extraintestinal symptoms (e.g., arthralgia), few clinicians will suspect the diagnosis unless or until gastrointestinal (GI) symptoms are present. Weight loss, diarrhea, and arthropathies are found together in 75% of patients at time of diagnosis. The GI manifestations are those seen in malabsorption of any cause:

- Diarrhea: five to 10 semiformed, malodorous steatorrheic stools per day
- Abdominal bloating and cramps
- Anorexia

Extraintestinal manifestations of malabsorption:

- Weight loss, fatigue
- Anemia
- Bleeding diathesis
- Edema and ascites
- Osteomalacia

Extraintestinal involvement:

- Arthritis (intermittent, migratory; affecting small, large, and axial joints)
- Pleuritic chest pain and cough
- Pericarditis, endocarditis
- Dementia, ophthalmoplegia, myoclonus, and many other symptoms because any portion of the central nervous system may be a disease site
- Fever

ETIOLOGY & PATHOGENESIS

- Infectious disease caused by *Tropheryma whippelii,* an actinobacter.
- The bacillus has never been cultured, nor has direct transmission from patient to patient ever been documented; however, the agent can be seen in tissue samples by electron microscopy and identified by polymerase chain reaction (PCR).
- Predictable response to appropriate antibiotic therapy confirms the pathogenic role of the infection.
- Tissue infiltration by macrophages is believed to be the mechanism of specific organ dysfunction and symptoms.
- Subtle defects of the cell-mediated immunity exist in active and inactive Whipple's disease that may predispose certain individuals to clinical manifestations. HLA-B27 positivity is found in 26% of patients (four times higher than expected).

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

Malabsorption/maldigestion:

- Celiac disease
- *Mycobacterium avium-intracellulare* intestinal infection in patients with AIDS
- Intestinal lymphoma
- Abetalipoproteinemia
- Amyloidosis
- Systemic mastocytosis
- Radiation enteritis
- Crohn's disease
- Short bowel syndrome
- Pancreatic insufficiency
- Intestinal bacterial overgrowth
- Lactose deficiency
- Postgastrectomy syndrome
- Other cause of diarrhea (see Section III, "Diarrhea, Acute" and "Diarrhea, Chronic")
- Seronegative inflammatory arthritis
- Pericarditis and pleuritis
- Lymphadenitis
- Neurologic disorders

WORKUP

Laboratory tests and imaging studies are useful; however, the diagnosis of Whipple's disease is usually made by upper endoscopy and biopsy. Endoscopic findings reveal a pale yellow, shaggy mucosa alternating with an erythematous, erosive, or friable mucosa in the duodenum or jejunum.

LABORATORY TESTS

- Anemia (iron, folate, or vitamin B_{12} deficiency)
- Hypokalemia
- Hypocalcemia
- Hypomagnesemia
- Hypoalbuminemia
- Prolonged prothrombin time
- Low serum carotene
- Low cholesterol
- Leukocytosis
- Steatorrhea demonstrated by a Sudan fecal fat stain
- 72-hr stool collection demonstrating more than 7 g/24 hr of fat in the stool is impractical to perform, especially in ambulatory patients
- Defective D-xylose absorption

IMAGING STUDIES

Small bowel radiographs after barium ingestion often show thickening of mucosal folds.

BIOPSY

Infiltration of the intestinal lamina propria by PAS-positive macrophages containing gram-positive, acid-fast negative bacilli, associated with lymphatic dilation (diagnostic); PCR of the involved tissue in uncertain cases. If PAS staining of the small-bowel biopsy specimen is positive and the PCR assay is negative, the diagnosis of Whipple's disease must be confirmed; this can be done by immunohistochemical testing with an antibody to *T. whippelii.* If this test is positive, Whipple's disease is confirmed.

TREATMENT

- Antibiotics: TMP/SMX DS bid for 12 months, usually preceded by parenteral administration of ceftriaxone (2 g/day) for 2 weeks *or* penicillin G 2 million units q4h for 2 weeks
- Alternative regimen for sulfa-allergic patients consists of doxycycline (200 mg/day) *plus* hydroxychloroquine (200 mg tid) for 12 months following parenteral ceftriaxone or penicillin G for 2 weeks.
- Treat specific vitamin, mineral, and nutrient deficiencies.
- Patients with a neurologic recurrence of Whipple's disease have a poor prognosis. Interferon gamma has been proposed for treatment of recurrent central nervous system disease.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **FRED F. FERRI, M.D.**

SUGGESTED READINGS

Fenollar F et al.: Whipple's disease, *N Engl J Med* 356:55, 2007.

BASIC INFORMATION

DEFINITION

Wilson's disease is an autosomal recessive disorder of copper transport with inadequate biliary copper excretion, leading to an accumulation of the metal in liver, brain, kidneys, and corneas.

SYNONYMS

Progressive hepatolenticular degeneration

ICD-9CM CODES
275.1 Wilson's disease
ICD-10CM CODES
E83.00 Disorder of copper metabolism

EPIDEMIOLOGY & DEMOGRAPHICS

PREVALENCE: One case in 30,000
PREDOMINANT SEX: Affects men and women equally (autosomal recessive gene)
ONSET OF SYMPTOMS: Ages 3 to 40 yr

PHYSICAL FINDINGS & CLINICAL PRESENTATION

Hepatic presentation:
- Acute hepatitis with malaise, anorexia, nausea, jaundice, elevated transaminase, prolonged prothrombin time; rarely fulminant hepatic failure
- Chronic active (or autoimmune) hepatitis with fatigue, malaise, rashes, arthralgia, elevated transaminase, elevated serum immunoglobulin G, positive antinuclear antibody and antismooth muscle antibody
- Chronic liver disease/cirrhosis with hepatosplenomegaly, ascites, low serum albumin, prolonged prothrombin time, portal hypertension

Neurologic presentation:
- Movement disorder: tremors, ataxia
- Spastic dystonia: masklike facies, rigidity, gait disturbance, dysarthria, drooling, dysphagia
- The most common neurologic presentation in a young adult is parkinsonism.

Ophthalmic:
- Kayser-Fleischer ring; indicates copper deposition in the Descemet's membrane of the iris
- Sunflower cataracts

Psychiatric presentation:
- Depression, obsessive-compulsive disorder, psychopathic behaviors, neuroses

Other organs:
- Hemolytic anemia
- Renal disease (i.e., Fanconi's syndrome with hematuria, phosphaturia, renal tubular acidosis, vitamin D–resistant rickets)
- Cardiomyopathy
- Arthritis
- Hypoparathyroidism
- Hypogonadism

PHYSICAL FINDINGS:
- Ocular: the Kayser-Fleischer ring is a gold-yellow ring seen at the periphery of the iris (Fig. W1-6); It is present in virtually all persons with neurologic involvement. These should be sought with slit-lamp examination by a skilled examiner.
- Stigmata of acute or chronic liver disease.
- Neurologic abnormalities: see previous.

ETIOLOGY & PATHOGENESIS

- Dietary copper is transported from the intestine to the liver, where normally it is metabolized into ceruloplasmin. In Wilson's disease, defective incorporation of copper into ceruloplasmin and a decrease of biliary copper excretion lead to accumulation of this mineral.
- The disease results from an autosomal recessive inborn error of metabolism caused by a mutation of the copper P-type adenosine triphosphatase encoded on chromosome *13q14.3.*

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Hereditary hypoceruloplasminemia
- Menkes' disease
- Consider the diagnosis of Wilson's disease in all cases of acute or chronic liver disease for which another cause has not been established.
- Consider Wilson's disease in patients with movement disorders or dystonia even without symptomatic liver disease.

LABORATORY TESTS

- Low serum ceruloplasmin level (<200 mg/L) present in 95% of affected patients
- 24-hr urinary copper excretion greater than 100 mcg (normal <30 mcg); increases to greater than 1200 mcg/24 hr after 500 mg of d-penicillamine (normal <500 mcg/24 hr)
- Low serum copper (<65 mcg/L)
- Abnormal liver function tests (note that aspartate aminotransferase may be higher than alanine aminotransferase)
- Low serum uric acid and phosphorus
- Abnormal urinalysis (hematuria)

BIOPSY

- Early:
  1. Steatosis, focal necrosis, glycogenated hepatocyte nuclei
  2. May reveal inflammation and piecemeal necrosis
- Late: cirrhosis
- Hepatic copper content (>250 mcg/g of dry weight) (normal is 20 to 50 mcg) gold standard for diagnosis
- Histochemical confirmation of excess copper can be helpful in diagnosis, but if absent, does not exclude Wilson's disease. The lack of immunoreactivity to copper-binding protein can occur because of the diffuse presence of copper in the cytoplasm and because of the assay's low sensitivity. Rhodamine and rubeanic acid stains can show dense granular lysosomal copper deposition in hepatocytes at the stage of cirrhotic nodular regeneration.

TREATMENT

- Penicillamine: (chelator therapy)
  1. 0.75 to 1.5 g/day divided bid (with pyridoxine 25 mg/day)
  2. Monitor complete blood count (CBC) and urinalysis weekly
- Trientine (triethylenetetramine): (chelator therapy)
  1. 1 to 2 g/day divided tid
  2. Monitor CBC
- Zinc: (inhibits intestinal copper absorption)
  1. 50 mg tid
  2. Monitor zinc level
- Ammonium tetrathiomolybdate for neurologic symptoms
- Antioxidants
- Liver transplantation (for severe hepatic failure unresponsive to chelation); liver transplantation corrects the underlying pathophysiology and can be lifesaving

PROGNOSIS

Good with early chelation treatment

REFERRAL

To gastroenterologist, neurologist

PEARLS & CONSIDERATIONS

COMMENTS

Family screening of first-degree relatives must be undertaken. Genetic diagnosis is also useful in patients with indeterminate clinical and biochemical features.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Wilson's Disease (Patient Information)

AUTHOR: **FRED F. FERRI, M.D.**

FIGURE W1-6 Deposition of copper (Kayser-Fleischer ring, arrows) in the periphery of the cornea as seen in hepatolenticular degeneration (Wilson's disease). (From Haines DE: *Fundamental neuroscience for basic and clinical applications,* ed 3, Philadelphia, 2005, Churchill Livingstone.)

SUGGESTED READING

Ala A et al.: Wilson's disease, *Lancet* 369:397, 2007.

BASIC INFORMATION

DEFINITION

Wolff-Parkinson-White (WPW) syndrome is defined as the presence of preexcitation of the ventricles of the heart due to an abnormal electrical communication from the atria to the ventricles through an accessory pathway. Patients with WPW syndrome have both ventricular preexcitation and arrhythmias, which may be atrial fibrillation (AF), atrioventricular (AV) reentrant tachycardia, or both. Patients with WPW pattern have characteristic ECG findings of preexcitation: short PR interval <120 ms and the presence of a delta wave but no subjective or objective evidence of arrhythmia.

SYNONYMS

Preexcitation syndrome
WPW

ICD-9CM CODES
426.7 Wolff-Parkinson-White syndrome
ICD-10CM CODES
I45.6 Pre-excitation syndrome

EPIDEMIOLOGY & DEMOGRAPHICS

- The prevalence of a WPW pattern on the surface ECG is 0.15% to 0.25% in the general population. The prevalence is increased to 0.55% in first-degree relatives of affected patients.
- In a study of a presumed healthy population of more than 20,000 patients, the WPW pattern was recognized in 0.25%. Of these patients, only 1.8% had documented arrhythmias that were consistent with the WPW syndrome.
- The prevalence of WPW is higher among males and decreases with age.
- Most patients with WPW syndrome have structurally normal hearts, but associations with mitral valve prolapse, cardiomyopathies, and Ebstein's anomaly have been reported.

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- The physical examination may be entirely normal.
- Symptoms are typically related to tachyarrhythmias, including the following:
  - Palpitations, anxiety dyspnea, chest pain or tightness
  - Syncope or near syncope
  - Sudden cardiac death (rarely; <0.4%)
- Over time, 25% of cases become asymptomatic and remain symptom free if past age 40.
- The type of tachycardia can be any of the following:
  - Supraventricular tachycardia: AV reentrant tachycardia (AVRT) most common arrhythmia, further classified as orthodromic (narrow complex and occurs in 70% of symptomatic patients), or antidromic (wide complex, in 4%-5% of patients)
  - AF (~10% to 38%), the second most common tachycardia, can be complicated by a very rapid ventricular response via conduction over the accessory pathway (AP), which can lead to ventricular fibrillation and sudden death. This risk is dependent on the antegrade refractory period of AP during AF.
  - Atrial flutter (<5%)
- Presence of WPW can be associated with other congenital cardiac defects (e.g., Ebstein anomaly and L-transposition of the great vessels).
- Incidence of sudden cardiac death in WPW syndrome is estimated at 0.15%-0.39% per patient per yr. The risk of death is lower in asymptomatic patients.
- Left free wall accessory pathways are most common, followed by posteroseptal, right free wall, and anteroseptal locations.

ETIOLOGY & PATHOGENESIS

- The existence of an accessory pathway allows for conduction from the atria to the ventricles while bypassing the AV node.
- If the accessory pathway is capable of anterograde conduction, two parallel routes of AV conduction are possible: one is subject to delay through the AV node, and the other occurs without delay through the accessory pathway and results in preexcitation of the ventricle. The resulting QRS complex is a fusion beat, as a portion of the ventricle is activated via the accessory pathway giving rise to the delta wave, and the remainder of the ventricle is activated by the normal activation pathway (Fig. W1-7).
- Tachycardias occur when conduction is anterograde in one pathway (usually the normal AV pathway) and retrograde in the other (usually the accessory pathway) as a result of different refractory periods. This is usually initiated by a premature atrial or ventricular depolarization. Some patients (~5% to 10%) with WPW syndrome have multiple accessory pathways.
- Because of the involvement of usually a significant portion of the ventricle, the tachycardia circuit can be long and thus AVRT is known as a long R-P tachycardia, as opposed to AVNRT, which is usually a short R-P tachycardia.

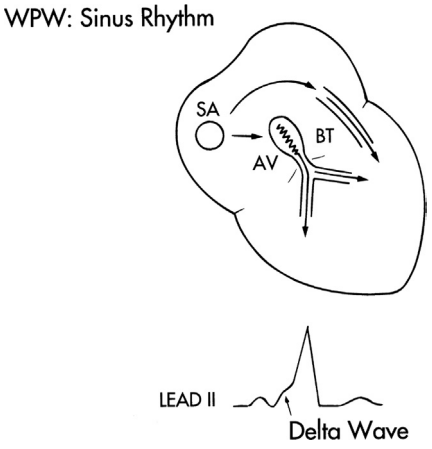

FIGURE W1-7 With Wolff-Parkinson-White *(WPW)* syndrome, an abnormal accessory conduction pathway called a *bypass tract (BT)* connects the atria and the ventricles. (From Goldberger AL [ed]: *Clinical electrocardiography: a simplified approach,* ed 6, St Louis, 1999, Mosby.)

DIAGNOSIS

- Three basic features characterize the ECG abnormalities associated with WPW pattern (Fig. W1-8):
  1. PR interval <120 msec
  2. QRS complex can be >120 msec with a slurred, slowly rising onset of QRS in some leads (delta wave) and a normal terminal QRS portion. The width of the QRS complex depends directly on the level of pre-excitation during the ECG
  3. Secondary ST-T wave changes directed in an opposite direction to the major delta and QRS vectors.
- ECG patterns with abnormal QRS complexes and ST and T changes can mask or mimic myocardial infarction, bundle branch block, or ventricular hypertrophy.
- Most commonly seen tachycardia is characterized by a normal QRS with a regular rate of 150-250 bpm. Onset and termination are abrupt.
- Variants of preexcitation:
  1. Lown-Ganong-Levine syndrome: fibers from the atrium to the His bundle bypass the physiologic delay of the AV node (atriohisian pathways) with a short PR interval and a normal QRS complex on ECG (no delta wave)
  2. Atriofascicular accessory pathways: duplication of the AV node and distal conducting system with normal baseline ECG

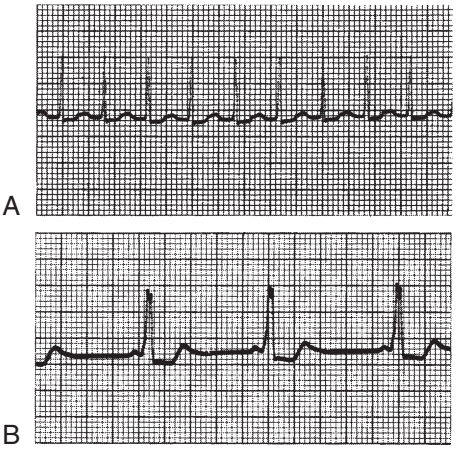

FIGURE W1-8 A, Supraventricular tachycardia in a child with Wolff-Parkinson-White syndrome. Note the normal QRS complexes during the tachycardia. **B,** Later, the typical features of Wolff-Parkinson-White syndrome are apparent: a short P-R interval, a delta wave, and a wide QRS. (From Behrman RE: *Nelson textbook of pediatrics,* ed 18, Philadelphia, 2007, Saunders.)

3. The only way to be certain of the accessory pathways' properties and propensity for rapid conduction is via an electrophysiology (EP) study.

RISK STRATIFICATION

- Intermittent loss or appearance of preexcitation on a beat-to-beat basis is indicative of lower risk, assessed with Holter monitoring or with exercise testing. The loss of preexcitation after administration of the antiarrhythmic drug procainamide has also been used to indicate a low-risk subgroup
- In patients with a persistent preexcitation pattern, EP study is the procedure of choice for risk stratification by inducing AF, indicating high risk.

Rx TREATMENT

- Goals of electrophysiologic evaluation in patients with WPW syndrome are described in Box W1-1.
- Urgent cardioversion, for an acute tachycardia episode with hemodynamic instability
- Stable patients treated medically
  1. Narrow QRS width tachycardias:
  2. Carotid sinus massage or vagal maneuvers
  3. Atrial pacing (transvenous or transesophageal)
  4. Adenosine and verapamil are usually contraindicated given the prevalence of underlying atrial fibrillation in this population and the risk of causing ventricular fibrillation by direct ventricular stimulation through the accessory pathway when the AV node is completely blocked.
  5. AF is potentially life threatening
  6. Wide QRS complex tachycardias (WCTs):
  7. Because atrial arrhythmias (Aflutter/AF) with antegrade conduction down an AP are *not* AV node dependent, AV nodal blocking therapies are ineffective and potentially dangerous.
  8. Beta-blockers, calcium channel blockers, digoxin, and adenosine should be avoided. Can try procainamide. If tachycardia persists, synchronized DCCV is the treatment of choice.
- Long-term management:
  1. Priority of therapy:
  2. Asymptomatic: no therapy unless high risk or family history of sudden death, competitive athletes, high-risk occupation (pilots)
  3. Symptomatic, prior AF, aborted sudden death: further study/therapy
  4. Medical therapy (asymptomatic high risk):
  5. Single drug: amiodarone, sotalol, flecainide, propafenone
  6. Combination AV nodal blocker (beta-blocker/calcium channel blocker) and drugs that exclusively work on AP (class IA arrhythmics [quinidine, procainamide, and disopyramide])
  7. Recommendations for radiofrequency catheter ablation of accessory pathways:
  8. Class 1: patients with symptomatic AVRT and AF (or other atrial tachyarrhythmia) with rapid ventricular rates (RVR) via the AP when the tachycardia is drug resistant or the patient is intolerant or does not desire long-term drug therapy.
- For patients with a rapid ventricular response with hemodynamic compromise, urgent electrical cardioversion is warranted.
- Digitalis should not be used as a single drug in patients who have atrial flutter or AF, because it can reduce refractoriness in the accessory pathway and accelerate the tachycardia.
- Drug therapy for the chronic prevention of narrow complex regular tachyarrhythmias includes class IC antiarrhythmics, β-blockers, calcium channel blockers, amiodarone, or sotalol.
- For the treatment of AF in patients with WPW, the administration of AV nodal–blocking agents may not slow the ventricular rate, because the accessory pathways capable of rapid conduction do not respond to AV-blocking agents. Procainamide is the drug of choice for controlling the ventricular rate and restoring the sinus rhythm in patients with WPW who have AF.
- For long-term therapy to prevent recurrence, radiofrequency catheter ablation has become the first-line therapy for most patients. When medical therapy fails or patients are drug intolerant, or for those patients who do not wish to take drugs, or cannot tolerate the tachyarrhythmias, radiofrequency ablation should be performed (class 1 indication).
- Most patients with asymptomatic preexcitation have a good prognosis; cardiac arrest is rarely the first manifestation of the disease. Usually no intervention or EP testing is indicated, as the 2% risk of catheter ablation is usually not justified considering the low risk of sudden cardiac death in asymptomatic individuals.

BOX W1-1 Goals of Electrophysiologic Evaluation in Patients with Wolff-Parkinson-White Syndrome

- Confirmation of the presence of an atrioventricular bypass tract (BT)
- Evaluation for the presence of multiple BTs
- Localization of the BT(s)
- Evaluation of the refractoriness of the BT and its implications for life-threatening arrhythmias
- Induction and evaluation of tachycardias
- Demonstration of the BT role in the tachycardia
- Evaluation of other tachycardias not dependent on the presence of the BT
- Termination of the tachycardias

From Issa Z et al: *Clinical arrhythmology and electrophysiology,* ed 2, Philadelphia, 2012, Saunders.

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Wolff-Parkinson-White Syndrome (Patient Information)

AUTHOR: **BARRY FINE, M.D., PH.D.**

SUGGESTED READINGS

Epstein AE et al.: ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons, *Circulation* 117:e350, 2008.

Fitzsimmons PJ et al.: The natural history of Wolff-Parkinson-White syndrome in 228 military aviators: a long-term follow-up of 22 years, *Am Heart J* 142(3):530–536, 2001.

Marine JE: Catheter ablation therapy for supraventricular arrhythmias, *JAMA* 298(23):2768, 2007.

Mark DG et al.: Preexcitation syndromes: diagnostic considerations in the ED, *Am J Emerg Med* 27:878–888, 2009.

Shafqaut A et al.: Cardiac electrophysiology studies and ablations for treatment of SV arrhythmias–an initial experience from Karachi, *J Pak Med Assoc* 61(2):173–175, 2011.

Wellens HJ: When to perform catheter ablation in asymptomatic patients with a Wolff-Parkinson-White electrocardiogram, *Circulation* 112:2201–2216, 2005.

Zipes DP et al.: ACC/AHA Task Force on Practice Guidelines (Committee on Clinical Intracardiac Electrophysiological and Catheter Ablation Procedures). Developed in Collaboration with the North American Society of Pacing and Electrophysiology, *Circulation* 92:673–691, 1995.

BASIC INFORMATION

DEFINITION

Yellow fever is a mosquito-borne infection, primarily of the liver, with systemic manifestations caused by the yellow fever virus (YFV). The clinical spectrum ranges from asymptomatic infection to life-threatening disease with severity and mortality highest in the elderly.

SYNONYMS

Tropical hemorrhagic fever from YFV

ICD-9CM CODES
060.9 Yellow fever
ICD-10CM CODES
A95.9 Yellow fever, unspecified

EPIDEMIODLOGY & DEMOGRAPHICS

GEOGRAPHIC DISTRIBUTION

- South America and Africa, in countries between +15 and –15 degrees latitude
- The World Health Organization estimates there are more than 200,000 cases a yr with 30,000 deaths per yr. More than 90% of cases occur in Africa.

INCIDENCE: Approximate attack rates of 3% in Africa and Amazon
PREVALENCE: Endemic areas: 20% of population
PREDOMINANT SEX: In Africa and the Amazon, male agricultural workers

PHYSICAL FINDINGS & CLINICAL PRESENTATION

- Most subclinical
- The onset of illness appears suddenly 3 to 6 days after the bite of an infected mosquito.
- Viremic (early) phase:
  1. Fever, chills
  2. Severe headache
  3. Lumbosacral pain
  4. Myalgias, nausea, malaise
  5. Conjunctivitis
  6. Relative bradycardia (Faget's sign)
- After brief recovery, toxic phase:
  1. Jaundice
  2. Oliguria
  3. Albuminuria
  4. Hemorrhage
  5. Encephalopathy
  6. Shock
  7. Acidosis
- Case-fatality rate: 25% to 50%

ETIOLOGY

- YFV *(L. flavus)*
  1. Flavivirus infects hepatic cells
  2. Late in infection, cytopathic effects (antibody- and cell-mediated) produce pathology
- Vector
  1. *Aedes aegypti* (urban)
  2. *Aedes* spp., *Haemagogus* (especially in Amazon) mosquitos (sylvan)
  3. Primary hosts: humans and simian species
  4. Exists in two transmission cycles:
     a. Sylvatic or jungle cycle involving mosquitos and nonhuman primates
     b. Urban cycle involving mosquitos and humans

PATHOGENESIS & PATHOLOGY

- Virus replication begins at site of mosquito bite, spreading to lymphatic channels and regional lymph nodes. Viremic spread to other organs, especially liver, spleen, and bone marrow.
- Shock and fatal illness result from direct damage to organs and vasoactive cytokines.
- Viral antigen found in hepatocytes, kidneys, and myocardium.
- Midzone necrosis of liver lobules primarily affected and is highly characteristic.
- Hemorrhages of mucosal surfaces of GI tract.

DIAGNOSIS

DIFFERENTIAL DIAGNOSIS

- Viral hepatitis
- Leptospirosis
- Malaria
- Typhoid fever
  1. Typhus
  2. Relapsing fever
- Other hemorrhagic fevers such as dengue (see Table EY1-1)

LABORATORY TESTS

- CBC
  1. Mild leukopenia
  2. Thrombocytopenia
  3. Anemia
- LFTs
  1. AST levels exceed ALT levels
  2. Alkaline phosphatase normal or slightly elevated
  3. Elevated bilirubin levels
- Elevated BUN and creatinine
- Proteinuria
- Coagulation studies
  1. Demonstrate abnormal prothrombin time *or*
  2. Reveal DIC
- Terminal hypoglycemia
- CSF
  1. Pleocytosis
  2. Elevated protein count
- Specific diagnosis confirmed by:
  1. Viral isolation from blood
  2. Viral antigen in serum (ELISA)
  3. Viral RNA by polymerase chain reaction (PCR)
  4. IgM-capture ELISA
     a. Preferred serologic test
     b. Appears within 5 to 7 days
     c. Rising Ab confirmed by paired sera
     d. Cross-reactivity with other flavivirus infections
  5. Immunohistochemical staining of postmortem liver biopsy specimens

TREATMENT

ACUTE GENERAL Rx

- Acetaminophen (for headache and fever) and H_2 blockers (GI bleeding); avoid aspirin because of bleeding risk
- Blood transfusion, volume replacement for hemorrhage and shock
- Dialysis for renal failure
- Avoidance of sedatives and drugs dependent on hepatic metabolism

DISPOSITION

Follow up until hepatic, renal, CNS disease resolved. Infection in humans is capable of producing hemorrhagic fever and is fatal in 20% to 50% of persons with severe disease

REFERRAL

To infectious diseases expert for accurate diagnosis and management

TABLE EY1-1 Viral Hemorrhagic Fevers (HFs)

Mode of Transmission	Disease	Virus
Tick-borne	Crimean-Congo HF*	Congo
	Kyasanur Forest disease	Kyasanur Forest disease
	Omsk HF	Omsk
Mosquito-borne†	Dengue HF	Dengue (four types)
	Rift Valley fever	Rift Valley fever
	Yellow fever	Yellow fever
Infected animals or materials to humans	Argentine HF	Junin
	Bolivian HF	Machupo
	Lassa fever*	Lassa
	Marburg disease*	Marburg
	Ebola HF*	Ebola
	HF with renal syndrome	Hantaan

*Patients may be contagious; nosocomial infections are common.
†Chikungunya virus is associated infrequently with petechiae and epistaxis. Severe hemorrhagic manifestations have been reported in some cases.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

PEARLS & CONSIDERATIONS

PREVENTION

- Yellow fever is preventable by immunization.
- Recovery from yellow fever confers lasting immunity.
- Live, attenuated yellow fever vaccine (YF-Vax) provides protective immunity in 95% of vaccinated patients within 10 days of vaccination. Reimmunization is required at 10-yr intervals for travelers. Vaccine certificate to verify immunization status is required before travel in many tropical countries in South America and Africa. Vaccine nonresponders are uncommon but exhibit excess anti-inflammatory cytokine profiles and with high levels of T regulatory cells; this problem is more likely to be observed in elderly individuals.
- Vaccine contraindicated in:
  1. Infants <6 mo (postvaccinal encephalitis)
  2. Immunosuppressed patients
  3. Pregnant women and nursing mothers
  4. Patients with egg hypersensitivity
- Adverse effects of vaccine:
  1. General
     a. Mild headaches, myalgias, low-grade fevers (25% vaccinees in clinical trials)
     b. Immediate hypersensitivity reaction (history of egg allergy)
  2. Vaccine-associated neurotropic disease (postvaccine encephalitis) (1.8 cases per million)
     a. Primarily among infants
     b. Adult cases only in first-time vaccine recipients
  3. Vaccine-associated viscerotropic disease (2.2 cases per million)
     a. Disease syndrome resembling wild-type yellow fever, often fatal
     b. All cases in first-time vaccinees; age >60 yr are at particular risk.
- Yellow fever vaccine response can be significantly reduced by coadministration of the live virus combined vaccine with measles, mumps, and rubella.
- A new inactivated vaccine is in development which could eliminate the rare risk of the current live virus yellow fever vaccine-associated neurotropic or viscerotropic disease.

SUGGESTED READINGS

Available at www.expertconsult.com

AUTHOR: **STEVEN M. OPAL, M.D.**

SUGGESTED READINGS

Centers for Disease Control and Prevention: Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 59(RR-7):1–27, 2010.

Doblas A et al.: Yellow fever vaccine-associated viscerotropic disease and death in Spain, *J Clin Virol* 36(2):156, 2006.

Massad E et al.: Yellow fever vaccination: how much is enough? *Vaccine* 23(30):3908, 2005.

Monath TP: An inactivated cell-culture vaccine against yellow fever, *N Engl J Med* 346:1326–1333, 2011.

Nascimento Silva JR: Mutual interference on the immune response to yellow fever vaccine and a combined vaccine to measles mumps and rubella, *Vaccine* 29:6327–6334, 2011.

Zenker's (Pharyngoesophageal) Diverticulum

BASIC INFORMATION

DEFINITION

Zenker's diverticulum (ZD) refers to the acquired physiologic obstruction of the esophageal introitus that results from mucosal herniation posteriorly between the cricopharyngeus muscle and the inferior pharyngeal constrictor muscle (Fig. EZ1-1).

SYNONYMS

Pharyngoesophageal diverticulum
Pulsion diverticulum

ICD-9CM CODES
530.6 Zenker's diverticulum (esophagus)
ICD-10CM CODES
K22.5 Diverticulum of esophagus, acquired

EPIDEMIOLOGY & DEMOGRAPHICS

- The most common type of diverticulum of the upper gastrointestinal tract
- Rare disease with annual incidence estimated 1/50,000 per year
- Most commonly presents after the age of 60 yr, more commonly seen in males
- Peak incidence is seventh to ninth decades
- Associated with gastroesophageal reflux disease (GERD) and hiatal hernia

PHYSICAL FINDINGS & CLINICAL PRESENTATION

A small ZD may be asymptomatic. As it becomes larger, symptoms may include:

- Dysphagia to solids and liquids (most common)
- Regurgitation of undigested food
- Sensation of globus or fullness in the neck
- Cough
- Halitosis
- Aspiration pneumonia
- Weight loss
- Voice changes
- Sialorrhea (excessive drooling)

ETIOLOGY

- The specific cause is not known. The leading hypothesis suggests a discoordination of the swallowing muscles (specifically, incomplete relaxation of the cricopharyngeus muscle) that leads to an increased pressure on the mucosa of the hypopharynx, resulting in a progressive distention of that mucosa in its weakest area (posterior wall in "Killian's triangle," the point between the oblique fibers of the inferior pharyngeal muscle and the horizontal fibers of the cricopharyngeus muscle). The end result is the formation of a false diverticulum where food elements and secretions may be lodged, causing the symptoms listed previously.
- ZD may also occur after anterior spinal surgery or cervical spine injury.

DIAGNOSIS

- Clinical presentation and barium swallow typically make the diagnosis of ZD.
- Neck ultrasound can also be used.
- Esophageal manometry can help elucidate the pathogenesis but not required for diagnosis

DIFFERENTIAL DIAGNOSIS

The differential diagnosis is similar to anyone presenting with dysphagia:

- Achalasia
- Esophageal spasm
- Esophageal carcinoma
- Esophageal webs
- Peptic stricture
- Lower esophageal (Schatzki) ring
- Foreign bodies
- Central nervous system disorders (stroke, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, myasthenia gravis, muscular dystrophies)
- Dermatomyositis
- Infection

WORKUP

Barium swallow is the test of choice. Upper endoscopy runs the risk of perforation.

LABORATORY TESTS

Not specific

IMAGING STUDIES

- Barium swallow: demonstrates a herniated sac with a narrow diverticular neck that typically originates proximal to the cricopharyngeus at the level of C5-C6 (Fig. EZ1-2).
- Endoscopy is only indicated if barium studies show mucosal irregularities to rule out neoplasia.
- Oropharyngeal-esophageal scintigraphy has recently been shown to be an effective, sensitive, and simple diagnostic study for both qualitative and quantitative analyses.
- A chest x-ray is performed in cases of suspected aspiration pneumonia.

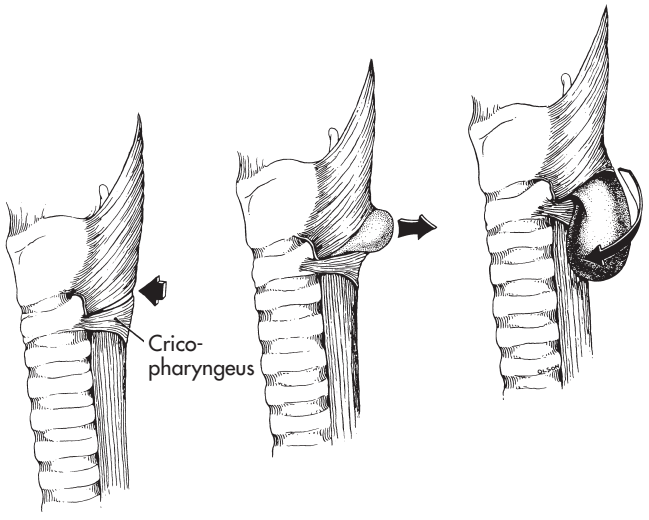

FIGURE EZ1-1 Formation of pharyngoesophageal (Zenker's) diverticulum. *Left,* Herniation of the pharyngeal mucosa and submucosa occurs at the point of transition *(arrow)* between the oblique fibers of the thyropharyngeus muscle and the more horizontal fibers of the cricopharyngeus muscle. *Center and right,* As the diverticulum enlarges, it dissects toward the left side and downward into the superior mediastinum in the prevertebral space. (From Sabiston D: *Textbook of surgery,* ed 15, Philadelphia, 1997, Saunders.)

TREATMENT

NONPHARMACOLOGIC THERAPY

- Soft mechanical diet can be tried in patients with symptoms of dysphagia.
- Avoid seeds, skins, and nuts.

ACUTE GENERAL Rx

- Surgical repair is the conventional treatment for symptomatic patients (dysphagia, cough, aspiration) with excellent relief of symptoms in nearly all patients and low procedural mortality (<1.5%). Procedures include:
  1. Cervical diverticulectomy with cricopharyngeal myotomy (most common approach)
  2. Diverticulopexy or diverticular inversion with cricopharyngeal myotomy
  3. Diverticulectomy alone
  4. Cricopharyngeal myotomy alone
- Endoscopic techniques (esophagodiverticulostomy) have largely replaced conventional surgery and include:
  1. Endoscopic stapler diverticulotomy (may be the initial treatment of choice)
  2. Microendoscopic carbon dioxide laser surgical diverticulotomy
  3. Diverticulum <3 cm is a contraindication to endosurgical approach.
  4. Head-to-head comparison with surgical repairs showed endoscopic techniques to be similar in results, relief of symptoms, and patient satisfaction.

CHRONIC Rx

In patients not having surgery, treatment is directed toward any complications that may occur:

- Antibiotics for aspiration pneumonia
- H_2 antagonists for ulcerations that can develop within the diverticulum
- Botulinum toxin for temporary relief of dysphagia

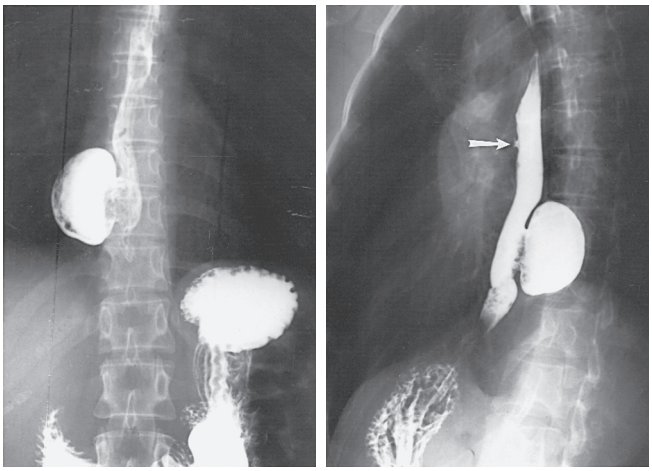

FIGURE EZ1-2 Posteroanterior *(left)* and oblique *(right)* views from barium esophagogram showing both a typical diverticulum of the junction of the mid-esophagus and distal esophagus and a small traction diverticulum *(arrow)* of the mid-esophagus. (From Sabiston D: *Textbook of surgery,* ed 15, Philadelphia, 1997, Saunders.)

DISPOSITION

- If left untreated, progressive enlargement of the diverticulum occurs.
- The risk of complications (e.g., aspiration pneumonia) increases with the size of the diverticulum.
- Postsurgical recurrence can occur (4%); however, these are usually asymptomatic.

REFERRAL

Any patient with dysphagia requires a gastroenterology consultation. A thoracic surgical, ENT, or head and neck surgeon may be consulted if surgery is considered.

COMMENTS

The association with cancer is rare (0.4%).

SUGGESTED READINGS

Available at www.expertconsult.com

RELATED CONTENT

Zenker's Diverticulum (Patient Information)

AUTHORS: **ROBERT M. KIRCHNER, M.D.,** and **PAUL GORDON, M.D.**

SUGGESTED READINGS

Bonavina L et al.: Long-term results of endosurgical and open surgical approach for Zenker diverticulum, *World J Gastroenterol* 14(18):2586, 2007.

Ferreira LE et al.: Zenker's diverticula: pathophysiology, clinical presentation, and flexible endoscopic management, *Dis Esophagus* 21(1):1–8, 2008.

Ruiz-Tovar J et al.: 20 years experience in the management of Zenker's diverticulum in a third-level hospital, *Rev Esp Enferm Dig* 98(6):429, 2006.

Wirth D et al.: Outcome and quality of life after open surgery versus endoscopic stapler-assisted esophagodiverticulostomy for Zenker's diverticulum, *Dis Esophagus* 19(4):294, 2006.

SECTION II

Differential Diagnosis

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ABDOMINAL DISTENTION

ICD-9CM # 787.3
ICD-10CM # R14.0 Abdominal Distension (Gaseous)

NONMECHANICAL OBSTRUCTION

Excessive intraluminal gas.
Intraabdominal infection.
Trauma.
Retroperitoneal irritation (renal colic, neoplasms, infections, hemorrhage).
Vascular insufficiency (thrombosis, embolism).
Mechanical ventilation.
Extraabdominal infection (sepsis, pneumonia, empyema, osteomyelitis of spine).
Metabolic/toxic abnormalities (hypokalemia, uremia, lead poisoning).
Chemical irritation (perforated ulcer, bile, pancreatitis).
Peritoneal inflammation.
Severe pain, pain medications.

MECHANICAL OBSTRUCTION

Neoplasm (intraluminal, extraluminal).
Adhesions, endometriosis.
Infection (intraabdominal abscess, diverticulitis).
Gallstones.
Foreign body, bezoars.
Pregnancy.
Hernias.
Volvulus.
Stenosis at surgical anastomosis, radiation stenosis.
Fecaliths.
Inflammatory bowel disease.
Gastric outlet obstruction.
Hematoma.
Other: parasites, superior mesenteric artery (SMA) syndrome, pneumatosis intestinalis, annular pancreas, Hirschsprung's disease, intussusception, meconium.

ABDOMINAL PAIN, ADOLESCENCE[26]

ICD-9CM # 789.67
ICD-10CM # R10.817 Generalized Abdominal Tenderness
R10.827 Generalized Rebound Abdominal Tenderness

Acute gastroenteritis.
Irritable bowel syndrome (IBS).
Anxiety.
Mittelschmerz.
Appendicitis.
Inflammatory bowel disease.
Peptic ulcer disease (PUD).
Cholecystitis.
Neoplasm.
Diabetic ketoacidosis.
Functional abdominal pain.
Pelvic inflammatory disease (PID).
Pregnancy.
Pyelonephritis.
Renal stone.
Trauma.

ABDOMINAL PAIN, CHILDHOOD[26]

ICD-9CM # 789.67
ICD-10CM # R10.817 Generalized Abdominal Tenderness
R10.827 Generalized Rebound Abdominal Tenderness

Acute gastroenteritis.
Appendicitis.
Constipation.
Cholecystitis, acute.
Intestinal obstruction.
Pancreatitis.
Neoplasm.
Inflammatory bowel disease.
Other:
Functional abdominal pain.
Pyelonephritis.
Pneumonia.
Diabetic ketoacidosis.
Heavy metal poisoning.
Sickle cell crisis.
Trauma.
Anxiety.
Sexual abuse.

ABDOMINAL PAIN, CHRONIC LOWER[38]

ICD-9CM # 789.64 Abdominal Pain, Left Lower Quadrant
789.63 Abdominal Pain, Right Lower Quadrant
789.85 Abdominal Pain, Suprapubic
ICD-10CM # R10.814 Left Lower Quadrant Abdominal Tenderness
R10.824 Left Lower Quadrant Rebound Abdominal Tenderness
R10.813 Right Lower Quadrant Abdominal Tenderness
R10.823 Right Lower Quadrant Rebound Abdominal Tenderness
R10.30 Lower Abdominal Pain, Unspecified

ORGANIC DISORDERS

Common
Gynecologic disease.
Lactase deficiency.
Diverticulitis/diverticulosis.
Crohn's disease.
Intestinal obstruction.
Uncommon
Chronic intestinal pseudoobstruction.
Mesenteric ischemia.
Malignancy (e.g., ovarian carcinoma).
Abdominal wall pain.
Spinal disease.
Testicular disease.
Metabolic diseases (e.g., diabetes mellitus, familial Mediterranean fever, C1 esterase deficiency [angioneurotic edema], porphyria, lead poisoning, tabes dorsalis, renal failure).

FUNCTIONAL DISORDERS

Common
Irritable bowel syndrome.
Functional abdominal bloating.
Uncommon
Functional abdominal pain.

ABDOMINAL PAIN, DIFFUSE

ICD-9CM # 789.67
ICD-10CM # R10.817 Generalized Abdominal Tenderness
R10.827 Generalized Rebound Abdominal Tenderness

Early appendicitis.
Aortic aneurysm.
Gastroenteritis.
Intestinal obstruction.
Diverticulitis.
Peritonitis.
Mesenteric insufficiency or infarction.
Pancreatitis.
Inflammatory bowel disease.
Irritable bowel.
Mesenteric adenitis.
Metabolic: toxins, lead poisoning, uremia, drug overdose, diabetic ketoacidosis (DKA), heavy metal poisoning.
Sickle cell crisis.
Pneumonia (rare).
Trauma.
Urinary tract infection, PID.
Other: anxiety, acute intermittent porphyria, tabes dorsalis, periarteritis nodosa, Henoch-Schönlein purpura, adrenal insufficiency.

ABDOMINAL PAIN, EPIGASTRIC

ICD-9CM # 789.66
ICD-10CM # R10.816 Epigastric Abdominal Tenderness
R10.826 Epigastric Rebound Abdominal Tenderness

Gastric: PUD, gastric outlet obstruction, gastric ulcer.
Duodenal: PUD, duodenitis.
Biliary: cholecystitis, cholangitis, biliary dyskinesia.
Hepatic: hepatitis.
Pancreatic: pancreatitis.
Intestinal: high small bowel obstruction, early appendicitis.
Cardiac: angina, MI, pericarditis.
Pulmonary: pneumonia, pleurisy, pneumothorax.
Subphrenic abscess.
Vascular: dissecting aneurysm, mesenteric ischemia.
Psychiatric: anxiety.

ABDOMINAL PAIN, INFANCY[26]

ICD-9CM #	789.67	
ICD-10CM #	R10.817	Generalized Abdominal Tenderness
	R10.827	Generalized Rebound Abdominal Tenderness

Acute gastroenteritis.
Appendicitis.
Intussusception.
Volvulus.
Meckel diverticulum.
Other: colic, trauma.

ABDOMINAL PAIN, LEFT LOWER QUADRANT

ICD-9CM #	789.64	
ICD-10CM #	R10.814	Left Lower Quadrant Abdominal Tenderness
	R10.824	Left Lower Quadrant Rebound Abdominal Tenderness

Intestinal: diverticulitis, diverticulosis, intestinal obstruction, perforated ulcer, inflammatory bowel disease, perforated descending colon, inguinal hernia, neoplasm, appendicitis.
Reproductive: ectopic pregnancy, ovarian cyst, torsion of ovarian cyst, tuboovarian abscess, mittelschmerz, endometriosis, seminal vesiculitis.
Renal: renal or ureteral calculi, pyelonephritis, neoplasm.
Vascular: leaking aortic aneurysm.
Psoas abscess.
Trauma.

ABDOMINAL PAIN, LEFT UPPER QUADRANT

ICD-9CM #	789.32	
ICD-10CM #	R19.02	Left Upper Quadrant Abdominal Swelling, Mass, and Lump

Gastric: PUD, gastritis, pyloric stenosis, hiatal hernia.
Pancreatic: pancreatitis, neoplasm, stone in pancreatic duct or ampulla.
Cardiac: MI, angina pectoris.
Splenic: splenomegaly, ruptured spleen, splenic abscess, splenic infarction.
Renal: calculi, pyelonephritis, neoplasm.
Pulmonary: pneumonia, empyema, pulmonary infarction.
Vascular: ruptured aortic aneurysm.
Cutaneous: herpes zoster.
Trauma.
Intestinal: high fecal impaction, perforated colon, diverticulitis.

ABDOMINAL PAIN, NONSURGICAL CAUSES

ICD-9CM #	789.9	
ICD-10CM #	R19.8	Other Specified Symptoms and Signs Involving the Digestive System and Abdomen
	R10.817	Generalized abdominal tenderness

Irritable bowel syndrome.
Urinary tract infection, pyelonephritis, salpingitis, PID.
Gastroenteritis, gastritis, peptic ulcer.
Diverticular spasm.
Hepatitis, mononucleosis.
Pancreatitis.
Inferior wall myocardial infarction.
Basilar pneumonia, pulmonary embolism.
Diabetic ketoacidosis.
Strain or hematoma of rectus muscle.
Ruptured Graafian follicle.
Herpes zoster.
Nerve root compression.
Sickle cell crisis.
Acute adrenal insufficiency.
Other: acute porphyria, familial Mediterranean fever, tabes dorsalis, anxiety, sexual abuse.

ABDOMINAL PAIN, PERIUMBILICAL

ICD-9CM #	789.65	
ICD-10CM #	R10.815	Periumbilic Abdominal Tenderness
	R10.825	Periumbilic Rebound Abdominal Tenderness

Intestinal: small bowel obstruction or gangrene, early appendicitis.
Vascular: mesenteric thrombosis, dissecting aortic aneurysm.
Pancreatic: pancreatitis.
Metabolic: uremia, DKA.
Trauma.

ABDOMINAL PAIN, POORLY LOCALIZED[26]

ICD-9CM #	789.60	
ICD-10CM #	R10.819	Abdominal Tenderness, Unspecified Site

EXTRAABDOMINAL

Metabolic
DKA, acute intermittent porphyria, hyperthyroidism, hypothyroidism, hypercalcemia, hypokalemia, uremia, hyperlipidemia, hyperparathyroidism.
Hematologic
Sickle cell crisis, leukemia or lymphoma, Henoch-Schönlein purpura.
Infectious
Infectious mononucleosis, Rocky Mountain spotted fever, acquired immunodeficiency syndrome (AIDS), streptococcal pharyngitis (in children), herpes zoster.
Drugs and Toxins
Heavy metal poisoning, black widow spider bites, withdrawal syndromes, mushroom ingestion.
Referred Pain
Pulmonary: pneumonia, pulmonary embolism, pneumothorax.
Cardiac: angina, MI, pericarditis, myocarditis.
Genitourinary: prostatitis, epididymitis, orchitis, testicular torsion.
Musculoskeletal: rectus sheath hematoma.
Functional
Somatization disorder, malingering, hypochondriasis, Münchausen syndrome.

INTRAABDOMINAL

Early appendicitis, gastroenteritis, peritonitis, pancreatitis, abdominal aortic aneurysm, mesenteric insufficiency or infarction, intestinal obstruction, volvulus, ulcerative colitis.

ABDOMINAL PAIN, PREGNANCY

ICD-9CM #	789.67	
ICD-10CM #	R10.817	Generalized Abdominal Tenderness
	R10.827	Generalized Rebound Abdominal Tenderness

GYNECOLOGIC (GESTATIONAL AGE IN PARENTHESES)

Miscarriage	(<20 wk; 80% <12 wk)
Septic abortion	(<20 wk)
Ectopic pregnancy	(<14 wk)
Corpus luteum cyst rupture	(<12 wk)
Ovarian torsion	(especially <24 wk)
Pelvic inflammatory disease	(<12 wk)
Chorioamnionitis	(>16 wk)
Abruptio placentae	(>16 wk)

NONGYNECOLOGIC

Appendicitis	(Throughout)
Cholecystitis	(Throughout)
Hepatitis	(Throughout)
Pyelonephritis	(Throughout)
Preeclampsia	(>20 wk)

ABDOMINAL PAIN, RIGHT LOWER QUADRANT

ICD-9CM #	789.63	
ICD-10CM #	R10.813	Right Lower Quadrant Abdominal Tenderness
	R10.823	Right Lower Quadrant Rebound Abdominal Tenderness

Intestinal: acute appendicitis, regional enteritis, incarcerated hernia, cecal diverticulitis, intestinal obstruction, perforated ulcer, perforated cecum, Meckel diverticulitis.
Reproductive: ectopic pregnancy, ovarian cyst, torsion of ovarian cyst, salpingitis, tuboovarian

abscess, mittelschmerz, endometriosis, seminal vesiculitis.
Renal: renal and ureteral calculi, neoplasms, pyelonephritis.
Vascular: leaking aortic aneurysm.
Cutaneous: herpes zoster.
Psoas abscess.
Trauma.
Cholecystitis.

ABDOMINAL PAIN, RIGHT UPPER QUADRANT

ICD-9CM #	789.61	
ICD-10CM #	R10.811	Right Upper Quadrant Abdominal Tenderness
	R10.821	Right Upper Quadrant Rebound Abdominal Tenderness

Biliary: calculi, infection, inflammation, neoplasm.
Hepatic: hepatitis, abscess, hepatic congestion, neoplasm, trauma.
Gastric: PUD, pyloric stenosis, neoplasm, alcoholic gastritis, hiatal hernia.
Pancreatic: pancreatitis, neoplasm, stone in pancreatic duct or ampulla.
Renal: calculi, infection, inflammation, neoplasm, rupture of kidney.
Pulmonary: pneumonia, pulmonary infarction, right-sided pleurisy.
Intestinal: retrocecal appendicitis, intestinal obstruction, high fecal impaction, diverticulitis.
Cardiac: myocardial ischemia (particularly involving the inferior wall), pericarditis.
Cutaneous: herpes zoster.
Trauma.
Fitz-Hugh-Curtis syndrome (perihepatitis).

ABDOMINAL PAIN, RIGHT UPPER QUADRANT, DIFFERENTIAL DIAGNOSIS IN PREGNANCY[12d]

ICD-9CM #	789.61	
ICD-10CM #	R10.811	Right Upper Quadrant Abdominal Tenderness
	R10.821	Right Upper Quadrant Rebound Abdominal Tenderness

DIFFERENTIAL DIAGNOSIS OF RIGHT UPPER QUADRANT ABDOMINAL PAIN DURING PREGNANCY

Hepatic Disorders:
Hepatitis.
Hepatic vascular engorgement.
Hepatic hematoma.
Hepatic malignancy.
Biliary Tract Disease:
Biliary colic.
Choledocholithiasis.
Cholangitis.
Cholecystitis.
Diseases Related to Pregnancy:
Preeclampsia or eclampsia.
Hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome.
Acute fatty liver of pregnancy.
Hepatic hemorrhage or rupture.
Renal Disorders:
Pyelonephritis.
Nephrolithiasis.
Gastrointestinal Disorders:
Peptic ulcer disease.
Perforated duodenal ulcer.
Other Conditions in RUQ:
Rib fracture.
Shingles.
Referred Pain from Other Organ Disease:
Pneumonia.
Pulmonary embolus or infarct.
Pleural effusion.
Radiculopathy.
Inferior wall myocardial infarction.
Colon cancer.

ABDOMINAL PAIN, SUPRAPUBIC

ICD-9CM #	789.85	
ICD-10CM #	R10.30	Lower Abdominal Pain, Unspecified

Intestinal: colon obstruction or gangrene, diverticulitis, appendicitis.
Reproductive system: ectopic pregnancy, mittelschmerz, torsion of ovarian cyst, PID, salpingitis, endometriosis, rupture of endometrioma.
Cystitis, rupture of urinary bladder.

ABDOMINAL WALL MASSES[38]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	R19.00	Intra-abdominal and Pelvic Swelling, Mass and Lump, Unspecified Site

LUMPS ARISING IN THE SKIN AND SUBCUTANEOUS FAT (THAT COULD OCCUR ANYWHERE ON THE BODY)

Lipoma.
Sebaceous cyst.

LUMPS ARISING IN THE SKIN AND SUBCUTANEOUS FAT (SPECIFIC TO THE ANTERIOR ABDOMINAL WALL)

Tumor nodule of the umbilicus (secondary to the intraperitoneal malignancy, also called *Sister Mary Joseph nodule*).

LUMPS ARISING IN THE FASCIA AND MUSCLE

Rectus sheath hematoma (usually painful).
Desmoid tumor (associated with Gardner's syndrome).

HERNIA

Incisional: It has an overlying scar. The sac may be very much larger than the neck of the hernia.
Umbilical: The hernia is through the umbilical scar. Those presenting at birth commonly resolve in the first years of life.
Paraumbilical: The neck is just lateral to the umbilical scar. Patients usually present later in life.
Epigastric: It occurs in the midline between the xiphoid process and the umbilicus. They are usually small (<2 cm). They result when a knuckle of extraperitoneal fat extrudes through a small defect in the linea alba. Commonly irreducible and without an expansile cough impulse.
Spigelian: A rare hernia found along the linea semilunaris at the lateral edge of the rectus sheath, most commonly a third of the way between the umbilicus and the pubis.

DIVARICATION OF THE RECTI

Supraumbilical elliptical swelling of the attenuated linea alba (no cough impulse).

ABORTION, RECURRENT

ICD-9CM #	761.8	
ICD-10CM #	P01.8	Newborn (Suspected to Be) Affected by Other Maternal Complications of Pregnancy

Congenital anatomic abnormalities.
Adhesions (uterine synechiae).
Uterine fibroids.
Endometriosis.
Endocrine abnormalities (luteal phase insufficiency, hypothyroidism, uncontrolled diabetes mellitus [DM]).
Parenteral chromosome abnormalities.
Maternal infections (cervical mycoplasma, ureaplasma, chlamydia).
DES exposure, heavy metal exposure.
Thrombocytosis.
Allogenic immunity, autoimmunity, lupus anticoagulant.

ACHES AND PAINS, DIFFUSE[24]

ICD-9CM #	719.49	
ICD-10CM #	M25.50	Pain in Unspecified Joint

Postviral arthralgias/myalgias.
Bilateral soft tissue rheumatism.
Overuse syndromes.
Fibrositis.
Hypothyroidism.
Metabolic bone disease.
Paraneoplastic syndrome.
Myopathy (polymyositis, dermatomyositis).

Rheumatoid arthritis (RA).
Sjögren's syndrome.
Polymyalgia rheumatica.
Hypermobility.
Benign arthralgias/myalgias.
Chronic fatigue syndrome.
Hypophosphatemia.

ACIDOSIS, HYPERCHLORIC METABOLIC[38b]

ICD-9CM # 276.2
ICD-10CM # E87.2 Acidosis

GASTROINTESTINAL BICARBONATE LOSS

Diarrhea.
External pancreatic or small bowel drainage.
Ureterosigmoidostomy, jejunal loop.
Drugs:
- Calcium chloride (acidifying agent).
- Magnesium sulfate (diarrhea).
- Cholestyramine (bile acid diarrhea).

RENAL ACIDOSIS

Hypokalemic:
- Proximal RTA (type 2).
- Distal (classic) RTA (type 1).
- Drug-induced hypokalemia:
  - Acetazolamide (proximal RTA).
  - Amphotericin B (distal RTA).

Hyperkalemic:
- Generalized distal nephron dysfunction (type 4 RTA).
- Mineralocorticoid deficiency or resistance (pseudohypoaldosteronism type 1) PHA-I, PHA-II.
- ↓ Na^+ delivery to distal nephron.
- Tubulointerstitial disease.
- Ammonium excretion defect.
- Drug-induced hyperkalemia:
  - Potassium-sparing diuretics (amiloride, triamterene, spironolactone).
  - Trimethoprim.
  - Pentamidine.
  - Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.
  - Nonsteroidal anti-inflammatory drugs.
  - Cyclosporine, tacrolimus.

Normokalemic:
- Early renal insufficiency.

OTHER

Acid loads (ammonium chloride, hyperalimentation).
Loss of potential bicarbonate: ketosis with ketone excretion.
Dilution acidosis (rapid saline administration).
Hippurate.
Cation-exchange resins.

ACIDOSIS, LACTIC[38b]

ICD-9CM # 276.2
ICD-10CM # E87.2 Acidosis

CAUSES OF LACTIC ACIDOSIS

L-Lactic Acidosis

Conditions associated with type A lactic acidosis:
Poor tissue perfusion.
Shock:
- Cardiogenic.
- Hemorrhagic.
- Septic.

Profound hypoxemia:
- Severe asthma.
- Carbon monoxide poisoning.

Conditions associated with type B lactic acidosis:
Liver disease.
Metformin.
Inborn errors of metabolism.
Pyroglutamic acidosis.
Kombucha tea.

d-Lactic Acidosis

Short bowel syndrome.
Ischemic bowel.
Small bowel obstruction.

ACIDOSIS, METABOLIC

ICD-9CM # 276.2
ICD-10CM # E87.2 Acidosis

METABOLIC ACIDOSIS WITH INCREASED ANION GAP (AG ACIDOSIS)

Lactic acidosis.
Ketoacidosis (DM, alcoholic ketoacidosis).
Uremia (chronic renal failure).
Ingestion of toxins (paraldehyde, methanol, salicylate, ethylene glycol).
High-fat diet (mild acidosis).

METABOLIC ACIDOSIS WITH NORMAL AG (HYPERCHLOREMIC ACIDOSIS)

Renal tubular acidosis (including acidosis of aldosterone deficiency).
Intestinal loss of HCO_3^- (diarrhea, pancreatic fistula).
Carbonic anhydrase inhibitors (e.g., acetazolamide).
Dilutional acidosis (as a result of rapid infusion of bicarbonate-free isotonic saline).
Ingestion of exogenous acids (ammonium chloride, methionine, cystine, calcium chloride).
Ileostomy.
Ureterosigmoidostomy.
Drugs: amiloride, triamterene, spironolactone, β-blockers.

ACIDOSIS, RESPIRATORY

ICD-9CM # 276.2
ICD-10CM # E87.2 Acidosis

Pulmonary disease (COPD, severe pneumonia, pulmonary edema, interstitial fibrosis).
Airway obstruction (foreign body, severe bronchospasm, laryngospasm).
Thoracic cage disorders (pneumothorax, flail chest, kyphoscoliosis).
Defects in muscles of respiration (myasthenia gravis, hypokalemia, muscular dystrophy).
Defects in peripheral nervous system (amyotrophic lateral sclerosis, poliomyelitis, Guillain-Barré syndrome, botulism, tetanus, organophosphate poisoning, spinal cord injury).
Depression of respiratory center (anesthesia, narcotics, sedatives, vertebral artery embolism or thrombosis, increased intracranial pressure).
Failure of mechanical ventilator.

ACUTE KIDNEY INJURY AND LIVER DISEASE, CAUSES[12ab]

ICD-9CM # varies with specific diagnosis
ICD-10CM # S37.009A Unspecified Injury of Unspecified Kidney, Initial Encounter
K76.89 Other Specified Diseases of Liver

Prerenal uremia:	Diuretic use, gastrointestinal loss, peritoneal aspiration, hypoalbuminemia
Hepatorenal syndrome	
Acute tubular necrosis:	Hyperbilirubinemia, sepsis, toxic shock syndrome
Drugs:	Acetaminophen (paracetamol), NSAIDs, tetracycline, rifampicin, isoniazid, anesthetic agents, sulfonamides, allopurinol, methotrexate
Infections:	Hepatitis C and cryoglobulinemia, hepatitis B and polyarteritis nodosa, leptospirosis, hantavirus, Epstein-Barr virus, gram-negative sepsis, spontaneous bacterial peritonitis
Other:	Papillary necrosis and obstruction, inhalation of chlorinated hydrocarbons, mushroom poisoning *(Amanita phalloides)*

ACUTE KIDNEY INJURY, HIV PATIENT, CAUSES[12ab]

ICD-9CM # varies with specific diagnosis
ICD-10CM # S37.009A Unspecified Injury of Unspecified Kidney, Initial Encounter with B20 Human Immunodeficiency Virus (HIV) Disease

Prerenal:	Diarrhea, nausea and vomiting, cirrhosis and hepatorenal syndrome, sepsis
Vascular:	Thrombotic microangiopathy
Glomerular:	Immune complex glomerulonephritis (MPGN secondary to hepatitis C virus, postinfectious glomerulonephritis), HIVAN
Acute tubular necrosis:	Sepsis, hypotension, nephrotoxins (aminoglycosides, amphotericin, acyclovir, cidofovir, tenofovir, pentamidine)

Acute interstitial nephritis:	Drug-induced (co-trimoxazole), rifampicin, foscarnet, nevirapine), CMV infection, DILS
Drug-induced intratubular obstruction:	Sulfadiazine, indinavir, foscarnet, acyclovir
Postrenal obstruction:	Stones, tuberculosis, fungal ball, tumor
Associated with IV drug use:	Sepsis, endocarditis, heroin-associated nephropathy (FSGS), rhabdomyolysis

CMV, Cytomegalovirus; *DILS,* diffusive infiltrative lymphocytosis syndrome; *FSGS,* focal segmental glomerulosclerosis; *HIVAN,* HIV-associated nephropathy; *MPGN,* membranoproliferative glomerulonephritis

ACUTE LUNG INJURY, DISEASE AND DISORDERS ASSOCIATIONS[26a]

ICD-9CM # varies with specific disorder
ICD-10CM # S27.3 Injury, lung

CLINICAL DISORDERS ASSOCIATED WITH ACUTE LUNG INJURY

Infectious Causes
Gram-negative or gram-positive sepsis.
Bacterial pneumonia.
Viral pneumonia.
Fungal pneumonia
Parasitic infections.
Mycobacterial disease.
Aspiration
Gastric acid.
Food and other particulate matter.
Fresh or sea water (near drowning).
Hydrocarbon fluids.
Trauma
Lung contusion.
Fat emboli.
Nonthoracic trauma.
Thermal injury (burns).
Blast injury (explosion, lightning).
Overdistention (mechanical ventilation).
Inhaled gases (phosgene, ammonia).
Hemodynamic Disturbances
Shock of any etiology.
Anaphylaxis.
High-altitude pulmonary edema.
Reperfusion.
Air embolism.
Amniotic fluid embolism.
Drugs
Heroin.
Methadone.
Propoxyphene.
Naloxone.
Cocaine.
Barbiturates.
Colchicine.
Salicylates.
Ethchlorvynol.
Interleukin-2.
Protamine.
Hydrochlorothiazide.
Hematologic Disorders
Disseminated intravascular coagulation.
Incompatible blood transfusion.
Rh incompatibility.
Antileukocyte antibodies.
Leukoagglutinin reactions.
Post–cardiopulmonary bypass, pump oxygenator.
Metabolic Disorders
Pancreatitis.
Diabetic ketoacidosis.
Neurologic Disorders
Head trauma.
Grand mal seizures.
Increased intracranial pressure (any cause).
Subarachnoid or intracerebral hemorrhage.
Miscellaneous Disorders
Lung reexpansion.
Upper airway obstruction.

ACUTE SCROTUM

ICD-9CM # 608.9
ICD-10CM # R10.2 Pelvic and Perineal Pain

Testicular torsion.
Epididymitis.
Testicular neoplasm.
Orchitis.
Trauma.

ADNEXAL MASS[26]

ICD-9CM # varies with specific disorder
ICD-10CM # R19.00 Intra-abdominal and Pelvic Swelling, Mass and Lump, Unspecified Site

Ovary (neoplasm, endometriosis, functional cyst).
Fallopian tube (ectopic pregnancy, neoplasm, tubo-ovarian abscess, hydrosalpinx, paratubal cyst).
Uterus (fibroid, neoplasm).
Retroperitoneum (neoplasm, abdominal wall hematoma or abscess).
Urinary tract (pelvic kidney, distended bladder, urachal cyst).
Inflammatory bowel disease.
GI tract neoplasm.
Diverticular disease.
Appendicitis.
Bowel loop with feces.

ADRENAL MASSES[36]

ICD-9CM #	194.0	Adrenocortical Carcinoma
	255.8	Adrenal Hyperplasia
ICD-10CM #	C74.90	Malignant Neoplasm of Unspecified Part of Unspecified Adrenal Gland
	E27.8	Other Specified Disorders of Adrenal Gland

UNILATERAL ADRENAL MASSES

Functional Lesions
Adrenal adenoma.
Adrenal carcinoma.
Pheochromocytoma.
Primary aldosteronism, adenomatous type.
Nonfunctional Lesions
Incidentaloma of adrenal.
Ganglioneuroma.
Myelolipoma.
Hematoma.
Adenolipoma.
Metastasis.

BILATERAL ADRENAL MASSES

Functional Lesions
ACTH-dependent Cushing's syndrome.
Congenital adrenal hyperplasia.
Pheochromocytoma.
Conn's syndrome, hyperplastic variety.
Micronodular adrenal disease.
Idiopathic bilateral adrenal hypertrophy.
Nonfunctional Lesions
Infection (tuberculosis, fungi).
Infiltration (leukemia, lymphoma).
Replacement (amyloidosis).
Hemorrhage.
Bilateral metastases.

ADRENOCORTICAL HYPERFUNCTION[1a]

ICD-9CM # 255.1
ICD-10CM # E26.9 Hyperaldosteronism, Unspecified

SYNDROMES OF ADRENOCORTICAL HYPERFUNCTION

States of Glucocorticoid Excess
Physiologic states
Stress.
Strenuous exercise.
Last trimester of pregnancy.
Pathologic States
Psychiatric conditions (pseudo-Cushing's disorders):
Depression.
Alcoholism.
Anorexia nervosa.
Panic disorders.
Alcohol and drug withdrawal.
ACTH-dependent states:
Pituitary adenoma (Cushing's disease).
Ectopic ACTH syndrome.
- Bronchial carcinoid.
- Thymic carcinoid.
- Islet cell tumor.
- Small cell lung carcinoma.

Ectopic CRH secretion.
ACTH-independent states:
Adrenal adenoma.
Adrenal carcinoma.
Micronodular adrenal disease.
Exogenous Sources
Glucocorticoid intake.
ACTH intake.
States of Mineralocorticoid Excess
Primary Aldosteronism
Aldosterone-secreting adenoma.
Bilateral adrenal hyperplasia.
Aldosterone-secreting carcinoma.
Glucocorticoid-suppressible hyperaldosteronism.

Adrenal Enzyme Deficiencies
11b-Hydroxylase deficiency.
17a-Hydroxylase deficiency.
11b-Hydroxysteroid dehydrogenase, type II.
Exogenous Mineralocorticoids
Licorice.
Carbenoxolone.
Fludrocortisone.
Secondary Hyperaldosteronism
Associated with hypertension:
- Accelerated hypertension.
- Renovascular hypertension.
- Estrogen administration.
- Renin-secreting tumors.

Without hypertension:
- Bartter syndrome.
- Sodium-wasting nephropathy.
- Renal tubular acidosis.
- Diuretic and laxative abuse.
- Edematous states (cirrhosis, nephrosis, congestive heart failure).

ACTH, Adrenocorticotropin hormone; *CRH,* corticotropin-releasing hormone.

ADRENOCORTICAL HYPOFUNCTION

ICD-9CM # 255.4
ICD-10CM # E27.49 Other Adrenocortical Insufficiency

SYNDROMES OF ADRENOCORTICAL HYPOFUNCTION

Primary Adrenal Disorders
Combined Glucocorticoid and Mineralocorticoid Deficiency
Autoimmune:
- Isolated autoimmune disease (Addison disease).
- Polyglandular autoimmune syndrome, type I.
- Polyglandular autoimmune syndrome, type II.

Infectious:
- Tuberculosis.
- Fungal.
- Cytomegalovirus.
- Human immunodeficiency virus.

Vascular:
- Bilateral adrenal hemorrhage.
- Sepsis.
- Coagulopathy.
- Thrombosis; embolism.
- Adrenal infarction.

Infiltration:
- Metastatic carcinoma and lymphoma.
- Sarcoidosis.
- Amyloidosis.
- Hemochromatosis.

Congenital:
- Congenital adrenal hyperplasia.
  - 21-Hydroxylase deficiency.
  - 3b-ol Dehydrogenase deficiency.
  - 20,22-Desmolase deficiency.
- Adrenal unresponsiveness to ACTH.
- Congenital adrenal hypoplasia.
- Adrenoleukodystrophy.
- Adrenomyeloneuropathy.

Iatrogenic
Bilateral adrenalectomy.
Drugs:
Metyrapone, aminoglutethimide, trilostane, ketoconazole, o,p¢-DDD, mifepristone.
Mineralocorticoid deficiency without glucocorticoid deficiency:
Cortiscosterone methyl oxidase deficiency.
Isolated zona glomerulosa defect.
Heparin therapy.
Critical illness.
Converting-enzyme inhibitors.
Secondary Adrenal Disorders
Secondary Adrenal Insufficiency
Hypothalamic-pituitary dysfunction.
Exogenous glucocorticoids.
After removal of an ACTH-secreting tumor.
Hyporeninemic Hypoaldosteronism
Diabetic nephropathy.
Tubulointerstitial diseases.
Obstructive uropathy.
Autonomic neuropathy.
Nonsteroidal anti-inflammatory drugs.
β-Adrenergic drugs.

ACTH, Adrenocorticotropic hormone.

ADVERSE FOOD REACTIONS, DIFFERENTIAL DIAGNOSIS[22a]

ICD-9CM # varies with specific diagnosis
ICD-10CM # T78.1XXA Other Adverse Food Reactions, Not Elsewhere Classified, Initial Encounter

GASTROINTESTINAL DISORDERS (WITH VOMITING AND/OR DIARRHEA)

Structural abnormalities (pyloric stenosis, Hirschsprung's disease).
Enzyme deficiencies (primary or secondary):
- Disaccharidase deficiency—lactase, fructase, sucrase-isomaltase.
- Galactosemia.

Other: pancreatic insufficiency (cystic fibrosis), peptic disease.

CONTAMINANTS AND ADDITIVES

Flavorings and preservatives—rarely cause symptoms: Sodium metabisulfite, monosodium glutamate, nitrites.
Dyes and colorings—very rarely cause symptoms (urticaria, eczema): Tartrazine.
Toxins: Bacterial, fungal (aflatoxin), fish-related (scombroid, ciguatera).
Infectious organisms:
- Bacteria *(Salmonella, Escherichia coli, Shigella).*
- Virus (rotavirus, enterovirus).
- Parasites (*Giardia, Akis simplex* [in fish]).

Accidental contaminants: Heavy metals, pesticides.
Pharmacologic agents: Caffeine, glycosidal alkaloid solanine (potato spuds), histamine (fish), serotonin (banana, tomato), tryptamine (tomato), tyramine (cheese).

PSYCHOLOGIC REACTIONS

Food phobias.

ADYNAMIC ILEUS[26]

ICD-9CM # 560.1
ICD-10CM # K56.0 Paralytic Ileus
K56.7 Ileus, Unspecified

Abdominal trauma.
Infection (retroperitoneal, pelvic, intrathoracic).
Laparotomy.
Metabolic disease (hypokalemia).
Renal colic.
Skeletal injury (rib fracture, vertebral fracture).
Medications (e.g., narcotics).

AEROPHAGIA (BELCHING, ERUCTATION)

ICD-9CM # 787.3
ICD-10CM # R14.0 Abdominal Distension (Gaseous)
R14.1 Gas Pain
R14.2 Eructation
R14.3 Flatulence

Anxiety disorders.
Rapid food ingestion.
Carbonated beverages.
Nursing infants (especially when nursing in horizontal position).
Eating or drinking in supine position.
Gum chewing.
Poorly fitting dentures, orthodontic appliances.
Hiatal hernia, gastritis, nonulcer dyspepsia.
Cholelithiasis, cholecystitis.
Ingestion of legumes, onions, peppers.

AIR-SPACE OPACIFICATION ON X-RAY[16a]

ICD-9CM # varies with specific diagnosis
ICD-10CM # R91.8 Other nonspecific abnormal finding of lung field

CAUSES OF AIR-SPACE OPACIFICATION

Edema
Cardiogenic.
Non-cardiogenic.
Inflammation/Infection
Wegener's granulomatosis.
Cryptogenic organizing pneumonia.
Blood
Idiopathic pulmonary hemosiderosis.
Antibasement membrane antibody disease.
Systemic lupus erythematosus.
Miscellaneous Causes
Eosinophilic pneumonia.
Alveolar proteinosis.
Alveolar cell carcinoma.
Alveolar microlithiasis.
Lymphoma (MALToma).
Sarcoidosis.

AIRWAY OBSTRUCTION, PEDIATRIC AGE[19]

ICD-9CM #	496	Obstruction Due to Bronchospasm
	934.9	Obstruction Due to Foreign Body
	478.75	Obstruction Due to Laryngospasm
	506.9	Obstruction Due to Inhalation of Fumes or Vapors
ICD-10CM #	J44.9	Chronic Obstructive Pulmonary Disease, Unspecified
	T17.900A	Unspecified Foreign Body in Respiratory Tract, Part Unspecified Causing Asphyxiation, Initial Encounter
	T17.908A	Unspecified Foreign Body in Respiratory Tract, Part Unspecified Causing Other Injury, Initial Encounter
	T17.910A	Gastric Contents in Respiratory Tract, Part Unspecified Causing Asphyxiation, Initial Encounter
	T17.918A	Gastric Contents in Respiratory Tract, Part Unspecified Causing Other Injury, Initial Encounter
	T17.920A	Food in Respiratory Tract, Part Unspecified Causing Asphyxiation, Initial Encounter
	T17.928A	Food in Respiratory Tract, Part Unspecified Causing Other Injury, Initial Encounter
	T17.990A	Other Foreign Object in Respiratory Tract, Part Unspecified in Causing Asphyxiation, Initial Encounter
	T17.998A	Other Foreign Object in Respiratory Tract, Part Unspecified Causing Other Injury, Initial Encounter
	J38.5	Laryngeal Spasm
	J68.9	Unspecified Respiratory Condition Due To Chemicals, Gases, Fumes, and Vapors

CONGENITAL CAUSES

Craniofacial dysmorphism.
Hemangioma.
Laryngeal cleft/web.
Laryngoceles, cysts.
Laryngomalacia.
Macroglossia.
Tracheal stenosis.
Vascular ring.
Vocal cord paralysis.

ACQUIRED INFECTIOUS CAUSES

Acute laryngotracheobronchitis.
Epiglottitis.
Laryngeal papillomatosis.
Membranous croup (bacterial tracheitis).
Mononucleosis.
Retropharyngeal abscess.
Spasmodic croup.
Diphtheria.

ACQUIRED NONINFECTIOUS CAUSES

Anaphylaxis.
Foreign body aspiration.
Supraglottic hypotonia.
Thermal/chemical burn.
Trauma.
Vocal cord paralysis.
Angioneurotic edema.

AKINETIC/RIGID SYNDROME[1a]

ICD-9CM # code not available
ICD-10CM # R29.8 Akinesis

Parkinsonism (idiopathic, drug-induced).
Catatonia (psychosis).
Progressive supranuclear palsy.
Multisystem atrophy (Shy-Drager syndrome, olivopontocerebellar atrophy).
Diffuse Lewy-body disease.
Toxins (MPTP, manganese, carbon monoxide).
Huntington's disease and other hereditary neurodegenerative disorders.

ALKALOSIS, METABOLIC

ICD-9CM # 276.3
ICD-10CM # E87.3 Alkalosis

CAUSES OF METABOLIC ALKALOSIS

Exogenous HCO_3– Loads
Acute alkali administration.
Milk-alkali syndrome.
Effective Extracellular Volume Contraction, Normotension, Hypokalemia, and Secondary Hyperreninemic Hyperaldosteronism
Gastrointestinal origin:
- Vomiting.
- Gastric aspiration.
- Congenital chloridorrhea.
- Villous adenoma.
- Combined administration of sodium polystyrene sulfonate (Kayexalate and aluminum hydroxide).

Renal origin:
- Diuretics (especially thiazides and loop diuretics).
- Acute.
- Chronic.
- Edematous states.
- Posthypercapnic state.
- Hypercalcemia-hypoparathyroidism.
- Recovery from lactic acidosis or ketoacidosis.
- Nonreabsorbable anions such as penicillin, carbenicillin.
- Mg^{++} deficiency.
- K^+ depletion.

Bartter syndrome (loss-of-function mutation of Cl– transport in thick ascending limb of Henle loop).
Gitelman syndrome (loss-of-function mutation in Na^+/Cl– cotransporter).
Carbohydrate refeeding after starvation.
Extracellular Volume Expansion, Hypertension, K^+ Deficiency, and Hypermineralocorticoidism
Associated with high renin:
- Renal artery stenosis.
- Accelerated hypertension.
- Renin-secreting tumor.
- Estrogen therapy.

Associated with low renin:
- Primary aldosteronism.
- Adenoma.
- Hyperplasia.
- Carcinoma.
- Glucorticoid suppressible.
- Adrenal enzymatic defects:
- 11β-Hydroxylase deficiency.
- 17α-Hydroxylase deficiency.
- Cushing syndrome or disease:
- Ectopic corticotropin.
- Adrenal carcinoma.
- Adrenal adenoma.
- Primary pituitary.

Other:
- Licorice.
- Carbenoxolone.
- Chewer's tobacco.
- Lydia Pinkham tablets.

Gain-of-Function Mutation of ENaC with Extracellular Fluid Volume Expansion, Hypertension, K^+ Deficiency, and Hyporeninemic Hypoaldosteronism
Liddle syndrome.

ALKALOSIS, RESPIRATORY

ICD-9CM # 276.3
ICD-10CM # E87.3 Alkalosis

Hypoxemia (pneumonia, pulmonary embolism, atelectasis, high-altitude living).
Drugs (salicylates, xanthenes, progesterone, epinephrine, thyroxine, nicotine).
Central nervous system (CNS) disorders (tumor, cerebrovascular accident [CVA], trauma, infections).
Psychogenic hyperventilation (anxiety, hysteria).
Hepatic encephalopathy.
Gram-negative sepsis.
Hyponatremia.
Sudden recovery from metabolic acidosis.
Assisted ventilation.

ALOPECIA[14,28]

ICD-9CM #	704.00	Alopecia NOS
	704.01	Alopecia, Androgenic
	704.01	Alopecia, Areata
	757.4	Alopecia, Congenital
	316	Alopecia, Psychogenic
ICD-10CM #	L65.9	Nonscarring Hair Loss, Unspecified
	L63.2	Ophiasis
	L63.8	Other Alopecia Areata
	Q84.0	Congenital Alopecia
	Q84.1	Congenital Morphological Disturbances of Hair, Not Elsewhere Classified
	Q84.2	Other Congenital Malformations of Hair
	F54	Psychological and Behavioral Factors Associated with Disorders or Diseases Classified Elsewhere

SCARRING ALOPECIA

Congenital (aplasia cutis).
Tinea capitis with inflammation (kerion).
Bacterial folliculitis.
Discoid lupus erythematosus.
Lichen planopilaris.
Folliculitis decalvans.
Neoplasm.
Trauma.

NONSCARRING ALOPECIA

Cosmetic treatment.
Tinea capitis.
Structural hair shaft disease.
Trichotillomania (hair pulling).
Anagen arrest.
Telogen arrest.
Alopecia areata.
Androgenetic alopecia.

ALOPECIA AND HYPOTRICHOSIS, IN CHILDREN AND ADOLESCENTS

ICD-9CM #	704.00	
ICD-10CM #	L65.9	Nonscarring Hair Loss, Unspecified
	L63.2	Ophiasis
	L63.8	Other Alopecia Areata
	Q84.0	Congenital Alopecia
	Q84.1	Congenital Morphological Disturbances Of Hair, Not Elsewhere Classified
	Q84.2	Other Congenital Malformations Of Hair

Congenital total alopecia: atrichia with papules, Moynahan alopecia syndrome.
Congenital localized alopecia: aplasia cutis, triangular alopecia, sebaceous nevus.
Hereditary hypotrichosis: Marie-Unna syndrome, hypotrichosis with juvenile macular dystrophy, hypotrichosis–Mari type, ichthyosis with hypotrichosis, cartilage-hair hypoplasia, Hallermann-Streiff syndrome, trichorhinophalangeal syndrome, ectodermal dysplasia ("pure" hair and nail and other ectodermal dysplasias).
Diffuse alopecia of endocrine origin: hypopituitarism, hypothyroidism, hypoparathyroidism, hyperthyroidism.
Alopecia of nutritional origin: marasmus, kwashiorkor, iron deficiency, zinc deficiency (acrodermatitis enteropathica), gluten-sensitive enteropathy, essential fatty acid deficiency, biotinidase deficiency.
Disturbances of the hair cycle: telogen effluvium.
Toxic alopecia: anagen effluvium.
Autoimmune alopecia: alopecia areata.
Traumatic alopecia: traction alopecia, trichotillomania.
Cicatricial alopecia: lupus erythematosus, lichen planopilaris, pseudopelade, morphea (en coup de saber), dermatomyositis, infection (kerion, favus, tuberculosis, syphilis, folliculitis, leishmaniasis, herpes zoster, varicella), acne keloidalis, follicular mucinosis, sarcoidosis.
Hair shaft abnormalities: monilethrix, pili annulati, pili torti, trichorrhexis invaginata, trichorrhexis nodosa, woolly hair syndrome, Menkes disease, trichothiodystrophy, trichodento-osseous syndrome, uncombable hair syndrome (spun-glass hair, pili trianguli et canaliculi).

ALOPECIA, DRUG-INDUCED

ICD-9CM #	704.00	
ICD-10CM #	L65.9	Nonscarring hair loss, unspecified
	L63.8	Alopecia areata

DRUGS REPORTED TO INDUCE HAIR LOSS

ACE inhibitors (captopril, enalapril, moexipril, ramipril).
Allopurinol.
Amiodarone.
Amphetamines.*†
Analgesics, anti-inflammatories (ibuprofen, indomethacin, naproxen).
Androgens.*¶
Anticoagulants (coumarin, dextran, heparin/heparinoids).*†
Antiepileptics (carbamazepine, hydantoins, lamotrigine, troxidone, valproic acid, vigabatrin).*†
Antipsychotics (flupenthixol decanoate, fluphenazine decanoate).
Antithyroid drugs (carbimazole, iodine, thiouracil).*
Appetite suppressants.
Aromatase inhibitors (fadrozole, 4-OHA, vorozole).*¶
Benzimidazoles (albendazole, mebendazole)
β-Blockers (levobunolol, metoprolol, nadolol, propranolol, timolol).*
Bromocriptine.
Buspirone.
Butyrophenones.
Cantharidin.
Chloramphenicol.
Cholestyramine.
Cidofovir.
Cimetidine.
Clonazepam.
Clotrimezole.
Colchicine.
Contraceptives (oral).‖
Danazol.
Diazoxide.
Diclofenac.
Dixyrazine.
Ethambutol.
Ethionamide.
Fibrates (clofibrate, fenofibrate).
G-CSF (granulocyte-colony stimulating factor)
Gefitinib.‡
Gentamicin.
Glatiramer acetate.
Glibenclamide.
Gold salts.
Haloperidol.
Immunoglobulins.
Indanediones.
Indinavir.*
Interferons.*†
Isonicotinic acid hydrazide.§
Leflunomide.*
Levodopa.
Lithium. *
Maprotiline.
Mesalazine.
Methyldopa.
Methysergide.
Metyrapone.
Minoxidil.‖
Nicotinic acid.
Nitrofurantoin.
Octreotide.
Olanzapine.
Pentosan polysulfate.
Phenindione.
Potassium thiocyanate.
Pyridostigmine.
Radiation (<700 Gy).*§
Retinoids (acitretin, etretinate, isotretinoin).*†
Retinol (vitamin A).*
Risperidone.
Salicylates.
Serotonin reuptake inhibitors (fluoxetine, fluvoxamine, paroxetine, sertraline).*
Sorafenib.
Spironolactone.
Strontium ranelate.*†
Sulfasalazine.
Tamoxifen.
Terbinafine.
Terfenadine.
Thiamphenicol.
Thyroxine.
Tocopherol (vitamin E).
Trazodone.
Triazoles (fluconazole, itraconazole).
Tricyclic antidepressants (amitriptyline, desipramine, doxepin, imipramine, maprotiline).

Trimethadione.
Triparanol.
Vasopressin.

*Established by multiple reports or proved by rechallenge.
†Hair loss usually severe.
‡May produce permanent alopecia.
§May produce anagen effluvium.
‖May produce telogen effluvium 3 months after discontinuation.
¶May produce androgenetic alopecia.

ALVEOLAR CONSOLIDATION

ICD-9CM # 514
ICD-10CM # J18.2 Hypostatic Pneumonia, Unspecified Organism
J81.1 Hypostatic Pneumonia, Unspecified Organism

Infection.
Neoplasm (bronchoalveolar carcinoma, lymphoma).
Aspiration.
Trauma.
Hemorrhage (Wegener's, Goodpasture's, bleeding diathesis).
ARDS.
CHF.
Renal failure.
Eosinophilic pneumonia.
Bronchiolitis obliterans.
Pulmonary alveolar proteinosis.

ALVEOLAR HEMORRHAGE[28]

ICD-9CM # 770.3
ICD-10CM # P26.1 Massive Pulmonary Hemorrhage Originating in the Perinatal Period
K08.8 Alveolar hemorrhage
P26.8 Other Pulmonary Hemorrhages Originating in the Perinatal Period

Hematologic disorders (coagulopathies, thrombocytopenia).
Goodpasture's syndrome (anti-basementmembrane antibody disease).
Granulomatosis with polyangiitis (Wegener's vasculitis).
Immune complex-mediated vasculitis.
Idiopathic pulmonary hemosiderosis.
Drugs (penicillamine).
Lymphangiogram contrast.
Mitral stenosis.

AMENORRHEA

ICD-9CM # 626.0
ICD-10CM # N91.2 Amenorrhea, Unspecified

PREGNANCY

Early Menopause

HYPOTHALAMIC DYSFUNCTION: defective synthesis or release of LHRH, anorexia nervosa, stress, exercise.

PITUITARY DYSFUNCTION: neoplasm, postpartum hemorrhage, surgery, radiotherapy.

OVARIAN DYSFUNCTION: gonadal dysgenesis, 17a-hydroxylase deficiency, premature ovarian failure, polycystic ovarian disease, gonadal stromal tumors.

UTEROVAGINAL ABNORMALITIES

Congenital: imperforate hymen, imperforate cervix, imperforate or absent vagina, Müllerian agenesis.
Acquired: destruction of endometrium with curettage (Asherman's syndrome), closure of cervix or vagina caused by traumatic injury, hysterectomy.

OTHER

Metabolic diseases (liver, kidney), malnutrition, rapid weight loss, exogenous obesity, endocrine abnormalities (Cushing's syndrome, Graves' disease, hypothyroidism).

AMNESIA

ICD-9CM # 292.83 Drug Induced
300.12 Hysterical
780.9 Retrograde
437.7 Transient Global
ICD-10CM # F19.96 Other Psychoactive Substance Use, Unspecified With Psychoactive Substance-Induced Persisting Amnestic Disorder
F44.0 Dissociative Amnesia
R41.2 Retrograde Amnesia
G45.4 Transient Global Amnesia

Degenerative diseases (e.g., Alzheimer's, Huntington's disease).
CVA (especially when involving thalamus, basal forebrain, and hippocampus).
Head trauma.
Postsurgical (e.g., mammillary body surgery, bilateral temporal lobectomy).
Infections (herpes simplex encephalitis, meningitis).
Wernicke-Korsakoff syndrome.
Cerebral hypoxia.
Hypoglycemia.
CNS neoplasms.
Creutzfeldt-Jakob disease.
Medications (e.g., midazolam and other benzodiazepines).
Psychosis.
Malingering.

AMNIOTIC FLUID α-FETOPROTEIN ELEVATION[16a]

ICD-9CM # V28.1
ICD-10CM # Z36 Encounter for Antenatal Screening of Mother

CAUSES OF ELEVATED AMNIOTIC FLUID α-FETOPROTEIN

Craniospinal defect (open neural tube defect).
Omphalocele.
Gastroschisis.
Duodenal atresia.
Congenital nephrosis.
Cystic hygroma.
Unbalanced D/G dislocation.
Down, Tay-Sachs, Klinefelter's, Turner's syndromes.
Fetal tumors.
Epidermolysis bullosa.
Pilonidal sinus.
Rhesus disease.
Fetal demise.
Incorrect dates.
Multiple pregnancy.

ANAL ABSCESS AND FISTULA[38]

ICD-9CM # 566
ICD-10CM # K61.0 Anal Abscess
K61.1 Rectal Abscess
K61.3 Ischiorectal Abscess
K60.3 Anal fistula

Primary anal gland infection.
Secondary abscess:
Inflammatory bowel disease:
- Crohn's disease.
- Ulcerative colitis.

Infection:
- Tuberculosis.
- Actinomycosis.
- Threadworm.

Trauma.
Leukopenia.
Immunosuppression:
- HIV.
- Drugs.

Rectal cancer.
Diabetes mellitus.

ANAL INCONTINENCE[26]

ICD-9CM # 787.6
ICD-10CM # R15.9 Full Incontinence of Feces

TRAUMATIC

Nerve injured in surgery.
Spinal cord injury.
Obstetric trauma.
Sphincter injury.

NEUROLOGIC

Spinal cord lesions.
Dementia.
Autonomic neuropathy (e.g., DM).
Obstetrics: pudendal nerve stretched during surgery.
Hirschsprung's disease.

MASS EFFECT

Carcinoma of anal canal.
Carcinoma of rectum.
Foreign body.
Fecal impaction.
Hemorrhoids.

MEDICAL

Procidentia.
Inflammatory disease.
Diarrhea.
Laxative abuse.

PEDIATRIC
Congenital.
Meningocele.
Myelomeningocele.
Spina bifida.
After corrective surgery for imperforate anus.
Sexual abuse.
Encopresis.

ANAPHYLAXIS[21]
ICD-9CM # 995.0
ICD-10CM # T78.2 Anaphylactic Shock, Unspecified, Initial Encounter

PULMONARY
Laryngeal edema.
Epiglottitis.
Foreign body aspiration.
Pulmonary embolus.
Asphyxiation.
Hyperventilation.

CARDIOVASCULAR
Myocardial infarction.
Arrhythmia.
Hypovolemic shock.
Cardiac arrest.

CNS
Vasovagal reaction.
CVA.
Seizure disorder.
Drug overdose.

ENDOCRINE
Hypoglycemia.
Pheochromocytoma.
Carcinoid syndrome.
Catamenial (progesterone-induced anaphylaxis).

PSYCHIATRIC
Vocal cord dysfunction syndrome.
Münchausen syndrome.
Panic attack/globus hystericus.

OTHER
Hereditary angioedema.
Cord urticaria.
Idiopathic urticaria.
Mastocytosis.
Serum sickness.
Idiopathic capillary leak syndrome.
Sulfite exposure.
Scombroid poisoning (tuna, blue fish, mackerel).

ANAPHYLACTOID SYNDROME OF PREGNANCY[1]
ICD-9CM # 673.11
ICD-10CM # 088.113

CARDIOVASCULAR COLLAPSE, HYPOTENSION
Acute coronary syndromes, myocardial infarction.
Cardiomyopathy.
Pulmonary embolism.
Anesthesia complications, transfusion reaction.
Sepsis, systemic inflammatory response syndrome.

RESPIRATORY ARREST
Pulmonary embolism, air embolism.
Anesthesia complications, transfusion reaction.
Aspiration.

ALTERED MENTAL STATUS, SEIZURE
Eclampsia.
Cerebrovascular accident.
Hypoglycemia.

COAGULOPATHY
Disseminated intravascular coagulation.
Consumptive coagulopathy from hemorrhage.

ANDROGEN EXCESS, REPRODUCTIVE-AGE WOMAN
ICD-9CM # varies with specific disorder
ICD-10CM # E28.1 Androgen Excess

Polycystic ovary syndrome.
Idiopathic.
Medications (e.g., anabolizing agents, testosterone, danazol).
Pregnancy (luteoma, hyperreaction luteinalis).
Sertoli-Leydig ovarian neoplasm.
Adrenal adenoma or hyperplasia.
Cushing's syndrome.
Glucocorticoid resistance.
Hypothyroidism.
Hyperprolactinemia.

ANDROGEN RESISTANCE[25]
ICD-9CM # 257.2
ICD-10CM # E34.5 Androgen resistance syndrome

CONGENITAL OR DEVELOPMENTAL DISORDERS
Uncommon causes:
- Kennedy disease (spinal and bulbar muscular atrophy).
- Partial androgen insensitivity syndrome (AR mutations).
- 5α-reductase type 2 deficiency.
- Complete androgen insensitivity syndrome (female phenotype).

ACQUIRED DISORDERS
Common causes:
- AR antagonists (bicalutamide, nilutamide).
- Drugs (spironolactone, cyproterone acetate, marijuana, histamine 2 receptor antagonists).

Uncommon causes:
- Celiac disease.

ANEMIA, APLASTIC[20]
ICD-9CM # 284
ICD-10CM # D61.09 Other Constitutional Aplastic Anemia

ACQUIRED APLASTIC ANEMIA
Secondary aplastic anemia.
Irradiation.
Drugs and chemicals.
Regular effects.
Cytotoxic agents.
Benzene.
Idiosyncratic reactions.
Chloramphenicol.
Nonsteroidal anti-inflammatory drugs.
Antiepileptics.
Gold.
Other drugs and chemicals.
Viruses.
Epstein-Barr virus (infectious mononucleosis).
Hepatitis virus (non-A, non-B, non-C, non-G hepatitis).
Parvovirus (transient aplastic crisis, some pure red cell aplasia).
Human immunodeficiency virus (acquired immunodeficiency syndrome).
Immune diseases.
Eosinophilic fasciitis.
Hyperimmunoglobulinemia.
Thymoma and thymic carcinoma.
Graft-versus-host disease in immunodeficiency.
Paroxysmal nocturnal hemoglobinuria.
Pregnancy.
Idiopathic aplastic anemia.

INHERITED APLASTIC ANEMIA
Fanconi anemia.
Dyskeratosis congenita.
Shwachman-Diamond syndrome.
Reticular dysgenesis.
Amegakaryocytic thrombocytopenia.
Familial aplastic anemias.
Preleukemia (e.g., monosomy 7).
Nonhematologic syndromes (e.g., Down, Dubowitz, Seckel).

ANEMIA, APLASTIC, DUE TO DRUGS AND CHEMICALS[1]
ICD-9CM # 284.89
ICD-10CM # D61.1 Drug-Induced Aplastic Anemia
D61.2 Aplastic Anemia Due to Other External Agents
D61.89 Other Specified Aplastic Anemias and Other Bone Marrow Failure Syndromes

Agents that regularly produce marrow depression as a major toxic effect when used in commonly employed doses or normal exposures:
Cytotoxic drugs used in cancer chemotherapy.
Alkylating agents (busulfan, melphalan, cyclophosphamide).
Antimetabolites (antifolic compounds, nucleotide analogs), antimitotics (vincristine, vinblastine, colchicine).
Some antibiotics (daunorubicin, doxorubicin [Adriamycin]).
Benzene (and less often benzene-containing chemicals; kerosene, carbon tetrachloride, Stoddard's solvent, chlorophenols).

Agents probably associated with aplastic anemia but with a relatively low probability relative to their use:
Chloramphenicol.
Insecticides.
Antiprotozoals (quinacrine and chloroquine).
Nonsteroidal anti-inflammatory drugs (including phenylbutazone, indomethacin, ibuprofen, sulindac, diclofenac, naproxen, piroxicam, fenoprofen, fenbufen, aspirin).
Anticonvulsants (hydantoins, carbamazepine, phenacemide, ethosuximide).
Gold, arsenic, and other heavy metals such as bismuth and mercury.
Sulfonamides as a class.
Antithyroid medications (methimazole, methylthiouracil, propylthiouracil).
Antidiabetes drugs (tolbutamide, carbutamide, chlorpropamide).
Carbonic anhydrase inhibitors (acetazolamide, methazolamide, mesalazine).
D-Penicillamine.
2-Chlorodeoxyadenosine.
Agents more rarely associated with aplastic anemia:
Antibiotics (streptomycin, tetracycline, methicillin, ampicillin, mebendazole and albendazole, sulfonamides, flucytosine, mefloquine, dapsone).
Antihistamines (cimetidine, ranitidine, chlorpheniramine).
Sedatives and tranquilizers (chlorpromazine, prochlorperazine, piperacetazine, chlordiazepoxide, meprobamate, methyprylon, remoxipride).
Antiarrhythmics (tocainide, amiodarone).
Allopurinol (can potentiate marrow suppression by cytotoxic drugs).
Ticlopidine.
Methyldopa.
Quinidine.
Lithium.
Guanidine.
Canthaxanthin.
Thiocyanate.
Carbimazole.
Cyanamide.
Deferoxamine.
Amphetamines.

ANEMIA, CAUSES IN PREGNANCY[12d]

ICD-9CM # varies with specific diagnosis
- 280.9 Iron Deficiency
- 281.0 Pernicious Anemia
- 281.1 B_{12} Deficiency
- 281.2 Folate Deficiency
- 281.3 B_{12} with Folate Deficiency
- 281.4 Protein or Amino Acid Deficiency
- 281.8 Nutritional
- 281.9 NOS
- 285.0 Sideroblastic

ICD-10CM #
- D50.8 Other Iron Deficiency Anemias
- D50.9 Iron Deficiency Anemia, Unspecified
- D51.0 Vitamin B_{12} Deficiency Anemia Due to Intrinsic Factor Deficiency
- D51.1 Vitamin B_{12} Deficiency Anemia Due to Selective Vitamin B_{12} Malabsorption with Proteinuria
- D51.3 Other Dietary Vitamin B_{12} Deficiency Anemia
- D51.8 Other Vitamin B_{12} Deficiency Anemias
- D52.0 Dietary Folate Deficiency Anemia
- D52.1 Drug-Induced Folate Deficiency Anemia
- D52.8 Other Folate Deficiency Anemias
- D52.9 Folate Deficiency Anemia, Unspecified
- D53.1 Other Megaloblastic Anemias, Not Elsewhere Classified
- D53.0 Protein Deficiency Anemia
- D53.2 Scorbutic Anemia
- D53.8 Other Specified Nutritional Anemias
- D53.9 Nutritional Anemia, Unspecified
- D64.0 Hereditary Sideroblastic Anemia
- D64.1 Secondary Sideroblastic Anemia Due to Disease
- D64.2 Secondary Sideroblastic Anemia Due to Drugs and Toxins
- D64.3 Other Sideroblastic Anemias

CAUSES OF ANEMIA DURING PREGNANCY

Common Causes—85% of Anemia:
Physiologic anemia.
Iron deficiency.
Uncommon Causes:
Folic acid deficiency.
Vitamin B_{12} deficiency(due to the rapid increase in bariatric surgery).
Hemoglobinopathies:
- Sickle cell disease.
- Hemoglobin SC.
- β-Thalassemia minor.

Bariatric surgery.
Gastrointestinal bleeding.
Rare Causes:
Hemoglobinopathies.
- β-Thalassemia major.
- α-Thalassemia.

Syndromes of chronic hemolysis:
- Hereditary spherocytosis.
- Paroxysmal nocturnal hemoglobinuria.

Hematologic malignancy.

ANEMIA, DRUG-INDUCED[17]

ICD-9CM # 283.0
ICD-10CM # D61.1 Drug-Induced Aplastic Anemia

DRUGS THAT MAY INTERFERE WITH RED CELL PRODUCTION BY INDUCING MARROW SUPPRESSION OR APLASIA

Alcohol.
Antineoplastic drugs.
Antithyroid drugs.
Antibiotics.
Oral hypoglycemic agents.
Phenylbutazone.
Azidothymidine (AZT).

DRUGS THAT INTERFERE WITH VITAMIN B_{12}, FOLATE, OR IRON ABSORPTION OR UTILIZATION

Nitrous oxide.
Anticonvulsant drugs.
Antineoplastic drugs.
Isoniazid
Cycloserine A.

DRUGS CAPABLE OF PROMOTING HEMOLYSIS

Immune Mediated
Penicillins.
Quinine.
α-methyldopa.
Procainamide.
Mitomycin C.
Oxidative Stress
Antimalarials.
Sulfonamide drugs.
Nalidixic acid.

DRUGS THAT MAY PRODUCE OR PROMOTE BLOOD LOSS

Aspirin.
Alcohol.
Nonsteroidal anti-inflammatory agents.
Corticosteroids.
Anticoagulants.

ANEMIA, HYPOCHROMIC[20]

ICD-9CM # varies with specific diagnosis
- 280.9 Iron Deficiency
- 285.0 Sideroblastic

ICD-10CM #
- D50.8 Other Iron Deficiency Anemias
- D50.9 Iron Deficiency Anemia, Unspecified
- D64.0 Hereditary Sideroblastic Anemia
- D64.1 Secondary Sideroblastic Anemia Due to Disease
- D64.2 Secondary Sideroblastic Anemia Due to Drugs and Toxins
- D64.3 Other Sideroblastic Anemias

DECREASED BODY IRON STORES

Iron-deficiency anemia.

NORMAL OR INCREASED BODY IRON STORES

Impaired iron metabolism.
Anemia of chronic disease.
Defective absorption, transport, or use of iron.
Disorders of globin synthesis:
- Thalassemia.
- Other microcytic hemoglobinopathies.

Disorders of heme synthesis: sideroblastic anemias:
- Hereditary.
- Acquired.

ANEMIA, LOW RETICULOCYTE COUNT[1a]

ICD-9CM # 285.9
ICD-10CM # D64.9 Anemia, Unspecified

MICROCYTIC ANEMIA (MCV <80)

Iron deficiency.
Thalassemia minor.
Sideroblastic anemia.
Lead poisoning.

MACROCYTIC ANEMIA (MCV >100)

Megaloblastic anemias.
Folate deficiency.
Vitamin B_{12} deficiency.
Drug-induced megaloblastic anemia.
Nonmegaloblastic macrocytosis.
Liver disease.
Hypothyroidism.

NORMOCYTIC ANEMIA (MCV 80-100)

Early iron deficiency.
Aplastic anemia.
Myelophthisic disorders.
Endocrinopathies.
Anemia of chronic disease.
Uremia.
Mixed nutritional deficiency.

ANEMIA, MEGALOBLASTIC[36]

ICD-9CM #
281.0 Pernicious Anemia
281.1 B_{12} Deficiency
281.2 Folate Deficiency
281.3 B_{12} with Folate Deficiency
281.4 Protein or Amino Acid Deficiency
281.8 Nutritional
281.9 NOS

ICD-10CM #
D51.0 Vitamin B12 Deficiency Anemia Due to Intrinsic Factor Deficiency
D51.1 Vitamin B12 Deficiency Anemia Due to Selective Vitamin B12 Malabsorption with Proteinuria
D51.3 Other Dietary Vitamin B12 Deficiency Anemia
D51.8 Other Vitamin B12 Deficiency Anemias
D52.0 Dietary Folate Deficiency Anemia
D52.1 Drug-Induced Folate Deficiency Anemia
D52.8 Other Folate Deficiency Anemias
D52.9 Folate Deficiency Anemia, Unspecified
D53.1 Other Megaloblastic Anemias, Not Elsewhere Classified
D53.0 Protein Deficiency Anemia
D53.2 Scorbutic Anemia
D53.8 Other Specified Nutritional Anemias
D53.9 Nutritional Anemia, Unspecified

COBALAMIN (CBL) DEFICIENCY

Nutritional CBL Deficiency (Insufficient CBL Intake)
Vegetarians, vegans, breastfed infants of mothers with pernicious anemia.
Abnormal Intragastric Events (Inadequate Proteolysis of Food CBL)
Atrophic gastritis, partial gastrectomy with hypochlorhydria.
Loss/Atrophy of Gastric Oxyntic Mucosa (Deficient Intrinsic Factor [If] Molecules)
Total or partial gastrectomy, pernicious anemia (PA), caustic destruction (lye).
Abnormal Events in Small Bowel Lumen
Inadequate pancreatic protease (R-CBL not degraded, CBL not transferred to IF).
- Insufficiency of pancreatic protease—pancreatic insufficiency.
- Inactivation of pancreatic protease—Zollinger-Ellison syndrome.

Usurping of luminal CBL (inadequate CBL binding to IF).
- By bacteria—stasis syndromes (blind loops, pouches of diverticulosis, strictures, fistulas, anastomoses); impaired bowel motility (scleroderma, pseudoobstruction), hypogammaglobulinemia.
- By *Diphyllobothrium latum.*

Disorders of Ileal Mucosa/If Receptors (IF-CBL not Bound to IF Receptors)
Diminished or absent IF receptors—ileal bypass/resection/fistula.
Abnormal mucosal architecture/function—tropical/nontropical sprue, Crohn's disease, TB ileitis, infiltration by lymphomas, amyloidosis.
IF-/post IF-receptor defects—Imerslund-Graesbeck syndrome, TC II deficiency.
Drug-induced effects (slow K, biguanides, cholestyramine, colchicine, neomycin, PAS).

DISORDERS OF PLASMA CBL TRANSPORT (TC II-CBL NOT DELIVERED TO TC II RECEPTORS)

Congenital TC II deficiency, defective binding of TC II-CBL to TC II receptors (rare).

METABOLIC DISORDERS (CBL NOT UTILIZED BY CELL)

Inborn enzyme errors (rare).
Acquired disorders: (CBL oxidized to cob[III] alamin)—N_2O inhalation.

FOLATE DEFICIENCY

Nutritional Causes
Decreased dietary intake—poverty and famine (associated with kwashiorkor, marasmus), institutionalized individuals (psychiatric/nursing homes), chronic debilitating disease/goats' milk (low in folate), special diets (slimming), cultural/ethnic cooking techniques (food folate destroyed) or habits (folate-rich foods not consumed).
Decreased diet and increased requirements:
- Physiologic: pregnancy and lactation, prematurity, infancy.
- Pathologic: intrinsic hematologic disease (autoimmune hemolytic disease), drugs, malaria; hemoglobinopathies (SS, thalassemia), RBC membrane defects (hereditary spherocytosis, paroxysmal nocturnal hemoglobinopathy); abnormal hematopoiesis (leukemia/lymphoma, myelodysplastic syndrome, agnogenic myeloid metaplasia with myelofibrosis); infiltration with malignant disease; dermatologic (psoriasis).

Folate Malabsorption
With normal intestinal mucosa:
- Some drugs (controversial).
- Congenital folate malabsorption (rare).

With mucosal abnormalities—tropical and nontropical sprue, regional enteritis.
Defective Cellular Folate Uptake—Familial Aplastic Anemia (Rare), Inadequate Cellular Utilization
Folate antagonists (methotrexate).
Hereditary enzyme deficiencies involving folate.
Drugs (Multiple Effects on Folate Metabolism)
Alcohol, sulfasalazine, triamterene, pyrimethamine, trimethoprim-sulfamethoxazole, diphenylhydantoin, barbiturates.

MISCELLANEOUS MEGALOBLASTIC ANEMIAS (NOT CAUSED BY CBL OR FOLATE DEFICIENCY)

Congenital Disorders of DNA Synthesis (Rare)
Orotic aciduria, Lesch-Nyhan syndrome, congenital dyserythropoietic anemia.
Acquired Disorders of DNA Synthesis
Thiamine-responsive megaloblastosis (rare).
Malignancy—erythroleukemia—refractory sideroblastic anemias—all antineoplastic drugs that inhibit DNA synthesis.
Toxins—alcohol.

ANEMIA, MICROCYTIC, HYPOCHROMIC, DIFFERENTIAL DIAGNOSIS[18c]

ICD-9CM # varies with specific diagnosis
280.9 Iron Deficiency
285.0 Sideroblastic
ICD-10CM # D50.8 Other Iron Deficiency Anemias
D50.9 Iron Deficiency Anemia, Unspecified
D64.0 Hereditary Sideroblastic Anemia
D64.1 Secondary Sideroblastic Anemia Due to Disease
D64.2 Secondary Sideroblastic Anemia Due to Drugs and Toxins
D64.3 Other Sideroblastic Anemias

DIFFERENTIAL DIAGNOSIS OF MICROCYTIC HYPOCHROMIC ANEMIA

Decreased Body Iron Stores
Iron-deficiency anemia.
Normal or Increased Body Iron Stores
Anemia of chronic disease.
Defective absorption, transport, or use of iron.
Iron-refractory, iron-deficiency anemia after parenteral iron.
Atransferrinemia.
Aceruloplasminemia.
Divalent metal transporter 1 (DMT1 or SLC11A2) deficiency.
Ferroportin-associated hemochromatosis with impaired iron export (type 4A).
Heme oxygenase 1 deficiency.
Disorders of globin synthesis.
Decreased Body Iron Stores
Thalassemia.
Other microcytic hemoglobinopathies.
Disorders of heme synthesis:
Sideroblastic anemias.
Hereditary.
Acquired.

ANERGY, CUTANEOUS[36]

ICD-9CM # 279.9
ICD-10CM # D89.9 Disorder Involving the Immune Mechanism, Unspecified

IMMUNOLOGIC

Acquired (AIDS, acute leukemia, carcinoma, CLL, Hodgkin's lymphoma, NHL).
Congenital (ataxia-telangiectasia, Di George's syndrome, severe combined immunodeficiency, Wiskott-Aldrich syndrome).

INFECTIONS

Bacterial (bacterial pneumonia, brucellosis).
Disseminated mycotic infections.
Mycobacterial (lepromatous leprosy, TB).
Viral (varicella, hepatitis, influenza, mononucleosis, measles, mumps).

IMMUNOSUPPRESSIVE MEDICATIONS

Systemic corticosteroids.
Methotrexate, cyclophosphamide.
Rifampin.

OTHER

Alcoholic cirrhosis, biliary cirrhosis, sarcoidosis, rheumatic disease.
Diabetes, Crohn's disease, uremia.
Anemia, pyridoxine deficiency, sickle cell anemia.
Burns, malnutrition, pregnancy, old age, surgery.

ANEURYSMS, THORACIC AORTA

ICD-9CM # 441.2
ICD-10CM # I71.2 Thoracic Aortic Aneurysm, Without Rupture

Trauma.
Infection.
Inflammatory (syphilis, Takayasu's disease).
Collagen vascular disease (RA, ankylosing spondylitis).
Annuloaortic ectasia (Marfan's syndrome, Ehlers-Danlos syndrome).
Congenital.
Coarctation.
Cystic medial necrosis.

ANHIDROSIS

ICD-9CM # 705.1
ICD-10CM # L74.0 Miliaria Rubra
L74.1 Miliaria Crystallina
L74.2 Miliaria Profunda

Drugs (anticholinergics).
Dehydration.
Hysteria.
Obstruction of sweat ducts (e.g., inflammation, miliaria).
Local radiant heat or pressure.
CNS lesions (medulla, hypothalamus, pons).
Spinal cord lesions.
Lesions of sympathetic nerves.
Congenital sweat gland disturbances.

ANION GAP ACIDOSIS[38b]

ICD-9CM # 276.9
ICD-10CM # E87.2 Acidosis

CLINICAL CAUSES OF HIGH ANION GAP AND NORMAL ANION GAP ACIDOSIS

High Anion Gap
Ketoacidosis:
Diabetic ketoacidosis (acetoacetate).
Alcoholic (β-hydroxybutyrate).
Starvation.
Lactic acid acidosis:
L-Lactic acid acidosis (types A and B).
D-Lactic acid acidosis.
Renal failure: sulfate, phosphate, urate, hippurate.
Ingestions (toxins and their metabolites):
Ethylene glycol → glycolate, oxalate.
Methyl alcohol → formate.
Salicylate → ketones, lactate, salicylate.
Paraldehyde → organic anions.
Toluene → hippurate (commonly presents with normal anion gap).
Propylene glycol → lactate.
Pyroglutamic acidosis (acetaminophen use) → 5-oxoproline.
Normal Anion Gap
Gastrointestinal loss of HCO_3^- (negative urine anion gap):
Diarrhea.
Fistula, external.
Renal loss of HCO_3^- or failure to excrete NH_4^+ (positive urine anion gap):
Proximal renal tubular acidosis (RTA type 2).
Acetazolamide.
Classic distal renal tubular acidosis (low serum K^+) RTA type 1.
Generalized distal renal tubular defect (high serum K^+) RTA type 4.
Miscellaneous:
NH_4Cl ingestion.
Sulfur ingestion.
Dilutional acidosis.
Late stages in treatment of diabetic ketoacidosis.

ANION GAP INCREASE

ICD-9CM # 276.9
ICD-10CM # E87.8 Other Disorders of Electrolyte and Fluid Balance, Not Elsewhere Classified

Uremia.
Ketoacidosis (diabetic, starvation, alcoholic).
Lactic acidosis.
Ethylene glycol poisoning.
Salicylate overdose.
Methanol poisoning.

ANISOCORIA

ICD-9CM # 379.41
ICD-10CM # H57.02 Anisocoria

Mydriatic or miotic drugs.
Prosthetic eye.
Inflammation (keratitis, iridocyclitis).
Infections (herpes zoster, syphilis, meningitis, encephalitis, TB, diphtheria, botulism).
Subdural hemorrhage.
Cavernous sinus thrombosis.
Intracranial neoplasm.
Cerebral aneurysm.
Glaucoma.
CNS degenerative diseases.
Internal carotid ischemia.
Toxic polyneuritis (alcohol, lead).
Adie's syndrome.
Horner's syndrome.
DM.
Trauma.
Congenital.

ANOREXIA[38]

ICD-9CM # 783.0
ICD-10CM # R63.0 Anorexia

SELECTED CAUSES OF ANOREXIA

Gastrointestinal Tract/Liver
Gastric outlet obstruction or small bowel obstruction.
Gastric cancer.
Hepatic metastases.
Acute viral hepatitis.
Metabolic
Addison's disease.
Hypopituitarism.
Hyperparathyroidism.
Functional
Extremely unpleasant sight/smell.
Systemic
Chronic pain.
Renal failure.
Severe congestive heart failure.
Respiratory failure.
Psychiatric
Depression.
Anorexia nervosa.
Medications
Digoxin.
Narcotic analgesics.
Diuretics.
Antihypertensives.
Chemotherapeutic agents.
Amphetamines.
Miscellaneous
Excessive smoking.
Excessive alcohol intake.
Oral cavity disease.
Thiamine deficiency.
Early pregnancy.
Hypogeusia or dysgeusia.

ANOVULATION

ICD-9CM # 628.0
ICD-10CM # N97.0 Female Infertility Associated with Anovulation

Anorexia and bulimia.
Strenuous exercise.
Weight loss/malnutrition.
Empty sella syndrome.
Pituitary disorders (infarction, infection, trauma, irradiation, surgery, microadenomas, macroadenomas).
Idiopathic hypopituitarism.
Drug induced.
Thyroid dysfunction (hypothyroidism, hyperthyroidism).
Systemic diseases (e.g., liver disease).
Adrenal hyperfunction (Cushing's syndrome, congenital adrenal hyperplasia).
Polycystic ovarian syndrome.
Isolated gonadotropin deficiency.

APPENDICITIS, DIFFERENTIAL DIAGNOSIS IN PREGNANCY[12d]

ICD-9CM # codes vary with specific diagnosis
ICD-10CM # codes vary with specific

DIFFERENTIAL DIAGNOSIS OF APPENDICITIS DURING PREGNANCY

Gynecologic Conditions
Ruptured ovarian cyst.
Adnexal torsion.
Pelvic inflammatory disease or salpingitis.
Endometriosis.
Ovarian cancer.
Obstetrical Causes
Abruptio placentae.
Chorioamnionitis.
Endometritis.
Uterine fibroid degeneration.
Labor (preterm or term).
Viscus perforation after abortion.
Ruptured ectopic pregnancy.
Gastrointestinal Causes
Crohn's disease.
Colonic diverticulitis (right side).
Cholecystitis.
Pancreatitis.
Mesenteric lymphadenitis.
Gastroenteritis.
Colon cancer.
Intestinal obstruction.
Hernia (incarcerated inguinal or internal).
Colonic intussusception.
Ruptured Meckel's diverticulum.
Colonic perforation.
Acute mesenteric ischemia.
Other Causes
Pyelonephritis.
Urolithiasis.

APPETITE LOSS IN INFANTS AND CHILDREN[19]

ICD-9CM #	783.0	Appetite Loss
	307.59	Appetite Loss, Psychogenic Origin
ICD-10CM #	R63.0	Anorexia
	F50.8	Other Eating Disorders
	F98.29	Other Feeding Disorders of Infancy and Early Childhood

ORGANIC DISEASE

Infection (Acute or Chronic) Neurologic
Congenital degenerative disease.
Hypothalamic lesion.
Increased intracranial pressure (including a brain tumor).
Swallowing disorders (neuromuscular).
Gastrointestinal
Oral lesions (e.g., thrush or herpes simplex).
Gastroesophageal reflux.
Obstruction (especially with gastric or intestinal distention).
Inflammatory bowel disease.
Celiac disease.
Constipation.
Cardiac
Congestive heart failure (especially associated with cyanotic lesions).
Metabolic
Renal failure and/or renal tubule acidosis.
Liver failure.
Congenital metabolic disease.
Lead poisoning.
Nutritional
Marasmus.
Iron deficiency.
Zinc deficiency.
Fever
RA.
Rheumatic fever.
Drugs
Morphine.
Digitalis.
Antimetabolites.
Methylphenidate.
Amphetamines.
Miscellaneous
Prolonged restriction of oral feedings, beginning in the neonatal period.
Systemic lupus erythematosus (SLE).
Tumor.

PSYCHOLOGIC FACTORS

Anxiety, fear, depression, mania (limbic influence on the hypothalamus).
Avoidance of symptoms associated with meals (abdominal pain, diarrhea, bloating, urgency, dumping syndrome).
Anorexia nervosa.
Excessive weight loss and food aversion in athletes, simulating anorexia nervosa.

ARTERIAL OCCLUSION[15]

ICD-9CM #	444.22	Arterial Occlusion, Lower Extremities
	444.21	Arterial Occlusion, Upper Extremities
ICD-10CM #	I74.3	Embolism and Thrombosis of Arteries of the Lower Extremities
	I74.2	Embolism and Thrombosis of Arteries of the Upper Extremities

Thromboembolism (post-MI, mitral stenosis, rheumatic valve disease, atrial fibrillation, atrial myxoma, marantic endocarditis, bacterial endocarditis, Libman-Sacks endocarditis).
Atheroembolism (microemboli composed of cholesterol, calcium, and platelets from proximal atherosclerotic plaques).
Arterial thrombosis (endothelial injury, altered arterial blood flow, trauma, severe atherosclerosis, acute vasculitis).
Vasospasm.
Trauma.
Hypercoagulable states.
Miscellaneous (irradiation, drugs, infections, necrotizing).

ARTHRITIS AND ABDOMINAL PAIN

ICD-9CM #	varies with specific disorder	
ICD-10CM #	M00.9	Pyogenic Arthritis, Unspecified
	R10.817	Generalized Abdominal Tenderness
	M02.9	Reactive arthropathy

Viral syndrome.
Inflammatory bowel disease.
Celiac disease.
Vasculitis.
SLE.
RA.
Scleroderma.
Amyloidosis.
Chronic hepatitis C.
Whipple's disease.
Polyarteritis nodosa.
Behçet's disease.
Familial Mediterranean fever.
Blind loop syndrome.
Babesiosis.
Lyme disease.
Ehrlichiosis.

ARTHRITIS AND DIARRHEA

ICD-9CM #	varies with specific disorder	
ICD-10CM #	M00.9	Pyogenic Arthritis, Unspecified
	R19.7	Diarrhea, Unspecified

Viral syndrome.
Inflammatory bowel disease.
Celiac disease.
Whipple's disease.
Enterogenic (bacterial) reactive arthritis.
Collagenous colitis.
Behçet's disease.
Hyperthyroidism.
Spondyloarthropathy.
Blind loop syndrome.

ARTHRITIS AND EYE LESIONS[6]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	M00.9	Pyogenic Arthritis, Unspecified
	M02.3	Reiter disease
	M02.9	Reactive arthropathy

SLE.
Sjögren's syndrome.
Behçet's syndrome.
Sarcoidosis.
Subacute bacterial endocarditis (SBE).
Lyme disease.
Granulomatosis with polyangiitis (Wegener's granulomatosis).
Giant cell arteritis.
Takayasu's arteritis.
RA, JRA.
Scleroderma.
Inflammatory bowel disease.
Whipple's disease.
Ankylosing spondylitis.
Reactive arthritis.
Psoriatic arthritis.

ARTHRITIS AND HEART MURMUR[6]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	M00.9	Pyogenic Arthritis, Unspecified
	I01.8	Other Acute Rheumatic Heart Disease
	M02.9	Reactive arthropathy

SBE.
Cardiac myxoma.
Ankylosing spondylitis.
Reactive arthritis.
Acute rheumatic fever.
RA.
SLE with Libman-Sacks endocarditis.
Relapsing polychondritis.

ARTHRITIS AND MUSCLE WEAKNESS[8]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	M00.9	Pyogenic Arthritis, Unspecified
	M62.9	Disorder of Muscle, Unspecified
	M02.9	Reactive arthropathy

RA.
Ankylosing spondylitis.
Polymyositis.
Dermatomyositis.
SLE, scleroderma, mixed connective tissue disease.
Sarcoidosis.
HIV-associated arthritis.
Whipple's disease.

ARTHRITIS AND RASH[6]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	M00.9	Pyogenic Arthritis, Unspecified
	R21	Rash and Other Nonspecific Skin Eruption
	M02.9	Reactive arthropathy

Chronic urticaria.
Vasculitic urticaria.
SLE.
Dermatomyositis.
Polymyositis.
Psoriatic arthritis.
Reactive arthritis.
Chronic sarcoidosis.
Serum sickness.
Sweet's syndrome.
Leprosy.

ARTHRITIS AND SUBCUTANEOUS NODULES[6]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	M00.9	Pyogenic Arthritis, Unspecified
	A18.4	Tuberculosis of Skin and Subcutaneous Tissue
	M02.9	Reactive arthropathy

RA.
Gout.
Pseudogout (rare).
Sarcoidosis.
Light chain (LA) amyloidosis (primary, multiple myeloma).
Acute rheumatic fever (ARF).
Hemochromatosis.
Whipple's disease.
Multicentric reticulohistiocytosis.

ARTHRITIS AND WEIGHT LOSS[6]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	M00.9	Pyogenic Arthritis, Unspecified
	R63.4	Abnormal Weight Loss
	M02.9	Reactive arthropathy

Severe RA.
RA with vasculitis.
Reactive arthritis.
RA or psoriatic arthritis or ankylosing spondylitis with amyloidosis.
Cancer.
Enteropathic arthritis (Crohn's, ulcerative colitis).
HIV infection.
Whipple's disease.
Blind loop syndrome.
Scleroderma with intestinal bacterial overgrowth.

ARTHRITIS OR EXTREMITY PAIN, IN CHILDREN AND ADOLESCENTS[22a]

ICD-9CM #	varies with specific diagnosis
ICD-10CM #	M02.9 Reactive arthropathy

CAUSES OF ARTHRITIS OR EXTREMITY PAIN IN CHILDREN AND ADOLESCENTS

Rheumatic and Inflammatory Diseases
Juvenile idiopathic arthritis.
Systemic lupus erythematosus.
Juvenile dermatomyositis.
Polyarteritis.
Vasculitis.
Scleroderma.
Sjögren syndrome.
Behçet disease.
Overlap syndromes.
Granulomatosis with polyangiitis (Wegener granulomatosis).
Sarcoidosis.
Kawasaki syndrome.
Henoch-Schönlein purpura.
Chronic recurrent multifocal osteomyelitis.

Seronegative Spondyloarthropathies
Juvenile ankylosing spondylitis.
Inflammatory bowel disease.
Psoriatic arthritis.
Reactive arthritis associated with urethritis, iridocyclitis, and mucocutaneous lesions.

Infectious Illnesses
Bacterial arthritis (septic arthritis, *Staphylococcus aureus,* pneumococcus, gonococcus, *Haemophilus influenzae*).
Lyme disease.

Viral illness (parvovirus, rubella, mumps, Epstein-Barr virus, hepatitis B).
Fungal arthritis.
Mycobacterial infection.
Spirochetal infection.
Endocarditis.
Reactive Arthritis
Acute rheumatic fever.
Reactive arthritis (postinfectious due to *Shigella, Salmonella, Yersinia, Chlamydia,* or meningococcus).
Serum sickness.
Toxic synovitis of the hip.
Postimmunization.
Immunodeficiencies
Hypogammaglobulinemia.
Immunoglobulin A deficiency.
Human immunodeficiency virus.
Congenital and Metabolic Disorders
Gout.
Pseudogout.
Mucopolysaccharidoses.
Thyroid disease (hypothyroidism, hyperthyroidism).
Hyperparathyroidism.
Vitamin C deficiency (scurvy).
Hereditary connective tissue disease (Marfan syndrome, Ehlers-Danlos syndrome).
Fabry disease.
Farber disease.
Amyloidosis (familial Mediterranean fever).
Bone and Cartilage Disorders
Trauma.
Patellofemoral syndrome.
Hypermobility syndrome.
Osteochondritis dissecans.
Avascular necrosis (including Legg-Calvé-Perthes disease).
Hypertrophic osteoarthropathy.
Slipped capital femoral epiphysis.
Osteolysis.
Benign bone tumors (including osteoid osteoma).
Histiocytosis.
Rickets.
Neuropathic Disorders
Peripheral neuropathies.
Carpal tunnel syndrome.
Charcot joints.
Neoplastic Disorders
Leukemia.
Neuroblastoma.
Lymphoma.
Bone tumors (osteosarcoma, Ewing sarcoma).
Histiocytic syndromes.
Synovial tumors.
Hematologic Disorders
Hemophilia.
Hemoglobinopathies (including sickle cell disease).
Miscellaneous Disorders
Pigmented villonodular synovitis.
Plant-thorn synovitis (foreign body arthritis).
Myositis ossificans.
Eosinophilic fasciitis.
Tendinitis (overuse injury).
Raynaud phenomenon.
Pain Syndromes
Fibromyalgia.
Growing pains.
Depression (with somatization).
Reflex sympathetic dystrophy.
Regional myofascial pain syndromes.

ARTHRITIS, AXIAL SKELETON

ICD-9CM #	720.0	Arthritis, Rheumatoid, Spine
	696.0	Arthritis, Psoriatic
	715.9	Arthritis, Degenerative, NOS
	720.0	Ankylosing Spondylitis
ICD-10CM #	M45.9	Ankylosing Spondylitis of Unspecified Sites in Spine
	L40.54	Psoriatic Juvenile Arthropathy
	L40.59	Other Psoriatic Arthropathy
	M15.9	Polyosteoarthritis, Unspecified
	M45.9	Ankylosing Spondylitis of Unspecified Sites in Spine

RA.
Psoriatic arthritis.
Reiter's syndrome (reactive arthritis).
Ankylosing spondylitis.
Juvenile RA.
Degenerative disease of the nucleus pulposus.
Spondylosis deformans.
Diffuse idiopathic skeletal hyperostosis (DISH).
Alkaptonuria.
Infection.

ARTHRITIS, FEVER, AND RASH[6]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	M00.9	Pyogenic Arthritis, Unspecified
	M02.9	Reactive arthropathy
	R21	Rash and Other Nonspecific Skin Eruption
	R50.9	Fever, Unspecified

Rubella, parvovirus B19.
Gonococcemia, meningococcemia.
Secondary syphilis, Lyme borreliosis.
Adult acute rheumatic fever, adult Still's disease, adult Kawasaki disease.
Vasculitic urticaria.
Acute sarcoidosis.
Familial Mediterranean fever.
Hyperimmunoglobulinemia D and periodic fever syndrome.

ARTHRITIS, MONOARTICULAR AND OLIGOARTICULAR[2]

ICD-9CM #	715.3	Osteoarthritis, Localized
	711.9	Infectious Arthritis
	716.6	Monoarticular Arthritis; 5th digit to be added to the above depending on site of arthritis 0. Site Unspecified 1. Shoulder Region 2. Upper Arm 3. Forearm 4. Hand 5. Pelvic Region and Thigh 6. Lower Leg 7. Ankle and/or Foot 8. Other Specified Except Spine
ICD-10CM #	M19.90	Unspecified Osteoarthritis, Unspecified Site
	M01.X0	Direct Infection of Unspecified Joint in Infectious and Parasitic Diseases Classified Elsewhere
	M13.10	Monoarthritis, Not Elsewhere Classified, Unspecified Site

Septic arthritis (*S. aureus, Neisseria gonorrhoeae,* meningococci, streptococci, *Streptococcus pneumoniae,* enteric gram-negative bacilli).
Crystalline-induced arthritis (gout, pseudogout, calcium oxalate, hydroxyapatite and other basic calcium/phosphate crystals).
Traumatic joint injury.
Hemarthrosis.
Monoarticular or oligoarticular flare of an inflammatory polyarticular rheumatic disease (RA, psoriatic arthritis, Reiter's syndrome [reactive arthritis], SLE).

ARTHRITIS, PEDIATRIC AGE[19]

ICD-9CM #	711.9	Infectious Arthritis
	714.30	Juvenile Chronic or Unspecified
	714.31	Juvenile Rheumatoid Polyarticular Acute
	714.32	Juvenile Rheumatoid Pauciarticular
	714.33	Juvenile Rheumatoid Monoarticular
ICD-10CM #	M01.X0	Direct Infection of Unspecified Joint in Infectious and Parasitic Diseases Classified Elsewhere
	M08.00	Unspecified Juvenile Rheumatoid Arthritis of Unspecified Site
	M08.3	Juvenile Rheumatoid Polyarthritis (Seronegative)
	M08.40	Pauciarticular Juvenile Rheumatoid Arthritis, Unspecified Site

RHEUMATIC DISEASES OF CHILDHOOD

Acute rheumatic fever.
SLE.
Juvenile ankylosing spondylitis.
Polymyositis and dermatomyositis.
Vasculitis.
Scleroderma.
Psoriatic arthritis.
Mixed connective tissue disease and overlap syndromes.
Kawasaki disease.
Behçet's syndrome.
Familial Mediterranean fever.
Reiter's syndrome (reactive arthritis).
Reflex sympathetic dystrophy.
Fibromyalgia (fibrositis).

INFECTIOUS DISEASES

Bacterial arthritis.
Viral or postviral arthritis.
Fungal arthritis.
Osteomyelitis.
Reactive arthritis.

NEOPLASTIC DISEASES

Leukemia.
Lymphoma.
Neuroblastoma.
Primary bone tumors.

NONINFLAMMATORY DISORDERS

Trauma.
Avascular necrosis syndromes.
Osteochondroses.
Slipped capital femoral epiphysis.
Diskitis.
Patellofemoral dysfunction (chondromalacia patellae).
Toxic synovitis of the hip.
Overuse syndromes.

GENETIC OR CONGENITAL SYNDROMES

Hematologic Disorders

Sickle cell disease.
Hemophilia.

INFLAMMATORY BOWEL DISEASE

Miscellaneous

Growing pains.
Psychogenic arthralgias (conversion reactions).
Hypermobility syndrome.
Villonodular synovitis.
Foreign body arthritis.

ARTHRITIS, POLYARTICULAR

ICD-9CM #	715.09	Generalized Osteoarthritis, Multiple Sites
	716.89	Arthritis, Multiple Sites
	714.31	Juvenile Rheumatoid, Polyarticular, Acute
ICD-10CM #	M15.0	Primary Generalized (Osteo)Arthritis
	M12.89	Other Specific Arthropathies, Not Elsewhere Classified, Multiple Sites
	M08.3	Juvenile Rheumatoid Polyarthritis (Seronegative)

RA, juvenile (rheumatoid) polyarthritis.
SLE, other connective tissue diseases, erythema nodosum, palindromic rheumatism, relapsing polychondritis.
Psoriatic arthritis, ankylosing spondylitis.
Sarcoidosis.
Lyme arthritis, bacterial endocarditis, *Neisseria gonorrhoeae* infection, rheumatic fever, Reiter's disease (reactive arthritis).
Crystal deposition disease.
Hypersensitivity to serum or drugs.
Hepatitis B, HIV, rubella, mumps.
Other: serum sickness, leukemias, lymphomas, enteropathic arthropathy, Whipple's disease, Behçet's syndrome, Henoch-Schönlein purpura, familial Mediterranean fever, hypertrophic pulmonary osteoarthropathy.

ASCITES

ICD-9CM #	789.5	Ascites NOS
	197.6	Ascites, Cancerous (Malignant)
	457.8	Ascites, Chylous
ICD-10CM #	R18.0	Malignant Ascites
	C78.6	Secondary Malignant Neoplasm of Retroperitoneum and Peritoneum
	I89.8	Other Specified Noninfective Disorders of Lymphatic Vessels and Lymph Nodes

Hypoalbuminemia: nephrotic syndrome, protein-losing gastroenteropathy, starvation.
Cirrhosis.
Hepatic congestion: CHF, constrictive pericarditis, tricuspid insufficiency, hepatic vein obstruction (Budd-Chiari syndrome), inferior vena cava or portal vein obstruction.
Peritoneal infections: TB and other bacterial infections, fungal diseases, parasites.
Neoplasms: primary hepatic neoplasms, metastases to liver or peritoneum, lymphomas, leukemias, myeloid metaplasia.
Lymphatic obstruction: mediastinal tumors, trauma to the thoracic duct, filariasis.
Ovarian disease: Meigs' syndrome, struma ovarii.
Chronic pancreatitis or pseudocyst: pancreatic ascites.
Leakage of bile: bile ascites.
Urinary obstruction or trauma: urine ascites.
Myxedema.
Chylous ascites.

ASPIRATION LUNG INJURY, CHILDREN[22a]

ICD-9CM #	507.0	
ICD-10CM #	P24.8	Neonatal aspiration syndromes

CONDITIONS PREDISPOSING TO ASPIRATION LUNG INJURY IN CHILDREN

Anatomic and Mechanical

Tracheoesophageal fistula.
Laryngeal cleft.
Vascular ring.
Cleft palate.
Micrognathia.
Macroglossia.
Achalasia.
Esophageal foreign body.
Tracheostomy.
Endotracheal tube.
Nasoenteric tube.
Collagen vascular disease (scleroderma, dermatomyositises).
Gastroesophageal reflux disease.
Obesity.

Neuromuscular

Altered consciousness.
Immaturity of swallowing/prematurity.
Dysautonomia.
Increased intracranial pressure.
Hydrocephalus.
Vocal cord paralysis.
Cerebral palsy.
Muscular dystrophy.
Myasthenia gravis.
Guillain-Barré syndrome.
Werdnig-Hoffmann disease.
Ataxia-telangiectasia.
Cerebral vascular accident.

Miscellaneous

Poor oral hygiene.
Gingivitis.
Prolonged hospitalization.
Gastric outlet or intestinal obstruction.
Poor feeding techniques (bottle propping, overfeeding, inappropriate foods for toddlers).
Bronchopulmonary dysplasia.
Viral infection.

ASTHENIA

ICD-9CM #	780.79	
ICD-10CM #	G93.3	Postviral Fatigue Syndrome
	R53.1	Weakness
	R53.81	Other Malaise
	R53.83	Other Fatigue

Depression.
Chronic fatigue syndrome.
Sleep disorders.
Anemia.
Hypothyroidism.
Sedentary lifestyle.
Medications (e.g., narcotics, sedatives).
Infections.
Dehydration/electrolyte disorders.
COPD and other pulmonary disorders.

Renal failure.
CHF.
Diabetes.
Addison's disease.
Paraneoplastic syndrome.

ASTHMA, CHILDHOOD[4]

ICD-9CM #	493.0	Use 5th digit
	0	Without Mention of Status Asthmaticus
	1	With Status Asthmaticus
ICD-10CM #	J45.20	Mild Intermittent Asthma, Uncomplicated
	J45.22	Mild Intermittent Asthma with Status Asthmaticus

INFECTIONS

Bronchiolitis (RSV).
Pneumonia.
Croup.
Tuberculosis, histoplasmosis.
Bronchiectasis.
Bronchiolitis obliterans.
Bronchitis.
Sinusitis.

ANATOMIC, CONGENITAL

Cystic fibrosis.
Vascular rings.
Ciliary dyskinesia.
B-lymphocyte immune defect.
Congestive heart failure.
Laryngotracheomalacia.
Tumor, lymphoma.
H-type tracheoesophageal fistula.
Repaired tracheoesophageal fistula.
Gastroesophageal reflux.

VASCULITIS, HYPERSENSITIVITY

Allergic bronchopulmonary aspergillosis.
Allergic alveolitis, hypersensitivity pneumonitis.
Churg-Strauss syndrome.
Periarteritis nodosa.

OTHER

Foreign body aspiration.
Pulmonary thromboembolism.
Psychogenic cough.
Sarcoidosis.
Bronchopulmonary dysplasia.
Vocal cord dysfunction.

ATAXIA

ICD-9CM #	781.3	Ataxia NOS
	303.0	Alcoholic, Acute
	303.9	Alcoholic, Chronic
	334.3	Cerebellar
	331.89	Cerebral
	334.0	Friedreich's
	300.11	Hysterical
ICD-10CM #	R27.0	Ataxia, Unspecified
	R27.8	Other Lack of Coordination
	R27.9	Unspecified Lack of Coordination
	F10.229	Alcohol Dependence with Intoxication, Unspecified
	F10.20	Alcohol Dependence, Uncomplicated
	G11.1	Early-Onset Cerebellar Ataxia
	G31.89	Other Specified Degenerative Diseases of Nervous System
	F44.4	Conversion Disorder with Motor Symptom or Deficit
	F44.6	Conversion Disorder with Sensory Symptom or Deficit

Vertebral-basilar artery ischemia.
Diabetic neuropathy.
Tabes dorsalis.
Vitamin B_{12} deficiency.
Multiple sclerosis and other demyelinating diseases.
Meningomyelopathy.
Cerebellar neoplasms, hemorrhage, abscess, infarct.
Nutritional (Wernicke's encephalopathy).
Paraneoplastic syndromes.
Parainfectious: Guillain-Barré syndrome, acute ataxia of childhood and young adults.
Toxins: phenytoin, alcohol, sedatives, organophosphates.
Wilson's disease (hepatolenticular degeneration).
Hypothyroidism.
Myopathy.
Cerebellar and spinocerebellar degeneration: ataxia/telangiectasia, Friedreich's ataxia.
Frontal lobe lesions: tumors, thrombosis of anterior cerebral artery, hydrocephalus.
Labyrinthine destruction: neoplasm, injury, inflammation, compression.
Hysteria.
AIDS.

ATAXIA, ACUTE OR RECURRENT[11]

ICD-9CM #	781.3	Ataxia NOS
	303.0	Alcoholic, Acute
	303.9	Alcoholic, Chronic
	334.3	Cerebellar
	331.89	Cerebral
	334.0	Friedreich's
	300.11	Hysterical
ICD-10CM #	R27.0	Ataxia, Unspecified
	R27.8	Other Lack of Coordination
	R27.9	Unspecified Lack of Coordination
	F10.229	Alcohol Dependence with Intoxication, Unspecified
	F10.20	Alcohol Dependence, Uncomplicated
	G11.1	Early-Onset Cerebellar Ataxia
	G31.89	Other Specified Degenerative Diseases of Nervous System
	F44.4	Conversion Disorder with Motor Symptom or Deficit
	F44.6	Conversion Disorder with Sensory Symptom or Deficit

Drug ingestion (e.g., phenytoin, carbamazepine, sedatives, hypnotics, and phencyclidine) or intoxication (e.g., alcohol, ethylene glycol, hydrocarbon fumes, lead, mercury, or thallium).
Postinfectious (cerebellitis [e.g., varicella], acute disseminated encephalomyelitis).
Head trauma.
Basilar migraine.
Benign paroxysmal vertigo (migraine equivalent).
Brain tumor or neuroblastoma (if accompanied by opsoclonus or myoclonus [i.e., "dancing eyes, dancing feet"]).
Hydrocephalus.
Infection (e.g., labyrinthitis, abscess).
Seizure (ictal or postictal).
Vascular events (e.g., cerebellar hemorrhage or stroke).
Miller-Fisher variant of Guillain-Barré syndrome (ataxia, ophthalmoplegia, and areflexia). Warning: If bulbar signs present, disease is likely progressive; patient may lose ability to protect airway and/or ability to breathe.
Inherited ataxias.
Inborn errors of metabolism (e.g., mitochondrial disorders, amino-acidopathies, urea cycle defects).
Conversion reaction.
Multiple sclerosis.

ATAXIA, CEREBELLAR, ADULT ONSET[34a]

ICD-9CM #	334.2	
ICD-10CM #	G11.0	Congenital Nonprogressive Ataxia
	G11.2	Late-Onset Cerebellar Ataxia

CAUSES OF ADULT ONSET CEREBELLAR ATAXIA

Inherited
Later onset SCA syndromes.
Rarely Friedreich's ataxia.
Congenital
Arnold–Chiari malformation (cerebellar ectopia).
Inflammatory
Multiple sclerosis.
Sarcoidosis.
Infections (TB, viral).
Neoplastic
Often metastatic in adults.
Meningioma, neurofibroma.
Hemangioblastoma.
Paraneoplastic
Usually with small cell bronchial carcinoma.
Vascular
Infarction, hemorrhage.
Arteriovenous malformations.

Trauma
Head injury.
Postsurgical.
Toxic
Alcohol, phenytoin, solvent abuse.
Endocrine
Hypothyroidism (very rare).
Degenerative
Multiple system atrophy (MSA).

ATAXIA, CEREBELLAR, CHILDREN[34a]

ICD-9CM #	334.2	
ICD-10CM #	G11.0	Congenital Nonprogressive Ataxia
	G11.2	Late-Onset Cerebellar Ataxia

CAUSES OF CEREBELLAR ATAXIA IN CHILDREN

Congenital Malformations
Cerebellar agenesis/hypoplasia.
Dandy–Walker syndrome.*
Arnold–Chiari malformation.**
Hereditary Ataxias
Friedreich's ataxia.
Trauma
Birth trauma.*
Head injury in childhood.*
Infectious
Secondary to bacterial meningitis.
Secondary to encephalitis.
Hydrocephalus*
Tumors
Medulloblastoma.
Astrocytoma.
Hemangioblastoma.

*May persist into adult life. fn2
**May present in adult life. fn3

ATAXIA, CHRONIC OR PROGRESSIVE[11]

ICD-9CM #	varies with specific diagnosis	
	781.3	Ataxia NOS
	0.94	Locomotor Ataxia
	334.0	Friedreich's Ataxia
	334.2	Cerebellar Ataxia, Primary
	334.3	Other Cerebellar Ataxia
	334.8	Ataxia-telangiectasia
ICD-10CM #	R27.0	Ataxia, Unspecified
	R27.8	Other Lack of Coordination
	R27.9	Unspecified Lack of Coordination
	G11.1	Early-Onset Cerebellar Ataxia
	G11.0	Congenital Nonprogressive Ataxia
	G11.2	Late-Onset Cerebellar Ataxia
	G11.3	Cerebellar Ataxia with Defective DNA Repair
	G11.8	Other Hereditary Ataxia

Hydrocephalus.
Hypothyroidism.
Tumor or paraneoplastic syndrome.
Low vitamin E levels (e.g., cystic fibrosis).
Wilson disease.
Inborn errors of metabolism.
Inherited ataxias (e.g., ataxia-telangiectasia, Friedreich's ataxia).

ATELECTASIS

ICD-9CM #	518.0	
ICD-10CM #	J98.11	Atelectasis

Lung neoplasm (primary or metastatic).
Infection (pneumonia, TB, fungal, histoplasmosis).
Postoperative (lower lobes).
Sarcoidosis.
Mucoid impaction.
Foreign body.
Postinflammatory (middle lobe syndrome).
Pneumothorax.
Pleural effusion.
Pneumoconiosis.
Interstitial fibrosis.
Bulla.
Mediastinal or adjacent mass.

ATRIAL ENLARGEMENT, LEFT ATRIUM[16a]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	I51.7	Cardiomegaly

CAUSES OF LARGE LEFT ATRIUM

Causes Due to Volume Overload
Mitral regurgitation (often with left ventricular failure).
Ventricular septal defect.
Patent ductus arteriosus.
Atrial septal defect with shunt reversal (i.e., pulmonary hypertension).
ASD with tricuspid atresia (obligatory shunt reversal).
Aortopulmonary window.
Causes Due to Pressure Overload
Mitral stenosis.
Noncompliant left ventricle: hypertension, hypertrophic cardiomyopathy, aortic stenosis.
Left ventricular failure (often with secondary mitral regurgitation).
Left atrial myxoma.
Other Causes (Both Rare)
Atrial fibrillation.
Isolated/idiopathic.

ATRIAL ENLARGEMENT, RIGHT ATRIUM

ICD-9CM #	varies with specific disorder	
ICD-10CM #	I51.7	Cardiomegaly

Right ventricular failure.
Atrial septal defect.
Tricuspid regurgitation.
Tricuspid stenosis.
Pulmonary hypertension.
Restrictive cardiomyopathy.
Right atrial myxoma.
Ebstein's anomaly.
Anomalous pulmonary venous drainage to the right atrium.
Endomyocardial fibrosis.
Sinus of Valsalva fistula.
Arrhythmogenic right ventricular dysplasia.

ATYPICAL LYMPHOCYTOSIS, HETEROPHIL NEGATIVE, INFECTIOUS CAUSES[1a]

ICD-9CM #	288.61	
ICD-10CM #	D72.820	Lymphocytosis (Symptomatic)

MOST COMMON INFECTIOUS CAUSES OF HETEROPHIL-NEGATIVE ATYPICAL LYMPHOCYTOSIS

Babesiosis.
Cytomegalovirus.
Epstein-Barr virus (particularly in children).
Human herpesvirus 6.
Human immunodeficiency virus (especially during acute seroconversion).
Infectious mononucleosis.
Malaria.
Measles.
Toxoplasmosis.
Varicella.
Infectious hepatitis.

AV NODAL BLOCK[15]

ICD-9CM #	426.10	AV Block (Incomplete, Partial)
	426.0	AV Block, Complete
ICD-10CM #	I44.30	Unspecified Atrioventricular Block
	I44.2	Atrioventricular Block, Complete

Idiopathic fibrosis (Lenègre's disease).
Sclerodegenerative processes (e.g., Lev's disease with calcification of the mitral and aortic annuli).
AV node radiofrequency ablation procedure.
Medications (e.g., digoxin, beta-blockers, calcium channel blockers, class III antiarrhythmics).
Acute inferior wall MI.
Myocarditis.
Infections (endocarditis, Lyme disease).
Infiltrative diseases (e.g., hemochromatosis, sarcoidosis, amyloidosis).
Trauma (including cardiac surgical procedures).
Collagen vascular diseases.
Aortic root diseases (e.g., spondylitis).
Electrolyte abnormalities (e.g., hyperkalemia).

BACK PAIN

ICD-9CM #	724.5	Back Pain (Postural)
	724.2	Low Back Pain
	307.89	Back Pain Psychogenic
	724.8	Stiff Back
	847.9	Back Strain
	724.6	Backache, Sacroiliac

ICD-10CM #	M54.89	Other Dorsalgia
	M54.9	Dorsalgia, Unspecified
	M54.5	Low Back Pain
	F45.42	Pain Disorder with Related Psychological Factors
	M54.08	Panniculitis Affecting Regions of Neck and Back, Sacral and Sacrococcygeal Region
	S23.9XXA	Sprain of Unspecified Parts of Thorax, Initial Encounter
	M43.27	Fusion of Spine, Lumbosacral Region
	M43.28	Fusion of Spine, Sacral and Sacrococcygeal Region
	M53.2X7	Spinal Instabilities, Lumbosacral Region
	M53.3	Sacrococcygeal Disorders, Not Elsewhere Classified

Trauma: injury to bone, joint, or ligament.
Mechanical: pregnancy, obesity, fatigue, scoliosis.
Degenerative: osteoarthritis.
Infections: osteomyelitis, subarachnoid or spinal abscess, TB, meningitis, basilar pneumonia.
Metabolic: osteoporosis, osteomalacia.
Vascular: leaking aortic aneurysm, subarachnoid or spinal hemorrhage/infarction.
Neoplastic: myeloma, Hodgkin's disease, carcinoma of pancreas, metastatic neoplasm from breast, prostate, lung.
GI: penetrating ulcer, pancreatitis, cholelithiasis, inflammatory bowel disease.
Renal: hydronephrosis, calculus, neoplasm, renal infarction, pyelonephritis.
Hematologic: sickle cell crisis, acute hemolysis.
Gynecologic: neoplasm of uterus or ovary, dysmenorrhea, salpingitis, uterine prolapse.
Inflammatory: ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome (reactive arthritis).
Lumbosacral strain.
Psychogenic: malingering, hysteria, anxiety.
Endocrine: adrenal hemorrhage or infarction.

BACK PAIN, CHILDREN AND ADOLESCENTS[22a]

ICD-9CM #	724.2	
ICD-10CM #	M54.5	Low Back Pain
	M54.9	Dorsalgia

INFLAMMATORY OR INFECTIOUS

Diskitis.
Vertebral osteomyelitis (pyogenic, tuberculous).
Spinal epidural abscess.
Pyelonephritis.
Pancreatitis.

RHEUMATOLOGIC

Pauciarticular juvenile rheumatoid arthritis.
Reiter syndrome (reactive arthritis).
Ankylosing spondylitis.
Psoriatic arthritis.

DEVELOPMENTAL

Spondylolysis.
Spondylolisthesis.
Scheuermann disease.
Scoliosis.

TRAUMATIC (ACUTE VERSUS REPETITIVE)

Hip-pelvis anomalies.
Herniated disk.
Overuse syndromes.
Vertebral stress fractures.
Upper cervical spine instability.

NEOPLASTIC

Vertebral Tumors
Benign
Eosinophilic granuloma.
Aneurysmal bone cyst.
Osteoid osteoma.
Osteoblastoma.
Malignant
Osteogenic sarcoma.
Leukemia.
Lymphoma.
Metastatic tumors.
Spinal Cord, Ganglia, and Nerve Roots
Intramedullary spinal cord tumor.
Sympathetic chain.
Ganglioneuroma.
Ganglioneuroblastoma.
Neuroblastoma.

OTHER

Intraabdominal or pelvic pathology.
Following lumbar puncture.
Conversion reaction.
Juvenile osteoporosis.

BACK PAIN, LOW, ACUTE[2]

ICD-9CM #	724.2	
ICD-10CM #	M54.5	Low Back Pain

DIFFERENTIAL CONSIDERATIONS IN ACUTE LOW BACK PAIN

Emergent
Aortic dissection.
Cauda equina syndrome.
Epidural abscess or hematoma.
Meningitis.
Ruptured/expanding aortic aneurysm.
Spinal fracture or subluxation with cord or root impingement.
Urgent
Back pain with neurologic deficits.
Disk herniation causing neurologic compromise.
Malignancy.
Sciatica with motor nerve root compression.
Spinal fractures without cord impingement.
Spinal stenosis.
Transverse myelitis.
Vertebral osteomyelitis.
Common or Stable
Acute ligamentous injury.
Acute muscle strain.
Ankylosing spondylitis.
Degenerative joint disease.
Intervertebral disk disease without impingement.
Pathologic fracture without impingement.
Seropositive arthritis.
Spondylolisthesis.
Referred or Visceral
Cholecystitis.
Esophageal disease.
Nephrolithiasis.
Ovarian torsion, mass, or tumor.
Pancreatitis.
Peptic ulcer disease.
Pleural effusion.
Pneumonia.
Pulmonary embolism.
Pyelonephritis.
Retroperitoneal hemorrhage or mass.

BACK PAIN, VISCEROGENIC ORIGIN

ICD-9CM #	varies with specific disorder	
ICD-10CM #	F45.41	Pain Disorder Exclusively Related to Psychological Factors
	M54	Dorsalgia
	M54.5	Low back pain

Urolithiasis.
Aortic aneurysm.
Colorectal carcinoma.
Endometriosis.
Tubal pregnancy.
Prostatitis.
Peptic ulcer.
Pancreatitis.
Diverticular spasm.
Metastatic neoplasm (e.g., bladder, uterus, ovary, kidney).

BACTERIAL OVERGROWTH, SMALL INTESTINE[38]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	A04.9	Bacterial intestinal infection, unspecified

Gastric surgery—Billroth II.
Small bowel diverticula.
Small bowel stricture:
- Crohn's disease.
- Radiation enteritis.

Impaired small intestinal motility:
- Scleroderma.
- Diabetes mellitus.
- Chronic intestinal pseudoobstruction.

Miscellaneous/multifactorial
- Elderly.
- Immune deficiency syndromes.
- Chronic pancreatitis.
- Cirrhosis.

BALLISM*

ICD-9CM # 333.5
ICD-10CM # G25.4 Drug-Induced Chorea
G25.5 Other Chorea

Cerebral infarction or hemorrhage.
Medications (e.g., dopamine agonists, phenytoin).
CNS neoplasm (primary or metastatic).
Nonketotic hyperosmolar state.

*Violent, flinging, nonpatterned rapid movements

BILE DUCT, DILATED[38]

ICD-9CM # varies with specific diagnosis
ICD-10CM # K83.1 Obstruction of bile duct

Normal variant.
Post-cholecystectomy.
Unsuspected bile duct stone.
Sphincter of Oddi stenosis.
Occult bile duct stricture.
Previous bile duct injury.
Early carcinoma of the pancreas, carcinoma of the bile duct, or carcinoma of the ampulla.
Extrinsic compression of the bile duct by a primary or secondary neoplasm.

BLEEDING, LOWER GI

ICD-9CM # 578.9
ICD-10CM # K92.2 Gastrointestinal Hemorrhage, Unspecified

(ORIGINATING BELOW THE LIGAMENT OF TREITZ)

Small Intestine

Ischemic bowel disease (mesenteric thrombosis, embolism, vasculitis, trauma).
Small bowel neoplasm: leiomyomas, carcinoids.
Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome).
Meckel diverticulum and other small intestine diverticula.
Aortoenteric fistula.
Intestinal hemangiomas: blue rubber-bleb nevi, intestinal hemangiomas, cutaneous vascular nevi.
Hamartomatous polyps: Peutz-Jeghers syndrome (intestinal polyps, mucocutaneous pigmentation).
Infections of small bowel: tuberculous enteritis, enteritis necroticans.
Volvulus.
Intussusception.
Lymphoma of small bowel, sarcoma, Kaposi's sarcoma.
Irradiation ileitis.
AV malformation of small intestine.
Inflammatory bowel disease.
Polyarteritis nodosa.
Other: pancreatoenteric fistulas, Henoch-Schönlein purpura, Ehlers-Danlos syndrome, SLE, amyloidosis, metastatic melanoma.

Colon

Carcinoma (particularly left colon).
Diverticular disease.
Inflammatory bowel disease.
Ischemic colitis.
Colonic polyps.
Vascular abnormalities: angiodysplasia, vascular ectasia.
Radiation colitis.
Infectious colitis.
Uremic colitis.
Aortoenteric fistula.
Lymphoma of large bowel.
Hemorrhoids.
Anal fissure.
Trauma, foreign body.
Solitary rectal/cecal ulcers.
Long-distance running.

BLEEDING, LOWER GI, PEDIATRIC[2]

ICD-9CM # 578.9
ICD-10CM # K92.2 Gastrointestinal Hemorrhage, Unspecified

<3 MO

Swallowed maternal blood.
Infectious colitis.
Milk allergy.
Bleeding diathesis.
Intussusception.
Midgut volvulus.
Meckel diverticulum.
Necrotizing enterocolitis.

<2 YR

Anal fissure.
Infectious colitis.
Milk allergy.
Colitis.
Intussusception.
Meckel diverticulum.
Polyp.
Duplication.
Hemolytic-uremic syndrome.
Inflammatory bowel disease.
Pseudomembranous enterocolitis.

<5 YR

Infectious colitis.
Anal fissure.
Polyp.
Intussusception.
Meckel diverticulum.
Henoch-Schönlein purpura.
Hemolytic-uremic syndrome.
Inflammatory bowel disease.
Pseudomembranous enterocolitis.

5 TO 18 YR

Infectious colitis.
Inflammatory bowel disease.
Pseudomembranous enterocolitis.
Polyp.
Hemolytic-uremic syndrome.
Hemorrhoids.

BLEEDING, RECTAL[38]

ICD-9CM # 578.9
ICD-10CM # K92.2 Gastrointestinal Hemorrhage, Unspecified

IN PATIENTS <40 YR

Very Common:

Hemorrhoids.
Anal fissure.
Inflammatory bowel disease (mainly proctitis).

Less Common:

Polyps (hamartomatous or adenomatous).
Infective colitis.
Meckel's diverticulum.
Intussusception.

Rare:

Colorectal cancer.

IN PATIENTS >40 YR

Hemorrhoids.
Anal fissure.
Colorectal cancer.
Colorectal polyps (mostly adenomas).
Angiodysplasia.
Diverticular disease.
Inflammatory bowel disease.
Ischemic colitis.
Infective colitis.

BLEEDING, THIRD TRIMESTER[1]

ICD-9CM # 623.8
ICD-10CM # N93.9 Abnormal uterine and vaginal bleeding, unspecified

Placental abruption.
Placenta previa.
Bloody show (extrusion of cervical mucus).
Vasa previa.
Disseminated intravascular coagulopathy.
Uterine rupture.
Cervicitis, cervical cancer, or other cervical abnormality.
Vaginal laceration.

BLEEDING, UPPER GI

ICD-9CM # 578.9
ICD-10CM # K92.2 Gastrointestinal Hemorrhage, Unspecified

(ORIGINATING ABOVE THE LIGAMENT OF TREITZ)

Swallowed Hemoptysis

Oral or pharyngeal lesions: swallowed blood from nose or oropharynx.
Esophageal: varices, ulceration, esophagitis, Mallory-Weiss tear, carcinoma, trauma.
Gastric: peptic ulcer (including Cushing and Curling's ulcers), gastritis, angiodysplasia, gastric neoplasms, hiatal hernia, gastric diverticulum, pseudoxanthoma elasticum, Rendu-Osler-Weber syndrome.

Duodenal: peptic ulcer, duodenitis, angiodysplasia, aortoduodenal fistula, duodenal diverticulum, duodenal tumors, carcinoma of ampulla of Vater, parasites (e.g., hookworm), Crohn's disease.
Biliary: hematobilia (e.g., penetrating injury to liver, hepatobiliary malignancy, endoscopic papillotomy).

BLEEDING, UPPER GI, PEDIATRIC[2]

ICD-9CM # 578.9
ICD-10CM # K92.2 Gastrointestinal Hemorrhage, Unspecified

<3 MO

Swallowed maternal blood.
Gastritis.
Ulcer, stress.
Bleeding diathesis.
Foreign body (NG tube).
Vascular malformation.
Duplication.

<2 YR

Esophagitis.
Gastritis.
Ulcer.
Pyloric stenosis.
Mallory-Weiss syndrome.
Vascular malformation.
Duplication.

<5 YR

Esophagitis.
Gastritis.
Ulcer.
Esophageal varices.
Foreign body.
Mallory-Weiss syndrome.
Hemophilia.
Vascular malformations.

5 TO 18 YR

Esophagitis.
Gastritis.
Ulcer.
Esophageal varices.
Mallory-Weiss syndrome.
Inflammatory bowel disease.
Hemophilia.
Vascular malformation.

BLEEDING, VAGINAL, NON-PREGNANT FEMALE[1]

ICD-9CM # 623.8
ICD-10CM # N93.9 Abnormal uterine and vaginal bleeding, unspecified

TRAUMA

Blunt force.
Penetrating force.
Foreign bodies.

INFECTIOUS

Vaginitis.
Cervicitis.
Endometritis.

DYSFUNCTIONAL UTERINE BLEEDING

Ovulatory.
Anovulatory.
Adenomyosis.

BENIGN GROWTHS

Uterine leiomyomas.
Cervical polyps.

MALIGNANCY

Vulvar.
Cervical.
Uterine.
Ovarian.

SYSTEMIC DISEASE

Medications

Anticoagulation (warfarin [Coumadin], low-molecular-weight heparin, clopidogrel [Plavix]).
Antipsychotics.
Corticosteroids.
Tamoxifen.
Selective serotonin reuptake inhibitors.
Contraceptives (oral, intrauterine devices, intramuscular).

BLINDNESS, GERIATRIC AGE

ICD-9CM # 369.4
ICD-10CM # H54.8 Legal Blindness, as Defined in USA

Cataracts.
Glaucoma.
Diabetic retinopathy.
Macular degeneration.
Trauma.
CVA.
Corneal scarring.
Giant cell arteritis.
Ocular herpes zoster.

BLINDNESS, MONOCULAR, TRANSIENT

ICD-9CM # 369.67
ICD-10CM # H54.41 Blindness, Right Eye, Normal Vision Left Eye
H54.42 Blindness, Left Eye, Normal Vision Right Eye

Migraine (vasospasm).
Embolic cerebrovascular disease.
Intermittent angle-closure glaucoma.
Partial retinal vein occlusion.
Hyphema.
Optic disc edema.
Giant cell arteritis.
Psychogenic.
Hypotension.
Hypercoagulopathy disorders.
Multiple sclerosis.

BLINDNESS, PEDIATRIC AGE[23]

ICD-9CM # varies with specific disorder
ICD-10CM # H54.41 Blindness, Right Eye, Normal Vision Left Eye
H54.42 Blindness, Left Eye, Normal Vision Right Eye

CONGENITAL

Optic nerve hypoplasia or aplasia.
Optic coloboma.
Congenital hydrocephalus.
Hydranencephaly.
Porencephaly.
Microencephaly.
Encephalocele, particularly occipital type.
Morning glory disc.
Aniridia.
Anterior microphthalmia.
Peter's anomaly.
Persistent pupillary membrane.
Glaucoma.
Cataracts.
Persistent hyperplastic primary vitreous.

PHAKOMATOSES

Tuberous sclerosis.
Neurofibromatosis (special association with optic glioma).
Sturge-Weber syndrome.
von Hippel–Lindau disease.

TUMORS

Retinoblastoma.
Optic glioma.
Perioptic meningioma.
Craniopharyngioma.
Cerebral glioma.
Posterior and intraventricular tumors when complicated by hydrocephalus.
Pseudotumor cerebri.

NEURODEGENERATIVE DISEASES

Cerebral storage disease.
Gangliosidoses, particularly Tay-Sachs disease (infantile amaurotic familial idiocy), Sandhoff's variant, generalized gangliosidosis.
Other lipidoses and ceroid lipofuscinoses, particularly the late-onset amaurotic familial idiocies such as those of Jansky-Bielschowsky and of Batten-Mayou-Spielmeyer-Vogt.
Mucopolysaccharidoses, particularly Hurler's syndrome and Hunter's syndrome.
Leukodystrophies (dysmyelination disorders), particularly metachromatic leukodystrophy and Canavan's disease.
Demyelinating sclerosis (myelinoclastic diseases), especially Schilder's disease and Devic's neuromyelitis optica.
Special types: Dawson's disease, Leigh's disease, Bassen-Kornzweig syndrome, Refsum's disease.
Retinal degenerations: retinitis pigmentosa and its variants, Leber's congenital type.
Optic atrophies: congenital autosomal recessive type, infantile and congenital autosomal dominant types, Leber's disease, and atrophies associated with hereditary ataxias—the types of Behr, of Marie, and of Sanger-Brown.

INFECTIOUS PROCESSES

Encephalitis, especially in the prenatal infection syndromes caused by *Toxoplasma gondii,* cytomegalovirus, rubella virus, *Treponema pallidum,* herpes simplex.
Meningitis, arachnoiditis.
Chorioretinitis.
Endophthalmitis.
Keratitis.

HEMATOLOGIC DISORDERS

Leukemia with central nervous system involvement.

VASCULAR AND CIRCULATORY DISORDERS

Collagen vascular diseases.
Arteriovenous malformations—intracerebral hemorrhage, subarachnoid hemorrhage.
Central retinal occlusion.

TRAUMA

Contusion or avulsion of optic nerves, chiasm, globe, cornea.
Cerebral contusion or laceration.
Intracerebral, subarachnoid, or subdural hemorrhage.

DRUGS AND TOXINS OTHER

Retinopathy of prematurity.
Sclerocornea.
Conversion reaction.
Optic neuritis.
Osteopetrosis.

BLISTERS, SUBEPIDERMAL

ICD-9CM #	919.2	
ICD-10CM #	T07	Unspecified Multiple Injuries

Burns.
Porphyria cutanea tarda.
Bullous pemphigoid.
Bullous drug reaction.
Arthropod bite reaction.
Toxic epidermal necrosis.
Dermatitis herpetiformis.
Polymorphous light eruption.
Variegate porphyria.
SLE.
Epidermolysis bullosa.
Pseudoporphyria.
Acute graft-versus-host reaction.
Linear IgA disease.
Leukocytoclastic vasculitis.
Pressure necrosis.
Urticaria pigmentosa.
Amyloidosis.

BONE DENSITY, DECREASED, GENERALIZED[16a]

ICD-9CM #	733.00	
ICD-10CM #	M85.80	Other Specified Disorders of Bone Density and Structure, Unspecified Site

DISORDERS ASSOCIATED WITH GENERALIZED LOSS OF BONE DENSITY

Disorders of Multiple or Uncertain Cause
Senile osteoporosis.*
Juvenile osteoporosis.
Osteogenesis imperfecta.†
Secondary Bone Disorders
ENDOCRINE
Adrenal cortex.†
  Cushing's disease.
  Addison's disease.
Gonadal disorders.
  Postmenopausal osteoporosis.*
  Hypogonadism.†
Pituitary.
  Acromegaly.
  Hypopituitarism.
Pancreas.
  Diabetes mellitus.*
Thyroid.
  Hyperthyroidism.
  Hypothyroidism.
Parathyroid.
  Hyperparathyroidism.*
Marrow Replacement and Expansion
Myeloma.
Leukemia.
Lymphoma.
Metastatic disease.*
Gaucher's disease.
Anemias (sickle cell, thalassaemia, hemophilia).†
Drugs And Other Substances
Steroids.*†
Heparin (osteoporosis).
Anticonvulsants (osteomalacia).
Immunosuppressants.
Alcohol.*
Chronic Disease
Chronic renal disease.†
Hepatic insufficiency.†
GI malabsorption syndromes.
Chronic inflammatory polyarthropathies.
Chronic debility or immobilization.

*Common cause of decrease in bone density in adults.
†Common cause of decrease in bone density in children.

BONE DENSITY, DECREASED, LOCALIZED[16a]

ICD-9CM #	V17.81	
ICD-10CM #	Z82.62	Family History of Osteoporosis
	M85.80	Other specified disorders of bone density and structure, unspecified site

DISORDERS ASSOCIATED WITH LOCALIZED LOSS OF BONE DENSITY

Disuse osteoporosis.*
Reflex sympathetic dystrophy (Sudeck's).*
Osteolytic syndromes.
  Acro-osteolysis, primary and secondary.
  Massive osteolysis of Gorham.
  Carpotarsal osteolysis.
Transient regional osteoporosis.
Neuromuscular disorders.
Infection.*
Arthropathies.*
Tumors, primary and secondary, myelomatosis.

*Common causes.

BONE LESIONS, PREFERENTIAL SITE OF ORIGIN[35]

ICD-9CM #	170.0	Skull and Face
	170.1	Mandible
	170.2	Vertebral Column
	170.3	Ribs, Sternum, Clavicle
	170.4	Scapula, Long Bones, Upper Limb
	170.5	Short Bones and Upper Limb
	170.6	Pelvic Bones, Sacrum, Coccyx
	170.7	Long Bones, Lower Limb
	170.8	Short Bones, Lower Limb
	170.9	Bone Cancer NOS
	198.5	Bone Cancer, Metastatic
ICD-10CM #	C41.0	Malignant Neoplasm of Bones of Skull and Face
	C41.1	Malignant Neoplasm of Mandible
	C41.2	Malignant Neoplasm of Vertebral Column
	C41.3	Malignant Neoplasm of Ribs, Sternum and Clavicle
	C40.00	Malignant Neoplasm of Scapula and Long Bones of Unspecified Upper Limb
	C40.10	malignant neoplasm of Short Bones of Unspecified Upper Limb
	C41.4	Malignant Neoplasm of Pelvic Bones, Sacrum and Coccyx
	C40.20	Malignant Neoplasm of Long Bones of Unspecified Lower Limb
	C40.30	Malignant Neoplasm of Short Bones of Unspecified Lower Limb
	C41.9	Malignant Neoplasm of Bone and Articular Cartilage, Unspecified
	C79.51	Secondary Malignant Neoplasm of Bone
	C79.52	Secondary Malignant Neoplasm of Bone Marrow

EPIPHYSIS

Chondroblastoma.
Giant cell tumor—after fusion of growth plate.
Langerhans' cell histiocytosis.
Clear cell chondrosarcoma.
Osteosarcoma.

METAPHYSIS

Parosteal sarcoma.
Chondrosarcoma.
Fibrosarcoma.
Nonossifying fibroma.
Giant cell tumor—before fusion of growth plate.
Unicameral bone cyst.
Aneurysmal bone cyst.

DIAPHYSIS

Myeloma.
Ewing's tumor.
Reticulum cell sarcoma.

METADIAPHYSEAL

Fibrosarcoma.
Fibrous dysplasia.
Enchondroma.
Osteoid osteoma.
Chondromyofibroma.

BONE MARROW FAILURE SYNDROMES, INHERITED[20]

ICD-9CM # 284
ICD-10CM # D61.89 Other Specified Aplastic Anemias and Other Bone Marrow Failure Syndromes

BI-LINEAGE AND TRI-LINEAGE CYTOPENIAS

Fanconi anemia.
Shwachman-Diamond syndrome.
Dyskeratosis congenita.
Amegakaryocytic thrombocytopenia:
- Other inherited thrombocytopenia disorders.

Other genetic syndromes:
- Down syndrome.
- Dubowitz syndrome.
- Seckel syndrome.
- Reticular dysgenesis.
- Schimke immunoosseous dysplasia.
- Noonan syndrome.
- Cartilage-hair hypoplasia.
- Familial marrow failure (non-Fanconi).

UNI-LINEAGE CYTOPENIA

Diamond-Blackfan anemia.
Kostmann syndrome/Congenital neutropenia:
- *ELA2* mutations.
- *HAX1* mutations.
- *GFI1* mutations.
- *WASP* mutations.
- Constitutive cell surface G-CSF-R mutations.

Other inherited neutropenia syndromes:
- Barth syndrome.
- Glycogen storage disease 1b.
- Miscellaneous.

Thrombocytopenia with absent radii.
Congenital dyserythropoietic anemias (CDAs):
- Types I, II, III, IV.
- Variants.
- Nonclassifiable CDAs.
- Groups IV, V, VI, VII.

BONE MARROW FIBROSIS[14]

ICD-9CM # 289.9
ICD-10CM # D75.9 Disease of Blood and Blood-Forming Organs, Unspecified

MYELOID DISORDERS

Myelofibrosis with myeloid metaplasia.
Metastatic cancer.
Chronic myeloid leukemia.
Myelodysplastic syndrome.
Atypical myeloid disorder.
Acute megakaryocytic leukemia.
Other acute myeloid leukemias.
Gray platelet syndrome.

LYMPHOID DISORDERS

Hairy cell leukemia.
Multiple myeloma.
Lymphoma.

NONHEMATOLOGIC DISORDERS

Connective tissue disorder.
Infections (tuberculosis, kala-azar).
Vitamin D deficiency (rickets).
Renal osteodystrophy.

BONE MASS, LOW[1a]

ICD-9CM # varies with specific diagnosis
ICD-10CM # M85.80 Other specified disorders of bone density and structure, unspecified site

SECONDARY CAUSES OF LOW BONE MASS

Endocrine Diseases
Female hypogonadism.
Hyperprolactinemia.
Hypothalamic amenorrhea.
Anorexia nervosa.
Premature and primary ovarian failure.
Female athlete triad.
Male hypogonadism.
Primary gonadal failure (e.g., Klinefelter's syndrome).
Secondary gonadal failure (e.g., idiopathic hypogonadotropic hypogonadism, androgen deprivation therapy for prostate cancer).
Hyperthyroidism.
Hyperparathyroidism.
Hypercortisolism.
Vitamin D insufficiency or deficiency.
Gastrointestinal Diseases
Subtotal gastrectomy.
Gastric bypass surgery.
Malabsorption syndromes.
Chronic obstructive jaundice.
Primary biliary cirrhosis and other cirrhoses.
Bone Marrow Disorders
Multiple myeloma.
Monoclonal gammopathy of unknown significance (MGUS).
Lymphoma.
Leukemia.
Hemolytic anemias.
Systemic mastocytosis.
Disseminated carcinoma.
Connective Tissue Diseases
Osteogenesis imperfecta.
Ehlers-Danlos syndrome.
Marfan's syndrome.
Homocystinuria.
Drugs
Alcohol.
Antiseizure medications.
Aromatase inhibitors.
Chemotherapy.
Cyclosporine.
Depo-medroxyprogesterone.
Excess thyroid hormone.
Glucocorticoids.
Gonadotropin-releasing hormone agonists.
Heparin.
Miscellaneous Causes
Immobilization.
Rheumatoid arthritis.
Chronic obstructive pulmonary disease.
Weight loss.

BONE MINERAL DENSITY, INCREASED

ICD-9CM # 733.99
ICD-10CM # M89.30 Hypertrophy of Bone, Unspecified Site
M89.8X9 Other Specified Disorders of Bone, Unspecified Site
M94.8X9 Other Specified Disorders of Cartilage, Unspecified Sites

Paget's disease of bone.
Skeletal metastases.
DISH.
Osteonecrosis.
Sarcoidosis.
Hypoparathyroidism, pseudohypoparathyroidism.
Milk-alkali syndrome.
Osteopetrosis.
Hypervitaminosis A or D.
Dysplasias (craniodiaphyseal, craniometaphyseal, frontometaphyseal).
Endosteal hyperostosis.
Fluorosis.
Heavy metal poisoning.
Ionizing radiation.
Other: lymphoma, leukemia, mastocytosis, multiple myeloma, polycythemia vera.

BONE PAIN

ICD-9CM # varies with specific diagnosis
ICD-10CM # M89.8 Pain, bone

Trauma.
Neoplasm (primary or metastatic).

Osteoporosis with compression fracture.
Paget's disease of bone.
Infection (osteomyelitis, septic arthritis).
Osteomalacia.
Viral syndrome.
Sickle cell disease.
Anxiety.

BONE RESORPTION[35]

ICD-9CM #	733.90	Bone Disorder
ICD-10CM #	M89.9	Disorder of Bone, Unspecified
	M94.9	Disorder of Cartilage, Unspecified

DISTAL CLAVICLE

Hyperparathyroidism.
RA.
Scleroderma.
Posttraumatic osteolysis.
Progeria.
Pycnodysostosis.
Cleidocranial dysplasia.

INFERIOR ASPECT OF RIBS

Vascular impression, associated with but not limited to coarctation of the aorta.
Hyperparathyroidism.
Neurofibromatosis.

TERMINAL PHALANGEAL TUFTS

Scleroderma.
Raynaud's phenomenon.
Vascular disease.
Frostbite, electrical burns.
Psoriasis.
Tabes dorsalis.
Hyperparathyroidism.

GENERALIZED RESORPTION

Paraplegia.
Myositis ossificans.
Osteoporosis.

BOW LEGS (GENU VARUM), CLASSIFICATION[22a]

ICD-9CM #	736.42	Bow Legs (Genu Varum)
ICD-10CM #	E64.3	Genu varum, acquired
	Q74.1	Congenital malformation of knee

PHYSIOLOGIC

ASYMMETRIC GROWTH

Tibia vara (Blount disease).
- Infantile.
- Juvenile.
- Adolescent.

Focal fibrocartilaginous dysplasia.
Physeal injury.
Trauma.
Infection.
Tumor.

METABOLIC DISORDERS

Vitamin D deficiency (nutritional rickets).
Vitamin D–resistant rickets.
Hypophosphatasia.

SKELETAL DYSPLASIA

Metaphyseal dysplasia.
Achondroplasia.
Enchondromatosis.

BRADYCARDIA, SINUS[15]

ICD-9CM #	427.89	
ICD-10CM #	I49.8	Other Specified Cardiac Arrhythmias
	R00.1	Bradycardia, Unspecified

Idiopathic.
Degenerative processes (e.g., Lev's disease, Lenègre's disease).
Medications
β-Blockers.
Some calcium channel blockers (diltiazem, verapamil).
Digoxin (when vagal tone is high).
Class I antiarrhythmic agents (e.g., procainamide).
Class III antiarrhythmic agents (amiodarone, sotalol).
Clonidine.
Lithium carbonate.

ACUTE MYOCARDIAL ISCHEMIA AND INFARCTION

Right or left circumflex coronary artery occlusion or spasm.
High vagal tone (e.g., athletes).

BRAIN MASS[1]

ICD-9CM #		varies with specific diagnosis
ICD-10CM #	C71	Malignant neoplasm of brain
	D33	Benign neoplasm of brain
	I61.9	Intracranial hemorrhage, unspecified

METASTATIC BRAIN TUMOR

Primary brain tumor
- Meningioma.
- Glioma.
- Pituitary adenoma.
- Vestibular schwannoma.
- Primary or secondary central nervous system lymphoma.

Infections
- Abscess.
- Toxoplasmosis.
- Neurocysticercosis.
- Tuberculoma.
- Progressive multifocal leukoencephalopathy.

VASCULAR DISEASE

Hemorrhage
- Anomalies (arteriovenous malformation).
- Intratumoral.
- Hypertensive.

Infarct
- Embolism.
- Thrombosis (sinus venous).

Inflammatory
- Multiple sclerosis.
- Encephalomyelitis.

BREAST INFLAMMATORY LESION[12]

ICD-9CM #	611.0	Acute Mastitis
	610.1	Chronic Cystic Mastitis
	771.5	Neonatal Infective Mastitis
	778.7	Neonatal Noninfective Mastitis
ICD-10CM #	N61	Inflammatory Disorders of Breast
	N60.19	Diffuse Cystic Mastopathy of Unspecified Breast
	P39.0	Neonatal Infective Mastitis
	P83.4	Breast Engorgement of Newborn

Mastitis (*S. aureus,* β-hemolytic *Streptococcus*).
Trauma.
Foreign body (sutures, breast implants).
Granuloma (TB, fungal).
Fat necrosis post biopsy.
Necrosis or infarction (anticoagulant therapy, pregnancy).
Breast malignancy.

BREAST MASS

ICD-9CM #	611.72	
ICD-10CM #	N63	Unspecified Lump in Breast

Fibrocystic breasts.
Benign tumors (fibroadenoma, papilloma).
Mastitis (acute bacterial mastitis, chronic mastitis).
Malignant neoplasm.
Fat necrosis.
Hematoma.
Duct ectasia.
Mammary adenosis.

BREATH ODOR[34]

ICD-9CM #	784.9	Halitosis
ICD-10CM #	R19.6	Halitosis

Sweet, fruity: DKA, starvation ketosis.
Fishy, stale: uremia (trimethylamines).
Ammonia-like: uremia (ammonia).
Musty fish, clover: fetor hepaticus (hepatic failure).
Foul, feculent: intestinal obstruction/diverticulum.
Foul, putrid: nasal/sinus pathology (infection, foreign body, cancer), respiratory infections (empyema, lung abscess, bronchiectasis).

Halitosis: tonsillitis, gingivitis, respiratory infections, Vincent's angina, gastroesophageal reflux, achalasia, certain foods (garlic, onions, protein drinks, etc.)
Cinnamon: pulmonary TB.

BREATHING, NOISY[34]

ICD-9CM #	786.09	Breathing, Labored
	786.1	Stridor
ICD-10CM #	R06.00	Dyspnea, Unspecified
	R06.09	Other Forms of Dyspnea
	R06.3	Periodic Breathing
	R06.83	Snoring
	R06.89	Other Abnormalities of Breathing
	R06.1	Stridor

Infection: upper respiratory infection, peritonsillar abscess, retropharyngeal abscess, epiglottitis, laryngitis, tracheitis, bronchitis, bronchiolitis.
Irritants and allergens: hyperactive airway, asthma (reactive airway disease), rhinitis, angioneurotic edema.
Compression from outside of the airway: esophageal cysts or foreign body, neoplasms, lymphadenopathy.
Congenital malformation and abnormality: vascular rings, laryngeal webs, laryngomalacia, tracheomalacia, hemangiomas within the upper airway, stenoses within the upper airway, cystic fibrosis.
Acquired abnormality (at every level of the airway): nasal polyps, hypertrophied adenoids and/or tonsils, foreign body, intraluminal tumors, bronchiectasis.
Neurogenic disorder: vocal cord paralysis.

BRONCHIAL OBSTRUCTION[16a]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	J98.0	Tracheobronchial collapse

CAUSES OF BRONCHIAL OBSTRUCTION

Outside the Bronchus
Lymph nodes and other masses.
In the Wall of the Bronchus
Tumors
Lung carcinoma (commonly squamous cell).
Bronchial carcinoid.
Metastasis.
Hamartoma.
Inflammation
Tuberculosis.
Sarcoidosis.
Granulomatosis with polyangiitis (Wegener's granulomatosis).
Inflammatory bowel disease.
Bronchomalacia
Broncholith.
Inside the Bronchus
Mucus plug.
Inhaled foreign body.

BRONCHOPLEURAL FISTULA[16a]

ICD-9CM #	510.0	
ICD-10CM #	J86.0	Bronchopleural fistula

CAUSES OF BRONCHOPLEURAL FISTULA

Trauma
Penetrating.
Iatrogenic (especially post-pneumonectomy, post-lobectomy, post-biopsy).
Infection
Necrotizing pneumonia.
Empyema.
Tuberculosis.
Septic embolus.
Infected pulmonary infarct.

BROWN URINE

ICD-9CM #	788.69	
ICD-10CM #	R82	Other abnormal findings in urine

Bile pigments.
Myoglobin.
Concentrated urine.
Use of multivitamin supplements.
Medications (antimalarials, metronidazole, nitrofurantoin, levodopa, methyldopa, phenazopyridine).
Diet rich in fava beans.
Urinary tract infection.

BRUISING

ICD-9CM #	459.89	
ICD-10CM #	I99.8	Other Disorder of Circulatory System

Medication-induced (warfarin, aspirin, NSAIDs, prednisone).
Alcohol abuse.
Senile purpura.
Purpura simplex.
Physical abuse.
Vasculitis.
Platelet disorders.
Coagulation factor deficiencies.
Cushing's disease.
Vitamin C deficiency.
Marfan's syndrome.
Ehlers-Danlos syndrome.
Disseminated intravascular coagulation.
Leukemia.
Hereditary hemorrhagic telangiectasia.

BULLOUS DISEASES

ICD-9CM #	694.9	Bullous Dermatoses
	694.5	Bullous Pemphigoid
	694.4	Pemphigus Vulgaris
	694.4	Pemphigus Foliaceus
ICD-10CM #	L13.9	Bullous Disorder, Unspecified
	L12.0	Bullous Pemphigoid
	L12.8	Other Pemphigoid
	L10.0	Pemphigus Vulgaris
	L10.1	Pemphigus Vegetans
	L10.2	Pemphigus Foliaceous
	L10.4	Pemphigus Erythematosus
	L10.9	Pemphigus, Unspecified
	L10.0	Pemphigus Vulgaris
	L10.1	Pemphigus Vegetans
	L10.2	Pemphigus Foliaceous
	L10.4	Pemphigus Erythematosus
	L10.9	Pemphigus, Unspecified

Bullous pemphigoid.
Pemphigus vulgaris.
Pemphigus foliaceus.
Paraneoplastic pemphigus.
Cicatricial pemphigoid.
Erythema multiforme.
Dermatitis herpetiformis.
Herpes gestationis.
Impetigo.
Erosive lichen planus.
Linear IgA bullous dermatosis.
Epidermolysis bullosa acquisita.

CAFÉ-AU-LAIT SPOTS[22a]

ICD-9CM #	709	
ICD-10CM #	L81.3	Cafe au lait spots

Neurofibromatosis types 1 and 2.
McCune-Albright syndrome.
Russell-Silver syndrome.
Ataxia-telangiectasia.
Fanconi anemia.
Tuberous sclerosis.
Bloom syndrome.
Basal cell nevus syndrome.
Gaucher disease.
Chédiak-Higashi syndrome.
Hunter syndrome.
Maffucci syndrome.
Multiple mucosal neuroma syndrome.
Watson syndrome.
Proteus syndrome.
Turner syndrome.
Ring chromosome syndrome.
Jaffe-Campanacci syndrome.

CALCIFICATION ON CHEST X-RAY

ICD-9CM #	722.92	
ICD-10CM #	J98.4	Calcification of lung
	M51.84	Other Intervertebral Disc Disorders, Thoracic Region
	M51.85	Other Intervertebral Disc Disorders, Thoracolumbar Region

Lung neoplasm (primary or metastatic).
Silicosis.
Idiopathic pulmonary fibrosis.

Tuberculosis.
Histoplasmosis.
Disseminated varicella infection.
Mitral stenosis (end-stage).
Secondary hyperparathyroidism.

CALCIFICATIONS, ABDOMINAL, NONVISCERAL ON X-RAY[16a]

ICD-9CM #	728.10	
ICD-10CM #	M61.9	Calcification and Ossification of Muscle, Unspecified

NONVISCERAL ABDOMINAL CALCIFICATION

Common
Atherosclerosis.
Mesenteric lymph nodes.
Phleboliths.
Aneurysm.
Dermoid cyst.
Differentiate
- Rib cartilage.
- Injections in the buttocks.

Uncommon
Infestations.
- *Armillifer armillatus.*
- Cysticercosis.
- Guinea worm.
- Hydatid.

Tumors.
- Lipoma.
- Hemangioma.
- Neuroblastoma.
- Osteo/chondrosarcoma of soft tissues.
- Retroperitoneal sarcoma of soft tissues.
- Peritoneal metastases.
- Pheochromocytoma.

Tuberculosis.
- Peritonitis.
- Psoas abscess.

Meconium peritonitis.
Pseudomyxoma Peritonei
Mesenteric cyst.
Pancreatitis with saponification.
Lithopedion.
Appendices Epiploicae
Ligaments.
Foreign bodies.
Posttraumatic buttock cysts.

CALCIFICATIONS, ADRENAL GLAND ON X-RAY[16a]

ICD-9CM #	275.49	
ICD-10CM #	E27.4	Calcification, adrenal gland

ADRENAL GLAND CALCIFICATION

Common
Idiopathic.
Hemorrhage.
Tuberculosis.
Neuroblastoma/ganglioneuroma.
Pheochromocytoma.

Uncommon
Other tumors:
- Adenoma.
- Carcinoma.

Dermoid.
Addison's disease.
Cyst.
Histoplasmosis.

CALCIFICATIONS, CARDIAC ON X-RAY[16a]

ICD-9CM #	275.49	
ICD-10CM #	I51.5	Calcification, myocardium
	I25.1	Calcification, ateriosclerotic

CAUSES OF VISIBLE CALCIFICATION WITHIN THE HEART

Coronary Artery
Atherosclerosis.
Aortic Root
Atherosclerotic aorta.
Thrombus.
Syphilis.
Ankylosing spondylitis.
Homograft calcification.
Pericardium
Chronic pericarditis, tuberculosis, hemopericardium, pyogenic or viral pericarditis.
Posttraumatic.
Postoperative.
Uremic pericarditis.
Asbestosis (may be pleural calcification applied to pericardium).
Myocardium
Ventricular aneurysm (may mimic pericardial calcification).
Calcified myocardial infarction.
Postmyocarditis.
Endocardium
Endomyocardial fibrosis.
Thrombus.
Valve Cusps
Calcified valves (particularly mitral and aortic valves).
Mitral annulus calcification.
Homograft calcification.
Old vegetation.
Valve Annulus
Submitral.
Mitral.
Aortic.
Left Atrium
Wall.
Thrombus.
Atrial myxoma.
Pulmonary Artery
Pulmonary hypertension.
Postoperative.
Postoperative Serumoma Calcified Hydatid Cyst

CALCIFICATIONS, CUTANEOUS

ICD-9CM #	709.3	
ICD-10CM #	L94.2	Calcinosis Cutis
	L98.8	Other Specified Disorders of the Skin and Subcutaneous Tissue

Calcification, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia (CREST) syndrome.
Trauma.
Pancreatitis or pancreatic cancer.
Chronic renal failure.
Sarcoidosis.
Hyperparathyroidism.
Milk-alkali syndrome.
Hypervitaminosis D.
Panniculitis.
Idiopathic.
Iatrogenic (e.g., application of calcium alginate dressing to skin).
Multiple myeloma.
Dermatomyositis.
Parasitic infections.
Leukemia.
Lymphoma.

CALCIFICATIONS, GENITAL TRACT, FEMALE ON X-RAY[16a]

ICD-9CM #	275.49	
ICD-10CM #	E83.59	Other Disorders of Calcium Metabolism

FEMALE GENITAL TRACT CALCIFICATION

Uterus
Leiomyomas.
Squamous cell carcinoma.
Adenocarcinoma of endometrium.
Leiomyosarcoma.
Lithopedion.
Fallopian Tubes
Ovary.
Dermoid cyst.
Serous cystadenoma/carcinoma.
Tuberculosis.
Cysts.
Autoamputation.

CALCIFICATIONS, LIVER ON X-RAY[16a]

ICD-9CM #	573	
ICD-10CM #	K76.89	Other Specified Diseases of Liver
	NEC K75.3	Granuloma, hepatic

LIVER CALCIFICATION

Common
Granuloma (tuberculosis, histoplasmosis, brucellosis).
- Multiple scattered round densities.

Hydatid cyst.

- Fine curvilinear in wall, or dense and irregular if contracted.

Primary liver tumor (hemangioma, hepatoblastoma, hepatoma, cholangiocarcinoma).

- Irregular patterns or multiple nodules.

Metastases (mucinous primary of colon or breast, cystadenocarcinoma of ovary).

- Finely stippled, may be extensive.

Uncommon

Hepatic artery aneurysm.
Armillifer armillatus infestation.
Chronic granulomatous disease of childhood.
Cyst (congenital or acquired).
Hematoma.
Intrahepatic gallstones.
Old liver abscess.
Portal vein thrombosis.

Differentiate

Hemochromatosis.
Thorotrast, thallium, iron.

CALCIFICATIONS, PANCREAS ON X-RAY[16a]

ICD-9CM # 275.49
ICD-10CM # K86.8 Calcification, pancreas

PANCREATIC CALCIFICATION

Common

Chronic pancreatitis.

Uncommon

Acute pancreatitis (saponification).
Tumors.
  Cystadenoma.
  Cystadenocarcinoma.
  Islet cell tumor.
  Metastases.
Hereditary pancreatitis (large clumps).
Hemorrhage.
Hyperparathyroidism.
Pseudocyst.
Cavernous lymphangioma.
Mucoviscidosis.
Kwashiorkor.

CALCIFICATIONS, SPLEEN ON X-RAY[16a]

ICD-9CM # 275.49
ICD-10CM # D73.8 Calcification, spleen

SPLENIC CALCIFICATION

Larger than 10 mm

Splenic artery aneurysm.
Splenic artery atheroma.
Cyst.
  Posttraumatic.
  Dermoid.
  Epidermoid.
  Hydatid.
Hematoma.
Infarct.
Abscess.
Tuberculosis.

Smaller than 10 mm

Histoplasmosis.
Tuberculosis.
Phleboliths.
Armillifer armillatus infestation.
Brucellosis.
Infarcts.

CALCIFICATIONS, VALVULAR ON X-RAY[16a]

ICD-9CM # 275.49
ICD-10CM # I51.5 Calcification, heart

CAUSES OF RADIOGRAPHICALLY VISIBLE VALVE CALCIFICATION

Aortic Valve

Rheumatic aortic valve disease.
Bicuspid aortic valve.
Age/degenerate aortic valve.
Syphilis.
Ankylosing spondylitis.
Homograft calcification.

Mitral Valve

Rheumatic mitral valve disease.
Mitral annulus calcification.
Old vegetation (may only be visible on CT).
Homograft calcification.

Pulmonary Valve

Congenital pulmonary valve stenosis.
Rheumatic pulmonary valve disease (rare).
Fallot's tetralogy (usually after repair).
Pulmonary hypertension.
Homograft calcification.

Tricuspid Valve

Rheumatic tricuspid valve disease.
Old vegetation (may only be visible on ultrafast CT).

CALCIUM STONES

ICD-9CM # 592.9
ICD-10CM # N20.9 Urinary Calculus, Unspecified

Medications (e.g., antacids, loop diuretics, vitamin D, acetazolamide, glucocorticoids).
Primary hyperparathyroidism.
Hypercalcemia from malignancy.
Sarcoidosis.
Prolonged immobilization.
Hyperoxaluria (e.g., Crohn's disease, celiac disease, chronic pancreatitis).
Hyperuricosuria (e.g., hyperuricemia, excessive dietary purine, allopurinol, probenecid).
Renal tubular acidosis.
Milk-alkali syndrome.
Thyrotoxicosis.
Hypocitraturia (e.g., metabolic acidosis, hypomagnesemia, hypokalemia).

CARDIAC ARREST, NONTRAUMATIC[26]

ICD-9CM # 427.5 Cardiac Arrest NOS
ICD-10CM # I46.9 Cardiac Arrest, Cause Unspecified

Cardiac (coronary artery disease, cardiomyopathies, structural abnormalities, valve dysfunction, arrhythmias).
Respiratory (upper airway obstruction, hypoventilation, pulmonary embolism, asthma, COPD exacerbation, pulmonary edema).
Circulatory (tension pneumothorax, pericardial tamponade, PE, hemorrhage, sepsis).
Electrolyte abnormalities (hypokalemia or hyperkalemia, hypomagnesemia or hypermagnesemia, hypocalcemia).
Medications (tricyclic antidepressants, digoxin, theophylline, calcium channel blockers).
Drug abuse (cocaine, heroin, amphetamines).
Toxins (carbon monoxide, cyanide).
Environmental (drowning/near-drowning, electrocution, lightning, hypothermia or hyperthermia, venomous snakes).

CARDIAC DEATH, SUDDEN[1a]

ICD-9CM # varies with specific disorder
ICD-10CM # Z86.74 Personal History of Sudden Cardiac Arrest

Ventricular tachycardia.
Bradyarrhythmia, sick sinus syndrome.
Aortic stenosis.
Tetralogy of Fallot.
Pericardial tamponade.
Cardiac tumors.
Complications of infective endocarditis.
Hypertrophic cardiomyopathy (arrhythmia or obstruction).
Myocardial ischemia.
Atherosclerosis.
Prinzmetal's angina.
Kawasaki's arteritis.

CARDIAC ENLARGEMENT[15]

ICD-9CM #	429.3	Cardiomegaly, Idiopathic
	746.89	Cardiomegaly, Congenital
	402.0	Cardiomegaly, Malignant
	402.1	Cardiomegaly, Benign
ICD-10CM #	I51.7	Cardiomegaly
	Q23.8	Other Congenital Malformations of Aortic and Mitral Valves
	Q24.8	Other Specified Congenital Malformations of Heart
	I11.9	Hypertensive Heart Disease Without Heart Failure
	I11.9	Hypertensive Heart Disease Without Heart Failure

CARDIAC CHAMBER ENLARGEMENT

Chronic Volume Overload

Mitral or aortic regurgitation.
Left-to-right shunt (PDA, VSD, AV fistula).

Cardiomyopathy

Ischemic.
Nonischemic.

Decompensated Pressure Overload

Aortic stenosis.
Hypertension.

High-Output States

Severe anemia.
Thyrotoxicosis.

Bradycardia
Severe sinus bradycardia.
Complete heart block.

LEFT ATRIUM
LV failure of any cause.
Mitral valve disease.
Myxoma.

RIGHT VENTRICLE
Chronic volume overload.
Tricuspid or pulmonic regurgitation.
Left-to-right shunt (ASD).
Decompensated pressure overload:
- Pulmonic stenosis.
- Pulmonary artery hypertension:
  - Primary.
  - Secondary (PE, COPD).

Pulmonary venoocclusive disease.

RIGHT ATRIUM
RV failure of any cause.
Tricuspid valve disease.
Myxoma.
Ebstein's anomaly.

MULTICHAMBER ENLARGEMENT
Hypertrophic cardiomyopathy.
Acromegaly.
Severe obesity.

PERICARDIAL DISEASE
Pericardial effusion with or without tamponade.
Effusive constrictive disease.
Pericardial cyst, loculated effusion.

PSEUDOCARDIOMEGALY
Epicardial fat.
Chest wall deformity (pectus excavatum, straight back syndrome).
Low lung volumes.
AP chest x-ray.
Mediastinal tumor, cyst.

CARDIAC MURMURS

ICD-9CM #	varies with specific disorder	
ICD-10CM #	R01.0	Benign and Innocent Cardiac Murmurs
	R01.1	Cardiac murmur, unspecified

SYSTOLIC
Mitral regurgitation (MR).
Tricuspid regurgitation (TR).
Ventricular septal defect (VSD).
Aortic stenosis (AS).
Idiopathic hypertrophic subaortic stenosis (IHSS).
Pulmonic stenosis (PS).
Innocent murmur of childhood.
Coarctation of aorta.
Mitral valve prolapse (MVP).

DIASTOLIC
Aortic regurgitation (AR).
Atrial myxoma.
Mitral stenosis (MS).
Pulmonary artery branch stenosis.
Tricuspid stenosis (TS).
Graham Steell murmur (diastolic decrescendo murmur heard in severe pulmonary hypertension).
Pulmonic regurgitation (PR).
Severe mitral regurgitation (MR).
Austin Flint murmur (diastolic rumble heard in severe AR).
Severe VSD and patent ductus arteriosus.

CONTINUOUS
Patent ductus arteriosus.
Pulmonary AV fistula.

CARDIAC TUMORS[14a]

ICD-9CM #	164	Cardiac Tumors
ICD-10CM #	C38.0	Malignant Neoplasm of Heart
	D15.7	Benign neoplasm of other specified intrathoracic origin

PRIMARY
Benign.
- Myxoma.
- Lipoma.
- Fibroma.
- Rhabdomyoma.
- Fibroelastoma.

Malignant.
- Sarcoma.
- Mesothelioma.
- Lymphoma.

SECONDARY
Direct Extension
Lung cancer.
Breast cancer.
Mediastinal tumors.
Metastatic Tumors
Malignant melanoma.
Leukemia.
Lymphoma.
Venous Extension
Renal cell cancer.
Adrenal cancer.
Liver cancer.

CARDIOEMBOLISM

ICD-9CM #	410.9	
ICD-10CM #	I21.3 ST	Elevation (STEMI) Myocardial Infarction of Unspecified Site
	I21.9	Acute myocardial infarction, unspecified

Acute MI.
Atrial fibrillation.
Left ventricular aneurysm.
Valvular heart disease (e.g., rheumatic mitral valve disease, mitral valve prolapse).
Dilated cardiomyopathy.
Atrial septal defect.
Patent foramen ovale.
Cardioversion for atrial fibrillation.
Infective endocarditis.
Atrial septal aneurysm.
Sick sinus syndrome and cardiac arrhythmias.
Nonbacterial thrombotic endocarditis.
Prosthetic heart valves.
Atrial myxoma and other intracardiac tumors.
Cyanotic heart disease.
Balloon angioplasty.
Coronary artery bypass grafting.
Aneurysms of sinus of Valsalva.
Other: VVI pacing, ventricular support devices, heart transplantation, intracardiac defects with paradoxical embolism.

CARDIOGENIC SHOCK

ICD-9CM #	785.51	
ICD-10CM #	R57.0	Cardiogenic Shock

Myocardial infarction.
Arrhythmias.
Pericardial effusion/tamponade.
Chest trauma.
Valvular heart disease.
Myocarditis.
Cardiomyopathy.
CHF, end-stage.

CATARACTS, PEDIATRIC AGE

ICD-9CM #	366	
ICD-10CM #	H26.0	Infantile, juvenile and presenile cataracts

DEVELOPMENTAL VARIANTS
Prematurity (Y-suture vacuoles) with or without retinopathy of prematurity.

GENETIC DISORDERS
Simple Mendelian Inheritance
Autosomal dominant (most common).
Autosomal recessive.
X-linked.
Major Chromosomal Defects
Trisomy disorders (13, 18, 21).
Turner syndrome (45X).
Deletion syndromes (11p13, 18p, 18q).
Duplication syndromes (3q, 20p, 10q).
Multisystem Genetic Disorders
Alport syndrome (hearing loss, renal disease).
Alström syndrome (nerve deafness, diabetes mellitus).
Apert disease (craniosynostosis, syndactyly).
Cockayne syndrome (premature senility, skin photosensitivity).
Conradi disease (chondrodysplasia punctata).
Crouzon disease (dysostosis craniofacialis).
Hallermann-Streiff syndrome (microphthalmia, small pinched nose, skin atrophy, hypotrichosis).
Hypohidrotic ectodermal dysplasia (anomalous dentition, hypohidrosis, hypotrichosis).
Ichthyosis (keratinizing disorder with thick, scaly skin).
Incontinentia pigmenti (dental anomalies, mental retardation, cutaneous lesions).
Lowe syndrome (oculocerebrorenal syndrome: hypotonia, renal disease).
Marfan syndrome.

Marinesco-Sjögren syndrome (cerebellar ataxia, hypotonia).
Meckel-Gruber syndrome (renal dysplasia, encephalocele).
Myotonic dystrophy.
Nail-patella syndrome (renal dysfunction, dysplastic nails, hypoplastic patella).
Nevoid basal cell carcinoma syndrome (autosomal dominant, basal cell carcinoma erupts in childhood).
Peters anomaly (corneal opacifications with iris-corneal dysgenesis).
Reiger syndrome (iris dysplasia, myotonic dystrophy).
Rothmund-Thomson syndrome (poikiloderma: skin atrophy).
Rubinstein-Taybi syndrome (broad great toe, mental retardation).
Smith-Lemli-Opitz syndrome (toe syndactyly, hypospadias, mental retardation).
Sotos syndrome (cerebral gigantism).
Spondyloepiphyseal dysplasia (dwarfism, short trunk).
Werner syndrome (premature aging in 2nd decade of life).

Inborn Errors of Metabolism

Abetalipoproteinemia (absent chylomicrons, retinal degeneration).
Fabry disease (α-galactosidase A deficiency).
Galactokinase deficiency.
Galactosemia (galactose-1-phosphate uridyl transferase deficiency).
Homocystinemia (subluxation of lens, mental retardation).
Mannosidosis (acid α-mannosidase deficiency).
Niemann-Pick disease (sphingomyelinase deficiency).
Refsum disease (phytanic acid α-hydrolase deficiency).
Wilson disease (accumulation of copper leads to cirrhosis and neurologic symptoms).

ENDOCRINOPATHIES

Hypocalcemia (hypoparathyroidism).
Hypoglycemia.
Diabetes mellitus.

CONGENITAL INFECTIONS

Toxoplasmosis.
Cytomegalovirus infection.
Syphilis.
Rubella.
Perinatal herpes simplex infection.
Measles (rubeola).
Poliomyelitis.
Influenza.
Varicella-zoster.

OCULAR ANOMALIES

Microphthalmia.
Coloboma.
Aniridia.
Mesodermal dysgenesis.
Persistent papillary membrane.
Posterior lenticonus.
Persistent hyperplastic primary vitreous.
Primitive hyaloid vascular system.

MISCELLANEOUS DISORDERS

Atopic dermatitis.
Drugs (corticosteroids).
Radiation.
Trauma.

IDIOPATHIC

CAVITARY LESION ON CHEST X-RAY[16]

ICD-9CM #	793.1	Chest X-Ray Lung Shadow
ICD-10CM #	R91.8	Other Nonspecific Abnormal Finding of Lung Field

NECROTIZING INFECTIONS

Bacteria: anaerobes, *Staphylococcus aureus*, enteric gram-negative bacteria, *Pseudomonas aeruginosa*, *Legionella* species, *Haemophilus in fluenzae, Streptococcus pyogenes, Streptococcus pneumoniae, Rhodococcus, Actinomyces*.
Mycobacteria: *Mycobacterium tuberculosis, Mycobacterium kansasii*, MAI.
Bacteria-like: *Nocardia* species.
Fungi: *Coccidioides immitis, Histoplasma capsulatum, Blastomyces hominis, Aspergillus* species, *Mucor* species.
Parasitic: *Entamoeba histolytica, Echinococcus, Paragonimus westermani*.

CAVITARY INFARCTION

Bland infarction (with or without superimposed infection).
Lung contusion.

SEPTIC EMBOLISM

S. aureus, anaerobes, others.

VASCULITIS

Wegener's granulomatosis, periarteritis.

NEOPLASMS

Bronchogenic carcinoma, metastatic carcinoma, lymphoma.

MISCELLANEOUS LESIONS

Cysts, blebs, bullae, or pneumatocele with or without fluid collections.
Sequestration.
Empyema with air-fluid level.
Bronchiectasis.

CEREBRAL INFARCTION SECONDARY TO INHERITED DISORDERS

ICD-9CM #	434.91	
ICD-10CM #	I63.50	Cerebral Infarction Due to Unspecified Occlusion or Stenosis of Unspecified Cerebral Artery

Homocystinuria.
Marfan's syndrome.
Ehlers-Danlos syndrome.
Rendu-Osler-Weber syndrome.
Pseudoxanthoma elasticum.
Fabry's disease.

CEREBRAL VASCULITIS, CAUSES[12c]

ICD-9CM #	varies with specific diagnosis
ICD-10CM #	varies with specific diagnosis

PRIMARY CEREBRAL VASCULITIDES

Takayasu arteritis.
Primary cerebral vasculitis.
Polyarteritis nodosa.

SECONDARY VASCULITIDES

Immune Disorders

Systemic lupus erythematosus.
Wegner granulomatosis.
Kawasaki syndrome.
Sarcoidosis.
Henoch-Schönlein purpura.

Primary Intracranial Infections

Bacterial meningitis (especially *Diplococcus pneumoniae*).
Tuberculous meningitis.
Mycotic infections.
Cat-scratch disease.
Human immunodeficiency virus/acquired immunodeficiency syndrome.
Malaria.
Lyme disease.
Rickettsial infections.
Brucellosis.

CEREBROVASCULAR DISEASE, ISCHEMIC[40]

ICD-9CM #	437.9	
ICD-10CM #	I67.9	Cerebrovascular Disease, Unspecified

VASCULAR DISORDERS

Large-vessel atherothrombotic disease.
Lacunar disease.
Arterial-to-arterial embolization.
Carotid or vertebral artery dissection.
Fibromuscular dysplasia.
Migraine.
Venous thrombosis.
Radiation.
Complications of arteriography.
Multiple, progressive intracranial arterial occlusions.

INFLAMMATORY DISORDERS

Giant cell arteritis.
Polyarteritis nodosa.
SLE.
Granulomatous angiitis.
Takayasu's disease.
Arteritis associated with amphetamine, cocaine, or phenylpropanolamine.
Syphilis, mucormycosis.
Sjögren's syndrome.
Behçet's syndrome.

CARDIAC DISORDERS

Rheumatic heart disease.
Mural thrombus.
Arrhythmias.
Mitral valve prolapse.
Prosthetic heart valve.
Endocarditis.
Myxoma.
Paradoxical embolus.

HEMATOLOGIC DISORDERS

Thrombotic thrombocytopenic purpura.
Sickle cell disease.
Hypercoagulable states.
Polycythemia.
Thrombocytosis.
Leukocytosis.
Lupus anticoagulant.

CERVICAL INSTABILITY, PEDIATRIC

ICD-9CM #	722.2	
ICD-10CM #	M50	Cervical disc disorders

CONGENITAL

Vertebral (Bony Anomalies)

Cranio-occipital defects (occipital vertebrae, basilar impression, occipital dysplasias, condylar hypoplasia, occipitalized atlas).
Atlantoaxial defects (aplasia of atlas arch, aplasia of odontoid process).
Subaxial anomalies (failure of segmentation and/or fusion, spina bifida, spondylolisthesis).

Ligamentous or Combined Anomalies

Found at birth as an element of somatogenic aberration.

Syndromic Disorders

Down syndrome.
Klippel-Feil syndrome.
22q11.2 deletion syndrome.
Larsen syndrome.
Marfan syndrome.
Ehlers-Danlos syndrome.

ACQUIRED

Trauma.
Infection (pyogenic, granulomatous).
Tumor (including neurofibromatosis).
Inflammatory conditions (e.g., juvenile rheumatoid arthritis).
Osteochondrodysplasias (e.g., achondroplasia, diastrophic dysplasia, metatropic dysplasia, spondyloepiphyseal dysplasia).
Storage disorders (e.g., mucopolysaccharidoses).
Metabolic disorders (rickets).
Miscellaneous (including osteogenesis imperfecta, sequela of surgery).

CHEST PAIN, CHILDREN[4]

ICD-9CM #	786.50	Chest Pain NOS
	786.59	Chest Pressure
	786.52	Chest Pain, Pleuritic
ICD-10CM #	R07.9	Chest Pain, Unspecified
	R07.82	Intercostal Pain
	R07.89	Other Chest Pain
	R07.1	Chest Pain on Breathing
	R07.81	Pleurodynia

MUSCULOSKELETAL (COMMON)

Trauma (accidental, abuse).
Exercise, overuse injury (strain, bursitis).
Costochondritis (Tietze's syndrome).
Herpes zoster (cutaneous).
Pleurodynia.
Fibrositis.
Slipping rib.
Sickle cell anemia vasoocclusive crisis.
Osteomyelitis (rare).
Primary or metastatic tumor (rare).

PULMONARY (COMMON)

Pneumonia.
Pleurisy.
Asthma.
Chronic cough.
Pneumothorax.
Infarction (sickle cell anemia).
Foreign body.
Embolism (rare).
Pulmonary hypertension (rare).
Tumor (rare).

GASTROINTESTINAL (LESS COMMON)

Esophagitis (gastroesophageal reflux).
Esophageal foreign body.
Esophageal spasm.
Cholecystitis.
Subdiaphragmatic abscess.
Perihepatitis (Fitz-Hugh-Curtis syndrome).
Peptic ulcer disease.

CARDIAC (LESS COMMON)

Pericarditis.
Postpericardiotomy syndrome.
Endocarditis.
Mitral valve prolapse.
Aortic or subaortic stenosis.
Arrhythmias.
Marfan's syndrome (dissecting aortic aneurysm).
Anomalous coronary artery.
Kawasaki disease.
Cocaine, sympathomimetic ingestion.
Angina (familial hypercholesterolemia).

IDIOPATHIC (COMMON)

Anxiety, hyperventilation.
Panic disorder.

OTHER (LESS COMMON)

Spinal cord or nerve root compression.
Breast-related pathologic condition.
Castleman's disease (lymph node neoplasm).

CHEST PAIN, NONPLEURITIC[9]

ICD-9CM #	786.50	Chest Pain NOS
	786.59	Chest Discomfort
ICD-10CM #	R07.9	Chest Pain, Unspecified
	R07.82	Intercostal Pain
	R07.89	Other Chest Pain

Cardiac: myocardial ischemia/infarction, myocarditis.
Esophageal: spasm, esophagitis, ulceration, neoplasm, achalasia, diverticula, foreign body.
Referred pain from subdiaphragmatic GI structures.
Gastric and duodenal: hiatal hernia, neoplasm, PUD.
Gallbladder and biliary: cholecystitis, cholelithiasis, impacted stone, neoplasm.
Pancreatic: pancreatitis, neoplasm.
Dissecting aortic aneurysm.
Pain originating from skin, breasts, and musculoskeletal structures: herpes zoster, mastitis, cervical spondylosis.
Mediastinal tumors: lymphoma, thymoma.
Pulmonary: neoplasm, pneumonia, pulmonary embolism/infarction.
Psychoneurosis.
Chest pain associated with mitral valve prolapse.

CHEST PAIN, PLEURITIC

ICD-9CM #	786.52	Chest Pain, Pleuritic
ICD-10CM #	R07.1	Chest Pain on Breathing
	R07.81	Pleurodynia

Cardiac: pericarditis, postpericardiotomy/Dressler's syndrome.
Pulmonary: pneumothorax, hemothorax, embolism/infarction, pneumonia, empyema, neoplasm, bronchiectasis, pneumomediastinum, TB, carcinomatous effusion.
GI: liver abscess, pancreatitis, esophageal rupture, Whipple's disease with associated pericarditis or pleuritis.
Subdiaphragmatic abscess.
Pain originating from skin and musculoskeletal tissues: costochondritis, chest wall trauma, fractured rib, interstitial fibrositis, myositis, strain of pectoralis muscle, herpes zoster, soft tissue and bone tumors.
Collagen vascular diseases with pleuritis.
Psychoneurosis.
Familial Mediterranean fever.

CHEST WALL TUMORS, PRIMARY[5a]

ICD-9CM #	varies with specific diagnosis
ICD-10CM #	varies with specific diagnosis

SOFT TISSUE

Benign

Lipoma.
Hemangioma.
Lymphangioma.
Fibroma.
Rhabdomyoma.
Neurofibroma.
Desmoid tumor.

Malignant

Malignant fibrous histiocytoma.
Rhabdosarcoma.
Liposarcoma.
Neurofibrosarcoma.
Leiomyosarcoma.

BONY AND CARTILAGINOUS

Benign

Fibrous dysplasia.
Osteochondroma.
Chondroma.
Askin tumor.
Plasmacytoma.

Malignant
Chondrosarcoma.
Osteogenic sarcoma.
Ewing sarcoma.

CHILDHOOD EOSINOPHILIA

ICD-9CM # 288.3
ICD-10CM # D72.1 Eosinophilia

PHYSIOLOGIC
Prematurity.
Infants receiving hyperalimentation.
Familial.

INFECTIOUS
Parasitic (with tissue-invasive helminths, e.g., trichinosis, strongyloidiasis, pneumocystosis, filariasis, cysticercosis, cutaneous and visceral larva migrans, echinococcosis).
Bacterial (brucellosis, tularemia, cat-scratch disease, *Chlamydia*).
Fungal (histoplasmosis, blastomycosis, coccidioidomycosis, allergic bronchopulmonary aspergillosis).
Mycobacterial (tuberculosis, leprosy).
Viral (hepatitis A, hepatitis B, hepatitis C, Epstein-Barr virus).

PULMONARY
Allergic (rhinitis, asthma).
Loeffler syndrome.
Hypersensitivity pneumonitis.
Eosinophilic pneumonia.
Pulmonary interstitial eosinophilia.

DERMATOLOGIC
Atopic dermatitis.
Pemphigus.
Dermatitis herpetiformis.
Infantile eosinophilic pustular folliculitis.
Episodic angioedema and urticaria.
Eosinophilic fasciitis (Schulman syndrome).
Eosinophilic cellulitis (Wells syndrome).
Kimura disease.

ONCOLOGIC
Neoplasm (lung, gastrointestinal, uterine).
Hodgkin disease.
Leukemia.
Myelofibrosis.

IMMUNOLOGIC
T-cell immunodeficiencies.
Hyperimmunoglobulin E (Job) syndrome.
Wiskott-Aldrich syndrome.
Graft-versus-host disease.
Drug hypersensitivity.
Post-irradiation.
Post-splenectomy.

ENDOCRINE
Post-adrenalectomy.
Addison disease.
Panhypopituitarism.

CARDIOVASCULAR
Loeffler disease (fibroplastic endocarditis).
Congenital heart disease.
Hypersensitivity vasculitis.

GASTROINTESTINAL
Milk protein allergy.
Inflammatory bowel disease.
Eosinophilic esophagitis.
Eosinophilic gastroenteritis.

CHOLANGITIS, ACUTE[5a]

ICD-9CM # 576.1 Cholangitis
ICD-10CM # K83.0 Cholangitis

NONIATROGENIC
Benign Conditions
Choledocholithiasis.
  Primary.
  Secondary.
Pancreatitis (chronic/acute), including pancreatic pseudocyst.
Papillary stenosis.
Mirizzi syndrome.
Choledochal cysts (type V, Caroli disease).
Primary sclerosing cholangitis.
Malignancies
Pancreatic cancer.
Cholangiocarcinoma.
Porta hepatis tumor/metastasis.

IATROGENIC
Obstructed biliary endoprosthesis.
Iatrogenic biliary stricture.
Direct surgical trauma.
Ischemia-induced stricture.
Anastomotic stricture (biliobiliary/bilioenteric anastomosis).

CHOLESTASIS[14]

ICD-9CM # 574.71
ICD-10CM # K80.65 Calculus of Gallbladder and Bile Duct with Chronic Cholecystitis with Obstruction

EXTRAHEPATIC
Choledocholithiasis.
Bile duct stricture.
Cholangiocarcinoma.
Pancreatic carcinoma.
Chronic pancreatitis.
Papillary stenosis.
Ampullary cancer.
Primary sclerosing cholangitis.
Choledochal cysts.
Parasites (e.g., ascaris, clonorchis).
AIDS.
Cholangiography.
Biliary atresia.
Portal lymphadenopathy.
Mirizzi's syndrome.

INTRAHEPATIC
Viral hepatitis.
Alcoholic hepatitis.
Drug induced.
Ductopenia syndromes.
Primary biliary cirrhosis.
Benign recurrent intrahepatic cholestasis.
Byler's disease.
Primary sclerosing cholangitis.
Alagille's syndrome.
Sarcoid.
Lymphoma.
Postoperative.
Total parenteral nutrition.
α-1-antitrypsin deficiency.

CHOLESTASIS, NEONATAL AND INFANTILE, DIFFERENTIAL DIAGNOSIS[22a]

ICD-9CM # varies with specific diagnosis
ICD-10CM # O26.6 Liver disorders in pregnancy, childbirth and the puerperium

INFECTIOUS
Generalized bacterial sepsis.
Viral hepatitis.
- Hepatitis A, B, C, D.
- Cytomegalovirus.
- Rubella virus.
- Herpesvirus: herpes simplex, human herpesvirus 6 and 7.
- Varicella virus.
- Coxsackievirus.
- Echovirus.
- Reovirus type 3.
- Parvovirus B19.
- HIV.
- Adenovirus.

Others.
- Toxoplasmosis.
- Syphilis.
- Tuberculosis.
- Listeriosis.
- Urinary tract infection.

TOXIC
Sepsis.
Parenteral nutrition related.
Drug related.

METABOLIC
Disorders of amino acid metabolism.
- Tyrosinemia.

Disorders of lipid metabolism.
- Wolman disease.
- Niemann-Pick disease (type C).
- Gaucher disease.

Cholesterol ester storage disease.
Disorders of carbohydrate metabolism.
- Galactosemia.
- Fructosemia.
- Glycogenosis IV.

Disorders of bile acid biosynthesis.
Other metabolic defects.
- α1-Antitrypsin deficiency.
- Cystic fibrosis.
- Hypopituitarism.
- Hypothyroidism.
- Zellweger (cerebrohepatorenal) syndrome.
- Neonatal iron storage disease.

- Indian childhood cirrhosis/infantile copper overload.
- Congenital disorders of glycosylation.
- Mitochondrial hepatopathies.
- Citrin deficiency.

GENETIC OR CHROMOSOMAL

Trisomy 17, 18, 21.
Donahue syndrome.

INTRAHEPATIC CHOLESTASIS SYNDROMES

"Idiopathic" neonatal hepatitis.
Alagille syndrome (arteriohepatic dysplasia).
Nonsyndromic bile duct paucity syndrome.
Intrahepatic cholestasis (PFIC):
- FIC-1 deficiency.
- BSEP deficiency.
- MDR3 deficiency.

Familial benign recurrent cholestasis associated with lymphedema (Aagenaes).
Congenital hepatic fibrosis.
Caroli disease (cystic dilatation of intrahepatic ducts).

EXTRAHEPATIC DISEASES

Biliary atresia.
Sclerosing cholangitis.
Bile duct stricture/stenosis.
Choledochal-pancreaticoductal junction anomaly.
Spontaneous perforation of the bile duct.
Choledochal cyst.
Mass (neoplasia, stone).
Bile/mucous plug ("inspissated bile").

MISCELLANEOUS

Shock and hypoperfusion.
Associated with enteritis.
Associated with intestinal obstruction.
Neonatal lupus erythematosus.
Myeloproliferative disease (trisomy 21).
Hemophagocytic lymphohistiocytosis.
Arthrogryposis cholestatic pigmentary syndrome.

CHOREA

ICD-9CM #	333.5	
ICD-10CM #	G25.4	Drug-Induced Chorea
	G25.5	Other Chorea

Medications (e.g., neuroleptics, tricyclics, antiparkinsonian drugs).
Cerebral palsy.
Huntington's disease.
Benign hereditary chorea.
Thyroid disorder (hyperthyroidism, hypothyroidism).
Friedreich's ataxia.
Ataxia-telangiectasia.
Hypoglycemia, hyperglycemia.
Electrolyte abnormalities (hyponatremia, hypocalcemia, hypomagnesemia, hypernatremia).
Vitamin B_{12} deficiency.
SLE.
Wilson's disease.
Alcohol.
Cocaine.
Carbon monoxide poisoning.
Mercury poisoning.

CHOREOATHETOSIS[28]

ICD-9CM #	275.1	Choreoathetosis-Agitans Syndrome
	33.5	Choreoathetosis, Paroxysmal
ICD-10CM #	G25.5	Choreoathetosis

SYSTEMIC DISEASES

SLE.
Polycythemia.
Thyrotoxicosis.
Rheumatic fever.
Cirrhosis of the liver (acquired hepatocerebral degeneration).
DM.
Wilson's disease.

PRIMARY DEGENERATIVE BRAIN DISEASES

Huntington's chorea.
Olivopontocerebellar atrophies.
Neuroacanthocytosis.

FOCAL BRAIN DISEASES

Hemichorea.
Stroke.
Tumor.
Arteriovenous malformation.

DRUG-INDUCED CHOREOATHETOSIS

Parkinson's Disease Drugs
Levodopa.

EPILEPSY DRUGS

Phenytoin.
Carbamazepine.
Phenobarbital.
Gabapentin.
Valproate.
Psychostimulant Drugs
Cocaine.
Amphetamine.
Methamphetamine.
Dextroamphetamine.
Methylphenidate.
Pemoline.
Psychotropic Drugs
Lithium.
Tricyclic antidepressant drugs.
Oral Contraceptive Drugs Cimetidine

CHYLOTHORAX

ICD-9CM #	457.8	
ICD-10CM #	I89.8	Other Specified Noninfective Disorders of Lymphatic Vessels and Lymph Nodes

Post-lymph node dissection of neck or chest.
Subclavian venous catheterization.
Thoracic aneurysm repair.
Trauma to chest and neck.
Mediastinal tumor resection.
Esophagectomy, pneumonectomy.
Lymphangitis, mediastinitis.
Neoplasms (lymphoma, carcinoma of esophagus, lung, mediastinal malignancies).
Sympathectomy.
Venous thrombosis.
Congenital.

CLOUDY URINE

ICD-9CM #	788.69	
ICD-10CM #	R82	Other abnormal findings in urine

Concentrated urine.
Use of multivitamin supplements.
Diet high in purine-rich foods.
Pyuria.
Phosphaturia.
Urinary tract infection.
Lipiduria.
Chyluria.
Hyperoxaluria.

CLUBBING

ICD-9CM #	781.5	Clubbing Finger
ICD-10CM #	R68.3	Clubbing of Fingers

Pulmonary neoplasm (lung, pleura).
Other neoplasm (GI, liver, Hodgkin's, thymus, osteogenic sarcoma).
Pulmonary infectious process (empyema, abscess, bronchiectasis, TB, chronic pneumonitis).
Extrapulmonary infectious process (subacute bacterial endocarditis, intestinal TB, bacterial or amebic dysentery, arterial graft sepsis).
Pneumoconiosis.
Cystic fibrosis.
Sarcoidosis.
Cyanotic congenital heart disease.
Endocrine (Graves' disease, hyperparathyroidism).
Inflammatory bowel disease.
Celiac disease.
Chronic liver disease, cirrhosis (particularly biliary and juvenile).
Pulmonary AV malformations.
Idiopathic.
Thyroid acropachy.
Hereditary (pachydermoperiostosis).
Chronic trauma (jackhammer operators, machine workers).

COBALAMIN DEFICIENCY[20]

ICD-9CM #	266.2	
ICD-10CM #	E53.8	Deficiency of Other Specified B Group Vitamins

ETIOPATHOPHYSIOLOGIC CLASSIFICATION OF COBALAMIN DEFICIENCY

Nutritional cobalamin deficiency (i.e., insufficient cobalamin intake):
  Vegetarians, poverty-imposed near-vegetarians, breastfed infants of mothers with pernicious anemia.
Abnormal intragastric events (i.e., inadequate proteolysis of food cobalamin):
  Atrophic gastritis, partial gastritis with hypochlorhydria, proton-pump inhibitors, H_2 blockers.

Loss or atrophy of gastric oxyntic mucosa (i.e., deficient intrinsic factor [IF] molecules):
Total or partial gastrectomy, pernicious anemia, caustic destruction (lye).
Abnormal events in small bowel lumen:
Inadequate pancreatic protease (e.g., R-cobalamin not degraded, cobalamin not transferred to IF):
- Insufficient pancreatic protease (i.e., pancreatic insufficiency).
- Inactivation of pancreatic protease (i.e., Zollinger–Ellison syndrome).

Usurping of luminal cobalamin (i.e., inadequate cobalamin binding to IF):
- By bacteria, during stasis syndromes (e.g., blind loops, pouches of diverticulosis, strictures, fistulas, anastomosis), impaired bowel motility (e.g., scleroderma), hypogammaglobulinemia.
- By *Diphyllobothrium latum* (fish tapeworm).

Disorders of ileal mucosa/IF–cobalamin receptors (i.e., IF–cobalamin not bound to IF–cobalamin receptors):
Diminished or absent IF–cobalamin receptors (e.g., ileal bypass, resection, fistula).
Abnormal mucosal architecture/function (e.g., tropical or nontropical sprue, Crohn's disease, tuberculosis ileitis, infiltration by lymphomas, amyloidosis).
IF-/post-IF–cobalamin receptor defects (e.g., Imerslund–Gräsbeck syndrome, transcobalamin II [TC II] deficiency).
Drug effects (e.g., slow K, metformin, cholestyramine, colchicine, neomycin).
Disorders of plasma cobalamin transport (i.e., TC II–cobalamin not delivered to TC II receptors):
Congenital TC II deficiency, defective binding of TC II–cobalamin to TC II receptors (rare).
Metabolic disorders (i.e., cobalamin not used by cells):
Inborn enzyme errors (rare).
Acquired disorders (e.g., cobalamin functionally inactivated by irreversible oxidation, N_2O inhalation).

COLIC, ACUTE ABDOMINAL[38]

ICD-9CM # 789.0
ICD-10CM # R10.0 Acute Abdomen

Acute gastroenteritis.
Food poisoning.
Nonspecific causes.
Constipation.
Gastric outlet obstruction:
- Chronic peptic ulceration.
- Gastric cancer.

Small bowel obstruction:
Adhesions:
- Postsurgical.
- Inflammatory (e.g., diverticular).
- Radiation.
- Meckel's diverticulum.
- Metastatic.

Stricture:
- Ischemic.
- Radiation.
- Inflammatory (e.g., Crohn's disease).

Volvulus intussusception:
- Tumor (e.g., Peutz-Jeghers syndrome).
- Superior mesenteric artery syndrome.

Intraluminal bolus:
- Gallstone.
- Bezoar.

Hernia:
- Abdominal wall.
- Internal.

Neoplasm:
- Benign (e.g., leiomyoma).
- Malignant (e.g., carcinoid tumor, adenocarcinoma).

Large bowel obstruction:
- Colon cancer.
- Diverticular disease.
- Volvulus.

Uterine:
- Missed abortion.
- Parturition.
- Period pain.

COLOR CHANGES, CUTANEOUS[34]

ICD-9CM # 709.00 Pigmentation Anomaly
ICD-10CM # L81.9 Disorder of Pigmentation, Unspecified

BROWN

Generalized: pituitary, adrenal, liver disease, ACTH-producing tumor (e.g., oat cell lung carcinoma).
Localized: nevi, neurofibromatosis.

WHITE

Generalized: albinism.
Localized: vitiligo, Raynaud's syndrome.

RED (ERYTHEMA)

Generalized: fever, polycythemia, urticaria, viral exanthems.
Localized: inflammation, infection, Raynaud's syndrome.

YELLOW

Generalized: liver disease, chronic renal disease, anemia.
Generalized (except sclera): hypothyroidism, increased intake of vegetables containing carotene.
Localized: resolving hematoma, infection, peripheral vascular insufficiency.

BLUE

Lips, mouth, nail beds: cardiovascular and pulmonary diseases, Raynaud's.

COMA

ICD-9CM # 780.01
ICD-10CM # R40.20 Unspecified Coma

Vascular: hemorrhage, thrombosis, embolism.
CNS infections: meningitis, encephalitis, cerebral abscess.
Cerebral neoplasms with herniation.
Head injury: subdural hematoma, cerebral concussion, cerebral contusion.
Drugs: narcotics, sedatives, hypnotics.
Ingestion or inhalation of toxins: CO, alcohol, lead.
Metabolic disturbances.
Hypoxia.
Acid-base disorders.
Hypoglycemia, hyperglycemia.
Hepatic failure.
Electrol yte disorders.
Uremia.
Hypothyroidism.
Hypothermia, hyperthermia.
Hypotension, malignant hypertension.
Postictal.

COMA, NORMAL COMPUTED TOMOGRAPHY[1a]

ICD-9CM # 780.01
ICD-10CM # R40.20 Unspecified coma

MENINGEAL DISORDERS

Subarachnoid hemorrhage (uncommon).
Bacterial meningitis.
Encephalitis.
Subdural empyema.

EXOGENOUS TOXINS

Sedative drugs and barbiturates.
Anesthetics and γ-hydroxybutyrate.*
Alcohols.
Stimulants:
Phencyclidines.†
Cocaine and amphetamines.‡

Psychotropic drugs:
Cyclic antidepressants.
Phenothiazines.
Lithium.

Anticonvulsants.
Opioids.
Clonidine.§
Penicillins.
Salicylates.
Anticholinergics.
Carbon monoxide, cyanide, and methemoglobinemia.

ENDOGENOUS TOXINS/ DEFICIENCIES/DERANGEMENTS

Hypoxia and ischemia.
Hypoglycemia.
Hypercalcemia.
Osmolar:
Hyperglycemia.
Hyponatremia.
Hypernatremia.

Organ system failure:
Hepatic encephalopathy.
Uremic encephalopathy.
Pulmonary insufficiency (carbon dioxide narcosis).

SEIZURES

Prolonged postictal state.
Spike-wave stupor.

HYPOTHERMIA OR HYPERTHERMIA

Brain stem ischemia.
Basilar artery stroke.

Brain stem or cerebellar hemorrhage.
Conversion or malingering.

*General anesthetic, similar to g-aminobutyric acid; recreational drug and body building aid. Rapid onset, rapid recovery often with myoclonic jerking andconfusion. Deep coma (2-3 hr; Glasgow Coma Scale = 3) with maintenance of vital signs.

†Coma associated with cholinergic signs: lacrimation, salivation, bronchorrhea, and hyperthermia.

‡Coma after seizures or status (i.e., a prolonged postictal state).

§An antihypertensive agent active through the opiate receptor system; frequent overdose when used to treat narcotic withdrawal.

COMA, PEDIATRIC POPULATION[31]

ICD-9CM # 780.01
ICD-10CM # R40.20 Unspecified coma

ANOXIA

Birth asphyxia.
Carbon monoxide poisoning.
Croup/epiglottitis.
Meconium aspiration.

INFECTION

Hemolysis.
Blood loss.
Hydrops fetalis.
Infection.
Meningoencephalitis.
Sepsis.
Postimmunization encephalitis.

INCREASED INTRACRANIAL PRESSURE

Anoxia.
Inborn metabolic errors.
Toxic encephalopathy.
Reye's syndrome.
Head trauma/intracranial bleed.
Hydrocephalus.
Posterior fossa tumors.

HYPERTENSIVE ENCEPHALOPATHY

Coarctation of aorta.
Nephritis.
Vasculitis.
Pheochromocytoma.

ISCHEMIA

Hypoplastic left heart.
Shunting lesions.
Aortic stenosis.
Cardiovascular collapse (any cause).

PURPURIC CAUSES

Disseminated intravascular coagulation.
Hemolytic-uremic syndrome.
Leukemia.
Thrombotic purpura.

HYPERCAPNIA

Cystic fibrosis.
Bronchopulmonary dysplasia.
Congenital lung anomalies.

NEOPLASM

Medulloblastoma.
Glioma of brain stem.
Posterior fossa tumors.

DRUGS/TOXINS

Maternal sedation.
Alcohol.
Any drug.
Lead.
Salicylism.
Arsenic.
Pesticides.

ELECTROLYTE ABNORMALITIES

Hypernatremia (diarrhea, dehydration, salt poisoning).
Hyponatremia (SIADH, androgenital syndrome, gastroenteritis).
Hyperkalemia (renal failure, salicylism, androgenitalism).
Hypokalemia (diarrhea, hyperaldosteronism, salicylism, DKA).
Hypocalcemia (vitamin D deficiency, hyperparathyroidism).
Severe acidosis (sepsis, cold injury, salicylism, DKA).

HYPOGLYCEMIA

Birth injury or stress.
Diabetes.
Alcohol.
Salicylism.
Hyperinsulinemia.
Iatrogenic.

POSTSEIZURE

Renal Causes
Nephritis.
Hypoplastic kidneys.
Hepatic Causes
Acute hepatitis.
Fulminant hepatic failure.
Inborn metabolic errors.
Bile duct atresia.

CONGESTIVE HEART FAILURE AND CARDIOMYOPATHY[1a]

ICD-9CM #	428.0	Congestive Heart Failure
	425.9	Cardiomyopathy, Secondary, Unspecified
ICD-10CM #	I50.9	Heart failure, unspecified
	I42.7	Cardiomyopathy due to drug and external agent

CAUSES OF CONGESTIVE HEART FAILURE AND CARDIOMYOPATHY

Coronary Artery Disease
Acute ischemia.
Myocardial infarction.
Ischemic cardiomyopathy with hibernating myocardium.
Idiopathic
Idiopathic dilated cardiomyopathy.
Idiopathic restrictive cardiomyopathy.
Peripartum.
Pressure Overload
Hypertension.
Aortic stenosis.
Volume Overload
Mitral regurgitation.
Aortic insufficiency.
Anemia.
Atrioventricular fistula.
Toxins
Ethanol.
Cocaine.
Doxorubicin (Adriamycin).
Methamphetamine.
Metabolic-Endocrine
Thiamine deficiency.
Diabetes.
Hemochromatosis.
Thyrotoxicosis.
Obesity.
Infiltrative
Amyloidosis.
Inflammatory
Viral myocarditis.
Hereditary
Hypertrophic.
Dilated.

*Genetic bases for these cardiomyopathies have been identified in a large number of individual patients and families. Most of the mutations have been found in cardiac contractile or structural proteins.

CONGESTIVE HEART FAILURE, INFANT[1]

ICD-9CM #	428.9	
ICD-10CM #	105.9	Heart failure, unspecified

Critical coarctation of the aorta.
Interrupted aortic arch.
Congenital aortic stenosis.
Hypoplastic left heart syndrome.
Large ventricular septal defect.
Truncus arteriosus.
Unrecognized supraventricular tachycardia.
Cardiac tamponade.
Myocarditis.

CONJUNCTIVAL NEOPLASM

ICD-9CM # varies with specific disorder
ICD-10CM # varies with specific diagnosis

MALIGNANT

Squamous cell carcinoma.
Melanoma.
Sebaceous carcinoma.
Kaposi's sarcoma.
Metastatic neoplasms.

BENIGN

Melanocytic nevus.
Squamous papilloma.
Hemangioma.
Lymphangioma.
Myxoma.

CONSCIOUSNESS IMPAIRMENT, ACUTE, IN CRITICALLY ILL PATIENT

ICD-9CM # 293.1
ICD-10CM # F05.9 Delirium, unspecified

GENERAL CAUSES OF ACUTELY IMPAIRED CONSCIOUSNESS IN THE CRITICALLY ILL

Infection
Sepsis encephalopathy.
Central nervous system infection.
Drugs
Narcotics.
Benzodiazepines.
Anticholinergics.
Anticonvulsants.
Tricyclic antidepressants.
Selective serotonin uptake inhibitors.
Phenothiazines.
Steroids.
Immunosuppressants (cyclosporine, FK-506, OKT3).
Anesthetics.
Electrolyte and Acid-Base Disturbances
Hyponatremia.
Hypernatremia.
Hypercalcemia.
Hypermagnesemia.
Severe acidemia and alkalemia.
Organ System Failure
Shock.
Renal failure.
Hepatic failure.
Pancreatitis.
Respiratory failure (hypoxia, hypercapnia).
Endocrine Disorders
Hypoglycemia.
Hyperglycemia.
Hypothyroidism.
Hyperthyroidism.
Pituitary apoplexy.
Drug Withdrawal
Alcohol.
Opiates.
Barbiturates.
Benzodiazepines.
Vascular Causes
Shock.
Hypotension.
Hypertensive encephalopathy.
Central nervous system vasculitis.
Cerebral venous sinus thrombosis.
Central Nervous System Disorders
Hemorrhage.
Stroke.
Brain edema.
Hydrocephalus.
Increased intracranial pressure.
Meningitis.
Ventriculitis.
Brain abscess.
Subdural empyema.
Seizures.
Vasculitis.
Seizures
Convulsive and nonconvulsive status epilepticus.
Miscellaneous
Fat embolism syndrome.
Neuroleptic malignant syndrome.
Thiamine deficiency (Wernicke encephalopathy).
Psychogenic unresponsiveness.

CONSTIPATION

ICD-9CM # 564.0
ICD-10CM # K59.00 Constipation, unspecified

Intestinal obstruction.
Fecal impaction.
Diverticular disease.
GI neoplasm.
Strangulated femoral hernia.
Gallstone ileus.
Tuberculous stricture.
Adhesions.
Ameboma.
Volvulus.
Intussusception.
Inflammatory bowel disease.
Hematoma of bowel wall, secondary to trauma or anticoagulants.
Poor dietary habits: insufficient bulk in diet, inadequate fluid intake.
Change from daily routine: travel, hospital admission, physical inactivity.
Acute abdominal conditions: renal colic, salpingitis, biliary colic, appendicitis, ischemia.
Hypercalcemia or hypokalemia, uremia.
Irritable bowel syndrome, pregnancy, anorexia nervosa, depression.
Painful anal conditions: hemorrhoids, fissure, stricture.
Decreased intestinal peristalsis: old age, spinal cord injuries, myxedema, diabetes, multiple sclerosis, Parkinsonism and other neurologic diseases.
Drugs: codeine, morphine, antacids with aluminum, verapamil, anticonvulsants, anticholinergics, disopyramide, cholestyramine, alosetron, iron supplements.
Hirschsprung's disease, meconium ileus, congenital atresia in infants.

CONSTIPATION, ADULT PATIENT[38]

ICD-9CM # 564
ICD-10CM # K59.00 Constipation, unspecified

NO GROSS STRUCTURAL ABNORMALITY

Inadequate fiber intake.
Irritable bowel syndrome (associated with abdominal pain) or functional constipation.
Idiopathic slow-transit constipation.
"Obstructed defecation" pelvic floor dysfunction (or dyssynergia).

STRUCTURAL DISORDERS

Anal fissure, infection, or stenosis.
Colon cancer or stricture.
Aganglionosis and/or abnormal myenteric plexus:
- Hirschsprung's disease.
- Chagas' disease.
- Neuropathic pseudoobstruction.

Abnormal colonic muscle:
- Myopathy.
- Dystrophia myotonica.
- Systemic sclerosis.

Idiopathic megarectum and/or megacolon.
Proximal megacolon.

NEUROLOGIC CAUSES

Diabetic autonomic neuropathy.
Damage to the sacral parasympathetic outflow.
Spinal cord damage or disease (e.g., multiple sclerosis).
Parkinson's disease.
Blunting of consciousness, mental retardation, psychosis.
Pain induced by straining (e.g., sciatic nerve compression).

ENDOCRINE OR METABOLIC CAUSES

Hypothyroidism.
Hypercalcemia.
Porphyria.
Pregnancy.

PSYCHOLOGIC DISORDERS

Depression.
Anorexia nervosa.
Denied bowel habit.

DRUG SIDE EFFECTS

CORNEAL SENSATION, DECREASED

ICD-9CM # 371.89
ICD-10CM # H18.899 Other specified disorders of cornea, unspecified eye

Herpes (simplex, zoster).
Contact lens wear.
Topical agents (NSAIDs, anesthetics, beta-blockers).
Diabetes.
Eye trauma.
Postsurgery.

COUGH

ICD-9CM # 786.2
ICD-10CM # R05 Cough

Infectious process (viral, bacterial).
Postinfectious.
"Smoker's cough."
Rhinitis (allergic, vasomotor, postinfectious).
Asthma.
Exposure to irritants (noxious fumes, smoke, cold air).
Drug-induced (especially ACE inhibitors, beta-blockers).
GERD.
Interstitial lung disease.
Lung neoplasms.
Lymphomas, mediastinal neoplasms.
Bronchiectasis.

Cardiac (CHF, pulmonary edema, mitral stenosis, pericardial inflammation).
Recurrent aspiration.
Inflammation of larynx, pleura, diaphragm, mediastinum.
Cystic fibrosis.
Anxiety.
Other: pulmonary embolism, foreign body inhalation, aortic aneurysm, Zenker's diverticulum, osteophytes, substernal thyroid, thyroiditis, PMR.

CUTANEOUS INFECTIONS, ATHLETES

ICD-9CM # 686.9
ICD-10CM # L08.9 Local infection of the skin and subcutaneous tissue, unspecified

Tinea pedis.
Tinea cruris.
Molluscum contagiosum.
Herpes simplex.
Verruca vulgaris.
Folliculitis.
Impetigo.
Furuncles.
Otitis externa.
Erythrasma.

CYANOSIS[2]

ICD-9CM # 782.5
ICD-10CM # R23.0 Cyanosis

DIFFERENTIAL DIAGNOSIS OF CYANOSIS

Peripheral Cyanosis
Low cardiac output states
Shock.
Left ventricular failure.
Hypovolemia.
Environmental exposure (cold)
Air or water.
Arterial occlusion
Thrombosis.
Embolism.
Vasospasm (Raynaud's phenomenon).
Peripheral vascular disease.
Venous obstruction
Redistribution of blood flow from extremities
Central Cyanosis
Decreased arterial oxygen saturation
High altitude (>8000 ft).
Impaired pulmonary function.
  Hypoventilation.
  Impaired oxygen diffusion.
  Ventilation-perfusion mismatching.
  - Pulmonary embolism.
  - Acture respiratory distress syndrome.
  - Pulmonary hypertension.

  Respiratory compromise.
  - Upper airway obstruction.
  - Pneumonia.
  - Diaphragmatic hernia.
  - Tension pneumothorax.
  - Polycythemia.

Anatomic Shunts
Pulmonary arteriovenous fistulae and intrapulmonary shunts.
Cerebral, hepatic, peripheral arteriovenous fistulae.
Cyanotic congenital heart disease.
  Endocardial cushion defects.
  Ventricular septal defects.
  Coarctation of aorta.
  Tetralogy of Fallot.
  Total anomalous pulmonary venous drainage.
  Hypoplastic left ventricle.
  Pulmonary vein stenosis.
  Tricuspid atresia and anomalies.
  Premature closure of foramen ovale.
  Dextrocardia.
  Pulmonary stenosis of atrial septal defect.
  Patent ductus arteriosus with reversed shunt.
Abnormal Hemoglobin
Methemoglobinemia.
  Hereditary.
  Acquired.
Sulfhemoglobinemia.
Mutant hemoglobin with low oxygen affinity (e.g., hemoglobin Kansas).

CYANOSIS, NEONATAL[1]

ICD-9CM # 782.5
ICD-10CM # R23.0 Cyanosis

RESPIRATORY

Upper Airway
Choanal atresia.
Macroglossia.
Glossoptosis (secondary to micrognathia).
Laryngomalacia.
Laryngeal web or cyst.
Vascular anomalies (e.g., cystic hygromas, rings).
Subglottic stenosis (commonly secondary to intubation).
Foreign body.
Lower Airway
Pneumonia.
Bronchiolitis.
Pulmonary edema.
Atelectasis.
Bronchopulmonary dysplasia.

SYSTEMIC

Sepsis.
Trauma.
Poisons.

CARDIAC

Cyanotic congenital heart diseases.
Transposition of the great vessels (most common neonatal).
Tetralogy of Fallot.
Truncus arteriosus.
Tricuspid atresia.
Total anomalous pulmonary venous return.
Ebstein anomaly.
Gastrointestinal.
Gastroesophageal reflux.

NEUROLOGIC

Seizures.
Central hypoventilation syndrome (Ondine curse).
Spinal muscular atrophy type I (Werdnig-Hoffmann).
Botulism.
Congenital myopathies.

HEMATOLOGIC

Methemoglobinemia.

DAYTIME SLEEPINESS

ICD-9CM # varies with specific disorder
ICD-10CM # R53.82 Chronic fatigue, unspecified

Sleep deprivation.
Medication induced (e.g., benzodiazepines, beta-blockers, narcotics, sedative antidepressants, gabapentin).
Depression.
Obstructive sleep apnea.
Medical illness (e.g., severe anemia, hypothyroidism, COPD, hepatic failure, renal insufficiency, CHF, electrolyte disturbances).
Circadian rhythm abnormalities (e.g., jet lag, shift work sleep disorder).
Restless legs syndrome.
Posttrauma.
Narcolepsy.
Neurologic disorders (e.g., neurodegenerative disorders; parkinsonism; multiple sclerosis; lesions affecting thalamus, hypothalamus, or brain stem).

DELAYED PASSAGE OF MECONIUM[16a]

ICD-9CM # 777.1
ICD-10CM # P76.0 Meconium plug syndrome

Ileal atresia.
Meconium ileus.
Functional immaturity of the colon.
Colon atresia.
Anorectal malformations.
Hirschsprung's disease.
Megacystis-microcolon-intestinal hypoperistalsis syndrome.
Extrinsic compression of the distal bowel by a mass lesion.
  Mesenteric cyst.
  Enteric duplication cyst.
Paralytic ileus, sepsis, drugs, and metabolic upset.

DELIRIUM[26]

ICD-9CM # 780.09 Delirium NOS
293.0 Acute Delirium
ICD-10CM # R40.0 Somnolence
R40.1 Stupor
F05 Delirium due to known physiological condition

PHARMACOLOGIC AGENTS

Anxiolytics (benzodiazepines).

Antidepressants (e.g., amitriptyline, doxepin, imipramine).
Cardiovascular agents (e.g., methyldopa, digitalis, reserpine, propranolol, procainamide, captopril, disopyramide).
Antihistamine.
Cimetidine.
Corticosteroids.
Antineoplastics.
Drugs of abuse (alcohol, cannabis, amphetamines, cocaine, hallucinogens, opioids, sedative-hypnotics, phencyclidine).

METABOLIC DISORDERS

Hypercalcemia.
Hypercarbia.
Hypoglycemia.
Hyponatremia.
Hypoxia.

INFLAMMATORY DISORDERS

Sarcoidosis.
SLE.
Giant cell arteritis.

ORGAN FAILURE

Hepatic encephalopathy.
Uremia.

NEUROLOGIC DISORDERS

Alzheimer's disease.
CVA.
Encephalitis (including HIV).
Encephalopathies.
Epilepsy.
Huntington's disease.
Multiple sclerosis.
Neoplasms.
Normal-pressure hydrocephalus.
Parkinson's disease.
Pick's disease.
Wilson's disease.

ENDOCRINE DISORDERS

Addison's disease.
Cushing's disease.
Panhypopituitarism.
Parathyroid disease.
Postpartum psychosis.
Recurrent menstrual psychosis.
Sydenham's chorea.
Thyroid disease.

DEFICIENCY STATES

Niacin.
Thiamine, vitamin B_{12}, and folate.

DELIRIUM AND AGITATION, DRUG-INDUCED

ICD-9CM # 293.1
ICD-10CM # F05.9 Delirium, unspecified

COMMONLY USED DRUGS ASSOCIATED WITH DELIRIUM AND AGITATION

Benzodiazepines.
Opiates (especially meperidine).
Anticholinergics.
Antihistamines.
H_2 blockers.
Antibiotics.
Corticosteroids.
Metoclopramide.

DELIRUM, AGITATED[2]

ICD-9CM # 293.1
ICD-10CM # F05 Delirium due to known physiological condition

Metabolic causes:
  Electrolyte abnormalities.
  Hypoglycemia.
  Hypoxia.
  Uremia/hyperammonemia.
Structural lesions of the CNS:
  Trauma.
  Stroke.
  Hemorrhage.
  Mass.
Endocrine disease:
  Thyrotoxicosis.
Infections:
  Bacterial/viral meningitis/encephalitis.
Toxicologic causes:
  Sympathomimetic/stimulants.
  - Cocaine.
  - Amphetamines and derivatives.
  - Caffeine.
  - Phencyclidine/ketamine.

  Anticholinergics.
  Serotonin syndrome.
  Sedative-hypnotic withdrawal.
Heatstroke.
Postictal state.

CNS, Central nervous system.

DELIRIUM, DIALYSIS PATIENT[26]

ICD-9CM # 293.0 Acute Delirium
293.9 Encephalopathy from Dialysis
ICD-10CM # F05 Delirium due to known physiological condition
F06.8 Other specified mental disorders due to known physiological condition

STRUCTURAL

Cerebrovascular accident (particularly hemorrhage).
Subdural hematoma.
Intracerebral abscess.
Brain tumor.

METABOLIC

Disequilibrium syndrome.
Uremia.
Drug effects.
Meningitis.
Hypertensive encephalopathy.
Hypotension.
Postictal state.
Hypernatremia or hyponatremia.
Hypercalcemia.
Hypermagnesemia.
Hypoglycemia.
Severe hyperglycemia.
Hypoxemia.
Dialysis dementia.

DEMYELINATING DISEASES[40]

ICD-9CM # 341.9
ICD-10CM # G37.9 Demyelinating disease of central nervous system, unspecified

MULTIPLE SCLEROSIS

Relapsing and chronic progressive forms.
Acute multiple sclerosis.
Neuromyelitis optica (Devic's disease).

DIFFUSE CEREBRAL SCLEROSIS

Schilder's encephalitis periaxialis diffusa.
Baló's concentric sclerosis.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

After measles, chickenpox, rubella, influenza, mumps.
After rabies or smallpox vaccination.

NECROTIZING HEMORRHAGIC ENCEPHALITIS

Hemorrhagic leukoencephalitis.

LEUKODYSTROPHIES

Krabbe's globoid leukodystrophy.
Metachromatic leukodystrophy.
Adrenoleukodystrophy.
Adrenomyeloneuropathy.
Pelizaeus-Merzbacher leukodystrophy.
Canavan's disease.
Alexander's disease.

DIAPHRAGM ELEVATION, BILATERAL, SYMMETRICAL[16a]

ICD-9CM # 519.4
ICD-10CM # J98.6 Disorders of diaphragm

CAUSES OF BILATERAL SYMMETRICAL ELEVATION OF THE DIAPHRAGM

Supine position.
Poor inspiration.
Obesity.
Pregnancy.
Abdominal distention (ascites, intestinal obstruction, abdominal mass).
Diffuse pulmonary fibrosis.
Lymphangitis carcinomatosa.
Disseminated lupus erythematosus.
Bilateral basal pulmonary emboli.
Painful conditions (after abdominal surgery).
Bilateral diaphragmatic paralysis.

DIAPHRAGM ELEVATION, UNILATERAL[16a]

ICD-9CM # 519.4
ICD-10CM # J98.6 Disorders of diaphragm

CAUSES OF UNILATERAL ELEVATION OF THE DIAPHRAGM

Posture—lateral decubitus position (dependent side).
Gaseous distention of stomach or colon.
Dorsal scoliosis.
Pulmonary hypoplasia.
Pulmonary collapse.
Phrenic nerve palsy.
Eventration.
Pneumonia or pleurisy.
Pulmonary thromboembolism.
Rib fracture and other painful conditions.
Subphrenic infection.
Subphrenic mass.

DIARRHEA, ACUTE WATERY AND BLOODY[38]

ICD-9CM #	varies with specific diagnosis	
	009.3	Infectious Diarrhea
	558.9	Non-infectious Diarrhea
	564.5	Functional Diarrhea
	787.91	Diarrhea
ICD-10CM #	K52.2	Allergic and dietetic gastroenteritis and colitis
	K52.89	Other specified noninfective gastroenteritis and colitis
	R19.7	Diarrhea, unspecified

ACUTE WATERY DIARRHEA

Gastrointestinal infections:
- Protozoal (e.g., *Giardia*).
- Bacterial (e.g., enterotoxigenic *Escherichia coli,* cholera).
- Viral (e.g., rotavirus, Norwalk virus).

Drugs.
Toxins.
Dietary constituents (e.g., lactose intolerance).
Onset of chronic diarrheal illness.

ACUTE BLOODY DIARRHEA

Infectious colitis:
- Confluent proctocolitis (e.g., *Shigella*, *Campylobacter*, *Salmonella*, *Entamoeba histolytica*).
- Segmental colitis (e.g., *Campylobacter*, *Salmonella*, enteroinvasive *E. coli*, *Aeromonas*, *E. histolytica*).

Drug-induced colitis (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs]).
Inflammatory bowel disease.
Ischemic colitis (usually elderly patient with underlying heart disease or arrhythmias).
Antibiotic-associated colitis.

DIARRHEA, INFECTIOUS[2]

ICD-9CM #	009.2	
ICD-10CM #	A09	Infectious gastroenteritis and colitis, unspecified

ETIOLOGIC AGENTS OF INFECTIOUS DIARRHEA

Viral (60% of Cases)
Astrovirus.
Calicivirus.
Coronavirus.
Cytomegalovirus.*
Enteric adenovirus.
Hepatitis A through G.
Herpes simplex virus.
HIV enteropathy.
Norwalk-like agents.
Pararotavirus.
Norwalk virus.
Picomavirus.
Rotavirus.
Small round viruses.
Bacterial (20% of Cases)

Invasive*

Aeromonas spp.
Campylobacter spp.
Clostridium difficile.
Enteroinvasive *E. coli.*
Mycobacterium spp.
Plesiomonas shigelloides.
Salmonella spp.
Shigella spp.
Vibrio fluvialis.
Vibrio parahaemolyticus.
Vibrio vulnificus.
Yersinia enterocolitica.
Yersinia pseudotuberculosis.

Toxigenic

Food poisoning with preformed toxins.
Bacillus cereus.
Clostridium botulinum.
Staphylococcus aureus.
Toxin formation after colonization.
Aeromonas hydrophila.
Clostridium perfringens.
Enterohemorrhagic *E. coli* O157:H7.*
Enterotoxigenic *E. coli.*
Klebsiella pneumoniae.
Shigella spp.
Vibrio cholerae.
Other bacteria
Parasitic (5% of Cases)
Protozoa
*Balantidium coli.**
Blastocystis hominis.
Cryptosporidium.
Cyclospora.
Dientamoeba fragilis.
*Entamoeba histolytica.**
Entamoeba polecki.
Enteromonas hominis.
Giardia lamblia.
Isospora belli.
Microsporidia.
Sarcocystis hominis.
Helminths
Angiostrongylus costaricense.
Anisakiasis.
Ascaris lumbricoides.
Diphyllobothrium latum.
Enterobius vermicularis.
Hookworms.
Schistosoma spp.
Strongyloides stercoralis.
Taenia spp.
Trichinella spiralis.
Trichuris trichiura.

*Associated with fever, abdominal pain, and fecal red blood cells or white blood cells. % indicates the estimated contribution to total cases.

DIARRHEA, NONINFECTIOUS[2]

ICD-9CM #	564.5	
ICD-10CM #	K59.1	Functional diarrhea

CAUSES OF NONINFECTIOUS DIARRHEA

Toxins
Drugs
ACE inhibitors.
Alprazolam.
Antacids (Mg).
Antibiotics.
Antidepressants.
Antiepileptic drugs.
Antihypertensives.
Antiparkinson drugs.
Beta-blockers.
Caffeine.
Cardiac antiarrhythmics.
Chemotherapy agents.
Cholesterol-lowering drugs.
Cholinergic agents.
Cholinesterase inhibitors.
Colchicine.
Digitalis.
Diuretics.
Flurouracil.
Fluoxetine.
Histamine H_2-receptor antagonists.
Hydralazine.
Lactulose.
Laxatives/cathartics.
Levodopa.
Lithium.
NSAIDs.
Neomycin.
Podophyllin.
Procainamide.
Prostaglandins.
Quinidine.
Ricinoleic acid.
Theophylline.
Thyroid hormone.
Valproic acid.
Dietetic foods
Mannitol.
Sorbitol.
Xylitol.
Fish-associated toxins
Amnestic shellfish poisoning.
Ciguatera.
Echinoderms.
Neurotoxic shellfish poisoning.
Paralytic shellfish poisoning.
Scombroid.
Tetroton.
Plant-associated toxins
Herbal preparations.
Horse chestnut.

Mushrooms—*Amanita* spp.
Nicotine.
Other plant toxins:
  Pesticides—organophosphates.
  Pokeweed.
  Rhubarb.
Miscellaneous:
  Allergic reactions.
  Carbon monoxide poisoning.
  Ethanol.
  Heavy metals.
  Monosodium glutamate (MSG).
  Opiate withdrawal.

Gastrointestinal Pathology

Appendicitis.
Autonomic dysfunction.
Bile acid malabsorption.
Blind loop.
Bowel obstruction.
Celiac disease.
Cirrhosis.
Defects in amino acid transport.
Diverticular disease.
Familial dysautonomia.
Fecal impaction.
Fecal incontinence.
GI bleed.
GI cancer.
Hirschsprung's disease.
Inflammatory bowel disease (ulcerative colitis, Crohn's disease).
Intussusception.
Irritable bowel syndrome.
Ischemic bowel.
Lactose/fructose intolerance.
Malabsorption syndromes.
Malrotation.
Postsurgical.
Postvagotomy.
Radiation therapy.
Short gut syndrome.
Small bowel resection.
Strictures.
Toxic megacolon.
Tropical sprue.
Volvulus.
Whipple's disease.

Endocrine Related

Carcinoid syndrome (serotonin).
Hormonal hypersecretion.
Hyperthyroidism (thyroid hormone).
Medullary carcinoma of the thyroid (calcitonin).
Pancreatic cholera (VIP).
Somatostatinoma (somatostatin).
Systemic mastocytosis (histamine).
Zollinger-Ellison syndrome (gastrin).

Endocrine pathology

Adrenal insufficiency.
Diabetes enteropathy.
Hypoparathyroidism.
Pancreatic insufficiency.

Systemic Illness/Other

Alcoholism.
Amyloidosis.
Connective tissue disease.
Cystic fibrosis.
Ectopic pregnancy.
Hemolytic-uremic syndrome.
Henoch-Schönlein purpura.
Lymphoma.
Otitis media—infants.
Pelvic inflammatory disease.
Pneumonia/sepsis.
Pyelonephritis.
Scleroderma/SLE.
Severe malnutrition.
Stevens-Johnson syndrome.
Toxic shock syndrome.
Wilson's disease.
Miscellaneous:
  Factitious diarrhea.
  Runner's diarrhea.

ACE, Angiotensin-converting enzyme; *GI,* gastrointestinal; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *SLE,* systemic lupus erythematosus; *VIP,* vasoactive intestinal polypeptide.

DIARRHEA, TUBE-FED PATIENT[14]

ICD-9CM # 564.4
ICD-10CM # K91.89 Other postprocedural complications and disorders of digestive system

COMMON CAUSES UNRELATED TO TUBE FEEDING

Elixir medications containing sorbitol.
Magnesium-containing antacids.
Antibiotic-induced sterile gut.
Pseudomembranous colitis.

POSSIBLE CAUSES RELATED TO TUBE FEEDING

Inadequate fiber to form stool bulk.
High fat content of formula (in the presence of fat malabsorption syndrome).
Bacterial contamination of enteral products and delivery systems (causal association with diarrhea not documented).
Rapid advancement in rate (after the GI tract is unused for prolonged periods).

UNLIKELY CAUSES RELATED TO TUBE FEEDING

Formula hyperosmolality (proven not to be the cause of diarrhea).
Lactose (absent from nearly all enteral feeding formulas).

DIPLOPIA, BINOCULAR

ICD-9CM # 368.2
ICD-10CM # H53.2 Diplopia

Cranial nerve palsy (3rd, 4th, 6th).
Thyroid eye disease.
Myasthenia gravis.
Decompensated strabismus.
Orbital trauma with blowout fracture.
Orbital pseudotumor.
Cavernous sinus thrombosis.

DIPLOPIA, MONOCULAR

ICD-9CM # 368.2
ICD-10CM # H53.2 Diplopia

Postoperative corrected longstanding tropia.
Defective contact lenses.
Poorly fitting bifocals.
Trauma to iris.
Corneal disorder (e.g., dry eye, astigmatism).
Cataracts.
Lens subluxation.
Nystagmus.
Eyelid twitching.
Foreign body in aqueous or vitreous media.
Migraine.
Lesions of occipital cortex.
Psychogenic.

DIPLOPIA, VERTICAL

ICD-9CM # 368.2
ICD-10CM # H53.2 Diplopia

Myasthenia.
Superior oblique palsy.
Myositis or pseudotumor with orbital involvement.
Lymphoma or metastases affecting the orbits.
Brain stem or cerebellar lesions.
Hydrocephalus.
Third nerve palsy.
Botulism.
Wernicke's encephalopathy.
Dysthyroid orbitopathy (muscle infiltration).

DIZZINESS

ICD-9CM # 780.4
ICD-10CM # R42 Dizziness and giddiness

Viral syndrome.
Anxiety, hyperventilation.
Benign positional paroxysmal vertigo.
Medications (e.g., sedatives, antihypertensives, analgesics).
Withdrawal from medications (e.g., benzodiazepines, SSRIs).
Alcohol or drug abuse.
Postural hypotension.
Hypoglycemia, hyperglycemia.
Hematologic disorders (e.g., anemia, polycythemia, leukemia).
Head trauma.
Menière's disease.
Vertebrobasilar ischemia.
Cervical osteoarthritis.
Cardiac abnormalities (arrhythmias, cardiomyopathy, CHF, pericarditis).
Multiple sclerosis.
Peripheral vestibulopathy.
Air or sea travel.
Electrolyte abnormalities.
Eye problems (cornea, lens, retina).
Migraine.
Brain stem infarct.
Autonomic neuropathy.
Chronic otomastoiditis.
Complex partial seizures.
Ramsey Hunt syndrome.
Arteritis.
Syncope and presyncope.
Perilymph fistula.
Cerebellopontine tumor.
Hepatic or renal disease.

DRY EYE

ICD-9CM # 375.15
ICD-10CM # H04.129 Dry eye syndrome of unspecified lacrimal gland

Contacts.
Medications (antihistamines, clonidine, beta-blockers, ibuprofen, scopolamine).
Keratoconjunctivitis sicca.
Trauma.
Environmental causes (air conditioning in patient with contacts).

DYSLIPOPROTEINEMIAS, SECONDARY CAUSES[4a]

ICD-9CM # 272.4
ICD-10CM # E78.4 Other hyperlipidemia

Cause	Disorder
Metabolic	Diabetes
	Lipodystrophy
	Glycogen storage disorders
Renal	Chronic renal failure
	Glomerulonephritis with nephritic syndrome
Hepatic	Cirrhosis
	Biliary obstruction
	Porphyria
Hormonal	Estrogens
	Progesterones
	Growth hormone
	Thyroid disorders (hypothyroidism)
	Corticosteroids
Lifestyle	Physical inactivity
	Obesity
	Diet rich in fats, saturated fats
	Alcohol intake
	Smoking
Medications	Retinoic acid derivatives
	Glucocorticoids
	Exogenous estrogens
	Thiazide diuretics
	Beta-adrenergic blockers (non-selective)
	Testosterone and other anabolic steroids
	Immunosuppressive medications (cyclosporine)
	Antiviral medications (human immunodeficiency virus protease inhibitors)
	Antischizophrenic agents

DYSPAREUNIA[12]

ICD-9CM # 625.0 Dyspareunia
608.89 Dyspareunia, Male
302.76 Dyspareunia, Psychogenic

ICD-10CM # N94.1 Dyspareunia
N44.8 Other noninflammatory disorders of the testis
N50.8 Other specified disorders of male genital organs
N53.12 Painful ejaculation
F52.6 Dyspareunia not due to a substance or known physiological condition

INTROITAL

Vaginismus.
Intact or rigid hymen.
Clitoral problems.
Vulvovaginitis.
Vaginal atrophy: hypoestrogen.
Vulvar dystrophy.
Bartholin or Skene gland infection.
Inadequate lubrication.
Operative scarring.

MIDVAGINAL

Urethritis.
Trigonitis.
Cystitis.
Short vagina.
Operative scarring.
Inadequate lubrication.

DEEP

Endometriosis.
Pelvic infection.
Uterine retroversion.
Ovarian pathology.
GI.
Orthopedic.
Abnormal penile size or shape.

DYSPEPSIA AND PYROSIS, DIFFERENTIAL DIAGNOSIS DURING PREGNANCY[12d]

ICD-9CM # 536.8 Dyspepsia and other specified disorder of stomach
ICD-10CM # K30 Dyspepsia, atonic
F45.3 Dyspepsia, psychogenic

DIFFERENTIAL DIAGNOSIS OF DYSPEPSIA OR PYROSIS DURING PREGNANCY

Gastroesophageal reflux disease.
Peptic ulcer disease.
Nausea and vomiting of pregnancy.
Hyperemesis gravidarum.
Pancreatitis.
Biliary colic.
Acute cholecystitis.
Viral hepatitis.
Appendicitis.
Acute fatty liver of pregnancy (in late pregnancy).
Irritable bowel syndrome/nonulcer dyspepsia.

DYSPHAGIA

ICD-9CM # 787.2
ICD-10CM # R13.10 Dysphagia, unspecified

Esophageal obstruction: neoplasm, foreign body, achalasia, stricture, spasm, esophageal web, diverticulum, Schatzki's ring.
Peptic esophagitis with stricture, Barrett's stricture.
External esophageal compression: neoplasms (thyroid neoplasm, lymphoma, mediastinal tumors), thyroid enlargement, aortic aneurysm, vertebral spurs, aberrant right subclavian artery (dysphagia lusoria).
Hiatal hernia, GERD.
Oropharyngeal lesions: pharyngitis, glossitis, stomatitis, neoplasms.
Hysteria: globus hystericus.
Neurologic and/or neuromuscular disturbances: bulbar paralysis, myasthenia gravis, ALS, multiple sclerosis, Parkinsonism, CVA, diabetic neuropathy.
Toxins: poisoning, botulism, tetanus, postdiphtheritic dysphagia.
Systemic diseases: scleroderma, amyloidosis, dermatomyositis.
Candida and herpes esophagitis.
Presbyesophagus.

DYSPHAGIA, OROPHARYNGEAL[38]

ICD-9CM # 787.22
ICD-10CM # R13.12 Dysphagia, oropharyngeal phase

FUNCTIONAL DISORDERS

Central Nervous System
Stroke.
Head injury.
Parkinson's disease.
Motor neuron disease.
Multiple sclerosis.
Tumor.
Drugs (e.g., phenothiazines).
Malformations (e.g., syrinx, Arnold–Chiari).
Neural
Motor neuron disease.
Myasthenia gravis.
Radiotherapy.
Poliomyelitis.
Familial dysautonomia.
Muscle
Autoimmune myopathy (polymyositis, dermatomyositis, systemic lupus erythematosus).
Thyrotoxic myopathy.
Guillain-Barré motor neuropathy.
Muscular dystrophies.

STRUCTURAL DISORDERS

Head/neck surgery.
Stricture.
Radiotherapy.
Tumor.
Pharyngeal pouch.
Web.
Extrinsic (e.g., osteophytes).

MISCELLANEOUS

Xerostomia.

DYSPNEA

ICD-9CM #	786.00	
ICD-10CM #	R06.9	Unspecified abnormalities of breathing

Upper airway obstruction: trauma, neoplasm, epiglottitis, laryngeal edema, tongue retraction, laryngospasm, abductor paralysis of vocal cords, aspiration of foreign body.
Lower airway obstruction: neoplasm, COPD, asthma, aspiration of foreign body.
Pulmonary infection: pneumonia, abscess, empyema, TB, bronchiectasis.
Pulmonary hypertension.
Pulmonary embolism/infarction.
Parenchymal lung disease.
Pulmonary vascular congestion.
Cardiac disease: ASHD, valvular lesions, cardiac dysrhythmias, cardiomyopathy, pericardial effusion, cardiac shunts.
Space-occupying lesions: neoplasm, large hiatal hernia, pleural effusions.
Disease of chest wall: severe kyphoscoliosis, fractured ribs, sternal compression, morbid obesity.
Neurologic dysfunction: Guillain-Barré syndrome, botulism, polio, spinal cord injury.
Interstitial pulmonary disease: sarcoidosis, collagen vascular diseases, DIP, Hamman-Rich pneumonitis, etc.
Pneumoconioses: silicosis, berylliosis, etc.
Mesothelioma.
Pneumothorax, hemothorax, pleural effusion.
Inhalation of toxins.
Cholinergic drug intoxication.
Carcinoid syndrome.
Hematologic: anemia, polycythemia, hemoglobinopathies.
Thyrotoxicosis, myxedema.
Diaphragmatic compression caused by abdominal distention, subphrenic abscess, ascites.
Lung resection.
Metabolic abnormalities: uremia, hepatic coma, DKA.
Sepsis.
Atelectasis.
Psychoneurosis.
Diaphragmatic paralysis.
Pregnancy.

DYSURIA

ICD-9CM #	788.1	Dysuria
	306.53	Dysuria, Psychogenic
ICD-10CM #	R30.0	Dysuria
	R30.9	Painful micturition, unspecified

Urinary tract infection.
Estrogen deficiency (in postmenopausal female).
Vaginitis.
Genital infection (e.g., herpes, condyloma).
Interstitial cystitis.
Chemical irritation (e.g., deodorant aerosols, douches).
Meatal stenosis or stricture.
Reiter's syndrome.
Bladder neoplasm.
GI etiology (diverticulitis, Crohn's disease).
Impaired bladder or sphincter action.
Urethral carbuncle.
Chronic fibrosis posttrauma.
Radiation therapy.
Prostatitis.
Urethritis (gonococcal, *Chlamydia*).
Behçet's syndrome.
Stevens-Johnson syndrome.

EARACHE[33]

ICD-9CM #	388.70	Earache
	388.72	Ear Pain, Referred
ICD-10CM #	H92.09	Otalgia, unspecified ear

Otitis media.
Serous otitis media.
Eustachitis.
Otitis externa.
Otitic barotrauma.
Mastoiditis.
Foreign body.
Impacted cerumen.
Referred otalgia, as with TMJ dysfunction, dental problems, and tumors.

ECTOPIC ACTH SECRETION[14]

ICD-9CM #	255.0	
ICD-10CM #	E34.2	Ectopic hormone secretion, not elsewhere classified

Small cell carcinoma of lung.
Endocrine tumors of foregut origin.
- Thymic carcinoid.
- Islet cell tumor.
- Medullary carcinoid, thyroid.
- Bronchial carcinoid.

Pheochromocytoma.
Ovarian tumors.

EDEMA, CHILDREN[19]

ICD-9CM #	782.3	Edema NOS
ICD-10CM #	R60.0	Localized edema
	R60.1	Generalized edema
	R60.9	Edema, unspecified

CARDIOVASCULAR

Congestive heart failure.
Acute thrombi or emboli.
Vasculitis of many types.

RENAL

Nephrotic syndrome.
Glomerulonephritis of many types.
End-stage renal failure.

ENDOCRINE OR METABOLIC

Thyroid disease.
Starvation.
Hereditary angioedema.

IATROGENIC

Drugs (diuretics and steroids).
Water or salt overload.

HEMATOLOGIC

Hemolytic disease of the newborn.

GASTROINTESTINAL

Hepatic cirrhosis.
Protein-losing enteritis.
Lymphangiectasis.
Cystic fibrosis.
Celiac disease.
Enteritis of many types.

LYMPHATIC ABNORMALITIES

Congenital (gonadal dysgenesis).
Acquired.

EDEMA, GENERALIZED

ICD-9CM #	782.3	Edema NOS
ICD-10CM #	R60.0	Localized edema
	R60.1	Generalized edema
	R60.9	Edema, unspecified

Congestive heart failure (CHF).
Cirrhosis.
Nephrotic syndrome.
Pregnancy.
Idiopathic.
Acute nephritic syndrome.
Myxedema.
Medications (NSAIDs, estrogens, vasodilators).

EDEMA, LEG, UNILATERAL[26]

ICD-9CM #	782.3	
ICD-10CM #	R60.0	Localized edema
	R60.9	Edema, unspecified

WITH PAIN

DVT.
Postphlebitic syndrome.
Popliteal cyst rupture.
Gastrocnemius rupture.
Cellulitis.
Psoas or other abscess.

WITHOUT PAIN

DVT.
Postphlebitic syndrome.
Other venous insufficiency (after saphenous vein harvest, varicosities).
Lymphatic obstruction/lymphedema (carcinoma, lymphoma, sarcoidosis, filariasis, retroperitoneal fibrosis).

EDEMA OF LOWER EXTREMITIES

ICD-9CM #	782.3	
ICD-10CM #	R60.0	Localized edema
	R60.9	Edema, unspecified

CHF (right-sided).
Hepatic cirrhosis.
Nephrosis.
Myxedema.
Lymphedema.
Pregnancy.
Abdominal mass: neoplasm, cyst.
Venous compression from abdominal aneurysm.
Varicose veins.

Bilateral cellulitis.
Bilateral thrombophlebitis.
Vena cava thrombosis, venous thrombosis.
Retroperitoneal fibrosis.

EJECTION SOUND OR CLICK

ICD-9CM #	785.3	
ICD-10CM #	R01.2	Other cardiac sounds

Aortic regurgitation.
Aortic root dilatation.
Systemic hypertension.
Chronic pulmonary hypertension.
Tetralogy of Fallot.
Atrial septal defect.
Pulmonary valve stenosis.
Aortic aneurysm.

ELBOW PAIN

ICD-9CM #	719.42	
ICD-10CM #	M25.529	Pain in unspecified elbow

Trauma.
Infection.
Inflammatory arthritis.
Lateral or medial epicondylitis.
Entrapment neuropathy.
Olecranon bursitis.
Osteoarthritis.
Gout.
Cervical disease (referred pain).
Shoulder disease (referred pain).
Partial subluxation.
Synovial osteochondromatosis.
Loose body.

ELEVATED HEMIDIAPHRAGM

ICD-9CM #	519.4	Diaphragm Disorder
	519.4	Diaphragm Paralysis
	756.6	Diaphragm Eventration, Congenital
ICD-10CM #	J98.6	Disorders of diaphragm
	Q79.0	Congenital diaphragmatic hernia
	Q79.1	Other congenital malformations of diaphragm

Neoplasm (bronchogenic carcinoma, mediastinal neoplasm, intrahepatic lesion).
Substernal thyroid.
Infectious process (pneumonia, empyema, TB, subphrenic abscess, hepatic abscess).
Atelectasis.
Idiopathic.
Eventration.
Phrenic nerve dysfunction (myelitis, myotonia, herpes zoster).
Trauma to phrenic nerve or diaphragm (e.g., surgery).
Aortic aneurysm.
Intraabdominal mass.
Pulmonary infarction.
Pleurisy.
Radiation therapy.
Rib fracture.

EMBOLI, ARTERIAL[26]

ICD-9CM #	444.22	Embolism, Artery, Lower Extremity
	444.21	Embolism, Artery, Upper Extremity
ICD-10CM #	I74.3	Embolism and thrombosis of arteries of the lower extremities
	I74.2	Embolism and thrombosis of arteries of the upper extremities

Myocardial infarction with mural thrombi.
Atrial fibrillation.
Cardiomyopathies.
Prosthetic heart valves.
CHF.
Endocarditis.
Left ventricular aneurysm.
Left atrial myxoma.
Sick sinus syndrome.
Paradoxical embolus from venous thrombosis.
Aneurysms of large blood vessels.
Atheromatous ulcers of large blood vessels.

EMESIS, PEDIATRIC AGE[19]

ICD-9CM #	787.03	
ICD-10CM #	R11.10	Vomiting, unspecified
	R11.11	Vomiting without nausea
	R11.12	Projectile vomiting

INFANCY

Gastrointestinal Tract

Congenital:

Regurgitation—chalasia, gastroesophageal reflux.
Atresia—stenosis (tracheoesophageal fistula, prepyloric diaphragm, intestinal atresia).
Duplication.
Volvulus (errors in rotation and fixation, Meckel diverticulum).
Congenital bands.
Hirschsprung's disease.
Meconium ileus (cystic fibrosis), meconium plug.

Acquired:

Acute infectious gastroenteritis, food poisoning (staphylococcal, clostridial).
Pyloric stenosis.
Gastritis, duodenitis.
Intussusception.
Incarcerated hernia—inguinal, internal secondary to old adhesions.
Cow's milk protein intolerance, food allergy, eosinophilic gastroenteritis.
Disaccharidase deficiency.
Celiac disease—presents after introduction of gluten in diet; inherited risk.
Adynamic ileus—the mediator for many nongastrointestinal causes.
Neonatal necrotizing enterocolitis.
Chronic granulomatous disease with gastric outlet obstruction.

Nongastrointestinal Tract

Infectious—otitis, urinary tract infection, pneumonia, upper respiratory tract infection, sepsis, meningitis.
Metabolic—aminoaciduria and organic aciduria, galactosemia, fructosemia, adrenogenital syndrome, renal tubular acidosis, diabetic ketoacidosis, Reye's syndrome.
Central nervous system—trauma, tumor, infection, diencephalic syndrome, rumination, autonomic responses (pain, shock).
Medications—anticholinergics, aspirin, alcohol, idiosyncratic reaction (e.g., codeine).

CHILDHOOD

Gastrointestinal Tract

Peptic ulcer—vomiting is a common presentation in children younger than 6 yr old.
Trauma—duodenal hematoma, traumatic pancreatitis, perforated bowel.
Pancreatitis—mumps, trauma, cystic fibrosis, hyperparathyroidism, hyperlipidemia, organic acidemias.
Crohn's disease.
Idiopathic intestinal pseudoobstruction.
Superior mesenteric artery syndrome.

Nongastrointestinal Tract

Central nervous system—cyclic vomiting, migraine, anorexia nervosa, bulimia.

ENCEPHALOMYELITIS, NONVIRAL CAUSES[25b]

ICD-9CM #	varies with specific disorder	
ICD-10CM #	G04.81	Other encephalitis and encephalomyelitis

Subacute bacterial endocarditis.
Rocky Mountain spotted fever.
Typhus.
Ehrlichia.
Q fever.
Chlamydia.
Mycoplasma.
Legionella.
Brucellosis.
Listeria.
Whipple's disease.
Cat-scratch disease.
Syphilis (meningovascular).
Relapsing fever.
Lyme disease.
Leptospirosis.
Nocardia.
Actinomycosis.
Tuberculosis.
Cryptococcus.
Histoplasma.
Toxoplasma.
Plasmodium falciparum.
Trypanosomiasis.
Behçet's disease.
Vasculitis.
Carcinoma.
Drug reactions.

ENCEPHALOPATHY, HYPERTENSIVE[38b]

ICD-9CM #	293.9

Cerebral infarction.
Subarachnoid hemorrhage.
Intracerebral hemorrhage.
Subdural or epidural hematoma.
Brain tumor or other mass lesion.
Seizure disorder.
Central nervous system vasculitis.
Encephalitis/meningitis.
Drug ingestion.
Drug withdrawal.

ENCEPHALOPATHY, METABOLIC[36]

ICD-9CM #	291.2	Alcoholic Encephalopathy
	572.2	Hepatic Encephalopathy
	251.2	Hypoglycemic Encephalopathy
	349.82	Toxic Encephalopathy
	984.9	Lead Encephalopathy
	293.9	Encephalopathy
ICD-10CM #	F10.27	Alcohol dependence with alcohol-induced persisting dementia
	K72.90	Hepatic failure, unspecified without coma
	K72.91	Hepatic failure, unspecified with coma
	G92	Toxic encephalopathy
	T56.0X1A	Toxic effect of lead and its compounds, accidental (unintentional), initial encounter
	T56.0X2A	Toxic effect of lead and its compounds, intentional self-harm, initial encounter

Substrate deficiency: hypoxia/ischemia, carbon monoxide poisoning, hypoglycemia.
Cofactor deficiency: thiamine, vitamin B_{12}, pyridoxine (INH administration).
Electrolyte disorders: hyponatremia, hypercalcemia, carbon dioxide narcosis, dialysis, hypermagnesemia, disequilibrium syndrome.
Endocrinopathies: DKA, hyperosmolar coma, hypothyroidism, hyperadrenocorticism, hyperparathyroidism.
Endogenous toxins: liver disease, uremia, porphyria.
Exogenous toxins: drug overdose (sedative/hypnotics, ethanol, narcotics, salicylates, tricyclic antidepressants), drug withdrawal, toxicity of therapeutic medications, industrial toxins (e.g., organophosphates, heavy metals), sepsis.
Heat stroke.
Epilepsy (postictal).

ENTHESOPATHY

ICD-9CM #	code not available	
ICD-10CM #	M46.00	Spinal enthesopathy, site unspecified

Viremia or bacteremia.
Ankylosing spondylitis.
Psoriatic arthritis.
Drug-induced (quinolones, etretinate).
Reactive arthritis.
DISH.
Reiter's syndrome.

EOSINOPHILIA, DISEASE ASSOCIATIONS[25a]

ICD-9CM #	288.3	Eosinophilia
	518.3	Pulmonary eosinophilia
ICD-10CM #	D72.1	Eosinophilia
	NEC J82	Eosinophilia, pulmonary

DISEASES, SYNDROMES, AND CONDITIONS COMMONLY ASSOCIATED WITH PERIPHERAL BLOOD EOSINOPHILIA AND/OR TISSUE EOSINOPHILIA

Infectious Agents
Parasitic Infections
- Tropical eosinophilia
- Visceral larval migrans (VLM, toxocariasis)
- Helminth infections
- Filariasis (*Wuchereria bancrofti, Brugia malay*)
- Onchocerciasis
- Schistosomiasis
- Fascioliasis
- Paragonimiasis
- Strongyloidiasis
- Trichinosis
- Hookworm
- Ascariasis
- Echinococcosis/hydatid disease

Fungal Infections
- Coccidioidomycosis
- Cryptococcosis (CSF eosinophilia) in HIV

Allergic Diseases
- Asthma (atopic and intrinsic, nasal polyps, aspirin intolerance syndromes)
- Bronchopulmonary aspergillosis
- Allergic rhinitis
- Urticarias (acute allergic and chronic idiopathic)
- Atopic dermatitis
- Acute drug (hypersensitivity) reactions (interstitial nephritis, cholestatic hepatitis, exfoliative dermatitis)

Respiratory Tract Disorders
- Hypersensitivity pneumonitis (rare)
- Allergic bronchopulmonary aspergillosis
- Eosinophilic pneumonia
- Transient pulmonary infiltrates (Löeffler syndrome)
- Prolonged pulmonary infiltrates with eosinophilia (PIE syndrome)
- Tropical pulmonary eosinophilia (TPE)
- Bronchiectasis
- Cystic fibrosis

Endocrinologic Disorders
Addison disease
Gastrointestinal Diseases
- Inflammatory bowel disease (IBD)
- Eosinophilic gastroenteritis, eosinophilic esophagitis (EE)
- Allergic gastroenteritis (young children)
- Celiac disease (when associated with EE)

Toxic Reactions to Ingested Agents
- Eosinophil myalgia syndrome (L-tryptophan)
- Toxic oil syndrome

Reactions to Cytokine Therapies
- IL-2 and IL-2 plus lymphokine activated killer (LAK) cells
- GM-CSF therapy

Cutaneous Disorders
- Atopic dermatitis
- Immunologic skin diseases
- Scabies
- Myiasis
- Chlamydial pneumonia of infancy
- Scarlet fever and pneumococcal pneumonia (convalescent phase)
- Cat scratch disease
- Eosinophilic cellulitis (Wells syndrome)
- Episodic angioedema with eosinophilia
- Chronic idiopathic urticaria
- Bullous pemphigoid
- Herpes gestationis
- Angioblastic lymphoid hyperplasia (Kimura disease)

Immunodeficiency Syndromes
- Wiskott-Aldrich syndrome
- Selective IgA deficiency with atopy
- Hyper-IgE recurrent infection syndrome (Job syndrome)
- Swiss-type and sex-linked combined immunodeficiency
- Nezelof syndrome
- Graft-versus-host-disease (GVHD)

Connective Tissue Diseases
Vasculitis/Collagen Vascular Disorders
- Hypersensitivity vasculitis
- Allergic granulomatosis with angiitis (Churg-Strauss syndrome)
- Serum sickness
- Eosinophilic fasciitis
- Sjögren syndrome
- Rheumatoid arthritis (severe)

Neoplastic, Myeloproliferative, and Ly Neoplasms and Syndromes
Neoplastic
- Ovarian carcinoma
- Solid tumors (mucin-secreting, epithelial cell origin)

Chronic eosinophil leukemia
Idiopathic hypereosinophilic syndromes (HES)
Systemic mastocytosis
Myeloproliferative
- Chronic myelogenous leukemia (CML) acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS)
- Myelomonocytic leukemia with bone marrow eosinophilia (M4Eo, inversion 16)

Lymphoproliferative
- T-cell lymphocytic leukemia
- Lymphomas (T cell, Hodgkin disease)
- Angioimmunoblastic lymphadenopathy

Rare Causes
Chronic active hepatitis
Chronic dialysis
Acute pancreatitis
Postirradiation
Hypopituitarism

EOSINOPHILIC LUNG DISEASE[16a]

ICD-9CM # 518.3
ICD-10CM # NEC J82 Eosinophilia, pulmonary

IDIOPATHIC
Simple pulmonary eosinophilia (Löffler's syndrome).
Acute eosinophilic pneumonia.
Chronic eosinophilic pneumonia.
Hypereosinophilic syndrome.

DRUG-INDUCED
Aminosalicylic acid.
Para-arminosalicylic acid.
NSAIDs.
Captopril.
Cocaine.
Minocycline.
Nitrofurantoin.
Phenytoin.

INFECTION
Parasitic (ascariasis, paragonimiasis. tropical eosinophilia).
Fungal (aspergillus).
Bacterial (TB, atypical mycobacterial infection, brucella).
Viral (respiratory syncytial virus).

IMMUNOLOGIC DISEASES
Wegener's granulomatosis.
Churg–Strauss syndrome.
Rheumatoid disease.
Sarcoidosis.

NEOPLASMS
Bronchogenic carcinoma.
Bronchial carcinoid.
Lymphoma (Hodgkin's, non-Hodgkin's).

EPIGASTRIC PAIN[38]

ICD-9CM # 789.66
ICD-10CM # R10.816 Epigastric abdominal tenderness
R10.826 Epigastric rebound abdominal tenderness

Peptic ulceration (uncomplicated).*
Peptic ulceration (perforated).*
Biliary colic.*
Acute pancreatitis.*
Abdominal aortic aneurysm.
Anxiety.
Inferior wall MI.

*Conditions that also cause right upper quadrant pain

EPILEPSY

ICD-9CM # 345.9 Epilepsy NOS
ICD-10CM # G40.909 Epilepsy, unspecified, not intractable, without status epilepticus

Psychogenic spells.
Transient ischemic attack.
Hypoglycemia.
Syncope.
Narcolepsy.
Migraine.
Paroxysmal vertigo.
Arrhythmias.
Drug reaction.

EPISTAXIS

ICD-9CM # 784.7
ICD-10CM # R04.0 Epistaxis

Trauma.
Medications (nasal sprays, NSAIDs, anticoagulants, antiplatelets).
Nasal polyps.
Cocaine use.
Coagulopathy (hemophilia, liver disease, DIC, thrombocytopenia).
Systemic disorders (hypertension, uremia).
Infections.
Anatomic malformations.
Rhinitis.
Nasal polyps.
Local neoplasms (benign and malignant).
Desiccation.
Foreign body.

ERECTILE DYSFUNCTION, ORGANIC[31]

ICD-9CM # 607.84
ICD-10CM # N52.9 Male erectile dysfunction, unspecified

Neurogenic abnormalities: Somatic nerve neuropathy, central nervous system abnormalities.
Psychogenic causes: Depression, performance anxiety, marital conflict.
Endocrine causes: Hyperprolactinemia, hypogonadotropic hypogonadism, testicular failure, estrogen excess.
Trauma: Pelvic fracture, prostate surgery, penile fracture.
Systemic disease: DM, renal failure, hepatic cirrhosis.
Medications: Diuretics, antidepressants, H_2 blockers, exogenous hormones, alcohol, antihypertensives, nicotine abuse, finasteride, etc.
Structural abnormalities: Peyronie's disease.

EROSIONS, GENITALIA

ICD-9CM # 599.84
ICD-10CM # N36.8 Other specified disorders of urethra

Candidiasis.
Intraepithelial neoplasia.
Squamous cell carcinoma.
Lichen planus.
Pemphigus vulgaris.
Erythema multiforme.
Lichen sclerosus.
Bullous pemphigoid.
Extramammary Paget's disease.
Impetigo.

ERYTHEMATOUS ANNULAR SKIN LESIONS

ICD-9CM # varies with diagnosis
ICD-10CM # L53.8 Other specified erythematous conditions

Tinea corporis.
Warfarin plaques.
Erythema multiforme.
Erythema annulare.
Cutaneous lupus.
Cutaneous sarcoidosis.
Trauma.
Acute febrile neutrophilic dermatosis (Sweet's syndrome).

ERYTHROCYTOSIS[20]

ICD-9CM # 289.6
ICD-10CM # D75.0 Familial erythrocytosis

CAUSES OF ERYTHROCYTOSIS

Relative or Spurious Erythrocytosis (Normal Red Cell Mass)
Hemoconcentration secondary to dehydration (diarrhea, diaphoresis, diuretics, water deprivation, emesis, ethanol, hypertension, preeclampsia, pheochromocytoma, carbon monoxide intoxication).

True or Absolute Erythrocytosis
Polycythemia vera.
Primary congenital polycythemia.
Secondary erythrocytosis caused by:
Congenital causes (e.g., activating mutation of erythropoietin receptor).
Hypoxia caused by carbon monoxide poisoning, high oxygen affinity hemoglobin, high-altitude residence, chronic pulmonary disease, hypoventilation syndromes such as sleep apnea, right to left cardiac shunt, neurologic defects involving the respiratory center.
Nonhypoxic causes with pathologic erythropoietin production.
- Renal disease (cysts, hydronephrosis, renal artery stenosis, focal glomerulonephritis, renal transplantation).
- Tumors (renal cell cancer, hepatocellular carcinoma, cerebellar hemangioblastoma, uterine fibromyoma, adrenal tumors, meningioma, pheochromocytoma).

Drug-associated causes:
- Androgen therapy.
- Exogenous erythropoietin growth factor therapy.

ERYTHRODERMA

ICD-9CM #	695.9	Secondary
	696.2	Maculopapular
	696.1	Psoriaticum
	695.89	Exfoliative
	778.8	Neonatorum
ICD-10CM #	L53.9	Erythematous condition, unspecified

Drug reaction (e.g., allopurinol, ampicillin, phenytoin, vancomycin, dapsone, omeprazole, carbamazepine).
Atopic dermatitis.
Psoriasis.
Contact dermatitis.
Idiopathic.
Pityriasis rubra.
Chronic actinic dermatitis.
Bullous pemphigoid.
Paraneoplastic.
Cutaneous T-cell lymphoma.
Connective tissue disease.
Hypereosinophilia syndrome.

ESOPHAGEAL PERFORATION[26]

ICD-9CM #	530.4	Perforation, Nontraumatic
	862.22	Injury, Traumatic
ICD-10CM #	K22.3	Perforation of esophagus
	S27.819A	Unspecified injury of esophagus (thoracic part), initial encounter

Trauma.
Caustic burns.
Iatrogenic.
Foreign bodies.
Spontaneous rupture (Boerhaave's syndrome).
Postoperative breakdown of anastomosis.

ESOPHAGITIS[25b]

ICD-9CM #	530.12	
ICD-10CM #	K20.9	Esophagitis, unspecified

INFECTIOUS

Candidiasis.
Cytomegalovirus.
Herpes simplex virus.
HIV infection, acute.

NONINFECTIOUS

Gastroesophageal reflux.
Mucositis from cancer chemotherapy.
Mucositis from radiation therapy.
Aphthous ulcers.

ESOTROPIA

ICD-9CM #	378.00	Nonaccommodative
	378.35	Accommodative
	378.05	Alternating
ICD-10CM #	H50.00	Unspecified esotropia
	H50.43	Accommodative component in esotropia
	H50.05	Alternating esotropia

Congenital.
Accommodative esotropia.
Myasthenia gravis.
Abducens palsy.
Pseudo-sixth nerve palsy.
Medial rectus entrapment (e.g., blowout fracture).
Posterior internuclear ophthalmoplegia.
Wernicke's encephalopathy.
Thyroid myopathy.
Chiari malformation.

EXANTHEMS[28]

ICD-9CM #	782.1	
ICD-10CM #	R21	Rash and other nonspecific skin eruption

Measles.
Rubella.
Erythema infectiosum (fifth disease).
Roseola exanthema.
Varicella.
Enterovirus.
Adenovirus.
Epstein-Barr virus.
Kawasaki disease.
Staphylococcal scalded skin.
Scarlet fever.
Meningococcemia.
Rocky Mountain spotted fever.

EYELID NEOPLASM

ICD-9CM #	varies with specific disorder	
ICD-10CM #	C44.101	Unspecified malignant neoplasm of skin of unspecified eyelid, including canthus

MALIGNANT

Melanoma.
Basal cell carcinoma.
Squamous cell carcinoma.
Bowen's disease.
Sebaceous cell carcinoma.
Metastatic lymphoma/leukemia.

BENIGN

Melanocytic nevus.
Pilar, eccrine, or apocrine tumor.
Neurofibroma.
Keratosis.
Squamous papilloma.
Keratoacanthoma.

EYELID RETRACTION

ICD-9CM #	374.89	
ICD-10CM #	H02.89	Other specified disorders of eyelid

Congenital.
Graves' ophthalmopathy.
Myasthenia gravis.
Postsurgical.
Guillain-Barré syndrome.
Cerebellar disease.
Horizontal gaze palsy.
Partial palsy of superior rectus muscle.
Encephalitis.
Closed head injury.
Disseminated sclerosis.
Eye trauma.
Contact lens wear.
Proptosis.
Eyelid neoplasm.
Atopic dermatitis.
Herpes zoster ophthalmicus.
Botulinum toxin injection.
Cyclic oculomotor paralysis.
Spheroid wing meningioma.
Hepatic cirrhosis.
Down syndrome.
Essential hypertension.
Meningitis.
Paget's disease of bone.

EYE PAIN

ICD-9CM #	379.91	
ICD-10CM #	H57.13	Ocular pain, bilateral

Foreign body.
Herpes zoster.
Trauma.
Conjunctivitis.
Iritis.
Iridocyclitis.
Uveitis.
Blepharitis.
Ingrown lashes.
Orbital or periorbital cellulitis/abscess.
Sinusitis.
Headache.
Glaucoma.
Inflammation of lacrimal gland.
Tic douloureux.
Cerebral aneurysm.
Cerebral neoplasm.
Entropion.
Retrobulbar neuritis.
UV light.
Dry ey-88 ptes.
Irritation or inflammation from eye drops, dust, cosmetics, etc.

FACIAL PAIN

ICD-9CM #	784.0	
ICD-10CM #	G50.1	Atypical facial pain

Infection, abscess.
Postherpetic neuralgia.
Trauma, posttraumatic neuralgia.
Tic douloureux.
Cluster headache, "lower-half headache."
Geniculate neuralgia.
Anxiety, somatization syndrome.
Glossopharyngeal neuralgia.
Carotidynia.

FACIAL PARALYSIS[28]

ICD-9CM #	351.0	Facial (7th Nerve) Palsy
ICD-10CM #	G51.0	Bell's palsy

INFECTION

Bacterial: otitis media, mastoiditis, meningitis, Lyme disease.
Viral: herpes zoster, mononucleosis, varicella, rubella, mumps, Bell's palsy.
Mycobacterial: TB, meningitis, leprosy.
Miscellaneous: syphilis, malaria.

TRAUMA

Temporal bone fracture, facial laceration.
Surgery.

NEOPLASM

Malignant: squamous cell carcinoma, basal cell and adenocystic tumors, leukemia, parotid neoplasms, metastatic tumors.
Benign: facial nerve neuroma, vestibular schwannoma, congenital cholesteatoma.

IMMUNOLOGIC

Guillain-Barré syndrome, periarteritis nodosa.
Reaction to tetanus antiserum.

METABOLIC

Pregnancy.
Hypothyroidism.
DM.

FAILURE TO THRIVE

ICD-9CM #	783.4	
ICD-10CM #	R62.50	Unspecified lack of expected normal physiological development in childhood

PSYCHOSOCIAL/BEHAVIORAL

Inadequate diet because of poverty/food insufficiency, errors in food preparation.
Poor parenting skills (lack of knowledge of sufficient diet).
Child/parent interaction problems (autonomy struggles, coercive feeding, maternal depression).
Food refusal.
Rumination.
Parental cognitive or mental health problems.
Child abuse or neglect; emotional deprivation.

NEUROLOGIC

Cerebral palsy.
Hypothalamic and other CNS tumors (diencephalic syndrome).
Neuromuscular disorders.
Neurodegenerative disorders.

RENAL

Recurrent urinary tract infection.
Renal tubular acidosis.
Renal failure.

ENDOCRINE

Diabetes mellitus.
Diabetes insipidus.
Hypothyroidism/hyperthyroidism.
Growth hormone deficiency.
Adrenal insufficiency.

GENETIC/METABOLIC/CONGENITAL

Sickle cell disease.
Inborn errors of metabolism (organic acidosis, hyperammonemia, storage disease).
Fetal alcohol syndrome.
Skeletal dysplasias.
Chromosomal disorders.
Multiple congenital anomaly syndromes (VATER [vertebral defects, imperforate anus, tracheoesophageal fistula, radial and renal dysplasia], CHARGE [coloboma, heart disease, atresia choanae, retarded growth and retarded development and/or central nervous system anomalies, genital hypoplasia, ear anomalies and/or deafness]).

GASTROINTESTINAL

Pyloric stenosis.
Gastroesophageal reflux.
Repair of tracheoesophageal fistula.
Malrotation.
Malabsorption syndromes.
Celiac disease.
Milk intolerance: lactose, protein.
Pancreatic insufficiency syndromes (cystic fibrosis).
Chronic cholestasis.
Inflammatory bowel disease.
Chronic congenital diarrhea states.
Short bowel syndrome.
Pseudoobstruction.
Hirschsprung disease.
Food allergy.

CARDIAC

Cyanotic heart lesions.
Congestive heart failure.
Vascular rings.

PULMONARY/RESPIRATORY

Severe asthma.
Cystic fibrosis; bronchiectasis.
Chronic respiratory failure.
Bronchopulmonary dysplasia.
Adenoid/tonsillar hypertrophy.
Obstructive sleep apnea.

MISCELLANEOUS

Collagen vascular disease.
Malignancy.
Primary immunodeficiency.
Transplantation.

INFECTIONS

Perinatal infection (TORCHES [toxoplasma, other, rubella, cytomegalovirus, herpes simplex]).
Occult/chronic infections.
Parasitic infestation.
Tuberculosis.
HIV.

FATIGUE

ICD-9CM #	780.7	Fatigue NOS
	300.5	Fatigue Psychogenic
	780.7	Chronic Fatigue Syndrome
ICD-10CM #	R53.83	Other fatigue
	F48.0	Neurasthenia

Depression.
Anxiety, emotional stress.
Inadequate sleep.
Chronic fatigue syndrome.
Prolonged physical activity.
Pregnancy and postpartum period.
Anemia.
Hypothyroidism.
Medications (β-blockers, anxiolytics, antidepressants, sedating antihistamines, clonidine, methyldopa).
Viral or bacterial infections.
Sleep apnea syndrome.
Dieting.
Renal failure, CHF, COPD, liver disease.

FATIGUE, CHRONIC

ICD-9CM #	780.7	
ICD-10CM #	R53.83	Other fatigue
	F48.0	Neurasthenia

CHRONIC INFECTIONS

Hepatitis C.
Lyme disease.
Parasitic and fungal infections.
Tuberculosis.
Human immunodeficiency virus.
Xenotropic murine leukemia retrovirus.

SLEEP DISORDERS

Obstructive sleep apnea.
Restless leg syndrome.
Circadian rhythm disorder.
Upper airway resistance syndrome.
Narcolepsy/parasomnias.
Alpha-delta sleep disorder.

ENDOCRINE/METABOLIC DISORDERS

Addison's disease.
Cushing's syndrome.
Poorly controlled diabetes.
Thyroid disorders.
Hemochromatosis.
Hypopituitarism.
Diabetes insipidus.

GENERAL MEDICAL DISORDERS

Anemia (any cause).
Chronic renal/hepatic failure.
Malnutrition.
Medication side effects.
Chronic pain disorders.

PSYCHOLOGICAL

Mood disorders (depression, anxiety, bipolar).
Schizophrenia.
Posttraumatic stress disorder.
Anorexia nervosa/bulimia.
Childhood abuse and/or neglect.

CHRONIC INFLAMMATION
Rheumatoid arthritis.
Systemic lupus erythematosus.
Sjögren's syndrome.
Polymyositis/dermatomyositis.
Vasculitis.
Sarcoidosis.

CARDIOPULMONARY
Congestive heart failure.
Neurally mediated hypotension.
Postural orthostatic tachycardia syndrome.
Pulmonary hypertension.
Chronic obstructive pulmonary disease.
Mitral valve prolapse.

GASTROINTESTINAL
Celiac disease.
Inflammatory bowel disease.
Autoimmune hepatitis.
Hepatic cirrhosis.

MALIGNANCY
Lymphoma and occult malignancies.
Postchemotherapy syndrome.

NEUROLOGIC DISORDERS
Multiple sclerosis.
Myasthenia gravis.
Muscular dystrophies.
Parkinson's disease.
Early dementia.

LIFESTYLE FACTORS
Chronic overwork.
Persistent unresolved stress.
Inadequate exercise.
Morbid obesity (body mass index >40).
Alcoholism/drug abuse.

FATTY LIVER

ICD-9CM #	571.8	
ICD-10CM #	K76.0	Fatty (change of) liver, not elsewhere classified
	K76.89	Other specified diseases of liver

Obesity.
Alcohol abuse.
DM.
Acute fatty liver of pregnancy.
Medications (tetracycline, valproic acid, glucocorticoids, amiodarone, estrogen, methotrexate).
Reye's syndrome.
Wilson's disease.
Nonalcoholic steatosis.

FEVER AND JAUNDICE

ICD-9CM #	789.6	Fever
	782.4	Jaundice
ICD-10CM #	R50.9	Fever, unspecified
	R17	Unspecified jaundice

Bacterial sepsis.
Cholangitis.
Hepatic abscess.
Leptospirosis.
Malaria.
Viral hepatitis.
Yellow fever.

FEVER AND LYMPHADENOPATHY

ICD-9CM # 780.60

Regional
Cervical
Streptococci.
Tuberculosis.
Viral upper respiratory infection.
Peripheral
Bartonella henselae.
Herpesviruses.
Lymphoma.
Metastatic cancer.
Sporotrichosis.
Streptococci.
Inguinal
Chancroid.
Herpes.
Lymphogranuloma venereum.
Syphilis (primary).
GENERALIZED
Cytomegalovirus.
Epstein-Barr virus.
HIV.
Lymphoma.
Sarcoidosis.
Syphilis (secondary).
Toxoplasmosis.
Viral hepatitis.

FEVER AND RASH

ICD-9CM #	782.1	Exanthem
	57.9	Exanthem, Viral
	789.6	Fever
ICD-10CM #	R21	Rash and other nonspecific skin eruption
	R21	Rash and other nonspecific skin eruption
	R50.9	Fever, unspecified

Drug hypersensitivity: penicillin, sulfonamides, thiazides, anticonvulsants, allopurinol.
Viral infection: measles, rubella, varicella, erythema infectiosum, roseola, enterovirus infection, viral hepatitis, infectious mononucleosis, acute HIV.
Other infections: meningococcemia, staphylococcemia, scarlet fever, typhoid fever, *Pseudomonas* bacteremia, Rocky Mountain spotted fever, Lyme disease, secondary syphilis, bacterial endocarditis, babesiosis, brucellosis, listeriosis.
Serum sickness.
Erythema multiforme.
Erythema marginatum.
Erythema nodosum.
SLE.
Dermatomyositis.
Allergic vasculitis.
Pityriasis rosea.
Herpes zoster.

FEVER AND RASH IN ICU[38]

ICD-9CM #	782.1	Exanthem
	789.6	Fever
ICD-10CM #	R21	Rash and other nonspecific skin eruption
	R50.9	Fever, unspecified

DIFFERENTIAL DIAGNOSTIC CLINICAL FEATURES OF FEVER AND RASH IN THE ICU

Rash with Shock
Infectious causes: toxic shock syndrome, meningococcemia, postsplenectomy sepsis, overwhelming *Staphylococcus aureus* bacteremia/acute bacterial endocarditis, arboviral hemorrhagic fevers, hemorrhagic smallpox, *Vibrio vulnificus,* gas gangrene, dengue fever.
Noninfectious cause: systemic lupus erythematosus (on steroids).

Rash with Mental Changes
Infectious causes: Rocky Mountain spotted fever, meningococcemia (with meningitis), *S. aureus* acute bacterial endocarditis, Chikungunya fever, typhus.
Noninfectious cause: systemic lupus erythematosus.

Rash with Conjunctival Suffusion
Infectious causes: Rocky Mountain spotted fever, dengue fever, arboviral hemorrhagic fevers, toxic shock syndrome.
Noninfectious cause: adult Kawasaki's disease.

Rash with Relative Bradycardia
Infectious causes: Rocky Mountain spotted fever, typhus, dengue fever, typhoid, arboviral hemorrhagic fevers.
Noninfectious cause: drug rash.

Rash with Abdominal Pain
Infectious causes: *V. vulnificus,* gas gangrene, *Clostridium sordelli,* scarlet fever.
Noninfectious causes: cholesterol emboli syndrome, systemic lupus erythematosus.

Rash on Palms and Soles
Infectious causes: Rocky Mountain spotted fever, toxic shock syndrome, chickenpox, smallpox, monkeypox, scarlet fever.
Noninfectious cause: drug rash.

Rash with Diarrhea
Infectious causes: *V. vulnificus,* gas gangrene, toxic shock syndrome, dengue fever, arboviral hemorrhagic fevers.
Noninfectious cause: none.

Rash with Edema of Dorsum of Hands/Feet
Infectious causes: Rocky Mountain spotted fever, toxic shock syndrome.
Noninfectious cause: adult Kawasaki's disease.

Rash with Bullae
Infectious causes: *V. vulnificus, S. aureus* complicated skin/skin structure infection, gas gangrene.
Noninfectious cause: none.

Rash with Heart Murmur
Infectious cause: acute bacterial endocarditis.

Noninfectious cause: systemic lupus erythematosus.
Rash with gangrene of nose tip
Infectious cause: *S. aureus* acute bacterial endocarditis.
Noninfectious causes: systemic lupus erythematosus, vasculitis.
Rash with Cerebrovascular Accident
Infectious causes: cholesterol emboli syndrome, *S. aureus* acute bacterial endocarditis.
Noninfectious cause: none.
Rash with Splenomegaly
Infectious causes: Rocky Mountain spotted fever, typhus.
Noninfectious causes: systemic lupus erythematosus, adult Kawasaki's disease.
Rash with Deafness
Infectious causes: Rocky Mountain spotted fever, typhus, meningococcal meningitis.
Noninfectious cause: none.
Rash with Hepatosplenomegaly
Infectious causes: Rocky Mountain spotted fever, typhus.
Noninfectious cause: atypical measles.
Rash with Hepatomegaly
Infectious cause: typhus.
Noninfectious cause: none.

FEVER, AFTER TRAVEL TO THE TROPICS[1a]

ICD-9CM #	789.6	
ICD-10CM #	R50.81	Fever presenting with conditions classified elsewhere

CAUSES OF FEVER AFTER TRAVEL TO THE TROPICS

80% of Specific Infections Causing Fever (Includes Respiratory and Urinary Tract Infection)
Malaria.
Viral hepatitis.
Febrile illness unrelated to foreign travel.
Dengue fever.
Enteric fever (typhoid and paratyphoid fevers).
Other Causes
Gastroenteritis.
Rickettsia.
Leptospirosis.
Schistosomiasis.
Amebic liver abscess.
Tuberculosis.
Acute HIV infection.
Others.

FEVER, DRUG-INDUCED[14a]

ICD-9CM #	789.6

SELECTED AGENTS ASSOCIATED WITH DRUG-INDUCED FEVER

Common
Antimicrobial:
- Amphotericin B.
- β-Lactams.
- Sulfonamides.

Cardiovascular:
- Procainamide.
- Quinidine.

Central nervous system:
- Carbamazepine.
- Phenytoin.

Miscellaneous:
- Bleomycin.
- Interferon-α.
- Interleukin-2.

Less Common
Antimicrobial:
- Clindamycin.
- Fluoroquinolones.
- Rifampin.

Cardiovascular:
- Diltiazem.
- Hydralazine.

Central nervous system:
- Haloperidol.
- Serotonin reuptake inhibitors.

Miscellaneous:
- Allopurinol.
- Cimetidine.
- Tacrolimus.

FEVER, HOSPITAL ASSOCIATED[14a]

ICD-9CM #	780.60	Fever
ICD-10CM #	R50.2	Drug induced fever
	R50.9	Fever, unspecified

SELECTED CAUSES OF HOSPITAL-ASSOCIATED FEVER

Common
Infectious:
- *Clostridium difficile* enterocolitis.
- Pneumonia.
- Surgical wound.
- Urinary tract.
- Vascular catheter.

Noninfectious:
- Drug-induced fever.
- Hematoma.
- Immediate postoperative state.
- Transfusion reaction.
- Venous thromboembolism.

Less Common
Infectious:
- Biliary tract disease.
- Endometritis.
- Intraabdominal abscess.
- Mediastinitis.
- Sinusitis.

Noninfectious:
- Adrenal insufficiency.
- Gout.
- Myocardial infarction.
- Organ infarction.
- Pancreatitis.

FEVER IN RETURNING TRAVELERS AND IMMIGRANTS[28]

ICD-9CM #	varies with specific disorder	
ICD-10CM #	R50.81	Fever presenting with conditions classified elsewhere

Differential Diagnosis of some selected systemic febrile illnesses to consider in returned travelers and immigrants.*

COMMON

Acute respiratory tract infection (worldwide).
Gastroenteritis (worldwide) [foodborne, waterborne, fecal-oral].
Enteric fever, including typhoid (worldwide) [food, water].
Urinary tract infection (worldwide) [sexual contact].
Drug reactions [antibiotics, prophylactic agents, other] {rash frequent}.
Malaria (tropics, limited areas of temperate zones) [mosquitoes].
Arboviruses (Africa; tropics) [mosquitoes, ticks, mites].
Dengue (Asia, Caribbean, Africa) [mosquitoes].
Viral hepatitis (worldwide).
Hepatitis A (worldwide) [food, fecal-oral].
Hepatitis B (worldwide, especially Asia, sub-Saharan Africa) [sexual contact] {long incubation period}.
Hepatitis C (worldwide) [blood or sexual contact].
Hepatitis E (Asia, North Africa, Mexico, others) [food, water].
Tuberculosis (worldwide) [airborne, milk] {long period to symptomatic infection}.
Sexually transmitted diseases (worldwide) [sexual contact].

LESS COMMON

Filariasis (Asia, Africa, South America) [biting insects] {long incubation period, eosinophilia}.
Measles (developing world) [airborne] {in susceptible individual}.
Amebic abscess (worldwide) [food].
Brucellosis (worldwide) [milk, cheese, food, animal contact].
Listeriosis (worldwide) [foodborne] {meningitis}.
Leptospirosis (worldwide) [animal contact, open fresh water] {jaundice, meningitis}.
Strongyloidiasis (warm and tropical areas) [soil contact] {eosinophilia}.
Toxoplasmosis (worldwide) [undercooked meat].

RARE

Relapsing fever (western Americas, Asia, northern Africa) [ticks, lice].
Hemorrhagic fevers (worldwide) [arthropod and nonarthropod transmitted].
Yellow fever (tropics) [mosquitoes] {hepatitis}.
Hemorrhagic fever with renal syndrome (Europe, Asia, North America) [rodent urine] {renal impairment}.
Hantavirus pulmonary syndrome (western North America, other) [rodent urine] {respiratory distress syndrome}.
Lassa fever (Africa) [rodent excreta, person to person] {high mortality rate}
Other—chikungunya, Rift Valley, Ebola-Marburg, etc. (various) [insect bites, rodent excreta, aerosols, person to person] {often severe}.
Rickettsial infections {rashes and eschars}.
Leishmaniasis, visceral (Middle East, Mediterranean, Africa, Asia, South America) [biting flies] {long incubation period}.
Acute schistosomiasis (Africa, Asia, South America, Caribbean) [fresh water].

Chagas' disease (South and Central America) [reduviid bug bites] {often asymptomatic}.
African trypanosomiasis (Africa) [tsetse fly bite] {neurologic syndromes, sleeping sickness}.
Bartonellosis (South America) [sandfly bite] {skin nodules}.
HIV infection/AIDS (worldwide) [sexual and blood contact].
Trichinosis (worldwide) [undercooked meat] {eosinophilia}.
Plague (temperate and tropical plains) [animal exposures and fleas].
Tularemia (worldwide) [animal contact, fleas, aerosols] {ulcers, lymph nodes}.
Anthrax (worldwide) [animal, animal product contact] {ulcers}.
Lyme disease (North America, Europe) [tick bites] {arthritis, meningitis, cardiac abnormalities}.

*Diagnoses for which particular symptoms are indicative are in *italics*. Exposure to regions of the world that are most likely to be significant to the diagnosis are presented in (parentheses). Vectors, risk behaviors, and sources associated with acquisition are presented in [brackets]. Special clinical characteristics are listed within {braces}.

FEVER, NONINFECTIOUS CAUSES[2]

ICD-9CM # 780.60
ICD-10CM # R50.9 Fever, unspecified

DIFFERENTIAL DIAGNOSIS—NONINFECTIOUS CAUSES OF FEVER

Critical Diagnoses
Acute myocardial infarction.
Pulmonary embolism/infarction.
Intracranial hemorrhage.
Cerebrovascular accident.
Neuroleptic-malignant syndrome.
Thyroid storm.
Acute adrenal insufficiency.
Transfusion reaction.
Pulmonary edema.
Emergent Diagnoses
Congestive heart failure.
Dehydration.
Recent seizure.
Sickle cell disease.
Transplant rejection.
Pancreatitis.
Deep vein thrombosis.
Nonemergent Diagnoses
Drug fever.
Malignancy.
Gout.
Sarcoidosis.
Crohn's disease.
Postmyocardiotomy syndrome.

FEVER, POSTPARTUM[1]

ICD-9CM # 780.60
ICD-10CM # R50.9 Fever, unspecified

MOST COMMON

Metritis.
Urinary tract infection.
Pneumonia.
Wound infection.
Mastitis.
Superficial or deep vein thrombosis.

MOST THREATENING

Toxic shock syndrome.
Necrotizing fasciitis.
Pelvic phlegmon.
Pelvic abscess.
Peritonitis.
Septic pelvic thrombosis.
Breast abscess.

FEVER, PERIODIC[12c]

ICD-9CM # 780.60
ICD-10CM # R50.9 Fever, unspecified

HEREDITARY

NONHEREDITARY

Infectious
Hidden infectious focus (e.g., aortoenteric fistula, Caroli's disease).
Recurrent reinfection (e.g., chronic meningococcemia, host defense defect).
Specific infection (e.g., Whipple's disease, malaria).
Noninfectious inflammatory disorder, e.g.:
Adult-onset Still's disease.
Juvenile chronic rheumatoid arthritis.
Periodic fever, aphthous stomatitis, pharyngitis, and adenitis.
Schnitzler syndrome.
Behçet's syndrome.
Crohn's disease.
Sarcoidosis.
Extrinsic alveolitis.
Humidifier lung, polymer fume fever.
Neoplastic.
Lymphoma (e.g., Hodgkin's disease, angioimmunoblastic lymphoma).
Solid tumor (e.g., pheochromocytoma, myxoma, colon carcinoma).
Vascular (e.g., recurrent pulmonary embolism)
Hypothalamic
Psychogenic periodic fever.
Factitious or fraudulent.

FEVER, PEDIATRIC, ACUTE[1]

ICD-9CM # 780.60
ICD-10CM # R50.9 Fever, unspecified

COMMON VIRAL INFECTIONS

Central Nervous System
Meningitis.
Encephalitis.
Tumor.
Brain abscess.
Head, Ears, Eyes, Nose, and Throat
Otitis media.
Pharyngitis.
Retropharyngeal abscess.
Peritonsillar abscess.
Lateral pharyngeal wall abscess.
Stomatitis.
Influenza.
Sinusitis.
Parotitis.
Cervical adenitis.
Periorbital cellulitis.
Orbital cellulitis or abscess.
Respiratory System
Bronchiolitis.
Croup.
Epiglottitis.
Pneumonia.
Upper respiratory infection.
Cardiovascular System
Myocarditis.
Pericarditis.
Endocarditis.
Genitourinary System
Urinary tract infection.
Tuboovarian abscess.
Gastrointestinal Tract
Acute viral gastroenteritis.
Bacterial enteritis.
Appendicitis.
Focal Soft Tissue Infections
Cellulitis.
Musculoskeletal System
Osteomyelitis.
Septic arthritis.
Rheumatologic Disorders
Acute rheumatic fever.
Juvenile rheumatoid arthritis.
Henoch-Schönlein purpura.
Vasculitis
Behçet syndrome.
Malignancy
Leukemia.
Lymphoma.
Sarcoma.
Systemic Illness
Bacteremia.
Viremia.
Sepsis.
Kawasaki disease.
Toxic shock syndrome.
Rocky Mountain spotted fever.
Meningococcemia.

MISCELLANEOUS DISORDERS

Toxicologic
Anticholinergic toxidromes.
Salicylate overdose.
Amphetamine.
Cocaine.
Endocrine
Thyrotoxicosis.

FEVER, RECURRENT OR PERIODIC, IN CHILDREN[22a]

ICD-9CM # 780.60 Fever
ICD-10CM # R50.2 Drug induced fever
R50.9 Fever, unspecified

INFECTIOUS DISEASES

Brucellosis.
Rat-bite fever.
Relapsing fever.

RHEUMATIC DISEASES

Juvenile idiopathic arthritis (systemic onset).
Behçet disease.
Systemic lupus erythematosus.
Relapsing polychondritis.
Crohn's disease.

HEREDITARY AUTOINFLAMMATORY SYNDROMES

Familial Mediterranean fever (FMF).
Cryopyrinopathies:
- Familial cold autoinflammatory syndrome (FCAS).
- Muckle-Wells syndrome (MWS).
- Chronic infantile neurologic cutaneous and articular (CINCA) syndrome, also called neonatal-onset multisystem inflammatory disease (NOMID).

Tumor necrosis factor receptor–associated periodic syndrome (TRAPS).
Hyperimmunoglobulinemia D with periodic fever syndrome (HIDS).

CYCLIC HEMATOPOIESIS

Hereditary form.
Acquired form.

IDIOPATHIC CONDITIONS

Periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA).

FINGER LESIONS, INFLAMMATORY

ICD-9CM #	varies with specific disorder	
ICD-10CM #	B08.8	Other specified viral infections characterized by skin and mucous membrane lesions
	L03.0	Cellulitis of finger and toe

Paronychia.
Herpes simplex type 1 (herpetic whitlow).
Dyshidrotic eczema (pompholyx).
Herpes zoster.
Bacterial endocarditis (Osler's nodes).
Psoriatic arthritis.

FLACCID PARALYSIS, ACUTE, DIFFERENTIAL DIAGNOSIS[22a]

ICD-9CM #	344.9	Flaccid Paralysis
ICD-10CM #	G83.9	Paralytic syndrome, unspecified

Brain stem stroke.
Brain stem encephalitis.
Acute anterior poliomyelitis.
- Caused by poliovirus.
- Caused by other neurotropic viruses.

Acute myelopathy.
- Space-occupying lesions.
- Acute transverse myelitis.

Peripheral neuropathy.
- Guillain-Barré syndrome.
- Post-rabies vaccine neuropathy.
- Diphtheritic neuropathy.
- Heavy metals, biologic toxins, or drug intoxication.
- Acute intermittent porphyria.
- Vasculitic neuropathy.
- Critical illness neuropathy.
- Lymphomatous neuropathy.

Disorders of neuromuscular transmission.
- Myasthenia gravis.
- Biologic or industrial toxins.
- Tic paralysis.

Disorders of muscle.
- Hypokalemia.
- Hypophosphatemia.
- Inflammatory myopathy.
- Acute rhabdomyolysis.
- Trichinosis.
- Periodic paralyses.

FLATULENCE AND BLOATING[33]

ICD-9CM #	787.3	
ICD-10CM #	R14.0	Abdominal distension (gaseous)
	R14.1	Gas pain
	R14.2	Eructation
	R14.3	Flatulence

Ingestion of nonabsorbable carbohydrates.
Ingestion of carbonated beverages.
Malabsorption: pancreatic insufficiency, biliary disease, celiac disease, bacterial overgrowth in small intestine.
Lactase deficiency.
Irritable bowel syndrome.
Anxiety disorders.
Food poisoning, giardiasis.

FLUSHING[27]

ICD-9CM #	782.62	
ICD-10CM #	R23.2	Flushing

Physiologic flushing: menopause, ingestion of monosodium glutamate (Chinese restaurant syndrome), ingestion of hot drinks.
Drugs: alcohol (with or without disulfiram, metronidazole, or chlorpropamide), nicotinic acid, diltiazem, nifedipine, levodopa, bromocriptine, vancomycin, amyl nitrate.
Neoplastic disorders: carcinoid syndrome, VIPoma syndrome, medullary carcinoma of thyroid, systemic mastocytosis, basophilic chronic myelocytic leukemia, renal cell carcinoma.
Anxiety.
Agnogenic flushing.

FOLATE DEFICIENCY[20]

ICD-9CM #	281.2	
ICD-10CM #	D52.0	Dietary folate deficiency anemia
	D52.1	Drug-induced folate deficiency anemia
	D52.8	Other folate deficiency anemias
	D52.9	Folate deficiency anemia, unspecified

ETIOPATHOPHYSIOLOGIC CLASSIFICATION OF FOLATE DEFICIENCY

Nutritional causes:
- Decreased dietary intake:
  - Poverty and famine.
  - Institutionalized individuals (e.g., psychiatric, nursing homes), chronic debilitating disease.
  - Prolonged feeding of infants with goat's milk, special slimming diets or food fads (i.e., folate-rich foods not consumed), cultural or ethnic cooking techniques (i.e., food folate destroyed).
- Decreased diet and increased requirements:
  - Physiologic (e.g., pregnancy and lactation, prematurity, hyperemesis gravidarum, infancy).
  - Pathologic (e.g., intrinsic hematologic diseases involving hemolysis with compensatory erythropoiesis, abnormal hematopoiesis, or bone marrow infiltration with malignant disease and dermatologic disease such as psoriasis).

Folate malabsorption:
- With normal intestinal mucosa:
  - Some drugs (controversial).
  - Congenital folate malabsorption (rare).
- With mucosal abnormalities (e.g., tropical and nontropical sprue, regional enteritis).

Defective cellular folate uptake:
- Familial aplastic anemia (rare).
- Acute cerebral folate deficiency.

Inadequate cellular use:
- Folate antagonists (e.g., methotrexate).
- Hereditary enzyme deficiencies involving folate.

Drugs:
- Multiple effects on folate metabolism (e.g., alcohol, sulfasalazine, triamterene, pyrimethamine, trimethoprim-sulfamethoxazole, diphenylhydantoin, barbiturates).

Acute folate deficiency:
- Intensive care unit setting.
- Uncertain origin.

FOOT AND ANKLE PAIN[12a]

ICD-9CM #	varies with specific disorder	
ICD-10CM #	M25.5	Pain in joint
	M25.9	Joint disorder, unspecified

TENDON, LIGAMENT, AND MUSCLE

Gastrocnemius-soleus strain.
Plantaris rupture.
Anterior talofibular ligament tear.
Calcaneofibular ligament tear.
Deltoid ligament tear.
Anterolateral impingement due to complete tear of anterior talofibular ligament and anterior inferior tibiofibular ligament.
Syndesmotic impingement due to tear of syndesmosis.
Sinus tarsi syndrome (lateral hindfoot pain and instability due to injury of contents of the sinus and tarsal tunnel).
Achilles tendinitis.

Achilles rupture.
Plantar fasciitis.
Posterior tibial tendon dysfunction.
Flexor hallucis longus dysfunction.
Tibialis anterior tendon tear.
Peroneus brevis tendon tear.

BONE

Fracture of talus.
Calcaneal fracture.
Navicular fractures.
Lisfranc fracture-dislocation (fracture of the first metatarsal base with dislocation of medial cuneiform).
Metatarsal stress fracture.
Freiberg's infraction (sclerosis and flattening of the second metatarsal head due to trauma or microtrauma).
Avascular necrosis of the talus.
Fracture of the phalanges.
Fracture of the sesamoids.
Sesamoiditis.
Metatarsalgia.

JOINT

Osteoarthritis.
Gout.
Rheumatoid arthritis.
Other inflammatory arthritides.
Charcot's joint.
Osteochondral lesion of the talus.

PERIARTICULAR STRUCTURES

Shin splint (periosteal avulsion and periostitis at the insertion of the medial soleus due to repetitive overuse, such as in running and hiking).
Hallux rigidus.
Hallux valgus.
Ingrown toenail.
Toe deformities.
Turf toe (sprain of the first metatarsophalangeal joint due to hyperextension forces).
Plantar fasciitis.
Plantar fibromatosis.

NERVES

Anterior tarsal tunnel syndrome (involvement of deep peroneal nerve under the superficial fascia of the ankle).
Morton's neuroma.

VESSELS

Atherosclerosis.
Compartment syndrome.

REFERRED PAIN

Complex regional pain syndrome.

FOOT AND ANKLE PAIN, IN DIFFERENT AGE GROUPS[8]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	M25.579	Pain in unspecified ankle and joints of unspecified foot

COMMON CAUSES OF FOOT AND ANKLE PAIN IN DIFFERENT AGE GROUPS

Childhood (2-10 yr)
Intraarticular:
Club foot.
Congenital midfoot and forefoot deformities.
Septic arthritis.
Periarticular:
Osteomyelitis.
Adolescence (10-18 yr)
Intraarticular:
Arch disorders (pes cavus, pes planus).
Periarticular:
Osteomyelitis.
Tumors.
Early Adulthood (18-30 yr)
Intraarticular:
Metatarsalgia.
Hallux valgus.
Hallux rigidus.
Osteochondritis.
Accessory ossicles.
Periarticular:
Achilles tendonitis.
Achilles tendon rupture.
Fasciitis.
Referred:
Lumbar spine.
Knee.
Adulthood (30-50 yr)
Intraarticular:
Osteoarthritis.
Inflammatory arthritis.
Gout.
Metatarsalgia.
Hallux valgus.
Hallux rigidus.
Osteochondritis.
Accessory ossicles.
Periarticular:
Ischemic foot pain.
Diabetes.
Bursitis.
Tendonitis.
Plantar fasciitis.
Corns.
Referred:
Lumbar spine.
Knee.
Old Age (>50 yr)
Intraarticular:
Osteoarthritis.
Inflammatory arthritis.
Gout.
Metatarsalgia.
Hallux valgus.
Hallux rigidus.
Periarticular:
Ischemic foot pain.
Diabetes.
Bursitis.
Tendonitis.
Plantar fasciitis.
Corns.
Referred:
Lumbar spine.
Knee.

FOOT DERMATITIS

ICD-9CM #	varies with specific disorder	
ICD-10CM #	B35.3	Tinea pedis
	K25	Unspecified contact dermatitis

Tinea pedis.
Dyshidrotic eczema.
Tylosis (mechanically induced hyperkeratosis, fissuring, and dryness).
Allergic contact dermatitis.
Psoriasis.
Peripheral vascular insufficiency.
Neuropathic foot ulcers (DM, poorly fitting shoes).
Acquired plantar keratoderma.
Sézary's syndrome.

FOOTDROP

ICD-9CM #	varies with specific disorder	
ICD-10CM #	M21.379	Foot drop, unspecified foot

Peripheral neuropathy.
L5 radiculopathy.
Peroneal nerve compression.
Sciatic nerve palsy.
Scapuloperoneal syndromes.
Spasticity.
Peroneal nerve compression.
Myopathy.
Dystonia.

FOOT LESION, ULCERATING

ICD-9CM #	917.9	
ICD-10CM #	S90.929A	Unspecified superficial injury of unspecified foot, initial encounter
	S90.933A	Unspecified superficial injury of unspecified great toe, initial encounter
	S90.936A	Unspecified superficial injury of unspecified lesser toe(s), initial encounter
	L08.89	Other specified local infections of the skin and subcutaneous tissue

Cellulitis.
Plantar wart.
Squamous cell carcinoma.
Actinomycosis (Madura foot).
Plantar fibromatosis.
Pseudoepitheliomatous hyperplasia.

FOOT PAIN

ICD-9CM # varies with specific diagnosis
ICD-10CM # M25.579 Pain in unspecified ankle and joints of unspecified foot

Trauma (fractures, musculoskeletal and ligamentous strain).
Inflammation (plantar fasciitis, Achilles tendonitis or bursitis, calcaneal apophysitis).
Arterial insufficiency, Raynaud's phenomenon, thromboangiitis obliterans.
Gout, pseudogout.
Calcaneal spur.
Infection (cellulitis, abscess, lymphangitis, gangrene).
Decubitus ulcer.
Paronychia, ingrown toenail.
Thrombophlebitis, postphlebitic syndrome.

FOOT PAIN BY AGE[22a]

ICD-9CM # varies with specific diagnosis
ICD-10CM # M25.579 Pain in unspecified ankle and joints of unspecified foot

0-6 YEARS

Poorly fitting shoes.
Foreign body.
Fracture.
Osteomyelitis.
Leukemia.
Puncture wound.
Drawing of blood.
Dactylitis.
Juvenile rheumatoid arthritis (JRA).

6-12 YEARS

Poorly fitting shoes.
Sever disease.
Enthesopathy (JRA).
Foreign body.
Accessory navicular.
Tarsal coalition.
Ewing sarcoma.
Hypermobile flatfoot.
Trauma (sprains, fractures).
Puncture wound.

12-20 YEARS

Poorly fitting shoes.
Stress fracture.
Foreign body.
Ingrown toenail.
Metatarsalgia.
Plantar fasciitis.
Osteochondroses (avascular necrosis).
Freiberg infarction.
Köhler disease.
Achilles tendinitis.
Trauma (sprains).
Plantar warts.
Tarsal coalition.

FOREARM AND HAND PAIN

ICD-9CM #	959.3	Forearm Injury
	959.4	Hand Injury
ICD-10CM #	S59.809A	Other specified injuries of unspecified elbow, initial encounter
	S59.919A	Unspecified injury of unspecified forearm, initial encounter
	S69.80XA	Other specified injuries of unspecified wrist, hand and finger(s), initial encounter
	S69.90XA	Unspecified injury of unspecified wrist, hand and finger(s), initial encounter

Epicondylitis.
Tenosynovitis.
Osteoarthritis.
Cubital tunnel syndrome.
Carpal tunnel syndrome.
Trauma.
Herpes zoster.
Peripheral vascular insufficiency.
Infection (cellulitis, abscess).

FOREARM FRACTURES[1aa]

ICD-9CM # 759.33
ICD-10CM # S52 Fracture of forearm

TRAUMATIC

Wrist sprain, elbow sprain.
Ligamentous injuries, forearm contusions, hematomas.
Dislocations of the elbow or wrist (including nursemaid's elbow).

INFECTIOUS

Cellulitis of the forearm, abscesses.
Necrotizing fasciitis.

VASCULAR

Acute arterial occlusion.
Venous thrombosis.

NEUROLOGIC

Neurapraxias, carpal tunnel syndrome.
Systemic neurologic syndromes involving the nerves of the upper extremities.

ARTHRITIS

Septic joint, gonococcal arthritis, rheumatoid arthritis, osteoarthritis.
Pseudogout, gout.
Systemic lupus erythematosus, rheumatic fever, viral syndrome.
Reiter syndrome, Lyme disease, serum sickness.

OTHER

Olecranon bursitis, soft tissue masses.
Normal growth plates, nutrient vessels.

GAIT ABNORMALITY

ICD-9CM #	781.2	Gait Abnormality
ICD-10CM #	R26.0	Ataxic gait
	R26.1	Paralytic gait
	R26.89	Other abnormalities of gait and mobility
	R26.9	Unspecified abnormalities of gait and mobility

Parkinsonism.
Degenerative joint disease (hips, back, knees).
Multiple sclerosis.
Trauma, foot pain.
CVA.
Cerebellar lesions.
Infections (tabes, encephalitis, meningitis).
Sensory ataxia.
Dystonia, cerebral palsy, neuromuscular disorders.
Metabolic abnormalities.

GALACTORRHEA[28]

ICD-9CM # 611.6
ICD-10CM # N64.3 Galactorrhea not associated with childbirth

Prolonged suckling.
Drugs (INH, phenothiazines, reserpine derivatives, amphetamines, spironolactone and tricyclic antidepressants).
Major stressors (surgery, trauma).
Hypothyroidism.
Pituitary tumors.

GASTRIC DILATATION[16a]

ICD-9CM # 536.1
ICD-10CM # K31.0 Acute dilatation of stomach

CAUSES OF A MASSIVELY DILATED STOMACH

Mechanical Gastric Outlet Obstruction
Duodenal or pyloric canal ulceration.
Carcinoma of pyloric antrum.
Extrinsic compression.
Paralytic Ileus
Surgery.
Trauma.
Peritonitis.
Pancreatitis.
Cholecystitis.
Diabetes mellitus.
Hepatic coma.
Drugs.
Gastric Volvulus
Intubation.
Air swallowing.

GASTRIC EMPTYING, DELAYED[1a]

ICD-9CM # 578.89
ICD-10CM # K30 Functional dyspepsia

CAUSES OF DELAYED GASTRIC EMPTYING

Mechanical Causes

Peptic ulcer disease, scarred pylorus.
Malignancy: gastric cancer, gastric lymphoma, pancreatic cancer.
Gastric surgery: vagotomy, gastric resection, Roux-en-Y anastomosis.
Crohn's disease.

Endocrine and Metabolic Causes

Diabetes mellitus.
Hypothyroidism.
Hypoadrenal states.
Electrolyte abnormalities.
Chronic renal failure.
Medications.
Anticholinergics.
Opiates.
Dopamine agonists.
Tricyclic antidepressants.

Abnormalities of Gastric Smooth Muscle

Scleroderma.
Polymyositis, dermatomyositis.
Amyloidosis.
Pseudo-obstruction.
Myotonic dystrophy.
Neuropathy.
Scleroderma.
Amyloidosis.
Autonomic neuropathy.

Central Nervous System or Psychiatric Disorders

Brain stem tumors.
Spinal cord injury.
Anorexia nervosa.
Stress.

Miscellaneous

Idiopathic gastroparesis.
Gastroesophageal reflux disease.
Nonulcer (functional) dyspepsia.
Cancer cachexia or anorexia.

GASTRIC EMPTYING, RAPID

ICD-9CM #	536.8	Gastric Motility Disorder
ICD-10CM #	K30	Functional dyspepsia

Pancreatic insufficiency.
Dumping syndrome.
Peptic ulcer.
Celiac disease.
Promotility agents.
Zollinger-Ellison disease.

GENITAL DISCHARGE, FEMALE[12]

ICD-9CM #	629.9	
ICD-10CM #	N94.9	Unspecified condition associated with female genital organs and menstrual cycle

Physiologic discharge: cervical mucus, vaginal transudation, bacteria, squamous epithelial cells.
Individual variation.
Pregnancy.
Sexual response.
Menstrual cycle variation.
Infection.
Foreign body: tampon, cervical cap, other.
Neoplasm.
Fistula.
IUD.
Cervical ectropion.
Spermicide.
Nongenital causes: urinary incontinence, urinary tract fistula, Crohn's disease, rectovaginal fistula.

GENITAL SORES[1a]

ICD-9CM #	054.10	Genital Herpes
	91.0	Genital Syphilis
	078.11	Condyloma Acuminatum
	099.0	Chancroid
	099.2	Granuloma Inguinale
	099.1	Lymphogranuloma Venereum
	629.8	Ulcer, Genital Site, Female
	608.89	Ulcer, Genital Site, Male
ICD-10CM #	A60.9	Anogenital herpesviral infection, unspecified
	A51.0	Primary genital syphilis
	A63.0	Anogenital (venereal) warts
	A57	Chancroid
	A58	Granuloma inguinale
	A55	Chlamydial lymphogranuloma (venereum)
	N94.89	Other specified conditions associated with female genital organs and menstrual cycle
	N50.8	Other specified disorders of male genital organs

Herpes genitalis.
Syphilis.
Chancroid.
Lymphogranuloma venereum.
Granuloma inguinale.
Condyloma acuminatum.
Neoplastic lesion.
Trauma.

GLOMERULONEPHRITIS, RAPIDLY PROGRESSIVE[1a]

ICD-9CM #	583.4	
ICD-10CM #	N05.9	Unspecified nephritic syndrome with unspecified morphologic changes

DIFFERENTIAL DIAGNOSIS OF RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS

Linear Immune Staining

Anti-GBM disease.
Goodpasture's syndrome.
Rarely membranous glomerulonephritis.

Granular Immune Staining

Subacute bacterial endocarditis (past infectious).
Lupus nephritis.
Cryoglobulinemia.
Membranoproliferative glomerulonephritis (type II more than type I).
Immunoglobulin A nephropathy, Henoch-Schönlein purpura.
Idiopathic.

No Immune Staining (Pauci-immune)

Antineutrophil cytoplasmic antibody-associated vasculitis (Wegener granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome).
Idiopathic.

GLOMERULOPATHIES, THROMBOTIC, MICROANGIOPATHIC[1a]

ICD-9CM #	446.6	
ICD-10CM #	M31.1	Thrombotic microangiopathy

THROMBOTIC MICROANGIOPATHIC GLOMERULOPATHIES

Thrombotic thrombocytopenic purpura.
Hemolytic-uremic syndrome.
Malignant hypertension.
Scleroderma renal crisis.
Preeclampsia, eclampsia.
HELLP syndrome (hemolysis, elevated liver enzymes, low platelets).
Antiphospholipid antibody syndrome.
Drugs: oral contraceptives, quinine, cyclosporine, tacrolimus, ticlopidine, clopidogrel.

GLOMERULOSCLEROSIS, FOCAL SEGMENTAL[1a]

ICD-9CM #	582.1	
ICD-10CM #	N03.3	Chronic nephritic syndrome with diffuse mesangial proliferative glomerulonephritis

ETIOLOGY OF FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

Primary idiopathic FSGS.
Secondary FSGS.
HIV (usually collapsing variant).
Reflux nephropathy.
Heroin abuse.
Sickle cell disease.
Oligomeganephronia.
Renal dysgenesis or agenesis (low nephron mass).
Radiation nephritis.
Familial podocytopathies.
NPHS1 (nephrin) mutation.
NPHS2 (podocin) mutation.
TRPC6 (cation channel) mutation.
ACTN4 (α-actinin 4 mutation).

GLOSSODYNIA[38]

ICD-9CM #	529.6	
ICD-10CM #	K14.6	Glossodynia

DENTURE-RELATED

Dentures (ill-fitting, monomer from denture base).
Dental plaque.
Oral parafunction.

INFECTIVE/DERMATOLOGIC

Candidiasis.
Lichen planus.

DEFICIENCY STATES

Iron, B_{12}, folate, B_2 (riboflavin), B_6 (pyridoxine), zinc.

ENDOCRINE

Diabetes.
Myxedema.*
Hormonal changes occurring during menopause.*

NEUROLOGICALLY MEDIATED

Referred from tonsils, teeth.
Lingual nerve neuropathy.
Glossopharyngeal neuralgia.
Esophageal reflux.*

IATROGENIC

Mouthwash.

XEROSTOMIA

PSYCHOGENIC

IDIOPATHIC

*Unproven associations

GLUCOCORTICOID DEFICIENCY[14]

ICD-9CM #	255.4	
ICD-10CM #	E27.1	Primary adrenocortical insufficiency
	E27.3	Drug-induced adrenocortical insufficiency

ACTH-independent causes.
TB.
Autoimmune (idiopathic).
Other rare causes:
- Fungal infection.
- Adrenal hemorrhage.
- Metastases.
- Sarcoidosis.
- Amyloidosis.
- Adrenoleukodystrophy.
- Adrenomyeloneuropathy.
- HIV infection.
- Congenital adrenal hyperplasia.
- Medications (e.g., ketoconazole).

ACTH-dependent causes:
Hypothalamic-pituitary-adrenal suppression.
- Exogenous.
- Glucocorticoid.
- ACTH.
- Endogenous—cure of Cushing's syndrome.

Hypothalamic-pituitary lesions.
- Neoplasm:
  - Primary pituitary tumor.
  - Metastatic tumor.
  - Craniopharyngioma.
- Infection:
  - Tuberculosis.
  - Actinomycosis.
  - Nocardiosis.
- Sarcoid.
- Head trauma.
- Isolated ACTH deficiency.

GOITER

ICD-9CM #	240.9	Goiter, Unspecified
	241.9	Goiter, Adenomatous
	246.1	Goiter, Congenital
	240.9	Goiter, Nontoxic Diffuse
	241.1	Goiter, Nontoxic Multinodular
	240.0	Simple Goiter
	242.1	Thyrotoxic Goiter
ICD-10CM #	E01.2	Iodine-deficiency related (endemic) goiter, unspecified
	E04.9	Nontoxic goiter, unspecified
	E04.9	Nontoxic goiter, unspecified
	E07.1	Dyshormogenetic goiter
	E01.2	Iodine-deficiency related (endemic) goiter, unspecified
	E04.9	Nontoxic goiter, unspecified
	E04.2	Nontoxic multinodular goiter
	E04.0	Nontoxic diffuse goiter
	E05.10	Thyrotoxicosis with toxic single thyroid nodule without thyrotoxic crisis or storm

Thyroiditis.
Toxic multinodular goiter.
Graves' disease.
Medications (PTU, methimazole, sulfonamides, sulfonylureas, ethionamide, amiodarone, lithium, etc.).
Iodine deficiency.
Sarcoidosis, amyloidosis.
Defective thyroid hormone synthesis.
Resistance to thyroid hormone.

GRANULOMATOUS DERMATITIDES

ICD-9CM #	varies with specific disorder	
ICD-10CM #	L92.9	Granulomatous disorder of the skin and subcutaneous tissue, unspecified

Granuloma annulare.
Sarcoidosis.
Necrobiosis lipoidica diabeticorum.
Cutaneous Crohn's disease.
Rheumatoid nodules.
Annular elastolytic giant cell granuloma (actinic granuloma).
Foreign body granuloma.

GRANULOMATOUS DISORDERS[32]

ICD-9CM #	446.4	Granulomatosis
	288.1	Granulomatous Disease
ICD-10CM #	M31.30	Wegener's granulomatosis without renal involvement
	K75.3	Granulomatous hepatitis
	L92.9	Granulomatous disorder of skin and subcutaneous tissue, unspecified

INFECTIONS

Fungi
Histoplasma.
Coccidioides.
Blastomyces.
Sporothrix.
Aspergillus.
Cryptococcus.
Protozoa
Toxoplasma.
Leishmania.
Metazoa
Toxocara.
Schistosoma.
Spirochetes
Treponema pallidum.
T. *pertenue.*
T. *carateum.*
Mycobacteria
M. *tuberculosis.*
M. *leprae.*
M. *kansasii.*
M. *marinum.*
M. *avian.*
Bacille Calmette-Guérin (BCG) vaccine.
Bacteria
Brucella.
Yersinia.
Other Infections
Cat-scratch disease.
Lymphogranuloma.

NEOPLASIA

Carcinoma.
Reticulosis.
Pinealoma.
Dysgerminoma.
Seminoma.
Reticulum cell sarcoma.
Malignant nasal granuloma.

CHEMICALS
Beryllium.
Zirconium.
Silica.
Starch.

IMMUNOLOGIC ABERRATIONS
Sarcoidosis.
Crohn's disease.
Primary biliary cirrhosis.
Wegener's granulomatosis.
Giant cell arteritis.
Peyronie's disease.
Hypogammaglobulinemia.
SLE.
Lymphomatoid granulomatosis.
Histiocytosis X.
Hepatic granulomatous disease.
Immune complex disease.
Rosenthal-Melkersson syndrome.
Churg-Strauss allergic granulomatosis.

LEUKOCYTE OXIDASE DEFECT
Chronic granulomatous disease of childhood.

EXTRINSIC ALLERGIC ALVEOLITIS
Farmer's lung.
Bird fancier's.
Mushroom worker's.
Suberosis (cork dust).
Bagassosis.
Maple bark stripper's.
Paprika splitter's.
Coffee bean.
Spatlese lung.

OTHER DISORDERS
Whipple's disease.
Pyrexia of unknown origin.
Radiotherapy.
Cancer chemotherapy.
Panniculitis.
Chalazion.
Sebaceous cyst.
Dermoid.
Sea urchin spine injury.

GRANULOMATOUS LIVER DISEASE

ICD-9CM #	572.8	
ICD-10CM #	K75.3	Granulomatous hepatitis

Sarcoidosis.
Wegener's granulomatosis.
Vasculitis.
Inflammatory bowel disease.
Allergic granulomatosis.
Erythema nodosum.
Infections (fungal, viral, parasitic).
Primary biliary cirrhosis.
Lymphoma.
Hodgkin's disease.
Drugs (e.g., allopurinol, hydralazine, sulfonamides, penicillins).
Toxins (copper sulfate, beryllium).

GREEN OR BLUE URINE

ICD-9CM #	788.69	
ICD-10CM #	R82	Other abnormal findings in urine

Pseudomonal urinary tract infection
Medications: triamterene, amitriptyline, IV cimetidine, IV promethazine.
Biliverdin.
Dyes (methylene blue, indigo carmine).

GROIN LUMP[38]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	R19.09	Other intraabdominal and pelvic swelling, mass and lump
	R22.9	Localized swelling, mass and lump, unspecified

COMMON CAUSES
Inguinal hernia.
Femoral hernia.
Lymph node.

OTHER CAUSES
Saphena varix.
Femoral artery aneurysm/pseudoaneurysm.
Psoas abscess.
Lipoma of the cord.
Encysted hydrocele of the cord (male).
Testicular maldescent (male).
Hydrocele of canal of Nuck (female).

GROIN MASSES

ICD-9CM #	959.1	
ICD-10CM #	R22.9	Localized swelling, mass and lump, unspecified
	S39.848A	Other specified injuries of external genitals, initial encounter

Hernia (inguinal, femoral).
Hydrocele.
Varicocele.
Sebaceous cyst.
Hidradenitis of inguinal apocrine glands.
Neoplasm: lymphoma, metastases.
Lipoma.
Hematoma.
Reactive inguinal adenopathy, femoral adenitis.
Folliculitis, psoas abscess.
Epididymitis, testicular torsion, ectopic testes.
Aneurysm or pseudoaneurysm of femoral artery.

GROIN PAIN[5a]

ICD-9CM #	338	Groin Pain
ICD-10CM #	R52	Pain, unspecified

DIFFERENTIAL DIAGNOSIS OF GROIN PAIN
Surgery
Workers' Compensation.
Hernia.
Recurrent hernia.
Posthernia.
Orthopedic
Hip disorders.
- Acetabular labral tears.
- Avascular necrosis.
- Chondritis dissecans.
- Legg-Calvé-Perthes disease.
- Osteoarthritis.
- Pelvic stress fractures.
- Slipped femoral capital epiphysis.
- Synovitis.

Urology
Cystitis.
Epididymitis.
Nephrolithiasis.
Prostate cancer.
Prostatitis.
Torsion of testes.
Urethral extravasation.
Urinary tract infection.
Vas granuloma/fibrosis.
Dermatology
Lymphadenitis.
Psoriasis/burn.
Sebaceous cyst/hidradenitis.
Thrombophlebitis/cellulitis.
Neurosurgery
Disk disease.
Spinal injuries, inflammation, tumors.
Spondylolisthesis.
Spondylolysis.
Rheumatology
Connective tissue disorders.
Iliopsoas bursitis.
Osteitis pubis.
Systemic lupus erythematosus.
Neurology
Lumbosacral disorders.
Neurofibromatosis.
Infectious Disease
Herpes zoster.
HIV/tuberculosis.
Lyme disease.
Psoas abscess.
Sports Medicine
"Sports hernia" (adductor strains).
Gilmore's groin.
Vascular
Abscess hematoma.
Post-vein stripping.
Pseudoaneurysm.
Vascular graft.
Gastroenterology
Appendicitis/adhesions.
Diverticulitis.
Inflammatory retroperitoneal phlegmon (pancreatitis).
Meckel diverticulum.
Granulomatous colitis.
Gynecology
Cesarean section.
Cervical cancer.
Endometriosis.
Tubal/ovarian disorders.

GROIN PAIN, ACTIVE PATIENT[37]

ICD-9CM #	959.1	Groin Injury
	848.8	Groin Pain
ICD-10CM #	S39.848A	Other specified injuries of external genitals, initial encounter
	R52	Pain, unspecified

MUSCULOSKELETAL

Avascular necrosis of the femoral head.
Avulsion fracture (lesser trochanter, anterior superior iliac spine, anterior inferior iliac spine).
Bursitis (iliopectineal, trochanteric).
Entrapment of the ilioinguinal or iliofemoral nerve.
Gracilis syndrome.
Muscle tear (adductors, iliopsoas, rectus abdominis, gracilis, sartorius, rectus femoris).
Myositis ossificans of the hip muscles.
Osteitis pubis.
Osteoarthritis of the femoral head.
Slipped capital femoral epiphysis.
Stress fracture of the femoral head or neck and pubis.
Synovitis.

HERNIA-RELATED

Avulsion of the internal oblique muscle in the conjoined tendon.
Defect at the insertion of the rectus abdominis muscle.
Direct inguinal hernia.
Femoral ring hernia.
Indirect inguinal hernia.
Inguinal canal weakness.

UROLOGIC

Epididymitis.
Fracture of the testis.
Hydrocele.
Kidney stone.
Posterior urethritis.
Prostatitis.
Testicular cancer.
Torsion of the testis.
Urinary tract infection.
Varicocele.

GYNECOLOGIC

Ectopic pregnancy.
Ovarian cyst.
Pelvic inflammatory disease.
Torsion of the ovary.
Vaginitis.

LYMPHATIC ENLARGEMENT IN GROIN

GYNECOMASTIA

ICD-9CM #	611.1	Gynecomastia, Nonpuerperal
ICD-10CM #	N62	Hypertrophy of breast

Physiologic (puberty, newborns, aging).
Drugs (estrogen and estrogen precursors, 5-α reductase inhibitors, digitalis, testosterone and exogenous androgens, clomiphene, cimetidine, spironolactone, ketoconazole, amiodarone, ACE inhibitors, isoniazid, phenytoin, methyldopa, metoclopramide, phenothiazine).
Increased prolactin level (prolactinoma).
Liver disease.
Adrenal disease.
Thyrotoxicosis.
Increased estrogen production (hCG-producing tumor, testicular tumor, bronchogenic carcinoma).
Secondary hypogonadism.
Primary gonadal failure (trauma, castration, viral orchitis, granulomatous disease).
Defects in androgen synthesis.
Testosterone deficiency.
Klinefelter's syndrome.

HALITOSIS

ICD-9CM #	784.9	
ICD-10CM #	R19.6	Halitosis

Tobacco use.
Alcohol use.
Dry mouth (mouth breathing, inadequate fluid intake).
Foods (onion, garlic, meats, nuts, protein drinks).
Disease of mouth or nose (infections, cancer, inflammation).
Medications (antihistamines, antidepressants).
Systemic disorders (diabetes, uremia).
GI disorders (esophageal diverticula, hiatal hernia, GERD, achalasia).
Sinusitis.
Pulmonary disorders (bronchiectasis, pneumonia, neoplasms, TB).

HAND PAIN AND SWELLING[6]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	729.5	Pain in limb

Trauma.
Gout.
Pseudogout.
Cellulitis.
Lymphangitis.
DVT of upper extremity.
Thrombophlebitis.
RA.
Remitting seronegative symmetrical synovitis with pitting edema (RS3PE).
Polymyalgia rheumatica.
Mixed connective tissue disease.
Scleroderma.
Rupture of the olecranon bursa.
Metzger's syndrome (neoplasia).
The puffy hand of drug addiction.
Reflex sympathetic dystrophy.
Eosinophilic fasciitis.
Sickle cell (hand-foot syndrome).
Leprosy.
Factitial (the rubber band syndrome).

HEADACHE[13]

ICD-9CM #	784.0	Headache NOS
	307.81	Headache, Tension
	346.2	Headache, Cluster
	346.9	Headache, Migraine
	784.0	Headache, Vascular
ICD-10CM #	G44.1	Vascular headache, not elsewhere classified
	R51	Headache
	G44.209	Tension-type headache, unspecified, not intractable
	G44.009	Cluster headache syndrome, unspecified, not intractable
	G43.909	Migraine, unspecified, not intractable, without status migrainosus
	G44.1	Vascular headache, not elsewhere classified

Vascular: migraine, cluster headaches, temporal arteritis, hypertension, cavernous sinus thrombosis.
Musculoskeletal: neck and shoulder muscle contraction, strain of extraocular and/or intraocular muscles, cervical spondylosis, temporomandibular arthritis.
Infections: meningitis, encephalitis, brain abscess, sepsis, sinusitis, osteomyelitis, parotitis, mastoiditis.
Cerebral neoplasm.
Subdural hematoma.
Cerebral hemorrhage/infarct.
Pseudotumor cerebri.
Normal-pressure hydrocephalus (NPH).
Postlumbar puncture.
Cerebral aneurysm, arteriovenous malformations.
Posttrauma.
Dental problems: abscess, periodontitis, poorly fitting dentures.
Trigeminal neuralgia, glossopharyngeal neuralgia.
Otitis and other ear diseases.
Glaucoma and other eye diseases.
Metabolic: uremia, carbon monoxide inhalation, hypoxia.
Pheochromocytoma, hypoglycemia, hypothyroidism.
Effort induced: benign exertional headache, cough, headache, coital cephalalgia.
Drugs: alcohol, nitrates, histamine antagonists.
Paget's disease of the skull.
Emotional, psychiatric.

HEADACHE, ACUTE[11]

ICD-9CM #	784.0	
ICD-10CM #	R51	Headache

DIFFERENTIAL DIAGNOSIS OF ACUTE HEADACHE

Evaluation of the first acute headache should exclude pathologic causes listed here before consideration of more common etiologies.
Increased intracranial pressure (ICP): Trauma, hemorrhage, tumor, hydrocephalus, pseudotumor cerebri, abscess, arachnoid cyst, cerebral edema.
Decreased ICP: After ventriculoperitoneal shunt, lumbar puncture, cerebrospinal fluid leak from basilar skull fracture.
Meningeal inflammation: Meningitis, leukemia, subarachnoid or subdural hemorrhage.
Vascular: Vasculitis, arteriovenous malformation, hypertension, cerebrovascular accident.
Bone, soft tissue: Referred pain from scalp, eyes, ears, sinuses, nose, teeth, pharynx, cervical spine, temporomandibular joint.
Infection: Systemic infection, encephalitis, sinusitis, etc.
First migraine.

HEADACHE AND FACIAL PAIN[36]

ICD-9CM #	784.0	Headache NOS
	784.0	Facial Pain
ICD-10CM #	R51	Headache
	G44.1	Vascular headache, not elsewhere classified

VASCULAR HEADACHES

Migraine

Migraine with headaches and inconspicuous neurologic features:
- Migraine without aura ("common migraine").

Migraine with headaches and conspicuous neurologic features:
- With transient neurologic symptoms:

Migraine with typical aura ("classic migraine").
Sensory, basilar, and hemiplegic migraine.
- With prolonged or permanent neurologic features ("complicated migraine"):

Ophthalmoplegic migraine.
Migrainous infarction.
Migraine without headaches but with conspicuous neurologic features ("migraine equivalents"):
- Abdominal migraine.
- Benign paroxysmal vertigo of childhood.
- Migraine aura without headache ("isolated auras," transient migrainous accompaniments).

Cluster Headaches

Episodic cluster headache ("cyclic cluster headaches").
Chronic cluster headaches.
Chronic paroxysmal hemicrania.

Other Vascular Headaches

Headaches of reactive vasodilation (fever, drug-induced, postictal, hypoglycemia, hypoxia, hypercarbia, hyperthyroidism).
Headaches associated with arterial hypertension:
- Chronic severe hypertension (diastolic 120 mm Hg).
- Paroxysmal severe hypertension (pheochromocytoma, some coital headaches).

Headaches caused by cranial arteritis:
- Giant cell arteritis ("temporal arteritis").
- Other vasculitides.

HEADACHES ASSOCIATED WITH DEMONSTRABLE MUSCLE SPASM

Headache caused by posturally induced or perilesional muscle spasm:
- Headaches of sustained or impaired posture (e.g., prolonged close work, driving).
- Headaches associated with cervical spondylosis and other diseases of cervical spine.
- Myofascial pain dysfunction syndrome (headache or facial pain associated with disorders of teeth, jaws, and related structures, or "TMJ syndrome").

Headaches caused by psychophysiologic muscular contraction ("muscle contraction headaches," or tension-type headache associated with disorder of pericranial muscles).

HEADACHES AND FACIAL PAIN WITHOUT DEMONSTRABLE PHYSICAL SUBSTRATE

Headaches of uncertain etiology:
- "Tension headaches" (tension-type headache unassociated with disorder of pericranial muscles).
- Some forms of posttraumatic headache.

Psychogenic headaches (e.g., hypochondriacal, conversional, delusional, malingered).
Facial pain of uncertain etiology ("atypical facial pain").

COMBINED TENSION-MIGRAINE HEADACHES

Episodic migraine superimposed on chronic tension headaches.
Chronic daily headaches:
- Associated with analgesic and/or ergotamine overuse ("rebound headaches").
- Not associated with drug overuse.

HEADACHES AND HEAD PAINS CAUSED BY DISEASES OF EYES, EARS, NOSE, SINUSES, TEETH, OR SKULL

HEADACHES CAUSED BY MENINGEAL INFLAMMATION

Subarachnoid hemorrhage.
Meningitis and meningoencephalitis.
Others (e.g., meningeal carcinomatosis).

HEADACHES ASSOCIATED WITH ALTERED INTRACRANIAL PRESSURE ("TRACTION HEADACHES")

Increased Intracranial Pressure

Intracranial mass lesions (neoplasm, hematoma, abscess, etc.).
Hydrocephalus.
Benign intracranial hypertension.
Venous sinus thrombosis.

Decreased Intracranial Pressure

Post–lumbar puncture headaches.
Spontaneous hypoliquorrheic headaches.

HEADACHES AND HEAD PAINS CAUSED BY CRANIAL NEURALGIAS

Presumed Irritation of Superficial Nerves

Occipital neuralgia.
Supraorbital neuralgia.

Presumed Irritation of Intracranial Nerves

Trigeminal neuralgia ("tic douloureux").
Glossopharyngeal neuralgia.

HEADACHE, CHRONIC[11]

ICD-9CM #	784.0	
ICD-10CM #	R51	Headache

DIFFERENTIAL DIAGNOSIS OF RECURRENT OR CHRONIC HEADACHES

Migraine (with or without aura).
Tension.
Analgesic rebound.
Caffeine withdrawal.
Sleep deprivation (e.g., in children with sleep apnea) or chronic hypoxia.
Tumor.
Psychogenic: Conversion disorder, malingering.
Cluster headache.

HEAD AND NECK, SOFT TISSUE MASSES

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	R22.0	Localized swelling, mass and lump, head
	R22.1	Localized swelling, mass and lump, neck

Lipoma.
Pilar cyst.
Epidermal inclusion cyst.
Dermoid cyst.
Bone cyst.
Hemangioma.
Eosinophilic granuloma.
Other: facial nerve neuroma, teratoma, rhabdomyoma, rhabdomyosarcoma, branchial cleft cyst.

HEARING LOSS, ACUTE[26]

ICD-9CM #	388.2	
ICD-10CM #	H91.23	Sudden idiopathic hearing loss, bilateral

Infectious: mumps, measles, influenza, herpes simplex, herpes zoster, CMV, mononucleosis, syphilis.
Vascular: macroglobulinemia, sickle cell disease, Berger's disease, leukemia, polycythemia, fat emboli, hypercoagulable states.
Metabolic: diabetes, pregnancy, hyperlipoproteinemia.
Conductive: cerumen impaction, foreign bodies, otitis media, otitis externa, barotrauma, trauma.
Medications: aminoglycosides, loop diuretics, antineoplastics, salicylates, vancomycin.
Neoplasm: acoustic neuroma, metastatic neoplasm.

HEARTBURN AND INDIGESTION[33]

ICD-9CM #	787.1	Heartburn
	536.8	Indigestion
ICD-10CM #	R12	Heartburn
	K30	Functional dyspepsia

Reflux esophagitis.
Gastritis.
Nonulcer dyspepsia.
Functional GI disorder (anxiety disorder, social/environmental stresses).
Excessive intestinal gas (ingestion of flatulogenic foods, GI stasis, constipation).
Gas entrapment (hepatitis or splenic flexure syndrome).
Neoplasm (adenocarcinoma of stomach or esophagus, lymphoma).
Gallbladder disease.

HEART FAILURE WITH PRESERVED LEFT VENTRICULAR EJECTION FRACTION[14a]

ICD-9CM #	428.9	
ICD-10CM #	I50.9	Heart failure, unspecified

CAUSES OF (AND ALTERNATIVE EXPLANATIONS FOR) HEART FAILURE WITH PRESERVED LEFT VENTRICULAR EJECTION FRACTION (>45%-50%)

Inaccurate diagnosis of heart failure (e.g., pulmonary disease, obesity).
Inaccurate measurements of ejection fraction.
Systolic function overestimated by ejection fraction (e.g., mitral regurgitation).
Episodic, unrecognized systolic dysfunction.
Intermittent ischemia.
Arrhythmia.
Severe hypertension.
Alcohol abuse.
Diastolic dysfunction.
Abnormalities of myocardial relaxation:
- Ischemia.
- Hypertrophy.

Abnormalities of myocardial compliance:
- Hypertrophy.
- Aging.
- Fibrosis.
- Diabetes mellitus.
- Infiltrative disease (amyloidosis, sarcoidosis).
- Storage disease (hemochromatosis).
- Endomyocardial disease (endomyocardial fibrosis, radiation, anthracyclines).

Pericardial disease (constriction, tamponade).

HEART FAILURE, ACUTE[2]

ICD-9CM #	428.9	
ICD-10CM #	I50.9	Heart failure, unspecified

COMMON PRECIPITATING CAUSES OF ACUTE HF

Systemic hypertension.
Myocardial infarction or ischemia.
Dysrhythmia.
Systemic infection.
Anemia.
Dietary, physical, environmental, and emotional excesses.
Pregnancy.
Thyrotoxicosis or hypothyroidism.
Acute myocarditis.
Acute valvular dysfunction.
Pulmonary embolus.
Pharmacologic complications.

HEART FAILURE, CHRONIC[4a]

ICD-9CM #	428.0	
ICD-10CM #	I50.9	Heart failure, unspecified

Myocardial disease.
Coronary artery disease.
- Myocardial infarction.*
- Myocardial ischemia.*

Chronic pressure overload.
- Hypertension.*
- Obstructive valvular disease.*

Chronic volume overload.
- Regurgitant valvular disease.
- Intracardiac (left-to-right) shunting.
- Extracardiac shunting.

Nonischemic dilated cardiomyopathy.
- Familial or genetic disorders.
- Infiltrative disorders.*
- Toxic or drug-induced damage.
- Metabolic disorder.*
- Viral or other infectious agents.

Disorders of rate and rhythm.
- Chronic bradyarrhythmias.
- Chronic tachyarrhythmias.

Pulmonary heart disease
- Cor pulmonale.
- Pulmonary vascular disorders.

High-output states.
Metabolic disorders.
- Thyrotoxicosis.
- Nutritional disorders (beriberi).

Excessive blood flow requirements.
- Systemic arteriovenous shunting.
- Chronic anemia.

*Indicates conditions that can also lead to HF with a preserved EF.

HEART FAILURE, PATHOGENIC CAUSES[14a]

ICD-9CM #	428.9	
ICD-10CM #	I50.9	Heart failure, unspecified

IMPAIRED SYSTOLIC (CONTRACTILE) FUNCTION

Ischemic damage or dysfunction:
- Myocardial infarction.
- Persistent or intermittent myocardial ischemia.
- Hypoperfusion (shock).

Chronic pressure overloading:
- Hypertension.
- Obstructive valvular disease.

Chronic volume overload:
- Regurgitant valvular disease.
- Intracardiac left-to-right shunting.
- Extracardiac shunting.

Nonischemic dilated cardiomyopathy:
- Familial/genetic disorders.
- Toxic/drug-induced damage
- Immunologically mediated necrosis.
- Infectious agents.
- Metabolic disorders.
- Infiltrative processes.
- Idiopathic conditions.

IMPAIRED DIASTOLIC FUNCTION (RESTRICTED FILLING, INCREASED STIFFNESS)

Pathologic myocardial hypertrophy:
- Primary (hypertrophic cardiomyopathies).
- Secondary (hypertension).

Aging.
Ischemic fibrosis.
Restrictive cardiomyopathy:
- Infiltrative disorders (amyloidosis, sarcoidosis).
- Storage diseases (hemochromatosis, genetic abnormalities).

Endomyocardial disorders.

MECHANICAL ABNORMALITIES

Intracardiac:
- Obstructive valvular disease.
- Regurgitant valvular disease.
- Intracardiac shunts.
- Other congenital abnormalities.

Extracardiac:
- Obstructive (coarctation, supravalvular aortic stenosis).
- Left-to-right shunting (patent ductus arteriosus).

DISORDERS OF RATE AND RHYTHM

Bradyarrhythmias (sinus node dysfunction, conduction abnormalities).
Tachyarrhythmias (ineffective rhythms, chronic tachycardia).

PULMONARY HEART DISEASE

Cor pulmonale.
Pulmonary vascular disorders.

HIGH-OUTPUT STATES

Metabolic disorders:
Thyrotoxicosis.
Nutritional disorders (beriberi).
Excessive blood flow requirements:
- Chronic anemia.
- Systemic arteriovenous shunting.

HEART FAILURE, PREGNANCY

ICD-9CM #	428.90	
ICD-10CM #	I50.9	Heart failure, unspecified

Congenital valvular heart disease exacerbated by pregnancy.

Peripartum cardiomyopathy.
Untreated thyrotoxicosis.
Hypothyroidism.
Pulmonary hypertension.
Myocardial infarction.

HEAT STROKE[1]

ICD-9CM #	992	
ICD-10CM #	T67.0	Heatstroke and sunstroke

Sepsis.
Encephalitis.
Meningitis.
Brain abscess.
Malaria (cerebral falciparum).
Typhoid fever.
Tetanus.
Alcohol withdrawal syndrome.
Neuroleptic malignant syndrome (see Tips and Tricks box).
Anticholinergic toxicity.
Salicylate toxicity.
Phencyclidine hydrochloride (PCP), cocaine, or amphetamine toxicity.
Status epilepticus.
Cerebral hemorrhage.
Diabetic ketoacidosis.
Thyroid storm.

HEEL PAIN

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	M25.50	Pain in unspecified joint

Achilles tendonitis/tendinopathy (insertional, noninsertional).
Retrocalcaneal bursitis (superficial, deep).
Plantar fasciopathy.
Neuropathy (tarsal tunnel, posterior tibial nerve [medial calcaneal branch], abductor digiti quinti).
Calcaneal stress fracture.
Puncture wound, foreign body.
Cellulitis.
Spondyloarthropathy.
Fat pad atrophy.
Soft tissue tumor.
S1 radiculopathy.
Paget's disease of bone.
Haglund deformity.
Primary or metastatic bone tumor.

HEEL PAIN, PLANTAR[24]

ICD-9CM #	729.5	
ICD-10CM #	M79.609	Pain in unspecified limb

SKIN

Keratoses.
Verruca.
Ulcer.
Fissure.

CONNECTIVE TISSUE

Fat
Atrophy.
Panniculitis.

Dense Connective Tissue
Inflammatory fasciitis.
Fibromatosis.
Enthesopathy.
Bursitis.

Bone (Calcaneus)
Stress fracture.
Paget's disease.
Benign bone cyst/tumor.
Malignant bone tumor.
Metabolic bone disease (osteopenia).

Nerve
Tarsal tunnel.
Plantar nerve entrapment.
S1 nerve root radiculopathy.
Painful peripheral neuropathy.

INFECTION

Dermatomycoses.
Acute osteomyelitis.
Plantar abscess.

MISCELLANEOUS

Foreign body.
Nonunion calcaneus fracture.
Psychogenic.
Idiopathic.

HEMARTHROSIS

ICD-9CM #	848.9	Hemarthrosis (Sprain) NOS
ICD-10CM #	T14.90	Injury, unspecified

Trauma.
Anticoagulant therapy.
Thrombocytopenia, thrombocytosis.
Bleeding disorders (e.g., von Willebrand's disease).
Charcot's joint.
Idiopathic.
Other: pigmented villonodular synovitis, hemangioma, synovioma, AV fistula, ruptured aneurysm.

HEMATEMESIS[38]

ICD-9CM #	578.0	
ICD-10CM #	K92.0	Hematemesis

CAUSES OF HEMATEMESIS

Very Common
Gastric or duodenal ulcer or erosions.

Common
Mallory-Weiss tear (a laceration at the gastroesophageal junction).
Ulcerative esophagitis.
Esophageal varices.

Uncommon
Vascular malformations.
Ulcerated gastrointestinal stromal tumor.
Carcinoma of esophagus or stomach.
Aortoenteric fistula.

HEMATURIA

ICD-9CM #	599.7	Hematuria, Benign (Essential)
ICD-10CM #	R31.9	Hematuria, unspecified

Use the mnemonic TICS:

T (trauma): blow to kidney, insertion of Foley catheter or foreign body in urethra, prolonged and severe exercise, very rapid emptying of overdistended bladder.
(tumor): hypernephroma, Wilms' tumor, papillary carcinoma of the bladder, prostatic and urethral neoplasms.
(toxins): turpentine, phenols, sulfonamides and other antibiotics, cyclophosphamide, NSAIDs.
I (infections): glomerulonephritis, TB, cystitis, prostatitis, urethritis, *Schistosoma haematobium,* yellow fever, blackwater fever.
(inflammatory processes): Goodpasture's syndrome, periarteritis, postirradiation.
C (calculi): renal, ureteral, bladder, urethra.
(cysts): simple cysts, polycystic disease.
(congenital anomalies): hemangiomas, aneurysms, AVM.
S (surgery): invasive procedures, prostatic resection, cystoscopy.
(sickle cell disease and other hematologic disturbances): hemophilia, thrombocytopenia, anticoagulants.
(somewhere else): bleeding genitals, factitious (drug addicts).

HEMATURIA, DIFFERENTIAL BASED ON AGE AND SEX

ICD-9CM #	599.7	Hematuria Benign (Essential)other codes vary with cause
ICD-10CM #	R31.9	Hematuria, unspecified

0 TO 20 YR

Acute urinary tract infections.
Acute glomerulonephritis.
Congenital urinary tract anomalies with obstruction.
Trauma to genitals.

20 TO 40 YR

Acute urinary tract infection.
Trauma to genitals.
Urolithiasis.
Bladder cancer.

40 TO 60 YR (WOMEN)

Acute urinary tract infection.
Bladder cancer.
Urolithiasis.

40 TO 60 YR (MEN)

Acute urinary tract infection.
Bladder cancer.
Urolithiasis.

60 YR AND OLDER (WOMEN)

Acute urinary tract infection.
Bladder cancer.
Vaginal trauma or irritation.
Urolithiasis.

60 YR AND OLDER (MEN)

Acute urinary tract infection.
Benign prostatic hyperplasia.
Bladder cancer.
Urolithiasis.
Trauma.

HEMATURIA, IN CHILDREN[2]

ICD-9CM #	599.7	
ICD-10CM #	R31.9	Hematuria, unspecified

EXTRARENAL

Trauma.
Meatal stenosis or posterior urethral valves.
Exercise.
Menstruation or rectal bleeding.
Foreign bodies.
Cystitis, urethritis, or epididymitis.

INTRARENAL

Pyelonephritis.
Renal or bladder stones or tumors.
Poststrepotococcal or idiopathic glomerulonephritis.
Acute interstitial nephritis.
Acute tubular necrosis.
Basement membrane glomerular disease.
Renal vein or arterial thrombosis.
Recurrent familial hematuria.
Polycystic kidney disease.

SYSTEMIC

Henoch-Schönlein purpura.
Systemic lupus erythematosus.
Hemolytic-uremic syndrome.
Infectious mononucleosis.
Sickle cell disease or other hemoglobinopathies.
Bacterial endocarditis or artificial cardiac valves.
Bleeding disorders, warfarin, or aspirin.
Medications such as amitriptyline or chlorpromazine, radiocontrast dyes.
Munchausen syndrome or factitious.

HEMIPARESIS/HEMIPLEGIA

ICD-9CM #	436.0	Acquired Due to Acute CVA, Flaccid
	436.1	Acquired Due to CVA, Acute, Spastic
ICD-10CM #	G81.00	Flaccid hemiplegia affecting unspecified side
	G81.10	Spastic hemiplegia affecting unspecified side

CVA.
Transient ischemic attack.
Cerebral neoplasm.
Multiple sclerosis or other demyelinating disorder.
CNS infection.
Migraine.
Hypoglycemia
Subdural hematoma.
Vasculitis.
Todd's paralysis.
Epidural hematoma.
Metabolic (hyperosmolar state, electrolyte imbalance).
Psychiatric disorders.
Congenital disorders.
Leukodystrophies.

HEMOLYSIS AND HEMOGLOBINURIA

ICD-9CM #	773.2	Hemolysis
	791.2	Hemoglobinuria
ICD-10CM #	P55.8	Other hemolytic diseases of newborn
	P55.9	Hemolytic disease of newborn, unspecified
	R82.3	Hemoglobinuria

Erythrocyte trauma (prosthetic cardiac valves, marching and severe trauma, extensive burns).
Infections (malaria, *Bartonella, Clostridium welchii*).
Brown recluse spider bite.
Incompatible blood transfusions.
Hemolytic-uremic syndrome.
Thrombotic thrombocytopenic purpura (TTP).
Paroxysmal nocturnal hemoglobinuria (PNH).
Drugs (penicillins, quinidine, methyldopa, sulfonamides, nitrofurantoin).
Erythrocyte enzyme deficiencies (e.g., exposure to fava beans in patients with glucose-6-phosphate dehydrogenase deficiency).

HEMOLYSIS, INTRAVASCULAR

ICD-9CM #	283.2	
ICD-10CM #	D59.6	Hemoglobinuria due to hemolysis from other external causes
	D59.8	Other acquired hemolytic anemias

Infections.
Exertional hemolysis (e.g., prolonged march).
Valve hemolysis.
Microangiopathic hemolytic anemia.
Osmotic and chemical agents.
Thermal injury.
Cold agglutinins.
Venoms (snakes, spiders).
Paroxysmal nocturnal hemoglobinuria (PNH).

HEMOLYSIS, MECHANICAL

ICD-9CM #	283.19	
ICD-10CM #	D59.4	Other nonautoimmune hemolytic anemias

Prosthetic heart valves.
Aortic stenosis.
Malignant hypertension.
Metastatic adenocarcinoma.
Traumatic exercise.
Renal transplants.
Renal cortical necrosis.
Glomerulonephritis.
Thrombotic thrombocytopenic purpura (TTP), hemolytic-uremic syndrome (HUS).
Renal vasculitis.
Scleroderma.
Diabetes mellitus.

HEMOPERITONEUM

ICD-9CM #	568.81	
ICD-10CM #	K66.1	Hemoperitoneum

Ruptured Graafian follicle.
Ruptured spleen.
Ectopic pregnancy.
Traumatic laceration of liver.
Ruptured aneurysm.
Ruptured bladder.
Traumatic laceration of bowel, pancreas, uterus.

HEMOPTYSIS

ICD-9CM #	786.3	
ICD-10CM #	R04.2	Hemoptysis

CARDIOVASCULAR

Pulmonary embolism/infarction.
Left ventricular failure.
Mitral stenosis.
AV fistula.
Severe hypertension.
Erosion of aortic aneurysm.

PULMONARY

Neoplasm (primary or metastatic).
Infection.
Pneumonia: *Streptococcus pneumoniae, Klebsiella pneumoniae, Staphylococcus aureus, Legionella pneumophila.*
Bronchiectasis.
Abscess.
TB.
Bronchitis.
Fungal infections (aspergillosis, coccidioidomycosis).
Parasitic infections (amebiasis, ascariasis, paragonimiasis).
Vasculitis: Wegener's granulomatosis, Churg-Strauss syndrome, Henoch-Schönlein purpura.
Goodpasture's syndrome.
Trauma (needle biopsy, foreign body, right-sided heart catheterization, prolonged and severe cough).
Cystic fibrosis, bullous emphysema.
Pulmonary sequestration.
Pulmonary AV fistula.
SLE.
Idiopathic pulmonary hemosiderosis.
Drugs: aspirin, anticoagulants, penicillamine.
Pulmonary hypertension.
Mediastinal fibrosis.

OTHER

Epistaxis, trauma.
Laryngeal bleeding (laryngitis, laryngeal neoplasm).
Hematologic disorders (clotting abnormalities, DIC, thrombocytopenia).

HEPATIC CYSTS[36]

ICD-9CM #	751.62	Hepatic Cyst, Congenital
	122.8	*Echinococcus* Infection, Liver
ICD-10CM #	Q44.6	Cystic disease of liver
	B67.8	Echinococcosis, unspecified, of liver

CONGENITAL HEPATIC CYSTS

Parenchymal: solitary cyst, polycystic disease.
Ductal: localized dilatation, multiple cystic dilatations of intrahepatic ducts (Caroli's disease).

ACQUIRED HEPATIC CYSTS

Inflammatory cysts: retention cysts, echinococcal cyst, amebic cyst.
Neoplastic cyst.
Peliosis hepatis.

HEPATIC GRANULOMAS[1a]

ICD-9CM #	572.8	
ICD-10CM #	K75.3	Granulomatous hepatitis

INFECTIONS

Bacterial, spirochetal: TB and atypical mycobacterial infections, tularemia, brucellosis, leprosy, syphilis, Whipple's disease, listeriosis.
Viral: mononucleosis, CMV.
Rickettsial: Q fever.
Fungal: coccidioidomycosis, histoplasmosis, cryptococcal infections, actinomycosis, aspergillosis, nocardiosis.
Parasitic: schistosomiasis, clonorchiasis, toxocariasis, ascariasis, toxoplasmosis, amebiasis.

HEPATOBILIARY DISORDERS

Primary biliary cirrhosis, granulomatous hepatitis, jejunoileal bypass.

SYSTEMIC DISORDERS

Sarcoidosis, Wegener's granulomatosis, inflammatory bowel disease, Hodgkin's disease, lymphoma.

DRUGS/TOXINS

Beryllium, parenteral foreign material (starch, talc, silicone, etc.), phenylbutazone, α-methyldopa, procainamide, allopurinol, phenytoin, nitrofurantoin, hydralazine.

HEPATITIS, ACUTE[25b]

ICD-9CM #	varies with specific disorder	
ICD-10CM #	B17.8	Acute viral hepatitis, unspecified
	B15	Acute hepatitis A
	B16	Acute hepatitis B
	B17.1	Acute hepatitis C
	B17.2	Acute hepatitis E

Infectious:
- Hepatitis A, B, C, D, G.
- Epstein-Barr virus.
- Cytomegalovirus.
- Herpes simplex virus.
- Yellow fever.
- Leptospirosis.
- Q fever.
- HIV.
- Brucellosis.
- Lyme disease.
- Syphilis.

Noninfectious:
- Drug induced.
- Autoimmune.
- Ischemic.
- Acute fatty liver of pregnancy.
- Acute Budd-Chiari syndrome.
- Wilson's disease.

HEPATITIS, CHRONIC[25b]

ICD-9CM #	571.40	Hepatitis, Noninfectious, Chronic
	072.22	Hepatitis B, Chronic
	070.44	Hepatitis C, Chronic
ICD-10CM #	K73.9	Chronic hepatitis, unspecified
	B18.0	Chronic viral hepatitis B with δ-agent
	B18.2	Chronic viral hepatitis C

Chronic viral hepatitis:
- Hepatitis B.
- Hepatitis C.
- Hepatitis D.

Autoimmune hepatitis and variant syndromes.
Hereditary hemochromatosis.
Wilson's disease.
α_1-Antitrypsin deficiency.
Fatty liver and nonalcoholic steatohepatitis.
Alcoholic liver disease.
Drug-induced liver disease.
Hepatic granulomas:
- Infectious.
- Drug induced.
- Neoplastic.
- Idiopathic.

HEPATITIS, IN CHILDREN[22a]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	B17.9	Acute viral hepatitis, unspecified
	K73.9	Chronic hepatitis, unspecified

CAUSES AND DIFFERENTIAL DIAGNOSIS OF HEPATITIS IN CHILDREN

Infectious

Hepatotropic viruses:
- HAV.
- HBV.
- HCV.
- HDV.
- HEV.
- Hepatitis non–A-E viruses.

Systemic infection that can include hepatitis:
- Adenovirus.
- Arbovirus.
- Coxsackievirus.
- Cytomegalovirus.
- Enterovirus.
- Epstein-Barr virus.
- "Exotic" viruses (e.g., yellow fever).
- Herpes simplex virus.
- Human immunodeficiency virus.
- Paramyxovirus.
- Rubella.
- Varicella zoster.

Other.

Nonviral liver infections

Abscess.
Amebiasis.
Bacterial sepsis.
Brucellosis.
Fitz-Hugh-Curtis syndrome.
Histoplasmosis.
Leptospirosis.
Tuberculosis.
Other.

Autoimmune

Autoimmune hepatitis.
Sclerosing cholangitis.
Other (e.g., systemic lupus erythematosus, juvenile rheumatoid arthritis).

Metabolic

α1-Antitrypsin deficiency.
Tyrosinemia.
Wilson disease.
Other.

Toxic

Iatrogenic or drug induced (e.g., acetaminophen).
Environmental (e.g., pesticides).

Anatomic

Choledochal cyst.
Biliary atresia.
Other.

Hemodynamic

Shock.
Congestive heart failure.
Budd-Chiari syndrome.
Other.

Nonalcoholic Fatty Liver Disease

Idiopathic.
Reye syndrome.
Other.

HEPATOMEGALY

ICD-9CM #	789.1	
ICD-10CM #	R16.0	Hepatomegaly, not elsewhere classified

FREQUENT JAUNDICE

Infectious hepatitis.
Toxic hepatitis.
Carcinoma: liver, pancreas, bile ducts, metastatic neoplasm to liver.
Cirrhosis.
Obstruction of common bile duct.
Alcoholic hepatitis.
Biliary cirrhosis.
Cholangitis.
Hemochromatosis with cirrhosis.

INFREQUENT JAUNDICE

CHF.
Amyloidosis.
Liver abscess.
Sarcoidosis.
Infectious mononucleosis.
Alcoholic fatty infiltration.
Nonalcoholic steatohepatitis.
Lymphoma.
Leukemia.
Budd-Chiari syndrome.
Myelofibrosis with myeloid metaplasia.
Familial hyperlipoproteinemia type 1.
Other: amebiasis, hydatid disease of liver, schistosomiasis, kala-azar *(Leishmania donovani),* Hurler's syndrome, Gaucher's disease, kwashiorkor.

HEPATOMEGALY, BY SHAPE OF LIVER[38]

ICD-9CM #	789.1	
ICD-10CM #	R16.0	Hepatomegaly, not elsewhere classified

DIFFUSELY ENLARGED AND SMOOTH

Massive

Metastatic disease.
Alcoholic liver disease with fatty infiltration.
Myeloproliferative diseases (e.g., polycythemia rubra vera, myelofibrosis).

Moderate

The above causes.
Hemochromatosis.
Hematologic disease (e.g., chronic myeloid leukemia, lymphoma).
Fatty liver (e.g., diabetes mellitus, obesity).
Infiltrative disorders (e.g., amyloid).

Mild

The above causes.
Hepatitis (viral, drugs).
Cirrhosis.
Biliary obstruction.
Granulomatous disorders (e.g., sarcoid).
HIV infection.

DIFFUSELY ENLARGED AND IRREGULAR

Metastatic disease.
Cirrhosis.
Hydatid disease.
Polycystic liver disease.

LOCALIZED SWELLINGS

Riedel's lobe (a normal variant—the lobe may be palpable in the right lumbar region).
Metastasis.
Large simple hepatic cyst.
Hydatid cyst.
Hepatoma.
Liver abscess (e.g., amebic abscess).

HERMAPHRODITISM[4]

ICD-9CM #	752.7	Hermaphroditism, Congenital
ICD-10CM #	Q56.3	Pseudohermaphroditism, unspecified
	Q56.4	Indeterminate sex, unspecified

FEMALE PSEUDOHERMAPHRODITISM

Androgen exposure:
- Fetal source:
  - 21-Hydroxylase (P450 c21) deficiency.
  - 11β-Hydroxylase (P450 c11) deficiency.
  - 3β-Hydroxysteroid dehydrogenase II (3β-HSD II) deficiency.
  - Aromatase (P450arom) deficiency.
- Maternal source.
- Virilizing ovarian tumor.
- Virilizing adrenal tumor.
- Androgenic drugs.

Undetermined origin:
- Associated with genitourinary and GI tract defects.

MALE PSEUDOHERMAPHRODITISM

Defects in testicular differentiation:
- Denys-Drash syndrome (mutation in WT1 gene).
- WAGR syndrome (*W*ilms tumor, *a*niridia, *g*enitourinary malformation, *r*etardation).
- Deletion of 11p13.
- Camptomelic syndrome (autosomal gene at 17q24.3-q25.1) and SOX 9 mutation.
- XY pure gonadal dysgenesis (Swyer syndrome).
  - Mutation in SRY gene.
  - Unknown cause.
- XY gonadal agenesis.

Deficiency of testicular hormones:
- Leydig cell aplasia.
- Mutation in LH receptor.
- Lipoid adrenal hyperplasia (P450 scc) deficiency; mutation in StAR (steroidogenic acute regulatory protein).
- 3α-HSD II deficiency.
- 17-Hydroxylase/17, 20-lyase (P450 c17) deficiency.
- Persistent Müllerian duct syndrome.
  - Gene mutations, Müllerian-inhibiting substance (MIS).
  - Receptor defects for MIS.

Defect in androgen action:
- 5α-Reductase II mutations.
- Androgen receptor defects:
  - Complete androgen insensitivity syndrome.
  - Partial androgen insensitivity syndrome.
  - Reifenstein and other syndromes.
  - Smith-Lemli-Opitz syndrome.

Defect in conversion of 7-dehydrocholesterol to cholesterol.

TRUE HERMAPHRODITISM

XX.
XY.
XX/XY chimeras.

HICCUPS[21]

ICD-9CM #	786.8	
ICD-10CM #	R06.6	Hiccough

TRANSIENT HICCUPS

Sudden excitement, emotion.
Gastric distention.
Esophageal obstruction.
Alcohol ingestion.
Sudden change in temperature.

PERSISTENT OR CHRONIC HICCUPS

Toxic/metabolic: uremia, DM, hyperventilation, hypocalcemia, hypokalemia, hyponatremia, gout, fever.
Drugs: benzodiazepines, steroids, α-methyldopa, barbiturates.
Surgery/general anesthesia.
Thoracic/diaphragmatic disorders: pneumonia, lung cancer, asthma, pleuritis, pericarditis, myocardial infarction, aortic aneurysm, esophagitis, esophageal obstruction, diaphragmatic hernia or irritation.
Abdominal disorders: gastric ulcer or cancer, hepatobiliary or pancreatic disease, IBD, bowel obstruction, intraabdominal or subphrenic abscess, prostatic infection or cancer.
Central nervous system disorders: traumatic, infectious, vascular, structural.
Ear, nose, and throat disorders: pharyngitis, laryngitis, tumor, irritation of auditory canal.
Psychogenic disorders.
Idiopathic disorders.

HILAR AND MEDIASTINAL LYMPH NODE ENLARGEMENT[14a]

ICD-9CM #	85.6	
ICD-10CM #	R59.0	Mediastinal adenopathy

DISORDERS ASSOCIATED WITH HILAR AND MEDIASTINAL LYMPH NODE ENLARGEMENT

Sarcoidosis.
Lymphoma.
Fungal disease.
Tuberculosis.
Metastatic cancer.
Silicosis, coal worker's pneumoconiosis, beryllium lung.

HIP PAIN, CHILDREN[26]

ICD-9CM #	959.6	Hip Injury
	719.95	Hip Joint Disorder
	843.9	Hip Strain
ICD-10CM #	S79.819A	Other specified injuries of unspecified hip, initial encounter
	S79.829A	Other specified injuries of unspecified thigh, initial encounter
	S79.919A	Unspecified injury of unspecified hip, initial encounter

TRAUMA

Hip or pelvis fractures.
Overuse injuries.

INFECTION

Septic arthritis.
Osteomyelitis.

INFLAMMATION

Transient synovitis.
Juvenile RA.
Rheumatic fever.

NEOPLASM

Leukemia.
Osteogenic or Ewing's sarcoma.
Metastatic disease.

HEMATOLOGIC DISORDERS
Hemophilia.
Sickle cell anemia.

MISCELLANEOUS
Legg-Calvé-Perthes disease.
Slipped capital femoral epiphysis.

HIP PAIN, DIFFERENTIAL DIAGNOSIS[18b]

ICD-9CM # varies with specific diagnosis
ICD-10CM # M25.559 Pain in unspecified hip

ARTICULAR
Inflammatory joint diseases.
  Rheumatoid arthritis.
  Spondyloarthropathies.
  Polymyalgia rheumatica.
Degenerative joint disease.
  Primary osteoarthritis.
  Secondary osteoarthritis.
Metabolic joint diseases.
  Gout.
  Pseudogout.
  Ochronosis.
  Hemochromatosis.
  Wilson's disease.
  Acromegaly.
Femoroacetabular impingement.
Acetabular labral tear.
Infections.
Tumors.
  Benign.
  • Pigmented villonodular sclerosis.
  • Osteochondromatosis.
  Malignant.
  • Synovial sarcoma.
  • Synovial metastasis.
Hemarthrosis.
In children:
  Toxic synovitis.
  Juvenile chronic arthritis.

REFERRED PAIN
Thoracolumbar spine.
Intraabdominal structures.
Retroperitoneal structures.

PERIARTICULAR
Bursitis.
  Trochanteric.
  Iliopsoas.
  Ischiogluteal.
Tendinitis.
  Trochanteric.
  Adductor.
Acute calcific periarthritis.
Heterotropic ossification.

OSSEOUS
Bone lesions.
Fractures.
Neoplasms.
Infection.
Osteonecrosis of the femoral head.
Paget's disease.
Metabolic bone disease.
Stress fracture.
Transient osteoporosis.
In children:
  Congenital dislocation of the hip.
  Acetabular dysplasia.
  Coxa vara.
  Slipped capital femoral epiphysis.
  Legg-Calvé-Perthes disease.
  Rickets.

NEUROLOGIC
Entrapment neuropathies.
Lateral femoral cutaneous nerve (meralgia paresthetica).
Lumbar nerve root compression.
L2, L3, and L4.

VASCULAR
Atherosclerosis of aorta, iliac vessels.

HIP PAIN, IN DIFFERENT AGE GROUPS[8]

ICD-9CM # 719.45
ICD-10CM # M25.559 Pain in unspecified hip

COMMON CAUSES OF HIP PAIN IN DIFFERENT AGE GROUPS
Childhood (2-10 yr)
Intraarticular:
Developmental dislocation of the hip.
Perthes' disease.
Irritable hip.
Rickets.
Periarticular:
Osteomyelitis.
Referred:
Abdominal.
Adolescence (10-18 yr)
Intraarticular:
Slipped upper femoral epiphysis.
Torn labrum.
Periarticular:
Trochanteric bursitis.
Snapping hip.
Osteomyelitis.
Tumors.
Referred:
Abdominal.
Lumbar spine.
Early Adulthood (18-30 yr)
Intraarticular:
Inflammatory arthritis.
Torn labrum.
Periarticular:
Bursitis.
Referred:
Abdominal.
Lumbar spine.
Adulthood (30-50 yr)
Intraarticular:
Osteoarthritis.
Inflammatory arthritis.
Osteonecrosis.
Transient osteoporosis.
Periarticular:
Bursitis.
Referred:
Abdominal.
Lumbar spine.
Old Age (>50 yr)
Intraarticular:
Osteoarthritis.
Inflammatory arthritis.
Referred:
Abdominal.
Lumbar spine.

HIP PAIN WITHOUT OBVIOUS FRACTURE[2]

ICD-9CM # 338
ICD-10CM # R52 Pain, unspecified
M25.559 Pain in unspecified hip

DIFFERENTIAL DIAGNOSIS OF A PAINFUL HIP WITHOUT OBVIOUS FRACTURE
Referred pain (lumbar spine, hip, or knee).
Avascular necrosis of the femoral head.
Degenerative joint disease or osteoarthritis.
Herniation of a lumbar disk.
Diskitis.
Toxic synovitis of the hip.
Septic arthritis.
Bursitis.
Tendonitis.
Ligamentous injuries of the knee or hip.
Occult fracture.
Slipped capital femoral epiphysis.
Perthes' disease.
Tumor (lymphoma).
Deep venous thrombosis.
Arterial insufficiency.
Osteomyelitis.
Iliopsoas abscess.
Retroperitoneal hematoma.
Inguinal hernia.
Inguinal lymphadenopathy.
Genitourinary complaints.
Sports-related hernia.

HIRSUTISM

ICD-9CM # 704.1
ICD-10CM # L68.0 Hirsutism

Idiopathic: familial, possibly increased sensitivity to androgens.
Menopause.
Polycystic ovarian syndrome.
Drugs: androgens, anabolic steroids, methyltestosterone, minoxidil, diazoxide, phenytoin, glucocorticoids, cyclosporine.
Congenital adrenal hyperplasia.
Adrenal virilizing tumor.
Ovarian virilizing tumor: arrhenoblastoma, hilus cell tumor.
Pituitary adenoma.
Cushing's syndrome.
Hypothyroidism (congenital and juvenile).
Acromegaly.
Testicular feminization.

HIV INFECTION, ANORECTAL LESIONS[26]

ICD-9CM #	042	HIV Infection, Symptomatic
	V08	HIV Infection, Asymptomatic
ICD-10CM #	B20	Human immunodeficiency virus [HIV] disease
	Z21	Asymptomatic human immunodeficiency virus [HIV] infection status

COMMON CONDITIONS

Anal fissure.
Abscess and fistula.
Hemorrhoids.
Pruritus ani.
Pilonidal disease.

COMMON STDs

Gonorrhea.
Chlamydia.
Herpes.
Chancroid.
Syphilis.
Condylomata acuminata.

ATYPICAL CONDITIONS

Infectious: TB, CMV, actinomycosis, cryptococcus.
Neoplastic: lymphoma, Kaposi's sarcoma, squamous cell carcinoma.
Other: idiopathic and ulcer.

HIV INFECTION, CHEST RADIOGRAPHIC ABNORMALITIES[26]

ICD-9CM #	042	HIV Infection, Symptomatic
	V08	HIV Infection, Asymptomatic
ICD-10CM #	B20	Human immunodeficiency virus [HIV] disease
	Z21	Asymptomatic human immunodeficiency virus [HIV] infection status

DIFFUSE INTERSTITIAL INFILTRATION

Pneumocystis jiroveci.
Cytomegalovirus.
Mycobacterium tuberculosis.
Mycobacterium avium complex.
Histoplasmosis.
Coccidioidomycosis.
Lymphoid interstitial pneumonitis.

FOCAL CONSOLIDATION

Bacterial pneumonia.
Mycoplasma pneumoniae.
Pneumocystis jiroveci.
Mycobacterium tuberculosis.
Mycobacterium avium complex.

NODULAR LESIONS

Kaposi's sarcoma.
Mycobacterium tuberculosis.
Mycobacterium avium complex.
Fungal lesions.
Toxoplasmosis.

CAVITARY LESIONS

Pneumocystis jiroveci.
Mycobacterium tuberculosis.
Bacterial infection.

PLEURAL EFFUSION

Kaposi's sarcoma.
(Small effusion may be associated with any infection).

ADENOPATHY

Kaposi's sarcoma.
Lymphoma.
Mycobacterium tuberculosis.
Cryptococcus.

PNEUMOTHORAX

Kaposi's sarcoma.

HIV INFECTION, COGNITIVE IMPAIRMENT[25b]

ICD-9CM #	042	HIV Infection, Symptomatic
ICD-10CM #	B20	Human immunodeficiency virus [HIV] disease

EARLY TO MID-STAGE HIV DISEASE

Depression.
Alcohol and substance abuse.
Medication-induced cognitive impairment.
Metabolic encephalopathies.
HIV-related cognitive impairment.

ADVANCED HIV DISEASE (CD4+ <100/MM^3)

Opportunistic infection of CNS.
Neurosyphilis.
CNS lymphoma.
Progressive multifocal leukoencephalopathy.
Depression.
Metabolic encephalopathies.
Medication-induced cognitive impairment.
Stroke.
HIV dementia.

HIV INFECTION, CUTANEOUS MANIFESTATIONS[21]

ICD-9CM #	042	HIV Infection, Symptomatic
	V08	HIV Infection, Asymptomatic
ICD-10CM #	B20	Human immunodeficiency virus [HIV] disease
	Z21	Asymptomatic human immunodeficiency virus [HIV] infection status

BACTERIAL INFECTION

Bacillary angiomatosis: Numerous angiomatous nodules associated with fever, chills, weight loss.
Staphylococcus aureus: Folliculitis, ecthyma, impetigo, bullous impetigo, furuncles, carbuncles.
Syphilis: May occur in different forms (primary, secondary, tertiary); chancre may become painful because of secondary infection.

FUNGAL INFECTION

Candidiasis: Mucous membranes (oral, vulvovaginal), less commonly candida intertrigo or paronychia.
Cryptococcoses: Papules or nodules that strongly resemble molluscum contagiosum; other forms include pustules, purpuric papules, and vegetating plaques.
Seborrheic dermatitis: Scaling and erythema in the hair-bearing areas (eyebrows, scalp, chest, and pubic area).

ARTHROPOD INFESTATIONS

Scabies: Pruritus with or without rash, usually generalized but can be limited to a single digit.

VIRAL INFECTION

Herpes simplex: Vesicular lesion in clusters; perianal, genital, orofacial, or digital; can be disseminated.
Herpes zoster: Painful dermatomal vesicles that may ulcerate or disseminate.
HIV: Discrete erythematous macules and papules on the upper trunk, palms, and soles are the most characteristic cutaneous finding of acute HIV infection.
Human papillomavirus: Genital warts (may become unusually extensive).
Kaposi's sarcoma (herpesvirus): Erythematous macules or papules; enlarge at varying rates; violaceous nodules or plaques; occasionally painful.
Molluscum contagiosum: Discrete umbilicated papules commonly on the face, neck, and intertriginous sites (axilla, groin, or buttocks).

NONINFECTIOUS

Drug reactions: More frequent and severe in HIV patients.
Nutritional deficiencies: Mainly seen in children and patients with chronic diarrhea; diffuse skin manifestations, depending upon the deficiency.
Psoriasis: Scaly lesions; diffuse or localized; can be associated with arthritis.
Vasculitis: Palpable purpuric eruption (can resemble septic emboli).

HIV INFECTION, ESOPHAGEAL DISEASE

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	B20	Human immunodeficiency virus [HIV] disease
	K21.9	Gastro-esophageal reflux disease without esophagitis

Candida infection.
Cytomegalovirus infection.
Aphthous ulcer.
Herpes simplex.

HIV INFECTION, HEPATIC DISEASE[25b]

ICD-9CM #	042	HIV Infection, Symptomatic
ICD-10CM #	B20	Human immunodeficiency virus [HIV] disease

VIRUSES

Hepatitis A.
Hepatitis B.
Hepatitis C.
Hepatitis D (with HBV).
Epstein-Barr virus.
Cytomegalovirus.
Herpes simplex virus.
Adenovirus.
Varicella-zoster virus.

MYCOBACTERIA

Mycobacterium avium complex.
Mycobacterium tuberculosis.

FUNGI

Histoplasma capsulatum.
Cryptococcus neoformans.
Coccidioides immitis.
Candida albicans.
Pneumocystis jiroveci.
Penicillium marneffei.

PROTOZOA

Toxoplasma gondii.
Cryptosporidium parvum.
Microsporida.
Schistosoma.

BACTERIA

Bartonella henselae (peliosis hepatis).

MALIGNANCY

Kaposi's sarcoma (HHV-8).
Non-Hodgkin's lymphoma.
Hepatocellular carcinoma.

MEDICATIONS

Zidovudine.
Didanosine.
Ritonavir.
Other HIV-1 protease inhibitors.
Fluconazole.
Macrolide antibiotics.
Isoniazid.
Rifampin.
Trimethoprim-sulfamethoxazole.

HIV INFECTION, LOWER GI TRACT DISEASE[25b]

ICD-9CM #	042	HIV Infection, Symptomatic
ICD-10CM #	B20	Human immunodeficiency virus [HIV] disease

CAUSES OF ENTEROCOLITIS

Bacteria
Campylobacter jejuni and other spp.
Salmonella spp.
Shigella flexneri.
Aeromonas hydrophila.
Plesiomonas shigelloides.
Yersinia enterocolitica.
Vibrio spp.
Mycobacterium avium complex.
Mycobacterium tuberculosis.
Escherichia coli (enterotoxigenic, enteroadherent).
Bacterial overgrowth.
Clostridium difficile (toxin).
Parasites
Cryptosporidium parvum.
Microsporida (*Enterocytozoon bieneusi, Septata intestinalis*).
Isospora belli.
Entamoeba histolytica.
Giardia lamblia.
Cyclospora cayetanensis.
Viruses
Cytomegalovirus.
Adenovirus.
Calicivirus.
Astrovirus.
Picobirnavirus.
Human immunodeficiency virus.
Fungi
Histoplasma capsulatum.

CAUSES OF PROCTITIS

Bacteria
Chlamydia trachomatis.
Neisseria gonorrhoeae.
Treponema pallidum.
Viruses
Herpes simplex.
Cytomegalovirus.

HIV INFECTION, OCULAR MANIFESTATIONS[36]

ICD-9CM #	042	HIV Infection, Symptomatic
	V08	HIV Infection, Asymptomatic
ICD-10CM #	B20	Human immunodeficiency virus [HIV] disease
	Z21	Asymptomatic human immunodeficiency virus [HIV] infection status

EYELIDS

Molluscum contagiosum.
Kaposi's sarcoma.

CORNEA/CONJUNCTIVA

Keratoconjunctivitis sicca.
Bacterial/fungal ulcerative keratitis.
Herpes simplex.
Herpes zoster ophthalmicus.
Conjunctival microvasculopathy.
Kaposi's sarcoma.

RETINA, CHOROID, AND VITREOUS

Microvasculopathy.
Endophthalmitis.
Cytomegalovirus retinitis.
Acute retinal necrosis.
Syphilis.
Toxoplasmosis.
Pneumocystis choroidopathy.
Cryptococcosis.
Mycobacterial infection.
Intraocular lymphoma.
Candidiasis.
Histoplasmosis.

DRUGS ASSOCIATED WITH OCULAR TOXICITY

Rifabutin.
Didanosine.

NEUROOPHTHALMIC

Disc edema.
Primary or secondary optic neuropathy.
Cranial nerve palsies.

ORBITAL

Lymphoma.
Infection.
Pseudotumor.

HIV INFECTION, PULMONARY DISEASE[25b]

ICD-9CM #	042	HIV Infection, Symptomatic
ICD-10CM #	B20	Human immunodeficiency virus [HIV] disease
	I28.8	Other diseases of pulmonary vessels

MYCOBACTERIAL

M. tuberculosis.
M. kansasii.
M. avium complex.
Other nontuberculous mycobacteria.

OTHER BACTERIAL

Streptococcus pneumoniae.
Staphylococcus aureus.
Haemophilus influenzae.
Enterobacteriaceae.
Pseudomonas aeruginosa.
Moraxella catarrhalis.
Group A *Streptococcus.*
Nocardia spp.
Rhodococcus equi.
Chlamydia pneumoniae.

FUNGAL

Pneumocystis carinii.
Cryptococcus neoformans.
Histoplasma capsulatum.
Coccidioides immitis.
Aspergillus spp.
Blastomyces dermatitidis.
Penicillium marneffei.

VIRAL

Cytomegalovirus.
Herpes simplex virus.
Adenovirus.
Respiratory syncytial virus.
Influenza viruses.
Parainfluenza virus.

OTHER

Toxoplasma gondii.
Strongyloides stercoralis.
Kaposi's sarcoma.
Lymphoma.
Lung cancer.
Lymphocytic interstitial pneumonitis.
Nonspecific interstitial pneumonitis.
Bronchiolitis obliterans with organizing pneumonia.
Pulmonary hypertension.
Emphysema-like or bullous disease.
Pneumothorax.
Congestive heart failure.
Diffuse alveolar damage.
Pulmonary embolus.

HOARSENESS

ICD-9CM #	784.49	
ICD-10CM #	R49.8	Other voice and resonance disorders

Allergic rhinitis.
Infections (laryngitis, epiglottitis, tracheitis, croup).
Vocal cord polyps.
Voice strain.
Irritants (tobacco smoke).
Vocal cord trauma (intubation, surgery).
Neoplastic involvement of vocal cord (primary or metastatic).
Neurologic abnormalities (multiple sclerosis, ALS, parkinsonism).
Endocrine abnormalities (puberty, menopause, hypothyroidism).
Other (laryngeal webs or cysts, psychogenic, muscle tension abnormalities).

HYDROCEPHALUS

ICD-9CM #	331.4	
ICD-10CM #	G91.1	Obstructive hydrocephalus

Head trauma.
Brain neoplasm (primary or metastatic).
Spinal cord tumor.
Cerebellar infarction.
Exudative or granulomatous meningitis.
Cerebellar hemorrhage.
Subarachnoid hemorrhage.
Aqueductal stenosis.
Third ventricle colloid cyst.
Hindbrain malformation.
Viral encephalitis.
Metastases to leptomeninges.

HYPERCALCEMIA

ICD-9CM #	275.42	Hypercalcemia Disorder
ICD-10CM #	E83.52	Hypercalcemia

Malignancy: increased bone resorption via osteoclast-activating factors, secretion of PTH-like substances, prostaglandin E_2, direct erosion by tumor cells, transforming growth factors, colony-stimulating activity.
Hypercalcemia is common in the following neoplasms:
Solid tumors: breast, lung, pancreas, kidneys, ovary.
Hematologic cancers: myeloma, lymphosarcoma, adult T-cell lymphoma, Burkitt's lymphoma.
Hyperparathyroidism: increased bone resorption, GI absorption, and renal absorption; etiology:
Parathyroid hyperplasia, adenoma.
Hyperparathyroidism or renal failure with secondary hyperparathyroidism.
Granulomatous disorders: increased GI absorption (e.g., sarcoidosis).
Paget's disease: increased bone resorption, seen only during periods of immobilization.
Vitamin D intoxication, milk-alkali syndrome; increased GI absorption.
Thiazides: increased renal absorption.
Other causes: familial hypocalciuric hypercalcemia, thyrotoxicosis, adrenal insufficiency, prolonged immobilization, vitamin A intoxication, recovery from acute renal failure, lithium administration, pheochromocytoma, disseminated SLE.

HYPERCALCEMIA, MALIGNANCY-INDUCED

ICD-9CM #	275.42	
ICD-10CM #	E83.52	Hypercalcemia

Lung carcinoma	(6% frequency, 35% of hypercalcemic cases)
Breast carcinoma	(10% frequency, 25% of hypercalcemic cases)
Multiple myeloma	(33% frequency, 10% of hypercalcemic cases)
Lymphoma	(4% of hypercalcemic cases)
Genitourinary cancer	(6% of hypercalcemic cases)

HYPERCAPNIA, PERSISTENT[36]

ICD-9CM #	786.09	
ICD-10CM #	R06.00	Dyspnea, unspecified
	R06.09	Other forms of dyspnea
	R06.89	Other abnormalities of breathing

Hypercapnia with normal lungs: CNS disturbances (CVA, parkinsonism, encephalitis), metabolic alkalosis, myxedema, primary alveolar hypoventilation, spinal cord lesions.
Diseases of the chest wall (e.g., kyphoscoliosis, ankylosing spondylitis).
Neuromuscular disorders (e.g., myasthenia gravis, Guillain-Barré syndrome, amyotrophic lateral sclerosis, muscular dystrophy, poliomyelitis).
COPD.

HYPERCOAGULABLE STATE, ASSOCIATED DISORDERS[20]

ICD-9CM #	289.82	
ICD-10CM #	D68.69	Other thrombophilia

Systemic lupus erythematosus in association with the presence of a lupus anticoagulant or antiphospholipid antibodies.

MALIGNANCY:

Disease-related: includes migratory superficial thrombophlebitis (Trousseau syndrome), nonbacterial thrombotic endocarditis, thrombosis associated with chronic DIC, thrombotic microangiopathy.
Treatment-related: associated with the administration of various chemotherapeutic agents (L-asparaginase, mitomycin, some adjuvant chemotherapeutic agents for treatment of breast cancer, thalidomide or lenalidomide in conjunction with high doses of dexamethasone).
Infusion of prothrombin complex concentrates.
Nephrotic syndrome.
Heparin-induced thrombocytopenia.
Myeloproliferative disorders.
Paroxysmal nocturnal hemoglobinuria.

DIC, Disseminated intravascular coagulopathy.

HYPERGASTRINEMIA

ICD-9CM #	varies with specific disorder	
ICD-10CM #	E16.4	Abnormal secretion of gastrin

Decreased gastrin release inhibition from medications (proton pump inhibitors [PPIs], H_2 receptor antagonists), vagotomy.
Chronic renal failure.
Hypochlorhydria due to atrophic gastritis, gastric carcinoma, pernicious anemia.
Gastrinoma (Zollinger-Ellison syndrome).
Pyloric obstruction.
Hyperplasia of antral G cells.
RA.

HYPERHIDROSIS[4]

ICD-9CM #	780.8	Hyperhidrosis
ICD-10CM #	R61	Generalized hyperhidrosis

CORTICAL

Emotional.
Familial dysautonomia.
Congenital ichthyosiform erythroderma.
Epidermolysis bullosa.

Nail-patella syndrome.
Jadassohn-Lewandowsky syndrome.
Pachyonychia congenita.
Palmoplantar keratoderma.

HYPOTHALAMIC

Drugs
Antipyretics.
Emetics.
Insulin.
Meperidine.
Exercise Infection
Defervescence.
Chronic illness.
Metabolic
Debility.
DM.
Hyperpituitarism.
Hyperthyroidism.
Hypoglycemia.
Obesity.
Porphyria.
Pregnancy.
Rickets.
Infantile scurvy.
Cardiovascular
Heart failure.
Shock.
Vasomotor
Cold injury.
Raynaud phenomenon.
RA.
Neurologic
Abscess.
Familial dysautonomia.
Postencephalitic.
Tumor.
Miscellaneous
Chédiak-Higashi syndrome.
Compensatory.
Phenylketonuria.
Pheochromocytoma.
Vitiligo.
Medullary
Physiologic gustatory sweating.
Encephalitis.
Granulosis rubra nasi.
Syringomyelia.
Thoracic sympathetic trunk injury.
Spinal
Cord transection.
Syringomyelia.
Changes in Blood Flow
Mallucci syndrome.
Arteriovenous fistula.
Klippel-Trenaunay syndrome.
Glomus tumor.
Blue rubber bleb nevus syndrome.

HYPERKALEMIA

ICD-9CM # 276.7
ICD-10CM # E87.5 Hyperkalemia

Pseudohyperkalemia.
  Hemolyzed specimen.
  Severe thrombocytosis (platelet count 0.106 ml).
  Severe leukocytosis (white blood cell count 0.105 ml).
  Fist clenching during phlebotomy.
Excessive potassium intake (often in setting of impaired excretion).
  Potassium replacement therapy.
  High potassium diet.
  Salt substitutes with potassium.
  Potassium salts of antibiotics.
Decreased renal excretion.
  Potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride).
  Renal insufficiency.
  Mineralocorticoid deficiency.
  Hyporeninemic hypoaldosteronism.
  Tubular unresponsiveness to aldosterone (e.g., SLE, multiple myeloma, sickle cell disease).
  Type 4 RTA.
  ACE inhibitors.
  Heparin administration.
  NSAIDs.
  Trimethoprim-sulfamethoxazole.
  Beta-blockers.
  Pentamidine.
Redistribution (excessive cellular release).
  Acidemia (each 0.1 decrease in pH increases the serum potassium by 0.4 to 0.6 mEq/L). Lactic acidosis and ketoacidosis cause minimal redistribution.
  Insulin deficiency.
  Drugs (e.g., succinylcholine, markedly increased digitalis level, arginine, beta-adrenergic blockers).
  Hypertonicity.
  Hemolysis.
  Tissue necrosis, rhabdomyolysis, burns.
  Hyperkalemic periodic paralysis.

HYPERKALEMIA, DRUG-INDUCED[38b]

ICD-9CM # 276.7
ICD-10CM # E87.5 Hyperkalemia

IMPAIRED RENIN-ALDOSTERONE ELABORATION/FUNCTION

Cyclooxygenase inhibitors (NSAIDs).
β-Adrenergic antagonists.
Spironolactone.
Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.
Heparin.

INHIBITORS OF RENAL POTASSIUM SECRETION

Potassium-sparing diuretics (amiloride, triamterene).
Trimethoprim.
Pentamidine.
Cyclosporine.
Digitalis overdose.
Lithium.

ALTERED POTASSIUM DISTRIBUTION

Insulin antagonists (somatostatin, diazoxide).
β-Adrenergic antagonists.
α-Adrenergic agonists.
Hypertonic solutions.
Digitalis.
Succinylcholine.
Arginine hydrochloride, lysine hydrochloride.

HYPERKINETIC MOVEMENT DISORDERS[30]

ICD-9CM #	314.8	Hyperkinetic Syndrome
	275.1	Choreoathetosis
	335.5	Hemiballism
	333.7	Dystonia Due to Drugs
	333.6	Dystonia, Idiopathic
ICD-10CM #	F90.8	Attention-deficit hyperactivity disorder, other type
	E83.00	Disorder of copper metabolism, unspecified
	E83.01	Wilson's disease
	E83.09	Other disorders of copper metabolism
	G24.02	Drug induced acute dystonia
	G24.1	Genetic torsion dystonia

Chorea, choreoathetosis: drug-induced, Huntington's chorea, Sydenham's chorea.
Tardive dyskinesia (e.g., phenothiazines).
Hemiballismus (lacunar CVA near subthalamic nuclei in basal ganglia, metastatic lesions, toxoplasmosis [in AIDS]).
Dystonia (idiopathic, familial, drug-induced [prochlorperazine, metoclopramide]), Wilson's disease.
Liver failure.
Thyrotoxicosis.
SLE, polycythemia.

HYPERMAGNESEMIA

ICD-9CM #	275.2	
ICD-10CM #	E83.40	Disorders of magnesium metabolism, unspecified
	E83.41	Hypermagnesemia

Renal failure (decreased GFR).
Decreased renal excretion secondary to salt depletion.
Abuse of antacids and laxatives containing magnesium in patients with renal insufficiency.
Endocrinopathies (deficiency of mineralocorticoid or thyroid hormone).
Increased tissue breakdown (rhabdomyolysis).
Redistribution: acute DKA, pheochromocytoma.
Other: lithium, volume depletion, familial hypocalciuric hypercalcemia.

HYPEROSTOSIS, CORTICAL BONE[16a]

ICD-9CM # varies with specific diagnosis
ICD-10CM # M48.19 Ankylosing hyperostosis [Forestier], multiple sites in spine

DISORDERS ASSOCIATED WITH HYPEROSTOSIS OF CORTICAL BONE

Progressive diaphyseal dysplasia.
Endosteal hyperostosis.
Pachydermoperiostosis.
Hypertrophic oseoarthropathy.
Thyroid acropachy.
Hypervitaminosis A.
Paget's disease.
Infantile cortical hyperostosis.

HYPERPHOSPHATEMIA

ICD-9CM # 275.3
ICD-10CM # E83.30 Disorder of phosphorus metabolism, unspecified

Excessive phosphate administration.
Excessive oral intake or IV administration.
Laxatives containing phosphate (phosphate tablets, phosphate enemas).
Decreased renal phosphate excretion.
Acute or chronic renal failure.
Hypoparathyroidism or pseudohypoparathyroidism.
Acromegaly, thyrotoxicosis.
Bisphosphonate therapy.
Tumor calcinosis.
Sickle cell anemia.
Transcellular shift out of cells.
Chemotherapy of lymphoma or leukemia, tumor lysis syndrome, hemolysis.
Acidosis.
Rhabdomyolysis, malignant hyperthermia.
Artifact: in vitro hemolysis.
Pseudohyperphosphatemia: hyperlipidemia, paraproteinemia, hyperbilirubinemia.

HYPERPIGMENTATION[5]

ICD-9CM # 709.00
ICD-10CM # L81.4 Other melanin hyperpigmentation

Addison's disease.*
Arsenic ingestion.
ACTH- or MSH-producing tumors (e.g., oat cell carcinoma of the lung).*
Drug induced (e.g., antimalarials, some cytotoxic agents).
Hemochromatosis ("bronze" diabetes).
Malabsorption syndrome (Whipple's disease and celiac sprue).
Melanoma.
Melanotropic hormone injection.*
Pheochromocytoma.
Porphyrias (porphyria cutanea tarda and variegate porphyria).
Pregnancy.
Progressive systemic sclerosis and related conditions.
PUVA therapy (psoralen administration) for psoriasis and vitiligo.*

ACTH, Adrenocorticotropic hormone; *MSH,* melanocyte-stimulating hormone; *PUVA,* psoralen plus ultraviolet A.
*Accentuation on sun-exposed surfaces.

HYPERPROLACTINEMIA[26b]

ICD-9CM # 253.1
ICD-10CM # E22.1 Hyperprolactinemia

PHYSIOLOGIC

Pregnancy.
Lactation.
Stress.
Sleep.
Coitus.
Exercise.

PATHOLOGIC

Hypothalamic-Pituitary Stalk Damage
Tumors: craniopharyngioma, suprasellar pituitary mass extension, meningioma, dysgerminoma, hypothalamic metastases.
Granulomas.
Infiltrations.
Rathke's cyst.
Irradiation.
Trauma: pituitary stalk section, sellar surgery, head trauma.
Pituitary
Prolactinoma.
Acromegaly.
Macroadenoma (compressive).
Idiopathic.
Plurihormonal adenoma.
Lymphocytic hypophysitis or parasellar mass.
Macroprolactinemia.
Systemic Disorders
Chronic renal failure.
Polycystic ovary syndrome.
Cirrhosis.
Pseudocyesis.
Epileptic seizures.
Cranial irradiation.
Chest: neurogenic chest wall trauma, surgery, herpes zoster.

PHARMACOLOGIC

Neuropeptide
Thyrotropin-releasing hormone.
Drug-Induced Hypersecretion
Dopamine receptor blockers:
Phenothiazines: chlorpromazine, perphenazine.
Butyrophenones: haloperidol.
Thioxanthenes.
Metoclopramide.
Dopamine synthesis inhibitors:
α-Methyldopa.
Catecholamine depleters:
Reserpine.
Cholinergic Agonist
Physostigmine.
Antihypertensives
Labetalol.
Reserpine.
Verapamil.
H_2 Antihistamines
Cimetidine.
Ranitidine.
Estrogens
Oral contraceptives.
Oral contraceptive withdrawal.
Anticonvulsant
Phenytoin.
Anesthetics
Neuroleptics
Chlorpromazine.
Risperidone.
Promazine.
Promethazine.
Trifluoperazine.
Fluphenazine.
Butaperazine.
Perphenazine.
Thiethylperazine.
Thioridazine.
Haloperidol.
Pimozide.
Thiothixene.
Molindone.
Opiates and Opiate Antagonists
Heroin.
Methadone.
Apomorphine.
Morphine.
Antidepressants
Tricyclic antidepressants: chlorimipramine, amitriptyline.
Selective serotonin reuptake inhibitors: fluoxetine.

HYPERSPLENISM, ASSOCIATED CONDITIONS

ICD-9CM # 289.4
ICD-10CM # D73.1 Hypersplenism

Cirrhosis.
Portal vein thrombosis.
Myeloproliferative diseases.
Lymphomas.
Leukemias.
Splenic vein thrombosis.
Autoimmune disease.
Sickle cell disease.
Thalassemias.
Gaucher's disease.
Niemann-Pick disease.

HYPERTENSION, ADRENOCORTICAL CAUSES[26b]

ICD-9CM # 401
ICD-10CM # I15.8 Other secondary hypertension

LOW RENIN AND HIGH ALDOSTERONE

Primary Aldosteronism

Aldosterone-producing adenoma (APA)	35% of cases
Bilateral idiopathic hyperplasia (IHA)	60% of cases
Primary (unilateral) adrenal hyperplasia	2% of cases
Aldosterone-producing adrenocortical carcinoma	<1% of cases

Familial hyperaldosteronism (FH)

Glucocorticoid-remediable aldosteronism (FH type I) <1% of cases
FH type II (APA or IHA)—<2% of cases
Ectopic aldosterone-producing adenoma or carcinoma <0.1% of cases

LOW RENIN AND LOW ALDOSTERONE

Hyperdeoxycorticosteronism
Congenital adrenal hyperplasia.
11β-Hydroxylase deficiency.
17α-Hydroxylase deficiency.
Deoxycorticosterone-producing tumor.
Primary cortisol resistance.
Apparent mineralocorticoid excess (AME)/11β-HSD* deficiency.
Genetic: Type 1 AME.
Acquired: Licorice or carbenoxolone ingestion (type 1 AME), Cushing's syndrome (type 2 AME).
Cushing's Syndrome
Exogenous glucocorticoid administration—most common cause.
Endogenous.
ACTH†-dependent—85% of cases: Pituitary, ectopic.
ACTH-independent—15% of cases: Unilateral adrenal disease (adenoma or carcinoma), bilateral adrenal disease (massive macronodular hyperplasia [rare], primary pigmented nodular adrenal disease [rare]).

*HSD, hydroxysteroid dehydrogenase
†ACTH, corticotropin

HYPERTENSION, ENDOCRINE CAUSES[26b]

ICD-9CM # 401
ICD-10CM # I15.8 Other secondary hypertension

ADRENAL-DEPENDENT CAUSES

Pheochromocytoma.
Primary aldosteronism.
Hyperdeoxycorticosteronism.
Congenital adrenal hyperplasia: 11β-Hydroxylase deficiency, 17α-hydroxylase deficiency.
Deoxycorticosterone-producing tumor.
Primary cortisol resistance.
Cushing's syndrome.

AME/11β-HSD (HYDROXYSTEROID DEHYDROGENASE) DEFICIENCY

Genetic.
Type 1 apparent mineralocorticoid excess (AME).
Acquired.
Licorice or carbenoxolone ingestion (type 1 AME).
Cushing's syndrome (type 2 AME).

THYROID-DEPENDENT CAUSES

Hypothyroidism.
Hyperthyroidism.

PARATHYROID-DEPENDENT CAUSES

Hyperparathyroidism.

PITUITARY-DEPENDENT CAUSES

Acromegaly.
Cushing's syndrome.

HYPERTENSION, IN CHILDREN[2]

ICD-9CM # 401
ICD-10CM # I10 Essential (primary) hypertension

PRIMARY

Essential hypertension.

SECONDARY

Renal
Glomerulonephritis.
Henoch-Schönlein purpura.
Pyelonephritis.
Obstruction of reflux.
Polycystic kidney disease.
Diabetic nephropathy.
Trauma.
Renal transplant or hemodialysis.
Tuberous sclerosis.
Systemic lupus nephritis.
Endocrine
Pheochromocytoma.
Cushing's syndrome.
Congenital adrenal hyperplasia.
Corticosteroid treatment.
Hyperthyroidism.
Neuroblastoma.
Ovarian tumor.
Cardiac
Congestive heart failure.
Coarctation of the aorta.
Vascular
Hemolytic-uremic syndrome.
Kawasaki syndrome.
Renal artery thrombosis or stenosis.
Neurologic
Central nervous system tumor or infection.
Central nervous system trauma or abuse.
Increased intracranial pressure.
Guillain-Barré syndrome.
Neoplastic
Neuroblastoma.
Wilms' tumor.
Pheochromocytoma.
Adrenal carcinoma.
Drugs
Corticosteroids.
Cocaine.
Sympathomimetics.
Oral contraceptives.
Phencyclidine.
Beta-blocker or clonidine withdrawal.
Lead, mercury.
Others
Iatrogenic fluid overload.
Volume overload from end-stage renal disease.

HYPERTENSIVE CRISIS SYNDROMES[38b]

ICD-9CM # 997.91
ICD-10CM # I13 Hypertensive heart and renal disease
I15 Secondary hypertension

Malignant hypertension.
Nonmalignant hypertension with target organ disorders:
Patient requiring emergency surgery with poorly controlled hypertension.
Hyperviscosity syndrome.
Postoperative patient.
Renal transplant patient: acute rejection, transplant renal artery stenosis.
Quadriplegic patient with autonomic hyperreflexia.
Severe burns.
Acute aortic dissection.
Intracranial hemorrhage, ischemic stroke, or subarachnoid hemorrhage.
Hypertensive encephalopathy.
Myocardial ischemia/acute left ventricular failure.
Preeclampsia/eclampsia.
Antiphospholipid antibody syndrome.
Acute renal failure:
- Scleroderma renal crisis.
- Chronic glomerulonephritis.
- Reflux nephropathy.
- Analgesic nephropathy.
- Acute glomerulonephritis.
- Radiation nephritis.
- Ask-Upmark kidney.
- Chronic lead intoxication.

Renovascular hypertension:
- Fibromuscular dysplasia.
- Atherosclerosis.

Endocrine hypertension:
- Congenital adrenal hyperplasia.
- Pheochromocytoma.
- Oral contraceptives.
- Aldosteronism.
- Cushing disease.

Systemic vasculitis.
Atheroembolic renal crisis.
Drugs:
- Oral contraceptives.
- Nonsteroidal antiinflammatory agents.
- Atropine.
- Corticosteroids.
- Sympathomimetics.
- Erythropoietin.
- Lead intoxication.
- Cyclosporine.

Catecholamine excess states:
- Pheochromocytoma.
- MAO/tyramine interaction.
- Antihypertensive withdrawal.
- Cocaine intoxication, sympathomimetic overdose.

HYPERTRICHOSIS[7]

ICD-9CM #	704.1	Hypertrichosis NOS
	757.4	Hypertrichosis, Congenital
ICD-10CM #	L68.0	Hirsutism
	L68.1	Acquired hypertrichosis lanuginosa
	L68.3	Polytrichia
	L68.9	Hypertrichosis, unspecified
	Q84.1	Congenital morphological disturbances of hair, not elsewhere classified

DRUGS

Dilantin.
Streptomycin.
Hexachlorobenzene.
Penicillamine.
Diazoxide.
Minoxidil.
Cyclosporine.

SYSTEMIC ILLNESS

Hypothyroidism.
Anorexia nervosa.
Malnutrition.
Porphyria.
Dermatomyositis.

IDIOPATHIC

HYPERTROPHIC OSTEOARTHROPATHY

ICD-9CM #	731.2	
ICD-10CM #	M89.40	Other hypertrophic osteoarthropathy, unspecified site

Idiopathic.
Pulmonary disease (e.g., pulmonary fibrosis, cystic fibrosis, sarcoidosis).
Bronchogenic carcinoma.
AIDS.
GI neoplasm (e.g., esophagus, colon).
Hepatic neoplasm, cirrhosis.
Cardiovascular diseases, aortic aneurysm, aortic prosthesis.
Congenital cyanotic heart disease, patent ductus arteriosus.
Pulmonary infections, bacterial endocarditis, amebic dysentery.
Inflammatory bowel disease.
Connective tissue diseases.
Lymphomas.
Thyroid acropachy.

HYPERVENTILATION, PERSISTENT[36]

ICD-9CM #	786.01	
ICD-10CM #	R06.4	Hyperventilation

Fibrotic lung disease.
Metabolic acidosis (e.g., diabetes, uremia).
CNS disorders (midbrain and pontine lesions).
Hepatic coma.
Salicylate intoxication.
Fever.
Sepsis.
Psychogenic (e.g., anxiety).

HYPOCALCEMIA

ICD-9CM #	275.41	
ICD-10CM #	E83.51	Hypocalcemia

Renal insufficiency: hypocalcemia caused by:
- Increased calcium deposits in bone and soft tissue secondary to increased serum phosphate level.
- Decreased production of 1,25-dihydroxyvitamin D.
- Excessive loss of 25-OHD (nephrotic syndrome).

Hypoalbuminemia: each decrease in serum albumin (g/L) will decrease serum calcium by 0.8 mg/dl but will not change free (ionized) calcium.
Vitamin D deficiency:
- Malabsorption (most common cause).
- Inadequate intake.
- Decreased production of 1,25-dihydroxyvitamin D (vitamin D–dependent rickets, renal failure).
- Decreased production of 25-OHD (parenchymal liver disease).
- Accelerated 25-OHD catabolism (phenytoin, phenobarbital).
- End-organ resistance to 1,25-dihydroxyvitamin D.

Hypomagnesemia: hypocalcemia caused by:
- Decreased PTH secretion.
- Inhibition of PTH effect on bone.

Pancreatitis, hyperphosphatemia, osteoblastic metastases: hypocalcemia is secondary to increased calcium deposits (bone, abdomen).
Pseudohypoparathyroidism (PHP): autosomal recessive disorder characterized by short stature, shortening of metacarpal bones, obesity, and mental retardation; the hypocalcemia is secondary to congenital end-organ resistance to PTH.
Idiopathic hypoparathyroidism, surgical removal of parathyroids (e.g., neck surgery).
"Hungry bones syndrome": rapid transfer of calcium from plasma into bones after removal of a parathyroid tumor.
Sepsis.
Massive blood transfusion (as a result of EDTA in blood).

HYPOCAPNIA

ICD-9CM #	786.01	
ICD-10CM #	R06.8	Hypoventilation

Hyperventilation.
Pneumonia, pneumonitis.
Fever, sepsis.
Medications (salicylates, beta-adrenergic agonists, progesterone, methylxanthines).
Pulmonary disease (asthma, interstitial fibrosis).
Pulmonary embolism.
Hepatic failure.
Metabolic acidosis.
High altitude.
CHF.
Pregnancy.
Pain.
CNS lesions.

HYPOGLYCEMIA

ICD-9CM #	251.2	Spontaneous
	250.3	Diabetic
	251.0	Due to Insulin
	579.3	Postoperative
	251.2	Reactive
ICD-10CM #	E16.2	Hypoglycemia, unspecified
	E10.65	Type 1 diabetes mellitus with hyperglycemia
	E15	Nondiabetic hypoglycemic coma
	K91.2	Postsurgical malabsorption, not elsewhere classified
	E16.2	Hypoglycemia, unspecified

Oral hypoglycemics (therapeutic, factitious).
Exogenous insulin (therapeutic, factitious).
Postoperative gastric emptying (alimentary hyperinsulinism).
Severe malnutrition.
Liver disease.
Hypermetabolic state (sepsis).
Ketotic hypoglycemia.
Insulinoma.
Antibodies to endogenous insulin.
Hormone deficiencies (glucagon, growth hormone, hypoadrenalism).
Enzyme disorders in metabolism of glycogen, hexose, glycolysis, and Krebs cycle.
Idiopathic.

HYPOGLYCEMIA, IN INFANTS AND CHILDREN[22a]

ICD-9CM #	251.2	Hypoglycemia
ICD-10CM #	E16.2	Hypoglycemia, unspecified

CLASSIFICATION OF HYPOGLYCEMIA IN INFANTS AND CHILDREN

NEONATAL TRANSIENT HYPOGLYCEMIA

Associated with Inadequate Substrate or Immature Enzyme Function in Otherwise Normal Neonates

Prematurity.
Small for gestational age.
Normal newborn.

Transient Neonatal Hyperinsulinism Also Present in

Infant of diabetic mother.
Discordant twin.
Birth asphyxia.
Infant of toxemic mother.

NEONATAL, INFANTILE, OR CHILDHOOD PERSISTENT HYPOGLYCEMIAS

Hormonal Disorders

Hyperinsulinism.

Recessive K_{ATP} channel HI.
Recessive HADH (hydroxyl acyl CoA dehydrogenase) mutation HI.
Recessive UCP2 (mitochondrial uncoupling protein 2) mutation HI.
Focal K_{ATP} channel HI.
Dominant K_{ATP} channel HI.
Dominant glucokinase HI.
Dominant glutamate dehydrogenase HI (hyperinsulinism/hyperammonemia syndrome).
Dominant mutation in HNF4A (hepatic nuclear factor 4 alpha) HI with MODY later in life.
Dominant mutation in SLC16A1 (the pyruvate transporter)-exercise-induced hypoglycemia.
Acquired islet adenoma.
Beckwith-Wiedemann syndrome.
Insulin administration (Munchausen syndrome by proxy).
Oral sulfonylurea drugs.
Congenital disorders of glycosylation.
Counter-Regulatory Hormone Deficiency
Panhypopituitarism.
Isolated growth hormone deficiency.
Addison disease.
Epinephrine deficiency.
Glycogenolysis and Gluconeogenesis Disorders
Glucose-6-phosphatase deficiency (GSD 1a).
Glucose-6-phosphate translocase deficiency (GSD 1b).
Amylo-1,6-glucosidase (debranching enzyme) deficiency (GSD 3).
Liver phosphorylase deficiency (GSD 6).
Phosphorylase kinase deficiency (GSD 9).
Glycogen synthetase deficiency (GSD 0).
Fructose-1,6-diphosphatase deficiency.
Pyruvate carboxylase deficiency.
Galactosemia.
Hereditary fructose intolerance.
Lipolysis Disorders
Fatty Acid Oxidation Disorders
Carnitine transporter deficiency (primary carnitine deficiency).
Carnitine palmitoyltransferase-1 deficiency.
Carnitine translocase deficiency.
Carnitine palmitoyltransferase-2 deficiency.
Secondary carnitine deficiencies.
Very long, long-, medium-, short-chain acyl-CoA dehydrogenase deficiency.

OTHER ETIOLOGIES

Substrate-Limited
Ketotic hypoglycemia.
Poisoning—drugs.
Salicylates.
Alcohol.
Oral hypoglycemic agents.
Insulin.
Propranolol.
Pentamidine.
Quinine.
Disopyramide.
Ackee fruit (unripe)—hypoglycin.
Vacor (rat poison).
Trimethoprim-sulfamethoxazole (with renal failure).
Liver Disease
Reye syndrome.
Hepatitis.
Cirrhosis.
Hepatoma.
Amino Acid and Organic Acid Disorders
Maple syrup urine disease.
Propionic acidemia.
Methylmalonic acidemia.
Tyrosinosis.
Glutaric aciduria.
3-Hydroxy-3-methylglutaric aciduria.
Systemic Disorders
Sepsis.
Carcinoma/sarcoma (secreting—insulin-like growth factor II).
Heart failure.
Malnutrition.
Malabsorption.
Anti-insulin receptor antibodies.
Anti-insulin antibodies.
Neonatal hyperviscosity.
Renal failure.
Diarrhea.
Burns.
Shock.
Postsurgical.
Pseudohypoglycemia (leukocytosis, polycythemia).
Excessive insulin therapy of insulin-dependent diabetes mellitus.
Factitious.
Nissen fundoplication (dumping syndrome).
Falciparum malaria.

GSD, Glycogen storage disease; *HI,* hyperinsulinemia; K_{ATP} regulated potassium channel.

HYPOGONADISM

ICD-9CM #	256.3	Female
	257.2	Male
	256.3	Ovarian
	253.4	Pituitary
	257.2	Testicular
ICD-10CM #	E28.310	Symptomatic premature menopause
	E29.1	Testicular hypofunction
	E28.39	Other primary ovarian failure
	E23.6	Other disorders of pituitary gland

HYPERGONADOTROPIC HYPOGONADISM

Hormone resistance (androgen, LH insensitivity).
Gonadal defects (e.g., Klinefelter's syndrome, myotonic dystrophy).
Drug-induced (e.g., spironolactone, cytotoxins).
Alcoholism, radiation-induced.
Mumps orchitis.
Anatomic defects, castration.

HYPOGONADOTROPIC HYPOGONADISM

Pituitary lesions (neoplasms, granulomas, infarction, hemochromatosis, vasculitis).
Drug-induced (e.g., glucocorticoids).
Hyperprolactinemia.
Genetic disorders (Laurence-Moon-Biedl syndrome, Prader-Willi).
Delayed puberty.
Other: chronic disease, nutritional deficiency, Kallmann's syndrome, idiopathic isolated LH or FSH deficiency.

HYPOKALEMIA

ICD-9CM #	276.8	
ICD-10CM #	E87.6	Hypokalemia

Cellular shift (redistribution) and undetermined mechanisms.
Alkalosis (each 0.1 increase in pH decreases serum potassium by 0.4 to 0.6 mEq/L).
Insulin administration.
Vitamin B_{12} therapy for megaloblastic anemias, acute leukemias.
Hypokalemic periodic paralysis: rare familial disorder manifested by recurrent attacks of flaccid paralysis and hypokalemia.
Beta-adrenergic agonists (e.g., terbutaline), decongestants, bronchodilators, theophylline, caffeine.
Barium poisoning, toluene intoxication, verapamil intoxication, chloroquine intoxication.
Correction of digoxin intoxication with digoxin antibody fragments (Digibind).
Increased renal excretion.
Drugs:
- Diuretics, including carbonic anhydrase inhibitors (e.g., acetazolamide).
- Amphotericin B.
- High-dose sodium penicillin, nafcillin, ampicillin, or carbenicillin.
- Cisplatin.
- Aminoglycosides.
- Corticosteroids, mineralocorticoids.
- Foscarnet sodium.

RTA: distal (type 1) or proximal (type 2).
Diabetic ketoacidosis (DKA), ureteroenterostomy.
Magnesium deficiency.
Postobstruction diuresis, diuretic phase of ATN.
Osmotic diuresis (e.g., mannitol).
Bartter's syndrome: hyperplasia of juxtaglomerular cells leading to increased renin and aldosterone, metabolic alkalosis, hypokalemia, muscle weakness, and tetany (seen in young adults).
Increased mineralocorticoid activity (primary or secondary aldosteronism), Cushing's syndrome.
Chronic metabolic alkalosis from loss of gastric fluid (increased renal potassium secretion).
GI loss:
- Vomiting, nasogastric suction.
- Diarrhea.
- Laxative abuse.
- Villous adenoma.
- Fistulas.
- Inadequate dietary intake (e.g., anorexia nervosa).
- Cutaneous loss (excessive sweating).
- High dietary sodium intake, excessive use of licorice.

HYPOMAGNESEMIA

ICD-9CM #	275.2	
ICD-10CM #	E83.40	Disorders of magnesium metabolism, unspecified
	E83.42	Hypomagnesemia

GASTROINTESTINAL AND NUTRITIONAL

Defective GI absorption (malabsorption).
Inadequate dietary intake (e.g., alcoholics).
Parenteral therapy without magnesium.
Chronic diarrhea, villous adenoma, prolonged nasogastric suction, fistulas (small bowel, biliary).

EXCESSIVE RENAL LOSSES

Diuretics.
RTA.
Diuretic phase of ATN.
Endocrine disturbances (DKA, hyperaldosteronism, hyperthyroidism, hyperparathyroidism), SIADH, Bartter's syndrome, hypercalciuria, hypokalemia.
Cisplatin, alcohol, cyclosporine, digoxin, pentamidine, mannitol, amphotericin B, foscarnet, methotrexate.
Antibiotics (gentamicin, ticarcillin, carbenicillin).
Redistribution: hypoalbuminemia, cirrhosis, administration of insulin and glucose, theophylline, epinephrine, acute pancreatitis, cardiopulmonary bypass.
Miscellaneous: sweating, burns, prolonged exercise, lactation, "hungry-bones" syndrome.

HYPONATREMIA

ICD-9CM # 276.1
ICD-10CM # E87.1 Hypo-osmolality and hyponatremia

Renal loss from renal disease, diuretics.
GI loss (diarrhea, vomiting, suction).
Hypertonic hyponatremia (e.g., increased serum osmolality from hyperglycemia).
Transcutaneous loss (extensive burns, excessive sweating).
Fluid sequestration (e.g., ascites).
Osmotic diuresis (e.g., mannitol, glucose).
Dilutional (psychogenic polydipsia, iatrogenic).
Syndrome of inappropriate antidiuretic hormone secretion.
Edema with water and sodium retention.
Artifact (e.g., severe hyperlipidemia).
Laboratory error.
Adrenal insufficiency.

HYPOPHOSPHATEMIA

ICD-9CM # 275.3
ICD-10CM # E83.30 Disorder of phosphorus metabolism, unspecified
E83.31 Familial hypophosphatemia

Decreased intake (prolonged starvation [alcoholics], hyperalimentation, or IV infusion without phosphate).
Malabsorption.
Phosphate-binding antacids.
Renal loss:
  RTA.
  Fanconi syndrome, vitamin D–resistant rickets.
  ATN (diuretic phase).
  Hyperparathyroidism (primary or secondary).
  Familial hypophosphatemia.
  Hypokalemia, hypomagnesemia.
  Acute volume expansion.
  Glycosuria, idiopathic hypercalciuria.
  Acetazolamide.
Transcellular shift into cells:
  Alcohol withdrawal.
  DKA (recovery phase).
  Glucose-insulin or catecholamine infusion.
  Anabolic steroids.
  Total parenteral nutrition.
  Theophylline overdose.
  Severe hyperthermia; recovery from hypothermia.
  "Hungry bones" syndrome.

HYPOPIGMENTATION

ICD-9CM # 709.00
ICD-10CM # L81.9 Disorder of pigmentation, unspecified

Vitiligo.
Tinea versicolor.
Atopic dermatitis.
Chemical leukoderma.
Idiopathic hypomelanosis.
Sarcoidosis.
SLE.
Scleroderma.
Oculocutaneous albinism.
Phenylketonuria.
Nevoid hypopigmentation.

HYPOTENSION, POSTURAL

ICD-9CM # 458.0
ICD-10CM # I95.89 Other hypotension

Antihypertensive medications (especially a-blockers, diuretics, ACE inhibitors).
Volume depletion (hemorrhage, dehydration).
Impaired cardiac output (constrictive pericarditis, aortic stenosis).
Peripheral autonomic dysfunction (DM, Guillain-Barré).
Idiopathic orthostatic hypotension.
Central autonomic dysfunction (Shy-Drager syndrome).
Peripheral venous disease.
Adrenal insufficiency.

HYPOTHYROIDISM, CONGENITAL[22a]

ICD-9CM # 243
ICD-10CM # E03.0 Congenital hypothyroidism with diffuse goiter
E03.1 Congenital hypothyroidism without goiter

ETIOLOGIC CLASSIFICATION OF CONGENITAL HYPOTHYROIDISM

PRIMARY HYPOTHYROIDISM

Defect of fetal thyroid development (dysgenesis):
  Aplasia.
  Hypoplasia.
  Ectopia.
Defect in thyroid hormone synthesis (dyshormonogenesis):
  Iodide transport defect: mutation in thyroglobulin gene.
  Thyroid organification, or coupling defect: mutation in thyroid peroxidase gene.
  Defects in H_2O_2 generation: mutations in DUOXA2 maturation factor or *DUOX2* gene.
  Thyroglobulin synthesis defect: mutation in thyroglobulin gene.
  Deiodination defect: mutation in *DEHAL1* gene.
TSH unresponsiveness:
  $G_s\alpha$ mutation (e.g., type 1A pseudohypothyroidism).
  Mutation in TSH receptor.
Defect in thyroid hormone transport: mutation in monocarboxylate transporter 8 *(MCT8)* gene.
Iodine deficiency (endemic goiter).
Maternal antibodies: thyrotropin receptor–blocking antibody (TRBAb, also termed *thyrotropin-binding inhibitor immunoglobulin*).
Maternal medications:
  Iodides, amiodarone.
  Propylthiouracil, methimazole.
  Radioiodine.

CENTRAL (HYPOPITUITARY) HYPOTHYROIDISM

PIT-1 mutations:
  Deficiency of thyroid-stimulating hormone (TSH).
  Deficiency of growth hormone.
  Deficiency of prolactin.
PROP-1 mutations:
  Deficiency of TSH.
  Deficiency of growth hormone.
  Deficiency of prolactin.
  Deficiency of luteinizing hormone.
  Deficiency of follicle-stimulating hormone.
  ±Deficiency of adrenocorticotropic hormone.
TSH deficiency: mutation in TSH β subunit gene (manifests as primary hypothyroidism with elevated TSH level).
Multiple pituitary deficiencies (e.g., craniopharyngioma).
Thyroid-releasing hormone (TRH) deficiency:
  Isolated.
  Multiple hypothalamic deficiencies (e.g., septooptic dysplasia).
TRH unresponsiveness.
Mutations in TRH receptor.

HYPOTONIA, INFANTILE, DIFFERENTIAL DIAGNOSIS[22a]

ICD-9CM # 360.30 Hypotonia
ICD-10CM # H44.40 Unspecified hypotony of eye

Cerebral hypotonia.
  Benign congenital hypotonia.
  Chromosome disorders.
  - Prader-Willi syndrome.
  - Trisomy.

  Chronic nonprogressive encephalopathy.
  - Cerebral malformation.
  - Perinatal distress.
  - Postnatal disorders.

  Peroxisomal disorders.
  - Cerebrohepatorenal syndrome (Zellweger syndrome).
  - Neonatal adrenoleukodystrophy.

Other genetic defects.
- Familial dysautonomia.
- Oculocerebrorenal syndrome (Lowe syndrome).

Other metabolic defects.
- Acid maltase deficiency (see "Metabolic Myopathies").
- Infantile G_M, gangliosidosis.

Spinal cord disorders.
Spinal muscular atrophies.
Acute infantile.
- Autosomal dominant.
- Autosomal recessive.
- Cytochrome-*c* oxidase deficiency.
- X-linked.

Chronic infantile.
- Autosomal dominant.
- Autosomal recessive.
- Congenital cervical spinal muscular atrophy.
- Infantile neuronal degeneration.
- Neurogenic arthrogryposis.

Polyneuropathies.
Congenital hypomyelinating neuropathy.
Giant axonal neuropathy.
Hereditary motor-sensory neuropathies.
Disorders of neuromuscular transmission.
Familial infantile myasthenia.
Infantile botulism.
Transitory myasthenia gravis.
Fiber-type disproportion myopathies.
Central core disease.
Congenital fiber-type disproportion myopathy.
Myotubular (centronuclear) myopathy.
- Acute.
- Chronic.

Nemaline (rod) myopathy.
- Autosomal dominant.
- Autosomal recessive.

Metabolic myopathies.
Acid maltase deficiency.
Cytochrome-*c* oxidase deficiency.
Muscular dystrophies.
- Bethlem myopathy.
- Congenital dystrophinopathy.

Congenital muscular dystrophy.
- Merosin deficiency, primary.
- Merosin deficiency, secondary.
- Merosin positive.

Congenital myotonic dystrophy.

HYPOVOLEMIC SHOCK, PEDIATRIC POPULATION[12c]

ICD-9CM #	785.59	Hypovolemic Shock
ICD-10CM #	R57.1	Hypovolemic shock
	R57.8	Other shock

ETIOLOGIES OF HYPOVOLEMIC SHOCK

Whole blood loss.
- Absolute loss: hemorrhage.

External bleeding.
Internal bleeding.
- Gastrointestinal.
- Intraabdominal (spleen, liver).
- Major vessel injury.
- Intracranial (in infants).
- Fractures.
- Relative loss.

Pharmacologic (barbiturates, vasodilators).
Positive pressure ventilation.
Spinal cord injury.
Sepsis.
Anaphylaxis.

Plasma loss.
- Burns.
- Capillary leak syndromes.

Inflammation, sepsis.
Anaphylaxis.
- Protein-losing syndromes.

Fluid and electrolyte loss.
- Vomiting and diarrhea.
- Excessive diuretic use.
- Endocrine:

Adrenal insufficiency.
Diabetes insipidus.
Diabetes mellitus.

ILIAC FOSSA PAIN, LEFT SIDED[38]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	M25.5	Pain in joint

GASTROINTESTINAL CAUSES OF ACUTE LEFT ILIAC FOSSA PAIN

Nonspecific left iliac fossa pain including constipation.
Acute gastroenteritis.
Acute diverticulitis.
Colonic carcinoma.
Colonic ischemia.
Localized small bowel perforation.

ILIAC FOSSA PAIN, RIGHT SIDED[38]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	M25.5	Pain in joint

DIFFERENTIAL DIAGNOSIS OF RIGHT ILIAC FOSSA PAIN

Gastrointestinal Causes

Nonspecific right iliac fossa pain.
Acute appendicitis.
Mesenteric adenitis.
Terminal ileitis.
Acute inflammation of Meckel's diverticulum.
Crohn's disease of the terminal ileum.
Cecal carcinoma.
Inflammatory cecal lesion (e.g., diverticulitis in a solitary cecal diverticulum).
Inflammatory lesion of the terminal ileum (e.g., foreign body perforation).

Non-Gastrointestinal Causes

Ruptured ovarian follicle (mittelschmerz).
Acute salpingitis (pelvic inflammatory disease).
Rupture/torsion or hemorrhage of an ovarian cyst.
Endometriosis.
Ectopic pregnancy.
Urinary tract infection.

IMMUNODEFICIENCY, CONGENITAL (PRIMARY)

ICD-9CM #	279.2	
ICD-10CM #	D80.0	Hereditary hyopgammaglobulinemia
	D80.1	Nonfamilial hypogammaglobulinemia
	D80.2	Selective deficiency of IgA
	D80.3	Selective deficiency of IgG
	D80.4	Selective deficiency of IgM

CONGENITAL (PRIMARY) CAUSES OF IMMUNODEFIENCY

T-lymphocyte Deficiencies

DiGeorge syndrome (thymic aplasia with reduced CD4 and CD3 cells).
Purine nucleoside phosphorylase deficiency (marked T-cell depletion).

B-lymphocyte Deficiencies

Bruton X-linked agammaglobulinemia (absence of B cells, plasma cells, and antibody).
Selective immunoglobulin G (IgG) subclass deficiencies.
Selective IgA deficiency.
Hyper-IgM immunodeficiency (elevated IgM but reduced IgG and IgA).

Mixed T- and B-lymphocyte Deficiencies

Common variable immunodeficiency (leads to various B-cell activation or differentiation defects and gradual deterioration of T-cell number and function).
Severe combined immunodeficiency (severe reduction in IgG and absence of T cells).
Wiskott-Aldrich syndrome (decreased T-cell number and function, low IgM, occasionally low IgG).
Ataxia-telangiectasia (decreased T-cell number and function; IgA, IgE, IgG_2, and IgG_4 deficiency).

Disorders of Complement

C3 deficiency (congenital absence of C3 or consumption of C3 due to deficiency of C3b inactivator).

Phagocyte Defects

Chronic granulomatous disease (defect in nicotinamide adenine dinucleotide phosphate oxidase in phagocytic cells).
Chédiak-Higashi syndrome (impaired microbicidal activity of phagocytes).
Kostmann syndrome, Shwachman-Diamond syndrome, cyclic neutropenia (low neutrophil count).

IMPOTENCE[27]

ICD-9CM #	302.72	Psychosexual
	607.84	Organic
	997.99	Organic Postprostatectomy
ICD-10CM #	F52.21	Male erectile disorder
	F52.8	Other sexual dysfunction not due to a substance or known physiological condition
	N52.9	Male erectile dysfunction, unspecified

Psychogenic.
Endocrine: hyperprolactinemia, DM, Cushing's syndrome, hypothyroidism or hyperthyroidism, abnormality of hypothalamic-pituitary-testicular axis.
Vascular: arterial insufficiency, venous leakage, AV malformation, local trauma.
Medications.
Neurogenic: autonomic or sensory neuropathy, spinal cord trauma or tumor, CVA, multiple sclerosis, temporal lobe epilepsy.
Systemic illness: renal failure, COPD, cirrhosis of liver, myotonic dystrophy.
Peyronie's disease.
Prostatectomy.

INCONTINENCE, FECAL[38]

ICD-9CM #	787.6	
ICD-10CM #	R15.9	Full incontinence of feces

NORMAL SPHINCTER

Diarrhea.
Anorectal conditions:
- Rectal carcinoma.
- Inflammatory bowel disease.
- Hemorrhoids.
- Mucosal prolapse.
- Fissure-in-ano.
- Abnormal rectal sensation.

ABNORMAL SPHINCTER

Congenital abnormalities.
Anal sepsis.
Neurologic conditions.
Rectal prolapse.
Sphincter trauma.
Neurogenic (idiopathic) incontinence.

INFERTILITY, FEMALE[14]

ICD-9CM #	628.9	
ICD-10CM #	N97.9	Female infertility, unspecified

FALLOPIAN TUBE PATHOLOGY

PID or puerperal infection.
Congenital anomalies.
Endometriosis.
Secondary to past peritonitis of nongenital origin.
Amenorrhea and anovulation.
Minor anovulatory disturbances.

CERVICAL AND UTERINE FACTORS

Leiomyomas and polyps.
Uterine anomalies.
Intrauterine synechiae (Asherman's syndrome).
Destroyed endocervical glands (postsurgery or postinfection).

VAGINAL FACTORS

Congenital absence of vagina.
Imperforate hymen.
Vaginismus.
Vaginitis.

IMMUNOLOGIC FACTORS

Sperm-immobilizing antibodies.
Sperm-agglutinating antibodies.

NUTRITIONAL AND METABOLIC FACTORS

Thyroid disorders.
DM.
Severe nutritional disturbances.

INFERTILITY, MALE[14]

ICD-9CM #	606.9	
ICD-10CM #	N46.9	Male infertility, unspecified

DECREASED PRODUCTION OF SPERMATOZOA

Varicocele.
Testicular failure.
Endocrine disorders.
Cryptorchidism.
Stress, smoking, caffeine, nicotine, recreational drugs.

DUCTAL OBSTRUCTION

Epididymal (postinfection).
Congenital absence of vas deferens.
Ejaculatory duct (postinfection).
Postvasectomy.

INABILITY TO DELIVER SPERM INTO VAGINA

Ejaculatory disturbances.
Hypospadias.
Sexual problems (i.e., impotence), medical or psychological.

ABNORMAL SEMEN

Infection.
Abnormal volume.
Abnormal viscosity.
Abnormal sperm motion.

IMMUNOLOGIC FACTORS

Sperm-immobilizing antibodies.
Sperm-agglutinating antibodies.

INSOMNIA[33]

ICD-9CM #	780.52	Insomnia NOS
	307.42	Insomnia, Chronic Associated with Anxiety or Depression
	780.51	Insomnia with Sleep Apnea
ICD-10CM #	G47.00	Insomnia, unspecified
	F51.01	Primary insomnia
	F51.03	Paradoxical insomnia
	F51.09	Other insomnia not due to a substance or known physiological condition

Anxiety disorder, psychophysiologic insomnia.
Depression.
Drugs (e.g., caffeine, amphetamines, cocaine), hypnotic-dependent sleep disorder.
Pain, fibromyalgia.
Inadequate sleep hygiene.
Restless leg syndrome.
Obstructive sleep apnea.
Sleep bruxism.
Medical illness (e.g., GERD, sleep-related asthma, parkinsonism and movement disorders).
Narcolepsy.
Other: periodic leg movement of sleep, central sleep apnea, REM behavioral disorder.

INTESTINAL PSEUDOOBSTRUCTION[36]

ICD-9CM #	560.1	Adynamic Intestinal Obstruction
	564.9	Intestinal Disorder, Functional
ICD-10CM #	K56.0	Paralytic ileus
	K56.7	Ileus, unspecified
	K59.9	Functional intestinal disorder, unspecified

"PRIMARY" (IDIOPATHIC INTESTINAL PSEUDOOBSTRUCTION)

Hollow visceral myopathy:
  Familial.
  Sporadic.
Neuropathic:
  Abnormal myenteric plexus.
  Normal myenteric plexus.

SECONDARY

Scleroderma.
Myxedema.
Amyloidosis.
Muscular dystrophy.
Hypokalemia.
Chronic renal failure.
DM.
Drug toxicity caused by:
  Anticholinergics.
  Opiate narcotics.
Ogilvie's syndrome.

INTRAABDOMINAL MASS LESION, NEONATAL[16a]

ICD-9CM #	789.3	
ICD-10CM #	R19.00	Intraabdominal and pelvic swelling, mass and lump, unspecified site

CAUSES OF A NEONATAL INTRA-ABDOMINAL MASS LESION

Complicated meconium ileus.
Dilated bowel proximal to an obstruction.
Mesenteric or duplication cyst.
Abscess.
GU causes:
  Hydronephrosis.
  Renal cystic disease.
  Mesoblastic nephroma.
  Wilms' tumor.
  Adrenal hemorrhage.
  Neuroblastoma.
  Retroperitoneal teratoma.

Ovarian cyst.
Hydrometrocolpos.
Hemangioendothelioma.
Hepatoblastoma.
Choledochal, hepatic, or splenic cysts.

INTRACEREBRAL HEMORRHAGE, NONHYPERTENSIVE CAUSES

ICD-9CM #	431	
ICD-10CM #	I61.9	Nontraumatic intracerebral hemorrhage, unspecified

Trauma.
Anticoagulation.
Intracranial tumors.
Vascular malformations.
Bleeding disorders.
Vasculitides (e.g., polyarteritis nodosa, granulomatous angiitis).
Cocaine and other sympathomimetic agents.
Cerebral amyloid angiopathy.

INTRACRANIAL LESION

ICD-9CM #	348.8	
ICD-10CM #	G93.89	Other specified disorders of brain

Tumor (primary or metastatic).
Abscess.
Stroke.
Intracranial hemorrhage.
Angioma.
Multiple sclerosis (initial single lesion).
Granuloma.
Herpes encephalitis.
Artifact.

INTRAOCULAR NEOPLASM

ICD-9CM #	varies with specific disorder	
ICD-10CM #	C69.9	Malignant disorder of eye, unspecified

MALIGNANT

Retinoblastoma.
Melanoma.
Reticulum cell sarcoma.
Metastatic tumor.

BENIGN

Melanocytic nevus.
Hemangioma.
Reactive lymphoid hyperplasia.

IRON OVERLOAD[20]

ICD-9CM #	275.0	
ICD-10CM #	E83.10	Disorder of iron metabolism, unspecified

HEREDITARY IRON OVERLOAD

Hereditary hemochromatosis:
HFE-associated (type 1).
Non–HFE-associated:
- Transferrin receptor 2–associated (type 3).

Juvenile hemochromatosis (type 2):
Hemojuvelin-associated (type 2A).
Hepcidin-associated (type 2B).
Autosomal dominant hemochromatosis:
Ferroportin-associated (type 4).
DMT1-associated hemochromatosis.
Atransferrinemia.
Aceruloplasminemia.

ACQUIRED IRON OVERLOAD

Iron-loading anemias (refractory anemias with hypercellular erythroid marrow).
Chronic liver disease.
Porphyria cutanea tarda.
Insulin resistance–associated hepatic iron overload.
African dietary iron overload.[a]
Medical iron ingestion.[a]
Parenteral iron overload:
Transfusional iron overload.
Inadvertent iron overload from therapeutic injections.

PERINATAL IRON OVERLOAD

Neonatal hemochromatosis.
Trichohepatoenteric syndrome.
Cerebrohepatorenal syndrome.
GRACILE[b] (Fellman) syndrome.

FOCAL SEQUESTRATION OF IRON

Idiopathic pulmonary hemosiderosis.
Renal hemosiderosis.
Associated with neurologic abnormalities:
Pantothenate kinase–associated neurodegeneration (formerly called Hallervorden-Spatz syndrome).
Neuroferritinopathy.
Friedreich's ataxia.

[a] May have a genetic component.
[b] *GRACILE,* Growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis, and early death.

ISCHEMIA, UPPER EXTREMITY, CAUSES[5a]

ICD-9CM #	903.8	Ischemia, Upper Extremity
ICD-10CM #	S45.809A	Unspecified injury of other specified blood vessels at shoulder and upper arm level, unspecified arm, initial encounter

VASOSPASM

Raynaud disease.
Medication induced: vasopressors, b-blockers.
Ergot poisoning.

INTRINSIC ARTERIAL DISEASE

Atherosclerosis.
Radiation arteritis.
Azotemic arteriopathy.
Spontaneous dissection.
Fibromuscular dysplasia.

INFLAMMATORY DISEASES

Connective tissue disorders.
Buerger disease.
Takayasu arteritis.
Temporal (giant cell) arteritis.
Hypersensitivity angiitis.

NONINFLAMMATORY MEDICAL DISEASE

Thrombophilic states.
Myeloproliferative disorders.
Cold injury.
Hepatitis-associated vasculitis.
Cryoglobulinemia.
Vinyl chloride exposure.

EMBOLISM

Cardiac (most common).
Proximal aneurysm.
Arterial thoracic outlet syndrome.
Atheroembolism.
Paradoxic embolus (with accompanying septal defect).

TRAUMA

Iatrogenic.
Blunt arterial injury.
Penetrating arterial injury.
Hypothenar hammer syndrome.
Vibration.

ISCHEMIC BOWEL DISEASE[1]

ICD 9CM #	557.1	
ICD 10CM #	K55.1	Vascular disorder of intestine
	I99	Other and unspecified disorders of circulatory system

Abdominal aortic aneurysm: rupture or expansion.
Perforated ulcer or viscus.
Ruptured ectopic pregnancy (woman of childbearing age).
Incarcerated or strangulated hernia.
Septic shock.
Intussusception.
Volvulus.
Salpingitis or tuboovarian abscess.
Torsion of the ovary or testicle.
Appendicitis.
Pelvic mass or torsion.
Pancreatitis.
Diverticulitis.
Ruptured ovarian cyst.
Renal colic.
Biliary colic.
Also consider atypical manifestations of:
Inferior wall myocardial infarction.
Pulmonary embolism.
Pneumonia.
Diabetic ketoacidosis.
Acute glaucoma.
Differential diagnoses are listed in order of urgency.

ISCHEMIC COLITIS, NONOCCLUSIVE[21]

ICD-9CM # 557.1
ICD-10CM # K55.1 Chronic vascular disorders of intestine

ACUTE DIMINUTION OF COLONIC INTRAMURAL BLOOD FLOW

Small Vessel Obstruction
Collagen-vascular disease.
Vasculitis, diabetes.
Oral contraceptives.
Nonocclusive Hypoperfusion
Hemorrhage.
CHF, MI, arrhythmias.
Sepsis.
Vasoconstricting agents: vasopressin, ergot.
Increased viscosity: polycythemia, sickle cell disease, thrombocytosis.

INCREASED DEMAND ON MARGINAL BLOOD FLOW

Increased Motility
Mass lesion, stricture.
Constipation.
Increased Intraluminal Pressure
Bowel obstruction.
Colonoscopy.
Barium enema.

ISCHEMIC NECROSIS OF CARTILAGE AND BONE[14]

ICD-9CM # 733.90
ICD-10CM # M89.9 Disorder of bone, unspecified
M94.9 Disorder of cartilage, unspecified

ENDOCRINE/METABOLIC

Ethanol abuse.
Glucocorticoid therapy.
Cushing's disease.
DM.
Hyperuricemia.
Osteomalacia.
Hyperlipidemia.

STORAGE DISEASES (E.G., GAUCHER'S DISEASE)

Hemoglobinopathies (e.g., sickle cell disease).
Trauma (e.g., dislocation, fracture).
HIV infection.
Dysbaric conditions (e.g., caisson disease).
Collagen-vascular disorders.
Irradiation.
Pancreatitis.
Organ transplantation.
Hemodialysis.
Burns.
Intravascular coagulation.
Idiopathic, familial.

JAUNDICE

ICD-9CM # 782.4 Jaundice NOS
576.8 Jaundice, Obstructive
277.4 Bilirubin Excretion Disorders
ICD-10CM # R17 Unspecified jaundice
K83.8 Other specified diseases of biliary tract
E80.7 Disorder of bilirubin metabolism, unspecified

PREDOMINANCE OF DIRECT (CONJUGATED) BILIRUBIN

Extrahepatic obstruction.
Common duct abnormalities: calculi, neoplasm, stricture, cyst, sclerosing cholangitis.
Metastatic carcinoma.
Pancreatic carcinoma, pseudocyst.
Ampullary carcinoma.
Hepatocellular disease: hepatitis, cirrhosis.
Drugs: estrogens, phenothiazines, captopril, methyltestosterone, labetalol.
Cholestatic jaundice of pregnancy.
Hereditary disorders: Dubin-Johnson syndrome, Rotor's syndrome.
Recurrent benign intrahepatic cholestasis.

PREDOMINANCE OF INDIRECT (UNCONJUGATED) BILIRUBIN

Hemolysis: hereditary and acquired hemolytic anemias.
Inefficient marrow production.
Impaired hepatic conjugation: chloramphenicol.
Neonatal jaundice.
Hereditary disorders: Gilbert's syndrome, Crigler-Najjar syndrome.

JAUNDICE, CLASSIFICATION[1a]

ICD-9CM # 782.4
ICD-10CM # R17 Unspecified jaundice

PREHEPATIC (PREDOMINANTLY UNCONJUGATED HYPERBILIRUBINEMIA)

Overproduction
Hemolysis (e.g., spherocytosis, sickle cell disease, hemolysis of the newborn, autoimmune disorders).
Ineffective erythropoiesis (e.g., megaloblastic anemias).
Hematomas.
Pulmonary emboli.

HEPATIC (UNCONJUGATED HYPERBILIRUBINEMIA)

Decreased Hepatic Uptake
Gilbert syndrome.
Drugs (e.g., rifampin, radiographic contrast agents).
Neonatal jaundice.
Posthepatitis.
Decreased cystolic binding proteins (e.g., newborn or premature infants).
Portacaval shunt.
Prolonged fasting.
Decreased Conjugation Due to Limited Glucuronyl Transferase Activity
Gilbert's disease.
Crigler-Najjar syndrome, types I and II.
Neonatal jaundice.
Breast-milk jaundice.
Chronic persistent hepatitis.
Wilson's disease.
Noncirrhotic portal fibrosis.
Drug inhibition (e.g., chloramphenicol).

PREDOMINANTLY CONJUGATED HYPERBILIRUBINEMIA

Impaired Hepatic Excretion
Familial disorders (Dubin-Johnson syndrome, Rotor syndrome, benign recurrent cholestasis, cholestasis of pregnancy).
Hepatocellular infiltrative disorders.
Liver metastasis.
Liver cirrhosis.
Hepatitis (viral, bacterial, parasitic, autoimmune, ethanol, and drug-induced).
Drug-induced cholestasis (especially chlorpromazine, erythromycin estolate, isoniazid, halothane).
Primary biliary cirrhosis.
Primary sclerosing cholangitis.
Pericholangitis.
Congestive heart failure.
Shock.
Toxemia of pregnancy.
Sarcoidosis.
Hepatic trauma.
Amyloidosis.
Autoimmune cholangiopathy.
Vanishing bile duct syndrome.
Sepsis.
Postoperative complications.

EXTRAHEPATIC

Extrahepatic Biliary Obstruction
Gallstones, choledocholithiasis.
Cholecystitis.
Tumors of the head of the pancreas (adenocarcinoma, mucinous duct ectasia, neuroendocrine tumors, metastasis).
Tumors of bile ducts (cholangiocarcinoma, Klatskin tumor: cholangiocarcinoma at the bifurcation).
Gallbladder cancer.
Tumors of the ampulla of Vater (adenoma, adenocarcinoma).
Tumors of the duodenum (adenocarcinoma, lymphoma).
Hemobilia (blood in the biliary tree).
Biliary strictures (postcholecystectomy, postliver transplantation, primary sclerosing cholangitis).
Congential disorders (biliary atresia, idiopathic dilation of common bile duct, cystic fibrosis).
Metastasis to the hepatic hilum.
Primary bile duct lymphoma.
Cholangiopathy of acquired immunodeficiency syndrome.
Choledochal cysts.
Infectious cholangiopathy *(Clonorchis sinensis, Ascaris lumbricoides, Fasciola hepatica).*
Chronic pancreatitis (fibrosis of the head of the pancreas).

JAUNDICE, NEONATAL[1a]

ICD-9CM #	774.6	
ICD-10CM #	P59.9	Neonatal jaundice, unspecified

PREHEPATIC

Hereditary spherocytosis.
Nonspherocytic hemolytic anemia (glucose-6-phosphate dehydrogenase deficiency, α-thalassemia, vitamin K_3–induced hemolysis, pyruvate kinase deficiency).

HEPATIC

Crigler-Najjar syndrome, types I and II.
α_1-Antitrypsin deficiency.
Sepsis.
Drug-induced.
Hypothyroidism.
Breast-milk jaundice.
Fetomaternal blood group incompatibility (Rhesus, Landsteiner groups ABO).

POSTHEPATIC

Extrahepatic biliary obstruction.
Biliary atresia.
Bile duct paucity.
Alagille syndrome.

JOINT AND PERIARTICULAR PAIN, ACUTE[12a]

ICD-9CM #	719.40	
ICD-10CM #	M25.50	Joint pain

COMMON ACUTE MONOARTHRITIS

Septic arthritis (nongonococcal, gonococcal).
Crystal arthritis (gout, pseudogout).
Reactive arthritides.
Lyme disease.
Plant thorn synovitis.
Other infections (mycobacterial, viral, soft tissue).

TRAUMA OR INTERNAL DERANGEMENT

Loose bodies.
Stress fractures.
Ischemic necrosis.
Hemarthrosis.

ACUTE MONOARTHRITIS OF POLYARTHRITIS

Psoriatic arthritis.
Enteropathic arthritis.
Rheumatoid arthritis/palindromic rheumatism.
Juvenile inflammatory arthritides.

MONOARTHROPATHIES FROM NONINFLAMMATORY DISEASE

Osteoarthritis.
Charcot's joints.
Storage diseases (hemochromatosis, ochronosis).

SYNOVIAL DISEASES

Pigmented villonodular synovitis.
Lipoma arborescens.
Synovial osteochondromatosis.
Reflex sympathetic dystrophy.
Sarcoidosis.
Amyloid.

ACUTE MONOARTHRITIS OF SYSTEMIC DISEASE

Systemic lupus erythematosus.
Vasculitides (antineutrophil cytoplasmic antibody positive and negative).
Henoch-Schönlein purpura.
Behçet's disease.
Bacterial endocarditis.
Familial Mediterranean fever.
Relapsing polychondritis.

SOFT TISSUE LESIONS

BONE DISEASES

Paget's disease.
Osteomyelitis (Brodie's abscess).
Osteogenic/osteoid tumors.
Metastatic disease.
Pulmonary hypertrophic osteoarthropathy.

This table shows the causes of inflammation in any one joint (monoarthritis) and pain around the joint that presents without inflammation (monoarthropathy).

JOINT PAIN, ANTERIOR HIP, MEDIAL THIGH, KNEE[28]

ICD-9CM #	719.4 add 5th digit	
	0 Site NOS	
	1 Shoulder Region	
	2 Upper Arm (Elbow, Humerus)	
	3 Forearm (Radius, Wrist, Ulna)	
	4 Hand	
	5 Pelvic Region and Thigh	
	6 Lower Leg (Fibula, Patella, Tibia)	
	7 Ankle and/or Foot	
ICD-10CM #	M25.50	Pain in unspecified joint
	M25.559	Pain in unspecified hip
	M25.569	Pain in unspecified knee

ACUTE

Acute rheumatic fever.
Adductor muscle strain.
Avascular necrosis.
Crystal arthritis.
Femoral artery (pseudo) aneurysm.
Fracture (femoral neck or intertrochanteric).
Hemarthrosis.
Hernia.
Herpes zoster.
Iliopectineal bursitis.
Iliopsoas tendinitis.
Inguinal lymphadenitis.
Osteomalacia.
Painful transient osteoporosis of hip.
Septic arthritis.

SUBACUTE AND CHRONIC

Adductory muscle strain.
Amyloidosis.
Acute rheumatic fever.
Femoral artery aneurysm.
Hernia (inguinal or femoral).
Iliopectineal bursitis.
Iliopsoas tendinitis.
Inguinal lymphadenopathy.
Osteochondromatosis.
Osteomyelitis.
Osteitis deformans (Paget's disease).
Osteomalacia (pseudofracture).
Postherpetic neuralgia.
Sterile synovitis (e.g., RA, psoriatic, SLE).

JOINT PAIN, HIP, LATERAL THIGH[28]

ICD-9CM #	959.6	Hip Injury
	719.95	Hip Joint Disorder
	843.9	Hip Strain
ICD-10CM #	S79.919A	Unspecified injury of unspecified hip, initial encounter
	S79.929A	Unspecified injury of unspecified thigh, initial encounter
	M25.9	Joint disorder, unspecified

ACUTE

Herpes zoster.
Iliotibial tendinitis.
Impacted fracture of femoral neck.
Lateral femoral cutaneous neuropathy (meralgia paresthetica).
Radiculopathy: L4-5.
Trochanteric avulsion fracture (greater trochanter).
Trochanteric bursitis.
Trochanteric fracture.

SUBACUTE AND CHRONIC

Lateral femoral cutaneous neuropathy (meralgia paresthetica).
Osteomyelitis.
Postherpetic neuralgia.
Radiculopathy: L4-5.
Tumors.

JOINT PAIN, POLYARTICULAR

ICD-9CM #	719.40	
ICD-10CM #	M25.50	Pain in unspecified join

Osteoarthritis.
RA.
Fibromyalgia.
Viral syndrome (e.g., human parvovirus B19 infection).
SLE.
Psoriatic arthritis.
Ankylosing spondylitis.

JOINT PAIN, POSTERIOR HIPS, THIGH, BUTTOCKS[28]

ICD-9CM # 719.4 add 5th digit
0 Site NOS
1 Shoulder Region
2 Upper Arm (Elbow, Humerus)
3 Forearm (Radius, Wrist, Ulna)
4 Hand
5 Pelvic Region and Thigh
6 Lower Leg (Fibula, Patella, Tibia)
7 Ankle and/or Foot

ICD-10CM #

M25.50	Pain in unspecified joint
M25.559	Pain in unspecified hip
M25.569	Pain in unspecified knee

ACUTE

Gluteal muscle strain.
Herpes zoster.
Ischial bursitis.
Ischial or sacral fracture.
Osteomalacia (pseudofracture).
Sciatic neuropathy.
Radiculopathy: L5-S1.

SUBACUTE AND CHRONIC

Gluteal muscle strain.
Ischial bursitis.
Lumbar spinal stenosis.
Osteoarthritis of hip.
Osteitis deformans (Paget's disease).
Osteomyelitis.
Osteochondromatosis.
Osteomalacia (pseudofracture).
Postherpetic neuralgia.
Radiculopathy: L5-S1.
Tumors.

JOINT SWELLING

ICD-9CM # 719.0 add 5th digit
0 Site NOS
1 Shoulder Region
2 Upper Arm (Elbow, Humerus)
3 Forearm (Radius, Wrist, Ulna)
4 Hand
5 Pelvic Region and Thigh
6 Lower Leg (Fibula, Patella, Tibia)
7 Ankle and/or Foot

ICD-10CM #

M25.40	Effusion, unspecified joint

Trauma.
Osteoarthritis.
Gout.
Pyogenic arthritis.
Pseudogout.
RA.
Viral syndrome.

JUGULAR VENOUS DISTENTION

ICD-9CM #	459.89	Increased Venous Pressure
ICD-10CM #	I99.8	Other disorder of circulatory system

Right-sided heart failure.
Cardiac tamponade.
Constrictive pericarditis.
Goiter.
Tension pneumothorax.
Pulmonary hypertension.
Cardiomyopathy (restrictive).
Superior vena cava syndrome.
Valsalva maneuver.
Right atrial myxoma.
COPD.

KERATITIS, NONINFECTIOUS

ICD-9CM #	370.9	
ICD-10CM #	H16.9	Unspecified keratitis

Collagen vascular disease.
Atopic keratoconjunctivitis.
Chemical injury.
Thermal injury.
Ectropion/entropion.
Lid defects.
Exophthalmos.
Keratoconjunctivitis sicca.
Erythema multiforme.
Mucous membrane pemphigoid.
DM (delayed epithelial healing).
Neuroparalytic (cranial nerve VII).
Neurotrophic (diabetes, cranial nerve V).

KIDNEY ENLARGEMENT, UNILATERAL[38]

ICD-9CM #	591	
ICD-10CM #	N13.30	Unspecified hydronephrosis

Hydronephrosis (may be bilateral).
Polycystic kidney (may be bilateral).
Simple cyst of kidney.
Renal cell carcinoma.
Pyonephrosis (may be bilateral).
Acute renal vein thrombosis.

KNEE PAIN[28]

ICD-9CM #	844.1	Collateral Ligament Sprain, Medial
	844.2	Cruciate Ligament Sprain
	716.96	Knee Inflammation
	959.7	Knee Injury
	718.86	Knee Instability
	836.1	Lateral Meniscus Tear
	836.0	Medial Meniscus Tear
	844.8	Patellar Sprain
	719.56	Knee Stiffness
	719.06	Knee Swelling

ICD-10CM #

S83.419A	Sprain of medial collateral ligament of unspecified knee, initial encounter
S83.509A	Sprain of unspecified cruciate ligament of unspecified knee, initial encounter
M23.50	Chronic instability of knee, unspecified knee
M23.8X9	Other internal derangements of unspecified knee
S83.289A	Other tear of lateral meniscus, current injury, unspecified knee, initial encounter
S83.249A	Other tear of medial meniscus, current injury, unspecified knee, initial encounter
M25.669	Stiffness of unspecified knee, not elsewhere classified

DIFFUSE

Articular.
Anterior.
Prepatellar bursitis.
Patellar tendon enthesopathy.
Chondromalacia patellae.
Patellofemoral osteoarthritis.
Cruciate ligament injury.
Medial plica syndrome.

MEDIAL

Anserine bursitis.
Spontaneous osteonecrosis.
Osteoarthritis.
Medial meniscal tear.
Medial collateral ligament bursitis.
Referred pain from hip and L3.
Fibromyalgia.

LATERAL

Iliotibial band syndrome.
Meniscal cyst.
Lateral meniscal tear.
Collateral ligament.
Peroneal tenosynovitis.

POSTERIOR

Popliteal cyst (Baker's cyst).
Tendinitis.
Aneurysms, ganglions, sarcoma.

KNEE PAIN, IN DIFFERENT AGE GROUPS[8]

ICD-9CM #	719.46	
ICD-10CM #	M25.569	Pain in unspecified knee

COMMON CAUSES OF KNEE PAIN IN DIFFERENT AGE GROUPS

Childhood (2-10 yr)
Intraarticular
Juvenile arthritis.
Osteochondritis dissecans.
Infection.
Torn discoid meniscus.
Periarticular
Osteomyelitis.
Referred
Perthes' disease.
Irritable hip.
Adolescence (10-18 yr)
Intraarticular
Osteochondritis dissecans.
Torn meniscus.
Anterior knee pain syndrome.
Patellar instability.
Periarticular
Osgood–Schlatter disease.
Sinding–Larsen–Johansson syndrome.
Osteomyelitis.
Bone tumors.
Referred
Slipped upper femoral epiphysis.
Early Adulthood (18-30 yr)
Intraarticular
Torn meniscus.
Patellar instability.
Anterior knee pain syndrome.
Inflammatory arthritis.
Periarticular
Ligament injuries.
Bursitis.
Adulthood (30-50 yr)
Intraarticular
Degenerate meniscal tears.
Osteoarthritis.
Inflammatory arthritis.
Periarticular
Bursitis.
Referred
Osteoarthritis of hip.
Spinal disorders.
Old Age (>50 yr)
Intraarticular
Osteoarthritis.
Inflammatory arthritis.
Periarticular
Bursitis.
Referred
Osteoarthritis of hip.
Spinal disorders.

LARGE BOWEL STRICTURE[16a]

ICD-9CM # 751.2
ICD-10CM # S36.5 Injury of colon

CAUSES OF LARGE BOWEL STRICTURES

Physiologic:
- Spasm.
- Distended bladder.

Maligant:
- Annular carcinoma.
- Scirrhous carcinoma.
- Lymphoma.

Diverticular disease:
- Muscle thickening.
- Pericolic abscess.
- Superimposed malignancy.

Ischemia.
Radiation colitis.
Inflammatory bowel disease:
- Ulcerative colitis.
- Crohn's disease.
- Tuberculosis.
- Lymphogranuloma venereum.
- Amebiasis.

Extrinsic disease:
- Intraabdominal masses.
- Melastatic carcinoma.
- Endometriosis.
- Pelvic lipomatosis.
- Cholecystitis.
- Pancreatitis.

Miscellaneous:
- Postoperative anastomosis.
- Trauma.
- Hirschsprung's disease.

LEFT AXIS DEVIATION[22]

ICD-9CM #	426.3	Left Bundle Branch Block
	426.2	Left Bundle Branch Hemiblock
	429.3	Left Ventricular Hypertrophy
ICD-10CM #	I44.7	Left bundle-branch block, unspecified
	I44.4	Left anterior fascicular block
	I44.5	Left posterior fascicular block
	I44.60	Unspecified fascicular block
	I44.69	Other fascicular block

Normal variation.
Left anterior fascicular block (hemiblock).
Left bundle branch block.
Left ventricular hypertrophy.
Mechanical shifts causing a horizontal heart, high diaphragm, pregnancy, ascites.
Some forms of ventricular tachycardia.
Endocardial cushion defects and other congenital heart disease.

LEFT BUNDLE BRANCH BLOCK

ICD-9CM #	426.3	
ICD-10CM #	I44.7	Left bundle-branch block, unspecified

Ischemic heart disease.
Electrolyte abnormalities (e.g., hyperkalemia).
Cardiomyopathy.
Idiopathic.
LVH.
Pulmonary embolism.
Cardiac trauma.
Bacterial endocarditis.

LEG CRAMPS, NOCTURNAL

ICD-9CM #	729.82	Muscle Cramps
ICD-10CM #	R25.2	Cramp and spasm

Diabetic neuropathy.
Medications.
Electrolyte abnormalities (hypokalemia, hyponatremia, hypocalcemia, hyperkalemia, hypophosphatemia).
Respiratory alkalosis.
Uremia.
Hemodialysis.
Peripheral nerve injury.
ALS.
Alcohol use.
Heat cramps.
Vitamin B_{12} deficiency.
Hyperthyroidism.
Contractures.
DVT.
Hypoglycemia.
Peripheral vascular insufficiency.
Baker's cyst.

LEG LENGTH DISCREPANCIES[23]

ICD-9CM #	736.81	Leg Length Discrepancy, Acquired
	755.30	Leg Length Discrepancy, Congenital
ICD-10CM #	M21.759	Unequal limb length (acquired), unspecified femur
	M21.769	Unequal limb length (acquired), unspecified tibia and fibula
	Q72.899	Other reduction defects of unspecified lower limb

CONGENITAL

Proximal femoral local deficiency.
Coxa vara.
Hemiatrophy-hemihypertrophy (anisomelia).
Developmental dysplasia of the hip.

DEVELOPMENTAL

Legg-Calvé-Perthes disease.

NEUROMUSCULAR

Polio.
Cerebral palsy (hemiplegia).

INFECTIOUS

Pyogenic osteomyelitis with physeal damage.

TRAUMA

Physeal injury with premature closure.
Overgrowth.
Malunion (shortening).

TUMOR

Physeal destruction.
Radiation-induced physeal injury.
Overgrowth.

LEG MOVEMENT WHEN STANDING, INVOLUNTARY

ICD-9CM # varies with specific disorder
ICD-10CM # R25.8 Other abnormal involuntary movements

Benign essential tremor.
Orthostatic tremor.
Spastic ataxia.
Cerebellar truncal tremor.
Postanoxic myoclonus.

LEG PAIN WITH EXERCISE

ICD-9CM # 729.82 Muscle Cramps
ICD-10CM # R25.2 Cramp and spasm

Shin splints.
Arteriosclerosis obliterans.
Neurogenic (spinal cord compression or ischemia).
Venous claudication.
Popliteal cyst.
DVT.
Thromboangiitis obliterans.
Adventitial cysts.
Popliteal artery entrapment syndrome.
McArdle syndrome.

LEG SWELLING[1]

ICD-9CM # 782.3
ICD-10CM # R60.0

Deep vein thrombosis.
Cellulitis.
Baker cyst rupture or inflammation.
Congestive heart failure.
Renal failure.
Liver failure.
Inferior vena cava compression.
Musculoskeletal trauma.
Polyarteritis nodosa.
Erythema nodosum.
Myositis.
Tendinitis.
Lymphedema.
Superficial thrombophlebitis.
Compartment syndrome.

LEG ULCERS[28]

ICD-9CM #	440.23	Lower Limb, Arteriosclerotic
	707.1	Lower Limb, Chronic
	707.1	Lower Limb, Neurogenic
	250.70	Lower Limb, Chronic DM Type 2
	250.71	Lower Limb, Chronic DM Type 1
ICD-10CM #	I70.25	Atherosclerosis of native arteries of other extremities with ulceration
	L97.909	Non-pressure chronic ulcer of unspecified part of unspecified lower leg with unspecified severity

VASCULAR

Arterial: arteriosclerosis, thromboangiitis obliterans, AV malformation, cholesterol emboli.
Venous: superficial varicosities, incompetent perforators, DVT, lymphatic abnormalities.

VASCULITIS HEMATOLOGIC

Sickle cell anemia, thalassemia, polycythemia vera, leukemia, cold agglutinin disease.
Macroglobulinemia, protein C and protein S deficiency, cryoglobulinemia, lupus anticoagulant, antiphospholipid syndrome.

INFECTIOUS

Fungal: Blastomycosis, coccidioidomycosis, histoplasmosis, sporotrichosis.
Bacterial: Furuncle, ecthyma, septic emboli.
Protozoal: leishmaniasis.

METABOLIC

Necrobiosis lipoidica diabeticorum.
Localized bullous pemphigoid.
Gout, calcinosis cutis, Gaucher's disease.

TUMORS

Basal cell carcinoma, squamous cell carcinoma, melanoma.
Mycosis fungoides, Kaposi's sarcoma, metastatic neoplasms.

TRAUMA

Burns, cold injury, radiation dermatitis.
Insect bites.
Factitial, excessive pressure.

NEUROPATHIC

Diabetic trophic ulcers.
Tabes dorsalis, syringomyelia.

DRUGS

Warfarin, IV colchicine extravasation, methotrexate, halogens, ergotism, hydroxyurea.

PANNICULITIS

Weber-Christian disease.
Pancreatic fat necrosis, alpha-antitrypsinase deficiency.

LEPTOMENINGEAL LESIONS

ICD-9CM # varies with specific disorder
ICD-10CM # G03.9 Leptomeningitis

Metastases.
Multiple sclerosis.
Bacterial or viral meningitis.
Vasculitis.
Lyme disease.
Tuberculosis.
Fungal infections (e.g., *Cryptococcus*).
Sarcoidosis.
Wegener's granulomatosis.
Neurocysticercosis.
Rheumatoid nodules.
Histiocytosis.

LEUKOCORIA

ICD-9CM # 379.90
ICD-10CM # H57.9 Unspecified disorder of eye and adnexa

Cataract.
Retinal detachment.
Retinoblastoma.
Retinal telangiectasia.
Retrolenticular vascularized membrane.
Familial exudative vitreoretinopathy.

LID RETRACTION, CAUSES[20a]

ICD-9CM # 374.41 Lid Retraction
ICD-10CM # H02.539 Eyelid retraction unspecified eye, unspecified lid

Thyroid eye disease.
Neurogenic.
- Contralateral unilateral ptosis.
- Unopposed levator action due to facial palsy.
- 3rd nerve misdirection.
- Marcus Gunn jaw-winking syndrome.
- Collier sign of the dorsal midbrain (Parinaud syndrome).
- Infantile hydrocephalus (setting sun sign).
- Parkinsonism.
- Sympathomimetic drops.

Mechanical.
- Surgical over-correction of ptosis.
- Scarring of upper lid skin.

Congenital.
- Isolated.
- Duane retraction syndrome.
- Down syndrome.
- Transient "eye popping" reflex in normal infants.

Miscellaneous.
- Prominent globe (pseudo-lid retraction).
- Uremia (Summerskill sign).
- Idiopathic.

LIMB ISCHEMIA, ACUTE, NONTRAUMATIC[5a]

ICD-9CM # 903.8
ICD-10CM # Atherosclerosis of arteries of extremities

CAUSES OF NONTRAUMATIC ACUTE LIMB ISCHEMIA

Atherosclerotic
In situ thrombosis.
Atheroembolism from thoracic aortic aneurysm/abdominal aortic aneurysm.
Femoral/popliteal aneurysm with or without compression.
Dissection.
Nonatherosclerotic
Embolism from cardiac thrombosis (atrial fibrillation, post–myocardial infarction akinesis).
Graft thrombosis, graft aneurysm.
Mycotic emboli.
Raynaud syndrome.
Arteritis with thrombosis.
Inherited and acquired hypercoagulable states.
Drug-induced vasospasm.

External compression (Baker cyst, popliteal entrapment).

Mimics

Phlegmasia cerulea dolens.
Acute neuropathy.
Hypovolemia.
Systemic shock.

LIMP

ICD-9CM #	781.2	Gait Abnormality
	719.75	Gait Disorder Due to Joint Abnormality in Hip, Buttock, or Femur
	719.76	Gait Disorder Due to Joint Abnormality in Lower Leg
	719.77	Gait Disorder Due to Joint Abnormality in Ankle and/or Foot
	300.11	Hysterical Gait Disorder
ICD-10CM #	R26.0	Ataxic gait
	R26.1	Paralytic gait
	R26.89	Other abnormalities of gait and mobility
	R26.9	Unspecified abnormalities of gait and mobility
	M25.80	Other specified joint disorders, unspecified joint
	F44.4	Conversion disorder with motor symptom or deficit
	F44.6	Conversion disorder with sensory symptom or deficit

Degenerative joint disease, osteochondritis dissecans, chondromalacia patellae.
Trauma to extremities, vertebral disk, hips.
Poorly fitting shoes, foreign body in shoe, unequal leg length.
Splinter in foot.
Joint infection (septic arthritis, osteomyelitis), viral arthritis.
Abdominal pain (e.g., appendicitis, incarcerated hernia), testicular torsion.
Polio, neuromuscular disorders, Guillain-Barré syndrome, multiple sclerosis.
Osgood-Schlatter disease.
Legg-Calvé-Perthes disease.
Factitious, somatization syndrome.
Neoplasm (local or metastatic).
Other: diskitis, periostitis, sickle cell disease, hemophilia.

LIMPING, PEDIATRIC AGE[23]

ICD-9CM #	781.2	Gait Abnormality
ICD-10CM #	R26.0	Ataxic gait
	R26.1	Paralytic gait
	R26.89	Other abnormalities of gait and mobility
	R26.9	Unspecified abnormalities of gait and mobility

TODDLER (1-3 YR)

Infection:
  Septic arthritis:
    • Hip.
    • Knee.
  Osteomyelitis.
  Diskitis.
Occult trauma:
  Toddler's fracture.
Neoplasia.

CHILDHOOD (4-10 YR)

Infection:
  Septic arthritis:
    • Hip.
    • Knee.
  Osteomyelitis.
  Diskitis.
  Transient synovitis, hip.
LCPD.
Tarsal coalition.
Rheumatologic disorder:
  JRA.
Trauma.
Neoplasia.

ADOLESCENCE (11 + YR)

SCFE.
Rheumatologic disorder:
  JRA.
Trauma.
Tarsal coalition.
Hip dislocation (DDH).
Neoplasia.

DDH, Developmental dysplasia of the hip; *JRA,* juvenile RA; *LCPD,* Legg-Calvé-Perthes disease; *SCFE,* slipped capital femoral epiphysis.

LIVEDO RETICULARIS

ICD-9CM #	code not available	
ICD-10CM #	L95.0	Livedoid vasculitis

Emboli (SBE, left atrial myxoma, cholesterol emboli).
Thrombocythemia or polycythemia.
Antiphospholipid antibody syndrome.
Cryoglobulinemia, cryofibrinogenemia.
Leukocytoclastic vasculitis.
SLE, RA, dermatomyositis.
Pancreatitis.
Drugs (quinine, quinidine, amantadine, catecholamines).
Physiologic (cutis marmorata).
Congenital.

LIVER DISEASE, PREGNANCY[38]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	K75.89	Other specified inflammatory liver diseases

INCIDENTAL TO PREGNANCY

Viral hepatitis.
Alcohol related.
Autoimmune chronic active hepatitis.

RELATED TO PREGNANCY (POSSIBLY INFLUENCED BY HORMONES PRESENT IN PREGNANCY)

Complicated gallstone disease.
Hepatic adenoma.
Focal nodular hyperplasia.
Budd-Chiari syndrome.

SPECIFIC TO PREGNANCY

Severe hyperemesis gravidarum.
Benign intrahepatic cholestasis.
Acute fatty liver of pregnancy.
Preeclampsia (HELLP).

LIVER LESIONS, BENIGN, OFTEN CONFUSED WITH MALIGNANCY

ICD-9CM #	573.8	
ICD-10CM #	K76.1	Chronic passive congestion of liver
	K76.89	Other specified diseases of liver

Fatty infiltration.
Adenoma.
Hemangioma.
Cysts.
Flow artifacts.
Focal nodular hyperplasia.
Nonenhanced vessels.

LOW-VOLTAGE ECG

ICD-9CM #	794.31	
ICD-10CM #	R94.31	Abnormal electrocardiogram [ECG] [EKG]

Hypothyroidism.
Obesity.
Pericardial effusion.
Anasarca.
Pleural effusion.
Pneumothorax.
Amyloidosis.
Aortic stenosis.

LUNG CANCER, OCCUPATIONAL CAUSES[16a]

ICD-9CM #	162.9	
ICD-10CM #	C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung

CAUSES OF OCCUPATIONAL LUNG CANCER

Asbestos	Lagging, insulation
Arsenic	Metal smelting, pesticide manufacture
Beryllium	Electronics, dental prosthetic manufacture
Chromium	Coloring pigment production, electroplating
Nickel	Electroplating
Silica	Grinding, quarrying, sandblasting
Radon	Mining
Uranium	Mining

LUNG DISEASE AND GASTROINTESTINAL AND LIVER INVOLVEMENT[26a]

ICD-9CM # codes vary with specific diagnosis
ICD-10CM # codes vary with specific diagnosis

ESOPHAGEAL REFLUX

Aspiration pneumonia.
Asthma.
Scleroderma.
Bronchitis.
Bronchiectasis.
Cough.
Pulmonary fibrosis.
Mycobacterial disease.

INFLAMMATORY BOWEL DISEASE

Bronchitis.
Bronchiectasis.
Bronchiolitis.
Colobronchial fistula.
Desquamative interstitial lung disease.
Drug reactions for agents that treat inflammatory bowel disease.
Eosinophilic lung disease.
Interstitial lung disease.
Necrobiotic nodules.
Obstructive lung disease.
Organizing pneumonia.
Reduced diffusing capacity.
Sarcoidosis.
Serositis affecting pleura or pericarditis.
Tracheal stenosis.

LIVER

Alpha1-antitrypsin deficiency.
Chronic active hepatitis.
Hepatopulmonary syndrome.
Portapulmonary hypertension.
Primary biliary cirrhosis.
Hepatosplenomegaly.
- Amyloidosis.
- Collagen vascular disease.
- Eosinophilic granulomatosis.
- Lymphatic interstitial pneumonia.
- Sarcoidosis.

LUNG DISEASE AND RENAL INVOLVEMENT[26a]

ICD-9CM # codes vary with specific diagnosis
ICD-10CM # codes vary with specific diagnosis

LUNG DISEASE WITH RENAL INVOLVEMENT

Glomerulonephritis
- Systemic vasculitis.
- Collagen vascular disease.
- Antibasement membrane.
- Sarcoidosis.

Nephrotic Syndrome
- Amyloidosis.
- Disseminated Langerhans cell histiocytosis.
- Drug-induced lung disease.
- Paraneoplastic syndrome.
- Post transplantation.
- Pulmonary hydatid disease.
- Systemic lupus erythematosus.
- Vasculitis.
- Venous thrombosis.

Renal Mass
- Lymphangioleiomyomatosis.
- Metastasis neoplasm.
- Renal carcinoid.
- Tuberous sclerosis.
- Wegener's granulomatosis.

Nephrolithiasis
- Alveolar proteinosis.
- Cystic fibrosis.
- Hypercalcemic syndromes.
- Osteolysis from mycobacteria or fungi.
- Sarcoidosis.

Systemic Hypertension
- Collagen vascular disease.
- Diffuse alveolar hemorrhage.
- Pulmonary renal syndromes.
- Neurofibromatosis.
- Sleep apnea.

LUNG DISEASE AND SKIN AND SUBCUTANEOUS LESIONS[26a]

ICD-9CM # codes vary with specific diagnosis
ICD-10CM # codes vary with specific diagnosis

SKIN AND SUBCUTANEOUS LESIONS ASSOCIATED WITH LUNG DISEASE

Skin Lesions

Diffuse pigment change.
- Acanthosis nigricans—lung neoplasm.
- Albinism—Hermansky-Pudlak syndrome.
- Bronze pigmentation—hemosiderosis.
- Gray-brown—Whipple's disease.

Cutaneous draining sinus.
- Fungal infections (especially histoplasmosis).
- Mycobacterial infections (especially tuberculosis).
- Neoplasms (especially mesothelial tumors).
- Necrotizing vasculitis.
- Other bacterial infections (especially actinomycosis).

Cutaneous ulcers.
- Beryllium disease.
- Chronic venous insufficiency.
- Fungal infections (especially histoplasmosis).
- Mycobacterial disease.
- Necrotizing vasculitis.
- Parasitic disease.
- Polycythemia.
- Sickle cell disease.
- Tularemia.

Cutaneous vasculitis.
- Behçet's syndrome.
- Churg-Strauss syndrome.
- Collagen vascular disease.
- Sarcoidosis.
- Wegener's granulomatosis.

Erythema multiforme.
- Drug reactions.
- Fungi (especially coccidiomycosis).
- Mycoplasma and other infectious agents.
- Neoplasms.
- Exfoliative dermatitis.
- Adverse drug reactions.
- Chemotherapy.
- Disseminated malignancy.
- Graft-versus-host disease.
- Radiation therapy.

Flushing.
- Bronchial carcinoid, pheochromocytoma, other neoplasms.
- Carbon dioxide, cyanide, and other toxins.
- Drugs.
- Foods and vasodilatory substances.
- Hormones.
- Mastocytosis.
- Metabolic states (e.g., hyperthyroidism, fever).

Macular rash.
- Anti-basement membrane disease.
- Café-au-lait spots (neurofibromatosis).
- Coal miner's scars.
- Collagen vascular disease.
- Idiopathic pulmonary fibrosis.
- Rose spots (psittacosis).
- Sarcoidosis.
- Syphilis.
- Viral pneumonia.

Maculopapular rash.
- Amyloidosis.
- Drug-induced lung disease.
- Collagen vascular disease.
- Gaucher's disease.
- Kaposi's sarcoma.
- Lung neoplasm.
- Lymphomatoid granulomatosis.
- Lymphoma.
- Parasites.
- Sarcoidosis.
- Syphilis.
- Vasculitis.
- Viral pneumonia

Telangiectasia
- Arteriovenous malformation
- Ataxia-telangiectasia
- Carcinoid syndrome
- Cushing's disease
- Hepatopulmonary syndrome and other chronic liver diseases
- Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu)
- Mastocytosis
- Systemic sclerosis and other collagen vascular diseases

Urticaria
- Asthma
- Drug reactions
- Cystic fibrosis
- Exercise-induced urticaria
- Food allergy
- Hereditary angioneurotic edema
- Inhaled antigens
- Insect bites and stings

Infectious agents, such as mycoplasma and helicobacter
Mastocytosis
Occupational sensitization
Parasites
Vasculitis

Nail Changes with Lung Disease

Color changes
Cigarette smoking discoloration
Splinter hemorrhages
Yellow nail syndrome
Beau's lines (any severe illness)
Dermatomyositis
Sarcoidosis
Seronegative arthropathies.
Systemic sclerosis.

Lung Disease with Subcutaneous Involvement

Adenopathy.
Environmental mycobacteria.
Fungal infections.
Human immunodeficiency visurs infections.
Metastatic neoplasm.
Leukemia.
Lymphoma.
Sarcoidosis.
Tuberculosis.
Calcinosis.
Dermatomyositis.
Metastatic osteosarcoma.
Mixed connective tissue disease
Scleroderma
Tuberculosis
Uremic metastatic calcification
Erythema induratum (Bazin's disease)
Aortic stenosis
Cryoglobulinemia
Nodular vasculitis
Panniculitis
Peripheral neuropathy
Takayasu's disease
Streptococcus infection
Tuberculosis and other mycobacterial disease
Weber-Christian disease
Erythema nodosa
Neoplasm
Other infectious and inflammatory diseases
Primary coccidiomycosis, histoplasmosis
Primary tuberculosis
Psittacosis
Sarcoidosis
Subcutaneous nodules
Amyloidosis
Neoplasm
Neurofibromatosis
Rheumatoid arthritis.
Tuberous sclerosis (angiofibromas).
von Recklinghausen.
Weber-Christian disease.

Lung Disease with Salivary Gland Enlargement

Bulimia and aspiration.
Gaucher's disease.
Lymphoid interstitial pneumonitis.
Lymphatic carcinoma.
Lymphoma.
Other causes of lymphadenopathy.
Sarcoidosis.
Sjögren disease.

LUNG DISEASE WITH BONE, JOINT, NERVE, AND MUSCLE INVOLVEMENT[26a]

ICD-9CM # codes vary with specific diagnosis
ICD-10CM # codes vary with specific diagnosis

ARTHRITIS

Ankylosing spondylitis.
Collagen vascular diseases.
Reactive arthritis.
Sarcoidosis.
Systemic vasculitis.
Tuberculosis.

BONE LESIONS

Ankylosing spondylitis.
Blastomycosis and other fungal disease.
Collagen vascular diseases.
Eosinophilic granulomatosis.
Fibrous histiocytoma.
Gaucher's disease.
Neoplasm.
Sarcoidosis.
Tuberculosis.

MUSCLE DISEASE

Collagen vascular disease.
L-Tryptophan.
Diabetes insipidus.
Eosinophilic granulomatosis.
Polymyositis.
Sarcoidosis.

NEUROLOGIC DISEASE

Acute inflammatory polyneuropathy.
Amyotrophic lateral sclerosis.
Aspiration.
Botulism.
Lambert-Eaton syndrome.
Myasthenia gravis.
Organophosphate poisoning.
Polio and postpolio syndrome.
Sarcoidosis.
Churg-Strauss syndrome.
Wegener's granulomatosis.

LUNG VOLUMES IN DIFFUSE LUNG DISEASE[14a]

ICD-9CM # varies with specific disorder
ICD-10CM # varies with specific disorder

LARGE LUNG VOLUMES

Emphysema.
Chonic asthma.
Diffuse bronchiolitis obliterans.
Highly trained athletes.
Lymphangioleiomyomatosis.

SMALL LUNG VOLUMES

End-stage lung fibrosis.
Bilateral diaphragmatic paralysis.
Massive ascites.

NORMAL LUNG VOLUMES

Sarcoidosis.
Langerhans cell histiocytosis.
Neurofibromatosis.
Emphysema with pulmonary fibrosis.

LYMPHADENOPATHY[14]

ICD-9CM # 785.6
ICD-10CM # R59.9 Enlarged lymph nodes, unspecified

GENERALIZED

AIDS.
Lymphoma: Hodgkin's disease, non-Hodgkin's lymphoma.
Leukemias, reticuloendotheliosis.
Infectious mononucleosis, CMV, and other viral infections.
Diffuse skin infection: generalized furunculosis, multiple tick bites.
Parasitic infections: toxoplasmosis, filariasis, leishmaniasis, Chagas' disease.
Serum sickness.
Collagen vascular diseases (RA, SLE).
Dengue (arbovirus infection).
Sarcoidosis and other granulomatous diseases.
Drugs: INH, hydantoin derivatives, antithyroid and antileprosy drugs.
Secondary syphilis.
Hyperthyroidism, lipid-storage diseases.

LOCALIZED

Cervical Nodes

Infections of the head, neck, ears, sinuses, scalp, pharynx.
Mononucleosis.
Lymphoma.
TB.
Malignancy of head and neck.
Rubella.

Scalene/Supraclavicular Nodes

Lymphoma.
Lung neoplasm.
Bacterial or fungal infection of thorax or retroperitoneum.
GI malignancy.

Axillary Nodes

Infections of hands and arms.
Cat-scratch disease.
Neoplasm (lymphoma, melanoma, breast carcinoma).
Brucellosis.

Epitrochlear Nodes

Infections of the hand.
Lymphoma.
Tularemia.
Sarcoidosis, secondary syphilis (usually bilateral).

Inguinal Nodes

Infections of leg or foot, folliculitis (pubic hair).
LGV, syphilis.
Lymphoma.
Pelvic malignancy.
Pasteurella pestis.

Hilar Nodes

Sarcoidosis.
TB.
Lung carcinoma.
Fungal infections, systemic.

Mediastinal Nodes
Sarcoidosis.
Lymphoma.
Lung neoplasm.
TB.
Mononucleosis.
Histoplasmosis.
Abdominal/Retroperitoneal Nodes
Lymphoma.
TB.
Neoplasm (ovary, testes, prostate, and other malignancies).

LYMPHANGITIS[25b]

ICD-9CM # 457.2
ICD-10CM # I89.1 Lymphangitis

Acute:
- Group A streptococci.
- *Staphylococcus aureus*.
- *Pasteurella multocida*.

Chronic:
- *Sporothrix schenckii* (sporotrichosis).
- *Mycobacterium marinum* (swimming pool granuloma).
- *Mycobacterium kansasii*.
- *Nocardia brasiliensis*.
- *W. bancrofti*.

LYMPHOCYTOSIS, ATYPICAL[25b]

ICD-9CM # 288.8
ICD-10CM # D72.89 Other specified disorders of white blood cells

Epstein-Barr virus primary infection (infectious mononucleosis).
Cytomegalovirus primary infection (heterophile-negative mono).
Human herpesvirus 6 primary infection (roseola).
Primary HIV infection.
Toxoplasmosis.
Acute viral hepatitis.
Rubella, mumps.
Drug reactions (e.g., phenytoin, sulfa).

MACROTHROMBOCYTOPENIA, INHERITED[20]

ICD-9CM # varies with specific diagnosis
ICD-10CM # varies with specific disorder

Bernard-Soulier syndrome.
MHY9-related disorders:
- May-Hegglin anomaly.
- Sebastian syndrome.
- Fechtner syndrome.
- Epstein syndrome.

Gray platelet syndrome.
Montreal platelet syndrome.
Mediterranean macrothrombocytopenia.
Mediterranean stomatocytosis/macrothrombocytemia.
GATA1 mutations.
Sialyl-Lewis-S antigen deficiency.
Paris-Trousseau syndrome.
Platelet-type von Willebrand's disease.

MALABSORPTION[38]

ICD-9CM # 579
ICD-10CM # K90.89 Other intestinal malabsorption

CAUSES OF MALABSORPTION

More Common
Celiac disease.
Chronic pancreatitis.
Post gastrectomy.
Crohn's disease.
Small bowel resection.
Small intestinal bacterial overgrowth.
Lactase deficiency.
Less Common
AIDS (*Myobacterium avium* intracellulare, AIDS enteropathy).
Whipple's disease.
Intestinal lymphoma.
Immunoproliferative small intestinal disease (alpha heavy chain disease).
Radiation enteritis.
Collagenous sprue.
Tropical sprue.
Non-granulomatous ulcerative jejunoileitis.
Eosinophilic gastroenteritis.
Amyloidosis.
Zollinger-Ellison syndrome.
Intestinal lymphangiectasia.
Systemic mastocytosis.
Chronic mesenteric ischemia.
Abetalipoproteinemia (autosomal recessive).

MALNUTRITION, CAUSES IN EARLY LIFE[22a]

ICD-9CM # V77.2
ICD-10CM # E46 Unspecified protein-energy malnutrition

0-6 MO

Breastfeeding difficulties.
Improper formula preparation.
Impaired parent/child interaction.
Congenital syndromes.
Prenatal infections or teratogenic exposures.
Poor feeding (sucking, swallowing) or feeding refusal (aversion).
Maternal psychological disorder (depression or attachment disorder).
Congenital heart disease.
Cystic fibrosis.
Neurologic abnormalities.
Child neglect.
Recurrent infections.

6-12 MO

Celiac disease.
Food intolerance.
Child neglect.
Delayed introduction of age-appropriate foods or poor transition to food.
Recurrent infections.
Food allergy.

AFTER INFANCY

Acquired chronic diseases.
Highly distractible child.
Inappropriate mealtime environment.
Inappropriate diet (e.g., excessive juice consumption, avoidance of high-calorie foods).
Recurrent infections.

MEDIASTINAL COMPARTMENTS, ANATOMY AND PATHOLOGY[39]

ICD-9CM # varies with specific diagnosis
ICD-10CM # varies with specific disorder

ANTERIOR

Normal Structures
Lymph nodes.
Connective tissue.
Thymus (remnant in adults).
Masses
Thymoma.
Germ cell neoplasm.
Lymphoma.
Thyroid enlargement (intrathoracic goiter).
Other tumors.

MIDDLE

Normal Structures
Pericardium.
Heart.
Vessels: Ascending aorta, venae cavae, main pulmonary arteries.
Trachea.
Lymph nodes.
Nerves: Phrenic, upper vagus.
Masses
Carcinoma.
Lymphoma.
Pericardial cyst.
Bronchogenic cyst.
Benign lymph node enlargement (granulomatous disease).

POSTERIOR

Normal Structures
Vessels: Descending aorta.
Esophagus.
Vertebral column.
Nerves: Sympathetic chain, lower vagus.
Lymph nodes.
Connective tissue.
Masses
Neurogenic tumor.
Diaphragmatic hernia.

MEDIASTINAL MASSES OR WIDENING ON CHEST X-RAY

ICD-9CM # 785.6 Adenopathy
519.3 Disease NEC
793.2 Shift (CXR)
ICD-10CM # R59.9 Enlarged lymph nodes, unspecified
J98.5 Diseases of mediastinum, not elsewhere classified

Lymphoma: Hodgkin's disease and non-Hodgkin's lymphoma.
Sarcoidosis.
Vascular: aortic aneurysm, ectasia, or tortuosity of aorta or bronchocephalic vessels.
Carcinoma: lungs, esophagus.

Esophageal diverticula.
Hiatal hernia.
Achalasia.
Prominent pulmonary outflow tract: pulmonary hypertension, pulmonary embolism, right-to-left shunts.
Trauma: mediastinal hemorrhage.
Pneumomediastinum.
Lymphadenopathy caused by silicosis and other pneumoconioses.
Leukemias.
Infections: TB, viral (rare), *Mycoplasma* (rare), fungal, tularemia.
Substernal thyroid.
Thymoma.
Teratoma.
Bronchogenic cyst.
Pericardial cyst.
Neurofibroma, neurosarcoma, ganglioneuroma.

MEDIASTINITIS, ACUTE[25b]

ICD-9CM # 519.2
ICD-10CM # J98.5 Diseases of mediastinum, not elsewhere classified

Esophageal perforation.
Iatrogenic.
EGD, esophageal dilation, esophageal variceal sclerotherapy, nasogastric tube, Sengstaken-Blackmore tube, endotracheal intubation, esophageal surgery, paraesophageal surgery, transesophageal echocardiography, anterior stabilization of cervical vertebral bodies.
Swallowed foreign bodies.
Trauma.
Spontaneous perforation (e.g., emesis, carcinoma).
Head and neck infections (e.g., tonsillitis, pharyngitis, parotitis, epiglottitis, odontogenic).
Infections originating at another site (e.g., TB, pneumonia, pancreatitis, osteomyelitis of sternum, clavicle, ribs).
Cardiothoracic surgery (median sternotomy) (e.g., CABG, valve replacement, other types of cardiothoracic surgery).

MELANONYCHIA

ICD-9CM # varies with specific disorder
ICD-10CM # NEC L81.4 Melanin hyperpigmentation

Pregnancy.
Trauma.
Medications (e.g., AZT, 5-fluorouracil, doxorubicin, psoralens).
Nail matrix nevus.
HIV infection.
Onychomycosis.
Melanocyte hyperplasia.
Verrucae.
Pustular psoriasis.
Lichen planus.
Basal cell carcinoma.
Nail matrix melanoma.
Subungual keratosis.
Addison's disease.
Bowen's disease.

MEMORY LOSS SYMPTOMS, ELDERLY PATIENTS

ICD-9CM # varies with specific disorder
ICD-10CM # R41.2 Retrograde amnesia

Age-related mild cognitive impairment.
Depression (pseudodementia).
Medications (e.g., anticholinergics, sedatives).
Hypothyroidism.
Chronic hypoxia.
Cerebrovascular infarcts.
Alzheimer's disease.
Hepatic disease.
Chronic renal failure.
Hyperthyroidism.
Frontotemporal dementia.
Lewy body dementia.

MENINGITIS, CHRONIC[26]

ICD-9CM # 322.2
ICD-10CM # G03.1 Chronic meningitis

TB.
Fungal CNS infection.
Tertiary syphilis.
CNS neoplasm.
Metabolic encephalopathies.
Multiple sclerosis.
Chronic subdural hematoma.
SLE cerebritis.
Encephalitides.
Sarcoidosis.
NSAIDs.
Behçet's syndrome.
Anatomic defects (traumatic, congenital, postoperative).
Granulomatous angiitis.

MENINGITIS, RECURRENT[25b]

ICD-9CM # varies with specific disorder
ICD-10CM # G03.2 Benign recurrent meningitis [Mollaret]

Drug induced (with rechallenge).
Parameningeal focus.
  Infection (sinusitis, mastoiditis, osteomyelitis, brain abscess).
  Tumor (epidermoid cyst, craniopharyngioma).
Posttraumatic (bacterial).
Mollaret's meningitis.
SLE.
Herpes simplex virus.

MENTAL STATUS CHANGES AND COMA[2]

ICD-9CM # 780.97
ICD-10CM # R41.82 Altered mental status, unspecified

METABOLIC/SYSTEMIC ETIOLOGY OF ALTERED MENTAL STATUS AND COMA

Hypoxia
Severe pulmonary disease (hypoventilation).
Severe anemia.
Environmental/toxin:
  Methemoglobinemia.
  Cyanide.
  Carbon monoxide.
  Decreased atmospheric oxygen (high altitude).
  Near-drowning.

Disorders of Glucose
Hypoglycemia:
  Chronic alcohol abuse and liver disease.
  Excessive use of insulin or other hypoglycemic agents.
  Insulinoma.
Hyperglycemia:
  Diabetic ketoacidosis.
  Nonketotic hyperosmolar coma.

Decreased Cerebral Blood Flow
Hypovolemic shock.
Cardiac:
  Vasovagal syncope.
  Arrhythmias.
  Myocardial infarction.
  Valvular disorders.
  Congestive heart failure.
  Pericardial effusion/tamponade.
  Myocarditis.
Infectious:
  Septic shock.
  Bacterial meningitis.
Vascular/hematologic:
  Hypertensive encephalopathy.
  Pseudotumor cerebri.
  Hyperviscosity (sickle cell, polycythemia).
  Hyperventilation.
  Cerebral lupus vasculitis.
  Thrombotic thrombocytopenic purpura.
  Disseminated intravascular coagulation.

Metabolic Cofactor Deficiency
Thiamine (Wernicke-Korsakoff syndrome).
Pyridoxine (isoniazid overdose).
Folic acid (chronic alcohol abuse).
Cyanocobalamin.
Niacin.

Electrolye/pH Disturbances
Acidosis/alkalosis.
Hypernatremia/hyponatremia.*
Hypercalcemia/hypocalcemia.
Hypophosphatemia.
Hypermagnesemia/hypomagnesemia.

Endocrine Disorders
Myxedema coma, thyrotoxicosis.
Hypopituitarism.
Addison's disease (primary or secondary).
Cushing's disease.
Pheochromocytoma.
Hyperparathyroidism/hypoparathyroidism.

Endogenous Toxins
Hyperammonemia (liver failure).
Uremia (renal disease).
Carbon dioxide narcosis (pulmonary disease).
Porphyria.

Exogenous Toxins
Alcohols:
  Ethanol, isopropyl alcohol, methanol, ethylene glycol.
Acid poisons:
  Salicylates.
  Paraldehyde.
  Ammonium chloride.

Antidepressant medications:
- Lithium.
- Tricyclic antidepressants (TCAs).
- Selective serotonin reuptake inhibitors (SSRIs).
- Monamine oxidase inhibitors (MAOIs).

Stimulants:
- Amphetamines/methamphetamines.
- Cocaine.
- Over-the-counter sympathomimetics.

Narcotics/opiates:
- Morphine.
- Heroin.
- Codeine, oxycodone, meperidine, hydrocodone.
- Methadone.
- Fentanyl.
- Propoxyphene.

Sedative-hypnotics:
- Benzodiazepines.
- Barbiturates.
- Rohypnol.
- Bromide.

Hallucinogens:
- Lysergic acid diethylamide (LSD).
- Marijuana.
- Mescaline, peyote.
- Mushrooms.
- Phencyclidine (PCP).

Herbs/plants
- Aconite.
- Jimson weed.
- Morning glory.

Volatile substances:
- Hydrocarbons (gasoline, butane, toluene, benzene, chloroform).
- Nitrites.
- Anesthetic agents (nitrous oxide, ether).

Other:
- γ-Hydroxybutyrate (GHB).
- Ketamine.
- Penicillin.
- Cardiac glycosides.
- Anticonvulsants.
- Steroids.
- Heavy metals.
- Cimetidine.
- Organophosphates.

Disorders of Temperature Regulation/ Environmental

Hypothermia.
Heat stroke.
Malignant hyperthermia.
Neuroleptic malignant syndrome.
High-altitude cerebral edema (HACE).
Dysbarism.

Primary Glial or Neuronal Disorders

Adrenoleukodystrophy.
Creutzfeldt-Jakob disease.
Progressive multifocal leukoencephalopathy.
Marchiava-Bignami disease.
Gliomatosis cerebri.
Central pontine myelinolysis.

Other Disorders of Unknown Etiology

Seizures.
Postictal states.
Reye's syndrome.†
Intussuception.†

*Can be associated with dilution of formula in infant feeding.
†Prominent in the pediatric population

MENTAL STATUS CHANGES AND COMA, STRUCTURAL CAUSES[1]

ICD-9CM # 780.09
ICD-10CM # R40.1

COMMON AGE-RELATED CAUSES OF ALTERED MENTAL STATUS AND COMA

Infant

Infection.
Trauma, abuse.
Metabolic.

Child

Toxic ingestion.

Adolescent, Young Adult

Toxic ingestion.
Recreational drug use.
Trauma.

Elderly

Medication changes.
Over-the-counter medications.
Infection.
Alterations in living environment.
Stroke.
Trauma.

MENTAL STATUS CHANGES AND COMA, METABOLIC AND SYSTEMIC CAUSES[1]

ICD-9CM # 780.09
ICD-10CM # CM40.1

METABOLIC AND SYSTEMIC CAUSES OF ALTERED MENTAL STATUS AND COMA

Hypoxia, Hypercapnia

Severe pulmonary disease (hypoventilation).
Severe anemia.
Environmental, toxic.
Methemoglobinemia.
Cyanide.
Carbon monoxide.
Decreased atmospheric oxygen (high altitude).
Near-drowning.

Glucose Disorders

Hypoglycemia:
- Chronic alcohol abuse and liver disease.
- Excessive dosage of insulin or other hypoglycemic agents.
- Insulinoma.

Hyperglycemia:
- Diabetic ketoacidosis.
- Nonketotic hyperosmolar coma.

Decreased Cerebral Blood Flow

Hypovolemic shock.
Cardiac:
- Vasovagal syncope.
- Arrhythmias.
- Myocardial infarction.
- Valvular disorders.
- Congestive heart failure.
- Pericardial effusion, tamponade.
- Myocarditis.

Infectious
- Septic shock.
- Bacterial meningitis.

Vascular, hematologic
- Hypertensive encephalopathy.
- Pseudotumor cerebri.
- Hyperviscosity (sickle cell, polycythemia).
- Hyperventilation.
- Cerebral vasculitis as a manifestation of systemic lupus erythematosus.
- Thrombotic thrombocytopenic purpura.
- Disseminated intravascular coagulation.

Metabolic Cofactor Deficiency

Thiamine (Wernicke-Korsakoff syndrome).
Pyridoxine (isoniazid overdose).
Folic acid (chronic alcohol abuse).
Cyanocobalamin.
Niacin.

Electrolyte, pH Disturbances

Acidosis, alkalosis.
Hypernatremia, hyponatremia.*
Hypercalcemia, hypocalcemia.
Hypophosphatemia.
Hypermagnesemia, hypomagnesemia.

Endocrine Disorders

Myxedema coma, thyrotoxicosis.
Hypopituitarism.
Addison disease (primary or secondary).
Cushing disease.
Pheochromocytoma.
Hyperparathyroidism, hypoparathyroidism.

Endogenous Toxins

Hyperammonemia (liver failure).
Uremia (renal disease).
Carbon dioxide narcosis (pulmonary disease).
Porphyria.

Exogenous Toxins

Alcohols:
- Ethanol, isopropyl alcohol, methanol, ethylene glycol.

Acid poisons:
- Salicylates.
- Paraldehyde.
- Ammonium chloride.

Antidepressant medications:
- Lithium.
- Tricyclic antidepressants.
- Selective serotonin reuptake inhibitors.
- Monoamine oxidase inhibitors.

Stimulants:
1. Amphetamines, methamphetamines.
2. Cocaine.
3. Over-the-counter sympathomimetics.

Narcotics, opiates:
- Morphine.
- Heroin.
- Codeine, oxycodone, meperidine, hydrocodone.
- Methadone.
- Fentanyl.
- Propoxyphene.

Sedative-hypnotics:
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- Barbiturates.
- Rohypnol.
- Bromide.

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- Lysergic acid diethylamide.
- Marijuana.

- Mescaline, peyote.
- Mushrooms.
- Phencyclidine.

Herbs, plants:
- Aconite.
- Jimsonweed.
- Morning glory.

Volatile substances:
- Hydrocarbons (gasoline, butane, toluene, benzene, chloroform).
- Nitrites.
- Anesthetic agents (nitrous oxide, ether).

Other:
- γ-Hydroxybutyrate.
- Ketamine.
- Penicillin.
- Cardiac glycosides.
- Anticonvulsants.
- Steroids.
- Heavy metals.
- Cimetidine.
- Organophosphates.

Disorders of Temperature Regulation, Environmental
Hypothermia.
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Dysbarism.

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Marchiafava-Bignami disease.
Gliomatosis cerebri.
Central pontine myelinolysis.

Other Disorders with Unknown Etiology
Seizures.
Postictal states.
Reye syndrome.†
Intussusception.†

*Can be associated with dilution of formula in infant feeding.
†Prominent in the pediatric population.

MESENTERIC ARTERIAL EMBOLISM, ASSOCIATED FACTORS[2]

ICD-9CM #	557.0	
ICD-10CM #	I74.09	Other arterial embolism and thrombosis of abdominal aorta

FACTORS ASSOCIATED WITH MESENTERIC ARTERIAL EMBOLISM

Coronary artery disease.
  Post-myocardial infarction mural thrombi.
  Congestive heart failure.
Valvular heart disease.
  Rheumatic mitral valve disease.
  Nonbacterial endocarditis.
Arrhythmias.
  Chronic atrial fibrillation.
Aortic aneurysms or dissections.
Coronary angiography.

MESENTERIC ISCHEMIA, NONOCCLUSIVE[26]

ICD-9CM #	557.0	Mesenteric Artery Embolism or Infarction
	557.1	Mesenteric Artery Insufficiency, Chronic
	902.39	Mesenteric Vein Injury
ICD-10CM #	K55.0	Acute vascular disorders of intestine
	K55.1	Chronic vascular disorders of intestine
	S35.8X9A	Unspecified injury of other blood vessels at abdomen, lower back and pelvis level, initial encounter

Cardiovascular disease resulting in low-flow states (CHF, cardiogenic shock, post cardiopulmonary bypass, dysrhythmias).
Septic shock.
Drug induced (cocaine, vasopressors, ergot alkaloid poisoning).

MESENTERIC VENOUS THROMBOSIS[26]

ICD-9CM #	557.0	
ICD-10CM #	I82.91	Chronic embolism and thrombosis of unspecified vein

Hypercoagulable states (protein C or S deficiency, antithrombin III deficiency, Factor V Leyden, malignancy, polycythemia vera, sickle cell disease, homocystinemia, lupus anticoagulant, cardiolipin antibody).
Trauma (operative venous injury, abdominal trauma, postsplenectomy).
Inflammatory conditions (pancreatitis, diverticulitis, appendicitis, cholangitis).
Other: CHF, renal failure, portal hypertension, decompression sickness.

METASTATIC NEOPLASMS

ICD-9CM #	198.5	Bone and Bone Marrow
	198.3	Brain and Spinal Cord
	197.7	Liver
	197.0	Lung
ICD-10CM #	C79.51	Secondary malignant neoplasm of bone
	C79.52	Secondary malignant neoplasm of bone marrow
	C79.31	Secondary malignant neoplasm of brain
	C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
	C78.00	Secondary malignant neoplasm of unspecified lung

To: Bone	**To: Brain**
Breast	Lung
Lung	Breast
Prostate	Melanoma
Thyroid	GU tract
Kidney	Colon
Bladder	Sinuses
Endometrium	Sarcoma
Cervix	Skin
Melanoma	Thyroid
To: Liver	**To: Lung**
Colon	Breast
Stomach	Colon
Pancreas	Kidney
Breast	Testis
Lymphomas	Stomach
Bronchus	Thyroid
Lung	Melanoma
Sarcoma	
Choriocarcinoma	
Kidney	

METHAEMOGLOBINAEMIA, DRUG INDUCED[18c]

ICD-9CM #	codes vary with specific diagnosis	
ICD-10CM #	D74	Methaemoglobinaemia

SUBSTANCES ASSOCIATED WITH METHAEMOGLOBINAEMIA

Acetaminophen (nitrobenzene derivative).
Acetanilide.
Local anesthetics.
  Benzocaine.
  Lidocaine.
  Prilocaine.
Aniline dyes.
Celecoxib.
Dapsone.
Flutamide.
Ifosfamide.
Metoclopramide.
Nitric oxide.
Nitrites.
  Amyl nitrite.
  Isobutyl nitrite.
  Sodium nitrite.
  Nitrates (bacterial conversion to nitrites).
Nitrobenzenes/nitrobenzoates.
Nitroethane (nail polish remover).
Nitrofurans.
Nitroglycerin.
Paraquat/monolinuron.
Phenacetin.
Phenazopyridine (pyridium).
Primaquine.
Rasburicase.
Sulfamethoxazole.

MICROCEPHALY[4]

ICD-9CM #	742.1	Microcephalus
ICD-10CM #	Q02	Microcephaly

PRIMARY (GENETIC)

Familial (autosomal recessive).
Autosomal dominant.
Syndromes:
- Down (21-trisomy).
- Edward (18-trisomy).
- Cri-du-chat (5 p-).
- Cornelia de Lange.
- Rubinstein-Taybi.
- Smith-Lemli-Opitz.

SECONDARY (NONGENETIC)

Radiation.
Congenital infections:
- Cytomegalovirus.
- Rubella.
- Toxoplasmosis.

Drugs:
- Fetal alcohol.
- Fetal hydantoin.

Meningitis/encephalitis.
Malnutrition.
Metabolic.
Hyperthermia.
Hypoxic-ischemic encephalopathy.

MICROPENIS[27]

ICD-9CM #	752.69	Penile Agenesis or Atresia
	607.89	Penile Atrophy
	752.64	Micropenis (Congenital)
ICD-10CM #	N48.89	Other specified disorders of penis
	Q55.62	Hypoplasia of penis

HYPOGONADOTROPIC HYPOGONADISM (HYPOTHALAMIC OR PITUITARY DEFICIENCIES)

Kallmann's syndrome: autosomal dominant; associated with hyposmia.
Prader-Willi syndrome: hypotonia, mental retardation, obesity, small hands and feet.
Rud syndrome: hyposomia, ichthyosis, mental retardation.
De Morsier's syndrome (septooptic dysplasia): hypopituitarism, hypoplastic optic discs, absent septum pellucidum.

HYPERGONADOTROPIC HYPOGONADISM

Primary testicular defect: disorders of testicular differentiation or inborn errors of testosterone synthesis.
Klinefelter's syndrome.
Other X polysomies (i.e., XXXXY, XXXY).
Robinow's syndrome: brachymesomelic dwarfism, dysmorphic facies.

PARTIAL ANDROGEN INSENSITIVITY

IDIOPATHIC

Defective morphogenesis of the penis.

MIOSIS

ICD-9CM #	379.42	Miosis, Persistent Not Due to Miotics
ICD-10CM #	H57.03	Miosis

Medications (e.g., morphine, pilocarpine).
Neurosyphilis.
Congenital.
Iritis.
CNS pontine lesion.
CNS infections.
Cavernous sinus thrombosis.
Inflammation/irritation of cornea or conjunctiva.

MONOARTHRITIS, ACUTE

ICD-9CM #	716.60	
ICD-10CM #	M13.10	Monoarthritis, not elsewhere classified, unspecified site

Overuse.
Trauma.
Gout.
Pseudogout.
Osteoarthritis.
Infectious arthritis (e.g., gonococcal, Lyme disease, viral, mycobacteria, fungi).
Osteomyelitis.
Avascular necrosis of bone.
Hemarthrosis.
Bowel disease–associated arthritis.
Bone malignancy.
Psoriatic arthritis.
Juvenile RA.
Sarcoidosis.
Hemoglobinopathies.
Vasculitic syndromes.
Behçet's syndrome.
Foreign body synovitis.
Hypertrophic pulmonary osteoarthropathy.
Amyloidosis, familial Mediterranean fever.

MONOCYTOSIS[20]

ICD-9CM #	288.63	
ICD-10CM #	D72.821	Monocytosis (symptomatic)

Inflammatory diseases:
- Infectious diseases:
  - Tuberculosis.
  - Syphilis.
  - Subacute bacterial endocarditis.
  - Fever of unknown origin.
- Autoimmune/granulomatous.
  - Systemic lupus erythematosus.
  - Rheumatoid arthritis.
  - Temporal arteritis.
  - Myositis.
  - Polyarteritis.
  - Ulcerative colitis.
  - Regional enteritis.
  - Sarcoidosis.

Malignant disorders:
- Preleukemia.
- Nonlymphocytic leukemia.
- Histiocytoses.
- Hodgkin's disease.
- Non-Hodgkin's lymphoma.
- Carcinomas.

Miscellaneous:
- Chronic neutropenia.
- Post splenectomy.

MONONEUROPATHY

ICD-9CM #	355.9	
ICD-10CM #	G58.9	Mononeuropathy, unspecified

Herpes zoster.
Herpes simplex.
Vasculitis.
Trauma, compression.
Diabetes.
Postinfectious or inflammatory.

MONONEUROPATHY, ISOLATED[2]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	G56.90	Unspecified mononeuropathy of unspecified upper limb

UPPER EXTREMITY

Radial nerve.
- Axilla.
- Humerus.
- Elbow (posterior interosseous neuropathy).
- Wrist (superficial cutaneous radial neuropathy).

Ulnar nerve.
- Axilla.
- Humerus.
- Elbow.
- Condylar groove.
- Cubital tunnel.

Wrist (Guyon's canal).
Hand.
- Superficial terminal ulnar neuropathy.
- Deep terminal ulnar neuropathy.
  - Proximal hypothenar.
  - Distal hypothenar.

Median nerve.
Axilla.
Humerus (musculocutaneous mononeuropathy).
Forearm.
- Anterior interosseus.
- Pronator syndrome.

Wrist (carpal tunnel).
Hand (recurrent motor branch).
Suprascapular mononeuropathy.
- Axillary mononeuropathy.

LOWER EXTREMITY

Sciatic nerve.
Femoral nerve.
- Iliacus compartment (proximal).
- Saphenous mononeuropathy (distal).

Lateral femoral cutaneous (meralgia paresthetica).
Peroneal nerve.
- Common peroneal mononeuropathy (fibular head, popliteal fossa).
- Deep peroneal mononeuropathy (anterior compartment).

Tibial nerve.
- Popliteal fossa (proximal).
- Tarsal tunnel (distal).

Sural nerve.
Popliteal fossa, calf (proximal).
Fifth metatarsal base (distal).
Plantar nerve.
Distal to tarsal tunnel.
Interdigital neuropathies (Morton's neuroma).
Obturator mononeuropathy.

MONONUCLEOSIS, MONOSPOT NEGATIVE[1a]

ICD-9CM #	075	
ICD-10CM #	B27.90	Infectious mononucleosis, unspecified without complication

DIFFERENTIAL DIAGNOSIS OF MONOSPOT-NEGATIVE MONONUCLEOSIS

Acute HIV infection.
EBV mononucleosis (particularly in children).
Cytomegalovirus.
Acute toxoplasmosis.
Streptococcal pharyngitis.
Acute hepatitis B infection.

EBV, Epstein-Barr virus; *HIV,* human immunodeficiency virus.

MUSCLE DISEASE[34a]

ICD-9CM #	728	
ICD-10CM #	M60.009	Infective myositis, unspecified site

CLASSIFICATION OF MUSCLE DISEASE

Muscular Dystrophies
Duchenne.
Becker.
Limb girdle.
Childhood.
Facioscapulohumeral.
Myotonic Disorders
Dystrophia myotonica.
Myotonica congenita.
Inflammatory
Infective: bacterial, viral, parasitic.
Unknown cause: polymyositis, dermatomyositis, sarcoidosis.
Endocrine
Thyroid disease—hyper- and hypothyroidism.
Cushing's disease.
Addison's disease.
Hyperparathyroidism.
Metabolic
Glycogen storage diseases.
Periodic paralyses.
Mitochondrial diseases.
Drug-induced
Corticosteroids.
Chloroquine.
Amiodarone.
Penicillamine.
Alcohol.
Zidovudine.
Clofibrate.
Other
Inclusion body myositis.

MUSCLE WEAKNESS

ICD-9CM #	728.9	
ICD-10CM #	M62.9	Disorder of muscle, unspecified

Physical deconditioning.
Impaired cardiac output (e.g., mitral stenosis, mitral regurgitation).
Uremia, liver failure.
Electrolyte abnormalities (hypokalemia, hyperkalemia, hypophosphatemia, hypercalcemia), hypoglycemia.
Drug induced (e.g., statin myopathy).
Muscular dystrophies.
Steroid myopathy.
Alcoholic myopathy.
Myasthenia gravis, Lambert-Eaton syndrome.
Infections (polio, botulism, HIV, hepatitis, diphtheria, tick paralysis, neurosyphilis, brucellosis, TB, trichinosis).
Pernicious anemia, other anemias, beriberi.
Psychiatric illness (depression, somatization syndrome).
Organophosphate or arsenic poisoning.
Inflammatory myopathies (e.g., collagen vascular disease, RA, sarcoidosis).
Endocrinopathies (e.g., adrenal insufficiency, hypothyroidism), diabetic neuropathy.
Other: motor neuron disease, mitochondrial myopathy, l-tryptophan (eosinophilia-myalgia), rhabdomyolysis, glycogen storage disease, lipid storage disease.

MUSCLE WEAKNESS, LOWER MOTOR NEURON VERSUS UPPER MOTOR NEURON[40]

ICD-9CM #	728.9	
ICD-10CM #	M62.9	Disorder of muscle, unspecified

LOWER MOTOR NEURON

Weakness, usually severe.
Marked muscle atrophy.
Fasciculations.
Decreased muscle stretch reflexes.
Clonus not present.
Flaccidity.
No Babinski sign.
Asymmetric and may involve one limb only in the beginning to become generalized as the disease progresses.

UPPER MOTOR NEURON

Weakness, usually less severe.
Minimal disuse muscle atrophy.
No fasciculations.
Increased muscle stretch reflexes.
Clonus may be present.
Spasticity.
Babinski sign.
Often initial impairment of only skilled movements.
In the limbs the following muscles may be the only ones weak or weaker than the others: triceps; wrist and finger extensors; interossei; iliopsoas; hamstrings; and foot dorsiflexors, inverters, and extroverters.

MYDRIASIS

ICD-9CM #	379.43	Mydriasis, Persistent Not Due to Mydriatics
ICD-10CM #	H57.04	Mydriasis

Coma.
Medications (cocaine, atropine, epinephrine, etc.).
Glaucoma.
Cerebral aneurysm.
Ocular trauma.
Head trauma.
Optic atrophy.
Cerebral neoplasm.
Iridocyclitis.

MYELIN DISORDERS

ICD-9CM #	varies with specific disorder
ICD-10CM #	varies with specific diagnosis

Multiple sclerosis.
Vitamin B_{12} deficiency.
Radiation.
Hypoxia.
Toxicity from carbon monoxide, alcohol, mercury.
Progressive multifocal encephalopathy.
Acute disseminated encephalomyelitis.
Acute hemorrhagic leukoencephalopathy.
Phenylketonuria.
Adrenoleukodystrophy.
Krabbe's disease.

MYELOPATHY AND MYELITIS[36]

ICD-9CM #	722.70	Myelopathy, Discogenic Intervertebral NOS
	336.9	Myelopathy, Nondiscogenic Unspecified
ICD-10CM #	M51.9	Unspecified thoracic, thoracolumbar and lumbosacral intervertebral disc disorder
	G95.9	Disease of spinal cord, unspecified

INFLAMMATORY

Infectious: spirochetal TB, zoster, rabies, HIV, polio, rickettsial, fungal, parasitic.
Noninfectious: idiopathic transverse myelitis, multiple sclerosis.

TOXIC/METABOLIC

DM, pernicious anemia, chronic liver disease, pellagra, arsenic.

TRAUMA COMPRESSION

Spinal neoplasm, cervical spondylosis, epidural abscess, epidural hematoma.

VASCULAR

AV malformation, SLE, periarteritis nodosa, dissecting aortic aneurysm.

PHYSICAL AGENTS
Electrical injury, irradiation.

NEOPLASTIC
Spinal cord tumors, paraneoplastic myelopathy.

MYOCARDIAL ISCHEMIA[36]

ICD-9CM #	414.8	Ischemia (Chronic)
	411.89	Ischemia, Acute without MI
ICD-10CM #	I25.5	Ischemic cardiomyopathy
	I25.89	Other forms of chronic ischemic heart disease
	I25.9	Chronic ischemic heart disease, unspecified
	I24.8	Other forms of acute ischemic heart disease

Atherosclerotic obstructive coronary artery disease.
Nonatherosclerotic coronary artery disease:
Coronary artery spasm.
Congenital coronary artery anomalies:
- Anomalous origin of coronary artery from pulmonary artery.
- Aberrant origin of coronary artery from aorta or another coronary artery.
- Coronary arteriovenous fistula.
- Coronary artery aneurysm.

Acquired disorders of coronary arteries:
- Coronary artery embolism.
- Dissection:
  - Surgical.
  - During percutaneous coronary angioplasty.
  - Aortic dissection.
  - Spontaneous (e.g., during pregnancy).
- Extrinsic compression:
  - Tumors.
  - Granulomas.
  - Amyloidosis.
- Collagen-vascular disease:
  - Polyarteritis nodosa.
  - Temporal arteritis.
  - RA.
  - SLE.
  - Scleroderma.
- Miscellaneous disorders:
  - Irradiation.
  - Trauma.
  - Kawasaki disease.

Syphilis.
Hereditary disorders:
- Pseudoxanthoma elasticum.
- Gargoylism.
- Progeria.
- Homocystinuria.
- Primary oxaluria.

"Functional" causes of myocardial ischemia in absence of anatomic coronary artery disease:
- Syndrome X.
- Hypertrophic cardiomyopathy.
- Dilated cardiomyopathy.
- Muscle bridge.
- Hypertensive heart disease.
- Pulmonary hypertension.
- Valvular heart disease; aortic stenosis, aortic regurgitation.

MYOCLONUS

ICD-9CM #	333.2	
ICD-10CM #	G25.3	Myoclonus

Physiologic (e.g., exercise or anxiety induced).
Renal failure.
Hepatic failure.
Hyponatremia.
Hypoglycemia or severe hyperglycemia.
Postdialysis.
Epileptic myoclonus.
Postencephalitis.
CNS lesion (stroke, neoplasm).
CNS trauma.
Parkinson's disease.
Medications (e.g., tricyclics, L-dopa).
Friedreich's ataxia.
Ataxia-telangiectasia.
Wilson's disease.
Huntington's disease.
Progressive supranuclear palsy.
Heavy metal poisoning.
Benign familial.

MYOPATHIC SYNDROMES, DRUG-INDUCED[18b]

ICD-9CM #	359.9	Myopathic Syndromes
ICD-10CM #	G72.9	Myopathy, unspecified

TYPE OF MYOPATHY
Necrotizing myopathy
Inflammatory myopathy
Mitochondrial myopathy
Hypokalemic myopathy
Antimicrotubular myopathy
Lysosomal storage myopathy
Corticosteroid myopathy
Others

DRUGS
HMG-CoA reductase inhibitors (statins), fibrates, alcohol
Penicillamine, interferon-a, procainamide
Zidovudine
Diuretics, laxatives, licorice, amphotericin B, alcohol
Colchicine, vincristine
Chloroquine, hydroxychloroquine, quinacrine, amiodarone, perhexiline
Corticosteroids, especially fluorinated
Ipecac syrup, emetine

MYOPATHIES ASSOCIATED WITH REST PAIN[18b]

ICD-9CM #	359.9	Myopathies
ICD-10CM #	G72.9	Myopathy, unspecified

Childhood dermatomyositis.
Hypothyroid myopathy.
Acute alcoholic myopathy.
Drug-induced myopathies.
Infectious myopathies.
Myopathies associated with metabolic bone disease.
Carnitine palmitoyl transferase deficiency.
Rhabdomyolysis from any cause.

MYOPATHIES, HIV ASSOCIATED[12a]

ICD-9CM #	729.82	
ICD-10CM #	R25.2	

HIV-Associated Myopathies	Myopathies Secondary to Antiretrovirals	Others
HIV polymyositis	Zidovudine myopathy	Opportunistic infections involving muscle (toxoplasmosis)
Inclusion body myositis	Toxic mitochondrial myopathies related to other NRTIs[a]	Tumor infiltrations of skeletal muscle
Nemaline myopathy		Rhabdomyolysis
Diffuse infiltrative lymphocytosis syndrome	HIV-associated lipodystrophy syndrome	
HIV wasting syndrome	Immune reconstitution syndrome related to HAART[b]	
Vasculitic processes		
Myasthenia gravis and other myasthenic syndromes		
Chronic fatigue and fibromyalgia		

[a]NRTIs, nucleoside reverse transcriptase inhibitors.
[b]HAART, highly active antiretroviral therapy

MYOPATHIES, INFECTIOUS

ICD-9CM #	359.8	
ICD-10CM #	G72.9	Myopathy, unspecified

HIV.
Viral myositis.
Trichinosis.
Toxoplasmosis.
Cysticercosis.

MYOPATHIES, INFLAMMATORY

ICD-9CM #	359.9	
ICD-10CM #	G72.9	Myopathy, unspecified

SLE, RA.
Sarcoidosis.
Paraneoplastic syndrome.
Polymyositis, dermatomyositis.
Polyarteritis nodosa.
Mixed connective tissue disease.
Scleroderma.
Inclusion body myositis.
Sjögren's syndrome.
Cimetidine, D-penicillamine.

MYOPATHIES, METABOLIC[18b]

ICD-9CM #	359.9	Myopathies
ICD-10CM #	G72.9	Myopathy, unspecified

DISORDERED GLYCOGEN METABOLISM

- Myophosphorylase deficiency (McArdle disease).
- Phosphorylase b kinase deficiency.
- Phosphofructokinase deficiency.
- Debrancher enzyme deficiency.
- Brancher enzyme deficiency.
- Phosphoglycerate kinase deficiency.
- Phosphoglycerate mutase deficiency.
- Lactate dehydrogenase deficiency.
- Acid maltase deficiency.
- Aldolase deficiency.
- b-Enolase deficiency.

DISORDERED LIPID METABOLISM

- Carnitine deficiencies.
- Carnitine palmitoyltransferase deficiency.
- Fatty acid acyl-CoA dehydrogenase deficiencies.

MITOCHONDRIAL MYOPATHIES

- Coenzyme Q10 deficiency.
- Respiratory chain complex deficiencies.

ENDOCRINE

- Acromegaly.
- Hypothyroidism.
- Hyperthyroidism.
- Hyperparathyroidism.
- Cushing disease.
- Addison disease.
- Hyperaldosteronism.

METABOLIC-NUTRITIONAL

- Uremia.
- Hepatic failure.
- Malabsorption.
- Periodic paralysis.
- Vitamin D deficiency.
- Vitamin E deficiency.

ELECTROLYTE DISORDERS

- Sodium: hypernatremia and hyponatremia.
- Potassium: hyperkalemia and hypokalemia.
- Calcium: hypercalcemia and hypocalcemia.
- Phosphate: hypophosphatemia.
- Magnesium: hypomagnesemia.

MYOPATHIES, TOXIC[1a]

ICD-9CM # 359.4
ICD-10CM # G72.2 Myopathy due to other toxic agents

Inflammatory: cimetidine, D-penicillamine.
Noninflammatory necrotizing or vacuolar: cholesterol-lowering agents, chloroquine, colchicine.
Acute muscle necrosis and myoglobinuria: cholesterol-lowering drugs, alcohol, cocaine.
Malignant hyperthermia: halothane, ethylene, others; succinylcholine.
Mitochondrial: zidovudine.
Myosin loss: nondepolarizing neuromuscular blocking agents; glucocorticoids.

MYOSITIS, INFECTIOUS CAUSES[18b]

ICD-9CM # 728.0 Myositis

VIRAL

Influenza A and B viruses.
Enteroviruses (coxsackieviruses, echoviruses).
Human immunodeficiency virus.
Human T-cell lymphotrophic virus type 1.
Hepatitis B and C viruses.
Cytomegalovirus.
Epstein-Barr virus.
Adenovirus.
Varicella-zoster virus.
Parainfluenza.

PARASITIC

Trichinella species.
Echinococcus species.
Schistosoma species.
Toxoplasma gondii.
Trypanosoma cruzi.
Sarcocystis species.

BACTERIAL

Staphylococcus aureus.
Streptococcus, groups A and B.
Aeromonas hydrophila.
Borrelia burgdorferi.
Clostridium perfringens.
Anaerobic streptococci.
Mycobacterium species.
Rickettsia species.

FUNGAL

Candida species.
Cryptococcus neoformans.
Microsporida.

MYOSITIS, INFLAMMATORY[1a]

ICD-9CM # 729.1
ICD-10CM # M60.009 Infective myositis, unspecified site

INFECTIOUS

Viral myositis:
  Retroviruses (HIV, HTLV-I).
  Enteroviruses (echovirus, Coxsackievirus).
  Other viruses (influenza, hepatitis A and B, Epstein-Barr virus).
Bacterial: pyomyositis.
Parasites: trichinosis, cysticercosis.
Fungi: candidiasis.

IDIOPATHIC

Granulomatous myositis (sarcoid, giant cell).
Eosinophilic myositis.
Eosinophilia-myalgia syndrome.

ENDOCRINE/METABOLIC DISORDERS

Hypothyroidism.
Hyperthyroidism.
Hypercortisolism.
Hyperparathyroidism.
Hypoparathyroidism.
Hypocalcemia.
Hypokalemia.

METABOLIC MYOPATHIES

Myophosphorylase deficiency (McArdle's disease).
Phosphofructokinase deficiency.
Myoadenylate deaminase deficiency.
Acid maltase deficiency.
Lipid storage diseases.
Acute rhabdomyolysis.

DRUG-INDUCED MYOPATHIES

Alcohol.
D-Penicillamine.
Zidovudine.
Colchicine.
Chloroquine, hydroxychloroquine.
Lipid-lowering agents.
Cyclosporine.
Cocaine, heroin, barbiturates.
Corticosteroids.

NEUROLOGIC DISORDERS

Muscular dystrophies.
Congenital myopathies.
Motor neuron disease.
Guillain-Barré syndrome.
Myasthenia gravis.

NAIL CLUBBING

ICD-9CM # 729.1
ICD-10CM # R68.3 Clubbing of nails

COPD.
Pulmonary malignancy.
Cirrhosis.
Inflammatory bowel disease.
Chronic bronchitis.
Congenital heart disease.
Endocarditis.
AV malformations.
Asbestosis.
Trauma.
Idiopathic.

NAIL, HORIZONTAL WHITE LINES (BEAU'S LINES)

ICD-9CM # 703.9
ICD-10CM # L60.4 Beau's lines

Malnutrition.
Idiopathic.
Trauma.
Prolonged systemic illnesses.
Pemphigus.
Raynaud's disease.

NAIL KOILONYCHIA

ICD-9CM # 703.8
ICD-10CM # L60.8 Other nail disorders

Trauma.
Iron deficiency.
SLE.
Hemochromatosis.
Raynaud's disease.
Nail-patella syndrome.
Idiopathic.

NAIL ONYCHOLYSIS

ICD-9CM # 703.8
ICD-10CM # L60.1 Onycholysis

Infection.
Trauma.
Psoriasis.
Connective tissue disorders.
Sarcoidosis.
Hyperthyroidism.
Amyloidosis.
Nutritional deficiencies.

NAIL PITTING

ICD-9CM # 703.8
ICD-10CM # L60.8 Other nail disorders

Psoriasis.
Alopecia areata.
Reiter's syndrome.
Trauma.
Idiopathic.

NAIL SPLINTER HEMORRHAGE

ICD-9CM # 703.8
ICD-10CM # L60.8 Other nail disorders

SBE.
Trauma.
Malignancies.
Oral contraceptives.
Pregnancy.
SLE.
Antiphospholipid syndrome.
Psoriasis.
RA.
Peptic ulcer disease.

NAIL STRIATIONS

ICD-9CM # 703.8
ICD-10CM # L60.8 Other nail disorders

Psoriasis.
Alopecia areata.
Trauma.
Atopic dermatitis.
Vitiligo.

NAIL TELANGIECTASIA

ICD-9CM # 703.8
ICD-10CM # L60.8 Other nail disorders

RA.
Scleroderma.
Trauma.
SLE.
Dermatomyositis.

NAIL WHITENING (TERRY'S NAILS)

ICD-9CM # 703.8
ICD-10CM # L60.8 Other nail disorders

Malnutrition.
Trauma.
Liver disease (cirrhosis, hepatic failure).
DM.
Hyperthyroidism.
Idiopathic.

NAIL YELLOWING

ICD-9CM # 703.8
ICD-10CM # L60.8 Other nail disorders

Tobacco abuse.
Nephrotic syndrome.
Chronic infections (TB, sinusitis).
Bronchiectasis.
Lymphedema.
Raynaud's disease.
RA.
Pleural effusions.
Thyroiditis.
Immunodeficiency.

NASAL AND PARANASAL SINUS TUMORS[16a]

ICD-9CM # 873.23
ICD-10CM # C30.0 Malignant neoplasm of nasal cavity

BENIGN AND MALIGNANT NASAL AND PARANASAL SINUS TUMORS

Epithelial Tumors

BENIGN

Papilloma.
Adenoma.
Inverting papilloma.

MALIGNANT

Squamous carcinoma.
Adenocarcinoma.
Melanoma.
Adenoid cystic carcinoma.
Malignant salivary tumors.

MESENCHYMAL TUMORS

Benign
Osteoma.
Ossifying fibroma complex.
Angiofibroma.
Chondroma.
Malignant
Osteogenic sarcoma.
Fibrosarcoma.
Angiosarcoma.
Chondrosarcoma.
Lymphoma.
Rhabdomyosarcoma.

NASAL MASSES, CONGENITAL[16a]

ICD-9CM # 478.19
ICD-10CM # J34.1 Cyst and mucocele of nose and nasal sinus
J34.89 Other specified disorders of nose and nasal sinuses

Dermoid.
Nasal cerebral heterotopia (glioma).
Frontal meningoencephalocele.
Nasolacrimal duct mucocele.
Nasal hamartoma.
Nasal hemangioma.

NAUSEA AND VOMITING

ICD-9CM # 787.01
ICD-10CM # R11.2 Nausea with vomiting, unspecified

Infections (viral, bacterial).
Intestinal obstruction.
Metabolic (uremia, electrolyte abnormalities, DKA, acidosis, etc.).
Severe pain.
Anxiety, fear.
Psychiatric disorders (bulimia, anorexia nervosa).
Pregnancy.
Medications (NSAIDs, erythromycin, morphine, codeine, aminophylline, chemotherapeutic agents, etc.).
Withdrawal from substance abuse (drugs, alcohol).
Head trauma.
Vestibular or middle ear disease.
Migraine headache.
CNS neoplasms.
Radiation sickness.
PUD.
Carcinoma of GI tract.
Reye's syndrome.
Eye disorders.
Abdominal trauma.

NAUSEA AND VOMITING, CAUSES DURING PREGNANCY[12d]

ICD-9CM # 787.01
ICD-10CM # R11.2 Nausea with vomiting, unspecified

DIFFERENTIAL DIAGNOSIS OF NAUSEA AND VOMITING DURING PREGNANCY

Nausea and vomiting of pregnancy.
Hyperemesis gravidarum.
Pancreatitis.
Symptomatic cholelithiasis.
Viral hepatitis.
Peptic ulcer disease.
Gastric cancer.
Intestinal obstruction.
Intestinal pseudo-obstruction.
Gastroparesis diabeticorum.
Gastritis.
Gastroesophageal reflux disease.
Acute pyelonephritis.
Drug toxicity.
Vagotomy.
Preeclampsia/eclampsia.
Acute fatty liver of pregnancy.
Hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome.
Anorexia nervosa/bulimia.
Other neuropsychiatric disorders.

NECK AND ARM PAIN

ICD-9CM #	723.1	Neck Pain
	847.0	Neck Strain
	959.09	Neck Injury
	959.2	Arm Injury
	840.9	Arm Strain
ICD-10CM #	M54.2	Cervicalgia
	S46.919A	Strain of unspecified muscle, fascia and tendon at shoulder and upper arm level, unspecified arm, initial encounter

Cervical disk syndrome.
Trauma, musculoskeletal strain.
Rotator cuff syndrome.
Bicipital tendonitis.
Glenohumeral arthritis.
Acromioclavicular arthritis.
Thoracic outlet syndrome.
Pancoast tumor.
Infection (cellulitis, abscess).
Angina pectoris.

NECK MASS[28]

ICD-9CM #	784.2	
ICD-10CM #	R22.1	Localized swelling, mass and lump, neck

CONGENITAL ANOMALIES

Thyroglossal duct cyst.
Bronchial apparatus anomalies.
Teratomas.
Ranula.
Dermoid cysts.
Hemangioma.
Laryngoceles.
Cystic hygroma.

NONNEOPLASTIC INFLAMMATORY ETIOLOGIES

Folliculitis.
Adenopathy secondary to peritonsillar abscess.
Retropharyngeal or parapharyngeal abscess.
Salivary gland infections.
Viral infections (mononucleosis, HIV, CMV).
TB.
Cat-scratch disease.
Toxoplasmosis.
Actinomyces.
Atypical mycobacterium.
Jugular vein thrombus.

NEOPLASM (PRIMARY OR METASTATIC)

Lipoma.

NECK PAIN[28]

ICD-9CM #	723.1	Neck Pain (Nondiscogenic)
	959.09	Neck Injury
ICD-10CM #	M54.2	Cervicalgia

INFLAMMATORY DISEASES

RA.
Spondyloarthropathies.
Juvenile RA.

NONINFLAMMATORY DISEASE

Cervical osteoarthritis.
Diskogenic neck pain.
Diffuse idiopathic skeletal hyperostosis.
Fibromyalgia or myofascial pain.

INFECTIOUS CAUSES

Meningitis.
Osteomyelitis.
Infectious diskitis.

NEOPLASMS

Primary.
Metastatic.

REFERRED PAIN

Temporomandibular joint pain.
Cardiac pain.
Diaphragmatic irritation.
GI sources (gastric ulcer, gallbladder, pancreas).

NECK PAIN FROM RHEUMATOLOGIC DISORDERS[12a]

ICD-9CM #	723.1	
ICD-10CM #	M54.2	Cervicalgia

Rheumatoid arthritis
  Without disease of the C1-C2 joint.
  With structural cervical abnormalities: C1-C2 subluxation, C1-C2 facet involvement.
Spondyloarthropathies.
Reactive arthritis.
Psoriatic arthritis.
Enteropathic arthritis.
Polymyalgia rheumatica.
Osteoarthritis.
Fibromyalgia.
Nonspecific musculoskeletal pain.
Miscellaneous spondyloarthropathies.
  Whipple's disease.
  Behçet's disease.
  Paget's disease.
  Acromegaly.
  Ossification of the posterior longitudinal ligament.
  Diffuse idiopathic skeletal hyperostosis.

NECROTIZING PNEUMONIAS[1a]

ICD-9CM #	482.8	
ICD-10CM #	J15.8	Pneumonia due to other specified bacteria

COMMON

Tuberculosis.
Staphylococcus.
Gram-negative bacilli.
Anaerobes.
Fungi.
Pneumocystis jirovecii.

RARE

Streptococcus pneumoniae.
Legionella.
Viruses.
Mycoplasma pneumoniae.

NEPHRITIC SYNDROME, ACUTE[1a]

ICD-9CM #	580.89	
ICD-10CM #	N00.8	Acute nephritic syndrome with other morphologic changes

LOW SERUM COMPLEMENT LEVEL

Acute postinfectious glomerulonephritis.
Membranoproliferative glomerulonephritis.
SLE.
Subacute bacterial endocarditis.
Visceral abscess "shunt" nephritis.
Cryoglobulinemia.

NORMAL SERUM COMPLEMENT LEVEL

IgA nephropathy.
Antiglomerular basement membrane disease.
Polyarteritis nodosa.
Wegener's glomerulonephritis.
Henoch-Schönlein purpura.
Goodpasture's syndrome.

NEPHROCALCINOSIS

ICD-9CM #	275.49	
ICD-10CM #	E83.59	Other disorders of calcium metabolism

Sarcoidosis.
Hyperparathyroidism.
Chronic glomerulonephritis.
Milk-alkali syndrome.
Distal renal tubular acidosis.
Medullary sponge kidney.
Bartter's syndrome.
Hypervitaminosis D.
Idiopathic hypercalciuria.
Hyperoxaluria.
Cortical necrosis.
Tuberculosis.
Idiopathic hypercalciuria.
Rapidly progressive osteoporosis.

NEUROGENIC BLADDER[29]

ICD-9CM #	396.54	
ICD-10CM #	N31.9	Neuromuscular dysfunction of bladder, unspecified

SUPRATENTORIAL

CVA.
Parkinson's disease.
Alzheimer's disease.
Cerebral palsy.

SPINAL CORD

Spinal cord injury.
Spinal stenosis.

Central cord syndrome.
ALS.
Multiple sclerosis.
Myelodysplasia.

PERIPHERAL NEUROPATHY

Diabetes.
Alcohol.
Shingles.
Syphilis.

NEUROLOGIC DEFICIT, FOCAL[26]

ICD-9CM #	436	CVA
	435.9	TIA
ICD-10CM #	G45.9	Transient cerebral ischemic attack, unspecified
	I67.848	Other cerebrovascular vasospasm and vasoconstriction

TRAUMATIC: INTRACRANIAL, INTRASPINAL

Subdural hematoma.
Intraparenchymal hemorrhage.
Epidural hematoma.
Traumatic hemorrhagic necrosis.

INFECTIOUS

Brain abscess.
Epidural and subdural abscesses.
Meningitis.

NEOPLASTIC

Primary central nervous system tumors.
Metastatic tumors.
Syringomyelia.
Vascular.
Thrombosis.
Embolism.
Spontaneous hemorrhage: arteriovenous malformation, aneurysm, hypertensive.

METABOLIC

Hypoglycemia.
B_{12} deficiency.
Postseizure.
Hyperosmolar nonketotic.

OTHER

Migraine.
Bell's palsy.
Psychogenic.

NEUROLOGIC DEFICIT, MULTIFOCAL[26]

ICD-9CM #	436	CVA
	435.9	TIA
ICD-10CM #	I67.89	Other cerebrovascular disease
	G45.9	Transient cerebral ischemic attack, unspecified
	I67.848	Other cerebrovascular vasospasm and vasoconstriction

Acute disseminated encephalomyelitis: postviral or postimmunization.
Infectious encephalomyelitis: poliovirus, enteroviruses, arbovirus, herpes zoster, Epstein-Barr virus.
Granulomatous encephalomyelitis: sarcoid.
Autoimmune: SLE.
Other: familial spinocerebellar degenerations.

NEUROMUSCULAR JUNCTION DYSFUNCTION[1a]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	N31.9	Neuromuscular dysfunction of bladder, unspecified

DISORDERS OF THE NEUROMUSCULAR JUNCTION

Autoimmune
Myasthenia gravis.
Lambert-Eaton myasthenic syndrome.
Congenital
Presynaptic defects in ACh resynthesis, packaging, or release.
Synaptic defect: congenital end plate AChE deficiency.
Postsynaptic defects: slow-channel syndromes.
Postsynaptic defects: decreased response to ACh.
Fast-channel syndromes.
AChR deficiency without kinetic abnormality.
Familial limb-girdle myasthenia.
Toxic
Botulism.
Drug-induced disorders.
Organophosphate intoxication.

Ach, Acetylcholine; *AChE,* acetylcholinesterase; *AChR,* acetylcholine receptor.

NEURONOPATHIES, SENSORY (GANGLIONOPATHIES)[2]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	G60.0	Hereditary motor and sensory neuropathy

Herpes:
Herpes simplex I and II.
Varicella zoster (shingles).
Inflammatory sensory polyganglionopathy (ISP).
Paraneoplastic.
Primary biliary cirrhosis.
Sjögren's syndrome (keratoconjunctivitis sicca).
Toxin-induced:
Pyridoxine (vitamin B_6) overdose.
Metals:
- Platinum (cisplatin).
- Methyl mercury.

Vitamin E deficiency.

NEUROPATHIC BLADDER

ICD-9CM #	596.59	
ICD-10CM #	N31.9	Neuromuscular dysfunction of bladder, unspecified

Diabetes.
Stroke.
Multiple sclerosis.
Parkinson's disease.
Dementia.
Encephalopathy.
Brain trauma.
Spinal cord trauma.
Pelvic surgery.
Spina bifida.

NEUROPATHIES WITH FACIAL NERVE INVOLVEMENT

ICD-9CM #	varies with specific disorder	
ICD-10CM #	G51.8	Other disorders of facial nerve

Sarcoidosis.
HIV.
Lyme disease.
Guillain-Barré.
Others: chronic inflammatory polyneuropathy, Tangier disease, amyloidosis.

NEUROPATHIES, AUTONOMIC[22a]

ICD-9CM #	357	Neuropathies
ICD-10CM #	G63	Polyneuropathy in diseases classified elsewhere

GUILLAIN-BARRÉ SYNDROME

Non–Gulllain-Barré syndrome autoimmunity.
- Paraneoplastic (type I antineuronal nuclear antibody).
- Lambert-Eaton syndrome.
- Antibodies to neuronal nicotinc acetylcholine receptors.
- Antibodies to P/Q type calcium channels.
- Other autoantibodies.
- Systemic lupus erythematosus.

HEREDITARY

- Type I autosomal dominant.
- Type II autosomal recessive (Morvan disease).
- Type III autosomal recessive (Riley-Day).
- Type IV autosomal recessive (congenital insensitivity to pain with anhidrosis).
- Type V absence of pain.

METABOLIC

- Fabry disease.
- Diabetes mellitus.
- Tangier disease.
- Porphyria.

INFECTIOUS

- HIV.
- Chagas' disease.
- Botulism.

- Leprosy.
- Diphtheria.

OTHER

- Triple A (Allgrove) syndrome.
- Navajo Indian neuropathy.
- Multiple endocrine neoplasia type 2b.

TOXINS

NEUROPATHIES, AUTONOMIC, PERIPHERAL, CAUSES[14a]

ICD-9CM #	337.00	Neuropathies
ICD-10CM #	G90.09	Other idiopathic peripheral autonomic neuropathy

METABOLIC

Diabetes mellitus.
Alcohol.
Acute intermittent porphyria.
Uremia.

AUTOIMMUNE

Autoimmune autonomic ganglionopathy.
Guillain-Barré syndrome.
Morvan's syndrome.
Lambert-Eaton myasthenic syndrome.
Chronic inflammatory demyelinating polyradiculoneuropathy.
Sjögren syndrome.
Systemic lupus erythematosus.
Mixed connective tissue diseases.

PARAPROTEINEMIC

Amyloidosis.

NUTRITIONAL

Cyanocobalamin deficiency.
Thiamine deficiency.
Gluten-sensitive neuropathy.

TOXIC

Heavy metals.
Organic solvents.
Organophosphates.
Vacor.
Acrylamide.

DRUG INDUCED

Cisplatin.
Vincristine.
Amiodarone.
Metronidazole.
Perhexiline.
Paclitaxel.

INFECTIOUS

Human immunodeficiency virus.
Leprosy.
Chagas' disease.
Botulism.
Diphtheria.
Lyme disease.

GENETIC

Hereditary sensory and autonomic neuropathies.
- Types I and II.
- Type III (familial dysautonomia).
- Type IV (congenital insensitivity to pain).
- Type V.

Fabry disease.

IDIOPATHIC

Adie's syndrome.
Ross' syndrome.
Acute cholinergic neuropathy.
Chronic idiopathic anhidrosis.
Amyotrophic lateral sclerosis.

NEUROPATHIES, PAINFUL[40]

ICD-9CM #	355.9	Neuropathy NOS
	357.5	Alcoholic
	357.8	Chronic Progressive or Relapsing
	356.2	Congenital Sensory
	356.0	Dejerine-Sottas
	356.60	Diabetic Polyneuropathy, Type II
	356.61	Diabetic Polyneuropathy Type I
ICD-10CM #	G58.9	Mononeuropathy, unspecified
	G62.1	Alcoholic polyneuropathy
	G61.89	Other inflammatory polyneuropathies
	G60.0	Hereditary motor and sensory neuropathy
	G60.0	Hereditary motor and sensory neuropathy
	E11.42	Type 2 diabetes mellitus with diabetic polyneuropathy
	E10.42	Type 1 diabetes mellitus with diabetic polyneuropathy

MONONEUROPATHIES

Compressive neuropathy (carpal tunnel, meralgia paresthetica).
Trigeminal neuralgia.
Ischemic neuropathy.
Polyarteritis nodosa.
Diabetic mononeuropathy.
Herpes zoster.
Idiopathic and familial brachial plexopathy.

POLYNEUROPATHIES

DM.
Paraneoplastic sensory neuropathy.
Nutritional neuropathy.
Multiple myeloma.
Amyloid.
Dominantly inherited sensory neuropathy.
Toxic (arsenic, thallium, metronidazole).
AIDS-associated neuropathy.
Tangier disease.
Fabry's disease.

NEUROPATHIES, PERIPHERAL, ASYMMETRICAL PROXIMAL/DISTAL[2]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	G99.0	Autonomic neuropathy in diseases classified elsewhere

BRACHIAL PLEXOPATHY

Open
Direct plexus injury (knife or gunshot wound).
Neurovascular (plexus ischemia).
Iatrogenic (central line insertion).
Closed
Traction injuries:
  "Stingers."
  Traction neurapraxia.
  Partial or complete nerve root avulsion.
Radiation.
Neoplastic.
Idiopathic brachial plexitis.
Throracic outlet.

LUMBOSACRAL PLEXOPATHIES

Open
Closed
Traction injuries:
  Pelvic double vertical shearing fracture.
  Posterior hip dislocation.
  Retroperitoneal hemorrhage.
Vasospastic (deep buttock injection).
Neoplastic.
Radiation.
Idiopathic lumbosacral plexitis.
Infectious:
  Herpesvirus (sacrococcygeal).
  Herpes simplex II.
  Herpes zoster.
Cytomegalovirus (CMV) polyradiculopathy (HIV).

NEUROPATHIES, TOXIC AND METABOLIC[22a]

ICD-9CM #	337.00	Neuropathies
ICD-10CM #	NEC G62.2	Toxic neuropathy

METALS

Arsenic (insecticide, herbicide).
Lead (paint, batteries, pottery).
Mercury (metallic, vapor).
Thallium (rodenticides).
Gold.

OCCUPATIONAL OR INDUSTRIAL CHEMICALS

Acrylamide (grouting, flocculation).
Carbon disulfide (solvent).
Cyanide.
Dichlorophenoxyacetate.
Dimethylaminopropionitrite.
Ethylene oxide (gas sterilization).
Hexacarbons (glue, solvents).
Organophosphates (insecticides, petroleum additive).
Polychlorinated biphenyls.
Tetrachlorbiphenyl.
Trichloroethylene.

DRUGS

Amiodarone.
Chloramphenicol.
Chloroquine.
Cisplatin.
Colchicine.
Dapsone.
Ethambutol.
Ethanol.
Gold.
Hydralazine.
Isoniazid.
Metronidazole.
Nitrofurantoin.
Nitrous oxide.
Nucleosides (antiretroviral agents ddC, ddI, d4T, others).
Penicillamine.
Pentamidine.
Phenytoin.
Pyridoxine (excessive).
Statins.
Stilbamidine.
Suramin.
Taxanes (paclitaxel, docetaxel).
Thalidomide.
Tryptophan (eosinophilia-myalgia syndrome).
Vincristine.

METABOLIC DISORDER

Fabry disease.
Krabbe disease.
Leukodystrophies.
Porphyria.
Tangier disease.
Tyrosinemia.
Uremia.

NEUTROPENIA, DRUG-INDUCED[18c]

ICD-9CM # 288.03
ICD-10CM # D70

DRUGS COMMONLY ASSOCIATED WITH NEUTROPENIA

Antibiotics:
- Vancomycin.
- Semisynthetic penicillins.
- Chloramphenicol.
- Sulfa.
- Linezolid.

Antithyroid drugs:
- Methimazole.
- Propylthiouracil.

Cardiovascular:
- Ticlopidine.
- Procainamide.

Antipsychotics:
- Clozapine.
- Olanzapine.
- Chlorpromazine.

Anticonvulsants:
- Phenytoin.
- Carbamazepine
- Valproic acid.

Anti-inflammatory agents:
- Indomethacin.
- Sulfasalazine.
- Phenylbutazone.

H2 blockers:
- Cimetidine.
- Ranitidine.

Analgesics:
- Dipyrone.

Antineoplastic:
- Rituximab.

Anthelminthic:
- Levamisole.

NEUTROPENIA WITH DECREASED MARROW RESERVE[20]

ICD-9CM # 288.09
ICD-10CM # D70.8 Other neutropenia

PRIMARY

Severe congenital neutropenia.
Shwachman–Diamond syndrome.
Cyclic neutropenia.

SECONDARY

Lymphoproliferative disorder of granular lymphocytes.
Chemotherapy.
Drug induced (nonimmune).
Nutritional.
Viral infection (varicella, EBV, measles, CMV, hepatitis, HIV).

NEUTROPENIA WITH NORMAL MARROW RESERVE[20]

ICD-9CM # 288.0
ICD-10CM # D70.9 Neutropenia, unspecified

Chronic benign neutropenia of infancy and childhood.
Ethnic or benign familial neutropenia.
Autoimmune neutropenia.
Alloimmune neutropenia.
Drug-induced neutropenia.
Infection-related neutropenia.
Hypersplenism.

NEUTROPENIA, IN CHILDHOOD[38a]

ICD-9CM # 288.09
ICD-10CM # D70.8 Other neutropenia
D70.9 Neutropenia unspecified

ACQUIRED

Infection.
Immune mediated.
Hypersplenism.
Vitamin B_{12}, folate, copper deficiency.
Drugs or toxic substances.
Aplastic anemia.
Malignancies or preleukemic disorders.
Ionizing radiation.

CONGENITAL

Cyclic neutropenia.
Severe congenital neutropenia (Kostmann syndrome).
Chronic benign neutropenia of childhood.
Shwachman-Diamond syndrome.
Fanconi anemia.
Metabolic disorders (amino acidopathies, Barth syndrome, glycogen storage disorders).
Osteopetrosis.
Neutropenia with pigmentation abnormalities, e.g., Chédiak-Higashi.

NEUTROPHILIA[20]

ICD-9CM # 288.60
ICD-10CM # D72.0 Neutrophilia, hereditary giant
D71 Functional disorders of polymorphonuclear neutrophils

CLASSIFICATION OF NEUTROPHILIA

Primary (No Other Evident Associated Disease)
Hereditary neutrophilia.
Chronic idiopathic neutrophilia.
Chronic myelogenous leukemia (CML) and other myeloproliferative diseases.
Familial myeloproliferative disease.
Congenital anomalies and leukemoid reaction.
Leukocyte adhesion factor deficiency (LAD).
Familial cold urticaria and leukocytosis.
Secondary
Infection.
Stress neutrophilia.
Chronic inflammation.
Drug induced.
Nonhematologic malignancy.
Generalized marrow stimulation as in hemolysis.
Asplenia and hyposplenism.

NIPPLE LESIONS

ICD-9CM # varies with specific disorder
ICD-10CM # varies with specific diagnosis

Contact dermatitis.
Trauma.
Paget's disease.
Sebaceous hyperplasia.
Neurofibroma.
Accessory nipple.
Papillary adenoma.
Nevoid hyperkeratosis.
Cellulitis.

NODULAR LESIONS, SKIN

ICD-9CM # 782.2
ICD-10CM # R22.9 Localized swelling, mass and lump, unspecified

Lipoma.
Cherry angioma.
Angiokeratoma.
Hemangioma.

Classic Kaposi's sarcoma.
Nodular melanoma.
Pyogenic granuloma.
Angiosarcoma.
Eccrine poroma.

NODULES, PAINFUL

ICD-9CM #	varies with specific disorder	
ICD-10CM #	R22.9	Localized swelling, mass and lump, unspecified

Arthropod bite or sting.
Erythema nodosum.
Glomus tumor.
Neuroma.
Leiomyoma.
Angiolipoma.
Dermatofibroma.
Osler's node.
Blue rubber bleb nevus.
Vasculitis.
Sweet's syndrome.

NYSTAGMUS

ICD-9CM #	379.50	Nystagmus NOS
	386.11	Benign Positional
	386.2	Central Positional
	379.59	Congenital
ICD-10CM #	H55.00	Unspecified nystagmus
	H55.89	Other irregular eye movements

Medications (meperidine, barbiturates, phenytoin, phenothiazines, etc.).
Multiple sclerosis.
Congenital.
Neoplasm (cerebellar, brain stem, cerebral).
Labyrinthine or vestibular lesions.
CNS infections.
Optic atrophy.
Other: Arnold–Chiari malformation, syringobulbia, chorioretinitis, meningeal cysts.

NYSTAGMUS, MONOCULAR

ICD-9CM #	379.50	
ICD-10CM #	H55.09	Other forms of nystagmus
	H55.00	Unspecified nystagmus

Amblyopia.
Strabismus.
Multiple sclerosis.
Monocular blindness.
Internuclear ophthalmoplegia.
Lid fasciculations.
Brain stem infarct.

ODYNOPHAGIA[38]

ICD-9CM #	varies with specific diagnosis
ICD-10CM #	varies with specific diagnosis

CAUSES OF ODYNOPHAGIA

Infections
Herpes simplex virus.
Cytomegalovirus.
Candidiasis.
Chemical, Inflammatory
Gastroesophageal reflux.
Drug induced (Slow-K, tetracyclines, quinidine).
Radiation.
Graft-versus-host disease.
Crohn's disease.
Dermatologic diseases (pemphigus and pemphigoid).

OPACIFICATION OF HEMIDIAPHRAGM ON X-RAY[16a]

ICD-9CM #	419.4
ICD-10CM #	varies with specific diagnosis

CAUSES OF OPACIFICATION OF A HEMITHORAX

Pleural effusion.
Consolidation.
Collapse.
Massive tumor.
Fibrothorax.
Combination of above lesions.
Pneumonectomy.
Lung agenesis.

OPHTHALMOPLEGIA[1a]

ICD-9CM #	378.9	Ophthalmoplegia NOS
	378.52	Cerebellar Ataxia Syndrome
	376.22	Exophthalmic
ICD-10CM #	H51.9	Unspecified disorder of binocular movement
	H49.00	Third [oculomotor] nerve palsy, unspecified eye

BILATERAL

Botulism.
Myasthenia gravis.
Wernicke's encephalopathy.
Acute cranial polyneuropathy.
Brain stem stroke.

UNILATERAL

Carotid-posterior (3rd cranial nerve, pupil involved communicating aneurysm).
Diabetic-idiopathic (3rd or 6th cranial nerve, pupil spared).
Myasthenia gravis.
Brain stem stroke.

OPSOCLONUS*

ICD-9CM #	379.59	
ICD-10CM #	H55.89	Other irregular eye movements

Multiple sclerosis.
Encephalitis.
CNS lymphoma.
Hydrocephalus.
Pontine hemorrhage.
Thalamic disorder (glioma, hemorrhage).
Hyperosmolar coma.
Carcinoma, paraneoplastic.
Cocaine.
Medications (e.g., phenytoin, haloperidol, amitriptyline, diazepam, vidarabine).

*Spontaneous, multivector, chaotic eye movement

OPTIC ATROPHY[34a]

ICD-9CM #	377.1	
ICD-10CM #	H47.20	Unspecified optic atrophy

CAUSES OF OPTIC ATROPHY

Optic Nerve Compression
Pituitary tumor.
Carotid aneurysm.
Glaucoma.
Optic nerve tumor.
Sphenoid meningioma.
Olfactory groove meningioma.
Optic Neuritis Following Longstanding Papilledema Central Retinal Artery Occlusion Toxic/Metabolic
Diabetes.
Methyl alcohol.
Tobacco.
Quinine.
Ethambutol.
Lead and arsenic.
Anemia.
Secondary to Retinal Disease
Senile macular degeneration.
Retinitis pigmentosa.
Severe chorioretinitis.
Secondary to Trauma
Orbital fracture.
Hereditary
Leber's optic atrophy.
Hereditary ataxias.
Spinocerebellar degeneration.

ORAL MUCOSA, ERYTHEMATOUS LESIONS[9]

ICD-9CM #	528.3	Oral Abscess
	528.9	Oral Disease (Soft Tissue)
	528.8	Hyperplasia (Tongue)
ICD-10CM #	K12.2	Cellulitis and abscess of mouth
	K13.70	Unspecified lesions of oral mucosa
	K13.79	Other lesions of oral mucosa

Allergy.
Erythroplakia.
Candidiasis.
Geographic tongue.
Stomatitis areata migrans.
Plasma cell gingivitis.
Pemphigus vulgaris.

ORAL MUCOSA, PIGMENTED LESIONS[9]

ICD-9CM #	528.3	Oral Abscess
	528.9	Oral Disease (Soft Tissue)
	528.8	Hyperplasia (Tongue)
ICD-10CM #	K12.2	Cellulitis and abscess of mouth
	K13.70	Unspecified lesions of oral mucosa
	K13.79	Other lesions of oral mucosa
	K13.5	Oral submucous fibrosis

Racial pigmentation.
Oral melanotic macule.
Peutz-Jeghers syndrome.
Neurofibromatosis.
Albright's syndrome.
Addison's disease.
Chloasma.
Drug reaction: quinacrine, Minocin, chlorpromazine, Myleran.
Amalgam tattoo.
Lead line.
Smoker's melanosis.
Nevi.
Melanoma.

ORAL MUCOSA, PUNCTATE EROSIVE LESIONS[9]

ICD-9CM #	528.3	Oral Abscess
	528.9	Oral Disease (Soft Tissue)
	528.8	Hyperplasia (Tongue)
ICD-10CM #	K12.2	Cellulitis and abscess of mouth
	K13.70	Unspecified lesions of oral mucosa
	K13.79	Other lesions of oral mucosa

Viral lesion: Herpes simplex, coxsackievirus (A, B, A16), herpes zoster.
Aphthous stomatitis.
Sutton's disease (giant aphthae).
Behçet's syndrome.
Reiter's syndrome.
Neutropenia.
Acute necrotizing ulcerative gingivostomatitis (ANUG).
Drug reaction.
Inflammatory bowel disease.
Contact allergy.

ORAL MUCOSA, WHITE LESIONS[9]

ICD-9CM #	528.3	Oral Abscess
	528.9	Oral Disease (Soft Tissue)
	528.8	Hyperplasia (Tongue)
ICD-10CM #	K12.2	Cellulitis and abscess of mouth
	K13.70	Unspecified lesions of oral mucosa
	K13.79	Other lesions of oral mucosa
	K13.5	Oral submucous fibrosis

Leukoplakia.
White, hairy leukoplakia.
Squamous cell carcinoma.
Lichen planus.
Stomatitis nicotinica.
Benign intraepithelial dyskeratosis.
White spongy nevus.
Leukoedema.
Darier-White disease.
Pachyonychia congenital.
Candidiasis.
Allergy.
SLE.

ORAL ULCERS, ACUTE

ICD-9CM #	varies with diagnosis	
	528.9	Traumatic Ulcer of Oral Mucosa
ICD-10CM #	K13.70	Unspecified lesions of oral mucosa
	K13.79	Other lesions of oral mucosa

Trauma (including thermal trauma).
Aphthous stomatitis.
Syphilis.
Herpes simplex infection.
Herpes zoster.

ORAL VESICLES AND ULCERS[1a]

ICD-9CM #	528.9	
ICD-10CM #	K13.70	Unspecified lesions of oral mucosa
	K13.79	Other lesions of oral mucosa

Aphthous stomatitis.
Primary herpes simplex infection.
Vincent's stomatitis.
Syphilis.
Coxsackievirus A (herpangina).
Fungi (histoplasmosis).
Behçet's syndrome.
SLE.
Reiter's syndrome.
Crohn's disease.
Erythema multiforme.
Pemphigus.
Pemphigoid.

ORBITAL LESIONS, CALCIFIED

ICD-9CM #	376.89	
ICD-10CM #	H05.89	Other disorders of orbit

Chronic inflammation.
Phlebolith.
Dermoid cyst.
Mucocele walls.
Tumors (lacrimal gland, fibro-osseous).
Meningioma (optic sheath).
Lymphangioma.
Orbital varix.

ORBITAL LESIONS, CYSTIC

ICD-9CM #	376.9	
ICD-10CM #	H05.9	Unspecified disorder of orbit

Sweat gland cyst.
Dermoid cyst.
Lacrimal gland cyst.
Abscess.
Conjunctival cyst.
Lymphangioma.
Schwannoma.

ORGASM DYSFUNCTION[12]

ICD-9CM #	302.73	Orgasm Inhibited, Female Psychosexual
	302.74	Orgasm Inhibited, Male Psychosexual
ICD-10CM #	F52.31	Female orgasmic disorder
	F52.32	Male orgasmic disorder

Anorgasmia: inadequate stimulation or learning.
Spinal cord lesion or injury.
Multiple sclerosis.
Alcoholic neuropathy.
Amyotrophic lateral sclerosis.
Spinal cord accident.
Spinal cord trauma.
Peripheral nerve damage.
Radical pelvic surgery.
Herniated lumbar disk.
Hypothyroidism.
Addison's disease.
Cushing's disease.
Acromegaly.
Hypopituitarism.
Pharmacologic agents (e.g., SSRIs, beta-blockers).
Psychogenic.

OROFACIAL PAIN

ICD-9CM #	784.0	
ICD-10CM #	R51	Facial pain

Dental abscess.
Sinusitis.
Otitis media.
Otitis externa.
Wisdom tooth eruption.
Sialoadenitis.
Herpes zoster.
Trigeminal neuralgia.
Parotitis.
Anxiety disorder.
Malingering.

OSTEOPOROSIS, SECONDARY CAUSES

ICD-9CM #	733.00	
ICD-10CM #	M81.0	Age-related osteoporosis without current pathological fracture

Medication induced (e.g., glucocorticoids, anticonvulsants, heparin, LHRH agonists or antagonists).
Hyperparathyroidism.
Hyperthyroidism.
Prolonged immobilization.
Chronic renal failure.
Sickle cell disease.
Multiple myeloma.
Myeloproliferative diseases.
Leukemias and lymphomas.
Acromegaly.
Prolactinoma.
DM.
Total parenteral nutrition.
Malabsorption.
Chronic hypophosphatemia.
Connective tissue disorders (e.g., osteogenesis imperfecta, Marfan's syndrome, Ehlers-Danlos).
Hepatobiliary disease.
Postgastrectomy.
Aluminum-containing antacids.
Systemic mastocytosis.
Homocystinuria.

OSTEOSCLEROSIS, DIFFUSE[16a]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	Q77.4	Congenital osteosclerosis

DISORDERS ASSOCIATED WITH DIFFUSE OSTEOSCLEROSIS

Neoplastic Causes*
Prostate carcinoma, breast carcinoma, gastrointestinal adenocarcinoma, carcinoid tumors, transitional cell carcinoma of the bladder, myeloma, lymphoma, leukemia.
Hematologic Causes*
Sickle cell disorders, mastocytosis, myelofibrosis, polycythemia vera.
Metabolic Causes*
Renal osteodystrophy, primary hyperparathyroidism, familial hypophosphatemic osteomalacia, hypervitaminosis D, fluorosis, hypoparathyroidism, pseudohypoparathyroidism.
Primary Osseous Disorders†
Osteoporosis.
Pyknodysostosis.
Paget's disease.

*Involvement principally of cancellous bone
†Involvement of cancellous and cortica bone

OVULATORY DYSFUNCTION[21]

ICD-9CM #	628.0	Anovulatory Cycle
	626.5	Ovulation Pain
ICD-10CM #	N97.0	Female infertility associated with anovulation
	N92.3	Ovulation bleeding

HYPERANDROGENIC ANOVULATION

Polycystic ovarian syndrome.
Late-onset congenital adrenal hyperplasias.
Ovarian hyperthecosis.
Androgen-producing ovarian tumors.
Androgen-producing adrenal tumors.
Cushing's syndrome.

HYPOESTROGENIC ANOVULATION (HYPOTHALAMIC OR PITUITARY ETIOLOGY)

Hypogonadotropic Hypoestrogenic States
Reversible:
Functional hypothalamic amenorrheas:
- Eating disorders (anorexia nervosa, excessive weight loss).
- Excessive athletic training.

Neoplastic:
Craniopharyngioma.
Pituitary stalk compression.
Infiltrative diseases:
Histiocytosis-X.
Sarcoidosis.
Hypophysitis.
Pituitary adenomas:
Hyperprolactinemia.
Euprolactinemic galactorrhea.
Endocrinopathies:
Hypothyroidism/hyperthyroidism.
Cushing's disease.
Irreversible:
Kallmann's syndrome.
Isolated gonadotropin deficiency (hypothalamic or pituitary origin).
Panhypopituitarism/pituitary insufficiency:
- Sheehan's syndrome, pituitary apoplexy.
- Pituitary irradiation or ablation.

Hypergonadotropic Hypoestrogenic States
Physiologic states:
Menopause.
Perimenopause.
Premature ovarian failure.
Immune-related:
Radiation/chemotherapy-induced.
Ovarian dysgenesis.
Turner's syndrome.
46XX with mutations of X.
Androgen insensitivity syndrome.

MISCELLANEOUS

Endometriosis.
Luteal phase defect.

PAIN, MIDFOOT

ICD-9CM #	719.47	
ICD-10CM #	M25.579	Pain in unspecified ankle and joints of unspecified foot

MEDIAL ASPECT

Tendonitis of posterior tibialis.
Tendonitis of flexor digitorum longus.
Tendonitis of flexor hallucis longus.
Infection (osteomyelitis, septic arthritis, cellulitis) of foot.
Peripheral vascular insufficiency.
Fracture.
Osteoarthritis.
Gout, pseudogout.
Neuropathy.
Tumor.

LATERAL ASPECT

Peroneus longus tendonitis.
Peroneus brevis tendonitis.
Infection (osteomyelitis, septic arthritis, cellulitis) of foot.
Peripheral vascular insufficiency.
Fracture.
Osteoarthritis.
Gout, pseudogout.
Neuropathy.
Tumor.

PAIN, PLANTAR ASPECT, HEEL

ICD-9CM #	719.47	
ICD-10CM #	M25.579	Pain in unspecified ankle and joints of unspecified foot

Plantar fasciitis.
Tarsal tunnel syndrome.
Neuroma.
Infection (osteomyelitis, septic arthritis, cellulitis) of foot.
Peripheral vascular insufficiency.
Fracture.
Bone cyst.
Osteoarthritis.
Gout, pseudogout.
Neuropathy.
Tumor.
Heel pad atrophy.
Plantar fascia rupture.

PAIN, POSTERIOR HEEL

ICD-9CM #	729.5	
ICD-10CM #	M79.609	Pain in unspecified limb

Achilles tendonitis.
Retrocalcaneal bursitis.
Retroachilles bursitis.
Infection (osteomyelitis, septic arthritis, cellulitis) of foot.
Peripheral vascular insufficiency.
Fracture.
Osteoarthritis.
Gout, pseudogout.
Neuropathy.
Tumor.

PALINDROMIC RHEUMATISM[6]

ICD-9CM #	719.3	use 5th digit 0 Site Unspecified 1 Shoulder Region 2 Upper Arm (Elbow, Humerus) 3 Forearm (Radius, Wrist, Ulna) 4 Hand (Carpal, Metacarpal, Fingers) 5 Pelvic Region and Thigh 6 Lower Leg 7 Ankle and Foot 8 Other 9 Multiple
ICD-10CM #	M12.30	Palindromic rheumatism, unspecified site
	M12.319	Palindromic rheumatism, unspecified shoulder
	M12.329	Palindromic rheumatism, unspecified elbow
	M12.339	Palindromic rheumatism, unspecified wrist
	M12.349	Palindromic rheumatism, unspecified hand
	M12.359	Palindromic rheumatism, unspecified hip
	M12.369	Palindromic rheumatism, unspecified knee
	M12.379	Palindromic rheumatism, unspecified ankle and foot
	M12.38	Palindromic rheumatism, vertebrae
	M12.39	Palindromic rheumatism, multiple sites

Palindromic RA.
Essential palindromic rheumatism.
Crystal synovitis (gout, CPPD, pseudogout, calcific periarthritis).
Lyme borreliosis, stages 2 and 3.
Sarcoidosis.
Whipple's disease.
Acute rheumatic fever.
Reactive arthritis (rare).

PALMOPLANTAR HYPERKERATOSIS

ICD-9CM #	701.1	
ICD-10CM #	L85.1	Acquired keratosis [keratoderma] palmaris et plantaris
	L85.2	Keratosis punctata (palmaris et plantaris)
	L87.0	Keratosis follicularis et parafollicularis in cutem penetrans

Superficial skin infection.
Chronic eczema.
Repeated trauma.
Psoriasis.
Reiter's syndrome.
Paraneoplastic acrokeratosis.

PALPITATIONS[33]

ICD-9CM #	785.1	Palpitations
ICD-10CM #	R00.2	Palpitations

Anxiety.
Electrolyte abnormalities (hypokalemia, hypomagnesemia).
Exercise.
Hyperthyroidism.
Ischemic heart disease.
Ingestion of stimulant drugs (cocaine, amphetamines, caffeine).
Medications (digoxin, beta-blockers, calcium channel antagonists, hydralazines, diuretics, minoxidil).
Hypoglycemia in type 1 DM.
Mitral valve prolapse.
Wolff-Parkinson-White (WPW) syndrome.
Sick sinus syndrome.

PANCREATIC CALCIFICATIONS

ICD-9CM #	577.8	
ICD-10CM #	K86.1	Other chronic pancreatitis
	K86.8	Other specified diseases of pancreas

Chronic pancreatitis.
Hyperparathyroidism.
Metastatic neoplasm.
Pseudocyst.
Hereditary pancreatitis.
Cystoadenoma.
Cystoadenocarcinoma.
Cavernous lymphangioma.
Hemorrhage.
Acute pancreatitis (saponification).

PANCREATITIS, ACUTE, IN CHILDREN[22a]

ICD-9CM #	577.0	
ICD-10CM #	K85	Acute pancreatitis

CAUSES OF ACUTE PANCREATITIS IN CHILDREN

Drugs and Toxins
Acetaminophen overdose.
Alcohol.
L-Asparaginase.
Azathioprine.
Carbamazepine.
Cimetidine.
Corticosteroids.
Enalapril.
Erythromycin.
Estrogen.
Furosemide.
Isoniazid.
Lisinopril.
6-Mercaptopurine.
Methyldopa.
Metronidazole.
Organophosphate poisoning.
Pentamidine.
Retrovirals: DDC, DDI, tenofovir.
Sulfonamides: mesalamine, 5-aminosalicylates, sulfasalazine, trimethoprim/sulfamethoxazole.
Sulindac.
Tetracycline.
Thiazides.
Valproic acid.
Venom (spider, scorpion, Gila monster lizard).
Vincristine.

Genetic
Cationic trypsinogen gene *(PRSS1).*
Chymotrypsin C gene *(CTRC).*
Cystic fibrosis gene *(CFTR).*
Trypsin inhibitor gene *(SPINK1).*

Infectious
Ascariasis.
Coxsackie B virus.
Epstein-Barr virus.
Hepatitis A, B.
Influenza A, B.
Leptospirosis.
Malaria.
Measles.
Mumps.
Mycoplasma.
Reye syndrome: varicella, influenza B.
Rubella.
Rubeola.
Septic shock.

Obstructive
Ampullary disease.
Ascariasis.
Biliary tract malformations.
Choledochal cyst.
Choledochocele.
Cholelithiasis, microlithiasis, and choledocholithiasis (stones or sludge).
Duplication cyst.
Endoscopic retrograde cholangiopancreatography (ERCP) complication.
Pancreas divisum.
Pancreatic ductal abnormalities.
Postoperative.
Sphincter of Oddi dysfunction.
Tumor.

Systemic Disease
Autoimmune pancreatitis.
Brain tumor.
Collagen vascular diseases.
Crohn disease.
Diabetes mellitus.
Head trauma.
Hemochromatosis.
Hemolytic-uremic syndrome.
Hyperlipidemia: type I, IV, V.
Hyperparathyroidism/Hypercalcemia.
Kawasaki disease.
Malnutrition.
Organic acidemia.

Peptic ulcer.
Periarteritis nodosa.
Renal failure.
Systemic lupus erythematosus.
Transplantation: bone marrow, heart, liver, kidney, pancreas.
Vasculitis.
Traumatic
Blunt injury.
Burns.
Child abuse.
Hypothermia.
Surgical trauma.
Total body cast.

PANCREATITIS, DRUG-INDUCED[2]

ICD-9CM # 577.0
ICD-10CM # K85.3 Drug induced acute pancreatitis

DEFINITE

Acetaminophen.
Azathioprine.
Cimetidine.
Cisplatin.
Corticosteroids.
Didanosine.
Erythromycin.
Estrogens.
Ethyl alcohol.
Furosemide.
L-Asparaginase.
Mercaptopurine.
Metronidazole.
Methyldopa.
Nitrofurantoin.
Octreotide.
Organophosphates.
Pentamidine.
Ranitidine.
Tetracycline.
Salicylates.
Sulfonamides, trimethoprim-sulfamethoxazole, sulfasalazine.
Sulindac.
Valproic acid.

POSSIBLE

Bumetanide.
Carbamazepine.
Chlorthalidone.
Clonidine.
Colchicine.
Cyclosporine.
Cytarabine.
Diazoxide.
Enalapril.
Ergotamine.
Ethacrynic acid.
Indomethacin.
Isoniazid.
Isotretinoin.
Mefenamic acid.
Opiates.
Phenformin.
Piroxicam.
Procainamide.
Rifampin.
Thiazides.

PANCYTOPENIA[20]

ICD-9CM # 284.1
ICD-10CM # D61.818 Other pancytopenia

PANCYTOPENIA WITH HYPOCELLULAR BONE MARROW

Acquired aplastic anemia.
Inherited aplastic anemia (Fanconi anemia and others).
Some myelodysplasia syndromes.
Rare aleukemic leukemia (acute myelogenous leukemia).
Some acute lymphoblastic leukemias.
Some lymphomas of bone marrow.

PANCYTOPENIA WITH CELLULAR BONE MARROW

Primary bone marrow diseases.
Myelodysplasia syndromes.
Paroxysmal nocturnal hemoglobinuria.
Myelofibrosis.
Some aleukemic leukemias.
Myelophthisis.
Bone marrow lymphoma.
Hairy cell leukemia.
Secondary to systemic diseases.
Systemic lupus erythematosus, Sjögren syndrome.
Hypersplenism.
Vitamin B_{12}, folate deficiency (familial defect).
Overwhelming infection.
Alcohol.
Brucellosis.
Ehrlichiosis.
Sarcoidosis.
Tuberculosis and atypical mycobacteria.

HYPOCELLULAR BONE MARROW ± CYTOPENIA

Q fever.
Legionnaires disease.
Mycobacteria.
Tuberculosis.*
Anorexia nervosa, starvation.
Hypothyroidism.

*Pancytopenia in tuberculosis only rarely is associated with a hypocellular bone marrow at biopsy or autopsy. Marrow failure in the setting of tuberculosis is almost always fatal; exceptional patients probably had underlying myelodysplasia or acute leukemia.

PANCYTOPENIA SYNDROME, INHERITED[22a]

ICD-9CM # 284.1
ICD-10CM # D61.818 Other pancytopenia

Fanconi anemia.
Shwachman-Diamond syndrome.
Dyskeratosis congenita.
Congenital amegakaryocytic thrombocytopenia.
Unclassified inherited bone marrow failure syndromes.
Other genetic syndromes:
Down syndrome.
Dubowitz syndrome.
Seckel syndrome.
Reticular dysgenesis.
Schimke immunoosseous dysplasia.
Familial aplastic anemia (non-Fanconi).
Cartilage-hair hypoplasia.
Noonan syndrome.

PAPILLEDEMA

ICD-9CM # 377.00 Papilledema NOS
377.02 With Decreased Ocular Pressure
377.01 With Increased Intracranial Pressure
377.03 With Retinal Disorder
ICD-10CM # H47.10 Unspecified papilledema

CNS infections (viral, bacterial, fungal).
Medications (lithium, cisplatin, corticosteroids, tetracycline, etc.).
Head trauma.
CNS neoplasm (primary or metastatic).
Pseudotumor cerebri.
Cavernous sinus thrombosis.
SLE.
Sarcoidosis.
Subarachnoid hemorrhage.
Carbon dioxide retention.
Arnold–Chiari malformation and other developmental or congenital malformations.
Orbital lesions.
Central retinal vein occlusion.
Hypertensive encephalopathy.
Metabolic abnormalities.

PAPULOSQUAMOUS DISEASES[14]

ICD-9CM # 709.8
ICD-10CM # L98.8 Other specified disorders of the skin and subcutaneous tissue

Psoriasis.
Pityriasis rubra pilaris.
Pityriasis rosea.
Lichen planus.
Lichen nitidus.
Secondary syphilis.
Pityriasis lichenoides.
Parapsoriasis.
Mycosis fungoides.
Dermatophytosis.
Tinea versicolor.

PARANEOPLASTIC NEUROLOGIC SYNDROMES

ICD-9CM # varies with specific disorder
ICD-10CM # G13.0 Paraneoplastic neuromyopathy and neuropathy

Lambert-Eaton myasthenic syndrome.
Myasthenia gravis.
Guillain-Barré syndrome.
Amyotrophic lateral sclerosis.
Dermatomyositis.
Carcinoid myopathy.

Cerebellar degeneration.
Encephalomyelitis.
Optic neuritis, uveitis, retinopathy.
Stiff-man syndrome.
Autonomic neuropathy.
Brachial neuritis.
Sensory neuropathy.
Progressive multifocal leukoencephalopathy.

PARANEOPLASTIC SYNDROMES, ENDOCRINE[36]

ICD-9CM # varies specific disorder
ICD-10CM # G13.0 Paraneoplastic neuromyopathy and neuropathy

Hypercalcemia.
Syndrome of inappropriate secretion of antidiuretic hormone.
Hypoglycemia.
Zollinger-Ellison syndrome.
Ectopic secretion of human chorionic gonadotropin.
Cushing's syndrome.

PARANEOPLASTIC SYNDROMES, NONENDOCRINE[36]

ICD-9CM # varies with specific disorder
ICD-10CM # G13.0 Paraneoplastic neuromyopathy and neuropathy

CUTANEOUS

Dermatomyositis.
Acanthosis nigricans.
Sweet's syndrome.
Erythema gyratum repens.
Systemic nodular panniculitis (Weber-Christian disease).

RENAL

Nephrotic syndrome.
Nephrogenic diabetes insipidus.

NEUROLOGIC

Subacute cerebellar degeneration.
Progressive multifocal leukoencephalopathy.
Subacute motor neuropathy.
Sensory neuropathy.
Ascending acute polyneuropathy (Guillain-Barré syndrome).
Myasthenic syndrome (Eaton-Lambert syndrome).

HEMATOLOGIC

Microangiopathic hemolytic anemia.
Migratory thrombophlebitis (Trousseau's syndrome).
Anemia of chronic disease.

RHEUMATOLOGIC

Polymyalgia rheumatica.
Hypertrophic pulmonary osteoarthropathy.

PARAPARESIS, ACUTE OR SUBACUTE[34a]

ICD-9CM # varies with specific diagnosis
ICD-10CM # G82.2 Paraparesis

CAUSES OF ACUTE OR SUBACUTE PARAPARESIS

Trauma to a Previously Normal Spine
Vertebral Disease
Metastatic carcinoma.
Cervical spondylosis.
Dorsal disk prolapse.
Paget's disease.
Rheumatoid arthritis.
Pott's disease of spine.
Tumors
Extradural or intradural carcinoma, lymphoma, myeloma, leukemia.
Dorsal meningioma.
Neurofibroma.
Hematologic Disease
Any cause of thrombocytopenia.
Other clotting disorders.
Leukemia.
Anticoagulant treatment.
Epidural or intramedullary hemorrhage.
Infection
Epidural abscess.
TB abscess.
Syphilitic myelitis.
HIV infection.
Vascular myelopathy.
Vascular
Anterior spinal artery occlusion.
Infarction secondary to hypotension.
Embolic infarction.
Infarction secondary to aortic dissection.
Arteriovenous malformation: infarction or hemorrhage.
Primary intramedullary hemorrhage.
Vasculitis—polyarteritis nodosa (PAN).
Inflammatory
Myelitis of unknown cause.
Multiple sclerosis.
Systemic lupus erythematosus.
Sarcoidosis.
Metabolic
Subacute degeneration of the cord.

PARAPARESIS, CHRONIC PROGRESSIVE[34a]

ICD-9CM # varies with specific diagnosis
ICD-10CM # G82.2 Paraparesis

CAUSES OF CHRONIC PROGRESSIVE PARAPARESIS

Vertebral Disease
Cervical spondylosis.
Dorsal disk prolapse.
Rheumatoid arthritis.
Pott's disease of spine.
Ankylosing spondylitis.
Tumors
Meningioma.
Neurofibroma.
Glioma.
Ependymoma.
Chordoma.
Lipoma.
Syringomyelia
With Arnold–Chiari malformation.
With tumor.
Posttraumatic.
Infection
Tropical spastic paraparesis (HTLV 1 infection).
Syphilitic myelitis.
Vascular
Arteriovenous malformation.
Inflammatory
Multiple sclerosis.
Sarcoidosis.
Radiation myelopathy.
Arachnoiditis.
Metabolic
Subacute combined degeneration of the cord.
Paget's disease.
Degenerative
Motor neuron disease.
Hereditary
Hereditary spastic paraplegia.

PARAPLEGIA

ICD-9CM #	344.1	Paraplegia, Acquired
	343.0	Paraplegia, Congenital
	438.50	Paraplegia, Late Effect of CVA
ICD-10CM #	G82.20	Paraplegia, unspecified
	G80.1	Spastic diplegic cerebral palsy
	I69.969	Other paralytic syndrome following unspecified cerebrovascular disease affecting unspecified side

Trauma: penetrating wounds to motor cortex, fracture-dislocation of vertebral column with compression of spinal cord or cauda equina, prolapsed disk, electrical injuries.
Neoplasm: parasagittal region, vertebrae, meninges, spinal cord, cauda equina, Hodgkin's disease, NHL, leukemic deposits, pelvic neoplasms.
Multiple sclerosis and other demyelinating disorders.
Mechanical compression of spinal cord, cauda equina, or lumbosacral plexus: Paget's disease, kyphoscoliosis, herniation of intervertebral disk, spondylosis, ankylosing spondylitis, RA, aortic aneurysm.
Infections: spinal abscess, syphilis, TB, poliomyelitis, leprosy.
Thrombosis of superior sagittal sinus.
Polyneuritis: Guillain-Barré syndrome, diabetes, alcohol, beriberi, heavy metals.
Heredofamilial muscular dystrophies.
ALS.
Congenital and familial conditions: syringomyelia, myelomeningocele, myelodysplasia.
Hysteria.

PARASELLAR MASSES[26b]

ICD-9CM # code varies with specific diagnosis
ICD-10CM # code varies with specific diagnosis

GENETIC

Transcription factor mutations (e.g., PROP1[a]).

CYSTS

Rathke's.
Arachnoid.
Epidermoid.
Dermoid.

TUMORS

Hormone-secreting or nonfunctional pituitary adenoma.
Granular cell tumor.
Craniopharyngioma (cystic components).
Chordoma.
Meningioma.
Sarcoma.
Glioma.
Schwannoma.
Germ cell tumor.
Vascular tumor.
Solid or hematological metastasis.

MALFORMATION AND HAMARTOMAS

Ectopic pituitary, neurohypophyseal, or salivary tissue.
Hypothalamic hamartoma.
Gangliocytoma.

MISCELLANEOUS LESIONS

Aneurysms.
Hypophysitis.
Infections.
Sarcoidosis.
Giant cell granuloma.
Histiocytosis X.

[a]PROP1, prophet of Pit1 (paired-like homeodomain transcription factor).

PARESTHESIAS

ICD-9CM #	782.0	
ICD-10CM #	R20.2	Paresthesia of skin
	G54.8	Other nerve root and plexus disorders

Multiple sclerosis.
Nutritional deficiencies (thiamin, vitamin B_{12}, folic acid).
Compression of spinal cord or peripheral nerves.
Medications (e.g., INH, lithium, nitrofurantoin, gold, cisplatin, hydralazine, amitriptyline, sulfonamides, amiodarone, metronidazole, dapsone, disulfiram, chloramphenicol).
Toxic chemicals (e.g., lead, arsenic, cyanide, mercury, organophosphates).
DM.
Myxedema.
Alcohol.
Sarcoidosis.
Neoplasms.
Infections (HIV, Lyme disease, herpes zoster, leprosy, diphtheria).
Charcot-Marie-Tooth syndrome and other hereditary neuropathies.
Guillain-Barré neuropathy.

PARKINSONISM-PLUS SYNDROMES

ICD-9CM #	varies with specific disorder	
ICD-10CM #	G21.8	Other secondary parkinsonism

Parkinson's disease.
Shy-Drager syndrome.
Corticobasal degeneration.
Olivo-ponto-cerebellar atrophy.
Dementia with Lewy bodies.
Progressive supranuclear palsy.
Striatonigral degeneration.

PAROTID SWELLING[3]

ICD-9CM #	527.2	Allergic Parotitis
	72.9	Infectious Parotitis
	527.8	Salivary Gland Obstruction
	527.5	Salivary Gland Obstruction with Calculus
	527.8	Salivary Gland Stricture
	527.3	Salivary Gland Abscess
	235.1	Salivary Gland Neoplasm
ICD-10CM #	K11.20	Sialoadenitis, unspecified
	B26.9	Mumps without complication
	K11.8	Other diseases of salivary glands
	K11.5	Sialolithiasis
	K11.3	Abscess of salivary gland

INFECTIOUS

Mumps.
Parainfluenza.
Influenza.
Cytomegalovirus infection.
Coxsackievirus infection.
Lymphocytic choriomeningitis.
Echovirus infection.
Suppuration (bacterial).
Actinomyces infection.
Mycobacterial infection.
Cat-scratch disease.

NONINFECTIOUS

Drug hypersensitivity (thiouracil, phenothiazines, thiocyanate, iodides, copper, isoprenaline, lead, mercury, phenylbutazone).
Sarcoidosis.
Tumors, mixed.
Hemangioma, lymphangioma.
Sialectasis.
Sjögren's syndrome.
Mikulicz's syndrome (scleroderma, mixed connective tissue disease, SLE).
Recurrent idiopathic parotitis.
Pneumoparotitis.
Trauma.
Sialolithiasis.
Foreign body.
Cystic fibrosis.
Malnutrition (marasmus, alcohol cirrhosis).
Dehydration.
DM.
Waldenström's macroglobulinemia.
Reiter's syndrome (reactive arthritis).
Amyloidosis.

NONPAROTID SWELLING

Hypertrophy of masseter muscle.
Lymphadenopathy.
Rheumatoid mandibular joint swelling.
Tumors of jaw.
Infantile cortical hyperostosis.

PELVIC MASS

ICD-9CM #	789.39	
ICD-10CM #	R19.09	Other intraabdominal and pelvic swelling, mass and lump

Hemorrhagic ovarian cyst.
Simple ovarian cyst (follicle or corpus luteum).
Ovarian carcinoma, carcinoma of fallopian tube, colorectal carcinoma, metastatic carcinoma, prostate carcinoma, bladder carcinoma, lymphoma, Hodgkin's disease.
Cystadenoma, teratoma, endometrioma.
Leiomyoma.
Leiomyosarcoma.
Diverticulitis, diverticular abscess.
Appendiceal abscess, tuboovarian abscess.
Ectopic pregnancy, intrauterine pregnancy.
Paraovarian cyst.
Hydrosalpinx.

PELVIC PAIN, CAUSES IN WOMEN[2]

ICD-9CM #	338.4	
ICD-10CM #	N94	Pain and other conditions associated with female genital organs and menstrual cycle
	G10.2	Pelvic and perineal pain
	G89.4	Chronic pain syndrome

POTENTIAL CAUSES OF PELVIC PAIN IN WOMEN

Reproductive Tract

Ovarian torsion.
Ovarian cyst.
Salpingitis/tubo-ovarian abscess.
Septic pelvic thrombophlebitis.
Endometritis.
Endometriosis.
Uterine perforation.
Uterine fibroids.
Dysmenorrhea.

Pregnancy-related

First Trimester

Ectopic pregnancy.
Threatened abortion.
Nonviable pregnancy.
Ovarian hyperstimulation syndrome.
Second and Third Trimesters
Placenta previa.
Placental abruption.
Round ligament pain.
Intestinal Tract
Appendicitis.
Diverticulitis.
Ischemic bowel.
Perforated viscus.
Bowel obstruction.
Incarcerated/strangulated hernia.
Inflammatory bowel disease.
Gastroenteritis.
Urinary Tract
Pyelonephritis.
Cystitis.
Ureteral stone.

PELVIC PAIN, CHRONIC[7]

ICD-9CM #	625.9	Pelvic Pain, Female
	789.09	Pelvic Pain, Male
ICD-10CM #	N94.89	Other specified conditions associated with female genital organs and menstrual cycle
	R10.2	Pelvic and perineal pain
	R10.10	Upper abdominal pain, unspecified
	R10.2	Pelvic and perineal pain
	R10.30	Lower abdominal pain, unspecified

GYNECOLOGIC DISORDERS

Primary dysmenorrhea.
Endometriosis.
Adenomyosis.
Adhesions.
Fibroids.
Retained ovary syndrome after hysterectomy.
Previous tubal ligation.
Chronic pelvic infection.

MUSCULOSKELETAL DISORDERS

Myofascial pain syndrome.

GASTROINTESTINAL DISORDERS

Irritable bowel syndrome.
Inflammatory bowel disease.

URINARY TRACT DISORDERS

Interstitial cystitis.
Nonbacterial urethritis.

PELVIC PAIN, GENITAL ORIGIN[26]

ICD-9CM #	625.9	Pelvic Pain, Female
	789.09	Pelvic Pain, Male
ICD-10CM #	N94.89	Other specified conditions associated with female genital organs and menstrual cycle
	R10.2	Pelvic and perineal pain
	R10.10	Upper abdominal pain, unspecified
	R10.2	Pelvic and perineal pain
	R10.30	Lower abdominal pain, unspecified

PERITONEAL IRRITATION

Ruptured ectopic pregnancy.
Ovarian cyst rupture.
Ruptured tuboovarian abscess.
Uterine perforation.

TORSION

Ovarian cyst or tumor.
Pedunculated fibroid.

INTRATUMOR HEMORRHAGE OR INFARCTION

Ovarian cyst.
Solid ovarian tumor.
Uterine leiomyoma.

INFECTION

Endometritis.
Pelvic inflammatory disease.
Trichomonas cervicitis or vaginitis.
Tuboovarian abscess.

PREGNANCY-RELATED

First Trimester
Ectopic pregnancy.
Abortion.
Corpus luteum hematoma.
Late Pregnancy
Placental problems.
Preeclampsia.
Premature labor.

MISCELLANEOUS

Endometriosis.
Foreign objects.
Pelvic adhesions.
Pelvic neoplasm.
Primary dysmenorrhea.

PELVIC PAIN, NON-PREGNANT FEMALE[1]

ICD-9CM #	625.9	
ICD-10CM #	N94.89	Other specified conditions associated with female genital organs and menstrual cycle
	R10.2	Pelvic and perineal pain
	R10.10	Upper abdominal pain, unspecified
	R10.30	Lower abdominal pain, unspecified

DIFFERENTIAL DIAGNOSIS OF PELVIC PAIN IN NONPREGNANT FEMALES

Gynecologic Diagnoses
Infectious:
- Vaginitis.
- Cervicitis.
- Endometritis.
- Tuboovarian abscess.
- Pelvic inflammatory disease.

Ovarian:
- Ovarian torsion.
- Ruptured ovarian cyst.
- Ovarian tumor.
- Degenerating ovarian tumor.
- Mittelschmerz.

Cervical:
- Cervical polyps.
- Cervical stenosis.
- Cervical cancer.

Uterine:
- Uterine fibroids.
- Degenerating uterine fibroids.
- Adenomyosis.
- Endometrial carcinoma.

Extrauterine:
- Endometriosis.
- Adhesions.
- Residual accessory ovary.

Nongynecologic Diagnoses
Gastrointestinal:
- Acute appendicitis.
- Mesenteric lymphadenitis.
- Diverticulitis.
- Inflammatory bowel disease.
- Irritable bowel syndrome.
- Bowel obstruction.
- Intraabdominal abscess.
- Colorectal carcinoma.

Urinary:
- Cystitis.
- Renal colic.
- Bladder cancer.

Musculoskeletal:
- Abdominal wall pain.
- Lumbar back pain.
- Fibromyalgia.
- Muscular strain.
- Piriformis syndrome.

Neurologic:
- Lumbar radiculopathy.
- Shingles.
- Spondylosis.

Psychologic:
- Personality disorders.
- Major depressive disorder.

PENILE RASH

ICD-9CM #	782.1	
ICD-10CM #	R21	Rash and other nonspecific skin eruption

Herpes simplex 2.
Balanitis (Candida).
Condyloma acuminatum.
Molluscum contagiosum.
Scabies.
Pediculosis pubis.

Pearly penile papules.
Lichen nitidus.
Fox-Fordyce disease (follicular papules).
Trauma.

PERIANAL PAIN[38]

ICD-9CM #	569.42	
ICD-10CM #	K62.89	Other specified diseases of anus and rectum

Fissure-in-ano
Anal sepsis
- Anal abscess
- Anal fistula

Hemorrhoids
- Internal hemorrhoids
- External hemorrhoids

Pruritus ani
Proctalgia fugax
Chronic perianal pain syndromes
- Coccygodynia
- Descending perineum syndrome
- Levator ani syndrome
- Idiopathic perineal pain

PERICARDIAL EFFUSION

ICD-9CM #	420.90	
ICD-10CM #	I30.9	Acute pericarditis, unspecified
	I31.3	Pericardial effusion

Pericarditis.
Uremia.
Myxedema.
Neoplasm (leukemia, lymphoma, metastatic).
Hemorrhage (trauma, leakage of thoracic aneurysm).
SLE, rheumatoid disease.
Myocardial infarction.

PERIODIC PARALYSIS, HYPERKALEMIC

ICD-9CM #	344.9	
ICD-10CM #	G83.9	Paralytic syndrome, unspecified

Chronic renal failure.
Renal insufficiency with excessive potassium supplementation.
Potassium-sparing diuretics.
Endocrinopathies (hypoaldosteronism, adrenal insufficiency).

PERIODIC PARALYSIS, HYPOKALEMIC

ICD-9CM #	344.9	
ICD-10CM #	G83.9	Paralytic syndrome, unspecified

Chronic diarrhea (laxative abuse, sprue, villous adenoma).
Potassium-depleting diuretics.
Medications (amphotericin B, corticosteroids).
Chronic licorice ingestion.
Thyrotoxicosis.
Renal tubular acidosis.
Conn's syndrome.
Barter's syndrome.
Barium intoxication.

PERITONEAL CARCINOMATOSIS[14]

ICD-9CM #	197.6	
ICD-10CM #	C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum

PRIMARY DISORDERS OF THE PERITONEUM: MESOTHELIOMA

Metastatic spread from:
Stomach.
Colon.
Pancreas.
Carcinoid.

Other Intraabdominal Organs
Ovary.
Pseudomyxoma peritonei.

Extraabdominal Primary Tumors
Breast.
Lung.

Hematologic Malignancy
Lymphoma.

PERITONEAL EFFUSION[18]

ICD-9CM #	792.9	
ICD-10CM #	R18	Ascites
	R85.9	Unspecified abnormal finding in specimens from digestive organs and abdominal cavity
	R88.8	Abnormal findings in other body fluids and substances

TRANSUDATES

Increased hydrostatic pressure or decreased plasma oncotic pressure.
Congestive heart failure.
Hepatic cirrhosis.
Hypoproteinemia.

EXUDATES

Increased capillary permeability or decreased lymphatic resorption.
Infections (TB, spontaneous bacterial peritonitis, secondary bacterial peritonitis).
Neoplasms (hepatoma, metastatic carcinoma, lymphoma, mesothelioma).
Trauma.
Pancreatitis.
Bile peritonitis (e.g., ruptured gallbladder).

CHYLOUS EFFUSION

Damage or obstruction to thoracic duct.
Trauma.
Lymphoma.
Carcinoma.
Tuberculosis.
Parasitic infection.

PERIUMBILICAL SWELLING

ICD-9CM #	789.3	
ICD-10CM #	R19.00	Intraabdominal and pelvic swelling, mass and lump, unspecified site

Umbilical hernia.
Lipoma.
Epigastric hernia.
Umbilical granuloma.
Omphalocele.
Gastroschisis.
Caput medusae.

PHARYNGEAL OBSTRUCTION, CAUSES[26a]

ICD-9CM #	varies with specific diagnosis
ICD-10CM #	varies with specific diagnosis

CAUSES OF PHARYNGEAL OBSTRUCTION

Malignant or benign tumors (e.g., papillomas, polyps).
Infection (e.g., croup, epiglottitis, tonsillar abscess).
Edema or hypertrophy (e.g., angioneurotic edema, anaphylactic reactions, postradiation therapy, obstructive sleep apnea).
Trauma (e.g., cricoid fracture, cervical subluxation, precervical hematoma).
Burn injury.
Extrinsic compression (e.g., goiter or pregnancy-related thyroid enlargement).
Foreign body.
Congenital web (infants).
Sarcoidosis and other granulomatous diseases.
Amyloid.

PHEOCHROMOCYTOMA-TYPE SPELLS[26b]

ICD-9CM #	255.6	
ICD-10CM #	I15.2	Hypertension due to pheochromocytoma

DIFFERENTIAL DIAGNOSIS OF PHEOCHROMOCYTOMA-TYPE SPELLS

Endocrine Causes
Carbohydrate intolerance.
Hyperadrenergic spells.
Hypoglycemia.
Pancreatic tumors (e.g., insulinoma).
Pheochromocytoma.
Primary hypogonadism (menopausal syndrome).
Thyrotoxicosis.

Cardiovascular Causes
Angina.
Cardiovascular deconditioning.
Labile essential hypertension.
Orthostatic hypotension.
Paroxysmal cardiac arrhythmia.
Pulmonary edema.
Renovascular disease.
Syncope (e.g., vasovagal reaction).

Psychologic Causes
Factitious (e.g., drugs, Valsalva).
Hyperventilation.
Severe anxiety and panic disorders.
Somatization disorder.
Pharmacologic Causes
Chlorpropamide-alcohol flush.
Combination of a monoamine oxidase inhibitor and a decongestant.
Illegal drug ingestion (cocaine, phencyclidine, lysergic acid diethylamide).
Sympathomimetic drug ingestion.
Vancomycin ("red man syndrome").
Withdrawal of adrenergic-inhibitor.
Neurologic Causes
Autonomic neuropathy.
Cerebrovascular insufficiency.
Diencephalic epilepsy (autonomic seizures).
Migraine headache.
Postural orthostatic tachycardia syndrome.
Stroke.
Other Causes
Carcinoid syndrome.
Mast cell disease.
Recurrent idiopathic anaphylaxis.
Unexplained flushing spells.

PHOTODERMATOSES[14]

ICD-9CM #	692.72	
ICD-10CM #	L56.0	Drug phototoxic response
	L56.1	Drug photoallergic response
	L56.2	Photocontact dermatitis [berloque dermatitis]

Polymorphous light eruption.
Chronic actinic dermatitis.
Solar urticaria.
Phototoxicity and photoallergy.
Porphyrias.

PHOTOSENSITIVITY

ICD-9CM #	692.72	
ICD-10CM #	L56.0	Drug phototoxic response
	L56.1	Drug photoallergic response
	L56.2	Photocontact dermatitis [berloque dermatitis]

Solar urticaria.
Photoallergic reaction.
Phototoxic reaction.
Polymorphous light eruption.
Porphyria cutanea tarda.
SLE.
Drug induced (e.g., tetracyclines).

PIGMENTURIA[2]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	R82	Other abnormal findings in urine

HEMOGLOBINURIA
Hemolysis.

HEMATURIA
Renal causes.
Trauma.

ACUTE INTERMITTENT PORPHYRIA
Bilirubinuria
FOOD
Beets.
DRUGS
Vitamin B_{12}.
Rifampin.
Phenytoin.
Laxatives.

PITUITARY REGION TUMORS[16a]

ICD-9CM #	varies with specific diagnosis
ICD-10CM #	varies with specific diagnosis

PRIMARY TUMORS IN THE SELLAR AND PARASELLAR REGION
Tumor
Pituitary macroadenoma.
Meningioma.
Schwannoma (e.g., of fifth nerve).
Chordoma.
Chondrosarcoma.
Crangiopharyngioma.
Rathke's cleft cyst.
Dermoid.
Epidermoid.
Tuber cinerum hamartoma.
Optic glioma.
Germ cell tumors.

PLEURAL EFFUSIONS

ICD-9CM #	511.9	Pleural Effusion, Unspecified
ICD-10CM #	J91.8	Pleural effusion in other conditions classified elsewhere

EXUDATIVE
Neoplasm: bronchogenic carcinoma, breast carcinoma, mesothelioma, lymphoma, ovarian carcinoma, multiple myeloma, leukemia, Meigs' syndrome.
Infections: viral pneumonia, bacterial pneumonia, *Mycoplasma,* TB, fungal and parasitic diseases, extension from subphrenic abscess.
Trauma.
Collagen vascular diseases: SLE, RA, scleroderma, polyarteritis, granulomatosis with polyangiitis (Wegener's granulomatosis).
Pulmonary infarction.
Pancreatitis.
Postcardiotomy/Dressler's syndrome.
Drug-induced SLE (hydralazine, procainamide).
Postabdominal surgery.
Ruptured esophagus.
Chronic effusion secondary to congestive failure.

TRANSUDATIVE
CHF.
Hepatic cirrhosis.
Nephrotic syndrome.
Hypoproteinemia from any cause.
Meigs' syndrome.

PLEURAL EFFUSIONS, MALIGNANCY-ASSOCIATED

ICD-9CM #	197.2	
ICD-10CM #	C78.2	Secondary malignant neoplasm of pleura

Lung cancer	(30% to 40%)
Breast cancer	(20% to 25%)
Lymphoma	(10% to 15%)
Leukemia	(5% to 10%)
GI tract	(5%)
GU tract	(5%)
Reproductive	(3%)

PNEUMATOSIS INTESTINALIS IN NEONATE AND OLDER CHILD[16a]

ICD-9CM #	varies with specific diagnosis
ICD-10CM #	varies with specific diagnosis

CAUSES OF PNEUMATOSIS INTESTINALIS IN THE NEONATE AND THE OLDER CHILD
Necrotizing enterocolitis.
Bowel ischemia, inflammation, and obstruction.
Cyanotic congenital heart disease.
Hirschsprung's disease.
Gastroschisis.
Anorectal atresia.
Inflammatory bowel disease.
Lymphoma.
Leukemia.
CMV and rotavirus gastroenteritis.
Colonoscopy.
Caustic ingestion.
Short bowel syndrome.
Congenital immune deficiency states.
Clostridium infection.
Chronic steroid use.
Posthepatic, renal, or bone marrow transplant.
Collagen vascular disease.
Graft-versus-host disease.
AIDS.

PNEUMONIA, NONRESPONDING, CAUSES[26a]

ICD-9CM #	482.9	Bacterial Pneumonia
	480.9	Viral Pneumonia
	484.1	Fungal Pneumonia
	485	Segmental Pneumonia
ICD-10CM #	J15.9	Unspecified bacterial pneumonia
	J12.9	Viral pneumonia, unspecified
	B25.0	Cytomegaloviral pneumonitis
	J18.0	Bronchopneumonia, unspecified organism

CAUSES OF NONRESPONDING PNEUMONIA

Infectious Pneumonia

Resistant microorganisms:
- Community-acquired pneumonia (e.g., *Streptococcus pneumoniae, Staphylococcus aureus*).
- Nosocomial pneumonia (e.g., *Acinetobacter*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*).

Uncommon microorganisms (e.g., *Mycobacterium tuberculosis, Nocardia* spp., fungi, *Pneumocystis jirovecii*).

Complications of pneumonia:
- Empyema.
- Abscess or necrotizing pneumonia.
- Metastatic infection.

Noninfectious Pneumonia

Neoplasms.
Pulmonary hemorrhage.
Pulmonary embolism.
Sarcoidosis.
Eosinophilic pneumonia.
Pulmonary edema.
Acute respiratory distress syndrome.
Bronchiolitis obliterans with organizing pneumonia.
Drug-induced pulmonary disease.
Pulmonary vasculitis.

PNEUMONIA, RECURRENT

ICD-9CM #	482.9	Bacterial Pneumonia
	480.9	Viral Pneumonia
	484.1	Fungal Pneumonia
	485	Segmental Pneumonia
ICD-10CM #	J15.9	Unspecified bacterial pneumonia
	J12.9	Viral pneumonia, unspecified
	B25.0	Cytomegaloviral pneumonitis
	J18.0	Bronchopneumonia, unspecified organism

Mechanical obstruction from neoplasm.
Chronic aspiration (tube feeding, alcoholism, CVA, neuromuscular disorders, seizure disorder, inability to cough).
Bronchiectasis.
Kyphoscoliosis.
COPD, CHF, asthma, silicosis, pulmonary fibrosis, cystic fibrosis.
Pulmonary TB, chronic sinusitis.
Immunosuppression (HIV, corticosteroids, leukemia, chemotherapy, splenectomy).

PNEUMOPERITONEUM, NEONATAL[16a]

ICD-9CM #	varies with specific diagnosis
ICD-10CM #	varies with specific diagnosis

CAUSES OF NEONATAL PNEUMOPERITONEUM

Necrotizing enterocolitis.
Spontaneous perforation of a hollow viscus.
- Stomach.
- Duodenum.
- Ileum.
- Colon.

Malrotation and volvulus.
Distal obstruction.
Perforation of Meckel's diverticulum.
Anterior abdominal wall defects.
- Pentalogy of Cantrell.
- Omphalocele.
- Gastroschisis.
- Cloacal exstrophy.

Stress and peptic ulcers.
Mechanical ventilation (air leak) or resuscitation ("bagging").
Post-laparotomy.
Iatrogenic gastric perforation with an orogastric tube.
Iatrogenic colon perforation.
- Thermometer.
- During an enema.

Indomethacin.
Dexamethasone treatment.

PNEUMOTHORAX, IN CHILDREN[22a]

ICD-9CM #	512	Pneumothorax
ICD-10CM #	J93.0	Spontaneous tension pneumothorax
	J93	Pneumothorax
	J93.9	Pneumothorax unspecified

SPONTANEOUS

Primary idiopathic—usually resulting from ruptured subpleural blebs.
Secondary blebs.
Congenital lung disease:
- Congenital cystic adenomatoid malformation.
- Bronchogenic cysts.
- Pulmonary hypoplasia.

Conditions associated with increased intrathoracic pressure:
- Asthma.
- Bronchiolitis.
- Air-block syndrome in neonates.
- Cystic fibrosis.
- Airway foreign body.

Infection:
- Pneumatocele.
- Lung abscess.
- Bronchopleural fistula.

Diffuse lung disease:
- Langerhans cell histiocytosis.
- Tuberous sclerosis.
- Marfan syndrome.
- Ehlers-Danlos syndrome.

Metastatic neoplasm—usually osteosarcoma (rare).

TRAUMATIC

Noniatrogenic.
- Penetrating trauma.
- Blunt trauma.
- Loud music (air pressure).

Iatrogenic.
- Thoracotomy.
- Thoracoscopy, thoracentesis.
- Tracheostomy.
- Tube or needle puncture.

Mechanical ventilation.

POLYCYTHEMIA

ICD-9CM #	790.0	
ICD-10CM #	D45	Polycythemia primary
	D75.1	Polycythemia secondary

Tobacco abuse.
Chronic lung disease.
High altitude.
Sleep apnea.
Right-to-left cardiac shunts.
Erythropoietin administration.
Androgens/anabolic steroids.
Polycystic kidney disease.
Renal cell carcinoma.
Hepatocellular carcinoma.
Polycythemia vera.
Carbon monoxide exposure.
Primary familial and congenital polycythemia.
High-oxygen–affinity hemoglobins.
Uterine leiomyoma, meningioma, pheochromocytoma, parathyroid carcinoma.
Cobalt exposure.

POLYCYTHEMIAS, DIFFERENTIAL DIAGNOSIS[18c]

ICD-9CM #	790	
ICD-10CM #	D45	Polycythemia primary
	D75.1	Polycythemia secondary

DIFFERENTIAL DIAGNOSIS OF THE POLYCYTHEMIAS

Relative or Spurious Polycythemia
- Decreased plasma volume—reduced fluid intake, marked loss of body fluids (diaphoresis, vomiting, diarrhea, "third spacing").
- Gaisböck syndrome.
- Overfilling of blood in collection vacuum tubes.

Absolute Polycythemia
- Secondary polycythemia.
- Acquired.
- Hypoxia.
  - Pulmonary disease.
  - Cyanotic congenital heart disease.
  - Hypoventilation syndromes:
  - Sleep apnea.
  - Pickwickian syndrome.
  - High altitude.
  - Smokers' polycythemia, hookah polycythemia, carbon monoxide intoxication caused by industrial exposure.
- Postrenal transplantation erythrocytosis.
- Aberrant erythropoietin production.
  - Tumors:
  - Renal cell carcinoma.
  - Wilms tumor.
  - Hepatic carcinoma.
  - Uterine leiomyomata.
  - Virilizing ovarian tumors.
  - Vascular cerebellar tumors.
  - Miscellaneous renal and hepatic disorders:
  - Solitary renal cysts.

Polycystic kidney disease.
Renal artery stenosis hydronephrosis.
Viral hepatitis.
Endocrine disorders:
Cushing syndrome.
Primary aldosteronism.
Androgen use.
Erythropoietin use.
Congenital Polycythemias:
Abnormal high-affinity hemoglobin variants.
Bisphosphoglycerate deficiency.
Congenital methemoglobinemia.
Chuvash polycythemia (von Hippel Lindau mutations).
Prolyl hydroxylase mutations.
Hypoxia-inducible factor gene mutations.
Primary polycythemias:
Primary congenital and familial polycythemia.
Polycythemia vera.

POLYCYTHEMIA, RELATIVE VERSUS ABSOLUTE[20]

ICD-9CM # 790.0
ICD-10CM # D75.1 Secondary polycythemia

RELATIVE OR SPURIOUS POLYCYTHEMIA

Decreased plasma volume—reduced fluid intake, marked loss of body fluids (diaphoresis, vomiting, diarrhea, "third-spacing").
Gaisböck syndrome.
Overfilling of blood in collection vacuum tubes.

ABSOLUTE POLYCYTHEMIA

Primary Congenital and Familial Polycythemia
Secondary Polycythemia:
Acquired:
Hypoxia:
- Pulmonary disease.
- Cyanotic congenital heart disease.
- Hypoventilation syndromes—sleep apnea, Pickwickian syndrome.

High altitude.
Smokers' polycythemia, carbon monoxide intoxication due to industrial exposure.
Postrenal transplantation erythrocytosis.
Aberrant erythropoietin production:
- Tumors—renal cell carcinoma, Wilms' tumor, hepatic carcinoma, uterine leiomyomata, virilizing ovarian tumors, vascular cerebellar tumors.
- Miscellaneous renal and hepatic disorders—solitary renal cysts, polycystic kidney disease, renal artery stenosis, hydronephrosis, viral hepatitis.

Endocrine disorders—Cushing's syndrome, primary aldosteronism.
Androgen use.
Erythropoietin use.
Congenital:
Abnormal high-affinity hemoglobin variants.
Bisphosphoglycerate deficiency.
Congenital methemoglobinemia.
Chuvash polycythemia (von Hippel–Lindau mutations).
Prolyl hydroxylase mutations.

POLYCYTHEMIA VERA

POLYMYALGIAS[18b]

ICD-9CM # varies with specific diagnosis
ICD-10CM # M35.3 Polymyalgia rheumatic

DISEASE ENTITIES WITH POLYMYALGIAS

Rheumatoid arthritis.
Rotator cuff syndrome.
Osteoarthritis of shoulder and hip joints.
Fibromyalgia.
Polymyositis/dermatomyositis.
Spondyloarthritis.
Systemic lupus erythematosus.
Vasculitides.
Paraneoplastic myalgias.
Infection-associated myalgias.
Statin therapy.
RS3PE (remitting seronegative symmetric synovitis and pitting edema).
Parkinson's disease.
Hypothyroidism.

POLYNEUROPATHY[40]

ICD-9CM # 357.9
ICD-10CM # G61.9 Inflammatory polyneuropathy, unspecified

PREDOMINANTLY MOTOR

Guillain-Barré syndrome.
Porphyria.
Diphtheria.
Lead.
Hereditary sensorimotor neuropathy, types I and II.
Paraneoplastic neuropathy.

PREDOMINANTLY SENSORY

Diabetes.
Amyloidosis.
Leprosy.
Lyme disease.
Paraneoplastic neuropathy.
Vitamin B_{12} deficiency.
Hereditary sensory neuropathy, types I-IV.

PREDOMINANTLY AUTONOMIC

Diabetes.
Amyloidosis.
Alcoholic neuropathy.
Familial dysautonomias.

MIXED SENSORIMOTOR

Systemic diseases: renal failure, hypothyroidism, acromegaly, RA, periarteritis nodosa, SLE, multiple myeloma, macroglobulinemia, remote effect of malignancy.
Medications: isoniazid, nitrofurantoin, ethambutol, chloramphenicol, chloroquine, vincristine, vinblastine, dapsone, disulfiram, diphenylhydantoin, cisplatin, 1-tryptophan.
Environmental toxins: *N*-hexane, methyl *N*-butyl ketone, acrylamide, carbon disulfide, carbon monoxide, hexachlorophene, organophosphates.
Deficiency disorders: malabsorption, alcoholism, vitamin B_1 deficiency, Refsum's disease, metachromatic leukodystrophy.

POLYNEUROPATHY, DEMYELINATING[2]

ICD-9CM # varies with specific diagnosis
ICD-10CM # G37.9 Demyelinating disease of central nervous system, unspecified

Guillain-Barré syndrome.
Acute inflammatory demyelinating polyradiculoneuropathy (AIDP).
Acute motor axonal neuropathy (AMAN).
Acute motor and sensory axonal neuropathy (AMSAN).
Miller Fisher syndrome.
Chronic inflammatory demyelinating polyradiculoplexo-neuropathy.
Malignancy.
HIV.
Hepatitis B.
Buckthorn.
Diphtheria.

POLYNEUROPATHY, DISTAL SENSORIMOTOR[2]

ICD-9CM # varies with specific diagnosis
ICD-10CM # G63 Polyneuropathy in diseases classified elsewhere

Diabetes mellitus.
Alcoholism.
Neoplastic or paraneoplastic.
Hereditary motor and sensory neuropathies (Charcot-Marie-Tooth).
Cryptogenic sensorimotor polyneuropathies (CSPN).
HIV.
Toxins:
Organic or industrial agents:
- Acrylamide.
- Allyl chloride.
- Carbon disulfide.
- Ethylene oxide.
- Hexacarbons.
- Methyl bromide.
- Organophosphate-induced delayed polyneuropathy (OPIDP).
- Polychlorinated biphenyls (PCBs).
- Trichloroethylene.
- Vacor.

Metals:
- Arsenic.
- Gold.
- Mercury (inorganic).
- Thallium.

Therapeutic agents:
- Amiodarone.
- Antiretrovirals.
- Dapsone.

- Disulfiram.
- Isoniazid.
- Metronidazole.
- Nitrofurantoin.
- Paclitaxel (Taxol).
- Phenytoin.
- Statins (HMG-CoA reductase inhibitors).
- Thalidomide.
- Vinca alkaloids (vincristine, vinblastine).

Nutritional:
- Beriberi (thiamine or vitamin B_1).
- Pellagra (niacin, B vitamins).
- Pernicious anemia (vitamin B_{12}).
- Pyridoxine deficiency (vitamin B_6).

End-organ dysfunction:
- Acromegaly.
- Chronic pulmonary disease.
- Hypothyroidism.
- Renal failure (uremic neuropathy).

Paraproteinemias:
- Amyloidosis.
- Monoclonal gammopathy of unknown significance (MGUS).
- Multiple myeloma.
- Waldenström's macroglobulinemia.

Porphyria.

HMG-CoA, Hydroxymethylglutaryl coenzyme A.

POLYNEUROPATHY, DRUG-INDUCED[40]

ICD-9CM #	357.6	
ICD-10CM #	G62.0	Drug-induced polyneuropathy

DRUGS IN ONCOLOGY

Vincristine.
Procarbazine.
Cisplatin.
Misonidazole.
Metronidazole (Flagyl).
Taxol.

DRUGS IN INFECTIOUS DISEASES

Isoniazid.
Nitrofurantoin.
Dapsone.
ddC (dideoxycytidine).
ddI (dideoxyinosine).

DRUGS IN CARDIOLOGY

Hydralazine.
Perhexiline maleate.
Procainamide.
Disopyramide.

DRUGS IN RHEUMATOLOGY

Gold salts.
Chloroquine.

DRUGS IN NEUROLOGY AND PSYCHIATRY

Diphenylhydantoin.
Glutethimide.
Methaqualone.

MISCELLANEOUS

Disulfiram (Antabuse).
Vitamin: (pyridoxine in megadoses).

POLYNEUROPATHY, SYMMETRIC[40]

ICD-9CM #	357.9	
ICD-10CM #	G61.9	Inflammatory polyneuropathy, unspecified

ACQUIRED NEUROPATHIES

Toxic:
- Drugs.
- Industrial toxins.
- Heavy metals.
- Abused substances.

Metabolic/endocrine:
- Diabetes.
- Chronic renal failure.
- Hypothyroidism.
- Polyneuropathy of critical illness.

Nutritional deficiency:
- Vitamin B_{12} deficiency.
- Alcoholism.
- Vitamin E deficiency.

Paraneoplastic:
- Carcinoma.
- Lymphoma.

Plasma cell dyscrasia:
- Myeloma, typical, atypical, and solitary forms.
- Primary systemic amyloidosis.

Idiopathic chronic inflammatory demyelinating polyneuropathies.
Polyneuropathies associated with peripheral nerve autoantibodies.
Acquired immunodeficiency syndrome.

INHERITED NEUROPATHIES

Neuropathies with Biochemical Markers

Refsum's disease.
Bassen-Kornzweig disease.
Tangier disease.
Metachromatic leukodystrophy.
Krabbe's disease.
Adrenomyeloneuropathy.
Fabry's disease.

Neuropathies without Biochemical Markers or Systemic Involvement

Hereditary motor neuropathy.
Hereditary sensory neuropathy.
Hereditary sensorimotor neuropathy.

POLYURIA

ICD-9CM #	788.42	
ICD-10CM #	R35.8	Other polyuria

DM.
Diabetes insipidus.
Primary polydipsia (compulsive water drinking).
Hypercalcemia.
Hypokalemia.
Postobstructive uropathy.
Diuretic phase of renal failure.
Drugs: diuretics, caffeine, alcohol, lithium.
Sickle cell trait or disease, chronic pyelonephritis (failure to concentrate urine).
Anxiety, cold weather.

POPLITEAL SWELLING

ICD-9CM #	459.2	Venous Obstruction
	747.4	Vein Anomaly, Lower Limb Vessel
	442.3	Artery Aneurysm
	904.41	Artery Injury
	447.8	Entrapment Syndrome
	727.51	Baker's Cyst
	451.2	Phlebitis, Lower Extremity
	727.67	Rupture of Achilles Tendon
ICD-10CM #	I87.1	Compression of vein
	I72.4	Aneurysm of artery of lower extremity
	S85.009A	Unspecified injury of popliteal artery, unspecified leg, initial encounter
	I77.3	Arterial fibromuscular dysplasia
	M71.20	Synovial cyst of popliteal space [Baker], unspecified knee
	I80.3	Phlebitis and thrombophlebitis of lower extremities, unspecified
	M66.369	Spontaneous rupture of flexor tendons, unspecified lower leg

Phlebitis (superficial).
Lymphadenitis.
Trauma: fractured tibia or fibula, contusion, traumatic neuroma.
DVT.
Ruptured varicose vein.
Baker's cyst.
Popliteal abscess.
Osteomyelitis.
Ruptured tendon.
Aneurysm of popliteal artery.
Neoplasm: lipoma, osteogenic sarcoma, neurofibroma, fibrosarcoma.

PORTAL HYPERTENSION[1a]

ICD-9CM #	572.3	
ICD-10CM #	K76.6	Portal hypertension

INCREASED RESISTANCE TO FLOW

Presinusoidal

Portal or splenic vein occlusion (thrombosis, tumor).
Schistosomiasis.
Congenital hepatic fibrosis.
Sarcoidosis.

Sinusoidal

Cirrhosis (all causes).
Alcoholic hepatitis.

Postsinusoidal
Venoocclusive disease.
Budd-Chiari syndrome.
Constrictive pericarditis.

INCREASED PORTAL BLOOD FLOW

Splenomegaly not caused by liver disease.
Arterioportal fistula.

POSTMENOPAUSAL BLEEDING

ICD-9CM #	627.1	
ICD-10CM #	N95.0	Postmenopausal bleeding

Hormone replacement therapy.
Neoplasm (uterine, ovarian, cervical, vaginal, vulvar).
Atrophic vaginitis.
Vaginal infection.
Polyp.
Extragenital (GI, urinary).
Tamoxifen.
Trauma.

POSTURAL HYPOTENSION, NONNEUROLOGIC CAUSES

ICD-9CM #	458.0	
ICD-10CM #	I95.1	Orthostatic hypotension

Diuretics and hypertensive agents.
GI hemorrhage.
Alcohol.
Excessive heat.
Rapid volume loss from diarrhea, vomiting.
Hemodialysis.
Extensive burns.
Pyrexia.
Aortic stenosis (impaired output).
Constrictive pericarditis, atrial myxoma (impaired cardiac filling).
Adrenal insufficiency.
Diabetes insipidus.
Vasodilatory agents (e.g., nitrates).

PREMATURE GRAYING, SCALP HAIR

ICD-9CM #	varies with specific disorder
ICD-10CM #	varies with specific diagnosis

Chemical exposure (e.g., phenol/catechol derivatives, sulfhydryls, arsenic).
Physical agents (e.g., ionizing radiation, lasers).
Hyperthyroidism.
Vitamin B_{12} deficiency.
Down syndrome.
Chronic and severe protein deficiency.
Vitiligo.
Idiopathic.
Myotonic dystrophy.
Ataxia-telangiectasia.
Progeria.
Werner's syndrome.

PREMATURE VENTRICULAR CONTRACTIONS AND VENTRICULAR TACHYCARDIA[2]

ICD-9CM #	427.6	
ICD-10CM #	I49.40	Unspecified premature depolarization
	I47.2	Ventricular tachycardia

CAUSES OF PREMATURE VENTRICULAR CONTRACTIONS AND VENTRICULAR TACHYCARDIA

Acute or previous myocardial infarction/ischemia.
Hypokalemia.
Hypoxemia.
Ischemic heart disease.
Valvular disease.
Catecholamine excess.*
Other drug intoxications (especially cyclic antidepressants).
Idiopathic causes.†
Digitalis toxicity.
Hypomagnesemia.
Hypercapnia.
Class I antidysrhythmic agents.
Ethanol.
Myocardial contusion.
Cardiomyopathy.
Acidosis.
Alkalosis.
Methylxanthine toxicity.

*Relative increase in sympathetic tone from drugs (direct or indirect) or conditions that augment catecholamine release or decrease parasympathetic tone.
†Isolated premature ventricular contractions (PVCs) can occur in up to 50% of young subjects without obvious cardiac or noncardiac disease; however, multiform and repetitive PVCs and ventricular tachycardia are rarely seen in this population.

PROPTOSIS[30]

ICD-9CM #	376.30	
ICD-10CM #	H05.20	Unspecified exophthalmos
	H05.2	Ocular proptosis

Thyrotoxicosis.
Orbital pseudotumor.
Optic nerve tumor.
Cavernous sinus AV fistula, cavernous sinus thrombosis.
Cellulitis.
Metastatic tumor to orbit.

PROPTOSIS AND PALATAL NECROTIC ULCERS

ICD-9CM #	528.9	Ulcer of Palate
	376.30	Proptosis
ICD-10CM #	K13.70	Unspecified lesions of oral mucosa
	K13.79	Other lesions of oral mucosa
	H05.20	Unspecified exophthalmos

Cavernous sinus thrombosis.
Bacterial orbital cellulitis.
Metastatic neoplasm.
Rhinocerebral mucormycosis.
Ecthyma gangrenosum.
CNS aspergillosis.

PROTEIN-LOSING ENTEROPATHY, PEDIATRIC AGE[22a]

ICD-9CM #	579.8	
ICD-10CM #	E44.0	Moderate protein-energy malnutrition

CAUSES OF PROTEIN-LOSING ENTEROPATHY

Mucosal inflammation:
  Infection:
  - Cytomegalovirus.
  - Bacterial overgrowth.
  - Invasive bacterial infection.

  Gastric inflammation:
  - Ménétrier disease.
  - Eosinophilic gastroenteropathy.

  Intestinal inflammation:
  - Celiac disease.
  - Crohn disease.

  Eosinophilic gastroenteropathy:
  - Tropical sprue.
  - Radiation enteritis.

Primary intestinal lymphangiectasia.
Secondary intestinal lymphangiectasia:
  Constrictive pericarditis.
  Congestive heart failure.
  Post–Fontan procedure.
  Malrotation.
  Lymphoma.
  Sarcoidosis.
  Radiation therapy.
  Colonic inflammation:
  - Inflammatory bowel diseases.
  - Necrotizing enterocolitis.

  Congenital disorders of glycosylation.

PROTEINURIA

ICD-9CM #	791.0	
ICD-10CM #	R80.9	Proteinuria, unspecified

'Nephrotic syndrome as a result of primary renal diseases.
Malignant hypertension.
Malignancies: multiple myeloma, leukemias, Hodgkin's disease.
CHF.
DM.
SLE, RA.
Sickle cell disease.
Goodpasture's syndrome.
Malaria.
Amyloidosis, sarcoidosis.
Tubular lesions: cystinosis.
Functional (after heavy exercise).
Pyelonephritis.
Pregnancy.
Constrictive pericarditis.
Renal vein thrombosis.
Toxic nephropathies: heavy metals, drugs.

Radiation nephritis.
Orthostatic (postural) proteinuria.
Benign proteinuria: fever, heat, or cold exposure.

PRURITUS

ICD-9CM #	698.9	Pruritus NOS
	697.0	Pruritus Ani
	698.1	Pruritus, Genital Organs
ICD-10CM #	L29.9	Pruritus, unspecified
	L29.3	Anogenital pruritus, unspecified

Dry skin.
Drug-induced eruption, fiberglass exposure.
Scabies.
Skin diseases.
Myeloproliferative disorders: mycosis fungoides, Hodgkin's lymphoma, multiple myeloma, polycythemia vera.
Cholestatic liver disease.
Endocrine disorders: DM, thyroid disease, carcinoid, pregnancy.
Carcinoma: breast, lung, gastric.
Chronic renal failure.
Iron deficiency.
AIDS.
Neurosis.
Sjögren's syndrome.

PRURITUS ANI[26]

ICD-9CM #	697.0	
ICD-10CM #	L29.0	Pruritus ani

FECAL IRRITATION

Poor hygiene.
Anorectal conditions (fissure, fistula, hemorrhoids, skin tags, perianal clefts).
Spicy foods, citrus foods, caffeine, colchicine, quinidine.

CONTACT DERMATITIS

Anesthetic agents, topical corticosteroids, perfumed soap.

DERMATOLOGIC DISORDERS

Psoriasis, seborrhea, lichen simplex or sclerosus.

SYSTEMIC DISORDERS

Chronic renal failure, myxedema, DM, thyrotoxicosis, polycythemia vera, Hodgkin's disease.

SEXUALLY TRANSMITTED DISEASES

Syphilis, herpes simplex virus, human papillomavirus.

OTHER INFECTIOUS AGENTS

Pinworms.
Scabies.
Bacterial infection, viral infection.

PRURITUS VULVAE[34a]

ICD-9CM #	698.1	
ICD-10CM #	L29.3	Anogenital pruritus, unspecified

CAUSES OF PRURITUS VULVAE

Diseases Special to Vulval Skin
Lichen sclerosus et atrophicus.
Leukoplakia.
Carcinoma.
Skin Disease
Psoriasis.
Atopic dermatitis.
Irritant and allergic contact dermatitis (especially medicaments).
Infection
Candidiasis.
Trichomonas.
Infestation
Pediculosis.
Psychogenic
Anxiety.
Depression.
Unknown

PSEUDOCYANOSIS, ETIOLOGY

ICD-9CM #	varies with etiology
ICD-10CM #	varies with etiology

Medications: amiodarone, minocycline, chlorpromazine.
Heavy metals:
Gold (systemic absorption).
Silver (systemic absorption).
Local contact with color dyes, gold, silver.

PSEUDOHERMAPHRODITISM, FEMALE

ICD-9CM #	255.2	Adrenal
	752.7	Without Adrenocortical Disorder
ICD-10CM #	E25.0	Congenital adrenogenital disorders associated with enzyme deficiency
	E25.8	Other adrenogenital disorders
	E25.9	Adrenogenital disorder, unspecified
	Q56.3	Pseudohermaphroditism, unspecified
	Q56.4	Indeterminate sex, unspecified

Congenital adrenal hyperplasia.
Maternal use of testosterone or related steroids.
Virilizing ovarian or adrenal tumor.
Virilizing luteoma of pregnancy.
Disturbances in differentiation of urogenital structures, non-androgen related.
Maternal virilizing adrenal hyperplasia.
Fetal P450 aromatase deficiency.

PSEUDOHERMAPHRODITISM, MALE

ICD-9CM #	255.2	Adrenal
	752.7	Without Adrenocortical Disorder
ICD-10CM #	E25.0	Congenital adrenogenital disorders associated with enzyme deficiency
	E25.8	Other adrenogenital disorders
	E25.9	Adrenogenital disorder, unspecified
	Q56.3	Pseudohermaphroditism, unspecified
	Q56.4	Indeterminate sex, unspecified

Maternal ingestion of progestogens.
End-organ resistance to androgenic hormones.
5-α-reductase-2 deficiency.
XY gonadal dysgenesis.
Testicular regression syndrome.
Defects in testosterone metabolism by peripheral tissues.
Testosterone biosynthesis defects.

PSEUDOINFARCTION[22]

ICD-9CM #	code varies with specific diagnosis
ICD-10CM #	varies with specific diagnosis

Cardiac tumors, primary and secondary.
Cardiomyopathy (particularly hypertrophic and dilated).
Chagas' disease.
Chest deformity.
COPD (particularly emphysema).
HIV infection.
Hyperkalemia.
Left anterior fascicular block.
Left bundle branch block.
Left ventricular hypertrophy.
Myocarditis and pericarditis.
Normal variant.
Pneumothorax.
Poor R wave progression, rotational changes, and lead placement.
Pulmonary embolism.
Trauma to chest (nonpenetrating).
Wolff-Parkinson-White syndrome.
Rare causes: pancreatitis, amyloidosis, sarcoidosis, scleroderma.

PSYCHOSIS[28]

ICD-9CM #	298.9	Psychosis NOS
	298.90	Psychosis, Affective
	291.0	Psychosis, Alcoholic
	290.41	Psychosis, Acute Arteriosclerotic

ICD-10CM #	# F29	Unspecified psychosis not due to a substance or known physiological condition
	F29	Unspecified psychosis not due to a substance or known physiological condition
	F10.231	Alcohol dependence with withdrawal delirium
	F01.51	Vascular dementia with behavioral disturbance

PRIMARY

Schizophrenia related.*
Major depression.
Dementia.
Bipolar disorder.

SECONDARY

Drug use.†
Drug withdrawal.‡
Drug toxicity.§
Charles Bonnet syndrome.
Infections (pneumonia).
Electrolyte imbalance.
Syphilis.
Congestive heart failure.
Parkinson's disease.
Trauma to temporal lobe.
Postpartum psychosis.
Hypothyroidism/hyperthyroidism.
Hypomagnesemia.
Epilepsy.
Meningitis.
Encephalitis.
Brain abscess.
Herpes encephalopathy.
Hypoxia.
Hypercarbia.
Hypoglycemia.
Thiamine deficiency.
Postoperative states.

*Includes schizophrenia, schizophreniform disorder, brief reactive psychosis.
†Includes hypnotics, glucocorticoids, marijuana, phencyclidine, atropine, dopaminergic agents (e.g., amantadine, bromocriptine, l-dopa), immunosuppressants.
‡Includes alcohol, barbiturates, benzodiazepines.
§Includes digitalis, theophylline, cimetidine, anticholinergics, glucocorticoids, catecholaminergic agents.

PTOSIS

ICD-9CM #	374.30	Ptosis NOS
	743.61	Congenital
	374.33	Mechanical
	374.32	Myogenic
	374.31	Paralytic
ICD-10CM #	H02.409	Unspecified ptosis of unspecified eyelid
	Q10.0	Congenital ptosis
	H02.419	Mechanical ptosis of unspecified eyelid
	H02.429	Myogenic ptosis of unspecified eyelid
	H02.439	Paralytic ptosis unspecified eyelid

Third nerve palsy.
Myasthenia gravis.
Horner's syndrome.
Senile ptosis.

PUBERTY, DELAYED[27]

ICD-9CM #	259.0	
ICD-10CM #	E30.0	Delayed puberty

NORMAL OR LOW SERUM GONADOTROPIN LEVELS

Constitutional delay in growth and development.
Hypothalamic and/or pituitary disorders:
- Isolated deficiency of growth hormone.
- Isolated deficiency of Gn-RH.
- Isolated deficiency of LH and/or FSH.
- Multiple anterior pituitary hormone deficiencies.
- Associated with congenital anomalies: Kallmann's syndrome; Prader-Willi syndrome; Laurence-Moon-Biedl syndrome; Friedreich's ataxia.
- Trauma.
- Postinfection.
- Hyperprolactinemia.
- Postirradiation.
- Infiltrative disease (histiocytosis).
- Tumor.
- Autoimmune hypophysitis.
- Idiopathic.

Functional:
- Chronic endocrinologic or systemic disorders.
- Emotional disorders.
- Drugs: cannabis.

INCREASED SERUM GONADOTROPIN LEVELS

Gonadal abnormalities:
- Congenital:
  - Gonadal dysgenesis.
  - Klinefelter's syndrome.
  - Bilateral anorchism.
  - Resistant ovary syndrome.
  - Myotonic dystrophy in males.
  - 17-Hydroxylase deficiency in females.
  - Galactosemia.
- Acquired:
  - Bilateral gonadal failure resulting from trauma or infection or after surgery, irradiation, or chemotherapy.
  - Oophoritis: isolated or with other autoimmune disorders.

Uterine or vaginal disorders:
- Absence of uterus and/or vagina.
- Testicular feminization: complete or incomplete androgen insensitivity.

PUBERTY, PRECOCIOUS

ICD-9CM #	255.2	
ICD-10CM #	E25.0	Congenital adrenogenital disorders associated with enzyme deficiency
	E25.8	Other adrenogenital disorders
	E25.9	Adrenogenital disorder, unspecified

Idiopathic.
Congenital virilizing adrenal hyperplasia.
Hypothalamic tumors.
Head trauma.
Hydrocephalus.
Degenerative CNS disease.
Arachnoid cyst.
Sex chromosome abnormalities (e.g., 47, XXY, 48, XXXY).
Perinatal asphyxia.
CNS infection (e.g., meningitis, encephalitis).

PULMONARY CRACKLES

ICD-9CM #	code not available	
ICD-10CM #	R09.8	Friction sounds, chest

Pneumonia.
Left ventricular failure.
Asbestosis, silicosis, interstitial lung disease.
Chronic bronchitis.
Alveolitis (allergic, fibrosing).
Neoplasm.

PULMONARY CYSTS ON X-RAY[16a]

ICD-9CM #	793.1	
ICD-10CM #	Q33.0	Polycystic lungs, congenital
	J98.4	Pulmonary manifestations

CAUSES OF CYSTS IN THE LUNG ON CHEST RADIOGRAPH

Cystic fibrosis.
Cystic bronchiectasis.
Bronchopulmonary dysplasia (neonate and older).
Tuberculosis (apical thick walled).
Pulmonary abscess (thick wall, fluid level).
Empyema.
Streptococcal pneumatocele (thin wall, postinfective).
Cavitating pneumonia.
Mycetoma (apical cyst with contents).
Cystic congenital adenomatoid malformation (basal cysts of varying size).
Diaphragmatic hernia (cysts of similar size).
Hiatal hernia (posterior).
Morgagni hernia (midline anterior).
Bronchopulmonary sequestration (basal).
Congenital lobar emphysema.
Hydatid disease (in endemic areas).
Kerosene inhalation (pneumatocele).
Histiocytosis and other causes of interstitial disease.

PULMONARY EDEMA, NONCARDIOGENIC[16a]

ICD-9CM #	518.4	
ICD-10CM #	J81.0	Acute pulmonary edema

CAUSES OF NONCARDIOGENIC PULMONARY EDEMA

Adult respiratory distress syndrome.
Drowning.
Asphyxia.
Upper airway obstruction (usually with cardiomegaly).
High altitude.
Increased intracranial pressure.
Postictal.
Noxious gases:
- Smoke.
- Nitrous dioxide (silo filler's disease).
- Sulfur dioxide.
- Nitrogen mustard.

Drugs:
- Asprin.
- Diazepam, chlordiazepoxide, barbiturates.
- Narcotics (heroin, methadone, morphine).
- β-adrenergic drugs (terbutaline).
- Contrast media.
- Colchicine.
- Fluorescein.
- Hydrochlorothiazide.
- Nitrofurantoin.
- Propoxyphene.

Poisons:
- Parathion.

Transfusion reactions.
Renal failure: transplantation.
Bone marrow transplantation.
Fat embolism.
Pancreatitis.

PULMONARY HEMORRHAGE, PEDIATRIC AGE

ICD-9CM #	770.3	
ICD-10CM #	P26.9	Pulmonary hemorrhage newborn

CAUSES OF PULMONARY HEMORRHAGE (HEMOPTYSIS)

Focal Hemorrhage

Bronchitis and bronchiectasis (especially cystic fibrosis related).
Infection (acute or chronic), pneumonia, abscess.
Tuberculosis.
Trauma.
Pulmonary arteriovenous malformation.
Foreign body (chronic).
Neoplasm including hemangioma.
Pulmonary embolus with or without infarction.
Bronchogenic cysts.
Diffuse Hemorrhage
Idiopathic of infancy.
Congenital heart disease (including pulmonary hypertension, venoocclusive disease, congestive heart failure).
Prematurity.
Cow's milk hyperreactivity (Heiner syndrome).
Goodpasture syndrome.
Collagen vascular diseases (systemic lupus erythematosus, rheumatoid arthritis).
Henoch-Schönlein purpura and vasculitic disorders.
Granulomatous disease (Wegener granulomatosis).
Celiac disease.
Coagulopathy (congenital or acquired).
Malignancy.
Immunodeficiency.
Exogenous toxins.
Hyperammonemia.
Pulmonary hypertension.
Pulmonary alveolar hemosiderosis.
Tuberous sclerosis.
Lymphangiomyomatosis or lymphangioleiomyomatosis.
Physical injury or abuse.

PULMONARY HEMORRHAGIC SYNDROMES, DIFFUSE[16a]

ICD-9CM #	770.3	
ICD-10CM #	P26.1	Massive pulmonary hemorrhage originating in the perinatal period
	R04.8	Pulmonary hemorrhage

CLASSIFICATION OF DIFFUSE PULMONARY HEMORRHAGE SYNDROMES

Non-immunocompromised patients

Antibasement membrane antibody disease/ Goodpasture's syndrome.
Diseases of presumed immune etiology, with or without nephropathy:
- Systemic lupus erythematosus.
- Rheumatoid arthritis.
- Systemic sclerosis.
- Systemic necrotizing vasculitis.
- Granulomatosis with polyangiitis (Wegener's granulomatosis).
- Microscopic polyarteritis.

Diseases with no known immune etiology:
- Idiopathic pulmonary hemosiderosis.
- Rapidly progressive glomerulonephritis without immune complexes.
- Fibrillary glomerulonephritis.
- Drug-induced (anticoagulants, trimellitic anhydride, cocaine, lymphangiography).
- Valvular heart disease.
- Disseminated intravascular coagulation.
- Acute lung injury.
- Tumors.

Immunocompromised Patients

Blood dyscrasias.
Infection.
Tumors.

PULMONARY INFILTRATES, IMMUNOCOMPROMISED HOST[39]

ICD-9CM #	518.3	
ICD-10CM #	J82	Pulmonary eosinophilia, not elsewhere classified
	J98.4	Other disorders of lung

CAUSES OF PULMONARY INFILTRATES IN THE IMMUNOCOMPROMISED HOST

Infections:

Bacteria:
- Gram-positive cocci, especially *Staphylococcus.*
- Gram-negative bacilli.
- *Mycobacterium tuberculosis.*
- Nontuberculous mycobacteria.
- *Nocardia.*

Viruses:
- Cytomegalovirus.
- Herpesvirus.

Fungi:
- *Aspergillus.*
- *Cryptococcus.*
- *Candida.*
- *Mucor.*
- *Pneumocystis jiroveci.*

Protozoa:
- *Toxoplasma gondii* (rare).

Pulmonary effects of therapy:
- Chemotherapeutic agents.
- Radiation therapy.

Pulmonary hemorrhage.
Congestive heart failure.
Disseminated malignancy.
Nonspecified interstitial pneumonitis (no defined etiology).

PULMONARY LESIONS

ICD-9CM #	518.3	Pulmonary Infiltrate
	518.89	Pulmonary Nodule
	508.9	Pulmonary Disorder Due to Unspecified External Agent
	861.20	Pulmonary Injury NOS
ICD-10CM #	J82	Pulmonary eosinophilia, not elsewhere classified
	J98.4	Other disorders of lung
	J70.9	Respiratory conditions due to unspecified external agent
	S27.309A	Unspecified injury of lung, unspecified, initial encounter

TB.
Legionella pneumonia.
Mycoplasma pneumonia.
Viral pneumonia.
Pneumocystis carinii.
Hypersensitivity pneumonitis.
Aspiration pneumonia.
Fungal disease (aspergillosis, histoplasmosis).
ARDS associated with pneumonia.
Psittacosis.
Sarcoidosis.
Septic emboli.

Metastatic cancer.
Multiple pulmonary emboli.
Rheumatoid nodules.

PULMONARY MASS, SOLITARY, CAUSES[16a]

ICD-9CM #	793.1	
ICD-10CM #	R91.1	Solitary pulmonary nodule

CAUSES OF A SOLITARY PULMONARY MASS

Bronchial carcinoma.
Bronchial carcinoid.
Granuloma.
Hamartoma.
Metastasis.
Chronic pneumonia or abscess.
Hydatid cyst.
Pulmonary hematoma.
Bronchocele.
Fungus ball.
Massive fibrosis in coal workers.
Bronchogenic cyst.
Sequestration.
Arteriovenous malformation.
Pulmonary infarct.
Round atelectasis.

PULMONARY MASS, SOLITARY, MIMICS[16a]

ICD-9CM #	varies with specific diagnosis
ICD-10CM #	varies with specific diagnosis

SIMULANTS OF A SOLITARY PULMONARY MASS

Extrathoracic artifacts.
Cutaneous masses.
Bony lesions.
Pleural tumors or plaques.
Encysted pleural fluid.
Pulmonary vessels.

PULMONARY NODULE, SOLITARY

ICD-9CM #	518.89	
ICD-10CM #	J98.4	Other disorders of lung

Bronchogenic carcinoma.
Granuloma from histoplasmosis.
TB granuloma.
Granuloma from coccidioidomycosis.
Metastatic carcinoma.
Bronchial adenoma.
Bronchogenic cyst.
Hamartoma.
AV malformation.
Other: fibroma, intrapulmonary lymph node, sclerosing hemangioma, bronchopulmonary sequestration.

PULMONARY–RENAL SYNDROMES, CAUSES[12b]

ICD-9CM #	varies with specific diagnosis
ICD-10CM #	varies with specific diagnosis

Systemic vasculitis	Anti-GBM disease (Goodpasture's) ANCA associated • Granulomatosis with polyangiitis (Wegener's granulomatosis) • Microscopic polyarteritis • Churg-Strauss syndrome • Drugs (penicillamine, hydralazine, propylthiouracil) Immune complex disease • Lupus erythematosus • Henoch-Schönlein purpura • Mixed cryoglobulinemia • Rheumatoid vasculitis
Infection	Severe bacterial pneumonia; postinfectious glomerulonephritis; *Legionella;* hantavirus; opportunistic infection in immunocompromised patients; infective endocarditis
Pulmonary edema and AKI	Volume overload; severe left ventricular failure
Multiorgan failure	Acute respiratory distress syndrome and AKI
Other	Paraquat poisoning; renal vein or IVC thrombosis with pulmonary emboli

AKI, Acute kidney injury; *ANCA,* anti-neutrophil cytoplasmic antibody; *GBM,* glomerular basement membrane; *IVC,* inferior vena cava.

PULSELESS ELECTRICAL ACTIVITY

ICD-9CM #	427.5	
ICD-10CM #	I46.9	Cardiac arrest, cause unspecified

Hypovolemia.
Hypoxia.
Hyperkalemia.
Acidosis.
Cardiac tamponade.
Tension pneumothorax.
Pulmonary embolus.
Drug overdose.
Hypothermia.

PUPILLARY DILATATION, POOR RESPONSE TO DARKNESS

ICD-9CM #	varies with specific disorder	
ICD-10CM #	H21.569	Pupillary abnormality, unspecified eye

Drugs (narcotics, general anesthetics, cholinergics).
Acute trauma (spasm from prostaglandin release).
Inflammation, infection (interruption of inhibitory fibers to the Edinger-Westphal nucleus).
Old age (loss of inhibition at midbrain from reticular activating formation).
Horner's syndrome (sympathetic neuron interruption).
Adie's syndrome tonic pupil.
Lymphoma.
Congenital miosis.

PURPURA

ICD-9CM #	287.2	Purpura NOS
	287.0	Autoimmune
	287.0	Henoch-Schönlein
	287.3	Idiopathic Thrombocytopenic
	446.6	Thrombocytopenic
ICD-10CM #	D69.2	Other nonthrombocytopenic purpura
	D69.0	Allergic purpura
	D69.49	Other primary thrombocytopenia
	M31.1	Thrombotic microangiopathy

THROMBOTIC

Trauma.
Septic emboli, atheromatous emboli.
DIC.
Thrombocytopenia.
Meningococcemia.
Rocky Mountain spotted fever.
Hemolytic-uremic syndrome.
Viral infection: echo, coxsackie.
Scurvy.
Other: left atrial myxoma, cryoglobulinemia, vasculitis, hyperglobulinemic purpura.

PURPURA, NONPALPABLE[20]

ICD-9CM #	287.2	
ICD-10CM #	D69.2	Other nonthrombocytopenic purpura

INCREASED TRANSMURAL PRESSURE GRADIENT

Acute (Valsalva, coughing, vomiting, high altitude, weight lifting).
Chronic—Venous stasis.

DECREASED MECHANICAL INTEGRITY OF MICROCIRCULATION AND SUPPORTING TISSUES

Age related (infancy and actinic purpura).
Glucocorticoid excess—Cushing syndrome and glucocorticoid therapy.
Vitamin C deficiency (scurvy).
Abnormal connective tissue—Ehlers-Danlos syndrome.
Amyloid infiltration of blood vessels.
Colloid milium.
Hormonal—Female easy bruising syndrome (purpura simplex).
Lorenzo's oil.
MELAS syndrome.

TRAUMA TO BLOOD VESSELS

Physical:
- Injuries.
- Child abuse.
- Factitial purpura.

Ultraviolet purpura:
- Purpuric sunburn.
- Solar purpura.

Infectious:
- Bacterial.
- Rickettsial.
- Fungal.
- Viral.
- Parasitic.

Embolic:
- Infectious organisms.
- Atheroemboli (cholesterol crystal emboli).
- Fat emboli.

Allergic and/or inflammatory:
- Serum sickness.
- Pigmented purpuric eruptions.
- Pyoderma gangrenosum.
- Contact dermatitis.
- Familial Mediterranean fever.

Neoplastic.

Metabolic:
- Erythropoietic porphyria.
- Calciphylaxis.

Immunoglobulin related (hyperglobulinemic purpura of Waldenström and light-chain vasculitis).

Drug related.

Thrombotic:
- Disseminated intravascular coagulation.
- Warfarin (Coumadin)-induced skin necrosis.
- Protein C or protein S deficiency, factor V Leiden, prothrombin G20201A.
- Purpura fulminans.
- Paroxysmal nocturnal hemoglobinuria.
- Antiphospholipid antibody syndrome.
- Hemangioma with thrombocytopenia and consumptive coagulopathy (Kasabach-Merritt syndrome).

UNKNOWN CAUSE—PSYCHOGENIC PURPURA

PURPURA, NONPURPURIC DISORDERS SIMULATING PURPURA[1a]

ICD-9CM # varies with specific diagnosis
ICD-10CM # varies with specific diagnosis

Disorders with telangiectasias:
- Cherry angiomas.
- Hereditary hemorrhagic telangiectasia.
- Chronic actinic telangiectasia.
- Scleroderma.
- CREST syndrome.
- Ataxia-telangiectasia.
- Chronic liver disease.
- Pregnancy-related telangiectasia.

Kaposi sarcoma and other vascular sarcomas.

Fabry disease.

Neonatal extramedullary hematopoiesis.

Angioma serpiginosum.

PURPURA, PALPABLE[20]

ICD-9CM # 287.2
ICD-10CM # D69.2 Other nonthrombocytopenic purpura

Cutaneous vasculitis:
- Systemic vasculitides.
- Paraneoplastic vasculitis.
- Henoch-Schönlein purpura.
- Acute hemorrhagic edema of infancy.
- Livedoid vasculitis.
- Idiopathic.
- Urticarial.

Cryoglobulinemia.

Cryofibrinogenemia.

Primary cutaneous diseases.

QT INTERVAL PROLONGATION[22]

ICD-9CM # 794.31
ICD-10CM # R94.31 Abnormal electrocardiogram [ECG] [EKG]

Drugs:
- Class I antiarrhythmics (e.g., disopyramide, procainamide, quinidine).
- Class III antiarrhythmics.
- Tricyclic antidepressants.
- Phenothiazines.
- Astemizole.
- Terfenadine.
- Adenosine.
- Antibiotics (e.g., erythromycin and other macrolides).
- Antifungal agents.
- Pentamidine, chloroquine.

Ischemic heart disease.

Cerebrovascular disease.

Rheumatic fever.

Myocarditis.

Mitral valve prolapse.

Electrolyte abnormalities.

Hypocalcemia.

Hypothyroidism.

Liquid protein diets.

Organophosphate insecticides.

Congenital prolonged QT syndrome.

RECTAL MASS, PALPABLE[38]

ICD-9CM # varies with specific diagnosis
ICD-10CM # R22.9 Localized swelling, mass and lump, unspecified

Rectal carcinoma.

Rectal polyp.

Hypertrophied anal papilla.

Diverticular phlegmon (prolapsing into the pouch of Douglas).

Sigmoid colon carcinoma (prolapsing into the pouch of Douglas).

Metastatic deposits at the pelvic reflection (Blumer's shelf).

Primary pelvic malignancy (uterine, ovarian, prostatic, or cervical).

Mesorectal lymph nodes.

Endometriosis.

Solitary rectal ulcer syndrome.

Foreign body.

Feces.

Presacral cyst.

Amebic granuloma.

Vaginal tampon and even the pubic bone may be mistaken for a rectal mass.

RECTAL PAIN

ICD-9CM # 569.42
ICD-10CM # K62.89 Other specified diseases of anus and rectum

Anal fissure.

Thrombosed hemorrhoid.

Anorectal abscess.

Foreign bodies.

Fecal impaction.

Endometriosis.

Neoplasms (primary or metastatic).

Pelvic inflammatory disease.

Inflammation of sacral nerves.

Compression of sacral nerves.

Prostatitis.

Other: proctalgia fugax, uterine abnormalities, myopathies, coccygodynia.

RED BLOOD CELL APLASIA, ACQUIRED, ETIOLOGY

ICD-9CM # 284.0
ICD-10CM # D61.01 Constitutional (pure) red blood cell aplasia

Idiopathic (>50% of cases).

Medications (most frequent with phenytoin).

Non-Hodgkin's lymphoma.

Viral infections (parvovirus B19, EB virus, mumps, hepatitis).

Myelodysplastic syndromes.

Thymoma.

Autoimmune diseases.

Allogenic bone marrow transplant from ABO incompatible donor.

Pregnancy.

RED BLOOD CELL FRAGMENTATION HEMOLYSIS, CAUSES[18c]

ICD-9CM # varies with specific disorder
ICD-10CM # varies with specific disorder

CAUSES OF RED BLOOD CELL FRAGMENTATION HEMOLYSIS

Damaged microvasculature.

Thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP–HUS).

Associated with pregnancy: preeclampsia or eclampsia; hemolysis plus elevated liver enzymes plus low platelets (HELLP syndrome).

Associated with malignancy, with or without mitomycin C treatment.

Vasculitis: polyarteritis, Wegener granulomatosis, acute glomerulonephritis, or *Rickettsia*-like infections.

Systemic lupus erythematosus.

Abnormalities of renal vasculature: malignant hypertension, acute glomerulonephritis, scleroderma, or allograft rejection with or without cyclosporine treatment.
Disseminated intravascular coagulation.
Malignant hypertension.
Catastrophic antiphospholipid antibody syndrome.
Atrioventricular malformations.
Kasabach-Merritt syndrome.
Hemangioendotheliomas.
Atrioventricular shunts for congenital and acquired conditions (e.g., stents, coils, transjugular intrahepatic portosystemic shunt, Levine shunts).
Cardiac abnormalities:
Replaced valve, prosthesis, graft, or patch.
Aortic stenosis or regurgitant jets (e.g., in ruptured sinus of Valsalva).
Drugs:
Cyclosporine.
Mitomycin.
Ticlopidine.
Clopidogrel.
Tacrolimus.
Cocaine.
Systemic infection:
Bacterial endocarditis.
Brucellosis.
Cytomegalovirus.
Human immunodeficiency virus.
Ehrlichiosis.
Rocky Mountain spotted fever

RED EYE

ICD-9CM # 379.93
ICD-10CM # H57.8 Other specified disorders of eye and adnexa

Infectious conjunctivitis (bacterial, viral).
Allergic conjunctivitis.
Acute glaucoma.
Keratitis (bacterial, viral).
Iritis.
Trauma.

RED EYE, ACUTE[1b]

ICD-9CM # 379.93
ICD-10CM # H57.8

Obvious open globe.
Corneal abrasion.
Corneal ulcer.
Subconjunctival hemorrhage.
Hyphema.
Occult open globe.
Herpes simplex virus glaucoma.
Iritis, traumatic iritis.
Scleritis.
Conjunctivitis.
Blepharitis.
Ultraviolet keratitis.
Episcleritis.
Conjunctival foreign body.
Dry eye.
Contact lens overwear syndrome.

RED HOT JOINT

ICD-9CM # varies with specific disorder
ICD-10CM # varies with specific diagnosis

Trauma.
Gout.
Infection (septic joint).
Pseudogout (calcium pyrophosphate dehydrate crystal deposition).
Psoriatic arthropathy.
Reactive arthritis.
Palindromic rheumatism.

RED URINE

ICD-9CM # 788.69
ICD-10CM # R39.19 Other difficulties with micturition

Hematuria.
Porphyrins.
Hemoglobinuria.
Myoglobinuria.
Medications (phenazopyridine, aminosalicylic acid, deferoxamine, phenazopyridine, phenolphthalein, NSAIDs, rifampin, phenytoin, methyldopa, doxorubicin, phenacetin).
Foods (beets, berries, maize).
Urate crystalluria.

RENAL ALLOGRAFT DYSFUNCTION[14a]

ICD-9CM # 593.9
ICD-10CM # T86.1 Complications of renal allograft

IMMEDIATE/DELAYED GRAFT FUNCTION (1-3 DAYS)

Acute tubular necrosis.
Hyperacute humoral rejection.
Urinary leak or obstruction.
Renal artery or vein thrombosis.
Recurrence of disease (e.g., focal segmental glomerulosclerosis).

EARLY POSTTRANSPLANTATION PERIOD (FIRST MONTH)

Acute cellular rejection.
Acute humoral rejection.
Calcineurin inhibitor toxicity.
Urinary tract obstruction.
Volume depletion.
Recurrence of disease.
Late Acute dysfunction
Acute rejection.
Cyclosporine or tacrolimus toxicity.
Recurrence of primary disease.
Tubulointerstitial nephritis, drug-induced.
Renal artery stenosis.
Infection (bacterial urinary tract infection [UTI], cytomegalovirus, BK virus).
Hemodynamic (volume; use of angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker).
Chronic Dysfunction
Chronic rejection.
Cyclosporine or tacrolimus toxicity.
Recurrent renal disease.
De novo renal disease.
Urinary tract obstruction.
Bacterial UTI.
Hypertensive nephrosclerosis.

RENAL ARTERY OCCLUSION, CAUSES

ICD-9CM # 593.81
ICD-10CM # N28.0 Ischemia and infarction of kidney

Atrial fibrillation.
Angiography or stent placement.
Abdominal aortic surgery.
Trauma.
Renal artery aneurysm/dissection.
Vasculitis.
Thrombosis in patient with fibromuscular dysplasia.
Atherosclerosis.
Septic embolism.
Mural thrombus thromboembolism.
Atrial myxoma thromboembolism.
Mitral stenosis thromboembolism.
Prosthetic valve thromboembolism.
Renal cell carcinoma.

RENAL COLIC[1b]

ICD-9CM # 788.0
ICD-10CM # N23

Vascular:
Abdominal aortic aneurysm.
Aortic dissection.
Renal artery dissection.
Renal artery stenosis.
Renal vein thrombosis.
Renal infarct.
Mesenteric ischemia.
Retroperitoneal hemorrhage.
Gastrointestinal:
Incarcerated hernia.
Appendicitis.
Cholecystitis.
Biliary colic.
Pancreatitis.
Bowel obstruction.
Diverticulitis.
Gynecologic:
Ectopic pregnancy.
Ovarian torsion.
Tuboovarian abscess.
Pelvic inflammatory disease.
Endometriosis.
Genitourinary:
Testicular torsion.
Pyelonephritis.
Perinephric abscess.
Urinary tract tumor.
Renal papillary necrosis.
Upper urinary tract hemorrhage.
Musculoskeletal:
Lumbar strain.
Radiculopathy.
Disk herniation.
Vertebral compression fracture.
Dermatologic:
Herpes zoster.
Miscellaneous:
Factitious.

RENAL CYSTIC DISORDERS

ICD-9CM # varies with specific disorder
ICD-10CM # Q61.01 Congenital single renal cyst

Simple cysts.
Acquired cystic kidney disease.
Autosomal dominant polycystic kidney disease.
Autosomal recessive polycystic kidney disease.
Medullary cystic disease.
Medullary sponge kidney.

RENAL FAILURE, ACUTE, PIGMENT-INDUCED[2]

ICD-9CM # 586
ICD-10CM # N19 Unspecified kidney failure

CAUSES OF PIGMENT-INDUCED ACUTE RENAL FAILURE

Rhabdomyolysis and myoglobinuria.
Vigorous exercise.
Arterial embolization.
Status epilepticus.
Status asthmaticus.
Coma-induced and pressure-induced myonecrosis.
Heat stress.
Diabetic ketoacidosis.
Myopathy.
Alcoholism.
Hypokalemia.
Hypophosphatemia.
Hemoglobinuria.
Transfusion reactions.
Snake envenomation.
Malaria.
Mechanical destruction of RBCs by prosthetic valves.
G6PD deficiency.

G6PD, Glucose-6-phosphate dehydrogenase; *RBCs,* red blood cells.

RENAL FAILURE, CHRONIC[14a]

ICD-9CM # 585.9

CAUSES OF CHRONIC RENAL FAILURE

Diabetic glomerulosclerosis (systemic disease involving the kidney).
Hypertensive nephrosclerosis.
Glomerular disease:
- Glomerulonephritis.
- Amyloidosis, light chain disease (systemic disease involving the kidney).
- Systemic lupus erythematosus, Wegener granulomatosis (systemic disease involving the kidney).

Tubulointerstitial disease:
- Reflux nephropathy (chronic pyelonephritis).
- Analgesic nephropathy.
- Obstructive nephropathy (stones, benign prostatic hypertrophy).
- Myeloma kidney (systemic disease involving the kidney).

Vascular disease:
- Scleroderma (systemic disease involving the kidney).
- Vasculitis (systemic disease involving the kidney).
- Renovascular renal failure (ischemic nephropathy).
- Atheroembolic renal disease (systemic disease involving the kidney).

Cystic disease:
- Autosomal dominant polycystic kidney disease.
- Medullary cystic kidney disease.

RENAL FAILURE, INTRINSIC OR PARENCHYMAL CAUSES[36]

ICD-9CM #	584	Acute, use 4th digit
	5	With Acute Tubular Necrosis
	6	With Cortical Necrosis
	7	With Medullary Necrosis
	8	With Other Unspecified Pathologic Condition in Kidney
	9	Renal Failure Unspecified
	585	Renal Failure, Chronic
ICD-10CM #	N17.0	Acute kidney failure with tubular necrosis
	N17.1	Acute kidney failure with acute cortical necrosis
	N17.2	Acute kidney failure with medullary necrosis
	N17.8	Other acute kidney failure
	N17.9	Acute kidney failure, unspecified
	N18.9	Chronic kidney disease, unspecified

ABNORMALITIES OF THE VASCULATURE

Renal arteries: atherosclerosis, thromboembolism, arteritis.
Renal veins: thrombosis.
Microvasculature: vasculitis, thrombotic microangiopathy.

ABNORMALITIES OF GLOMERULI (ACUTE GLOMERULONEPHRITIS)

Antiglomerular membrane disease (Goodpasture's syndrome).
Immune complex glomerulonephritis: SLE, postinfectious, idiopathic, membranoproliferative.

ABNORMALITIES OF INTERSTITIUM (ACUTE INTERSTITIAL NEPHRITIS)

Drugs (e.g., antibiotics, NSAIDs, diuretics, anticonvulsants, allopurinol).
Infectious pyelonephritis.
Infiltrative: lymphoma, leukemia, sarcoidosis.

ABNORMALITIES OF TUBULES

Physical obstruction (uric acid, oxalate, light chains).
Acute tubular necrosis:
- Ischemic.
- Toxic (antibiotics, chemotherapy, immunosuppressives, radiocontrast dyes, heavy metals, myoglobin, hemolyzed RBCs).

RENAL FAILURE, POSTRENAL CAUSES[36]

ICD-9CM #	584	Acute, use 4th digit
	5	With Acute Tubular Necrosis
	6	With Cortical Necrosis
	7	With Medullary Necrosis
	8	With Other Unspecified Pathologic Condition in Kidney
	9	Renal Failure Unspecified
	585	Renal Failure, Chronic
ICD-10CM #	N17.0	Acute kidney failure with tubular necrosis
	N17.1	Acute kidney failure with acute cortical necrosis
	N17.2	Acute kidney failure with medullary necrosis
	N17.8	Other acute kidney failure
	N17.9	Acute kidney failure, unspecified
	N18.9	Chronic kidney disease, unspecified

URETER AND RENAL PELVIS

Intrinsic obstruction:
- Blood clots.
- Stones.
- Sloughed papillae: diabetes, sickle cell disease, analgesic nephropathy.
- Inflammatory: fungus ball.

Extrinsic obstruction:
- Malignancy.
- Retroperitoneal fibrosis.
- Iatrogenic: inadvertent ligation of ureters.

BLADDER

Prostatic hypertrophy or malignancy.
Neuropathic bladder.
Blood clots.
Bladder cancer.
Stones.

URETHRAL

Strictures.
Congenital valves.

RENAL FAILURE, PRERENAL CAUSES[36]

ICD-9CM #	584	Acute, use 4th digit
	5	With Acute Tubular Necrosis
	6	With Cortical Necrosis
	7	With Medullary Necrosis
	8	With Other Unspecified Pathologic Condition in Kidney

	9	Renal Failure Unspecified
	585	Renal Failure, Chronic
ICD-10CM #	N17.0	Acute kidney failure with tubular necrosis
	N17.1	Acute kidney failure with acute cortical necrosis
	N17.2	Acute kidney failure with medullary necrosis
	N17.8	Other acute kidney failure
	N17.9	Acute kidney failure, unspecified
	N18.9	Chronic kidney disease, unspecified

DECREASED CARDIAC OUTPUT

CHF.
Arrhythmias.
Pericardial constriction or tamponade.
Pulmonary embolism.

HYPOVOLEMIA

GI tract loss (vomiting, diarrhea, nasogastric suction).
Blood losses (trauma, GI tract surgery).
Renal losses (diuretics, mineralocorticoid deficiency, postobstructive diuresis).
Skin losses (burns).

VOLUME REDISTRIBUTION (DECREASE IN EFFECTIVE BLOOD VOLUME)

Hypoalbuminemic states (cirrhosis, nephrosis).
Sequestration of fluid in "third" space (ischemic bowel, peritonitis, pancreatitis).
Peripheral vasodilation (sepsis, vasodilators, anaphylaxis).

ALTERED RENAL VASCULAR RESISTANCE

Increase in afferent vascular resistance (NSAIDs, liver disease, sepsis, hypercalcemia, cyclosporine).
Decrease in efferent arteriolar tone (ACE inhibitors).

RENAL INFARCTION[12b]

ICD-9CM #	593.81	Renal Infarction
ICD-10CM #	N28.0	Ischemia and infarction of kidney

CAUSES OF RENAL INFARCTION

Thrombosis: Spontaneous
Atherosclerotic disease of aorta and renal artery.
Fibromuscular dysplasia of renal artery.
Aneurysms of aorta or renal artery.
Dissection of aorta or renal artery.
  Marfan's syndrome.
  Ehlers-Danlos syndrome.
Vasculitis involving renal artery.
  Polyarteritis nodosa.
  Takayasu's arteritis.
  Kawasaki disease.
  Thromboangiitis obliterans.
  Other necrotizing vasculitides.
Inflammatory disease of the aorta or renal artery.
  Syphilis.
  Tuberculosis.
  Mycoses.
Hypercoagulable states.
  Nephrotic syndrome.
  Antiphospholipid syndrome.
  Antithrombin III deficiency.
  Homocystinuria.
Thrombotic microangiopathies.
  Hemolytic-uremic syndrome.
  Thrombotic thrombocytopenic purpura.
  Antiphospholipid syndrome.
  Malignant hypertension.
  Scleroderma.
  Sickle cell nephropathy.
  Polycythemia vera.
  Postpartum hemolytic-uremic syndrome.
  Hyperacute vascular allograft rejection.
Thrombosis: Induced
Traumatic.
Following endovascular intervention.
Post renal transplantation.
Embolism
Cardiac source.
  Atrial fibrillation or other arrhythmias.
  Native and prosthetic valvular heart disease.
  Infective endocarditis.
  Marantic endocarditis.
Myocardial infarction with mural thrombi.
  Left atrial myxoma or other tumor.
Noncardiac sources.
  Atheromatous embolic disease.
  Paradoxical emboli.
  Fat emboli.
  Tumor emboli.
Therapeutic renal embolization.
Segmental renal infarction of childhood.
Cisplatinum and gemcitabine.
Sickle cell disease or sickle cell trait.

RENAL PARENCHYMAL DISEASE, CHRONIC[16a]

ICD-9CM #	593.9	
ICD-10CM #	N28.9	Disorder of kidney and ureter, unspecified

DIFFERENTIAL DIAGNOSIS OF CHRONIC RENAL PARENCHYMAL DISEASE

No Papillary/Caliceal Abnormality
Diffuse parenchymal loss
Bilateral:
  Chronic glomerulonephritis.
  Diffuse small-vessel disease.
  Hereditary nephropathies.
Unilateral:
  Renal artery stenosis.
  Postirradiation.
  Rare:
  - Hypoplastic kidney.
  - Postobstructive atrophy.

FOCAL PARENCHYMAL LOSS

Infarct.
Previous trauma.
Papillary/Caliceal Abnormality
Diffuse parenchymal loss
Obstructive nephropathy.
Generalized reflux nephropathy.
No Parenchymal Loss
Papillary necrosis.
TB.
Medullary sponge kidney.
Megacalices.
Pelvicaliceal cyst.
Focal Parenchymal Loss
Focal reflux nephropathy (chronic atrophic pyelonephritis).
TB.
Calculus disease.

RENAL VEIN THROMBOSIS, CAUSES

ICD-9CM #	453.3	
ICD-10CM #	I82.3	Embolism and thrombosis of renal vein

Nephrotic syndrome.
Renal cell carcinoma.
Aortic aneurysm causing compression.
Lymphadenopathy.
Retroperitoneal fibrosis.
Estrogen therapy.
Pregnancy.
Renal cell carcinoma with vein invasion.
Severe dehydration.

RESPIRATORY DISTRESS IN THE NEWBORN, CAUSES[12d]

ICD-9CM #	518.81	Respiratory failure
ICD-10CM #	J96.00	Acute respiratory failure

RESPIRATORY DISTRESS IN THE NEWBORN

Noncardiopulmonary
Hypothermia or hyperthermia.
Hypoglycemia.
Metabolic acidosis.
Drug intoxications; withdrawal.
Polycythemia.
Central nervous system insult.
Asphyxia.
Hemorrhage.
Neuromuscular disease.
Werdnig-Hoffman disease.
Myopathies.
Phrenic nerve injury.
Skeletal abnormalities.
Asphyxiating thoracic dystrophy.
Cardiovascular
Left-sided outflow obstruction.
Hypoplastic left heart.
Aortic stenosis.
Coarctation of the aorta.
Cyanotic lesions.
Transposition of the great vessels.
Total anomalous pulmonary venous return
Tricuspid atresia.
Right-sided outflow obstruction.
Pulmonary
Upper airway obstruction.
Choanal atresia.
Vocal cord paralysis.
Meconium aspiration.

Clear fluid aspiration.
Transient tachypnea.
Pneumonia.
Pulmonary hypoplasia.
Primary.
Secondary.
Hyaline membrane disease.
Pneumothorax.
Pleural effusions.
Mass lesions.
Lobar emphysema.
Cystic adenomatoid malformation.

RESPIRATORY FAILURE, HYPOVENTILATORY[28]

ICD-9CM #	518.81	Respiratory Failure
ICD-10CM #	J96.00	Acute respiratory failure, unspecified whether with hypoxia or hypercapnia
	J96.90	Respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia

ABNORMAL RESPIRATORY CAPACITY (NORMAL RESPIRATORY WORKLOADS)

Acute depression of central nervous system:
- Various causes.

Chronic central hypoventilation syndromes:
- Obesity-hypoventilation syndrome.
- Sleep apnea syndrome.
- Hypothyroidism.
- Shy-Drager syndrome (multisystem atrophy syndrome).

Acute toxic paralysis syndromes:
- Botulism.
- Tetanus.
- Toxic ingestion or bites.
- Organophosphate poisoning.

Neuromuscular disorders (acute and chronic):
- Myasthenia gravis.
- Guillain-Barré syndrome.
- Drugs.
- Amyotrophic lateral sclerosis.
- Muscular dystrophies.
- Polymyositis.
- Spinal cord injury.
- Traumatic phrenic nerve paralysis.

ABNORMAL PULMONARY WORKLOADS

Chronic obstructive pulmonary disease:
- Chronic bronchitis.
- Asthmatic bronchitis.
- Emphysema.

Asthma and acute bronchial hyperreactivity syndromes.
Upper airway obstruction.
Interstitial lung diseases.

ABNORMAL EXTRAPULMONARY WORKLOADS

Chronic thoracic cage disorders:
- Severe kyphoscoliosis.
- After thoracoplasty.
- After thoracic cage injury.

Acute thoracic cage trauma and burns.
Pneumothorax.
Pleural fibrosis and effusions.
Abdominal processes.

RETINOPATHY, HYPERTENSIVE

ICD-9CM #	362.11	
ICD-10CM #	H35.039	Hypertensive retinopathy, unspecified eye

Retinal venous obstruction.
Diabetic retinopathy.
Ocular ischemic syndrome.
Hyperviscosity.
Tortuosity of retinal artery.

RHINITIS

ICD-9CM #	472.0	
ICD-10CM #	J31.0	Chronic rhinitis

Allergic rhinitis.
Infectious rhinitis.
Vasomotor rhinitis.
Exercise-induced rhinitis.
Emotional rhinitis.
Rhinitis medicamentosa.
Hormone-mediated rhinitis (menses, pregnancy, oral contraceptives, hypothyroidism).
GERD.
Chemical- or irritant-induced rhinitis.
Rhinitis mimics:
- Deviated septum.
- Enlarged adenoids.
- Nasal polyps/tumors.
- Foreign bodies.
- CSF rhinorrhea.
- Sarcoidosis.
- Midline granuloma.
- Granulomatosis with polyangiitis (Wegener's granulomatosis).
- SLE.
- Sjögren's syndrome.

RHINOSINUSITIS, DIFFERENTIAL DIAGNOSIS[26a]

ICD-9CM #	varies with specific diagnosis
ICD-10CM #	varies with specific diagnosis

DIFFERENTIAL DIAGNOSIS OF RHINOSINUSITIS

Allergic Rhinitis
Seasonal.
Perennial.
Combined seasonal and perennial.
Allergic fungal rhinosinusitis.

Nonallergic Rhinitis
Nonallergic, noninflammatory idiopathic rhinopathy (vasomotor rhinitis).
Nonallergic rhinitis with eosinophilia syndrome (NARES).
Cold dry air–induced rhinitis.
Gustatory rhinitis.

Infectious Rhinosinusitis
Bacterial.
Viral.
Fungal.
Granulomatous.

Drug-Induced Rhinitis
Oral contraceptives.
Various antihypertensives and ocular β-blockers.
Topical decongestants (rhinitis medicamentosa).
Phosphodiesterase-5 antagonists.

Mechanical Causes Of Rhinosinusitis
Septal deviation.
Nasal foreign body.
Choanal atresia or stenosis.
Adenoid hypertrophy.
Encephalocele.
Glioma.
Dermoid.

Innate and Acquired Immunity Disorders
Congenital or acquired immunodeficiencies.
Cystic fibrosis.
Immotile cilia syndrome.

Systemic Inflammatory Disorders
Sarcoidosis.
Wegener's granulomatosis.
Vasculitis.

Neoplastic Causes
Benign:
Polyps.
Nasopharyngeal angiofibroma.
Inverting papilloma.
Malignant:
Adenocarcinoma.
Squamous cell carcinoma.
Aesthesioneuroblastoma.
Lymphoma.
Rhabdomyosarcoma.

RIB DEFECTS ON X-RAY[16a]

ICD-9CM #	varies with specific diagnosis
ICD-10CM #	varies with specific diagnosis

CAUSES OF SUPERIOR MARGINAL RIB DEFECTS

Normal
Isolated defects.
Projectional artifacts (due to lordosis).

Neurologic
Paralytic poliomyelitis.
Quadriparesis.

Collagen Vascular Disease
Rheumatoid arthritis.
SLE.
Systemic sclerosis.

Local Pressure
Chest drainage tube.
Osteochondroma.
Neural tumor.
Coarctation of aorta.

Hyperparathyroidism Miscellaneous
Osteogenesis imperfecta.
Marfan's syndrome.

RIB NOTCHING ON X-RAY[16a]

ICD-9CM # varies with specific diagnosis
ICD-10CM # varies with specific diagnosis

CAUSES OF INFERIOR RIB NOTCHING

ARTERIAL

Aortic Obstruction

Aortic coarctation.
Aortic thrombosis.
Aortitis.

Subclavian Artery Obstruction

Blalock-Taussig operation.
Arteritis.
Atherosclerotic occlusion.

Pulmonary Oligemia

Pulmonary atresia.
Tetralogy of Fallot.
Multiple pulmonary arterial stenoses.

Venous

Chronic Superior Vena Caval Obstruction

Arteriovenous
Arteriovenous malformation
Pulmonary.
Chest wall.
Neural

Neurofibromas

RIGHT AXIS DEVIATION[22]

ICD-9CM # varies with specific diagnosis
ICD-10CM # varies with specific diagnosis

Normal variation.
Right ventricular hypertrophy.
Left posterior fascicular block.
Lateral myocardial infarction.
Pulmonary embolism.
Dextrocardia.
Mechanical shifts or emphysema causing a vertical heart.

SALIVARY GLAND ENLARGEMENT

ICD-9CM # 527.1
ICD-10CM # K11.1 Hypertrophy of salivary gland

Neoplasm.
Sialolithiasis.
Infection (mumps, bacterial infection, HIV, TB).
Sarcoidosis.
Idiopathic.
Acromegaly.
Anorexia/bulimia.
Chronic pancreatitis.
Medications (e.g., phenylbutazone).
Cirrhosis.
DM.

SALIVARY GLAND SECRETION, DECREASED

ICD-9CM # 527.7
ICD-10CM # K11.7 Disturbances of salivary secretion
R68.2 Dry mouth, unspecified

Medications (antihistamines, antidepressants, neuroleptics, antihypertensives).
Dehydration.
Anxiety.
Sjögren's syndrome.
Sarcoidosis.
Mumps.
Amyloidosis.
CNS disorders.
Head and neck radiation.

SCLERODERMA-LIKE SYNDROMES[1a]

ICD-9CM # varies with specific diagnosis
ICD-10CM # varies with specific diagnosis

OTHER DISEASES

Morphea.
Eosinophilic fasciitis.
Scleredema (of Buschke).
Scleromyxedema.
Graft-versus-host disease.
Nephrogenic-fibrosing dermopathy.

ENVIRONMENTAL AGENTS AND DRUGS

Bleomycin.
L-Tryptophan.
Organic solvents.
Pentazocine.
Toxic oil syndrome.
Vinyl chloride disease.
Gadolinium.

SCROTAL MASSES, BOYS AND ADOLESCENTS[22a]

ICD-9CM # varies with specific diagnosis
ICD-10CM # R22.9 Localized swelling, mass and lump, unspecified

PAINFUL

Testicular torsion.
Torsion of appendix testis.
Epididymitis.
Trauma: ruptured testis, hematocele.
Inguinal hernia (incarcerated).
Mumps orchitis.

PAINLESS

Hydrocele.
Inguinal hernia.*
Varicocele.*
Spermatocele.*
Testicular tumor.*
Henoch-Schönlein purpura.*
Idiopathic scrotal edema.

*May be associated with discomfort.

SCROTAL PAIN[28]

ICD-9CM #	878.2	Scrotal Injury, Traumatic
	608.9	Scrotal Disorder NOS
	608.4	Scrotal Cellulitis
	608.83	Scrotal Hemorrhage, Nontraumatic
	608.4	Scrotal Nodule, Inflammatory
ICD-10CM #	S31.30XA	Unspecified open wound of scrotum and testes, initial encounter
	N50.9	Disorder of male genital organs, unspecified
	R10.2	Pelvic and perineal pain
	N49.9	Inflammatory disorder of unspecified male genital organ
	N50.1	Vascular disorders of male genital organs
	N49.9	Inflammatory disorder of unspecified male genital organ

Torsion:
  Appendages.
  Spermatic cord.
Infection:
  Orchitis.
  Abscess.
  Epididymitis.
Neoplasia:
  Benign.
  Malignant.
Incarcerated hernia.
Trauma.
Hydrocele.
Spermatocele.
Varicocele.

SCROTAL SWELLING

ICD-9CM # 608.86
ICD-10CM # N50.8 Other specified disorders of male genital organs

Hydrocele.
Varicocele.
Neoplasm.
Acute epididymitis.
Orchitis.
Trauma.
Hernia.
Torsion of spermatic cord.
Torsion of epididymis.
Torsion of testis.
Insect bite.
Folliculitis.
Sebaceous cyst.
Thrombosis of spermatic vein.
Other: lymphedema, dermatitis, fat necrosis, Henoch-Schönlein purpura, idiopathic scrotal edema.

SEIZURE

ICD-9CM # 780.39
ICD-10CM # R56.9 Unspecified convulsions

Syncope.
Alcohol abuse/withdrawal.
TIA.
Hemiparetic migraine.
Psychiatric disorders.
Carotid sinus hypersensitivity.
Hyperventilation, prolonged breath holding.
Hypoglycemia.
Narcolepsy.
Movement disorders (tics, hemiballismus).
Hyponatremia.
Brain tumor (primary or metastatic).
Tetanus.
Strychnine, phencyclidine poisoning.

SEIZURE, PEDIATRIC[2]

ICD-9CM #	780.39	Infantile Seizures
	779.0	Seizures, Newborn
ICD-10CM #	R56.9	Unspecified convulsions
	P90	Convulsions of newborn

FIRST MONTH OF LIFE

First Day
Hypoxia.
Drugs.
Trauma.
Infection.
Hyperglycemia.
Hypoglycemia.
Pyridoxine deficiency.
Day 2-3
Infection.
Drug withdrawal.
Hypoglycemia.
Hypocalcemia.
Developmental malformation.
Intracranial hemorrhage.
Inborn error of metabolism.
Hyponatremia or hypernatremia.
Day >4
Infection.
Hypocalcemia.
Hyperphosphatemia.
Hyponatremia.
Developmental malformation.
Drug withdrawal.
Inborn error of metabolism.

1 TO 6 MO

As above.

6 MO TO 3 YR

Febrile seizures.
Birth injury.
Infection.
Toxin.
Trauma.
Metabolic disorder.
Cerebral degenerative disease.

>3 YR

Idiopathic.
Infection.
Trauma.
Cerebral degenerative disease.

SEIZURE MIMICS[1a]

ICD-9CM # varies with specific diagnosis
ICD-10CM # varies with specific diagnosis

NON-EPILEPTIC EPISODIC DISORDERS THAT MAY RESEMBLE SEIZURES

Movement disorders: myoclonus, paroxysmal choreoathetosis, episodic ataxias, hyperexplexia (startle disease).
Migraine: confusional, vertebrobasilar, visual auras.
Syncope.
Behavioral and psychiatric: psychogenic nonepileptic attacks (pseudoseizures), hyperventilation syndrome, panic or anxiety disorder, dissociative states.
Cataplexy (usually associated with narcolepsy).
Transient ischemic attack.
Alcoholic blackouts.
Hypoglycemia.

SEXUAL DYSFUNCTION, FEMALE[1a]

ICD-9CM #	302.7	
ICD-10CM #	R37	Sexual dysfunction, unspecified

FACTORS THAT MAY INFLUENCE SEXUAL FUNCTIONING IN WOMEN

Biological
Medications (e.g., antidepressants, antihypertensives).
Vaginal atrophy, pain with intercourse.
Low testosterone levels (e.g., bilateral oophorectomy).
Illness (e.g., diabetes, hypothyroidism, cerebrovascular accident).
Sleep disturbances, fatigue.
Disability or pain from illness (e.g., arthritis).
Incontinence.
Psychological
Depression.
Body image.
Interpersonal
Marital issues.
Poor communication.
Partner's sexual problems (e.g., erectile dysfunction).
Partner's health problems (e.g., myocardial infarction).
Sociocultural
Ageism ("too old" to want sex).
Multiple other obligations and commitments.
Lack of partner.

SEXUALLY TRANSMITTED DISEASES, ANORECTAL REGION[26]

ICD-9CM #	569.49	Infection and Region
ICD-10CM #	K62.89	Other specified diseases of anus and rectum

ULCERATIVE

Lymphogranuloma venereum.
Herpes simplex virus.
Early (primary) syphilis.
Chancroid *(Haemophilus ducreyi).*
Cytomegalovirus.
Idiopathic (usually HIV positive).

NONULCERATIVE

Condyloma acuminatum.
Gonorrhea.
Chlamydia *(Chlamydia trachomatis).*
Syphilis.

SEXUAL PRECOCITY[41]

ICD-9CM #	259.1	
ICD-10CM #	E30.1	Precocious puberty
	E30.8	Other disorders of puberty

TRUE PRECOCIOUS PUBERTY

Premature reactivation of LHRH pulse generator.

INCOMPLETE SEXUAL PRECOCITY

(Pituitary gonadotropin independent).
Males
Chorionic gonadotropin-secreting tumor.
Leydig cell tumor.
Familial testotoxicosis.
Virilizing congenital adrenal hyperplasia.
Virilizing adrenal tumor.
Premature adrenarche.
Females
Granulosa cell tumor (follicular cysts may be manifested similarly).
Follicular cyst.
Feminizing adrenal tumor.
Premature thelarche.
Premature adrenarche.
Late-onset virilizing congenital adrenal hyperplasia.
In Both Sexes
McCune-Albright syndrome.
Primary hypothyroidism.

SHOULDER PAIN

ICD-9CM #	952.2	Shoulder Injury
	718.81	Shoulder Instability
	726.19	Shoulder Ligament or Muscle Instability
	840.9	Shoulder Strain, Site Unspecified
ICD-10CM #	M24.819	Other specific joint derangements of unspecified shoulder, not elsewhere classified
	M75.80	Other shoulder lesions, unspecified shoulder
	S43.409A	Unspecified sprain of unspecified shoulder joint, initial encounter

	S46.919A	Strain of unspecified muscle, fascia and tendon at shoulder and upper arm level, unspecified arm, initial encounter

WITH LOCAL FINDINGS IN SHOULDER

Trauma: contusion, fracture, muscle strain, trauma to spinal cord.
Arthrosis, arthritis, RA, ankylosing spondylitis.
Bursitis, synovitis, tendinitis, tenosynovitis.
Aseptic (avascular) necrosis.
Local infection: septic arthritis, osteomyelitis, abscess, herpes zoster, TB.

WITHOUT LOCAL FINDINGS IN SHOULDER

Cardiovascular disorders: ischemic heart disease, pericarditis, aortic aneurysm.
Subdiaphragmatic abscess, liver abscess.
Cholelithiasis, cholecystitis.
Pulmonary lesions: apical bronchial carcinoma, pleurisy, pneumothorax, pneumonia.
GI lesions: PUD, gastric neoplasm, peptic esophagitis.
Pancreatic lesions: carcinoma, calculi, pancreatitis.
CNS abnormalities: neoplasm, vascular abnormalities.
Multiple sclerosis.
Syringomyelia.
Polymyositis/dermatomyositis.
Psychogenic.
Polymyalgia rheumatica.
Ectopic pregnancy.

SHOULDER PAIN BY LOCATION

ICD-9CM #	952.2	Shoulder Injury
	726.19	Shoulder Ligament or Muscle Instability
	840.8	Shoulder Separation
ICD-10CM #	M75.80	Other shoulder lesions, unspecified shoulder
	S43.499A	Other sprain of unspecified shoulder joint, initial encounter
	S46.019A	Strain of muscle(s) and tendon(s) of the rotator cuff of unspecified shoulder, initial encounter
	S46.819A	Strain of other muscles, fascia and tendons at shoulder and upper arm level, unspecified arm, initial encounter

TOP OF SHOULDER (C4)

Cervical source.
Acromioclavicular.
Sternoclavicular.
Diaphragmatic.

SUPEROLATERAL (C5)

Rotator cuff tendinitis.
Impingement.
Adhesive capsulitis.
Glenohumeral arthritis.

ANTERIOR

Bicipital tendinitis and rupture.
Glenoid labral tear.
Adhesive capsulitis.
Glenohumeral arthritis.
Osteonecrosis.

AXILLARY

Neoplasm (Pancoast's, mediastinal).
Herpes zoster.

SHOULDER PAIN, IN DIFFERENT AGE GROUPS[8]

ICD-9CM #	719.41	
ICD-10CM #	M25.519	Pain in unspecified shoulder

COMMON CAUSES OF SHOULDER PAIN IN DIFFERENT AGE GROUPS

Childhood (2-10 yr)
Intraarticular:
Instability.
Periarticular:
Osteochondromas.
Adolescence (10-18 yr)
Intraarticular:
Instability.
Early Adulthood (18-30 yr)
Intraarticular:
Instability.
Acromioclavicular joint sprain.
Periarticular:
Calcific tendonitis.
Impingement.
Referred:
Cervical.
Adulthood (30-60 yr)
Intraarticular:
Osteochondritis.
Osteoarthritis.
Frozen shoulder.
Inflammatory arthritis.
Periarticular:
Calcific tendonitis.
Impingement.
Rotator cuff tear.
Bicipital tendonitis.
Referred:
Cervical.
Old Age (>60 yr)
INTRAARTICULAR.
Osteochondritis.
Osteoarthritis.
Frozen shoulder.
Inflammatory arthritis.
PERIARTICULAR.
Impingement.
Rotator cuff tear.
REFERRED.
Cervical.

SINUS NODE DYSFUNCTION[14a]

ICD-9CM #	427.81
ICD-10CM #	varies with specific diagnosis

CAUSES OF SINUS NODE DYSFUNCTION

Intrinsic
Hypothyroidism.
Fibrocalcific degeneration.
Increased vagal tone, especially in sleep apnea.
Congenital mutations.
Scleroderma.
Amyloidosis.
Chagas disease.
Extrinsic
Trauma, including cardiac surgery.
Drugs:
- Calcium-channel blockers.
- β-Blockers.
- Digoxin.
- Antiarrhythmic medications (amiodarone, dronedarone, sotalol, flecainide, propafenone).
- Lithium.

SKIN INDURATION, CHRONIC[18b]

ICD-9CM #	varies with specific diagnosis
ICD-10CM #	varies with specific diagnosis

CONDITIONS ASSOCIATED WITH CHRONIC SKIN INDURATION

Systemic sclerosis.
Localized scleroderma.
Scleroderma variants.
Scleredema.
- Scleredema adultorum of Buschke.
- Scleredema diabeticorum.
- Scleredema neonatorum.

Scleromyxedema.
Nephrogenic fibrosing dermopathy.
Eosinophilic syndromes.
- Eosinophilic fasciitis (diffuse fasciitis with eosinophilia, Schulman disease).
- Eosinophilia-myalgia syndrome.
- Toxic oil syndrome.

Chronic graft-versus-host disease.
Pseudoscleroderma (local injection of vitamin K, bleomycin, pentazocine).
Metabolic diseases.
- Porphyria cutanea tarda.
- Phenylketonuria.
- Werner syndrome.
- Acromegaly.

Pachydermoperiostitis.
Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy (POEMS).
Stiff skin syndrome.

Reflex sympathetic dystrophy.
Hemiplegia.

SMALL BOWEL MASSES[38]

ICD-9CM # varies with specific diagnosis
ICD-10CM # varies with specific diagnosis

Cyst:
  Mesenteric cyst.
Tumor:
  Benign.
  Malignant.
Intussusception.
Inflammation:
  Crohn's disease.

SMALL BOWEL OBSTRUCTION[26]

ICD-9CM #	751.1	Small Intestine Obstruction, Congenital
	560.81	Small Intestine Obstruction Due to Adhesion
ICD-10CM #	K56.5	Intestinal adhesions [bands] with obstruction (postprocedural) (postinfection)
	Q41.9	Congenital absence, atresia and stenosis of small intestine, part unspecified

INTRINSIC

Congenital (atresia, stenosis).
Inflammatory (Crohn's, radiation enteritis).
Neoplasms (metastatic or primary).
Intussusception.
Traumatic (hematoma).

EXTRINSIC

Hernias (internal and external).
Adhesions.
Volvulus.
Compressing masses (tumors, abscesses, hematomas).

INTRALUMINAL

Foreign body.
Gallstones.
Bezoars.
Barium.
Ascaris infestation.

SMALL INTESTINE ULCERATION

ICD-9CM # 569.82
ICD-10CM # K63.3 Ulcer of intestine

Inflammatory bowel disease.
Celiac disease.
Vasculitis, SLE, Behçet's syndrome.
Uremia.
Infections *(Campylobacter,* TB, *Yersinia,* parasites, typhoid, cytomegalovirus [CMV], *Clostridium).*
Mesenteric insufficiency.
Neoplasms.
Radiation.
Drugs (salicylates, potassium, indomethacin, antimetabolites).
Meckel diverticulum.
Zollinger-Ellison syndrome.
Lymphocytic enterocolitis.
Stomal ulceration.

SMELL DISTURBANCE

ICD-9CM # varies with specific disorder
ICD-10CM # R43.8 Other disturbances of smell and taste

Upper respiratory tract infection.
Nasal or paranasal sinus disease.
Exposure to noxious vapors.
Head trauma.
Idiopathic.
Dental caries, periodontal disease.
Medications.

SORE THROAT[2]

ICD-9CM # 484.1
ICD-10CM # J02 Acute pharyngitis

DIFFERENTIAL DIAGNOSIS FOR SORE THROAT

Infectious Causes

Aerobes

Common:
  Streptococcus pyogenes (GABHS).
  GABHS.
  Peptostreptococcus spp.
  Non–group A streptococcus.
  Neisseria gonorrhoeae.
  Neisseria meningitides.
  Mycoplasma pneumoniae.
  Arcanobacterium hemolyticum.
  Chlamydia trachomatis.
  Staphylococcus aureus.
Uncommon:
  Haemophilus influenzae.
  Haemophilus parainfluenzae.
  Coccidioides spp.
  Corynebacterium diphtheriae.
  Streptococcus pneumoniae.
  Yersinia enterocolitica.
  Treponema pallidum.
  Francisella tularensis.
  Legionella pneumophila.
  Mycobacterium spp.

Anaerobes

Bacteroides spp.
Peptococcus spp.
Clostridium spp.
Fusobacterium spp.
Prevotella spp.

Other

Candida spp.

Viral

Rhinovirus.
Adenovirus.
Coronavirus.
Herpes simplex 1, 2.
Influenza A, B.
Parainfluenza.
Cytomegalovirus.
Epstein-Barr.
Varicella-zoster.
Hepatitis virus.

Noninfectious Causes

Systemic

Kawasaki disease.
Stevens-Johnson syndrome.
Cyclic neutropenia.
Thyroiditis.
Connective tissue disease.

Trauma, miscellaneous

Penetrating injury.
Angioneurotic edema.
Retained foreign body.
Anomalous aortic arch.
Laryngeal fracture.
Calcific retropharyngeal tendinitis.
Retropharyngeal hematoma.
Caustic exposure.

Tumor

Tongue.
Larynx.
Thyroid.
Leukemia.

SPASTIC PARAPLEGIAS

ICD-9CM #	344.1	
ICD-10CM #	G82.20	Paraplegia, unspecified

Cervical spondylosis.
Friedreich's ataxia.
Multiple sclerosis.
Spinal cord tumor.
HIV.
Tertiary syphilis.
Vitamin B_{12} deficiency.
Spinocerebellar ataxias.
Syringomyelia.
Spinal cord AV malformations.
Adrenoleukodystrophy.

SPINAL CORD COMPRESSION, EPIDURAL

ICD-9CM # varies with specific disorder
ICD-10CM # varies with specific diagnosis

Osteoarthritis.
Meningioma.
Spinal epidural abscess.
Spinal epidural hematoma.
Spinal epidural vascular malformations.
RA.
Metastatic cancer (vertebral, intramedullary, leptomeninges).
Radiation myelopathy.
Neurofibroma.
Sarcoidosis.
Paraneoplastic myelopathy.
Histiocytosis.

SPINAL CORD DYSFUNCTION

ICD-9CM #	336.9	Spinal Cord Compression
	336.9	Spinal Cord Disease NOS
	742.9	Spinal Cord Disease, Congenital
	281.1	Spinal Cord Degeneration, B_{12} Deficiency Anemia
	336.8	Spinal Cord Atrophy, Acute
	336.10	Spinal Cord Atrophy, Adult
ICD-10CM #	G95.9	Disease of spinal cord, unspecified
	G95.9	Disease of spinal cord, unspecified
	Q07.9	Congenital malformation of nervous system, unspecified
	D51.1	Vitamin B_{12} deficiency anemia due to selective vitamin B_{12} malabsorption with proteinuria
	D51.3	Other dietary vitamin B_{12} deficiency anemia
	D51.8	Other vitamin B_{12} deficiency anemias
	G95.89	Other specified diseases of spinal cord
	G95.19	Other vascular myelopathies

Trauma.
Multiple sclerosis.
Transverse myelitis.
Neoplasm (primary, metastatic).
Syringomyelia.
Spinal epidural abscess.
HIV myelopathy.
Diskitis.
Spinal epidural hematoma.
Spinal cord infarction.
Spinal AV malformation.
Subarachnoid hemorrhage.

SPINAL CORD DYSFUNCTION, NONTRAUMATIC[2]

ICD-9CM #	742.9	
ICD-10CM #	Q07.9	Congenital malformation of nervous system, unspecified

NONTRAUMATIC ETIOLOGIES OF SPINAL CORD DYSFUNCTION

Processes Affecting the Spinal Cord or Blood Supply Directly

Multiple sclerosis.
Transverse myelitis.
Spinal arteriovenous malformation/subarachnoid hemorrhage.
Syringomyelia.
HIV myelopathy.
Other myelopathies.
Spinal cord infarction.

Compressive Lesions Affecting the Spinal Cord

Spinal epidural abscess.
Spinal epidural hematoma.
Diskitis.
Neoplasm.
Metastatic.
Primary CNS.

HIV, Human immunodeficiency virus; *CNS,* central nervous system.

SPINAL CORD ISCHEMIC SYNDROMES

ICD-9CM #	varies with specific disorder
ICD-10CM #	varies with specific diagnosis

Systemic hypotension.
Venous or arterial occlusion.
Arterial dissection.
Thromboembolism.
Endovascular procedures.
Vasculitis.
Fibrocartilaginous embolism.
Regional hemodynamic compromise.

SPINAL TUMORS[14]

ICD-9CM #	299.7
ICD-10CM #	varies with specific diagnosis

EXTRADURAL

Metastases.
Primary bone tumors arising in spine.

INTRADURAL EXTRAMEDULLARY

Meningiomas.
Neurofibromas.
Schwannomas.
Lipomas.
Arachnoid cysts.
Epidermoid cysts.
Metastasis.

INTRAMEDULLARY

Ependymoma.
Glioma.
Hemangioblastoma.
Lipoma.
Metastases.

SPLENIC CYSTS, CLASSIFICATION[5a]

ICD-9CM #	289.59	Splenic Cysts
ICD-10CM #	D73.4	Cyst of spleen

Primary (true).
Parasitic.
Nonparasitic.
Congenital.
Epidermoid.
Dermoid.
Mesothelial (serous).
Transitional.
Neoplastic.
Secondary (false): pseudocysts.
Traumatic.
Degenerative.
Inflammatory.
Hemorrhagic.

SPLENIC TUMORS, CLASSIFICATION[5a]

ICD-9CM #	159.1	Splenic Tumors
ICD-10CM #	C26.1	Malignant neoplasm of spleen

Malignant.
Lymphoproliferative disease.
Non-Hodgkin lymphoma.
Hodgkin disease.
Hairy cell leukemia.
Chronic lymphocytic leukemia.
Myeloproliferative disease.
Chronic myelogenous leukemia.
Myelofibrosis.
Primary tumors.
Angiosarcoma.
Metastatic tumors.
Benign.
Hemangiomas.
Hamartomas.
Lymphangiomas.
Sclerosing angiomatoid nodular transformation (SANT).

SPLENOMEGALY

ICD-9CM #	789.2	Splenomegaly Unspecified
	289.51	Chronic Congestive
	759.0	Congenital
	789.2	Unknown Origin
ICD-10CM #	R16.1	Splenomegaly, not elsewhere classified
	D73.2	Chronic congestive splenomegaly
	R16.1	Splenomegaly, not elsewhere classified

Hepatic cirrhosis.
Neoplastic involvement: CML, CLL, lymphoma, multiple myeloma.
Bacterial infections: TB, infectious endocarditis, typhoid fever, splenic abscess.
Viral infections: infectious mononucleosis, viral hepatitis, HIV.
Gaucher's disease and other lipid storage diseases.
Sarcoidosis.
Parasitic infections (malaria, kala-azar, histoplasmosis).
Hereditary and acquired hemolytic anemias.
Idiopathic thrombocytopenic purpura (ITP).
Collagen vascular disorders: SLE, RA (Felty's syndrome), polyarteritis nodosa.
Serum sickness, drug hypersensitivity reaction.
Splenic cysts and benign tumors: hemangioma, lymphangioma.
Thrombosis of splenic or portal vein.
Polycythemia vera, myeloid metaplasia.

SPLENOMEGALY AND HEPATOMEGALY[38]

ICD-9CM #	789.2	Splenomegaly
	789.1	Hepatomegaly
ICD-10CM #	R16.1	Splenomegaly, not elsewhere classified
	R16.0	Hepatomegaly, not elsewhere classified

CAUSES OF SPLENOMEGALY AND HEPATOSPLENOMEGALY

Massive Splenomegaly

Hematologic disease (e.g., chronic myeloid leukemia, myelofibrosis).

Moderate Splenomegaly

The above causes.
Portal hypertension.
Hematologic disease (e.g., lymphoma, leukemia, thalassemia).
Storage disease (e.g., Gaucher's disease).

Small Splenomegaly

The above causes.
Infective (hepatitis, leptospirosis, malaria, bacterial endocarditis).
Hematologic disease (e.g., hemolytic anemias, essential thrombocythemia, polycythemia rubra vera).
Connective tissue diseases or vasculitis (e.g., rheumatoid arthritis, systemic lupus erythematosus, polyarteritis nodosa).
Solitary cyst, polycystic syndrome, hydatid cyst.
Infiltration (amyloid, sarcoid).

Hepatosplenomegaly

Chronic liver disease with portal hypertension.
Hematologic disease (e.g., myeloproliferative disease, lymphoma).
Infection (e.g., amyloid, sarcoid).
Connective tissue disease (e.g., systemic lupus erythematosus).

SPLENOMEGALY, CHILDREN[20]

ICD-9CM #	782.2	
ICD-10CM #	R16.1	Splenomegaly, not elsewhere classified

DISORDERS OF THE BLOOD

Hemolytic anemia: congenital/acquired.
Thalassemia.
Sickle cell disease.
Leukemia.
Osteopetrosis.
Myelofibrosis/myeloid metaplasia/thrombocythemia.

INFECTIONS: ACUTE AND CHRONIC

Viral:
- Congenital (e.g., TORCH association).
- Mononucleosis (e.g., EBV, CMV infection).
- Virus-associated hemophagocytic syndrome.
- Human immunodeficiency virus.

Bacterial:
- Sepsis/abscess.
- Brucellosis.
- Salmonellosis.
- Tularemia.
- Tuberculosis.
- Subacute bacterial endocarditis.
- Syphilis.
- Lyme disease.

Fungal:
- Histoplasmosis (disseminated).

Rickettsial:
- Rocky Mountain spotted fever.
- Cat scratch disease.

Parasitic:
- Toxoplasmosis.
- Malaria.
- Leishmaniasis (kala-azar).
- Schistosomiasis.
- Echinococcosis.

HEPATIC/PORTAL SYSTEM DISORDERS

Acute/chronic active hepatitis.
Cirrhosis/hepatic fibrosis/biliary atresia.
Portal or splenic venous obstruction (Banti syndrome).

AUTOIMMUNE DISEASE

Juvenile rheumatoid arthritis.
Systemic lupus erythematosus.
Autoimmune lymphoproliferative syndrome (Canale–Smith syndrome).

NEOPLASMS/CYSTS

Lymphomas (Hodgkin and non-Hodgkin).
Hemangiomas/lymphangiomas.
Hamartomas.
Congenital or acquired (posttraumatic) cysts.

STORAGE DISEASES/INBORN ERRORS OF METABOLISM

Lipidoses: Gaucher disease, Niemann–Pick disease, others.
Mucopolysaccharidoses.
Defects in carbohydrate metabolism: galactosemia, fructose intolerance.
Sea-blue histiocyte syndrome.

MISCELLANEOUS DISORDERS

Histiocytoses:
- Reactive.
- Langerhans cell.
- Malignant.

Sarcoidosis.
Congestive heart failure.
Familial Mediterranean fever.

CMV, Cytomegalovirus; *EBV,* Epstein-Barr virus; *TORCH,* toxoplasmosis, other infections, rubella, cytomegalovirus infection, herpes simplex.

STATURAL OVERGROWTH[26b]

ICD-9CM #	253.0	
ICD-10CM #	E34.4	

FETAL OVERGROWTH

Maternal diabetes mellitus.
Cerebral gigantism (Sotos syndrome).
Weaver's syndrome.
Beckwith-Wiedemann syndrome.
Other insulin-like growth factor 2 (IGF2) excess syndromes.

POSTNATAL OVERGROWTH LEADING TO CHILDHOOD TALL STATURE

Familial (constitutional) tall stature.
Cerebral gigantism.
Beckwith-Wiedemann syndrome.
Exogenous obesity.
Excess growth hormone (GH) secretion (pituitary gigantism).
McCune-Albright syndrome or multiple endocrine neoplasia (MEN) associated with excess GH secretion.
Precocious puberty.
Marfan's syndrome.
Klinefelter's syndrome (XXY).
Weaver's syndrome.
Fragile X syndrome.
Homocystinuria.
XYY.
Hyperthyroidism.

POSTNATAL OVERGROWTH LEADING TO ADULT TALL STATURE

Familial (constitutional) tall stature.
Androgen or estrogen deficiency/estrogen resistance (in males).
Testicular feminization.
Excess GH secretion.
Marfan's syndrome.
Klinefelter's syndrome (XXY).
XYY.

STEATOHEPATITIS

ICD-9CM #	571.8	
ICD-10CM #	K76.0	Fatty (change of) liver, not elsewhere classified
	K76.89	Other specified diseases of liver

Alcohol abuse.
Obesity.
DM.
Parenteral nutrition.
Medications (high-dose estrogen, amiodarone, corticosteroids, methotrexate, nifedipine).
Jejunoileal bypass.
Abetalipoproteinemia.
Wilson's disease, Weber-Christian disease.

STOMATITIS, BULLOUS

ICD-9CM #	528.0	
ICD-10CM #	K12.30	Oral mucositis (ulcerative), unspecified

Erythema multiforme.
Erosive lichen planus.
Bullous pemphigoid.
SLE.
Pemphigus vulgaris.
Mucous membrane pemphigoid.

STRIDOR IN NEONATES[1]

ICD-9CM #	786.1	
ICD-10CM #	R06.1	Stridor

INTRINSIC LESIONS

Larynx
Laryngomalacia.
Infection (laryngitis).
Vocal cord paralysis.
Laryngeal web.
Laryngocele or laryngeal cyst.
Laryngotracheal esophageal cleft.
Foreign body.
Trachea
Tracheomalacia.
Tracheal stenosis.
Tracheoesophageal fistula.
Subglottic hemangioma.
Tracheal web.
Extrinsic Compression
Vascular ring.
Anomalous innominate artery.
Mediastinal mass.
Esophageal foreign body.
Other
Macroglossia.
Gastroesophageal reflux.

STRIDOR, PEDIATRIC AGE[4]

ICD-9CM #	786.1	Stridor
	748.3	Stridor, Laryngeal, Congenital
ICD-10CM #	R06.1	Stridor

RECURRENT

Allergic (spasmodic) croup.
Respiratory infections in a child with otherwise asymptomatic anatomic narrowing of the large airways.
Laryngomalacia.

PERSISTENT

Laryngeal obstruction:
- Laryngomalacia.
- Papillomas, other tumors.
- Cysts and laryngoceles.
- Laryngeal webs.
- Bilateral abductor paralysis of the cords.
- Foreign body.

Tracheobronchial disease:
- Tracheomalacia.
- Subglottic tracheal webs.

Endotracheal, endobronchial tumors.
Subglottic tracheal stenosis.
Congenital.
Acquired.
Extrinsic masses.
Mediastinal masses.
Vascular ring.
Lobar emphysema.
Bronchogenic cysts.
Thyroid enlargement.
Esophageal foreign body.
Tracheoesophageal fistulas.
Other.
Gastroesophageal reflux.
Macroglossia, Pierre Robin syndrome.
Cri-du-chat syndrome.
Hysterical stridor.
Hypocalcemia.

STROKE[36]

ICD-9CM #	436	Acute Stroke
ICD-10CM #	I64	Stroke
	I67.89	Other cerebrovascular disease

Hypoglycemia.
Drug overdose or intoxication.
Hysterical conversion reaction.
Hyperventilation.
Metabolic encephalopathy.
Migraine.
Syncope.
Transient global amnesia.
Seizures.
Vestibular vertigo.

STROKE, PEDIATRIC AGE[23]

ICD-9CM #	436	Stroke, Acute
ICD-10CM #	I67.89	Other cerebrovascular disease

CARDIAC DISEASE

Congenital:
- Aortic stenosis.
- Mitral stenosis; mitral prolapse.
- Ventricular septal defects.
- Patent ductus arteriosus.
- Cyanotic congenital heart disease involving right-to-left shunt.

Acquired:
- Endocarditis (bacterial, SLE).
- Kawasaki disease.
- Cardiomyopathy.
- Atrial myxoma.
- Arrhythmia.
- Paradoxical emboli through patent foramen ovale.
- Rheumatic fever.
- Prosthetic heart valve.

HEMATOLOGIC ABNORMALITIES

Hemoglobinopathies:
- Sickle cell (SS) disease.
- Sickle (SC) disease.

Polycythemia.
Leukemia/lymphoma.
Thrombocytopenia.
Thrombocytosis.
Disorders of coagulation:
- Protein C deficiency.
- Protein S deficiency.
- Factor V Leiden.
- Antithrombin III deficiency.
- Lupus anticoagulant.

Oral contraceptive pill use.
Pregnancy and the postpartum state.
Disseminated intravascular coagulation.
Paroxysmal nocturnal hemoglobinuria.
Inflammatory bowel disease (thrombosis).

INFLAMMATORY DISORDERS

Meningitis:
- Viral.
- Bacterial.
- Tuberculosis.

Systemic infection:
- Viremia.
- Bacteremia.
- Local head and neck infections.

Drug-induced inflammation:
- Amphetamine.
- Cocaine.

Autoimmune disease:
- SLE.
- Juvenile RA.
- Takayasu's arteritis.
- Mixed connective tissue disease.
- Polyarteritis nodosum.
- Primary CNS vasculitis.
- Sarcoidosis.
- Behçet's syndrome.
- Granulomatosis with polyangiitis (Wegener's granulomatosis).

METABOLIC DISEASE ASSOCIATED WITH STROKE

Homocystinuria.
Pseudoxanthoma elasticum.
Fabry's disease.
Sulfite oxidase deficiency.
Mitochondrial disorders:
- MELAS.
- Leigh syndrome.

Ornithine transcarbamylase deficiency.

INTRACEREBRAL VASCULAR PROCESSES

Ruptured aneurysm.
Arteriovenous malformation.
Fibromuscular dysplasia.
Moyamoya disease.
Migraine headache.
Postsubarachnoid hemorrhage vasospasm.
Hereditary hemorrhagic telangiectasia.
Sturge-Weber syndrome.
Carotid artery dissection.
Postvaricella.

TRAUMA AND OTHER EXTERNAL CAUSES

Child abuse.
Head trauma/neck trauma.
Oral trauma.
Placental embolism.
ECMO therapy.

CNS, Central nervous system; *ECMO,* extracorporeal membrane oxygenation; *MELAS,* mitochondrial encephalomyopathy, lactic acidosis, and stroke.

STROKE, YOUNG ADULT, CAUSES[1a]

ICD-9CM #	436	
ICD-10CM #	I64	Stroke
	I67.89	Other cerebrovascular disease

Cardiac factors (ASD, MVP, patent foramen ovale).
Inflammatory factors (SLE, polyarteritis nodosa).
Infections (endocarditis, neurosyphilis).
Drugs (cocaine, heroin, oral contraceptives, decongestants).
Arterial dissection.

Hematolic factors (DIC, TTP, deficiency of protein S, protein C, antithrombin III).
Migraine.
Postpartum angiopathy.
Other: premature atherosclerosis, fibromuscular dysplasia.

ST-SEGMENT DEPRESSION, NON-CORONARY CAUSES[4a]

ICD-9CM # 794.31
ICD-10CM # R94.31

NONCORONARY CAUSES OF ST-SEGMENT DEPRESSION

Anemia.
Cardiomyopathy.
Digitalis use.
Glucose load.
Hyperventilation.
Hypokalemia.
Intraventricular conduction disturbance.
Left ventricular hypertrophy.
Mitral valve prolapse.
Preexcitation syndrome.
Severe aortic stenosis.
Severe hypertension.
Severe hypoxia.
Severe volume overload (aortic, mitral regurgitation).
Sudden excessive exercise.
Supraventricular tachyarrhythmias.

ST-SEGMENT ELEVATION[1]

ICD-9CM # 794.31
ICD-10CM # R94.31 Abnormal ECG

DIFFERENTIAL DIAGNOSIS OF ST-SEGMENT ELEVATION ON ELECTROCARDIOGRAPHY

ST-segment elevation myocardial infarction.
Pericarditis.
Benign early repolarization.
Left bundle branch block.
Left ventricular hypertrophy.
Left ventricular aneurysm.
Paced ventricular rhythms.
Prinzmetal angina.
Hyperkalemia.
Hypothermia with Osborne waves.
Intracranial hemorrhage.
Brugada syndrome.
Normal variant.

ST SEGMENT ELEVATIONS, NONISCHEMIC

ICD-9CM # 794.31
ICD-10CM # R94.31 Abnormal electrocardiogram [ECG] [EKG]

Early repolarization.
Acute pericarditis.
LVH.
Normal pattern variant.
LBBB.
Pulmonary embolism.
Hyperkalemia.
Postcardioversion.

SUDDEN DEATH, PEDIATRIC AGE[4]

ICD-9CM # varies with specific disorder
ICD-10CM # R99 Ill-defined and unknown cause of mortality

SIDS AND SIDS "MIMICS"

SIDS.
Long QT syndromes.
Inborn errors of metabolism.
Child abuse.
Myocarditis.
Duct-dependent congenital heart disease.

CORRECTED OR UNOPERATED CONGENITAL HEART DISEASE

Aortic stenosis.
Tetralogy of Fallot.
Transposition of great vessels (postoperative atrial switch).
Mitral valve prolapse.
Hematologic left heart syndrome.
Eisenmenger's syndrome.

CORONARY ARTERIAL DISEASE

Anomalous origin.
Anomalous tract.
Kawasaki disease.
Periarteritis.
Arterial dissection.
Marfan's syndrome.
Myocardial infarction.

MYOCARDIAL DISEASE

Myocarditis.
Hypertrophic cardiomyopathy.
Dilated cardiomyopathy.
Arrhythmogenic right ventricular dysplasia.

CONDUCTION SYSTEM ABNORMALITY/ARRHYTHMIA

Long Q-T syndromes.
Proarrhythmic drugs.
Preexcitation syndromes.
Heart block.
Commotio cordis.
Idiopathic ventricular fibrillation.
Heart tumor.

MISCELLANEOUS

Pulmonary hypertension.
Pulmonary embolism.
Heat stroke.
Cocaine.
Anorexia nervosa.
Electrolyte disturbances.

SIDS, Sudden infant death syndrome.

SUDDEN DEATH, YOUNG ATHLETE

ICD-9CM # varies with specific diagnosis
ICD-10CM # R99 Ill-defined and unknown cause of mortality

Hypertrophic cardiomyopathy.
Coronary artery anomalies.
Myocarditis.
Ruptured aortic aneurysm (Marfan's syndrome).
Arrhythmias.
Aortic valve stenosis.
Asthma.
Trauma (cerebral, cardiac).
Drug and alcohol abuse.
Heat stroke.
Cardiac sarcoidosis.
Atherosclerotic coronary artery disease.
Dilated cardiomyopathy.

SWOLLEN LIMB

ICD-9CM # 729.81 Swollen Arm or Hand
729.81 Swollen Leg or Foot
ICD-10CM # M79.89 Other specified soft tissue disorders

Trauma.
Insect bite.
Abscess.
Lymphedema.
Thrombophlebitis.
Lipoma.
Neurofibroma.
Postphlebitic syndrome.
Myositis ossificans.
Nephrosis, cirrhosis, CHF.
Hypoalbuminemia.
Varicose veins.

TALL STATURE[27]

ICD-9CM # 253.0 Growth Hormone Overproduction, Gigantism
ICD-10CM # E22.0 Acromegaly and pituitary gigantism

Constitutional (familial or genetic)—most common cause

ENDOCRINE CAUSES

Growth hormone excess—gigantism.
Sexual precocity (tall as children, short as adults):
  True sexual precocity.
  Pseudosexual precocity.
Androgen deficiency:
  Klinefelter's syndrome.
  Bilateral anorchism.

GENETIC CAUSES

Klinefelter's syndrome.
Syndromes of XYY, XXYY.

MISCELLANEOUS SYNDROMES AND DISORDERS

Cerebral gigantism or Sotos' syndrome: prominent forehead, hypertelorism, high arched palate, dolichocephaly, mental retardation, large hands and feet, and premature eruption of teeth. Large at birth, with most rapid growth in first 4 yr of life.
Marfan's syndrome: disorder of mesodermal tissues, subluxation of the lenses, arachnodactyly, and aortic aneurysm.

Homocystinuria: same phenotype as Marfan's syndrome.
Obesity: tall as infants, children, and adolescents.
Total lipodystrophy: large hands and feet, generalized loss of subcutaneous fat, insulin-resistant DM, and hepatomegaly.
Beckwith-Wiedemann syndrome: neonatal tallness, omphalocele, macroglossia, and neonatal hypoglycemia.
Weaver-Smith syndrome: excessive intrauterine growth, mental retardation, megalocephaly, widened bifrontal diameter, hypertelorism, large ears, micrognathia, camptodactyly, broad thumbs, and limited extension of elbows and knees.
Marshall-Smith syndrome: excessive intrauterine growth, mental retardation, blue sclerae, failure to thrive, and early death.

TARDIVE DYSKINESIA[13]

ICD-9CM #	781.3	Dyskinesia
	300.11	Hysterical Dyskinesia
	333.82	Orofacial Dyskinesia
	307.9	Psychogenic Dyskinesia
ICD-10CM #	R27.9	Unspecified lack of coordination
	F44.4	Conversion disorder with motor symptom or deficit
	F44.6	Conversion disorder with sensory symptom or deficit
	G24.4	Idiopathic orofacial dystonia

DIFFERENTIAL DIAGNOSIS

Medications (antidepressants, anticholinergics, amphetamines, lithium, l-dopa, phenytoin).
Brain neoplasms.
Ill-fitting dentures.
Huntington's disease.
Idiopathic dystonias (tics, blepharospasm, aging).
Wilson's disease.
Extrapyramidal syndrome (postanoxic or postencephalitic).
Torsion dystonia.

TASTE AND SMELL LOSS[1a]

ICD-9CM #	781.1	Smell and Taste Disturbance of Sensation
ICD-10CM #	R43.0	Anosmia
	R43.1	Parosmia
	R43.2	Parageusia

TASTE

Local: radiation therapy.
Systemic: cancer, renal failure, hepatic failure, nutritional deficiency (vitamin B_{12}, zinc), Cushing's syndrome, hypothyroidism, DM, infection (influenza), drugs (antirheumatic and antiproliferative).
Neurologic: Bell's palsy, familial dysautonomia, multiple sclerosis.

SMELL

Local: allergic rhinitis, sinusitis, nasal polyposis, bronchial asthma.
Systemic: renal failure, hepatic failure, nutritional deficiency (vitamin B_{12}), Cushing's syndrome, hypothyroidism, DM, infection (viral hepatitis, influenza), drugs (nasal sprays, antibiotics).
Neurologic: head trauma, multiple sclerosis, Parkinson's disease, frontal brain tumor.

TELANGIECTASIA

ICD-9CM #	448.9	
ICD-10CM #	I78.8	Other diseases of capillaries
	I78.9	Disease of capillaries, unspecified

Oral contraceptive agents.
Pregnancy.
Rosacea.
Varicose veins.
Trauma.
Drug induced (corticosteroids, systemic or topical).
Spider telangiectases.
Hepatic cirrhosis.
Mastocytosis.
SLE, dermatomyositis, systemic sclerosis.

TENDINOPATHY[26]

ICD-9CM #	727.9	
ICD-10CM #	M67.90	Unspecified disorder of synovium and tendon, unspecified site
	M71.9	Bursopathy, unspecified

INTRINSIC FACTORS

Anatomic Factors
Malalignment.
Muscle weakness or imbalance.
Muscle inflexibility.
Decreased vascularity.
Systemic Factors
Inflammatory conditions (e.g., SLE).
Pregnancy.
Quinolone-induced tendinopathy.
Age-Related Factors
Tendon degeneration.
Increased tendon stiffness.
Tendon calcification.
Decreased vascularity.

EXTRINSIC FACTORS

Repetitive Mechanical Load
Excessive duration.
Excessive frequency.
Excessive intensity.
Poor technique.
Workplace factors.
Equipment Problems
Footwear.
Athletic field surface.
Equipment factors (e.g., racquet size).
Protective gear.

TESTICULAR FAILURE[10]

ICD-9CM #	257.1	Testicular Failure
ICD-10CM #	E29	Testicular dysfunction

PRIMARY

Klinefelter's syndrome (XXY).
XYY.
Vanishing testes syndrome (in utero or early postnatal torsion).
Noonan's syndrome.
Varicocele.
Myotonic dystrophy.
Orchitis (mumps, gonorrhea).
Cryptorchidism.
Chemical exposure.
Irradiation to testes.
Spinal cord injury.
Polyglandular failure.
Idiopathic oligospermia or azoospermia.
Germinal cell aplasia (Sertoli cell–only syndrome).
Idiopathic testicular failure.
Testicular torsion.
Testicular trauma.
Diethylstilbestrol (maternal use during pregnancy leading to in utero estrogen exposure).
Testicular tumor with subsequent irradiation therapy, chemotherapy, or surgery (retroperitoneal lymph node dissection or orchiectomy).

SECONDARY

Delayed puberty.
Kallmann's syndrome.
Isolated gonadotropin deficiency.
Prader-Labhart-Willi syndrome.
Lawrence-Moon-Biedl syndrome.
Central nervous system irradiation.
Prepubertal panhypopituitarism.
Postpubertal panhypopituitarism.
Hypogonadism secondary to hyperprolactinemia.
Adrenogenital syndrome.
Chronic liver disease.
Chronic renal failure/uremia.
Hemochromatosis.
Cushing's syndrome.
Malnutrition.
Massive obesity.
Sickle cell anemia.
Hyper/hypothyroidism.
Anabolic steroid use.

TESTICULAR PAIN

ICD-9CM #	608.9	
ICD-10CM #	N50.9	Disorder of male genital organs, unspecified
	R10.2	Pelvic and perineal pain

Testicular torsion.
Trauma.
Epididymitis.
Orchitis.
Neoplasm.
Urolithiasis.
Inguinal hernia.
Infection (cellulitis, abscess, folliculitis).
Anxiety.

TESTICULAR SIZE VARIATIONS[10]

ICD-9CM #	608.3	Testicular Atrophy
	608.89	Testicular Mass
	257.2	Hypogonadism
ICD-10CM #	N50.0	Atrophy of testis
	N44.2	Benign cyst of testis
	N44.8	Other noninflammatory disorders of the testis
	N50.3	Cyst of epididymis
	N50.8	Other specified disorders of male genital organs
	N53.12	Painful ejaculation
	E29.1	Testicular hypofunction

SMALL TESTES

Hypothalamic-pituitary dysfunction.
Gonadotropin deficiency.
Growth hormone deficiency.
Normal variant.
Primary hypogonadism.
Autoimmune destruction.
Chemotherapy.
Cryptorchidism.
Irradiation.
Klinefelter's syndrome.
Orchiditis.
Testicular regression syndrome.
Torsion.
Trauma.

LARGE TESTES

Adrenal rest tissue.
Compensatory.
Fragile X syndrome.
Idiopathic.
Tumor.

TETANUS[26]

ICD-9CM #	037	
ICD-10CM #	A35	Other tetanus

Acute abdomen.
Black widow spider bite.
Dental abscess.
Dislocated mandible.
Dystonic reaction.
Encephalitis.
Head trauma.
Hyperventilation syndrome.
Hypocalcemia.
Meningitis.
Peritonsillar abscess.
Progressive fluctuating muscular rigidity (stiff-man syndrome).
Psychogenic.
Rabies.
Sepsis.
Subarachnoid hemorrhage.
Status epilepticus.
Strychnine poisoning.
Temporomandibular joint syndrome.

THROMBOCYTOPENIA

ICD-9CM #	287.3	Congenital or Primary
	287.4	Secondary
	287.5	Thrombocytopenia NOS
ICD-10CM #	D47.3	Essential (hemorrhagic) thrombocythemia
	D69.59	Other secondary thrombocytopenia
	D69.6	Thrombocytopenia, unspecified

INCREASED DESTRUCTION

Immunologic

Drugs: quinine, quinidine, digitalis, procainamide, thiazide diuretics, sulfonamides, phenytoin, aspirin, penicillin, heparin, gold, meprobamate, sulfa drugs, phenylbutazone, nonsteroidal anti-inflammatory drugs (NSAIDs), methyldopa, cimetidine, furosemide, INH, cephalosporins, chlorpropamide, organic arsenicals, chloroquine, platelet glycoprotein IIb/IIIa receptor inhibitors, ranitidine, indomethacin, carboplatin, ticlopidine, clopidogrel.
Idiopathic thrombocytopenic purpura (ITP).
Transfusion reaction: transfusion of platelets with plasminogen activator (PLA) in recipients without PLA-1.
Fetal/maternal incompatibility.
Collagen vascular diseases (e.g., SLE).
Autoimmune hemolytic anemia.
Lymphoreticular disorders (e.g., CLL).

Nonimmunologic

Prosthetic heart valves.
Thrombotic thrombocytopenic purpura (TTP).
Sepsis.
DIC.
Hemolytic-uremic syndrome (HUS).
Giant cavernous hemangioma.

DECREASED PRODUCTION

Abnormal marrow.
Marrow infiltration (e.g., leukemia, lymphoma, fibrosis).
Marrow suppression (e.g., chemotherapy, alcohol, radiation).
Hereditary disorders.
Wiskott-Aldrich syndrome: X-linked disorder characterized by thrombocytopenia, eczema, and repeated infections.
May-Hegglin anomaly: increased megakaryocytes but ineffective thrombopoiesis.
Vitamin deficiencies (e.g., vitamin B_{12}, folic acid).

SPLENIC SEQUESTRATION, HYPERSPLENISM

DILUTIONAL, AS A RESULT OF MASSIVE TRANSFUSION

THROMBOCYTOPENIA, IN PREGNANCY[20]

ICD-9CM #	287.4	
ICD-10CM #	D69.59	Other secondary thrombocytopenia

Incidental thrombocytopenia of pregnancy (gestational thrombocytopenia).
Preeclampsia/eclampsia.*
Peripartum/postpartum thrombotic microangiopathy.
Disseminated intravascular coagulation (DIC) secondary to:
Abruptio placentae.
Endometritis.
Amniotic fluid embolism.
Retained fetus.
Thrombotic thrombocytopenic purpura.
Hemolytic-uremic syndrome.

*Preeclampsia/eclampsia usually is not associated with overt DIC.

THROMBOCYTOPENIA, INHERITED DISORDERS[1a]

ICD-9CM #	287.3	
ICD-10CM #	D47.3	Essential (hemorrhagic) thrombocythemia

Amegakaryocytic thrombocytopenia.
Thrombocytopenia–absent radii.
MYH9-related thrombocytopenia:
May-Hegglin anomaly.
Fechtner syndrome.
Epstein syndrome.
Sebastian syndrome.
X-linked macrothrombocytopenia.
Wiskott-Aldrich syndrome.
X-linked thrombocytopenia.
Thrombocytopenia and radioulnar synostosis.
Familial platelet disorder—AML.
Familial dominant thrombocytopenia.
Paris-Trousseau thrombocytopenia.
Bernard-Soulier syndrome.
Bernard-Soulier carrier/Mediterranean macrothrombocytopenia.

THROMBOCYTOPENIA IN NEWBORNS, DIFFERENTIAL DIAGNOSIS[18c]

ICD-9CM #	287.3	Congenital or Primary
	287.4	Secondary
	287.5	Thrombocytopenia NOS
ICD-10CM #	D47.3	Essential (hemorrhagic) thrombocythemia
	D69.59	Other secondary thrombocytopenia
	D69.6	Thrombocytopenia, unspecified

DIFFERENTIAL DIAGNOSIS OF THROMBOCYTOPENIA IN NEWBORNS

Perinatal hypoxemia.
Placental insufficiency.
Congenital infection:
Sepsis.
Toxoplasmosis.
Rubella.
Cytomegalovirus.

Autoimmune:
Maternal immune thrombocytopenia.
Maternal systemic lupus erythematosus.
Disseminated intravascular coagulation.
Maternal drug exposure.
Congenital heart disease.
Hereditary thrombocytopenia:
MYH9 macrothrombocytopenia (including May-Hegglin anomaly).
Thrombocytopenia absent radii syndrome.
Amegakaryocytic thrombocytopenia.
Wiskott-Aldrich syndrome.
Fanconi anemia.
Hemangioma with thrombocytopenia:
Kasabach-Merritt syndrome.
Bone marrow infiltration:
Congenital leukemia.

THROMBOCYTOSIS

ICD-9CM #	289.9	Thrombocytosis, Essential
ICD-10CM #	D75.9	Disease of blood and blood-forming organs, unspecified

Iron deficiency.
Posthemorrhage.
Neoplasms (GI tract).
CML.
Polycythemia vera.
Myelofibrosis with myeloid metaplasia.
Infections.
After splenectomy.
Postpartum.
Hemophilia.
Pancreatitis.
Cirrhosis.
Idiopathic.

THROMBOSIS OR THROMBOTIC DIATHESIS[1a]

ICD-9CM #	444	
ICD-10CM #	I74.09	Other arterial embolism and thrombosis of abdominal aorta

DIFFERENTIAL DIAGNOSIS OF THE PATIENT PRESENTING WITH THROMBOSIS OR THROMBOTIC DIATHESIS

Inherited (Primary) Hypercoagulable States
Activated protein C resistance caused by factor V Leiden mutation.
Prothrombin gene mutation (G to A transition at position 20210 in the 3-untranslated region).
Antithrombin III deficiency.
Protein C deficiency.
Protein S deficiency.
Dysfibrinogenemias (rare).
Acquired (Secondary) Hypercoagulable States
In association with physiologic or thrombogenic stimuli:
Pregnancy (especially the postpartum period).
Estrogen use (oral contraceptives, hormone replacement therapy).
Immobilization.
Trauma.
Postoperative state.
Advancing age.
Obesity.
Prolonged air travel.
Lupus anticoagulant or antiphospholipid antibody syndrome.
In association with other clinical disorders.
Mixed/Unknown
Activated protein C resistance in the absence of factor V Leiden.
Elevated factor VIII level.
Elevated factor XI level.
Elevated factor IX level.
Elevated thrombin activatable fibrinolysis inhibitor (TAFI) level.
Decreased free tissue factor pathway inhibitor (TFPI) level.
Decreased plasma fibrinolytic activity.

THYROMEGALY

ICD-9CM #	varies with specific diagnosis
ICD-10CM #	varies with specific diagnosis

Goiter.
Graves' disease.
Thyroiditis (lymphocytic, granulomatous, suppurative).
Toxic adenoma.
Neoplasm (primary, metastatic).

THYROTOXICOSIS[26b]

ICD-9CM #	242.8
ICD-10CM #	E05.80

CAUSES OF THYROTOXICOSIS

Sustained Hormone Overproduction (Hyperthyroidism)
Low TSH, High RAIU:
Graves' disease (von Basedow's disease).
Toxic multinodular goiter.
Toxic adenoma.
Chorionic gonadotropin-induced.
- Gestational hyperthyroidism: physiologic hyperthyroidism of pregnancy, familial gestational hyperthyroidism due to TSH receptor mutations.
- Trophoblastic tumors

Inherited nonimmune hyperthyroidism associated with TSH receptor or G protein mutations.
Low TSH, Low RAIU:
Iodide-induced hyperthyroidism (Jod-Basedow effect).
Amiodarone-associated hyperthyroidism due to iodide release.
Struma Ovarii:
Metastatic functioning thyroid carcinoma.
Normal or Elevated TSH:
TSH-secreting pituitary tumors.
Thyroid hormone resistance with pituitary predominance.
Transient Hormone Excess (Thyrotoxicosis)
Low TSH, Low RAIU
Thyroiditis.
- Autoimmune: lymphocytic thyroiditis (silent thyroiditis, painless thyroiditis, postpartum thyroiditis), acute exacerbation of Hashimoto's disease.

Viral or postviral.
- Subacute (granulomatous, painful, postviral) thyroiditis.

Drug-induced or associated thyroiditis.
- Amiodarone.
- Lithium, interferon-α, interleukin-2, GM-CSF.

Infectious thyroiditis.
Exogenous Thyroid Hormone.
Iatrogenic overreplacement.
Thyrotoxicosis factitia.
Ingestion of natural products containing thyroid hormone.
- "Hamburger" thyrotoxicosis.
- Natural foodstuffs.
- Thyromimetic compounds (e.g., tiratricol PLB).
- Occupational exposure to thyroid hormone (e.g., pill manufacturing, veterinary occupations).

GM-CSF, granulocyte-macrophage colony-stimulating factor; *RAIU*, radioactive iodine uptake; *TSH*, thyroid-stimulating hormone.

TICK-RELATED INFECTIONS

ICD-9CM #	082.0	Rocky Mountain Spotted Fever
	066.1	Colorado Tick Fever
	088.82	Babesiosis
	082.8	Ehrlichiosis
	088.81	Lyme Disease
ICD-10CM #	A77.0	Spotted fever due to Rickettsia rickettsii
	A93.2	Colorado tick fever
	B60.0	Babesiosis
	A77.8	Other spotted fevers
	A69.20	Lyme disease, unspecified

Lyme disease.
Rocky Mountain spotted fever.
Babesiosis.
Tularemia.
Q fever.
Colorado tick fever.
Ehrlichiosis.
Relapsing fever.

TICS

ICD-9CM #	307.20	
ICD-10CM #	F95.9	Tic disorder, unspecified

Tourette's syndrome.
Physiologic tic.
Anxiety disorder.
Huntington's disease.
Medications (e.g., antipsychotics, carbamazepine, phenytoin, phenobarbital).
Encephalitis.
Head trauma.
Schizophrenia.
Carbon monoxide poisoning.
Stroke.
Sydenham's chorea.
Creutzfeldt-Jakob disease.

TORSADES DE POINTES[22]

ICD-9CM # code not available
ICD-10CM # I47.2 Ventricular tachycardia

Antiarrhythmics known to increase the QT interval (e.g., quinidine, procainamide, amiodarone, disopyramide, sotalol).
Tricyclic antidepressants and phenothiazines.
Histamine (H_1) antagonists (e.g., astemizole, terfenadine).
Antiviral and antifungal agents and antibiotics.
Hypokinemia.
Hypomagnesemia.
Insecticide poisoning.
Bradyarrhythmias.
Congenital long QT syndrome.
Subarachnoid hemorrhage.
Chloroquinine, pentamidine.
Cocaine abuse.

TOXIC MEGACOLON, CAUSES[5a]

ICD-9CM # 564.7 Toxic Megacolon
ICD-10CM # K59.3 Megacolon, not elsewhere classified

INFLAMMATORY

Ulcerative colitis.
Crohn's disease.

INFECTIOUS

Bacterial.
- *Clostridium difficile* pseudomembranous colitis.
- *Salmonella* (typhoid and nontyphoid).
- *Shigella.*
- *Campylobacter.*
- *Yersinia.*

Parasitic.
- *Entamoeba histolytica.*
- *Cryptosporidium.*

Viral.
- Cytomegalovirus colitis.

OTHER

- Ischemia.
- Kaposi sarcoma.

TRACHEOBRONCHIAL NARROWING ON X-RAY[16a]

ICD-9CM # varies with specific diagnosis
ICD-10CM # varies with specific diagnosis

CAUSES OF TRACHEOBRONCHIAL NARROWING

Long-segment/Diffuse Narrowing

Sarcoidosis.
Amyloidosis.
Granulomatosis with polyangiitis (Wegener's granulomatosis).
Relapsing polychondritis.
Tracheobronchopathia osteochondroplastica.
Pemphigoid.

Short-segment Narrowing

Previous intubation or tracheostomy.
Congenital stenosis or web.
Extrinsic compression (from thyroid).
Adenoid cystic carcinoma.
Squamous carcinoma.

TREMOR

ICD-9CM # 781.0 Tremor NOS
333.1 Benign Essential Tremor
333.1 Familial Tremor
ICD-10CM # R25.0 Abnormal head movements
R25.1 Tremor, unspecified
R25.2 Cramp and spasm
R25.3 Fasciculation
R25.9 Unspecified abnormal involuntary movements
G25.0 Essential tremor
G25.1 Drug-induced tremor
G25.2 Other specified forms of tremor

REST TREMORS

Parkinson's disease.
Other parkinsonian syndromes (less commonly).
Midbrain (rubral) tremor: rest < postural < kinetic.
Wilson's disease (also acquired hepatocerebral degeneration).
Essential tremor—only if severe: rest < postural and action.

POSTURAL AND ACTION (TERMINAL) TREMORS

Physiologic tremor.
Exaggerated physiologic tremor (these factors can also aggravate other forms of tremor).
Stress, fatigue, anxiety, emotion.
Endocrine: hypoglycemia, thyrotoxicosis, pheochromocytoma, adrenocorticosteroids.
Drugs and toxins: b-agonists, dopamine agonists, amphetamines, lithium, tricyclic antidepressants, neuroleptics, theophylline, caffeine, valproic acid, alcohol withdrawal, mercury (Hatter's shakes), lead, arsenic, others.
Essential tremor (familial or sporadic)
Primary writing tremor.
With other CNS disorders.
Parkinson's disease.
Other akinetic-rigid syndromes.
Idiopathic dystonia, including focal dystonias.
With peripheral neuropathy.
Charcot-Marie-Tooth syndrome (controversial whether to call this the Roussy-Levy syndrome).
Variety of other peripheral neuropathies (especially dysgammaglobulinemia).
Cerebellar tremor.

KINETIC (INTENTION) TREMOR

Disease of cerebellar outflow (dentate nucleus and superior cerebellar peduncle): multiple sclerosis, trauma, tumor, vascular disease, Wilson's acquired hepatocerebral degeneration, drugs, toxins (e.g., mercury), others.

MISCELLANEOUS RHYTHMICAL MOVEMENT DISORDERS

Psychogenic tremor.
Orthostatic tremor.
Rhythmical movements in dystonia (dystonic tremor).
Rhythmical myoclonus (segmental myoclonus—e.g., palatal or branchial myoclonus, spinal myoclonus, limb myorhythmia).
Oscillatory myoclonus.
Asterixis.
Clonus.
Epilepsia partialis continua.
Hereditary chin quivering.
Spasmus nutans.
Head bobbing with third ventricular cysts.
Nystagmus.

TREMOR, IN CHILDREN, CAUSES[22a]

ICD-9CM # 781.0 Tremor
ICD-10CM # R25.0 Abnormal head movements
R25.1 Tremor, unspecified
R25.2 Cramp and spasm
R25.3 Fasciculation
R25.9 Unspecified abnormal involuntary movements

BENIGN

Enhanced physiologic tremor.
Shuddering attacks.
Jitteriness.
Spasmus nutans.

STATIC INJURY/STRUCTURAL

Cerebellar malformation.
Stroke (particularly in the midbrain or cerebellum).
Multiple sclerosis.

HEREDITARY/DEGENERATIVE

Familial essential tremor.
Fragile X premutation.
Wilson disease.
Huntington disease.
Juvenile parkinsonism (tremor is rare).
Pallidonigral degeneration.

METABOLIC

Hyperthyroidism.
Hyperadrenergic state (including pheochromocytoma and neuroblastoma).
Hypomagnesemia.
Hypocalcemia.
Hypoglycemia.
Hepatic encephalopathy.
Vitamin B_{12} deficiency.
Inborn errors of metabolism.
Mitochondrial disorders.

DRUGS/TOXINS

Valproate, phenytoin, carbamazepine, lamotrigine, gabapentin, lithium, tricyclic antidepressants, stimulants (cocaine, amphetamine, caffeine, thyroxine, bronchodilators), neuroleptics, cyclosporin, toluene, mercury, thallium, amiodarone, nicotine, lead, manganese, arsenic, cyanide, naphthalene, ethanol, lindane, serotonin reuptake inhibitors.

PERIPHERAL NEUROPATHIES

PSYCHOGENIC

TUBULOINTERSTITIAL DISEASE, ACUTE[14]

ICD-9CM #	584.5	
ICD-10CM #	N17.0	Acute kidney failure with tubular necrosis

DRUGS

Antibiotics, penicillins, cephalosporins, rifampin.
Sulfonamides: cotrimoxazole, sulfamethoxazole.
NSAIDs: propionic acid derivatives.
Miscellaneous: phenytoin, thiazides, allopurinol, cimetidine, ifosfamide.

INFECTIONS

Invasion of renal parenchyma.
Reaction to systemic infections: streptococcal, diphtheria, hantavirus.

SYSTEMIC DISEASES

Immune mediated: SLE, transplanted kidney, cryoglobulinemias.
Metabolic: Urate, oxalate.
Neoplastic: Lymphoproliferative diseases.

IDIOPATHIC

TUBULOINTERSTITIAL KIDNEY DISEASE[14]

ICD-9CM #	584.5	
ICD-10CM #	N17.0	Acute kidney failure with tubular necrosis

Ischemic and toxic acute tubular necrosis.
Allergic interstitial nephritis.
Interstitial nephritis secondary to immune complex-related collagen vascular disease (e.g., SLE, Sjögren's).
Granulomatous diseases (sarcoidosis, uveitis).
Pigment-related tubular injury (myoglobinuria, hemoglobinuria).
Hypercalcemia with nephrocalcinosis.
Tubular obstruction (drugs such as indinavir, uric acid in tumor lysis syndrome).
Myeloma kidney or cast nephropathy.
Infection-related interstitial nephritis: *Legionella, Leptospira.*
Infiltrative diseases (e.g., lymphoma).

TUMOR MARKERS ELEVATION[38]

ICD-9CM #	795.8	
ICD-10CM #	R97.8	Other abnormal tumor markers

CAUSES OF ELEVATED LEVELS OF TUMOR MARKERS

Carcinoembryonic Antigen (CEA)
Colonic cancer (higher levels if the tumor is more differentiated or is extensive or has spread to the liver).
Lung or breast cancer; seminoma.
Cigarette smokers.
Cirrhosis, inflammatory bowel disease, rectal polyps, pancreatitis.
Advanced age.

Alpha-Fetoprotein
Hepatocellular cancer: very high titers or a rising titer is strongly suggestive, but >10% of patients do not have an elevated level.
Hepatic regeneration (e.g., cirrhosis, alcoholic or viral hepatitis).
Cancer of the stomach, colon, pancreas, or lung.
Teratocarcinoma or embryonal cell carcinoma (testis, ovary, extragonadal).
Pregnancy.
Ataxia-telangiectasia.
Normal variant.

Prostate-Specific Antigen
Prostate carcinoma (localized disease).
Prostatic hyperplasia.
Prostatitis.
Prostatic infarction.

Cancer-Associated Antigen (CA-19-9)*
Pancreatic carcinoma (80% with advanced, well-differentiated cancer have an elevated level).
Other gastrointestinal cancers: colon, stomach, bile duct.
Acute or chronic pancreatitis.
Chronic liver disease.
Biliary tract disease.

*Patients who cannot synthesize Lewis blood group antigens (~5% of the population) do not produce CA-19-9 antigen.

UREMIC ENCEPHALOPATHY, DIFFERENTIAL DIAGNOSIS[12b]

ICD-9CM #	348.30	Uremic Encephalopathy
ICD-10CM #	G93.40	Encephalopathy, unspecified

Differential Diagnosis	*Comment*
Hypertensive encephalopathy	
Systemic inflammatory response syndrome (SIRS):	Observed in septic patients
Systemic vasculitis:	Vasculitis or lupus with cerebral involvement
Drug-induced neurotoxicity	
Analgesics:	Meperidine, codeine, morphine, gabapentin
Antibiotics:	High-dose penicillins (may cause seizures), acyclovir, ethambutol (optic nerve damage), erythromycin and aminoglycosides (may cause ototoxicity), nitrofurantoin and isoniazid (peripheral neuropathy)
Psychotropics:	Lithium, haloperidol, clonazepam, diazepam, chlorpromazine
Immunosuppressants:	Cyclosporine, tacrolimus
Chemotherapeutics:	Cisplatinum, ifosfamide
Others:	High doses of loop diuretics (ototoxic), ephedrine, methyldopa, aluminum
Cerebral atheroembolic disease:	Follows recent aortic or cardiac angiography; associated with peripheral manifestations, including lower extremity cyanosis, livedo reticularis, and eosinophilia
Subdural hematoma	
Posterior leukoencephalopathy:	• Observed particularly following renal transplantation due to reversible, abnormal permeability of the blood-brain barrier • Often manifests as headache followed by mental depression, visual loss, and seizures in the context of volume expansion, acute hypertension, and often treatment with corticosteroids or calcineurin inhibitors • Lesions in the parietal, temporal, and occipital lobes may be seen on imaging studies

URETERAL COLIC[24a]

ICD-9CM #	788.0	
ICD-10CM #	R33.8	Other retention of urine
	N13.8	Other obstructive and reflux uropathy

DIAGNOSTIC DIFFERENTIALS OF RENAL OR URETERAL COLIC

Acute cholecystitis, acute cholelithiasis.
Acute appendicitis.
Pelvic inflammatory disease.
Diverticulosis and/or diverticulitis.
Intestinal obstruction.
Leaking abdominal aortic aneurysm.
Musculoskeletal sprains.
Herniated disk.
Hepes zoster (shingles).
Gastrointestinal dysfunction with ileus and/or toxic colonic dilatation.

URETERIC OBSTRUCTION, CONGENITAL[16a]

ICD-9CM #	593.4	
ICD-10CM #	N13.8	Other obstructive and reflux uropathy
	N20.9	Urolithiasis

CONGENITAL CAUSES OF URETERIC OBSTRUCTION

Primary megaureter.
Ureterocele (ectopic and orthotopic).
Ureteric valve.
Distal ureteric stenosis.
Ureteric atresia.
Circumcaval ureter and variants.
Bladder diverticulum.

URETHRAL DISCHARGE AND DYSURIA

ICD-9CM #	788.7	Urethral Discharge
	599.9	Urethral Discharge, Bloody
	788.1	Dysuria
ICD-10CM #	R36.0	Urethral discharge without blood
	R36.9	Urethral discharge, unspecified
	N36.9	Urethral disorder, unspecified
	N39.9	Disorder of urinary system, unspecified
	R30.0	Dysuria
	R30.9	Painful micturition, unspecified

Urethritis (gonococcal, chlamydial, trichomonal).
Cystitis.
Prostatitis.
Vaginitis (candidiasis, chemical).
Meatal stenosis.
Interstitial cystitis.
Trauma (foreign body, masturbation, horseback or bike riding).

URETHRAL OBSTRUCTION, CHILDREN[16a]

ICD-9CM #	593.4	
ICD-10CM #	N13.8	Other obstructive and reflux uropathy

CAUSES OF URETHRAL OBSTRUCTION IN CHILDREN

Intrinsic Lesions
Valve (posterior, anterior, saccular diverticulum).
Stenosis, atresia.
Inflammatory stricture.
Traumatic stricture:
- External trauma (saddle injury, and so on).
- Iatrogenic trauma (catheter, cystoscopy, surgery).

Urethral "tumors":
- Girls: leiomyoma.
- Boys: polyp, rhabdomyosarcoma.

Miscellaneous (epidemolysis bullosa).

Extrinsic Lesions
Presacral mass dissecting inferiorly (tumor, cyst).
Fecal impaction (Hirschsprung's, postrepair anal atresia, habitual constipation, neuropathy).
Mass originating in genital organs:
- Boys: utricle cyst, prostate rhabdomyosarcoma, seminal vesicle cyst, Cowper's duct cyst.
- Girls: hydrometrocolpos, hydrocolpos, fused labia.

URIC ACID STONES

ICD-9CM #	792.9	
ICD-10CM #	N20.9	Urolithiasis

Hyperuricemia.
Excessive dietary purine.
Medications (salicylates, allopurinol, probenecid).
Urine pH <5.5 (e.g., diarrhea, high animal protein diet).
Decreased urine output (dehydration, malabsorption, diarrhea, inadequate fluid intake).
Tumor lysis.
Hemolytic anemia.
Myeloproliferative disorders.

URINARY INCONTINENCE, CHILDREN[22a]

ICD-9CM #	788.3	Urinary Incontinence
ICD-10CM #	R32	Unspecified urinary incontinence

CAUSES OF URINARY INCONTINENCE IN CHILDHOOD

Overactive bladder.
Infrequent voiding.
Detrusor-sphincter dyssynergia.
Non-neurogenic neurogenic bladder (Hinman syndrome).
Vaginal voiding.
Giggle incontinence.
Cystitis.
Bladder outlet obstruction (posterior urethral valves).
Ectopic ureter and fistula.
Sphincter abnormality (epispadias, exstrophy; urogenital sinus abnormality).
Neuropathic.
Overflow incontinence.
Traumatic.
Iatrogenic.
Behavioral.
Combination.

URINARY RETENTION[24a]

ICD-9CM #	788.20	
ICD-10CM #	R33.9	Retention of urine, unspecified

COMMON CAUSES OF URINARY RETENTION

Obstructive Cause
Urethral stricture.
Enlarged prostate.
Lower genitourinary tract malignancy.
Pelvic malignancy.
Bladder stones.
Foreign body.
Blood clot.
Posterior urethral valves.
Ureterocele.

Primary Detrusor Insufficiency
Detrusor areflexia.
Multiple sclerosis.
Iatrogenic injury during abdominal or back surgery.
Spinal cord injury.
Myelomeningocele.

URINARY RETENTION, ACUTE

ICD-9CM #	788.20	
ICD-10CM #	R33.9	Retention of urine, unspecified

Mechanical obstruction: urethral stone, foreign body, urethral stricture, BPH, prostate carcinoma, prostatitis, trauma with hematoma formation.
Neurogenic bladder.
Neurologic disease (MS, parkinsonism, tabes dorsalis, CVA).
Spinal cord injury.
CNS neoplasm (primary or metastatic).
Spinal anesthesia.
Lower urinary tract instrumentation.
Medications (antihistamines, antidepressants, narcotics, anticholinergics).
Abdominal or pelvic surgery.
Alcohol toxicity.
Pregnancy.
Anxiety.
Encephalitis.
Postoperative pain.
Spina bifida occulta.

URINARY TRACT OBSTRUCTION[14a]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	N21.8	Other lower urinary tract calculus
	N20.9	Urolithiasis

INTRARENAL

Uric acid nephropathy.
Sulfonamide precipitates.
Acyclovir, indinavir precipitates.
Multiple myeloma.

URETERAL

Intrinsic
Intraluminal.
- Nephrolithiasis.
- Papillary necrosis.
- Blood clots.
- Fungus balls.

Intramural.
- Ureteropelvic junction dysfunction.
- Ureterovesical junction dysfunction.
- Ureteral valve, polyp, or tumor.
- Ureteral stricture.
  - Schistosomiasis.
  - Tuberculosis.
  - Scarring from instrumentation.
  - Drugs (e.g., nonsteroidal anti-inflammatory agents [NSAIDs]).

Extrinsic
Vascular system.
- Aneurysm: abdominal aorta or iliac vessels.
- Aberrant vessels: ureteropelvic junction.
- Venous: retrocaval ureter.

Gastrointestinal tract.
- Crohn's disease.
- Diverticulitis.
- Appendiceal abscess.
- Colon cancer.
- Pancreatic tumor, abscess, or cyst.

Reproductive system.
- Uterus: pregnancy, prolapse, tumor, endometriosis.
- Ovary: abscess, tumor, ovarian remnants.
- Gartner's duct cyst, tubo-ovarian abscess.

Retroperitoneal disease.
- Retroperitoneal fibrosis: radiation, drugs, idiopathic.
- Inflammatory: tuberculosis, sarcoidosis.
- Hematoma.
- Primary tumor (e.g., lymphoma, sarcoma).
- Metastatic tumor (e.g., cervix, ovarian, bladder, colon).
- Lymphocele.
- Pelvic lipomatosis.

BLADDER

Neurogenic bladder.
- Diabetes mellitus.
- Spinal cord defect.
- Trauma.
- Multiple sclerosis.
- Stroke.
- Parkinson's disease.
- Spinal anesthesia.
- Anticholinergics.

Bladder neck dysfunction.
Bladder calculus.
Bladder cancer.

URETHRA

Urethral stricture.
Prostate hypertrophy or cancer.
Obstruction from instrumentation.

URINE CASTS

ICD-9CM #	791.7	
ICD-10CM #	R82.99	Other abnormal findings in urine

Normal finding.
Pyelonephritis.
Chronic renal disease.
Nephrotic syndrome.
Acute tubular necrosis.
Interstitial nephritis.
Nephritic syndrome.
Glomerulonephritis.
Eclampsia.
Heavy metal ingestion.
Allograft rejection.
Hypothyroidism.

URINE COLOR ABNORMALITIES[24a]

ICD-9CM #	791.9	
ICD-10CM #	R82.5	Elevated urine levels of drugs, medicaments and biological substances
	R82.99	Other abnormal findings in urine

COMMON CAUSES OF ABNORMAL URINE COLOR

Colorless

Disease
- Diabetes mellitus.
- Diabetes insipidus.

Drug
- Ethyl alcohol.
- Diuretics.

Miscellaneous
- Overhydration.

Yellow-orange

Drug
- Tetracycline.
- Flutamide.
- Pyridium.
- Azo Gantrisin (Roche Labs, Nutley, NJ).
- Sulfasalazine.
- Vitamin B.

Miscellaneous
- Dehydration.

Milky White

Disease
- Urinary tract infection/pyuria.

Blue-green

Disease
- *Pseudomonas* urinary tract infection.

Drug
- Methylene blue.
- Urised (Polymedica Pharmaceuticals, Woburn, MA).
- Indigo carmine.
- Doan's pills (Novartis Consumer Health, Parsippany, NJ).
- Clorets (Cadbury Adams, Parsippany, NJ).
- Amitriptyline.

Red-brown

Disease
- Hematuria.
- Hemolytic anemia.
- Hemoglobinuria.
- Lead poisoning.
- Mercury poisoning.
- Porphyria.

Drug
- Rifampin.
- Ex-Lax (Novartis Consumer Health, Parsippany, NJ).
- Phenolphthalein.
- Phenothiazines.
- Nitrofurantoin.
- Doxorubicin.

Miscellaneous
- Beets.
- Blackberries.
- Rhubarb.

Brown-black

DISEASE
- Fecaluria.
- Methemoglobinuria.
- Melaninuria.

DRUG
- Metronidazole.
- Methyldopa.
- Methocarbamol.

MISCELLANEOUS
- Fava beans.
- Aloe.

URINE, RED[29]

ICD-9CM #	varies with specific diagnosis	
ICD-10CM #	varies with specific diagnosis	

WITH A POSITIVE DIPSTICK

Hematuria.
Hemoglobinuria: negative urinalysis.
Myoglobinuria: negative urinalysis.

WITH A NEGATIVE DIPSTICK

Drugs
Aminosalicylic acid.
Deferoxamine mesylate.
Ibuprofen.
Phenacetin.
Phenolphthalein.
Phensuximide.
Rifampin.
Anthraquinone laxatives.
Doxorubicin.
Methyldopa.
Phenazopyridine.
Phenothiazine.
Phenytoin.

Dyes
Azo dyes.
Eosin.

Foods
Beets, berries, maize.
Rhodamine B.

Metabolic
Porphyrins.
Serratia marcescens (red diaper syndrome).
Urate crystalluria.

UROPATHY, OBSTRUCTIVE[36]

ICD-9CM #	599.6	
ICD-10CM #	N13.9	Obstructive and reflux uropathy, unspecified
	N20.9	Urolithiasis

INTRINSIC CAUSES

Intraluminal
Intratubular deposition of crystals (uric acid, sulfas).
Stones.
Papillary tissue.
Blood clots.

Intramural
Functional.
Ureter (ureteropelvic or ureterovesical dysfunction).
Bladder (neurogenic): spinal cord defect or trauma, diabetes, multiple sclerosis, Parkinson's disease, cerebrovascular accidents.
Bladder neck dysfunction.

Anatomic
Tumors.

Infection, granuloma.
Strictures.

EXTRINSIC CAUSES

Originating in the Reproductive System
Prostate: benign hypertrophy or cancer.
Uterus: pregnancy, tumors, prolapse, endometriosis.
Ovary: abscess, tumor, cysts.
Originating in the Vascular System
Aneurysms (aorta, iliac vessels).
Aberrant arteries (ureteropelvic junction).
Venous (ovarian veins, retrocaval ureter).
Originating in the Gastrointestinal Tract
Crohn's disease.
Pancreatitis.
Appendicitis.
Tumors.
Originating in the Retroperitoneal Space
Inflammations.
Fibrosis.
Tumor, hematomas.

UROSEPSIS[24a]

ICD-9CM #	995.91	
ICD-10CM #	A41.9	Sepsis, unspecified organism

COMMON CAUSES OF UROSEPSIS

Obstructing ureteral stone with pyonephrosis.
Staghorn calculus with urinary tract infection.
Ureteral obstruction with proximal urinary tract infection.
Urinary retention with urinary tract infection.
Acute prostatitis with prostatic abscess.
Perinephric abscess or renal carbuncle.
Urethral stricture with periurethral abscess.
Fournier gangrene.
Foreign body within urinary tract (e.g., Foley catheter).

UTERINE BLEEDING, ABNORMAL[12]

ICD-9CM #	626.9	
ICD-10CM #	N92.6	Irregular menstruation, unspecified
	N93.9	Abnormal uterine and vaginal bleeding, unspecified

PREGNANCY

Threatened abortion.
Incomplete abortion.
Complete abortion.
Molar pregnancy.
Ectopic pregnancy.
Retained products of conception.

OVULATORY

Vulva: infection, laceration, tumor.
Vagina: infection, laceration, tumor, foreign body.
Cervix: polyps, cervical erosion, cervicitis, carcinoma.
Uterus: fibroids (submucous fibroids most likely to cause abnormal bleeding), polyps, adenomyosis, endometritis, intrauterine device, atrophic endometrium.
Pregnancy complications: ectopic pregnancy; threatened, incomplete, complete abortion; retained products of conception.
Abnormality of clotting system.
Midcycle bleeding.
Halban's disease (persistent corpus luteum).
Menorrhagia.
Pelvic inflammatory disease.

ANOVULATORY

Physiologic causes:
- Puberty.
- Perimenopausal.

Pathologic causes:
- Ovarian failure (FSH over 40 IU/ml).
- Hyperandrogenism.
- Hyperprolactinemia.
- Obesity.
- Hypothalamic dysfunction (polycystic ovaries); LH/FSH ratio greater than 2:1.
- Hyperplasia.
- Endometrial carcinoma.
- Estrogen-producing tumors.
- Hypothyroidism.

UVEITIS, PEDIATRIC AGE

ICD-9CM #	364.3	
ICD-10CM #	H20.9	Anterior uveitis

ANTERIOR UVEITIS

Juvenile rheumatoid arthritis (pauciarticular).
Sarcoidosis.
Trauma.
Tuberculosis.
Kawasaki disease.
Ulcerative colitis.
Postinfectious (enteric or genital) with arthritis and rash.
Spirochetal (syphilis, leptospiral).
Heterochromic iridocyclitis (Fuchs).
Viral (herpes simplex, herpes zoster).
Ankylosing spondylitis.
Stevens-Johnson syndrome.
Idiopathic.
Drugs.

POSTERIOR UVEITIS (CHOROIDITIS—MAY INVOLVE RETINA)

Toxoplasmosis.
Parasites (toxocariasis).
Sarcoidosis.
Tuberculosis.
Viral (rubella, herpes simplex, HIV, cytomegalovirus).
Subacute sclerosing panencephalitis.
Idiopathic.

ANTERIOR AND/OR POSTERIOR UVEITIS

Sympathetic ophthalmia (trauma to other eye).
Vogt-Koyanagi-Harada syndrome (uveo-otocutaneous syndrome: poliosis, vitiligo, deafness, tinnitus, uveitis, aseptic meningitis, retinitis).
Behçet syndrome.
Lyme disease.

VAGINAL BLEEDING, PREGNANCY[7]

ICD-9CM #	626.6	Irregular Vaginal Bleeding
ICD-10CM #	N93.9	Abnormal uterine and vaginal bleeding, unspecified

FIRST TRIMESTER

Implantation bleeding.
Abortion.
- Threatened.
- Complete.
- Incomplete.
- Missed.

Ectopic pregnancy.
Neoplasia.
Hydatidiform mole.
Cervix.

THIRD TRIMESTER

Placenta previa.
Placental abruption.
Premature labor.
Choriocarcinoma.

VAGINAL DISCHARGE, PREPUBERTAL GIRLS[19]

ICD-9CM #	623.5	Vaginal Discharge
ICD-10CM #	N89.8	Other specified noninflammatory disorders of vagina

Irritative (bubble baths, sand).
Poor perineal hygiene.
Foreign body.
Associated systemic illness (group A streptococci, chickenpox).
Infections.
Escherichia coli with foreign body.
Shigella organisms.
Yersinia organisms.
Infections (consider sexual abuse).
- *Chlamydia trachomatis.*
- *Neisseria gonorrhoeae.*
- *Trichomonas vaginalis.*

Tumor (rare).

VALVULAR HEART DISEASE[1a]

ICD-9CM #	varies with specific diagnosis
ICD-10CM #	varies with specific diagnosis

MAJOR CAUSES OF VALVULAR HEART DISEASE IN ADULTS

Aortic Stenosis
Bicuspid aortic valve.
Rheumatic fever.
Degenerative stenosis.
Aortic Regurgitation
Bicuspid aortic valve.
Aortic dissection.
Endocarditis.
Rheumatic fever.

Aortic root dilation.
Mitral Stenosis
Rheumatic fever.
Mitral Regurgitation

Chronic

Mitral valve prolapse.
Left ventricular dilation.
Posterior wall myocardial infarction.
Rheumatic fever.
Endocarditis.

Acute

Posterior wall or papillary muscle ischemia.
Papillary muscle or chordal rupture.
Endocarditis.
Prosthetic valve dysfunction.
Systolic anterior motion of mitral valve.

TRICUSPID REGURGITATION

Functional (annular) dilation.
Tricuspid valve prolapse.
Endocarditis.
Carcinoid heart disease.

VASCULITIS, CLASSIFICATION[26]

ICD-9CM # 447.6
ICD-10CM # I77.6 Arteritis, unspecified

LARGE VESSEL DISEASE

Arteritis
Giant cell arteritis.
Takayasu's arteritis.
Arteritis associated with Reiter's syndrome (reactive arthritis), ankylosing spondylitis.

MEDIUM AND SMALL VESSEL DISEASE

Polyarteritis Nodosa
Primary (idiopathic).
Associated with viruses (hepatitis B or C, CMV, HIV, herpes zoster).
Associated with malignancy (hairy cell leukemia).
Familial Mediterranean fever.
Granulomatous Vasculitis
Granulomatosis with polyangiitis (Wegener's granulomatosis).
Lymphomatoid granulomatosis.
Behçet's Disease
Kawasaki Disease (Mucocutaneous Lymph Node Syndrome)

PREDOMINANTLY SMALL VESSEL DISEASE

Hypersensitivity Vasculitis (Leukocytoclastic Vasculitis)
Henoch-Schönlein purpura.
Mixed cryoglobulinemia.
Serum sickness.
Vasculitis associated with connective tissue diseases (SLE, Sjögren's syndrome).
Vasculitis associated with specific syndromes:
Primary biliary cirrhosis.
Lyme disease.
Chronic active hepatitis.
Drug-induced vasculitis.
Churg-Strauss Syndrome
Goodpasture's Syndrome
Erythema Nodosum
Panniculitis
Buerger's Disease (Thrombophlebitis Obliterans)

VASCULITIS (DISEASES THAT MIMIC VASCULITIS)[28]

ICD-9CM # varies with specific disease
ICD-10CM # varies with specific diagnosis

EMBOLIC DISEASE

Infectious or marantic endocarditis.
Cardiac mural thrombus.
Atrial myxoma.
Cholesterol embolization syndrome.

NONINFLAMMATORY VESSEL WALL DISRUPTION

Atherosclerosis.
Arterial fibromuscular dysplasia.
Drug effects (vasoconstrictors, anticoagulants).
Radiation.
Genetic disease (neurofibromatosis, Ehlers-Danlos syndrome).
Amyloidosis.
Intravascular malignant lymphoma.

DIFFUSE COAGULATION

Disseminated intravascular coagulation.
Thrombotic thrombocytopenic purpura.
Hemolytic-uremic syndrome.
Protein C and S deficiencies, factor V/Leiden mutation.
Antiphospholipid syndrome.

VEGETATIVE STATE, PERSISTENT[1a]

ICD-9CM # 780.03
ICD-10CM # R40.3 Persistent vegetative state

PERSISTENT VEGETATIVE STATE: COMMON CAUSES*

Trauma (diffuse axonal injury).
Cardiac arrest and hypoperfusion (laminar necrosis of cortical mantle and/or thalamic necrosis).
Bihemispheric infarctions.
Purulent meningitis or encephalitis (cortical injury).
Carbon monoxide.
Prolonged hypoglycemic coma.

*A vegetative state may not necessarily begin with coma but can also develop as the end stage of neurodegenerative diseases (e.g., Alzheimer's disease) of adults or children and can accompany severe congenital developmental abnormalities of the brain such as anencephaly.

VENTILATION–PERFUSION MISMATCH ON LUNG SCAN

ICD-9CM # varies with specific disorder
ICD-10CM # varies with specific diagnosis

Pulmonary embolism.
Emphysema.
Irradiation.
Pulmonary hypertension.
AV malformations.
Pulmonary thrombosis.
External compression of pulmonary artery (neoplasm, cysts, fibrosing mediastinitis).
Vasculitis.
Tuberculosis.
Pulmonary thrombosis.
Congenital (pulmonary artery hypoplasia, congenital heart disease with upper lobe diversion).
Sequestered segment.
Parasitic lung disease.
Intraluminal obstruction from catheter fragments.

VENTRICULAR FAILURE

ICD-9CM # 429.9 Ventricular Dysfunction
ICD-10CM # I51.9 Heart disease, unspecified

LEFT VENTRICULAR FAILURE

Systemic hypertension.
Valvular heart disease (AS, AR, MR).
Cardiomyopathy, myocarditis.
Bacterial endocarditis.
Myocardial infarction.
Idiopathic hypertrophic subaortic stenosis.

RIGHT VENTRICULAR FAILURE

Valvular heart disease (mitral stenosis).
Pulmonary hypertension.
Bacterial endocarditis (right-sided).
Right ventricular infarction.

BIVENTRICULAR FAILURE

Left ventricular failure.
Cardiomyopathy.
Myocarditis
Arrhythmias.
Anemia.
Thyrotoxicosis.
Arteriovenous fistula.
Paget's disease.
Beriberi.

VERRUCOUS LESIONS

ICD-9CM # varies with specific disorder
ICD-10CM # varies with specific diagnosis

Warts.
Seborrheic keratosis.
Lichen simplex.
Acanthosis nigricans.
Scabies (Norwegian, crusted).
Verrucous carcinoma.
Nevus sebaceous.
Deep fungal infection.

VERTIGO

ICD-9CM #	780.4	Vertigo NOS
	386.11	Benign Paroxysmal Positional
	386.2	Central Origin
	386.10	Peripheral
	386.12	Vestibular (Neuronitis)
ICD-10CM #	R42	Dizziness and giddiness
	H81.13	Benign paroxysmal vertigo, bilateral
	H81.49	Vertigo of central origin, unspecified ear
	H81.399	Other peripheral vertigo, unspecified ear
	H81.23	Vestibular neuronitis, bilateral

PERIPHERAL

Otitis media.
Acute labyrinthitis.
Vestibular neuronitis.
Benign positional vertigo.
Meniere's disease.
Ototoxic drugs: streptomycin, gentamicin.
Lesions of the eighth nerve: acoustic neuroma, meningioma, mononeuropathy, metastatic carcinoma.
Mastoiditis.

CNS OR SYSTEMIC

Vertebrobasilar artery insufficiency.
Posterior fossa tumor or other brain tumors.
Infarction/hemorrhage of cerebral cortex, cerebellum, or brain stem.
Basilar migraine.
Metabolic: drugs, hypoxia, anemia, fever.
Hypotension/severe hypertension.
Multiple sclerosis.
CNS infections: viral, bacterial.
Temporal lobe epilepsy.
Arnold–Chiari malformation, syringobulbia.
Psychogenic: ventilation, hysteria.

VERTIGO, CENTRAL[1]

ICD-9CM #	780.4	
ICD-10CM #	R42	

MAJOR CAUSES OF CENTRAL VERTIGO

Demyelination.
- Acquired.
- Leukodystrophies.
- Multiple sclerosis.

Familial disorders.
- Friedreich ataxia.
- Spinocerebellar ataxia.
- Familial episodic ataxia (type 1 and type 2).
- Olivopontocerebellar atrophy.

Central nervous system infections.
- Lyme neuroborreliosis.
- Meningitis.
- Tuberculosis.

Intrinsic brainstem lesion.
- Tumor.
- Arteriovenous malformation.
- Trauma.

Migraine.
- Basilar.
- Benign paroxysmal positional vertigo of childhood.

Toxins.
- Drugs, alcohol.
- Analgesics.
- Anticonvulsants.
- Antihypertensives.
- Hypnotics.
- Tranquilizers.

Metabolic and endocrine disorders.
- Hyperinsulinism.
- Impaired glucose tolerance.
- Diabetes mellitus.
- Hypertriglyceridemia.
- Hypothyroidism.

Systemic conditions.
- Paget disease.

Stroke/ischemia.
- Vertebrobasilar.
- Cerebellar.
- Posterior inferior cerebellar artery syndrome.
- Lateral medullary syndrome.
- Medial medullary infarct.
- Basilar artery syndrome.
- Anterior inferior cerebellar artery.

Other causes of posterior ischemia.
- Subclavian steal syndrome.
- Rotational vertebral artery occlusion syndrome.
- Vertebral artery dissection.
- Vertebral or basilar artery dolichoectasia.
- Neoplasm of the fourth ventricle.
- Chiari malformation.

Superficial siderosis of the central nervous system.
Vestibular epilepsy.

VESICULOBULLOUS DISEASES[14]

ICD-9CM #	709.8	
ICD-10CM #	L94.2	Calcinosis cutis
	L98.8	Other specified disorders of the skin and subcutaneous tissue

IMMUNOLOGICALLY MEDIATED DISEASES

Bullous pemphigoid.
Herpes gestationis.
Mucous membrane pemphigoid.
Epidermolysis bullosa acquisita.
Dermatitis herpetiformis.
Pemphigus (vulgaris, foliaceus, paraneoplastic).

HYPERSENSITIVITY DISEASES

Erythema multiforme minor.
Erythema multiforme major (Stevens-Johnson syndrome).
Toxic epidermal necrolysis.

METABOLIC DISEASES

Porphyria cutanea tarda.
Pseudoporphyria.
Diabetic blisters.

INHERITED GENETIC DISORDERS

Epidermolysis bullosa.
Simplex.
Junctional.
Dystrophic.

INFECTIOUS DISEASES

Impetigo.
Staphylococcal scalded skin syndrome.
Herpes simplex.
Varicella.
Herpes zoster.

VISION LOSS, ACUTE, PAINFUL

ICD-9CM #	368.11	Vision Loss, Sudden
ICD-10CM #	H53.139	Sudden visual loss, unspecified eye

Acute angle-closure glaucoma.
Corneal ulcer.
Uveitis.
Endophthalmitis.
Factitious.
Somatization syndrome.
Trauma.

VISION LOSS, ACUTE, PAINLESS

ICD-9CM #	368.11	Vision Loss, Sudden
ICD-10CM #	H53.139	Sudden visual loss, unspecified eye

Retinal artery occlusion.
Optic neuritis.
Retinal vein occlusion.
Vitreous hemorrhage.
Retinal detachment.
Exudative macular degeneration.
CVA.
Ischemic optic neuropathy.
Factitious.
Somatization syndrome, anxiety reaction.

VISION LOSS AFTER DIVING[1b]

ICD-9CM #	368.11
ICD-10CM #	H53.139

DIFFERENTIAL DIAGNOSIS OF DECREASED VISION AFTER DIVING

Decompression sickness.
Arterial gas embolism.
Bubbles under contact lenses.
Displaced contact lens.
Antifog agent keratopathy.
Contact lens adherence syndrome.
Transdermal scopolamine
Hyperoxic myopia.
Oxymetazoline optic neuropathy.
Diving-induced migraine phenomena.
Eye disorders not related to diving.

VISION LOSS, CHILDREN

ICD-9CM #	368.9	
ICD-10CM #	H53.9	Unspecified visual disturbance

Craniopharyngioma.
Hereditary optic atrophy.
Optic nerve glioma.
Glioma of chiasm.
Albinism.
Optic nerve hypoplasia.

VISION LOSS, CHRONIC, PROGRESSIVE

ICD-9CM #	369.9	Vision Loss NOS
ICD-10CM #	H54.7	Unspecified visual loss

Cataract.
Macular degeneration.
Cerebral neoplasm.
Refractive error.
Open-angle glaucoma.

VISION LOSS, MONOCULAR, TRANSIENT

ICD-9CM #	369.9	
ICD-10CM #	H54.7	Unspecified visual loss

Thromboembolism.
Vasculitis.
Migraine (vasospasm).
Anxiety reaction.
CNS tumor.
Temporal arteritis.
Multiple sclerosis.

VITREOUS HEMORRHAGE[20a]

ICD-9CM #	379.23	Vitreous Hemorrhage
ICD-10CM #	H43.13	Vitreous hemorrhage, bilateral

CAUSES OF VITREOUS HEMORRHAGE

Acute posterior vitreous detachment associated either with a retinal tear or avulsion of a peripheral vessel.
Proliferative retinopathies.
- Diabetic.
- Following retinal vein occlusion.
- Sickle cell disease.
- Eales disease.
- Vasculitis.

Miscellaneous retinal disorders.
- Macroaneurysm.
- Telangiectasis.
- Capillary hemangioma.

Trauma.
- Blunt.
- Penetrating.
- Iatrogenic.

Systemic.
- Bleeding disorders.
- Terson syndrome.

VOCAL CORD PARALYSIS

ICD-9CM #	478.30	Unspecified
	478.31	Unilateral Partial
	478.32	Unilateral Complete
	478.33	Bilateral Partial
	478.34	Bilateral Complete
ICD-10CM #	J38.00	Paralysis of vocal cords and larynx, unspecified
	J38.01	Paralysis of vocal cords and larynx, unilateral
	J38.02	Paralysis of vocal cords and larynx, bilateral

Neoplasm: primary or metastatic (e.g., lung, thyroid, parathyroid, mediastinum).
Neck surgery (parathyroid, thyroid, carotid endarterectomy, cervical spine).
Idiopathic.
Viral, bacterial, or fungal infection.
Trauma (intubation, penetrating neck injury).
Cardiac surgery.
RA.
Multiple sclerosis.
Parkinsonism.
Toxic neuropathy.
CVA.
CNS abnormalities: hydrocephalus, Arnold–Chiari malformation, meningomyelocele.

VOLUME DEPLETION[1a]

ICD-9CM #	276.5	
ICD-10CM #	E86.9	Volume depletion, unspecified

GI losses:
  Upper: bleeding, nasogastric suction, vomiting.
  Lower: bleeding, diarrhea, enteric or pancreatic fistula, tube drainage.
Renal losses:
  Salt and water: diuretics, osmotic diuresis, postobstructive diuresis, acute tubular necrosis (recovery phase), salt-losing nephropathy, adrenal insufficiency, renal tubular acidosis.
Water loss: diabetes insipidus.
Skin and respiratory losses:
  Sweat, burns, insensible losses.
Sequestration without external fluid loss:
  Intestinal obstruction, peritonitis, pancreatitis, rhabdomyolysis, internal bleeding.

VOLUME EXCESS[1a]

ICD-9CM #	varies with specific diagnosis
ICD-10CM #	varies with specific diagnosis

PRIMARY RENAL SODIUM RETENTION (INCREASED EFFECTIVE CIRCULATING VOLUME)

Renal failure, nephritic syndrome, acute glomerulonephritis.
Primary hyperaldosteronism.
Cushing's syndrome.
Liver disease.

SECONDARY RENAL SODIUM RETENTION (DECREASED EFFECTIVE CIRCULATING VOLUME)

Heart failure.
Liver disease.
Nephrotic syndrome (minimal change disease).
Pregnancy.

VOMITING

ICD-9CM #	787.03	
ICD-10CM #	R11.10	Vomiting, unspecified
	R11.11	Vomiting without nausea
	R11.12	Projectile vomiting

GI disturbances:
  Obstruction: esophageal, pyloric, intestinal.
  Infections: viral or bacterial enteritis, viral hepatitis, food poisoning, gastroenteritis.
  Pancreatitis.
  Appendicitis.
  Biliary colic.
  Peritonitis.
  Perforated bowel.
  Diabetic gastroparesis.
Other: gastritis, PUD, IBD, GI tract neoplasms.
Drugs: morphine, digitalis, cytotoxic agents, bromocriptine.
Severe pain: MI, renal colic.
Metabolic disorders: uremia, acidosis/alkalosis, hyperglycemia, DKA, thyrotoxicosis.
Trauma: blows to the testicles, epigastrium.
Vertigo.
Reye's syndrome.
Increased intracranial pressure.
CNS disturbances: trauma, hemorrhage, infarction, neoplasm, infection, hypertensive encephalopathy, migraine.
Radiation sickness.
Nausea and vomiting of pregnancy, hyperemesis gravidarum.
Motion sickness.
Bulimia, anorexia nervosa.
Psychogenic: emotional disturbances, offensive sights or smells.
Severe coughing.
Pyelonephritis.
Boerhaave's syndrome.
Carbon monoxide poisoning.

VOMITING, NEONATAL[1]

ICD-9CM #	787.03
ICD-10CM #	R11.10

CAUSES OF NEONATAL VOMITING

Anatomic Causes

Esophagus, trachea, great vessels:
- Stricture.
- Web.
- Tracheoesophageal fistula.
- Laryngeal cleft.
- Double aortic arch.

Stomach and duodenum:
- Pyloric stenosis.
- Duodenal atresia (usually noted on the first day of life)

Small and large intestine:
- Volvulus secondary to malrotation.
- Incarcerated hernia.
- Hirschsprung disease (secondary to obstipation).
- Necrotizing enterocolitis.

Genitourinary:
- Testicular torsion.

Nonanatomic Causes

Infection:
- Septicemia.
- Meningitis.
- Urinary tract infection.
- Gastroenteritis.
- Otitis media

Increased intracranial pressure:
- Cerebral edema.
- Subdural hematoma.
- Hydrocephalus.
- Brain tumor.

Congenital adrenal hyperplasia (salt-losing variety).
Inborn errors of metabolism.
Renal disease.

VULVAR LESIONS[12]

ICD-9CM #	625.8	Vulvar Mass
	098.0	Vulvar Ulcer, Gonococcal
	091.0	Vulvar Ulcer, Syphilitic
	616.51	Behçet's
	624.0	Leukoplakia
	624.8	Dysplasia
	233.3	Carcinoma
	616.9	Inflammatory Lesion
	624.4	Vulvar Scar (Old)
	624.1	Vulvar Atrophy
ICD-10CM #	N77.0	Ulceration of vulva in diseases classified elsewhere
	N90.7	Vulvar cyst
	N90.89	Other specified noninflammatory disorders of vulva and perineum
	D07.1	Carcinoma in situ of vulva
	N90.89	Other specified noninflammatory disorders of vulva and perineum
	N90.5	Atrophy of vulva

RED LESION

Infection/Infestation

Fungal infection:
- *Candida.*
- *Tinea cruris.*
- Intertrigo.
- *Pityriasis versicolor.*

Sarcoptes scabiei.
Erythrasma: *Corynebacterium minutissimum.*
Granuloma inguinale: Calymmatobacterium granulomatis.
Folliculitis: *Staphylococcus aureus.*
Hidradenitis suppurativa.
Behçet's syndrome.

Inflammation

Reactive vulvitis.
Chemical irritation:
- Detergent.
- Dyes.
- Perfume.
- Spermicide.
- Lubricants.
- Hygiene sprays.
- *Podophyllum.*
- Topical 5-FU.
- Saliva.
- Gentian violet.
- Semen.

Mechanical trauma: scratching.
Vestibular adenitis.
Essential vulvodynia.
Psoriasis.
Seborrheic dermatitis.

Neoplasm

Vulvar intraepithelial neoplasia (VIN):
- Mild dysplasia.
- Moderate dysplasia.
- Severe dysplasia.
- Carcinoma-in-situ.

Vulvar dystrophy.
Bowen's disease.
Invasive cancer:
- Squamous cell carcinoma.
- Malignant melanoma.
- Sarcoma.
- Basal cell carcinoma.
- Adenocarcinoma.
- Paget's disease.
- Undifferentiated.

WHITE LESION

Vulvar dystrophy:
- Lichen sclerosus.
- Vulvar dystrophy.
- Vulvar hyperplasia.
- Mixed dystrophy.

VIN.
Vitiligo.
Partial albinism.
Intertrigo.
Radiation treatment.

DARK LESION

Lentigo.
Nevi (mole).
Neoplasm (see "Neoplasm, Vulvar," below).
Reactive hyperpigmentation.
Seborrheic keratosis.
Pubic lice.

ULCERATIVE LESION

Infection

Herpes simplex.
Vaccinia.
Treponema pallidum.
Granuloma inguinale.
Pyoderma.
Tuberculosis.

Noninfectious

Behçet's disease.
Crohn's disease.
Pemphigus.
Pemphigoid.
Hidradenitis suppurativa (see "Neoplasm, Vulvar," below).

Neoplasm

Basal cell carcinoma.
Squamous cell carcinoma.
Vulvar tumor <1 cm:
- Condyloma acuminatum.
- Molluscum contagiosum.
- Epidermal inclusion.
- Vestibular cyst.
- Mesonephric duct.
- VIN.
- Hemangioma.
- Hidradenoma.
- Neurofibroma.
- Syringoma.
- Accessory breast tissue.
- Acrochordon.
- Endometriosis.
- Fox-Fordyce disease.
- Pilonidal sinus.

Vulvar tumor >1 cm:
- Bartholin cyst or abscess.
- Lymphogranuloma venereum.
- Fibroma.
- Lipoma.
- Verrucous carcinoma.
- Squamous cell carcinoma.
- Hernia.
- Edema.
- Hematoma.
- Acrochordon.
- Epidermal cysts.
- Neurofibromatosis.
- Accessory breast tissue.

WEAKNESS, ACUTE, EMERGENT[26]

ICD-9CM #	780.7	
ICD-10CM #	M62.81	Muscle weakness (generalized)

Demyelinating disorders (Guillain-Barré, chronic inflammatory demyelinating polyneuropathy [CIDP]).
Myasthenia gravis.
Infectious (poliomyelitis, diphtheria).
Toxic (botulism, tick paralysis, paralytic shellfish toxin, puffer fish, newts).
Metabolic (acquired or familial hypokalemia, hypophosphatemia, hypermagnesemia).
Metal poisoning (arsenic, thallium).
Porphyria.

WEAKNESS, GRADUAL ONSET

ICD-9CM #	780.7	
ICD-10CM #	M62.81	Muscle weakness (generalized)

Depression.
Malingering.
Anemia.
Hypothyroidism.
Medications (e.g., sedatives, antidepressants, narcotics).
CHF.
Renal failure.

Liver failure.
Respiratory insufficiency.
Alcoholism.
Nutritional deficiencies.
Disorders of motor unit.
Basal ganglia disorders.
Upper motor neuron lesions.

WEAKNESS, NONNEUROMUSCULAR CAUSES

ICD-9CM #	780.79	
ICD-10CM #	G93.3	Postviral fatigue syndrome
	R53.1	Weakness
	R53.81	Other malaise
	R53.83	Other fatigue

Anxiety disorder.
Infectious process.
Anemia.
Renal insufficiency.
Hyperventilation.
Malignancy.
Hypothyroidism.
Hypotension.
Hypercapnia.
Hypoglycemia.
Cardiac arrhythmias.
Hepatic insufficiency.
Electrolyte imbalance.
Malnutrition.
Cerebrovascular insufficiency.

WEIGHT GAIN

ICD-9CM #	783.1	Abnormal Weight Gain
	278.00	Obesity
ICD-10CM #	R63.5	Abnormal weight gain
	E66.9	Obesity, unspecified

Sedentary lifestyle.
Fluid overload.
Discontinuation of tobacco abuse.
Endocrine disorders (hypothyroidism, hyperinsulinism associated with maturity-onset DM, Cushing's syndrome, hypogonadism, insulinoma, hyperprolactinemia, acromegaly).
Medications (nutritional supplements, oral contraceptives, glucocorticoids, etc.).
Anxiety disorders with compulsive eating.
Laurence-Moon-Biedl syndrome, Prader-Willi syndrome, other congenital diseases.
Hypothalamic injury (rare; <100 cases reported in medical literature).

WEIGHT LOSS

ICD-9CM #	783.2	Abnormal Weight Loss
ICD-10CM #	R63.4	Abnormal weight loss

Malignancy.
Psychiatric disorders (depression, anorexia nervosa).
New-onset DM.
Malabsorption.
COPD.
AIDS.
Uremia, liver disease.
Thyrotoxicosis, pheochromocytoma, carcinoid syndrome.
Addison's disease.
Intestinal parasites.
Peptic ulcer disease.
Inflammatory bowel disease.
Food faddism.
Postgastrectomy syndrome.

WHEEZING

ICD-9CM #	786.09	
ICD-10CM #	R06.2	Wheezing

Asthma.
COPD.
Interstitial lung disease.
Infections (pneumonia, bronchitis, bronchiolitis, epiglottitis).
Cardiac asthma.
GERD with aspiration.
Foreign body aspiration.
Pulmonary embolism.
Anaphylaxis.
Obstruction of airway (neoplasm, goiter, edema or hemorrhage from trauma, aneurysm, congenital abnormalities, strictures, spasm).
Carcinoid syndrome.

WHEEZING, PEDIATRIC AGE[4]

ICD-9CM #	786.09	Wheezing
ICD-10CM #	R06.2	Wheezing

Reactive airways disease.
Atopic asthma.
Infection-associated airway reactivity.
Exercise-induced asthma.
Salicylate-induced asthma and nasal polyposis.
Asthmatic bronchitis.
Other hypersensitivity reactions:
- Hypersensitivity pneumonitis.
- Tropical eosinophilia.
- Visceral larva migrans.
- Allergic bronchopulmonary aspergillosis.

Aspiration:
- Foreign body.
- Food, saliva, gastric contents.
- Laryngotracheoesophageal cleft.
- Tracheoesophageal fistula, H-type.
- Pharyngeal incoordination or neuromuscular weakness.

Cystic fibrosis.
Primary ciliary dyskinesia.
Cardiac failure.
Bronchiolitis obliterans.
Extrinsic compression of airways:
- Vascular ring.
- Enlarged lymph node.
- Mediastinal tumor.
- Lung cysts.

Tracheobronchomalacia.
Endobronchial masses.
Gastroesophageal reflux.
Pulmonary hemosiderosis.
Sequelae of bronchopulmonary dysplasia.
"Hysterical" glottic closure.
Cigarette smoke, other environmental insults.

WRIST AND HAND PAIN, IN DIFFERENT AGE GROUPS[8]

ICD-9CM #	959.3	
ICD-10CM #	S69.80XA	Other specified injuries of unspecified wrist, hand and finger(s), initial encounter
	S69.90XA	Unspecified injury of unspecified wrist, hand and finger(s), initial encounter

COMMON CAUSES OF WRIST AND HAND PAIN IN DIFFERENT AGE GROUPS

CHILDHOOD (2-10 YR)
Intraarticular:
Infection.
Periarticular:
Fracture.
Osteomyelitis.

ADOLESCENCE (10-18 YR)
Intraarticular:
Infection.
Periarticular:
Trauma.
Osteomyelitis.
Tumors.
Ganglion.
Idiopathic wrist pain.

EARLY ADULTHOOD (18-30 YR)
Intraarticular:
Inflammatory arthritis.
Infection.
Osteoarthritis.
Periarticular:
Peripheral nerve entrapment.
Tendonitis.
Referred:
Cervical.

ADULTHOOD (30-50 YR)
Intraarticular:
Inflammatory arthritis.
Infection.
Osteoarthritis.
Periarticular:
Peripheral nerve entrapment.
Tendonitis.
Referred:
Cervical.
Chest.
Cardiac.

OLD AGE (>50 YR)
Intraarticular:
Inflammatory arthritis.
Osteoarthritis.
Periarticular:
Peripheral nerve entrapment.
Tendonitis.
Referred:
Cervical.
Chest.
Cardiac.

WRIST PAIN

ICD-9CM #	959.3	
ICD-10CM #	S69.80XA	Other specified injuries of unspecified wrist, hand and finger(s), initial encounter
	S69.90XA	Unspecified injury of unspecified wrist, hand and finger(s), initial encounter

MECHANICAL

Osteoarthritis.
Ligament tear.
Fracture.
Ganglion.
De Quervain's tenosynovitis.
Avascular necrosis (scaphoid, lunate).
Nonunion of scaphoid or lunate.
Neoplasm.

METABOLIC

Pregnancy.
Diabetes.
Gout.
Pseudogout.
Paget's disease.
Acromegaly.
Hypothyroidism.
Hyperparathyroidism.

INFECTIOUS

Osteomyelitis.
Septic arthritis.
Cat-scratch disease.
Tick bite (Lyme disease, babesiosis).
Tuberculosis.

NEUROLOGIC

Peripheral neuropathy.
Nerve injury (median, ulnar, radial nerve).
Thoracic outlet compression syndrome.
Distal posterior interosseous nerve syndrome.

RHEUMATOLOGIC

Psoriasis.
RA.
SLE, mixed connective tissue disorder (MCTD).
Scleroderma.

MISCELLANEOUS

Granulomatous (sarcoidosis).
Amyloidosis.
Multiple myeloma.
Leukemia.

XEROPHTHALMIA[28]

ICD-9CM #	372.53	Xerophthalmia
ICD-10CM #	H11.149	Conjunctival xerosis, unspecified, unspecified eye

MEDICATIONS

Tricyclic antidepressants: amitriptyline (Elavil), doxepin (Sinequan).
Antihistamines: diphenhydramine (Benadryl), chlorpheniramine (Chlor-Trimeton), promethazine (Phenergan), and many cold and decongestant preparations.
Anticholinergic agents: antiemetics such as scopolamine, antispasmodic agents such as oxybutynin chloride (Ditropan).

ABNORMALITIES OF EYELID FUNCTION

Neuromuscular disorders.
Aging.
Thyrotoxicosis.

ABNORMALITIES OF TEAR PRODUCTION

Hypovitaminosis A.
Stevens-Johnson syndrome.
Familial diseases affecting sebaceous secretions.

ABNORMALITIES OF CORNEAL SURFACES

Scarring from past injuries and herpes simplex infection.

XEROSTOMIA[28]

ICD-9CM #	527.7	
ICD-10CM #	K11.7	Disturbances of salivary secretion
	R68.2	Dry mouth, unspecified

MEDICATIONS

Tricyclic antidepressants: amitriptyline (Elavil), doxepin (Sinequan).
Antihistamines: diphenhydramine (Benadryl), chlorpheniramine (Chlor-Trimeton), promethazine (Phenergan), and many cold and decongestant preparations.
Anticholinergic agents: antiemetics such as scopolamine, antispasmodic agents such as oxybutynin chloride (Ditropan).

DEHYDRATION

Debility.
Fever.

POLYURIA

Alcohol intake.
Arrhythmia.
Diabetes.

PREVIOUS HEAD AND NECK IRRADIATION SYSTEMIC DISEASES

Sjögren's syndrome.
Sarcoidosis.
Amyloidosis.
Human immunodeficiency virus (HIV) infection.
Graft-versus-host disease.

YELLOW URINE

ICD-9CM #	788.69	
ICD-10CM #	R82	Other abnormal findings in urine

Normal coloration.
Concentrated urine.
Use of multivitamin supplements.
Diet rich in carrots.
Use of Cascara.
Urinary tract infection

REFERENCES

1. Adams JG, et al.: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.
1a. Andreoli TE: *Cecil essentials of medicine*, ed 5, Philadelphia, 2001, Saunders.
1b. Auerbach P: *Wilderness medicine*, Philadelphia, 2012, Saunders.
1c. Ballinger A: *Kumar & Clark's essentials of clinical medicine*, ed 6, Edinburgh, 2012, Saunders.
2. Barkin RM, Rosen P: *Emergency pediatrics: a guide to ambulatory care*, ed 5, St Louis, 1998, Mosby.
3. Baude AI: *Infectious diseases and medical microbiology*, ed 2, Philadelphia, 1986, Saunders.
4. Behrman RE: *Nelson textbook of pediatrics*, ed 16, Philadelphia, 2000, Saunders.
4a. Bonow RO, et al.: *Braunwauld's heart disease*, ed 9, Philadelphia, 2012, Elsevier.
5. Callen JP: *Color atlas of dermatology*, ed 2, Philadelphia, 2000, WB Saunders.
5a. Cameron JL, Cameron AM: *Current surgical therapy*, ed 10, Philadelphia, 2011, Saunders.
6. Canoso J: *Rheumatology in primary care*, Philadelphia, 1997, Saunders.
7. Carlson KJ: *Primary care of women*, ed 2, St Louis, 2000, Mosby.
8. Carr A, Hamilton W: *Orthopedics in primary care*, ed 2, Philadelphia, 2005, Saunders.
9. Conn R: *Current diagnosis*, ed 9, Philadelphia, 1997, Saunders.
10. Copeland LJ: *Textbook of gynecology*, ed 2, Philadelphia, 2000, Saunders.
11. Custer JW, Rau RE: *The Harriet Lane handbook*, ed 18, St Louis, 2009, Mosby.
12. Danakas G: *Practical guide to the care of the gynecologic/obstetric patient*, St Louis, 1997, Mosby.
12a. Firestein GS, Budd RC, Gabriel SE, et al.: *Kelly's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.
12b. Floege J, et al.: *Comprehensive clinical nephrology*, ed 4, Philadelphia, 2010, Saunders.
12c. Fuhrman BP, et al.: *Pediatric critical care*, ed 4, Philadelphia, 2011, Saunders.
12d. Gabbe SG: *Obstetrics*, ed 6, Philadelphia, 2012, Saunders.
13. Goldberg RJ: *The care of the psychiatric patient*, ed 3, St Louis, 2006, Mosby.
14. Goldman L, Ausiello D: *Cecil textbook of medicine*, ed 21, Philadelphia, 2004, Saunders.
14a. Goldman L, Schafer AI: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Saunders.
15. Goldman L, Braunwald E: *Braunwauld Primary cardiology*, Philadelphia, 1998, Saunders.
16. Gorbach SL: *Infectious diseases*, ed 2, Philadelphia, 1998, Saunders.
16a. Grainger RG, Allison D: *Grainger & Allison's diagnostic radiology, a textbook of medical imaging*, ed 4, London, 2001, Churchill Livingstone.
17. Harrington J: *Consultation in internal medicine*, ed 2, St Louis, 1997, Mosby.
18. Henry JB: *Clinical diagnosis and management by laboratory methods*, ed 20, Philadelphia, 2001, Saunders.

References

18b. Hochberg MC, et al.: *Rheumatology*, ed 5, St. Louis, 2011, Mosby.

18c. Hoffman R: *Hematology, basic principles and practice*, ed 6, Philadelphia, 2013, Saunders.

19. Hoekelman R: *Primary pediatric care*, ed 3, St Louis, 1997, Mosby.

20. Hoffmann R, et al.: *Hematology: basic principles and practice*, ed 5, Philadelphia, 2009, Churchill Livingstone.

20a. Kanski JJ, Bowling B: *Clinical ophthalmology, a systematic approach*, ed 7, Philadelphia, 2011, Saunders.

21. Kassirer J: *Current therapy in adult medicine*, ed 4, St Louis, 1998, Mosby.

22. Khan MG: *Rapid ECG interpretation*, Philadelphia, 2003, Saunders.

22a. Kliegman RM, et al.: *Nelson textbook of pediatrics*, ed 19, Philadelphia, 2011, Saunders.

23. Kliegman R: *Practical strategies in pediatric diagnosis and therapy*, Philadelphia, 1996, Saunders.

24. Kassirer J: *Practical rheumatology*, London, 1995, Mosby.

24a. Lipshultz LI, Khera M, Atwal DT: *Urology and the primary care practitioner*, ed 3, Philadelphia, 2008, Elsevier.

25. Melmed S, Polonsky KS, Larsen PR: *H.M. Kronenberg: Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.

25a. Mahanty S, Nutman TB: Eosinophilia and eosinophil-related disorders. In Middleton EJ, Reed CE, Ellis EF, et al, editors: *Allergy: Principles and practice*, ed 4, St Louis, 1993, Mosby-Year Book, p 1077.

25b. Mandell GL: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases*, ed 6, New York, 2005, Churchill Livingstone.

26. Marx J: *Rosen's emergency medicine: concepts and clinical practice*, ed 5, St Louis, 2002, Mosby.

26a. Mason RJ: *Murray & Nadel's Textbook of Respiratory Medicine*, ed 5, Philadelphia, 2010, Saunders.

26b. Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.

27. Moore WT, Eastman RC: *Diagnostic endocrinology*, ed 2, St Louis, 1996, Mosby.

28. Noble J: *Primary care medicine*, ed 3, St Louis, 2001, Mosby.

29. Nseyo UO: *Urology for primary care physicians*, Philadelphia, 1999, Saunders.

30. Palay D: *Ophthalmology for the primary care physician*, St Louis, 1997, Mosby.

31. Rakel RE: *Principles of family practice*, ed 6, Philadelphia, 2002, Saunders.

32. Schwarz MI: *Interstitial lung disease*, ed 2, St Louis, 1993, Mosby.

33. Seller RH: *Differential diagnosis of common complaints*, ed 4, Philadelphia, 2000, Saunders.

34. Siedel HM: *Mosby's guide to physical examination*, ed 4, St Louis, 1999, Mosby.

34a. Souhami RL, Moxham J: *Textbook of medicine*, ed 4, London, 2002, Churchill Livingstone.

35. Specht N: *Practical guide to diagnostic imaging*, St Louis, 1998, Mosby.

36. Stein JH: *Internal medicine*, ed 5, St Louis, 1998, Mosby.

37. Swain R, Snodgrass JG: Managing groin pain, *Phys Sportmed* 23:56, 1995.

38. Talley NJ, Martin CJ: *Clinical gastroenterology*, ed 2, Sydney, 2006, Churchill Livingstone.

38a. Tschudy MM, Arcara KM: *The Harriet Lane handbook*, ed 19, Philadelphia, 2012, Mosby.

38b. Vincent JL, et al.: *Textbook of critical care*, ed 6, Philadelphia, 2011, Saunders.

39. Weinberg SE, et al.: *Principles of pulmonary medicine*, ed 5, Philadelphia, 2008, Saunders.

40. Wiederholt WC: *Neurology for non-neurologists*, ed 4, Philadelphia, 2000, Saunders.

41. Wilson JD: *Williams textbook of endocrinology*, ed 9, Philadelphia, 1998, Saunders.

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SECTION III

Clinical Algorithms

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PLEASE NOTE: These algorithms are designed to assist clinicians in the evaluation and treatment of patients. They may not apply to all patients with a particular disorder and are not intended to replace the clinician's individual judgment.

Additional algorithms available at www.expertconsult.com

Adrenal Incidentaloma (Fig. E3-6)
Anemia in Newborn (Fig. E3-13)
Anemia with Reticulocytosis (Fig. E3-16)
Aspiration, Gastric Contents (Fig. E3-23)
Aspiration, Oral Contents (Fig. E3-24)
Bleeding Disorder, Congenital (Fig. E3-28)
Bleeding, Early Pregnancy (Fig. E3-30)
Bleeding, Neonate (Fig. E3-32)
Bradycardia, Pediatric Patient (Fig. E3-37)
Breast, Radiologic Evaluation (Fig. E3-39)
Breastfeeding Difficulties (Fig. E3-41)
Bullae on Lower Extremities (Fig. E3-42)
Cardiomyopathy, Ischemic (Fig. E3-45)
Convulsive Disorder, Suspected, Pediatric Age (Fig. E3-51)
Corneal Disorders (Fig. E3-52)
Cutaneous Microvascular Occlusion Syndromes (Fig. E3-54, Tables E3-4 and E3-5)
Cystitis, Acute (Fig. E3-56)
Dehydration Correction, Pediatric Patient (Fig. E3-57, Tables E3-6 to E3-9)
Dementia, Management (Fig. E3-58, Table E3-10)
Developmental Delay (Fig. E3-59)
Diarrhea, Chronic, in Patients with HIV Infection (Fig. E3-62, Table E3-11)
Diarrhea, Watery (Fig. E3-63)
Eosinophilic Dermatoses (Fig. E3-71)
Fever and Infection in High-Risk Hematology Patient without Obvious Source (Fig. E3-76)
Fever and Neutropenia, Pediatric Patient (Fig. E3-78)
Flushing (Fig. E3-79)
Fracture, Bone (Fig. E3-81)
Genitalia, Ambiguous (Fig. E3-83)
GI Bleeding, Pediatric Patient (Fig. E3-84)
Goiter Evaluation and Management (Fig. E3-86)
Hematochezia, Management (Fig. E3-89)
Hematuria, Pediatric Patient (Fig. E3-91)
Intubation, Pediatric Patient (Fig. E3-114, Table E3-19)
Ischemia, Colon Management (Fig. E3-115)
Knee Dislocation Treatment (Fig. E3-120)
Liver Mass, Solid (Fig. E3-124)
Lymphadenopathy, Axillary (Fig. E3-126)
Lymphadenopathy, Cervical (Fig. E3-127)
Lymphadenopathy, Epitrochlear (Fig. E3-128)
Lymphadenopathy, Inguinal (Fig. E3-130)
Myocardial Ischemia, Suspected (Fig. E3-139)
Myositis (Fig. E3-140)
Nail Dystrophy (Fig. E3-141)
Nutrition Assessment and Intervention in Cancer Patients (Fig. E3-144)
Nutritional Support (Fig. E3-145, Box E3-5)
Onycholysis (Fig. E3-151)
Pancreatic Islet Cell Tumors (Fig. E3-153)
Papulosquamous Disorders, Pediatric Patient (Fig. E3-155)
Pericardial Effusion, Malignant (Fig. E3-159)
Photosensitivity (Fig. E3-161)
Pleural Effusion, Malignant (Fig. E3-163)
Polycythemia (Fig. E3-168)
Pruritus, Pregnant Patient (Fig. E3-171)
Pseudohermaphroditism (Fig. E3-172)
Reactive Erythema, Pediatric Patient (Fig. E3-175)
Renal Disease, Ischemic, Management (Fig. E3-177)
Rhinorrhea (Fig. E3-180)
Sexual Dysfunction Evaluation (Fig. E3-182)
Sexual Precocity, Female Breast Development (Fig. E3-183)
Sexual Precocity, Female Pubic Hair Development (Fig. E3-184, Table E3-28)
Sexual Precocity, Male (Fig. E3-185, Table E3-29)
Shin Splints (Fig. E3-186)
Short Stature (Fig. E3-188)
Skin Blisters (Fig. E3-190, Table E3-30)
Spine Tumor (Fig. E3-192)
Spondylosis, Cervical (Fig. E3-196)
Stroke (Fig. E3-197)
Subcutaneous Ossification, Evaluation (Fig. E3-198)
Tachycardia, Pediatric Patient (Fig. E3-201)
Thrombotic Microangiopathies, Differential Diagnosis (Fig. E3-204)
Unconscious Patient (Fig. E3-209)
Vaginal Prolapse (Fig. E3-212)

ICD-9CM # 789.61
ICD-10CM # R10.1 Abdominal pain, upper abdomen

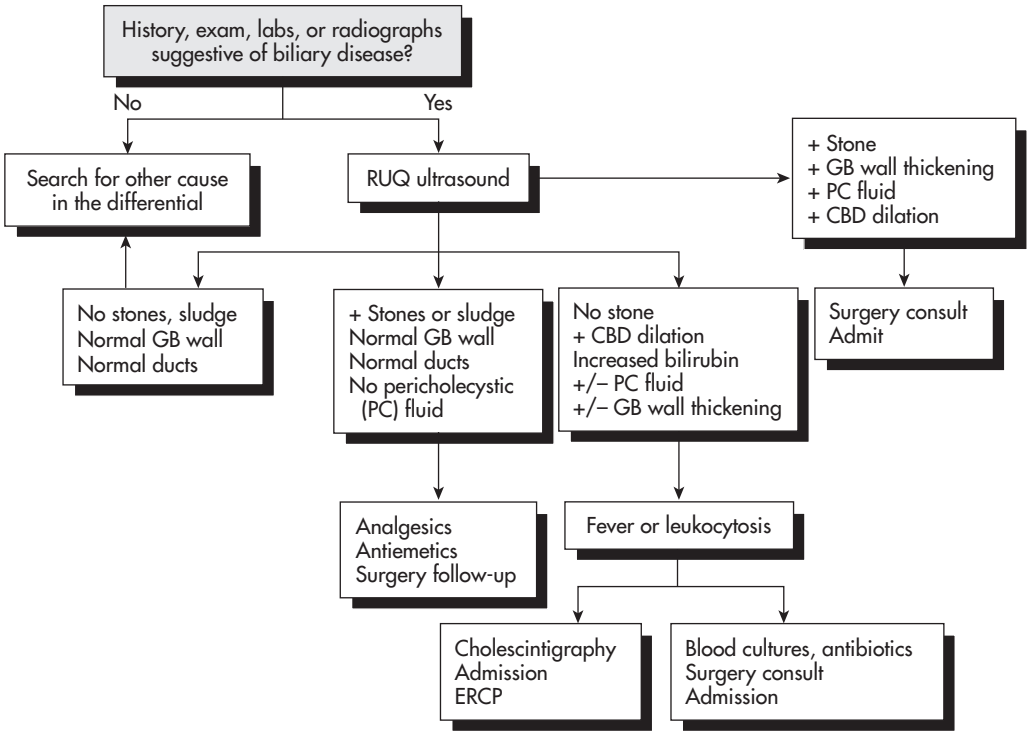


FIGURE 3-1 Treatment algorithm for right upper quadrant (RUQ) pain. *CBD*, Common bile duct; *ERCP*, endoscopic retrograde cholangiopancreatography; *GB*, gallbladder; *RUQ*, right upper quadrant; +, with; –, without; ±, with or without. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

ICD-9CM # 276.2 Lactic acidosis
276.2 Metabolic acidosis
276.2 Respiratory acidosis
276.3 Respiratory alkalosis
276.3 Metabolic alkalosis
ICD-10CM # E87.2 Acidosis
E87.3 Alkalosis

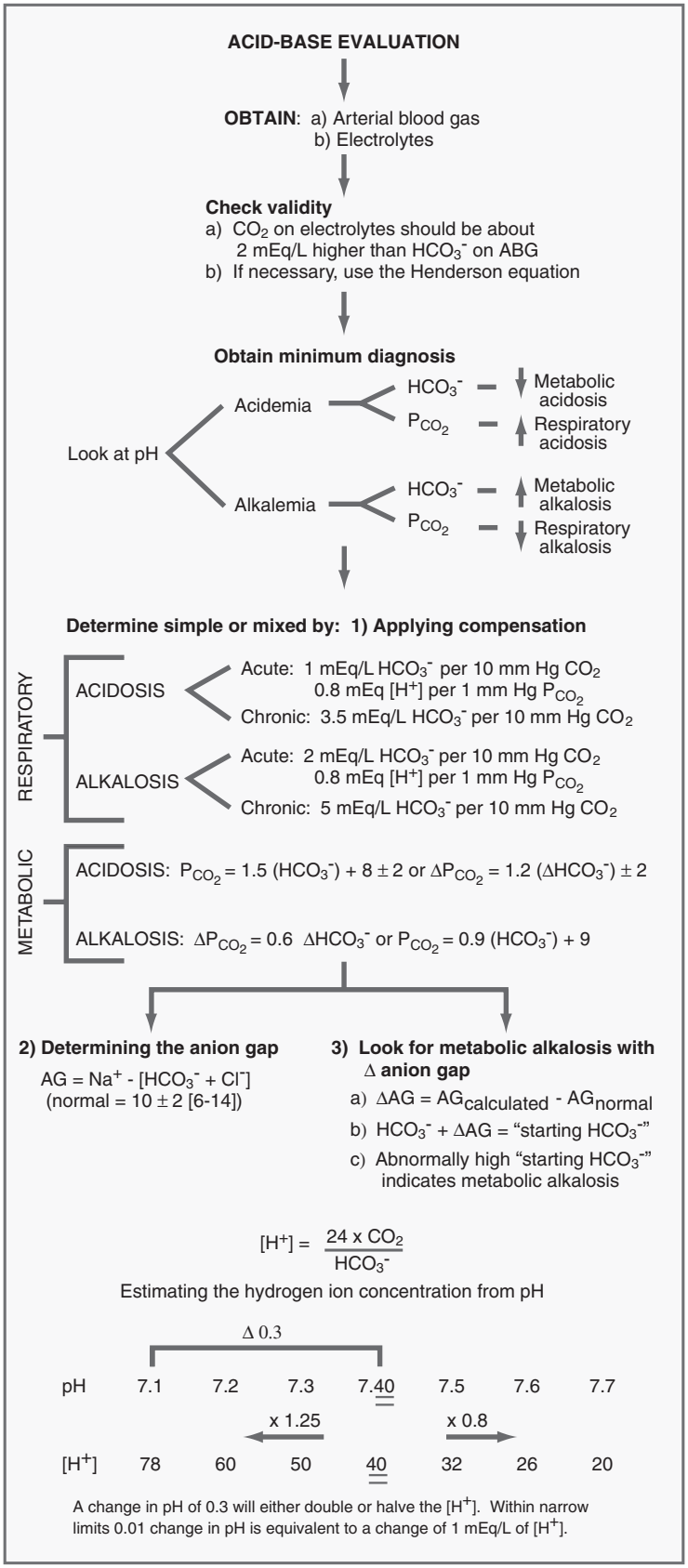


FIGURE 3-2 Scheme for assessing acid-base homeostasis. (Modified from Andreoli TE [ed]: *Cecil essentials of medicine,* ed 7, Philadelphia, 2008, Saunders.)

Continued on next page

ICD-9CM # 276.2 Lactic acidosis
276.2 Metabolic acidosis
276.2 Respiratory acidosis
276.3 Respiratory alkalosis
276.3 Metabolic alkalosis
ICD-10CM # E87.2 Acidosis
E87.3 Alkalosis

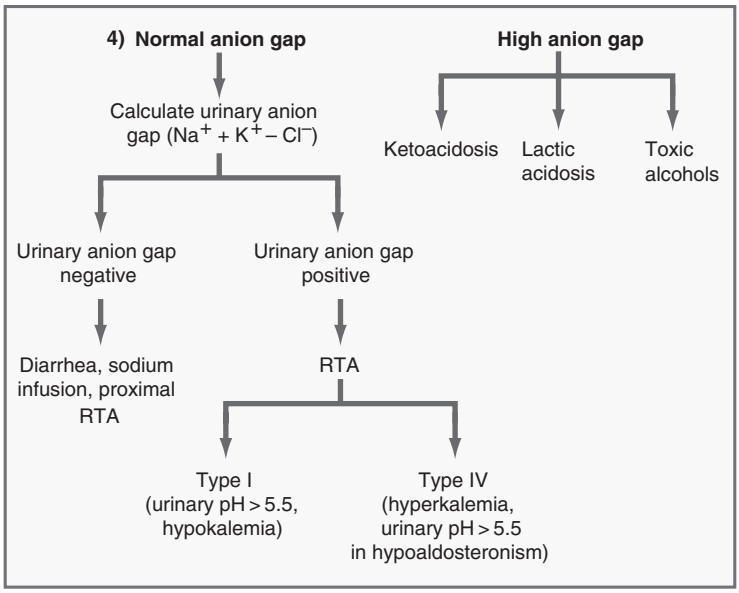


FIGURE 3-2 (Continued)

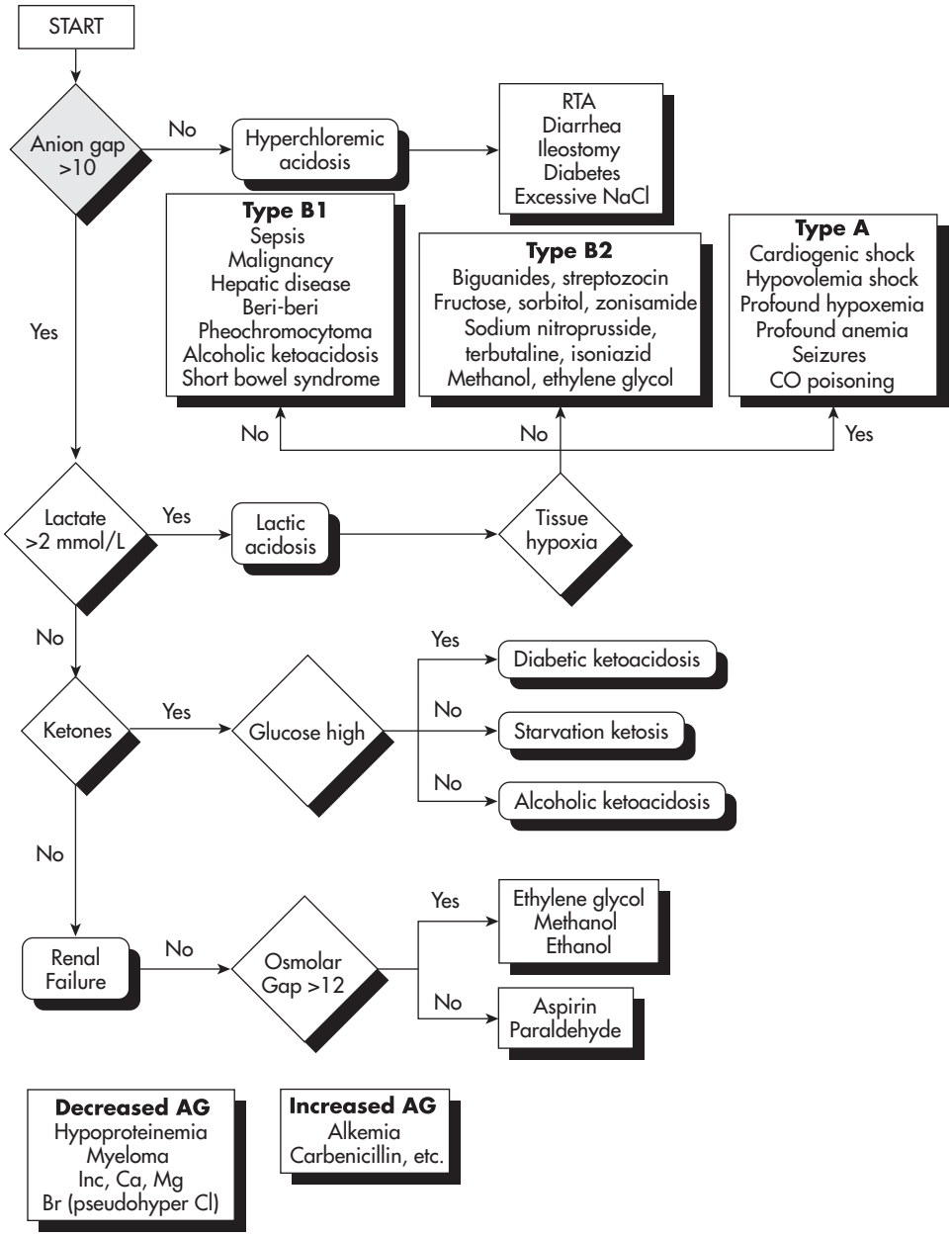


FIGURE 3-3 Diagnostic approach to metabolic acidosis. (Modified from Vincent JL, Ahraham E, Moore FA, et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, Saunders.)

ACIDOSIS, RESPIRATORY, ACUTE

ICD-9CM # 276.2
ICD-10CM # E87.2 Acidosis

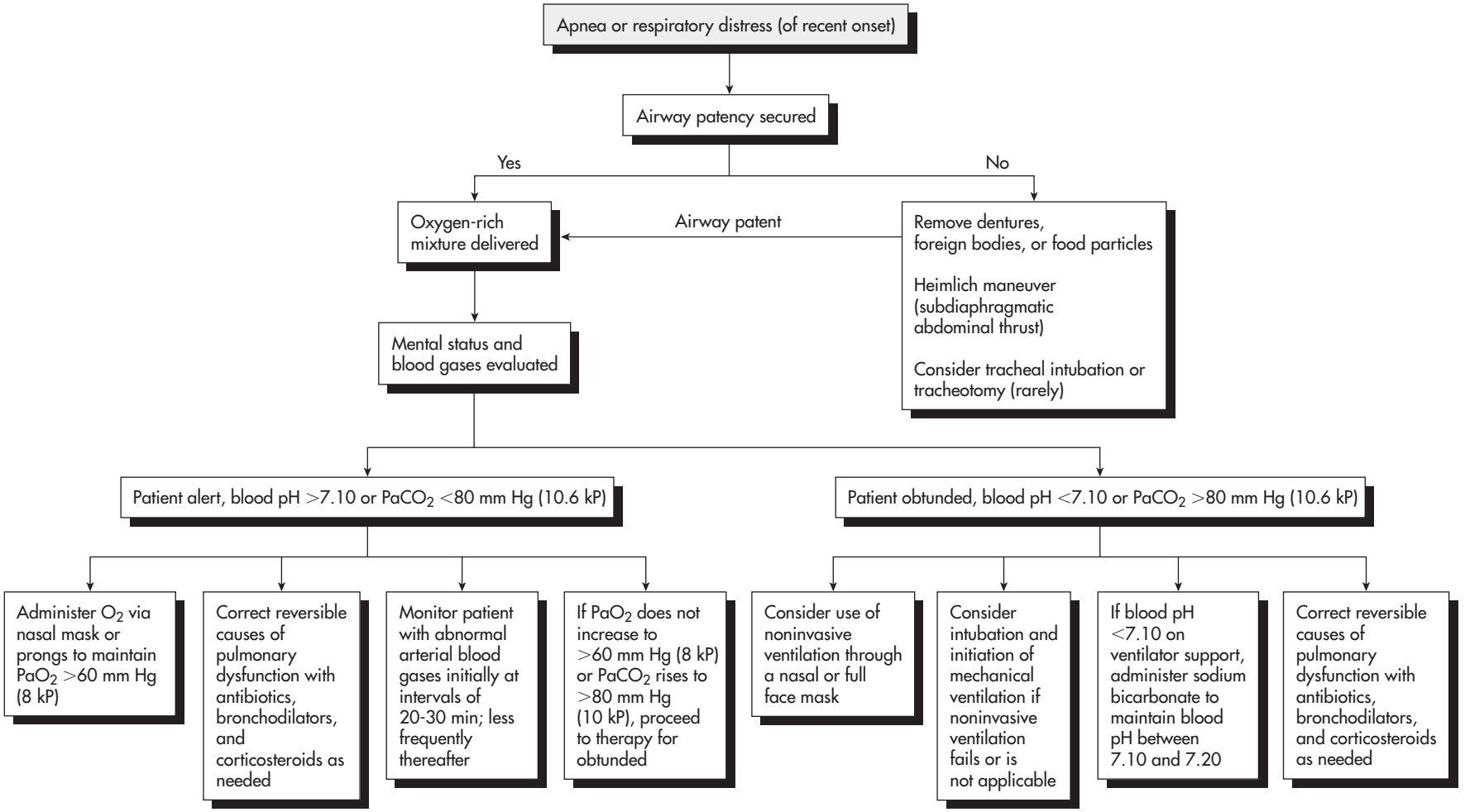


FIGURE 3-4 Algorithm for management of acute respiratory acidosis. (From Feehally J, Floege J, Johnson RJ [eds]: *Comprehensive clinical nephrology,* ed 3, St Louis, 2007, Mosby.)

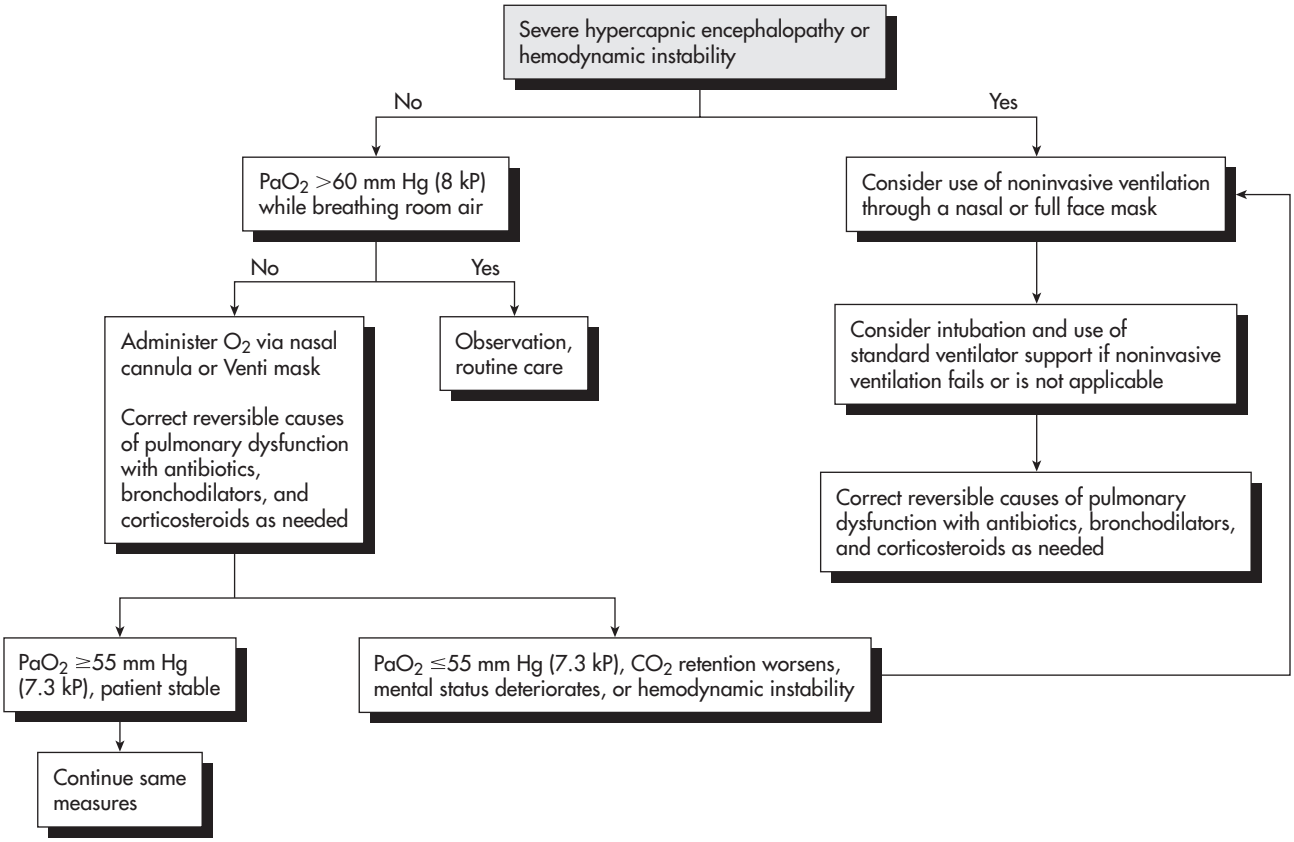


FIGURE 3-5 Algorithm for management of chronic respiratory acidosis. (From Feehally J, Floege J, Johnson RJ [eds]: *Comprehensive clinical nephrology,* ed 3, St Louis, 2007, Mosby.)

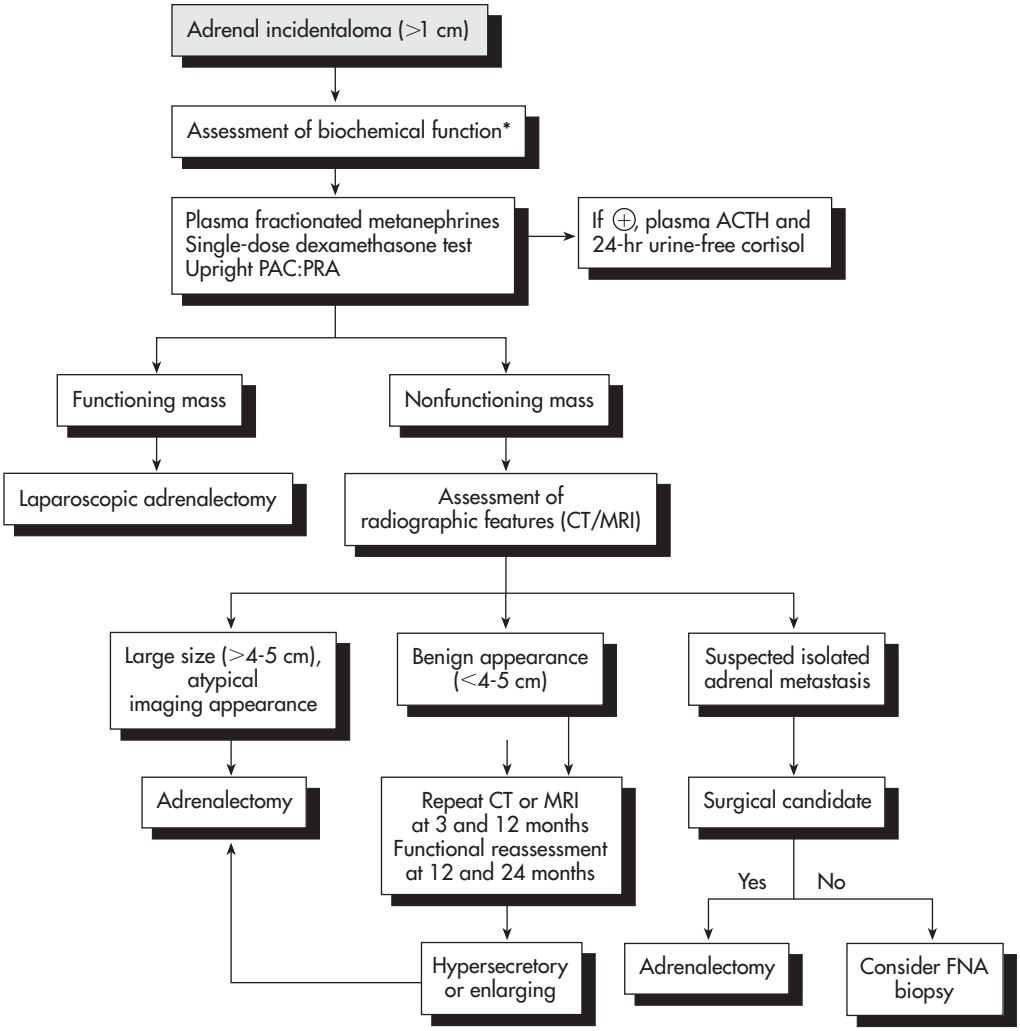


FIGURE E3-6 Algorithm for evaluation of an adrenal incidentaloma. Evaluation and management algorithm for an incidental adrenal mass. The asterisk indicates details are in text (see section I, Aldosteronism, Primary). Screening for hyperaldosteronism is done only if the patient is hypertensive or hypokalemic. *ACTH,* Adrenocorticotropic hormone; *CT,* computed tomography; *FNA,* fine-needle aspiration; *MRI,* magnetic resonance imaging; *PAC:PRA,* plasma aldosterone concentration to plasma renin activity ratio. (Modified from Townsend CM et al [eds]: *Sabiston textbook of surgery,* ed 17, Philadelphia, 2004, Saunders.)

ICD-9CM # 194.0 Adrenal cortical carcinoma site NOS M8370/3
255.8 Adrenal hyperplasia
ICD-10CM # C74.90 Malignant neoplasm of unspecified part of unspecified adrenal gland
E27.8 Other specified disorders of adrenal gland

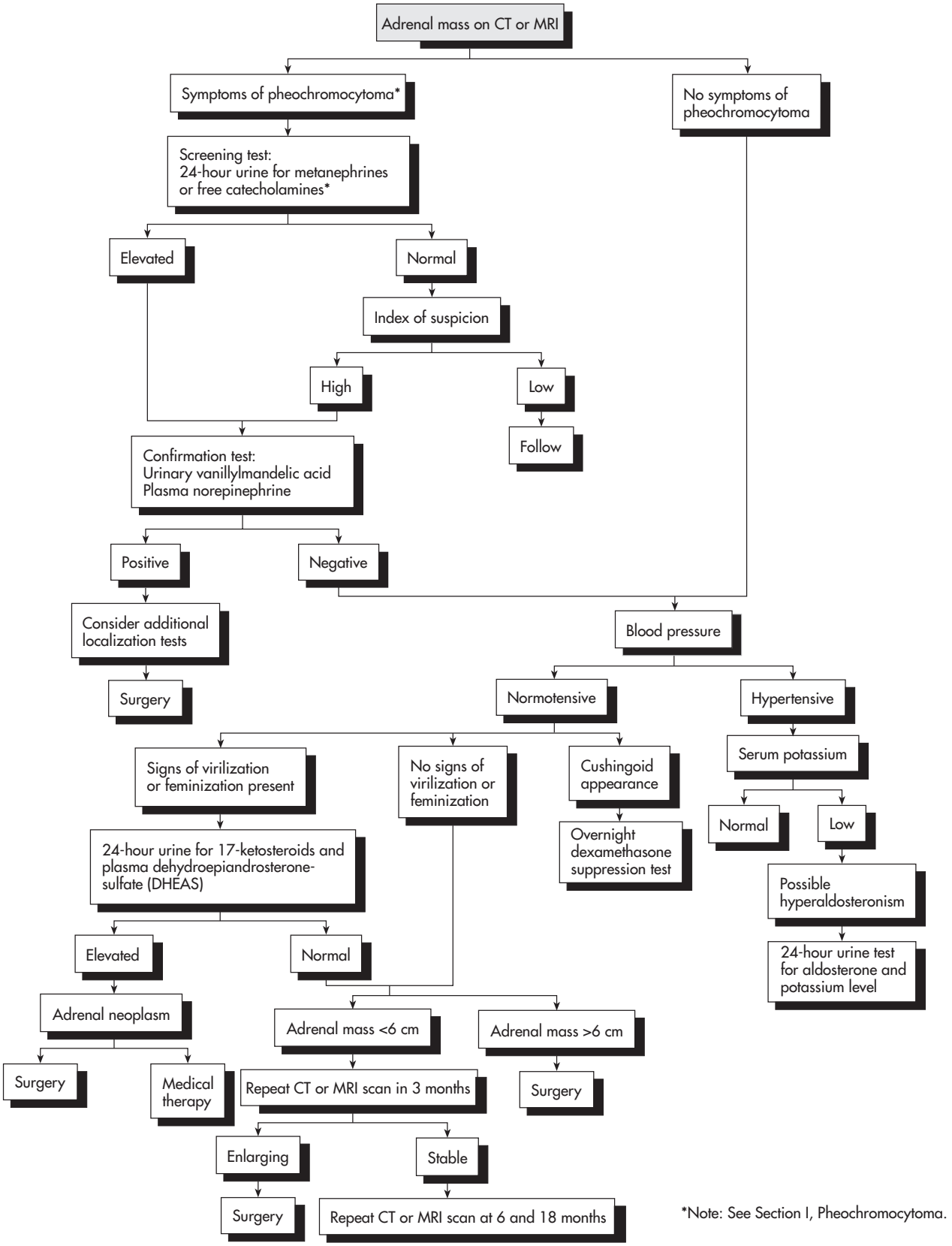


FIGURE 3-7 Evaluation of adrenal mass. *CT,* Computed tomography; *MRI,* magnetic resonance imaging. (Modified from Greene HL, Johnson WP, Lemcke D [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

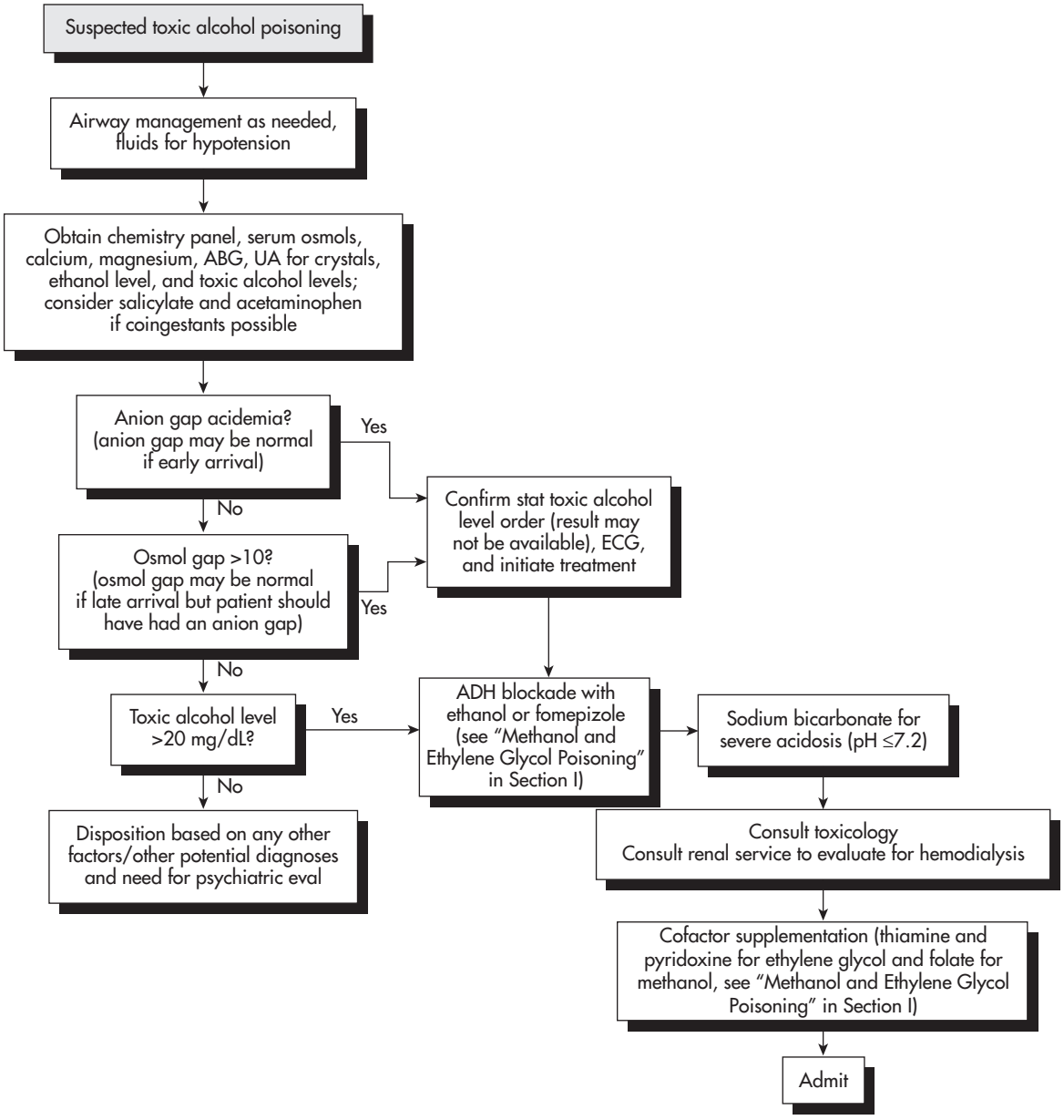


FIGURE 3-8 Treatment algorithm for toxic alcohol poisoning. *ABG*, arterial blood gas measurements; *ADH*, alcohol dehydrogenase; *ECG*, electrocardiography; *UA*, urinalysis. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

ICD-9CM # 276.3
ICD-10CM # E87.3 Alkalosis

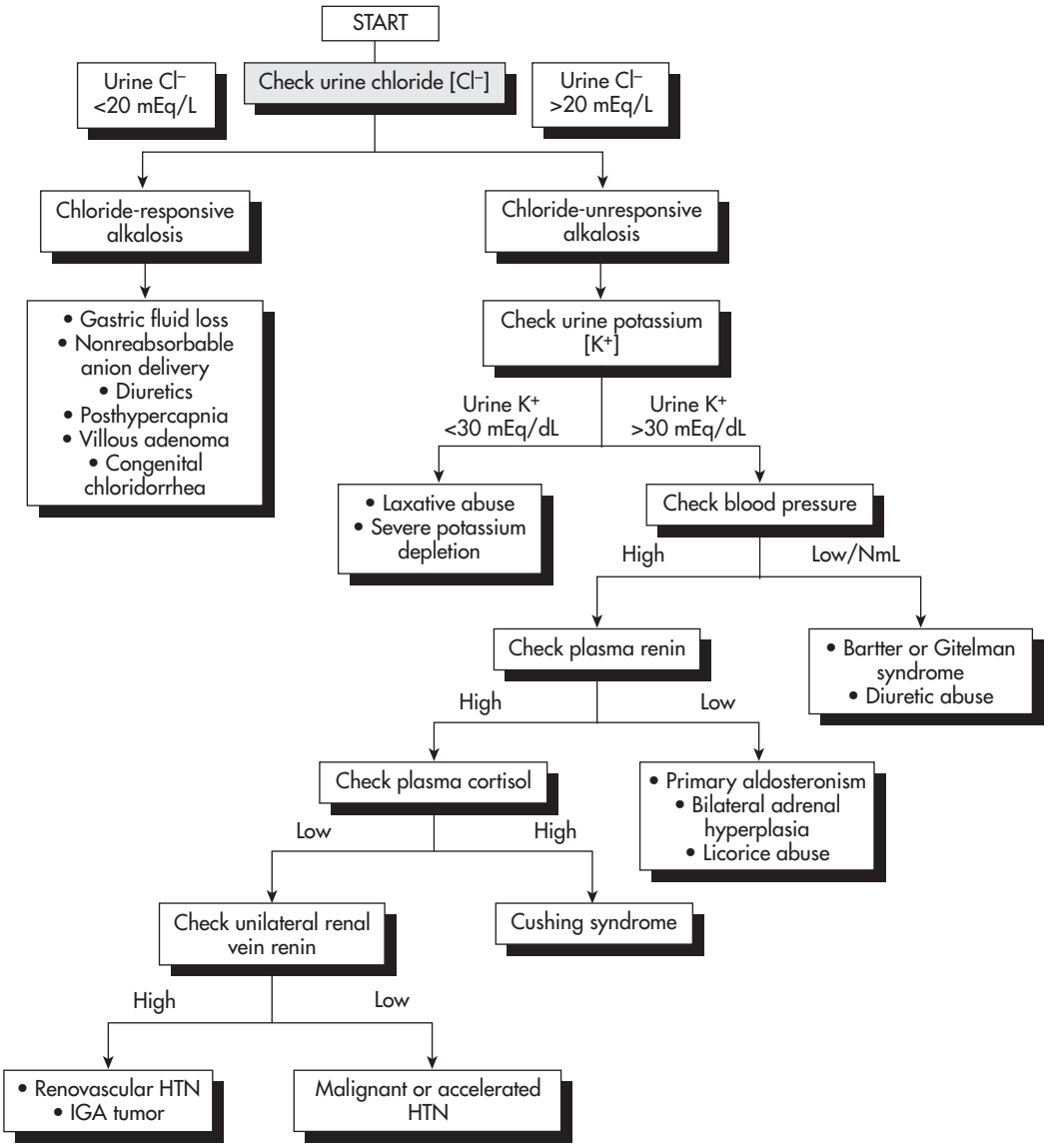


FIGURE 3-9 Workup of metabolic alkalosis. (Data from DuBose TD Jr. Acid-base disorders. In: Brenner BM (ed). *Brenner and Rector's the kidney*, ed 8, Philadelphia, 2008, Saunders, p. 513.)

ICD-9CM # 276.3
ICD-10CM # E87.3 Alkalosis

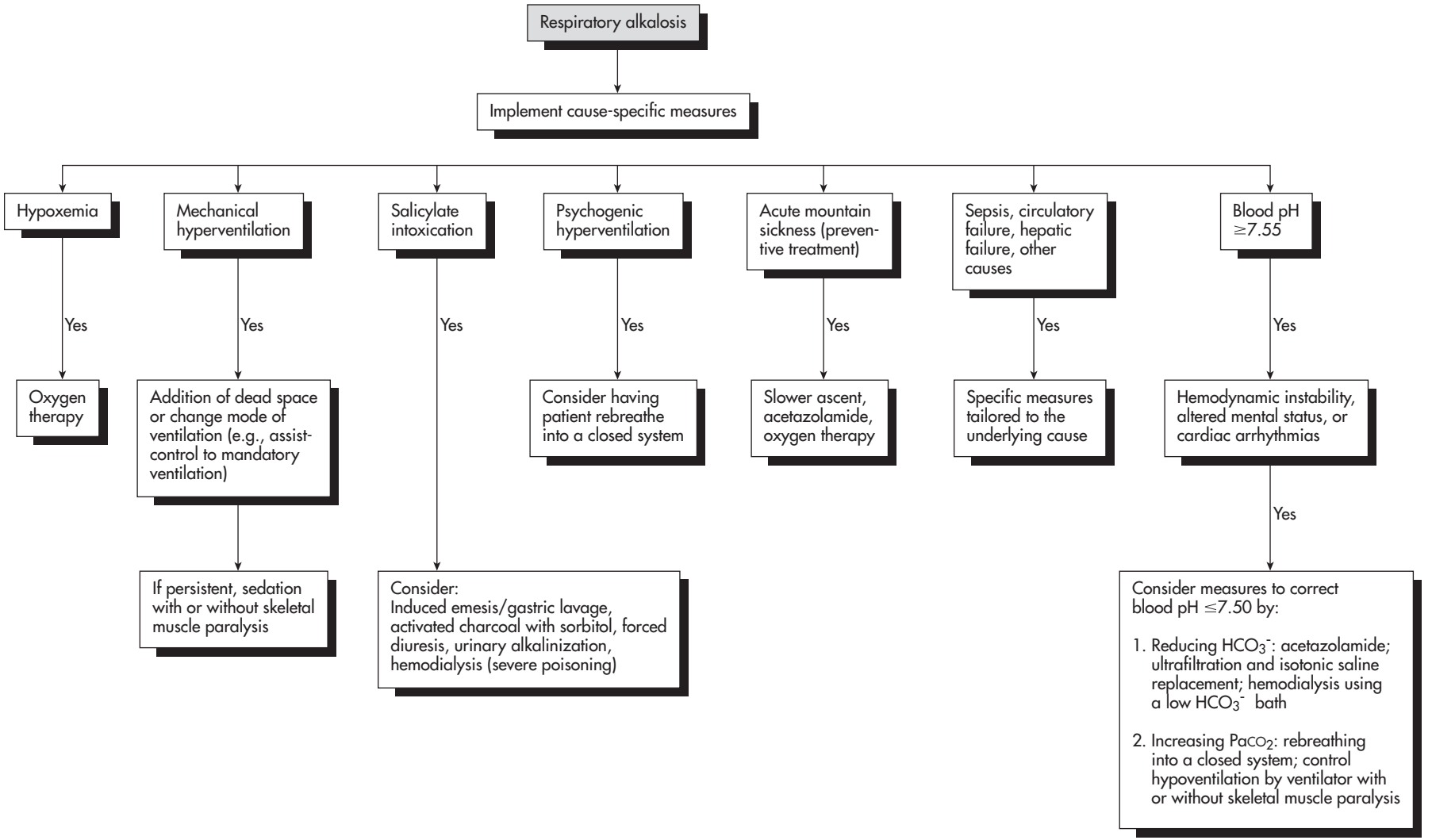


FIGURE 3-10 Recommended treatment of respiratory alkalosis. (From Feehally J, Floege J, Johnson RJ [eds]: *Comprehensive clinical nephrology,* ed 3, St Louis, 2007, Mosby.)

ICD-9CM # 780.09
ICD-10CM # R40.1 Stupor

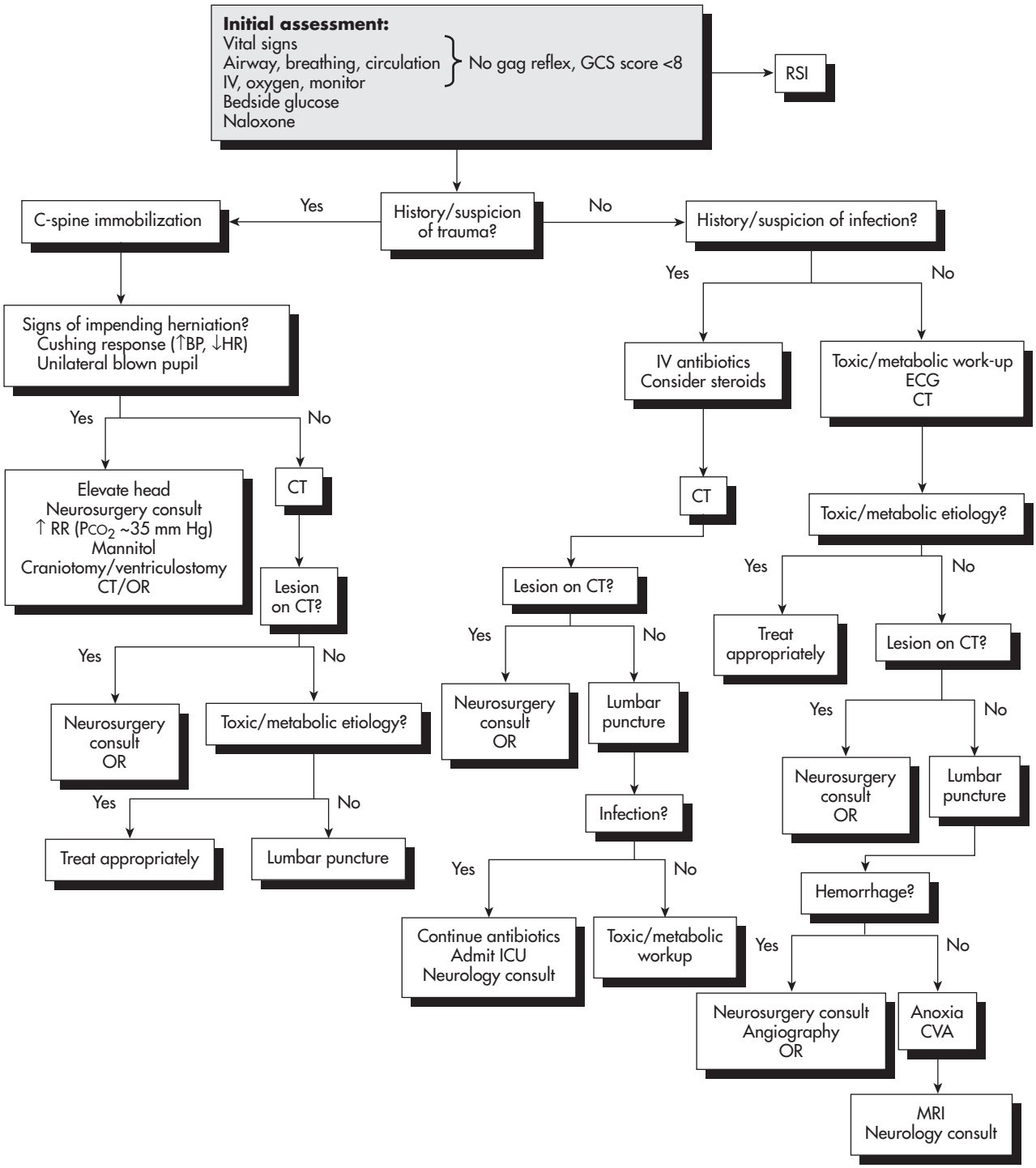


FIGURE 3-11 Diagnostic approach to altered mental status and coma. *BP*, Blood pressure; *CT*, computed tomography; *CVA*, cerebrovascular accident; *ECG*, electrocardiography; *GCS*, Glasgow Coma Scale; *HR*, heart rate; *ICU*, intensive care unit; *MRI*, magnetic resonance imaging; *OR*, operating room; *RR*, respiratory rate; *RSI*, rapid-sequence intubation. (From Adams JG et al: *Emergency medicine, clinical essentials,* ed 2, Philadelphia, 2013, Elsevier.)

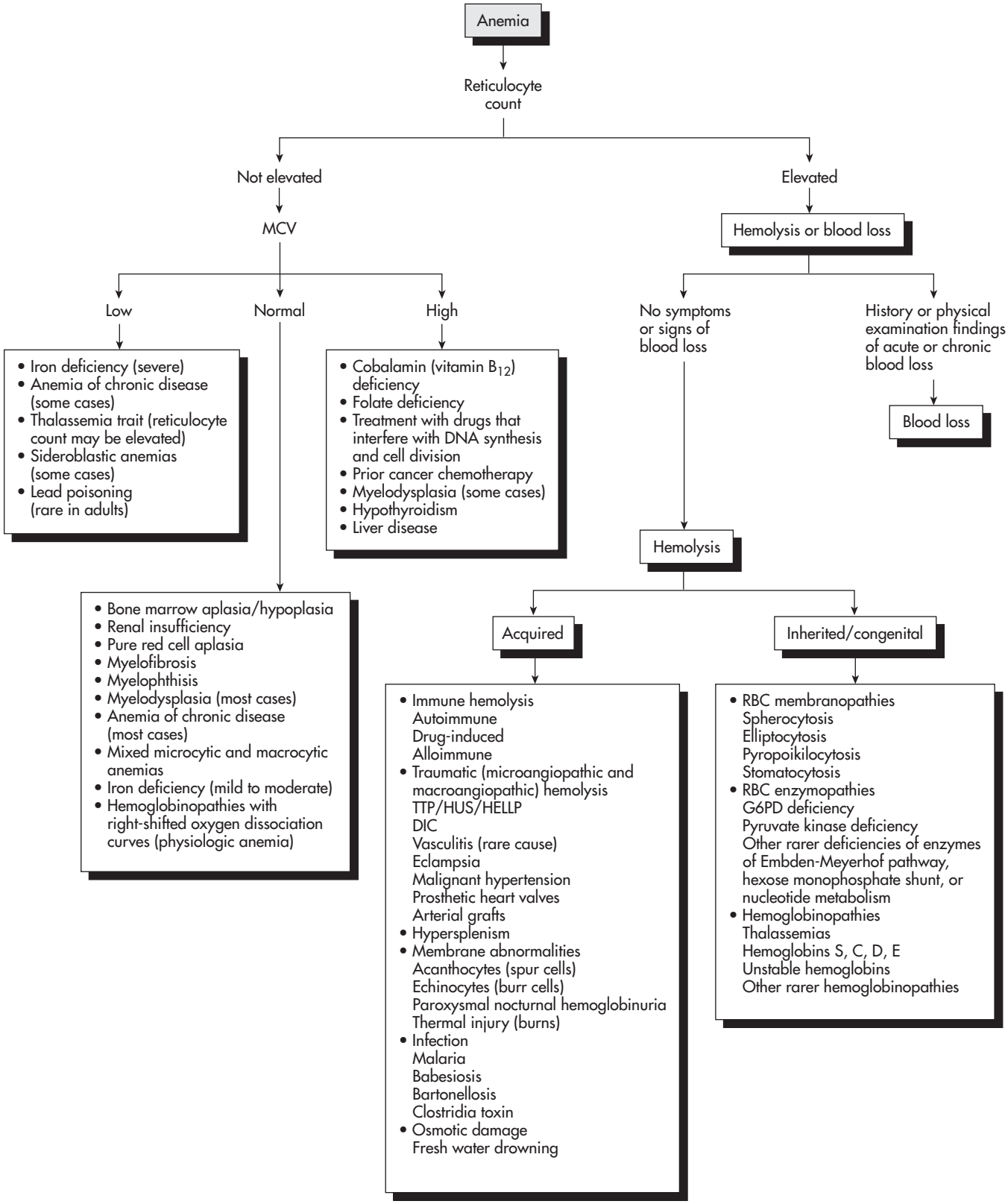


FIGURE 3-12 Algorithm for diagnosis of anemias. *DIC,* Disseminated intravascular coagulation; *G6PD,* glucose-6-phosphate-dehydrogenase; *HELLP, h*epatomegaly-*e*levated *l*iver (function tests)-*l*ow *p*latelets; *HUS,* hemolytic-uremic syndrome; *MCV,* mean corpuscular volume; *RBC,* red blood cell; *TTP,* thrombotic thrombocytopenic purpura. (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 23, Philadelphia, 2008, Saunders.)

ICD-9CM # 285.9 Anemia NOS
ICD-10CM # P61.4 Anemia, newborn

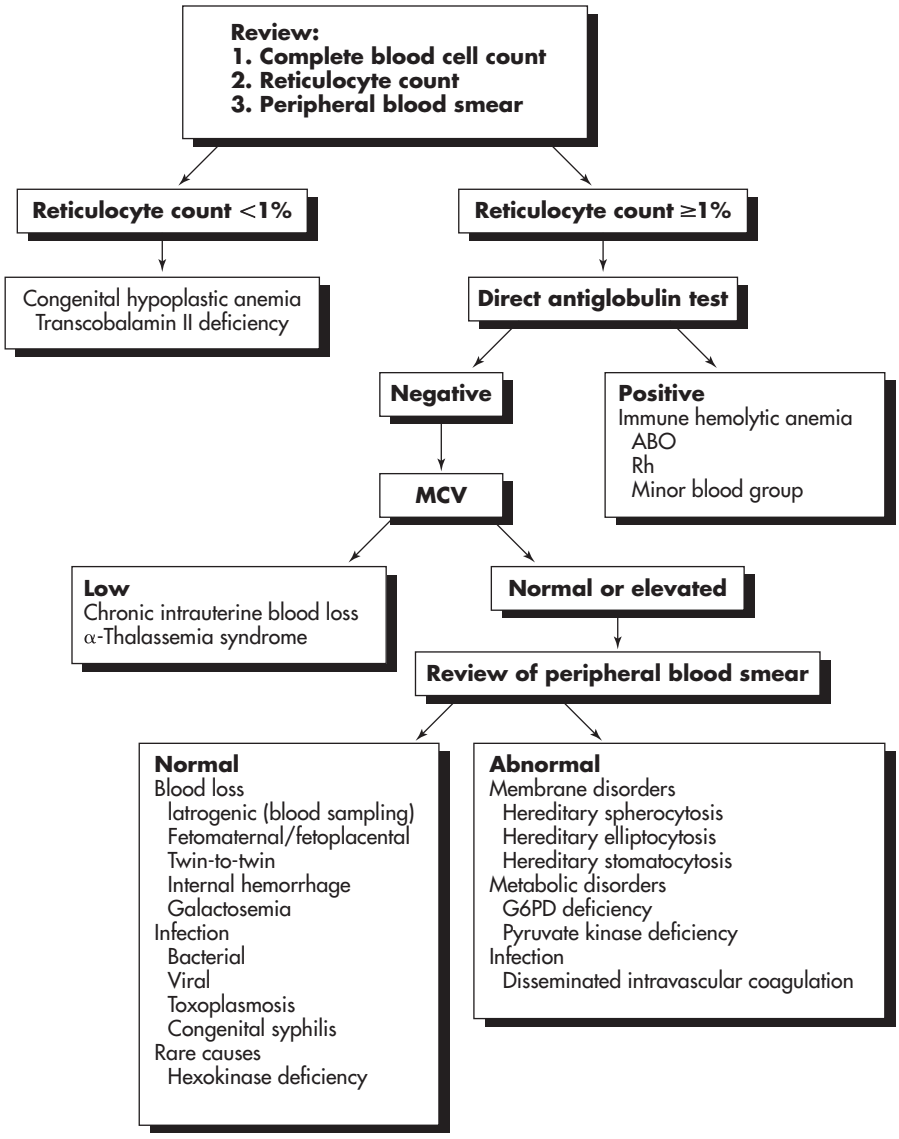


FIGURE E3-13 Approach to the differential diagnosis of anemia in the newborn. *G6PD,* Glucose-6-phosphate dehydrogenase; *MCV,* mean corpuscular volume. (From Hoffmann R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

ANEMIA, MACROCYTIC

ICD-9CM # 281.9
ICD-10CM # D53.9 Macrocytic anemia

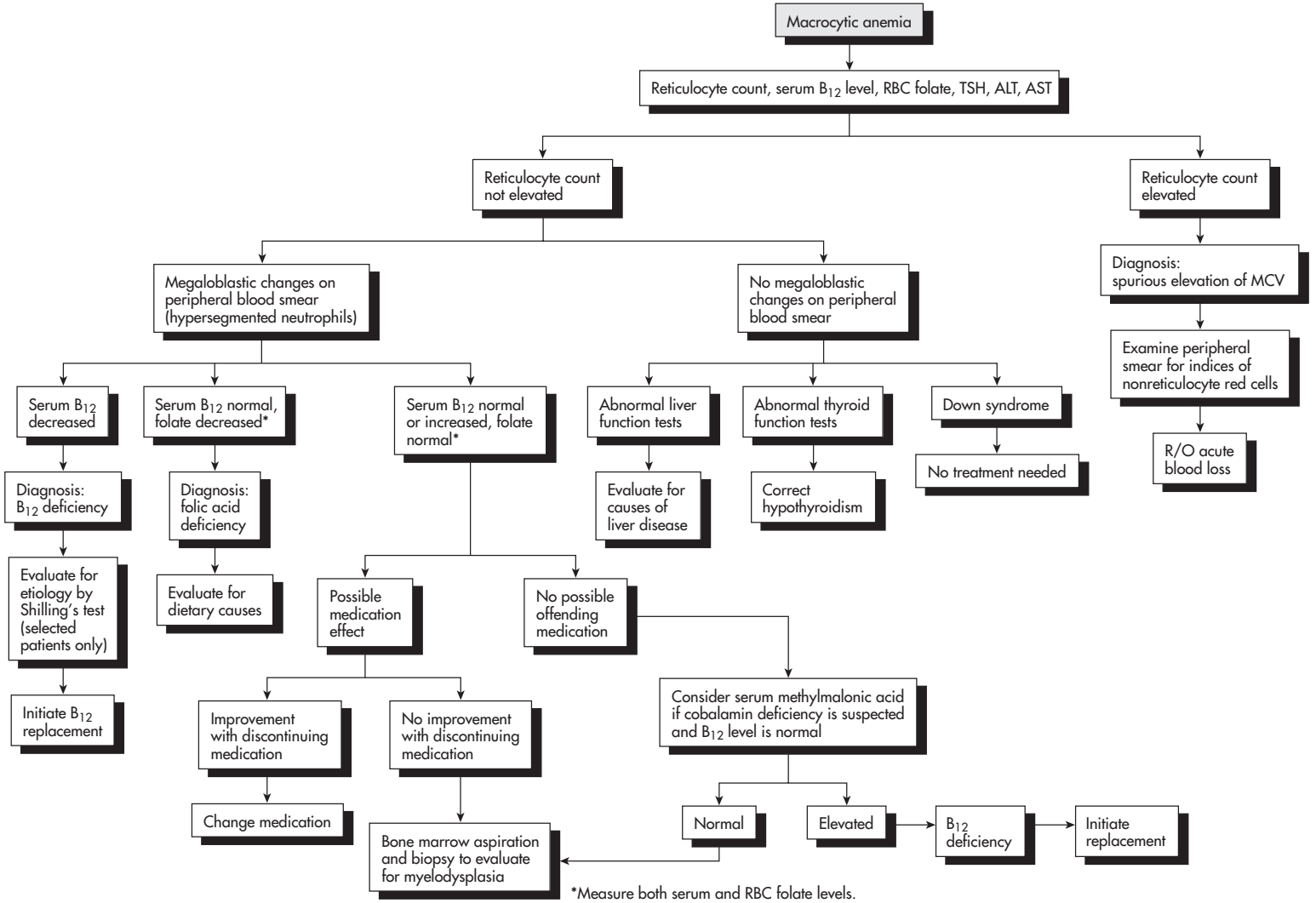


FIGURE 3-14 Differential diagnosis of macrocytic anemia. *MCV,* Mean corpuscular volume. (Modified from Rakel RE [ed]: *Principles of family practice,* ed 7, Philadelphia, 2007, Saunders.)

ICD-9CM # 282.4
ICD-10CM # D50.9 Microcytic (hypochromic) anemia

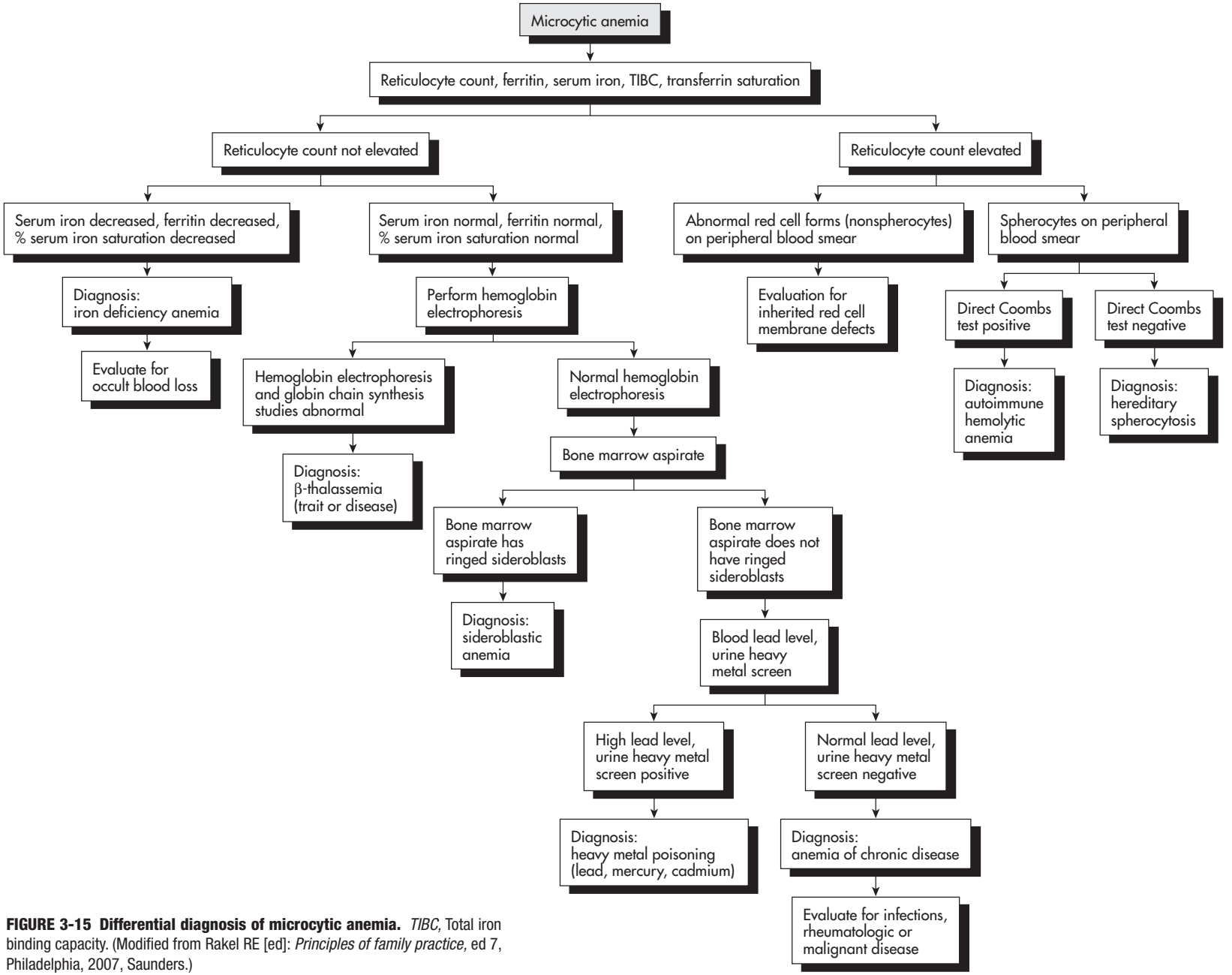


FIGURE 3-15 Differential diagnosis of microcytic anemia. *TIBC*, Total iron binding capacity. (Modified from Rakel RE [ed]: *Principles of family practice*, ed 7, Philadelphia, 2007, Saunders.)

ANEMIA WITH RETICULOCYTOSIS

ICD-9CM # 790.99
ICD-10CM # D64.9 Anemia, unspecified

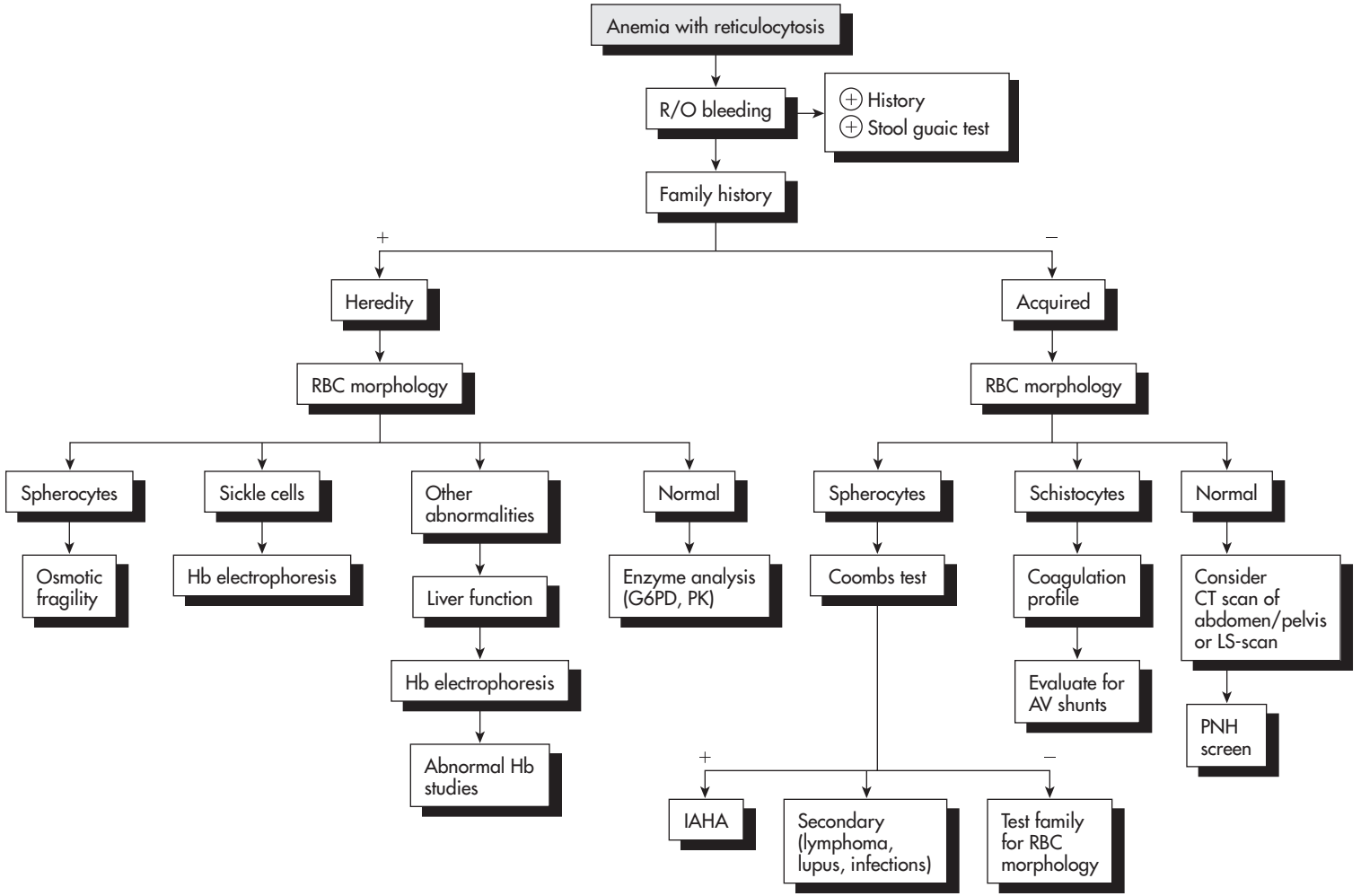


FIGURE E3-16 Evaluation of patients with hemolytic anemia. *AV,* Arteriovenous; *G6PD,* glucose-6-phosphate dehydrogenase; *Hb,* hemoglobin; *IAHA,* idiopathic autoimmune hemolytic anemia; *LS,* liver spleen; *PK,* pyruvate kinase; *PNH,* paroxysmal nocturnal hemoglobinuria; *RBC,* red blood cell, *R/O,* rule out.

ICD-9CM # 379.41
ICD-10CM # H57.02 Anisocoria

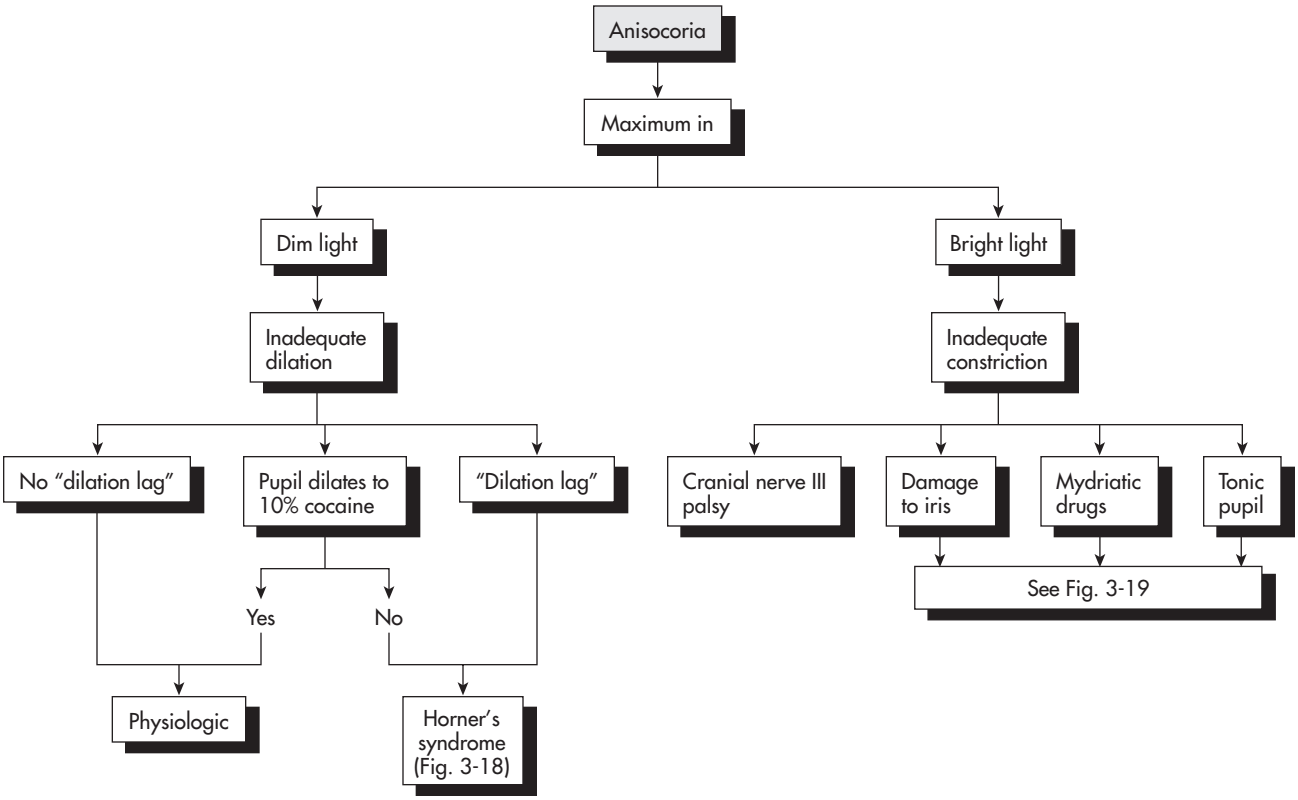


FIGURE 3-17 Algorithm for the approach to unequal pupils (anisocoria). (From Andreoli TE [ed]: *Cecil essentials of medicine,* ed 7, Philadelphia, 2008, Saunders.)

FIGURE 3-18 Horner's syndrome clearly acquired in infancy must be evaluated for neuroblastoma, a treatable tumor. This baby, with a right ptosis and miosis, developed a flush during cycloplegia that made the vasomotor abnormality very clear—the Horner's side remained pale. The baby had no sign of Horner's syndrome during her first 8 months, but at 16 months Horner's syndrome is obvious (ptosis, miosis, and upside-down ptosis). Because the syndrome was acquired, a chest radiograph was ordered; it showed a mass in the pulmonary apex. Magnetic resonance imaging confirmed the lesion. Surgery showed it to be a neuroblastoma. (From Yanoff M, Duker JS: *Ophthalmology,* ed 2, St Louis, 2004, Mosby.)

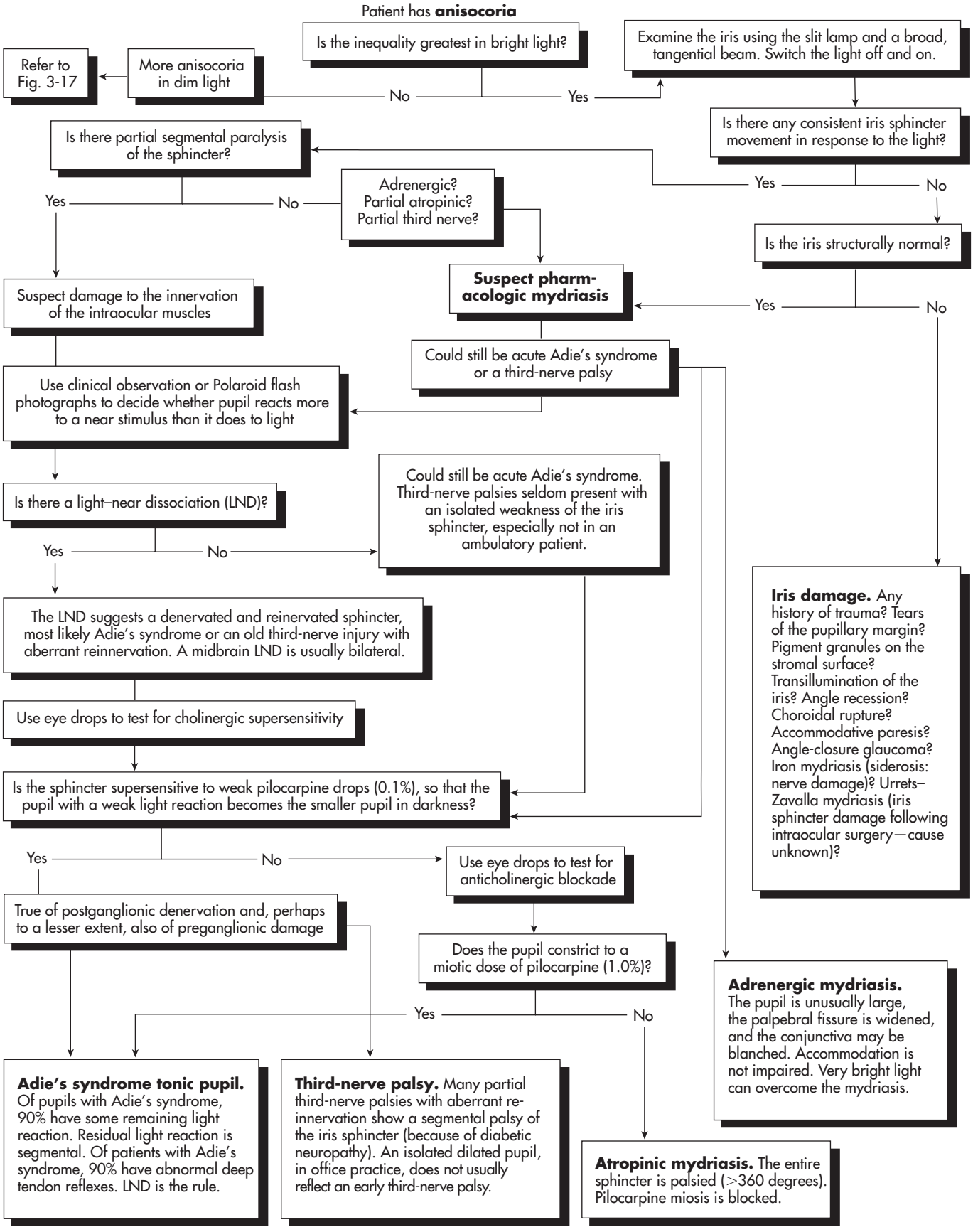


FIGURE 3-19 Diagnosis of pupillary abnormalities in which anisocoria increases in bright light. Initial pupillary inequality is greater in bright light than in darkness, which indicates that the sphincter of the large pupil is weak or that a parasympathetic lesion is present on that side. (From Yanoff M, Duker JS: *Ophthalmology,* ed 2, St Louis, 2004, Mosby.)

ICD-9CM # 783.0
ICD-10CM # R63.0 Anorexia

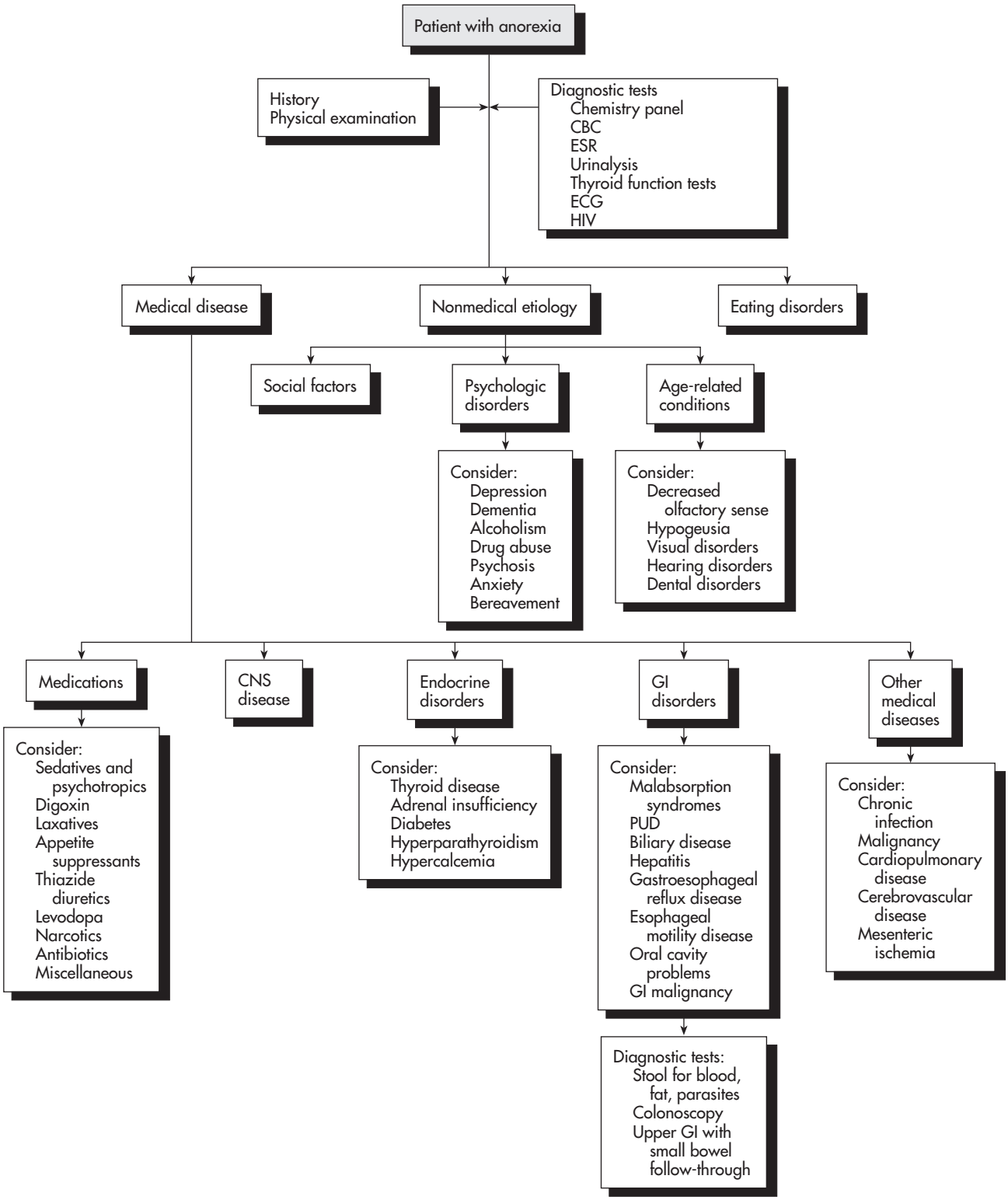


FIGURE 3-20 Evaluation of anorexia. *CBC,* Complete blood count; *CNS,* central nervous system; *ECG,* electrocardiogram; *ESR,* erythrocyte sedimentation rate; *GI,* gastrointestinal; *PUD,* peptic ulcer disease. (Modified from Greene HL, Johnson WP, Lemcke D [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

ICD-9CM # V82.5
ICD-10CM # X43 Accidental poisoning by an exposure to other drugs acting on the autonomic nervous system

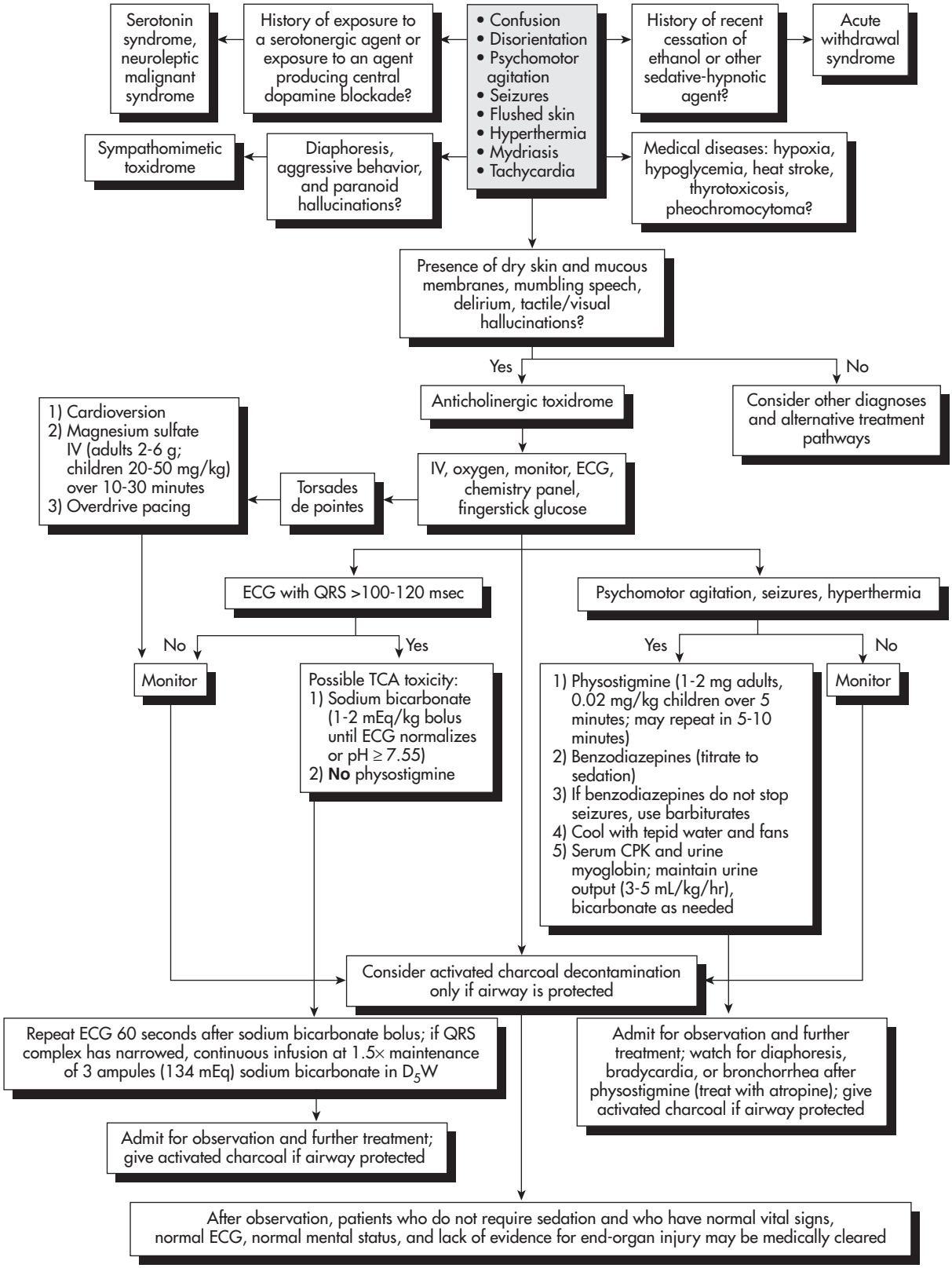


FIGURE 3-21 Algorithm for the recognition and treatment of anticholinergic toxicity. *CPK*, Creatine phosphokinase; *D_5W*, 5% dextrose in water; *ECG*, electrocardiogram; *IV*, intravenous line; *TCA*, tricyclic antidepressant. (From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

ARTHRALGIA LIMITED TO ONE OR FEW JOINTS

ICD-9CM # 719.40 Arthralgia site NOS
719.41 Arthralgia, shoulder region
719.42 Arthralgia, upper arm
719.43 Arthralgia, forearm
719.44 Arthralgia, hand
719.45 Arthralgia, pelvic region and thigh
719.46 Arthralgia, lower leg
719.47 Arthralgia, ankle and/or foot

ICD-10CM # M25.50 Pain in unspecified joint
M25.519 Pain in unspecified shoulder
M25.529 Pain in unspecified elbow
M25.539 Pain in unspecified wrist
M79.643 Pain in unspecified hand
M25.559 Pain in unspecified hip
M25.569 Pain in unspecified knee
M25.579 Pain in unspecified ankle and joints of unspecified foot
M79.646 Pain in unspecified finger(s)

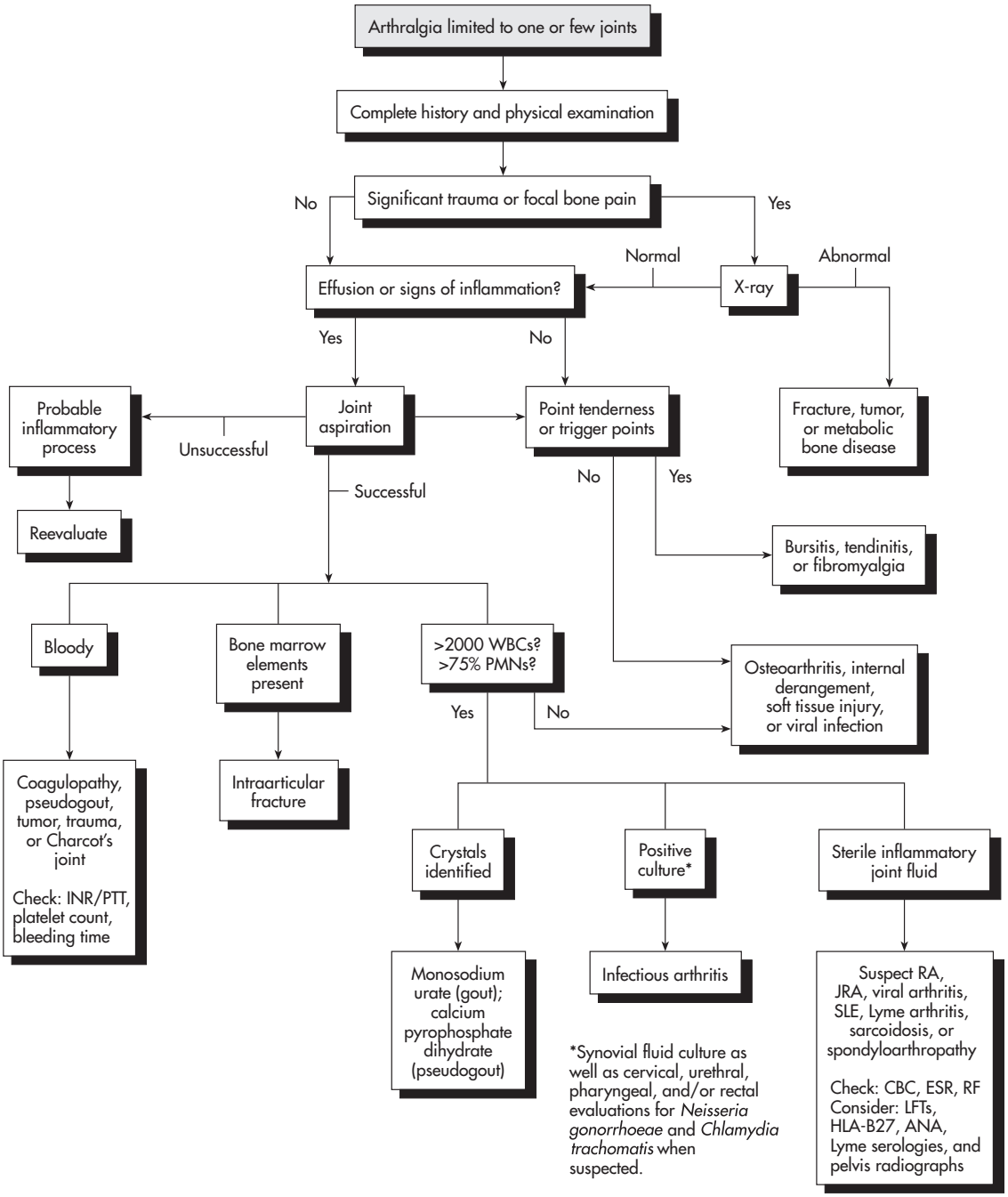


FIGURE 3-22 A diagnostic approach to arthralgia in a few joints. *ANA,* Antinuclear antibodies; *CBC,* complete blood count; *ESR,* erythrocyte sedimentation rate; *JRA,* juvenile rheumatoid arthritis; *LFTs,* liver function tests; *PMNs,* polymorphonuclear neutrophils; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *RA,* rheumatoid arthritis; *RF,* rheumatoid factor; *SLE,* systemic lupus erythematosus; *WBCs,* white blood cells. (Modified from American College of Rheumatology Ad Hoc Committee on Clinical Guidelines: *Arthritis Rheum* 39:1, 1996.)

ASPIRATION, GASTRIC CONTENTS

ICD-9CM # 507.0
ICD-10CM # J69.8 Pneumonitis due to inhalation of other solids and liquids

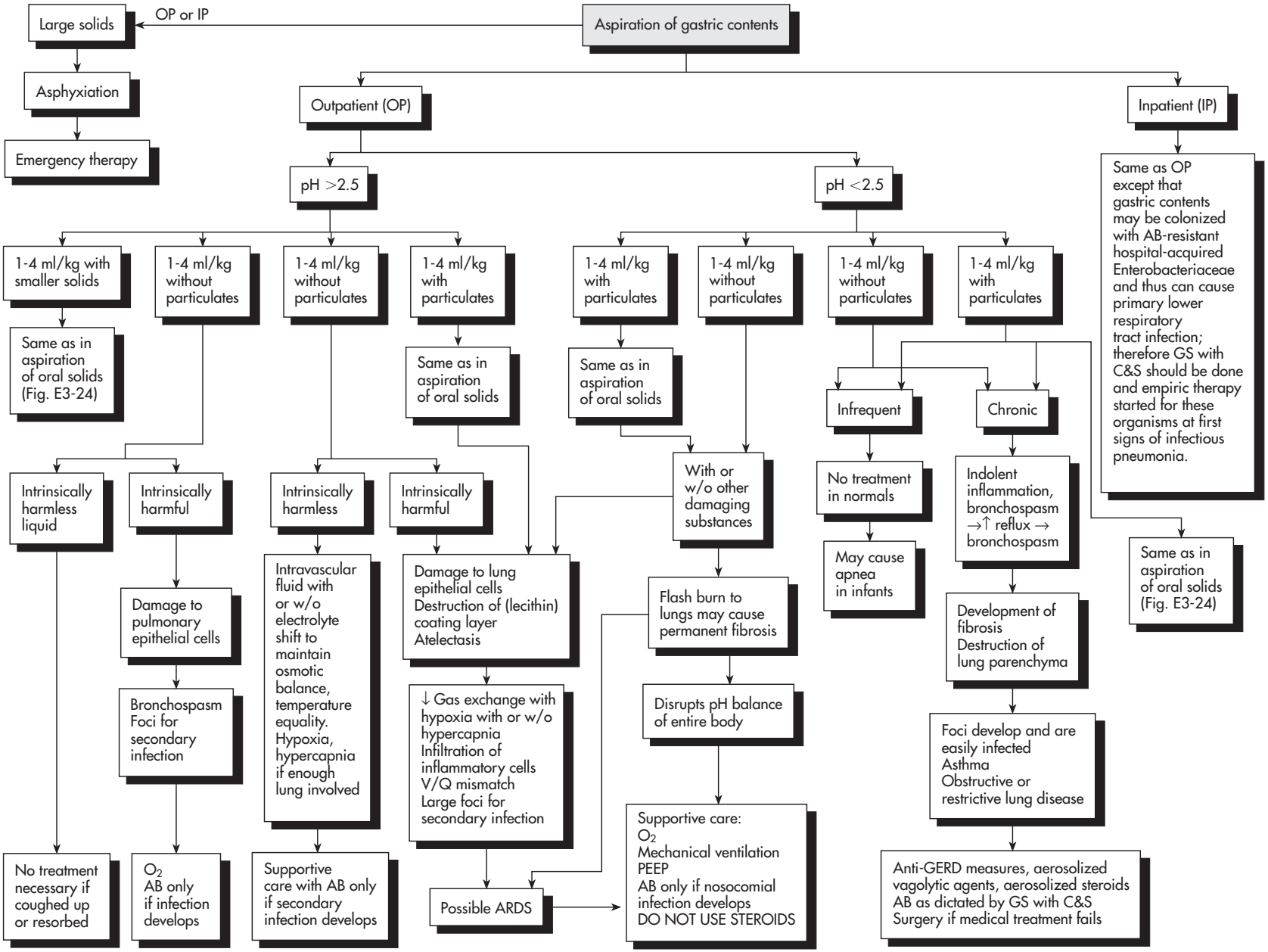


FIGURE E3-23 Management of aspiration of gastric contents. *AB,* Antibiotics; *ARDS,* acute respiratory distress syndrome; *C&S,* culture and sensitivity; *GERD,* gastroesophageal reflux disease; *GS,* Gram stain; *PEEP,* positive end-expiratory pressure; *V/Q,* ventilation-perfusion. (From Kassirer J [ed]: *Current therapy in adult medicine,* ed 4, St Louis, 1998, Mosby.)

ASPIRATION, ORAL CONTENTS

ICD-9CM # 507.0
ICD-10CM # J69.0 Pneumonitis due to inhalation of food and vomit

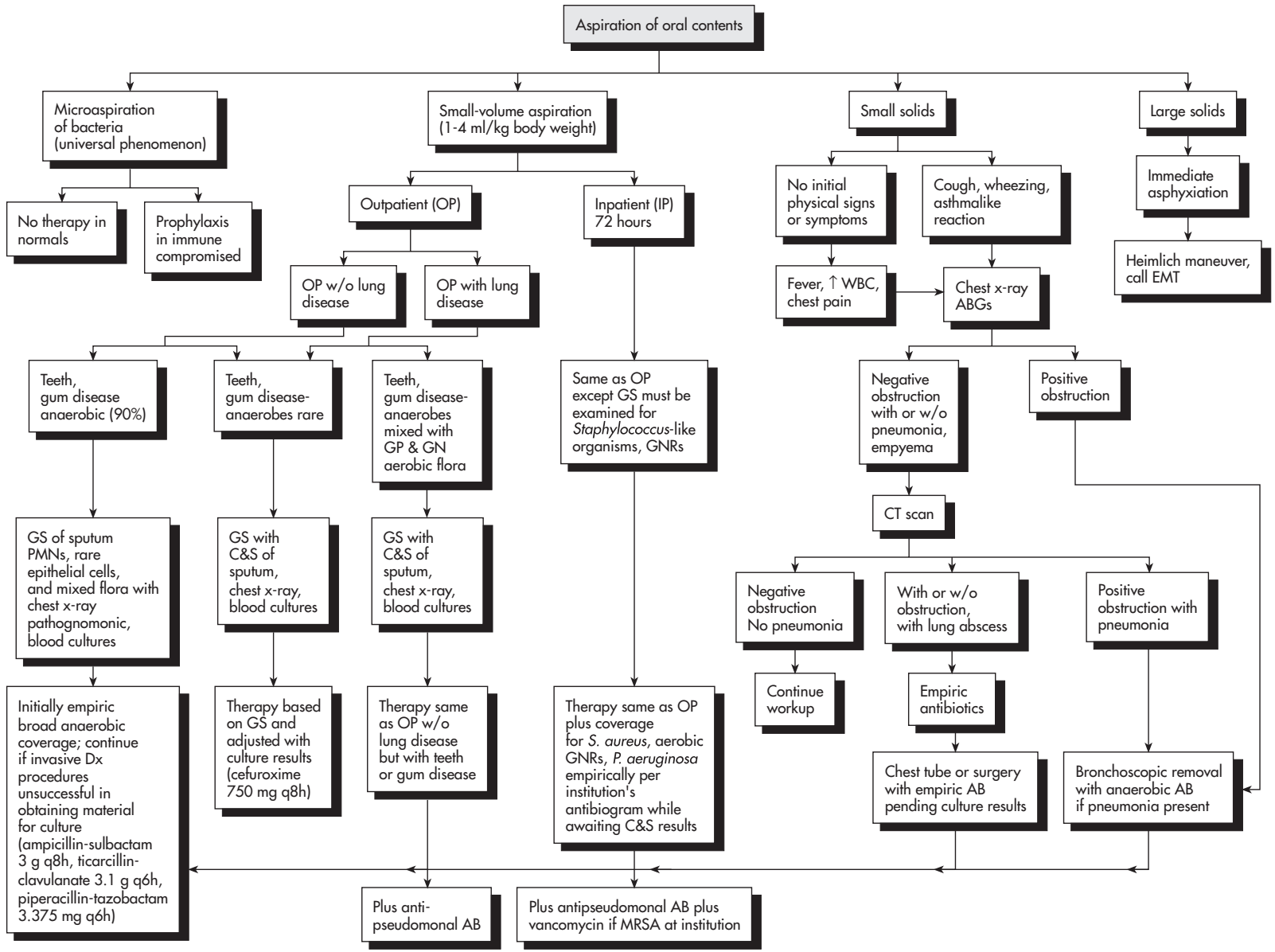


FIGURE E3-24 Management of aspiration of oral contents. *AB,* Antibiotics; *ABGs,* arterial blood gases; *C&S,* culture and sensitivity; *CT,* computed tomography; *Dx,* diagnostic; *EMT,* emergency medical technician; *GN,* gram-negative; *GNRs,* gram-negative rods; *GP,* gram-positive; *GS,* Gram stain; *MRSA,* methicillin-resistant *Staphylococcus aureus; PMNs,* polymorphonuclear leukocytes; *WBC,* white blood cells. (From Kassirer J [ed]: *Current therapy in adult medicine,* ed 4, St Louis, 1998, Mosby.)

ICD-9CM #	781.3	Ataxia NOS
	303.9	Alcoholic, chronic
	334.3	Cerebellar
	331.89	Cerebral
	334.0	Friedreich's
ICD-10CM #	A52.11	Tabes dorsalis
	G11.1	Early-onset cerebellar ataxia
	G31.89	Other specified degenerative diseases of nervous system
	G11.1	Early-onset cerebellar ataxia
	R27.0	Ataxia, unspecified
	R27.8	Other lack of coordination
	R27.9	Unspecified lack of coordination

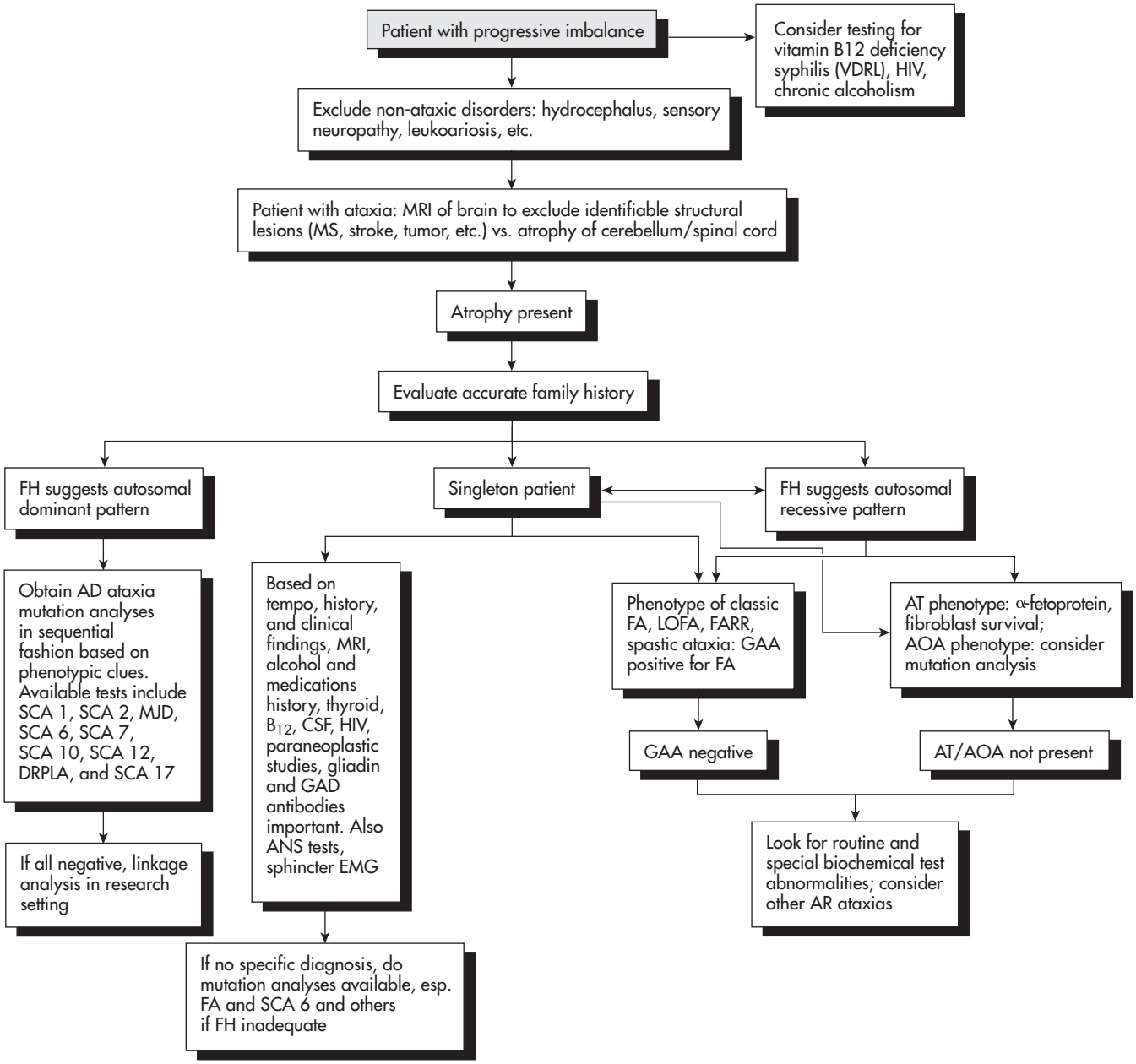


FIGURE 3-25 An algorithm for a diagnostic approach to patients with progressive ataxia. *AD,* Autosomal dominant; *AOA,* ataxia with oculomotor apraxia; *AR,* autosomal recessive; *AT,* ataxia-telangiectasia; *CSF,* cerebrospinal fluid; *DRPLA,* dentatorubral-pallidoluysian atrophy; *EMG,* electromyelography; *FA,* Friedreich's ataxia; *FH,* family history; *GAD,* glutamate decarboxylase; *HIV,* human immunodeficiency virus; *MRI,* magnetic resonance imaging; *MS,* multiple sclerosis; *SCA,* spinocerebellar ataxia. (Modified from Bradley WG et al [eds]: *Neurology in clinical practice,* ed 4, Philadelphia, 2004, Butterworth Heinemann.)

ICD-9CM #	724.5	Back Pain (Postural)
	724.2	Low Back Pain
	307.89	Back Pain Psychogenic
	724.8	Stiff Back
	847.9	Back Strain
	724.6	Backache, Sacroiliac
ICD-10CM #	M54.89	Other dorsalgia
	M54.9	Dorsalgia, unspecified
	M54.5	Low back pain
	F45.42	Pain disorder with related psychological factors
	M54.08	Panniculitis affecting regions of neck and back, sacral and sacrococcygeal region
	S23.9XXA	Sprain of unspecified parts of thorax, initial encounter
	M43.27	Fusion of spine, lumbosacral region
	M43.28	Fusion of spine, sacral and sacrococcygeal region
	M53.2X7	Spinal instabilities, lumbosacral region
	M53.3	Sacrococcygeal disorders, not elsewhere classified

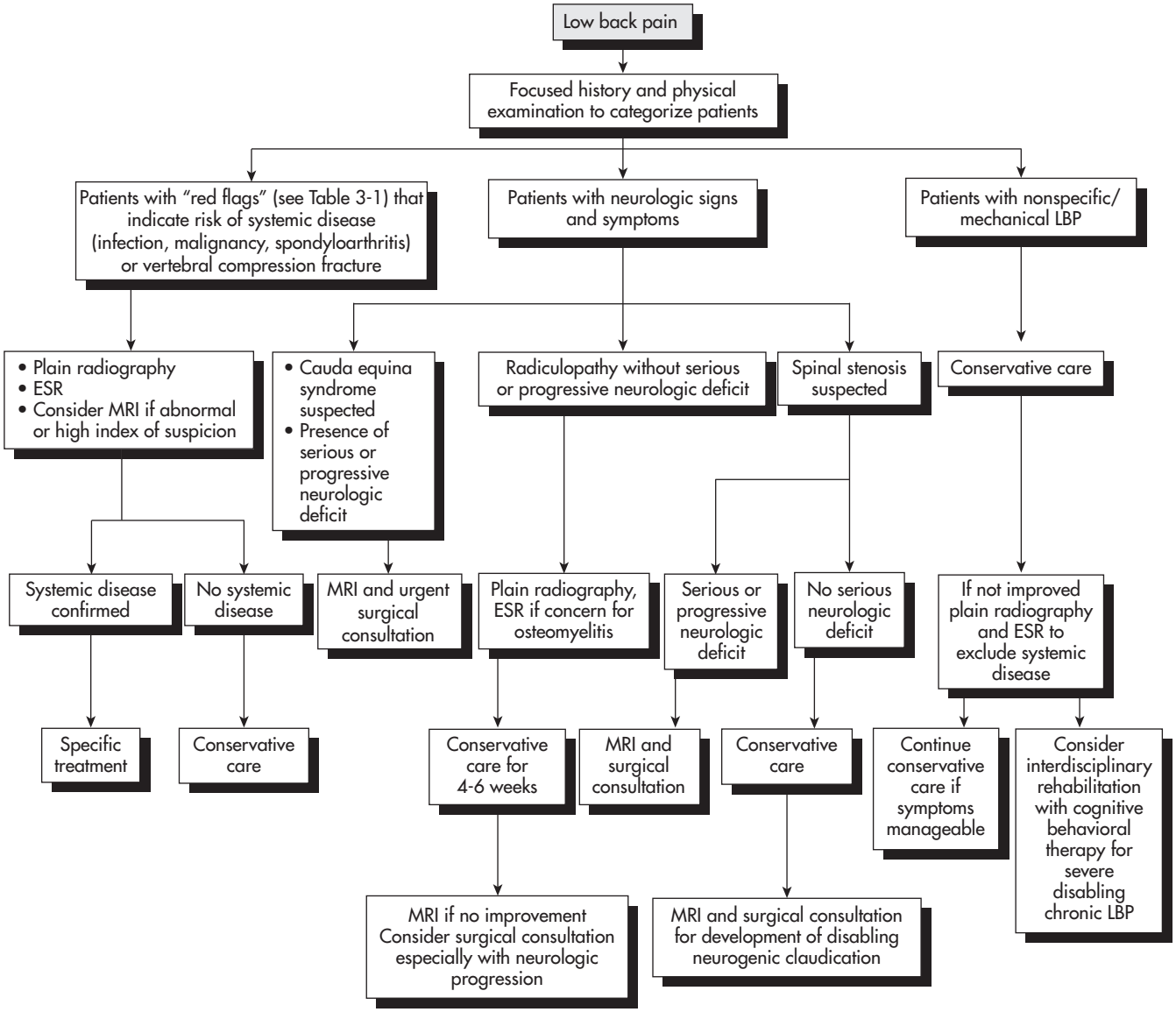


FIGURE 3-26 Algorithm for the differential diagnosis and treatment of low back pain. *ESR*, erythrocyte sedimentation rate; *LBP*, low back pain; *MRI*, magnetic resonance imaging. (From Firestein GS, Budd RC, Gabriel SE, et al: *Kelley's textbook of rheumatology,* ed 9, Philadelphia, 2013, Saunders.)

ICD-9CM #	724.5	Back Pain (Postural)
	724.2	Low Back Pain
	307.89	Back Pain Psychogenic
	724.8	Stiff Back
	847.9	Back Strain
	724.6	Backache, Sacroiliac
ICD-10CM #	M54.89	Other dorsalgia
	M54.9	Dorsalgia, unspecified
	M54.5	Low back pain
	F45.42	Pain disorder with related psychological factors
	M54.08	Panniculitis affecting regions of neck and back, sacral and sacrococcygeal region
	S23.9XXA	Sprain of unspecified parts of thorax, initial encounter
	M43.27	Fusion of spine, lumbosacral region
	M43.28	Fusion of spine, sacral and sacrococcygeal region
	M53.2X7	Spinal instabilities, lumbosacral region
	M53.3	Sacrococcygeal disorders, not elsewhere classified

TABLE 3-1 Red Flags for Potentially Serious Conditions

Possible Fracture	Possible Tumor or Infection	Possible Cauda Equina Syndrome
From Medical History		
Major trauma, such as vehicle accident or fall from height	Age over 50 or under 20 yr	Saddle anesthesia
Minor trauma or even strenuous lifting (in older or potentially osteoporotic patient)	History of cancer	Recent onset of bladder dysfunction, such as urinary retention, increased frequency, or overflow incontinence
	Constitutional symptoms, such as recent fever or chills or unexplained weight loss	Severe or progressive neurologic deficit in the lower extremity
	Risk factors for spinal infection: recent bacterial infection (e.g., urinary tract infection), intravenous drug abuse, or immune suppression (from steroids, transplant, or human immunodeficiency virus)	
	Pain that worsens when supine; severe nighttime pain	

ICD-9CM # 286.9
ICD-10CM # D68.8 Other specified coagulation defects
D68.9 Coagulation defect, unspecified

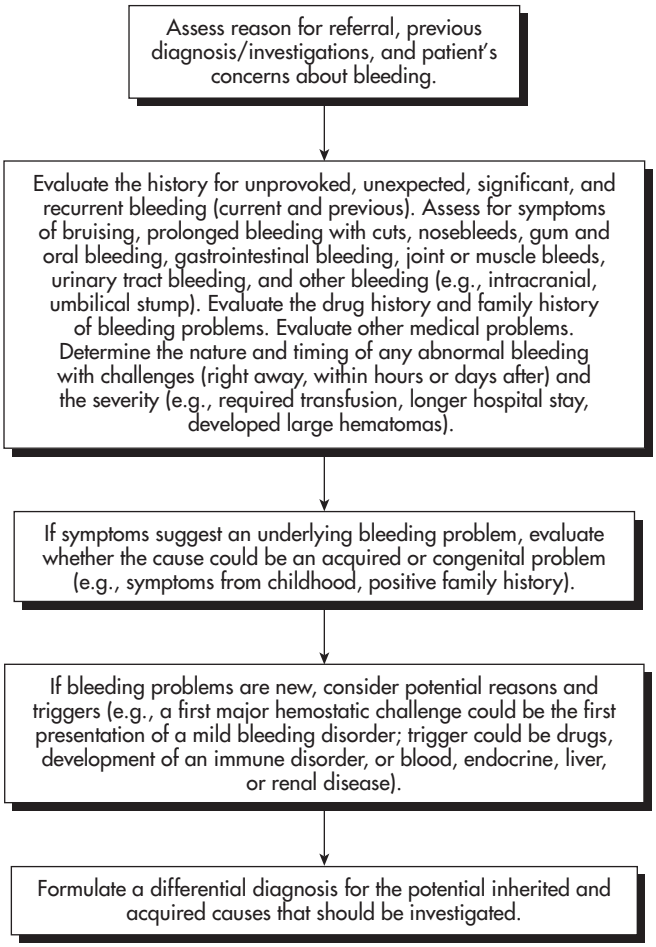


FIGURE 3-27 Steps to evaluate bleeding and bruising problems. (From Hoffman R: *Hematology, basic principles and practice*, 6th ed, Philadelphia, Saunders, 2013, Figure 130-1.)

ICD-9CM # 286.9
ICD-10CM # D68.8 Other specified coagulation defects
D68.9 Coagulation defect, unspecified

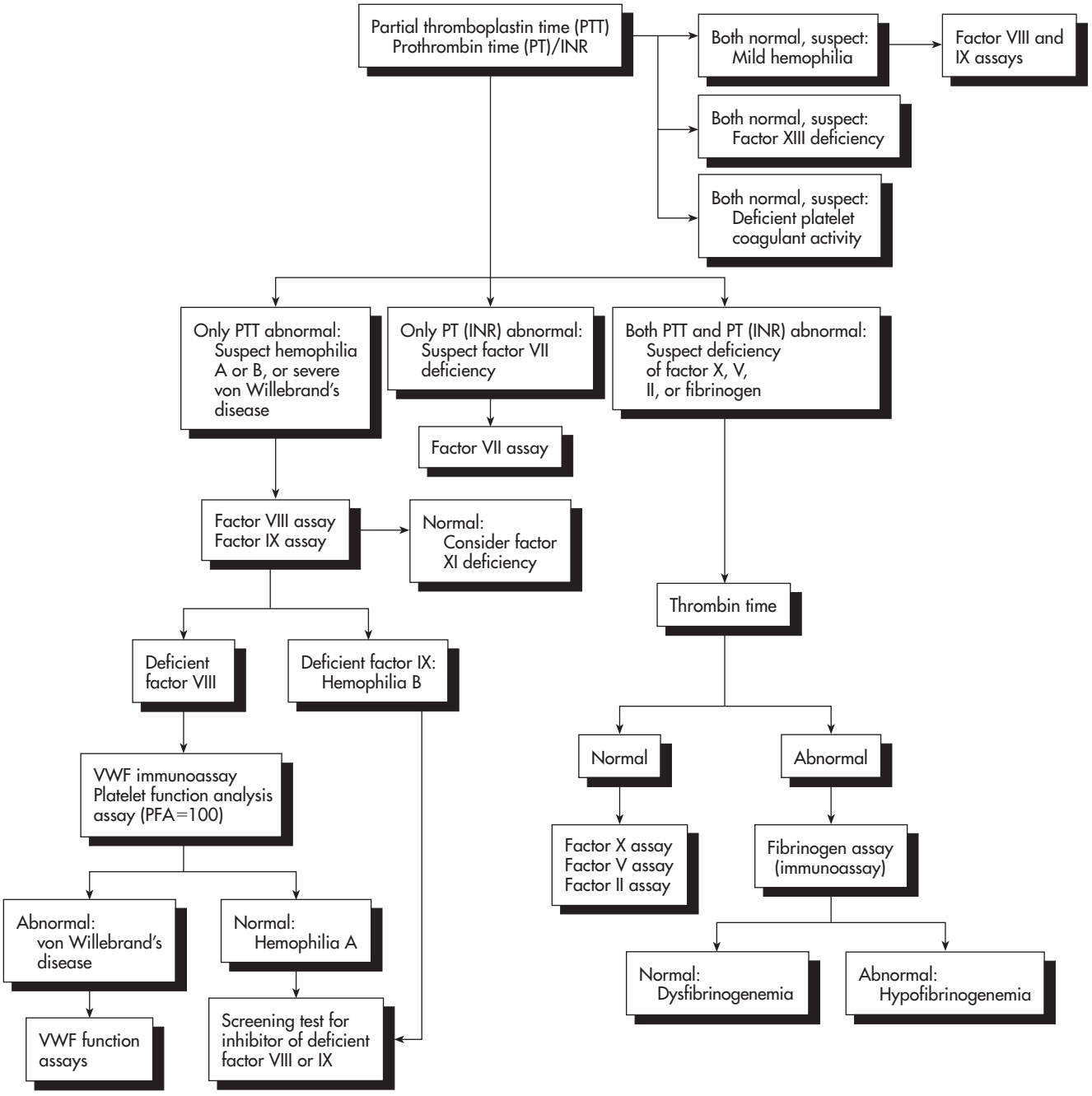


FIGURE E3-28 Laboratory evaluation of a patient with a bleeding disorder in whom the history and physical examination suggest a congenital coagulation disorder. *INR,* International normalized ratio; *VWF,* von Willebrand factor. (Modified from Stein JH [ed]: *Internal medicine,* ed 5, St Louis, 1998, Mosby.)

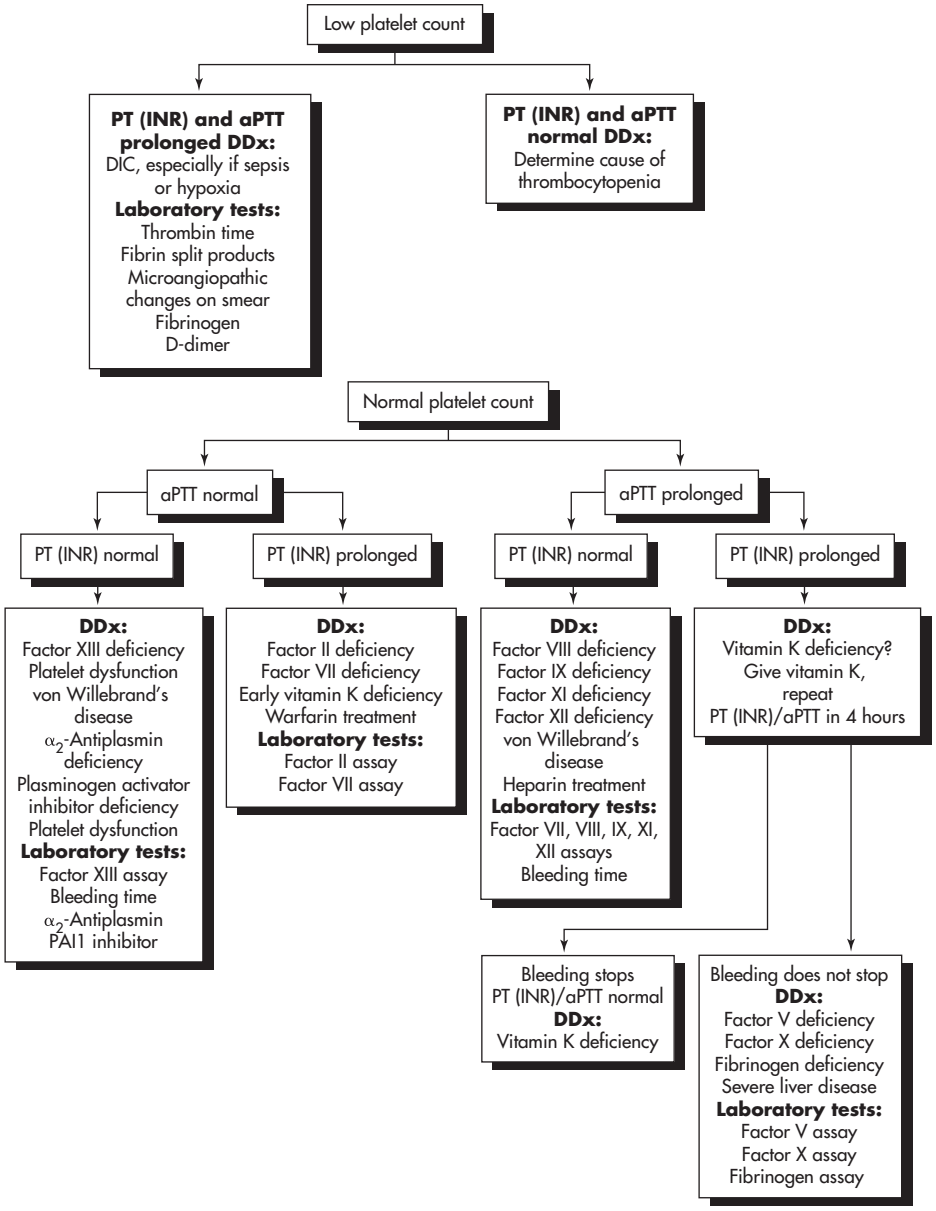


FIGURE 3-29 Differential diagnosis (DDx) of bleeding disorders. (From Cluster JW, Rau RE: *The Harriet Lane handbook,* ed 18, St Louis, 2009, Mosby.)

BOX 3-1 Bleeding Disorders

Congenital

Disorder of platelet number or function
Thrombocytopenia: Secondary to bone marrow disease or defective megakaryocyte maturation
Disorders of platelet function: Bernard-Soulier syndrome, Glanzmann thrombasthenia, storage pool diseases
Factor VIII deficiency: See text (Section I)
Factor IX deficiency: See text (Section I)
von Willebrand's disease: See text (Section I)

Acquired

Disseminated intravascular coagulation: Characterized by prolonged PT and aPTT, decreased fibrinogen and platelets, increased fibrin degradation products, and elevated D-dimers. Treatment includes identifying and treating underlying disorder. Replacement of depleted coagulation factors with FFP may be necessary in severe cases, especially when bleeding is present; 10-15 ml/kg will raise clotting factors 20%. Fibrinogen, if depleted, can be given as cryoprecipitate. Platelet transfusions may also be necessary.

Liver disease: The liver is the major site of synthesis of factors V, VII, IX, X, XI, XII, XIII, prothrombin, plasminogen, fibrinogen, protein C and S, and ATIII. Treatment with FFP and platelets may be needed, but this will increase hepatic protein load. Vitamin K should be given to patients with liver disease and clotting abnormalities.

Vitamin K deficiency: Factors II, VII, IX, X, protein C, and protein S are vitamin K dependent. Early vitamin K deficiency may present with isolated prolonged PT because factor VII has the shortest half-life. Fibrinogen should be normal.

Hemolytic-uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP): Characterized by the triad of microangiopathic hemolytic anemia, uremia, and thrombocytopenia. HUS/TTP is often triggered by bacterial enteritis, especially caused by *Escherichia coli* O157:H7, although there are a variety of causes. HUS does not typically include coagulation abnormalities, such as those seen in DIC. Avoid blood products in patients with HUS thought to be secondary to pneumococcal infection. TTP includes the triad of HUS in addition to fever and CNS changes and is more common in older adolescents and adults.

From Custer JW, Rau RE: *The Harriet Lane handbook,* ed 18, St Louis, 2009, Mosby.

ICD-9CM # 641.9 Vaginal bleeding NOS in pregnancy
ICD-10CM # 046.90 Antepartum hemorrhage, unspecified, unspecified trimester

FIGURE E3-30 Diagnosis of vaginal bleeding in early pregnancy. *D&C,* Dilation and curettage; *β-hCG,* β-human chorionic gonadotropin; *IUP,* intrauterine pregnancy. (From Carlson KJ et al: *Primary care of women,* ed 2, St Louis, 2002, Mosby.)

ICD-9CM # 578.9
ICD-10CM # K92.2 Gastrointestinal bleeding

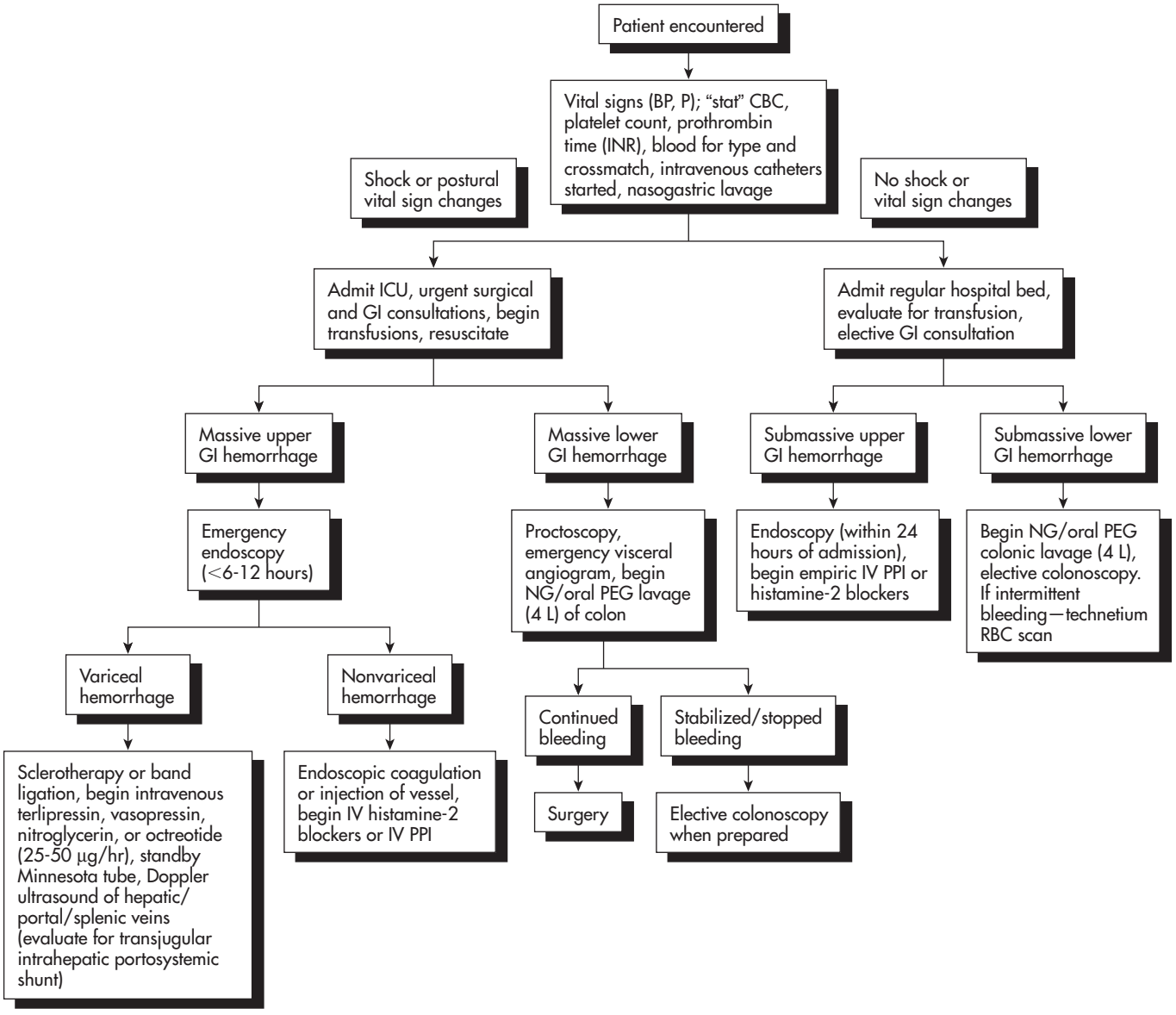


FIGURE 3-31 Approach to the patient with gastrointestinal hemorrhage. *BP,* Blood pressure; *CBC,* complete blood count; *GI,* gastrointestinal; *ICU,* intensive care unit; *IV,* intravenous; *INR,* International Normalized Ratio; *NG,* nasogastric; *P,* weight; *PEG,* percutaneous endoscopic gastrostomy; *PPI,* proton pump inhibitor; *RBC,* red blood cell. (Modified from Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 23, Philadelphia, 2008, Saunders.)

BLEEDING, NEONATE

ICD-9CM # 286.9 Bleeding disorder
578.9 Bleeding gastrointestinal
ICD-10CM # K92.2 Gastrointestinal bleeding
D68.8 Other specified coagulation defect
D68.9 Coagulation defect, unspecified

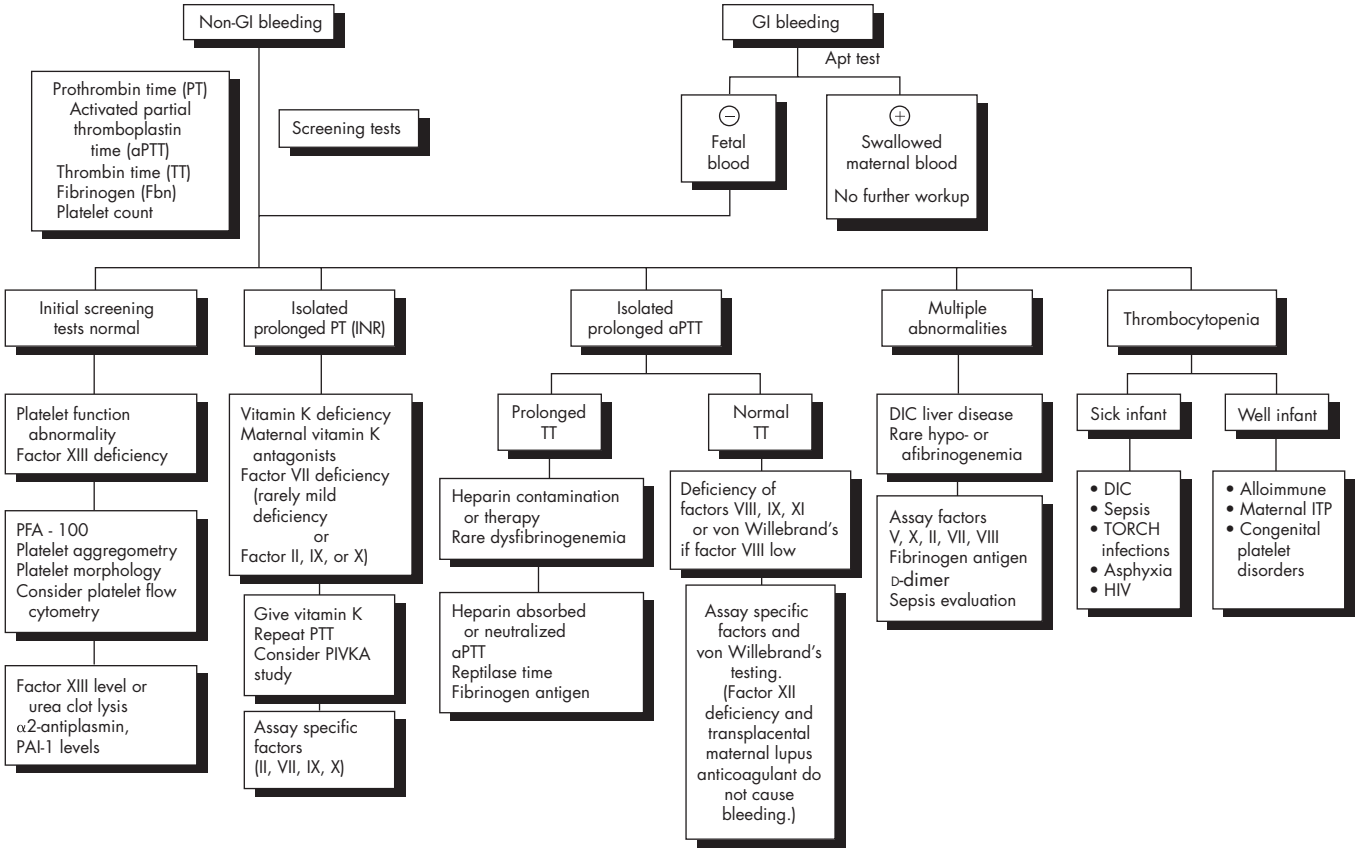


FIGURE E3-32 Diagnostic approach to the bleeding neonate. (From Hoffmann R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

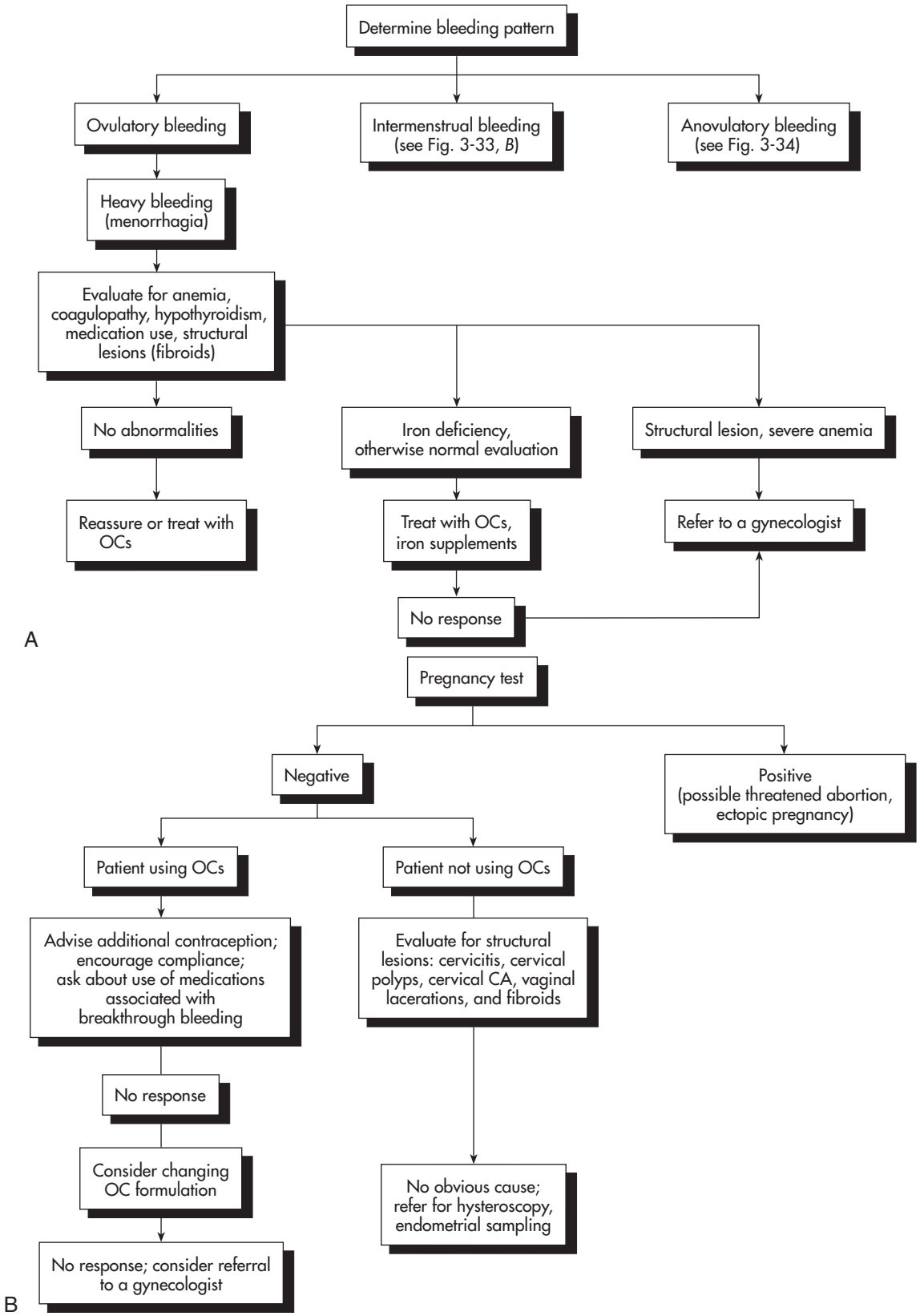


FIGURE 3-33 A, Evaluation of ovulatory bleeding. **B,** Evaluation of intermenstrual bleeding. *OCs,* Oral contraceptives. (Modified from Appleby J, Henderson M, Wathen PI: *Intern Med* Sept:17, 1996.)

ICD-9CM # 623.8 Vaginal bleeding NOS
ICD-10CM # N93.9 Vaginal bleeding

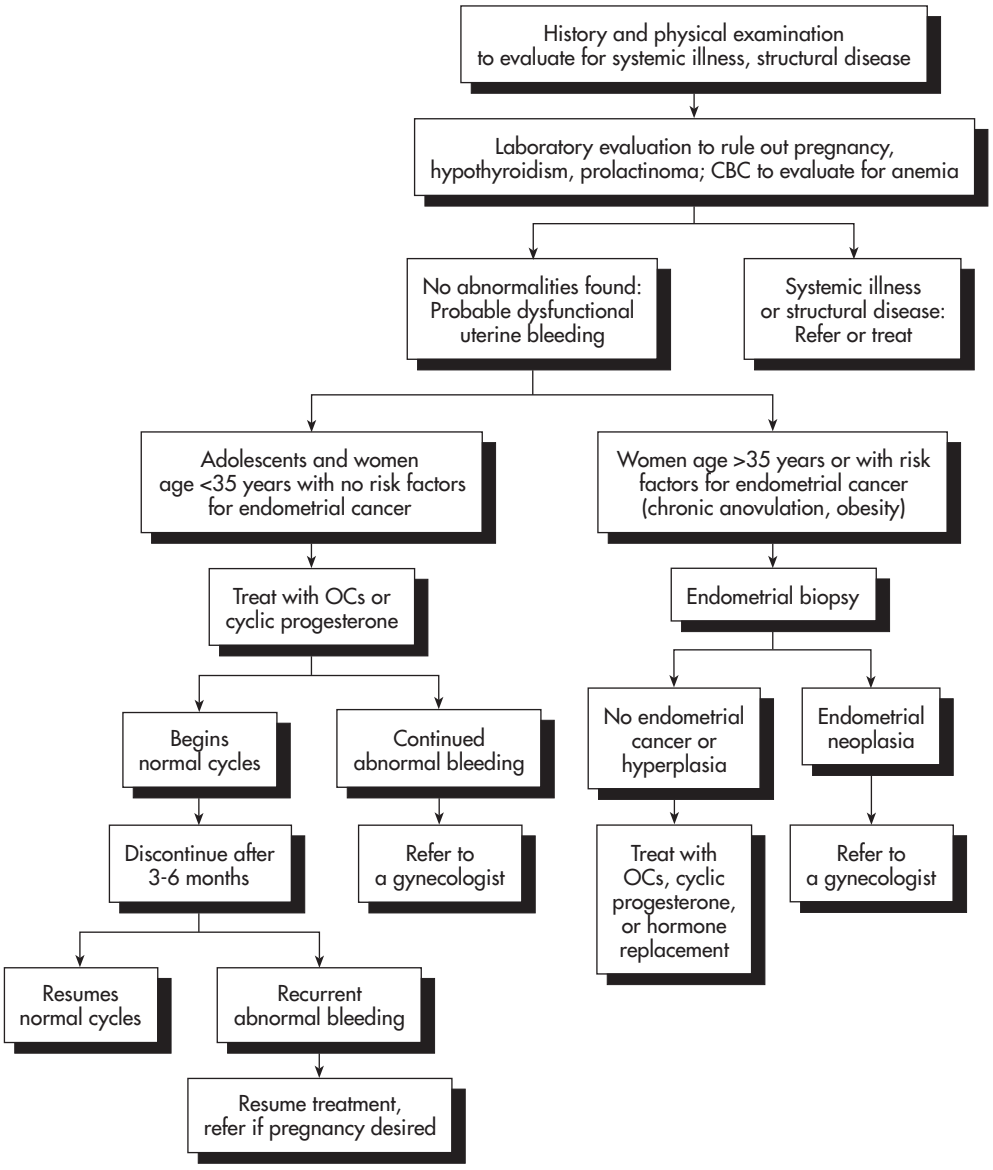
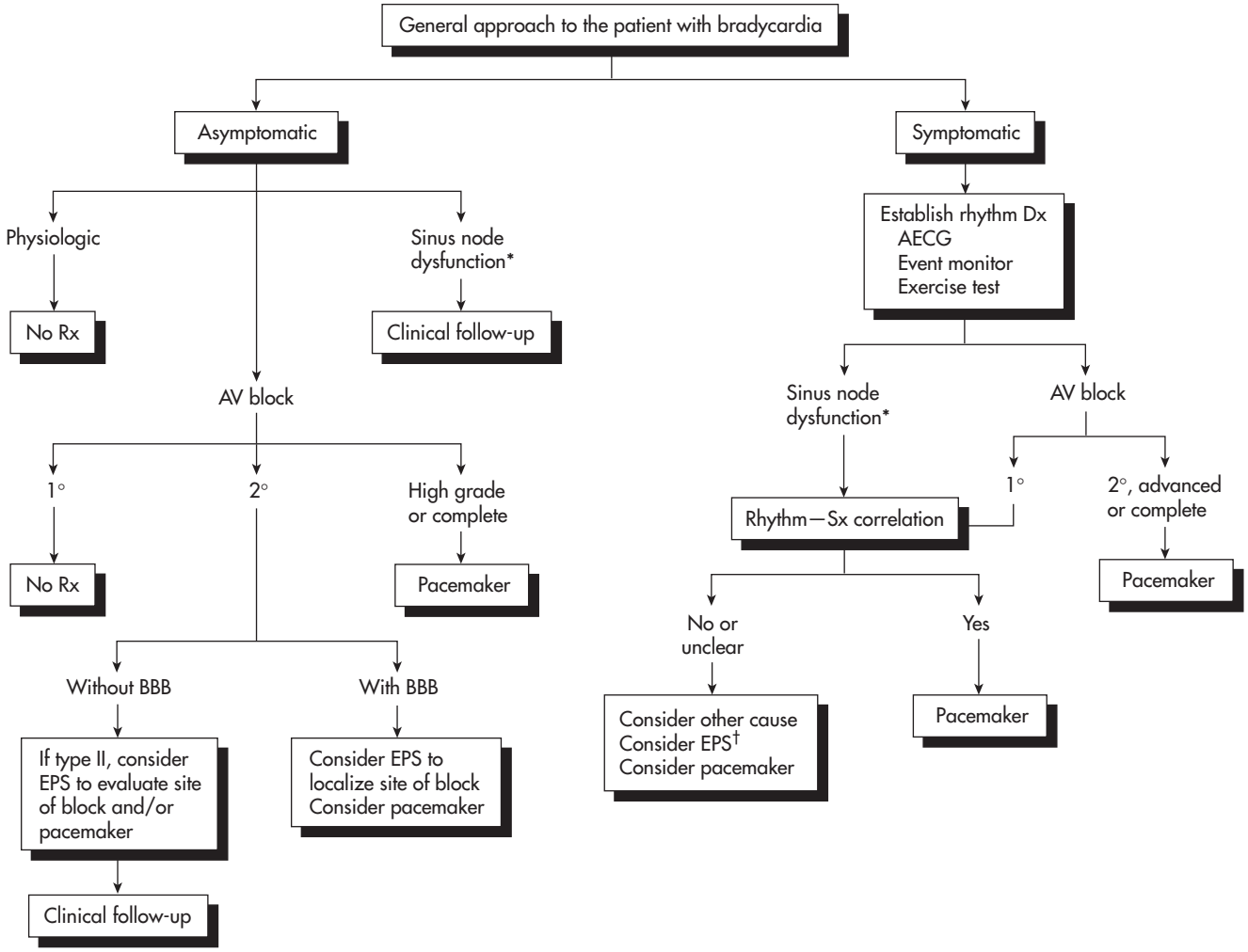


FIGURE 3-34 Evaluation of anovulatory bleeding. *CBC,* Complete blood count; *OCs,* oral contraceptives. (From Appleby J, Henderson M, Wathen PI: *Intern Med,* Sept:17, 1996.)

ICD-9CM # 456.0
ICD-10CM # D68.8 Other specified coagulation defects
K92.2 Gastrointestinal bleeding

FIGURE 3-35 Management algorithm for variceal bleeding. (From Goldman L, Schafer AL [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

ICD-9CM # 427.89 Unspecified bradycardia
427.81 Chronic bradycardia
770.8 Newborn bradycardia
337 Reflex bradycardia
ICD-10CM # R00.1 Bradycardia
I49.8 Other specified cardiac arrhythmias
I49.5 Sick sinus syndrome



*Includes bradycardia-tachycardia syndrome.
†EPS includes sinus node function and ventricular arrhythmia induction studies.

FIGURE 3-36 General approach to the patient with bradycardia. *AECG,* Ambulatory electrocardiography; *AV,* atrioventricular; *BBB,* bundle branch block; *Dx,* diagnostic; *EPS,* electrophysiologic study; *Rx,* treatment; *Sx,* symptoms; *1°*, first-degree; *2°*, second-degree. (From Goldman L, Braunwald E [eds]: *Primary cardiology,* ed 2, Philadelphia, 2003, Saunders.)

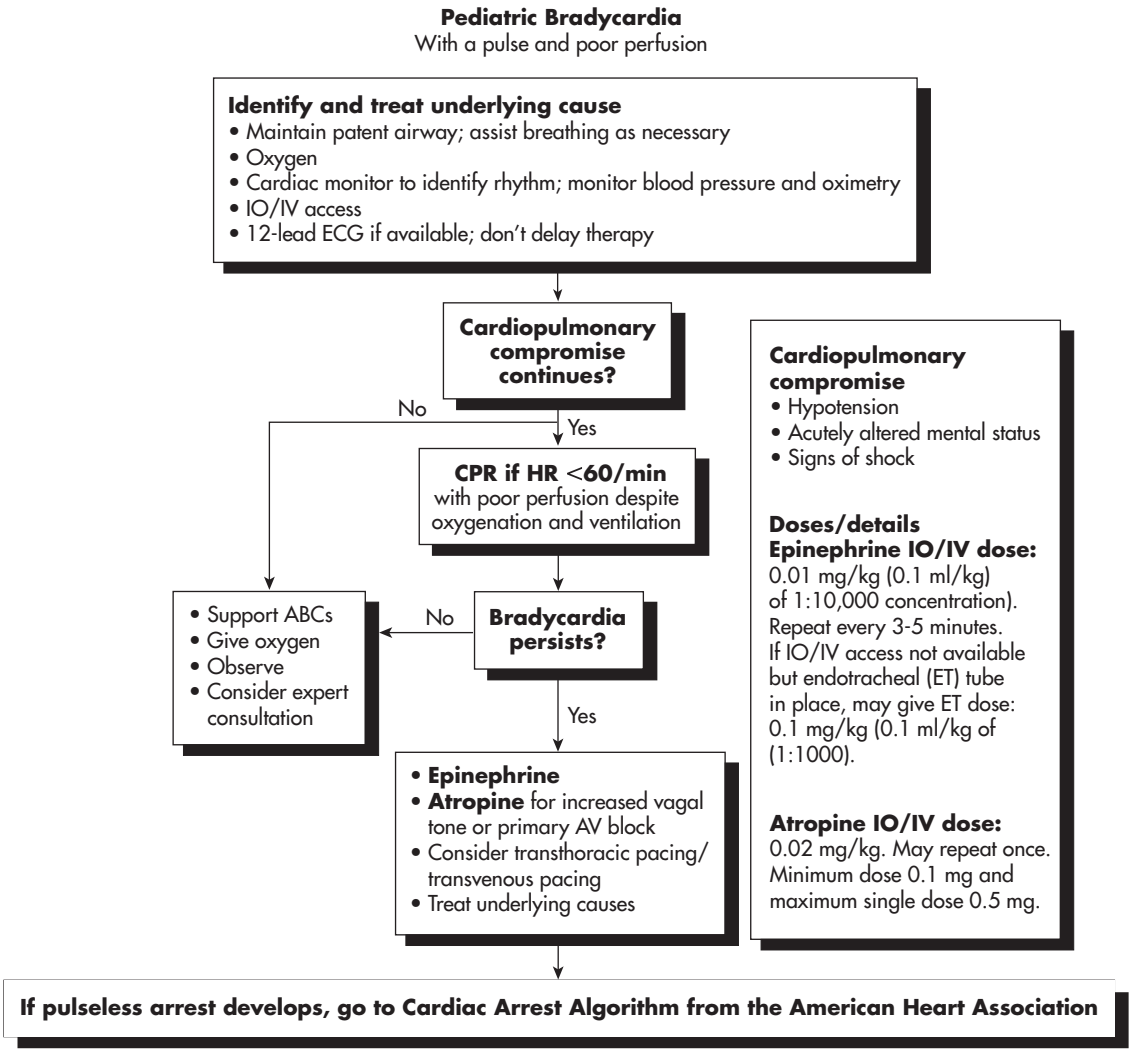
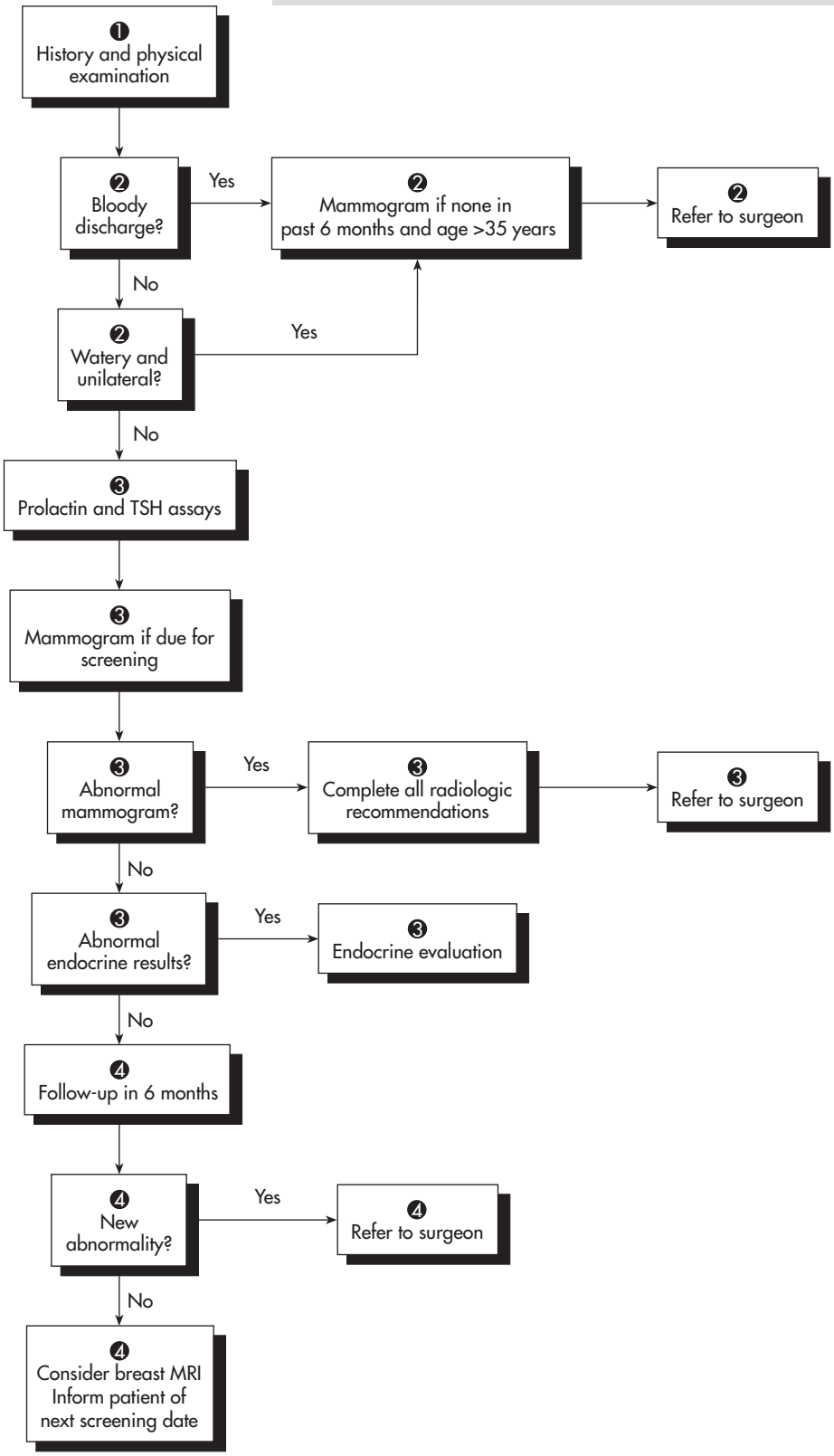


FIGURE E3-37 American Heart Association (AHA) guidelines for management of bradycardia. *ABCs,* Airway, breathing, and circulation; *AV,* atrioventricular; *CPR,* cardiopulmonary resuscitation; *IO,* intraosseous; *IV,* intravenous. (From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.)

BREAST, NIPPLE DISCHARGE EVALUATION

ICD-9CM # 611.79
ICD-10CM # N64.52 Nipple discharge
N64.51 Induration of breast
N64.53 Retraction of nipple
N64.59 Other signs and symptoms in breast



*Without palpable mass.

FIGURE 3-38 Breast cancer screening and evaluation. (Modified from Institute for Clinical Systems Integration, Minneapolis: *Postgrad Med* 100:182, 1996.)

Continued on next page

BREAST, NIPPLE DISCHARGE EVALUATION—cont'd

ICD-9CM # 611.79
ICD-10CM # N64.52 Nipple discharge
N64.51 Induration of breast
N64.53 Retraction of nipple
N64.59 Other signs and symptoms in breast

FIGURE 3-38 (Continued)

1. **History and physical examination***. Patients who present with a complaint of nipple discharge should be evaluated with breast-related history taking and a physical examination. History taking is aimed at uncovering and characterizing any other breast-related symptom. A risk assessment should also be undertaken for identified risk factors, including patient age over 50 years, any past personal history of breast cancer, history of hyperplasia on previous breast biopsies, and family history of breast cancer in first-degree relatives (mother, sister, daughter). Physical examination should include inspection of the breast for any evidence of ulceration or contour changes and inspection of the nipple for Paget's disease. Palpation should be performed with the patient in both the upright and the supine positions to determine the presence of any palpable mass.
2. **Bloody discharge?** If the discharge appears frankly bloody, the patient should be referred to a surgeon for evaluation. At the time of referral, a mammogram of the involved breast should be obtained if the patient is over 35 years of age and has not had a mammogram within the preceding 6 months. Similarly, patients with a watery, unilateral discharge should be referred to a surgeon for evaluation and possible biopsy.
3. **Endocrine tests. Mammogram.** If the discharge appears frankly milky or is bilateral, serum prolactin and serum thyroidstimulating hormone *(TSH)* assays should be performed to rule out the presence of an endocrinologic basis for the symptoms. At the time of that visit, a mammogram should also be performed if the patient is due for routine mammographic screening according to the recommended intervals. A patient with an abnormal mammogram should be further evaluated radiologically to better characterize the lesion and then be referred to a surgeon if appropriate. Make certain that all recommended additional views, ultrasound examinations, and follow-up studies have been obtained before referral to a surgeon. Should the mammogram appear normal, results of the assays for TSH and prolactin should be reviewed. If the results are abnormal, the patient should undergo appropriate evaluation for etiology, either by a primary care physician or by an endocrinologist.
4. **Six-month follow-up results.** If results of the mammogram and the endocrinologic screening studies are normal, the patient should return for a follow-up visit in 6 months to ensure that there has been no specific change in the character of the discharge, such as development of frank bleeding or Paget's disease, that would warrant surgical evaluation. If the evaluation at that follow-up visit fails to reveal any palpable or visible abnormalities, the patient should be returned to the routine screening process with studies performed at the recommended intervals.

*ICSI health care guidelines are designed to assist clinicians by providing an analytic framework for the evaluation and treatment of patients. They are not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem. In addition, guidelines are "living documents" that are expected to be imperfect and are subject to annual review and revision.

ICD-9CM # V76.10
ICD-10CM # R92.8 Abnormal breast diagnostic imaging
Z12.39 Encounter for other screening for malignant neoplasm of breast

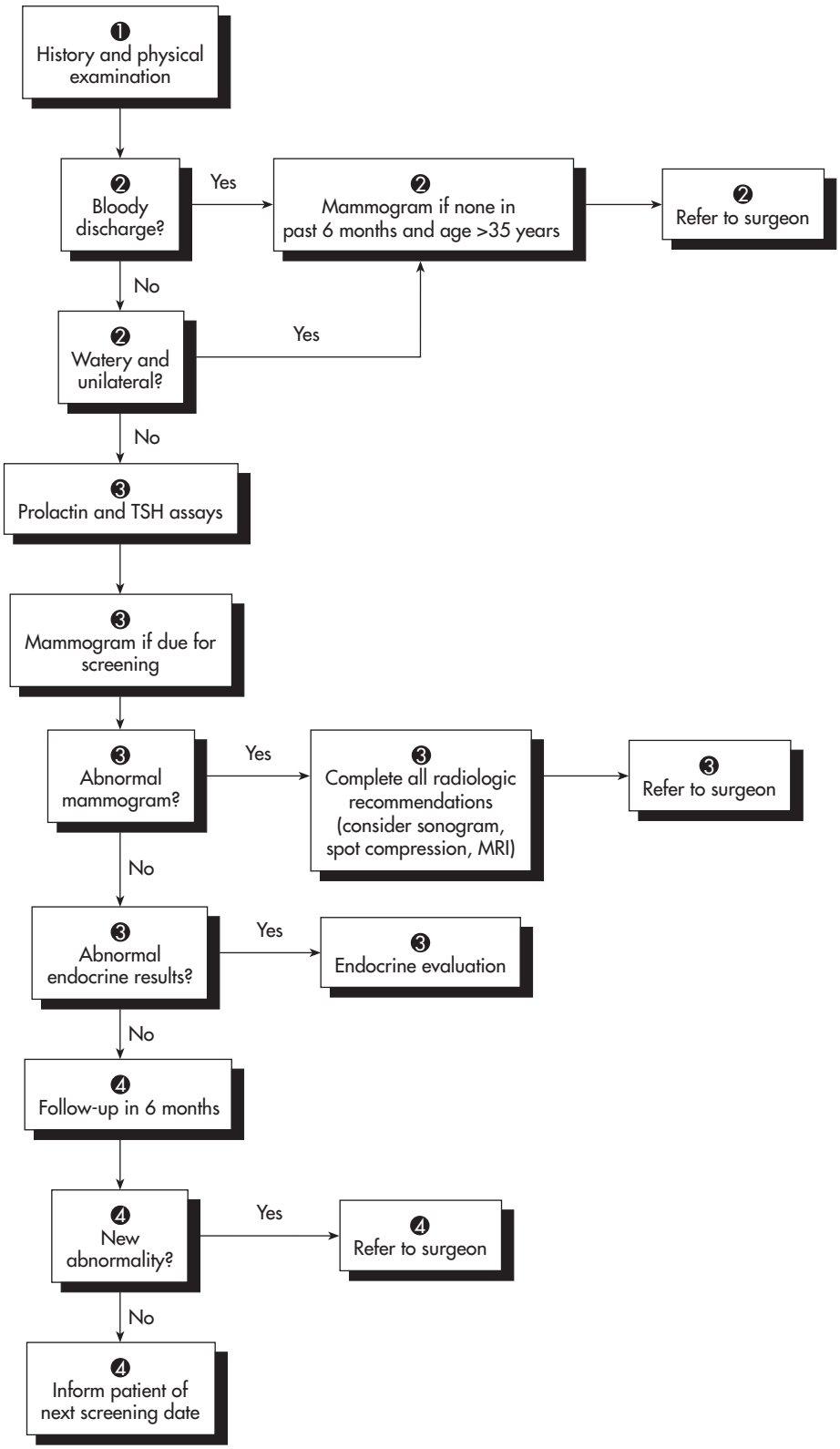


FIGURE E3-39 Breast cancer screening and evaluation (Modified from Institute for Clinical Systems Integration, Minneapolis: *Postgrad Med* 100:182-187, 1996.)

Continued on following page

ICD-9CM # V76.10
ICD-10CM # R92.8 Abnormal breast diagnostic imaging
Z12.39 Encounter for other screening for malignant neoplasm of breast

FIGURE E3-39 (Continued)

1. **Screening mammogram.*** Patients are most commonly referred to a radiologist for screening mammography. Occasionally, however, patients are referred for diagnostic mammography based on symptoms or findings on breast exam. In the event of an abnormal finding on the mammogram, complete evaluation under the direction of a radiologist is recommended. It is the responsibility of the radiologist to complete the radiologic assessment so that the best possible characterization of the abnormality can be provided in an expeditious fashion to the primary care physician who ordered the original study. Any recommendations for referral to a surgeon for possible biopsy should be made directly to the primary care physician. The ultimate responsibility to make the referral will rest with the primary care physician.
2. **Abnormal mammogram.** Sorting abnormalities. Suspicious for cancer? On obtaining an abnormal finding on a mammogram, the radiologist determines whether further mammographic images are required for completion of the evaluation process. This may include a repeated image of the involved breast at 6 months to document stability of a low-risk, probably benign lesion. Alternatively, spot compression, magnification, or both may be necessary to obtain further characterization of indeterminate breast lesions. These additional studies should be done with the radiologist present to reduce the risk of patient recall for further studies necessary to evaluate the same lesion. MRI of the breast should be considered.
3. **Ultrasound results.** When the mass is not immediately suggestive of cancer, an ultrasound should be performed to determine whether the lesion is solid. A solid mass should be further characterized for its level of benignity according to three criteria:
   - Size less than 15 mm
   - Three or fewer lobulations
   - More than 50% of the margin of the lesion appearing well circumscribed in any view
4. **Aspiration and results**. If the ultrasound of the soft-tissue mass demonstrates that it is a cystic lesion, the cyst should be further categorized by the criteria listed in the algorithm: irregular wall, as seen on ultrasonography; internal echoes; complex, septated appearance; and palpability within the region of the ultrasound-proven cyst. A positive finding for any of these criteria would be an indication for ultrasound-directed aspiration of the cyst. Aspiration should also be offered if the patient requests it.

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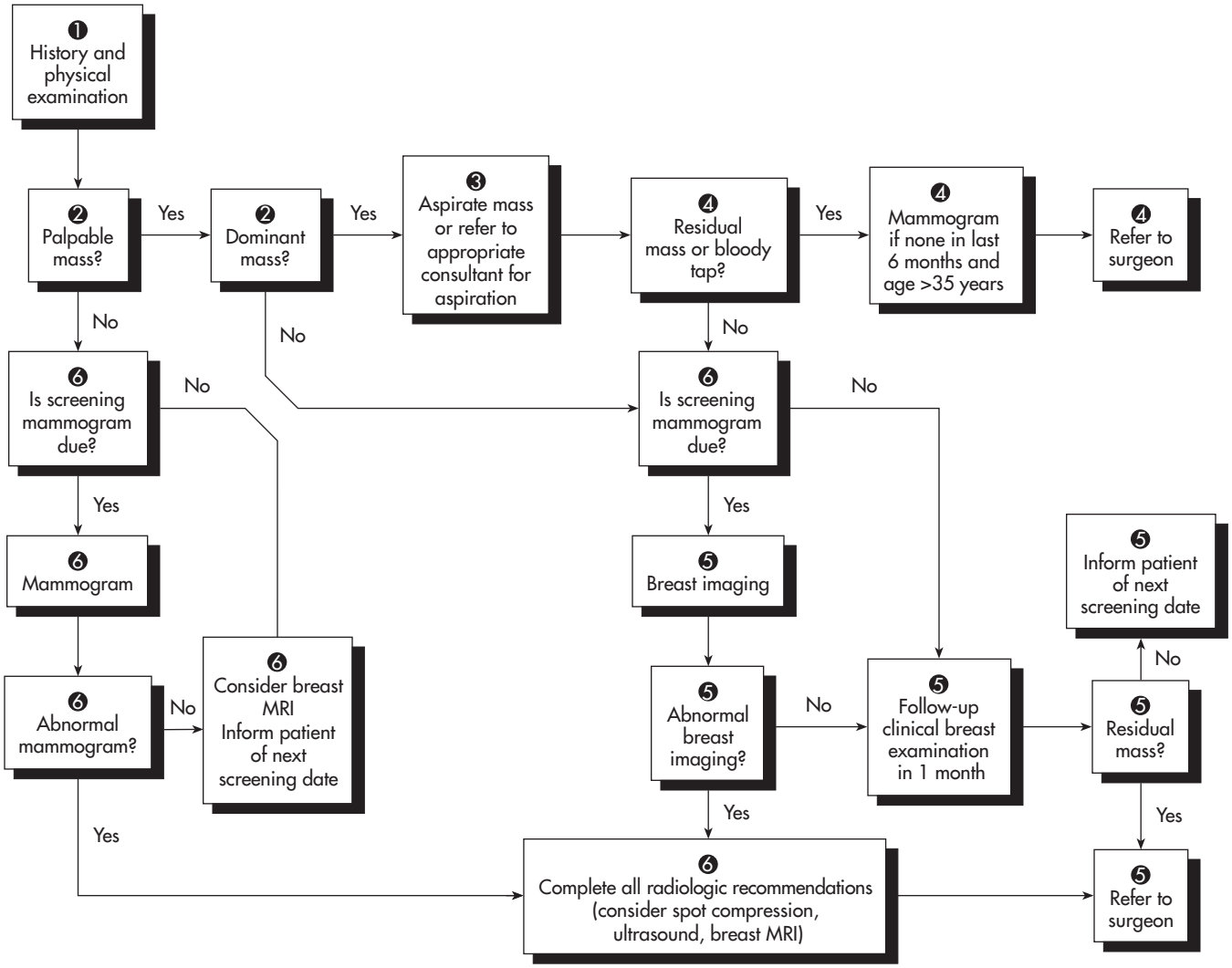

FIGURE 3-40 Breast cancer screening and evaluation. (Modified from Institute for Clinical Systems Integration, Minneapolis: *Postgrad Med* 100:182, 1996.)

1. **History and physical examination.***Primary care evaluation is initiated with history taking aimed at uncovering and characterizing any breast-related symptom. A risk assessment should also be undertaken for identified risk factors, including patient age over 50 years, any past personal history of breast cancer, history of hyperplasia on previous breast biopsies, and family history of breast cancer in first-degree relatives (mother, sister, daughter). Physical examination should include inspection of the breast for any evidence of ulceration or contour changes and inspection of the nipple for Paget's disease. Palpation should be performed with the patient in both the upright and supine positions to determine the presence of any palpable mass.
2. **Palpable mass? Dominant mass?** A dominant mass is a palpable finding that is discrete and clearly different from the surrounding parenchyma. If a palpable mass is identified, it should be determined whether it represents a dominant (i.e., discrete) mass, which requires immediate evaluation. The primary care physician or appropriate consultant should attempt to aspirate any dominant mass because a simple cyst may be uncovered, in which case aspiration completes the evaluation process.
3. **Aspirate mass or refer for aspiration.** Aspiration of a dominant palpable mass should be performed by the primary care physician or by the appropriate consultant. The breast skin is prepped with alcohol. Then, with the lesion immobilized by the nonoperating hand, an 18- to 25-gauge needle mounted on a 10-ml syringe is directed to the central portion of the mass for a single attempt at aspiration. Successful aspiration of a simple cyst would yield a nonbloody fluid with complete resolution of the dominant mass. Typical watery fluid may be discarded. However, cyst fluid that is bloody or unusually tenacious should be examined cytologically.
4. **Residual mass or bloody tap?** Mammogram if none in past 6 months. Refer to surgeon. Should the mass remain after the attempt at aspiration or should frank blood be aspirated during the process, the presence of a malignant process cannot be ruled out. Patients with a residual mass or bloody tap should be referred to a surgeon for possible biopsy. Before the referral, a mammogram should be obtained for any patient over age 35 years who has not had a mammogram within the preceding 6 months. In patients 35 years and under, obtaining any other breast-imaging studies should be left to the discretion of the surgeon or radiologist.

Continued on following page

FIGURE 3-40 (Continued)

5. **Is screening mammogram due?** Breast imaging. Follow-up clinical breast examination. Refer to surgeon. Should physical examination demonstrate a palpable mass that is not clearly a discrete and dominant mass, its size, location, and character should be documented in anticipation of a follow-up examination. A screening mammogram should be obtained if one has not been done within the recommended interval. If no mammogram is required or if a required mammogram demonstrates no abnormality, a follow-up examination in 1 month is indicated. Breast MRI should be considered. Should any residual mass be identified, the patient should be referred to a surgeon for possible biopsy. Patients with a persisting nondominant palpable mass that does not resolve within 1 month and those with any recurring cystic mass should be referred for surgical evaluation. If no mass is apparent at the time of the follow-up examination, the patient should then be informed of the appropriate date for her next screening examination, according to the recommended intervals.
6. **Screening mammogram and results.** After completion of the physical examination, the appropriateness of a routine screening mammogram should be determined. If a mammogram is done, the radiologist should provide the results to the primary care physician for reporting to the patient. Should any abnormalities be uncovered, it will be the responsibility of the radiologist to complete any additional imaging studies required for the complete radiographic characterization of the lesion. The radiologist should make certain that all recommended additional views, follow-up studies, and ultrasound examinations have been completed before referral to a surgeon. However, it is important that the primary care physician who ordered the mammogram review the results of these studies to understand fully the opinion of the radiologist and to ensure that all recommendations of the radiologist have been completed. Should the radiologist recommend that surgical consultation is warranted, it will be the responsibility of the primary care physician to establish this referral.

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*CSI health care guidelines are designed to assist clinicians by providing an analytic framework for the evaluation and treatment of patients. They are not intended either to replace a clinician's judgment or to establish a protocol for all patients with a particular condition. A guideline will rarely establish the only approach to a problem. In addition, guidelines are living documents that are expected to be imperfect and are subject to annual review and revision.

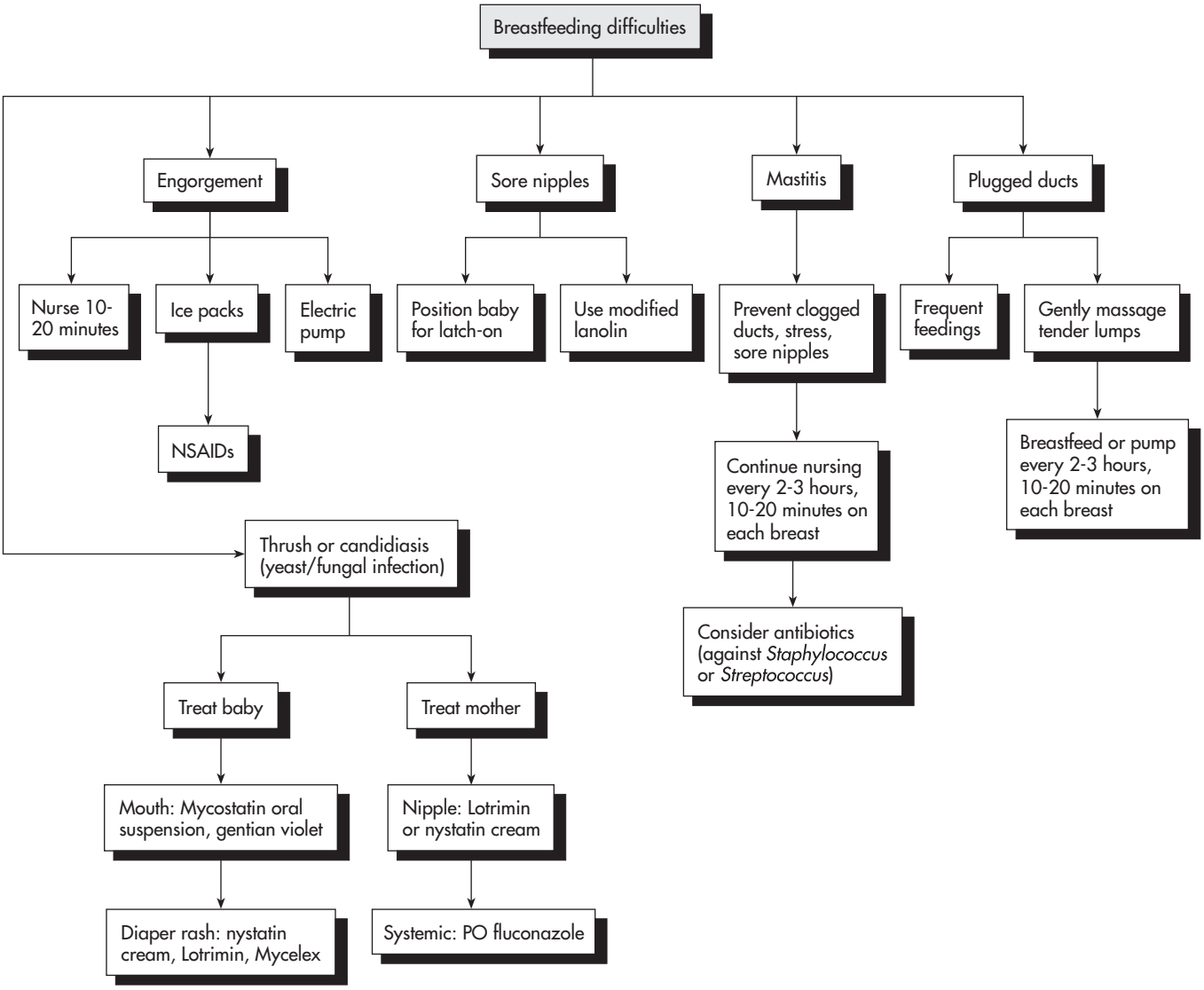
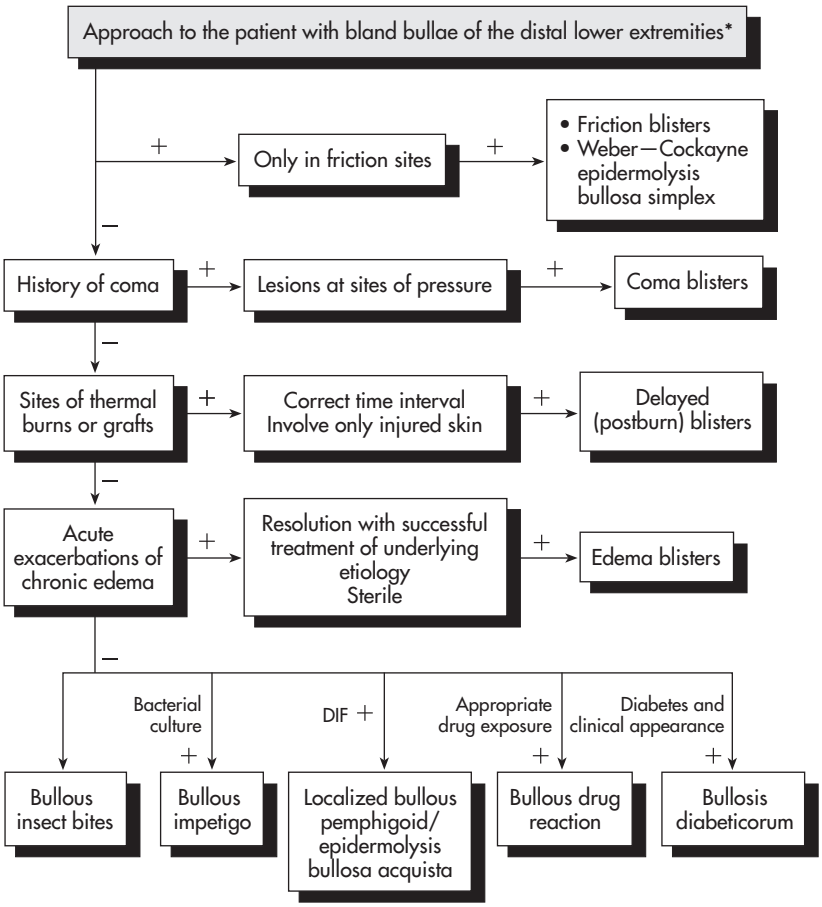


FIGURE E3-41 Management of breastfeeding difficulties. *NSAIDs,* Nonsteroidal anti-inflammatory drugs. (Modified from Zuspan FP [ed]: *Handbook of obstetrics, gynecology, and primary care,* St Louis, 1998, Mosby.)



*Ankles and dorsa of feet

FIGURE E3-42 Approach to the patient with bland bullae of the distal lower extremities. (Modified from Bolognia JL, Jorizzo JL, Rapini RP: *Dermatology,* St Louis, 2003, Mosby.)

CARDIOMEGALY ON CHEST X-RAY

ICD-9CM # 429.3 Idiopathic cardiomegaly
746.89 Congenital cardiomegal
402.0 Hypertensive cardiomegaly, malignant
402.1 Hypertensive cardiomegaly, benign
402.11 Hypertensive cardiomegaly with congestive heart failure
ICD-10CM # I51.7 Cardiomegaly
Q24.8 Other specified congenital malformations of heart
I11.9 Hypertensive heart disease without heart failure
I11.0 Hypertensive heart disease with heart failure
Q23.8 Other congenital malformations of aortic and mitral valves

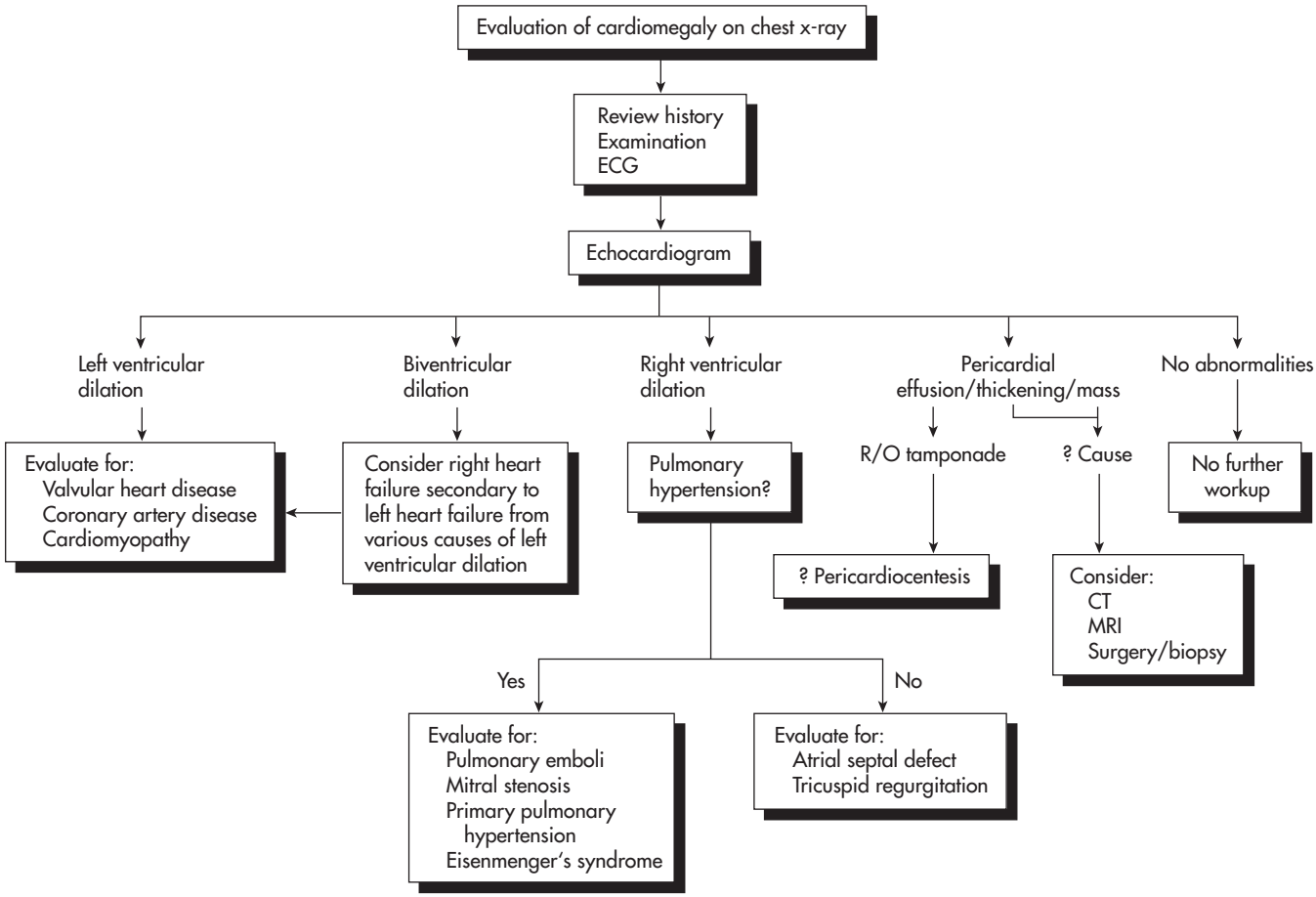


FIGURE 3-43 Approach to the patient with cardiomegaly. When cardiomegaly is found on the chest radiograph, the history and physical examination should be reviewed and an electrocardiogram *(ECG)* performed before obtaining a two-dimensional Doppler echocardiographic study. Cardiomegaly may be explained by left ventricular dilation, biventricular dilation, right ventricular dilation, or pericardial abnormalities, or it may be found to be spurious on the echocardiogram. Rarely, isolated abnormalities of the atrium, particularly the left atrium, may cause abnormalities on the chest radiograph but will not cause true cardiomegaly. Depending on the echocardiographic findings, further tests can help elucidate the cause of echocardiographically confirmed cardiomegaly. *CT*, Computed tomography; *MRI,* magnetic resonance imaging; *R/O,* rule out. (From Goldman L, Braunwald E [eds]: *Primary cardiology,* ed 2, Philadelphia, 2003, Saunders.)

ICD-9CM # 425.4
ICD-10CM # I42.5 Other restrictive cardiomyopathy
I42.8 Other cardiomyopathies

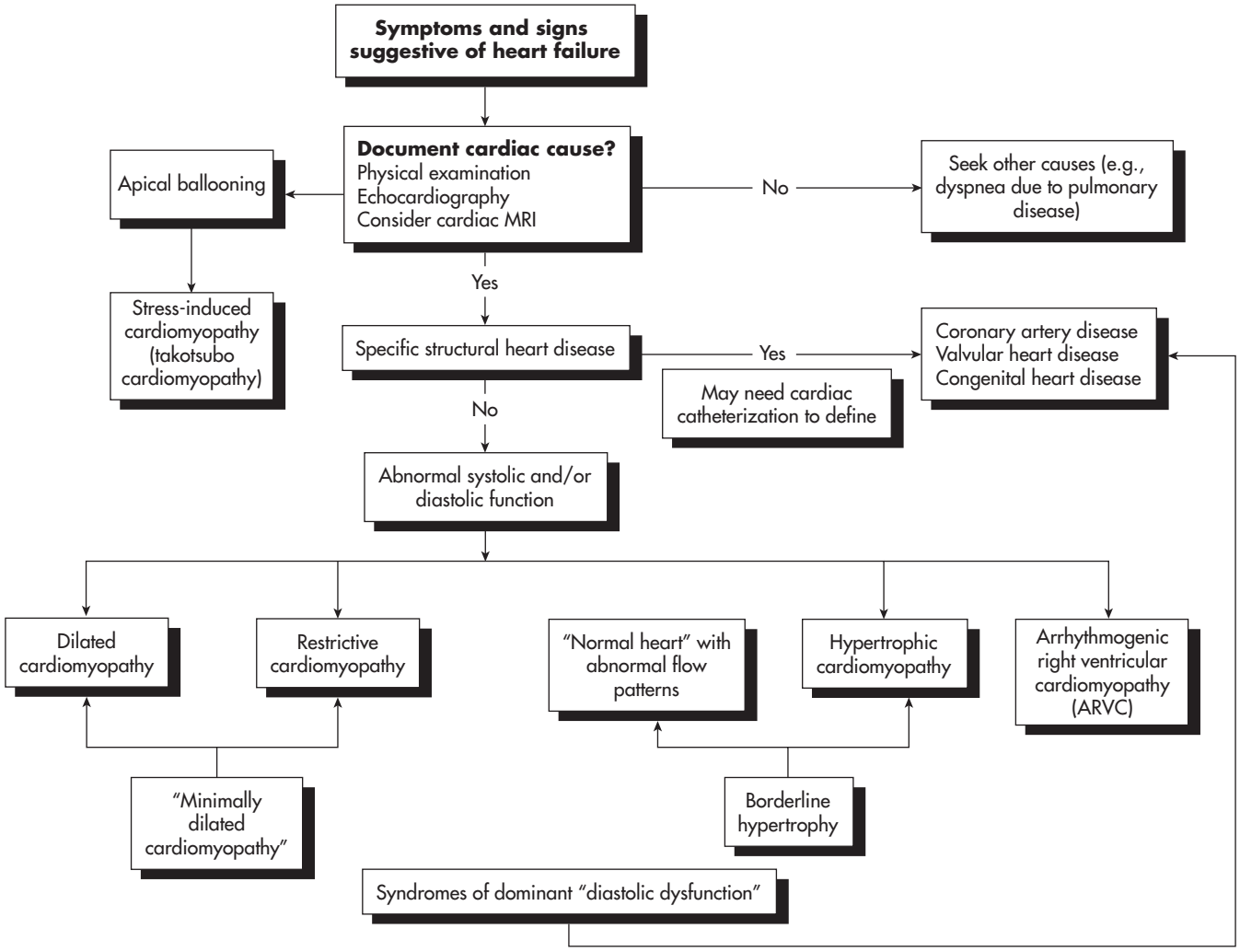


FIGURE 3-44 Initial approach to classification of cardiomyopathy. The evaluation of symptoms or signs consistent with heart failure first includes confirmation that they can be attributed to a cardiac cause. Although this conclusion is often apparent from routine physical examination, echocardiography serves to confirm cardiac disease and provides clues to the presence of other cardiac disease, such as focal abnormalities, suggesting primary valve disease or congenital heart disease. Having excluded these conditions, cardiomyopathy is generally considered to be dilated, restrictive, or hypertrophic. Patients with apparently normal cardiac structure and contraction are occasionally found to demonstrate abnormal intracardiac flow patterns consistent with diastolic dysfunction but should also be evaluated carefully for other causes of their symptoms. Most patients with so-called diastolic dysfunction also demonstrate at least borderline criteria for left ventricular hypertrophy, frequently in the setting of chronic hypertension and diabetes. A moderately decreased ejection fraction without marked dilation or a pattern of restrictive cardiomyopathy is sometimes referred to as "minimally dilated cardiomyopathy," which may represent either a distinct entity or a transition between acute and chronic disease. (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 23, Philadelphia, 2008, Saunders.)

ICD-9CM # 425.4
ICD-10CM # I42.5 Other restrictive cardiomyopathy
I42.8 Other cardiomyopathies

TABLE 3-2 Profiles of Myocardial Disease

	Hypertrophic	Dilated	Restrictive	ARVC
Causes	Genetic	Myocarditis Metabolic/endocrine Genetic	Infiltrative or storage diseases Endomyocardial (e.g., Löffler's, carcinoid) Genetic	Genetic
Ejection fraction	Increased	Reduced	25%-50%	Normal until end stage 30% regional LV disease
Left ventricular End-diastolic dimension	Usually decreased	Increased	Normal	Normal until end stage Right ventricle dilated
Left ventricular wall thickness	Increased	Normal	Normal or mildly increased	Normal
Atrial size	Increased	Increased	Increased; may be massive	Left atrium normal; right dilated in severe disease
Valvular disease	Mitral regurgitation (SAM)	Mitral (functional); tricuspid regurgitation in late stages	Mitral and tricuspid regurgitation, rarely severe	Tricuspid regurgitation in severe disease
Common symptoms	Dyspnea; chest pain, syncope Late: orthopnea, PND	Dyspnea, fatigue Late: orthopnea, PND	Dyspnea Late: orthopnea, PND, right heart failure	Palpitations, syncope Late: right heart failure
Arrhythmia	Atrial fibrillation, ventricular tachycardia; conduction block in PRKAG2, mitochondrial; Fabry's disease	Ventricular tachyarrhythmias; heart block in Chagas' disease, giant cell myocarditis, laminopathies	Atrial fibrillation; conduction block in sarcoid, amyloidosis, desminopathy	Ventricular ectopy and tachycardia

ARVC, Arrhythmogenic right ventricular cardiomyopathy; *LV,* left ventricular; *SAM,* systolic anterior motion of mitral valve; *PND,* paroxysmal nocturnal dyspnea.
From Goldman L, Schafer AI [eds]: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

CARDIOMYOPATHY, ISCHEMIC

ICD-9CM # 414.8
ICD-10CM # I25.5 Ischemic cardiomyopathy
I25.89 Other forms of chronic ischemic heart disease
I25.9 Chronic ischemic heart disease, unspecified

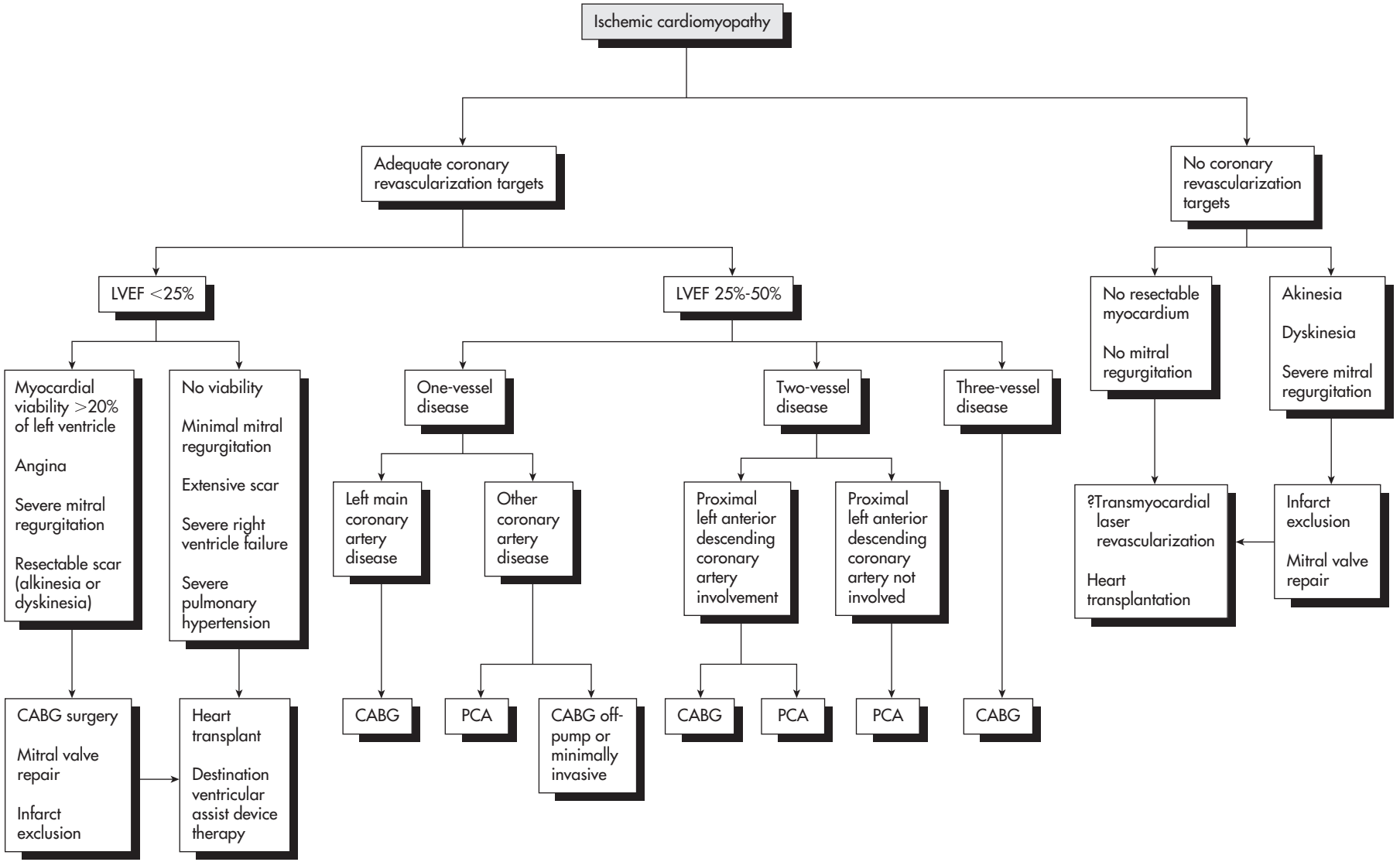


FIGURE E3-45 Choice of revascularization procedures in heart failure. Approaches should be dictated by the degree of left ventricular dysfunction, the presence of significant amounts of viable myocardium, the severity of valvular regurgitation, the amount of resectable myocardial scar, and suitability for ventricular assist device of heart transplant "bail out." Targets for revascularization must also be present. These considerations will dictate, in large part, which patients may be candidates for percutaneous revascularization strategies as well. All patients, regardless of procedure, require appropriate medication treatments and atherosclerotic cardiovascular risk factor prevention. *CABG,* Coronary artery bypass graft; *LVEF,* left ventricular ejection fraction; *PCA,* percutaneous coronary angioplasty. (From Crawford MH, DiMarco JP, Paulus WJ [eds]: *Cardiology,* ed 2, St Louis, 2004, Mosby.)

ICD-9CM #	437.1	Cerebral ischemia (chronic)
	435.9	Cerebral ischemia intermittent (transient)
ICD-10CM #	I67.82	Cerebral ischemia
	I67.81	Acute cerebrovascular insufficiency
	I67.89	Other cerebrovascular disease
	I67.848	Other cerebrovascular vasospasm and vasoconstriction
	G45.9	Transient cerebral ischemic attack, unspecified

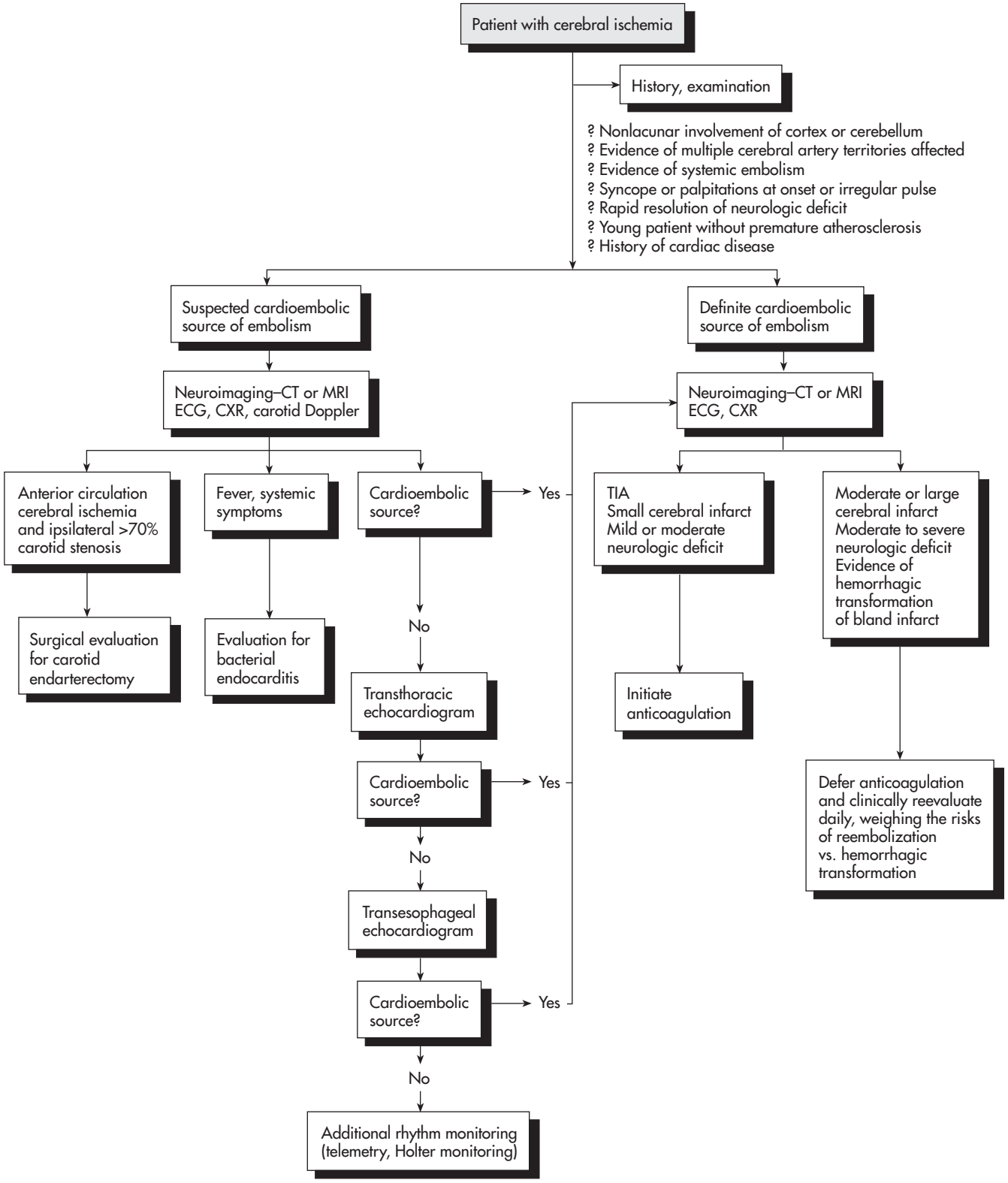


FIGURE 3-46 Evaluation of patients with cerebral ischemia for a cardioembolic source. *CT,* Computed tomography; *CXR,* chest radiograph; *ECG,* electrocardiogram; *MRI,* magnetic resonance imaging; *TIA,* transient ischemic attack. (Modified from Johnson R [ed]: *Current therapy in neurologic disease,* ed 5, St Louis, 1997, Mosby.)

ICD-9CM # 786.50
ICD-10CM # R07.2 Pain(s) heart
R07.3 Pain(s) chest anterior wall
R07.4 Pain(s) chest

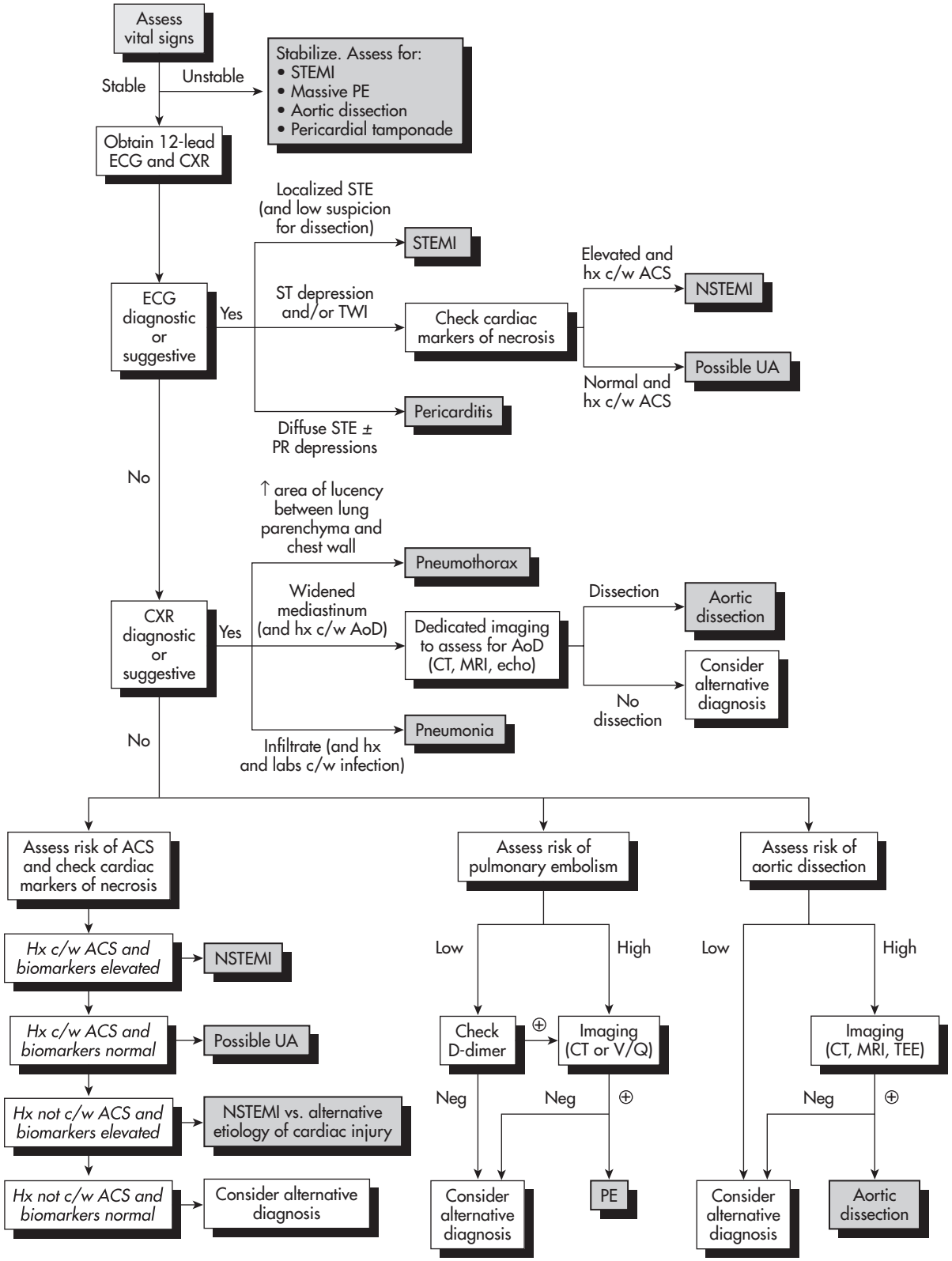
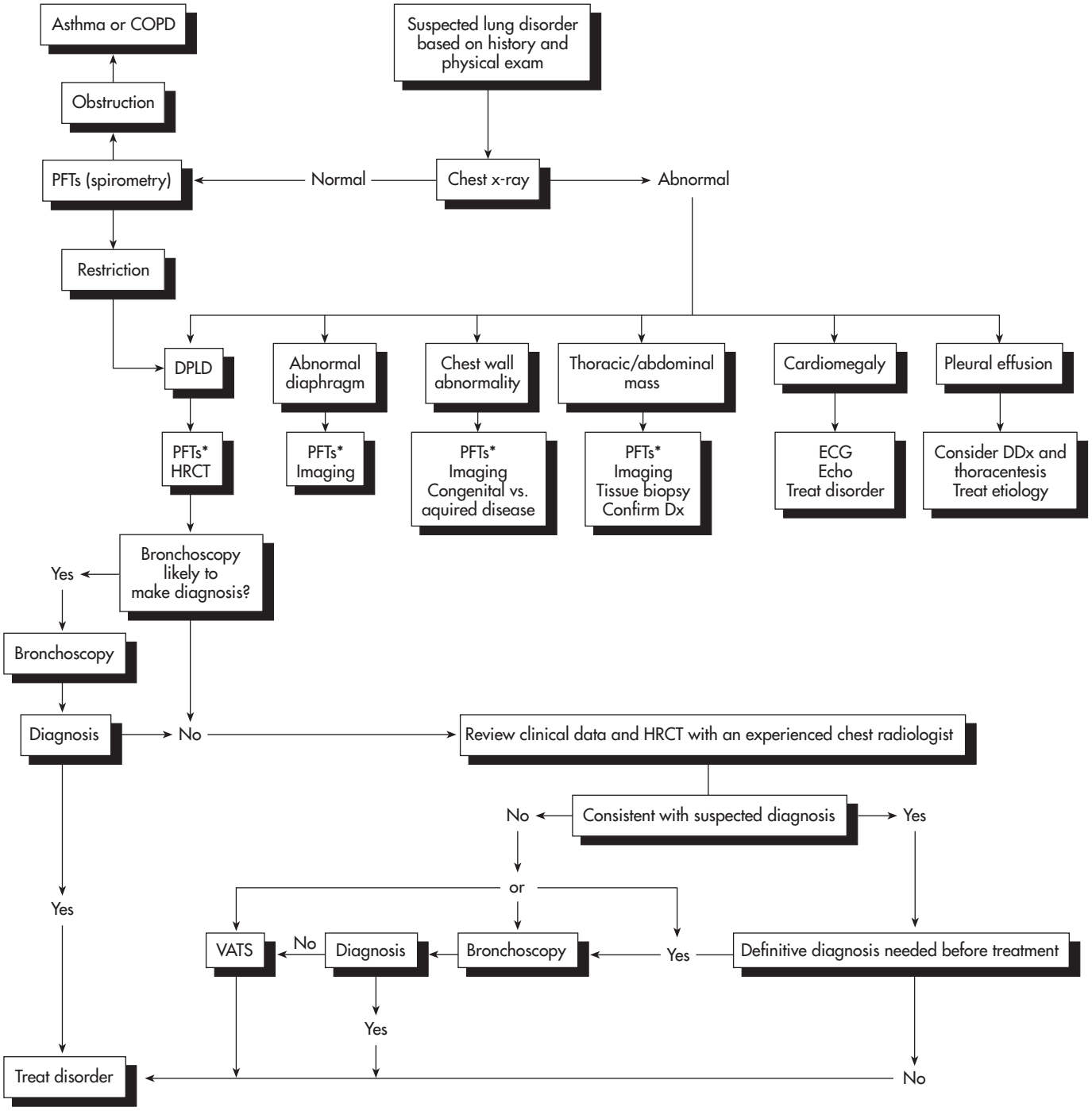


FIGURE 3-47 Algorithm for the initial diagnostic approach to a patient with chest pain. *AoD*, aortic dissection; *c/w*, consistent with; *CXR*, chest x-ray; *hx*, history; *NSTEMI*, non–ST-segment myocardial infarction; *PE*, pulmonary embolism; *STE*, ST elevation; *STEMI*, ST-segment myocardial infarction; *TEE*, transesophageal echocardiography; *UA*, unstable angina; *V/Q*, ventilation-perfusion scan. (From Bonow RO et al: *Braunwauld's heart disease*, ed 9, Philadelphia, 2012, Elsevier.)

CHEST X-RAY ABNORMALITY (SUSPECTED)

ICD-9CM # 793.1
ICD-10CM # R91.8 Other nonspecific abnormal finding of lung field



*PFTs = Full set including lung volumes and DLCO

FIGURE 3-48 Diagnostic algorithm. *COPD,* Chronic obstructive pulmonary disease; *DDx,* differential diagnosis; *D LCO*, diffusion capacity; *DPLD,* diffuse parenchymal lung disease; *ECG,* electrocardiogram; *HRCT,* high-resolution computed tomography; *PFTs,* pulmonary function tests; *VATS,* video-assisted thoracoscopic surgery. (Modified from Runge MS, Greganti MA: *Netter's internal medicine,* Philadelphia, 2008, Saunders.)

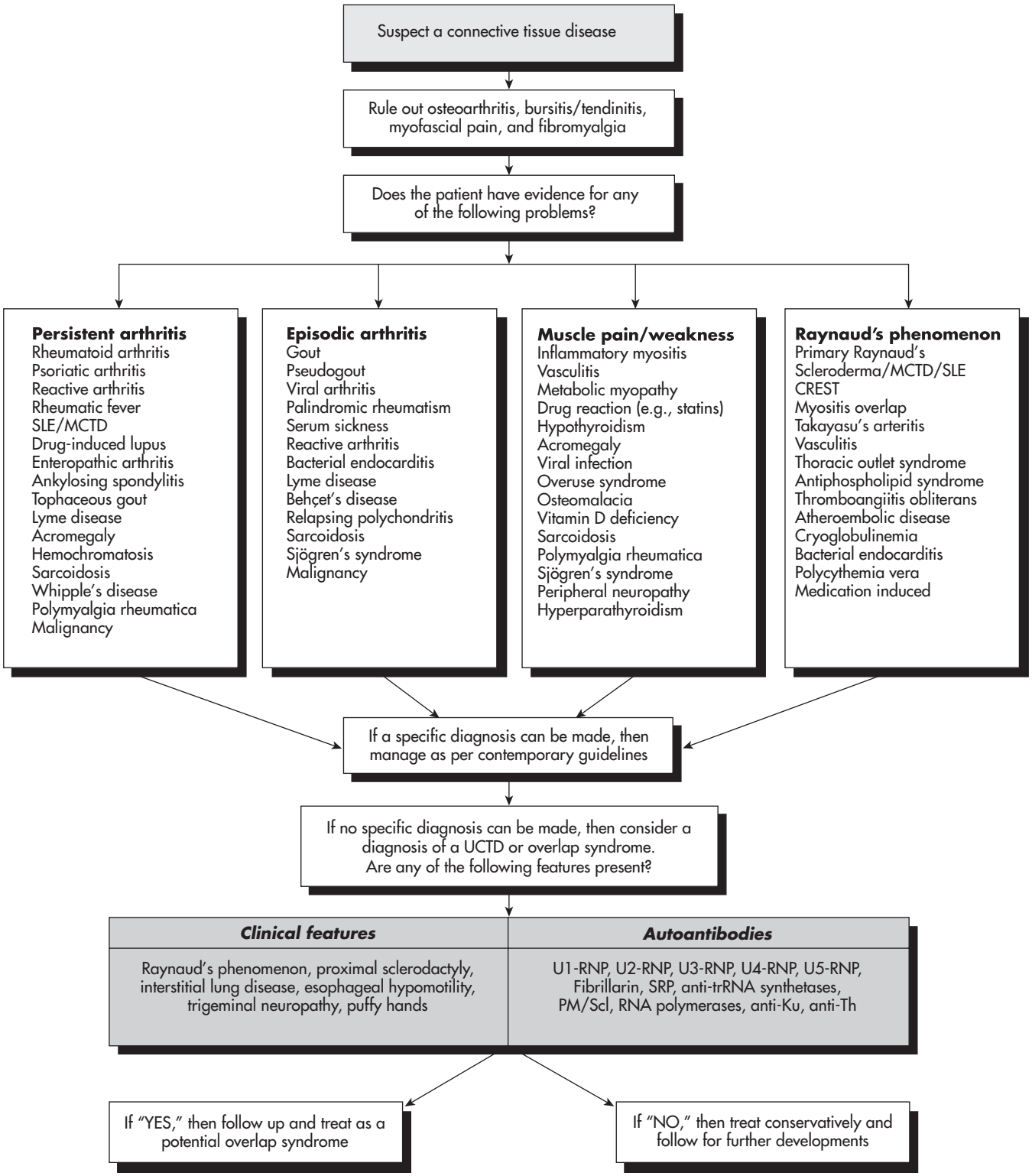


FIGURE 3-49 Algorithm for evaluating patients with undifferentiated connective tissue disease (UCTD). *CREST,* calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia; *MCTD*, mixed connective tissue disease; *SLE*, systemic lupus erythematosus. (From Firestein GS, Budd RC, Gabriel SE, et al: *Kelley's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders. [Original credit: Courtesy Dr. George Raj, Non Surgical Spine and Joint Clinic PS, Bellingham, Wash.])

ICD-9CM # 564.0
ICD-10CM # K59.00 Constipation, unspecified

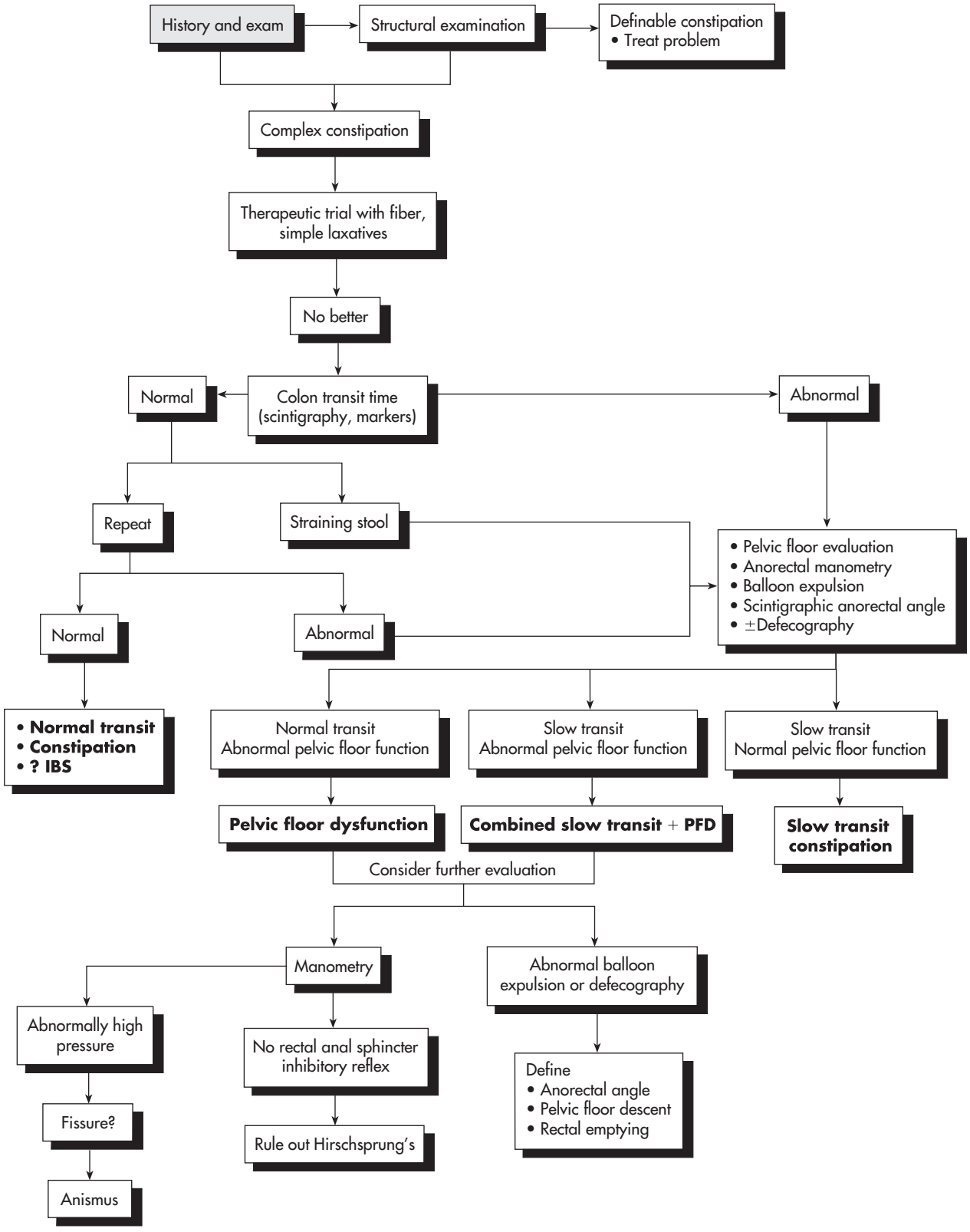


FIGURE 3-50 Evaluation of constipation. *IBS,* Irritable bowel syndrome; *PFD,* pelvic floor dysfunction. (From Pemberton JH et al: *The pelvic floor: its functions and disorders,* Philadelphia, 2001, Saunders.)

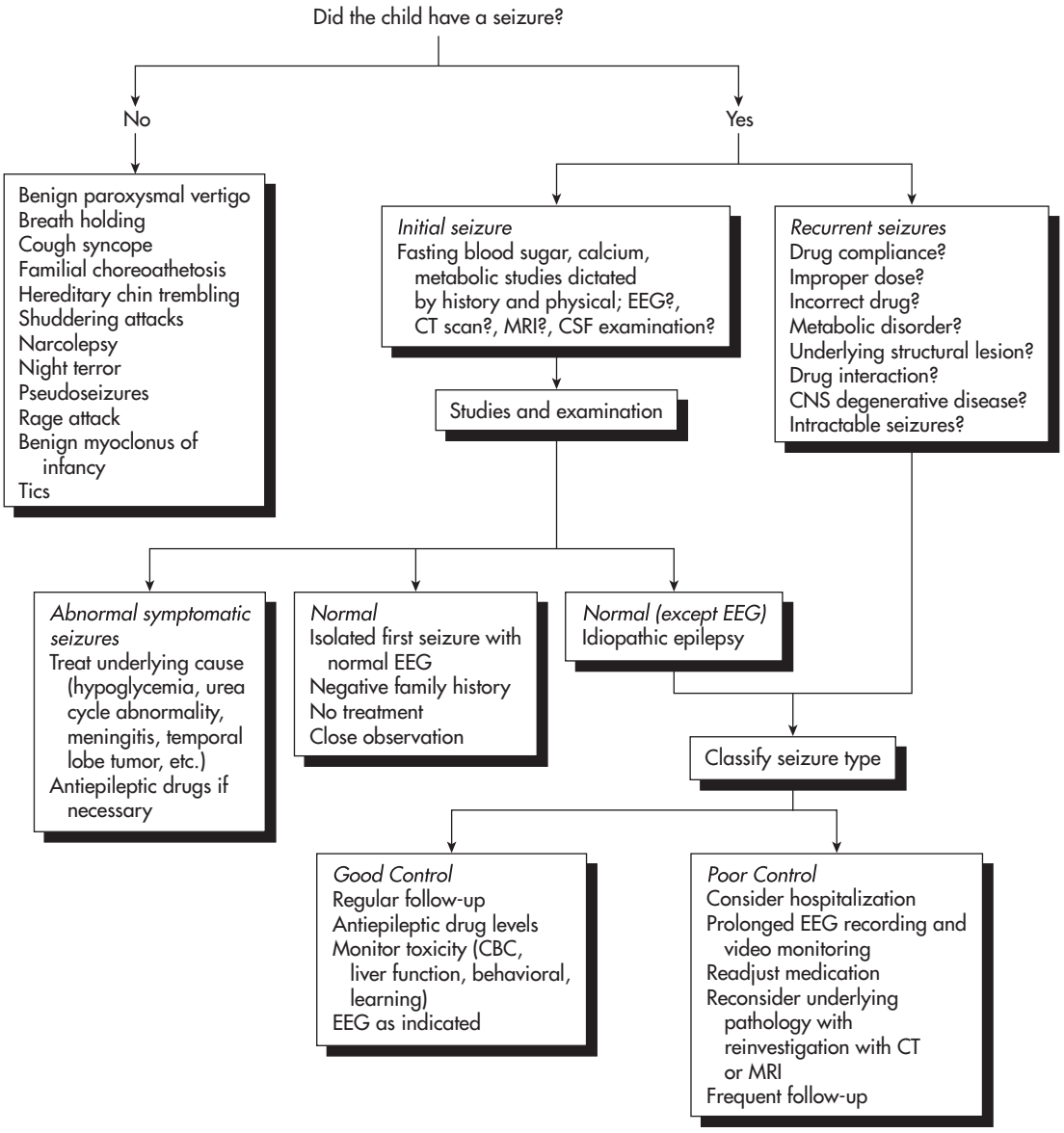


FIGURE E3-51 An approach to the child with a suspected convulsive disorder. *CBC,* Complete blood count; *CNS,* central nervous system; *CSF,* cerebrospinal fluid; *CT,* computed tomography; *EEG,* electroencephalogram; *MRI,* magnetic resonance imaging. (From Behrman RE: *Nelson textbook of pediatrics,* ed 18, Philadelphia, 2007, Saunders.)

ICD-9CM # 918.1 Corneal abrasion
743.9 Corneal anomalies NOS
ICD-10CM # H18.9 Cornea disorders
S05.00XA Injury of conjunctiva and corneal abrasion without foreign body, unspecified eye, initial encounter
Q15.9 Congenital malformation of eye, unspecified

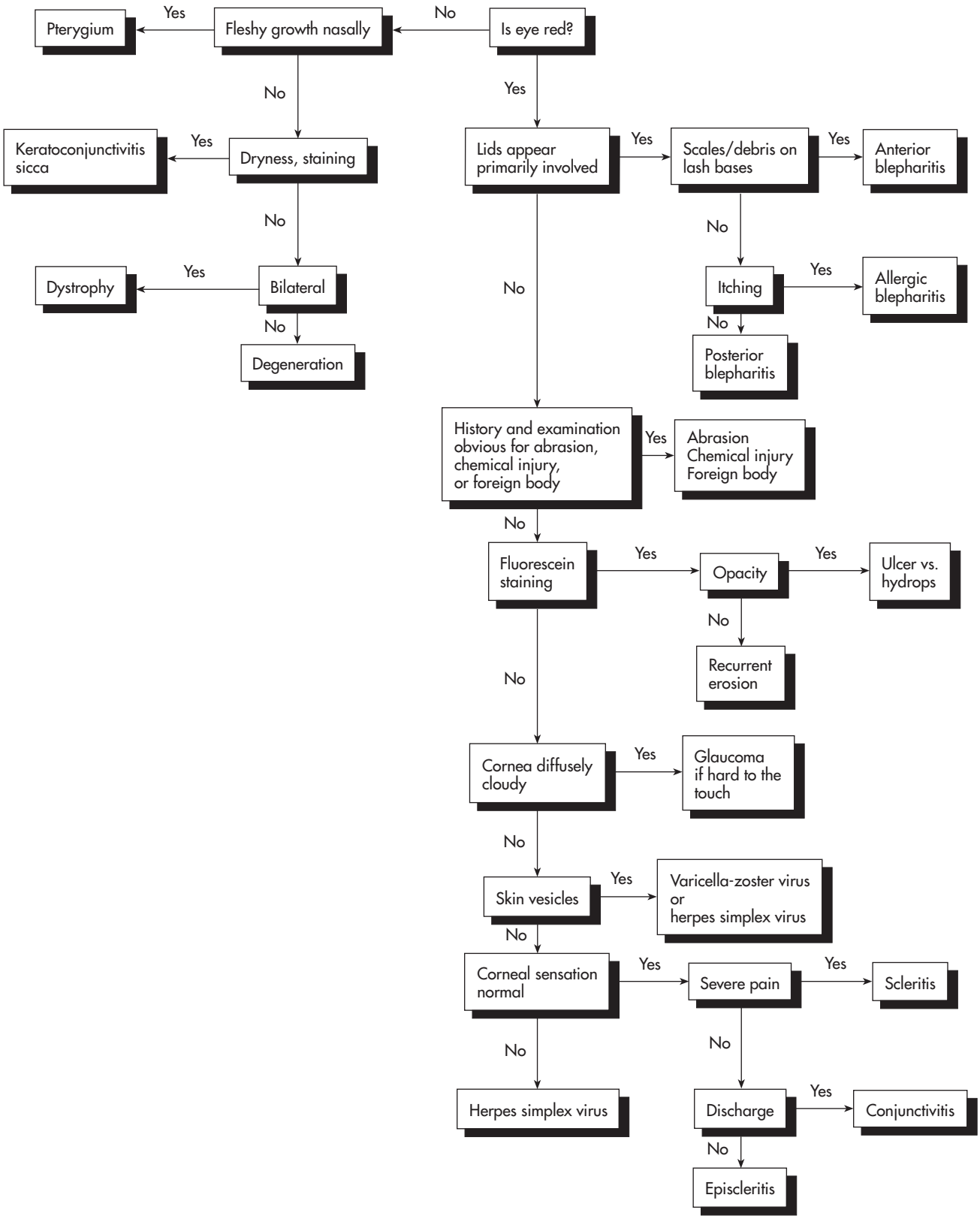


FIGURE E3-52 Approach to the patient with corneal disorders. (From Noble J [ed]: *Primary care medicine,* ed 3, St Louis, 2001, Mosby.)

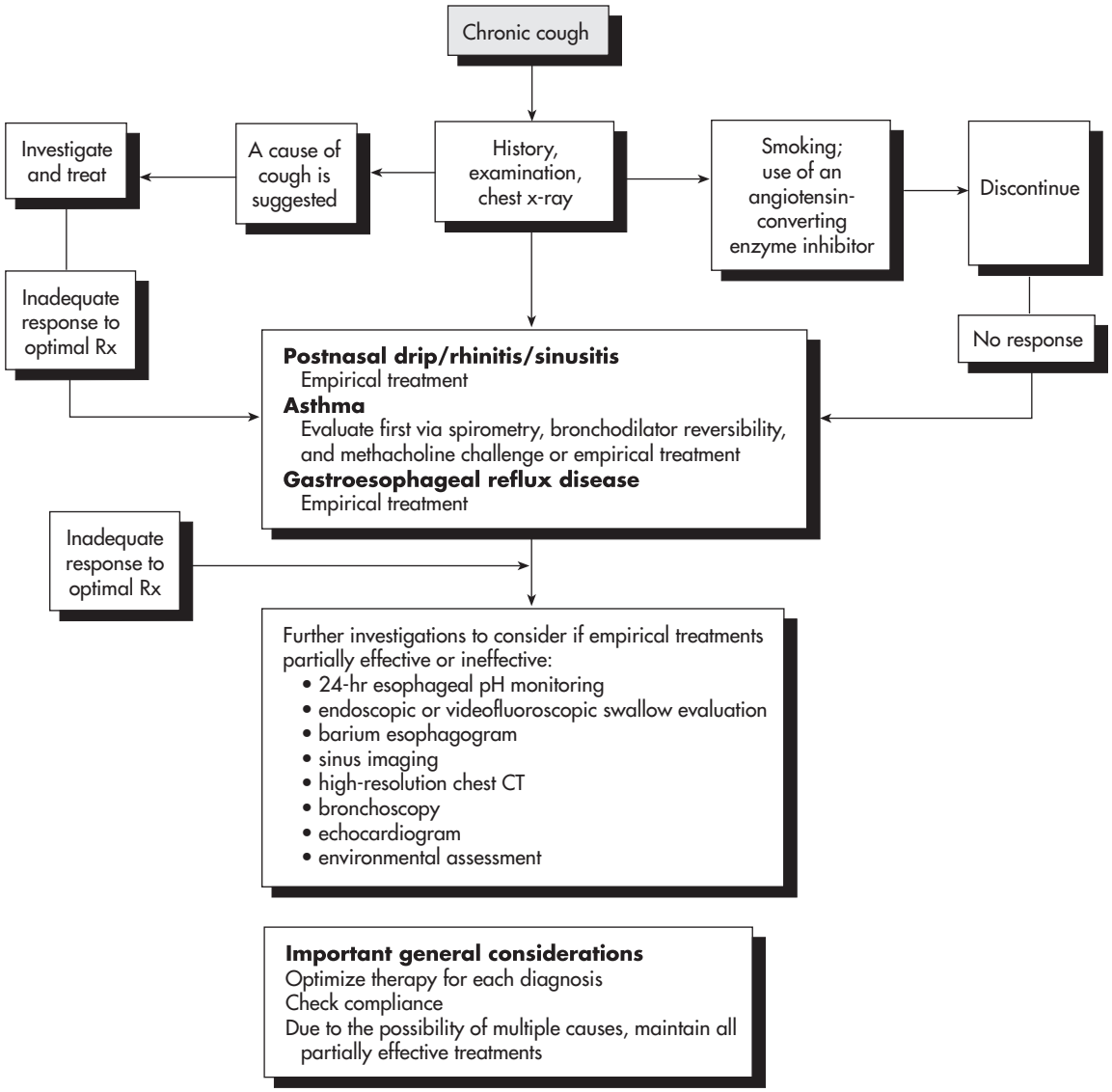


FIGURE 3-53 Algorithm for the management of chronic cough lasting >8 weeks. *CT,* Computed tomography; *Rx,* prescription. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

TABLE 3-3 Testing Characteristics of Diagnostic Protocol for Evaluation of Chronic Cough

Tests	Diagnosis	Positive Predictive Value (%)	Negative Predictive Value (%)
Sinus radiograph	Sinusitis	57-81	95-100
Methacholine inhalation challenge	Asthma	60-82	100
Modified barium esophagography	GERD, esophageal stricture	38-63	63-93
Esophageal pH*	GERD	89-100	>100
Bronchoscopy	Endobronchial mass/lesion	50-89	100

*24-Hour esophageal pH monitoring. *GERD,* Gastroesophageal reflux disease.
(From Goldman L, Schafer AI [eds]: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

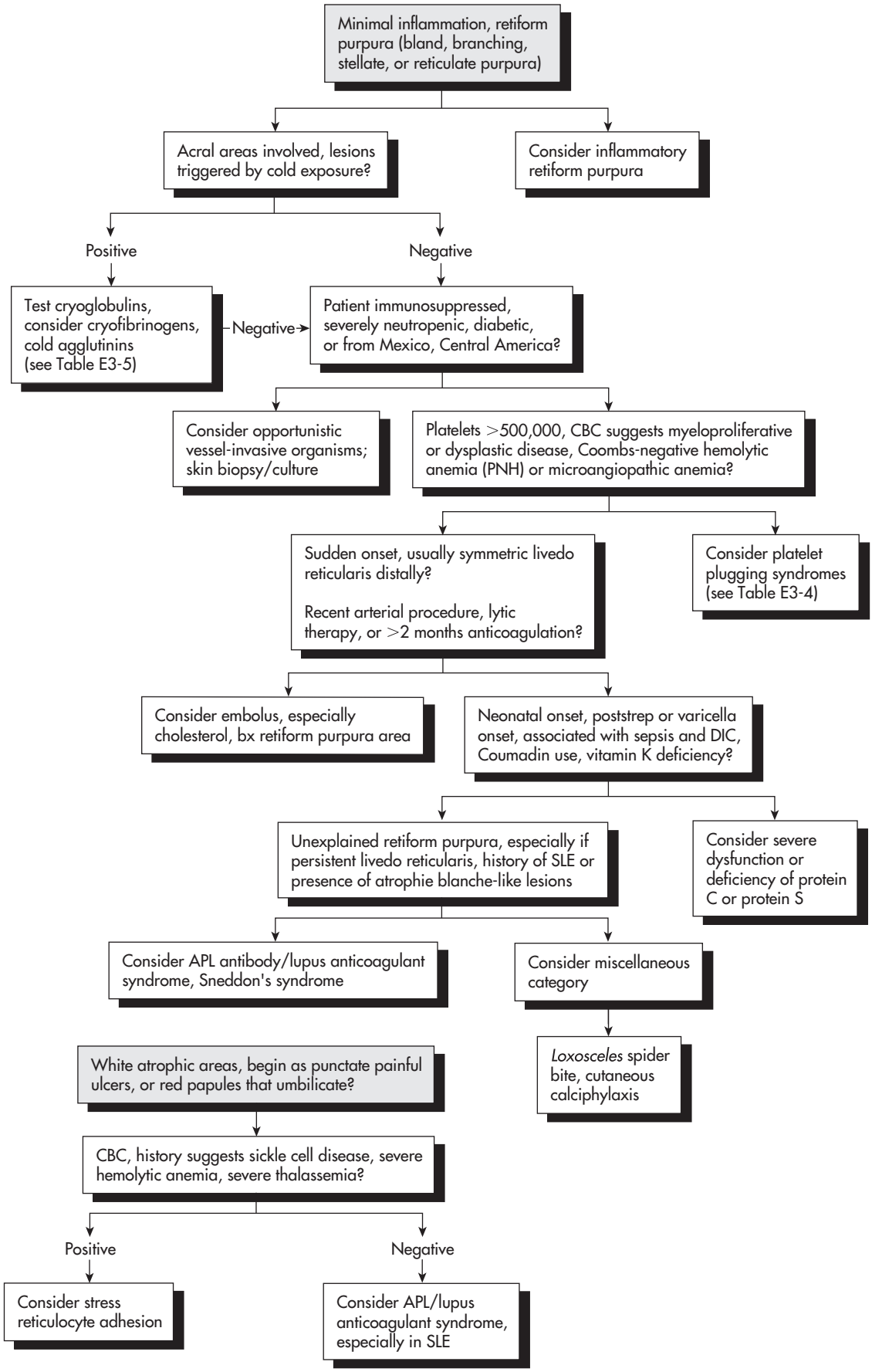


FIGURE E3-54 Cutaneous microvascular occlusion syndromes. *APL,* Antiphospholipid; *bx,* biopsy; *CBC,* complete blood count; *DIC,* disseminated intravascular coagulation; *PNH,* paroxysmal nocturnal hemoglobinuria; *SLE,* systemic lupus erythematosus. (From Bolognia JL et al [eds]: *Dermatology,* ed 2, St Louis, 2008, Mosby.)

TABLE E3-4 Differential Diagnosis of Cutaneous Microvascular Occlusion Based on Pathophysiology

Platelet Plugging

- Heparin necrosis
- Myeloproliferative thrombocytosis
- Paroxysmal nocturnal hemoglobinuria
- Thrombotic thrombocytopenic purpura

Cold-related Gelling or Agglutination

- Cryoglobulinemia
- Cryofibrinogenemia
- Cold agglutinins

Vessel-invasive Organisms

- Ecthyma gangrenosum
- Opportunistic fungi
- Disseminated strongyloidiasis
- Lucio phenomenon of leprosy

Embolization

- Cholesterol embolus
- Oxalate embolus
- Atrial myxoma
- Marantic endocarditis
- Libman–Sacks/antiphospholipid antibody
- Crystal globulin vasculopathy
- Hypereosinophilic syndrome

Systemic Coagulopathies

- Neonatal purpura fulminans
- Coumadin (warfarin) necrosis
- Purpura fulminans of sepsis/DIC
- Postinfectious purpura fulminans
- Antiphospholipid antibody/lupus anticoagulant syndrome

Vascular Coagulopathies

- Sneddon's syndrome
- Livedoid vasculopathy
- Malignant atrophic papulosis/Degos' disease

Miscellaneous

- Stress reticulocyte adhesion
- Cutaneous calciphylaxis

DIC, Disseminated intravascular coagulation.
From Bolognia JL et al [eds]: *Dermatology,* ed 2, St Louis, 2008, Mosby.

TABLE E3-5 Basic Screening Tests for Occlusive Syndrome

Complete Blood Count with Differential, Platelet Count, and Blood Smear

- Polycythemia or anemia, granulocytosis, thrombocytosis, poikilocytosis
  - May be sign of myeloproliferative or myelodysplastic diseases
- Evidence of red cell fragmentation (schistocytes) and microangiopathy, consider:
  - TTP/HUS
  - Purpura fulminans with DIC, occasionally
  - Antiphospholipid antibody syndrome, occasionally
- Thrombocytopenia, consider:
  - Heparin necrosis, some patients
  - Purpura fulminans with DIC
  - TTP/HUS
  - Antiphospholipid antibody syndrome, some patients
- Severe neutropenia
  - Immunocompromised; opportunistic infections very likely

Partial Thromboplastin Time (PTT)

- Minimally prolonged in TTP/HUS
- Prolonged in purpura fulminans and DIC
- Prolonged if lupus anticoagulant activity present and assay sensitive

Cryoglobulins (occasionally cryofibrinogen and cold agglutinins) when Location and History Suggest Cold Occlusion Syndrome

Biopsy

- Confirms occlusion versus other mechanisms of vessel injury
- May suggest platelet plugs instead of fibrin thrombi
- May suggest cryoglobulin gelling
- May suggest cholesterol, oxalate, or crystal globulin occlusion
- Special stains for organisms in immunocompromised hosts, when appropriate

Basic Hepatic and Renal Function Screens

- Hepatic function can affect vitamin K–dependent factors and Coumadin metabolism
- Renal disease moves cutaneous calciphylaxis higher in the differential diagnosis

ANCA

To reduce the likelihood of the uncommon noninflammatory retiform purpura presentation of Wegener's granulomatosis or microscopic polyangiitis. ANCA may be available before permanent histology sections.

ANCA, Antineutrophil cytoplasmic antibody; *DIC,* disseminated intravascular coagulation; *HUS,* hemolytic-uremic syndrome; *TTP,* thrombotic thrombocytopenic purpura.
From Bolognia JL et al [eds]: *Dermatology,* ed 2, St Louis, 2008, Mosby.

CYANOSIS

ICD-9CM # 782.5 Cyanosis NOS
ICD-10CM # R23.0 Cyanosis

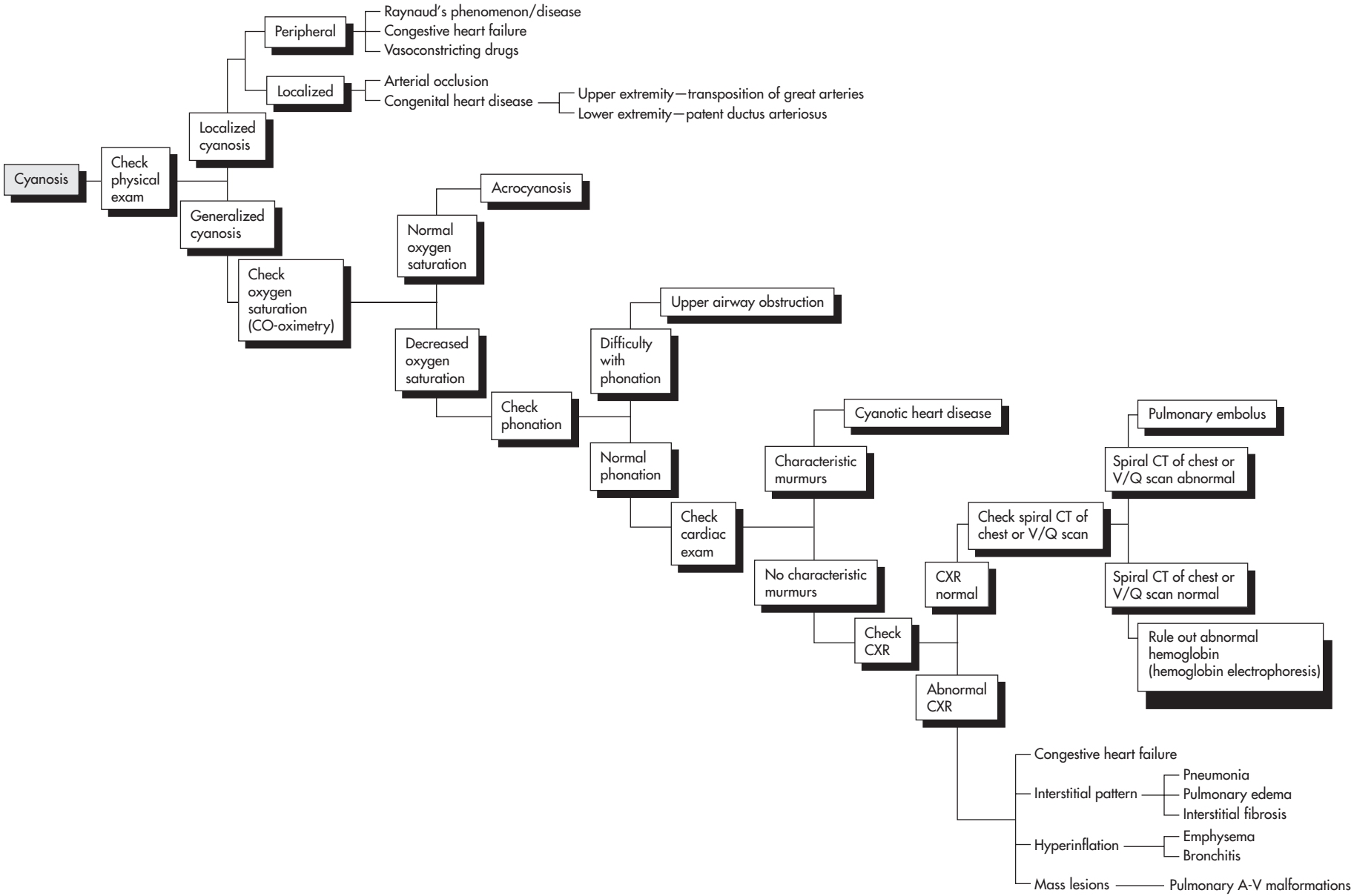


FIGURE 3-55 Cyanosis. *A-V,* Arteriovenous; *CXR,* chest x-ray; *V/Q,* ventilation-perfusion. (From Healey PM: *Common medical diagnosis: an algorithmic approach,* ed 3, Philadelphia, 2000, Saunders.)

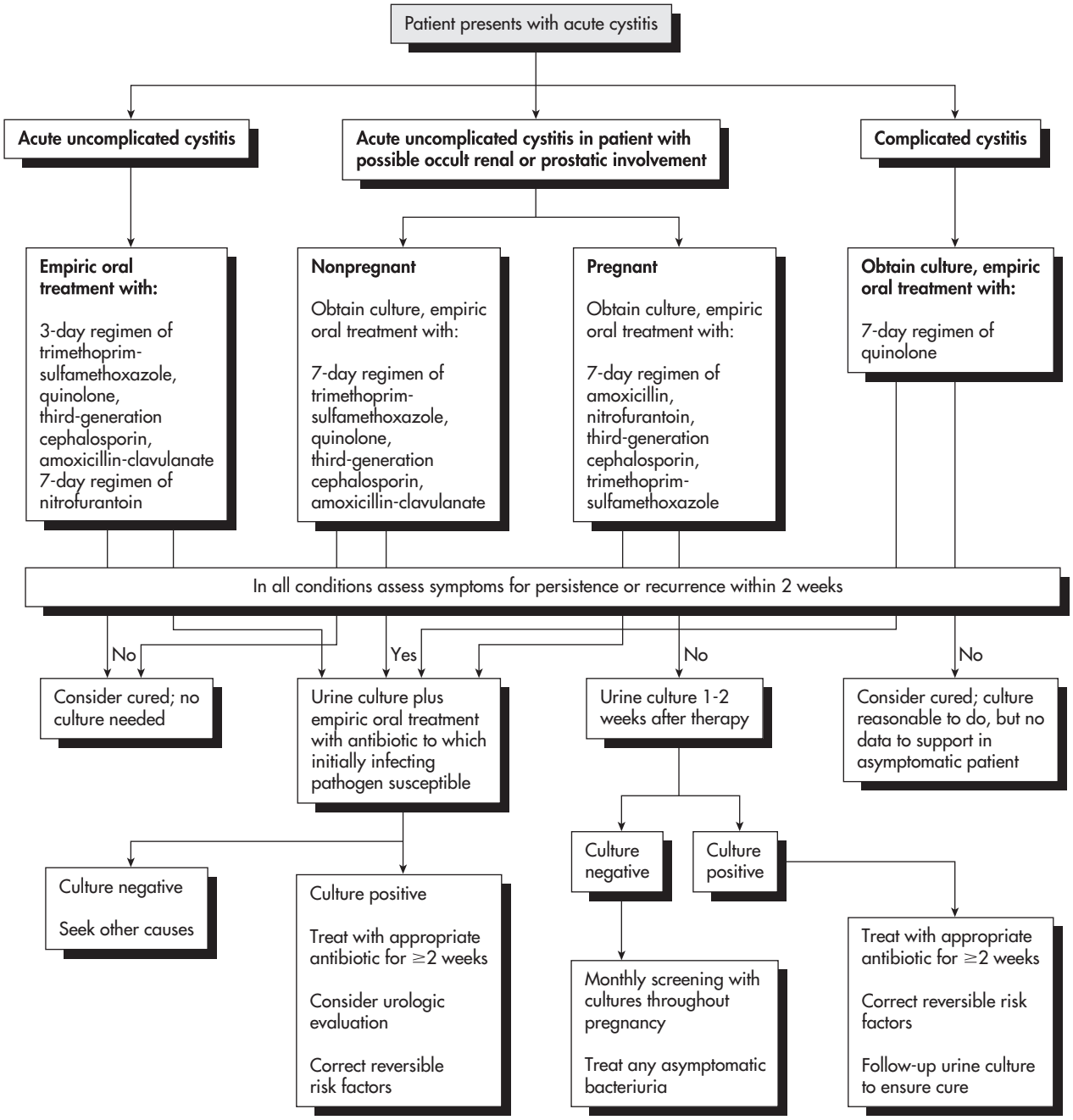


FIGURE E3-56 Algorithm for management of acute cystitis. (Modified from Feehally J, Floege J, Johnson RJ [eds]: *Comprehensive clinical nephrology,* ed 3, St Louis, 2007, Mosby.)

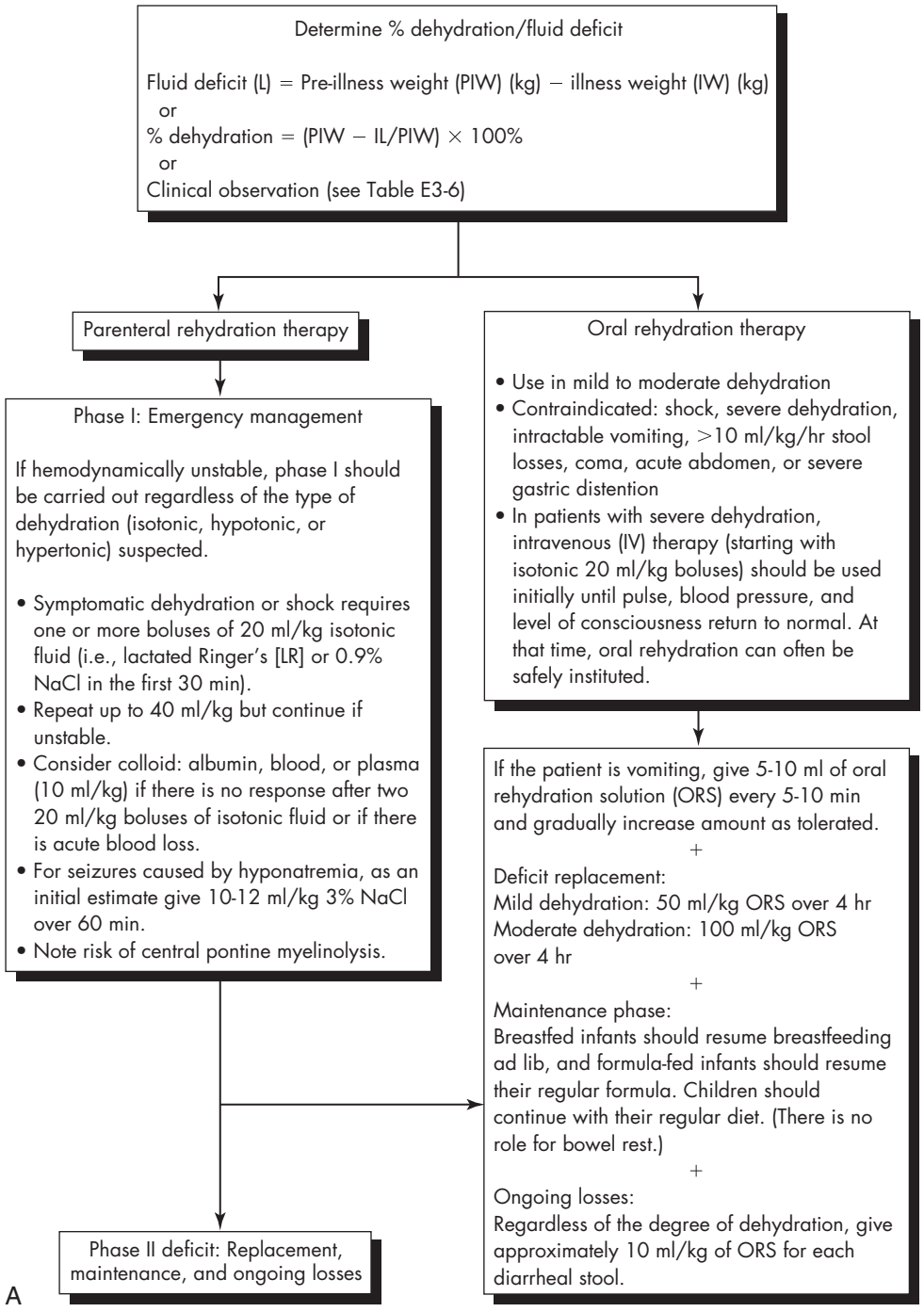
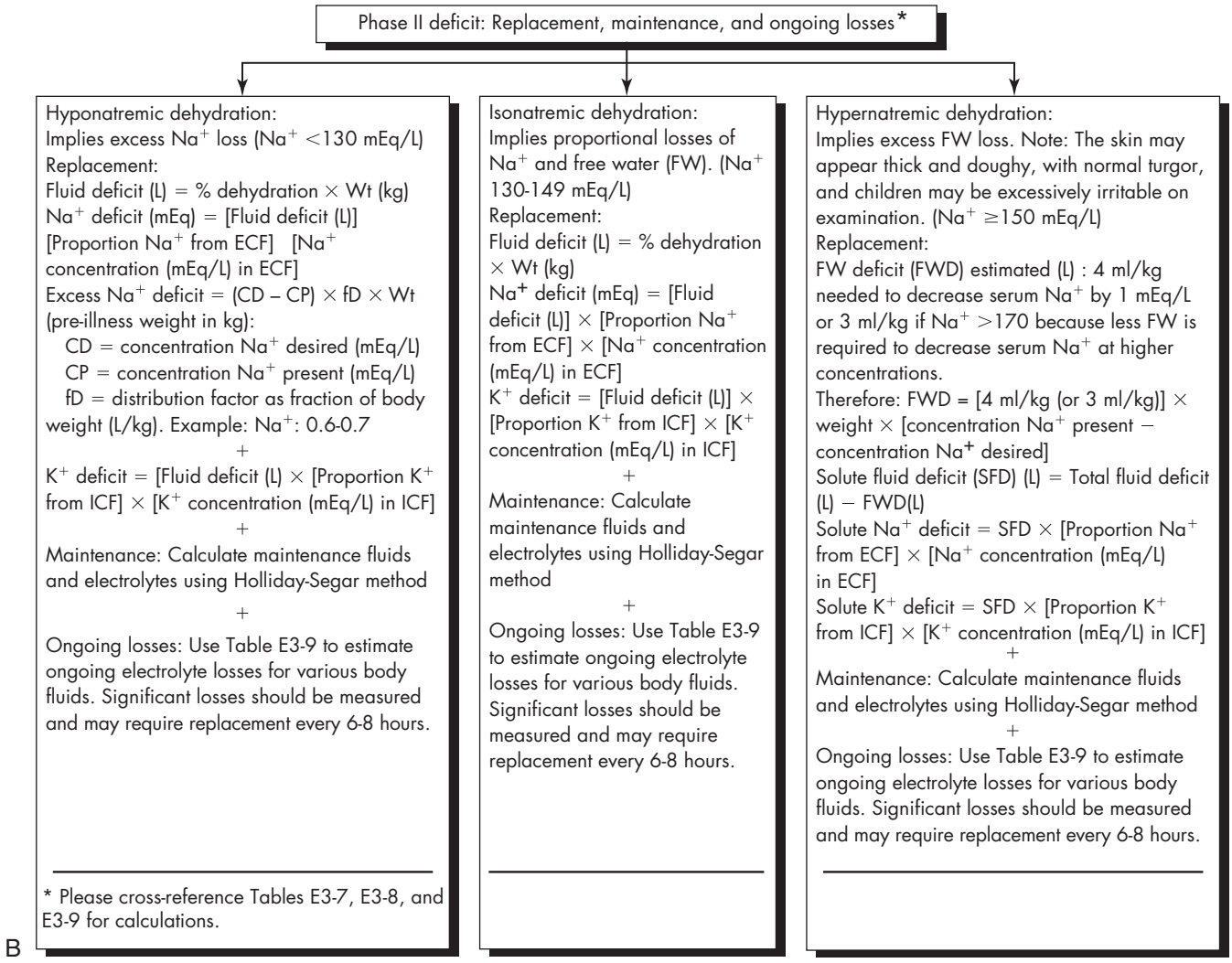


FIGURE E3-57 A and **B, Algorithm for dehydration correction in pediatric patient.** (From Custer JW, Rau RE: *The Harriet Lane handbook,* ed 18, St Louis, 2009, Mosby.)



B

FIGURE E3-57 A and **B** (Continued)

TABLE E3-6 Clinical Observations in Dehydration*

	OLDER CHILD		
	3% (30 ml/kg)	6% (60 ml/kg)	9% (90 ml/kg)
		INFANT	
Examination	**5% (50 ml/kg)**	**10% (100 ml/kg)**	**15% (150 ml/kg)**
Dehydration	Mild	Moderate	Severe
Skin turgor	Normal	Tenting	None
Skin (touch)	Normal	Dry	Clammy
Buccal mucosa/lips	Moist	Dry	Parched/cracked
Eyes	Normal	Deep set	Sunken
Tears	Present	Reduced	None
Fontanelle	Flat	Soft	Sunken
CNS	Consolable	Irritable	Lethargic/obtunded
Pulse rate	Normal	Slightly increased	Increased
Pulse quality	Normal	Weak	Feeble/impalpable
Capillary refill	Normal	~2 sec	>3 sec
Urine output	Normal	Decreased	Anuric

CNS, Central nervous system.

*For the same degree of dehydration, clinical symptoms are generally worse for hyponatremic dehydration than for hypernatremic dehydration.

Data from Behrman RE et al: *Nelson textbook of pediatrics,* ed 17, Philadelphia, 2003, Saunders, and Oski FA: *Principles and practice of pediatrics,* ed 4, Philadelphia, 2006, JB Lippincott.

TABLE E3-7 Intracellular and Extracellular Fluid Composition

	Intracellular (mEq/L)	Extracellular (mEq/L)
Na^+	20	133-145
K^+	150	3-5
Cl^-	—	98-110
HCO_3^-	10	20-25
PO_4^{3-}	110-115	5
Protein	75	10

From Custer JW, Rau RE: *The Harriet Lane handbook,* ed 18, St Louis, 2009, Mosby.

TABLE E3-8 Deficits of Water and Electrolytes in Severe Dehydration

Condition	H_2O (ml/kg)	Na^+ (mEq/kg)	K^+ (mEq/kg)	Cl^- (mEq/kg)
Diarrheal Dehydration				
Hyponatremic				
[Na^+]* <130 mEq/L	100-120	10-15	8-15	10-12
Isotonic				
[Na^++]* 130-150 mEq/L	100-120	8-10	8-10	8-10
Hypernatremic				
[Na^+]* >150 mEq/L	100-120	2-4	0-6	0-3
Pyloric stenosis	100-120	8-10	10-12	10-12
Diabetic ketoacidosis	100	8	6-10	6

*[Na], serum or plasma sodium concentration.
Data from Hellerstein S: Fluid and electrolytes: clinical aspects, *Pediatr Rev* 14(3):103-115, 1993.

TABLE E3-9 Electrolyte Composition of Various Body Fluids*

Fluid	Na^+ (mEq/L)	K^+ (mEq/L)	Cl^- (mEq/L)
Gastric	20-80	5-20	100-150
Pancreatic	120-140	5-15	90-120
Small bowel	100-140	5-15	90-130
Bile	120-140	5-15	80-120
Ileostomy	45-135	3-15	20-115
Diarrhea	10-90	10-80	10-110
Burns†	140	5	110
Sweat			
Normal	10-30	3-10	10-35
Cystic fibrosis	50-130	5-25	50-110

*This table is useful in determining ongoing electrolyte losses in dehydration.
†3-5 g/dl of protein may be lost in fluid from burn wounds.
Data from Behrman RE et al: *Nelson textbook of pediatrics,* ed 17, Philadelphia, 2003, Saunders.

ICD-9CM #	290.10	Dementia, presenile
	290.0	Dementia, senile
	437.0	Dementia, arteriosclerotic
ICD-10CM #	F03.90	Unspecified dementia without behavioral disturbance
	I67.2	Cerebral atherosclerosis

FIGURE E3-58 Management of dementia. *MMSE,* Mini mental status examination; *VA,* ventriculoatrial; *VP,* ventriculoperitoneal.

TABLE E3-10 Screening Tests for Diagnosis of Dementia

Test	Rationale	Remarks
Blood Test		
Complete blood count	Assess general nutritional status	
Serum B_{12} level	Exclude vitamin B_{12} deficiency	Consider Schilling's test if B_{12} level is low
TSH + free T_4 *or* TSH + FTI	Exclude primary and secondary hypothyroidism	
HIV serology	Exclude HIV infection	Perform only if indicated; consent from patient required
Cerebrospinal Fluid		
Cell count/protein level	Exclude chronic meningitis	Perform only if indicated
Cytology	Exclude carcinomatous meningitis	Perform only if indicated
VDRL	Exclude neurosyphilis	Perform only if indicated; check serum TPHA and HIV serology if CSF VDRL is positive
CT Scan/MRI/PET Scan of the Brain		
	Identify infarcts and white matter changes; exclude presence of neoplasm, demyelinating disease, and hydrocephalus; location of atrophy may suggest the diagnosis (e.g., para-hippocampal atrophy in Alzheimer's disease, frontotemporal atrophy in Pick's disease)	Perform only if indicated
Electroencephalogram		
	Exclude metabolic encephalopathies; useful if Creutzfeldt-Jakob disease or status epilepticus is suspected	Perform only if indicated
Neuropsychologic Evaluation		
	Help to characterize pattern of cognitive impairment, which may aid in the classification of dementia; rule out pseudo-dementia from depression	

CSF, Cerebrospinal fluid; *CT,* computed tomography; *FTI,* free thyroxine index; *HIV,* human immunodeficiency virus; *MRI,* magnetic resonance imaging; *PET,* positron emission tomography; T_4, thyroxine; *TPHA,* Treponema pallidum hemagglutination assay; *TSH,* thyroid-stimulating hormone; *VDRL,* Venereal Disease Research Laboratory.
Modified from Johnson RT, Griffin JW: *Current therapy in neurologic disease,* ed 5, St Louis, 1997, Mosby.

DEVELOPMENTAL DELAY

ICD-9CM # 783.4 Developmental delay, physiological
ICD-10CM # R62.50 Unspecified lack of expected normal physiological development in childhood

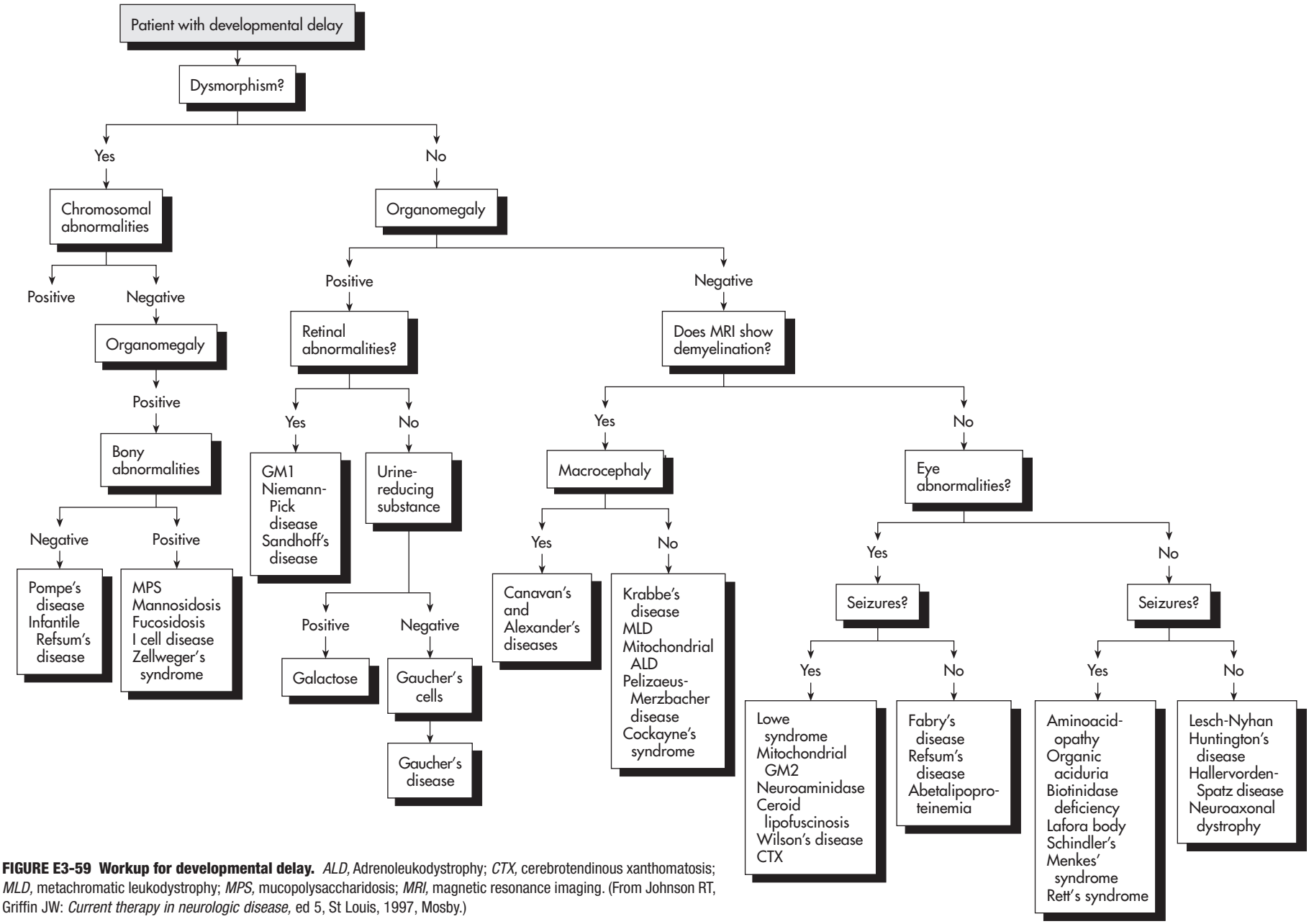


FIGURE E3-59 Workup for developmental delay. *ALD,* Adrenoleukodystrophy; *CTX,* cerebrotendinous xanthomatosis; *MLD,* metachromatic leukodystrophy; *MPS,* mucopolysaccharidosis; *MRI,* magnetic resonance imaging. (From Johnson RT, Griffin JW: *Current therapy in neurologic disease,* ed 5, St Louis, 1997, Mosby.)

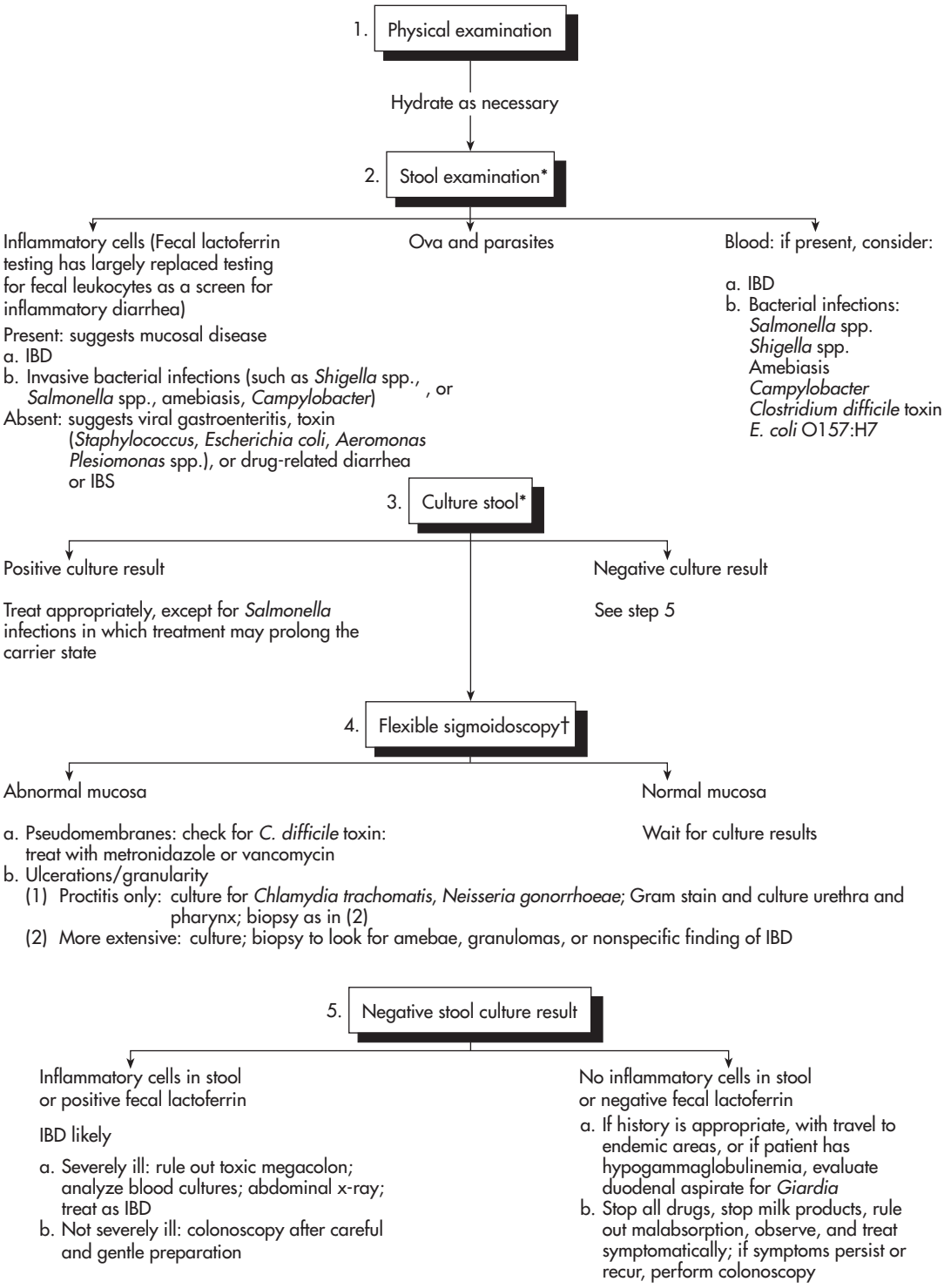


FIGURE 3-60 Diagnostic steps in the assessment of acute diarrhea. *For most uses of acute diarrhea, testing is not indicated. Stool examination and culture should be reserved for patients with severe illness, bloody stool, severe dehydration, immunosuppression, and for suspected nosocomial infection. †The role of lower endoscopy in acute diarrhea is limited. It should be considered only if the diagnosis is unclear after blood and stool tests in severely symptomatic patients. ‡Acute diarrhea is defined as stool with increased water content, volume, or frequency that lasts less than 14 days. *IBD*, Inflammatory bowel disease; *IBS*, irritable bowel syndrome. (Modified from Stein JH [ed]: *Internal medicine*, ed 5, St Louis, 1998, Mosby.)

ICD-9CM # 787.91
ICD-10CM # R19.7 Diarrhea, unspecified

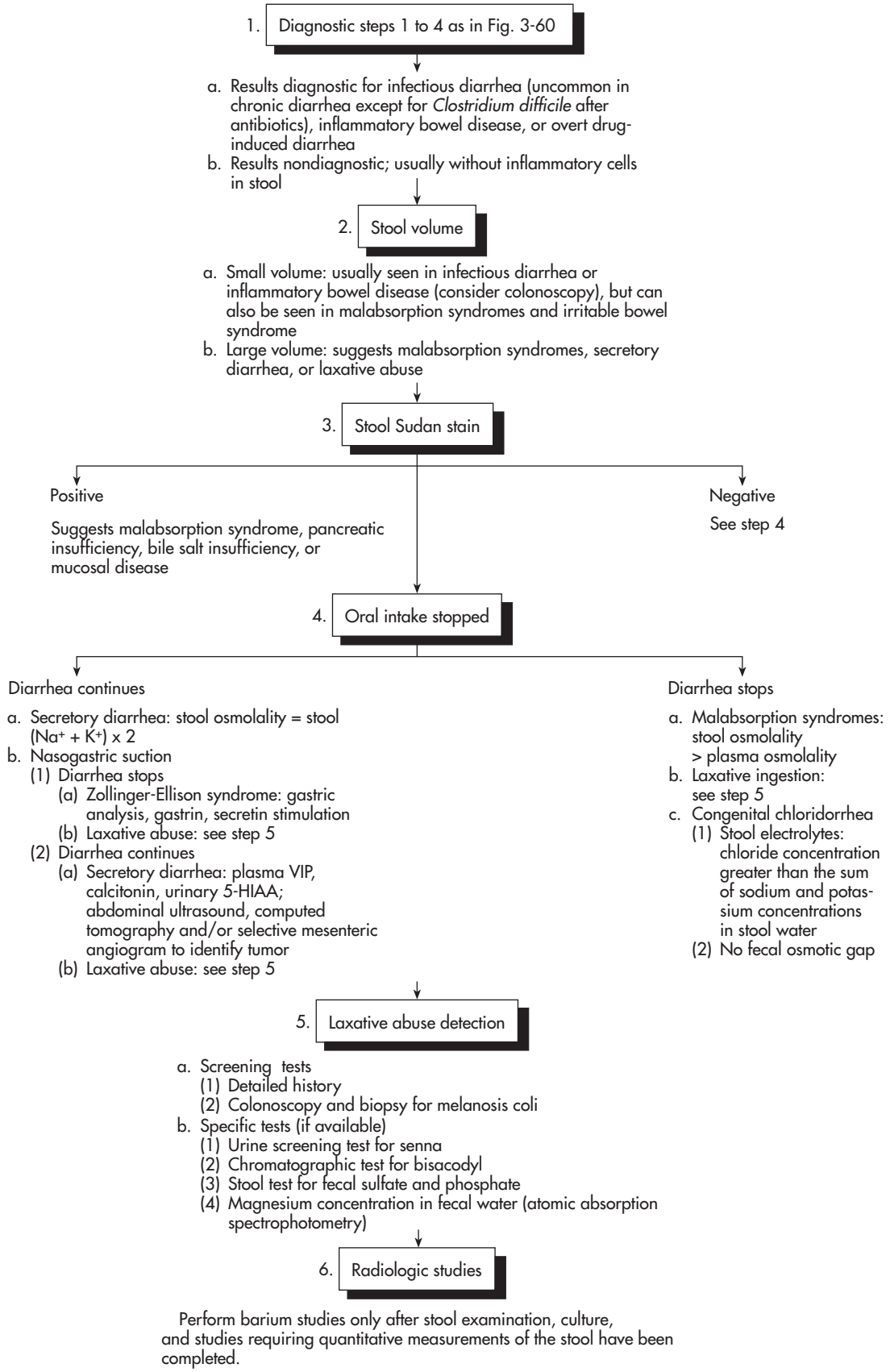


FIGURE 3-61 Diagnostic approach to the patient with chronic diarrhea (patients who are HIV negative). *5-HIAA,* 5-Hydroxyindoleacetic acid; *VIP,* vasoactive intestinal polypeptide. (Modified from Stein JH [ed]: *Internal medicine,* ed 5, St Louis, 1998, Mosby.)

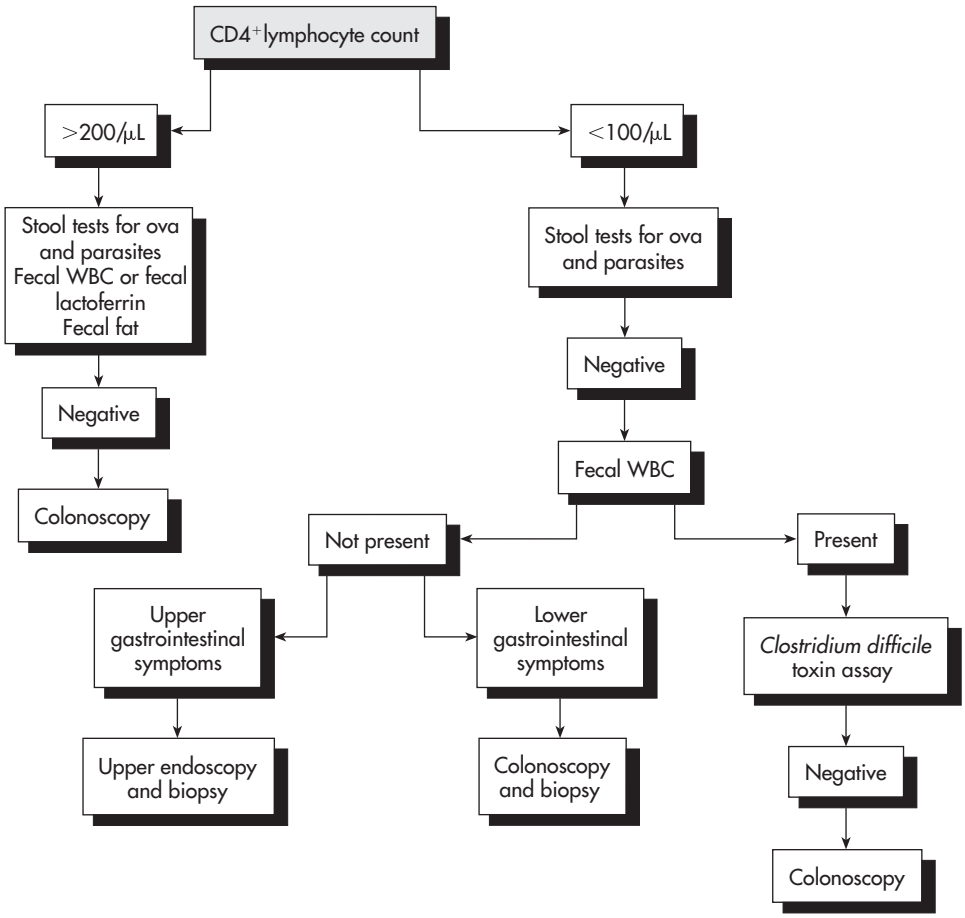
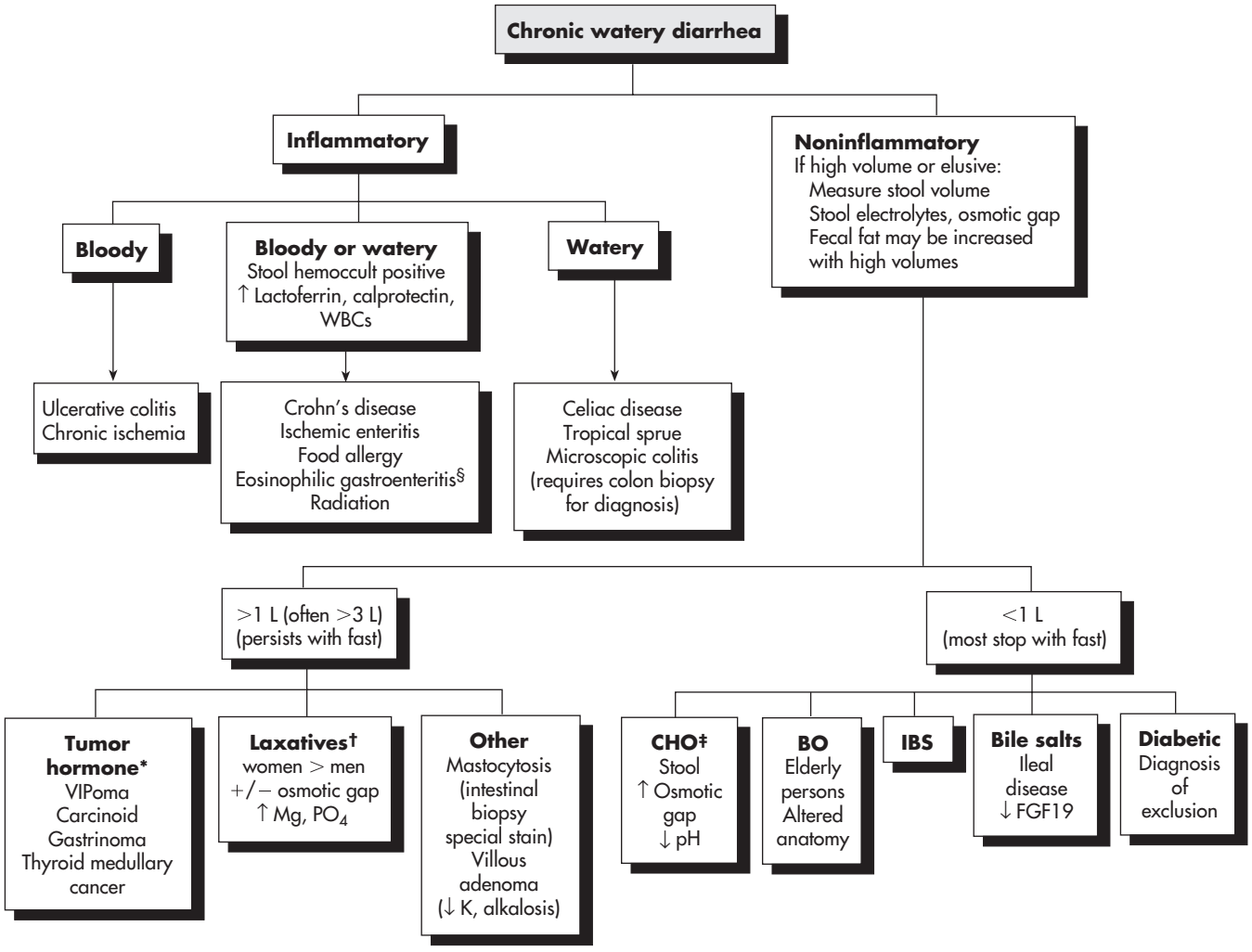


FIGURE E3-62 Approach to evaluating chronic diarrhea in patients with HIV infection. *WBC,* White blood cell count. (Modified from Wilcox CM: *Gastrointest Dis Today* 5:9, 1996.)

TABLE E3-11 Common Gastrointestinal Pathogens Associated with HIV Infection

Pathogen	CD4+ Cells/μL	Stool Volume and Frequency	Abdominal Pain	Weight Loss	Fever	Fecal Leukocytes
Cytomegalovirus*	<100	Mild to moderate	++	++	++	–
Cryptosporidiosis	<100	Moderate to severe	–	++	–	–
Microsporidiosis	<100	Mild to moderate	–	+	–	–
Mycobacterium avium complex†	<100	Mild to moderate	+	++ ++++	+++	–

*Can have proctitis symptoms when involving the distal colon.
†Typical presentation is fever and wasting; diarrhea is usually secondary.
+ + +, Very common; + +, frequent; +, can occur; –, absent.
From Wilcox CM: *Gastrointest Dis Today* 5:9, 1996.



*VIPoma: >3L output daily "pancreatic cholera," elevated VIP level. Carcinoid: elevated urine 5-hydroxyindole acetic acid, positive OctreoScan. Gastrinoma (Zollinger-Ellison syndrome): elevated gastrin level, positive secretin stimulation test, diarrhea due to high volume of acid secretion. Thyroid medullary cancer: elevated calcitonin level.
†May be high or low depending on dose ingested, may respond to fast.
‡Carbohydrate malabsorption (CHO) may be due to lactase deficiency, dietary fructose, sorbitol in diabetic candies or liquid medications.
§Full-thickness biopsy may be needed for diagnostic.

FIGURE E3-63 Approach to the evaluation of watery diarrheas. Many diarrheas have more than one mechanism (i.e., osmotic, secretory, inflammatory). Other causes include medications, postsurgical (vagotomy, Nissan wrap, cholecystectomy), hyperthyroidism, and alcohol. *BO,* Bacterial overgrowth; *FGF,* fibroblast growth factor; *IBS,* irritable bowel syndrome; *WBCs,* white blood cells. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

ICD-9CM # 379.43 Pupil dilation
ICD-10CM # H57.04 Mydriasis

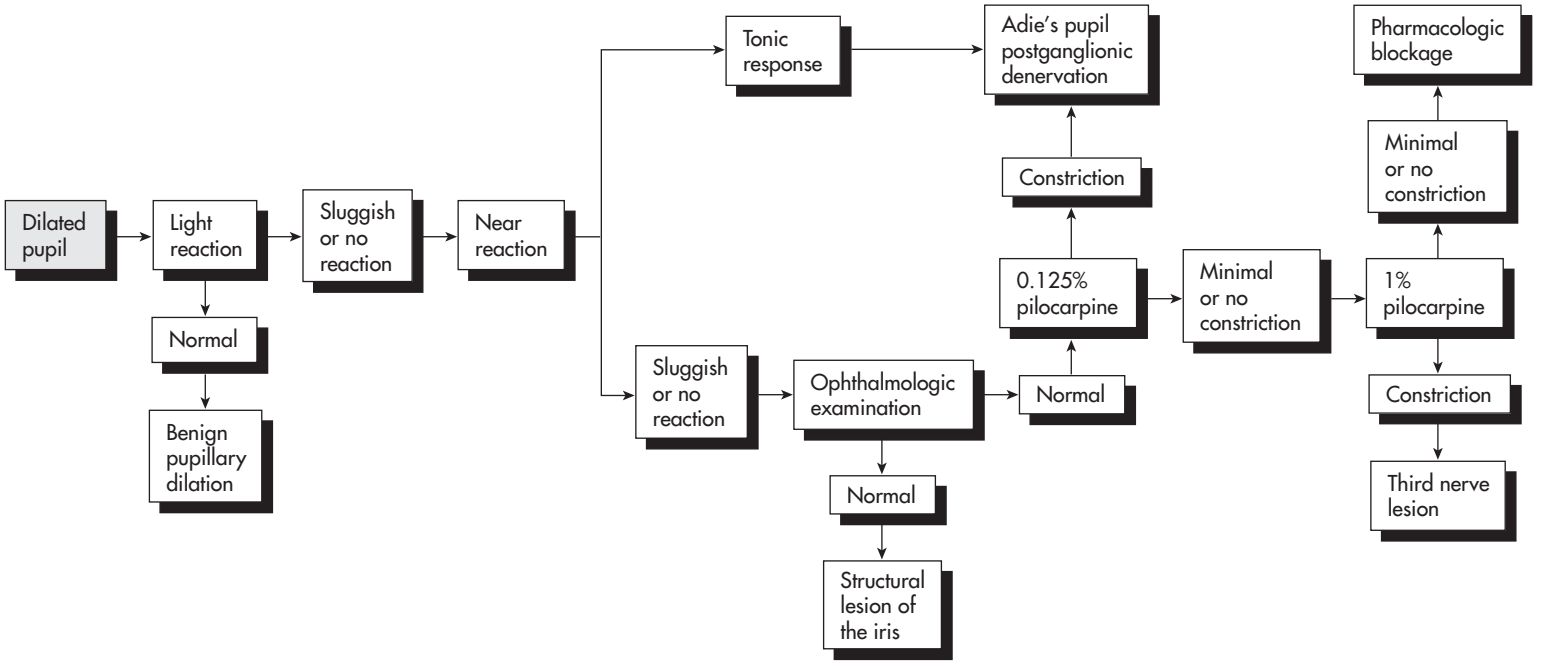


FIGURE 3-64 Use of pilocarpine to help differentiate between different causes of a dilated pupil. (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 23, Philadephia, 2008, Saunders.)

ICD-9CM # 563.3 Dyspepsia, atonic
536.8 Dyspepsia disorders other unspecified function of stomach
306.4 Dyspepsia, psychogenic
ICD-10CM # K30 Functional dyspepsia
F45.8 Other somatoform disorders

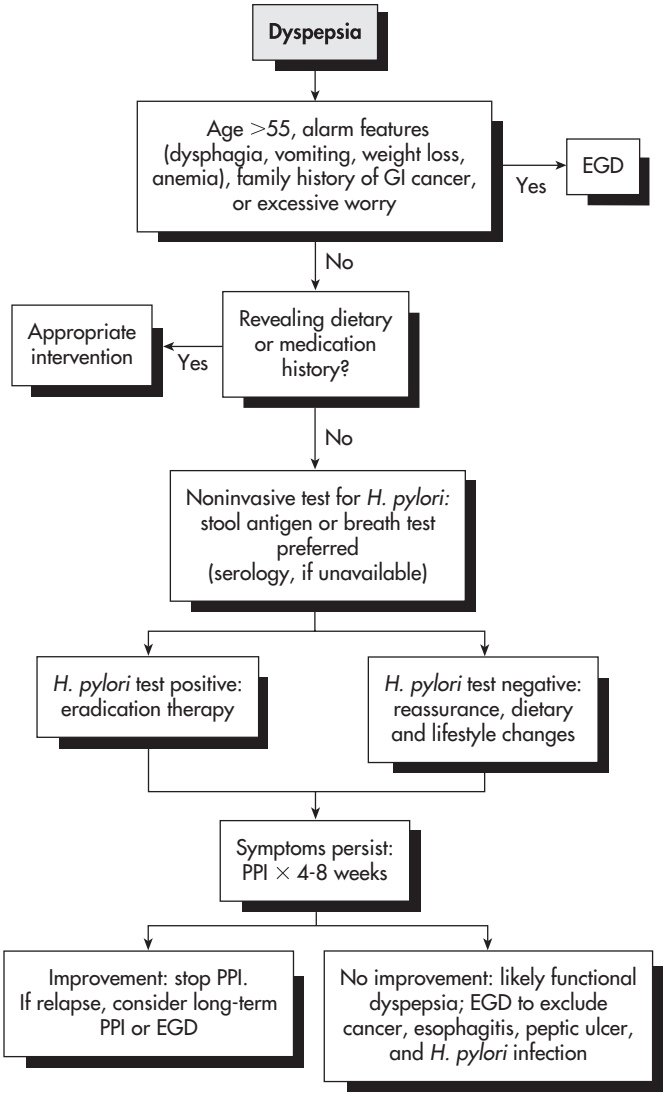


FIGURE 3-65 Approach to the patient with dyspepsia. *EGD,* Esophagastroduodenoscopy; *GI,* gastrointestinal; *PPI,* proton pump inhibitor. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

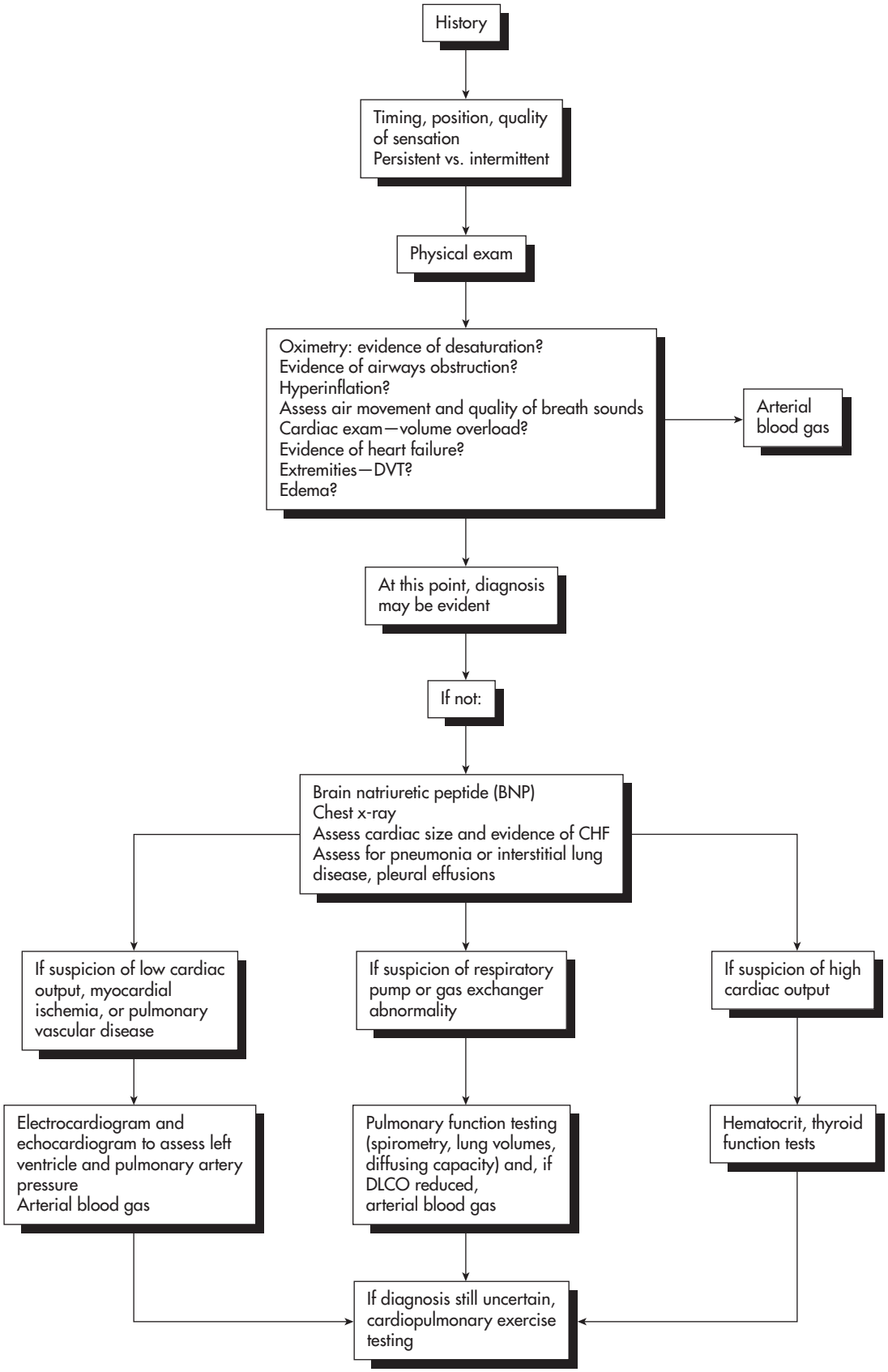


FIGURE 3-66 Algorithm for the evaluation of the patient with dyspnea. The pace and completeness with which one approaches this framework depends on the intensity and acuity of the patient's symptoms. In a patient with severe, acute dyspnea, for example, an arterial blood gas measurement may be one of the first laboratory evaluations, whereas this measurement might not be obtained until much later in the workup in a patient with chronic breathlessness of unclear cause. A therapeutic trial of a medication, for example, a bronchodilator, may be instituted at any point if one is fairly confident of the diagnosis based on the data available at that time. *CHF,* Congestive heart failure; *DLCO,* diffusing capacity of the lung for carbon monoxide; *DVT,* deep venous thrombosis. (Modified from Schwartzstein RM, Feller-Kopman D: Approach to the patient with dyspnea. In Braunwald E, Goldman L [eds]: *Primary cardiology,* ed 2, Philadelphia, 2003, Saunders.)

DYSURIA AND/OR URETHRAL/ VAGINAL DISCHARGE

ICD-9CM # 788.1 Dysuria
788.7 Urethral discharge
623.5 Vaginal discharge
ICD-10CM # R30.0 Dysuria
R30.9 Painful micturition, unspecified
R36.0 Urethral discharge without blood
R36.9 Urethral discharge, unspecified
N89.8 Other specified noninflammatory disorders of vagina

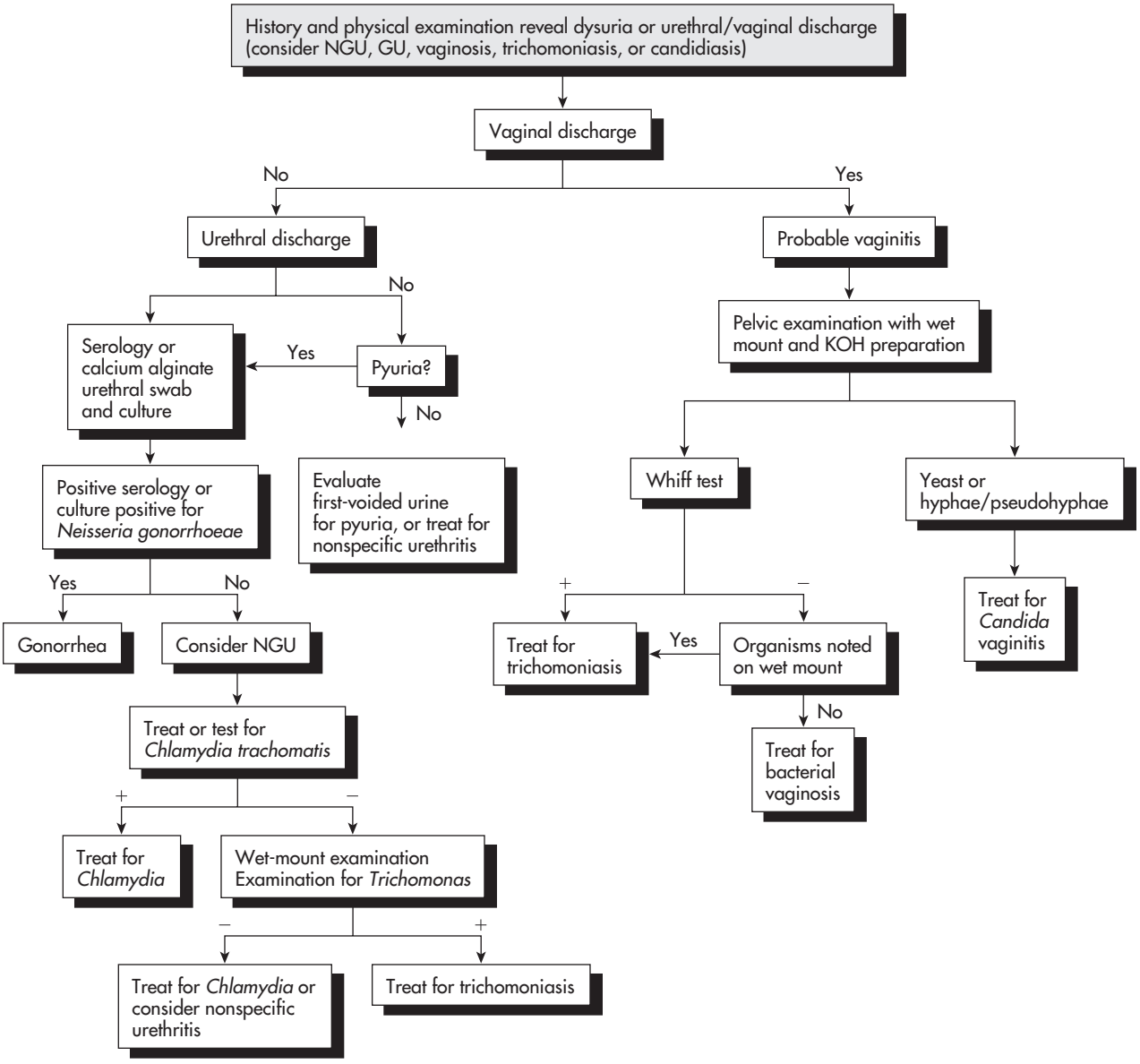


FIGURE 3-67 Evaluation of patients with dysuria and/or urethral/vaginal discharge. *GU,* Gonococcal urethritis; *KOH,* potassium hydroxide; *NGU,* nongonococcal urethritis. (Modified from Nseyo UO [ed]: Urology for primary care physicians, Philadelphia, 1999, Saunders.)

Management of Ear Pain

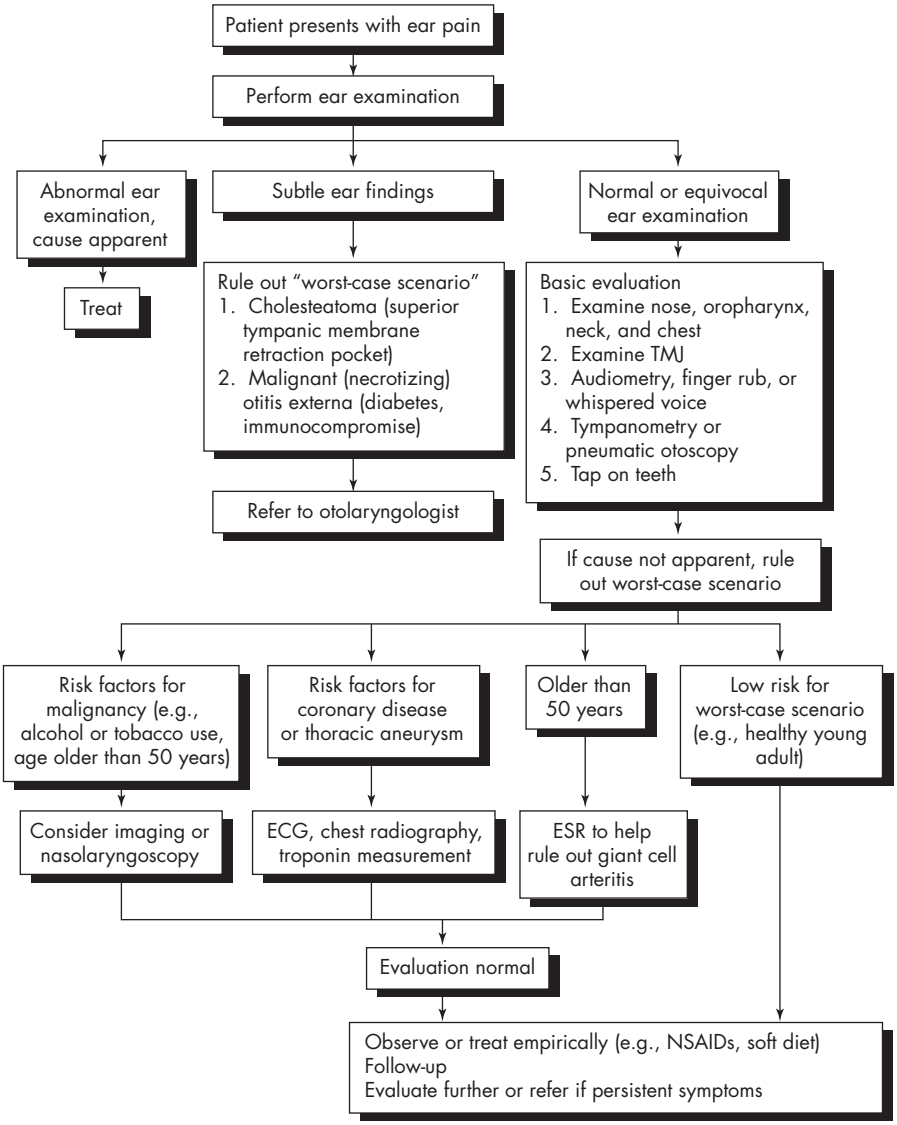


FIGURE 3-68 Management of ear pain. *ECG*, Electrocardiography; *ESR*, erythrocyte sedimentation rate; *NSAIDs*, nonsteroidal anti-inflammatory drugs; *TMJ*, temporomandibular joint. (Modified from Ely JW et al: Diagnosis of ear pain, *Am Fam Physician* 77[5]:622, 2008.)

ICD-9CM # 782.3 Edema NOS
782.3 Edema, lower extremities
ICD-10CM # R60.0 Localized edema
R60.1 Generalized edema
R60.9 Edema, unspecified

FIGURE 3-69 Evaluation of generalized edema. *BNP,* B-type natriuretic peptide; *BUN,* blood urea nitrogen; *CHF,* congestive heart failure; *JVP,* jugular venous pressure; *LFT,* liver function tests; *TFTs,* thyroid function tests. (Modified from Greene HL, Johnson WP, Lemcke D [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

ICD-9CM # 250.6
ICD-10CM # T78.3 Edema, essential, acute

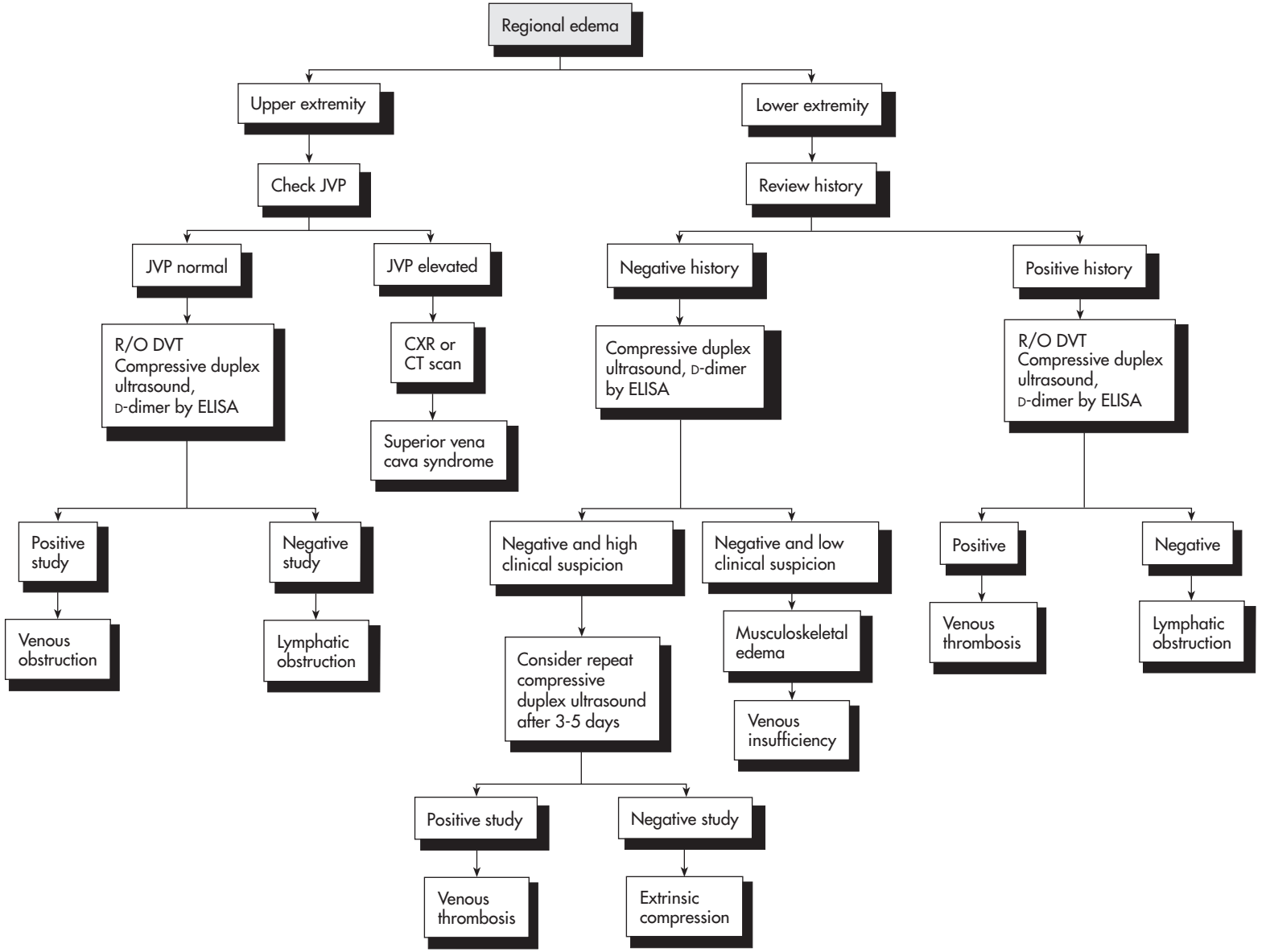


FIGURE 3-70 Evaluation of regional edema. *CT,* Computed tomography; *CXR,* chest x-ray examination; *DVT,* deep venous thrombosis; *ELISA,* enzyme-linked immunosorbent assay; *JVP,* jugular venous pressure. (Modified from Greene HL, Johnson WP, Lemcke D [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

EOSINOPHILIC DERMATOSES

ICD-9CM # 691.8
ICD-10CM # L20.89 Other atopic dermatitis
L20.0 Besnier's prurigo
L20.81 Atopic neurodermatitis

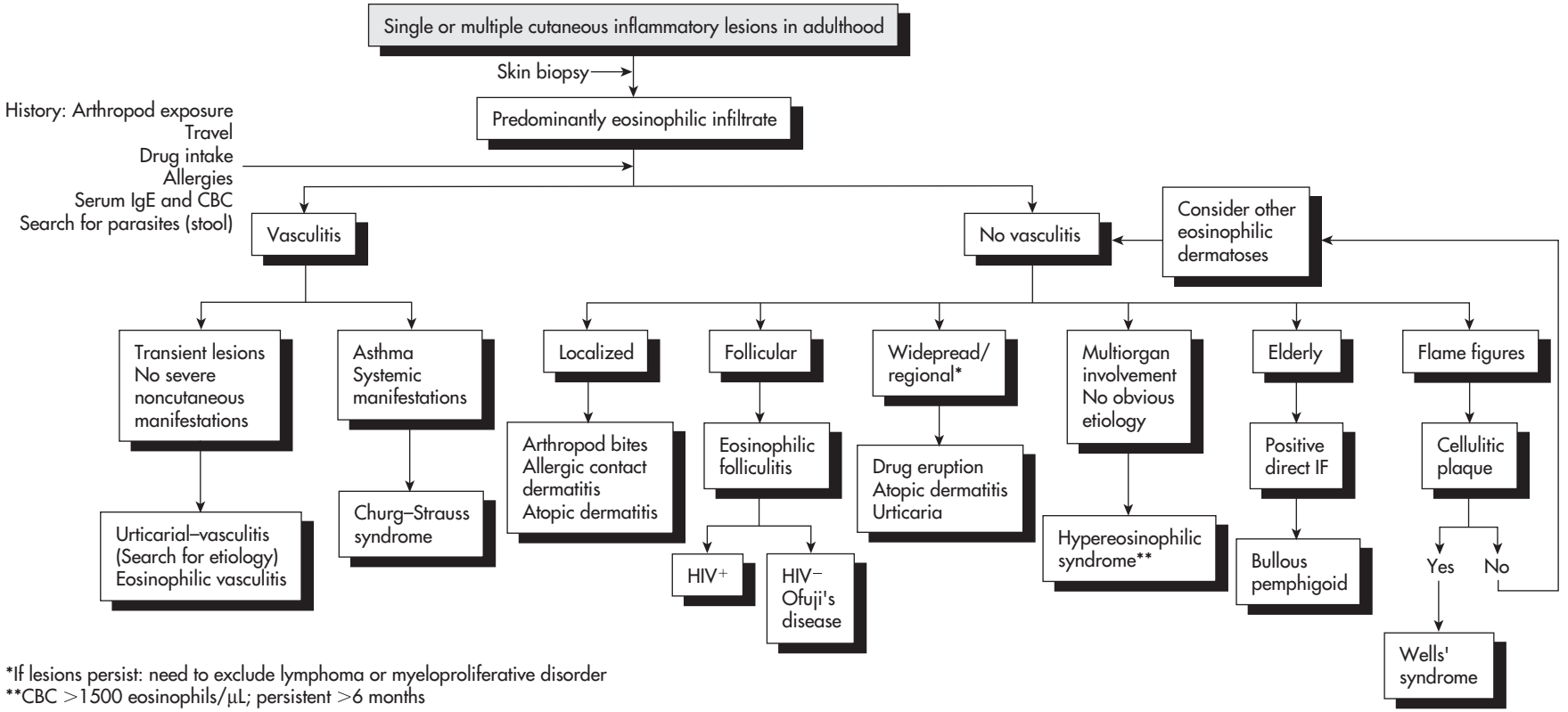
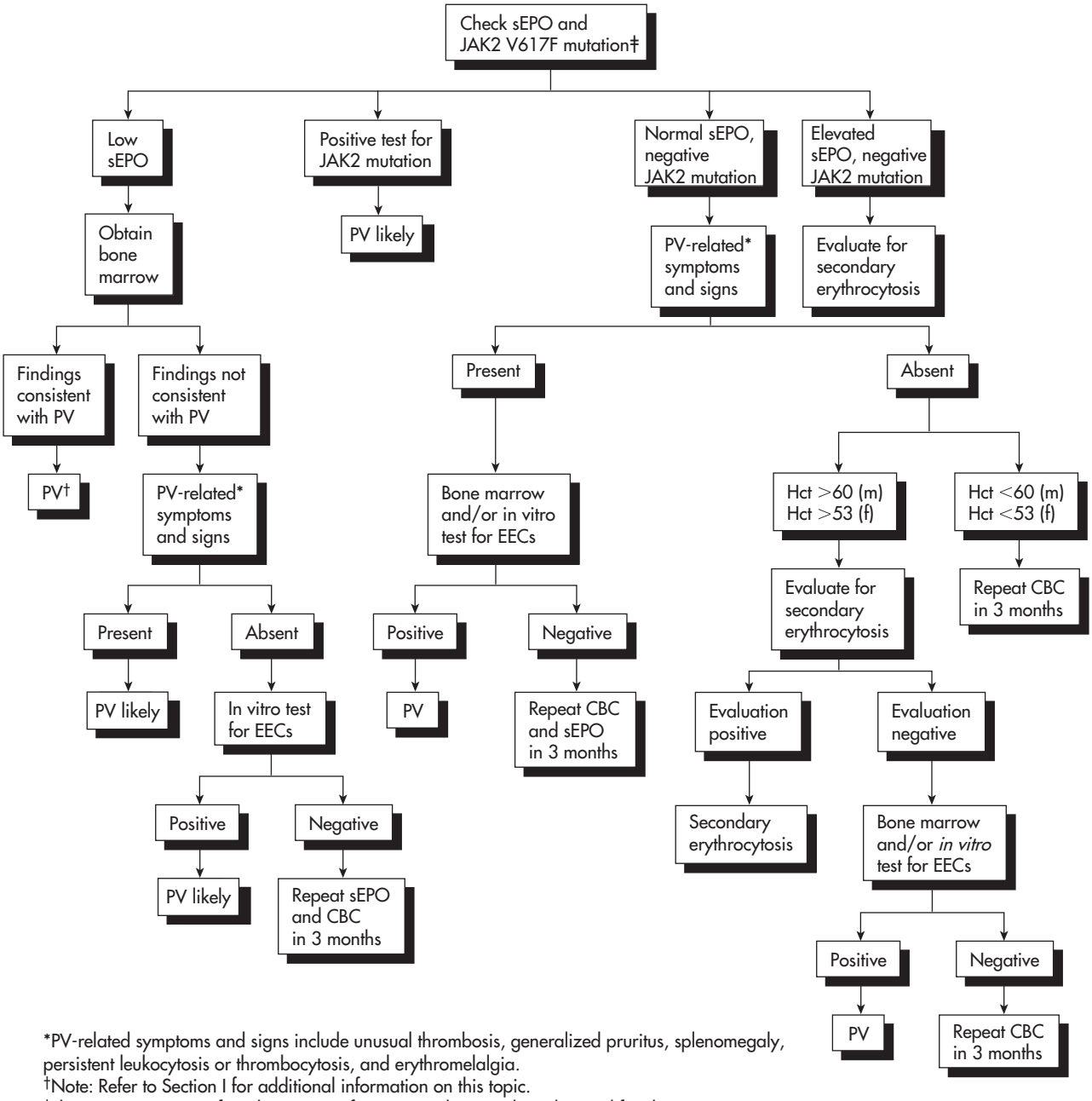


FIGURE E3-71 Evaluation of adult patients with eosinophilic dermatoses. Histologically, these dermatoses are characterized by a prominent eosinophilic infiltrate. *CBC,* Complete blood count; *HIV,* human immunodeficiency virus; *IF,* intrinsic factor; *IgE,* immunoglobulin E. (From Bolognia JL et al [eds]: *Dermatology,* ed 2, St Louis, 2008, Mosby.)

ICD-9CM # 289.0 Polycythemia, acquired
ICD-10CM # D75.0 Familial erythrocytosis



*PV-related symptoms and signs include unusual thrombosis, generalized pruritus, splenomegaly, persistent leukocytosis or thrombocytosis, and erythromelalgia.
†Note: Refer to Section I for additional information on this topic.
‡The JAK2 mutation is found in >95% of patients with PV and can be used for diagnostic purposes.

FIGURE 3-72 A diagnostic approach to acquired erythrocytosis. *CBC,* Complete blood cell count; *EEC,* endogenous (spontaneous) erythroid colonies; *f,* female; *Hct,* hematocrit; *m,* male; *PV,* polycythemia vera; *sEPO,* serum erythropoietin level. (Modified from Goldman L, Schafer AL [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

ERYTHRODERMA

ICD-9CM #	695.9	Secondary
	695.89	Exfoliative
	696.2	Maculopapular
	696.1	Psoriaticum
	778.8	Neonatorum
ICD-10CM #	L53.9	Erythematous condition, unspecified
	L41.0	Pityriasis lichenoides et varioliformis acuta
	L41.1	Pityriasis lichenoides chronica
	L41.8	Other parapsoriasis
	L40.0	Psoriasis vulgaris
	L40.1	Generalized pustular psoriasis
	L40.2	Acrodermatitis continua
	L40.3	Pustulosis palmaris et plantaris
	L40.4	Guttate psoriasis
	L40.8	Other psoriasis
	L26	Exfoliative dermatitis
	L30.4	Erythema intertrigo
	L53.8	Other specified erythematous conditions
	L92.0	Granuloma annulare
	L95.1	Erythema elevatum diutinum
	L98.2	Febrile neutrophilic dermatosis [Sweet]
	P83.8	Other specified conditions of integument specific to newborn

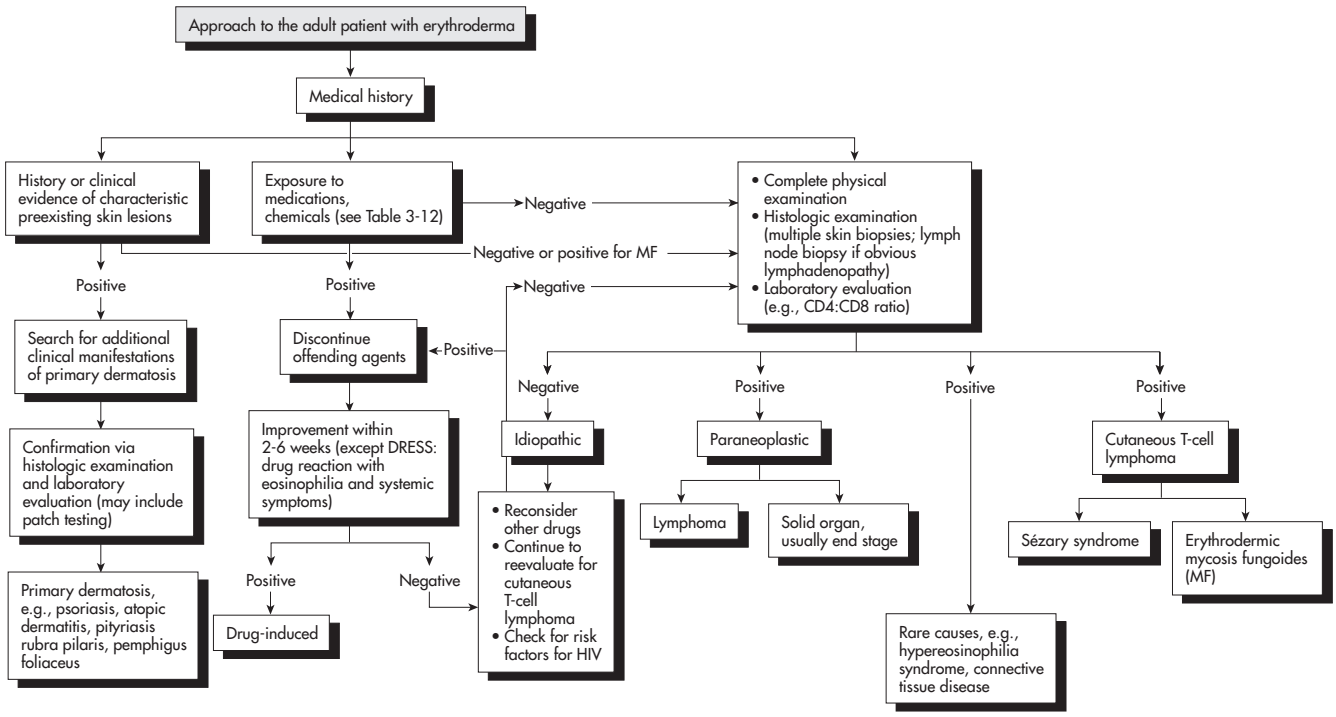


FIGURE 3-73 Approach to the differential diagnosis of adult erythroderma. (From Bolognia JL et al [eds]: *Dermatology,* ed 2, St Louis, 2008, Mosby.)

ICD-9CM #	695.9	Secondary
	695.89	Exfoliative
	696.2	Maculopapular
	696.1	Psoriaticum
	778.8	Neonatorum
ICD-10CM #	L53.9	Erythematous condition, unspecified
	L41.0	Pityriasis lichenoides et varioliformis acuta
	L41.1	Pityriasis lichenoides chronica
	L41.8	Other parapsoriasis
	L40.0	Psoriasis vulgaris
	L40.1	Generalized pustular psoriasis
	L40.2	Acrodermatitis continua
	L40.3	Pustulosis palmaris et plantaris
	L40.4	Guttate psoriasis
	L40.8	Other psoriasis
	L26	Exfoliative dermatitis
	L30.4	Erythema intertrigo
	L53.8	Other specified erythematous conditions
	L92.0	Granuloma annulare
	L95.1	Erythema elevatum diutinum
	L98.2	Febrile neutrophilic dermatosis [Sweet]
	P83.8	Other specified conditions of integument specific to newborn

TABLE 3-12 Drugs Associated with Erythroderma

Common

- Allopurinol
- Ampicillin/amoxicillin/penicillin G
- Carbamazepine/oxcarbazepine
- Dapsone
- Omeprazole/lansoprazole
- Phenobarbital
- Phenothiazines
- Phenytoin
- Sulfasalazine
- Sulfonamides
- Vancomycin

Less Common

- Captopril
- Carboplatin/cisplatin
- Cytokines (IL-2/GM-CSF)
- Diflunisal
- Gold
- Hydroxychloroquine/mefloquine
- Isoniazid
- Mercury
- Minocycline
- Nifedipine
- Thalidomide

Rare

- Amiodarone
- Aztreonam
- Cimetidine
- Chlorpromazine
- Clofazimine
- Codeine
- Diltiazem
- Erythropoietin
- Fluorouracil
- Indinavir sulfate
- Lithium
- Mitomycin C
- Pentostatin
- Piroxicam
- Practolol
- Ranitidine
- Rifampin (rifampicin)
- Tear gas (CS gas)
- Teicoplanin
- Terbinafine
- Tobramycin
- Tramadol
- Vinca alkaloids
- Zidovudine

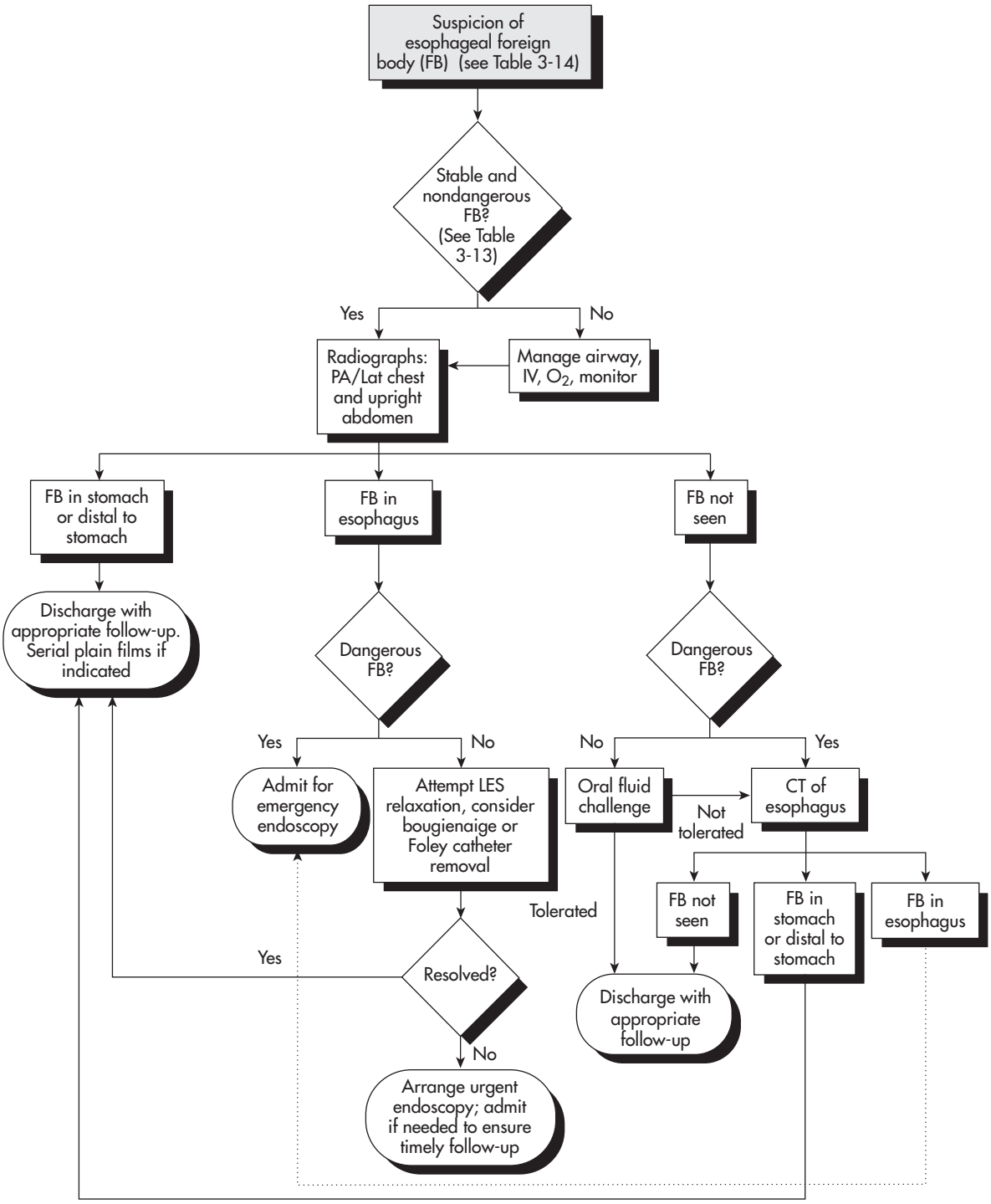


FIGURE 3-74 Diagnostic algorithm for the evaluation of a suspected esophageal foreign body. *CT*, Computed tomography; *IV*, intravenous line; *Lat*, lateral; *LES*, lower esophageal sphincter; *PA*, posteroanterior. (From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

ICD-9CM # 938
ICD-10CM # T18.8 Foreign body entering through orifice, gastrointestinal tract, specified part

TABLE 3-13 Most Threatening and Most Common Esophageal Foreign Bodies

Most Threatening

In Children

Disc batteries
Bones
Needles
Other sharp objects

In Adults

Disc batteries
Bones
Packets of illicit drugs
Toothpicks

Most Common

In Children

Coins
Marbles
Buttons
Toys

In Adults

Food boluses
Bones
Dentures
Oral piercings

From Adams JG, et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

TABLE 3-14 Differential Diagnosis for Esophageal Foreign Bodies

In Children

Perforation
Abrasion or laceration
Airway foreign body
Esophagitis
Epiglottitis
Globus hystericus
Reactive airways disease

In Adults

Perforation
Abrasion or laceration
Spasm
Esophagitis
Diverticulum
Malignancy
Myocardial infarction
Globus hystericus

From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

FATIGUE

ICD-9CM # 780.7 Fatigue NOS
300.5 Fatigue, Psychogenic
780.7 Chronic Fatigue Syndrome
ICD-10CM # R53.83 Other fatigue
F48.8 Other specified nonpsychotic mental disorders
R53.83 Other fatigue

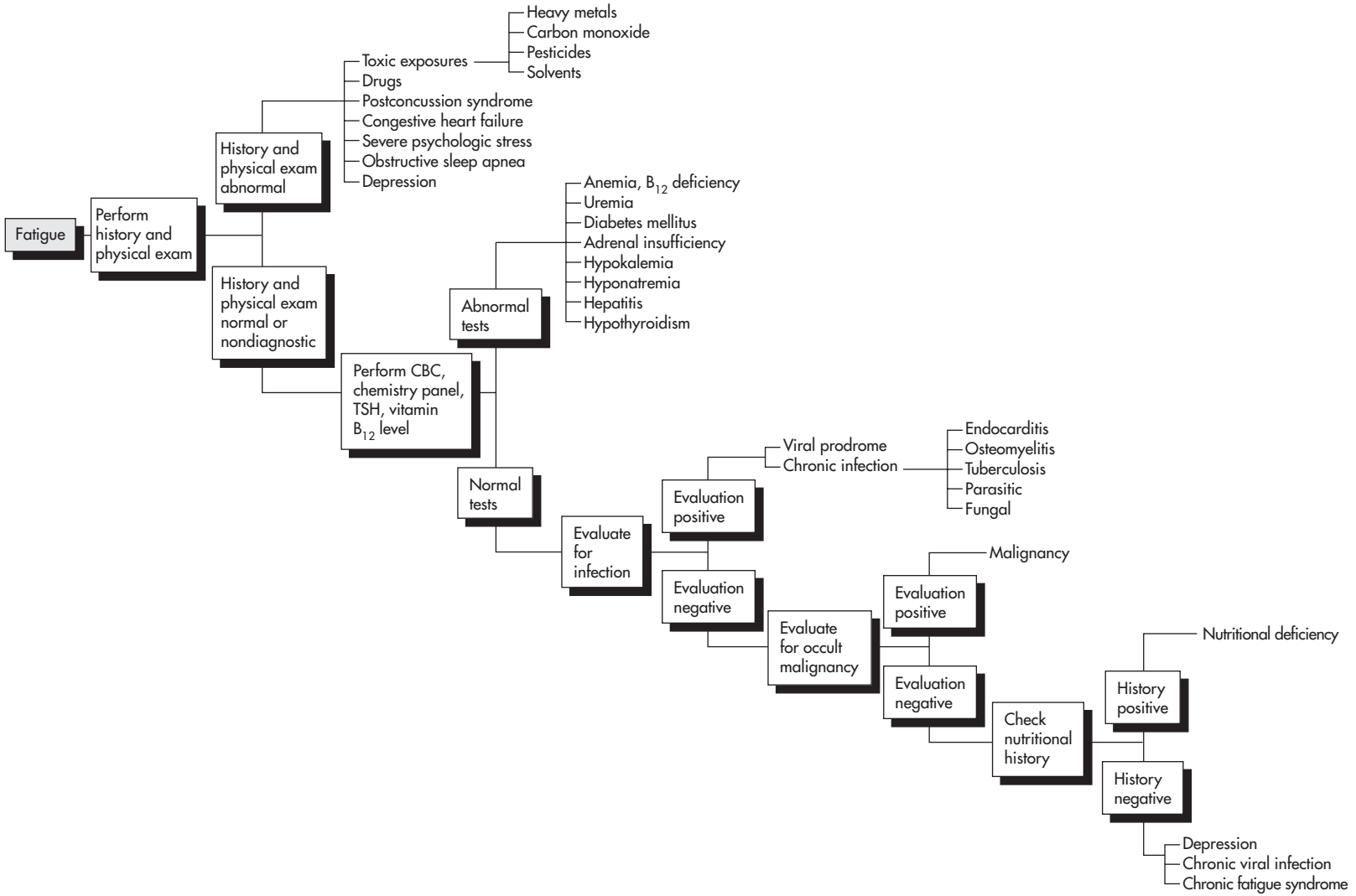


FIGURE 3-75 Evaluation of fatigue. *CBC,* Complete blood count. (Modified from Healey PM: *Common medical diagnosis: an algorithmic approach,* ed 3, Philadelphia, 2000, Saunders.)

FEVER AND INFECTION IN HIGH-RISK HEMATOLOGY PATIENT WITHOUT OBVIOUS SOURCE

ICD-9CM # 780.60 Fever, unspecified
ICD-10CM # R50.81 Fever presenting with conditions classified elsewhere
R50.2 Drug-induced fever
R50.9 Fever, unspecified

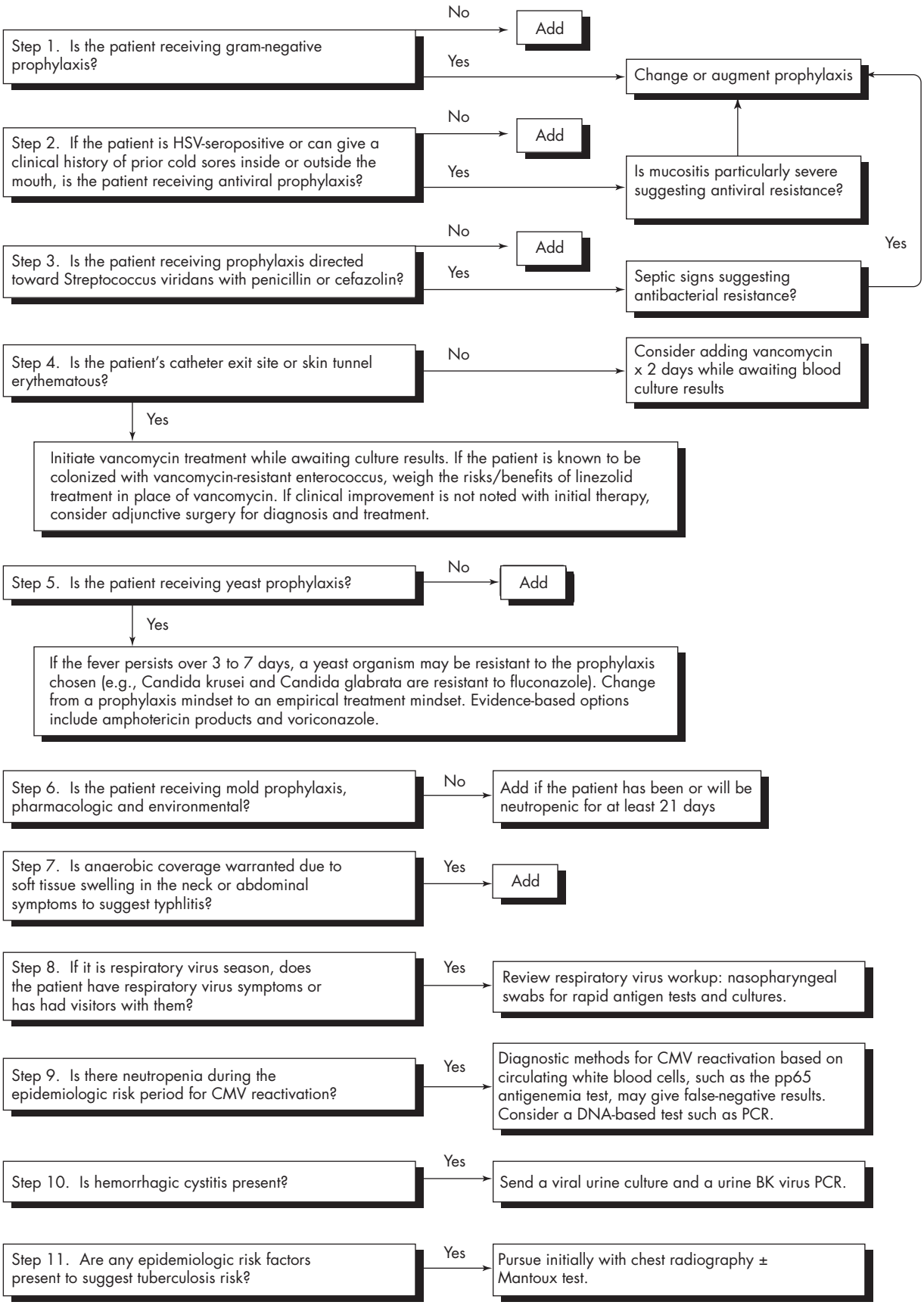
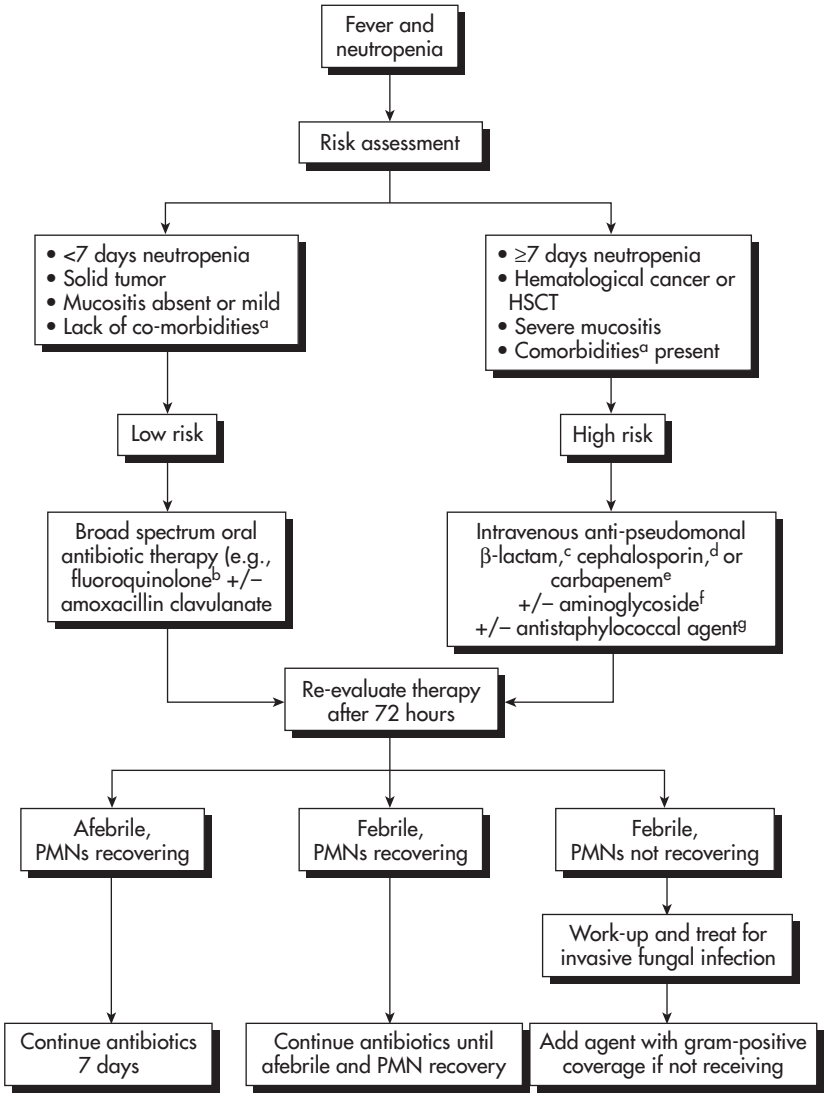


FIGURE E3-76 Systematic approach to causes of fever and infection in the high-risk hematology patient without an obvious source. This algorithm can be used for hematopoietic cell transplantation patients before engraftment or for patients who are receiving conventional, high-dose therapy for hematologic malignancies and are profoundly neutropenic. *CMV,* Cytomegalovirus; *HSV,* herpes simplex virus; *PCR,* polymerase chain reaction. (From Hoffmann R et al: *Hematology, basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.)

ICD-9CM # 288.04 Neutropenia due to infection
780.60 Fever, unspecified
ICD-10CM # R50.9 Fever, unspecified
D70.3 Neutropenia due to infection



[a] Hypotension, altered mental status, neurologic changes, respiratory failure, abdominal pain, hemorrhage, cardica compromise or new arrythmia, catheter tunnel infection, extensive cellulitis, acute renal or liver failure
[b] Institution sensitivity dependent, ciprofloxacin, levofloxacin, moxifloxacin
[c] Drug selection and dosing institution-specific: piperacillin tazobactam, ticarcillin/clavulanate
[d] Drug selection and dosing institution-specific: ceftazidime, cefepime, [e]imipenem/cilastatin, meropenem, doripenem
[f] Gentamin, tobramycin, or amakacin
[g] Drug selection and instituion institutio-specfic: vancomycin, linezolid, daptomycin, ceftaroline

FIGURE 3-77 Approach to patient with fever and neutropenia. (From Hoffman R: Hematology, basic principles and practice, 6th ed, Philadelphia, Saunders, 2013, Figure 88-3.)

FEVER AND NEUTROPENIA, PEDIATRIC PATIENT

ICD-9CM # 288.04 Neutropenia due to infection
780.60 Fever, unspecified
ICD-10CM # D70.3 Neutropenia due to infection
R50.9 Fever, unspecified

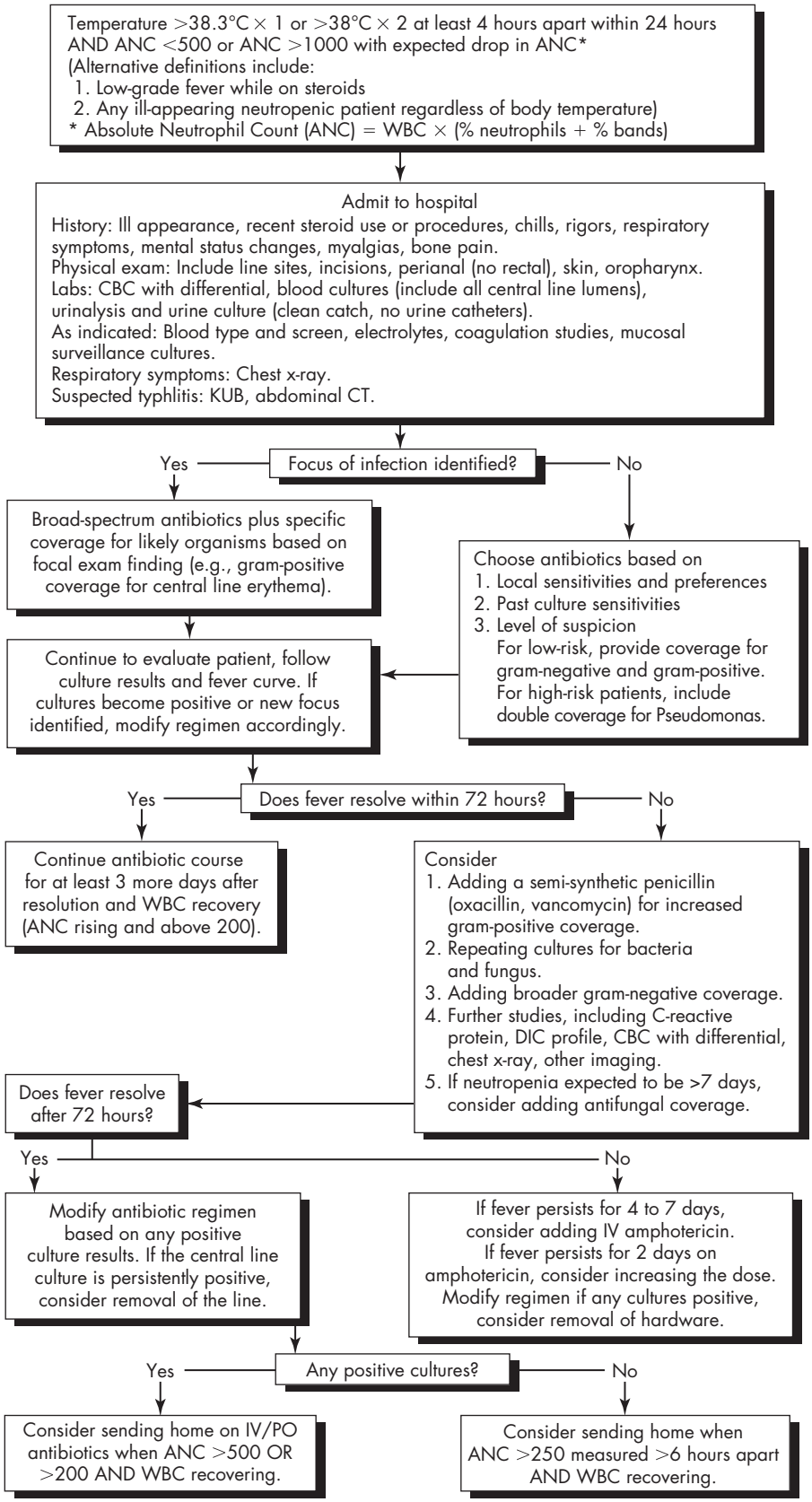


FIGURE E3-78 Fever and neutropenia. (From Custer JW, Rau RE: *The Harriet Lane handbook*, ed 18, St Louis, 2009, Mosby.)

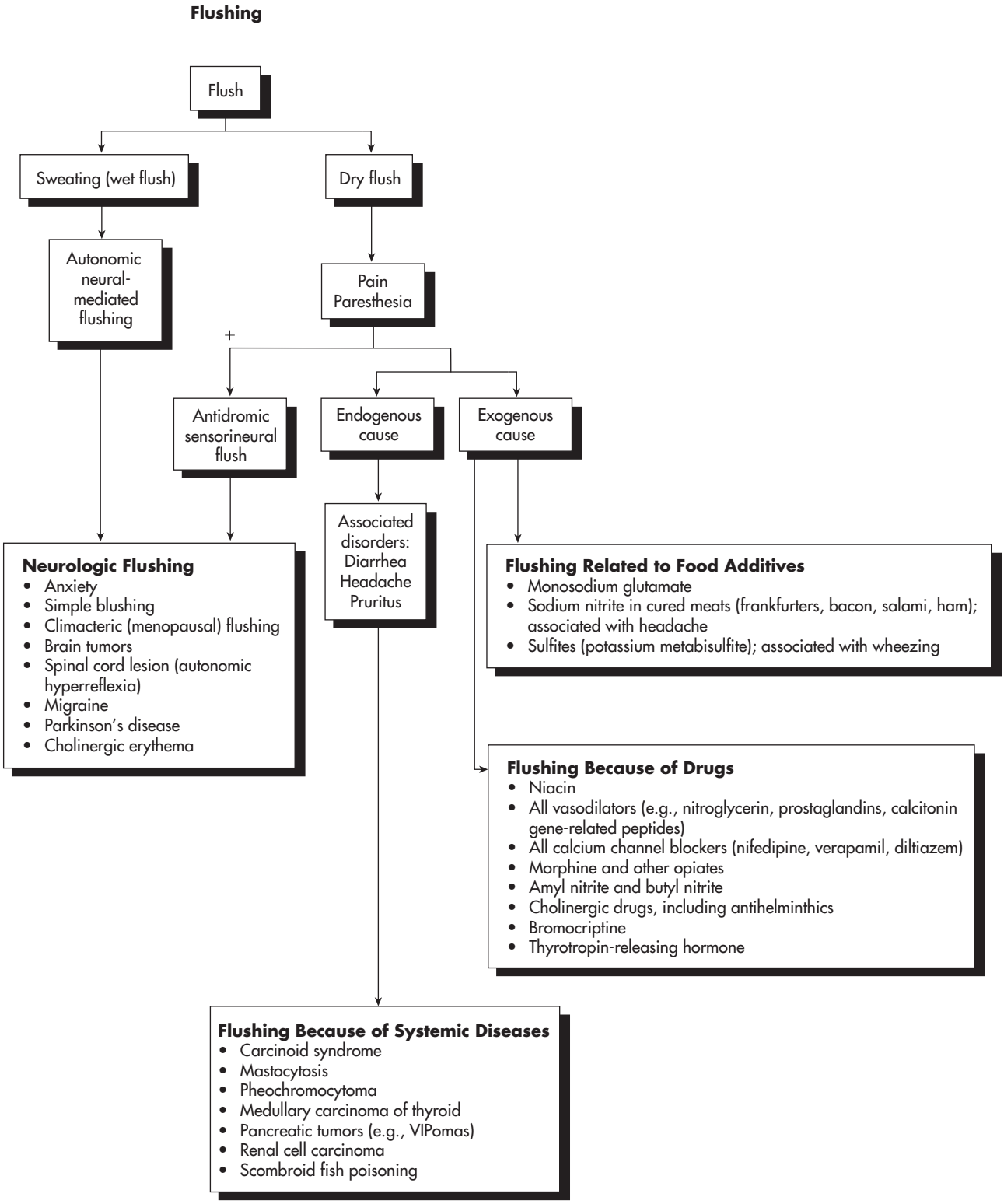


FIGURE E3-79 Evaluation of patients with flushing. (From Bolognia JL et al [eds]: *Dermatology,* ed 2, St Louis, 2008, Mosby.)

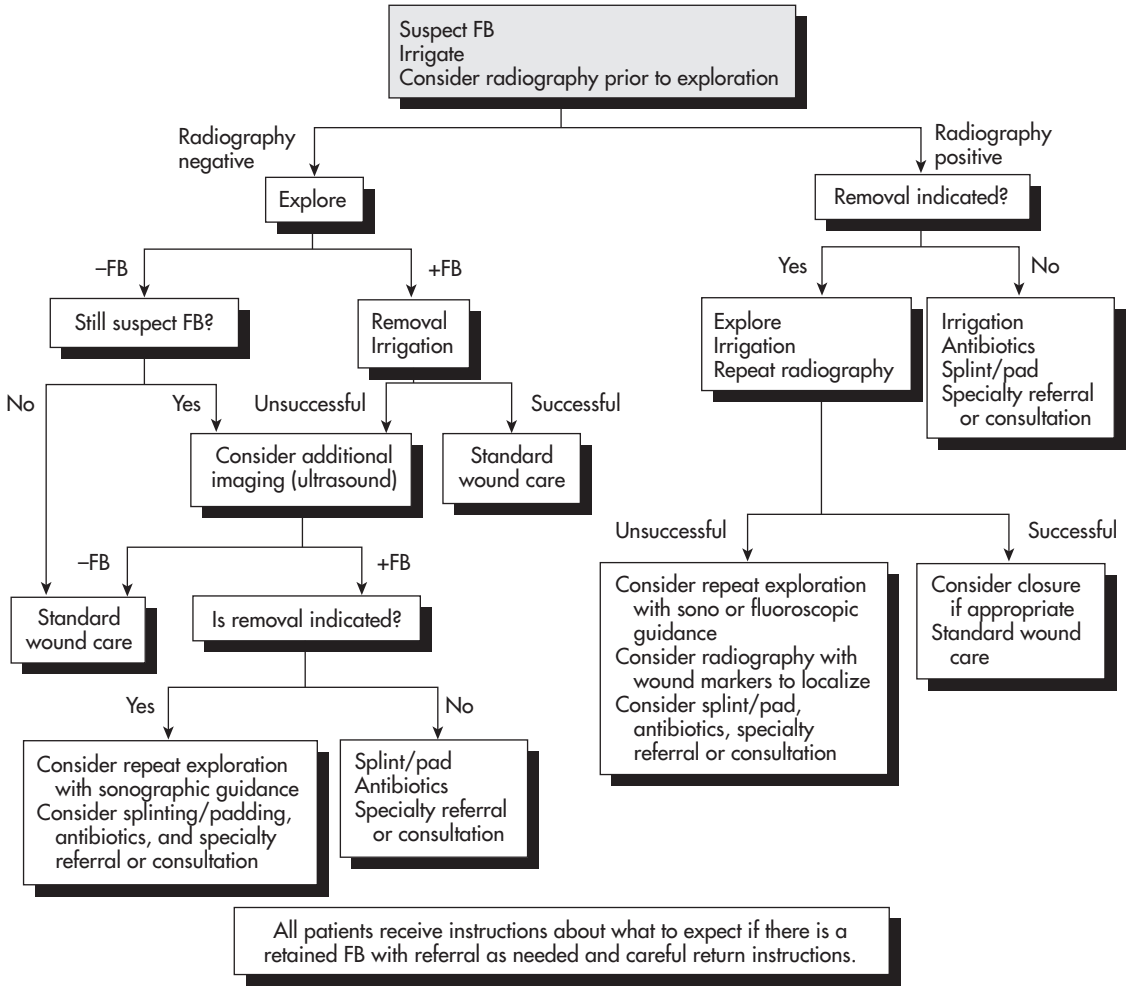


FIGURE 3-80 Approach to managing a wound foreign body. *FB*, Foreign body (From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

FRACTURE, BONE

ICD-9CM # 829.0 Fracture, bone(s) NOS closed
829.1 Fracture, bone(s) NOS open
995.5 Child maltreatment syndrome
ICD-10CM # T14.8 Other injury of unspecified body region

FIGURE E3-81 Bone fracture. *CT,* Computed tomography; *ESR,* erythrocyte sedimentation rate; *MRI,* magnetic resonance imaging; *SPEP,* serum protein electrophoresis; *UEP,* urine electrophoresis. (Modified from Greene HL, Johnson WP, Lemcke D [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

ICD-9CM # 829.0 Fracture, bone(s) NOS closed
829.1 Fracture, bone(s) NOS open
995.5 Child maltreatment syndrome
ICD-10CM # T14.8 Other injury of unspecified body region

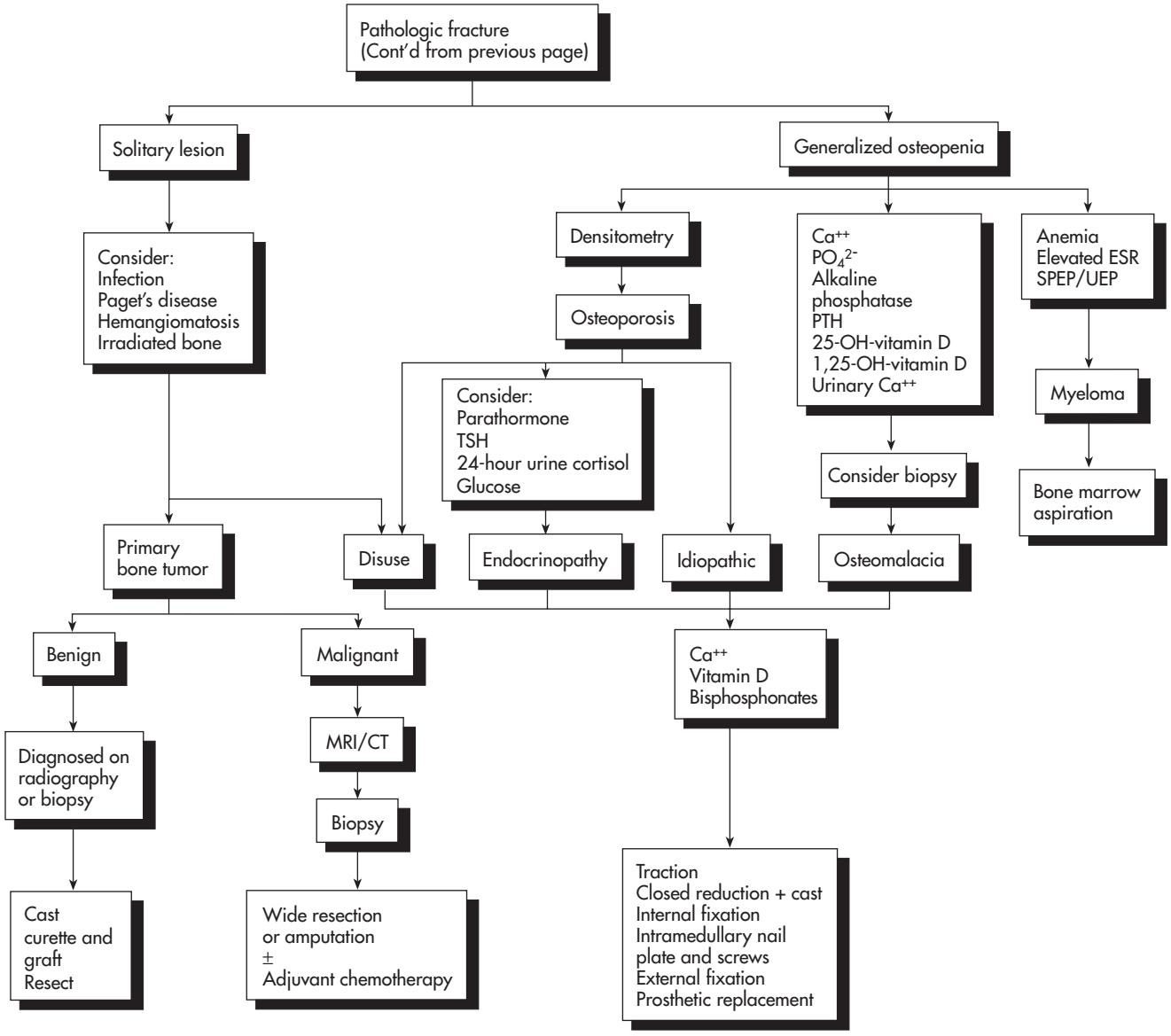


FIGURE E3-81 (Continued)

GENITAL LESIONS OR ULCERS

ICD-9CM #	054.10	Genital herpes
	91.0	Genital syphilis
	078.11	Condyloma acuminatum
	099.0	Chancroid
	099.2	Granuloma inguinale
	099.1	Lymphogranuloma venereum
	629.8	Ulcer, genital site, female
	608.89	Ulcer, genital site, male
ICD-10CM #	A60.9	Anogenital herpesviral infection, unspecified
	A51.0	Primary genital syphilis
	A63.0	Anogenital (venereal) warts
	A57	Chancroid
	A58	Granuloma inguinale
	A55	Chlamydial lymphogranuloma (venereum)
	N94.89	Other specified conditions associated with female genital organs and menstrual cycle
	N50.8	Other specified disorders of male genital organs

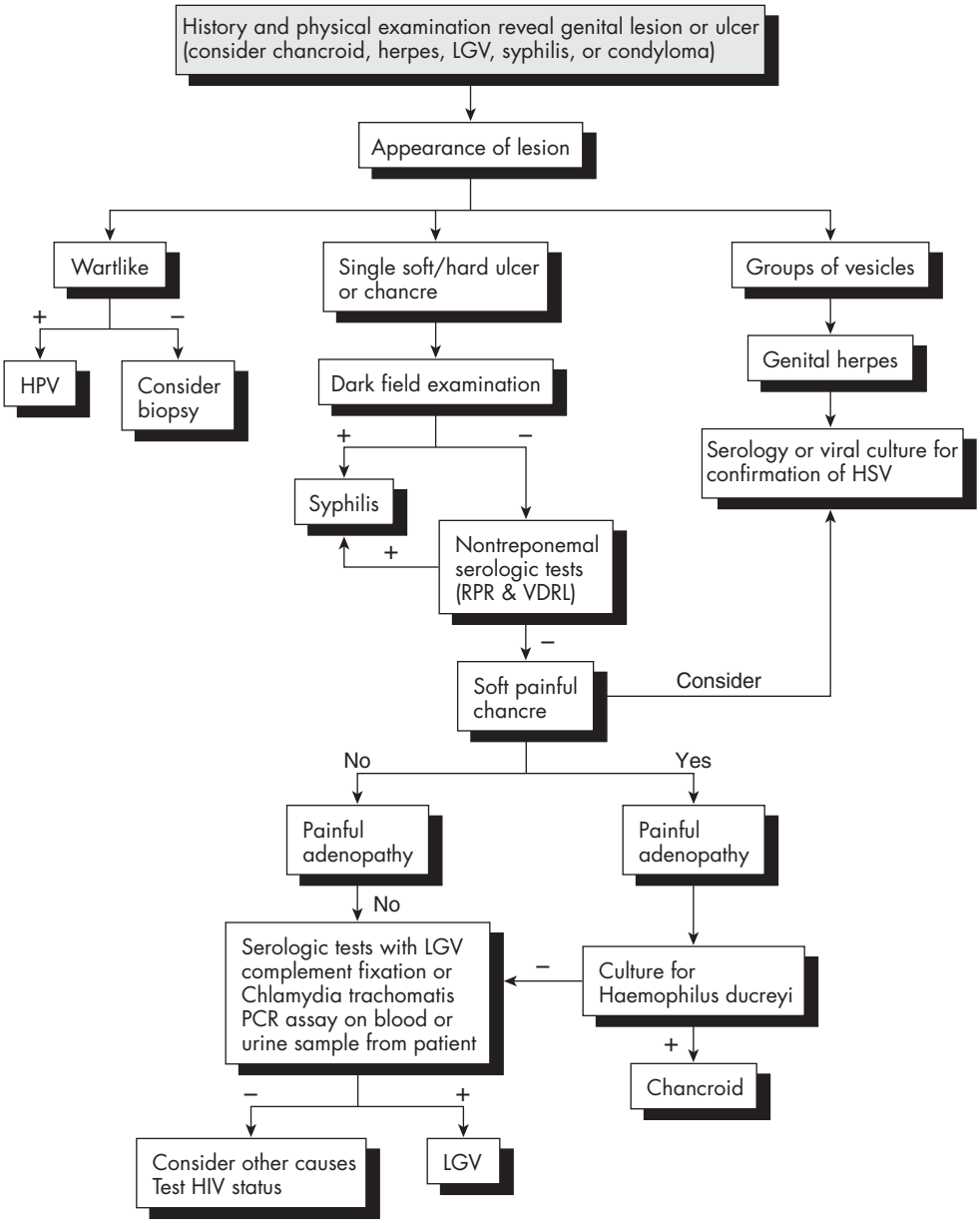
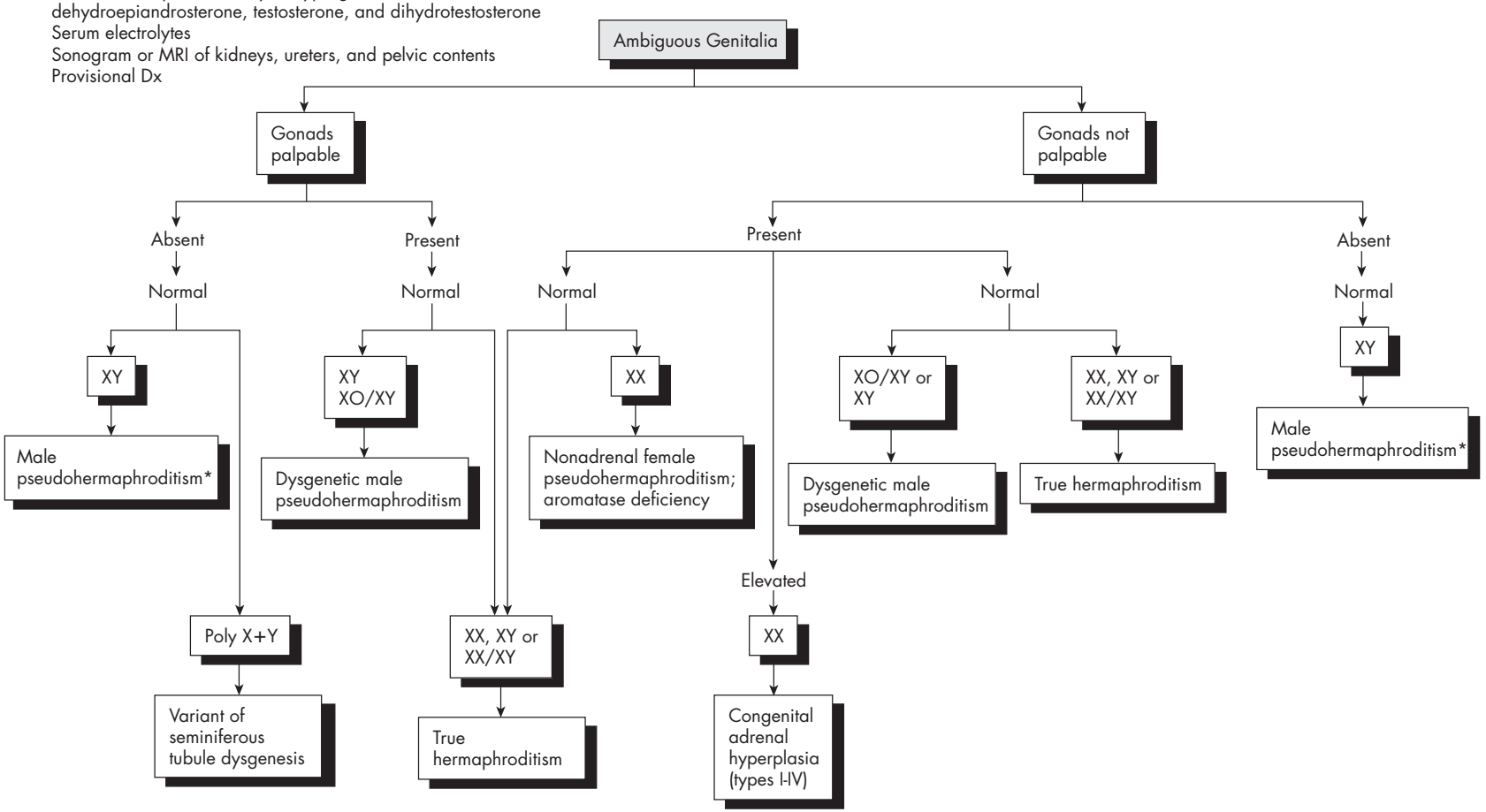


FIGURE 3-82 Evaluation of patients with genital lesions or ulcers. *HIV,* Human immunodeficiency virus; *HPV,* human papillomavirus; *HSV,* herpes simplex virus; *LGV,* lymphogranuloma venereum; *RPR,* rapid plasma reagin; *VDRL,* Venereal Disease Research Laboratory. (Modified from Nseyo UO [ed]: *Urology for primary care physicians,* Philadelphia, 1999, Saunders.)

GENITALIA, AMBIGUOUS

ICD-9CM # 752.7
ICD-10CM # Q56.4 Indeterminate sex, unspecified
Q56.3 Pseudohermaphroditism, unspecified

1. History: family history, pregnancy (hormones, virilization inspection)
   Palpation of inguinal region and labioscrotal folds; rectal examination
   Karyotype analysis
   Initial studies: plasma 17-hydroxyprogesterone, androstenedione, dehydroepiandrosterone, testosterone, and dihydrotestosterone
   Serum electrolytes
   Sonogram or MRI of kidneys, ureters, and pelvic contents
   Provisional Dx



2. "Vaginogram" (urogenital sinogram): selected cases
   Endoscopy, laparotomy, gonadal biopsy: restricted to male pseudohermaphrodites, true hermaphrodites, and selected instances of nonadrenal female pseudohermaphroditism

*Plasma 17-hydroxyprogesterone levels may be modestly elevated in patients with CYP11 (Type III), 3β-hydroxysteroid dehydrogenase deficiency (Type IV) and are "low" in patients with CYP17 (Type V) and CYP11A1 deficiency (Type VI)

FIGURE E3-83 Steps in the diagnosis of intersexuality in infancy and childhood. Step 1 involves initial workup and provisional diagnosis. Step 2 is used in selected cases. *MRI*, magnetic resonance imaging. (From Larsen PR et al [eds]: *Williams textbook of endocrinology*, ed 11, Philadelphia, 2008, Saunders.)

ICD-9CM # 578.9 GI Bleeding
ICD-10CM # K92.2 Gastrointestinal hemorrhage, unspecified

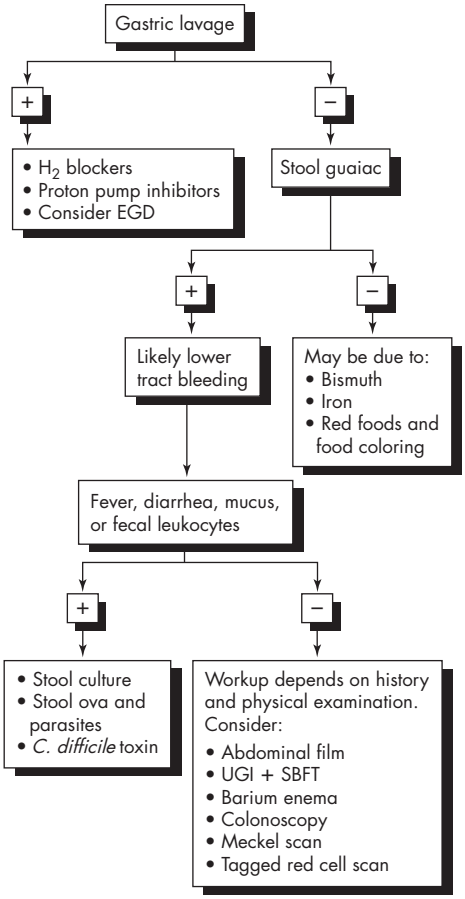


FIGURE E3-84 Evaluation of GI bleeding. May use gastrostomy tube (G tube) if present; use nasogastric tube with caution if esophageal varices suspected. *EGD,* Esophagogastroduodenoscopy; *SBFT,* small-bowel follow-through; *UGI,* upper gastrointestinal. (From Custer JW, Rau RE: *The Harriet Lane handbook,* ed 18, St Louis, 2009, Mosby.)

GOITER

ICD-9CM # 240.0 Goiter, specified as simple
241.0 Non-toxic uninodular goiter
241.1 Non-toxic multinodular goiter
242.00 Toxic diffuse goiter with thyrotoxic crisis
ICD-10CM # E04.0 Nontoxic diffuse goiter
E04.1 Nontoxic uninodular goiter
E04.2 Nontoxic multinodular goiter
E05.0 Toxic goiter

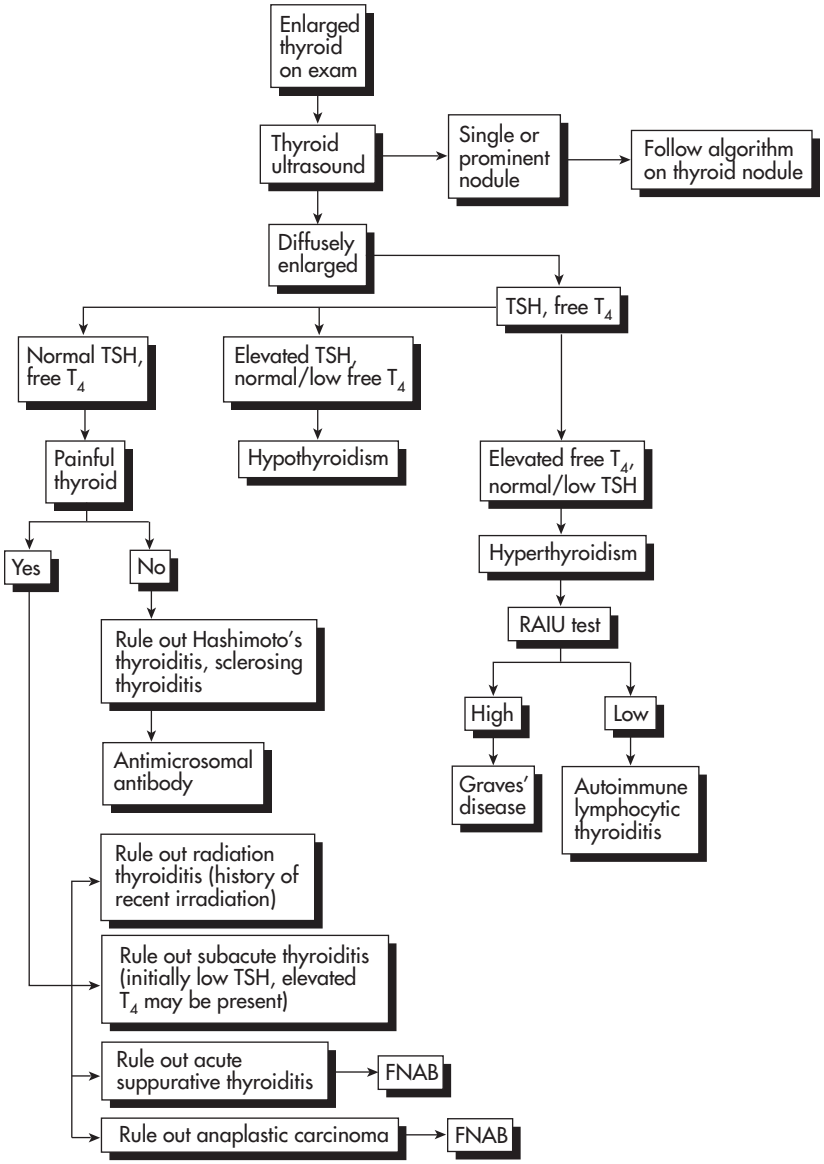


FIGURE 3-85 Diagnostic algorithm. *FNAB*, Fine needle aspiration biopsy. (From Ferri, F: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging* 3rd ed, Philadelphia, Saunders, 2014.)

Diagnostic Imaging
Best Test(s)
- Ultrasound of thyroid

Ancillary Tests
- RAIU scan of thyroid

Lab Evaluation
Best Test(s)
- TSH, free T_4

Ancillary Tests
- CBC with differential
- Antimicrosomal Ab
- Thyroglobulin level

GOITER EVALUATION AND MANAGEMENT

ICD-9CM #	240.9	Goiter, unspecified
	240.0	Goiter, simple
	241.9	Goiter, adenomatous
	246.1	Goiter, congenital
	242.1	Goiter, uninodular with thyrotoxicosis
	242.2	Goiter, multinodular with thyrotoxicosis
ICD-10CM #	E04.9	Nontoxic goiter, unspecified
	E01.2	Iodine-deficiency related (endemic) goiter, unspecified
	E04.0	Nontoxic diffuse goiter
	E05.10	Thyrotoxicosis with toxic single thyroid nodule without thyrotoxic crisis or storm
	E05.20	Thyrotoxicosis with toxic multinodular goiter without thyrotoxic crisis or storm
	E07.1	Dyshormogenetic goiter

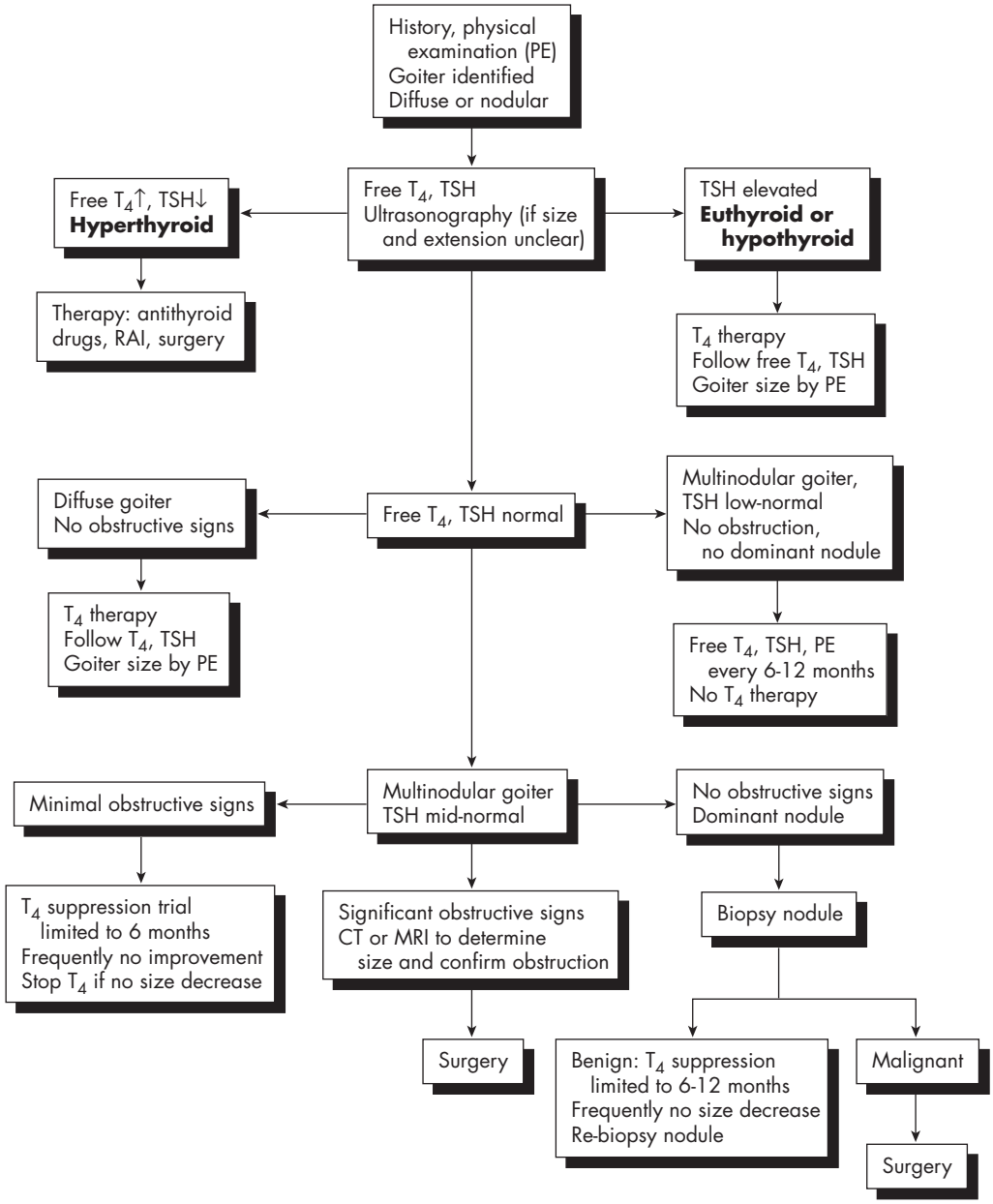


FIGURE E3-86 Evaluation and management of patients with nontoxic diffuse and nodular goiter and undetermined thyroid status. *CT,* Computed tomography; *MRI,* magnetic resonance imaging; *RAI,* radioactive iodine; *TSH,* thyroid-stimulating hormone. (From Goldman L, Schafer AL [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

ICD-9CM # variable with specific diagnosis
ICD-10CM # A58 Granuloma inguinale

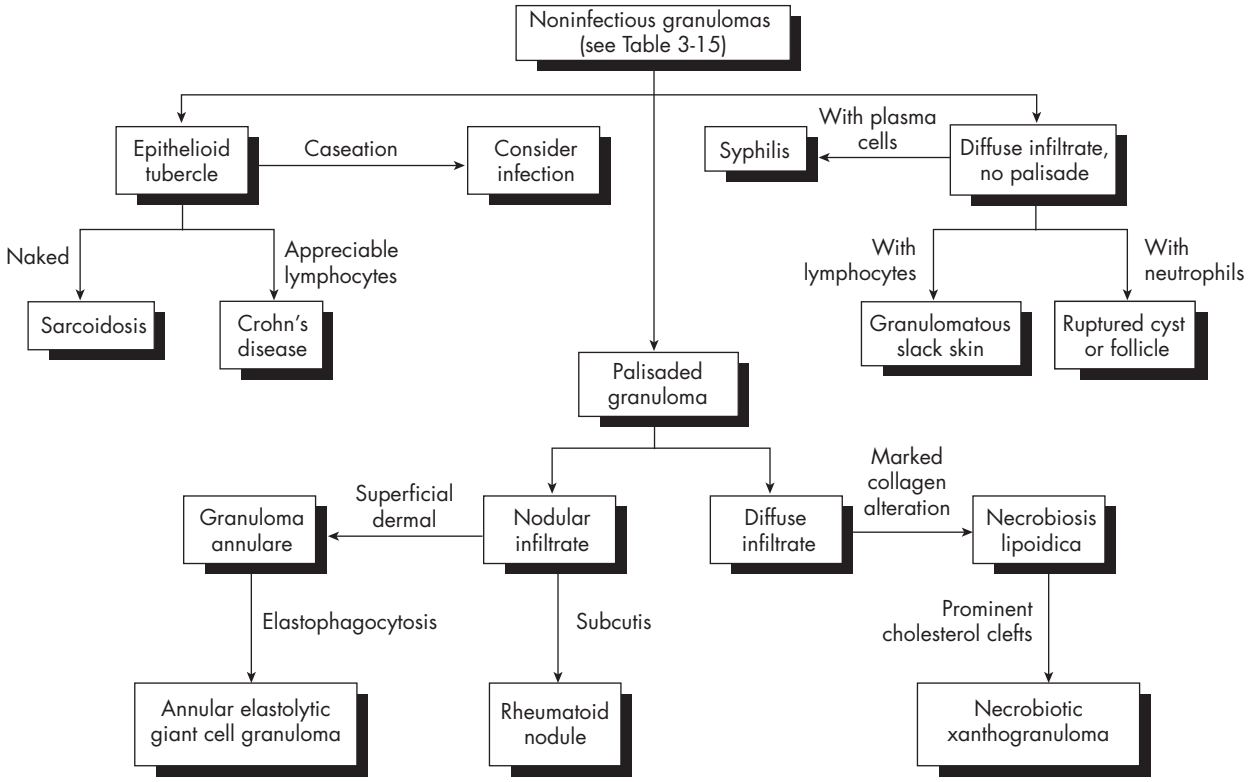


FIGURE 3-87 Noninfectious granulomas. Paradigm for histologic diagnosis.

TABLE 3-15 Clinical Features of the Major Granulomatous Dermatitides

	Sarcoidosis	Classic GA*	NLD	AEGCG	Crohn's Disease	Rheumatoid Nodule
Average age (years)	25-35, 45-65	<30		40	35	30-40
Sex	Female	Female	Female	Female	Female	Female
Racial predilection in United States	African American	None	None	Caucasian	None	None
Site	Symmetric on face, neck, upper trunk, extremities	Hands, feet, extremities	Anterior and lateral distal lower extremities	Face, neck, forearms	Genital areas, lower >upper extremities	Juxtaarticular areas, elbows, hands, ankles, feet
Appearance	Red to red-brown papules and plaques	Papules coalescing into annular plaques	Plaques with elevated borders, telangiectasias centrally	Annular plaques	Dusky erythema and swelling, ulceration	Skin-colored, firm, mobile subcutaneous nodules
Size of lesions	1-5 cm	1-2 mm papules, <5 cm annular plaques	>10 cm	1-6 cm	Variable	1-3 cm
Number of lesions	Variable	1-10	1-10	1-10	1-5	1-10
Associations	Systemic manifestations of sarcoidosis	Rare diabetes mellitus, malignancy	Diabetes mellitus	Actinic damage	Intestinal Crohn's disease	Rheumatoid arthritis
Special clinical characteristics	Occasional central atrophy and hypopigmentation	Central hyperpigmentation	Yellow-brown atrophic centers, ulceration	Central atrophy and hypopigmentation	Draining sinuses and fistulae	Occasional ulceration, especially at site of trauma

*Clinical variants include generalized, micropapular, nodular, perforating, subcutaneous, and patch GA.
AEGCG, Annular elastolytic giant cell granuloma; *GA,* granuloma annulare; *NLD,* necrobiosis lipoidica diabeticorum.
From Bolognia JL et al: *Dermatology,* ed 2, St Louis, 2008, Mosby.

ICD-9CM # 389.00 Hearing loss, conductive
389.10 Hearing loss, sensorineural
ICD-10CM # H90.2 Conductive hearing loss, unspecified
H90.5 Unspecified sensorineural hearing loss

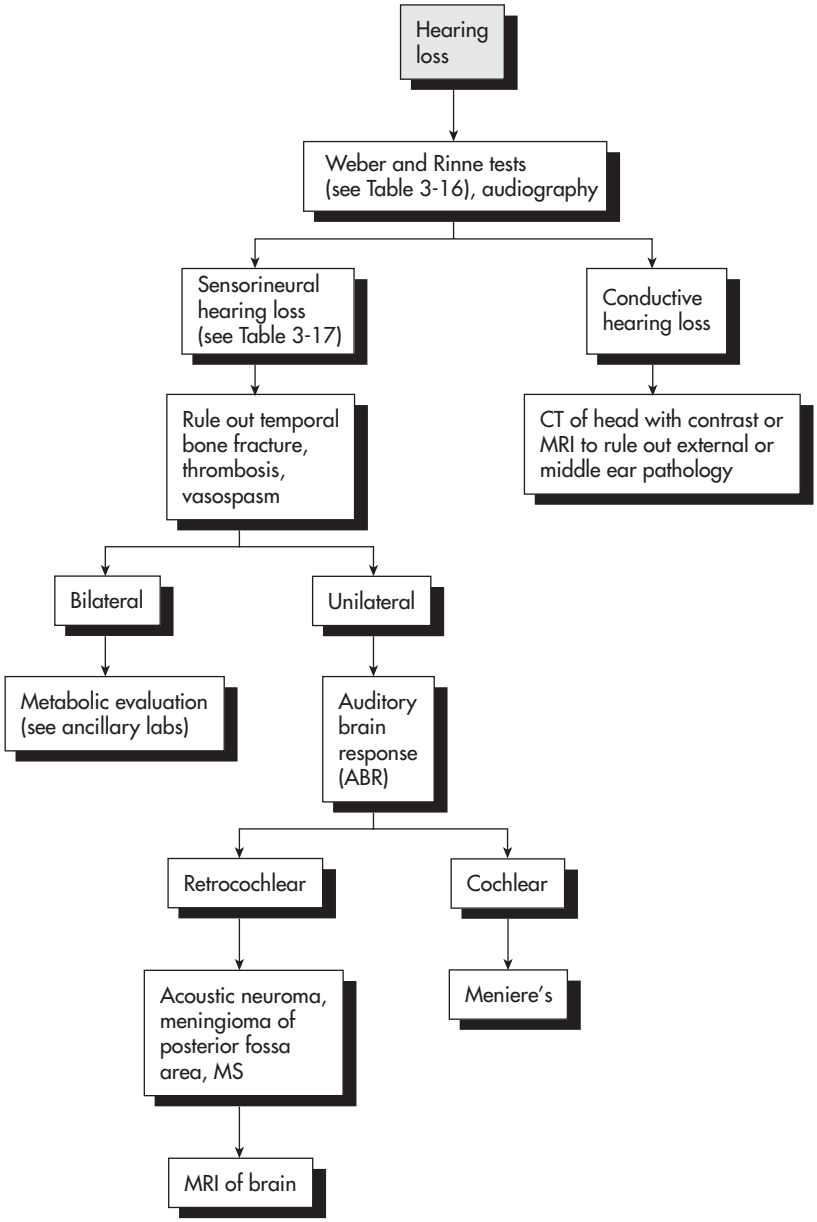


FIGURE 3-88 Evaluation of hearing loss. *CT,* Computed tomography; *MRI,* magnetic resonance imaging; *MS,* multiple sclerosis. (From Ferri FF: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 3, Philadelphia, 2014, Mosby.)

BOX 3-2 Hearing Loss

Diagnostic imaging
Best test
None

Ancillary tests
CT of head with contrast or MRI with contrast
CT of temporal bone without contrast

Lab evaluation
Best test
None

Ancillary tests
CBC
ALT, AST
ANA, VDRL
TSH

ALT, Alanine aminotransferase; *ANA,* antibody to nuclear antigens; *AST,* angiotensin sensitivity test; *CBC,* complete blood count; *CT,* computed tomography; *TSH,* thyroid-stimulating hormone; *VDRL,* Venereal Disease Research Laboratory.
From Ferri FF: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 3, Philadelphia, 2014, Mosby.

HEARING LOSS—cont'd

ICD-9CM # 389.00 Hearing loss, conductive
389.10 Hearing loss, sensorineural
ICD-10CM # H90.2 Conductive hearing loss, unspecified
H90.5 Unspecified sensorineural hearing loss

TABLE 3-16 Interpretation of the Weber and Rinne Tests

	WEBER WITHOUT LATERALIZATION	WEBER LATERALIZES RIGHT	WEBER LATERALIZES LEFT
Rinne both ears: AC >BC	Normal	S/N loss in the left ear	S/N loss in the right ear
Rinne left ear: BC >AC	–	Combined loss: conduction and S/N loss in the left ear	Conduction loss in the left ear
Rinne right ear: BC >AC	–	Conduction loss in the right ear	Combined loss: conduction and S/N loss in the right ear

AC, Air conduction; *BC*, bone conduction; *S/N*, sensorineural.
From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

TABLE 3-17 Lesions That Cause Hearing Loss

	Description of Pathology	Onset/Course	Actions or Treatment	Prognosis
Conductive Lesion				
Foreign body	Mass in external canal blocks sound conduction	Acute onset associated or not with pain, drainage, or odor	Removal. Evaluate for infection. Evaluate for TM perforation	Excellent
Otitis externa	Edema and detritus obstruct external canal	Rapid onset. Pain, edema, swelling. Drainage, odor often present	Aural toilet to remove debris. Topical (± oral) antibiotics. Evaluate for necrotizing otitis	Excellent if treated appropriately
Exostosis	Bony growths obstruct canal. Often seen with prolonged exposure to cold water (divers)	Slow insidious onset. No pain or drainage unless causes complete obstruction	Evaluate for infection. Reassure patient. Refer to ENT	Good
Tympanosclerosis	TM scarring from perforations or infections. Decreased mobility impairs sound conduction	Slow onset following perforations, trauma or infections	ENT referral. Reassurance	Variable
Perforated TM	Disruption of TM integrity results in impaired transmission of sound to ossicle	Acute onset. May follow direct trauma or sudden barotrauma. May have sudden relief from pain if caused by otitis media	Treat infectious causes. Counsel on importance of keeping water out of ear canal. ENT referral	Good
Sterile effusion (barotrauma)	Fluid in middle ear dampens conduction through ossicles	Often following flight, diving, or URI. Bubbles can cause intermittent pain	Decongestants. Evaluate for infection. Follow-up	Excellent
Acute otitis media	Pus (or fluid) in middle ear dampens conduction through ossicles	Acute to subacute onset, often following URI. Often associated with pain ± fever	Antibiotics (unless viral cause suspected), decongestants, pain control	Excellent if treated appropriately
Cholesteatoma	Trapped stratified squamous epithelial mass in middle ear. Interferes with ossicle conduction	Slow onset. Often history of previous perforations or chronic infections	ENT referral	Variable. May destroy ossicles or erode into surrounding structures
Glomus tumor	Vascular tumor occupies middle ear space. Interferes with ossicle conduction	Slow onset. May be associated with rushing pulsatile sensation	ENT referral	Variable
Cancer	Squamous cell most common. Obstructs external canal	Slow onset. Often noticed first by others. Painless unless occlusion causes otitis externa	ENT referral. Evaluate for secondary infection	Variable
Sensorineural Lesion				
Perilymph fistula (inner ear barotrauma)	Disruption of round or oval window allows leakage of perilymph into middle ear	Sudden onset of hearing loss often with tinnitus and vertigo. Frequently follows straining or abrupt change in pressure. Turning in direction of fistula exacerbates symptoms	Complete bed rest. Elevate head of bed and avoid increases in CSF pressure. Severe symptoms or noncompliance may require hospitalization. ENT consultation for possible oval or round window patch	Variable
Viral cochleitis	Cochlear inflammation. Often following URI	Rapid onset. Often following URI	Steroids often used (no good data)	Variable
Presbycusis	Age-related hearing loss. May be related to previous chronic noise exposure	Slow onset. Usually symmetric. High frequencies most affected. Tinnitus may occur	Hearing aid may help with both hearing loss and tinnitus	Variable
Acoustic neuroma	Benign schwannoma of 8th cranial nerve	Slow onset. Usually unilateral. May exhibit tinnitus, vertigo. May exhibit facial hyperesthesias or twitching	May require surgical excision if symptoms debilitating	Variable

ICD-9CM # 389.00 Hearing loss, conductive
389.10 Hearing loss, sensorineural
ICD-10CM # H90.2 Conductive hearing loss, unspecified
H90.5 Unspecified sensorineural hearing loss

TABLE 3-17 Lesions That Cause Hearing Loss—cont'd

	Description of Pathology	Onset/Course	Actions or Treatment	Prognosis
Ototoxic agents	Direct toxicity to inner ear structures	Variable onset. High frequency most affected. Exposure to ototoxic drugs. May have associated tinnitus	Stop use of offending agent	Variable. Hearing loss at time of stopping offending agent is usually permanent
Multiple sclerosis	Multiple demyelinating lesions interfere with nerve conduction	Often other associated neurologic findings. May wax and wane	Standard multiple sclerosis treatment (steroids, cytotoxic agents)	Variable
Stroke/CVA	Focal ischemic lesion of auditory nerve or auditory cortex	Sudden onset. Often associated with other neurologic deficits	Treat CVA risk factors (ASA, anticoagulants, glycemic control, BP control)	Variable
Meningitis	Infection enters inner ear through CNS-perilymph connection. Damages organ of Corti	Follows clinical picture of meningitis	Treat infection. Steroids may limit inflammation and damage	Variable
Meniere's disease (endolymphatic hydrops)	Abnormal homeostasis of inner ear fluids (clinical diagnosis; definitive diagnosis made histologically)	Episodic spells of vertigo. Associated sensation of fullness, tinnitus, and SNHL or auditory distortion. Low-frequency ranges most affected	Reduce salt, caffeine, nicotine (vasoconstrictors) intake. Consider diuretics, antihistamines, anticholinergics. ENT referral	Variable
Chronic noise exposure	Direct mechanical damage to cochlear structures and hair cells	Slow onset. Usually high frequency most affected	Prevention measures (earplugs). Stop exposure	Usually permanent
Skull trauma	Interruption of cranial nerve VIII, ossicle disruption, or shearing effects on organ of Corti	Sudden onset after trauma	ENT consultation for possible surgical repair	Variable: ossicle disruption has better prognosis than nerve or organ of Corti damage
Autoimmune causes	Vascular or neuronal inflammatory changes	Bilateral asymmetric SNHL. May be fluctuating or progressive. Often other systemic autoimmune findings	Outpatient autoimmune evaluation. Steroids and cytotoxic agents may slow progression	Variable

ASA, Acetylsalicylic acid; *BP*, blood pressure; *CNS*, central nervous system; *CSF*, cerebrospinal fluid; *CVA*, cerebrovascular accident; *ENT*, ear, nose, and throat; *SNHL*, sensorineural hearing loss; *TM*, tympanic membrane; *URI*, upper respiratory infection.

From Adams JG et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

ICD-9CM # 569.3 Hematochezia
ICD-10CM # K62.5 Hemorrhage of anus and rectum

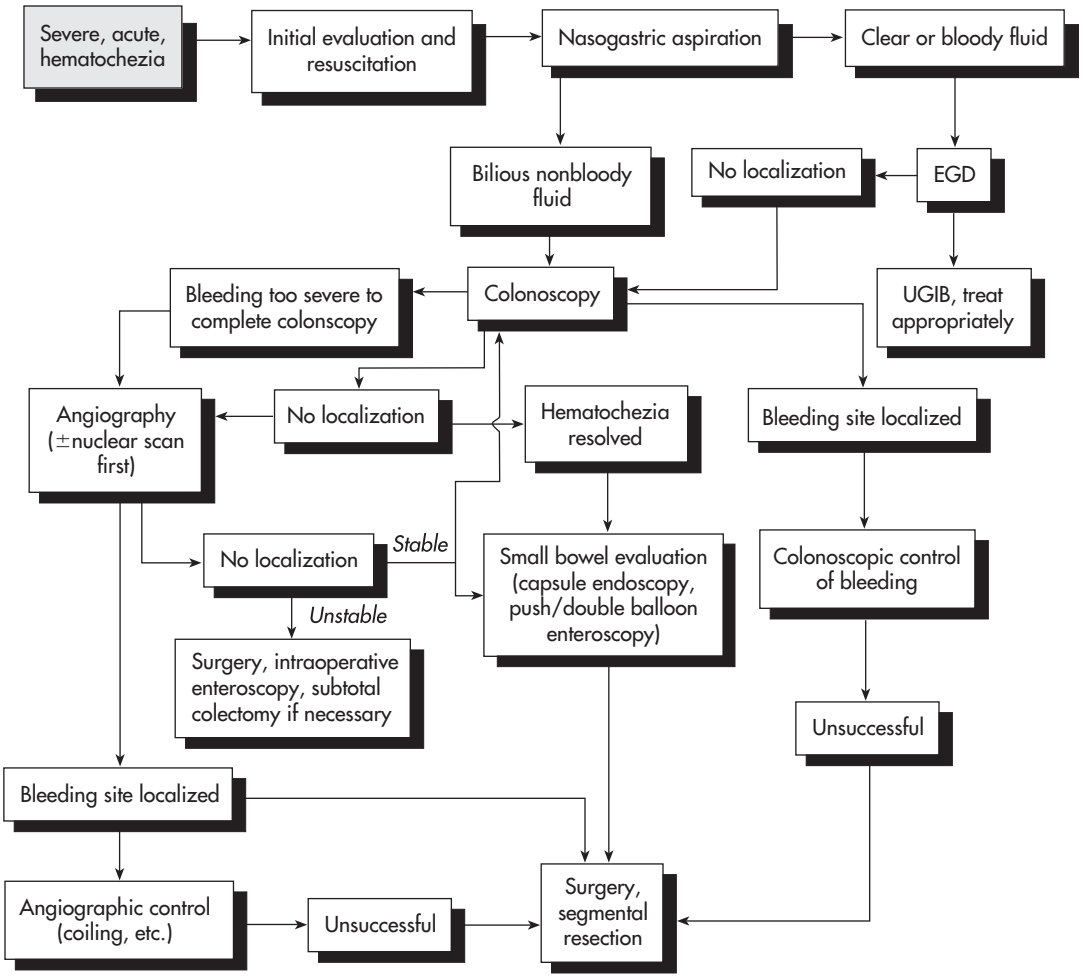


FIGURE E3-89 Management algorithm for hematochezia. *EGD,* Esophagogastroduodenoscopy; *UGIB,* upper gastrointestinal biopsy. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

ICD-9CM # 599.7
ICD-10CM # R31.9 Hematuria, unspecified

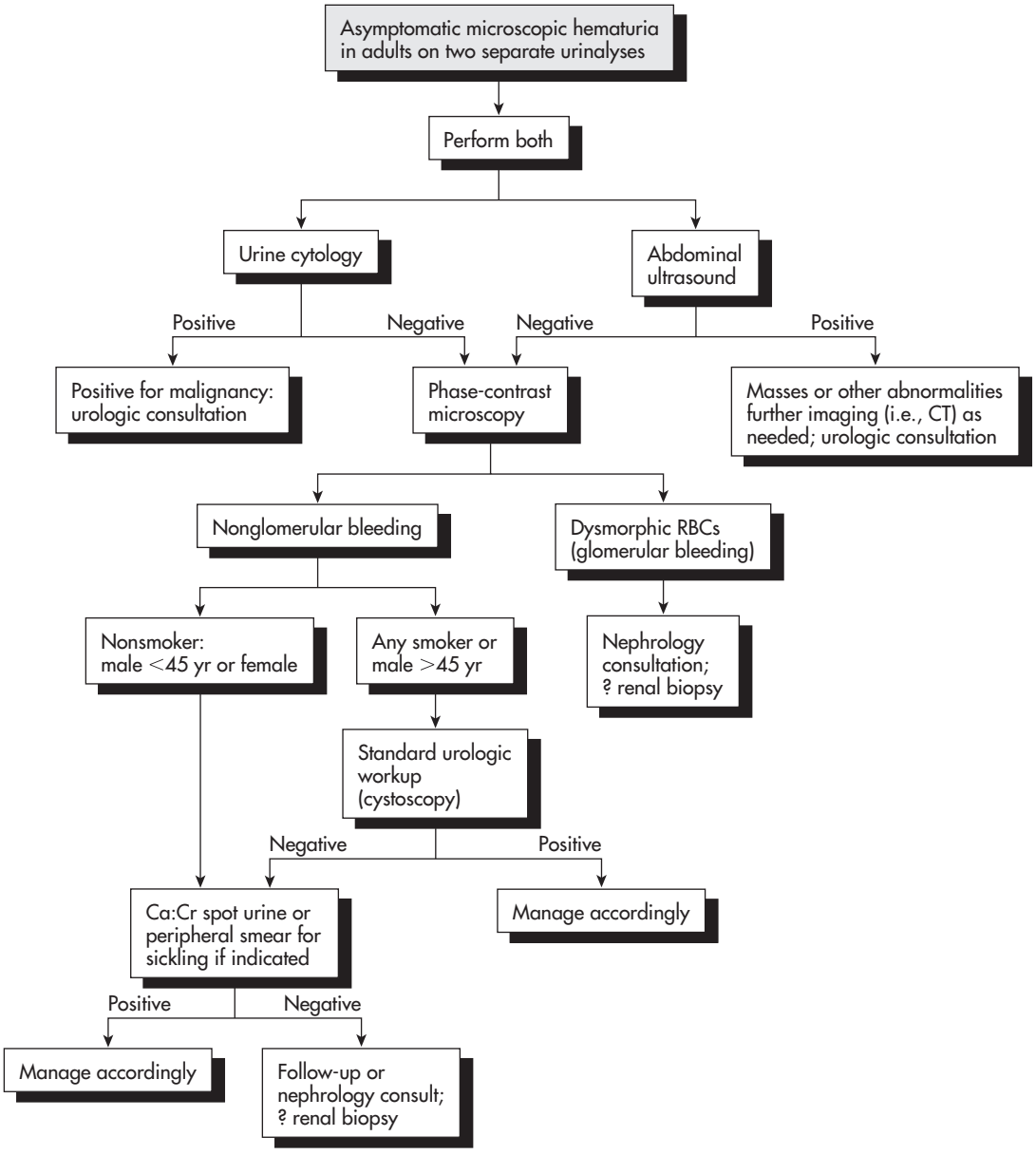


FIGURE 3-90 Suggested algorithm for the evaluation of adult asymptomatic microscopic hematuria. These patients must have no symptoms referable to the hematuria and a negative urinalysis except for red blood cells *(RBCs).* Adults with gross hematuria require a full urologic evaluation. *Ca:Cr,* Calcium:creatinine ratio. (Modified from Nseyo UO [ed]: *Urology for primary care physicians,* Philadelphia, 1999, Saunders.)

ICD-9CM # 599.70 Hematuria, unspecified
ICD-10CM # R31.9 Hematuria, unspecified

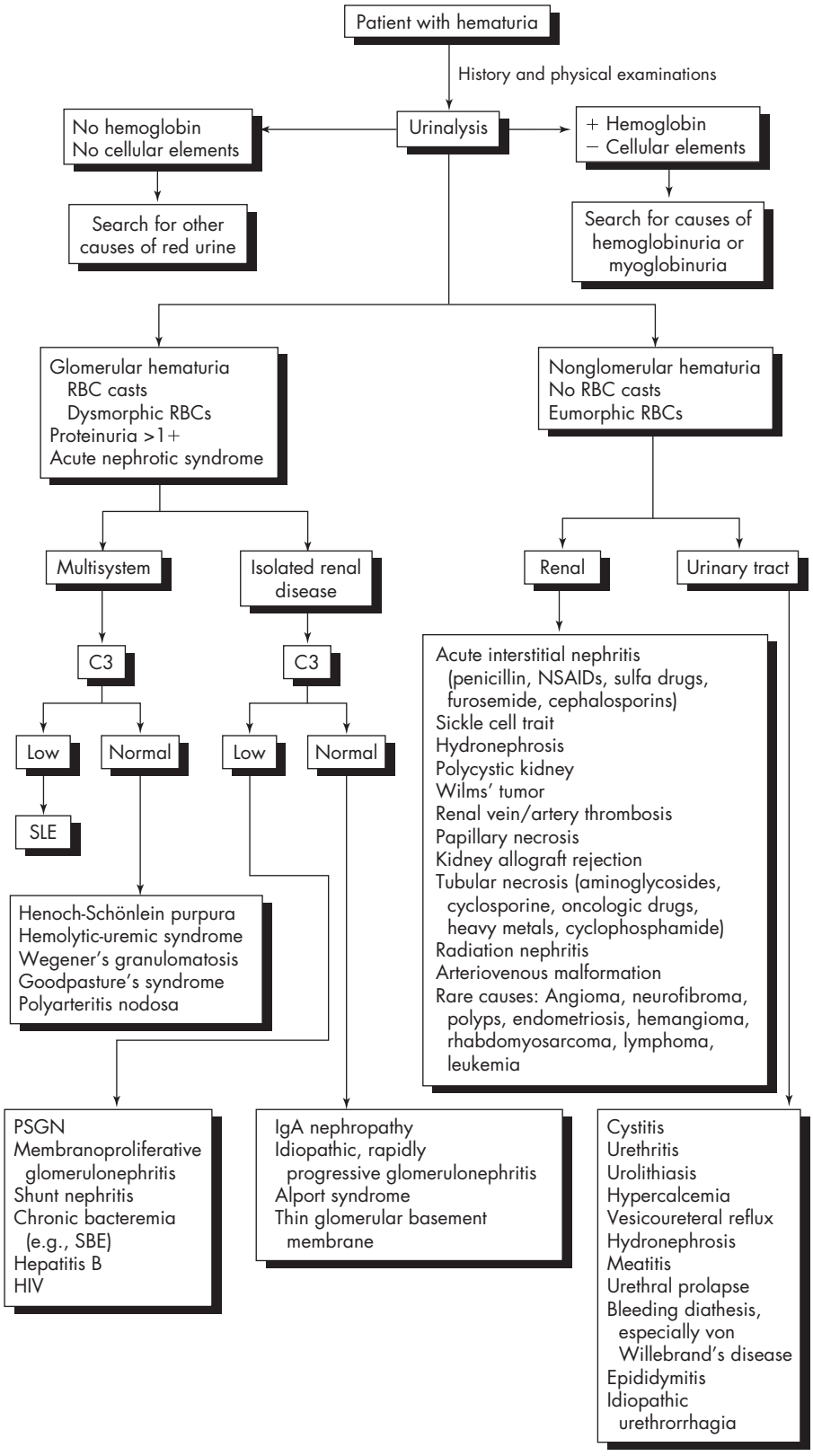


FIGURE E3-91 A diagnostic strategy for hematuria. *HIV,* Human immunodeficiency virus; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *PSGN,* poststreptococcal glomerulonephritis; *RBC,* red blood cell; *SBE,* subacute bacterial endocarditis; *SLE,* systemic lupus erythematosus. (From Custer JW, Rau RE: *The Harriet Lane handbook,* ed 18, St Louis, 2009, Mosby.)

HEMOPTYSIS

ICD-9CM # 786.3
ICD-10CM # R04.2 Hemoptysis

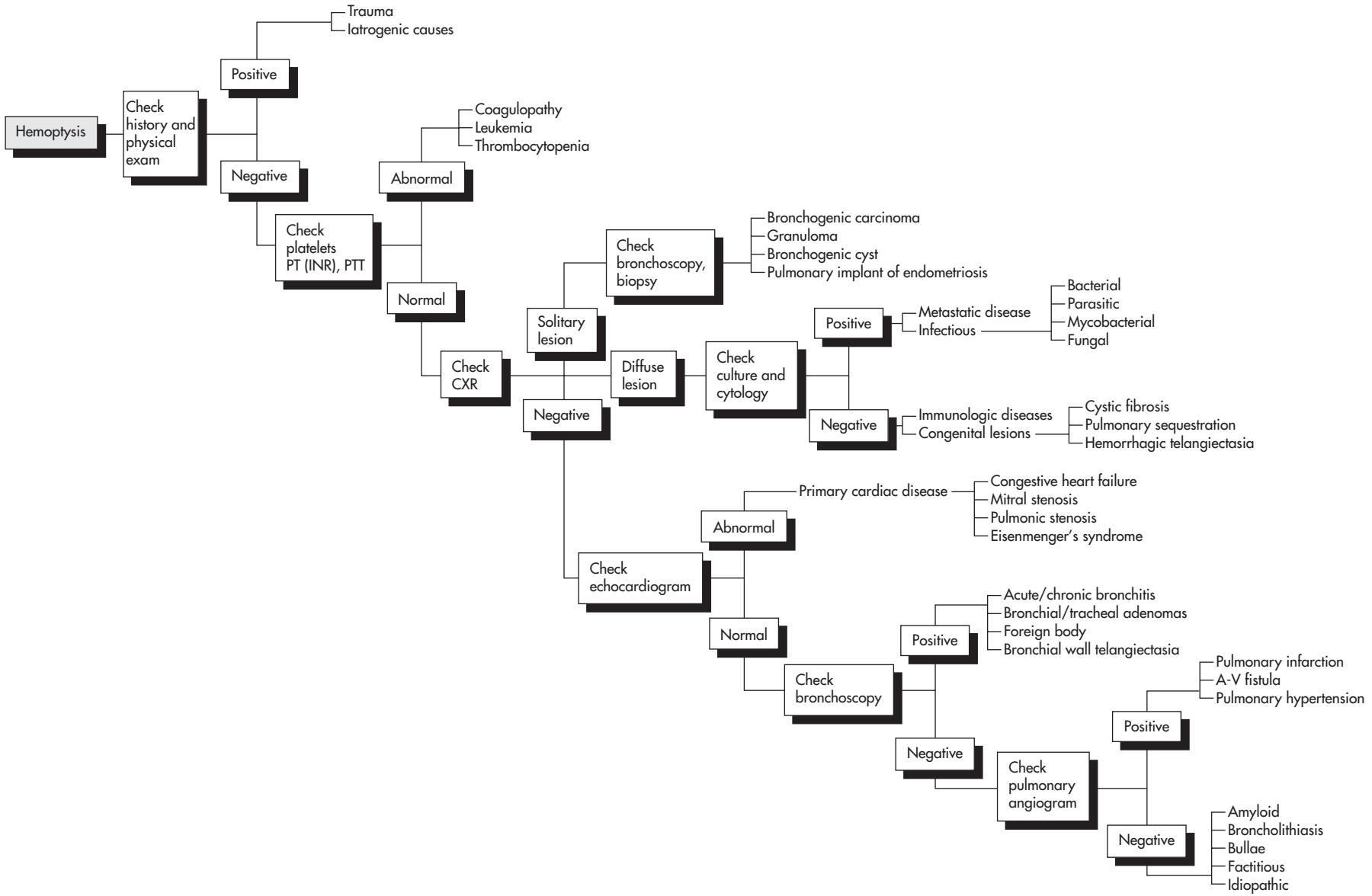


FIGURE 3-92 Evaluation of hemoptysis. *A-V,* Arteriovenous; *CXR,* chest x-ray; *INR,* International Normalized Ratio; *PT,* prothrombin time; *PTT,* partial thromboplastin time. (From Healey PM: *Common medical diagnosis: an algorithmic approach,* ed 3, Philadelphia, 2000, Saunders.)

ICD-9CM # 751.60
ICD-10CM # Q44.7 Other congenital malformations of liver

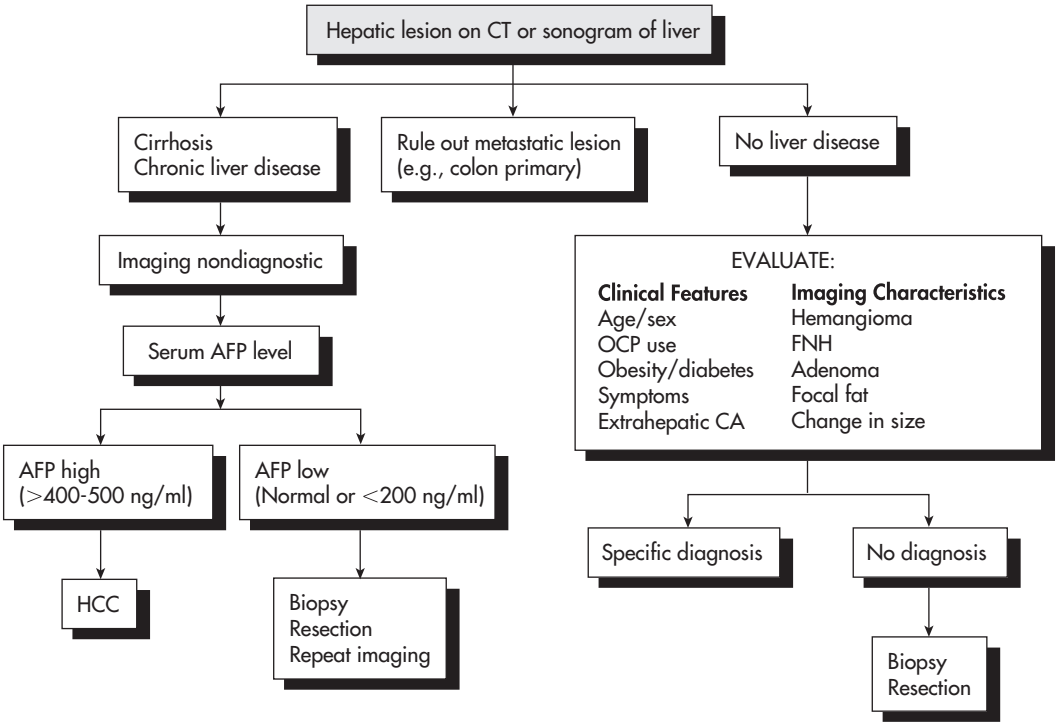


FIGURE 3-93 Diagnostic approach to space-occupying lesions of the liver. *AFP,* α-Fetoprotein; *CA,* cancer antigen; *FNH,* focal nodular hyperplasia; *HCC,* hepatocellular carcinoma; *OCP,* oral contraceptives. (Modified from Goldman L, Schafer AL [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

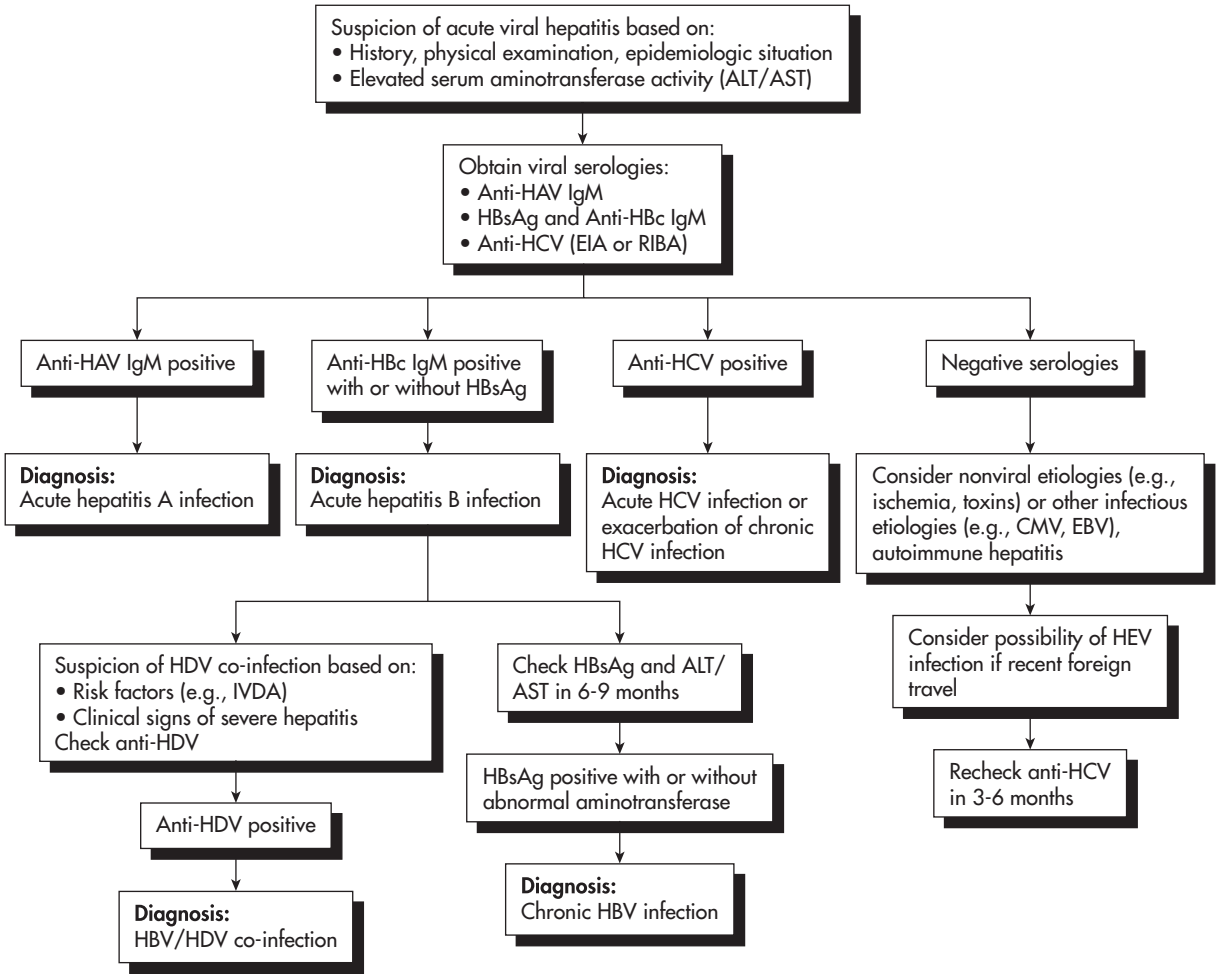


FIGURE 3-94 A flow diagram showing the use of specific serologic tests for the diagnosis of acute viral hepatitis in relation to the clinical and epidemiologic setting. Co-infections and superinfections of chronic hepatitis B or C patients should always be considered in cases that do not fit well with the clinical or serologic picture. *CMV,* Cytomegalovirus; *EBV,* Epstein-Barr virus; *EIA,* enzyme immunoassay; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HDV,* hepatitis D virus; *HEV,* hepatoencephalomyelitis virus; *IVDA,* intravenous drug abuse; *RIBA,* recombinant immunoblot assay. (Modified from Mandell GL et al: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 7, New York, 2008, Churchill Livingstone.)

HEPATOMEGALY

ICD-9CM # 789.1
ICD-10CM # R16.0 Hepatomegaly, not elsewhere classified

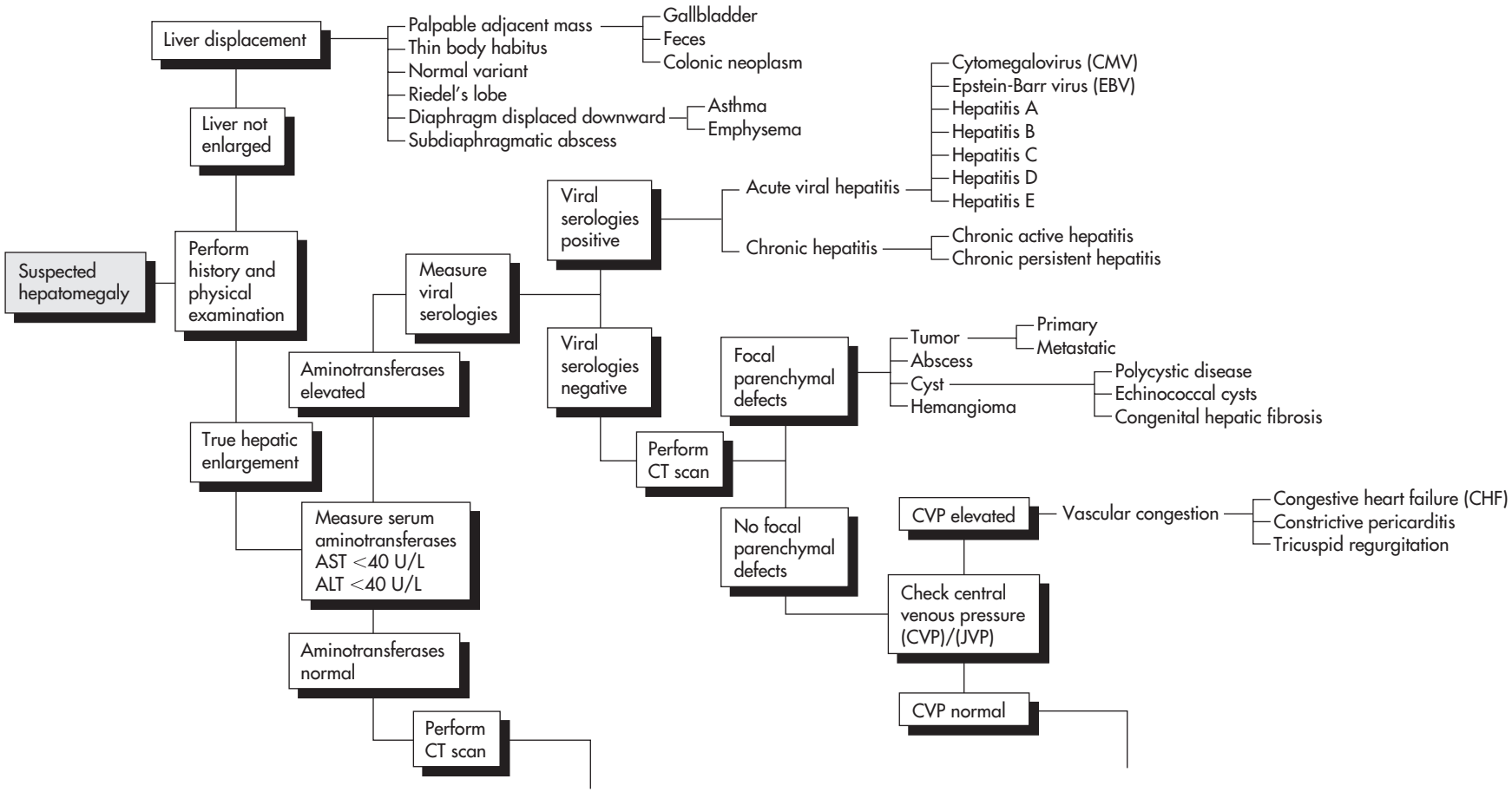


FIGURE 3-95 Hepatomegaly. *ALT,* Alanine aminotransferase; *AST,* aspartate aminotransferase; *CT,* computed tomography; *JVP,* jugular venous pressure. (Modified from Healey PM: *Common medical diagnosis: an algorithmic approach,* ed 3, Philadelphia, 2000, Saunders.)

ICD-9CM # 789.1
ICD-10CM # R16.0 Hepatomegaly, not elsewhere classified

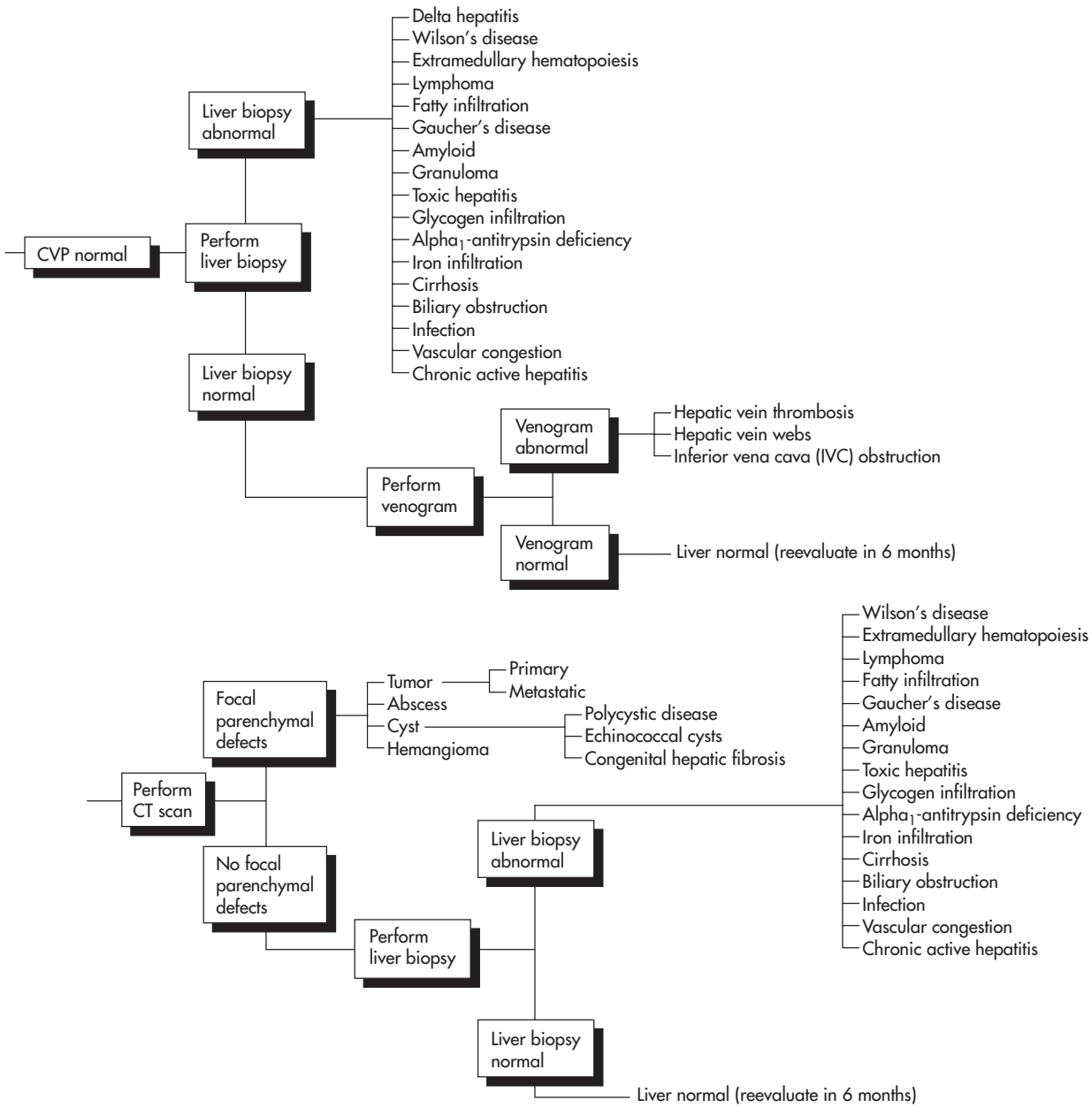


FIGURE 3-95 (Continued)

ICD-9CM # 275.42 Hypercalcemia
ICD-10CM # E83.52 Hypercalcemia

FIGURE 3-96 Diagnostic algorithm. (From Ferri, *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 3, Philadelphia, Saunders, 2014.)

Diagnostic Imaging
Best Test(s)
- None

Ancillary Tests
- Radiograph of painful bones (r/o bone neoplasm, multiple myeloma)
- Tc-99m parathyroid scan (r/o parathyroid adenoma)
- Ultrasound of parathyroid glands
- Ultrasound of kidneys (r/o renal cell carcinoma)

Lab Evaluation
Best Test(s)
- Serum calcium level
- PTH level

Ancillary Tests
- Serum phosphate, magnesium, alkaline phosphatase, albumin
- Electrolytes, BUN, creatinine
- 24-hour urine collection for calcium
- Urinary cyclic AMP
- PSA (if prostate carcinoma is suspected)
- Serum and urine protein immunoelectrophoresis (if multiple myeloma suspected)

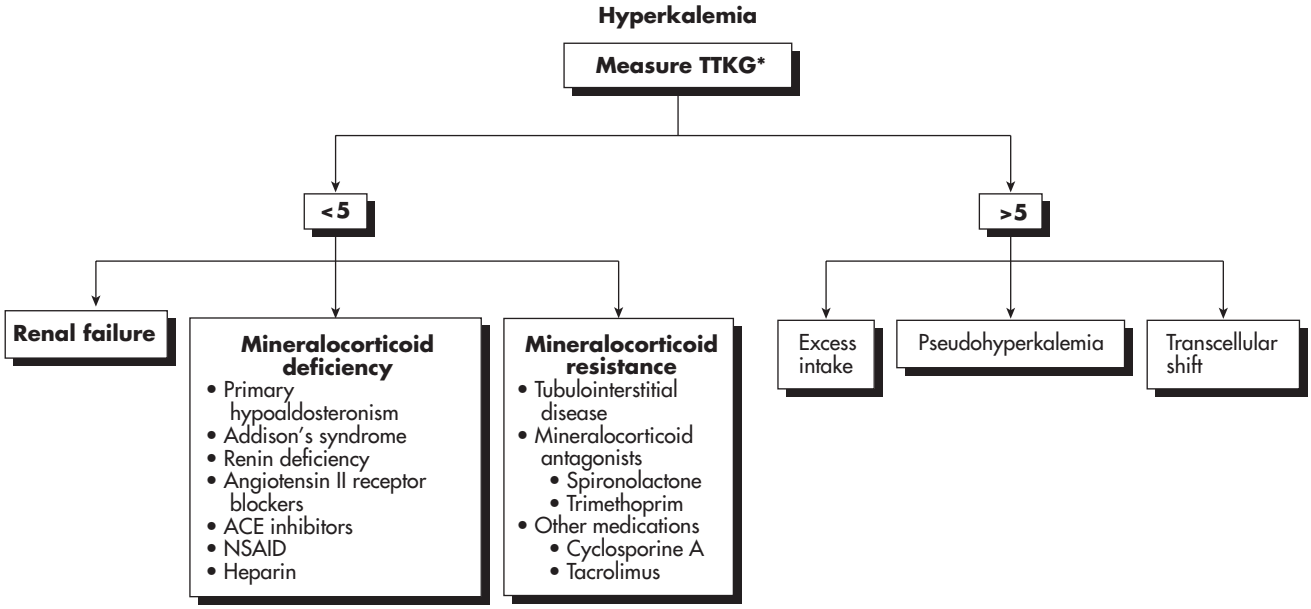


FIGURE 3-97 Algorithm for evaluation of hyperkalemia. Transtubular potassium gradient (TTKG) = Urine K^+ / Plasma K^+ / Urine OSM / Plasma OSM. The transtubular potassium gradient (TTKG) is typically less than 5 when a renal cause of hyperkalemia is present. Note that this formula is valid only when UOSM > 300 and UNa > 25. (From Cameron JL, Cameron AM: *Electrolyte disorders, Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

Diagnostic Imaging
Best Test(s)
- None

Ancillary Tests
- None

Lab Evaluation
Best Test(s)
- Heparinized potassium level

Ancillary Tests
- Serum electrolytes, BUN, plasma osmolality, urine osmolality creatinine, urine potassium, calculation of TTKG (see Fig. E3-91)
- Glucose, CBC
- CPK (when rhabdomyolysis is suspected)

ICD-9CM # 275.2 Hypermagnesemia
ICD-10CM # E83.41 Hypermagnesemia

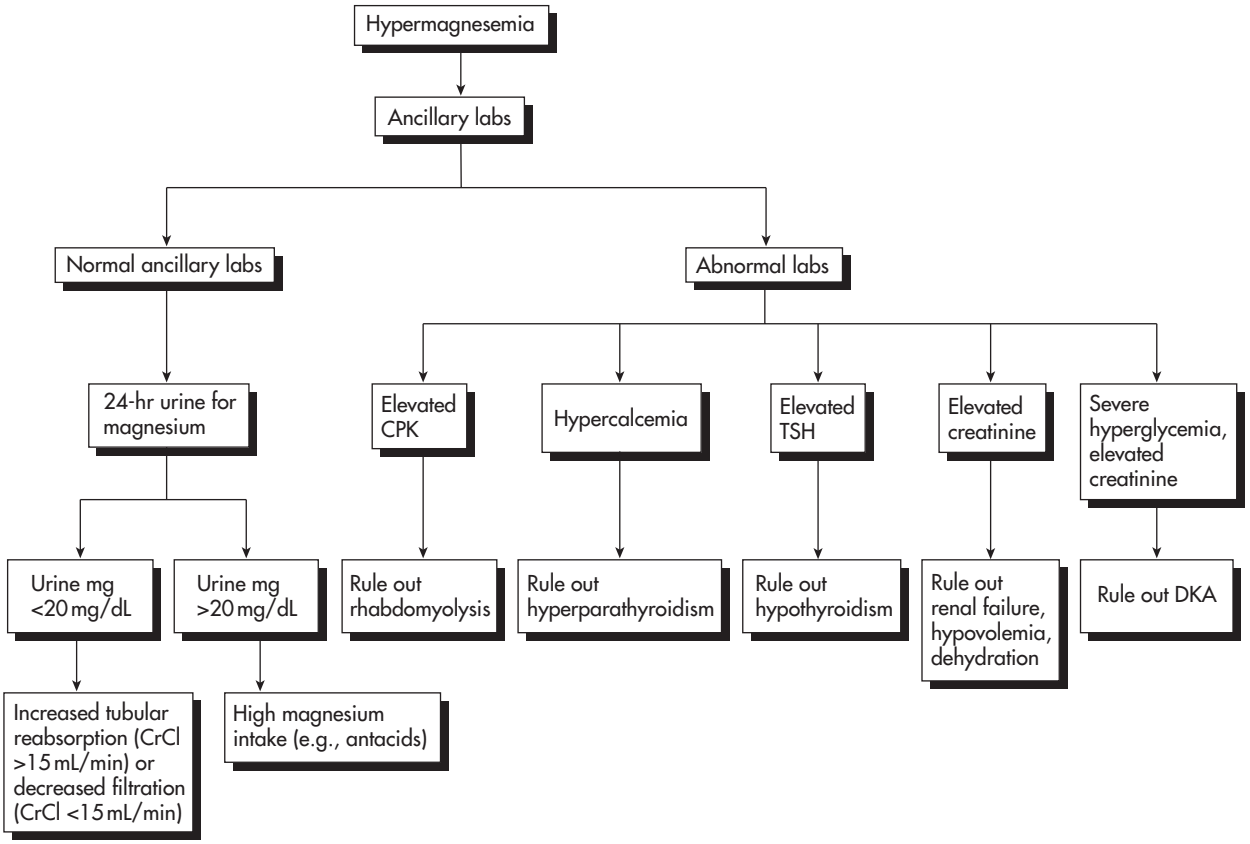


FIGURE 3-98 Diagnostic algorithm. (From Ferri, F: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 3, Philadelphia, 2014, Saunders.)

Diagnostic Imaging
Best Test(s)
- None

Ancillary Tests
- None

Lab Evaluation
Best Test(s)
- 24-hour urine magnesium level

Ancillary Tests
- Serum electrolytes, calcium
- BUN, creatinine, glucose
- TSH
- CPK

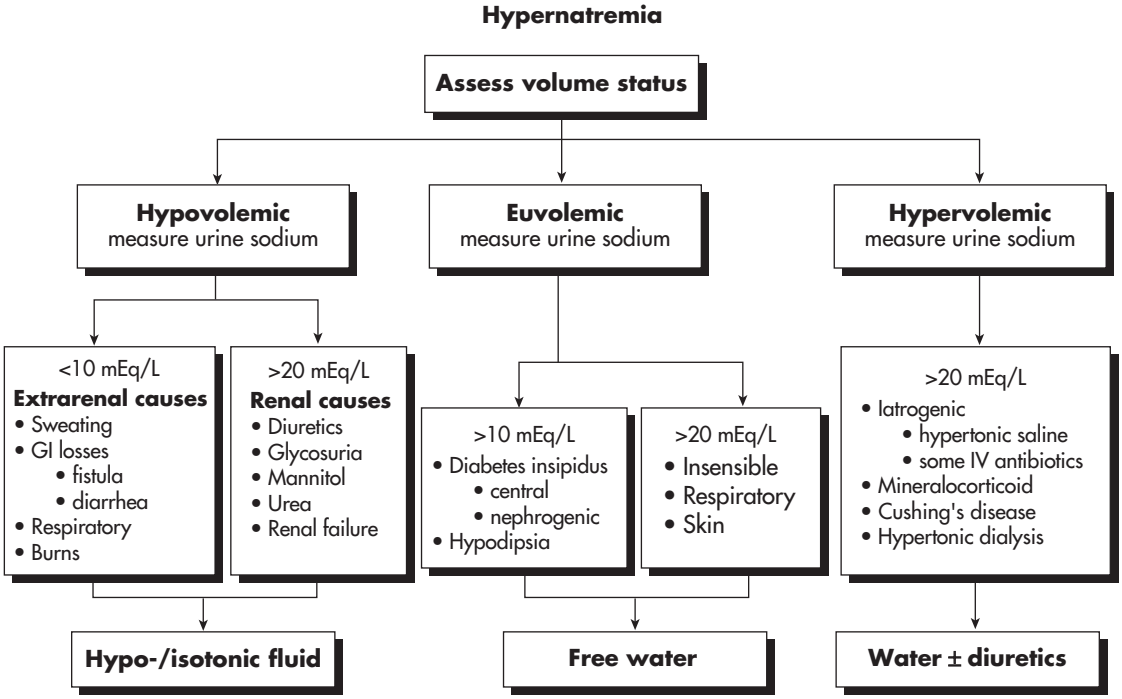


FIGURE 3-99 Algorithm for treatment of hypernatremia. (From Cameron JL, Cameron AM: Electrolyte disorders, Current surgical therapy, ed 10, Philadelphia, 2011, Saunders.)

Diagnostic Imaging
Best Test(s)
- None

Ancillary Tests
- None

Lab Evaluation
Best Test(s)
- Serum electrolytes, urine sodium

Ancillary Tests
- Urine osmolality
- BUN, creatinine

HYPERPIGMENTATION

ICD-9CM # 709.00
ICD-10CM # L81.4 Other melanin hyperpigmentation

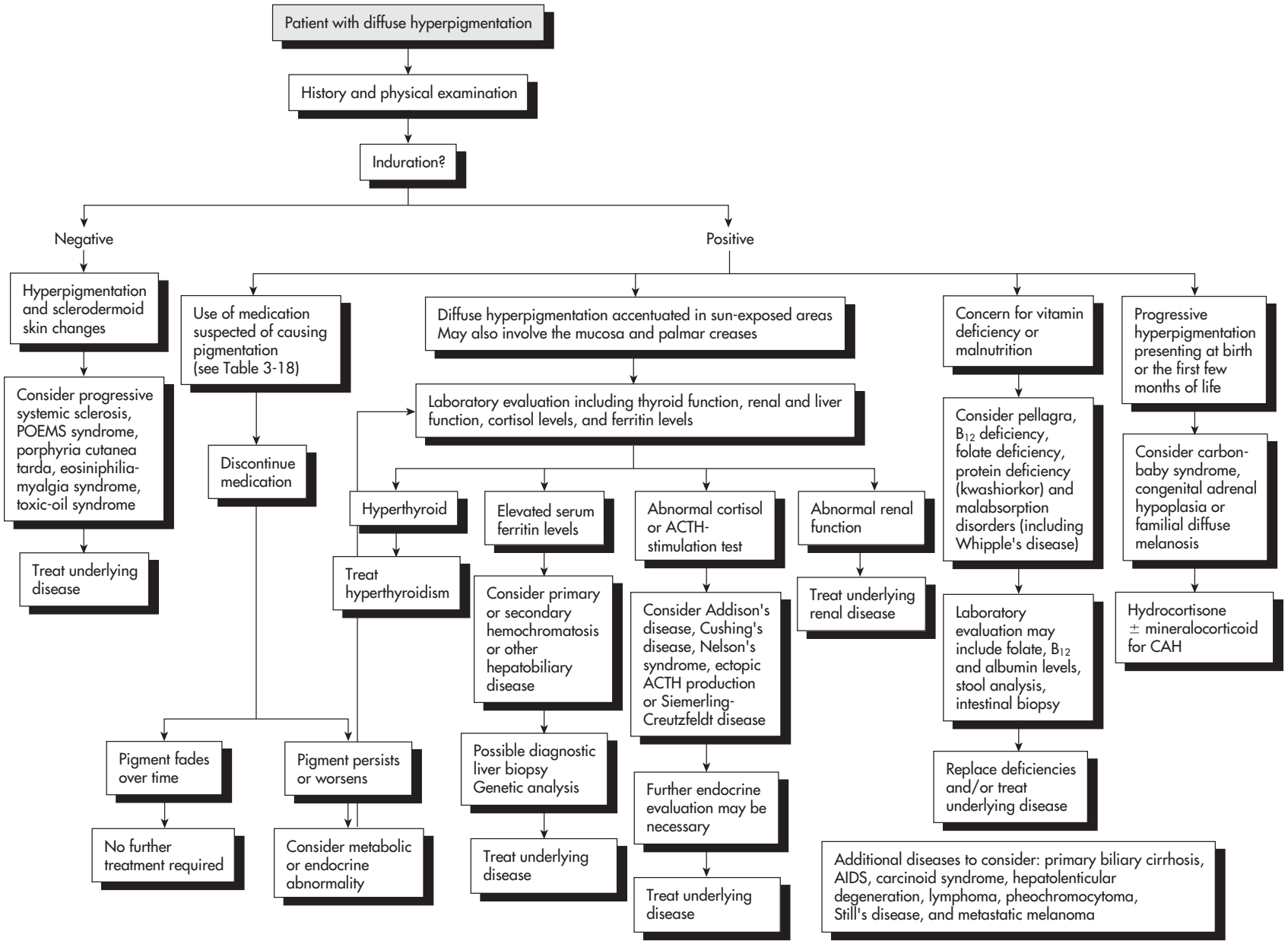


FIGURE 3-100 Approach to the adult patient with diffuse hyperpigmentation. *ACTH,* Adrenocorticotropic hormone; *AIDS,* acquired immunodeficiency syndrome; *CAH,* congenital adrenal hyperplasia; POEMS, polyneuropathy, organomegaly, endocrinopathies, monoclonal gammopathy, skin changes. (From Bolognia JL et al [eds]: *Dermatology,* ed 2, St Louis, 2008, Mosby.)

TABLE 3-18 Drugs and Chemicals Associated with Hyperpigmentation

Drug or Chemical	Clinical Features	Histopathology/Comment
Cancer Chemotherapeutic Agents		
BCNU (Topical)	• Hyperpigmentation at site of application (no reaction seen with parenteral administration)	• Hyperplasia of basal melanocytes consistent with postinflammatory hyperpigmentation
Bleomycin	• Linear, flagellate bands, associated with minor trauma • Nails may be involved • Hyperpigmentation overlying joints	• Increased epidermal melanin • Little dermal pigment incontinence • No increase in epidermal melanocytes
Busulfan	• Generalized hyperpigmentation resembling Addison's disease; sometimes seen in association with drug-induced pulmonary fibrosis	• Increased melanin in basal keratinocytes and in dermal macrophages
Cyclophosphamide	• Diffuse hyperpigmentation of the skin and mucous membranes • Localized pigment of the nails (transverse or longitudinal bands), palms and soles, or teeth	• Pigmentation usually regresses within 6 to 12 months after therapy is discontinued
Dactinomycin	• Generalized hyperpigmentation, most prominent on the face	• Pigmentation fades after treatment discontinued
Daunorubicin	• Hyperpigmentation of light-exposed areas • Transverse brown-black nail bands	• Structurally similar to doxorubicin
Doxorubicin	• Pigmentation of the nails; hyperpigmentation of the palmar creases, palms, soles, buccal mucosa, dorsae of the knuckles and tongue	• Increased epidermal melanin • Increased number of melanocytes
5-Fluorouracil	• Hyperpigmentation in sun-exposed areas • Increased pigmentation of skin overlying veins used for infusion, dorsae of the hands and trunk	• Synergistic hyperpigmentation of irradiation portal sites
Hydroxyurea	• Reversible hyperpigmentation over pressure points and the back • Nails may be involved	• Lichenoid eruption with secondary hyperpigmentation
Mechlorethamine (nitrogen mustard)	• Topical use for cutaneous lymphoma may result in generalized hyperpigmentation • More intense in lesional skin	• Disaggregation of melanosomes within keratinocytes • Increased number of melanocytes
Methotrexate	• Uniform hyperpigmentation in sun-exposed areas	• Uncommon • May be postinflammatory hyperpigmentation secondary to photosensitivity reaction
Antimalarials		
Amino quinolones (chloroquine, hydroxychloroquine, amodiaquine)	• Yellow-brown or gray to blue-black pigment, usually in pretibial areas; face, hard palate, and subungual areas may be involved	• Dyspigmentation in up to 25% of patients • Dermal deposition of melanin-drug complexes; hemosiderin around capillaries • May fade, but rarely resolves, upon discontinuation of drug
Heavy Metals		
Arsenic	• Areas of bronze hyperpigmentation ± superimposed raindrops • Keratoses on the palms and soles associated with pigmentation	• May appear 1-20 years after exposure • Dermal and epidermal deposition of arsenic • Increased epidermal melanin synthesis
Bismuth	• Generalized blue-gray discoloration of face, neck, dorsal hands • Oral mucosa and gingivae may be involved	• Bismuth granules in the papillary and reticular dermis
Gold	• Permanent blue-gray discoloration in sun-exposed areas, mostly around the eyes (chrysiasis)	• Gold particles within macrophage lysosomes in the dermis
Iron	• Permanent brown pigment at injection or application sites	• Pigment coats collagen fibers and is deposited in dermal macrophages
Lead	• "Lead line" in gingival margin • Nail pigmentation	• Lead line is due to subepithelial deposition of lead granules
Mercury	• Slate-gray pigmentation, particularly in skin folds	• Brown-black granules free in dermis, in association with elastic fibers, and within macrophages
Silver	• Generalized slate-gray pigmentation, increased in sun-exposed areas • Nails and sclerae may also be involved • Localized at sites of application	• Silver granules in the basement membrane and on the membrana propria of eccrine glands
Hormones		
Oral contraceptives	• Melasma; increased pigment of nipples and nevi	• Increased melanocytes and increased melanin synthesis
ACTH/MSH	• Diffuse brown or bronze pigmentation; seen in Addison's disease and Cushing's syndrome	• Increased melanin synthesis

Continued

ICD-9CM # 709.00
ICD-10CM # L81.4 Other melanin hyperpigmentation

TABLE 3-18 Drugs and Chemicals Associated with Hyperpigmentation—cont'd

Drug or Chemical	Clinical Features	Histopathology/Comment
Miscellaneous Compounds		
Amiodarone	• Slate-gray to violaceous discoloration of sun-exposed skin	• Yellow-brown granules in dermis, mostly perivascular • Lysosomal inclusions with a lipid-like substance
Azidothymidine (zidovudine, AZT)	• Nail and mucocutaneous hyperpigmentation	• Skin biopsy shows increased epidermal and dermal melanin
Clofazimine	• Diffuse red to red-brown discoloration of skin • Violet-brown to bluish discoloration, especially lesional skin	• Redness secondary to drug in fat • Phagolysosomes with lipofuscin material
Dioxins	• Chloracne most common skin finding • Hyperpigmentation may occur in sun-exposed areas	• Rare, except in accidental exposure
Hydroquinone	• Hyperpigmentation in areas of application due to exogenous ochronosis	• Yellow-brown banana-shaped fibers in papillary dermis
Minocycline	• Blue-black discoloration in old acne scars or sites of inflammation as well as lower extremities • May also involve nails, sclerae, oral mucosa, bones, and teeth • Generalized "muddy brown" pigmentation pattern in some patients	• Iron-containing granules and/or increased melanin, depending on clinical type
Psoralens	• Increased pigmentation after exposure to UVA light (PUVA)	• Proliferation of follicular melanocytes • Increased synthesis and transfer of melanin
Psychotropic drugs (phenothiazine, chlorpromazine, imipramine, desipramine)	• Slate-gray discoloration in sun-exposed areas	• Golden-brown granules in the upper dermis • Electron-dense inclusion bodies

From Bolognia JL et al [eds]: *Dermatology,* ed 2, St Louis, 2008, Mosby.

FIGURE 3-101 Diagnostic algorithm. (From Ferri, F: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 3, Philadelphia, 2014, Saunders.)

Diagnostic Imaging*
Best Test(s)
- None

Ancillary Tests
- None

Lab Evaluation
Best Test(s)
- 24-hour urine phosphate collection

Ancillary Tests
- Serum electrolytes, BUN, creatinine, magnesium, calcium, glucose
- Urinalysis, CPK

*Indicated only after biochemical confirmation of insulinoma.

ICD-9CM # 275.41 Hypocalcemia
ICD-10CM # E83.51 Hypocalcemia

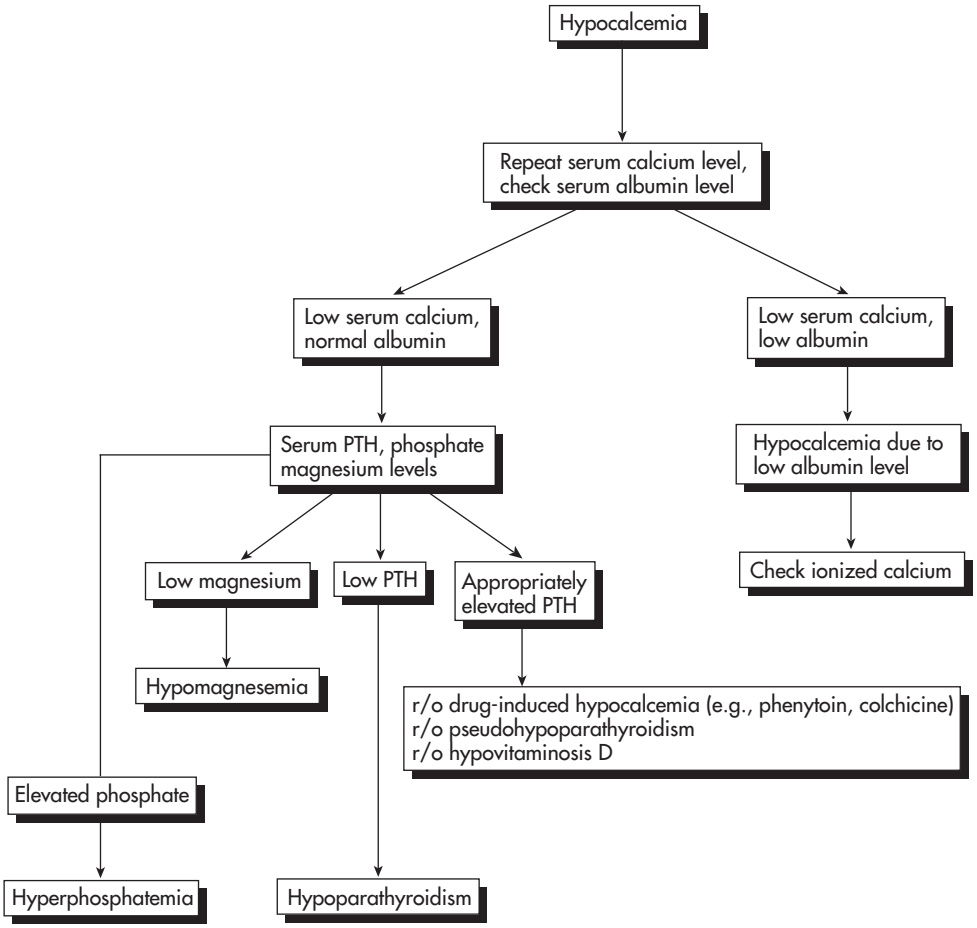


FIGURE 3-102 Diagnostic algorithm. (From Ferri, F: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 3, Philadelphia, 2014, Saunders.)

Diagnostic Imaging
Best Test(s)
- None

Ancillary Tests
- None

Lab Evaluation
Best Test(s)
- PTH

Ancillary Tests
- Serum albumin level
- Serum phosphate, magnesium level

ICD-9CM # 251.2
ICD-10CM # E16.2 Hypoglycemia, spontaneous
E16.0 Hypoglycemia, drug-induced
E16.1 Hypoglycemia, reactive
E16.3 Hypersecretion, glucagon

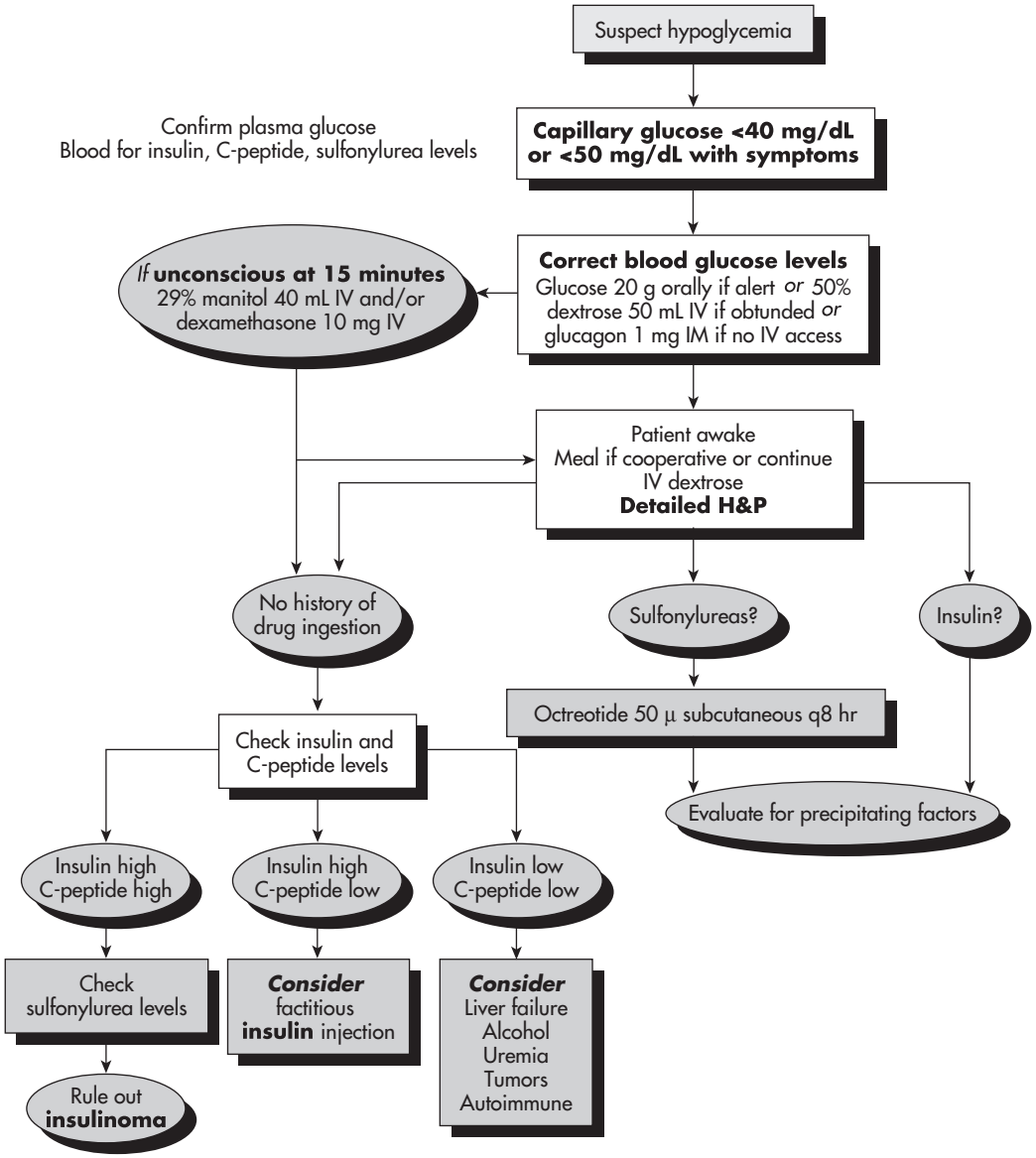


FIGURE 3-103 Decision tree for suspected hypoglycemia in adults. (From Vincent JL, Ahraham E, Moore FA, et al: *Textbook of critical care*, ed 6, Philadelphia, 2011, Saunders.)

ICD-9CM #	256.3	Female
	257.2	Male
	256.3	Ovarian
	253.4	Pituitary
	257.2	Testicular
ICD-10CM #	E28.310	Symptomatic premature menopause
	E29.1	Testicular hypofunction
	E28.39	Other primary ovarian failure
	E23.6	Other disorders of pituitary gland
	E29.1	Testicular hypofunction

FIGURE 3-104 Laboratory evaluation of hypogonadism in men. *FSH,* Follicle-stimulating hormone; *hCG,* human chorionic gonadotropin; *LH,* luteinizing hormone; *MRI,* magnetic resonance imaging; *NL,* normal; *PRL,* prolactin; ↑, elevated; ↓, decreased or low. (From Andreoli TE [ed]: *Cecil essentials of medicine,* ed 7, Philadelphia, 2008, Saunders.)

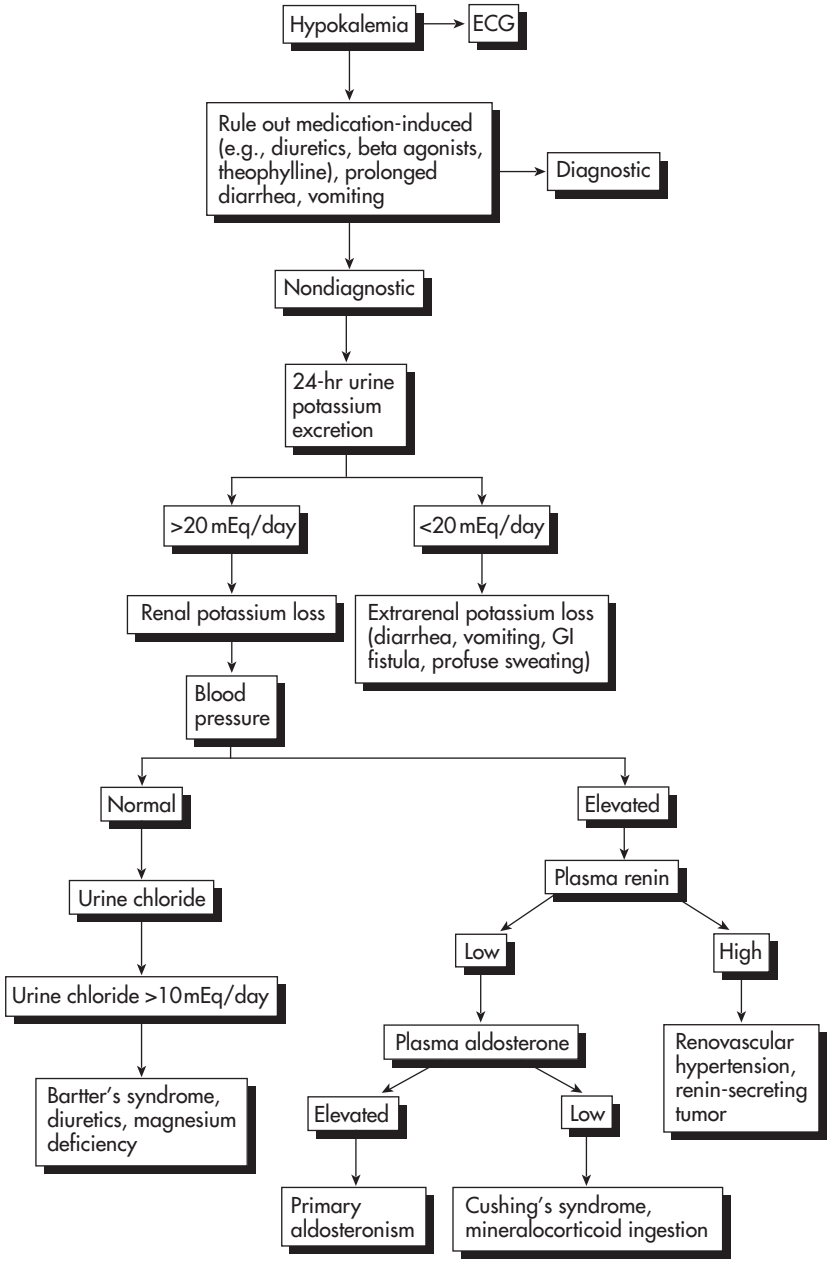


FIGURE 3-105 Diagnostic algorithm. (From Ferri, F: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 3, Philadelphia, 2014, Saunders.)

Diagnostic Imaging
Best Test(s)
- None

Ancillary Tests
- ECG

Lab Evaluation
Best Test(s)
- 24-hour urine potassium excretion

Ancillary Tests
- Serum electrolyte, BUN, creatinine
- Urine chloride
- Plasma renin, aldosterone

ICD-9CM # 275.2 Hypomagnesemia
ICD-10CM # E83.42 Hypomagnesemia

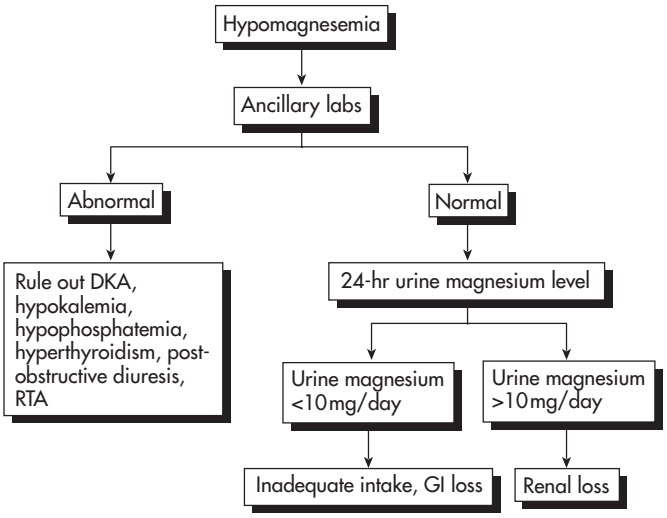


FIGURE 3-106 Diagnostic algorithm. (From Ferri, F: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 3, Philadelphia, 2014, Saunders.)

Diagnostic Imaging
Best Test(s)
- None

Ancillary Tests
- None

Lab Evaluation
Best Test(s)
- 24-hour urine magnesium level

Ancillary Tests
- Serum electrolytes, calcium, phosphate, glucose, albumin
- BUN, creatinine
- TSH
- Urine sodium

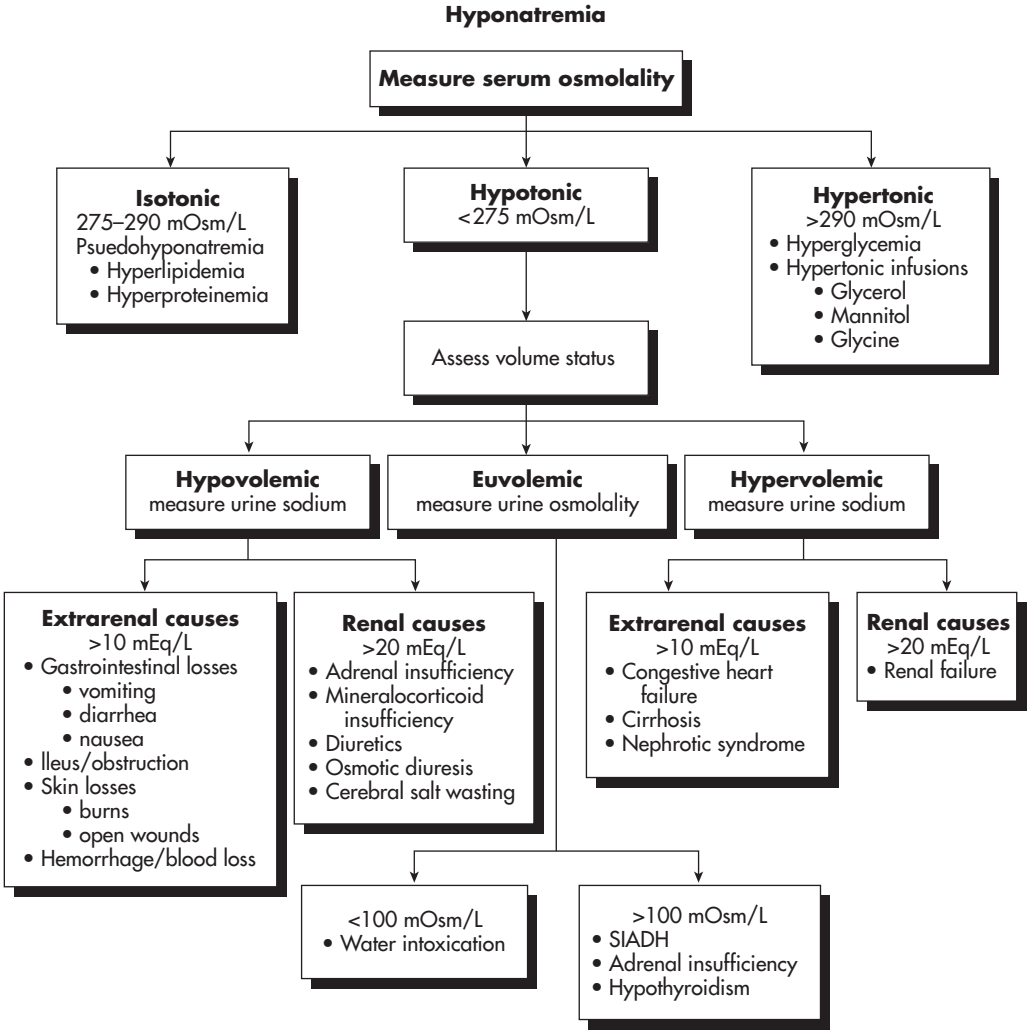


FIGURE 3-107 Algorithm for treatment of hyponatremia. *SIADH*, Syndrome of inappropriate antidiuretic hormone. (From Cameron JL, Cameron AM: Electrolyte disorders. Current surgical therapy, ed 10, Philadelphia, Saunders, 2011.)

Diagnostic Imaging
Best Test(s)
- None

Ancillary Tests
- None

Lab Evaluation
Best Test(s)
- Serum electrolytes
- Serum osmolality, urine osmolality, urine sodium

Ancillary Tests
- Serum glucose, BUN, creatinine
- Uric acid
- TSH
- Serum cortisol

HYPOPHOSPHATEMIA

ICD-9CM # Hypophosphatemia
ICD-10CM # E83.30 Disorder of phosphorus metabolism, unspecified
E83.31 Familial hypophosphatemia

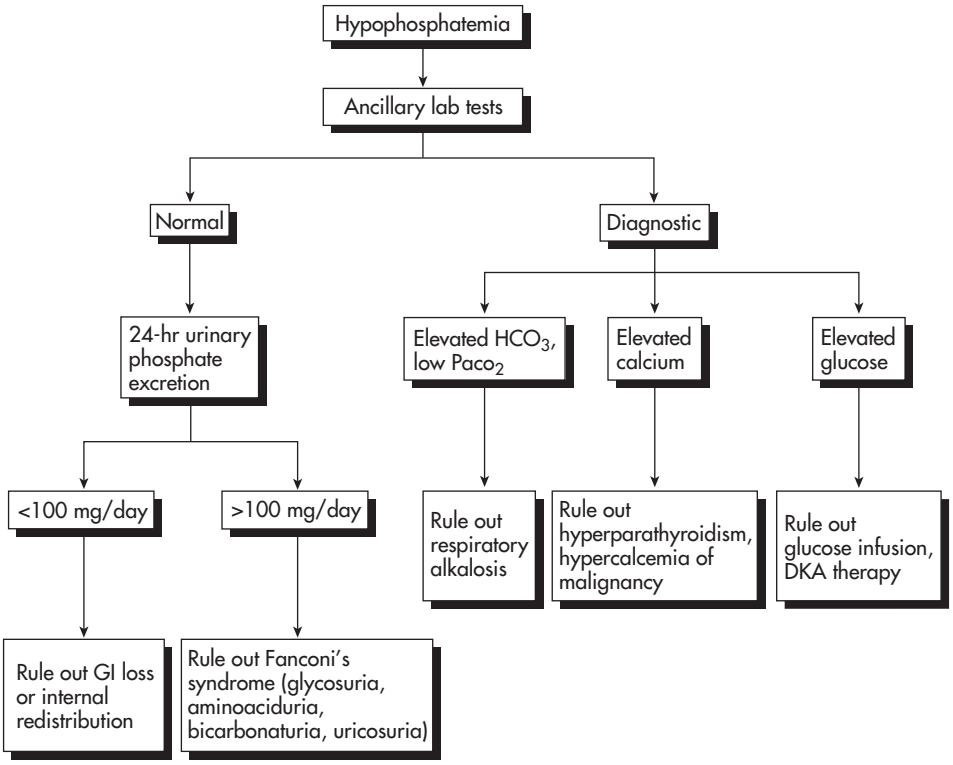


FIGURE 3-108 Diagnostic algorithm. (From Ferri, F: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 3, Philadelphia, 2014, Saunders.)

Diagnostic Imaging
Best Test(s)
- None

Ancillary Tests
- None

Lab Evaluation
Best Test(s)
- 24-hour urine phosphate excretion

Ancillary Tests
- Serum calcium, electrolytes, creatinine, glucose
- ABGs

HYPOTENSION

ICD-9CM # 458.9 Hypotension, NOS
458.1 Hypotension, chronic
458.2 Hypotension, iatrogenic
458.0 Hypotension, orthostatic or postural
ICD-10CM# I95.9 Hypotension, unspecified
I95.89 Other hypotension
I95.3 Hypotension of hemodialysis
I95.1 Orthostatic hypotension

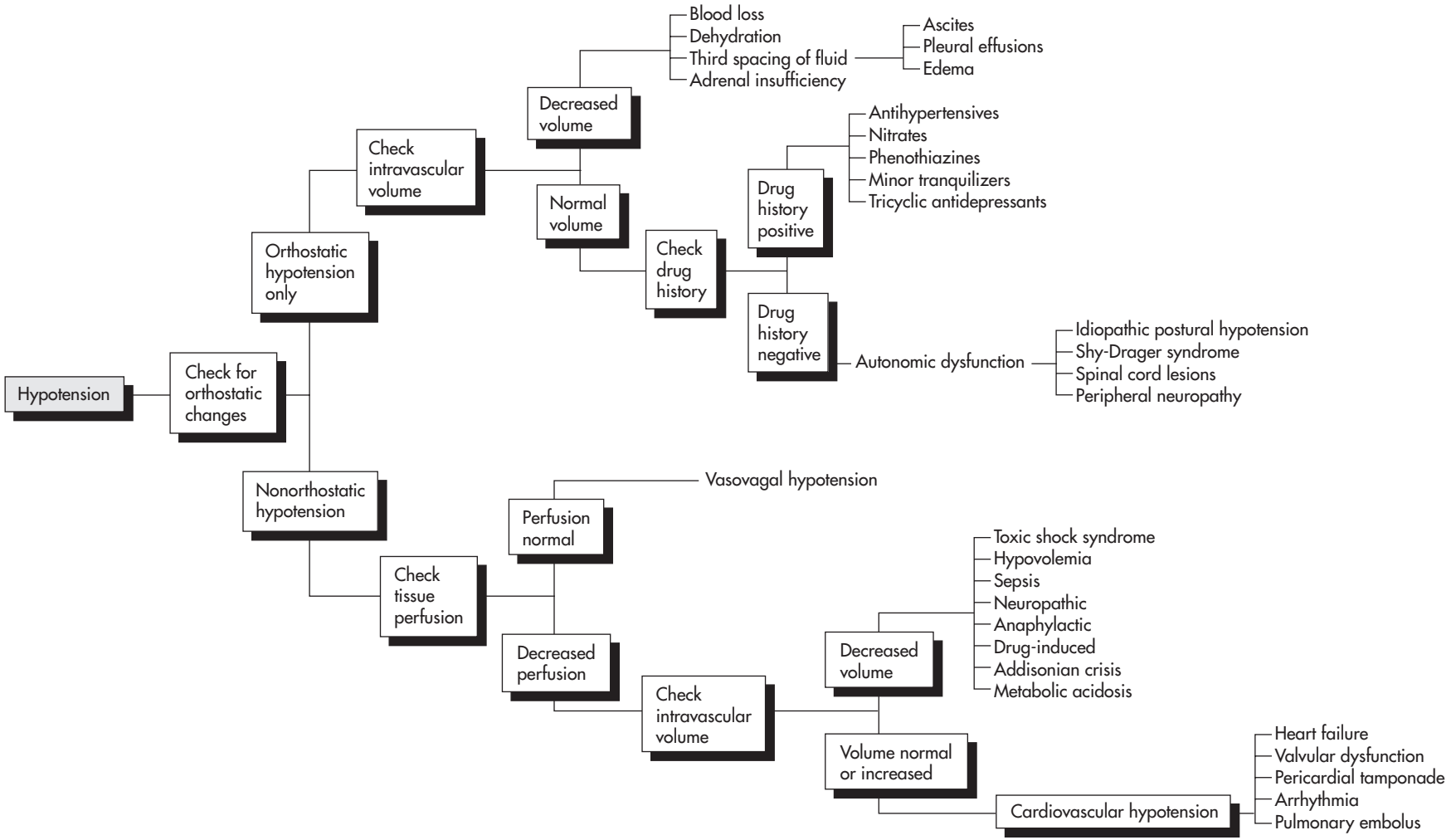


FIGURE 3-109 Hypotension. (From Healey PM: *Common medical diagnosis: an algorithmic approach,* ed 3, Philadelphia, 2000, Saunders.)

ICD-9CM # 279.9
ICD-10CM # D89.9 Disorder involving the immune mechanism, unspecified

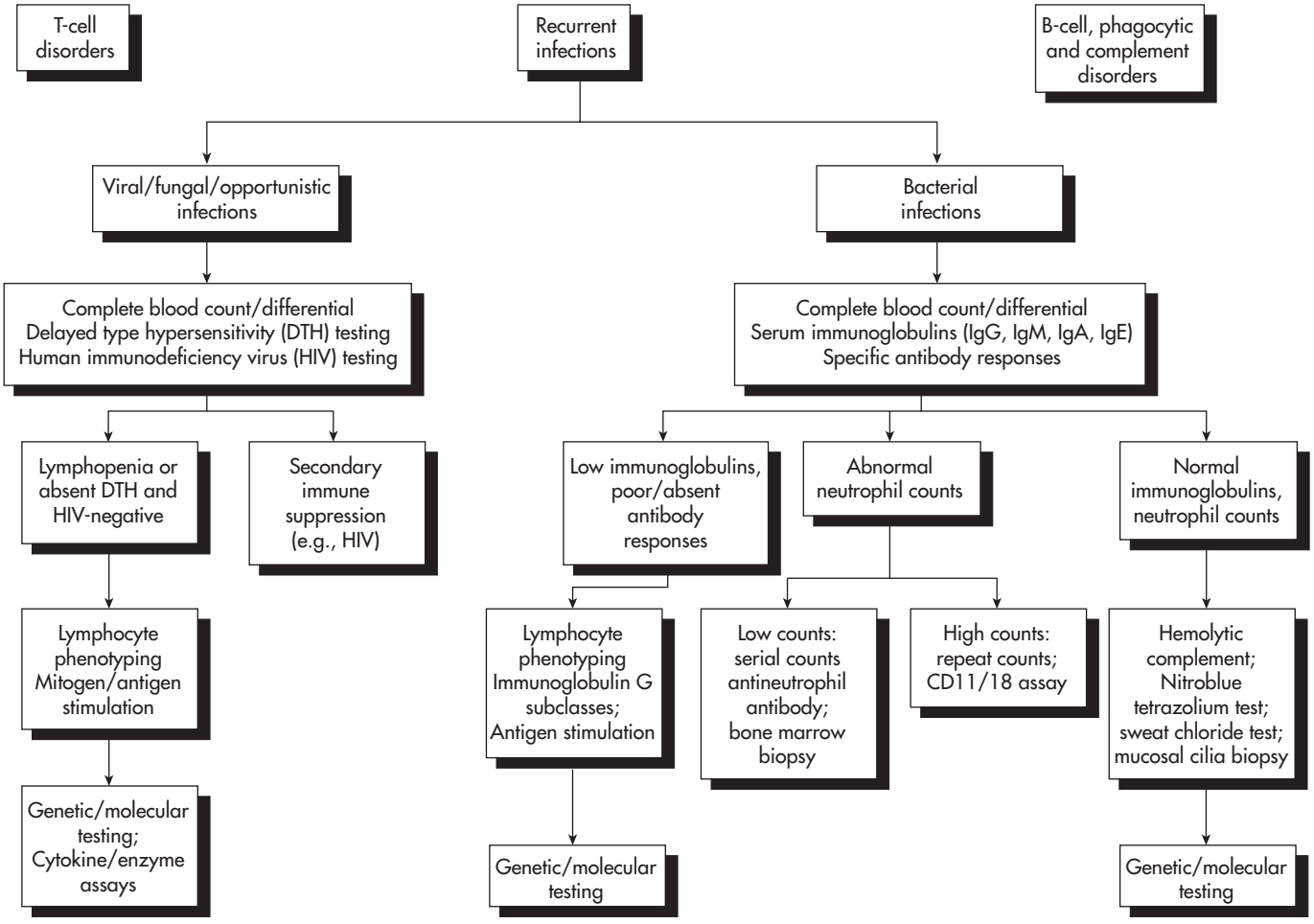


FIGURE 3-110 A diagnostic testing algorithm for primary immunodeficiency diseases. (From Lindegren ML et al: Applying public health strategies to primary immunodeficiency diseases: a potential approach to genetic disorders, *MMWR Recomm Rep* 53[RR-1]:1-29, 2004.)

ICD-9CM # variable with specific disorder
ICD-10CM # M00.9 Pyogenic arthritis, unspecified
M86.9 Osteomyelitis unspecified
T84.3 Infection and inflammatory reaction
M79.9 Soft tissue disorder, unspecified

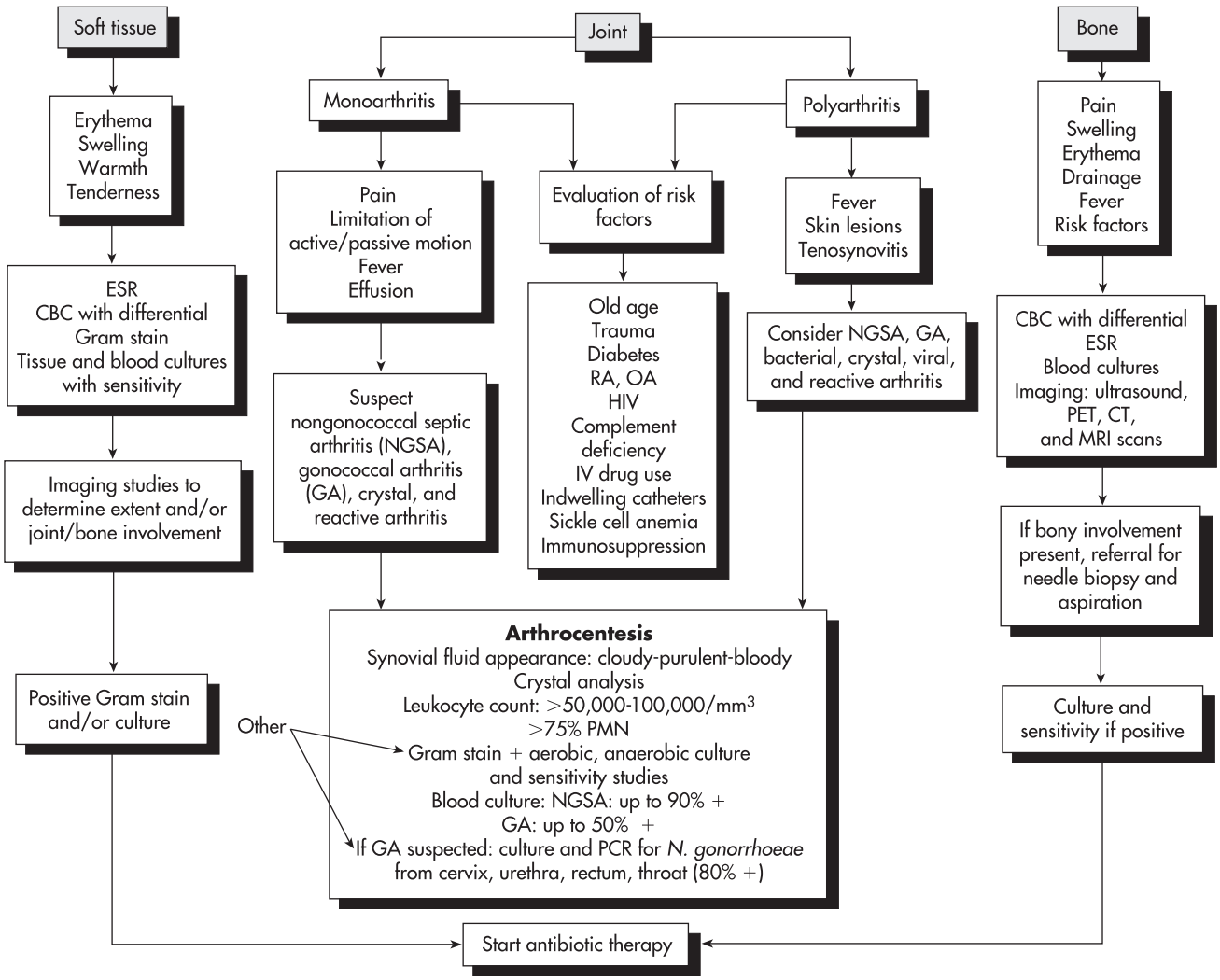


FIGURE 3-111 Clinical evaluation of infections of soft tissues, joints, and bone. *CBC,* Complete blood count; *CT,* computed tomography; *ESR,* erythrocyte sedimentation rate; *GA,* gonococcal arthritis; *HIV,* human immunodeficiency virus; *IV,* intravenous; *MRI,* magnetic resonance imaging; *NGSA,* nongonococcal septic arthritis; *OA,* osteoarthritis; *PCR,* polymerase chain reaction; *PET,* positron emission tomography; *PMN,* polymorphonuclear leukocyte; *RA,* rheumatoid arthritis. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

ICD-9CM # variable with specific disorder
ICD-10CM # M00.9 Pyogenic arthritis, unspecified
M01.1 Tuberculous arthritis
M01.2 Arthritis in Lyme disease
M01.5 Arthritis in viral disease
M02.9 Reactive arthropathy, unspecified
M08.9 Juvenile arthritis, unspecified
M10.9 Gout, unspecified

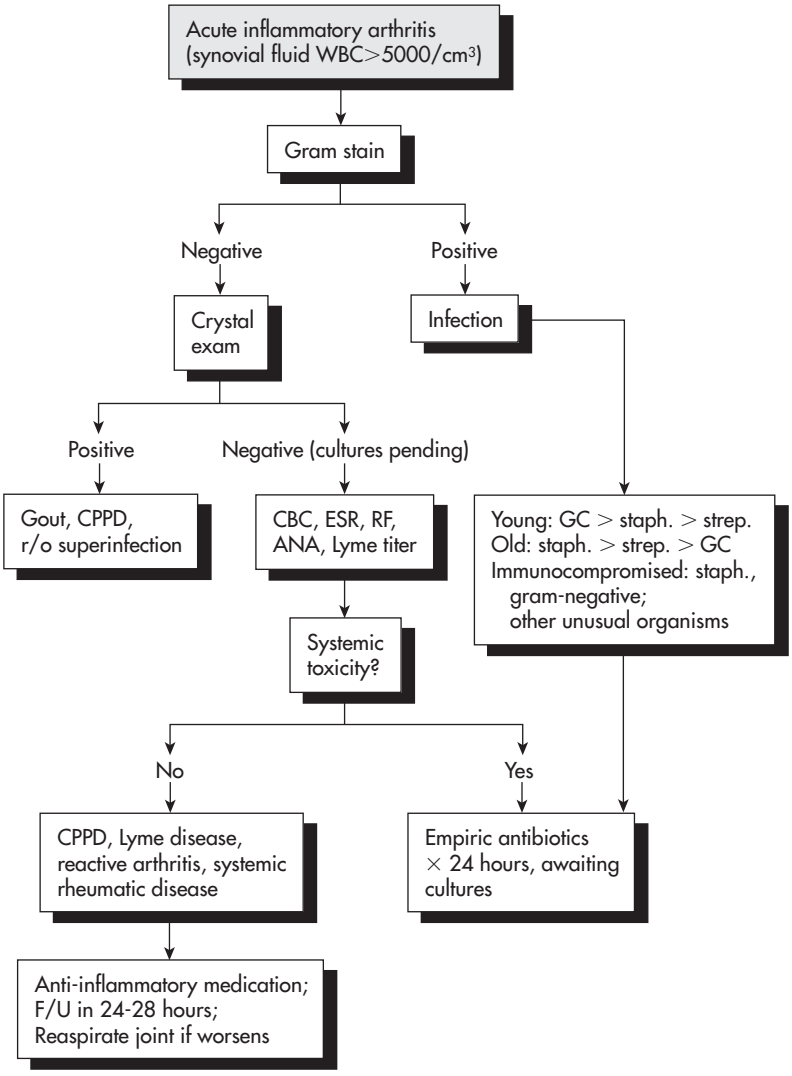


FIGURE 3-112 Approach to acute inflammatory arthritis. *ANA,* Antinuclear antibody test; *CBC,* complete blood count; *CPPD;* calcium pyrophosphate deposition disease; *ESR,* erythrocyte sedimentation rate; *F/U,* follow-up; *GC,* gonococcal infection; *RF,* rheumatoid factor; *r/o,* rule out; *staph.,* staphylococcal infection; *strep.,* streptococcal infection; *WBC,* white blood cell count. (From Harris ED et al [eds]: *Kelley's textbook of rheumatology,* ed 7, Philadelphia, 2005, Saunders.)

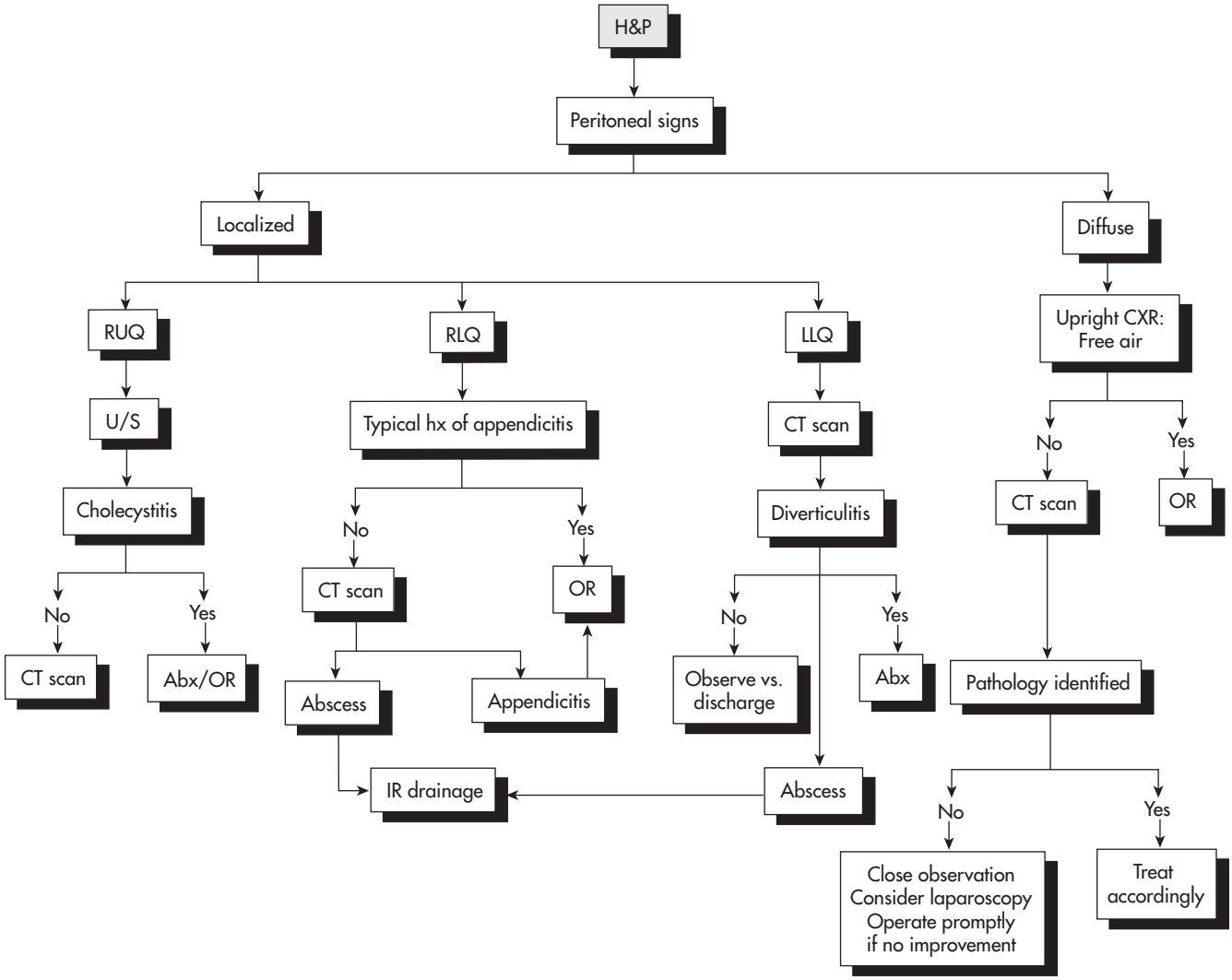
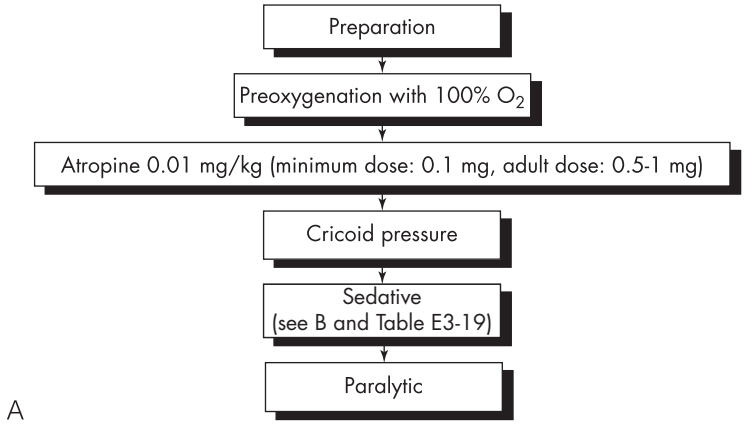
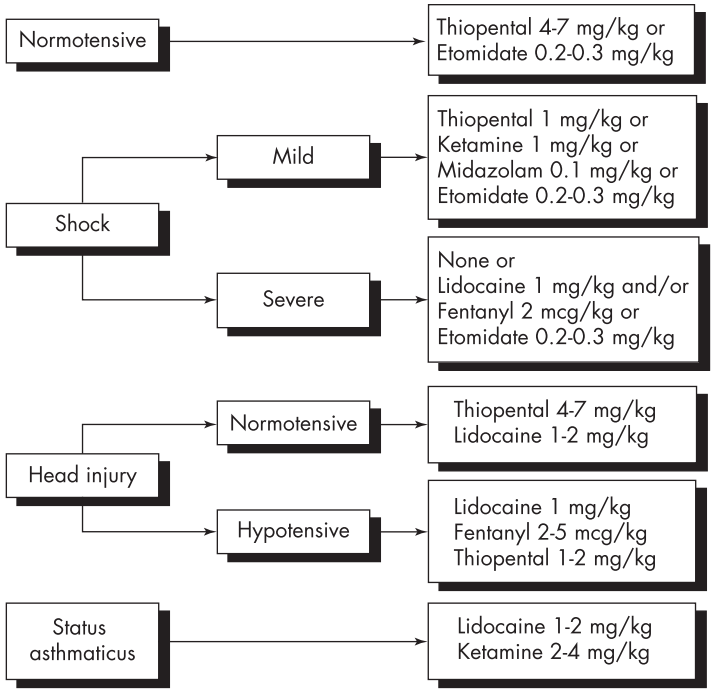


FIGURE 3-113 Algorithm for the diagnosis and management of patients with suspected intraabdominal infection. *H&P,* History and physical exam; *Abx,* antibiotics; *CXR,* chest radiograph; *hx,* history; *IR,* interventional radiology; *LLQ,* left lower quadrant; *RLQ,* right lower quadrant; *RUQ,* right upper quadrant; *U/S,* ultrasound. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

ICD-9CM # 96.0 Non-operative intubation of gastrointestinal and respiratory tracts
ICD-10CM # T88.4 Failed or difficult intubation



A



B

FIGURE E3-114 A, Treatment algorithm for intubation. B, Sedation options. (Modified from Nichols DG et al [eds]: *Golden hour: the handbook of advanced pediatric life support,* St Louis, 1996, Mosby.) (From Custer JW, Rau RE: *The Harriet Lane handbook,* ed 18, St Louis, 2009, Mosby.)

TABLE E3-19 Rapid-Sequence Intubation Medications

Drug	Dose (IV) (mg/kg)	Comments
Adjuncts (First)		
Atropine (vagolytic)	0.01-0.02 Min: 0.1 mg Max: 1 mg	Vagolytic; prevents bradycardia and reduces oral secretions; may increase HR
Lidocaine (optional anesthetic)	1-2	Blunts ICP spike, cough reflex, and CV effects of intubation; controls ventricular arrhythmias
Sedative-Hypnotic (Second)		
Thiopental	1-5	May cause hypotension; myocardial depression (barbiturate); decreases ICP and cerebral blood flow; use low dose in hypovolemia (1-2 mg/kg); may increase oral secretions, cause bronchospasm and laryngospasm; contraindicated in status asthmaticus
or		
Ketamine	1-4	May increase ICP, BP, HR, and oral secretions (general anesthetic); causes bronchodilation, emergence delirium; give with atropine; contraindicated in eye injuries
or		
Midazolam (benzodiazepine)	0.05-0.1	May cause decreased BP and HR and respiratory depression; amnestic properties; reversible with flumazenil (seizure warning applies)
or		
Fentanyl (opiate)	1-5 mcg/kg	Fewest hemodynamic effects of all opiates; chest wall rigidity with high-dose or rapid administration; opiates reversible with naloxone (seizure warning applies); don't use with MAO inhibitors
or		
Etomidate (imidazole/ hypnotic)	0.2-0.3	Does not cause hypotension or increased ICP; may cause further suppression in patients with adrenal suppression (use cautiously)
Paralytics (Third)*		
Rocuronium	0.6-1.2	Onset 30-60 sec, duration 30-60 min; administer with sedative; may reverse in 30 min with atropine and neostigmine; minimal effect on HR or BP; precipitates when in contact with other drugs, so flush line before and after use
or		
Vecuronium	0.1-0.2	Onset 70-120 sec, duration 30-90 min; minimal effect on BP or HR; may reverse in 30-45 min with atropine and neostigmine
or		
Succinylcholine	1-2	Onset 30-60 sec, duration 3-10 min; increases ICP, irreversible; contraindicated in burns, massive trauma, neuromuscular disease, eye injuries, malignant hyperthermia, and pseudocholinesterase deficiency. Risk: Lethal hyperkalemia in undiagnosed muscular dystrophy

*Nondepolarizing neuromuscular blockers, except succinylcholine, which is depolarizing.
BP, Blood pressure; *CV,* cardiovascular; *HR,* heart rate; *ICP,* intracranial pressure; *MAO,* monoamine oxidase.
(From Custer JW, Rau RE: *The Harriet Lane handbook,* ed 18, St Louis, 2009, Mosby.)

ICD-9CM # 557.9
ICD-10CM # K55.9 Vascular disorder of intestine, unspecified

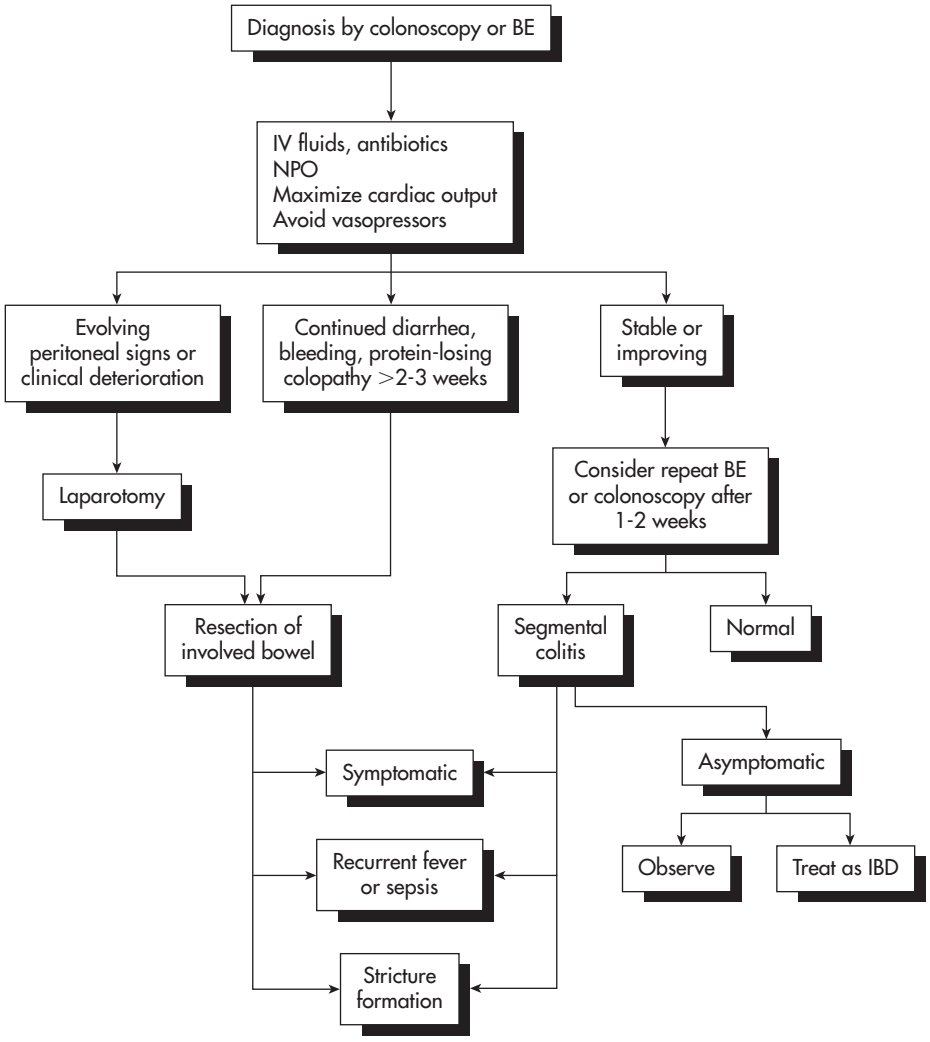


FIGURE E3-115 Management of colonic ischemia. *BE,* Barium enema; *IBD,* inflammatory bowel disease; *IV,* intravenous; *NPO,* nil per os. (From Townsend CM, Beauchamp RD, Evers BM, Mattox KL [eds]: *Sabiston textbook of surgery,* ed 17, Philadelphia, 2004, Saunders.)

ICD-9CM # 782.4 Jaundice NOS
576.8 Jaundice, obstructive
277.4 Bilirubin excretion disorder
ICD-10CM # R17 Unspecified jaundice
K83.8 Other specified diseases of biliary tract
E80.7 Disorder of bilirubin metabolism, unspecified

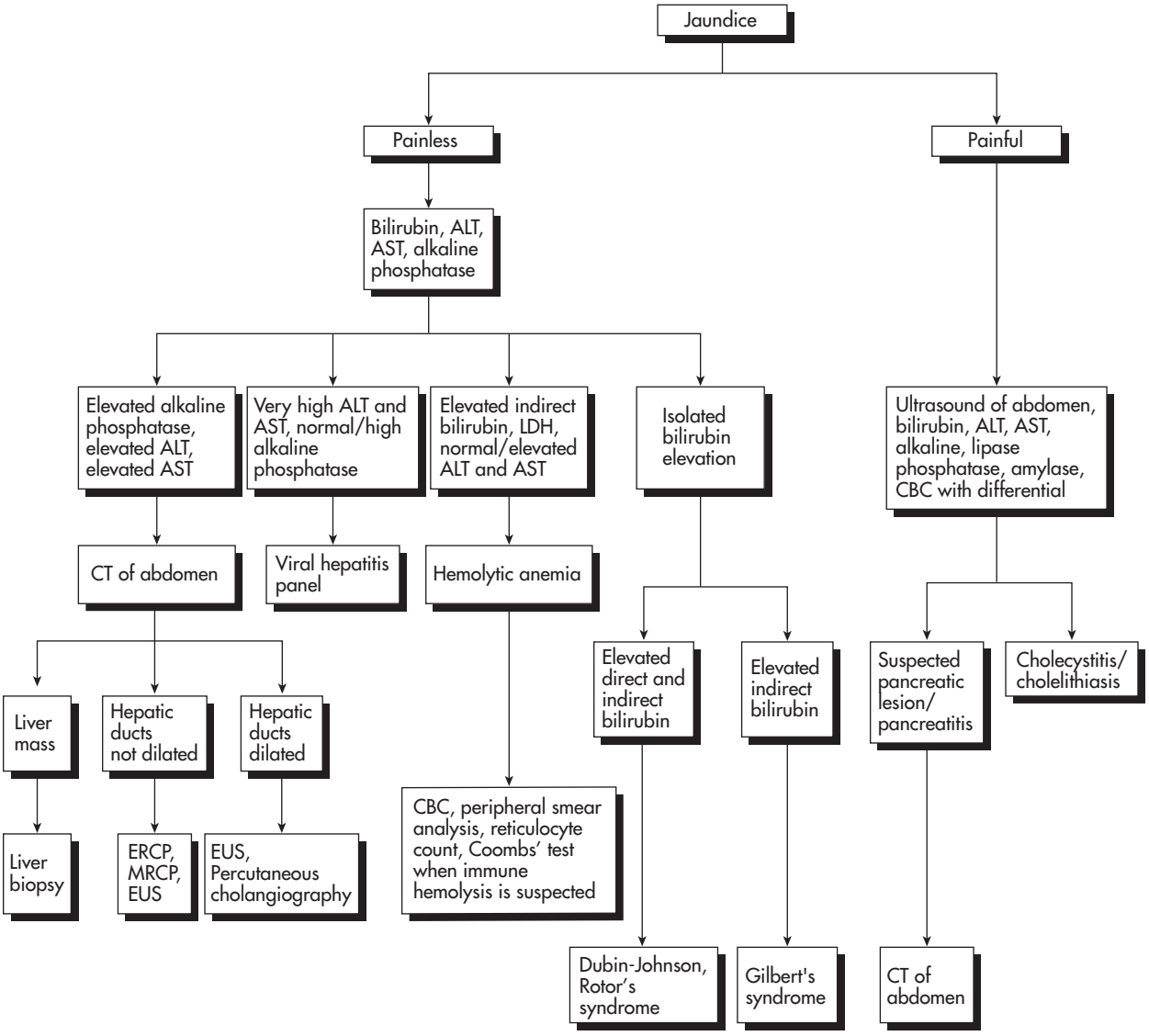


FIGURE 3-116 Diagnostic algorithm. (From Ferri, F: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 3, Philadelphia, 2014, Saunders.)

Diagnostic Imaging
Best Test(s)
- CT of abdomen with contrast if painless jaundice
- Ultrasound of abdomen if painful jaundice

Ancillary Tests
- MRCP
- ERCP
- EUS

Lab Evaluation
Best Test(s)
- Bilirubin with fractionation
- Alkaline phosphatase, ALT, AST
- Viral hepatitis panel

Ancillary Tests
- Serum amylase, lipase, LDH
- CBC, reticulocyte count, Coombs' test
- BUN, creatinine, electrolytes
- Liver biopsy

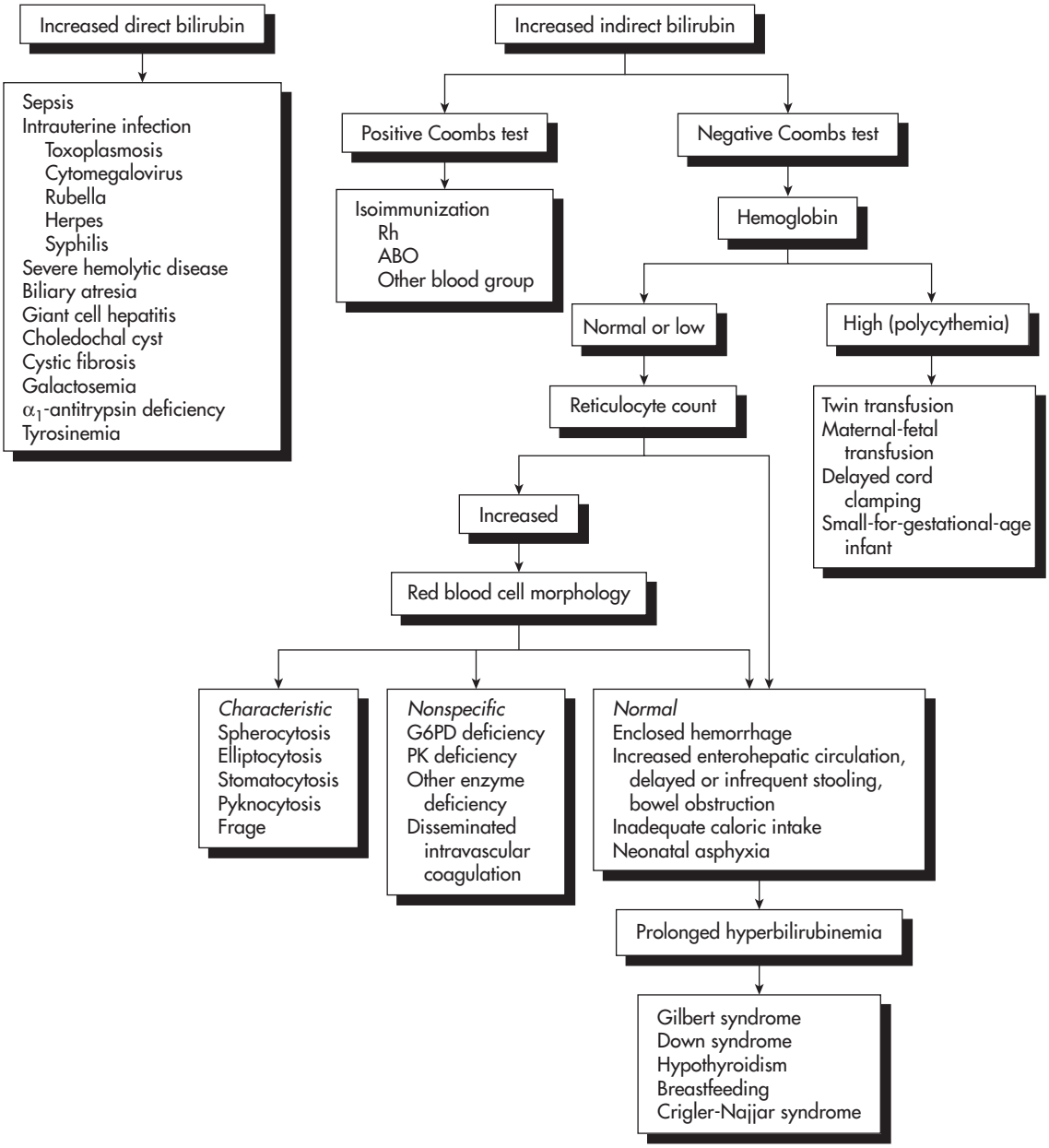


FIGURE 3-117 Schematic approach to the diagnosis of neonatal jaundice. *G6PD,* Glucose-6-phosphate dehydrogenase; *PK,* pyruvate kinase. (From Oski FA: Differential diagnosis of jaundice. In Taeusch HW, Ballard RA, Avery MA [eds]: *Schaffer and Avery's diseases of the newborn,* ed 6, Philadelphia, 1991, Saunders.)

ICD-9CM # 719.00
ICD-10CM # M25.40 Effusion, unspecified joint

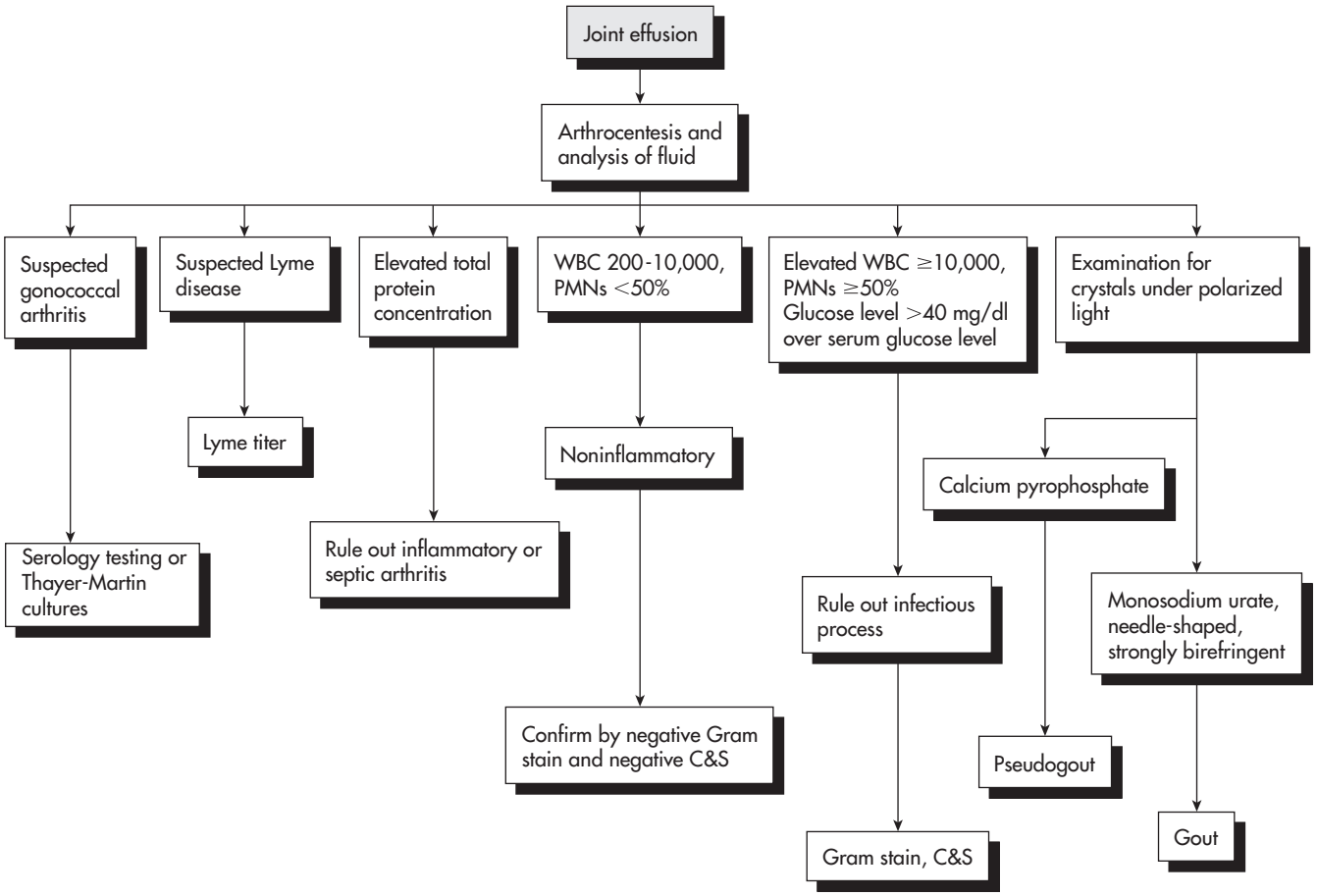


FIGURE 3-118 Joint effusion. *C&S,* Culture and sensitivity; *PMNs,* polymorphonuclear leukocytes; *WBC,* white blood cell count.

ICD-9CM # 719.00
ICD-10CM # M25.40 Effusion, unspecified joint

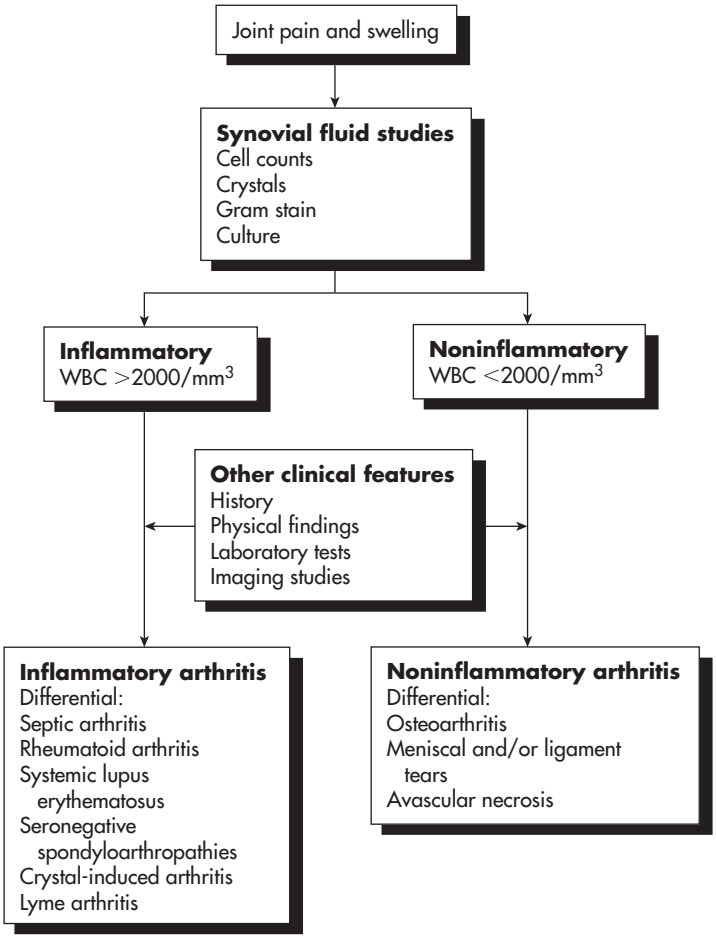


FIGURE 3-119 Diagnostic approach for swollen joints. *WBC,* White blood cell count. (From Goldman L, Schafer AL [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

IDC-9CM # 836.50
ICD-10CM # S83.4 Sprain or strain involving collateral ligament of knee
S83.5 Sprain or strain involving cruciate ligament of knee
S83.6 Sprain or strain of other and unspecified parts of knee

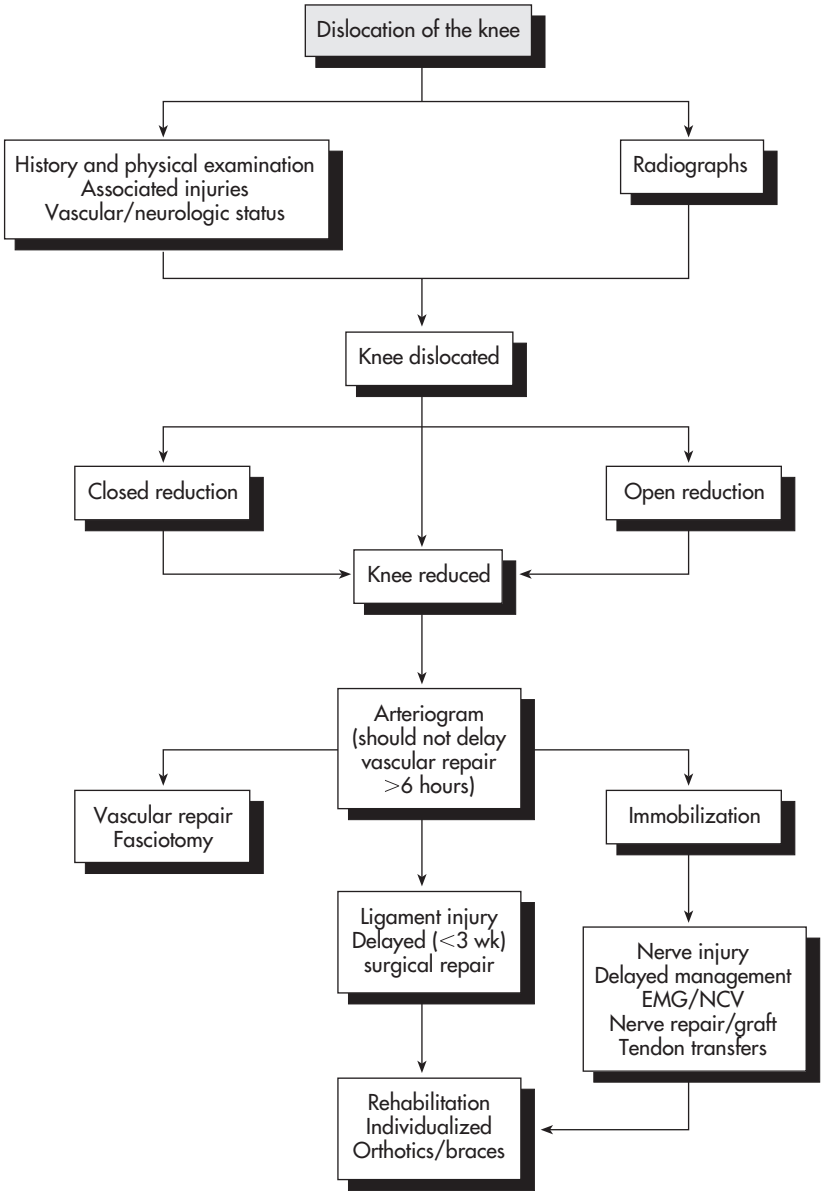


FIGURE E3-120 Treatment algorithm for dislocation of the knee. *EMG/NCV,* Electromyography/nerve conduction velocity. (From Siliski JM: Dislocations and soft tissue injuries of the knee. In Browner BD, Jupiter TB, Levine AM, Trafton PG [eds]: *Skeletal trauma,* ed 3, Philadelphia, 2003, Saunders.)

ICD-9CM #	716.96	Knee inflammation
	959.7	Knee injury
	719.56	Knee stiffness
	719.06	Knee swelling
ICD-10CM #	M12.9	Arthropathy, unspecified
	S99.919A	Unspecified injury of unspecified ankle, initial encounter
	M25.669	Stiffness of unspecified knee, not elsewhere classified
	M25.469	Effusion, unspecified

FIGURE 3-121 Evaluation and management of knee extensor mechanism pain. Focused treatment based on specific etiology will prevent recurrence. *AP,* Anteroposterior; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *VMO,* vastus medialis obliquus muscle. (From Scudieri G [ed]: *Sports medicine, principles of primary care,* St Louis, 1997, Mosby.)

LEG ULCER

ICD-9CM #	440.23	Ulcer, lower limb, arteriosclerotic
	707.1	Ulcer, lower limb, chronic
	707.9	Ulcer, non-healing
	707.0	Pressure ulcer
ICD-10CM #	I70.25	Atherosclerosis of native arteries of other extremities with ulceration
	L97.909	Non-pressure chronic ulcer of unspecified part of unspecified lower leg with unspecified severity
	L98.499	Non-pressure chronic ulcer of skin of other sites with unspecified severity
	L89.90	Pressure ulcer of unspecified site, unspecified stage

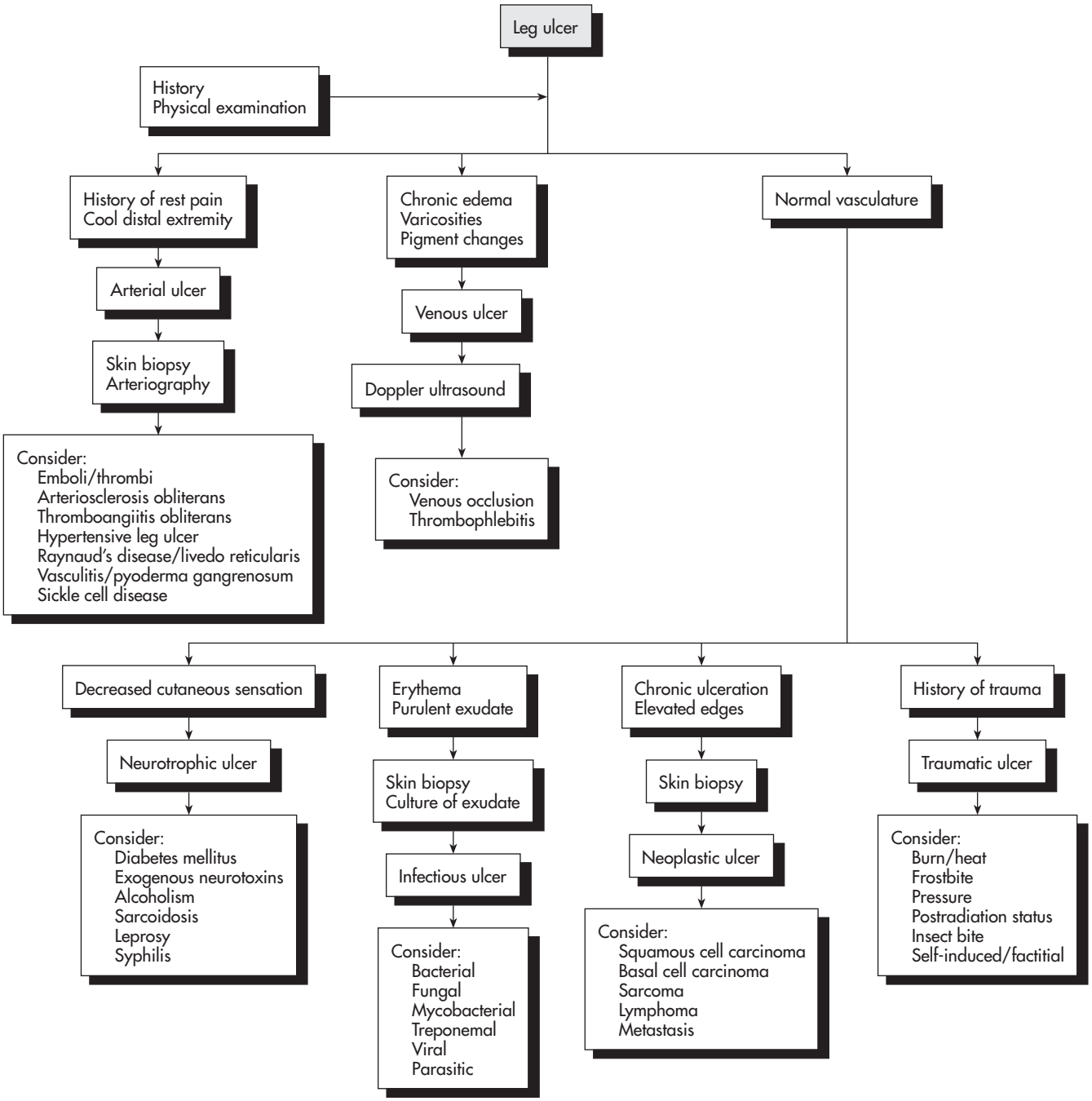


FIGURE 3-122 Leg ulcer. (From Greene HL, Johnson WP, Lemcke D [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

ICD-9CM # 573.9
ICD-10CM # K76.9 Liver disease, unspecified

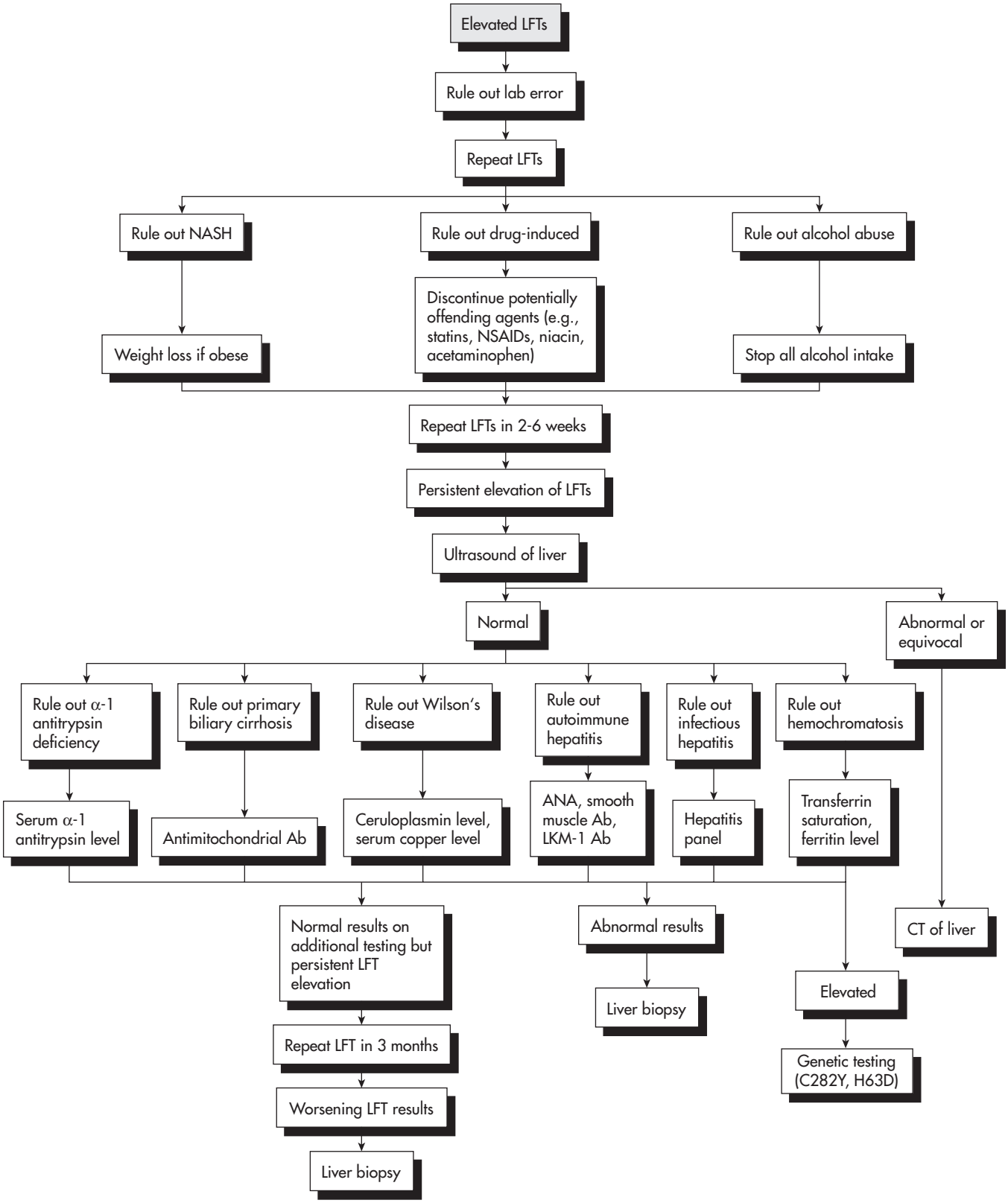


FIGURE 3-123 Liver function test elevations. *Ab,* Antibody; *ANA,* antibody to nuclear antigens; *CT,* computed tomography; *IEP,* immuno-electrophoresis; *LFTs,* liver function tests; *LKM,* liver-kidney microsome; *NASH,* nonalcoholic steatohepatitis; *NSAIDs,* nonsteroidal anti-inflammatory drugs.

ICD-9CM # 794.8 Liver mass
ICD-10CM # R94.5 Abnormal results of liver function studies

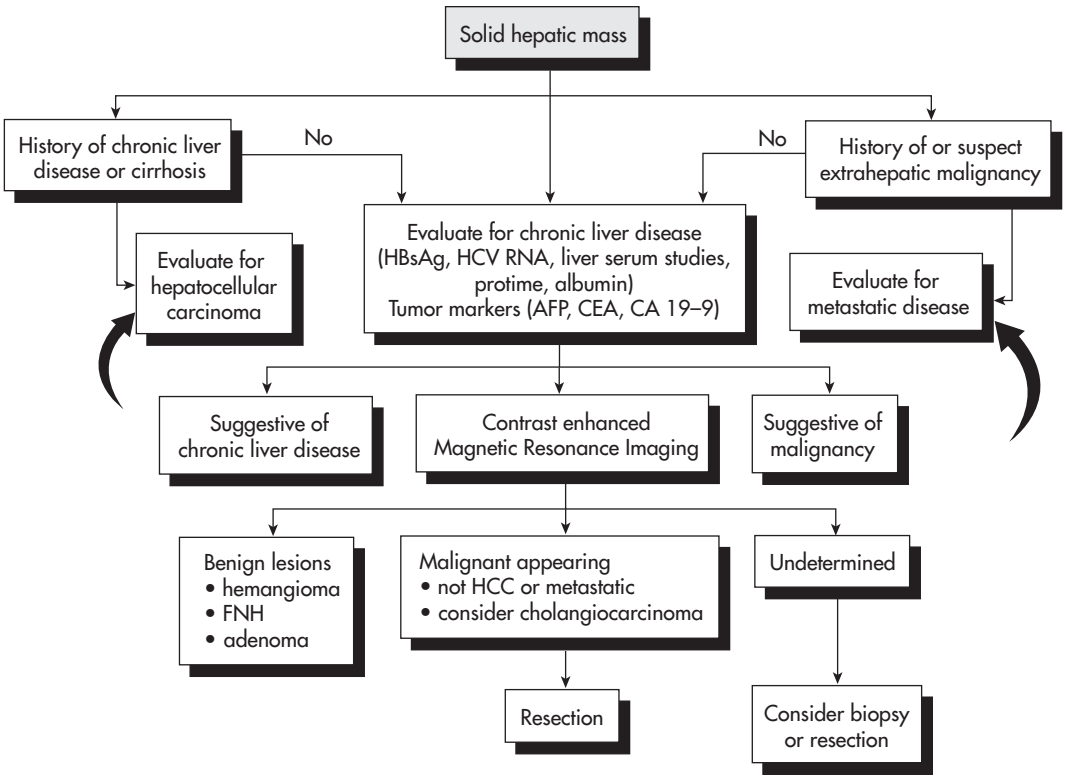


FIGURE E3-124 Evaluation algorithm for a solid liver mass. *FNH,* Focal nodular hyperplasia; *HCC,* hepatocellular carcinoma. (From Cameron JL, Cameron AM: *Current surgical therapy,* ed 10, Philadelphia, 2011, Saunders.)

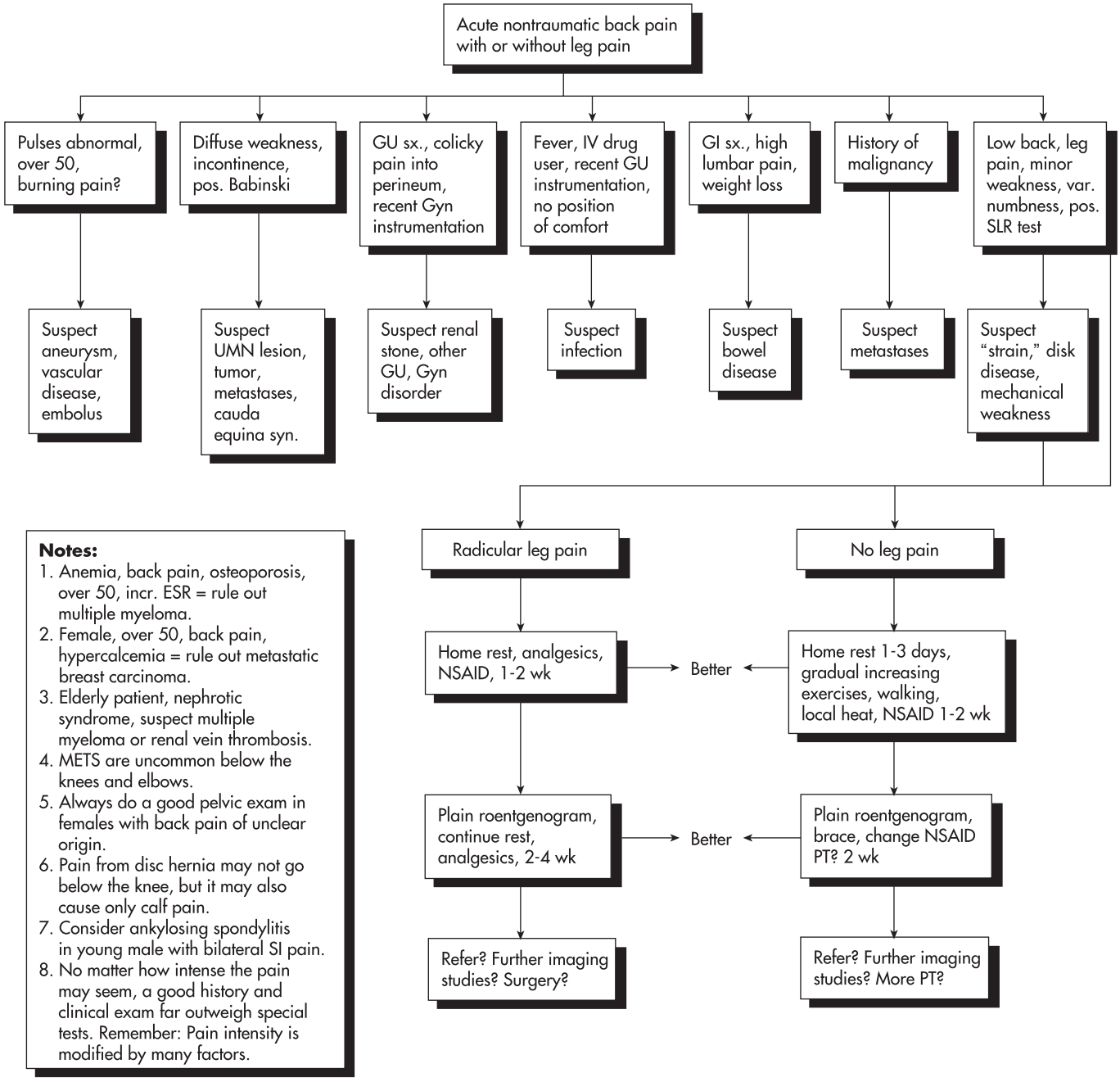


FIGURE 3-125 Algorithm for low back and/or leg pain. *GI,* Gastrointestinal; *GU,* genitourinary; *IV,* intravenous; *METS,* metabolic equivalents; *NSAID,* nonsteroidal anti-inflammatory drug; *PT,* physical therapy; *SI,* sacroiliac; *SLR,* straight-leg raising; *UMN,* upper motor neuron. (From Mercier LR: *Practical orthopedics,* ed 2, St Louis, 2000, Mosby.)

LYMPHADENOPATHY, AXILLARY

ICD-9CM # 785.6 Lymphadenopathy, unknown etiology
ICD-10CM # L04.2 Lymphadentits acute axilla
R59.9 Enlarged lymph nodes, unspecified

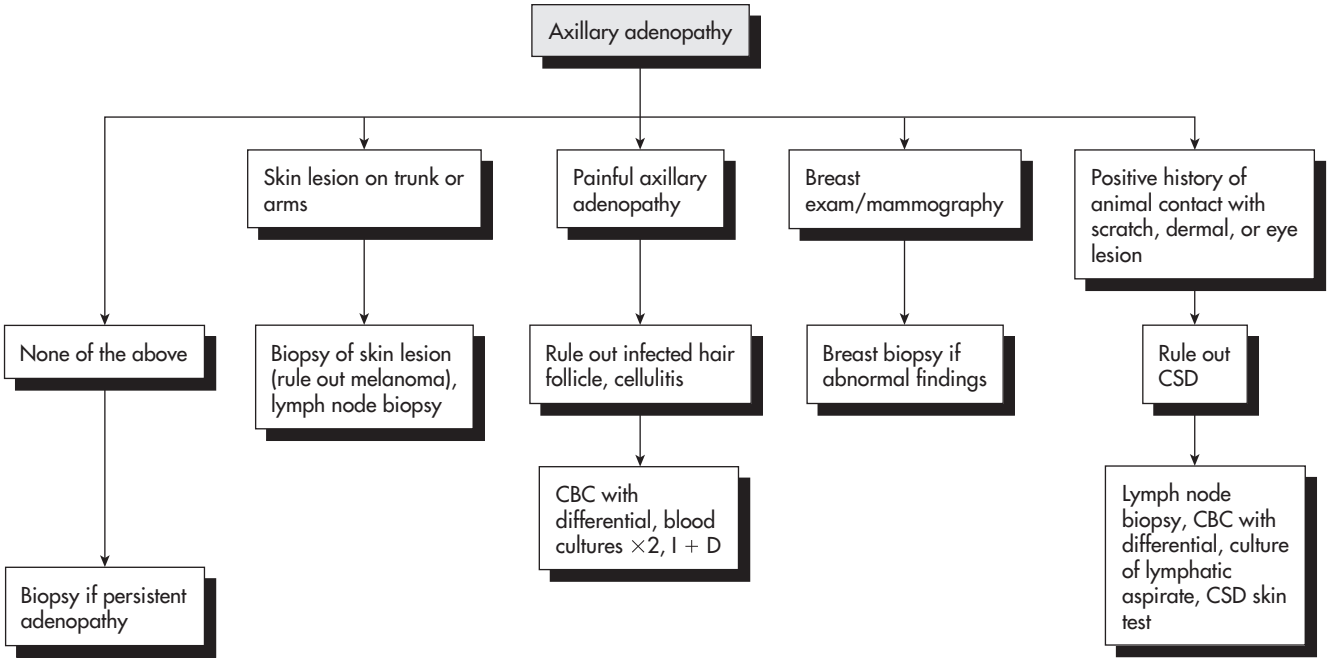


FIGURE E3-126 Lymphadenopathy, axillary. *CBC,* Complete blood count; *CSD,* cat-scratch disease.

ICD-9CM # 785.6 Lymphadenopathy, unknown etiology
ICD-10CM # L04.8 Lymphadentits, specific site NOS
R59.9 Enlarged lymph nodes, unspecified

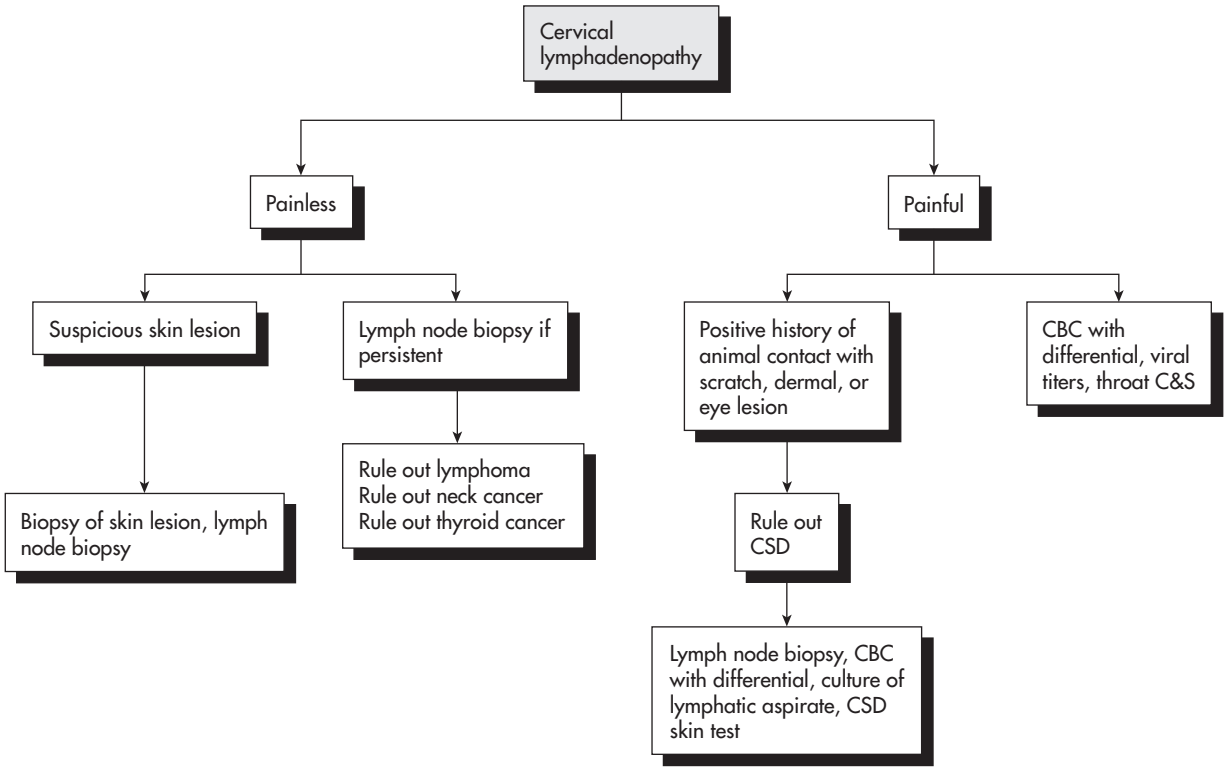


FIGURE E3-127 Lymphadenopathy, cervical. *CBC*, Complete blood count; *C&S*, culture and sensitivity; *CSD*, cat-scratch disease.

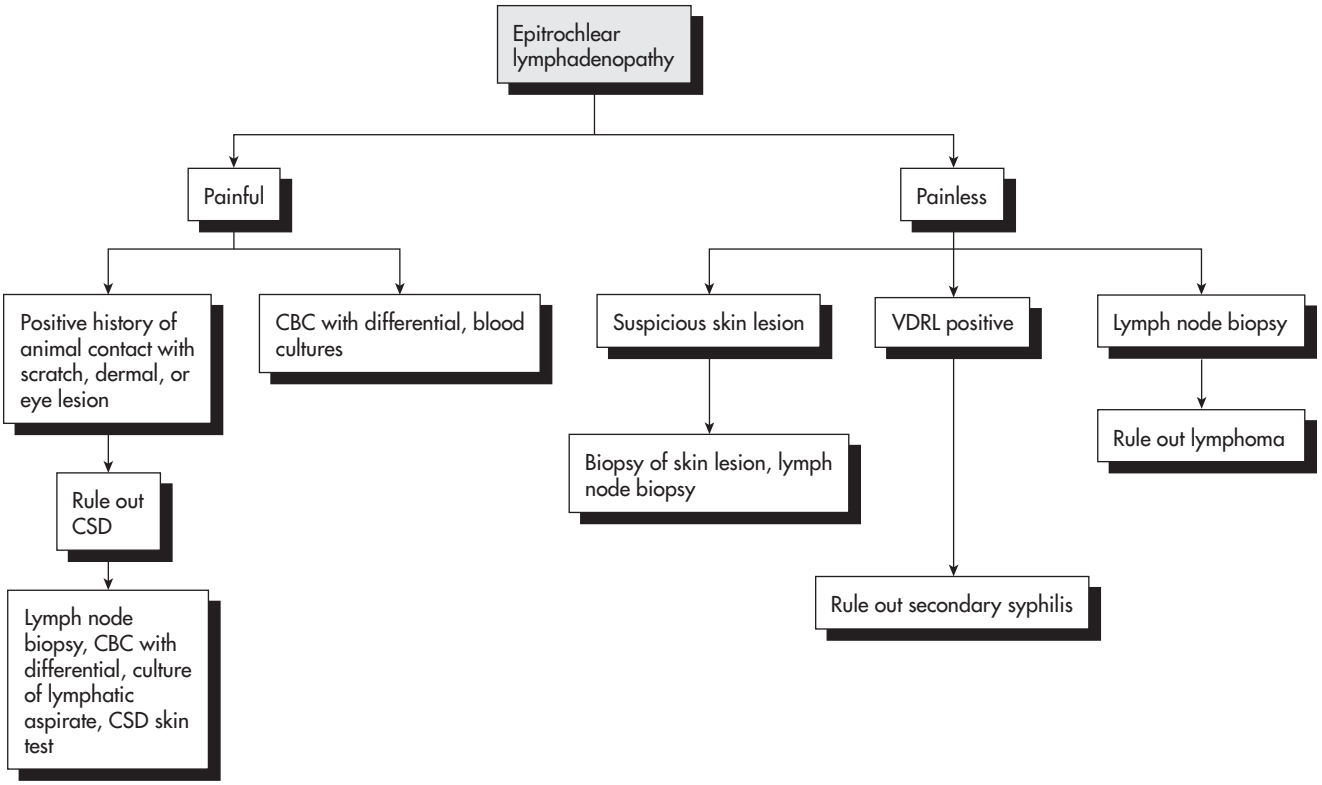


FIGURE E3-128 Lymphadenopathy, epitrochlear. *CBC*, Complete blood count; *CSD*, cat-scratch disease; *VDRL*, Venereal Disease Research Laboratory.

ICD-9CM # 785.6 Lymphadenopathy, unknown etiology
ICD-10CM # I88.9 Lymphadenitis
R59.9 Enlarged lymph nodes

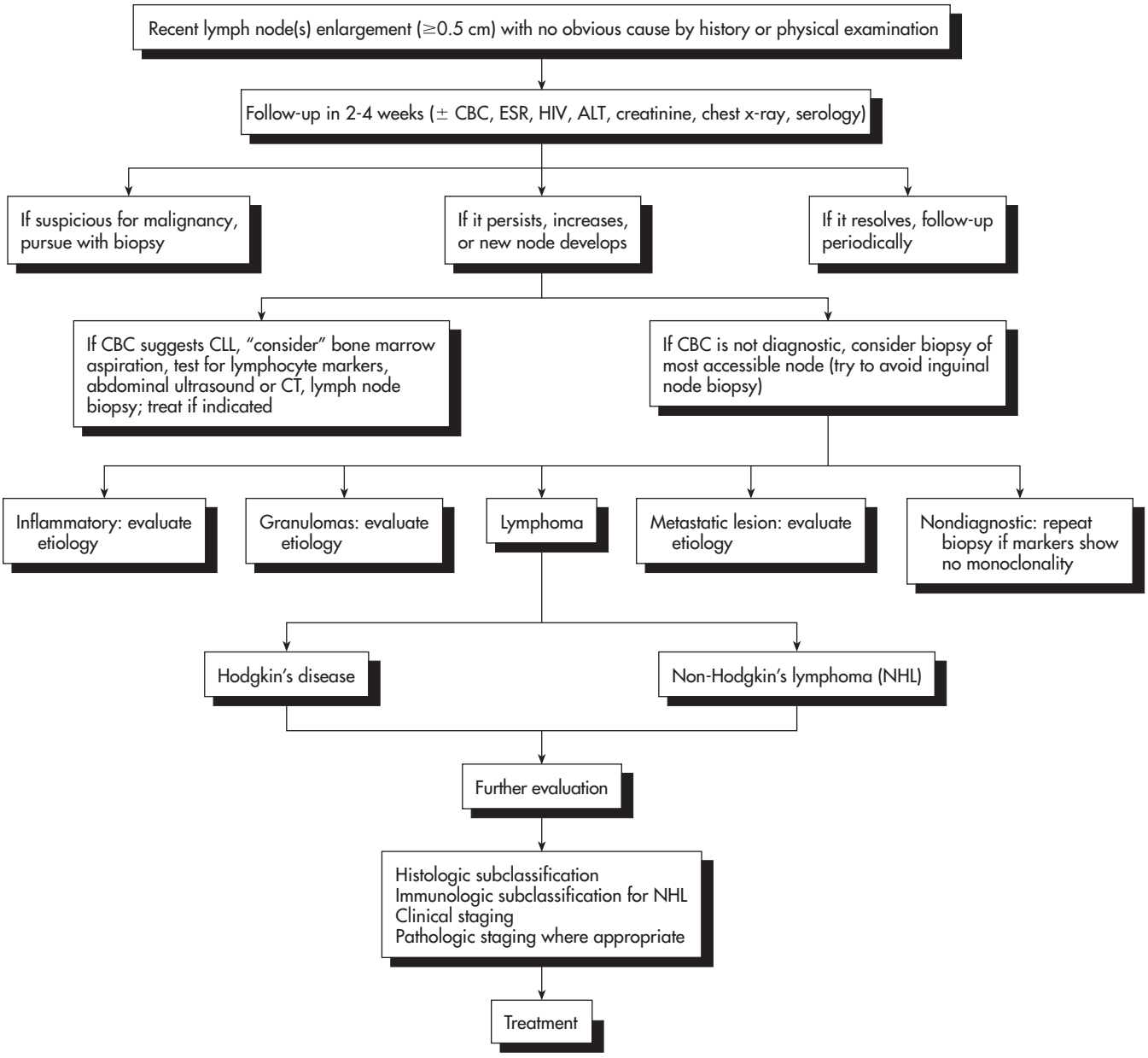


FIGURE 3-129 Workup of lymphadenopathy. *ALT*, Alanine aminotransferase; *CBC*, complete blood count; *CLL*, chronic lymphocytic leukemia; *CT*, computed tomography; *ESR*, erythrocyte sedimentation rate. (Modified from Noble J [ed]: *Primary care medicine*, ed 3, St Louis, 2001, Mosby.)

ICD-9CM # 785.6 Lymphadenopathy, unknown etiology
ICD-10CM # L04.8 Lymphadenitis, specific site NOS
R59.9 Enlarged lymph nodes, unspecified

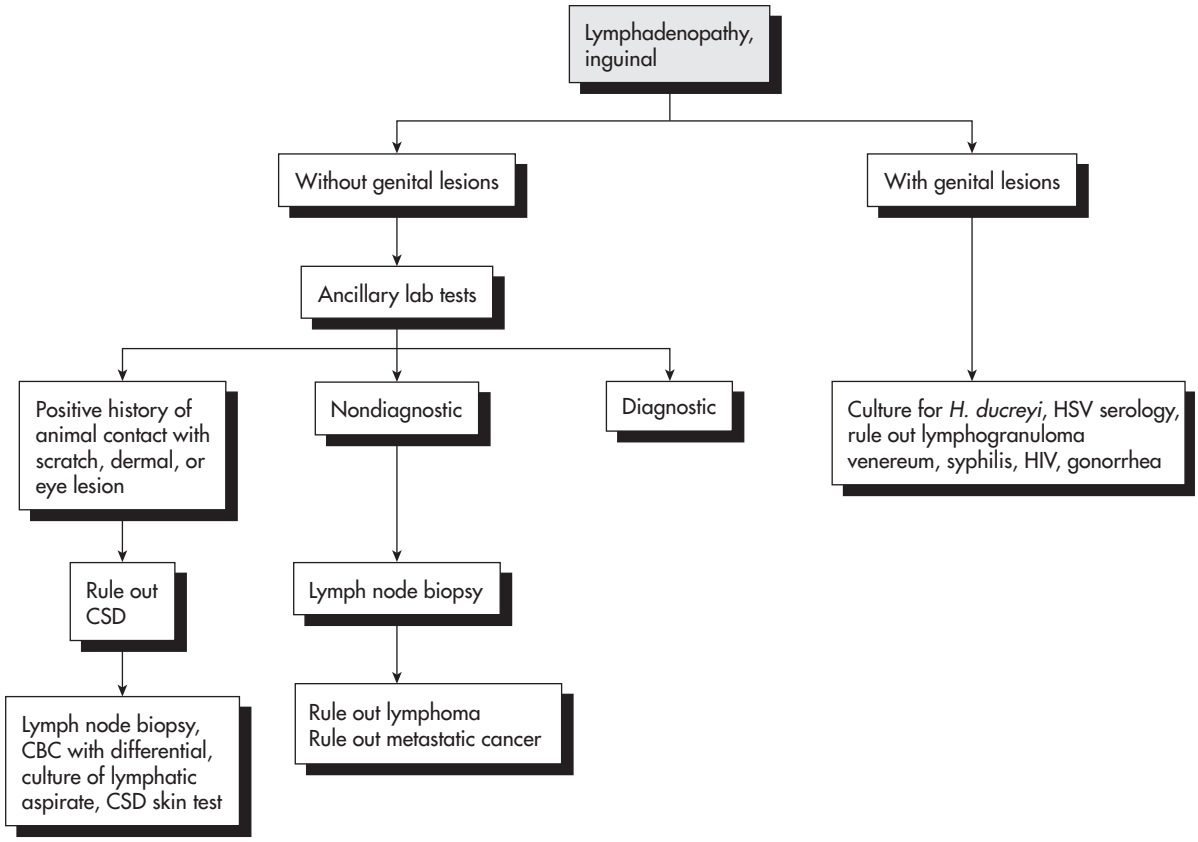


FIGURE E3-130 Lymphadenopathy, inguinal. *CBC*, Complete blood count; *CSD*, cat-scratch disease; *HSV*, herpes simplex virus.

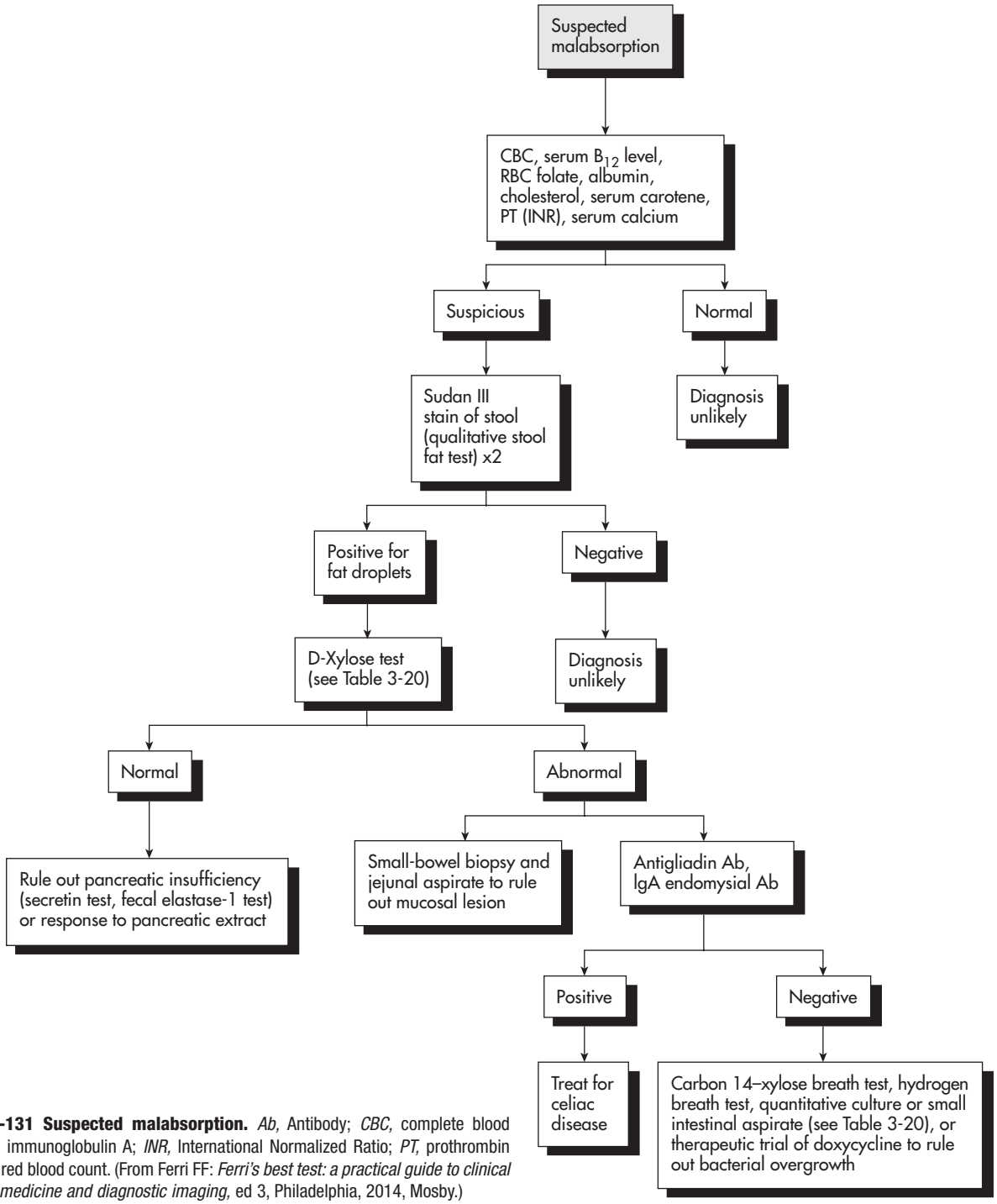


FIGURE 3-131 Suspected malabsorption. *Ab,* Antibody; *CBC,* complete blood count; *IgA,* immunoglobulin A; *INR,* International Normalized Ratio; *PT,* prothrombin time; *RBC,* red blood count. (From Ferri FF: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 3, Philadelphia, 2014, Mosby.)

BOX 3-3 Malabsorption, Suspected

Diagnostic Imaging
Best Test
Small-bowel series
Ancillary Test
CT of pancreas with IV contrast

Lab Evaluation
Best Test
Biopsy of small bowel

Ancillary Tests
Albumin, total protein
ALT, AST, PT
Serum lytes, BUN, creatinine
Sudan III stain of stool for fecal leukocytes
CBC, RBC folate, serum iron, serum carotene, cholesterol, serum calcium
Hydrogen 14-C xylose breath test
D-Xylose test, secretin test
Quantitative fecal test
Antigliadin antibody, IgA endomysial antibody

ALT, Alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CBC, complete blood count; CT, computed tomography; IgA, immunoglobulin A; IV, intravenous; PT, prothrombin time; RBC, red blood count.
From Ferri FF: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 3, Philadelphia, 2014, Elsevier Mosby.

ICD-9CM # 579.9
ICD-10CM # K90.89 Other intestinal malabsorption

TABLE 3-20 Tests for the Evaluation of Malabsorption*

Test	Comments
General Tests of Absorption	
Quantitative stool fat test	Gold standard test of fat malabsorption, with which all other tests are compared. Requires ingestion of a high-fat diet (100 g) for 2 days before and during the collection. Stool is collected for 3 days. Normally, <7 g/24 hr is excreted on a high-fat diet. Borderline abnormalities of 8-14 g/24 hr may be seen in secretory or osmotic diarrheas that are not caused by malabsorption. There are false-negative findings if fat intake is inadequate. False-positive results can occur if mineral oil laxatives or rectal suppositories (e.g., cocoa butter) are given to the patient before stool collection.
Qualitative stool fat test	Sudan stain of a stool sample for fat. Many fat droplets per medium-power field (×40) constitute a positive test result. The nuclear magnetic resonance method determines the percentage of fat in the stool (normal, <20%). The test depends on an adequate fat intake (100 g/day). There is high sensitivity (90%) and specificity (90%) with fat malabsorption of >10 g/24 hr. Sensitivity drops with stool fat in the range of 6-10 g/24 hr.
D-Xylose test	A test of small intestinal mucosal absorption, used to distinguish mucosal malabsorption from malabsorption due to pancreatic insufficiency. An oral dose of D-xylose (24 g/500 ml water) is administered, and D-xylose excretion is measured in a 5-hr urine collection. Normally, >4 g of D-xylose is excreted in the urine over 5 hr. The test also may be positive in bacterial overgrowth owing to metabolism of D-xylose by bacteria in the intestinal lumen. False-positive test results occur with renal failure, ascites, and an incomplete urine collection. Blood levels at 1 and 3 hr improve sensitivity. May be normal with mild or limited mucosal disease.
Hydrogen breath test	Most useful in the diagnosis of lactase deficiency. An oral dose of lactose (1 g/kg body weight) is administered after measurement of basal breath H_2 levels. The sole source of H_2 in the mammal is bacterial fermentation; unabsorbed lactose makes its way to colonic bacteria, resulting in excess breath H_2. A *late peak* (within 3-6 hr) of >20 ppm of exhaled H_2 after lactose ingestion suggests lactose malabsorption. Absorption of other carbohydrates (e.g., sucrose, glucose, fructose) also can be tested.
Specific Tests for Malabsorption	
Tests for Pancreatic Function	
Secretin stimulation test	The gold standard test of pancreatic function. Requires duodenal test intubation with a double-lumen tube and collection of pancreatic juice in response to IV secretin. Allows measurement of bicarbonate (HCO_3–) and pancreatic enzymes. A sensitive test of pancreatic function, but labor intensive and invasive.
Fecal elastase-1 test	Stool test for pancreatic function. Equal sensitivity to the secretin stimulation test for the diagnosis of moderate-to-severe pancreatic insufficiency. More specific than the fecal chymotrypsin test. Unreliable with mild insufficiency. False-positive results occur with increased stool volume and intestinal mucosal diseases.
Tests for Bacterial Overgrowth	
Quantitative culture of small intestinal aspirate	Gold standard test for bacterial overgrowth. Greater than 10^5 colony-forming units (CFU)/ml in the jejunum suggests bacterial overgrowth. Requires special anaerobic sample collection, rapid anaerobic and aerobic plating, and care to avoid oropharyngeal contamination. False-negative results occur with focal jejunal diverticula and when overgrowth is distal to the site aspirated.
Hydrogen breath test	The 50-g glucose breath test has a sensitivity of 90% for growth of 10^5 colonic-type bacteria in the small intestine. If bacterial overgrowth is present, increased H_2 is excreted in the breath. A hydrogen level (within 2 hr) of >20 ppm suggests bacterial overgrowth. False-negative results occur with non-hydrogen-producing organisms.
^{14}C-D-xylose breath test	This test uses 1 g of carbon 14–labeled D-xylose. It has a sensitivity and specificity >90% for growth of 10^5 test colonic-type bacteria in the small intestine. Bacteria metabolize D-xylose with release of $^{14}CO_2$, which is absorbed and exhaled. Nondegraded D-xylose is absorbed in the small bowel and does not reach the colon, yielding a greater specificity than the lactulose H_2 breath test. A nonradioactive ^{13}C-D-xylose breath test is suitable for children and pregnant women.
Tests for Mucosal Disease	
Small bowel biopsy	Obtained for a specific diagnosis when there is a high index of suspicion for small intestinal disease. Several biopsy specimens (4-5) must be obtained to maximize the diagnostic yield. Distal duodenal biopsy specimens are usually adequate for diagnosis, but occasionally enteroscopy with jejunal biopsy specimens is necessary. Small intestinal biopsy provides a specific diagnosis in some diseases (e.g., intestinal infection, Whipple's disease, abetalipoproteinemia, agammaglobulinemia, lymphangiectasia, lymphoma, amyloidosis). In other conditions, such as celiac disease and tropical sprue, the biopsy specimens show characteristic findings, but the diagnosis is made on improvement after treatment.
Tests of Ileal Function	
Schilling test	A test of vitamin B_{12} absorption
^{75}SeHCAT test	This is a test of bile acid absorption. Seven days after ingestion of radiolabeled synthetic selenium-homocholic acid conjugated with taurine (^{75}SeHCAT), whole body retention is measured by a gamma-counting device. The result is expressed as a fraction of baseline ingestion. Retention values of less than 10% are abnormal and indicate bile acid malabsorption with a sensitivity of 80-90% and specificity of 70%-100%. The radiation dose is equivalent to a plain chest x-ray. Liver disease and bacterial overgrowth may give false results. Not approved for use in the United States.

*Not all these tests are readily available. A strong suspicion for any disease may warrant foregoing an extensive work-up and obtaining the test with highest diagnostic yield. In some cases, empirical treatment, such as removing lactose from the diet of an otherwise healthy individual with lactose intolerance, is warranted without any testing.

From Goldman L, Schafer AI: *Goldman's Cecil Medicine,* ed 24, Philadelphia, 2012, Saunders.

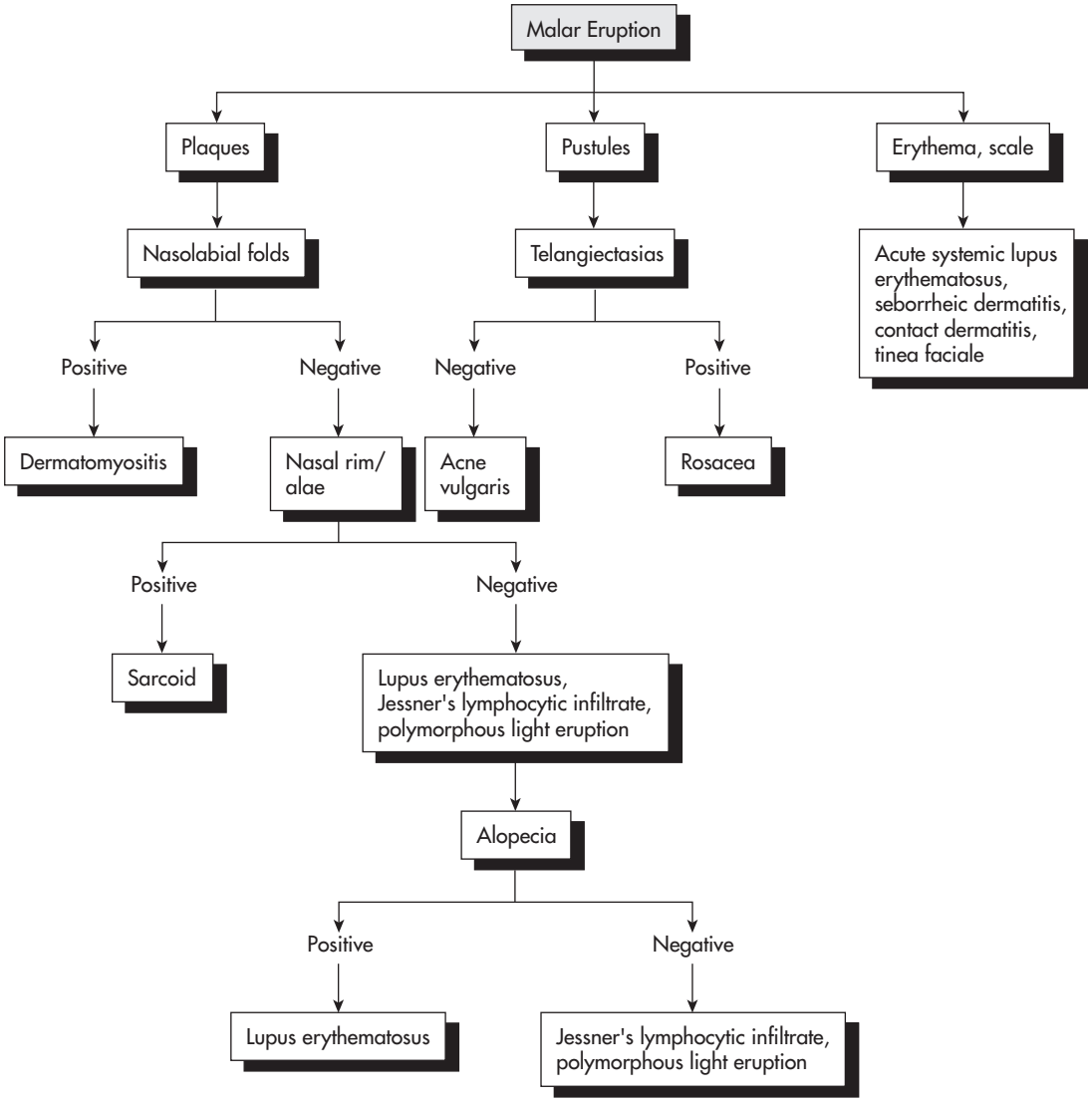


FIGURE 3-132 Clinical algorithm for diagnosis of a malar eruption, which must be confirmed by appropriate cultures, serology, and biopsy. (From Harris ED et al [eds]: *Kelley's textbook of rheumatology,* ed 7, Philadelphia, 2005, Saunders.)

MENTAL STATUS CHANGE, ELDERLY PATIENT

ICD-9CM # 780.97 Mental status change
ICD-10CM # R41.82 Altered mental status, unspecified

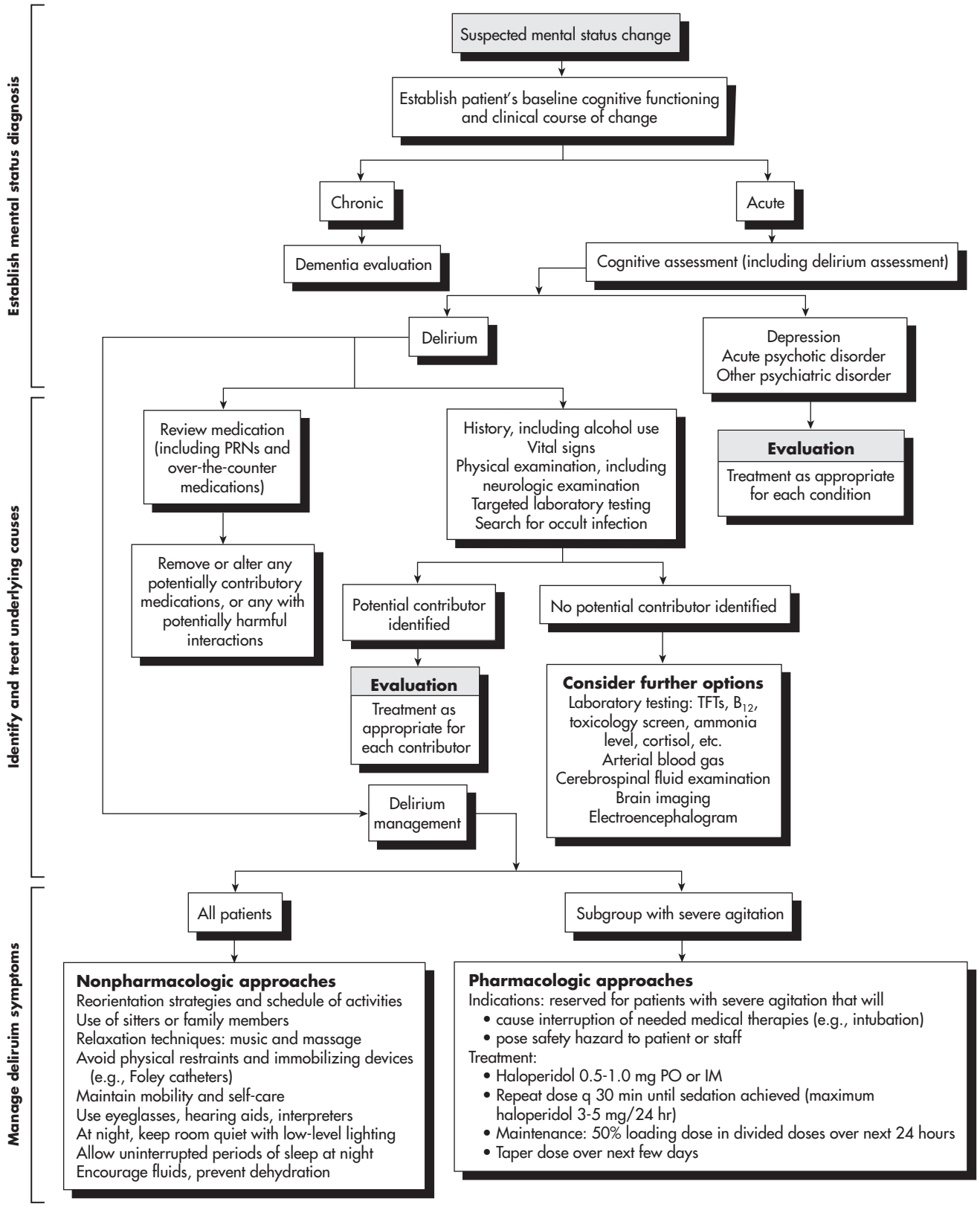


FIGURE 3-133 Algorithm for the evaluation of suspected mental status change in older patients. *PRN,* As needed; *TFTs,* thyroid function tests. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

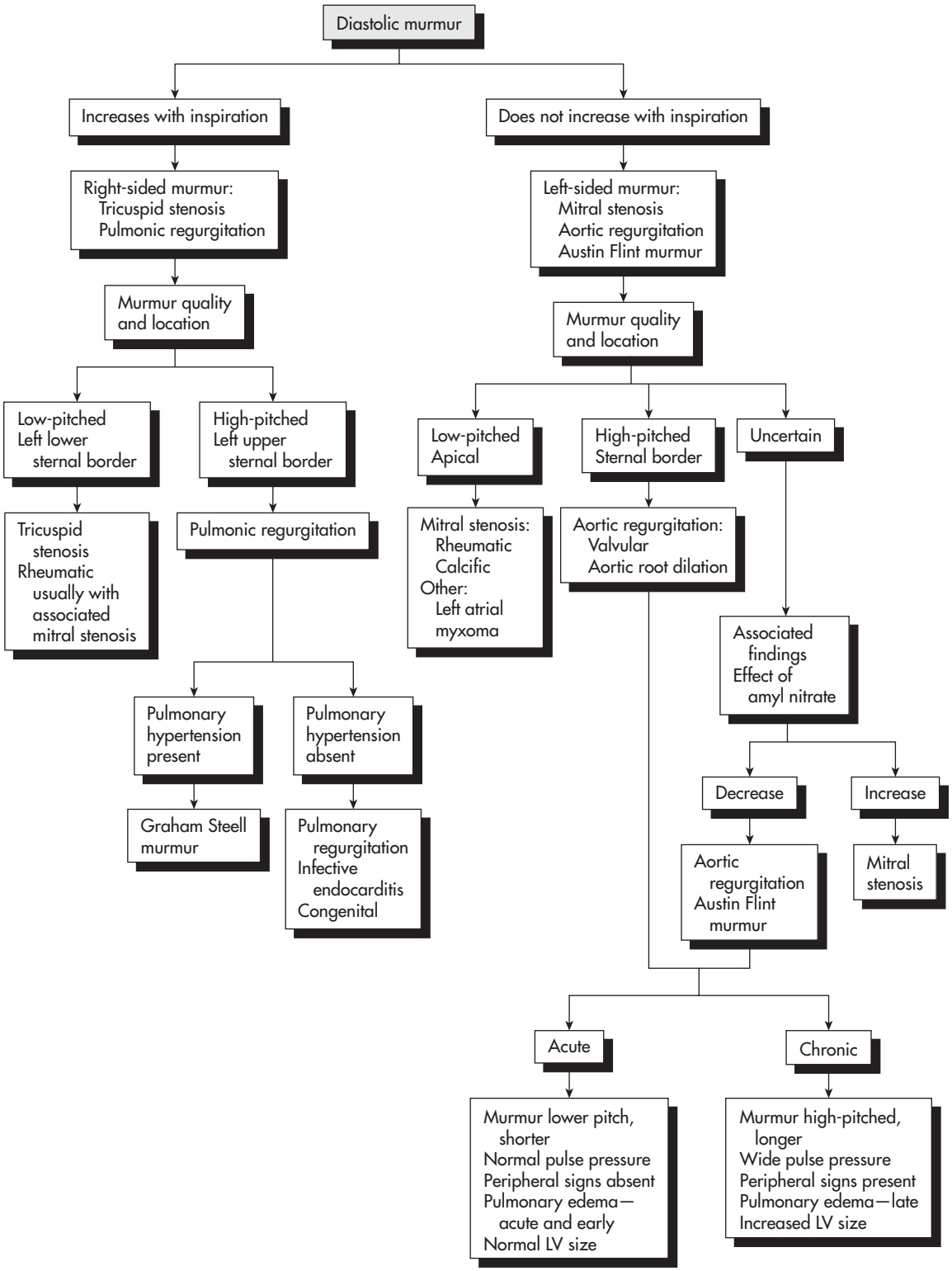


FIGURE 3-134 Diastolic murmur. *LV,* Left ventricle. (From Greene HL, Johnson WP, Lemcke DL [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

ICD-9CM # 785.2 Murmur, heart
ICD-10CM # R01.1 Cardiac murmur, unspecified

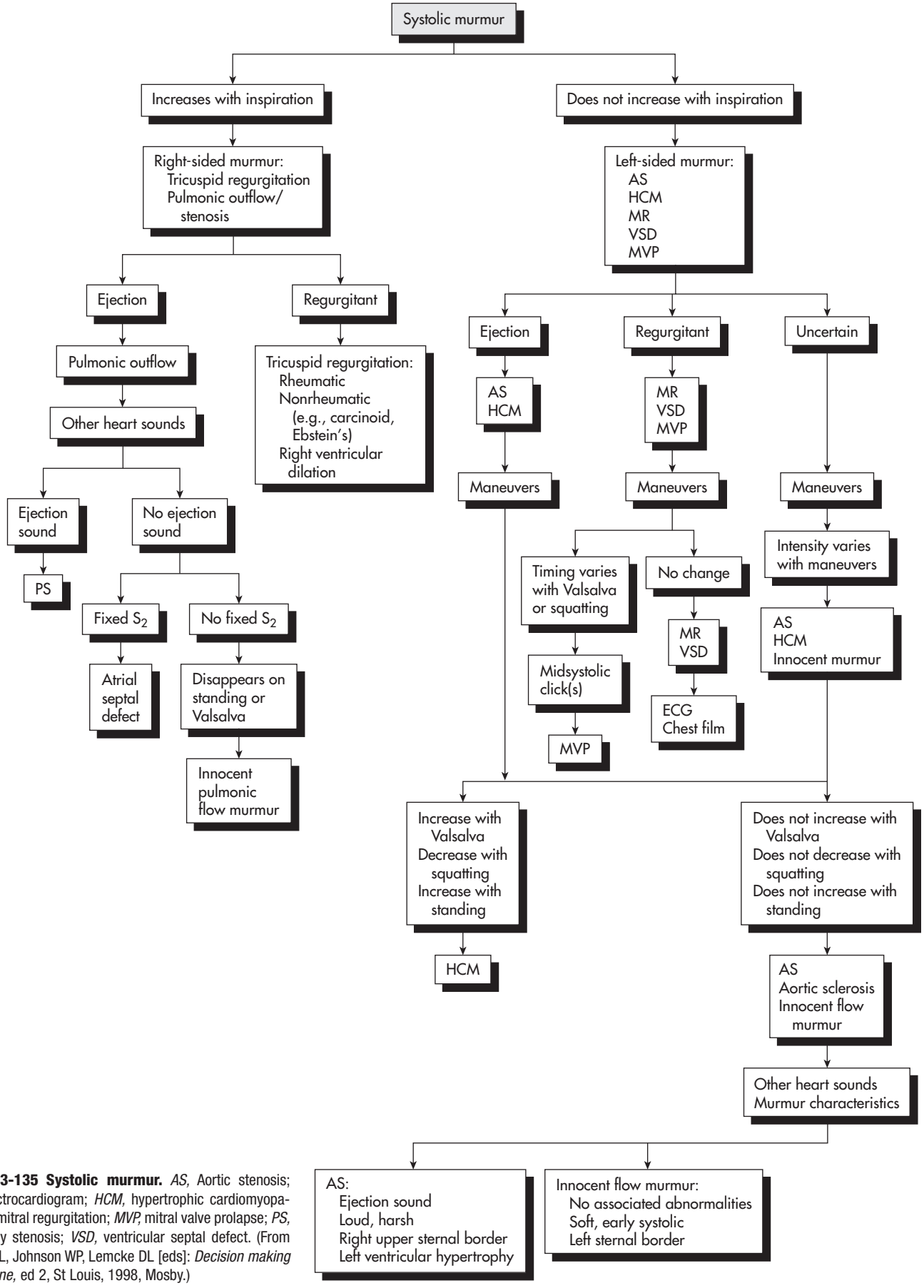


FIGURE 3-135 Systolic murmur. *AS,* Aortic stenosis; *ECG,* electrocardiogram; *HCM,* hypertrophic cardiomyopathy; *MR,* mitral regurgitation; *MVP,* mitral valve prolapse; *PS,* pulmonary stenosis; *VSD,* ventricular septal defect. (From Greene HL, Johnson WP, Lemcke DL [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

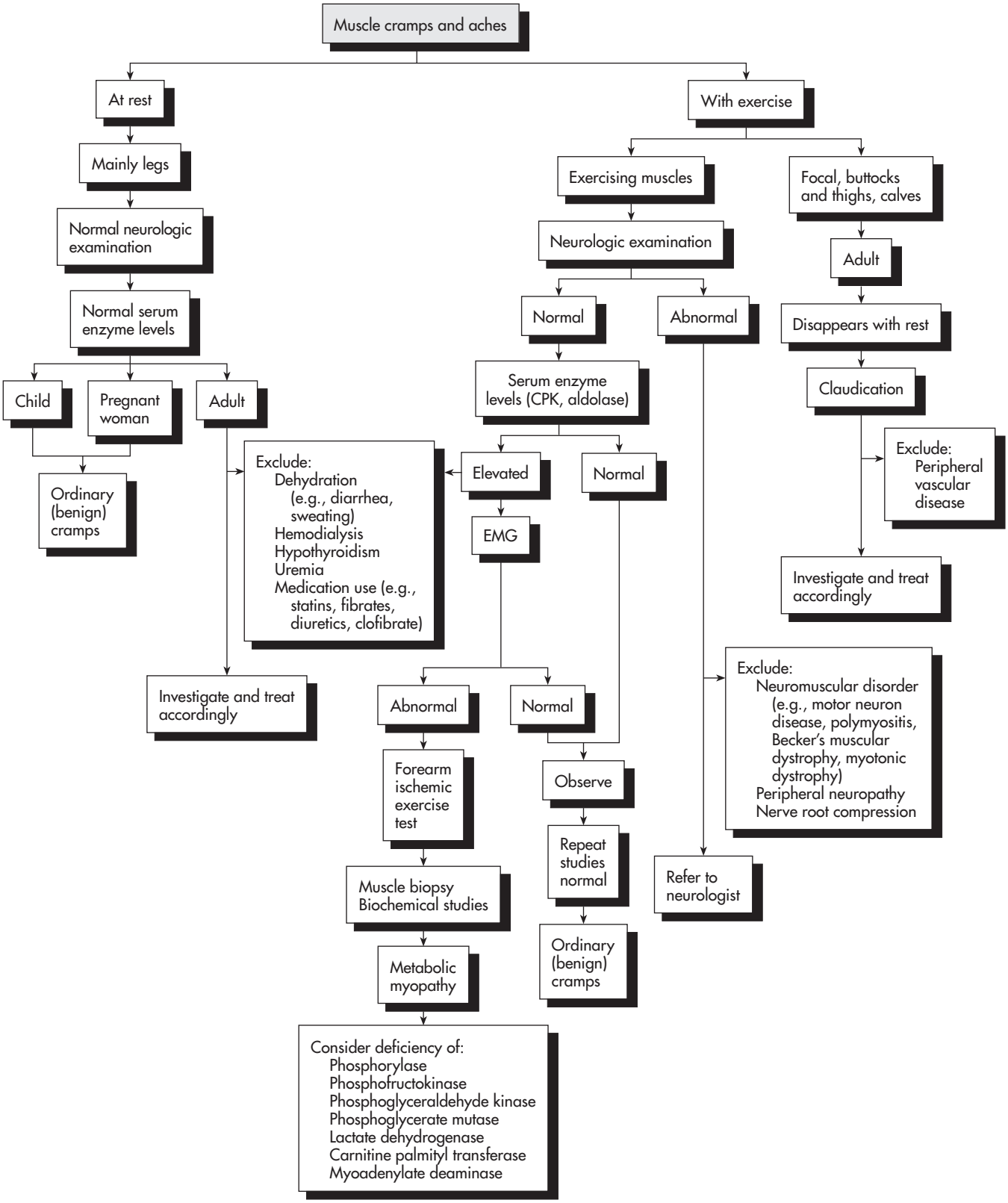


FIGURE 3-136 Evaluation of muscle cramps and aches. *CPK*, Creatine phosphokinase; *EMG*, electromyography. (From Greene HL, Johnson WP, Lemcke D [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

MUSCLE WEAKNESS

ICD-9CM # 728.9
ICD-10CM # M62.9 Disorder of muscle, unspecified

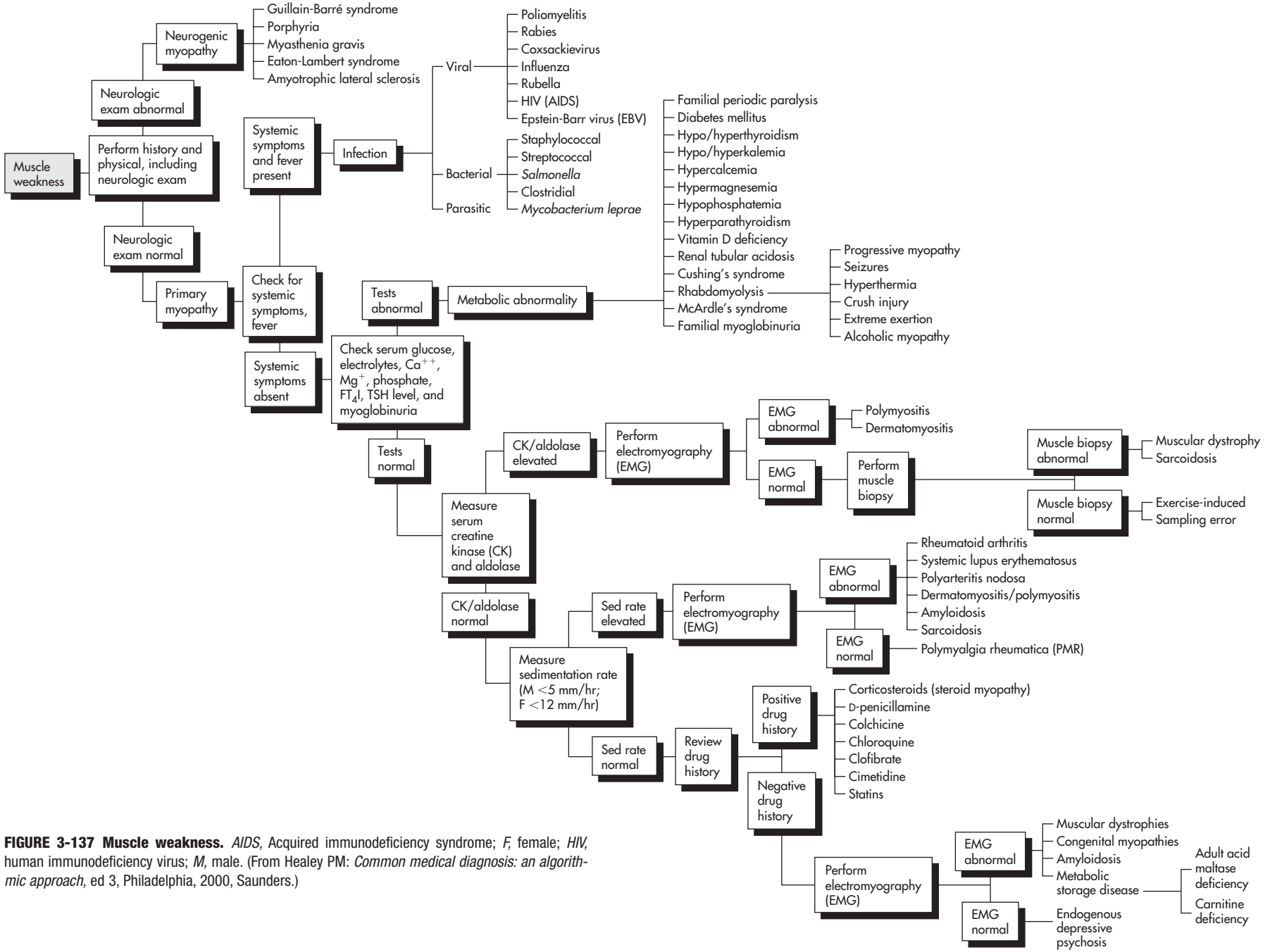


FIGURE 3-137 Muscle weakness. *AIDS,* Acquired immunodeficiency syndrome; *F,* female; *HIV,* human immunodeficiency virus; *M,* male. (From Healey PM: *Common medical diagnosis: an algorithmic approach,* ed 3, Philadelphia, 2000, Saunders.)

ICD-9CM # 719.40
ICD-10CM # M25.50 -Pain(s) joint
-Arthralgia (allergic)
-Arthrodynia
-Polyarthralgia

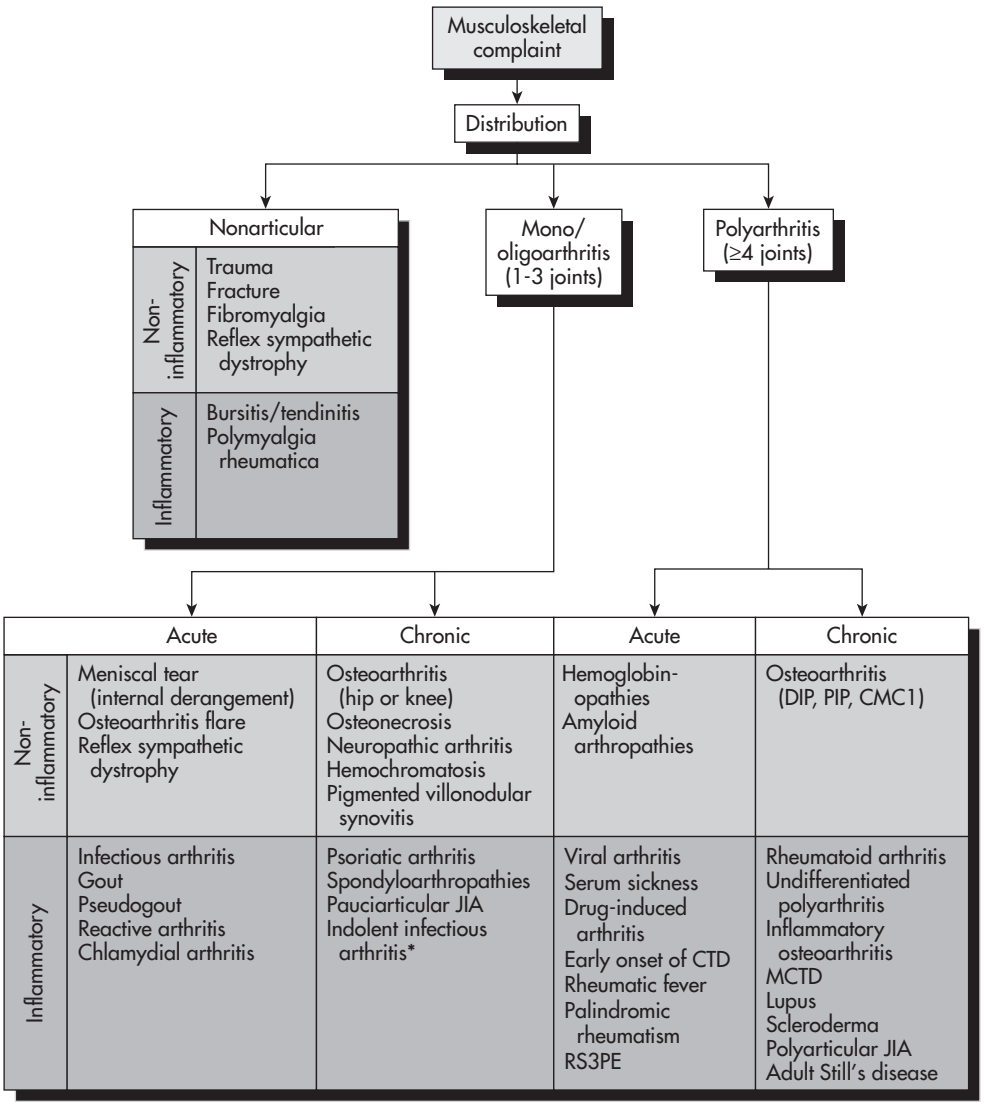


FIGURE 3-138 Algorithm for assessing initial history and examination. *CMC*, carpometacarpal; *CTD*, connective tissue disease; *DIP*, distal interphalangeal; *JIA*, juvenile idiopathic arthritis; *MCTD*, mixed connective tissue disease; *PIP*, proximal interphalangeal. (Firestein GS, Budd RC, Gabriel SE, et al: *Kelley's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.)

MYOCARDIAL ISCHEMIA, SUSPECTED

ICD-9CM # 411.1 Angina, stable
413 Angina pectoris
413.1 Prinzmetal's angina
413.9 Angina, unspecified
ICD-10CM # I25.6 Silent myocardial ischemia

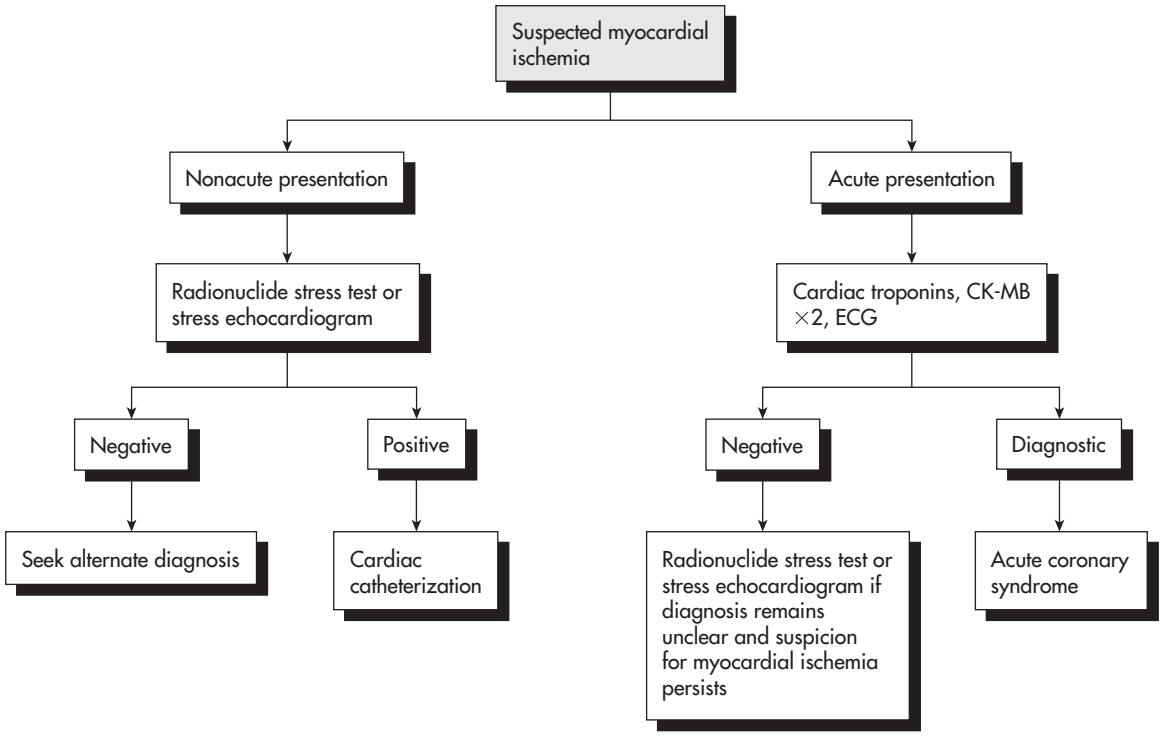


FIGURE E3-139 Myocardial ischemia, suspected. *CK-MB,* Myocardial muscle creatine kinase isoenzyme; *ECG,* electrocardiogram.

ICD-9CM # 729.1
ICD-10CM # M60.9 Myositis, unspecified
M79.1 Myalgia
M79.7 Fibromyalgia

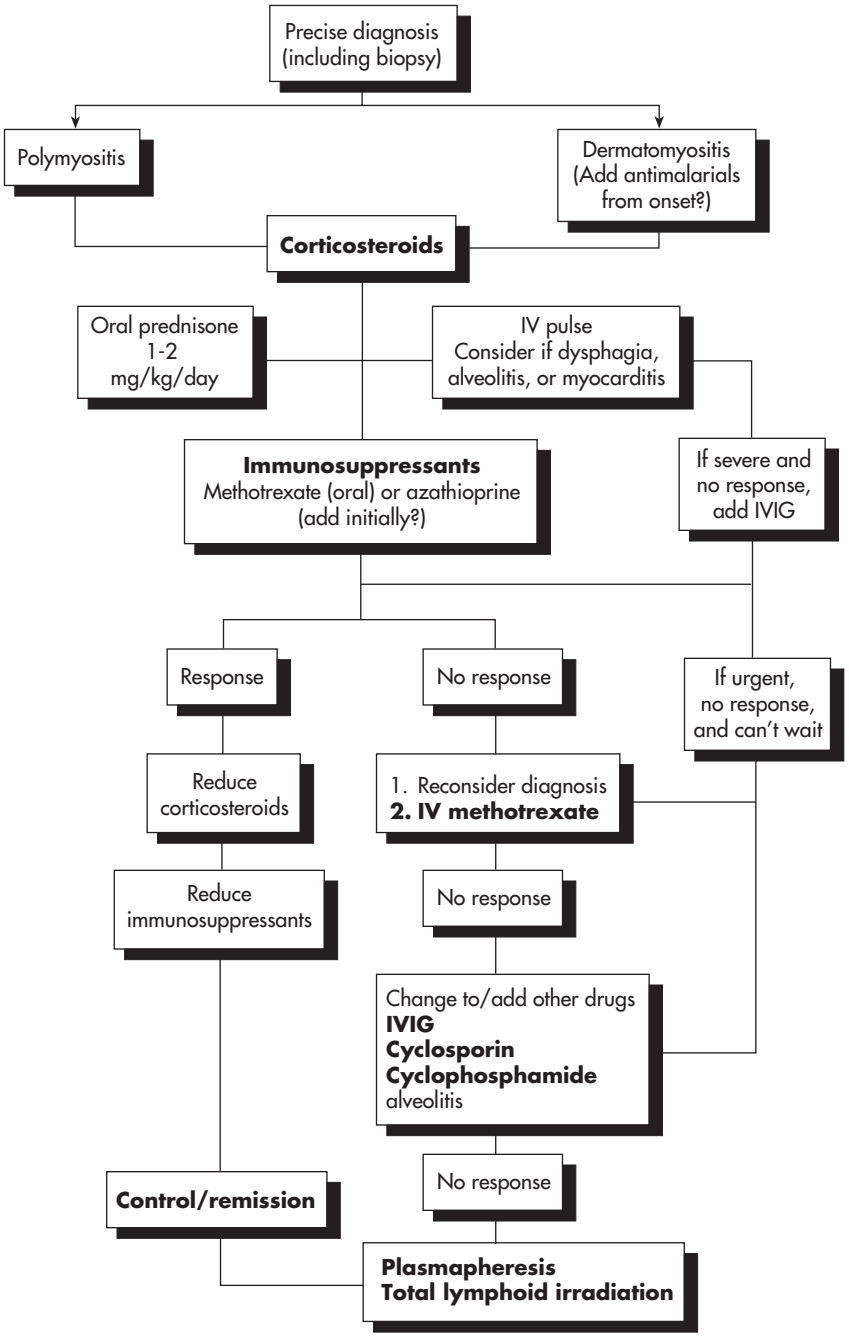


FIGURE E3-140 Drug management of myositis. Algorithm for drug management of polymyositis and dermatomyositis. *IV,* Intravenous; *IVIG,* IV immunoglobulins. (Modified from Hochberg MC et al: *Rheumatology,* ed 3, St Louis, 2003, Mosby.)

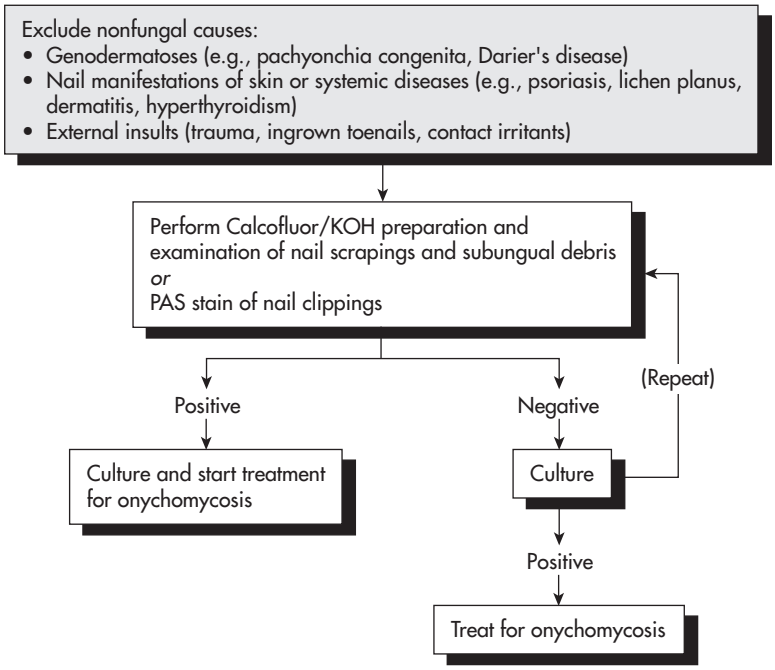


FIGURE E3-141 Diagnostic algorithm for dystrophy of one or more nails. An organized approach is essential in correctly and efficiently diagnosing onychomycosis. (From Bolognia JL et al [eds]: *Dermatology,* ed 2, St Louis, 2008, Mosby.)

ICD-9CM # 784.2
ICD-10CM # R22.0 Localized swelling, mass and lump, head
R22.1 Localized swelling, mass and lump, neck

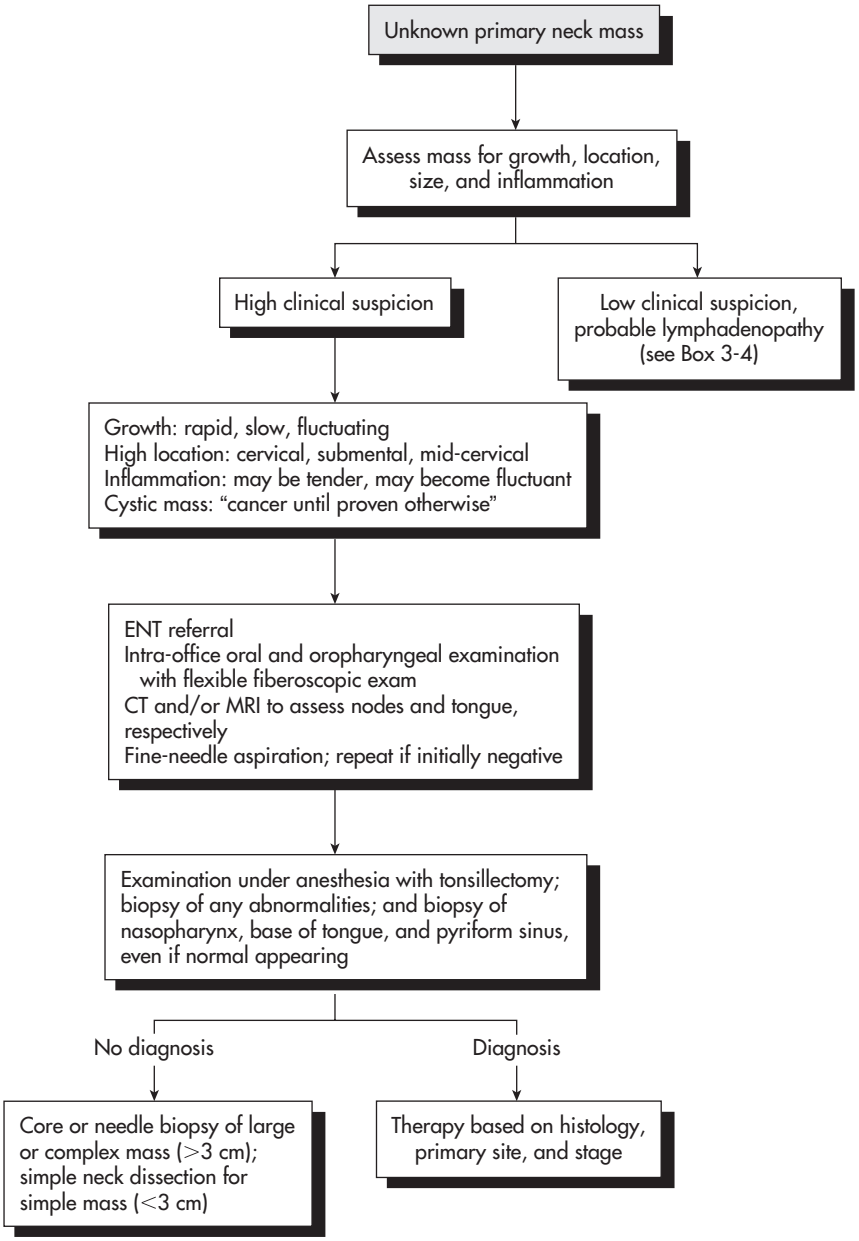


FIGURE 3-142 Evaluation of an unknown primary neck mass. *CT,* Computed tomography; *ENT,* ear, nose, and throat; *MRI,* magnetic resonance imaging. (From Goldman L, Schafer AL [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

BOX 3-4 An Approach to the Patient with Lymphadenopathy

1. Does the patient have a known illness that causes lymphadenopathy? Treat and monitor for resolution.
2. Is there an obvious infection to explain the lymphadenopathy (e.g., infectious mononucleosis)? Treat and monitor for resolution.
3. Are the nodes very large and/or very firm and thus suggestive of malignancy? Perform a biopsy.
4. Is the patient very concerned about malignancy and unable to be reassured that malignancy is unlikely? Perform a biopsy.
5. If none of the preceding are true, perform a complete blood cell count and if it is unrevealing, monitor for a predetermined period (usually 2 to 6 weeks). If the nodes do not regress or if they increase in size, perform a biopsy.

From Goldman L, Ausiello D (eds): *Cecil textbook of medicine,* ed 23, Philadelphia, 2008, Saunders.

ICD-9CM # 723.1 Neck Pain (Nondiscogenic)
959.09 Neck Injury
ICD-10CM # M54.2 Cervicalgia
S19.9XXA Unspecified injury of neck, initial encounter

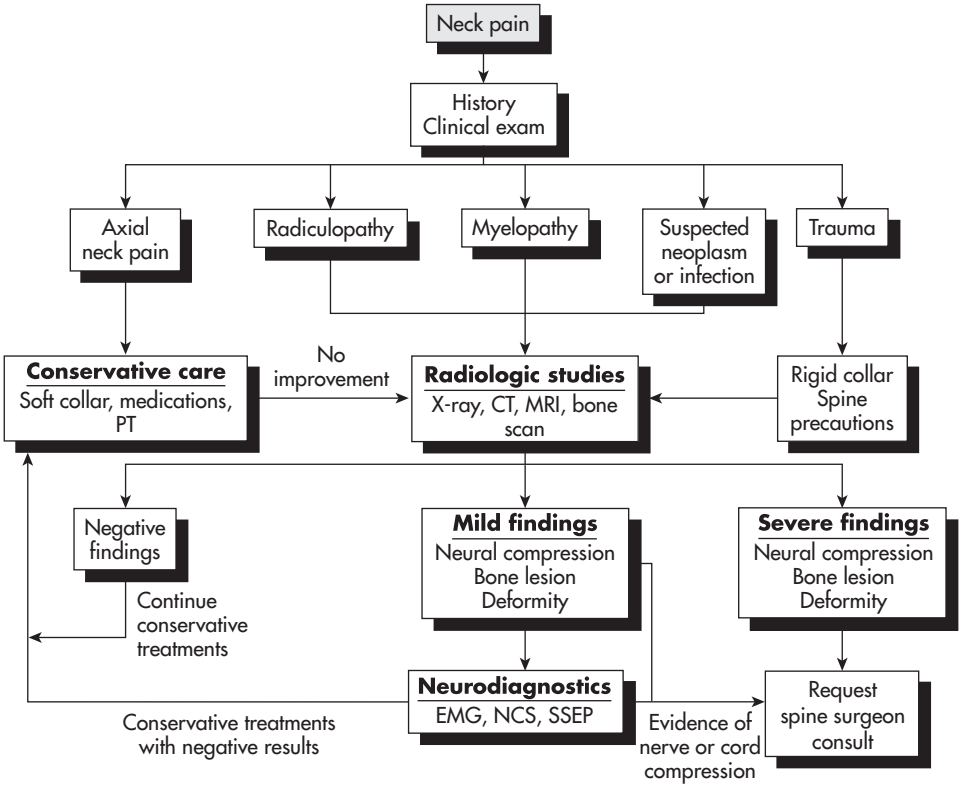


FIGURE 3-143 Algorithm of neck pain. CT, computed tomography; EMG, electromyogram; MRI, magnetic resonance imaging; NCS, nerve conduction study; PT, physical therapy; SSEP, somatosensory evoked potentials. (From Firestein GS, Budd RC, Gabriel SE, et al: Kelley's textbook of rheumatology, ed 9, Philadelphia, 2013, Saunders.)

ICD-9CM # 269.9 Unspecified nutritional deficiency
ICD-10CM # E63.9 Nutritional deficiency, unspecified

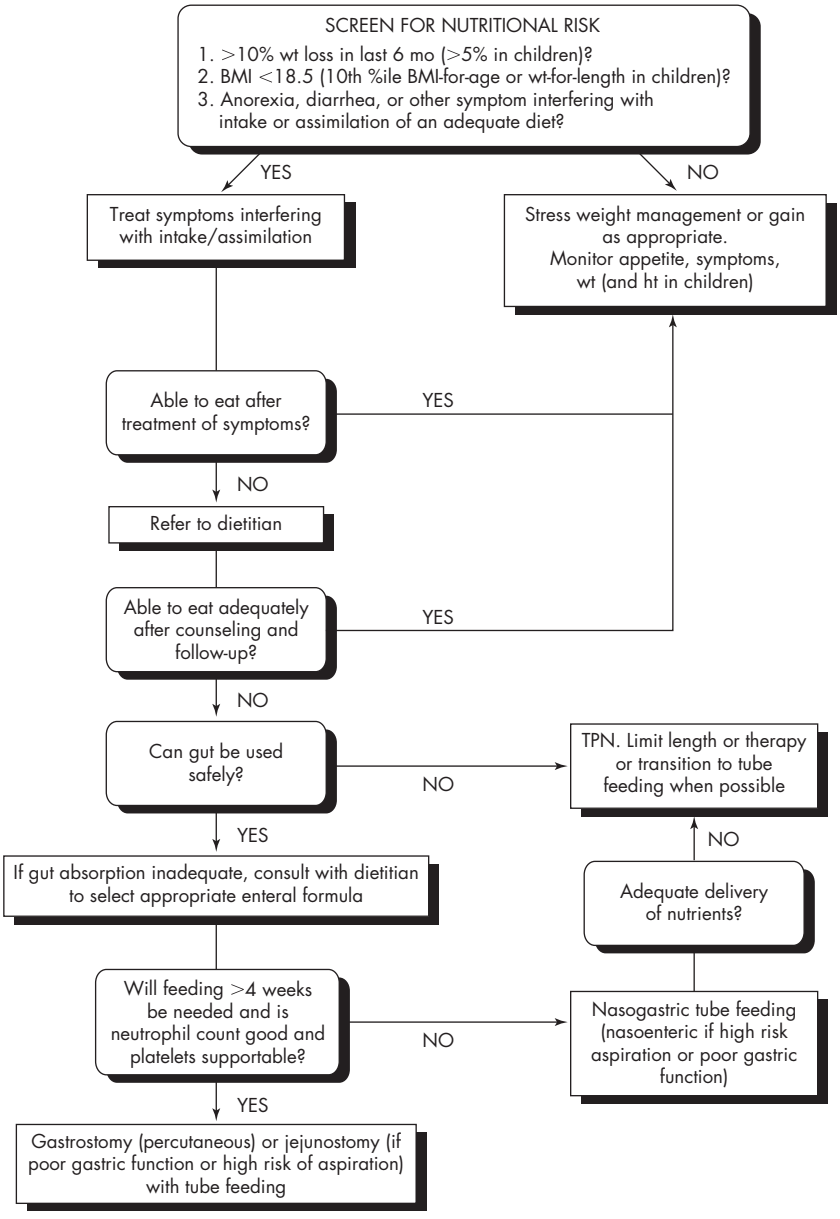


FIGURE E3-144 Algorithm for nutrition assessment and intervention. (From Hoffmann R et al: *Hematology, basic principles and practice*, ed 5, Philadelphia, 2009, Churchill Livingstone.)

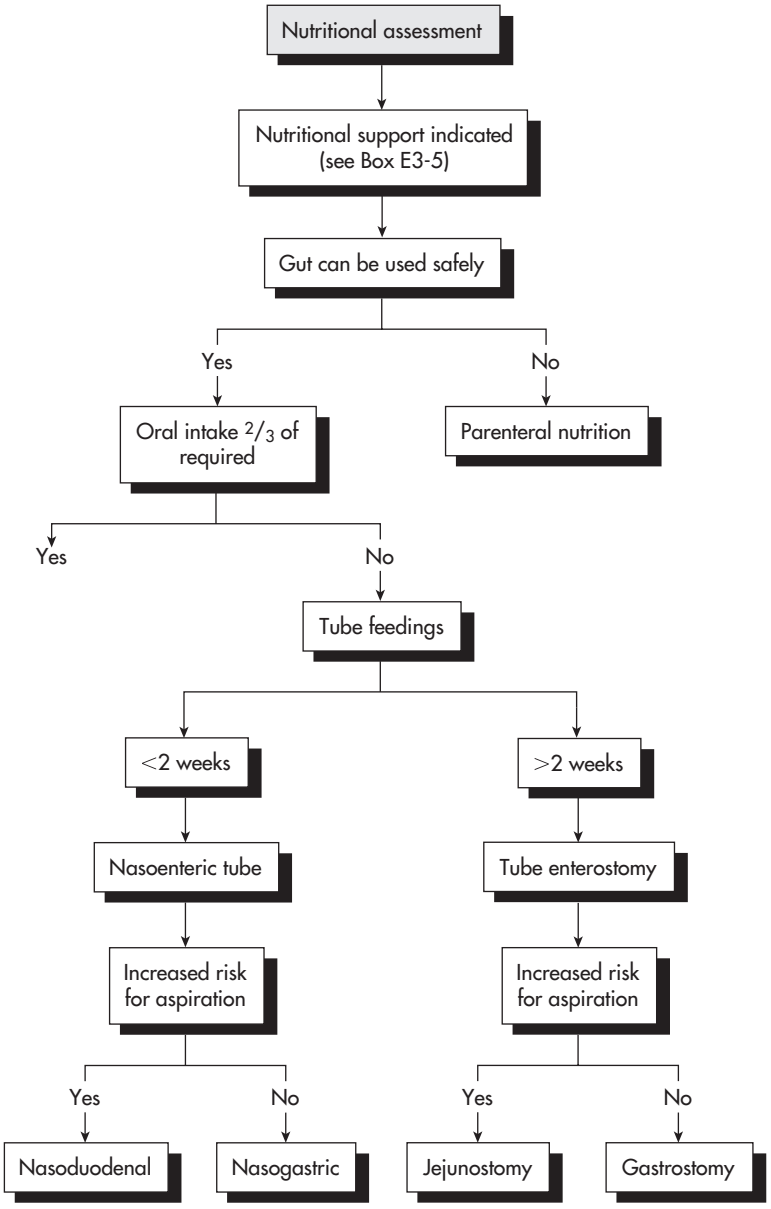


FIGURE E3-145 Decision approach for the type and route of nutritional support. (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 23, Philadelphia, 2008, Saunders.)

BOX E3-5 Indications for the Use of Enteral Nutrition in Adult Medical Patients

- Protein-energy malnutrition with anticipated significantly decreased oral intake for at least 7 days
- Anticipated significantly decreased oral intake for 10 days
- Severe dysphagia
- Massive small bowel resection (used in combination with total parenteral nutrition)
- Low-output (<500 ml/day) enterocutaneous fistula

From Goldman L, Ausiello D (eds): *Cecil textbook of medicine,* ed 23, Philadelphia, 2008, Saunders.

NYSTAGMUS

ICD-9CM # 379.50 Nystagmus NOS
386.11 Benign Positional
386.2 Central Positional
379.59 Congenital
ICD-10CM # H55.00 Unspecified nystagmus
H81.13 Benign paroxysmal vertigo, bilateral
H81.49 Vertigo of central origin, unspecified ear
H55.89 Other irregular eye movements

Identification of Types of Nystagmus

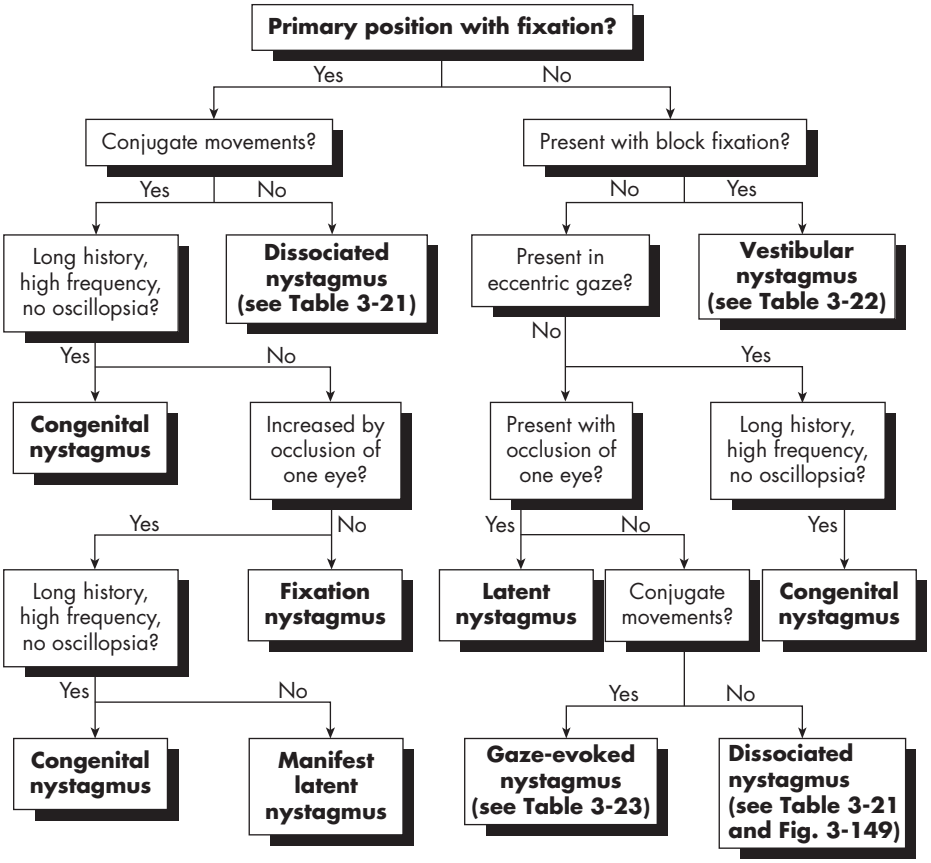


FIGURE 3-146 Identification of types of nystagmus. (From Yanoff M, Duker JS: *Ophthalmology,* ed 2, St Louis, 2004, Mosby.)

TABLE 3-21 Characteristics and Localizations of Dissociated Nystagmus

Nystagmus	Characteristics	Localization
Acquired pendular in adults	Pendular, horizontal, vertical, torsional, disconjugate (coexisting palatal myoclonus)	Brain stem, cerebellum
Superior oblique myokymia	Pendular, jerk, torsional, vertical, high frequency, small amplitude, monocular	Trochlear nucleus
See-saw	Pendular, vertical, torsional, rising eye intorts, falling eye extorts; rarely jerk	Midbrain (interstitial nucleus of Cajal)
Abducting "nystagmus" of internuclear ophthalmoplegia	Jerk, horizontal, decreasing velocity slow components, larger in abducting eye	Medial longitudinal fasciculus in pons, midbrain horizontal gaze
Abducting nystagmus of myasthenia gravis	Gaze-paretic nystagmus in horizontal gaze, greater paresis of medial rectus muscle	Myoneural junction—myasthenia gravis

From Yanoff M, Duker JS: *Ophthalmology,* ed 2, St Louis, 2004, Mosby.

ICD-9CM # 379.50 Nystagmus NOS
386.11 Benign Positional
386.2 Central Positional
379.59 Congenital
ICD-10CM # H55.00 Unspecified nystagmus
H81.13 Benign paroxysmal vertigo, bilateral
H81.49 Vertigo of central origin, unspecified ear
H55.89 Other irregular eye movements

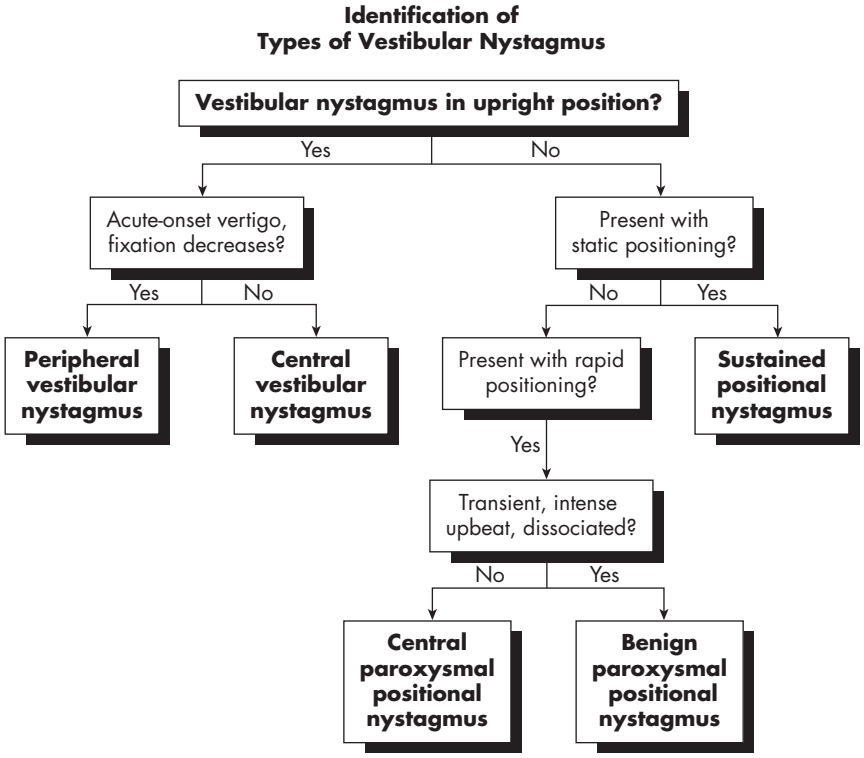


FIGURE 3-147 Identification of types of vestibular nystagmus. (From Yanoff M, Duker JS: *Ophthalmology,* ed 2, St Louis, 2004, Mosby.)

TABLE 3-22 Characteristics and Localizations of Vestibular Nystagmus

Nystagmus	Characteristics	Localization
Spontaneous peripheral vestibular	Jerk, horizontal, small torsional, inhibited by fixation	Labyrinth, eighth nerve (acute)
Central vestibular (fixation) nystagmus	Jerk, pendular, horizontal, vertical, torsional, not inhibited by fixation	Brain stem, cerebellum
Sustained positional vestibular	Jerk, horizontal, small torsional, direction fixed, direction changing (static positioning)	Labyrinth, eighth nerve or brain stem, cerebellum
Benign paroxysmal positional	Jerk, dissociated upbeat, latency, not inhibited by fixation, fatigue (Nylen–Barany maneuver)	Posterior vertical canal
Central paroxysmal positional	Jerk, symmetric, upbeat, downbeat	Brain stem, cerebellum

From Yanoff M, Duker JS: *Ophthalmology,* ed 2, St Louis, 2004, Mosby.

NYSTAGMUS—cont'd

ICD-9CM # 379.50 Nystagmus NOS
386.11 Benign Positional
386.2 Central Positional
379.59 Congenital
ICD-10CM # H55.00 Unspecified nystagmus
H81.13 Benign paroxysmal vertigo, bilateral
H81.49 Vertigo of central origin, unspecified ear
H55.89 Other irregular eye movements

TABLE 3-23 Characteristics and Localizations of Gaze-Evoked Nystagmus

Nystagmus	Characteristics	Localization
Physiologic, endpoint	Jerk, small amplitude, intermittent, extremes of horizontal and up gaze	Physiologic
Gaze-paretic (symmetric)	Jerk (decreasing velocity slow components) at 30° eccentric gaze	Nonlocalizing (drugs, mental fatigue)
Gaze-paretic (asymmetric)	Jerk (decreasing velocity slow components), horizontal, at 30° eccentric gaze, larger amplitude toward side of lesion	Lesions of brain stem, cerebellum, cerebral hemisphere
Rebound	Jerk, horizontal, decreases and direction can reverse in eccentric gaze, transient jerk nystagmus on return to primary gaze, fast components beating toward eccentric gaze	Cerebellum
Myasthenia gravis	Jerk, horizontal or vertical, gradual onset in prolonged eccentric gaze	Myoneural junction (fatigue—increasing transmission block)

From Yanoff M, Duker JS: *Ophthalmology,* ed 2, St Louis, 2004, Mosby.

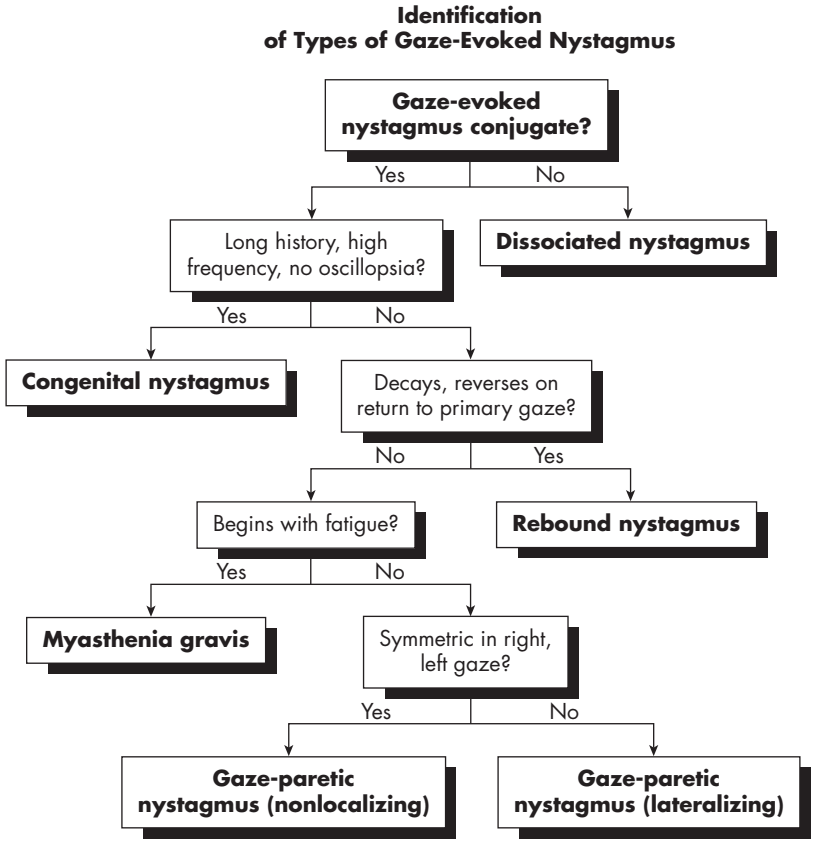


FIGURE 3-148 Identification of types of gaze-evoked nystagmus. (From Yanoff M, Duker JS: *Ophthalmology,* ed 2, St Louis, 2004, Mosby.)

ICD-9CM # 379.50 Nystagmus NOS
386.11 Benign Positional
386.2 Central Positional
379.59 Congenital
ICD-10CM # H55.00 Unspecified nystagmus
H81.13 Benign paroxysmal vertigo, bilateral
H81.49 Vertigo of central origin, unspecified ear
H55.89 Other irregular eye movements

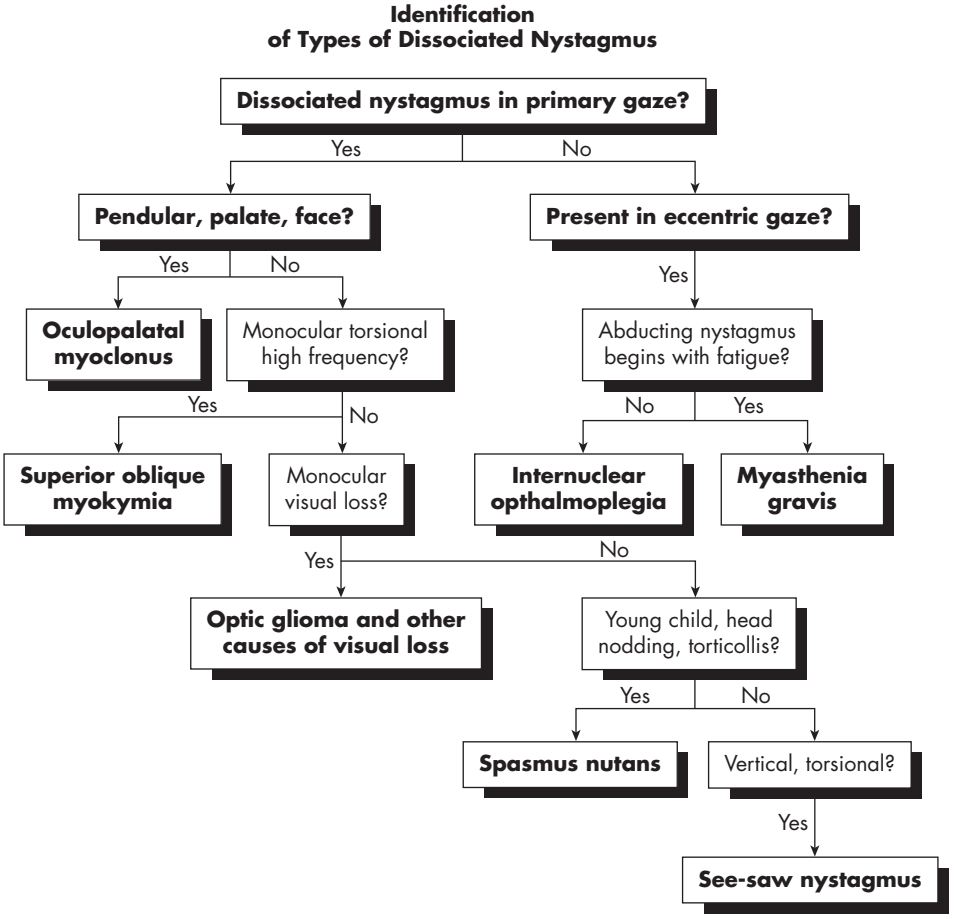


FIGURE 3-149 Identification of types of dissociated nystagmus. (From Yanoff M, Duker JS: *Ophthalmology,* ed 2, St Louis, 2004, Mosby.)

OLIGURIA

ICD-9CM # 788.5
ICD-10CM # R34 Anuria and oliguria

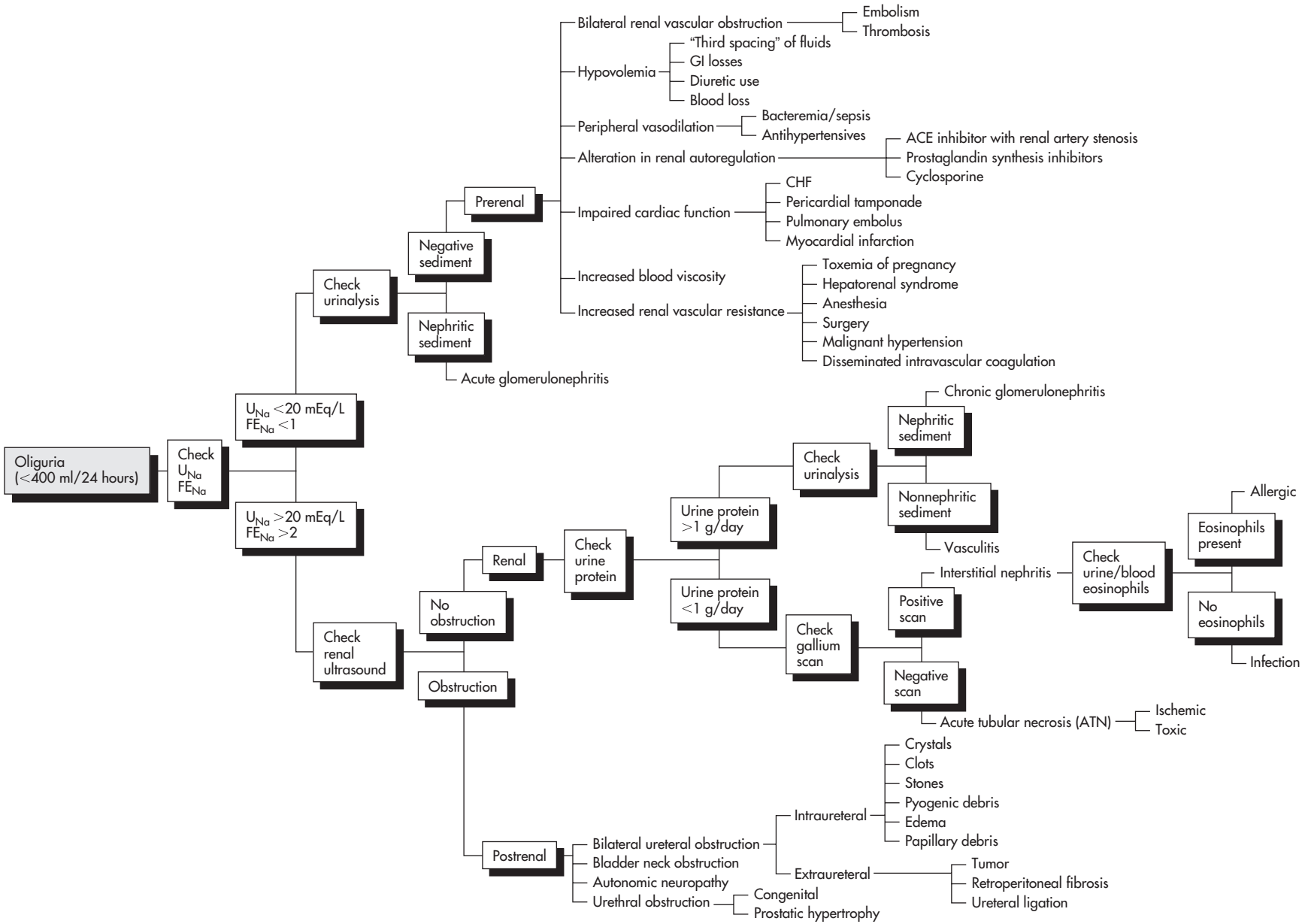


FIGURE 3-150 Evaluation of oliguria. *ACE,* Angiotensin-converting enzyme; *CHF,* congestive heart failure; *GI,* gastrointestinal. (From Healey PM: *Common medical diagnosis: an algorithmic approach,* ed 3, Philadelphia, 2000, Saunders.)

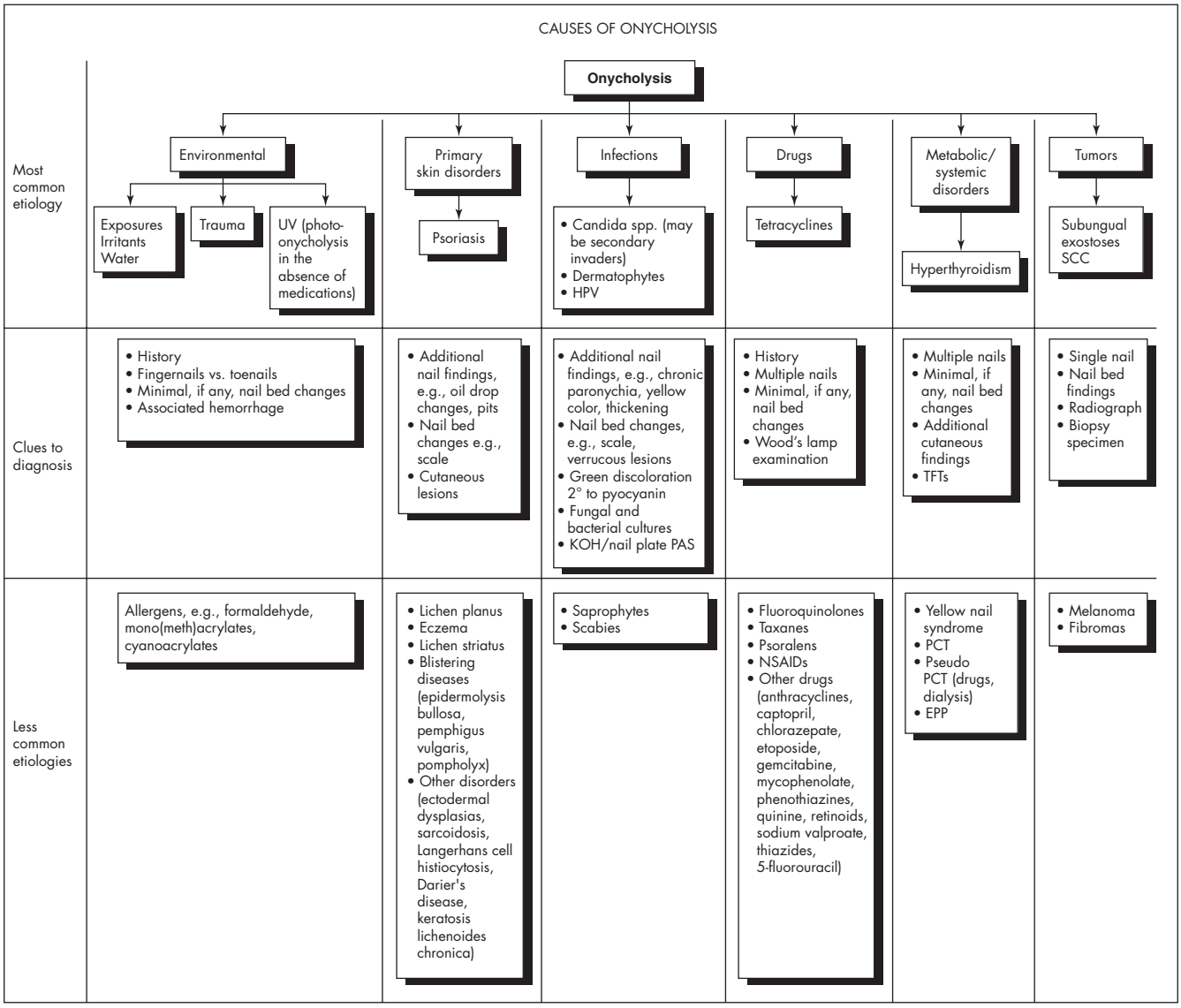


FIGURE E3-151 Causes of onycholysis. (From Bolognia JL et al: *Dermatology,* ed 2, St Louis, 2009, Mosby.)

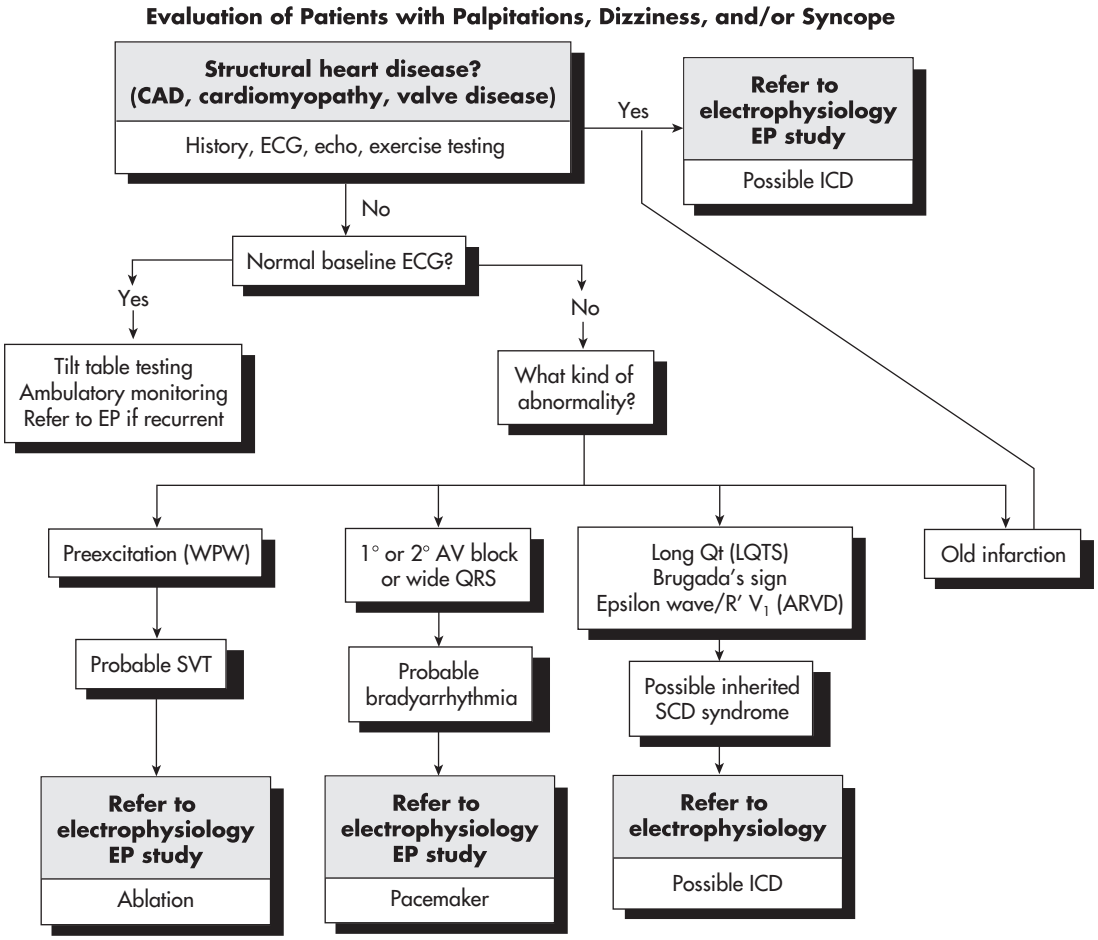


FIGURE 3-152 Algorithm for evaluating patients with symptoms of palpitation, dizziness, or syncope. *ARVD,* Arrhythmogenic right ventricular dysplasia; *AV,* atrioventricular; *CAD,* coronary artery disease; *ECG,* electrocardiogram; *echo,* echocardiogram; *EP,* electrophysiology; *ICD,* implantable cardioverter-defibrillator; *LQTS,* long QT syndrome; *SCD,* sudden cardiac death; *SVT,* supraventricular tachycardia; *WPW,* Wolff-Parkinson-White syndrome. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

TABLE 3-24 Items to be Covered in History of Patient with Palpitation

Does the Palpitation Occur:	If So, Suspect:
As isolated "jumps" or "skips"?	Extrasystoles
In attacks known to be of abrupt beginning, with a heart rate of 120 beats/min or over, with regular or irregular rhythm?	Paroxysmal rapid heart action
Independent of exercise or excitement adequate to account for the symptom?	Atrial fibrillation, atrial flutter, thyrotoxicosis, anemia, febrile states, hypoglycemia, anxiety state
In attacks developing rapidly though not absolutely abruptly, unrelated to exertion or excitement?	Hemorrhage, hypoglycemia, tumor of the adrenal medulla
In conjunction with the taking of drugs?	Tobacco, coffee, tea, alcohol, epinephrine, ephedrine, aminophylline, atropine, thyroid extract, monoamine oxidase inhibitors
On standing?	Postural hypotension
In middle-aged women, in conjunction with flushes and sweats?	Menopausal syndrome
When the rate is known to be normal and the rhythm regular?	Anxiety state

From Goldman L, Braunwald E: Chest discomfort and palpitation. In Isselbacher KJ, Braunwald E et al [eds]: *Harrison's principles of internal medicine,* ed 13, New York, 1994, McGraw-Hill.

PANCREATIC ISLET CELL TUMORS

ICD-9CM # 211.7
ICD-10CM # D13.7 Benign neoplasm of endocrine pancreas

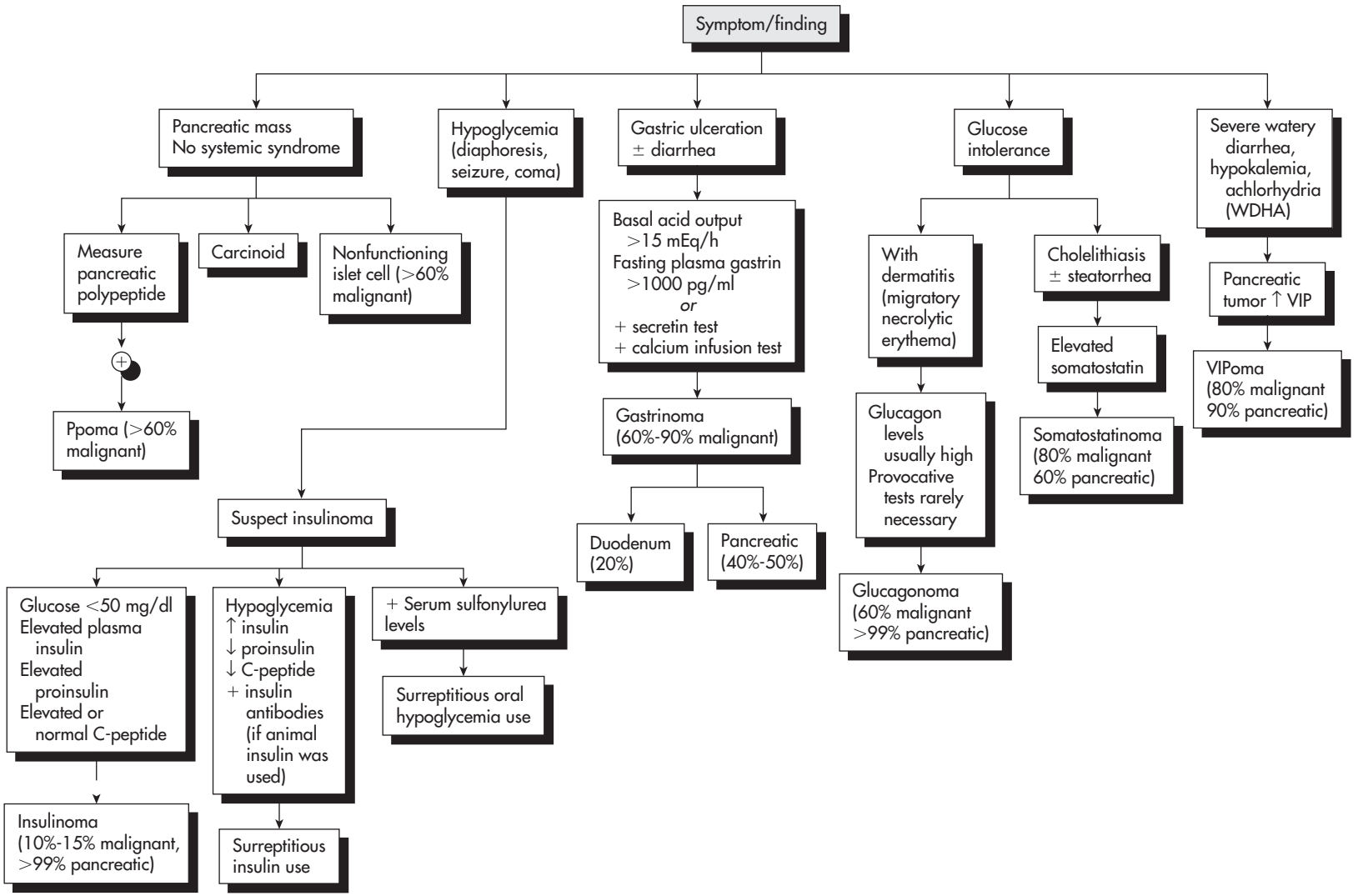


FIGURE E3-153 Diagnosis of pancreatic islet cell tumors. *Ppoma,* Islet cell tumor secreting pancreatic polypeptide; *VIP,* vasoactive intestinal peptide; *VIPoma,* islet cell tumor secreting vasoactive intestinal peptide. (Modified from Abeloff MD: *Clinical oncology,* ed 3, New York, 2004, Churchill Livingstone.)

ICD-9CM # 789.36
ICD-10CM # C25.3 Malignant neoplasm of pancreatic duct
R19.06 Epigastric swelling, mass or lump

FIGURE 3-154 Diagnostic algorithm for pancreatic cancer. Intraoperative fine-needle aspiration (FNA) if found inoperable during surgery. *CT,* Computed tomography; *ERCP,* endoscopic retrograde cholangiopancreatography; *EUS,* endoscopic ultrasonography; *MRI,* magnetic resonance imaging. (From Goldman L, Schafer AL [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

PAPULOSQUAMOUS DISORDERS, PEDIATRIC PATIENT

ICD-9CM # code varies with specific diagnosis
709.8 Other specified disorders of skin
ICD-10CM # L44.9 Papulosquamous disorder, unspecified
L98.8 Other specified disorders of the skin and subcutaneous tissue

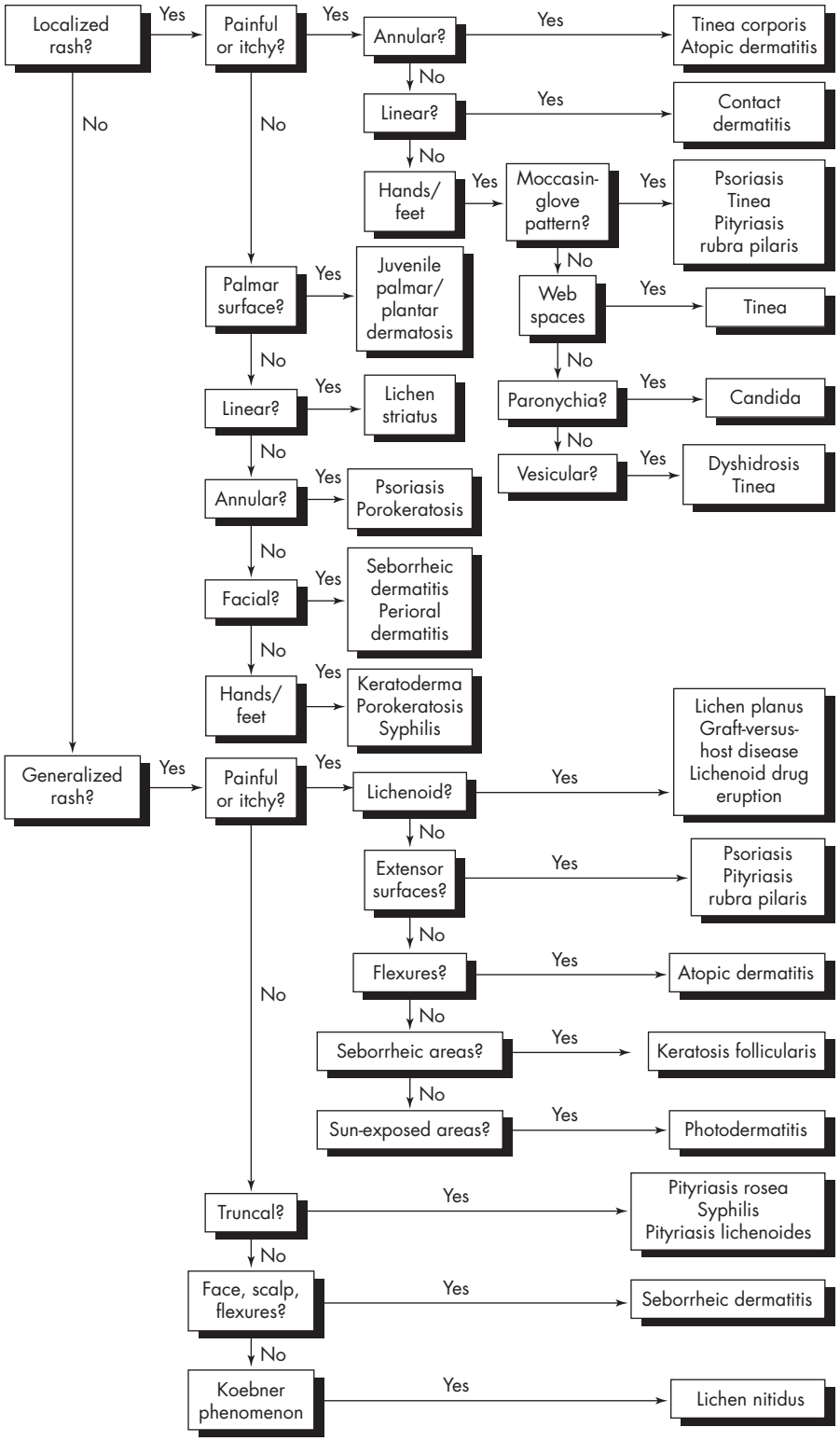


FIGURE E3-155 Papulosquamous disorders algorithm. (Modified from Cohen BA: *Atlas of pediatric dermatology,* ed 3, St Louis, 2005, Mosby.)

PATIENT WITH ILL-DEFINED PHYSICAL COMPLAINTS

ICD-9CM # 301.9 Personality disorder NOS
301.51 Munchausen syndrome
ICD-10CM # F68.12 Factitious disorder with predominantly physical signs and symptoms

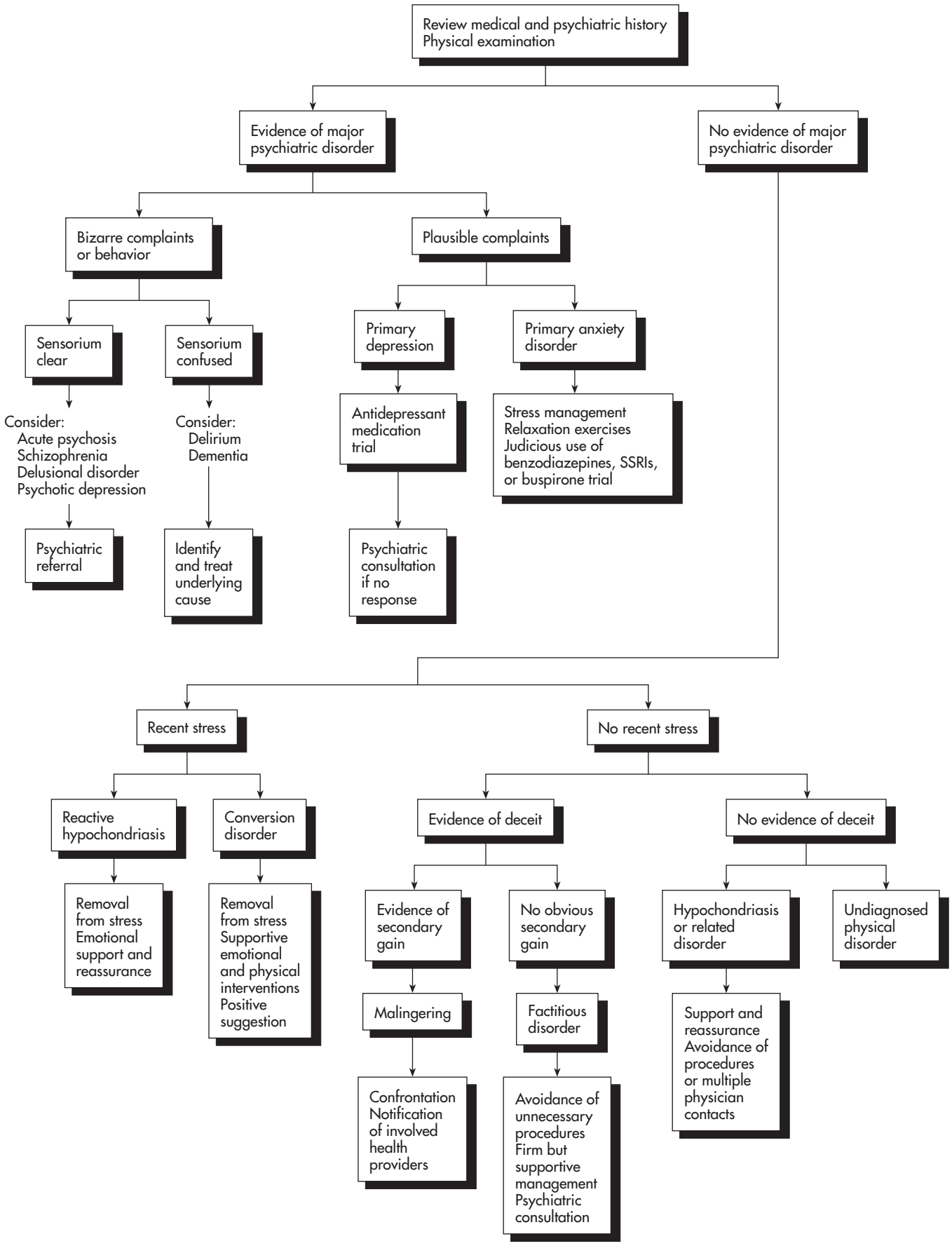


FIGURE 3-156 Patient with ill-defined physical complaints. Previous or recent evaluations are noncontributory. *SSRIs,* Selective serotonin reuptake inhibitors. (From Greene H, Johnson WP, Lemcke D [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

ICD-9CM # 789.39
ICD-10CM # R19.09 Other intraabdominal and pelvic swelling, mass and lump

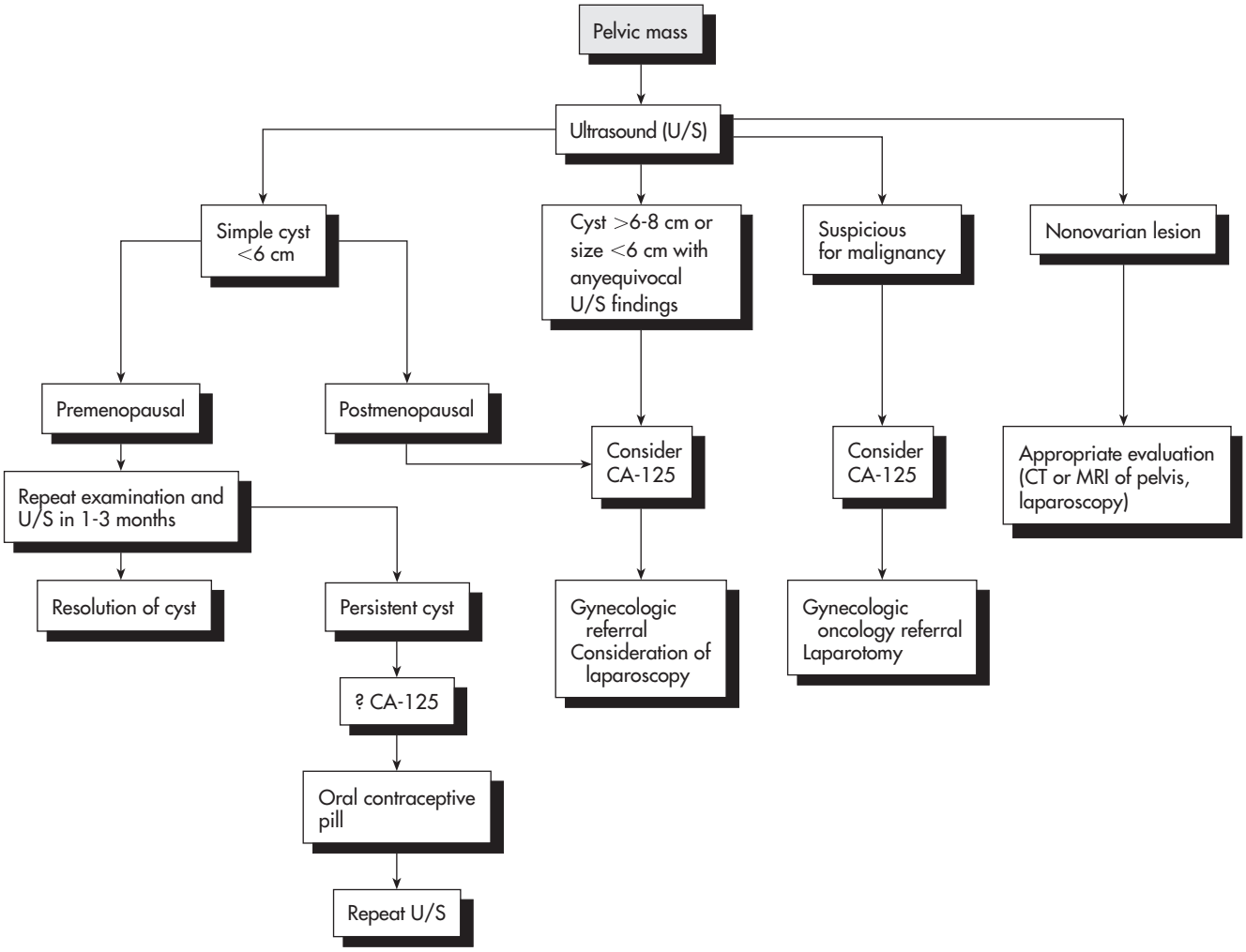


FIGURE 3-157 Approach to the patient with a pelvic mass. *CT,* Computed tomography; *MRI,* magnetic resonance imaging. (Modified from Carlson KJ et al: *Primary care of women,* ed 2, St Louis, 2002, Mosby.)

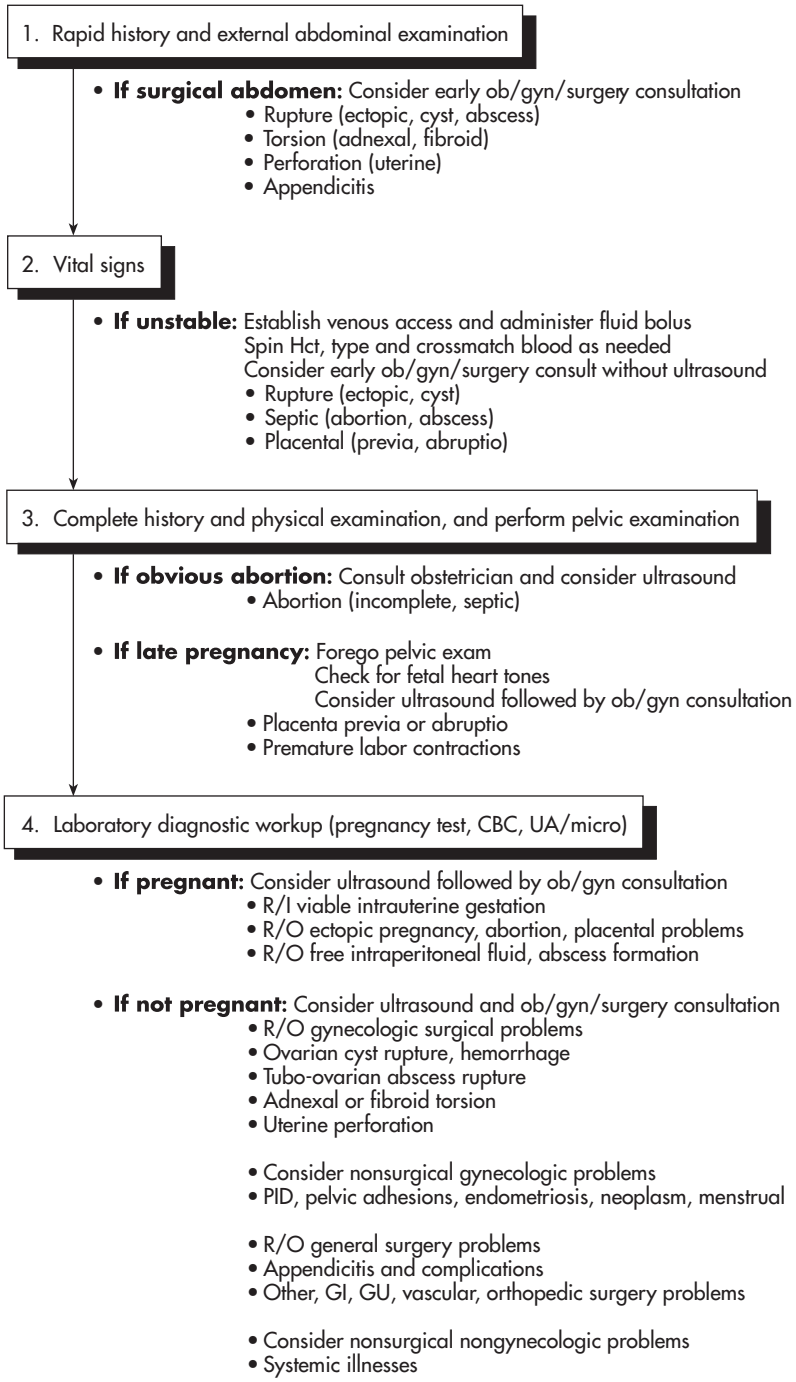


FIGURE 3-158 Evaluation and management of reproductive-age women with acute pelvic pain. *CBC,* Complete blood count; *GI,* gastrointestinal; *GU,* genitourinary; *Hct,* hematocrit; *PID,* pelvic inflammatory disease; *UA/micro,* urinalysis with microscopy. (From Marx JA [ed]: *Rosen's emergency medicine,* ed 6, St Louis, 2006, Mosby.)

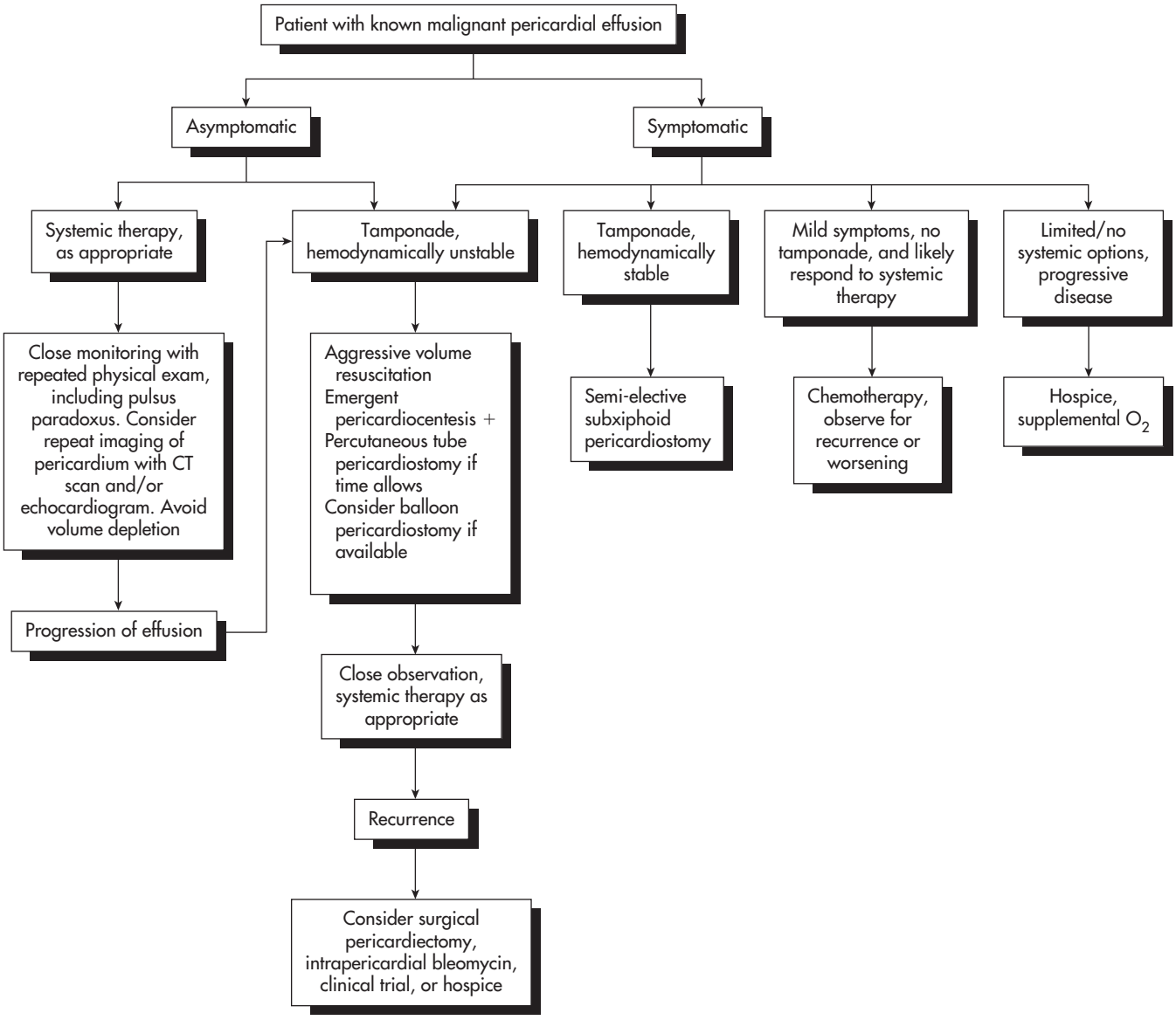


FIGURE E3-159 Treatment approach to patient with known malignant pericardial effusion. *CT,* Computed tomography. (From Abeloff MD: *Clinical oncology,* ed 3, Philadelphia, 2004, Saunders.)

ICD-9CM # 356.9 Peripheral nerve neuropathy
355.10 Lower extremity neuropathy
354.11 Upper extremity neuropathy
ICD-10CM # G60.9 Hereditary and idiopathic neuropathy, unspecified
G57.10 Meralgia paresthetica, unspecified lower limb
G90.09 Other idiopathic peripheral autonomic neuropathy

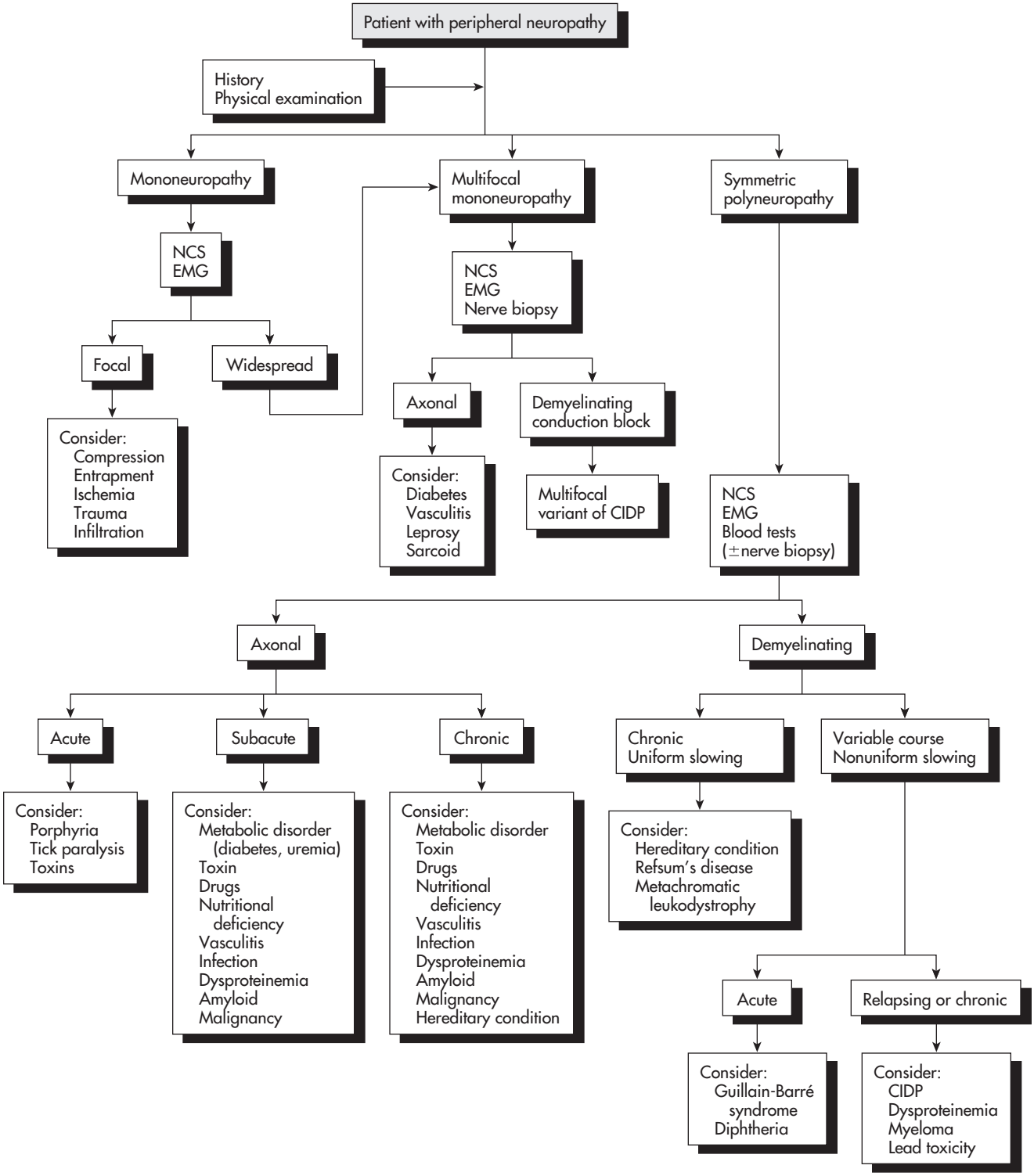


FIGURE 3-160 Approach to the patient with peripheral neuropathy. *CIDP,* Chronic inflammatory demyelinating polyradiculopathy; *EMG,* electromyogram; *NCS,* nerve conduction studies. (From Greene HL, Johnson WP, Lemcke DL: *Decision making in medicine,* ed 2, St Louis, 1988, Mosby.)

PHOTOSENSITIVITY

ICD-9CM # 692.72
ICD-10CM # L56.0 Drug phototoxic response
L56.1 Drug photoallergic response
L56.2 Photocontact dermatitis [berloque dermatitis]

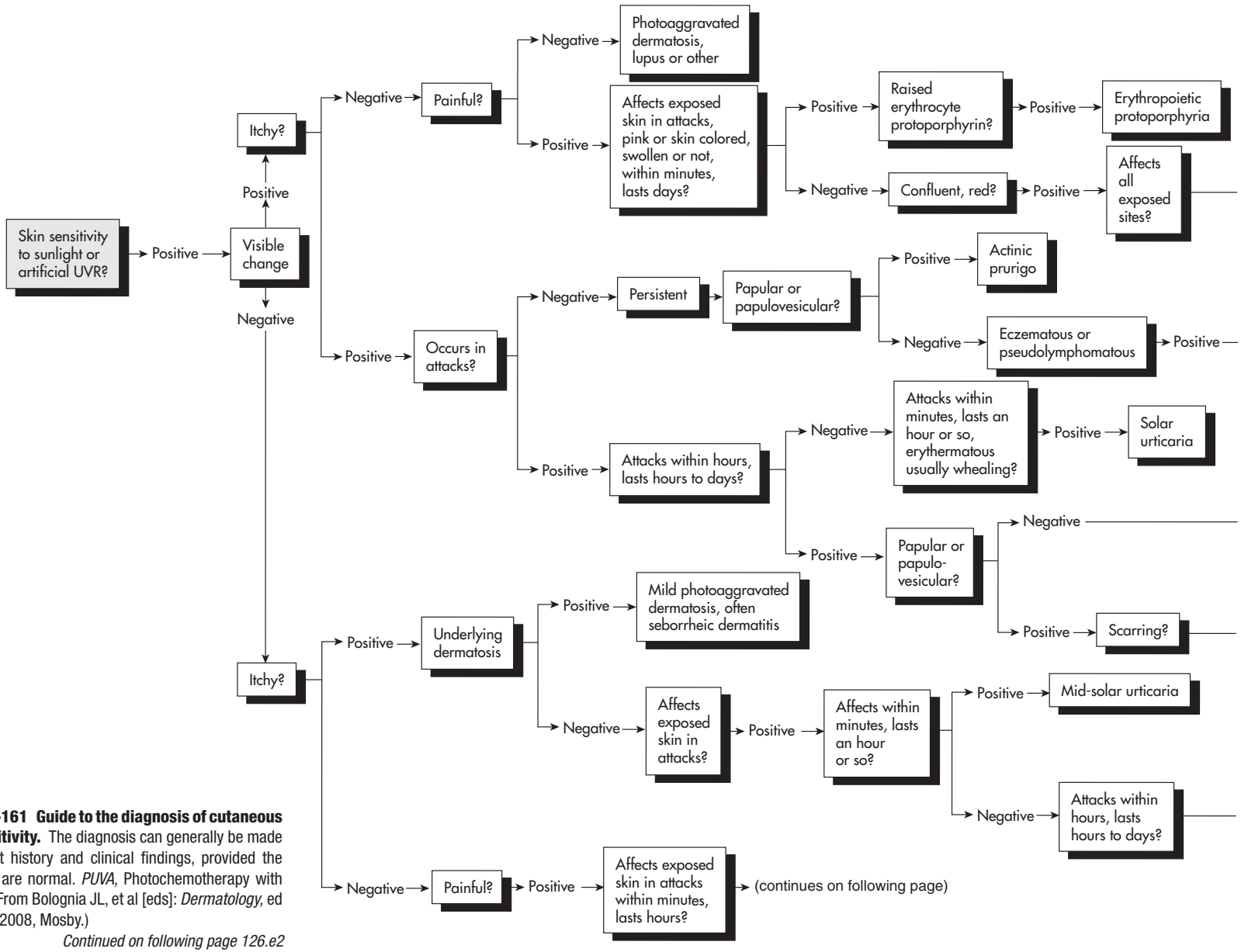


FIGURE E3-161 Guide to the diagnosis of cutaneous photosensitivity. The diagnosis can generally be made from patient history and clinical findings, provided the lupus titers are normal. *PUVA,* Photochemotherapy with psoralens. (From Bolognia JL, et al [eds]: *Dermatology,* ed 2, St Louis, 2008, Mosby.)

Continued on following page 126.e2

PHOTOSENSITIVITY—cont'd

ICD-9CM # 692.72
ICD-10CM # L56.0 Drug phototoxic response
L56.1 Drug photoallergic response
L56.2 Photocontact dermatitis [berloque dermatitis]

FIGURE E3-161 (Continued)

PHOTOSENSITIVITY—cont'd

ICD-9CM # 692.72
ICD-10CM # L56.0 Drug phototoxic response
L56.1 Drug photoallergic response
L56.2 Photocontact dermatitis [berloque dermatitis]

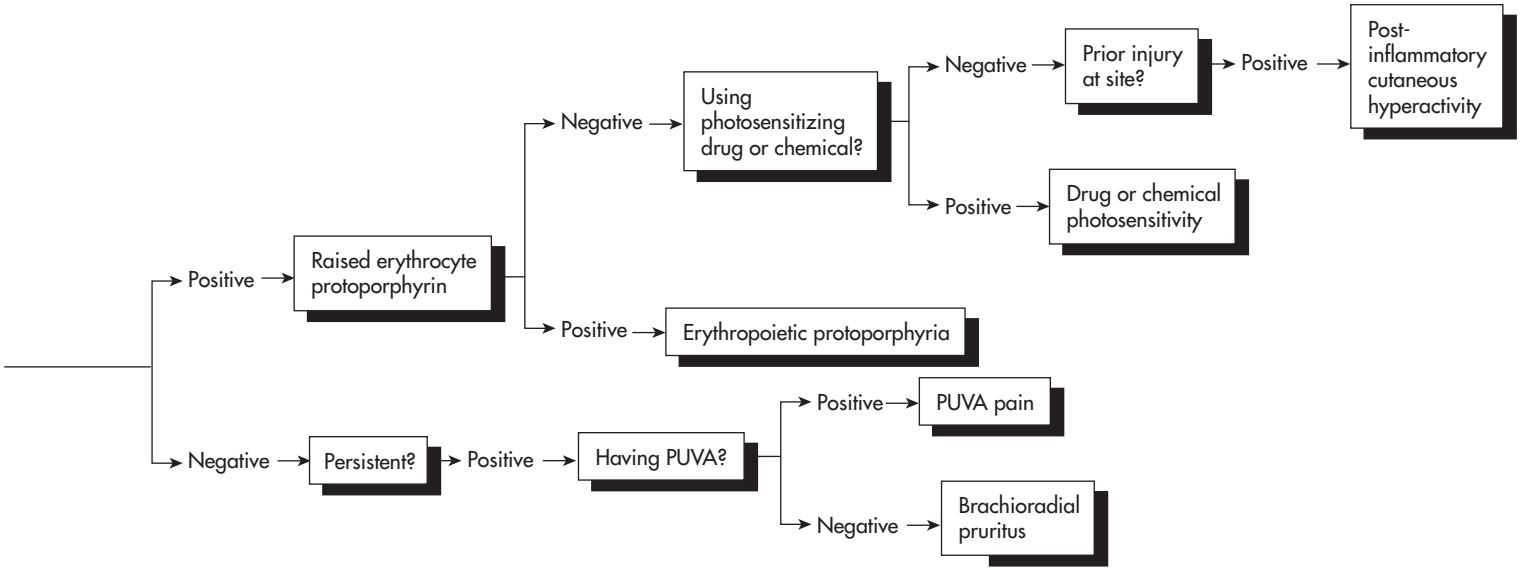


FIGURE E3-161 (Continued)

PITUITARY TUMOR

ICD-9CM # 253 Pituitary adenoma
253.0 Acromegaly
253.1 Prolactinoma
ICD-10CM # D44.3 Neoplasm of uncertain behavior of pituitary gland
E22.8 Other hyperfunction of pituitary gland
E22.0 Acromegaly and pituitary gigantism

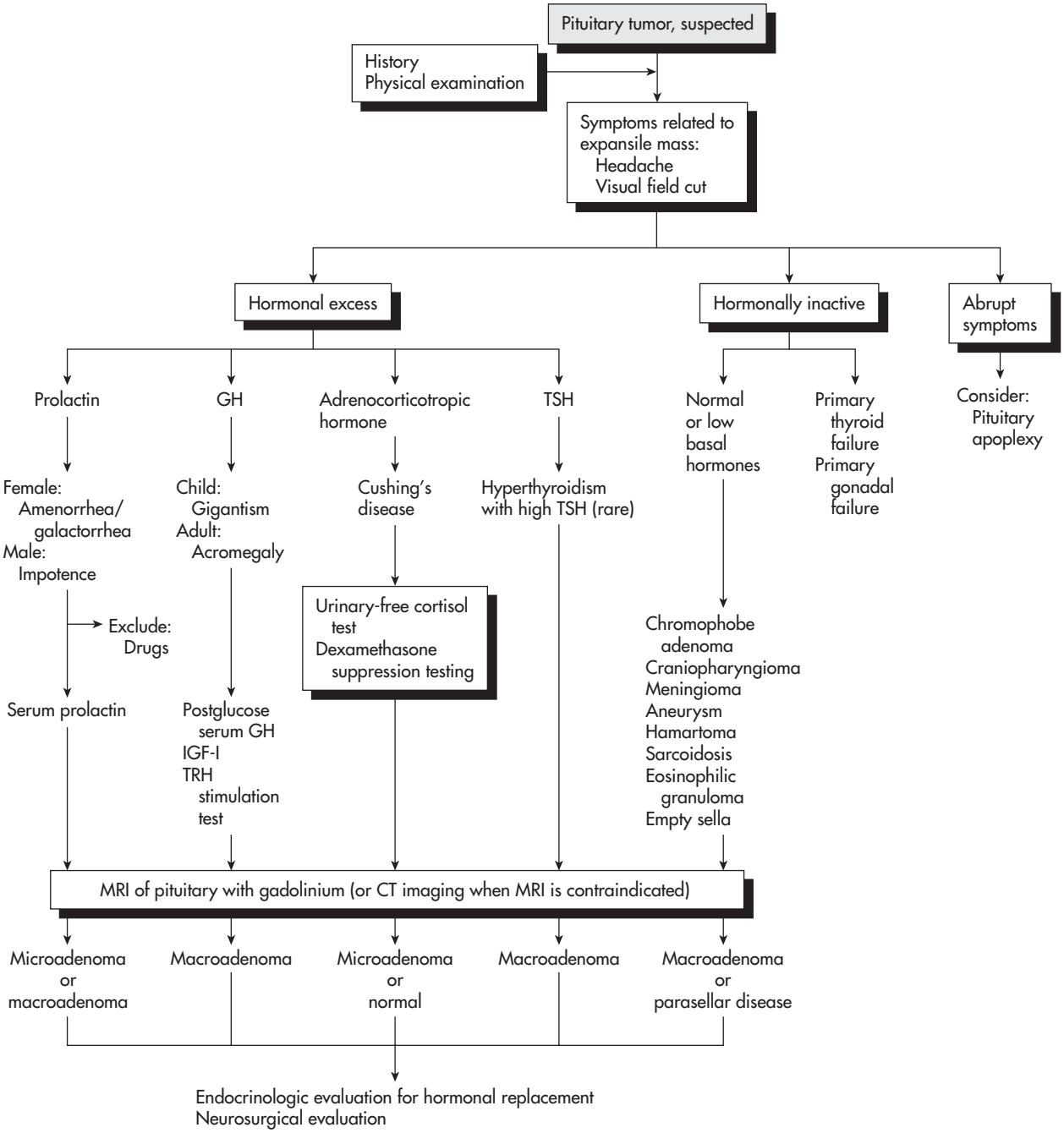


FIGURE 3-162 Evaluation of suspected pituitary tumor. *CT,* Computed tomography; *GH,* growth hormone; *IGF-I,* one of the insulin-like growth factors; *MRI,* magnetic resonance imaging; *TRH,* thyrotropin-releasing hormone; *TSH,* thyroid-stimulating hormone. (From Greene HL, Johnson WP, Lemcke DL: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

ICD-9CM # 197.2
ICD-10CM # C78.2 Secondary malignant neoplasm of pleura

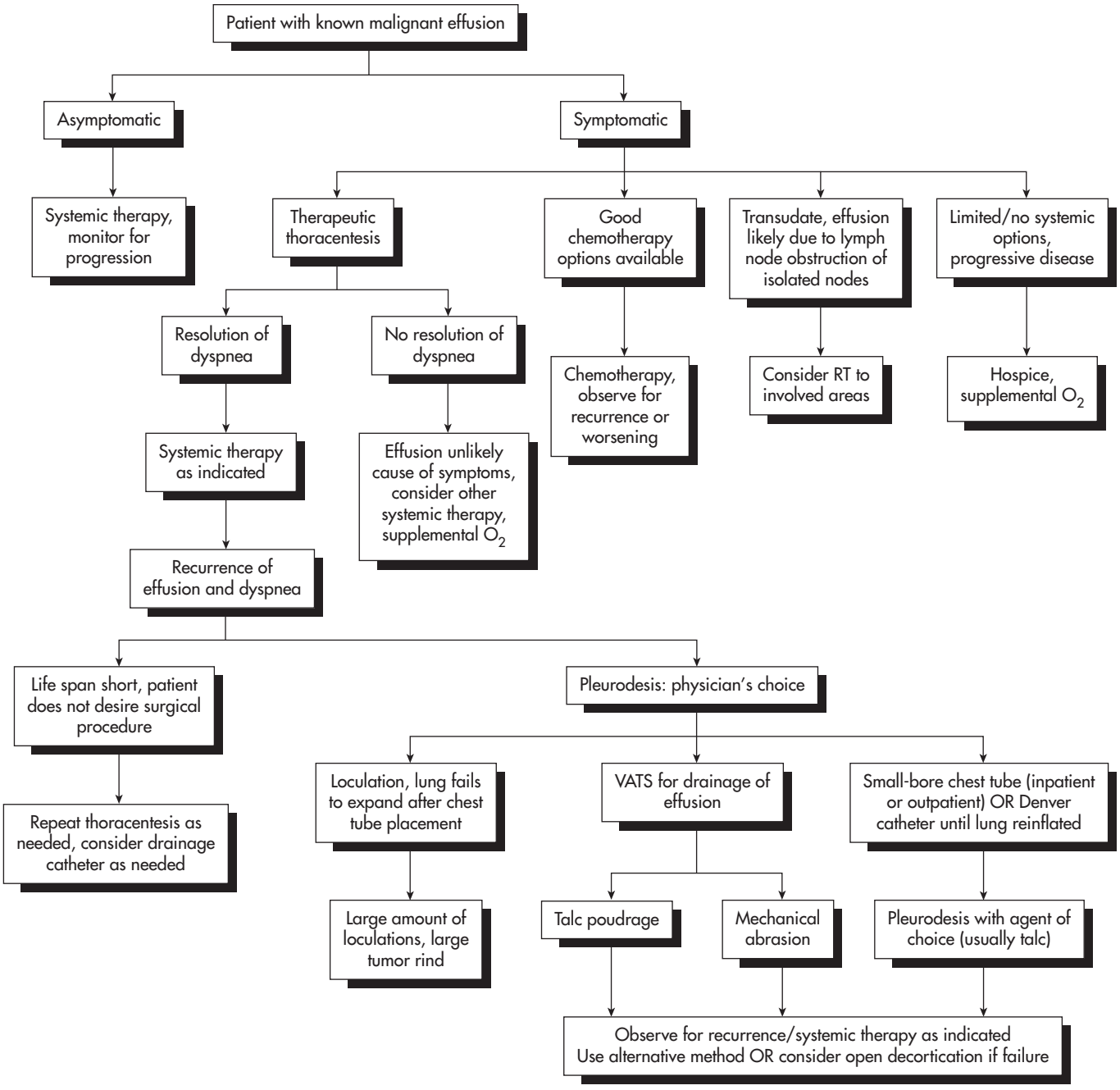


FIGURE E3-163 Treatment approach to patient with known malignant effusion. *RT,* Radiation therapy; *VATS,* video-assisted thoracic surgery. (From Abeloff MD: *Clinical oncology,* ed 3, Philadelphia, 2004, Saunders.)

ICD-9CM # 511.9 Pleural effusion, unspecified
ICD-10CM # J91.8 Pleural effusion in other conditions classified elsewhere

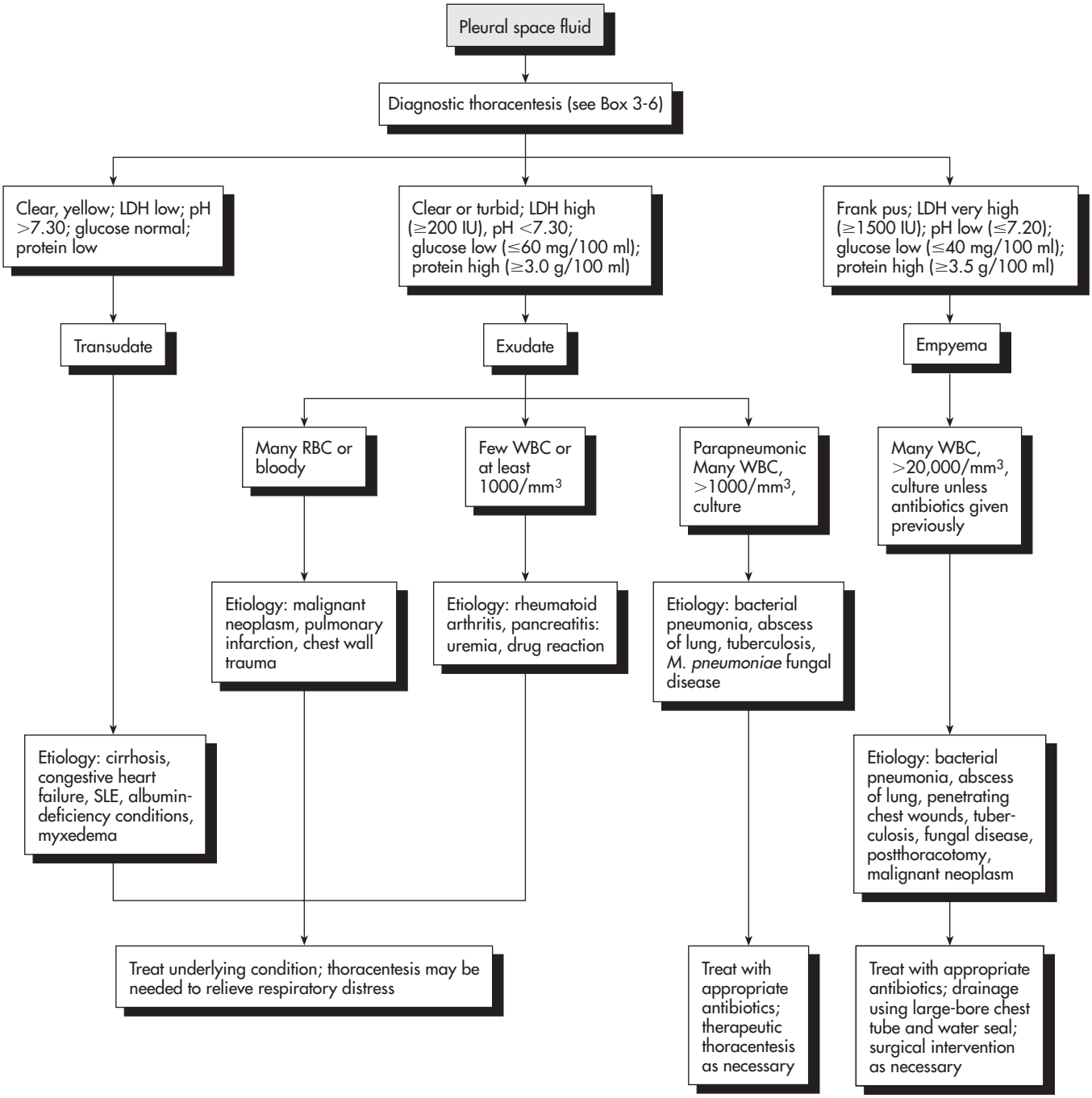


FIGURE 3-164 Evaluation, common etiologies, and management of pleural effusion and empyema.
LDH, Lactate dehydrogenase; *RBC,* red blood cells; *SLE,* systemic lupus erythematosus; *WBC,* white blood cells.
(From Kassirer J [ed]: *Current therapy in adult medicine,* ed 4, St Louis, 1998, Mosby.)

ICD-9CM # 511.9 Pleural effusion, unspecified
ICD-10CM # J91.8 Pleural effusion in other conditions classified elsewhere

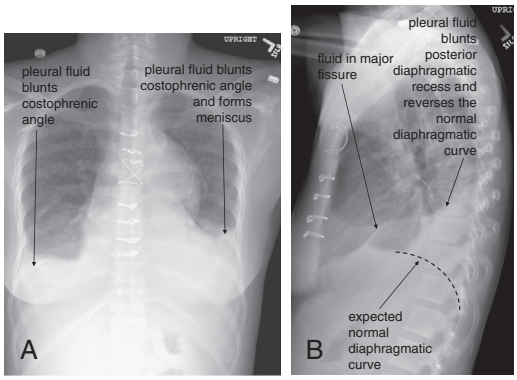


FIGURE 3-165 Pleural effusions: Posterior-anterior (PA) and lateral upright views. A, A PA upright view, where a pleural effusion is most evident on this patient's left side. Both costophrenic angles are blunted. The pleural effusion forms a meniscus against the left lateral chest wall. **B,** The lateral upright view shows two meniscus densities, suggesting bilateral pleural effusions. The posterior diaphragmatic recess is filled with pleural fluid, which forms a meniscus with the posterior chest wall. (From Broder JS: *Diagnostic imaging for the emergency physician*, Philadelphia, 2011, Saunders.)

BOX 3-6 Light Criteria for Classification of Pleural Effusions

In 1972, Light et al. developed the currently accepted benchmark for classifying pleural fluid, as follows:

- Pleural fluid protein-to-serum protein ratio >0.5:1
- Pleural fluid lactate dehydrogenase (LDH)-to-serum LDH ratio >0.6:1
- Pleural fluid LDH greater than two thirds the upper limit of normal for serum LDH (a cutoff value of 200 IU/L was used previously)

Pleural fluid is classified as an exudate if it meets any of the aforementioned criteria. Conversely, if all three characteristics are absent, the fluid is classified as a transudate. These researchers achieved a diagnostic sensitivity of 99% and a specificity of 98% for classification of an exudate.

From Adams JG, et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

BOX 3-7 Signs and Symptoms of Effusion*

- Dyspnea
- Cough (dry, nonproductive)
- Chest pain (pleuritic or nonpleuritic)
- Chest wall discomfort
- Decreased breath sounds
- Dullness to percussion
- Egophony, tactile fremitus
- Pleural friction rub

Disease-specific signs and symptoms may include:

- Orthopnea
- Paroxysmal nocturnal dyspnea
- Fever
- Night sweats

*A detailed past medical history may uncover the cause of the effusion.
From Adams JG, et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

BOX 3-8 Causes of Pleural Effusions

Transudates

- Atelectasis (early)
- Congestive heart failure
- Cirrhosis
- Glomerulonephritis
- Hypoalbuminemia
- Myxedema
- Nephrotic syndrome
- Peritoneal dialysis
- Pulmonary embolism
- Superior vena cava syndrome

Exudates

Infectious

- Bacterial infection
- Bronchiectasis
- Fungal infection
- Lung abscess
- Parasitic infection
- Traumatic hemothorax
- Tuberculosis
- Viral illness

Malignancies

- Lymphoma
- Mesothelioma
- Primary lung cancer
- Pulmonary metastasis

Connective Tissue Disease

- Rheumatoid arthritis
- Systemic lupus erythematosus

Abdominal/Gastrointestinal

- Esophageal rupture
- Pancreatic disorders
- Subphrenic abscess

Other

- Atelectasis (chronic)
- Chylothorax
- Drug reactions (amiodarone)
- Postpartum state
- Pulmonary infarction or embolism
- Uremia

From Adams JG, et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

ICD-9CM # 860
ICD-10CM # S27.0 Pneumothorax, traumatic

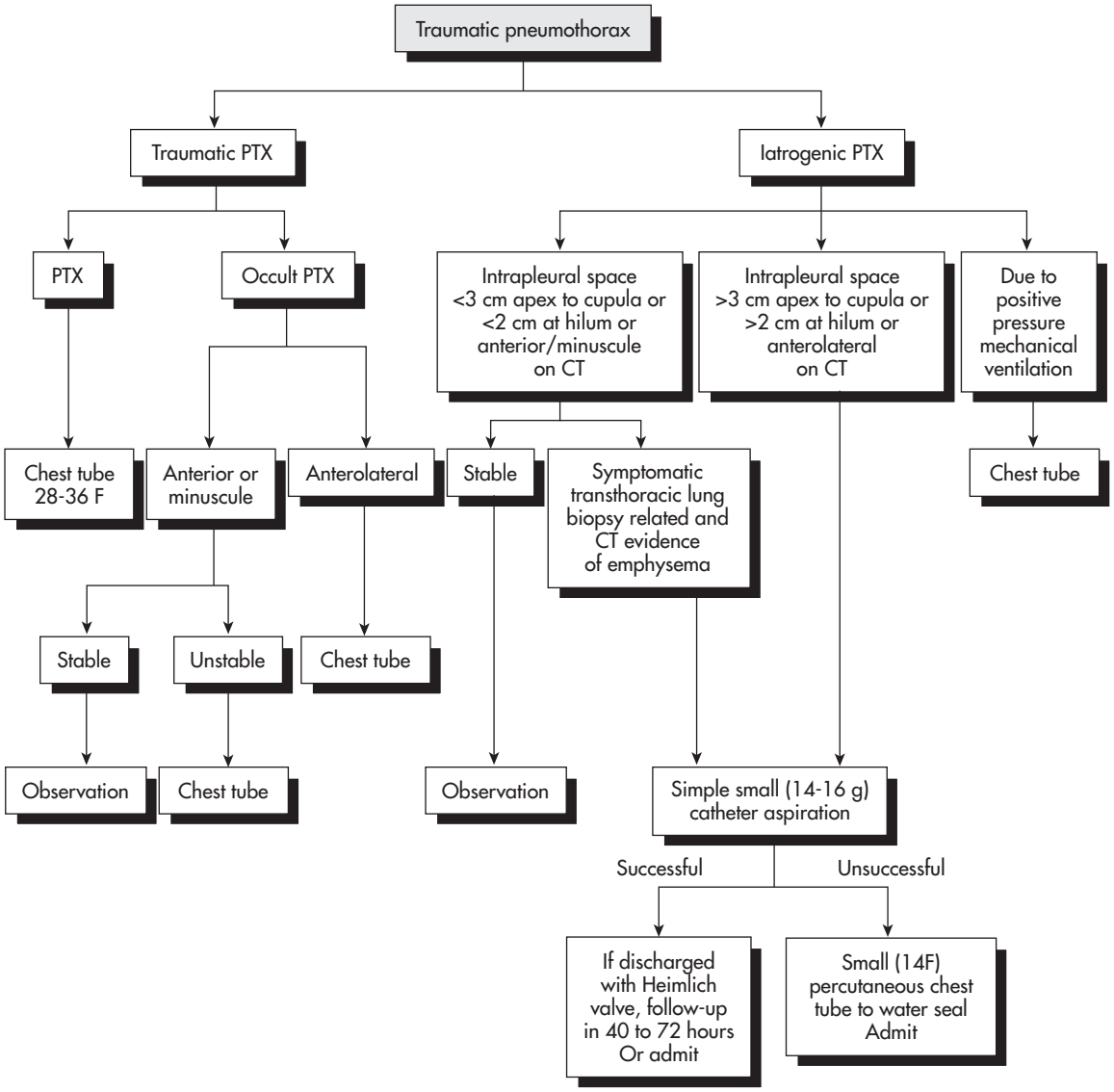


FIGURE 3-166 Algorithmic approach to the treatment of traumatic pneumothorax. *CT*, Computed tomography; *PTX*, pneumothorax. (From Adams JG, et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

ICD-9CM # V82.5 Chemical poisoning
E 865 Accidental poisoning from foodstuffs and poisonous plants
ICD-10CM # Z13.88 Encounter for screening for disorder due to exposure to contaminants
E865.8 Accidental poisoning from other specified foods

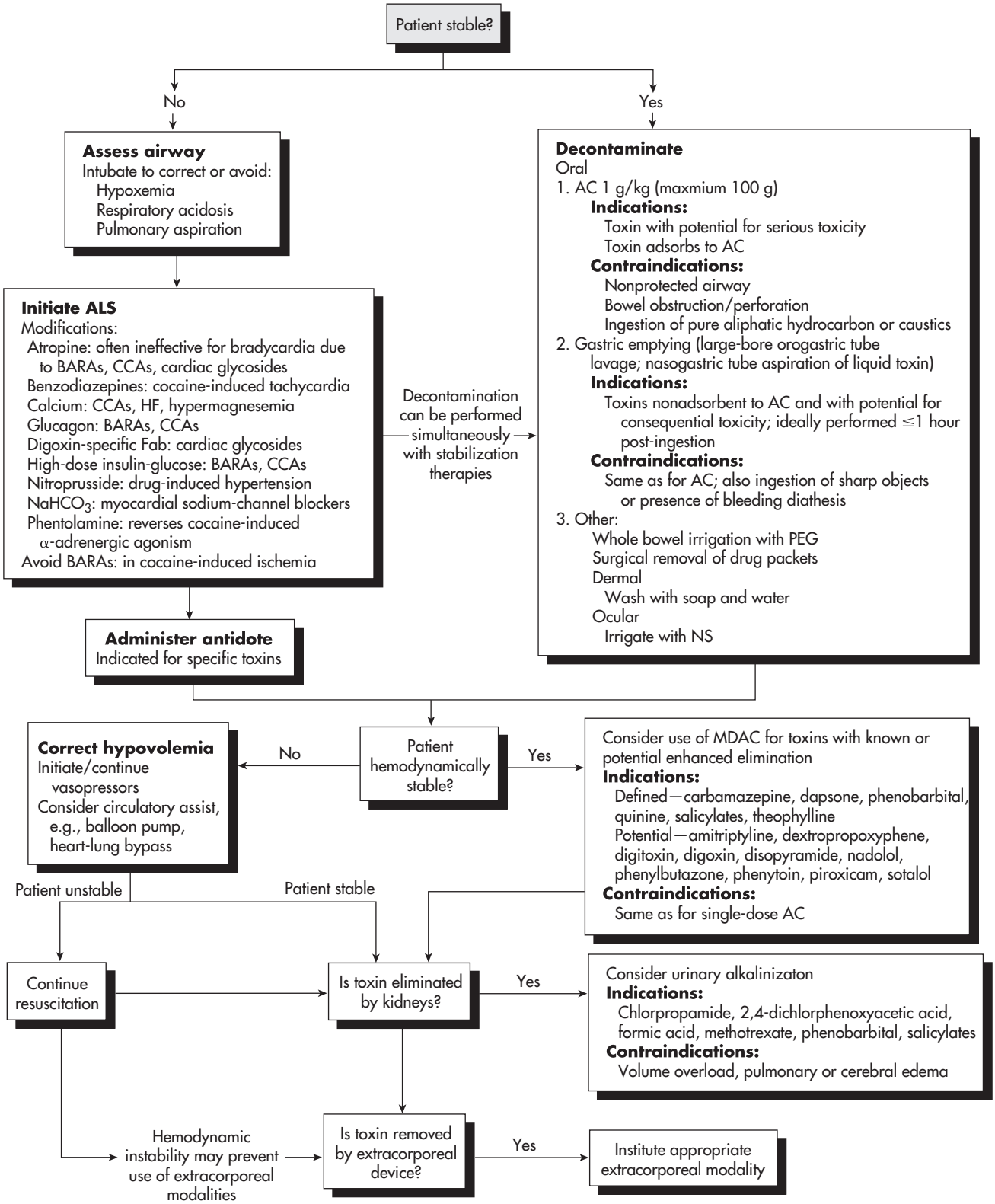


FIGURE 3-167 Algorithm for the management of acute poisoning. See also Table 3-25. *AC,* Activated charcoal; *ALS,* advanced life support; *BARAs,* β-adrenergic receptor antagonists; *CCAs,* L-type calcium-channel antagonists; *HF,* hydrofluoric acid; *MDAC,* multidose activated charcoal; *NS,* 0.9% saline solution; *PEG,* nonabsorbable polyethylene glycol solution. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

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TABLE 3-25 Pathophysiology, Clinical Effects, and Management of Specific Drugs and Toxicants

Drug or Toxicant	Pathophysiology	Clinical Effects	Laboratory	Specific Therapy
Acetaminophen	NAPQI (toxic metabolite) binds hepatic and renal tubular cells; acetaminophen itself induces transient decrease in functional factor VII	Initial: nausea, vomiting, coma, lactic acidosis in severe cases Days 1-3: elevated INR, aminotransferase, and bilirubin levels; RUQ tenderness; increased creatinine level in severe cases Days 4-14: gradual recovery or continued increase in INR and creatinine, lactic acidosis, coma, cerebral edema, death	Potentially toxic level ≥150 μg/ml 4 hr after ingestion* INR may be transiently elevated in first 24 hr because of decrease in functional factor VII; further increases indicate hepatic necrosis; elevated aminotransferase and bilirubin levels not predictive of hepatic failure Creatinine elevated in severe cases	NAC can increase INR but not aPTT†
Amphetamines	Increased release of presynaptic norepinephrine and dopamine Increased serotonin release (especially MDMA, PMA, DOB, other synthetic amphetamines)	Mild: euphoria, decreased appetite, repetitive behavior Moderate: vomiting, agitation, hypertension, tachycardia, mydriasis, bruxism, diaphoresis Severe: hypertension or hypotension, arrhythmias, hyperthermia, seizures, coma, hepatotoxicity, rhabdomyolysis, DIC, hyponatremia (SIADH), renal failure, cerebral infarction or hemorrhage	Not helpful; many false-positives and false-negatives on screening tests	IV crystalloids External cooling Benzodiazepines or barbiturates to control agitation or seizures Benzodiazepines or nitroprusside for hypertension See SSRIs/SRIs for features and treatment of serotonin syndrome
β-Adrenergic receptor antagonists	Blocks catecholamines from β-adrenergic receptors α- and β-adrenergic receptor antagonism: carvedilol, labetalol Delayed rectifier potassium-channel blockade: sotalol	Bradyarrhythmias, decreased myocardial contractility, hypotension, respiratory depression, decreased consciousness with seizures or coma (lipophilic agents, e.g., propranolol), prolonged QT interval (sotalol)	ECG No specific tests	IV glucagon, 3.5-5 mg over 2-min period; if no increase in BP or HR, can repeat up to 10 mg; if effective, immediately start continuous infusion at 2-10 mg/hr; if still unstable, options include (1) regular insulin, 1 U/kg by IV bolus, followed by 1 U/kg/hr, plus dextrose to maintain euglycemia; (2) norepinephrine or dobutamine infusion titrated to desirable BP and HR; (3) IV milrinone, 50 μg/kg over 10-min period, then 0.375-0.75 μg/kg/min based on hemodynamic status‡ Electrical pacing and IABP in refractory cases
L-type calcium-channel antagonists	Blocks L-type voltage-sensitive calcium channels, thereby decreasing calcium entry into myocardial and vascular smooth muscle cells Decreases pancreatic insulin release and increases insulin resistance	Bradyarrhythmias (verapamil, diltiazem), hypotension, hyperglycemia	ECG No specific tests	IV 10% calcium chloride, 10-20 mg/kg (0.1-0.2 ml/kg); can repeat once; if BP improves, continuous infusion at 0.2-0.5 ml/kg/hr (20-50 mg/kg/hr) Ionized Ca^{2+} levels should not exceed 2× normal (severe cases will be refractory to calcium therapy) Glucagon, high-dose insulin and dextrose, catecholamines, and milrinone (as for β-adrenergic antagonists)

*A nomogram to evaluate the potential toxicity of levels drawn more than 4 hours after ingestion is provided in Fig. 3-3, from Rumack BH, Matthew H: Acetaminophen poisoning and toxicity, *Pediatrics* 1975(55):871-876. The nomogram is valid only for levels drawn after a single acute ingestion.
†NAC can be discontinued in patients with uncomplicated disease after a loading dose plus six maintenance doses if hepatic aminotransferase levels are normal and acetaminophen is not detected; otherwise, the full regimen should be administered.
‡Adjust infusion for reduced renal function.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

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ICD-9CM # V82.5 Chemical poisoning
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TABLE 3-25 Pathophysiology, Clinical Effects, and Management of Specific Drugs and Toxicants—cont'd

Drug or Toxicant	Pathophysiology	Clinical Effects	Laboratory	Specific Therapy
Cardiac glycosides, including digoxin, bufadienolides (toxic toad venom), or cardenolides (e.g., oleander, lily of the valley, dogbane)	Inhibits Na^+, K^+-ATPase Decreased CNS sympathetic output Decreased baroreceptor sensitivity Increased vagal acetylcholine discharge	Bradyarrhythmias, including second- and third-degree AV block and asystole Ventricular ectopy, tachycardia, fibrillation Junctional tachycardia, paroxysmal atrial tachycardia with block Weakness, visual disturbances, nausea, vomiting	Serum digoxin level Serum potassium (hyperkalemia occurs in acute poisoning; hypokalemia may be present in chronic poisoning), magnesium, and creatinine levels	Correct hypokalemia and hypomagnesemia; do not give calcium Digoxin-specific antibody fragments (Fab) indicated if patient has hemodynamically significant arrhythmias, serum potassium ≥5 mg/L, Mobitz II or third-degree AV block, ingestion of bufadienolide- or cardenolide-containing agents, or renal insufficiency Empirical dose Chronic: 2-5 vials Acute: 10-20 vials Calculated dose Chronic: number of vials = 2 × serum digoxin level (ng/ml) × 5.6 × weight (kg)/1000 Acute: number of vials = 2 × oral digoxin dose (mg) × 0.8
Cyclic antidepressants	Myocardial sodium- and potassium-channel blockade Blockade of α-adrenergic and cholinergic muscarinic receptors Inhibition of norepinephrine re-uptake	Decreased level of consciousness (can develop rapidly), myoclonus, seizures, coma Anticholinergic toxidrome Sinus tachycardia, ventricular conduction delays, ventricular arrhythmias, asystole Hypotension	Serum levels not helpful in management	Intermittent IV boluses of $NaHCO_3$ (1 mEq/kg) to maintain arterial pH at 7.5 because acidemia can worsen cardiovascular complications Intubation and neuroparalytic drugs may be useful to ameliorate acidemia from muscular hyperactivity while seizures are being treated Contraindicated drugs: types IA and IC antiarrhythmic agents; physostigmine, flumazenil
Ethylene glycol, methanol (e.g., antifreeze, window cleaners, camping stove fuels)	Ethylene glycol: toxic metabolites produce cytotoxicity in CNS, kidneys, lungs, heart, liver, muscles; metabolic acidosis is due to glycolate accumulation; oxalate complexes with calcium, so hypocalcemia can develop Methanol: metabolized to formic acid, which is responsible for metabolic acidosis and inhibition of cytochrome aa_3; target organs include retina, optic nerve, CNS	Ethylene glycol: CNS depression, cerebral edema, seizures, anion gap metabolic acidosis, renal failure with acute tubular necrosis, pulmonary edema, myositis Methanol: nausea, vomiting; cerebral edema, hemorrhage, infarcts; necrosis of thalamus and putamen; anion gap metabolic acidosis; visual disturbances, papilledema, hyperemic optic disc, nonreactive pupils	Serum ethylene glycol and methanol levels; levels may be low or undetectable if significant metabolism has occurred Ethylene glycol: serum calcium, creatinine, BUN levels; examine urine for calcium oxalate crystals; false hyperlactatemia occurs with certain analyzers using L-lactate oxidase, which cross-reacts with glycolic and glyoxylic acids	For both: fomepizole (which inhibits alcohol dehydrogenase and blocks formation of toxic metabolites), 15 mg/kg IV loading dose, then 10 mg/kg IV for 4 doses during the next 48 hr, then 15 mg/kg for subsequent doses; interval dosing is q12h (q4h during hemodialysis, with dosing interval adjustments at start and finish); continue until ethylene glycol or methanol is no longer detectable Use of ethanol is no longer recommended Hemodialysis: initiate if level is ≥50 mg/dl or metabolic acidosis with end-organ toxicity; continue until acidosis resolves and serum level of ethylene glycol or methanol is undetectable Monitor for cerebral edema with possible herniation Ethylene glycol: IV calcium for symptomatic hypocalcemia Methanol: folinic acid, 50 mg IV q4h until methanol not detectable and acidosis cleared

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ICD-9CM # V82.5 Chemical poisoning
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ICD-10CM # Z13.88 Encounter for screening for disorder due to exposure to contaminants
E865.8 Accidental poisoning from other specified foods

TABLE 3-25 Pathophysiology, Clinical Effects, and Management of Specific Drugs and Toxicants—cont'd

Drug or Toxicant	Pathophysiology	Clinical Effects	Laboratory	Specific Therapy
γ-Hydroxybutyrate (GHB) and its precursors (γ-butyrolactone and 1,4-butanediol [1,4-BD])	Agonist effect on CNS GHB receptors; indirect action with opioid receptors (may increase proenkephalins); metabolized to GABA, interacts with $GABA_B$ receptors; decreases dopamine release	CNS: rapid loss of consciousness, with recovery typical within 2-4 hr; myoclonus (possible seizures) Respiratory depression; bradycardia; nausea, vomiting	No specific tests	Supportive care, including respiratory support as needed Withdrawal resembles sedative-hypnotic withdrawal and can be treated with benzodiazepines or pentobarbital
Lithium	Decreases brain inositol; alters CNS serotonin, dopamine, and norepinephrine; inhibits adenylate cyclases, including those that mediate vasopressin-induced renal concentration and thyroid function	Chronic toxicity usually more severe than acute toxicity: tremor, hyperreflexia, drowsiness, incoordination, clonus, confusion, ataxia; in severe cases, seizures, coma, death; recovery may take weeks, and CNS deficits may persist Sinus node dysfunction, QT prolongation, T wave abnormalities, U waves Nephrogenic diabetes insipidus, hypothyroidism, hyperthyroidism, hypercalcemia, pseudotumor cerebri Acute toxicity: nausea, vomiting, diarrhea, and milder neurologic findings	Peak serum levels: Normal dose 2-3 hr; up to 5 hr for sustained-release lithium Acute overdose: peak may be delayed ≥4-12 hr	Replenish intravascular volume, maintain urinary output at 1-2 ml/kg/hr Consider GI decontamination with oral polyethylene glycol electrolyte solution within 1-2 hr after acute overdose of sustained-release drug Hemodialysis[§] in patients with altered mental status, ataxia, seizures, or coma or in patients with mild symptoms in the setting of acute overdose or renal insufficiency Ineffective or contraindicated therapies include oral activated charcoal, diuretics, and aminophylline
Opioids (e.g., heroin, morphine, oxycodone, fentanyl)	Agonist effect at CNS μ, κ, and δ opioid receptors; result is cell hyperpolarization and decreased neurotransmitter release	CNS depression, respiratory depression, miosis Dextromethorphan increases CNS serotonin and inhibits NMDA receptors, which causes hallucinations Propoxyphene and its metabolite norpropoxyphene block sodium channels and can cause seizures and wide-complex arrhythmias similar to cyclic antidepressants; $NaHCO_3$ treats arrhythmias Seizure risk with tramadol, meperidine, propoxyphene Rapid, powerful heroin-like effect when sustained-release oxycodone is crushed before ingestion, snorting, or smoking QTc prolongation and torsades de pointes with methadone	Rapid urine drug screens detect morphine and codeine but may not detect semisynthetic and synthetic opioids; some interferents/irrelevants	IV naloxone, 0.4-2 mg; can repeat up to 10 mg if no response Continuous infusion for recurrent symptoms or sustained-release opioid ingestion; give 50% of dose that produces desired effect 15 min after initial effect is obtained, then infuse two thirds of this dose every hr; infusion rate can be increased or decreased to maintain normal respiration and avoid withdrawal symptoms Contraindicated therapies: nalmefene and naltrexone should not be used for acute opioid reversal

[§]Continue hemodialysis until the serum lithium level is less than 1 mEq/L. Recheck the level 8 hr after dialysis, and restart hemodialysis if the level is higher than 1 mEq/L. Repeat this cycle until the serum lithium level remains lower than 1 mEq/L.
[‖]A double-blind, randomized, placebo-controlled trial of pralidoxime in acute organophosphorus poisoning found no significant difference in mortality rates or need for intubation.

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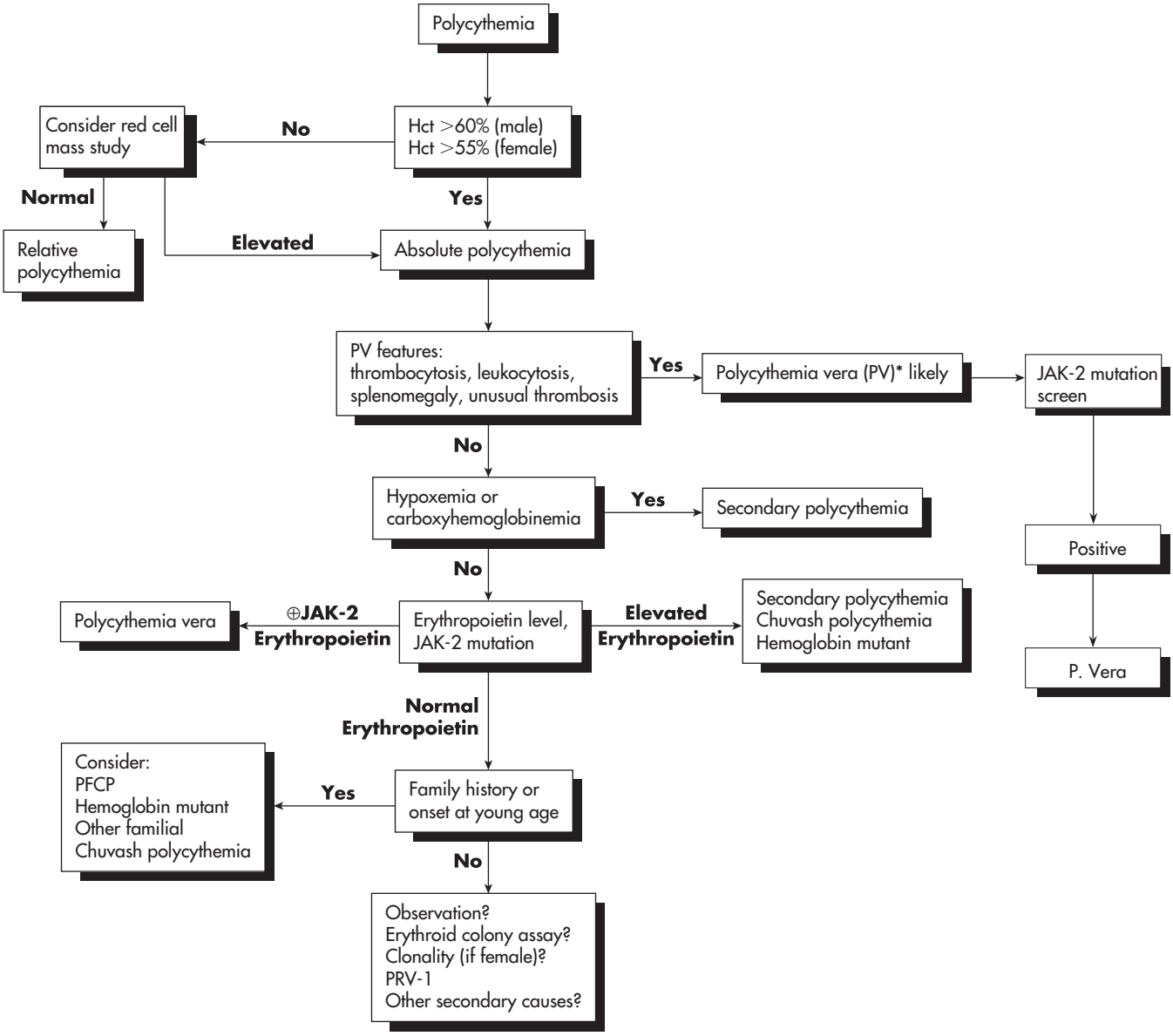
E865.8 Accidental poisoning from other specified foods

TABLE 3-25 Pathophysiology, Clinical Effects, and Management of Specific Drugs and Toxicants—cont'd

Drug or Toxicant	Pathophysiology	Clinical Effects	Laboratory	Specific Therapy
Organophosphorus compounds and carbamates (e.g., diazinon, mevinphos, fenthion, aldicarb)	Inhibits acetylcholinesterase, resulting in excessive acetylcholine stimulation of nicotinic and muscarinic receptors in autonomic and somatic motor nervous systems and CNS	Nicotinic-mediated effects: tachycardia, mydriasis, hypertension, delirium, coma, seizures, muscle weakness, fasciculations Muscarinic-mediated effects: salivation, lacrimation, urination, vomiting, defecation, miosis, bronchorrhea, bronchospasm, bradycardia	Serum (butyrylcholinesterase) or RBC (acetylcholinesterase) activity <50% of normal Clinical recovery occurs before serum cholinesterase levels normalize	Atropine, 1-2 mg by initial IV bolus; double the dose every 5 min (2 mg, 4 mg, 8 mg, 16 mg, etc.) until drying of bronchial secretions, adequate oxygenation, pulse >80 bpm, systolic blood pressure >80 mm Hg achieved; continuous infusion at 10%-20% of total stabilizing dose per hr; stop infusion if patient develops any signs or symptoms of anticholinergic toxidrome; restart infusion at lower rate when signs or symptoms abate Pralidoximeǁ chloride 30 mg/kg (maximum 2 g) IV bolus over 30 min, then 8-10 mg/kg/hr (maximum 650 mg/hr) continuous infusion; administer as soon as possible after poisoning; continue 12-24 hr after atropine no longer required and symptoms resolve
Salicylates	Inhibits cyclooxygenase; decreases formation of prostaglandins and thromboxane A_2; stimulates CNS medullary respiratory receptor and chemoreceptor trigger zone; impairs platelet function; disrupts carbohydrate metabolism; uncouples oxidative phosphorylation; increases vascular permeability	Acute toxicity Mild: nausea, vomiting, diaphoresis, tinnitus, decreased hearing, hyperpnea, tachypnea Moderate–severe: confusion, delirium, coma, seizures, hyperthermia, ALI; death can occur within hours of overdose Chronic toxicity: same as acute, but may not have diaphoresis or vomiting Consider diagnosis in patients with new-onset confusion, anion gap metabolic acidosis, or ALI	Serum salicylate level: toxic ≥30 mg/dl; level ≥100 mg/dL indicates life-threatening toxicity with possible sudden, rapid clinical deterioration; in chronic toxicity, levels may be minimally elevated (>30 mg/dl), and clinical evaluation is more reliable for gauging degree of toxicity Arterial blood gases: respiratory alkalosis with metabolic acidosis Anion gap metabolic acidosis Prolonged PT and PTT, ketonuria, ketonemia	Multidose activated charcoal q2-3h in acute overdose with progressive symptoms or rising salicylate level
SSRIs/SRIs	Inhibits re-uptake of serotonin SRIs have additional effects (e.g., duloxetine inhibits norepinephrine re-uptake, nefazodone inhibits serotonergic 5-HT2 receptors, trazodone inhibits peripheral α-adrenergic receptors, venlafaxine inhibits norepinephrine and dopamine re-uptake)	Vomiting, blurred vision, CNS depression, tachycardia Seizures and coma rare Torsades de pointes reported with citalopram Serotonin syndrome: clonus, agitation, tremor, diaphoresis, hyperreflexia; hyperthermia and hypertonicity in severe cases	No specific tests If serotonin syndrome suspected: electrolytes, BUN, glucose, liver enzymes, coagulation panel, blood gases, chest radiograph	Respiratory support as needed Benzodiazepines for agitation or seizures Serotonin syndrome: consider cyproheptadine, 12 mg PO initial dose then 2 mg PO q2h (to a maximum of 32 mg/day) until symptoms resolve Critical care therapies for hyperthermia, rhabdomyolysis, DIC, ARDS, renal and hepatic dysfunction, torsades de pointes

ALI, Acute lung injury; *aPTT,* activated partial thromboplastin time; *ARDS,* acute respiratory distress syndrome; *AV,* atrioventricular; *BP,* blood pressure; *bpm,* beats per minute; *BUN,* blood urea nitrogen; *CNS,* central nervous system; *DIC,* disseminated intravascular coagulation; *DOB,* 4-bromo-2,5-dimethoxyamphetamine; *ECG,* electrocardiogram; *GABA,* α-aminobutyric acid; *GI,* gastrointestinal; *HR,* heart rate; *IABP,* intra-aortic balloon counterpulsation; *INR,* international normalized ratio; *IV,* intravenous; *MDMA,* 3,4-methylenedioxymethamphetamine; *Na^1,K^1-ATPase,* sodium, potassium adenosine triphosphatase; *NAC,* N-acetylcysteine; *NAPQI,* N-acetyl-p-benzoquinone imine; *NMDA,* N-methyl-d-aspartate; *PMA,* paramethoxyamphetamine; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *RBC,* red blood cell; *RUQ,* upper right quadrant (abdomen); *SIADH,* syndrome of inappropriate antidiuretic secretion; *SRI,* serotonin re-uptake inhibitor; *SSRI,* selective serotonin re-uptake inhibitor.



*Note: Refer to Section I for additional information on this topic.

FIGURE E3-168 Diagnostic algorithm for polycythemia. *JAK-2 mutation*, JAK2V617F; *PFCP,* primary familial and congenital polycythemia; *PRV-1,* polycythemia rubra vera 1; *P. Vera,* polycythemia vera. (Modified from Young NS, Gerson SL, High KA [eds]: *Clinical hematology,* St Louis, 2006, Mosby.)

ICD-9CM # 791.0
ICD-10CM # R80.9 Proteinuria, unspecified

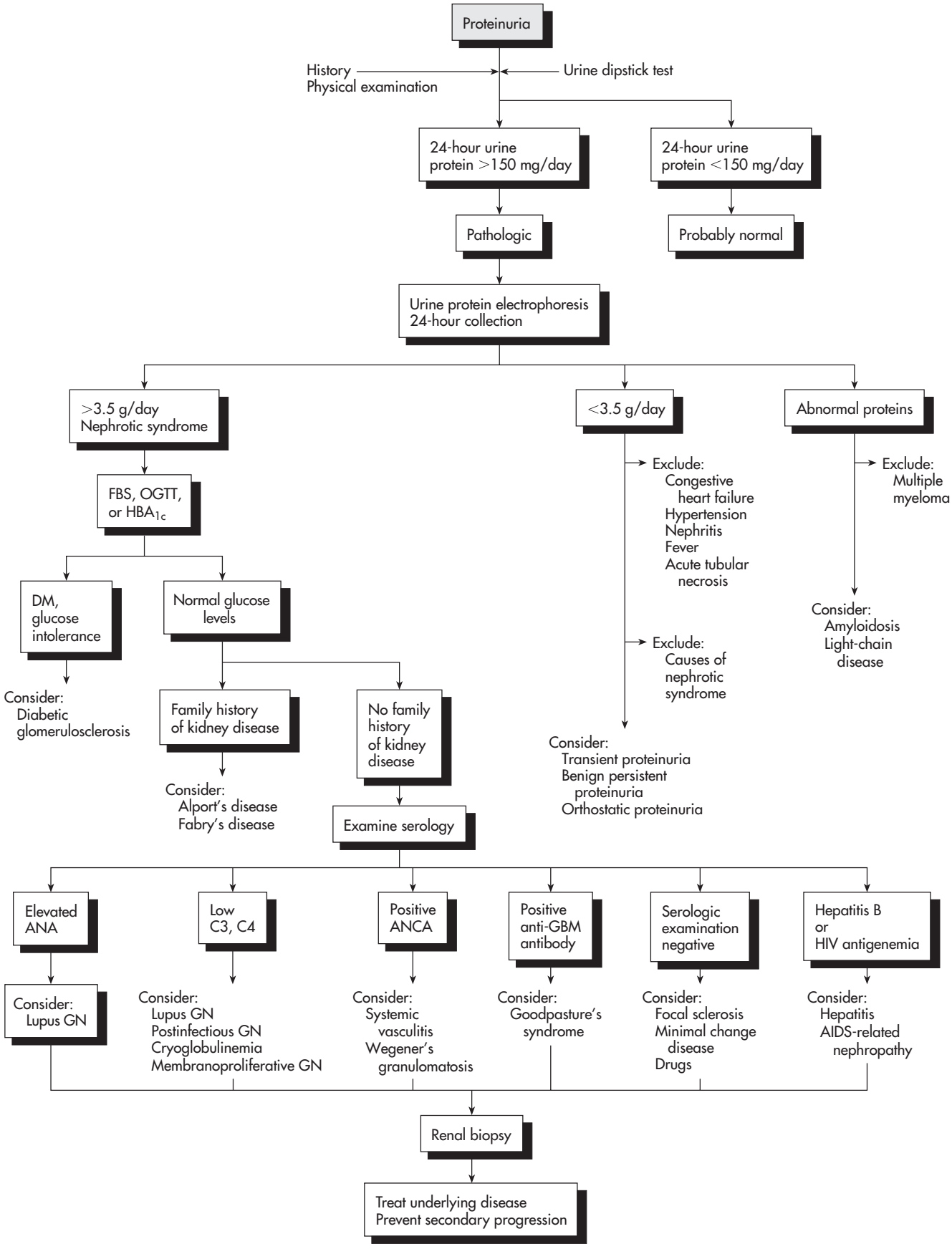


FIGURE 3-169 Proteinuria. *AIDS,* Acquired immunodeficiency syndrome; *ANA,* antinuclear antibody; *ANCA,* antineutrophil cytoplasmic autoantibody; *anti-GBM,* anti-glomerular basement membrane; *FBS,* fasting blood sugar; *GN,* glomerulonephritis; *OGTT,* oral glucose tolerance test. (Modified from Greene HL, Johnson WP, Lemcke DL [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

ICD-9CM # 698.9 Pruritus NOS
ICD-10CM # L29.9 Pruritus, unspecified

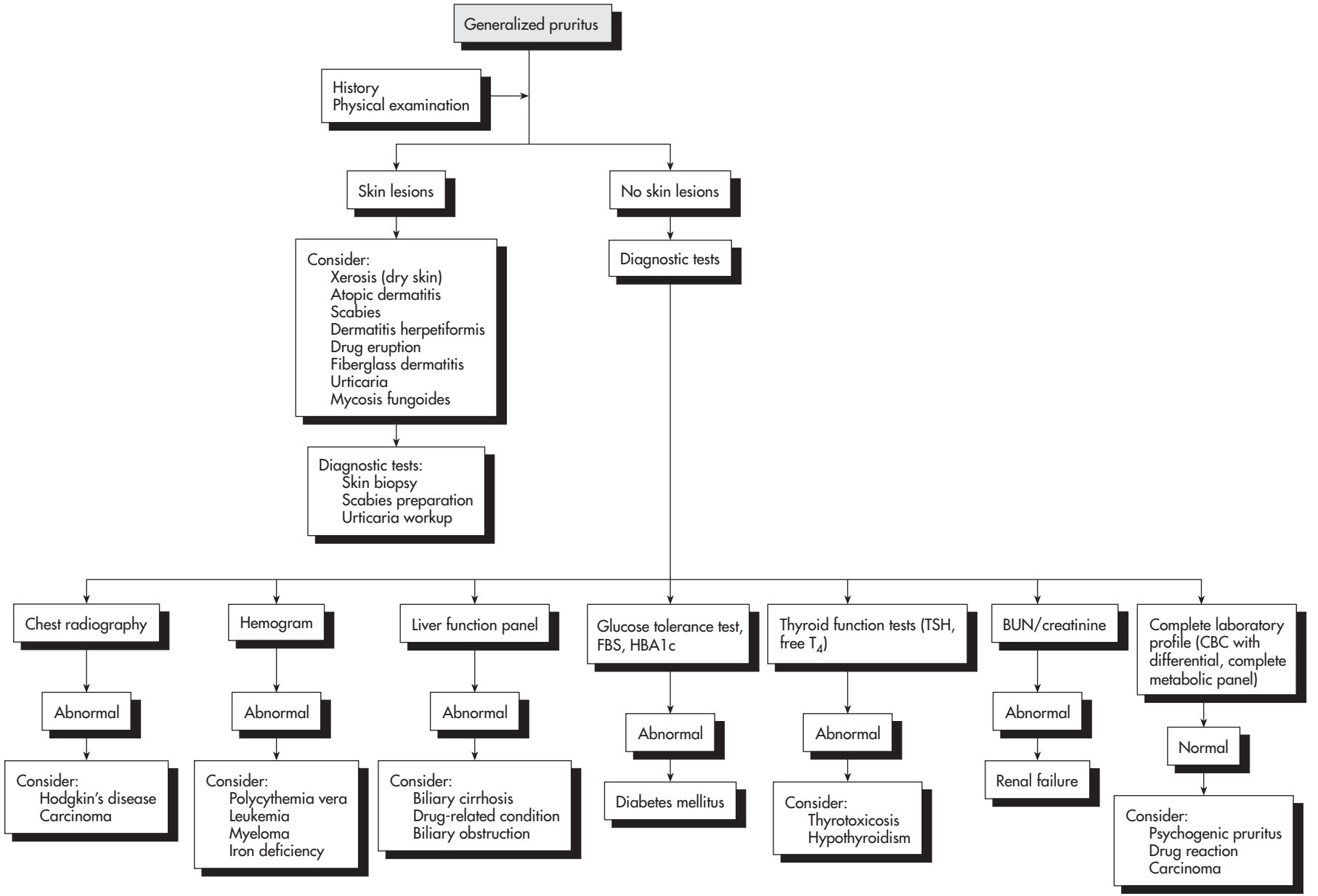


FIGURE 3-170 Evaluation of generalized pruritus. *BUN,* Blood urea nitrogen; *CBC,* complete blood count; *FBS,* fasting blood sugar; *HBA1c,* hemoglobin A1c; *T_4,* thyroxine; *TSH,* thyroid-stimulating hormone. (From Greene HL, Johnson WP, Lemcke DL [eds]: *Decision making in medicine*, ed 2, St Louis, 1998, Mosby.)

ICD-9CM # 698.9
ICD-10CM # L29.9 Pruritus, unspecified

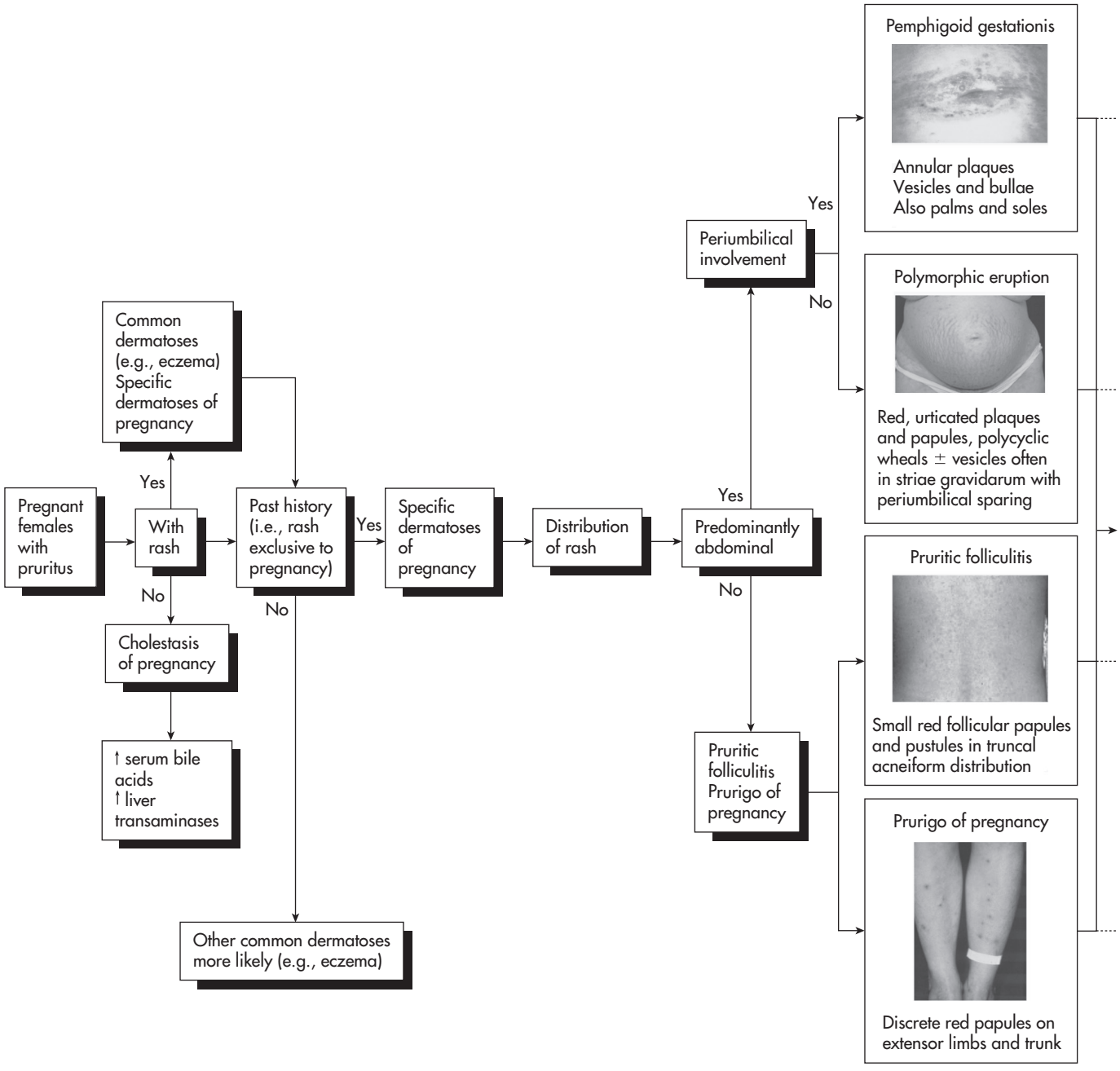


FIGURE E3-171 An algorithmic approach to the pregnant woman presenting with pruritus.
(From Black M, McKay M: *Obstetrics and gynecological dermatology,* ed 2, St Louis, 2002, Mosby.)

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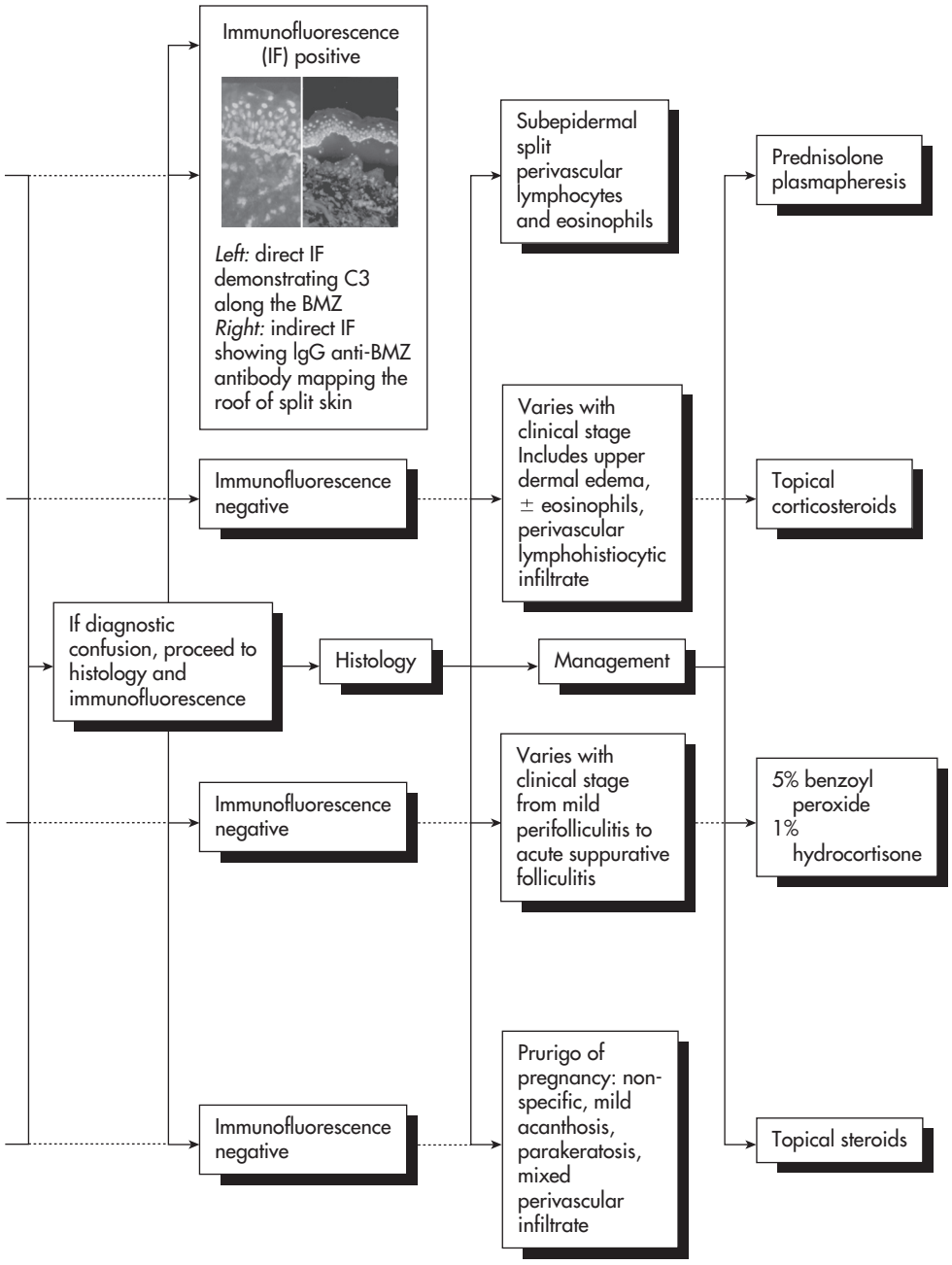
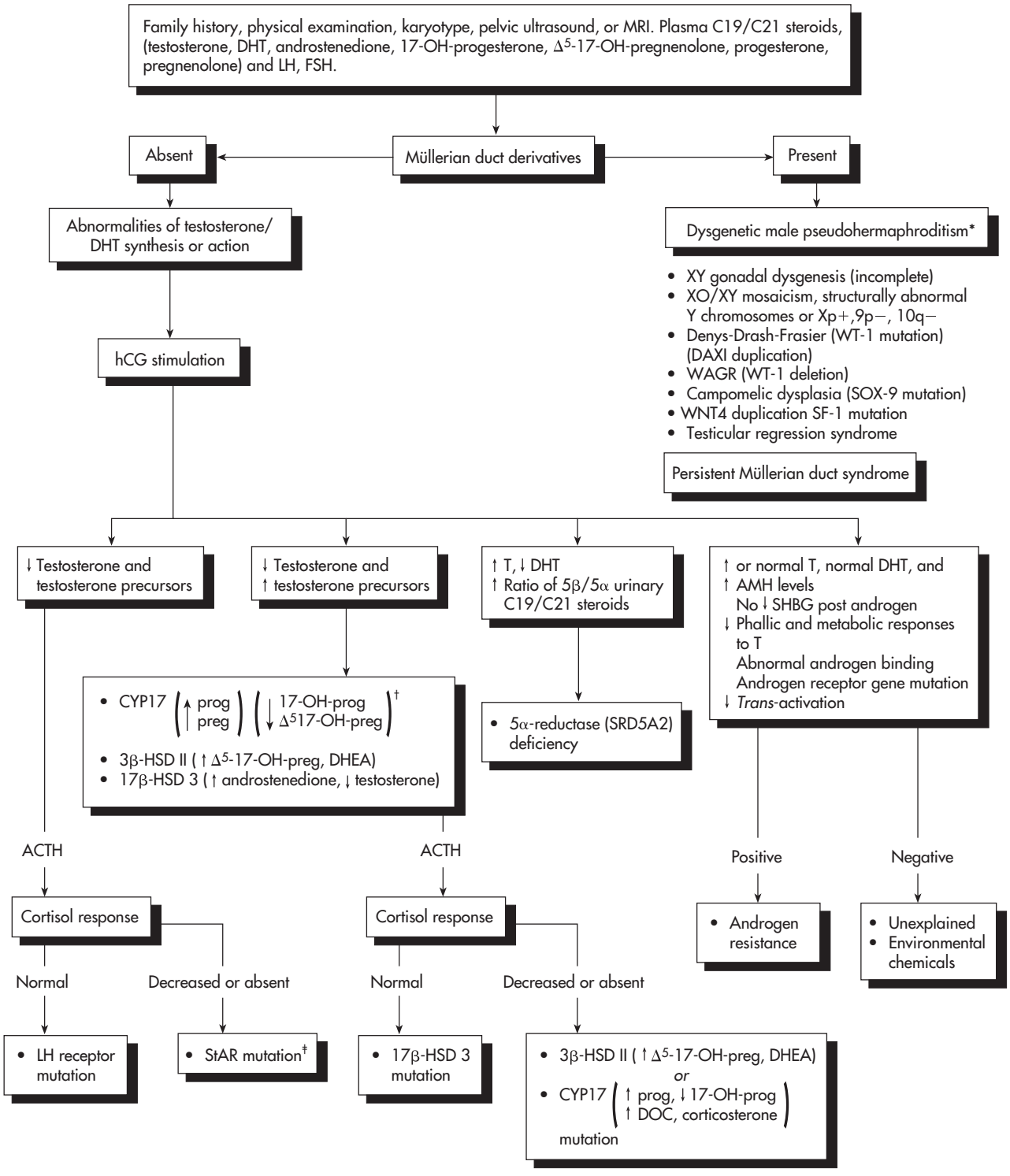


FIGURE E3-171 (Continued)

ICD-9CM # 752.7
ICD-10CM # Q56.3 Pseudohermaphroditism, unspecified
Q56.4 Indeterminate sex, unspecified



*Patients with dysgenetic male pseudohermaphroditism may manifest varying degrees of testicular dysgenesis with either complete or partial testosterone/DHT and/or AMH deficiency. Therefore, not all patients may manifest either ambiguous genitalia or the presence of Müllerian ducts. †CYP17 (P450??) catalyzes the 17-hydroxylation of progesterone and pregnenolone to 17-hydroxyprogesterone and Δ5-17-hydroxypregnenolone as well as the scission (lyase) of 17-hydroxypregnenolone to DHEA. Patients with 17, 20- lyase deficiency have elevated levels of 17-hydroxyprogesterone and Δ5-17-hydroxypregnenolone in relation to andro-stenedione and DHEA whether before or after hCG stimulation. ‡The StAR (steroidogenic acute regulatory) protein is involved in the transport of cholesterol from the outer to the inner mitochondrial membrane where the enzyme CYP11A1(P450??) resides. Patients with a mutation in the gene for this protein have a markedly diminished ability to convert cholesterol to Δ5-pregnenolone, although their CYP11A1 enzymatic activity is intact. They manifest congenital lipoid adrenal hyperplasia.

FIGURE E3-172 Steps in the differential diagnosis of male pseudohermaphroditism. *3β-HSD II,* 3β-hydroxysteroid dehydrogenase/Δ5-isomerase; *17β-HSD 3,* 17β-hydroxysteroid dehydrogenase (oxido-reductase) type 3; *ACTH,* adrenocorticotropic hormone; *AMH,* antimüllerian hormone; *CYP17,* 17α-hydroxylase/17,20-lyase; *DHEA,* dehydroepiandrosterone; *DHT,* dihydrotestosterone; *FSH,* follicle-stimulating hormone; *LH,* luteinizing hormone; *MRI,* magnetic resonance imaging; *SHBG,* sex hormone-binding globulin; *SF1,* steroidogenic factor-1; *T,* testosterone; *WAGR,* Wilms tumor, aniridia, genital anomalies, and mental retardation. (From Larsen PR, Kronenberg HM, Memlmed S, Polansky KS: *Williams textbook of endocrinology,* ed 11, Philadelphia, 2008, Saunders.)

ICD-9CM # 793.11 Coin lesion of lung
ICD-10CM # R91 Coin lesion lung

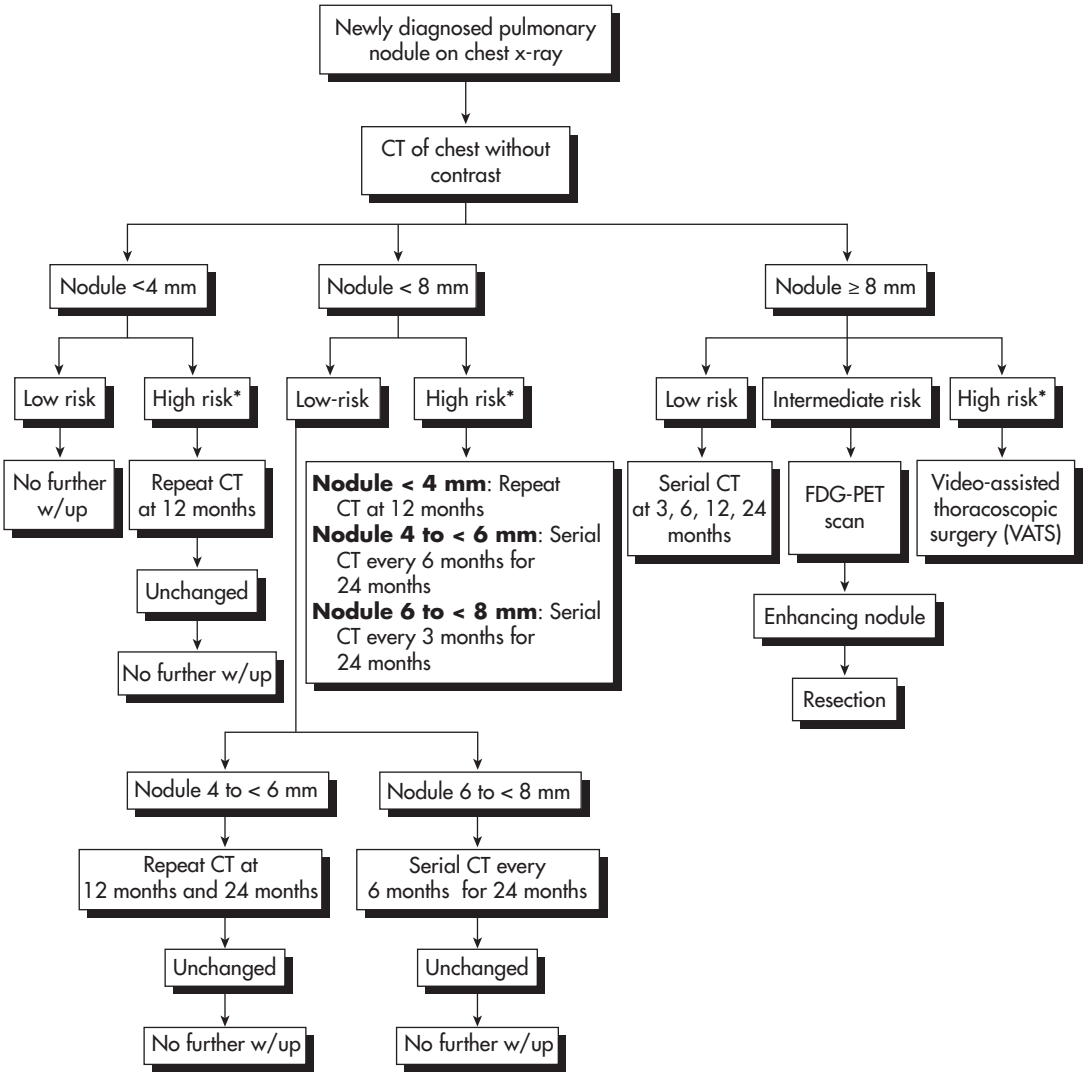


FIGURE 3-173 Diagnostic algorithm. *High risk: history of smoking, history of malignancy, age > 40. (From Ferri, F: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 3, Philadelphia, 2014, Saunders.)

Diagnostic Imaging
Best Test(s)
- CT of chest without contrast

Ancillary Tests
- PET scan

Lab Evaluation
Best Test(s)
- Needle biopsy of nodule

Ancillary Tests
- None

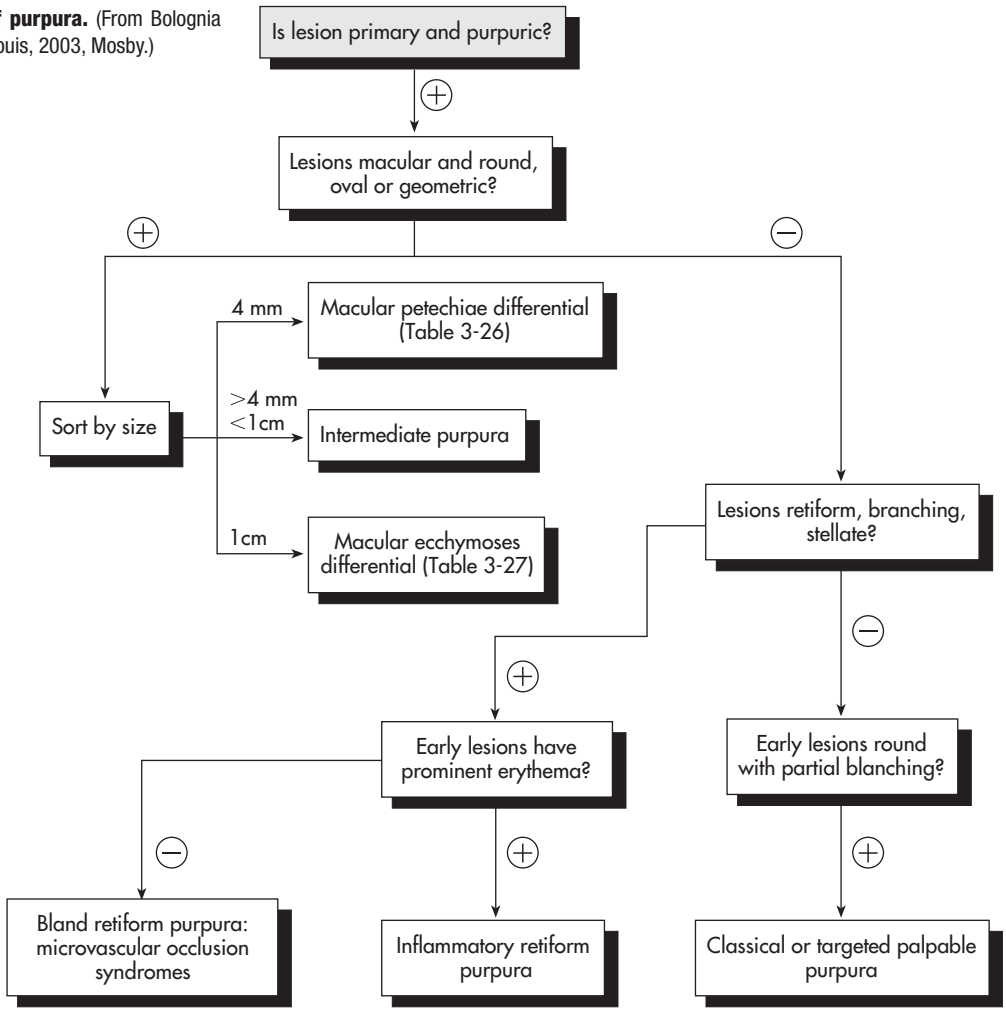


FIGURE 3-174 Differential diagnosis of purpura. (From Bolognia JL, Jorizzo JL, Rapini RP: *Dermatology,* St Louis, 2003, Mosby.)

TABLE 3-26 Differential Diagnosis of Petechial Hemorrhage—Non-Palpable, Non-Retiform and ≤4 mm in Diameter

Pathophysiology: Hemostatically Relevant Thrombocytopenia (<550,000/mm^3) **

Major etiologies*

1. Idiopathic thrombocytopenic purpura
2. Thrombotic thrombocytopenic purpura
3. Disseminated intravascular coagulation
4. Other acquired thrombocytopenias, including drug-related
   a. Peripheral destruction (e.g., quinine, quinidine)
   b. Decreased production, idiosyncratic or dose-related (e.g., chemotherapy)
   c. Bone marrow infiltration, fibrosis or failure

Pathophysiology: Abnormal Platelet Function

Major etiologies*

1. Congenital or hereditary platelet function defects
2. Acquired platelet function defects
   a. Aspirin, NSAIDs
   b. Renal insufficiency
   c. Monoclonal gammopathy
3. Thrombocytosis in myeloproliferative disease (often >1,000,000/mm^3)

Pathophysiology: Non-Platelet Etiologies

Major etiologies*

1. Spiking elevations of intravascular venous pressure (Valsalva maneuver-like, e.g., repetitive vomiting, childbirth, paroxysmal coughing, seizure)
2. Fixed increased pressure (e.g., stasis, ligatures)
3. Trauma (often linear)
4. Perifollicular (vitamin C deficiency)
5. Mildly inflammatory conditions
   a. Chronic pigmented purpura
   b. Hypergammaglobulinemic purpura of Waldenström

TABLE 3-27 Differential Diagnosis for Macular Purpura and Ecchymoses—Non-Palpable and Non-Retiform

Intermediate Macular Purpura (>4 mm, <1 cm in diameter)

Major etiologies*

1. Hypergammaglobulinemic purpura of Waldenström
2. Infection/inflammation in patients with thrombocytopenia
3. Rarely, minimally inflamed immune complex vasculitis (usually dependent distribution)

Ecchymoses (≥1 cm in diameter)

A. Pathophysiology: procoagulant defect plus minor trauma*
   1. Anticoagulant use
   2. Hepatic insufficiency with poor procoagulant synthesis
   3. Vitamin K deficiency
   4. Disseminated intravascular coagulation (some)

B. Pathophysiology: poor dermal support of vessels plus minor trauma*
   1. Actinic (solar, senile) purpura
   2. Corticosteroid therapy, topical or systemic
   3. Vitamin C deficiency (scurvy)
   4. Systemic amyloidosis (light chain-related, some familial types)
   5. Ehlers-Danlos syndrome (primarily type IV)

C. Pathophysiology: other causes plus minor trauma*
   1. Hypergammaglobulinemic purpura of Waldenström
   2. Platelet function defects, including von Willebrand disease, medications, metabolic diseases
   3. Acquired or congenital thrombocytopenia

*Partial list.

**Most patients do not have petechiae until platelets ≤20,000/mm^3.

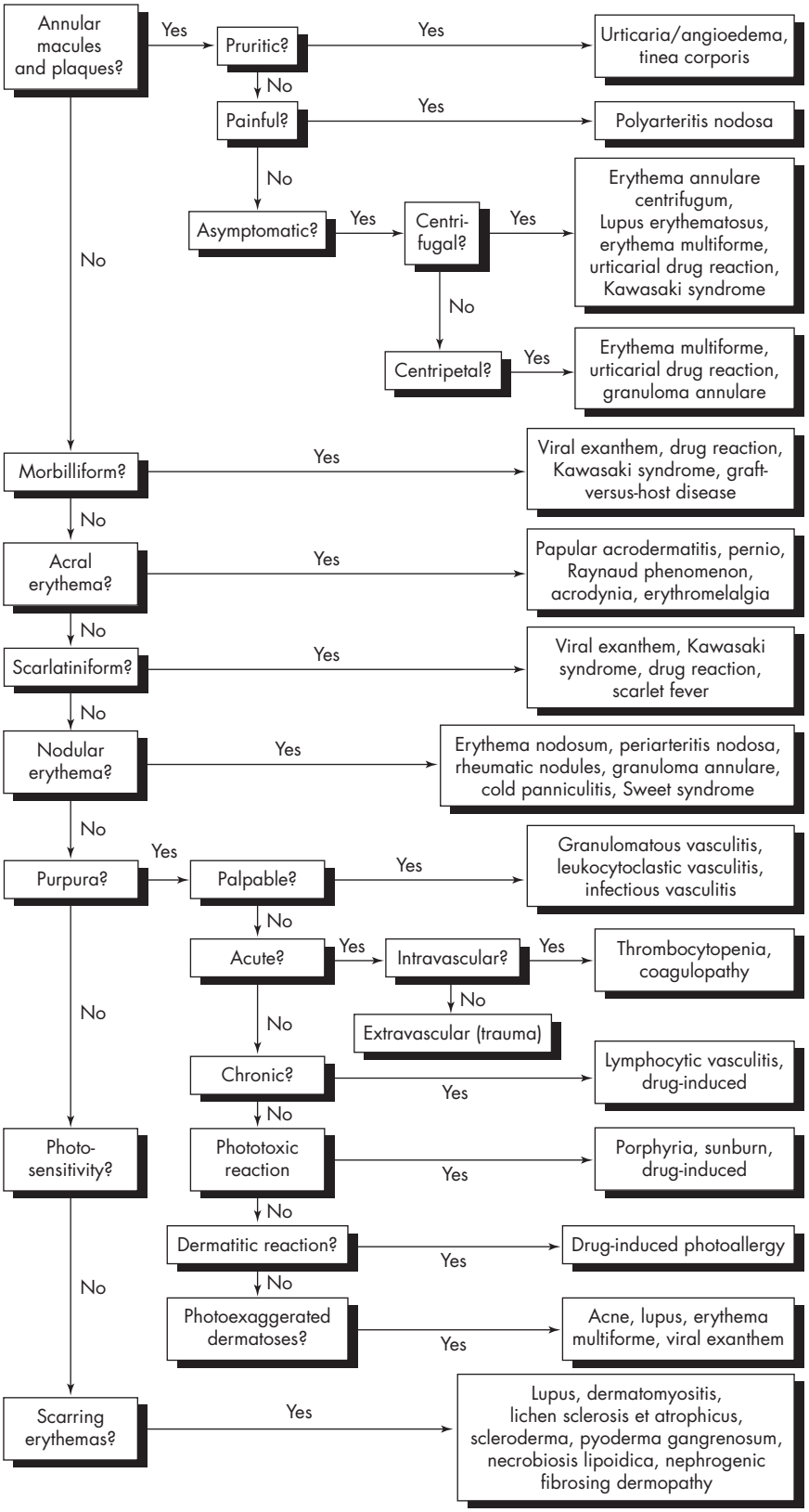


FIGURE E3-175 Reactive erythema. (Modified from Cohen BA: *Atlas of pediatric dermatology,* ed 3, St Louis, 2005, Mosby.)

ICD-9CM # 788.0
ICD-10CM # N23

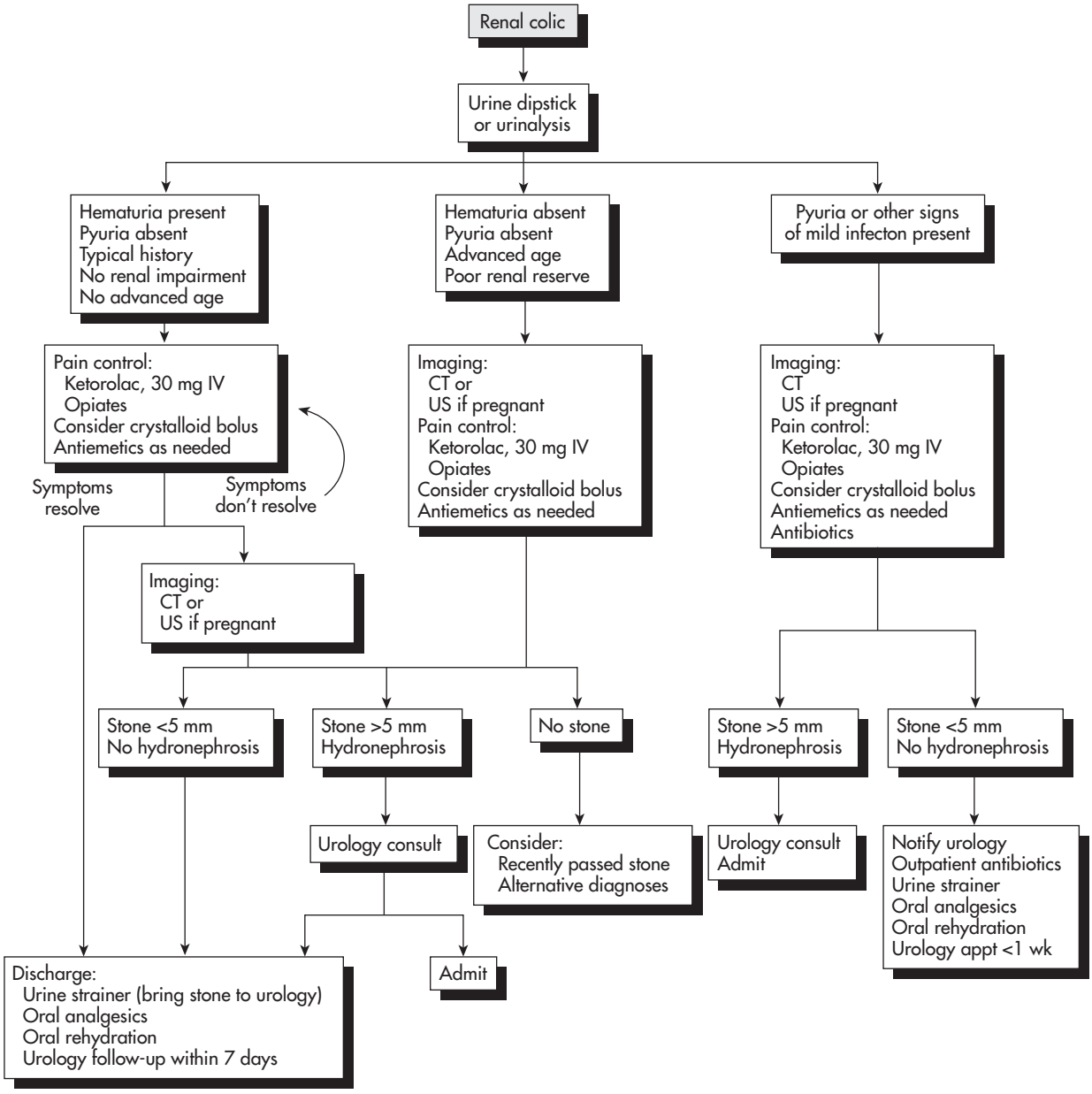


FIGURE 3-176 Guideline algorithm for the evaluation, treatment, and disposition of patients with presumed renal colic. *CT*, Computed tomography; *IV*, intravenously; *US*, ultrasonography. (From Adams JG, et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

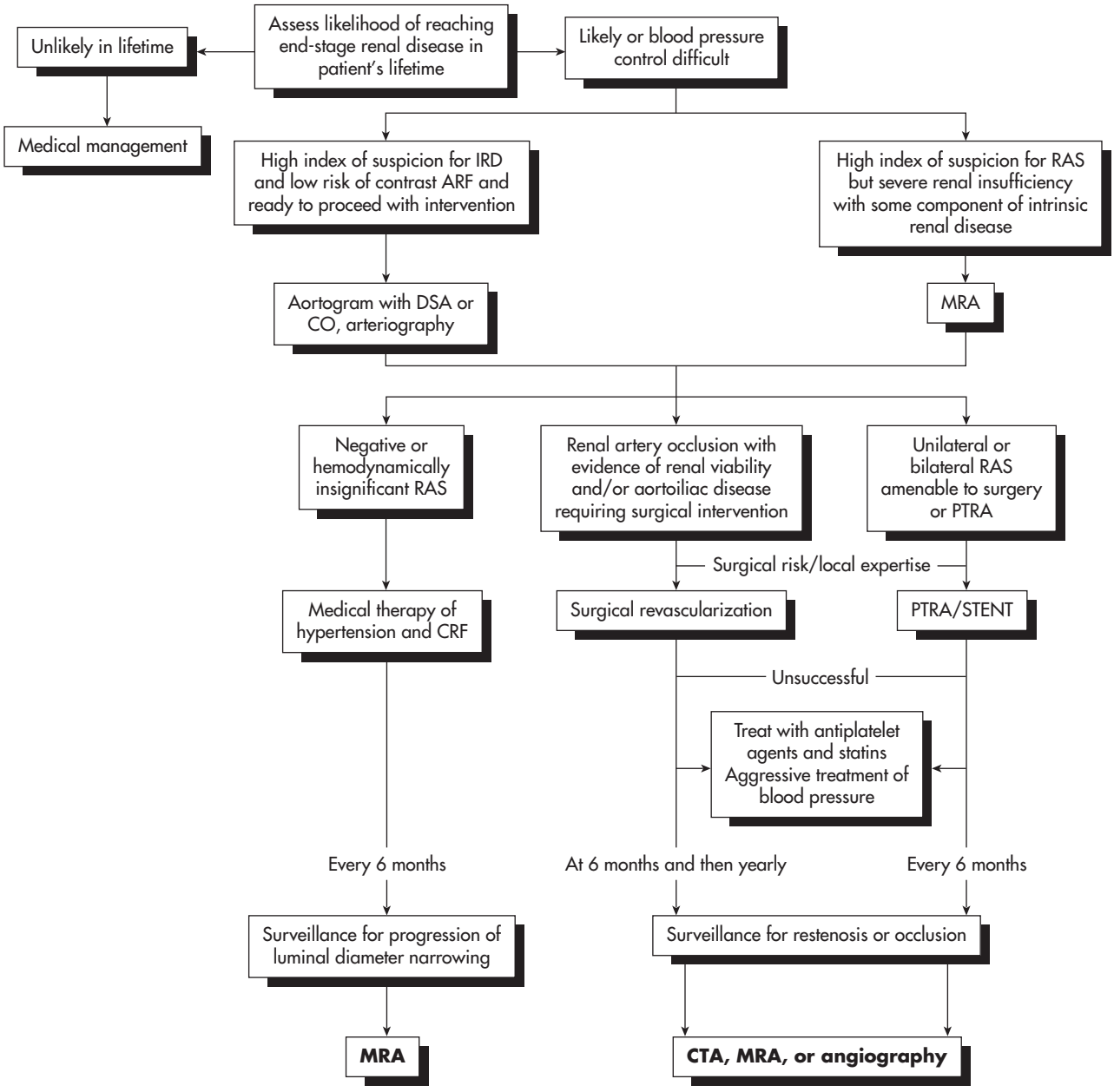


FIGURE E3-177 Clinical presentation suggestive of ischemic renal disease. *ARF,* Acute renal failure; *CTA,* computed tomography angiography; *CRF,* chronic renal failure; *DSA,* digital subtraction angiogram; *IRD,* ischemic renal disease; *MRA,* magnetic resonance angiography; *PTRA,* percutaneuos transluminal renal angioplasty; *RAS,* renal artery stenosis; *RDS,* respiratory distress syndrome. (Modified from Feehally J, Floege J, Johnson RJ: *Comprehensive clinical nephrology,* ed 3, St Louis, 2007, Mosby.)

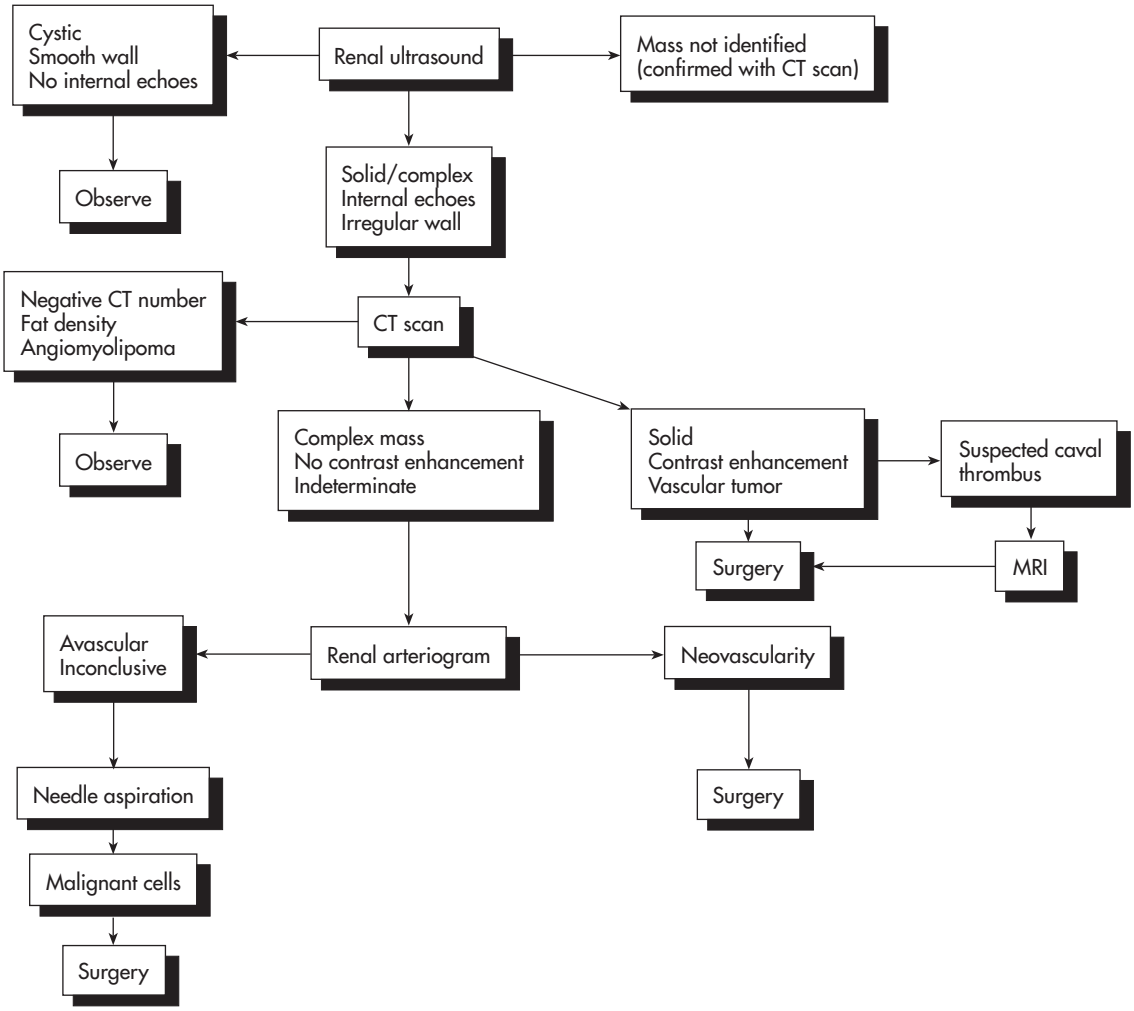


FIGURE 3-178 Evaluation of a patient with a renal mass on renal ultrasound. *CT,* Computed tomography; *MRI,* magnetic resonance imaging. (Modified from Williams RD: Tumors of the kidney, ureter, and bladder. In Goldman L, Schafer AL [eds]: *Cecil textbook of medicine,* ed 23, Philadelphia, 2008, Saunders.)

RESPIRATORY DISTRESS

ICD-9CM # 786.09 Respiratory distress NOS
518.82 Respiratory distress, acute
ICD-10CM # R06.00 Dyspnea, unspecified
R06.09 Other forms of dyspnea
R06.3 Periodic breathing
R06.89 Other abnormalities of breathing
J80 Acute respiratory distress syndrome

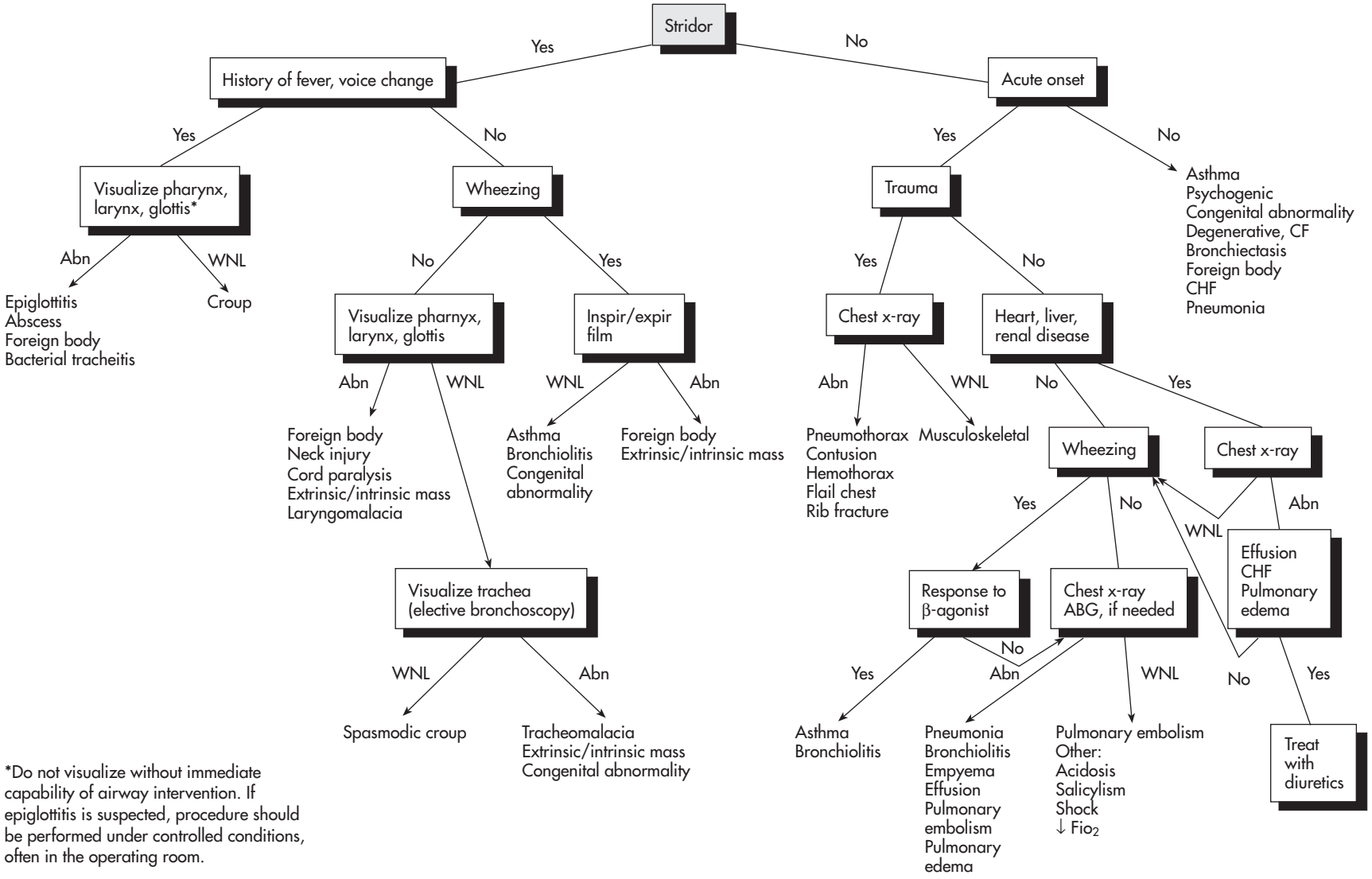


FIGURE 3-179 Respiratory distress in a pediatric patient. *ABG,* Arterial blood gas; *Abn,* abnormal; *CF,* cystic fibrosis; *CHF,* congestive heart failure; *WNL,* within normal limits. (From Barkin RM, Rosen P: *Emergency pediatrics,* St Louis, 1999, Mosby.)

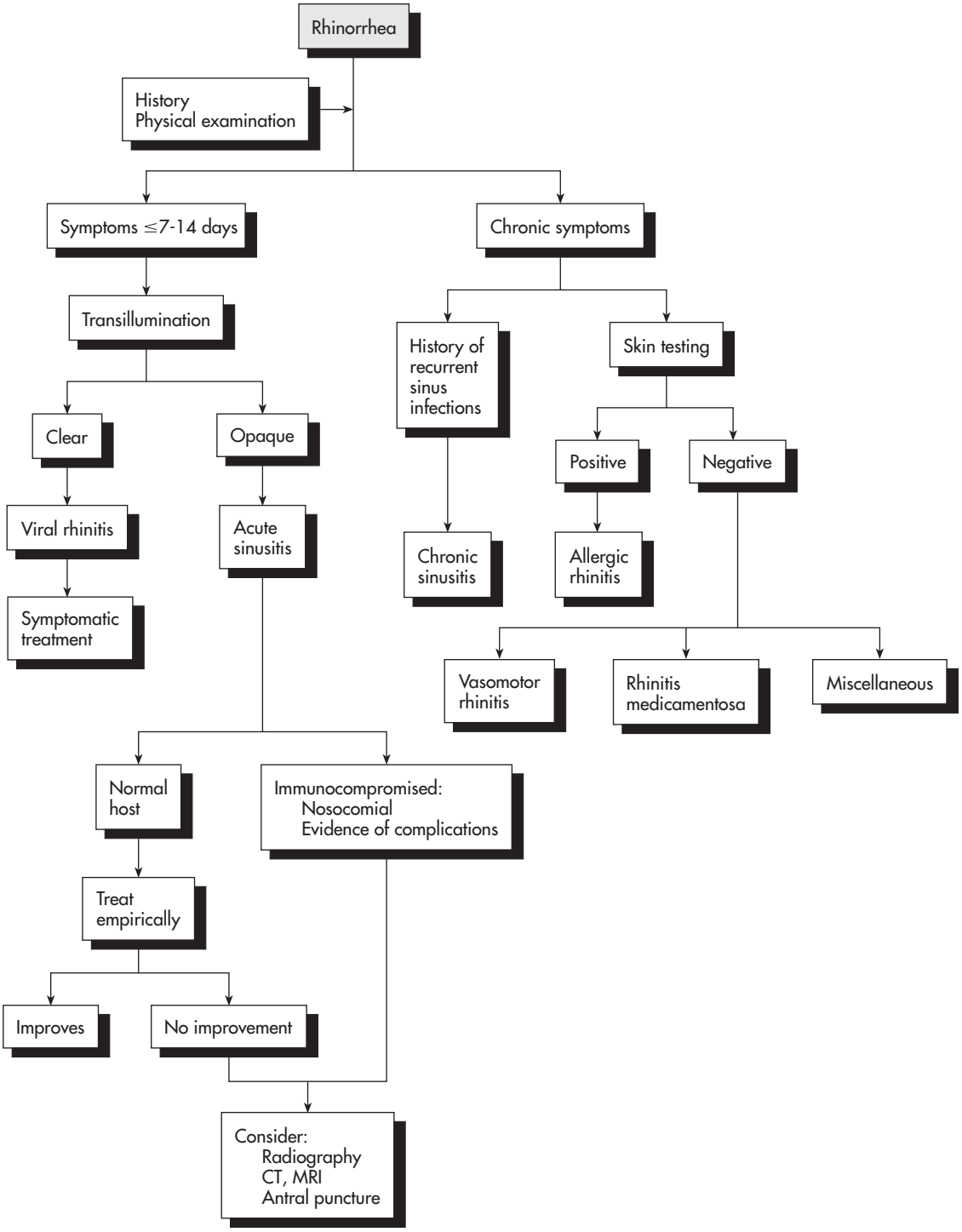


FIGURE E3-180 Approach to a patient with rhinorrhea. *CT,* Computed tomography; *MRI,* magnetic resonance imaging. (From Noble J [ed]: *Primary care medicine,* ed 3, St Louis, 2001, Mosby.)

SCROTAL MASS

ICD-9CM # 608.89
ICD-10CM # N44.2 Benign cyst of testis
N44.8 Other noninflammatory disorders of the testis
N50.3 Cyst of epididymis
N50.8 Other specified disorders of male genital organs

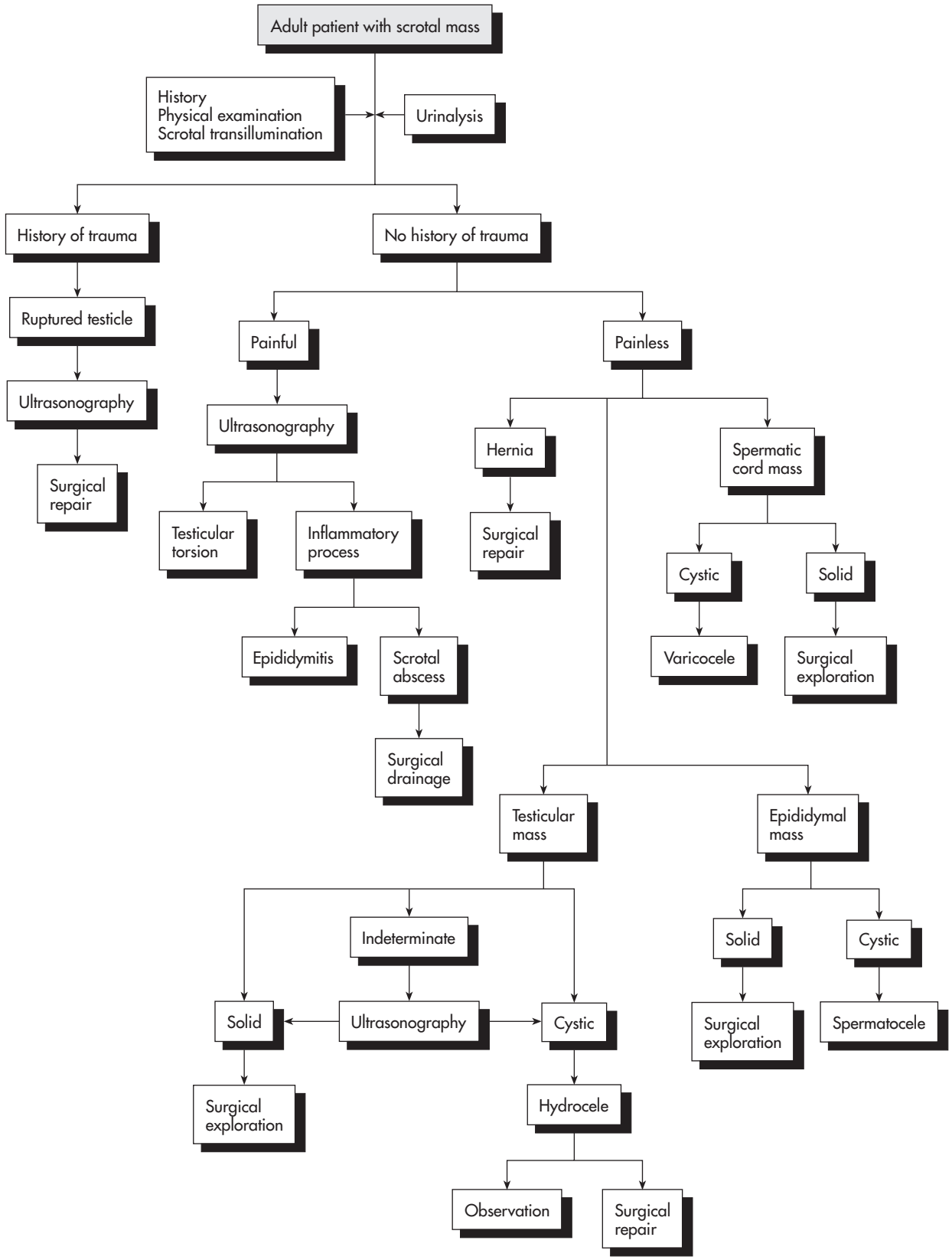
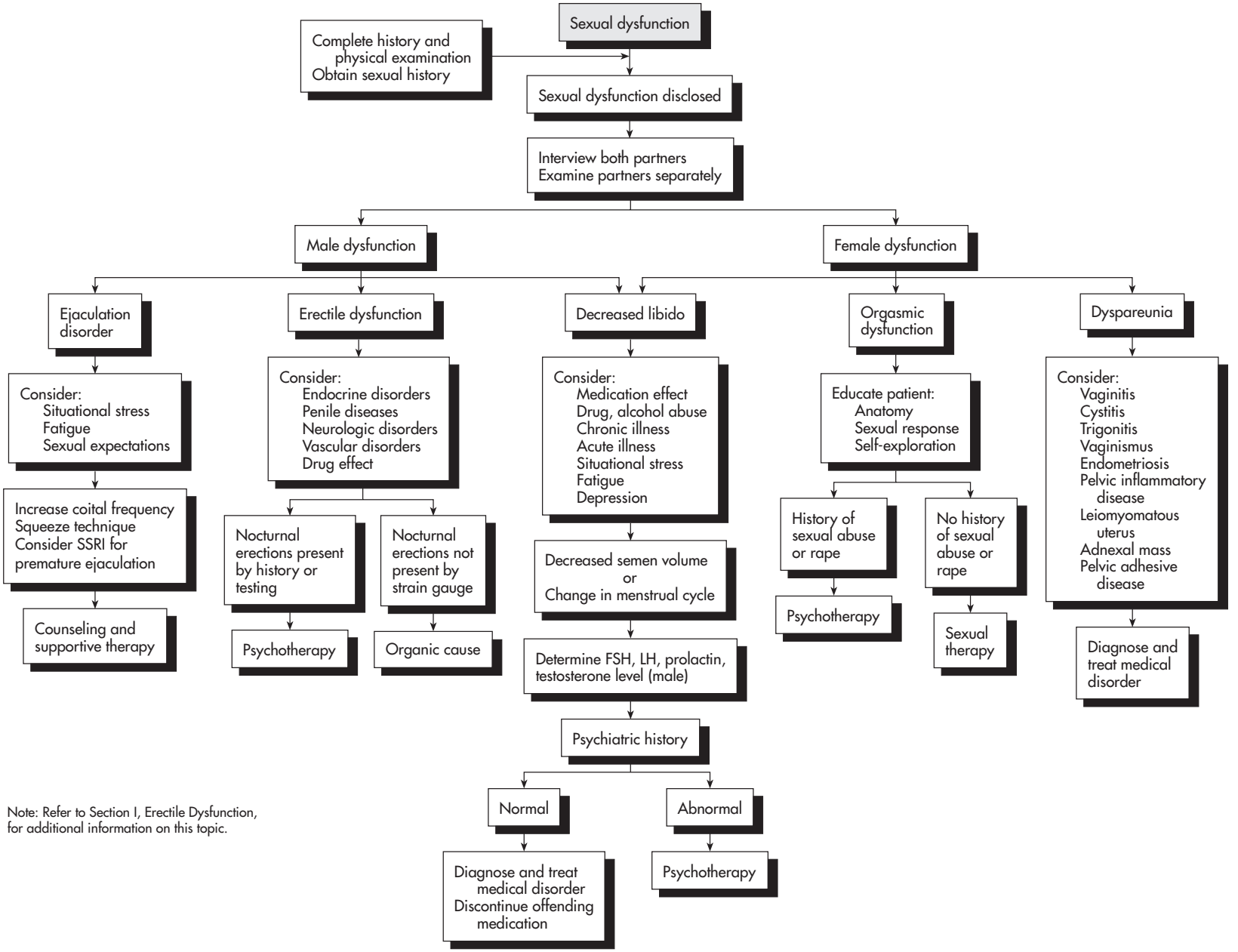


FIGURE 3-181 Evaluation of scrotal mass. (From Greene HL, Johnson WP, Lemcke DL [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

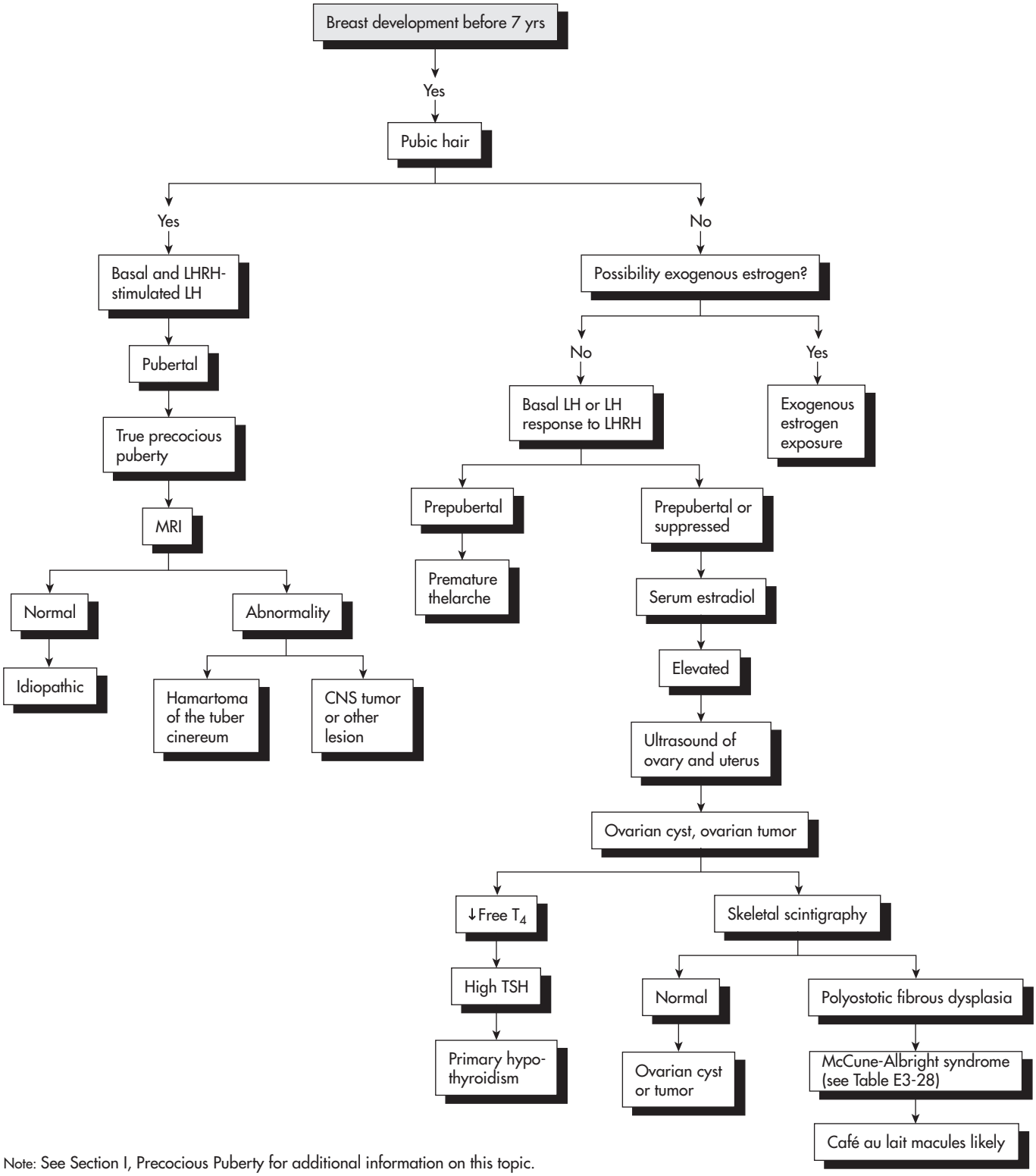
SEXUAL DYSFUNCTION EVALUATION

ICD-9CM # 309.2 Sexual disorder (psychosexual)
V41.7 Sexual function problem



Note: Refer to Section I, Erectile Dysfunction, for additional information on this topic.

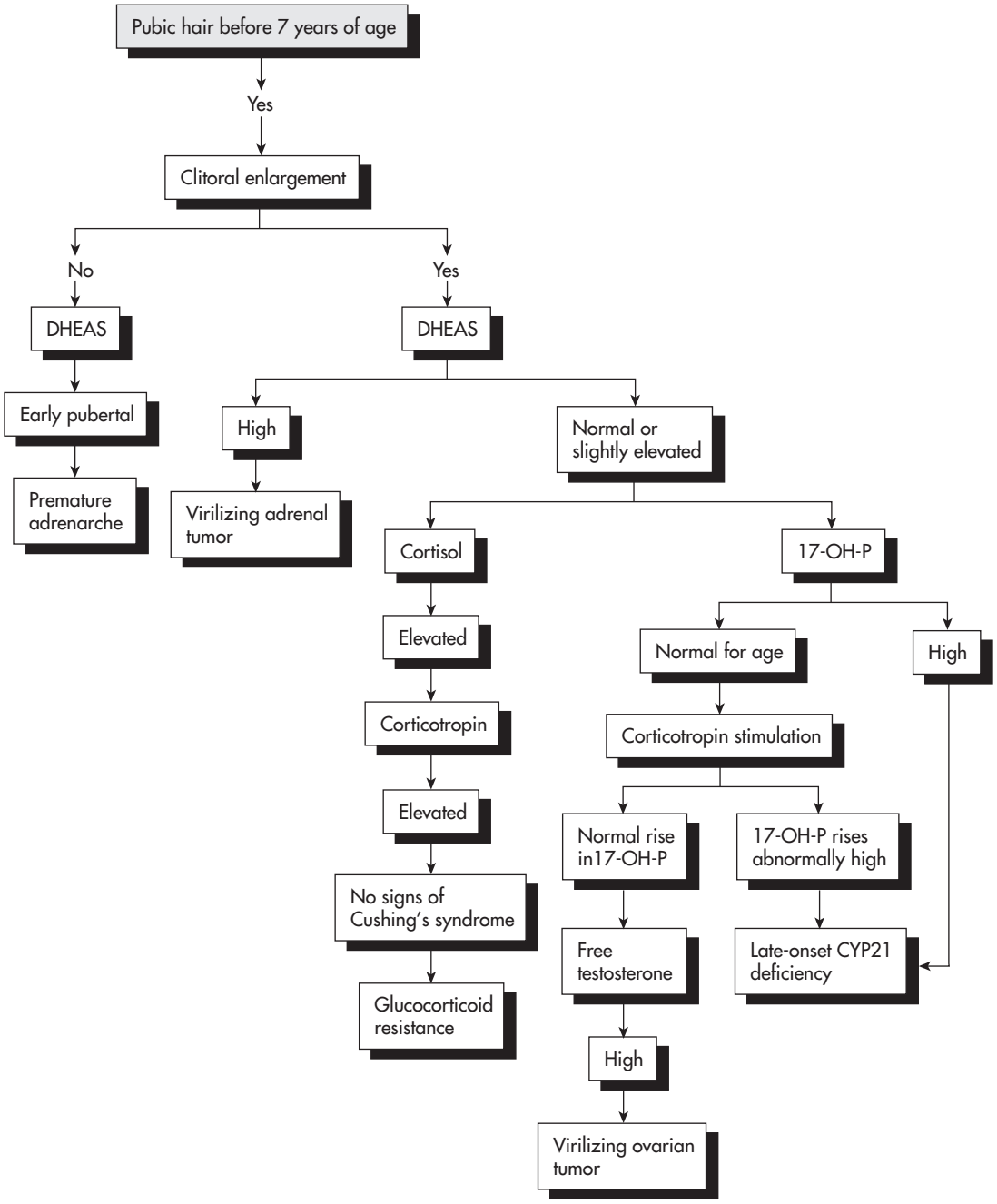
FIGURE E3-182 Evaluation of sexual dysfunction. *FSH,* Follicle-stimulating hormone; *LH,* luteinizing hormone; *SSRI,* selective serotonin reuptake inhibitor. (Modified from Greene HL, Johnson WP, Lemcke DL [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)



Note: See Section I, Precocious Puberty for additional information on this topic.

FIGURE E3-183 The diagnosis of sexual precocity in girls. *LH,* Luteinizing hormone; *LHRH,* luteinizing hormone-releasing hormone; *MRI,* magnetic resonance imaging; T_4, thyroxine; *TSH,* thyroid-stimulating hormone; *yrs,* years. (From Larsen PR, Kronenberg HM, Memlmed S, Polansky KS [eds]: *Williams textbook of endocrinology,* ed 11, Philadelphia, 2008, Saunders.)

ICD-9CM # 259.1
ICD-10CM # E30.1 Precocious puberty
E30.8 Other disorders of puberty



Note: Refer to Section I for additional information on precocious puberty.

FIGURE E3-184 The evaluation of pubic hair in normal phenotypic girls before 7 years. *DHEAS,* Dehydroepiandrosterone sulfate; *17-OH-P,* 17-hydroxy progesterone. (From Larsen PR, Kronenberg HM, Memlmed S, Polansky, KS [eds]: *Williams textbook of endocrinology,* ed 11, Philadelphia, 2008, Saunders.)

ICD-9CM # 259.1
ICD-10CM # E30.1 Precocious puberty
E30.8 Other disorders of puberty

TABLE E3-28 Differential Diagnosis of Sexual Precocity

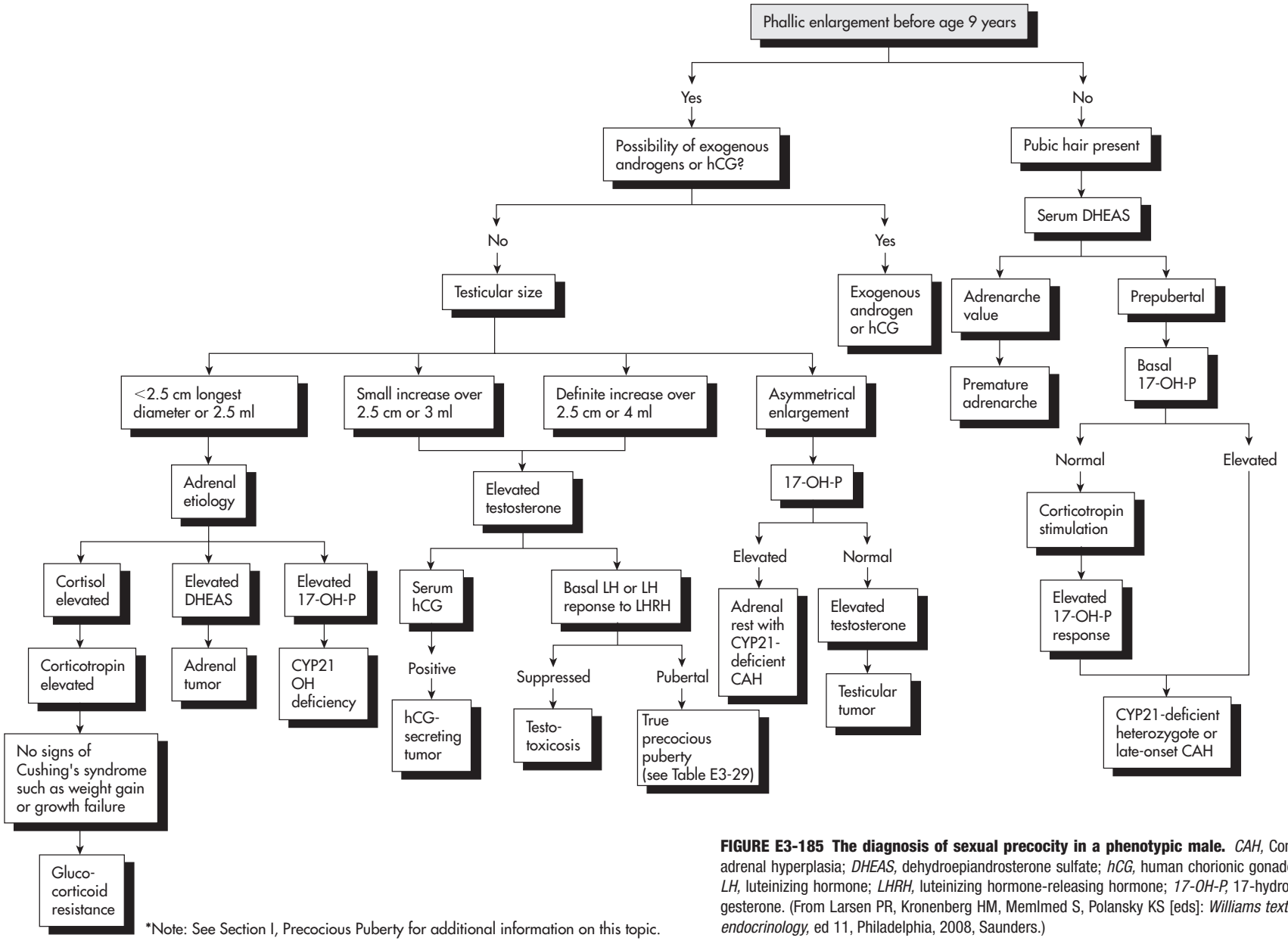
	Plasma Gonadotropins	LH Response to LHRH	Serum Sex Steroid Concentration	Gonadal Size	Miscellaneous
			In Both Sexes		
McCune-Albright syndrome	Suppressed	Suppressed	Sex steroids pubertal or higher	Ovarian (on ultrasound); slight testicular enlargement	Skeletal survey for polyostotic fibrous dysplasia and skin examination for café-au-lait spots
Primary hypothyroidism	LH prepubertal; FSH may be slightly elevated	Prepubertal FSH may be increased	Estradiol may be pubertal	Testicular enlargement; ovaries cystic	TSH and prolactin elevated; T_4 low
			Females		
Granulosa cell tumor (follicular cysts may present similarly)	Suppressed	Prepubertal LH response	Very high estradiol	Ovarian enlargement on physical examination, CT, or ultrasonography	Tumor often palpable on abdominal examination
Follicular cyst	Suppressed	Prepubertal LH response	Prepubertal to very high estradiol	Ovarian enlargement on physical examination, CT, or ultrasonography	Single or recurrent episodes of menses and/or breast development; exclude McCune-Albright syndrome
Feminizing adrenal tumor	Suppressed	Prepubertal LH response	High estradiol and DHEAS values	Ovaries prepubertal	Unilateral adrenal mass
Premature thelarche	Prepubertal	Prepubertal LH, pubertal estradiol response	Prepubertal or early	Ovaries prepubertal	Onset usually before 3 years of age
Premature adrenarche	Prepubertal	Prepubertal LH response	Prepubertal estradiol; DHEAS or urinary 17-ketosteroid values appropriate for pubic hair stage 2	Ovaries prepubertal	Onset usually after 6 years of age; more frequent in brain-injured children
Late-onset virilizing congenital adrenal hyperplasia	Prepubertal	Prepubertal LH response	Elevated 17-OHP in basal or corticotropin-stimulated state	Ovaries prepubertal	Autosomal recessive

CNS, Central nervous system; *CT,* computed tomography; *DHEAS,* dehydroepiandrosterone sulfate; *FSH,* follicle-stimulating hormone; *hCG,* human chorionic gonadotropin; *LH,* luteinizing hormone; *MRI,* magnetic resonance imaging; *17-OHP,* 17-hydroxy progesterone; T_4, thyroxine; *TSH,* thyrotropin.

From Larson PR, Kronenberg HM, Memlmed S, Polansky KS [eds]: *Williams textbook of endocrinology,* ed 11, Philadelphia, 2008, Saunders.

SEXUAL PRECOCITY, MALE

ICD-9CM # 259.1
ICD-10CM # E30.1 Precocious puberty
E30.8 Other disorders of puberty



*Note: See Section I, Precocious Puberty for additional information on this topic.

FIGURE E3-185 The diagnosis of sexual precocity in a phenotypic male. *CAH,* Congenital adrenal hyperplasia; *DHEAS,* dehydroepiandrosterone sulfate; *hCG,* human chorionic gonadotropin; *LH,* luteinizing hormone; *LHRH,* luteinizing hormone-releasing hormone; *17-OH-P,* 17-hydroxy progesterone. (From Larsen PR, Kronenberg HM, Memlmed S, Polansky KS [eds]: *Williams textbook of endocrinology,* ed 11, Philadelphia, 2008, Saunders.)

Continued on next page

SEXUAL PRECOCITY, MALE—cont'd

ICD-9CM # 259.1
ICD-10CM # E30.1 Precocious puberty
E30.8 Other disorders of puberty

TABLE E3-29 Differential Diagnosis of Sexual Precocity

	Plasma Gonadotropins	LH Response to LHRH	Serum Sex Steroid Concentration	Gonadal Size	Miscellaneous
True Precocious Puberty (premature reactivation of LHRH pulse generator)	Prominent LH pulses, initially during sleep	Pubertal LH response	Pubertal values of testosterone or estradiol	Normal pubertal testicular enlargement or ovarian and uterine enlargement (by ultrasonography)	MRI of brain to rule out CNS tumor or other abnormality; skeletal survey for McCune-Albright syndrome
Incomplete Sexual Precocity (pituitary gonadotropin-independent)					
			Males		
Chorionic gonadotropin-secreting tumor in males	High hCG, low LH	Prepubertal LH response	Pubertal value of testosterone	Slight to moderate uniform enlargement of testes	Hepatomegaly suggests hepatoblastoma; CT scan of brain if chorionic gonadotropin-secreting CNS tumor suspected
Leydig cell tumor in males	Suppressed	No LH response	Very high testosterone	Irregular asymmetrical enlargement of testes	
Familial testotoxicosis	Suppressed	No LH response	Pubertal values of testosterone	Testes symmetrical and larger than 2.5 cm but smaller than expected for pubertal development; spermatogenesis occurs	Familial; probably sex-limited, autosomal dominant trait
Virilizing congenital adrenal hyperplasia	Prepubertal	Prepubertal LH response	Elevated 17-OHP in CYP21 deficiency or elevated 11-deoxycortisol in CYP11B1 deficiency	Testes prepubertal	Autosomal recessive, may be congenital or late-onset form, may have salt loss in CYP21 deficiency or hypertension in CYP11B1 deficiency
Virilizing adrenal tumor	Prepubertal	Prepubertal LH response	High DHEAS and androstenedione values	Testes prepubertal	CT, MRI, or ultrasonography of abdomen
Premature adrenarche	Prepubertal	Prepubertal LH response	Prepubertal testosterone, DHEAS, or urinary 17-ketosteroid values appropriate for pubic hair stage 2	Testes prepubertal	Onset usually after 6 years of age; more frequent in CNS-injured children
			In Both Sexes		
McCune-Albright syndrome	Suppressed	Suppressed	Sex steroids pubertal or higher	Ovarian (on ultrasound); slight testicular enlargement	Skeletal survey for polyostotic fibrous dysplasia and skin examination for café-au-lait spots
Primary hypothyroidism	LH prepubertal; FSH may be slightly elevated	Prepubertal FSH may be increased	Estradiol may be pubertal	Testicular enlargement; ovaries cystic	TSH and prolactin elevated; T_4 low

17-OHP, 17-hydroxy progesterone; *CNS,* Central nervous system; *CT,* computed tomography; *DHEAS,* dehydroepiandrosterone sulfate; *hCG,* human chorionic gonadotropin; *LH,* luteinizing hormone; *MRI,* magnetic resonance imaging; T_4, thyroxine; *TSH,* thyrotropin.
From Larson PR, Kronenberg HM, Memlmed S, Polansky, KS [eds]: *Williams textbook of endocrinology,* ed 11, Philadelphia, 2008, Saunders.

ICD-9CM # 844.9
ICD-10CM # S83.90XA Sprain of unspecified site of unspecified knee, initial encounter
S86.919A Strain of unspecified muscle(s) and tendon(s) at lower leg level, unspecified leg, initial encounter

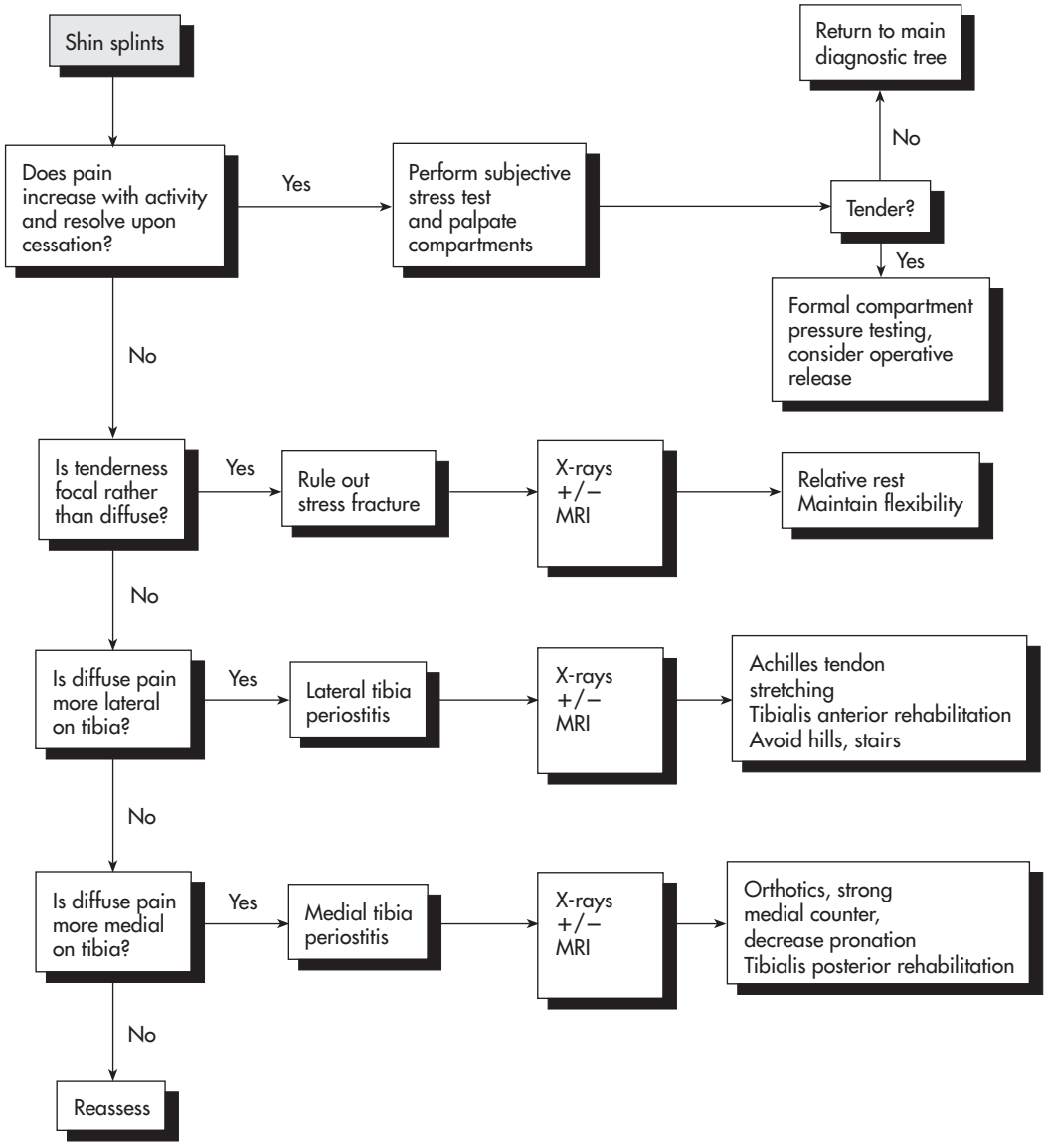


FIGURE E3-186 Evaluation and management of shin splints. *MRI,* Magnetic resonance imaging. (Modified from Scudieri G [ed]: *Sports medicine, principles of primary care,* St Louis, 1997, Mosby.)

SHOCK

ICD-9CM # 785.50 Shock NOS
995.0 Shock, anaphylactic
785.51 Shock, cardiogenic
785.59 Shock, septic
958.4 Shock, traumatic
977.9 Shock due to drug, medicine incorrectly administered
ICD-10CM # R57.9 Shock, unspecified
R57.0 Cardiogenic shock
R57.1 Hypovolemic shock
R57.8 Other shock

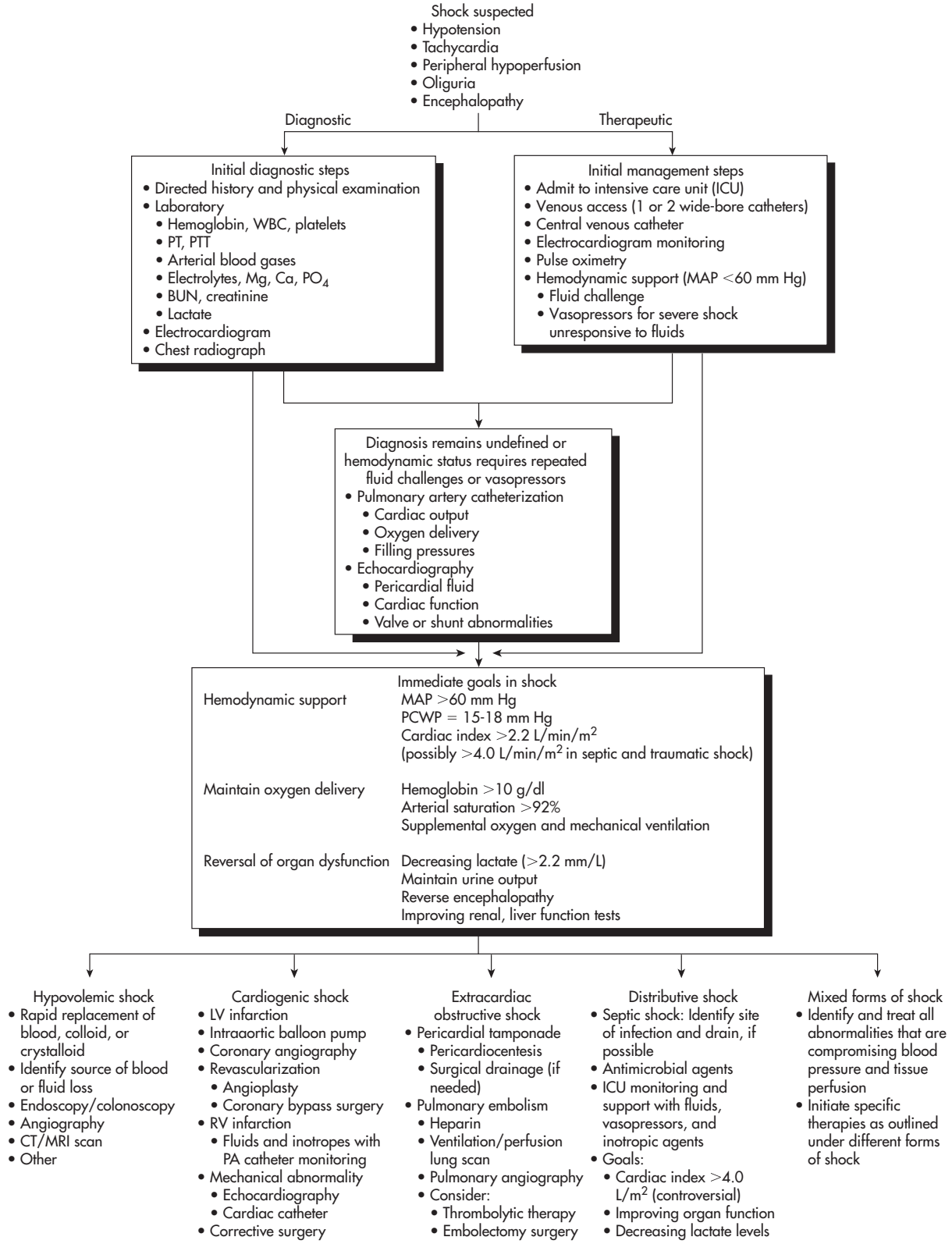


FIGURE 3-187 An approach to the diagnosis and treatment of shock. *BUN,* Blood urea nitrogen; *CT,* computed tomography; *LV,* left ventricular; *MAP,* mean arterial pressure; *MRI,* magnetic resonance imaging; *PA,* pulmonary arterial; *PCWP,* pulmonary capillary wedge pressure; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *RV,* right ventricular; *WBC,* white blood cell count. (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

ICD-9CM # 783.43 Short stature
ICD-10CM # R62.52 Short stature (child)

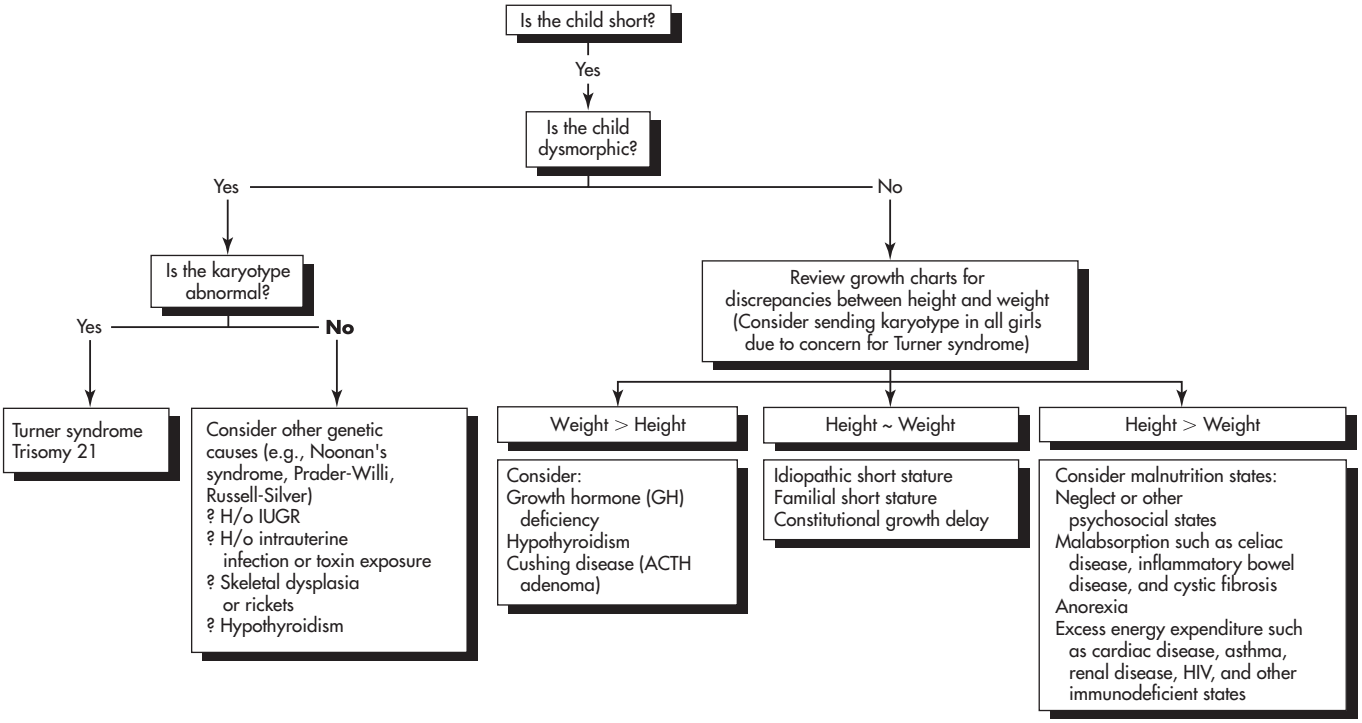


FIGURE E3-188 Differential diagnosis of short stature. (From Custer JW, Rau RE: *The Harriet Lane handbook*, ed 18, St Louis, 2009, Mosby.)

SHOULDER PAIN

ICD-9CM # variable with specific disorder

ICD-10CM #
S34.109A Unspecified injury to unspecified level of lumbar spinal cord, initial encounter
M24.819 Other specific joint derangements of unspecified shoulder, not elsewhere classified
M75.80 Other shoulder lesions, unspecified shoulder
S43.409A Unspecified sprain of unspecified shoulder joint, initial encounter
S46.919A Strain of unspecified muscle, fascia and tendon at shoulder and upper arm level, unspecified arm, initial encounter

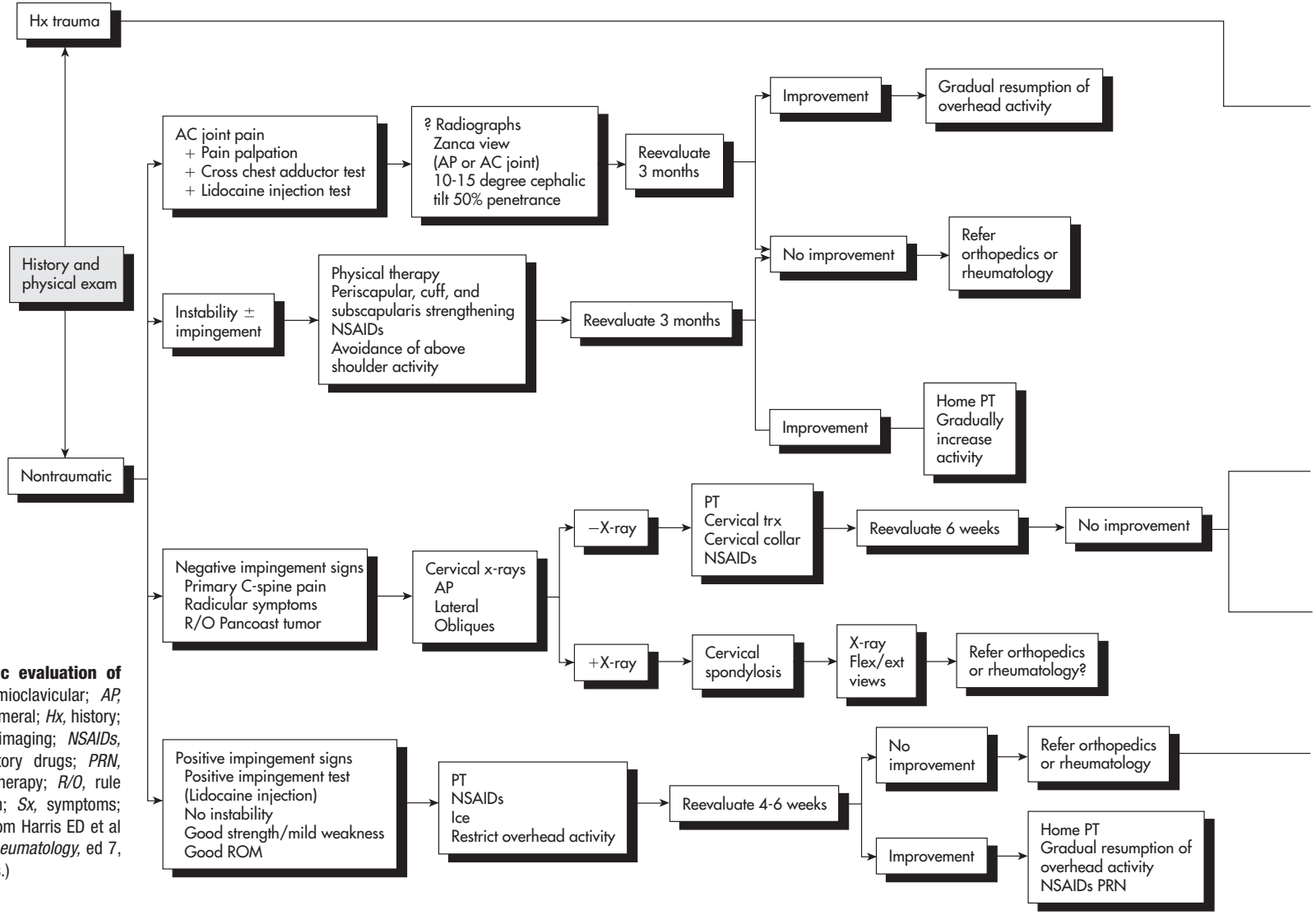


FIGURE 3-189 Algorithmic evaluation of shoulder pain. *AC,* Acromioclavicular; *AP,* anteroposterior; *GH,* glenohumeral; *Hx,* history; *MRI,* magnetic resonance imaging; *NSAIDs,* nonsteroidal anti-inflammatory drugs; *PRN,* as required; *PT,* physical therapy; *R/O,* rule out; *ROM,* range of motion; *Sx,* symptoms; *trx,* traction; *Tx,* therapy. (From Harris ED et al [eds]: *Kelley's textbook of rheumatology,* ed 7, Philadelphia, 2005, Saunders.)

Continued on next page

SHOULDER PAIN—cont'd

ICD-9CM # variable with specific disorder

ICD-10CM # S34.109A Unspecified injury to unspecified level of lumbar spinal cord, initial encounter
M24.819 Other specific joint derangements of unspecified shoulder, not elsewhere classified
M75.80 Other shoulder lesions, unspecified shoulder
S43.409A Unspecified sprain of unspecified shoulder joint, initial encounter
S46.919A Strain of unspecified muscle, fascia and tendon at shoulder and upper arm level, unspecified arm, initial encounter

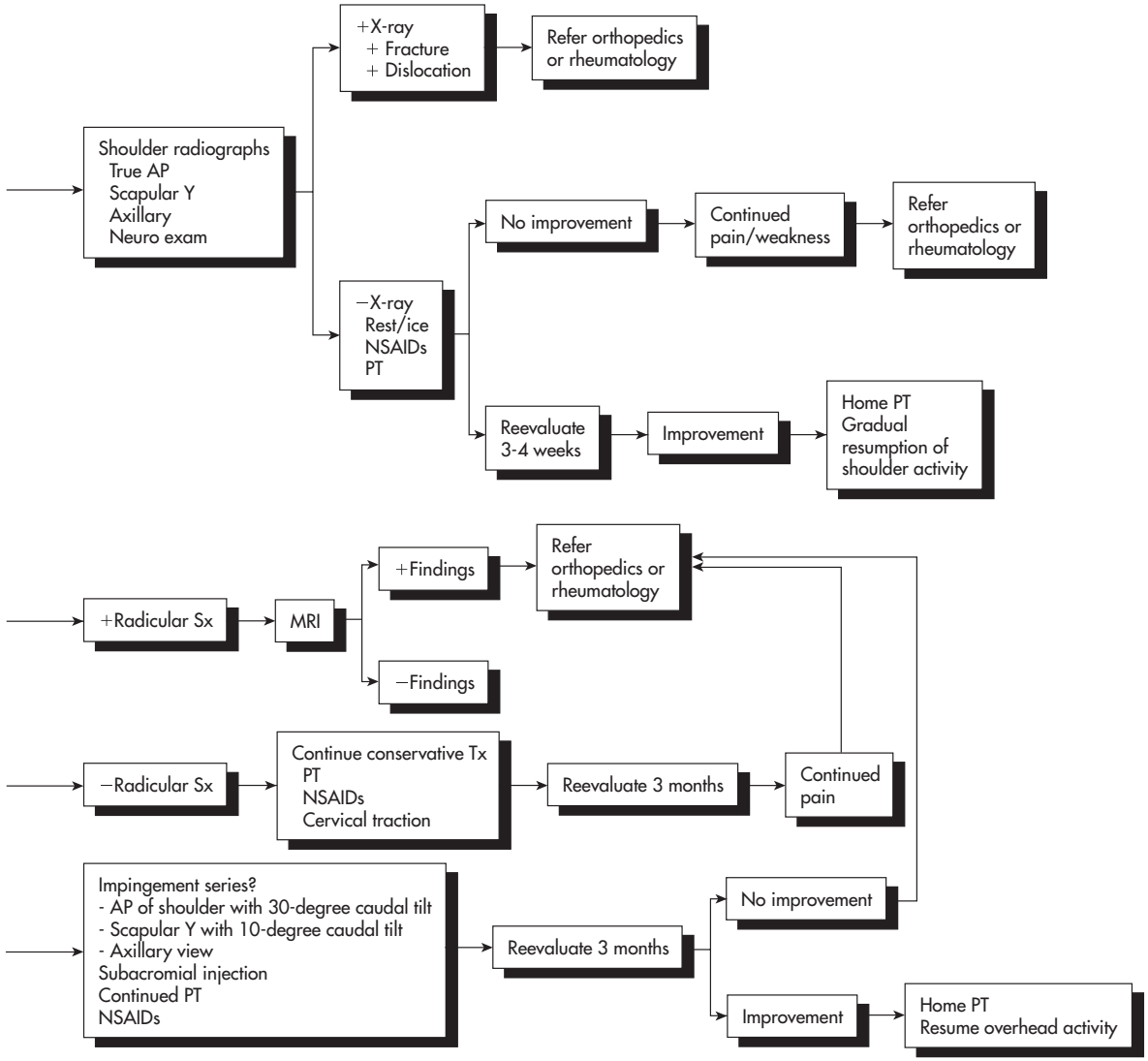


FIGURE 3-189 (Continued)

ICD-9CM # variable with specific disorder

ICD-10CM # S34.109A Unspecified injury to unspecified level of lumbar spinal cord, initial encounter
M24.819 Other specific joint derangements of unspecified shoulder, not elsewhere classified
M75.80 Other shoulder lesions, unspecified shoulder
S43.409A Unspecified sprain of unspecified shoulder joint, initial encounter
S46.919A Strain of unspecified muscle, fascia and tendon at shoulder and upper arm level, unspecified arm, initial encounter

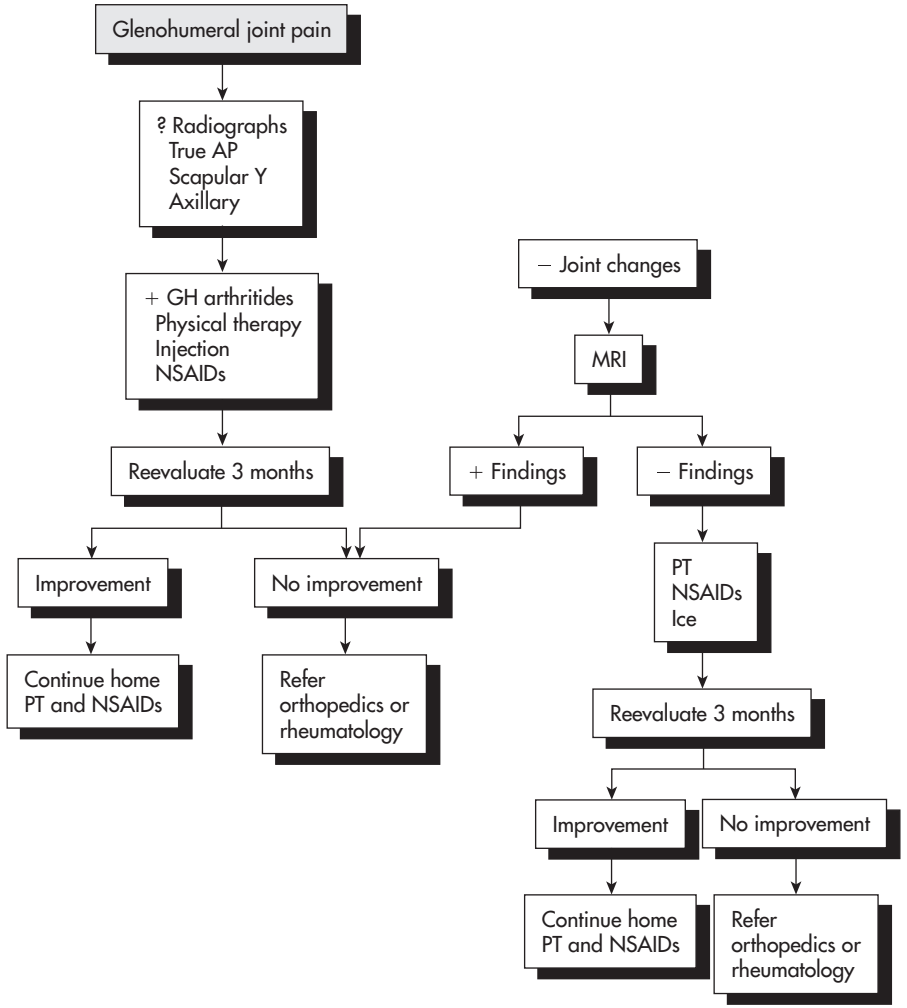


FIGURE 3-189 (Continued)

ICD-9CM # 709.8
ICD-10CM # L94.2 Calcinosis cutis
L98.8 Other specified disorders of the skin and subcutaneous tissue

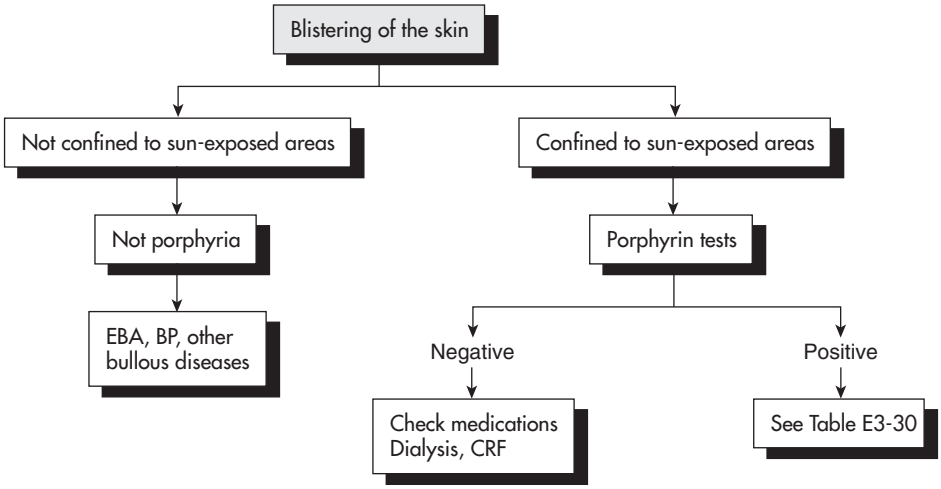


FIGURE E3-190 An approach to the patient with blistering of the skin. *BP,* Bullous pemphigoid; *CRF,* chronic renal failure; *EBA,* epidermolysis bullosa acquisita. (From Bolognia JL et al [eds]: *Dermatology,* ed 2, St Louis, 2008, Mosby.)

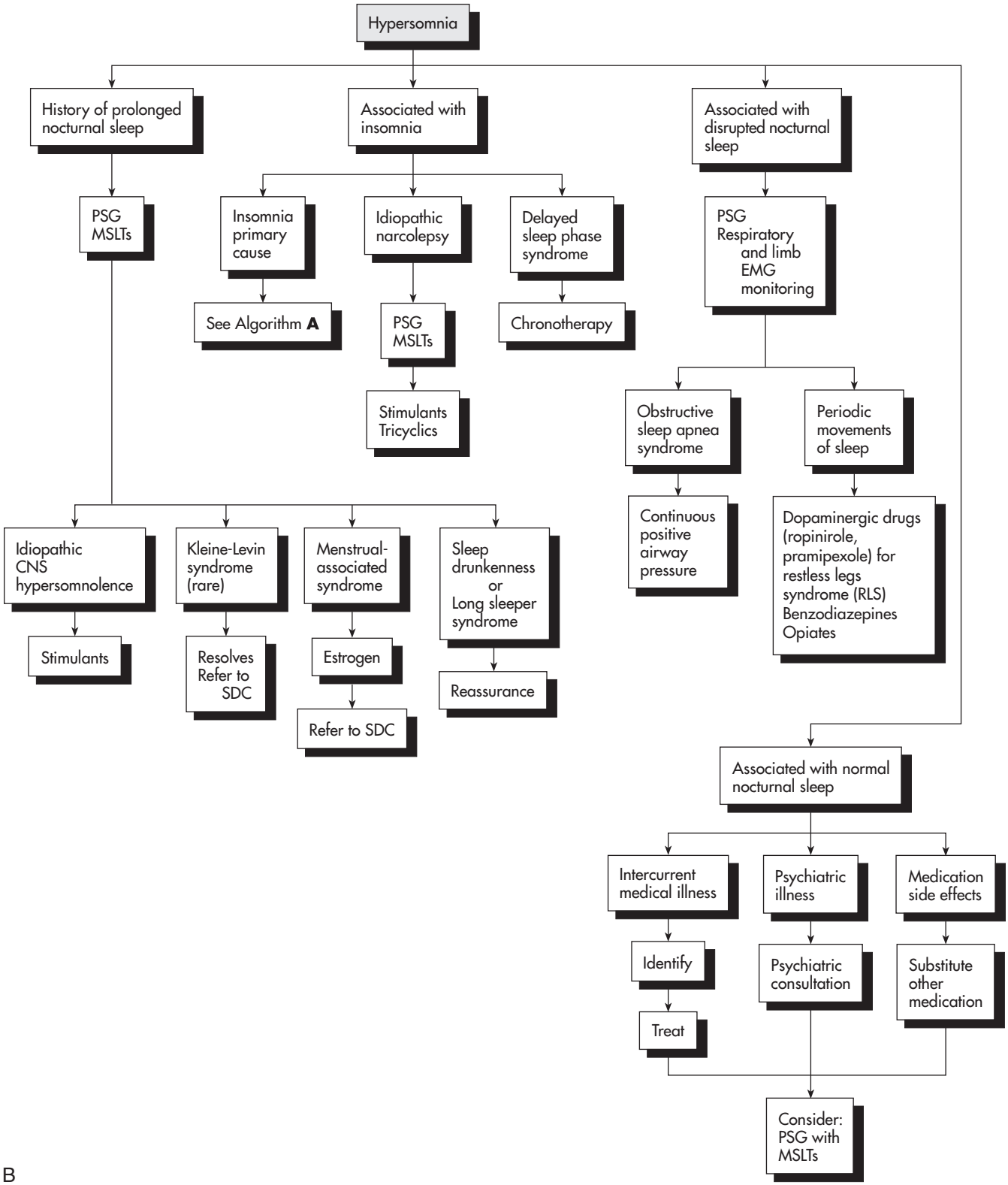
TABLE E3-30 Investigative Tests Used in the Diagnosis of Porphyria

Porphyria	Enzyme	Urine	Stool	Plasma	RBC
Porphyria cutanea tarda	Uroporphyrinogen decarboxylase	URO+ + + COPRO+ 7COOH III>I	ISO-COPRO+ +7COOH	+	–
Erythropoietic protoporphyria	Ferrochelatase	Normal	PROTO+	+	free PROTO+ +
Congenital erythropoietic porphyria	Uroporphyrinogen III synthase	URO I+ COPRO I++	COPRO I+	+	URO I+ COPRO I+ PROTO+
Acute intermittent porphyria	Porphobilinogen deaminase	*ALA+ + + *PBG+ + +	*ALA+ *PBG+	–	–
Variegate porphyria	Protoporphyrinogen oxidase	*ALA+ + *PBG+ + URO+ COPRO+ +	COPRO+ PROTO+ + PORPH X+ + +	625-627 nm peak	–
Heriditary coproporphyria	Coproporphyrinogen oxidase	*ALA+ + *PBG+ + COPRO+ + URO+	COPRO+	+	–
Aminolevulinic acid (ALA) dehydratase-deficient porphyria	ALA dehydratase	ALA+ + + COPRO III	–	–	Zn PROTO+
Hepatoerythropoietic porphyria	Uroporphyrinogen decarboxylase	URO+ + + COPRO+ 7COOH III>I	ISO-COPRO+ + 7COOH	+	Zn and free PROTO+ +
Tyrosinemia	ALA dehydratase	ALA	–	–	–
Iron deficiency	Ferrochelatase	–	–	–	Zn PROTO+ +
Lead poisoning	ALA dehydratase Coproporphyrinogen oxidase Ferrochelatase	ALA+ + + COPRO±	–	–	Zn PROTO+

COPRO, Coproporphyrin; *ISO-COPRO,* isocoproporphyrin; *PROTO,* protoporphyrin; *RBC,* red blood cells; *URO,* uroporphyrin; +, positive; –, negative; *, during acute attack.
From Bolognia JL et al (eds): *Dermatology,* ed 2, St Louis, 2008, Mosby.

ICD-9CM # 780.50 Sleep disorder, unspecified cause
ICD-10CM # G47.9 Sleep disorder, unspecified

FIGURE 3-191 A, Patient with sleep disturbance. *PSG,* Polysomnography. (Modified from Greene HL, Johnson WP, Lemcke DL [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)



B

FIGURE 3-191 (Continued) **B, Hypersomnia.** *CNS,* Central nervous system; *EMG,* electromyelogram; *MSLTs,* multiple sleep latency tests; *PSG,* polysomnography; *SDC,* sleep disorders clinic. (Modified from Greene HL, Johnson WP, Lemcke DL [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

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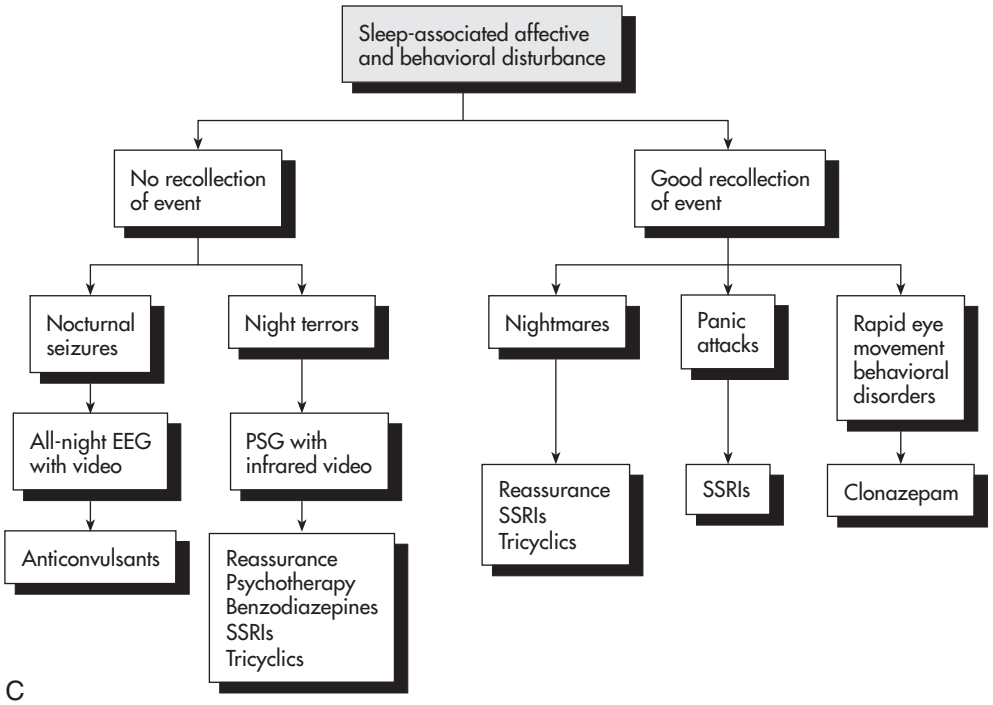
ICD-9CM # 780.50 Sleep disorder, unspecified cause
ICD-10CM # G47.9 Sleep disorder, unspecified



C

FIGURE 3-191 (Continued) **C, Sleep-associated affective and behavioral disturbance.** *EEG,* Electroencephalogram; *PSG,* polysomnography; *SSRIs,* selective serotonin reuptake inhibitors. (Modified from Greene HL, Johnson WP, Lemcke DL [eds]: *Decision making in medicine,*ed 2, St Louis, 1998, Mosby.)

ICD-9CM # 192.2
ICD-10CM # C72.0 Malignant neoplasm of spinal cord
C72.1 Malignant neoplasm of cauda equina

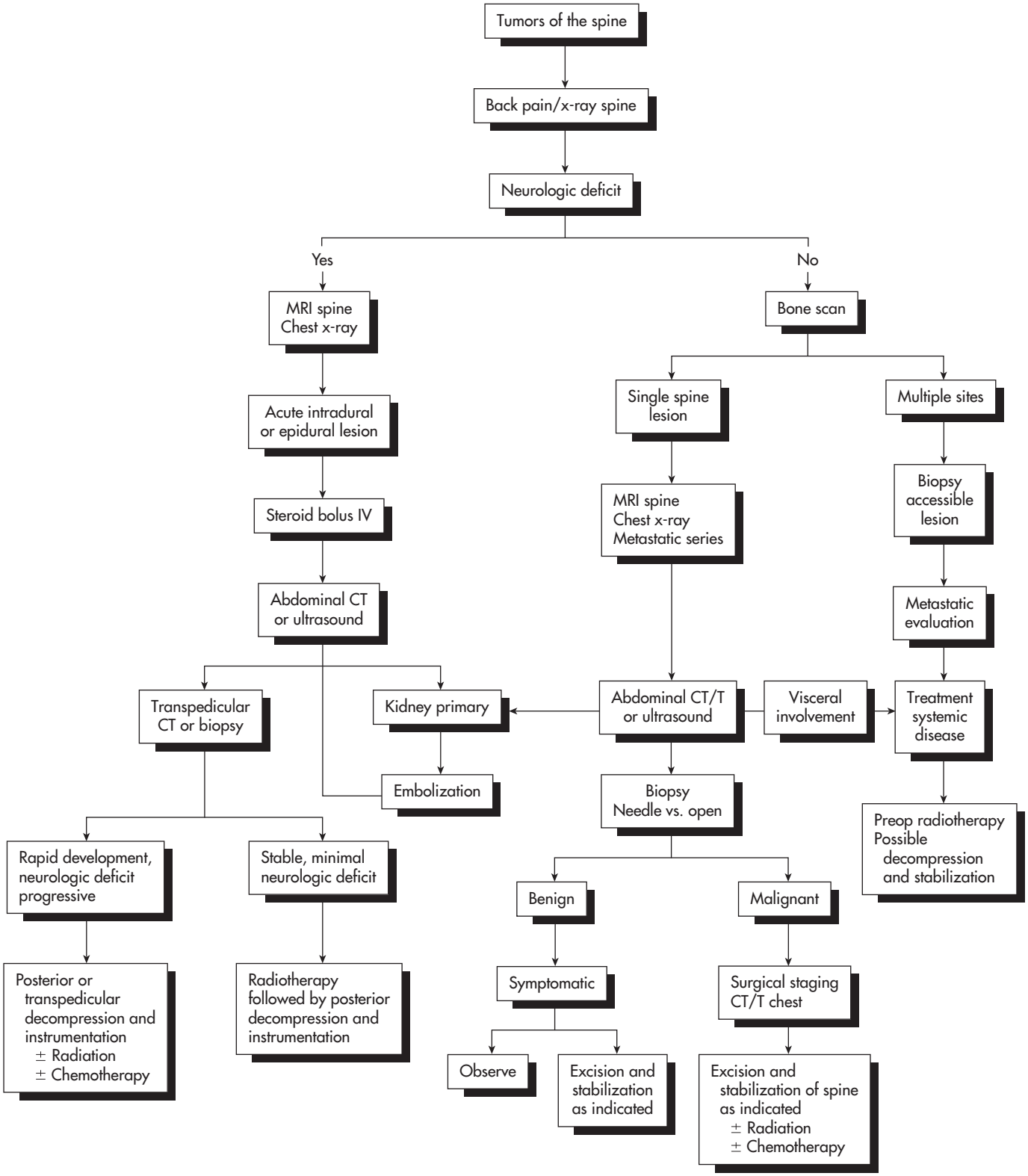


FIGURE E3-192 Diagnostic and therapeutic approach to tumors of the spine. *CT,* Computed tomography; *IV,* intravenous; *MRI,* magnetic resonance imaging. (From Abeloff MD: *Clinical oncology,* ed 3, Philadelphia, 2004, Saunders.)

SPLENOMEGALY

ICD-9CM # 789.2 Splenomegaly, unspecified
289.51 Splenomegaly, chronic congestive
759.0 Splenomegaly, congenital
789.2 Splenomegaly, unknown etiology
ICD-10CM # R16.1 Splenomegaly, not elsewhere classified
D73.2 Chronic congestive splenomegaly
Q89.01 Asplenia (congenital)
Q89.09 Congenital malformations of spleen
R16.1 Splenomegaly, not elsewhere classified

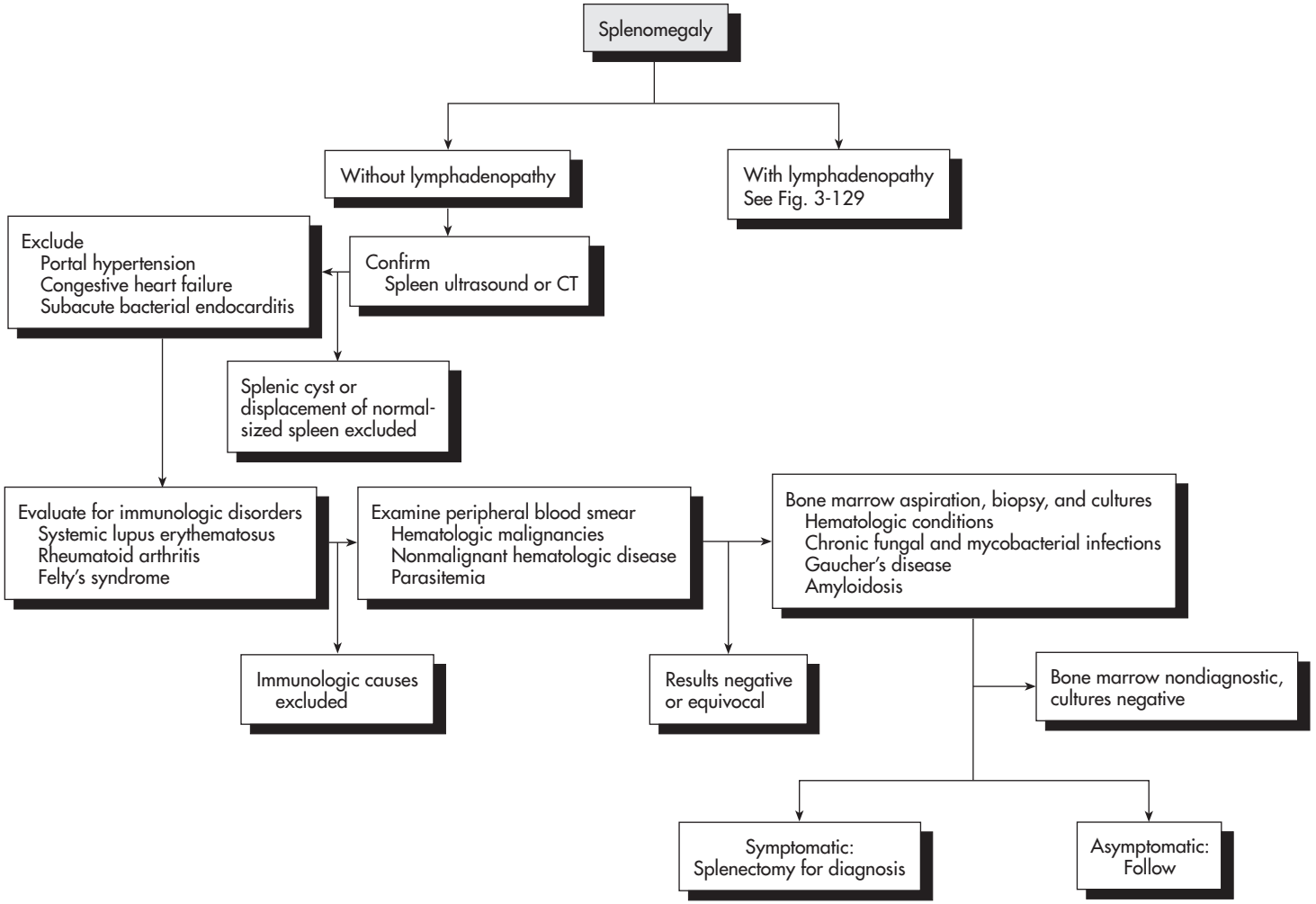


FIGURE 3-193 Clinical approach to patient with splenomegaly. *CT,* Computed tomography. (Modified from Stein JH [ed]: *Internal medicine,* ed 5, St Louis, 1998, Mosby.)

ICD-9CM # 720.7
ICD-10CM # M46.90 Unspecified inflammatory spondylopathy, site unspecified

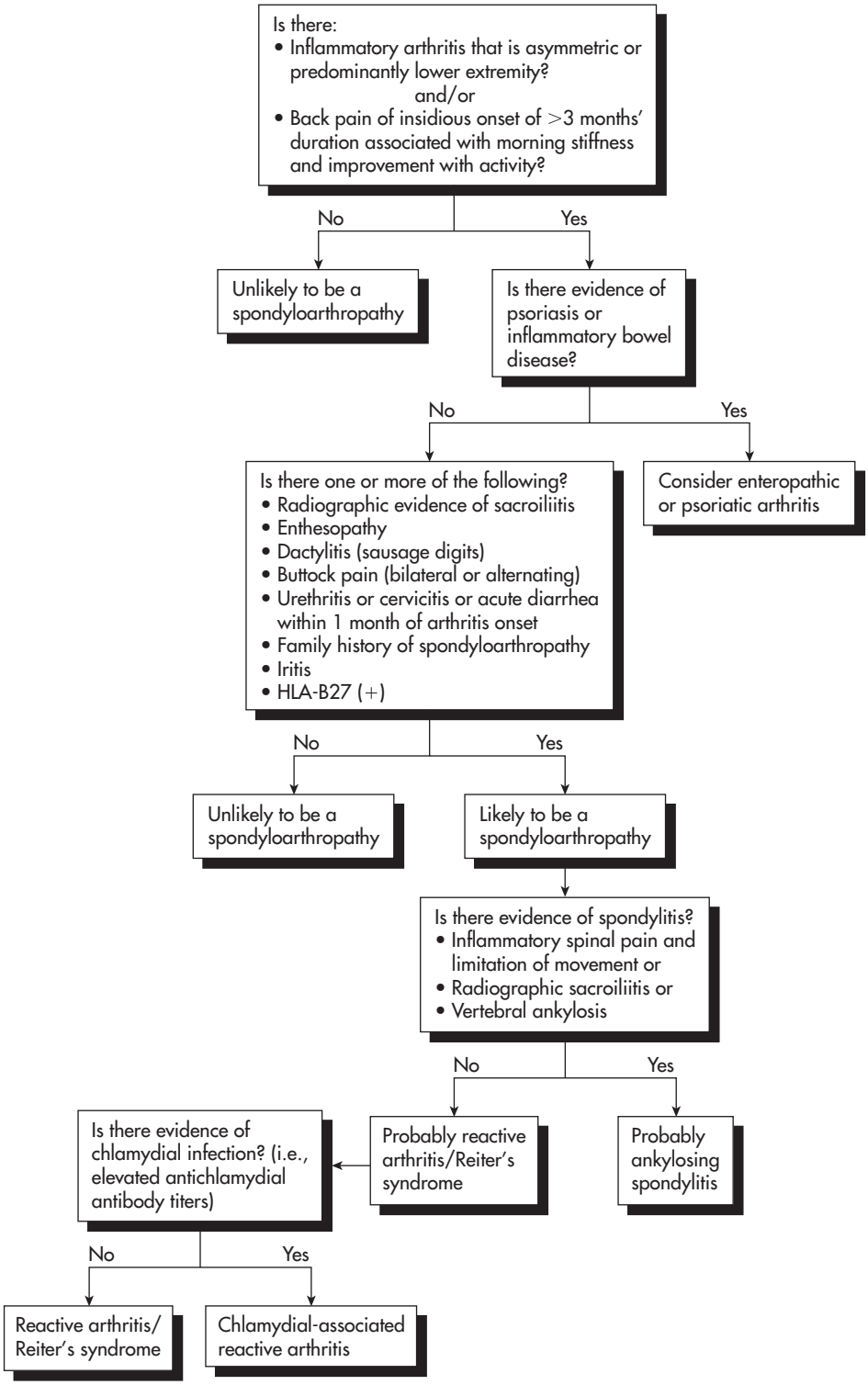
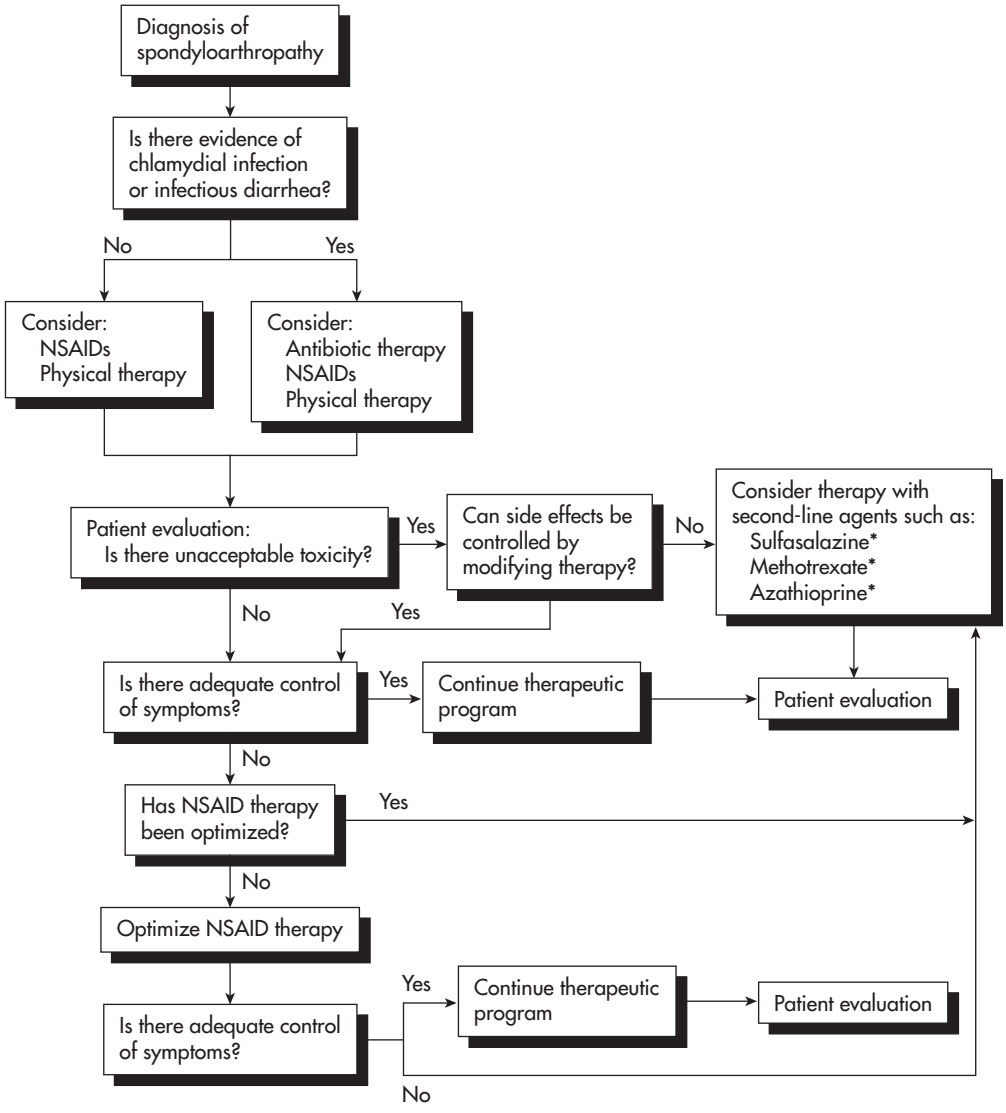


FIGURE 3-194 Algorithm for diagnosis of the spondyloarthropathies. (From Goldman L, Schafer AL: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)



*Not approved by the FDA for treatment of spondyloarthropathies.

FIGURE 3-195 Treatment algorithm for patients with a spondyloarthropathy. *FDA,* Food and Drug Administration; *NSAID,* nonsteroidal anti-inflammatory drug. (From Goldman L, Schafer AL: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

ICD-9CM # 721.0
ICD-10CM # M47.812 Spondylosis without myelopathy or radiculopathy, cervical region

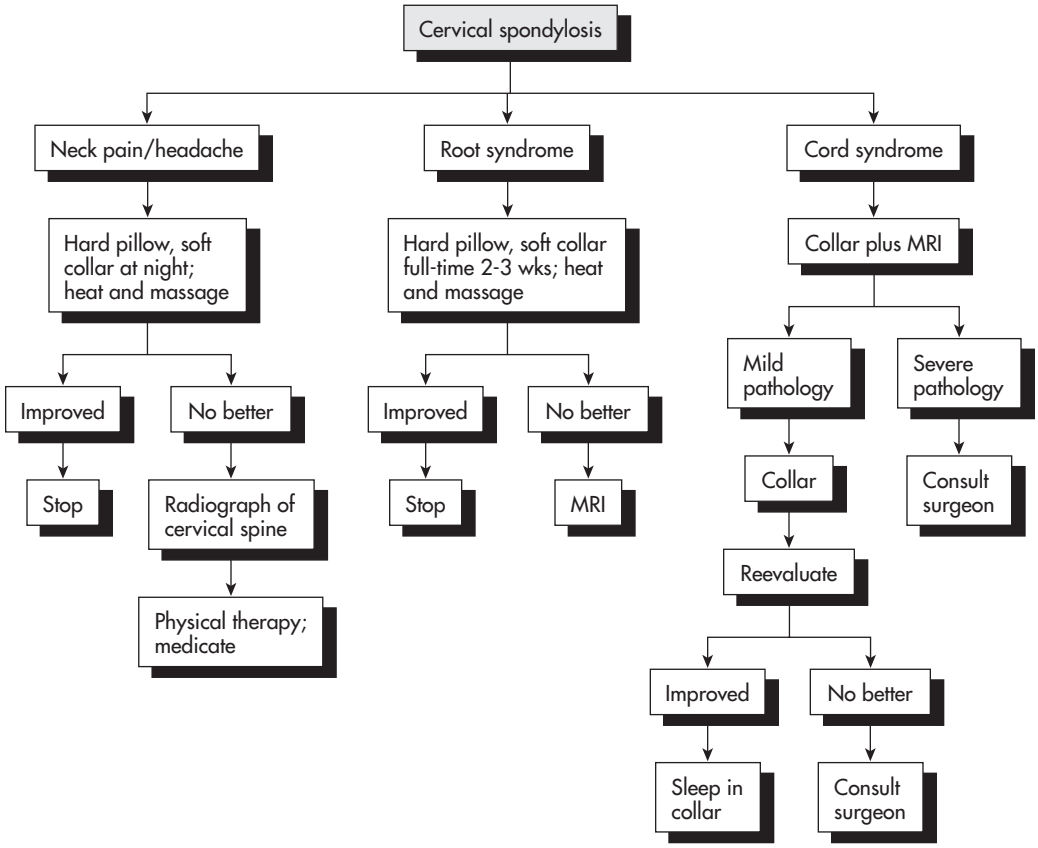
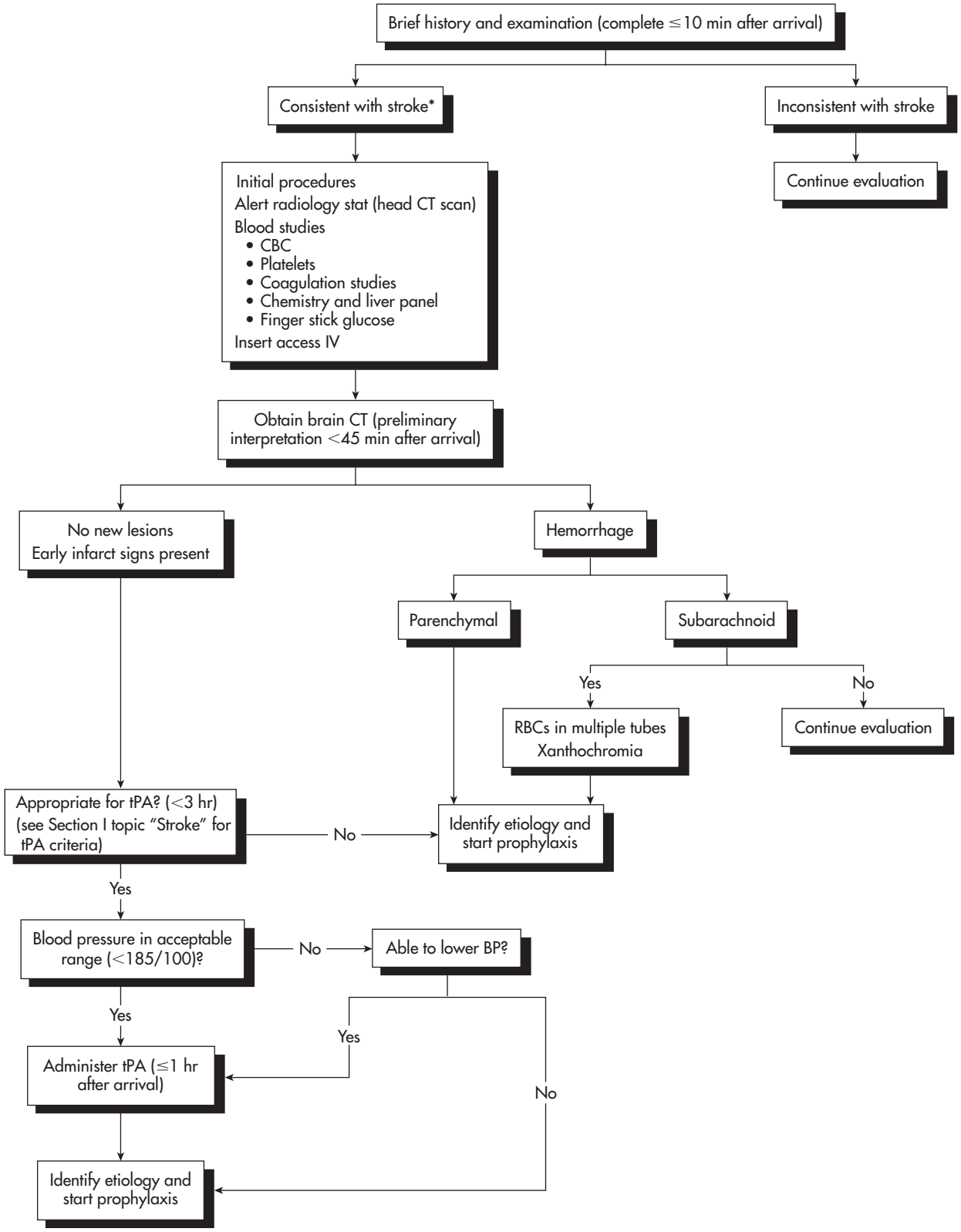


FIGURE E3-196 Algorithm for the treatment of cervical spondylosis. *MRI,* Magnetic resonance imaging. (From Ronthal M, Rachlin JR: Cervical spondylosis. In Johnson RT, Griffin JW [eds]: *Current therapy in neurologic disease,* ed 5, St Louis, 1997, Mosby.)



*Note: Refer to Section I for additional information on this topic.

FIGURE E3-197 Algorithm for the emergency evaluation of a patient with suspected stroke. *BP,* Blood pressure; *CBC,* complete blood count; *CT,* computed tomography; *RBCs,* red blood cells; *tPA,* tissue plasminogen activator. (From Goldman L, Schafer AL [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

SUBCUTANEOUS OSSIFICATION, EVALUATION

ICD-9CM # 709.3
ICD-10CM # L94.2 Calcinosis cutis
L98.8 Other specified disorders of the skin and subcutaneous tissue

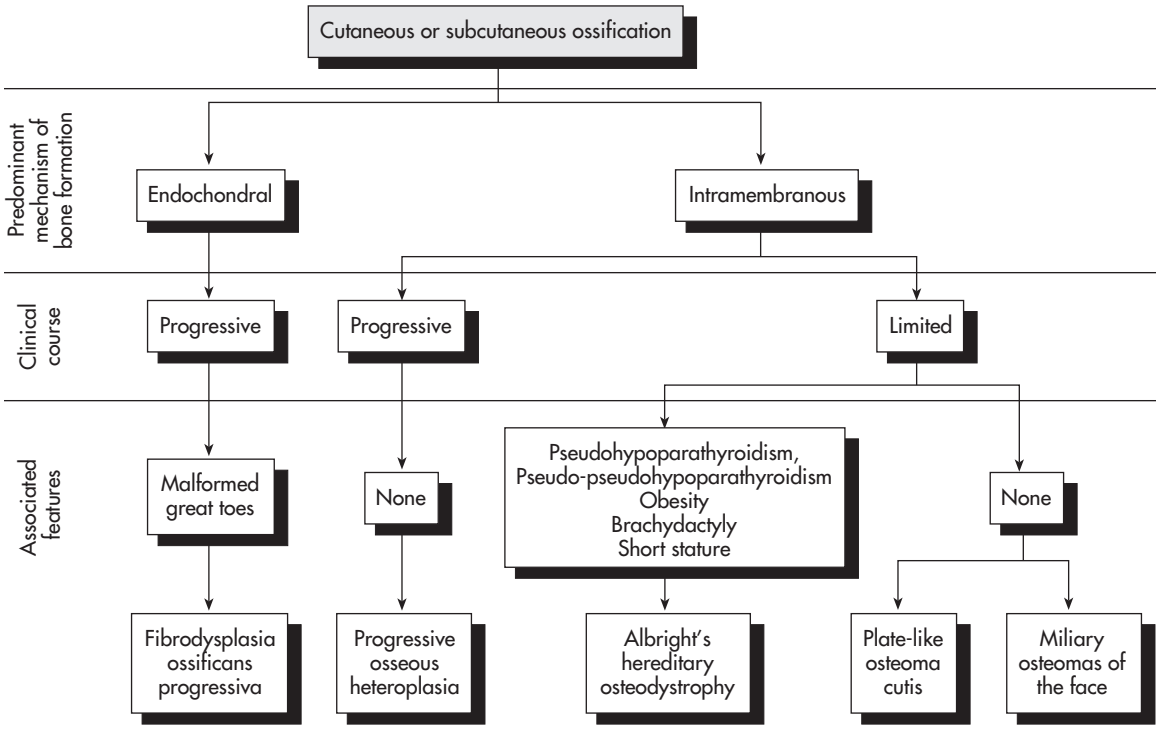


FIGURE E3-198 Algorithm for the evaluation of a patient with cutaneous or subcutaneous ossification. (From Bolognia JL, Jorizzo JL, Rapini RP: *Dermatology,* St Louis, 2003, Mosby.)

ICD-9CM # 785.0
ICD-10CM # R00.0 Tachycardia, unspecified

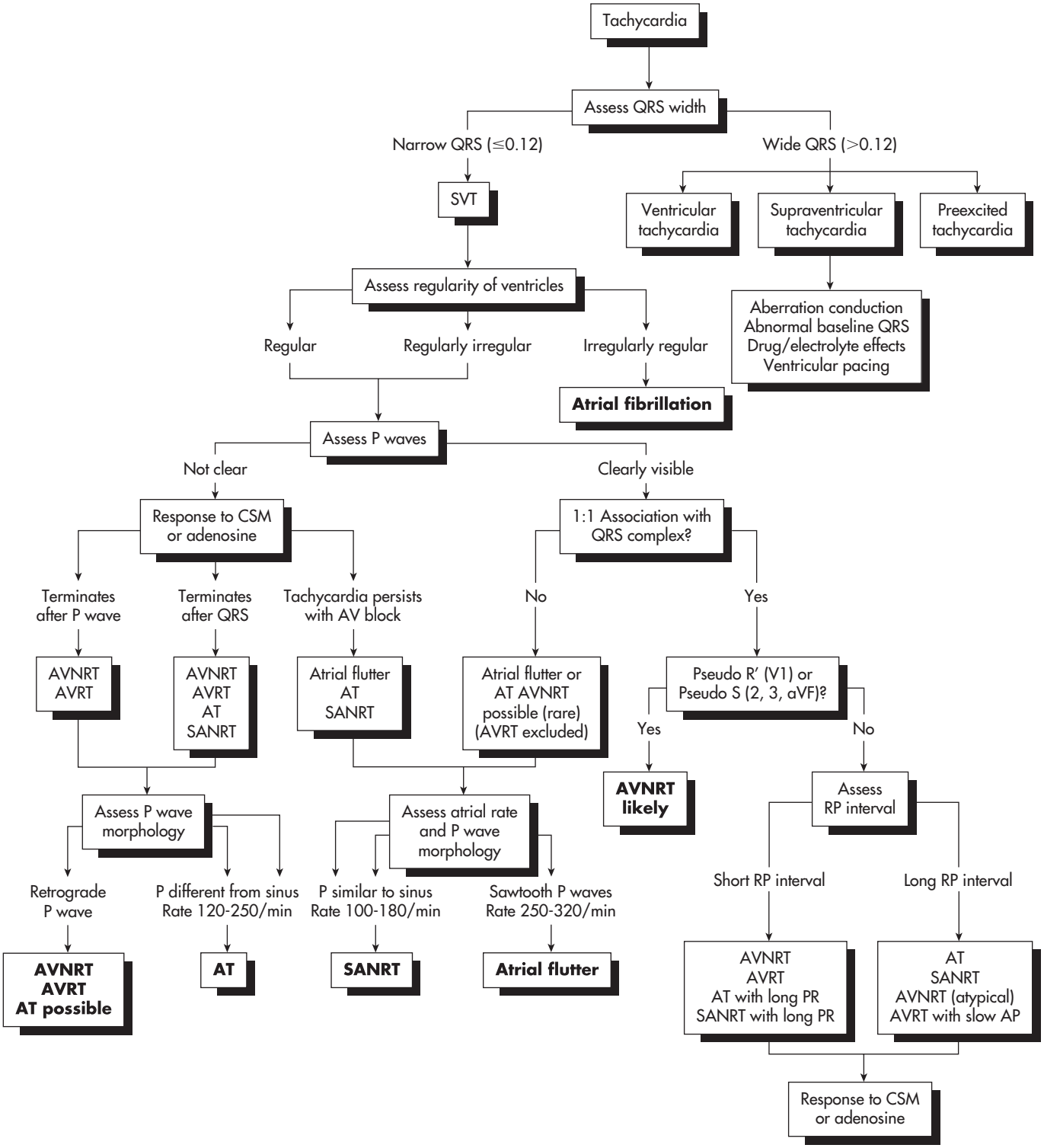


FIGURE 3-199 Stepwise approach to the diagnosis of type of tachycardia based on 12-lead electrocardiogram during the episode. The initial step is to determine whether the tachycardia has a wide or narrow QRS complex (see Fig. 3-200). For wide complex tachycardia, see Figure 3-202; the remainder of the algorithm is helpful in diagnosing the type of narrow-complex tachycardia. *AP,* Accessory pathway; *AT,* atrial tachycardia; *AV,* atrioventricular; *AVNRT,* AV nodal reentrant tachycardia; *AVRT,* AV reciprocating tachycardia; *CSM,* carotid sinus massage; *SANRT,* sinoatrial nodal reentry tachycardia; *SVT,* supraventricular tachycardia. (From Zipes DP, Libby P, Bonow RO, Braunwald E [eds]: *Braunwald's heart disease,* ed 7, Philadelphia, 2005, Saunders.)

ICD-9CM # 427.2 Paroxysmal tachycardia
427.0 Supraventricular paroxysmal tachycardia
427.42 Ventricular flutter
427.1 Ventricular paroxysmal tachycardia
427.89 Atrial tachycardia
ICD-10CM # I49.02 Ventricular flutter
I49.8 Other specified cardiac arrhythmias
R00.1 Bradycardia, unspecified

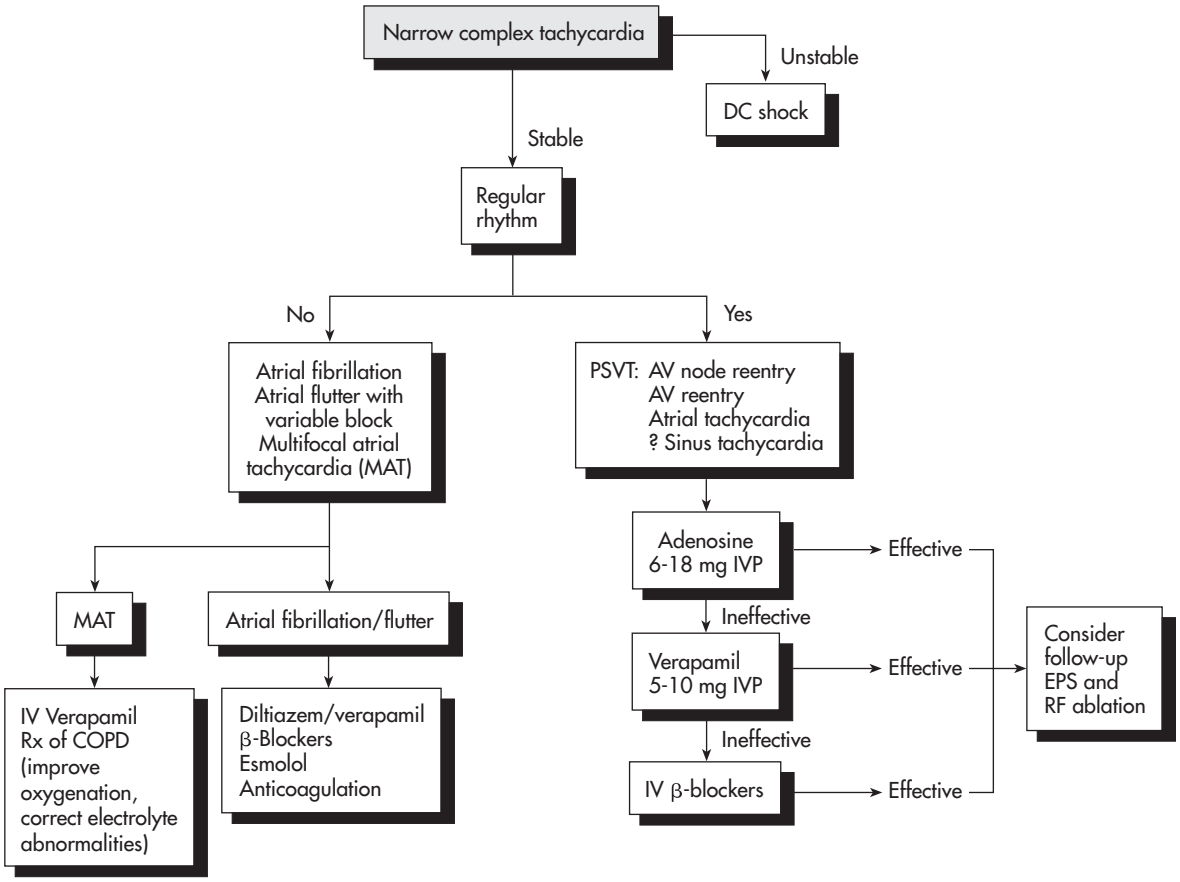


FIGURE 3-200 Evaluation and management of narrow complex tachycardia. *AV,* Atrioventricular; *COPD,* chronic obstructive pulmonary disease; *EPS,* electrophysiologic studies; *IV,* intravenous; *IVP,* intravenous push; *PSVT,* paroxysmal supraventricular tachycardia; *RF,* radiofrequency.

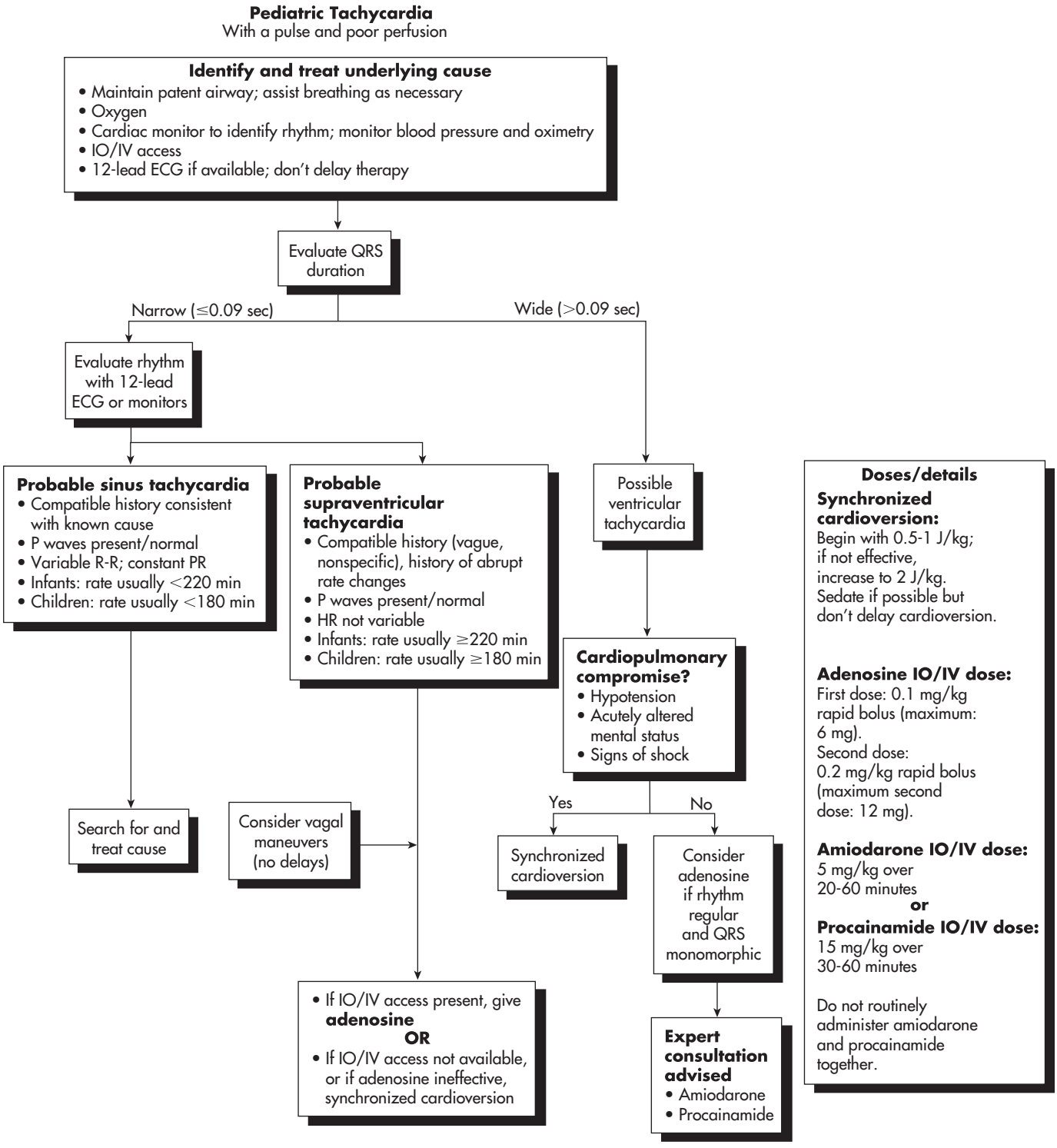


FIGURE E3-201 American Heart Association (AHA) guidelines for management of ventricular arrhythmias. *ECG,* electrocardiogram; *IO,* intraosseous; *IV,* intravenous. (From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.)

ICD-9CM # 427.2 Paroxysmal tachycardia
427.0 Supraventricular paroxysmal tachycardia
427.42 Ventricular flutter
427.1 Ventricular paroxysmal tachycardia
427.89 Atrial tachycardia
ICD-10CM # I49.02 Ventricular flutter
I49.8 Other specified cardiac arrhythmias
R00.1 Bradycardia, unspecified

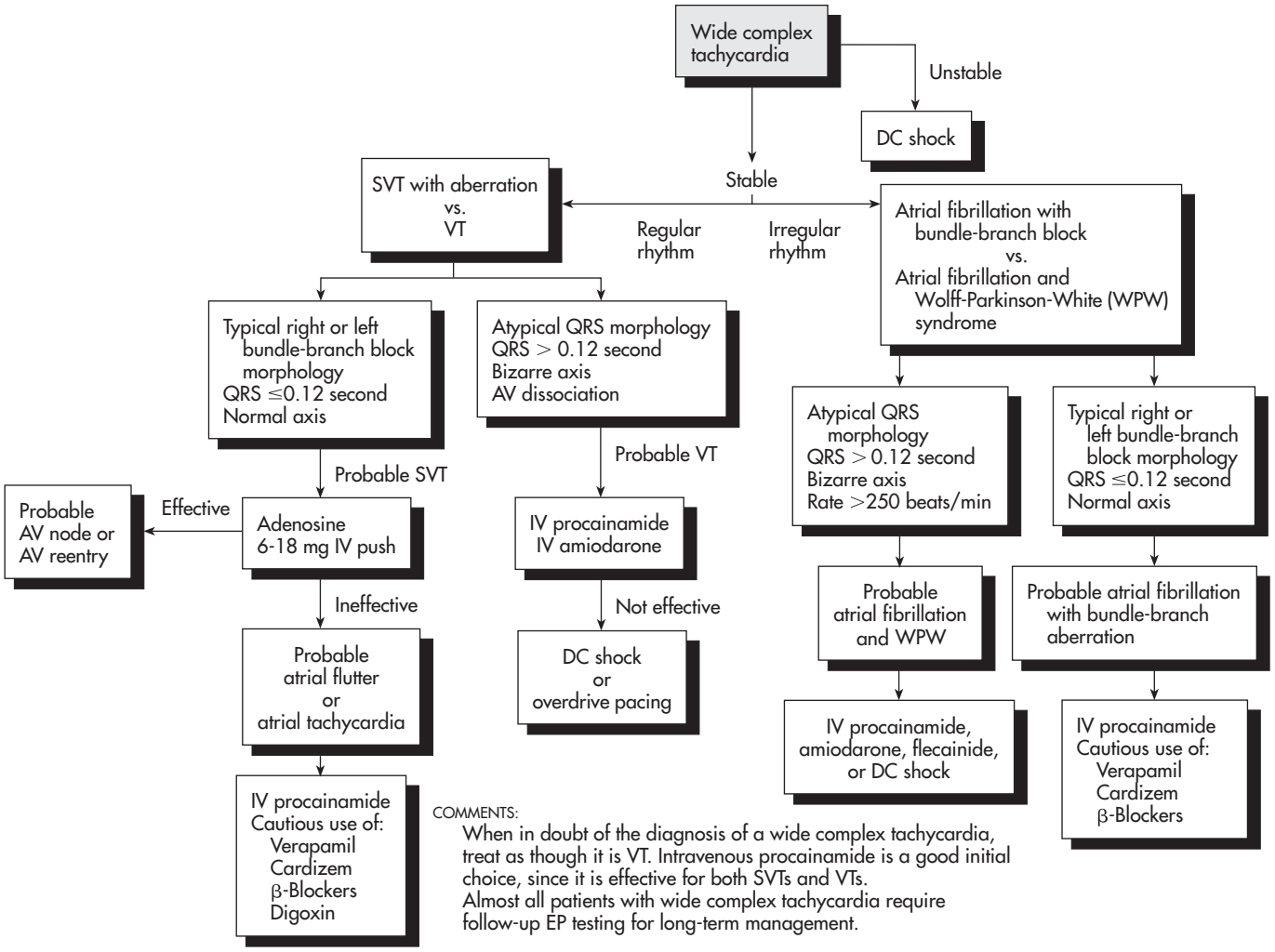


FIGURE 3-202 Evaluation and management of wide complex tachycardia. *AV,* Atrioventricular; *EP,* electrophysiologic; *IV,* intravenous; *SVT,* supraventricular tachycardia; *VT,* ventricular tachycardia. (From Driscoll CE et al: *The family practice desk reference,* ed 3, St Louis, 1996, Mosby.)

TABLE 3-31 Major Features in the Differential Diagnosis of Wide QRS Beats

Supports SVT	Supports VT
Slowing or termination by vagal tone	Fusion beats
Onset with premature P wave	Capture beats
RP interval <100 msec	AV dissociation
P and QRS rate and rhythm linked to suggest that ventricular activation depends on atrial discharge, e.g., 2:1 AV block rSR′ V1	P and QRS rate and rhythm linked to suggest that atrial activation depends on ventricular discharge, e.g., 2:1 VA block
Long-short cycle sequence	"Compensatory" pause
	Left axis deviation; QRS duration >140 msec
	Specific QRS contours (see text)

SVT, Supraventricular tachycardia; *VT,* ventricular tachycardia.
From Zipes DP et al [eds]: *Braunwauld's heart disease,* ed 7, Philadelphia, 2005, Saunders.

ICD-9CM # 186.9 Testicular neoplasm
M906/3 (seminoma)
M9101/3 (embryonal carcinoma or teratoma)
M9100/3 (choriocarcinoma)
ICD-10CM # C62.90 Malignant neoplasm of unspecified testis, unspecified whether descended or undescended

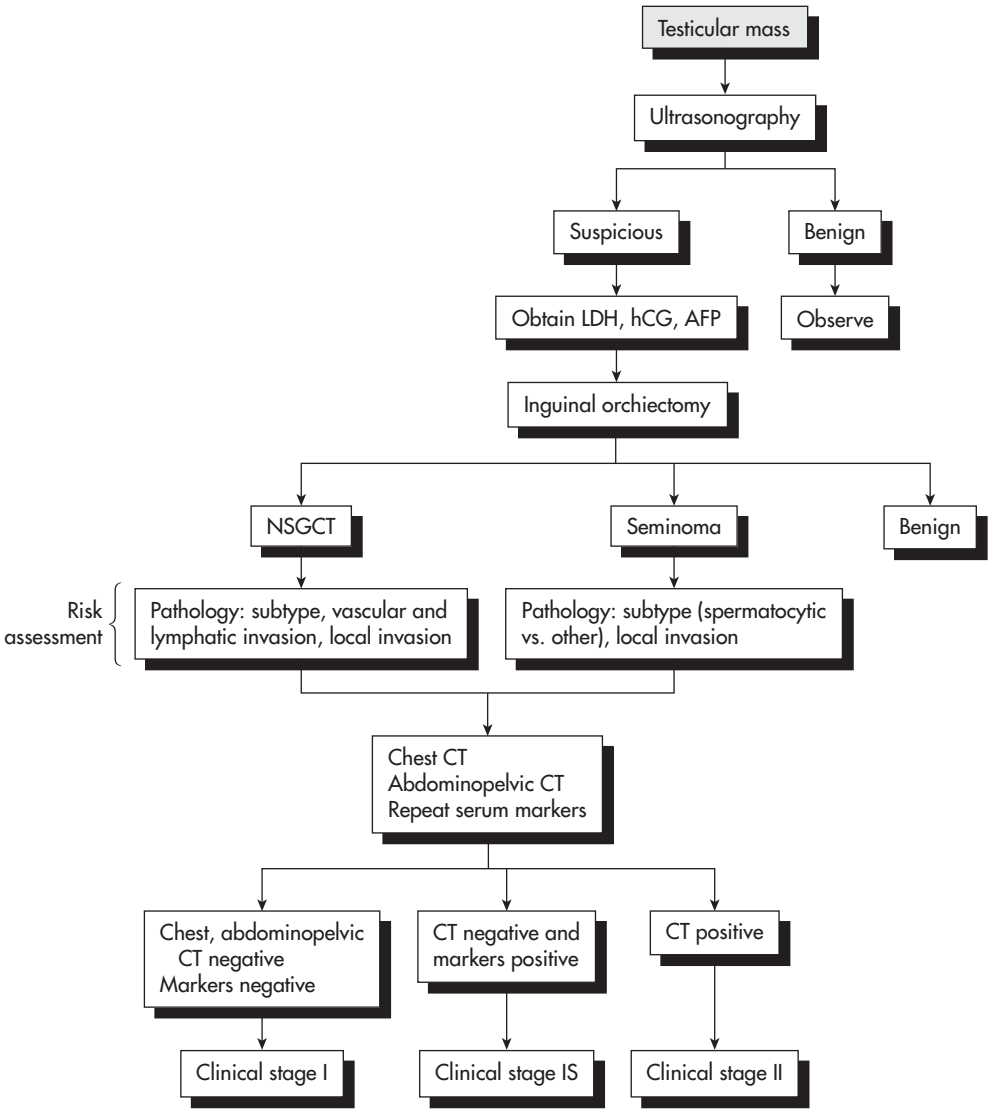


FIGURE 3-203 Diagnosis, staging, and risk assessment of patients with testicular germ cell tumor. *AFP,* α-fetoprotein; *CT,* computed tomography; *hCG,* human chorionic gonadotropin; *LDH,* lactic dehydrogenase; *NSGCT,* nonseminoma germ cell tumor. (From Abeloff MD: *Clinical oncology,* ed 4, New York, 2007, Churchill Livingstone.)

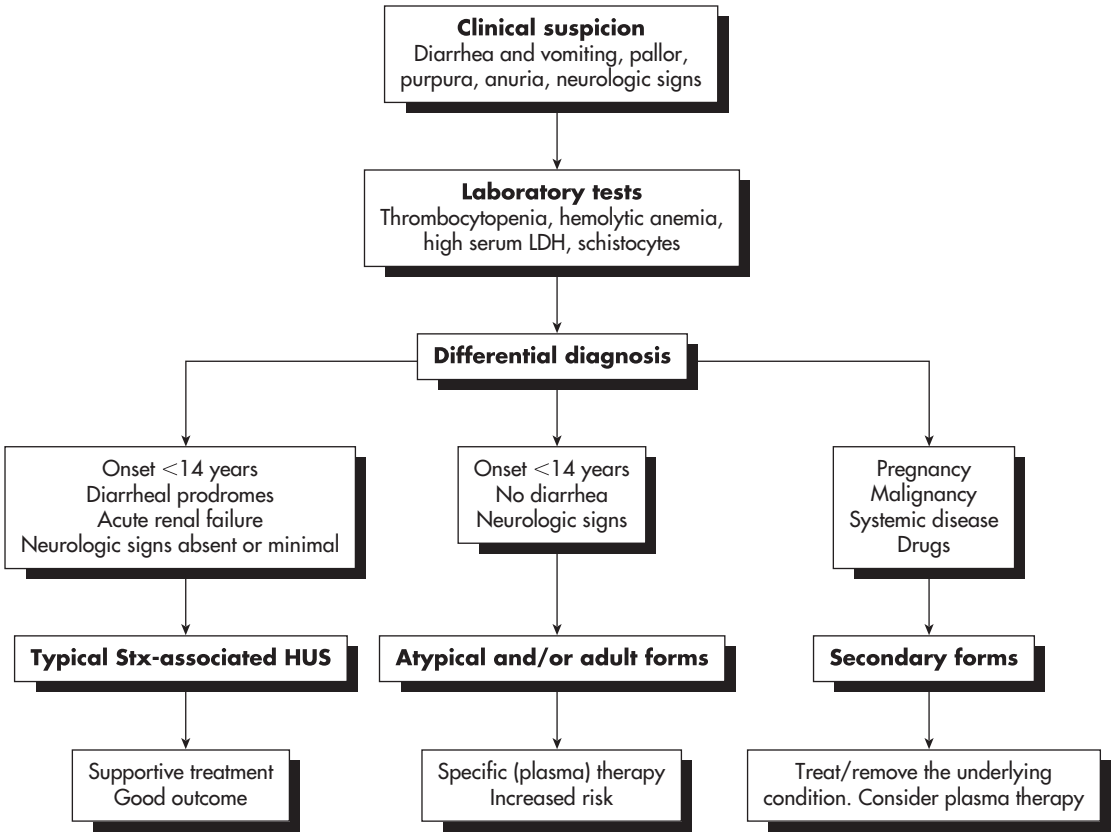


FIGURE E3-204 Algorithm for the differential diagnosis of thrombotic microangiopathies. Patients with suggestive symptoms should be investigated for specific signs of microangiopathic hemolysis. In adults, secondary forms of the disease must be ruled out. Early diagnosis may help establish the most appropriate therapy. In children with Stx-associated HUS, supportive treatment is mandatory. Specific therapies should be considered only in adults and in atypical forms. In secondary forms, treating and/or removing the underlying disease is fundamental. *HUS,* Hemolytic-uremic syndrome; *LDH,* lactate dehydrogenase; *Stx,* Shiga toxin. (From Feehally J, Floege J, Johnson RJ: *Comprehensive clinical nephrology,* ed 3, St Louis, 2007, Mosby.)

ICD-9CM # 245.0 Acute thyroiditis
ICD-10CM # E06.0 Acute thyroiditis

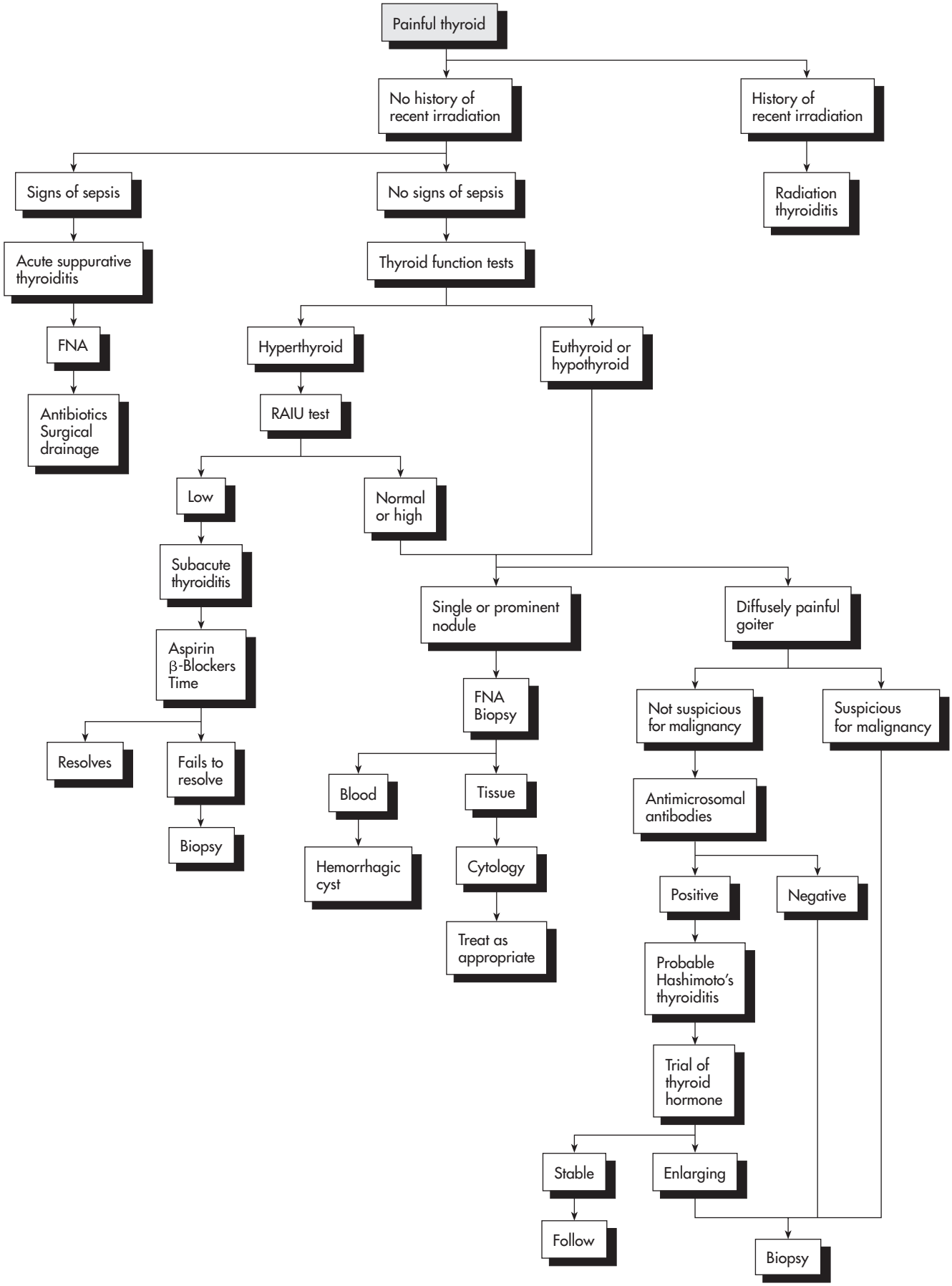


FIGURE 3-205 Painful thyroid. *FNA,* Fine-needle aspiration; *RAIU,* radioactive iodine uptake. (From Greene HL, Johnson WP, Lemcke DL [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

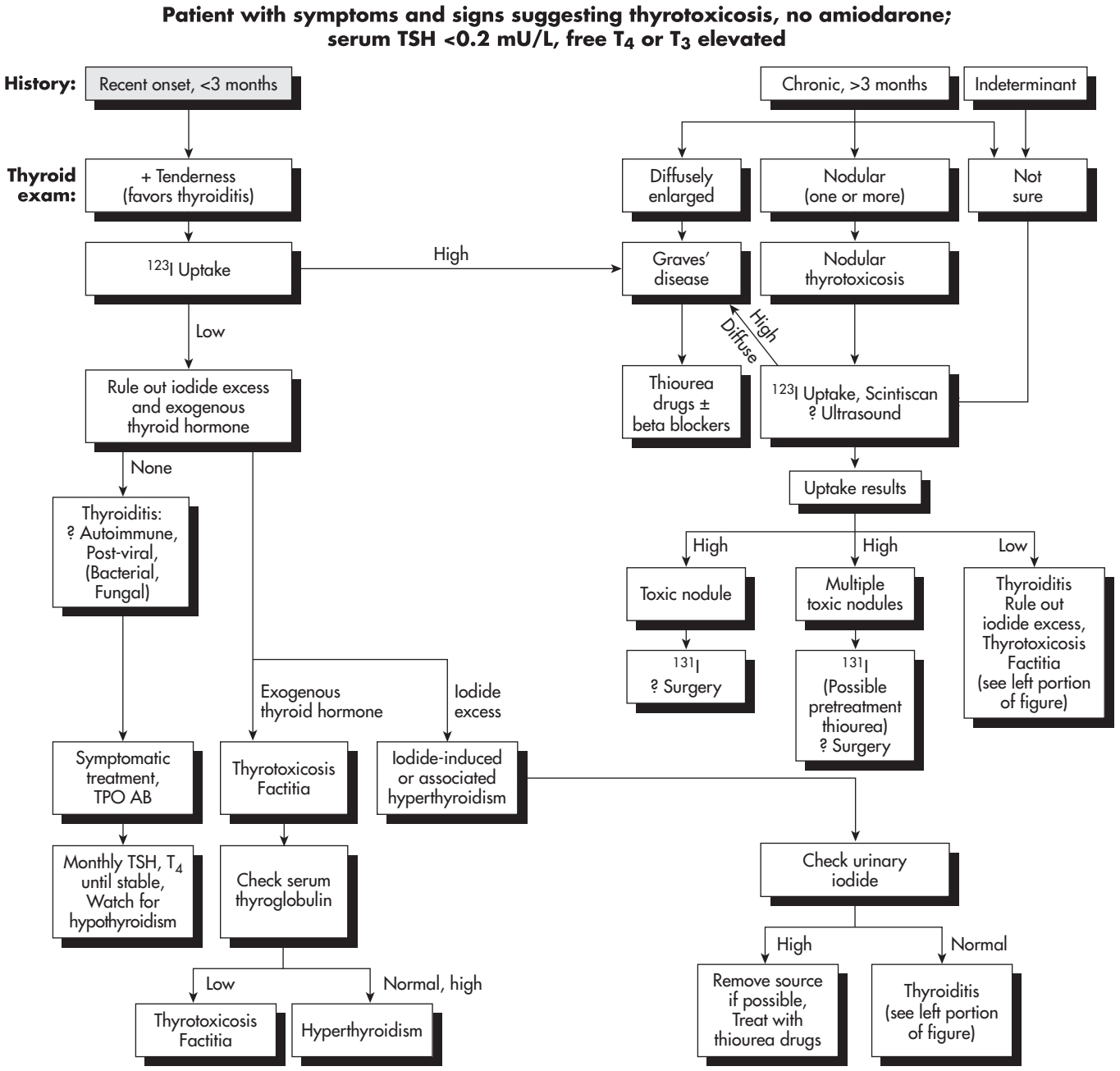


FIGURE 3-206 Algorithm for determining the cause of thyrotropin-independent thyrotoxicosis. *T_3*, triiodothyronine; *T_4*, thyroxine; *TPO AB*, thyroid peroxidase antibody; *TSH*, thyroid-stimulating hormone (thyrotropin). (From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.)

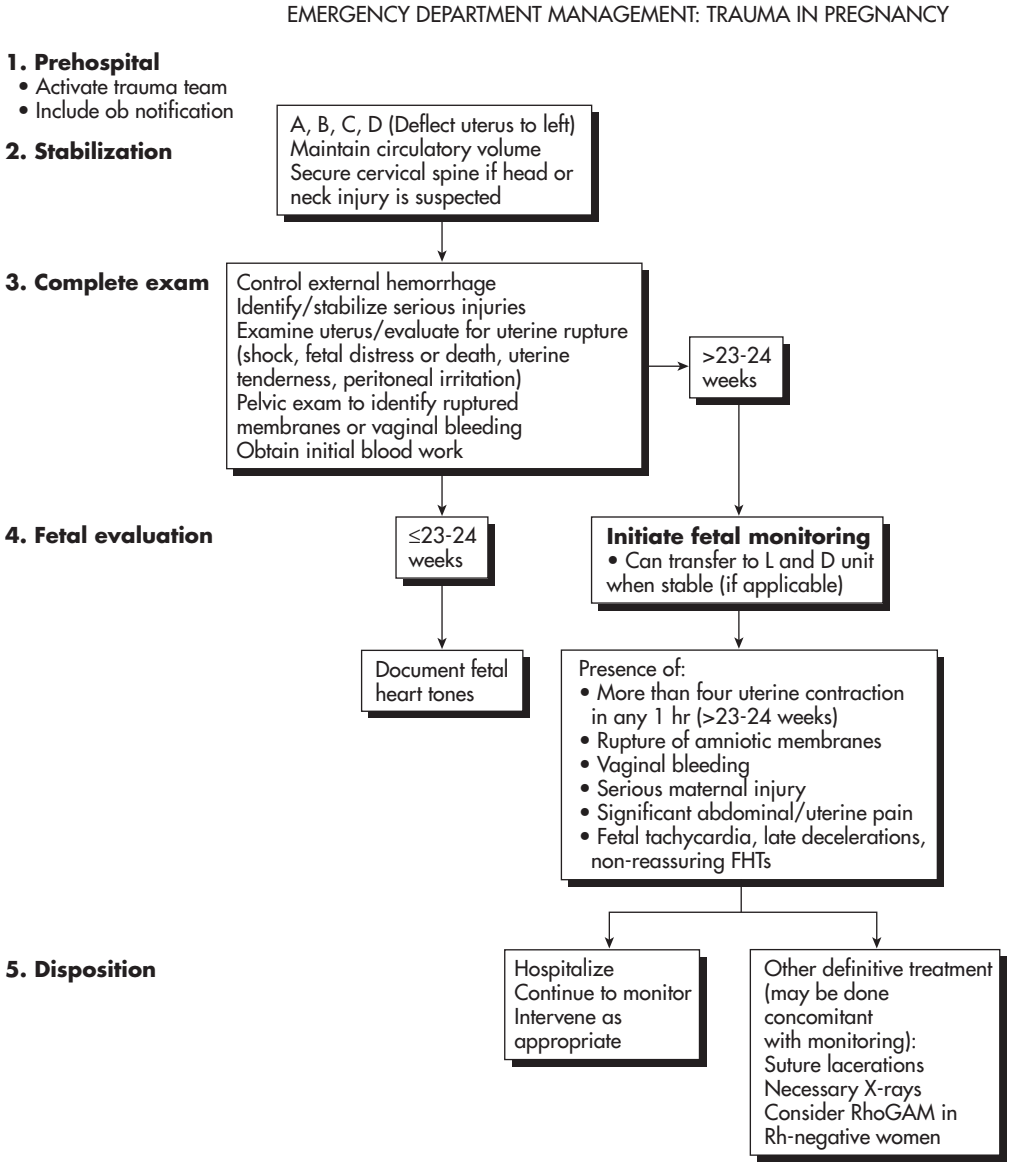


FIGURE 3-207 Algorithm with suggested plan of care for pregnant women experiencing trauma.
(From Gabbe SG: *Obstetrics,* 6th ed, Philadelphia, Saunders, 2012, Figure 25-2.)

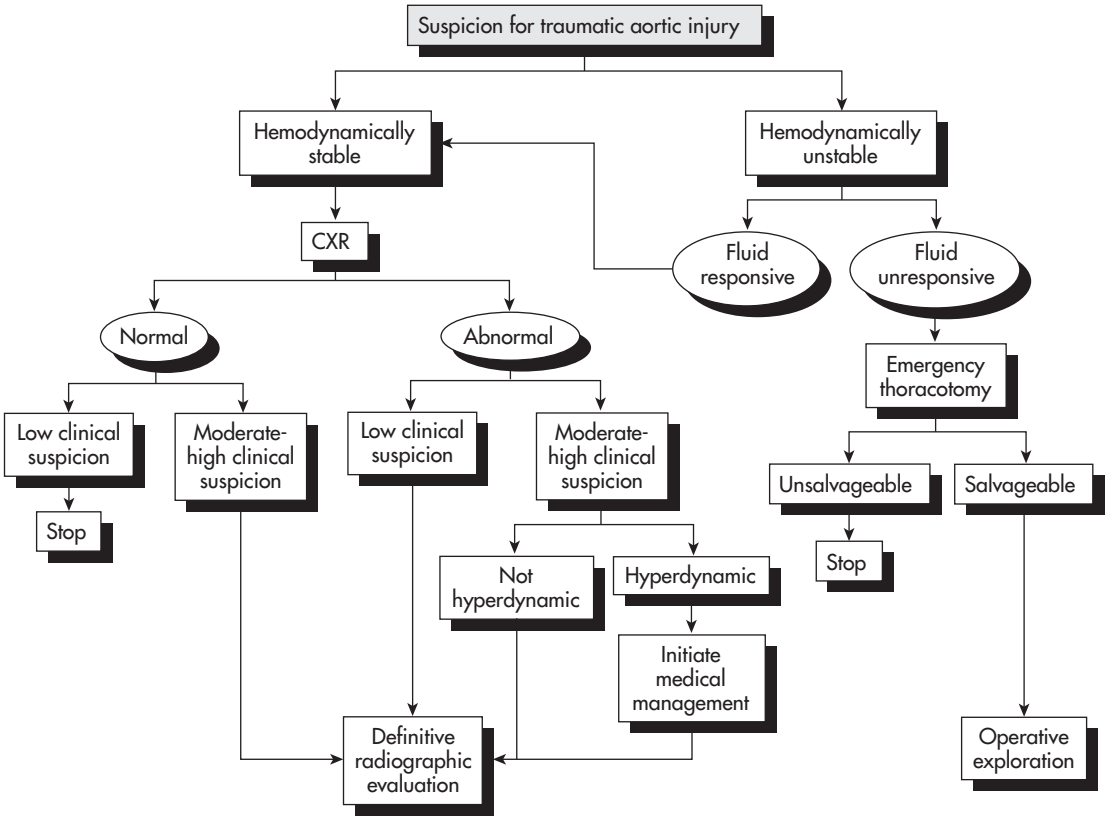


FIGURE 3-208 Diagnostic management algorithm for suspected traumatic aortic injury. *CXR,* Chest radiograph. (From Adams JG, et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

BOX 3-9 Pros and Cons of Imaging Modalities for Great Vessel Injury

Chest Radiography
Pros
- Inexpensive
- Performed at the bedside
- Easy to interpret

Cons
- Nonspecific
- False-negative rate of 7% to 10% for traumatic aortic injury

Computed Tomographic Angiography
Pros
- Identifies mediastinal hematoma and differentiates its causes
- Identifies aortic injury, including intimal tears
- Sensitivity and specificity approaching 100% for traumatic aortic injury

Cons
- Poor delineation of nonaortic vascular injuries
- Requires relative hemodynamic stability to obtain

Aortography
Pros
- Traditional "gold standard"
- Beneficial in the diagnosis of branch vessel injuries
- Delineates equivocal computed tomographic angiographic findings

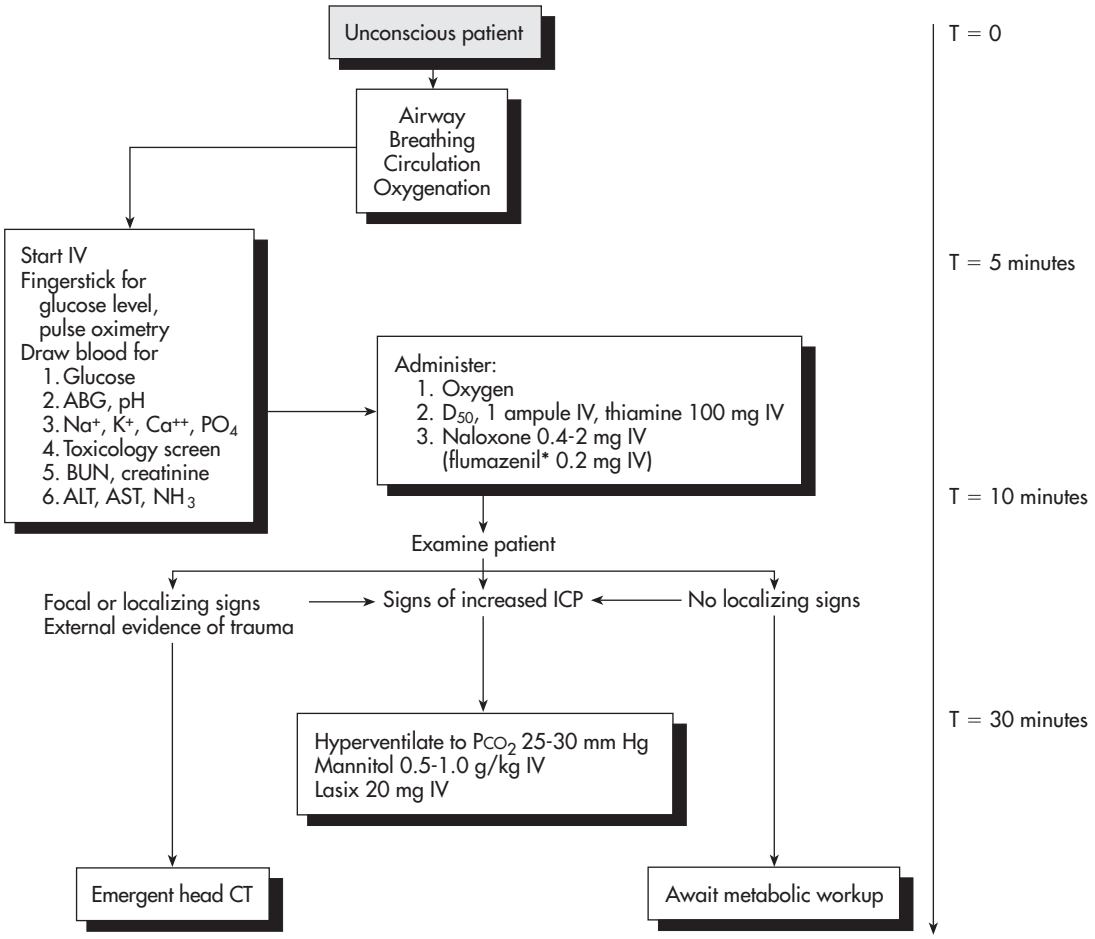
Cons
- Difficult to obtain on an emergency basis
- Requires relative hemodynamic stability

Transesophageal Echocardiography
Pros
- May be performed at the bedside
- Not limited by body habitus

Cons
- Poor availability on an emergency basis
- Contraindicated in patients with an unstable cervical spine or suspected esophageal trauma

From Adams JG, et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.

ICD-9CM # 780.09
ICD-10CM # R40.0 Somnolence
R40.1 Stupor



* Use of flumazenil should not be considered routine because it can precipitate seizures in certain subsets of patients.

FIGURE E3-209 Approach to the unconscious patient. *ABG,* Arterial blood gas; *ALT,* alanine aminotransferase; *AST,* aspartate aminotransferase; *BUN,* blood urea nitrogen; *CT,* computed tomography; *ICP,* intracranial pressure. (Modified from Johnson RT, Griffin JW: *Current therapy in neurologic disease,* ed 5, St Louis, 1997, Mosby.)

ICD-9CM # varies with specific diagnosis
ICD-10CM # N21.8 Other lower urinary tract calculus

Investigation and Management of Suspected Urinary Tract Obstruction

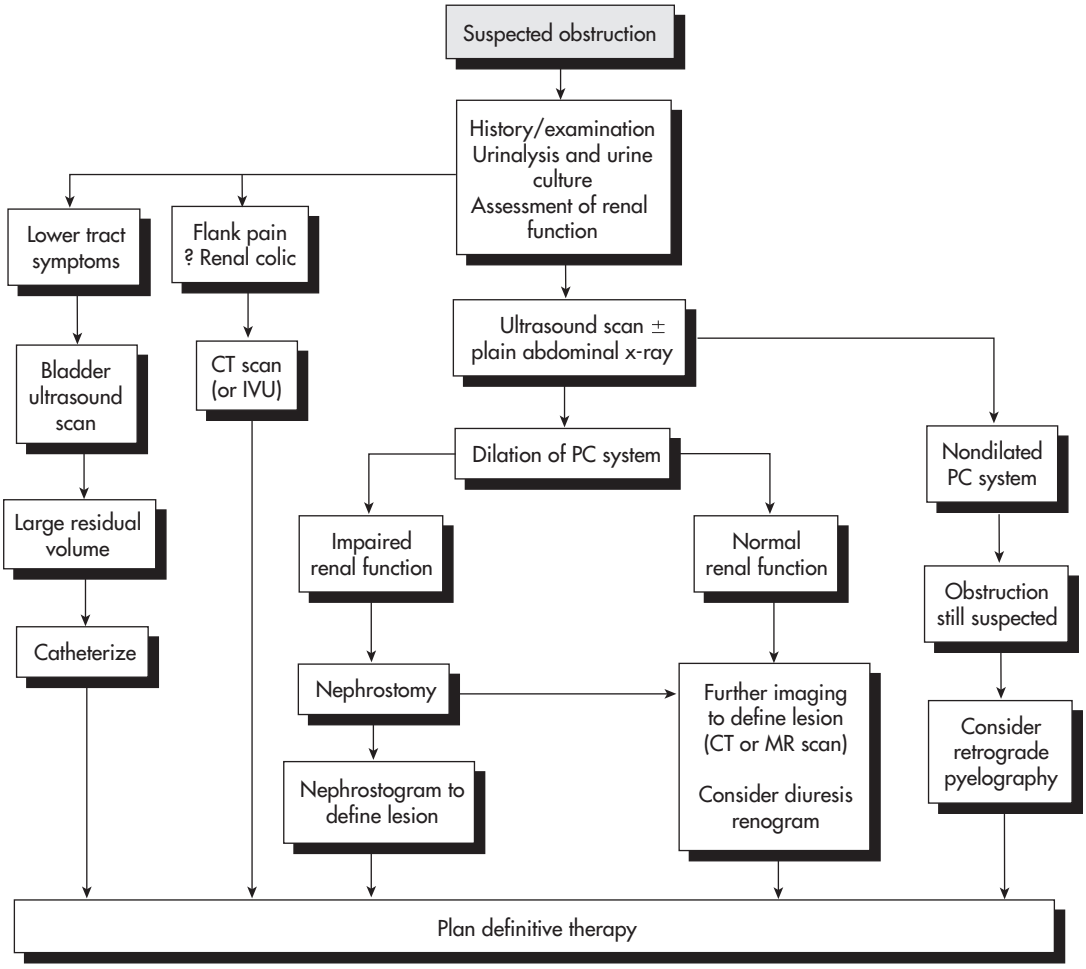


FIGURE 3-210 Investigation and management of suspected urinary tract obstruction. A full history and examination should be performed together with urinalysis, urine microscopy and culture, and measurement of renal function and serum electrolytes. Ultrasound is a useful first-line investigation for any patient with suspected urinary tract obstruction. Helical (spiral) computed tomography (CT) is now the preferred imaging technique when renal calculi are suspected. Either CT or magnetic resonance (MRI) urography can accurately diagnose both the site and the cause of obstruction in most cases. If there is renal impairment, insertion of a nephrostomy allows the effective relief of the obstruction and time for renal function to recover while definitive therapy is planned. *IVU,* Intravenous urography; *PC,* pelvicalyceal. (From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.)

BOX 3-10 Diagnostic Tests Used in Obstructive Uropathy

Upper Urinary Tract Obstruction	Lower Urinary Tract Obstruction
Sonography (ultrasound)	Some of the tests listed at left
Plain films of the abdomen (KUB)	Cystoscopy
Excretory or intravenous pyelography (very rarely needed)	Voiding cystourethrogram
Retrograde pyelography	Retrograde urethrography
Isotopic renography	Urodynamic tests
Computed tomography (helical CT)	Debimetry
Magnetic resonance imaging	Cystometrography
Pressure flow studies (the Whitaker test)	Electromyography
	Urethral pressure profile

KUB, Kidneys, ureter, bladder.

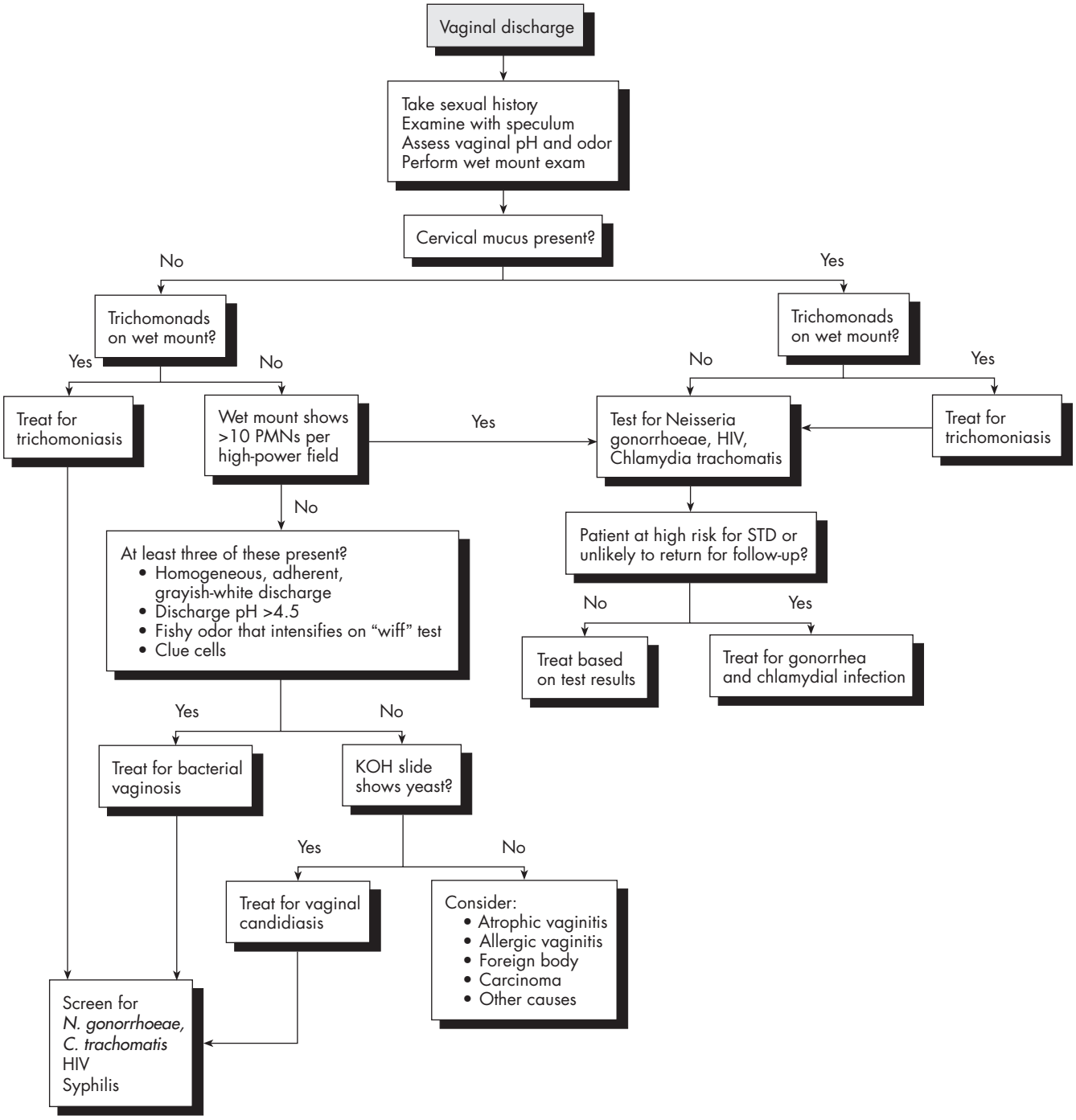


FIGURE 3-211 Evaluation of vaginal discharge. *HIV,* Human immunodeficiency virus; *KOH,* potassium hydroxide; *PMN,* polymorphonuclear leukocyte; *STD,* sexually transmitted disease.

ICD-9CM # 618.0
ICD-10CM # N81.9 Female genital prolapse, unspecified

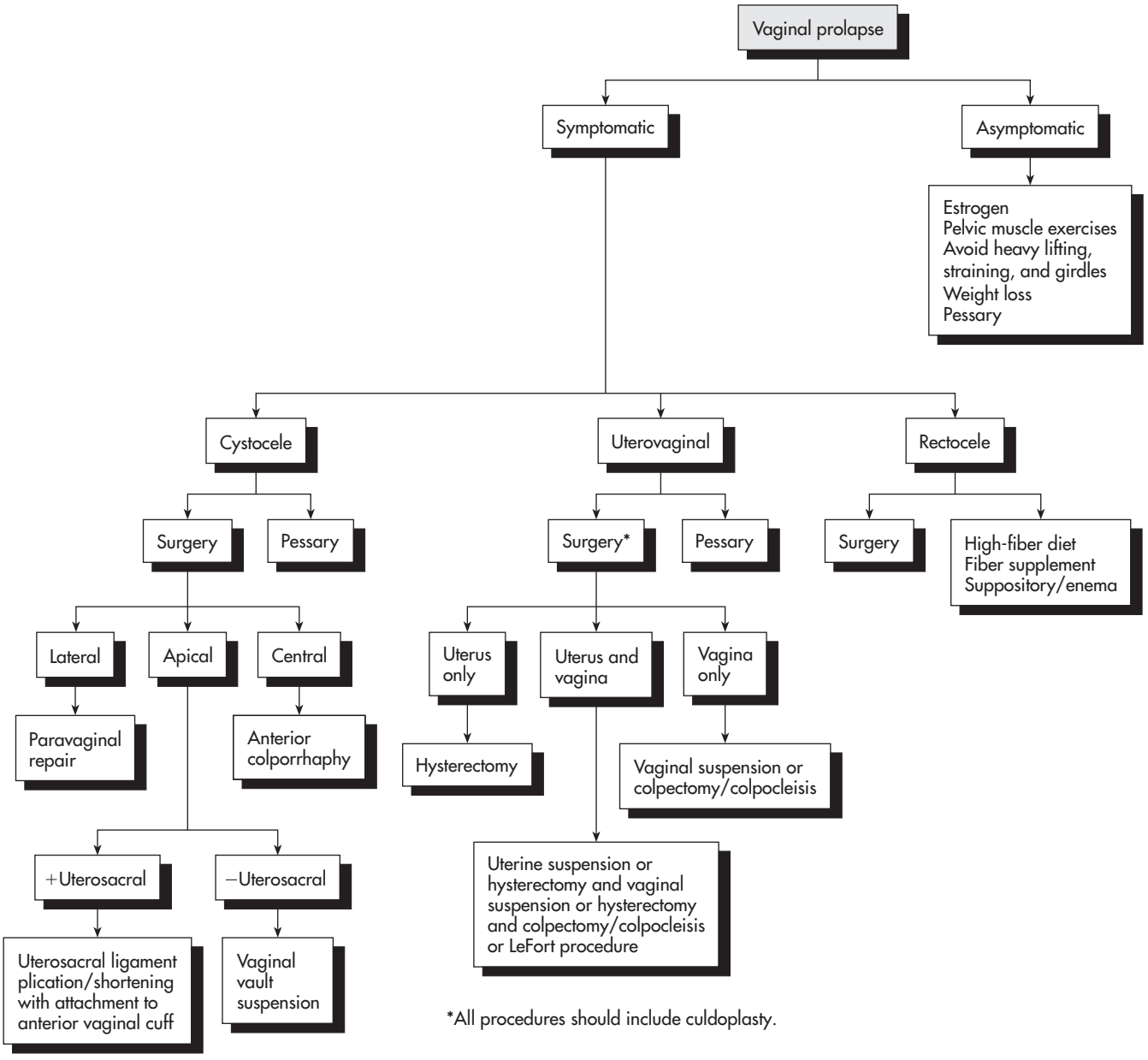


FIGURE E3-212 Management of vaginal prolapse. (From Zuspan FP [ed]: *Handbook of obstetrics, gynecology, and primary care,* St Louis, 1998, Mosby.)

VAGINITIS, PEDIATRIC

ICD-9CM # 616.10
ICD-10CM # N76.0

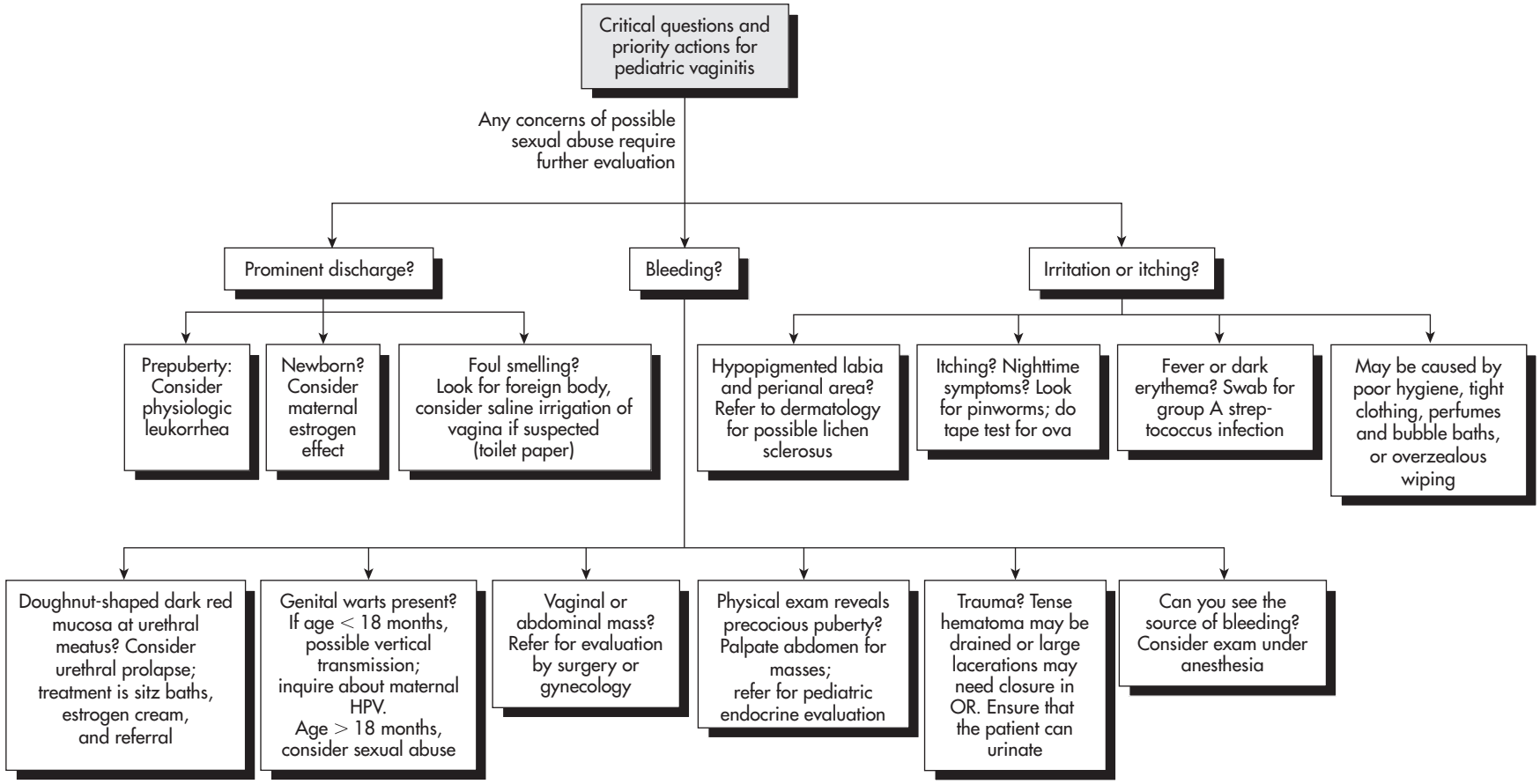


FIGURE 3-213 Algorithm showing critical questions and priority actions for pediatric vaginitis. *HPV*, Human papillomavirus; *OR*, operating room. (From Adams JG, et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

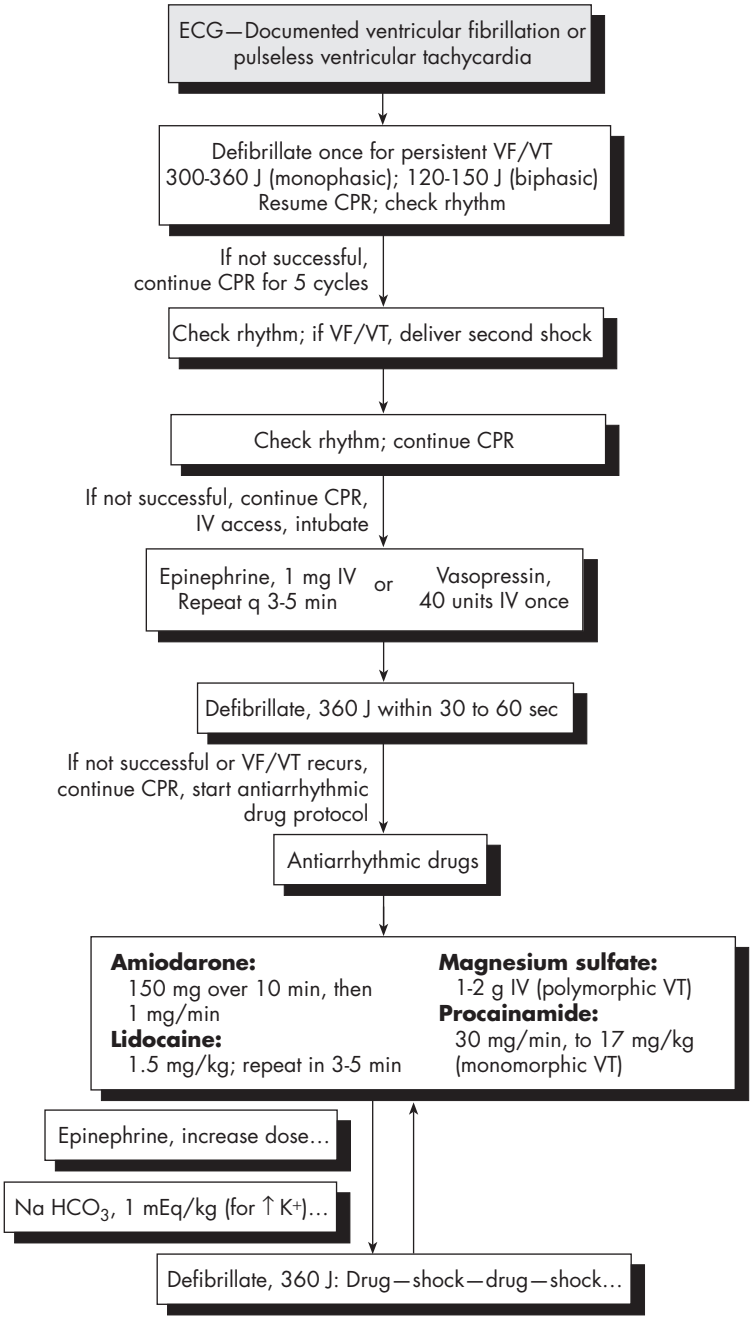


FIGURE 3-214 General algorithm for advanced cardiac life support (ACLS) response to ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT). *Note:* In a 2008 advisory, 200 compression-only sequences were suggested as an alternative to standard CPR cycles between shocks, and this approach is under consideration for future guidelines. *CPR,* Cardiopulmonary resuscitation; *ECG,* electrocardiogram. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

ICD-9CM # 780.4 Vertigo NOS
386.11 Benign Paroxysmal Positional
386.2 Central Origin
386.10 Peripheral
386.12 Vestibular (Neuronitis)
ICD-10CM # R42 Dizziness and giddiness
H81.13 Benign paroxysmal vertigo, bilateral
H81.49 Vertigo of central origin, unspecified ear
H81.399 Other peripheral vertigo, unspecified ear
H81.23 Vestibular neuronitis, bilateral

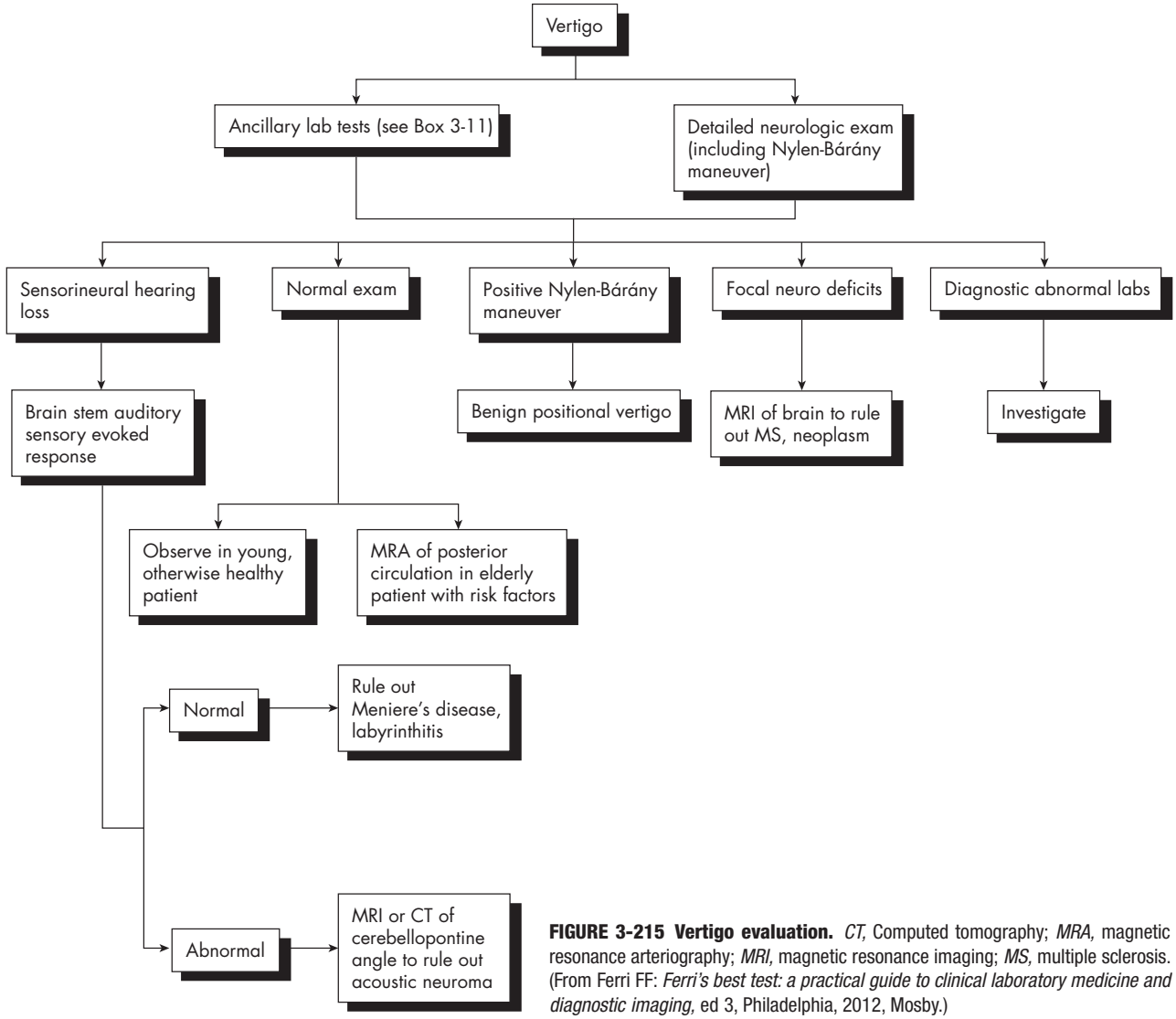


FIGURE 3-215 Vertigo evaluation. *CT,* Computed tomography; *MRA,* magnetic resonance arteriography; *MRI,* magnetic resonance imaging; *MS,* multiple sclerosis. (From Ferri FF: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 3, Philadelphia, 2012, Mosby.)

BOX 3-11 Vertigo

Diagnostic Imaging
Best Test
MRI of brain
Ancillary Tests
MRA of posterior circulation
CT of cerebellopontine region if MRI is contraindicated

Lab Evaluation
Best test
None
Ancillary Tests
CBC with differential
Serum glucose, creatinine, ALT, electrolytes

ALT, Alanine aminotransferase; *CBC,* complete blood count; *CT,* computed tomography; *MRA,* magnetic resonance angiography; *MRI,* magnetic resonance imaging.

From Ferri FF: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 2, Philadelphia, 2009, Elsevier Mosby.

ICD-9CM # 787.03 Vomiting
ICD-10CM # R11.10 Vomiting, unspecified
R11.11 Vomiting without nausea
R11.12 Projectile vomiting

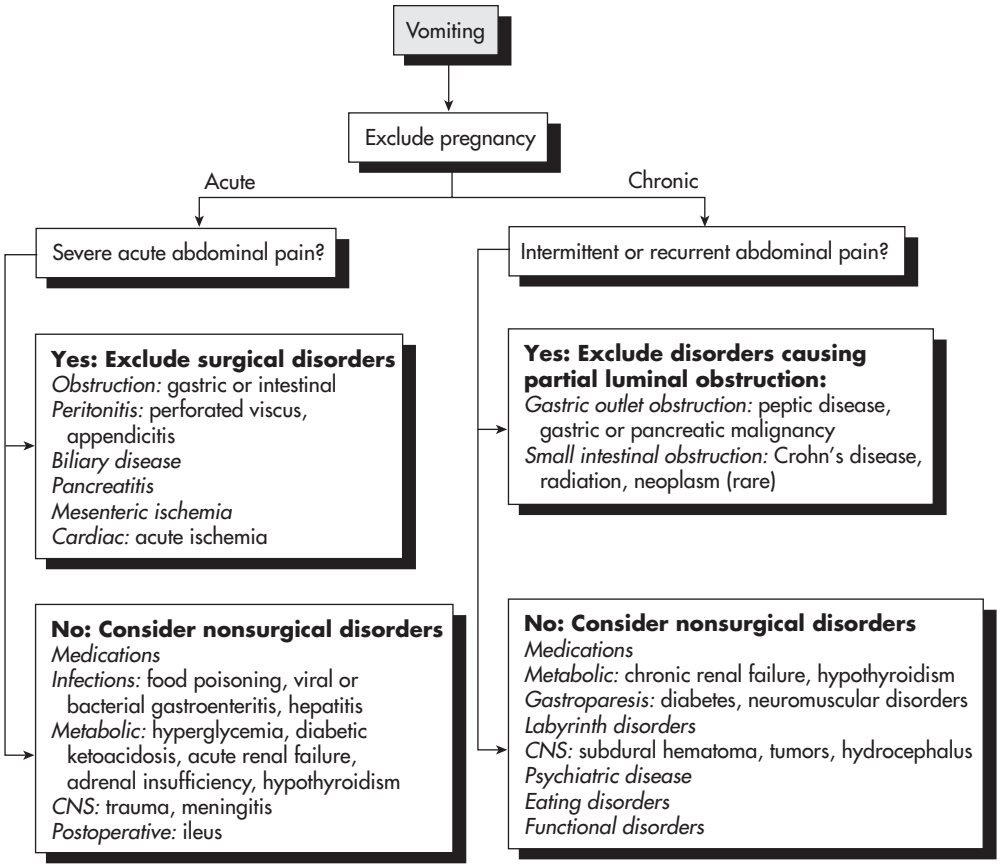


FIGURE 3-216 Approach to the patient with vomiting. *CNS,* Central nervous system. (From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.)

ICD-9CM # 780.79
ICD-10CM # G93.3 Postviral fatigue syndrome
R53.1 Weakness
R53.81 Other malaise
R53.83 Other fatigue

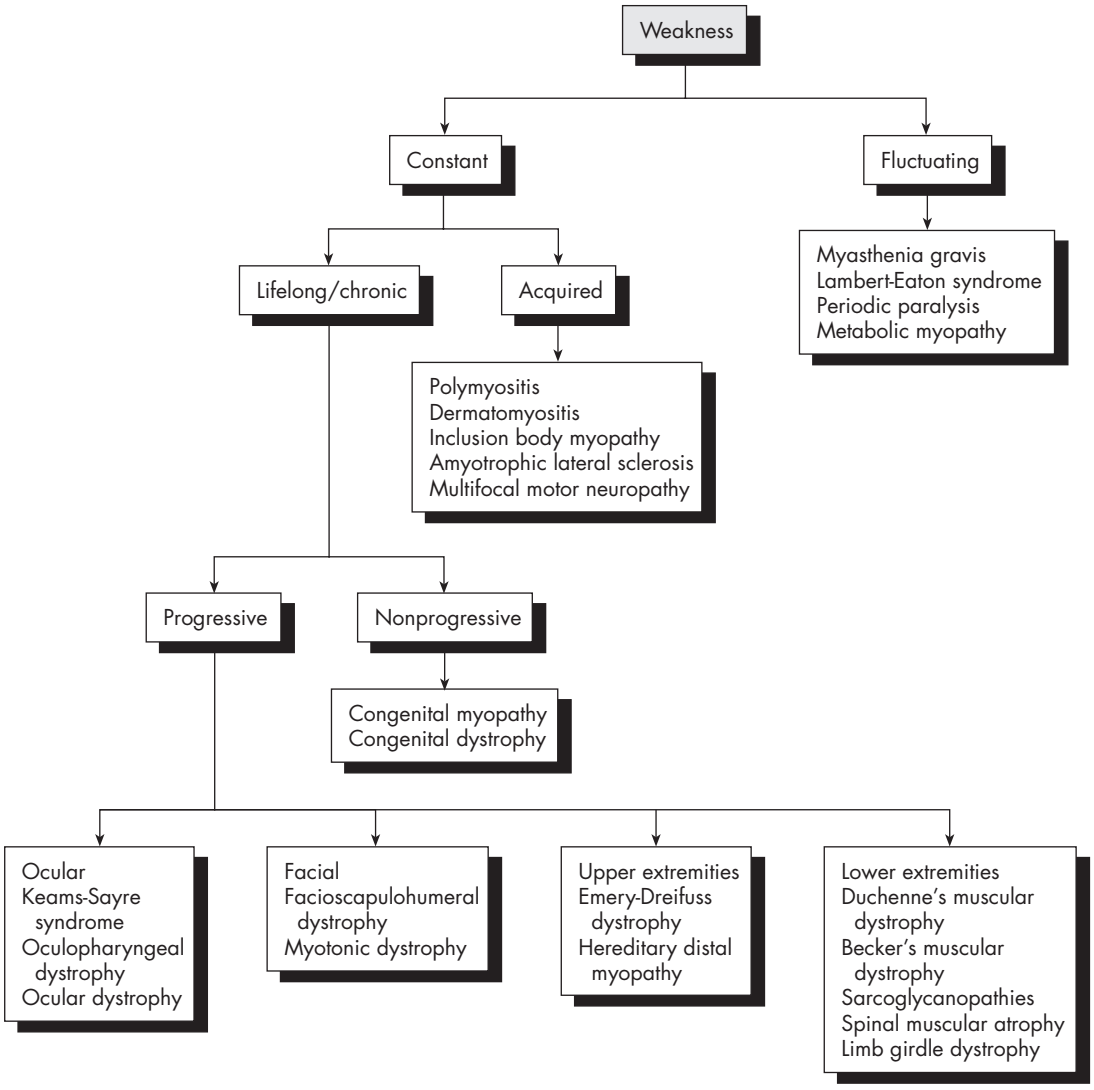


FIGURE 3-217 An algorithm for the approach to the patient with weakness. (From Bradley WG, Daroff RB, Fenichel GM, Jankovic J [eds]: *Neurology in clinical practice,* ed 4, Philadelphia, 2004, Butterworth Heinemann.)

WEIGHT GAIN

ICD-9CM # 783.1 Abnormal weight gain
278.00 Obesity
ICD-10CM # R63.5 Abnormal weight gain
E66.9 Obesity, unspecified

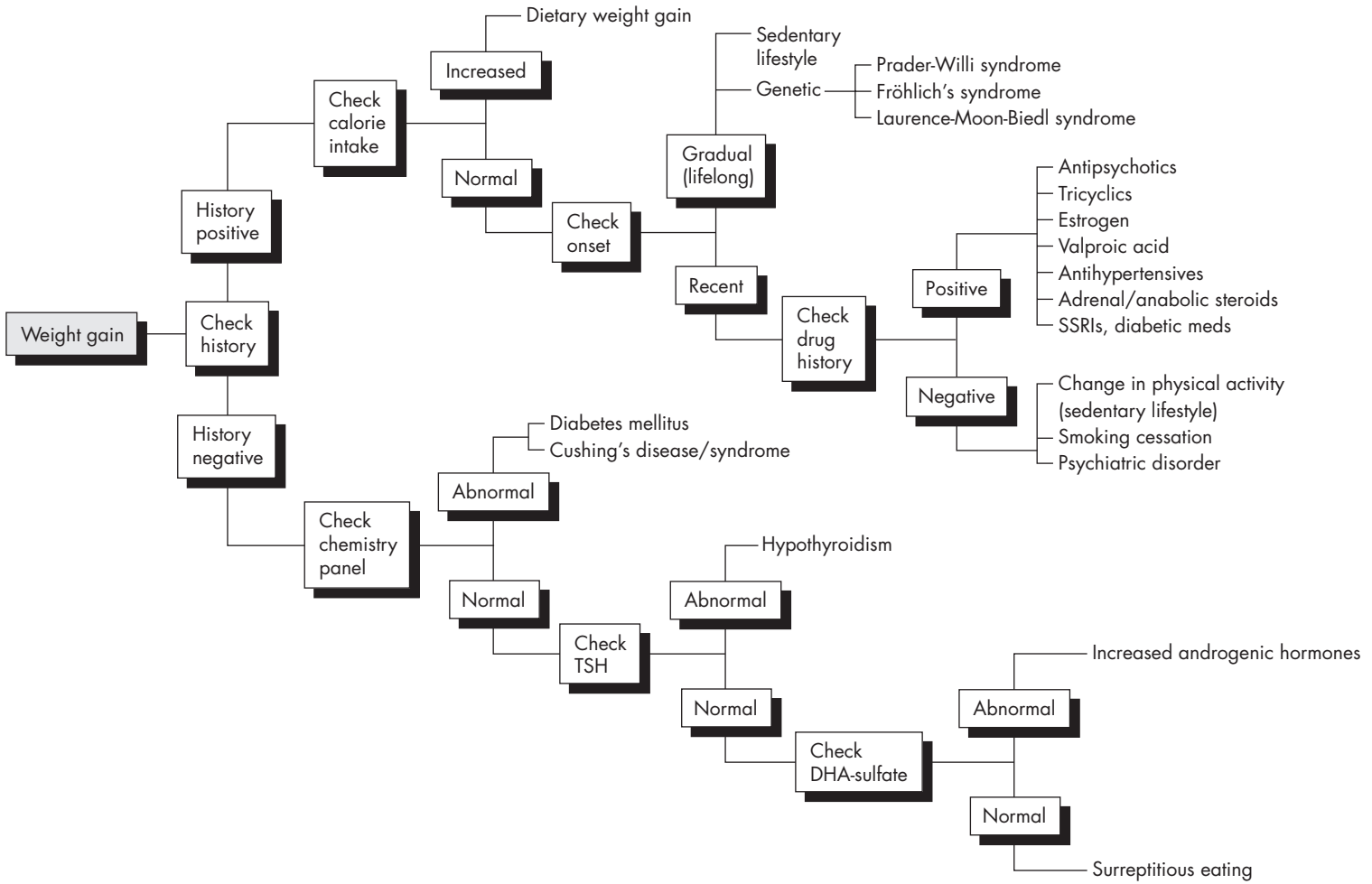


FIGURE 3-218 Weight gain. *DHA,* Dehydroepiandrosterone; *SSRIs,* serotonin reuptake inhibitors; *TSH,* thyroid-stimulating hormone. (Modified from Healey PM: *Common medical diagnosis: an algorithmic approach,* ed 3, Philadelphia, 2000, Saunders.)

ICD-9CM # 783.2 Weight loss
ICD-10CM # R63.4 Abnormal weight loss

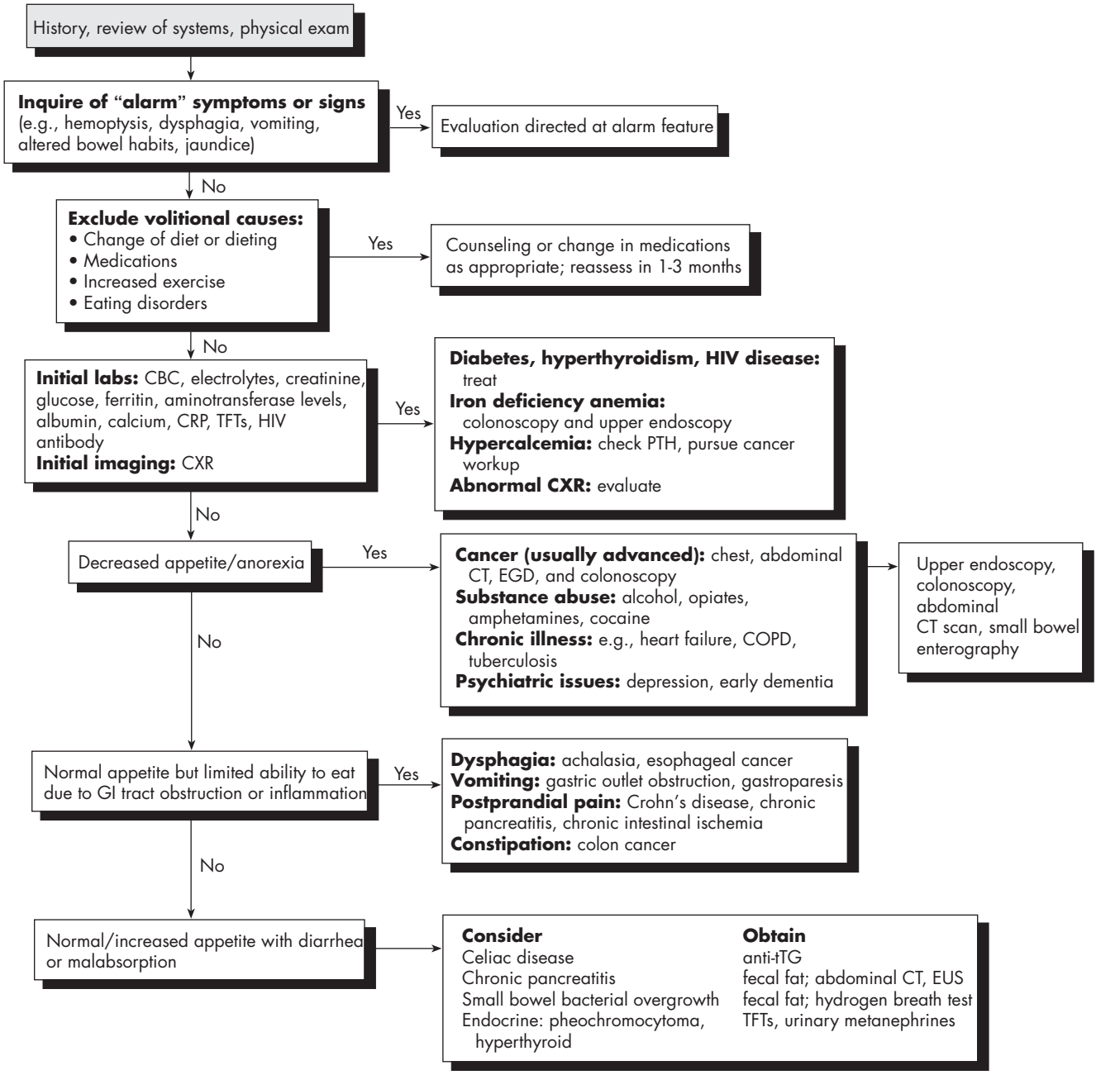


FIGURE 3-219 Approach to the patient with unintentional weight loss greater than 5%. *CBC,* Complete blood count; *COPD,* chronic obstructive pulmonary disease; *CRP,* C-reactive protein; *CT,* computed tomography; *CXR,* chest radiograph; *EGD,* esophagogastroduodenoscopy; *EUS,* endoscopic ultrasound; *GI,* gastrointestinal; *HIV,* human immunodeficiency virus; *PTH,* parathyroid hormone; *TFTs,* thyroid function tests; *tTG,* tissue transglutaminase; *U/A,* urinalysis. (From Goldman L, Schafer AI: *Goldman's Cecil Medicine,* ed 24, Philadelphia, 2012, Saunders.)

SECTION **IV**

Laboratory Tests and Interpretation of Results

This section contains more than 300 commonly performed laboratory tests. In general, the tests are discussed in the following format:

1. Laboratory test.
2. Normal range in adult patients. Normal values are given using the present (traditional) reference interval, followed by the Système Internationale (SI) reference interval, the conversion factor (CF), and the suggested minimum increment (SMI).
3. Common abnormalities, such as positive test, increased, or decreased value.
4. Causes of abnormal result.

The normal ranges may differ slightly, depending on the laboratory. The reader should be aware of the "normal range" of the particular laboratory performing the test. Every attempt has been made to present current laboratory test data, with emphasis on practical considerations.

ACE LEVEL
See ANGIOTENSIN-CONVERTING ENZYME

ACETONE (serum or plasma)
Normal: Negative
Elevated in: DKA, starvation, isopropanol ingestion

ACETYLCHOLINE RECEPTOR (AChR) ANTIBODY
Normal: <0.03 nmol/L
Elevated in: Myasthenia gravis. Changes in AChR concentration correlate with the clinical severity of myasthenia gravis following therapy and during therapy with prednisone and immunosuppressants. False-positive AChR antibody results may be found in patients with Eaton-Lambert syndrome.

ACID-BASE REFERENCE VALUES
See Tables 4-1 and 4-2.

ACID PHOSPHATASE (serum)
Normal range: 0-5.5 U/L (0-90 nkat/L [CF: 16.67; SMI:2 nkat/L])
Elevated in: Carcinoma of prostate, other neoplasms (breast, bone), Paget's disease, osteogenesis imperfecta, malignant invasion of bone, Gaucher's disease, multiple myeloma, myeloproliferative disorders, benign prostatic hypertrophy, prostatic palpation or surgery, hyperparathyroidism, liver disease, chronic renal failure, idiopathic thrombocytopenic purpura, bronchitis

ACID SERUM TEST
See HAM TEST

ACTIVATED CLOTTING TIME (ACT)
Normal: This test is used to determine the dose of protamine sulfate to reverse the effect of heparin as an anticoagulant during angioplasty, cardiac surgery, and hemodialysis. The accepted goal during cardiopulmonary bypass surgery is usually 400-500 sec.

ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT, aPTT)
See PARTIAL THROMBOPLASTIN TIME

ADRENOCORTICOTROPIC HORMONE
Normal: 9-52 pg/ml
Elevated in: Addison's disease, ectopic ACTH-producing tumors, congenital adrenal hyperplasia, Nelson's syndrome, pituitary-dependent Cushing's disease
Decreased in: Secondary adrenocortical insufficiency, hypopituitarism, adrenal adenoma or adrenal carcinoma

ALANINE AMINOPEPTIDASE
Normal:
Male: 1.11-1.71 mcg/ml
Female: 0.96-1.52 mcg/ml
Elevated in: Liver or pancreatic disease, ethanol use, oral contraceptives use, malignancy, tobacco use, pregnancy
Decreased in: Abortion

ALANINE AMINOTRANSFERASE (ALT, SGPT)
See Fig. 4-1, an algorithm for evaluation of elevated ALT.
Normal range: 0-35 U/L (0.058 μkat/L [CF: 0.02 μkat/L])
Elevated in: Liver disease (hepatitis, cirrhosis, Reye's syndrome), hepatic congestion, infectious mononucleosis, myocardial infarction, myocarditis, severe muscle trauma, dermatomyositis/polymyositis, muscular dystrophy, drugs (antibiotics, narcotics, antihypertensive agents, heparin, labetalol, statins, NSAIDs, amiodarone, chlorpromazine, phenytoin), malignancy, renal and pulmonary infarction, convulsions, eclampsia, shock liver

TABLE 4-1 Commonly Used Acid-Base Reference Values for Arterial and Venous Plasma or Serum (Averaged from Various Sources)

	ARTERIAL		VENOUS	
	Conventional Units	SI Units*	Conventional Units	SI Units*
pH	7.40 (7.35-7.45)	7.40 (7.35-7.45)	7.37 (7.32-7.42)	7.37 (7.32-7.42)
Pco_2	40 mm Hg (35-45)	5.33 kPa (4.67-6.10)	45 mm Hg (45-50)	6.10 kPa (5.33-6.67)
Po_2	80-100 mm Hg	10.66-13.33 kPa	40 mm Hg (37-43)	5.33 kPa (4.93-5.73)
HCO_3 (CO_2 combining power)	24 mEq/L (20-28)	24 mmol/L (20-28)	26 mEq/L (22-30)	26 mmol/L (22-30)
CO_2 content	25 mEq/L (22-28)	25 mmol/L (22-28)	27 mEq/L (24-30)	27 mmol/L(24-30)

From Ravel R: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.
*International system.

TABLE 4-2 Summary of Laboratory Findings in Primary Uncomplicated Respiratory and Metabolic Acid-Base Disorders*

Disorder	Pco_2	pH	Base Excess
Acute primary respiratory hypoactivity (respiratory acidosis)	Increase	Decrease	Normal/positive
Acute primary respiratory hyperactivity (respiratory alkalosis)	Decrease	Increase	Normal/negative
Uncompensated metabolic acidosis	Normal	Decrease	Negative
Uncompensated metabolic alkalosis	Normal	Increase	Positive
Partially compensated metabolic acidosis	Decrease	Decrease	Negative
Partially compensated metabolic alkalosis	Increase	Increase	Positive
Chronic primary respiratory hypoactivity (compensated respiratory acidosis)	Increase	Normal	Positive
Fully compensated metabolic alkalosis	Increase	Normal	Positive
Chronic primary respiratory hyperactivity (compensated respiratory alkalosis)	Decrease	Normal	Negative
Fully compensated metabolic acidosis	Decrease	Normal	Negative

From Ravel R: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.
*Base excess results refer to negative (–) values more than 22 and positive (+) values more than 12.

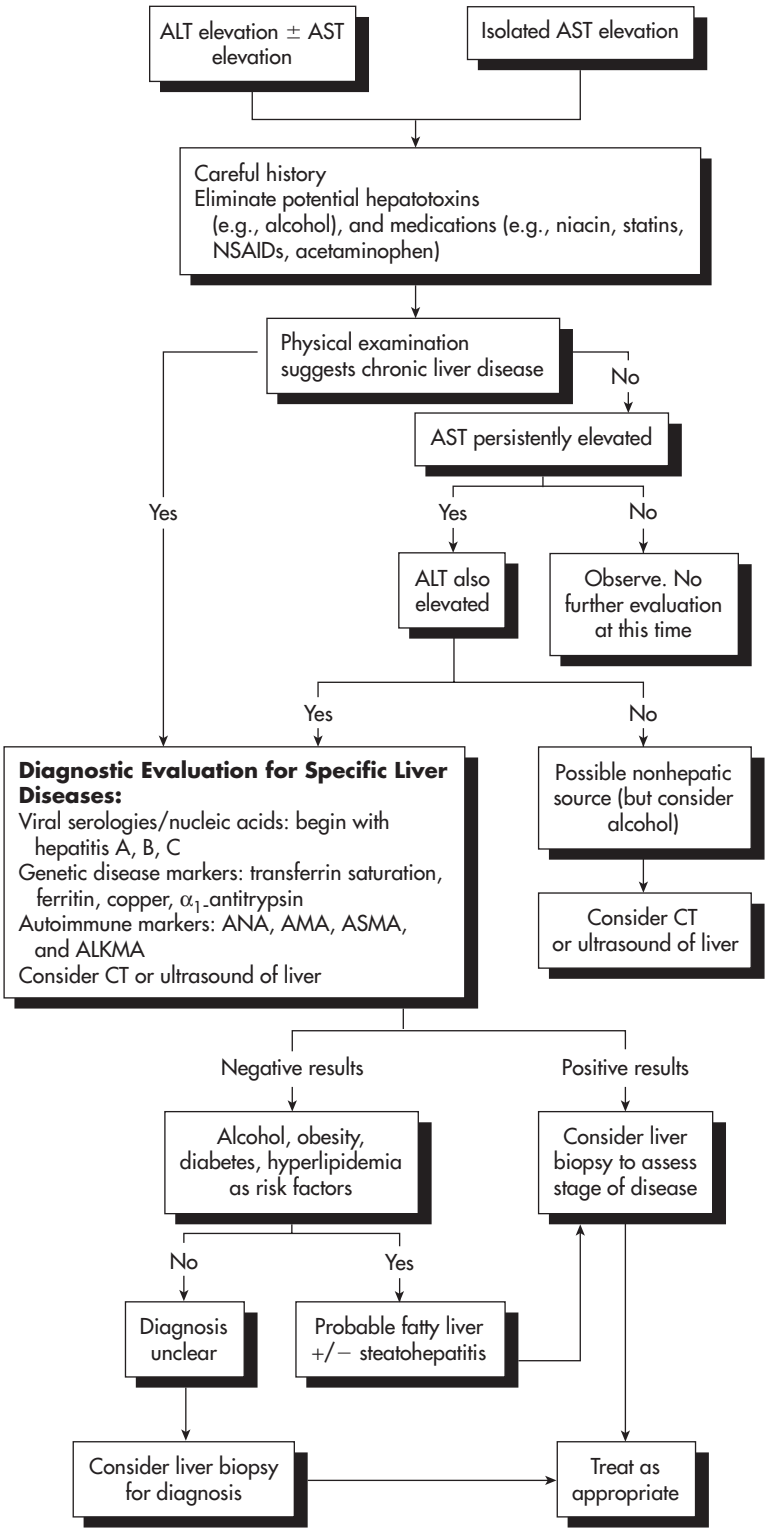


FIGURE 4-1 Approach to the evaluation of isolated elevated levels of serum alanine aminotransferase *(ALT)* and/or aspartate aminotransferase *(AST)* in the asymptomatic patient. *ALKMA,* Anti–liver/kidney microsomal antibody; *AMA,* antimitochondrial antibody; *ANA,* antinuclear antibody; *ASMA,* anti–smooth muscle antibody; *NSAIDs,* nonsteroidal anti-inflammatory drugs. (Modified from Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

ALBUMIN (serum)
Normal range: 4-6 g/dl (40-60 g/L [CF:10; SMI: 1 g/L])
Elevated in: Dehydration (relative increase)
Decreased in: Liver disease, nephrotic syndrome, poor nutritional status, rapid IV hydration, protein-losing enteropathies (e.g., inflammatory bowel disease), severe burns, neoplasia, chronic inflammatory diseases, pregnancy, oral contraceptives, prolonged immobilization, lymphomas, hypervitaminosis A, chronic glomerulonephritis

ALCOHOL DEHYDROGENASE
Normal: 0-7 U/L
Elevated in: Drug-induced hepatocellular damage, obstructive jaundice, malignancy, inflammation, infection

ALDOLASE (serum)
Normal range: 0-6 U/L (0-100 nkat/L [CF: 16.67; SMI: 20 nkat/L])
Elevated in: Muscular dystrophy, rhabdomyolysis, dermatomyositis/polymyositis, trichinosis, acute hepatitis and other liver diseases, myocardial infarction, prostatic carcinoma, hemorrhagic pancreatitis, gangrene, delirium tremens, burns
Decreased in: Loss of muscle mass, late stages of muscular dystrophy

ALDOSTERONE
Normal range:
Recumbent: 50-150 ng/L
Upright: 150-300 ng/L
(Highest levels in neonates, decreasing over time to adult levels)
Elevated in: Primary aldosteronism, secondary aldosteronism, pseudoprimary aldosteronism
Decreased in:
Patient with hypertension: diabetes mellitus, Turner's syndrome, acute alcohol intoxication, excess secretion of deoxycorticosterone, corticosterone, and 18-hydroxycorticosterone
Patient without hypertension: Addison's disease, hypoaldosteronism resulting from renin deficiency, isolated aldosterone deficiency

ALKALINE PHOSPHATASE (ALP) (serum)
See Fig. E4-2 for approach to elevated ALP.
Normal range: 30-120 U/L (0.5-2 μkat/L [CF:0.01667; SMI: 0.1 μkat/L])
Elevated in:
LIVER AND BILIARY TRACT ORIGIN
Extrahepatic bile duct obstruction
Intrahepatic biliary obstruction
Liver cell acute injury
Liver passive congestion
Drug-induced liver cell dysfunction
Space-occupying lesions
Primary biliary cirrhosis
Sepsis
BONE ORIGIN (OSTEOBLAST HYPERACTIVITY)
Physiologic (rapid) bone growth (childhood and adolescence)
Metastatic tumor with osteoblastic reaction
Fracture healing
Paget's disease of bone
CAPILLARY ENDOTHELIAL ORIGIN
Granulation tissue formation (active)
PLACENTAL ORIGIN
Pregnancy
Some parenteral albumin preparations
OTHER
Thyrotoxicosis
Benign transient hyperphosphatasemia
Primary hyperparathyroidism
Decreased in: Hypothyroidism, pernicious anemia, hypophosphatemia, hypervitaminosis D, malnutrition

ALPHA-1-ANTITRYPSIN (serum)
Normal range: 110-140 mg/dl
Decreased in: Homozygous or heterozygous deficiency

ALPHA-1-FETOPROTEIN (serum)
See α-1 FETOPROTEIN

ALT
See ALANINE AMINOTRANSFERASE

ALUMINUM (serum)
Normal range: 0-6 ng/ml
Elevated in: Chronic renal failure on dialysis, parenteral nutrition, industrial exposure

AMA
See ANTIMITOCHONDRIAL ANTIBODY

AMEBIASIS SEROLOGIC TEST
Test description: Test is used to support diagnosis of amebiasis caused by *Entamoeba histolytica*. Serum acute and convalescent titers are drawn 1-3 weeks apart. A fourfold increase in titer is the most indicative result.

AMINOLEVULINIC ACID (δ-ALA) (24-hr urine collection)
Normal: 1.5-7.5 mg/day
Elevated in: Acute porphyrias, lead poisoning, DKA, pregnancy, anticonvulsant drugs, hereditary tyrosinemia
Decreased in: Alcoholic liver disease

AMMONIA (serum)
See Fig. E4-3 for approach to hyperammonemia in pediatric patients.
Normal range: 10-80 μg/dl (5-50 μmol/L [CF: 0.5872; SMI:5 μmol/L])
Elevated in: Hepatic failure, hepatic encephalopathy, Reye's syndrome, portacaval shunt, drugs (diuretics, polymyxin B, methicillin)
Decreased in: Drugs (neomycin, lactulose, tetracycline), renal failure

AMYLASE (serum)
Normal range: 0-130 U/L (0-2.17 μkat/L [CF: 0.01667; SMI: 0.01 μkat/L])
Elevated in: Acute pancreatitis, pancreatic neoplasm, abscess, pseudocyst, ascites, macroamylasemia, perforated peptic ulcer, intestinal obstruction, intestinal infarction, acute cholecystitis, appendicitis, ruptured ectopic pregnancy, salivary gland inflammation, peritonitis, burns, diabetic ketoacidosis, renal insufficiency, drugs (morphine), carcinomatosis (of lung, esophagus, ovary), acute ethanol ingestion, mumps, prostate tumors, post-endoscopic retrograde cholangiopancreatography, bulimia, anorexia nervosa
Decreased in: Advanced chronic pancreatitis, hepatic necrosis, cystic fibrosis

AMYLASE, URINE
See URINE AMYLASE

AMYLOID A PROTEIN (serum)
Normal: <10 mcg/ml
Elevated in: Inflammatory disorders (acute phase–reacting protein), infections, acute coronary syndrome, malignancies

ANA
See ANTINUCLEAR ANTIBODY

ANCA
See ANTINEUTROPHIL CYTOPLASMIC ANTIBODY

ANDROSTENEDIONE (serum)
Normal:
Male: 75-205 ng/dl
Female: 85-275 ng/dl
Elevated in: Congenital adrenal hyperplasia, polycystic ovary syndrome, ectopic ACTH-producing tumor, Cushing's syndrome, hirsutism, hyperplasia of ovarian stroma, ovarian neoplasm
Decreased in: Ovarian failure, adrenal failure, sickle cell anemia

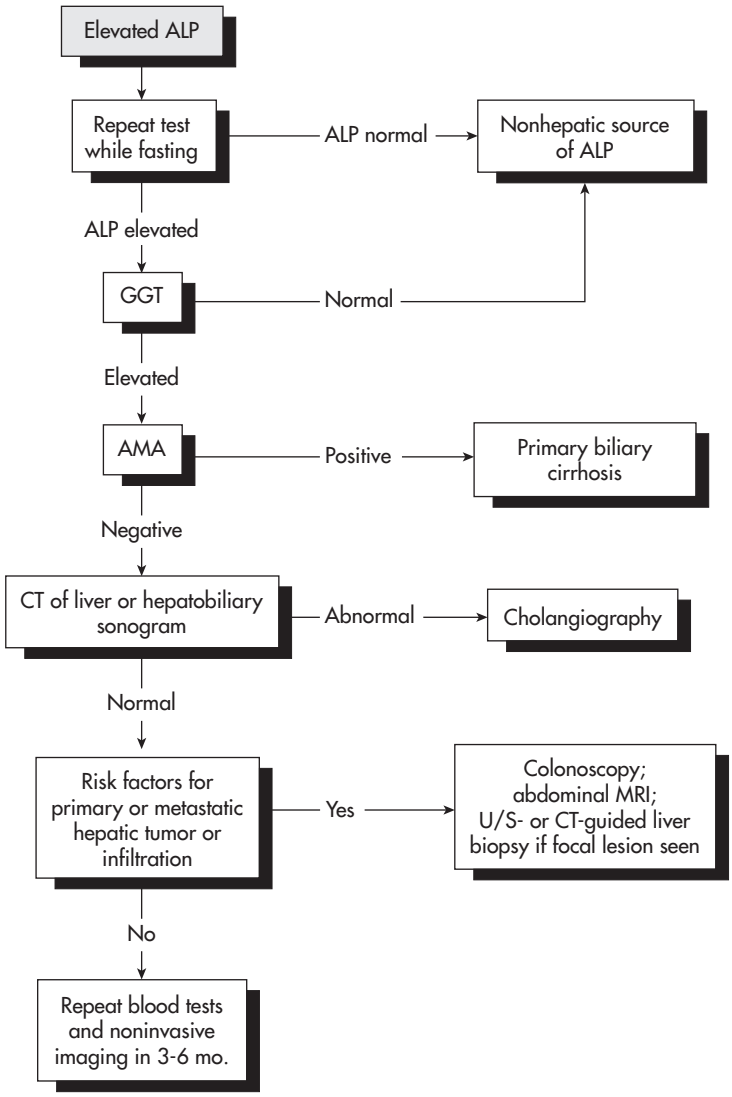


FIGURE E4-2 Approach to the asymptomatic patient with isolated elevated levels of serum alkaline phosphatase *(ALP).* *AMA,* Antimitochondrial antibody; *CT,* computed tomography; *GGT,* g-glutamyl transpeptidase; *MRI,* magnetic resonance imaging; *U/S,* ultrasonography. (Modified from Goldman L, Ausiello D [eds]: *Cecil textbook of medicine*, ed 24, Philadelphia, 2012, Saunders.)

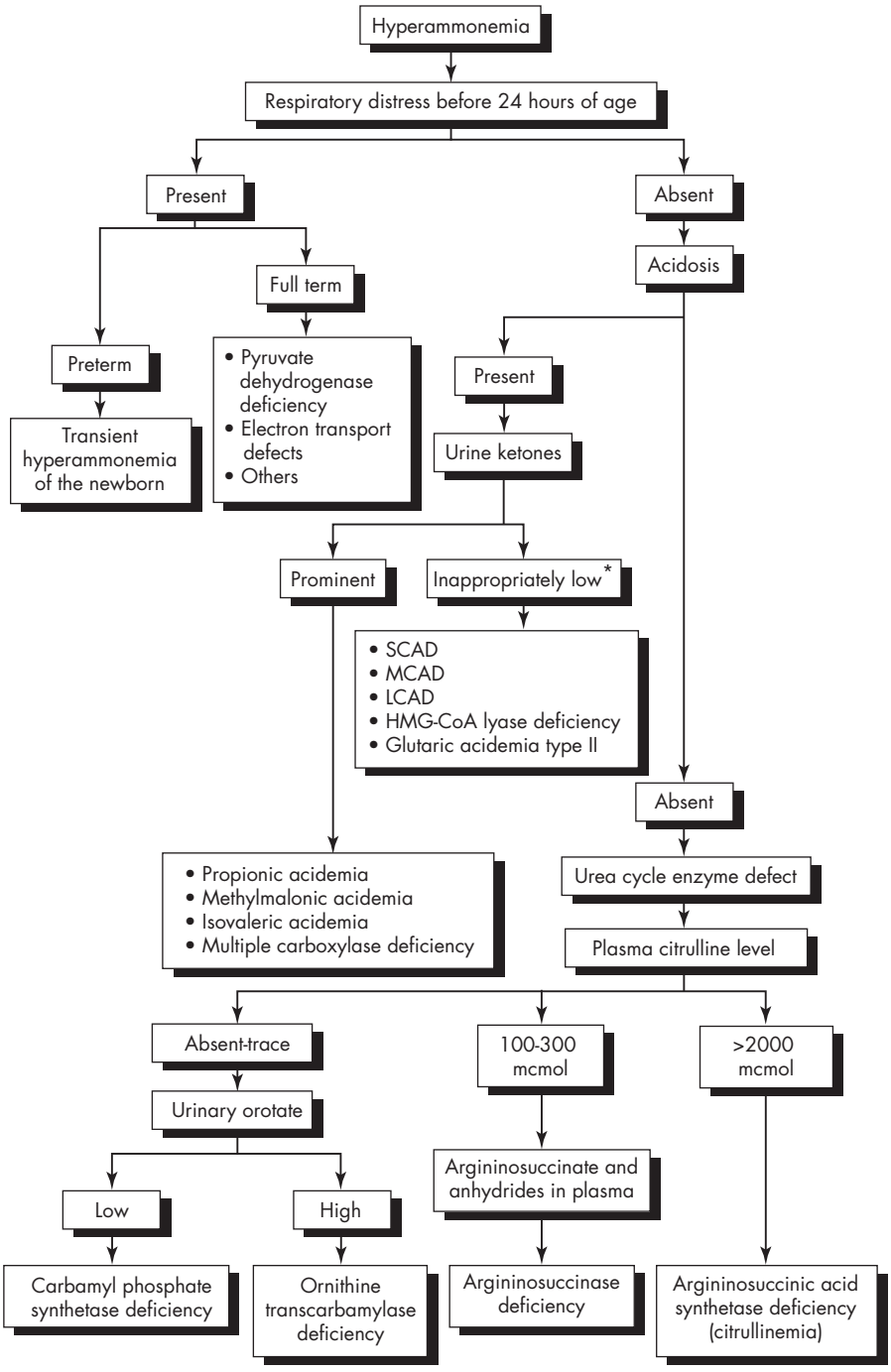


FIGURE E4-3 Differential diagnosis of hyperammonemia. *Indicates inappropriately low urinary ketones in settling of symptomatic hypoglycemia. *HMG-CoA,* Hydroxymethylglutaryl-CoA; *LCAD,* long-chain acyl-CoA dehydrogenase; *MCAD,* medium-chain acyl-CoA dehydrogenase; *SCAD,* short-chain acyl-CoA dehydrogenase. (From Custer JW, Rau RE: *The Harriet Lane handbook,* ed 18, St Louis, 2009, Mosby.)

ANGIOTENSIN II

Normal: 10-60 pg/ml
Elevated in: Hypertension, CHF, cirrhosis, renin-secreting renal tumor, volume depletion
Decreased in: ACE inhibitor drugs, ARB drugs, primary aldosteronism, Cushing's syndrome

ANGIOTENSIN-CONVERTING ENZYME (ACE level)

Normal range: <40 nmol/ml/min (<670 nkat/L [CF: 16.67; SMI: 10 nkat/L])
Elevated in: Sarcoidosis, primary biliary cirrhosis, alcoholic liver disease, hyperthyroidism, hyperparathyroidism, diabetes mellitus, amyloidosis, multiple myeloma, lung disease (asbestosis, silicosis, berylliosis, allergic alveolitis, coccidioidomycosis), Gaucher's disease, leprosy

ANH

See ATRIAL NATRIURETIC HORMONE

ANION GAP

Normal range: 9-14 mEq/L
Elevated in: Lactic acidosis, ketoacidosis (diabetes, alcoholic starvation), uremia (chronic renal failure), ingestion of toxins (paraldehyde, methanol, salicylates, ethylene glycol), hyperosmolar nonketotic coma, antibiotics (carbenicillin)
Decreased in: Hypoalbuminemia, severe hypermagnesemia, IgG myeloma, lithium toxicity, laboratory error (falsely decreased sodium or overestimation of bicarbonate or chloride), hypercalcemia of parathyroid origin, antibiotics (e.g., polymyxin)

ANTICARDIOLIPIN ANTIBODY (ACA)

Normal range: Negative. Test includes detection of IgG, IgM, and IgA antibodies to phospholipid, cardiolipin
Present in: Antiphospholipid antibody syndrome, chronic hepatitis C

ANTICOAGULANT

See CIRCULATING ANTICOAGULANT

ANTIDIURETIC HORMONE

Normal range: mOsm/kg 295-300 (4-12 pg/ml)
Elevated in: SIADH, antipsychotic medications, ectopic ADH from systemic neoplasm, Guillain-Barré syndrome, CNS infections, brain tumors, nephrogenic diabetes insipidus
Decreased in: Central diabetes insipidus, nephritic syndrome, psychogenic polydipsias, demeclocycline, lithium, phenytoin, alcohol

ANTI-DNA

Normal range: Absent
Present in: Systemic lupus erythematosus, chronic active hepatitis, infectious mononucleosis, biliary cirrhosis

ANTI-DS DNA

Normal: <25 U
Elevated in: Systemic lupus erythematosus

ANTIGLOMERULAR BASEMENT ANTIBODY

See GLOMERULAR BASEMENT MEMBRANE ANTIBODY

ANTIHISTONE

Normal: <1 U
Elevated in: Drug-induced lupus erythematosus

ANTIMITOCHONDRIAL ANTIBODY (AMA, MITOCHONDRIAL ANTIBODY)

Normal range: <1:20 titer
Elevated in: Primary biliary cirrhosis (85%-95%), chronic active hepatitis (25%-30%), cryptogenic cirrhosis (25%-30%)

ANTINEUTROPHIL CYTOPLASMIC ANTIBODY (ANCA)

Positive test: Cytoplasmic pattern (cANCA): positive in Wegener's granulomatosis (see Fig. E4-4 and Table E4-3 for approach to patient with positive c-ANCA)

Perinuclear pattern (pANCA): positive in inflammatory bowel disease, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune chronic active hepatitis, crescentic glomerulonephritis (see Fig. E4-5 and Table E4-3 for approach to patient with positive P-ANCA)

ANTINUCLEAR ANTIBODY (ANA)

See Fig. E4-6 for approach to positive ANA pattern
Normal range: <1:20 titer
Positive test: Systemic lupus erythematosus (more significant if titer >1:160), drugs (phenytoin, ethosuximide, primidone, methyldopa, hydralazine, carbamazepine, penicillin, procainamide, chlorpromazine, griseofulvin, thiazides), chronic active hepatitis, age over 60 years (particularly age over 80 years), rheumatoid arthritis, scleroderma, mixed connective tissue disease, necrotizing vasculitis, Sjögren's syndrome, tuberculosis, pulmonary interstitial fibrosis. Table 4-4 describes diseases associated with ANA subftypes. Fig. 4-7 illustrates various fluorescent ANA test patterns.

TABLE 4-4 Disease-Associated ANA Subtypes

Nuclear Location	Disease(s)
"Native" DNA (dsDNA, or dsDNA/ssDNA complex)	SLE (60%-70%; range, 35%-75%) Also PSS (5%-55%), MCTD (11%-25%), RA (5%-40%), DM (5%-25%), SS (5%)
sNP	SLE (50%) Also other collagen diseases
DNP (DNA-histone complex)	SLE (52%) Also MCTD (8%), RA (3%)
Histones	Drug-induced SLE (95%) Also SLE (30%), RA (15%-24%)
ENA Sm	SLE (30%-40%; range, 28%-40%) Also MCTD (0%-8%); RNP (U1-RNP) MCTD (in high titer without any other ANA subtype present: 95%-100%) Also SLE (26%-50%), PSS (11%-22%), RA (10%), SS (3%)
SS-A (Ro)*	SS without RA (60%-70%) Also SLE (26%-50%), neonatal SLE (over 95%), PSS (30%), MCTD (50%), SS with RA (9%), PBC (15%-19%)
SS-B (La)	SS without RA (40%-60%) Also SLE (5%-15%), SS with RA (5%)
Scl-70*	PSS (15%-43%)
Centromere*	CREST syndrome (70%-90%; range, 57%-96%) Also PSS (4%-20%), PBC (12%)
Nucleolar	PSS (scleroderma) (54%-90%) Also SLE (25%-26%), RA (9%)
RAP (RANA)	SS with RA (60%-76%) Also SS without RA (5%)
Jo-1	Polymyositis (30%)
PM-1	Polymyositis or PMS/PSS overlap syndrome (60%-90%) Also DM (17%)
ssDNA	SLE (60%-70%) Also CAH, infectious mononucleosis, RA, chronic GN, chronic infections, PBC
Cytoplasmic Location	**Disease(s)**
Mitochondrial	PBC (90%-100%) Also CAH (7%-30%), cryptogenic cirrhosis (30%), acute hepatitis, viral hepatitis (3%), other liver diseases (0%-20%), SLE (5%), SS and PSS (8%)
Microsomal†	Chronic active hepatitis (60%-80%), Hashimoto's thyroiditis (97%)
Ribosomal	SLE (5%-12%)
Smooth muscle‡	Chronic active hepatitis (60%-91%)

From Ravel R: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.
*CAH,*Chronic active hepatitis; *DM,* dermatomyositis; *GN,* glomerulonephritis; *MS,* multiple sclerosis; *PBC,* primary biliary cirrhosis; *SS,* Sjögren's syndrome.
*Not detected using rat or mouse liver or kidney tissue method.
†Not detected by cultured cell method.
‡Detected by cultured cells but better with rat or mouse tissue.

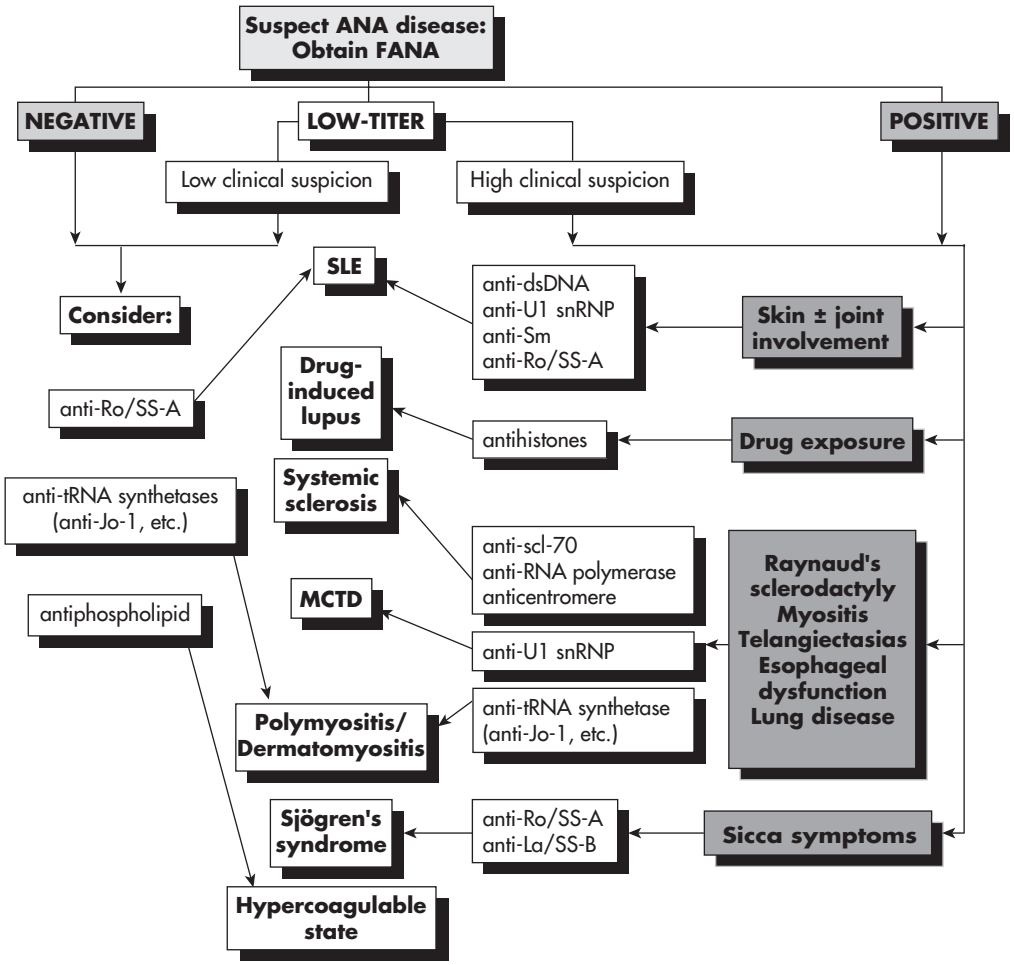


FIGURE E4-4 Algorithm for the use of antinuclear antibodies in the diagnosis of connective tissue disorder. *ANA*, antinuclear antibody; *FANA*, fluorescent antinuclear antibody; *MCTD*, mixed connective tissue disease; *SLE*, systemic lupus erythematosus. (From Firestein GS, Budd RC, Gabriel SE, et al: *Kelly's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.)

TABLE E4-3 Other Disorders Associated with Antineutrophil Cytoplasmic Antibodies (ANCA)

	Type of ANCA*	Major Antigen(s)**	Evaluation
Inflammatory bowel disease	P >C	Catalase, BPI, α-enolase, LF, CG, HMG1/2>MPO, PR3	Colonoscopy
Ulcerative colitis (50%-70%) >Crohn's disease (20%-40%)			
Autoimmune liver disease	P >C	Actin, HMG1/2	LFTs; ANA; antismooth muscle Ab; antimitochondrial Ab
Autoimmune hepatitis (type 1; 80%), primary sclerosing cholangitis (70%) >primary biliary cirrhosis (30%)			
Connective tissue disease	P >C	MPO, PR3, BPI, CG, LF, lysozyme, HMG1/2	ANA panel; RF; anticardiolipin Ab
Systemic lupus erythematosus (20%-30%), rheumatoid arthritis (20%-30%) >Sjögren's syndrome, dermatomyositis, reactive arthritis, relapsing polychondritis, antiphospholipid syndrome			
Drug-induced vasculitis/lupus/hepatitis	P >C	MPO>PR3, elastase	Skin biopsy, ANA panel; LFTs; discontinue drug
Propylthiouracil (20%), minocycline >levamisole, sulfasalazine	P	MPO, elastase	
Hydralazine, penicillamine >allopurinol†	C	—	
High-dose intravenous immunoglobulin			
Other cutaneous and/or systemic vasculitides‡	P >C	Variable	Skin biopsy; cryoglobulins; hepatitis B, C panels; exclude malignancy
Mixed cryoglobulinemia, Behçet's disease, paraneoplastic	P	Variable	
Henoch–Schönlein purpura, Buerger's disease			
Other glomerulonephritides	P	MPO	UA; BUN/creatinine; ASO; renal biopsy
Anti-GBM Ab-associated (30%) >immune complex (15%) >poststreptococcal			
Infections	P, C	MPO, others	Cultures; serologies; echocardiogram
Respiratory tract infections (bacterial/mycobacterial/fungal), enteritis, periodontitis, HIV, parvovirus B19, malaria, leprosy	P	Defensin	
Onchocerciasis	C	PR3	
Subacute bacterial endocarditis, chromomycosis, invasive amebiasis			
Cystic fibrosis (80%)	C >P	BPI	Sweat test
Hypergammaglobulinemia	P, C	—	Serum protein electrophoresis

Courtesy of Julie V Schaffer, MD.

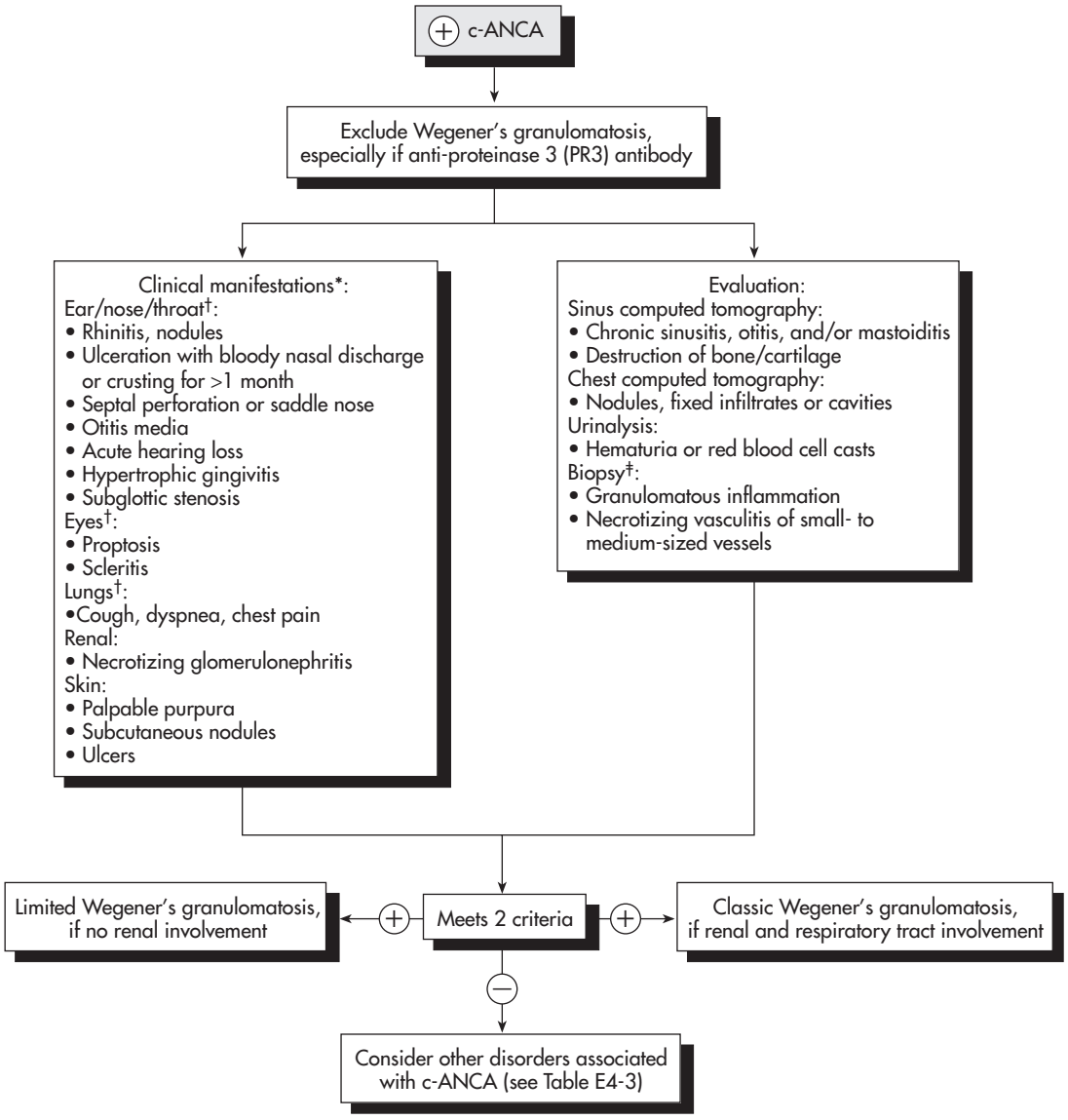
Ab, Antibodies; *ANA,* antinuclear antibodies; *ASO,* antistreptolysin O; *C,* cytoplasmic [c-ANCA or c-ANCA (atypical)]; *GBM,* glomerular basement membrane; *LFTs,* liver function tests; *P,* perinuclear [P-ANCA]; *RF,* rheumatoid factor; *UA,* urinalysis.

*C-ANCA are often atypical; in addition, immunofluorescence testing in some laboratories may not distinguish c-ANCA (atypical) from atypical ANCA.

**P-ANCA often have antigen specificity other than myeloperoxidase (MPO), e.g., lactoferrin (LF), elastase, cathepsin G (CG), lysozyme, bactericidal/permeability-increasing protein (BPI), high mobility group non-histone chromosomal proteins (HMG1/2), α-enolase, catalase, actin, defensin; c-ANCA (atypical) have antigen specificity other than proteinase 3 (PR3), e.g., BPI, lysozyme, or multiple antigens.

†Other drugs associated with P-ANCA in single case reports include cimetidine, cefotaxime, phenytoin, and isotretinoin.

‡Although primarily associated with c-ANCA, 5% to 15% of patients with Wegener's granulomatosis have P-ANCA; likewise, although primarily associated with P-ANCA, 5% to 15% of patients with Churg-Strauss syndrome and >40% of those with microscopic polyangiitis have c-ANCA; ANCA have also been reported in leukocytoclastic vasculitis of unknown etiology and unclassified vasculitis.



* Some patients also have gastrointestinal, cardiac, and/or neurologic involvement
† Granulomatous inflammation
‡ Of skin, mucosa, respiratory tract (upper/lower), or kidney

FIGURE E4-5 Approach to the patient with perinuclear antineutrophil cytoplasmic antibodies (P-ANCA). (Courtesy of Julie V Schaffer, MD. From Bolognia JL, Jorizzo JL, Rapini RP: *Dermatology,* St Louis, 2003, Mosby.)

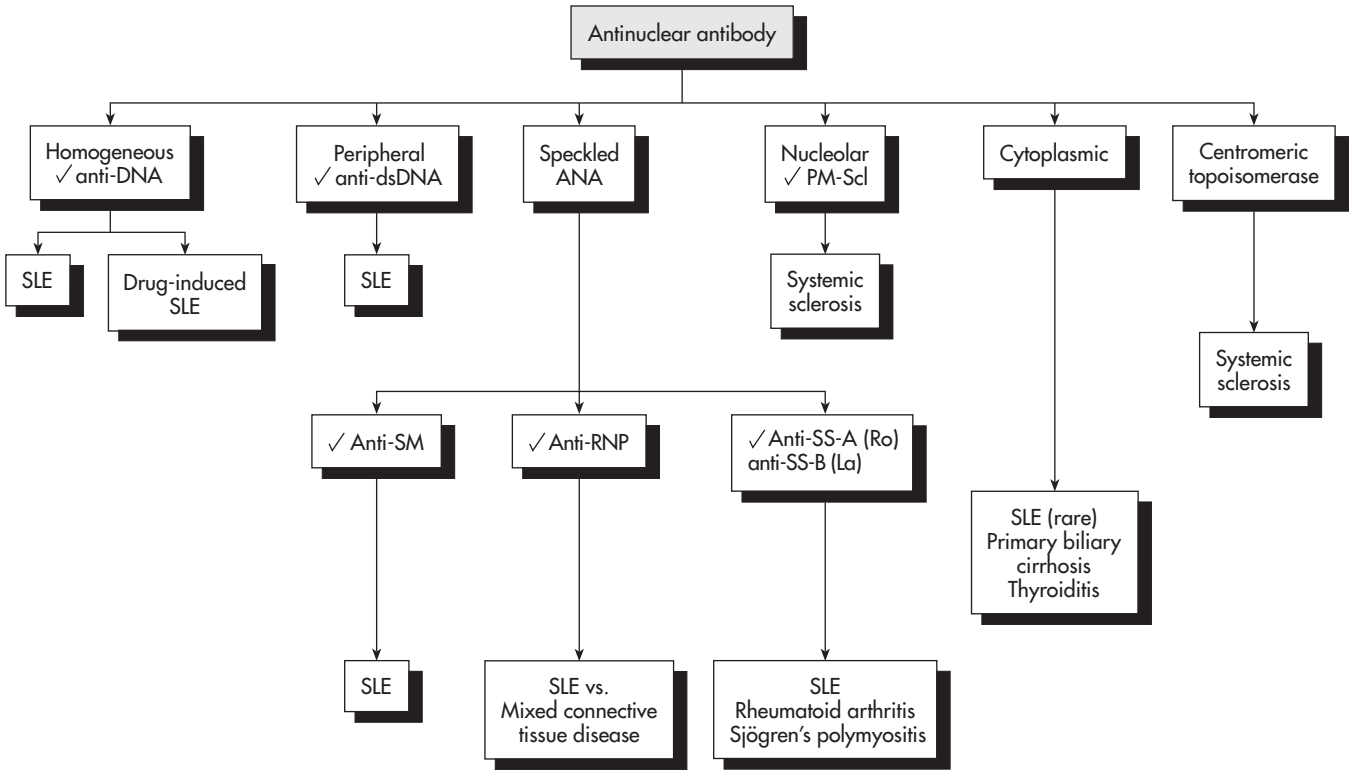


FIGURE E4-6 Diagnostic tests and diagnoses to consider from antinuclear antibody pattern. *ANA,* Antinuclear antibody; *SLE,* systemic lupus erythematosus. (From Carlson KJ et al: *Primary care of women,* ed 2, St Louis, 2002, Mosby.)

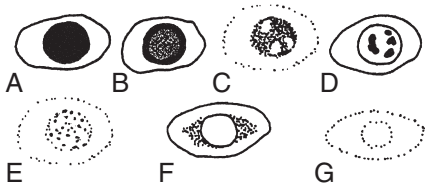


FIGURE 4-7 Fluorescent antinuclear antibody test patterns (HEP-2 cells). **A,** Solid (homogeneous). **B,** Peripheral (rim). **C,** Speckled. **D,** Nucleolar. **E,** Anticentromere. **F,** Antimitochondrial. **G,** Normal (nonreactive). (From Ravel R [ed]: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.)

ANTI-RNP ANTIBODY

See EXTRACTABLE NUCLEAR ANTIGEN

ANTI-Scl-70

Normal: Absent
Elevated in: Scleroderma

ANTI-Sm (anti-Smith) ANTIBODY

See EXTRACTABLE NUCLEAR ANTIGEN

ANTI-SMOOTH MUSCLE ANTIBODY

See SMOOTH MUSCLE ANTIBODY

ANTISTREPTOLYSIN O TITER (Streptozyme, ASLO titer)

Normal range for adults: <160 Todd units
Elevated in: Streptococcal upper airway infection, acute rheumatic fever, acute glomerulonephritis, increased levels of β-lipoprotein

NOTE: A fourfold increase in titer between acute and convalescent specimens is diagnostic of streptococcal upper airway infection regardless of the initial titer.

ANTITHROMBIN III

See Table 4-5.

TABLE 4-5 Assay Measurements in Heterozygous Antithrombin (ATIII) Deficiency for Diagnosis

	ACTIVITY		
Type	**Antigen**	**Heparin Cofactor**	**Progressive ATIII**
I	Low	Low	Low
II			
Active site defect	Normal	Low	Low
Heparin-binding site defect	Normal	Low	Normal

From Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

Normal range: 81%-120% of normal activity; 17-30 mg/dl
Decreased in: Hereditary deficiency of antithrombin III, disseminated intravascular coagulation, pulmonary embolism, cirrhosis, thrombolytic therapy, chronic liver failure, postsurgery, third trimester of pregnancy, oral contraceptives, nephrotic syndrome, IV heparin >3 days, sepsis, acute leukemia, carcinoma, thrombophlebitis
Elevated in: Warfarin drugs, post-myocardial infarction

APOLIPOPROTEIN A-1 (Apo A-1)

Normal: Desirable >120 mg/dl
Elevated in: Familial hyperalphalipoproteinemia, statins, niacin, estrogens, weight loss, familial cholesteryl ester transfer protein (CETP) deficiency
Decreased in: Familial hypoalphalipoproteinemia, Tangier disease, diuretics, androgens, cigarette smoking, hepatocellular disorders, chronic renal failure, nephritic syndrome, coronary heart disease, cholestasis

APOLIPOPROTEIN B (Apo B)

Normal: Desirable <100 mg/dl; high risk >120 mg/dl
Elevated in: High saturated fat diet, high-cholesterol diet, hyperapobetalipoproteinemia, familial combined hyperlipidemia, anabolic steroids, diuretics, beta-blockers, corticosteroids, progestins, diabetes, hypothyroidism, chronic renal failure, liver disease, Cushing's syndrome, coronary heart disease
Decreased in: Statins, niacin, low-cholesterol diet, malnutrition, abetalipoproteinemia, hypobetalipoproteinemia, hyperthyroidism

ARTERIAL BLOOD GASES

Normal range:
Po_2: 75-100 mm Hg
Pco_2: 35-45 mm Hg
HCO_3: 24-28 mEq/L
pH: 7.35-7.45
Abnormal values: Acid-base disturbances (see the following)

METABOLIC ACIDOSIS
Metabolic acidosis with increased AG (AG acidosis)
Lactic acidosis
Ketoacidosis (diabetes mellitus, alcoholic ketoacidosis)
Uremia (chronic renal failure)
Ingestion of toxins (paraldehyde, methanol, salicylate, ethylene glycol)
High-fat diet (mild acidosis)
Metabolic acidosis with normal AG (hyperchloremic acidosis)
Renal tubular acidosis (including acidosis of aldosterone deficiency)
Intestinal loss of HCO_3^- (diarrhea, pancreatic fistula)
Carbonic anhydrase inhibitors (e.g., acetazolamide)
Dilutional acidosis (as a result of rapid infusion of bicarbonate-free isotonic saline)
Ingestion of exogenous acids (ammonium chloride, methionine, cystine, calcium chloride)
Ileostomy
Ureterosigmoidostomy
Drugs: amiloride, triamterene, spironolactone, β-blockers

RESPIRATORY ACIDOSIS
Pulmonary disease (COPD, severe pneumonia, pulmonary edema, interstitial fibrosis)
Airway obstruction (foreign body, severe bronchospasm, laryngospasm)
Thoracic cage disorders (pneumothorax, flail chest, kyphoscoliosis)
Defects in muscles of respiration (myasthenia gravis, hypokalemia, muscular dystrophy)
Defects in peripheral nervous system (amyotrophic lateral sclerosis, poliomyelitis, Guillain-Barré syndrome, botulism, tetanus, organophosphate poisoning, spinal cord injury)
Depression of respiratory center (anesthesia, narcotics, sedatives, vertebral artery embolism or thrombosis, increased intracranial pressure)
Failure of mechanical ventilator

METABOLIC ALKALOSIS
Divided into chloride-responsive (urinary chloride <15 mEq/L) and chloride-resistant forms (urinary chloride level >15 mEq/L)
Chloride-responsive:
Vomiting
Nasogastric (NG) suction
Diuretics
Posthypercapnic alkalosis
Stool losses (laxative abuse, cystic fibrosis, villous adenoma)
Massive blood transfusion
Exogenous alkali administration
Chloride-resistant:
Hyperadrenocorticoid states (Cushing's syndrome, primary hyperaldosteronism, secondary mineralocorticoidism [licorice, chewing tobacco])
Hypomagnesemia
Hypokalemia
Bartter's syndrome

RESPIRATORY ALKALOSIS
Hypoxemia (pneumonia, pulmonary embolism, atelectasis, high-altitude living)
Drugs (salicylates, xanthines, progesterone, epinephrine, thyroxine, nicotine)
Central nervous system (CNS) disorders (tumor, cerebrovascular accident [CVA], trauma, infections)

Psychogenic hyperventilation (anxiety, hysteria)
Hepatic encephalopathy
Gram-negative sepsis
Hyponatremia
Sudden recovery from metabolic acidosis
Assisted ventilation

ARTHROCENTESIS FLUID

Interpretation of results:

1. **Color:** Normally it is clear or pale yellow; cloudiness indicates inflammatory process or presence of crystals, cell debris, fibrin, or triglycerides.
2. **Viscosity:** Normally it has a high viscosity because of hyaluronate; when fluid is placed on a slide, it can be stretched to a string >2 cm in length before separating (low viscosity indicates breakdown of hyaluronate [lysosomal enzymes from leukocytes] or the presence of edema fluid).
3. **Mucin clot:** Add 1 ml of fluid to 5 ml of a 5% acetic acid solution and allow 1 minute for the clot to form; a firm clot (does not fragment on shaking) is normal and indicates the presence of large molecules of hyaluronic acid (this test is nonspecific and infrequently done).
4. **Glucose:** Normally it approximately equals serum glucose level; a difference of more than 40 mg/dl is suggestive of infection.
5. **Protein:** Total protein concentration is <2.5 g/dl in the normal synovial fluid; it is elevated in inflammatory and septic arthritis.
6. **Microscopic examination for crystals**
   a. **Gout:** Monosodium urate crystals
   b. **Pseudogout:** Calcium pyrophosphate dihydrate crystals

ASLO TITER

See ANTISTREPTOLYSIN O TITER

ASPARTATE AMINOTRANSFERASE (AST, SGOT)

Normal range: 0-35 U/L (0-0.58 μkat/L [CF: 0.01667, SMI: 0.01μkat/L])
Elevated in:
HEART
Acute myocardial infarction
Pericarditis (active: some cases)
LIVER
Hepatitis virus, Epstein-Barr, or cytomegalovirus infection
Active cirrhosis
Liver passive congestion or hypoxia
Alcohol- or drug-induced liver dysfunction
Space-occupying lesions (active)
Fatty liver (severe)
Extrahepatic biliary obstruction (early)
Drug-induced
SKELETAL MUSCLE
Acute skeletal muscle injury
Muscle inflammation (infectious or noninfectious)
Muscular dystrophy (active)
Recent surgery
Delirium tremens
KIDNEY
Acute injury or damage
Renal infarct
OTHER
Intestinal infarction
Shock
Cholecystitis
Acute pancreatitis
Hypothyroidism
Heparin therapy (60%-80% of cases)
Fig. 4-1 describes an approach to the evaluation of AST elevation.

ATRIAL NATRIURETIC HORMONE (ANH)

Normal: 20-77 pg/ml
Elevated in: CHF, volume overload, cardiovascular disease with high filling pressure
Decreased with: Prazosin and other alpha blockers

B-TYPE NATRIURETIC PEPTIDE (BNP)

Normal range: up to 100 mcg/L. Natriuretic peptides are secreted to regulate fluid volume, blood pressure, and electrolyte balance. They have activity in both the central and peripheral nervous systems. In humans the main source of circulatory BNP is the heart ventricles.
Elevated in: Heart failure. This test is useful to differentiate heart failure patients from those with chronic obstructive pulmonary disease presenting with dyspnea. Levels are also increased in asymptomatic left ventricular dysfunction, arterial and pulmonary hypertension, cardiac hypertrophy, valvular heart disease, arrhythmia, and acute coronary syndrome. See Figure 4-8.

BASOPHIL COUNT

Normal range: 0.4%-1% of total WBC; 40-100/mm^3
Elevated in: Leukemia, inflammatory processes, polycythemia vera, Hodgkin's lymphoma, hemolytic anemia, after splenectomy, myeloid metaplasia, myxedema
Decreased in: Stress, hypersensitivity reaction, steroids, pregnancy, hyperthyroidism, postirradiation

BICARBONATE

Normal: Arterial: 21-28 mEq/L
Venous: 22-29 mEq/L

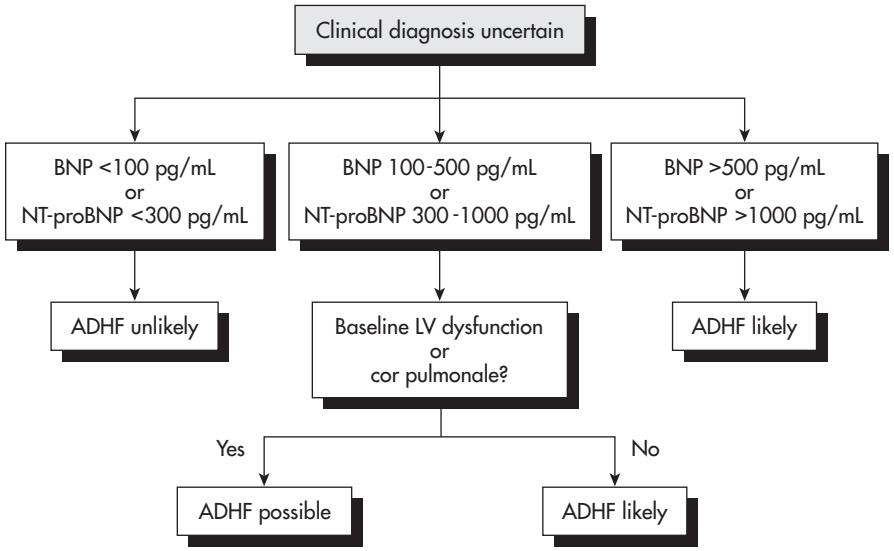


FIGURE 4-8 Interpretation of natriuretic peptide levels. *ADHF*, Acute decompensated heart failure; *BNP*, B-type natriuretic peptide; *NT-proBNP*, inactive N-terminal fragment of BNP. (From Adams JG, et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

Elevated in: Metabolic alkalosis, compensated respiratory acidosis, diuretics, corticosteroids, laxative abuse
Decreased in: Metabolic acidosis, compensated respiratory alkalosis, acetazolamide, cyclosporine, cholestyramine, methanol or ethylene glycol poisoning

BILE, URINE

See URINE BILE

BILIRUBIN, DIRECT (conjugated bilirubin)

Normal range: 0-0.2 mg/dl (0-4 μmol/L [CF: 17.10; SMI: 2 μmol/L])
Elevated in: Hepatocellular disease, biliary obstruction, drug-induced cholestasis, hereditary disorders (Dubin-Johnson syndrome, Rotor's syndrome)

BILIRUBIN, INDIRECT (unconjugated bilirubin)

Normal range: 0-1.0 mg/dl (2-18 μmol/L [CF: 17.10; SMI: 2 μmol/L])
Elevated in:
A. Increased bilirubin production (if normal liver, serum unconjugated bilirubin is usually less than 4 mg/100 ml)
   1. Hemolytic anemia
      a. Acquired
      b. Congenital
   2. Resorption from extravascular sources
      a. Hematomas
      b. Pulmonary infarcts
   3. Excessive ineffective erythropoiesis
      a. Congenital (congenital dyserythropoietic anemias)
      b. Acquired (pernicious anemia, severe lead poisoning; if present, bilirubinemia is usually mild)
B. Defective hepatic unconjugated bilirubin clearance (defective uptake or conjugation)
   1. Severe liver disease
   2. Gilbert's syndrome
   3. Crigler-Najjar type I or II
   4. Drug-induced inhibition
   5. Portacaval shunt
   6. Congestive heart failure
   7. Hyperthyroidism (uncommon)

BILIRUBIN, TOTAL

See Fig. E4-9 and Table E4-6, for evaluation of hyperbilirubinemia and liver disease.
Normal range: 0-1.0 mg/dl (2-18 μmol/L [CF: 17.10, SMI: 2 μmol/L])
Elevated in: Liver disease (hepatitis, cirrhosis, cholangitis, neoplasm, biliary obstruction, infectious mononucleosis), hereditary disorders (Gilbert's disease, Dubin-Johnson syndrome), drugs (steroids, statins, niacin, acetaminophen, diphenylhydantoin, phenothiazines, penicillin, erythromycin, clindamycin, captopril, amphotericin B, sulfonamides, azathioprine, isoniazid, 5-aminosalicylic acid, allopurinol, methyldopa, indomethacin, halothane, oral contraceptives, procainamide, tolbutamide, labetalol), hemolysis, pulmonary embolism or infarct, hepatic congestion secondary to congestive heart failure

BILIRUBIN, URINE

See URINE BILE

BLADDER TUMOR ASSOCIATED ANTIGEN

Normal: ≤14 U/ml. Test is used to detect bladder cancer recurrence. Sensitivity 57%-83% and specificity 68%-72%.
Elevated in: Bladder cancer, renal stones, nephritis, UTI, hematuria, renal cancer, cystitis, recent bladder or urinary tract trauma

BLEEDING TIME (modified Ivy method)

See Fig. E4-10 for evaluation of patients with prolonged bleeding time.
Normal range: 2 to 9.5 min
Elevated in: Thrombocytopenia, capillary wall abnormalities, platelet abnormalities (Bernard-Soulier disease, Glanzmann's disease), drugs (aspirin, warfarin, anti-inflammatory medications, streptokinase, urokinase, dextran, β-lactam antibiotics, moxalactam), disseminated intravascular coagulation, cirrhosis, uremia, myeloproliferative disorders, von Willebrand's disease.

Bleeding time tests are no longer performed at many hospitals and have been replaced by the platelet function analyzer (PFA-100) assay.

BLOOD VOLUME, TOTAL

Normal: 60-80 ml/kg
Elevated in: Polycythemia vera, pulmonary disease, CHF, renal insufficiency, pregnancy, acidosis, thyrotoxicosis
Decreased in: Anemia, hemorrhage, vomiting, diarrhea, dehydration, burns, starvation

BNP

See B-TYPE NATRIURETIC PEPTIDE

BORDETELLA PERTUSSIS SEROLOGY

Test description: PCR of nasopharyngeal aspirates or secretions is used to identify *Bordetella pertussis,* the organism responsible for whooping cough.

BRCA ANALYSIS

DESCRIPTION OF ANALYSIS

Comprehensive BRCA analysis:

BRCA1: Full sequence determination in both forward and reverse directions of approximately 5500 base pairs comprising 22 coding exons and one noncoding exon (exon 4) and approximately 800 adjacent base pairs in the noncoding intervening sequence (intron). Exon 1, which is noncoding, is not analyzed. The wild-type *BRCA1* gene encodes a protein comprising 1863 amino acids.

BRCA2: Full sequence determination in both forward and reverse directions of approximately 10,200 base pairs comprising 26 coding exons and approximately 900 adjacent base pairs in the noncoding intervening sequence (intron). Exon 1, which is noncoding, is not analyzed. The wild-type *BRCA2* gene encodes a protein comprising 3418 amino acids.

The noncoding intronic regions of *BRCA1* and *BRCA2* that are analyzed do not extend more than 20 base pairs proximal to the 5' end and 10 base pairs distal to the 3' end of each exon.

Single-site BRCA analysis: DNA sequence analysis for a specified mutation in *BRCA1* and/or *BRCA2.*

Multisite 3 BRCA analysis: DNA sequence analysis of specific portions of *BRCA1* exon 2, *BRCA1* exon 20, and *BRCA2* exon 11 designed to detect only mutations 187delAG and 5385insC in *BRCA1* and 6174delT in *BRCA2.*

Interpretive Criteria:

"Positive for a deleterious mutation": Includes all mutations (nonsense, insertions, deletions) that prematurely terminate ("truncate") the protein product of *BRCA1* at least 10 amino acids from the C-terminus, or the protein product of *BRCA2* at least 110 amino acids from the C-terminus (based on documentation of deleterious mutations in *BRCA1* and *BRCA2*).

In addition, specific missense mutations and noncoding intervening sequence (IVS) mutations are recognized as deleterious on the basis of data derived from linkage analysis of high-risk families, functional assays, biochemical evidence, and/or demonstration of abnormal mRNA transcript processing.

"Genetic variant, suspected deleterious": Includes genetic variants for which the available evidence indicates a likelihood, but not proof, that the mutation is deleterious. The specific evidence supporting such an interpretation will be summarized for individual variants on each such report.

"Genetic variant, favor polymorphism": Includes genetic variants for which available evidence indicates that the variant is highly unlikely to contribute substantially to cancer risk. The specific evidence supporting such an interpretation will be summarized for individual variants on each such report.

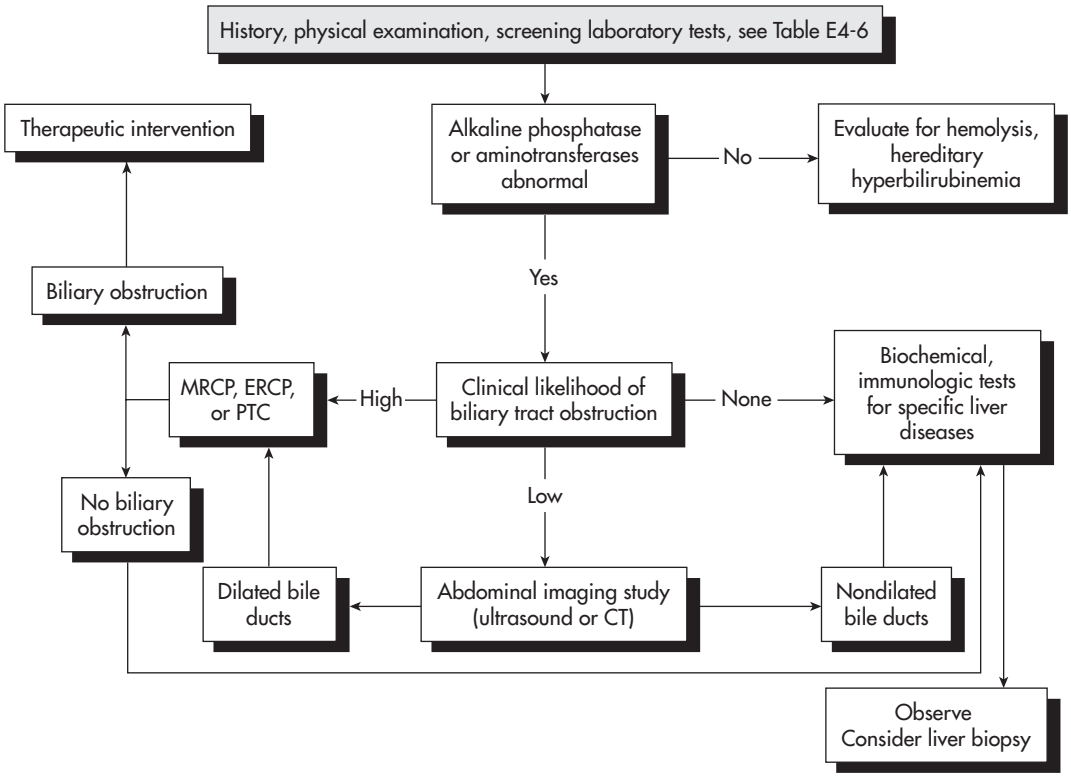


FIGURE E4-9 Diagnosis algorithm for the evaluation of hyperbilirubinemia and other liver test abnormalities and/or signs and symptoms suggestive of liver disease. *CT,* Computed tomography; *ERCP,* endoscopic retrograde cholangiopancreatography; *MRCP,* magnetic resonance cholangiopancreatography; *PTC,* percutaneous cholangiogram. (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders. Modified from Lidofsky SD, Scharschmidt BF: Jaundice. In Feldman M, Scharschmidt BF, Sleisenger MH [eds]: *Gastrointestinal and liver disease,* ed 6, Philadelphia, 1998, Saunders.)

TABLE E4-6 Obstructive Jaundice versus Cholestatic Liver Disease

Feature	Suggests Obstructive Jaundice	Suggests Parenchymal Liver Disease
History	Abdominal pain Fever, rigors Prior biliary surgery Older age Acholic stools	Anorexia, malaise, myalgias, suggestive of viral prodrome- Known infectious exposure Receipt of blood products, use of intravenous drugs Exposure to known hepatotoxin Family history of jaundice
Physical examination	High fever Abdominal tenderness Palpable abdominal mass Abdominal scar	Ascites Other stigmata of liver disease (e.g., prominent abdominal veins, gynecomastia, spider angiomata, asterixis, encephalopathy, Kayser-Fleischer rings)
Laboratory studies	Predominant elevation of serum bilirubin and alkaline phosphatase Prothrombin time that is normal or normalizes with vitamin K administration Elevated serum amylase	Predominant elevation of serum aminotransferases Prolonged prothrombin time that does not correct with vitamin K administration Blood tests indicative of specific liver disease

From Goldman L, Ausiello D (eds): *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.

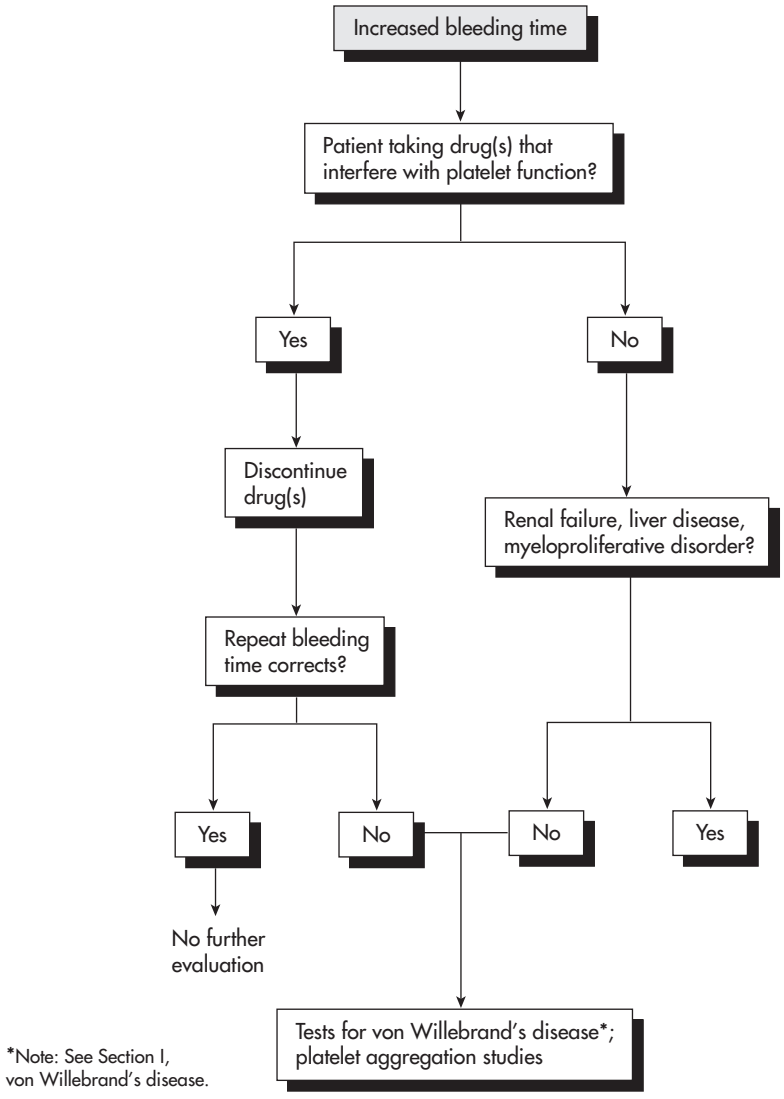


FIGURE E4-10 An algorithm for diagnostic decisions in evaluating patients with a prolonged bleeding time. The scheme assumes that the platelet count is normal because thrombocytopenia itself can prolong the bleeding time. (Modified from Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

"Genetic variant of uncertain significance": Includes missense mutations and mutations that occur in analyzed intronic regions whose clinical significance has not yet been determined, as well as chain-terminating mutations that truncate *BRCA1* and *BRCA2* distal to amino acid positions 1853 and 3308, respectively.

"No deleterious mutation detected": Includes nontruncating genetic variants observed at an allele frequency of approximately 1% of a suitable control population (providing that no data suggest clinical significance), as well as all genetic variants for which published data demonstrate absence of substantial clinical significance. Also includes mutations in the protein-coding region that neither alter the amino acid sequence nor are predicted to significantly affect exon splicing, and base pair alterations in noncoding portions of the gene that have been demonstrated to have no deleterious effect on the length or stability of the mRNA transcript.

There may be uncommon genetic abnormalities in *BRCA1* and *BRCA2* that will not be detected by *BRCA* analysis. This analysis, however, is believed to rule out the majority of abnormalities in these genes, which are believed responsible for most hereditary susceptibility to breast and ovarian cancer.

"Specific variant/mutation not identified": Specific and designated deleterious mutations or variants of uncertain clinical significance are not present in the individual being tested. If one (or rarely two) specific deleterious mutations have been identified in a family member, a negative analysis for the specific mutation(s) indicates that the tested individual is at the general population risk of developing breast or ovarian cancer.

BREATH HYDROGEN TEST (Hydrogen breath test)

Normal: This test is for bacterial overgrowth. H_2 excretion fasting: 4.6 ± 5.1, after lactulose, early increase <12. Lactulose usually results in a colonic response >30 min after ingestion.

Elevated in: A high fasting breath H_2 level and an increase of at least 12 ppm within 30 min after lactulose challenge are indicative of bacterial overgrowth in the small intestine. The increase must precede the colonic response.

False positives in: Accelerated gastric emptying, laxative use

False negatives in: Use of antibiotics and patients who are nonhydrogen producers

BUN

See UREA NITROGEN, BLOOD

C282Y AND H63D MUTATION ANALYSIS

Procedure: Detection of the C282Y and H63D mutations is accomplished by amplification of exons 2 and 4 of the *HFE* gene on chromosome 6 by polymerase chain reaction (PCR) followed by allele-specific hybridization and chemiluminescent detection of hybridized probes. H63D is viewed by some as a polymorphism rather than a mutation because of its prevalence in the population, because 15% of the individuals affected with hereditary hemochromatosis (HH) are compound heterozygotes for C282Y and H63D and about 1% of patients are H63D homozygotes, which suggests that H63D may be causative in the development of the disorder at reduced penetrance.

Interpretation: Homozygosity for the C282Y mutation has been associated with an increased risk of being affected with HH compared with the general population. The genotype is observed in 60%-90% of individuals affected with HH and occurs in less than 1% of the general population. However, approximately 25% of asymptomatic individuals with this genotype do not develop the disorder.

C3

See COMPLEMENT

C4

See COMPLEMENT

CALCITONIN (serum)

Normal range: <100 pg/ml (<100 ng/L [CF: 1; SMI: 10 ng/L])

Elevated in: Medullary carcinoma of the thyroid (particularly if level >1500 pg/ml), carcinoma of the breast, apudomas, carcinoids, renal failure, thyroiditis

CALCIUM (serum)

Normal range: 8.8-10.3 mg/dl (2.2-2.58 μmol/L [CF: 0.2495; SMI: 0.02 μmol/L])

ELEVATED

Relatively common:

Neoplasia
Bone primary
Myeloma
Acute leukemia
Nonbone solid tumors
Breast
Lung
Squamous nonpulmonary
Kidney
Neoplasm secretion of parathyroid hormone-related protein (PTHrP, "ectopic PTH")
Primary hyperparathyroidism
Thiazide diuretics
Tertiary (renal) hyperparathyroidism
Idiopathic
Spurious (artifactual) hypercalcemia
Dehydration
Serum protein elevation
Laboratory technical problem (lab error)

Relatively uncommon:

Sarcoidosis
Hyperthyroidism
Immobilization (mostly seen in children and adolescents)
Diuretic phase of acute renal tubular necrosis
Vitamin D intoxication
Milk-alkali syndrome
Addison's disease
Lithium therapy
Idiopathic hypercalcemia of infancy
Acromegaly
Theophylline toxicity

Table 4-7 describes the laboratory differential diagnosis of hypercalcemia.

DECREASED

Artifactual
Hypoalbuminemia
Hemodilution
Primary hypoparathyroidism
Pseudohypoparathyroidism
Vitamin D related
Vitamin D deficiency
Malabsorption
Renal failure
Magnesium deficiency
Sepsis
Chronic alcoholism
Tumor lysis syndrome
Rhabdomyolysis
Alkalosis (respiratory or metabolic)
Acute pancreatitis
Drug-induced hypocalcemia
Large doses of magnesium sulfate
Anticonvulsants
Mithramycin
Gentamicin
Cimetidine

Table 4-8 describes the laboratory differential diagnosis of hypocalcemia.

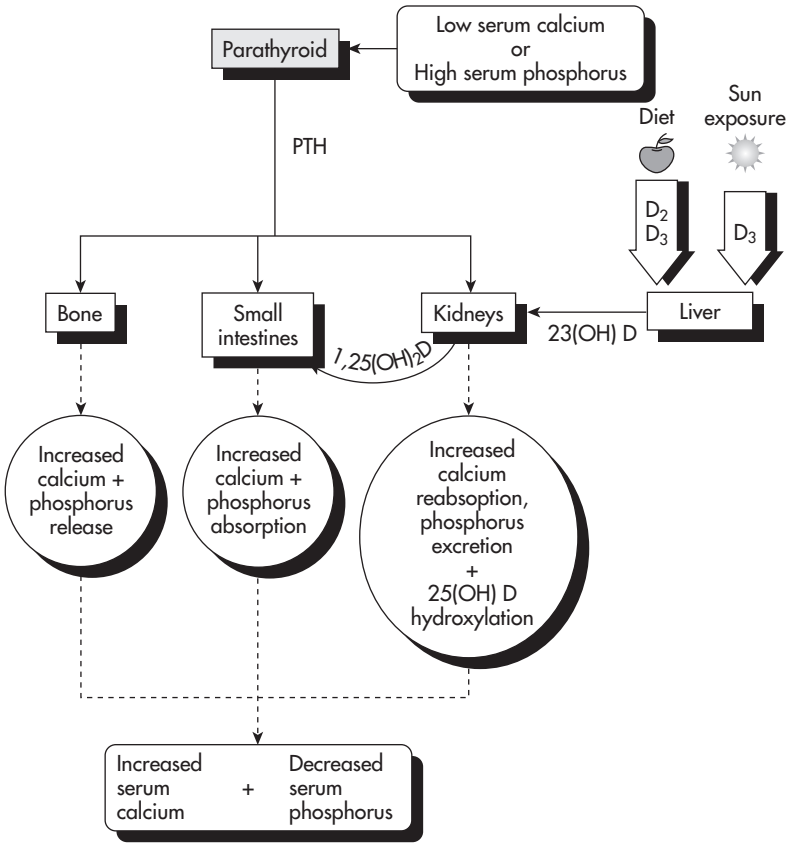


FIGURE 4-11 Calcium homeostasis. Parathyroid hormone (PTH) is released from the parathyroid glands in response to hypocalcemia and hyperphosphatemia. PTH acts on bone, the small intestines, and the kidneys to effect a rise in serum calcium and a net decrease in serum phosphorus. Hydroxylation of inactive forms of vitamin D occurs in the liver and kidneys. 1,25(OH)2D facilitates intestinal absorption of calcium and phosphorus. *1,25(OH)2D*, 1,25-Dihydroxyvitamin D; *25(OH) D*, 25-hydroxyvitamin D; *D2*, vitamin D2; *D3*, vitamin D3. (From Adams JG, et al: *Emergency medicine, clinical essentials*, ed 2, Philadelphia, 2013, Elsevier.)

TABLE 4-7 Laboratory Differential Diagnosis of Hypercalcemia

	PLASMA TESTS					URINE TESTS			
Diagnosis	**Ca**	**PO_4**	**PTH**	**25(OH)D**	**1,25(OH)$_2$D**	**cAMP**	**TmP/GFR**	**Ca**	**Comments**
Primary hyperparathyroidism	↑	N/↓	↑	N	N/↑	↑	↓	↑	Parathyroid adenoma most common
MEN I									Parathyroid hyperplasia; also includes pituitary and pancreatic neoplasms
MEN IIa									Parathyroid hyperplasia; also includes medullary thyroid carcinoma and pheochromocytoma
MEN IIb									Parathyroid disease uncommon, primarily medullary thyroid carcinoma and pheochromocytoma
FHH	↑	N	N/↑	N	N	N/↑	N/↓	↓↓	Autosomal dominant inheritance; hypercalcemia present within first decade; benign
Malignancy									
Solid tumor, humoral	↑	N/↓	↓	N	N	↑	↓	↑↑	Primarily epidermoid tumors; PTH-related protein(s) is mediator
Solid tumor, osteolytic	↑	N/↑	↓	N	N	↓	↑	↑↑	
Lymphoma	↑	N/↑	↓	N/↓	↑	↓	↑	↑↑	
Granulomatous disease	↑	N/↑	↓	N/↓	↑↑	↓	↑	↑↑	Sarcoid most common etiology
Vitamin D intoxication	↑	N/↑	↓	↑↑	N	↓	↑	↑↑	
Hyperthyroidism	↑	N	↓	N	N	N	N	↑↑	Plasma concentrations of T_4 and/or T_3 are elevated

Ca, Calcium; *cAMP,* cyclic adenosine monophosphate; *FHH,* familial hypocalciuric hypercalcemia; *GFR,* glomerular filtration rate; *MEN,* multiple endocrine neoplasia; *25(OH)D,* 25 hydroxyvitamin D; *PO_4*, phosphate; *PTH,* parathyroid hormone; *T_3*, triiodothyronine; *T_4*, thyroxine; *TmP,* renal threshold for phosphorus.
From Moore WT, Eastman RC: *Diagnostic endocrinology,* ed 2, St Louis, 1996, Mosby.

TABLE 4-8 Laboratory Differential Diagnosis of Hypocalcemia

	PLASMA TESTS					URINE TESTS					
Diagnosis	**Ca**	**PO_4**	**PTH**	**25(OH)D**	**1,25$(OH)_2$D**	**cAMP**	**cAMP after PTH**	**TmP/GFR**	**TmP/GFR after PTH**	**Ca**	**Comments**
Hypoparathyroidism	↓	↑	N/↓	N	↓	↓	↑↑	↑	↓↓	N/↓	Deficiency of PTH
Pseudohypoparathyroidism											
Type I	↓	↑	↑↑	N	↓	↓	NC	↑	↑	N/↓	Resistance to PTH; patients may have Albright's hereditary osteodystrophy and resistance to multiple hormones
Type II	↓	N	↑↑	N	↓	↓	↑	↑	↑	N/↓	Renal resistance to cAMP
Vitamin D deficiency	↓	N/↓	↑↑	↓↓	N/↓	↑	↑	↓	↓	↓↓	Deficient supply (e.g., nutrition) or absorption (e.g., pancreatic insufficiency) of vitamin D
Vitamin D–dependent Rickets											
Type I	↓	N/↓	↑↑	N	↓	↑↑		↓		↓↓	Deficient activity of renal 25(OH)D-1α-hydroxylase
Type II	↓	N/↓	↑↑	N	↑↑	↑		↓		↓↓	Resistance to 1,25$(OH)_2$D

Ca, Calcium; *cAMP,* cyclic adenosine monophosphate; *FHH,* familial hypocalciuric hypercalcemia; *GFR,* glomerular filtration rate; *MEN,* multiple endocrine neoplasia; *NC,* no change or small increase; *(OH)D,* hydroxycalciferol D; *PO_4,* phosphate; *PTH,* parathyroid hormone; *T_3,* triiodothyronine; *T_4,* thyroxine; *TmP,* renal threshold for phosphorus.
From Moore WT, Eastman RC: Diagnostic endocrinology, ed 2, St Louis, 1996, Mosby.

CALCIUM, URINE

See URINE CALCIUM

CANCER ANTIGEN 15-3 (CA 15-3)

Normal: <30 U/ml
Elevated in: Approximately 80% of women with metastatic breast cancer. Clinical sensitivity is 0.60, specificity 0.87, positive predictive value 0.91. This test is generally used to predict recurrence of breast cancer and evaluate response to therapy. May also be elevated in liver cancer, pancreatic cancer, ovarian cancer, colorectal cancer. Elevations can also occur with benign breast and liver disease.

CANCER ANTIGEN 27-29 (CA 27-29)

Normal: <38 U/ml
Elevated in: Approximately 75% of women with metastatic breast cancer. Clinical sensitivity is 0.57, specificity 0.97, positive predictive value 0.83, negative predictive value 0.92. This test is generally used to predict recurrence of breast cancer and evaluate response to therapy. May also be elevated in liver cancer, pancreatic cancer, ovarian cancer, colorectal cancer. Elevations can also occur with benign breast and liver disease.

CANCER ANTIGEN 72-4 (CA 72-4)

Normal: <4.0 ng/ml
Elevated in: Gastric cancer (elevated in >50% of patients). Often used in combination with CA 72-4, CA 19-9, and CEA to monitor gastric cancer after treatment.

CANCER ANTIGEN 125 (CA 125)

Normal range: <1.4%
This test uses an antibody against antigen from tissue culture of an ovarian tumor cell line. Various published evaluations report sensitivity of about 75%-80% in patients with ovarian carcinoma. There is also an appreciable incidence of elevated values in nonovarian malignancies and in certain benign conditions (see below). Test values may transiently increase during chemotherapy.

MALIGNANT
Epithelial ovarian carcinoma, 75%-80% (range, 25%-92%; better in serous than mucinous cystadenocarcinoma)
Endometrial carcinoma, 25%-48% (2%-90%)
Pancreatic carcinoma, 59%
Colorectal carcinoma, 20% (15%-56%)
Endocervical adenocarcinoma, 83%
Squamous cervical or vaginal carcinoma, 7%-14%
Lung carcinoma, 32%
Breast carcinoma, 12%-40%
Lymphoma, 35%
BENIGN
Cirrhosis, 40%-80%
Acute pancreatitis, 38%
Acute peritonitis, 75%
Endometriosis, 88%
Acute pelvic inflammatory disease, 33%
Pregnancy first trimester, 2%-24%
During menstruation (occasionally)
Renal failure (?frequency)
Normal persons, 0.6%-1.4%

CAPTOPRIL STIMULATION TEST

Normal: Test performed by giving 25 mg captopril orally after overnight fast. Patient should be seated during test. After captopril, aldosterone <15 ng/dl, renin >2 ng angiotensin L/ml/hr.
Interpretation: In patients with primary aldosteronism, plasma aldosterone remains high and plasma renin activity remains low after captopril.

CARBAMAZEPINE (TEGRETOL)

Normal therapeutic range: 4-12 mcg/ml

CARBOHYDRATE ANTIGEN 19-9

Normal: <37.0 U/ml
Elevated in: GI cancer, most frequently pancreatic cancer. Amount of elevation has no relation to tumor mass. Elevations can also occur with cirrhosis, cholangitis, and chronic or acute pancreatitis.

CARBON DIOXIDE, PARTIAL PRESSURE

Normal:
Male: 35-48 mm Hg
Female: 32-45 mm Hg
Elevated in: Respiratory acidosis
Decreased in: Respiratory alkalosis

CARBON MONOXIDE

See CARBOXYHEMOGLOBIN

CARBOXYHEMOGLOBIN

Normal range: Saturation of hemoglobin <2%; smokers <9%
Elevated in: Smoking, exposure to smoking, exposure to automobile exhaust fumes, malfunctioning gas-burning appliances

CARCINOEMBRYONIC ANTIGEN (CEA)

Normal range:
Nonsmokers: 0-2.5 ng/ml (0-2.5 μg/L [CF: 1; SMI: 0.1 μg/L])
Smokers: 0-5 ng/ml (0-5 μg/L [CF: 1; SMI: 0.1 μg/L])
Elevated in:
Colorectal carcinomas, pancreatic carcinomas, and metastatic disease (usually produce higher elevations: >20 ng/ml)
Carcinomas of the esophagus, stomach, small intestine, liver, breast, ovary, lung, and thyroid (usually produce lesser elevations)
Benign conditions (smoking, inflammatory bowel disease, hypothyroidism, cirrhosis, pancreatitis, infections) (usually produce levels <10 ng/ml)

CAROTENE (serum)

Normal range: 50-250 μg/dl (0.9-4.6 μmol/L [CF: 0.01863; SMI: 0.1 μmol/L])
Elevated in: Carotenemia, chronic nephritis, diabetes mellitus, hypothyroidism, nephrotic syndrome, hyperlipidemia
Decreased in: Fat malabsorption, steatorrhea, pancreatic insufficiency, lack of carotenoids in diet, high fever, liver disease

CATECHOLAMINES, URINE

See URINE CATECHOLAMINES

CBC

See COMPLETE BLOOD COUNT

CD40 LIGAND

Normal: <5 mcg/L. CD40 ligand is a soluble protein that is shed from activated leukocytes and platelets and used in risk stratification for acute coronary syndrome.
Elevated in: Acute coronary syndrome. Increased CD40 ligand is associated with higher incidence of death or nonfatal MI.

CD4+ T-LYMPHOCYTE COUNT (CD4+ T-cells)

Calculated as total WBC × % lymphocytes × % lymphocytes stained with CD4.

This test is used primarily to evaluate immune dysfunction in HIV infection. It is useful as a prognostic indicator and as a criterion for initiating prophylaxis for several opportunistic infections that are sequelae of HIV infection. Progressive depletion of CD4+ T-lymphocytes is associated with an increased likelihood of clinical complications (Table 4-9).

TABLE 4-9 Relation of CD4 Lymphocyte Counts to the Onset of Certain HIV-Associated Infections and Neoplasms in North America

CD4 Count (Cells/mm³)*	Opportunistic Infection or Neoplasm	Frequency (%)†
>500	Herpes zoster, polydermatomal	5-10
200-500	*Mycobacterium tuberculosis* infection, pulmonary and extrapulmonary	2-20
	Oral hairy leukoplakia	40-70
	Candida pharyngitis (thrush)	40-70
	Recurrent *Candida* vaginitis	15-30 (F)
	Kaposi's sarcoma, mucocutaneous	15-30 (M)
	Bacterial pneumonia, recurrent	15-20
	Cervical neoplasia	1-2 (F)
100-200	*Pneumocystis carinii* pneumonia	15-60
	Herpes simplex, chronic, ulcerative	5-10
	Histoplasma capsulatum infection, disseminated	0-20
	Kaposi's sarcoma, visceral	3-8 (M)
	Progressive multifocal leukoencephalopathy	2-3
	Lymphoma, non-Hodgkin's	2-5
<100	*Candida* esophagitis	15-20
	Mycobacterium avium-intracellulare, disseminated	25-40
	Toxoplasma gondii encephalitis	5-25
	Cryptosporidium enteritis	2-10
	CMV retinitis	20-35
	Cryptococcus neoformans encephalitis	2-5
	CMV esophagitis or colitis	6-12
	Lymphoma, central nervous system	4-8

*Table indicates CD4 count at which specific infections or neoplasms generally begin to appear. Each infection may recur or progress during the subsequent course of HIV disease.
†Even within the United States, great regional differences in the incidence of specific opportunistic infections are apparent. For example, disseminated histoplasmosis is common in the Mississippi River drainage area but very rare in individuals who have lived exclusively on the East or West Coast.
CMV, Cytomegalovirus; *F,* exclusively in women; *HIV,* human immunodeficiency virus; *M,* almost exclusively in men.
From Andreoli TE (ed): *Cecil essentials of medicine,* ed 5, Philadelphia, 2000, Saunders.

CEA

See CARCINOEMBRYONIC ANTIGEN

CEREBROSPINAL FLUID (CSF)

Interpretation of results:
1. Appearance of the fluid
   a. Clear: normal.
   b. Yellow color (xanthochromia) in the supernatant of centrifuged CSF within 1 hour or less after collection is usually the result of previous bleeding (subarachnoid hemorrhage); it may also be caused by increased CSF protein, melanin from meningeal melanosarcomas, or carotenoids.
   c. Pinkish color is usually the result of a bloody tap; the color generally clears progressively from tubes 1 to 4 (the supernatant is usually crystal clear in traumatic taps).
   d. Turbidity usually indicates the presence of leukocytes (bleeding introduces approximately 1 WBC/500 RBCs into the CSF).
2. CSF pressure: elevated pressure can be seen with meningitis, meningoencephalitis, pseudotumor cerebri, mass lesions, and intracerebral bleeding.
3. Cell count: in the adult the CSF is normally free of cells (although up to 5 mononuclear cells/mm³ is considered normal); the presence of granulocytes is never normal.
   a. Neutrophils: seen in bacterial meningitis, early viral meningoencephalitis, and early tuberculosis (TB) meningitis.
   b. Increased lymphocytes: TB meningitis, viral meningoencephalitis, syphilitic meningoencephalitis, fungal meningitis.
4. Protein: serum proteins are generally too large to cross the normal blood–CSF barrier; however, increased CSF protein is seen with meningeal inflammation, traumatic tap, increased CNS synthesis, tissue degeneration, obstruction to CSF circulation, and Guillain-Barré syndrome.
5. Glucose
   a. Decreased glucose is seen with bacterial meningitis, TB meningitis, fungal meningitis, subarachnoid hemorrhage, and some cases of viral meningitis.
   b. A mild increase in CSF glucose can be seen in patients with very elevated serum glucose levels.

Table 4-10 describes CSF findings in central nervous system disorders.

TABLE 4-10 Cerebrospinal Fluid Findings in Central Nervous System Disorders

Condition	Pressure (mm H_2O)	Leukocytes (mm^3)	Protein (mg/dl)	Glucose (mg/dl)	Comments
Normal	50-80	<5, ≥75% lymphocytes	20-45	>50 (or 75% serum glucose)	
Common Forms of Meningitis					
Acute bacterial meningitis	Usually elevated (100-300)	100-10,000 or more; usually 300-2000; PMNs predominate	Usually 100-500	Decreased, usually <40 (or <66% serum glucose)	Organisms usually seen on Gram stain and recovered by culture; latex agglutination of CSF usually positive
Partially treated bacterial meningitis	Normal or elevated	5-10,000; PMNs usual but mononuclear cells may predominate if pretreated for extended period	Usually 100-500	Normal or decreased	Organisms may be seen on Gram stain; latex agglutination CSF may be positive; pretreatment may render CSF sterile
Viral meningitis or meningoencephalitis	Normal or slightly elevated (80-150)	Rarely >1000 cells; eastern equine encephalitis and lymphocytic choriomeningitis may have cell counts of several thousand; PMNs early but mononuclear cells predominate through most of the course	Usually 50-200	Generally normal; may be decreased to <40 in some viral diseases, particularly mumps (15%-20% of cases)	HSV encephalitis is suggested by focal seizures or by focal findings on CT or MRI scans or EEG. Enteroviruses and HSV infrequently recovered from CSF. HSV and enteroviruses may be detected by PCR of CSF.
Uncommon Forms of Meningitis					
Tuberculous meningitis	Usually elevated	10-500; PMNs early but lymphocytes predominate through most of the course	100-3000; may be higher in presence of block	<50 in most cases; decreases with time if treatment is not provided	Acid-fast organisms almost never seen on smear; organisms may be recovered in culture of large volumes of CSF; *Mycobacterium tuberculosis* may be detected by PCR of CSF
Fungal meningitis	Usually elevated	5-500; PMNs early but mononuclear cells predominate through most of the course; cryptococcal meningitis may have no cellular inflammatory response	25-500	<50; decreases with time if treatment is not provided	Budding yeast may be seen; organisms may be recovered in culture; cryptococcal antigen (CSF and serum) may be positive in cryptococcal infection
Syphilis (acute) and leptospirosis	Usually elevated	50-500; lymphocytes predominate	50-200	Usually normal	Positive CSF serology; spirochetes not demonstrable by usual techniques of smear or culture; darkfield examination may be positive
Amebic *(Naegleria)* meningoencephalitis	Elevated	1000-10,000 or more; PMNs predominate	50-500	Normal or slightly decreased	Mobile amebae may be seen by hanging-drop examination of CSF at room temperature
Brain and Parameningeal Abscesses					
Brain abscess	Usually elevated (100-300)	5-200; CSF rarely acellular; lymphocytes predominate; if abscess ruptures into ventricle, PMNs predominate and cell count may reach >100,000	75-500	Normal unless abscess ruptures into ventricular system	No organisms on smear or culture unless abscess ruptures into ventricular system
Subdural empyema	Usually elevated (100-300)	100-5000; PMNs predominate	100-500	Normal	No organisms on smear or culture of CSF unless meningitis also present; organisms found on tap of subdural fluid
Cerebral epidural abscess	Normal to slightly elevated	10-500; lymphocytes predominate	50-200	Normal	No organisms on smear or culture of CSF
Spinal epidural abscess	Usually low, with spinal block	10-100; lymphocytes predominate	50-400	Normal	No organisms on smear or culture of CSF
Chemical (drugs, dermoid cysts, myelography dye)	Usually elevated	100-1000 or more; PMNs predominate	50-100	Normal or slightly decreased	Epithelial cells may be seen within CSF by use of polarized light in some children with dermoids
Noninfectious Causes					
Sarcoidosis	Normal or elevated slightly	0-100; mononuclear	40-100	Normal	No specific findings
Systemic lupus erythematosus with CNS involvement	Slightly elevated	0-500; PMNs usually predominate; lymphocytes may be present	100	Normal or slightly decreased	No organisms on smear or culture; LE preparation may be positive; positive neuronal and ribosomal P protein antibodies in CSF
Tumor, leukemia	Slightly elevated to very high	0-100 or more; mononuclear or blast cells	50-1000	Normal to decreased (20-40)	Cytology may be positive

CNS, Central nervous system; *CSF,* cerebrospinal fluid; *CT,* computed tomography; *EEG,* electroencephalogram; *HSV,* herpes simplex virus; *MRI,* magnetic resonance imaging; *PCR,* polymerase chain reaction; *PMN,* polymorphonuclear neutrophils.

From Behrman RE: *Nelson textbook of pediatrics,* ed 17, Philadelphia, 2004, Saunders.

CERULOPLASMIN (serum)

Normal range: 20-35 mg/dl (200-350 mg/L [CF: 10; SMI: 10 mg/L])
Elevated in: Pregnancy, estrogens, oral contraceptives, neoplastic diseases (leukemias, Hodgkin's lymphoma, carcinomas), inflammatory states, systemic lupus erythematosus, primary biliary cirrhosis, rheumatoid arthritis
Decreased in: Wilson's disease (values often <10 mg/dl), nephrotic syndrome, advanced liver disease, malabsorption, total parenteral nutrition, Menkes' syndrome

CHLAMYDIA GROUP ANTIBODY SEROLOGIC TEST

Test description: Acute and convalescent sera is drawn 2-4 weeks apart. A fourfold increase in titer between acute and convalescent sera is necessary for confirmation. A single titer ≥1:64 is considered indicative of psittacosis or LGV.

CHLAMYDIA TRACHOMATIS PCR

Test description: Test is performed on endocervical swab, urine, and intraurethral swab
Normal: Negative

CHLORIDE (serum)

Normal range: 95-105 mEq/L (95-105 mmol/L [CF: 1; SMI: 1 mmol/L])
Elevated in: Dehydration, excessive infusion of normal saline solution, cystic fibrosis (sweat test), hyperparathyroidism, renal tubular disease, metabolic acidosis, prolonged diarrhea, drugs (ammonium chloride administration, acetazolamide, boric acid, triamterene)
Decreased in: Congestive heart failure, syndrome of inappropriate antidiuretic hormone secretion, Addison's disease, vomiting, gastric suction, salt-losing nephritis, continuous infusion of D_5W, thiazide diuretic administration, diaphoresis, diarrhea, burns, diabetic ketoacidosis

CHLORIDE (sweat)

Normal: 0-40 mmol/L
Borderline/indeterminate: 41-60 mmol/L
Consistent with cystic fibrosis: >60 mmol/L
False low results can occur with edema, excessive sweating, and hypoproteinemia.

CHLORIDE, URINE

See URINE CHLORIDE

CHOLECYSTOKININ-PANCREOZYMIN (CCK, CCK-PZ)

Normal: <80 pg/ml
Elevated in: Pancreatic disease, celiac disease, gastric ulcer, postgastrectomy, IBS, fatty food intolerance

CHOLESTEROL, HIGH-DENSITY LIPOPROTEIN

See HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

CHOLESTEROL, LOW-DENSITY LIPOPROTEIN

See LOW-DENSITY LIPOPROTEIN CHOLESTEROL

CHOLESTEROL, TOTAL

Normal range: Varies with age
Generally <200 mg/dl (<5.20 mmol/L [CF: 0.02586; SMI: 0.05 mmol/L])
Elevated in: Primary hypercholesterolemia, biliary obstruction, diabetes mellitus, nephrotic syndrome, hypothyroidism, primary biliary cirrhosis, high-cholesterol diet, pregnancy third trimester, myocardial infarction, drugs (steroids, phenothiazines, oral contraceptives)
Decreased in: Medications (statins, niacin), starvation, malabsorption, sideroblastic anemia, thalassemia, abetalipoproteinemia, hyperthyroidism, Cushing's syndrome, hepatic failure, multiple myeloma, polycythemia vera, chronic myelocytic leukemia, myeloid metaplasia, Waldenström's macroglobulinemia, myelofibrosis

CHORIONIC GONADOTROPINS, HUMAN (serum) (HCG)

Normal range, serum: Female, premenopausal: <0.8 IU/L; postmenopausal <3.3 IU/L
Male: <0.7 IU/L
Elevated in:
Pregnancy, choriocarcinoma, gestational trophoblastic neoplasia (including molar gestations), placental site trophoblastic tumors; human antimouse antibodies (HAMA) can produce false serum assay for hCG.
The principal use of this test is to diagnose pregnancy. The concentration of hCG increases significantly during the initial 6 weeks of pregnancy.
Normal range: Varies with gestational stage:
1 wk: 5-50 mU/ml
1-2 wk: 50-550 mU/ml
2-3 wk: up to 5000 mU/ml
3-4 wk: up to 10,000 mU/ml
4-5 wk: up to 50,000 mU/ml
2-3 mo: 10,000-100,000 mU/ml
Peak values approaching 100,000 IU/L occur 60-70 days following implantation.
hCG levels generally double every 1-3 days. In patients with concentration <2000 IU/L, an increase of serum hCG <66% after 2 days is suggestive of spontaneous abortion or ruptured ectopic gestation.

CHYMOTRYPSIN

Normal: <10 mcg/L
Elevated in: Acute pancreatitis, chronic renal failure, oral enzyme preparations, gastric cancer, pancreatic cancer
Decreased in: Chronic pancreatitis, late cystic fibrosis

CIRCULATING ANTICOAGULANT (lupus anticoagulant)

Normal: Negative
Detected in: Systemic lupus erythematosus, drug-induced lupus, long-term phenothiazine therapy, multiple myeloma, ulcerative colitis, rheumatoid arthritis, postpartum, hemophilia, neoplasms, chronic inflammatory states, AIDS, nephrotic syndrome
NOTE: The name is a misnomer because these patients are prone to hypercoagulability and thrombosis.

CK

See CREATINE KINASE

CLONIDINE SUPPRESSION TEST

Interpretation: Clonidine inhibits neurogenic catecholamine release and will cause a decrease in plasma norepinephrine into the reference interval in hypertensive subjects without pheochromocytoma.Test is performed by giving 4.3 mcg clonidine/kg orally after overnight fast. Norepinephrine is measured at 3 hr. Result should be within established reference range and decrease to <50% of baseline concentration. Lack of decrease in norepinephrine is suggestive of pheochromocytoma.

CLOSTRIDIUM DIFFICILE TOXIN ASSAY (stool)

Normal: Negative
Detected in: Antibiotic-associated diarrhea and pseudomembranous colitis

CO

See CARBOXYHEMOGLOBIN

COAGULATION FACTORS

See Table 4-11 for characteristics of coagulation factors.
See Table 4-12 for differential diagnosis of low factor VIII.
Factor reference ranges:
V: >10%
VII: >10%
VIII: 50%-170%
IX: 60%-136%
X: >10%
XI: 50%-150%
XII: >30%
Table 4-13 describes screening laboratory results in coagulation factor deficiencies.

TABLE 4-11 Characteristics of Coagulation Factors

Factor	Descriptive Name	Source	Approximate Half-Life (hr)	Function
I	Fibrinogen	Liver	120	Substrate for fibrin clot (CP)
II	Prothrombin	Liver (VKD)	60	Serine protease (CP)
V	Proaccelerin, labile factor	Liver	12-36	Cofactor (CP)
VII	Serum prothrombin conversion accelerator, proconvertin	Liver (VKD)	6	(?) Serine protease (EP)
VIII	Antihemophilic factor or globulin	Endothelial cells and (?) elsewhere	12	Cofactor (IP)
IX	Plasma thromboplastin component, Christmas factor	Liver (VKD)	24	Serine protease (IP)
X	Stuart-Prower factor	Liver (VKD)	36	Serine protease (CP)
XI	Plasma thromboplastin antecedent	(?) Liver	40-84	Serine protease (IP)
XII	Hageman factor	(?) Liver	50	Serine protease contact activation (IP)
XIII	Fibrin-stabilizing factor	(?) Liver	96-180	Transglutaminase (CP)
Prekallikrein	Fletcher factor	(?) Liver	?	Serine protease contact activation (IP)
High-molecular-weight kininogen	Fitzgerald factor, Flaujeac or Williams factor	(?) Liver	?	Cofactor, contact activation (IP)

CP, Common pathway; *EP,* extrinsic pathway; *IP,* intrinsic pathway; *VKD,* vitamin K dependent.
From Noble J (ed): *Primary care medicine,* ed 3, St Louis, 2001, Mosby.

TABLE 4-12 Differential Diagnosis of a Low Factor VIII Level

1. FVIII <10%
   - Severe or moderately severe hemophilia A
   - Severe type 1 vWD
   - Type 3 vWD
   - Type 2N vWD
   - Acquired hemophilia A
   - Acquired vWD
2. FVIII: 10% to 50%
   - Mild hemophilia A
   - Type 1 vWD
   - Type 2N vWD
   - Combined FVIII and FV deficiency

FV, Factor V; *FVIII,* factor VIII; *VWD,* von Willebrand disease.
From Hoffman R: *Hematology: basic principles and practice,* ed 6, Philadelphia, Saunders, 2013.

TABLE 4-13 Screening Laboratory Results in Coagulation Factor Deficiencies

Deficient Factor	Frequency	PT	PTT	TT
I (fibrinogen)	Rare	↑	↑	↑
II (prothrombin)	Very rare	↑	↑	↑
V 1:1,000,000	↑	↑	NL	
VII	1:500,000	↑	NL	NL
VIII	1:5000 (male)	NL	↑	NL
IX	1:30,000 (male)	NL	↑	NL
X 1:500,000	↑	↑	NL	
XI	Rare*	NL	↑	NL
XII or HMWK or PK†	Rare	NL	↑	NL
XIII	Rare	NL	NL	↑

*Except in those of Ashkenazi Jewish descent (approximately 4% are heterozygous for factor XI deficiency).
†Not associated with clinical bleeding.
↑Increased over normal range; *HMWK,* high-molecular-weight kininogen; *NL,* normal; *PK,* prekallikrein; *PT,* prothrombin time; *PTT,* partial thromboplastin time; *TT,* thrombin time.
From Andreoli TE (ed): *Cecil essentials of medicine,* ed 5, Philadelphia, 2001, Saunders.

COLD AGGLUTININS TITER

Normal range: <1:32
Elevated in:
Primary atypical pneumonia (*Mycoplasma* pneumonia), infectious mononucleosis, CMV infection
Others: hepatic cirrhosis, acquired hemolytic anemia, frostbite, multiple myeloma, lymphoma, malaria

COMPLEMENT

Normal range:
C3: 70-160 mg/dl (0.7-1.6 g/L [CF: 0.01; SMI: 0.1 g/L])
C4: 20-40 mg/dl (0.2-0.4 g/L [CF: 0.01; SMI: 0.1 g/L])
Abnormal values:
Decreased C3: Active SLE, immune complex disease, acute glomerulonephritis, inborn C3 deficiency, membranoproliferative glomerulonephritis, infective endocarditis, serum sickness, autoimmune/chronic active hepatitis
Decreased C4: Immune complex disease, active SLE, infective endocarditis, inborn C4 deficiency, hereditary angioedema, hypergammaglobulinemic states, cryoglobulinemic vasculitis

COMPLEMENT DEFICIENCY

Table 4-14 describes complement deficiency states.

COMPLETE BLOOD COUNT (CBC)

See Fig. E4-12, which describes an algorithm for the evaluation of patients with neutropenia.
White blood cells 3200-9800/mm^3 (3.2-9.8 × 10^9/L [CF: 0.001; SMI: 0.1 × 10^9/L])
Red blood cells
Male: 4.3-5.9 × 10^6/mm^3 (4.3-5.9 × 10^{12}/L [CF: 0.001; SMI: 0.1 × 10^{12}/L])
Female: 3.5-5 × 10^6/mm^3 (3.5-5 × 10^{12}/L [CF: 0.001; SMI: 0.1 × 10^{12}/L])
Hemoglobin
Male: 13.6-17.7 g/dl (136-172 g/L [CF: 10; SMI: 1 g/L])
Female: 12-15 g/dl (120-150 g/L [CF: 10; SMI: 1 g/L])
Hematocrit
Male: 39%-49% (0.39-0.49 [CF: 0.01; SMI: 0.01])
Female: 33%-43% (0.33-0.43 [CF: 0.01; SMI: 0.01])
Mean corpuscular volume (MCV): 76-100 μm^3 (76-100 fL [CF: 1; SMI: 1 fL])
Mean corpuscular hemoglobin (MCH): 27-33 pg (27-33 pg [CF: 1; SMI: 1 pg])
Mean corpuscular hemoglobin concentration (MCHC): 33-37 g/dl (330-370 g/L [CF: 10; SMI: 10 g/L])

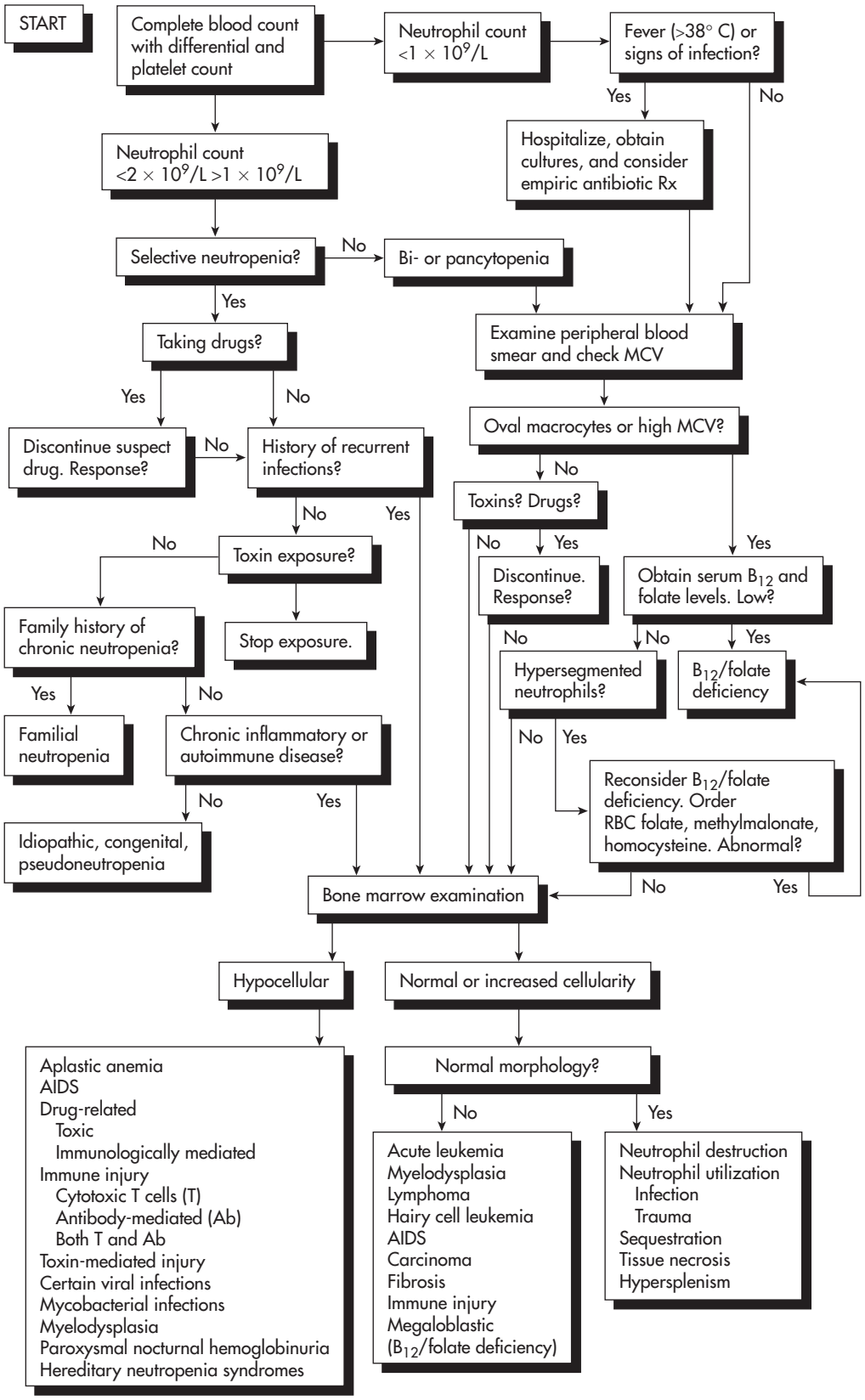


FIGURE E4-12 A practical algorithm for the evaluation of patients with neutropenia. The fundamental diagnostic principle is that for patients with severe neutropenia or for those with bicytopenia or pancytopenia, bone marrow examination will likely be necessary unless the following diagnoses are made: (1) a nutritional (folate or vitamin B_{12}) deficiency or (2) drug- or toxin-induced neutropenia in a patient whose neutropenia resolves after discontinuation of the offending agent. *AIDS,* Acquired immunodeficiency syndrome; *MCV,* mean corpuscular volume; *RBC,* red blood cell. (From Goldman L, Ausiello D [eds]: *Cecil textbook of medicine,* ed 24, Philadelphia, 2012, Saunders.)

TABLE 4-14 Complement Deficiency States

Component	No. of Reported Patients	Mode of Inheritance	Functional Defects	Disease Associations
Classic Pathway				
C1qrs	31	ACD	Impaired IC handling, delayed C' activation, impaired immune response	CVD, 48%; infection (encapsulated bacteria), 22%; both, 18%; healthy, 12%
C4	21	ACD	Impaired C' activation in absence of specific antibody	Infection (meningococcal), 74%; healthy, 26%
C2	109	ACD		
Alternative Pathway				
D	3	ACD	Impaired IC handling, opson/phag; granulocytosis, CTX, immune response and absent SBA	CVD, 79%; recurrent infection (encapsulated bacteria), 71%
P	70	XL		
Junction of Classic and Alternative Pathways				
C3	19	ACD	Impaired CTX; absent SBA	Infection (*Neisseria,* primarily meningococcal), 58%; CVD, 4%
Terminal Components				
C5	27	ACD	Absent SBA	Both, 1%
C6	77	ACD		Healthy, 25%
C7	73	ACD		
C8	73	ACD		
C9	165	ACD	Impaired SBA	Healthy, 91%; infection, 9%
Plasma Proteins Regulating C' Activation				
C1-INH	Many	AD	Uncontrolled generation of an inflammatory mediator on C' activation	Hereditary angioedema
H	13	Acq	Uncontrolled AP activation → low C3	CVD, 40%; CVD plus infection (encapsulated bacteria), 40%; healthy, 20%
I	14	ACD	Uncontrolled AP activation → low C3	Infection (encapsulated bacteria), 100%
Membrane proteins regulating C' activation	Many	Acq	Impaired regulation of C3b and C8 deposited on host RBCs; PMN, platelets → cell lysis	Paroxysmal nocturnal hemoglobinuria
Decay-accelerating factor				
Homologous restriction factor				
CD59	>20	ACD	Impaired PMN adhesive functions (i.e., margination), CTX, C3bi-mediated opson/phag	Infection (*Staphylococcus aureus, Pseudomonas* spp.), 100%
CR3 autoantibodies				
C3 nephritic factors	>59	Acq	Stabilize AP, convertase → low C3	MPGN, 41%; PLD, 25%; infection (encapsulated bacteria), 16%; MPGN plus PLD, 10%; PLD plus infection, 5%; MPGN plus PLD plus infection, 3%; MPGN plus infection, 2%
C4 nephritic factor		Acq	Stabilize CP, C3 convertase → low C3	Glomerulonephritis, 50%; CVD, 50%

ACD, Autosomal codominant; *Acq,* acquired; *AD,* autosomal dominant; *AP,* alternative pathway; *C',* complement; *CP,* classic pathway; *CTX,* chemotaxis; *CVD,* collagen-vascular disease; *IC,* immune complex, *MPGN,* membranoproliferative glomerulonephritis; *PLD,* partial lipodystrophy; *PMN,* polymorphonuclear neutrophil; *RBCs,* red blood cells; *SBA,* serum bactericidal activity; *XL,* X-linked.
From Mandell GL: *Mandell, Douglas, and Bennett's principles and practice of infectious diseases,* ed 6, New York, 2005, Churchill Livingstone.

Red blood cell distribution width index (RDW): 11.5%-14.5%
Platelet count: 130-400 × 10^3/mm^3 (130-400 × 10^9/L [CF: 1; SMI: 5 × 10^9/L])
Differential:
- 2-6 stabs (bands, early mature neutrophils)
- 60-70 segs (mature neutrophils)
- 1-4 eosinophils
- 0-1 basophils
- 2-8 monocytes
- 25-40 lymphocytes

CONJUGATED BILIRUBIN

See BILIRUBIN, DIRECT

COOMBS, DIRECT

Normal: Negative
Positive: Autoimmune hemolytic anemia, erythroblastosis fetalis, transfusion reactions, drugs (α-methyldopa, penicillins, tetracycline, sulfonamides, levodopa, cephalosporins, quinidine, insulin)
False-positive: May be seen with cold agglutinins

COOMBS, INDIRECT

Normal: Negative
Positive: Acquired hemolytic anemia, incompatible cross-matched blood, anti-Rh antibodies, drugs (methyldopa, mefenamic acid, levodopa)

COPPER (serum)

Normal range: 70-140 μg/dl (11-22 μmol/L [CF: 0.1574, SMI: 0.2 μmol/L])
Decreased in: Wilson's disease, Menkes' syndrome, malabsorption, malnutrition, nephrosis, total parenteral nutrition, acute leukemia in remission
Elevated in: Aplastic anemia, biliary cirrhosis, systemic lupus erythematosus, hemochromatosis, hyperthyroidism, hypothyroidism, infection, iron deficiency anemia, leukemia, lymphoma, oral contraceptives, pernicious anemia, rheumatoid arthritis

COPPER, URINE

See URINE COPPER

CORTICOTROPIN RELEASING HORMONE (CRH) STIMULATION TEST

Normal: A dose of 0.5 mg of dexamethasone is given every 6 hours for 2 days; 2 hours after last dose 1 mcg/kg CRH is given IV. Samples are drawn after 15 min. Normally there is a twofold to fourfold increase in mean baseline concentration of ACTH or cortisol. Cortisol >1.4 mcg/L is virtually 100% specific and 100% diagnostic.

Interpretation:

Normal or exaggerated response: Pituitary Cushing's disease

No response: Ectopic ACTH-secreting tumor

A positive response to CRH or a suppressed response to high-dose dexamethasone has a 97% positive predictive value for Cushing's disease. However, a lack of response to either test excludes Cushing's disease in only 64%-78% of patients. When the tests are considered together, negative responses from both have a 100% predictive value for ectopic ACTH secretion.

CORTISOL, PLASMA

Normal range: Varies with time of collection (circadian variation):

8 AM: 4-19 μg/dl (110-520 nmol/L [CF: 27.59; SMI: 10 nmol/L])

4 PM: 2-15 μg/dl (50-410 nmol/L [CF: 27.59; SMI: 10 nmol/L])

Elevated in: Ectopic adrenocorticotropic hormone production (i.e., oat cell carcinoma of lung), loss of normal diurnal variation, pregnancy, chronic renal failure, iatrogenic, stress, adrenal or pituitary hyperplasia, or adenomas

Decreased in: Primary adrenocortical insufficiency, anterior pituitary hypofunction, secondary adrenocortical insufficiency, adrenogenital syndromes

C-PEPTIDE

Elevated in: Insulinoma, sulfonylurea administration

Decreased in: Insulin-dependent diabetes mellitus, factitious insulin administration

CPK

See CREATINE KINASE

C-REACTIVE PROTEIN

Normal range: 6.8-820 μg/dl (68-8200 μg/L [CF: 10; SMI: 10 μg/L])

Elevated in: Rheumatoid arthritis, rheumatic fever, inflammatory bowel disease, bacterial infections, myocardial infarction, oral contraceptives, third trimester of pregnancy (acute phase reactant), inflammatory and neoplastic diseases Table 4-15 shows a comparison of erythrocyte sedimentation rate and C-reactive protein, and Table 4-16 shows conditions associated with elevated C-reactive protein levels.

C-REACTIVE PROTEIN, HIGH SENSITIVITY (hs-CRP, cardio-CRP)

This is a cardiac risk marker. It is increased in patients with silent atherosclerosis years before a cardiovascular event and is independent of cholesterol level and other lipoproteins. It can be used to help stratify cardiac risk.

INTERPRETATION OF RESULTS

Cardio-CRP result (mg/L)	Risk
0.6	Lowest risk
0.7-1.1	Low risk
1.2-1.9	Moderate risk
2.0-3.8	High risk
3.9-4.9	Highest risk
≥5.0	Results may be confounded by acute inflammatory disease. If clinically indicated, a repeat test should be performed in 2 or more weeks.

CREATINE KINASE (CK, CPK)

Fig. E4-13 describes a diagnostic approach to creatine kinase elevation.

Normal range: 0-130 U/L (0-2.16 μkat/L [CF: 0.01667; SMI: 0.01 μkat/L])

Elevated in: Myocardial infarction, myocarditis, rhabdomyolysis, myositis, crush injury/trauma, polymyositis, dermatomyositis, vigorous exercise, muscular dystrophy, myxedema, seizures, malignant hyperthermia syndrome, IM injections, cerebrovascular accident, pulmonary embolism and infarction, acute dissection of aorta

Decreased in: Steroids, decreased muscle mass, connective tissue disorders, alcoholic liver disease, metastatic neoplasms

CREATINE KINASE ISOENZYMES

CK-BB

Elevated In: Cerebrovascular accident, subarachnoid hemorrhage, neoplasms (prostate, gastrointestinal tract, brain, ovary, breast, lung), severe shock, bowel infarction, hypothermia, meningitis

CK-MB

Elevated In: Myocardial infarction (MI), myocarditis, pericarditis, muscular dystrophy, cardiac defibrillation, cardiac surgery, extensive rhabdomyolysis, strenuous exercise (marathon runners), mixed connective tissue disease, cardiomyopathy, hypothermia

NOTE: CK-MB exists in the blood in two subforms. MB_2 is released from cardiac cells and converted in the blood to MB_1. Rapid assay of CK-MB subforms can detect MI (CK-MB_2 ≥1.0 U/L, with a ratio of CK-MB_2/CK-MB_1 ≥1.5) within 6 hours of onset of symptoms.

Fig. 4-14 illustrates the time course of CK, AST, troponins, and LDH activity after acute MI.

CK-MM

Elevated In: Crush injury, seizures, malignant hyperthermia syndrome, rhabdomyolysis, myositis, polymyositis, dermatomyositis, vigorous exercise, muscular dystrophy, IM injections, acute dissection of aorta

CREATININE (serum)

See Fig. 4-15.

TABLE 4-15 Comparison of Erythrocyte Sedimentation Rate and C-Reactive Protein

	Erythrocyte Sedimentation Rate	C-Reactive Protein
Advantages	• Much clinical information in the literature • May reflect overall health status	• Rapid response to inflammatory stimuli • Wide range of clinically relevant values are detectable • Unaffected by age and gender • Reflects value of a single acute phase protein • Can be measured on stored sera • Quantitation is precise and reproducible
Disadvantages	• Affected by age and gender • Affected by red blood cell morphology • Affected by anemia and polycythemia • Reflects levels of many plasma proteins, not all of which are acute phase proteins • Responds slowly to inflammatory stimuli • Requires fresh sample • May be affected by drugs	• None

From Firestein GS, Budd RC, Gabriel SE, et al: *Kelley's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.

TABLE 4-16 Conditions Associated with Elevated C-Reactive Protein Levels

Normal or Minor Elevation (<1 mg/dL)	Moderate Elevation (1-10 mg/dL)	Marked Elevation (>10 mg/dL)
• Vigorous exercise • Common cold • Pregnancy • Gingivitis • Seizures • Depression • Insulin resistance and diabetes • Several genetic polymorphisms • Obesity	• Myocardial infarction • Malignancies • Pancreatitis • Mucosal infection (bronchitis, cystitis) • Most connective tissue diseases • Rheumatoid arthritis	• Acute bacterial infection (80%-85%) • Major trauma • Systemic vasculitis

From Firestein GS, Budd RC, Gabriel SE, et al: *Kelley's textbook of rheumatology*, ed 9, Philadelphia, 2013, Saunders.

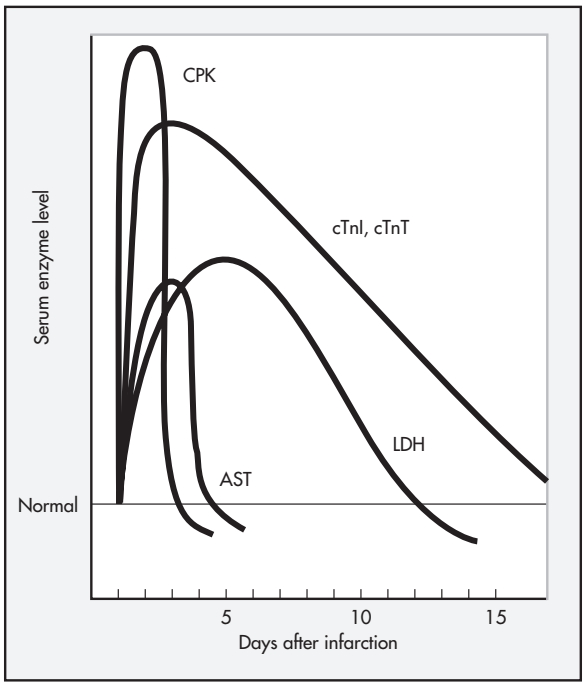


FIGURE 4-14 Evaluation of creatine kinase elevation. *AST,* Aspartate aminotransferase; *CPK,* creatine kinase; *cTnI,* cardiac troponin I; *cTnT,* cardiac troponin T; *LDH,* lactate dehydrogenase. (From Greene HL, Johnson WP, Lemcke D [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

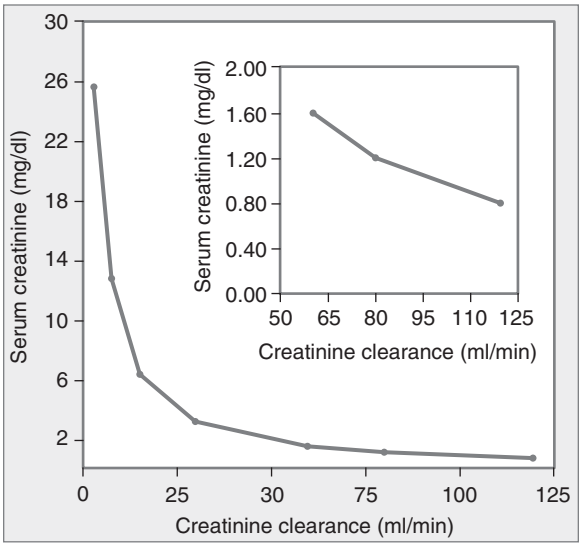


FIGURE 4-15 Relationship between creatinine clearance and serum creatinine. In steady state, serum creatinine should increase twofold for each 50% reduction in creatinine clearance. *Inset* represents enlarged view of changes in serum creatinine as creatinine clearance decreases from 120 to 60 ml/min. If serum creatinine is 0.8 mg/dl when creatinine clearance is 120 ml/min, creatinine clearance can decrease by 33% such that increased serum creatinine is still within normal range. (From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.)

Normal range: 0.6-1.2 mg/dl (50-110 μmol/L [CF: 88.4; SMI: 10 μmol/L])
Elevated in: Renal insufficiency (acute and chronic), decreased renal perfusion (hypotension, dehydration, congestive heart failure), urinary tract infection, rhabdomyolysis, ketonemia

Drugs (antibiotics [aminoglycosides, cephalosporins], hydantoin, diuretics, methyldopa)
Falsely elevated in: Diabetic ketoacidosis, administration of some cephalosporins (e.g., cefoxitin, cephalothin)
Decreased in: Decreased muscle mass (including amputees and older persons), pregnancy, prolonged debilitation

CREATININE CLEARANCE

Normal range: 75-124 ml/min (1.24-2.08 ml/sec [CF: 0.01667; SMI: 0.02 ml/sec])

Box 4-1 describes a formula for calculation of creatinine clearance.

The Cockcroft-Gault formula to calculate creatinine clearance is described in Box 4-2
Elevated in: Pregnancy, exercise
Decreased in: Renal insufficiency, drugs (cimetidine, procainamide, antibiotics, quinidine)

BOX 4-1 Calculation of the Creatinine Clearance

$C_{cr} = U_{cr} \times V/P_{cr}$
where C_{cr}= clearance of creatinine (ml/min)
U_{cr} = urine creatinine (mg/dl)
V = volume of urine (ml/min) (for 24-hr volume: divide by 1440)
P_{cr} = plasma creatinine (mg/dl)
Normal range: 95 to 105 ml/min/1.75m^2

BOX 4-2 Cockcroft-Gault Formula to Calculate Creatinine Clearance (C_{cr})

$$C_{cr} = \frac{(140 - \text{age in year}) \times (\text{lean body weight in kg})}{S_{cr}\text{in mg/dl} - 72}$$

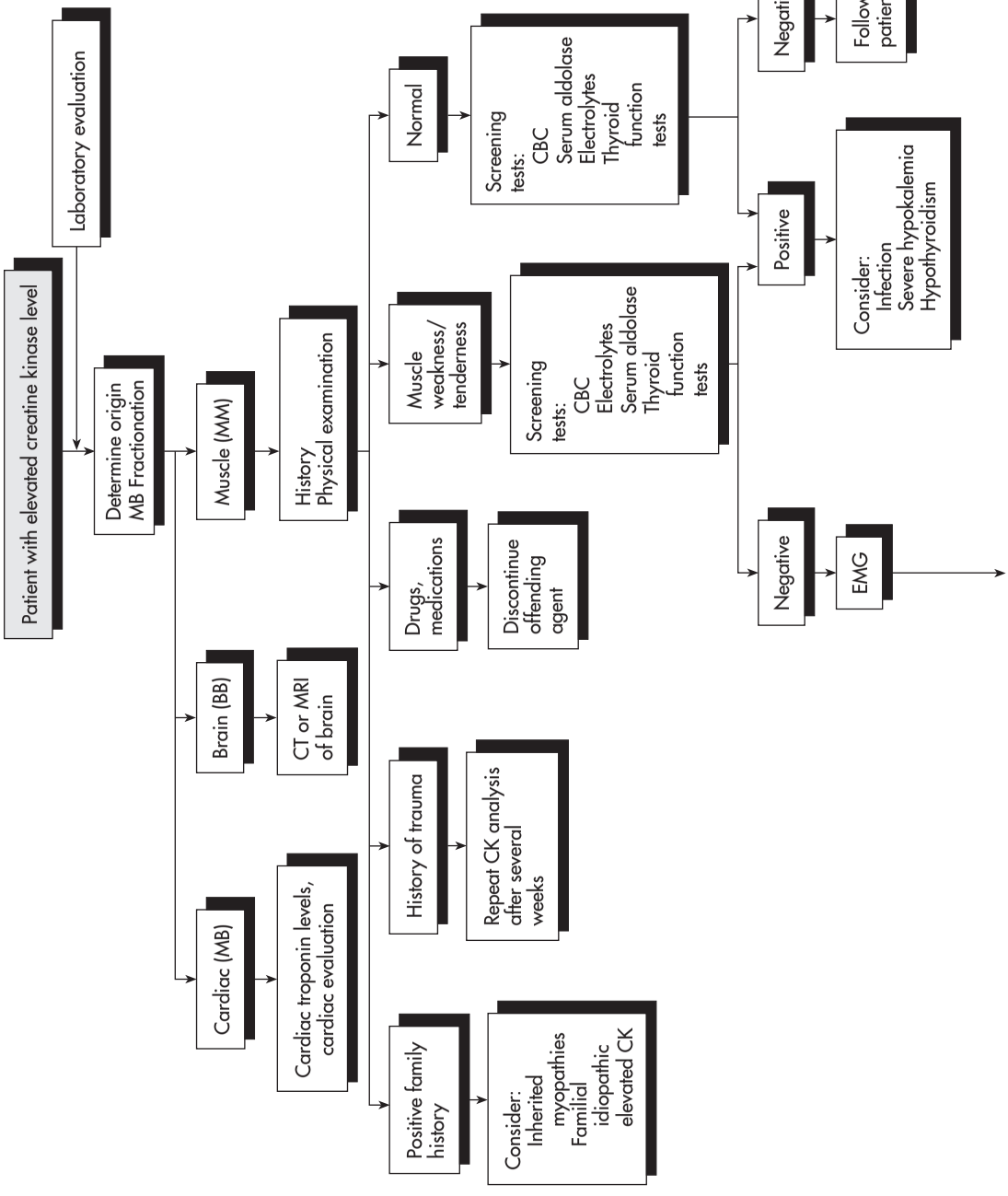


FIGURE E4-13 Evaluation of creatine kinase elevation. *CBC,* Complete blood count; *CK,* creatine kinase; *CT,* computed tomography; *EMG,* electromyography; *MRI,* magnetic resonance imaging. (Modified from Greene HL, Johnson WP, Lemcke D [eds]: *Decision making in medicine,* ed 2, St Louis, 1998, Mosby.)

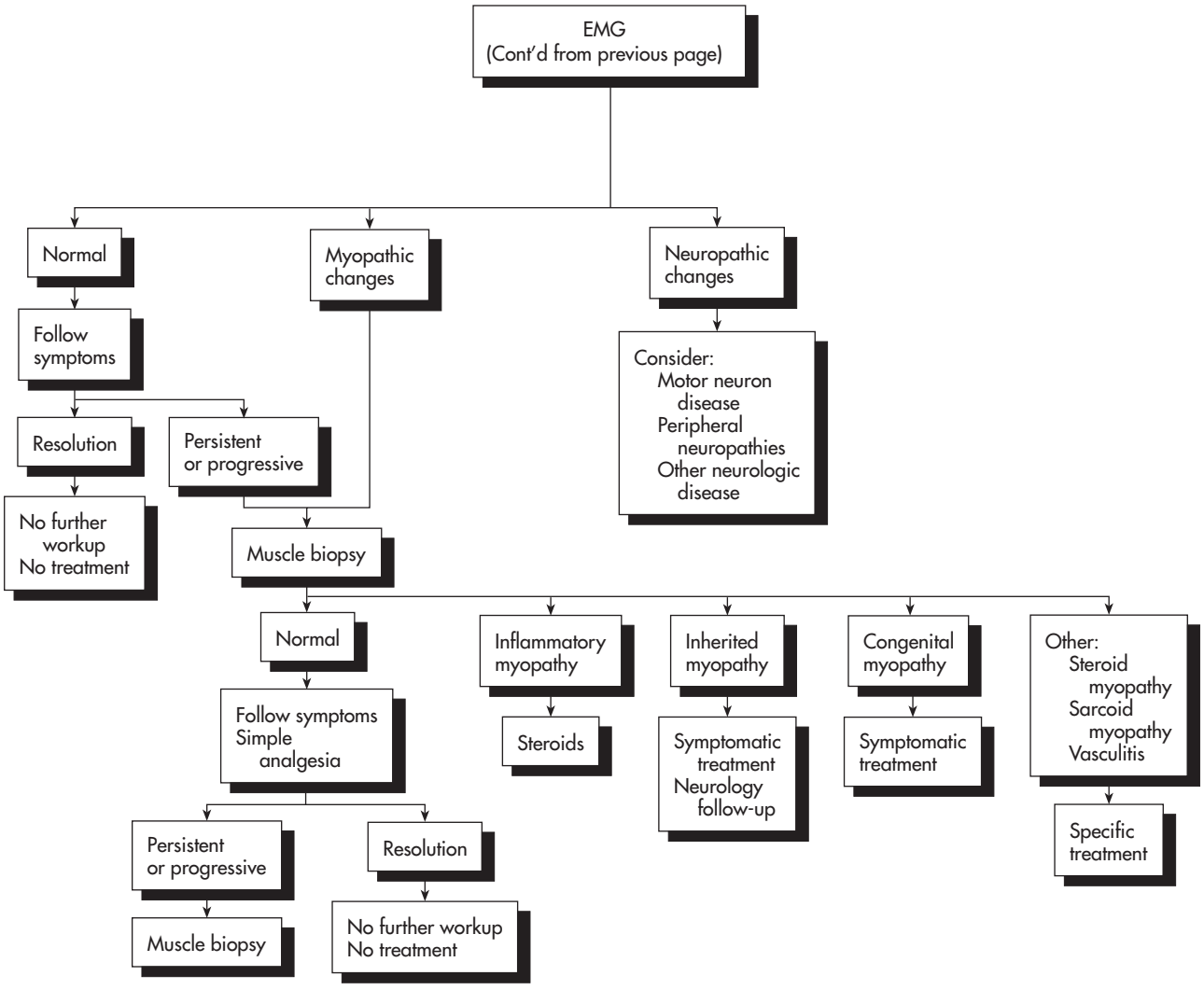


FIGURE E4-13 (Continued)

CREATININE, URINE
See URINE CREATININE

CRYOGLOBULINS (serum)
Normal range: Not detectable
Present in: Collagen vascular diseases, chronic lymphocytic leukemia, hemolytic anemias, multiple myeloma, Waldenström's macroglobulinemia, chronic active hepatitis, Hodgkin's disease

CRYPTOSPORIDIUM ANTIGEN BY EIA (stool)
Normal range: Not detected
Present in: Cryptosporidiosis

CSF
See CEREBROSPINAL FLUID

CYSTATIN C
Normal: Cystatin C is a cysteine protease inhibitor that is produced at a constant rate by all nucleated cells. It is freely filtered by the glomerulus and reabsorbed (but not secreted) by the renal tubules with no extrarenal excretion. Its concentration is not affected by diet, muscle mass, or acute inflammation. Normal range when measured by particle-enhanced nephelometric immunoassay (PENIA) is <0.28 mg/L.
Elevated in: Renal disorders. Good predictor of the severity of acute tubular necrosis. Cystatin C increases more rapidly than creatinine in the early stages of GFR impairment. The cystatin C concentration is an independent risk factor for heart failure in older adults and appears to provide a better measure of risk assessment than the serum creatinine concentration.

CYSTIC FIBROSIS PCR
Test description: Test can be performed on whole blood or tissue. Common mutations in the cystic fibrosis transmembrane regulator (CFTR) gene can be used to detect 75%-80% of mutant alleles.

CYTOMEGALOVIRUS BY PCR
Test description: Test can be performed on whole blood, plasma, or tissue. Qualitative PCR is highly sensitive but may not be able to differentiate between latent and active infection.

D-DIMER
Normal range: <0.5 mcg/ml
Elevated in: DVT, pulmonary embolism, high levels of rheumatoid factor, activation of coagulation and fibrolytic system from any cause

D-dimer assay by ELISA assists in the diagnosis of DVT and pulmonary embolism. This test has significant limitations because it can be elevated whenever the coagulation and fibrinolytic systems are activated and can also be falsely elevated with high rheumatoid factor levels.

DEHYDROEPIANDROSTERONE SULFATE
Normal:

Males:

Ages 19-30:	125-619 mcg/dl
31-50:	59-452 mcg/dl
51-60:	20-413 mcg/dl
61-83:	10-285 mcg/dl

Females:

Ages 19-30:	29-781 mcg/dl
31-50:	12-379 mcg/dl
Postmenopausal:	30-260 mcg/dl

Elevated in: Hirsutism, congenital adrenal hyperplasia, adrenal carcinomas, adrenal adenomas, polycystic ovary syndrome, ectopic ACTH-producing tumors, Cushing's disease, spironolactone

DEHYDROTESTOSTERONE (serum, urine)
Normal: Serum: Males: 30-85 ng/dl; females: 4-22 ng/dl
Urine, 24 h: Males: 20-50 mcg/day; females: <8 mcg/day
Elevated in: Hirsutism
Decreased in: 5-α-reductase deficiency, hypogonadism

DEOXYCORTICOSTERONE (11-deoxycorticosterone, DOC) (serum)
Normal: 2-19 ng/dl. Normal secretion depends on ACTH and is suppressible by dexamethasone.
Elevated in: Adrenogenital syndromes due to 17- and 11-hydroxylase deficiencies, pregnancy
Decreased in: Preeclampsia

DEXAMETHASONE SUPPRESSION TEST, OVERNIGHT
Normal: Test is performed by giving 1 mg dexamethasone orally at 11 PM and measuring serum cortisol at 8 AM the following morning. Normal response is cortisol suppression to <3 mcg/dl; If dose of 4 mg dexamethasone is given, cortisol suppression will be to <50% of baseline.
Interpretation: Cushing's syndrome (<10 mcg/dl), endogenous depression (half of patients suppress test values <5 mcg/dl). Most patients with pituitary Cushing's disease demonstrate suppression, whereas patients with adrenal adenoma, carcinoma, and ectopic ACTH-producing tumors do not.

DIGOXIN
Normal therapeutic range: 0.5-2 ng/ml
Elevated in: Impaired renal function, excessive dosing, concomitant use of quinidine, amiodarone, verapamil, fluoxetine, nifedipine. Toxicity may occur at a lower blood concentration in the presence of hypokalemia, hypomagnesemia, and hypercalcemia.

DILANTIN
See PHENYTOIN

DISACCHARIDE ABSORPTION TESTS
Normal: Test is used to diagnose malabsorption due to disaccharide deficiency. It is performed by giving disaccharide orally 1 g/kg body weight to a total of 25 g. Blood is drawn at 0, 30, 60, 90, and 120 min. Normal response is a change in glucose from fasting value >30 mg/dl, inconclusive when increase is 20-30 mg/dl, abnormal when increase is >20 mg/dl. Test can also be performed by measuring air at 0, 30, 60, 90, and 120 min. Normal is H_2 >20 ppm above baseline level before a colonic response.
Decreased in: Disaccharide deficiency (lactose, fructose, sorbitol), celiac disease, sprue, acute gastroenetetitis

DOC
See DEOXYCORTICOSTERONE

DONATH-LANDSTEINER (D-L) TEST FOR PAROXYSMAL COLD HEMOGLOBINURIA
Normal: No hemolysis
Interpretation: Hemolysis indicates presence of bithermic cold hemolysins or Donath-Landsteiner antibodies (D-L Ab)

DOPAMINE
Normal range: 175 pg/ml
Elevated in: Pheochromocytomas, neuroblastomas, stress, vigorous exercise, certain foods (bananas, chocolate, coffee, tea, vanilla)

D-XYLOSE ABSORPTION
Normal range: 21%-31% excreted in 5 hours
Decreased in: Malabsorption syndrome

D-XYLOSE ABSORPTION TEST
Normal range:
URINE: ≥4 g/5 hours (5-hour urine collection in adults >12 years [25-g dose])

SERUM: ≥25 mg/dl (adult, 1 hour, 25-g dose, normal renal function)
Normal results: In patients with malabsorption, normal results suggest pancreatic disease as an etiology of the malabsorption.
Abnormal results: Celiac disease, Crohn's disease, tropical sprue, surgical bowel resection, AIDS. False-positives can occur with decreased renal function, dehydration/hypovolemia, surgical blind loops, decreased gastric emptying, vomiting.

ELECTROPHORESIS, HEMOGLOBIN

See HEMOGLOBIN ELECTROPHORESIS

ELECTROPHORESIS, PROTEIN

See PROTEIN ELECTROPHORESIS

ENA COMPLEX

See EXTRACTABLE NUCLEAR ANTIGEN

ENDOMYSIAL ANTIBODIES

Normal: Not detected
Present in: Celiac disease, dermatitis herpetiformis

EOSINOPHIL COUNT

Normal range: 1%-4% eosinophils (0-440/mm^3)
Elevated in:
HELMINTHIC PARASITES
Ascaris lumbricoides (invasive larval stage)
Hookworms (invasive larval stage)
Strongyloides stercoralis (initial infection and autoinfection)
Trichinosis
Filariasis
Echinococcus granulosus and *E. multilocularis*
Toxocara species
Animal hookworms
Angiostrongylus cantonensis and *A. costaricensis*
Schistosomiasis
Liver flukes
Fasciolopsis buski
Anisakiasis
Capillaria philippinensis
Paragonimus westermani
"Tropical eosinophilia" (unidentified microfilariae)
OTHER INFECTIONS/INFESTATIONS
Pulmonary aspergillosis
Severe scabies
ALLERGIES
Asthma
Hay fever
Drug reactions
Atopic dermatitis
AUTOIMMUNE AND RELATED DISORDERS
Polyarteritis nodosa
Necrotizing vasculitis
Eosinophilic fasciitis
Pemphigus
NEOPLASTIC DISEASES
Hodgkin's disease
Mycosis fungoides
Note: Table 4-17 describes an approach to investigation of eosinophilia in a returning traveler
Chronic myelocytic leukemia
Eosinophilic leukemia
Polycythemia vera
Mucin-secreting adenocarcinomas
IMMUNODEFICIENCY STATES
Hyperimmunoglobulin E with recurrent infection
Wiskott-Aldrich syndrome
OTHER
Addison's disease
Inflammatory bowel disease

TABLE 4-17 Eosinophilia Investigation in Returning Travelers

History	Allergies Drugs and vitamins (L-tryptophan) Regions, localities, and duration of exposure
Physical examination	Skin, subcutaneous tissues Liver/spleen Signs of other systemic disease
Initial investigations	Full blood count and differential white blood cell count Stool examination for ova and parasites (×3) Urine analysis Examination of midday urine for ova and parasites (×3) (in those who have traveled to Africa or the Middle East)
Further investigations as suggested by travel and exposure from history	*Strongyloides* culture and serologic testing Duodenal aspirate (strongyloidiasis, hookworm) Serologic testing (schistosomiasis, filariasis) Day/night blood films (filariasis)
Further studies if suggested by history and physical examination	Skin snips (onchocerciasis) Chest x-ray examination (hydatid cyst, tropical pulmonary eosinophilia, paragonimiasis) Soft tissue x-ray examination (cysticercosis) Sputum examination for ova and parasites (paragonimiasis) Abdominal ultrasound examination (hydatid cyst) Cystoscopy with or without biopsy (schistosomiasis) Rectal snips (schistosomiasis)

From Hoffman R: *Hematology: basic principles and practice,* ed 6, Philadelphia, Saunders, 2013.

Dermatitis herpetiformis
Toxic/chemical syndrome
Eosinophilic myalgia syndrome, tryptophan, toxic oil syndrome
Hypereosinophilic syndrome (unknown etiology)

EPINEPHRINE, PLASMA

Normal range: 0-90 pg/ml
Elevated in: Pheochromocytomas, neuroblastomas, stress, vigorous exercise, certain foods (bananas, chocolate, coffee, tea, vanilla), hypoglycemia

EPSTEIN-BARR VIRUS SEROLOGY (Box 4-3)

Normal range: IgG anti-VCA <1:10 or negative

BOX 4-3 Epstein-Barr Virus–Associated Malignancies

Malignancy	Epstein-Barr Virus Frequency
Hodgkin disease	≈40%
Non-Hodgkin lymphomas	
Burkitt lymphoma	20%-95%
Diffuse large B-cell lymphoma and CD30$^+$ Ki-1$^+$ anaplastic large cell lymphoma	10%-35%
Lymphomatoid granulomatosis	80%-95%
T cell–rich B-cell lymphoma	20%
Angioimmunoblastic lymphoma	>80%
T-cell, NK cell, and T/NK-cell lymphomas	30%-90%
Nasopharyngeal carcinoma	>95%
Gastric adenocarcinoma	5%-10%
Pyothorax-associated lymphoma	>95%
Leiomyosarcoma in immunocompromised patients	>95%

From Hoffman R: *Hematology: basic principles and practice,* ed 6, Philadelphia, Saunders, 2013.

TABLE 4-18 Antibody Tests in Epstein-Barr Viral Infection

	Appearance	Peak	Disappears
Heterophil Ab	3-5 days after onset of Sx (range, 0-21 days)	During second wk after onset of Sx (1-4 wk)	2-3 mo after onset of Sx (still found at 1 yr in 20% of cases)
VCA-IgM	Beginning of Sx (1 wk before to 1 wk after Sx begin)	During first wk after onset of Sx (0-21 days)	2-3 mo after onset of Sx (1-6 mo)
VCA-IgG	3 days after onset of Sx (0-2 wk)	During second wk after onset of Sx (1-3 wk)	Decline to lower level, then persists for life
EBNA-IgG	3 wk after onset of Sx (1-4 wk)	8 mo after appearance (3-12 mo)	Lifelong
EA-D	5 days after onset of Sx (during first 1-2 wk after onset of Sx)	14-21 days after onset of Sx (1-4 wk)	9 wk after appearance (2-6 mo)
EBNA-IgM	Same as VCA-IgM	Same as VCA-IgM	Same as VCA-IgM

Ab, Antibody; *EA,* early antigen; *EBNA,* Epstein-Barr virus nuclear antigen; *Sx,* symptoms; *VCA,* viral capsid antigen.
From Ravel R: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.

Abnormal:
IgG anti-VCA >1:10 or positive indicates either current or previous infection
IgM anti-VCA >1:10 or positive indicates current or recent infection
Anti-EBNA ≥ 1.5 or positive indicates previous infection
Table 4-18 and Fig. 4-16 describe test interpretation.

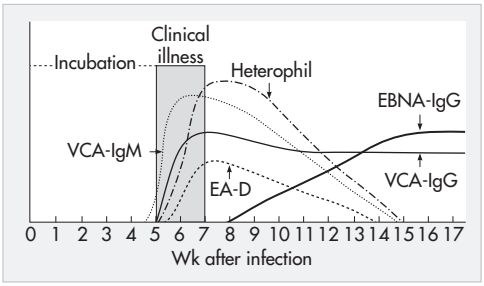


FIGURE 4-16 Tests in Epstein-Barr viral infection. See Table 4-18 for abbreviations. (From Ravel R [ed]: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.)

ERYTHROCYTE SEDIMENTATION RATE (ESR, sed rate, sedimentation rate)

Normal range:
Male: 0-15 mm/hr
Female: 0-20 mm/hr
Elevated in: Collagen vascular diseases, infections, myocardial infarction, neoplasms, inflammatory states (acute phase reactant), hyperthyroidism, hypothyroidism, rouleaux formation
Decreased in: Sickle cell disease, polycythemia, corticosteroids, spherocytosis, anisocytosis, hypofibrinogenemia, increased serum viscosity

ERYTHROPOIETIN (EP)

Normal: 3.7-16.0 IU/L by radioimmunoassay
Erythropoietin is a glycoprotein secreted by the kidneys that stimulates RBC production by acting on erythroid-committed stem cells.
Increased in:
Extremely high: Generally seen in patients with severe anemia (Hct, <25; Hb<7) such as in cases of aplastic anemia, severe hemolytic anemia, hematologic cancers
Very high: Patients with mild to moderate anemia (Hct, 25-35; Hb, 7-10)
High: Patients with mild anemia (e.g., AIDS, myelodysplasia)
Erythropoietin can be inappropriately elevated in patients with malignant neoplasms, renal cysts, postrenal transplant, meningioma, hemangioblastoma, and leiomyoma.
Decreased in: Renal failure, polycythemia vera, autonomic neuropathy

ESTRADIOL (serum)

Normal range:
Female, premenopausal: 30-400 pg/ml, depending on phase of menstrual cycle
Female, postmenopausal: 0-30 pg/ml
Male, adult: 10-50 pg/ml
Decreased in: Ovarian failure
Elevated in: Tumors of ovary, testis, adrenal, or nonendocrine sites (rare)

ESTROGEN

Normal range (serum).

Males:	20-80 pg/ml
Females:	
Follicular:	60-200 pg/ml
Luteal:	160-400 pg/ml
Postmenopausal:	<130 pg/ml

Normal Range (urine).

Males:	4-23 μg/g creatinine
Females:	
Follicular:	7-65 μg/g creatinine
Midcycle:	32-104 μg/g creatinine
Luteal:	8-135 μg/g creatinine

Elevated in: Hyperplasia of adrenal cortex, ovarian tumors producing estrogen, granulosa and thecal cell tumors, testicular tumors
Decreased in: Menopause, hypopituitarism, primary ovarian malfunction, anorexia nervosa, hypofunction of adrenal cortex, ovarian agenesis, psychogenic stress, gonadotropin-releasing hormone deficiency

ETHANOL (blood)

Normal range: Negative (values <10 mg/dl are considered negative)
Ethanol is metabolized at 10-25 mg/dl/hr. Levels ≥80 mg/dl are considered evidence of impairment for driving. Fatal blood concentration is considered to be >400 mg/dl.

EXTRACTABLE NUCLEAR ANTIGEN (ENA complex, anti-RNP antibody, anti-SM, anti-Smith)

Normal: Negative
Present in: Systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, mixed connective tissue disease

FACTOR V LEIDEN

Test description: PCR test performed on whole blood or tissue. This single mutation, found in 2%-8% of the general Caucasian population, is the single most common cause of hereditary thrombophilia.

FASTING BLOOD SUGAR

See GLUCOSE, FASTING

FBS
See GLUCOSE, FASTING

FDP
See FIBRIN DEGRADATION PRODUCT

FECAL FAT, QUANTITATIVE (72-hr collection)
Normal range: 2-6 g/24 hr (7-21 mmol/dl [CF: 3.515; SMI: 1 mmol/dl])
Elevated in: Malabsorption syndrome

FECAL GLOBIN IMMUNOCHEMICAL TEST
Normal: Negative. This test is performed by immunochromatography on a cellulose strip that has been impregnated with various antibodies. The test uses a small amount of toilet water as the specimen and is placed onto absorbent pads of card similar to traditional OB card. There is no direct handling of stool. This test is specific for the globin portion of the hemoglobin molecule, which confers lower GI bleeding specificity. It specifically detects blood from the lower GI tract; guaic tests are not lower GI specific. It is more sensitive than typical Hemoccult test (detection limit 50 mcg Hb/g feces versus >500 mcg Hb/g feces for Hemoccult). It has no dietary restrictions and gives no false-positives due to plant peroxidases and red meats. It has no medication restrictions. Iron supplements and NSAIDs do not cause false-positives. Vitamin C does not cause false-negatives.
Positive in: Lower GI bleeding

FERRITIN (serum)
Normal range: 18-300 ng/ml (18-300 μg/L [CF: 1; SMI: 10 μg/L])
Elevated in: Hyperthyroidism, inflammatory states, liver disease (ferritin elevated from necrotic hepatocytes), neoplasms (neuroblastomas, lymphomas, leukemia, breast carcinoma), iron replacement therapy, hemochromatosis, hemosiderosis
Decreased in: Iron deficiency anemia

α-1 FETOPROTEIN
Normal range: 0-20 ng/ml (0-20 μg/L [CF: 1; SMI: 1 μg/L])
Elevated in: Hepatocellular carcinoma (usually values >1000 ng/ml), germinal neoplasms (testis, ovary, mediastinum, retroperitoneum), liver disease (alcoholic cirrhosis, acute hepatitis, chronic active hepatitis), fetal anencephaly, spina bifida, basal cell carcinoma, breast carcinoma, pancreatic carcinoma, gastric carcinoma, retinoblastoma, esophageal atresia

FIBRIN DEGRADATION PRODUCT (FDP)
Normal range: <10 μg/ml
Elevated in: Disseminated intravascular coagulation, primary fibrinolysis, pulmonary embolism, severe liver disease
NOTE: The presence of rheumatoid factor may cause falsely elevated FDP.

FIBRINOGEN
Normal range: 200-400 mg/dl (2-4 g/L [CF: 0.01; SMI: 0.1 g/L])
Elevated in: Tissue inflammation or damage (acute phase protein reactant), oral contraceptives, pregnancy, acute infection, myocardial infarction
Decreased in: Disseminated intravascular coagulation, hereditary afibrinogenemia, liver disease, primary or secondary fibrinolysis, cachexia

FOLATE (folic acid)
Normal range:
Plasma: 2-10 ng/ml (4-22 nmol/L [CF: 2.266; SMI: 2 nmol/L])
Red blood cells: 140-960 ng/ml (550-2200 nmol/L [CF: 2.266; SMI: 10 nmol/L])
Decreased in: Folic acid deficiency (inadequate intake, malabsorption), alcoholism, drugs (methotrexate, trimethoprim, phenytoin, oral contraceptives, Azulfidine), vitamin B_{12} deficiency (defective red cell folate absorption), hemolytic anemia
Elevated in: Folic acid therapy (see Box 4-4)

BOX 4-4 Etiopathophysiologic Classification of Folate Deficiency

I. Nutritional causes
  A. Decreased dietary intake—poverty and famine, institutionalized individuals (psychiatric/nursing homes)/chronic debilitating disease, prolonged feeding of infants with goat's milk, special slimming diets or food fads (folate-rich foods not consumed), cultural/ethnic cooking techniques (food folate destroyed)
  B. Decreased diet and increased requirements
    1. Physiologic—pregnancy and lactation, prematurity, hyperemesis gravidarum, infancy
    2. Pathologic
      a. Intrinsic hematologic diseases involving hemolysis with compensatory erythropoiesis, abnormal hematopoiesis, or bone marrow infiltration with malignant disease
      b. Dermatologic disease—psoriasis
II. Folate malabsorption
  With normal intestinal mucosa
    1. Drugs—sulfasalazine, pyrimethamine, proton pump inhibitors (via inhibition of proton-coupled folate transporter [PCFT])
    1. Hereditary folate malabsorption (mutations in PCFTs) (rare)
  With mucosal abnormalities—tropical and nontropical sprue, regional enteritis
III. Defective cerebral spinal fluid folate transport—cerebral folate deficiency (mutation or autoantibodies to folate receptors) (rare)
IV. Inadequate cellular utilization
    3. Folate antagonists (methotrexate)
    4. Hereditary enzyme deficiencies involving folate
V. Drugs (multiple effects on folate metabolism)—alcohol, sulfasalazine, triamterene, pyrimethamine, trimethoprim-sulfamethoxazole, diphenylhydantoin, barbiturates

From Hoffman R: *Hematology: basic principles and practice,* ed 6, Philadelphia, Saunders, 2013.

FOLLICLE-STIMULATING HORMONE (FSH)
Normal range: 5-20 mIU/ml
Elevated in: Menopause, primary gonadal failure, alcoholism, castration, Klinefelter's syndrome, gonadotropin-secreting pituitary hormones
Decreased in: Pregnancy, polycystic ovary disease, anorexia nervosa, anterior pituitary hypofunction

FREE T_4
See T_4, FREE

FREE THYROXINE INDEX
Normal range: 1.1-4.3
INCREASED THYROXINE OR FREE THYROXINE VALUES
Laboratory error
Primary hyperthyroidism (T_4/T_3 type)
Severe thyroxine-binding globulin elevation
Excess therapy of hypothyroidism
Excessive dose of levothyroxine
Active thyroiditis (subacute, painless, early active Hashimoto's disease)
Familial dysalbuminemic hyperthyroxinemia (some FT_4 kits, especially analog types)
Peripheral resistance to T_4 syndrome
Amiodarone or propranolol
Postpartum transient toxicosis
Factitious hyperthyroidism
Jod-Basedow (iodine-induced) hyperthyroidism
Severe nonthyroid illness
Acute psychosis (especially paranoid schizophrenia)
T_4 sample drawn 2-4 hr after levothyroxine dose

Struma ovarii
Pituitary thyroid-stimulating hormone–secreting tumor
Certain x-ray contrast media (Telepaque and Oragrafin)
Acute porphyria
Heparin effect (some T_4 and FT_4 kits)
Amphetamine, heroin, methadone, and phencyclidine abuse
Perphenazine or 5-fluorouracil
Antithyroid or anti-IgG heterophil (HAMA) autoantibodies
"T_4" hyperthyroidism
Hyperemesis gravidarum; about 50% of patients
High altitudes

DECREASED THYROXINE OR FREE THYROXINE VALUES

Laboratory error
Primary hypothyroidism
Severe nonthyroid illness
Lithium therapy
Severe thyroxine-binding globulin decrease (congenital, disease, or drug-induced) or severe albumin decrease
Dilantin, Depakene, or high-dose salicylate drugs
Pituitary insufficiency
Large doses of inorganic iodide (e.g., saturated solution of potassium iodide)
Moderate or severe iodine deficiency
Cushing's syndrome
High-dose glucocorticoid drugs
Pregnancy, third trimester (low normal or small decrease)
Addison's disease; some patients (30%)
Heparin effect (a few FT_4 kits)
Desipramine or amiodarone drugs
Acute psychiatric illness

FTA-ABS (serum)

Normal: Nonreactive
Reactive in: Syphilis, other treponemal diseases (yaws, pinta, bejel), SLE, pregnancy

FUROSEMIDE STIMULATION TEST

Normal: Test is performed by giving 60 mg furosemide orally after overnight fast. Patient should be on a normal diet without medications the week before the test. Normal results: renin 1-6 ng angiotensin L/ml/hr.
Elevated in: Renovascular hypertension, Barrter's syndrome, high-renin essential hypertension, pheochromocytoma
No response in: Primary aldosteronism, low-renin essential hypertension, hyporeninemic hypoaldosteronism

GAMMA-GLUTAMYL TRANSFERASE (GGT)

See γ-GLUTAMYL TRANSFERASE

GASTRIN (serum)

Normal range: 0-180 pg/ml (0-180 ng/L [CF: 1; SMI: 10 ng/L])
Elevated in: Zollinger-Ellison syndrome (gastrinoma), pernicious anemia, hyperparathyroidism, retained gastric antrum, chronic renal failure, gastric ulcer, chronic atrophic gastritis, pyloric obstruction, malignant neoplasms of the stomach, H_2-blockers, omeprazole, calcium therapy, ulcerative colitis, rheumatoid arthritis

GASTRIN STIMULATION TEST

Normal: Gastrin stimulation test after calcium infusion is performed by giving a calcium infusion (15 mg/kg in 500 ml normal saline over 4 hours). Serum is drawn in fasting state before infusion and at 1, 2, 3, and 4 hr. Normal response is little or no increase over baseline gastrin level.
Elevated in: Gastrinoma (gastrin >400 pg/ml), duodenal ulcer (gastrin level increase <400 ng/L)
Decreased in: Pernicious anemia, atrophic gastritis

GLIADIN ANTIBODIES, IgA AND IgG

Normal: <25 U, equivocal 20-25 U, positive >25 U. Test is useful to monitor compliance with gluten-free diet in patients with celiac disease.
Elevated in: Celiac disease with dietary noncompliance

GLOMERULAR BASEMENT MEMBRANE (gBm) ANTIBODY

Normal: Negative
Present in: Goodpasture's syndrome

GLOMERULAR FILTRATION RATE

See Box 4-5.

Normal:

Ages 20-29	116 ml/min/1.73 m^2
Ages 30-39	107 ml/min/1.73 m^2
Ages 40-49	99 ml/min/1.73 m^2
Ages 50-59	93 ml/min/1.73 m^2
Ages 60-69	85 ml/min/1.73 m^2
Ages >75	75 ml/min/1.73 m^2

Decreased in. Renal insufficiency, decreased renal blood flow

BOX 4-5 Common Equations for Estimating Glomerular Filtration Rate or Creatinine Clearance

Cockcroft-Gault (C_{Cr} · BSA/1.73 m^2)
For men: $C_{Cr} = [(140 - age) \cdot weight\ (kg)]/S_{Cr} \cdot 72$
For women: $C_{Cr} = ([(140 - age) \cdot weight\ (kg)]/S_{Cr} \cdot 72) \cdot 0.85$

MDRD (1)
$GFR = 170 \cdot [S_{Cr}]^{-0.999} \cdot [age]^{-0.176} \cdot [0.762\ if\ patient\ is\ female] \cdot [1.18\ if\ patient\ is\ black] \cdot [BUN]^{-0170} \cdot [Alb]^{0.318}$

MDRD (2)
$GFR = 186 \cdot [S_{Cr}]^{-1.154} \cdot [age]^{-0.203} \cdot [0.742\ if\ patient\ is\ female] \cdot [1.212\ if\ patient\ is\ black]$

Jellife (1) (C_{Cr} · BSA/1.73 m^2)
For men: $(98 - [0.8 \cdot (age - 20)])/S_{Cr}$
For women: $(98 - [0.8 \cdot (age - 20)])S_{Cr} \cdot 0.90$

Jellife (2)
For men: $(100/S_{Cr}) - 12$
For women: $(80/S_{Cr}) - 7$

Mawer
For men: $weight \cdot [29.3 - (0.203 \cdot age)] \cdot [1 - (0.03 \cdot S_{Cr})]$
For women: $weight \cdot [25.3 - (0.175 \cdot age)] \cdot [1 - (0.03 \cdot S_{Cr})]$

Bjornsson
For men: $[27 - (0.173 \cdot age)] \cdot weight \cdot 0/S_{Cr}$
For women: $[25 - (0.175 \cdot age)] \cdot weight \cdot 0.07/S_{Cr}$

Gates
For men: $(89.4 \cdot S_{Cr}^{-1.2}) + (55 - age) \cdot (0.447 \cdot S_{Cr}^{-1.1})$
For women: $(89.4 \cdot S_{Cr}^{-1.2}) + (55 - age) \cdot (0.447 \cdot S_{Cr}^{-1.1})$

Salazar-Corcoran
For men: $[137 - age] \cdot [(0.285 \cdot weight) + (12.1 \cdot height^2)]/(51 \cdot S_{Cr})$
For women: $[146 - age] \cdot [(0.287 \cdot weight) + (9.74 \cdot height^2)]/(60 \cdot S_{Cr})$

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

GLUCAGON

Normal: 20-100 pg/ml
Elevated in: Glucagonoma (900-7800 pg/ml), chronic renal failure, diabetes mellitus, glucocorticoids, insulin, nifedipine, danazol, sympathomimetic amines
Decreased in: Hyperlipoproteinemia (types III, IV), beta-blockers, secretin

GLUCOSE, FASTING (FBS, fasting blood sugar)

Fig. E4-17 describes the approach to hypoglycemia. An algorithm for evaluation of hypoglycemia in children is described in Fig. E4-18.
Normal range: 60-99 mg/dl (3.8-6.0 mmol/L [CF: 0.05551; SMI: 0.1 mmol/L])
Elevated in: Diabetes mellitus, stress, infections, myocardial infarction, cerebrovascular accident, Cushing's syndrome, acromegaly, acute

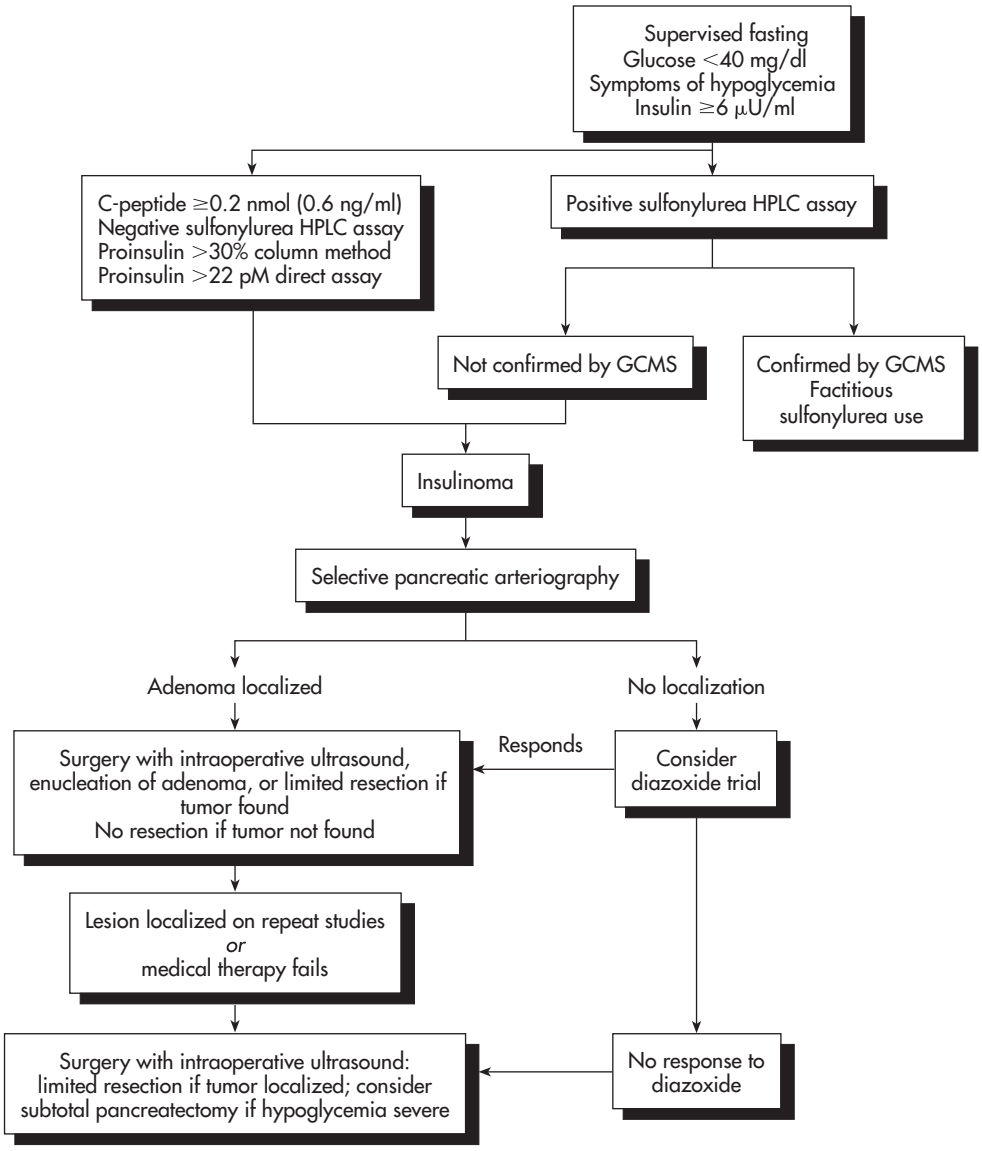


FIGURE E4-17 Diagnostic evaluation of patients with documented hypoglycemia and elevated insulin. *GCMS,* Gas chromatography mass spectrometry; *HPLC,* high-pressure liquid chromatography. (Modified from Moore WT, Eastman RC: *Diagnostic endocrinology,* ed 2, St Louis, 1996, Mosby.)

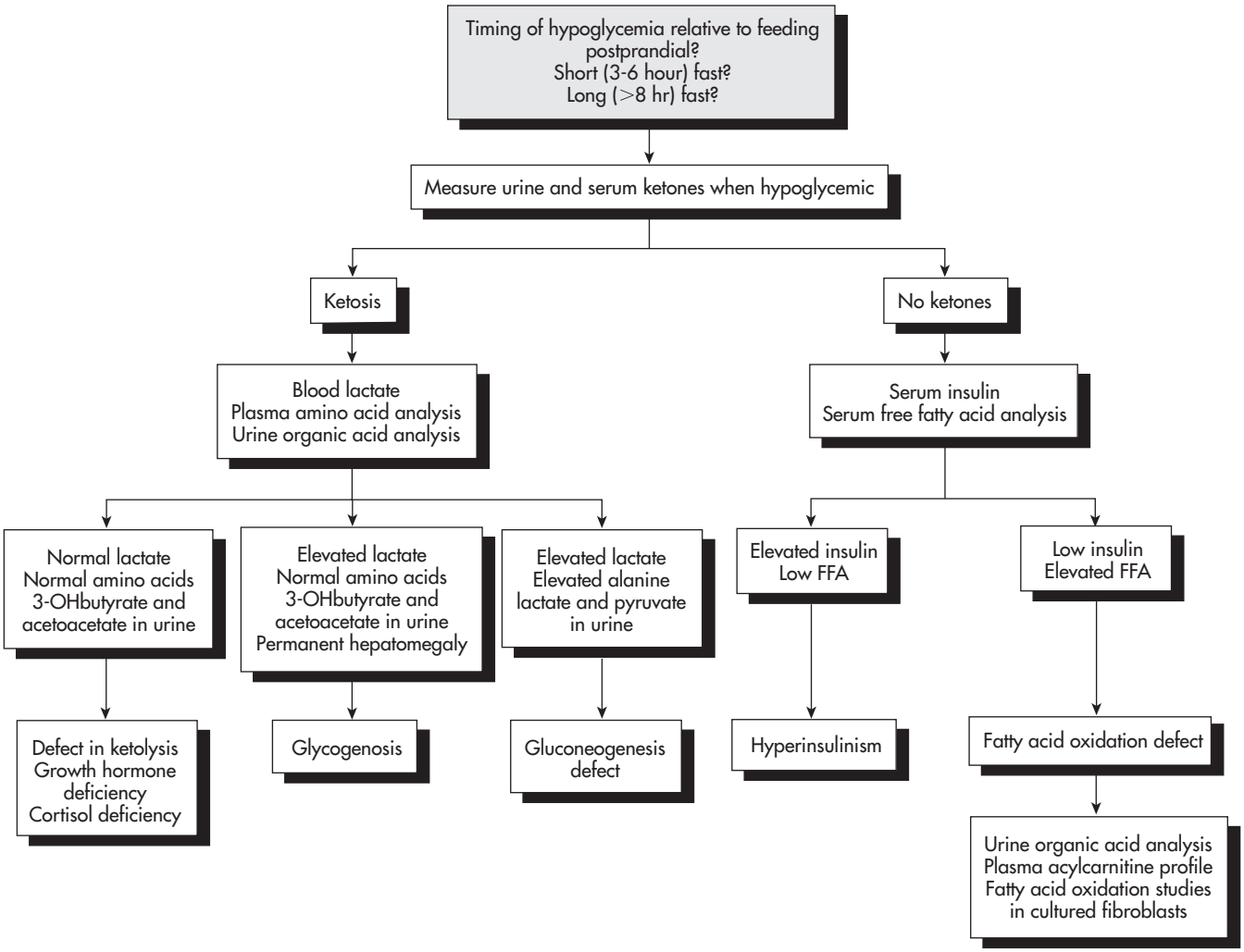


FIGURE E4-18 Algorithm for evaluation of hypoglycemia in children. *FFA,* Free fatty acid. (From Fuhrman BP et al: *Pediatric critical care*, ed 4, Philadelphia, 2011, Saunders.)

pancreatitis, glucagonoma, hemochromatosis, drugs (glucocorticoids, diuretics [thiazides, loop diuretics]), glucose intolerance, impaired fasting glucose
Decreased in. Sulfonylurea therapy, insulin therapy, reactive hypoglycemia (e.g., subtotal gastrectomy), starvation, insulinoma, glycogen storage disorders, severe liver disease or renal disease, ethanol-induced hypoglycemia, mesenchymal tumors that secrete insulin-like hormones

GLUCOSE, POSTPRANDIAL
Normal range: <140 mg/dl (<7.8 mmol/L [CF: 0.05551; SMI: 0.1 mmol/L])
Elevated in: Diabetes mellitus, glucose intolerance
Decreased in: Post-gastrointestinal resection, reactive hypoglycemia, hereditary fructose intolerance, galactosemia, leucine sensitivity

GLUCOSE TOLERANCE TEST
Normal values above fasting:
30 min: 30-60 mg/dl (1.65-3.3 mmol/L [CF: 0.05551; SMI: 0.1 mmol/L])
60 min: 20-50 mg/dl (1.1-2.75 mmol/L [CF: 0.05551; SMI: 0.1 mmol/L])
120 min: 5-15 mg/dl (0.28-0.83 mmol/L [CF: 0.05551; SMI: 0.1 mmol/L])
180 min: fasting level or below
Abnormal in: Glucose intolerance, diabetes mellitus, Cushing's syndrome, acromegaly, pheochromocytoma, gestational diabetes

GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD) SCREEN (blood)
Normal: G6PD enzyme activity detected
Abnormal: If a deficiency is detected, quantitation of G6PD is necessary; a G6PD screen may be falsely interpreted as "normal" after an episode of hemolysis because most G6PD-deficient cells have been destroyed.

γ-GLUTAMYL TRANSFERASE (GGT)
Normal range: 0-30 U/L (0.050 μkat/L [CF: 0.01667; SMI: 0.01 μkat/L])
Elevated in: Chronic alcoholic liver disease, neoplasms (hepatoma, metastatic disease to the liver, carcinoma of the pancreas), systemic lupus erythematosus, congestive heart failure, trauma, nephrotic syndrome, sepsis, cholestasis, drugs (phenytoin, barbiturates)

GLYCOHEMOGLOBIN (glycated glycosylated] hemoglobin), (HbA_{1C})
Normal range: 4.0%-5.9%
Elevated in: Uncontrolled diabetes mellitus (glycated hemoglobin levels reflect the level of glucose control over the preceding 120 days), lead toxicity, alcoholism, iron deficiency anemia, hypertriglyceridemia
Decreased in: Hemolytic anemias, decreased red blood cell survival, pregnancy, acute or chronic blood loss, chronic renal failure, insulinoma, congenital spherocytosis, hemoglobin S, C, and D diseases

GROWTH HORMONE
Normal: Male: 1-9 ng/ml; female: 1-16 ng/ml
Elevated in: Pituitary gigantism, acromegaly, ectopic GH secretion, cirrhosis, renal failure, anorexia nervosa, stress, exercise, prolonged fasting, amphetamines, beta-blockers, insulin, levodopa, metoclopramide, clonidine, vasopressin, human growth hormone (HGH) supplementation
Decreased in: Hypopituitarism, pituitary dwarfism, adrenocortical hyperfunction, bromocriptine, corticosteroids, glucose

GROWTH HORMONE RELEASING HORMONE (GHRH)
Normal: <50 pg/ml
Elevated in: Acromegaly caused by GHRH secretion by neoplasms

GROWTH HORMONE SUPPRESSION TEST (after glucose)
Normal: Test is done by giving 1.75 g glucose/kg orally after overnight fast. Blood is drawn at baseline, after 60 min, and after 120 min of glucose load. Normal response is growth hormone suppression to <2 ng/ml or undetectable levels.
Abnormal: There is no or incomplete suppression from the high basal level in gigantism or acromegaly.

HAM TEST (acid serum test)
Normal: Negative
Positive in: Paroxysmal nocturnal hemoglobinuria
False-positive in: Hereditary or acquired spherocytosis, recent transfusion with aged red blood cells, aplastic anemia, myeloproliferative syndromes, leukemia, hereditary dyserythropoietic anemia type II

HAPTOGLOBIN (serum)
Normal range: 50-220 mg/dl (0.50-2.2 g/L [CF: 0.01; SMI: 0.01 g/L])
Elevated in: Inflammation (acute phase reactant), collagen vascular diseases, infections (acute phase reactant), drugs (androgens), obstructive liver disease
Decreased in: Hemolysis (intravascular more than extravascular), megaloblastic anemia, severe liver disease, large tissue hematomas, infectious mononucleosis, drugs (oral contraceptives)

HBA_{1C}
See GLYCOHEMOGLOBIN

HDL
See HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

HELICOBACTER PYLORI (serology, stool antigen)
Normal range: Not detected
Detected in: *H. pylori* infection. Positive serology can indicate current or past infection. Positive stool antigen test indicates acute infection (sensitivity and specificity >90%). Stool testing should be delayed at least 4 weeks after eradication therapy.

HEMATOCRIT
Normal range: Male: 39%-49% (0.39-0.49 [CF: 0.01; SMI: 0.01])
Female: 33%-43% (0.33-0.43 [CF: 0.01; SMI: 0.01])
Elevated in: Polycythemia vera, smoking, chronic obstructive pulmonary disease, high altitudes, dehydration, hypovolemia
Decreased in: Blood loss (gastrointestinal, genitourinary) anemia

HEMOGLOBIN
Normal range: Male: 13.6-17.7 g/dl (136-172 g/L [CF: 10; SMI: 1 g/L])
Female: 12.0-15.0 g/dl (120-150 g/L [CF: 10; SMI: 1 g/L])
Elevated in: Hemoconcentration, dehydration, polycythemia vera, chronic obstructive pulmonary disease, high altitudes, false elevations (hyperlipemic plasma, white blood cells >50,000/mm^3), stress
Decreased in: Hemorrhagic (gastrointestinal, genitourinary) anemia

HEMOGLOBIN A_{1C}
See GLYCATED HEMOGLOBIN

HEMOGLOBIN ELECTROPHORESIS
Table 4-19 describes neonatal hemoglobin electrophoresis patterns, Table 4-20 summarizes types of hemoglobin, and Table 4-21 describes classifications of hemoglobinopathies.
Normal range: *HbA_1*: 95%-98%
HbA_2: 1.5%-3.5%
HbF: <2%
HbC: absent
HbS: absent

HEMOGLOBIN, GLYCATED
See GLYCOHEMOGLOBIN

HEMOGLOBIN, GLYCOSYLATED
See GLYCOHEMOGLOBIN

HEMOGLOBIN H
See Table 4-20.
Normal: Negative
Present in: Hemoglobin H disease, alpha-thalassemia trait, unstable hemoglobin disorders

TABLE 4-19 Neonatal Hemoglobin (Hb) Electrophoresis Patterns*

FA	Fetal Hb and adult normal Hb; the normal newborn pattern.
FAV	Indicates the presence of both HbF and HbA. However, an anomalous band (V) is present, which does not appear to be any of the common Hb variants.
FAS	Indicates fetal Hb, adult normal HbA, and HbS, consistent with benign sickle cell trait.
FS	Fetal and sickle HbS without detectable adult normal HbA. Consistent with clinically significant homozygous sickle Hb genotype (S/S) or sickle β-thalassemia, with manifestations of sickle cell anemia during childhood.
FC†	Designates the presence of HbC without adult normal HbA. Consistent with clinically significant homozygous HbC genotype (C/C), resulting in a mild hematologic disorder presenting during childhood.
FSC	HbS and HbC present. This heterozygous condition could lead to the manifestations of sickle cell disease during childhood.
FAC	HbC and adult normal HbA present, consistent with benign HbC trait.
FSA	Heterozygous HbS/β-thalassemia, a clinically significant sickling disorder.
F†	Fetal HbF is present without adult normal HbA. Although this may indicate a delayed appearance of HbA, it is also consistent with homozygous β-thalassemia major, or homozygous hereditary persistence of fetal HbF.
FV†	Fetal HbF and an anomalous Hb variant (V) are present.
AF	May indicate prior blood transfusion. Submit another filter paper blood specimen when the infant is 4 mo of age, at which time the transfused blood cells should have been cleared.

NOTE: HbA: $\alpha 2\beta 2$; HbF: $\alpha 2\gamma 2$; HbA2: $\alpha 2\delta 2$.
*Hemoglobin variants are reported in order of decreasing abundance; for example, FA indicates more fetal than adult hemoglobin.
†Repeat blood specimen should be submitted to confirm the original interpretation.
From Tschudy MM, Arcara KM: *The Harriet Lane handbook,* ed 19, Philadelphia, 2012, Mosby.

TABLE 4-20 Types of Hemoglobin

	Hemoglobin	Structure	Comment
Normal	A	$\alpha_2\beta_2$	97% of adult hemoglobin
	A_2	$\alpha_2\delta_2$	2% of adult Hb; elevated in β-thalassemia
	F	$\alpha_2\gamma_2$	Normal Hb in fetus from 3rd to 9th month; increased in β-thalassemia
Abnormal chain production	H	β_4	Found in α-thalassemia, biologically useless
	Barts	γ_4	Found in α-thalassemia, biologically useless
Abnormal chain structure	S	$\alpha_2\beta_2$	Substitution of valine for glutamic acid in position 6 of β chain
	C	$\alpha_2\beta_2$	Substitution of lysine for glutamic acid in position 6 of β chain

From Ballinger A: *Kumar & Clark's essentials of clinical medicine,* ed 6, Edinburgh, 2012, Saunders.

HEMOGLOBIN, URINE

See URINE HEMOGLOBIN, FREE

HEMOSIDERIN, URINE

See URINE HEMOGLOBIN, FREE

HEPARIN-INDUCED THROMBOCYTOPENIA ANTIBODIES

Normal: Antigen assay: Negative, <0.45; weak, 0.45-1.0; strong, >1.0
Elevated in: Heparin-induced thrombocytopenia

TABLE 4-21 Classification of Hemoglobinopathies

Structural hemoglobinopathies—hemoglobins with altered amino acid sequences that result in deranged function or altered physical or chemical properties

Abnormal Hemoglobin Polymerization—HBS

Altered Oxygen Affinity

High affinity—polycythemia
Low affinity—cyanosis, pseudoanemia

Hemoglobins That Oxidize Readily

Unstable hemoglobins, hemolytic anemia, jaundice
M hemoglobins—methemoglobinemia, cyanosis

Thalassemias—Defective Production of Globin Chains

α-Thalassemias
β-Thalassemias
δβ-, γδβ-, αβ-Thalassemias
Structural hemoglobinopathies—structurally abnormal Hb associated with coinherited thalassemia phenotype
HbE
Hb Constant Spring
Hb Lepore

Hereditary Persistence of Fetal Hemoglobin—Persistence of High Levels of Hbf Into Adult Life

Pancellular—all red blood cells contain elevated HbF levels
Nondeletion forms
Deletion forms
Hb Kenya
Heterocellular—only specific subpopulation of red blood cells contain elevated levels of HbF

Acquired Hemoglobinopathies

Methemoglobin due to toxic exposures
Sulfhemoglobin due to toxic exposures
Carboxyhemoglobin
HbH in erythroleukemia
Elevated HbF in states of erythroid stress and bone marrow dysplasia, usually heterocellular

Hb, Hemoglobin.
From Hoffman R: *Hematology: basic principles and practice*, 6th ed, Philadelphia, Saunders, 2013.

HEPATITIS A ANTIBODY

Normal: Negative
Present in: Viral hepatitis A; can be IgM or IgG (if IgM, acute hepatitis A; if IgG, previous infection with hepatitis A)
See Fig. 4-19 for serologic tests in HAV infection.

HAV-IGM ANTIBODY

Appearance: About the same time as clinical symptoms (3-4 weeks after exposure; range, 14-60 days), or just before beginning of AST/ALT elevation (range, 10 days before to 7 days after)
Peak: About 3-4 weeks after onset of symptoms (1-6 weeks)
Becomes nondetectable: 3-4 months after onset of symptoms (1-6 months). In a few cases HAV-IgM antibody can persist as long as 12-14 months.

HAV TOTAL ANTIBODY

Appearance: About 3 weeks after IgM becomes detectable (therefore about the middle of clinical symptom period to early convalescence)
Peak: About 1-2 months after onset
Becomes nondetectable: Remains elevated for life but can somewhat slowly fall

HEPATITIS A VIRAL INFECTION

Best all-purpose test(s) to diagnose acute HAV infection = HAV-Ab (IgM)
Best all-purpose test(s) to demonstrate past HAV infection/immunity = HAV-Ab (total)

HEPATITIS B SURFACE ANTIGEN (HBsAg)

Normal: Not detected
Detected in: Acute viral hepatitis type B, chronic hepatitis B
Appearance: 2-6 weeks after exposure (range, 6 days to 6 months); 5%-15% of patients are negative at onset of jaundice

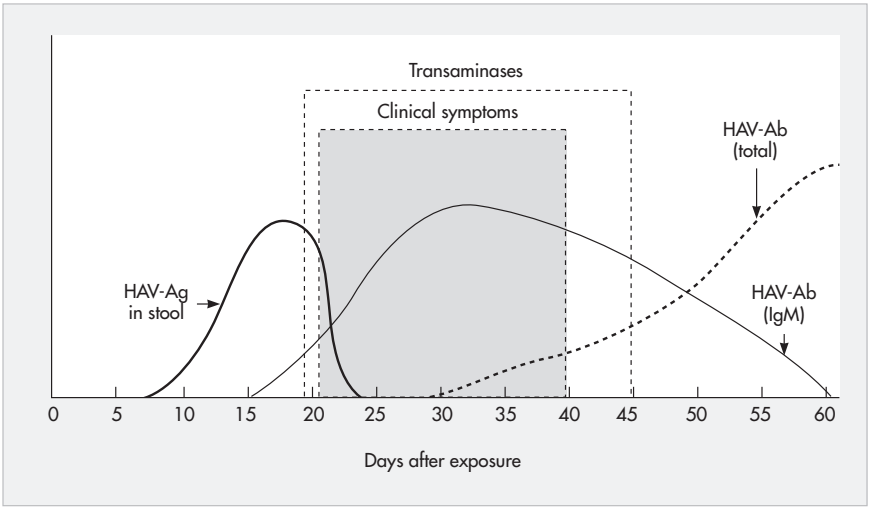


FIGURE 4-19 Serologic tests in HAV infection. (From Ravel R [ed]: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.)

Peak: 1-2 weeks before to 1-2 weeks after onset of symptoms
Becomes nondetectable: 1-3 months after peak (range, 1 week to 5 months)

HEPATITIS B VIRAL INFECTION

See Table 4-22

Figs. 4-20, 4-21, and 4-22 illustrate antigens and antibodies in hepatitis B infection.

HB_S
-Ag
HB_SAg: shows current active HBV infection.
Persistence over 6 months indicates carrier/chronic HBV infection.
HBV nucleic acid probe: present before and longer than HB_SAg.
More reliable marker for increased infectivity than HB_SAg and/or HB_eAg.
-Ab
HB_SAb-total: shows previous healed HBV infection and evidence of immunity.
HB_C
-Ab
HB_CAb-IgM: shows either acute or very recent infection by HBV.
In convalescent phase of acute HBV, may be elevated when HB_SAg has disappeared (core window).
Negative HB_CAb-IgM with positive HB_SAg suggests either very early acute HBV or carrier/chronic HBV.
HB_CAb-total: only useful to show past HBV infection if HB_SAg and HB_cAb-IgM are both negative.
HB_E
-Ag
HB_e-AbAg: when present, especially without HB_eAb, suggests increased patient infectivity.
HB_eAb-total: when present, suggests less patient infectivity.

I. HB_SAg positive, HB_CAb negative
   About 5% (range, 0%-17%) of patients with early-stage HBV acute infection (HB_CAb rises later)
II. HB_SAg positive, HB_CAb positive, HB_SAb negative
   a. Most of the clinical symptom stage
   b. Chronic HBV carriers without evidence of liver disease ("asymptomatic carriers")
   c. Chronic HBV hepatitis (chronic persistent type or chronic active type)
III. HB_SAg negative, HB_CAb positive,* HB_SAb negative
   a. Late clinical symptom stage or early convalescence stage (core window)
   b. Chronic HBV infection with HB_SAg below detection levels with current tests
   c. Old previous HBV infection

TABLE 4-22 Serologic Markers of Hepatitis B Infection

	HBsAg	anti-HBc	anti-HBs	IgM anti-HBc
Susceptible to infection	Negative	Negative	Negative	Negative
Immune due to natural infection	Negative	Positive	Positive	Negative
Immune due to hepatitis B vaccination	Negative	Negative	Positive	Negative
Acutely infected	Positive	Positive	Negative	Positive
Chronically infected	Positive	Positive	Negative	Negative

From Ballinger A: *Kumar & Clark's essentials of clinical medicine,* ed 6, Edinburgh, 2012, Saunders.

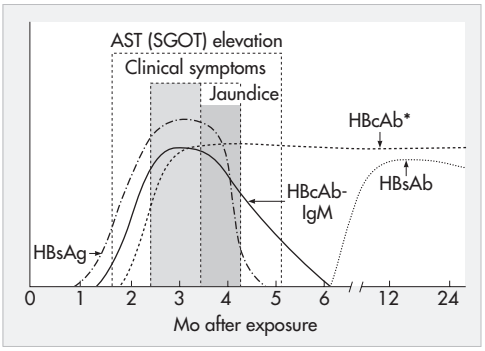


FIGURE 4-20 HBV surface antigen-antibody and core antibodies. Note "core window." *HB_CAb = HB_CAb-IgM + HBCAb-IgG (combined). (From Ravel R [ed]: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.)

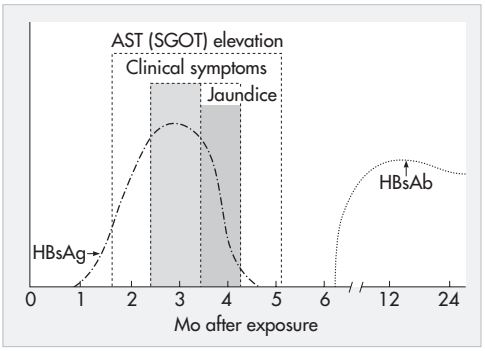


FIGURE 4-21 HBV surface antigen and antibody (HB_SAg and HB_SAb-total). (From Ravel R [ed]: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.)

IV. HB_SAg negative, HB_CAb positive, HB_SAb positive
   a. Late convalescence to complete recovery
   b. Old infection

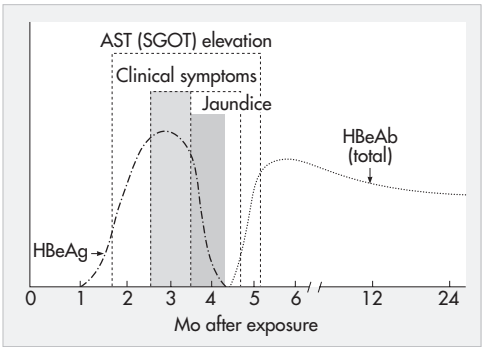


FIGURE 4-22 HBVe antigen and antibody. (From Ravel R [ed]: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.)

HEPATITIS C VIRAL INFECTION

Fig. 4-23 illustrates antigens and antibodies in hepatitis C infection.

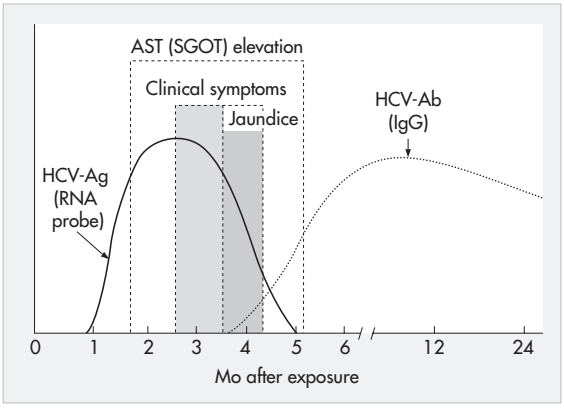


FIGURE 4-23 HCV antigen and antibody. (From Ravel R [ed]: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.)

HEPATITIS C RNA

Normal: Negative
Elevated in: Hepatitis C. Detection of hepatitis C-RNA is used to confirm current infection and to monitor treatment. Quantitative assays (viral load) are needed before treatment to assess response (<2 log decrease after 12-week treatment indicates lack of response).

HCV
-Ag
HCV nucleic acid probe: shows current infection by HCV (especially with PCR amplification).
-Ab
HCV-Ab (IgG): current, convalescent, or old HCV infection.

HAV
-Ag
HAV-Ag by EM: shows presence of virus in stool early in infection.
-Ab
HAV-Ab (IgM): current or recent HAV infection.
HAV-Ab (total): convalescent or old HAV infection.

HEPATITIS D VIRAL INFECTION

Fig. 4-24 illustrates antigens and antibodies in hepatitis D infection.
Best current all-purpose screening test = HDV-Ab (total)
Best test to differentiate acute from chronic infection = HDV-Ab (IgM)

DELTA HEPATITIS COINFECTION (acute HDV1 acute HBV) OR SUPERINFECTION (acute HDV1 chronic HBV)

HDV
-Ag
HDV-Ag: shows current infection (acute or chronic) by HDV.
HDV nucleic acid probe: detects antigen before and longer than HDV-Ag by EIA.
-Ab
HDV-Ab (IgM): high elevation in acute HDV; does not persist.
Low or moderate elevation in convalescent HDV; does not persist.
Low to high persistent elevation in chronic HDV (depends on degree of cell injury and sensitivity of the assay).
HDV-Ab (total): high elevation in acute HDV; does not persist.
High persistent elevation in chronic HDV.

HDV-AG

Detected by DNA probe, less often by immunoassay
Appearance: Prodromal stage (before symptoms); just at or after initial rise in ALT (about a week after appearance of HB_SAg and about the time HB_CAb-IgM level begins to rise)
Peak: 2-3 days after onset

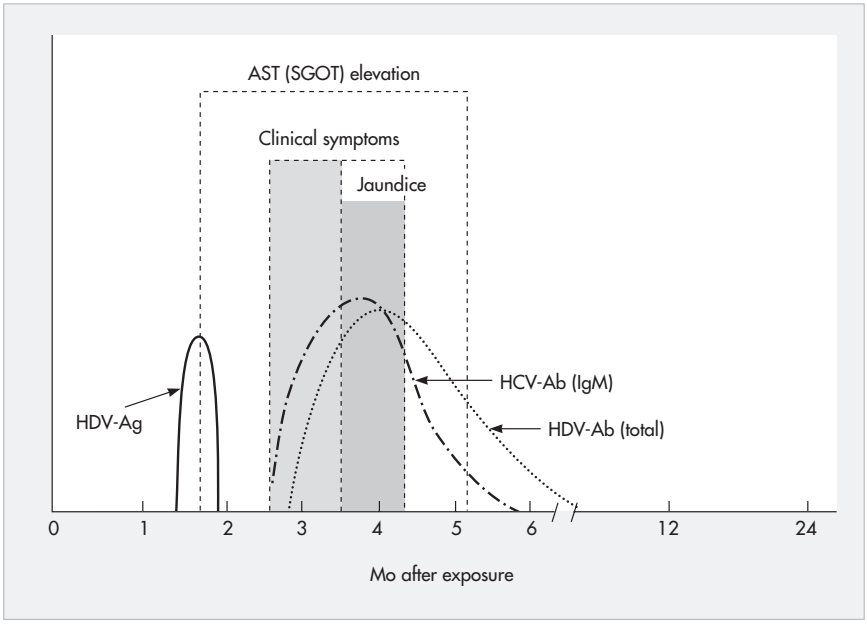


FIGURE 4-24 HDV antigen and antibodies. (From Ravel R [ed]: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.)

Becomes nondetectable: 1-4 days (may persist until shortly after symptoms appear)

HDV-AB (IgM)

Appearance: About 10 days after symptoms begin (range, 1-28 days)
Peak: About 2 weeks after first detection
Becomes nondetectable: About 35 days (range, 10-80 days) after first detection (most other IgM antibodies take 3-6 months to become nondetectable)

HDV-Ab (total)

Appearance: About 50 days after symptoms begin (range, 14-80 days); about 5 weeks after HDV-Ag (range, 3-11 weeks)
Peak: About 2 weeks after first detection
Becomes nondetectable: About 7 months after first detection (range, 4-14 months)

HER-2/*NEU*

Normal: Negative
Present in: 25%-30% of primary breast cancers. It can also be found in other epithelial tumors, including lung, hepatocellular, pancreatic, colon, stomach, ovarian, cervical, and bladder cancer. Trastuzumab (Herceptin) is a humanized monoclonal antibody against Her-2/*neu*. This test is useful to identify patients with metastatic; recurrent; and/or treatment refractory, unresectable, locally advanced breast cancer for trastuzumab treatment.

HERPES SIMPLEX VIRUS (HSV)

Test description: The PCR test can be performed on serum biopsy samples, CSF, vitreous humor.

HFE SCREEN FOR HEREDITARY HEMOCHROMATOSIS

Test description: PCR test can be performed on whole blood or tissue. One mutation (C282Y) and two polymorphisms (H63D, S65C) account for the majority of alleles associated with this disease.

HETEROPHIL ANTIBODY

Normal: Negative
Positive in: Infectious mononucleosis

HIGH-DENSITY LIPOPROTEIN (HDL) CHOLESTEROL

Normal range: Male: 40-70 mg/dl (0.8-1.8 mmol/L [CF: 0.02586; SMI: 0.05 mmol/L])
Female: 50-90 mg/dl (1.1-2.35 mmol/L [CF: 0.02586; SMI: 0.05 mmol/L])
Increased in: Use of gemfibrozil, statins, fenofibrate, nicotinic acid, estrogens, regular aerobic exercise, small (1 oz) daily alcohol intake
Decreased in: Deficiency of apoproteins, liver disease, probucol ingestion, Tangier disease

NOTE: A cholesterol/HDL ratio >4.0 is associated with increased risk of coronary artery disease.

HLA ANTIGENS

Associated disorders: see Table 4-23.

TABLE 4-23 HLA Antigens Associated with Specific Diseases

Antigen	Condition	Antigen	Condition
HLA-B27	Ankylosing spondylitis	HLA-B8, Dw3	Celiac disease
	Reiter's syndrome	HLA-B8, Dw3	Dermatitis herpetiformis
	Psoriatic arthritis	HLA-B8	Myasthenia gravis
HLA-A10, B18, Dw2	C2 deficiency	HLA-B8	Chronic active hepatitis in children
HLA-A2, B40, Cw3	C4 deficiency	HLA-Drw4	Active chronic hepatitis in adults
HLA-B7, Dw2	Multiple sclerosis	HLA-B13, Bw17	Psoriasis
HLA-A3	Hemochromatosis		

From Cerra FB: *Manual of critical care,* St Louis, 1987, Mosby.
HLA, Human leukocyte antigen.

HOMOCYSTEINE (Plasma)

Normal range:
0-30 years: 4.6-8.1 mcmol/L
30-59 years: 6.3-11.2 mcmol/L (males), 4.5-7.9 mcmol/L (females)
>59 years: 5.8-11.9 mcmol/L
Increased: Thrombophilic states, B_6, B_{12}, folic acid, riboflavin deficiency, pregnancy, homocystinuria

NOTE: An increased homocysteine level is an independent risk factor for atherosclerosis.

HUMAN CHORIONIC GONADOTROPIN (hCG)

Normal range: Varies with gestational stage:
1 wk: 5-50 mU/ml
1-2 wk: 50-550 mU/ml
2-3 wk: up to 5000 mU/ml
3-4 wk: up to 10,000 mU/ml
4-5 wk: up to 50,000 mU/ml
2-3 mo: 10,000-100,000 mU/ml

Elevated in: Normal pregnancy, hydatidiform mole, choriocarcinoma, germ cell tumors of testicle, some nontrophoblastic neoplasms (e.g., neoplasms of cervix, gastrointestinal tract, ovary, lung, breast)

HUMAN HERPES VIRUS 8 (HHV8)

Test description: PCR test can be performed on whole blood, tissue, bone marrow, and urine. HHV8 is found in all forms of Kaposi's sarcoma.

HUMAN IMMUNODEFICIENCY VIRUS ANTIBODY, TYPE 1 (HIV-1)

Normal range: Not detected
Abnormal result: HIV antibodies usually appear in the blood 1-4 months after infection.
Testing sequence:

1. ELISA is the recommended initial screening test. Sensitivity and specificity are >99%. False-positive ELISA may occur with autoimmune disorders, administration of immune globulin manufactured before 1985, within 6 weeks of testing, in the presence of rheumatoid factor, in the presence of DLA-DR antibodies in multigravida female, with administration of influenza vaccine within 3 months of testing, with hemodialysis, with positive plasma reagin test, and with certain medical disorders (hemophilia, hypergammaglobulinemia, alcoholic hepatitis).
2. A positive ELISA is confirmed with Western blot. False-positive Western blot may result from connective tissue disorders, human leukocyte antigen antibodies, polyclonal gammopathies, hyperbilirubinemia, presence of antibody to another human retrovirus, or cross-reaction with other non-virus-derived proteins in healthy persons. Undetermined Western blot may occur in AIDS patients with advanced immunodeficiency (caused by loss of antibodies) and in recent HIV infections.
3. PCR is used to confirm indeterminate Western blot results or negative results in persons with suspected HIV infection.

Fig. 4-25 describes tests in HIV infection; indications for plasma HIV RNA testing are described in Table 4-24.

HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1) ANTIGEN (p24), QUALITATIVE (p24 ANTIGEN)

Normal range: Negative. This test detects uncomplexed HIV-1 p24 antigen. The core protein p24 is the first detectable protein encoded by the group-specific antigen *(gag)* gene. This protein is a marker for viremia. This test should not be used in place of HIV-1 antibody testing as a screen for HIV-1 infection. HIV-1 p24 may be detectable in the first month of acute HIV-1 infection and generally falls to undetectable levels during the asymptomatic stage of HIV-1 infection. A negative result does not exclude the possibility of infection or exposure to HIV-1. It is recommended that a negative result be followed with repeat testing at least 8 weeks after the original test. This test is used primarily for screening of donated blood and plasma and as an aid for the prognosis of HIV-1 infection.

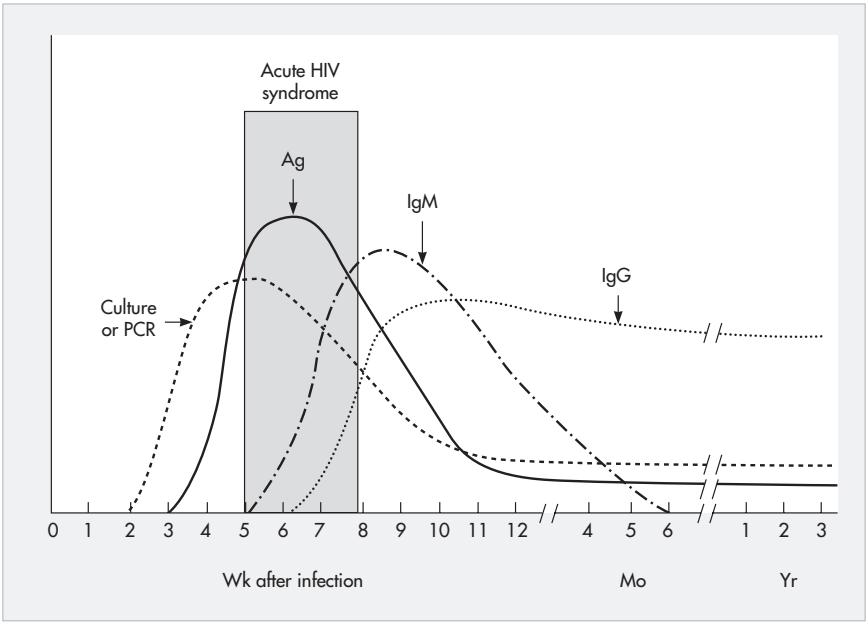


FIGURE 4-25 Tests in HIV-1 infection. (From Ravel R [ed]: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.)

TABLE 4-24 Indications for Plasma HIV RNA Testing*

Clinical Indication	Information	Use
Syndrome consistent with acute HIV infection	Establishes diagnosis when HIV antibody test is negative or indeterminate	Diagnosis†
Initial evaluation of newly diagnosed HIV infection	Baseline viral load set point	Decision to start or defer therapy
Every 3-4 mo in patients not on therapy	Changes in viral load	Decision to start therapy
4-8 wk after initiation of antiretroviral therapy	Initial assessment of drug efficacy	Decision to continue or change therapy
3-4 mo after start of therapy	Maximal effect of therapy	Decision to continue or change therapy
Every 3-4 mo in patients on therapy	Durability of antiretroviral effect	Decision to continue or change therapy
Clinical event or significant decline in CD4+ T cells	Association with changing or stable	Decision to continue, initiate, or change

*Acute illness (e.g., bacterial pneumonia, tuberculosis, HSV, PCP) and immunizations can cause increase in plasma HIV RNA for 2-4 wk; viral load testing should not be performed during this time. Plasma HIV RNA results should usually be verified with a repeat determination before starting or making changes in therapy. HIV RNA should be measured using the same laboratory and the same assay.
†Diagnosis of HIV infection determined by HIV RNA testing should be confirmed by standard methods (e.g., Western blot serology) performed 2-4 mo after the initial indeterminate or negative test.
From Report of the NIH Panel to Define Principles of Therapy of HIV Infection, *MMWR Recomm Rep* 47(RR-5):1-41, 1998.

HUMAN IMMUNODEFICIENCY VIRUS TYPE 1 (HIV-1) VIRAL LOAD

Normal range: HIV-1 RNA, quant. bDNA 3: less than 50 copies/ml or less than 1.7 log copies/ml

This test should be used only in individuals with documented HIV-1 infection for monitoring the progression of infection, response to antiretroviral therapy, and disease prognosis. It is not indicated for diagnosis of HIV infection.

HUMAN PAPILLOMA VIRUS (HPV)

Test description: PCR test can be performed on cervical smears, biopsies, scrapings, liquid cytology specimen, and anogenital tissues.

HUNTINGTON'S DISEASE PCR

Test description: PCR can be performed on whole blood. Huntington's disease is caused by the expansion of the trinucleotide repeat CAG within IT 15 (huntingtin). Pre- and post-test counseling should be performed when ordering this test.

HYDROGEN BREATH TEST

See BREATH HYDROGEN TEST

5-HYDROXYINDOLE-ACETIC ACID, URINE

See URINE 5-HYDROXYINDOLE-ACETIC ACID

IMMUNE COMPLEX ASSAY

Normal: Negative

Detected in: Collagen vascular disorders, glomerulonephritis, neoplastic diseases, malaria, primary biliary cirrhosis, chronic acute hepatitis, bacterial endocarditis, vasculitis

IMMUNOGLOBULINS

Normal range:

IgA: 50-350 mg/dl (0.5-3.5 g/L [CF: 0.01; SMI: 0.01 g/L])
IgD: <6 mg/dl (<60 mg/L [CF: 0.01; SMI: 0.01 g/L])
IgE: <25 μg/dl (<0.00025 g/L [CF: 0.01; SMI: 0.01 g/L])
IgG: 800-1500 mg/dl (8-15 g/L [CF: 0.01; SMI: 0.01 g/L])
IgM: 45-150 mg/dl (0.45-1.5 g/L [CF: 0.01; SMI: 0.01 g/L])

Elevated in:

IgA: Lymphoproliferative disorders, Berger's nephropathy, chronic infections, autoimmune disorders, liver disease
IgE: Allergic disorders, parasitic infections, immunologic disorders, IgE myeloma
IgG: Chronic granulomatous infections, infectious diseases, inflammation, myeloma, liver disease
IgM: Primary biliary cirrhosis, infectious diseases (brucellosis, malaria), Waldenström's macroglobulinemia, liver disease

Decreased in:

IgA: Nephrotic syndrome, protein-losing enteropathy, congenital deficiency, lymphocytic leukemia, ataxia-telangiectasia, chronic sinopulmonary disease

IgE: Hypogammaglobulinemia, neoplasms (breast, bronchial, cervical), ataxia-telangiectasia
IgG: Congenital or acquired deficiency, lymphocytic leukemia, phenytoin, methylprednisolone, nephrotic syndrome, protein-losing enteropathy
IgM: Congenital deficiency, lymphocytic leukemia, nephrotic syndrome

INFLUENZA A AND B TESTS

Test description: PCR can be performed on nasopharyngeal swab, wash, or aspirate
Normal: Negative

INSULIN AUTOANTIBODIES

Normal: Negative
Present in: Exogenous insulin from insulin therapy. The presence of islet cell antibodies indicates ongoing beta cell destruction. This test is useful in the early diagnosis of type 1a diabetes mellitus and in the identification of patients at high risk for type 1a diabetes.

INSULIN, FREE

Normal: <17 mcU/ml
Elevated in: Insulin overdose, insulin resistance syndromes, endogenous hyperinsulinemia
Decreased in: Inadequately treated type 1 diabetes mellitus

INSULIN-LIKE GROWTH FACTOR-1 (IGF-1) (Serum)

Normal range:
Ages 16-24: 182-780 ng/ml
Ages 25-39: 114-492 ng/ml
Ages 40-54: 90-360 ng/ml
Ages >55: 71-290 ng/ml
Elevated in: Adolescence, acromegaly, pregnancy, precocious puberty, obesity
Decreased in: Malnutrition, delayed puberty, diabetes mellitus, hypopituitarism, cirrhosis, old age

INSULIN-LIKE GROWTH FACTOR-II

Normal range: 288-736 ng/ml
Elevated in: Hypoglycemia associated with non–islet cell tumors, hepatoma, and Wilms' tumor
Decreased in: Growth hormone deficiency

INTERNATIONAL NORMALIZED RATIO (INR)

The INR is a comparative rating of prothrombin time (PT) ratios. The INR represents the observed PT ratio adjusted by the International Reference Thromboplastin. It provides a universal result indicative of what the patient's PT result would have been if measured using the primary World Health Organization International Reference reagent. For proper interpretation of INR values, the patient should be on stable anticoagulant therapy.

RECOMMENDED INR RANGES:

Proximal deep vein thrombosis:	2-3
Pulmonary embolism:	2-3
Transient ischemic attacks:	2-3
Atrial fibrillation:	2-3
Mechanical prosthetic valves:	2.5-3.5
Recurrent venous thromboembolic disease:	2.5-3.5

INTRINSIC FACTOR ANTIBODIES

Normal: Negative
Present in: Pernicious anemia (>50% of patients). Cyanocobalamin may give false-positive results.

IRON (Serum)

Normal: Male: 65-175 mcg/dl; female: 50-1170 mcg/dl
Elevated in: Hemochromatosis, excessive iron therapy, repeated transfusions, lead poisoning, hemolytic anemia, aplastic anemia, pernicious anemia
Decreased in: Iron deficiency anemia, hypothyroidism, chronic infection

IRON-BINDING CAPACITY, TOTAL (TIBC)

Normal range: 250-460 μg/dl (45-82 μmol/L [CF: 0.1791; SMI: 1 μmol/L])
Elevated in: Iron deficiency anemia, pregnancy, polycythemia, hepatitis, weight loss
Decreased in: Anemia of chronic disease, hemochromatosis, chronic liver disease, hemolytic anemias, malnutrition (protein depletion)
Table 4-25 describes TIBC and serum iron abnormalities.

IRON SATURATION (% TRANSFERRIN SATURATION)

Normal:
Male: 20%-50%
Female: 15%-50%
Elevated in: Hemochromatosis, excessive iron intake, aplastic anemia, thalassemia, vitamin B_6 deficiency
Decreased in: hypochromic anemias, GI malignancy

TABLE 4-25 Serum Iron and Total Iron-Binding Capacity Patterns

SI↓	TIBC↓	Chronic diseases Uremia
SI↓	TIBC	Chronic iron deficiency anemia Pregnancy in third trimester
SI	TIBC↓	Hemachromatosis Iron therapy overload (TIBC may be normal) Hemolytic anemia; thalassemia; lead poisoning; megaloblastic anemia; aplastic, pyridoxine deficiency, or other sideroblastic anemias
SI	TIBC	Oral contraceptives Acute hepatitis (some report TIBC is low normal) Chronic hepatitis (some patients)
SI	TIBC NL	B_{12} or folate deficiency
SI↓	TIBC	Chronic iron deficiency (some patients)
	NL	Acute infection, surgery, tissue damage
SI NL	TIBC	B_{12}/folate deficiency plus iron deficiency

NL, Normal; *SI,* serum iron; *TIBC,* total iron-binding capacity.
From Ravel R: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.

LACTATE (blood)

Normal range: 0.5-2.0 mEq/L
Elevated in: Tissue hypoxia (shock, respiratory failure, severe CHF, severe anemia, carbon monoxide or cyanide poisoning), systemic disorders (liver or renal failure, seizures), abnormal intestinal flora (d-lactic acidosis), drugs or toxins (salicylates, ethanol, methanol, ethylene glycol), G6PD deficiency

LACTATE DEHYDROGENASE (LDH)

Normal range: 50-150 U/L (0.82-2.66 μkat/L [CF: 0.01667; SMI: 0.02 μkat/L])
Elevated in:
Infarction of myocardium, lung, kidney
Diseases of cardiopulmonary system, liver, collagen, central nervous system
Hemolytic anemias, megaloblastic anemias, transfusions, seizures, muscle trauma, muscular dystrophy, acute pancreatitis, hypotension, shock, infectious mononucleosis, inflammation, neoplasia, intestinal obstruction, hypothyroidism

LACTATE DEHYDROGENASE ISOENZYMES

Normal range:
LDH_1: 22%-36% (cardiac, red blood cell) (0.22-0.36 [CF: 0.01, SMI: 0.01])
LDH_2: 35%-46% (cardiac, red blood cell) (0.35-0.46)
LDH_3: 13%-26% (pulmonary) (0.15-0.26)
LDH_4: 3%-10% (striated muscle, liver) (0.03-0.1)
LDH_5: 2%-9% (striated muscle, liver) (0.02-0.09)
Normal ratios:
$LDH_1 < LDH_2$
$LDH_5 < LDH_4$
Abnormal values:
$LDH_1 > LDH_2$: Myocardial infarction (can also be seen with hemolytic anemias, pernicious anemia, folate deficiency, renal infarct)
$LDH_5 > LDH_4$: Liver disease (cirrhosis, hepatitis, hepatic congestion)

LACTOSE TOLERANCE TEST (serum)

Normal: Test is performed by giving 2 g/kg body weight lactose orally and drawing glucose level at 0, 30, 45, 60, and 90 min. Normal response is change in glucose from fasting value to >30 mg/dl. Inconclusive response is increase of 20-30 mg/dl, abnormal response is increase <20 mg/dl.
Abnormal in: Lactase deficiency

LAP SCORE

See LEUKOCYTE ALKALINE PHOSPHATASE

LEAD

Normal: Child, <10 mcg/dl; adult, <25 mcg/dl; acceptable for industrial exposure, <50 mcg/dl
Elevated in: Lead exposure, lead poisoning

LDH

See LACTATE DEHYDROGENASE

LDL

See LOW-DENSITY LIPOPROTEIN CHOLESTEROL

LEGIONELLA PNEUMOPHILA PCR

Test description: PCR can be performed on lung tissue, water sputum, bronchoalveolar lavage, and other respiratory fluids.

LEGIONELLA TITER

Normal: Negative
Positive in: Legionnaire's disease (presumptive: ≥1:256 titer; definitive: fourfold titer increase to ≥1:128)

LEUKOCYTE ALKALINE PHOSPHATASE (LAP)

Normal range: 13-100 (33-188 U)
Elevated in: Leukemoid reactions, neutrophilia secondary to infections (except in sickle cell crisis—no significant increase in LAP score), Hodgkin's disease, polycythemia vera, hairy cell leukemia, aplastic anemia, Down syndrome, myelofibrosis
Decreased in: Acute and chronic granulocytic leukemia, thrombocytopenic purpura, paroxysmal nocturnal hemoglobinuria, hypophosphatemia, collagen disorders

LEUKOCYTE COUNT

See COMPLETE BLOOD COUNT

LIPASE

Normal range: 0-160 U/L (0-2.66 μkat/L [CF: 0.01667; SMI: 0.02 μkat/L])
Elevated in: Acute pancreatitis, perforated peptic ulcer, carcinoma of pancreas (early stage), pancreatic duct obstruction, bowel infarction, intestinal obstruction

LIPOPROTEIN(a)

Normal: Male: 1.35-19.6 mg/dl; female: 1.24-20.1 mg/dl
Elevated in: Coronary artery disease, uncontrolled diabetes, hypothyroidism, chronic renal failure, pregnancy, tobacco use, infections, nephritic syndrome
Decreased in: Niacin, omega-3 fatty acids, estrogens, tamoxifen, statins

LIPOPROTEIN CHOLESTEROL, HIGH-DENSITY

See HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

LIPOPROTEIN CHOLESTEROL, LOW-DENSITY

See LOW-DENSITY LIPOPROTEIN CHOLESTEROL

LIVER KIDNEY MICROSOME TYPE 1 ANTIBODIES (LKM1)

Normal: <20 U
Elevated in: Autoimmune hepatitis type 2

LKM1

See LIVER KIDNEY MICROSOME TYPE 1 ANTIBODIES

LOW-DENSITY LIPOPROTEIN (LDL) CHOLESTEROL

Normal range: 50-130 mg/dl (1.30-1.68 mmol/L [CF: 0.02586; SMI: 0.05 mmol/L])

<70	Optimal in diabetics, prior MI, and patients with cardiac risk factors
100-129	Near or above optimal
130-159	Borderline high
160-189	High
≥190	Very high

LUPUS ANTICOAGULANT

See CIRCULATING ANTICOAGULANT

LUTEINIZING HORMONE

Normal range: 5-25 mIU/ml
Elevated in: Postmenopause, pituitary adenoma, primary gonadal dysfunction, polycystic ovary syndrome
Decreased in: Severe illness, anorexia nervosa, malnutrition, pituitary or hypothalamic impairment, severe stress

LYME DISEASE ANTIBODY TITER

Normal range: Negative
Positive result
Figure 4-26 illustrates the usual serologic response in Lyme disease.

A serologic test is not necessary or helpful for several days after a tick bite because it is only 40%-50% sensitive in this stage, and a negative test does not rule out the diagnosis.

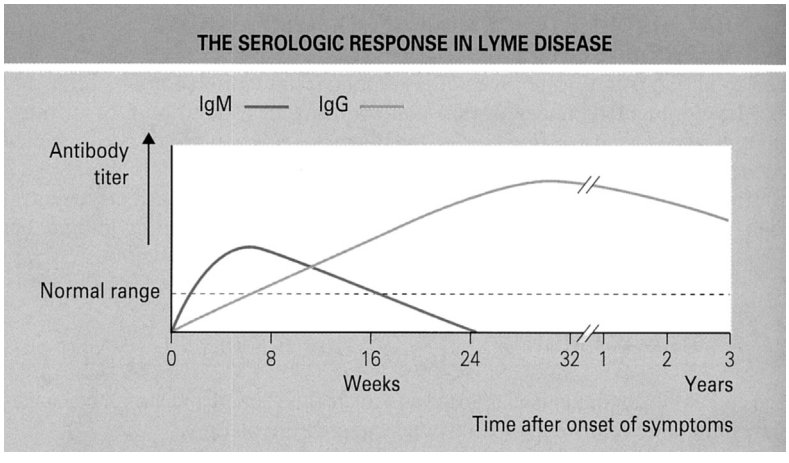


FIGURE 4-26 IgM and IgG responses in Lyme disease.

LYMPHOCYTES

Normal range: 15%-40%
Total lymphocyte count = 800-2600/mm^3
Total T lymphocyte = 800-2200/mm^3
CD4 lymphocytes = ≥ 400/mm^3
CD8 lymphocytes = 200-800/mm^3
Normal CD4/CD8 ratio is 2.0.

Elevated in: Chronic infections, infectious mononucleosis and other viral infections, chronic lymphocytic leukemia, Hodgkin's disease, ulcerative colitis, hypoadrenalism, idiopathic thrombocytopenia

Decreased in:
AIDS, bone marrow suppression from chemotherapeutic agents or chemotherapy, aplastic anemia, neoplasms, steroids, adrenocortical hyperfunction, neurologic disorders (multiple sclerosis, myasthenia gravis, Guillain-Barré syndrome)

CD4 lymphocytes are calculated as total white blood cells × % lymphocytes × % lymphocytes stained with CD4. They are decreased in AIDS and other immune dysfunction.

Table 4-26 describes various lymphocyte abnormalities in peripheral blood.

MAGNESIUM (Serum)

Normal range: 1.8-3.0 mg/dl (0.80-1.20 mmol/L [CF: 0.4114; SMI: 0.02 mmol/L])

CAUSES OF HYPERMAGNESEMIA

I. Decreased renal excretion
  A. Renal failure—glomerular filtration rate less than 30 ml/min
  B. Hyperparathyroidism
  C. Hypothyroidism
  D. Addison's disease
  E. Lithium intoxication
  F. Familial hypocalciuric hypercalcemia
II. Other causes: usually in association with decrease in glomerular filtration rate
  A. Endogenous loads
    1. Diabetic ketoacidosis
    2. Severe tissue injury—burns
  B. Exogenous loads
    1. Gastrointestinal
      a. Magnesium-containing laxatives and antacids
      b. High-dose vitamin D analogs
    2. Parenteral: management of toxemia of pregnancy

CAUSES OF HYPOMAGNESEMIA

Alcoholic abuse
Diuretic use
Renal losses
Acute and chronic renal failure
Postobstructive diuresis
Acute tubular necrosis
Chronic glomerulonephritis
Chronic pyelonephritis
Interstitial nephropathy
Renal transplantation
Gastrointestinal losses
Chronic diarrhea
Nasogastric suctioning
Short bowel syndrome
Protein-calorie malnutrition
Bowel fistula
Total parenteral nutrition
Acute pancreatitis
Endocrine
Diabetes mellitus
Hyperaldosteronism
Hyperthyroidism
Hyperparathyroidism
Acute intermittent porphyria
Pregnancy
Drugs
Aminoglycosides
Amphotericin
β-agonists
Cisplatin

TABLE 4-26 Differential Diagnosis of Abnormal Lymphocytes in Peripheral Blood

Lymphocyte Type	Usual Disease Association	Cytologic Features	Laboratory Features	Clinical Features
Small lymphocyte	Chronic lymphocytic leukemia	B-cell surface markers with low concentration of surface immunoglobulin, CD5 antigen	Hypogammaglobulinemia in 50%; positive direct Coombs test in 15%; on node biopsy, diffuse, well-differentiated lymphocytic infiltrate	Elderly adults; presentation runs gamut from asymptomatic with lymphocytosis only to bulky disease with adenopathy, splenomegaly, and "packed" bone marrow
Atypical lymphocyte	Infectious mononucleosis, other viral illnesses	Suppressor T-cell markers	Heterophil agglutinin; positive serology for Epstein-Barr virus, cytomegalovirus, Toxoplasma, HBsAg	Pharyngitis, fever, adenopathy, rash, splenomegaly, palatal petechiae, jaundice
Plasmacytoid lymphocyte	Waldenström's macroglobulin anemia	Cytoplasmic IgM, periodic acid-Schiff positivity	IgM paraprotein, rouleaux, cryoglobulins	Adenopathy, splenomegaly, absence of bone lesions, hyperviscosity syndrome, cryopathic phenomena
Lymphoblast	ALL	Terminal transferase positivity, common ALL antigen, B- or T-precursor markers	Anemia, granulocytopenia, thrombocytopenia, hyperuricemia, diffuse bone marrow infiltration	Peak incidence in childhood, acute onset, bone pain frequent
Lymphosarcoma cell	Lymphocytic lymphoma	B-cell surface markers with high concentration of monoclonal surface immunoglobulin	Nodular or diffuse, poorly differentiated lymphocytic lymphoma on node biopsy, patchy, peritrabecular bone marrow involvement	Middle-aged to older adults, generalized adenopathy, constitutional symptoms
Sézary cell	Cutaneous lymphomas	T-lymphocyte surface markers	Skin biopsy is diagnostic	Exfoliative erythroderma, cutaneous plaques or tumors
Hairy cell	Hairy cell leukemia	B-lymphocyte markers, cytoplasmic projections, tartrate-resistant acid phosphatase, interleukin-2 receptors, CD11 antigen	Pancytopenia	Middle-aged males, moderate to marked splenomegaly without adenopathy
Prolymphocyte	Prolymphocytic leukemia	B-cell surface markers with high concentration of surface immunoglobulin, CD5 negative	Marked lymphocytosis (frequently >100 × 10^9/L)	Elderly adults, massive splenomegaly, minimum adenopathy, poor response to therapy

ALL, Acute lymphoblastic leukemia.
From Stein JH (ed): *Internal medicine,* ed 5, St Louis, 1998, Mosby.

TABLE 4-27 Clinical Conditions Not to Be Confused With Megaloblastosis

Macrocytosis* Without Megaloblastosis†

Reticulocytosis
Liver disease
Aplastic anemia
Myelodysplastic syndromes (especially 5q-)
Multiple myeloma
Hypoxemia
Smokers

Spurious Increases In MCV Without Macro-Ovalocytosis‡

Cold agglutinin disease
Marked hyperglycemia
Leukocytosis
Older individuals

*The central pallor that normally occupies about one-third of the normal red blood cell is decreased in macro-ovalocytes. This contrasts with the finding of thin macrocytes, in which the central pallor is increased.
†Although megaloblastosis implies that a bone marrow test has been performed, with the addition of highly sensitive tests for the specific diagnosis of cobalamin and folate deficiency, the need for a bone marrow test is often dictated by the urgency to make the diagnosis.
‡When the Coulter counter readings of a high MCV are not confirmed by looking at the peripheral smear.
MCV, Mean corpuscular volume.
From Hoffman R: *Hematology: basic principles and practice,* 6th ed, Philadelphia, Saunders, 2013.

TABLE 4-28 Some Causes of Increased Mean Corpuscular Volume (Macrocytosis)

Causes	% of all Macrocytosis Patients*	% of Macrocytosis in Each Disease†
Common		
Folate or B_{12} deficiency	20-30 (5-50)‡	80-90 (4-100)
Chronic liver disease	15-20 (6-28)	25-30 (8-65)
Chronic alcoholism	10-12 (3-15)	60 (26-90)
Cytotoxic chemotherapy	10-15 (2-20)	30-40 (13-82)
Cardiorespiratory abnormality	8 (7-9.5)	?
Reticulocytosis	6-7 (0-15)	Depends on severity
Myelodysplastic syndromes	Frequent over age 40 yr	>60 in RAEB and RARS
Unexplained	25 (22.5-27)	—
Normal newborn		
Less Common	**<4%**	
Noncytotoxic drugs		
> Zidovudine		
Phenytoin		30 (14-50)
Azathioprine		
Hypothyroidism		20-30 (8-55)
Chronic leukemia/myelofibrosis		
Radiotherapy for malignancy		
Chronic renal disease (occasional patients)		
Distance-runner macrocytosis (some persons)		
Down syndrome		
Artifactual (e.g., cold agglutinins)		

*Percentage of all patients with macrocytosis.
†Percentage of patients with each condition listed who have macrocytosis.
‡Numbers in parentheses are literature range.
RAEB, Refractory anemia with excessive blasts; *RARS,* refractory anemia with ring sideroblasts (formerly called "IASA," or idiopathic acquired sideroblastic anemia).
From Ravel R: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.

Cyclosporine
Diuretics
Foscarnet
Pentamidine
Theophylline
Congenital disorders
Familial hypomagnesemia
Maternal diabetes
Maternal hypothyroidism
Maternal hyperparathyroidism

MEAN CORPUSCULAR VOLUME (MCV) (Table 4-27)

Normal range: 76-100 μm^3 (76-100 fL) (76-100 fL [CF: 1; SMI: 1 fL])
See Tables 4-28 and 4-29 for descriptions of MCV abnormalities.

TABLE 4-29 Some Causes of Decreased Mean Corpuscular Volume (Microcytosis)

Common	Less Common
Chronic iron deficiency	Some cases of polycythemia
α- or β-thalassemia (minor)	Some cases of lead poisoning
Anemia of chronic disease	Some cases of congenital spherocytosis
	Some cases of sideroblastic anemia
	Certain abnormal hemoglobins (HbE, Hb Lepore)

From Ravel R: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.

METANEPHRINES, URINE

See URINE METANEPHRINES

METHYLMALONIC ACID (Serum)

Normal: <0.2 mcmol/L
Elevated in: Vitamin B_{12} deficiency, pregnancy, methylmalonic acidemia

MITOCHONDRIAL ANTIBODY (AMA)

Normal: Negative
Present in: Primary biliary cirrhosis (>90% of patients)

MONOCYTE COUNT

Normal range: 2%-8%
Elevated in: Viral diseases, parasites, infections, neoplasms, inflammatory bowel disease, monocytic leukemia, lymphomas, myeloma, sarcoidosis
Decreased in: Aplastic anemia, lymphocytic leukemia, glucocorticoid administration
See Table 4-30 for changes in monocyte number.

TABLE 4-30 Changes in Monocyte Number

Monocytosis

Infections: tuberculosis, granulomatous infection, brucellosis, subacute bacterial endocarditis
Connective tissue disorder
Recovery from myelosuppression
Hematologic malignancies

1. MDS, MPD, MDS–MPD overlap, CMML
2. Acute and chronic monocytic leukemia, myelomonocytic leukemia
3. Hodgkin and non-Hodgkin lymphomas

Monocytopenia

Hairy cell leukemia
MonoMAC syndrome
Aplastic anemia
Drugs: chemotherapy, IFN-α, glucocorticoids (transient)
Radiation therapy

CMML, Chronic myelomonocytic leukemia; *IFN,* interferon; *MDS,* myelodysplastic syndrome; *monoMAC,* monocytopenia and mycobacterium avium complex syndrome; *MPD,* myeloproliferative disorder.
From Hoffman R: Hematology, basic principles and practice, 6th ed, Philadelphia, Saunders, 2013.

MYCOPLASMA PNEUMONIAE PCR

Test description: PCR can be performed on sputum, bronchoalveolar lavage, nasopharyngeal and throat swabs, other respiratory fluids, and lung tissue

MYELIN BASIC PROTEIN, CEREBROSPINAL FLUID

Normal: <2.5 ng/ml
Elevated in: Multiple sclerosis, CNS trauma, stroke, encephalitis

MYOGLOBIN, URINE

See URINE MYOGLOBIN

NEISSERIA GONORRHOEAE PCR

Test description: Test can be performed on endocervical swab, urine, and intraurethral swab
Normal: Negative

NEUTROPHIL COUNT

Normal range: 50%-70%
Subsets:
Stabs (bands, early mature neutrophils): 2%-6%
Segs (mature neutrophils): 60%-70%
Elevated in: Acute bacterial infections, acute myocardial infarction, stress, neoplasms, myelocytic leukemia
Decreased in: Viral infections, aplastic anemias, immunosuppressive drugs, radiation therapy to bone marrow, agranulocytosis, drugs (antibiotics, antithyroidals, clopidogrel), lymphocytic and monocytic leukemias

Box 4-6 describes various drugs that can cause neutropenia. Table 4-31 describes miscellaneous inherited neutropenia disorders.

BOX 4-6 Drugs That Cause Neutropenia

Antiarrhythmics: tocainide, procainamide, propranolol, quinidine
Antibiotics: chloramphenicol, penicillins, sulfonamides, *p*-aminosalicylic acid (PAS), rifampin, vancomycin, isoniazid, nitrofurantoin
Antimalarials: dapsone, quinine, pyrimethamine
Anticonvulsants: phenytoin, mephenytoin, trimethadione, ethosuximide, carbamazepine
Hypoglycemic agents: tolbutamide, chlorpropamide
Antihistamines: cimetidine, brompheniramine, tripelennamine
Antihypertensives: methyldopa, captopril
Anti-inflammatory agents: aminopyrine, phenylbutazone, gold salts, ibuprofen, indomethacin
Antithyroid agents: propylthiouracil, methimazole, thiouracil
Diuretics: acetazolamide, hydrochlorothiazide, chlorthalidone
Phenothiazines: chlorpromazine, promazine, prochlorperazine
Immunosuppressive agents: antimetabolites
Cytotoxic agents: alkylating agents, antimetabolites, anthracyclines, *Vinca* alkaloids, cisplatin, hydroxyurea, dactinomycin
Other agents: recombinant interferons, allopurinol, ethanol, levamisole, penicillamine, zidovudine, streptokinase, carbamazepine, clopidogrel, ticlopidine

Modified from Goldman L, Ausiello D (eds): *Cecil textbook of medicine,* ed 22, Philadelphia, 2004, Saunders.

NOREPINEPHRINE

Normal range: 0-600 pg/ml
Elevated in: Pheochromocytomas, neuroblastomas, stress, vigorous exercise, certain foods (bananas, chocolate, coffee, tea, vanilla)

5′-NUCLEOTIDASE

Normal range: 2-16 IU/L (3-27 × 10^8 kat/L [CF: 1.67 × 10^8; SMI: 1 × 10^8 kat/L])
Elevated in: Biliary obstruction, metastatic neoplasms to liver, primary biliary cirrhosis, renal failure, pancreatic carcinoma, chronic active hepatitis

OSMOLALITY (serum)

Normal range: 280-300 mOsm/kg (280-300 mmol/kg [CF: 1; SMI: 1 mmol/kg])

It can also be estimated by the following formula:

$$2\left([\mathrm{Na}] + [\mathrm{K}] + \mathrm{glucose}/18 + \mathrm{BUN}/2.8\right)$$

Elevated in: Dehydration, hypernatremia, diabetes insipidus, uremia, hyperglycemia, mannitol therapy, ingestion of toxins (ethylene glycol, methanol, ethanol), hypercalcemia, diuretics
Decreased in: Syndrome of inappropriate diuretic hormone secretion, hyponatremia, overhydration, Addison's disease, hypothyroidism

OSMOLALITY, URINE

See URINE OSMOLALITY

OSMOTIC FRAGILITY TEST

Normal: Hemolysis begins at 0.50, w/v [5.0 g/L] and is complete at 0.30, w/v [3.0 g/L] NaCl.
Elevated in: Hereditary spherocytosis, hereditary stomatocytosis, spherocytosis associated with acquired immune hemolytic anemia
Decreased in: Iron deficiency anemia, thalassemias, liver disease, leptocytosis associated with asplenia

PARACENTESIS FLUID

Testing and evaluation of results:

1. Process the fluid as follows:
   a. Tube 1: LDH, glucose, albumin
   b. Tube 2: protein, specific gravity
   c. Tube 3: cell count and differential
   d. Tube 4: save until further notice
2. Draw serum LDH, protein, albumin.
3. Gram stain, AFB stain, bacterial and fungal cultures, amylase, and triglycerides should be ordered only when clearly indicated; bedside inoculation of blood-culture bottles with ascitic fluid improves sensitivity in detecting bacterial growth.
4. If malignant ascites is suspected, consider a carcinoembryonic antigen level on the paracentesis fluid and cytologic evaluation.
5. In suspected spontaneous bacterial peritonitis (SBP) the incidence of positive cultures can be increased by injecting 10 to 20 ml of ascitic fluid into blood culture bottles.

TABLE 4-31 Miscellaneous Inherited Neutropenia Disorders

Diagnosis	Genetics	Mapping	Mutant Gene	Additional Features
Hyper IgM syndrome, type 1	X-L	Xq26	*CD40L*	↓IgG, IgA, IgE, autoimmune cytopenias
Hermansky-Pudlak syndrome, type 2	AR	5q14.1	*AP3B1*	↓IgG, partial albinism, platelet dysfunction
Griscelli syndrome, type 1	AR	15q21	*MYO5A*	Neurologic dysfunction, partial albinism
Griscelli syndrome, type 2	AR	15q21	*RAB27A*	Same as type 1 plus hemophagocytosis
Chediak-Higashi syndrome	AR	1q42.1-q42.2	*LYST (CHSI)*	Immunodeficiency, partial albinism
Poikiloderma with Neutropenia	AR	16q13	*C160RF57*	Rash, short stature, dystrophic nails
P14 deficiency	AR	1q22	*MAPBPIP*	Immunodeficiency, hypopigmentation
Cohen syndrome	AR	8q22-q23	*VPS13B/COH1*	Retinopathy, retardation, skeletal anomalies
Charcot-Marie-Tooth syndrome, type 2	AD	19p13.2	*DMN2*	Axonal demyelinating neuropathy

AD, Autosomal dominant; *AR,* autosomal recessive; *Ig,* immunoglobulin; *X-L,* X-linked recessive.
Data compiled from Online Mendelian Inheritance in Man (http://ncbi.nlm.nih.gov/omim); From Hoffman R: *Hematology: basic principles and practice,* 6th ed, Philadelphia, Saunders, 2013.

6. Peritoneal effusion can be subdivided as exudative or transudative based on its characteristics (see Section II).
7. The serum-ascites albumin gradient (serum albumin level–ascitic fluid albumin level [SAAG]) correlates directly with portal pressure and can also be used to classify ascites. Patients with gradients ≥1.1 g/dl have portal hypertension, and those with gradients ≤1.1 g/dl do not; the accuracy of this method is >95%.
8. For the differential diagnosis of ascites, refer to Section II.
9. An ascitic fluid polymorphonuclear leukocyte count >500/μl is suggestive of SBP.
10. A blood-ascitic fluid albumin gradient.

PARATHYROID HORMONE (PTH)

Normal:
Serum, intact molecule 10-65 pg/ml
Plasma 1.0-5.0 pmol/L
Elevated in: Hyperparathyroidism (primary or secondary), pseudohypoparathyroidism, anticonvulsants, corticosteroids, lithium, INH, rifampin, phosphates, Zollinger-Ellison syndrome, hereditary vitamin D deficiency
Decreased in: Hypoparathyroidism, sarcoidosis, cimetidine, beta-blockers, hyperthyroidism, hypomagnesemia

PARIETAL CELL ANTIBODIES

Normal: Negative
Present in: Pernicious anemia (>90%), atrophic gastritis (up to 50%), thyroiditis (30%), Addison's disease, myasthenia gravis, Sjögren's syndrome, type 1 DM

PARTIAL THROMBOPLASTIN TIME (PTT), ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT)

See Table 4-32.
Normal range: 25-41 sec
Elevated in: Heparin therapy, coagulation factor deficiency (I, II, V, VIII, IX, X, XI, XII), liver disease, vitamin K deficiency, disseminated intravascular coagulation, circulating anticoagulant, warfarin therapy, specific factor inhibition (PCN reaction, rheumatoid arthritis), thrombolytic therapy, nephrotic syndrome
NOTE: Useful to evaluate the intrinsic coagulation system.

TABLE 4-32 Clinical Peculiarities of Coagulation Protein Screening Tests

Long aPTT, normal or long PT, no bleeding	Normal aPTT, PT, *with bleeding*
Long aPTT Only	
Factor XII deficiency	Factor XIII deficiency or inhibitor
Prekallikrein deficiency	α_2-Antiplasmin deficiency or defect
High-molecular-weight kininogen	Plasminogen activator inhibitor deficiency or defect
Lupus anticoagulant	α_1-Antitrypsin Pittsburgh defect
Long aPTT and PT	
Dysfibrinogenemia with fibrinopeptide B release	
Lupus anticoagulant	

From Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

PEPSINOGEN I

Normal: 124-142 ng/ml
Elevated in: ZE syndrome, duodenal ulcer, acute gastritis
Decreased in: Atrophic gastritis, gastric carcinoma, myxedema, pernicious anemia, Addison's disease

pH, BLOOD

Normal values:
Arterial: 7.35-7.45
Venous: 7.32-7.42
For abnormal values, refer to ARTERIAL BLOOD GASES.

pH, URINE

See URINE pH

PHENOBARBITAL

Normal therapeutic range: 15-30 mcg/ml for epilepsy control

PHENYTOIN (Dilantin)

Normal therapeutic range: 10-20 mcg/ml

PHOSPHATASE, ACID

See ACID PHOSPHATASE

PHOSPHATASE, ALKALINE

See ALKALINE PHOSPHATASE

PHOSPHATE (serum)

Normal range: 2.5-5 mg/dl (0.8-1.6 mmol/L [CF: 0.3229; SMI: 0.05 mmol/L])
DECREASED
Parenteral hyperalimentation
Diabetic acidosis
Alcohol withdrawal
Severe metabolic or respiratory alkalosis
Antacids that bind phosphorus
Malnutrition with refeeding using low-phosphorus nutrients
Renal tubule failure to reabsorb phosphate (Fanconi's syndrome; congenital disorder; vitamin D deficiency)
Glucose administration
Nasogastric suction
Malabsorption
Gram-negative sepsis
Primary hyperthyroidism
Chlorothiazide diuretics
Therapy of acute severe asthma
Acute respiratory failure with mechanical ventilation
INCREASED
Renal failure
Severe muscle injury
Phosphate-containing antacids
Hypoparathyroidism
Tumor lysis syndrome

PLASMINOGEN

Normal: Immunoassay (antigen): <20 mg/dl
Elevated in: Infection, trauma, neoplasm, myocardial infarction (acute phase reactant), pregnancy, bilirubinemia
Decreased in: DIC, severe liver disease, thrombolytic therapy with streptokinase or urokinase, alteplase

PLATELET AGGREGATION

Normal: Full aggregation (generally >60%) in response to epinephrine, thrombin, ristocetin, ADP, collagen
Elevated in: Heparin, hemolysis, lipemia, nicotine, hereditary and acquired disorders of platelet adhesion, activation, and aggregation
Decreased in: Aspirin, some penicillins, chloroquine, chlorpromazine, clofibrate, captopril, Glanzmann's thrombasthenia, Bernard-Soulier syndrome, Wiskott-Aldrich syndrome, cyclooxygenase deficiency. In von Willebrand's disease there is normal aggregation with ADP, collagen, and epinephrine but abnormal agglutination with ristocetin.

PLATELET ANTIBODIES

Normal: Absent
Present in: ITP (>90% of patients with chronic ITP). Patients with nonimmune thrombocytopenias may have false-positive results.

PLATELET COUNT

See Fig. E4-27 for evaluation of thrombocytosis. Box E4-7 describes testing for thrombocytopenia. See Table 4-33 for differential diagnosis.
Normal range: 130-400 × 10^3/mm^3 (130-400 × 10^9/L [CF: 1; SMI: 5 × 10^9/L])

Platelet Count

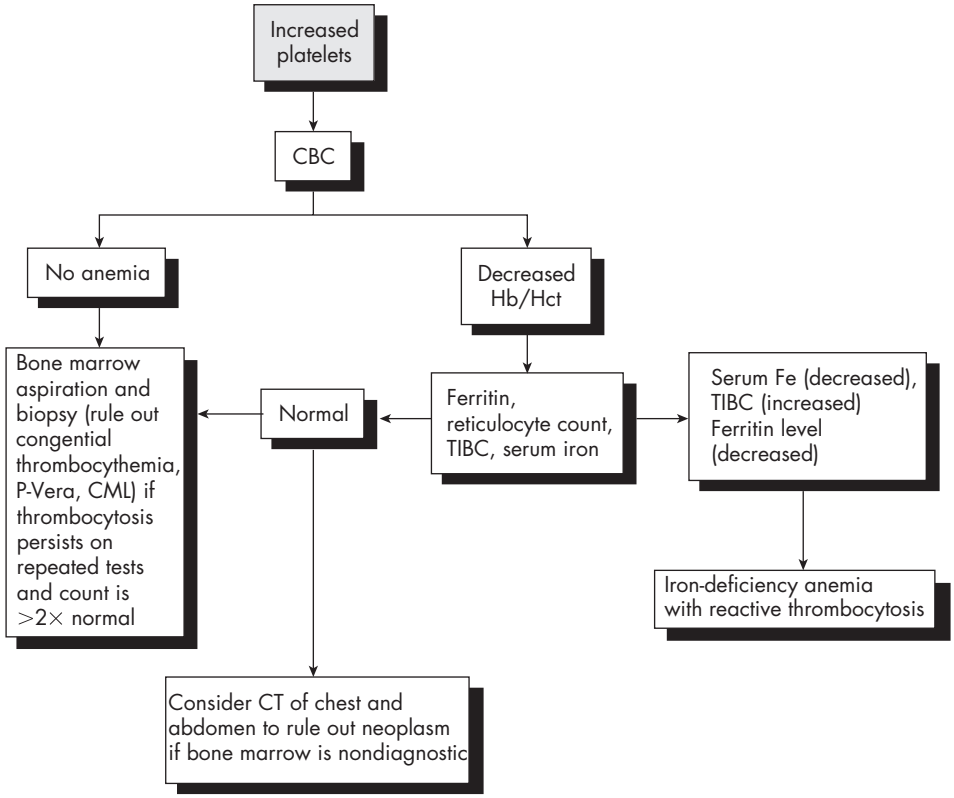


FIGURE E4-27 Thrombocytosis diagnosis. *CBC,* Complete blood count; *CML,* chronic myelogenous leukemia; *CT,* computed tomography; *Fe,* iron; *Hb/Hct,* hemoglobin/hematocrit; *TIBC,* total iron-binding capacity. (From Ferri FF: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging*, ed 3, Philadelphia, 2011, Elsevier Mosby.)

BOX E4-7 Thrombocytopenia

Diagnostic Imaging **Best Test** None **Ancillary Test** CT of abdomen if splenomegaly is present	**Lab Evaluation** **Best Test** Bone marrow examination **Ancillary Tests** CBC, PT, PTT LDH HIV, ANA Antiplatelet Ab D-dimer Coombs tests

ANA, Antibody to nuclear antigens; *CBC,* complete blood count; *CT,* computed tomography; *HIV,* human immunodeficiency virus; *LDH,* lactic dehydrogenase; *PT,* prothrombin time; *PTT,* partial thromboplastin time.
From Ferri FF: *Ferri's best test: a practical guide to clinical laboratory medicine and diagnostic imaging,* ed 3, Philadelphia, 2014, Elsevier Mosby.

TABLE 4-33 Differential Diagnosis of Thrombocytopenia in Suspected Disseminated Intravascular Coagulation

Differential Diagnosis	Additional Diagnostic Clues
DIC	Prolonged aPTT and PT, increased FDP, low levels of AT or protein C
Sepsis without DIC	Positive (blood) cultures, positive sepsis criteria, hematophagocytosis in BM aspirate
Massive blood loss	Major bleeding, low hemoglobin, prolonged aPTT and PT
Thrombotic microangiopathy	Schistocytes in blood smear, Coombs-negative hemolysis, fever, neurologic symptoms, renal insufficiency, coagulation test results usually normal, ADAMTS13 levels decreased
Heparin-induced thrombocytopenia	Use of heparin, venous or arterial thrombosis, positive HIT test (usually immunoassay for heparin-platelet factor 4 antibodies), increase in platelet count after cessation of heparin; coagulation tests usually normal
Immune thrombocytopenia	Antiplatelet antibodies, normal or increased number of megakaryocytes in BM aspirate, TPO decreased; coagulation tests usually normal
Drug-induced thrombocytopenia	Decreased number of megakaryocytes in BM aspirate or detection of drug-induced antiplatelet antibodies, increase in platelet count after cessation of drug; coagulation test results usually normal

ADAMTS13, A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; *aPTT,* activated partial thromboplastin time; *AT,* antithrombin; *BM,* bone marrow; *DIC,* disseminated intravascular coagulation; *FDP,* fibrin degradation product; *HIT,* heparin-induced thrombocytopenia; *PT,* prothrombin time; TPO, thrombopoietin.
From Hoffman R: *Hematology, basic principles and practice,* ed 6, Philadelphia, Saunders, 2013.

Elevated in:
Reactive Thrombocytosis
Infections or inflammatory states: vasculitis, allergic reactions, etc.
Surgery and tissue damage: myocardial infarction, pancreatitis, etc.
Postsplenectomy state
Malignancy: solid tumors, lymphoma
Iron deficiency anemia, hemolytic anemia, acute blood loss
Uncertain etiology
Rebound effect after chemotherapy or immune thrombocytopenia
Renal disorders: renal failure, nephrotic syndrome
MYELOPROLIFERATIVE DISORDERS
Chronic myeloid leukemia
Primary thrombocythemia
Polycythemia vera
Idiopathic myelofibrosis
Decreased:
A. Increased destruction
   1. Immunologic
      a. Drugs: quinine, quinidine, digitalis, procainamide, thiazide diuretics, sulfonamides, phenytoin, aspirin, penicillin, heparin, gold, meprobamate, sulfa drugs, phenylbutazone, NSAIDs, methyldopa, cimetidine, furosemide, INH, cephalosporins, chlorpropamide, organic arsenicals, chloroquine
      b. Idiopathic thrombocytopenic purpura
      c. Transfusion reaction: transfusion of platelets with platelet antigen HPA-1a (PL^{A1}) in recipients without PL^{A1}
      d. Fetal/maternal incompatibility
      e. Vasculitis (e.g., systemic lupus erythematosus)
      f. Autoimmune hemolytic anemia
      g. Lymphoreticular disorders (e.g., chronic lymphocytic leukemia)
   2. Nonimmunologic
      a. Prosthetic heart valves
      b. Thrombotic thrombocytopenic purpura
      c. Sepsis
      d. Disseminated intravascular coagulation
      e. Hemolytic-uremic syndrome
      f. Giant cavernous hemangioma
B. Decreased production
   1. Abnormal marrow
      a. Marrow infiltration (e.g., leukemia, lymphoma, fibrosis)
      b. Marrow suppression (e.g., chemotherapy, alcohol, radiation)
   2. Hereditary disorders
      a. Wiskott-Aldrich syndrome: X-linked disorder characterized by thrombocytopenia, eczema, and repeated infections
      b. May-Hegglin anomaly: increased megakaryocytes but ineffective thrombopoiesis
   3. Vitamin deficiencies (e.g., vitamin B_{12}, folic acid)
C. Splenic sequestration, hypersplenism
D. Dilutional, secondary to massive transfusion

PLATELET FUNCTION ANALYSIS 100 ASSAY (PFA)

Normal: This test is a two-component assay where blood is aspirated through two capillary tubes, one of which is coated with collagen and ADP (COL/ADP) and the other with collagen and epinephrine (COL/EPI). The test measures the ability of platelets to occlude an aperture in a biologically active membrane treated with COL/ADP and COL/EPI. During the test, the platelets adhere to the surface of the tube and cause blood flow to cease. The closing time refers to the cessation of blood flow and is reported in conjunction with the hematocrit and platelet count. Hematocrit count must be >25% and platelet count >50 K/microliter for the test to be performed
COL/ADP: 70-120 sec
COL/EPI: 75-120 sec
Elevated in: Acquired platelet dysfunction, von Willebrand's disease, anemia, thrombocytopenia, use of aspirin and NSAIDs

POTASSIUM (serum)

Normal range: 3.5-5 mEq/L (3.5-5 mmol/L [CF: 1; SMI: 0.1 mmol/L])
CAUSES OF HYPERKALEMIA
See Fig. E4-28 for evaluation and treatment of hyperkalemia, and Fig. E4-29 for electrocardiographic changes in hyperkalemia.)
I. Pseudohyperkalemia
   A. Hemolysis of sample
   B. Thrombocytosis
   C. Leukocytosis
   D. Laboratory error
II. Increased potassium intake and absorption
   A. Potassium supplements (oral and parenteral)
   B. Dietary: salt substitutes
   C. Stored blood
   D. Potassium-containing medications
III. Impaired renal excretion
   A. Acute renal failure
   B. Chronic renal failure
   C. Tubular defect in potassium secretion
      1. Renal allograft
      2. Analgesic nephropathy
      3. Sickle cell disease
      4. Obstructive uropathy
   D. Hypoaldosteronism
      1. Primary (Addison's disease)
      2. Secondary
         a. Hyporeninemic hypoaldosteronism (type IV RTA)
         b. Congenital adrenal hyperplasia
         c. Drug-induced
            (1) NSAIDs
            (2) ACE inhibitors
            (3) Heparin
            (4) Cyclosporine
IV. Transcellular shifts
   A. Acidosis
   B. Hypertonicity
   C. Insulin deficiency
   D. Drugs
      1. β-blockers

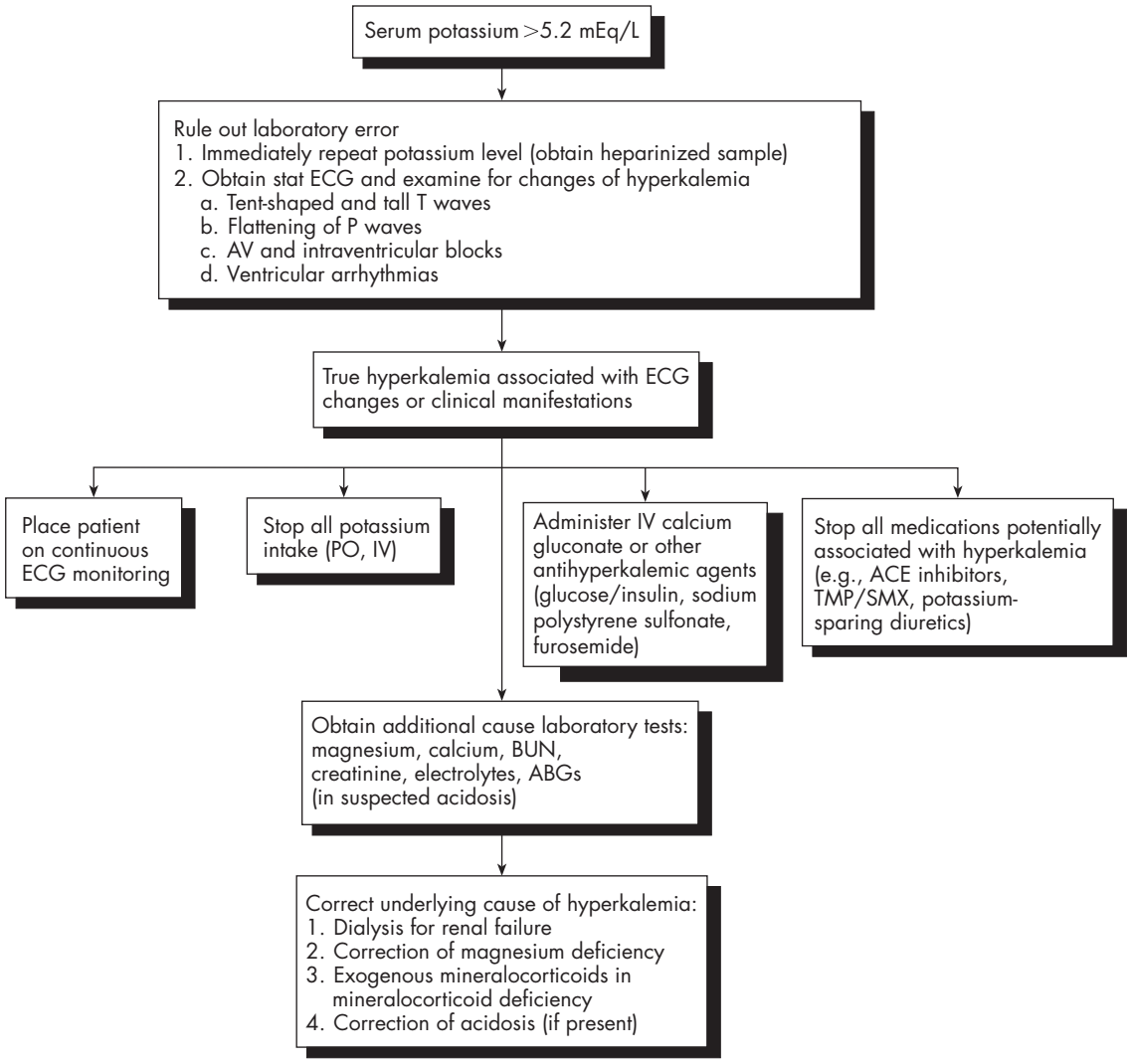


FIGURE E4-28 Evaluation and treatment of hyperkalemia. *ABGs,* Arterial blood gases; *ACE,* angiotensin-converting enzyme; *AV,* atrioventricular; *BUN,* blood urea nitrogen; *ECG,* electrocardiogram; *IV,* intravenous; *PO,* oral; *TMP/SMX,* trimethoprim-sulfamethoxazole. (From Ferri F: *Practical guide to the care of the medical patient,* ed 9, St Louis, 2014, Mosby.)

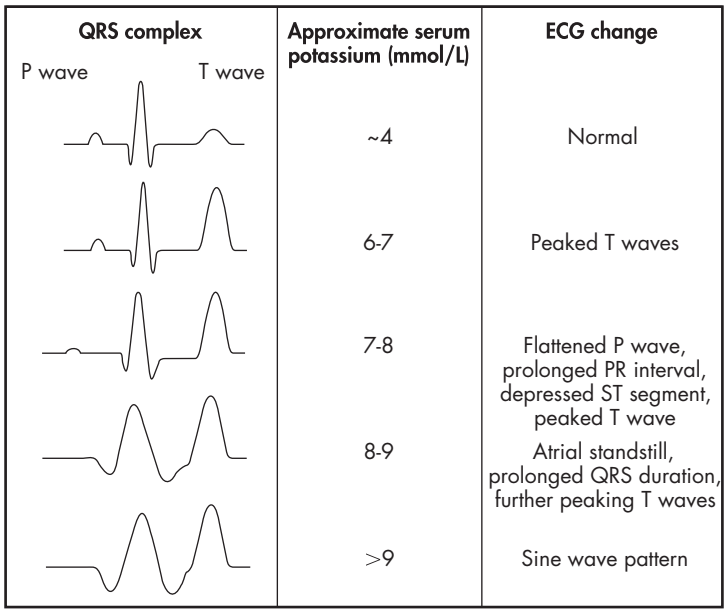


FIGURE E4-29 Electrocardiographic changes in hyperkalemia. Progressive hyperkalemia results in identifiable changes in the electrocardiogram *(ECG).* These include peaking of the T wave, flattening of the P wave, prolongation of the PR interval, ST segment depression, prolongation of the QRS complex, and, eventually, progression to a sine wave pattern. Ventricular fibrillation may occur at any time during this progression. (From Feehally J, Floege J, Johnson RJ: *Comprehensive clinical nephrology,* ed 3, St Louis, 2007, Mosby.)

2. Digitalis toxicity
3. Succinylcholine

E. Exercise
F. Hyperkalemic periodic paralysis

V. Cellular injury
A. Rhabdomyolysis
B. Severe intravascular hemolysis
C. Acute tumor lysis syndrome
D. Burns and crush injuries

CAUSES OF HYPOKALEMIA

I. Decreased intake
A. Decreased dietary potassium
B. Impaired absorption of potassium
C. Clay ingestion
D. Kayexalate

II. Increased loss
A. Renal
1. Hyperaldosteronism
a. Primary
(1) Conn's syndrome
(2) Adrenal hyperplasia
b. Secondary
(1) Congestive heart failure
(2) Cirrhosis
(3) Nephrotic syndrome
(4) Dehydration
c. Bartter's syndrome
2. Glycyrrhizic acid (licorice, chewing tobacco)
3. Excessive adrenal corticosteroids
a. Cushing's syndrome
b. Steroid therapy
c. Adrenogenital syndrome
4. Renal tubular defects
a. Renal tubular acidosis
b. Obstructive uropathy
c. Salt-wasting nephropathy
5. Drugs
a. Diuretics
b. Aminoglycosides
c. Mannitol
d. Amphotericin
e. Cisplatin
f. Carbenicillin

B. Gastrointestinal
1. Vomiting
2. Nasogastric suction
3. Diarrhea
4. Malabsorption
5. Ileostomy
6. Villous adenoma
7. Laxative abuse

C. Increased losses from the skin
1. Excessive sweating
2. Burns

III. Transcellular shifts
A. Alkalosis
1. Vomiting
2. Diuretics
3. Hyperventilation
4. Bicarbonate therapy

B. Insulin
1. Exogenous
2. Endogenous response to glucose

C. β_2-Agonists (albuterol, terbutaline, epinephrine)
D. Hypokalemia periodic paralysis
1. Familial
2. Thyrotoxic

IV. Miscellaneous
A. Anabolic state
B. Intravenous hyperalimentation
C. Treatment of megaloblastic anemia
D. Acute mountain sickness

POTASSIUM, URINE

See URINE POTASSIUM

PROCAINAMIDE

Normal therapeutic range: 4-10 mcg/ml

PROGESTERONE (serum)

Normal:
Female: Follicular phase: 15-70 ng/dl
Luteal phase: 200-2500 ng/dl
Male: 15-70 ng/dl
Elevated in: Congenital adrenal hyperplasia, clomiphene, corticosterone, 11-deoxycortisol, dihydroprogesterone, molar pregnancy, lipoid ovarian tumor
Decreased in: Primary or secondary hypogonadism, oral contraceptives, ampicillin, threatened abortion

PROLACTIN

See Fig. E4-30 for the evaluation of hyperprolactinemia.
Normal range: <20 ng/ml (<20 μg/L [CF: 1; SMI: 1 μg/L])
Elevated in: Prolactinomas (level >200 highly suggestive), drugs (phenothiazines, cimetidine, tricyclic antidepressants, metoclopramide, estrogens, antihypertensives [methyldopa], verapamil, haloperidol), postpartum, stress, hypoglycemia, hypothyroidism

PROSTATE-SPECIFIC ANTIGEN (PSA)

Normal range: 0-4 ng/ml
Table 4-34 describes age-specific reference ranges for PSA.
Elevated in: Benign prostatic hypertrophy, carcinoma of prostate, prostatitis, postrectal examination, prostate trauma.
Factors affecting serum PSA are described in Table 4-35.

TABLE 4-34 Age-Specific Reference Ranges for PSA

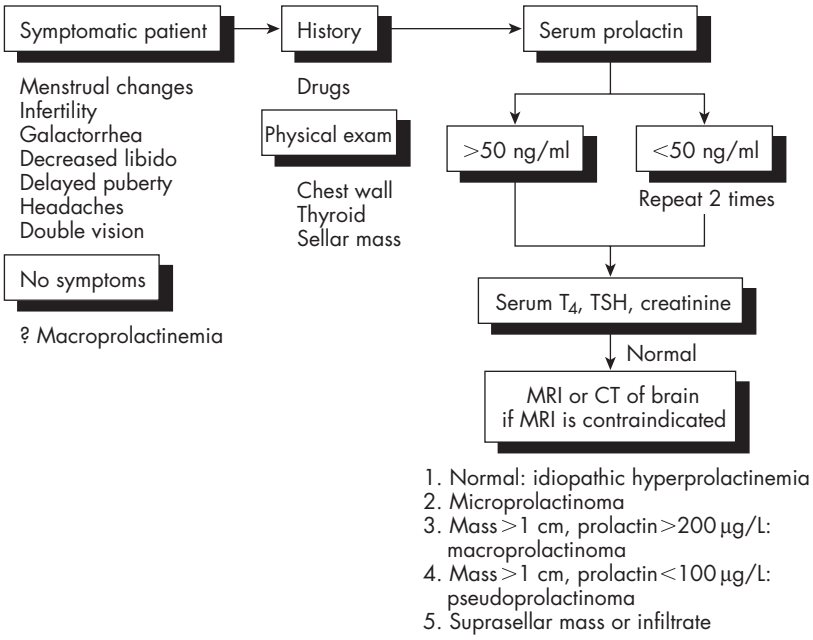
	Serum PSA (ng/ml)		
Age (yr)	Whites	Japanese	African Americans
40-49	0-2.5	0-2.0	0-2.0
50-59	0-3.5	0-3.0	0-4.0
60-69	0-4.5	0-4.0	0-4.5
70-79	0-6.5	0-5.0	0-5.5

PSA, Prostate-specific antigen.
From Nseyo UO (ed): *Urology for primary care physicians,* Philadelphia, 1999, Saunders.

TABLE 4-35 Factors Affecting Serum PSA

Factors Affecting Serum PSA	Duration of Effect
Prostate cell number	NA
Prostate size	NA
Recent ejaculation	6-48 hours
Prostate manipulation	
Vigorous massage	1 week
Cystoscopy	1 week
Prostate biopsy	4-6 weeks
Prostatitis	
Acute	3-6 months
Chronic	Unknown
Prostate cancer	NA
Drugs: finasteride*	3-6 months

*Lowers PSA for as long as patient is on the medication.
NA, Not applicable; *PSA,* prostate-specific antigen.
From Nseyo UO (ed): *Urology for primary care physicians,* Philadelphia, 1999, Saunders.



NOTE: Refer to Section I for additional information on Prolactinoma.

FIGURE E4-30 Approach to hyperprolactinemia. *CT,* Computed tomography; *MRI,* magnetic resonance imaging; *T4,* thyroxine; *TSH,* thyroid-stimulating hormone. (From Copeland LJ: *Textbook of gynecology,* ed 2, Philadelphia, 2000, Saunders.)

NOTE: Measurement of free PSA is useful to assess the probability of prostate cancer in patients with normal digital rectal examination and total PSA between 4 and 10 ng/ml. In these patients, the global risk of prostate cancer is 25%; however, if the free PSA is >25%, the risk of prostate cancer decreases to 8%, whereas if the free PSA is <10%, the risk of cancer increases to 56%. Free PSA is also useful to evaluate the aggressiveness of prostate cancer. A low free PSA percentage generally indicates a high-grade cancer, whereas a high free PSA percentage is generally associated with a slower-growing tumor.
Decreased in: 5-α reductase inhibitors (finasteride, dutasteride), saw palmetto use, antiandrogens

PROSTATIC ACID PHOSPHATASE

Normal: 0-0.8 U/L
Elevated in: Prostate cancer (especially in metastatic prostate cancer), BPH, prostatitis, post-prostate surgery or manipulation, hemolysis, androgens, clofibrate
Decreased in: Ketoconazole

PROTEIN (serum)

Normal range: 6-8 g/dl (60-80 g/L [CF: 10; SMI: 1 g/L])
Elevated in: Dehydration, multiple myeloma, Waldenström's macroglobulinemia, sarcoidosis, collagen vascular diseases
Decreased in: Malnutrition, low-protein diet, overhydration, malabsorption, pregnancy, severe burns, neoplasms, chronic diseases, cirrhosis, nephrosis

PROTEIN C ASSAY

See Table 4-36.
Normal: 70%-140%
Elevated in: Oral contraceptives, stanozol
Decreased in: Congenital protein C deficiency, warfarin therapy, Vitamin K deficiency, renal insufficiency, consumptive coagulopathies

TABLE 4-36 Assay Measurement in Heterozygote Protein C Deficiency

	ACTIVITY		
Type	**Antigen**	**Amidolytic**	**Coagulant**
I	Low	Low	Low
II	Normal	Low	Low
	Normal	Normal	Low

From Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

PROTEIN ELECTROPHORESIS (serum)

Normal range:
Albumin: 60%-75% (0.6-0.75 [CF: 0.01; SMI: 0.01])
α-1: 1.7%-5% (0.02-0.05)
α-2: 6.7%-12.5% (0.07-0.13)
β: 8.3%-16.3% (0.08-0.16)
γ: 10.7%-20% (0.11-0.2)
Albumin: 3.6-5.2 g/dl (36-52 g/L [CF: 0.01; SMI: 1 g/L])
α-1: 0.1-0.4 g/dl (1-4 g/L)
α-2: 0.4-1 g/dl (4-10 g/L)
β: 0.5-1.2 g/dl (5-12 g/L)
γ: 0.6-1.6 g/dl (6-16 g/L)
Elevated in:
Albumin: dehydration
α-1: neoplastic diseases, inflammation
α-2: neoplasms, inflammation, infection, nephrotic syndrome
β: hypothyroidism, biliary cirrhosis, diabetes mellitus
γ: See IMMUNOGLOBULINS
Decreased in: Albumin: malnutrition, chronic liver disease, malabsorption, nephrotic syndrome, burns, systemic lupus erythematosus
α-1: emphysema (α-1 antitrypsin deficiency), nephrosis
α-2: hemolytic anemias (decreased haptoglobin), severe hepatocellular damage
β: hypocholesterolemia, nephrosis
γ: See IMMUNOGLOBULINS
Fig. 4-31 describes serum protein electrophoretic patterns.

PROTEIN S ASSAY

See Table 4-37.
Normal: 65%-140%
Elevated in: Presence of lupus anticoagulant
Decreased in: Hereditary deficiency, acute thrombotic events, DIC, surgery, oral contraceptives, pregnancy, hormone replacement therapy, l-asparaginase treatment

TABLE 4-37 Assay Measurements in Heterozygote Protein S Deficiency

	ACTIVITY		
Type	**Protein S Total Antigen**	**Protein S Free Antigen**	**Protein S Activity**
I (classic)	Low	Low	Low
II	Normal	Normal	Low
III	Normal	Low	Low

From Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

PROTHROMBIN TIME (PT)

Normal range: 10-12 sec
Elevated in: Liver disease, oral anticoagulants (warfarin), heparin, factor deficiency (I, II, V, VII, X), disseminated intravascular coagulation, vitamin K deficiency, afibrinogenemia, dysfibrinogenemia, drugs (salicylate, chloral hydrate, diphenylhydantoin, estrogens, antacids, phenylbutazone, quinidine, antibiotics, allopurinol, anabolic steroids)
Decreased in: Vitamin K supplementation, thrombophlebitis, drugs (glutethimide, estrogens, griseofulvin, diphenhydramine)

PROTOPORPHYRIN (Free erythrocyte)

Normal range: 16-36 μg/dl of red blood cells (0.28-0.64 μmol/L [CF: 0.0177; SMI: 0.02 μmol/L])
Elevated in: Iron deficiency, lead poisoning, sideroblastic anemias, anemia of chronic disease, hemolytic anemias, erythropoietic protoporphyria

PSA

See PROSTATE-SPECIFIC ANTIGEN

PT

See PROTHROMBIN TIME

PTH

See PARATHYROID HORMONE

PTT

See PARTIAL THROMBOPLASTIN TIME

RAPID PLASMA REAGIN (RPR)

Description: Non-treponemal test traditionally used as a screening test for syphilis. It is a quantitative test and antibody titers can be monitored to assess treatment response.
Normal: Negative
Positive: Syphilis. False positive results may occur with pregnancy, autoimmune diseases, tuberculosis, and other inflammatory conditions. Positive results should be confirmed with treponemal serologic tests (e.g., T-pallidum enzyme immunoassay [TP-EIA])

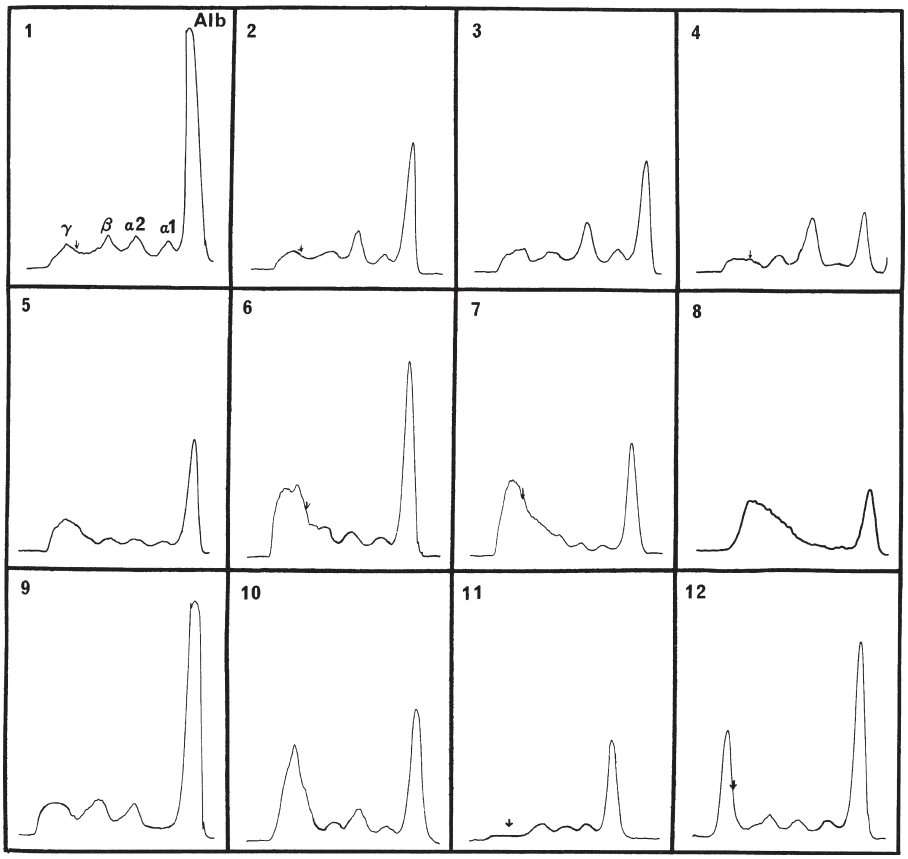


FIGURE 4-31 Typical serum protein electrophoretic patterns. ***1,*** Normal (*arrow* near γ region indicates serum application point). ***2,*** Acute reaction pattern. ***3,*** Acute reaction or nephrotic syndrome. ***4,*** Nephrotic syndrome. ***5,*** Chronic inflammation, cirrhosis, granulomatous diseases, rheumatoid-collagen group. ***6,*** Same as 5, but γ elevation is more pronounced. There is also partial (but not complete) β-γ fusion. ***7,*** Suggestive of cirrhosis but could be found in the granulomatous diseases or the rheumatoid-collagen group. ***8,*** Characteristic pattern of cirrhosis. ***9,*** α-1 Antitrypsin deficiency with mild γ elevation suggesting concurrent chronic disease. ***10,*** Same as 5, but the γ elevation is marked. The configuration of the γ peak superficially mimics that of myeloma, but is more broad-based. There are superimposed acute reaction changes. ***11,*** Hypogammaglobulinemia or light-chain myeloma. ***12,*** Myeloma, Waldenström's macroglobulinemia, idiopathic or secondary monoclonal gammopathy. (From Ravel R [ed]: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.)

RDW

See RED BLOOD CELL DISTRIBUTION WIDTH

RED BLOOD CELL (RBC) COUNT

Normal range:
Male: 4.3-5.9 × 10^6/mm^3 (4.3-5.9 × 10^{12}/L [CF: 1; SMI: 0.1 × 10^{12}/L])
Female: 3.5-5 × 10^6/mm^3 (3.5-5 × 10^{12}/L [CF: 1; SMI: 0.1 × 10^{12}/L])
Elevated in: Polycythemia vera, smokers, high altitude, cardiovascular disease, renal cell carcinoma and other erythropoietin-producing neoplasms, stress, hemoconcentration/dehydration
Decreased in: Anemias, hemolysis, chronic renal failure, hemorrhage, failure of marrow production

RED BLOOD CELL DISTRIBUTION WIDTH (RDW)

Measures variability of red cell size (anisocytosis)
Normal range: 11.5-14.5
Normal RDW and elevated mean corpuscular volume (MCV): Aplastic anemia, preleukemia
Normal MCV: Normal, anemia of chronic disease, acute blood loss or hemolysis, chronic lymphocytic leukemia (CLL), chronic myelocytic leukemia, nonanemic enzymopathy or hemoglobinopathy
Decreased MCV: Anemia of chronic disease, heterozygous thalassemia
Elevated RDW and elevated MCV: Vitamin B_{12} deficiency, folate deficiency, immune hemolytic anemia, cold agglutinins, CLL with high count, liver disease
Normal MCV: Early iron deficiency, early vitamin B_{12} deficiency, early folate deficiency, anemic globinopathy
Decreased MCV: Iron deficiency, red blood cell fragmentation, HbH disease, thalassemia intermedia

RED BLOOD CELL FOLATE

See FOLATE

RED BLOOD CELL MASS (volume)

Normal range:
Male: 20-36 ml/kg body weight (1.15-1.21 L/m^2 body surface area)
Female: 19-31 ml/kg body weight (0.95-1.00 L/m^2 body surface area)
Elevated in: Polycythemia vera, hypoxia (smokers, high altitude, cardiovascular disease), hemoglobinopathies with high oxygen affinity, erythropoietin-producing tumors (renal cell carcinoma)
Decreased in: Hemorrhage, chronic disease, failure of marrow production, anemias, hemolysis

RED BLOOD CELL MORPHOLOGY

See Fig. 4-32.

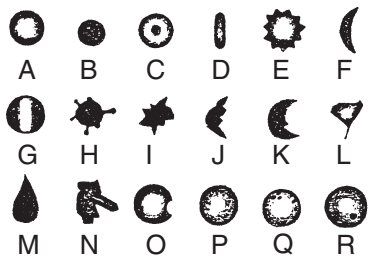


FIGURE 4-32 Abnormal red blood cells (RBCs). A, Normal RBC. **B,** Spherocyte. **C,** Target cell. **D,** Elliptocyte. **E,** Echinocyte. **F,** Sickle cell. **G,** Stomatocyte. **H,** Acanthocyte. **I** to **L,** Schistocytes. **M,** Teardrop RBC. **N,** Distorted RBC with Hb C crystal protruding. **O,** Degmacyte. **P,** Basophilic stippling. **Q,** Pappenheimer bodies. **R,** Howell-Jolly body. (From Ravel R [ed]: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.)

RENIN (SERUM)

Elevated in: Drugs (thiazides, estrogen, minoxidil), chronic renal failure, Bartter's syndrome, pregnancy (normal), pheochromocytoma, renal hypertension, reduced plasma volume, secondary aldosteronism
Decreased in: Adrenocortical hypertension, increased plasma volume, primary aldosteronism, drugs (propranolol, reserpine, clonidine)

Table 4-38 describes typical renin-aldosterone patterns in various conditions.

TABLE 4-38 Typical Renin-Aldosterone Patterns in Various Conditions

	Plasma Renin	Aldosterone
Primary aldosteronism	Low	High
"Low-renin" essential hypertension	Low	Normal
Cushing's syndrome	Low	Low-normal
Licorice ingestion syndrome	Low	Low
High-salt diet	Low	Low
Oral contraceptives	High	Normal
Cirrhosis	High	High
Malignant hypertension	High	High
Unilateral renal disease	High	High
"High-renin" essential hypertension	High	High
Pregnancy	High	High
Diuretic overuse	High	High
Juxtaglomerular tumor (Bartter's syndrome)	High	High
Low-salt diet	High	High
Addison's disease	High	Low
Hypokalemia	High	Low

From Ravel R: *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.

RESPIRATORY SYNCYTIAL VIRUS (RSV) SCREEN

Test description: PCR test can be performed on nasopharyngeal swab, wash, or aspirate

RETICULOCYTE COUNT

See Fig. E4-33 and Table 4-39.
Normal range: 0.5%-1.5%
Elevated in: Hemolytic anemia (sickle cell crisis, thalassemia major, autoimmune hemolysis), hemorrhage, postanemia therapy (folic acid, ferrous sulfate, vitamin B_{12}), chronic renal failure
Decreased in: Aplastic anemia, marrow suppression (sepsis, chemotherapeutic agents, radiation), hepatic cirrhosis, blood transfusion, anemias of disordered maturation (iron deficiency anemia, megaloblastic anemia, sideroblastic anemia, anemia of chronic disease)

TABLE 4-39 Combining the Reticulocyte Count and Red Blood Cell Parameters for Diagnosis

MCV, RDW	Reticulocyte Count <75,000/µL	Reticulocyte Count >100,000/µL
Low, Normal	Anemia of chronic disease	
Normal, Normal	Anemia of chronic disease	
High, Normal	Chemotherapy/antivirals/alcohol Aplastic anemia	Chronic liver disease
Low, High	Iron deficiency anemia	Sickle cell-β-thalassemia
Normal, High	Early iron, folate, vitamin B_{12} deficiency Myelodysplasia	Sickle cell anemia, sickle cell disease
High, High	Folate or vitamin B_{12} deficiency Myelodysplasia	Immune hemolytic anemia Chronic liver disease

MCV, Mean corpuscular volume; *RDW,* red blood cell distribution width.
From Hoffman R et al: *Hematology: basic principles and practice,* ed 5, Philadelphia, 2009, Churchill Livingstone.

RHEUMATOID FACTOR

Normal: Negative. Present in titer >1:20
RHEUMATIC DISEASES
Rheumatoid arthritis
Sjögren's syndrome
Systemic lupus erythematosus
Polymyositis/dermatomyositis
Mixed connective tissue disease
Scleroderma
INFECTIOUS DISEASES
Subacute bacterial endocarditis
Tuberculosis
Infectious mononucleosis
Hepatitis
Syphilis
Leprosy
Influenza
MALIGNANCIES
Lymphoma
Multiple myeloma
Waldenström's macroglobulinemia
Postradiation or postchemotherapy
MISCELLANEOUS
Normal adults, especially the elderly
Sarcoidosis
Chronic pulmonary disease (interstitial fibrosis)
Chronic liver disease (chronic active hepatitis, cirrhosis)
Mixed essential cryoglobulinemia
Hypergammaglobulinemic purpura

RNP

See EXTRACTABLE NUCLEAR ANTIGEN

RPR

See RAPID PLASMA REAGIN

ROTAVIRUS SEROLOGY

Test description: PCR test is performed on stool specimen
Normal: Negative

SED RATE

See ERYTHROCYTE SEDIMENTATION RATE

SEDIMENTATION RATE

See ERYTHROCYTE SEDIMENTATION RATE

SEMEN ANALYSIS

Table 4-40 describes semen analysis reference ranges.

FIGURE E4-33 Differential diagnosis of elevated reticulocyte count. *DIC,* Disseminated intravascular coagulation; *G6PD,* glucose-6-phosphate dehydrogenase; *HIV,* human immunodeficiency virus; *LDH,* lactic dehydrogenase; *TTP,* thrombotic thrombocytopenic purpura. (From Rakel RE [ed]: *Principles of family practice,* ed 7, Philadelphia, 2007, Saunders.)

TABLE 4-40 Semen Analysis Reference Ranges

Color	Grayish white
pH	7.3-7.8 (literature range, 7.0-7.8)
Volume	2.0-5.0 ml (literature range, 1.5-6.0 ml)
Sperm count	20-250 million/ml (literature range for upper limit varies from 100-250 million/ml)
Motility	>60% motile <3 hours after specimen is obtained (literature range, >40% to >70%)
% Normal sperm	>60% (literature range, >60% to >70%)
Viscosity	Can be poured from a pipet in droplets rather than a thick strand

From Ravel R (ed): *Clinical laboratory medicine,* ed 6, St Louis, 1995, Mosby.

SGOT

See ASPARTATE AMINOTRANSFERASE

SGPT

See ALANINE AMINOTRANSFERASE

SICKLE CELL TEST

Normal: Negative
Positive in: Sickle cell anemia, sickle cell trait, combination of *Hb S* gene with other disorders such as alpha-thalassemia, beta-thalassemia.

SMOOTH MUSCLE ANTIBODY

Normal: Negative
Present in: Chronic acute hepatitis, primary sclerosing cholangitis, primary biliary cirrhosis, autoimmune hepatitis, infectious mononucleosis

SODIUM (serum)

Normal range: 135-147 mEq/L (135-147 mmol/L [CF: 1; SMI: 1 mmol/L])
HYPONATREMIA
Table E4-41 describes drugs associated with hyponatremia.
A. Sodium and water depletion (deficit hyponatremia)
   1. Loss of gastrointestinal secretions with replacement of fluid but not electrolytes
      a. Vomiting
      b. Diarrhea
      c. Tube drainage
   2. Loss from skin with replacement of fluids but not electrolytes
      a. Excessive sweating
      b. Extensive burns
   3. Loss from kidney
      a. Diuretics
      b. Chronic renal insufficiency (uremia) with acidosis
   4. Metabolic loss
      a. Starvation with acidosis
      b. Diabetic acidosis
   5. Endocrine loss
      a. Addison's disease
      b. Sudden withdrawal of long-term steroid therapy
   6. Iatrogenic loss from serous cavities
      a. Paracentesis or thoracentesis
B. Excessive water (dilution hyponatremia)
   1. Excessive water administration
   2. Congestive heart failure
   3. Cirrhosis
   4. Nephrotic syndrome
   5. Hypoalbuminemia (severe)
   6. Acute renal failure with oliguria
C. Inappropriate antidiuretic hormone (IADH) syndrome
D. Intracellular loss (reset osmostat syndrome)
E. False hyponatremia (actually a dilutional effect)
   1. Marked hypertriglyceridemia
   2. Marked hyperproteinemia
   3. Severe hyperglycemia

HYPERNATREMIA
Dehydration is the most frequent overall clinical finding in hypernatremia.
1. Deficient water intake (either orally or intravenously)
2. Excess kidney water output (diabetes insipidus, osmotic diuresis)
3. Excess skin water output (excess sweating, loss from burns)
4. Excess gastrointestinal tract output (severe protracted vomiting or diarrhea without fluid therapy)
5. Accidental sodium overdose
6. High-protein tube feedings

STREPTOZYME

See ANTISTREPTOLYSIN O TITER

SUCROSE HEMOLYSIS TEST (sugar water test)

Normal: Absence of hemolysis
Positive in:
Paroxysmal nocturnal hemoglobinuria
False-positive: autoimmune hemolytic anemia, megaloblastic anemias
False-negative: may occur with use of heparin or EDTA

SUDAN III STAIN (qualitative screening for fecal fat)

Normal: Negative. Test should be preceded by diet containing 100-150 g of dietary fat/day for 1 week, avoidance of high-fiber diet, and avoidance of suppositories or oily material before specimen collection.
Positive in: Steatorrhea, use of castor oil or mineral oil droplets

SYNOVIAL FLUID ANALYSIS

Table 4-42 describes the classification and interpretation of synovial fluid analysis.

T_3 (triiodothyronine)

See Table 4-43 for T_3 abnormalities.

TABLE 4-42 Classification and Interpretation of Synovial Fluid Analysis

Group	Diseases	Appearance	Viscosity	Mucin Clot	WBC/mm³	% PMN	Glucose (mg/dl) (Blood-Synovial Fluid)	Protein (g/dl)
Normal	—	Clear	↑	Firm	<200	<25	<10	<2.5
I (noninflammatory)	Osteoarthritis, aseptic necrosis, traumatic arthritis, erythema nodosum, osteochondritis dissecans	Clear, yellow (may be xanthochromic if traumatic arthritis)	↑	Firm	↑ Up to 10,000	<25	<10	<2.5
II (inflammatory)	Crystal-induced arthritis, rheumatoid arthritis, Reiter's syndrome, collagen vascular disease, psoriatic arthritis, serum sickness, rheumatic fever	Clear, yellow, turbid	↓	Friable	↑↑ Up to 100,000	40-90	<40	<2.5
III (septic)	Bacterial (staphylococcal, gonococcal, tuberculosis)	Turbid	↓/↑	Friable	↑↑↑ Up to 5 million	40-100	20-100	>2.5

↑, Elevated; ↑↑ >markedly high; ↓, decreased; *PMN,* polymorphonuclear leukocytes. Note that there is considerable overlap in the numbers listed above.

TABLE E4-41 Drugs Associated with Hyponatremia*

Vasopressin Analogs	Drugs That Potentiate Renal Action of Vasopressin
Desmopressin (DDAVP)	Chlorpropamide
Oxytocin	Cyclophosphamide
	Nonsteroidal anti-inflammatory agents
	Acetaminophen (paracetamol)
Drugs That Enhance Vasopressin Release	**Drugs That Cause Hyponatremia by Unknown Mechanisms**
Chlorpropamide	*Haloperidol*
Clofibrate	Fluphenazine
Carbamazepine–oxycarbazepine	Amitriptyline
Vincristine	Thioridazine
Nicotine	Fluoxetine
Narcotics	*Methamphetamine (MDMA or Ecstasy)*
Antipsychotics/antidepressants	Sertraline
Ifosfamide	

Italics: The common causes.
*Not including diuretics.
From Johnson RJ, Feehally J: *Comprehensive clinical nephrology,* ed 2, St Louis, 2000, Mosby.

TABLE 4-43 Findings in Thyroid Function Tests in Various Clinical Conditions

Condition	T_4	FT_4I	T_3	FT_3I	TSH	TSI	TRH Stimulation
Hyperthyroidism							
Graves' disease	↑	↑	↑	↑	↓	+	↓
Toxic nodular goiter	↑	↑	↑	↑	↓	–	↓
Pituitary TSH-secreting tumors	↑	↑	↑	↑	↑	–	↓
T_3 thyrotoxicosis	N	N	↑	↑	↓	+, –	↓
T_4 thyrotoxicosis	↑	↑	N	N	↓	+, –	↓
Hypothyroidism							
Primary	↓	↓	↓	↓	↑	+, –	↑
Secondary	↓	↓	↓	↓	↓ N	–	↓
Tertiary	↓	↓	↓	↓	↓, N	–	N
Peripheral unresponsiveness	↑, N	↑, N	↑, N	↑	↑, N	–	N,↑

↑, Increased; ↓, decreased; +, – variable; *N,* normal.
From Tilton RC, Barrows A: *Clinical laboratory medicine,* St Louis, 1992, Mosby.

Normal range: 75-220 ng/dl (1.2-3.4 nmol/L [CF: 0.01536; SMI: 0.1 nmol/L])
Abnormal values:
A. Elevated in hyperthyroidism (usually earlier and to a greater extent than serum T_4).
B. Useful in diagnosing:
   1. T_3 hyperthyroidism (thyrotoxicosis): increased T_3, normal FTI.
   2. Toxic nodular goiter: increased T_3, normal or increased T_4. See Figure 4-34.
   3. Iodine deficiency: normal T_3, possibly decreased T_4.
   4. Thyroid replacement therapy with liothyronine (Cytomel): normal T_4, increased T_3 if patient is symptomatically hyperthyroid.

Not ordered routinely but indicated when hyperthyroidism is suspected and serum-free T_4 or FTI inconclusive.

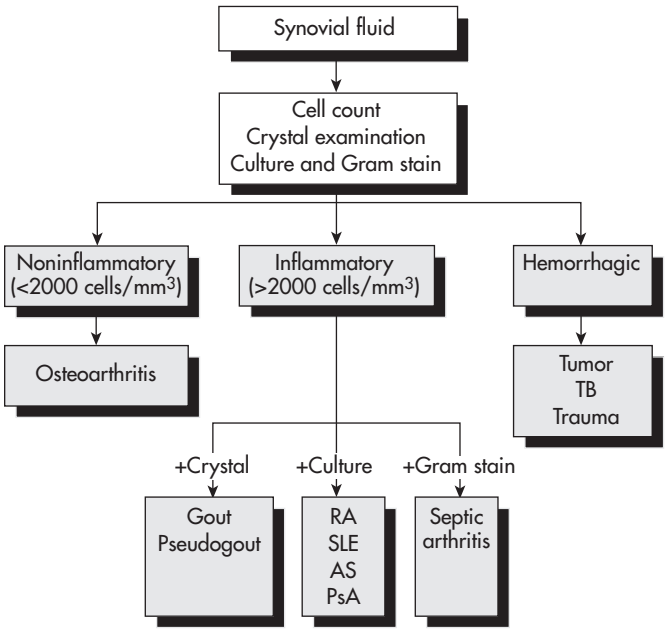


FIGURE 4-34 Algorithm for analysis of joint fluid. Examples of inflammatory arthritis are indicated, although many conditions can produce these findings. *AS,* ankylosing spondylitis; *PsA*, psoriatic arthritis; *RA*, rheumatoid arthritis; *SLE*, systemic lupus erythematosus; *TB*, tuberculosis. (From Goldman L, Schafer AI: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Saunders.)

T_3 RESIN UPTAKE (T_3RU)

Normal range: 25%-35%
Abnormal values: Increased in hyperthyroidism. T_3 resin uptake (T_3RU or RT_3U) measures the percentage of free T_4 (not bound to protein); it does not measure serum T_3 concentration; T_3RU and other tests that reflect thyroid hormone binding to plasma protein are also known as *thyroid hormone-binding ratios* (THBR).

T_4, FREE (Free thyroxine)

Normal range: 0.8-2.8 ng/dl
Elevated in:
Graves' disease, toxic multinodular goiter, toxic adenoma, iatrogenic and factitious causes, transient hyperthyroidism
Serum-free T_4 directly measures unbound thyroxine. Free T_4 can be measured by equilibrium dialysis (gold standard of free T_4 assays) or by immunometric techniques (influenced by serum levels of lipids, proteins, and certain drugs). The free thyroxine index (FTI) can also be easily calculated by multiplying T_4 times T_3RU and dividing the result by 100; the FTI corrects for any abnormal T_4 values secondary to protein binding: $FTI = T_4 \times T_3RU/100$.
Normal values equal 1.1 to 4.3.

T_4, SERUM T_4

Normal range: 0.8-2.8 ng/dl (10-36 pmol/L [CF: 12.87; SMI: 1 pmol/L])
Abnormal values: Serum thyroxine (T_4)
Elevated in:
1. Graves' disease
2. Toxic multinodular goiter
3. Toxic adenoma
4. Iatrogenic and factitious
5. Transient hyperthyroidism
   a. Subacute thyroiditis
   b. Hashimoto's thyroiditis
   c. Silent thyroiditis
6. Rare causes: hypersecretion of TSH (e.g., pituitary neoplasms), struma ovarii, ingestion of large amounts of iodine in a patient with preexisting thyroid hyperplasia or adenoma (Jod-Basedow phenomenon), hydatidiform mole, carcinoma of thyroid, amiodarone therapy of arrhythmias.

Serum thyroxine test measures both circulating thyroxine bound to protein (represents >99% of circulating T_4) and unbound (free) thyroxine. Values vary with protein binding; changes in the concentration of T_4 secondary to changes in thyroxine-binding globulin (TBG) can be caused by the following:

Increased TBG (↑T_4)	*Decreased TBG (↓T_4)*
Pregnancy	Androgens, glucocorticoids
Estrogens	Nephrotic syndrome, cirrhosis
Acute infectious hepatitis	Acromegaly
Oral contraceptives	Hypoproteinemia
Familial	Familial
Fluorouracil, clofibrate	Phenytoin, ASA and other NSAIDs, heroin, methadone, high-dose penicillin, asparaginase
	Chronic debilitating illness

To eliminate the suspected influence of protein binding on thyroxine values, two additional tests are available: T_3 resin uptake and serum free thyroxine. See Table 4-44.

TABLE 4-44 Effects of Pregnancy on Thyroid Physiology

Physiologic Change	Thyroid-Related Consequences
↑ Serum thyroxine-binding globulin	↑ Total T_4 and T_3; ↑ T_4 production
↑ Plasma volume	↑ T_4 and T_3 pool size; ↑ T_4 production; ↑ cardiac output
D3 expression in placenta and (?) uterus	↑ T_4 production
First-trimester ↑ in hCG	↑ Free T_4; ↓ basal thyrotropin; ↑ T_4 production
↑ Renal I– clearance	↑ Iodine requirements
↑ T_4 production; fetal T_4 synthesis during second and third trimesters	
↑ Oxygen consumption by fetoplacental unit, gravid uterus, and mother	↑ Basal metabolic rate; ↑ cardiac output

D3, type 3 iodothyronine deiodinase; *I–*, plasma iodide; *hCG*, human chorionic gonadotropin; *T_3*, triiodothyronine; *T_4*, thyroxine.
From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.

TEGRETOL

See CARBAMAZEPINE.

TESTOSTERONE (total testosterone)

Normal range: Variable with age and sex.

Serum/plasma

Males: 280-1100 ng/dl Females: 15-70 ng/dl

Urine

Males: 50-135 μg/day Females: 2-12 μg/day

Elevated in: Testicular tumors, ovarian masculinizing tumors, testosterone replacement therapy
Decreased in: Hypogonadism, sleep apnea. See Figure 4-35.

THEOPHYLLINE

Normal therapeutic range: 10-20 mcg/ml

THORACENTESIS FLUID

Testing and evaluation of results:

1. Pleural effusion fluid should be differentiated in exudate or transudate. The initial laboratory studies should be aimed only at distinguishing an exudate from a transudate.
   a. Tube 1: protein, LDH, albumin.
   b. Tubes 2, 3, 4: save the fluid until further notice. In selected patients with suspected empyema, a pH level may be useful (generally ≤7.0). See following for proper procedure to obtain a pH level from pleural fluid.
2. A serum/effusion albumin gradient of ≤1.2 g/dl is indicative of exudative effusions, especially in patients with congestive heart failure (CHF) treated with diuretics.
3. Note the appearance of the fluid:
   a. A grossly hemorrhagic effusion can be a result of a traumatic tap, neoplasm, or an embolus with infarction.
   b. A milky appearance indicates either of the following:
      (1) Chylous effusion: caused by trauma or tumor invasion of the thoracic duct; lipoprotein electrophoresis of the effusion reveals chylomicrons and triglyceride levels >115 mg/dl.
      (2) Pseudochylous effusion: often seen with chronic inflammation of the pleural space (e.g., TB, connective tissue diseases).
4. If transudate, consider CHF, cirrhosis, chronic renal failure, and other hypoproteinemic states and perform subsequent workup accordingly.
5. If exudate, consider ordering these tests on the pleural fluid:
   a. Cytologic examination for malignant cells (for suspected neoplasm).
   b. Gram stain, cultures (aerobic and anaerobic), and sensitivities (for suspected infectious process).
   c. AFB stain and cultures (for suspected TB).
   d. pH: a value <7.0 suggests parapneumonic effusion or empyema; a pleural fluid pH must be drawn anaerobically and iced immediately; the syringe should be prerinsed with 0.2 ml of 1:1000 heparin.
   e. Glucose: a low glucose level suggests parapneumonic effusions and rheumatoid arthritis.
   f. Amylase: a high amylase level suggests pancreatitis or ruptured esophagus.
   g. Perplexing pleural effusions are often a result of malignancy (e.g., lymphoma, malignant mesothelioma, ovarian carcinoma), TB, subdiaphragmatic processes, prior asbestos exposure, and postcardiac injury syndrome.

THROMBIN TIME (TT)

Normal range: 11.3-18.5 sec

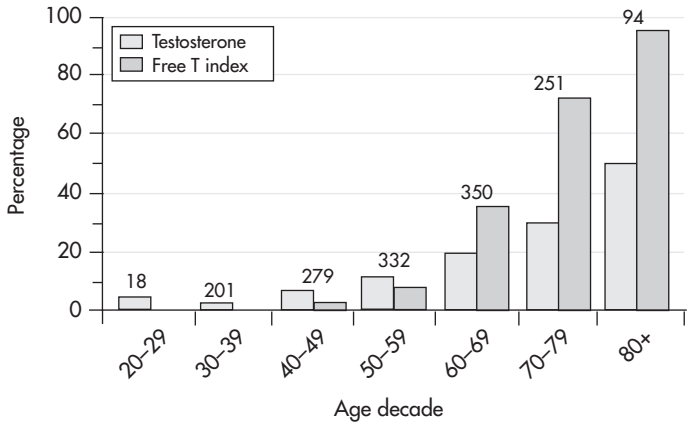


FIGURE 4-35 Hypogonadism in aging men. Bar height indicates the percentage of men in each 10-year interval, from the third to the ninth decades, with at least one testosterone value in the hypogonadal range. The criteria used for these determinations are total testosterone less than 11.3 nmol/L (325 ng/dL) and testosterone and sex hormone–binding globulin (free T index) less than 0.153 nmol/nmol. The numbers above each pair of bars indicate the number of men studied in the corresponding decade. The fraction of men who are hypogonadal increases progressively after age 50 years by either criterion. More men are hypogonadal by free T index than by total testosterone after 50 years, and there seems to be a progressively greater difference with increasing age between the two criteria. (From Goldman L, Schafer AI: *Goldman's Cecil medicine*, ed 24, Philadelphia, 2012, Saunders.)

Elevated in: Thrombolytic and heparin therapy, disseminated intravascular coagulation, hypofibrinogenemia, dysfibrinogenemia

THYROGLOBULIN

Normal: 3-40 ng/ml. Thyroglobulin is a tumor marker for monitoring the status of patients with papillary or follicular thyroid cancer following resection.
Elevated in: Papillary or follicular thyroid cancer, Hashimoto's thyroiditis, Graves' disease, subacute thyroiditis

THYROID MICROSOMAL ANTIBODIES

Normal: Undetectable. Low titers may be present in 5%-10% of normal individuals
Elevated in: Hashimoto's disease, thyroid carcinoma, early hypothyroidism, pernicious anemia

THYROID-STIMULATING HORMONE (TSH)

See Fig. 4-36 for an algorithmic approach to thyroid testing.
Normal range: 2-11 μU/ml (2-11 mU/L [CF: 1; SMI: 1 mU/L])
CONDITIONS THAT INCREASE SERUM THYROID-STIMULATING HORMONE VALUES
Laboratory error
Primary hypothyroidism
Synthroid therapy with insufficient dose
Lithium or amiodarone; some patients
Hashimoto's thyroiditis in later stage
Large doses of inorganic iodide (e.g., SSKI)
Severe nonthyroid illness in recovery phase
Iodine deficiency (moderate or severe)
Addison's disease
TSH specimen drawn in evening (peak of diurnal variation)
Pituitary TSH-secreting tumor
Therapy of hypothyroidism (3-6 wk after beginning therapy [range, 1-8 wk]; sometimes longer when pretherapy TSH is over 100 μU/ml)
Acute psychiatric illness
Peripheral resistance to T_4 syndrome
Antibodies (e.g., HAMA) interfering with monoclonal sandwich method of TSH assay
Telepaque (iopanoic acid) and Oragrafin (ipodate) x-ray contrast media
Amphetamines
High altitudes
CONDITIONS THAT DECREASE SERUM THYROID-STIMULATING HORMONE VALUES
Laboratory error
T_4/T_3 toxicosis (diffuse or nodular etiology)
Excessive therapy for hypothyroidism
Active thyroiditis (subacute, painless, or early active Hashimoto's disease)
Multinodular goiter containing areas of autonomy
Severe nonthyroid illness (especially acute trauma, dopamine, or glucocorticoid)
T_3 toxicosis
Pituitary insufficiency
Cushing's syndrome (and some patients on high-dose glucocorticoid)
Jod-Basedow (iodine-induced) hyperthyroidism
Thyroid-stimulating hormone drawn 2-4 hr after levothyroxine dose
Postpartum transient toxicosis
Factitious hyperthyroidism
Struma ovarii
Radioimmunoassay, surgery, or antithyroid drug therapy for hyperthyroidism 4-6 weeks (range, 2 wk to 2 yr) after the treatment
Interleukin-2 drugs (3%-6% of cases) or α-interferon therapy (1% of cases)
Hyperemesis gravidarum
Amiodarone therapy.
See Table 4-45 for changes in thyroid hormone levels during illness.

TABLE 4-45 Changes in Thyroid Hormone Levels during Illness

Severity of Illness	Free T_3	Free T_4	Reverse T_3	TSH	Probable Cause
Mild	↓	N	↑	N	↓ D2, D1
Moderate	↓↓	N, ↑↓	↑↑	N, ↓	↓↓ D2, D1,?↑ D3
Severe	↓↓↓	↓	↑	↓↓	↓↓ D2, D1, ↑D3
Recovery	↓	↓	↑	↑	?

D1 through *D3*, iodothyronine deiodinases; *N,* no change; T_3, triiodothyronine; T_4, thyroxine; *TSH,* thyroid-stimulating hormone.
From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.

THYROTROPIN (TSH) RECEPTOR ANTIBODIES

Normal: <130% of basal activity
Elevated in: Values between 1.3 and 2.0 are found in 10% of patients with thyroid disease other than Graves' disease. Values >2.8 have been found only in patients with Graves' disease.

THYROTROPIN-RELEASING HORMONE (TRH) STIMULATION TEST

Normal: Baseline TSH <11 microU/ml; Stimulated TSH: more than double the baseline.

In primary hypothyroidism the TSH increase is 2× to 3× the normal result. In secondary hypothyroidism no TSH response occurs. In tertiary hypothyroidism (hypothalamic failure) there is a delayed rise in the TSH level.

THYROXINE (T_4)

Normal range: 4-11 μg/dl (51-142 nmol/L [CF: 12.87; SMI: 1 nmol/L])

TIBC

See IRON-BINDING CAPACITY, TOTAL

TISSUE TRANSGLUTAMINASE ANTIBODY

Normal: Negative
Present in: Celiac disease (specificity; 94%-97%, sensitivity, 90%-98%), dermatitis herpetiformis

TRANSFERRIN

Normal range: 170-370 mg/dl (1.7-3.7 g/L [CF: 0.01; SMI: 0.01 g/L])
Elevated in: Iron deficiency anemia, oral contraceptive administration, viral hepatitis, late pregnancy
Decreased in: Nephrotic syndrome, liver disease, hereditary deficiency, protein malnutrition, neoplasms, chronic inflammatory states, chronic illness, thalassemia, hemochromatosis, hemolytic anemia

TRIGLYCERIDES

Normal range: <150 mg/dl (<1.80 mmol/L [CF: 0.01129; SMI: 0.02 mmol/L])
Elevated in: Hyperlipoproteinemias (types I, IIb, III, IV, V), hypothyroidism, pregnancy, estrogens, acute myocardial infarction, pancreatitis, alcohol intake, nephrotic syndrome, diabetes mellitus, glycogen storage disease
Decreased in: Malnutrition, congenital abetalipoproteinemias, drugs (e.g., gemfibrozil, fenofibrate, nicotinic acid, clofibrate)

TRIIODOTHYRONINE

See T_3

TROPONINS (serum)

See Box 4-8 for causes of troponin elevations.
Normal range: 0-0.4 ng/ml (negative). If there is clinical suspicion of evolving acute MI or ischemic episode, repeat testing in 5-6 hours is recommended.
Indeterminate: 0.05-0.49 ng/ml. Suggest further tests. In a patient with unstable angina and this troponin I level, there is an increased risk of a cardiac event in the near future.

FIGURE 4-36 Diagnostic approach to thyroid testing. *N,* Normal; *RAIU,* radioactive iodine uptake; *TRH,* thyrotropin-releasing hormone; *TSH,* thyroid-stimulating hormone. (From Ferri FF: *Practical guide to the care of the medical patient*, ed 8, St Louis, 2011, Mosby.)

BOX 4-8 Causes of Serum Troponin T and I Elevations, Including Both Acute Coronary Syndromes, Noncoronary Cardiac Events, and Noncardiac Ailments

Acute coronary syndrome/acute myocardial infarction
Shock of any form (cardiogenic, obstructive, distributive)
Myocarditis and myopericarditis
Cardiomyopathies
Acute congestive heart failure (pulmonary edema)
Sepsis
Pulmonary embolism
Renal failure
Sympathomimetic ingestions
Polytrauma
Burns
Acute CNS event
Rhabdomyolysis
Cardiac neoplasm, inflammatory syndromes, and infiltrative diseases
Congenital coronary anomalies
Extreme physical exertion

From Vincent JL et al: *Textbook of critical care,* ed 6, Philadelphia, 2011, Saunders.

Strong probability of acute MI:
≥ 0.05 ng/ml

Cardiac troponin T (cTnT) is a highly sensitive marker for myocardial injury for the first 48 hours after MI and for up to 5-7 days (see Fig. 4-15, under "Creatine Kinase Isoenzymes"). It may also be elevated in renal failure, chronic muscle disease, and trauma.

Cardiac troponin I (cTnI) is highly sensitive and specific for myocardial injury (≥CK-MB) in the initial 8 hours, peaks within 24 hours and lasts up to 7 days. With progressively higher levels of cTnI, the risk of mortality increases because the amount of necrosis increases.

TSH

See THYROID-STIMULATING HORMONE

TT

See THROMBIN TIME

TUBERCULIN TEST (PPD)

Abnormal results: see Box 4-9. Box 4-10 describes factors associated with false-negative tuberculin tests.

BOX 4-9 PPD Reaction Size Considered "Positive" (Intracutaneous 5 TU Mantoux Test at 48 hr)

5 mm or More
- HIV infection or risk factors for HIV
- Close recent contact with active TB case
- Persons with chest x-ray consistent with healed TB

10 mm or More
- Foreign-born persons from countries with high TB prevalence in Asia, Africa, and Latin America
- IV drug users
- Medically underserved low-income population groups (including Native Americans, Hispanics, and blacks)
- Residents of long-term care facilities (nursing homes, mental institutions)
- Medical conditions that increase risk for TB (silicosis, gastrectomy, undernourishment, diabetes mellitus, high-dose corticosteroids or immunosuppression Rx, leukemia or lymphoma, other malignancies)
- Employees of long-term care facilities, schools, child care facilities, health care facilities

15 mm or More
- All others not already listed

TB, Tuberculosis; *TU,* tuberculin units.

BOX 4-10 Factors Associated with False-Negative Tuberculin Tests

Technical Errors
- Improper administration
- Inaccurate reading
- Loss of potency of antigen

Patient-Related Factors (Anergy)
- Age (elderly)
- Nutritional status
- Medications: corticosteroids, immunosuppressive agents
- Severe tuberculosis
- Coexisting diseases
  - HIV infection
  - Viral illness or vaccination
  - Lymphoreticular malignancies
  - Sarcoidosis
  - Solid tumors
  - Lepromatous leprosy
  - Sjögren's syndrome
  - Ataxia telangiectasia
  - Uremia
  - Primary biliary cirrhosis
  - Systemic lupus erythematosus
- Severe systemic disease of any etiology

From Stein JH (ed): *Internal medicine,* ed 4, St Louis, 1994, Mosby.

UNCONJUGATED BILIRUBIN

See BILIRUBIN, DIRECT

UREA NITROGEN, BLOOD (BUN)

Normal range: 8-18 mg/dl (3-6.5 mmol/L [CF: 0.357; SMI: 0.5 mmol/L])

Box 4-11 describes factors affecting BUN level independent of renal function.

Elevated in: Drugs (aminoglycosides and other antibiotics, diuretics, lithium, corticosteroids), dehydration, gastrointestinal bleeding, decreased renal blood flow (shock, congestive heart failure, myocardial infarction), renal disease (glomerulonephritis, pyelonephritis, diabetic nephropathy), urinary tract obstruction (prostatic hypertrophy)

Decreased in: Liver disease, malnutrition, third trimester of pregnancy, overhydration, acromegaly, celiac disease

BOX 4-11 Factors Affecting Blood Urea Nitrogen Level Independent of Renal Function

Disproportionate Increase in Blood Urea Nitrogen
- Volume depletion ("prerenal azotemia")
- Gastrointestinal hemorrhage
- Corticosteroid or cytotoxic agents
- High-protein diet
- Obstructive uropathy
- Sepsis
- Catabolic states, tissue breakdown

Disproportionate Decrease in Blood Urea Nitrogen
- Low-protein diet
- Liver disease

From Andreoli TE (ed): *Cecil essentials of medicine,* ed 5, Philadelphia, 2001, Saunders.

URIC ACID (serum)

Normal range: 2-7 mg/dl

Elevated in: Renal failure, gout, excessive cell lysis (chemotherapeutic agents, radiation therapy, leukemia, lymphoma, hemolytic anemia), hereditary enzyme deficiency (hypoxanthine-guanine-phosphoribosyl transferase), acidosis, myeloproliferative disorders, diet high in purines or protein, drugs (diuretics, low doses of ASA, ethambutol, nicotinic acid), lead poisoning,

hypothyroidism, Addison's disease, nephrogenic diabetes insipidus, active psoriasis, polycystic kidneys
Decreased in: Drugs (allopurinol, febuxostat, high doses of ASA, probenecid, warfarin, corticosteroid), deficiency of xanthine oxidase, syndrome of inappropriate antidiuretic hormone secretion, renal tubular deficits (Fanconi's syndrome), alcoholism, liver disease, diet deficient in protein or purines, Wilson's disease, hemochromatosis

URINALYSIS

Normal range:
Color: light straw
Appearance: clear
Ketones: absent
pH: 4.5-8 (average, 6)
Protein: absent
Glucose: absent
Specific gravity: 1.005-1.030
Occult blood absent
Microscopic examination:
Red blood cells: 0-5 (high-power field)
White blood cells: 0-5 (high-power field)
Bacteria (spun specimen): absent
Casts: 0-4 hyaline (low-power field)
Abnormalities in the microscopic examination of urine are described in Table 4-46.

TABLE 4-46 Microscopic Examination of the Urine

Finding	Associations
Casts	
Red blood cell	Glomerulonephritis, vasculitis
White blood cell	Interstitial nephritis, pyelonephritis
Epithelial cell	Acute tubular necrosis, interstitial nephritis, glomerulonephritis
Granular	Renal parenchymal disease (nonspecific)
Waxy, broad	Advanced renal failure
Hyaline	Normal finding in concentrated urine
Fatty	Heavy proteinuria
Cells	
Red blood cell	Urinary tract infection, urinary tract inflammation
White blood cell	Urinary tract infection, urinary tract inflammation
Eosinophil	Acute interstitial nephritis
(Squamous) epithelial cell	Contaminants
Crystals	
Uric acid	Acid urine, acute uric acid nephropathy, hyperuricosuria
Calcium phosphate	Alkaline urine
Calcium oxalate	Acid urine, hyperoxaluria, ethylene glycol poisoning
Cystine	Cystinuria
Sulfur	Sulfa-containing antibiotics

From Andreoli TE (ed): *Cecil essentials of medicine,* ed 5, Philadelphia, 2001, Saunders.

URINE AMYLASE

Normal range: 35-260 U Somogyi/hr (6.5-48.1 U/hr [CF: 0.185; SMI: 1 U/hr])
Elevated in: Pancreatitis, carcinoma of the pancreas

URINE BILE

Normal: Absent
Abnormal:
Urine bilirubin: hepatitis (viral, toxic, drug-induced), biliary obstruction
Urine urobilinogen: hepatitis (viral, toxic, drug-induced), hemolytic jaundice, liver cell dysfunction (cirrhosis, infection, metastases)

URINE CALCIUM

Normal range: <250 mg/24 hr (<6.2 mmol/dl [CF: 0.02495; SMI: 0.1 mmol/dl])
Elevated in: Primary hyperparathyroidism, hypervitaminosis D, bone metastases, multiple myeloma, increased calcium intake, steroids, prolonged immobilization, sarcoidosis, Paget's disease, idiopathic hypercalciuria, renal tubular acidosis
Decreased in: Hypoparathyroidism, pseudohypoparathyroidism, vitamin D deficiency, vitamin D–resistant rickets, diet low in calcium, drugs (thiazide diuretics, oral contraceptives), familial hypocalciuric hypercalcemia, renal osteodystrophy, potassium citrate therapy

URINE cAMP

Elevated in: Hypercalciuria, familial hypocalciuric hypercalcemia, primary hyperparathyroidism, pseudohypoparathyroidism, rickets
Decreased in: Vitamin D intoxication, sarcoidosis

URINE CATECHOLAMINES

Normal range:
Norepinephrine: <100 μg/24 hr (<590 nmol/day [CF: 5.911; SMI: 10 nmol/day])
Epinephrine: <10 μg/24 hr (55 nmol/day [CF: 5.458; SMI: 5 nmol/day])
Elevated in: Pheochromocytoma, neuroblastoma, severe stress

URINE CHLORIDE

Normal range: 110-250 mEq/day (110-250 mmol/day [CF: 1; SMI: 1 mmol/day])
Elevated in: Corticosteroids, Bartter's syndrome, diuretics, metabolic acidosis, severe hypokalemia
Decreased in: Chloride depletion (vomiting), colonic villous adenoma, chronic renal failure, renal tubular acidosis

URINE COPPER

Normal range: <40 μg/24 hr (<0.6 μmol/day [CF: 0.01574; SMI: 0.2 μmol/day])

URINE CORTISOL, FREE

Normal range: 10-110 μg/24 hr (30-300 nmol/day [CF: 2.759; SMI: 10 nmol/day])
Elevated: See CORTISOL, PLASMA

URINE CREATININE (24 HR)

Normal range:
Male: 0.8-1.8 g/day (7-16 mmol/day [CF: 8.840; SMI: 0.1 mmol/day])
Female: 0.6-1.6 g/day (5.3-14 mmol/day)
NOTE: Useful test as an indicator of completeness of 24-hr urine collection.

URINE CRYSTALS

Uric acid: acid urine, hyperuricosuria, uric acid nephropathy
Sulfur: antibiotics containing sulfa
Calcium oxalate: ethylene glycol poisoning, acid urine, hyperoxaluria
Calcium phosphate: alkaline urine
Cystine: cystinuria

URINE EOSINOPHILS

Normal: Absent
Present in: Interstitial nephritis, acute tubular necrosis, urinary tract infection, kidney transplant rejection, hepatorenal syndrome

URINE GLUCOSE (qualitative)

Normal: Absent
Present in: Diabetes mellitus, renal glycosuria (decreased renal threshold for glucose), glucose intolerance

URINE HEMOGLOBIN, FREE

Normal: Absent
Present in: Hemolysis (with saturation of serum haptoglobin binding capacity and renal threshold for tubular absorption of hemoglobin)

URINE HEMOSIDERIN

Normal: Absent
Present in: Paroxysmal nocturnal hemoglobinuria, chronic hemolytic anemia, hemochromatosis, blood transfusion, thalassemias

URINE 5-HYDROXYINDOLE-ACETIC ACID (URINE 5-HIAA)

Normal range: 2-8 mg/24 hr (10-40 μmol/day [CF: 5.23; SMI: 5 μmol/day])
Elevated in: Carcinoid tumors, after ingestion of certain foods (bananas, plums, tomatoes, avocados, pineapples, eggplant, walnuts), drugs (monoamine oxidase inhibitors, phenacetin, methyldopa, glycerol guaiacolate, acetaminophen, salicylates, phenothiazines, imipramine, methocarbamol, reserpine, methamphetamine). See Table 4-47.

TABLE 4-47 Factors That Interfere with Determination of Urinary 5-HIAA

Foods	Drugs
Factors That Produce False-Positive Results	
Avocado	Acetaminophen
Banana	Acetanilid
Chocolate	Caffeine
Coffee	Fluorouracil
Eggplant	Guaifenesin
Pecan	l-Dopa
Pineapple	Melphalan
Plum	Mephenesin
Tea	Methamphetamine
Walnuts	Methocarbamol
	Methysergide maleate
	Phenmetrazine
	Reserpine
	Salicylates
Factors That Cause False-Negative Results	
None	Corticotropin
	p-Chlorophenylalanine
	Chlorpromazine
	Heparin
	Imipramine
	Isoniazid
	Methenamine mandelate
	Methyldopa
	Monoamine oxidase inhibitors
	Phenothiazine
	Promethazine

5-HIAA, 5-hydroxyindoleacetic acid.
From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.

URINE INDICAN

Normal: Absent
Present in: Malabsorption secondary to intestinal bacterial overgrowth

URINE KETONES (semiquantitative)

Normal: Absent
Present in: Diabetic ketoacidosis, alcoholic ketoacidosis, starvation, isopropanol ingestion

URINE METANEPHRINES

Normal range: 0-2.0 mg/24 hr (0-11.0 μmol/day [CF: 5.458; SMI: 0.5 μmol/day])
Elevated in: Pheochromocytoma, neuroblastoma, drugs (caffeine, phenothiazines, monoamine oxidase inhibitors), stress See Table 4-48.

TABLE 4-48 Medications That May Increase Measured Levels of Fractionated Catecholamines and Metanephrines

- Tricyclic antidepressants (including cyclobenzaprine)
- Levodopa
- Drugs containing adrenergic receptor agonists (e.g., decongestants)
- Amphetamines
- Buspirone and antipsychotic agents
- Prochlorperazine
- Reserpine
- Withdrawal from clonidine and other drugs (e.g., illicit drugs)
- Illicit drugs (e.g., cocaine, heroin)
- Ethanol

From Melmed S, Polonsky KS, Larsen PR, Kronenberg HM: *Williams textbook of endocrinology*, ed 12, Philadelphia, 2011, Saunders.

URINE MYOGLOBIN

Normal: Absent
Present in: Severe trauma, hyperthermia, polymyositis/dermatomyositis, carbon monoxide poisoning, drugs (narcotic and amphetamine toxicity), hypothyroidism, muscle ischemia

URINE NITRITE

Normal: Absent
Present in: Urinary tract infections

URINE OCCULT BLOOD

Normal: Negative
Positive in: Trauma to urinary tract, renal disease (glomerulonephritis, pyelonephritis), renal or ureteral calculi, bladder lesions (carcinoma, cystitis), prostatitis, prostatic carcinoma, menstrual contamination, hematopoietic disorders (hemophilia, thrombocytopenia), anticoagulants, ASA

URINE OSMOLALITY

Normal range: 50-1200 mOsm/kg (50-1200 mmol/kg [CF: 1; SMI: 1 mmol/kg])
Elevated in: Syndrome of inappropriate antidiuretic hormone secretion, dehydration, glycosuria, adrenal insufficiency, high-protein diet
Decreased in: Diabetes insipidus, excessive water intake, IV hydration with D_5W, acute renal insufficiency, glomerulonephritis

URINE pH

Normal range: 4.6-8 (average, 6)
Elevated in: Bacteriuria, vegetarian diet, renal failure with inability to form ammonia, drugs (antibiotics, sodium bicarbonate, acetazolamide)
Decreased in: Acidosis (metabolic, respiratory), drugs (ammonium chloride, methenamine mandelate), diabetes mellitus, starvation, diarrhea

URINE PHOSPHATE

Normal range: 0.8-2.0 g/24 hr
Elevated in: Acute tubular necrosis (diuretic phase), chronic renal disease, uncontrolled diabetes mellitus, hyperparathyroidism, hypomagnesemia, metabolic acidosis, metabolic alkalosis, neurofibromatosis, adult-onset vitamin D–resistant hypophosphatemic osteomalacia
Decreased in: Acromegaly, acute renal failure, decreased dietary intake, hypoparathyroidism, respiratory acidosis

URINE POTASSIUM

Normal range: 25-100 mEq/24 hr (25-100 mmol/day [CF: 1; SMI: 1 mmol/day])
Elevated in: Aldosteronism (primary, secondary), glucocorticoids, alkalosis, renal tubular acidosis, excessive dietary potassium intake
Decreased in: Acute renal failure, potassium-sparing diuretics, diarrhea, hypokalemia

URINE PROTEIN (quantitative)

Normal range: <150 mg/24 hr (<0.15 g/day [CF: 0.001; SMI: 0.01 g/day])

Elevated in:
Nephrotic syndrome as a result of primary renal diseases
Malignant hypertension
Malignancies: multiple myeloma, leukemias, Hodgkin's disease
Congestive heart failure
Diabetes mellitus
Systemic lupus erythematosus, rheumatoid arthritis
Sickle cell disease
Goodpasture's syndrome
Malaria
Amyloidosis, sarcoidosis
Tubular lesions: cystinosis
Functional (after heavy exercise)
Pyelonephritis
Pregnancy
Constrictive pericarditis
Renal vein thrombosis
Toxic nephropathies: heavy metals, drugs
Radiation nephritis
Orthostatic (postural) proteinuria
Benign proteinuria: fever, heat or cold exposure

URINE SEDIMENT

See Fig. 4-37 for evaluation of common abnormalities.

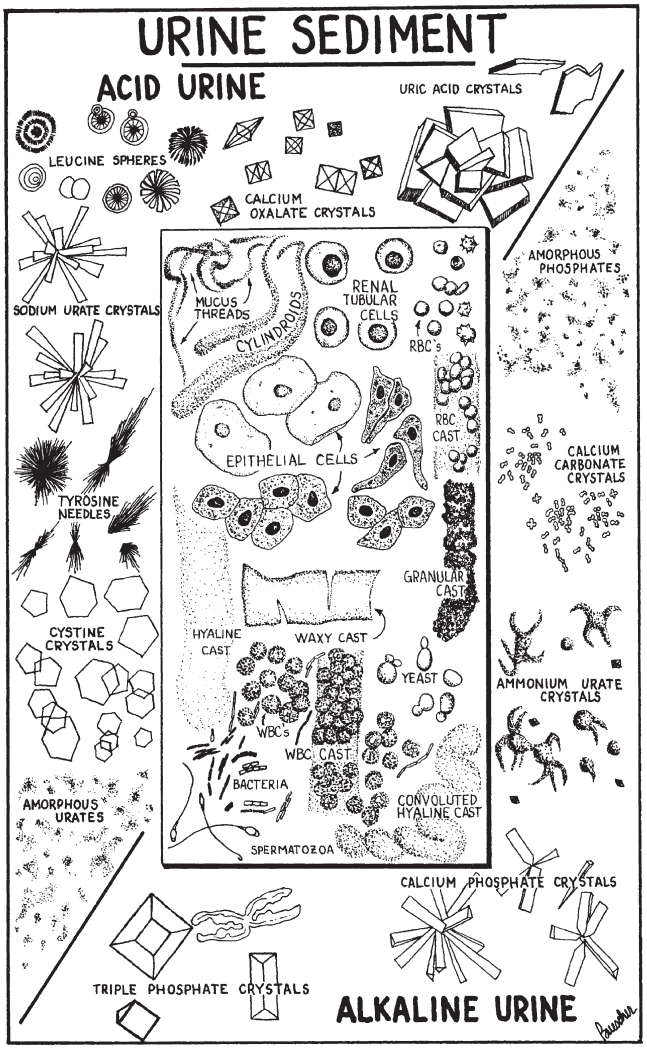


FIGURE 4-37 Microscopic examination of urinary sediment. (From Grigorian Greene M: *The Harriet Lane handbook: a manual for pediatric house officers,* ed 17, St Louis, 2007, Mosby.)

URINE SODIUM (QUANTITATIVE)

See Table 4-49 for use of urine electrolytes in the differential diagnosis of hypokalemia.
Normal range: 40-220 mEq/day (40-220 mmol/day [CF: 1; SMI: 1 mmol/day])
Elevated in: Diuretic administration, high sodium intake, salt-losing nephritis, acute tubular necrosis, vomiting, Addison's disease, syndrome of inappropriate antidiuretic hormone secretion, hypothyroidism, congestive heart failure, hepatic failure, chronic renal failure, Bartter's syndrome, glucocorticoid deficiency, interstitial nephritis caused by analgesic abuse, mannitol, dextran, or glycerol therapy, milk-alkali syndrome, decreased renin secretion, postobstructive diuresis
Decreased In: Increased aldosterone, glucocorticoid excess, hyponatremia, prerenal azotemia, decreased salt intake

TABLE 4-49 Urine Electrolytes* in the Differential Diagnosis of Hypokalemia

Condition	Urine Electrolyte	
	Na^+	Cl^-
Vomiting		
Recent	High†	Low‡
Remote	Low	Low
Diuretics		
Recent	High	High
Remote	Low	Low
Diarrhea or Laxative Abuse	Low	High
Bartter's or Gitelman's Syndrome	High	High

From Vincent JL et al: *Textbook of Critical Care,* ed 6, Philadelphia, 2011, Saunders.
*Do not use the urine electolytes in this fashion during polyuric states.
†High = urine concentration >15 mmol/L.
‡Low = urine concentration <15 mmol/L.

URINE SPECIFIC GRAVITY

Normal range: 1.005-1.030
Elevated in: Dehydration, excessive fluid losses (vomiting, diarrhea, fever), x-ray contrast media, diabetes mellitus, congestive heart failure, syndrome of inappropriate antidiuretic hormone secretion, adrenal insufficiency, decreased fluid intake
Decreased in: Diabetes insipidus, renal disease (glomerulonephritis, pyelonephritis), excessive fluid intake or IV hydration

URINE VANILLYLMANDELIC ACID (VMA)

Normal range: <6.8 mg/24 hr (<35 μmol/day [CF: 5.046; SMI: 1 μmol/day])
Elevated in: Pheochromocytoma, neuroblastoma, ganglioblastoma, drugs (isoproterenol, methocarbamol, levodopa, sulfonamides, chlorpromazine), severe stress, after ingestion of bananas, chocolate, vanilla, tea, coffee
Decreased in: Drugs (monoamine oxidase inhibitors, reserpine, guanethidine, methyldopa)

VARICELLA-ZOSTER VIRUS (VZV) SEROLOGY

Test description: Test can be performed on whole blood, tissue, skin lesions, and CSF

VASOACTIVE INTESTINAL PEPTIDE (VIP)

Normal: <50 pg/ml
Elevated in: Pancreatic VIP-omas, neuroblastoma, pancreatic islet call hyperplasia, liver disease, MEN I, ganglioneuroma, ganglioneuroblastoma

VDRL

Normal range: Negative
Positive test: Syphilis, other treponemal diseases (yaws, pinta, bejel)
NOTE: A false-positive test may be seen in patients with systemic lupus erythematosus and other autoimmune diseases, infectious mononucleosis, HIV, atypical pneumonia, malaria, leprosy, typhus fever, rat-bite fever, relapsing fever.
NOTE: See Table 4-50 for interpretation of serologic tests for syphilis.

TABLE 4-50 Interpretation of Serologic Tests for Syphilis*

Nontreponemal Tests	Treponemal Tests	Interpretation of Finding: Is Syphilis Present?*
Nonreactive	Nonreactive	Early primary syphilis is not ruled out by negative serologic tests. Early syphilis is present in 13%-30% of patients who have a negative microhemagglutination *Treponema pallidum* test; in about 30% of patients who present with chancre but have a nonreactive reagin test; and in about 10% of patients who have a negative FTA-ABS test. Late syphilis is present in a very small fraction of patients. Adequately treated syphilis in remote past may produce these results, but treponemal tests usually remain reactive.
	Reactive	Observed in about 10% of patients with chancre. The treponemal tests may turn positive shortly before the reagin tests. Reagin tests repeated after several days are generally positive. In adequately treated early syphilis, the reagin test may return to nonreactive within 1-2 yr, whereas the treponemal tests generally do not. Late syphilis is not ruled out by a negative reagin test. The sensitivity of the reagin tests is lower than that of treponemal tests in untreated late syphilis. In secondary syphilis, rarely, a highly reactive serum appears negative when tested undiluted with a reagin test because flocculation is inhibited by relative antibody excess. Not reported to occur with treponemal tests. Quantitative reagin tests are positive. False-positive treponemal tests occur in 40% of patients with Lyme disease.
Reactive	Nonreactive borderline (FTA-ABS)	Finding is not diagnostic of syphilis but constitutes a classic biologic false-positive reaction. Not diagnostic of syphilis; most patients (90%) with this pattern do not develop clinical or serologic evidence of syphilis. Repeat test is indicated. Chronic borderline results are associated with a variety of conditions other than syphilis.
	Beaded (FTA-ABS)	Not diagnostic of syphilis. Seen with collagen vascular disease.
	Reactive	Findings diagnostic of syphilis or other treponemal disease. In adequately treated syphilis, one would expect (1) a sustained fourfold drop in titer of reagin test, although reagin test may remain positive after adequate therapy; (2) treponemal tests remain positive after adequate therapy. Concurrent false-positive results on both nontreponemal and treponemal tests could occur in rare instances. It may be impossible to rule out syphilis in an individual with this test profile.

*Serologic data must always be interpreted in the light of a total clinical evaluation. Diagnosis based on serologic criteria alone is fraught with error. Serologic tests apparently in conflict with clinical diagnosis should be confirmed by repetition or possibly referral to a reference laboratory.
FTA-ABS, Fluorescent treponemal antibody, absorbed.
From Stein JH (ed): *Internal medicine,* ed 4, St Louis, 1994, Mosby.

VISCOSITY (serum)

Normal range: 1.4-1.8 relative to water (1.10-1.22 centipoise)
Elevated in: Monoclonal gammopathies (Waldenström's macroglobulinemia, multiple myeloma), hyperfibrinogenemia, systemic lupus erythematosus, rheumatoid arthritis, polycythemia, leukemia

VITAMIN B_{12}

See Fig. E4-38 for the Schilling test. See Box 4-12 for etiopathophysiologic classification of cobalamin deficiency.
Normal:
190-900 ng/ml
Causes of vitamin B_{12} deficiency:
1. Pernicious anemia (antibodies against intrinsic factor and gastric parietal cells)
2. Dietary (strict lacto-ovovegetarians, food faddists)
3. Malabsorption (achlorhydria, gastrectomy, ileal resection, pancreatic insufficiency, drugs [omeprazole, cholestyramine])

Falsely low levels occur in patients with severe folate deficiency, in patients using high doses of ascorbic acid, and when cobalamin levels are measured after nuclear medicine studies (radioactivity interferes with cobalamin radioimmunoassay).
Falsely high or normal levels in patients with cobalamin deficiency can occur in severe liver disease and chronic granulocytic leukemia.
The absence of anemia or macrocytosis does not exclude the diagnosis of cobalamin deficiency.

VITAMIN D, 1,25 DIHYDROXY CALCIFEROL

Normal: 16-65 pg/ml
Elevated in: Tumor calcinosis, primary hyperparathyroidism, sarcoidosis, tuberculosis, idiopathic hypercalciuria
Decreased in: Nutritional deficiency postmenopausal osteoporosis, chronic renal failure, hypoparathyroidism, tumor-induced osteomalacia, rickets, elevated blood lead levels

VITAMIN K

Normal: 0.10-2.20 ng/ml
Decreased in: Primary biliary cirrhosis, anticoagulants, antibiotics, cholestyramine, GI disease, pancreatic disease, cystic fibrosis, obstructive jaundice, hypoprothrombinemia, hemorrhagic disease of the newborn

VON WILLEBRAND FACTOR

Normal: Levels vary according to blood type; blood type O: 50-150 U/dl; blood type non-O: 90-200 U/dl
Decreased in: von Willebrand's disease (however, in type II von Willebrand's disease the antigen may be normal but the function is impaired)

WBC

See COMPLETE BLOOD COUNT

WESTERGREN

See ERYTHROCYTE SEDIMENTATION RATE

WHITE BLOOD COUNT

See COMPLETE BLOOD COUNT

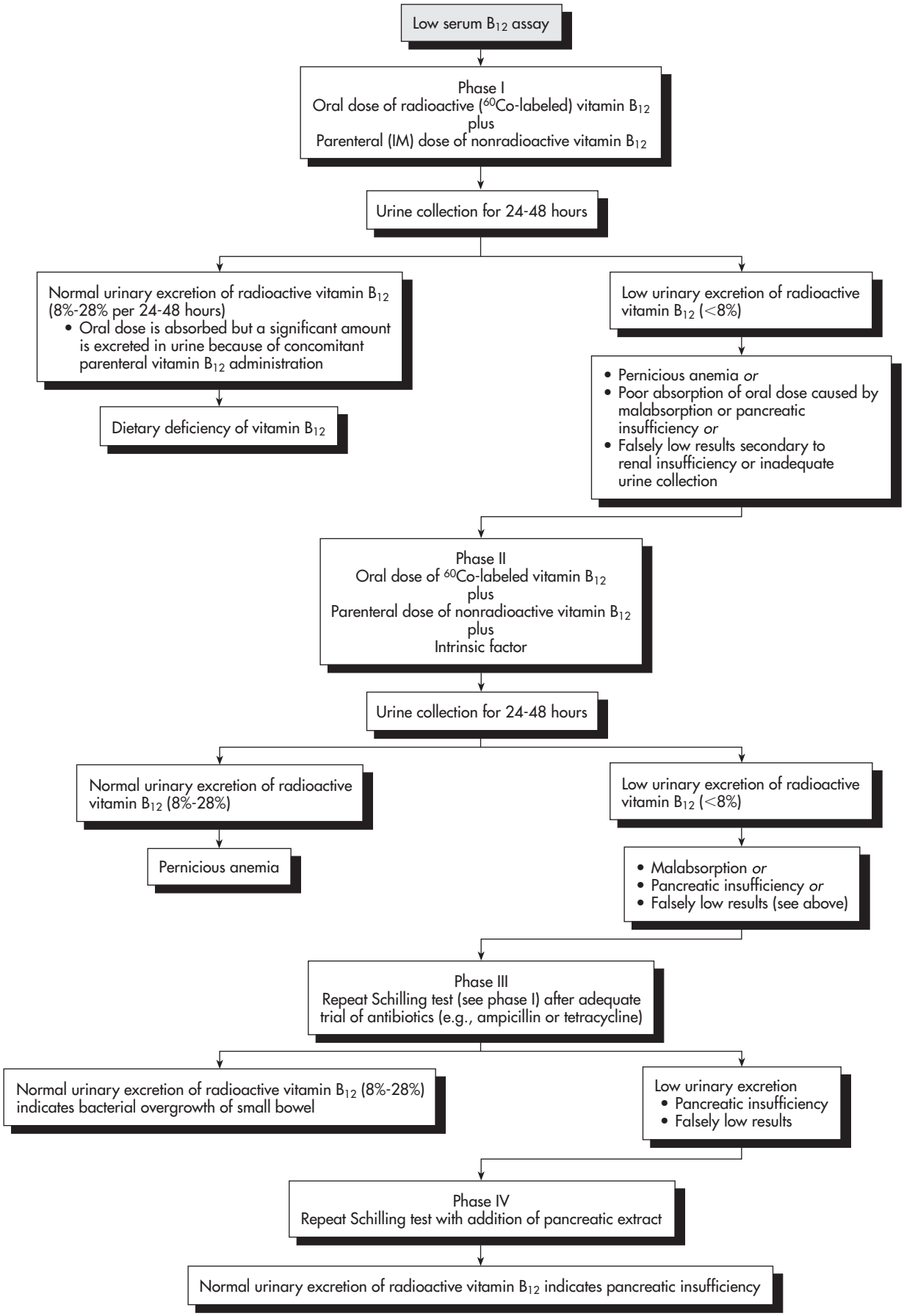


FIGURE E4-38 Schilling test. *IM,* Intramuscular. (From Ferri FF: *Practical guide to the care of the medical patient*, ed 9, St Louis, 2014, Mosby.)

BOX 4-12 Etiopathophysiologic Classification of Cobalamin Deficiency

I. Nutritional cobalamin deficiency (insufficient cobalamin intake)—vegetarians, poverty-imposed near-vegetarians, breastfed infants of mothers with pernicious anemia
II. Abnormal intragastric events (inadequate proteolysis of food cobalamin)—atrophic gastritis, hypochlorhydria, proton pump inhibitors, H_2 blockers
III. Loss/atrophy of gastric oxyntic mucosa (deficient intrinsic factor [IF] molecules)—total or partial gastrectomy, adult and juvenile pernicious anemia, caustic destruction (lye)
IV. Abnormal events in the small bowel lumen
  A. Inadequate pancreatic protease (R factor–cobalamin not degraded, cobalamin not transferred to IF)
    1. Insufficient pancreatic protease—pancreatic insufficiency
    2. Inactivation of pancreatic protease—Zollinger-Ellison syndrome
  B. Usurping of luminal cobalamin (inadequate binding of cobalamin to IF)
    1. By bacteria-stasis syndromes (blind loops, pouches of diverticulosis, strictures, fistulas, anastomosis), impaired bowel motility (scleroderma), hypogammaglobulinemia
    2. By *Diphyllobothrium latum* (fish tapeworm)
V. Disorders of ileal mucosa/IF-cobalamin receptors (IF-cobalamin not bound to IF-cobalamin receptors [cubam receptors])
  A. Diminished or absent cubam receptors—ileal bypass/resection/fistula
  B. Abnormal mucosal architecture/function—tropical/nontropical sprue, Crohn disease, tuberculous ileitis, amyloidosis
  C. Cubam receptor defects—Imerslund-Gräsbeck syndrome
  D. Drug-effects—metformin, cholestyramine, colchicine, neomycin
VI. Disorders of plasma cobalamin transport (transcobalamin [TCII]-cobalamin not delivered to TCII receptors)—congenital TCII deficiency, defective binding of TCII-cobalamin to TCII receptors (rare)
VII. Metabolic disorders (cobalamin not used by cell)
  A. Inborn enzyme errors—cblA to cblG disorders
  B. Acquired disorders (cobalamin inactivated by irreversible oxidation)—nitrous oxide

From Hoffman R: *Hematology: basic principles and practice,* ed 6, Philadelphia, Saunders, 2013.

SECTION V

Clinical Practice Guidelines

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THE PERIODIC HEALTH EXAMINATION*

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*Data modified from U.S. Preventive Services Task Force: *Guide to clinical preventive services: report of the U.S. Preventive Services Task Force,* ed 2, Washington, DC, 1996 (revised 2001), U.S. Department of Health and Human Services. Text downloaded from http://text.nlm.nih.gov

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Age-Specific Charts

TABLE 5-1 Birth to 10 Years

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Leading causes of death
- Conditions originating in perinatal period
- Congenital anomalies
- Sudden infant death syndrome
- Unintentional injuries (non–motor vehicle)
- Motor vehicle injuries

INTERVENTIONS FOR THE GENERAL POPULATION

Screening
- Height and weight
- Blood pressure
- Vision screen (ages 3-4 yr)
- Hemoglobinopathy screen (birth)[1]
- Phenylalanine level (birth)[2]
- Thyroxine and/or thyroid-stimulating hormone (birth)[3]
- Lead level

Counseling

Injury prevention
- Child safety car seats (age <5 yr)
- Lap/shoulder belts (age ≥5 yr)
- Bicycle helmet; avoid bicycling near traffic
- Smoke detector, flame-retardant sleepwear
- Hot water heater temperature <120°-130° F
- Window/stair guards, pool fence
- Safe storage of drugs, toxic substances, firearms, and matches
- Syrup of ipecac, poison control phone number
- CPR training for parents/caretakers

Diet and exercise
- Breastfeeding, iron-enriched formula and foods (infants and toddlers)
- Limit fat and cholesterol; maintain caloric balance; emphasize grains, fruits, vegetables (age ≥2 yr)
- Regular physical activity*

Substance use
- Effects of passive smoking*
- Antitobacco message*

Dental health
- Regular visits to dental care provider*
- Floss, brush with fluoride toothpaste daily*
- Advice about baby bottle tooth decay*

Immunizations
- Diphtheria-tetanus-pertussis (DTaP)[4]
- Inactivated poliovirus vaccine (IPV)[5]
- Measles-mumps-rubella (MMR)[6]
- *Haemophilus influenzae* type b (Hib) conjugate[7]
- Hepatitis A vaccine (HR4)
- Hepatitis B[8]
- Varicella[9]
- Pneumococcal vaccine[10]
- Influenza[11]
- Meningococcal conjugate vaccine (MCV)[12]
- Rotavirus (RV)[13]
- Human papillomavirus vaccine (HPV)[14]

Chemoprophylaxis
- Ocular prophylaxis (birth)

INTERVENTIONS FOR HIGH-RISK POPULATIONS

Population	*Potential Interventions (see detailed high-risk definitions)*
Preterm or low birth weight	Hemoglobin/hematocrit (HR1)
Infants of mothers at risk for HIV	HIV testing (HR2)
Low income; immigrants	Hemoglobin/hematocrit (HR1); PPD (HR3)
TB contacts	PPD (HR3)
Native American/Alaska Native	Hemoglobin/hematocrit (HR1); PPD (HR3); pneumococcal vaccine (HR5)
Residents of long-term care facilities	PPD (HR3); hepatitis A vaccine (HR4); influenza vaccine (HR6)
Certain chronic medical conditions	PPD (HR3); pneumococcal vaccine (HR5); influenza vaccine (HR6)
Increased individual or community lead exposure	Blood lead level (HR7)
Inadequate water fluoridation	Daily fluoride supplement (HR8)
Family history of skin cancer; nevi; fair skin, eyes, hair	Avoid excess/midday sun, use protective clothing* (HR9)

CPR, Cardiopulmonary resuscitation; *HR,* high risk; *PPD,* purified protein derivative; *STDs,* sexually transmitted diseases; *TB,* tuberculosis.

[1]Whether screening should be universal or targeted to high-risk groups depends on the proportion of high-risk individuals in the screening area and other considerations. [2]If done during first 24 hr of life, repeat by age 2 wk. [3]Optimally between day 2 and 6, but in all cases before newborn nursery discharge. [4]2, 4, 6, and 12-18 mo; once between age 4-6 yr. [5]2, 4, 6-18 mo; once between age 4-6 yr. [6]12-15 mo and 4-6 yr. [7]2, 4, 6 and 12-15 mo; no dose needed at 6 mo if PRP-OMP vaccine is used for first 2 doses. [8]Birth, 1 mo, 6 mo; or, 0-2 mo, 1-2 mo later, and 6-18 mo. If not done in infancy: current visit, and 1 and 6 mo later. [9]12-18 mo; or any child without history of chickenpox or previous immunization. Include information on risk in adulthood, duration of immunity, and potential need for booster doses. Administer a second dose of varicella vaccine at age 4-6 yr. [10]Pneumococcal polysaccharide vaccine (PPSV) can be administered at the same time as the other childhood vaccines at a separate site. [11]Influenza vaccine is recommended in children 6 mo-18 yr of age. [12]Administer meningococcal conjugate vaccine (MCV) to children aged 2 through 10 yr with terminal complement component deficiency, anatomic or functional asplenia, and certain other high risk groups (see *MMWR* 54[RR-7], 2005). Persons who received MPSV 3 or more years previously and who remain at increased risk for meningococcal disease should be revaccinated with MCV. [13]Administer first dose at 2 mo. If Rotarix® is administered at ages 2 and 4 mo, a dose at 6 mo is not indicated. [14]HPV4 may be administered in a 3-dose series to males aged 9 through 26 yr and females aged 11 to 26 yr to reduce the likelihood of acquiring genital warts.

*The ability of clinician counseling to influence this behavior is unproven.

HR1: Infants aged 6-12 mo who are living in poverty, black, Native American or Alaska Native, immigrants from developing countries, preterm and low-birth-weight infants, infants whose principal dietary intake is unfortified cow's milk.

HR2: Infants born to high-risk mothers whose HIV status is unknown. Women at high risk include past or present injection drug users; persons who exchange sex for money or drugs and their sex partners; injection drug–using, bisexual, or HIV-positive sex partners currently or in past; persons seeking treatment for STDs; persons who received a blood transfusion between 1978 and 1985.

HR3: Persons infected with HIV, close contacts of persons with known or suspected TB, persons with medical risk factors associated with TB, immigrants from countries with high TB prevalence, medically underserved low-income populations (including homeless), residents of long-term care facilities.

HR4: Hepatitis A vaccine (Hep A) is recommended for all children at 1 yr of age (i.e., 12-23 mo). The two doses in the series should be administered at least 6 mo apart. Children who are not vaccinated by 2 yr of age can be vaccinated at subsequent visits.

HR5: Immunocompetent persons ≥2 yr with certain medical conditions, including chronic cardiac or pulmonary disease, diabetes mellitus, and anatomic asplenia, as well as cochlear implant candidates and recipients. Immunocompetent persons ≥2 yr living in high-risk environments or social settings (e.g., certain Native American and Alaska Native populations).

HR6: Annual vaccinations of children ≥6 mo who are residents of chronic care facilities or who have chronic cardiopulmonary disorders, metabolic diseases (including diabetes mellitus), hemoglobinopathies, immunosuppression, or renal dysfunction.

HR7: Children approximately age 12 mo who (1) live in communities in which the prevalence of lead levels requiring individual intervention, including residential lead hazard control or chelation, is high or undefined; (2) live in or frequently visit a home built before 1950 with dilapidated paint or with recent or ongoing renovation or remodeling; (3) have close contact with a person who has an elevated lead level; (4) live near lead industry or heavy traffic; (5) live with someone whose job or hobby involves lead exposure; (6) use lead-based pottery; or (7) take traditional ethnic remedies that contain lead.

HR8: Children living in areas with inadequate water fluoridation (<0.6 ppm).

HR9: Persons with a family history of skin cancer; a large number of moles; atypical moles; poor tanning ability; or light skin, hair, and eye color.

TABLE 5-2 Ages 11 to 24 Years

Interventions considered and recommended for the Periodic Health Examination

Leading causes of death
- Motor vehicle accidents/other unintentional injuries
- Homicide
- Suicide
- Malignant neoplasms
- Heart diseases

INTERVENTIONS FOR THE GENERAL POPULATION

Screening
- Height and weight
- Blood pressure[1]
- Papanicolaou (Pap) test[2] (females)
- *Chlamydia* screen[3] (females <25 yr)
- HIV screening
- Lipid panel (in high-risk young adults only)
- Rubella serology or vaccination history[4] (females >12 yr)
- Assess for problem drinking
- Lead level

Counseling

Injury prevention
- Lap/shoulder belts
- Bicycle/motorcycle/ATV helmets*
- Smoke detector*
- Safe storage/removal of firearms*

Substance use
- Avoid tobacco use
- Avoid underage drinking and illicit drug use*
- Avoid alcohol/drug use while driving, swimming, boating, etc.*

Sexual behavior
- STD prevention: abstinence*; avoid high-risk behavior*; condoms/female barrier with spermicide*
- Unintended pregnancy: contraception

Diet and exercise
- Limit fat and cholesterol; maintain caloric balance; emphasize grains, fruits, vegetables
- Adequate calcium intake (females)
- Regular physical activity*

Dental health
- Regular visits to dental care provider*
- Floss, brush with fluoride toothpaste daily

Immunizations
- Tetanus, diphtheria, pertussis†
- Hepatitis B[5]
- Measles-mumps-rubella (MMR) (11-12 yr)[6]
- Varicella (11-12 yr)[7]
- Rubella (females >12 yr)[4]
- Meningococcal[8]
- Human papilloma virus (females 11-26 yr, males 9-26 yr)[9]
- Influenza[10]
- Pneumococcal polysaccharide vaccine (PPSV)[11]

Chemoprophylaxis
- Multivitamin with folic acid (females)

INTERVENTIONS FOR HIGH-RISK POPULATIONS

Population	*Potential Interventions (see detailed high-risk definitions)*
High-risk sexual behavior	RPR/VDRL (HR1); screen for gonorrhea (female) (HR2), HIV (HR3), chlamydia (female) (HR4); hepatitis A vaccine (HR5)
Injection or street drug use	RPR/VDRL (HR1); HIV screen (HR3); hepatitis A vaccine (HR5); PPD (HR6); advice to reduce infection risk (HR7)
TB contacts; immigrants; low income	PPD (HR6)
Native Americans/Alaska Natives	Hepatitis A vaccine (HR5); PPD (HR6); pneumococcal vaccine (HR8)
Travelers to developing countries	Hepatitis A vaccine (HR5)
Certain chronic medical conditions	PPD (HR6); pneumococcal vaccine (HR8); influenza vaccine (HR9)
Settings where adolescents and young adults congregate	Second MMR (HR10)
Susceptible to varicella, measles, mumps	Varicella vaccine (HR11); MMR (HR12)
Institutionalized persons; health care/lab workers	Hepatitis A vaccine (HR5); PPD (HR6); influenza vaccine (HR9)
Family history of skin cancer; nevi; fair skin, eyes, hair	Avoid excess/midday sun, use protective clothing* (HR13)
Prior pregnancy with neural tube defect	Folic acid 4.0 mg (HR14)
Inadequate water fluoridation	Daily fluoride supplement (HR15)
Pregnancy	HIV screen, Tdap vaccine (given in second or early third trimester of pregnancy)
Infants 6-11 mo of age travelling internationally	MMR

ATV, All-terrain vehicle; *HR,* high risk; *PPD,* purified protein derivative; *RPR,* rapid plasmin reagin; *STD,* sexually transmitted disease; *TB,* tuberculosis; *VDRL,* Venereal Disease Research Laboratory.

[1]Periodic blood pressure for persons aged ≥21 yr. [2]Screening for cervical cancer should begin at 21 years of age, regardless of sexual behaviors and risk factors. [3]If sexually active, Table 5-6 summarizes cervical cancer screening guidelines. [4]Serologic testing, documented vaccination history, and routine vaccination against rubella (preferably with MMR) are equally acceptable alternatives. [5]If not previously immunized: current visit and 1 and 6 mo later. [6]If no previous second dose of MMR. [7]If susceptible to chickenpox. [8]Meningococcal conjugate vaccine (MCV) can be administered at 11-12 yr visit, at high school entry, or at beginning of college (especially indicated in students living in college dormitories). [9]Quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine (Gardasil) should be given to all females aged 11-26 yr who have not been previously vaccinated. The vaccine is indicated for the prevention of cervical cancer and genital warts caused by the human papilloma virus (HPV) 6, 11, 16, or 18. Gardasil is an intramuscular injection for administration to the thigh or upper arm. The schedule consists of three 0.5-ml doses, with the second dose given 2 mo after the first, and the final dose administered 6 mo after the initial dose. HPV4 may also be administered in a 3-dose series to males aged 9 through 26 years to reduce their likelihood of acquiring genital warts. A bivalent HPV vaccine is available for prevention of cervical dysplasia in females. [10]Influenza vaccine is recommended for children 6 mo to 18 yr of age and all adults. [11]Administer to children with certain underlying medical conditions (see *MMWR* 46[RR-8], 1997), including a cochlear implant. A single revaccination should be administered to children with functional or anatomic asplenia or other immunocompromising condition after 5 yr.

*The ability of clinician counseling to influence this behavior is unproven.

†Tdap vaccine is recommended for adolescents aged 11-12 yr who have completed the recommended childhood DTP/DTaP vaccination series and have not received a Td booster dose. Adolescents aged 13-18 yr who missed the 11-12-yr Td/Tdap booster dose should also receive a single dose of Tdap if they have completed the recommended childhood DTP/DTaP vaccination series. A 5-yr interval from the last Td dose is encouraged when Tdap is used as a booster drug; however, a shorter interval may be used if pertussis immunity is needed.

HR1: Persons who exchange sex for money or drugs and their sex partners, persons with other STDs (including HIV), and sexual contacts of persons with active syphilis. Clinicians should also consider local epidemiology.

HR2: Females who have had two or more sex partners in the last year or a sex partner with multiple sexual contacts; exchanged sex for money or drugs; or have a history of repeated episodes of gonorrhea. Clinicians should also consider local epidemiology.

HR3: Males who had sex with males after 1975; past or present injection drug users; persons who exchange sex for money or drugs and their sex partners; injection drug–using, bisexual, or HIV-positive sex partner currently or in the past; recipients of a blood transfusion between 1978 and 1985; persons seeking treatment for STDs. Clinicians should also consider screening for HIV in general population.

HR4: Sexually active females with multiple risk factors, including history of prior STD, new or multiple sex partners, age <25 yr, nonuse or inconsistent use of barrier contraceptives, or cervical ectopy. Clinicians should consider local epidemiology of the disease in identifying other high-risk groups.

HR5: Persons living in, traveling to, or working in areas where the disease is endemic and where periodic outbreaks occur (e.g., countries with high or intermediate endemicity; certain Alaska Native, Pacific Island, Native American, and religious communities); men who have sex with men; injection or street drug users; persons with clotting factor disorders or chronic liver disease, diabetics. Vaccine may be considered for institutionalized persons and workers in these institutions; military personnel; and day-care, hospital, and laboratory workers. Clinicians should also consider local epidemiology.

HR6: HIV-positive, close contacts of persons with known or suspected TB, health care workers, persons with medical risk factors associated with TB, immigrants from countries with high TB prevalence, medically underserved low-income populations (including homeless), alcoholics, injection drug users, and residents of long-term care facilities.

HR7: Persons who continue to inject drugs.

HR8: Immunocompetent persons with certain medical conditions, including chronic cardiac, renal, or pulmonary disease; diabetes mellitus; cochlear implant candidates and recipients; and anatomic asplenia. Immunocompetent persons who live in high-risk environments or social settings (e.g., certain Native American and Alaska Native populations). Adults who smoke cigarettes, persons with asymptomatic or symptomatic HIV infection.

HR9: Annual vaccination of residents of chronic care facilities; persons with chronic cardiopulmonary disorders, metabolic diseases (including diabetes mellitus), hemoglobinopathies, immunosuppression, or renal dysfunction; and health care providers for high-risk patients.

HR10: Adolescents and young adults in settings where such individuals congregate (e.g., high schools and colleges) if they have not previously received a second dose.

HR11: Healthy persons aged ≥13 yr without a history of chickenpox or previous immunization. Consider serologic testing for presumed susceptible persons aged ≥13 yr.

HR12: Persons born after 1956 who lack evidence of immunity to measles or mumps (e.g., documented receipt of live vaccine on or after the first birthday, laboratory evidence of immunity, or a history of physician-diagnosed measles or mumps).

HR13: Persons with a family or personal history of skin cancer; a large number of moles; atypical moles; poor tanning ability; or light skin, hair, and eye color.

HR14: Women with prior pregnancy affected by neural tube defect who are planning pregnancy.

HR15: Persons aged <17 yr living in areas with inadequate water fluoridation (<0.6 ppm).

TABLE 5-3 Ages 25 to 64 Years

Interventions considered and recommended for the Periodic Health Examination

Leading causes of death
- Malignant neoplasms
- Heart diseases
- Motor vehicle and other unintentional injuries
- HIV infection
- Suicide and homicide

INTERVENTIONS FOR THE GENERAL POPULATION

Screening
- Blood pressure
- Height and weight
- Lipid panel (men aged 35-64 yr, women aged 45-64 yr)
- HIV screening
- Papanicolaou (Pap) test (women)[1]
- Fecal occult blood test[2] and/or colonoscopy (≥50 yr)
- Mammogram ± clinical breast examination[3] (women 40-69 yr)
- Bone density scan in postmenopausal women
- Assess for problem drinking
- Rubella serology or vaccination history[4] (women of childbearing age)

Counseling

Substance use
- Tobacco cessation
- Avoid alcohol/drug use while driving, swimming, boating, etc.*

Diet and exercise
- Limit fat and cholesterol; maintain caloric balance; emphasize grains, fruits, vegetables
- Adequate calcium intake (women)
- Regular physical activity*

Injury prevention
- Lap/shoulder belts
- Motorcycle/bicycle/ATV helmets*
- Smoke detector*
- Safe storage/removal of firearms*

Sexual behavior
- STD prevention: avoid high-risk behavior*; condoms/female barrier with spermicide*
- Unintended pregnancy: contraception

Dental health
- Regular visits to dental care provider*
- Floss, brush with fluoride toothpaste daily*

Immunizations
- Tetanus-diphtheria-pertussis (Tdap) booster
- Rubella[4] (women of childbearing age)
- Influenza vaccine†
- Human papillomavirus[5]
- Herpes zoster (≥60 yr)[6]

Chemoprophylaxis
- Multivitamin with folic acid (women planning or capable of pregnancy)

INTERVENTIONS FOR HIGH-RISK POPULATIONS

Population	*Potential Interventions (see detailed high-risk definitions)*
High-risk sexual behavior	RPR/VDRL (HR1); screen for gonorrhea (female) (HR2), HIV (HR3), chlamydia (female) (HR4); hepatitis B vaccine (HR5); hepatitis A vaccine (HR6)
Injection or street drug use	RPR/VDRL (HR1); HIV screen (HR3); hepatitis B vaccine (HR5); hepatitis A vaccine (HR6); PPD (HR7); advice to reduce infection risk (HR8)
Low income; TB contacts; immigrants; alcoholics	PPD (HR7)
Native Americans/Alaska Natives	Hepatitis A vaccine (HR6); PPD (HR7); pneumococcal vaccine (HR9)
Travelers to developing countries	Hepatitis B vaccine (HR5); hepatitis A vaccine (HR6)
Certain chronic medical conditions	PPD (HR7); pneumococcal vaccine (HR9); influenza vaccine (HR10)
Blood product recipients	HIV screen (HR3); hepatitis B vaccine (HR5); hepatitis C screen
Susceptible to measles, mumps, or varicella	MMR (HR11); varicella vaccine (HR12)
Institutionalized persons	Hepatitis A vaccine (HR6); PPD (HR7); pneumococcal vaccine (HR9); influenza vaccine (HR10)
Health care/lab workers	Hepatitis B vaccine (HR5); hepatitis A vaccine (HR6); PPD (HR7); influenza vaccine (HR10)
Family history of skin cancer; fair skin, eyes, hair	Avoid excess/midday sun, use protective clothing* (HR13)
Previous pregnancy with neural tube defect	Folic acid 4.0 mg (HR14)
Cardiovascular risk factors	Lipid panel (HR 15)
Pregnancy	HIV screen, Tdap vaccine (in second or early third trimester of pregnancy)
Diabetes mellitus	Hepatitis B vaccine (HR5)

ATV, All-terrain vehicle; *HPV,* human papillomavirus; *HR,* high risk; *MMR,* measles-mumps-rubella; *PPD,* purified protein derivative; *RPR,* rapid plasma reagin; *STD,* sexually transmitted disease; *TB,* tuberculosis; *Tdap,* tetanus and diphtheria toxoids and acellular pertussis; *VDRL,* Venereal Disease Research Laboratory.

[1]Women who are or have been sexually active and who have a cervix: q ≤3 yr. Routine Pap smear screening is unnecessary for women who have undergone a complete hysterectomy for benign disease. The American College of Obstetricians and Gynecologists (ACOG) recommends that routine Pap smears should start at age 21. Women 30 and older should wait 3 yrs between paps once they have had three consecutive clear tests. For women 21-29 years old, cervical cytology alone should be performed every 3 years. For women 30-65 years old, co-testing with cervical cytology and human papilloma virus (HPV) testing should be performed every 5 years. Screening should occur more frequently in women who have established risk factors for cervical cancer (including immunocompromised status, HIV infection, history of cervical intraepithelial neoplasia, exposure to diethylstilbesterol in utero). [2]Annually. [3]Mammogram q1-2 yr, or mammogram q1-2 yr with annual clinical breast examination. [4]Serologic testing, documented vaccination history, and routine vaccination (preferably with MMR) are equally acceptable. [5]Quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine (Gardasil) should be given to all females aged 9-26 yr who have not been previously vaccinated. The vaccine is indicated for the prevention of cervical cancer and genital warts caused by the human papillomavirus (HPV) 6, 11, 16, or 18. Gardasil is an intramuscular injection for administration to the thigh or upper arm. The schedule consists of three 0.5-ml doses, with the second dose given 2 mo after the first, and the final dose administered 6 mo after the initial dose. Gardasil is also indicated in males aged 9 to 26 yr for prevention of genital warts. A bivalent HPV vaccine is available for prevention of cervical dysplasia in females. [6]Herpes zoster vaccine (Zostavax) is indicated for prevention of herpes zoster (shingles) in individuals 60 yr or older. Zostavax is administered as a single dose subcutaneously. It is a lyophilic preparation of the Oka/Merck strain of live, attenuated varicella-zoster virus (VZV). It should not be administered to individuals with a history of primary or acquired immunodeficiency states, persons on immunosuppressive therapy (including high-dose corticosteroids), those with active untreated tuberculosis, and those who may be pregnant.

*The ability of clinician counseling to influence this behavior is unproven.

†A live attenuated influenza vaccine (LAIV, Flumist) administered intranasally is available for healthy persons aged 2 to 49 yr.

HR1: Persons who exchange sex for money or drugs and their sex partners, persons with other STDs (including HIV), and sexual contacts of persons with active syphilis. Clinicians should also consider local epidemiology.

HR2: Women who exchange sex for money or drugs or who have had repeated episodes of gonorrhea. Clinicians should also consider local epidemiology.

HR3: Men who had sex with men after 1975; past or present injection drug users; persons who exchange sex for money or drugs and their sex partners; persons with current or past injection drug–using, bisexual, or HIV-positive sex partners; recipients of a blood transfusion between 1978 and 1985; persons seeking treatment for STDs. Clinicians should also consider local epidemiology and HIV screening in the general population.

HR4: Sexually active women with multiple risk factors, including history of STD, new or multiple sex partners, nonuse or inconsistent use of barrier contraceptives, or cervical ectopy. Clinicians should also consider local epidemiology.

HR5: Blood product recipients (including hemodialysis patients), persons with frequent occupational exposure to blood or blood products, men who have sex with men, injection drug users and their sex partners, persons with multiple recent sex partners, persons with other STDs (including HIV), travelers to countries with endemic hepatitis B, all diabetics age 19 to 59.

HR6: Persons living in, traveling to, or working in areas where the disease is endemic and where periodic outbreaks occur (e.g., countries with high or intermediate endemicity; certain Alaska Native, Pacific Island, Native American, and religious communities); men who have sex with men; injection or street drug users; patients with clotting factor disorders or chronic liver disease. Consider for institutionalized persons and workers in these institutions; military personnel; and day-care, hospital, and laboratory workers. Clinicians should also consider local epidemiology.

HR7: HIV-positive, close contacts of persons with known or suspected TB, health care workers, persons with medical risk factors associated with TB, immigrants from countries with high TB prevalence, medically underserved low-income populations (including homeless), alcoholics, injection drug users, and residents of long-term care facilities.

HR8: Persons who continue to inject drugs.

HR9: Immunocompetent institutionalized persons and immunocompetent persons with certain medical conditions, including chronic cardiac, renal, or pulmonary disease; anatomic asplenia; diabetes mellitus; or cochlear implant candidates and recipients. Immunocompetent persons who live in high-risk environments or social settings (e.g., certain Native American and Alaska Native populations), adults who smoke cigarettes, persons with asymptomatic or symptomatic HIV infection.

HR10: Annual vaccination of residents of long-term care facilities; persons with chronic cardiopulmonary disorders, metabolic diseases (including diabetes mellitus), hemoglobinopathies, immunosuppression, or renal dysfunction; and health care providers of high-risk patients.

HR11: Persons born after 1956 who lack evidence of immunity to measles or mumps (e.g., documented receipt of live vaccine on or after the first birthday, laboratory evidence of immunity, or a history of physician-diagnosed measles or mumps).

HR12: Healthy adults without a history of chickenpox or previous immunization. Consider serologic testing for presumed susceptible adults.

HR13: Persons with a family or personal history of skin cancer; a large number of moles; atypical moles; poor tanning ability; or light skin, hair, and eye color.

HR14: Women with previous pregnancy affected by neural tube disorder who are planning pregnancy.

HR15: Clinicians should consider a fasting serum lipid panel on a case-by-case basis.

TABLE 5-4 Ages 65 and Older

Interventions considered and recommended for the Periodic Health Examination

Leading causes of death
- Heart diseases
- Malignant neoplasms (lung, colorectal, breast)
- Cerebrovascular disease
- Chronic obstructive pulmonary disease
- Pneumonia and influenza

INTERVENTIONS FOR THE GENERAL POPULATION

Screening
- Blood pressure
- Height and weight
- Fecal occult blood test[1] and/or colonoscopy
- Mammogram ± clinical breast examination[2] (women ≤69 yr)
- Papanicolaou (Pap) test (women)[3]
- Bone density scan in postmenopausal patients
- Vision screening
- Assess for hearing impairment
- Assess for problem drinking
- Offer HIV screen

Counseling

Substance use
- Tobacco cessation
- Avoid alcohol/drug use while driving, swimming, boating, etc.*
- Diet and exercise
- Limit fat and cholesterol; maintain caloric balance; emphasize grains, fruits, vegetables
- Adequate calcium intake (women)
- Regular physical activity*

Injury prevention
- Lap/shoulder belts
- Motorcycle and bicycle helmets*
- Fall prevention*
- Safe storage/removal of firearms*
- Smoke detector*
- Set hot water heater to <120°-130° F
- CPR training for household members

Dental health
- Regular visits to dental care provider*
- Floss, brush with fluoride toothpaste daily*

Sexual behavior
- STD prevention: avoid high-risk sexual behavior*; use condoms

Immunizations
- Pneumococcal vaccine
- Influenza[1]
- Tetanus-diphtheria (Td) boosters every 10 years, with 1 substitute Tdap dose
- Herpes zoster[4]

INTERVENTIONS FOR HIGH-RISK POPULATIONS

Population	*Potential Interventions (see detailed high-risk definitions)*
Institutionalized persons	PPD (HR1); hepatitis A vaccine (HR2); amantadine/rimantadine (HR4)
Chronic medical conditions; TB contacts; low income; immigrants; alcoholics	PPD (HR1)
Persons ≥75 yr or ≥70 yr with risk factors for falls	Fall prevention intervention (HR5)
Cardiovascular disease risk factors	Consider lipid screening (HR6)
Family history of skin cancer; nevi; fair skin, eyes, hair	Avoid excess/midday sun, use protective clothing* (HR7)
Native Americans/Alaska Natives	PPD (HR1); hepatitis A vaccine (HR2)
Travelers to developing countries	Hepatitis A vaccine (HR2); hepatitis B vaccine (HR8)
Blood product recipients	HIV screen (HR3); hepatitis B vaccine (HR8)
High-risk sexual behavior	Hepatitis A vaccine (HR2); HIV screen (HR3); hepatitis B vaccine (HR8); RPR/VDRL (HR9)
Injection or street drug use	PPD (HR1); hepatitis A vaccine (HR2); HIV screen (HR3); hepatitis B vaccine (HR8); RPR/VDRL (HR9); advice to reduce infection risk (HR10)
Health care/lab workers	PPD (HR1); hepatitis A vaccine (HR2); amantadine/rimantadine (HR4); hepatitis B vaccine (HR8)
Persons susceptible to varicella	Varicella vaccine (HR11)
Men aged 65 to 75 who have ever smoked	Ultrasound of abdominal aorta (HR12)

HR, High risk; *PPD,* purified protein derivative; *RPR,* rapid plasma reagin; *STD,* sexually transmitted disease; *TB,* tuberculosis; *VDRL,* Venereal Disease Research Laboratory.

[1]Annually. [2]Mammogram q1-2 yr, or mammogram q1-2 yr with annual clinical breast exam. [3]The American Cancer Society (ACS) recommends that Pap testing can be discontinued at age 65 after three negative Pap tests or two negative HPV tests in past three years. ACOG (American College of Obstetricians and Gynecologists) recommends discontinuing Pap testing at age 65 to 70 after three negative tests in preceding 10 years. [4]Herpes zoster vaccine (Zostavax) is indicated for prevention of herpes zoster (shingles) in individuals age ≥60 yr. Zostavax is administered as a single dose subcutaneously. It is a lyophilic preparation of the Oka/Merck strain of live, attenuated varicella zoster virus (VZV). It should not be administered to individuals with a history of primary or acquired immunodeficiency states, persons on immunosuppressive therapy (including high-dose corticosteroids), those with active untreated tuberculosis, and those who may be pregnant.

*The ability of clinician counseling to influence this behavior is unproven.

HR1: HIV-positive persons, close contacts of persons with known or suspected TB, health care workers, persons with medical risk factors associated with TB, immigrants from countries with high TB prevalence, medically underserved low-income populations (including homeless), alcoholics, injection drug users, and residents of long-term care facilities.

HR2: Persons living in, traveling to, or working in areas where the disease is endemic and where periodic outbreaks occur (e.g., countries with high or intermediate endemicity; certain Alaska Native, Pacific Island, Native American, and religious communities); men who have sex with men; injection or street drug users; persons with clotting factor disorders or chronic liver disease. Consider for institutionalized persons and workers in these institutions and day care, hospital, and laboratory workers. Clinicians should also consider local epidemiology and HIV screening in the general population.

HR3: Men who had sex with men after 1975; past or present injection drug users; persons who exchange sex for money or drugs and their sex partners; persons with current or past injection drug–using, bisexual, or HIV-positive sex partners; recipients of a blood transfusion between 1978 and 1985; persons seeking treatment for STDs. Clinicians should also consider local epidemiology.

HR4: Consider for persons who have not received influenza vaccine or are vaccinated late, when the vaccine may be ineffective because of major antigenic changes in the virus; for unvaccinated persons who provide home care for high-risk persons; as supplemental protection in persons who are expected to have a poor antibody response; and for high-risk persons in whom the vaccine is contraindicated.

HR5: Persons aged ≥75 yr or 70-74 yr with one or more additional risk factors, including use of certain psychoactive and cardiac medications (e.g., benzodiazepines, antihypertensives); use of four or more prescription medications; impaired cognition, strength, balance, or gait. Intensive individualized, home-based multifactorial fall prevention intervention is recommended in settings where adequate resources are available to deliver such services.

HR6: Clinicians should consider fasting lipid panel screening on a case-by-case basis for persons aged 65 to 75 yr, especially in those with additional risk factors (e.g., smoking, diabetes, or hypertension).

HR7: Persons with a family or personal history of skin cancer; a large number of moles; atypical moles; poor tanning ability; or light skin, hair, and eye color.

HR8: Blood product recipients (including hemodialysis patients), persons with frequent occupational exposure to blood or blood products, men who have sex with men, injection drug users and their sex partners, persons with multiple recent sex partners, persons with other STDs (including HIV), travelers to countries with endemic hepatitis B.

HR9: Persons who exchange sex for money or drugs and their sex partners, persons with other STDs (including HIV), and sexual contacts of persons with active syphilis. Clinicians should also consider local epidemiology.

HR10: Persons who continue to inject drugs.

HR11: Healthy adults without a history of chickenpox or previous immunization. Consider serologic testing for presumed susceptible adults.

HR12: Consider ultrasound of abdominal aorta to screen for abdominal aortic aneurysm in all men aged 65 to 75 yr who have ever smoked.

TABLE 5-5 Pregnant Women*

Interventions considered and recommended for the Periodic Health Examination

INTERVENTIONS FOR THE GENERAL POPULATION	
Screening	Offer amniocentesis (15-18 wk)[1] (age ≥35 yr)
First visit	Offer multiple marker testing[1] (15-18 wk)
Blood pressure	Offer serum α-fetoprotein[1] (16-18 wk)
Hemoglobin/hematocrit	***Counseling***
Hepatitis B surface antigen (HBsAg)	Tobacco cessation; effects of passive smoking
RPR/VDRL	Alcohol/other drug use
Chlamydia screen (<25 yr)	Nutrition, including adequate calcium intake
Rubella serology or vaccination history	Encourage breastfeeding
D(Rh) typing, antibody screen	Lap/shoulder belts
Offer CVS (<13 wk)[1] or amniocentesis (15-18 wk)[1] (age ≥35 yr)	Infant safety car seats
Offer hemoglobinopathy screening	STD prevention: avoid high-risk sexual behavior†; use condoms†
Assess for problem or risk drinking	***Chemoprophylaxis***
Offer HIV screening[2]	Multivitamin with folic acid[3]
Follow-up visits	
Blood pressure	
Urine culture (12-16 wk)	

INTERVENTIONS FOR HIGH-RISK POPULATIONS	
Population	***Potential Interventions (see detailed high-risk definitions)***
High-risk sexual behavior	Screen for chlamydia (first visit) (HR1), gonorrhea (first visit) (HR2), HIV (first visit) (HR3); HBsAg (third trimester) (HR4); RPR/VDRL (third trimester) (HR5)
Blood transfusion between 1978 and 1985	HIV screen (first visit) (HR3)
Injection drug use	HIV screen (HR3); HBsAg (third trimester) (HR4); advice to reduce infection risk (HR6)
Unsensitized D-negative women	D(Rh) antibody testing (24-28 wk) (HR7)
Risk factors for Down syndrome	Offer CVS (first trimester), amniocentesis (15-18 wk)[1] (HR8)
Prior pregnancy with neural tube defect	Offer amniocentesis (15-18 wk),[1] folic acid 4.0 mg[3] (HR9)

CVS, Chorionic villus sampling; *HR,* high risk; *RPR,* rapid plasma reagin; *VDRL,* Venereal Disease Research Laboratory.

[1]Women with access to counseling and follow-up services, reliable standardized laboratories, skilled high-resolution ultrasound and, for those receiving serum marker testing, amniocentesis capabilities. [2]Universal screening is recommended. [3]Beginning at least 1 mo before conception and continuing through the first trimester. *See Tables 5-2 and 5-3 for other preventive services recommended for women of this age group.

†The ability of clinician counseling to influence this behavior is unproven.

HR1: Women with history of STD or new or multiple sex partners. Clinicians should also consider local epidemiology. Chlamydia screen should be repeated in third trimester if at continued risk.

HR2: Women younger than 25 yr with two or more sex partners in the last year or whose sex partner has multiple sexual contacts, women who exchange sex for money or drugs, and women with a history of repeated episodes of gonorrhea. Clinicians should also consider local epidemiology. Gonorrhea screen should be repeated in the third trimester if at continued risk.

HR3: Universal screening for HIV infection is recommended for all pregnant women. It is especially important in women with the following individual risk factors: past or present injection drug use; history of exchanging sex for money or drugs; injection drug–using, bisexual, or HIV-positive sex partner currently or in the past; recipients of a blood transfusion between 1978 and 1985; persons seeking treatment for STDs.

HR4: Women who are initially HBsAg negative who are at high risk because of injection drug use, who have suspected exposure to hepatitis B during pregnancy, and who have had multiple sex partners.

HR5: Women who exchange sex for money or drugs, women with other STDs (including HIV), and sexual contacts of persons with active syphilis. Clinicians should also consider local epidemiology.

HR6: Women who continue to inject drugs.

HR7: Unsensitized D-negative women.

HR8: Prior pregnancy affected by Down syndrome, advanced maternal age (≥35 yr), known carriage of chromosome rearrangement.

HR9: Women with previous pregnancy affected by neural tube defect.

TABLE 5-6 Cervical Cancer Screening Guidelines

Group	ACOG 2009	USPSTF 2012	ACS 2012
Women age <21	No screening	No screening	No screening
Women age 21-29	Cytology every 2 years; HPV testing not recommended	Cytology every 3 years; HPV testing not recommended	Cytology every 3 years; HPV testing not recommended
Women age 30-65	Cytology every 3 years if three consecutive normal results; addition of HPV testing also appropriate	Cytology every 3 years or cytology plus HPV testing every 5 years	Cytology plus HPV every 5 years (preferred) or cytology alone every 3 years; both are regardless of screening history
Women age <65	Following three normal screening results and no abnormal results in the last 10 years, screening may be discontinued	If adequately screened in the past, screening should be discontinued	If adequately screened in the past, screening should be discontinued
Women with total hysterectomy and no prior history of high-grade CIN	No need to continue screening if hysterectomy was for benign indication	Screening should be discontinued	Screening should be discontinued

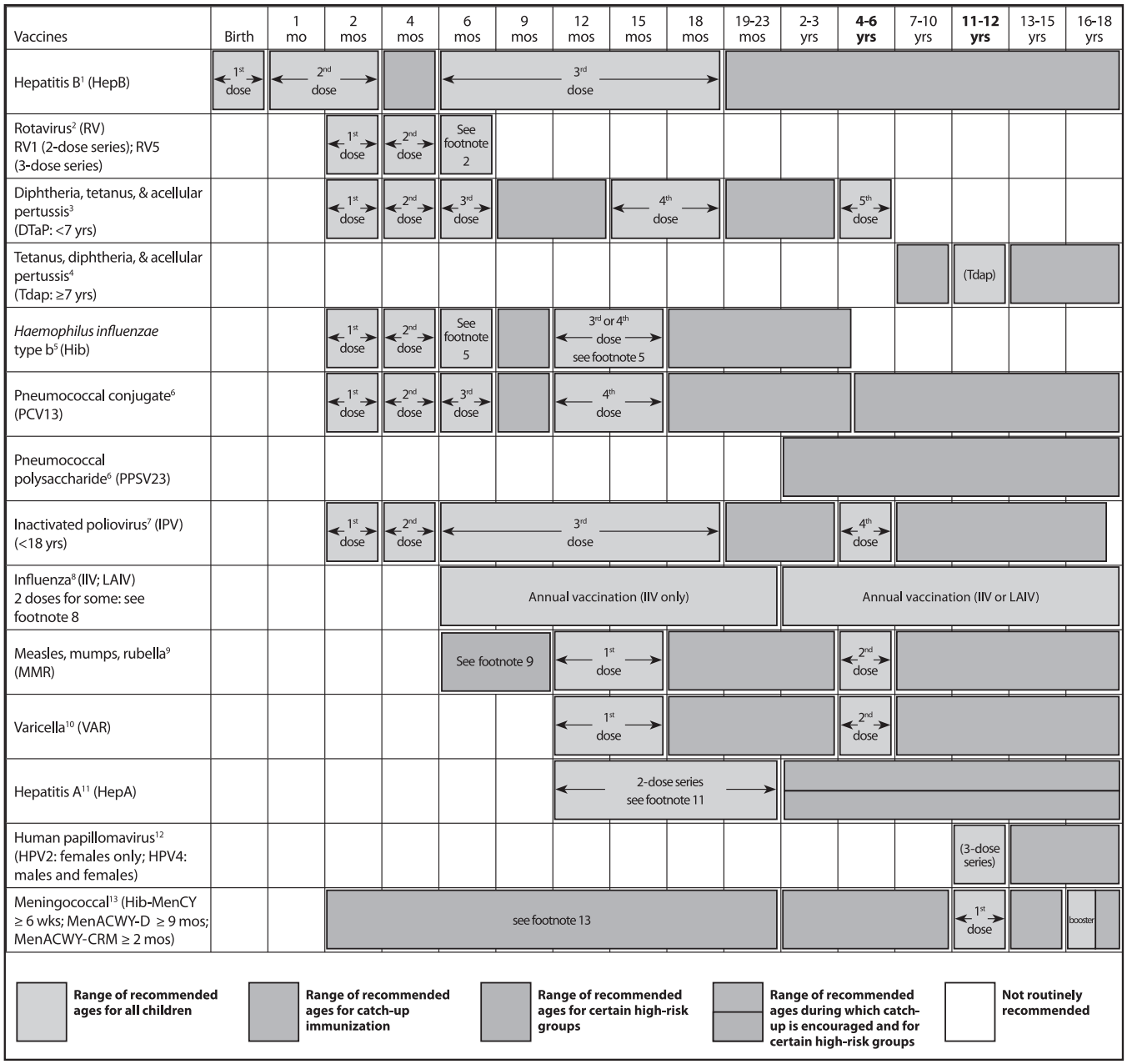
ACOG, American College of Obstetricians and Gynecologists; *ACS,* American Cancer Society; *CIN,* Cervical intraepithelial neoplasia; *HPV,* human papillomavirus; *USPSTF,* U.S. Preventive Services Task Force.

PART B • IMMUNIZATIONS AND CHEMOPROPHYLAXIS

Childhood and Adolescent Immunizations

TABLE 5-7 Recommended Immunization Schedule for Persons Aged 0 Through 18 Years: United States, 2014 (For those who fall behind or start late, see the schedule below and the catch-up schedule [Table 5-8])

These recommendations must be read with the footnotes that follow. For those who fall behind or start late, provide catch-up vaccination at the earliest opportunity as indicated by the divided bars. To determine minimum intervals between doses, see the catch-up schedule (Table 5-8). School entry and adolescent vaccine age groups are in bold.



This schedule includes recommendations in effect as of January 1, 2014. Any dose not administered at the recommended age should be administered at a subsequent visit, when indicated and feasible. The use of a combination vaccine generally is preferred over separate injections of its equivalent component vaccines. Vaccination providers should consult the relevant Advisory Committee on Immunization Practices (ACIP) statement for detailed recommendations, available online at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html. Clinically significant adverse events that follow vaccination should be reported to the Vaccine Adverse Event Reporting System (VAERS) online (http://www.vaers.hhs.gov) or by telephone (800-822-7967). Suspected cases of vaccine-preventable diseases should be reported to the state or local health department. Additional information, including precautions and contraindications for vaccination, is available from CDC online (http://www.cdc.gov/vaccines/recs/vac-admin/contraindications.htm) or by telephone (800-CDC-INFO [800-232-4636]).

This schedule is approved by the Advisory Committee on Immunization Practices (http://www.cdc.gov/vaccines/acip), the American Academy of Pediatrics (http://www.aap.org), the American Academy of Family Physicians (http://www.aafp.org), and the American College of Obstetricians and Gynecologists (http://www.acog.org).

NOTE: The above recommendations must be read along with the footnotes for Table 5-8.

TABLE 5-8 Catch-up Immunization Schedule for Persons Aged 4 Months Through 18 Years Who Start Late or Who Are More Than 1 Month Behind: United States

The table below provides catch-up schedules and minimum intervals between doses for children whose vaccinations have been delayed. A vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Use the section appropriate for the child's age. Always use this table in conjunction with Table 5-7 and the footnotes that follow.

Persons aged 4 months through 6 years					
Vaccine	Minimum Age for Dose 1	Minimum Interval Between Doses			
		Dose 1 to dose 2	Dose 2 to dose 3	Dose 3 to dose 4	Dose 4 to dose 5
Hepatitis B[1]	Birth	4 weeks	8 weeks and at least 16 weeks after first dose; minimum age for the final dose is 24 weeks		
Rotavirus[2]	6 weeks	4 weeks	4 weeks[2]		
Diphtheria, tetanus, pertussis[3]	6 weeks	4 weeks	4 weeks	6 months	6 months[3]
Haemophilus influenzae type b[5]	6 weeks	4 weeks if first dose administered at younger than age 12 months 8 weeks (as final dose) if first dose administered at age 12 through 14 months No further doses needed if first dose administered at age 15 months or older	4 weeks[5] if current age is younger than 12 months **and** first dose was administered at younger than age 7 months, **and** at least 1 previous dose was PRP-T (ActHib, Pentacel) or unknown. 8 weeks *and* age 12 through 59 months (as final dose)[5] • if current age is younger than 12 months **and** first dose was administered at age 7 through 11 months; OR • if current age is 12 through 59 months **and** first dose was administered before the 1st birthday, **and** second dose administered at younger than 15 months; OR • if both doses were PRP-OMP (PedvaxHIB; Comvax) **and** were administered before the 1st birthday. No further doses needed if previous dose was administered at age 15 months or older.	8 weeks (as final dose) This dose only necessary for children age 12 through 59 months who received 3 doses before the 1st birthday.	
Pneumococcal[6]	6 weeks	4 weeks if first dose administered at younger than age 12 months 8 weeks (as final dose for healthy children) if first dose administered at age 12 months or older No further doses needed for healthy children if first dose administered at age 24 months or older	4 weeks if current age is younger than 12 months and previous dose given at <7months old. 8 weeks (as final dose for healthy children) if previous dose given between 7-11 months (wait until at least 12 months old); OR if current age is 12 months or older and at least 1 dose was given before age 12 months. No further doses needed for healthy children if previous dose administered at age 24 months or older.	8 weeks (as final dose) This dose only necessary for children aged 12 through 59 months who received 3 doses before age 12 months or for children at high risk who received 3 doses at any age	
Inactivated poliovirus[7]	6 weeks	4 weeks[7]	4 weeks[7]	6 months[7] minimum age 4 years for final dose	
Meningococcal[13]	6 weeks	8 weeks[13]	see footnote 13	see footnote 13	
Measles, mumps, rubella[9]	12 months	4 weeks			
Varicella[10]	12 months	3 months			
Hepatitis A[11]	12 months	6 months			
Persons aged 7 through 18 years					
Tetanus, diphtheria; tetanus, diphtheria, & acellular pertussis[4]	7 years[4]	4 weeks	4 weeks if first dose administered at younger than age 12 months 6 months (as final dose) if first dose administered at 12 months or older	6 months if first dose of DTaP/DT administered at younger than age 12 months	
Human papillomavirus[12]	9 years	Routine dosing intervals are recommended[12]			
Hepatitis A[11]	Not applicable (N/A)	6 months			
Hepatitis B[1]	N/A	4 weeks	8 weeks (and at least 16 weeks after first dose)		
Inactivated poliovirus[7]	N/A	4 weeks	4 weeks[7]	6 months[7]	
Meningococcal[13]	N/A	8 weeks[13]			
Measles, mumps, rubella[9]	N/A	4 weeks			
Varicella[10]	N/A	3 months if person is younger than age 13 years 4 weeks if person is aged 13 years or older			

NOTE: The above recommendations must be read along with the footnotes on the following pages.

Footnotes — Recommended immunization schedule for persons aged 0 through 18 years—United States, 2014

For further guidance on the use of the vaccines mentioned below, see: http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.
For vaccine recommendations for persons 19 years of age and older, see the adult immunization schedule.

Additional information

- For contraindications and precautions to use of a vaccine and for additional information regarding that vaccine, vaccination providers should consult the relevant ACIP statement available online at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- For purposes of calculating intervals between doses, 4 weeks = 28 days. Intervals of 4 months or greater are determined by calendar months. Vaccine doses administered 4 days or less before the minimum interval are considered valid. Doses of any vaccine administered ≥5 days earlier than the minimum interval or minimum age should not be counted as valid doses and should be repeated as age-appropriate. The repeat dose should be spaced after the invalid dose by the recommended minimum interval. For further details, see *MMWR, General Recommendations on Immunization and Reports* / Vol. 60 / No. 2; Table 1. *Recommended and minimum ages and intervals between vaccine doses* available online at http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.
- Information on travel vaccine requirements and recommendations is available at http://wwwnc.cdc.gov/travel/destinations/list.
- For vaccination of persons with primary and secondary immunodeficiences, see Table 13, "Vaccination of persons with primary and secondary immundeficienc," in General Recommendations on Immunization (ACIP), available at http://www.cdc.gov/mmwr/pdf/rr/rr6002.pdf.; and American Academy of Pediatrics. Immunization in Special Clinical Circumstances, in Pickering LK, Baker CJ, Kimberlin DW, Long SS eds. *Red Book: 2012 report of the Committee on Infectious Diseases. 29th ed.* Elk Grove Village, IL: American Academy of Pediatrics.

1. **Hepatitis B (HepB) vaccine. (Minimum age: birth)**
   Routine vaccination:
   At birth:
   - Administer monovalent HepB vaccine to all newborns before hospital discharge.
   - For infants born to hepatitis B surface antigen (HBsAg)-positive mothers, administer HepB vaccine and 0.5 mL of hepatitis B immune globulin (HBIG) within 12 hours of birth. These infants should be tested for HBsAg and antibody to HBsAg (anti-HBs) 1 to 2 months after completion of the HepB series, at age 9 through 18 months (preferably at the next well-child visit).
   - If mother's HBsAg status is unknown, within 12 hours of birth administer HepB vaccine regardless of birth weight. For infants weighing less than 2,000 grams, administer HBIG in addition to HepB vaccine within 12 hours of birth. Determine mother's HBsAg status as soon as possible and, if mother is HBsAg-positive, also administer HBIG for infants weighing 2,000 grams or more as soon as possible, but no later than age 7 days.

   Doses following the birth dose:
   - The second dose should be administered at age 1 or 2 months. Monovalent HepB vaccine should be used for doses administered before age 6 weeks.
   - Infants who did not receive a birth dose should receive 3 doses of a HepB-containing vaccine on a schedule of 0, 1 to 2 months, and 6 months starting as soon as feasible. See Table 5-8.
   - Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks), administer the third dose at least 8 weeks after the second dose AND at least 16 weeks after the **first** dose. The final (third or fourth) dose in the HepB vaccine series should be administered no earlier than age 24 weeks.
   - Administration of a total of 4 doses of HepB vaccine is permitted when a combination vaccine containing HepB is administered after the birth dose.

   Catch-up vaccination:
   - Unvaccinated persons should complete a 3-dose series.
   - A 2-dose series (doses separated by at least 4 months) of adult formulation Recombivax HB is licensed for use in children aged 11 through 15 years.
   - For other catch-up guidance, see Table 5-8.

2. **Rotavirus (RV) vaccines. (Minimum age: 6 weeks for both RV1 [Rotarix] and RV5 [RotaTeq])**
   Routine vaccination:
   - Administer a series of RV vaccine to all infants as follows:
     1. If Rotarix is used, administer a 2-dose series at 2 and 4 months of age.
     2. If RotaTeq is used, administer a 3-dose series at ages 2, 4, and 6 months.
     3. If any dose in the series was RotaTeq or vaccine product is unknown for any dose in the series, a total of 3 doses of RV vaccine should be administered.

   Catch-up vaccination:
   - The maximum age for the first dose in the series is 14 weeks, 6 days.
   - Vaccination should not be initiated for infants aged 15 weeks, 0 days or older.
   - The maximum age for the final dose i n the series is 8 months, 0 days.
   - If RV-1(Rotraix) is adminitered for the first and second doses, a third dose is not indicted.
   - For other catch-up guidance, see Table 5-8.

3. **Diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine. (Minimum age: 6 weeks. Exception: DTaP-IPV [Kinrix]: 4 years)**
   Routine vaccination:
   - Administer a 5-dose series of DTaP vaccine at ages 2, 4, 6, 15 through 18 months, and 4 through 6 years. The fourth dose may be admintered as early as age 12 months, provided at least 6 months have elapsed since the third dose. However, the fourth dose of DTaP need not be repeated if it was administered at least 4 months after the third dose of DTaP.

   Catch-up vaccination:
   - The fifth dose of DTaP vaccine is not necessary if the fourth dose was administered at age 4 years or older.
   - For other catch-up guidance, see Table 5-8.

4. **Tetanus and diphtheria toxoids and acellular pertussis (Tdap) vaccine. (Minimum age: 10 years for Boostrix, 11 years for Adacel)**
   Routine vaccination:
   - Administer 1 dose of Tdap vaccine to all adolescents aged 11 through 12 years.
   - Tdap may be administered regardless of the interval since the last tetanus and diphtheria toxoid-containing vaccine.
   - Administer 1 dose of Tdap vaccine to pregnant adolescents during each pregnancy (preferred during 27 through 36 weeks gestation) regardless of time since prior Td or Tdap vaccination.

   Catch-up vaccination:
   - Persons aged 7 through 10 years who are not fully immunized with DTaP vaccine should receive Tdap vaccine as 1 (preferably the first) dose in the catch-up series; if additional doses are needed, use Td vaccine.
     For children 7 through 10 years who receive a dose of Tdap as part of the catch-up series, an adolescent Tdap vaccine dose at age 11 through 12 years should NOT be administered. Td should be administered instead 10 years after the Tdap dose.
   - Persons aged 11 through 18 years who have not received Tdap vaccine should receive a dose followed by tetanus and diphtheria toxoids (Td) booster doses every 10 years thereafter.
   - Inadvertent doses of DTaP vaccine:
     - If administered inadvertently to a child aged 7 through 10 years may count as part of the catch-up series. This dose may count as the adolescent Tdap dose, or the child can later receive a Tdap booster dose at age 11 through 12 years.
     - If administered inadvertently to an adolescent aged 11 through 18 years, the dose should be counted as the adolescent Tdap booster.
   - For other catch-up guidance, see Table 5-8.

5. ***Haemophilus influenzae*** **type b (Hib) conjugate vaccine. (Minimum age: 6 weeks for PRP-T [ACTHIB, DTaP-IPV/Hib (Pentacel) and Hib-Men CY (MenHibrix)], PRP-OMP [PedvaxHIB or COMVAX], 12 months for PRP-T [Hiberix])**

Routine vaccination:

- Administer a 2- or 3-dose Hib vaccine primary series and a booster dose (dose 3 or 4 depending on vaccine used in primary series) at age 12 through 15 months to complete a full Hib vaccine series.
- The primary series with ActHIB, MenHibrix, or Pentacel consists of 3 doses and should be administered at 2, 4, and 6 months of age. The primary series with PedvaxHib or COMVAX consists of 2 doses and should be administered at 2 and 4 months of age; a dose at age 6 months is not indicated.
- One booster dose (dose 3 or 4 depending on vaccine used in primary series) of any Hib vaccine should be administered at age 12 through 15 months. An exception is Hiberix vaccine. Hiberix should only be used for the booster (final) dose in children aged 12 months through 4 years who have received at least 1 prior dose of Hib-containing vaccine.
- For recommendations on the use of MenHibrix in patients at increased risk for meningococcal disease, please refer to the meningococcal vaccine footnotes and also to *MMWR* March 22, 2013; 62(RR02);1-22, available at http://www.cdc.gov/mmwr/pdf/rr/rr6202.pdf.

Catch-up vaccination:

- If dose 1 was administered at ages 12 through 14 months, administer a second (final) dose at least 8 weeks after dose 1, regardless of Hib vaccine used in the primary series.
- If both doses were PRP-OMP (PedvaxHIB or COMVAX), and were administered before the first birthday, the third (and final) dose should be administered at age 12 through 59 months and at least 8 weeks after the second dose.
- If the first dose was administered at age 7 through 11 months, administer the second dose at least 4 weeks later and a third (and final) dose at age 12 through 15 months or 8 weeks after second dose, whichever is later, regardless of Hib vaccine used for first dose.
- If first dose is administered at younger than 12 months of age and second dose is given between 12 through 14 months of age, a third (and final) dose should be given 8 weeks later.
- For unvaccinated children aged 15 months or older, administer only 1 dose.
- For other catch-up guidance, see Table 5-8. For catch-up guidance related to MenHibrix, please see the meningococcal vaccine footnotes and also *MMWR* March 22, 2013; 62(RR02);1-22, available at http://www.cdc.gov/mmwr/pdf/rr/rr6202.pdf.

Vaccination of persons with high-risk conditions:

- Children aged 12 through 59 months who are at increased risk for Hib disease, including chemotherapy recipients and those with anatomic or functional asplenia (including sickle cell disease), human immunodeficiency virus (HIV) infection, immunoglobulin deficiency, or early component complement defiency, who have either no doses or only 1 dose of Hib vaccine before 12 months of age, should receive 2 additional doses of Hib vaccine 8 weeks apart; children who received 2 or more doses of Hib vaccine before 12 months of age should receive 1 additional dose.
- For patients younger than 5 years of age undergoing chemotherapy or radiation treatment who received a Hib vaccine dose(s) within 14 days of starting therapy or during therapy, repeat the dose(s) at least 3 months following therapy completion.
- Recipients of hematopoietic stem cell transplant (HSCT) should be revaccinated with a 3-dose regimen of Hib vaccine starting 6 to 12 months after successful transplant, regardless of vaccination history; doses should be administered at least 4 weeks apart.
- A single dose of any Hib-containing vaccine should be administered to unimmunized* children and adolescents 15 months of age and older undergoing an elective splenectomy; if possible, vaccine should be administered at least 14 days before procedure.
- Hib vaccine is not routinely recommended for patients 5 years or older. However, 1 dose of Hib vaccine should be administered to unimmunized* persons aged 5 years or older who have anatomic or functional asplenia (including sickle cell disease) and unvaccinated persons 5 through 18 years of age with human immunodeficiency virus (HIV) infection.

** Patients who have not received a primary series and booster dose or at least 1 dose of Hib vaccine after 14 months of age are considered unimmunized.*

6. **Pneumococcal vaccines. (Minimum age: 6 weeks for PCV13, 2 years for PPSV23) Routine vaccination with PCV13:**

- Administer a 4-dose series of PCV13 vaccine at ages 2, 4, and 6 months and at age 12 through 15 months.
- For children aged 14 through 59 months who have received an age-appropriate series of 7-valent PCV (PCV7), administer a single supplemental dose of 13-valent PCV (PCV13).

Catch-up vaccination with PCV13:

- Administer 1 dose of PCV13 to all healthy children aged 24 through 59 months who are not completely vaccinated for their age.
- For other catch-up guidance, see Table 5-8.

Vaccination of persons with high-risk conditions with PCV13 and PPSV23:

- All recommended PCV13 doses should be administered prior to PPSV23 vaccination if possible.
- For children 2 through 5 years of age with any of the following conditions: chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure); chronic lung disease (including asthama if treated with high-dose oral corticosteroid therapy); diabetes mellitus; cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; solid organ transplantation; or congenital immunodeficiency:
  1. Administer 1 dose of PCV13 if 3 doses of PCV (PCV7 and/or PCV13) were received previously.
  2. Administer 2 doses of PCV13 at least 8 weeks apart if fewer than 3 doses of PCV (PCV7 and/or PCV13) were received previously.
  3. Administer 1 supplemental dose of PCV13 if 4 doses of PCV7 or other age-appropriate complete PCV7 series was received previously.
  4. The minimum interval between doses of PCV (PCV7 or PCV13) is 8 weeks.
  5. For children with no history of PPSV23 vaccination, administer PPSV23 at least 8 weeks after the most recent dose of PCV13.
- For children aged 6 through 18 years who have cerebrospinal fluid leak; cochlear implant; sickle cell disease and other hemoglobinopathies; anatomic or functional asplenia; congential or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; generalized malignancy; solid organ transplantation; or multiple myeloma:
  1. If neither PCV13 nor PPSV23 has been received previously, administer 1 dose of PCV13 now and 1 dose of PPSV23 at least 8 weeks later.
  2. If PCV13 has been received previously but PPSV23 has not, administer 1 dose of PPSV23 at least 8 weeks after the most recent dose of PCV13.
  3. If PPSV23 has been received but PCV13 has not, administer 1 dose of PCV13 at least 8 weeks after the most recent dose of PPSV23.
- For children aged 6 through 18 years with chronic heart disease (particularly cyanotic congenital heart disease and cardiac failure), chronic lung disease (including asthma if treated with high-dose oral corticosteroid therapy), diabetes mellitus, alcoholism, or chronic liver disease, who have not received PPSV23, administer 1 dose of PPSV23. If PCV13 has been received previously, then PPSV23 should be administered at least 8 weeks after any prior PCV13 dose.
- A single revaccination with PPSV23 should be administered 5 years after the first dose to children with sickle cell disease or other hemoglobinopathies; anatomic or functional asplenia; congenital or acquired immunodeficiencies; HIV infection; chronic renal failure; nephrotic syndrome; diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; generalized malignancy; solid organ transplantation; or multiple myeloma.

7. **Inactivated poliovirus vaccine (IPV). (Minimum age: 6 weeks)**
Routine vaccination:
- Administer a 4-dose series of IPV at ages 2, 4, 6 through 18 months, and 4 through 6 years. The final dose in the series should be administered on or after the fourth birthday and at least 6 months after the previous dose.

Catch-up vaccination:
- In the first 6 month of life, minimum age and minimum intervals are only recommended if the person is at risk for imminent exposure to circulating poliovirus (i.e., travel to a polio-endemic region or during an outbreak).
- If 4 or more doses are administered before age 4 years, an additional dose should be administered at age 4 through 6 years and at least 6 months after the previous dose.
- A fourth dose is not necessary if the third dose was administered at age 4 years or older and at least 6 months after the previous dose.
- If both OPV and IPV were administered as part of a series, a total of 4 doses should be administered, regardless of the child's current age. IPV is not routinely recommended for U.S. residents aged 18 years or older.
- For other catch-up guidance, see Table 5-8.

8. **Influenza vaccines. (Minimum age:6 months for inactivated influenza) vaccine [IIV], 2 years for live, attenuated influenza vaccine [LAIV])**
Routine vaccination:
- Administer influenza vaccine annually to all children beginning at age 6 months. For most healthy, nonpregnant persons aged 2 through 49 years, either LAIV or IIV may be used. However, LAIV should NOT be administered to some persons, including 1) persons who have experienced severe allergic reactions to LAIV, any of its components, or to a previous dose of any other influenza vaccine; 2) children 2 through 17 years receiving aspirin or aspirin-containing products; 3) persons who are allergic to eggs; 4) pregnant women; 5) immunosuppressed persons; 6) children 2 through 4 years of age with asthma or who had wheezing in the past 12 months; or 7) persons who have taken influenza antiviral medications in the previous 48 hours. For all other contraindications and precautions to use of LAIV, see *MMWR* August 15, 2014 / 63(32);691-697 [40 pages] available at http://www.cdc.gov/mmwr/pdf/wk/mm6332.pdf.

For children aged 6 months through 8 years:
- For the 2014-15 season, administer 2 doses (separated by at least 4 weeks) to children who are receiving influenza vaccine for the first time. Some children in this age group who have been vaccinated previously will also need 2 doses. For additional guidance, follow dosing guidelines in the 2014-15 ACIP influenza vaccine recommendations, *MMWR* August 15, 2014 / 63(32);691-697 [40 pages] available at http://www.cdc.gov/mmwr/pdf/wk/mm6332.pdf.
- For the 2015-16 season, follow dosing guidlines in the 2015 ACIP influenza vaccine recommendations.

For persons aged 9 years and older:
- Administer 1 dose.

9. **Measles, mumps, and rubella (MMR) vaccine. (Minimum age: 12 months for routine vaccination)**
Routine vaccination:
- Administer a 2-dose series of MMR vaccine at ages12 through 15 months and 4 through 6 years. The second dose may be administered before age 4 years, provided at least 4 weeks have elapsed since the first dose.
- Administer 1 dose of MMR vaccine to infants aged 6 through 11 months before departure from the United States for international travel. These children should be revaccinated with 2 doses of MMR vaccine, the fist at age 12 through 15 months (12 months if the child remains in an area where disease risk is high), and the second dose at least 4 weeks later.
- Administer 2 doses of MMR vaccine to children aged 12 months and older before departure from the United States for international travel. The first dose should be administered on or after age 12 months and the second dose at least 4 weeks later.

Catch-up vaccination:
- Ensure that all school-aged children and adolescents have had 2 doses of MMR vaccine; the minimum interval between the 2 doses is 4 weeks.

10. **Varicella (VAR) vaccine. (Minimum age: 12 months)**
Routine vaccination:
- Administer a 2-dose series of VAR vaccine at ages 12 through 15 months and 4 through 6 years. The second dose may be administered before age 4 years, provided at least 3 months have elapsed since the first dose. If the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid.

Catch-up vaccination:
- Ensure that all persons aged 7 through 18 years without evidence of immunity (see *MMWR* 2007; 56 [No. RR-4], available at http://www.cdc.gov/mmwr/pdf/rr/rr5604.pdf) have 2 doses of varicella vaccine. For children aged 7 through 12 years, the recommended minimum interval between doses is 3 months (if the second dose was administered at least 4 weeks after the first dose, it can be accepted as valid); for persons aged 13 years and older, the minimum interval between doses is 4 weeks.

11. **Hepatitis A vaccine (HepA). (Minimum age: 12 months)**
Routine vaccination:
- Initiate the 2-dose HepA vaccine series at 12 through 23 months; separate the 2 doses by 6 to 18 months.
- Children who have received 1 dose of HepA vaccine before age 24 months should receive a second dose 6 to 18 months after the first dose.
- For any person aged 2 years and older who has not already received the HepA vaccine series, 2 doses of HepA vaccine separated by 6 to 18 months may be administered if immunity against hepatitis A virus infection is desired.

Catch-up vaccination:
- The minimum interval between the two doses is 6 months.

Special populations:
- Administer 2 doses of HepA vaccine at least 6 months apart to previously unvaccinated persons who live in areas where vaccination programs target older children, or who are at increased risk for infection. This includes persons traveling to or working in countries that have high or intermediate endemicity of infection; men having sex with men; users of injection and non-injection illicit drugs; persons who work with HAV-infected primates or with HAV in a research laboratory; persons with clotting-factor disorders; persons with chronic liver disease; and persons who anticipate close, personal contact (e.g., household or regular babysitting) with an international adoptee during the first 60 days after arrival in the United States frm a country with high or intermediate endemicity. The first should be administered as soon as the adoption is planned, ideally 2 or more weeks before the arrival of the adoptee.

12. **Human papillomavirus (HPV) vaccines. (Minimum age: 9 years for HPV2 [Cervarix] and HPV4 [Gardisil])**
Routine vaccination:
- Administer a 3-dose series of HPV vaccine on a schedule of 0, 1-2, and 6 months to all adolescents aged 11 through 12 years. Either HPV4 or HPV2 may be used for females, and only HPV4 may be used for males.
- The vaccine series may be started at age 9 years.
- Administer the second dose 1 to 2 months after the first dose (minimum interval of 4 weeks), administer the third dose 24 weeks after the first dose and 16 weeks after the second dose (minimum interval of 12 weeks).

Catch-up vaccination:
- Administer the vaccine series to females (either HPV2 or HPV4) and males (HPV4) at age 13 through 18 years if not previously vaccinated.
- Use recommended routine dosing intervals (see above) for vaccine series catch-up.

13. **Meningococcal conjugate vaccines. (Minimum age: 6 weeks for Hib-MenCY [MenHibrix], 9 months for MenACWY-D [Menactra], 2 years for MenACWY-CRM [Menveo])**
Routine vaccination:
- Administer a single dose of Menactra or Menveo vaccine at age 11 through 12 years, with a booster dose at age 16 years.

- Adolescents aged 11 through 18 years with human immunodeficiency virus (HIV) infection should receive a 2-dose primary series of Menactra or Menveo with at least 8 weeks between doses.
- For children aged 2 months through 18 years with high-risk conditions, see below.

Catch-up vaccination:

- Administer Menactra or Menveo vaccine at age 13 through 18 years if not previously vaccinated.
- If the first dose is administered at age 13 through 15 years, a booster dose should be administered at age 16 through 18 years with a minimum interval of at least 8 weeks between doses.
- If the first dose is administered at age 16 years or older, a booster dose is not needed.
- For other catch-up guidance, see Table 5-8.

Vaccination of persons with high-risk conditions and other persons at increased risk of disease:

- Children with anatomic or functional asplenia (including sickle cell disease):
  1. Menveo
     - *Children who initiate vaccination at 8 weeks through 6 months:* Administer doses at 2, 4, 6, and 12 months of age.
     - *Unvaccinated children 7 through 23 months:* Administer 2 doses, with the second dose at least 12 weeks after the first dose AND after the first birthday.
     - *Children 24 months and older who have not received a complete series:* Administer 2 primary doses at least 8 weeks apart.
  2. MenHibrix
     - *Children 6 weeks through 18 months:* Administer doses at 2, 4, 6, and 12 through 15 months of age.
     - If the first dose of MenHibrix is given at or after 12 months of age, a total of 2 doses should be given at least 8 weeks apart to ensure protection against serogroups C and Y meningococcal disease.
  3. Menactra
     - *Children 24 months and older who have not received a complete series:* Administer 2 primary doses at least 8 weeks apart. If Menactra is administered to a child with asplenia (including sickle cell disease), do not administer Menactra until 2 years of age and at least 4 weeks after the completion of all PCV13 doses.
- Children with persistent complement component deficiency:
  1. Menveo
     - *Children who initiate vaccination at 8 weeks through 6 months:* Administer doses at 2, 4, 6, and 12 months of age.
     - *Unvaccinated children 7 through 23 months:* Administer 2 doses, with the second dose at least 12 weeks after the first dose AND after the first birthday.
     - *Children 24 months and older who have not received a complete series:* Administer 2 primary doses at least 8 weeks apart.
  2. MenHibrix
     - *Children 6 weeks through 18 months:* Administer doses at 2, 4, 6, and 12 through 15 months of age.
     - If the first dose of MenHibrix is given at or after 12 months of age, a total of 2 doses should be given at least 8 weeks apart to ensure protection against serogroups C and Y meningococcal disease.
  3. Menactra
     - *Children 9 through 23 months:* Administer 2 primary doses at least 12 weeks apart.
     - *Children 24 months and older who have not received a complete series:* Administer 2 primary doses at least 8 weeks apart.
- For children who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic, including countries in the African meningitis belt or the Hajj, administer an age-appropriate formulation and series of Menactra or Menveo for protection against serogroups A and W menigococcal disease. Prior receipt of MenHibrix is not sufficiant for children traveling to the meningitis belt or the Hajj because it does not contain serogroups A or W.
- For children at risk during a community outbreak attributable to a vaccine serogroup, administer or complete an age- and formulation-appropriate series of MenHibrix, Menactra, or Menveo.
- For booster doses among persons with high-risk conditions, refer to *MMWR* 2013; 62(RR02);1-22, available at http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6202a1.htm.

For other catch-up recommendations for these persons, and complete information on use of meningococcal vaccines, including guidance related to vaccination of persons at increased risk of infection, see MMWR March 22, 2013 / 62(RR02);1-22, available at http://www.cdc.gov/mmwr/pdf/rr/rr6202.pdf.

General Recommendations on Immunization

TABLE 5-9 Recommended and Minimum Ages and Intervals between Vaccine Doses*†

Vaccine and Dose Number	Recommended Age for this Dose	Minimum Age for this Dose	Recommended Interval to Next Dose	Minimum Interval to Next Dose
HepB-1§	Birth	Birth	1-4 months	4 weeks
HepB-2	1-2 months	4 weeks	2-17 months	8 weeks
HepB-3¶	6-18 months	24 weeks	—	—
DTaP-1§	2 months	6 weeks	2 months	4 weeks
DTaP-2	4 months	10 weeks***	2 months	4 weeks
DTaP-3	6 months	14 weeks	6-12 months	6 months**††
DTaP-4	15-18 months	12 months	3 years	6 months**
DTaP-5	4-6 years	4 years	—	—
Hib-1§§§	2 months	6 weeks	2 months	4 weeks
Hib-2	4 months	10 weeks	2 months	4 weeks
Hib-3¶¶	6 months	14 weeks	6-9 months	8 weeks
Hib-4	12-15 months	12 months	—	—
IPV-1§	2 months	6 weeks	2 months	4 weeks
IPV-2	4 months	10 weeks	2-14 months	4 weeks
IPV-3	6-18 months	14 weeks	3-5 years	6 months
IPV-4***	4-6 years	4 years	—	—
PCV-1§§	2 months	6 weeks	8 weeks	4 weeks
PCV-2	4 months	10 weeks	8 weeks	4 weeks
PCV-3	6 months	14 weeks	6 months	8 weeks
PCV-4	12-15 months	12 months	—	—
MMR-1†††	12-15 months	12 months	3-5 years	4 weeks
MMR-2†††	4-6 years	13 months	—	—
Varicella-1†††	12-15 months	12 months	3-5 years	12 weeks§§§
Varicella-2†††	4-6 years	15 months	—	—
HepA-1	12-23 months	12 months	6-18 months**	6 months**
HepA-2	≥18 months	18 months	—	—
Influenza inactivated¶¶¶	≥6 months	6 months****	1 month	4 weeks
LAIV (intranasal)¶¶¶	2-49 years	2 years	1 month	4 weeks
MCV4-1††††	11-12 years	2 years	5 years	8 weeks
MCV4-2	16 years	11 years (+8 weeks)	—	—
MPSV4-1††††	—	2 years	5 years	5 years
MPSV4-2	—	7 years	—	—
Td	11-12 years	7 years	10 years	5 years
Tdap§§§§	≥11 years	7 years	—	—
PPSV-1	—	2 years	5 years	5 years
PPSV-2¶¶¶¶	—	7 years	—	—
HPV-1*****	11-12 years	9 years	2 months	4 weeks
HPV-2	11-12 years (+2 months)	9 years (+4 weeks)	4 months	12 weeks†††††
HPV-3†††††	11-12 years (+6 months)	9 years (+24 weeks)	—	—
Rotavirus-1§§§§§	2 months	6 weeks	2 months	4 weeks
Rotavirus-2	4 months	10 weeks	2 months	4 weeks
Rotavirus-3¶¶¶¶¶	6 months	14 weeks	—	—
Herpes zoster******	≥60 years	60 years	—	—

DTaP, Diphtheria and tetanus toxoids and acellular pertussis; *HepA,* hepatitis A; *HepB,* hepatitis B; *Hib, Haemophilus influenzae* type b; *HPV,* human papillomavirus; *IPV,* inactivated poliovirus; *LAIV,* live, attenuated influenza vaccine; *MCV4,* quadrivalent meningococcal conjugate vaccine; *MMR,* measles, mumps, and rubella; *MMRV,* measles, mumps, rubella, and varicella; *MPSV4,* quadrivalent meningococcal polysaccharide vaccine; *PCV,* pneumococcal conjugate vaccine; *PPSV,* pneumococcal polysaccharide vaccine; *PRP-OMB,* polyribosylribitol phosphate-meningococcal outer membrane protein conjugate; *Td,* tetanus and diphtheria toxoids; *Tdap,* tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

*Combination vaccines are available. Use of licensed combination vaccines is generally preferred to separate injections of their equivalent component vaccines. When administering combination vaccines, the minimum age for administration is the oldest age for any of the individual components; the minimum interval between doses is equal to the greatest interval of any of the individual components.

†Information on travel vaccines, including typhoid, Japanese encephalitis, and yellow fever, is available at http://www.cdc.gov/travel. Information on other vaccines that are licensed in the United States but not distributed, including anthrax and smallpox, is available at http://www.bt.cdc.gov.

§Combination vaccines containing the hepatitis B component are available. These vaccines should not be administered to infants aged <6 weeks because of the other components (i.e., Hib, DTaP, HepA, and IPV).

¶HepB-3 should be administered at least 8 weeks after HepB-2 and at least 16 weeks after HepB-1 and should not be administered before age 24 weeks.

**Calendar months.

††The minimum recommended interval between DTaP-3 and DTaP-4 is 6 months. However, DTaP-4 need not be repeated if administered at least 4 months after DTaP-3.

§§For Hib and PCV, children receiving the first dose of vaccine at age ≥7 months require fewer doses to complete the series.

¶¶If PRP-QMP (Pedvax-Hib, Merck Vaccine Division) was administered at ages 2 and 4 months, a dose at age 6 months is not necessary.

***A fourth dose is not needed if the third dose was administered at ≥4 years and at least 6 months after the previous dose.

†††Combination MMRV vaccine can be used for children aged 12 months to 12 years.

TABLE 5-9 Recommended and Minimum Ages and Intervals between Vaccine Doses—cont'd

§§§The minimum interval from Varicella-1 to Varicella-2 for persons beginning the series at age ≥13 years is 4 weeks.
¶¶¶One dose of influenza vaccine per season is recommended for most persons. Children aged <9 years who are receiving influenza vaccine for the first time or who received only 1 dose the previous season (if it was their first vaccination season) should receive 2 doses this season.
****The minimum age for inactivated influenza vaccine varies by vaccine manufacturer. See package insert for vaccine-specific minimum ages.
††††Revaccination with meningococcal vaccine is recommended for previously vaccinated persons who remain at high risk for meningococcal disease. (Source: CDC. Updated recommendations from the Advisory Committee on Immunization Practices (ACIP) for revaccination of persons at prolonged increased risk for meningococcal disease. *MMWR* 2009;58:[1042-3]).
§§§§Only 1 dose of Tdap is recommended. Subsequent doses should be given as Td. For one brand of Tdap, the minimum age is 11 years. For management of a tetanus-prone wound in persons who have received a primary series of tetanus-toxoid–containing vaccine, the minimum interval after a previous dose of any tetanus-containing vaccine is 5 years.
¶¶¶¶A second dose of PPSV 5 years after the first dose is recommended for persons aged ≤65 years at highest risk for serious pneumococcal infection and those who are likely to have a rapid decline in pneumococcal antibody concentration. (Source: CDC. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices [ACIP]. *MMWR* 1997;46[No. RR-8]).
*****Bivalent HPV vaccine is approved for females aged 10-25 years. Quadrivalent HPV vaccine is approved for males and females aged 9-26 years.
†††††The minimum age for HPV-3 is based on the baseline minimum age for the first dose (i.e., 108 months) and the minimum interval of 24 weeks between the first and third dose. Dose 3 need not be repeated if it is administered at least 16 weeks after the first dose.
§§§§§The first dose of rotavirus must be administered at age 6 weeks through 14 weeks and 6 days. The vaccine series should not be started for infants aged ≥15 weeks, 0 days. Rotavirus should not be administered to children older than 8 months, 0 days of age regardless of the number of doses received between 6 weeks and 8 months, 0 days of age.
¶¶¶¶¶If 2 doses of Rotarix (GlaxoSmithKline) are administered as age appropriate, a third dose is not necessary.
******Herpes zoster vaccine is recommended as a single dose for persons aged ≥60 years.

TABLE 5-10 Guidelines for Spacing of Live and Inactivated Antigens

Antigen Combination	Recommended Minimum Interval between Doses
Two or more inactivated*	May be administered simultaneously or at any interval between doses
Inactivated and live	May be administered simultaneously or at any interval between doses
Two or more live intranasal or injectable†	28 days minimum interval, if not administered simultaneously

From Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 60(2):38, 2011.
*Certain experts suggest a 28-day interval between tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine and tetravalent meningococcal conjugate vaccine if they are not administered simultaneously.
†Live oral vaccines (e.g., Ty21a typhoid vaccine and rotavirus vaccine) may be administered simultaneously or at any interval before or after inactivated or live injectable vaccines.

TABLE 5-11 Guidelines for Administering Antibody-Containing Products* and Vaccines

Type of Administration	Products Administered		Recommended Minimum Interval Between Doses
Simultaneous (during the same office visit)	Antibody-containing products and inactivated antigen		Can be administered simultaneously at different anatomic sites or at any time interval between doses
	Antibody-containing products and live antigen		Should not be administered simultaneously.† If simultaneous administration of measles-containing vaccine or varicella vaccine is unavoidable, administer at different sites and revaccinate or test for seroconversion after the recommended interval
Nonsimultaneous	**Administered First**	**Administered Second**	
	Antibody-containing products	Inactivated antigen	No interval necessary
	Inactivated antigen	Antibody-containing products	No interval necessary
	Antibody-containing products	Live antigen	Dose related†‡
	Live antigen	Antibody-containing products	2 weeks†

From Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 60: (RR-2), 2011.
*Blood products containing substantial amounts of immune globulin include intramuscular and intravenous immune globulin, specific hyperimmune globulin (e.g., hepatitis B immune globulin, tetanus immune globulin, varicella zoster immune globulin, and rabies immune globulin), whole blood, packed red blood cells, plasma, and platelet products.
†Yellow fever vaccine; rotavirus vaccine; oral Ty21a typhoid vaccine; live, attenuated influenza vaccine; and zoster vaccine are exceptions to these recommendations. These live, attenuated vaccines can be administered at any time before or after or simultaneously with an antibody-containing product.
‡The duration of interference of antibody-containing products with the immune response to the measles component of measles-containing vaccine, and possibly varicella vaccine, is dose related.

TABLE 5-12 Recommended Intervals between Administration of Antibody-Containing Products and Measles- or Varicella-Containing Vaccine, by Product and Indication for Vaccination

Product/Indication	Dose (mg IgG/kg) and Route*	Recommended Interval before Measles- or Varicella-Containing Vaccine† Administration (months)
Tetanus IG	250 units (10 mg IgG/kg) IM	3
Hepatitis A IG		
Contact prophylaxis	0.02 ml/kg (33 mg IgG/kg) IM	3
International travel	0.06 ml/kg (10 mg IgG/kg) IM	3
Hepatitis B IG	0.06 ml/kg (10 mg IgG/kg) IM	3
Rabies IG	20 IU/kg (22 mg IgG/kg) IM	4
Varicella IG	125 units/10 kg (60–200 mg IgG/kg) IM, maximum 625 units	5
Measles prophylaxis IG		
Standard (i.e., nonimmunocompromised) contact	0.25 ml/kg (40 mg IgG/kg) IM	5
Immunocompromised contact	0.50 ml/kg (80 mg IgG/kg) IM	6
Blood transfusion		
RBCs, washed	10 ml/kg negligible IgG/kg IV	None
RBCs, adenine-saline added	10 ml/kg (10 mg IgG/kg) IV	3
Packed RBCs (hematocrit 65%)§	10 ml/kg (60 mg IgG/kg) IV	6
Whole blood (hematocrit 35%-50%)§	10 ml/kg (80-100 mg IgG/kg) IV	6
Plasma/platelet products	10 ml/kg (160 mg IgG/kg) IV	7
Cytomegalovirus IGIV	150 mg/kg maximum	6
IGIV		
Replacement therapy for immune deficiencies¶	300-400 mg/kg IV¶	8
Immune thrombocytopenic purpura treatment	400 mg/kg IV	8
Postexposure varicella prophylaxis**	400 mg/kg IV	8
Immune thrombocytopenic purpura treatment	1000 mg/kg IV	10
Kawasaki disease	2 g/kg IV	11
Monoclonal antibody to respiratory syncytial virus F protein (Synagis [MedImmune])††	15 mg/kg IM	None

From Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 60: (RR-2), 2011.
HIV, human immunodeficiency virus; *IG,* immune globulin; *IgG,* immune globulin G; *IGIV,* intravenous immune globulin; *mg IgG/kg,* milligrams of immune globulin G per kilogram of body weight; *IM,* intramuscular; *IV,* intravenous; *RBCs,* red blood cells.
*This table is not intended for determining the correct indications and dosages for using antibody-containing products. Unvaccinated persons might not be protected fully against measles during the entire recommended interval, and additional doses of IG or measles vaccine might be indicated after measles exposure. Concentrations of measles antibody in an IG preparation can vary by manufacturer's lot. Rates of antibody clearance after receipt of an IG preparation also might vary. Recommended intervals are extrapolated from an estimated half-life of 30 days for passively acquired antibody and an observed interference with the immune response to measles vaccine for 5 months after a dose of 80 mg IgG/kg.
†Does not include zoster vaccine. Zoster vaccine may be given with antibody-containing blood products.
§Assumes a serum IgG concentration of 16 mg/mL.
¶Measles and varicella vaccinations are recommended for children with asymptomatic or mildly symptomatic HIV infection but are contraindicated for persons with severe immunosuppression from HIV or any other immunosuppressive disorder.
**The investigational VariZIG, similar to licensed varicella-zoster IG (VZIG), is a purified human IG preparation made from plasma containing high levels of antivaricella antibodies (IgG). The interval between VariZIG and varicella vaccine (Var or MMRV) is 5 months.
††Contains antibody only to respiratory syncytial virus.

TABLE 5-13 Contraindications and Precautions* to Commonly Used Vaccines

Vaccine	Contraindications	Precautions
DTaP	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Encephalopathy (e.g., coma, decreased level of consciousness, or prolonged seizures), not attributable to another identifiable cause, within 7 days of administration of previous dose of DTP or DTaP	Progressive neurologic disorder, including infantile spasms, uncontrolled epilepsy, progressive encephalopathy; defer DTaP until neurologic status clarified and stabilized Temperature of ≥105° F (≥40° C) within 48 hours after vaccination with a previous dose of DTP or DTaP Collapse or shock-like state (i.e., hypotonic hyporesponsive episode) within 48 hours after receiving a previous dose of DTP/DTaP Seizure ≤3 days after receiving a previous dose of DTP/DTaP Persistent, inconsolable crying lasting ≥3 hours within 48 hours after receiving a previous dose of DTP/DTaP GBS <6 weeks after previous dose of tetanus toxoid-containing vaccine History of arthus-type hypersensitivity reactions after a previous dose of tetanus toxoid-containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus-toxoid–containing vaccine Moderate or severe acute illness with or without fever
DT, Td	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	GBS <6 weeks after previous dose of tetanus toxoid-containing vaccine History of Arthus-type hypersensitivity reactions after a previous dose of tetanus toxoid-containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus-toxoid–containing vaccine Moderate or severe acute illness with or without fever
Tdap	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Encephalopathy (e.g., coma, decreased level of consciousness, or prolonged seizures), not attributable to another identifiable cause, within 7 days of administration of previous dose of DTP, DTaP, or Tdap	GBS <6 weeks after a previous dose of tetanus toxoid-containing vaccine Progressive or unstable neurologic disorder, uncontrolled seizures, or progressive encephalopathy until a treatment regimen has been established and the condition has stabilized History of Arthus-type hypersensitivity reactions after a previous dose of tetanus toxoid-containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus toxoid-containing vaccine Moderate or severe acute illness with or without fever
IPV	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Pregnancy Moderate or severe acute illness with or without fever
MMR†§	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Pregnancy Known severe immunodeficiency (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, or long-term immunosuppressive therapy¶ or patients with HIV infection who are severely immunocompromised)§	Recent (≤11 months) receipt of antibody-containing blood product (specific interval depends on product) History of thrombocytopenia or thrombocytopenic purpura Need for tuberculin skin testing†† Moderate or severe acute illness with or without fever
Hib	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Age <6 weeks	Moderate or severe acute illness with or without fever
Hepatitis B	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Infant weight <2000 g§§ Moderate or severe acute illness with or without fever
Hepatitis A	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Pregnancy Moderate or severe acute illness with or without fever
Varicella	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Known severe immunodeficiency (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, or long-term immunosuppressive therapy¶ or patients with HIV infection who are severely immunocompromised)§ Pregnancy	Recent (≤11 months) receipt of antibody-containing blood product (specific interval depends on product)¶¶ Moderate or severe acute illness with or without fever
PCV	Severe allergic reaction (e.g., anaphylaxis) after a previous dose (of PCV7, PCV13, or any diphtheria toxoid-containing vaccine) or to a component of a vaccine (PCV7, PCV13, or any diphtheria toxoid-containing vaccine)	Moderate or severe acute illness with or without fever
TIV	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to vaccine component, including egg protein	GBS <6 weeks after a previous dose of influenza vaccine Moderate or severe acute illness with or without fever
LAIV	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to vaccine component, including egg protein Pregnancy Immunosuppression Certain chronic medical conditions***	GBS <6 weeks after a previous dose of influenza vaccine Moderate or severe acute illness with or without fever
PPSV	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Moderate or severe acute illness with or without fever
MCV4	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Moderate or severe acute illness with or without fever

TABLE 5-13 Contraindications and Precautions* to Commonly Used Vaccines—cont'd

Vaccine	Contraindications	Precautions
MPSV4	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Moderate or severe acute illness with or without fever
HPV	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component	Pregnancy Moderate or severe acute illness with or without fever
Rotavirus	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component SCID	Altered immunocompetence other than SCID History of intussusception Chronic gastrointestinal disease††† Spina bifida or bladder exstrophy††† Moderate or severe acute illness with or without fever
Zoster	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component Substantial suppression of cellular immunity Pregnancy	Moderate or severe acute illness with or without fever

From Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 60: (RR-2), 2011.
DT, diphtheria and tetanus toxoids; *DTaP,* diphtheria and tetanus toxoids and acellular pertussis; *GBS,* Guillian-Barré syndrome; *HBsAg,* hepatitis B surface antigen; *Hib, Haemophilus influenzae* type b; *HIV,* human immunodeficiency virus; *HPV,* human papillomavirus; *IPV,* inactivated poliovirus; *LAIV,* live, attenuated influenza vaccine; *MCV4,* quadrivalent meningococcal conjugate vaccine; *MMRV* measles, mumps, rubella; *MPSV4,* quadrivalent meningococcal polysaccharide vaccine; *PCV,* pneumococcal conjugate vaccine; *PPSV,* pneumococcal polysaccharide vaccine; *SCID,* severe combined immunodeficiency; *Td,* tetanus and diphtheria toxoids; *Tdap,* tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; *TIV,* trivalent inactivated influenza vaccine.

*Events or conditions listed as precautions should be reviewed carefully. Benefits of and risks for administering a specific vaccine to a person under these circumstances should be considered. If the risk from the vaccine is believed to outweigh the benefit, the vaccine should not be administered. If the benefit of vaccination is believed to outweigh the risk, the vaccine should be administered. Whether and when to administer DTaP to children with proven or suspected underlying neurologic disorders should be decided on a case-by-case basis.

†HIV-infected children may receive varicella and measles vaccine if $CD4^+$ T-lymphocyte count is <15%. (Source: Adapted from American Academy of Pediatrics. Passive immunization. In: Pickering LK, ed. *Red book: 2009 report of the committee on infectious diseases.* 28th ed. Elk Grove Village. IL: American Academy of Pediatrics: 2009.)

§MMR and varicella vaccines can be administered on the same day. If not administered on the same day, these vaccines should be separated by at least 28 days.

¶Substantially immunosuppressive steroid dose is considered to be ≥2 weeks of daily receipt of 20 mg or 2 mg/kg body weight of prednisone or equivalent.

††Measles vaccination might suppress tuberculin reactivity temporarily. Measles-containing vaccine can be administered on the same day as tuberculin skin testing. If testing cannot be performed until after the day of MMR vaccination, the test should be postponed for ≥4 weeks after the vaccination. If an urgent need exists to skin test, do so with the understanding that reactivity might be reduced by the vaccine.

§§Hepatitis B vaccination should be deferred for infants weighing <2000 g if the mother is documented to be HBsAg-negative at the time of the infant's birth. Vaccination can commence at chronological age 1 month or at hospital discharge. For infants born to HBsAg-positive women, hepatitis B immune globulin and hepatitis B vaccine should be administered within 12 hours after birth, regardless of weight.

¶¶Vaccine should be deferred for the appropriate interval if replacement immune globulin products are being administered.

***Source: CDC. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR* 2010;59(No. RR-8).

†††For details see CDC. Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2009;58(No. RR-2).

TABLE 5-14 Conditions Commonly Misperceived as Contraindications to Vaccination

Vaccine	Conditions Commonly Misperceived as Contraindications (i.e., Vaccination May be Administered under These Conditions)
General for all vaccines, including DTaP, pediatric DT, adult Td, adolescent-adult Tdap, IPV, MMR, Hib, hepatitis A, hepatitis B, varicella, rotavirus, PCV, TIV, LAIV, PPSV, MCV4, MPSV4, HPV, and herpes zoster	Mild acute illness with or without fever Mild-to-moderate local reaction (i.e., swelling, redness, soreness); low-grade or moderate fever after previous dose Lack of previous physical examination in well-appearing person Current antimicrobial therapy* Convalescent phase of illness Preterm birth (hepatitis B vaccine is an exception in certain circumstances)† Recent exposure to an infectious disease History of penicillin allergy, other nonvaccine allergies, relatives with allergies, or receiving allergen extract immunotherapy
DTaP	Fever of <105° F (<40° C), fussiness or mild drowsiness after a previous dose of DTP/DTaP Family history of seizures Family history of sudden infant death syndrome Family history of an adverse event after DTP or DTaP administration Stable neurologic conditions (e.g., cerebral palsy, well-controlled seizures, or developmental delay)
Tdap	Fever of ≥105° F (≥40° C) for <48 hours after vaccination with a previous dose of DTP or DTaP Collapse or shock-like state (i.e., hypotonic hyporesponsive episode) within 48 hours after receiving a previous dose of DTaP Seizure <3 days after receiving a previous dose of DTP/DTaP Persistent, inconsolable crying lasting <3 hours within 48 hours after receiving a previous dose of DTP/DTaP History of extensive limb swelling after DTP/DTaP/Td that is not an arthus-type reaction Stable neurologic disorder History of brachial neuritis Latex allergy that is not anaphylactic Breastfeeding Immunosuppression
IPV	Previous receipt of ≥1 dose of oral polio vaccine
MMR§,¶	Positive tuberculin skin test Simultaneous tuberculin skin testing** Breastfeeding Pregnancy of recipient's mother or other close or household contact Recipient is female of childbearing age Immunodeficient family member or household contact Asymptomatic or mildly symptomatic HIV infection Allergy to eggs
Hepatitis B	Pregnancy Autoimmune disease (e.g., systemic lupus erythematosus or rheumatoid arthritis)
Varicella	Pregnancy of recipient's mother or other close or household contact Immunodeficient family member or household contact†† Asymptomatic or mildly symptomatic HIV infection Humoral immunodeficiency (e.g., agammaglobulinemia)
TIV	Nonsevere (e.g., contact) allergy to latex, thimerosal, or egg Concurrent administration of Coumadin or aminophylline
LAIV	Health care providers that see patients with chronic diseases or altered immunocompetence (an exception is providers for severely immunocompromised patients requiring care in a protected environment) Breastfeeding Contacts of persons with chronic disease or altered immunocompetence (an exception is contacts of severely immunocompromised patients requiring care in a protected environment)
PPSV	History of invasive pneumococcal disease or pneumonia
HPV	Immunosuppression Previous equivocal or abnormal Papanicolaou test Known HPV infection Breastfeeding History of genital warts
Rotavirus	Prematurity Immunosuppressed household contacts Pregnant household contacts
Zoster	Therapy with low-dose methotrexate (≤0.4 mg/kg/week), azathioprine (≤3.0 mg/kg/day), or 6-mercaptopurine (≤1.5 mg/kg/day) for treatment of rheumatoid arthritis, psoriasis, polymyositis, sarcoidosis, inflammatory bowel disease, or other conditions Health care providers of patients with chronic diseases or altered immunocompetence Contacts of patients with chronic diseases or altered immunocompetence Unknown or uncertain history of varicella in a U.S.-born person

From Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 60: (RR-2), 2011.
DT, Diphtheria and tetanus toxoids; *DTP,* diphtheria toxoid, tetanus toxoid, and pertussis; *DTaP,* diphtheria and tetanus toxoids and acellular pertussis; *HBsAg,* hepatitis B surface antigen; *Hib, Haemophilus influenzae* type b; *HPV,* human papillomavirus; *IPV,* inactivated poliovirus; *LAIV,* live, attenuated influenza vaccine; *MCV4,* quadrivalent meningococcal conjugate vaccine; *MMR,* measles, mumps, and rubella; *MPSV4,* quadrivalent meningococcal polysaccharide vaccine; *PCV,* pneumococcal conjugate vaccine; *PPSV,* pneumococcal polysaccharide vaccine; *Td,* tetanus and diphtheria toxoids; *Tdap,* tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis; *TIV,* trivalent inactivated influenza vaccine.

TABLE 5-14 Conditions Commonly Misperceived as Contraindications to Vaccination—cont'd

*Antibacterial drugs might interfere with Ty21a oral typhoid vaccine, and certain antiviral drugs might interfere with varicella-containing vaccines and LAIV.

†Hepatitis B vaccination should be deferred for infants weighing <2000 g if the mother is documented to be HBsAg-negative at the time of the infant's birth. Vaccination can commence at chronologic age 1 month or at hospital discharge. For infants born to HBsAg-positive women, hepatitis B immune globulin and hepatitis B vaccine should be administered within 12 hours after birth, regardless of weight.

§MMR and varicella vaccines can be administered on the same day. If not administered on the same day, these vaccines should be separated by at least 28 days.

¶HIV-infected children should receive immune globulin after exposure to measles. HIV-infected children can receive varicella and measles vaccine if $CD4^+$ T-lymphocyte count is >15%. (Source: Adapted from American Academy of Pediatrics. Passive immunization. In: Pickering LK, ed. *Red book: 2009 report of the Committee on Infectious Diseases,* 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009.)

**Measles vaccination might suppress tuberculin reactivity temporarily. Measles-containing vaccine can be administered on the same day as tuberculin skin testing. If testing cannot be performed until after the day of MMR vaccination, the test should be postponed for at least 4 weeks after the vaccination. If an urgent need exists to skin test, do so with the understanding that reactivity might be reduced by the vaccine.

††If a vaccinee experiences a presumed vaccine-related rash 7-25 days after vaccination, the person should avoid direct contact with immunocompromised persons for the duration of the rash.

VACCINE ADMINISTRATION*

INFECTION CONTROL AND STERILE TECHNIQUE

Persons administering vaccines should follow appropriate precautions to minimize risk for spread of disease. Hands should be cleansed with an alcohol-based, waterless antiseptic hand rub or washed with soap and water between each patient contact. Occupational Safety and Health Administration (OSHA) regulations do not require that gloves be worn when administering vaccinations unless persons administering vaccinations are likely to come into contact with potentially infectious body fluids or have open lesions on their hands. Needles used for injections must be sterile and disposable to minimize the risk for contamination. A separate needle and syringe should be used for each injection. Changing needles between drawing vaccine from a vial and injecting it into a recipient is not necessary. Different vaccines should never be mixed in the same syringe unless specifically licensed for such use, and no attempt should be made to transfer between syringes.

For all intramuscular injections, the needle should be long enough to reach the muscle mass and prevent vaccine from seeping into subcutaneous tissue, but not so long as to involve underlying nerves, blood vessels, or bone. Vaccinators should be familiar with the anatomy of the area where they are injecting vaccine. Intramuscular injections are administered at a 90-degree angle to the skin, preferably into the anterolateral aspect of the thigh or the deltoid muscle of the upper arm depending on the age of the patient.

Decision on needle size and site of injection must be made for each person on the basis of the size of the muscle, the thickness of adipose tissue at the injection site, the volume of the material to be administered, injection technique, and the depth below the muscle surface into which the material is to be injected (Fig. E5-1). Aspiration before injection of vaccines or toxoids (i.e., pulling back on the syringe plunger after needle insertion before injection) is not required because no large blood vessel exists at the recommended injection sites.

INFANTS (AGED <12 MONTHS)

For the majority of infants, the anterolateral aspect of the thigh is the recommended site for injection because it provides a large muscle mass (Fig. E5-2). The muscles of the buttock have not been used for administration of vaccines in infants and children because of concern about potential injury to the sciatic nerve, which is well documented after injection of antimicrobial agents into the buttock. If the gluteal muscle must be used, care should be taken to define the anatomic landmarks.† Injection technique is the most important parameter to ensure efficient intramuscular vaccine delivery. If the subcutaneous and muscle tissue are bunched to minimize the chance of striking bone, a 1-inch needle is required to ensure intramuscular administration in infants. For the majority of infants, a 1-inch, 22- to 25-gauge needle is sufficient to penetrate muscle in an infant's thigh. For newborn (first 28 days of life) and premature infants, a ⅝-inch-long needle usually is adequate if the skin is stretched flat between thumb and forefinger and the needle inserted at a 90-degree angle to the skin.

TODDLERS AND OLDER CHILDREN (AGED 12 MONTHS TO 10 YEARS)

The deltoid muscle should be used if the muscle mass is adequate. The needle size for deltoid site injections can range from 22 to 25 gauge and from ⅝ to 1 inch on the basis of the size of the muscle and the thickness of adipose tissue at the injection site (Fig. E5-3). A ⅝-inch needle is adequate only for the deltoid muscle and only if the skin is stretched flat between the thumb and forefinger and the needle inserted at a 90-degree angle to the skin. For toddlers, the anterolateral thigh can be used, but the needle should be at least 1 inch in length.

ADOLESCENTS AND ADULTS (AGED >11 YEARS)

For adults and adolescents, the deltoid muscle is recommended for routine intramuscular vaccinations. The anterolateral thigh also can be used. For men and women weighing <130 lb (<60 kg) a ⅝- to 1-inch needle is sufficient to ensure intramuscular injection. For women weighing 130 to 200 lb (60 to 90 kg) and men 130 to 260 lb (60 to 118 kg), a 1- to 1½-inch needle is needed. For women weighing >200 lb (>90 kg) or men weighing >260 lb (>118 kg), a 1½-inch needle is required.

SUBCUTANEOUS INJECTIONS

Subcutaneous injections are administered at a 45-degree angle, usually into the thigh for infants younger than 12 months and in the upper-outer triceps area of persons aged 12 months and older. Subcutaneous injections can be administered into the upper-outer triceps area of an infant if necessary. A ⅝-inch, 23- to 25-gauge needle should be inserted into the subcutaneous tissue (Figs. E5-4 and E5-5).

TABLE 5-15 Treatment of Anaphylaxis in Children and Adults with Drugs Administered Intramuscularly or Orally

Drug	Dosage
Children	
Primary Regimen	
Epinephrine 1:1000 (aqueous) (1 mg/ml)*	0.01 mg/kg up to 0.5 mg (administer 0.01 ml/kg/dose up to 0.5 mL) IM repeated every 10-20 minutes up to 3 doses
Secondary Regimen	
Diphenhydramine	1-2 mg/kg oral, IM, or IV, every 4-6 hours (100 mg, maximum single dose)
Hydroxyzine	0.5-1 mg/kg oral, IM, every 4-6 hours (100 mg, maximum single dose)
Prednisone	1.5-2 mg/kg oral (60 mg, maximum single dose); use corticosteroids as long as needed
Adults	
Primary Regimen	
Epinephrine 1:1000 (aqueous)*	0.01 mg/kg up to 0.5 mg (administer 0.01 ml/kg/dose up to 0.5 ml) IM repeated every 10-20 minutes up to 3 doses
Secondary Regimen	
Diphenhydramine	1-2 mg/kg up to l00 mg IM or oral, every 4-6 hours

From Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 60:(RR-2), 2011. Adapted from American Academy of Pediatrics. Passive immunization. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds: *Red book: 2009 report of the Committee on Infectious Diseases,* 28th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2009:66-7; Immunization Action Coalition. Medical management of vaccine reactions in adult patients (available at www.immunize.org/catg.d/p3082.pdf); and *Mosby's drug consult,* St Louis, 2005, Mosby.

IM, Intramuscular; *IV,* intravenous.

*If the agent causing the anaphylactic reaction was administered by injection, epinephrine may be injected into the same site to slow absorption.

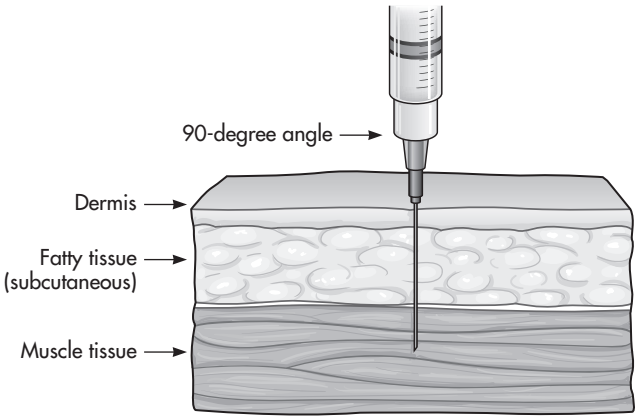


FIGURE E5-1 Intramuscular needle insertion. (Adapted from California Immunization Branch. In Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices [ACIP], *MMWR* 55[RR-15]:16, 2006.)

FIGURE E5-2 Intramuscular/subcutaneous site of administration: anterolateral thigh. (Adapted from Minnesota Department of Health. In Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices [ACIP], *MMWR* 55[RR-15]:6, 2006.)

FIGURE E5-3 Intramuscular site of administration: deltoid. (Adapted from Minnesota Department of Health. In Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices [ACIP], *MMWR* 55[RR-15]:17, 2006.)

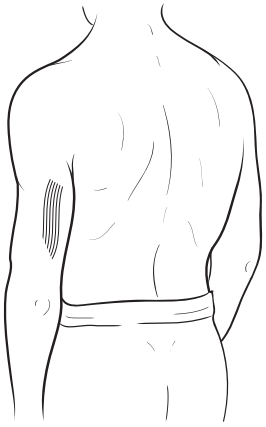


FIGURE E5-4 Subcutaneous site of administration: triceps. (Adapted from Minnesota Department of Health. In Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices [ACIP], *MMWR* 55[RR-15]:17, 2006.)

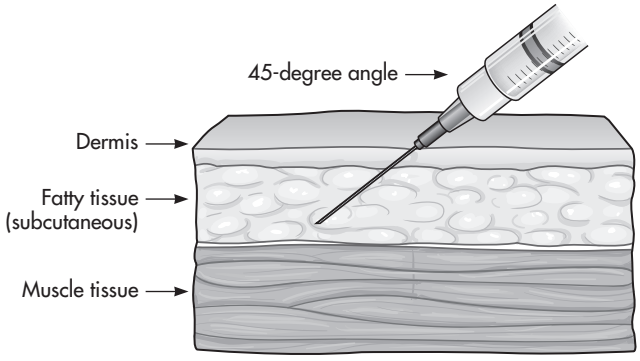


FIGURE E5-5 Subcutaneous needle insertion. (Adapted from California Administration Branch. In Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices [ACIP], *MMWR* 55[RR-15]:17, 2006.)

TABLE 5-16 Vaccination of Persons with Primary and Secondary Immunodeficiencies

Primary	Specific Immunodeficiency	Contraindicated Vaccines*	Risk-Specific Recommended Vaccines*	Effectiveness and Comments
B-lymphocyte (humoral)	Severe antibody deficiencies (e.g., X-linked agammaglobulinemia and common variable immunodeficiency)	OPV† Smallpox LAIV BCG Ty21a (live typhoid) Yellow fever	Pneumococcal Consider measles and varicella vaccination	The effectiveness of any vaccine is uncertain if it depends only on the humoral response (e.g., PPSV or MPSV4). IVIG interferes with the immune response to measles vaccine and possibly varicella vaccine.
	Less severe antibody deficiencies (e.g., selective IgA deficiency and IgG subclass deficiency	OPV† BCG Yellow fever Other live vaccines appear to be safe.	Pneumococcal	All vaccines likely effective; immune response might be attenuated.
T-lymphocyte (cell-mediated and humoral)	Complete deficits (e.g., severe combined immunodeficiency [SCID] disease, complete DiGeorge syndrome)	All live vaccines§,¶,**	Pneumococcal	Vaccines might be ineffective.
	Partial defects (e.g., most patients with DiGeorge syndrome, Wiskott-Aldrich syndrome, ataxia-telangiectasia)	All live vaccines§,¶,**	Pneumococcal Meningococcal Hib (if not administered in infancy)	Effectiveness of any vaccine depends on degree of immune suppression.
Complement	Persistent complement, properdin, or factor B deficiency	None	Pneumococcal Meningococcal	All routine vaccines likely effective.
Phagocytic function	Chronic granulomatous disease, leukocyte adhesion defect, and myeloperoxidase deficiency	Live bacterial vaccines§	Pneumococcal††	All inactivated vaccines safe and likely effective. Live viral vaccines likely safe and effective.
Secondary	HIV/AIDS	OPV† Smallpox BCG LAIV Withhold MMR and varicella in severely immunocompromised persons. Yellow fever vaccine might have a contraindication or a precaution depending on clinical parameters of immune function***	Pneumococcal Consider Hib (if not administered in infancy) and meningococcal vaccination.	MMR, varicella, rotavirus, and all inactivated vaccines, including inactivated influenza, might be effective.§§
	Malignant neoplasm, transplantation, immunosuppressive or radiation therapy	Live viral and bacterial, depending on immune status§,¶	Pneumococcal	Effectiveness of any vaccine depends on degree of immune suppression.
	Asplenia	None	Pneumococcal Meningococcal Hib (if not administered in infancy)	All routine vaccines likely effective.
	Chronic renal disease	LAIV	Pneumococcal Hepatitis B¶¶	All routine vaccines likely effective.

From Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 60:(RR-2), 2011. Adapted from American Academy of Pediatrics. Passive immunization. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds: *Red book: 2009 report of the Committee on Infectious Diseases,* 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009:74–5.

AIDS, acquired immunodeficiency syndrome; *BCG,* bacille Calmette-Guérin; *Hib, Haemophilus influenzae* type b; *HIV,* human immunodeficiency virus; *Ig,* immunoglobulin; *IGIV,* immune globulin intravenous; *LAIV,* live, attenuated influenza vaccine; *MMR,* measles, mumps, and rubella; *MPSV4,* quadrivalent meningococcal polysaccharide vaccine; *OPV,* oral poliovirus polysaccharide vaccine; *PPSV,* pneumococcal polysaccharide vaccine.

*Other vaccines that are universally or routinely recommended should be given if not contraindicated.

†OPV is no longer available in the United States.

§Live bacterial vaccines: BCG and oral Ty21a *Salmonella typhi* vaccine.

¶Live viral vaccines: MMR, MMRV, OPV, LAIV, yellow fever, zoster, rotavirus, varicella, and vaccinia (smallpox). Smallpox vaccine is not recommended for children or the general public.

**Regarding T-lymphocyte immunodeficiency as a contraindication for rotavirus vaccine, data exist only for severe combined immunodeficiency.

††Pneumococcal vaccine is not indicated for children with chronic granulomatous disease beyond age-based universal recommendations for PCV. Children with chronic granulomatous disease are not at increased risk for pneumococcal disease.

§§HIV-infected children should receive IG after exposure to measles and may receive varicella and measles vaccine if $CD4^+$ T-lymphocyte count is ≥15%.

¶¶Indicated based on the risk from dialysis-based bloodborne transmission.

***Symptomatic HIV infection or $CD4^+$ T-lymphocyte count of <200/mm^3 or <15% of total lymphocytes for children aged <6 years is a contraindication to yellow fever vaccine administration. Asymptomatic HIV infection with $CD4^+$ T-lymphocyte count of 200–499/mm^3 for persons aged ≥6 years or 15%–24% of total lymphocytes for children aged <6 years is a precaution for yellow fever vaccine administration. Details of yellow fever vaccine recommendations are available from CDC. (CDC. Yellow fever vaccine recommendations of the Advisory Committee on Immunization Practices [ACIP]. *MMWR* 2010;59[No. RR-7].)

TABLE 5-17 Immunizations for Pediatric Oncology Patients

Vaccine	Indications and Comments
DtaP	Indicated for incompletely immunized children <7 yr, even during active chemotherapy
Td	Indicated 1 yr after completion of therapy in children 7 yr
Hib	Indicated for incompletely immunized children if <7 yr
HBV	Indicated for incompletely immunized children
23PS	Indicated for asplenic patients
PCV13	Indicated for incompletely immunized children <5 yr
Meningococcus	Consider in asplenic patients
IPV	Indicated for incompletely immunized children; also recommended for all household contacts requiring immunization to reduce the risk of vaccine-associated polio
MMR	Contraindicated until child is in remission and finished with all chemotherapy for 3-6 mo; may need to reimmunize after chemotherapy if titers have fallen below protective levels
Influenza	Defer in active chemotherapy; may give as early as 3-4 wk after remission and off chemotherapy if during influenza season; peripheral granulocyte and lymphocyte counts should be >1000/μL; should also be given to household contact of children with cancer
Varicella	Consider immunizing children who have remained in remission and have finished chemotherapy for >1 yr; with absolute lymphocyte count of >700/μl and platelet count of >100,000/μL within 24 hr of immunization; check titers of previously immunized children to verify protective levels of antibodies

From *MMWR* 49(RR-10):1-147, 2000.

DtaP, Diphtheria, tetanus, and pertussis; *HBV,* hepatitis B virus; *Hib, Haemophilus influenzae* type b; *IPV,* inactivated polio vaccine; *MMR,* measles, mumps, rubella; *PCV13,* pneumococcal conjugate vaccine; *Td,* tetanus, diphtheria; *23PS,* 23-valent pneumococcal polysaccharide vaccine.

TABLE 5-18 Approaches to the Evaluation and Vaccination of Persons Vaccinated Outside the United States Who Have No (or Questionable) Vaccination Records

Vaccine	Recommended Approach	Alternative Approach*
MMR	Revaccination with MMR	Serologic testing for IgG antibodies to measles, mumps, and rubella
Hib	Age-appropriate revaccination	—
Hepatitis A	Age-appropriate revaccination	Serologic testing for IgG antibodies to hepatitis A
Hepatitis B	Age-appropriate revaccination and serologic testing for HBsAg†	—
Poliovirus	Revaccinate with inactivated poliovirus vaccine	Serologic testing for neutralizing antibody to poliovirus types 1, 2, and 3 (limited availability)
DTaP	Revaccination with DTaP, with serologic testing for specific IgG antibody to tetanus and diphtheria toxins in the event of a severe local reaction	Persons whose records indicate receipt of ≥3 doses: serologic testing for specific IgG antibody to diphtheria and tetanus toxins before administering additional doses, or administer a single booster dose of DTaP, followed by serologic testing after 1 month for specific IgG antibody to diphtheria and tetanus toxins with revaccination as appropriate
Tdap	Age-appropriate vaccination of persons who are candidates for Tdap vaccine on the basis of time since last diphtheria and tetanus-toxoid–containing vaccines.	—
Varicella	Age-appropriate vaccination of persons who lack evidence of varicella immunity	—
Pneumococcal conjugate	Age-appropriate vaccination	—
Rotavirus	Age-appropriate vaccination	—
HPV	Age-appropriate vaccination	—
Zoster	Age-appropriate vaccination	—

From Centers for Disease Control and Prevention: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 60:(RR-2), 2011.
DTaP, Diphtheria and tetanus toxoids and acellular pertussis; *HBsAg,* hepatitis B surface antigen; *Hib, Haemophilus influenzae* type b; *HPV,* human papillomavirus; *IgG,* immune globulin G; *MMR,* measles, mumps, and rubella; *Tdap,* tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.
*There is a recommended approach for all vaccines and an alternative approach for some vaccines.
†In rare instances, hepatitis B vaccine can give a false-positive HBsAg result up to 18 days after vaccination; therefore, blood should be drawn to test for HBsAg before vaccinating. (Source: CDC. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices [ACIP]; Part I: Immunization in infants, children, and adolescents, *MMWR* 2005;54(No. RR-16.])

Immunizations for Adults

TABLE 5-19 Recommended Adult Immunization Schedule, by Vaccine and Age Group[1]

These recommendations must be read with the footnotes that follow.

VACCINE ▼ AGE GROUP ►	19-21 years	22-26 years	27-49 years	50-59 years	60-64 years	≥65 years
Influenza [2,*]	1 dose annually					
Tetanus, diphtheria, pertussis (Td/Tdap) [3,*]	Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 yrs					
Varicella [4,*]	2 doses					
Human papillomavirus (HPV) Female [5,*]	3 doses					
Human papillomavirus (HPV) Male [5,*]	3 doses					
Zoster [6]					1 dose	
Measles, mumps, rubella (MMR) [7,*]	1 or 2 doses					
Pneumococcal 13-valent conjugate (PCV13) [8,*]	1 or 2 doses					1 dose
Pneumococcal polysaccharide (PPSV23) [8]	1 dose					
Meningococcal [9,*]	1 or more doses					
Hepatitis A [10,*]	2 doses					
Hepatitis B [11,*]	3 doses					
Haemophilus influenzae type b (Hib) [12,*]	1 or 3 doses					

*Covered by the Vaccine Injury Compensation Program

For all persons in this category who meet the age requirements and who lack documentation of vaccination or have no evidence of previous infection; zoster vaccine recommended regardless of prior episode of zoster

Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indication)

No recommendation

Report all clinically significant postvaccination reactions to the Vaccine Adverse Event Reporting System (VAERS). Reporting forms and instructions on filing a VAERS report are available at www.vaers.hhs.gov or by telephone, 800-822-7967.

Information on how to file a Vaccine Injury Compensation Program claim is available at www.hrsa.gov/vaccinecompensation or by telephone, 800-338-2382. To file a claim for vaccine injury, contact the U.S. Court of Federal Claims, 717 Madison Place, N.W., Washington, D.C. 20005; telephone, 202-357-6400.

Additional information about the vaccines in this schedule, extent of available data, and contraindications for vaccination is also available at www.cdc.gov/vaccines or from the CDC-INFO Contact Center at 800-CDC-INFO (800-232-4636) in English and Spanish, 8:00 a.m. - 8:00 p.m. Eastern Time, Monday - Friday, excluding holidays.

Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

The recommendations in this schedule were approved by the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP), the American Academy of Family Physicians (AAFP), the American College of Physicians (ACP), American College of Obstetricians and Gynecologists and American College of Nurse-Midwives (ACNM).

TABLE 5-20A Vaccines That Might Be Indicated for Adults Based on Medical and Other Indications: United States[1]

Note: These recommendations *must* be read with the footnotes that follow containing number of doses, intervals between doses, and other important information.

VACCINE ▼ INDICATION ►	Pregnancy	Immuno-compromising conditions (excluding human immunodeficiency virus [HIV])[4,6,7,8,15]	HIV infection CD4+ T lymphocyte count[4,6,7,8,15]		Men who have sex with men (MSM)	Kidney failure, end-stage renal disease, receipt of hemodialysis	Heart disease, chronic lung disease, chronic alcoholism	Asplenia (including elective splenectomy and persistent complement component deficiencies)[8,12]	Chronic liver disease	Diabetes	Healthcare personnel
			< 200 cells/μL	≥ 200 cells/μL							
Influenza[2,*]	1 dose IIV annually				1 dose IIV or LAIV annually	1 dose IIV annually					1 dose IIV or LAIV annually
Tetanus, diphtheria, pertussis (Td/Tdap)[3,*]	1 dose Tdap each pregnancy	Substitute 1-time dose of Tdap for Td booster; then boost with Td every 10 yrs									
Varicella[4,*]	Contraindicated			2 doses							
Human papillomavirus (HPV) Female[5,*]	3 doses through age 26 yrs					3 doses through age 26 yrs					
Human papillomavirus (HPV) Male[5,*]	3 doses through age 26 yrs					3 doses through age 21 yrs					
Zoster[6]	Contraindicated				1 dose						
Measles, mumps, rubella (MMR)[7,*]	Contraindicated			1 or 2 doses							
Pneumococcal 13-valent conjugate (PCV13)[8,*]	1 dose										
Pneumococcal polysaccharide (PPSV23)[8]	1 or 2 doses										
Meningococcal[9,*]	1 or more doses										
Hepatitis A[10,*]	2 doses										
Hepatitis B[11,*]	3 doses										
Haemophilus influenzae type b (Hib)[12,*]	post-HSCT recipients only	1 or 3 doses									

*Covered by the Vaccine Injury Compensation Program

- For all persons in this category who meet the age requirements and who lack documentation of vaccination or have no evidence of previous infection; zoster vaccine recommended regardless of prior episode of zoster
- Recommended if some other risk factor is present (e.g., on the basis of medical, occupational, lifestyle, or other indications)
- No recommendation

These schedules indicate the recommended age groups and medical indications for which administration of currently licensed vaccines is commonly indicated for adults ages 19 years and older, as of February 1, 2015. For all vaccines being recommended on the Adult Immunization Schedule: a vaccine series does not need to be restarted, regardless of the time that has elapsed between doses. Licensed combination vaccines may be used whenever any components of the combination are indicated and when the vaccine's other components are not contraindicated. For detailed recommendations on all vaccines, including those used primarily for travelers or that are issued during the year, consult the manufacturers' package inserts and the complete statements from the Advisory Committee on Immunization Practices (www.cdc.gov/vaccines/hcp/acip-recs/index.html.) Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

The recommendations in this schedule were approved by the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP), the American Academy of Family Physicians (AAFP), American College of Physicians (ACP), American College of Obstetricians and Gynecologists (ACOG), and American College of Nurse-Midwives (ACNM).

Footnotes: Recommended Immunization Schedule for Adults Aged 19 Years or Older — United States, 2014

1. Additional information
- Additional guidance for the use of the vaccines described in this supplement is available at http://www.cdc.gov/vaccines/hcp/acip-recs/index.html.
- Information on vaccination recommendations when vaccination status is unknown and other general immunization information can be found in the General Recommendations on Immunization at www.cdc.gov/mmwr/preview/mmwrhtml/rr6002a1.htm.
- Information on travel vaccine requirements and recommendations (e.g., for hepatitis A and B, meningococcal, and other vaccines) is available at wwwnc.cdc.gov/travel/destinations.list.
- Additional information and resources regarding vaccination of pregnant women can be found at www.cdc.gov/vaccines/adults/rec-vac/pregnant.html.

2. Influenza vaccination
- Annual vaccination against influenza is recommended for all persons aged 6 months or older.
- Persons aged 6 months or older, including pregnant women and persons with hives-only allergy to eggs, can receive the inactivated influenza vaccine (IIV). An age-appropriate IIV formulation should be used.
- Adults aged 18 to 49 years can receive the recombinant influenza vaccine (RIV) (FluBlok). RIV does not contain any egg protein and can be given to age-appropriate persons with egg allergy of any severity.
- Healthy, nonpregnant persons aged 2 to 49 years without high-risk medical conditions can receive either intranasally administered live, attenuated influenza vaccine (LAIV) (FluMist), or IIV.
- Health care personnel who care for severely immunocompromised persons (i.e., those who require care in a protected environment) should receive IIV or RIV; health care personnel who receive LAIV should avoid providing care for severely immunosuppressed persons for 7 days after vaccination.
- The intramuscularly or intradermally administered IIV are options for adults aged 18 to 64 years.
- Adults aged 65 years or older can receive the standard-dose IIV or the high-dose IIV (Fluzone High-Dose).

* A list of currently available influenza vaccines can be found at www.cdc.gov/flu/protect/vaccine/vaccines.htm.

3. Tetanus, diphtheria, and acellular pertussis (Td/Tdap) vaccination
- Administer 1 dose of Tdap vaccine to pregnant women during each pregnancy (preferred during 27 to 36 weeks' gestation) regardless of interval since prior Td or Tdap vaccination.
- Persons aged 11 years or older who have not received Tdap vaccine or for whom vaccine status is unknown should receive a dose of Tdap followed by tetanus and diphtheria toxoids (Td) booster doses every 10 years thereafter. Tdap can be administered regardless of interval since the most recent tetanus or diphtheria-toxoid containing vaccine.
- Adults with an unknown or incomplete history of completing a 3-dose primary vaccination series with Td-containing vaccines should begin or complete a primary vaccination series including a Tdap dose.
- For unvaccinated adults, administer the first 2 doses at least 4 weeks apart and the third dose 6 to 12 months after the second.
- For incompletely vaccinated (i.e., less than 3 doses) adults, administer remaining doses.
- Refer to the Advisory Commitee on Immunization Practices (ACIP) statement for recommendations for administering Td/Tdap as prophylaxis in wound management (see footnote 1).

4. Varicella vaccination
- All adults without evidence of immunity to varicella (as defined below) should receive 2 doses of single-antigen varicella vaccine or a second dose if they have received only 1 dose.
- Vaccination should be emphasized for those who have close contact with persons at high risk for severe disease (e.g., health care personnel and family contacts of persons with immunocompromising conditions) or are at high risk for exposure or transmission (e.g., teachers; child care employees; residents and staff members of institutional settings, including correctional institutions; college students; military personnel; adolescents and adults living in households with children; nonpregnant women of childbearing age; and international travelers).
- Pregnant women should be assessed for evidence of varicella immunity. Women who do not have evidence of immunity should receive the first dose of varicella vaccine upon completion or termination of pregnancy and before discharge from the health care facility. The second dose should be administered 4 to 8 weeks after the first dose.

- Evidence of immunity to varicella in adults includes any of the following:
  - documentation of 2 doses of varicella vaccine at least 4 weeks apart;
  - U.S.-born before 1980, except health care personnel and pregnant women;
  - history of varicella based on diagnosis or verification of varicella disease by a health care provider;
  - history of herpes zoster based on diagnosis or verification of herpes zoster disease by a health care provider; or
  - laboratory evidence of immunity or laboratory confirmation of disease.

5. Human papillomavirus (HPV) vaccination
- Two vaccines are licensed for use in females, bivalent HPV vaccine (HPV2) and quadrivalent HPV vaccine (HPV4), and one HPV vaccine for use in males (HPV4).
- For females, either HPV4 or HPV2 is recommended in a 3-dose series for routine vaccination at age 11 or 12 years and for those aged 13 through 26 years, if not previously vaccinated.
- For males, HPV4 is recommended in a 3-dose series for routine vaccination at age 11 or 12 years and for those aged 13 through 21 years, if not previously vaccinated. Males aged 22 through 26 years may be vaccinated.
- HPV4 is recommended for men who have sex with men through age 26 years for those who did not get any or all doses when they were younger.
- Vaccination is recommended for immunocompromised persons (including those with HIV infection) through age 26 years for those who did not get any or all doses when they were younger.
- A complete series for either HPV4 or HPV2 consists of 3 doses. The second dose should be administered 4 to 8 weeks (minimum interval of 4 weeks) after the first dose; the third dose should be administered 24 weeks after the first dose and 16 weeks after the second dose (minimum interval of at least 12 weeks).
- HPV vaccines are not recommended for use in pregnant women. However, pregnancy testing is not needed before vaccination. If a woman is found to be pregnant after initiating the vaccination series, no intervention is needed; the remainder of the 3-dose series should be delayed until completion or termination of pregnancy.

6. Zoster vaccination
- A single dose of zoster vaccine is recommended for adults aged 60 years and older regardless of whether they report a prior episode of herpes zoster. Although the vaccine is licensed by the U.S. Food and Drug Administration for use among and can be administered to persons aged 50 years and older, ACIP recommends that vaccination begin at age 60 years.
- Persons aged 60 years and older with chronic medical conditions may be vaccinated unless their condition constitutes a contraindication, such as pregnancy or severe immunodeficiency.

7. Measles, mumps, rubella (MMR) vaccination
- Adults born before 1957 are generally considered immune to measles and mumps. All adults born in 1957 or later should have documentation of 1 or more doses of MMR vaccine unless they have a medical contraindication to the vaccine or laboratory evidence of immunity to each of the 3 diseases. Documentation of provider-diagnosed disease is not considered acceptable evidence of immunity for measles, mumps, or rubella.

Measles component:
- A routine second dose of MMR vaccine, administered a minimum of 28 days after the first dose, is recommended for adults who:
  - are students in postsecondary educational institutions;
  - work in a health care facility; or
  - plan to travel internationally.
- Persons who received inactivated (killed) measles vaccine or measles vaccine of unknown type during 1963-1967 should be revaccinated with 2 doses of MMR vaccine.

Mumps component:
- A routine second dose of MMR vaccine, administered a minimum of 28 days after the first dose, is recommended for adults who:
  - are students in a postsecondary educational institution;
  - work in a health care facility; or
  - plan to travel internationally.
- Persons vaccinated before 1979 with either killed mumps vaccine or mumps vaccine of unknown type who are at high risk for mumps infection (e.g., persons who are working in a health care facility) should be considered for revaccination with 2 doses of MMR vaccine.

Rubella component:
- For women of childbearing age, regardless of birth year, rubella immunity should be determined. If there is no evidence of immunity, women who are not pregnant should be vaccinated. Pregnant women who do not have evidence of immunity should receive MMR vaccine upon completion or termination of pregnancy and before discharge from the health care facility.

Health care personnel born before 1957:
- For unvaccinated health care personnel born before 1957 who lack laboratory evidence of measles, mumps, and/or rubella immunity or laboratory confirmation of disease, health care facilities should consider vaccinating personnel with 2 doses of MMR vaccine at the appropriate interval for measles and mumps or 1 dose of MMR vaccine for rubella.

8. Pneumococcal vaccination (13-valent pneumococcal conjugate vaccine [PCV13] and 23-valent pneumococcal polysaccharide vaccine [PPSV23])
- General information
  - When indicated, only a single dose of PCV13 is recommended for adults.
  - No additional dose of PPSV23 is indicated for adults vaccinated with PPSV23 at of after age 65 years.
  - When both PCV13 and PPSV23 are indicated, PCV13 should be administered first; PCV13 and PPSV23 should not be administered during the during the same visit.
  - When indicated, PCV13 and PPSV23 should be administered to adults whose pneumococcal vaccination history is incomplete or unknown.
- Adults aged 65 years or older who
  - Have not received PCV13 or PPSV23: Administer PCV13 followed by PPSV23 in 6 to 12 months.
  - Have not received PCV13 but have received a dose of PPSV23 at age 65 years or older: Administer PCV13 at least 1 year after the dose of PPSV23 received at age 65 years or older.
  - Have not received PCV13 but have received 1 or more doses of PPSV23 before age 65: Administer PCV13 at least 1 year after the most recent dose of PPSV23; administer a dose of PPSV23 6 to 12 months after PCV13, or as soon as possible if this time window has passed, and at least 5 years after the most recent dose of PPSV23.
  - Have received PCV13 but not PPSV23 before age 65 years: Administer PPSV23 6 to 12 months after PCV13 or as soon as possible if this time window has passed.
  - Have received PCV13 and 1 or more doses of PPSV23 before age 65 years: Administer PPSV23 6 to 12 months after PCV13, or as soon as possible if this time window has passed, and at least 5 years after the most recent dose of PPSV23.
- Adults aged 19 through 64 years with immunocompromising conditions or anatomical or functional asplenia (defined below) who
  - Have not received PCV13 or PPSV23: Administer PCV13 followed by PPSV23 at least 8 weeks after PCV13; administer a second dose of PPSV23 at least 5 years after the first dose of PPSV23.
  - Have not received PCV13 but have received 1 dose of PPSV23: Administer PCV13 at least 1 year after the PPSV23; administer a second dose of PPSV23 at least 8 weeks PCV13 and at least 5 years after the first dose of PPSV23.
  - Have not received PCV13 but have received 2 doses of PPSV23: Administer PCV13; administer a second dose of PPSV23 at least 5 years after the first dose of PPSV23.
  - Have received PCV13 but not PPSV23: Administer PPSV23 at least 8 weeks after PCV13; administer a second dose of PPSV23 at least 5 years after the first dose of PPSV23.
  - Have received PCV13 and 1 dose of PPSV23: Administer a second dose of PPSV23 at least 5 years after the first dose of PPSV23.
- Adults aged 19 through 64 years with cerebrospinal fluid leak or cochlear implant: Administer PCV13 followed by PPSV23 at least 8 weeks after PCV13.
- Adults aged 19 through 64 years with chronic heart disease (including congestive heart failure and cardiomyopathies, excluding hypertension), chronic lung disease (including chronic obstructive lung disease, emphysema, and asthma), chronic liver disease (including cirrhosis), alcoholism, or diabetes mellitus: Administer PPSV23
- Adults aged 19 through 64 years who smoke cigarettes or reside in nursing home or long-term care facilities: Administer PPSV23.
- Routine pneumococcal vaccination is not recommended for American Indian/Alaska Native or other adults unless they have the indications as above; however, public health authorities may consider recommending the use of pneumococcal vaccines for American Indians/Alaska Natives or other adults who live in areas with increased risk of invasive penumococcal disease.
- Immunocompromising conditions that are indications for pneumococcal vaccination are congenital or acquired immunodeficiency (including B- or T-lymphocyte deficiency, complement deficiencies, and phagocytic disorders excluding chronic granulomatous disease), HIV infection, chronic renal failure, nephrotic syndrome, leukemia, lymphoma, Hodgkin disease, generalized malignancy, multiple myeloma, solid-organ transplant, and iatrogenic immunosuppression (including long-term systemic corticosteroids and radiation therapy).
- Anatomical or functional asplenia that are indications for pneumococcal vaccination are sickle cell disease and other hemoglobinopathies, congential or acquired asplenia, splenic dysfunction, and splenectomy. Administer pneumococcal vaccines at least 2 weeks before immunosuppressive therapy or elective splenectomy, and as soon as possible to adults who are newly diagnosed with asymptomatic or symptomatic HIV infection.

9. Meningococcal vaccination
- Administer 2 doses of quadrivalent meningococcal conjugate vaccine (MenACWY-D [Menactra, Menveo]) at least 2 months apart to adults of all ages with anatomical or functional asplenia or persistent complement component deficiencies. HIV infection is not an indication for routine vaccination with MenACWY-D. If an HIV-infected person of any age is vaccinated, 2 doses of MenACWY-D should be administered at least 2 months apart.

- Administer a single dose of meningococcal vaccine to microbiologists routinely exposed to isolates of *Neisseria meningitidis*, military recruits, persons at risk during an outbreak attributable to a vaccine serogroup, and persons who travel to or live in countries in which meningococcal disease is hyperendemic or epidemic.
- First-year college students up through age 21 years who are living in residence halls should be vaccinated if they have not received a dose on or after their 16th birthday.
- MenACWY-D is preferred for adults with any of the preceding indications who are aged 55 years or younger as well as for adults aged 56 years or older who a) were vaccinated previously with MenACWY-D and are recommended for revaccination, or b) for whom multiple doses are anticipated. Meningococcal polysaccharide vaccine MPSV4 [Menomune]) is preferred for adults aged 56 years or older who have not received MenACWY-D previously and who require a single dose only (e.g., travelers.)
- Revaccination with MenACWY-D every 5 years is recommended for adults previously vaccinated with MenACWY-D or MPSV4 who remain at increased risk for infection (e.g., adults with anatomic or functional asplenia, those with persistent complement component deficiencies, or microbiologists).

10. Hepatitis A vaccination

- Vaccinate any person seeking protection from hepatitis A virus (HAV) infection and persons with any of the following indications:
  - men who have sex with men and persons who use injection or non-injection illicit drugs;
  - persons working with HAV-infected primates or with HAV in a research laboratory setting;
  - persons with chronic liver disease and persons who receive clotting factor concentrates;
  - persons traveling to or working in countries that have high or intermediate endemicity of hepatitis A; and
  - unvaccinated persons who anticipate close personal contact (e.g., household or regular babysitting) with an international adoptee during the first 60 days after arrival in the United States from a country with high or intermediate endemicity. (See footnote 1 for more information on travel recommendations). The first dose of the 2-dose hepatitis A vaccine series should be administered as soon as adoption is planned, ideally 2 or more weeks before the arrival of the adoptee.
- Single-antigen vaccine formulations should be administered in a 2-dose schedule at either 0 and 6 to 12 months (Havrix), or 0 and 6 to 18 months (Vaqta). If the combined hepatitis A and hepatitis B vaccine (Twinrix) is used, administer 3 doses at 0, 1, and 6 months; alternatively, a 4-dose schedule may be used, administered on days 0, 7, and 21 to 30 followed by a booster dose at month 12.

11. Hepatitis B vaccination

- Vaccinate persons with any of the following indications and any person seeking protection from hepatitis B virus (HBV) infection:
  - sexually active persons who are not in a long-term, mutually monogamous relationship (e.g., persons with more than 1 sex partner during the previous 6 months); persons seeking evaluation or treatment for a sexually transmitted disease (STD); current or recent injection drug users; and men who have sex with men;
  - health care personnel and public safety workers who are potentially exposed to blood or other infectious body fluids;
  - persons with diabetes who are younger than age 60 years as soon as feasible after diagnosis; persons with diabetes who are age 60 years or older at the discretion of the treating clinician based on the likelihood of acquiring HBV infection, including the risk posed by an increased need for assisted blood glucose monitoring in long-term care facilities, the likelihood of experiencing chronic sequelae if infected with HBV, and the likelihood of immune response to vaccination;
  - persons with end-stage renal disease, including patients receiving hemodialysis, persons with HIV infection, and persons with chronic liver disease;
  - all adults in the following settings: STD treatment facilities, HIV testing and treatment facilities, facilities providing drug abuse treatment and prevention services, health care settings targeting services to injection drug users or men who have sex with men, correctional facilities, end-stage renal disease programs and facilities for chronic hemodialysis patients, and institutions and nonresidential day care facilities for persons with developmental disabilities.
- Administer missing doses to complete a 3-dose series of hepatitis B vaccine to those persons not vaccinated or not completely vaccinated. The second dose should be administered 1 month after the first dose; the third dose should be given at least 2 months after the second dose (and at least 4 months after the first dose). If the combined hepatitis A and hepatitis B vaccine (Twinrix) is used, give 3 doses at 0, 1, and 6 months; alternatively, a 4-dose Twinrix schedule, administered on days 0, 7, and 21 to 30 followed by a booster dose at month 12 may be used.
- Adult patients receiving hemodialysis or with other immunocompromising conditions should receive 1 dose of 40 mcg/mL (Recombivax HB) administered on a 3-dose schedule at 0, 1, and 6 months or 2 doses of 20 mcg/mL (Engerix-B) administered simultaneously on a 4-dose schedule at 0, 1, 2, and 6 months.

12. *Haemophilus influenzae* type b (Hib) vaccination

- One dose of Hib vaccine should be administered to persons who have functional or anatomic asplenia or sickle cell disease or are undergoing elective splenectomy if they have not previously received Hib vaccine. Hib vaccination 14 or more days before splenectomy is suggested.
- Recipients of a hematopoietic stem cell transplant should be vaccinated with a 3-dose regimen 6 to 12 months after a successful transplant, regardless of vaccination history; at least 4 weeks should separate doses.
- Hib vaccine is not recommended for adults with HIV infection since their risk for Hib infection is low.

13. Immunocompromising conditions

- Inactivated vaccines generally are acceptable (e.g., pneumococcal, meningococcal, and inactivated influenza vaccine) and live vaccines generally are avoided in persons with immune deficiencies or immunocompromising conditions. Information on specific conditions is available at http://www.cdc.gov/vaccines/pubs/acip-list.htm.

TABLE 5-20B Contraindications and Precautions to Commonly Used Vaccines in Adults*†‡

Vaccine	Contraindications	Precautions
Influenza, inactivated vaccine (IIV)§	Severe allergic reaction (e.g., anaphylaxis) after previous dose of any influenza vaccine or to a vaccine component, including egg protein.	Moderate or severe acute illness with or without fever. History of Guillain-Barré Syndrome (GBS) within 6 weeks of previous influenza vaccination. Adults who experience only hives with exposure to eggs should receive RIV or, with additional safety precautions, IIV.§
Influenza, recombinant (RIV)	Severe allergic reactions (e.g., anaphylaxis) after previous dose of RIV or to a vaccine component. RIV does not contain any egg protein.§	Moderate or severe acute illness with or without fever. History of Guillain-Barre syndrome within 6 weeks of previous influenza vaccination.
Influenza, live attenuated (LAIV)§,ll	Severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine, or to a previous dose of any influenza vaccine. In addition, ACIP recommends that LAIV not be used in the following populations: -pregnant women; -immunosuppressed adults; -adults with egg allergy of any severity; or -adults who have taken influenza antiviral medications (amatadine, rimantadine, zanamivir, or oseltamivir) within the previous 48 hours; avoid use of these antiviral drugs for 14 days after vaccination.	Moderate or severe acute illness with or without fever. History of GBS within 6 weeks of previous influenza vaccination. Asthma in persons aged 5 years or older. Other chronic medical conditions (e.g., other chronic lung diseases, chronic cardiovascular disease [excluding isolated hypertension], diabetes, chronic renal or hepatic disease, hematologic disease, neurologic disease, and metabolic disorders).
Tetanus, diphtheria, pertussis (Tdap); tetanus, diphtheria (Td)	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component. For pertussis-containing vaccines: encephalopathy (e.g., coma, decreased level of consciousness, or prolonged seizures) not attributable to another identifiable cause within 7 days of administration of a previous dose of Tdap or diphtheria and tetanus toxoids and pertussis (DTP) or diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine.	Moderate or severe acute illness with or without fever. GBS within 6 weeks after a previous dose of tetanus toxoid–containing vaccine. History of arthus-type hypersensitivity reactions after a previous dose of tetanus or diptheria toxoid–containing vaccine; defer vaccination until at least 10 years have elapsed since the last tetanus toxoid-containing vaccine. For pertussis-containing vaccines: progressive or unstable neurologic disorder, uncontrolled seizures, or progressive encephalopathy until a treatment regimen has been established and the condition has stabilized.
Varicella‖	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component. Known severe immunodeficiency (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, or long-term immunosuppressive therapy¶ or patients with human immunodeficiency virus (HIV) infection who are severely immunocompromised). Pregnancy.	Recent (within 11 months) receipt of antibody-containing blood product (specific interval depends on product).** Moderate or severe acute illness with or without fever. Receipt of specific antivirals (i.e., acyclovir, famciclovir, or valacyclovir) 24 hours before vaccination; avoid use of these antiviral drugs for 14 days after vaccination.
Human papillomavirus (HPV)	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component.	Moderate or severe acute illness with or without fever. Pregnancy.
Zoster‖	Severe allergic reaction (e.g., anaphylaxis) to a vaccine component. Known severe immunodeficiency (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, or long-term immunosuppressive therapy¶ or patients with HIV infection who are severely immunocompromised). Pregnancy.	Moderate or severe acute illness with or without fever. Receipt of specific antivirals (i.e., acyclovir, famciclovir, or valacyclovir) 24 hours before vaccination; avoid use of these antiviral drugs for 14 days after vaccination.

TABLE 5-20B Contraindications and Precautions to Commonly Used Vaccines in Adults*†‡—cont'd

Vaccine	Contraindications	Precautions
Measles, mumps, rubella (MMR)[II]	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component. Known severe immunodeficiency (e.g., from hematologic and solid tumors, receipt of chemotherapy, congenital immunodeficiency, or long-term immunosuppressive therapy[¶] or patients with HIV infection who are severely immunocompromised). Pregnancy.	Moderate or severe acute illness with or without fever. Recent (within 11 months) receipt of antibody-containing blood product (specific interval depends on product).[**] History of thrombocytopenia or thrombocytopenic purpura. Need for tuberculin skin testing.[††]
Pneumococcal conjugate (PCV13)	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component, including to any vaccine containing diphtheria toxoid.	Moderate or severe acute illness with or without fever.
Pneumococcal polysaccharide (PPSV23)	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component.	Moderate or severe acute illness with or without fever.
Meningococcal, conjugate,(MenACWY); meningococcal, polysaccharide (MPSV4)	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component.	Moderate or severe acute illness with or without fever.
Hepatitis A	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component.	Moderate or severe acute illness with or without fever.
Hepatitis B	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component.	Moderate or severe acute illness with or without fever.
Haemophilus influenzae type b (Hib)	Severe allergic reaction (e.g., anaphylaxis) after a previous dose or to a vaccine component.	Moderate or severe acute illness with or without fever.

* Adapted from CDC. Table 6. Contraindications and precautions to commonly used vaccines. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices. MMWR 2011;60(No. RR-2):40–41 and from Atkinson W, Wolfe S, Hamborsky J, eds. Appendix A. Epidemiology and prevention of vaccine preventable diseases. 12th ed. Washington, DC: Public Health Foundation, 2011. Available at http://www.cdc.gov/vaccines/pubs/pinkbook/index.html.

† Regarding latex allergy. Consult the package insert for any vaccine administered.

‡ Vaccine package inserts and the full ACIP recommendations for these vaccines should be consulted for additional information on vaccine-related contraindications and precautions and for more information on vaccine excipients. Events or conditions listed as precautions should be reviewed carefully. Benefits of and risks for administering a specific vaccine to a person under these circumstances should be considered. If the risk from the vaccine is believed to outweigh the benefit, the vaccine should not be administered. If the benefit of vaccination is believed to outweigh the risk, the vaccine should be administered. A contraindication is a condition in a recipient that increases the chance of a serious adverse reaction. Therefore, a vaccine should not be administered when a contraindication is present.

§ For more information on use of influenza vaccines among persons with egg allergies and a complete list of conditions that CDC considers to be reasons to avoid receiving LAIV, see Grohskopf LA, Olsen SJ, Sokolow LZ, Bresee JS, Cox NJ, Broder KR et al; Centers for Disease Control and Prevention/ Prevention and and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices.

II LAIV, MMR, varicella, and zoster vaccines can be administered on the same day. If not administered on the same day, these live vaccines should be separated by at least 28 days.

¶ Immunosuppressive steroid dose is considered to be 2 or more weeks of daily receipt of 20 mg prednisone or the equivalent. Vaccination should be deferred for at least 1 month after discontinuation of such therapy. Providers should consult ACIP recommendations for complete information on the use of specific live vaccines among persons on immune-suppressing medications or with immune suppression because of other reasons.

** Vaccine should be deferred for the appropriate interval if replacement immune globulin products are being administered. See General recommendations on immunization: recommendations of the Advisory Committee on Immunization of Practices (ACIP). MMWR Recomm Rep. 2011:60;1-64 (available at www.cdc.gov/vaccines/pubs/pinkbook/index.html).

†† Measles vaccination might suppress tuberculin reactivity temporarily. Measles-containing vaccine may be administered on the same day as tuberculin skin testing. If testing cannot be performed until after the day of MMR vaccination, the test should be postponed for at least 4 weeks after the vaccination. If an urgent need exists to skin test, do so with the understanding that reactivity might be reduced by the vaccine.

TABLE 5-21 Immunization and Pregnancy

Vaccine	Before Pregnancy	During Pregnancy	After Pregnancy	Type of Vaccine	Route
Hepatitis A	If at high risk for disease	If at high risk for disease	If at high risk for disease	Inactivated	IM
Hepatitis B	Yes, if at risk	Yes, if at risk	Yes, if at risk	Inactivated	IM
Human papillomavirus (HPV)	Yes, if 9 to 26 years of age	No, under study	Yes, if 9 to 26 years of age	Inactivated	IM
Influenza TIV	Yes	Yes	Yes	Inactivated	IM
Influenza LAIV	Yes, if <50 years and healthy; avoid conception for 4 weeks	No	Yes, if <50 years and healthy; avoid conception for 4 weeks	Live	Nasal spray
MMR	Yes, avoid conception for 4 weeks	No	Yes, give immediately postpartum if susceptible to rubella	Live	SC
Meningococcal:	If indicated	If indicated	If indicated		
• Polysaccharide				Inactivated	SC
• Conjugate				Inactivated	IM
Pneumococcal polysaccharide	If indicated	If indicated	If indicated	Inactivated	IM or SC
Tetanus/diphtheria Td	Yes, Tdap preferred	If indicated	Yes, Tdap preferred	Toxoid	IM
Tdap, one dose only	Yes, preferred	If high risk of pertussis; otherwise, Td preferred	Yes, preferred	Toxoid/inactivated	IM
Varicella	Yes, avoid conception for 4 weeks	No	Yes, give immediately postpartum if susceptible	Live	SC

IM, Intramuscular; *LAIV,* live, attenuated influenza vaccine; *SC,* subcutaneous; *Tdap,* tetanus and diphtheria toxoids and acellular pertussis; *TIV,* trivalent inactivated influenza vaccine.

TABLE 5-22 Immunizing Agents and Immunization Schedules for Health Care Workers (HCWs)*

Generic Name	Primary Schedule and Booster(s)	Indications	Major Precautions and Contraindications	Special Considerations
Immunizing Agents Strongly Recommended for Health Care Workers				
Hepatitis B (HB) recombinant vaccine	Two doses IM 4 wk apart; third dose 5 mo after second; booster doses not necessary	**Preexposure:** HCWs at risk for exposure to blood or body fluids	Based on limited data no risk of adverse effects to developing fetuses is apparent. Pregnancy should *not* be considered a contraindication to vaccination of women. Previous anaphylactic reaction to common baker's yeast is a contraindication to vaccination.	The vaccine produces neither therapeutic nor adverse effects on HB-infected persons. Prevaccination serologic screening is not indicated for persons being vaccinated because of occupational risk. HCWs who have contact with patients or blood should be tested 1-2 mo after vaccination to determine serologic response.
Hepatitis B immune globulin (HBIG)	0.06 ml/kg IM as soon as possible after exposure. A second dose of HBIG should be administered 1 mo later if the HB vaccine series has not been started.	**Postexposure prophylaxis:** For persons exposed to blood or body fluids containing HBsAg and who are not immune to HBV infection—0.06 ml/kg IM as soon as possible (but no later than 7 days after exposure)		
Influenza vaccine (inactivated whole-virus and split-virus vaccines)	Annual vaccination with current vaccine Administered IM	HCWs who have contact with patients at high risk for influenza or its complications; HCWs who work in long-term care facilities; HCWs with high-risk medical conditions or who are aged ≥65 yr	History of anaphylactic hypersensitivity to egg ingestion	No evidence exists of risk to mother or fetus when the vaccine is administered to a pregnant woman with an underlying high-risk condition. Influenza vaccination is recommended during second and third trimesters of pregnancy because of increased risk for hospitalization.
Measles live-virus vaccine	One dose SC; second dose at least 1 mo later	HCWs† born during or after 1957 who do not have documentation of having received two doses of live vaccine on or after the first birthday **or** a history of physician-diagnosed measles or serologic evidence of immunity. Vaccination should be considered for all HCWs who lack proof of immunity, including those born before 1957.	Pregnancy; immunocompromised persons,‡ including HIV-infected persons who have evidence of severe immunosuppression; anaphylaxis after gelatin ingestion or administration of neomycin; recent administration of immune globulin	MMR is the vaccine of choice if recipients are likely to be susceptible to rubella and/or mumps as well as measles. Persons vaccinated between 1963 and 1967 with a killed measles vaccine alone, killed vaccine followed by live vaccine, or with a vaccine of unknown type should be revaccinated with two doses of live measles virus vaccine.
Mumps live-virus vaccine	One dose SC; second dose at least 1 mo later	HCWs† believed to be susceptible can be vaccinated. Adults born before 1957 can be considered immune.	Pregnancy; immunocompromised persons,‡ history of anaphylactic reaction after gelatin ingestion or administration of neomycin	MMR is the vaccine of choice if recipients are likely to be susceptible to measles and rubella, as well as mumps.
Hepatitis A virus (HAV) vaccine	Two doses of vaccine either 6-12 mo apart (HAVRIX), or 6 mo apart (VAQTA)	Not routinely indicated for HCWs in the United States. Persons who work with HAV-infected primates or with HAV in a research laboratory setting should be vaccinated.	History of anaphylactic hypersensitivity to alum or, for HAVRIX, the preservative 2-phenoxyethanol. The safety of the vaccine in pregnant women has not been determined; the risk associated with vaccination should be weighed against the risk for hepatitis A in women who may be at high risk for exposure to HAV.	
Meningococcal vaccine	One dose in volume and by route specified by manufacturer; single booster for adults 19 to 21 years of age if the first dose was given before age 16	Laboratory personnel and others with exposure risk.	The safety of the vaccine in pregnant women has not been evaluated; it should not be administered during pregnancy unless the risk for infection is high.	

Continued

TABLE 5-22 Immunizing Agents and Immunization Schedules for Health Care Workers (HCWs)—cont'd

Generic Name	Primary Schedule and Booster(s)	Indications	Major Precautions and Contraindications	Special Considerations
Typhoid vaccine, IM, SC, and oral	IM vaccine: One 0.5-ml/dose, booster 0.5 ml every 2 yr SC vaccine: Two 0.5-ml doses, ≥4 wk apart, booster 0.5 ml SC or 0.1 ID every 3 yr if exposure continues Oral vaccine: Four doses on alternate days. The manufacturer recommends revaccination with the entire 4-dose series every 5 yr	Workers in microbiology laboratories who frequently work with *Salmonella typhi*	Severe local or systemic reaction to a previous dose. Ty21a (oral) vaccine should not be administered to immunocompromised persons† or to persons receiving antimicrobial agents.	Vaccination should not be considered an alternative to the use of proper procedures when handling specimens and cultures in the laboratory.
Vaccinia vaccine (smallpox)	One dose administered with a bifurcated needle; boosters administered every 10 yr	Laboratory workers who directly handle cultures with vaccinia, recombinant vaccinia viruses, or orthopox viruses that infect human beings	The vaccine is contraindicated in pregnancy, in persons with eczema or a history of eczema, and in immunocompromised persons† and their household contacts.	Vaccination may be considered for HCWs who have direct contact with contaminated dressings or other infectious material from volunteers in clinical studies involving recombinant vaccinia virus.
Other Vaccine-Preventable Diseases				
Tetanus and diphtheria and pertussis (Tdap)	Two IM doses 4 wk apart or tetanus and diphtheria toxoid for adults with uncertain or incomplete primary vaccination; third dose 6-12 mo after second dose; booster every 10 yr. Substitute a one-time dose of Tdap for one of the doses of Td, either in the primary series or for the routine booster, whichever comes first.	All adults	Except in the first trimester, pregnancy is not a precaution. History of a neurologic reaction or immediate hypersensitivity reaction after a previous dose. History of severe local (Arthus-type) reaction after a previous dose. Such persons should not receive further routine or emergency doses of Td for 10 yr.	Tetanus prophylaxis in wound management‡
Pneumococcal polysaccharide vaccine (23 valent)	One dose, 0.5 ml, IM or SC; revaccination recommended for those at highest risk ≥5 yr after the first dose	Adults who are at increased risk of pneumococcal disease and its complications because of underlying health conditions; older adults, especially those age ≥65 who are healthy	The safety of vaccine in pregnant women has not been evaluated; it should not be administered during pregnancy unless the risk for infection is high. Previous recipients of any type of pneumococcal polysaccharide vaccine who are at highest risk for fatal infection or antibody loss may be revaccinated ≥5 yr after the first dose.	
Rubella live-virus vaccine	One dose SC; second dose at least 1 mo later	Indicated for HCWs,† both men and women, who do not have documentation of having received live vaccine on or after their first birthday **or** laboratory evidence of immunity. Adults born before 1957, **except women who can become pregnant,** can be considered immune.	Pregnancy; immunocompromised persons†; history of anaphylactic reaction after administration of neomycin	The risk for rubella vaccine–associated malformations in the offspring of women pregnant when vaccinated or who become pregnant within 3 mo after vaccination is negligible. Such women should be counseled regarding the theoretic basis of concern for the fetus. MMR is the vaccine of choice if recipients are likely to be susceptible to measles or mumps as well as rubella.
Varicella-zoster live-virus vaccine	Two 0.5-ml doses SC 4-8 wk apart if ≥13 yr	Indicated for HCWs† who do not have either a reliable history of varicella or serologic evidence of immunity	Pregnancy, immunocompromised persons,‡ history of anaphylactic reaction after receipt of neomycin or gelatin. Avoid salicylate use for 6 wk after vaccination.	Vaccine is available from the manufacturer for certain patients with acute lymphocytic leukemia in remission. Because 71%-93% of persons without a history of varicella are immune, serologic testing before vaccination is likely to be cost effective.

TABLE 5-22 Immunizing Agents and Immunization Schedules for Health Care Workers (HCWs)—cont'd

Generic Name	Primary Schedule and Booster(s)	Indications	Major Precautions and Contraindications	Special Considerations
Varicella-zoster immune globulin (VZIG)	Persons <50 kg: 125 μg/10 kg IM; persons ≥50 kg: 625 μg[§]	Persons known or likely to be susceptible (particularly those at high risk for complications, e.g., pregnant women) who have close and prolonged exposure to a contact case or to an infectious hospital staff worker or patient		Serologic testing may help in assessing whether to administer VZIG. If use of VZIG prevents varicella disease, patient should be vaccinated subsequently.
BCG Vaccination				
Bacille Calmette-Guérin (BCG) vaccine (TB)	One percutaneous dose of 0.3 ml; no booster dose recommended	Should be considered only for HCWs in areas where multidrug TB is prevalent, a strong likelihood of infection exists, and where comprehensive infection control precautions have failed to prevent TB transmission to HCWs	Should not be administered to immunocompromised persons,[‡] pregnant women	In the United States TB-control efforts are directed toward early identification, treatment of cases, and preventive therapy with isoniazid.
Other Immunobiologics That Are or May Be Indicated for HCWs				
Immune globulin (hepatitis A)	**Postexposure**—One IM dose of 0.02 ml/kg administered ≤2 wk after exposure	Indicated for HCWs exposed to feces of infectious patients	Contraindicated in persons with IgA deficiency; do not administer within 2 wk after MMR vaccine or 3 wk after varicella vaccine. Delay administration of MMR vaccine for ≥3 mo and varicella vaccine ≥5 mo after administration of immune globulin	Administer in large muscle mass (deltoid, gluteal).

Modified from *MMWR* 46(RR-18), 1998.

HBsAg, Hepatitis B surface antigen; *HBV,* hepatitis B virus; *HIV,* human immunodeficiency virus; *IM,* intramuscular; *MMR,* measles, mumps, rubella vaccine; *SC,* subcutaneous; *TB,* tuberculosis.

*Persons who provide health care to patients or work in institutions that provide patient care (e.g., physicians, nurses, emergency medical personnel, dental professionals and students, medical and nursing students, laboratory technicians, hospital volunteers, and administrative and support staff in health care institutions).

†All HCWs (i.e., medical or nonmedical, paid or volunteer, full time or part time, student or nonstudent, with or without patient-care responsibilities) who work in health care institutions (e.g., inpatient and outpatient, public and private) should be immune to measles, rubella, and varicella.

‡Persons immunocompromised because of immune deficiency diseases, HIV infection, leukemia, lymphoma or generalized malignancy, or immunosuppressed as a result of therapy with corticosteroids, alkylating drugs, antimetabolites, or radiation.

§Some experts recommend 125 μg/10 kg regardless of total body weight.

TABLE 5-23 Recommendations for Persons with Medical Conditions Requiring Special Vaccination Considerations

Condition	Tdap	MMR	Varicella	HBV	HAV	Pneumovax[a]	Influenza[b]	HbCV	Meningococcal	IPV	Other Live Vaccines[c]	Other Killed Vaccines[d]
HIV infection	Rou	Rou/Contr[e]	Contr[f]	Rou[g]	Rou	Rec	Rec	Cons	Rou	Rou	Contr	Rou
Severe immunocompromise[h]	Rou	Contr	Contr[f]	Rou[g]	Rou	Rec	Rec	Rou[i]	Rou	Rou	Contr	Rou
Renal failure	Rou	Rou	Rou	Rec[g]	Rou	Rec	Rec	Rou	Rou	Rou	Rou	Rou
Diabetes	Rou	Rou	Rou	Rou	Rou	Rec	Rec	Rou	Rou	Rou	Rou	Rou
Chronic liver disease	Rou	Rou	Rou	Rou	Rec	Rec	Rec	Rou	Rou	Rou	Rou	Rou
Cardiac disease	Rou	Rou	Rou	Rou	Rou	Rec	Rec	Rou	Rou	Rou	Rou	Rou
Pulmonary disease	Rou	Rou	Rou	Rou	Rou	Rec	Rec	Rou	Rou	Rou	Rou	Rou
Alcoholism	Rou	Rou	Rou	Rou	Rou	Rec	Rec	Rou	Rou	Rou	Rou	Rou
Functional/anatomic asplenia	Rou	Rou	Rou	Rou	Rou	Rec[j]	Rec	Rec[j]	Rec[j]	Rou	Rou	Rou
Terminal complement deficiency	Rou	Rou	Rou	Rou	Rou	Rou	Rou	Rou	Rec	Rou	Rou	
Clotting factor disorders	Rou	Rou	Rou	Rec	Rec	Rou	Rou	Rou	Rou	Rou	Rou	Rou

Modified and updated from *MMWR* 42(RR-4):16, 1993.

Cons, Consider vaccination; *Contr,* contraindicated; *HAV,* hepatitis A virus; *HbCV, Haemophilus influenzae* conjugate vaccine; *HBV,* hepatitis B virus; *IPV,* inactivated poliomyelitis vaccine; *MMR,* measles-mumps-rubella; *Rec,* recommended; *Rou,* routine as outlined for all adults; *Tdap,* tetanus and diphtheria toxoids and acellular pertussis.

[a]Pneumovax should be repeated in 5 yr for patients in whom vaccine is recommended. Asthma without chronic obstructive pulmonary disease is not an indication for the vaccine.

[b]Influenza vaccine should also be given to caregivers and household members.

[c]Includes bacille Calmette-Guérin, vaccinia, oral typhoid, yellow fever (if exposure cannot be avoided, persons with HIV can be given yellow fever vaccine; see text).

[d]Includes rabies (check postvaccination titers in HIV or severely immunocompromised persons), Lyme disease, inactivated typhoid, cholera, plague, and anthrax.

[e]For asymptomatic, nonseverely immunocompromised persons with HIV, MMR can be used; it is contraindicated in severely immunocompromised persons. MMR can be considered in symptomatic HIV patients without severe immunocompromise.

[f]Varicella can be given to household members and caregivers, but if varicella-like rash develops after vaccination, contact should be avoided.

[g]Recommended for persons with severe chronic renal failure approaching or already receiving dialysis, and higher doses should be given. Antibody titers should be measured after vaccination in these patients and in those with HIV or severe immunocompromise (who may require higher doses) to ensure adequate response. Yearly titers should be measured in dialysis patients.

[h]Severe immunocompromise can result from congenital immunodeficiency, leukemia, lymphoma, malignancy, organ transplant, chemotherapy, radiation therapy, or high-dose corticosteroids.

[i]Only for persons with Hodgkin's disease.

[j]Give at least 2 wk in advance of elective splenectomy.

TABLE 5-24 Vaccinations for International Travel

Disease*	Areas Affected†	Prophylaxis Recommended	Ideal Time between Last Vaccine Dose and Travel
Tetanus	All	All travelers; vaccine series/booster	Probably 30 days for series; anamnestic response to booster
Measles	All	If born after 1956; ensure immunity by antibody titer, diagnosed measles, or two doses of vaccine	As MMR, 7-14 days
Rubella	All	If born after 1956 and any female of childbearing age; rubella titer or one dose of vaccine	As MMR, 7-14 days
Mumps	All	If born after 1956; ensure immunity by antibody titer, diagnosed mumps, or one dose of vaccine	As MMR, 7-14 days
Varicella	All	All travelers; antibody titer, reported illness, or vaccine series	7-14 days
Hepatitis B	5%-20% of population are carriers in Africa, Middle East except Israel, all Southeast Asia, Amazon basin, Haiti, and Dominican Republic; 1%-5% of population are carriers in south-central and southwest Asia, Israel, Japan, Americas, Russia, and eastern and southern Europe	Travelers for more than 6 mo in close contact with population or for less time but with high-risk activities (close household contact, seeking dental or medical care, sex); vaccine series	Probably 30 days
Hepatitis A	Developing countries	Travelers to rural areas; eating and drinking in settings of poor sanitation; vaccine or pooled immune globulin	Vaccine, 30 days Pooled IG, 2 days
Influenza	Tropics throughout the year; southern hemisphere from April to September	Travelers for whom vaccine is otherwise indicated; give current vaccine and revaccinate in fall as usual	7-14 days
Meningococcus*	Sub-Saharan Africa "belt" (Senegal to Ethiopia) from December to June; required for pilgrims to Saudi Arabia during Hajj; epidemics reported in other African nations, India, Nepal, and Mongolia	All travelers; vaccine	7-10 days
Rabies	Endemic dog rabies exists in Mexico, El Salvador, Guatemala, Peru, Colombia, Ecuador, India, Nepal, Philippines, Sri Lanka, Thailand, and Vietnam	Travelers staying for more than 30 days or at high risk of exposure to domestic or wild animals; vaccine series/booster	7-14 days
Poliomyelitis	Developing countries not in western hemisphere; at risk all year in tropics; in temperate zones, incidence increases in summer and fall	All travelers; vaccine series/booster	Parenteral vaccine series, 28 day
Typhoid fever	Many countries in Asia, Africa, Central America, and South America	Travelers with prolonged stay in rural areas with poor sanitation; vaccine series/booster	Oral vaccine, 7 days Parenteral vaccine, probably 14 days
Yellow fever*	North and central South America, forest-savannah zones of Africa; some countries in Africa, Asia, and Middle East require travelers from endemic areas to be vaccinated	All travelers; vaccine/booster at approved yellow fever vaccination center.	10 days
Japanese encephalitis	Seasonally in most areas of Asia, Indian subcontinent, and western Pacific islands; in temperate zones, incidence increases in summer and early fall; in tropics, year-round incidence	Travelers staying for more than 30 days in high-risk rural areas; staying outdoors during transmission season; vaccine series	10 days
Cholera*	Certain undeveloped countries	If required by local authorities, one dose usually suffices; primary series only for those living in high-risk areas under poor sanitary conditions or those with compromised gastric defense mechanisms (achlorhydria, antacid therapy, previous ulcer surgery); booster every 6 mo	Probably 30 days
Plague	Africa, Asia, and Americas in rural mountainous or upland areas	Travelers whose research or field activities bring them in contact with rodents; vaccine series/booster; consider taking tetracycline (500 mg four times a day) for chemoprophylaxis (inferred from clinical experience in treating plague)	Probably 30 days

From Noble J: *Primary care medicine,* ed 3, St Louis, 2001, Mosby.
IG, Immune globulin; *MMR,* measles-mumps-rubella.
*Only yellow fever vaccine is required for entry by any country; cholera vaccine may be required by some local authorities. Meningococcus vaccine is required for pilgrims to Mecca, in Saudia Arabia, during Hajj. However, it is important to follow Centers for Disease Control and Prevention (CDC) recommendations for all vaccines to prevent disease. If a required vaccine is contraindicated or withheld for any reason, attempts should be made to obtain a waiver from the country's consulate or embassy.
†Because areas affected can change, and for more specific details, consult the CDC's traveler's hotline.

Recommendations and Implementation Strategies for Hepatitis B Vaccination of Adults

BOX 5-1 Adults Recommended to Receive Hepatitis B Vaccination

Persons at Risk for Infection by Sexual Exposure
- Sex partners of persons who are HBsAg positive
- Sexually active persons who are not in a long-term, mutually monogamous relationship (e.g., persons who have had more than one sex partner during the previous 6 months)
- Persons seeking evaluation or treatment for a sexually transmitted disease
- Men who have sex with men

Persons at Risk for Infection by Percutaneous or Mucosal Exposure to Blood
- Current or recent users of injection drugs
- Household contacts of persons who are HBsAg positive
- Residents and staff of facilities for developmentally disabled persons
- Health care and public safety workers with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids
- Persons with end-stage renal disease, including predialysis, hemodialysis, peritoneal dialysis, and home dialysis patients

Others
- International travelers to regions with high or intermediate levels (HBsAg prevalence of ≥2%) of endemic HBV infection
- Persons with chronic liver disease
- Persons with HIV infection
- All other persons seeking protection from HBV infection

From CDC: A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 55(RR-16):15, 2006.
HbsAg, Hepatitis B surface antigen; *HBV,* hepatitis B virus.

BOX 5-2 Hepatitis B Vaccine Schedules for Adults (Aged ≥20 yr)*

0, 1, and 6 months
0, 1, and 4 months
0, 2, and 4 months
0, 1, 2, and 12 months†

From CDC: A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 55(RR-16):15, 2006.
*All schedules are applicable to single-antigen hepatitis B vaccines; Twinrix (combined hepatitis A and hepatitis B vaccine) may be administered at 0, 1, and 6 months.
†A 4-dose schedule of Engerix-B is licensed for all age groups.

TABLE 5-25 Recommended Doses of Currently Licensed Formulations of Adult Hepatitis B Vaccine by Group and Vaccine Type

	SINGLE-ANTIGEN VACCINE				COMBINATION VACCINE	
	Recombivax HB[a]		Engerix-B[b]		Twinrix[b,c]	
Group	Dose (μg)[d]	Vol. (ml)	Dose (μg)[d]	Vol. (ml)	Dose (μg)[d]	Vol. (ml)
Adults (aged ≥20 yr)	10	1.0	20	1.0	20	1.0
Hemodialysis patients and other immunocompromised persons aged ≥20 yr	40[e]	1.0	40[f]	2.0	—[g]	—

From Centers for Disease Control and Prevention: A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 55(RR-16):10, 2006.
HB, Hepatitis B.
[a]Merck & Co., Inc., Whitehouse Station, New Jersey.
[b]GlaxoSmithKline Biologicals, Rixensart, Belgium.
[c]Combined hepatitis A and hepatitis B vaccine, recommended for persons aged >18 yr who are at increased risk for both hepatitis B virus and hepatitis A virus infections.
[d]Recombinant hepatitis B surface antigen protein dose.
[e]Dialysis formulation administered on a 3-dose schedule at 0, 1, and 6 mo.
[f]Two 1.0-ml doses administered in 1 or 2 injections on a 4-dose schedule at 0, 1, 2, and 6 mo.
[g]Not applicable.

TABLE 5-26 Recommended HIV/AIDS, Sexually Transmitted Disease (STD), and Viral Hepatitis Prevention Services by Risk Population

Risk Population[a]	Recommended Services
High-Risk Heterosexuals	
Persons seeking sexually transmitted disease evaluation or treatment	Hepatitis B vaccination Testing for HIV infection[b] Testing for syphilis, gonorrhea, and chlamydia, as clinically indicated[c]
Sexually active men not in a long-term, mutually monogamous relationship	Hepatitis B vaccination Annual testing for HIV infection[b,d]
Sexually active women not in a long-term, mutually monogamous relationship	Hepatitis B vaccination[e] Annual testing for HIV infection[b,d] Annual testing for chlamydia (NOTE: Also recommended for all sexually active females aged <25 yr)[c]
Men Who Have Sex with Men (MSM)	
All MSM	Hepatitis A vaccination Hepatitis B vaccination[e]
Sexually active MSM not in a long-term, mutually monogamous relationship	Hepatitis A vaccination Hepatitis B vaccination[e] Annual testing for HIV infection[b] Annual testing for syphilis, gonorrhea, and chlamydia[c]
Injection-Drug Users	
	Hepatitis A vaccination[f] Hepatitis B vaccination Testing for hepatitis C virus infection[g] Annual testing for HIV infection[b] Substance-abuse treatment[h]

From Centers for Disease Control and Prevention (CDC): A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 55(RR-16):17, 2006.
[a]Testing for HIV infection, chlamydia, gonorrhea, syphilis, and hepatitis B surface antigen also is recommended for pregnant women. (CDC: Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health care settings, *MMWR* 55[RR-14], 2006; CDC: Sexually transmitted diseases treatment guidelines, *MMWR* 55[RR-11], 2006; CDC: A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices [ACIP]. Part 1: immunization of infants, children, and adolescents, *MMWR* 54[RR-16], 2005.)
[b]CDC: Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health care settings, *MMWR* 55(RR-14), 2006.
[c]CDC: Sexually transmitted diseases treatment guidelines 2006, *MMWR* 55(RR-11), 2006.
[d]HIV screening is recommended for all persons aged 13-64 yr. Repeat screening is recommended at least annually for persons likely to be at high risk for HIV infection, including MSM or heterosexuals who themselves or whose sex partners have had more than one partner since their most recent HIV test.
[e]Hepatitis B vaccination is recommended for persons who have had more than one sex partner during the previous 6 mo.
[f]CDC: Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 55(RR-7), 2006.
[g]CDC: Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease, *MMWR* 47(RR-19), 1998. Recommended frequency of testing for hepatitis C virus infection has not been determined.
[h]CDC: *Substance abuse treatment for injection drug users: a strategy with many benefits,* Atlanta, 2002, U.S. Department of Health and Human Services, CDC. Available at http://www.cdc.gov/idu/facts/treatment.htm.

TABLE 5-27 Guidelines for Postexposure Prophylaxis* of Persons with Nonoccupational Exposures† to Blood or Body Fluids That Contain Blood by Exposure Type and Vaccination Status

Exposure	TREATMENT	
	Unvaccinated Person‡	Previously Vaccinated Person§
HBsAg-Positive Source		
Percutaneous (e.g., bite or needlestick) or mucosal exposure to HBsAg-positive blood or body fluids	Administer hepatitis B vaccine series and hepatitis B immune globulin (HBIG)	Administer hepatitis B vaccine booster dose
Sex or needle-sharing contact with a person who is HBsAg positive	Administer hepatitis B vaccine series and HBIG	Administer hepatitis B vaccine booster dose
Victim of sexual assault/abuse by a perpetrator who is HBsAg positive	Administer hepatitis B vaccine series and HBIG	Administer hepatitis B vaccine booster dose
Source with Unknown HBsAg Status		
Victim of sexual assault/abuse by a perpetrator with unknown HBsAg status	Administer hepatitis B vaccine series	No treatment
Percutaneous (e.g., bite or needlestick) or mucosal exposure to potentially infectious blood or body fluids from a source with unknown HBsAg status	Administer hepatitis B vaccine series	No treatment
Sexual or needle-sharing contact with person with unknown HBsAg status	Administer hepatitis B vaccine series	No treatment

From Centers for Disease Control and Prevention: A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 55(RR-16):30, 2006.
HBsAg, Hepatitis B surface antigen.
*When indicated, immunoprophylaxis should be initiated as soon as possible, preferably within 24 hours. Studies are limited on the maximum interval after exposure during which postexposure prophylaxis is effective, but the interval is unlikely to exceed 7 days for percutaneous exposures or 14 days for sexual exposures. The hepatitis B vaccine series should be completed.
†These guidelines apply to nonoccupational exposures. Guidelines for management of occupational exposures have been published separately and also can be used for management of nonoccupational exposures if feasible.
‡A person who is in the process of being vaccinated but has not completed the vaccine series should complete the series and receive treatment as indicated.
§A person who has written documentation of a complete hepatitis B vaccine series and did not receive postvaccination testing.

TABLE 5-28 Typical Interpretation of Serologic Test Results for Hepatitis B Virus Infection

SEROLOGIC MARKER				
HBsAg	Total Anti-HBc	IgM Anti-HBc	Anti-HBs	Interpretation
–*	–	–	–	Never infected
+†‡	–	–	–	Early acute infection; transient (up to 18 days) after vaccination
+	+	+	–	Acute infection
–	+	+	+ or –	Acute resolving infection
–	+	–	+	Recovered from past infection and immune
+	+	–	–	Chronic infection
–	+	–	–	False-positive (i.e., susceptible), past infection, "low-level" chronic infection,§ or passive transfer of anti-HBc to infant born to mother who is HBsAg positive
–	–	–	+	Immune if concentration is >10 mIU/ml after vaccine series completion‖; passive transfer after hepatitis B immune globulin administration

From Centers for Disease Control and Prevention: A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 55(RR-16):4, 2006.
HBc, Antibody to hepatitis B core antigen; *HBs,* antibody to HBsAg; *HBsAg,* hepatitis B surface antigen; *Ig,* immunoglobulin.
*Negative test result.
†Positive test result.
‡To ensure that an HBsAg-positive test result is not a false-positive, samples with reactive HBsAg results should be tested with a licensed neutralizing confirmatory test if recommended in the manufacturer's package insert.
§Persons positive only for anti-HBc are unlikely to be infectious except under unusual circumstances in which they are the source for direct percutaneous exposure of susceptible recipients to large quantities of virus (e.g., blood transfusion or organ transplant).
‖Milliinternational units per milliliter.

Hepatitis A Prophylaxis

TABLE 5-29 Recommended Dosages of Hepatitis A Immune Globulin

Setting	Duration of Coverage	Dose
Preexposure prophylaxis	Short term (<3 mo) Long term (3-5 mo)*	0.02 ml/kg 0.06 ml/kg
Postexposure prophylaxis	—	0.02 ml/kg

Modified from Centers for Disease Control and Prevention: Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 55(RR-07):9, 2006.
NOTE: Immune globulin should be administered intramuscularly into the deltoid or gluteal muscle in children younger than 24 mo; it may be administered in the anterolateral thigh muscle.
*Repeat every 5 mo if continued exposure to hepatitis A virus occurs.

TABLE 5-30 Licensed Dosages of Hepatitis A Vaccines

Vaccine	Patient's Age	Dose	Volume (ml)	Number of Doses	Schedule (mo)*
Hepatitis A vaccine, inactivated (Havrix)	12 mo to 18 yr ≥19 yr	720 EL.U. 1440 EL.U.	0.5 1.0	2 2	0, 6-12 0, 6-12
Hepatitis A vaccine, inactivated (Vaqta)	12 mo to 18 yr ≥19 yr	25 U 50 U	0.5 1.0	2 2	0, 6-18 0, 6-18
Combined hepatitis A and hepatitis B vaccine (Twinrix)	≥18 yr	720 EL.U. of hepatitis A antigen and 20 mcg of hepatitis B surface antigen protein	1.0	3	0, 1, and 6

Modified from Centers for Disease Control and Prevention: Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR* 55(RR-07):10, 2006.
*Zero represents the timing of the initial dose; subsequent numbers represent months after the initial dose.

Influenza Treatment and Prophylaxis

BOX 5-3 Summary of Seasonal Influenza Vaccination Recommendations

Children

All children aged 6 months to 18 years should be vaccinated annually.

Children and adolescents at higher risk for influenza complications should continue to be a focus for vaccination efforts as providers and programs transition to routinely vaccinating all children and adolescents, including those who:

- are aged 6 months to 4 years (59 months)
- have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, cognitive, neurologic/neuromuscular, hematologic, or metabolic disorders (including diabetes mellitus)
- are immunosuppressed (including immunosuppression caused by medications or by human immunodeficiency virus)
- are receiving long-term aspirin therapy and therefore might be at risk for experiencing Reye's syndrome after influenza virus infection
- are residents of long-term care facilities
- will be pregnant during the influenza season

Note: Children aged <6 months cannot receive influenza vaccination. Household and other close contacts (e.g., day-care providers) of children aged <6 months, including older children and adolescents, should be vaccinated.

Adults

Annual vaccination against influenza is recommended for any adult who wants to reduce the risk of becoming ill with influenza or of transmitting it to others. Vaccination is recommended for all adults without contraindications in the following groups, because these persons either are at higher risk for influenza complications, or are close contacts of the persons at higher risk:

- persons aged ≥50 years
- women who will be pregnant during the influenza season
- persons who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, cognitive, neurologic/neuromuscular, hematologic, or metabolic disorders (including diabetes mellitus)
- persons who have immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus)
- residents of nursing homes and other long-term care facilities
- health care personnel
- household contacts and caregivers of children aged <5 years and adults aged ≥50 years, with particular emphasis on vaccinating contacts of children aged <6 months
- household contacts and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza

Modified from *MMWR* 58:(RR-8), 2009.

RECOMMENDED VACCINES FOR DIFFERENT AGE GROUPS

When vaccinating children aged 6 to 35 months with TIV, health care providers should use TIV that has been licensed by the FDA for this age group (i.e., TIV manufactured by Sanofi Pasteur [FluZone]). TIV from Novartis (Fluvirin) is FDA approved in the United States for use among persons aged 4 years and older. TIV from GlaxoSmithKline (Fluarix and FluLaval) or CSL Biotherapies (Afluria) is labeled for use in persons aged 18 years and older because data to demonstrate efficacy among younger persons have not been provided to the FDA. LAIV from MedImmune (FluMist) is licensed for use by healthy, nonpregnant persons aged 2 to 49 years. A vaccine dose does not need to be repeated if inadvertently administered to a person who does not have an age indication for the vaccine formulation given. Expanded age and risk group indications for licensed vaccines are likely over the next several years, and vaccination providers should be alert to these changes. In addition, several new vaccine formulations are being evaluated in immunogenicity and efficacy trials; when licensed, these new products will increase the influenza vaccine supply and provide additional vaccine choices for practitioners and their patients.

INFLUENZA VACCINES AND USE OF INFLUENZA ANTIVIRAL MEDICATIONS

Administration of TIV and influenza antivirals during the same medical visit is acceptable. The effect on safety and effectiveness of LAIV coadministration with influenza antiviral medications has not been studied. However, because influenza antivirals reduce replication of influenza viruses, LAIV should not be administered until 48 hours after cessation of influenza antiviral therapy, and influenza antiviral medications should not be administered for 2 weeks after receipt of LAIV. Persons receiving antivirals within the period 2 days before to 14 days after vaccination with LAIV should be revaccinated at a later date.

PERSONS WHO SHOULD NOT BE VACCINATED WITH TIV

TIV should not be administered to persons known to have anaphylactic hypersensitivity to eggs or other components of the influenza vaccine. Prophylactic use of antiviral agents is an option for preventing influenza among such persons. Information about vaccine components is located in package inserts from each manufacturer. Persons with moderate to severe acute febrile illness usually should not be vaccinated until their symptoms have abated. However, minor illnesses with or without fever do not contraindicate use of influenza vaccine. Guillain-Barré syndrome within 6 weeks after a previous dose of TIV is considered a precaution for use of TIV.

CONSIDERATIONS WHEN USING LAIV

LAIV is an option for vaccination of healthy, nonpregnant persons aged 2 to 49 years, including health care providers and other close contacts of high-risk persons (except severely immunocompromised persons who require care in a protected environment). No preference is indicated for LAIV or TIV when considering vaccination of healthy, nonpregnant persons aged 2 to 49 years. Use of the term *healthy* in this recommendation refers to persons who do not have any of the underlying medical conditions that confer high risk for severe complications (see "Persons Who Should Not Be Vaccinated with LAIV"). However, during periods when inactivated vaccine is in short supply, use of LAIV is encouraged when feasible for eligible persons (including health care providers) because use of LAIV by these persons might increase availability of TIV for persons in groups targeted for vaccination but who cannot receive LAIV. Possible advantages of LAIV include its potential to induce a broad mucosal and systemic immune response in children, its ease of administration, and possibly increased acceptability of an intranasal rather than intramuscular route of administration.

If the vaccine recipient sneezes after administration, the dose should not be repeated. However, if nasal congestion is present that might impede delivery of the vaccine to the nasopharyngeal mucosa, deferral of administration should be considered until resolution of the illness, or TIV should be administered instead. No data exist about concomitant use of nasal corticosteroids or other intranasal medications.

Although FDA licensure of LAIV excludes children aged 2 to 4 years with a history of asthma or recurrent wheezing, the precise risk, if any, of wheezing caused by LAIV among these children is unknown because experience with LAIV among these young children is limited. Young children might not have a history of recurrent wheezing if their exposure to respiratory viruses has been limited because of their age. Certain children might have a history of wheezing with respiratory illnesses but have not had asthma diagnosed. The following screening recommendations should be used to assist persons who administer influenza vaccines in providing the appropriate vaccine for children aged 2 to 4 years.

Clinicians and vaccination programs should screen for possible reactive airways diseases when considering use of LAIV for children aged 2 to 4 years and should avoid use of this vaccine in children with asthma or a recent wheezing episode. Health care providers should consult the medical record, when available, to identify children aged 2 to 4 years with asthma or recurrent wheezing that might indicate asthma. In addition, to identify children who might be at greater risk for asthma and possibly at increased risk for wheezing after receiving LAIV, parents or caregivers of children aged 2 to 4 years should be asked, "In the past 12 months, has a health care provider ever told you that your child had wheezing or asthma?" Children whose parents or caregivers answer "yes" to this question and children who have asthma or who had a wheezing episode noted in the medical record during the preceding 12 months should not receive LAIV. TIV is available for use in children with asthma or possible reactive airways diseases.

LAIV can be administered to persons with minor acute illnesses (e.g., diarrhea or mild upper respiratory tract infection with or without fever). However, if nasal congestion is present that might impede delivery of the vaccine to the nasopharyngeal mucosa, deferral of administration should be considered until resolution of the illness.

PERSONS WHO SHOULD NOT BE VACCINATED WITH LAIV

The effectiveness or safety of LAIV is not known for the following groups, who should not be vaccinated with LAIV:

- Persons with a history of hypersensitivity, including anaphylaxis, to any of the components of LAIV or eggs
- Persons younger than 2 years or aged 50 years or older
- Persons with any of the underlying medical conditions that serve as an indication for routine influenza vaccination, including asthma, reactive airways disease, or other chronic disorders of the pulmonary or cardiovascular systems; other underlying medical conditions, including metabolic diseases such as diabetes, renal dysfunction, and hemoglobinopathies; or known or suspected immunodeficiency diseases or immunosuppressed states
- Children aged 2 to 4 years whose parents or caregivers report that a health care provider has told them during the preceding 12 months that their child had wheezing or asthma, or whose medical record indicates a wheezing episode has occurred during the preceding 12 months
- Children or adolescents receiving aspirin or other salicylates (because of the association of Reye syndrome with wild-type influenza virus infection)
- Persons with a history of Guillain-Barré syndrome after influenza vaccination
- Pregnant women

CONCURRENT ADMINISTRATION OF INFLUENZA VACCINE WITH OTHER VACCINES

Use of LAIV concurrently with measles, mumps, rubella (MMR) alone, and MMR and varicella vaccine among children aged 12 to 15 months has been studied, and no interference with immunogenicity to antigens in any of the vaccines was observed. Among adults aged 50 years or older, the safety and immunogenicity of zoster vaccine and TIV were similar whether administered simultaneously or spaced 4 weeks apart. In the absence of specific data indicating interference, following ACIP's general recommendations for vaccination is prudent. Inactivated vaccines do not interfere with the immune response to other inactivated vaccines or to live vaccines. Inactivated or live vaccines can be administered simultaneously with LAIV. However, after administration of a live vaccine, at least 4 weeks should pass before another live vaccine is administered.

TABLE 5-31 Live, Attenuated Influenza Vaccine (LAIV) Compared with Inactivated Influenza Vaccine (TIV) for Seasonal Influenza, United States Formulations

Factor	LAIV	TIV
Route of administration	Intranasal spray	Intramuscular injection
Type of vaccine	Live virus	Noninfectious virus (i.e., inactivated)
Number of included virus strains	3 (2 influenza A, 1 influenza B)	3 (2 influenza A, 1 influenza B)
Vaccine virus strains updated	Annually	Annually
Frequency of administration	Annually*	Annually*
Approved age	Persons aged 2-49 yr	Persons aged ≥6 mo
Interval between 2 doses recommended for children aged ≥6 mo to 8 yr who are receiving influenza vaccine for the first time	4 wk	4 wk
Can be administered to persons with medical risk factors for influenza-related complications†	No	Yes
Can be administered to children with asthma or children aged 2-4 yr with wheezing during the preceding year§	No	Yes
Can be administered to family members or close contacts of immunosuppressed persons not requiring a protected environment	Yes	Yes
Can be administered to family members or close contacts of immunosuppressed persons requiring a protected environment (e.g., hematopoietic stem cell transplant recipient)	No	Yes
Can be administered to family members or close contacts of persons at high risk but not severely immunosuppressed	Yes	Yes
Can be simultaneously administered with other vaccines	Yes¶	Yes**
If not simultaneously administered, can be administered within 4 wk of another live vaccine	Prudent to space 4 wk apart	Yes
If not simultaneously administered, can be administered within 4 wk of an inactivated vaccine	Yes	Yes

Modified from *MMWR* 56(RR-6), 2007.

*Children aged 6 months to 8 years who have never received influenza vaccine before should receive 2 doses. Those who only receive 1 dose in their first year of vaccination should receive 2 doses in the following year, spaced 4 weeks apart.

†Persons at higher risk for complications of influenza infection because of underlying medical conditions should not receive LAIV. Persons at higher risk for complications of influenza infection because of underlying medical conditions include adults and children with chronic disorders of the pulmonary or cardiovascular systems; adults and children with chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression; children and adolescents receiving long-term aspirin therapy (at risk for developing Reye's syndrome after wild-type influenza infection); persons who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration; pregnant women; and residents of nursing homes and other chronic-care facilities that house persons with chronic medical conditions.

§Clinicians and immunization programs should screen for possible reactive airways diseases when considering use of LAIV for children aged 2-4 years and should avoid use of this vaccine in children with asthma or a recent wheezing episode. Health care providers should consult the medical record, when available, to identify children aged 2-4 years with asthma or recurrent wheezing that might indicate asthma. In addition, to identify children who might be at greater risk for asthma and possibly at increased risk for wheezing after receiving LAIV, parents or caregivers of children aged 2-4 years should be asked: "In the past 12 months, has a health care provider ever told you that your child had wheezing or asthma?" Children whose parents or caregivers answer "yes" to this question and children who have asthma or who had a wheezing episode noted in the medical record during the preceding 12 months should not receive LAIV.

¶LAIV coadministration has been evaluated systematically only among children aged 12-15 months who received measles, mumps, and rubella vaccine or varicella vaccine.

**TIV coadministration has been evaluated systematically only among adults who received pneumococcal polysaccharide or zoster vaccine.

INDICATIONS FOR USE OF ANTIVIRALS

PERSONS FOR WHOM ANTIVIRAL TREATMENT SHOULD BE CONSIDERED

If possible, antiviral treatment should be started within 48 hours of influenza illness onset. The effectiveness of initiating antiviral treatment more than 48 hours after illness onset has not been established. Persons for whom antiviral treatment should be considered include:

- Persons hospitalized with laboratory-confirmed influenza (limited data suggest benefit even for persons whose antiviral treatment is initiated more than 48 hours after illness onset)
- Persons with laboratory-confirmed influenza pneumonia
- Persons with laboratory-confirmed influenza and bacterial coinfection
- Persons with laboratory-confirmed influenza infection who are at higher risk for influenza complications
- Persons presenting to medical care with laboratory-confirmed influenza within 48 hours of influenza illness onset who want to decrease the duration or severity of their symptoms and transmission of influenza to others at higher risk for complications

PERSONS FOR WHOM ANTIVIRAL CHEMOPROPHYLAXIS SHOULD BE CONSIDERED DURING PERIODS OF INCREASED INFLUENZA ACTIVITY IN THE COMMUNITY

- Persons at high risk during the 2 weeks after influenza vaccination (after the second dose for children younger than 9 years who have not previously been vaccinated) if influenza viruses are circulating in the community
- Persons at high risk for whom influenza vaccine is contraindicated
- Family members or health care providers who are unvaccinated and are likely to have ongoing, close exposure to persons at high risk or unvaccinated persons or infants younger than 6 months
- Persons and their family members and close contacts and health care workers when circulating strains of influenza virus in the community are not matched with vaccine strains
- Persons with immune deficiencies or those who might not respond to vaccination (e.g., persons infected with HIV or other immunosuppressed conditions or who are receiving immunosuppressive medications)
- Unvaccinated staff and persons during response to an outbreak in a closed institutional setting with residents at high risk (e.g., extended-care facilities)

Modified from *MMWR* 57(RR-7), 2008.

NOTE: Recommended antiviral medications (neuraminidase inhibitors) are not licensed for chemoprophylaxis of children younger than 1 year (oseltamivir) or younger than 5 years (zanamivir). Updates or supplements to these recommendations (e.g., expanded age or risk group indications for licensed vaccines) might be required. Health care providers should be alert to announcements of recommendation updates and should check the CDC influenza website periodically for additional information (http://www.cdc.gov/flu).

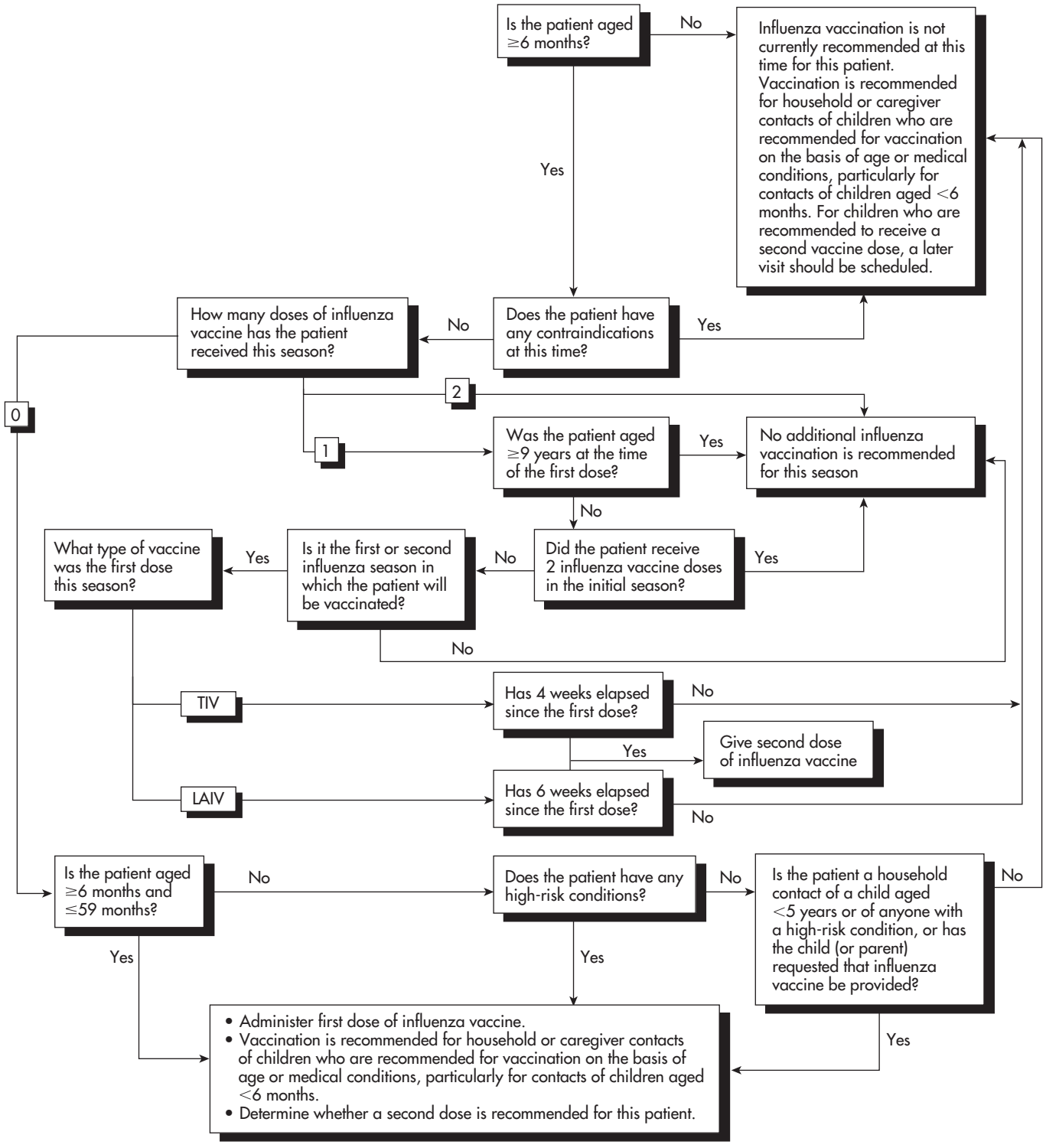


FIGURE 5-6 Algorithm for determining recommended influenza immunization actions for children. *TIV,* Trivalent inactivated influenza vaccine; *LAIV,* Live attenuated influenza vaccine. (Modified with permission from the American Academy of Pediatrics' Committee on Infectious Diseases: Prevention of influenza: recommendations for influenza immunization of children, 2006-2007, *Pediatrics* 119:846-51.315, 2007.)

HIV Testing and Postexposure Prophylaxis

RECOMMENDATIONS FOR HIV TESTING OF ADULTS, ADOLESCENTS, AND PREGNANT WOMEN

RECOMMENDATIONS FOR ADULTS AND ADOLESCENTS*

The CDC recommends that diagnostic human immunodeficiency virus (HIV) testing and opt-out HIV screening be a part of routine clinical care in all health care settings while also preserving the patient's option to decline HIV testing and ensuring a provider-patient relationship conducive to optimal clinical and preventive care. The recommendations are intended for providers in all health care settings, including hospital emergency departments, urgent-care clinics, inpatient services, sexually transmitted disease (STD) clinics or other venues offering clinical STD services, tuberculosis (TB) clinics, substance abuse treatment clinics, other public health clinics, community clinics, correctional health care facilities, and primary care settings. The guidelines address HIV testing in health care settings only; they do not modify existing guidelines concerning HIV counseling, testing, and referral for persons at high risk for HIV who seek or receive HIV testing in nonclinical settings (e.g., community-based organizations, outreach settings, or mobile vans).

SCREENING FOR HIV INFECTION

- In all health care settings, screening for HIV infection should be performed routinely for all patients aged 13 to 64 years. Health care providers should initiate screening unless prevalence of undiagnosed HIV infection in their patients has been documented to be less than 0.1%. In the absence of existing data for HIV prevalence, health care providers should initiate voluntary HIV screening until they establish that the diagnostic yield is less than 1 per 1000 patients screened, at which point such screening is no longer warranted.
- All patients initiating treatment for TB should be screened routinely for HIV infection.
- All patients seeking treatment for STDs, including all patients visiting STD clinics, should be screened routinely for HIV during each visit for a new complaint, regardless of whether the patient is known or suspected to have specific behavior risks for HIV infection.

REPEAT SCREENING

- Health care providers should subsequently test all persons likely to be at high risk for HIV at least annually. Persons likely to be at high risk include users of injection drugs and their sex partners, persons who exchange sex for money or drugs, sex partners of persons who are HIV infected, and men who have sex with men (MSM) or heterosexual persons who themselves or whose sex partners have had more than one sex partner since their most recent HIV test.
- Health care providers should encourage patients and their prospective sex partners to be tested before initiating a new sexual relationship.
- Repeat screening of persons not likely to be at high risk for HIV should be performed on the basis of clinical judgment.
- Unless recent HIV test results are immediately available, any person whose blood or body fluid is the source of an occupational exposure for a health care provider should be informed of the incident and tested for HIV infection at the time the exposure occurs.

CONSENT AND PRETEST INFORMATION

- Screening should be voluntary and undertaken only with the patient's knowledge and understanding that HIV testing is planned.
- Patients should be informed orally or in writing that HIV testing will be performed unless they decline (opt-out screening). Oral or written information should include an explanation of HIV infection and the meanings of positive and negative test results, and the patient should be offered an opportunity to ask questions and decline testing. With such notification, consent for HIV screening should be incorporated into the patient's general informed consent for medical care on the same basis as are other screening or diagnostic tests; a separate consent form for HIV testing is not recommended.
- Easily understood informational materials should be made available in the languages of the commonly encountered populations within the service area. The competence of interpreters and bilingual staff to provide language assistance to patients with limited English proficiency must be ensured.
- If a patient declines an HIV test, this decision should be documented in the medical record.

DIAGNOSTIC TESTING FOR HIV INFECTION

- All patients with signs or symptoms consistent with HIV infection or an opportunistic illness characteristic of acquired immunodeficiency syndrome (AIDS) should be tested for HIV.
- Clinicians should maintain a high level of suspicion for acute HIV infection in all patients who have a compatible clinical syndrome and who report recent high-risk behavior. When acute retroviral syndrome is a possibility, a plasma RNA test should be used in conjunction with an HIV antibody test to diagnose acute HIV infection.
- Patients or persons responsible for the patient's care should be notified orally that testing is planned, advised of the indication for testing and the implications of positive and negative test results, and offered an opportunity to ask questions and decline testing. With such notification, the patient's general consent for medical care is considered sufficient for diagnostic HIV testing.

HIV SCREENING FOR PREGNANT WOMEN AND THEIR INFANTS*

UNIVERSAL OPT-OUT SCREENING

- All pregnant women in the United States should be screened for HIV infection.
- Screening should occur after a woman is notified that HIV screening is recommended for all pregnant patients and that she will receive an HIV test as part of the routine panel of prenatal tests unless she declines (opt-out screening).
- HIV testing must be voluntary and free from coercion. No woman should be tested without her knowledge.
- Pregnant women should receive oral or written information that includes an explanation of HIV infection, a description of interventions that can reduce HIV transmission from mother to infant, and the meanings of positive and negative test results. They should be offered an opportunity to ask questions and decline testing.
- No additional process or written documentation of informed consent beyond what is required for other routine prenatal tests should be required for HIV testing.
- If a patient declines an HIV test, this decision should be documented in the medical record.

ADDRESSING REASONS FOR DECLINING TESTING

- Providers should discuss and address reasons for declining an HIV test (e.g., lack of perceived risk, fear of the disease, and concerns regarding partner violence or potential stigma or discrimination).
- Women who decline an HIV test because they have had a previous negative test result should be informed of the importance of retesting during each pregnancy.
- Logistical reasons for not testing (e.g., scheduling) should be resolved.
- Certain women who initially decline an HIV test might accept at a later date, especially if their concerns are discussed. Certain women will continue to decline testing, and their decisions should be respected and documented in the medical record.

TIMING OF HIV TESTING

- To promote informed and timely therapeutic decisions, health care providers should test women for HIV as early as possible during each pregnancy. Women who decline the test early in prenatal care should be encouraged to be tested at a subsequent visit.

*Data from *MMWR* 57(RR-10), 2008.

- A second HIV test during the third trimester, preferably less than 36 weeks of gestation, is cost effective even in areas of low HIV prevalence and may be considered for all pregnant women. A second HIV test during the third trimester is recommended for women who meet one or more of the following criteria:
  - Women who receive health care in jurisdictions with elevated incidence of HIV or AIDS among women aged 15 to 45 years. In 2004, these jurisdictions included Alabama, Connecticut, Delaware, the District of Columbia, Florida, Georgia, Illinois, Louisiana, Maryland, Massachusetts, Mississippi, Nevada, New Jersey, New York, North Carolina, Pennsylvania, Puerto Rico, Rhode Island, South Carolina, Tennessee, Texas, and Virginia.[†]
  - Women who receive health care in facilities in which prenatal screening identifies at least one pregnant woman who is infected with HIV per 1000 women screened.
  - Women who are known to be at high risk for acquiring HIV (e.g., users of injection drugs and their sex partners, women who exchange sex for money or drugs, women who are sex partners of persons who are infected with HIV, and women who have had a new or more than one sex partner during this pregnancy).
  - Women who have signs or symptoms consistent with acute HIV infection. When acute retroviral syndrome is a possibility, a plasma RNA test should be used in conjunction with an HIV antibody test to diagnose acute HIV infection.

[†]A second HIV test in the third trimester is as cost effective as other common health interventions when HIV incidence among women of childbearing age is ≥17 HIV cases per 100,000 person-years. In 2004, in jurisdictions with available data on HIV case rates, a rate of 17 new HIV diagnoses per year per 100,000 women aged 15 to 45 years was associated with an AIDS case rate of at least nine AIDS diagnoses per year per 100,000 women aged 15 to 45 years (CDC, unpublished data, 2005). As of 2004, the jurisdictions listed above exceeded these thresholds. The list of specific jurisdictions where a second test in the third trimester is recommended will be updated periodically based on surveillance data.

RAPID TESTING DURING LABOR

- Any woman with undocumented HIV status at the time of labor should be screened with a rapid HIV test unless she declines (opt-out screening).
- Reasons for declining a rapid test should be explored (see "Addressing Reasons for Declining Testing").
- Immediate initiation of appropriate antiretroviral prophylaxis should be recommended to women on the basis of a reactive rapid test result without waiting for the result of a confirmatory test.

POSTPARTUM/NEWBORN TESTING

- When a woman's HIV status is still unknown at the time of delivery, she should be screened immediately postpartum with a rapid HIV test unless she declines (opt-out screening).
- When the mother's HIV status is unknown postpartum, rapid testing of the newborn as soon as possible after birth is recommended so that antiretroviral prophylaxis can be offered to infants exposed to HIV. Women should be informed that identifying HIV antibodies in the newborn indicates that the mother is infected.
- For infants whose HIV exposure status is unknown and who are in foster care, the person legally authorized to provide consent should be informed that rapid HIV testing is recommended for infants whose biologic mothers have not been tested.
- The benefits of neonatal antiretroviral prophylaxis are best realized when it is initiated within 12 hours after birth.

CONFIRMATORY TESTING

- Whenever possible, uncertainties regarding laboratory test results indicating HIV infection status should be resolved before final decisions are made regarding reproductive options, antiretroviral therapy, cesarean delivery, or other interventions.
- If the confirmatory test result is not available before delivery, immediate initiation of appropriate antiretroviral prophylaxis should be recommended to any pregnant patient whose HIV screening test result is reactive to reduce the risk for perinatal transmission.

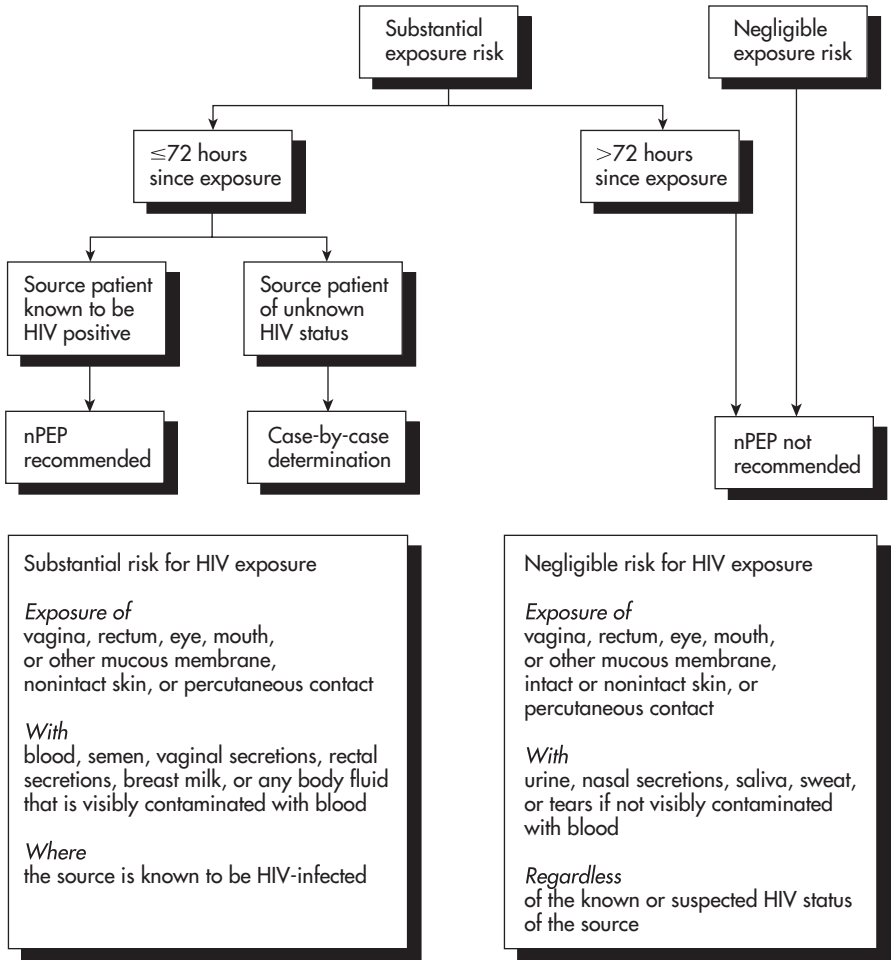


FIGURE 5-7 Algorithm for evaluation and treatment of possible nonoccupational HIV exposure. *nPEP,* Nonoccupational postexposure prophylaxis. (Modified from *MMWR* 54[RR-2], 2005.)

TABLE 5-32 HIV Exposure, Estimated Per-Act Risk

Exposure Route	Risk per 10,000 Exposures to an Infected Source
Blood transfusion	9000
Needle-sharing injection drug use	67
Receptive anal intercourse	50
Percutaneous needle stick	30
Receptive penile-vaginal intercourse	10
Insertive anal intercourse	6.5
Insertive penile-vaginal intercourse	5
Receptive oral intercourse	1
Insertive oral intercourse	0.5

Modified from *MMWR* 54(RR-2), 2005.

NOTE: Estimates of risk for transmission from sexual exposures assume no condom use. Source refers to oral intercourse performed on a man.

TABLE 5-33 Regimens for 28-Day Postexposure Prophylaxis for HIV Infection*

Regimen	Dose	Daily Pill Burden† no.	Advantages	Disadvantages
Two-Drug Regimens				
Tenofovir–emtricitabine (Truvada)‡	One tablet (300 mg of tenofovir with 200 mg of emtricitabine) once daily	1	Well-tolerated; once-daily dosing	Potential nephrotoxicity
Zidovudine–lamivudine (Combivir)§	One tablet (300 mg of zidovudine with 150 mg of lamivudine) twice daily	2	Preferred in pregnancy	Twice-daily dosing; less well-tolerated than tenofovir–emtricitabine (nausea, asthenia, neutropenia, anemia, abnormal liver-enzyme levels)
Three-Drug Regimens‖				
Ritonavir–lopinavir (Kaletra) (plus either tenofovir–emtricitabine or zidovudine–lamivudine)	Two tablets (50 mg of ritonavir with 200 mg of lopinavir per tablet) twice daily, or four tablets once daily	5 or 6	Either once-daily or twice-daily dosing; one copayment; no refrigeration required; most experience in pregnancy; high genetic barrier to resistance	Gastrointestinal side effects such as diarrhea; may cause elevated liver-enzyme levels or hepatitis
Ritonavir plus atazanavir (plus either tenofovir–emtricitabine or zidovudine–lamivudine)	100 mg of ritonavir plus 300 mg of atazanavir once daily	3 or 4	Once-daily dosing; well tolerated	Ritonavir must be refrigerated; potential for asymptomatic jaundice, renal stones; may cause elevated liver-enzyme levels or hepatitis
Ritonavir plus darunavir (plus either tenofovir–emtricitabine or zidovudine–lamivudine)	100 mg of ritonavir plus two tablets, each containing 400 mg of darunavir, once daily	4 or 5	Once-daily dosing; high genetic barrier to resistance	Ritonavir must be refrigerated; gastrointestinal side effects; may cause elevated liver-enzyme levels or hepatitis

From Landovitz RJ, Currier JS: Postexposure prophylaxis for HIV infection, *N Engl J Med* 361:1768-75, 2009.

*Tenofovir, emtricitabine, and lamivudine all have activity against hepatitis B. Patients with chronic active hepatitis B (i.e., patients who are positive for hepatitis B surface antigen) may have flares of hepatitis on withdrawal of these agents at the completion of postexposure prophylaxis treatment. Referral to a hepatitis specialist or serial monthly monitoring of liver-enzyme levels for up to 6 months after treatment should be considered.

†The daily pill burden in the three-drug regimens depends on which two-drug regimen is chosen.

‡The dose of tenofovir–emtricitabine should be reduced to one tablet every 48 hours in patients with a creatinine clearance of 30 to 49 ml per minute. Tenofovir–emtricitabine is not recommended in patients with a creatinine clearance of less than 30 ml per minute or in patients who are undergoing hemodialysis; see the guidelines from the Department of Health and Human Services for considerations regarding doses of individual agents in patients with advanced renal dysfunction.

§Zidovudine–lamivudine is not recommended in patients with a creatinine clearance of less than 50 ml per minute; see the guidelines from the Department of Health and Human Services for considerations regarding doses of individual agents in patients with renal dysfunction.

‖The boosting agent ritonavir is not considered to be an active drug in tabulating the number of agents in the three-drug regimen.

TABLE 5-34 Antiretroviral Therapy Medications, Adult Dosage, and Side Effects

Medication	Adult Dosage*	Side Effects and Toxicities
Combination Tablets		
Lopinavir/ritonavir (Kaletra)‡	3 tablets twice daily 400 mg lopinavir/100 mg ritonavir	Diarrhea, nausea, vomiting; asthenia; elevated transaminases; hyperglycemia; fat redistribution; lipid abnormalities; possible increased bleeding in persons with hemophilia; pancreatitis
Zidovudine/lamivudine (Combivir)	1 tablet twice daily 300 mg zidovudine/150 mg lamivudine	See following individual medications
Zidovudine/lamivudine/abacavir (Trizivir)	1 tablet twice daily 300 mg zidovudine/150 mg lamivudine/300 mg abacavir	See following individual medications
Lamivudine/abacavir (Epzicom)	1 tablet once daily 300 mg lamivudine/600 mg abacavir	See following individual medications
Emtricitabine/tenofovir (Truvada)	1 tablet once daily 200 mg emtricitabine/300 mg tenofovir	See following individual medications
Single Agents		
Nucleoside and nucleotide reverse transcriptase inhibitors (side effects as a class: lactic acidosis, severe hepatomegaly with steatosis, including some fatal cases)		
Abacavir (Ziagen, ABC)‡	300 mg twice daily or 600 mg once daily	Severe hypersensitivity reaction (can be fatal); nausea; vomiting
Didanosine (Videx, ddI)‡	>60 kg (132 lb) body weight: 200 mg twice daily or 400 mg daily; if with tenofovir, 250 mg/daily <60 kg (132 lb): 125 mg twice daily or 250 mg daily; if with tenofovir, dose not established Do not use with stavudine (d4T, Zerit) during pregnancy; avoid ddI/d4T combination in general because of increased risk for adverse events (e.g., neuropathy, pancreatitis, and hyperlactatemia)	Pancreatitis; nausea, diarrhea; peripheral neuropathy
Emtricitabine (Emtriva, FTC)	200 mg once daily	Minimal toxicity; lactic acidosis and hepatic steatosis a rare but possibly life-threatening event
Lamivudine (Epivir, 3TC)‡	150 mg twice daily or 300 mg once daily	Minimal toxicity; lactic acidosis and hepatic steatosis a rare but possibly life-threatening event
Stavudine (Zerit, d4T)‡	>60 kg (132 lb) body weight: 40 mg twice daily <60 kg (132 lb) body weight: 30 mg twice daily Do not use with didanosine (ddI, Videx) during pregnancy; avoid ddI/d4T combination in general because of increased risk of adverse events (e.g., neuropathy, pancreatitis, and hyperlactatemia)	Pancreatitis; peripheral neuropathy; rapidly progressive ascending neuromuscular weakness (rare)
Tenofovir (Viread)	300 mg daily	Nausea, vomiting, diarrhea; headache; asthenia; flatulence; renal impairment
Zidovudine (Retrovir, AZT)‡	200 mg three times daily or 300 mg twice daily	Bone marrow suppression (anemia, neutropenia); gastrointestinal intolerance; headache; insomnia; asthenia; and myopathy
Nonnucleoside reverse transcriptase inhibitors (side effects as a class: Stevens-Johnson syndrome)		
Efavirenz (Sustiva)	600 mg daily at bedtime	Rash; central nervous system symptoms (e.g., dizziness, impaired concentration, insomnia, and abnormal dreams); transaminase elevation; false-positive cannabinoid test
Protease inhibitors (side effects as a class: gastrointestinal intolerance, hyperlipidemia, hyperglycemia, diabetes, fat redistribution, and possible increased bleeding in hemophiliacs; do not use during known or possible pregnancy)		
Atazanavir (Reyataz)	400 mg once daily; if administered with tenofovir plus ritonavir, 300 mg once daily	Indirect hyperbilirubinemia; prolonged PR interval (use caution in patients with underlying cardiac conduction defects or on concomitant medications that can cause PR prolongation)
Fosamprenavir (Lexiva)‡	1400 mg twice daily	Gastrointestinal intolerance, nausea, vomiting, diarrhea; rash; elevated transaminases; headache
Indinavir (Crixivan)	800 mg q8h With ritonavir (might increase risk for renal adverse events): 800 mg indinavir and 100 mg ritonavir q12h or 800 mg indinavir and 200 mg ritonavir every q12h	Gastrointestinal intolerance, nausea; nephrolithiasis; headache; asthenia; blurred vision; metallic taste; thrombocytopenia; hemolytic anemia; indirect hyperbilirubinemia (inconsequential)
Nelfinavir (Viracept)‡	750 mg three times daily or one 250 mg twice daily	Diarrhea; elevated transaminases
Ritonavir (Norvir)‡	See doses used in combination with other specific protease inhibitors	Gastrointestinal intolerance; nausea, vomiting, diarrhea; paresthesias; hepatitis; pancreatitis; asthenia; taste perversion; many drug interactions
Saquinavir (hard-gel capsule) (Invirase)	With ritonavir: 400 mg saquinavir and 400 mg ritonavir twice daily or 1000 mg saquinavir and 100 mg ritonavir twice daily	Gastrointestinal intolerance; nausea, diarrhea; headache; elevated transaminases
Saquinavir (soft-gel capsule) (Fortavase)	With ritonavir: 400 mg saquinavir and 400 mg ritonavir twice daily or 1000 mg saquinavir and 100 mg ritonavir twice daily	Gastrointestinal intolerance; nausea, diarrhea; abdominal pain; dyspepsia; headache; elevated transaminases

*For pediatric dosing information, see *Guidelines for use of antiretroviral agents in pediatric HIV infection*. Available at http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=51.
‡Pediatric formulation available.
Sources: Modified from U.S. Department of Health and Human Services and the Henry J. Kaiser Family Foundation: *Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents*. Available at http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=50 (refer to website for updated versions); Bartlett JG, Finkbeiner AK: HIV drugs: the guide to living with HIV infection, 2001. Available at http://www.thebody.com/jh/bartlett/drugs.html.

TABLE 5-35 Laboratory Tests Generally Recommended for Persons after Exposure to HIV*

Test	RECOMMENDED DURING TREATMENT		RECOMMENDED AT FOLLOW-UP		
	Baseline	Symptom-Directed†	4-6 wk	12 wk	24 wk
ELISA for HIV antibodies	Yes	Yes	Yes	Yes	Yes
Creatinine, liver function, and complete blood count with differential count	Yes	Yes	No	No	No
HIV viral load	No	Yes	No	No	No
Anti-HBs antibodies	Yes‡	No	No	No	No
HBsAg	Yes‡§	No	No	No	No
HCV antibodies	Yes	No	Yes	Yes	Yes
HCV RNA‖	No	Yes	Yes	Yes	Yes
Screening, including rapid plasma reagin test, for other sexually transmitted infections¶	Yes	Yes	No	Yes	No

From Landovitz RJ, Currier JS: Postexposure prophylaxis for HIV infection, *N Engl J Med* 361:1768-1775, 2009.

Anti-HBs antibodies, Hepatitis B virus surface antibodies; *ELISA,* enzyme-linked immunosorbent assay; *HBsAg,* hepatitis B surface antigen; *HCV,* hepatitis C virus.

*Patients who receive zidovudine plus lamivudine–based regimens should have a complete blood count and measurement of liver-enzyme levels at 2 weeks of treatment, irrespective of the presence or absence of clinical symptoms. Tenofovir plus emtricitabine–based regimens generally involve few side effects, and symptom-directed assessment of serum creatinine or liver-enzyme levels should be considered. The addition of a ritonavir-boosted protease inhibitor should be followed by symptom-directed assessment of liver-enzyme levels, serum glucose levels, or both.

†Symptom-directed tests are for signs or symptoms of toxic effects (rash, nausea, vomiting, or abdominal pain) or HIV seroconversion (fever, fatigue, lymphadenopathy, rash, or oral or genital ulcers).

‡If tests for anti-HBs antibodies and HBsAg are both negative, a vaccination series against HBV infection should be initiated and completed.

§If the patient is HBsAg-positive, he or she should have monthly follow-up of liver function tests after discontinuation of postexposure prophylactic regimens containing tenofovir, lamivudine, or emtricitabine; referral to a specialist in viral hepatitis should be considered.

‖HCV RNA testing may identify early HCV seroconversion; early detection and treatment during acute HCV infection may avert or ameliorate chronic disease. Data are from Dienstag and McHutchison.

¶Rapid plasma reagin testing and testing of urethral-swab and rectal-swab specimens for gonorrhea and chlamydia and of pharyngeal-swab specimens for gonorrhea should be performed as appropriate, according to the patient's sexual risk-taking behaviors and the type of exposure to HIV.

BOX 5-4 Situations for Which Expert Consultation for HIV Postexposure Prophylaxis Is Advised*

- Delayed (i.e., later than 24-36 hours) exposure report
  - The interval after which there is no benefit from postexposure prophylaxis (PEP) is undefined
- Unknown source (e.g., needle in sharps disposal container or laundry)
  - Decide use of PEP on a case-by-case basis
  - Consider the severity of the exposure and the epidemiologic likelihood of HIV exposure
  - Do not test needles or other sharp instruments for HIV
- Known or suspected pregnancy in the exposed person
  - Does not preclude the use of optimal PEP regimens
  - Do not deny PEP solely on the basis of pregnancy
- Resistance of the source virus to antiretroviral agents
  - Influence of drug resistance on transmission risk is unknown
  - Selection of drugs to which the source person's virus is unlikely to be resistant is recommended if the source person's virus is known or suspected to be resistant to one or more of the drugs considered for the PEP regimen
  - Resistance testing of the source person's virus at the time of the exposure is not recommended
- Toxicity of the initial PEP regimen
  - Adverse symptoms such as nausea and diarrhea are common with PEP
  - Symptoms often can be managed without changing the PEP regimen by prescribing antimotility and/or antiemetic agents
  - Modification of dose intervals (i.e., administering a lower dose of drug more frequently throughout the day, as recommended by the manufacturer) in other situations might help alleviate symptoms

*Local experts and/or the National Clinicians' Postexposure Prophylaxis Hotline (PEPline [888-448-4911]).

BOX 5-5 Occupational Exposure Management Resources

National Clinicians' Postexposure Prophylaxis Hotline (PEPline) Run by University of California–San Francisco/San Francisco General Hospital staff; supported by the Health Resources and Services Administration, Ryan White CARE Act, HIV/AIDS Bureau, AIDS Education and Training Centers, and CDC	Phone: 888-448-4911 Internet: http://www.ucsf.edu/hivcntr
Needlestick! A website to help clinicians manage and document occupational blood and body fluid exposures. Developed and maintained by the University of California, Los Angeles (UCLA), Emergency Medicine Center, UCLA School of Medicine, and funded in part by CDC and the Agency for Healthcare Research and Quality	Internet: http://www.needlestick.mednet.ucla.edu
Hepatitis Hotline	Phone: 888-443-7232 Internet: http://www.cdc.gov/ncidod/diseases/hepatitis/index.htm
Reporting to CDC: Occupationally acquired HIV infections and failures of PEP	Phone: 800-893-0485
HIV Antiretroviral Pregnancy Registry	Phone: 800-258-4263 Fax: 800-800-1052 Address: 1410 Commonwealth Dr., Suite 215, Wilmington, NC 28405 Internet: http://www.glaxowellcome.com/preg_reg/antiretroviral
Food and Drug Administration Report unusual or severe toxicity to antiretroviral agents	Phone: 800-332-1088 Address: MedWatch, HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857 Internet: http://www.fda.gov/medwatch
HIV/AIDS Treatment Information Service	Internet: http://www.hivatis.org

BOX 5-6 Management of Occupational Blood Exposures

Provide Immediate Care to the Exposure Site
- Wash wounds and skin with soap and water
- Flush mucous membranes with water

Determine Risk Associated with Exposure
- Type of fluid (e.g., blood, visibly bloody fluid, other potentially infectious fluid or tissue, and concentrated virus)
- Type of exposure (e.g., percutaneous injury, mucous membrane or nonintact skin exposure, and bites resulting in blood exposure)

Evaluate Exposure Source
- Assess the risk of infection using available information
- Test known sources for HBsAg, anti-HCV, and HIV antibodies (consider using rapid testing)
- For unknown sources, assess risk of exposure to HBV, HCV, or HIV infection
- Do not test discarded needles or syringes for virus contamination

Evaluate the Exposed Person
- Assess immune status for HBV infection (i.e., by history of hepatitis B vaccination and vaccine response)

Give PEP for Exposures Posing Risk of Infection Transmission
- HBV: See Table 5-27
- HCV: PEP not recommended
- HIV: See Tables 5-34, 5-35, and 5-36 and Figure 5-7
  - Initiate PEP as soon as possible, preferably within hours of exposure
  - Offer pregnancy testing to all women of childbearing age not known to be pregnant
  - Seek expert consultation if viral resistance is suspected
  - Administer PEP for 4 weeks if tolerated

Perform Follow-up Testing and Provide Counseling
- Advise exposed persons to seek medical evaluation for any acute illness occurring during follow-up

HBV Exposures
- Perform follow-up anti-HBs testing in persons who receive hepatitis B vaccine
  - Test for anti-HBs 1 to 2 months after last dose of vaccine
  - Anti-HBs response to vaccine cannot be ascertained if HBIG was received in the previous 3 to 4 months

HCV Exposures
- Perform baseline and follow-up testing for anti-HCV and alanine aminotransferase 4 to 6 months after exposures
- Perform HCV RNA at 4 to 6 weeks if earlier diagnosis of HCV infection desired
- Confirm repeatedly reactive anti-HCV enzyme immunoassays with supplemental tests

HIV Exposures
- Perform HIV-antibody testing for at least 6 months after exposure (e.g., at baseline, 6 weeks, 3 months, and 6 months)
- Perform HIV-antibody testing if illness compatible with an acute retroviral syndrome occurs
- Advise exposed persons to use precautions to prevent secondary transmission during the follow-up period
- Evaluate exposed persons taking PEP within 72 hr after exposure and monitor for drug toxicity for at least 2 weeks

HBIG, Hepatitis B immune globulin; *HBsAg,* hepatitis B surface antigen; *HBV,* hepatitis B virus; *HCV,* hepatitis C virus; *HIV,* human immunodeficiency virus; *PEP,* postexposure prophylaxis; *RNA,* ribonucleic acid.

Endocarditis Prophylaxis*

TABLE 5-36 Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from Endocarditis for Which Prophylaxis with Dental Procedures Is Recommended

Prosthetic cardiac valve
Previous infective endocarditis
CHD*
Unrepaired cyanotic CHD, including palliative shunts and conduits
Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 mo after the procedure†
Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (that inhibit endothelialization)
Cardiac transplant recipients who develop cardiac valvulopathy

CHD, Congenital heart disease.
*Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD.
†Prophylaxis is recommended because endothelialization of prosthetic material occurs within 6 mo after the procedure.

TABLE 5-37 Dental Procedures for Which Endocarditis Prophylaxis Is Recommended for Patients in Table 5-36

All dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa*

*The following procedures and events do not need prophylaxis: routine anesthetic injections through noninfected tissue, taking dental radiographs, placement of removable prosthodontic or orthodontic appliances, adjustment of orthodontic appliances, placement of orthodontic brackets, shedding of deciduous teeth, and bleeding from trauma to the lips or oral mucosa.

TABLE 5-38 Regimens for a Dental Procedure

	REGIMEN: SINGLE DOSE 30-60 MIN BEFORE PROCEDURE		
Situation	**Agent**	**Adults**	**Children**
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin	2 g IM or IV	50 mg/kg IM or IV
	OR		
	Cefazolin or ceftriaxone*	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin, oral	Cephalexin*†	2 g	50 mg/kg
	OR		
	Clindamycin	600 mg	20 mg/kg
	OR		
	Azithromycin or clarithromycin	500 mg	15 mg/kg
Allergic to penicillins or ampicillin and unable to take oral medicine	Cefazolin or ceftriaxone†	1 g IM or IV	50 mg/kg IM or IV
	OR		
	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV

IM, Intramuscular; *IV,* intravenous.
*Or other first-generation or second-generation oral cephalosporin in equivalent adult or pediatric dosage.
†Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillins or ampicillin.

From Prevention of infective endocarditis. A guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation* published online Apr 19, 2007, DOI: 10.1161/CIRCULATIONAHA.106.183095. Copyright © 2007 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539.

TABLE 5-39 Summary of Major Changes in Updated Recommendations

We concluded that bacteremia resulting from daily activities is much more likely to cause IE than bacteremia associated with a dental procedure.

We concluded that only an extremely small number of cases of IE might be prevented by antibiotic prophylaxis even if prophylaxis is 100% effective.

Antibiotic prophylaxis is not recommended based solely on an increased lifetime risk of acquisition of IE.

Limit recommendations for IE prophylaxis only to those conditions listed in Table 5-36.

Antibiotic prophylaxis is no longer recommended for any other form of CHD, except for the conditions listed in Table 5-36.

Antibiotic prophylaxis is recommended for all dental procedures that involve manipulation of gingival tissues or periapical region of teeth or perforation of oral mucosa only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE (see Table 5-36).

Antibiotic prophylaxis is recommended for procedures on respiratory tract or infected skin, skin structures, or musculoskeletal tissue only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE (see Table 5-36).

Antibiotic prophylaxis solely to prevent IE is not recommended for GU or GI tract procedures.

The writing group reaffirms the procedures noted in the 1997 prophylaxis guidelines for which endocarditis prophylaxis is not recommended and extends this to other common procedures, including ear and body piercing, tattooing, and vaginal delivery and hysterectomy.

NOTE: A guide to the clinical preventive services described is available online at http://www.ahrq.gov/clinic/pocketgd07/.
CHD, Congenital heart disease; *GI,* gastrointestinal; *GU,* genitourinary; *IE,* infective endocarditis.

Hepatitis C Testing

BOX 5-7 Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-Related Chronic Diseases

Recommendations for the Identification of Chronic Hepatitis C Virus Infection Among Persons Born During 1945–1965*
- Adults born during 1945-1965 should receive one-time testing for HCV without prior ascertainment of HCV risk.
- All persons with identified HCV infection should receive a brief alcohol screening and intervention as clinically indicated, followed by referral to appropriate care and treatment services for HCV infection and related conditions.

Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents†
- HIV-infected patients should be tested routinely for evidence of chronic HCV infection. Initial testing for HCV should be performed using the most sensitive immunoassays licensed for detection of antibody to HCV (anti-HCV) in blood.

Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-Related Chronic Disease‡

Routine HCV testing is recommended for:
- Persons who ever injected illegal drugs, including those who injected once or a few times many years ago and do not consider themselves as drug users.
- Persons with selected medical conditions, including:
  - persons who received clotting factor concentrates produced before 1987;
  - persons who were ever on chronic (long-term) hemodialysis;
  - persons with persistently abnormal alanine aminotransferase levels.
- Prior recipients of transfusions or organ transplants, including:
  - persons who were notified that they received blood from a donor who later tested positive for HCV infection;
  - persons who received a transfusion of blood or blood components before July 1992; and
  - persons who received an organ transplant before July 1992.

Routine HCV testing is recommended for persons with recognized exposures, including:
- Health care, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood.
- Children born to HCV-positive women.

From Centers for Disease Control and Prevention: Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. MMWR 2012:61(4).

*Source: Centers for Disease Control and Prevention: Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945–1965. *MMWR* 2012;61(No. RR–4).

†Source: Centers for Disease Control and Prevention: Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR* 2009;58(No. RR–4).

‡Source: Centers for Disease Control and Prevention: Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. *MMWR* 1998;47(No. RR–19).

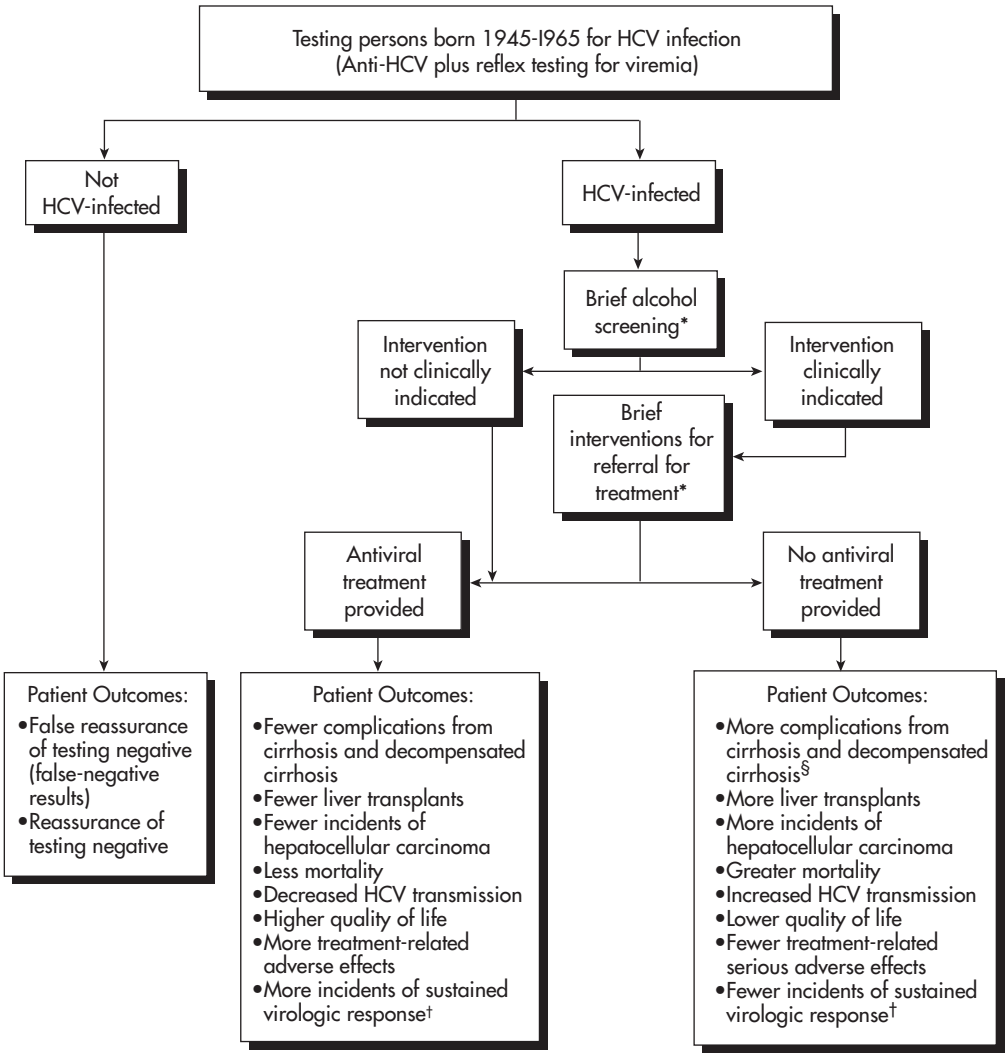


FIGURE 5-8 Analytic Framework for Guiding HCV Testing Among Persons Born During 1945-1965.
*Together, these interventions are known as alcohol screening and brief interventions (SBI) For referral for treatment. †Viral eradication after treatment completion. §Cirrhosis with the diagnosis of at least one of the following: ascites, variceal bleeding, encephalopathy, or impaired hepatitis synthetic function. From Centers for Disease Control and Prevention: Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR* 2012:61(4).

Prevention and Control of Meningococcal Disease

BOX 5-8 Meningococcal Vaccination Recommendations—Advisory Committee on Immunization Practices, 2013

ACIP recommends meningococcal vaccination for the following groups:

- Routine vaccination of adolescents aged 11 through 18 years (a single dose of vaccine should be administered at age 11 or 12 years, with a booster dose at age 16 years for persons who receive the first dose before age 16 years).
- Routine vaccination of persons aged ≥2 months at increased risk for meningococcal disease, including:
  - Persons aged ≥2 months with certain medical conditions, such as anatomical or functional asplenia or complement component deficiency (dosing schedule and interval for booster dose varies by age at time of previous vaccination).
  - Special populations, such as unvaccinated or incompletely vaccinated first-year college students living in residence halls, military recruits, or microbiologists with occupational exposure (indication for booster dose 5 years after prior dose if at continued risk).
  - Persons aged ≥9 months who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic, particularly if contact with the local population will be prolonged.
- Vaccination of persons in at-risk groups (see Table 5-41) to control outbreaks.

From Centers for Disease Control and Prevention: Prevention and control of meningococcal disease, recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2013:63(2).

TABLE 5-40 Recommended Meningococcal Vaccines for Use in Children and Adults—Advisory Committee on Immunization Practices (ACIP), United States, 2012

Age Group	Vaccine	Status
2 mo-10 yr	MenACWY-D (Menactra, Sanofi)*	Not routinely recommended; see Table 5-41 for persons at increased risk
	MenACWY-CRM (Menveo, Novartis)†	Not routinely recommended; see Table 5-41 for persons at increased risk
	HibMenCY-TT (MenHibrix, GSK)‡	Not routinely recommended; see Table 5-41 for persons at increased risk
11-21 yr	MenACWY-D or MenACWY-CRM	Primary: • Age 11-12 yr, 1 dose • Age 13-18 yr, 1 dose if not vaccinated previously • Age 19-21 yr, not routinely recommended but may be administered as catch-up vaccination for those who have not received a dose after their 16th birthday Booster: • 1 dose recommended if first dose administered before 16th birthday
22-55 yr	MenACWY-D or MenACWY-CRM	Not routinely recommended; see Table 5-41 for persons at increased risk
≥56 yr	MPSV4, MenACWY-D, or MenACWY-CRM	Not routinely recommended; see Table 5-41 for persons at increased risk

Adapted from American Academy of Pediatrics. Meningococcal infections. In: Pickering LK, Baker CJ, Kimberlin DW, eds. *Red book: 2012 report of the Committee on Infectious Diseases*. 29th ed. Elk Grove, IL: American Academy of Pediatrics; 2012:500-9; From Centers for Disease Control and Prevention: Prevention and control of meningococcal disease, Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2013:63(2).

*Licensed only for persons aged 9 months-55 years.

†Licensed only for persons aged 2-55 years. Under investigation for use at ages 2, 4, 6, and 12-15 months.

‡Licensed only for children aged 6 weeks-18 months.

TABLE 5-41 Recommended Immunization Schedule and Intervals for Persons at Increased Risk for Meningococcal Disease—Advisory Committee on Immunization Practices (ACIP), United States, 2012*

Age Group	Subgroup	Primary Vaccination	Booster Dose†
2-18 mo with high-risk conditions‡	Children who: • have persistent complement deficiencies • have functional or anatomic asplenia • are at risk during a community outbreak attributable to a vaccine serogroup	Four doses of Hib-MenCY-TT (MenHibrix), at 2, 4, 6, and 12-15 mo	Person remains at increased risk and completed the primary dose or series at age: • 2 mo-6 yr: Should receive additional dose of MenACWY 3 yr after primary immunization; boosters should be repeated every 5 yr thereafter • ≥7 yrs: Should receive additional dose of MenACWY 5 yr after primary immunization; boosters should be repeated every 5 yr thereafter
9-23 mo with high-risk conditions§	Children who: • have persistent complement deficiencies • travel to or are residents of countries where meningococcal disease is hyperendemic or epidemic • are at risk during a community outbreak attributable to a vaccine serogroup	Two doses of MenACWY-D (Menactra), 12 weeks apart‖	
2-55 yr with high-risk conditions and not vaccinated previously	Persons who: • have persistent complement deficiencies • have functional or anatomic asplenia • have HIV, if another indication for vaccination exists	Two doses of MenACWY, 8-12 wk apart¶	
	Persons who: • are first-year college students aged ≤21 yr living in residential housing • travel to or are residents of countries where meningococcal disease is hyperendemic or epidemic • are at risk during a community outbreak attributable to a vaccine serogroup • are microbiologists routinely exposed to isolates of *Neisseria meningitidis*	One dose of MenACWY‖	

Adapted from American Academy of Pediatrics. Meningococcal infections. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red book: 2012 report of the Committee on Infectious Diseases*. 29th ed. Elk Grove, IL: American Academy of Pediatrics; 2012: 500-9; Centers for Disease Control and Prevention: Prevention and control of meningococcal disease, recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 62(2).

*Includes persons who have persistent complement deficiencies (e.g., C5-C9, properdin, factor H, or factor D), and anatomic or functional asplenia; travelers to or residents of countries in which meningococcal disease is hyperendemic or epidemic; and persons who are part of a community outbreak of a vaccine-preventable serogroup.

†If the person remains at increased risk for meningococcal disease.

‡Infants and children who received Hib-MenCY-TT and are travelling to areas with high endemic rates of meningococcal disease such as the African "meningitis belt" are not protected against serogroups A and W-135 and should receive a quadrivalent meningococcal vaccination licensed for children aged ≥9 mo prior to travel.

§Because of high risk for invasive pneumococcal disease, children with functional or anatomic asplenia should not be immunized with MenACWY-D (Menactra) before age 2 yr to avoid interference with the immune response to the pneumococcal conjugate vaccine (PCV) series.

‖If an infant is receiving the vaccine prior to travel, 2 doses may be administered as early as 8 wk apart.

¶If MenACWY-D is used, it should be administered at least 4 wk after completion of all PCV doses.

TABLE 5-42 Recommended Chemoprophylaxis Regimens for Protection Against Meningococcal Disease—Advisory Committee on Immunization Practices (ACIP), United States, 2012

Drug	Age Group	Dosage	Duration and Route of Administration
Rifampin†	Children aged <1 mo	5 mg/kg every 12 hr	2 d
	Children aged ≥1 mo	10 mg/kg every 12 hr	2 d
	Adults	600 mg every 12 hr	2 d
Ciprofloxacin‡	Adults	500 mg	Single dose
Ceftriaxone	Children age <15 yr	125 mg	Single IM dose
Ceftriaxone	Adults	250 mg	Single IM dose

Burstein GR, Berman SM, Blumer JL, Moran JS. Ciprofloxacin for the treatment of uncomplicated gonorrhea infection in adolescents: does the benefit outweigh the risk? *Clin Infect Dis* 2002;35: S191-9; Centers for Disease Control and Prevention: Prevention and control of meningococcal disease, recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 62(2).

IM, Intramuscular.

* Oral administration unless indicated otherwise.

†Rifampin is not recommended for pregnant women because the drug is teratogenic in laboratory animals. Because the reliability of oral contraceptives might be affected by rifampin therapy, consideration should be given to using alternative contraceptive measures while rifampin is being administered.

‡Ciprofloxacin is not generally recommended for persons aged <18 yr or for pregnant and lactating women because the drug causes cartilage damage for immature laboratory animals. However, ciprofloxacin may be used for chemoprophylaxis of children when no acceptable alternative therapy is available. A recent review identified no reports of irreversible cartilage toxicity or age-associated adverse events in children and adolescents.

Hepatitis B Virus Postexposure Protection for Health Care Personnel

TABLE 5-43 Postexposure Management of Health Care Personnel After Occupational Percutaneous and Mucosal Exposure to Blood and Body Fluids, by Health Care Personnel HepB Vaccination and Response Status

	POSTEXPOSURE TESTING		POSTEXPOSURE PROPHYLAXIS		
Health Care Personnel Status	**Source Patient (HBsAg)**	**HCP Testing (anti-HBs)**	**HBIG***	**Vaccination**	**Postvaccination Serologic Testing†**
Documented responder‡ after complete series (≥3 doses)	No action needed				
Documented nonresponder§ after 6 doses	Positive/unknown	—‖	HBIG ×2 separated by 1 mo	—	No
	Negative	No action needed			
Response unknown after 3 doses	Positive/unknown	<10 mIU/mL‖	HBIG ×1	Initiate revaccination	Yes
	Negative	<10 mIU/mL	None		
	Any result	≥10 mIU/mL	No action needed		
Unvaccinated/incompletely vaccinated or vaccine refusers	Positive/unknown	—‖	HBIG ×1	Complete vaccination	Yes
	Negative	—	None	Complete vaccination	Yes

From Centers for Disease Control and Prevention: CDC guidance for evaluating health-care personnel for hepatitis B virus protection and for administering post-exposure management. *MMWR* 2013:62(10).

anti-HBs, Antibody to hepatitis B surface antigen; *HBIG*, hepatitis B immune globulin; *HBsAg*, hepatitis B surface antigen; *HCP*, health care personnel.

*HBIG should be administered transmuscularly as soon as possible after exposure when indicated. The effectiveness of HBIG when administered >7 d after percutaneous, mucosal, or nonintact skin exposures is unknown. HBIG dosage is 0.06 mL/kg.

†Should be performed 1-2 mo after the last dose of the HepB vaccine series (and 4-6 mo after administration of HBIG to avoid detection of passively administered anti-HBs) using a quantitative method that allows detection of the protective concentration of anti-HBs (≥10 mIU/mL).

‡A responder is defined as a person with anti-HBs ≥10 mIU/mL after ≥3 doses of HepB vaccine.

§A nonresponder is defined as a person with anti-HBs <10 mIU/mL after ≥6 doses of HepB vaccine.

‖HCP who have anti-HBs <10 mIU/mL, or who are unvaccinated or incompletely vaccinated, and sustain an exposure to a source patient who is HBsAg-positive or has unknown HBsAg status, should undergo baseline testing for HBV infection as soon as possible after exposure, and follow-up testing approximately 6 mo later. Initial baseline tests consist of total anti-HBc; testing at approximately 6 months consists of HBsAg and total anti-HBc.

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APPENDIX

I. Complementary and Alternative Medicine

II. Nutrition

III. Acute Poisoning

IV. Impairment and Disability Issues

V. Primary Care Procedures (available online)

VI. Patient Teaching Guides (available online)

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Appendix Ia

Definitions of Complementary and Alternative Medicine Terms

Acupuncture Thin needles are inserted superficially on the skin at locations throughout the body. These points are located along "channels" of energy. Heat can be applied by burning (moxibustion), electric current (electroacupuncture), or pressure (acupressure). Healing is proposed by the restoration of a balance of energy flow called *Qi.* Another explanation suggests that, possibly, the stimulation activates endorphin receptors.

Alexander Technique A bodywork technique in which rebalancing of "postural sets" (i.e., physical alignment) is taught by mentally focusing on the way correct alignments should look and feel and through verbal and tactile guidance by the practitioner.

Applied Kinesiology A form of treatment that uses nutrition, physical manipulation, vitamins, diets, and exercise to restore and energize the body. Weak muscles are proposed as a source of dysfunctional health.

Aromatherapy A form of herbal medicine that uses various oils from plants. Route of administration can be through absorption in the skin or inhalation. The aromatic biochemical structures of certain herbs are thought to act in areas of the brain related to past experiences and emotions (e.g., limbic system).

Ayurveda A major health system that originated in India and incorporates the body, mind, and spirit to prevent and treat disease. Includes special types of diets, herbs, and minerals.

Biofeedback A mind-body therapy procedure in which sensors are placed on the body to measure muscle tension, heart rate, and sweat responses or neural activity. Information is provided by visual, auditory, or body-muscle cell activation so as to teach either to increase or decrease physiologic activity, which, when reconstituted, is proposed to improve health problems (e.g., pain, anxiety, or high blood pressure). In some cases, relaxation exercises complement this procedure.

Chelation Therapy Involves the removal—through intravenous infusion of a chelating agent (synthetic amino acid ethylenediamine tetraacetic acid [EDTA])—of heavy metals, including lead, nickel, and cadmium, as a way to treat certain diseases. Ancillary treatments include the use of vitamins, changes in diet, and exercise.

Cognitive Therapy Psychological therapy in which the major focus is altering and changing irrational beliefs through a type of Socratic dialogue and self-evaluation of certain illogical thoughts. Conditioning and learning are important components of this therapy.

Craniosacral Therapy A form of gentle manual manipulation used for diagnosis and for making corrections in a system made up of cerebrospinal fluid, cranial and dural membranes, cranial bones, and sacrum. This system is proposed to be dynamic, with its own physiologic frequency. Through touch and pressure, tension is proposed to be reduced and cranial rhythms normalized, leading to improvement in health and disease.

Diathermy The use of high-frequency electrical currents as a form of physical therapy and in surgical procedures. The term *diathermy,* derived from the Greek words *dia* and *therma,* literally means "heating through." The three forms of diathermy used by physical therapists are short wave, ultrasound, and microwave.

Eye Movement Desensitization and Reprocessing (EMDR) A technique that proposes to remove painful memories by behavioral techniques. Rhythmic, multisaccadic eye movements are produced by allowing the patient to track and follow a moving object while imagining a stressful memory or event. By using deconditioning, including verbal interaction with the therapist, the painful memory is extinguished and health improved.

Feldenkrais Method A bodywork technique that integrates physics, judo, and yoga. The practitioner directs sequences of movement using verbal or hands-on techniques or teaches a system of self-directed exercise to treat physical impairments through the learning of new movement patterns.

Hatha Yoga The branch of yoga practice that involves physical exercise, breathing practices, and movement. These exercises are designed to have a salutary effect on posture, flexibility, and strength and are intended ultimately to prepare the body to remain still for long periods of meditation.

Hellerwork A bodywork technique that treats and improves proper body alignment through the development of a more complete awareness of the physical body. The goal is to realign fascia for improvement of standing, sitting, and breathing using "body energy," verbal feedback, and changing emotions and attitudes.

Homeopathy A form of treatment in which substances (minerals, plant extracts, chemicals, or disease-producing germs), which in sufficient doses would produce a set of illness symptoms in healthy individuals, are given in microdoses to produce a "cure" of those same symptoms. The *symptom* is not thought to be part of the illness but part of a curative process.

Hyperbaric Oxygen A therapy in which 100% oxygen is given at or above atmospheric pressure. An increase in oxygen in the tissue is proposed to increase blood circulation and improve healing and health and influence the course of disease.

Jin Shin Jyutsu An ancient bodywork technique to harmonize body, mind, and spirit by gentle touch that uses specific "healing points" at the body surface. The points are proposed to overlie flowing energy (Qi). The therapist's fingers are used to "redirect, balance, and provide a more efficient energy flow" to and throughout the body.

Light Therapy Natural light or light of specified wavelengths is used to treat disease. This may include ultraviolet light, colored light, or low-intensity laser light. Generally, the eye is the initial entry point for the light because of its direct connection to the brain.

Magnetic Therapy Magnets are placed directly on the skin, theoretically stimulating living cells and increasing blood flow by ionic currents that are created from polarities on the magnets.

Modified from Spencer JW: *Complementary/alternative medicine: an evidence-based approach*, St Louis, 1999, Mosby.

Mediterranean Diet A diet that is thought to provide optimal distribution of daily caloric intake of different nutrients and includes 50% to 60% carbohydrates, 30% fats, and 10% proteins. The diet is derived from the eating habits of people in the Mediterranean area, who were shown to have reduced rates of cardiovascular disease.

Mind-Body Therapies A group of therapies that emphasize using the mind or brain in conjunction with the body to assist healing. Mind-body therapies can involve varying degrees of levels of consciousness, including *hypnosis,* in which selective attention is used to induce a specific altered state (trance) for memory retrieval, relaxation, or suggestion; *visual imagery,* in which the focus is on a target visual stimulus; *yoga,* which involves integration of posture and controlled breathing, relaxation, and/or meditation; *relaxation,* which includes lighter levels of altered states of consciousness through indirect or direct focus; and *meditation,* in which there is an intentional use of posture, concentration, contemplation, and visualization.

Muscle Energy Technique A manual therapy in osteopathic medicine that includes both passive mobilization and muscle reeducation. Diagnosis of somatic dysfunction is performed by the practitioner, after which the patient is guided to provide corrective muscle contraction.

Music Therapy The use of music in an either active or passive mode. Used mainly to reduce stress, anxiety, and pain.

Naturopathy A major health system that includes practices that emphasize diet, nutrition, homeopathy, acupuncture, herbal medicine, manipulation, and various mind-body therapies. Focal points include self-healing and treatment through changes in lifestyle and emphasis on health prevention.

Ornish Diet A life-choice program based on eating a vegetarian diet containing less than 10% fat. The diet is high in complex carbohydrates and fiber. Meat and fish are generally avoided.

Oslo Diet An eating plan that emphasizes increased intake of fish and reduced total fat intake. Diet is combined with regular endurance exercise.

Pilates An educational and exercise approach using the proper body mechanics, movements, truncal and pelvic stabilization, coordinated breathing, and muscle contractions to promote strengthening. Attention is paid to the entire musculoskeletal system.

Prayer The use of prayer(s) that are offered to "some higher being" or authority to heal and/or arrest disease. May be practiced by the individual patient, by groups, or by other(s) with or without the patient's knowledge (e.g., intercessory).

Pritikin Diet A weight management plan that is based on a vegetarian framework. Meals are low in fat, high in fiber, and high in complex carbohydrates.

Qi Gong A form of Chinese exercise-stimulation therapy that proposes to improve health by redirecting mental focus, breathing, coordination, and relaxation. The goal is to "rebalance" the body's own healing capacities by activating proposed electrical or energetic currents that flow along meridians located throughout the body. These meridians, however, do not follow conventional nerve or muscle pathways. In Chinese medical training and practice this therapy includes "external Qi," which is energy transmitted from one person to another so as to heal.

Raja Yoga Yoga practice that includes all of the other forms of yoga. The practitioner is instructed to follow moral directives, physical exercises, breathing exercises, meditation, devotion, and service to others to facilitate religious awakening.

Reflexology A bodywork technique that uses reflex points on the hands and feet. Pressure is applied at points that correspond to various body parts, to eliminate blockages thought to produce pain or disease.

Reiki Comes from the Japanese word meaning "universal life force energy." The practitioner serves as a conduit for healing energy directed into the body or energy field of the recipient without physical contact with the body.

Rolfing A bodywork technique that involves the myofascia. The body is realigned by using the hands to apply deep pressure and friction that allow more sufficient posture, movement, and the "release" of emotions from the body.

Shiatsu A Japanese bodywork technique involving finger pressure at specific points on the body mainly to balance "energy" in the body. The major focus is on prevention by keeping the body healthy. The therapy uses more than 600 points on the skin that are proposed to be connected to pathways through which energy flows.

T'ai Chi A technique that uses slow, purposeful motor-physical movements of the body to control and achieve a more balanced physiologic and psychological state.

Therapeutic Touch A body energy field technique in which hands are passed over the body without actually touching to recreate and change proposed "energy imbalances" for restoring innate healing forces. Verbal interaction between patient and therapist helps maximize effects.

Traditional Chinese Medicine An ancient form of medicine that focuses on prevention and secondarily treats disease with an emphasis on maintaining balance through the body by stimulating a constant, smooth-flowing Qi energy. Herbs, acupuncture, massage, diet, and exercise are also used.

Trager Psychophysical Integration A bodywork technique in which the practitioner enters a meditative state and guides the client through gentle, light, rhythmic, nonintrusive movements. "Mentastics" exercises using self-healing movements are taught to the clients.

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Appendix Ib

Relaxation Techniques

Relaxation Techniques

Relaxation Technique	Summary	Further Resources
Breathing exercise	This is the foundation of most relaxation techniques. Have patients place one hand on the chest and the other on the abdomen. Instruct them to take a slow, deep breath, as if they were sucking in all the air in the room. While doing this, the hand on the abdomen should rise higher than the hand on the chest. This promotes diaphragmatic breathing that increases alveolar expansion in the bases of the lungs. Have them hold the breath for a count of 7 and then exhale. Exhalation should take twice as long as inhalation. Repeat this for a total of five breaths, and encourage patients to do this three times a day.	*Conscious Breathing* by Gay Hendricks is one of many good resources on using breathing for relaxation and health.
Meditation		
Transcendental/The relaxation response	To prevent distracting thoughts, the subject repeats a mantra (a word or sound) over and over again while sitting in a comfortable position. If a distracting thought comes to mind, it is accepted and let go, with the mind focusing again on the mantra.	www.mindbody.harvard.edu or *The Relaxation Response* by Herbert Benson; www.tm.org for information on transcendental meditation.
Mindful meditation	This represents the philosophy of living in the present or in the moment. The *body scan* is one technique where the subject uses breathing to obtain a relaxed state while lying or sitting. The mind progressively focuses on different parts of the body, where it feels any and all sensations intentionally but nonjudgmentally before moving on to another part of the body. A patient with back pain may focus on the quality and characteristics of the pain as if to better understand it and bring it under control.	*Full Catastrophe Living* by Jon Kabat-Zinn describes this technique in full and the program for stress reduction at the University of Massachusetts Medical Center.
Centering prayer	This is a form similar to transcendental meditation that has a more religious foundation. The subject repeats a "sacred word" similar to a mantra. As thoughts come to mind, they are accepted and let go, clearing the mind to become more centered on the spirit within, as if the mind's preoccupied thoughts are the layers of an onion that are peeled away, allowing better understanding of the spirit at the core.	www.centeringprayer.com; look under "method of centering prayer" for a nondenominational discussion.
Progressive muscle relaxation (PMR)	A form of relaxation in which the subject is attuned to the difference in feeling when the muscles are tensed and then relaxed. In a comfortable position, start by tensing the whole body from head to toe. While doing this, notice the feelings of tightness. Take a deep breath in and as you let it out, let the tension release and the muscles relax. This is then followed by progressive tension and relaxation throughout the body. One may start by clenching the fists and then tensing the arms, shoulders, chest, abdomen, hips, legs, and so on, with each step followed by relaxation.	www.uaex.edu/publications/pub/fshei28.htm is a good review of PMR as well as other relaxation exercises. It is sponsored by the University of Arkansas. *You Must Relax* is a book by the founder of this technique, Edmund Jacobson.
Visualization/Self-hypnosis	The subject uses visualization to recruit images that create a relaxed state. For example, if a person is anxious, visualizing images of a place and a time that were peaceful and comforting would help induce relaxation. This is best used in conjunction with a breathing exercise.	There are many CDs, MP3s, and DVDs that can guide people through a visualization "script" that can result in relaxation. Emmett Miller is one well-known author.
Autogenic training	This induces a physiologic response by using simple phrases. For example, "My legs are heavy and warm" is meant to increase the blood flow to this area, resulting in relaxation. This is done progressively from head to toe with the use of deep breathing and repetition of the phrase. After completing this, focus attention on any body part that may still be tense, and then focus the breath and phrase to that area until the whole body is relaxed.	The British Autogenic Society at www.autogenictherapy.org.uk is a good resource for more information.

Continued on following page

Relaxation Techniques—cont'd

Relaxation Technique	Summary	Further Resources
Exercise/Movement		
Aerobic	While performing an aerobic exercise, focus attention on a phrase, sound, word, or prayer and passively disregard other thoughts that may enter the mind. Some may focus on their breathing, saying to themselves, "In" with inhalation and "Out" with exhalation, or repeating "one-two, one-two" with each step they take with jogging. Doing this will help the mind focus, preventing other thoughts that may cause tension.	*Beyond the Relaxation Response* by Herbert Benson includes discussion of his research on inducing the relaxation response while exercising.
Yoga	This has been practiced for thousands of years in India. In America, it has been divided into three aspects: breathing (pranayama yoga), bodily postures or asanas (hatha yoga), and meditation to maintain balance and health. Regular practice induces relaxation.	For Yoga, t'ai chi, and qi gong therapies, it is best to encourage patients to take a class at a local community center or gym and to pick up an introductory book at a library or bookstore.
T'ai chi	An ancient Chinese martial art that uses slow, graceful movements combined with inner mindfulness and breathing techniques to help bring balance between the mind and body.	See above.
Qi gong	A traditional Chinese practice that uses movement, meditation, and controlled breathing to balance the body's vital energy force, Qi.	See above.

From Rakel RE (ed): *Principles of family practice,* ed 6, Philadelphia, 2002, Saunders.

Appendix Ic

Overview of Selected Natural Products

This table includes a few of the common uses and side effects of selected natural products. The evidence supporting the uses and side effects of these products varies considerably and may be based on anecdotal information or theoretical concerns with the natural products.

Natural Products	Common Use(s)	Adverse Effects/Potential Concerns
African plum (Pygeum)	Benign prostatic hyperplasia	Nausea and abdominal pain have been reported, but pygeum is generally well tolerated. Pygeum does not decrease prostate size or influence PSA concentrations.
Andrographis	Prevention and treatment of viral respiratory infections	Headache, fatigue, rash, diarrhea, and vomiting. Products are standardized to 4%-6% andrographolide; this botanical is commonly used in combination products.
Black cohosh	Menopausal symptoms (hot flashes), induction of labor in pregnant women, premenstrual syndrome	Dyspepsia, rash, weight gain, headache, and cramping have been reported. Concern exists that black cohosh causes liver toxicity. The potential development of mild estrogen-like adverse effects, especially endometrial hyperplasia, is of concern.
Butterbur	Prevention of migraine headaches; allergic rhinitis; urinary tract spasms; pain	Diarrhea, stomach upset, fatigue, belching, headache, and drowsiness may occur. Due to concern about hepatotoxicity, butterbur products should be free of pyrrolizidine alkaloids. Products should be standardized to 15% petasin and isopetasin.
Chamomile (German)	Motion sickness, anxiety, insomnia; gastrointestinal spasms; mucositis	Allergic reactions occur on rare occasion. Patients with a ragweed allergy should use chamomile with caution.
Chasteberry	Premenstrual dysphoric disorder, premenstrual syndrome, menopausal symptoms, female infertility, mastalgia	Gastrointestinal upset, headache, rash, acne, weight gain, and menstrual bleeding have been reported.
Chitosan	Weight loss, Crohn's disease, hypercholesterolemia, anemia	Gastrointestinal upset, nausea, flatulence, and constipation have been reported. Patients with a shellfish allergy should avoid the use of chitosan.
Chondroitin sulfate	Osteoarthritis, osteoporosis, hyperlipidemia	Gastrointestinal upset, nausea, diarrhea, constipation, and alopecia. Concern exists that chondroitin may have anticoagulant activity due to its structural similarity to part of heparin.
Cinnamon	Type 2 diabetes mellitus, flatulence, gastrointestinal spasms, anorexia, menopausal symptoms, impotence	Cassia cinnamon is one of three types of cinnamon in commercial food products; this is the only type that may have minor effects to improve blood glucose concentrations.
Coenzyme Q10	Congestive heart failure, angina, dilated cardiomyopathy, statin-induced myopathy, Parkinson's disease, chronic fatigue syndrome, HIV/AIDS	Nausea, vomiting, diarrhea, anorexia, heartburn, and rash have been reported. Coenzyme Q10 is structurally similar to vitamin K; concern exists about potential interaction with warfarin.
Cranberry	Prevention and treatment of urinary tract infections; type 2 diabetes mellitus; chronic fatigue syndrome; pleurisy	Gastrointestinal upset and diarrhea have been reported with large doses of cranberry. Uric acid kidney stone formation is also possible with large doses of cranberry over prolonged periods of time.
Dehydroepiandrosterone (DHEA)	Slow or reverse aging, weight loss, metabolic syndrome, erectile dysfunction, immune stimulant, osteoporosis, systemic lupus erythematosus, multiple sclerosis, depression, schizophrenia	Acne and other androgenic effects commonly occur in women. Alopecia, insulin resistance, hepatic dysfunction, and hypertension have been reported. Ingested wild yam and soy cannot be converted into DHEA by humans.
Devil's claw	Osteoarthritis, atherosclerosis, gout, myalgias, fever, migraines	Diarrhea, nausea, and vomiting, as well as allergic reactions, have been reported.
Echinacea	Prevention and treatment of viral respiratory infections; urinary tract infections; chronic fatigue syndrome; attention deficit hyperactivity disorder	Nausea, vomiting, diarrhea, heartburn, headaches, dizziness, arthralgias, and allergic reactions have been reported with echinacea. Patients with a ragweed allergy should use echinacea with caution because the risk of allergic reactions may be increased.

Continued on following page

Overview of Selected Natural Products

Natural Products	Common Use(s)	Adverse Effects/Potential Concerns
Eleuthero (Siberian ginseng)	Maintenance of a normal blood pressure; atherosclerosis; Alzheimer's disease; chronic fatigue syndrome; diabetes; herpes simplex infections	Drowsiness, anxiety, and irritability have been reported.
Evening primrose oil (EPO)	Premenstrual syndrome, mastalgia, osteoporosis, asthma, menopausal symptoms, eczema, chronic fatigue syndrome	EPO is well tolerated.
Fenugreek	Type 2 diabetes mellitus, anorexia, atherosclerosis; also used as galactogogue	Gastrointestinal upset, flatulence, and hypoglycemia are possible side effects. Patients with a peanut allergy (and an allergy to related plants) should use fenugreek with caution. Nursing mothers who use fenugreek may notice a "maple syrup" smell in their sweat and in the urine of their infants. This may be mistaken to be maple syrup urine disease in the infant.
Feverfew	Prevention of migraines; fever; menstrual-related problems; arthritis; infertility; asthma	Gastrointestinal side effects are the most common with feverfew. A "post-feverfew syndrome" has been reported in individuals who have taken feverfew for prolonged periods of time and then have abruptly stopped the herbal.
Fish oil	Hypertriglyceridemia, coronary heart disease, hypertension, asthma, depression, rheumatoid arthritis, osteoporosis, psoriasis	Heartburn, nausea, rash, and a "fishy" aftertaste can occur. Contamination with pesticides (as well as with mercury and other heavy metals) is a potential concern, although this is unlikely.
Garlic	Hyperlipidemia, hypertension, peripheral arterial disease, type 2 diabetes mellitus	Nausea, vomiting, heartburn, and body odor are most common. "Deodorized" garlic products may lack the active ingredient, allicin.
Ginger	Nausea and vomiting secondary to pregnancy, chemotherapy, motion sickness, surgery	Heartburn, belching, and dermatitis have been reported. In overdoses, ginger has been associated with central nervous system depression and arrhythmias. Efficacy for hyperemesis gravidarum is unknown, and use is not recommended.
Ginkgo	Alzheimer's disease, vascular dementias, tinnitus, acute mountain sickness, intermittent claudication	Gastrointestinal side effects, headaches, dizziness, and allergic skin reactions. Seizures have been reported in several case reports. Products should contain 24% ginkgo flavone glycosides and 6% terpenoids.
Ginseng (Panax)	Increased resistance to stress and improved well-being; increased physical stamina; depression; diabetes; erectile dysfunction	Insomnia has been reported with ginseng. Vaginal bleeding, mastalgia, and amenorrhea have also been reported.
Glucosamine sulfate	Osteoarthritis	Nausea, heartburn, skin reactions, and headache have been reported. Increased glucose concentrations have been a concern but have not been well documented. Patients with a shellfish allergy should use glucosamine with caution.
Green tea	Improve cognitive performance; prevention of breast, prostate, and colon cancer; hyperlipidemia; Parkinson's disease; obesity; diabetes; cardiovascular disease	Nausea, vomiting, dyspepsia, dizziness, insomnia, and nervousness have been reported. Side effects may be a result of the large amount of caffeine in green tea products. Hepatotoxicity has been a potential concern with green tea.
Hawthorn	Mild heart failure, angina, arrhythmias, hypertension	Mild gastrointestinal effects, dizziness, rash, palpitations, and nervousness have been reported.
Hoodia	Obesity	Side effects have not been reported. Many products lack the actual ingredient.
Horse chestnut	Chronic venous insufficiency, including varicose veins; benign prostate hyperplasia; diarrhea	Mild nausea, vomiting, dizziness, headache, and itching. Products are standardized to 16%-20% aescin.
Huperzine	Alzheimer's disease, increased alertness and energy, myasthenia gravis, memory enhancement	Nausea, vomiting, diarrhea, sweating, and blurred vision as a result of the cholinergic effects of huperzine have been reported.
Kava	Anxiety, insomnia, restlessness, seizure disorders, depression, chronic fatigue syndrome	Gastrointestinal upset, headache, dizziness, "kava" dermopathy, and allergic skin reactions. Hepatotoxicity is the primary concern with kava; some countries have banned the use of kava.
Melatonin	Jet lag, insomnia, migraine, chronic fatigue syndrome, breast cancer, osteoporosis; also used for insomnia in children with ADHD	Daytime drowsiness, headache, and dizziness have been reported. Vaginal bleeding has occurred in perimenopausal women. Melatonin from animal sources should be avoided.
Melissa	Cold sores (topically), anxiety, insomnia, Alzheimer's disease, hypertension, dyspepsia	Nausea, vomiting, dizziness, and wheezing have occurred with oral melissa.
Methylsulfonylmethane (MSM)	Chronic pain, arthritis, diabetes, osteoporosis, allergies, obesity, premenstrual syndrome	Nausea, bloating, diarrhea, fatigue, and insomnia have been associated with MSM. This substance is used frequently in combination with glucosamine and chondroitin.
Milk thistle	Protective agent against liver damage due to alcohol, acetaminophen, and carbon tetrachloride; hepatitis C	Nausea, abdominal fullness, diarrhea, and allergic reactions. Patients with a ragweed allergy should use milk thistle with caution.
Peppermint	Irritable bowel syndrome, sinusitis, morning sickness, dysmenorrhea	Heartburn has been reported, as well as laryngeal and bronchial spasm in infants and children.
Policosanol	Hyperlipidemia, intermittent claudication, atherosclerosis	Migraines, insomnia, dizziness, skin rash, and bleeding have been reported with policosanol. The product has antiplatelet effects.
Probiotics	Treatment and prevention of diarrhea including antibiotic-associated diarrhea; irritable bowel syndrome; atopic dermatitis; Crohn's disease	Theoretically, probiotic products may increase risk of infections in immunocompromised individuals.
Red clover phytoestrogens	Menopausal symptoms, premenstrual syndrome, asthma	Rash, myalgias, headaches, and vaginal bleeding have been reported. Theoretically, endometrial hyperplasia is an adverse effect from the use of these compounds.
Red yeast rice	Hyperlipidemia, indigestion, diarrhea, circulatory conditions, HIV/AIDS	Gastrointestinal upset and dizziness may occur. Red yeast rice may contain lovastatin-like compounds and potentially cause rhabdomyolysis.

Natural Products	Common Use(s)	Adverse Effects/Potential Concerns
S-adenosylmethionine (SAM-e)	Depression, anxiety, dementia, osteoarthritis, heart disease	Nausea, vomiting, diarrhea, headache, and nervousness have been reported. Concern exists that SAM-e raises homocysteine levels.
St. John's wort	Depression, anxiety, chronic fatigue syndrome, HIV/AIDS	Anxiety, gastrointestinal upset, vaginal bleeding, neuropathy, and rash can occur. Hypomania has been induced by St. John's wort.
Tea tree oil	Topical use for acne, fungal infections, lice, scabies	Local inflammation and contact dermatitis may occur.
Valerian	Insomnia, depression, chronic fatigue syndrome, menstrual cramps	Headaches, gastrointestinal upset, and drowsiness can occur. Hepatotoxicity is a potential concern with valerian.

AIDS, Acquired immune deficiency syndrome; *HIV,* human immunodeficiency virus.

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Appendix Id

Natural Products and Drug Interactions

This table lists interactions between selected natural products and prescription and nonprescription drugs. Although many of the listed interactions are theoretical in nature and have not been documented to occur in humans, those involving St. John's wort are potentially life threatening in nature, depending on the individual drug. Other interactions are based on small studies of healthy volunteers and use pharmaceutical-quality natural products that may or may not be commercially available.

Natural Products	Drugs	Interactions
Andrographis	Immune suppressants	Andrographis may stimulate immune function, potentially decreasing the effectiveness of drugs such as cyclosporine, tacrolimus, and prednisone.
	Antihypertensive agents	Andrographis may lower blood pressure, potentiating the hypotensive effects of antihypertensive agents.
	Antiplatelet and anticoagulant agents	Andrographis may have antiplatelet activity, potentially increasing the risk of bleeding.
Black cohosh	Hepatotoxic drugs	Concern exists that the risk of hepatotoxicity with black cohosh is increased in the presence of hepatotoxic drugs such as acetaminophen.
	Cisplatin	Animal studies suggest that the efficacy of cisplatin against breast cancer cells may be decreased by black cohosh.
	CYP2D6 substrates	Black cohosh may modestly inhibit CYP2D6 enzyme activity to result in higher drug concentrations.
Butterbur	CYP3A4 inducers (rifampin, carbamazepine, etc.)	Drugs that induce the activity of CYP3A4 increase the risk of the formation of hepatotoxic metabolites from pyrrolizidine alkaloids from some butterbur products.
Chamomile	CNS depressants (benzodiazepines, opiates, barbiturates, etc.)	Chamomile may have additive CNS depressant effects.
	CYP1A2 substrates	Chamomile may inhibit CYP1A2 enzyme activity to result in higher drug concentrations.
	CYP3A4 substrates	Chamomile may inhibit CYP3A4 enzyme activity to result in higher drug concentrations.
	Estrogens	Chamomile may compete for estrogen receptors.
	Tamoxifen	Chamomile may interfere with the effects of tamoxifen because of its estrogenic effects.
Chaste tree berry	Antipsychotic agents	Chaste tree berry may antagonize the effects of antipsychotic agents through its dopaminergic activity.
	Metoclopramide	Chaste tree berry may antagonize the effects of metoclopramide through its dopaminergic activity.
	Dopamine agonists	Chaste tree berry may possess additive effects to drugs such as levodopa and ropinirole through its dopaminergic activity.
	Oral contraceptives/estrogens	Chaste tree berry may possess additive hormonal effects.
Chondroitin	Warfarin	High-dose chondroitin has structural similarity to a heparinoid and may possess weak anticoagulant effects.
Cinnamon	Hypoglycemic agents	Cinnamon may possess additive effects on blood glucose to those of hypoglycemic agents.
Coenzyme Q10	Antihypertensive agents	Coenzyme Q10 may possess additive effects on blood pressure to those of antihypertensive agents.
	Warfarin	Coenzyme Q10 may lessen the anticoagulant effects of warfarin because of its structural similarity to vitamin K.
	Chemotherapy	The antioxidant effects of coenzyme Q10 may blunt the efficacy of certain chemotherapeutic agents that depend on the formation of free radicals.
Cranberry	CYP2C9 substrates (warfarin)	Cranberry may inhibit CYP2C9 enzyme activity to result in higher drug concentrations; evidence with warfarin is contradictory.
Dehydroepiandrosterone (DHEA)	Tamoxifen and aromatase inhibitors such as anastrozole and exemestane	DHEA may interfere with the antiestrogenic effects of these drugs.
	CYP3A4 substrates	DHEA may slightly inhibit CYP3A4 enzyme activity to result in higher drug concentrations.

Natural Products	Drugs	Interactions
Devil's claw	Antihypertensive agents	Devil's claw may possess additive effects on blood pressure to those of antihypertensive agents.
	Hypoglycemic agents	Devil's claw may possess additive effects on blood glucose to those of hypoglycemic agents.
	H_2 antagonists and PPIs	Devil's claw may raise gastric pH and blunt the efficacy of H_2 antagonists and PPIs.
	CYP3A4 substrates	Devil's claw may inhibit CYP3A4 enzyme activity to result in higher drug concentrations.
	CYP2C9 substrates	Devil's claw may inhibit CYP2C9 enzyme activity to result in higher drug concentrations.
	CYP2C19 substrates	Devil's claw may inhibit CYP2C19 enzyme activity to result in higher drug concentrations.
	Warfarin	Devil's claw may inhibit CYP2C9 enzyme activity to result in higher concentrations of warfarin; purpura has been reported.
Echinacea	Immune suppressants	Echinacea may stimulate immune function, potentially decreasing the effectiveness of drugs such as cyclosporine, tacrolimus, and prednisone.
	CYP3A4 substrates	Echinacea may modestly induce hepatic CYP3A4 enzyme activity to result in lower drug concentrations.
	CYP1A2 substrates	Echinacea may inhibit CYP1A2 enzyme activity to result in higher drug concentrations.
Eleuthero (Siberian ginseng)	CNS depressants (benzodiazepines, opiates, barbiturates, etc.)	Eleuthero may have additive CNS depressant effects.
	Antiplatelet and anticoagulant agents	Eleuthero may have antiplatelet activity, potentially increasing the risk of bleeding.
	CYP3A4 substrates	Eleuthero may inhibit CYP3A4 enzyme activity to result in higher drug concentrations.
	CYP1A2 substrates	Eleuthero may modestly inhibit CYP1A2 enzyme activity to result in higher drug concentrations.
	CYP2C9 substrates	Eleuthero may modestly inhibit CYP2C9 enzyme activity to result in higher drug concentrations.
	CYP2D6 substrates	Eleuthero may inhibit CYP2D6 enzyme activity to result in higher drug concentrations.
	Digoxin	Concentration of digoxin has been reported to increase but without evidence of toxicity.
Evening primrose oil (EPO)	Antiplatelet and anticoagulant agents	EPO may have anticoagulant activity, potentially increasing the risk of bleeding.
Fenugreek	Antiplatelet and anticoagulant agents	Fenugreek may have antiplatelet activity, potentially increasing the risk of bleeding.
	Hypoglycemic agents	Fenugreek may potentially lower blood glucose concentrations and have additive effects with hypoglycemic agents.
Feverfew	Antiplatelet and anticoagulant agents	Feverfew may have antiplatelet activity, potentially increasing the risk of bleeding.
	CYP3A4 substrates	Feverfew may inhibit CYP3A4 enzyme activity to result in higher drug concentrations.
	CYP1A2 substrates	Feverfew may inhibit CYP1A2 enzyme activity to result in higher drug concentrations.
	CYP2C9 substrates	Feverfew may inhibit CYP2C9 enzyme activity to result in higher drug concentrations.
	CYP2C19 substrates	Feverfew may inhibit CYP2C19 enzyme activity to result in higher drug concentrations.
Fish oils (omega-3 fatty acids)	Antiplatelet and anticoagulant agents	Fish oils may have antiplatelet activity, potentially increasing the risk of bleeding, although this has not been documented in humans.
	Antihypertensive agents	Fish oils may possess additive effects on blood pressure to those of antihypertensive agents.
	Oral contraceptives	Oral contraceptives may potentially interfere with the triglyceride-lowering effects of fish oil.
Garlic	Antiplatelet and anticoagulant agents	Garlic may have antiplatelet activity, potentially increasing the risk of bleeding.
	CYP3A4 substrates	Garlic may potentially induce CYP3A4 enzyme activity to result in lower drug concentrations; evidence is contradictory.
	CYP2E1 substrates	Garlic may modestly inhibit CYP2E1 enzyme activity to result in higher drug concentrations.
Ginger	Antiplatelet and anticoagulant agents	Ginger may have antiplatelet activity, potentially increasing the risk of bleeding.
	Hypoglycemic agents	Ginger may potentially lower blood glucose concentrations and have additive effects with hypoglycemic agents.
Ginkgo	Antiplatelet and anticoagulant agents	Ginkgo may have antiplatelet activity, potentially increasing the risk of bleeding.
	CYP2C19 substrates	Ginkgo may induce CYP2C19 enzyme activity to result in lower drug concentrations.
	CYP1A2 substrates	Ginkgo may modestly inhibit CYP1A2 enzyme activity to result in higher drug levels.
	CYP2C9 substrates	Ginkgo may modestly inhibit CYP2C9 enzyme activity to result in higher drug concentrations.
	CYP2D6 substrates	Ginkgo may inhibit CYP2D6 enzyme activity to result in higher drug concentrations.
Ginseng (Panax)	Antiplatelet and anticoagulant agents	Panax ginseng may have antiplatelet properties; American ginseng may decrease the effectiveness (international normalized ration [INR]) of warfarin.
	CYP2D6 substrates	Panax ginseng may modestly inhibit CYP2D6 enzyme activity to result in higher drug concentrations.
	Immune suppressants	Panax ginseng may stimulate immune function, potentially decreasing the effectiveness of drugs such as cyclosporine, tacrolimus, and prednisone.
	Hypoglycemic agents	Panax ginseng may potentially lower blood glucose levels and have additive effects with hypoglycemic agents.
Glucosamine	Warfarin	High-dose glucosamine (along with high-dose chondroitin) may have additive effects to those of warfarin because of structural similarity to heparin.

Continued on following page

Natural Products	Drugs	Interactions
Green tea extract	Antiplatelet agents	Green tea possesses compounds that may have antiplatelet activity, potentially increasing the risk of bleeding.
	Amphetamines	Caffeine in green tea may increase the risk of CNS toxicity.
	Cocaine	Caffeine in green tea may increase the risk of CNS toxicity.
	Oral contraceptives	Oral contraceptives may decrease the clearance of caffeine in green tea.
	Warfarin	Small amounts of vitamin K have been reported to be present in green tea, potentially decreasing the effectiveness of warfarin.
	Theophylline	Caffeine potentially decreases theophylline clearance.
	Verapamil	Verapamil decreases caffeine clearance, resulting in increased concentrations.
	Quinolone antibiotics	Some quinolone antibiotics decrease the clearance of caffeine.
	Hepatotoxic drugs	Concern exists that the risk of hepatotoxicity with green tea is increased in the presence of hepatotoxic drugs such as acetaminophen.
Hawthorn	β-Blockers	Hawthorn and β-blockers may have additive effects on blood pressure and heart rate.
	CCBs, nitrates	Hawthorn and CCBs (or nitrates) may have additive effects due to coronary vasodilation.
	Digoxin	Hawthorn may have additive effects to those of digoxin.
	Phosphodiesterase inhibitors	Hawthorn may have additive vasodilatory and hypotensive effects with sildenafil, tadalafil, and vardenafil.
Horse chestnut seed extract (HCSE)	Antiplatelet and anticoagulant agents	HCSE may have antiplatelet activity, potentially increasing the risk of bleeding.
	Hypoglycemic agents	HCSE may potentially lower blood glucose concentrations and have additive effects with hypoglycemic agents.
Huperzine	AChE inhibitors (donepezil, etc.)	Huperzine may have additive effects when combined with AChE inhibitors.
	Anticholinergic drugs	The effectiveness of huperzine and/or the anticholinergic drug may be decreased by their concomitant administration.
	Cholinergic drugs (bethanechol, neostigmine, etc.)	Huperzine may have additive effects when combined with cholinergic drugs.
Kava	CYP3A4 substrates	Kava may inhibit CYP3A4 enzyme activity to result in higher drug concentrations.
	CYP1A2 substrates	Kava may inhibit CYP1A2 enzyme activity to result in higher drug concentrations.
	CYP2C9 substrates, CYP2C19 substrates	Kava may inhibit CYP2C9 and CYP2C19 enzyme activity to result in higher drug concentrations.
	CYP2D6 substrates	Kava may inhibit CYP2D6 enzyme activity to result in higher drug concentrations.
	P-glycoprotein substrates (digoxin; etoposide, paclitaxel, vinblastine, vincristine; itraconazole; diltiazem, verapamil; and many other drugs)	Kava may inhibit P-glycoprotein transporter systems.
	Hepatotoxic drugs	Concern exists that the risk of hepatotoxicity from kava is increased in the presence of hepatotoxic drugs such as acetaminophen.
Melatonin	Antiplatelet and anticoagulant agents	Melatonin may potentiate the effects of antiplatelets and anticoagulants, although the mechanism is unknown.
	CNS depressants	Melatonin may have additive CNS depressant effects.
	Fluvoxamine	Fluvoxamine may increase levels of melatonin.
	Immune suppressants	Melatonin may stimulate immune function, potentially decreasing the effectiveness of drugs such as cyclosporine, tacrolimus, and prednisone.
	Hypoglycemic agents	Melatonin may impair glucose utilization and may decrease the efficacy of hypoglycemic agents.
Milk thistle	Estrogens (and other drugs that undergo glucuronidation)	Silymarin may increase the clearance of estrogens.
	CYP2C9 substrates	Milk thistle may modestly inhibit CYP2C9 enzyme activity to result in higher drug concentrations.
Peppermint oil	H_2 antagonists and proton pump inhibitors	Peppermint oil may raise gastric pH and blunt efficacy of H_2 antagonists and PPIs.
	CYP3A4 substrates	Peppermint oil may modestly inhibit CYP3A4 enzyme activity to result in higher drug concentrations.
	CYP1A2 substrates	Peppermint oil may modestly inhibit CYP1A2 enzyme activity to result in higher drug concentrations.
	CYP2C9 substrates, CYP2C19 substrates	Peppermint oil may modestly inhibit CYP2C9 and CYP2C19 enzyme activity to result in higher drug concentrations.
Policosanol	Antiplatelet and anticoagulant agents	Policosanol may have antiplatelet activity, potentially increasing the risk of bleeding.
Probiotics	Antibiotics	Antibiotics may kill the live organisms in different probiotic preparations.
	Immune suppressants	Theoretically, probiotics may cause bacterial or fungal infections in patients who are taking immune suppressants chronically.

Natural Products	Drugs	Interactions
Red clover phytoestrogens	Antiplatelet and anticoagulant agents	Theoretically, red clover may possess coumarins, which increase the risk of bleeding with antiplatelet and anticoagulants.
	CYP3A4 substrates	Red clover may inhibit CYP3A4 enzyme activity to result in higher drug concentrations.
	CYP2C9 substrates, CYP2C19 substrates	Red clover may inhibit CYP2C9 and CYP2C19 enzyme activity to result in higher drug concentrations.
	CYP1A2 substrates	Red clover may inhibit CYP1A2 enzyme activity to result in higher drug concentrations.
Red yeast rice	CYP3A4 inhibitors	Drugs that inhibit CYP3A4 may decrease the metabolism of lovastatin in red yeast rice.
	Statins	Red yeast rice contains lovastatin and increases the risk of myopathy (and hepatotoxicity).
	Fibrates and niacin	Fibrates and niacin may increase concentrations of lovastatin in red yeast rice.
S-adenosylmethionine (SAM-e)	Antidepressants (including MAOIs)	Additive effects are possible, and there is potential for toxicity.
	Serotonergic drugs (triptans, SSRIs, tramadol, meperidine, dextromethorphan, etc.)	SAM-e may increase the risk of development of serotonin syndrome when used concomitantly.
Soy phytoestrogens	Antibiotics	Antibiotics may decrease the efficacy of soy because intestinal bacteria convert isoflavones into more active forms.
	Estrogens	Soy potentially may inhibit the effects of estrogen.
	Tamoxifen/aromatase inhibitors	Soy's estrogenic effects may antagonize the antitumor effects of tamoxifen/aromatase inhibitors.
	MAOIs	Fermented soy products may contain tyramine.
St. John's wort	CYP3A4 substrates	St. John's wort strongly induces CYP3A4 enzyme activity to result in lower drug concentrations.
	CYP1A2 substrates	St. John's wort modestly induces CYP1A2 enzyme activity to result in lower drug levels.
	CYP2C9 substrates	St. John's wort induces CYP2C9 enzyme activity to result in lower drug concentrations.
	P-glycoprotein substrates (digoxin; etoposide, paclitaxel, vinblastine, vincristine; itraconazole; diltiazem, verapamil; and other drugs)	St. John's wort induces P-glycoprotein transporter systems.
	Serotonergic drugs (triptans, SSRIs, tramadol, meperidine, dextromethorphan, etc.)	St. John's wort may increase the risk of development of serotonin syndrome when used concomitantly.
Valerian	CNS depressants (benzodiazepines, opiates, barbiturates, alcohol, etc.)	Valerian may increase the sedative effects of CNS depressants.
	CYP3A4 substrates	Valerian may modestly inhibit the CYP3A4 enzyme activity.

AChE, Acetylcholinesterase; *CCBs,* calcium channel blockers; *CNS,* central nervous system; *MAOIs,* monoamine oxidase inhibitor; *PPIs,* proton pump inhibitors; *SSRIs,* selective serotonin reuptake inhibitors.

EXAMPLES OF DRUGS METABOLIZED BY CYP ENZYMES

The following are examples of drugs that are metabolized through the different cytochrome P450 isoenzymes:

CYP1A2 substrates: theophylline, imipramine, clozapine, naproxen

CYP2C9 substrates: warfarin, tamoxifen, irbesartan, ibuprofen, glipizide

CYP2C19 substrates: omeprazole and other proton pump inhibitors, phenytoin, phenobarbital, cyclophosphamide

CYP2D6 substrates: S-metoprolol, propafenone, paroxetine, risperidone, tramadol

CYP2E1 substrates: acetaminophen, alcohol

CYP3A4 substrates: most statins, indinavir, amlodipine, verapamil, alprazolam, buspirone

(For a complete list of drugs and their respective metabolic pathways through the cytochrome P450 isoenzyme systems go to http://medicine.iupui.edu/flockhart.)

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Appendix Ie

Commonly Ingested Plants with Significant Toxic Potential

Plant	Symptoms	Management
Autumn crocus *(Colchicum autumnale)*	Vomiting Diarrhea Initial leukocytosis followed by bone marrow failure Multisystem organ failure	Activated charcoal decontamination Aggressive fluid resuscitation and supportive care
Belladonna alkaloids: jimson weed *(Datura stramonium)* Belladonna ("deadly nightshade"; *Atropa belladonna*)	Anticholinergic toxidrome Seizures	Supportive care, benzodiazepines Consider physostigmine if patient is a threat to self or others; only use if no conduction delays on ECG
Cardiac glycoside–containing plants (foxglove, lily of the valley, oleander, yellow oleander, etc.)	Nausea Vomiting Bradycardia Dysrhythmias (AV block, ventricular ectopy) Hyperkalemia	Digoxin-specific Fab fragments
Jequirity bean and other abrin-containing species (e.g., rosary pea, precatory bean)	Oral pain Vomiting Diarrhea Shock Hemolysis Renal failure	Supportive care, including aggressive volume resuscitation and correction of electrolyte abnormalities
Monkshood (*Aconitum* species)	Numbness and tingling of lips/tongue Vomiting Bradycardia	Atropine for bradycardia Supportive care
Oxalate-containing plants: *Philodendron, Diffenbachia, Colocasia* ("elephant ear")	Local tissue injury Oral pain Vomiting	Supportive care, pain control
Poison hemlock *(Conium maculatum)*	Vomiting Agitation followed by CNS depression Paralysis Respiratory failure	Supportive care
Pokeweed	Hemorrhagic gastroenteritis Burning of mouth and throat	Supportive care
Rhododendron	Vomiting Diarrhea Bradycardia	Atropine for symptomatic bradycardia Supportive care
Tobacco	Vomiting Agitation Diaphoresis Fasciculations Seizures	Supportive care
Water hemlock (*Cicuta* species)	Abdominal pain Vomiting Delirium Seizures	Supportive care, including benzodiazepines for seizures
Yew (*Taxus* species)	GI symptoms QRS widening Hypotension CV collapse	Supportive care Atropine for bradycardia Sodium bicarbonate does not appear to be effective

AV, Atrioventricular; *CNS,* central nervous system; *CV,* cardiovascular; *ECG,* electrocardiogram; *Fab,* fragment, antigen binding; *GI,* gastrointestinal.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

Appendix If

Herbs Associated with Toxicity

Herbal Product	Toxic Chemicals	Toxic Effects
Aconite (*Aconitum* spp.)	Aconitine alkaloids	Nausea, vomiting, paresthesias, weakness, hypotension, asystole, arrhythmias, bradycardia
Chamomile (*Matricaria chamomilla, Anthemis nobilis*)	Allergens	Anaphylaxis, contact dermatitis
Chapparal (*Larrea divaricate, Larrea tridentate*)	Nordihydroguaiaretic acid	Nausea, vomiting, lethargy, hepatitis
Cinnamon oil (*Cinnamomum* spp.)	Cinnamaldehyde	Dermatitis, abuse syndrome
Coltsfoot (*Tussilago farfara*)	Pyrrolizidines	HVOD
Comfrey (*Symphytum officinale*)	Pyrrolizidines	HVOD
Crotalaria spp.	Pyrrolizidines	HVOD
Echinacea (*Echinacea angustifolia*, Compositae spp.)	Polysaccharides	Asthma, atopy, angioedema, anaphylaxis, urticaria
Eucalyptus (*Eucalyptus globulus*)	1,8-cineole	Drowsiness, ataxia, nausea, vomiting, seizures, coma, respiratory failure
Garlic (*Allium sativum*)	Allicin	Dermatitis, chemical burns, oxidizing agent
Germander (*Teucrium chamaedrys*)		Hepatotoxicity
Ginseng (*Panax ginseng*)	Ginsenoside	Ginseng abuse, diarrhea, anxiety, insomnia, hypertension
Glycerated asafetida	Oxidants	Methemoglobinemia
Groundsel (*Senecio longilobus*)	Pyrrolizidines	HVOD
Heliotrope, turnsole (*Crotalaria fulva, Heliotropium, Cynoglossum officinale*)	Pyrrolizidines	HVOD
Jin bu huan (*Stephania* spp., *Corydalis* spp.)	L-Tetrahydropalmitine	Hepatitis, lethargy, coma
Kava-kava (*Piper methysticum*)	Kawain, methysticin	Hepatic failure, "kavaism," neurotoxicity
Kelp	Iodine	Thyroid dysfunction
Laetrile	Cyanide	Coma, seizures, death
Licorice (*Glycyrrhiza glabra*)	Glycyrrhetic acid	Hypertension, cardiac arrhythmias, hypokalemia
Ma huang (*Ephedra sinica*)	Ephedrine	Cardiac arrhythmias, seizures, stroke, hypertension
Monkshood (*Aconitum napellus*, *A. columbianum*)	Aconite	Cardiac arrhythmias, weakness, coma, shock, paresthesias, vomiting, seizures
Nutmeg (*Myristica fragrans*)	Myristicin, eugenol	Hallucinations, emesis, headache
Nux vomica	Strychnine	Seizures, abdominal pain, respiratory arrest
Pennyroyal (*Mentha pulegium* or *Hedeoma* spp.)	Pulegone	Centrilobular liver necrosis, fetotoxicity, seizures, shock
Ragwort (golden) (*Senecio aureus, Echium*)	Pyrrolizidines	HVOD
Wormwood (*Artemisia* spp.)	Thujone	Seizures, dementia, tremors, headache

HVOD, Hepatic venoocclusive disease.
From Fuhrman BP et al: *Pediatric critical care,* ed 4, Philadelphia, 2011, Saunders.

Appendix Ig

Websites Providing Data on Herbal Therapy Hazards

Web Address	Website
http://www.fda.gov or http://www.vmcfsan.fda.gov/-dms/aems/html	On the U.S. Food and Drug Administration website under the title "Medwatch," some herb warnings can be found ("special adverse event monitoring system" link)
http://www.faseb.org/aspet/H&MIG3.htm#top	ASPET Herbal and Medicinal Plant Interest Group: a site for an herb discussion group with pharmacologists
http://www.nnlm.nlm.nih.gov/pnr/uwmhg/	University of Washington Medicinal Herb Garden
http://www.nim.nih.gov/medlineplus/herbalmedicine.html	Provides an update on ongoing clinical studies involving herbal products, news, and many links
http://www.update-software.com/abstracts/mainindex.html	The Cochrane Collaboration maintains an updated international database of clinical trials involving complementary and alternative medicine
http://www.amfoundation.org/	Providing consumers and professionals with responsible evidence-based information on the integration of alternative and conventional medicine
http://www.herbmed.org/	An interactive electronic herbal database provides hyperlinked access to scientific data underlying the use of herbs for health; an evidence-based information resource for professionals, researchers, and the general public
http://nccam.nih.gov/	The National Center for Complementary and Alternative Medicine is 1 of 27 institutes and centers that make up the U.S. National Institutes of Health; their mission is to support rigorous research on complementary and alternative medicine, train researchers, and disseminate information to the general public and professionals
http://toxnet.nlm.nih.gov/	A cluster of databases on toxicology, hazardous chemicals, and related areas

From Floege J et al: *Comprehensive clinical nephrology,* ed 4, Philadelphia, 2010, Saunders.

Appendix IIa

Dietary Supplements: What Every Primary Care Provider Should Know

Primary care providers must be knowledgeable regarding the safety, efficacy, and drug interactions associated with common dietary supplements because of the following:

- An estimated 38% of adults ages 18 years and older reported the use of at least one form of complementary and alternative medicine (CAM) according to the National Health Interview Survey in 2007.
- Almost 17.8% of adults specifically reported the use of dietary supplements, with fish oil, glucosamine, echinacea, flaxseed, and ginseng most frequently used.
- Although the use of dietary supplements has plateaued as a result of consumer concerns about effectiveness and potential adverse effects, usage remains common and potentially dangerous.

COMMON TERMINOLOGY

- A *dietary supplement* is defined as an oral product containing vitamins, minerals, herbs, or other botanicals; amino acids; dietary substances used to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination.
- *CAM* refers to the broad domain of healing practices that include diverse health systems, modalities, and practices and their accompanying theories and beliefs (see glossary of terms in Appendix Ia).
- *Complementary therapies* are those that are used *in addition to* conventional therapies, whereas *alternative therapies* are those that are used *instead of* conventional therapies. Most consumers in the United States use dietary supplements as a complementary therapy.
- *Standardization* refers to the practice of producing dietary supplements with a specific amount of a given compound that may or may not include the actual active ingredient. For example, feverfew has been standardized to its parthenolide content.

LEGISLATION

The U.S. Food and Drug Administration (FDA) is frequently criticized for not closely regulating dietary supplements and monitoring their safety. However, although the agency regulates prescription drugs and over-the-counter (OTC) products, the FDA has limited regulatory authority over dietary supplements. This is because the Dietary Supplement and Health Education Act (DSHEA) of 1994 and its resulting regulations limit the FDA's authority. As a result of DSHEA, the FDA is able to act only when a dietary supplement has been documented to contain a prescription drug, as was the case with glyburide in a natural treatment for diabetes and diazepam in an osteoarthritis preparation. In addition, the FDA can act when safety issues related to a product have been clearly documented, although these cases are frequently challenged in the courts.

HEALTH CLAIMS

Dietary supplements generally are marketed under three types of health claims. The first category is the "nutrient content" claim, in which the product is identified as an excellent source of, typically, a mineral such as calcium, based on recommended daily values. The second type is the "significant scientific agreement" claim; these claims are used when some evidence of the product's efficacy exists (e.g., fish oil supplements). The third and most common type of health claim is called a "structure/function" claim; these claims state that the product has some effect on health—for example, "helps to maintain a healthy heart." However, dietary supplements are not permitted to carry claims stating that they are effective in preventing, treating, or curing diseases.

INFORMATION RESOURCES

Appendix Ic provides a brief overview of common dietary supplements. Until recently, few evidence-based resources on dietary supplements were available. Clinical studies and systematic reviews on dietary supplements are now widely available through PubMed, EMBASE, and the Cochrane Database of Systematic Reviews. Although more information is available, references on specific products vary in their interpretation of the available evidence and may exhibit an unintentional bias, either pro or con, regarding the safety and efficacy of dietary supplements.

"Gold standard" evidence-based databases on dietary supplements (subscription required) include the following:

- Natural Medicines Comprehensive Database (http://www.naturaldatabase.com): This database includes listings for many dietary supplements and is organized in a clinician-friendly manner. Monographs include the different common and scientific names; uses and likely effectiveness for different uses; chemical constituents; interactions with drugs, diseases, foods, and laboratory tests; adverse effects; and cautions. The information is extensively referenced and is updated on a daily basis. The primary limitation is that the evaluation of data on clinical effectiveness could be more rigorous.
- Natural Standard (http://www.naturalstandard.com): This database includes listings for dietary supplements and other forms of complementary and alternative medicine. The evidence supporting the assessments in this database is critically evaluated and rigorous in nature. The primary limitation is that many fewer dietary supplements are included in this database.

Evidence-based free websites on dietary supplements include the following:

- National Center for Complementary and Alternative Medicine (NCCAM) (http://nccam.nih.gov)
- Office of Dietary Supplements International Bibliographic Information on Dietary Supplements (http://dietary-supplements.info.nih.gov/Health_Information/IBIDS.aspx)
- Memorial Sloan-Kettering Cancer Center (http://www.mskcc.org/mskcc/html/11570.cfm)

DRUG INTERACTIONS

Clinically significant interactions have been documented between dietary supplements and prescription or OTC drugs. The challenge for primary care

providers is to identify real, clinically relevant interactions versus potential or theoretical interactions. Data on interactions with dietary supplements are usually based on isolated case reports or on studies enrolling healthy volunteers. As with drug-drug interactions, the likelihood of an interaction and its severity are influenced especially by concomitant medical conditions, such as heart failure and presence or absence of impaired kidney and liver function.

Appendix Id lists interactions between selected natural products and prescription and nonprescription drugs. The following two broad interactions are particularly important in primary care practice:

- St. John's wort, commonly used for depression, is a potent inducer of cytochrome P450 3A4 isoenzymes and has been documented to increase the clearance of many drugs that are metabolized through this (and other) pathways. (For a list of common drugs cleared in this manner, readers should consult http://medicine.iupui.edu/flockhart/clinlist.htm.) In addition, St. John's wort may induce P-glycoprotein transporter systems that are important for digoxin and some chemotherapeutic agents. St. John's wort has also been associated with the development of serotonin syndrome when used with drugs that have significant serotonergic activity.
- Dietary supplements such as garlic, ginkgo, and feverfew, as well as many others, have been purported to either have antiplatelet activity or have effects on the clotting cascade. This may be important for adults also taking aspirin (and other platelet-active agents) or warfarin.

COUNSELING POINTS

The single most important counseling point related to dietary supplements is always to ask patients about their use of these products and to do so in an open, nonjudgmental manner. The approach should emphasize that many consumers have been interested in vitamins, minerals, herbs, teas, and so on, to maintain their health or to treat illness. If the clinician is unaware of the safety, efficacy, and interactions of a specific product, several websites are available to quickly scan for information. Also, access to drug information centers at colleges of pharmacy is almost always available, and some hospitals now offer programs in integrative medicine.

Patients should be asked about their goals in using the product, as well as how long they have taken it and in what dosage. Allergies to plants should be documented because cross-allergies are common. Clinicians should appreciate that individuals who use dietary supplements may be interested in making lifestyle changes and potentially decreasing their use of prescription drugs. In addition, if an individual is also consulting an alternative medicine practitioner, clinicians should recognize that some alternative health systems discourage the use of established therapies such as vaccines.

Although problems with safety and efficacy have been identified, many dietary supplements are benign except for their cost. Some patients are at higher risk for adverse outcomes from the use of dietary supplements (e.g., those with chronic kidney and liver disease). Patients should be counseled specifically to avoid purchasing dietary supplements over the Internet.

RESEARCH ISSUES

Many clinical and observational studies of dietary supplements have been published. In the past, clinicians frequently stated either that published studies of dietary supplements did not exist or that only a few were available. The reason for this finding was that until recently the National Library of Medicine did not abstract from the peer-reviewed alternative medicine literature. Fortunately, much more research is now readily available. As with all research, the more rigorous the study methodology, the less likely the dietary supplement is to demonstrate clinical benefit.

In evaluating published studies of dietary supplements, the following should be considered:

- Has the correct plant and part of the plant (root, stem, leaf) been used? This critical information may not be known to many clinicians. Consulting a resource such as the National Medicines Comprehensive Database can usually provide the needed information to judge this component of the study.
- Has the content of active ingredients been verified throughout the study? In a recent review of 81 major randomized controlled trials of herbal products, only 12 (15%) reported performing tests to quantify actual contents, and 3 (4%) provided adequate data to compare actual with expected content values of at least one chemical constituent.
- Is the severity of the disease appropriate for study? Negative studies with dietary supplements sometimes inappropriately enroll participants who have moderate-to-severe disease (e.g., those with depression or benign prostatic hyperplasia) when only mild disease would be appropriate.
- Is the duration of the study appropriate? Early studies comparing glucosamine and nonsteroidal anti-inflammatory agents (NSAIAs) demonstrated greater efficacy with the NSAIAs because of an inadequate study duration for glucosamine to show any benefit.
- Is a placebo group included? Recent studies with dietary supplements for menopausal symptoms and osteoarthritis have demonstrated placebo responses over 40% to 50%.
- Was the blinding maintained throughout the study? Some dietary supplements, such as saw palmetto, have distinctive odors and tastes that are not easily masked.
- Is the preparation commercially available? Most important, when a study with dietary supplements does show benefit, it frequently is difficult to use the product in practice because the specific formulation studied is not commercially available.

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Appendix IIb

Vitamins and Their Functions

	Biochemistry and Physiology	Deficiency [RDA*]	Toxicity [TUL†]	Assessment of Status
Fat-Soluble Vitamins				
Vitamin A	A family of the retinoid compounds, each member having biologic activity qualitatively similar to retinol. Carotenoids are structurally related to retinoids. Some carotenoids, most notably β-carotene, are metabolized into compounds with vitamin A activity and are therefore considered to be provitamin A compounds. Vitamin A is an integral component of rhodopsin and iodopsins, light-sensitive proteins in rod and cone cells in the retina. *Additional functions:* induction and maintenance of cellular differentiation in certain tissues; signal for appropriate morphogenesis in the developing embryo; maintenance of cell-mediated immunity. One microgram of retinol = 3.33 IU of vitamin A.	Follicular hyperkeratosis and night blindness are early indicators. Conjunctival xerosis, degeneration of the cornea (keratomalacia), and de-differentiation of rapidly proliferating epithelia are later indications of deficiency. *Bitot spots* (focal areas of the conjunctiva or cornea with foamy appearance) are an indication of xerosis. Blindness, due to corneal destruction and retinal dysfunction, ensues if left uncorrected. Increased susceptibility to infection is also a consequence. [F: 700 μg; M: 900 μg]	In adults, >150,000 μg may cause acute toxicity: fatal intracranial hypertension, skin exfoliation, and hepatocellular necrosis. *Chronic* toxicity may occur with habitual daily intake of >10,000 μg: alopecia, ataxia, bone and muscle pain, dermatitis, cheilitis, conjunctivitis, pseudotumor cerebri, hepatocellular necrosis, hyperlipidemia, and hyperostosis are common. Single, large doses of vitamin A (30,000 μg), or habitual intake of >4500 μg/day in early pregnancy can be teratogenic. Excessive intake of carotenoids causes a benign condition characterized by yellowish discoloration of the skin. Habitually large doses of canthaxanthin, a carotenoid, have the additional capability of inducing a retinopathy. [3000 μg]	Retinol concentration in the plasma and vitamin A concentrations in the milk and tears are reasonably accurate measures of adequate status. Toxicity is best assessed by elevated levels of retinyl esters in plasma. A quantitative measure of dark adaptation for night vision or an electroretinogram are useful functional tests.
Vitamin D	A group of sterol compounds whose parent structure is cholecalciferol (vitamin D_3). Cholecalciferol is formed in the skin from 7-dehydrocholesterol (provitamin D_3) by exposure to UVB radiation. A plant sterol, ergocalciferol (provitamin D_2) can be similarly converted into vitamin D_2 and has similar vitamin D activity. The vitamin undergoes sequential hydroxylations in the liver and kidney at the 25 and 1 positions, respectively, producing the most bioactive form of the vitamin, 1,25-dihydroxy vitamin D. Maintains intracellular and extracellular concentrations of calcium and phosphate by enhancing intestinal absorption of the two ions and, in conjunction with PTH, promoting their mobilization from bone mineral. Retards proliferation and promotes differentiation in certain epithelia. One microgram = 40 IU.	Deficiency results in disordered bone modeling called *rickets* in childhood and *osteomalacia* in adults. Expansion of the epiphyseal growth plates and replacement of normal bone with unmineralized bone matrix are the cardinal features of rickets; the latter feature also characterizes osteomalacia. Deformity of bone and pathologic fractures occur. Decreased serum concentrations of calcium and phosphate may occur. [15 μg, ages 19-70 yr; 20 μg, age >70 yr]	Excess amounts result in abnormally high concentrations of calcium and phosphate in the serum: metastatic calcifications, renal damage, and altered mentation may occur. [50 μg]	The serum concentration of the major circulating metabolite, 25-hydroxyvitamin D, is an excellent indicator of systemic status except in chronic renal failure, in which the impairment of renal L-hydroxylation results in disassociation of the mono- and dihydroxyvitamin concentrations. Measuring the serum concentration of 1,25-dihydroxyvitamin D is then necessary.

Continued on following page

	Biochemistry and Physiology	Deficiency [RDA*]	Toxicity [TUL†]	Assessment of Status
Vitamin E	A group of at least 8 naturally occurring compounds, some of which are tocopherols and some of which are tocotrienols. At present, the only dietary form that is thought to be biologically active in humans is α-tocopherol. Acts as an antioxidant and free radical scavenger in lipophilic environments, most notably in cell membranes. Acts in conjunction with other antioxidants such as selenium.	Deficiency due to dietary inadequacy rare. Usually seen in (1) premature infants, (2) individuals with fat malabsorption, and (3) individuals with abetalipoproteinemia. Red blood cell fragility occurs and can produce a hemolytic anemia. Neuronal degeneration produces peripheral neuropathies, ophthalmoplegia, and destruction of posterior columns of spinal cord. Neurologic disease is frequently irreversible if deficiency is not corrected early enough. May contribute to the hemolytic anemia and retrolental fibroplasia seen in premature infants. Reported to suppress cell-mediated immunity. [15 mg]	Depressed levels of vitamin K-dependent procoagulants and potentiation of oral anticoagulants have been reported, as has impaired WBC function. Doses of 800 mg/day have been reported to increase slightly the incidence of hemorrhagic stroke. [1000 mg]	Plasma or serum concentration of α-tocopherol is most commonly used. Additional accuracy is obtained by expressing this value per mg of total plasma lipid. RBC peroxide hemolysis test is not entirely specific but is a useful functional measure of the antioxidant potential of cell membranes.
Vitamin K	A family of naphthoquinone compounds with similar biologic activity. Phylloquinone (vitamin K_1) is derived from plants; a variety of menaquinones (vitamin K_2) is derived from bacterial sources. Serves as an essential cofactor in the post-translational γ-carboxylation of glutamic acid residues in many proteins. These proteins include several circulating procoagulants and anticoagulants as well as proteins in a variety of tissues.	Deficiency syndrome, uncommon except in (1) breast-fed newborns, in whom it may cause "hemorrhagic disease of the newborn," (2) adults with fat malabsorption or who are taking drugs that interfere with vitamin K metabolism (e.g., coumarin, phenytoin, broad-spectrum antibiotics), and (3) individuals taking large doses of vitamin E and anticoagulant drugs. Excessive hemorrhage is the usual manifestation. [F: 90 μg; M: 120 μg]	Rapid intravenous infusion of K_1 has been associated with dyspnea, flushing, and cardiovascular collapse; this is likely related to the dispersing agents in the solution. Supplementation may interfere with coumarin-based anticoagulation. Pregnant women taking large amounts of the provitamin menadione may deliver infants with hemolytic anemia, hyperbilirubinemia, and kernicterus. [no TUL established]	Prothrombin time is typically used as a measure of functional K status; it is neither sensitive nor specific for vitamin K deficiency. Determination of undercarboxylated prothrombin in the plasma is more accurate but less widely available.
Water-Soluble Vitamins				
Thiamine (vitamin B_1)	A water-soluble compound containing substituted pyrimidine and thiazole rings and a hydroxyethyl side chain. The coenzyme form is thiamine pyrophosphate (TPP). Serves as a coenzyme in many α-ketoacid decarboxylation and transketolation reactions. Inadequate thiamine availability leads to impairments of above reactions, resulting in inadequate adenosine triphosphate synthesis and abnormal carbohydrate metabolism, respectively. May have an additional role in neuronal conduction independent of aforementioned actions.	Classic deficiency syndrome ("beriberi") described in Asian populations consuming polished rice diet. Alcoholism and chronic renal dialysis are also common precipitants. High carbohydrate intake increases need for B_1. *Mild deficiency:* irritability, fatigue, and headaches. *More severe deficiency:* combinations of peripheral neuropathy, cardiovascular dysfunction, and cerebral dysfunction. Cardiovascular involvement ("wet beriberi"): congestive heart failure and low peripheral vascular resistance. Cerebral disease: nystagmus, ophthalmoplegia, and ataxia (Wernicke's encephalopathy); hallucinations, impaired short-term memory, and confabulation ("Korsakoff's psychosis"). Deficiency syndrome responds within 24 hr to parenteral thiamine but is partially or wholly irreversible after a certain stage. [F: 1.1 mg; M: 1.2 mg]	Excess intake is largely excreted in the urine, although parenteral doses of > 400 mg/day are reported to cause lethargy, ataxia, and reduced tone of the gastrointestinal tract. [TUL not established]	The most effective measure of B_1 status is the erythrocyte transketolase activity coefficient, which measures enzyme activity before and after addition of exogenous TPP: RBCs from a deficient individual express a substantial increase in enzyme activity with addition of TPP. Thiamine concentrations in blood or urine are also used.
Riboflavin (vitamin B_2)	Consists of a substituted isoalloxazine ring with a ribitol side chain. Serves as a coenzyme for a diverse array of biochemical reactions. The primary coenzymatic forms are flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). Riboflavin holoenzymes participate in oxidation-reduction reactions in a myriad of metabolic pathways.	Deficiency is usually seen in conjunction with deficiencies of other B vitamins. Isolated deficiency of riboflavin produces hyperemia and edema of nasopharyngeal mucosa, cheilosis, angular stomatitis, glossitis, seborrheic dermatitis, and a normochromic, normocytic anemia. [F: 1.1; M: 1.3]	Toxicity not reported in humans. [TUL not established]	The most common method of assessment is determining the activity coefficient of glutathione reductase in RBCs (the test is invalid for individuals with glucose-6-phosphate dehydrogenase [G6PD] deficiency). Measurements of blood and urine concentrations are less desirable methods.

	Biochemistry and Physiology	Deficiency [RDA*]	Toxicity [TUL†]	Assessment of Status
Niacin (vitamin B_3)	Refers to nicotinic acid and the corresponding amide, nicotinamide. The active coenzymatic forms are composed of nicotinamide affixed to adenine dinucleotide, forming NAD or NADP. More than 200 apoenzymes use these compounds as electron acceptors or hydrogen donors, either as a coenzyme or as a co-substrate. The essential amino acid tryptophan is a precursor of niacin; 60 mg of dietary tryptophan yields approximately 1 mg of niacin. Dietary requirements thus depend partly on tryptophan intake. Requirement is often determined on basis of caloric intake (i.e., niacin equivalents/1000 kcal). Large doses of nicotinic acid (1.5-3 g/day) effectively lower low-density lipoprotein cholesterol and elevate high-density lipoprotein cholesterol.	Pellagra is the classic deficiency syndrome and is often seen in populations in which corn is the major source of energy. Still endemic in parts of China, Africa, and India. Diarrhea, dementia (or associated symptoms of anxiety or insomnia), and a pigmented dermatitis that develops in sun-exposed areas are typical features. Glossitis, stomatitis, vaginitis, vertigo, and burning dysesthesias are early signs. Reported to occasionally occur in carcinoid syndrome because tryptophan is diverted to other synthetic pathways. [F: 14 mg; M: 16 mg]	Human toxicity known largely through studies examining hypolipidemic effects. Includes vasomotor phenomenon (flushing), hyperglycemia, parenchymal liver damage, and hyperuricemia. [35 mg]	Assessment of status is problematic: blood levels of vitamin not reliable. Measurement of urinary excretion of the niacin metabolites, N-methylnicotinamide and 2-pyridone, is thought to be the most effective means of assessment at present.
Vitamin B_6	Refers to several derivatives of pyridine, including pyridoxine (PN), pyridoxal (PL), and pyridoxamine (PM), which are interconvertible in the body. The coenzymatic forms are pyridoxal-5-phosphate (PLP) and pyridoxamine-5-phosphate (PMP). As a coenzyme, B_6 is involved in many transamination reactions (and thereby in gluconeogenesis), in the synthesis of niacin from tryptophan, in the synthesis of several neurotransmitters, and in the synthesis of δ-aminolevulinic acid (and therefore in heme synthesis). It also has functions unrelated to coenzymatic activity: PL and PLP bind to hemoglobin and alter O_2 affinity; PLP also binds to steroid receptors, inhibiting receptor affinity to DNA and thereby modulating steroid activity.	Deficiency usually seen in conjunction with other water-soluble vitamin deficiencies. Stomatitis, angular cheilosis, glossitis, irritability, depression, and confusion occur in moderate to severe depletion; normochromic, normocytic anemia has been reported in severe deficiency. Abnormal electroencephalograms and, in infants, convulsions have also been observed. Some sideroblastic anemias respond to B_6 administration. Isoniazid, cycloserine, penicillamine, ethanol, and theophylline can inhibit B_6 metabolism. [Ages 19-50 yr: 1.3 mg; >50 yr: 1.5 mg for women, 1.7 mg for men]	Long-term use with doses exceeding 200 mg/day (in adults) may cause peripheral neuropathies and photosensitivity. [100 mg]	Many useful laboratory methods of assessment exist. The plasma or erythrocyte PLP levels are most common. Urinary excretion of xanthurenic acid after an oral tryptophan load or activity indices of RBC alanine or aspartic acid transaminases (ALT and AST, respectively) are all functional measures of B_6-dependent enzyme activity.
Folate	A group of related pterin compounds. More than 35 forms of the vitamin are found naturally. The fully oxidized form, folic acid, is not found in nature but is the pharmacologic form of the vitamin. All folate functions relate to its ability to transfer one-carbon groups. It is essential in the *de novo* synthesis of nucleotides and in the metabolism of several amino acids, and is an integral component for the regeneration of the "universal" methyl donor, S-adenosylmethionine. Inhibition of bacterial and cancer cell folate metabolism is the basis for the sulfonamide antibiotics and chemotherapeutic agents such as methotrexate and 5-fluorouracil, respectively.	Women of childbearing age are most likely to be deficient. *Classic deficiency syndrome:* megaloblastic anemia, diarrhea. The hematopoietic cells in bone marrow become enlarged and have immature nuclei, reflecting ineffective DNA synthesis. The peripheral blood smear demonstrates macro-ovalocytes and polymorphonuclear leukocytes with an average of more than 3.5 nuclear lobes. Megaloblastic changes also occur in other epithelia that proliferate rapidly (e.g., oral mucosa, gastrointestinal tract), producing glossitis and diarrhea, respectively. Sulfasalazine and diphenytoin inhibit absorption and predispose to deficiency. [400 μg of dietary folate equivalents (DFE); 1 DFE = 1 μg food folate = 0.6 μg folic acid]	Doses >1000 μg/day may partially correct the anemia of B_{12} deficiency and may therefore mask (and perhaps exacerbate) the associated neuropathy. Large doses also reported to lower seizure threshold in individuals prone to seizures. Parenteral administration is rarely reported to cause allergic phenomena, which is probably due to dispersion agents. [1000 μg]	Serum folate measures short-term folate balance, whereas RBC folate is a better reflection of tissue status. Serum homocysteine rises early in deficiency but is nonspecific because B_{12} or B_6 deficiency, renal insufficiency, and older age may also cause elevations.

Continued on following page

	Biochemistry and Physiology	Deficiency [RDA*]	Toxicity [TUL†]	Assessment of Status
Vitamin C (ascorbic and dehydroascorbic acid)	Ascorbic acid readily oxidizes to dehydroascorbic acid in aqueous solution. The latter can be reduced in vivo, so it possesses vitamin C activity. Total vitamin C is therefore the sum of ascorbic and dehydroascorbic acid content. It serves primarily as a biologic antioxidant in aqueous environments. Biosyntheses of collagen, carnitine, bile acids, and norepinephrine, as well as proper functioning of the hepatic mixed-function oxygenase system, depend on this property. Vitamin C in foodstuffs increases the intestinal absorption of nonheme iron.	Overt deficiency is uncommon in developed countries. The classic deficiency syndrome is scurvy: fatigue, depression, and widespread abnormalities in connective tissues, such as inflamed gingivae, petechiae, perifollicular hemorrhages, impaired wound healing, coiled hairs, hyperkeratosis, bleeding into body cavities. In infants, defects in ossification and bone growth may occur. Tobacco smoking lowers plasma and leukocyte vitamin C levels. [F: 75 mg; M: 90 mg; increase requirement for cigarette smokers by 35 mg/day]	≥500 mg/day (in adults) may cause nausea and diarrhea. >1 g/day modestly increases risk for oxalate kidney stones. Supplementation may interfere with laboratory tests based on redox potential (e.g., fecal occult blood testing, serum cholesterol, and glucose). Withdrawal from chronic ingestion of high doses of vitamin C supplements should be done gradually because accommodation appears to occur, raising a concern of "rebound scurvy." [2 g]	Plasma ascorbic acid concentration reflects recent dietary intake, whereas WBC levels more closely reflect tissue stores. Women's plasma levels are approximately 20% higher than men's for any given dietary intake.
Vitamin B_{12}	A group of closely related cobalamin compounds composed of a corrin ring (with a cobalt atom in its center) connected to a ribonucleotide through an aminopropanol bridge. Microorganisms are the ultimate source of all naturally occurring B_{12}. The two active coenzyme forms are deoxyadenosylcobalamin and methylcobalamin. These coenzymes are needed for the synthesis of succinyl coenzyme A (CoA), which is essential in lipid and carbohydrate metabolism, and for the synthesis of methionine. The latter reaction is essential for amino acid metabolism, for purine and pyrimidine synthesis, for many methylation reactions, and for the intracellular retention of folates.	Dietary inadequacy is a rare cause of deficiency except in strict vegetarians. Most deficiencies arise from loss of intestinal absorption, which may occur with pernicious anemia, pancreatic insufficiency, atrophic gastritis, small bowel bacterial overgrowth, or ileal disease. Megaloblastic anemia and megaloblastic changes in other epithelia (see "Folate") are the result of sustained depletion. Demyelination of peripheral nerves, posterior and lateral columns of spinal cord, and nerves within the brain may occur. Altered mentation, depression, and psychoses occur. Hematologic and neurologic complications may occur independently. Folate supplementation, in doses of 1000 μg/day, may partly correct the anemia, thereby masking (or perhaps exacerbating) the neuropathic complication. [2.4 μg]	A few allergic reactions have been reported to crystalline B_{12} preparations and are probably due to impurities, not the vitamin. [TUL not established]	Serum, or plasma, concentrations are generally accurate. Subtle deficiency with neurologic complications, as described in the "Deficiency" column, can best be established by concurrently measuring the concentration of plasma B_{12} and serum methylmalonic acid because the latter is a sensitive indicator of cellular deficiency.
Biotin	A bi-cyclic compound consisting of a ureido ring fused to a substituted tetrahydrothiophene ring. Endogenous synthesis by intestinal flora may contribute significantly to biotin nutriture. Most dietary biotin is linked to lysine, a compound called biotinyl lysine, or biocytin. The lysine must be hydrolyzed by an intestinal enzyme called biotinidase before intestinal absorption occurs. Acts primarily as a coenzyme for several carboxylases; each holoenzyme catalyzes an ATP-dependent CO_2 transfer. The carboxylases are critical enzymes in carbohydrate and lipid metabolism.	Isolated deficiency is rare. Deficiency in humans has been produced by prolonged total parenteral nutrition lacking the vitamin and by ingestion of large quantities of raw egg white, which contains avidin, a protein that binds biotin with such high affinity that it renders it biounavailable. Alterations in mental status, myalgias, hyperesthesias, and anorexia occur. Later, a seborrheic dermatitis and alopecia develop. Deficiency is usually accompanied by lactic acidosis and organic aciduria. [30 μg]	Toxicity has not been reported in humans with doses as high as 60 mg/day in children. [TUL not established]	Plasma and urine concentrations of biotin are diminished in the deficient state. Elevated urine concentrations of methyl citrate, 3-methylcrotonylglycine, and 3-hydroxyisovalerate are also observed in deficiency.

	Biochemistry and Physiology	Deficiency [RDA*]	Toxicity [TUL†]	Assessment of Status
Pantothenic acid	Consists of pantoic acid linked to β-alanine through an amide bond. An essential component of CoA and phosphopantetheine, which are essential for synthesis and β-oxidation of fatty acids, as well as synthesis of cholesterol, steroid hormones, vitamins A and D, and other isoprenoid derivatives. CoA is also involved in the synthesis of several amino acids and δ-aminolevulinic acid, a precursor for the corrin ring of vitamin B_{12}, the porphyrin ring of heme, and of cytochromes. CoA is also necessary for the acetylation and fatty acid acylation of a variety of proteins.	Deficiency rare: only reported as a result of feeding semisynthetic diets or an antagonist to the vitamin. Experimental, isolated deficiency in humans produces fatigue, abdominal pain, vomiting, insomnia, and paresthesias of the extremities. [5 mg]	In doses of 10 g/day, diarrhea is reported to occur. [TUL not established]	Whole blood and urine concentrations of pantothenate are indicators of status; serum levels are not thought to be accurate.

PTH, Parathyroid hormone; *UVB,* ultraviolet B.

*Recommended daily allowance (RDA) established for female (F) and male (M) adults by the U.S. Food and Nutrition Board, 1999-2001. In some instances, insufficient data exist to establish an RDA, in which case the adequate intake (AI) established by the board is listed.

†Tolerated upper intake (TUL) established for adults by the U.S. Food and Nutrition Board, 1999-2001.

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Appendix IIc

Nutritional Trace Elements and Their Clinical Implications

	Biochemistry and Physiology	Deficiency [RDA*]	Toxicity [TUL†]	Assessment of Status
Chromium	Dietary chromium consists of both inorganic and organic forms. Its primary function in humans is to potentiate insulin action. It accomplishes this function as a circulating complex called *glucose tolerance factor,* thereby affecting carbohydrate, fat, and protein metabolism.	Deficiency in humans only described in long-term total parenteral nutrition (TPN) patients receiving insufficient chromium. Hyperglycemia or impaired glucose tolerance occurs. Elevated plasma-free fatty acid concentrations, neuropathy, encephalopathy, and abnormalities in nitrogen metabolism are also reported. Whether supplemental chromium may improve glucose tolerance in glucose-intolerant individuals remains controversial. [F: 25 μg; M: 35 μg]	Toxicity after oral ingestion is uncommon and seems confined to gastric irritation. Airborne exposure may cause contact dermatitis, eczema, skin ulcers, and bronchogenic carcinoma. [no TUL established]	Plasma or serum concentration of chromium is a crude indicator of chromium status; it appears to be meaningful when the value is markedly above or below the normal range.
Copper	Copper is absorbed by a specific intestinal transport mechanism. It is carried to the liver where it is bound to ceruloplasmin, which circulates systemically and delivers copper to target tissues in the body. Excretion of copper is largely through bile, and then into the feces. Absorptive and excretory processes vary with the levels of dietary copper, providing a means of copper homeostasis. Copper serves as a component of many enzymes, including amine oxidases, ferroxidases, cytochrome c oxidase, dopamine β-hydroxylase, superoxide dismutase, and tyrosinase.	Dietary deficiency is rare; it has been observed in premature and low-birthweight infants fed exclusively a cow's milk diet and in individuals on long-term TPN without copper. Clinical manifestations include depigmentation of skin and hair, neurologic disturbances, leukopenia, hypochromic microcytic anemia, and skeletal abnormalities. Anemia arises from impaired utilization of iron and is therefore a conditioned form of iron deficiency anemia. The deficiency syndrome, except the anemia and leukopenia, is also observed in Menkes' disease, a rare inherited condition associated with impaired copper utilization. [900 μg]	Acute copper toxicity has been described after excessive oral intake and with absorption of copper salts applied to burned skin. Milder manifestations include nausea, vomiting, epigastric pain, and diarrhea; coma and hepatic necrosis may ensue in severe cases. Toxicity may be seen with doses as low as 70 μg/kg/day. Chronic toxicity is also described. Wilson's disease is a rare, inherited disease associated with abnormally low ceruloplasmin levels and accumulation of copper in the liver and brain, eventually leading to damage to these two organs. [10 mg]	Practical methods for detecting marginal deficiency are not available. Marked deficiency is reliably detected by diminished serum copper and ceruloplasmin concentrations as well as low red blood cell (RBC) superoxide dismutase activity.
Fluorine	Known more commonly by its ionic form, fluoride. It is incorporated into the crystalline structure of bone, thereby altering its physical characteristics.	Intake of <0.1 mg/day in infants and <0.5 mg/day in children is associated with an increased incidence of dental caries. Optimal intake in adults is between 1.5 and 4 mg/day. [F: 3 mg; M: 4 mg]	Acute ingestion of >30 mg/kg body weight is likely to cause death. Excessive chronic intake (0.1 mg/kg/day) leads to mottling of teeth (dental fluorosis), calcification of tendons and ligaments, and exostoses and may increase the brittleness of bones. [10 mg]	Estimates of intake or clinical assessment are used because no good laboratory test exists.

	Biochemistry and Physiology	Deficiency [RDA*]	Toxicity [TUL†]	Assessment of Status
Iodine	Readily absorbed from the diet, concentrated in the thyroid, and integrated into the thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3). These hormones circulate largely bound to thyroxine-binding globulin. They modulate resting energy expenditure and, in the developing human, growth and development.	In the absence of supplementation, populations relying primarily on food from soils with low iodine content have endemic iodine deficiency. Maternal iodine deficiency leads to fetal deficiency, which produces spontaneous abortions, stillbirths, hypothyroidism, cretinism, and dwarfism. Permanent cognitive deficits may result from iodine deficiency during first 2 years of life. In the adult, compensatory hypertrophy of the thyroid goiter occurs along with varying degrees of hypothyroidism. [150 μg]	Large doses (>2 mg/day in adults) may induce hypothyroidism by blocking thyroid hormone synthesis. Supplementation with >100 mg/day to an individual who was formerly deficient occasionally induces hyperthyroidism. [1.1 mg]	Iodine status of a population can be estimated by the prevalence of goiter. Urinary excretion of iodine is an effective laboratory means of assessment. Thyroid-stimulating hormone (TSH) blood level is an indirect, and therefore not entirely specific, means of assessment.
Iron	Conveys the capacity to participate in redox reactions to a number of metalloproteins such as hemoglobin, myoglobin, cytochrome enzymes, and many oxidases and oxygenases. Primary storage form is ferritin and, to a lesser degree, hemosiderin. Intestinal absorption is 15%-20% for "heme" iron and 1%-8% for iron contained in vegetables. Absorption of the latter form is enhanced by the ascorbic acid in foodstuffs; by poultry, fish, or beef; and by an iron-deficient state. It is decreased by phytate and tannins.	The most common micronutrient deficiency in the world. Women of childbearing age are the highest-risk group because of menstrual blood losses, pregnancy, and lactation. The classic deficiency syndrome is hypochromic, microcytic anemia. Glossitis and koilonychia ("spoon" nails) are also observed. Easy fatigability often is an early symptom, before anemia appears. In children, mild deficiency of insufficient severity to cause anemia is associated with behavioral disturbances and poor school performance. [postmenopausal F and M: 8 mg; premenopausal F: 18 mg]	Iron overload typically occurs when habitual dietary intake is extremely high, intestinal absorption is excessive, repeated parenteral administration occurs, or a combination of these factors exists. Excessive iron stores usually accumulate in the reticuloendothelial tissues and cause little damage ("hemosiderosis"). If overload continues, iron eventually begins to accumulate in tissues such as the hepatic parenchyma, pancreas, heart, and synovium, causing hemochromatosis. Hereditary hemochromatosis results from homozygosity of a common recessive trait. Excessive intestinal absorption of iron is seen in homozygotes. [45 mg]	Negative iron balance initially leads to depletion of iron stores in the bone marrow: a bone marrow biopsy and the concentration of serum ferritin are accurate indicators of early depletion. As the severity of deficiency proceeds, serum iron (SI) decreases and total iron-binding capacity (TIBC) increases: an iron saturation (SI/TIBC) of <16% suggests iron deficiency. Microcytosis, hypochromia, and anemia ensue. Elevated levels of serum ferritin or an iron saturation of >60% suggest iron overload, although systemic inflammation elevates serum ferritin regardless of iron status.
Manganese	A component of several metalloenzymes. Most manganese is in mitochondria, where it is a component of manganese superoxide dismutase.	Manganese deficiency in the human has not been conclusively demonstrated. It is said to cause hypocholesterolemia, weight loss, hair and nail changes, dermatitis, and impaired synthesis of vitamin K–dependent proteins. [F: 1.8 mg; M: 2.3 mg]	Toxicity by oral ingestion is unknown in humans. Toxic inhalation causes hallucinations, other alterations in mentation, and extrapyramidal movement disorders. [11 mg]	Until the deficiency syndrome is better defined, an appropriate measure of status will be difficult to develop.
Molybdenum	A cofactor in several enzymes, most prominently xanthine oxidase and sulfite oxidase.	A probable case of human deficiency is described as being secondary to parenteral administration of sulfite and resulted in hyperoxypurinemia, hypouricemia, and low sulfate excretion. [45 μg]	Toxicity not well described in humans, although it may interfere with copper metabolism at high doses. [2 mg]	Laboratory means of assessment not meaningful until deficiency syndrome is better described.
Selenium	Most dietary selenium is in the form of an amino acid complex. Nearly complete absorption of such forms occurs. Homeostasis is largely performed by the kidney, which regulates urinary excretion as a function of selenium status. Selenium is a component of several enzymes, most notably glutathione peroxidase and superoxide dismutase. These enzymes protect against oxidative and free radical damage of various cell structures. The antioxidant protection conveyed by selenium apparently operates in conjunction with vitamin E because deficiency of one seems to potentiate damage induced by a deficiency of the other. Selenium also participates in the enzymatic conversion of thyroxine to its more active metabolite, triiodothyronine.	Deficiency is rare in North America but has been observed in individuals on long-term TPN lacking selenium. Such individuals have myalgias and/or cardiomyopathies. Populations in some regions of the world, most notably some parts of China, have marginal intake of selenium. In these regions Keshan's disease, a condition characterized by cardiomyopathy, is endemic; it can be prevented (but not treated) by selenium supplementation. [55 μg]	Toxicity is associated with nausea, diarrhea, alterations in mental status, peripheral neuropathy, loss of hair and nails: such symptoms were observed in adults who inadvertently consumed 27-2400 mg. [400 μg]	Erythrocyte glutathione peroxidase activity and plasma, or whole blood, selenium concentrations are the most commonly used methods of assessment. They are moderately accurate indicators of status.

Continued on following page

	Biochemistry and Physiology	Deficiency [RDA*]	Toxicity [TUL†]	Assessment of Status
Zinc	Intestinal absorption occurs by a specific process that is enhanced by pregnancy and corticosteroids and diminished by coingestion of phytates, phosphates, iron, copper, lead, or calcium. Diminished intake of zinc leads to an increased efficiency of absorption and decreased fecal excretion, providing a means of zinc homeostasis. Zinc is a component of more than 100 enzymes, among which are DNA polymerase, RNA polymerase, and transfer RNA synthetase.	Zinc deficiency has its most profound effect on rapidly proliferating tissues. *Mild deficiency:* growth retardation in children. *More severe deficiency:* growth arrest, teratogenicity, hypogonadism and infertility, dysgeusia, poor wound healing, diarrhea, dermatitis on the extremities and around orifices, glossitis, alopecia, corneal clouding, loss of dark adaptation, and behavioral changes. Impaired cellular immunity is observed. Excessive loss of gastrointestinal secretions through chronic diarrhea and fistulas may precipitate deficiency. Acrodermatitis enteropathica is a rare, recessively inherited disease in which intestinal absorption of zinc is impaired. [F: 8 mg; M: 11 mg]	Acute zinc toxicity can usually be induced by ingestion of >200 mg of zinc in a single day (in adults). It is manifested as epigastric pain, nausea, vomiting, and diarrhea. Hyperpnea, diaphoresis, and weakness may follow inhalation of zinc fumes. Copper and zinc compete for intestinal absorption: long-term ingestion of >25 mg/day of zinc may lead to copper deficiency. Long-term ingestion of >150 mg/day has been reported to cause gastric erosions, low high-density lipoprotein cholesterol levels, and impaired cellular immunity. [40 mg]	No accurate indicators of zinc status exist for routine clinical use. Plasma, RBC, and hair zinc concentrations are often misleading. Acute illness, in particular, is known to diminish plasma zinc levels, in part by inducing a shift of zinc out of the plasma compartment and into the liver. Functional tests that determine dark adaptation, taste acuity, and rate of wound healing lack specificity.

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†Tolerated upper limit (TUL) established for adults by the U.S. Food and Nutrition Board, 1999-2001.

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Appendix IId

Summary of Vitamin and Mineral Deficiencies

Vitamin and Mineral Deficiencies	Neurologic Syndrome or Syndromes	Supporting Tests	Treatment	Causes (Other Than Malnutrition)
A (retinol)	Blindness from retinal or corneal damage	Visual fields, visual acuity Serum level <30-65 μg/dl	30,000 IU vitamin A daily × 1 wk	Hypothyroidism, diabetes, renal or liver failure
B_1 (thiamine)	Wernicke's encephalopathy: ataxia, nystagmus, ophthalmoparesis, confusion, delirium Korsakoff's syndrome: amnesia, confabulation Beriberi: axonal neuropathy	MRI: symmetric lesions of midbrain (periaqueductal area), pons, hypothalamus, thalamus, cerebellum MRI: necrosis of mammillary bodies, dorsomedial and anterior thalamus Nerve conduction tests: decreased amplitude Serum thiamine level <20 ng/dl Erythrocyte transketolase	Prevent by 100 mg PO daily before and 1 year after bariatric surgery, 100 mg IV before glucose administration or refeeding Treat Wernicke's encephalopathy with 5 days of thiamine, 100-500 mg IV or IM daily, then PO 100 mg daily Antioxidants (*N*-acetylcysteine)	Alcoholism, bariatric or other major GI surgery, prolonged vomiting, hemodialysis, diuretic treatment of heart failure, cachexia, 5-fluorouracil, other blockers of thiamine phosphate production
B_3 (niacin)	Pellagra: confusion, dementia, weakness, ataxia, spasticity, myoclonus, glossitis, dermatitis, photosensitivity	Erythrocyte NAD, plasma niacin, urinary N_1-methylnicotinamide	Nicotinic acid, 50 mg PO tid or 25 mg IV tid; nicotinamide, 50-100 mg IM or PO tid	Alcoholism, corn- or cereal-based diet, Hartnup's syndrome, carcinoid syndrome
B_5 (pantothenic acid)	Dysesthesias, foot paresthesias	Deficient coenzyme A	5 mg PO daily	Severe malnutrition
B_6 (pyridoxine)	Neuropathy, sensory ataxia, depression Infantile pyridoxine-deficient epilepsy	Plasma PLP <27 nmol/L; urinary 4-pyridoxic acid, <3 nmol ↑ Homocysteine after methionine loading challenge ↑ α-AASA in urine, plasma, CSF	50-100 mg PO daily for neuropathy (preventive use if taking B_6 antagonist) 100-200 mg daily for adult epilepsy	Diverticulosis, isoniazid, cycloserine, other antagonists Genetic defects in antiquitin (aldehyde dehydrogenase), pyridoxal synthesis
B_{12} (cobalamin)	Myelopathy with spastic paraparesis and sensory ataxia, peripheral neuropathy, optic neuropathy, memory loss, dementia; indirect contributor to stroke	Blood level <200 pg/ml ↑ Methylmalonic acid >145 nmol/L Intrinsic factor antibodies Schilling test, megaloblastic anemia Delayed somatosensory evoked potentials ↑ Homocysteine, total >12.5 μmol/L	IM B_{12}, 1000 μg daily for 1 week, then weekly for 1 month, then monthly or oral B_{12}, 1000 μg daily, or nasal B_{12}, 500 μg weekly for lifetime if abnormal absorption, 50-100 μg daily if normal absorption	Achlorhydria, gastric or ileal resection, blind loop syndrome, sprue, HIV infection, nitrous oxide anesthesia (especially abuse), fish tapeworm, vegan diet
D (calciferol)	Proximal myopathy, often painful; cognitive impairment Secondary compression of spinal cord, plexus, or peripheral nerves from rickets or osteomalacia	25-(OH) vitamin D_3 level <10 ng/ml in urine Serum calcium ↑ PTH >54 pg/ml Osteopenia/porosis on bone densitometry	Daily supplementation with 400 IU, >50,000 IU 3 times per wk if malabsorption; use blood level or urine calcium excretion to guide (should be >100 mg/day)	Lack of exposure to sunlight, including sunblock protection; chronic antiepileptic drug use
E (tocopherol)	Spinal and cerebellar ataxia, Babinski's sign, ophthalmoplegia, peripheral neuropathy, retinitis pigmentosa	Vitamin E level <2.5 mg/L (normal, 6-15 with normal lipid level) ↑ A-β-lipoprotein levels, antigliadin antibodies Genetic analysis to rule out other spinocerebellar ataxias such as Friedreich's ataxia	Supplement with 6-800 IU, 5-10 mg/kg twice daily, for ataxia of genetic causes, water-soluble 200 mg/kg/day or IM α-tocopherol for malabsorption	Biliary atresia, celiac sprue, Genetic: ↓ α-tocopherol transport protein (8q13), microsomal triglyceride transfer protein

Continued on following page

Summary of Vitamin and Mineral Deficiencies

Vitamin and Mineral Deficiencies	Neurologic Syndrome or Syndromes	Supporting Tests	Treatment	Causes (Other Than Malnutrition)
Folate	Dementia, B_{12} deficiency, stroke	↑ Homocysteine, plasma level <2.5 μg/L	1 mg 3 times per day until normal level, then maintenance of 1 mg/day Pregnancy: additional 0.4 mg/day if taking a folate antagonist	Malabsorption or use of antagonist (methotrexate) or antiepileptic medication
K (phytonadione)	Intracranial hemorrhage	INR or PT elevation	IM phytonadione at birth, maternal vitamin K for last month of pregnancy	Medication use that increases metabolism, such as phenytoin
Copper	Myelopathy, neuropathy	Serum Cu <75 μg/dl, ↓ urinary Cu, ceruloplasmin <23 mg/dl MRI: ↑ T_2 signal in cervical cord, dorsal column Mutation in ATP7A gene (Menkes' disease)	Elemental Cu, 8 mg/day PO week 1, 6 mg/day week 2, 4 mg/day week 3, 2 mg/day ongoing malabsorption Menkes' disease: 250 mg SC bid	Wilson's disease, Menkes' disease, alcoholism, malabsorption, gastric bypass, zinc toxicity
Magnesium	Seizures, encephalopathy	Serum magnesium <1.5 mg/ dl, correct for low albumin	Magnesium sulfate IV or PO Avoid magnesium-wasting drugs	Alcoholism, especially beer
Potassium	Muscle weakness, chronic, acute	Serum potassium <3.5 mEq/L, ECG	IV or PO KCl until normalized	Diuretic use, bulimia

AASA, Aminoadipic semialdehyde; *CSF,* cerebrospinal fluid; *ECG,* electrocardiography; *GI,* gastrointestinal; *HIV,* human immunodeficiency virus; *IM,* intramuscularly; *INR,* international normalized ratio; *IU,* international units; *IV,* intravenously; *MRI,* magnetic resonance imaging; *NAD,* nicotinamide adenine dinucleotide; *PLP,* pyridoxal-5-phosphate (active coenzyme of pyridoxine); *PO,* by mouth; *PT,* prothrombin time; *PTH,* parathyroid hormone; *tid,* three times a day.

From Goldman *L,* Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

Appendix IIIa

Historical and Physical Findings in Poisoning

Sign	Toxin
Odor	
Bitter almonds	Cyanide
Acetone	Isopropyl alcohol, methanol, paraldehyde, salicylates
Alcohol	Ethanol
Wintergreen	Methyl salicylate
Garlic	Arsenic, thallium, organophosphates, selenium
Ocular Signs	
Miosis	Opioids (except propoxyphene, meperidine, and pentazocine), organophosphates and other cholinergics, clonidine, phenothiazines, sedative-hypnotics, olanzapine
Mydriasis	Atropine, cocaine, amphetamines, antihistamines, TCAs, carbamazepine, serotonin syndrome, PCP, LSD, postanoxic encephalopathy
Nystagmus	Phenytoin, barbiturates, sedative-hypnotics, alcohols, carbamazepine, PCP, ketamine, dextromethorphan
Lacrimation	Organophosphates, irritant gas or vapors
Retinal hyperemia	Methanol
Cutaneous Signs	
Diaphoresis	Organophosphates, salicylates, cocaine and other sympathomimetics, serotonin syndrome, withdrawal syndromes
Alopecia	Thallium, arsenic
Erythema	Boric acid, elemental mercury, cyanide, carbon monoxide, disulfuram, scombroid, anticholinergics
Cyanosis (unresponsive to oxygen)	Methemoglobinemia (e.g., benzocaine, dapsone, nitrites, phenazopyridine), amiodarone, silver
Oral Signs	
Salivation	Organophosphates, salicylates, corrosives, ketamine, PCP, strychnine
Oral burns	Corrosives, oxalate-containing plants
Gum lines	Lead, mercury, arsenic, bismuth
Gastrointestinal Signs	
Diarrhea	Antimicrobials, arsenic, iron, boric acid, cholinergics, colchicine, withdrawal
Hematemesis	Arsenic, iron, caustics, NSAIDs, salicylates
Cardiac Signs	
Tachycardia	Sympathomimetics (e.g., amphetamines, cocaine), anticholinergics, antidepressants, theophylline, caffeine, antipsychotics, atropine, salicylates, cellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide), withdrawal
Bradycardia	β-Blockers, calcium channel blockers, digoxin, clonidine and other central α_2 agonists, organophosphates, opioids, sedative-hypnotics
Hypertension	Sympathomimetics (amphetamines, cocaine, LSD), anticholinergics, clonidine (early), monoamine oxidase inhibitors
Hypotension	β-Blockers, calcium channel blockers, cyclic antidepressants, iron, phenothiazines, barbiturates, clonidine, theophylline, opioids, arsenic, amatoxin mushrooms, cellular asphyxiants (cyanide, carbon monoxide, hydrogen sulfide), snake envenomation
Respiratory Signs	
Depressed respirations	Opioids, sedative-hypnotics, alcohol, clonidine, barbiturates
Tachypnea	Salicylates, amphetamines, caffeine, metabolic acidosis (ethylene glycol, methanol, cyanide), carbon monoxide, hydrocarbons

Continued on following page

Historical and Physical Findings in Poisoning

Sign	Toxin
Central Nervous System Signs	
Ataxia	Alcohol, anticonvulsants, benzodiazepines, barbiturates, lithium, dextromethorphan, carbon monoxide, inhalants
Coma	Opioids, sedative-hypnotics, anticonvulsants, cyclic antidepressants, antipsychotics, ethanol, anticholinergics, clonidine, GHB, alcohols, salicylates, barbiturates
Seizures	Sympathomimetics, anticholinergics, antidepressants (especially TCAs, bupropion, venlafaxine), isoniazid, camphor, lindane, salicylates, lead, organophosphates, carbamazepine, tramadol, lithium, ginkgo seeds, water hemlock, withdrawal
Delirium/psychosis	Sympathomimetics, anticholinergics, LSD, PCP, hallucinogens, lithium, dextromethorphan, steroids, withdrawal
Peripheral neuropathy	Lead, arsenic, mercury, organophosphates

GHB, Gamma hydroxybutyrate; *LSD,* lysergic acid diethylamide; *NSAID,* nonsteroidal anti-inflammatory drug; *PCP,* phencyclidine; *TCA,* tricylic antidepressant.
From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

Appendix IIIb

Recognizable Poison Syndromes

	SIGNS						
Poison Syndrome	**Vital**	**Mental Status**	**Pupils**	**Skin**	**Bowel Sounds**	**Other**	**Possible Toxins**
Sympathomimetic	Hypertension, tachycardia, hyperthermia	Agitated, psychosis, delirium	Dilated	Diaphoretic	Normal to increased		Amphetamines, cocaine, Ecstasy, pseudoephedrine, caffeine, theophylline
Anticholinergic	Hypertension, tachycardia, hyperthermia	Agitation, delirium, mumbling speech	Dilated	Dry	Decreased		Antihistamines, tricyclic antidepressants, atropine, jimson weed, phenothiazines
Cholinergic	Bradycardia (although may show tachycardia), BP and temp typically normal	Confusion, coma, fasciculations	Small	Diaphoretic	Hyperactive	Diarrhea, urination, bronchorrhea, bronchospasm, emesis, lacrimation, salivation	Organophosphates, nerve gases, Alzheimer medications
Opioids	Respiratory depression (hallmark of toxicity), bradycardia, hypotension, hypothermia	Depression, coma	Pinpoint	Normal	Normal to decreased		Methadone, suboxone, morphine, oxycodone, heroin, etc.
Sedative-hypnotics	Respiratory depression, HR normal to decreased, BP normal to decreased, temp normal to decreased	Somnolence, coma	Small	Normal	Normal		Barbiturates, benzodiazepines, ethanol
Serotonin syndrome	Hyperthermia, tachycardia, hypertension or hypotension (autonomic instability)	Agitation, confusion, coma	Dilated	Diaphoretic	Increased	Neuromuscular hyperexcitability: clonus, hyperreflexia (lower extremities > upper extremities)	SSRIs, lithium, MAOIs, linezolid, tramadol, meperidine, dextromethorphan
Salicylates	Tachypnea, hyperpnea, tachycardia, hyperthermia	Agitation, confusion, coma	Normal	Diaphoretic	Normal	Nausea, vomiting, tinnitus, ABG with primary respiratory alkalosis and primary metabolic acidosis	Aspirin, bismuth subsalicylate (Pepto-Bismol), methylsalicylates
Withdrawal	Tachycardia, tachypnea, hyperthermia	Lethargy, confusion, delirium	Dilated	Diaphoretic	Increased		Withdrawal from opioids, sedative-hypnotics, ethanol

ABG, Arterial blood gas; *BP,* blood pressure; *HR,* heart rate; *MAOI,* monoamine oxidase inhibitor; *SSRI,* selective serotonin reuptake inhibitor; *temp,* temperature.
From Kliegman RM et al: *Nelson textbook of pediatrics,* ed 19, Philadelphia, 2011, Saunders.

Appendix IIIc

Antidotes and Indications for Use

Antidote	Indication for Use	Dose*	Treatment End Point	Comments
Antivenom (Fab)†	Crotalines	4-6 vials; repeat for persistent or worsening clinical condition; repeat doses of 2 vials at 6, 12, and 18 hr after initial antivenom dose(s) are recommended	Halt in progression of circumferential and proximal swelling Resolving systemic effects	Better safety profile than equine-derived antivenom Repetitive dosing indicated for recurrent soft tissue swelling
Antivenom, *Latrodectus* (equine)†	Black widow spider (*Latrodectus* sp.)	1 vial diluted in 100 ml NS, infused over 1 hr; can repeat	Resolution of symptoms, vital signs normal	Dilution and slow infusion rate are critical to avoid anaphylactoid reaction Indications include severe pain unresponsive to opioids and severe hypertension Serum sickness can occur IV calcium is ineffective
Atropine	Carbamates Nerve agents Organophosphorus compounds	2 mg IV; double the dose every 5 min to achieve atropinization and hemodynamic stability; then start continuous infusion of 10%-20% of total stabilizing dose per hr	Cessation of excessive oral and pulmonary secretions, >80 bpm, systolic blood pressure >80 mm Hg	Doubling of the dose every 5 min (e.g., 2 mg, 4 mg, 8 mg, 16 mg) estimated to achieve atropinization within 30 min Stop infusion if patient develops any signs or symptoms of anticholinergic toxidrome; restart infusion at lower rate when signs or symptoms abate
Calcium‡	Calcium-channel antagonists	Calcium chloride 10%, 20-50 mg (0.2-0.5 ml)/kg/hr	Reversal of hypotension; may not reverse bradycardia	All indications: Monitor ionized calcium levels IV extravasation causes tissue necrosis, especially with calcium chloride Can administer at faster than stated rates for immediate, life-threatening conditions Taper infusions and monitor for relapse of toxicity when discontinuing therapy Calcium chloride contains three times more elemental calcium than calcium gluconate does Calcium-channel antagonists may be ineffective in severe toxicity
	Hydrofluoric acid	Systemic toxicity: calcium gluconate 10%, 1-3 g (10-30 ml) per dose IV over 10-min period; repeat as needed every 5-10 min	Reversal of life-threatening manifestations of hypocalcemia and hyperkalemia	Can dilute and give intraarterially or IV with a Bier block for extremity exposures and burns
	Hyperkalemia (except cardiac glycosides)	Calcium gluconate 10%, 1 g (10 ml) per dose IV over 10-min period; repeat as needed every 5-10 min	Reversal of myocardial depression and conduction delays	May precipitate ventricular arrhythmias
	Hypermagnesemia	Calcium gluconate 10%, 1-2 g (10-20 ml) per dose IV over 10-min period; repeat as needed every 5-10 min	Reversal of respiratory depression, hypotension, and cardiac conduction blocks	Simultaneous therapies to increase magnesium elimination should be instituted
	Hypocalcemia (e.g., ethylene glycol)	Calcium gluconate 10%, 0.5-1.0 g (5-10 ml) per dose over 10-min period; repeat as needed every 10 min	Reversal of tetany	Correct symptomatic hypocalcemia; avoid excessive administration that may increase production of calcium oxalate crystals in ethylene glycol poisoning

Antidote	Indication for Use	Dose*	Treatment End Point	Comments
L-Carnitine	Valproate-induced hyperammonemia or hepatotoxicity	100 mg/kg (maximum 6 g) IV over 30 min, then 15 mg/kg IV over 30-min period q4h (max 6 g/day)	Treat until clinical improvement occurs	Levocarnitine is active form Adjust dose for end-stage renal disease
Cyanide antidote kit	Cyanide		Resolution of lactic acidosis and moderate to severe clinical signs and symptoms: seizures, coma, dyspnea, apnea, hypotension, bradycardia	
Amyl nitrate		Amyl nitrite: 0.3-ml pearls, crush and inhale over 30-sec period		Coordinate amyl nitrite with continued oxygenation and give only until sodium nitrite infusion is begun; nitrites may produce hypotension and excess methemoglobinemia
Sodium nitrite		Sodium nitrite 3%: 10 ml IV over 10-min period		Sodium nitrite dose must be adjusted if patient has hemoglobin <12 g/dl
Sodium thiosulfate		Sodium thiosulfate 25%: 50 ml (12.5 g) IV over 10-min period		Sodium thiosulfate dosing can be repeated
Deferoxamine	Iron	15 ml/kg/hr IV (max 8 g/day) Mild to moderate: administer for 6-12 hr Severe toxicity: administer 24 hr	Resolution of clinical signs and symptoms Do not use urine color, which is an unreliable marker for iron clearance	Indications: symptomatic patients with lethargy, severe abdominal pain, hypovolemia, acidosis, shock; any symptomatic patient with peak serum iron level >350 g/dl Prolonged therapy can cause pulmonary toxicity
Digoxin-specific antibody fragments (Fab)	Digoxin Digitalis Other cardiac glycosides (e.g., bufodienalides [*Bufo toads*], oleander)	Unknown digoxin dose or serum level or for plant or toad source: acute toxicity—10-20 vials; chronic toxicity—3-6 vials Digoxin dose known: number of vials = (mg ingested × 0.8) ÷ 0.5 Digoxin serum level known: number of vials = [serum level (ng/ml) × weight (kg)] ÷ 100	Resolution of hyperkalemia, symptomatic bradydysrhythmias, ventricular arrhythmias, Mobitz II or third-degree heart block	Each vial binds 0.5 mg of digoxin or digitoxin Monitor ECG and potassium levels Digoxin serum levels unreliable after antidote administered unless test is specific for free serum digoxin
Dimercaprol (BAL)	Arsenic Lead Mercury, elemental and inorganic salts	Arsenic: 3-5 mg/kg IM q4h Lead: 75 mg/m^2 (4 mg/kg) IM q4h for 5 days Inorganic mercury: 5 mg/kg IM, then 2.5 mg/kg IM q12h for 10 days or until patient clinically improved	Arsenic: 24-hr urinary arsenic <50 μg/L Lead: encephalopathy resolved, blood lead level <100 μg/dl, and succimer therapy can be started Mercury, elemental and inorganic: 24-hr urinary mercury <20 μg/L	Maximum adult dose is 3 g/day BAL started 4 hr before initiation of concomitant $CaNa_2EDTA$ for lead encephalopathy Dosing not well established for arsenic and elemental or inorganic mercury toxicity; not used for organic mercury poisoning Adverse effects: painful injections, fever, diaphoresis, agitation, headache, salivation, nausea and vomiting, hemolysis in G6PD-deficient patients, chelation of essential metals Check essential metal levels if chelation is prolonged Succimer is replacing BAL for many indications except lead encephalopathy Treatment end points for arsenic and mercury include improving clinical condition
Edetate calcium disodium ($CaNa_2EDTA$)	Lead	1500 mg/m^2/24 hr (max 3 g) by continuous infusion	Treat for 5 days, followed by 2-day hiatus; repeat until encephalopathy resolved, lead level <100 μg/dl, and succimer therapy can be started	Use in patients with lead encephalopathy or lead level >100 g/dl Administer BAL 4 hr before initiating $CaNa_2EDTA$ Hydrate patient and establish good urinary output before starting therapy Avoid thrombophlebitis by diluting in NS or D_5W to a concentration ≤0.5% Substitution of Na_2EDTA can cause fatal hypocalcemia
Flumazenil	Benzodiazepines Venlafaxine	0.1 mg/min IV to a total dose of 1 mg	Reversal of respiratory depression	Limit use to reversal of inadequate respiration in benzodiazepine-toxic patients Increases intracranial pressure and risk for seizures in presence of underlying seizure disorder or ingestion of seizure-producing toxicants Monitor for resedation up to 2 hr after last dose

Continued on following page

Antidotes and Indications for Use

Antidote	Indication for Use	Dose*	Treatment End Point	Comments
Folinate (tetrahydrofolic acid [leucovorin])	Methanol Methotrexate	Methanol: 50 mg IV q4h Methotrexate: 100 mg/m^2 IV q3-6h	Methanol: methanol undetectable, metabolic acidosis cleared Methotrexate: serum level $<1 \times 10^{-8}$ mol/L	Essential therapy for both toxicants Methotrexate: large ingestions may require increased dose Glucarpidase administered 2-4 hr before or after folinate
Fomepizole	Ethylene glycol Methanol	Dose 1: 15 mg/kg IV Doses over next 48 hr: 10 mg/kg IV All subsequent doses: 15 mg/kg IV Administer q12h, except when HD performed: HD initiation: ½ next dose if >6 hr since last dose HD ongoing: q4h End of HD (based on time of last dose): <1 hr, no dose; 1-3 hr, ½ next dose; >3 hr, next dose	For both: serum level <20 mg/dl and metabolic acidosis resolved	Start immediately if toxic alcohol suspected, without waiting for confirmatory levels Dose amount is not affected by interval timing of doses
Glucagon	β-Adrenergic receptor antagonists Calcium-channel antagonists	Bolus of 3.5-5 mg IV; can repeat to achieve clinical effect, then infusion of 2-10 mg/hr	Reversal of hypotension and bradycardia; taper infusion	Can precipitate vomiting; be prepared to protect airway Mild hyperglycemia occurs Maximum dosing amounts unknown; bolus doses up to 30 mg reported Duration of effect is 15 min; thus infusion must be started immediately
Hydroxocobalamin	Cyanide	Initial: 5 g IV over 15-min period Second dose: 5 g IV over 15 min–2 hr; maximum total dose is 10 g Follow each hydroxocobalamin dose with sodium thiosulfate 25%: 50 ml (12.5 g) IV over 10-min period	Resolution of lactic acidosis and moderate to severe clinical signs and symptoms: seizures, coma, dyspnea, apnea, hypotension, bradycardia	Can be administered IV push if patient is in cardiac arrest Do not give hydroxocobalamin and sodium thiosulfate through the same IV line Adverse effects: red discoloration of plasma, urine, mucous membranes, skin; transient hypertension Interference with laboratory colorometric assays: Levels increased: bilirubin; creatinine; glucose; hemoglobin; magnesium; co-oximetry total Hb, COHb%, MetHb% Levels decreased: AST, ALT, creatinine, co-oximetry O_2Hb%
Hyperbaric oxygen (HBO)	Carbon monoxide Experimental: carbon tetrachloride, cyanide, hydrogen sulfide	3.0 atm pressure for 60 min (25 min O_2, 5 min air, 25 min O_2, 5 min air), then 2.0 atm for 65 min (30 min O_2, 5 min air, 30 min O_2), then "surface" to 1.0 atm	One treatment Second treatment rarely administered (controversial)	Carbon monoxide: treatment protocols may vary HBO indicated for loss of consciousness; seizures; cerebellar dysfunction; impaired cognition; headache, nausea/vomiting persisting after 4 hr O_2 therapy regardless of carboxyhemoglobin level Experimental indications: treatment protocols not established
Insulin-glucose	Calcium-channel antagonists β-Adrenergic receptor antagonists	Regular insulin, 1 U/kg bolus, followed by 0.5-1 U/kg/hr Titrate 50% dextrose IV to avoid hypoglycemia	Reversal of myocardial depression	Beneficial in case series and reports Initiate if glucagon and vasopressor or inotropic drugs fail to reverse myocardial depression; more effective if used before onset of cardiogenic shock Monitor glucose and potassium; hypoglycemia can occur during and after therapy Hyperglycemia results from toxicant-induced insulin resistance, and initial dextrose requirements may be less than anticipated Recovery may be heralded by normalization of glucose levels, with increased dextrose required to avoid hypoglycemia
Intralipid	Cardiac toxicity from local anesthetics (e.g., bupivacaine, ropivacaine) Experimental: verapamil, diltiazem, tricyclic antidepressants, bupropion, propranolol	Use 20% formulation Initial bolus: 1.5 ml/kg IV over 1 min, followed immediately by infusion of 0.25 ml/kg/min for 30-60 min Can repeat bolus for asystole	Return of hemodynamic stability	Use based on animal experiments and human case reports; numerous dosing regimens have been used Use if advanced life support measures fail; continue CPR as needed during drug administration

Antidote	Indication for Use	Dose*	Treatment End Point	Comments
Methylene blue	Methemoglobin-producing agents	1-2 mg/kg body weight (0.1-0.2 ml/kg) of 1% methylene blue is administered over 5-min period; repeat dose for persistent or recurrent symptoms or signs	Resolution of dyspnea and altered mental status	Use if patient is symptomatic (i.e., dyspneic, altered mental status) Maximum dose should not exceed 7 mg/kg (0.7 ml/kg) Contraindicated in G6PD-deficient patients; may cause hemolysis Some toxicants (e.g., dapsone) may require prolonged therapy
N-Acetylcysteine (NAC)	Acetaminophen Experimental: carbon tetrachloride, chloroform, pennyroyal oil	Oral: Load—140 mg/kg Maintenance (starting 4 hr after load)—70 mg/kg q4h IV: Load—150 mg/kg over 1-hr period Maintenance infusion—12.5 mg/kg over 4-hr period, then 6.25 mg/kg per hour as continuous infusion	Administer 24 hr of NAC and repeat AST and APAP levels: if AST normal and APAP not detected, stop NAC; if AST normal and APAP detected, continue NAC for 12 hr, then reassess AST and APAP levels; if AST elevated, continue NAC for total of 72 hr of therapy After 72 hr of therapy, if INR <2.0, stop NAC After patient has received 72 hr of therapy, if INR ≥2.0 or severe hepatotoxicity present, continue NAC until INR <2.0	Most effective if initiated within 8 hr after ingestion; may be started any time after ingestion and is beneficial in severe hepatotoxic states Use IV in patients unable to tolerate PO or with severe hepatotoxicity; the dose and timing differ from the oral regimen Dosage and administration of FDA-approved IV formulation assume early treatment of acute overdose without hepatotoxicity; longer duration of treatment required in patients with hepatotoxicity Treatment end points simplified for ease of use INR result not valid indicator if FFP recently administered
Naloxone	Opioids	Bolus: 0.4-2 mg via IV, sublingual injection, or endotracheal instillation; 0.4-0.8 mg SC Continuous infusion: establish bolus dose required to reverse respiratory depression Begin infusing two thirds of reversal dose every hour, and titrate to maintain adequate respirations Rebolus with half of reversal dose 15 min after reversing respiratory depression	Initial: reversal of respiratory depression with resolution of hypoxia and hypercapnia Final: resolution of CNS and respiratory depression	Preventilate patients with respiratory depression by bag-valve mask or intubation before administration Use smaller doses in opioid-dependent patients; some opioids (e.g., propoxyphene, pentazocine, fentanyls) may require larger doses of naloxone; use continuous infusion for recurrent symptoms and prolonged action of some formulations (e.g., sustained-release morphine, methadone) Resedation can occur Do not use nalmefene or naltrexone to reverse acute toxicity
Octreotide	Sulfonylureas	50 mg SC q6h	Resolution of hypoglycemia and dextrose not required	Maintain dextrose infusion as needed
Physostigmine	Anticholinergic agents (e.g., diphenhydramine, jimsonweed [*Datura* sp.], scopolamine)	1-2 mg IV over 5-min period; can repeat once after 10-15 min if no effect	Reversal of anticholinergic effects	Duration of effect is 60-90 min Benzodiazepine used for subsequent treatment of agitation and seizures; additional physostigmine used rarely (e.g., refractory seizures or agitation) Adverse effects include seizures, excessive oral secretions, bradyarrhythmias; contraindicated in cyclic antidepressant toxicity
Pralidoxime chloride	Organophosphorus compounds Nerve agents—sarin, VX	30 mg/kg IV bolus (max 2 g) over 30 min, followed by continuous infusion of 8-10 mg/kg/hr (max 650 mg/hr)	Resolution of signs and symptoms, atropine no longer required	Can give initial dose over 2-min period for life-threatening clinical effects Administer early when diagnosis known or strongly suspected Efficacy variable, depending on the organophosphate Fat-soluble organophosphates may require prolonged treatment
Pyridoxine	Ethylene glycol (theoretical efficacy)	100 mg IV	One dose	Efficacy theoretical Pyridoxine may stop seizures, but patient can remain comatose (isoniazid, mushrooms); use benzodiazepines and phenobarbital concomitantly to manage seizures Excessive dosing can cause neuropathy
	Isoniazid Monomethylhydrazine mushrooms	5 g IV, repeat for refractory seizures	Resolution of seizures	

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Antidotes and Indications for Use

Antidote	Indication for Use	Dose*	Treatment End Point	Comments
Sodium bicarbonate ($NaHCO_3$)	Reversal of myocardial sodium-channel blockers (e.g., cyclic antidepressants, cocaine, propoxyphene, sodium-channel-blocking antiarrhythmics with $\tau_{recovery}$ >1 sec, piperidine phenothiazines (thioridazine, mesoridazine)	1-2 mEq $NaHCO_3$/kg via intermittent bolus; repeat as needed	Narrowing of prolonged QRS, resolution of ventricular arrhythmias, reversal of hypotension	Monitor blood pH (optimal pH approximately 7.50); avoid pH >7.55
	Altered tissue distribution or enhanced elimination of salicylates; may be used in chlorophenoxy herbicides, chlorpropamide, formic acid, methotrexate, phenobarbital	1-2 mEq $NaHCO_3$/kg, followed by 3 ampules (150 ml) $NaHCO_3$ (44 mEq per 50 ml) in 850 ml of D_5W, infused at 2-3 times normal maintenance fluid rate	Serum salicylate <30 mg/dl and patient clinically stable	Monitor urinary pH hourly; adjust infusion to maintain urine pH of 7.5-8.0 (avoid blood pH >7.55) Monitor ABGs Maintain normokalemia
Succimer (DMSA)	All forms: Arsenic Lead Mercury	10 mg/kg/dose q8h for 5 days, followed by q12h for 14 days Drug holiday for 2 wk; repeat if treatment end point not reached	Arsenic: 24-hr urinary arsenic <50 μg/L Lead: resolution of encephalopathy, gastrointestinal symptoms, neuropathy, nephropathy, arthralgias, myalgias, and blood lead level <70 μg/dl Mercury, elemental and inorganic: 24-hr urinary mercury <20 μg/L Mercury, organic: end point not well established	Oral chelator; adverse effects include rash, transient AST and alkaline phosphatase elevations, and gastrointestinal distress; minimal chelation of essential metals occurs Dosing for arsenic and mercury not well established Therapeutic end point for organic mercury not established; neurotoxicity not responsive to chelation therapy; suggest chelation until blood mercury level within normal value range for reference laboratory
Vitamin K	Anticoagulants (e.g., warfarin, long-acting anticoagulant rodenticides [LAARs])	Subcutaneous: AquaMEPHYTON (K_1), 10-25 mg, repeat every 6-12 hr until oral vitamin K_1 started Oral: 25-50 mg q6h; larger doses may be required	INR is normal 48-72 hr after stopping vitamin K_1 therapy Can also monitor factor VII activity	Anaphylactoid reaction can occur with IV administration Severe bleeding may also require FFP or factor concentrates Base decision to treat on finding of elevated INR; do not administer prophylactic vitamin K_1 Oral therapy has been required for months with LAAR poisoning because of lipophilicity of toxicant, with slow body clearance

ABG, Arterial blood gas; *ALT,* alanine aminotransferase; *APAP,* acetyl-para-aminophenol (acetaminophen); *AST,* aspartate aminotransferase; *BAL,* British antilewisite; bpm, beats per minute; *CNS,* central nervous system; *COHb%,* percent carboxyhemoglobin; *CPR,* cardiopulmonary resuscitation; *D_5W,* 5% dextrose in water; *DMSA,* 2,3-dimercaptosuccinic acid; *ECG,* electrocardiogram; *FDA,* Food and Drug Administration; *FFP,* fresh-frozen plasma; *G6PD,* glucose-6-phosphate dehydrogenase; *Hb,* hemoglobin; *HD,* hemodialysis; *IM,* intramuscular; *INR,* international normalized ratio; *IV,* intravenous; *MetHb%,* percent methemoglobinemia; *NS,* normal saline; *O_2Hb%,* percent oxyhemoglobin; *PO,* per os (by mouth); *SC,* subcutaneous; $\tau_{recovery}$, drug blockade recovery rate.

*Dose concentrations and infusion times are not given. Drug dosages may require adjustment in patients with renal or hepatic failure.

†Administer antivenom in a monitored setting; antivenom must be reconstituted and then diluted; initially infuse at a rate of 2 to 5 ml/hr, and double the infusion rate every 5 minutes as tolerated to administer antivenom over a 1-hour period.

‡Ten percent calcium chloride solution = 100 mg/ml (27.2 mg/ml elemental calcium); 10% calcium gluconate solution = 100 mg/ml (9 mg/ml elemental calcium).

From Goldman L, Schafer AI: *Goldman's Cecil medicine,* ed 24, Philadelphia, 2012, Saunders.

Appendix IV

Impairment and Disability Issues

Impairment describes harm to anatomy and physiology, whereas *disability* denotes the difficulty a person has performing a function. Reporting disability for different sectors of society has its own nuances. Proper evaluation of impairment/disability starts with knowing who is asking for what. It is an area of practice in which an understanding of some basic concepts can make it rewarding rather than distressing.

- Ultimately, disability is a measure of function. Functional outcomes are becoming increasingly important in medicine, mirroring the shift towards patient-centeredness. All practitioners should have some facility with documenting the effects of an intervention on a patient's physical, psychological, and social functioning. For example, the continuation of an opioid analgesic should be predicated on meeting functional goals negotiated between the patient and physician before initiation of treatment. Even a brief comment on walking distance or work tolerance is better than nothing.
- Some concepts apply to all venues of disability. Primary care providers should rarely be in the position to determine whether a patient can be on or off a specific job. Rather, their task is to give general parameters about which physical exertions are medically dangerous. Try to be specific and use objective criteria where appropriate, but don't be intimidated by a form. Ballpark estimates can often suffice. For example, many chronic low back pain patients may conservatively and safely be described as able to lift/carry up 10 lbs, push/pull 25 lbs, and change positions as needed to keep comfortable. Have thorough medical records and be consistent; lawyers may focus on contradictions in your documentation to help their clients.
- Rehabilitation centers across the country are required to monitor function using a standardized set of criteria called the "Functional Independence Measure (FIM)," which categorizes activities of daily living into divisions such as mobility, transfers, feeding, grooming/hygiene, dressing, bathing, and toileting. In therapy notes, you may come across scores in these categories rating patients on a seven-point scale from totally dependent to moderate-assistance (mod A; patient can perform 50% of task) to modified-independent (patient requires an assistive device) to independent.
- Psychosocial contributing factors such medicolegal issues can profoundly influence patients' presentations through somatization from secondary gain. However, it is important to differentiate this from malingering, Munchausen's syndrome, or "gaming the system," which are remarkably less prevalent.
- The number of stakeholders expands in the disability system to include the employer, the government, the legal system, and the payer. Each sector has its own regulations. You may be required to fill out disability questionnaires as a condition of accepting payment for clinical services from a payer, such as in the workers' compensation system. Much more commonly, you will be seeing patients for clinical services paid for by an evaluation and management code. In these cases, you are not obligated to provide free medicolegal assessments. Settling payment issues in advance can avoid misunderstanding. Again, before assessing disability, understand who is asking and why.

GOVERNMENT-ADMINISTERED DISABILITY

State Temporary Disability Insurance (TDI) programs, the Family Medical Leave Act of 1993 (FMLA), the Social Security Administration (SSA), and the Department of Veterans Affairs offer disability benefits through the state and federal government.

- State TDI forms must be filled out for the patient to receive any income. They are generally very basic and just engage the social support network for a patient. This may not be the best venue to stipulate partial disability.
- The FMLA provides unpaid leave for qualified medical and family reasons. Because it is a federal program, the forms involved are standard across states and employers. They can be intimidating at first, but are reasonably easy to complete once the basic definitions used are understood. It is recommended that you familiarize yourself with this paperwork the first few times it is encountered. Completing the form for subsequent patients should not be overly burdensome.
- The SSA and the Department of Veterans Affairs have their own internal mechanisms for quantifying disability, but they may subpoena your records or request a summary narrative as part of their processes. If you've kept good clinical notes, your existing documentation should satisfy their requirements. Many patients choose to apply for Social Security Disability Insurance (SSDI) and/or Supplemental Security Income (SSI) through a legal representative. These lawyers may send you a lengthy questionnaire to prepare their case. There are physicians whose practices perform these services and who can be hired by attorneys to facilitate patients' applications. If this nonclinical work appeals to you, consider affiliating with the SSA or contracting your time to lawyers under separate indenture. If not, you may want to recommend the law office contact a suitable practice.

WORKERS' COMPENSATION

In workers' compensation, the payer and employer join the provider in trying to rehabilitate the injured worker. Confidentiality issues are handled differently because these stakeholders may have a right to protected health information.

- Each state has their own laws regarding reporting requirements, and the U.S. Department of Labor governs injured federal employees. If you plan on accepting workers' compensation patients, you must familiarize yourself with the necessary paperwork. Typically, this is a standard, short form that includes measures of function. It may make sense to copy your state's parameters and create a "work note" to be used uniformly in your practice for cases both inside and outside of the workers' compensation system. Functional limitations should pertain to any task, not just to the employee's vocation. In general, employees should not be labeled "on" or "off."
- A notification that an employee has reached "maximal medical improvement" should be made once an employee's condition is expected to change over months/years rather than days/weeks. At this juncture they will transition from temporary disability benefits to permanent disability benefits, possibly including vocational rehabilitation. If ongoing sequelae exist, a permanent impairment rating may be needed to resolve an employee's claim and allow them to progress to the next stage of their life. These are more sophisticated determinations, usually directed by the American Medical Association's (AMA) *Guides to the Evaluation of Permanent Impairment*, now in its sixth edition. Analysis of permanent impairment, causation, and apportionment generally fall out-

side of workers' compensation reporting requirements. Someone with appropriate training may be best suited to complete this task. Consider providing these more detailed services under a separate indenture, such as a consultation arrangement with the employee's attorney. Your state workers' compensation board may have specific guidelines governing these reports. In any case, the work should be done under a clear written agreement, not based on a verbal request by the employee. Very complex cases may also require a formal functional capacity evaluation through an appropriate rehabilitation resource.

PERSONAL INJURY

Patients hurt in car accidents or other personal injuries often are involved in legal cases covering medical care, personal damages, and pain and suffering. Most commonly, you will be helping these patients with their clinical issues under their regular medical insurance, although some providers agree to provide services under a legal lien on the claim. Regardless of your role in a personal injury case, it is helpful to document objective details about the injury and functional parameters. If you are asked to keep someone out of work, try to delineate functional limitations as you would in a workers' compensation employee.

- Similar to the workers' compensation system, it is helpful to state when a patient has reached maximal medical improvement. Personal injury claims can take longer to resolve than in the workers' compensation system, as the employer and insurance company are strongly incentivized to reach a resolution in those cases. In general, an ongoing legal case may hinder a patient from achieving a healthful balance of wellness. It is in the patient's best interest to move the claim toward completion.
- Quantifying permanent disability is a key component of resolving these cases. If a clinician is providing services under a legal lien, there may be a conflict of interest in having that provider quantify the permanent impairment. There may be financial implications to the degree of disability awarded, and this may influence whether or not the clinician will receive payment on their lien. These cases are almost always contentious, and may be best handled by providers with special training, such as an independent medical examiner. Again, the determination typically follows the AMA's *Guides to the Evaluation of Permanent Impairment.* A clinician's role is to manage the patient's injuries, not to negotiate medicolegal issues. If you are not appropriately trained, consider deferring questions regarding disability to someone who is.

PRIVATE DISABILITY

Some patients purchase private insurance plans to provide income in addition to that offered through the government in the case of long-term disability. These forms vary by insurance carrier and change over time. They may need to be filled out periodically to maintain benefits. Many providers opt to charge a separate fee for the completion of this type of paperwork.

CONCLUSION

In summary, impairment and disability are measures of function and should be followed by all good doctors as part of patient-centered care. Providers can be most effective interacting with the various disability systems if they know when they are acting as clinicians and when they are acting as legal consultants. Understanding the principles involved with the different sectors will help you avoid confusion between obligations and opportunities when doing this work.

SUGGESTED READINGS

American Academy of Physical Medicine and Rehabilitation: Disability evaluation. Accessed March 7, 2014, at http://now.aapmr.org/rehab-essentials/special-assessment-mgmt-strategy/Pages/Disability-evaluation.aspx.

Holmes EB: Impairment rating and disability determination. Accessed March 7, 2014, at http://emedicine.medscape.com/article/314195-overview#a1.

Rondinelli R.D.. In: *Guides to the evaluation of permanent impairment.* American Medical Association: Arlington, VA.

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Appendix V

Primary Care Procedures*

1. **Anesthesia**
   a. Local anesthesia
   b. Topical anesthesia
   c. Digital block
2. **Biopsy techniques**
   a. Excisional skin biopsy
   b. Punch biopsy
   c. Shave biopsy
3. **Sutures and dressings**
   a. Instrument tie
   b. Inverted subcuticular stitches
   c. Subcuticular running stitches
   d. Mattress stitches
   e. Tissue glue
   f. Topical hemostasis
   g. Unna boot application
4. **Needle aspiration**
   a. Breast cyst aspiration
5. **Dermatology**
   a. Skin tag removal
   b. Wart treatment
   c. Abscess incision and drainage
   d. Basal cell curettage and cautery
   e. Lipoma removal
   f. Ingrown toenail removal
6. **Eyes, ears, nose, throat**
   a. Nasopharyngoscopy
   b. Cerumen impaction removal
7. **Hand/Digit**
   a. Ring removal
8. **Orthopedics**
   a. Arthrocentesis—knee aspiration
   b. Joint injection—shoulder
   c. Joint injection—knee
   d. Trigger point injection
   e. Lateral epicondyle injection
9. **Gastroenterology**
   a. Anoscopy
   b. Flexible sigmoidoscopy
   c. Internal hemorrhoid banding
   d. External hemorrhoid excision
   e. Nasogastric intubation
10. **Gynecology**
   a. Pap smear
   b. Bartholin's marsupialization
   c. Bartholin's cyst Word catheter placement
   d. Vulvar biopsy
11. **Inpatient medicine**
   a. Lumbar puncture
   b. Subclavian lines
   c. Thoracentesis
   d. Abdominal paracentesis
12. **Obstetrics**
   a. Vaginal delivery
   b. Episiotomy-laceration repair
13. **Reproductive—female**
   a. Intrauterine device (IUD) insertion
   b. IUD removal
   c. Diaphragm insertion
14. **Urinary**
   a. Bladder catheterization—female
   b. Bladder catheterization—male

1. ANESTHESIA

A. LOCAL ANESTHESIA

Key Steps

1. Select anesthetic and needle.
2. Provide countertraction.
3. Infiltrate underneath entire lesion.
4. Use field block technique.

INSTRUCTIONS

1. Perform local anesthesia with either direct infiltration or a field block.
2. Block smaller lesions with direct infiltration.
3. Excellent anesthesia may be provided with 1% lidocaine with or without epinephrine.
4. Injection using a 27- or 30-gauge needle is well tolerated.
5. Buffering the lidocaine with bicarbonate suspension reduces the burning associated with infiltration.
6. Applying countertraction to the skin allows for more precise injection into the subcutaneous and dermal layers.
7. Depending on the type of incision, extend the area of infiltration at least 2 to 3 mm beyond the incision that has been planned.
8. Often the area needs several injections for a full block.
9. Perform field blocks by injecting widely around the lesion in a diamond-shaped pattern.

*Text adapted from Tuggy ML, Garcia J, Newkirk GR (eds): *Pocket procedures* text in *Multimedia primary care procedures,* Philadelphia, 2006, Saunders. Illustrations from Rosen R, Chan TC, Vilke GM, Sternbach G: *Atlas of emergency procedures,* St Louis, 2001, Mosby.

10. Pass the needle at 60-degree angles from one side of the lesion.
11. Perform the same needle passes on the opposite side to completely surround the area with anesthesia.
12. Perform a deep injection below the lesion to ensure that the block is complete in the center of the area.

INDICATIONS
- Pain relief for procedures
- Pain relief for trauma or for joint or fracture injection
- Adjunctive pain relief for steroid injection
- Diagnostic to assess origin of pain

CONTRAINDICATIONS
- Injecting into a sterile space through superficially infected area
- Attempting to anesthetize areas that are large enough that potential toxicity may occur

CPT AND ICD-9 CODES
No appropriate codes

B. TOPICAL ANESTHESIA

Key Steps

1. Cleanse area with alcohol.
2. Apply topical anesthetic.
3. Cover with occlusive dressing.
4. Remove cover in 30 minutes to 2 hours.

INSTRUCTIONS
1. To obtain topical anesthesia of the skin, first wipe the skin with alcohol to remove the surface oils.
2. Apply the topical anesthetic cream to the planned incision area.
3. Use 1 to 2 grams of cream to cover a 3-by-3-cm area.
4. Cover the area with an occlusive dressing for 30 to 120 minutes depending on the topical agent that is chosen and the desired depth of anesthesia.
5. At 30 to 60 minutes, 3-mm depth is usually anesthetized, with an additional 1-mm depth added for every 30 minutes up to 120 minutes total application time.
6. Remove the dressing and perform the procedure.
7. The skin should show some blanching in the area that is anesthetized.
8. For topical anesthesia for mucous membranes, use topical spray lidocaine or benzocaine.
9. Apply the spray; onset of action is under 3 minutes.
10. Start the procedure at that time.

C. DIGITAL BLOCK

Key Steps

1. Cleanse digit with antiseptic.
2. Inject local anesthesia without epinephrine.
3. Inject at 9 to 10 o'clock and at 2 to 3 o'clock.
4. Secondary injections.

INSTRUCTIONS
1. Perform digital blocks by injecting plain lidocaine alongside the base of the digit from 9 to 10 o'clock and from 2 to 3 o'clock to anesthetize the digital nerves.
2. Approximately 1 ml of lidocaine is sufficient to provide adequate anesthesia.
3. In some patients, injecting lidocaine toward the palmar surface may be necessary to obtain complete anesthesia of the digit.
4. In some instances, as with nail removal, a simple tourniquet from a latex drain may be used to minimize bleeding in the field and retain the injected anesthesia agent in vascular digits.

INDICATIONS
- Need for local anesthetic that encompasses the digit
- Ingrown nail removal
- Drainage of felon or paronychia
- Management of fracture of phalanx

CONTRAINDICATIONS
- Use of epinephrine in the anesthetic is contraindicated
- Patient with hypotension or sepsis leading to peripheral vasoconstriction
- Coagulation defect (either medication related, congenital, or acquired), relative

CPT AND ICD-9 CODES
No appropriate codes

2. BIOPSY TECHNIQUES

A. EXCISIONAL SKIN BIOPSY

Key Steps

1. Incise around lesion.
2. Excise lesion.
3. Undermine skin edges.
4. Perform deep layer closure.
5. Perform skin closure.

INSTRUCTIONS
1. Most lesions require an elliptical excision around the lesion.
2. The longitudinal axis of the ellipse should follow the skin lines.
3. Excise the skin through the dermis to obtain a full-thickness biopsy.
4. Once the ellipse is created, completely remove the tissue sample by severing the underlying subcutaneous attachments.
5. To reduce the tension on the wound while it is healing, undermine the tissue along the margins of the excision.
6. Use a subcuticular inverted mattress stitch to close the deep layer prior to placing the cutaneous stitches.
7. Two or three deep stitches are usually adequate to support the closure of small excisions.
8. Deep stitches help to control bleeding and reduce tension on the scar, allowing for improved healing.
9. Perform skin closure using nylon suture material that is appropriate for the size of the lesion and location on the body.
10. Place simple interrupted sutures to bring the wound edges together to allow healing with minimal scarring.
11. Nylon stitches are nonabsorbable and require removal in 5 to 10 days, depending on the site.
12. Send the specimen for pathologic review.

INDICATIONS
- Skin lesions that appear to be malignant; it is especially important to leave 1- to 2-mm margins beyond the lesion if attempting to cure
- Nevi of uncertain malignant potential—acquired, dysplastic, or atypical in appearance
- Benign growths that cause local irritation (pyogenic granulomas, dermatofibromas)
- Removal of subcutaneous growths (sebaceous cysts, lipomas)

CONTRAINDICATIONS
- Local infection at the site of planned biopsy
- Coagulation defect (medication related, congenital, or acquired)
- Nonexcisional treatment option available and not yet tried
- Patient who is unable to comply with wound care

B. PUNCH BIOPSY

Key Steps

1. Cleanse skin and inject local anesthesia.
2. Perform punch biopsy of lesion.
3. Sever base of punch.
4. Suture or topical hemostasis.

INSTRUCTIONS
1. The punch biopsy allows for a full-depth diagnostic sample to be taken from a lesion in a short period of time.
2. Clean the area with Betadine solution. (First check for iodine allergy.)
3. Then inject 1% lidocaine local anesthetic under the lesion.
4. Here use the 2-mm punch biopsy to create a small plug of tissue that you will excise.
5. Use a pair of Adson's forceps to lift the plug, and use iris scissors to sever the base.
6. Cauterize the open punch with ferrous subsulfate solution (Monsel's solution) on a cotton wick or swab.
7. Punch biopsy sites larger than 3 mm often require stitch closure on keratinized skin or any site where cosmetic result is more critical, such as the face.

INDICATIONS
- Skin lesions that appear to be malignant where diagnosis will affect excision of the lesion
- Nevi of uncertain malignant potential: acquired, dysplastic, or atypical in appearance
- Rashes where diagnosis is unclear
- Removal of a small lipoma, which usually requires a large punch biopsy (5 to 6 mm)

CONTRAINDICATIONS
- Local infection at the site of planned biopsy
- Coagulation defect (medication related, congenital, or acquired)
- Nonexcisional treatment option available and not yet tried
- Patient who is unable to comply with wound care

C. SHAVE BIOPSY

Key Steps

1. Cleanse skin.
2. Apply local anesthesia.
3. Shave lesion.
4. Topical hemostasis.

INSTRUCTIONS
1. Perform the shave biopsy in a clean manner, as complete sterile technique is not required for superficial lesions.
2. First, clean the skin with the antiseptic solution.
3. Then inject 1% lidocaine to create a wheal at the base of the lesion.
4. Whether or not epinephrine is used depends on the anatomic location of the lesion that is to be biopsied.
5. Once the lesion has been anesthetized, use a pair of pickups with teeth to raise the lesion and use a No. 15 blade to shave the lesion off at the dermis.
6. To obtain hemostasis, use ferrous subsulfate solution (Monsel's solution) to chemically cauterize the base of the lesion.
7. Use a simple adhesive bandage to cover the biopsy site.
8. The procedure is now complete.

INDICATIONS
- Skin lesions that appear to be benign where cosmetic removal is important
- Nevi of uncertain malignant potential: acquired, dysplastic, or atypical in appearance; complete excision would be required if the lesion is malignant
- Rashes where diagnosis is unclear
- Removal of a small lipoma, usually requiring a large punch biopsy (5 to 6 mm)
- For diagnosis of potential malignant lesions where punch biopsy is not feasible owing to location

CONTRAINDICATIONS
- Local infection at the site of planned biopsy
- Coagulation defect (either medication related, congenital, or acquired)
- Nonexcisional treatment option available and not yet tried
- Patient who is unable to comply with wound care

3. SUTURES AND DRESSINGS

A. INSTRUMENT TIE

Key Steps

1. Initiate tie with surgeon's knot.
2. Tighten knot so that it lies flat.
3. Perform second throw in opposite direction.
4. Perform two additional throws to secure knot.

INSTRUCTIONS
1. Initiate the instrument tie with a surgeon's knot.
2. Perform it by wrapping the suture around the needle holder twice before grasping the other end of suture and closing the knot.
3. When the first tie is completed, perform the next wrap of the suture in the opposite direction around the needle holder.
4. Now the knot is locked.
5. Perform two or more separate throws to secure the knot in place.
6. Alternating knot throws in different directions prevents premature unraveling of the knot.

INDICATIONS
- Low-tension wound closures
- Deep closure in confined wound space where manual ties would be difficult

CONTRAINDICATIONS
- Knots requiring significant tension or sutures applied for hemostasis

B. INVERTED SUBCUTICULAR STITCHES

Key Steps

1. Initial stitch enters deep.
2. Second stitch enters superficially.
3. Tie knot in subcutaneous layer.
4. Repeat for each stitch.

INSTRUCTIONS
1. Use inverted stitches to close deep layers of a wound and allow the knot to be buried in the process.
2. The needle tip enters the deeper layer of the subcutaneous tissue and is then brought upward so that it exits the same side more superficially, often in the subcuticular layer.
3. Bring the needle to the other side of the wound so that it enters in the superficial aspect of the wound at the same level as the first side.
4. Drive the needle deep so that it exits the tissue deep in the wound space where the stitch started.
5. Once that is done, tie the knot.
6. During the tightening of the knot, pull the wound together with the knot lying deep to the subcuticular layers that are brought together by the stitch.
7. Cut the suture short and apply the next stitch elsewhere in the wound to bring about further closure of the wound.
8. For small wounds, one or two inverted knots will close the deep layers well.

INDICATIONS
- High-tension wound closures that require deep-layer closure where knots are preferably buried
- Wound closures where external suture punctures would be cosmetically unfavorable
- Wounds that require prolonged support for optimal closure
- Adjunctive closure with subcuticular running stitches

CONTRAINDICATIONS
- Knots requiring significant tension or sutures applied for hemostasis

CPT AND ICD-9 CODES
No appropriate codes

C. SUBCUTICULAR RUNNING STITCHES

Key Steps

1. Make linear incision under minimal tension.
2. Running suture with knot at each end.
3. Reinforce with Steri-strips or tissue glue.

INSTRUCTIONS
1. Bury subcuticular sutures running horizontal sutures.
2. This technique is useful for wounds that are under minimal tension and in which cosmetic results are important.
3. It is possible to close deeper wounds with deep sutures of subcutaneous sutures first.
4. Begin with a knot beyond one apex of the incision, using polypropylene-coated nylon suture.
5. Place the needle through the skin to emerge in the wound.
6. Run the suture, taking horizontal bites through the superficial papillary dermis, alternating sides so that the exit point of one side matches the entry point of the other.
7. Keep the suture under minimal tension.
8. Emerge at the other end beyond the apex and place a second knot.
9. Reinforce the wound with Steri-strips or tissue glue.

INDICATIONS
- Low-tension to moderate-tension wound closures that follow skin lines or wounds partially closed by deep sutures to support the skin closure
- Wound closures where external suture punctures would be cosmetically unfavorable
- Wounds that require prolonged support for optimal closure

CONTRAINDICATIONS
- Knots requiring significant tension or sutures applied for hemostasis

CPT AND ICD-9 CODES
No appropriate codes

D. MATTRESS STITCHES

Key Steps

1. Deeply insert needle 0.5 to 1 cm from wound edge.
2. Pass needle deeply across the base of wound.
3. Exit opposite side at same distance.
4. Reinsert at 0.3 cm from edge on same side of wound.
5. Cross wound, exit at same shallow depth, and tie knot.

INSTRUCTIONS
1. Mattress sutures are useful in wounds that are under high or moderate tension and where eversion of wound edges is desired.
2. Vertical mattress sutures are initially a simple deep interrupted suture, with the needle penetrating the skin 0.5 to 1 cm from the wound edge, depending on the location and size of the wound (Fig. AIV-1, *A*).
3. Track the suture needle across the wound to 75% of the wound depth, and emerge from the opposite side at the same distance from the skin.
4. Reinsert the needle closer to the wound edge, 0.5 to 0.3 cm from the wound, and to 25% of the wound depth, emerging from the opposite side at the same distance from the wound edge.
5. Tie the knot, keeping the suture in sufficient tension to close the wound but not strangulate the tissue (Fig. AIV-1, *B*).
6. Repeat knots about 0.5 to 1 cm apart to close the wound (Fig. AIV-1, *C* and *D*).
7. These sutures risk producing cosmetically undesirable marks if left in too long and should be evaluated for removal at 1 week or less, depending on the site.

INDICATIONS
- Moderate-tension to high-tension wounds
- Wound closures where external suture punctures would be cosmetically tolerated

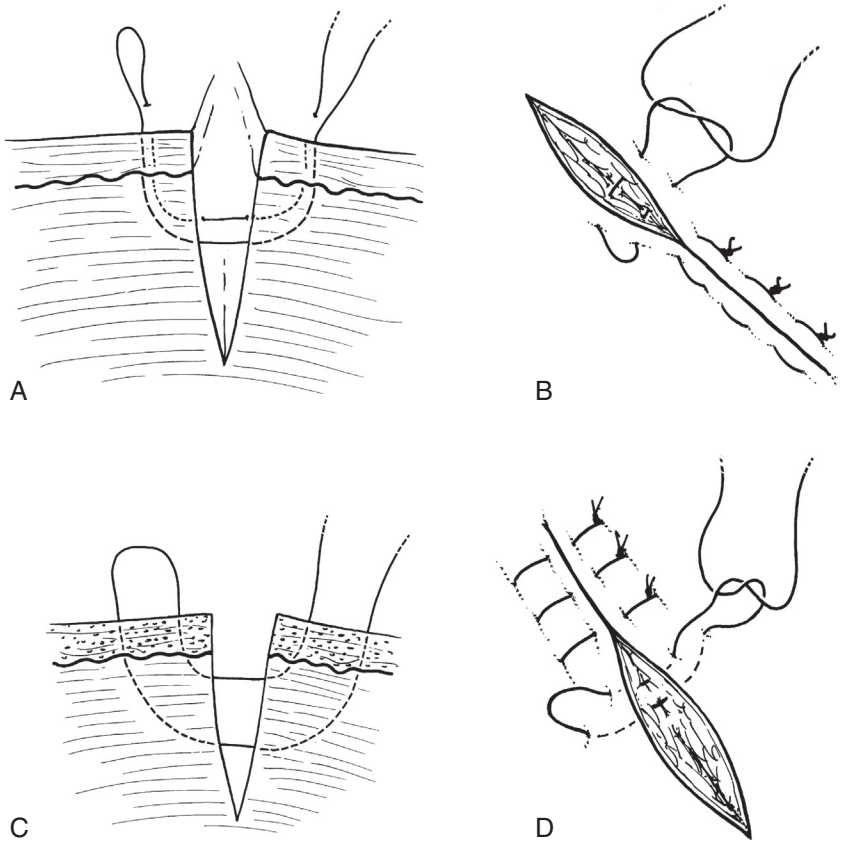


FIGURE AIV-1 Mattress stitches.

- Wounds that require prolonged support for optimal closure
- Wounds in areas where inversion of wound edges is more likely (chest, shoulder, thigh)

CONTRAINDICATIONS
- Wound closures where external suture punctures would be cosmetically unfavorable
- Cosmetically sensitive areas where the eversion of the wound may lead to thickened scar

CPT AND ICD-9 CODES
No appropriate codes

E. TISSUE GLUE

Key Steps

1. Identify appropriate wound type.
2. Cleanse and dry wound area.
3. Apply three or four layers of tissue glue.
4. Dry between each layer to bond skin edges.

INSTRUCTIONS
1. Tissue glues are useful for low-tension wound closures or for small wounds that need closure for improved hemostasis.
2. First, irrigate, clean, and dry the wound.
3. Crush the applicator ampule and allow the adhesive to fill the tip.
4. Pinch the wound shut and apply the glue to the surface in three or four layers, allowing for drying between each layer.
5. Take care to avoid gluing any unwanted materials or personnel to the patient.
6. Once the glue is dry, you may cover the wound or leave it open depending on the site and risk of contamination.

INDICATIONS
- Superficial lacerations
- Nail lacerations
- Superficial closure over deeper tension-reducing sutures
- Repair of lacerated nails or nail beds

CONTRAINDICATIONS
- Mucosal lesions
- Wounds under tension
- Contaminated lesions
- Puncture wounds and crush wounds
- Bite wounds
- Complex lacerations
- Lacerations in the axilla

CPT AND ICD-9 CODES
Codes are dependent on lesion size and location

F. TOPICAL HEMOSTASIS

Key Steps

1. Perform electrocautery.
2. Silver nitrate may be used.
3. Ferrous subsulfate solution (Monsel's solution) may be used.

INSTRUCTIONS
1. Obtain a topical hemostasis in several ways.
2. Use the Hyfrecator or radiofrequency device to cauterize or coagulate the base of superficial or deep excisions.
3. Silver nitrate sticks are useful for cauterizing superficial lesions, although they may leave a stain in the dermal layer.
4. Ferrous subsulfate solution is an effective topical agent that leaves little residue after its application and is ideal on mucous membranes such as the cervix, vagina, vulva, and penis.

INDICATIONS
- For bleeding after cutaneous surgery, especially partial-thickness shave or curetted biopsies
- To treat nail beds after full or partial nail removal
- To treat mucous membrane biopsy sites of the glans penis, vulva, vagina, and cervix

CONTRAINDICATIONS
- Allergy to topical agent
- Heavy bleeding, in which case the agent is usually not effective

G. UNNA BOOT APPLICATION

Key Steps

1. Apply moistened Unna boot wrap.
2. Wrap second layer with elastic wrap.
3. Ensure that ankle is at 90 degrees.

INSTRUCTIONS
1. Apply the Unna boot in a manner similar to the application of a cast to the lower leg. The Unna boot is much simpler, however, because it requires only two layers.
2. Place the Unna boot material directly against the skin, wrapping it on the leg.
3. If there are open ulcers or lesions on the foot or lower leg, ensure that the Unna boot covers them well.
4. In areas where there are excess amounts of the wrap owing to changes in the wrapping angle, simply fold in the Unna boot material to allow for compensation of these excess segments of the wrap.
5. Once the Unna boot is applied, wrap a second layer around the entire Unna boot to secure it.
6. Use an elastic wrap material for the second layer.
7. Position the ankle at 90 degrees at the conclusion of wrapping.
8. The Unna boot will dry slowly over the next 24 hours and provide an occlusive dressing to the lower leg and foot that can be left in place for 5 to 7 days.

INDICATIONS
- Venous stasis ulcers
- Post–venous thrombosis ulcers
- Severe lower-extremity edema with impending ulceration

CONTRAINDICATIONS
- Current venous thrombosis
- Current arterial disease
- Infected ulcers
- Cellulitis
- Allergy to components of the Unna boot

CPT CODES
29580 Unna boot application

ICD-9 CODES
457.1 Lymphedema
707.12 Decubitus ulcers, calf
707.13 Decubitus ulcers, ankle

4. NEEDLE ASPIRATION

A. BREAST CYST ASPIRATION

Key Steps

1. Cleanse skin and palpate nodule.
2. Insert aspiration needle.
3. Multiple passes into nodule.
4. Apply pressure to site.
5. Place aspirate on slide.

INSTRUCTIONS

1. The breast nodule is identified by palpation, and the skin is prepped with antiseptic solution.
2. Fix the cyst to the chest wall between the operator's fingers.
3. Place the needle into the center of the cyst, and then withdraw the plunger to allow for creation of a vacuum.
4. Larger fluid samples can be sent directly to the pathologist.
5. If only a small volume of fluid is obtained, express the contents of the syringe onto a slide and fix with cytology fixative.
6. A second pass may be performed to gather more material for sampling.
7. Apply pressure to the needle insertion site to prevent hematoma formation.
8. Spray the contents of the syringe onto a slide.
9. Use a second slide to gently layer the specimen.
10. Spray cytology fixative onto the slide to prevent drying before fixation.
11. Send the specimen to the laboratory for cytology analysis.

INDICATIONS

- Palpable lump in the breast
- Treatment of breast cyst
- Abnormal mammographic findings combined with stereotactic location of biopsy site

CONTRAINDICATIONS

- Poorly controlled infection over needle site
- Known malignancy (excisional surgery indicated)

CPT CODES

88170 Fine needle aspirate (FNA) with or without preparation of smears
19100 Biopsy of breast, needle (FNA)

ICD-9 CODES

611.72 Lump or mass in the breast
217 Benign neoplasm of the breast
174.9 Malignant neoplasm of breast (female) unspecified

5. DERMATOLOGY

A. SKIN TAG REMOVAL

Key Steps

1. Inject local anesthesia beneath tag.
2. Make a sharp excision.
3. Cauterize.

INSTRUCTIONS

1. Wipe the skin with antiseptic solution.
2. Treat skin tags with or without anesthesia depending on patient preference and the size of the tag to be removed.
3. Make a small wheal of local anesthetic under each skin tag.
4. Grasp the skin tag with a forceps and trim it at the base with iris scissors.
5. Cauterize the base of the skin tag with either electrical or chemical cautery methods.

INDICATIONS

- Symptomatic skin tags in areas of frequent microtrauma, such as the neck line or axilla
- Diagnostic concerns (diagnostic removal)
- Cosmetic concerns

CONTRAINDICATIONS

- Local skin infection
- Concern for uncontrollable cosmetic result

CPT CODES

11200 Skin tag removal by excision or destruction
11201 Each additional tag, up to 10, or portion thereof

ICD-9 CODES

701.9 Skin tags

B. WART TREATMENT

Key Steps

1. Perform cryotherapy: 1-second to 3-second freeze.
2. Refreeze lesions.
3. Use electrocautery method.

INSTRUCTIONS

1. Several options may be used to treat warts.
2. Cryotherapy offers a rapid method of treatment of superficial warts.
3. Cryotherapy is usually effective if the warts are small and the patient either returns for follow-up or continues to use topical medications after the initial treatment.
4. Perform cryotherapy using either a cotton swab dipped in liquid nitrogen and applied to the wart or a liquid nitrogen container equipped with a spray tip to apply the liquid nitrogen directly to the wart.
5. Spray each wart until the entire wart and a 1-mm margin have frozen to form a white disc.
6. Allow this to thaw, and then refreeze it.
7. This dual freeze cycle ensures necrosis of the frozen area.
8. Wart cryotherapy also may be done with a nitrous oxide cryotherapy unit fitted with a dermal tip.
9. Often, paring the wart down to skin level improves success with cryotherapy.
10. For persistent or recurrent warts that fail cryotherapy, injecting local anesthetic and using a Hyfrecator to ablate the lesion is an effective way to eradicate the warts.

INDICATIONS

- Painful, bleeding, or unsightly warts
- Warts failing to resolve spontaneously (up to 30% of warts disappear without treatment within 6 months)
- Warts have a negative impact on the patient's life (e.g., cosmetic issues, employment issues)
- Warts are growing or multiplying rapidly
- Patient has concerns about spreading the virus

CONTRAINDICATIONS

- Poorly controlled local infection, which should be treated prior to the procedure
- Caution in cosmetically sensitive areas such as face, lip, or eyelid

CPT CODES

17110 Destruction of warts
17111 Greater than 15 warts

ICD-9 CODES

078.19 Plantar warts
078.10 Verruca vulgaris
078.11 Condyloma acuminatum

C. ABSCESS INCISION AND DRAINAGE

Key Steps

1. Wear eye protection.
2. Perform field block.
3. Open abscess with incision that follows skin lines.
4. Liberate all areas of abscess.
5. Abrade surface of abscess wall and clear debris from wound.

INSTRUCTIONS

1. Wear eye splash protection. Identify abscess (Fig. AIV-2, *A*).
2. Perform a field block by inserting the needle at opposite ends of the area to be anesthetized (Fig. AIV-2, *B*).
3. Pass the needle alongside the edge of this region and then withdraw it while anesthesia is injected.
4. Reinsert the needle at 60 to 90 degrees to the initial block at the adjacent aspect of the first injection.
5. After the initial half of the block is completed, anesthetize the opposite side to complete a diamond-shaped field block.

6. Open abscesses with an incision that follows the skin lines (Fig. AIV-2, *C*).
7. Use a No. 15 blade to open the skin and express the material inside the abscess.
8. Use hemostats to break open adhesions or abscess pockets and to ensure that all areas of the abscess are liberated (Fig. AIV-2, *D*). Irrigate the abscess cavity (Fig. AIV-2, *E*).
9. A sebaceous abscess has a smooth capsular lining that needs to be stripped out to prevent recurrence.
10. Use a curved hemostat to grasp portions of this capsule wall, which may need to be removed piecemeal.
11. In lesions that are not actively inflamed, it may be possible to dissect out the entire wall.
12. Gauze can be used to abrade the surface of the abscess wall and clear debris from within the wound.
13. After draining the abscess and removing or disrupting the sebaceous cyst wall, pack iodoform gauze into the wound and leave it in place for 2 to 3 days (Fig. AIV-2, *F*).
14. After 2 to 3 days, the wound can be allowed to heal by secondary intention.
15. For larger abscesses, repacking may be necessary to prevent premature closure and abscess reformation.

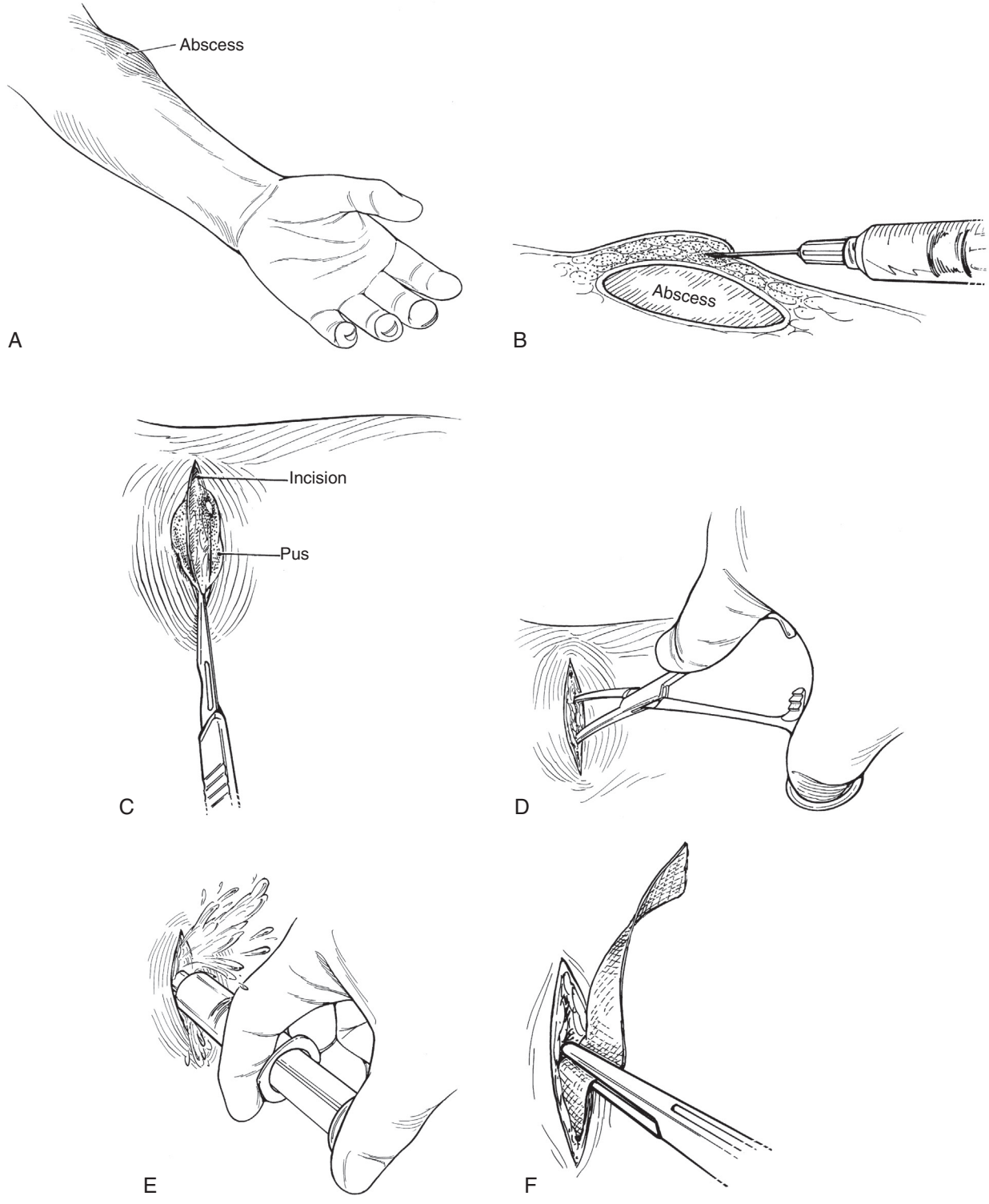


FIGURE AIV-2 Abscess incision and drainage.

INDICATIONS
- Abscess formation within the cutaneous layers anywhere on the body

CONTRAINDICATIONS
- Virtually none, unless the lesion is on the face within the nasolabial triangle and can be treated with warm compresses with a high probability of spontaneous drainage

CPT CODES
10060 I&D, one abscess
10061 I&D, multiple or complex abscess

ICD-9 CODES
682.9 Cellulitis, abscess, NOS

D. BASAL CELL CURETTAGE AND CAUTERY

Key Steps

1. Mark lesion.
2. Inject local anesthesia.
3. Cycles of curettage and cautery.

INSTRUCTIONS
1. Punch biopsy of a suspicious lesion on the patient's arm confirmed basal cell carcinoma.
2. Mark the lesion with a surgical marker to clearly delineate the extent of the superficial cancer.
3. Infiltrate local anesthesia consisting of lidocaine with epinephrine under the lesion.
4. Use a curette to scrape the lesion from the skin surface down into the dermal layer.
5. As curettage is performed, the operator should be able to sense the softness of the basal cell cancer in contrast to the normal dermal layer.
6. Remove all areas of abnormal density tissue.
7. Be especially attentive to the area where the punch biopsy was performed and the prior borders from the surgical marker.
8. Curette the lesion in every direction, performing cautery between each curettage episode.
9. Generally, perform four cycles of curettage and cautery to ensure that the process eradicates any dermal extension of the basal cell cancer.
10. Cover the wound with a simple adhesive bandage on completion of the procedure.
11. Cure is assured by finding normal skin on follow-up examination.

INDICATIONS
- Seborrheic and actinic keratoses
- Basal cell carcinoma
- Squamous cell carcinoma
- Condyloma
- Pyogenic granuloma

CONTRAINDICATIONS
- Cellulitis and other bacterial infections
- Lesions that require complete excision for diagnosis or treatment
- Pacemakers with electrodesiccation

CPT AND ICD-9 CODES
Codes dependent on lesion size and location

E. LIPOMA REMOVAL

Key Steps

1. Inject anesthesia and make incision.
2. Blunt and sharp dissection.
3. Extrude lipoma.
4. Place drain.
5. Close wound.

INSTRUCTIONS
1. The majority of lipoma excisions involve small tumors approximately 3 to 5 cm in size located in the subcutaneous tissues of the trunk or extremities.
2. Occasionally in practice, one will encounter large lipomas that require excisions done in an operating suite under general anesthesia to avoid lidocaine toxicity.
3. Place the patient under general anesthesia and situate the patient in the right lateral decubitus position.
4. Clean the skin with bactericidal solution and make an incision following the skin lines on the left lateral chest wall.
5. Use blunt dissection to expose the superficial surface of the lipoma using a hemostat to separate the layers of subcutaneous tissues that can moderately adhere to the surface of the lipoma.
6. With larger lesions, more extensive adhesions and subcutaneous fibers may prevent easy extrusion of the tumor.
7. After exposing the initial surface of the lipoma, the dissection continues, using both sharp and blunt dissection to liberate the lipoma from the connective tissue strands holding it to the chest wall.
8. Once the perimeter of the lipoma is fully palpable, use both sharp and manual dissection techniques to lift the lipoma off of the connective tissue overlying the rib cage.
9. After freeing the majority of the lipoma from the adhesions, extrude the mass out of the incision, then lift it to allow sharp dissection of the basal stalk connecting it to the rib cage.
10. Once this has been completed, inspect the wound for any active bleeding and cauterize the necessary vessels.
11. Irrigate and prepare the space for closure.
12. Prior to closing, inject Marcaine local anesthetic into the subcutaneous layer to provide anesthesia for several hours after the procedure.
13. There is significant reduction in pain with use of local anesthetic even in patients who are undergoing surgery with general anesthesia to reduce postoperative pain.
14. Place two deep sutures of 2-0 Vicryl to tack the subcutaneous layer to the connective tissue overlying the rib cage, closing the potential dead space.
15. After removal of a large tumor, place a Penrose drain to prevent accumulation of serous fluid within the potential dead space in the subcutaneous layer.
16. Then use a running subcuticular stitch to close the surface layer of skin and hold the Penrose drain in place.
17. Cover the wound with a sterile dressing and advise the patient to follow up in 48 hours.
18. At the follow-up visit, the patient should have minimal incisional pain, and you should remove the Penrose drain.

INDICATIONS
- Large, rapidly growing lipoma, where malignant degeneration is possible
- Lipomas in cosmetically sensitive areas that are visible
- Uncertain diagnosis of subcutaneous mass

CONTRAINDICATIONS
- Patient with numerous nonvisible lipomas
- Local infection at the site of planned excision
- Coagulation defect (medication related, congenital, or acquired)
- Nonexcisional treatment option available and not yet tried
- Patient unable to comply with wound care

F. INGROWN TOENAIL REMOVAL

Key Steps

1. Anesthetize with digital block.
2. Dissect nail.
3. Excise nail.
4. Ablate nail bed.

INSTRUCTIONS

1. Adequately anesthetize the toe with a digital block.
2. Then slip a single blade of the curved iris scissors between the nail and the nail plate along the ingrown area.
3. If the nail tightly adheres to the matrix, a small hemostat can help to separate these structures.
4. Feel a perceptible give when the tip of the scissors has passed the proximal edge of the nail.
5. Once this occurs, use a pair of straight mosquito hemostats to grasp the nail.
6. With firm pressure holding the nail to the nail plate, carefully roll out the affected edge to extract the ingrown portion of the nail out of its compartment.
7. Use bandage scissors to trim off the uplifted nail edge.
8. Take care to ensure that the entire portion of the nail segment to be removed has been excised down to the nail bed.
9. Phenol ablation is the most common method used to cauterize the nail bed to prevent or retard future growth of the unwanted portion of the nail.
10. Form a small plug of cotton by trimming the cotton from the tip of swab and soaking it with phenol.
11. Insert the plug into the opening left by the excised nail edge and push it into the nail bed to cauterize the area.
12. Once the nail bed has been cauterized, remove the plug.
13. Electrosurgical probes have been developed that can ablate the matrix with excellent cosmetic results.

INDICATIONS

- Onychocryptosis (ingrown nail)
- Onychomycosis (fungal infection of nail)
- Chronic, recurrent paronychia (inflammation of the nail fold)
- Onychogryposis (deformed curved nail)
- Symptomatic granulation overgrowth of nail fold, especially if recurrent
- Permanently deformed nails after trauma; nail matrix ablation is often performed at the same time

CONTRAINDICATIONS

- Noncooperative patient
- Unstable infection, may require pretreatment with antibiotics
- Marginal vascular status of digit; may require clarification prior to injection and surgery

CPT CODES

11730 Nail removal, partial or complete
11750 Permanent nail removal (matrixectomy), partial or complete

ICD-9 CODES

703.0 Ingrown toenail
110.1 Onychomycosis

6. EYES, EARS, NOSE, THROAT

A. NASOPHARYNGOSCOPY

Key Steps

1. Apply decongestant and inspect nares.
2. Apply topical anesthesia.
3. Insert into nasopharynx.
4. Inspect larynx.
5. Withdraw scope.

INSTRUCTIONS

1. The nasopharyngoscope allows the physician to visualize the upper airway precisely in patients who have upper airway complaints.
2. For right-hand-dominant persons, the base of the scope with the direction level is held in the right hand, allowing manipulation of the level by the thumb. The dial on the underside of the scope allows for upward and downward movement of the tip of the scope.
3. This movement, combined with rotation of the scope, allows for 360-degree viewing of the airway.
4. Apply a topical decongestant to allow the nares to open.
5. Inspect the nares to determine which side of the nose is the most patent to pass the nasopharyngoscope through for the examination.
6. Use the tripod technique to hold the nasopharyngoscope on the face while inserting into the nares to avoid any undue trauma.
7. Identify the nasal passage along the floor of the nose, where the scope should be passed to enter the nasopharynx.
8. To prepare for the scope insertion, spray the nares with a decongestant solution.
9. Then anesthetize the throat with a topical anesthetic, followed by application of the anesthetic into the selected side of the nose for scope passage.
10. First, spray the anterior aspect of the nares, then insert the spray tip perpendicular to the plane of the face along the floor of the nose.
11. As the patient holds his or her breath, apply the anesthetic to the deep aspect of the nose as the tip is withdrawn.
12. Now advance the nasopharyngoscope into the nares and along the floor of the nasal passage.
13. The initial structures that are encountered are the palatine tonsils.
14. Rotation of the tip of the scope with flexion laterally to approximately 90 degrees allows one to visualize the Eustachian tube openings and Rosenmüller's fossa.
15. After inspection of these surfaces, advance the scope down into the oropharynx.
16. The key structures of the oropharynx to inspect are the base of the tongue, the vallecula, and the posterior aspect of the tonsils.
17. Having a patient extend the tongue out of the mouth allows one to visualize the vallecula.
18. After inspecting the oropharynx, advance the scope into the hypopharynx, where one visualizes the laryngeal structures and vocal cords.
19. Here, inspect the true cords and false cords and the overlying soft tissue of the laryngeal cartilage.
20. Also inspect the pyriform sinuses on either side of the larynx.
21. The vocal cord movement and symmetry are important to document.
22. One can see clearly the movement of the arytenoid cartilage as the vocal cords are contracted.
23. On finishing the complete inspection, withdraw the scope in neutral position.

INDICATIONS

- Epistaxis
- Removal of foreign body
- Chronic rhinorrhea
- Chronic cough evaluation
- Dysphagia
- Chronic or recurrent sinusitis evaluation
- Snoring
- Dysphonia

CONTRAINDICATIONS

- Epiglottitis
- Profuse epistaxis

CPT CODES

31231 Nasopharyngoscopy

IDC-9 CODES

472.0 Rhinitis
473.9 Sinusitis, chronic

B. CERUMEN IMPACTION REMOVAL

Key Steps

1. Examine ear canal.
2. Select device for irrigation.
3. Irrigate until cerumen is released.
4. Conduct follow-up examination.

INSTRUCTIONS

1. To remove impacted cerumen, one can use a pulsating water device that allows for pressurized water flow to enter the ear canal.
2. Inject the water along the sidewall of the ear, gently forcing water around the impacted cerumen.
3. Within a few minutes, one can see small fragments of cerumen coming from the ear canal.
4. After several minutes of irrigation, the bulk of the cerumen plug is removed.
5. Other device options include a 20- to 30-ml syringe with a 16- to 20-gauge IV catheter attached to provide directed water flow into the ear canal.
6. Examine the ear after irrigation to ensure that adequate cerumen was removed.

INDICATIONS

- Cerumen impaction

CONTRAINDICATIONS

- Tympanic membrane perforation

CPT CODES

69210 Cerumen removal

ICD-9 CODES

380.4 Cerumen impaction

7. HAND/DIGIT

A. RING REMOVAL

Key Steps

1. Perform neurovascular examination.
2. Insert tape with hemostat.
3. Wind tape proximal to distal.
4. Do not compromise arterial supply.
5. Pull proximal edge to unwind.

INSTRUCTIONS

1. After careful neurovascular exam demonstrates intact sensation and arterial supply, lubricate the finger (Fig. AIV-3, *A*).
2. Carefully insert spooled suture, umbilical tape, or dental floss under the palmar aspect of the ring with a hemostat (Fig. AIV-3, *B*).
3. Secure the suture edge to the palm with an adhesive.
4. Proceed to wrap the suture firmly around the finger, starting immediately distal to the ring and moving distally.
5. Wrap the suture tightly enough to compress the edema without producing any arterial compromise (Fig. AIV-3, *C*).
6. After relubricating the finger and removing the suture, gently unwind the proximal edge of the suture by pulling distally and circumferentially (Fig. AIV-3, *D* and *E*).
7. After removing the ring, repeat the neurovascular exam.

INDICATIONS

- Distal finger injury with impending swelling of the finger
- Ring finger with signs of vascular compromise due to compression from the ring
- Ring made of conductive or magnetic metal in patient undergoing procedure in which such objects pose a threat to the patient or staff

CONTRAINDICATIONS

- Extensive bony injury or swelling where it is clear that cutting the ring is the only option

CPT CODES

20670 Superficial removal of constricting metal band
20680 Deep removal of constricting metal band

ICD-9 CODES

782.3 Traumatic edema

8. ORTHOPEDICS

A. ARTHROCENTESIS—KNEE ASPIRATION

Key Steps

1. Determine best access to effusion.
2. Cleanse skin.
3. Inject local anesthesia at insertion site.
4. Insert needle and aspirate.

INSTRUCTIONS

1. The patient is placed in the supine position.
2. The patient's knee is placed in extension (Fig. AIV-4, *A*).

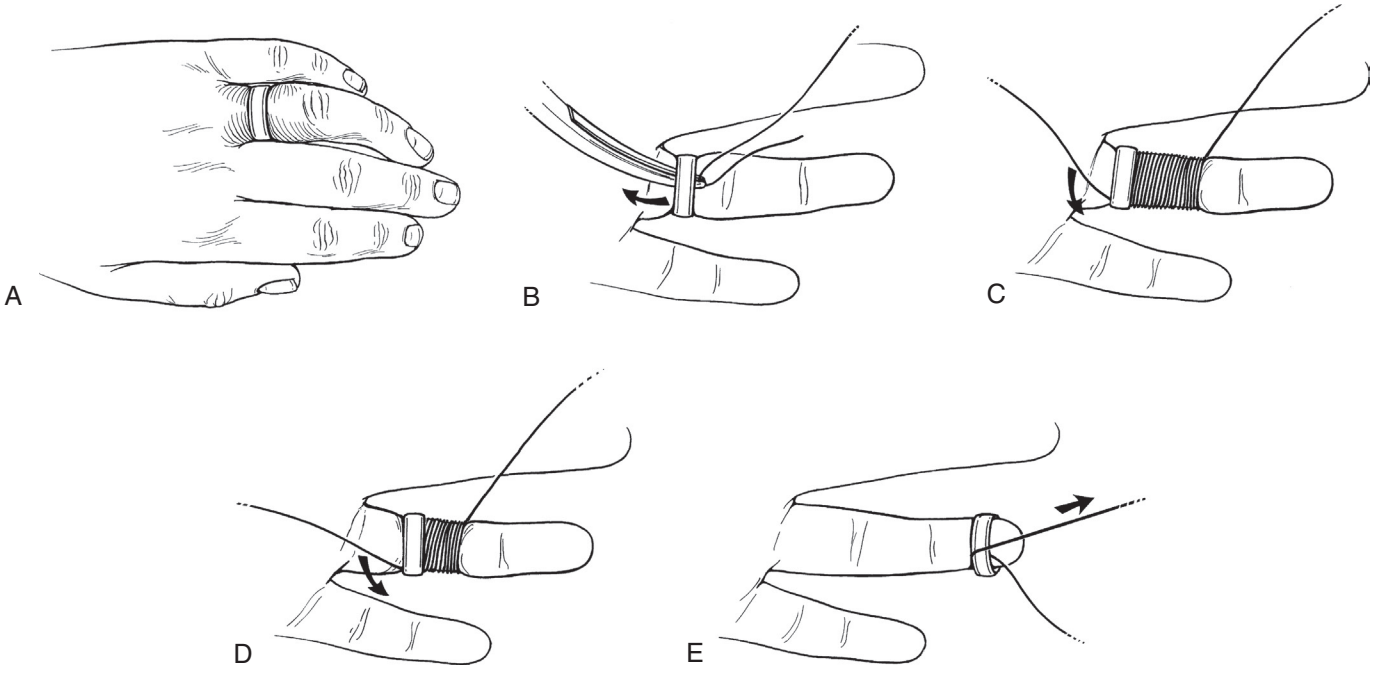


FIGURE AIV-3 Ring removal.

3. Carefully cleanse the skin with an antiseptic solution.
4. Identify the patella and palpate to determine the effusion size.
5. The ideal location to enter the synovial sac is in the upper outer quadrant of the knee joint space.
6. Local anesthetic injected along the planned trajectory of the arthrocentesis reduces the pain of passing the 18-gauge needle through the joint sac.
7. Pass the needle through the skin and into the palpable effusion.
8. Compress the medial aspect of the knee joint with the opposite hand to push the intraarticular fluid toward the needle and to stabilize the skin for penetration by the needle (Fig. AIV-4, *B*).
9. Once the fluid space is entered, obtain a sample for diagnostic purposes.
10. For tense effusions, withdrawing larger volumes of fluid—up to 50 ml at a time—can reduce pain and improve range of motion.
11. After obtaining the desired amount of fluid, withdraw the needle and cover the entry wound.

INDICATIONS
- Acute joint effusion
- Acute joint infection
- Joint pain secondary to large effusion (acute or chronic): therapeutic
- Gout

CONTRAINDICATIONS
- Local skin infection at the site of joint
- Local bursa infection overlying joint
- Coagulation defect (medication related, congenital, or acquired), relative
- Artificial joint
- Immunosuppressed patient with noninfected joint
- Sepsis or bacteremia not coming from the joint
- Unstable joint

CPT CODES
20610 Arthrocentesis of the knee

ICD-9 CODES
274.0 Gouty arthropathy
715.16 DJD knee
719.45 Knee pain

B. JOINT INJECTION—SHOULDER

Key Steps

1. Determine injection site.
2. Cleanse skin.
3. Withdraw joint fluid if effusion present.
4. Inject steroid and anesthetic solution.

INSTRUCTIONS
1. Cleanse the area over the acromion and upper deltoid to prepare for the injection.
2. Maintain sterility during the injection process.
3. Identify the space between the acromion and the humerus that is covered by the proximal deltoid attachments.
4. Inject local anesthetic in a wheal on the skin, then deeply along the planned injection path into the subacromial bursa.
5. Draw up 20 mg of methylprednisolone or its equivalent into a 3-ml syringe and mix with 1 to 2 ml of anesthetic solution.
6. Use a 25-gauge needle for injection of the steroid solution.
7. Insert the needle into the subacromial space.
8. Inject the entire volume of the syringe into the joint space.
9. Withdraw the needle and cover the site with a simple adhesive bandage.

INDICATIONS
- Tendinitis
- Bursitis
- Rheumatoid arthritis
- Osteoarthritis
- Gout and pseudogout
- Medical conditions with joint manifestations: inflammatory bowel disease, psoriasis, Reiter's syndrome (unless associated with human immunodeficiency virus [HIV]), and ankylosing spondylitis
- Ineffective anti-inflammatory drugs and analgesics

CONTRAINDICATIONS
- Acute trauma or fracture
- Metastatic cancer

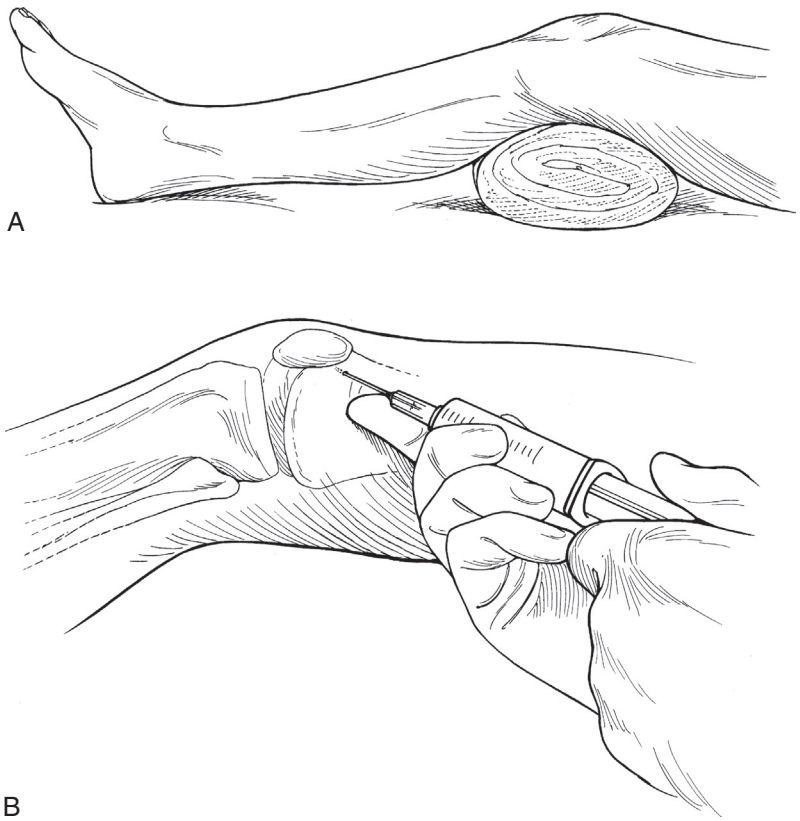


FIGURE AIV-4 Knee aspiration.

- Cellulitis over the injection site
- Septic periarticular bursa
- Suspected bacteremia unless the joint is the suspected source
- Broken skin over the injection point
- Primary coagulopathy
- Unstable joints (for steroid injection)
- Joint prosthesis
- Anticoagulant therapy
- Lack of response to two or three prior injections

CPT CODES
20610 Arthrocentesis of shoulder

ICD-9 CODES
274.0 Gouty arthritis
716.91 Arthropathy of shoulder
727.3 Bursitis, unspecified

C. JOINT INJECTION—KNEE

Key Steps

1. Determine injection site.
2. Cleanse skin.
3. Inject local anesthesia.
4. Inject steroid solution.

INSTRUCTIONS
1. Place the patient in the supine position and place the patient's knee in extension.
2. Carefully cleanse the skin over the upper outer quadrant with an antiseptic solution.
3. Identify the patella and determine the effusion size by palpation.
4. The ideal location to enter the synovial sac is in the upper lateral quadrant of the knee joint space, just above the patella.
5. Mix a solution of steroid, such as 40 mg of methylprednisolone, with bupivacaine to provide short-term anesthesia within the joint space.
6. Pass the needle through the skin and into the joint space.
7. With the opposite hand, compress the medial aspect of the knee joint to push the intraarticular fluid toward the needle.
8. Drain or partially drain any hemorrhagic effusion that is found.
9. After draining the fluid, inject the steroid solution.
10. Withdraw the needle and apply pressure to the site.
11. Cover the injection site with a simple bandage.

INDICATIONS
- To rule out septic arthritis
- To rule out crystal or rheumatoid arthritis
- Removal of excessive synovial fluid
- Diagnostic injection of analgesic
- Therapeutic injection of corticosteroid

CONTRAINDICATIONS
- Bleeding disorder or excessive anticoagulation
- Superficial infection or cellulitis

CPT CODES
20610 Injection of joint
May also charge for office visit

ICD-9 CODES
719.45 Knee pain

D. TRIGGER POINT INJECTION

Key Steps

1. Isolate trigger point by palpation.
2. Cleanse skin.
3. Inject trigger point area.
4. Local massage to disseminate injection.

INSTRUCTIONS
1. Easily inject painful trigger points with a combination of local anesthetics and steroids to obtain immediate and long-term pain relief.
2. Mix 1 ml of bupivacaine with 1.5 ml of lidocaine and the equivalent of 25 mg of hydrocortisone to make up a solution for this injection.
3. Precisely identify the trigger point.
4. Prep the skin with Betadine or alcohol. (First check for iodine allergy.)
5. Insert the needle into the palpable trigger point.
6. Inject the solution in 0.5-ml amounts spread over the region that encompasses the entire trigger point area.
7. After completing the injection, massage the solution into the surrounding soft tissue.
8. Obtain immediate feedback from the patient as the local anesthetic takes effect.

INDICATIONS
- Myofascial pain
- Tension headache due to cervical muscle strain
- Chronic neck or back pain due to trigger points
- Fibromyalgia

CONTRAINDICATIONS
- Infection at site of trigger point
- Bleeding disorder
- Allergy to any component of injection

CPT CODES
20522 Inject trigger point, one or two sites
20553 Inject trigger points, more than two sites

ICD-9 CODES
729.1 Fibromyalgia

E. LATERAL EPICONDYLE INJECTION

Key Steps

1. Identify focal tenderness over epicondyle.
2. Cleanse skin with antiseptic.
3. Inject steroid/anesthetic solution.
4. Massage injection site.

INSTRUCTIONS
1. Place the elbow in flexion and palpate the focally tender area over the lateral epicondyle.
2. Site of maximal inflammation should be at the proximal attachment of the extensor tendons of the forearm.
3. Cleanse the skin over the epicondyle with an antiseptic solution, maintaining sterility of the injection site.
4. The injection should contain 10 mg of triamcinolone acetate or its equivalent, with 0.5 ml of lidocaine and 0.5 ml of bupivacaine.
5. Insert the needle down to the bony surface of the epicondyle, then withdraw it back 1 to 2 mm.
6. Inject the solution into the area of maximal tenderness and reposition the needle slightly in all directions around this area to distribute the medication into a 1.5- to-2-cm diameter area.
7. Withdraw the needle and massage the area.
8. Cover the site with an adhesive bandage if there is bleeding from the injection.

INDICATIONS
- Lateral epicondylitis

CONTRAINDICATIONS
- Infection of skin over epicondyle

CPT CODES
20605 Infection of joint
May also charge for office visit

ICD-9 CODES
726.32 Lateral epicondylitis

9. GASTROENTEROLOGY

A. ANOSCOPY

Key Steps

1. Inspect anus.
2. Insert anoscope.
3. Remove obturator.
4. Inspect anorectal mucosa while withdrawing scope.
5. Rotate 90 degrees, reinsert, and inspect.

INSTRUCTIONS

1. The patient is placed in a lateral decubitus position with knees flexed upward toward the chest (Fig. AIV-5, *A*).
2. Hold the buttocks apart.
3. Perform a digital exam, allowing for palpation of the anal canal to check for tone, masses, or areas of unusual pain.
4. Lubricate the anoscope with its central guide plug, then slowly insert it past the anal sphincters (Fig. AIV-5, *B*).
5. Once the scope is inserted completely, remove the central guide plug for inspection of the distal rectum and the anus (Fig. AIV-5, *C* and *D*).
6. Slowly rotate the scope as it is withdrawn to maximize viewing of the mucosa above and below the pectinate line.
7. The operator should be evaluating the mucosa for the presence of mass lesions or hemorrhoids that may be within view (Fig. AIV-5, *E*).
8. Masses or polyps that are visible through the scope can be biopsied using a small biopsy forceps.

INDICATIONS

- Suspected anorectal malignancy
- Rectal bleeding
- Hemorrhoid evaluation
- Perianal condyloma
- Anal trauma or foreign body, including sexual assault
- Rectal prolapse
- Anorectal pain

CONTRAINDICATIONS

- Anal canal stenosis or congenital imperforate anus
- Acute cardiorespiratory compromise

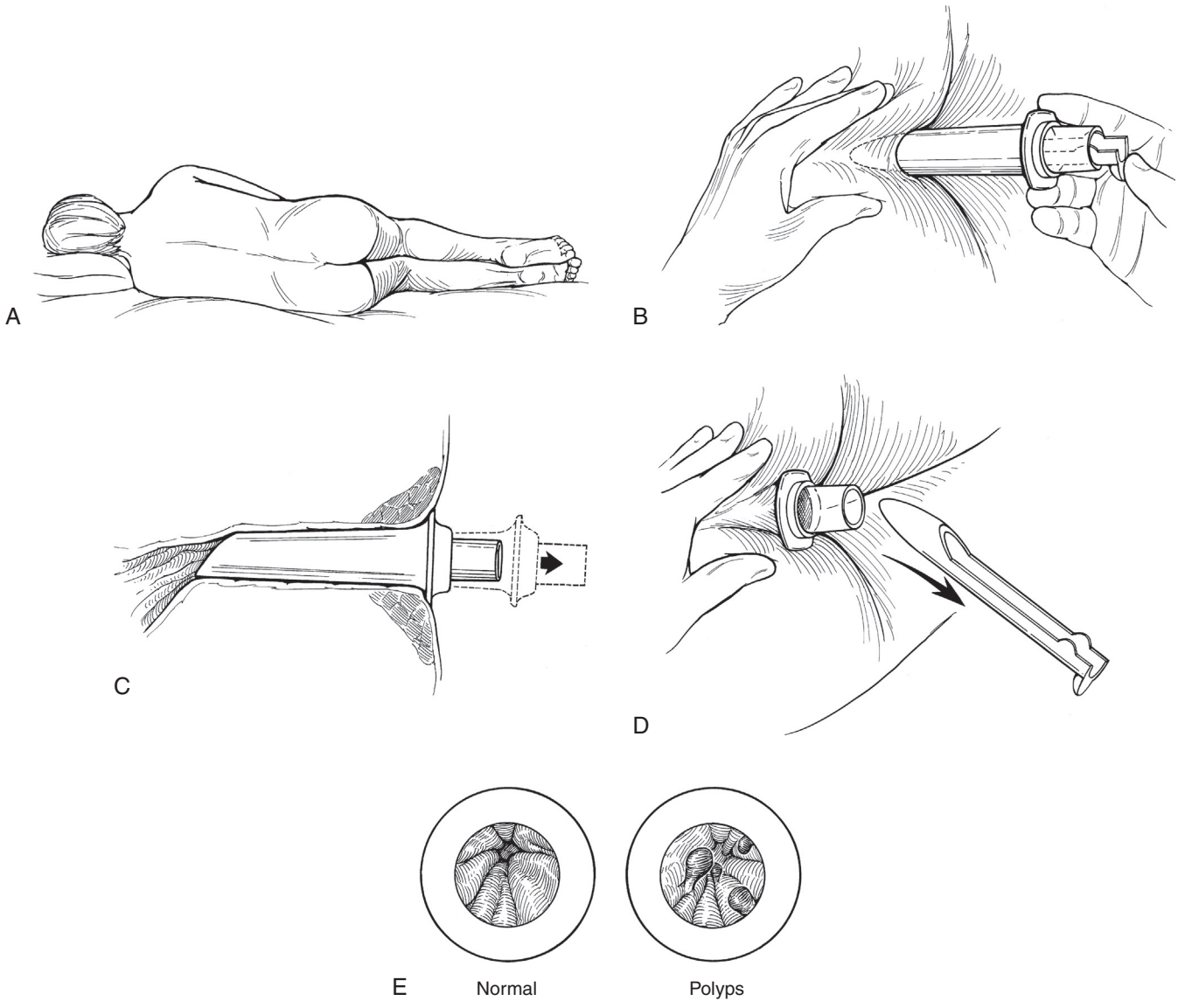


FIGURE AIV-5 Anoscopy.

CPT CODES
46600 Diagnostic
46606 Biopsy, single or multiple
46900 Destruction of lesion (e.g., condylomata), chemical
46910 Destruction of lesions, electrodesiccation

ICD-9 CODES
455.0 Internal hemorrhoids
455.2 Internal hemorrhoids, bleeding
455.3 External hemorrhoid
565.0 Anal fissure
569.0 Anal polyp
698.0 Pruritus ani

B. FLEXIBLE SIGMOIDOSCOPY

Key Steps

1. Insert scope.
2. Advance up the sigmoid.
3. Inspect colon while exiting.
4. Examine rectal vault.

INSTRUCTIONS
1. Anoscopy should be performed in all cases in which palpable abnormality is identified.
2. Place the patient in a left lateral position with knees flexed upward toward the chest.
3. Initial digital rectal examination assists in identifying anal fissures, polyps, and lesions, as well as allowing for initial application of lubricant.
4. Perform anoscopy in all cases in which palpable abnormality is identified.
5. Initially advance the scope at an acute angle with the index finger placed behind the advancing tip.
6. As the anal canal is entered, gently rotate the scope in line with the anal canal as the scope advances into the rectum.
7. Once the scope is inserted approximately 15 cm, insert air to see the rectal vault and find the opening to the lower sigmoid.
8. Easily advance the scope up to the most distal turn of the sigmoid.
9. After passing around the first curve, the operator may need to use one of several techniques to encourage the straightening of the colon around the scope.
10. Once the sigmoid has been traversed, enter the descending colon.
11. Here, the colon has a recognizable abundance of rounded haustra.
12. Once maximal insertion is achieved, slowly withdraw the scope and inspect the colon walls, using the 360-degree view technique, gradually rotating the scope.
13. Take care to inspect behind sharp turns in the sigmoid and behind rectal valves.
14. Once the rectum has been inspected, perform retroflexion to view the inside of the anus and lower rectum from above.
15. Insert the scope to approximately 15 cm and fully rotate the dials to a near maximal rotation to allow the scope to be fully retroflexed.
16. When completed, simple rotation of the shaft of the scope on its axis allows for inspection of the rectum and anus.

INDICATIONS
- Rectal bleeding of any type
- Screening for colorectal cancer
- Persons 50 years of age and older, regardless of symptoms
- Unexplained anemia
- Persistent abdominal pain
- Alteration in bowel habits, constipation (particularly unexplained new onset), diarrhea, altered stool diameter
- Unexplained weight loss, fever
- Follow-up of treatment regimens (e.g., for ulcerative colitis, irritable bowel disease)

For the following conditions, colonoscopy may be preferred as first choice to examine the entire colon in patients with higher risk:
- Follow-up for history of polyps or cancer
- Any person with a high-degree risk factor for cancer or other disease in the colon
- Hemoccult-positive stools (positive occult blood)
- Weight loss
- High suspicion of cancer

CPT CODES
45330 Sigmoidoscopy, flexible fiberoptic, diagnostic
45331 Sigmoidoscopy with biopsy
45336 Sigmoidoscopy with ablation of tumor or mucosal lesion

ICD-9 CODES
558.9 Colitis, nonspecific
564.0 Unspecified constipation
564.1 Irritable colon
569.3 Anal hemorrhage
578.1 Melena
789.0 Abdominal pain
V16.0 Family history of colon cancer

C. INTERNAL HEMORRHOID BANDING

Key Steps

1. Prepare banding tool.
2. Perform anorectal inspection.
3. Grasp hemorrhoid with forceps.
4. Release band at base of hemorrhoid.

INSTRUCTIONS
1. Prior to initiation of the banding procedure, prepare the instruments and load the rubber band on the banding forceps.
2. First, place the conical attachment on the banding forceps, slide the rubber band down, and gradually expand it until it fits around the ring portion of the banding forceps.
3. Then adjust the rubber band to the distal edge of the banding forceps so that only a small closure of the forceps will allow the release of the band.
4. Place the patient in a decubitus position, with knees flexed upward toward the chest.
5. Locate the anoscope and insert it into the rectal vault.
6. Prior to banding, ascertain that the hemorrhoid is anesthetized and truly is an internal hemorrhoid.
7. In most instances, identify internal hemorrhoids by their origin proximal to the dentate (or pectinate) line and the fact that they are not sensitive to simple grasping.
8. Insert the grasping forceps through the banding forceps and use it to grasp the body of the hemorrhoid to band.
9. Grasp the hemorrhoid and advance the banding forceps forward.
10. While squeezing the handle, release the rubber band around the proximal end of the hemorrhoid tissue.
11. Painless necrosis of the hemorrhoid will occur within 2 to 3 days, allowing the sloughed tissue to pass in the stool.

INDICATIONS
- Symptomatic internal hemorrhoids not responsive to conservative therapy

CONTRAINDICATIONS
- Coagulopathy
- Anal infection
- Anal fissure
- Anal tumor
- Pregnancy

CPT CODES
46221 Hemorrhoidectomy by simple ligature, banding

ICD-9 CODES
455.0 Internal hemorrhoids

D. EXTERNAL HEMORRHOID EXCISION

Key Steps

1. Cleanse perianal area.
2. Inject anesthesia.
3. Isolate hemorrhoidal tissue.
4. Excise hemorrhoid.

INSTRUCTIONS

1. The ideal position for anal surgery is to position the patient on the Ritter table with hip and knees flexed in the "bottoms up" position (Fig. AIV-6, *A* and *B*).
2. An acceptable alternative is to place the patient in a left lateral position with knees flexed upward toward the chest and with the buttocks held open by an assistant.
3. Clean the anal area with Betadine solution. (First check for iodine allergy.)
4. With an acutely thrombosed hemorrhoid, marked tenderness to palpation is common (Fig. AIV-6, *C*).
5. In this case of a chronic recurrent hemorrhoid, the hemorrhoid is nontender; however, the excision technique is the same.
6. Local anesthetic consisting of a combination of lidocaine and bupivacaine provides longer anesthesia and is used to provide a local block (Fig. AIV-6, *D*).
7. Prior application of topical 20% benzocaine solution can diminish injection site pain.

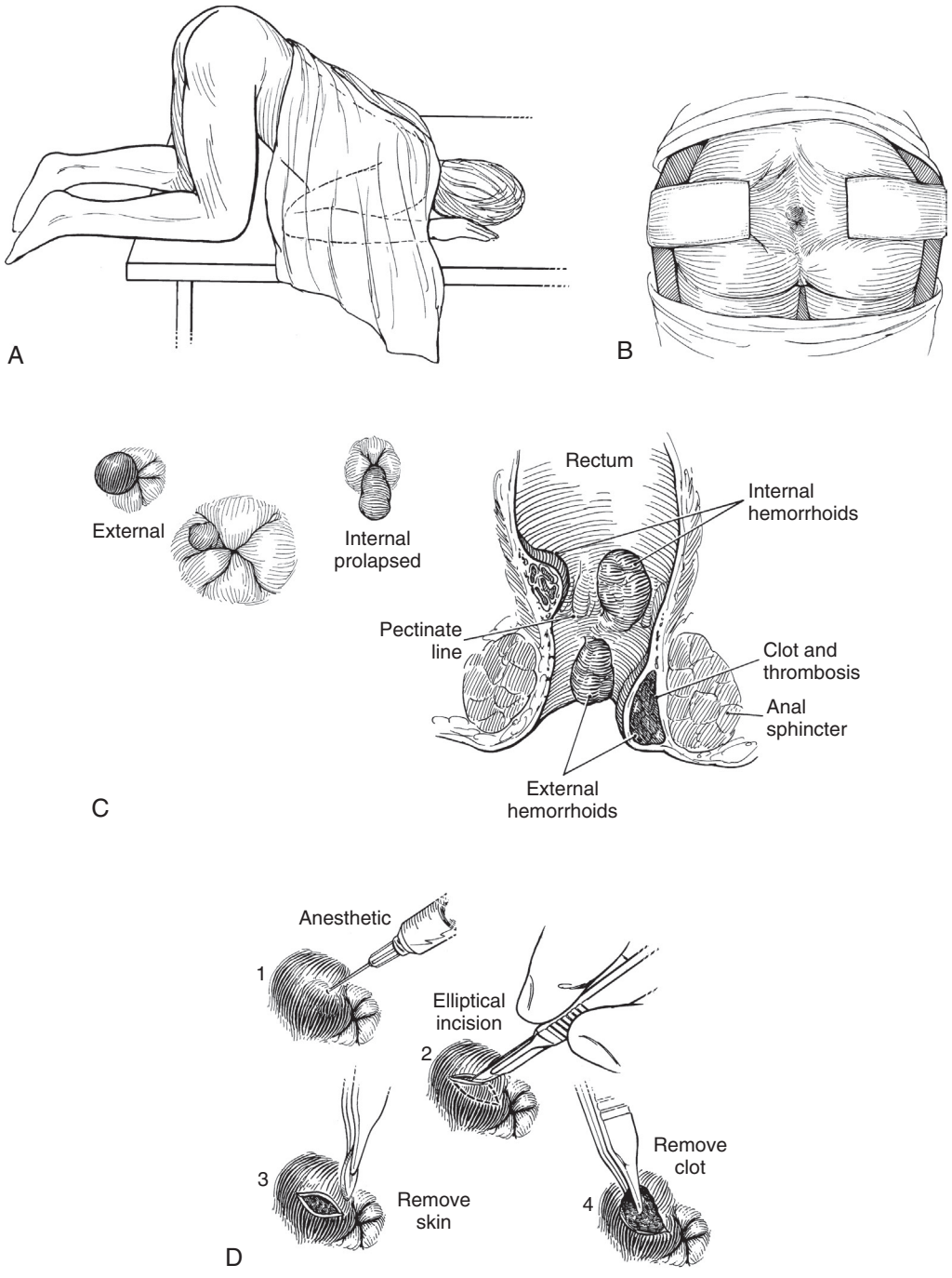


FIGURE AIV-6 External hemorrhoid excision.

8. Inject the hemorrhoid around all aspects of its base to ensure complete anesthesia.
9. Injecting the hemorrhoid itself is not necessary if the base is anesthetized.
10. A single, deep injection is also necessary for acute hemorrhoid to allow for extraction of clot within the lesion.
11. Once anesthesia is complete and has been allowed to take effect, test the hemorrhoid for sensation.
12. Once the hemorrhoid is anesthetized, clamp and stabilize it with hemostats and excise the hemorrhoid across the base of the lesion.
13. If there are any visible clots, extract them from the hemorrhoid using the hemostats.
14. Usually, there is minimal bleeding in the wound, which can be left open and allowed to drain while it is healing.
15. Persistent bleeding may require application of Surgicel or Monsel's solution.
16. Proper cleansing of the area postoperatively is important to ensure minimal likelihood of infection.

INDICATIONS
- Pain, itching, and burning of thrombosed hemorrhoids
- Poor hygiene and/or difficult stooling secondary to pain
- Failure to respond to local therapy such as sitz baths and topicals

CONTRAINDICATIONS
- Poorly characterized bleeding disorder

CPT CODES
46083 Incision and drainage of thrombosed hemorrhoids

ICD-9 CODES
455.3 External hemorrhoids
455.2.1 External hemorrhoids thrombosed

E. NASOGASTRIC INTUBATION

Key Steps

1. Determine widest nares for insertion.
2. Apply topical anesthetic in nares and throat.
3. Insert tube.
4. Check placement tube.

INSTRUCTIONS
1. Place the patient in a sitting position with the head angled forward in a sniffing posture.
2. Apply topical anesthetic either by spray or gel into the nares selected for insertion.
3. Anesthetizing the back of the throat can also reduce the risk of vomiting during nasogastric (NG) tube insertion.
4. Insert the NG tube along the floor of the nose gently and down the nasopharynx.
5. As the tube approaches the larynx and upper esophagus, the patient should tilt his or her head slightly downward to encourage the tube to pass posteriorly into the esophagus.
6. Advance the tube to the stomach.
7. Test and confirm the tube position by aspiration of gastric contents, which should have a pH of less than 6.
8. If the patient is unconscious or sedated, perform a confirmatory x-ray.
9. If feeding is planned through the tube, confirm its position by x-ray in all patients.

INDICATIONS
- Relief of upper gastrointestinal obstruction
- Drainage of gastric contents, bowel rest
- Need for tube-delivered nutrition, dye, or medications

CONTRAINDICATIONS
- Facial fractures involving the nose, maxilla, basal bones of the skull, or suspected cervical spine fracture
- Unprotected airway in nonresponsive patient
- Penetrating wound of the neck or chest
- Nasal obstruction
- Esophageal obstruction or anomaly
- Sepsis or bacteremia not coming from the joint
- Placement of percutaneous endoscopic gastrostomy tube would be more appropriate

CPT CODES
43752 Nasogastric or orogastric tube placement necessitating physician's skill
89130 Gastric intubation and aspiration, diagnostic
91105 Gastric intubation and aspiration, therapeutic

ICD-9 CODES
536.2 Vomiting, persistent
537.0 Gastric outlet obstruction
560.1 Ileus, paralytic
561.81 Small bowel obstruction, adhesions
578.0 Hematemesis
578.1 Hematochezia
578.9 GI bleeding, unspecified
787.01 Vomiting, NOS with nausea
977.9 Poisoning, unspecified

10. GYNECOLOGY

A. PAP SMEAR

Key Steps

1. Inspect external genitalia.
2. Insert speculum.
3. Obtain spatula and brush samples.
4. Liquid-based Pap smear sampling.

INSTRUCTIONS
1. Inspect the external genitalia for lesions, then carefully insert the speculum.
2. Advising the patient to relax the perineal musculature can make insertion much less uncomfortable.
3. Clearly visualize the cervix.
4. Perform the Pap smear in several ways.
5. Using a Pap spatula, place the tip of the spatula within the os, and rotate the spatula several times to collect cells on one face.
6. When spreading the spatula over a slide, one must take care that the side that is laden with cells is spread over the glass surface.
7. The cervical brush obtains excellent endocervical samples. It can be used alone, but use it most often in conjunction with the spatula.
8. Commonly use the broom-shaped Pap device with the wet prep and human papillomavirus (HPV) sampling.
9. Place the point of the broom within the os and rotate the brush five times to obtain the sample.
10. Remove the tip of the brush and place it within the wet prep container.
11. Send this sample for both cytology and HPV typing as indicated.

INDICATIONS
- Women aged 21 to 65 years old
- Women who are HIV positive
- Immunocompromised women
- During prenatal care workup

CONTRAINDICATIONS
- Active vaginal, cervical, or uterine infection

RELATIVE CONTRAINDICATION
- Blood contamination, especially if heavy

CPT CODES
87621 HPV sampling—Wet prep Pap
99201-99215 Pap smear and endocervical culture

ICD-9 CODES
795.00 Abnormal Pap

V25.9 Contraceptive management
V70.0 Well adult exam
V72.31 Gynecologic screening exam
V72.32 Follow up abnormal Pap
V13.29 Personal history other genital system and obstetric disorders

B. BARTHOLIN'S MARSUPIALIZATION

Key Steps

1. Determine incision site and anesthetize.
2. Make incision and remove cyst roof.
3. Identify layers for closure.
4. Suture with circumferential stitches.
5. Complete marsupialization.

INSTRUCTIONS

1. The patient is placed in the lithotomy position, and the perineum is washed with antiseptic solution.
2. Palpate the cyst manually to clearly identify its size and location.
3. Outline the incision with a surgical marker at the junction of the vaginal sidewall and labia minora.
4. The incision should be a 2- to 3-cm ellipse whose long axis follows the internal axis of the vaginal sidewall, not involving the external labial skin.
5. Use a No. 15 blade scalpel to create the ellipse to be excised.
6. Enter the vaginal mucosa followed by careful incision through the fascia overlying the cyst.
7. Several layers of fascia and vaginal wall smooth muscles are divided in this process.
8. Open these layers sharply until the cyst wall is entered and drainage occurs.
9. Once the cyst is entered and drained, excise fully the ellipse of tissue, effectively removing the roof of the cyst adjacent to the vaginal sidewall.
10. What remains is the smooth cyst cavity with its distinct edge that must be clearly identified before beginning closure.
11. Use a 3-0 Dexon or Vicryl suture to marsupialize the cyst.
12. Place the initial stitch by passing the needle through the mucosa and then passing through the cyst wall from the submucosal side to open the remaining portion of the cyst.
13. Run the suture continuously around the margin of the incision in small 2- to 3-mm bites.
14. Each stitch must take the vaginal mucosa and cyst wall together.
15. Once the last stitch is placed, overlapping the initial anchoring stitch, tie the suture securely.
16. At the completion of the procedure, one can see that the cyst wall is clearly opened and retracted by the circumferential stitches.
17. Immediately postop, the appearance is that of a small cleft on the side where the surgery was performed.
18. After several days, the repair is barely noticeable as the vaginal wall further contracts.

INDICATIONS

- Failed Word catheter treatment in the acute setting
- Recurrent infections or reaccumulation of Bartholin's gland cyst fluid

CONTRAINDICATIONS

- Cysts that could be adequately treated with a Word catheter
- Coagulation defect (medication related, congenital, or acquired) that is uncorrected
- Patient who is unable to comply with wound care

CPT CODES

56440 Bartholin's gland cyst marsupialization

ICD-9 CODES

616.2 Bartholin's cyst
616.3 Bartholin's abscess

C. BARTHOLIN'S CYST WORD CATHETER PLACEMENT

Key Steps

1. Inject local anesthesia.
2. Make incision into abscess.
3. Place catheter.
4. Inflate balloon.

INSTRUCTIONS

1. Place the patient in the lithotomy position and wash the perineum with antiseptic solution.
2. Manually palpate the Bartholin's abscess to clearly identify its size and location (Fig. AIV-7, *A*).
3. Identify the incision site at the junction of the vaginal mucosa and the labia minora.
4. Inject local anesthetic of 1% to 2% lidocaine at the incision site.
5. Anesthetize both the skin and deeper fascia overlying the abscess.
6. Test the Word catheter to ensure that it will function properly.
7. Inject 2 to 3 ml of saline into the catheter port, fill, and inspect the balloon.
8. Withdraw the fluid from the catheter prior to insertion.
9. Leave the needle in the catheter port to use promptly after inserting the catheter into the abscess.
10. Use a No. 15 blade scalpel to incise the wall overlying the abscess; spontaneous drainage of the abscess will occur (Fig. AIV-7, *B*).
11. After expressing and draining the entire abscess, insert the Word catheter through the opening (Fig. AIV-7, *C*).
12. Take care to insert the tip of the catheter fully into the Bartholin's cyst cavity, not just within the fascia space overlying the cyst.
13. Once the tip is in the infected cyst cavity, inflate the balloon with 3 ml of saline and withdraw the needle from the injection port (Fig. AIV-7, *D*).
14. Apply pressure to the syringe to avoid loss of fluid from the catheter.
15. Once the insertion is complete, inspect the area for bleeding.
16. Provide the patient with a perineal pad to collect any further drainage that may occur after the procedure.
17. Recommend postoperative follow-up in 2 to 3 days to ensure that the catheter placement is appropriate and that the abscess continues to drain.
18. Leave the catheter in place for 4 to 6 weeks to induce epithelialization of the cyst and drainage track, preventing further abscess formation.

INDICATIONS

- Acute infections
- Pain from cyst enlargement
- Obstructive Bartholin's gland cyst affecting the patient's sexual activity or obstructing the vaginal orifice

CONTRAINDICATIONS

- Cysts that should be treated by marsupialization
- Coagulation defect (either medication related, congenital, or acquired) that is uncorrected

CPT CODES

56420 I&D of Bartholin's gland cyst

ICD-9 CODES

616.2 Bartholin's cyst
616.3 Bartholin's abscess

D. VULVAR BIOPSY

Key Steps

1. Evaluate visible lesions.
2. Cleanse skin with antiseptic.
3. Infiltrate with local anesthesia.
4. Biopsy selected area.
5. Perform closure and hemostasis.

INSTRUCTIONS

1. Clean the vulva with Betadine solution. (First check for iodine allergy.)
2. Inject local anesthetic underneath the biopsy site, allowing it to elevate and provide an ideal platform for a punch biopsy.
3. Select a suitably sized punch biopsy to yield a sample through the dermal layer.
4. Excise the core of the punch biopsy using iris scissors and small Adson's forceps.
5. If bleeding is minimal, simple application of Monsel's solution provides adequate hemostasis.
6. If bleeding persists, use a single suture of 5-0 chromic or other absorbable suture.
7. Submit all samples for pathology.

INDICATIONS

- Any unidentifiable or concerning lesion
- Lesion that does not respond to conventional therapy
- Pigmented lesions
- Atypical nevi
- Vulvar ulceration of uncertain etiology
- Leukoplakia
- Acetowhite epithelium
- Vulvodynia with acetowhite epithelium (tissue that turns white after the application of vinegar)
- Presumed condylomata that are not responding to conventional therapy (following two treatment attempts of any kind)
- Postmenopausal woman with atrophic vaginitis that does not respond to estrogen therapy and no other cause is evident
- Any skin abnormality requiring definitive diagnosis

CONTRAINDICATIONS

- Poorly controlled infection over biopsy site (treat then biopsy)
- Caution with large excisional biopsies with anticoagulation

CPT CODES

56605 Biopsy of vulva
56606 Biopsy of vulva more than one lesion
56820 Colposcopy of vulva
56501 Lesion destruction of vulva

ICD-9 CODES

624.9 Unspecified noninflammatory disorder of vulva and perineum
078.11 Condyloma acuminatum
221.2 Benign vulvar neoplasm
624.8 Vulvar dysplasia

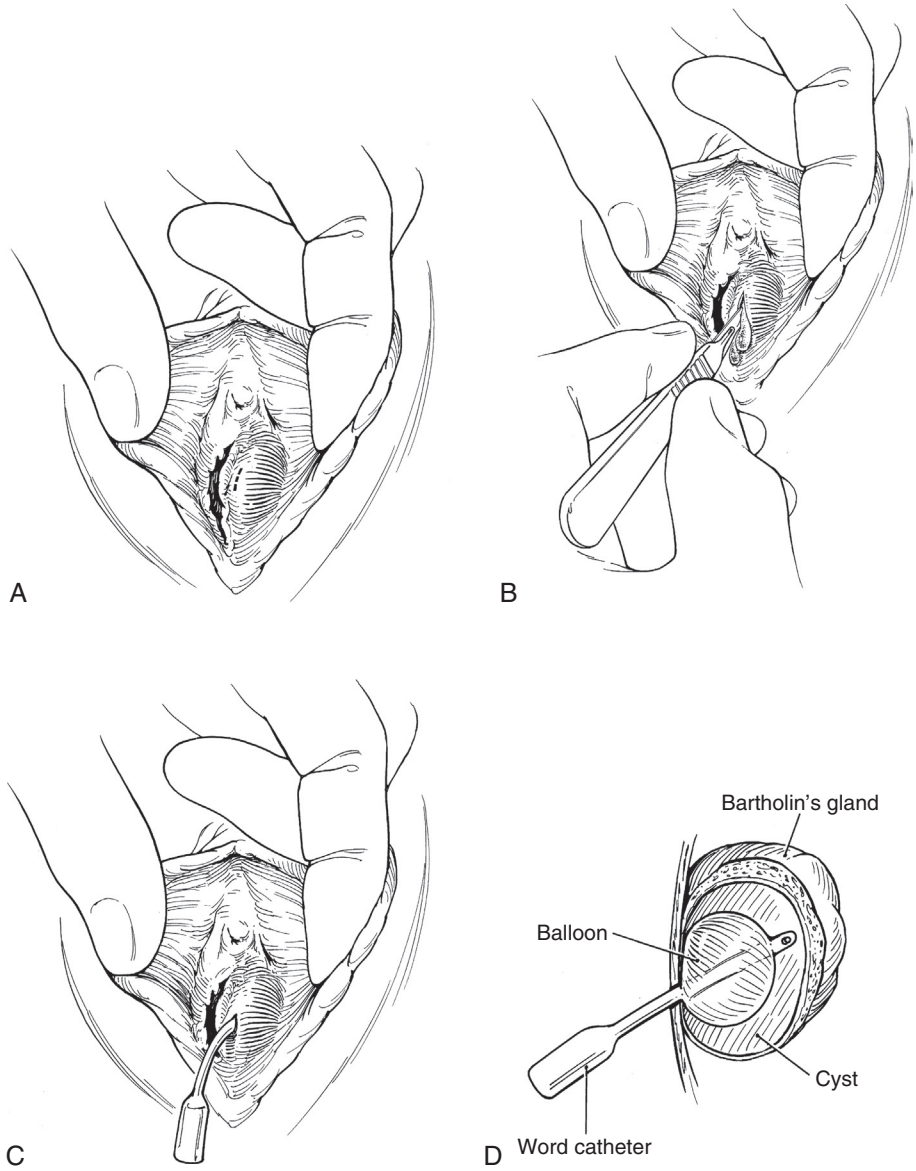


FIGURE AIV-7 Bartholin's cyst Word catheter placement.

11. INPATIENT MEDICINE

A. LUMBAR PUNCTURE

Key Steps

1. Identify landmarks.
2. Inject local anesthetic at insertion site.
3. Insert spinal needle into cerebrospinal fluid space.
4. Collect cerebrospinal fluid.
5. Remove spinal needle.

INSTRUCTIONS

1. Place the patient in the flexed lateral decubitus position (Fig. AIV-8, *A*). Upright position is also acceptable (Fig. AIV-8, *B*).
2. Cleanse the skin with antiseptic solution.
3. The iliac crest serves as the landmark that marks the interspace between the third and fourth lumbar vertebrae (Fig. AIV-8, *C*).
4. Place a fenestrated drape over this space after it is marked.
5. Anesthetize the skin and deep connective tissue with 1% lidocaine.
6. Insert a 21-gauge spinal needle through the interosseous ligament into the intervertebral space.
7. Advance the needle toward the umbilicus between the L3 and L4 vertebrae, checking periodically if the physician senses that the needle may have entered the dural space (Fig. AIV-8, *D*).
8. Usually a "pop" is felt on entering the spinal canal.
9. Once the canal is entered, remove the obturator and allow the spinal fluid to flow out into the collection tube.
10. Normally, collect three or four tubes with 1 to 3 ml of fluid each and label them sequentially for cerebrospinal fluid (CSF) studies.
11. After the collection of fluid is complete, replace the obturator and remove the needle.
12. Place an adhesive bandage over the puncture site.

INDICATIONS

- Suspected meningitis or cerebral infection
- Evaluation of CSF or pressures for diagnostic purposes (Guillain-Barré syndrome, lupus, multiple sclerosis, pseudotumor cerebri, suspected central nervous system malignancy)
- Intrathecal or spinal anesthetic
- Imaging procedures where dye infusion into the CSF is necessary

CONTRAINDICATIONS

- Local infection at the site of lumbar puncture
- Coagulation defect (medication related, congenital, or acquired), relative
- Suspected increased intracranial pressure
- Suspected brainstem herniation

CPT CODES

62270 Spinal puncture, diagnostic
62272 Spinal puncture, therapeutic for drainage of CSF

ICD-9 CODES

322.9 Suspected meningitis
340.00 Multiple sclerosis
348.2 Pseudotumor cerebri
357.0 Guillain-Barré syndrome
710.0 Systemic lupus erythematosus
852.00 Subarachnoid hemorrhage

B. SUBCLAVIAN LINES

Key Steps

1. Identify landmarks.
2. Inject local anesthesia at insertion site.
3. Insert trocar and place wire.
4. Exchange trocar for dilator and catheter over wire.
5. Suture catheter to skin.

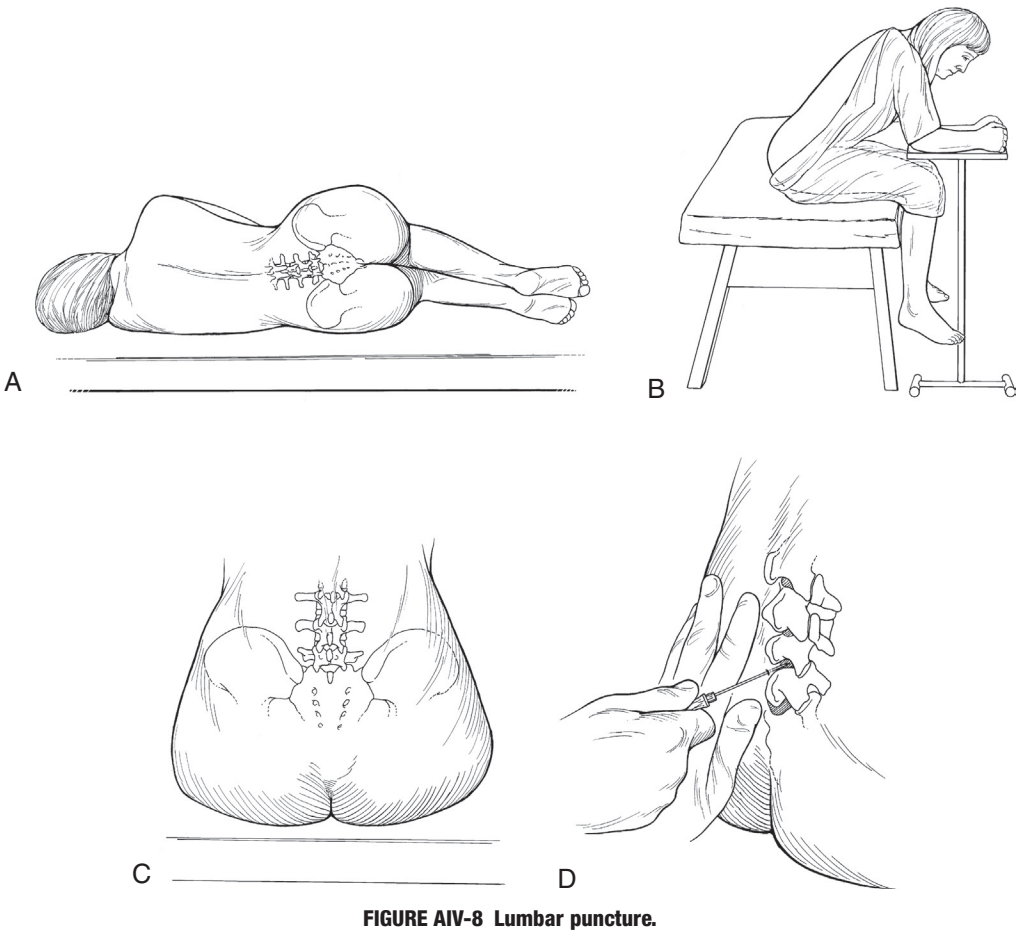


FIGURE AIV-8 Lumbar puncture.

INSTRUCTIONS

1. Place the patient in Trendelenburg's position at about 15 degrees and clean, shave, and drape the skin over the midclavicular region.
2. Identify the key landmarks of the midclavicle and the suprasternal notch by palpation.
3. Inject local anesthetic along the planned trajectory of the catheter insertion (Fig. AIV-9, *A*), notably anesthetizing the periosteum of the clavicle to avoid pain as the insertion needle passes underneath the clavicle.
4. Insert the introducer trocar at the midclavicular line and pass it under the clavicle, keeping its tip aiming toward the sternal notch (Fig. AIV-9, *B*).
5. Retract the syringe plunger to create negative pressure so that when the subclavian vein is entered, a flash is seen in the syringe.
6. Once this occurs, insert the wire through the trocar (Fig. AIV-9, *C*), taking care to use the thumb to prevent any air intake into the trocar during transfers.
7. At no time should the operator let go of the wire while it is in the patient (Fig. AIV-9, *D*).
8. Insert the wire at least 20 cm.
9. Remove the insertion trocar and incise the skin with a No. 11 blade to allow the dilator to pass easily (Fig. AIV-9, *E*).
10. Pass the catheter and dilator over the wire (Fig. AIV-9, *F*).
11. As soon as the wire is visible at the distal end of the catheter, release one hand from the wire proximally and grasp the wire at the distal end.
12. Fully insert the catheter before withdrawing the wire (Fig. AIV-9, *G*).
13. Then remove the dilator and test the catheter before securing it to the patient's skin with suture (Fig. AIV-9, *H*).
14. Proper venous flow through the catheter suggests proper placement of the catheter.
15. Connect the catheter hub to an IV set (Fig. AIV-9, *I*) and obtain a chest x-ray to confirm placement and ensure that a pneumothorax has not occurred due to catheter insertion.

INDICATIONS

- Central venous access for fluid resuscitation, hyperalimentation, or delivery of medications in intensive-care situations
- Delivery of medications that may cause sclerosis of smaller veins or necrosis of tissue if leaked from a peripheral vein
- Vascular access for plasmapheresis, dialysis, pacemakers, or Swan-Ganz catheter placement
- Vascular access for pulmonary or cardiac catheterization

CONTRAINDICATIONS

- Chest injury where a pneumothorax on the side of the line placement would compromise patient's survival
- Coagulation defect (medication related, congenital, or acquired)
- Chest wall deformity or defect, congenital or acquired
- Infection or burn of the chest wall where the line would be placed

CPT CODES

36010 Introduction of catheter, superior or inferior vena cava
36011 Selective catheter placement, venous system, first-order branch, e.g., jugular vein

ICD-9 CODES

276.5 Dehydration
785.5 Shock, unspecified
785.59 Shock (hypovolemic, septic)

C. THORACENTESIS

Key Steps

1. Determine level of effusion.
2. Inject local anesthesia at insertion site.
3. Insert trocar and catheter.
4. Remove catheter.

INSTRUCTIONS

1. Prior to performing a thoracentesis, the operator must determine the level of pleural fluid with the patient sitting in the upright position (Fig. AIV-10, *A*).
2. This can be done with percussion of the chest, egophony, or imaging studies.
3. Select an entry site just superior to a rib, along the posterior midclavicular line.
4. Clean the skin with an antiseptic solution and place a sterile drape over the area.
5. Draw up local anesthetic into a syringe using a 23-gauge, 1.5-inch needle to inject the anesthetic.
6. After creating a superficial wheal, pass the needle deep into the intercostal muscle, where 1 ml is injected.
7. Advance the needle 1 cm at a time, injecting 1 ml of anesthetic each time to anesthetize the deep layers superficial to the pleura.
8. Apply negative pressure to the syringe while advancing it.
9. A palpable "pop" can be felt when penetrating the tough, fibrous pleura.
10. Inject 2 ml of anesthetic into the pleural space and then withdraw the needle only slightly to infuse 1 ml more of anesthetic at the pleura.
11. This technique provides superb anesthesia.
12. Carefully insert the trocar just above the rib where the anesthesia has been placed.
13. Apply negative pressure to the syringe so that it is obvious when the pleural space is entered (Fig. AIV-10, *B*).
14. Advance the catheter and then withdraw the trocar, leaving the catheter in the pleural space to collect fluid.
15. The catheter is never withdrawn through the trocar as long as either device is in the patient.
16. Using a large syringe, withdraw 30 to 60 ml of fluid to send for pathologic studies.
17. If a large effusion is present, then perform a therapeutic thoracentesis during which as much as several liters of fluid can be removed in one setting (Fig. AIV-10, *C*).
18. After removing the desired amount of fluid, carefully and quickly withdraw the catheter to avoid an air leak into the chest cavity.
19. Cover the wound with a simple bandage and obtain a postthoracentesis x-ray.

INDICATIONS

- Diagnostic collection of pleural fluid
- Therapeutic extraction of pleural fluid affecting respiratory status
- Relief of spontaneous pneumothorax, though larger-caliber chest tubes are optimal

CONTRAINDICATIONS

- Coagulation defect (medication related, congenital, or acquired), relative
- Suspicion that the lung is adherent to pleura
- Loculated fluid collection in the chest, in which case ultrasound guidance is recommended

CPT CODES

32000 Thoracentesis, puncture of pleural cavity for aspiration, initial or subsequent

ICD-9 CODES

511.9 Pleural effusion
511.1 Bacterial effusion
512.8 Pneumothorax

D. ABDOMINAL PARACENTESIS

Key Steps

1. Cleanse skin site.
2. Inject local anesthesia at entry point.
3. Insert IV or fenestrated catheter.
4. Remove device.

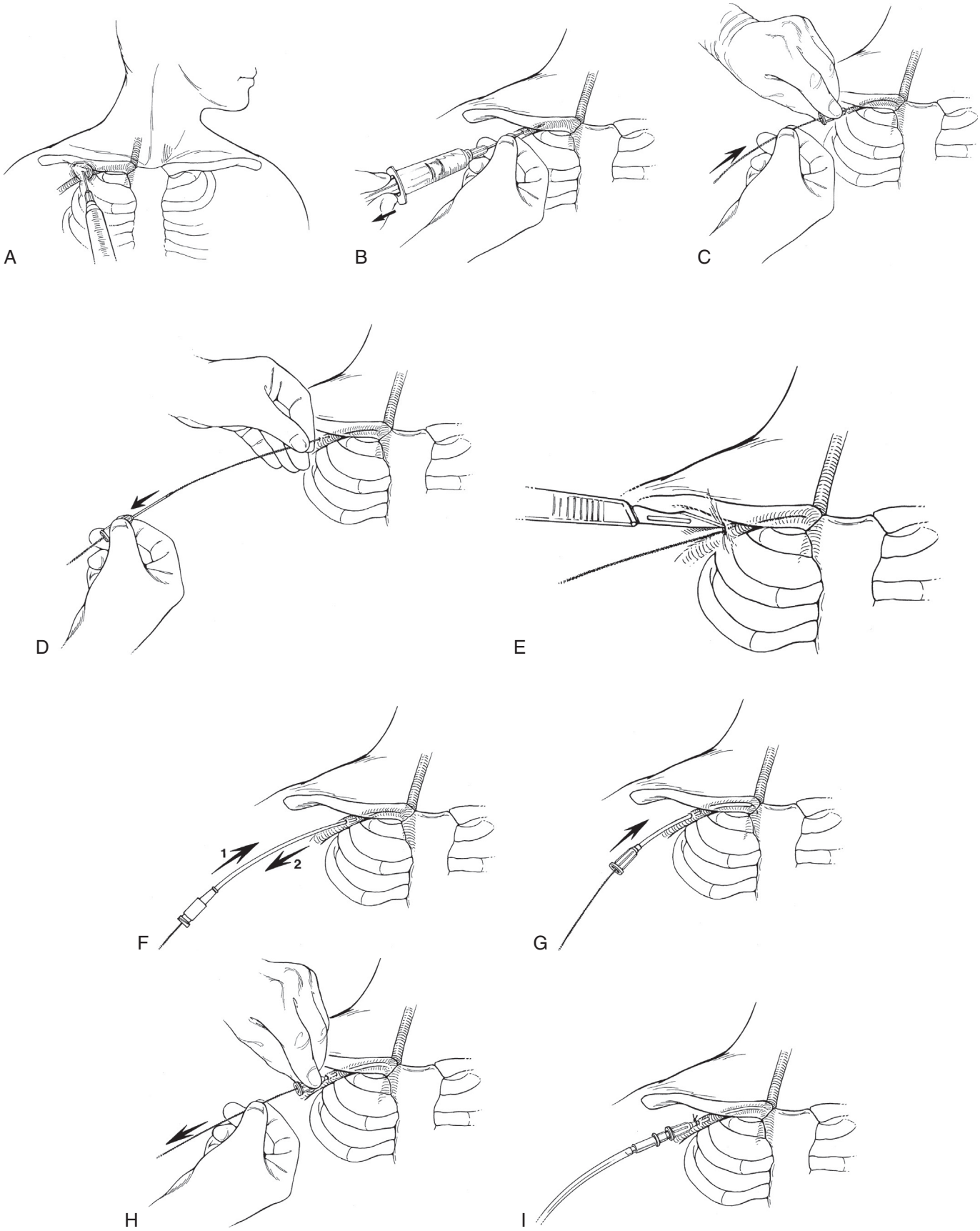
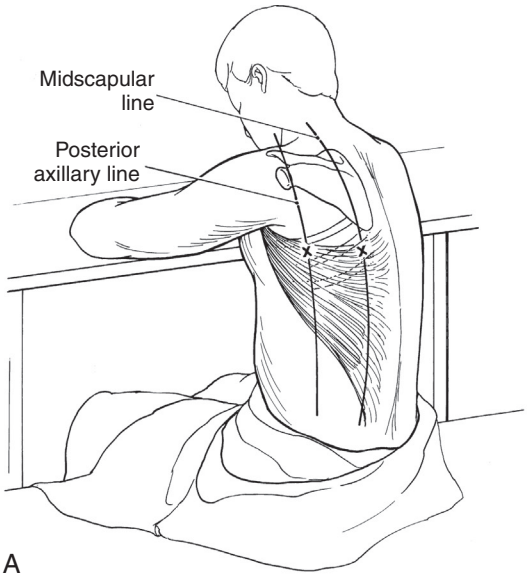


FIGURE AIV-9 Subclavian line.



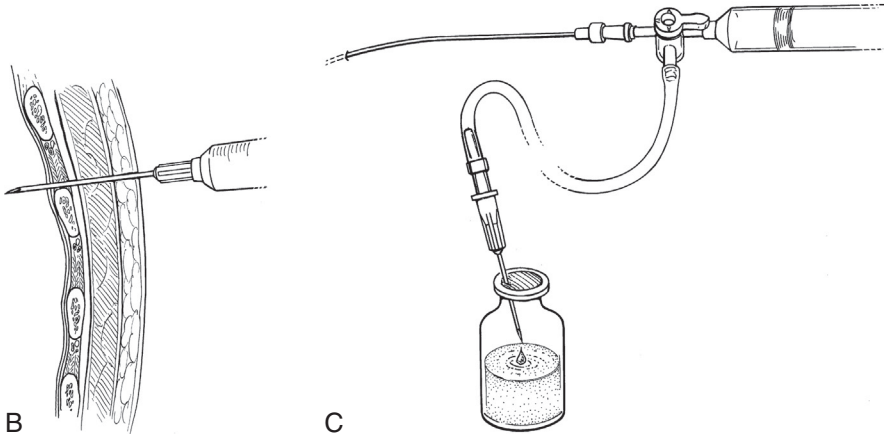


FIGURE AIV-10 Thoracentesis.

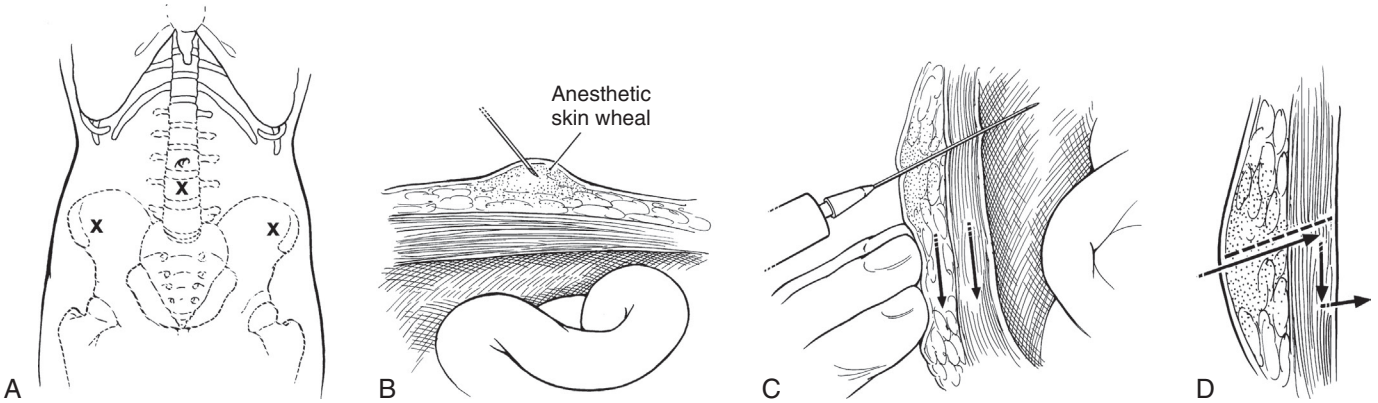


FIGURE AIV-11 Abdominal paracentesis.

INSTRUCTIONS

1. Place the patient in a supine position rolled toward the left and cleanse the site with antiseptic solution.
2. Select the insertion site on or near the midclavicular line (Fig. AIV-11, *A*).
3. Cover the area with a sterile protective drape.
4. Place a local anesthetic block.
5. First, place a wheal in the skin, then advance the needle into the subcutaneous layer and inject 1 ml of solution (Fig. AIV-11, *B*).
6. Advance the needle into the muscle and inject the anesthetic into that layer as well.
7. Finally, as the needle is slowly advanced through the peritoneum, maintain suction on the syringe until entering the abdominal cavity (Fig. AIV-11, *C*).
8. Once ascitic fluid is obtained, withdraw the needle slowly as 1 to 2 ml of lidocaine is injected to numb the peritoneal layer (Fig. AIV-11, *D*).
9. There are two options for draining fluid.

10. For diagnostic paracentesis when removing small volumes, use an IV catheter to obtain a fluid sample.
11. Advance the catheter while applying suction by a syringe until the cavity is entered and fluid enters the syringe.
12. For therapeutic paracentesis, pass a larger catheter through a trocar into the peritoneal cavity.
13. Advance the trocar through the anesthetic area into the peritoneal cavity.
14. Then advance the catheter into the peritoneal cavity through the trocar.
15. Several liters of fluid can be drained from the abdomen using vacuum bottles attached to the catheter system.
16. Attach a stopcock system to the catheter.
17. This allows for control of the suction as desired during collection of the fluid.
18. The fluid will flow until the majority of the fluid is removed.
19. At the conclusion of the procedure, remove the needle and catheter.
20. Apply a dressing over the wound in case there is any further fluid leak.

INDICATIONS
- Intraabdominal ascites
- Suspected bacterial peritonitis
- Need for tube-delivered nutrition, dye, or medications

CONTRAINDICATIONS
- Coagulation defect (medication related, congenital, or acquired)
- Second-trimester or third-trimester pregnancy
- Previous abdominal surgeries (multiple, in which adhesions are more likely)
- Local infection at the site of paracentesis
- Acute abdomen, acute distention (not ascites), or bowel obstruction

CPT CODES
49080 Abdominal paracentesis or peritoneal lavage, initial
49081 Abdominal paracentesis or peritoneal lavage, subsequent

ICD-9 CODES
789.5 Ascites
197.6 Ascites, malignant
567.2 Subacute bacterial peritonitis
014.0 Ascites, tuberculous

12. OBSTETRICS

A. VAGINAL DELIVERY

Key Steps

1. Complete the second stage.
2. Controlled delivery of the head.
3. Delivery of the shoulders.
4. Delivery of the placenta.

INSTRUCTIONS

First Stage of Delivery

1. During the ending of the first stage of delivery, the fetal head engages the maternal pelvis and rotates from a transverse lie to a coronal lie.
2. Normally, the head aligns with the fetal occiput anterior, although occiput posterior may occur approximately 20% of the time.
3. Once the rotation is complete, it allows for easier descent through the pelvic floor through the vagina.
4. Once the patient is fully dilated to 10 cm, she often has a strong urge to push with contractions.
5. Ideally, three or four pushes are done with each contraction, each push lasting 8 to 10 seconds.
6. The propulsive effort of both the uterine contraction and the Valsalva pressure supplied by the abdominal muscles and diaphragm moves the infant's head farther down the vaginal canal.

Second Stage of Delivery

1. The normal second stage of labor is approximately 1 hour for most multiparous patients and up to 2 hours for primiparous patients.
2. As the fetus moves farther down to +3 to +4 station, the infant's head becomes visible as the labia separate with each push (Fig. AVI-12, *A*).
3. If tolerated by the infant, allowing the perineum to stretch reduces the degree of tearing as the head is delivered.
4. When the head is crowning, slight counterpressure to the head applied during the delivery process can prevent a rapid expulsion of the head as it passes through the final resistance of the vulva (Fig. AVI-12, *B*).
5. Once the head is delivered, the operator tracks a finger along the neck to check for a nuchal cord (Fig. AVI-12, *C*). If a cord is present, reduce it before the shoulders are delivered. Reduction can be accomplished by slipping the cord over the head in most instances.
6. Apply traction to head and neck in a downward and forward direction to deliver the anterior shoulder. Minimal lateral extension of the neck reduces the risk of traction injury to the brachial plexus (Fig. AIV-12, *D*).
7. Immediately after the delivery of the anterior shoulder, raise the head to allow the posterior shoulder to deliver over the posterior fourchette.
8. Place the infant on the operator's lap, suction the airway, and cut the cord (Fig. AIV-12, *E* and *F*).
9. Place the stable newborn immediately on the mother to allow for early contact between mother and infant.

Third Stage of Delivery

1. After the infant is delivered, the third stage of labor begins.
2. Cross-clamp the cord with a hemostat to allow gentle traction to be applied to the cord, encouraging the progressive delivery of the placenta.
3. Administer oxytocin at this time to encourage placental delivery. Oxytocin administration in the third stage of labor reduces the risk of maternal hemorrhage at no increased risk of retained placenta.
4. The placenta delivers spontaneously after approximately 10 minutes and is inspected to ensure that there are no missing pieces that may suggest that a remnant of a cotyledon remains in the uterus (Fig. AIV-12, *G*).
5. Massage the uterus to encourage contraction and hemostasis.

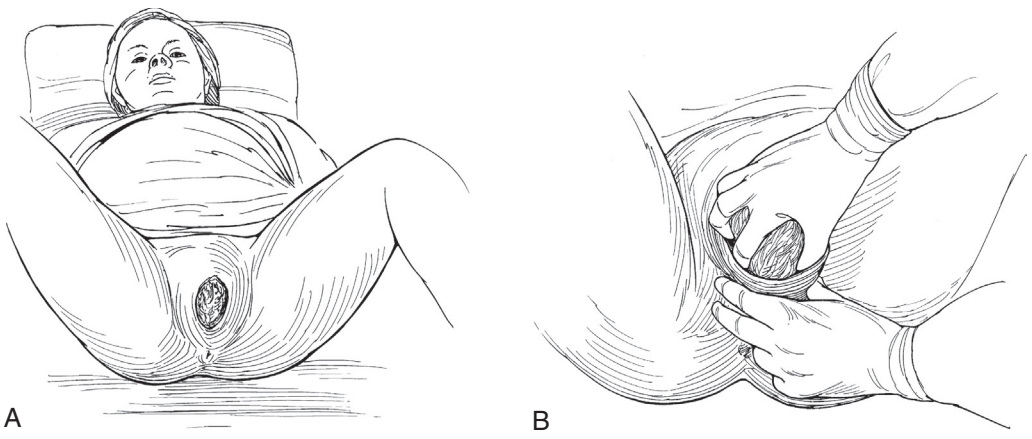


FIGURE AIV-12 Vaginal delivery.

6. After the patient's bleeding has slowed, inspect the perineum, vaginal orifice, and cervix for lacerations, which may require specific repair to avoid further bleeding and retain appropriate anatomy.

INDICATIONS

- Patient in active labor
- Fetus in no distress

CONTRAINDICATIONS

- Vasa previa or placenta previa
- Abnormal fetal lie
- Cord prolapse
- Prior classical cesarean section
- Active genital herpes infection
- Fetal deformities

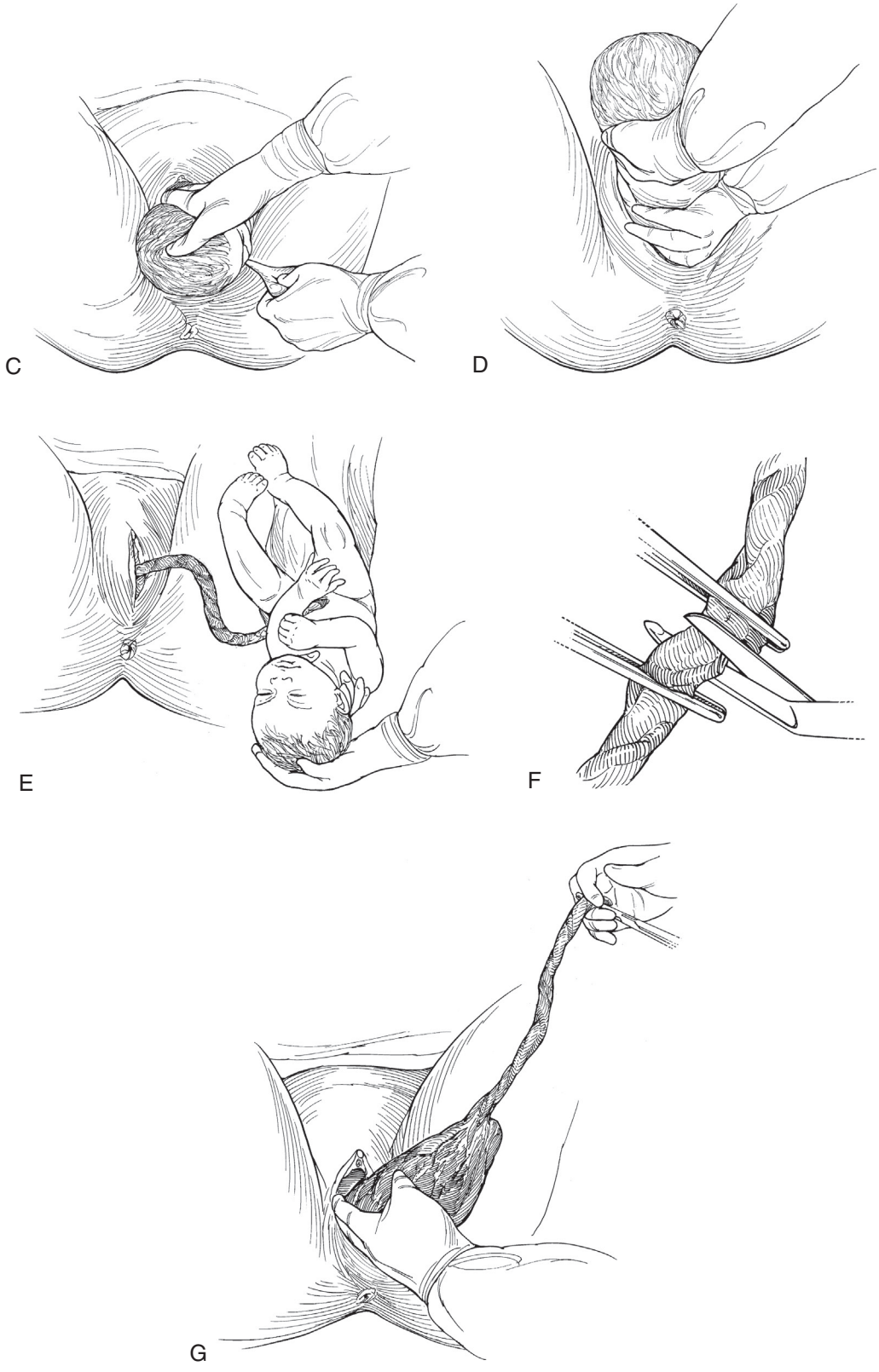


FIGURE AIV-12 (Continued)

CPT AND ICD-9 CODES
Vaginal delivery
CPT and ICD codes depend on many variables of prenatal and postnatal care. Please refer to manuals for appropriate codes.

B. EPISIOTOMY-LACERATION REPAIR

Key Steps

1. Inject anesthesia.
2. Place an anchor stitch and mucosal closure.
3. Perform deep layer closure.
4. Perform perineal subcuticular closure.
5. Place a final anchor stitch.

INSTRUCTIONS
1. To repair a midline laceration or episiotomy, first inspect the area to determine the extent of the laceration.
2. Identify the vaginal apex, posterior fourchette, and perineal apex.
3. It is critical that the two sides of the posterior fourchette are approximated during the repair.
4. Inject local anesthesia along the edges of the laceration to provide a block for the repair.
5. If an epidural is in place with a good block, local anesthesia is not required.
6. The choice of suture varies by operator, but 3-0 chromic, Dexon, or Vicryl absorbable is often selected for closure.
7. Place an anchoring stitch on the inner, or vaginal, aspect of the laceration just above the apex of the tear or episiotomy.
8. Use a continuous running suture to close the internal vaginal portion of the tear to the posterior fourchette.
9. Once near the posterior fourchette, direct the suture deep to begin a deep layer closure of the perineal aspect of the laceration.
10. Run the suture posteriorly in the subcutaneous and deep layers down to the posterior aspect of the tear.
11. Once at the posterior aspect, perform a subcuticular repair in the posterior to anterior direction along the perineal body.
12. Run the suture continuously to the posterior fourchette until the skin is fully closed.
13. Once the external skin is closed, bring the suture up into the vaginal mucosa and anchor it with another stitch along the posterior vaginal wall to bury the knot.
14. After the repair is completed, perform a digital rectal exam to test the integrity of the repair and to ensure that no sutures were placed through the rectal mucosa.
15. In instances in which there is significant tearing toward the anus, perform the rectal examination prior to the repair to ensure adequate layer-by-layer closure.
16. Clean the patient and reevaluate the amount of lochia to ensure that bleeding is well controlled.
17. Control the pain and swelling of the perineum with oral analgesics and ice packs as needed.

INDICATIONS
- Instrumented delivery
- Shoulder dystocia
- Perineal barrier to effective delivery
- Fetal prematurity
- Breech presentation

CONTRAINDICATIONS
- Extensive vulvar varices

CPT CODES
59300 Episiotomy or laceration repair by other than attending

ICD-9 CODES
664.04 First-degree perineal laceration
664.14 Second-degree perineal laceration

13. REPRODUCTIVE—FEMALE

A. INTRAUTERINE DEVICE (IUD) INSERTION

Key Steps

1. Determine uterine position.
2. Cleanse cervix with antiseptic solution.
3. Visualize cervix, stabilize with tenaculum if needed.
4. Sound uterus.
5. Mark IUD catheter and insert IUD.
6. Remove catheter, cut strings.

INSTRUCTIONS
1. Before inserting an IUD, the physician must know the position and size of the uterus, which can be determined with a bimanual examination.
2. In most instances, a preprocedure pregnancy test should be performed, and its outcome should be negative.
3. Insert the speculum and clearly visualize the cervix.
4. Clean the cervix with antiseptic solution.
5. Insert the sound and apply pressure to the internal os until it relaxes.
6. A palpable give will be felt when the internal os dilates.
7. It may be necessary to stabilize the uterus with the application of the tenaculum to the cervix.
8. Before being inserted, the IUD must be prepared in a sterile manner.
9. Arm the Paraguard device in a sterile manner within the inner packaging.
10. Retract the Mirena device into the insertion catheter and lock it into position, using the strings at the base of the handle.
11. Set the marker ring on the IUD insertion catheter to match the sound results for both devices.
12. Insert the IUD until the ring is flush to the cervix with the Paraguard device.
13. With the marker ring applied to the cervix, hold the center plunger still while withdrawing the insertion tube out of the cervix.
14. When inserting a Mirena IUD, leave the marker ring 1 cm short of the cervix before releasing the device in the uterus.
15. Pull back the release lever within the handle 1 cm and then advance the catheter up into the uterus so that the marker ring is flush with the cervix.
16. Finally, fully retract the release lever in the handle to free the IUD from the catheter.
17. Withdraw the catheter and see the strings protruding from the os.
18. Trim the strings down to 2 to 3 cm in length.

INDICATIONS
- Patient desires reversible, longer-term contraception
- Treatment of dysfunctional uterine bleeding and cramps with progestin-containing IUD
- Emergency contraception if insertion is performed soon after unprotected intercourse (5 days)

CONTRAINDICATIONS
- Active pelvic inflammatory disease (PID)
- Active cervical infection
- Nonreducible cervical stenosis, preventing insertion
- Poorly defined uterine position and anatomy as determined by pelvic examination
- Allergy to copper for copper-containing IUD

RELATIVE CONTRAINDICATIONS
- Multiple sexual partners, placing patient at risk for PID
- Nulligravida status

CPT CODES
58300 Insertion of IUD (not including device)

ICD-9 CODES
V25.1 Contraceptive management: IUD

B. IUD REMOVAL

Key Steps

1. Visualize cervix, identify IUD strings.
2. Grasp strings with ring forceps.
3. Extract IUD.

INSTRUCTIONS

1. Place the patient in the lithotomy position and insert a speculum to visualize the cervix.
2. Identify the IUD strings.
3. Remove the IUD by firmly grasping the IUD string in the vault, using a ring forceps.
4. With smooth, gentle traction, pull the IUD out of the uterus.

INDICATIONS

- Expired IUD (1 to 5 years for progesterone IUD, 10 years for copper IUD)
- Request for removal
- Overall medical condition that warrants removal
- Pregnancy
- Pelvic inflammatory disease
- Lower genital malignancy
- Dyspareunia
- Uterine perforation
- Partial expulsion
- Some precancerous lesions of cervix or endocervical canal to allow for treatment
- High risk for sexually transmitted diseases
- Menopause
- Desire to become pregnant
- Side effects causing significant patient discomfort
- Any condition that makes a woman ineligible for IUD use

CONTRAINDICATIONS

- None

CPT CODES

58301 IUD removal

ICD-9 CODES

V25.1 Contraceptive management: IUD
V25.42 IUD removal
996.76 IUD causing menorrhagia

C. DIAPHRAGM INSERTION

Key Steps

1. Place patient in lithotomy position.
2. Measure vaginal vault.
3. Determine size of diaphragm.
4. Gently insert and palpate diaphragm-covered cervix.

INSTRUCTIONS

1. Place the patient in the lithotomy position.
2. With index finger, gently determine the distance from the posterior fornix to the inside of the symphysis pubis, which will be the size of the diaphragm. Most women require a 70-mm to 80-mm size.
3. Apply lubricating jelly to the dome and entire rim of the diaphragm. The patient must understand that effectiveness requires use of spermicidal jelly, not lubricant.
4. With the diaphragm folded in half in one hand and the vulva separated with the other, gently insert the diaphragm into the vagina in the direction of the posterior fornix and gently place the anterior edge under the pubis.
5. Determine correct placement by feeling that the cervix is fully covered by the diaphragm.
6. The diaphragm should be comfortable to the patient.
7. Remove the diaphragm by hooking the anterior rim with the index finger and pulling it out through the introitus.
8. Teach the patient to insert, check position of, and remove the diaphragm; provide written instructions.

INDICATIONS

- Desire for self-administered reversible contraception of moderate effectiveness

CONTRAINDICATIONS

- When pregnancy must be prevented owing to maternal medical condition, use more effective method
- Inability to tolerate or understand application of self-insertion diaphragm device
- Not to be used for reliable prevention of sexually transmitted diseases

CPT CODES

57170 Diaphragm or cervical cap fitting with instructions

ICD-9 CODES

V2509 Family planning advice
V2502 Initiation of other contraceptive measures

14. URINARY

A. BLADDER CATHETERIZATION—FEMALE

Key Steps

1. Position patient.
2. Prepare catheter, check balloon.
3. Cleanse labia and urethral meatus.
4. Insert catheter completely into bladder.
5. Inflate catheter balloon.

INSTRUCTIONS

1. Place the patient in the lithotomy position (Fig. AIV-13, *A*).
2. After donning sterile gloves and draping the patient's genitals, prepare the catheter for insertion.
3. Thoroughly cleanse the labia and the urethral meatus with antiseptic solution (Fig. AIV-13, *B*).
4. Lubricate the catheter with 2% lidocaine jelly (Fig. AIV-13, *C*) and gently insert it through the urethra (Fig. AIV-13, *D*).
5. Pass at least 20 cm of the catheter into the urethra to ensure that it is fully within the bladder (Fig. AIV-13, *E*).
6. Once urine is obtained, if the catheter is to be left inside, inflate the balloon with 10 ml of sterile water and gently pull the catheter outward to ensure that the balloon is maintaining the catheter in position (Fig. AIV-13, *F*).
7. Set up the closed urine collection system and secure the catheter to the patient's thigh with tape.

INDICATIONS

- Relief of urinary obstruction
- Monitoring of urine output
- Obtaining a sterile urine specimen
- Instillation of medications or dyes into the bladder
- Incontinence management
- Measurement of post-void residual volumes

CONTRAINDICATIONS

- Suspected pubic symphysis fracture (blood at the urethral meatus in trauma patient)
- Known fixed obstruction of the urethra (stricture or malignant fixation of urethra)
- Acute infection of prostate or urethra likely

CPT CODES

53670 Simple catheterization

ICD-9 CODES

598.9 Urethral stricture (nontraumatic)
598.1 Urethral stricture (traumatic)
596.0 Bladder neck obstruction (acquired)
788.20 Urinary retention
788.30 Urinary incontinence

B. BLADDER CATHETERIZATION—MALE

Key Steps

1. Position and drape patient.
2. Prepare and lubricate catheter.
3. Cleanse urethra.
4. Advance catheter into bladder.
5. Obtain specimen, remove catheter.

INSTRUCTIONS

1. Place the patient in the supine position.
2. Don sterile gloves and drape the patient's genitals.
3. Lubricate the catheter with 2% lidocaine jelly.
4. Thoroughly cleanse the urethral meatus with antiseptic solution (Fig. AIV-14, *A*) and lubricate the urethra (Fig. AIV-14, *B*).
5. Gently insert the catheter through the urethra (Fig. AIV-14, *C*).
6. Pass the entire length of the catheter into the urethra up to the junction of the catheter and the inflation port (Fig. AIV-14, *D*).
7. Once urine is obtained, if the catheter is to be left inside, inflate the balloon with 10 ml of sterile water and gently pull the catheter outward to ensure that the balloon is maintaining the catheter in position (Fig. AIV-14, *E*).

INDICATIONS

- Relief of urinary obstruction
- Monitoring of urine output
- Obtaining a sterile urine specimen
- Instillation of medications or dyes into the bladder
- Incontinence management
- Measurement of post-void residual volumes

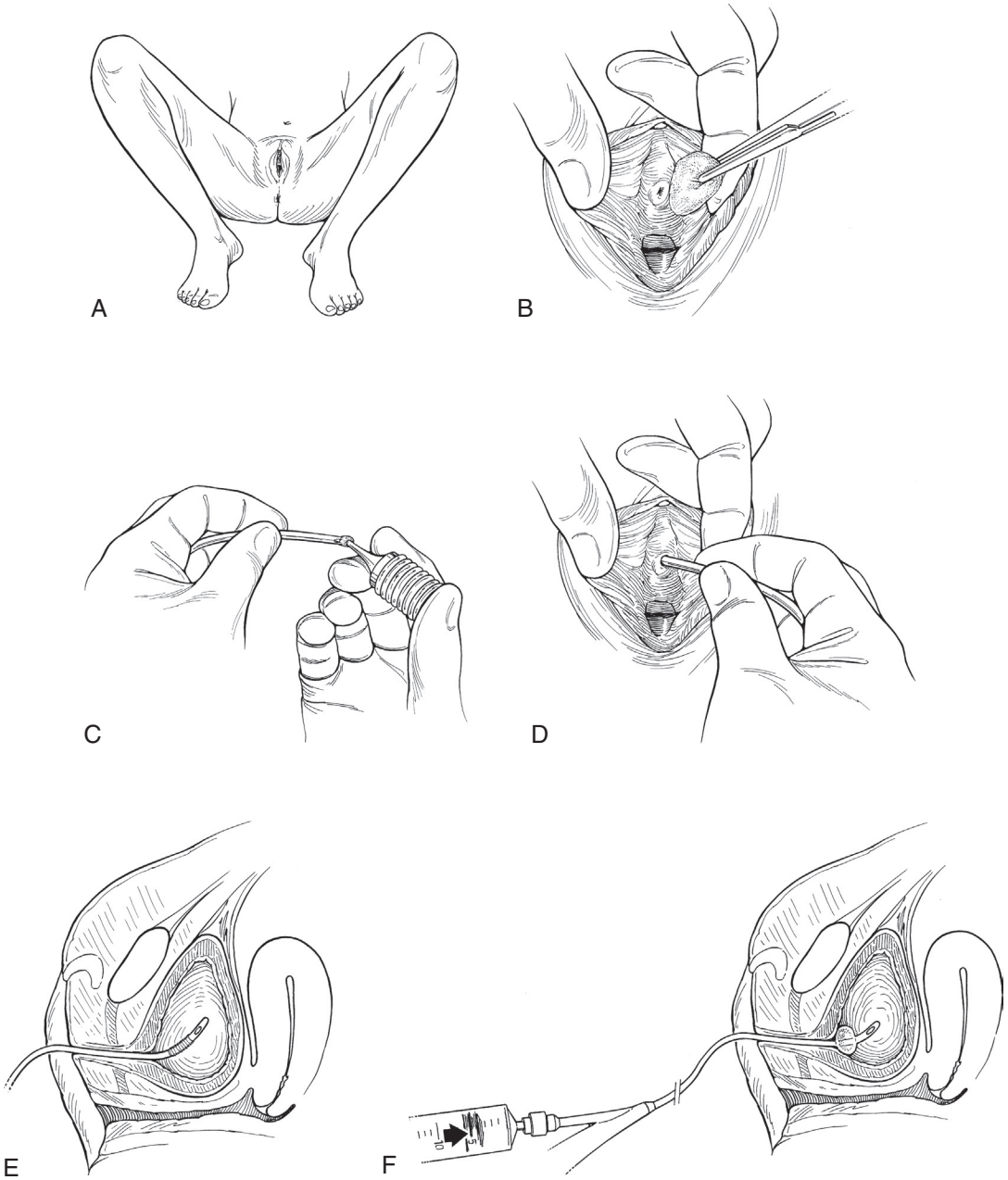


FIGURE AIV-13 Bladder catheterization—female.

CONTRAINDICATIONS

- Suspected pubic symphysis fracture (blood at the urethral meatus in trauma patient)
- Known fixed obstruction of the urethra (stricture or malignant fixation of urethra)
- Acute infection of prostate or urethra likely

CPT CODES

53670 Simple catheterization

ICD-9CM CODES

600.0 Prostatism
598.9 Urethral stricture (nontraumatic)
598.1 Urethral stricture (traumatic)
596.0 Bladder neck obstruction (acquired)
788.20 Urinary retention
788.30 Urinary incontinence

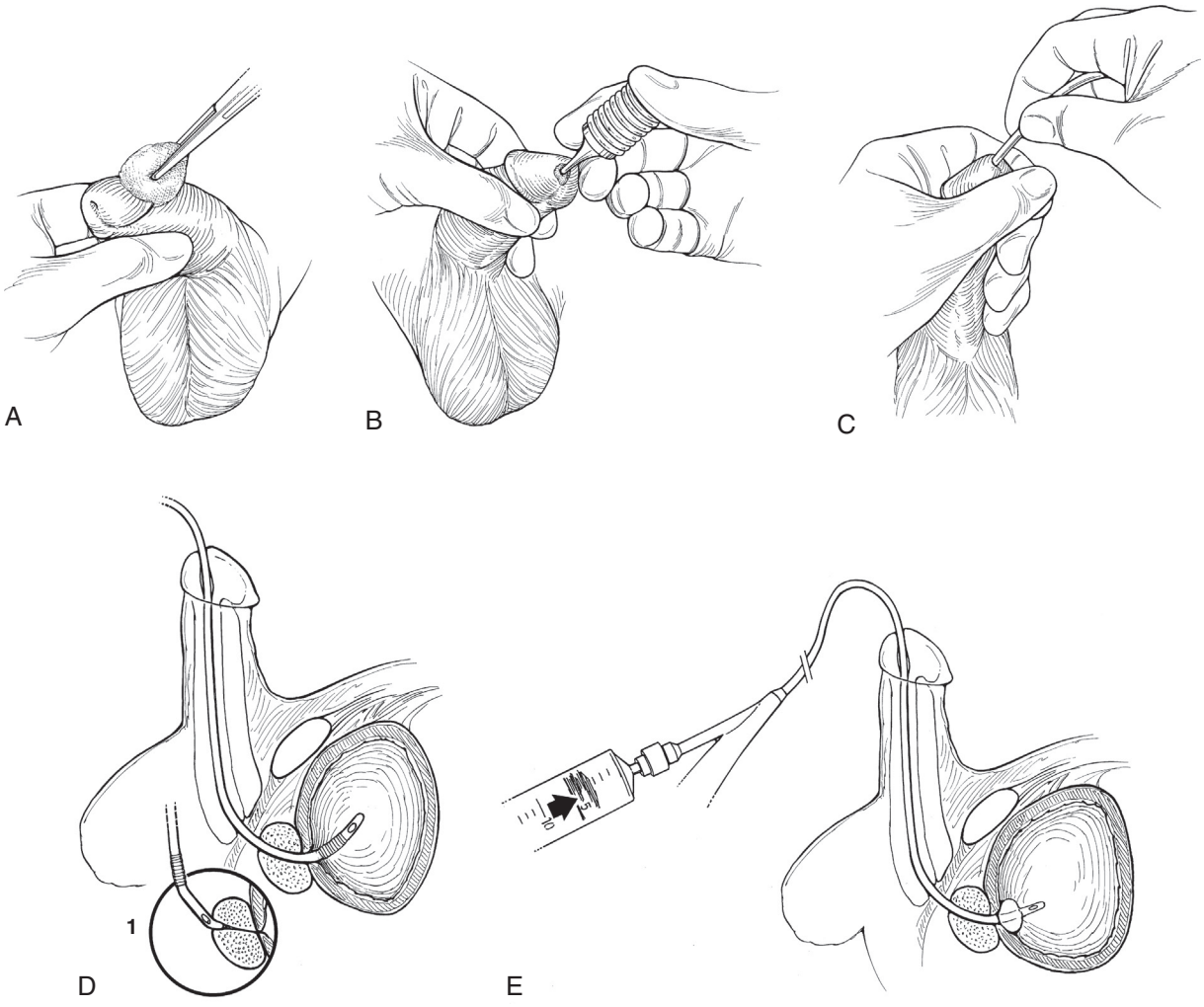


FIGURE AIV-14 Bladder catheterization—male.

MANAGING YOUR

ABDOMINAL AORTIC ANEURYSM

What Is an Abdominal Aortic Aneurysm?

An abdominal aortic aneurysm is a bulging of the aorta, the main blood vessel that takes blood from the heart to organs and tissues in the lower half of the body. The aorta is the largest artery in the body, and a stretching or bulging in the aorta is dangerous because this weakened area in the wall of the aorta may split open (rupture) if not treated.

These aneurysms commonly occur in people older than 60 and affect men more than women. Ruptured aneurysms are the 10th leading cause of death in men older than 55 in the United States.

What Causes an Abdominal Aortic Aneurysm?

High blood pressure (which makes the aorta lining expand), cigarette smoking, and atherosclerosis (hardening of the arteries) are major risk factors. Others are aging, trauma, infections, and rare connective tissue disorders (e.g., Ehlers-Danlos syndrome).

What Are the Symptoms of an Abdominal Aortic Aneurysm?

Abdominal aortic aneurysms often don't produce symptoms. When present, symptoms usually include pain in the middle of the abdomen (belly) or back.

How Is an Abdominal Aortic Aneurysm Diagnosed?

Many aneurysms are found during routine physical examinations by doctors. A doctor can feel a large aneurysm pulsating over the middle of the abdomen.

If an aneurysm is suspected, the doctor will order abdominal ultrasound (sonogram) or computed tomography (CT). Ultrasound is nearly 100% accurate in finding an aneurysm and can estimate the size, but CT is more accurate in estimating size.

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How Is an Abdominal Aortic Aneurysm Treated?

An aneurysm can be repaired if found early, before rupture. If it splits open suddenly, death is likely unless the rupture is treated immediately.

Treatment depends on aneurysm size and risk of rupture. If the aneurysm is small (less than 4 cm [1.6 inches] in diameter), no treatment may be needed, but regular check-ups (every 6 months to 1 year) and sonograms are advised to monitor if the aneurysm is becoming larger.

Surgery to fix aneurysms larger than 5 cm (2 inches) is usually recommended. The operation often involves putting a synthetic mesh tube (stent) in the aorta to make it stronger.

Treatment of aneurysms between 4 and 5 cm (1.6 and 2 inches) remains unclear. Some doctors recommend surgery and others just follow-up examinations. If the aneurysm is growing more than 0.4 inch per year, surgery may be the best option.

DOs and DON'Ts in Managing Abdominal Aortic Aneurysm:

✓ **DO** make sure that you control your blood pressure.

✓ **DO** remember that the major complication of these aneurysms is rupture.

✓ **DO** call your doctor if you know you have an abdominal aneurysm and get new back or abdominal pain.

✓ **DO** call your doctor if you have pain, fever, or drainage from incision sites after surgery.

⃠ **DON'T** forget the numbers 4 cm and 5 cm (surgery for aneurysms larger than 5 cm, watching aneurysms smaller than 4 cm).

⃠ **DON'T** smoke. Cigarette smoking and high blood pressure are believed to be major risk

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factors for these aneurysms.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Heart Association National Center

  7272 Greenville Avenue

  Dallas, TX 75231

  Tel: (800) 242-8721

- National Heart, Lung, and Blood Institute

  Tel: (301) 592-8573

  E-mail: NHLBIinfo@rover.nhlbi.nih.gov

  Website: http://www.nhlbi.nih.gov

  American College of Cardiology

  Tel: (800) 253-4636, (202) 375-6000

  Fax: (202) 375-7000

  Website: http://www.acc.org

- American College of Emergency Physicians

  Tel: (800) 798-1822, (972) 550-0911

  Fax: (972) 580-2816

  Website: http://www.acep.org

- Society for Vascular Surgery

  Website: http://www.vascularweb.org

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MANAGING YOUR

ABRUPTIO PLACENTAE

What Is Abruptio Placentae?

Abruptio placentae, also called premature separation of the placenta, is a serious complication of pregnancy. The placenta peels away from the inner wall of the uterus before delivery. It can be subdivided into 3 types known as grades I, II, and III, which range from mild to severe. A placenta that separates from the uterine wall cannot be reattached. Untreated abruption can harm both mother and baby. It can mean too little oxygen and nutrients for the baby and heavy bleeding in the mother. Complications are related to cesarean delivery, bleeding, and prematurity. It's a medical emergency.

What Causes Abruptio Placentae?

The cause is unknown, but it's not inherited. Risk factors include hypertension, trauma, and multiple pregnancies. Abnormalities of pregnancy called chorioamnionitis and polyhydramnios are also risk factors. Others are age (younger than 20 and older than 35), preeclampsia, diabetes, smoking, use of cocaine, and having more than 14 alcoholic drinks per week during pregnancy.

What Are the Symptoms of Abruptio Placentae?

The main symptoms are uterine bleeding, abnormal uterine contractions, and fetal distress as based on laboratory tests and checking the fetal heart. Contractions are painful and obvious. Weakness, low blood pressure, fast heart rate, abdominal pain, and back pain may occur. Grade 1 abruption includes mild bleeding from the vagina and uterine contractions, stable vital signs, and stable fetal heart rate. The laboratory test called a coagulation profile is normal. Grade 2 means moderate bleeding, abnormal contractions, low blood pressure, distressed fetus, and abnormal coagulation profile. Grade 3 is worst. It involves severe bleeding and contractions, very low

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blood pressure, fetal death, and very poor coagulation profile.

How Is Abruptio Placentae Diagnosed?

The health care provider makes a diagnosis from the medical history, physical examination, blood tests, and other laboratory tests. Other disorders must be ruled out. Abdominal ultrasonography and continuous fetal heart monitoring will be done to check for fetal distress.

How Is Abruptio Placentae Treated?

Stabilization of the mother is done first. Treatment takes place in the hospital. Intravenous fluids and medicines are given to help blood pressure and keep the urine flow steady. An emergency cesarean section and blood transfusions may be needed.

For almost full-term babies and mild abruption, vaginal delivery may be possible. A maternal-fetal medicine specialist may be involved in care.

DOs and DON'Ts in Managing Abruptio Placentae:

✓ **DO** call your health care provider if you feel faint, have a fast heartbeat, or feel pain.

✓ **DO** use a seat belt in vehicles to avoid trauma.

✓ **DO** get early and continuous prenatal care.

✓ **DO** get treatment for conditions such as diabetes and hypertension.

⃠ **DON'T** use any medicines (including over-the-counter medicines and herbal products) without first asking your health care provider.

⃠ **DON'T** smoke or use any other tobacco products.

⃠ **DON'T** use alcohol or recreational drugs such as cocaine.

⃠ **DON'T** miss scheduled follow-up health care provider appointments.

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⦸ **DON'T** continue an exercise program that causes pain or discomfort.

⦸ **DON'T** ignore symptoms. Call your health care provider if you have bleeding during pregnancy.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following source:

- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website: http://www.acog.org**

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MANAGING YOUR

ABSENCE SEIZURES

What Are Absence Seizures?

Absence seizures are seizures with periods of altered consciousness, which may be noted only as a blank stare. They may occur in adults but are more common in children. They may be mistaken for daydreaming. Warning signs such as a strange feeling, unusual taste or odor, or headache may come before the seizure.

What Causes Absence Seizures?

A seizure is caused by abnormal signals in the brain. Head injuries, strokes, brain infections, or tumors can cause these seizures, but often the reason for them is unknown.

What Are the Symptoms of Absence Seizures?

Symptoms in addition to those mentioned above include some fluttering of eyelids and twitching of muscles in the face. Seizures usually last less than 10 seconds and stop by themselves. People are completely unaware of these seizures and continue with their previous activity.

How Are Absence Seizures Diagnosed?

The doctor uses observations from eyewitnesses and the medical history to diagnose absence seizures. Also, an MRI or CT scan of the brain can tell whether there is a physical cause, such as damage to the brain from congenital defects, stroke, or trauma. The doctor may also order a brain wave study called an electroencephalogram (EEG). This safe and painless test records the brain's electrical activity with electrodes placed on the scalp.

How Are Absence Seizures Treated?

Until the seizure disorder is well controlled, precautions may be needed. People living alone should arrange to have help until the doctor believes that it is safe to resume living alone.

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The main treatment is medicine. Sometimes more than one drug may be used. The doctor may have to take blood samples to make sure that the correct dose is given and may adjust the dose as needed. Often, the medicine will reduce the frequency and severity of the seizures, but some people, even with the medicine, will continue to have seizures. Also, all drugs have side effects.

DOs and DON'Ts in Managing Absence Seizures:

✓ **DO** call the doctor if you have any problems with your medicines.

✓ **DO** take the medicine prescribed by your doctor and have blood tests to measure levels of the drug.

✓ **DO** wear an ID bracelet indicating that you have a seizure disorder and listing the drugs you take.

✓ **DO** call the doctor if your seizures become more frequent or severe.

✓ **DO** teach your family and friends about your disorder and what to do if you have a seizure.

✓ **DO** tell someone near you that you feel a seizure coming on and lie down.

✓ **DO** arrange to have someone call the doctor if you are injured during a seizure, have difficulty breathing, or do not regain consciousness shortly after the seizure.

✓ **DO** arrange to have someone call 911 for an ambulance when continuous seizures occur.

⦸ **DON'T** operate dangerous machinery or drive unless your doctor approves.

⦸ **DON'T** swim alone.

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⦸ **DON'T** climb on ladders or roofs or do anything that may be dangerous if you have a seizure.

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FOR MORE INFORMATION

Contact the following source:

- Epilepsy Foundation of America Tel: (800) EFA-1000, (301) 459-3700 **Website:** **http://www.epilepsyfoundation.org**

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MANAGING YOUR

ACETAMINOPHEN OVERDOSE

What Is Acetaminophen Overdose?

Acetaminophen (Tylenol) or paracetamol is the drug most often involved in planned and accidental overdoses in the United States. More than 100,000 cases occur yearly. Many products such as antihistamines, decongestants, and other pain relievers contain acetaminophen. Almost half of acetaminophen overdoses occur in children younger than 6. About 1 in 1000 cases leads to death, caused mainly by liver failure.

Acetaminophen usually comes in 80- to 600-mg dosages. Adults shouldn't take more than 3000 mg daily on a regular basis. Children younger than 12 shouldn't take more than 2000 mg daily. Toxic doses are usually more than 7500 mg in adults and more than 140 mg/kg of body weight in children.

What Causes Acetaminophen Overdose?

The liver metabolizes about 90% of acetaminophen. A toxic intermediate from breakdown of acetaminophen can hurt liver and kidney cells. Age, liver disease, and simultaneous use of alcohol, and other drugs can give people higher risks of overdose. Medical conditions (such as malnutrition) and some herbal supplements may also lead to higher risk.

What Are the Symptoms of Acetaminophen Overdose?

Poisoning can be divided into four phases on the basis of time after taking the drug. In phase 1 (0–24 hours), most people have no symptoms except for nausea, vomiting, and malaise. In phase 2 (24–48 hours), pain in the abdomen (belly), nausea, vomiting, and sweating may occur. Liver damage may start at this point. In phase 3 (72–96 hours), liver injury gets worse. Symptoms include jaundice (yellow skin), confusion, and lethargy. Other symptoms are irritability, appetite

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loss, coma, and convulsions. In phase 4 (4 days to 2 weeks), depending on the amount of overdose, the person has either recovered or is in the final stages of liver failure.

How Is Acetaminophen Overdose Diagnosed?

Emergency room and hospital health care provider make a diagnosis from the history, physical examination, and laboratory tests. These tests are of blood, kidney function, and liver function.

How Is Acetaminophen Overdose Treated?

For certain blood levels, no treatment is needed. However, treatment, if needed, includes using an antidote named *N*-acetylcysteine (NAC) or Mucomyst. If people are seen within 4 hours of taking toxic amounts, emergency room health care provider may use activated charcoal to try to prevent absorption of acetaminophen by the gastrointestinal tract. Most people recover fully and don't have lasting liver injury.

Referral to a psychiatrist is recommended after planned overdoses.

DOs and DON'Ts in Managing Acetaminophen Overdose:

✓ **DO** realize that most people have no symptoms in the early stages of acetaminophen poisoning. However, don't delay getting medical help. Call your health care provider, 911, the American Association of Poison Control Centers, or your local poison control center. Also, go to the hospital emergency department.

✓ **DO** remember to always close pill bottles. Use childproof bottle tops. Keep all drugs out of the reach of children and locked up.

✓ **DO** call your health care provider if you or a family member is depressed or suicidal. Call if you think that you took too much acetaminophen. Call if you have symptoms of an overdose.

⃠ **DON'T** drink alcohol and use acetaminophen.

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⦸ **DON'T** forget to read labels on many over-the-counter drugs. Many cold medicines, pain relievers, and allergy medicines include acetaminophen. Parents can easily give children too much acetaminophen by accident.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Association of Poison Control Centers Tel: (800) 222-1222 **Website: http://www.aapcc.org**
- American College of Emergency Physicians Tel: (800) 798-1822 or (972) 550-0911 Fax: (972) 580-2816 **Website: http://www.acep.org**

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MANAGING YOUR

ACHALASIA

What Is Achalasia?

Achalasia is a disorder of the esophagus, the tube connecting the mouth and stomach. With achalasia, the esophagus has trouble moving liquid and solids down to the stomach. This movement is called peristalsis. Also, the muscle between the esophagus and stomach (the lower esophageal sphincter) does not relax after swallowing. Achalasia may occur at any age but is more common in older people. It cannot be prevented.

What Causes Achalasia?

The causes are usually unknown but may include damage to nerves of the esophagus, infections, and heredity.

What Are the Symptoms of Achalasia?

The main symptom is difficulty swallowing. Problems with liquids usually occur first, followed by problems with solid foods. Weight loss can occur because eating is too difficult or painful.

Other symptoms include chest pain, painful swallowing, coughing, wheezing, heartburn, belching, and vomiting. In advanced cases, halitosis (bad breath) can occur.

How Is Achalasia Diagnosed?

The doctor may order a barium swallow x-ray, or esophagography. This study will show narrowing of the lower part of the esophagus and widening of the upper part.

Pressure measurements (manometry) may be done to prove an absence of peristalsis and increased pressure at the lower esophageal sphincter.

Endoscopy (using a small lighted tube with a tiny video camera at the tip) can confirm a tight sphincter or obtain a piece of tissue to make sure that other diseases aren’t causing symptoms.

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How Is Achalasia Treated?

There is no cure, but treatment can improve symptoms and help prevent complications.

The treatment goal is to reduce pressure at the lower esophageal sphincter. This is done by dilating the sphincter with special instruments or balloons. Even after dilation, the esophagus will not have normal movement. The dilation may have to be repeated if symptoms come back.

Medicines such as long-acting nitrates or calcium channel blockers can lower the pressure at the sphincter. The drugs are usually used in people who can't have the dilation.

Injection of Botox® (botulinum toxin) in the sphincter is a newer treatment that the doctor may try before considering surgery. If other treatments fail, the doctor may operate to reduce pressure in the sphincter (called esophagomyotomy). Surgery can be done laparoscopically (by using a very small incision instead the usual large one).

Without treatment, complications can arise. These include tearing (perforation) of the esophagus, return of acid or food from the stomach into the esophagus (gastroesophageal reflux disease, or GERD), and aspiration pneumonia. Some people may develop esophageal cancer.

DOs and DON'Ts in Managing Achalasia:

✓ **DO** eat and chew slowly.

✓ **DO** call your doctor if you have persistent difficulty swallowing, if painful swallowing develops, or if symptoms remain after treatment.

✓ **DO** call your doctor if you vomit blood or you have other new symptoms.

⃠ **DON'T** eat or drink while lying down.

⃠ **DON'T** drink hot or cold liquids, because they may make the condition worse.

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FOR MORE INFORMATION

Contact the following sources:

- National Digestive Diseases Information Clearinghouse E-mail: nddic@aerie.com **Website: http://www.niddk.nih.gov/health/digest/nddic.htm**
- American College of Gastroenterology Tel: (703) 820-7400 **Website: http://www.acg.gi.org**

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MANAGING YOUR

ACHILLES TENDINITIS

What Is Achilles Tendinitis?

A tendon is a band of tough tissue that usually connects muscle to bone. The Achilles tendon connects calf muscles to the heel. Achilles tendinopathy includes two conditions: tendinitis and tendinosis. Tendinitis is inflammation (swelling) of this tendon. Tendinosis means there are tiny tears in tissue in and around the tendon caused by overuse.

What Causes Achilles Tendinitis?

Causes include sports activities, such as basketball, that put stress on calf muscles and Achilles tendon. Other causes include sudden increase in intensity or frequency of exercise (overuse), poor conditioning, flattened arch, trauma, and infection.

Jumping or trauma can also cause the tendon to rupture (tear) partly or completely.

What Are the Symptoms of Achilles Tendinitis?

Symptoms include a dull ache or pain when pushing off the foot during walking or when rising on the toes. Others are tenderness or swelling over the Achilles tendon, stiffness that gets better with walking, and a crackling sound when touching or moving the tendon.

How Is Achilles Tendinitis Diagnosed?

The doctor uses a history and physical examination for diagnosis. The tendon will be painful on touching and can be made worse with flexing the ankle so tension is put on the tendon. The doctor will squeeze the calf to check for Achilles tendon rupture (tear).

X-rays and MRIs may be done when the diagnosis is unclear.

How Is Achilles Tendinitis Treated?

Self-care methods include rest, ice, compression, and elevation (RICE). Over-the-counter drugs

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such as nonsteroidal anti-inflammatory drugs (NSAIDs) may relieve pain. Improved stretching, night splints (to stretch the tendon), and immobilization for 2 to 4 weeks may help. Other treatments are orthotic devices (shoe inserts to raise the heel) and heel pads or cups for shoes. Severe cases may need walking boots and crutches. Physical therapy and maybe changes in the exercise program may let the tendon heal. The last resort is surgery to remove inflamed tissue around the tendon.

If tendinitis is untreated and the tendon continues to have small tears caused by exercise and repeated movement, the tendon can rupture. Then, surgery is needed

DOs and DON'Ts in Managing Achilles Tendinitis:

✓ **DO** use proper conditioning to prevent another tendon injury. Stretch daily, before and after exercising. Always do warm-up exercises and cool down after exercising.

✓ **DO** cross-train. Do high-impact activities, such as running and jumping, and then low-impact activities, such as cycling and swimming.

✓ **DO** strengthen calf muscles. Exercises such as toe raises trains the muscle-tendon unit to handle more force. These are best done by returning slowly to the ground after each toe raise.

✓ **DO** follow physical therapy and exercise instructions to recover muscle strength and range of motion at the ankle.

✓ **DO** take pain medicines as prescribed.

✓ **DO** call your doctor if you have increasing calf pain, cannot rise onto tiptoe or walk, or have increased swelling at the injury site.

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⦸ **DON'T** wear poorly fitting shoes. Exercise shoes should cushion the heel and have firm arch support.

⦸ **DON'T** do anything that causes too much force on the tendon until it's healed.

⦸ **DON'T** have frequent cortisone or steroid injections around the Achilles tendon. They can increase the risk of tendon rupture.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Medical Society for Sports Medicine Tel: (913) 327-1415 **Website: http://www.newamssm.org**

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MANAGING YOUR

ACHILLES TENDON RUPTURE

What Is Achilles Tendon Rupture?

A tendon is a band of tough tissue that usually connects muscle to bone. The Achilles tendon is the tendon connecting the calf muscles to the heel. Achilles tendon rupture is a common injury of this tendon. It often occurs in 40- to 50-year-old men who engage in athletic activities after a long hiatus from exercise.

What Causes Achilles Tendon Rupture?

The tendon can rupture or tear partially or completely by jumping, forcefully bending the foot toward the shin, or receiving a direct hit to the area. Certain medications such as quinolone antibiotics can increase the risk of tendon rupture.

What Are the Symptoms of Achilles Tendon Rupture?

The most common symptom is stabbing pain in the lower calf at the time of injury.

Walking without pain is often impossible, especially when trying to push off the toe. Swelling occurs, and calf muscles may appear bunched up. Standing on tiptoe of the injured foot may also be impossible.

How Is Achilles Tendon Rupture Diagnosed?

The doctor uses a history and physical examination. The doctor will also do a Thompson test, or squeeze test. With a normal or partially torn tendon, squeezing calf muscles causes the ankle to flex. With an Achilles tendon rupture, this squeezing doesn't produce the ankle motion.

How Is Achilles Tendon Rupture Treated?

The rupture is sometimes treated with casts but most commonly surgery is used. After surgery, the foot is immobilized with casts in different positions. The doctor will probably suggest using a

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heel lift or high-heeled shoe for a certain period after the casts are removed.

If the ends of the tendon can reattach without surgery, your doctor may suggest a cast for 10 to 12 weeks, with two cast changes, and then use of a heel lift.

Recovery is slow and may take up to 6 months, but with exercise and physical therapy, most people recover completely.

DOs and DON'Ts in Managing

Achilles Tendon Rupture:

✓ **DO** take pain medicines as prescribed.

✓ **DO** protect your cast. It is critical to protect the tendon until it has a chance to heal.

✓ **DO** follow physical therapy and exercise instructions to recover muscle strength and range of motion at the ankle.

✓ **DO** use proper conditioning to prevent another tendon injury. If you have a partial tear, you must follow your rehabilitation program exactly. A complete rupture is possible if the tendon is stressed too much.

✓ **DO** call your doctor if you damage your cast or have another injury.

✓ **DO** call your doctor if you have increasing pain in the calf, cannot rise onto tiptoe or walk, or have increased swelling at the injury site.

⦸ **DON'T** remove or damage your cast. If you tear the repair, treatment starts over again, which will prolong time for complete healing.

⦸ **DON'T** do anything that will cause excessive force on the tendon until healing is complete.

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⦸ **DON'T** have cortisone or steroid injections around the Achilles tendon. Such injections have a significant risk for tendon rupture.

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FOR MORE INFORMATION

Contact the following sources:

American Academy of Family Physicians **Website: http://www.familydoctor.org**

American Medical Association **Website: http://www.ama-assn.org**

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MANAGING YOUR

ACNE

What Is Acne?

Acne vulgaris is called simply acne, pimples, or zits. Almost all teenagers have it. Acne usually gets better with age, but sometimes older people, especially women, can get acne.

What Causes Acne?

Male hormones present in both males and in lesser amounts in females increase during puberty and stimulate oil glands of the skin. In the midteens, skin oil (sebaceous) glands begin to produce more oil. Oily skin usually results, but in some people this oil is blocked at skin pore openings. Bacteria, oil, and other materials block these pores. Blocked oil backs up and forms whiteheads; if pores are open to the air, blackheads form. Blocked oil in the skin causes redness (inflammation) and infection, and then pimples and cysts. Boys usually have more oily skin than girls and often worse acne. Foods do not affect acne. Acne is not an infection, so it cannot be caught from someone else.

What Are the Symptoms of Acne?

A rash usually occurs on the face, shoulders, and back. The small bumps can be whiteheads, blackheads, or pimples with pus.

How Is Acne Diagnosed?

Usually, the doctor just does a skin examination. Sometimes blood tests may be done to help pick the best medicine and to monitor side effects from treatment.

How Is Acne Treated?

Whatever the treatment, a few weeks may pass before acne improves. Sometimes, acne may worsen before improving.

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A healthy diet, regular exercise, daily skin care with salicylic acid compounds and cleansing soaps, and gentle washing (no scrubbing) are important.

All acne treatments work by preventing new acne. Treatment usually starts with lowest strength over-the-counter topical medicines (put on the skin). These drugs are usually antibiotics and peeling agents (comedolytics). Antibiotics include benzoyl peroxide, erythromycin, and clindamycin. The over-the-counter benzoyl peroxide has both peeling and antibiotic effects.

Additional prescription drugs include other peeling agents, antibiotics, and hormones.

Most people outgrow acne by their mid-20s. Rarely, severe cases may need special treatment, such as surgery.

DOs and DON'Ts in Managing Acne:

✓ **DO** eat a healthy diet, exercise regularly, and wash oily skin gently, at least twice daily, with medicated soap and water.

✓ **DO** use pills or creams according to your doctor's instruction.

✓ **DO** use oil-free cosmetics, suntan lotions, and shampoos.

✓ **DO** call your doctor if your acne gets worse despite treatment or if you have bad scarring.

✓ **DO** see a dermatologist if your doctor recommends it.

✓ **DO** call your doctor if you have emotional problems because of acne. Acne may cause embarrassment, anxiety, and social difficulties.

⦸ **DON'T** be impatient. Improvement usually takes a few weeks.

⦸ **DON'T** avoid specific foods unless you find that they make your acne worse.

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⦸ **DON'T** pinch, squeeze, or pick your pimples. Infection and scarring can result.

⦸ **DON'T** sunbathe. It can make acne worse.

⦸ **DON'T** use over-the-counter acne drugs while you take prescription drugs, unless your doctor knows.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Dermatology 930 North Meachum Road Schaumburg, IL 60173

  Tel: (866) 503-7546 **Website: http://www.aad.org/**

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MANAGING YOUR

ACOUSTIC NEUROMA

What Is an Acoustic Neuroma?

An acoustic neuroma is a benign (noncancerous) tumor that starts from a nerve of the brain, the eighth cranial nerve, also known as the vestibular nerve. Cranial nerves are 12 pairs of nerves that come from the bottom surface of the brain. Cells wrapping around this nerve are called Schwann cells. Acoustic neuromas are also called vestibular schwannomas.

Neuromas can affect either one ear (unilateral) or both ears (bilateral). Most occur in people 30 to 60 years old.

What Causes an Acoustic Neuroma?

The cause is unclear, but the tumor results from production of too many Schwann cells around the vestibular nerve. Unilateral neuromas occur sporadically and are not inherited. Bilateral neuromas are associated with the genetic disorder neurofibromatosis. Acoustic neuromas are not contagious and cannot spread from one person to another. No way to prevent acoustic neuromas is known.

What Are the Symptoms of an Acoustic Neuroma?

The first symptom in more than 90% of people is one-sided hearing loss. The usually subtle hearing loss occurs slowly. However, sudden acute hearing loss can occur.

Other symptoms include loss of balance and tinnitus (a ringing or hissing sound in the ear).

A growing tumor may press on nerves and cause numbness and tingling in the face or facial muscle paralysis and loss of facial expression. A large tumor can squeeze part of the brain and lead to headaches, clumsy walking, and confusion.

How Is an Acoustic Neuroma Diagnosed?

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If symptoms appear, the doctor will do complete neurological and ear examinations and hearing test (audiogram). Early diagnosis is critical.

The doctor will order an MRI or CT scan of the brain to help diagnose the acoustic neuroma.

How Is an Acoustic Neuroma Treated?

Treatments include surgery, radiation, and monitoring. Treatment is decided on the basis of tumor size and growth rate, degree of impairment, life expectancy, age, and surgical risk.

Surgery is the most reliable treatment. For very small tumors, hearing may be saved and symptoms may improve. Surgery for larger tumors is more complicated.

Another excellent choice, instead of traditional surgery, is gamma knife surgery. This method uses beams of high-energy gamma radiation aimed exactly at the tumor and leaves other areas alone.

Radiation therapy may reduce the size or limit the growth of a neuroma. This therapy is sometimes preferred for elderly people, people in poor health, people with tumors affecting both ears, or people with a tumor affecting their only hearing ear.

Just watching the tumor and repeating the brain MRI after a few months may be reasonable in some cases, usually in people with other serious illnesses.

DOs and DON'Ts in Managing an

Acoustic Neuroma:

✓ **DO** realize that one of the possible complications of tumor removal is that symptoms can worsen because pieces of nerves controlling hearing, balance, or facial nerves may also be removed.

✓ **DO** call your doctor if you notice hearing loss or have new balance problems.

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✓ **DO** call your doctor if you have problems swallowing, tinnitus, one-sided facial numbness, and tingling, especially with dizziness, headache, or other symptoms.

⃠ **DON'T** be afraid to ask for a second opinion.

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FOR MORE INFORMATION

Contact the following sources:

- National Institute on Deafness and Other Communication Disorders Tel: (800) 241-1044 E-mail: nidcdinfo@nidcd.nih.gov **Website: http://www.nidcd.nih.gov**
- Acoustic Neuroma Association Tel: (770) 205-8211, (877) 200-8211 Fax: (770) 205-0239, (877) 202-0239 E-mail: info@anausa.org **Website: http://www.anausa.org**

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MANAGING YOUR

ACQUIRED IMMUNODEFICIENCY SYNDROME

What Is Acquired Immunodeficiency Syndrome?

Acquired immunodeficiency syndrome (AIDS) is an infection caused by human immunodeficiency virus (HIV), which kills or damages the body's immune cells. The body can't fight infections and certain cancers. People with AIDS may get life-threatening opportunistic infections, which are caused by viruses or bacteria that usually don't make healthy people sick.

What Causes AIDS?

HIV infection can result from sexual activity, using an infected needle, or blood transfusion. It can also pass from a mother to her unborn child or to a baby through breastfeeding. AIDS develops when the immune system is so weak that it cannot fight infection, usually months or years after infection with HIV.

What Are the Symptoms of AIDS?

Many people have no symptoms when first infected with HIV. Most people stay symptom-free for months or years, even though the virus is still active.

Some people have a flulike illness, with fever, headache, tiredness, and enlarged lymph nodes, called swollen glands. Blood levels of CD4-positive T cells (also called T4 cells), key infection-fighting cells, drop. Other symptoms seen before full-blown AIDS may include lack of energy, weight loss, frequent fevers and sweats, long-lasting or frequent yeast infections, and short-term memory loss. Some people develop herpes infections that cause shingles or mouth, genital, or anal sores.

The most common symptoms of AIDS include infection of the lungs, brain, or eyes. Additional symptoms include trouble thinking, diarrhea, and loss of appetite. Thrush, a fungal infec-

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tion that causes painful swallowing and a white coating on the tongue, may occur. AIDS increases the risk of getting skin cancer and lymphoma (cancer of lymphatic tissue, part of the immune system).

How Is AIDS Diagnosed?

The doctor will take a medical history, do a physical examination, and test blood for HIV and for the presence of other infections. A chest x-ray and other tests may be done.

How Is AIDS Treated?

Medicine will help the immune system fight HIV. A specialist in infectious diseases will help coordinate your care. Several medicines may keep HIV from growing. Other medicines may treat additional symptoms. A nutritionist can help plan a healthy diet.

DOs and DON'Ts in Managing AIDS:

✓ **DO** practice safe sex (always use a latex condom).

✓ **DO** limit the number of sexual partners.

✓ **DO** follow your doctor's directions.

✓ **DO** tell your doctor about all your medicines and medical problems.

✓ **DO** tell your sexual partner about having AIDS so that he or she can be tested.

✓ **DO** avoid being with people with colds or stomach flu.

✓ **DO** call your doctor right away or go to the emergency room if you have a severe headache, fever, cough, severe diarrhea or vomiting, or bad stomach pain, or if bright lights bother you.

✓ **DO** talk to someone about your stress.

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✓ **DO** call your doctor if you have shortness of breath, new pain or skin lesions, new cough, changes in vision, worse fatigue or weakness, temperature higher than 101° F, trouble staying awake, or confusion.

⦸ **DON'T** skip medicine doses or doctor's appointments.

⦸ **DON'T** stop taking your medicine because you feel better unless your doctor says you should.

⦸ **DON'T** drink alcohol in excess or use drugs.

⦸ **DON'T** share needles or use injection drugs.

⦸ **DON'T** eat foods such as raw eggs, raw oysters, or unpasteurized milk (may have harmful bacteria).

⦸ **DON'T** donate blood, sperm, or organs.

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FOR MORE INFORMATION

Contact the following sources:

- Centers for Disease Control Tel: (800) 232-4636
- Internet Sites **http://www.healthfinder.gov** **http://www.healthanswers.com** **http://www.niaid.nih.gov/factsheets/hivinf.htm**

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MANAGING YOUR

ACQUIRED POLYNEUROPATHY

What Is Acquired Polyneuropathy?

Acquired polyneuropathies are diseases of many nerves affected simultaneously. Acquired means caused by some other disease or exposure. Therefore, acquired polyneuropathy isn't really a diagnosis. Instead, it indicates the presence of some disease. These are one of the most common nervous system disorders. They're classified according to which type of nerve (e.g., sensory, motor, autonomic), which nerves, and which parts of nerves are affected. Other classes are based on causes or pattern of inheritance.

Examples include Guillain-Barré syndrome (GBS), plexopathies, chronic inflammatory demyelinating polyneuropathy (CIDP), and paraneoplastic sensory neuronopathy (PSN) caused by small cell lung cancer.

What Causes Acquired Polyneuropathy?

More than 100 causes exist. The most common metabolic cause is diabetes. Other common ones are hypothyroidism, uremia from kidney failure, and deficiencies of nutrients (vitamin B_{12}). Alcohol and cancer treatment drugs can cause toxic neuropathies. Inflammatory and autoimmune disorders include GBS, amyloidosis, Sjögren syndrome, sarcoidosis, and CIDP. Infections (HIV, Lyme disease) are other causes. In 30–40% of people, no cause can be found (idiopathic neuropathy).

What Are the Signs and Symptoms of Acquired Polyneuropathy?

Symptoms depend on the cause. They include problems with movement (motor nerves) and senses (sensory nerves) that occur on both sides of the body. Sensory symptoms may be painful (burning, freezing, throbbing) or painless (tingling, swelling). Numbness or pain may first in-

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volve the feet, then legs, fingers, hands, and arms. Vibration, light touch, and pinprick sensations are affected. Weakness and wasting of feet and legs may occur. Eye movement can be affected. Symptoms can get worse with heat exposure, physical activity, or tiredness.

How Is Acquired Polyneuropathy Diagnosed?

The doctor takes a medical history and does a physical examination. The doctor may also order electromyography (EMG), spinal fluid analysis (spinal tap), sensory testing, nerve conduction studies (NCS), and skin biopsy. Blood tests, such as for vitamin B_{12} levels, are also done.

How Is Acquired Polyneuropathy Treated?

When a cause is found, treatment may help the polyneuropathy. Examples include treatment of uremia, nutritional deficiencies (vitamin B_{12} replacement therapy), GBS, and hypothyroidism. Stopping neurotoxic drugs may reverse mild neuropathies or prevent severe cases from getting worse. Prednisone, immunoglobulin, or plasmapheresis (PE) may help immune-related disorders such as CIDP. In PE, whole blood is withdrawn from the body and the fluid part (plasma) is removed. Blood cells are then returned to the body. Drugs may help symptoms. People with severe sensory ataxia may need canes, crutches, walkers, or wheelchairs. Ataxia means lack of coordination while making voluntary movements. Careful foot hygiene is critical when pain perception is lost. It can prevent serious infections.

DOs and DON'Ts in Managing Acquired Polyneuropathy:

✓ **DO** call your doctor right away when you have symptoms, so your doctor can find and treat the cause.

✓ **DO** be as active as possible.

✓ **DO** join a self-help group for support.

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✓ **DO** learn as much as you can about your disorder and what to do about it.

⃠ **DON'T** lose hope. The prognosis varies. Some disorders may progress very slowly.

⃠ **DON'T** stop using a prescribed medicine unless your doctor says so. The drug may not necessarily be causing your symptoms.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- The National Institute of Neurological Disorders and Stroke **Website:**

  http://www.ninds.nih.gov

- American Academy of Family Physicians Tel: (800) 274-2237 **Website:**

  http://www.aafp.org

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MANAGING YOUR

ACROMEGALY

What Is Acromegaly?

Acromegaly is an illness in which some soft skin and bones of the head, face, hands, and feet can grow out of proportion to the rest of your body. Acromegaly is rare; only about 750 people per year are diagnosed with it in the U.S.

Acromegaly usually occurs in adults who have completed their growth.

What Causes Acromegaly?

This illness is caused by production of too much growth hormone made by the body's pituitary gland. This gland makes too much growth hormone because of a benign (not cancerous) tumor, or growth. This tumor usually occurs in the same part of the brain as the pituitary gland.

What Are the Symptoms of Acromegaly?

Enlargement of bones of the hands, feet, head, or face is a common symptom. Others include headaches, blurred vision, joint pain, numbness and tingling of the fingers, high blood pressure, carpal tunnel syndrome (numbness of fingers), high blood sugar (glucose) level, changes in a woman's periods (menstrual cycle), impotence in men, and excess growth of skin on the forehead, jaw, lips, and tongue. Snoring and space between the teeth may increase, and the voice may get deeper. Acromegaly may contribute to arthritis, heart disease, and sleep apnea.

How Is Acromegaly Diagnosed?

The doctor will perform a physical examination and do blood tests to measure the amount of a substance called serum insulin-like growth factor 1 (IGF-1). If this test indicates the presence of excess growth hormone, additional tests will be performed by a specialist (endocrinologist) to confirm the diagnosis.

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An MRI (magnetic resonance imaging) or CT (computed tomography) scan of the pituitary gland will be done to find the tumor.

How Is Acromegaly Treated?

Early diagnosis and treatment of overproduction of growth hormone are needed to prevent acromegaly.

Surgery may be done to remove the tumor. Surgery is done by reaching the tumor in the pituitary gland through the nose or above the lip, so no scarring occurs.

Radiation to the pituitary gland and medicine are other treatments. Often, a combination of all these methods is used.

The doctor may suggest seeing an endocrinologist, a doctor who treats hormone problems.

Acromegaly requires lifelong treatment. Surgery often succeeds, but hormone levels may not return to normal, and medicines may be needed even after surgery.

DOs and DON'Ts in Managing Acromegaly:

✓ **DO** follow your doctor's recommendations about medicines.

✓ **DO** see your doctor regularly. Your doctor will check your blood pressure, blood sugar level, and heart to monitor for complications of this disease. Your eyes should also be checked regularly.

✓ **DO** contact your doctor if you have vision changes, worsening headaches, or get new nerve pains or numbness, or pain or pressure in the chest.

✓ **DO** call your doctor if you have side effects from your medicines, including nausea, dizziness, or lightheadedness.

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⦸ **DON'T** expect all your symptoms to go away immediately.

⦸ **DON'T** be afraid to try a combination of treatments.

⦸ **DON'T** forget to have your eyes examined.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following source:

- Pituitary Network Association Post Office Box 1958 Thousand Oaks, CA 91358 Tel: (805) 499-9973 **Website: http://www.pituitary.com**

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MANAGING YOUR

ACUTE BRONCHITIS

What Is Acute Bronchitis?

Acute bronchitis is inflammation (swelling) of the large airways (or bronchial tubes) in the lungs. Acute means that the bronchitis starts suddenly. This common condition is sometimes called a chest cold.

Coughing results from this inflammation and irritation of the lining of these large airways. Also, glands in the airways produce too much mucus (slimy, thick fluid that moistens and protects many passages in the body). This inflammation and mucus cause airways to narrow, resulting in noisy breathing.

Complete recovery can occur within 10 to 14 days, but the cough may last longer. Smokers have a slower recovery time. Acute bronchitis can sometimes lead to the more serious pneumonia. Repeated attacks of acute bronchitis may mean the presence of long-standing (chronic) bronchitis, asthma, or another lung disorder.

What Causes Acute Bronchitis?

The usual cause is a viral infection, most likely after cold or flu symptoms. Other causes include bacteria and irritation of the large airways by chemicals, fumes, dust, or pollutants.

Smokers and people with lung problems, such as chronic bronchitis, asthma, or cystic fibrosis, are more likely to get acute bronchitis.

What Are the Symptoms of Acute Bronchitis?

Symptoms include those of the common cold, such as runny nose and sore throat, fever, headache, aches and pains, cough with mucus, wheezing, shortness of breath, and chest pain when breathing deeply or coughing.

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How Is Acute Bronchitis Diagnosed?

The doctor will ask about symptoms, do a physical examination, and listen to the lungs with a stethoscope.

For long-term or severe symptoms, the doctor may order a chest x-ray to exclude more serious infections such as pneumonia. Blood tests aren't normally needed.

How Is Acute Bronchitis Treated?

Medicines to reduce body temperature if fever is present and analgesic drugs ease chest discomfort and body aches. These drugs include acetaminophen and ibuprofen.

Cough syrups may be prescribed if the cough is strong.

Decongestants can help with cold symptoms.

Bronchodilators, usually given by inhaler, open the airways and help with breathing.

People with acute bronchitis don't usually need antibiotics because the cause is a virus and antibiotics treat bacterial infections only. However, if the doctor suspects bacteria as the cause, antibiotics may be given.

DOs and DON'Ts in Managing Acute Bronchitis:

✓ **DO** quit smoking if you smoke.

✓ **DO** avoid smoky environments.

✓ **DO** drink plenty of noncaffeinated fluids, such as water and fruit juices.

✓ **DO** get plenty of rest.

✓ **DO** use a room humidifier or damp towels for increased humidity in your room.

✓ **DO** wash your hands often to prevent spread of infection.

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✓ **DO** call your doctor if you become short of breath or cough up blood.

✓ **DO** call your doctor if your cough lasts longer than 3 weeks.

⃠ **DON'T** go out in cold or damp weather.

⃠ **DON'T** delay in getting medical care if your symptoms worsen, don't improve, or you get new symptoms.

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FOR MORE INFORMATION

Contact the following source:

- Medline Plus U.S. National Library of Medicine 8600 Rockville Pike Bethesda, MD 20894 **Website: http://medlineplus.gov/**

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MANAGING YOUR

ACUTE CORONARY SYNDROME

What Is Acute Coronary Syndrome?

Acute coronary syndrome (ACS) is a term for several life-threatening conditions caused by not enough blood flow to the heart. Myocardial infarction (heart attacks) and unstable angina are part of ACS. In myocardial infarctions, some of the heart muscle dies because it doesn't get enough blood. In unstable angina, heart-related pain occurs during rest.

What Causes Acute Coronary Syndrome?

The cause is poor blood flow and not enough oxygen getting to the heart muscle. Low blood flow to the heart from coronary artery disease may be caused by atherosclerosis or vessel spasms. Atherosclerosis is scarring and fatty deposits in blood vessels. Coronary arteries are vessels that take blood to the heart. Abnormal heart valves and abnormal heart rhythms (arrhythmias) may also interfere with blood flow to the heart and coronary vessels.

Anemia (low blood) can also lower blood flow to the heart.

Age (older than 55), family history of heart disease, smoking, being overweight, not enough exercise, diabetes, high blood pressure (hypertension), high cholesterol levels, and high-fat diet increase the risk of ACS.

What Are the Symptoms of Acute Coronary Syndrome?

Main symptoms include feelings of tightness, dull ache, or heaviness that begin in the chest and may go to the neck, left shoulder, and down the arms (especially left arm). Pain may start slowly or suddenly and may be dull or smothering or crushing, as if someone is sitting on the chest. Other signs and symptoms of ACS are breathing problems, feeling faint, severe tiredness, weakness, nausea, and sweating. In some cases (especially in women and diabetics), the symptoms may differ and ACS may present with vague complaints such as jaw pain, stomach pain, or left arm discomfort.

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How Is Acute Coronary Syndrome Diagnosed?

The doctor starts with a medical history and physical examination. Tests for ACS may include electrocardiography (ECG, an electrical study of the heart), exercise stress test, ultrasonography, blood tests, and heart catheterization. In catheterization, a tube (catheter) is put through an artery into the heart to see whether the area is blocked.

How Is Acute Coronary Syndrome Treated?

Treatment involves getting more blood flow to the heart or reducing the work of the heart so it needs less blood. Time is crucial. The quicker the diagnosis is made, the better the chance to save heart tissue with medications that can dissolve the clot and open the arteries to increase blood flow. Medicines called nitrates (nitroglycerin) and aspirin also help blood flow. Drugs (such as beta-blockers) can treat hypertension and lessen the work of the heart by slowing down the heart rate.

Control of other conditions such as diabetes and high cholesterol levels is important. In some cases, surgery or other interventions may be needed to open blocked blood vessels. These procedures are angioplasty, placement of stents (mesh tubes), and coronary artery bypass grafting. In angioplasty, a balloon-like device opens blocked vessels.

DOs and DON'Ts in Managing Acute Coronary Syndrome:

✓ **DO** reduce stress to lower high blood pressure and the risk of angina. Learn new ways to relax.

✓ **DO** lose weight if you're overweight. It can lower blood pressure and improve blood fat and sugar levels.

⦸ **DON'T** smoke.

⦸ **DON'T** drink alcohol in excess.

⦸ **DON'T** eat high-salt or high-fat foods.

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:**

  http://www.americanheart.org

- American College of Cardiology Tel: (202) 375-6000 **Website: http://www.acc.org**

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MANAGING YOUR

ACUTE LYMPHOCYTIC LEUKEMIA

What Is Acute Lymphocytic Leukemia?

Leukemia is a cancer of the white blood cells known as lymphocytes. Bone marrow is spongy tissue in the middle of bones. White blood cells form and develop in marrow and then move into the bloodstream. Leukemia can be divided into acute and chronic types. Acute leukemia affects cells in bone marrow before they fully develop. Chronic leukemia affects fully grown cells. The four subcategories are acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CML).

ALL prevents the body from making normal blood cells and causes production of abnormal young, immature white blood cells. Normal white blood cells help fight infection, whereas leukemic cells are ineffective. ALL cells come from white blood cells called B cells or T cells. ALL usually occurs in children, especially boys, younger than 15. It is the most common cancer in children. Adults can also have ALL.

What Causes ALL?

The cause is unknown, and ALL can’t be prevented.

What Are the Symptoms of ALL?

Symptoms include low fever, tiredness, increasing paleness, feeling sick, easy bruising and bleeding, enlarged spleen, pain in the belly (abdomen), frequent infections, and headache. Swollen glands, enlarged liver and spleen, and confusion can occur.

How Is ALL Diagnosed?

The doctor examines the blood and performs a bone marrow biopsy. The biopsy involves removing marrow from bone and examining it under a microscope. Lymphocytic cells are examined

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for the presence of abnormalities to their chromosomes (cytogenetic analysis). The doctor will also check to see whether B or T cells are involved (immunophenotyping). The doctor also tests spinal fluid and may order a chest x-ray, CT (computed tomography) scan, and ultrasound.

How Is ALL Treated?

ALL can be cured; chemotherapy (anticancer drugs) is the main reason for better survival. At first, hospitalization is needed for blood transfusions, chemotherapy, and radiation.

Treatment usually involves four steps. The first two (using drugs for induction and consolidation) also remove normal blood cells, which can lead to serious complications.

After complete remission, the third step is radiation of the brain and chemotherapy, to get rid of leukemia cells.

Maintenance therapy uses drugs to prevent return of leukemia.

The doctor may consider bone marrow transplantation, also called stem cell transplantation. Healthy marrow containing stem cells (the source of all blood cells) is given, and stem cells produce new healthy cells to replace abnormal ones.

DOs and DON'Ts in Managing ALL:

✓ **DO** take good care of your mouth. Rinse often with warm saltwater, and use a soft toothbrush.

✓ **DO** drink extra fluids.

✓ **DO** eat and drink high-calorie foods and beverages if you are getting chemotherapy.

✓ **DO** apply pressure and ice and call your doctor for abnormal bleeding.

✓ **DO** understand that treatments depend on age, genetics, and availability of donor marrow.

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✓ **DO** call your doctor if you have a fever during treatment.

✓ **DO** avoid sick people, because your resistance to infection is low.

✓ **DO** go to a center where doctors treat people with ALL.

⃠ **DON'T** take aspirin or any medicine that contains it.

⃠ **DON'T** miss follow-up appointments. They are extremely important to check for complete remission and for return of leukemia.

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FOR MORE INFORMATION

Contact the following sources:

- The Leukemia & Lymphoma Society, Inc. Tel: (914) 949-5213, (800) 955-4572 **Website: http://www.leukemia.org**
- National Childhood Cancer Foundation **Website: http://www.curesearch.org**
- American Academy of Pediatrics **Website: http://www.aap.org**

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MANAGING YOUR

ACUTE MYELOGENOUS LEUKEMIA

What Is Acute Myelogenous Leukemia?

Leukemia is a cancer of the white blood cells. It originates in the bone marrow. Bone marrow is spongy tissue in the middle of bones. Blood cells form and develop in marrow and then move into the bloodstream. Leukemia can be acute and chronic. Acute leukemia affects white blood cells in bone marrow before they fully develop. Chronic leukemia affects fully grown cells. The four subcategories are acute myelogenous leukemia (AML), also known as acute myeloid leukemia, acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), and chronic myelogenous leukemia (CML). AML, the most common leukemia in adults, affects one type of white blood cells (these cells help fight infection).

What Causes AML?

The cause is unknown. An increased risk of developing AML occurs after exposure to high doses of radiation, the chemical benzene, and drugs used to treat cancers and in people with certain genetic disorders. No effective way to prevent AML is known.

What Are the Symptoms of AML?

Common symptoms include paleness, weakness, shortness of breath, weight loss, and discomfort in the belly (abdomen). Tiredness, easy bleeding, bruising, and frequent infections result from fewer red blood cells (anemia), white blood cells, and platelets. Too many young and immature (poorly developed) white cells invade lymph nodes, liver, and spleen and cause swollen glands and enlargement of these organs. Bleeding from lungs, digestive tract, and brain can occur. AML can affect skin, gums, and linings of the spinal cord and brain.

How Is AML Diagnosed?

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The doctor will use blood tests and perform a bone marrow biopsy. The biopsy involves removing marrow from bone and examining it under a microscope.

How Is AML Treated?

A cancer specialist called an oncologist manages treatment. The goal is complete remission, so that no leukemia cells remain in blood or bone marrow after treatment. First, combination chemotherapy (induction therapy) is given. If needed, additional chemotherapy is used. Chemotherapy also affects normal cells, which can lead to anemia, easy bleeding, and frequent infections.

The doctor will examine the bone marrow after therapy. After complete remission, more chemotherapy is given to prevent leukemia's return (consolidation therapy).

The doctor may consider bone marrow transplantation, also called stem cell transplantation, at this point. Stem cells are the source of all blood cells. For a bone marrow transplant, healthy marrow containing stem cells is given to replace the abnormal marrow. Donors of healthy marrow are usually close relatives. Stem cells start to produce new blood cells without any leukemia cells.

DOs and DON'Ts in Managing AML:

✓ **DO** understand that treatments vary and depend on factors such as age, genetics, and availability of donor marrow.

✓ **DO** get treated in a center with experienced blood specialists (hematologists).

✓ **DO** ask your doctor for help in coping with side effects.

✓ **DO** tell your doctor if you feel chest pain or shortness of breath during treatment.

✓ **DO** call your doctor if you are bleeding or have a fever after you start chemotherapy.

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⦸ **DON'T** miss follow-up appointments. They are extremely important to check for complete remission and for return of leukemia.

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FOR MORE INFORMATION

Contact the following sources:

- The Leukemia and Lymphoma Society, Inc. Tel: (914) 949-5213, (800) 955-4572 **Website: http://www.leukemia-lymphoma.org**
- National Cancer Institute **Website: http://www.cancer.gov**
- National Comprehensive Cancer Network **Website: http://www.nccn.org**
- Children's Oncology Group/National Childhood Cancer Foundation **Website: http://www.curesearch.org**

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MANAGING YOUR

ACUTE PANCREATITIS

What Is Acute Pancreatitis?

Acute pancreatitis is sudden inflammation (swelling) of the pancreas. The pancreas is a large gland behind the stomach, near the beginning of the small intestine. It releases digestive juices (enzymes) and the hormones insulin and glucagon. These hormones help the body control sugar (glucose) in food that's used for energy.

Acute pancreatitis can be life-threatening, with serious complications.

What Causes Acute Pancreatitis?

Alcoholism and gallstones (small, pebble-like pieces of bile) cause almost 80% of cases. More women than men have gallstone-related acute pancreatitis. Other causes include injuries to the abdomen (belly), surgery, drugs, viral infections, tumors, and genetics. It can be a complication of endoscopic retrograde cholangiopancreatography (ERCP) or cystic fibrosis. High blood lipid (fat) or calcium levels, diabetic ketoacidosis, kidney failure, hemodialysis, and anatomic abnormalities can also cause acute pancreatitis.

What Are the Symptoms of Acute Pancreatitis?

The main symptom is abdominal pain lasting for hours to days. Pain is moderate to severe. Sitting forward or lying down on one side with knees bent may relieve pain that reaches the back. Nausea, vomiting, and fever can occur. People can have rapid heartbeat, low blood pressure, dehydration, and a swollen, tender abdomen. High levels of certain blood enzymes can occur. The heart, lungs, or kidneys can fail. Shock and even death may follow bleeding in the pancreas. Symptoms also depend on the cause.

How Is Acute Pancreatitis Diagnosed?

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The doctor orders blood tests and X-rays. Computed tomography (CT) is the best way to see inflammation in the pancreas.

How Is Acute Pancreatitis Treated?

A short hospital stay is usually needed to manage pain, rest the pancreas, and fix fluid and electrolyte imbalances. Pain relievers may be given. To rest the pancreas, people must fast. In severe cases, people can get nutrients by intravenous fluids, peripheral parenteral nutrition (PPN), and tube feedings. Normal eating can usually start again after 2–3 days without more treatment.

Cholecystectomy (gallbladder removal) should be considered in gallstone pancreatitis when the pancreatitis has resolved.

Complications include low blood levels of calcium and albumin and high blood sugar and lipid levels. Blood clotting abnormalities, shock, breathing problems, and kidney disorders can also occur. Necrosis, pseudocysts, abscess, and ascites (too much fluid) can be complications in the pancreas.

DOs and DON'Ts in Managing Acute Pancreatitis:

✓ **DO** eat small, frequent meals. Avoid solid foods to let the pancreas recover.

✓ **DO** eat a diet high in carbohydrates and low in fats.

✓ **DO** stop drinking alcohol. In pancreatitis due to alcohol abuse, it's the only way to lower the chances of more attacks. It can also stop pancreatitis from worsening and prevent serious or even fatal complications.

✓ **DO** avoid medications that may have caused pancreatitis.

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⦸ **DON'T** smoke, drink alcohol, or eat fatty meals.

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FOR MORE INFORMATION

Contact the following sources:

- National Digestive Diseases Information Clearing house E-mail: nddic@aerie.com

  Website: http://www.niddk.nih.gov/health/digest/nddic.htm

- American College of Gastroenterology Tel: (703) 820-7400 **Website:**

  http://www.acg.gi.org

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MANAGING YOUR

ACUTE KIDNEY INJURY (AKI)

What Is Acute Kidney Injury?

Acute kidney injury, also known as acute renal failure, means that kidneys suddenly can't get rid of the body's waste. Kidneys normally do this by making urine. When they fail, waste products build up and are harmful.

What Causes Acute Kidney Injury?

Conditions that reduce the blood supply to kidneys, block flow of urine after it leaves kidneys, or injure kidneys can cause renal failure. These include chronic urinary infections and kidney damage from congestive heart failure, diabetes, or high blood pressure.

Causes of acute kidney injury include illnesses that have an indirect effect on kidneys (e.g., low blood pressure), kidney blockage, and direct kidney injury (e.g., by drugs and x-ray dyes).

What Are the Symptoms of Acute Kidney Injury?

An early symptom is little or no urine output.

Later ones include nausea, vomiting, diarrhea, and appetite loss. Being irritable, not able to sleep, convulsions, stupor, coma, severe itching, high or low blood pressure, unexplained bruising, and bleeding for no reason are additional signs.

How Is Acute Kidney Injury Diagnosed?

Blood and urine tests can measure how well kidneys work. A biopsy (taking a sample of tissue from kidneys) may be done in certain cases, as may x-rays of the chest, belly, kidneys, and ureters (tubes taking urine from kidneys to the bladder).

How Is Acute Kidney Injury Treated?

Treatment depends on the reason for acute Kidney Injury. However, most likely a hospital admission, may be necessary. Medicines may help increase the amount of urine made, and an artificial

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kidney machine may be used for dialysis (hemodialysis). In another type of dialysis known as peritoneal dialysis, fluid (called dialysate) is placed in the abdomen (belly) to help clean waste products from the blood and is then removed with a special tube (catheter). The doctor may suggest a reduced intake of protein, salt, and potassium and use of blood pressure pills and calcium supplements. In many cases, kidneys may recover completely, but recovery may take up to 6 weeks or longer.

DOs and DON'Ts in Managing

Acute Kidney Injury:

✓ **DO** follow a low-protein diet if your doctor recommends it. A proper diet is critical to prevent complications. You may have to eliminate some fruit, chocolate, and nuts because of high potassium levels. When kidneys don't work, high levels are dangerous for your heart.

✓ **DO** take medicines as prescribed.

✓ **DO** weigh yourself daily and keep a record of fluids you drink and the amount of fluid you pass if your doctor asks you to.

✓ **DO** tell your doctor of any exposure to toxic chemicals or drugs.

✓ **DO** keep to your fluid restriction to avoid fluid buildup in your lungs.

✓ **DO** tell your doctor about all your medicines, including over-the-counter and herbal preparations.

✓ **DO** call your doctor if you have chills, fever, vomiting, headache, muscle aches, or diarrhea.

✓ **DO** avoid anything poisonous to kidneys, such as some drugs.

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✓ **DO** treat anything that might damage kidneys, such as high blood pressure, diabetes, congestive heart failure, and infections.

⦸ **DON'T** stop taking your medicines before asking your doctor. Don't miss any doses.

⦸ **DON'T** take over-the-counter medicines or herbal preparations unless you check with your doctor.

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FOR MORE INFORMATION

Contact the following sources:

- National Kidney Foundation, Inc. Tel: (800) 622-9010, (212) 889-2210 E-mail: info@kidney.org **Website: http://www.kidney.org**
- National Institute of Diabetes, Digestive, and Kidney Diseases **Website: http://www2.niddk.nih.gov**

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MANAGING YOUR

ACUTE RESPIRATORY DISTRESS SYNDROME

What Is Acute Respiratory Distress Syndrome?

Acute respiratory distress syndrome (ARDS) is a life-threatening condition caused by inflammation of air sacs in the lung. It leads to buildup of fluid in air sacs, which stops oxygen from getting to the bloodstream and the rest of the body. This can cause lung failure resulting in death.

ARDS occurs in people of all ages and equally in men and women. It is not contagious or inherited.

What Causes ARDS?

ARDS often results from infections, trauma, or injury and occurs rapidly (usually within 24 to 48 hours of the cause). Other causes include aspiration of vomit; extensive burns; drug overdose; breathing in of chemicals, smoke, or other toxic fumes; and pancreatitis (inflammation of the pancreas). ARDS can lead to failure not only of lungs but other vital organs including kidneys and liver.

What Are the Symptoms of ARDS?

ARDS symptoms are shortness of breath, low blood pressure, and fever. In early stages of ARDS, a fast heartbeat (tachycardia), fast breathing (tachypnea), and cyanosis (blue skin and lips) are noted. Increasing agitation, lethargy, and confusion follow in later stages.

How Is ARDS Diagnosed?

Laboratory tests and imaging studies help confirm the doctor's belief that ARDS is present. A chest x-ray perhaps provides the first clue. The doctor may order a catheterization (putting a thin catheter, or tube, through a neck vein into the heart) to measure pressures in the heart for diagnosis and to help guide treatment.

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How Is ARDS Treated?

ARDS, a medical emergency, usually means admission to the intensive care unit. Supportive treatment is used, meaning treatments support and maintain oxygen status and blood pressure. A mechanical ventilator (breathing machine) helps people breathe, and intravenous medicines maintain normal blood pressure. The ventilator is used until people can breathe on their own.

When infection causes ARDS (more than 30% of the time), antibiotics are critical for treatment and cure.

DOs and DON'Ts in Managing ARDS:

✓ **DO** remember that pulmonary fibrosis (lung scarring) is a possible complication of ARDS that can lead to long-term use of a ventilator or shortness of breath after discharge from the hospital.

✓ **DO** understand that ARDS is a medical emergency that requires intensive medical care.

✓ **DO** realize that some people surviving ARDS may suffer from some memory loss because of poor oxygen supply to the brain.

✓ **DO** call your doctor if you have a fever or are short of breath.

⃠ **DON'T** forget that for people who survive ARDS, it may take 6 to 12 months to regain normal lung function again.

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Contact the following sources:

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• ARDS Support Center Inc. 7172 Regional Street, #278 Dublin, CA 94568-2324 **Website:**

http://www.ards.org

• National Heart Lung and Blood Institute Tel: (301) 592-8573 **Website:**

http://www.nhlbi.nih.gov/health/dci/Diseases/Ards/Ards_WhatIs.html

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MANAGING YOUR

ADDISON'S DISEASE

What Is Addison's Disease?

Addison's disease, also known as primary adrenal insufficiency, is a condition in which the adrenal glands don't work well. The two small adrenal glands sit atop the kidneys. They usually produce hormones called cortisol and aldosterone. Without these hormones, salt and water in the body is lost in urine, which makes blood pressure fall too low. Also, potassium builds up to a dangerous level. There is no effective way to prevent Addison's disease.

What Causes Addison's Disease?

Addison's disease develops because the immune system (disease-fighting system) doesn't work well. In an autoimmune disease, the body makes substances (antibodies) that damage adrenal glands. Other causes include infections (e.g., tuberculosis, AIDS), cancer, bleeding, and blocked blood vessels involving the adrenal glands. Adrenal glands may also develop poorly from birth. Surgery, medicines with harmful side effects, and x-ray treatments can also cause the disorder.

What Are the Symptoms of Addison's Disease?

Some people may have no symptoms. Others may feel weak, tired, or sick to the stomach; there may also be weight loss, decreased appetite, low blood pressure, depression, or skin and hair changes. Darkening of the skin over knuckles, knees, elbows, toes, or lips, creases of palms, and mucous membranes may be present.

People with addisonian crisis have a more serious illness that is a medical emergency. The sudden crisis usually results from stress, such as during surgery, trauma, or illness. Symptoms may include severe nausea and vomiting, diarrhea, very low blood pressure, leg and stomach pain, and coma.

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How Is Addison's Disease Diagnosed?

The doctor will order blood and urine laboratory tests and measurements of adrenal hormones.

The doctor may also want x-rays and CT (computed tomography) scans of the adrenal glands.

How Is Addison's Disease Treated?

Medicine to replace adrenal hormones includes hydrocortisone, fludrocortisone, and prednisone. These medications work well for this lifelong illness.

DOs and DON'Ts in Managing Addison's Disease:

✓ **DO** see your doctor regularly.

✓ **DO** take medicine as recommended by your doctor.

✓ **DO** talk to your doctor before you have surgery (to adjust your dose) and before using other prescription drugs.

✓ **DO** wear a medical alert bracelet.

✓ **DO** carry an emergency pack with medicine. Be sure that you and your family know how to give this medicine. Always be prepared for addisonian crisis.

✓ **DO** avoid stress.

✓ **DO** watch your lifestyle. Drink alcohol only in moderation. Eat a well-balanced diet with enough regular table salt.

✓ **DO** exercise, but don't overdo it.

✓ **DO** call your doctor when you feel poorly (nausea, vomiting, fever) or feel weak and tired

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and have weight loss.

✓ **DO** slowly decrease your medicine if your doctor recommends it. You'll avoid complications, such as weight gain, diabetes, and high blood pressure, from too much medicine.

⃠ **DON'T** eat too much potassium (foods like bananas, oranges, and salt substitutes).

⃠ **DON'T** skip doses of medicine.

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FOR MORE INFORMATION

Contact the following sources:

- National Adrenal Disease Foundation 505 Northern Boulevard, Suite 200 Great Neck, NY 11021 Tel: (516) 487-4992
- National Institute of Diabetes and Digestive and Kidney Diseases **Website:** **http://www.niddk.nih.gov/index.htm**
- Medic Alert Foundation International Tel: (209) 668-3333

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MANAGING YOUR

ALCOHOL ABUSE: FOR ADOLESCENTS

What Is Alcohol Abuse?

Alcohol is one of the four most common causes of death in the United States. Each year, alcohol is involved in death in car crashes of almost 2000 people younger than 21 and almost half of all violent deaths involving teens. Alcohol can cause or mask emotional problems, such as anxiety or depression. Teens who drink have trouble paying attention. They're more likely to have unprotected sex or have sex with strangers. The younger people are when they start drinking, the more likely they'll have an alcohol problem. Drinking can also increase the risk of using other drugs (marijuana, cocaine).

What Causes Alcohol Abuse?

Teens use alcohol because they're curious and want to feel good, lower stress, fit in, and feel older. Some teens have trouble managing impulses, emotions, and thrill-seeking behaviors. Parents and other adults often use alcohol socially, so teens may think that alcohol is harmless.

What Are the Symptoms of Alcohol Abuse?

Teens often deny that they have a problem or try to hide symptoms. Alcohol is a depressant, meaning it slows down the brain. Teens can feel more relaxed or less anxious, but they may also stagger, lose coordination, slur speech, and be confused and disoriented. They may be friendly or very aggressive. They may act totally out of character, have poor judgment, or be depressed. They may also lie, steal, break curfew, and have mood swings. Physical symptoms related to long-term alcohol damage include unsteadiness, nausea, stomach pains, diarrhea, vomiting, sweating, palpitations, blackouts, and yellow skin (jaundice) from liver disease.

How Is Alcohol Abuse Diagnosed?

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The doctor usually diagnoses alcohol abuse from a medical history. This history will show behaviors that cause school, social, and psychological problems. Blood tests may tell whether alcohol affected the blood, kidneys, liver, and overall health.

How Is Alcohol Abuse Treated?

Treatment varies depending on the degree of abuse. Brief treatment, including education about dangers of binge drinking and alcohol poisoning, can help abusers. Alcohol-dependent addicts usually need more help, such as detoxification (stopping drinking), medicine, counseling, and self-help group support.

Help with school, peer pressure, other medical problems, and coping skills is important. It's best to talk to parents, or to doctors, school counselors, clergy members, or adult relatives. Teens can find it hard to say no to drinking if friends drink. Different methods (saying no with or without explanations) work for different people.

DOs and DON'Ts in Managing Alcohol Abuse:

✓ **DO** get support from self-help groups, counselors, friends, and relatives.

✓ **DO** accept that relapsing is part of the illness, and work toward abstinence again.

✓ **DO** call the doctor for alcohol-related medical problems. These problems include vomiting, diarrhea, heartburn, chest tightness, and blood in bowel movements.

✓ **DO** call your doctor if you think about suicide.

⦸ **DON'T** drink. Don't have friends who drink.

⦸ **DON'T** lie to the doctor when asked about alcohol abuse. Bring it up if the doctor doesn't.

⦸ **DON'T** ever drive if you have been drinking.

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FOR MORE INFORMATION

Contact the following sources:

The best place to get additional information about alcoholism is at your local AA central office. In addition, most mental health centers can also give information, or you can check out the following websites.

- National Association for Children of Alcoholics **Website: http://www.nacoa.org**
- National Institute on Alcohol Abuse and Alcoholism E-mail: niaaaweb-r@exchange.nih.gov **Website: http://www.niaaa.nih.gov**
- Alcoholics Anonymous (International Office) Tel: (212) 870-3400 **Website: http://www.alcoholics-anonymous.org**

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MANAGING YOUR

ALCOHOL ABUSE: FOR WOMEN

What Is Alcohol Abuse?

Alcohol abuse occurs when a woman often drinks alcohol in amounts more than recommended. Problem drinking in women is having more than seven drinks weekly or more than three drinks per occasion. More than three or four drinks daily is called heavy drinking. One drink equals 12 oz of beer, 5 oz of wine, or 1.5 oz of 80-proof liquor. Alcohol abuse can manifest with heavy drinking, with immediate effects of drunkenness; and physically dependent alcoholism, with serious outcomes of long-term drinking.

Alcohol ranks as one of the four most common causes of death in the United States.

What Causes Alcohol Abuse?

Certain women prone to alcoholism are more likely to have relatives with alcoholism. They are also prone to other addictions (e.g., to nicotine).

What Are the Symptoms of Alcohol Abuse?

Alcohol abuse is often difficult to diagnose. People may deny that they have a problem or try to hide symptoms. Symptoms may be behavioral, physical, or psychological. Behavioral symptoms include feeling guilty and annoyed, being unable to stop drinking after starting, missing work or appointments, hurting yourself or others, and not remembering what was done. Physical symptoms can occur at once or be illnesses from long-term alcohol damage. These symptoms include unsteadiness, nausea, stomach pains, diarrhea, vomiting, sweating, palpitations, blackouts, and jaundice. Psychological symptoms include mood swings, depression, anxiety, poor sleep, and forgetfulness. Miscarriages can occur often, and babies born to women with alcohol abuse may have alcohol-caused abnormalities (called fetal alcohol syndrome).

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How Is Alcohol Abuse Diagnosed?

The doctor usually diagnoses alcoholism from the medical history. The doctor may suggest blood tests to see whether alcohol affected the blood, kidneys, liver, and general health.

How Is Alcohol Abuse Treated?

Successful treatment first requires a belief that a problem exists. Treatment often involves following a 12-step recovery plan (Alcoholics Anonymous, or AA) that includes abstinence, education, detoxification (withdrawal from drinking), and peer group support. Help with housing, jobs, social supports, other medical conditions, and coping skills is important. Detoxification may cause unpleasant symptoms, such as sweating and confusion. The doctor can help with detoxification. Medicines used for treatment include benzodiazepines to calm you down and other medications to reduce your craving for alcohol.

Stopping alcohol abuse is difficult. Women often relapse after treatment. However, they must accept that relapse is part of the illness and work toward abstinence again.

DOs and DON'Ts in Managing Alcohol Abuse:

✓ **DO** be honest about how much you drink.

✓ **DO** get support from self-help groups, counselors, friends, and relatives.

✓ **DO** understand that your attitude toward treatment will make a difference in whether you relapse.

✓ **DO** call your doctor if you have vomiting, diarrhea, heartburn, chest tightness, and blood in bowel movements. These may be related to alcohol abuse.

✓ **DO** call your doctor if you think about suicide.

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⦸ **DON'T** drink or see friends who do.

⦸ **DON'T** lie to your doctor when asked about alcohol abuse. Bring it up if the doctor doesn't.

⦸ **DON'T** give up when you have bad days.

⦸ **DON'T** drink and drive.

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FOR MORE INFORMATION

Contact the following sources:

The best place to get additional information about alcoholism is at your local AA central office. In addition, most mental health centers can also be of some assistance, or you can check out the following websites.

- National Association of Children of Alcoholics **Website: http://www.nacoa.org**
- National Institute on Alcohol Abuse and Alcoholism E-mail: niaaaweb-r@exhange.nih.gov **Website: http://www.niaaa.nih.gov**
- Alcoholics Anonymous (International Office) Tel: (212) 870-3400 **Website: http://www.alcoholics-anonymous.org**
- Women for Sobriety, Inc. Tel: (215) 536-8026 **Website: http://www.womenforsobriety.org**

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MANAGING YOUR

ALCOHOL ABUSE: FOR MEN

What Is Alcohol Abuse?

Alcohol abuse occurs when a man often drinks alcohol in amounts more than recommended. Problem drinking in men is having more than 14 drinks weekly or more than 4 drinks per occasion. More than 5 or 6 drinks daily is called heavy drinking. One drink equals one 12-oz bottle of beer, one 5-oz glass of wine, or 1.5 oz of 80-proof liquor. Alcohol abuse can manifest with heavy drinking, with immediate effects of drunkenness; and physically dependent alcoholism, with continuous drinking and serious outcomes of long-term drinking.

Alcohol ranks as one of the four most common causes of death in the United States.

What Causes Alcohol Abuse?

Certain men prone to developing alcoholism are more likely to have relatives with alcoholism. They are also more prone to other addictions (e.g., to nicotine).

What Are the Symptoms of Alcohol Abuse?

Alcohol abuse is often difficult to diagnose. People may deny that they have a problem or try to hide symptoms. Symptoms may be behavioral, physical, or psychological. Behavioral symptoms include feeling guilty and annoyed, being unable to stop drinking after starting, missing work or appointments, hurting yourself or others, and not remembering what was done while drinking. Physical symptoms can occur at once or be illnesses from long-term alcohol damage. These symptoms include unsteadiness, nausea, stomach pains, diarrhea, vomiting, sweating, palpitations, blackouts, and jaundice. Psychological symptoms include mood swings, depression, anxiety, poor sleeping, and forgetfulness.

How Is Alcohol Abuse Diagnosed?

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The doctor usually diagnoses alcoholism from the medical history. The doctor may suggest blood tests to see whether alcohol affected the blood, kidneys, liver, metabolism, and general health.

How Is Alcohol Abuse Treated?

Successful treatment first requires a belief that a problem exists. Treatment often involves following a 12-step recovery plan (Alcoholics Anonymous, or AA) that includes abstinence, education, detoxification (withdrawal from drinking), and peer group support. Help with housing, jobs, social supports, other medical conditions, and coping skills is important. Detoxification may cause unpleasant symptoms, such as sweating and confusion. The doctor can help with detoxification. Medicines used for treatment include benzodiazepines to calm you down and other medications to reduce your craving for alcohol.

Stopping alcohol abuse is difficult. Men often relapse after treatment. However, they must accept that relapse is part of the illness and work toward abstinence again.

DOs and DON'Ts in Managing Alcohol Abuse:

✓ **DO** be honest about how much you drink.

✓ **DO** get support from self-help groups, counselors, and friends and relatives.

✓ **DO** understand that your attitude toward treatment will make a difference in whether you relapse.

✓ **DO** call your doctor if you have nausea, vomiting, diarrhea, heartburn, chest tightness, and blood in stool; these may be related to your alcohol abuse.

✓ **DO** call your doctor if you think about suicide.

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⦸ **DON'T** drink. Don't see friends who drink. Don't keep alcohol at home.

⦸ **DON'T** lie to your doctor when asked about alcohol abuse. Bring it up if the doctor doesn't.

⦸ **DON'T** give up when you have bad days.

⦸ **DON'T** drink and drive.

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FOR MORE INFORMATION

Contact the following sources:

The best place to get additional information about alcoholism is at your local AA central office. In addition, most mental health centers can also be of some assistance, or you can check out the following websites.

- National Association for Children of Alcoholics **Website: http://www.nacoa.org**
- National Institute on Alcohol Abuse and Alcoholism (NIAAA) E-mail: niaaaweb-r@exhange.nih.gov **Website: http://www.niaaa.nih.gov**
- Alcoholics Anonymous (International Office) Tel: (212) 870-3400**Website: www.alcoholics-anonymous.org**

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MANAGING YOUR

ALCOHOL ADDICTION

What Is Alcohol Addiction?

Alcohol abuse is one of the four most common causes of death in the United States. Alcohol addiction is a complex disease involving long-term, excessive drinking of alcohol, so that stopping suddenly leads to unpleasant symptoms (withdrawal). Alcoholics are physically addicted to and crave alcohol, become tolerant to alcohol's effects (tolerance), and can relapse. They continue drinking despite serious medical and psychological harm and life disturbances. Over 17 million Americans overuse alcohol, about half being alcoholic (alcohol dependent).

What Causes Alcohol Addiction?

Certain people prone to developing alcohol addiction are more likely to have relatives with alcoholism. They often have other addictions (e.g., to nicotine).

What Are the Symptoms of Alcohol Addiction?

People often deny that they have a problem or try to hide symptoms. Symptoms may be behavioral, physical, or psychological. Behavioral symptoms include being unable to stop drinking after starting, missing work or appointments, hurting themselves or others, and not remembering what was done while drinking. Physical symptoms can be related to long-term alcohol damage and include unsteadiness, nausea, stomach pains, diarrhea, vomiting, sweating, palpitations, blackouts, and jaundice. Psychological symptoms include depression, anxiety, poor sleeping, and forgetfulness.

How Is Alcohol Addiction Diagnosed?

The doctor usually diagnoses alcoholism from the medical history showing behaviors that cause work, social, and psychological problems and signs of tolerance and withdrawal. Blood tests may

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tell whether alcohol affected the blood, kidneys, liver, and general health.

How Is Alcohol Addiction Treated?

Treatment varies depending on the degree of addiction and how seriously alcohol has affected the body's organs. Brief treatment, including education about dangers of binge drinking and alcohol poisoning, can help alcohol abusers. Alcohol addiction treatment may include detoxification (stopping drinking), medications, counseling, and self-help group support.

Successful treatment first requires a belief that a problem exists. Treatment often involves following a 12-step recovery plan (Alcoholics Anonymous) that includes abstinence, education, detoxification, and peer support. Help with housing, jobs, other medical problems, and coping skills is important. Detoxification may cause unpleasant symptoms (e.g., tremors, withdrawal seizures, and even delirium), but the doctor can prescribe medicine for withdrawal symptoms. Medicines used for treatment may include benzodiazepines, acamprosate, naltrexone, and disulfiram.

DOs and DON'Ts in Managing Alcohol Addiction:

✓ **DO** be honest about how much you drink.

✓ **DO** get support from your doctor, self-help groups, counselors, friends, and relatives.

✓ **DO** understand that your attitude toward treatment will make a difference in whether you relapse.

✓ **DO** accept that relapsing after treatment may be part of the illness, and work toward abstinence again.

✓ **DO** call your doctor if you have important medical problems because of alcohol, including

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vomiting, diarrhea, heartburn, chest tightness, and blood in bowel movements.

✓ **DO** call your doctor if you are depressed.

⃠ **DON'T** drink. Don't see friends who drink. Don't keep alcohol at home.

⃠ **DON'T** lie to your doctor when asked about alcohol abuse. Bring it up if the doctor doesn't.

⃠ **DON'T** give up when you have bad days.

⃠ **DON'T** ever drink and drive.

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FOR MORE INFORMATION

Contact the following sources:

The best place to get additional information about alcoholism is at your local AA central office. In addition, most mental health centers can also give information, or you can check out the following websites:

- National Association for Children of Alcoholics **Website: http://www.nacoa.org**
- National Institute on Alcohol Abuse and Alcoholism E-mail: niaaaweb-r@exchange.nih.gov **Website: http://www.niaaa.nih.gov**
- Alcoholics Anonymous (International Office) Tel: (212) 870-3400 **Website: http://www.alcoholics-anonymous.org**
- Women for Sobriety, Inc. Tel: (215) 536-8026 **Website: http://www.womenforsobriety.org**

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MANAGING YOUR

ALCOHOLIC HEPATITIS

What Is Alcoholic Hepatitis?

Alcoholic hepatitis is inflammation (swelling and irritation) of the liver. It is treatable, but for any treatment to work, drinking alcohol must stop. With continued drinking, alcoholic hepatitis can progress to cirrhosis of the liver. Cirrhosis is an illness that can't be cured. In cirrhosis, normal liver tissue is destroyed and replaced by scar tissue. In time, the liver stops working.

The disease usually affects people older than 30.

What Causes Alcoholic Hepatitis?

Alcoholic hepatitis is caused by drinking too much alcohol for a long time.

What Are the Symptoms of Alcoholic Hepatitis?

Symptoms may not appear until damage to the liver is severe.

Symptoms are similar to those of viral hepatitis. The first symptoms are rashes, pain in the joints, and a flu-like feeling. People who drink alcohol may also be malnourished.

As the disease progresses, later symptoms include yellowish skin and whites of the eyes (jaundice); pale or clay-colored stools; dark urine; general itching; high temperature; swelling of the abdomen (belly) caused by fluid; painful, tender, and enlarged liver; mental confusion; and possible coma.

How Is Alcoholic Hepatitis Diagnosed?

The doctor may suspect the disease because of a history of drinking too much alcohol, abnormal blood tests suggesting inflammation of the liver, and an abnormal physical examination that shows an enlarged liver. To confirm the diagnosis, the doctor may recommend a liver biopsy. For a biopsy, the doctor inserts a hollow needle through the skin and takes out a tiny piece of

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liver tissue for study in the laboratory.

How Is Alcoholic Hepatitis Treated?

Treatment of hepatitis is supportive, meaning that the goal is to improve the person's overall health and increase strength. The key is to stop drinking alcohol. An alcohol rehabilitation program can offer important help with this. Malnourishment is improved by following a good diet, one that is high in carbohydrates and calories. Intravenous feedings may be needed in people with extremely poor nutritional status. Eating less salt (sodium) may also be important to prevent abdominal swelling. Vitamin supplements are also needed, especially vitamin B and folic acid. It may take the liver weeks to months to heal.

DOs and DON'Ts in Managing

Alcoholic Hepatitis:

✓ **DO** stop drinking.

✓ **DO** seek treatment for your alcohol problem.

✓ **DO** eat a well-balanced, high-calorie diet. People who drink too much alcohol are often malnourished.

✓ **DO** take vitamins, especially vitamin B and folic acid.

✓ **DO** change your activity according to your symptoms. A good fitness program may help with fatigue.

✓ **DO** call your doctor if you develop symptoms suggesting alcoholic hepatitis.

✓ **DO** call your doctor if you develop symptoms after prolonged or heavy drinking.

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⦸ **DON'T** drink alcohol. You could get cirrhosis of the liver.

⦸ **DON'T** salt your food. Eating salt can make swelling of the abdomen worse.

⦸ **DON'T** use drugs, including acetaminophen, sedatives, and tranquilizers, that can harm the liver.

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FOR MORE INFORMATION

Contact the following sources:

- Alcoholics Anonymous Tel: (212) 870-3400 **Website: http://www.alcoholics-anonymous.org**
- American Liver Foundation Tel: (800) GOLIVER (465-4837) E-mail: webmail@liverfoundation.org **Website: http://www.liverfoundation.org**
- National Institute of Alcohol Abuse and Alcoholism Tel: (301) 443-3860 **Website: http://www.niaaa.nih.gov**

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MANAGING YOUR

ALDOSTERONISM

What Is Aldosteronism?

Aldosteronism is an illness caused by too much aldosterone, a hormone produced by adrenal glands. These two small glands sit atop the kidneys. Aldosteronism leads to high blood pressure and low blood potassium levels.

What Causes Aldosteronism?

Aldosterone is a hormone that regulates blood pressure and body fluids by increasing sodium and fluid levels in the blood and increasing removal of potassium by kidneys. The two main types of aldosteronism are primary and secondary. Primary aldosteronism means that extra aldosterone comes from adrenal glands themselves, usually because of a growth (or tumor). This usually benign (not cancerous) tumor is called an adenoma. This disorder is also called Conn's syndrome. Bilateral adrenal hyperplasia, an illness in which both glands are enlarged and overproduce aldosterone, may also cause this condition.

Secondary aldosteronism means that the illness results from other conditions, such as congestive heart failure, liver failure, kidney disease, and dehydration, or certain medicines, such as diuretics or fludrocortisone.

Aldosteronism accounts for less than 1% of cases of high blood pressure in the United States.

What Are The Symptoms Of Aldosteronism?

High blood pressure, weakness, cramping, nausea, constipation, muscle spasm, and frequent urination may occur. Some people have no symptoms.

How Is Aldosteronism Diagnosed?

High blood pressure and low blood potassium levels may indicate aldosteronism.

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High aldosterone levels can be measured in blood or urine. A special blood test called plasma renin activity (PRA) can help determine whether primary or secondary aldosteronism is present. A specialist called an endocrinologist will use special tests for primary aldosteronism. Endocrinologists treat diseases of glands and hormones.

An MRI (magnetic resonance imaging) or CT (computed tomography) scan of the belly (abdomen) may be done to help identify the cause of aldosteronism.

How Is Aldosteronism Treated*?*

Untreated aldosteronism can cause uncontrolled high blood pressure, which can be a risk factor for stroke or heart disease. People with very low potassium levels may also have an abnormal heartbeat. Treatment for Conn's syndrome involves tumor removal by surgery.

Bilateral adrenal hyperplasia can't be cured unless both adrenal glands are removed. This removal may cause more side effects than wanted. Therefore people with this illness take spironolactone, a diuretic. This drug helps keep blood potassium levels normal. Side effects may include gynecomastia (breast development in men), impotence, and feeling tired and drowsy.

For aldosteronism resulting from other illnesses, treatment of the condition causing higher aldosterone levels will help.

DOs and DON'Ts in Managing Aldosteronism:

✓ DO follow your doctor's instruction to add salt to each meal or take salt tablets for special tests.

✓ DO tell your doctor if you have a history of congestive heart failure before beginning this high-salt diet.

✓ DO find an experienced surgeon to remove the tumor if present and your doctor recommends surgery.

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✓ DO call your doctor if you have male breast development, impotence, nausea, drowsiness, or lethargy while taking spironolactone.

✓ DO call your doctor for cramps or rapid heartbeats. Your potassium level may be dangerously low.

✓ DO call your doctor if you feel extremely weak and tired or dizzy when you stand up. You may need extra hormone replacement after surgery.

⊘ DON'T let your potassium level fall below normal, especially if you're taking diuretics. Follow dietary instructions from your doctor and have frequent blood tests to check potassium levels.

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FOR MORE INFORMATION

Contact the following sources:

- National Adrenal Disease Foundation 505 Northern Boulevard, Suite 200 Great Neck, NY 11021 Tel: (516) 487-4992
- The Endocrine Society 435 East West Highway, Suite 500 Bethesda, MD 20814-4410 Tel: (888) 363-6274

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MANAGING YOUR

ALLERGIC RHINITIS

What Is Allergic Rhinitis?

Allergic rhinitis consists of symptoms that occur after exposure to certain substances. This reaction is called an allergy. Allergies can be seasonal (hay fever), especially in spring and fall for a sensitivity to tree and grass pollens. Allergies can also occur year-round (e.g., to pets or house dust mites). Having allergies tends to run in families. Allergies usually occur in people younger than 20 but can develop at any age.

Allergic rhinitis is not contagious and can be controlled.

What Causes Allergic Rhinitis?

Irritants include smoke, smog, pollens, molds, and dust.

What Are the Symptoms of Allergic Rhinitis?

The most common symptoms include sneezing, itchy eyes, scratchy throat, and runny, stuffed, and itchy nose. Other symptoms are headaches and pressure in the front of the face, and difficulty sleeping.

Long-term problems associated with allergic rhinitis are nasal polyps (growths in the nose) and loss of the sense of smell.

How Is Allergic Rhinitis Diagnosed?

The doctor usually uses symptoms alone for diagnosis. The doctor may do skin tests to see which substances cause the symptoms. In people with chronic cough, a lung function test may help rule out asthma.

How Is Allergic Rhinitis Treated?

The best treatment usually involves reducing or avoiding exposure to substances causing symp-

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toms (allergens), along with using antihistamines, and nasal decongestants. Preventing symptoms with drugs and using a mask in areas of high exposure to allergens may also help. People who respond poorly to drugs may get shots (injections, called desensitization). These injections of an allergen are given in increasing doses to get the body to block the allergic reaction. Possible drug side effects include sleepiness (oral antihistamines), palpitations or changes in blood pressure (oral decongestants), and thinning of tissues in the nose (intranasal steroids).

Treatment by an allergist (a doctor trained in treating allergies) or an ear, nose, and throat specialist may be needed in severe or resistant cases.

DOs and DON'Ts in Managing Allergic Rhinitis:

✓ **DO** avoid exposure to allergens. Close doors and windows, use air conditioning, and use special filters.

✓ **DO** avoid garden work (or wear a mask) if you are allergic to outdoor molds. Inside the house, use a dehumidifier.

✓ **DO** replace carpets and drapes with flooring and roller blinds, enclose mattresses and pillows in plastic bags, add a HEPA filter to the vacuum cleaner, and wash bedding at high temperatures if you are allergic to dust mites.

✓ **DO** keep the pet outdoors, if possible, if allergic to a pet. Have another household member wash and brush the animal weekly.

✓ **DO** take your medicine as recommended.

✓ **DO** contact your doctor if symptoms become constant and keep you awake, if nasal dis-

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charge becomes thick and colored, or you have problems with medicines.

✓ **DO** work with your doctor to identify triggers of symptoms. Your doctor may refer you to an allergist for allergy shots, or to an ear, nose, and throat specialist for advice on long-term management.

⃠ **DON'T** overuse nasal decongestants. These can have a rebound effect that produces the same symptoms as the allergy.

⃠ **DON'T** expose yourself to cigarette smoke or irritating substances.

⃠ **DON'T** forget to review your drugs and options with your doctor and pharmacist, especially if you take other medicines.

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FOR MORE INFORMATION

Contact the following sources:

• American Academy of Allergy, Asthma & Immunology Tel: (800) 822-2762, (414) 272-6071 E-mail: info@aaaai.org **Website: http://www.aaaai.org**

• Asthma and Allergy Foundation of America Tel: (800) 7-ASTHMA (727-8462) **Website: http://www.aafa.org**

• American Lung Association Tel: (800) LUNG-USA (586-4872), (212) 315-8700 **Website: http://www.lungusa.org**

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MANAGING YOUR

ALOPECIA

What Is Alopecia?

Alopecia means hair loss. Alopecia areata is hair loss in round patches on the scalp. Alopecia universalis refers to hair loss over the whole body.

What Causes Alopecia?

Heredity plays a major role in hair loss. Other contributing factors are the presence of male hormones, worry and stress, poor nutrition, low red blood cell count, thyroid problems, pregnancy, ringworm of the scalp, and medicines such as oral contraceptives, anticancer drugs, and statins.

Hair can also be lost because of hairstyles, pulling on hair, infections, burns, severe illness, and even after having major surgery.

Alopecia can be permanent or temporary (such as when caused by cancer treatment drugs).

What Are the Symptoms of Alopecia?

Hair can be lost from any part of the body, the scalp, eyebrows, underarms, genital area, arms, and legs. It can occur gradually or suddenly. Itching may occur, for example, when ringworm is the cause.

How Is Alopecia Diagnosed?

The doctor bases the diagnosis on the physical examination. Blood tests may be done to check for anemia, infection, arthritis, or hormone imbalances. Analysis of hair can also be performed.

How Is Alopecia Treated?

Treatment doesn't always work. The doctor may suggest a liquid medication (minoxidil) to put on areas with alopecia. It may help hair regrow but its effects vary greatly. The doctor may sometimes inject medicine (steroids) into small areas with alopecia.

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Hair transplants can restore hair, and wigs and hair weaves may reduce the look of alopecia.

For alopecia on the scalp, the doctor can use scalp reduction therapy. In this therapy, the doctor removes a strip of scalp about every few weeks until edges of hair meet, or until scalp tissue becomes too thin.

Men with male pattern baldness can take finasteride (Propecia®), a prescription drug taken by mouth, to minimize alopecia and promote regrowth of hair.

An illness causing alopecia, such as infection, ringworm, anemia, and hormone imbalance, will need treatment. Alopecia with reversible causes, such as pregnancy and stress, usually stops, and new hair grows, but this may take several months.

DOs and DON'Ts in Managing Alopecia:

✓ **DO** bathe and shampoo as usual.

✓ **DO** be sure to follow your doctor's advice if you have anemia or thyroid problems.

✓ **DO** avoid alkaline pH shampoos.

✓ **DO** pat your hair dry rather than rubbing it with a towel.

✓ **DO** use a comb rather than a brush, and avoid brushing your hair excessively when it is wet.

✓ **DO** use a conditioner for easier combing.

✓ **DO** call your doctor if signs of infection appear after treatment with steroid injections. These signs include redness, swelling, tenderness, and warmth at the site of injections.

✓ **DO** consider wearing a hairpiece or wig if you think this improves how you look.

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⦸ **DON'T** tug on normal hair close to areas of alopecia.

⦸ **DON'T** damage your hair by bleaching, permanent waving, straightening, using hot combs or overly hot dryers, or excessive sun exposure.

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FOR MORE INFORMATION

Contact the following source:

- The National Alopecia Areata Foundation Tel: (415) 472-3780 **Website:** **http://www.naaf.org/**

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MANAGING YOUR

ALPHA-1-ANTITRYPSIN DEFICIENCY

What Is Alpha-1-Antitrypsin Deficiency?

Alpha-1-antitrypsin (AAT) is a protein made by the liver. It protects the lungs from harmful effects of an enzyme named neutrophil elastase. In AAT deficiency, lungs can't expand and contract well. Breathing is more difficult, and lung damage (emphysema) can result. The signs and symptoms of AAT deficiency commonly present initially in people 20 to 40 years old.

What Causes AAT Deficiency?

AAT deficiency is inherited, which means parents pass it to children. It's one of the most common inherited disorders in Caucasians. It's not contagious.

What Are the Symptoms of AAT Deficiency?

Shortness of breath, being less able to exercise, coughing, sputum production, and wheezing are symptoms. The main manifestation is labored breathing that progressively gets worse. In some babies and children born with this disorder, it may also cause liver damage.

How Is AAT Deficiency Diagnosed?

The health care provider may suspect the diagnosis from the medical history and physical examination. X-rays and laboratory tests may be done to rule out similar disorders. A simple blood test that measures AAT will confirm the diagnosis. Chest X-rays and pulmonary function testing can help find out how severe emphysema is. Other blood tests may be done to check the liver function.

How Is AAT Deficiency Treated?

Treatment aims to prevent or slow progression of lung disease. Lungs should be protected from infections and inflammation. Immunizations should be given to prevent flu and pneumonia.

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Health care provider should provide treatment of lung infections at the first sign of infection. Avoid tobacco, smoke, noxious fumes, dust, and pollution. Stay fit by doing regular exercise. In severe cases, your doctor may recommend replacing the enzyme that's missing. A specialist in diseases of the lung can help in diagnosing and treatment of this disorder. Medicines such as inhalers may be used to help dilate bronchi (airways in the lung) and decrease lung inflammation. Oxygen and pulmonary rehabilitation programs may also help symptoms. In severe cases, lung surgery and transplantation are other possibilities.

DOs and DON'Ts in Managing AAT Deficiency:

✓ **DO** understand that AAT deficiency is inherited. People need two genes from their parents.

People with only one gene are called carriers and usually don't have symptoms of emphysema.

✓ **DO** understand that many cases aren't diagnosed. Family members should be tested if there's

any history of lung disease, especially in a young person who doesn't smoke.

✓ **DO** get your shots (flu, pneumonia, tetanus). Prevention of infections is critical.

✓ **DO** call your health care provider if you feel short of breath at rest or with little exertion.

Call if you have wheezing, flu-like symptoms, or coughing up discolored phlegm.

✓ **DO** call your health care provider if you need a referral to a lung specialist.

✓ **DO** call your health care provider if you want genetic counseling.

⦸ **DON'T** smoke.

⦸ **DON'T** be exposed to environmental pollutants that can worsen breathing.

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Contact the following sources:

- Alpha One Foundation Tel: (877) 228-7321 **Website: http://www.alphaone.org**
- American Lung Association Tel: (800) LUNG-USA **Website: http://www.lungusa.org**

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MANAGING YOUR

ALTITUDE SICKNESS

What is Altitude Sickness?

Altitude sickness is an illness that results from travel to high altitudes. Acute mountain sickness (AMS) is the most common such illness; as many as 50% of people may be affected at 15,000 feet, men and women equally. Younger adults may be more affected. AMS is more common in people with lung problems and people who usually live at very low altitudes.

What Causes Altitude Sickness?

High altitudes have less oxygen in the air. Breathing and heart rates increase to adjust to the thin air. High altitude may lead to swelling (edema) of hands, face, and feet. The body may not adapt to rapid exposure to 7000 to 8000 feet or more. Illnesses such as AMS and high-altitude lung (pulmonary) and brain (cerebral) edema can result.

What Are the Symptoms of Altitude Sickness?

Symptoms are headache, nausea, vomiting, shortness of breath, difficulty sleeping, dizziness, and malaise. They usually occur 6 to 48 hours after ascent. Symptoms may mimic alcohol hangover, exhaustion, or infection.

High-altitude pulmonary edema is a life-threatening condition often seen in young, fit climbers who made earlier high-altitude trips without problems. The first symptom is reduced ability to exercise. Later symptoms include cough, chest congestion, shortness of breath at rest, reduced alertness, and poor coordination.

Symptoms of high-altitude cerebral edema (brain swelling) are severe headache, impaired walking, and other neurologic problems (e.g., hallucinations and even coma).

How Is Altitude Sickness Diagnosed?

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Diagnosis is based on symptoms and a history of travel to higher altitudes.

How Is Altitude Sickness Treated?

Treatment depends on how severe the illness is and the altitude. The goal is to go down to a lower altitude quickly and safely and to begin oxygen therapy as soon as possible. Symptoms usually disappear in 1 to 3 days. Acetaminophen or aspirin can help with minor symptoms. Drugs such as acetazolamide and nifedipine can help with more severe symptoms.

For high-altitude cerebral edema, immediate descent and oxygen therapy, and often dexamethasone (a steroid), help prevent serious nerve damage or death.

DOs and DON'Ts in Managing Altitude Sickness:

✓ **DO** prevent altitude sickness by gradually ascending, taking 2 to 4 days to adjust to 6000 to 8000 feet.

✓ **DO** talk with your doctor about the need for medications to help prevent altitude sickness. Acetazolamide is usually started before ascent and continued at high altitude. Nausea and numbness or tingling of the lips, fingers, and toes may be side effects.

✓ **DO** get enough rest.

✓ **DO** increase fluid and carbohydrate intake to help minimize effects of altitude illness.

✓ **DO** start moving, as safely and quickly as possible, to a lower altitude if serious nerve or breathing problems develop.

⦸ **DON'T** use alcohol and sleeping pills.

⦸ **DON'T** overexert yourself when first arriving at high altitude. Exercise before traveling to high altitude does not help prevent altitude sickness.

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⦸ **DON'T** take acetazolamide if you're allergic to sulfa drugs.

⦸ **DON'T** go to high altitudes if you had previous high-altitude sickness.

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FOR MORE INFORMATION

Contact the following source:

- American Lung Association Tel: (212) 315-8700 **Website: http://www.lungusa.org**

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MANAGING YOUR

ALZHEIMER'S DISEASE

What Is Alzheimer's Disease?

Dementia is a serious brain disorder that affects a person's ability to carry out daily activities. Alzheimer's disease (AD) is the most common type of dementia among older people. It is a slow disease, starting with mild memory problems and ending with severe brain damage. It affects memory, thinking, and language.

The course of the disease and how fast changes occur vary from person to person. AD is usually not inherited but risk increases if there is a family history.

What Causes Alzheimer's Disease?

The cause remains unknown. In AD, brain cells that store and process information begin to fail and die. Also, more abnormal proteins are made, which form clumps and tangles around and inside these cells.

What Are the Symptoms of Alzheimer's Disease?

The first symptom is usually increased forgetfulness. People forget names or where they put things. However, some forgetfulness is normal with aging; not everyone with these symptoms has AD or dementia.

Later, memory and thinking problems grow. People forget recent events and names of familiar people or objects, ask the same question or tell the same story over and over, and have trouble organizing everyday life (e.g., paying bills).

In middle and later stages of AD, people need help with everyday activities. Eventually they need total care. People become unable to get dressed, lose awareness of events, become easily disoriented or anxious, get lost, show emotional and personality changes, and have greater physi-

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cal disability.

How Is Alzheimer's Disease Diagnosed?

No one test can show whether someone has AD. The doctor will diagnose it by checking general health, medical history, and mental abilities. The doctor will ask questions about a person's own life and wider world. The doctor may also test reasoning, hand-to-eye coordination, balance, and sensation, as well as look for depression. A brain scan may show other causes of dementia. Blood tests may be done to look for other disorders that can affect memory such as an underactive thyroid or vitamin B_{12} deficiency.

How Is Alzheimer's Disease Treated?

There is no cure. Drugs can sometimes slow the worsening of symptoms. These drugs include cholinesterase inhibitors and memantine. Other medicines can help anxiety, depression, agitation, behavior problems, or psychotic symptoms.

People with AD have trouble adapting to changing living environments. Printing information that is often forgotten and putting it around the home can help. A medical alert bracelet or tag giving the home address helps people who get lost.

DOs and DON'Ts in Managing

Alzheimer's Disease:

✓ **DO** find out about help and support.

✓ **DO** try to simplify daily routines and living spaces.

✓ **DO** think about home safety. Change objects or situations that could be dangerous (e.g., add handrails or door locks).

✓ **DO** join a support group.

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✓ **DO** keep socially, physically, and mentally active. Understand that nursing home care will be likely.

✓ **DO** wear an identification band.

✓ **DO** arrange for breaks for caregivers.

✓ **DO** call the doctor if you have sudden marked worsening of symptoms, new health issues, or problems with medicines.

⦸ **DON'T** assume that you have AD. Mental changes have many causes that are reversible or treatable.

⦸ **DON'T** change your living environments any more than absolutely necessary. Unfamiliar experiences and confusing environments are hard to handle and often cause anxiety.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- Alzheimer's Association Tel: (800) 272-3900 (24-hour helpline) **Website:** **http://www.alz.org**
- Alzheimer's Disease Education and Referral Center Tel: (800) 438-4380 **Website:** **http://www.alzheimers.org**
- The Alzheimer's Foundation of America Tel: (866) 232-8484 **http://www.alzfdn.org**

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CARING FOR SOMEONE WITH

ALZHEIMER'S DISEASE

What Is Alzheimer's Disease?

Dementia is a serious brain disorder affecting the ability to carry out daily activities. Alzheimer's disease (AD) is the most common type of dementia among older people. It is a slow disease, starting with mild memory problems and ending with severe brain damage. It affects memory, thinking, and language.

On average, people with AD live 8 to 10 years after diagnosis, although they can live for much longer.

AD affects both the person and the family. Caring for someone with AD is physically and emotionally exhausting, so caregivers should know about support resources and how to use them.

What Causes Alzheimer's Disease?

The cause remains unknown. In AD, brain cells that store and process information begin to fail and die. Also, more abnormal proteins make clumps and tangles around and inside these cells.

What Are the Symptoms of Alzheimer's Disease?

The first symptom is usually increased forgetfulness. People forget names or where they put things. However, some forgetfulness is normal with aging; not everyone with these symptoms has AD or dementia.

Later, memory and thinking problems grow. People forget names of familiar people or objects, ask the same question or tell the same story over and over, and have trouble in everyday life (e.g., paying bills).

In middle and later stages of AD, people need more help and eventually need total care.

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People wander away and get lost, have emotional and personality changes (including aggression, distrust), and have greater physical disability.

How Is Alzheimer's Disease Diagnosed?

No one test can show whether someone has AD. The doctor will diagnose it by checking general health, medical history, and mental abilities. The doctor may test reasoning, hand-to-eye coordination, balance, and sensation, as well as look for depression. A brain scan may show other causes of dementia.

How Is Alzheimer's Disease Treated?

There is no cure. Drugs can sometimes slow the worsening of symptoms. These drugs include cholinesterase inhibitors and memantine.

Medicine can also help anxiety, depression, agitation, and behavior problems.

People with AD have trouble adapting to changing living environments, so try not to change caregivers or residences more than needed. Print critical information and put it in several places in the home. A medical alert bracelet or tag giving the home address helps people who get lost.

DOs and DON'Ts in Managing Alzheimer's Disease:

✓ **DO** find out about help and support. Arrange for breaks in caregiving.

✓ **DO** try to simplify daily routines and living spaces.

✓ **DO** think about home safety. Change situations that could be dangerous (e.g., add handrails or door locks).

✓ **DO** create pleasant distractions if the person is upset or angry.

✓ **DO** keep people socially, physically, and mentally active. Supervise as needed. Understand

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that nursing home care will become likely.

✓ **DO** have the person wear an identification band.

✓ **DO** call the doctor if you see worse symptoms or problems with health or medicines.

⃠ **DON'T** neglect your own needs.

⃠ **DON'T** assume that someone has AD. Mental changes have many causes.

⃠ **DON'T** change the person's living environments more than absolutely necessary.

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FOR MORE INFORMATION

Contact the following sources:

- Alzheimer's Association Tel: (800) 272-3900 (24-hour helpline) **Website:** **http://www.alz.org**
- Alzheimer's Disease Education and Referral Center (ADEAR) Tel: (800) 438-4380 **Website: http://www.alzheimers.org**
- Alzheimer's Foundation of America Tel: (866) 232-8484 **Website: http://www.alzfdn.org**

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MANAGING YOUR

AMAUROSIS FUGAX

What Is Amaurosis Fugax?

Amaurosis fugax is blindness in one eye (monocular) that lasts for a short time. This condition usually starts suddenly and usually goes away in seconds to minutes.

What Causes Amaurosis Fugax?

The cause is a temporary blockage in the artery supplying blood to the eye. Usually, blood clots or plaques (small pieces of cholesterol or fat) block the vessel. Clots from a larger artery travel up to the brain or eye and become stuck in the artery supplying blood to the eye. Narrowing of one of the main blood vessels taking blood to the brain and eye can also cause low blood flow to the eye.

What Are the Symptoms of Amaurosis Fugax?

Symptoms include a sudden, temporary vision loss. It's as if a shade or curtain covers the eye. It may occur alone or be followed by more severe nervous system symptoms if there is additional blockage of arteries supplying the brain.

How Is Amaurosis Fugax Diagnosed?

In addition to obtaining a detailed history of your symptoms and performing a neurologic exam, the doctor will use imaging studies for diagnosis: ultrasonography (including echocardiography), magnetic resonance angiography (MRA), and angiography may be done. Echocardiography takes moving pictures of the heart to look for blood clots in the heart that may travel to the brain. MRA uses a magnetic field and pulses of radio wave energy to get pictures of blood vessels. Angiography uses dye injected into blood vessels to get special x-rays. These tests can find blockages and clots in blood vessels and the heart.

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How Is Amaurosis Fugax Treated?

Treatment depends on finding the source of the blood clots or ruptured cholesterol plaques that caused low blood flow or blocked the artery. Clots may come from arteries in the head or neck, or from the heart. Treatment depends on where the blockage is and how severe it is. If more than 70% of the carotid artery appears blocked, the doctor may use surgery to remove the blockage. The decision to do surgery is also based on overall health. Balloon angioplasty and stenting may also be used to open the blocked artery. Other treatments include medicines such as aspirin or other blood thinners.

DOs and DON'Ts in Managing Amaurosis Fugax:

✓ **DO** control your blood sugar if you're diabetic.

✓ **DO** control your blood pressure and cholesterol level.

✓ **DO** take your medicines as your doctor prescribes.

✓ **DO** quit smoking.

✓ **DO** call your doctor immediately if you have another episode of vision loss.

✓ **DO** call 911 and your doctor immediately if you have other neurologic symptoms such as weakness, difficulty speaking, headache, dizziness.

⦸ **DON'T** drive without permission from your doctor. Sudden vision loss in one eye could be dangerous.

⦸ **DON'T** use tobacco because it leads to blood vessel disease.

⦸ **DON'T** ignore any of these symptoms. They may be an early warning sign of a major stroke.

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Neurological Disorders and Stroke (NINDS) Tel: (301) 496-5751

  Website: http://www.ninds.nih.gov

- American Stroke association Tel: (888) 478-7653 **Website:**

  http://www.strokeassociation.org

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MANAGING YOUR

AMEBIASIS

What Is Amebiasis?

Amebiasis is an infection of the large intestine and sometimes the liver.

What Causes Amebiasis?

Amebiasis is caused by an ameba, the parasite *Entamoeba histolytica.* It is common in subtropical locations, especially in crowded or unsanitary living conditions. Amebic dysentery (or gastrointestinal amebiasis) is diarrhea caused by the parasite, which damages the stomach and intestine. People usually get the parasite by drinking dirty water or eating contaminated food. Flies or other insects also spread the infection. Amebic dysentery can also be caught from an infected sexual partner during anal sex.

What Are the Symptoms of Amebiasis?

Symptoms usually begin 2 to 4 weeks after infection, or in some cases, months later. Some people have no symptoms (but may be carriers). The most common symptoms are diarrhea (10 to 12 small bowel movements daily), bloody diarrhea**,** stomach cramps, stomach tenderness (soreness), mucus (slippery, thick liquid) in the stool (feces or diarrhea), and gas. Other symptoms include fever, back pain, and tiredness.

How Is Amebiasis Diagnosed?

The doctor will take a medical history and do an examination. Three or more samples of stool are studied under a microscope to find parasites or cysts. The doctor may recommend sigmoidoscopy or colonoscopy (using a small tube, or scope, with a lighted tip) to get small samples from the intestine to examine when the diagnosis remains uncertain after other tests.

How Is Amebiasis Treated?

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With treatment, most people get better in 10 to 20 days. In most cases, medicine kills the ameba. It is critical to take all the medicine prescribed by the doctor. The doctor will recheck the stool after treatment to make sure all parasites are gone.

Medicines include metronidazole and iodoquinol. Side effects include nausea, headache, dry mouth or metallic taste, and darkened urine. Don't drink alcohol when taking these drugs.

Bed rest may be needed in severe cases, with normal activities then resumed gradually. Fluids must be increased to prevent dehydration. In serious cases, intravenous fluids may be given.

DOs and DON'Ts in Managing Amebiasis:

✓ **DO** take your medicine as prescribed.

✓ **DO** increase fluid (water) intake.

✓ **DO** wash hands often with soap and warm water.

✓ **DO** drink bottled or boiled water or soda if traveling in developing countries.

✓ **DO** make sure all food is well cooked.

✓ **DO** call your doctor right away if you have a high fever, bloody diarrhea, stomach pain, pain in the right upper side of your stomach, or yellowing of the skin.

✓ **DO** practice safe sex (use a latex condom).

✓ **DO** call your doctor if you cannot take the fluids or medicines prescribed.

⦸ **DON'T** drink alcohol during treatment.

⦸ **DON'T** swim in fresh water outside the United States or Western Europe, or in dirty pools.

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⦸ **DON'T** eat raw vegetables, unpeeled fruit, raw fish, or shellfish in questionable areas. Don't have ice in your drinks or eat ice cream when traveling in countries with poor sanitation.

⦸ **DON'T** stop taking your medicine or change your dose because you feel better unless your doctor tells you to.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Allergy and Infectious Diseases Tel: (866) 284-4107 **Website:** **http://www.healthfinder.gov**
- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website:** **http://www.cdc.gov**

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MANAGING YOUR

AMENORRHEA

What Is Amenorrhea?

Periods normally stop in women who are pregnant, breastfeeding, or going through menopause. Other women of reproductive age who have no periods have the condition called amenorrhea. It is primary or secondary depending on whether it occurs before or after the first period. Primary amenorrhea (absence of initial menstrual period) occurs by age 16, but girls do have other signs they're maturing (secondary sex characteristics). Secondary amenorrhea means no periods for more than three cycles or 6 months. Less than 1% of U.S. women have primary amenorrhea. The secondary type occurs in 5% to 7% of women of reproductive age.

What Causes Amenorrhea?

Causes are usually disorders of the pituitary gland, hypothalamus, ovaries, or uterus. In the rare case of primary amenorrhea, some women may be born with anatomic abnormalities of the vagina and uterus, which may need surgery to correct the problem. Risk factors for amenorrhea include rapid and severe weight loss, underactive thyroid, medicines (such as progesterone), and chronic illness. Amenorrhea isn't contagious.

What Are the Symptoms of Amenorrhea?

The major sign is abnormal absence of periods. Other abnormalities depend on the cause of amenorrhea. For example, an underactive thyroid may cause weight gain, fatigue, hair loss, dry skin, constipation, and slow heart rate.

How Is Amenorrhea Diagnosed?

The health care provider makes a diagnosis from the medical history, physical examination, and laboratory tests. The health care provider may also use X-rays or ultrasonography to determine the

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cause of the amenorrhea. The first step is to rule out pregnancy by using a pregnancy test. Magnetic resonance imaging (MRI) of the brain may be done when abnormalities of the pituitary gland or hypothalamus are suspected. Computed tomography (CT) of the abdomen (belly) and pelvis is another possible test if abnormalities of the uterus or ovaries are suspected. The health care provider may suggest seeing specialists (endocrinologist and gynecologist) for additional evaluation and treatment. Endocrinologists specialize in endocrine diseases. Gynecologists specialize in the female reproductive system (uterus, vagina, ovaries).

How Is Amenorrhea Treated?

Treatment depends on the cause and on a woman's goals, such as wanting to get pregnant. Women may want to treat endocrine problems such as excess facial hair, deep voice, and baldness which in some cases are associated with amenorrhea. A drug called medroxyprogesterone will help periods start in most women. The health care provider may suggest estrogen replacement, calcium, and vitamin D for some women. Women on estrogen replacement who still have a uterus need progesterone, which protects against uterine cancer. Other drugs may be used for women with adult-onset congenital adrenal hyperplasia, premature ovarian failure, and hypothyroidism. Women with anatomic abnormalities may need surgery. Women with severe weight loss due to eating disorders or excessive exercise, may need behavioral treatment and nutritional counseling. In women with amenorrhea due to polycystic ovarian syndrome (PCOS), treatment consists of weight loss by dieting and exercise. Medicines such as metformin can also be given. Women with hereditary causes of amenorrhea can see a genetics specialist for additional evaluation and treatment. Women with major depression, anorexia, bulimia, or other major mental disorders should seek counseling with psychiatrists.

DOs and DON'Ts in Managing Amenorrhea:

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✓ **DO** see your health care provider and specialists regularly.

✓ **DO** keep to a healthy weight.

⃠ **DON'T** stop taking your medicine or change the dosage unless your health care provider tells you to.

⃠ **DON'T** use any over-the-counter drugs, herbal products, or other drugs without talking to your health care provider first.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website: http://www.acog.org**
- National Women's Health Resource Center Tel: (877) 986-9472 **Website: http://www.healthywomen.org**
- American Association of Clinical Endocrinologists Tel: (904) 353-7878 **Website: http://www.aace.com**

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MANAGING YOUR

AMPHETAMINE ABUSE

What Is Amphetamine Abuse?

Amphetamines are drugs that stimulate the brain and nervous system. Methamphetamine is one type of amphetamine with strong, long-lasting effects. Both types can be prescribed, mainly to treat attention deficit disorder, obesity, and narcolepsy (a sleep problem). The legal amphetamine is Dexedrine™. However, most amphetamines are made in illegal laboratories and sold as street drugs.

People smoke, sniff, swallow, or inject amphetamines (called speed, bennies, uppers, A, black beauties). Methamphetamine, a white, bitter powder, is called speed, meth, ice, chalk, glass, crank, and crystal.

Being high on amphetamines impairs judgment. Addicts crave more amphetamines to take away depression and tiredness, and their physical and mental health suffers. Regular users build up a tolerance (need higher doses for the same effect).

What Causes Amphetamine Abuse?

Stimulant drugs activate certain brain systems, which leads to addiction. Methamphetamine releases a chemical (dopamine) that stimulates some brain cells (enhancing mood) but damages others. Over time, methamphetamine reduces dopamine levels, which can cause symptoms like those of Parkinson's disease.

What Are the Symptoms of

Amphetamine Abuse?

Effects depend on the amount used and how it is taken. Lower doses make users feel energetic, confident, talkative, and reduce hunger and the need for sleep. Amphetamines also cause anxiety

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and panic. Higher doses, especially when smoked or injected, give an intense "rush" lasting a few minutes. Extreme tiredness follows the high. Users often have depression, unreasonable mistrust (paranoia), or mood swings.

Central nervous system (CNS) effects of even small amounts include increased wakefulness and physical activity, lower appetite, overheating, and intense happiness (euphoria). Other CNS effects include irritability, insomnia, tremors, convulsions, anxiety, and aggressiveness. Heart rate and blood pressure increase, damaging blood vessels in the brain. Use can cause death.

Long-term users get run-down from lack of food and sleep. Some become seriously mentally disturbed (psychotic).

How Is Amphetamine Abuse Diagnosed?

The doctor asks about symptoms and drug use and does an examination. The doctor may test urine for drugs.

How Is Amphetamine Abuse Treated?

The best treatments are behavioral. They help change thinking, expectancies, and behaviors and increase skills for coping with stress. Recovery support groups also seem to help.

No drug treatments are available. Antidepressants can be used to treat the depression often seen in users who abstain.

Emergency room treatment for overdoses focuses on physical symptoms and may include ice baths and anticonvulsant drugs. Antianxiety drugs may help relieve extreme excitement or panic.

DOs and DON'Ts in Managing

Amphetamine Abuse:

✓ **DO** get help from your doctor, counselor, support group, or rehabilitation program.

✓ **DO** examine problems and pressures that led to your drug abuse.

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✓ **DO** try to stay away from people and places that tempt you to take drugs.

✓ **DO** realize that serious infections (e.g., HIV, hepatitis) are more likely in people injecting drugs and sharing needles.

✓ **DO** call your doctor if you have tremors, irritability, greater wakefulness, reduced appetite, and paranoia.

⃠ **DON'T** forget that help is available. You must recognize the problem and seek help.

⃠ **DON'T** do drugs!

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Institute on Drug Abuse **Website: http://www.nida.nih.gov**
- NIDA for Teens **Website: http://www.teens.drugabuse.gov**
- Narcotics Anonymous World Services **Website: http://www.na.org**

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MANAGING YOUR

AMYOTROPHIC LATERAL SCLEROSIS

What Is Amyotrophic Lateral Sclerosis?

Amyotrophic lateral sclerosis (ALS) is a rare nervous system disease in which certain cells (neurons) in the brain and spinal cord slowly die. These cells send messages from the brain and spinal cord to voluntary muscles. Mild nerve and muscle problems appear first, but people slowly become more disabled. Some people live with ALS for several years. Eventually breathing muscles stop working. Slightly more men than women get it, usually 40 to 60 years old. There's no cure. It's also called Lou Gehrig's disease, after the famous baseball player who died from ALS.

What Causes ALS?

The cause is usually unknown and about 90% of cases are sporadic. In about 10% of people, it runs in families (inherited). ALS isn't contagious.

What Are the Signs and Symptoms of ALS?

ALS often starts with muscle weakness in an arm or leg, or with slurring of speech. Weakness slowly spreads to both arms and both legs and other parts of the body. Weak spinal and neck muscles lead to head drop. Problems lifting the front part of the foot and toes is foot drop. Some discomfort may occur. Loss of muscle tissue (atrophy) and tongue twitching (fasciculations) are common. Control of muscles needed to move, speak, eat (swallow), and breathe is eventually lost (paralysis). ALS doesn't affect senses (sight, smell, taste, hearing, touch), but people may have other neurologic problems (such as aphasia, or trouble finding words).

How Is ALS Diagnosed?

The doctor may suspect the diagnosis based on the medical history and physical examination, especially of nerves and muscles. The doctor tests walking, breathing, swallowing, and reflexes.

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The doctor may also order electromyography (EMG) and nerve conduction studies. Other studies include genetic testing, computed tomography (CT), magnetic resonance imaging (MRI), blood and urine tests, spinal tap, and muscle biopsy. EMG and nerve conduction studies help measure how well nerves and muscles work. In a biopsy, a small piece of muscle is removed and sent to a laboratory for study. A neurologist may confirm the diagnosis.

How Is ALS Treated?

Treatment aims to control symptoms and be supportive for as long as possible. One drug is riluzole, which may prolong life and in some people may slow ALS progression, but its effect is limited. Other drugs may help control spastic symptoms, swallowing problems, cramps, constipation, pain, and depression. A stomach tube may be used for feeding if choking occurs. A nutritionist is very important to help prevent weight loss. Education and counseling are also important. Physical, occupational, and speech therapy can help people stay strong and independent. Assistive devices include braces, walkers, wheelchairs, and breathing machines. In the later stages, the main goal is comfort.

DOs and DON'Ts in Managing ALS:

✓ **DO** learn as much as you can about ALS and what to do about it.

✓ **DO** choose which treatments you want for things such as breathing and eating problems.

✓ **DO** take time to grieve about the news that you have a fatal condition.

✓ **DO** join a support group.

✓ **DO** put your health care choices in writing, in a living will.

⦸ **DON'T** lose hope. Some people live much longer than the usual 3–5 years. Some live 10

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years or more.

⦸ **DON'T** concentrate on the physical changes. Because the intellect or spirit isn't usually affected, many people lead rich, rewarding lives.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- The National Institute of Neurological Disorders and Stroke **Website:** **http://www.ninds.nih.gov**
- American Academy of Family Physicians Tel: (800) 274-2237 **Website:** **http://www.aafp.org**

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MANAGING YOUR

ANAL CANCER

What Is Anal Cancer?

Food goes from the mouth and then, for digestion, through the stomach and small and large intestines. What's left (waste, or feces) leaves the body through the rectum and anus, which is the opening to the outside. The anal canal, about 1.5 inches long, is the last part of the digestive tract. It helps control defecation (discharge of feces, or bowel movements). It consists of muscles, glands, nerves, and valves. Types of cancer that grow in the lining of the anus depend on the different cell types found there. Major cancers in the anal canal are epidermoid cancer, adenocarcinoma, melanoma, squamous cell carcinoma, and verrucous carcinoma.

Anal cancer is rare and occurs slightly more often in women than men.

What Causes Anal Cancer?

The cause is unknown, but something happens to produce a genetic mutation in the cells of the anal canal. The mutation turns healthy cells into abnormal cancer cells. Risk factors for anal cancer include being HIV positive, anal sexual activity, many sexual partners, and anal warts from infection with human papillomavirus (HPV). Age (50 and older), smoking, history of cervical cancer, chronic inflammation of the anus, and drugs or conditions that weaken the immune (infection-fighting) system increase the risk of anal cancer.

What Are the Symptoms of Anal Cancer?

Symptoms include bleeding, itching, or discharge from the anus. Pain in the rectum or anus or the feeling of a rectal lump or mass can also be a sign or symptom of anal cancer.

How Is Anal Cancer Diagnosed?

For diagnosis, the doctor uses a medical history and physical examination including a digital

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rectal examination (DRE) and anoscopy. Anoscopy uses a short lighted tube to look at the area. A biopsy of the area will be done. In a biopsy, a piece of tissue is removed and a microscope is used to look for cancer cells in tissue. If cancer cells are found on the biopsy, other tests may be done including ultrasonography to see how deep the tumor is and computed tomography (CT) or magnetic resonance imaging (MRI) to find out whether the cancer has spread (staging). Checking the tumor's stage helps the doctor make treatment decisions.

How Is Anal Cancer Treated?

Anal cancer is often curable. Treatment depends on tumor size, how deep the tumor is, and whether the tumor spread to lymph nodes in the groin. Older treatments mainly involved an operation to remove the tumor and tissues around it. Often, a colostomy bag was needed. Today, radiation therapy, chemotherapy, and limited surgery allow most of the anal canal to be preserved. Many people have good anal function with this combination treatment. A team of specialists involved in care includes an oncologist (who prescribes chemotherapy), radiation oncologist (who uses radiation treatment), and surgeon. Prognosis depends on the tumor's size and spread.

DOs and DON'Ts in Managing Anal Cancer:

✓ **DO** follow all your doctor's instructions.

✓ **DO** contact your doctor if your medicine makes you sick.

✓ **DO** make healthy lifestyle choices: eat a good diet, exercise, and get enough sleep.

✓ **DO** practice safe sex.

✓ **DO** find a support group if you think that will help you cope.

⃠ **DON'T** smoke.

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⦸ **DON'T** delay telling your doctor about new symptoms or concerns.

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FOR MORE INFORMATION

Contact the following sources:

- American Society of Clinical Oncology Tel: (703) 299-0150 **Website:**

  http://www.asco.org

- American Cancer Society Tel: (800) ACS-2345 **Website: http://www.cancer.org**
- American Cancer Institute Tel: (800) 4-CANCER **Website: http://www.nci.nih.gov**

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MANAGING YOUR

ANAL FISSURE

What Are Anal Fissures?

An anal fissure is a tear in the lining of the anus or anal canal. The anal canal is the last part of the large intestine between the rectum and anus. This common condition affects men and women equally and both young and old people. Fissures are very common in babies 6 to 24 months old and during pregnancy.

What Causes Anal Fissures?

The usual cause is passing large, hard stool. Constipation and straining during bowel movements can also cause it. Another cause is inflammation of the anus and rectum. Crohn's disease and inflammatory bowel disease can also cause this inflammation. Risk factors include frequent bowel movements, diarrhea, infections, cancer, and trauma. Examples of infections causing anal fissures are tuberculosis, syphilis, and gonorrhea, herpes simplex virus, cytomegalovirus, and HIV. Trauma may be from surgery or anal sex. Older people may have anal fissures partly because of straining when moving bowels due to constipation and poor blood flow to the area. Anal fissures are also common in women after childbirth.

What Are the Symptoms of Anal Fissures?

The main symptoms are sharp, burning, or tearing pains that are made worse by bowel movements. Bright-red blood on toilet paper and on the stool or in the toilet water is another. Other problems include itching, discomfort, or cracks in the skin around the anus.

How Are Anal Fissures Diagnosed?

The health care provider makes a diagnosis from the medical history and physical examination, including a digital rectal examination. The health care provider may do laboratory tests and

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colonoscopy to rule out similar diseases. Colonoscopy involves using a flexible tube (colonoscope) with a lighted tip to look inside the colon. Biopsy and tests for infections may be done. A specialist (colorectal surgeon) may be seen.

How Are Anal Fissures Treated?

Anal fissures usually heal without treatment or with nonsurgical treatments. The main forms of treatment are stool softeners (docusate), sitz baths, and other lifestyle measures. These measures also include eating a high-fiber diet, increased drinking of fluids, and getting regular exercise. A local anesthetic jelly or nitroglycerin ointment may be applied to the anus. In resistant cases, botulinum toxin may be injected into each side of the internal anal sphincter muscle. This method helps heal chronic anal fissures in more than 90% of people. Most people improve in a few days with treatment. If conservative therapies don't work in 4 to 6 weeks, surgery can be done. It's usually done on an outpatient basis.

Keep the anal area dry. For babies, changing diapers regularly and keeping the anal area clean are important.

DOs and DON'Ts in Managing Anal Fissures:

✓ **DO** have a healthy lifestyle. Get enough exercise. Eat a well-balanced, high-fiber diet rich in fruits and vegetables. Drink enough liquids.

✓ **DO** call your health care provider if you have severe or lasting rectal bleeding.

⃠ **DON'T** stop taking your stool softener because you feel better, unless your health care provider tells you to.

⃠ **DON'T** use any medicines (including over-the-counter and herbal products) without first asking your health care provider.

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⦸ **DON'T** ignore symptoms. Call your health care provider if your symptoms don't improve or they worsen during treatment or if you see new symptoms.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American College of Surgeons Tel: (800) 621-4111 **Website: http://www.facs.org**

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MANAGING YOUR

ANAL ITCHING

What Is Anal Itching?

Anal itching has the medical name pruritus ani. It's a burning or itching of the anus and skin around it. It's common and affects both sexes and people of all ages. People with diabetes may have more risk of getting this condition. Treatment can control symptoms, but the problem can come back.

What Causes Anal Itching?

Often, the cause is unknown. The many causes include infections with yeast, herpesvirus, human papillomavirus (HPV, which causes genital warts), pinworms, mites (which cause scabies), and lice. Skin conditions, such as contact dermatitis, psoriasis, and seborrheic dermatitis, may start as anal itching. Soaps, contraceptive jellies and foams, scented toilet paper, deodorant sprays, and douches can cause contact dermatitis. People with chronic diarrhea may have itching. Diseases of the rectum, such as hemorrhoids, fissures (tears), fistulas, and rectal prolapse, may cause itching. Women near or after menopause (change of life) may have itching caused by vaginal discharge or low estrogen levels.

What Are the Symptoms of Anal Itching?

Symptoms include itching, redness of skin around the anus, and skin abrasions caused by scratching. Itching is often intense and worse at night. Skin thickening and chronic inflammation (swelling, redness) can occur. Damaged skin can get a bacterial infection.

How Is Anal Itching Diagnosed?

The doctor makes a diagnosis from symptoms and an examination of the rectum and the skin surrounding it. Laboratory studies are sometimes needed to identify fungi. Examinations with a mi-

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croscope may be needed to look for pinworm eggs or mites in skin.

How Is Anal Itching Treated?

The key to treatment is self-care and avoiding the things that lead to itching. Keep the area clean, cool, and dry. Over-the-counter hydrocortisone ointment or cream can control itching. It's applied three times a day, rubbed in gently until it disappears. Hydrocortisone shouldn't be used for longer than 5 days because it may cause more irritation and damage the skin.

If over-the-counter medicine doesn't help, the doctor may prescribe a stronger topical cortisone or other drugs. Yeast, herpes, genital warts, scabies, and infections with pinworms and lice if present must be treated with the right medicines. Rectal diseases may need other treatments.

DOs and DON'Ts in Managing Anal Itching:

✓ **DO** keep the area clean, cool, and dry.

✓ **DO** use plain, unscented soaps.

✓ **DO** clean the area with moistened unscented tissue or tufts of cotton after bowel movements.

✓ **DO** lose weight if you're overweight.

✓ **DO** wear loose clothing and cotton underwear.

✓ **DO** use tampons for your periods. They may be more comfortable than sanitary napkins.

✓ **DO** call your doctor if the area seems to be infected.

✓ **DO** call your doctor if you have a fever or if symptoms continue even with self-care.

⊘ **DON'T** have contact with irritating substances that can cause itching.

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⦸ **DON'T** wear tight-fitting underwear made from synthetic materials.

⦸ **DON'T** overdo activities that could cause the area to get too wet or sweaty.

⦸ **DON'T** eat spicy or highly seasoned foods that may irritate the area.

⦸ **DON'T** use laxatives.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following source:

- American Academy of Dermatology Tel: (847) 330-0230, (866) 503-7546 **Website:** **http://www.aad.org**

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MANAGING YOUR

ANAPLASMOSIS (HUMAN GRANULOCYTIC EHRLICHIOSIS)

What Is Anaplasmosis?

Ehrlichiosis is a disease of dogs, cattle, sheep, goats, and horses. In the United States, the disease was first described in humans in 1987. The two most important such diseases are human monocytic ehrlichiosis (HME) and human granulocytic ehrlichiosis (HGE). The bacterium *Ehrlichia chaffeensis* causes HME. HGE is caused by the bacterium *Anaplasma phagocytophilum*. HGE, now called anaplasmosis, was first described in 1994. It is more common in the elderly. The average age of people getting anaplasmosis is 67 years.

What Causes Anaplasmosis?

Ticks pass *A. phagocytophilum* to humans through a bite. These ticks are black-legged ticks named *Ixodes scapularis* (eastern United States) and *Ixodes pacificus* (western United States).

What Are the Symptoms of Anaplasmosis?

After the bite, generally 1 to 2 weeks will pass before symptoms start. Then, people may develop a sudden fever with headaches, muscle aches, chills, and general weakness. Nausea, vomiting, cough, diarrhea, and loss of appetite also occur. These symptoms can be confused with those of flu.

How Is Anaplasmosis Diagnosed?

After obtaining a complete history and physical examination, to make a diagnosis, the doctor will do blood tests. These include a complete blood count, tests of the kidneys and liver, and special tests such as polymerase chain reaction. Other tests to help exclude conditions that may mimic anaplasmosis may be needed. These diseases are Lyme disease, mononucleosis, blood malignancies, viral hepatitis, inflammation of bile ducts, and community-acquired pneumonia. If there are

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neurological signs or symptoms, the doctor may want a lumbar puncture to make sure that meningitis (inflammation of the membranes surrounding the brain) is not present. In a lumbar puncture, the doctor puts a needle into the spinal column through the lower back to get spinal fluid.

How Is Anaplasmosis Treated?

Antibiotics are given right away if the disorder may be anaplasmosis. Treatment shouldn't wait until the cause is confirmed. Unfortunately, because anaplasmosis causes symptoms that are similar to those of less severe diseases, many people aren't treated promptly. However, delaying treatment can lead to serious or even fatal infection.

Fever usually starts to go down 24 to 72 hours after starting treatment with an antibiotic (most often doxycycline). Doxycycline is given for 10 to 14 days. Severe or complicated disease may need longer treatment. Pregnant women and children younger than 8 shouldn't take doxycycline but can use rifampin.

DOs and DON'Ts in Managing Anaplasmosis:

✓ **DO** remember that symptoms may last up to 2 months without treatment.

✓ **DO** remember to wear light-colored clothing when in tick-infested areas. You can better see ticks on your clothes.

✓ **DO** call your doctor if you have a tick bite, you had a tick bite and now have a fever, or you have headaches with fever, nausea, and vomiting.

⦸ **DON'T** forget that complications may include seizures, kidney failure, respiratory failure, and congestive heart failure. From 5% to 10% of people die of this disease.

⦸ **DON'T** forget that it's best to limit your exposure to ticks to prevent anaplasmosis.

⦸ **DON'T** try to remove a tick by squeezing or crushing it. The best way is to use fine-tipped

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tweezers and hold the tick as close to the skin surface as possible.

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FOR MORE INFORMATION

Contact the following source:

- Centers for Disease Control and Prevention1600 Clifton Road, ME MS G-13 Atlanta, Georgia 30333 Tel: (404) 639-1075

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MANAGING YOUR

ANEMIA

What Is Anemia?

Anemia means low blood. People with anemia don't have enough red blood cells (RBCs) or hemoglobin. RBCs take oxygen to organs and tissues. Hemoglobin is the red pigment in RBCs that carries the oxygen to the cells. Iron-deficiency anemia, pernicious anemia, and anemia of chronic disease are common types.

What Causes Anemia?

Common causes include a lack of iron, folate, and vitamin B_{12} (cobalamin), which can result from poor diet, poor absorption from the intestines, autoimmune diseases and hereditary diseases (e.g., sickle cell anemia) that can cause destruction of RBCs or blood loss from bleeding. Blood can be lost from bleeding stomach ulcers, gastritis, colon cancer, and heavy periods. In autoimmune diseases, the body attacks its own RBCs and destroys them. Elderly people and people with alcoholism can have folate deficiency, which is mainly caused by poor diet. Any chronic disease lasting more than 1 or 2 months can also cause anemia.

What Are the Symptoms of Anemia?

Common symptoms include tiredness and shortness of breath. How severe the symptoms are depends on how bad the anemia is and if it is of sudden onset such as with acute blood loss. Long-lasting iron deficiency can cause other symptoms such as sore mouth, swallowing problems, or nails that soften and curl. Severe vitamin B_{12} deficiency can affect memory and cause problems with balance.

How Is Anemia Diagnosed?

The doctor makes a diagnosis from a medical history, physical examination, and blood tests. A

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specialist (hematologist) may be involved if causes aren't clear. In some cases, a test known as a bone marrow exam may be done to determine the cause of the anemia.

How Is Anemia Treated?

Treatment depends on the cause and severity of disease. Blood transfusions may be needed for severe anemia. For iron deficiency anemia, the doctor may prescribe iron tablets. For pernicious anemia, vitamin B_{12} injections are given, usually for life. People with vitamin B_{12} deficiency caused by poor diet can take vitamin tablets. Treatment of folate deficiency is folate pills. The main treatment of anemia of chronic disease is control of underlying disease. Erythropoietin, given as injections, may be used in severe anemia in renal failure and in cancer.

DOs and DON'Ts in Managing Anemia:

- ✓ **DO** follow your doctor's recommendations for controlling underlying conditions that may be causing anemia.
- ✓ **DO** talk with your doctor about new medicines and their effects on anemia.
- ✓ **DO** eat a well-balanced diet rich in iron, vitamin B_{12}, and folate.
- ✓ **DO** follow a nonstrenuous exercise program.
- ✓ **DO** use medical alert identification if you have severe anemia.
- ✓ **DO** use vitamin supplements if you eat a special diet, such as a vegetarian (especially vegan).
- ✓ **DO** call your doctor if you have symptoms of severe anemia, such as shortness of breath.
- ✓ **DO** tell your doctor if you're pregnant planning a pregnancy, or breast-feeding.

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✓ **DO** tell your doctor about stomach upset or constipation from an iron supplement. These side effects usually get better with a lower dose or change to a different iron pill.

⃠ **DON'T** stop taking your medicine or change your dosage because you because you feel better unless your doctor tells you to.

⃠ **DON'T** drink alcohol in excess.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Heart, Lung, and Blood Institute Information Center Tel: (301) 251-1222
- The American Society of Hematology Tel: (202) 776-0544

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MANAGING YOUR

ANGINA

What Is Angina?

Angina is chest pain usually caused by narrowing of blood vessels in the heart from blockage or spasm. Less blood can reach the heart, so it has less oxygen for pumping blood. Angina may mean serious heart problems and needs immediate attention.

What Causes Angina?

Coronary artery disease from atherosclerosis (i.e., fatty deposits and inflammatory cells in blood vessels to the heart), abnormal heart rhythms (arrhythmias), fewer oxygen-carrying red blood cells (anemia), and spasms of the coronary arteries can reduce blood flow.

At increased risk for angina are men older than age 60, women after menopause, people with a family history of heart disease, people who eat high-fat high-cholesterol foods, people who don't exercise regularly, smokers, and people with diabetes, high blood pressure (hypertension), or high cholesterol levels.

What Are the Symptoms of Angina?

The primary symptom is a feeling of tightness, dull ache, or heaviness that begins in the chest and sometimes spreads to the back, neck, left shoulder, and down the arms (especially left arm). Pain may be dull or sharp or feel like heartburn or indigestion. Some people describe a smothering or crushing pain. It may begin slowly or be severe and sudden. Sweating, nausea, feeling faint or weak, dizziness, or shortness of breath may also occur. Some women and diabetics may have atypical symptoms, such as jaw pain, arm pain, and stomach pain.

How Is Angina Diagnosed?

The doctor makes a diagnosis by checking symptoms, doing examinations and laboratory and other tests. Tests include electrocardiograms (ECGs) and treadmill or exercise tests. A heart

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catheterization (checking the heart's blood flow by putting a device through an artery into the heart) may also be done if the initial tests show signs of blocked heart (coronary) arteries.

How Is Angina Treated?

The goal is to improve blood flow to the heart or to reduce the heart's work. Resting or reducing activity is the first treatment.

Aspirin improves blood flow. Nitrates such as nitroglycerin can also help blood flow. Other medications such as beta blockers slow down the heartbeat and the work done by the heart. Medicine for other diseases (e.g., hypertension, arrhythmias, diabetes, high cholesterol) may be given if these diseases are present.

Anyone with angina should take aspirin daily unless told not to by a doctor.

Lifestyle changes (exercise, diet, weight control, quitting smoking) are important.

If medicine doesn't work, surgery (angioplasty, an operation to open clogged blood vessels with a balloonlike device) may be needed. A small wire mesh tube, called a stent, is often inserted into the blocked artery after it has been opened to prevent it from narrowing again. Open heart surgery (coronary artery bypass graft, or CABG) may be necessary for severely blocked arteries.

DOs and DON'Ts in Managing Angina:

✓ **DO** change your diet and reduce weight to lower blood pressure and improve blood fat and sugar levels.

✓ **DO** begin an exercise program under the guidance of your physician to strengthen the heart and reduce weight, blood pressure, blood fat levels, and stress.

✓ **DO** stop smoking.

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✓ **DO** take your medicines as directed.

✓ **DO** call your doctor if medicines don't control your pain.

✓ **DO** call 911 or get to the emergency room if you take nitroglycerin three times in a row without symptom relief.

✓ **DO** call your doctor immediately if you have new or worsening symptoms that your medicine doesn't control.

⦸ **DON'T** smoke, drink alcohol in excess, or eat salty or high-fat foods.

⦸ **DON'T** ignore your symptoms.

⦸ **DON'T** use Viagra®, Levitra®, or Cialis® if you take nitroglycerin.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- National Heart, Lung, and Blood Institute Tel: (301) 592-8573 **Website:** **http://www.nhlbi.nih.gov**
- American Heart Association Heart and stroke information: (800) AHA-USA1 (242-8721)Women's health information: (888) MY HEART (694-3278) **Website:** **http://www.americanheart.org**

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MANAGING YOUR

UNSTABLE ANGINA

What Is Unstable Angina?

Angina is chest pain resulting from reduced blood and oxygen to the heart. It can be a symptom of coronary artery disease, or atherosclerosis, when cholesterol and fats (plaque) build up inside arteries. Angina can also occur from a spasm of muscles in the coronary artery.

Unstable angina is increasing unpredictable chest pain. It is less common than stable angina. Unstable angina pain doesn't follow a pattern, can happen without exertion, and doesn't go away by resting or taking medicine. Unstable angina is an emergency.

What Causes Unstable Angina?

Blood clots, which form plaques in the arteries, break open and block arteries. Clots may form, partly dissolve, and re-form. Unstable angina can occur whenever a clot blocks the coronary artery. Untreated clots may grow enough to block an artery completely and cause a heart attack.

What Are the Symptoms of Unstable Angina?

Symptoms include mild or severe discomfort or pain in the chest, felt as tightness, dull ache, or heaviness that may spread down the arms (especially left arm) or to the neck, shoulder, or jaw; shortness of breath; nausea; sweating; or weakness. Symptoms often occur at rest or with little physical exertion and are severe, long-lasting, and can't be predicted or helped by rest or medicine.

How Is Unstable Angina Diagnosed?

The doctor will take a medical history, do an examination, blood tests to evaluate the presence of chemicals from cardiac cell injury, electrocardiography (ECG), and chest x-rays. Emergency room doctors start treatment while they quickly find out how badly the heart is affected. Heart and breathing rates, blood pressure, and blood oxygen levels are measured.

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If a blockage is suspected, the doctor may also look at heart arteries by a special x-ray test (coronary angiography). A specialist in heart diseases (cardiologist) passes a thin, flexible tube through an artery in the groin or arm to heart arteries.

How Is Unstable Angina Treated?

First, emergency room doctors stabilize a person's condition. Painkillers, aspirin (prevent blood clots), and oxygen (help breathing) may be given. A nitroglycerin capsule that dissolves inside the mouth widens the heart's blood vessels. Other drugs may be given to control blood pressure and open arteries.

Later treatments in the hospital (and after the hospital stay) include drugs (e.g., aspirin, clopidogrel, blood thinner) to stop clotting, medicines to lower blood pressure, and drugs (statins) to reduce blood cholesterol and fat levels.

Other treatments include operations called balloon angioplasty and stenting, and coronary artery bypass graft (CABG). For balloon angioplasty, blocked arteries are widened with a tiny balloon. A metal tube (stent) can be put in arteries to keep them open. In CABG, veins or arteries are transferred and sewn on (grafted) to blocked arteries so that blood flow can get past the blockage.

DOs and DON'Ts in Managing Unstable Angina:

✓ **DO** visit your doctor regularly and take all prescribed medicines.

✓ **DO** lose weight and eat healthy.

✓ **DO** always carry nitroglycerin with you and take it if needed.

✓ **DO** exercise only when approved to do so by your doctor.

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✓ **DO** quit smoking.

✓ **DO** lower stress.

✓ **DO** know how and when to get medical care, because of heart attack risk.

⃠ **DON'T** delay getting medical care if symptoms worsen.

⃠ **DON'T** stop taking medicine without talking to your doctor.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:** **http://www.americanheart.org**
- American College of Cardiology Tel: (202) 375-6000 **Website:** **http://www.acc.org**
- National Heart, Lung, and Blood Institute Tel: (301) 592-8573 **Website:** **http://www.nhlbi.nih.gov**

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MANAGING YOUR

ANGIOEDEMA

What Is Angioedema?

Angioedema is an allergic reaction that is like the common skin condition of hives (urticaria). Hives are raised, red, itchy, irregular bumps on the skin. In angioedema, the same thing happens but it is deeper in the skin. The bumps cannot be seen but can be felt. Anyone can get angioedema. About 15% to 20% of all people will have at least one episode of hives or angioedema in their lifetime.

What Causes Angioedema?

Usual causes are allergic reactions to new drugs, eating new foods, and wearing new perfumes. But even foods or drugs used in the past without problems can cause an allergic reaction later. Angioedema cannot be caught and is not an infection, although infections can cause it. Certain types are hereditary (may occur in family members).

What Are the Symptoms of Angioedema?

The main symptom is swollen skin that can be tender and painful. Swelling at one spot is usually present for only a day or two, but swelling will move from one spot to another and last for several days or may become chronic. Chronic angioedema, although uncomfortable and irritating, usually won't become more serious.

Angioedema can occur anywhere on the body but more often involves eyelids, lips, tongue, and genitals. Outside the body it is usually not dangerous. It can also occur inside the body, in intestines and lungs (airways), where it can potentially cause breathing difficulty, which can be serious and even fatal.

How Is Angioedema Diagnosed?

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The doctor examines the swollen skin and the tendency of swelling to come and go for diagnosis. Blood tests can be done but don't always help or affect treatment. A family history is very important, so the doctor will ask family members about any episodes of angioedema.

How Is Angioedema Treated?

No cure exists, but symptoms can be controlled.

The best treatment is to remove the cause. However, the exact cause is often unknown or impossible to remove. Therefore the main approach to management is control of symptoms.

Application of cold compresses may provide comfort. Lotions and creams don't usually help because they don't get deep enough when they're applied to the skin.

Oral antihistamines work well, but the right dose must be taken regularly, or the angioedema may return. Antihistamines also may have side effects (drowsiness, dry mouth), but newer antihistamines have fewer of these effects. Stronger drugs (prednisone or other steroids) may help if antihistamines don't control the angioedema.

DOs and DON'Ts in Managing Angioedema:

✓ **DO** call your doctor immediately if you have trouble breathing, are wheezing, or have chest or abdominal pain. Angioedema may require long-term treatment.

✓ **DO** use cold compresses on swollen areas.

✓ **DO** take antihistamines in proper doses.

✓ **DO** note any possible causes (new foods, drugs, soaps, perfumes, clothes). Avoid those items that trigger the reaction. Ask your doctor about your drugs.

✓ **DO** call your doctor if your angioedema doesn't respond to 2 or 3 days of continuous antihis-

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tamines.

✓ **DO** call your doctor if you have repeated attacks of angioedema.

⃠ **DON'T** treat swelling with heat, creams, ointments, or lotions.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Dermatology 930 North Meachum Road Schaumburg, IL 60173

  Tel: (866) 503-7546 **Website: http://www.aad.org/**

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MANAGING

ANIMAL AND HUMAN BITES

About Animal and Human Bites

Bites are worrisome because they can become infected. Both animal and human mouths have many germs (bacteria and viruses) that can cause infection. Bites on hands, forearms, lower legs, feet, and face are more likely to get infected. Also, human diseases such as hepatitis and HIV can be passed to others by bites. Bats, raccoons, foxes, and skunks can pass rabies to people. Rabies is a serious and often fatal illness. Dogs, cats, and farm animals don't usually cause rabies, and rodents (including rats) and rabbits don't carry rabies.

What Are the Major Concerns About Animal Bites?

With proper care, most animal bites don't get infected. Fever, redness and streaking at the bite site, drainage from the wound, pain, and swelling mean infection. Rabies treatment should be started if the biting animal could have rabies. If possible, the animal should be captured by an animal control officer and kept in quarantine.

What Are the Major Concerns About Human Bites?

With proper care, human bite wounds rarely cause serious or lasting problems. Bites in places other than hands should be watched closely for infection, the worst immediate problem. Redness, streaking, swelling, pain, drainage, and fever mean infection. Bite wounds to hands may need surgery and special treatment. Human bites are crush wounds, so bruising is common, with skin breakdown.

How Are Animal Bites Treated?

Treatment involves immediate cleaning with soap and water. Clean water (as from a faucet) should be allowed to run through the wound. Doctors or nurses should check wounds promptly.

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Sutures are best avoided due to increased risk of infection but may be needed in some cases. Dry bandages should be used and changed when soiled, moistened, or at least once daily. Antibacterial ointment should be applied with each bandage change. A tetanus toxoid injection should be given if more than 5 years passed since the last shot.

How Are Human Bites Treated?

Immediate and thorough wound cleaning is very important. Doctors should check bites before infection is noted. Antibiotics are often given for deep bites or bites in places such as hands and face. Ice packs and raising the bite area may help pain, swelling, and bruising. Sutures aren't usually used, but surgeons often help in care of bites to hands by removing dead tissue at the bite site.

DOs and DON'Ts in Managing Animal and Human Bites:

✓ **DO** immediately clean bites with soap and water. Clean wounds daily and use clean bandages.

✓ **DO** get prompt medical help.

✓ **DO** worry about rabies for bites of foxes, bats, skunks, raccoons, opossum, or sickly animals.

✓ **DO** make sure you had a tetanus toxoid injection in the last 5 years.

✓ **DO** notify your state or local health department.

✓ **DO** notify the police or animal control officer in your town.

✓ **DO** call your doctor right away if the area becomes red or swollen or drains pus, or you develop a fever.

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✓ **DO** call your doctor if numbness or pain with movements far from the bite develops.

✓ **DO** take all prescribed medicines as directed.

⃠ **DON'T** ignore symptoms of infection or fever.

⃠ **DON'T** attempt to capture disturbed animals.

⃠ **DON'T** stop your antibiotic until you finish all of it.

⃠ **DON'T** ignore seemingly minor wounds, especially bites to the hand.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following source:

- Contact your local state or local health department.

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MANAGING YOUR

ANKLE FRACTURE

What Is an Ankle Fracture?

An ankle fracture is a break in any bone of the ankle joint. It may be mild (like a bad sprain) or severe (including joint dislocation). Long-term pain and disability are possible.

What Causes an Ankle Fracture?

Causes include blows to the ankle, falls (landing on the feet), or, most often, twisting the ankle.

What Are the Symptoms of an Ankle Fracture?

Symptoms are pain, especially when putting weight on or moving the ankle, swelling, bruising, and a deformed joint.

How Is an Ankle Fracture Diagnosed?

The doctor uses a physical examination and x-rays.

How Is an Ankle Fracture Treated?

Treatment may be similar to treatment of a sprain (rest, ice, elevation, compression, and using a brace for protection). It may involve surgery and use of screws and plates to hold bones together during healing.

Most often, a cast or removable splint holds bones in position until they heal. If a cast is used, lower leg muscles will be a bit weak after removal of the cast. Physical therapy will help this common side effect. Complications include failure to heal, poor blood flow to the foot or toes (if cast is too tight or swelling occurs in the cast), and infection or bleeding related to surgery.

DOs and DON'Ts in Managing an Ankle Fracture:

✓ **DO** reduce the risk of injury by warming up and stretching before exercising.

✓ **DO** use good running shoes and run on an even surface.

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✓ **DO** reduce your weight, if overweight.

✓ **DO** keep fit.

✓ **DO** take pain medicines as prescribed.

✓ **DO** eat a diet with enough calcium to help healing.

✓ **DO** keep your foot raised for the first few days and apply ice to your ankle the first day or so, to minimize swelling.

✓ **DO** exercises or go to a physical therapist after cast removal to shorten recovery time and reduce the risk of developing a blood clot in the leg.

✓ **DO** call your doctor if you notice numbness, tingling, coldness, or darkening of your toes. The cast may be too tight or the ankle may be swollen, reducing blood circulation to your foot.

✓ **DO** call your doctor if you damage your splint or cast so that it is loose or allows your ankle to move more than it should.

✓ **DO** call your doctor if, after surgery, you have fever or you see redness, swelling, or pus at the incision (suggesting infection).

✓ **DO** call your doctor if you have increasing pain or cannot use your ankle at some time after surgery.

✓ **DO** call your doctor if you notice pain or swelling in your calf or leg, which may mean a

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blood clot.

⦸ **DON'T** spend too much time on your feet or with your foot hanging down. Don't put heat on the ankle. Swelling may hurt circulation.

⦸ **DON'T** get a plaster or fiberglass cast wet.

⦸ **DON'T** stick things such as coat hangers, pencils, or knitting needles down the cast to scratch. If you poke the skin, you may get an infection.

⦸ **DON'T** remove your cast too soon. Early removal may allow another injury.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Trauma Society Tel: (800) 556-7890 **Website: http://www.amtrauma.org**
- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website: http://www.aaos.org**
- The American Orthopaedic Society for Sports Medicine Tel: (847) 292-4900 Fax: (847) 292-4905 **Website: http://www.sportsmed.org**

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MANAGING YOUR

ANKLE SPRAIN

What Are Ankle Sprains?

Ankle sprains are injuries resulting from stretching, or partly or completely tearing one or more ligaments holding the ankle joint together. Ligaments are bands of strong, flexible fibers connecting bones. Tendons connect muscles and bones. Ankle sprains are common, especially in sports such as basketball and soccer.

What Causes Ankle Sprains?

Sprains occur when the joint is forced to bend more than normal, thus hurting ligaments. The most common type occurs when the foot turns in (called inversion), and full body weight comes down on the ankle. The foot can also turn too far out (called eversion).

What Are the Symptoms of Ankle Sprains?

Popping or tearing is felt at the time of injury. Pain occurs during the injury and after, when walking or moving the ankle. The ankle may swell and feel stiff. The skin around the ankle may be bruised.

With severe injuries, extreme pain makes weight bearing and moving the ankle hard. Tingling or numbness in the foot may mean nerve or blood vessel damage.

How Are Ankle Sprains Diagnosed?

The doctor will ask about the accident and examine the ankle by moving it to check ligaments and tendons.

For a minor sprain, no more tests are needed. For a severe sprain, the doctor may order x-rays or magnetic resonance imaging (MRI).

How Are Ankle Sprains Treated?

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Ice is applied immediately, because swelling starts quickly. The ankle is rested, which may mean using crutches. Walking is kept to a minimum. A compression wrap or splint is put on the ankle. The ankle is elevated above hip level. Remember these by thinking "RICE" (*R*est, *I*ce, *C*ompression, *E*levation). A compression wrap, splint, or brace lets the ankle move without injury. Never use heat before 72 hours after the injury (causes more swelling).

Physical therapy can strengthen muscles, help recovery, and help prevent more injuries.

Over-the-counter antiinflammatory medications (ibuprofen) can be taken to decrease swelling and provide pain relief.

Severe sprains may need surgery and physical therapy.

DOs and DON'Ts in Managing an Ankle Sprain:

✓ **DO** warm up and stretch before exercising.

✓ **DO** wear ankle braces when playing sports if you often get sprains.

✓ **DO** lose weight, if overweight.

✓ **DO** keep fit.

✓ **DO** take medicines and use crutches prescribed by your doctor.

✓ **DO** follow RICE and physical therapy instructions.

✓ **DO** call your doctor if you can't walk on your injured ankle, swelling hasn't left after 2 days or increases, the ankle becomes redder or hot, you have a fever, or you notice popping, catching, or the ankle giving way.

✓ **DO** call your doctor if your foot is numb, tingling, or is a blue or dusky color; or your toes

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are cold (signs of cut-off circulation).

✓ **DO** call your doctor if you don't see improvement in 7 to 10 days after the sprain.

✓ **DO** call your doctor if you have pain or swelling in the leg (may mean a blood clot).

⃠ **DON'T** do activities that will increase swelling. Avoid early use of heat or too much activity, standing, or sitting with the ankle hanging.

⃠ **DON'T** play sports again until pain and swelling are gone and the ankle is strong.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- The American Orthopaedic Society for Sports Medicine Tel: (847) 292-4900 Fax: (847) 292-4905 **Website: http://www.sportsmed.org**
- American College of Sports Medicine Tel: (317) 637-9200 **Website: http://www.acsm.org**

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MANAGING YOUR

ANKYLOSING SPONDYLITIS

What Is Ankylosing Spondylitis?

Ankylosing spondylitis is a painful, arthritic condition most often found in men younger than 40, although women and children can have it. Ankylosing means joining together, and spondylitis refers to inflammation (swelling) in joints of the spine. Joints of the lower back can fuse, resulting in stooped posture.

Swelling in ligaments attaching to bones causes bone to wear away and then try to heal. New bone replaces elastic tissue called ligaments (ligaments connect bones), and stiffness occurs.

Most often affected are the lower back, chest, and neck. Other affected joints can include hips, shoulders, knees, and ankles. The illness can also affect other organs, such as eyes, heart, and lungs.

What Causes Ankylosing Spondylitis?

The cause is unknown, but it is an autoimmune disease. This means that the body attacks itself, the result being inflammation. People with a gene called HLA-B27 are more likely to get this illness than people without the gene.

What Are the Symptoms of Ankylosing Spondylitis?

The most common symptom is back pain that may start gradually. Early morning stiffness and pain go away during the day with exercise. People lose weight. People feel weak, tired, and feverish and have severe twinges or nagging aches down one leg or through the buttock. People also have night sweats, limited range of motion, stooped posture, and trouble breathing.

How Is Ankylosing Spondylitis Diagnosed?

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The doctor takes a medical history, does a physical examination, and gets x-rays of the lower (lumbar) spine. X-rays show inflammation and fusion of the joint (sacroiliac joint) connecting lumbar spine and hip. The doctor may also order MRI.

The doctor may recommend going to a specialist called a rheumatologist.

How Is Ankylosing Spondylitis Treated?

Treatment is mainly for pain and stiffness. Special stretching and strengthening exercises may prevent fusion of joints in bad positions.

A physical therapist can help design an exercise program.

Antiinflammatory drugs, including ibuprofen and naproxen, can help control pain and inflammation. They can have side effects, such as nausea, vomiting, and stomach disorders. Other drugs such as methotrexate and infliximab may slow disease progress.

If the disease caused major deformity and damage to the lumbar spine or hip, an orthopedic surgeon (a specialist in bone diseases) can perform surgery. Other specialists (e.g., ophthalmologist, cardiologist, or pulmonologist (for diseases of the eyes, heart, and lungs) may be needed.

DOs and DON'Ts in Managing

Ankylosing Spondylitis:

✓ **DO** take medicines that your physician prescribes.

✓ **DO** begin a daily stretching, strengthening, and movement routine, including breathing exercises.

✓ **DO** use good posture, firm bed, and supportive chair at work help to maintain a straight spine.

✓ **DO** call your doctor if you fall and notice a sudden change in alignment of your neck or

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back.

✓ **DO** call your doctor if you have drug side effects.

✓ **DO** call your doctor if you need a referral to a specialist.

✓ **DO** call your doctor if you have eye pain, loss of vision, or red eye.

✓ **DO** call your doctor if you have blood in bowel movements.

⃠ **DON'T** smoke.

⃠ **DON'T** drink alcohol if your doctor tells you to stop. Your medicine may react with alcohol.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- North American Spine Society Tel: (630) 230-3600 **Website:** **http://www.spine.org/**
- Spondylitis Association of America Tel: (800) 777-8189 **Website:**

http://www.spondylitis.org/

- Arthritis Foundation Tel: (800) 568-4045 **Website:** **http://www.arthritis.org/**
- American College of Rheumatology Tel: (404) 633-3777 **Website:**

http://www.rheumatology.org/

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MANAGING YOUR

ANOREXIA NERVOSA

What Is Anorexia Nervosa?

Anorexia nervosa, or just anorexia, is an eating disorder in which people have an unreasonable fear of becoming fat. People lose so much weight that they become gaunt. Even then, they still see themselves as fat.

Anorexia nervosa is fairly rare, with groups at highest risk being adolescent girls and young women. It affects women much more than men, and is more common in some jobs (e.g., modeling, ballet dancing). It can be life threatening if untreated.

What Causes Anorexia Nervosa?

The cause is unknown, but anorexia probably results from a combination of factors, such as depression, other psychological problems, intense peer pressure, hormone changes at puberty, and stress. Adolescents may have concerns about sexuality, and these concerns lessen with anorexia because it delays sexual maturity. As children, anorexics were often obedient. As adolescents, they develop anorexia, which becomes their first rebellious act.

What Are the Symptoms of Anorexia Nervosa?

The most common symptoms include loss of weight, exercising too much, menstrual periods that stop, complaints of being fat from someone who is overly thin, depression, and loss of appetite. It can cause medical problems, including skin, heart, blood, bone, and hormone disorders. Dehydration, constipation, and frequent infections may occur.

How Is Anorexia Nervosa Diagnosed?

The doctor makes a diagnosis from the medical history (especially weight and diet), physical examination, and laboratory tests to rule out other conditions. No specific tests exist for anorexia.

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Extreme weight loss without physical illness, especially in a young woman, is usually an important sign.

Anorexics often deny their illness and may make themselves vomit with syrup of ipecac (causing dental cavities), misuse laxatives and enemas, and use diet and water pills.

How Is Anorexia Nervosa Treated?

Anorexia requires long-term care, including counseling or psychotherapy. Relapses are common, especially during periods of stress. Recovery depends on the individual.

Treatment first involves working with the person and family. Drugs may be prescribed for depression or anxiety. Programs may use negative and positive feedback, emotional support, education, and reassurance to address fears about gaining weight. Often, the whole family needs counseling. Other medical problems and illness that may have resulted from starvation need treatment, which may mean hospitalization.

Many people remain ill for a long time. Participation in an outpatient program after hospitalization is critical for successful treatment. The death rate associated with anorexia can be rather high.

DOs and DON'Ts in Managing Anorexia Nervosa:

✓ **DO** minimize stress.

✓ **DO** admit that you have an emotional problem.

✓ **DO** eat the diet prescribed by your doctor or nutritionist.

✓ **DO** attend counseling sessions.

✓ **DO** take medicines as directed.

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✓ **DO** buy clothes that fit, not clothes that you have to lose weight to get into.

✓ **DO** call your doctor if you have paranoia, hallucinations, depression, or thoughts about suicide.

⃠ **DON'T** vomit food or binge eat.

⃠ **DON'T** skip meals.

⃠ **DON'T** exercise more than what your doctor recommends.

⃠ **DON'T** weigh yourself daily.

⃠ **DON'T** use drugs, diet pills, laxatives, or caffeine to lose weight.

⃠ **DON'T** eat alone, if possible.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

• Anorexia Nervosa & Related Eating Disorders, Inc. (ANRED) **Website:**

http://www.anred.com

• National Association of Anorexia Nervosa (ANAD) and Associated Disorders **Website:**

http://www.anad.org Hotline: (847) 831-3438

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CARING FOR A YOUNG WOMAN WITH

ANOREXIA NERVOSA

What Is Anorexia Nervosa?

Anorexia nervosa, or just anorexia, is an eating disorder in which people have an unreasonable fear of becoming fat. People lose so much weight that they become gaunt. Even then, they still see themselves as fat.

Anorexia nervosa is fairly uncommon. At highest risk are adolescent girls and young women. It is more common in some jobs, such as modeling, figure skating, and ballet dancing. It can be life-threatening if untreated.

What Causes Anorexia Nervosa?

The cause is unknown, but anorexia probably results from a combination of factors, such as depression, other psychological problems, intense peer pressure to be thin, hormone changes at puberty, and stress. Some adolescents may have concerns about sexuality, and these concerns lessen with anorexia because it delays sexual maturity. As children, anorexics are often obedient, but as adolescents, they often rebel against parents. Anorexia nervosa is not hereditary but is slightly more common in certain families.

What Are the Symptoms of Anorexia Nervosa?

The most common symptoms include weight loss, excessive exercise, menstrual periods that stop, complaints of being fat even though the body is too thin, depression, and loss of appetite. Anorexia can cause medical problems, including skin, heart, blood, bone, and hormone disorders. Dehydration, constipation, and frequent infections may occur.

How Is Anorexia Nervosa Diagnosed?

The doctor diagnoses your child with anorexia from a medical history (especially weight and

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diet), physical examination, and laboratory tests to rule out other conditions. No special tests exist for anorexia. Extreme weight loss without physical illness, especially in a young woman, is usually an important sign.

Anorexic children and adolescents often deny that they have an illness. They may make themselves vomit, misuse laxatives and enemas, and use diet and water pills.

How Is Anorexia Nervosa Treated?

Anorexia requires care for a long time, including counseling or psychotherapy. Relapses are common, especially during stress. Recovery depends on admission that a problem exists.

Treatment first involves working with the whole family. Treatment programs may use emotional support, education, negative and positive feedback, and reassurance to deal with the child's fears about gaining weight, as well as drugs (for depression or anxiety). Other medical problems and illness that may have resulted from starvation need treatment, which may mean hospitalization in severe cases.

The illness can last for a very long time. Outpatient programs after hospitalization are critical.

DOs and DON'Ts in Managing Anorexia Nervosa:

✓ **DO** minimize stress in your child's life.

✓ **DO** admit that your child has an emotional problem and try to get your child to admit this too.

✓ **DO** follow the diet prescribed by the doctor or nutritionist for your child.

✓ **DO** have the whole family eat together.

✓ **DO** have your child attend counseling sessions.

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✓ **DO** find a support group for yourself to help you get through this difficult time. You are not alone and talking to other parents is often helpful.

✓ **DO** make sure that your child takes medicines as directed.

✓ **DO** work with your child on a new body image with a healthy weight.

✓ **DO** call the doctor if your child has thoughts about suicide, paranoia, hallucinations, or depression.

⦸ **DON'T** let your child exercise more than recommended.

⦸ **DON'T** weigh your child daily.

⦸ **DON'T** let your child use drugs, diet pills, laxatives, or caffeine to lose weight.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- ANRED: Anorexia Nervosa and Related Eating Disorders, Inc. **Website: http://www.anred.com**
- NAD: National Association of Anorexia Nervosa and Associated Disorders Hotline: (847) 831-3438 **Website: http://www.anad.org**

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MANAGING YOUR

ANOREXIA NERVOSA: FOR MEN

What Is Anorexia Nervosa?

Anorexia nervosa, or just anorexia, is an eating disorder in which people have an unreasonable fear of becoming fat. People lose so much weight that they become gaunt. Even then, they still see themselves as fat.

What Causes Anorexia Nervosa?

The cause is unknown, but anorexia probably results from a combination of factors, such as depression, other psychological problems, intense peer pressure, hormone changes at puberty, and stress.

What Are the Symptoms of Anorexia Nervosa?

The most common symptoms include weight loss, too much exercise, complaints of being fat from someone who is overly thin, depression, and loss of appetite. It can cause medical problems, including skin, heart, blood, bone, and hormone disorders. Dehydration, constipation, and frequent infections may occur.

How Is Anorexia Nervosa Diagnosed?

The doctor makes a diagnosis from the medical history (especially weight and diet), physical examination, and laboratory tests to rule out other conditions. No specific tests exist for anorexia. Extreme weight loss without physical illness is usually an important sign.

Anorexics often deny their illness and may make themselves vomit, misuse laxatives and enemas, and use diet and water pills.

How Is Anorexia Nervosa Treated?

Anorexia requires long-term care, including counseling or psychotherapy. Relapses are common,

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especially during periods of stress. Recovery depends on the individual.

Treatment first involves working with the person and family. Drugs may be prescribed for depression or anxiety. Programs may use negative and positive feedback, emotional support, education, and reassurance to address fears about gaining weight. Often, the whole family needs counseling. Other medical problems and illness that may have resulted from starvation need treatment, which may mean hospitalization in severe cases.

Many people remain ill for a long time. Participation in an outpatient program after hospitalization is critical for successful treatment. The death rate associated with anorexia can be rather high if left untreated.

DOs and DON'Ts in Managing Anorexia Nervosa:

✓ **DO** minimize stress.

✓ **DO** admit that you have an emotional problem.

✓ **DO** eat the diet prescribed by your doctor or nutritionist.

✓ **DO** attend counseling sessions.

✓ **DO** take medicines as directed.

✓ **DO** buy clothes that fit, not clothes that you have to lose weight to get into.

✓ **DO** call your doctor if you have paranoia, hallucinations, depression, or thoughts about suicide.

⦸ **DON'T** vomit food or binge eat.

⦸ **DON'T** skip meals.

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⦸ **DON'T** exercise more than what your doctor recommends.

⦸ **DON'T** weigh yourself daily.

⦸ **DON'T** use drugs, diet pills, laxatives, or caffeine to lose weight.

⦸ **DON'T** eat alone, if possible.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- Anorexia Nervosa and Related Eating Disorders, Inc. **Website: http://www.anred.com**
- National Association of Anorexia Nervosa and Associated Disorders Hotline: (847) 831-3438 **Website: http://www.anad.org**

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MANAGING YOUR

ANTIPHOSPHOLIPID ANTIBODY SYNDROME

What Is Antiphospholipid Antibody Syndrome?

In antiphospholipid antibody syndrome (abbreviated APS), people have too much blood clotting and have antiphospholipid antibodies in the blood. Antibodies are substances produced by the immune system (disease fighting system) to attack substances foreign to the body. Autoantibodies (antibodies against one's body) occur when there is a problem with the immune system. Problems with pregnancy, such as miscarriage or premature birth may occur.

What Causes APS?

The cause is unknown. It can't be caught or passed from generation to generation. Antiphospholipid antibodies are thought to interact with the body's clotting system, so people are prone to getting deep vein thrombosis (formation of a blood clot, or thrombus, usually in leg veins) and arterial thrombosis (clots in arteries). These clots can lead to heart attacks and strokes.

The antiphospholipid antibodies are called lupus anticoagulant and anticardiolipin antibodies. They are found in people with systemic lupus erythematosus (an autoimmune disease, meaning the body's immune system attacks itself). Other risk factors for development of APS include rheumatoid arthritis, Behçet's syndrome, and Sjögren's syndrome. Medicine including hydralazine (for blood pressure), quinine (for leg cramps), and certain antibiotics can sometimes cause APS.

What Are the Symptoms of APS?

Clots in both veins and arteries can occur. Most often, venous thrombosis occurs in deep veins of legs. The clots cause leg swelling, pain, redness, and warmth. The most common site for thrombosis in arteries is cerebral (brain) blood vessels. Stroke, with slurred speech, paralysis, numb-

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ness, weakness, loss of vision, and swallowing problems, can result.

Other parts of the body involved include the heart, lungs, gastrointestinal tract, kidneys, and skin. Pregnant women can suffer spontaneous abortions, and the blood system can be affected, so anemia (low red blood cell count) or thrombocytopenia (low platelet count) results.

How Is APS Diagnosed?

The doctor may suspect APS because of blood clots, and will order blood tests and x-rays to aid diagnosis and rule out complications.

At least one clinical feature and one laboratory feature are needed for diagnosis. Clinical features are clots or complications in pregnancy (death of a fetus, premature birth, or spontaneous abortions). Laboratory features include presence of anticardiolipin antibodies or lupus anticoagulant.

How Is APS Treated?

Blood thinners are used to prevent clots from forming. Common drugs are heparin and warfarin. If APS is caused by another disease, the doctor will treat that condition.

Regular blood tests are needed to monitor the level of blood thinner. Physical activity such as playing contact sports should be avoided.

DOs and DON'Ts in Managing APS:

✓ **DO** understand that although aspirin is a blood thinner, aspirin alone is not a useful APS treatment.

✓ **DO** understand that you can have antiphospholipid antibodies without having blood clotting, and blood thinners may not be needed.

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✓ **DO** call your doctor if you think that you're pregnant or if you have a history of APS and you're pregnant.

✓ **DO** call your doctor if you have symptoms of APS.

✓ **DO** call your doctor if you are using blood thinners and have signs of too much blood thinning, such as easy bruising and bleeding.

⃠ **DON'T** miss your warfarin dose. Its blood level must be kept at the recommended range to reduce clotting risk.

⃠ **DON'T** use oral contraceptives if you already have antiphospholipid antibodies.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- National Heart, Lung, and Blood Institute Tel: (800) 575-9355 **Website:** **http://www.nhlbi.nih.gov**
- National Stroke Association Tel: (800) 787-6537 **Website:** **http://www.stroke.org**

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MANAGING YOUR

ANXIETY

What Is Anxiety?

Feeling anxious is normal. However, a continuing problem with anxiety is called generalized anxiety disorder (GAD). People with GAD feel tense and worried much of the time, and some always feel this way.

GAD is fairly common, often occurring before age 18. It affects more women than men and seems more common in some families.

Certain medical conditions, such as colitis, asthma, hypertension, heart disease, ulcers, and headaches, are highly related to anxiety.

What Causes Anxiety?

People stressed at work or at home can have anxiety. GAD is also more likely in people who expect things to be perfect, are tired or overwhelmed, had stressful or harmful experiences, have a medical illness, are withdrawing from alcohol or drugs, or were abused as children.

Some people have panic attacks (extreme anxiety in certain situations) or phobias (anxiety caused by fears, such as of heights, or social situations, such as public speaking).

What Are the Symptoms of Anxiety?

People with GAD feel tense and worried. Other symptoms include restlessness, tiredness, difficulty concentrating, irritability, muscle tension, trouble sleeping, shakiness, headaches, pounding heart, shortness of breath, excessive sweating, and depression. These interfere with daily life.

How Is Anxiety Diagnosed?

The doctor makes the diagnosis after doing an examination and checking symptoms. The doctor may order blood tests or other tests to make sure another illness such as overactive thyroid isn't

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causing symptoms. People diagnosed with GAD have had tension and worry most days for at least 6 months, and they cannot control worrying even when reassured by others.

Forms of anxiety in addition to GAD, panic attacks, and phobias include obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, anxiety caused by legal drugs (e.g., caffeine) or drugs of abuse (e.g., amphetamines, cocaine), and anxiety caused by medical conditions and medicines.

How Is Anxiety Treated?

The doctor tries to find out, by taking a medical history, whether a medical condition or substance abuse is the cause. Drugs producing anxiety include corticosteroids (e.g., prednisone), antidepressants (e.g., fluoxetine), inhalers, thyroid medicine, diet pills, and over-the-counter medicines (e.g., antihistamines, cough and cold medicines). Too much caffeine can worsen anxiety.

Medicine to help symptoms include benzodiazepines, such as alprazolam, lorazepam, and clonazepam, and other anti-anxiety medications, such as buspirone. They do have side effects and can be habit forming.

Talk therapy (psychotherapy) and other methods to reduce stress and muscle tension (biofeedback, relaxation) may help symptoms. Regular exercise, such as walking and swimming, can reduce stress and tension.

DOs and DON'Ts in Managing Anxiety:

✓ **DO** tell your doctor about all medicines you take.

✓ **DO** take your medicine as instructed and tell your doctor about side effects.

✓ **DO** exercise regularly.

✓ **DO** tell your doctor or someone you trust if you have suicidal thoughts.

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✓ **DO** eat a healthy diet.

✓ **DO** make life changes to reduce stress. Join a support group if you think that may help.

✓ **DO** remember that most drugs for anxiety can sedate you, so avoid drinking alcohol.

⃠ **DON'T** overuse caffeine, alcohol, nicotine, diet pills, and common cold remedies.

⃠ **DON'T** make major decisions while you feel anxious.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- Anxiety Disorders Association of America Tel: (240) 485-1001 **Website:** **http://www.adaa.org**
- The Anxiety Network International **Website:** **http://www.anxietynetwork.com/**
- The Anxiety Panic Internet Resource (tAPir) **Website:** **http://www.algy.com/anxiety/**

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MANAGING YOUR

AORTIC DISSECTION

What Is Aortic Dissection?

Aortic dissection is a life-threatening condition in which bleeding occurs into the aorta wall layers and makes them pull apart (dissect). The three layers are the intima (inner), media (middle muscular), and adventitia (outer). The aorta is the largest artery and carries blood from the heart. It's divided into the ascending aorta, the connecting aortic arch, and the descending aorta. The ascending aorta attaches to the heart. The descending aorta goes from the chest into the abdomen (belly) and then divides into arteries to the legs.

Aortic dissection is more common in men 60 to 70 years old but can affect people as young as 40. It can be catastrophic and cause sudden death or heart failure.

What Causes Aortic Dissection?

A tear of the inner layer lets blood push the inner and outer aorta wall layers apart. The cause is unknown, but aortic dissection is usually associated with hypertension (high blood pressure) and atherosclerosis. It also occurs with connective tissue disorders such as Marfan's and Ehlers-Danlos syndromes. Infections such as syphilis can rarely lead to aneurysms (bulging of the artery), which are likely to dissect.

What Are the Symptoms of Aortic Dissection?

Symptoms include sharp, tearing chest pain under the chest bone (sternum) and going to the shoulders, neck, arms, and between shoulder blades or in the back. Pain is sudden and can be severe. Other symptoms include shortness of breath, sweating, confusion, fainting, lightheadedness, and apprehension.

Hypertension, rapid heart rate, different blood pressure readings in both arms, a new heart murmur, kidney failure, stroke, and heart attacks can occur.

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How Is Aortic Dissection Diagnosed?

If the doctor suspects aortic dissection based on your history and physical exam, additional tests may include computed tomography (CT), MRI, or transesophageal echocardiography. In transesophageal echocardiography, the doctor puts a probe into the mouth and down the esophagus to get special views of the aorta. MRI uses a magnetic field to look at the aorta. In angiography, the doctor puts a thin tube (catheter) into a leg artery and up to the aorta and injects dye to take pictures of the aorta.

How Is Aortic Dissection Treated?

Treatment depends on where the dissection is. Type A dissection involves the ascending aorta; type B means dissection of the descending aorta. Surgery is used for type A dissections. The tear in the aorta is stitched together as are the edges of the dissected wall. Type B dissections need medical treatment (control of blood pressure) to lower pressure inside the aorta.

DOs and DON'Ts in Managing Aortic Dissection:

✓ **DO** control your blood pressure. Most aortic dissections occur in people with long-standing hypertension. Follow a low-salt diet, exercise, and lose weight. Don't smoke!

✓ **DO** remember that the condition can be life-threatening. Less than 50% of people survive if the dissection bursts into the abdomen, heart, or sac around the heart.

✓ **DO** immediately call your doctor if you have chest pain, shortness of breath, or abdominal pain going to your back.

⦸ **DON'T** forget to take your medicine for hypertension.

⦸ **DON'T** miss follow-up doctor appointments.

⦸ **DON'T** ignore chest pain!

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FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Heart Association National Center Tel: (800) 242-8721
- American College of Cardiology Tel: (800) 253-4636 Fax: (202) 375-700 **Website:**

  http://www.acc.org
- Society for Vascular Surgery Tel: (800) 253-4636 **Website:**

  http://www.vascularweb.com

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MANAGING YOUR

AORTIC INSUFFICIENCY

What Is Aortic Insufficiency?

The aorta is the large artery that leaves the heart from the left lower chamber (ventricle). The aortic valve is between the left ventricle and the aorta. Aortic insufficiency (or aortic regurgitation) is the leaking of blood from the aorta through the aortic valve into the left ventricle when the ventricle contracts.

Aortic insufficiency causes the left ventricle to get larger because of the extra blood in it.

What Causes Aortic Insufficiency?

The cause is a defective aortic valve or enlarged bottom part of the aorta. Infections such as rheumatic fever (usually from streptococcal infections) and endocarditis (bacterial infection in the heart) affect the valve. Congenital abnormalities such as bicuspid valve (two valve sections instead of three) are a common cause. Direct blunt injury (e.g., the chest hitting a steering wheel in an accident), connective tissue disorders such as Marfan's disease, and hypertension can also lead to an enlarged aorta and subsequent aortic insufficiency.

What Are the Symptoms of Aortic Insufficiency?

Most people have no symptoms in early stages. Symptoms when present are tiredness, chest pain, difficulty breathing (especially when lying down), coughing, and shortness of breath.

How Is Aortic Insufficiency Diagnosed?

The doctor makes a diagnosis from a physical examination. Blood flowing through the valve creates a heart murmur (extra or unusual sound during the heartbeat) that the doctor hears with the stethoscope. The doctor will recommend echocardiography (a test that uses ultrasound waves to give a picture of the heart) to confirm the diagnosis.

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For severe insufficiency with effects on the heart's function, the doctor may suggest cardiac catheterization. In catheterization a small tube (catheter) is inserted into a leg artery and passed into the heart to get pictures of the heart and determine the severity of the aortic insufficiency.

How Is Aortic Insufficiency Treated?

For people without symptoms, the doctor may recommend regular check-ups including echocardiograms. If testing shows worsening aortic insufficiency and/or an enlarged heart, the doctor may suggest seeing a thoracic surgeon (a specialist who performs heart valve operations) to correct or replace the valve.

People with symptoms may also need medicines to prevent fluid and pressure from building up in the heart. The doctor may also recommend referral to a thoracic surgeon in anticipation of future need for surgery.

DOs and DON'Ts in Managing Aortic Insufficiency:

✓ **DO** remember that you may not have symptoms but may need to be checked with echocardiograms to follow the valve disease.

✓ **DO** take antibiotics (if prescribed) before dental or surgical procedures if you had infectious endocarditis or prior heart surgery.

✓ **DO** ask your doctor for referral to a cardiologist (a doctor who specializes in heart diseases) if you are having symptoms.

✓ **DO** call your doctor if you get shortness of breath, chest or upper back pain, palpitations or rapid heartbeat, or fainting.

⃠ **DON'T** do strenuous exercise if you have severe insufficiency.

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⦸ **DON'T** forget that periodic checkups to monitor for aortic insufficiency and its effect on the heart are important.

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:** **http://www.americanheart.org**
- American College of Cardiology Tel: (800) 253-4636 **Website: http://www.acc.org**
- Heart Center Online

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MANAGING YOUR

AORTIC STENOSIS

What Is Aortic Stenosis?

Aortic valve stenosis (AVS) is a disorder in which the opening of the aortic valve in the heart is too small or stiff. A valve is like a doorway, and the aortic valve is one of four valves controlling blood flow inside the heart. A normal aortic valve has three flaps (leaflets). The heart sends oxygen rich blood to the body through this valve. In AVS, the heart works harder to pump blood through the smaller opening. This extra effort can make the heart grow big and weak.

AVS occurs about three times more often in men than in women.

What Causes Aortic Stenosis?

Calcium and cholesterol deposits on the valve that occur with aging are the most common cause. Some people are born with damaged valves or have a two-sided (bicuspid), not three-sided, valve. Heart disease or rheumatic fever from childhood infections may also damage the valve.

What Are the Symptoms of Aortic Stenosis?

Most people at first have no symptoms. If the valve narrows enough, feeling tired, fainting with exercise, having chest pain with exercise or at rest, or having symptoms of left-sided heart failure (e.g., shortness of breath) may occur. Breathing problems during exercise may progress to problems at rest, or waking up at night unable to breathe.

How Is Aortic Stenosis Diagnosed?

The doctor will take a medical history and do a physical examination. The doctor may hear a heart murmur (an extra or unusual sound of blood flow through the valve during the heartbeat). If AVS is suspected, the doctor will order echocardiography (using sound waves to take heart pictures) to diagnose AVS.

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Additional tests such as heart catheterization (using x-rays and dye) may be done before surgery to replace the valve in order to estimate how severe the aortic stenosis is.

How Is Aortic Stenosis Treated?

People without symptoms and with mild stenosis may not need treatment but should be monitored on a periodic basis by their doctor. For people with symptoms or severe disease, surgery to replace the valve is best.

Sometimes, a special balloon is put in the valve and blown up so the valve stretches (valvuloplasty). Valvuloplasty is often used in younger people who will get a replacement valve after they grow.

DOs and DON'Ts in Managing Aortic Stenosis:

✓ **DO** ask your doctor if you can exercise.

✓ **DO** stop smoking.

✓ **DO** start a low-salt diet and lose weight if you have congestive heart failure.

✓ **DO** call your doctor if, after you get a new valve, you have chest pain, shortness of breath, palpitations or rapid heartbeat, fainting, sudden weakness in an arm or leg, eyesight problems, fever, or blood from the surgery site.

⦸ **DON'T** become dehydrated. Dehydration will worsen aortic stenosis.

⦸ **DON'T** use any over-the-counter medicine without asking your doctor.

⦸ **DON'T** ignore worsening symptoms.

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- American Heart Association Tel: (800) 242-8721 **Website:**

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- Heart Center Online

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MANAGING YOUR

AORTIC VALVE DISEASE

What Is Aortic Valve Disease?

Aortic valve disease includes aortic valve stenosis (AVS) and aortic insufficiency (or regurgitation). In the first disorder, the aortic valve gets thick and narrow (stenotic), so the heart must work harder to send blood through the valve. Less blood gets through to the body. The doctor may hear an abnormal heart sound (heart murmur) with a stethoscope. In aortic insufficiency, the valve doesn't close well, so some blood that was just pumped out leaks back. Over several years, the left ventricle (bottom heart chamber) gets too big because of the extra blood and becomes less efficient in pumping blood.

What Causes Aortic Valve Disease?

Causes include congenital heart disorders in children. In adults, endocarditis (bacterial heart infection), aging-related calcium deposits on the valve, and rheumatic fever can damage aortic valves. Rarer causes include radiation, rheumatoid arthritis, trauma, and other diseases (Paget's and Fabry's diseases, end-stage kidney disease).

What Are the Symptoms of Aortic Valve Disease?

AVS symptoms develop when valve narrowing is severe. They include chest pain or tightness, fainting, dizziness, tiredness, shortness of breath, palpitations (feeling a rapid, fluttering heartbeat), and heart murmur. People with chronic aortic insufficiency may not have symptoms for years. As it gets worse, similar symptoms occur. Other signs and symptoms include rapid or irregular pulse and swollen ankles and feet.

How Is Aortic Valve Disease Diagnosed?

For diagnosis, the doctor uses the medical history and physical examination. The doctor can hear

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a heart murmur, which is an extra or unusual sound of blood flowing through the valve during the heartbeat. The doctor will usually order electrocardiography (ECG), chest x-ray, and echocardiography. Two-dimensional echocardiography with Doppler is best for checking for AVS. In this test, sound waves are used to take heart pictures. Exercise test and cardiac catheterization may also be done if surgery is being considered.

How Is Aortic Valve Disease Treated?

People with mild to moderate conditions and no symptoms may just need regular checkups.

Drugs are usually initially used to treat symptoms of AVS. Surgery is performed in more severe cases. It includes aortic valve replacement and balloon valvuloplasty. Balloon valvuloplasty uses a soft, thin tube (catheter) tipped with a balloon to stretch the valve opening.

People with symptoms of aortic valve insufficiency generally need surgery. However, surgery (valve repair or replacement) may also be done even when no symptoms occur if there is evidence of worsening aortic insufficiency on echocardiogram. Certain drugs (vasodilators) can help relieve symptoms and prevent complications.

DOs and DON'Ts in Managing Aortic Valve Disease:

✓ **DO** control high blood pressure and high cholesterol levels. Eat low-fat, low-salt, low-cholesterol foods. Lose weight if you're overweight.

✓ **DO** exercise regularly.

✓ **DO** see your doctor for regular checkups.

✓ **DO** prevent rheumatic fever by seeing your doctor when you have a sore throat and fever. Untreated strep throat can become rheumatic fever. Take antibiotics before dental visits or

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operations if your doctor prescribes them.

- ⃠ **DON'T** take over-the-counter medicines unless your doctor says you can.
- ⃠ **DON'T** smoke or drink alcohol or caffeine.
- ⃠ **DON'T** become dehydrated.

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:**

  http://www.americanheart.org

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MANAGING YOUR

APLASTIC ANEMIA

What Is Aplastic Anemia?

In aplastic anemia, bone marrow doesn't make blood cells. Bone marrow is soft tissue inside bones. Counts of all blood cells—red, white, and platelets—are low. Severe aplastic anemia is life-threatening. It's rare and affects 1 in every 100,000 people.

What Causes Aplastic Anemia?

The cause is often unknown. Exposure to chemicals such as benzene, insecticides (DDT), and explosives (TNT) is related to some cases. Radiation, medicines such as the antibiotic chloramphenicol and gold salts (used for rheumatoid arthritis), and some viral infections (such as hepatitis) can lead to aplastic anemia. A problem with the immune (infection-fighting) system may reduce bone marrow production.

What Are the Symptoms of Aplastic Anemia?

Symptoms include weakness, fatigue, chest pain, dizziness, and shortness of breath. People cannot exercise as much. Skin color is pale. Low white blood cell counts (leukopenia) may lead to repeated infections, such as pneumonia, sinusitis, and skin infections. Low platelet counts may cause bleeding from the vagina or nose, bleeding into internal organs, and easy bruising. Low red blood cell counts lead to fatigue and weakness.

How Is Aplastic Anemia Diagnosed?

The doctor makes a diagnosis from a medical history, physical examination, and blood tests including a complete blood count (CBC). A blood specialist will do a bone marrow biopsy. In this biopsy, marrow is removed with a needle from inside the bone (usually the back of the pelvis). The marrow is then studied with a microscope and special tests.

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How Is Aplastic Anemia Treated?

Quick diagnosis and therapy are important. Most people need blood transfusions, often more than one. Drugs can help the bone marrow make new blood cells or stop the immune system from causing the disorder.

Transplantation of bone marrow from a family member or matched, unrelated donor may cure the anemia. Only certain people, based on age and other factors, can have transplantations, however. Transplantation involves high doses of chemotherapy drugs, special injection of bone marrow cells from a donor, and then medicines to make sure that the immune system doesn't reject the transplant. These immunosuppressive medicines (steroids such as prednisone) can lead to remissions for up to 70% of people who cannot have transplantation.

Transplantation involves risks (infection, toxic effects of chemotherapy) that can be fatal. Other side effects of steroids, such as high blood pressure and weight gain, can also occur.

Bone marrow cells of the donor can attack the body and cause a serious complication called graft-versus-host disease. A rash, diarrhea, and liver problems can develop. Immunosuppressive drugs may prevent this complication.

DOs and DON'Ts in Managing Aplastic Anemia:

✓ **DO** take your medicines as prescribed.

✓ **DO** get laboratory tests as directed.

✓ **DO** eat a special diet to limit bacterial contamination if you have a low white blood cell count.

✓ **DO** wear a medical alert bracelet.

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✓ **DO** call your doctor if you have a fever, bleeding, chest pain, or dizziness.

⦸ **DON'T** have contact with crowds or people with infections.

⦸ **DON'T** take aspirin and aspirin-like drugs. They can increase bleeding.

⦸ **DON'T** eat fresh leafy vegetables, fruit, cheese, and yogurt. Your weak immune system makes you more likely to get infections.

⦸ **DON'T** do contact sports and strenuous exercise.

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FOR MORE INFORMATION

Contact the following sources:

- American Cancer Society Tel: (800) 227-2345 **Website: http://www.cancer.org**
- Leukemia and Lymphoma Society Tel: (800) 955-4572 **Website: http://www.leukemia-lymphoma.org**
- National Cancer Institute National Institutes of Health Tel: (800) 422-6237 **Website: http://www.cancer.gov**

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MANAGING YOUR

APPENDICITIS

What Is Appendicitis?

The appendix is a tiny, worm-shaped structure attached to the part of the bowel (large intestine) called the cecum. Appendicitis is swelling (inflammation) and infection of the appendix. Although the appendix has no real purpose in the body, an infected appendix can be life-threatening.

Appendicitis occurs in up to 10% of the population, most often in people between 10 and 30 years old. With prompt treatment, appendicitis has an excellent prognosis.

What Causes Appendicitis?

The exact cause is unclear. The opening from the cecum to the appendix becomes blocked (obstructed), which leads to inflammation and growth of bacteria. Infection prevents blood flow, gangrene begins, and the appendix can burst open (rupture, or perforate).

Things that can obstruct the appendix include fecoliths (tiny pieces of undigested vegetable surrounded by stool) and enlarged lymph nodes caused by viruses, parasites, or tumors.

What Are the Symptoms of Appendicitis?

The classic symptom is pain in the abdomen (belly) that starts in the upper middle part near the umbilicus (belly button). The pain then usually moves down to the right lower corner of the abdomen.

Movement, coughing, and straining make the pain worse. Nausea, vomiting, abdominal swelling, and low-grade fever also occur. Waiting too long before seeking medical care can result in a burst appendix.

A burst appendix is a medical emergency and can produce an abdominal mass with pain, and a

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temperature higher than 102° F.

How Is Appendicitis Diagnosed?

The doctor makes a diagnosis by checking symptoms and doing a physical examination. Blood tests may help, but no specific blood tests can diagnose appendicitis. X-rays including ultrasound (using sound waves to view abdominal organs) and computed tomography (CT) may help in some cases to rule out other diseases.

How Is Appendicitis Treated?

Treatment is removal of the appendix, an operation called an appendectomy. An appendectomy is the most common emergency abdominal operation done in the United States. The preferred operation is by laparoscopy (laparoscopic appendectomy). A lighted tube (scope) is passed into the abdomen to see and remove the appendix. Another operation involves making a cut in the lower right side of the abdomen to remove the appendix (open appendectomy). Antibiotics for infection and drugs for pain, and maybe stool softeners, are usually prescribed.

In simple cases, most people will be in the hospital for 1 day or may go home the same day of surgery. For a ruptured appendix, the hospital stay will be longer, to give intravenous antibiotics and monitor for complications.

DOs and DON'Ts in Managing Appendicitis:

✓ **DO** report your symptoms. The earlier the diagnosis is made, the better the prognosis. Delays can lead to a burst appendix.

✓ **DO** call your doctor if you have vomiting, diarrhea or blood in your stool, a mass in your abdomen, or abdominal pain with fever.

✓ **DO** call your doctor if you need a referral to a surgeon.

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⦸ **DON'T** miss follow-up appointments.

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FOR MORE INFORMATION

Contact the following sources:

• MedlinePlus Health Information U.S. National Library of Medicine **Website:**

http://www.nlm.nih.gov/medlineplus/ appendicitis.html

• American College of Surgeons Tel: (800) 621-4111, (312) 202-5000 **Website:**

http://www.facs.org

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CARING FOR YOUR CHILD WITH

APPENDICITIS

What Is Appendicitis?

The appendix is a tiny, worm-shaped structure attached to the part of the bowel (large intestine) called the cecum. Appendicitis is swelling (inflammation) and infection of the appendix. It affects many children, most often those 11 to 20 years old and rarely babies. It's the most common cause of emergency surgery in childhood. An infected appendix can rupture (burst open) and be life-threatening. With treatment, children usually have no long-term problems.

What Causes Appendicitis?

The exact cause is unclear. The opening from the cecum to the appendix becomes blocked (obstructed), which leads to inflammation and growth of bacteria. Infection prevents blood flow, gangrene begins, and the appendix can burst and cause an abdominal infection called peritonitis.

Obstruction can be caused by fecoliths (tiny pieces of undigested vegetable surrounded by stool) and enlarged lymph nodes caused by viruses, parasites, or tumors.

A family history of appendicitis (especially for males) and cystic fibrosis can mean higher risks.

What Are the Symptoms of Appendicitis?

Symptoms vary according to age. In children 2 years old or younger, the most common ones are vomiting, swollen abdomen (belly), and pain. The classic symptom is abdominal pain that starts around the belly button. Pain then moves down to the right lower corner of the abdomen. Moving, coughing, sneezing, taking deep breaths, and straining can make pain worse. Nausea, vomiting, loss of appetite, abdominal swelling, low-grade fever, and diarrhea or constipation also occur.

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A burst appendix produces an abdominal mass with pain, and a temperature higher than 102° F.

How Is Appendicitis Diagnosed?

Because symptoms can be much like those of other medical conditions, diagnosis can be challenging. The doctor makes a diagnosis by using a medical history, symptoms, and physical examination. Blood tests may be done. Imaging studies including ultrasound (using sound waves to view abdominal organs) and computed tomography (CT scan) may help evaluate for appendicitis and other abdominal diseases.

How Is Appendicitis Treated?

Treatment is removal of the appendix, the operation is called an appendectomy. The laparoscopic type of operation is preferred. A small cut is made and the appendix is removed by using a lighted tube (scope). Another operation (open appendectomy) involves making a cut in the lower right side of the abdomen. After surgery, children are first given fluids intravenously (into a vein) but then can drink clear fluids and finally eat solid foods. Antibiotics for infection and drugs for pain, and maybe stool softeners, are usually prescribed.

Most simple cases need an overnight hospital stay. A burst appendix may mean a longer hospital stay. Most children need rest at home for 1 week before returning to school, and 2 to 3 weeks before returning to gym and sports.

DOs and DON'Ts in Managing Appendicitis:

✓ **DO** report your child's symptoms to the doctor. The earlier the diagnosis is made, the better the prognosis. Delays can lead to a burst appendix.

✓ **DO** call the doctor if your child develops fever; excessive swelling, redness, or drainage from

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the incision; bleeding; or increasing pain.

⦸ **DON'T** forget that the diagnosis is hard to make. Many other illnesses can mimic this disorder.

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FOR MORE INFORMATION

Contact the following sources:

- The American Academy of Pediatrics Tel: (847) 434-4000 **Website: http://www.aap.org**
- MedlinePlus Health Information U.S. National Library of Medicine **Website: http://www.nlm.nih.gov/medlineplus/appendicitis.html**
- American College of Surgeons Tel: (800) 621-4111, (312) 202-5000 **Website: http://www.facs.org**

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MANAGING YOUR

ASBESTOSIS

What Is Asbestosis?

Asbestosis is a disease that scars the lungs as a result of breathing asbestos. Asbestos is a name of a group of natural fibers that were formerly used in various industrial products due to their resistance to burning and for insulation. Up to 20 to 30 years may pass between exposure to asbestos and development of asbestosis.

The probability of developing disease, usually several years after exposure, increases with longer and more intense asbestos exposures. Asbestos-related diseases cannot be caught but can be prevented by avoiding asbestos exposure.

Asbestos can cause diseases of lungs and pleura (layer of tissue covering the lungs), including pleural plaques, pleural effusion, and development of cancer of the lining of the lung (malignant mesothelioma). It can also increase the risk of lung cancer.

What Causes Asbestosis?

Exposure most often occurred at work. Employees at greatest risk included those who mined, milled, or transported asbestos. Others at risk were people such as car repair and construction workers who installed, fixed, or tore down products made with asbestos; people (painters, carpenters) who worked near where asbestos was used; and those living near asbestos factories or mines.

What Are the Symptoms of Asbestosis?

Shortness of breath is the most common symptom because of small, stiff lungs that were scarred by breathing in asbestos fibers. Chronic cough and phlegm (mucus) production are also common.

Pleural plaques (thickened parts of lung linings) generally don’t cause symptoms but may be

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related to a greater risk of developing cancer of the lining of the lung (mesothelioma). Pleural effusion is fluid that collects in the space between the lungs and chest wall. Smaller effusions may cause no symptoms; larger ones can cause shortness of breath.

Symptoms of malignant mesothelioma include chest pain, weight loss, and shortness of breath.

How Is Asbestosis Diagnosed?

The doctor makes a diagnosis on the basis of symptoms (shortness of breath, chronic cough) plus asbestos exposure, and findings of lung examinations and chest x-rays.

How Is Asbestosis Treated?

Treatments are limited. None can reverse or prevent lung scarring. Some people with severe progressive disease may benefit from lung transplants. Oxygen may be prescribed to improve shortness of breath and stamina. Inhalers to help breathing may also be prescribed. Further asbestos exposure should be avoided, because more exposure seems to increase risk for additional disease. The amount of safe, low-level exposure isn't clear.

No treatment is needed for pleural plaques, except for follow-up. Prognosis is very poor for mesothelioma because there are no effective treatments.

DOs and DON'Ts in Managing Asbestosis:

✓ **DO** avoid all future asbestos exposures.

✓ **DO** follow all recommended procedures, such as wearing protective masks, when working with asbestos.

✓ **DO** get a yearly flu shot and a pneumococcal pneumonia shot.

✓ **DO** keep your heart healthy by exercising.

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✓ **DO** eat a healthy diet.

✓ **DO** call your doctor if you have increased cough, yellow or green sputum, more shortness of breath, fever, or chills.

✓ **DO** call your doctor if you have chest pain, new ankle swelling, weight loss, blood in the sputum, or dusky skin, fingertips, or lips.

⃠ **DON'T** go near people with respiratory infections.

⃠ **DON'T** come in contact with lung irritants such as smoke and very cold or humid air.

⃠ **DON'T** smoke.

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NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Lung Association Tel: (800) LUNG-USA (586-4872)
- Agency for Toxic Substances & Disease Registry **Website: http://www.atsdr.cdc.gov**

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MANAGING YOUR

ASCARIASIS

What Is Ascariasis?

Ascariasis is infection by the worm *Ascaris lumbricoides*. It is the most common intestinal worm. This large roundworm can easily be seen without a microscope.

Ascariasis affects only humans. Anybody can get it, but it is more common in children.

What Causes Ascariasis?

The parasite is generally not passed from person to person. Worm eggs are spread by contact with contaminated water, food, or hands (e.g., by eating poorly washed raw vegetables grown in contaminated soil). Untreated young worms (larvae) travel from the intestine to other parts of the body, such as the lungs. They then return to the intestine where they become adults and lay eggs.

What Are the Symptoms of Ascariasis?

Symptoms include restlessness at night, being irritable, tiredness, poor appetite, weight loss, pain in the abdomen (belly), and sometimes diarrhea and fever. Worms may sometimes be seen in bowel movements. In lungs, larvae can cause wheezing.

How Is Ascariasis Diagnosed?

Study of stool samples to find worms or eggs confirms the diagnosis.

How Is Ascariasis Treated?

Medicine is used to kill the worms. These drugs cannot be used in pregnant women.

Management includes attention to habits: wash hands carefully after using the toilet and always before eating. Shower daily and clean the anal area. Boil or soak linens, nightclothes, towels, and washcloths used by someone with roundworms in an ammonia solution (1 cup of ammonia to 5 gallons of water).

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After treatment, bathroom floors and fixtures should be scrubbed. Toys should be sterilized or scrubbed with ammonia solution and then rinsed with clear water.

DOs and DON'Ts in Managing Ascariasis:

✓ **DO** avoid contaminated food and drink.

✓ **DO** take medicine as directed by your doctor.

✓ **DO** tell your doctor if you think you're pregnant.

✓ **DO** wash your hands thoroughly before eating and after using the toilet.

✓ **DO** shower instead of taking tub baths.

✓ **DO** boil soiled linens if possible, or soak them in an ammonia solution before washing.

✓ **DO** sterilize toys or scrub with ammonia solution, then rinse with clear water.

✓ **DO** have pets treated for worms.

✓ **DO** clean bathroom fixtures thoroughly after treatment.

✓ **DO** have all family members checked for infection.

✓ **DO** drink only bottled water when traveling in underdeveloped countries.

✓ **DO** call your doctor if you have a fever, severe abdominal pain, chest pain, or shortness of breath.

✓ **DO** call your doctor if you continue to have symptoms after treatment.

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⦸ **DON'T** eat unwashed vegetables.

⦸ **DON'T** drink tap water when traveling in underdeveloped countries.

⦸ **DON'T** share towels or washcloths.

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FOR MORE INFORMATION

Contact the following sources:

- Intestinal Disease Foundation Tel: (412) 261-5888, Monday through Friday from 9:30 am to 3:30 pm (EST)
- National Institute of Allergy and Infectious Disease Tel: (866) 284-4107, (301) 496-5717

  Website: http://www3.niaid.nih.gov/

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MANAGING YOUR

ASCITES

What Is Ascites?

Ascites is the disorder in which too much fluid accumulates in the peritoneal cavity. This cavity is the space between tissues lining the abdomen (belly) and the abdominal organs. Half of people with cirrhosis have ascites within 10 years of diagnosis.

What Causes Ascites?

Ascites is the most common complication of cirrhosis (chronic liver disease). High pressure in the liver and a lower level of the protein called albumin lead to changes in a pressure difference (gradient). The pressure difference is an imbalance between high pressure inside the liver and low pressure outside, in the abdomen. These changes cause more fluid to flow and accumulate in the abdomen. Other causes include cancer, congestive heart failure, tuberculosis, and inflammation of the pancreas (pancreatitis). Ascites can also be seen with hepatitis and kidney dialysis.

What Are the Symptoms of Ascites?

Symptoms include a very bloated abdomen, bulging flanks, swollen legs, and signs of liver cirrhosis if the ascites is due to cirrhosis. These signs are spider veins, jaundice (yellow skin), loss of body hair, muscle wasting, bruising, larger male breasts, small testes, and hemorrhoids.

How Is Ascites Diagnosed?

The health care provider makes a diagnosis from the medical history and physical examination. Laboratory tests can rule out similar diseases and look for a cause. The health care provider may want abdominal ultrasonography or computed tomography (CT). Specialists that may be consulted include liver specialists, gastroenterologists, infectious disease, and surgeons.

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Special tests such as paracentesis, liver biopsy, and endoscopy of the upper gastrointestinal tract may be needed if the cause of the ascites is unclear. In paracentesis, a thin needle and catheter (tube) are used to remove abdominal fluid. In a liver biopsy, the health care provider takes a small piece of tissue for study. Endoscopy involves putting a lighted tube into the mouth and down the esophagus.

People with ascites should be asked about risk factors for liver disease. These include long-term heavy alcohol or intravenous drug use, chronic viral hepatitis, multiple sex partners, homosexual activity, blood transfusions, and tattoos.

How Is Ascites Treated?

The main treatment is limiting sodium intake and fluids. The maximum sodium intake is generally 1500 mg per day. People with low blood sodium levels should limit fluid intake to about 34 ounces per day. Alcohol should be avoided. People with ascites but no complications may be treated as outpatients. In severe cases, people may be hospitalized for paracentesis or therapy with diuretics (spironolactone and furosemide). They may need repeated large-volume paracentesis and infusion of albumin. In some cases, surgery may be necessary. It consists of placement of a transjugular intrahepatic portosystemic shunt (TIPS). TIPS reduces liver pressure by taking blood through another path around the liver.

DOs and DON'Ts in Managing Ascites:

✓ **DO** follow strict salt and fluid restrictions as suggested by your health care provider.

✓ **DO** learn about your condition so you can tell when treatment isn't working.

⃠ **DON'T** ignore symptoms. Call your health care provider if your symptoms don't improve or they worsen with treatment. Call if you get new symptoms.

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- ⃠ **DON'T** stop taking your medicine or change the dosage because you feel better unless your health care provider says to.
- ⃠ **DON'T** use any medicines (including over-the-counter and herbal products) without first asking your health care provider.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Gastroenterologists Tel: (703) 820-7400 **Website: http://www.acg.gi.org**
- American College of Surgeons Tel: (800) 621-4111 **Website: http://www.facs.org**

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MANAGING YOUR

ASPERGILLOSIS

What Is Aspergillosis?

Aspergillosis is a group of infections caused by the fungus (mold) named *Aspergillus*. Species such as *Aspergillus fumigatus, Aspergillus flavus*, and *Aspergillus niger* live in soil, decaying plant matter, dust, building materials, and dead leaves. Spores (reproductive parts of mold) thrive in air-conditioning and heating ducts, carpeting, insulation, certain plants, tap water, dust, and foods.

What Causes Aspergillosis?

The fungus can cause illness as an allergic reaction (allergic aspergillosis and allergic bronchopulmonary aspergillosis, or ABPA) in people with an asthmatic lung condition. It can cause "fungus balls" (aspergillomas) in lungs already damaged by another condition (e.g., scarring caused by tuberculosis or emphysema). People with weak immune (infection-fighting) systems because of another disease (e.g., HIV) or drugs (e.g., corticosteroids) can more easily be affected (invasive aspergillosis). The infection can spread from lungs to other organs. Low white blood cell counts, cystic fibrosis, hospital stays, and genetics can also mean higher risks of getting aspergillosis.

What Are the Symptoms of Aspergillosis?

Symptoms depend on the type of infection. They include coughing, shortness of breath, fever, chills, coughing up bloody mucus, poor appetite, and weight loss. Chest pain can be made worse with coughing or taking deep breaths. Infection of other organs may lead to headache, stiff neck, nausea, and vomiting. Strokes (from bleeding in the brain), abscesses (pockets of pus), bone pain, heart valve infections, and stomach and intestinal bleeding are others.

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How Is Aspergillosis Diagnosed?

After obtaining a detailed history and performing a physical examination, the doctor makes a diagnosis by using blood tests, chest X-ray, skin tests, and sputum cultures. The doctor may want additional tests such as computed tomography (CT), magnetic resonance imaging (MRI), bronchoscopy, or lung biopsy. In bronchoscopy, the doctor uses a small lighted tube to look inside the lungs and take samples. In a biopsy, the doctor takes a piece of lung tissue to be examined with a microscope.

How Is Aspergillosis Treated?

Treatment varies with the type of aspergillosis. People with ABPA can take a corticosteroid called prednisone or antifungal drugs until the chest X-ray improves. The best treatment of fungus balls is unknown. They may get better without treatment or may need treatment with antifungal drugs. Doctors may simply monitor people without symptoms (watchful waiting). People who cough up a lot of blood usually need surgery. Intravenous antifungal drugs are commonly used in people with invasive aspergillosis.

DOs and DON'Ts in Managing Aspergillosis:

✓ **DO** expect treatment to take a long time, from 3 to 6 months for ABPA, for example. Some antifungal drugs are given for 4 to 6 months and then tapered over the next 4 to 6 months.

✓ **DO** ask to see a pulmonologist (specialist in lung diseases) or infectious disease specialist.

✓ **DO** realize that your underlying disease and immune system affect prognosis.

✓ **DO** call your doctor if you cough up blood or have chest pain, fever, chills, or sweating with a productive cough.

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✓ **DO** be careful when taking immune-suppressing drugs. Stay away from places of possible exposure to the mold.

⦸ **DON'T** ignore symptoms. Report any fever to your doctor, especially if you take medicines to suppress your immune system.

⦸ **DON'T** forget that treatment of ABPA and aspergillomas is usually done outside the hospital. Invasive aspergillosis can be much more dangerous.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following source:

- Centers for Disease Control and Prevention Tel: (800) 311-3435

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MANAGING YOUR

ASPIRATION PNEUMONIA

What Is Aspiration Pneumonia?

Aspiration pneumonia is inflammation of the lungs and airways to the lungs (bronchial tubes). It's caused by breathing in foreign substances. These include food, liquids, vomit, or fluids from the mouth containing bacteria, viruses, or fungi. It makes up 20% to 35% of all pneumonias and 5% to 15% of all community-acquired pneumonias.

What Causes Aspiration Pneumonia?

Risks for getting this pneumonia include poor gag reflexes(often in elderly people), nasogastric tubes, intestinal blockage, ventilators, and contaminated nebulizers. Other risks include coma, alcoholism, and anesthesia. People with strokes, dementia, or swallowing problems (such as in amyotrophic lateral sclerosis and Parkinson's disease) and those receiving medications such as antacids, H_2 blockers, proton pump inhibitors, and sedatives are also at increased risk of aspiration pneumonia.

What Are the Signs and Symptoms of Aspiration Pneumonia?

The most common symptoms are fever, cough with thick yellow phlegm, and shortness of breath. Others include chest pain, shaking chills, confusion, headache, pain with breathing, sweating, and tiredness. Skin can look blue because of lack of oxygen.

How Is Aspiration Pneumonia Diagnosed?

The diagnosis is made from a medical history, examination (with attention to the lungs and throat), chest X-ray, and blood and sputum tests.

How Is Aspiration Pneumonia Treated?

Treatment depends on how severe the pneumonia is. Antibiotics should be started as soon as

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pneumonia is suspected. For milder disease, oral antibiotics may be used. People usually start getting better within 48 to 72 hours from starting therapy. More severely ill people will need treatment in the hospital and get several types of antibiotics given intravenously first and then orally. Hospitalized people may also get oxygen and special care to help clear phlegm. Mechanical ventilation in an intensive care unit may be necessary if breathing worsens. Antibiotic therapy is usually given for 7 to 10 days. Therapy for 14 to 21 days or longer may be given for certain types of bacteria and for people with other chronic medical conditions.

DOs and DON'Ts in Managing Aspiration Pneumonia:

✓ **DO** follow your health care provider's directions and get plenty of rest.

✓ **DO** tell your health care provider about your other medical problems and your medicines (prescription and over-the-counter).

✓ **DO** call your health care provider if you're getting worse or don't feel better after 2 to 3 days.

✓ **DO** tell your health care provider if you're pregnant or taking birth control pills.

✓ **DO** call your health care provider right away or go to the emergency room if the shortness of breath becomes worse.

✓ **DO** try to cough up as much phlegm as possible.

✓ **DO** drink plenty of fluids to avoid dehydration.

⃠ **DON'T** stop taking your medicine because you feel better.

⃠ **DON'T** use a cough medicine to suppress your cough unless your health care provider tells

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you to.

⦸ **DON'T** treat yourself. Aspiration pneumonia can be life threatening. See your health care provider.

⦸ **DON'T** smoke or drink alcohol.

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FOR MORE INFORMATION

Contact the following source:

- American Lung Association Tel: (212) 315-8700 **Website: http://www.lungusa.org**

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Managing your

ASTHMA

What Is Asthma?

Asthma is a lung disease in which normal airflow into and out of lungs is impaired. Smoke, exercise, cold air, infection, mold, dust, and mites, for example, make lung airway cells produce more mucus. The mucus becomes thicker and more sticky, and breathing tubes (airways) clog up and become very small. Wheezing and shortness of breath result.

Early-onset asthma (extrinsic, or allergic, asthma) has both genetic and environmental causes. Late-onset asthma (intrinsic asthma) in adults older than 35 can be triggered by infections and exercise.

What Are the Symptoms of Asthma?

- Wheezing (a whistling sound as breath is exhaled)
- Shortness of breath
- Chest tightness
- Cough

Emotional stress may also cause an asthma attack and result in a visit to the emergency room and use of oxygen and drugs.

How Is Asthma Diagnosed?

Asthma is diagnosed by reviewing symptoms; doing a physical checkup; and testing lung function, blood, and skin sensitivity. Lung (pulmonary) function tests can tell if breathing is normal and how sensitive airways are. These tests use a peak flow meter to measure air breathed in and out.

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Asthma can be mild irregular (intermittent—i.e., symptoms less than two times per week). Or it can be mild long-lasting (persistent—symptoms more than two times per week but less than once daily), moderate persistent (daily symptoms), or severe persistent (constant symptoms). The doctor will base the treatment on asthma's severity.

Drugs, often given by an inhaler, may control asthma. Some work almost immediately and are used during an asthma attack. Others help stop future attacks. Some medications to reduce inflammation, known as leukotriene receptor antagonists (such as Singulair®), can also be given in pill form.

The three types of common treatments are symptomatic, long-term, and immune therapy. For symptomatic treatment, short-acting drugs in inhalers are used as needed, usually by patients with mild intermittent asthma. Long-acting drugs in inhalers are used every 12 hours.

Long-term treatment involves corticosteroids given in inhalers to reduce lung swelling and redness (inflammation). They are for mild, moderate, and severe persistent asthma.

Immune therapy, often called allergy shots, is for patients who have asthma caused by uncontrolled allergies.

Asthma is treatable, and most flare-ups and deaths caused by asthma can be prevented.

DOs and DON'Ts in Managing Asthma:

✓ **DO** always carry your inhaler with you.

✓ **DO** visit your doctor regularly.

✓ **DO** use the peak flow meter to measure the amount of air you take in when you breathe. Keep records of the amounts and bring them to your doctor appointments.

✓ **DO** get a yearly flu shot and pneumococcal vaccine.

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✓ **DO** continue normal activities as tolerated.

✓ **DO** exercise regularly, but make sure your asthma is controlled before starting new exercises.

✓ **DO** reduce the dust mites in your house, e.g., by getting rid of carpets and using special (HEPA) filters.

✓ **DO** talk to your doctor about how pets may affect asthma.

✓ **DO** tell your doctor if your medicines do not control your asthma or have side effects, if your peak flow readings always go down, or if you feel more tired.

⃠ **DON'T** take aspirin and other over-the-counter medicines unless your doctor approves them.

⃠ **DON'T** come into contact with asthma triggers such as cold air or smoke.

⃠ **DON'T** do excessive exercise, especially in cold weather.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Lung Association Tel: (800) LUNG-USA **Website:** **http://www.lungusa.org**
- National Lung Health Education Program Tel: (303) 839-6755 **Website:** **http://www.nlhep.org**

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CARING FOR YOUR CHILD WITH

ASTHMA

What Is Asthma?

Asthma is a chronic disease in which normal airflow in airways is blocked. Airways are breathing tubes taking air into and out of lungs. In asthma, airway cells produce more mucus, which becomes thicker and more sticky. Airways clog up and become inflamed, swollen and very small.

Asthma most often starts in childhood. About 6 million children have it. Children have small airways, so their asthma can be especially serious.

What Causes Asthma?

Early-onset asthma (extrinsic, or allergic, asthma) has both genetic and environmental causes. Among these are allergens (molds, pollens, animals), irritants (tobacco smoke, air pollution), weather (cold air), exercise, and infections (flu, colds). Asthma runs in families. Emotional stress may cause asthma attacks.

What Are the Symptoms of Asthma?

Symptoms vary from child to child. They include wheezing (a whistling sound during breathing), coughing, chest tightness, and trouble breathing, especially in early morning or at night.

How Is Asthma Diagnosed?

The doctor checks symptoms, does a physical examination, and may test lung function, blood, and skin sensitivity. Lung (pulmonary) function tests (spirometry) can tell whether breathing is normal and how sensitive the airways are. However, these tests aren't accurate before age 6. For children younger than 3, doctors may use a "wait-and-see" approach.

How Is Asthma Treated?

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Asthma can be mild irregular (intermittent) (i.e., symptoms less than two times per week). It can be mild long-lasting (persistent), with symptoms more than two times per week but less than once daily. It can be moderate persistent (daily symptoms) or severe persistent (constant symptoms). Treatment depends on asthma's severity and involves preventing symptoms and treating attacks.

Preventive anti-inflammatory drugs are taken daily for long periods. Long-term treatment involves corticosteroids given in inhalers or pills to reduce lung inflammation. These drugs are for mild, moderate, and severe persistent asthma. Quick-relief medicines are for symptomatic treatment. Short-acting bronchodilators, often given by inhalers, quickly open swollen airways. Long-acting drugs in inhalers are used every 12 hours. Immunotherapy may help children with allergic asthma that can't be controlled by avoiding triggers.

Older children and teens may use small, hand-held devices called pressurized metered-dose inhalers (MDIs) or inhalers that release a fine powder. Babies and toddlers must use face masks attached to MDIs or nebulizers. A plastic tube device called a "spacer" should always be used with MDI's.

Lifestyle and home remedies are important for asthma control. Alternative treatments that may help include breathing techniques, acupuncture, and relaxation.

DOs and DON'Ts in Managing Asthma:

✓ **DO** have your child always carry an inhaler.

✓ **DO** always use a spacer with an inhaler to take your asthma medicine.

✓ **DO** make sure that your child maintains a healthy weight.

✓ **DO** encourage regular exercise.

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✓ **DO** reduce dust mites in your house, e.g., by getting rid of carpets and using special (HEPA) filters. Clean regularly.

✓ **DO** reduce pet dander by avoiding pets with fur or feathers or by regular bathing or grooming.

✓ **DO** review an asthma care plan with your doctor at least once per year.

✓ **DO** call the doctor if medicines don't control the asthma or have side effects.

✓ **DO** avoid triggers such as cold air and smoke. Maintain low humidity. Use the air conditioner and keep indoor air clean.

✓ **DO** learn the symptoms of an asthma flare so you can start treatment at the earliest signs.

⃠ **DON'T** give your child over-the-counter medicines unless your doctor says you can.

⃠ **DON'T** let your child come into contact with asthma triggers. Asthma may be related to cigarette smoke exposure.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- The American Academy of Pediatrics Tel: (847) 434-4000 **Website: http://www.aap.org**
- American Lung Association Tel: (800) LUNG-USA **Website: http://www.lungusa.org**
- National Lung Health Education Program Tel: (303) 839-6755 **Website: http://www.nlhep.org**

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MANAGING YOUR

ASTROCYTOMA

What Are Astrocytomas?

The brain is the major organ of your central nervous system and is made up of nerve cells (neurons) and supportive (glial) tissue. Different cells make up glial tissue, astrocytes and oligodendrocytes being the most numerous. Astrocytomas are brain cancers formed from astrocytes.

Astrocytomas are the most common brain tumors in adults. Children can also have them.

What Causes Astrocytomas?

The cause is unknown. Astrocytomas cannot be caught and aren't passed on from generation to generation.

What Are the Symptoms of Astrocytomas?

Symptoms are headaches (perhaps with nausea and vomiting) or new seizures. Other symptoms include weakness of arms or legs on one side of the body, vision and speech problems, and a change in mental abilities, such as confusion, disorientation, memory problems, and irritability.

How Are Astrocytomas Diagnosed?

The doctor makes a diagnosis on the basis of symptoms, but the first symptoms may be vague and often confused with tension headaches or sinus infections, so it's hard to diagnose. The doctor also uses magnetic resonance imaging (MRI) and computed tomography (CT). If MRI or CT scans show a mass, the only way to prove the diagnosis is to perform a biopsy. For a biopsy, a small piece of the mass is removed and studied under the microscope.

Astrocytomas can be grades I, II, III, or IV. Grades I and II are low-grade tumors, and grades III and IV are high-grade tumors. This system helps doctors decide about treatment and prognosis.

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How Are Astrocytomas Treated?

Rapid treatment, with surgery, radiation therapy, or chemotherapy, is very important. Treatment involves different specialists, including a neurosurgeon (a doctor specializing in nervous system surgery), oncologist (a doctor specializing in cancer treatment), and radiation oncologist (a doctor specializing in treating cancer with radiation).

Surgery is used first for almost all astrocytomas, to remove all or as much of the tumor as possible. Complications include bleeding, infection, and permanent nervous system problems.

Most people have radiation therapy after surgery. Complications include dry, red, itchy skin over the radiation site.

People with low-grade astrocytomas don't usually have chemotherapy. People with high-grade astrocytomas can be given chemotherapy with some good results. Side effects are nausea, vomiting, infections, hair loss, easy bruising, and easy bleeding.

DOs and DON'Ts in Managing Astrocytomas:

✓ **DO** realize that about 10% to 35% of astrocytomas (usually grade I) can be completely removed and cured.

✓ **DO** know that treatment of low-grade astrocytomas depends partly on tumor location.

✓ **DO** understand that astrocytomas are hard to remove completely.

✓ **DO** call your doctor if you have a severe headache with nausea and vomiting, muscle weakness on one side of your body, a seizure, or speech or vision problems.

✓ **DO** call your doctor if you have side effects from treatments, such as fever after chemotherapy.

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✓ **DO** call your doctor if you need a referral to a specialist.

⃠ **DON'T** miss follow-up appointments with your doctor.

⃠ **DON'T** be afraid to ask for a second opinion. Ask for the opinion of doctors who are experienced in the treatment of people with astrocytomas.

⃠ **DON'T** forget to take your medicines prescribed by your doctor.

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FOR MORE INFORMATION

Contact the following source:

- American Cancer Society Tel: (800) ACS-2345 (227-2345) **Website:** **http://www.cancer.org**

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MANAGING YOUR

ATELECTASIS

What Is Atelectasis?

Atelectasis is the collapse of part or all of a lung. It results from blockage (obstruction) of air movement through small or large air passages (bronchial tubes). The collapse interrupts the oxygen supply to the body.

What Causes Atelectasis?

Obstructive atelectasis can occur suddenly when thick mucus fills bronchial tubes or when foreign objects, such as peanuts, pills, powders, and small toys, are inhaled by accident. It's especially common when people cannot take deep breaths, such as after surgery or with certain drugs or chronic illnesses. Atelectasis can develop more slowly when caused by tumors growing inside the airway tubes. Something outside the lung that presses in, such as tumors, enlarged blood vessels, lymph nodes, fluid, injuries, and pneumonia, can cause nonobstructive atelectasis. Conditions that increase sputum production, such as infections, cystic fibrosis, chronic bronchitis, and bronchiectasis, raise the chance of getting atelectasis. Other risk factors are premature birth (lungs not fully grown), being confined to bed, and obesity.

What Are the Symptoms of Atelectasis?

Symptoms include chest pain, breathing problems such as shortness of breath, cough, and fever. Complete lung collapse may lead to shock, with rapid heart rate, low blood pressure, cool and clammy skin, and lethargy. A slow collapse may not cause symptoms or lead to lasting cough and fever.

How Is Atelectasis Diagnosed?

The doctor makes a diagnosis by using a chest examination and chest X-ray. Computed

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tomography (CT), and maybe bronchoscopy, may be done to determine the cause of the atelectasis. In bronchoscopy, the doctor uses a lighted tube to look into the lung.

How Is Atelectasis Treated?

Treatment involves getting rid of the cause, sometimes with medications, oxygen, or other therapies. Bronchoscopy can help clear obstructions such as a foreign body or phlegm. Surgery or radiation therapy may be needed for large tumors that block airflow. Respiratory therapists can perform special maneuvers after surgery to prevent phlegm from building up or to treat atelectasis. People with chronic lung diseases often use these special maneuvers (chest physiotherapy). Antibiotics are prescribed for infection-related disease. Inhalers can open the bronchial tubes. Atelectasis is usually not life-threatening. Untreated, however, it may lead to permanent partial lung collapse, pneumonia, or lung abscess.

DOs and DON'Ts in Managing Atelectasis:

✓ **DO** help prevent atelectasis by stopping smoking as soon as possible before surgery.

✓ **DO** get out of bed as soon as possible after surgery.

✓ **DO** use an incentive spirometer hourly while awake. This device helps expand your lungs by encouraging you to take deep, rapid breaths.

✓ **DO** work with nurses and respiratory therapists to loosen phlegm from your lungs. You may need to turn regularly and cough deeply. You may also get aerosol treatments and claps on your back.

✓ **DO** call your doctor if you have a lasting cough, bloody sputum, chest pain, fever, or worsening shortness of breath.

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- ⦸ **DON'T** get dehydrated, which can thicken lung secretions.
- ⦸ **DON'T** use pain medicines in excess after surgery. They may interfere with your coughing and taking deep breaths.
- ⦸ **DON'T** smoke!

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FOR MORE INFORMATION

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- American Lung Association Tel: (800) LUNG-USA **Website: http://www.lungusa.org**

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MANAGING YOUR

ATHLETE'S FOOT

What Is Tinea Pedis?

Tinea pedis is an infection of the foot caused by a fungus. It is one of the most common infections that people get. It's also called athlete's foot or ringworm of the feet. Ringworm is a general name for these common skin infections. The name comes from the appearance (ring-shaped or oval patches), not the cause, of the infection. These infections are named according to where they occur, such as ringworm of the body (tinea corporis), ringworm of the scalp (tinea capitis), athlete's foot (tinea pedis), and jock itch (tinea cruris, ringworm of the groin).

Tinea pedis is most often seen in adolescents and adults during warm weather, but it can occur at any time.

Tinea pedis can be cured in 2 to 3 weeks, but it reappears often if things aren't done to prevent it.

What Causes Tinea Pedis?

The cause is usually a fungus, ones named *Trichophyton* or *Epidermophyton.* These fungi are very small and can be seen only with a microscope. Moist, sweaty feet and socks, hot humid weather, and use of public showers increase the chance of getting this infection.

What Are the Symptoms of Tinea Pedis?

The most common symptoms are cracked and boggy skin between the toes, plus itching. Tinea pedis also affects the bottoms of the feet. Scaling, dead skin, burning, and small blisters sometimes occur, as well as a musty or unpleasant odor. Dry skin may flake, peel, or crack. Itching is often worst between the toes. Scratching it can cause a red (inflamed) or weeping rash.

How Is Tinea Pedis Diagnosed?

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The doctor makes a diagnosis by doing a physical examination and seeing the typical appearance of the skin. Sometimes, a small scraping of an affected area can be studied under a microscope to confirm the diagnosis.

How Is Tinea Pedis Treated?

It is important to keep the feet dry. Wear sandals if possible.

Feet should be washed, and then scales and dead skin can be removed.

An antifungal powder, cream, or ointment that is available without a prescription can be applied to affected areas. The doctor can also prescribe topical antifungal medicines.

To prevent the infection from returning, the medicine should be continued for 1 week after the symptoms and rash disappear.

DOs and DON'Ts in Managing Tinea Pedis:

✓ **DO** wash and dry your feet at least once per day during and after treatment, to make sure that the infection doesn't return.

✓ **DO** wear clean, dry socks made of cotton or wool.

✓ **DO** change socks daily or more often if necessary to keep your feet dry.

✓ **DO** wear sandals instead of going barefoot when in public places, such as locker rooms or showers. Also wear well-ventilated sneakers to keep your feet dry.

✓ **DO** wash and dry your feet immediately after exercising.

✓ **DO** call your doctor if your rash doesn't get better after 1 week of treatment.

✓ **DO** call your doctor if you see signs of another infection, such as fever, pus drainage, or red

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streaks on your feet.

⃠ **DON'T** scratch your feet.

⃠ **DON'T** wear synthetic socks. These keep moisture around the feet.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Dermatology Tel: (866) 503-SKIN (7546) **Website: http://www.aad.org**

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MANAGING YOUR

ATRIAL FIBRILLATION

What Is Atrial Fibrillation?

The speed and pattern of your heartbeat is called your heart rhythm and can be felt by feeling the pulse. Your heart rhythm is set by signals from the heart's electrical system. An abnormal heart rhythm is called an *arrhythmia*. Atrial fibrillation is one type of abnormal rhythm. The muscle looks as if it is wiggling instead of squeezing (contracting).

What Happens During Atrial Fibrillation?

The human heart has four chambers. The upper ones are called atria; the lower ones, ventricles. All chambers must squeeze in a certain way to move the blood properly. Your heart's electrical system involves specialized cells that tell the heart when to beat. If these cells malfunction and send extra electrical signals, the atria beat very quickly and uneven. A fibrillating atrium, however, has small, irregular, fast contractions. All the blood inside the atria is not pumped into ventricles, so blood pools. Pooled blood may clot, and clots can be pushed into the bloodstream and cause strokes. Ventricles work harder to get blood to the body, and heart failure may result.

What Causes Atrial Fibrillation?

Among the many causes, the most common is aging. Others are heart problems such as hypertension (high blood pressure), congestive heart failure (CHF), and mitral valve disease (mitral stenosis). Lung diseases, other illnesses (e.g., diabetes), and overactive thyroid are more causes. Caffeine, nicotine (cigarettes), and too much alcohol can cause it or make it worse.

What Are the Symptoms of Atrial Fibrillation?

Many people have atrial fibrillation and never feel it.

Symptoms often include the feeling of irregular or too fast (palpitations) heartbeats. Difficulty

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breathing, chest pain, or fainting may occur. Some people feel tired or cannot exercise.

Chest pain or signs of stroke must be checked immediately.

How Is Atrial Fibrillation Diagnosed?

The doctor looks for a certain pattern on an electrocardiogram (ECG), which shows the heart's electrical activity.

The doctor may check movements of the atria with an echocardiogram (using ultrasound to examine the heart and capture the moving images on a video). If your atrial fibrillation comes and goes, your doctor may order a portable recorder of your heart rhythm (Holter monitor).

How Is Atrial Fibrillation Treated?

Treatment focuses on the cause. For example, if the person has thyroid disease, that illness is treated. If the cause is too much caffeine or excess alcohol, less should be used.

Controlling heart rhythm and the fibrillation rate with drugs is important. These medications are known as anti-arrhythmics and are used to slow down the heart rate and make it regular. Sometimes atrial fibrillation stops on its own.

Clots are one complication of fibrillation. Blood thinners (anticoagulants) such as warfarin (e.g., Coumadin®) may be given for clots or to prevent them. This drug causes easy bruising or bleeding, so drug levels are checked regularly.

The abnormal rhythm can sometimes be shocked back to normal (called *cardioversion*). During this procedure, a heart specialist (cardiologist) will give your heart a brief electric shock in attempting to briefly stop all electrical activity, hoping that the normal heart rhythm will take over. Chest pain, low blood pressure, CHF, or other serious symptoms may require emergency cardioversion. A dual-chamber pacemaker may be placed. A heart catheter or surgery (maze procedure) may be used to destroy the part of the heart causing fibrillation.

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DOs and DON'Ts in Managing Atrial Fibrillation:

✓ **DO** eat a heart-healthy diet (less fat and cholesterol).

✓ **DO** keep to an ideal body weight.

✓ **DO** reduce stress.

✓ **DO** exercise as much as you can if you are taking the proper drugs and have no symptoms.

✓ **DO** take your medicines as prescribed. Have blood drug levels checked.

✓ **DO** call your doctor if you have drug side effects or if you have new or worsening symptoms (dizziness, chest pain or tightness, fainting, shortness of breath).

⃠ **DON'T** do activities that cause bruising if you are taking a blood thinner.

⃠ **DON'T** use tobacco.

⃠ **DON'T** drink too much alcohol or caffeine.

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- American Heart Association

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MANAGING YOUR

ATRIAL FLUTTER

What Is Atrial Flutter?

The atria are the top chambers of the heart. The ventricles are the bottom chambers. In atrial flutter, the atria start to beat rapidly because of too many abnormal electrical impulses. The atria flutter as they try to contract, but the contractions are too fast. Atria may beat up to 300 times per minute, instead of 60 to 100. About one-half to one-fourth of these impulses get to the ventricles. Atrial flutter more often occurs in older adults, mostly men.

What Causes Atrial Flutter?

Different illnesses can cause atrial flutter. Heart and lung disease, thyroid disease, and heart valve disorders are most often associated with atrial flutter.

What Are the Symptoms of Atrial Flutter?

Main symptoms are palpitations (feeling that the heart is pounding or racing), dizziness, lightheadedness, and feeling faint. Angina or heart failure can occur. Angina is heart pain caused by a low blood supply to the heart. Breathing problems, chest pain, and fainting occur with heart failure.

How Is Atrial Flutter Diagnosed?

The health care provider makes a diagnosis from the medical history, physical examination, and electrocardiography (ECG). ECG looks at the heart's electrical conduction system and can confirm the diagnosis. Echocardiography may also be done. This test can see the motion of the atria and whether blood clots are in the atria. The health care provider may want laboratory tests to rule out other disorders such as overactive thyroid gland.

How Is Atrial Flutter Treated?

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Treatment aims to fix the cause of the rhythm disturbance, slow the heart rate, and prevent blood clots. Keeping a normal regular heart rhythm is another goal.

Treatment depends on the symptoms and cause. Medicines help control the rate of contraction of ventricles and try to get back the heart's normal rhythm (chemical cardioversion). If that doesn't work or symptoms get worse, the heart is electrically shocked. This procedure is called electrical cardioversion. The brief electric shock stops the heart's electrical activity and may allow normal heart rhythm to take over.

If all these measures don't work, the health care provider may suggest an electrophysiologic study (EPS). A cardiologist specializing in heart rhythm problems does this test. EPS may help the health care provider decide about other treatment options such as radiofrequency ablation, pacemaker insertion, and surgery.

DOs and DON'Ts in Managing Atrial Flutter:

✓ **DO** stop smoking.

✓ **DO** reduce your alcohol intake.

✓ **DO** eat a heart-healthy, low-fat diet.

✓ **DO** lose weight if you're overweight.

✓ **DO** reduce your stress. Stress may worsen your symptoms.

✓ **DO** call your health care provider or doctor if you have side effects from medicines or have new or worsening symptoms. These include chest pain; shortness of breath; breathing problems; fainting; palpitations; or sudden changes in the ability to speak, eat, walk, or use

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your limbs.

- ⃠ **DON'T** take part in activities that cause bruising if you're taking anticoagulants.
- ⃠ **DON'T** stop taking your medicine or change the dosage because you feel better unless your health care provider tells you to.
- ⃠ **DON'T** use any medicines (including over-the-counter and herbal products) without first asking your health care provider.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:** **http://www.americanheart.org**
- The American College of Cardiology Tel: (800) 253-4636 or (301) 897-5400 **Website:** **http://www.acc.org**

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MANAGING YOUR

ATRIAL MYXOMA

What Is an Atrial Myxoma?

A myxoma of the heart is a primary benign (noncancerous) tumor that starts in the heart's lining (endocardium). It pushes into the heart's chambers. The heart has four chambers, two atria and two ventricles. The atria pump blood into the ventricles, which then contract and pump blood to the rest of the body. Ninety percent of heart myxomas occur in the atria, usually on the left and on the wall (septum) that separates the two sides of the heart. Some myxomas are flat, but many are attached by a thin stalk that lets them move easily. Although atrial myxomas are rare, they're the most common tumors of the heart. They're usually first seen at the average age of 56. Women have them twice as often as men.

What Causes an Atrial Myxoma?

Most myxomas have no known cause (called sporadic). About 10% are thought to be inherited (called familial) and are passed from one generation to the next. Inherited myxomas first occur at an average age of 25.

What Are the Symptoms of an Atrial Myxoma?

Symptoms include shortness of breath with exertion, leg swelling, dizziness, lightheadedness, fainting, and chest pain or tightness. New strokes can result from blood clots that break away from the tumor and travel to the brain. Lung clots can cause shortness of breath. Fever, weight loss, palpitations, and muscle aches are more symptoms. Symptoms of left atrial myxomas often mimic those of mitral stenosis. In severe cases, they also include blue skin, cough, curved fingernails (clubbing), and general discomfort.

How Is an Atrial Myxoma Diagnosed?

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The doctor uses a medical history and physical examination for diagnosis. The doctor may order blood tests and chest X-rays. However, the best test to detect atrial myxomas is echocardiography. This special imaging study uses sound waves to make a picture of the heart and blood flow within the heart.

How Is an Atrial Myxoma Treated?

The treatment is surgery and consists of removal of the tumor. Once the diagnosis is made, surgery should not be delayed because sudden death can occur while waiting for the operation. Complications of surgery include pain, infection, arrhythmias (rhythm disturbances of the heart), and sudden death.

DOs and DON'Ts in Managing Atrial Myxoma:

✓ **DO** realize that surgery leads to excellent survival, with a 95% survival rate after a follow-up of 3 years.

✓ **DO** understand that up to 5% of sporadic and up to 20% of familial myxomas may redevelop in the first 6 years after surgery.

✓ **DO** call your doctor if you have trouble breathing or have shortness of breath with exertion, with awakening, or only when lying down.

✓ **DO** call your doctor if your legs swell or you have heart palpitations.

⃠ **DON'T** forget to see a cardiologist (a specialist in diseases of the heart). After diagnosis, see a cardiovascular surgeon (a surgeon specializing in surgery of the heart) for quick surgical removal.

⃠ **DON'T** forget that although atrial myxoma can rarely come back after surgery, periodic

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follow-up with your physician is recommended to make sure that the tumor doesn't reoccur.

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:**

  http://www.americanheart.org

- American College of Cardiology Tel: (202) 375-6000 **Website: http://www.acc.org**

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MANAGING YOUR

ATRIAL SEPTAL DEFECT

What Is Atrial Septal Defect?

The atria are the top chambers of the heart that send blood to the ventricles (bottom chambers). A septum is a wall separating the left and right sides of these chambers. An atrial septal defect (ASD) is an inborn (congenital) heart condition. It is a hole in the septum separating the left and right atria. The left side of the heart normally pumps under higher pressure than the right side. The defect produces a left-to-right shunt that allows blood from the two sides of the heart to mix. Blood with less oxygen is pumped to the body, and oxygenated blood travels back to the lungs. Abnormal circulation on the right side of the system causes increased pressure in the lungs (pulmonary hypertension).

ASD is more common in girls than boys. Some defects close as a child grows, but others may last into adulthood. ASD is the most common congenital heart defect diagnosed in adults. ASD cannot be prevented.

What Causes Atrial Septal Defect?

The cause is unknown. ASD develops before birth and may last into adulthood. ASD is more common in children with Down syndrome. The most common type of ASD, consisting of a small opening, is called a patent (open) foramen ovale (PFO).

What Are the Symptoms of Atrial Septal Defect?

Small defects may not cause a problem.

A large hole may produce weakness, breathing difficulties, chest pain, bluish skin color, and abnormal heartbeats (arrhythmias). Larger defects eventually overload the system controlled by the right side of the heart, possibly causing heart failure (inefficient pumping).

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How Is Atrial Septal Defect Diagnosed?

The doctor may suspect the diagnosis on the basis of symptoms and findings at physical examination (heart murmur). An electrocardiogram (ECG) may show abnormalities. A chest x-ray may be abnormal, showing enlarged lung blood vessels and an enlarged heart. An echocardiogram (a test using ultrasound) can check the heart's structure and pumping and measure blood flow. The doctor may also recommend going to a cardiologist (a doctor who specializes in heart diseases) for more tests.

How Is Atrial Septal Defect Treated?

People with very small defects or defects that close may never have symptoms and need no treatment. People who need treatment may be referred to a cardiologist. Medicine may also be given to treat symptoms. If the defect lasts, symptoms may develop that require treatment to correct the defect. Surgery is the preferred treatment and is usually done around the age of 4 years. If there is no other heart disease, correcting the defect usually allows a normal life span and lifestyle.

DOs and DON'Ts in Managing Atrial Septal Defect:

✓ **DO** take medicines as prescribed by your doctor.

✓ **DO** exercise, if your doctor says to do so.

✓ **DO** follow your doctor's advice to make sure you have full recovery and return to a normal life.

✓ **DO** call your doctor if you have such symptoms as shortness of breath, irregular heartbeat, chest pain, or bluish discoloration of your fingers.

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⦸ **DON'T** ignore worsening symptoms. Get medical attention immediately.

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:** **http://www.americanheart.org**
- Congenital Heart Information Network Tel: (215) 627-4034Fax: (215) 627-4036 E-mail: mb@tchin.org **Website: http://www.tchin.org**

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CARING FOR YOUR CHILD WITH

ATTENTION DEFICIT HYPERACTIVITY DISORDER

What Is Attention Deficit Hyperactivity Disorder (ADHD)?

ADHD is a behavior disorder involving an inability to focus on tasks. Hyperactive behavior is part of ADHD.

Between 2% and 7% of children have ADHD, and in younger children, more boys than girls have it. Some children outgrow ADHD, others control problem behaviors as they grow older, and others may have ADHD into adulthood. Certain children become troubled teenagers and adults with problems such as failure in school, antisocial behavior, and sometimes even criminal behavior.

There are no known ways to prevent ADHD. ADHD is not contagious.

What Causes ADHD?

The cause is unknown. It may occur in more than one child in a family.

Environmental factors and hereditary factors may play a role.

What Are the Symptoms of ADHD?

Problem behaviors are the symptoms, usually in a child younger than 7.

Parents, teachers, and doctors may see the behaviors, which include inability to listen, follow instructions, wait turn in games and lines, or pay attention in school or at play; becoming easily distracted; losing things; shifting from one task to another; answering before a question is finished; interrupting or intruding; doing dangerous things without thinking; squirming or inability to stay seated; fidgeting with hands and feet; and talking constantly.

How Is ADHD Diagnosed?

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No specific test exists for ADHD. Observations of doctors, parents, teachers, and others are key. Depression and anxiety must be ruled out.

The doctor will ask about the family history, do a physical examination (including hearing and eye tests), and check for learning disabilities and development level. For an ADHD diagnosis, the child must have six or more of eight specific symptoms for at least 6 months, and these must interfere with daily functions.

Adults with ADHD often have failed relationships, problems at work, and sometimes alcohol and drug abuse. Many such adults may have been misdiagnosed with anxiety or manic depressive disorders.

How Is ADHD Treated?

The most effective treatment is combination of drugs and behavioral methods used together. Educational, behavioral, and cognitive methods may all be recommended. Drugs used most often are psychostimulants, which help people feel calmer, more relaxed, more focused, and less scattered in thinking.

The doctor may also suggest counseling for child and parents. Support for parents is essential.

DOs and DON'Ts in Managing ADHD:

✓ **DO** set clear behavior limits and reward good behavior.

✓ **DO** use time outs for bad behavior and stop problem behavior before it worsens.

✓ **DO** allow for more activity in safe environments.

✓ **DO** focus on one task at a time.

✓ **DO** try techniques such as anger training, social training, and family therapy, but avoid un-

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proven therapies.

✓ **DO** have realistic expectations.

✓ **DO** talk regularly with your child's teacher.

✓ **DO** call your doctor if symptoms worsen after treatment begins.

✓ **DO** consider support groups for anger control, if you're an adult. Exercise regularly and try to maintain structure and routine.

⃠ **DON'T** forget follow-up appointments.

⃠ **DON'T** self-medicate with drugs or alcohol, or use too much caffeine or sugar as a teenager or adult.

⃠ **DON'T** increase medicine doses unless your doctor says to.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

• CHADD (Children and Adults with Attention-Deficit/Hyperactivity Disorder) Tel: (301) 306-7070, (800) 233-4050 **Website: http://www.chadd.org/**

• National Institute of Mental Health Tel: (866) 615-6464 Email: nimhinfo@nih.gov **Website: http://www.nimh.nih.gov/**

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CARING FOR YOUR CHILD WITH

AUTISM

What Is Autism?

Autism is a brain development disorder that shows its first signs in early childhood. It results in a lifelong disorder with problems in reasoning, social interaction, and communication. Children with autism become self-focused, lose ability to relate to others, and have trouble with language, reasoning, and play.

What Causes Autism?

The cause is unknown, and autism cannot be prevented. It occurs more in boys than in girls and more in some families. Autism may result from chemical changes in the brain. Conditions (e.g., rubella in the mother, lack of oxygen at birth) affecting brain development before, during, or after birth may play a role.

It isn't due to bad parenting or a behavior disorder, however.

What Are the Symptoms of Autism?

Some children have mild symptoms, others have worse symptoms. Symptoms include turning inward and withdrawing from society. Some symptoms start when children are very young, even 1 to 2 years old. Children don't make eye contact, smile, or cuddle. They want to stay alone in a crib or bed, sometimes for many hours. They don't want to be disturbed. They don't want attention. They are quiet and passive. They may repeat gestures or behaviors, such as flicking fingers, arranging objects, and insisting on rituals. Autistic children have short attention spans.

Older children may be overly sensitive to sounds, smells, touch, or taste. They may lack imaginative play. They may not learn to speak when expected.

Children react to changes in the home or in the usual routine with temper tantrums. At about

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age 5 to 6, self-isolation, tantrums, and rituals tend to occur less often. Even then, children don't learn language and social skills normally. However, some children older than 10 have had a normal school education, and some adults with autism have lived alone and held jobs.

How Is Autism Diagnosed?

No specific test is available. A team of doctors and others makes the diagnosis. This team includes a neurologist (doctor specializing in nervous system diseases), psychologist, pediatrician, speech therapist, and learning consultant.

Tests may be done to rule out other illnesses.

How Is Autism Treated?

No cure exists, but with proper help children can learn to cope with symptoms.

Early intensive interventions are the most successful. Lifelong follow-up care will be needed. Therapy may include speech and language, occupational, and physical therapies. Therapy can help children learn how to communicate better, improve fine muscle movement, and help develop strength, coordination, and movement.

The doctor and counselor may suggest music therapy, behavior modification, and specific diets.

There are no specific medicines to treat autism. Sometimes, the doctor may suggest medicine to treat specific symptoms.

DOs and DON'Ts in Managing Autism:

✓ **DO** provide a regular routine in your home to help reduce repetitive behaviors.

✓ **DO** enroll your child in a treatment program that is led by a team of doctors and counselors.

✓ **DO** check out support services and local support groups for parents or caretakers.

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✓ **DO** call your doctor if you have questions about your child's health or need information about services for autistic children.

✓ **DO** call your doctor if your child has problems related to medicine, or if symptoms worsen.

⃠ **DON'T** deny your child the opportunity to reach full potential. Children with autism can be creative but need structure.

⃠ **DON'T** accept traditional therapies as the only methods.

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FOR MORE INFORMATION

Contact the following sources:

- Autism Society of America Tel: (800) 3AUTISM (328-8476), (301) 657-0881 **Website:** **http://www.autism-society.org**
- Autism Research Institute Tel: (866) 366-3361 **Website:** **http://www.autism.com**
- Autism Collaboration **Website:** **http://www.autism.org**

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MANAGING YOUR

AUTOIMMUNE HEPATITIS

What Is Autoimmune Hepatitis?

Autoimmune hepatitis is a disease in which the body's own immune system attacks its liver cells. This causes hepatitis, or liver inflammation (swelling). Autoimmune hepatitis is not contagious and cannot be prevented.

About 70% of people with autoimmune hepatitis are women, most between 15 and 40. Untreated, this serious disease gets worse. It can last for years and can lead to liver cirrhosis (scarring and hardening) and liver failure.

What Causes Autoimmune Hepatitis?

The cause is unknown. A substance (antigen) may cause the immune system to attack liver cells. Most experts think that genetics may make some people more likely to have autoimmune diseases.

What Are the Signs and Symptoms of Autoimmune Hepatitis?

Fatigue is common. Other signs are enlarged liver (hepatomegaly), jaundice (yellowish skin), itching, rashes, joint pain, and discomfort in the abdomen (belly). Symptoms range from mild to severe.

People with advanced disease are more likely to have such symptoms as fluid in the abdomen (ascites) and mental confusion.

How Is Autoimmune Hepatitis Diagnosed

The doctor makes a diagnosis on the basis of symptoms, blood test results, x-rays (ultrasound or computed tomography [CT] of the liver to rule out other causes), and liver biopsy.

Blood tests for liver enzymes and autoantibodies are needed. The tests also help tell autoim-

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mune hepatitis from viral hepatitis (e.g., hepatitis A, B, or C) or metabolic diseases. Antibodies are proteins made by the immune system. In autoimmune hepatitis, antibodies attack and destroy liver cells. The pattern and level of these antibodies can tell the type of disease (type I, usually in women, or type II, more common in girls).

For a liver biopsy, a tiny liver sample is removed with a hollow needle and examined under a microscope.

How Is Autoimmune Hepatitis Treated?

The main treatment for both types is medicine (corticosteroid called prednisone) to slow an over-active immune system.

In most people, the disease goes into remission with proper treatment, but may recur. Lifelong treatment may be needed.

People who don't respond to standard therapy or who have severe side effects may be helped by other immunosuppressive drugs.

People who develop liver failure may need a liver transplant, a promising treatment, with a 5-year survival rate of 70% to 80%.

DOs and DON'Ts in Managing Autoimmune Hepatitis:

✓ **DO** remember that monitoring of your condition is important. Report any new symptoms to your doctor promptly.

✓ **DO** call your doctor if you notice skin color changes, side effects from medicines, joint pains, or abdominal swelling.

⃠ **DON'T** ignore drug side effects, such as weight gain, anxiety, confusion, thinning of bones (called osteoporosis), thinning of the hair and skin, diabetes, high blood pressure, and cata-

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racts.

⦸ **DON'T** use alcohol. It may further damage your liver.

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FOR MORE INFORMATION

Contact the following source:

- National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) 2 Information Way Bethesda, MD 20892-3570 E-mail: nddic@info.nddk.nih.gov Tel: (800) 891-5389

  Website: http://digestive.niddk.nih.gov/ddiseases/pubs/autoimmunehep/

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MANAGING YOUR

AVASCULAR NECROSIS

What Is Avascular Necrosis?

Avascular necrosis, also known as osteonecrosis, is a bone disease resulting from temporary or permanent loss of blood supply to bones. Without blood, bones die. If bones are near a joint, the joint surface often collapses. Avascular necrosis most often affects the ends of long bones, such as the thigh, upper arm, knees, shoulders, ankles, hips, and wrists. The disease may involve one bone, more than one bone at the same time, or more than one bone at different times. Avascular necrosis is also called osteonecrosis, aseptic necrosis, and ischemic bone necrosis.

The disorder affects men and women equally, usually between ages of 30 and 50. Avascular necrosis is not contagious.

What Causes Avascular Necrosis?

Injuries, drinking too much alcohol (chronic alcohol abuse), blood coagulation disorders, and long-term use of corticosteroids (e.g., prednisone) are common causes.

What Are the Symptoms of Avascular Necrosis?

People may not have symptoms at the start. Later, most people have joint pain, first only with weight bearing and later, pain at rest. Pain usually develops gradually and may be mild or severe. Severe pain can also develop suddenly if the joint surface collapses.

How Is Avascular Necrosis Diagnosed?

The doctor makes the diagnosis by taking a medical history, doing a physical examination, and taking x-rays. The doctor may recommend magnetic resonance imaging (MRI), which is more sensitive for showing avascular necrosis.

How Is Avascular Necrosis Treated?

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The goals of treatment are to prevent further bone and joint damage, reduce pain, improve joint use, and ensure bone and joint survival.

Treatment includes using medicines called nonsteroidal antiinflammatory drugs (e.g., ibuprofen, naproxen), avoiding weight-bearing activities, and using range-of-motion exercises and electrical stimulation. These treatments rarely help for a long time, and most people will need surgery for permanent joint repair.

Surgery may include removing the inner bone layer to reduce the pressure in the bone and increase its blood flow. For advanced necrosis, another operation, osteotomy, reshapes the bone to reduce stress on the affected area. Total joint replacement with artificial parts is used for a destroyed joint in late-stage aseptic necrosis.

DOs and DON'Ts in Managing Avascular Necrosis:

✓ **DO** understand that pain may be severe enough to limit your joint's range of motion.

✓ **DO** remember in some cases, especially those involving the hip, osteoarthritis may develop.

✓ **DO** follow your doctor's instructions about activity limits.

✓ **DO** call your doctor if you have bone or joint pain or if you have drainage, redness, swelling, or pain after surgery.

✓ **DO** call your doctor if you need a referral to a bone specialist (orthopedic surgeon).

✓ **DO** call your doctor if you have a drinking problem.

⊘ **DON'T** abuse alcohol.

⊘ **DON'T** use long-term steroids (e.g., prednisone), if possible.

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⦸ **DON'T** miss doctor appointments. Untreated aseptic necrosis will cause severe pain and limited movement within 2 years.

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Arthritis and Musculoskeletal and Skin Diseases National Institutes of Health Tel: (877) 226-4267 **Website: http://www.niams.nih.gov**

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MANAGING YOUR

BABESIOSIS

What Is Babesiosis?

Babesiosis is an infectious disease that is transmitted by ticks. Ticks carry the microscopic organisms called *Babesia*. These organisms can also infect people and cause a nonspecific illness with fever. Most cases occur in the spring and summer months, May through September. The highest number of reported cases is in New York state and the New England region. Some cases occur in California, Georgia, Maryland, Minnesota, Virginia, Wisconsin, Washington state, and Missouri. The illness can be severe in people with weak immune systems.

What Causes Babesiosis?

Tiny parasites named *Babesia microti* account for most infections. The deer tick named *Ixodes scapularis* is the main tick that carries these parasites. People who are active outdoors are easily infected when bitten by these ticks, which also bite rodents and deer. People may not remember the bites because ticks at that stage are about the size of a poppy seed. Ticks must usually stay attached to the skin for more than 24 to 36 hours to transmit parasites.

People can also get the infection by having a blood transfusion with infected blood (platelets and red blood cells).

Infections with both *B. microti* and bacteria that cause Lyme disease, *Borrelia burgdorferi,* may occur since some ticks may carry both organisms. This happens in 10% of cases in Rhode Island and Connecticut and up to 60% of cases in New York.

What Are the Symptoms of Babesiosis?

Few people have no symptoms. Most people have flu-like symptoms, which start slowly. They include fever, chills, heavy sweating, headache, muscle aches, joint pains, fatigue, and dark

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urine. Others include a widespread rash, enlarged liver and spleen, and jaundice (yellow skin). The rash consists of tiny red or purple spots on the skin (petechiae).

How Is Babesiosis Diagnosed?

The health care provider makes a preliminary diagnosis from the medical history and physical examination especially when one lives or travels in an affected area. Laboratory blood tests will be done to find the microorganism and rule out similar diseases.

How Is Babesiosis Treated?

The main treatment is antibiotics. While the infection is being treated with antibiotics, symptoms such as pain can be helped with acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs).

DOs and DON'Ts in Managing Babesiosis:

✓ **DO** remember that prevention of the infection is important. Reduce your risk of exposure to ticks when you're in areas where babesiosis is prevalent. Use insect repellents with DEET. Wear long sleeves and pants and tuck pant legs into socks. Wear closed shoes instead of sandals. Brush off clothes, and check your body for ticks.

✓ **DO** remove a tick with tweezers. Hold the tick close to the skin and gently pull it out.

⃠ **DON'T** ignore symptoms. Call your health care provider if your symptoms don't improve or worsen with treatment.

⃠ **DON'T** stop taking your medicine or change the dosage because you feel better unless your health care provider tells you to.

⃠ **DON'T** use any medicines (including over-the-counter and herbal products) without first asking your health care provider.

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FOR MORE INFORMATION

Contact the following sources:

- Centers for Disease Control and Prevention Tel: (800) 311-3435
- National Institute of Environmental Health Sciences Tel: (919) 541-3345 **Website: http://www.niehs.nih.gov**
- National Heart, Lung, and Blood Institute Information Center Tel: (301) 592-8573 **Website: http://www.nhlbi.nih.gov**

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MANAGING YOUR

BACK PAIN

What Is Back Pain?

Back pain refers to pain along or near the spine. Most adults have had back pain at some time. Back pain is usually not serious and often goes away in 1 to 8 weeks, usually less than 1 month.

What Causes Back Pain?

Causes include strained muscles, pinched nerves, and sometimes a disc moving out of place. Discs are cushions between bones of the spine (vertebrae).

Older people may have back pain because of arthritis in joints in the spine. Older women can have weak bones, from osteoporosis, that can develop cracks.

Sometimes pain or disease in another part of the body, such as the hip, causes back pain.

Very few people have serious illnesses (cancer, infection).

What Are the Symptoms of Back Pain?

The most common symptoms are pain and stiffness of the lower back. Certain areas may feel tender. Pain often gets better at night or while resting. Symptoms of pinched nerves are pain going down into the back of the leg (called sciatica), numbness and tingling of the leg, weakness when moving, and pain that worsens while walking or exercising.

How Is Back Pain Diagnosed?

Most people don't need any tests beyond a doctor's examination. The doctor may do x-rays if pain might be due to spinal deformity or medical illness, or if it is long-term.

How Is Back Pain Treated?

Most back pain just needs pain medicine (e.g., acetaminophen or ibuprofen). Physical therapy may help if pain resulted from lifting or pushing done the wrong way. Most people are well

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within 8 weeks, no matter what treatment they receive. People with long-term pain may need to go to a pain clinic. Surgery and other treatments are needed only rarely.

Take steps for back health: strengthen the back by exercising, quit smoking, keep to a normal weight, learn how to properly move and lift things, and reduce stress.

DOs and DON'Ts in Managing Back Pain:

✓ **DO** take pain medicine if needed.

✓ **DO** rest to get past the worst of the pain, and start moving actively after the rest period.

✓ **DO** exercise to strengthen your back.

✓ **DO** see your doctor if pain continues, if you develop weakness or numbness in your legs, or if you have trouble urinating or holding your urine or bowels.

✓ **DO** call your doctor if pain is getting worse, especially if you are older than 50, younger than 20, or you've had cancer.

✓ **DO** call your doctor if pain is from major trauma.

✓ **DO** call your doctor if pain is related to fever, chills, or unexplained weight loss.

✓ **DO** call your doctor if you have severe pain at night or pain travels to your lower belly.

✓ **DO** use good posture and avoid lifting heavy weights. Lift correctly: bend your knees, not your back, and avoid jerking.

✓ **DO** sleep on your side with the legs drawn up toward your chest. Avoid waterbeds and use a

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stiff mattress.

⦸ **DON'T** rest in bed for more than 48 hours, to avoid blood clots and getting weaker.

⦸ **DON'T** lift or push any heavy objects unless you know how to do so safely.

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FOR MORE INFORMATION

Contact the following sources:

- Spine Health **Website: http://www.spine-health.com**
- American College of Rheumatology Tel: (404) 633-3777 **Website:**

http://www.rheumatology.org

- Arthritis Foundation Tel: (800) 283-7800 **Website: http://www.arthritis.org**

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MANAGING YOUR

BACTERIAL FOOD POISONING

What Is Bacterial Food Poisoning?

Bacterial food poisoning is a common illness resulting from eating contaminated food.

What Causes Bacterial Food Poisoning?

Various bacteria cause this condition. Bacteria named *Escherichia coli* (*E. coli*), *Salmonella*, and *Campylobacter* are common causes. Rarely, bacteria named *Clostridium* will cause the illness called botulism.

What Are the Symptoms of Bacterial Food Poisoning?

Symptoms usually start 24 to 48 hours after eating the food. Nausea and vomiting develop, with cramps in the abdomen (belly). Diarrhea is common. Certain bacteria may produce blood in the bowel movements (stool). Fever may also be present. In severe illness, diarrhea and vomiting can lead to severe dehydration and to abnormalities in chemicals called electrolytes.

How Is Bacterial Food Poisoning Diagnosed?

The doctor makes a diagnosis from the medical history, physical examination, symptoms, and the occurrence of similar symptoms in a group of people who ate the same foods. The doctor may order blood tests and stool cultures for more severe cases.

How Is Bacterial Food Poisoning Treated?

This self-limited disease will usually go away in a few days, but one rare form, botulism, is life-threatening. The key to treatment is to replace fluids and electrolytes. Fluids such as clear broth or special oral glucose-electrolyte preparations can be taken by mouth in small, frequent sips, even if vomiting continues. Sucking ice chips, if possible, will help. Special rehydration fluids can be used. Avoid dairy products until symptoms go away.

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Severe symptoms may mean a hospital stay and intravenous fluids. Antibiotics may help treat certain bacteria.

Medicines to stop vomiting (antiemetics) and others to control diarrhea are usually given only for severe illness.

DOs and DON'Ts in Managing Bacterial Food Poisoning:

✓ **DO** rest in bed if you are very tired, but stay near the bathroom or bedpan.

✓ **DO** try to drink fluids even when vomiting.

✓ **DO** eat a soft, bland diet if you can. Slowly (over 1 or 2 days) return to a normal diet.

✓ **DO** avoid dairy products and antacids containing magnesium if you have diarrhea.

✓ **DO** contact the local health department if many people who ate the same food are ill.

✓ **DO** use good hygiene when preparing foods. Wash hands between handling different foods. Keep cooking areas and utensils clean.

✓ **DO** cook and store foods properly. Throw out foods that don't smell right or are in bulging cans.

✓ **DO** wash your hands after using the bathroom.

✓ **DO** call your doctor if young children or older adults have symptoms.

✓ **DO** call your doctor if symptoms worsen after treatment begins.

✓ **DO** call your doctor if vomiting is so severe that you cannot keep liquids down.

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✓ **DO** drink only bottled water when traveling (especially in foreign countries). Don't use ice cubes in drinks because these may be made with contaminated water.

⦸ **DON'T** eat raw seafood or meat or unpasteurized foods.

⦸ **DON'T** eat fresh vegetables that weren't properly washed.

⦸ **DON'T** drink tap water or eat raw foods when traveling in foreign countries. Fruits that you can peel before eating are usually safe.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- U.S. Department of Agriculture, Food Safety and Inspection Service Tel: (888) 674-6854 **Website: http://www.usda.gov/**
- International Association for Medical Assistance to Travelers Tel: (716) 754-4883 **Website: http://www.iamat.org**

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MANAGING YOUR

BACTERIAL PNEUMONIA

What Is Bacterial Pneumonia?

Pneumonia is infection of the lungs. Bacterial pneumonia means that bacteria cause this infection. Bacteria get to lungs by breathing or by the bloodstream. Pneumonia can be mild or life-threatening.

Certain conditions may weaken the body's defense system and increase chances of getting bacterial pneumonia. These conditions include older age, smoking, drinking alcohol in excess, lung disease, congestive heart failure, diabetes, kidney failure, HIV infection, drugs such as anti-cancer agents and prednisone, and viral respiratory infections. Healthy people of all ages can also get pneumonia.

What Causes Bacterial Pneumonia?

Common types of bacteria that cause pneumonia include *Streptococcus*, *Mycoplasma*, *Staphylococcus*, *Haemophilus*, *Legionella*, and bacteria normally found in the intestines and mouth.

What Are the Symptoms

of Bacterial Pneumonia?

Symptoms include chest pain, chills, confusion, cough, fever, headache, and muscle and body pain. Others are pain with breathing, yellow or green phlegm (more than usual, sometimes with blood), shortness of breath, sweating, and tiredness. People with severe pneumonia have rapid breathing, low blood pressure, temperature higher than 102° F, and confusion. Some people, such as the very old, may have few symptoms.

How Is Bacterial Pneumonia Diagnosed?

The doctor will take a medical history and do an examination. The doctor will order chest x-rays.

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Sputum and blood tests, to find out which bacteria are causing pneumonia may be done in hospitalized patients.

How Is Bacterial Pneumonia Treated?

Treatment involves antibiotics. People with milder pneumonia take oral antibiotics and usually start feeling better after 2 to 3 days. Most recover after 7 to 10 days. More severely ill people are hospitalized and are first given antibiotics intravenously. They may get oxygen and have special treatment to help clear phlegm. They may need mechanical ventilation in an intensive care unit. After they improve, they take oral antibiotics. People infected with certain types of bacteria or with chronic medical conditions may need antibiotics for 14 to 21 days or longer.

DOs and DON'Ts in Managing

Bacterial Pneumonia:

✓ **DO** get pneumonia and flu shots.

✓ **DO** tell your doctor about medicines you take (prescription and over-the-counter).

✓ **DO** call your doctor if you're getting worse or don't feel better after 2 to 3 days.

✓ **DO** tell your doctor if you're pregnant or taking birth control pills.

✓ **DO** call your doctor right away or go to the emergency room if shortness of breath becomes worse.

✓ **DO** try to cough up as much phlegm as possible.

✓ **DO** wash your hands often, to avoid spreading infection.

✓ **DO** take antibiotics exactly as prescribed, until they're gone.

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✓ **DO** use acetaminophen or aspirin (except in children) to reduce fever and pain.

✓ **DO** drink plenty of fluids to avoid dehydration.

✓ **DO** breathe moist air (use a humidifier) to help get rid of phlegm.

✓ **DO** call your doctor if you have fever, green or yellow sputum, increased shortness of breath, chest pain, or dusky-colored skin, lips, or fingernails.

✓ **DO** avoid air pollution and smoke, especially if you have lung problems.

⃠ **DON'T** stop taking your medicine just because you feel better.

⃠ **DON'T** smoke.

⃠ **DON'T** drink alcohol in excess.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Lung Association Tel: (212) 315-8700, (800) 586-4872 **Website:** **http://www.lungusa.org**
- National Foundation for Infectious Disease **Website:** **http://www.nfid.org/pdf/factsheets/pneuadult.pdf**

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MANAGING YOUR

BAKER'S CYST

What Are Baker's Cysts?

Baker's cysts, also known as popliteal cysts, are a fluid-filled bursa at the back inner side of the knee. A bursa is a sac that acts like a shock absorber between muscles and bones or muscles and tendons (bands of fibrous tissue that connect muscles to bones). In Baker's cysts, the sac swells, which separates tendons of the hamstring muscles.

Baker's cysts can occur at any age and are curable. They can be uncomfortable and limit movement.

What Causes Baker's Cysts?

In children, trauma or irritation of the knee likely causes these cysts. In adults, they are related to gout, pseudogout, fractures, osteoarthritis, rheumatoid arthritis, torn knee cartilage, and infections in the knee. They cannot be caught or inherited.

What Are the Symptoms of Baker's Cysts?

The most common symptoms are leg and knee swelling and pain in the space behind the knee (popliteal space). Sometimes the knee feels as if it locked up, which limits flexing or extending the knee.

How Are Baker's Cysts Diagnosed?

The doctor diagnoses Baker's cysts by reviewing symptoms, x-rays of the knee, and an ultrasound scan (which uses sound waves to get an image). Sometimes, the doctor will want a sonogram, magnetic resonance imaging (MRI), blood tests, and other imaging studies to rule out other causes of knee pain (e.g., gout, infections, or blood clots in veins of the legs called deep vein thrombosis).

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How Are Baker's Cysts Treated?

Treatment is directed at the cause. Pain and swelling are treated by resting and avoiding stressful activity, and sometimes wearing a knee immobilizer to prevent flexing or extending the knee.

The doctor will usually prescribe antiinflammatory medicine (e.g., ibuprofen, naproxen) to relieve swelling and pain.

If medicines don't help the symptoms, the doctor may suggest a visit with a rheumatologist (a doctor specializing in diseases of joints and soft tissues) or orthopedic doctor (who specializes in bone diseases), for removing (aspirating) fluid from the knee joint or injecting a corticosteroid (cortisone) into the cyst or knee to reduce inflammation and the fluid volume produced.

If these treatments don't work, surgery (to remove the cyst) may be needed, especially if a torn knee cartilage or osteoarthritis is involved.

DOs and DON'Ts in Managing Baker's Cysts:

✓ **DO** take your medicines as prescribed by your doctor.

✓ **DO** realize that sometimes this cyst may get smaller without treatment.

✓ **DO** understand that Baker's cysts can lead to complications including pinched nerve, ruptured cyst, and deep vein thrombosis.

✓ **DO** call your doctor if you have knee pain, leg swelling, or shortness of breath.

✓ **DO** call your doctor if you have side effects from medicines.

✓ **DO** call your doctor if you need a referral to a specialist.

✓ **DO** keep to your ideal body weight and exercise regularly to prevent arthritis or knee injury.

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⦸ **DON'T** miss follow-up appointments with your doctor.

⦸ **DON'T** ignore symptoms of knee pain and leg swelling. Baker's cysts can in rare cases lead to serious complications.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Rheumatology Tel: (404) 633-3777 **Website:** **http://www.rheumatology.org**
- Arthritis Foundation Tel: (800) 283-7800 **Website:** **http://www.arthritis.org**
- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website:** **http://www.aaos.org**

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MANAGING YOUR

BALANITIS

What Is Balanitis?

Balanitis is swelling (inflammation) and soreness or irritation of the head (tip, or glans) of the penis. It tends to occur more often in men who are not circumcised. It usually occurs with posthitis (inflammation of the foreskin, the thin sheath of skin that covers the head of the penis). Together the two types of inflammation are called balanoposthitis. Circumcised men never have balanoposthitis because they have no foreskin. These common disorders affect men and boys of all ages.

What Causes Balanitis?

Causes include bacterial or yeast infections, urinary tract infection, sexually transmitted disease, poor hygiene, contraceptive foams or creams, injury or trauma, sexual intercourse, and allergies. Also, a tight foreskin can trap urine, bacteria, and other microorganisms, which can cause balanitis.

What Are the Symptoms of Balanitis?

Common symptoms include redness and swelling at the tip of the penis or foreskin, pain, difficulty urinating, inability to urinate, and bad-smelling discharge. The foreskin can become red, swollen, and tender. In untreated balanitis, the shaft of the penis may become involved, and blisters and ulcers can form.

How Is Balanitis Diagnosed?

The doctor takes a medical history and does a physical examination. In some cases, a sample of the discharge may be taken to see whether bacteria or yeast are causing symptoms.

The doctor may also do blood tests if a more serious disease, such as diabetes or syphilis,

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could be present.

How Is Balanitis Treated?

Balanitis and posthitis usually respond well to treatment. Treatment depends on age, cause, and whether the person is sexually active and circumcised. Treatment involves retracting the foreskin and soaking the area in lukewarm water. Mild cases need an antibiotic cream for the area. Men with more severe cases or with diabetes may take antibiotics by mouth. If the cause is a yeast or fungal infection, a topical antifungal cream is usually applied to the area. Sometimes corticosteroid creams are given to reduce swelling. Surgery is rarely required. Recovery time depends on the cause and whether the person follows the doctor's instructions. In simple cases, symptoms may improve or even disappear in 5 to 10 days. In complex cases, full recovery may take longer.

DOs and DON'Ts in Managing Balanitis:

- ✓ **DO** use good hygiene, including pushing back your foreskin and cleaning the tip of your penis.
- ✓ **DO** wear condoms during sex.
- ✓ **DO** use creams or antibiotic pills as directed by your doctor.
- ✓ **DO** try a milder soap to see if it helps relieve symptoms.
- ✓ **DO** call your doctor if swelling worsens even with treatment.
- ✓ **DO** call your doctor if your condition hasn't improved in 3 or 4 days.
- ✓ **DO** call your doctor if you have trouble producing urine or if you see blood or pus in your urine.

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✓ **DO** call your doctor if balanitis returns, and consider circumcision if you get balanitis or posthitis over and over.

⃠ **DON'T** stop treatment early, especially if you take antibiotics. Even if symptoms are getting better or are gone, you need to finish taking the antibiotic. Otherwise, your symptoms can return.

⃠ **DON'T** have unprotected sex while getting treatment.

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FOR MORE INFORMATION

Contact the following sources:

- American Urological Association Tel: (866) RING AUA (746-4282)
- American Academy of Dermatology 930 North Meachum Road Schaumburg, IL 60173 Tel: (866) 503-7546 **Website: http://www.aad.org/**

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MANAGING YOUR

COMPLICATIONS OF BARIATRIC SURGERY

What Is Bariatric Surgery?

Bariatric, or weight-loss, surgery limits how much food is eaten or digested. It's usually for men who are at least 100 pounds overweight and women who are at least 80 pounds overweight. Surgery can be standard or laparoscopic. Laparoscopic surgery uses a very small incision in the abdomen (belly). The most common type in the United States has been Roux en-Y gastric bypass (RYGB). It also has the most complications. Other operations are adjustable gastric band placement (AGB), biliopancreatic diversion with a duodenal switch (BPD-DS), and vertical sleeve gastrectomy (VSG).

What Are Complications of Bariatric Surgery?

Early complications include blood clots (deep venous thrombosis) and pulmonary embolism. Infections and leaks at places of attachment (anastomotic leaks) can happen. People can also have body aches, dry skin, hair thinning and loss, mood changes, and feel tired and cold. Late complications are strictures, ulcers, fistulas, bowel (intestine) blockage, and hernias. Strictures are narrow places where the intestine is joined. Dumping syndrome, malnutrition, and death can also occur. In dumping syndrome, stomach contents move too quickly through the small intestine.

What Are the Symptoms of Complications of Bariatric Surgery?

Small changes in vital signs can be the earliest clue about complications. Others include fast heartbeat; nausea, vomiting, and inability to eat solid foods (strictures, fistulas); pain in the abdomen, and bleeding (ulcers). The fast heartbeat (persistent tachycardia) is the most sensitive sign of anastomotic leaks. Fecal incontinence tends to get worse after surgery, but urinary

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incontinence, if present before surgery, tends to get better with weight loss.

How Are Complications of Bariatric Surgery Diagnosed?

For diagnosis, the doctor uses symptoms, blood tests, computed tomography (CT), gastrointestinal studies (such as barium swallows), and upper endoscopy.

How Are Complications of Bariatric Surgery Treated?

Treatment depends on cause. Surgery, endoscopy, total parenteral nutrition, intravenous antibiotics, and other drugs are used. Sometimes, a bypass or AGB must be reversed or removed. For internal herniation (bulging), surgery is needed to prevent further complications.

Heparin, compression stockings, and walking around soon after surgery may prevent blood clots. Smoking must stop.

Dietitians can help address nutrient deficiencies. People having gastric bypass should take lifelong nutritional and vitamin supplements and need regular checks of vitamins levels. Counseling, support groups, and doctors can support exercise and lifestyle changes.

DOs and DON'Ts in Managing Complications of Bariatric Surgery:

✓ **DO** keep your follow-up doctor visits. Frequent band adjustments in AGB are needed.

✓ **DO** find a support group if you think that would help.

✓ **DO** chew your food thoroughly and eat very slowly, so that your food can be digested. Wait 2–3 minutes after swallowing before putting the next bite in your mouth.

✓ **DO** eat healthy foods and exercise, which will help you have a healthy weight. Try probiotics (good bacteria found in yogurt) to lose more weight.

⦸ **DON'T** drink fluids while eating. You'll feel full before you eat enough food.

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⦸ **DON'T** drink alcohol, carbonated beverages, high-calorie nutritional supplements, or milk shakes.

⦸ **DON'T** eat snacks between meals.

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FOR MORE INFORMATION

Contact the following sources:

- National Digestive Diseases Information Clearinghouse E-mail: nddic@aerie.com **Website: http://www.niddk.nih.gov/health/digest/nddic.htm**
- American College of Gastroenterology Tel: (703) 820-7400 **Website: http://www.acg.gi.org**

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MANAGING YOUR

BARRETT'S ESOPHAGUS

What Is Barrett's Esophagus?

Barrett's esophagus is condition in which cells lining the esophagus are abnormal. The esophagus is a long muscular tube that moves food down from the mouth to the stomach. At its lower end is a small band of muscle (sphincter) that prevents stomach acid from moving back up into the esophagus (reflux). Cells called squamous (flat) cells normally line the esophagus. In Barrett's esophagus, these cells become another type, called columnar (cells that look like columns). About 5% to 10% of people with this disorder develop cancer of the esophagus.

What Causes Barrett's Esophagus?

The cause is unknown, but it is thought to start from acid reflux disease. It can occur in 10% to 15% of people with acid reflux. It is not hereditary and is not spread from person to person.

What Are the Symptoms of Barrett's Esophagus?

Most symptoms are similar to those in people with acid reflux or acid indigestion. Heartburn is characteristic and usually occurs at night, often waking people from sleep.

Other symptoms include chest pain, difficulty swallowing, food getting stuck or having to vomit food, shortness of breath, wheezing, laryngitis, and hoarseness.

How Is Barrett's Esophagus Diagnosed?

The doctor usually diagnoses the disorder by using endoscopy (placing a lighted tube into the mouth and down into the esophagus). The doctor examines the esophagus and can take samples of any possible problem areas (by a biopsy, or removing a small piece of tissue for study under a microscope).

How Is Barrett's Esophagus Treated?

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The goal is to prevent acid from refluxing into the esophagus. This protects the esophageal lining and may prevent development of Barrett's esophagus. Drugs can limit the amount of acid reaching the lining. These drugs including antacids, H_2-antagonists (e.g., ranitidine, cimetidine), proton pump inhibitors (e.g., omeprazole, lansoprazole), and medicines that improve gastrointestinal motion (e.g., metoclopramide). Proton pump inhibitors are most effective and preferred.

The major complication is development of esophageal cancer, but the doctor can monitor the esophagus by frequent endoscopy to check for cancer. Other complications include bleeding from ulcers and narrowing (stricture) of the esophagus.

DOs and DON'Ts in Managing Barrett's Esophagus:

✓ **DO** remember that the only way to diagnose the disorder is by tissue biopsy via endoscopy. A gastroenterologist (a specialist who treats diseases of the stomach and bowel) will do this.

✓ **DO** remember that acid reflux tends to occur more frequently at night when you lie flat. Elevating the head of the bed will help.

✓ **DO** lose weight.

✓ **DO** make lifestyle changes and take medicines to lower your risk of getting Barrett's esophagus.

✓ **DO** call your doctor if you have heartburn that medicine doesn't help, food gets stuck in your throat and you throw up, or you have trouble swallowing and lose weight.

✓ **DO** call your doctor if you vomit blood.

⊘ **DON'T** drink. Alcohol increases acid reflux.

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⦸ **DON'T** eat large meals before going to bed.

⦸ **DON'T** drink coffee or eat chocolate and fats; they can increase acid reflux. Calcium channel blockers, used for high blood pressure, can also trigger reflux.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Gastroenterology Tel: (703) 820-7400 **Website:** **http://www.acg.gi.org**
- Gastro-Intestinal Research Foundation Tel: (312) 332-1350 **Website:** **http://www.girf.org**

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MANAGING YOUR

BARTHOLIN CYST

What Are Bartholin Cysts?

A Bartholin cyst is a swelling or bulge on one or both sides of the vagina. Cysts can form when one of the sweat glands (Bartholin glands) is blocked. Bartholin cysts that aren't infected may go away without treatment.

What Causes Bartholin Cysts?

Many times, the cause is unknown. Several different kinds of bacteria can cause infection and promote development of the cyst. Any woman can develop a Bartholin cyst. However, pregnant women or women with diabetes are more likely to develop them. Infected cysts are also more common in women who have sexually transmitted diseases or who are very sexually active.

What Are the Symptoms of Bartholin Cysts?

Main symptoms are swelling near the vagina (which can be painless) and painful swelling if a cyst becomes infected, which makes walking and having sex difficult.

How Are Bartholin Cysts Diagnosed?

The doctor will examine the vaginal area for swelling. The doctor may use a swab to get a sample to see whether an infection is present. Blood tests may be done to check for sexually transmitted infections. The doctor may suggest seeing a gynecologist (a doctor who specializes in female genital problems).

How Are Bartholin Cysts Treated?

Small cysts without symptoms may clear up on their own. In these cases, the doctor may simply want regular examinations to monitor the cyst. The doctor will want a return visit in 2 to 3 months if the cyst doesn't go away or if symptoms worsen.

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Infected cysts are treated with hot baths, applying moist heat, and taking antibiotics. It's important to follow the doctor's instructions exactly and take the medicine for as long as prescribed.

If these steps don't work, the doctor (or a gynecologist or surgeon) may drain the cyst. For this procedure, a small cut is made in the cyst, and stitching is done around the edge. This lets fluid drain out.

It's unusual to have a Bartholin cyst more than once. If it occurs again, surgical removal may be needed.

DOs and DON'Ts in Managing Bartholin Cysts:

✓ **DO** follow your doctor's instructions about applying heat, taking antibiotics, and returning for follow-up visits.

✓ **DO** practice good hygiene to prevent infections. After using the toilet, always wipe from the front to the back to stop bacteria around the anus from entering the vagina.

✓ **DO** practice safe sex to help prevent sexually transmitted diseases.

✓ **DO** make sure your blood sugar levels are controlled if you have diabetes. High blood sugars can delay healing.

✓ **DO** examine yourself, so that you can spot another cyst right away.

✓ **DO** call your doctor if you have fever and swollen glands in the groin.

✓ **DO** call your doctor if you have pus draining from the cyst.

⦸ **DON'T** squeeze the cyst. Squeezing may spread the infection.

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⦸ **DON'T** have sex while you have a Bartholin cyst; it may be painful and worsen the infection.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website:** **http://www.acog.org**
- National Women's Health Information Center Tel: (800) 994-9662

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MANAGING YOUR

BASAL CELL SKIN CANCER

What Is Basal Cell Skin Cancer?

The most common type of skin cancer is basal cell carcinoma (BCC). It grows very slowly and almost never spreads to other parts of the body. It usually grows on parts of the head and neck that had a lot of sun exposure. It occurs more commonly after age 40.

What Causes BCC?

Exposure to ultraviolet light (both UVA and UVB) from the sun or light in tanning salons increases the risk of BCC.

Risk of getting BCC is also greater for people who have fair skin and tend to freckle or burn instead of tan. Repeated sunburns or excessive childhood sun exposures, an outdoor job, HIV, medicine that suppresses the body's infection-fighting system, personal or family history of BCC, and radiation treatment can also increase risk.

What Are the Symptoms of BCC?

BCC usually does not cause any symptoms; however, it can sometimes bleed or scab. It may also be itchy, but it usually doesn't hurt.

Doctors classify the different types of BCC according to shape, appearance, and color. The most common have a raised, white or pink border and a central depression.

How Is BCC Diagnosed?

The doctor will suspect BCC based on the appearance of the skin but will need a biopsy to confirm the diagnosis. In a biopsy, a small piece of the skin area is removed and sent to the laboratory for study under a microscope.

How Is BCC Treated?

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Treatment usually consists of doing a biopsy and later removing the skin lesion. Sometimes, the doctor will remove the abnormal area completely without doing a biopsy if the area is small.

BCC may in rare cases recur after treatment, especially on the ears, eyelids, scalp, and nose.

Other treatment methods are electrosurgery (using an electric needle), cryosurgery (freezing), radiation therapy, and Mohs' surgery. Mohs' surgery is a special method for removing BCCs on the nose or eyelid or large BCCs, or for recurrent BCC.

DOs and DON'Ts in Managing BCC:

✓ **DO** follow all your doctor's instructions after treatment.

✓ **DO** resume usual activities after you go home.

✓ **DO** avoid sunburns (especially small children).

✓ **DO** have a skin examination yearly, or more often if your doctor recommends it.

✓ **DO** call your doctor if you have a new mole or abnormal skin area, an area that doesn't heal or that bleeds often, a raised skin mole with a central depressed area, a mole that changes shape or color or that has irregular or unclear borders, or a mole that is asymmetric (one side looks different from the other).

✓ **DO** wear sunscreen with a sun protection factor (SPF) of 15 or higher, protective clothing, and hats.

✓ **DO** call your doctor if the incision becomes red and swollen or has drainage or if you have a temperature higher than 100° F.

⃠ **DON'T** go in the sun when it's hottest, especially from 11 am to 3 pm during summer days.

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⦸ **DON'T** delay seeing your doctor if you have any warning signs of skin cancer.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Dermatology Tel: (866) 503-SKIN (503-7546) **Website:** **http://www.aad.org**
- American Cancer Society Tel: (800) ACS-2345 (227-2345) **Website:** **http://www.cancer.org/**

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MANAGING YOUR

BEHÇET'S SYNDROME

What Is Behçet's Syndrome?

Behçet's syndrome is a lifelong illness that causes irritation (inflammation) and sores in blood vessels, mouth, genitals, eyes, joints, skin, brain, and nerves. This illness occurs when the immune system becomes too active and attacks parts of the body (autoimmune disease).

Behçet's syndrome occurs in men twice as often as in women and usually starts in early adulthood.

What Causes Behçet's Syndrome?

The cause of this rare syndrome is unknown. It is more common in people of Mediterranean, Middle Eastern, or Japanese descent.

What Are the Symptoms of Behçet's Syndrome?

Symptoms tend to come and go, with remissions sometimes lasting months or years. Most people have painful mouth sores; more than 70% have skin blisters that often occur after minor injuries to the skin. The many other possible symptoms include feeling tired, sluggish, or confused; fever; muscle and joint pain; feeling unwell or uncomfortable; eye pain and redness; trouble seeing; stomach pain or diarrhea; blood or mucus (thick slippery liquid) in bowel movements (stools); chest pain or trouble breathing; feeling tingling, numbness; feeling weak; having trouble with balance and walking; poor hearing; and headache or stiff neck.

How Is Behçet's Syndrome Diagnosed?

The doctor makes the diagnosis on the basis of a physical examination and blood tests to rule out other diseases and check general health. Some tests will show inflammation. However, there are no specific tests to prove that Behçet's syndrome is present.

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The doctor may also order a pathergy test. In this test, the skin of the forearm is poked with a needle and then checked later for a reaction (redness).

How Is Behçet's Syndrome Treated?

Treatment is effective in helping most symptoms. The doctor can prescribe medicine to reduce inflammation and help symptoms go away. Many types of drugs can be used, such as medicine to slow the immune system reaction, antibiotic mouthwashes for mouth sores, nonsteroidal anti-inflammatory drugs (NSAIDs) for joint pain, and blood thinners to stop clots from forming.

The doctor will suggest an eye doctor (ophthalmologist) for treatment of eye problems.

DOs and DON'Ts in Managing Behçet's Syndrome:

✓ **DO** take your medicine as instructed. It can prevent serious complications, such as vision problems.

✓ **DO** call your doctor if you have symptoms that worry you.

✓ **DO** talk to your doctor before taking herbal remedies. Some don't go well with prescribed medicine.

✓ **DO** call your doctor immediately if your eyesight is affected.

✓ **DO** call your doctor if you have problems with your medicines. These side effects can include stomach pain, feeling sick, being sick, thrush, high blood pressure, trouble sleeping, feeling either very down or very high, convulsions, acne, sores that heal very slowly, stretch marks, or blurred vision.

⊘ **DON'T** forget to take your medicines.

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⦸ **DON'T** forget doctor's appointments.

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FOR MORE INFORMATION

Contact the following sources:

- American Behçet's Disease Association Tel: (800) 7BEHCET (723-4238) **Website:** **http://www.behcets.com/**

Website: www.nlm.nih.gov/medlineplus/behcetssyndrome.html

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MANAGING YOUR

BED SORES

What Are Bed Sores?

Bed sores, also known as pressure ulcers or decubitus ulcers, are sores that result from injury to the skin and tissue below it. Skin dies over parts of the body that have pressure when people sit or lie still for long periods.

What Causes Bed Sores?

The weight of the body or body part causes circulation in the skin over that pressure point to slow down. With less circulation and nutrition, skin and tissues such as fat and muscle die, and ulcers or sores develop.

Other things that contribute to ulcers are poor nutrition, wet skin from urine and stool, and friction from moving over clothes and bedding.

What Are the Symptoms of Bed Sores?

Symptoms include red skin but not broken skin (stage 1 ulcers). In stage 2 ulcers, the outer skin layer is broken, with blistering and drainage. In stage 3 ulcers, tissue under the skin is affected. Sores may have a white or black base, can be painful around the edges, and have foul-smelling drainage. Stage 4 ulcers reach muscle or bone. They can be white or black at the base and have a bone infection and foul-smelling drainage. Greater risk of developing pressure ulcers is related to stroke, spinal cord injuries, or illnesses that prevent changing positions easily. Also, people who spend long periods in bed or wheelchairs, cannot control their bowels or bladder, or cannot tell caregivers that they're sore or need turning are more prone to getting pressure ulcers.

How Are Bed Sores Diagnosed?

The doctor will make a diagnosis by examining the skin and tissues near the skin.

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How Are Bed Sores Treated?

Prevention is by far the best treatment! Good nursing care, using pressure-relieving devices, and special dressings can prevent ulcers. Treatment depends on the ulcer's stage.

All ulcers must be kept clean with sterile saline and an irrigation tool. Don't use hydrogen peroxide, povidone-iodine solution, liquid detergents, and bleach.

The doctor cleans hard scabs and dead tissue by using a scalpel or scissors (débridement). Wet-to-dry dressings and moist wound dressings can be used to pull off scabs when they are changed. Enzymes on some of the medicated dressings can help remove dead tissue.

The doctor may prescribe antibiotic creams, pills, and injections to control infections.

DOs and DON'Ts in Managing Bed Sores:

✓ **DO** call your doctor if drainage, pain, or redness around an ulcer increases.

✓ **DO** call your doctor if drainage smells foul and looks like pus.

✓ **DO** call your doctor if you get fever, chills, confusion, weakness, or rapid heartbeat.

✓ **DO** know which pressure points may have ulcers and check them often. These points usually don't have fat padding.

✓ **DO** use pressure relief devices, such as pillows, gel or foam cushions or mattresses, and foam or gel heel protectors.

✓ **DO** move bedridden people or encourage them to move at least every 2 hours.

✓ **DO** keep skin clean and lubricated but not moist.

✓ **DO** keep down friction when moving someone. Keep the head of a bed no higher than 30

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degrees to prevent sliding and friction.

✓ **DO** promote good nutrition.

⃠ **DON'T** use a doughnut type of cushion, because they can cause pressure ulcers in other areas.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Dermatology Tel: (866) 503-7546, (847) 330-9239 **Website: http://www.aad.org**
- MedlinePlus **Website: http://nlm.nih.gov/medlineplus/pressuresores.html**
- American College of Surgeons Tel: (800) 621-4111 **Website: http://facs.org**

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MANAGING YOUR

BEDWETTING

What Is Bedwetting?

Bedwetting, or enuresis, is the unintentional (involuntary) passage of urine into bed or clothes by children aged 4 years or older who have no physical problems.

Having nighttime control of urinating is the final stage of one process of development. Most children can control the bladder at night by age 3 years. Bedwetting is as common in boys as in girls until the age of 5. By age 11, boys who wet the bed outnumber girls by 2 to 1.

What Causes Bedwetting?

The cause is usually unknown. However, emotional problems caused by stress or separation, diabetes, urinary tract infections, family history of bedwetting, and being the firstborn child increase bedwetting risk. Also, stress may play a role in children who have bedwetting after being dry at night. This stress may be the birth of another child, hospitalizations, and head injury. Daytime wetting occurs more in girls than in boys and has more associated emotional problems.

What Are the Symptoms of Bedwetting?

The symptom is losing bladder control, usually in the bed at night, and sometimes during the day in an older child.

How Is Bedwetting Diagnosed?

Because bedwetting may have medical causes, the doctor will look for problems in the urinary tract (e.g., bladder), hormone secretion, sleep patterns, family history, and development of the child. The doctor will do physical and mental status examinations, x-ray studies, and blood and urine tests to be sure that a physical reason is not the cause.

How Is Bedwetting Treated?

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Most children with bedwetting never see the doctor. Most families consider bedwetting part of normal childhood development and try to treat it at home. These attempts include restricting fluids (especially after dinner), and using rewards and punishments. Usually, punishing children makes bedwetting worse and may lead to self-esteem problems.

When initially treating bedwetting, the doctor reassures the child that bedwetting can be treated. About 10% of children who have this first visit improve without treatment. Children with no emotional or medical problems will likely stop bedwetting on their own. Other treatments involve waking the child to urinate or having the child urinate before going to bed, avoiding liquids at bedtime, and rewards for dry nights. Medicines can also reduce urine output or affect the way the bladder works.

Psychosocial treatments include using a night alarm or a vibrating pad under the pillow. Relapse after successful treatment usually takes place within 6 months after treatment stops (about one third of children relapse).

DOs and DON'Ts in Managing Bedwetting:

✓ **DO** avoid stressful events.

✓ **DO** avoid excessive criticism of your child.

✓ **DO** limit intake of liquids in the evening, and have your child urinate at certain times (e.g., after dinner, before bed).

✓ **DO** give your child positive rewards for dry nights.

✓ **DO** call your doctor if your child previously wet the bed only at night but now has daytime wetting.

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✓ **DO** call your doctor if your child's urine smells foul or has blood in it, or if your child has pain when urinating.

✓ **DO** find and treat physical causes promptly.

⃠ **DON'T** baby or smother your child.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Pediatrics Tel: (847) 434-4000 **Website: http://www.aap.org**
- American Psychiatric Association Tel: (888) 357-7924 **Website: http://www.psych.org**
- American Academy of Family Physicians Tel: (800) 274-2237 **Website: http://www.aafp.org**

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MANAGING YOUR

BEDBUGS

What Are Bedbugs?

Bedbugs are parasitic insects. The species named *Cimex lectularius,* also called common bedbug, feeds on mammals and birds. *Cimex hemipterus* is a tropical bedbug that bites mostly humans. Both types feed on blood of sleeping people. Bedbugs are attracted to carbon dioxide gas and warm bodies. They don't prefer specific age groups, ethnicity, or sex.

Adult bedbugs are wingless and about a quarter inch long. Mouthparts that pierce and suck usually leave a bite mark on skin. Bedbug saliva contains substances that cause skin reactions.

About Bedbug Infestations?

Bedbugs are now widespread, often found in areas of frequent travel. Infestations have increased dramatically in the United States and worldwide, maybe because of less pesticide use and more international travel. Bedbug infestations may spread easily in buildings and institutions with shared walls.

People should carefully examine bedrooms for infestation signs. Feces or flecks of blood can be seen on bed linens, in furniture cracks and crevices, inside electrical outlets, and behind peeling wallpaper. Feces consist mostly of dried blood and look like yellowish to reddish-black specks. Bedbugs may travel up to 20 feet for meals. Rooms with heavy infestation may have a distinctive, pungent, soda syrup–like odor.

What Are the Symptoms of Bedbugs Bites?

The most common reaction is itchy bumps at bite locations. Skin inflammation (swelling, redness) and fluid-filled rashes can occur there. Scratching may lead to a bacterial infection. People may at times see three bites in a line ("breakfast, lunch, and dinner"). Bites usually don't

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get through clothing, so they're usually seen on exposed skin.

How Are Bedbug Bites Diagnosed?

The health care provider makes a diagnosis from the medical history and physical examination. No specific tests, except for identifying the responsible insect, are needed.

How Are Bedbug Infestations and Bites Treated?

Bedbugs are very hard to eliminate. Insecticides may be used, but bedbug resistance to them has been growing. Using more than one insecticide is suggested. Deltamethrin and chlorfenapyr are commonly used. Use permethrin spray for clothing, bed sheets, and bed nets. DEET may be applied, but high concentrations can be toxic to children. Consult a pest control professional for safe pesticide use.

Vacuuming can remove bedbugs but generally not the eggs. Wash bed sheets and clothing in hot water with detergent with at least 20 minutes in a dryer. Bedbugs can live at high and low temperatures (up to 113° F and down to 44.6° F). Coating bedposts with adhesive substances such as petrolatum or duct tape may stop bedbugs from reaching mattresses.

Treatment of bites isn't often needed. Bites may go away by themselves within a week (milder cases) or a few weeks (more severe cases). Glucocorticoid creams such as hydrocortisone and systemic antihistamines such as loratadine may help severe itching.

DOs and DON'Ts in Managing Bedbugs:

✓ **DO** inspect your clothing and suitcases when you're traveling, especially before returning home.

⃠ **DON'T** ignore symptoms. Call your health care provider if your symptoms don't improve or worsen with treatment.

⃠ **DON'T** assume that bedbugs are found only in cheap hotels. Five-star hotels can also have

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bedbugs.

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FOR MORE INFORMATION

Contact the following sources:

- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website:**

  http://www.cdc.gov/eid

- National Institute of Environmental Health Sciences Tel: (919) 541-3345 **Website:**

  http://www.niehs.nih.gov

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MANAGING YOUR

BELL'S PALSY

What Is Bell's Palsy?

Bell's palsy is paralysis of the facial nerve that causes one side of the face to droop. It is the most common cause of paralysis in the face.

Bell's palsy affects both men and women, most often between ages 15 and 45. Most people recover completely. It cannot be prevented.

What Causes Bell's Palsy?

The cause is inflammation or damage to a nerve in the face (facial nerve). It is unclear why it occurs, but an infection, such as with a virus, may lead to it. Sometimes, bites from ticks carrying Lyme disease can result in Bell's palsy.

What Are the Symptoms of Bell's Palsy?

Symptoms can start suddenly and be distressing. Some people have mild weakness in the face. Others have severe symptoms such as not being able to close the eye or move half of the face. Sometimes complete paralysis occurs in hours. Symptoms also include being unable to raise the eyebrows or having drooping eyebrows, chewing problems, drooling, drooping eyelid, dry eye, ear pain, facial droop, facial numbness, loss of hearing and taste, sounds heard as too loud, and tearing. For most people, symptoms go away completely; sometimes facial weakness remains.

How Is Bell's Palsy Diagnosed?

The doctor takes a medical history and checks the ears, nose, and mouth. The doctor may get a CT or MRI scan of the brain and blood tests to look for other causes of Bell's palsy. A doctor who treats nerve problems (neurologist) may order a special test called electromyography (EMG) to study how the nerve works and predict chances of recovery.

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How Is Bell's Palsy Treated?

Most people with mild symptoms get all better without medicine. Medicines can help severe symptoms. The medicines (e.g., corticosteroids such as prednisone) reduce inflammation (swelling) in the nerve. If an infection such as Lyme disease is suspected to be the cause of Bell's palsy, the doctor may give medicine to treat the infection. An eye patch or eye drops or ointment will protect an open eye, which is critical. Rarely, people who don't recover completely will have an operation to reduce pressure on the facial nerve or improve facial movements.

DOs and DON'Ts in Managing Bell's Palsy:

✓ **DO** follow your doctor's directions and take your medicines as prescribed.

✓ **DO** tell your doctor about other medical problems, especially diabetes.

✓ **DO** tell your doctor about your prescription and over-the-counter drugs.

✓ **DO** tell your doctor if you're pregnant.

✓ **DO** tell your doctor if you recently had a vaccine or a tick bite.

✓ **DO** call your doctor if your symptoms don't get better or get worse or if you have ringing, dizziness, or deafness in your ear.

✓ **DO** call your doctor right away or go to the emergency room if another part of your body becomes weak or numb.

✓ **DO** protect your eye.

✓ **DO** call your doctor if your eye stays red and irritated or becomes painful or if you cannot

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stop drooling.

✓ **DO** call your doctor if you have problems with medicines.

⃠ **DON'T** stop taking your medicines or change your dose because you feel better unless your doctor tells you to.

⃠ **DON'T** reduce your activity level. Rest doesn't help Bell's palsy.

⃠ **DON'T** stop corticosteroids abruptly; they must be tapered.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Otolaryngology—Head and Neck Surgery Tel: (703) 836-4444 **Web-site: http://www.entnet.org**

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MANAGING YOUR

BIPOLAR DISORDER

What Is Bipolar Disorder?

Bipolar disorder is a psychiatric condition that was known before as manic depressive disorder. The main symptom involves swings between moods of mania (or hyperactivity) and depression.

It usually occurs by 30 years of age, in both men and women. The disorder seems to run in some families.

What Causes Bipolar Disorder?

The cause is unknown. Stress, drug or alcohol abuse, and use of some prescription drugs may increase the risk.

What Are the Symptoms of Bipolar Disorder?

People in the manic mood feel full of energy and happy. They need less sleep. Speech and thoughts race. Self-esteem is high. Overeating is common. People can have poor judgment and make reckless choices. Manic people can also hear voices or see things that aren't there. Some people do things like clean the house to burn energy.

In a depressed mood, people have less energy, feel sad and cry for no reason, sleep too much or have trouble falling asleep, lose pleasure in life, eat less, and struggle with feelings of worthlessness. Depression may lead to thoughts of death or suicide.

Bipolar disorder often occurs in cycles—an episode once a month, once a week, once a year, once a season, or as often as once a day.

How Is Bipolar Disorder Diagnosed?

The doctor makes the diagnosis after an examination and asking about symptoms. The doctor may order blood tests or other medical tests to make sure another illness isn't causing the symp-

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toms.

How Is Bipolar Disorder Treated?

Bipolar disorder is not curable. Medicine (lithium) is the usual treatment to help even out moods. Some people may need to take lithium for a lifetime, but it isn't addictive. Continuous treatment is necessary to prevent relapse of depressive or manic symptoms. Other effective medications are also available for those who do not respond well to lithium or have side effects from it.

People are often referred to a psychiatrist or for group therapy. Therapists can help people change behaviors that may make the illness worse.

DOs and DON'Ts in Managing Bipolar Disorder:

✓ **DO** tell your doctor or someone you trust if you have suicidal thoughts.

✓ **DO** talk to your doctor about any herbal remedies and medicines that you're taking.

✓ **DO** try to keep to a routine sleep schedule.

✓ **DO** stay active.

✓ **DO** find a support group if you think that it might help.

✓ **DO** tell your doctor about your medicine's side effects.

✓ **DO** avoid drugs of abuse, especially stimulants such as cocaine, amphetamines, and PCP. They may cause a manic episode.

✓ **DO** call your doctor if you feel that you're getting more energetic or can't relax, or your family members or others describe you as hyper.

✓ **DO** call your doctor if you notice a decreased need for sleep or have trouble sleeping.

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⦸ **DON'T** use alcohol or other drugs, such as antihistamines or drugs containing high amounts of caffeine.

⦸ **DON'T** drive when you first start a new medicine.

⦸ **DON'T** make any major decisions during a mood swing.

⦸ **DON'T** stop your medicine or change your dose because you feel better, unless your doctor tells you to.

⦸ **DON'T** change your diet or salt intake while you are taking lithium.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

• Bipolar Disorders Information Center **Website:** **http://www.mentalhelp.net/poc/center_index.php?id=4&cn=4**

• Depression and Bipolar Alliance Tel: (800) 826-3632, (312) 642-0049

• Mood Disorders Support Group of New York City Tel: (212) 533-MDSG (533-6374) **Website:** **http://www.mdsg.org**

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MANAGING YOUR

BITES AND STINGS

What Are Bites and Stings?

Biting insects include ants, fleas, flies, no-see-ums (flies called midges), and mosquitoes. Stinging insects include bees, wasps, and hornets. These insects are usually a nuisance, but some people are may have allergic responses to bites or stings. Some insects pass diseases to people.

The group called arthropods that includes insects also includes arachnids—spiders, scorpions, ticks, and mites. The main poisonous spiders in the United States are the brown recluse, black widow, tarantula, and hobo. Most spider bites are uncomfortable but heal without problems.

What Are the Symptoms of Bites and Stings?

Local pain or itching occur first, then redness and swelling. Bites can become infected. Stings cause local pain and swelling. Many stings can cause swelling, weakness, confusion, trouble breathing, fainting, vomiting, and diarrhea. Kidney failure, cardiac arrest, and death can occur with severe allergies. Disorders such as Lyme disease are spread by ticks, and encephalitis is spread by mosquitoes.

Brown recluse spider bites can cause stinging, redness, and swelling and blood-filled blisters, ulcers, and infection. Hobo spider bites cause similar problems plus headaches and muscle aches. Black widow spider bites usually cause intense burning, sometimes followed by spasms of the abdomen (belly), limbs, and back, with high blood pressure, sweating, and vomiting. Tarantula bites are like wasp stings with severe pain, redness, and swelling.

How Are Bites and Stings Diagnosed?

Diagnosis is based on a medical history and physical examination. Blood tests are needed for only Lyme disease or Rocky Mountain fever or if fever, rash, headache, or joint pains are pre-

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sent.

How Are Bites and Stings Treated?

It's best to avoid getting bitten or stung. Use repellents, wear long sleeves and pants and a hat, and put screens in doors and windows. For most bites and stings, ice or cold packs, steroid creams, and antihistamines help itching and swelling. Oral steroids are used to treat severe reactions or many bites or stings. Antibiotics are given for tick fevers such as Lyme disease.

Hives or more severe allergic reactions need quick medical care. Some people with severe allergy must use epinephrine self-injectors.

Most spiders try to avoid humans and bite only when trapped. Bites usually heal on their own, but applying cold packs (ice) and elevating the limb if the bite is on a leg or arm will help. A tetanus shot, pain medicines, and muscle relaxants may be needed. Black widow antivenin is given for very severe cases (trouble breathing) or for pregnant women with black widow bites. Steroids and antihistamines may help relieve itching from tarantula bites.

DOs and DON'Ts in Managing Bites and Stings:

✓ **DO** carry epinephrine self-injectors if you're sensitive to stings.

✓ **DO** remove ticks (especially the head) as soon as possible.

✓ **DO** rest an area bitten by a spider, keep it elevated, and consider applying ice. Take pain medicines as prescribed.

✓ **DO** call your doctor if you have an infected bite or allergic reactions (hives, itching, and trouble breathing, swallowing, or talking).

✓ **DO** call your doctor if a bite ulcer gets larger or becomes infected, you're pregnant, or you

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have new painful muscle spasms, trouble breathing, or chronic health problems.

⦸ **DON'T** go in wooded areas without wearing protective clothing.

⦸ **DON'T** scratch bite areas.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Dermatology Tel: (847) 330-0230 **Website: http://www.aad.org**
- National Institute of Allergy and Infectious Diseases Tel: (866) 284-4107 **Website: http://www.niaid.nih.gov**
- National Institute of Environmental Health Sciences Tel: (919) 541-3345 **Website: http://www.niehs.nih.gov**

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MANAGING YOUR

BLADDER CANCER

What Is Bladder Cancer?

The bladder is the organ that stores urine before it leaves the body. The bladder lining consists of transitional cells. Nearly 95% of all bladder cancers start from these cells (transitional cell carcinoma). Bladder cancer is a malignant tumor in this organ and may be small or large, growing deep into the bladder muscle, and it may spread (metastasize).

The other two types are squamous carcinoma and adenocarcinoma. These tumors are usually larger and often go into the bladder wall and may metastasize.

Bladder cancer develops most often in people older than 50. Men have bladder cancer more often than women do.

What Causes Bladder Cancer?

Many things can cause bladder cancer, most often cigarette smoking. Usually the exact cause is unknown. Chemicals used at jobs in dye, textile, tire, rubber, and petroleum industries are another cause.

What Are the Symptoms of Bladder Cancer?

Very small cancers usually cause no symptoms, but blood in the urine, burning when urinating, or needing to urinate small amounts are possible symptoms.

Larger tumors cause more symptoms, such as pain low in the belly or losing weight.

How Is Bladder Cancer Diagnosed?

The doctor will do an examination and order a urine test to see if the urine shows blood, signs of infection, or abnormal (cancerous) cells.

The doctor may also order blood tests and tests of the kidneys and liver function.

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X-rays of the bladder and urinary tract, ultrasound or computed tomography (CT) scans, and cystoscopy (using a lighted tube to see inside the bladder) may also be done. If abnormal areas are found, a piece of tissue (biopsy specimen) is taken for study under a microscope.

How Is Bladder Cancer Treated?

Surgery is needed to remove the cancer. The operation depends on the type of cancer and whether it has spread.

A small or large tumor is removed by endoscopy (using a lighted tube inserted into the bladder). For a very large cancer, the whole bladder may need to be taken out (radical cystectomy). After this operation, urine will empty out through a pouch through the skin (urostomy), which needs special care.

Pain pills, radiation treatment, and anticancer medicine (chemotherapy) may also be needed.

DOs and DON'Ts in Managing Bladder Cancer:

✓ **DO** take pills as your doctor prescribes.

✓ **DO** resume normal activities (including sexual relations) after surgery or other treatment when your doctor says you can.

✓ **DO** call your doctor if you had surgery and have new symptoms of infection (back pain, fever, and vomiting).

✓ **DO** call your doctor if you have blood in your urine; you feel the need to urinate frequently, with urgency, or with hesitancy; or if urination is painful.

✓ **DO** call your doctor if you have pain or trouble with erections after surgery.

✓ **DO** call your doctor if you have excess bleeding, fever, and chills after cystoscopy.

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⦸ **DON'T** smoke.

⦸ **DON'T** be frustrated if superficial cancer returns. The cancer can be controlled with close follow-up care and tumor removal.

⦸ **DON'T** miss follow-up doctor appointments, including cystoscopy every few months for the first year.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- The American Cancer Society Tel: (800) ACS-2345 (227-2345) **Website:** **http://www.cancer.org**
- The National Cancer Institute Cancer Information Service Tel: (800) 4-CANCER (422-6237)

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MANAGING YOUR

BLISTERS

What Are Blisters?

Blisters are one of the most common foot injuries of athletes. Blisters (bullae) are liquid-filled bubbles that form on skin where things rub together. Blisters occur in sports played on hard surfaces and in repetitive activities. They most often form on feet (heels, soles) but can also form on hands, as when bike riding without hand protection. People can get blisters if shoes don't fit right or no socks are worn.

What Causes Blisters?

Friction (repeated rubbing) of clothing (socks) or sports equipment on skin causes the top layer of skin to separate from the bottom layers and fill with liquid (blister). Changes in training pattern or poorly fitting equipment will cause rubbing. Other risk factors include moist skin, race, flat feet, and bulges such as bunions and hammertoes.

What Are the Symptoms of Blisters?

Redness and warmth on the skin called a hot spot usually warn that a blister is starting. Bubbles of skin filled with clear fluid can be pinpoint size to more than ½ inch in diameter. Pain and itching may also occur.

How Are Blisters Diagnosed?

People usually notice their own blisters because of symptoms (pain and redness). Doctors can diagnose very large or painful blisters from the look and location of the bubbles and medical history.

How Are Blisters Treated?

It's best to avoid getting blisters by minimizing friction and wearing protection. Good-fitting,

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comfortable shoes and cotton socks are important. Petroleum jelly on the area or moleskin and ring-shaped pads can reduce friction. Drying agents (antiperspirant sprays) limit moisture on feet. Gymnasts can use palm protectors called grips.

Hot spots should be treated right away to prevent blisters. Keep feet dry, or change shoes, socks, gloves, or other gear.

Treatment goals are reducing pain, keeping the blister from getting larger, and avoiding infection. Pus draining from a blister, very red or warm skin around the blister, red streaks leading away from the blister, and fever may mean infection. Small unbroken blisters that aren't painful can be left alone or covered with a loose bandage. For a small hole or break in the blister, leave on the flap of skin and gently flatten it over tender skin below. If the blister breaks, wash the area and use antiseptic (polymyxin B or bacitracin) creams or ointments and sterile bandage. Doctors can drain large, painful blisters.

DOs and DON'Ts in Managing Blisters:

✓ **DO** use powder to keep feet dry. Prevent blisters by reducing moisture and friction and wearing protective gear.

✓ **DO** wear socks with shoes.

✓ **DO** wear comfortable shoes that fit well. Get shoes fitted in the afternoon or evening. Feet swell during the day.

✓ **DO** avoid wearing the shoes or doing the activity that caused the blister until the blister heals.

✓ **DO** massage feet with lanolin every night for a month before a big walking or running event.

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✓ **DO** contact your doctor if the blister area is reddened and there are red streaks leading away from the blister.

⃠ **DON'T** wear poorly fitting shoes.

⃠ **DON'T** break (pop) the blister. Leave it alone, uncovered unless something rubs against it.

⃠ **DON'T** take off a flap of skin covering the blister unless it tears, gets dirty, or gets pus under it (infected). It protects the tender healing skin.

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FOR MORE INFORMATION

Contact the following sources:

- American Medical Society for Sports Medicine Tel: (913) 327-1415 **Website:** **http://www.newamssm.org**

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MANAGING YOUR

BODY DYSMORPHIC DISORDER

What Is Body Dysmorphic Disorder?

Body dysmorphic disorder (BDD) is an illness in which people are preoccupied with minor or imagined flaws in physical appearance. It can cause major problems in social life or at work. People may have other psychiatric conditions such as anorexia nervosa or depression along with BDD. About 1% to 2% of the general population are affected, males and females equally. More people who have cosmetic surgery have BDD, from 2% to 15%. BDD usually starts in teens or young adults.

What Causes BDD?

The cause is unknown. Mental disorders associated with BDD include major depression, obsessive-compulsive disorder (OCD), generalized anxiety disorder, agoraphobia, and eating disorders. It doesn't seem to be inherited from parents.

What Are the Symptoms of BDD?

People cannot stop thinking about a certain body part and believe that there's something wrong with it even if there isn't. People may try to hide the body from others or avoid social contacts because they're afraid that others may notice the so-called abnormal body part. Examples of body parts that cause excessive worries include nose, teeth, facial or body hair, breasts, hair on the head, moles, scars, and muscles. People obsess over their appearance and body image, often for many hours a day. They constantly look in the mirror or check and measure the body part. They often visit plastic surgeons, skin health care providers, or cosmetic dentists to ask for procedures to correct their flaws. However, they're not satisfied with the outcome of the procedures.

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Other features of BDD include grooming too much (such as hair plucking), refusing to appear in pictures, and wearing too much makeup or clothing as camouflage.

How Is BDD Diagnosed?

BDD is often not recognized or diagnosed because people avoid telling health care providers about symptoms. The health care provider makes a preliminary diagnosis from the medical history and physical examination. The health care provider may suggest seeing a specialist (psychiatrist, psychotherapist) for more evaluation. The diagnosis requires a preoccupation with the body that's not explained by another mental disorder.

How Is BDD Treated?

Treatment can be hard, especially if people don't really want to get help. Cognitive behavioral therapy and medicines are effective. Cognitive behavioral therapy can involve exposure and response prevention. Medicines include selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants. People should be advised to avoid cosmetic procedures. People often have unrealistic expectations about plastic surgery. Support groups may help. Untreated BDD tends to be chronic and can lead to social isolation, dropping out of school, major depression, unnecessary surgery, and even suicide. However, early diagnosis and treatment can lead to a favorable result.

DOs and DON'Ts in Managing BDD:

✓ **DO** understand that family behavioral treatment can help. This type of therapy is especially useful if the affected person is a teen.

✓ **DO** consider therapy with family members, spouse, and significant others.

✓ **DO** tell your health care provider if you have thoughts of hurting yourself.

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- ⦸ **DON'T** ignore symptoms. Call your health care provider if your symptoms don't get better or they worsen with treatment.
- ⦸ **DON'T** stop taking your medicine or change the dosage because you feel better unless your health care provider tells you to.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- Body Dysmorphic Disorder Central **Website: http://www.BDDCentral.com**
- American Psychiatric Association Tel: (888) 357-7924 **Website: http://www.psych.org**
- American Psychological Association Tel: (800) 374-2721 **Website: http://www.apa.org**

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MANAGING YOUR

BOILS

What Are Boils?

Boils are painful, deep sores of the skin. They are pus-filled infections of hair follicles. Furunculosis is another name for these infections.

Boils are uncommon in young children and are more frequent after puberty.

What Causes Boils?

The usual cause is the type of bacteria named *Staphylococcus*. The infection begins in a hair follicle and goes into deeper skin layers. People can pass the infection to others if contact is made with pus from a boil.

People have greater chances of getting boils if they have infected wounds, poor hygiene, tight clothing, chafing, and exposure to certain chemicals and cosmetics. Some disorders such as diabetes and alcoholism can increase the risk of getting boils. Boils can follow folliculitis (inflammation of hair follicles) made worse by irritation or sweating.

What Are the Symptoms of Boils?

A boil starts as a small, painful sore that quickly gets bigger and becomes a painful lump. Boils at first are usually ½ to 1 inch in diameter. They usually occur on the neck, face, waist, groin, underarms, and buttocks. Pain gets worse as the boils grow larger. Boils either remain deep in the skin and reabsorb or burst through at the skin surface. They may let out a white, bloody discharge. After the boils burst, pain gets better, but redness and swelling may last for days or weeks, and then scarring will occur. Without treatment, the infection may enter the bloodstream and spread to other body parts.

How Are Boils Diagnosed?

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The doctor will diagnose boils by examining the affected part of the skin. The doctor may want to take a sample of the pus to check for bacteria.

How Are Boils Treated?

Warm moist compresses, three or four times daily for 20 minutes each time, provide comfort and help boils come to a head and drain.

The doctor may cut and drain a boil when the skin over it becomes thin and the mass below is soft. Without treatment, boils heal in 10 to 20 days, but they'll heal faster and have less severe symptoms with treatment. The doctor may prescribe antibiotics for severe infections or ones that return.

A complication is formation of new boils if pus that drains when the boil opens contaminates nearby skin.

DOs and DON'Ts in Managing Boils:

✓ **DO** use your prescribed antibiotics.

✓ **DO** reduce activity until the infection heals. Avoid sweating and contact sports while boils are present.

✓ **DO** keep your skin clean.

✓ **DO** change clothes and bed linens daily and wash them in hot water.

✓ **DO** call your doctor if you have a fever or symptoms don't get better in 3 or 4 days with treatment.

✓ **DO** call your doctor if you or family members get new boils.

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⦸ **DON'T** use nonprescription antibiotic creams or ointments on the boil's surface. They usually don't work.

⦸ **DON'T** share towels, washcloths, or clothing with other household members.

⦸ **DON'T** try to squeeze the boil or manipulate it with objects. It may make the infection worse.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Dermatology Tel: (866) 503-7546 **Website: http://www.aad.org**

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MANAGING YOUR

BORDERLINE PERSONALITY DISORDER

What Is Borderline Personality Disorder?

Personality refers to the special traits and behaviors that make up a person. A personality disorder is a behavior pattern that differs from socially acceptable normal behavior. The main characteristic of this disorder is a broad instability in moods, interpersonal relations, self-image, and behavior. This instability often upsets family and work life, long-term planning, and a person's sense of self. People can't regulate emotions normally.

This disorder is common and affects 2% of the general population, usually young women. It accounts for 20% of all hospital stays for mental illness.

The disorder is not contagious.

What Causes Borderline Personality Disorder?

The exact cause is unknown. The cause is thought to be genetic, psychologic, social, and biologic factors that work together. A history of childhood abuse or neglect and abnormal chemicals (serotonin) in brain areas controlling emotion may also be involved.

What Are the Symptoms of

Borderline Personality Disorder?

According to a manual from the American Psychiatric Association used for diagnosing mental disorders, people with this disorder must have five or more of certain symptoms. These include unstable and intense personal relations, long-lasting unstable sense of self, impulsive behavior, suicidal or self- destructive behavior, mood problems, feelings of emptiness, intense anger or problems with control of anger, and paranoia (feelings that people are "out to get you").

How Is Borderline Personality

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Disorder Diagnosed?

A psychiatrist (a doctor specializing in mental and emotional illness) makes a diagnosis on the basis of the symptoms noted above.

How Is Borderline Personality Disorder Treated?

Treatment involves psychotherapy plus cognitive-behavioral therapy. Psychotherapy can be done by a psychiatrist (who can prescribe medicine) or a psychologist (a specialist, not a medical doctor, who diagnoses and treats mental and emotional problems but doesn't prescribe drugs). The goal is to relieve symptoms and change behavior so that relations with family, friends, and coworkers improve.

Cognitive therapy focuses on how certain thinking patterns cause symptoms. Behavioral therapy refers to treatment to break the connection between things that cause stress and reactions to them. The two types of therapy work together to stop symptoms.

Certain medicines may control impulses and brief psychotic events (e.g., hallucinations, delusions), stabilize mood (e.g., lithium), and help with mood swings and depression.

DOs and DON'Ts in Managing Borderline Personality Disorder:

✓ **DO** realize that this disorder can lead to major problems in relations with family and other people.

✓ **DO** understand that people can become suicidal and need monitoring.

✓ **DO** understand that people with this disorder don't get schizophrenia but can have major depression.

✓ **DO** call your doctor if you suspect that a family member may have borderline personality

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disorder.

✓ **DO** call your doctor if you need a referral to a psychiatrist.

✓ **DO** call your doctor if you feel depressed or are going to harm yourself or others.

⃠ **DON'T** forget that people with this disorder may also have other mental problems (e.g., depression, anxiety, and mood disorders).

⃠ **DON'T** forget that this disorder is chronic, with ups and downs. The most unstable period usually occurs in early adulthood, but most people often continue to have problems with intimate relations.

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FOR MORE INFORMATION

Contact the following sources:

• National Mental Health Association Tel: (703) 684-7722, (800) 969-6642 **Website:** **http://www.nmha.org/**

• Mental Health Resource Center Tel: (888) 284-3258 **Website:** **http://www.athealth.com/Consumer/rcenter/**

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MANAGING YOUR

BOTULISM

What Is Botulism?

Botulism is a disease caused by toxins (poisons) that are produced by a bacterium named *Clostridium botulinum*. These bacteria occur widely in soils and grow from spores (the resting stage) only in the right conditions. The three types of botulism are food related, wound related, and infant botulism. In the United States, an average of 110 cases are reported yearly. Of these, about 25% are related to the food type, 72% to the infant type, and 3% to the wound type.

These toxins also have value in medical treatments, such as relieving muscle spasms (twitching) and removing wrinkles (cosmetic use).

What Causes Botulism?

The bacteria produce seven toxins (labeled A through G). Types A, B, E, and F cause disease in humans, in people of all ages. Botulism cannot be transmitted from person to person.

People get food-borne botulism from eating food containing the toxin. A common cause is improperly preserved home-processed foods.

Wound botulism is most often related to illegal drug use and to crush injuries. Spores contaminate a wound and produce toxin that gets into the bloodstream.

Infants can eat spores, which then grow in the intestines and produce toxin.

What Are the Symptoms of Botulism?

First symptoms are drooping eyelids, blurred vision, double vision, slurred speech, difficulty swallowing, dry mouth, and muscle weakness. Most symptoms start 12 to 36 hours after eating tainted foods. If the disease isn't diagnosed and treated early, it may lead to paralysis of arms, legs, trunk, and breathing muscles. People may need a mechanical ventilator to help their breath-

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ing.

About 5% to 10% of people with food-borne botulism die.

How Is Botulism Diagnosed?

Botulism has symptoms similar to those of other neurological diseases, so diagnosis is difficult and it is often misdiagnosed. Laboratory tests to prove it can take up to 4 days to complete, and only certain laboratories can do them.

How Is Botulism Treated?

The doctor treats botulism by checking and observing symptoms, providing supportive care, and giving an antitoxin (a chemical to counteract the toxin). The antitoxin slows the paralysis and may also make the symptoms less severe and stop them sooner.

DOs and DON'Ts in Managing Botulism:

- ✓ **DO** realize that most outbreaks are related to eating home-canned foods, especially vegetables. Avoid eating contaminated food. You can get instructions on safe home canning from the U.S. Department of Agriculture.
- ✓ **DO** understand that the toxin is destroyed by high temperatures. Boil foods for at least 10 minutes.
- ✓ **DO** realize that infant botulism occurs when an infant eats spores of the bacteria. Many cases have occurred after eating contaminated honey.
- ✓ **DO** keep all wounds clean. Proper wound care and avoiding illegal drug use reduces your risk of getting wound botulism.
- ✓ **DO** call your doctor if you have trouble breathing or swallowing or note muscle weakness,

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double vision, or slurred speech.

✓ **DO** call your doctor if you have a contaminated wound.

⃠ **DON'T** do drugs to minimize the risk of wound botulism!

⃠ **DON'T** forget that botulism is not spread from one person to another.

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FOR MORE INFORMATION

Contact the following source:

- Centers for Disease Control and Prevention Tel: (800) 232-4636 **Website:** **http://www.bt.cdc.gov**

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MANAGING YOUR

BRAIN ABSCESS

What Is a Brain Abscess?

The brain is part of the central nervous system of your body. It works like the central processing unit of your computer. It receives, accepts, and inputs outside data, stores data, and organizes responses to data. The immune system, skull, and tissue layers around the brain protect it against infection. However, bacteria and other organisms can get through this protection and cause infection. The brain sometimes responds to infection by forming small hollow cavities filled with pus, called abscesses.

Brain abscesses are rare and can occur at any age, but are more common in people between 30 and 45. The risk increases with head injury, drug abuse, diabetes, cancer, AIDS, severe illness, and infections of the face, ears, nose, and eyes. Emergency hospital care is needed. Almost half of people affected continue to have nerve or behavioral effects after treatment. Since the use of antibiotics and computed tomography (CT) and magnetic resonance imaging (MRI), the death rate from brain abscesses has decreased to 10%.

What Causes a Brain Abscess?

Bacteria are the usual cause. Fungi are a common cause in people with poor immune system protection (e.g., with AIDS). Brain abscesses usually result from spreading of other infections, such as sinusitis or middle ear or dental infections, or from surgery for brain tumors.

What Are the Symptoms of a Brain Abscess?

The most common symptoms are fever, headache, and nervous system problems. Such problems may be confusion, disorientation, speech or walking difficulties, change in mental status, or arm and leg weakness on one side. Other symptoms include nausea, vomiting, stiff neck, and sei-

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zures.

How Is a Brain Abscess Diagnosed?

The doctor finds brain abscesses by obtaining a medical history, performing a physical exam, and looking at results from MRI or CT of the brain.

How Is a Brain Abscess Treated?

Treatment of brain abscess caused by bacteria involves antibiotics and surgical drainage or removal of the abscess. The decision to surgically drain or remove the abscess should be made with a neurosurgeon. Sometimes antibiotics alone may offer a cure, but surgery is usually needed. Complications from surgery include a worsening condition, stroke, and infection. Most people have antibiotics given intravenously and then by mouth. Special drugs are available for brain abscesses caused by a fungus.

DOs and DON'Ts in Managing a Brain Abscess:

✓ **DO** follow your doctor's instructions about antibiotics. Finish the full course of medicine.

✓ **DO** realize that the earlier the diagnosis is made the better the prognosis for remaining nervous system and behavioral effects.

✓ **DO** follow up with your appointments, including doctor visits and repeated CT or MRI, to be sure that the infection is gone.

✓ **DO** call your doctor if you have a headache and fever or a seizure or notice changes in your mental state (e.g., confusion or disorientation), speech or walking problems, or weakness on one side of your body.

⦸ **DON'T** ignore symptoms. Remember that most brain abscesses result from other infections that spread to the brain. Report all symptoms to your doctor.

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⦸ **DON'T** do drugs! Drug abuse increases the risk of infections.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Otolaryngology—Head and Neck Surgery Tel: (703) 836-4444

  Website: http://www.entnet.org

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MANAGING YOUR

BRAIN CANCER

What Is Brain Cancer?

Brain cancer is a malignant cell growth in the brain. The cancer can be primary (75%), meaning that it started in the brain, or secondary (25%), meaning that it spread from another part of the body to the brain. About 40% of brain cancers start from glial cells and are named gliomas. Gliomas include astrocytomas, glioblastomas, oligodendrogliomas, ependymomas, and medulloblastomas. The most common secondary cancers spread from cancers of the breast, lung, kidney, colon, and skin (melanoma).

Primary brain tumors can affect anyone but are more common in children younger than 15 and in middle-aged adults. Secondary brain tumors are more common in adults.

Brain cancer cannot be prevented. Most primary brain tumors, if found early, can be cured.

What Causes Brain Cancer?

The cause of primary brain tumors is unknown.

What Are the Symptoms of Brain Cancer?

Headaches and seizures are the most common symptoms. Headaches usually occur in early morning, sometimes waking people up, and worsen with coughing or sneezing. The growing tumor pressing up against the skull causes the headaches. Other symptoms depend on the location of the tumor, but can include behavior changes, confusion, and trouble with speech, memory, or concentration.

How Is Brain Cancer Diagnosed?

Magnetic resonance imaging (MRI) is usually used to find the cancer. Computed tomography (CT) can also be used. The only way to prove the diagnosis is to take a tissue sample from the

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tumor and study it under the microscope. Taking this sample can be done either by a biopsy or at surgery, if the whole tumor is to be removed.

How Is Brain Cancer Treated?

Primary brain tumors are usually removed. Depending on the tumor type and location, surgery gives the best chance for a cure if the whole tumor can be removed. Surgery also allows diagnosis of the type of cancer and relieves pressure in the brain.

Radiation therapy, another treatment method, is performed by specialists (radiation oncologists) and is usually used for tumors that cannot be removed (or removed completely), or after surgery for any brain cancer.

Chemotherapy is not often used for primary brain tumors.

An antiseizure medicine, such as phenytoin, is often used before and after surgery. For swelling in the brain, the doctor may prescribe a steroid (dexamethasone).

DOs and DON'Ts in Managing Brain Cancer:

✓ **DO** have a team of doctors help with your care: a neurosurgeon (a doctor specializing in surgery of the brain and spinal cord), neuro-oncologist (a doctor specializing in cancers of the nervous system), radiation oncologist (a doctor specializing in radiation treatment of cancer), and your primary care doctor.

✓ **DO** call your doctor if you have new headaches or seizures.

✓ **DO** call your doctor if you need a referral to a specialist.

⃠ **DON'T** be afraid to ask for second opinions.

⃠ **DON'T** miss follow-up appointments. Your doctor may repeat CT or MRI and blood tests to

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check for cancer and to keep your seizure medicine at the right dose.

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FOR MORE INFORMATION

Contact the following sources:

- American Cancer Society Tel: (800) ACS-2345 (227-2345)
- National Cancer Institute (NCI) Tel: (800) 4-CANCER (422-6237)
- American Brain Tumor Association Tel: (800) 886-2282 **Website: http://www.abta.org**

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MANAGING YOUR

BRAIN TRAUMA

What Is Brain Trauma?

Most people have minor head injuries during their lifetime, but head trauma causing traumatic brain injury (TBI) is a common cause of serious illness and death. Primary brain injury results directly from trauma. Secondary brain injury is any later injury. Types of TBI include bleeding, concussion (shaken brain), and contusion (bruised brain). Injuries are classified according to severity or type of injury (e.g., closed or open). Injuries are also classified according to the presence of a skull fracture or lesion inside the brain and location of bleeding.

Twice as many males than females have TBIs. TBI is also more common in people younger than 35 than older people.

What Causes Brain Trauma?

TBIs result when the head suddenly and violently hits an object, or when an object enters the skull. Common causes are blows to the head, motor vehicle accidents, falls, physical assaults, and sports. Penetrating injuries may be caused by high-speed missiles (bullets) or other objects (knives, tools, or bone pieces).

Low blood pressure, hypoxia, and increased pressure inside the skull (increased intracranial pressure, or ICP) can cause secondary injuries.

What Are the Signs and Symptoms of Brain Trauma?

Symptoms depend on the injury type and severity. They can start immediately or develop slowly. People with mild TBIs may be conscious or may lose consciousness briefly. Other symptoms include headache, confusion, feeling lightheaded or dizzy, blurred vision, ringing in the ears, and fatigue. Changes in sleep, behavior, or mood can occur. People can have trouble with memory,

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concentration, attention, or thinking. Moderate or severe TBIs may also cause severe headache, vomiting, nausea, convulsions, inability to wake up, dilated pupils, and slurred speech. Extremity weakness or numbness, loss of coordination, and increased confusion, restlessness, or agitation can occur.

How Is Brain Trauma Diagnosed?

The doctor does a physical examination (especially eye movement and pupils) and checks ABCs (airway, breathing, circulation). The doctor uses the Glasgow Coma Scale score (range is from 3 to 15) to decide TBI severity. Computed tomography (CT) is used as part of the initial evaluation for moderate to severe TBIs.

How Is Brain Trauma Treated?

Prevention is best. Minor injuries may need only observation and symptom control (e.g., pain medicine for headaches). In the initial 24 hours, people should be awakened every 2 hours and checked for signs of secondary injury. Elevating the head and sedation may help control the symptoms. Monitoring of all vital functions and intravenous mannitol are used for increased ICP and brain swelling. Deep or severe bleeding may require surgery (e.g., craniotomy to remove clots). Débridement and irrigation of penetrating injuries may be necessary to help reduce infections.

DOs and DON'Ts in Managing Brain Trauma:

✓ **DO** get emergency help (call 911) for people who aren't fully awake after injury.

✓ **DO** wear safety equipment when participating in sports (e.g., biking, playing contact sports).

✓ **DO** obey traffic signals and be visible (wear reflective clothing) when bike riding.

✓ **DO** make sure that children use seat belts or safety seats.

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✓ **DO** make sure that children receive follow-up medical care after head injuries, especially concussions.

⃠ **DON'T** drink and drive or let yourself be driven by someone who has been drinking.

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FOR MORE INFORMATION

Contact the following sources:

- Brain Injury Association of America Tel: (800) 444-6443 **Website: http://biausa.org**
- American Trauma Society Tel: (800) 556-7890 **Website: http://www.amtrauma.org**

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MANAGING YOUR

BREAST ABSCESS

What Are Breast Abscesses?

An abscess is a pocket containing pus that can occur in any part of the body. Breast abscess refers to an inflammation (swelling, redness) that results in such a collection of pus in the breast.

What Causes Breast Abscesses?

Bacteria most often cause breast abscesses. The most common types of bacteria are named *Staphylococcus aureus* and *Streptococcus*. Sometimes anaerobic bacteria (which grow without oxygen) can cause breast abscesses.

Breast abscesses usually occur in women of childbearing age. About 10% to 30% of all breast abscesses occur after pregnancy, when nursing mothers breastfeed newborns. Nursing mothers may first develop a condition called mastitis, or inflammation of the breast's soft tissue. About 1 in 15 of these women can develop breast abscesses.

Blockage of nipple ducts because of scarring can also cause breast abscesses.

Breast abscesses are not inherited and cannot be passed from one person to another. They usually present no risk of infection to a newborn.

What Are the Symptoms of Breast Abscesses?

A painful, swollen, hot red mass on the breast is usual. Sometimes, drainage through the skin over the abscess or nipple duct opening may be present. Other symptoms include fever, chills, nausea, and vomiting. Sometimes, the nipple may be inverted (pointing inward), and the abscess can look like other conditions, such as breast cancer or an infected cyst.

How Are Breast Abscesses Diagnosed?

The doctor makes a diagnosis by means of a physical examination. The doctor may in some

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cases consult a general surgeon to cut, drain, and perform a biopsy of the area. In a biopsy, a small piece of breast tissue is taken for study under the microscope. Pus can be studied to identify the bacteria, which helps the doctor select the right antibiotic for treatment.

How Are Breast Abscesses Treated?

Antibiotics are the first therapy used. If mastitis is found early, antibiotic therapy may cure the problem without surgery. However, most women with a breast abscess will need an incision (cutting) and drainage. Complications of incision and drainage include formation of a new abscess, scarring of ducts, and formation of fistulas. A fistula is a passage leading from the abscess to the outside skin.

DOs and DON'Ts in Managing Breast Abscesses:

✓ **DO** remember that you can use warm, moist compresses on the infected breast tissue.

✓ **DO** remember that up to 40% to 50% of breast abscesses can come back.

✓ **DO** call your doctor immediately if you feel a lump or have redness or pain in your breast. Prompt diagnosis and treatment with antibiotics may prevent the need for surgery.

✓ **DO** call your doctor if you notice nipple inversion or drainage from your nipple.

✓ **DO** call your doctor if you have fever or chills.

✓ **DO** call your doctor if you have pain with breastfeeding.

⃠ **DON'T** forget to tell your doctor if you are allergic to penicillin or other drugs.

⃠ **DON'T** forget that good nipple hygiene if you're breastfeeding can prevent skin cracking

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and abrasions that can lead to mastitis and breast abscesses.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website:** http://www.acog.org
- American College of Surgeons Tel: (800) 621-4111

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MANAGING YOUR

BREAST CANCER

What Is Breast Cancer?

Breast cancer is one of the most common cancers in women in the United States. It's the second most common cause of cancer death in women, and the main cause in women 45 to 55 years old. The death rate has decreased in the past 20 years, partly because better screening catches the disease earlier, so chances of recovery and cure are higher.

What Are the Symptoms of Breast Cancer?

Early breast cancer usually causes no pain and usually no other symptoms.

As a breast tumor grows, certain changes may occur. These include a lump or thickening (mass, swelling, skin irritation, or distortion) in or near the breast or under the arms or changes in breast size or shape. The color or feel of the skin of the breast, areola, or nipple (dimpled, puckered, or scaly) can change. Women can also have discharge, erosion, inversion, or tenderness of nipples.

How Is Breast Cancer Diagnosed?

Many women (or doctors during the physical exam) feel a lump or finds breast changes. An abnormal mammogram can suggest breast cancer. Some women at high risk of getting breast cancer may get magnetic resonance imaging (MRI) for screening.

A lump shouldn't be ignored. Mammograms may not show breast cancers in nearly 20% of cases.

When cancer is suspected, the doctor will remove (biopsy) a small piece of abnormal area for study.

How Is Breast Cancer Treated?

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The doctor must stage the cancer. Staging determines how far it has spread, to decide on treatment and prognosis. The stage of the cancer is based on tumor size, whether skin, chest wall, and local lymph nodes (glands) are involved, and whether cancer has spread to other organs (metastasis). The biology of the cancer is based on the look of the cancer under the microscope and the tumor's protein and gene markers.

These things help doctors choose the treatment: surgery, radiotherapy, and medical therapies, such as antiestrogens, chemotherapy, or other biological or targeted therapies.

Most women have surgery to remove the cancer, such as lumpectomy (removing only the lump). Operations to remove the breast, part or whole, include partial (segmental), modified radical, radical, or total (simple) mastectomies. Lymph nodes and muscles may be removed. Radiation therapy, chemotherapy, or hormone therapy can be used before or after surgery. Breasts can be rebuilt after surgery.

Radiotherapy uses high-energy x-rays to kill cancer cells. Radioactive substances in needles, seeds, wires, or catheters can be put into or near the cancer.

Chemotherapy uses drugs to kill cancer cells or stop them from dividing. Drugs can be taken by mouth, injected into veins or muscles, or placed near cancer cells.

Hormone therapy (tamoxifen and aromatase inhibitors) stops hormones, especially estrogen, from helping cancer cells grow. Biological therapy works by using the body's immune (infection-fighting) system to kill cancer cells.

DOs and DON'Ts in Managing Breast Cancer:

✓ **DO** take medicines if suggested by your doctor.

✓ **DO** find local support groups to help you get through this challenging time.

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✓ **DO** visit your doctor regularly to monitor your progress.

✓ **DO** eat a diet with enough calories, or maybe supplemental drinks.

✓ **DO** get enough fluids.

⃠ **DON'T** smoke.

⃠ **DON'T** drink alcohol in excess.

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FOR MORE INFORMATION

Contact the following sources:

- American Cancer Society **Website: http://www.cancer.org**
- National Comprehensive Cancer Network **Website: http://www.nccn.org**
- Susan G. Komen Breast Cancer Foundation **Website: http://www.komen.org**

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MANAGING YOUR

BREAST CANCER: FOR MEN

What Is Breast Cancer?

Male breast cancer is rare. It accounts for about 1% of all breast cancers, with about 2000 cases diagnosed each year. It's most common in men 60 to 70 years old and most often occurs as a type of breast cancer known as infiltrating ductal carcinoma. Greater risk of having breast cancer is related to radiation exposure, high estrogen levels, and family history of breast cancer. Abnormal breast cancer genes (BRCA1 or BCRA2) can increase risk, as can liver disease, being overweight, and drinking alcohol in excess.

Survival for men is similar to that for women with the same cancer stage at diagnosis. Staging means finding out how much cancer spread. Men are often diagnosed at a later stage and may be less likely to be cured.

What Are the Symptoms of Breast Cancer?

Men usually have a breast lump that can be felt, the most common sign. It usually presents as a painless mass or swelling, just below the nipple or in the breast or chest wall. Changes near the nipple include skin ulcers, skin puckering or dimpling, redness or scaling of the nipple or skin, inversion (turning inward) of the nipple, and bloody or opaque nipple discharge.

Most breast lumps in males are not cancerous and are a sign of gynecomastia (swelling of breasts with age and obesity).

How Is Breast Cancer Diagnosed?

Men (or doctors) may feel a lump or see breast changes. Doctors may order mammography, ultrasonography, and biopsy. In a biopsy, cells are removed for study with a microscope. Tests may be done for hormone (estrogen, progesterone) receptors and a protein (HER2). In about 30%

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of cases, HER2 makes cancer cells grow.

Breast cancer in men is staged just as in women. For staging, doctors use x-rays, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and biopsy results.

How Is Breast Cancer Treated?

Surgery, usually lumpectomy or modified radical mastectomy, is the most common first treatment. With mastectomy, the breast, lymph nodes (glands), and sometimes chest wall muscles are removed. Lumpectomy involves removing the cancer and area surrounding it.

Chemotherapy, radiation therapy, and hormone therapy are also given, alone or together. Chemotherapy uses drugs to kill cancer cells or stop them from dividing. Hormone therapy stops hormones, especially estrogen, from helping cancer cells grow. Prognosis depends mainly on tumor stage, as in women, but men respond better than women to hormone therapy.

Radiotherapy uses high-energy x-rays to kill cancer cells.

Other treatments include monoclonal antibodies and biological therapy (immunotherapy). Monoclonal antibodies attack and block the HER2 protein and kill cancer cells. Biological therapy gets the body's immune (infection-fighting) system to kill cancer cells.

DOs and DON'Ts in Managing Breast Cancer:

✓ **DO** take medicines if suggested by your doctor.

✓ **DO** find local support groups to help you handle your disease.

✓ **DO** visit your doctor regularly.

✓ **DO** maintain a healthy body weight. Eat a diet with enough calories, or maybe use

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supplemental drinks.

✓ **DO** get enough fluids.

⃠ **DON'T** smoke.

⃠ **DON'T** drink alcohol in excess.

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NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Cancer Society **Website: http://www.cancer.org**
- National Comprehensive Cancer Network **Website: http://www.nccn.org**

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MANAGING YOUR

BREAST PAIN

What Is Breast Pain?

Mastodynia is the medical term for breast pain. Pain can be cyclic or noncyclic, depending on whether it occurs with each period (cyclic) or not. Cyclic pain usually occurs in young women who haven't gone through menopause (change of life). Noncyclic pain occurs more in women older than 40.

What Causes Breast Pain?

The many causes include fibrocystic breast disease; use of estrogen hormones; infection of the breast (mastitis); pregnancy; puberty; normal hormonal changes before puberty or menopause; breastfeeding; and drugs, including digoxin, cimetidine, spironolactone, and methyldopa.

It's not contagious or passed from one generation to another.

What Are the Symptoms of Breast Pain?

Cyclic pain appears to be related to female hormones (estrogen, progesterone, and prolactin). A dull ache is felt in the whole breast but more on the upper outer area next to the armpit. Pain starts when the ovary releases the egg, continues until the period begins, and stops at the end of the period. Pain usually affects both breasts but sometimes one breast will be more painful than the other.

Noncyclic pain usually affects only one breast and isn't related to periods. Usually a sharp, burning, or stabbing pain is felt in the middle, around the nipple area.

Breast pain rarely means breast cancer.

How Is Breast Pain Diagnosed?

The doctor makes a diagnosis from a medical history and breast examination.

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Also, the doctor may order mammography (a special x-ray examination of the breast). If the mammogram shows a lump, the doctor may order ultrasound (a test using sound waves to see whether the lump is solid or fluid-filled).

How Is Breast Pain Treated?

Treatment is conservative, including dietary limits (e.g., low-fat, low-cholesterol foods and less caffeine).

For most women with breast pain unrelated to breast cancer, pain stops on its own. Symptoms that interfere with normal daily activities can be helped with pain medicines such as antiinflammatory drugs (e.g., ibuprofen, naproxen).

DOs and DON'Ts in Managing Breast Pain:

✓ **DO** remember that breast cancer very rarely (<10%) causes breast pain.

✓ **DO** eat low-fat foods, free of hydrogenated fats such as those in margarine. Eat whole grains instead of processed grains.

✓ **DO** call your doctor if you feel a lump in your breast.

✓ **DO** call your doctor if you see a discharge from your nipple.

✓ **DO** call your doctor if you see irregular dimpling of the breast or nipple.

✓ **DO** call your doctor if you have fever, fatigue, or nausea.

✓ **DO** call your doctor if you have long-lasting breast pain.

⊘ **DON'T** wear tight or loose-fitting bras.

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⦸ **DON'T** use too much caffeine. Avoid foods that trigger breast pain. Avoid margarine, trans fats, and salt.

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FOR MORE INFORMATION

Contact the following source:

- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website:** **http://www.acog.org**

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MANAGING YOUR

BREECH BIRTH

What Is Breech Birth?

Breech birth, or breech presentation, means that the baby is in an abnormal position for birth. The normal position is head down. In abnormal positions, the buttocks or feet enter the birth canal so that they would be delivered first. The three types of breech presentations are frank, complete, and footling. In frank breech, the most common type (in 48% to 73% of births), the buttocks would come out first. The legs are straight up, with hips bent and feet near the head. In a complete breech (4.6% to 11.5% of births), the hips and knees are bent, with feet near the buttocks. In a footling (incomplete) breech (12% to 38% of births), legs are stretched out and the feet would come out first during delivery.

What Causes Breech Birth?

Causes include abnormal placentas, problems with the uterus, and masses in the pelvic area. These problems include fibroids, odd uterine shapes, and too much or too little amniotic fluid. Breech birth is more common when there are problems with the baby (such as Down syndrome), two or more babies, and prematurity.

What Are the Signs and Symptoms of Breech Birth?

There are generally no symptoms, however, if the baby is in a breech position, the health care provider may be able to hear heartbeats of the baby above the belly button (umbilicus).

How Is a Breech Birth Diagnosed?

The health care provider makes a diagnosis from the medical history and physical examination. The health care provider's hands placed on the mother's lower abdomen (belly) can locate the baby's head, back, and buttocks. Ultrasonography will be used to confirm the diagnosis.

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How Is a Breech Birth Treated?

Health care providers can sometimes turn babies into the head-down position before labor starts. The procedure to do this is called external cephalic version. Usually, cesarean delivery is safest for breech babies. Cesarean section is needed for foot-ling presentations or for a baby whose head is too far back (hyperextended). It's also needed when labor isn't progressing normally, a baby's status isn't stable, the baby's weight is very low or high, or the mother's pelvis isn't big enough.

Vaginal delivery for breech birth can be dangerous. Only obstetricians who have training in vaginal breech deliveries should do these deliveries. Other requirements for vaginal deliveries to be attempted include normal birth weight, frank breech position, normal head position, normal progress of labor, continuous fetal monitoring, and informed consent. An immediate cesarean section must be possible if needed.

DOs and DON'Ts in Managing a Breech Birth:

✓ **DO** remember that the mortality rate for breech babies is increased 13 times. There may be more congenital anomalies, low oxygen levels, birth injury, and prematurity.

✓ **DO** talk to your health care provider about exercises to do at home that may help turn the baby to the head-first position.

⃠ **DON'T** miss appointments with your obstetrician.

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FOR MORE INFORMATION

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MANAGING YOUR

BRONCHIECTASIS

What Is Bronchiectasis?

In the lungs, cartilage and muscle support and keep the shape of the airways. Constant irritation of the structures supporting the airways destroys them, causing the airways to get bigger. Bronchiectasis is inflammation (swelling) and widening of lung airways.

Bronchiectasis is not contagious.

What Causes Bronchiectasis?

Severe infection with virus or bacteria, blocked airways, and poor clearing of lung secretions are common causes. Smoking, chronic bronchitis, cystic fibrosis, tuberculosis, pneumonia, and lung cancer increase the chance of getting this disease.

What Are the Symptoms of Bronchiectasis?

People have persistent cough with discolored bad-smelling sputum (lung secretions), wheezing, shortness of breath, tiredness, problems sleeping, and weight loss. Often, sputum contains streaks of blood. Fever may be present.

How Is Bronchiectasis Diagnosed?

Your doctor makes the diagnosis by checking symptoms and ordering tests such as studies of sputum, chest x-rays, lung function tests, and computed tomography (CT). A sputum sample may help tell which organisms are causing the disorder and which antibiotic to use. CT allows the doctor to look at the size of the airways. Bronchoscopy (a test allowing doctors to look into lungs through a lighted tube) may also help diagnosis and help remove mucus plugs.

How Is Bronchiectasis Treated?

Treatment may be medical or surgical. Medical treatment involves chest physical therapy, inhal-

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ers, and antibiotics. Physical therapy uses changes in posture for better drainage of secretions from lungs. Inhalers allow increased airflow through lungs and help clear secretions. Antibiotics reduce inflammation by killing bacteria that infected the airways.

For severe problems that don't respond to other treatments, surgery to remove affected parts of the lung is an option for certain people.

Some people gain back much lung function, but others such as those with bronchiectasis due to cystic fibrosis may have a disease that gets worse and can lead to death.

DOs and DON'Ts in Managing Bronchiectasis:

✓ **DO** make sure that you follow directions for your medicines. They are an important part of helping your lungs work well.

✓ **DO** chest physical therapy to allow your lungs to heal faster so you breathe easier. It is often time-consuming but plays an important role.

✓ **DO** get pneumococcal pneumonia vaccination and flu shots.

✓ **DO** drink lots of water to loosen lung secretions.

✓ **DO** exercise regularly and in moderation. Good exercises are walking, running, swimming, aerobics, and dancing. Exercise helps clear lung secretions.

✓ **DO** call your doctor if treatment doesn't help your symptoms.

✓ **DO** call your doctor if your cough or amount of sputum suddenly increases or if you have a fever.

✓ **DO** call your doctor if you cough up large amounts of blood.

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⦸ **DON'T** smoke. Quitting may slow progression of the disease and help symptoms.

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FOR MORE INFORMATION

Contact the following source:

• American Lung Association Tel: (800) LUNG-USA (586-4872) **Website:**

http://www.lungusa.org

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MANAGING YOUR

BRUXISM

What Is Bruxism?

Bruxism refers to the habit of grinding, clenching, or gnashing the teeth. People usually do this at night while they sleep. People who grind and clench their teeth are called bruxers. Most people don't know that they grind their teeth.

Nearly half of adults in the United States grind their teeth at night. About 20%, or more than 40 million people, grind their teeth enough so that normal dental anatomy is destroyed. Bruxism can lead to jaw disorders, headaches, and other problems. It most often occurs in adults older than 25 years. Children can also have it but it usually goes away on its own, before teeth are hurt. Bruxism affects men and women equally.

What Causes Bruxism?

No specific cause is known. However, bruxism can be related to stress, upper respiratory infections, allergies, earaches, and some medicines. Many people with bruxism also bite their fingernails or the inside of their cheeks.

What Are the Symptoms of Bruxism?

Symptoms include headaches, earaches, clicking or popping sounds of the jaw with chewing, and sensitive teeth. Loss of enamel, flattened and worn out tooth surfaces, loss of fillings, or fractured or chipped teeth can occur. People can have tongue indentations. Untreated bruxism can lead to abnormal jaw function, chronic jaw pain, and loss of teeth.

How Is Bruxism Diagnosed?

The dentist makes a diagnosis from the medical history and dental examination. Because people don't know that they grind their teeth, they usually don't get diagnosed until other symptoms

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occur. No specific blood tests or X-ray studies can diagnose bruxism. However, the health care provider may want them to rule out other causes of symptoms.

How Is Bruxism Treated?

Treatment aims to prevent more damage to the teeth. A night guard is usually suggested. A night guard is a plastic mouthpiece that is custom fitted by the dentist. It absorbs the force of grinding. Teeth grinders thus wear out the plastic mouthpiece and not their teeth.

People with tight jaw muscles can apply warm compresses to the face. Massage therapy may relieve symptoms. Sometimes, the dentist may prescribe a muscle relaxant to loosen tense jaw muscles.

Biofeedback and psychiatric treatment related to stress and anger management may be tried.

DOs and DON'Ts in Managing Bruxism:

✓ **DO** understand that anger, pain, irritation, and frustration can trigger bruxism. Certain personality types, including competitive, overachieving, rushed, and aggressive people, have higher risks for developing bruxism.

✓ **DO** get counseling for depression, anger, or stress management.

✓ **DO** call your health care provider if you have sensitive teeth, headaches, or earaches. Call if your significant other tells you that you grind your teeth in your sleep.

✓ **DO** call your health care provider if you need a referral to an oral surgeon or dentist.

✓ **DO** call your health care provider if you suffer from depression or anxiety.

⃠ **DON'T** miss appointments with your health care provider. It's important to make sure that you don't have other diseases that cause similar symptoms.

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⦸ **DON'T** miss appointments with your dentist. It's important to find out the amount of damage and to prevent further damage to your teeth.

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FOR MORE INFORMATION

Contact the following sources:

- Academy of General Dentistry Tel: (312) 440-4300 **Website: http://www.agd.org**
- American Dental Association Tel: (312) 440-2500 **Website: http://www.ada.org**

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MANAGING YOUR

BUDD-CHIARI SYNDROME

What Is Budd-Chiari Syndrome?

Blockage of the hepatic vein, which is the major vein that leaves the liver, leads to a condition in which blood enters but has difficulty leaving the liver. This rare condition is called the Budd-Chiari syndrome. It occurs equally in men and women, usually in people 30 to 50 years old.

What Causes Budd-Chiari Syndrome?

Any condition that can lead to excessive blood clotting can cause this syndrome. Some such diseases are blood disorders such as polycythemia vera and antiphospholipid syndrome. Inherited protein deficiencies can lead to a greater tendency of blood to clot (hypercoagulable state) and can affect the liver circulation. Oral contraceptives, pregnancy, infections, collagen vascular disorders, and liver, kidney, and adrenal tumors can increase the risk of this syndrome. Infections include tuberculosis and amebic abscess. Collagen vascular disorders include systemic lupus erythematosus, sarcoidosis, and inflammatory bowel disease.

This syndrome isn't contagious or passed on from parents to children.

What Are the Symptoms of Budd-Chiari Syndrome?

Symptoms may include pain in the abdomen (belly), ascites (fluid in the abdomen), and a large liver. Ankle swelling, icterus (yellow color of whites of the eyes), and enlarged spleen occur. Untreated people develop liver damage and complications from liver failure. These complications are hepatic encephalopathy, bleeding from varicose veins in the esophagus, and kidney failure.

How Is Budd-Chiari Syndrome Diagnosed?

The health care provider makes a diagnosis from the medical history, physical examination,

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blood tests, and imaging studies. These studies include ultrasonography and magnetic resonance imaging (MRI). In some cases, paracentesis or liver biopsy is needed. In paracentesis, the health care provider puts a needle into the abdomen to take out fluid for study. In a liver biopsy, the health care provider takes a piece of liver tissue to check abnormalities with a microscope.

How Is Budd-Chiari Syndrome Treated?

Treatment is surgery to take blood around the blocked hepatic vein into the larger vein called the inferior vena cava. Sometimes, a balloon catheter may be put into the hepatic vein to open it. People with end-stage liver failure may be candidates for liver transplantation.

Medical treatment can give people short-term relief. A blood thinner, warfarin, helps prevent clotting in other veins. In some cases, balloon angioplasty and clot-busting medicines such as urokinase can be tried to remove a clot from the hepatic vein.

DOs and DON'Ts in Managing Budd-Chiari Syndrome:

✓ **DO** understand that in about one-third of cases, no cause can be found.

✓ **DO** realize that if the syndrome isn't treated, less than one-third of people survive 1 year.

✓ **DO** realize that specialists (hematologist, gastroenterologist, surgeon) can be involved in care.

✓ **DO** call your health care provider if you have abdominal pain and bloating, ankle swelling, or jaundice (yellow skin).

✓ **DO** call your health care provider if you need referrals to specialists.

✓ **DO** call your health care provider if you see blood in your stool (bowel movement) or black,

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tarry stool.

✓ **DO** call your health care provider if you notice confusion, lethargy, or slurred speech.

⃠ **DON'T** forget that the earlier the diagnosis, the better the prognosis.

⃠ **DON'T** forget to take your medicines, especially warfarin. It prevents more blood clots.

⃠ **DON'T** use any medicines (including over-the-counter and herbal products) without first asking your health care provider.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Gastroenterologists Tel: (703) 820-7400 **Website:** **http://www.acg.gi.org**
- American Liver Foundation Tel: 800-465-4837 **Website:** **http://www.liverfoundation.org**

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MANAGING YOUR

BULIMIA

What Is Bulimia?

Bulimia is an eating disorder. People, usually young women, have an abnormal fear of being overweight and make themselves vomit or take drugs to lose weight. However, most bulimics aren't overweight. They often can't stop eating and secretly eat large amounts of food in a short time, which is called binge eating. Forced vomiting, fasting, and heavy exercise to lose weight follow binge eating. It can be treated, but most people need treatment for several years.

Bulimia is similar to another eating problem, anorexia, but in anorexia, binge eating doesn't occur.

What Causes Bulimia?

The cause is unclear. The disorder is more common in adolescent girls and young adult women. A personal or family history of obesity and depression appears to be a risk factor, as does society's focus on slimness. It occurs more often in people in certain jobs (e.g., modeling) and sports (e.g., running).

What Are the Symptoms of Bulimia?

Symptoms include binge eating, forced vomiting, dieting, eating in secret, fasting, guilt (after eating), nervousness, sadness, stomach pain, tooth decay, and weakness. Others are dehydration, menstrual problems, an enlarged stomach, and slowed stomach emptying.

How Is Bulimia Diagnosed?

After taking a medical history, the doctor does a physical examination, with special attention to feelings and eating habits. The doctor makes a diagnosis on the basis of episodes of binge eating and how often they occur. After overeating, people avoid gaining weight by vomiting or abusing

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laxatives. Overeating episodes occur at least twice a week for 3 months and are associated with behaviors to avoid weight gain. People are also too concerned with how they look.

The doctor may order electrocardiography (ECG) and blood tests to check for abnormalities of potassium, magnesium, and other chemicals that may be low due to vomiting and that can cause irregular heartbeat. The doctor may also suggest seeing a specialist in eating problems and a dentist (too much vomiting can damage teeth). Bulimics can also have other psychological disorders.

How Is Bulimia Treated?

The treatment goal is to reduce and then end binge eating and behaviors for losing weight, as well as change the basis of self-esteem. People usually admit that they have a problem, which helps treatment. Most often, treatment combines cognitive (deals with abnormal thinking) and behavioral (to change behaviors) therapy. Drugs, especially antidepressants, can also be given.

DOs and DON'Ts in Managing Bulimia:

✓ **DO** be open with your family and doctor about your feelings, eating, forced vomiting, and fasting.

✓ **DO** stay close to friends who support and understand you.

✓ **DO** follow your doctor's directions.

✓ **DO** tell your doctor about other medical problems and medicines you take.

✓ **DO** tell your doctor if you're pregnant.

✓ **DO** eat at regular times.

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✓ **DO** reduce stress.

✓ **DO** call your doctor if you notice physical problems related to bulimia or if you feel urges to overeat or binge and cannot control them.

⃠ **DON'T** stop taking medicine or change your dose because you feel better unless your doctor tells you to.

⃠ **DON'T** eat alone.

⃠ **DON'T** take prescription or over-the-counter drugs or exercise without getting your doctor's OK.

⃠ **DON'T** overdo exercise.

⃠ **DON'T** make yourself vomit.

⃠ **DON'T** take diet pills or illegal drugs or drink alcohol in excess.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

• National Eating Disorders Association Tel: (800) 931-2237 **Website:** **http://www.nationaleatingdisorders.org/**

• National Mental Health Association Tel: (703) 684-7722, (800) 969-6642 **Website:** **http://www.nmha.org/**

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MANAGING YOUR

BULLOUS PEMPHIGOID

What Is Bullous Pemphigoid?

Bullous pemphigoid is a chronic disease of the skin and mucous membranes. It usually starts as red wheals or swellings (urticaria, or hives). It changes over weeks to months to bullae (large blisters). It can last for a long time or can come back after it goes away. It affects men and women equally, usually those older than 60 years. Children may also have it.

What Causes Bullous Pemphigoid?

In this autoimmune disorder, the body's own immune system attacks normal parts of the body. This condition may be hereditary but isn't infectious or cancerous.

What Are the Symptoms of Bullous Pemphigoid?

Blisters are tense and oval or round. They may start on normal skin or red wheals. They may burst and cause ulcers or sores of the skin and mucous membranes of the mouth, throat, anus, and vagina that may hurt. Itching can occur. Usually, lower legs, armpits, inner thighs, abdomen, and forearms have the lesions.

Ulcers can get infected with bacteria, especially if they're scratched.

How Is Bullous Pemphigoid Diagnosed?

The health care provider makes a diagnosis from the medical history and skin examination. The health care provider checks the look of the lesions, tests skin samples, and in some cases, does blood tests. A skin biopsy is often done to confirm the diagnosis. A biopsy involves taking a small piece of skin for additional tests.

How Is Bullous Pemphigoid Treated?

Treatment depends on where and how severe the lesions are. It involves general measures and

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medicines.

General measures include having good skin hygiene and preventing skin injury, including scratching. These measures can avoid infections. People who get depressed or have trouble coping with the disorder may need psychological counseling.

The health care provider may prescribe medicines to help inflammation (redness, swelling) and symptoms. They include topical steroid creams, lotions, and ointments. To reduce the risk of side effects, use only the prescribed dosage. Corticosteroids and immunosuppressive drugs are also used, sometimes together.

Mouth or throat lesions can cause pain with eating or swallowing. A liquid or soft diet may be needed.

Cleaning and checking lesions are important to prevent infections.

DOs and DON'Ts in Managing Bullous Pemphigoid:

✓ **DO** take your prescribed medicines. Tell your health care provider about all your other medicines, including over-the-counter.

✓ **DO** eat a nutritious diet. Liquid or soft diets can help pain with eating or swallowing.

✓ **DO** use good skin hygiene to avoid bacterial infections.

✓ **DO** check your skin for healing. Watch for symptoms of infection: redness, pus, pain or swelling of skin lesions or lymph nodes, and fever.

✓ **DO** wash clothing, towels, and linens often if you have oozing, crusting, or infected lesions.

✓ **DO** call your health care provider if you have symptoms of infection, worsening lesions, or

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new lesions or new symptoms.

✓ **DO** call your health care provider if you have fever, lethargy, confusion, or weakness.

⃠ **DON'T** stop your medicine or change the dose without asking your health care provider.

⃠ **DON'T** take more than the prescribed doses of medicines.

⃠ **DON'T** use potent topical steroids on the face or genitals. These areas can be sensitive.

⃠ **DON'T** stop steroids or immunosuppressants suddenly. This may cause serious problems, including severe weakness, fatigue, and low blood pressure.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Dermatology Tel: (847) 330-0030 **Website: http://www.aad.org**

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MANAGING YOUR

BUNDLE BRANCH BLOCK

What Is Bundle Branch Block?

Many types of blocks of electrical signals occur in the heart. The heart has two bundle branches to carry electrical signals. The right and left bundles carry signals that cause the right and left ventricles (lower chambers of the heart) to contract. Signals start at the sinus (sinoatrial, or SA) node of the heart and spread through the atria (upper chambers) to the bundle of His and then to the bundle branches. Bundle branch block (BBB) is a delay of transmission of these signals from the upper heart chamber (atrium). These signals go through the bundle of His but are then blocked. The block can affect either the left or right side of the heart. The atria contract normally, but because the ventricles don't receive the signal at the same time, the timing of contraction is affected.

BBB cannot be prevented.

What Causes BBB?

About half of cases have no known cause. Most people have some type of heart disease. They may have had damage to the heart from a heart attack (myocardial infarction), myocarditis (inflammation of heart muscle), or rheumatic fever (bacterial infection). Also, excessive doses of certain medicines or congenital heart abnormality (present at birth) may be the cause.

What Are the Symptoms of BBB?

Most patients do not have any symptoms. Symptoms, when present, are related to not enough blood being pumped by the heart. Dizziness, fainting, angina (chest pain), or stroke (not enough blood flow to the brain) can occur in severe cases when there are other abnormalities present.

How Is BBB Diagnosed?

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The doctor diagnoses BBB with electrocardiography (ECG), a test that measures the heart's electrical activity.

How Is BBB Treated?

People without symptoms and heart disease need no treatment. People can exercise as tolerated (after checking with the doctor) and should have a healthy heart lifestyle.

People with symptoms and other heart rhythm abnormalities may have a pacemaker inserted. A pacemaker is an electrical device with a wire connected to the heart muscle to signal the ventricles to contract more regularly or faster (in response to more activity). Pacemakers can be outside the body, with the wire entering through a vein, or can be put inside the body. Newer pacemakers are safe and reliable. Still, strong magnetic or ultrasonic forces such as those used in physical therapy settings or airport security screening should be avoided.

DOs and DON'Ts in Managing BBB:

✓ **DO** take medicines as directed.

✓ **DO** eat a low-fat and low-cholesterol diet.

✓ **DO** stop smoking.

✓ **DO** exercise as directed by your doctor if you have a pacemaker that will adjust to increased activity.

✓ **DO** call your doctor if you have dizziness, fainting, chest pain, or shortness of breath.

⊘ **DON'T** ignore worsening symptoms.

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FOR MORE INFORMATION

Contact the following source:

- American Heart Association Tel: (800) 242-8721 **Website:**

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MANAGING YOUR

BURNS

What Are Burns?

Thermal burns are injuries to the skin (and deeper structures) caused by too much heat or certain types of light. Intense heat for a short time (e.g., hot grease) and low heat or light over long times (e.g., heating pads or sun) produce burns. The depth of tissue injury determines burn severity. Thermal burns are usually classified as first, second, and third degree. Fourth-degree burns extend into the muscle below the skin. Electricity and chemicals such as acids and alkali may also cause burns. Chemical burns are more complicated and hard to classify. Electrical burns may be deep enough to reach muscles and bones and are sometimes called fourth-degree (black or char) burns.

What Causes Burns?

Burns can be caused by fire, steam, electricity, sun, chemicals, and hot liquids or objects.

What Are the Symptoms of Burns?

Symptoms vary with the degree of damage to body tissues. First-degree burns produce painful, red areas in the surface (superficial) skin, but no blisters. Second-degree burns affect deeper skin, with blisters and light charring, and are very painful. Third-degree burns damage the whole skin depth, so the skin looks pale, charred, and leathery. These burns aren't painful because the nerves in the burned area have been damaged.

How Are Burns Diagnosed?

The diagnosis is made by examining the skin. Symptoms will help determine the degree of burn.

How Are Burns Treated?

Small first-degree burns may not require any treatment. Putting the burned area in cold water

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(not ice) or using wet compresses can reduce pain and swelling of minor burns. Breaking blisters can cause infection, so this should be avoided. Using aloe vera and acetaminophen or ibuprofen can help pain. Protection with dressings and antibiotic ointment may prevent infection.

Medical evaluation and treatment is needed for: (1) second-degree burns larger than the person's palm; (2) any second-degree burns of hands, feet, face, or genitals; and (3) second-degree burns anywhere on infants. All third- and fourth-degree burns (which are life-threatening) need a doctor's immediate care. A doctor should always see chemical burns.

The doctor will gently remove dead skin layers (débridement), change dressings, and watch for infections. Some severe burns need specialized treatment, including surgical grafting of skin and use of special pressure garments, at special centers.

For severe burns, call 911 for help.

DOs and DON'Ts in Managing Burns:

✓ **DO** change your dressing and apply fresh antibiotic ointment at prescribed times.

✓ **DO** use pain medicines as directed.

✓ **DO** drink extra fluids and eat a healthy diet.

✓ **DO** keep follow-up doctor appointments.

✓ **DO** call your doctor if you have fever; chills; increasing pain; or pus, foul odor, or red streaking from your wound.

✓ **DO** call your doctor if you have a reaction to medicine.

✓ **DO** practice fire safety: wear protection, fireproof your home and business, and teach chil-

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dren safety rules.

⃠ **DON'T** ignore second-degree burns.

⃠ **DON'T** put butter on burns.

⃠ **DON'T** let bandages become dirty or wet.

⃠ **DON'T** exercise or return to work until your doctor says to.

⃠ **DON'T** expose healing burns to sunlight (increases scarring).

⃠ **DON'T** try to peel dead skin layers.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- Burn Survivor Resource Center Tel: (800) 669-7700 **Website:** **http://burnsurvivor.com/survivorlinks.html**
- American Burn Association **Website:** **http://www.ameriburn.org**
- American College of Emergency Physicians **Website:** **http://www.acep.org**

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MANAGING YOUR

BURSITIS

What Is Bursitis?

Bursitis is inflammation (swelling, redness) of a fluid-filled sac called a bursa. Bursae are found in many parts of the body, usually where muscles and tendons move over bones. Tendons are tough bands of tissue that connect muscles to bones. Bursae help this motion by providing a gliding surface. Bursae are found in and around shoulders, elbows, hips, knees, and feet.

Bursitis can become frustrating. It tends to return, even after treatment, unless the activity causing it is stopped or changed.

What Causes Bursitis?

Injuries from too much use and continued irritation are usual causes. Direct trauma, disorders such as rheumatoid arthritis and gout, and puncture wounds followed by infection may also cause bursitis.

What Are the Symptoms of Bursitis?

Pain with swelling, redness, and tenderness are usual symptoms. Pain usually worsens with pressure against the affected muscle.

How Is Bursitis Diagnosed?

The doctor will diagnose bursitis on the basis of the medical history and physical examination. The doctor may also want x-rays to help rule out other causes of pain, such as a stress fracture.

How Is Bursitis Treated?

RICE (***R***est, ***I***ce, ***C***ompression, ***E***levation) is effective. Resting means stopping the activities for at least 2 weeks. Immobilizing the area with a splint or cast for 7 to 10 days sometimes works. Ice is placed on the area to reduce swelling and relieve pain. Antiinflammatory medications such

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as aspirin, ibuprofen, and naproxen can manage mild to moderate bursitis. Prescription antiinflammatory drugs are for severe bursitis that didn't respond to other treatments and for extreme pain.

Aspiration, or removing fluid from the bursa, can provide temporary relief and gives the doctor a chance to study the fluid for infection or gout. The fluid may return, however, which may lead to repeated aspiration and possible infection. Steroid injections can sometimes give relief. Infected tissue may need antibiotics or an operation to remove the tissue.

A physical therapist, occupational therapist, or athletic trainer may help retraining for activities to minimize the bursitis. Substituting other exercises for those that cause symptoms is important.

DOs and DON'Ts in Managing Bursitis:

✓ **DO** take over-the-counter anti-inflammatory medicines (aspirin, ibuprofen, naproxen) as directed for mild to moderate bursitis. You may need prescription anti-inflammatory drugs for severe symptoms.

✓ **DO** stop the problem activity and allow the area to rest for at least 2 weeks. Immobilizing the area may speed recovery.

✓ **DO** substitute the problem activity with those that don't cause symptoms.

✓ **DO** return to activity gradually, as long as you have no pain.

✓ **DO** call your doctor if usual treatments don't work. Your doctor should rule out other more dangerous conditions.

✓ **DO** wear protective gear for contact sports.

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✓ **DO** keep to your ideal body weight, avoid strenuous exercises, and don't be a "weekend warrior."

✓ **DO** avoid repeated movements.

⦸ **DON'T** return to activity too soon or too suddenly. Six weeks is the usual time needed for inflammation to stop.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Occupational Therapy Association Tel: (301) 652-2682 **Website:** **http://www.aota.org**
- American College of Rheumatology Tel: (404) 633-3777 **Website:** **http://rheumatology.org**

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MANAGING YOUR

CANDIDIASIS

What Is Candidiasis?

Candidiasis is infection with a type of fungus, a yeast called *Candida*. Candidiasis can occur in genital areas, mouth, skin folds, or nails. In the vagina, candidiasis is called yeast vaginitis. In the mouth, candidiasis is called thrush. Diaper rash in babies is often due to candidiasis.

What Causes Candidiasis?

Anyone can get candidiasis. *Candida* fungi normally live on the skin and are harmless. Too much moisture favors overgrowth of the fungus and can lead to infection. Pregnancy, diabetes mellitus, weak immune system, and certain medicines such as antibiotics and corticosteroids can increase chances of infection.

What Are the Symptoms of Candidiasis?

Women with vaginal candidiasis have intense itching in the vagina. Burning during urination, white patches on the vagina surface, and an odorless, cottage cheese–like liquid coming from the vagina may occur.

Mouth candidiasis causes raised white patches inside the mouth or on the tongue, splitting or cracking on the side of the mouth, and swollen gums or red and white sores on the gums.

Nail candidiasis causes swelling around nails and separation between nails and cuticles, pain around the nail base, and yellow or blackish-brown nails.

Skin with candidiasis may itch, look moist, and appear irritated.

How Is Candidiasis Diagnosed?

The doctor will use a swab to take samples from the affected area, such as the genitals or mouth, or will take scrapings from the nail and send them to a laboratory for diagnosis.

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How Is Candidiasis Treated?

The doctor will prescribe antifungal medicine (pills, ointment, vaginal cream, suppositories, powder, or spray). The doctor may want to treat partners with genital candidiasis to avoid spreading the infection. Wear loose cotton clothing to keep your skin cool and dry.

Genital candidiasis will clear up in 4 to 7 days. Mouth and skin candidiasis will clear up in 1 or 2 weeks. Nail candidiasis often needs longer treatment.

DOs and DON'Ts in Managing Candidiasis:

✓ **DO** keep your genital area clean and wear cotton, loose-fitting underpants if you have genital candidiasis. Lose weight if needed, and don't use harsh chemicals such as douches. Practice safe sex (use condoms).

✓ **DO** avoid oral sex if you have mouth candidiasis.

✓ **DO** dry your hands well after washing if you have nail candidiasis. Don't soak your hands in water.

✓ **DO** change the baby's diaper often and keep the area dry for diaper rash.

✓ **DO** keep your skin clean and dry.

✓ **DO** make sure that your diabetes is controlled.

✓ **DO** take antibiotics only when prescribed by your doctor.

✓ **DO** call your doctor if the infection continues despite treatment.

⃠ **DON'T** wear tight panty hose or have intercourse until the infection clears up if you have

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genital candidiasis.

⦸ **DON'T** put rubber pants on your baby. It will increase the risk of diaper rash.

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FOR MORE INFORMATION

Contact the following sources:

- The American College of Obstetricians and Gynecologists **Website:** **http://www.acog.org**
- Obgyn.net **Website:** **http://www.obgyn.net**
- American Academy of Dermatology Tel: (866) 503-SKIN (503-7546) **Website:** **http://www.aad.org**

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MANAGING YOUR

CARBON MONOXIDE POISONING

What Is Carbon Monoxide Poisoning?

Carbon monoxide (abbreviated as CO) is a colorless, odorless, toxic gas that doesn't irritate the skin or eyes. CO in air is breathed in and easily absorbed through lungs. It is better than oxygen in binding with hemoglobin in red blood cells. Hemoglobin is the iron-containing protein in these cells that carries oxygen to body tissues. This means that when too much carbon monoxide is in the environment, less oxygen gets to tissues, especially organs needing the most oxygen, such as the brain and heart.

CO poisoning accounts for almost 4000 deaths yearly in the United States. Exposures may be accidental (less often) or on purpose (suicide attempts).

What Causes Carbon Monoxide Poisoning?

CO is produced by incomplete burning of fuels. Sources include furnaces, motor vehicle exhaust fumes, wood stoves, kerosene heaters, and gas heaters. Even cigarette smoking causes a higher CO level in the bloodstream.

What Are the Symptoms of Carbon Monoxide Poisoning?

The most common symptom is headache. Others include nausea, weakness, dizziness, difficulty concentrating, chest pain, shortness of breath, and visual problems. Most common physical problems include cherry-red lips, bluish hands and feet, bleeding in the back of the eye (retina), and mental changes including confusion, lethargy, and coma.

How Is Carbon Monoxide Poisoning Diagnosed?

Symptoms can mimic other diseases. A blood test for carboxyhemoglobin (the form of hemoglobin bound to CO) can give CO concentrations in blood. The doctor can order other tests.

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How Is Carbon Monoxide Poisoning Treated?

First, people must be removed from the source of CO (e.g., defective appliances, house fire). Then, 100% oxygen is immediately given to compete for binding sites in hemoglobin and to improve oxygen delivery to the oxygen-deprived tissues. Oxygen is given until the level of carboxyhemoglobin in blood is zero. In severe cases, a mechanical ventilator may be used to deliver oxygen.

Another treatment is hyperbaric oxygen therapy. It increases the amount of oxygen dissolved in blood. Hyperbaric oxygen chambers are for certain people, such as those with a carboxyhemoglobin level higher than 40%, those in a coma or unconscious, and pregnant women with a CO level higher than 15%.

DOs and DON'Ts in Managing Carbon Monoxide Poisoning:

✓ **DO** remember that the best treatment is prevention. Avoid enclosed garages with running vehicles. Have furnaces, gas appliances, fireplaces, and heaters inspected and maintained properly.

✓ **DO** install CO alarms in your home and office.

✓ **DO** call your doctor if you think that you or someone else had exposure to CO or if you have symptoms of CO poisoning.

⃠ **DON'T** smoke. Smoking only increases the CO level in your system and leads to other medical problems.

⃠ **DON'T** use outdoor gas grills inside buildings.

⃠ **DON'T** work in a closed garage on a vehicle that is running. It only takes 10 minutes before

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life-threatening concentrations of CO build up in your body.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- Consumer Product Safety Commission Tel: (800) 638-2772
- Medline Plus Website:

  http://www.nlm.nih.gov/medlineplus/carbonmonoxidepoisoning.html

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MANAGING YOUR

CARCINOID SYNDROME

What Is Carcinoid Syndrome?

Carcinoid syndrome is a disorder that occurs when small tumors (carcinoid tumors) make chemicals that get into the bloodstream. The chemicals cause various symptoms. These slow-growing tumors are mainly found in the gastrointestinal tract or lungs (bronchi). They occur in the appendix (most often); small bowel (20%); rectum (15%); bronchi (12%); esophagus, stomach, and colon (10%); and ovary, biliary tract, and pancreas (3%). People usually find out about the disorder when the tumors are very advanced and cause symptoms. This syndrome is rare and occurs in about 3 in 100,000 people.

What Causes Carcinoid Syndrome?

Carcinoid tumors can make chemicals called serotonin, bradykinin, and histamine. Tumors grow from special cells called neuroendocrine cells. The cause of the tumors isn't clear.

What Are the Symptoms of Carcinoid Syndrome?

The main symptoms are skin flushing (75% to 90%), diarrhea, breathing problems, facial skin lesions, and at times, rapid heartbeat. Red-purple flushes usually start in the face and spread to the neck and upper trunk. Flushing lasts from a few minutes to hours. Flushes that last longer may be related to bronchial carcinoids. Emotion, alcohol, or foods may trigger flushes, but flushes may occur without warning. Dizziness, fast heartbeat (tachycardia), and low blood pressure (hypotension) may occur with flushing. Diarrhea occurs in more than 70% of people. It's often related to bloating of the abdomen (belly). Breathing problems include contraction of smooth muscles in the bronchi (bronchospasm). The result is shortness of breath and wheezing.

How Is Carcinoid Syndrome Diagnosed?

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The health care provider makes a diagnosis from the medical history, physical examination, chest X-rays, computed tomography (CT) of the abdomen, and laboratory tests. These tests measure levels of the chemicals produced by the tumor. Some foods and drugs can cause false higher levels. Bananas, pineapples, eggplant, avocados, and walnuts can do this. Drugs that can cause false elevations include acetaminophen, caffeine, guaifenesin, and reserpine. Before this test, people must have a restricted diet and avoid these drugs. Special tests may include using radioactive iodine to label somatostatin to find tumors. The health care provider may suggest seeing a specialist such as an endocrinologist and endocrine surgeon.

How Is Carcinoid Syndrome Treated?

Treating the syndrome means treating the tumor. Surgery may be done to remove the tumor. If surgery can't remove widespread tumors, medicines may shrink tumors and control symptoms. These drugs include octreotide and interferon alfa. Hepatic artery embolization and heating or freezing tumor cells may be treatment options in some patients.

DOs and DON'Ts in Managing Carcinoid Syndrome:

✓ **DO** avoid alcohol. It may cause flushing.

✓ **DO** eat a well-balanced diet. Avoid large meals, which can trigger flushing.

✓ **DO** keep track of what triggers flushing and avoid those triggers.

✓ **DO** learn as much as you can about your illness.

✓ **DO** find a support group if you think that would help.

⃠ **DON'T** ignore symptoms. Call your health care provider if your symptoms don't improve or get worse with treatment. Call if you have new symptoms.

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- ⦸ **DON'T** stop taking your medicine or change the dosage because you feel better unless your health care provider tells you to.
- ⦸ **DON'T** use any medicines (including over-the-counter and herbal products) without first asking your health care provider.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Association of Clinical Endocrinologists Tel: (904) 353-7878 **Website: http://www.aace.com**
- American Gastroenterological Association Tel: (301) 654-2055 **Website: http://www.gastro.org**
- American Society of Clinical Oncology Tel: (703) 299-0150 **Website: http://www.asco.org**

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MANAGING YOUR

CARDIAC PACEMAKER AND DEFIBRILLATOR

What Are Cardiac Pacemakers and Defibrillators?

Pacemakers are small electric devices, about the size of a pocket watch. They are put under the skin below the collarbone near the heart. Implantable cardioverter-defibrillators (ICDs) are also small, pager-sized devices. They're also put below the skin on the left side of the chest. Both devices control abnormal heartbeats (arrhythmias). Pacemakers send signals to the heart to speed up a slow beat. One-chamber pacemakers have one wire connected to the heart. Two-chamber pacemakers have wires to both top and bottom heart chambers (atria and ventricles). Another kind, biventricular, stimulates both bottom chambers. ICDs send electric shocks to the heart to make the heart rhythm normal.

Pacemakers and ICDs have two parts: a pulse generator (including battery and computer) and wires connecting the device and heart.

Who Needs Cardiac Pacemakers and Defibrillators?

Almost all pacemakers are used for slow heartbeats (bradycardia, heart block). These abnormal heartbeats are caused by aging, heart disease, or medications. People with fainting, dizziness, and shortness of breath due to heart rate abnormalities may need pacemakers. Other reasons for pacemakers are heart muscle damage, drugs, and genetic conditions. People with dangerously fast heartbeats (ventricular tachycardia) or fast, irregular heartbeats (ventricular fibrillation) may need ICDs. ICDs are also used for weakened hearts (e.g., from heart attacks), heart conditions involving abnormal heart muscle, and inherited heart disorders.

What Does Surgery Involve?

Before surgery, the doctor may order electrocardiography (ECG), 24-hour Holter monitoring

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(ECG), echocardiography, and stress tests. People getting ICDs may also need to have electrophysiology studies done.

Minor surgery to put in pacemakers and ICDs is usually done under local anesthesia. Surgery usually takes 1–3 hours. During the operation, a flexible, insulated wire is put into a large vein near the collarbone and guided to the heart. One end is attached to the heart, and the other ends go to the device.

What Are the Risks of Cardiac Pacemakers and Defibrillators?

Complications from surgery are rare (in less than 5% of people). They may include infection at the place of the incision and allergic reactions to anesthesia. Swelling, bruising or bleeding, damage to blood vessels or nerves near the pacemaker, and collapsed lungs may occur.

Cell phones, security systems (such as at airports), and power-generating equipment might cause problems. Medical procedures, including magnetic resonance imaging, might also. However, people with these devices need not worry about microwave ovens, televisions, remote controls, radios, toasters, and electric blankets, shavers, and drills.

DOs and DON'Ts in Managing Cardiac Pacemakers and Defibrillators:

✓ **DO** avoid vigorous above-the-shoulder activities or exercises soon after surgery. These include golf, tennis, swimming, bicycling, bowling, and vacuuming.

✓ **DO** exercise regularly but avoid playing contact sports soon after surgery.

✓ **DO** remember to use the ear away from the device when talking on cellphones.

✓ **DO** carry a wallet ID card with you. Equipment used by doctors and dentists can affect pacemakers. Tell them about yours.

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✓ **DO** see your doctors for regular follow-ups. Some people may have pacemakers checked monthly by telephone.

⃠ **DON'T** lift anything weighing more than 5 lb soon after surgery.

⃠ **DON'T** carry cellphones in the breast pocket above the device.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:** **http://www.americanheart.org**
- American College of Cardiology Tel: (800) 253-4636 **Website: http://www.acc.org**

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MANAGING YOUR

CARDIAC TAMPONADE

What Is Cardiac Tamponade?

The heart's major function is to pump blood. It is made up of muscle that contracts and pushes the blood in the circulation. A two-layered, fluid-filled sac of tissue, the pericardium, surrounds the heart. The pericardium keeps the heart in position and prevents the heart from moving too much or rubbing against other parts of the body.

Cardiac tamponade is a condition in which the heart is compressed by too much fluid in the pericardium, affecting its pumping action.

Cardiac tamponade can be life threatening. Prompt diagnosis and emergency treatment can be lifesaving. Intensive care monitoring is usually needed.

What Causes Cardiac Tamponade?

Tamponade can be chronic (occur slowly). The most common causes are cancers (lung, breast, lymphoma), kidney failure, underactive thyroid, and infections.

Tamponade can also be acute (sudden) and usually results from trauma, such as a penetrating knife wound or motor vehicle accident (when the chest hits the steering wheel and causes a tear of the main artery leaving the heart, called an aortic dissection).

Other causes of acute tamponade include bursting of the heart muscle after a heart attack and holes made in the heart during an operation (such as putting in a pacemaker).

What Are the Symptoms of Cardiac Tamponade?

People with chronic tamponade have shortness of breath, fast heartbeat, and possibly low blood pressure with abnormal heart sounds (friction rubs). Most people with acute tamponade are very ill and have low blood pressure with heart sounds that are hard to hear. Acute tamponade is a

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surgical emergency.

How Is Cardiac Tamponade Diagnosed?

The doctor may suspect cardiac tamponade by the person's symptoms and physical exam. Echocardiography (ultrasound of the heart) will confirm the diagnosis.

In people with life-threatening tamponade, a needle is put through the chest into the pericardium. This lets the doctor remove fluid as part of treatment and lets a doctor study the fluid under a microscope to determine the cause of the tamponade.

How Is Cardiac Tamponade Treated?

Treatment of chronic tamponade depends on the cause. In the case of cancer, drugs specific for the type of cancer will be suggested. Antibiotics or antifungal drugs can be used if the tamponade is due to a bacterial or fungal infection.

Acute tamponade is an emergency. A specialist called a cardiothoracic surgeon (who treats diseases of the heart and blood vessels) will likely be involved in care. Again, treatment depends on the specific cause of the tamponade.

DOs and DON'Ts in Managing Cardiac Tamponade:

✓ **DO** understand that cardiac tamponade affects the pumping action of the heart. This means that the heart cannot maintain blood pressure. Fluid must be removed very quickly to prevent shock and death.

✓ **DO** call your doctor if you are short of breath or have chest pain with fever, chills, and sweats.

⦸ **DON'T** forget that a cardiothoracic surgeon and a cardiologist (a medical doctor specializing in heart diseases) are best trained for treating cardiac tamponade.

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⦸ **DON'T** miss your follow-up doctor appointments after you are discharged from the hospital.

Pericardial fluid can sometimes build up again.

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FOR MORE INFORMATION

Contact the following source:

- American Heart Association National Center

  7272 Greenville Avenue

  Dallas, TX 75231

  Tel: (800) 242-8721

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MANAGING YOUR

CAROTID STENOSIS

What Is Carotid Stenosis?

Carotid stenosis is a narrowing of the lumen of the carotid artery. This artery is the main one that takes oxygen-rich blood to the brain. A lumen is the inside space of a tube such as an artery. Carotid stenosis occurs in 5 out of 1000 people 50 to 60 years old. It's more common in older people: 100 out of 1000 people older than 80 have it.

What Causes Carotid Stenosis?

The cause is usually buildup of fatty deposits called plaques (as in atherosclerosis). Less common causes are aneurysms, inflammation of arteries (arteritis), and tears (dissection) of the carotid. Fibromuscular dysplasia, tissue damage after radiation therapy (postradiation necrosis), and spasm of blood vessels (vasospasm) are others.

Risk factors include high blood pressure (hypertension), high lipid values, diabetes mellitus, and smoking.

What Are the Symptoms of Carotid Stenosis?

Most people often have no symptoms until the degree of narrowing is severe. Other people may have ministrokes called transient ischemic attacks (TIAs). Most TIAs last less than 10 minutes. They're caused when blood flow to a certain part of the brain stops for a short time. Symptoms depend on which arteries are affected. More common symptoms of TIAs include weakness or numbness on one side of the face or body (face, arm, leg). Vision changes, confusion, slurred speech, being unable to talk, and problems swallowing also occur.

How Is Carotid Stenosis Diagnosed?

The health care provider makes a diagnosis from the medical history and careful neurological

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examination. The health care provider listens to the carotid artery with a stethoscope for noises from abnormal blood flow called carotid bruit. Laboratory tests to measure levels of lipids (cholesterol, triglycerides) and a fasting glucose level are usually done. The health care provider will obtain an ultrasonography of the carotid arteries to evaluate the degree of narrowing of the lumen of the carotids. Angiography and magnetic resonance angiography (MRA) may be needed before surgery to better define the area that needs surgery. The health care provider may suggest seeing specialists (neurologist, vascular surgeon).

How Is Carotid Stenosis Treated?

Treatment depends on the degree of stenosis and symptoms. It can be medical or surgical. Medical management includes reducing risk (stopping smoking, controlling high lipid levels and diabetes) and low-dose aspirin (81 or 325 mg daily). Surgery for carotid stenosis is called carotid endarterectomy (CEA). It's usually done in people with recent symptoms and 70% to 99% stenosis if their life expectancy is more than 5 years. The expertise of the surgeon performing the CEA plays an important role in determining the success of the operation.

DOs and DON'Ts in Managing Carotid Stenosis:

- ✓ **DO** eat a well-balanced diet with lots of fruits, vegetables, and nuts. Limit your fats and eat little or no processed foods.
- ⦸ **DON'T** ignore symptoms. Call your health care provider if your symptoms don't improve or they get worse with treatment. Call if you get new symptoms.
- ⦸ **DON'T** stop taking your medicine or change the dosage because you feel better unless your health care provider tells you to.
- ⦸ **DON'T** use any medicines (including over-the-counter and herbal products) without first asking your health care provider.

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⦸ **DON'T** use tobacco products because they make vascular disease more likely and increase your risk of stroke.

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FOR MORE INFORMATION

Contact the following sources:

- American Stroke Association Tel: 88478-7653 **Website:**

  http://www.strokeassociation.org

- National Institute of Neurological Disorders and Stroke Tel: (800) 787-6537 **Website:**

  http://www.ninds.nih.gov

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Managing your

CARPAL TUNNEL SYNDROME

What Is Carpal Tunnel Syndrome?

Carpal tunnel syndrome (CTS) is an ailment affecting the wrist and hand. The nerve controlling feeling and movement in the wrist and hand involved in carpal tunnel syndrome is the median nerve. It lies in a passage in the wrist called the carpal tunnel.

What Causes Carpal Tunnel Syndrome?

In CTS, the tunnel becomes narrow because of swelling in the wrist. The smaller tunnel squeezes the median nerve, which causes pain and other symptoms.

Moving the hand and wrist repeatedly in the same way, such as typing, writing, and using a computer mouse, can cause CTS. Some occupations such as transcriptionists, cashiers, butchers, and janitors have an increased risk of CTS. Pregnant women often get CTS because their hormones change and they retain fluid. Several illnesses, for example, muscle and bone disorders, underactive thyroid (hypothyroidism), and diabetes, can also increase risk of CTS.

What Are the Symptoms of

Carpal Tunnel Syndrome?

In the wrist, hand, and fingers, CTS causes pain, tingling, numbness, and weak grip (a tendency to drop something). Symptoms often improve when the hand is wrung or shaken. Some people feel discomfort in the upper arm and shoulder.

Symptoms often worsen at night and can interfere with sleep.

How Is Carpal Tunnel Syndrome Diagnosed?

The doctor examines the wrist, and to cause symptoms, will tap it over the median nerve and will bend it and hold it there for a few seconds. Special tests (EMG) to check the wrist's nerves and

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muscles may also be done.

How Is Carpal Tunnel Syndrome Treated?

Treatment involves two steps. The first is a lifestyle change: stop doing whatever caused CTS. This change may be hard if it involves a job, but talk to your employer. Sometimes simple changes, such as using a wrist pad while typing so your wrist is in a better position, help. A physical therapist or occupational therapist can suggest ways to do things differently.

The second step is to take pressure off the median nerve. Medicine, wrist splints, and surgery are usually used. A wrist splint at night is best, but some people wear a splint during the day. Pills give relief for a short time by decreasing inflammation. Medicine can also be injected into the wrist and can help for a longer period.

Surgery to make more room for the nerve is the best way to reduce pressure on the nerve when other treatments are ineffective. With surgery, you usually get better quickly, but you should rest your wrist for at least 6 weeks to promote healing and avoid new symptoms.

DOs and DON'Ts in Managing Carpal

Tunnel Syndrome:

✓ **DO** change what caused CTS.

✓ **DO** take pills as directed by your doctor.

✓ **DO** briefly take off a wrist splint, if you wear it during the day, to exercise your wrist and hand.

⃠ **DON'T** hit things with the butt of your palm. This may injure your median nerve.

⃠ **DON'T** delay getting treatment. If muscle wasting occurs, chances of full recovery are less.

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⦸ **DON'T** use vibrating hand tools.

⦸ **DON'T** hold your hand or wrist in awkward positions.

⦸ **DON'T** use repetitive movements of the hand or wrist, especially forceful grasping or pinching.

⦸ **DON'T** use direct pressure over the palm and wrist.

⦸ **DON'T** completely stop using and exercising your hand.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopaedic Surgeons Tel: (800) 346-AAOS **Website:** **http://www.aaos.org**
- Arthritis Foundation Tel: (800) 283-7800 **Website:** **http://www.arthritis.org**

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MANAGING YOUR

CAT-SCRATCH DISEASE

What Is Cat-Scratch Disease?

Cat-scratch disease is an infection that is believed to be caused by bacteria carried on the claws of cats. The infection spreads to lymph glands (nodes) nearest the scratch. Lymph glands are masses of tissue that are part of the body's immune system, which fights infection.

Cat-scratch disease is rather rare. Most cases seem to happen in early autumn and the middle of winter. It occurs more often in children and young adults. About 80% of cases occur in people younger than 21, with most between 3 and 12 years old.

What Causes Cat-Scratch Disease?

The cause of the infection is a type of bacteria called *Bartonella henselae*. Most domestic cats have the infection but rarely show any signs of being infected.

What Are the Symptoms of Cat-Scratch Disease?

Symptoms appear a few days after the scratch. First a lump with or without pus or fluid forms at the injury. From 1 to 3 weeks later, lymph glands near the lump begin to swell. The swelling means that the number of white blood cells (lymphocytes), which are the infection-fighting cells, is increasing and they are attacking the bacteria. There may be a low-grade fever, fatigue, and headache.

How Is Cat-Scratch Disease Diagnosed?

The doctor will diagnose the disease on the basis of the history of a recent cat scratch and the look of the scratch, with reddened crusted blisters. The doctor may also see swollen lymph nodes filled with pus and draining through the skin near the scratch.

How Is Cat-Scratch Disease Treated?

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Unless the body's immune system isn't working well, the infection usually goes away with antibiotic treatment in 1 to 2 weeks. The body's own immune system may take care of the infection without antibiotics in very mild cases. People with poor infection-fighting ability (e.g., with HIV or AIDS) may develop a more severe infection and generally need antibiotics. Rest is best until the fever subsides and energy returns. No special diet is needed, but drinking more fluids during the fever helps. Using heat on the blisters and taking pain relievers also help symptoms.

DOs and DON'Ts in Managing Cat-Scratch Disease:

✓ **DO** rest until the fever subsides and energy returns.

✓ **DO** take antibiotics, if they're prescribed, until they're gone.

✓ **DO** watch scratches from a cat for signs of infection.

✓ **DO** use care when handling cats. Teach young children to avoid strange animals.

✓ **DO** have cats declawed, if possible.

✓ **DO** call your doctor if a high fever occurs (temperature of 102° F or above).

✓ **DO** call your doctor if a lymph gland becomes red and painful.

✓ **DO** call your doctor if red streaks appear near the scratch.

⊘ **DON'T** skip doses or stop antibiotics if they were prescribed.

⊘ **DON'T** isolate the infected person because the disease is not spread from person to person.

⊘ **DON'T** handle strange animals.

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FOR MORE INFORMATION

Contact the following source:

- National Institute of Allergy and Infectious Diseases Tel: (301) 496-5717 **Websites:**

  http://www.healthfinder.gov (Choose SEARCH to search by topic.)

  http://www.healthanswers.com

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MANAGING YOUR

CATARACTS

What Are Cataracts?

A cataract is a clouding of the lens of the eye. The lens is like a glass window that we look through to see. It is made of water, protein, and other chemicals. With aging, these proteins become cloudy and interfere with the passage of light. As cataracts progress, it is hard to see clearly. Cataracts are the leading cause of blindness worldwide.

What Causes Cataracts?

The cause of most cataracts is unknown. However, some cataracts can be caused by long-term use of steroids, redness and swelling (inflammation), infections of the eye, and illnesses such as diabetes.

Most often, cataracts develop with aging. The lens slowly becomes cloudy, thick, hard, and dry and eventually a cataract develops.

What Are the Symptoms of Cataracts?

The major symptom is blurred vision. At times, distance vision will be blurred more than reading vision, but at other times the reverse is true. Also, poor sight even with eyeglasses or contact lenses, ghost-like images, glare, and a halo around a light may be noticed.

How Are Cataracts Diagnosed?

Your doctor will suspect a cataract based on your history and eye exam. You will be referred to an eye specialist (optometrist or ophthalmologist), who will use equipment to look into the eye to see the cataract. An optometrist is someone who tests for vision defects to prescribe eyeglasses. An ophthalmologist is a medical doctor specializing in eye diseases.

How Are Cataracts Treated?

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Cataracts don't damage the eye. They only cause blurred vision. People who are happy with their overall vision don't need cataract surgery.

Once a person is no longer satisfied with their ability to see, and/or the doctor finds that vision is significantly impaired, cataract surgery should be considered. At times with early cataracts, vision can be improved with glasses. As the cataract progresses, just changing the glasses will not help vision.

Most cataract operations can be performed as outpatient procedures. The eye is numbed with eye drops. Medicine is given to make the person sleepy. In surgery, the clouded lens is removed and usually replaced with a permanent plastic lens, called an intraocular lens. After surgery, there are usually minimal restrictions on activities.

Cataract surgery is never performed on both eyes at the same time. People usually have surgery performed on the weaker eye first, so that they can depend on the stronger eye while the operated eye heals.

DOs and DON'Ts in Managing Cataracts:

✓ **DO** see your doctor right away if you suddenly start to have trouble seeing.

✓ **DO** have another examination if you have a cataract and notice that your vision has gotten worse. Problems other than the cataract may be occurring in the eyes.

✓ **DO** protect your eyes from injury. Wear sunglasses that block 100% of both forms of ultraviolet light, UVA and UVB, especially in sunny climates.

✓ **DO** keep your blood sugar (glucose) level well controlled if you have diabetes. Cataracts grow faster when the blood sugar level is high.

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⦸ **DON'T** worry about any restrictions. People with cataracts have no specific restrictions and no specific medicines, diet, or exercises that would help.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Ophthalmology Tel: (415) 561-8500 **Website: http://www.aao.org**
- National Eye Institute **Website: http://www.nei.nih.gov/health/cataract/ cataract_facts.asp**

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MANAGING YOUR

CAVERNOUS SINUS THROMBOSIS

What Is Cavernous Sinus Thrombosis?

In cavernous sinus thrombosis, a rare condition, a blood clot (thrombus) forms in the cavernous sinus. The cavernous sinus is a cavity at the bottom of the brain, in the skull. It helps drain blood from the brain and the middle part of the face back to the heart. Cranial nerves surround the sinus. These nerves are needed for eye movement and feeling at the top and middle parts of the head and face. People of any age, sex, or race can have this condition.

What Causes Cavernous Sinus Thrombosis?

The cause is usually an infection starting in the face (skin), eyes, eyelids, sphenoid sinus, or ears. Most often, infection of the sphenoid sinus, just below the cavernous sinus, lets bacteria spread easily. Infections caused by the bacteria *Streptococcus* and *Staphylococcus* are the most common.

What Are the Symptoms of Cavernous Sinus Thrombosis?

Symptoms include reduced vision or loss of vision, drooping eyelid, bulging eyeballs, and suddenly being unable to move the eye in a certain direction. Fever, headaches, rapid heart rate, and stiff neck can occur.

How Is Cavernous Sinus Thrombosis Diagnosed?

The health care provider makes a preliminary diagnosis from the medical history, physical examination, and blood tests for infection. To best way to find cavernous sinus thrombosis is magnetic resonance imaging (MRI) of the brain. Sometimes, lumbar puncture will be done to rule out meningitis. In lumbar puncture, the health care provider puts a needle in the lower back to get fluid from around the spinal cord to be analyzed for signs of infection.

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How Is Cavernous Sinus Thrombosis Treated?

Treatment involves high-dose intravenous antibiotics. The blood thinner called heparin may be used, but this use is controversial. In severe cases, a neurosurgeon will drain an infected sphenoid sinus during an operation, when this is the cause.

DOs and DON'Ts in Managing Cavernous Sinus Thrombosis:

- ✓ **DO** understand that the best treatment is prevention. The main cause of the disorder is infection of the face, middle ear, or sinus. Therefore, treating these infections promptly is the best prevention method.
- ✓ **DO** understand that cavernous sinus thrombosis can be a life-threatening, rapidly progressive infection. It can be fatal even after antibiotic treatment.
- ✓ **DO** call your health care provider if you have eye pain, vision loss, or problems seeing.
- ✓ **DO** call your health care provider if you have fever, headache, nausea, vomiting, and a stiff neck.
- ✓ **DO** call your health care provider if you have ear pain, hearing loss, or drainage from your ear.
- ✓ **DO** call your health care provider if yellow, green, or blood-tinged mucus drains from the sinus.
- ✓ **DO** call your health care provider if you see bulging of the eye or droopy eyelids.
- ✓ **DO** call your health care provider if you cannot move the eye in a certain direction.

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⦸ **DON'T** forget that this disorder is a medical emergency.

⦸ **DON'T** ignore symptoms that suggest infections of the face, eye, ears, and sinuses.

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FOR MORE INFORMATION

Contact the following sources:

- U.S. National Library of Medicine Website: **http://www.nlm.nih.gov/nlmhome.html**
- American Academy of Ophthalmology Phone:415-561-8500 **Website: www.aao.org**
- National Institute of Neurological Disorders and Stroke Tel: (800) 787-6537 **Website: www.ninds.nih.gov**

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MANAGING

CELIAC DISEASE

What Is Celiac Disease?

Celiac disease (CD) is a food allergy that prevents the body from using certain nutrients. The allergy is to a substance (protein) called gluten. Gluten is found in many grains, such as wheat, rye, oats, and barley. The allergy mostly affects the small intestine, which is where the food travels after it leaves the stomach.

It usually first appears in babies when they start eating food containing gluten. Celiac disease is more common in those of Western European descent. It often runs in families.

Celiac disease is not curable but can be controlled with a gluten-free diet.

What Causes Celiac Disease?

An allergic reaction to gluten causes celiac disease, which is also called nontropical sprue and gluten enteropathy. Immunologic, genetic, and environmental factors all play a role in the development of celiac disease. When people with celiac disease eat food products containing gluten, their immune system attacks and damages finger-like projections known as villi lining the small intestine. The small intestine cannot absorb some nutrients, and people can become malnourished.

What Are the Symptoms of Celiac Disease?

Symptoms include diarrhea, with light tan or gray stools that may be watery or part solid, often smell bad, and look oily or frothy; weight loss; failure to grow and develop (babies and children); frequent gas; swollen abdomen (belly) or abdominal pain; mouth ulcers; tiredness, or weakness; paleness; rash; and muscle cramps. Many adults with CD have fewer symptoms than children, and diagnosis is often suggested by blood tests showing unexplained anemia (low red

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blood count). A rare manifestation of celiac disease is an itchy rash known as dermatitis herpetiformis.

How Is Celiac Disease Diagnosed?

The doctor tests blood to check for lack of nutrients and antibodies produced in response to gluten.

The doctor may do other tests (such as endoscopy) to confirm the diagnosis and exclude other diseases. In endoscopy, a thin, flexible tube with a camera on one end is put into the throat and then down through the stomach into the small intestine. Then the doctor removes a piece of tissue for study under a microscope (biopsy). In a newer test, capsule endoscopy, a small camera in a swallowed pill can look inside the bowels.

In some cases, the doctor may also do x-rays (small bowel series), which are taken after drinking a white chalky liquid (barium).

How Is Celiac Disease Treated?

The main treatment is eating a special diet that avoids anything containing gluten, which includes grains, particularly wheat, barley, and rye.

Food supplements to help boost low nutrient levels and medicine to help control the allergy may also be required.

DOs and DON'Ts in Managing Celiac Disease:

✓ **DO** get the help of a dietitian or nutritionist to plan your diet.

✓ **DO** follow the gluten-free diet every day. Stay on your diet, even when you feel good.

✓ **DO** take recommended or prescribed food supplements.

✓ **DO** find a support group if you are interested in learning from others with celiac disease.

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✓ **DO** call your doctor if symptoms don't improve after 3 weeks of new diet.

✓ **DO** call your doctor if fever develops.

⃠ **DON'T** eat anything that has even a small amount of gluten.

⃠ **DON'T** eat or drink dairy products until your doctor or dietitian approves them since some of these may also cause gas, bloating and diarrhea that may be confused with celiac disease.

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FOR MORE INFORMATION

Contact the following sources:

- Celiac Disease Foundation Tel: (818) 990-2354 **Website:** **http://www.celiac.org**
- Celiac Sprue Association (CSA)/USA Tel: (877) CSA-4-CSA (272-4272) **Website:** **http://www.csaceliacs.org**

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MANAGING YOUR

CELLULITIS

What Is Cellulitis?

Cellulitis is an infection in the skin and soft tissue layers under the skin. People with diabetes, blood circulation problems, and weakened immune systems can easily develop cellulitis. Also, people who had recent medical procedures, such as heart or lung surgery, can get cellulitis, as can people who work on farms or in gardens or who handle fish.

What Causes Cellulitis?

Cellulitis is caused by bacteria, usually kinds of bacteria called *Staphylococcus* (staph) and *Streptococcus* (strep). Bacteria enter through a break in the skin, such as a cut, burn, insect bite, open sore, or crack (for example, between toes).

What Are the Symptoms of Cellulitis?

Symptoms include sudden redness, swelling, and tenderness in the skin and a rash. Sometimes a red line extends toward the closest lymph nodes (glands). Other signs of infection include fever, chills or sweating, headache, rapid heartbeat, and weakness.

Most often cellulitis affects lower legs and feet, but it can also occur on the face (especially cheeks), hands, or scalp, and in children, around the rectum. Cellulitis can also occur as an eye infection, with swollen eyelids, loss of sight, and problems with eye movement.

How Is Cellulitis Diagnosed?

The doctor will examine the area and do blood tests. Sometimes, a tiny sample of skin (biopsy) may also be taken when the diagnosis is unclear.

How Is Cellulitis Treated?

Medicine (antibiotics) will fight the infection and relieve pain. People with mild infections can

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take medicine by mouth and don't need to be hospitalized. People with cellulitis that is hard to treat are sometimes hospitalized and given intravenous antibiotics. In most people, the infection clears up in 7 to 10 days. People with diabetes or other medical problems may have a longer recovery.

DOs and DON'Ts in Managing Cellulitis:

✓ **DO** take medicine for as long as your doctor tells you, even if you feel better, unless your doctor says you can stop.

✓ **DO** elevate your leg if it has cellulitis, but wiggle your toes or flex your ankle frequently to prevent blood clots.

✓ **DO** apply cool, wet cloth dressings.

✓ **DO** tell your doctor at once if the infection spreads or you develop high fevers, vomiting, headache, or red streaks that don't go away.

✓ **DO** call your doctor at once if you notice areas of infection starting nearby, your skin becomes dark or discolored, or blisters appear.

✓ **DO** avoid injuring your skin by wearing protective clothing or equipment.

✓ **DO** clean a cut or injury and use an antibiotic ointment. If it seems to be infected (red or warm), call your doctor.

⃠ **DON'T** skip doses or stop taking antibiotics until finished.

⃠ **DON'T** resume normal activities until swelling and pain stop.

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⦸ **DON'T** swim if you have a skin wound.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Dermatology Tel: (888) 462-3376 **Website: http://www.aad.org**
- National Health Info Center Tel: (800) 336-4797 **Website: http://www.health.gov/nhic/**

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CARING FOR YOUR CHILD WITH

CEREBRAL PALSY

What Is Cerebral Palsy?

Cerebral palsy (CP) is the name of a group of conditions affecting muscles and nerves. It isn't inherited but begins early in life. The three types of CP are spastic (most common), athetoid, and ataxic.

CP is a lifelong condition that doesn't get worse, and most children with CP have a normal life span.

Some people are mildly affected and can live fairly normal lives. Others are more severely disabled. Many people have normal intelligence despite their severe physical disabilities.

What Causes CP?

The cause is injury to parts of the brain that control the ability to use muscles. Cerebral means related to the brain. Palsy means weakness or problems using muscles. The injury can happen during pregnancy, during birth, or early in childhood. It can involve not having enough oxygen during or after birth, an infection (e.g., German measles) that spreads from mother to baby, or a serious infection early in life.

What Are the Symptoms of CP?

CP can be mild, moderate, or severe. Symptoms include abnormal movements of arms and legs, feeding problems in an infant, poor muscle tone early in life, slow development of walking and talking, abnormal body posture, muscle spasms, body stiffness, poor coordination, and crossed eyes.

Children with spastic CP have muscle tightness, with stiff movements, especially in the legs, arms, and back. Athetoid CP affects the whole body, so children have problems with balance and

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coordination. They have slow, uncontrolled movements and low muscle tone that makes it hard to sit straight and walk. Symptoms of mixed CP are a combination of these two types.

Sometimes children with CP can have problems learning, hearing, or seeing, or have mental retardation.

How Is CP Diagnosed?

The doctor will do a physical examination and carefully check your child's movement.

The doctor may order tests to confirm CP, including CT and MRI of the brain, ultrasound, and nerve conduction tests.

How Is CP Treated?

CP cannot be cured, but symptoms and disabilities can be helped with physical therapy (PT), occupational therapy (OT), psychological counseling, and surgery. PT helps children develop stronger muscles and work on skills such as walking, sitting, and balance. Special equipment, such as braces and splints, may also benefit some children. With OT, children develop fine motor skills, such as those needed for dressing, feeding, and writing. Speech and language therapy helps children with speaking skills. Children and families are aided by support, special education, and related services.

DOs and DON'Ts in Managing CP:

✓ **DO** avoid preventable risks such as German measles during pregnancy.

✓ **DO** call your doctor about treatments that could help symptoms.

✓ **DO** remember that states must meet educational needs of children with disabilities, such as through early intervention services.

✓ **DO** make sure special education and related services are provided for school-age children

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and preschoolers through school systems.

✓ **DO** have a positive attitude about the person with CP.

⃠ **DON'T** smoke, use alcohol, or abuse drugs during pregnancy.

⃠ **DON'T** forget about assistive devices, such as voice synthesizers and computer technology.

⃠ **DON'T** give up hope. Progress in people with CP is usually slow.

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FOR MORE INFORMATION

Contact the following sources:

- United Cerebral Palsy Foundation Tel: (800) 872-5827 **Website: http://www.ucp.org**
- National Dissemination Center for Children with Disabilities Tel: (800) 695-0285 **Website: http://www.nichcy.org**

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MANAGING YOUR

CERVICAL CANCER

What Is Cervical Cancer?

The cervix is at the outer end of the uterus (womb). It looks like a button with a narrow opening that leads into the uterus. Cervical cancer is growth of malignant cells in the cervix. Finding cervical cancer early by using Pap tests has increased chances for cure.

What Causes Cervical Cancer?

Risks include having sex before age 18, having many sexual partners, smoking, using birth control pills, having a mother who took diethylstilbestrol (DES) during pregnancy, and being infected with human papillomavirus (HPV), which is a sexually transmitted disease (STD).

What Are the Symptoms of Cervical Cancer?

Women usually have no symptoms until cancer has reached nearby tissue. The most common symptom is vaginal bleeding or bleeding after sex. Discharge from the vagina may occur. Cancer that invades nearby tissues can cause back pain, the need to urinate often, and bowel changes.

How Is Cervical Cancer Diagnosed?

Pap smears are 95% accurate in finding early cervical cancer. Women older than 20 (or younger, if sexually active) should have routine Pap tests, at least until age 65. HPV testing is also a very important test performed in screening for cervical cancer.

If a Pap smear is abnormal, the gynecologist will use colposcopy (checking the cervix with a microscope to better identify abnormal cells). If needed, a cone biopsy may be done. In this biopsy, a cone-shaped sample of tissue is removed for study.

How Is Cervical Cancer Treated?

Treatment depends on the cancer stage. Staging means finding out whether cancer has spread, and if so, how much. Stages are numbered 0 to IV, depending on how far it has spread. A doctor

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uses a pelvic examination, blood and urine tests, x-rays, and computed tomography (CT) for staging. Additional tests such as cystoscopy and proctosigmoidoscopy (examinations with lighted tubes put into the bladder and rectum, respectively) may also be done.

Treatment may include surgery, radiation, and chemotherapy (anticancer drugs). Early cancer can be burned away by laser, frozen (cryotherapy), or cut out. Advanced cancer needs surgery such as hysterectomy, radiation therapy, and chemotherapy.

DOs and DON'Ts in Managing Cervical Cancer:

✓ **DO** understand that good nutrition after surgery, radiation, or chemotherapy is important.

✓ **DO** understand that a team of doctors, including a primary care doctor, gynecologist, oncologist, and radiation oncologist, can be involved in care.

✓ **DO** call your doctor if you have abnormal bleeding.

✓ **DO** call your doctor if you have pain, bowel or urinary problems, vaginal drainage, or fever after surgery.

✓ **DO** call your doctor if you have hot flashes, vaginal dryness, or vaginal pain with sex.

⊘ **DON'T** miss follow-up doctor appointments.

⊘ **DON'T** forget to stay active. Exercising daily helps you deal with the disease.

⊘ **DON'T** be afraid to ask about emotional support groups.

⊘ **DON'T** forget about social workers who can help with services such as rehabilitation, home care, finances, and transportation.

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FOR MORE INFORMATION

Contact the following sources:

- National Cancer Institute (NCI) Tel: (800) 4-CANCER (422-6237) **Website:** **http://www.cancer.gov**
- American Cancer Society Tel: (800) ACS-2345 (227-2345) **Website:** **http://www.cancer.org**

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MANAGING YOUR

CERVICAL DISC SYNDROME

What Is Cervical Disc Syndrome?

The neck (cervical) part of the spinal column is made of seven bones (vertebrae) separated by pillow-like discs. These discs are like shock absorbers for the head and neck. They cushion the bones and allow the head and neck to bend. Cervical disc syndrome refers to pain in this neck part of the spine.

What Causes Cervical Disc Syndrome?

Many causes include normal degenerative changes in discs with aging. Poor posture and strenuous work with poor lifting methods may make these changes worse. The discs slowly become worn, less plump, and flat. When the disc space becomes narrow enough that vertebrae rub together, edges of the vertebrae have wear-and-tear changes. Then, bone spurs develop that may start to press on the spinal cord or nerve root. As the nerve is irritated, pain, tingling, numbness, or weakness can occur.

Similar changes or trauma may burst the tough cartilage around each disc. Disc material may bulge (herniate) into the spinal canal and press on (compress) the spinal cord or nerve root.

What Are the Symptoms of Cervical

Disc Syndrome?

Neck pain or tingling and numbness may reach the shoulder, upper back, arm, or hand. Some people have weakness, clumsiness, and trouble walking. Pain from a bulging disc is worse during movement and during coughing or laughing.

How Is Cervical Disc Syndrome Diagnosed?

The doctor makes a diagnosis from a physical examination and x-rays of the cervical spine.

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Magnetic resonance imaging (MRI) of the neck and electromyography or nerve conduction velocity test (EMG/NCV), an electrical test of nerves and muscles, may also be done.

How Is Cervical Disc Syndrome Treated?

Most cases can be treated with physical therapy, pain control, and antiinflammatory drugs. Specialists (orthopedic surgeon, anesthesiologist, or neurosurgeon) may help with treatment. Conservative treatments can also be done by a physical therapist. These include local heat placed on the area, cervical traction, and special exercises.

Anesthesiologists can inject steroids and anesthetic medicine into the cervical spinal canal to help pain.

Symptoms often go away after few weeks. Surgery is usually the final option if other treatments don't relieve symptoms.

DOs and DON'Ts in Managing Cervical

Disc Syndrome:

✓ **DO** use good posture while sitting and walking.

✓ **DO** always wear a seat belt when traveling in a motor vehicle.

✓ **DO** put a pillow under your head and neck when lying in bed.

✓ **DO** daily exercises approved by your doctor. Gently stretch and bend your neck. Keep to your ideal weight.

✓ **DO** call your doctor if your symptoms become much worse or you have new weakness.

✓ **DO** call your doctor if you have trouble walking, have weakness, cannot move your limbs, or

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lose control of your bowels or bladder.

✓ **DO** minimize trauma to your cervical spine. Wear protective gear in contact sports.

⃠ **DON'T** make a habit of popping your neck.

⃠ **DON'T** return to work until your doctor says you can.

⃠ **DON'T** do strenuous activities until you check with your doctor.

⃠ **DON'T** resume driving until you're pain free without pain medicine.

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FOR MORE INFORMATION

Contact the following sources:

- North American Spine Society Tel: (630) 230-3600 **Website:** **http://www.spine.org**
- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website:** **http://www.aaos.org**

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MANAGING YOUR

CERVICAL DYSPLASIA

What Is Cervical Dysplasia?

The button-like cervix is at the end of the vaginal canal. Its narrow opening leads into the uterus (womb). Cervical dysplasia, sometimes called precancerous changes or abnormal Pap smear, is growth of abnormal cells in the lining of the cervix. It can be mild, moderate, or severe. Most cases are mild and get better without treatment. Untreated, severe dysplasia can lead to cervical cancer.

What Causes Cervical Dysplasia?

Human papillomavirus (HPV), which is sexually transmitted, and similar viruses can increase chances of getting dysplasia and cancer. Other risk factors include history of STDs, having sex at a young age, and having multiple sex partners.

What Are the Symptoms of Cervical Dysplasia?

Symptoms are generally not present. Cervical dysplasia is usually found by a Pap smear. Rarely, in very advanced dysplasia, abnormal bleeding occurs.

How Is Cervical Dysplasia Diagnosed?

HPV testing and Pap smears are important diagnostic tests. Pap screening may show an abnormal Pap smear, but actual abnormal tissue may or may not be present. The only way to diagnose this condition is to do an office procedure called colposcopy. The doctor checks the cervix closely with a colposcope. This tool is a large microscope that magnifies the view of the cervix. If colposcopy shows an abnormal-looking area, the doctor does a biopsy. In a biopsy, the doctor removes a small piece of the cervical tissue without anesthesia. A sharp pinch or cramp is felt, only for a moment. The tissue is sent to a laboratory to see whether dysplasia is present and whether it's mild, moderate, or severe.

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How Is Cervical Dysplasia Treated?

The most common method is the loop cone biopsy. The doctor does this procedure in the office with local anesthesia. It's usually very successful. After the procedure, women may have mild cramping for 1 to 2 days afterward and increased vaginal discharge for 1 to 2 weeks.

Cryosurgery, or freezing the cervix, is also used. When the cervix is frozen, abnormal tissue dies and falls off. Women usually have mild-to-moderate cramping after this office procedure. Vaginal discharge usually increases for 2 to 4 weeks afterward.

DOs and DON'Ts in Managing

Cervical Dysplasia:

✓ **DO** keep your follow-up doctor appointments. It's better to treat cervical dysplasia early.

✓ **DO** practice safe sex. Protecting yourself from sexually transmitted diseases, especially HPV, can reduce your risk of getting cervical dysplasia.

✓ **DO** use latex condoms when having sex, especially if your partner has had multiple sex partners.

✓ **DO** call your doctor if your bleeding lasts longer than a week after a cervical biopsy.

✓ **DO** call your doctor if you have more bleeding or vaginal discharge than expected after a loop cone biopsy.

✓ **DO** call your doctor if you have fever after a loop cone biopsy.

✓ **DO** get vaccinated with HPV vaccine (Gardasil®), which is for females 13 to 26 years old. It works for HPV types 6, 11, 16, and 18. It minimizes the risk of cervical cancer from HPV.

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✓ **DO** get regular Pap smears.

⃠ **DON'T** miss follow-up doctor appointments if you had a cone biopsy or you were told that you have dysplasia. Cervical dysplasia can come back, so it's very important to have follow-up Pap smears and colposcopy.

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FOR MORE INFORMATION

Contact the following source:

- American College of Obstetricians and Gynecologists Tel: 202-638-5577 **Website:** **http://www.acog.org**

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MANAGING YOUR

CERVICAL INCOMPETENCE

What Is Cervical Incompetence?

Cervical incompetence is abnormal weakness or opening (dilation) of the cervix early in pregnancy. The cervix is the mouth of the uterus. Cervical incompetence usually leads to dilation of the entire cervical canal during the second trimester. Membranes that hold the fetus (bag of waters) may break, and the baby may be delivered prematurely. Up to 2% of all pregnancies can be affected. This condition can cause 20% to 25% of all second trimester pregnancy losses.

What Causes Cervical Incompetence?

Different conditions can cause the weakness, but often the cause is unknown. Factors that increase the chance of having cervical incompetence include injury to the cervix (such as with dilation and curettage, known as D&C) and having a previous incompetent cervix with an earlier pregnancy. Also, hormones, surgery (such as “cone” biopsy), exposure to DES (diethylstilbestrol), and abnormalities of the uterus or cervix (such as a short cervix) may have an effect.

What Are the Symptoms of Cervical Incompetence?

Usually, women with cervical incompetence have no or few symptoms. The doctor can diagnose it only because of a suspicion that it’s present.

How Is Cervical Incompetence Diagnosed?

The doctor will do a vaginal examination of the cervix and take a medical history. Measurements made by using ultrasonography will confirm it. Ultrasonography can be used to view both the length and the shape of the cervix. Both factors affect the ability of the cervix to hold the pregnancy in place.

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How Is Cervical Incompetence Treated?

When the doctor thinks that cervical incompetence is possible, the doctor may want to do physical and ultrasound examinations more often than normal. If cervical incompetence is diagnosed, the cervix may be sewn closed with a special suture (stitch). This minor surgical procedure is done during an outpatient visit. This suture is left in place until about 38 weeks of pregnancy when it's removed in a simple office procedure. Possible complications include risk of bleeding, contractions, rupture of membranes, or infection. The suture also doesn't completely take away the risk of preterm delivery. This procedure is best done between 10 and 14 weeks of pregnancy. It generally cannot be done after about 24 weeks. The doctor may also suggest remaining at bed rest.

DOs and DON'Ts in Managing Cervical Incompetence:

✓ **DO** tell your doctor about a history of preterm labor or delivery. This is the greatest predictor for possible cervical incompetence.

✓ **DO** tell your doctor about bleeding, contractions, or loss of fluid that occur during pregnancy.

⦸ **DON'T** feel shy about asking your doctor whether your condition or its treatment will mean that you must have a cesarean section and cannot give birth normally.

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FOR MORE INFORMATION

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- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website:**

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http://www.acog.org

- WebMD **Website: http://www.webmd.com**
- U.S. Department of Health and Human Services **Website:** http://womenshealth.gov

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MANAGING YOUR

CERVICAL POLYPS

What Are Cervical Polyps?

The cervix is at the end of the uterus (womb). It looks like a button with a narrow opening that leads into the uterus. Cervical polyps are soft, fingerlike growths of tissue that usually start to grow from inside the cervical canal (entrance to the uterus). They hang from a stalk and often push through the opening.

Cervical polyps are common, especially in women older than 20 who have had children. Almost all are benign (not cancerous). They aren't contagious and seldom grow back. No specific ways to prevent them are known.

What Causes Cervical Polyps?

Cervical polyps are believed to grow because of inflammation. The reason for the inflammation isn't known, but cervical infections are suspected.

What Are the Symptoms of Cervical Polyps?

Many polyps don't cause symptoms. Sometimes a polyp will cause abnormal spotting or bleeding after sex or heavier bleeding during periods. An abnormal discharge from the vagina may also be seen. Polyps don't cause pain or discomfort.

How Are Cervical Polyps Diagnosed?

Polyps are often found during a routine gynecologic examination when a Pap test is done.

How Are Cervical Polyps Treated?

Cervical polyps are easily removed in the doctor's office. No anesthesia or pain medicine is needed. The polyp is simply held and twisted off gently or taken off with a special tool called a biopsy instrument. The procedure only takes a few minutes and usually is painless. It may some-

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times cause mild cramping. The polyp is sent to the laboratory for study, to make sure that there's no sign of cancer or any precancerous abnormality.

DOs and DON'Ts in Managing Cervical Polyps:

✓ **DO** keep your doctor's appointment to have the polyp removed. Even though the vast majority of polyps are benign (not cancerous), cancerous polyps do sometimes occur.

✓ **DO** continue your usual daily activities after the polyps are removed but avoid sexual intercourse and use of tampons until the follow-up visit with your doctor.

✓ **DO** call your doctor if you have vaginal bleeding after menopause (change of life), between periods, or after you have resumed sex.

✓ **DO** call your doctor if you have pain in the pelvic area.

✓ **DO** call your doctor if you have long or unusually heavy periods.

⃠ **DON'T** have sex until the polyp is removed if you've had bleeding after sex and were diagnosed with a polyp.

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MANAGING YOUR

CERVICAL RADICULOPATHY

What Is Cervical Radiculopathy?

The cervical (neck) spine has seven vertebrae (bones). Cervical radiculopathy, or pinched nerve, is damage to a nerve root near these vertebrae. The seventh and sixth nerve roots are most often affected. It's a common problem, affecting most adult age groups. It's less common in teenagers and children.

What Causes Cervical Radiculopathy?

Anything that puts pressure on nerves where they leave the spine can cause symptoms. Causes include sudden injuries, pressure from ruptured (burst) disks, and degenerative bone changes (as in arthritis). Spinal instability and cancer are others. Younger people usually have disk herniations (bulges) or acute injuries. Older people often have degenerative bone changes.

What Are the Signs and Symptoms of Cervical Radiculopathy?

Symptoms depend on which root is involved. The main symptom is pain spreading into the arms, neck, chest, or shoulders. Muscle weakness, numbness, tingling in fingers or hands, lack of coordination (especially in hands), and headaches are others. Reflexes in upper arm muscles are usually affected. Moving the neck can make pain worse.

How Is Cervical Radiculopathy Diagnosed?

The doctor takes a careful history and does a physical and sensory examination. It's important to know how long symptoms lasted and whether they've gotten worse. The doctor tests deep tendon reflexes. Because about 80% of people improve without treatment, imaging isn't often needed. However, the doctor can order magnetic resonance imaging (MRI), the best study. X-rays, computed tomography (CT), provocative tests, and maybe electromyography (EMG) and selective di-

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agnostic nerve root block (SNRB) can also be done.

How Is Cervical Radiculopathy Treated?

Treatment depends on the cause but aims to reduce pain and inflammation (swelling). First, nonoperative measures such as immobilization (keeping the neck still) in bed, local icing, and soft neck collar are used. The collar is worn for 1–2 weeks. A cervical pillow at night can help position the neck. Physical therapy for pain and inflammation may include gentle cervical traction, mobilization, and neck-strengthening exercises. Traction relieves muscle spasms. Traction with weights, by using a head halter, is usually applied at home. Electrical stimulation can calm muscle spasms and pain. Acupuncture is another option. Drugs including steroids and the nonsteroidal anti-inflammatory drugs (NSAIDs) ibuprofen and naproxen sometimes help. Most people get better without surgery. If other treatments don't work, surgery may be needed. Types of surgery include foraminotomy (making the passage for the nerve root bigger), discectomy (removing the disk where it presses against a nerve), and fusion (joining two or more bones into one).

For prevention and rehabilitation, certain activities (such as heavy lifting) are restricted and using proper sports technique (e.g., tackling in football) is important.

DOs and DON'Ts in Managing Cervical Radiculopathy:

✓ **DO** skip high-impact activities, such as running, if you have neck pain.

✓ **DO** exercises to maintain neck strength, flexibility, and range of motion.

✓ **DO** take breaks when driving, watching TV, or working on a computer to avoid holding your head in the same position for long periods.

✓ **DO** practice good posture.

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⦸ **DON'T** forget to protect your neck from injury by using seatbelts in motor vehicles. Use proper sports techniques.

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Contact the following sources:

- American Academy of Orthopedic Surgeons Tel: (847) 823-7186 **Website: http://www.aaos.org**
- American Academy of Family Physicians Tel: (800) 274-2237 **Website: http://www.aafp.org**

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MANAGING YOUR

CERVICAL SPONDYLOSIS

What Is Cervical Spondylosis?

The neck (cervical) part of the spinal column is made of seven bones called vertebrae. Discs separate the bones and act as shock absorbers or cushions to let the neck bend. Cervical spondylosis is a disorder that occurs with aging and causes neck pain. It's also called cervical osteoarthritis.

What Causes Cervical Spondylosis?

The disorder usually occurs in people older than 50 because of the wear and tear of aging. It involves arthritis in the neck and may put pressure on the nerves or spinal cord.

What Are the Symptoms of Cervical Spondylosis?

Symptoms include pain in the neck, shoulder blades, arm, hand, and fingers. Weakness in the arms may develop slowly. Numbness and tingling in arms, hands, and fingers, stiff neck, and headaches in back of the head also occur.

How Is Cervical Spondylosis Diagnosed?

The doctor will make a diagnosis from an examination and x-rays of the cervical spine. Magnetic resonance imaging (MRI) of the neck and an electromyogram/nerve conduction velocity test may also be done. This electrical test of nerves and muscles can help tell the extent to which the nerves are damaged.

How Is Cervical Spondylosis Treated?

A collar or neck brace to limit neck motion usually helps the pain. Using the collar too long will weaken neck muscles, however.

Rest and medicines (analgesics and antiinflammatory drugs) are used for acute pain. Muscle

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relaxants are used sparingly and only for short periods.

After the pain leaves, neck exercises are started and are used with the collar. Exercises to move the neck help increase motion and strength. Traction may help some people. Spinal manipulation is not suggested for this disorder.

Surgery is rarely needed. It is considered after other treatments don't work to relieve pressure on the nerves or spinal cord.

DOs and DON'Ts in Managing

Cervical Spondylosis:

✓ **DO** rest, immobilize your neck, and take medicines (analgesics and antiinflammatory drugs) as directed for acute pain.

✓ **DO** exercises that focus on active neck motion and strengthening.

✓ **DO** gently stretch and bend your neck.

✓ **DO** maintain good posture while sitting and walking.

✓ **DO** wear a seat belt when in a motor vehicle.

✓ **DO** minimize trauma to your cervical spine.

✓ **DO** avoid contact sports.

✓ **DO** exercise regularly and keep to your ideal body weight.

✓ **DO** call your doctor if rest and medicine don't help pain. Call immediately if you have sudden muscle weakness or paralysis.

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✓ **DO** call your doctor if you have medicine side effects.

✓ **DO** call your doctor if you have trouble walking, are weak, or cannot move your limbs.

⃠ **DON'T** have spinal manipulations if you have acute pain.

⃠ **DON'T** make your neck "pop."

⃠ **DON'T** slouch in a chair or bed.

⃠ **DON'T** do strenuous activities until your doctor says you can.

⃠ **DON'T** resume driving until you're pain free without pain drugs.

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FOR MORE INFORMATION

Contact the following sources:

- North American Spine Society **Website:** **http://www.spine.org**
- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website:** **http://www.aaos.org**

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MANAGING YOUR

CERVICITIS

What Is Cervicitis?

The cervix is a button-like structure is at the end of the vaginal canal. It has a narrow opening that leads into the uterus (womb). Cervicitis is inflammation of the cervix. It's common and will affect more than half of all women at some time during their lives.

What Causes Cervicitis?

Causes include infections such as gonorrhea, chlamydia, and trichomoniasis (infection with the parasite *Trichomonas vaginalis*). Infections with viruses such as herpes simplex virus or human papillomavirus (HPV), the virus that causes genital warts, can also cause cervicitis. Bacteria such as staphylococcus and streptococcus are other causes. Sometimes a foreign body such as an intrauterine device (IUD) or a forgotten tampon, diaphragm, or pessary can lead to cervicitis. Risk factors include being younger than 25 years old, being single, having many sex partners, and having a history of sexually transmitted disease.

What Are the Symptoms of Cervicitis?

Cervicitis may not cause symptoms and may be found only during a routine gynecological examination. Some women can have increased yellow or cream-colored vaginal discharge. Also, very slight vaginal bleeding may occur, as a pinkish or brownish discharge. Pain in the vagina or during sex may occur.

If cervicitis is caused by chlamydia or gonorrhea and the infection spreads to fallopian tubes, pelvic pain and infertility can result. Itching, irritation, and increased vaginal discharge can occur if *Trichomonas* is the cause. Herpes simplex virus may cause symptoms only if the infection is outside the body, on the vulva.

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How Is Cervicitis Diagnosed?

The doctor makes a diagnosis from a pelvic examination, cultures of the vaginal discharge, and blood tests to check for infections.

How Is Cervicitis Treated?

Treatment depends on the cause. Cervicitis caused by chlamydia, gonorrhea, or *Trichomonas* needs antibiotics. Taking antibiotics can make it more likely that a yeast infection will develop because the antibiotic kills healthy, protective bacteria, so yeast can grow.

Viral infections causing cervicitis cannot be cured, but antiviral medicines can make them less severe and shorten the duration of symptoms.

DOs and DON'Ts in Managing Cervicitis:

✓ **DO** take all your medicines as prescribed, even if your symptoms go away.

✓ **DO** protect yourself from sexually transmitted diseases such as gonorrhea, chlamydia, *Trichomonas*, herpes, and human immunodeficiency virus (HIV) and HPV infections. Know your partner. Use condoms.

✓ **DO** avoid sex until you finish the antibiotic treatment and your vaginal discharge has stopped.

✓ **DO** avoid douches or vaginal sprays. They can irritate the cervix.

✓ **DO** have regular Pap smears.

✓ **DO** call your doctor if you continue to have symptoms, such as vaginal discharge or bleeding, after you finish taking your medicine.

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✓ **DO** call your doctor if you get a fever or pelvic pain while you're taking medicine.

✓ **DO** call your doctor if you cannot tolerate the medicine (e.g., you have nausea), or you have allergic symptoms (e.g., you get a rash).

⃠ **DON'T** drink alcoholic beverages if you're taking metronidazole for *Trichomonas* infection. Combining metronidazole and alcohol can cause severe nausea.

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MANAGING YOUR

CHALAZION

What Is a Chalazion?

A chalazion is a cyst or lump on the eyelid. Chalazions usually cannot be prevented. However, using little or no eye makeup, keeping the eyelids clean, and keeping the face, scalp, eyebrows, and hands clean may reduce the chances of having a chalazion.

What Causes a Chalazion?

A chalazion can be caused by chronic inflammation (swelling, redness) of the eyelid glands. It can also be caused by a blocked oil gland in the eyelid. These glands are modified sweat glands and make secretions to keep the underside of the eyelid moist. An oil gland can become blocked with thickened secretions or dirt. When the gland is blocked, it can burst and become inflamed. Sometimes bacteria grow in the blocked gland and cause an infection.

What Are the Symptoms of a Chalazion?

The main symptom is a lump in the eyelid. A chalazion grows slowly. The lump can become large, but it usually doesn't hurt. In some cases, the eyelid may swell and irritate the eye.

How Is a Chalazion Diagnosed?

The doctor can make a diagnosis by looking at the eye and eyelid and feeling a firm lump on the eyelid. No other tests are needed.

How Is a Chalazion Treated?

As soon as the painless swelling appears, a warm, moist compress placed over the eyelid will help open the blocked eyelash openings and glands. It also helps reduce redness and swelling. The cloth should be kept in place for up to 10 minutes. It should be used four times per day. Squeezing the chalazion or trying to pop the chalazion should not be done.

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Contact the doctor if the eyelid shows no improvement after a couple of days of self-care. The doctor may remove the chalazion surgically, may inject medicine into it, or may prescribe other medicines to be applied directly to the eyelid.

The eyelid must be gently washed with a clean wash cloth or cotton swab.

A chalazion usually goes away after 2 weeks.

DOs and DON'Ts in Managing a Chalazion:

✓ **DO** keep your face, scalp, eyebrows, and hands clean.

✓ **DO** use little or no eye makeup.

✓ **DO** tell your doctor if you don't feel well while you're using the eyedrops or pills.

✓ **DO** call your doctor if your eyelid isn't getting better, hasn't improved in 2 weeks, or is getting worse.

✓ **DO** call your doctor if you get a fever.

⃠ **DON'T** squeeze or try to break open the swollen areas.

⃠ **DON'T** use eyedrops or ointment not given to you by your doctor.

⃠ **DON'T** touch the applicator tip of your eyedrops to any other surface.

⃠ **DON'T** drive, operate machinery, or do anything that could be dangerous if your vision is blurry. Eyedrops and ointment can cause blurred vision.

⃠ **DON'T** wear contact lenses until the chalazion goes away.

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⦸ **DON'T** rub your eyes.

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• American Academy of Ophthalmology Tel: (415) 561-8500 **Website: http://www.aao.org**

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MANAGING YOUR

CHANCROID

What Is Chancroid?

Chancroid is a sexually transmitted disease (STD) that causes painful ulcers involving skin of the genital area. It's very contagious but curable.

Chancroid is rare in the United States but common in other parts of the world. Most people in the United States with chancroid have traveled to countries where it more commonly occurs.

What Causes Chancroid?

A kind of bacteria named *Haemophilus ducreyi* causes chancroid, which is spread by direct contact with open sores.

What Are the Symptoms of Chancroid?

Symptoms appear 4 to 7 days after exposure. Many raised sores that have red skin around them appear. These sores rapidly break down and become painful ulcers. Women most often have ulcers on the outer part of the vagina. Lymph glands (nodes) on one side of the groin area, in the fold between the leg and lower abdomen (belly), may get larger. Fever, headache, chills, and fatigue may occur. Women may have no obvious signs of infection, but the most common symptoms they have are pain with urination and with sex.

How Is Chancroid Diagnosed?

The doctor makes a diagnosis by examining the skin and taking samples of the lesions for culture (to see whether the bacteria will grow).

The doctor will test blood for other STDs. Sexual contacts should also be tested.

How Is Chancroid Treated?

The doctor will prescribe antibiotics to be taken by mouth (azithromycin, ciprofloxacin, or eryth-

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romycin) or to be given by one injection (ceftriaxone). Pain medicine may also be prescribed. Lesions should be washed three times a day with soap and water and kept dry. No creams, lotions, or oils should be used on or near the sores, because they increase the chance of spreading the lesions. Sexual relations should be avoided until a follow-up examination shows complete healing, which usually occurs in 2 to 3 weeks.

DOs and DON'Ts in Managing Chancroid:

✓ **DO** take your prescribed antibiotics until they're gone.

✓ **DO** take pain medicine if needed.

✓ **DO** wash infected areas with soap and water three times a day and dry completely.

✓ **DO** tell your sexual contacts about your infection so that they can get treatment.

✓ **DO** avoid sexual relations until an examination by your doctor shows that it is safe to do so. Avoid STDs by using condoms during sex.

✓ **DO** get tested for other STDs.

✓ **DO** call your doctor if you still have a fever after you finish your antibiotics.

✓ **DO** call your doctor if over-the-counter pain medicine doesn't help your pain.

✓ **DO** call your doctor if any lesion appears infected.

⦸ **DON'T** skip doses or stop taking your antibiotics before they're finished, even if you feel better.

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⦸ **DON'T** put creams, lotions, or oils on or near the lesions.

⦸ **DON'T** have sexual relations until your doctor says you can.

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FOR MORE INFORMATION

Contact the following sources:

- Centers for Disease Control and Prevention National Center for HIV/AIDS, Viral, Hepatitis, STD, and TB Prevention **Website: http://www.cdc.gov/std**
- American Social Health Association STI Resource Center Hotline: (800) 227-8922 **Website: http://www.ashastd.org**

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MANAGING YOUR

CHARCOT JOINT

What Is Charcot Joint?

Charcot joint is a chronic condition that mainly affects joints in weight-bearing extremities, such as feet and ankles. It's a process in which joints are destroyed. People with a Charcot joint have reduced sensation in the affected area and problems with nerves that take information to and from the brain and spinal cord (called peripheral neuropathy).

What Causes Charcot Joint?

The most common cause is diabetes. People with diabetes first have peripheral neuropathy, and then develop Charcot joints.

What Are the Symptoms of Charcot Joint?

Symptoms may include swelling, pain, and increased skin temperature over the affected joint. Instability of the joint, loss of sensation, bleeding, and bone changes may also occur.

Charcot joint is relatively painless, often in spite of considerable joint destruction, and people often do not go to the doctor until the deformity is severe.

How Is Charcot Joint Diagnosed?

The doctor can make a diagnosis by doing a physical examination. X-rays will also be done. X-rays can show the degree of joint destruction and show loss of cartilage, new bone growth, and breaks at the joint.

Sometimes, Charcot joint can be confused with infection, but most people with this disorder have acute inflammation (swelling, redness) but no trauma or cuts or breaks in the skin, which would suggest infection.

Charcot joint is treatable but not curable. Early diagnosis, before the joint becomes badly

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damaged, is essential.

How Is Charcot Joint Treated?

No drugs are available for treatment. Immobilizing the extremity and using crutches, a cane, or a walker help manage the acute condition. These protect the joint by reducing or eliminating weight bearing by the extremity. Some diseases causing Charcot joint may be treated effectively. However, nerves will not grow back after treatment, and the joint condition may continue to get worse. Surgery is rarely used and is not very successful.

It can take as long as 6 weeks for acute inflammation to go away. Then, joints probably need a brace or other support to prevent flare-ups and joint destruction.

Prevention is key to minimizing joint deformities. Ignoring warning signs may lead to joint destruction with disintegration of the bones and collapse.

DOs and DON'Ts in Managing Charcot Joint:

✓ **DO** control your diabetes with proper medicines, diet, and exercise.

✓ **DO** modify your exercise program. Substitute non–weight-bearing exercises such as cycling and water exercises.

✓ **DO** call your doctor if you notice swelling, heat, or redness around any weight-bearing joint, especially if the joint was treated before.

✓ **DO** call your doctor at the earliest start of swelling, redness, and increased skin temperature over an affected joint.

⃠ **DON'T** begin an aggressive walking or running program right after being fitted with braces or splints.

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- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website: http://www.aaos.org**
- American Diabetes Association Tel: (800) 342-2383 **Website: http://www.diabetes.org**

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MANAGING YOUR

CHARCOT-MARIE-TOOTH DISEASE

What Is Charcot-Marie-Tooth Disease?

Charcot-Marie-Tooth disease has nothing to do with teeth. It's named after the three doctors who first diagnosed it. This inherited disease affects nerves and causes muscles of the legs, hands, and feet to weaken and lose feeling. The illness develops slowly and is usually noted between 10 and 20 years of age. It can also affect people 50 to 60 years old. Men are more likely than women to have it, by a ratio of 3 to 1. It doesn't usually shorten life.

What Causes Charcot-Marie-Tooth Disease?

The cause is mutations in genes affecting nerves going to and from the brain. The nerves don't send electrical signals to muscles to make them contract.

What Are the Symptoms of Charcot-Marie-Tooth Disease?

The most common symptoms are weak muscles, loss of muscle tone from knees down, unusual feet (high arches, curled-up toes), trouble walking, muscle cramping, bone and muscle pain, and foot sores that don't heal.

Foot deformities, hammer toes, and foot drop can occur. People can't feel hot, cold, vibration, and light touch. People also get numbness and feel off balance and unsteady. Loss of feeling can lead to cuts, infections, and ulcers.

How Is Charcot-Marie-Tooth Disease Diagnosed?

The doctor makes a diagnosis by doing nerve conduction studies. These tests record electrical responses of a muscle to stimulation of its nerve at two points along the nerve. Also, the doctor will order electromyography (EMG) to measure the pattern of electrical activity in the muscle. The doctor may also get a biopsy sample of a nerve. In a biopsy, a small piece of the nerve is

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removed for study with a microscope.

How Is Charcot-Marie-Tooth Disease Treated?

No treatment can cure the disease. The disease can later affect hand muscles, usually stopping at elbows and midthighs. Physical therapy can help make muscles stronger. Occupational therapy, leg braces, custom shoes, and shoe inserts help prevent ligament and tendon damage, skin breakdown, and ulcer formation.

The doctor can prescribe pain relievers. Surgery can sometimes correct major foot deformities.

DOs and DON'Ts in Managing

Charcot-Marie-Tooth Disease:

✓ **DO** have a positive attitude.

✓ **DO** follow your doctor's suggestions for physical and occupational therapy. Vigorous physical therapy may help preserve muscle function.

✓ **DO** get advice from people and facilities with experience in this disease. A neurologist (doctor specializing in diseases of the brain and spinal cord) is the best person to ask.

✓ **DO** call your doctor if you notice muscle weakness of your feet and hands.

✓ **DO** call your doctor if a family member was diagnosed with this disease. Get genetic counseling. The disease is inherited and cannot be prevented.

⃠ **DON'T** ignore symptoms. Early treatment may help preserve some muscle and nerve function.

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⦸ **DON'T** forget that Charcot-Marie-Tooth disease is NOT muscular dystrophy or multiple sclerosis. Muscular dystrophy involves muscles directly. Multiple sclerosis involves the brain and spinal cord.

⦸ **DON'T** confuse this disease with Lou Gehrig's disease (amyotrophic lateral sclerosis [ALS]).

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FOR MORE INFORMATION

Contact the following source:

- Charcot-Marie-Tooth Association Tel: (610) 499-9264, (800) 606-2682 **Website:** **http://www.charcot-marie-tooth.org**

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MANAGING YOUR

CHICKENPOX

What Is Chickenpox?

Chickenpox (also called varicella) is a highly contagious viral disease that affects skin and mucous membranes. Most cases occur in young people, often children 2 to 8 years old. Adults usually have a more severe illness that lasts longer.

People develop immunity or resistance to chickenpox when they get it the first time and are unlikely to get it again. Some people may later develop shingles (herpes zoster), a reactivation of chickenpox virus, if their immunity weakens.

Immunizations with varicella-zoster vaccine can prevent chickenpox and shingles.

What Causes Chickenpox?

The cause is varicella-zoster herpesvirus. People catch chickenpox, when they are around someone who has it, by breathing in droplets containing virus. People also catch it by direct contact with skin lesions on infected people.

What Are the Symptoms of Chickenpox?

Symptoms develop 7 to 21 days after exposure. They include slight fever, runny nose, slight cough, headache, tiredness, and no appetite.

Red spots that appear on the body 2 to 3 days later develop into an itchy rash that forms blisters, which dry and become scabs in 4 to 5 days. People may have only a few blisters, or more than 500 may appear. Chickenpox is usually contagious 1 to 2 days before the rash and up to 6 days after blisters form. The mouth, ears, and eyes can also have ulcers.

How Is Chickenpox Diagnosed?

The doctor will make a diagnosis by the medical history and by looking at the rash.

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How Is Chickenpox Treated?

Healthy children need no specific medicine but can get symptom relief. Nonaspirin products such as acetaminophen can reduce fever. DON'T give aspirin to children with chickenpox. Antihistamines, lotions such as calamine, and oatmeal baths can reduce itching. Drinking liquids and resting are recommended. To prevent spreading chickenpox, keep children away from others until blisters have crusted.

People at high risk for severe infection and people with impaired immune systems (e.g., those with bone marrow transplants or leukemia) may get antiviral drugs to prevent complications from chickenpox.

DOs and DON'Ts in Managing Chickenpox:

✓ **DO** call your doctor at once if you're pregnant and think that you were exposed to chickenpox.

✓ **DO** wash your hands regularly and wash bed linens and recently worn clothes with hot, soapy water.

✓ **DO** keep fingernails short to prevent scratching and avoid infection.

✓ **DO** rest, but allow quiet activity.

✓ **DO** use nonaspirin drugs for fever.

✓ **DO** notify school nurses and parents of playmates who may have been exposed.

✓ **DO** use antihistamines and cool sponge baths to reduce itching.

✓ **DO** call your doctor if your temperature is higher than 101° F or if weakness, headache, or sen-

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sitivity to light develop.

✓ **DO** call your doctor if vomiting, restlessness, and irritability occur, with decreased consciousness.

✓ **DO** know that a vaccine for chickenpox is available for those who have not yet had the disease.

⃠ **DON'T** scratch blisters or scabs.

⃠ **DON'T** expose pregnant women, newborns, elderly people, or those with low resistance to infection to chickenpox.

⃠ **DON'T** let infected children go to school or day care for at least 6 days after the first blisters appear. Dried, crusted scabs are not infectious.

⃠ **DON'T** give aspirin to children younger than 16 years because of the risk of Reye's syndrome.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- National Institute of Allergy and Infectious Diseases Tel: (866) 284-4107 **Website:** **http://www3.niaid.nih.gov**
- The American Academy of Pediatrics
- U.S. Department of Health & Human Services **Website:** **http://www.healthfinder.gov**

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PROTECTING CHILDREN FROM ABUSE

How Common Is Child Abuse?

Child abuse and neglect are major social problems in the United States. The number of alleged abuse incidents reported to state and local child protective services has skyrocketed, and statistics today show that physical abuse is the leading cause of death for children younger than 1 year. The highest incidence of child abuse from birth to 18 years occurs in first year of life, and more than two thirds of victims of physical abuse are younger than 6 years.

What Causes Child Abuse?

Child abuse and mistreatment appear to be associated with poverty, unemployment, child disability, psychiatric problems in parents, substance abuse by parents, parents being abused as children, antisocial behavior of parents, and whether pregnancy was planned. However, these factors alone don't seem to predict the occurrence of abuse. The problem may be more child neglect than abuse. Neglect sometimes results from depression or other mental illness in the parents. Some parents, especially young, first-time parents, may be overwhelmed by caring for a child, become frustrated, and direct anger and frustration at the child.

What Are the Symptoms of Child Abuse?

Children may have orthopedic injuries, bruises, or x-ray evidence of repeated fractures. Shaken infant syndrome is associated with high death rates and physical injury. Child abuse can result in bleeding into the brain, blindness, and injuries to abdominal organs. These injuries account for most of deaths from child abuse.

As many as 30% of cases of failure to thrive in children are thought to be caused by neglect. Failure to thrive may lead to severe behavioral problems later in life. Child abuse may also in-

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volve sexual abuse.

How Is Child Abuse Diagnosed?

Abused children have significant problems in emotional, social, and behavioral functioning. They have difficulty trusting others. They may feel guilt and low self-esteem because they believe that they were responsible for the abuse. Abused children have poor social behavior and tend to show anger and aggression toward playmates and schoolmates. They are more likely to have major psychiatric problems such as posttraumatic stress disorder, depression, anxiety, phobias, and personality disorders.

Staff in most emergency departments note children who come in frequently, especially with orthopedic injuries, and who have bruises or on x-ray evidence of old fractures. Physicians and other medical caregivers must report suspected child abuse and can face sanctions for not doing so.

How Is Child Abuse Handled?

Neighbors, family members, or medical personnel who report suspected abuse may prompt treatment.

The primary, most important goal is protection of the child. Medical consequences of abuse must be evaluated and treated, and the child should have psychological therapy. Such treatment often involves using play therapy, including dolls and puppets. Abusers also require treatment, regardless of whether they become involved in the criminal justice system. Support groups for such parents have helped. Many states have a program for monitoring pregnancies to assess whether it is safe for those babies to return home.

Many adults have flashbacks to childhood physical and sexual abuse that make it more likely that they will have psychiatric disorders, including borderline and multiple personality disorder,

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eating disorders, posttraumatic stress disorder, and alcohol and drug abuse.

The Approach to Child Abuse

The best approach to child abuse is prevention. Evaluating the level of support and the support network for new parents, providing parenting classes, and encouraging new parents to discuss concerns and fears would help. Overwhelmed parents should not be embarrassed to seek medical help and counseling.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- There are several commercial videos available through your local library or children's hospital. The book entitled *How to Raise a Street Smart Child* is particularly helpful.
- Child Abuse Prevention Association Tel: (816) 252-8388 **Website:** **http://www.childabuseprevention.org**
- Childhelp USA Tel: (480) 922-8212 **Website:** **http://www.childhelpusa.org**

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ENSURING YOUR

CHILD'S SAFETY

What Are Child Safety Issues?

Childhood accidents are one of the leading causes of pediatric injuries and death. Many can be prevented by paying attention to certain safety issues. Safety issues involve childproofing homes and vehicles to avoid major causes of injuries: burning, drowning, and poisoning. Care is also needed outside the home, during play and sports and in public places such as shopping malls.

What Causes Childhood Injuries?

Burns result from fire, hot water, and contact with electricity and chemicals. Males and children younger than 5 are at highest risk, especially from bathing injuries or hot liquid spills. Putting items into plugs, chewing on plugs or electrical cords, and risk-taking behaviors (in teens) can cause electrical burns. Acids (such as toilet cleaners) and alkaline agents (such as lye and bleach) can cause injuries by direct contact or swallowing.

Drowning is the second leading cause of accidental childhood death in the United States. It can also cause serious neurologic illness. Young toddlers and teens, more boys than girls, drown most often. Small sources such as bathtubs and buckets are dangerous to toddlers. Teens often drown during recreational activities such as boating.

Poisoning, frequently accidental, is one of the most common medical emergencies in young children and teens. Most often, household products (cosmetics, cleaning substances, painkillers) are to blame. The most lethal are usually related to medicines.

How Are Childhood Injuries Treated?

Treatment of minor burns involves basic first aid—running cool water over the area—but not ice, butter, or ointments. Doctors should treat more serious burns. Emergency services should be

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called for drowning victims. Poisoning treatments involve stabilizing children and getting rid of toxins, such as by flushing exposed eyes and decontaminating the stomach. All poisonings should be reported to local poison control centers, who can help parents initiate home management and facilitate care in the office or emergency room.

How Can Childhood Injuries Be Prevented?

Burn injury prevention includes measures such as lowering water heater temperatures, installing smoke detectors, and using flame-retardant sleepwear. Cover electrical outlets, and unplug irons when not in use. Teach children that flames, matches, lighters, and fireworks aren't toys. Keep fire extinguishers handy, and teach children what to do for house fires.

Toddlers can fall into toilets, buckets, or fish tanks, and children can drown in just 1 inch of water. More than 80% of drownings may be prevented by closely supervising toddlers, fencing home pools, and teaching teens about water safety.

Simple ways to prevent poisoning include using child-resistant pill bottle caps. Store medicines, cleaners, and other dangerous substances in locked cabinets.

Other safety measures include teaching children how to cross streets safely and be careful about talking to strangers. Using car seats is crucial and reduces risks of death by 71% for babies and 54% for toddlers. Put these seats in back seats of vehicles facing the rear of the car until your child is old enough and weighs enough to turn the car seat to face the front (12 months and 20 pounds). Use booster seats until children are big enough for regular seatbelts.

DOs and DON'Ts in Child Safety:

✓ **DO** childproof your home. Cover electrical outlets. Install safety latches and gates, in addition to door and drawer locks.

✓ **DO** supervise young children closely. You can help prevent all kinds of injuries by watching

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children carefully.

✓ **DO** use car seats and booster seats correctly. See www.seatcheck.org for tips.

✓ **DO** call 911 for drowning emergencies and 1-800-222-1222 for poisonings.

✓ **DO** lock up all firearms in the house and keep all ammunition in a separate locked cabinet or safe.

✓ **DO** install smoke detectors on all floors of your home. Set the water temperature to 120° F.

✓ **DO** supervise children while bathing AT ALL TIMES.

⊘ **DON'T** leave dangerous substances or tools where children can reach them.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Association of Poison Control Centers Tel: (800) 222-1222 **Website: http://www.aapcc.org**
- The American Academy of Pediatrics Tel: (847) 434-4000 **Website: http://www.aap.org**
- Seat Check Tel: (866) SEAT-CHECK **Website: http://www.seatcheck.org**

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MANAGING YOUR

CHOLECYSTITIS

What Is Cholecystitis?

The gallbladder is a small sac located under the liver. It stores bile that the liver makes and squirts bile into the bowel (intestine) when a meal is eaten. Bile helps digest fats in the food. Cholecystitis is inflammation of the gallbladder. It's often called a gallbladder attack. Cholecystitis is usually caused by gallstones that get stuck in the duct (tube) that takes bile from the gallbladder to the bowel.

What Causes Cholecystitis?

Cholecystitis is usually caused by gallstones (called cholelithiasis) but it can also be related to problems with bile being made or stored in the gallbladder. This other type is called acalculous, meaning without calculi (stones). Other causes are sickle cell disease, infections, and diabetes. The acalculous type is found more often in older men, very sick people, or bedridden elderly people. Other risk factors for cholecystitis are like those for gallstones. They include age, female sex, certain ethnic groups (such as Native Americans), obesity, fasting, high-fat diet, losing and gaining weight excessively, drugs, and pregnancy.

What Are the Symptoms of Cholecystitis?

The most common symptoms are pain and cramping in the upper right side of the abdomen (belly). Pain in the chest, upper back, or right shoulder may also occur. Pain is worse with breathing in or moving or when pressure is on the area. Belching, nausea, and vomiting can occur, usually after eating high-fat foods. Low temperature, yellow skin and whites of the eyes, pale stools (bowel movements), and itchy skin may occur if the main duct bringing bile to the intestines is blocked by a stone. An infected gallbladder may cause high temperature and chills.

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How Is Cholecystitis Diagnosed?

The doctor makes a diagnosis from a medical history and physical examination. X-rays, blood tests, and ultrasonography will confirm it. When ultrasonography shows unclear results, the doctor uses a special x-ray test (HIDA scan).

How Is Cholecystitis Treated?

For treatment, the gallbladder and gallstones are removed by surgery (cholecystectomy). Laparoscopic removal is the usual method. It allows shorter recovery and can be an outpatient surgery. For laparoscopic removal, the surgeon makes four tiny cuts in the abdomen. The surgeon uses instruments through these cuts to remove the gallbladder. If laparoscopic surgery cannot be used, standard surgery is done, which will require a prolonged hospital stay.

Removing the gallbladder doesn't affect normal living, except for occasional indigestion when eating fatty foo for 6 to 12 months after gallbladder removal. This problem usually goes away.

Drugs can also be used to dissolve stones, but medicines can take months or years to work and are only rarely used.

DOs and DON'Ts in Managing Cholecystitis:

✓ **DO** tell your doctor if you have pain that you think may be caused by gallstones.

✓ **DO** call your doctor right away if you get a fever with abdominal pain.

✓ **DO** maintain a normal weight.

⃠ **DON'T** eat meals high in fat, extra-large meals, and foods that cause symptoms. Fatty foods make the gallbladder contract and may squeeze a stone into the duct. Avoid high-fat meals.

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⦸ **DON'T** fast for long periods or go on crash diets.

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FOR MORE INFORMATION

Contact the following sources:

• National Digestive Diseases Information Clearinghouse Tel: (301) 654-3810, (800) 891-5389 **Website:** **http://www.niddk.nih.gov/health/digest/ nddic.htm**

• MedlinePlus **Website:** **http://www.nlm.nih.gov/medlineplus/ gallbladderdiseases.html**

• American Gastroenterological Association Tel: (301) 654-2055 **Website:** **http://www.gastro.org**

• American College of Gastroenterology Tel: (703) 820-7400 **Website:** **http://www.acg.gi.org**

• American College of Surgeons Tel: (312) 202-5000, (800) 621-4111 **Website:** **http://www.facs.org**

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MANAGING YOUR

CHRONIC FATIGUE SYNDROME

What Is Chronic Fatigue Syndrome?

Chronic fatigue syndrome (CFS) is a debilitating condition in which people feel tired most or all of the time. The symptoms often include muscle aches and difficulty concentrating and last at least 6 months. Symptoms can come and go over long periods, and many people can have serious problems, including being unable to work. With good lifestyle habits, many people, especially those with CFS that occurred after a viral infection, improve or recover completely after 2 to 3 years.

What Causes CFS?

The cause is unknown. Some believe that it is a complication of a viral infection, but no viruses have been identified. An abnormal response to an infection of the body's immune system (the system that fights infections) or stress may have a role in CSF.

What Are the Symptoms of CFS?

The most common complaints, apart from feeling tired, weak, or exhausted most of the time, include confusion and problems with concentration and memory, trouble sleeping, headache, sore throat, slight fever, vision changes, and pain in muscles, joints, and bones.

How Is CFS Diagnosed?

No specific test can diagnose CFS. The doctor makes a diagnosis after noting specific symptoms present for at least 6 months: lasting, unexplained fatigue that isn't the result of ongoing exertion, isn't helped by rest, and results in a considerable reduction in activities.

Other symptoms include problems with memory or concentration, sore throat, tender lymph nodes (swollen glands), muscle pain, headache, pain in many joints, and unrefreshing sleep.

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How Is CFS Treated?

No cure is available, but supportive care from the doctor and family members is very important. The doctor may prescribe antiinflammatory medications to help with muscle aches. Antidepressants may also be prescribed. The doctor will likely suggest an exercise program and a balanced diet. Counseling and behavior therapy may help with coping with CFS symptoms.

DOs and DON'Ts in Managing CFS:

✓ **DO** follow your doctor's advice.

✓ **DO** take your medicine.

✓ **DO** keep a positive mental outlook, and remember that setbacks may occur.

✓ **DO** begin an exercise program based on your doctor's advice.

✓ **DO** eat a balanced, low-fat, high-fiber diet.

✓ **DO** call your doctor if symptoms get worse after treatment starts.

⃠ **DON'T** get discouraged about CFS and its treatment if you have setbacks.

⃠ **DON'T** exercise too hard.

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FOR MORE INFORMATION

Contact the following source:

- Chronic Fatigue and Immune Dysfunction Syndrome Association of America Tel: (800) 442-

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3437 **Website: http://www.cfids.org**

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MANAGING YOUR

CHRONIC LYMPHOCYTIC LEUKEMIA

What Is Chronic Lymphocytic Leukemia?

Leukemia is cancer of the white blood cells. Bone marrow is spongy tissue in the middle of bones. Blood cells form and develop in marrow and then move into the bloodstream. Leukemia can be acute or chronic. Acute leukemia affects cells in bone marrow before they fully develop. Chronic leukemia affects fully grown cells.

Chronic lymphocytic leukemia (CLL) causes too many white blood cells to be produced. These cells don't work normally, so people have greater chances of getting serious infections and bleeding.

CLL is the most common type of leukemia in Western countries. It usually occurs among people older than 60, in women twice as often as men. Many people with CLL have a normal lifespan due to a long life expectancy with this disease and the elderly age of most people at time of diagnosis. CLL cannot be prevented.

What Causes CLL?

The cause of CLL is unknown. It cannot be caught but does seem to run in families. Also, one third of people with CLL have an extra chromosome 13 (producing trisomy 13).

What Are the Symptoms of CLL?

The most common symptoms are feeling sick and extremely tired. Swollen glands (enlarged lymph nodes) or recurrent infections due to a weakened immune system can sometimes be the first symptom. People may also have nosebleeds, easy bruising, or other bleeding problems, and weakness from anemia (low red blood cell count) or thrombocytopenia (low platelet count). Other symptoms in advanced stages are shortness of breath, weight loss, discomfort in the abdo-

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men (belly), joint pain and swelling, and fever. Problems with the body's immune (infection-fighting) system lead to special types of blood problems (anemia, thrombocytopenia) and increased chances for bacterial, fungal, and unusual viral infections.

How Is CLL Diagnosed?

About one quarter of people have no symptoms. CLL is often found from blood tests done for another reason. These people have too many white blood cells, swollen glands, or enlarged spleen (the spleen makes and stores blood cells). The doctor may order more blood tests, bone marrow sample, chest x-rays, and computed tomography to determine the stage of CLL.

How Is CLL Treated?

People with no symptoms may need no treatment, but the doctor will watch them carefully. The doctor will suggest seeing a hematologist, a specialist in leukemia treatment.

People with symptoms receive chemotherapy. Chemotherapy can cause side effects, including nausea, vomiting, diarrhea, mouth sores, weakness, bleeding, greater chance of getting more infections, and other cancers.

Radiation therapy to the spleen and lymphoid tissue can help control some symptoms. Sometimes the spleen is removed, but this doesn't affect normal living.

Bone marrow transplantation may cure younger people with CLL. Transplantation replaces diseased marrow with healthy marrow. It is not commonly done in CLL due to the advanced age of most patients.

DOs and DON'Ts in Managing CLL:

✓ **DO** take medicine as directed for infections.

✓ **DO** avoid being cut or injured, and use a soft toothbrush to avoid scraping your gums.

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✓ **DO** avoid dairy products, fresh fruits, and vegetables after chemotherapy.

✓ **DO** call your doctor if you have fever, abdominal pain, rapid increase in spleen or lymph gland size, or bleeding (e.g., from gums).

⃠ **DON'T** use aspirin or aspirin-containing products without consent from your doctor.

⃠ **DON'T** eat uncooked vegetables, fruits, and milk products.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- The American Cancer Society Tel: (800) ACS-2354 or (404) 320-3333 **Website:** **http://www.cancer.org**
- The Leukemia and Lymphoma Society Tel: (914) 949-5213 or (800) 955-4572 **Website:** **http://www.leukemia-lymphoma.org**
- Cancer Care Inc. Tel: (800) 813-HOPE (813-4673) **Website:** **http://www.cancercare.org**
- National Comprehensive Cancer Network Tel: (888) 909-6226 **Website:** **http://www.nccn.org**

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MANAGING YOUR

CHRONIC MYELOGENOUS LEUKEMIA

What Is Chronic Myelogenous Leukemia?

Leukemia is cancer of the white blood cells. Bone marrow is spongy tissue in the middle of bones. Blood cells form and develop in marrow and then move into the bloodstream. Leukemia can be acute or chronic. Acute leukemia affects young (immature) cells in bone marrow. Chronic leukemia affects fully grown cells. About 20% of adult leukemia cases are chronic myelogenous leukemia (CML).

CML causes bone marrow to make too many white blood cells. These cells don't work normally.

In chronic CML, white blood cells become more immature and cannot fight infection. In advanced CML, most white blood cells are myeloblasts, the most immature cell, and people can get serious infections. CML occurs among people of all ages but is most common after age 60. CML cannot be caught or prevented and usually isn't passed on from parents to children.

What Causes CML?

The cause is unknown, but exposure to chemicals such as benzene and high radiation doses may be involved. Also, CML cells contain a chromosome abnormality (Philadelphia chromosome, found in over 95 percent of people with CML).

What Are the Symptoms of CML?

Many people with chronic CML have no or few symptoms. Some feel fullness in the abdomen (belly) from a large spleen. Some people may have tiredness, loss of appetite and weight, sweating, swollen or bruised gums, shortness of breath, bleeding, and bone pain.

Anemia (low red blood cell count) and thrombocytopenia (low platelet count) occur later.

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People with advanced CML may have severe headaches or shortness of breath (high numbers of myeloblasts get stuck in the lungs and brain).

How Is CML Diagnosed?

The doctor diagnoses chronic CML by blood and bone marrow tests that show a high white blood cell count, high platelet count, and Philadelphia chromosomes in marrow cells. For a bone marrow biopsy, a long hollow needle is inserted into the bone to remove a marrow sample for study with a microscope.

How Is CML Treated?

Hematologists (specialists in blood diseases) or oncologists (specialists in cancer) treat people with CML. Treatment consists of medications or bone marrow transplantation (replacement of diseased marrow).

The best drug treatment is imatinib (Gleevec). In marrow transplantation, the abnormal bone marrow is replaced with healthy marrow or is treated with medicine. Marrow donors are usually close relatives (brother, sister) or volunteers whose marrow is a close match. Transplantation has many side effects or complications including hair loss and mouth sores, infections, and life-threatening graft-versus-host disease.

DOs and DON'Ts in Managing CML:

✓ **DO** keep an active lifestyle, but exercise with caution.

✓ **DO** ask your doctor about diet limits.

✓ **DO** get a flu shot every fall.

✓ **DO** brush your teeth with a soft toothbrush.

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✓ **DO** shave only with an electric razor if you have accelerated or advanced CML.

✓ **DO** tell your doctor if you have new symptoms or unexplained tiredness, weight loss, pain in the left side of your abdomen, bleeding, fever, sudden severe headaches, or shortness of breath.

⃠ **DON'T** eat uncooked fruits, vegetables, and milk products during or immediately after chemotherapy.

⃠ **DON'T** play contact sports if your platelet count is low.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Cancer Society Tel: (800) ACS-2345 or (403) 320-3333 **Website:** **http://www.cancer.org**
- The Leukemia and Lymphoma Society Tel: (800) 955-4572 **Website:** **http://www.leukemia-lymphoma.org**
- National Marrow Donor Program Tel: (800) 627-7692 **Website:** **http://www.marrow.org**
- National Cancer Institute Tel: (800) 4-CANCER (422-6237) **Website:** **http://www.cancer.gov**

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MANAGING YOUR

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

What Is Chronic Obstructive Pulmonary Disease (COPD)?

Chronic obstructive pulmonary disease (COPD) is the name of illnesses that damage lungs and make it hard to breathe. Traditionally, two common types of COPD were known as chronic bronchitis and emphysema. Most cases of COPD are a mixture of both diseases. Chronic bronchitis involves having excessive mucus (phlegm) for at least 3 months of 2 consecutive years. Emphysema is caused by destruction of air sacs in lungs. Air that's breathed in stays trapped in the lungs, and exchange of oxygen and carbon dioxide doesn't occur in the air sacs.

COPD is usually progressive and not curable, but stopping smoking and drugs can help people live longer.

What Causes COPD?

Long-term smoking and heredity are the most common causes. Others include air pollution, childhood infections, and inhalation injury. COPD isn't contagious.

What Are the Signs and Symptoms of COPD?

Signs and symptoms include shortness of breath that worsens with exercise or frequent upper respiratory infections (such as a cold). As COPD gets worse, people have more trouble breathing, even when resting; lasting cough or need to clear the throat; a lot of mucus; chest tightness; and anxiety. Chronic bronchitis may cause sleep problems from mucus in the airways. Other symptoms are frequent lung infections, wheezing, weight gain, and bluish color of lips or skin. Emphysema causes shortness of breath, barrel-shaped chest, and weight loss, but little cough or sputum production. These diseases can lead to increased strain on the heart.

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How Is COPD Diagnosed?

The doctor makes a diagnosis from symptoms, complete physical examination, pulmonary (lung) function tests, chest x-ray, and levels of oxygen and carbon dioxide in blood in arteries.

How Is COPD Treated?

Treatment goals are to relieve symptoms. A pulmonary doctor (specialist in breathing disorders) may be involved in care.

Treatments include stopping smoking, exercise, airway dilators, hydration, vaccinations for influenza and pneumonia, oxygen, antibiotics, decongestants, and breathing exercises. Oxygen can be supplied by tank, even a portable one, so people can travel with it. Decongestants help loosen airway mucus. Changes in posture help mucus to drain. Antibiotics and vaccinations reduce the number of infections. In rare cases, lung transplantation is for people with inherited disease.

DOs and DON'Ts in Managing COPD:

✓ **DO** stop smoking. This is extremely important.

✓ **DO** avoid substances that make it hard to breathe, such as chemicals on the job or fumes from heating or cooking.

✓ **DO** avoid contact with people that have colds or upper respiratory infections. Wash your hands often.

✓ **DO** get a flu shot each year.

✓ **DO** get a pneumonia vaccination every 5 years.

✓ **DO** keep your house well ventilated.

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✓ **DO** call your doctor if medicine doesn't help shortness of breath or cough.

✓ **DO** call your doctor if you always feel tired or are losing a lot of weight involuntarily.

✓ **DO** call your doctor if you notice a bluish color in your lips or nails.

⃠ **DON'T** adjust your medicines (including oxygen) without first talking with your doctor.

⃠ **DON'T** go outside or exercise if air is polluted or if the air quality index is poor.

⃠ **DON'T** spend a lot of money on air cleaners. They don't usually help much.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

• National Heart, Lung, and Blood Institute National Institutes of Health Tel: (301) 592-8573

Website: **http://www.nhlbi.nih.gov**

• National Lung Health Education Program Tel: (972) 910-8555 **Website:**

http://www.nlhep.org

• American Lung Association Tel: (800) 586-4872 **Website:** **http://www.lungusa.org**

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MANAGING YOUR

CHRONIC PANCREATITIS

What Is Chronic Pancreatitis?

The pancreas is a gland in the abdomen (belly), surrounded by the stomach, intestines, and other organs. It makes substances called pancreatic juices (containing digestive enzymes) and the hormones insulin and glucagon.

Pancreatitis is inflammation (swelling) of the pancreas. It occurs when these digestive enzymes begin attacking the pancreas. Pancreatitis can be acute (occurs suddenly). Continuing injury to the pancreas may lead to a long-lasting (chronic) form. The pancreas doesn't make its enzymes, causing an inability to digest and absorb fat in the diet. Insulin production also decreases.

Chronic pancreatitis isn't common. More men than women are affected. Pancreatitis cannot be caught.

What Causes Chronic Pancreatitis?

Alcohol abuse is the major cause. Other causes are hemochromatosis (too much iron in the blood) and cystic fibrosis. Sometimes the cause is unknown.

What Are the Symptoms of Chronic Pancreatitis?

The most common symptom is pain in the mid and upper back and abdomen that varies in intensity. It may be a low-grade, lasting pain with repeated acute attacks. The pain may be constant and severe.

Another symptom is weight loss, which occurs because the body cannot absorb fat properly (malabsorption). Large, foul, bulky bowel movements, or stools (called steatorrhea) occur because of this problem with fat absorption. People can also have a distended abdomen and fever.

How Is Chronic Pancreatitis Diagnosed?

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The doctor diagnoses chronic pancreatitis by reviewing the medical history and doing a physical examination. Samples of blood are studied for signs of this disease. A CT scan or ultrasound of the abdomen may also be done to exclude other causes of your symptoms.

How Is Chronic Pancreatitis Treated?

The first treatment goal is to manage pain, usually by using nonnarcotic pain relievers. Referral to a pain specialist may help. In rare cases, if pain cannot be controlled, surgery is a possibility. Surgery involves draining the pancreatic duct (tube connecting the pancreas and bile duct). In advanced cases, all or part of the pancreas can be removed.

The second goal is replacing digestive enzymes and insulin that the pancreas normally makes. In severe cases, insulin replacement may also be necessary. Pancreatic enzymes, as tablets, are taken with meals and snacks. Insulin injections are used to control the blood sugar (glucose) level. Supplements of vitamins A, D, and K may be needed because of poor absorption.

DOs and DON'Ts in Managing Chronic Pancreatitis:

✓ **DO** eat a low-fat, well-balanced diet.

✓ **DO** take oral fat-soluble vitamin supplements and calcium supplements.

✓ **DO** take pancreatic enzyme supplements as prescribed.

✓ **DO** call your doctor if you cannot control pain with prescribed drugs. See a pain specialist if pain control is difficult.

✓ **DO** call your doctor if you get symptoms of pancreatitis or symptoms worsen or don't improve with treatment.

✓ **DO** call your doctor if you get a fever.

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⦸ **DON'T** eat fatty foods.

⦸ **DON'T** drink alcohol or caffeinated beverages.

⦸ **DON'T** use narcotics for pain control for long periods.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Gastroenterological Association Tel: (301) 654-2055 **Website:** **http://www.gastro.org**
- National Digestive Diseases Information Clearinghouse Tel: (800) 891-5389 **Website:** **http://www.niddk.nih.gov/health/digest/nddic.htm**

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MANAGING YOUR

CHRONIC KIDNEY DISEASE (CKD)

What Is Chronic Kidney Disease?

CKD, also known as chronic renal failure, means that the kidneys have suffered damage over a prolonged period and are no longer functioning properly. Kidneys are important in many ways. They control the amount of water and by-products of metabolism. They get rid of waste products (make urine). They control the body's water, blood salt, and calcium levels. In renal failure (or kidney failure), kidneys can't get rid of the body's waste products. Waste products build up in the body and are harmful. Acute failure occurs suddenly. Chronic failure occurs slowly.

What Causes Chronic Kidney Disease?

The cause is any condition that reduces the blood supply to the kidneys, blocks urine after it leaves the kidneys, or injures the kidneys. Inflammation, urinary tract infections, congestive heart failure, diabetes, and high blood pressure can cause it. Medications used for other medical disorders can also damage the kidneys.

What Are the Symptoms of Chronic Kidney Disease?

Chronic kidney disease is often a silent disease and has no early symptoms. Later signs and symptoms may include nausea, vomiting, diarrhea, and appetite loss. Others are listless feelings; shortness of breath; mouth problems; stomach pain; numbness, tingling, and burning in legs and feet; lower sex drive; loss of menstrual periods; anemia; and muscle and bone pain. Being irritable, not sleeping well, depression, convulsions, stupor, and coma are seen; itching, abnormal blood pressure, and bleeding problems may also occur.

How Is Chronic Kidney Disease Diagnosed?

The doctor often finds impaired renal function at a routine examination that includes urine or

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blood tests. Additional tests will then be done to see how well the kidneys work. X-rays may also be done to check the size of the kidneys and exclude other disorders that can damage the kidneys and block flow of urine, such as kidney stones or tumors. Your doctor may refer you to a kidney specialist (nephrologist) for additional evaluation.

How Is Chronic Kidney Disease Treated?

Treatment can involve diet, medicine, dialysis, controlling diseases causing the failure, and transplantation. Foods containing potassium, phosphorous, and too much salt or protein should be avoided. Controlling blood pressure is important. Injections to correct anemia and calcium pills may be needed. Diuretics (water pills) can prevent gaining too much fluid. Your doctor may recommend a kidney transplant. Certain drugs that can affect the kidneys must be avoided. High blood pressure, diabetes, congestive heart failure, and infections must be treated.

Some people need dialysis if other treatments don't work. Dialysis removes waste products from the blood when kidneys can't. Dialysis may be done temporarily or permanently.

The doctor will recommend seeing a kidney specialist on a regular basis.

DOs and DON'Ts in Managing

Chronic Kidney Disease:

✓ **DO** follow the diet that your doctor suggests, including fluid restriction.

✓ **DO** take medicines exactly as prescribed. Don't miss doses.

✓ **DO** weigh yourself daily. Keep records of fluid intake and output.

✓ **DO** exercise as much as you can but limit strenuous activities.

✓ **DO** stop smoking.

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✓ **DO** call your doctor if you have chills, fever, headache, muscle aches, shortness of breath, nausea, vomiting, or chest pains.

⦸ **DON'T** become dehydrated, but don't drink water or liquids in excess. Don't get overtired.

⦸ **DON'T** eat foods you should avoid. Too much potassium can make you very ill.

⦸ **DON'T** take over-the-counter drugs without checking with your doctor.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Kidney Foundation Tel: (800) 622-9010 **Website:** http://www.kidney.org
- National Institute of Diabetes and Digestive and Kidney Diseases **Website:** http://www.niddk.nih.gov
- National Kidney and Urological Diseases Information Clearinghouse Tel: (800) 891-5390 **Website:** http://kidney.niddk.nih.gov

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MANAGING YOUR

CIRRHOSIS

What Is Cirrhosis?

Cirrhosis is a long-term illness involving scarring of the liver. Scarring stops the liver from working normally, which causes problems in the whole body.

Cirrhosis is one of the top 10 causes of death in the United States. Prognosis depends on how much the liver is damaged.

What Causes Cirrhosis?

Of the many causes, the usual one is chronic alcohol abuse. Others include prescription and illegal drugs, fatty liver, liver infections, inherited diseases (such as hemochromatosis and cystic fibrosis), chronic viral hepatitis, toxic substances, and primary biliary cirrhosis (which causes bile duct blockage).

What Are the Symptoms of Cirrhosis?

The most common symptoms of early stages are tiredness (fatigue), weakness, little or no appetite, nausea, weight loss, enlarged liver, and red palms of hands. The symptoms of late stages are yellowing of eyes and skin (jaundice), brown or dark yellow urine, hair loss, changes in blood vessels in skin and around the belly button (spider blood vessels), breast growth in men, easy bruising and bleeding, diarrhea, mental confusion, swollen belly from fluid accumulation (ascites) and swollen legs (edema), large spleen, hemorrhoids, and coma.

How Is Cirrhosis Diagnosed?

The doctor uses a medical history and physical examination for diagnosis. Blood tests, x-rays, computed tomography (CT), and liver biopsy may be done to make the diagnosis and exclude other causes of liver disease. In a biopsy, the best test for diagnosis, the doctor takes a small

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piece of liver tissue for study.

How Is Cirrhosis Treated?

The key to treatment is removing the cause. The main treatment is then supportive and includes a high-calorie diet and salt (sodium) and fluid restriction (to control fluid accumulation). For severe fluid accumulation in the belly (ascites) or edema, diuretic medicines can be given. Other drugs are given for mental confusion and coma.

Treatment of the complication of increased pressure in the blood vessels in the belly (portal hypertension) depends on its severity. Medicines and endoscopy (a lighted flexible tube used to look at the esophagus, stomach, and small intestine) can be used for treatment of enlarged veins in the esophagus (varices) to prevent bleeding. Surgery, shunting of the blood vessels (portacaval shunt), and liver transplantation are other treatment options.

DOs and DON'Ts in Managing Cirrhosis:

✓ **DO** stop drinking alcohol. An alcohol rehabilitation program can help.

✓ **DO** eat a well-balanced diet. You may need to limit protein because the liver may be unable to use it.

✓ **DO** change activities according to your symptoms. A good fitness program may help fatigue.

✓ **DO** get hepatitis B vaccine if you're in a high-risk group (e.g., health care worker, homosexual), and get treated promptly for hepatitis.

✓ **DO** have family members checked for cirrhosis if your family has a history of cirrhosis or inherited diseases that cause it.

✓ **DO** call your doctor if during treatment you vomit blood or have black stool (bowel move-

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ments), bright red blood in your stool, increase in fluid accumulation in your belly or feet, or fever.

⦸ **DON'T** use any alcohol.

⦸ **DON'T** use medicines, such as acetaminophen, sedatives, and tranquilizers, that can harm the liver.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Liver Foundation Tel: (800) GO-LIVER (465-4837) **Website: http://www.liverfoundation.org**
- American College of Gastroenterology Phone: (703) 820-7400 **Website: http://www.acg.gi.org**
- Alcoholics Anonymous Phone: (212) 870-3400 **Website: http://www.aa.org**

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MANAGING YOUR

POOR CIRCULATION

What Is Poor Circulation?

Poor circulation (also called claudication) refers to leg pain caused by exercise and relieved by rest. It is also called intermittent claudication, peripheral vascular disease (PVD), and poor circulation. The calf muscle is most likely affected, but feet, thighs, and buttocks can also be painful.

What Causes Poor Circulation?

The main cause is atherosclerosis, or narrowing of arteries that go to leg muscles. Risk factors leading to atherosclerosis are diabetes, high cholesterol level, high blood pressure, and smoking. Smoking tobacco is the major reason that disease worsens.

Claudication is not contagious or passed on from generation to generation.

What Are the Symptoms of Poor Circulation?

Symptoms are pain, muscle tension, weakness, and limping that occur after exercise and disappear after short rest. Other symptoms are cold feet at night, pain in the toe and foot, numbness of the leg, hair loss, brittle toenails, bluish toes, and foot sores that don't heal. Skin breakdown, ulcers, and gangrene can occur.

How Is Poor Circulation Diagnosed?

The doctor makes the diagnosis by checking symptoms and doing a physical exam. The doctor can order tests of blood vessels (including Doppler ultrasound) to find out about blood flow. If the tests show decreased circulation, angiography will be done before surgery to determine how severe the disease is. Angiography involves putting a catheter (small tube) into the artery of the leg and injecting dye to get a picture of the vessel.

How Is Poor Circulation Treated?

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The treatment goal is to relieve symptoms and prevent the condition from getting worse. Most people respond to lifestyle changes, including avoiding tobacco (the best treatment), losing weight, and changing the diet to control diabetes, hypertension, and high cholesterol. If symptoms remain, the doctor may prescribe medicine to help blood circulate better. A daily low dose of aspirin may be needed. Proper foot care is important to prevent infection.

If the blood flow is very reduced, a minor procedure called angioplasty may be advised to open up the blocked artery.

A balloon-tipped tube (catheter) is inserted into the narrowed vessel and inflated to widen the vessel. Also, a stent (small mesh tube) may be put into the vessel by angioplasty.

Sometimes, a tube of special material is joined to the vessel above and below where it is narrowed. This lets blood bypass the narrowed vessel.

People need surgery if they have ulcers that don't heal, their foot is cold and blue, the limb has gangrene, or they have severe pain at rest.

DOs and DON'Ts in Managing Poor Circulation:

- ✔ **DO** control risk factors of atherosclerosis (diabetes, high cholesterol, high blood pressure, smoking).
- ✔ **DO** exercise in moderation, control obesity, stop smoking, perform daily foot care, keep your blood pressure in check, and eat a low-fat diet.
- ✔ **DO** ask your doctor about your cholesterol, blood sugar, and blood pressure.
- ✔ **DO** call your doctor if you have calf, thigh, or buttock pain with walking.
- ✔ **DO** call your doctor if you have foot skin ulcers, a cold foot, or color changes in your feet.
- ⃠ **DON'T** smoke.
- ⃠ **DON'T** wear restrictive clothes on the legs, such as elastic stockings.

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⦸ **DON'T** miss follow-up doctor appointments, especially to check on ulcer healing.

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FOR MORE INFORMATION

Contact the following sources:

- National Heart, Lung, and Blood Institute Tel: (301) 592-8573
- American Heart Association Tel: (800) AHA-USA-1 (242-8721) **Website:**

  http://www.americanheart.org

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CARING FOR YOUR BABY WITH

CLEFT LIP AND PALATE

What Are Cleft Lip and Palate?

A cleft lip and cleft palate are facial birth defects. Cleft means an opening. These defects affect the upper lip and the roof of the mouth (palate). The parts that form the baby's face and palate don't join before birth.

A cleft lip or palate is the most common facial birth defect. Up to 5000 babies are born in the United States each year with this problem. Clefts occur more often in Asian, Latino, and Native American children.

What Causes Cleft Lip and Palate?

The cause is unknown. The defects sometimes run in families (are genetic). If either parent has a cleft lip or palate, the chance increases that the baby will also. If both parents are normal and have a baby with a cleft lip or palate, chances are higher that babies born later will have it.

What Are the Symptoms of Cleft Lip and Palate?

A cleft may occur on one side or both sides of the upper lip. The split usually affects only the lip but may extend into the nose. For a cleft palate, the soft part of the palate at the back of the mouth may be involved, or the cleft may affect the bony part of the palate (hard palate).

These defects can cause feeding and developmental problems, poor dental development, trouble with speech, and frequent colds, sore throats, and ear infections.

How Are Cleft Lip and Palate Diagnosed?

The doctor makes a diagnosis by a physical examination. The need for more tests depends on the defect's severity.

How Is Cleft Lip and Palate Treated?

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Surgery can improve a cleft lip or palate. Which type of surgery depends on how bad the defect is. At times the surgeon may be able to fix the baby's lip before sending the baby home. If the baby has a cleft palate, an operation may be done later.

Other treatments depend on which problems the cleft lip or palate causes. A cleft can make it hard for the baby to suck and feed. A speech and feeding therapist will describe ways to feed the baby. The cleft can cause problems in learning to speak. Care of a speech and language therapist will be needed. A cleft may cause frequent ear infections, which can lead to hearing loss.

A team of specialists can help check the baby. This team may include a surgeon who specializes in these defects, hearing specialist, dentist, orthodontist (dentist who straightens teeth), and speech-language specialist (for both speech and feeding problems). Psychologists and social workers may also be involved.

DOs and DON'Ts in Managing

Cleft Lip and Palate:

✓ **DO** make sure that your child gets care from doctors who can check for problems with teeth, feeding, hearing, and speaking.

✓ **DO** remember that surgery can correct most defects in 12 to 18 months after birth.

✓ **DO** have a positive attitude and encourage your child to be positive.

⃠ **DON'T** avoid getting help and emotional support from psychologists if needed.

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FOR MORE INFORMATION

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Contact the following source:

• Cleft Palate Foundation Tel: (919) 933-9044, (800) 242-5338 **Website:**

http://www.cleftline.org

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MANAGING YOUR

CLUSTER HEADACHEs

What Are Cluster Headaches?

Cluster headaches are one of the more severe types of head pain. They are more common in men than women. The pain is usually constant, intense, and nonthrobbing, deep in and around the eye on one side of the head. Pain often moves into the forehead, temple, and cheek. Pain may leave as quickly as it began or fade slowly.

Cluster headaches are unpredictable. Several months can pass without headaches, but then they start again. They are rather rare, occurring in less than 1% of people, and are most common between adolescence and middle age.

What Causes Cluster Headaches?

The exact cause is unknown. Triggers can include drugs (nitroglycerin), certain foods, smoking, drinking alcohol, changing the normal sleep pattern, heat, and exposure to hydrocarbons (perfumes, petroleum solvents).

What Are the Symptoms of Cluster Headaches?

Headaches occur in groups or clusters. Each cluster usually begins in spring or fall and lasts about 2 to 3 months. Headaches may occur nightly after 1 to 2 hours of sleep or several times during the day and night. Each attack may last almost an hour. They often have a pattern, occurring at the same time each day for 6 to 12 weeks, followed by no headaches for many months or years. Other symptoms are watering eyes, drooping eyelids, and vision problems on the side of the headache.

How Are Cluster Headaches Diagnosed?

The doctor makes a diagnosis from the medical history and examination. Other tests are gener-

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ally not needed. If the symptom pattern changes, the doctor may order additional tests such as magnetic resonance imaging (MRI) of the head to look for other disorders that can mimic cluster headaches.

How Are Cluster Headaches Treated?

Many treatments exist for cluster headaches. The goal is to help symptoms because cluster headaches cannot be cured. Certain medicines can prevent more headache attacks. For breakthrough headaches (which occur even with preventive medicine), inhaling pure oxygen may provide some relief. The doctor may prescribe oxygen therapy for use at home if breakthrough headaches occur often. If attacks are less frequent, drugs given by mouth, such as triptan medications, verapamil, or the steroid methylprednisolone, also work and are more convenient and less expensive than pure oxygen therapy.

DOs and DON'Ts in Managing

Cluster Headaches:

✓ **DO** keep to an adequate and regular sleep schedule.

✓ **DO** take your medicines as prescribed.

✓ **DO** check with your doctor before using over-the-counter pain relievers.

✓ **DO** keep your follow-up doctor appointments.

✓ **DO** call your doctor if you have a fever with your headache.

✓ **DO** call your doctor if you have a headache that is more severe than usual and your usual medicine doesn't help it.

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✓ **DO** call your doctor if you have weakness, numbness, or tingling in your arms or legs or you have trouble walking or talking.

✓ **DO** call your doctor if you have severe vomiting that your medicine doesn't control.

✓ **DO** call your doctor if you have problems with your medicine.

⃠ **DON'T** use alcohol, foods containing nitrates, and tobacco.

⃠ **DON'T** expose yourself to oil-based solvents; avoid high altitudes and strenuous exercise. These may start an attack.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Headache Society Tel: (800) 255-2243 **Website: http://www.achenet.org**
- National Headache Foundation Tel: (888) 643-5552 **Website: http://www.headaches.org**

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MANAGING YOUR

COARCTATION OF THE AORTA

What Is Coarctation of the Aorta?

The aorta is an important large blood vessel attached to the left side of the heart. Other medium-sized blood vessels branch from the aorta. They take blood and oxygen to the body. Coarctation is an abnormal narrowing of the aorta, usually in the part just past the place where blood vessels to the head and arms branch off. No way to prevent this disorder is known. Untreated, coarctation can lead to complications, such as high blood pressure, heart attack, heart failure, or stroke.

What Causes Coarctation of the Aorta?

This rare congenital heart defect is present before birth but may not be found until later. Other heart defects, including bicuspid aortic valve and ventricular septal defect, may be present. In bicuspid aortic valve, the valve has two flaps instead of three. In ventricular septal defect, the middle dividing wall of the heart has a hole.

What Are the Symptoms of Coarctation of the Aorta?

Older children and adults usually have less severe narrowing and no symptoms at first. Symptoms that develop include dizzy spells, breathlessness, chest pain, cold legs, leg cramps (especially with exercise), and nosebleeds. If blood goes through other vessels (collaterals) instead of the narrow aorta, they get larger, and the doctor may feel or see pulsations in the back.

How Is Coarctation of the Aorta Diagnosed?

The doctor makes a diagnosis from symptoms: heart murmur, high blood pressure (higher in arms than legs), and weak pulses in the groin, legs, and feet.

Tests include electrocardiography (ECG), chest x-ray, echocardiography, magnetic resonance

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imaging (MRI), and cardiac catheterization with aortography.

How Is Coarctation of the Aorta Treated?

Drugs may be used for high blood pressure, but surgery is usually needed. This major procedure can involve a hospital stay of several days. Risks include reactions to general anesthetic and, rarely, paralysis in the lower half of the body. Surgery can remove the narrow part and join two normal parts. Another option is using patches or grafts made of special material to replace the abnormal part. Sometimes a flap of tissue from an artery can be used to widen the narrow part.

Another treatment is balloon dilation. A small device (balloon) is slowly pumped up to widen the narrow part. Sometimes a small tube (stent) is left in the vessel to keep it open. This treatment leaves no large scar and has a faster recovery. Older children, not babies, and people with a second narrowing after treatment often have it done.

Because a vessel may get narrow again, follow-up visits with a heart specialist are recommended. That way, a narrowing can be found early and treated.

DOs and DON'Ts in Managing Coarctation of the Aorta:

✓ **DO** ask your doctor about the kind and amount of exercise you should do.

✓ **DO** take medicines prescribed by your doctor.

✓ **DO** call your doctor if you're trying to get pregnant. You may need to consider certain complications and may need special treatment.

⃠ **DON'T** forget to go for regular follow-up checkups. Have your blood pressure checked regularly, even after treatment.

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FOR MORE INFORMATION

Contact the following source:

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MANAGING YOUR

COCAINE ABUSE AND DEPENDENCE

What Is Cocaine Abuse and Dependence?

Cocaine is an illegal drug obtained from the coca plant, *Erythroxylon coca*. A strong stimulant, cocaine causes euphoria (makes people high). It can damage all organs but mostly affects the heart, brain, and lungs. Usually a white or off-white powder, it's called coke, C, snow, flake, or blow. People sniff it through a tube or straw, dissolve it in water and inject it, or burn it and breathe the smoke (crack).

Pregnant addicted women can have crack babies with major birth defects.

What Causes Cocaine Abuse and Dependence?

Cocaine causes high levels of a brain chemical called dopamine, which makes people feel good.

Because the high doesn't last long and a depressive period follows, people may need to use cocaine often, leading to addiction. As abuse continues, tolerance develops, so larger doses taken more often are needed for the same high.

What Are the Symptoms of Cocaine Abuse and Dependence?

Short-term effects include euphoria, high energy levels, and needing less food and sleep.

A binge can produce rapid heartbeat, high blood pressure, irritability, and aggression.

Regularly snorting can lead to loss of sense of smell, nosebleeds, trouble swallowing, hoarseness, being underweight, and chronic runny nose. Serious complications of cocaine use and overdose include stroke, seizures, and heart attacks.

Cocaine overdose usually causes high blood pressure and fast pulse, as well as chest pain, tremors, convulsions, and even death.

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How Are Cocaine Abuse and Dependence Diagnosed?

The doctor will ask questions about symptoms, medical conditions, work history, family medical history, and patterns of cocaine, tobacco, and alcohol use.

The doctor will also do a physical examination, order blood and urine tests, and check for nasal perforations and heart damage.

How Are Cocaine Abuse and Dependence Treated?

Cocaine-dependent people need a lot of help to quit. Behavioral therapy can help reduce or stop drug use.

Residential programs and outpatient substance abuse clinics can offer behavioral therapies and help with detoxification. Twelve-step recovery groups (Narcotics Anonymous) also help some people.

Cocaine overdose is an emergency. Treatment depends on symptoms and organs affected.

DOs and DON'Ts in Managing Cocaine Abuse and Dependence:

✓ **DO** admit that you have a cocaine problem.

✓ **DO** understand that a cocaine or crack habit can cost thousands of dollars weekly.

✓ **DO** understand that breaking a cocaine habit isn't easy. Cravings may last for a long time.

✓ **DO** call your doctor if you're pregnant and using cocaine.

✓ **DO** call your doctor if you share needles or have fevers and take cocaine intravenously.

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✓ **DO** call your doctor if you have chest pain or passed out while using cocaine or you have abnormal heartbeats, new seizures, shortness of breath, or headaches.

✓ **DO** call your doctor if you want detoxification.

⃠ **DON'T** try to deal with your cocaine dependence on your own. Get medical help.

⃠ **DON'T** take alcohol in excess and cocaine together. It can kill you.

⃠ **DON'T** be fooled that cocaine is a safe drug. All forms can lead to overdose and to life-threatening complications.

⃠ **DON'T** share needles. Sharing puts you at risk for HIV and AIDS.

⃠ **DON'T** use cocaine if you're pregnant.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Institute on Drug Abuse Tel: (301) 443-1124 **Website:** http://www.nida.nih.gov/
- Narcotics Anonymous Tel: (818) 773-9999 / Fax: (818) 700-0700 **Website:** http://www.na.org/

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MANAGING YOUR

COCCIDIOIDOMYCOSIS

What Is Coccidioidomycosis?

Coccidioidomycosis, also called San Joaquin Valley fever, is an infection with the spores of the fungus *Coccidioides immitis.*

What Causes Coccidioidomycosis?

Coccidioidomycosis is caused by a fungus named *Coccidioides immitis,* which is often found in Arizona, California, New Mexico, and Texas. It lives in the soil. It has spores that people breathe in and end up in lung alveoli. Alveoli are tiny sacs at ends of the smallest airway branches. Spores then become spherules, which have thick walls. Spherules burst and release spherical spores (endospores). These endospores mature into new spherules, which completes the parasitic cycle. In human tissues, the fungus causes a special kind of inflammation called granuloma.

What Are the Symptoms of Coccidioidomycosis?

Nearly 60% of people have minor symptoms and never see a health care provider. They often have an illness that seems like a nonspecific upper respiratory tract infection. Rash can also occur in early stages. Symptoms of primary infection include cough, malaise, fever, chills, night sweats, loss of appetite, weakness, and joint aches (desert rheumatism). About 40% of people have these within 3 weeks of exposure. Other symptoms may include headache and muscle aches and stiffness. Sensitivity to light, wheezing, and ankle, feet, and leg swelling can also occur. Less than 10% of people may develop lung nodules and cavities. People with weak immune (infection-fighting) systems or diabetes may get lung inflammation (pneumonitis). This illness can be fatal. Others may have chronic (long-lasting) lung disease with scarring, coughing, and spitting up of bloody phlegm.

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About 0.5% of people with acute infection can have widespread disease affecting the skin, brain, muscles, bones, and other organs.

How Is Coccidioidomycosis Diagnosed?

The health care provider makes a diagnosis from the medical history, physical examination, laboratory tests, and chest X-rays. Proof of diagnosis depends on growing the fungus (fungal culture) in fluids or tissues from the body. Special tests such as a lumbar puncture (spinal tap) may be needed if brain inflammation is possible. Lethargy, confusion, fever, or seizures can mean brain inflammation. The health care provider may, in some cases, suggest seeing infectious disease and lung specialists.

How Is Coccidioidomycosis Treated?

The main treatment is antifungal medicine, given by mouth or into a vein. Fluconazole, itraconazole, posaconazole, and amphotericin B are commonly used. Not everyone needs treatment. People with mild lung infection without symptoms and most people with mild symptoms of a primary infection may do well without antifungal medicine.

DOs and DON'Ts in Managing Coccidioidomycosis:

✓ **DO** call your health care provider if you cough up blood, have a high temperature, or have a severe headache.

⦸ **DON'T** ignore symptoms. Call your health care provider if symptoms don't get better or worsen with treatment. Call if you have new symptoms.

⦸ **DON'T** stop taking your medicine or change the dosage because you feel better unless your health care provider tells you to.

⦸ **DON'T** use any medicines (including over-the-counter and herbal products) without first asking your health care provider.

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Allergy and Infectious Disease 9000 Rockville Pike Bethesda, MD 20892 Tel: (301) 496-5717 **Website: http://www.healthfinder.gov**
- Centers for Disease Control and Prevention Tel: (800) 311-3435
- American Lung Association Tel: (800) LUNG-USA **Website: http://www.lungusa.org**

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CARING FOR YOUR INFANT WITH

COLIC

What Is Colic?

Colic is a term used to describe when a healthy baby cries or screams loudly, often for a long time (sometimes hours), for no clear reason and cannot be soothed. Crying can happen suddenly without warning at any time, but it often occurs at the end of a day. It is common and affects up to one third of babies in their first 3 months of life. No methods for predicting and preventing colic in babies are known.

What Causes Colic?

The cause is unknown. The previous belief was that babies had gas or cramps in the abdomen (belly), but doctors now think that this is not always the case. Experts say colicky babies generally have no pain but don't understand why it occurs.

Colicky crying usually begins in the first couple of weeks after birth. It's often worst at about 6 weeks and usually stops by 4 months. It's not caused by bad parenting, being a single parent, or postpartum depression. It doesn't affect normal development.

What Are the Symptoms of Colic?

Continuous crying or screaming loudly for no clear reason means a colicky baby. Babies may pull up their legs, arch their back, clench their fists, grimace, or look flushed.

Usual soothing methods may not work. Colic can cause babies to have feeding problems and lose sleep.

How Is Colic Diagnosed?

The doctor will take a medical history of the baby to rule out feeding, burping, or bowel problems.

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The doctor will also do a physical examination to make sure no medical problem (such as infection, rash, fever, or breathing, skin, or stomach disorders) is the cause. Other tests may also be done.

How Is Colic Treated?

Treating colic can be difficult and frustrating. It mainly involves trying different things that might help. Some of these things include a giving a different type of formula milk or whey-based milk or medicines that calm the stomach or reduce stomach gas. If the baby is breastfed, avoid foods that could stimulate the baby, such caffeine-containing foods (coffee, tea, chocolate) or foods containing substances that may cause an allergic reaction, such as dairy foods and nuts.

DOs and DON'Ts in Managing Colic:

✓ **DO** try things that usually stop your baby from crying, such as offering a pacifier, singing, walking or driving in the car, or gentle rocking.

✓ **DO** try snug wrapping of your baby (swaddling) and holding your baby in your arms or lap.

✓ **DO** hold your baby upright and walk the baby around.

✓ **DO** put your baby on your lap and gently massage the baby's back.

✓ **DO** ask for help if you feel unable to cope or are about to lose emotional control.

✓ **DO** put your baby in a safe place and let your baby cry for short periods if you can't find a soothing method.

⦸ **DON'T** worry too much about colic. Colic has no effect on a baby's health or development.

⦸ **DON'T** EVER shake a baby!

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⦸ **DON'T** ever cover a baby's face with a pillow or other object to quiet the crying!

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

• Colic **Website: http://familydoctor.org/036.xml**

• What to do when your newborn cries **Website:**

http://www.mayoclinic.com/health/healthy-baby/PR00037

• Infant and Newborn Care **Website: http://www.nlm.nih.gov/medlineplus/ infantandnew-borncare.html**

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MANAGING YOUR

COLON CANCER

What Is Colon Cancer?

Food that is swallowed goes from the stomach into the small intestine and then the large intestine. What's left after food is digested leaves the body as waste (stool) through the rectum. The colon is the last part of the large intestine, just before the rectum. Colon cancer is a tumor of the large intestine, often the lower rectum and sigmoid colon but can also involve the beginning (cecum). It's also called colorectal cancer or adenocarcinoma of the colon. It's the most common cancer of the digestive tract.

Colon cancer usually starts as a small growth, called a polyp, on the surface of the colon. Some polyps are harmless, but some can turn into cancer.

What Are the Symptoms of Colon Cancer?

Symptoms include a change in bowel habits, such as constipation or diarrhea, change in stool size (e.g., pencil thin) or appearance (e.g., black, tarry-looking), rectal bleeding, and pain in the abdomen (belly). Sometimes people have no symptoms, but iron deficiency anemia may occur from chronic blood loss and can be detected by blood tests ordered by your physician.

Early diagnosis is critical, because undetected or untreated cancer usually spreads (metastasizes) through the intestine wall into nearby areas, liver, and sometimes lungs and bones.

How Is Colon Cancer Diagnosed?

The doctor may suspect the diagnosis from a complete physical examination, including a digital rectal examination (DRE), and from blood tests showing iron deficiency anemia. Stool samples are tested for hidden (occult) blood. The doctor then looks inside the colon with a flexible tube called a colonoscope and obtains tissue samples of abnormal areas (biopsy). A computed

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tomography (CT) scan and other tests may be done to determine if the cancer has spread outside of the colon.

How Is Colon Cancer Treated?

Treatment depends on how far the cancer spread. Abdominal and pelvic CT can tell whether it spread outside the colon. This information is important because it's used to decide the kind of treatment. Surgery is best for complete tumor removal. If cancer hasn't spread past the colon, surgery offers the best chance for cure. Even if cancer can't be cured because it spread to other parts of the body, surgery can make people more comfortable by preventing obstruction of the colon lumen by the cancer.

Medicine (chemotherapy) and radiation can be used to try to kill cancer cells not removed by surgery. Both may have side effects, including inflammation with diarrhea and bloody stools (radiation) and bone marrow problems leading to infections, bleeding, and anemia (chemotherapy).

More than one half of people with colon cancer can be cured. The success rate depends on the cancer's stage.

DOs and DON'Ts in Managing Colon Cancer:

✓ **DO** make sure that after treatment, you have another colonoscopy 1 year after surgery or sooner. Colonoscopy should then be repeated regularly, or as recommended, to watch for the cancer's return.

✓ **DO** follow your doctor's advice.

✓ **DO** contact your doctor if medicine you take makes you sick.

✓ **DO** exercise and eat a healthy diet to reduce colon cancer risk.

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- ⃠ **DON'T** forget the importance of screening for everyone, starting at age 50 or earlier for people who have family members with colon cancer.
- ⃠ **DON'T** miss follow-up appointments with all your doctors.
- ⃠ **DON'T** be afraid to ask your primary care doctor about support groups. In these groups, you can share concerns with others who were also diagnosed and treated for colon cancer.
- ⃠ **DON'T** forget the importance of good nutrition after surgery. Eat a high-fiber diet and watch your weight.
- ⃠ **DON'T** smoke.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- Colon Cancer Alliance Tel: (877) 422-2030 **Website: http://www.ccalliance.org**
- American Cancer Society **Website: http://www.cancer.org**

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COLON CANCER

SCREENING AND PREVENTION

What Is the Colon?

The colon is part of the digestive system. Food moves from the mouth to the stomach. Several hours later, it moves into the intestines, first the small intestine and then the large intestine. After digestion of food is finished, what's left leaves the body as waste (stool) through the rectum. The colon is the last part of the large intestine, just before the rectum.

What Is Colon Cancer?

Colon cancer is a tumor in the colon. It is the most common cancer of the digestive tract. Other names are adenocarcinoma of the colon and colorectal cancer (often the lower rectum and sigmoid part of the colon are involved). The cancer can also be found in the first part of the colon (cecum). Colon cancer can also spread (metastasize) to other parts of the body.

Colon cancer usually starts as a small growth (polyp) on the surface of the colon. Some polyps are harmless, but some can turn into cancer.

Colon cancer tends to run in families. If you have a strong family history of colon cancer, you should discuss with your doctor genetic testing done with blood tests to look for genetic changes that predispose to rare hereditary colon cancers known as familial adenomatous polyposis (FAP) and Lynch syndrome.

What Are Symptoms of Colon Cancer?

Symptoms to be aware of are a change in bowel habits, such as constipation or diarrhea, a change in stool size (e.g., pencil-thin) or stool appearance (e.g., black and tarry), rectal bleeding, and abdominal pain.

Sometimes no symptoms are present, but iron deficiency anemia from long-term blood loss

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may occur.

Early diagnosis is critical because undetected or untreated cancer usually spreads through the intestine wall into neighboring areas and into the liver. Sometimes it can also spread to lungs and bones.

How Is Colon Cancer Diagnosed?

The doctor will do a complete physical examination, including a digital rectal examination (DRE), and take one or more stool samples. These samples are analyzed for any occult (hidden) blood. This testing can find bleeding in the intestine, but results can be inaccurate because certain medicines or red meat may produce positive results that are really normal (false-positive results).

The doctor also looks inside the colon with a flexible tube called a colonoscope. This scope is passed through the rectum to see the whole colon. The doctor can see problem areas and biopsy (take samples of) these areas and remove any polyps. The samples are studied under a microscope to look for cancerous cells. Other tests, such as computed tomography (CT), of the abdomen and pelvis may be done to see whether cancer has moved to other parts of the body.

A newer screening test involves using CT only for the intestine (CT colonography). This test is also called virtual colonoscopy. For this test, compressed air is pumped into your rectum through a tube and then a picture is taken of your colon. For this test you will also have to take laxatives the day before to clean out the colon. Any possible problem areas found by CT colonography will need a follow-up colonoscopy and biopsy of suspicious area to see whether they are cancerous.

DOs and DON'Ts in Diagnosing and Preventing Colon Cancer:

✓ **DO** realize the importance of colon screening for everyone, starting at age 50 or earlier for

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people who have family members with colon cancer.

✓ **DO** follow your doctor's advice.

✓ **DO** eat a high-fiber diet.

✓ **DO** watch your weight.

✓ **DO** exercise. Exercising can improve your overall health.

⃠ **DON'T** forget the importance of screening.

⃠ **DON'T** smoke.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- Colon Cancer Alliance Tel: (877) 422-2030 **Website:** **http://www.ccalliance.org**
- American Cancer Society Tel: (800) ACS-2345 **Website:** **http://www.cancer.org**
- American College of Gastroenterology Tel: (703) 820-7400 **Website:** **http://www.acg.gi.org**

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MANAGING YOUR

COMMON COLD

What Is a Common Cold?

The common cold, also called an acute upper respiratory tract infection (URI), is an infection of airways of the nose, throat, upper windpipe, and ears.

People in the United States have 1 billion colds yearly. They're most common in children, who usually have 6 to 10 colds yearly. Adults average two to four. Women, especially 20 to 30 years old, have more colds than men. People older than 60 average less than one cold a year.

What Causes a Common Cold?

More than 200 different viruses cause colds. The ones called rhinoviruses cause about one third of adult colds. Coronaviruses cause a large percentage of adult colds. Causes of 30% to 50% of adult colds aren't clear. Colds are most common in winter, when viruses spread easily among people indoors.

Being very tired or stressed (weakened immune system) and having allergies can increase chances of getting a cold.

What Are the Symptoms of a Common Cold?

Symptoms usually start 2 to 3 days after infection and last 2 to 14 days. Most are in the nose, throat, and ears and include sore throat, dry cough, low fever, watery eyes, hoarse voice, and stuffy, runny nose. Sneezing, headache, no appetite, and feeling tired are others.

How Is a Common Cold Diagnosed?

Seeing a doctor isn't needed for a cold. Symptoms that are severe or last more than a week might need tests to check for strep throat or sinus infection.

How Is a Common Cold Treated?

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Only symptoms are treated, by bed rest, fluids (water, fruit juice, tea, carbonated beverages), gargling with warm saltwater, and use of acetaminophen for headache or fever. Eat a regular diet.

Over-the-counter cold remedies (decongestants, cough suppressants) may relieve symptoms but won't prevent, cure, or shorten colds. Most also have side effects. Over-the-counter antihistamines may help a runny nose and watery eyes.

Sometimes people may get a bacterial infection following the cold that the doctor will need to treat.

DOs and DON'Ts in Managing a Common Cold:

✓ **DO** use saltwater drops for a stuffy nose.

✓ **DO** use a rubber bulb syringe to clean a really stuffy baby's nose. Loosen thick sticky nasal drainage with drops of saltwater solution.

✓ **DO** remember that cold weather has little or no effect on whether you get a cold.

✓ **DO** understand that hand washing is the easiest and best way to avoid getting colds. Not touching the nose or eyes is another. Sneeze or cough into a facial tissue and throw it right away. Stay away from people who have colds.

✓ **DO** eat a well-balanced, healthy diet with citrus fruits and other sources of vitamin C.

✓ **DO** realize that antibiotics don't kill viruses, so antibiotics aren't useful for colds.

✓ **DO** call your doctor if you have symptoms of a secondary bacterial infection.

✓ **DO** call your doctor if your baby won't drink fluids.

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⦸ **DON'T** put cotton swabs into a child's nose. Use a tissue or swab outside the nose.

⦸ **DON'T** give aspirin to children and teenagers with a viral illness, because of the risk of Reye's syndrome, a serious illness.

⦸ **DON'T** forget that taking large doses of vitamin C is not effective to prevent colds.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Family Physicians Tel: (800) 274-2237 **Website:** **http://www.aafp.org**

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MANAGING YOUR

COMPARTMENT SYNDROME

What Is Compartment Syndrome?

Compartment syndrome is a painful condition caused by a buildup of pressure in muscles. A tough membrane called a fascia covers groups of muscles. These groupings are called muscle compartments. Compartments also contain nerves and blood vessels. Fascia doesn't stretch. So if muscles inside swell, pressure in a compartment rises. Pressure that gets very high can cause blood vessels to be crushed. Blood cannot pass through the vessels to carry oxygen to muscles and nerves. This is compartment syndrome.

What Causes Compartment Syndrome?

This syndrome can be acute or chronic. The acute type usually follows injury or surgery. It can happen when an arm or leg swells inside a cast. Chronic (or exertional) compartment syndrome happens after exercise, usually to athletes and soldiers.

What Are the Symptoms of Compartment Syndrome?

Chronic compartment syndrome usually causes cramping pain in both legs that begins during exercise and gets worse as exercise continues. Tingling, numbness, or pressure may be felt. The area may be tight but doesn't look swollen. Pain stops after exercise stops. Acute compartment syndrome causes severe pain, which is worst when the muscle is stretched. The area may feel hard.

How Is Compartment Syndrome Diagnosed?

The doctor will probably first test for other, more common causes of pain. The doctor will take a medical history, do a physical examination, and maybe order x-rays, ultrasonography, or magnetic resonance imaging (MRI).

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The doctor may suggest seeing a specialist. The specialist will measure pressure inside the muscle compartment with a needle attached to a pressure meter.

How Is Compartment Syndrome Treated?

Emergency surgery is needed for the acute syndrome to prevent muscles and nerves from dying. Treated quickly, they'll likely return to normal. Untreated, people could be disabled or lose a leg or arm. The surgeon will cut open the fascia to relieve the pressure. Often, the wound is left open for 2 to 3 days and then closed in another operation. A graft of skin from another part of the body may be needed to repair the wound.

The chronic syndrome is usually treated by surgery. The surgeon cuts, or partly removes, the fascia so that muscles have room to swell. Most people who have surgery can exercise as before. Muscles may bulge out more, because the fascia doesn't hold them in.

Treatments other than surgery include doing different and various sports (for example, cycling or swimming instead of running), changing the technique for the same sport, taking a complete break from sports, and medications to control the pain. Compartment syndrome often comes back after nonsurgical treatment if the initial cause is untreated.

DOs and DON'Ts in Managing

Compartment Syndrome:

✓ **DO** warm up before exercise and cool down after.

✓ **DO** stop exercising if you feel pain.

✓ **DO** follow your doctor's instructions for recovery after surgery.

✓ **DO** call your doctor immediately if you get severe muscle pain after an injury.

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⦸ **DON'T** keep exercising through pain. You could damage your nerves or muscles permanently.

⦸ **DON'T** use bandages or supports. They may make pressure in muscle compartments worse.

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FOR MORE INFORMATION

Contact the following source:

- The American Academy of Orthopaedic Surgeons Tel: (800) 346-2267 **Website:** **http://www.aaos.org**

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MANAGING YOUR

COMPLETE HEART BLOCK

What Is Complete Heart Block?

The heart is a muscular pump with four chambers, two upper (left and right atria) and two lower (left and right ventricles). These contract and pump blood. Special tissue in the heart produces and sends electrical impulses to get the muscle to contract. Normal electrical signals start from the sinoatrial (SA) node in the wall of the right atrium. From there the signal goes to the left atrium and reaches the atrioventricular (AV) node between the atria and ventricles. The signal then goes to the left and right bundle branches and finally the ventricles. There it stimulates ventricles to contract.

Heart block refers to a disturbance of these impulses. Third-degree heart block, or complete heart block, is one of three types (first- and second-degree blocks are the others). In complete heart block, no impulses from the atria reach the ventricles. Signals are completely blocked at the AV node.

What Causes Complete Heart Block?

The exact cause is often unknown. Complete heart block isn't contagious or passed from generation to generation. It usually occurs in elderly people and may be the result of aging. Heart conditions including coronary artery disease, myocardial infarctions (heart attacks), heart valve disease, and congestive heart failure can cause complete heart block. Other causes are diseases, such as sarcoidosis, rheumatoid arthritis, or Lyme disease, and some medicines (e.g., digoxin, beta-blockers, and calcium channel blockers).

What Are the Symptoms of Complete Heart Block?

Symptoms can vary and include dizziness, lightheadedness, shortness of breath, chest pain, and

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fainting. Many people may have no symptoms.

How Is Complete Heart Block Diagnosed?

The doctor makes a diagnosis from the medical history and a very slow pulse at a physical examination.

The doctor will order electrocardiography (ECG) to measure the heart's electrical activity.

If additional tests are needed to confirm the diagnosis, a 24-hour recording of the heartbeat (Holter monitor) while following usual daily activities will be done. Sometimes, admission to a hospital is needed for constant monitoring in preparation for treatment.

How Is Complete Heart Block Treated?

No drugs can treat complete heart block. If excessive doses of a drug is the cause, stopping the drug is required. The best treatment for complete heart block not caused by drugs is insertion of a pacemaker. Pacemakers are small, electrical devices put into the heart to tell it to beat to stimulate the heart to beat in a normal fashion.

DOs and DON'Ts in Managing Complete Heart Block:

✓ **DO** carry your pacemaker ID card. The card describes the type of pacemaker, insertion date, model, and serial number.

✓ **DO** call your doctor if you pass out with no warning, feel faint, or have chest pain or shortness of breath.

⃠ **DON'T** forget that certain devices such as cell phones and powerful magnets can make the pacemaker malfunction.

⃠ **DON'T** forget to tell doctors who suggest procedures such as magnetic resonance imaging

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(MRI) that you have a pacemaker.

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FOR MORE INFORMATION

Contact the following source:

- American Heart Association Tel: (800) 242-8721 **Website:**

  http://www.americanheart.org

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MANAGING YOUR

CONCUSSION

What Is a Concussion?

A concussion is an injury to the brain caused by a blow to the head, or by hitting the head on another object. It may result in loss of consciousness or confusion. It may also cause amnesia (loss of memory) about the event related to the concussion as well as time before or after.

What Causes a Concussion?

Sudden movement of the brain in the skull can injure the brain. Most concussions result from motor vehicle accidents, industrial accidents, contact sports (such as football and hockey), falls, and physical attacks.

What Are the Symptoms of a Concussion?

Symptoms include temporary unconsciousness, short-term amnesia, dizziness, headache, confusion, mild lack of coordination, nausea, vomiting, and being unable to concentrate. Symptoms usually last for hours to several days.

How Is a Concussion Diagnosed?

The doctor makes a diagnosis from a detailed neurological examination and history of loss of consciousness, amnesia, or confusion after a blow to the head. The doctor may order computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, but these tests usually show normal findings.

How Is a Concussion Treated?

Treatment consists of rest and careful observation, usually at home. First symptoms of a concussion mimic those of a head injury with bleeding into the brain. If symptoms get worse or don't improve, swelling or bleeding inside the skull needs to be ruled out by your physician with addi-

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tional tests.

DOs and DON'Ts in Managing a Concussion:

✓ **DO** take medicines such as acetaminophen for headache.

✓ **DO** eat a light diet. For nausea, eat mostly small amounts of food or fluids.

✓ **DO** get plenty of rest until you feel normal. Ask your doctor about when you may return to work or may exercise. An ice pack to the spot that was hit may help with pain.

✓ **DO** watch for increasing confusion, worsening headache, drowsiness, loss of coordination, loss of memory, nausea, vomiting, muscle weakness, problems walking, unequal pupils, convulsions, and inability to wake from sleep. These signs mean a worsening condition and could mean an emergency.

✓ **DO** call your doctor if you don't improve in about 24 hours.

✓ **DO** prevent head injuries: always wear a seat belt in a motor vehicle. Always use helmets when riding a motorcycle. Use protective gear in sports and limit contact sports activities.

✓ **DO** avoid another concussion. Repeated concussions (especially within 3 months) may cause permanent brain damage and even death. Don't play football, hockey, box, or practice martial arts for at least 3 months after a concussion.

⦸ **DON'T** stay alone. Someone should check on you every couple of hours for the first 24 hours or until you feel normal.

⦸ **DON'T** take medicines or substances that cause drowsiness or changes in level of con-

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sciousness. These include narcotic pain medicines, alcohol, sleeping pills, muscle relaxants, tranquilizers, and recreational drugs. They may mask important symptoms of a worsening condition.

⦸ **DON'T** eat a heavy diet. It may lead to vomiting.

⦸ **DON'T** do strenuous activities. You may get a more severe headache. Don't operate dangerous machinery. Being dizzy or having decreased muscle coordination, ability to concentrate, or memory may make operation of machinery dangerous.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- Brain Injury Association of America (formerly the National Head Injury Foundation) Tel: (800) 444-6443 **Website: http://www.biausa.org**
- American Trauma Society Tel: (800) 556-7890 **Website: http://www.amtrauma.org**

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MANAGING YOUR

CONGESTIVE HEART FAILURE (CHF)

What Is Congestive Heart Failure (CHF)?

CHF is a condition in which the heart cannot (fails to) pump enough blood to organs and tissues. One side of the heart (or both sides) cannot force enough blood out, so blood backs up. Congestion, or abnormal buildup of fluid, occurs in tissues or organs, and blood doesn't move well through the vascular system.

If the left side of the heart fails, the system on the right side becomes congested. The congested side of the heart must work harder and may also fail. The same thing can happen on the right side.

What Causes CHF?

Diseases that stress heart muscle can cause CHF. These conditions include high blood pressure, heart attack, heart muscle and valve diseases, infections, arrhythmias (abnormal heart rhythms), anemia, thyroid disease, pulmonary disease, and too much fluid in the body.

What Are the Symptoms of CHF?

When the left side of the heart fails, fluid leaks into the lungs. Fatigue (tiredness), difficulty breathing (especially at night when lying down), coughing, or shortness of breath can result.

In right-sided heart failure, the liver swells, which may cause pain in the abdomen (belly). Legs and feet may swell also.

How Is CHF Diagnosed?

A physical examination will show changes, such as swelling in the legs or crackling breath sounds, indicating excess fluid in the lungs.

A chest x-ray can show an enlarged heart and signs of fluid accumulation into the lungs. An

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echocardiogram (a test using sound waves to show the moving heart) can also reveal heart size and disease of the heart muscle or valve problems.

How Is CHF Treated?

Initial symptoms should be managed so the failing heart doesn't have to work as hard.

The cause of CHF also needs treatment. For example, if a heart valve problem is the cause, surgery may be needed to repair or replace the valve. Lifestyle changes will be needed. Smoking lowers the blood oxygen level and makes the heart work harder, so avoid tobacco. Less fluid and salt in the diet reduces fluid in the body. Also, if overweight, losing weight will help. Dietitians and nutritionists can help plan a diet.

Oxygen may be given to reduce the workload on the lungs.

Medicines may be prescribed to reduce fluid in the body or help the ventricle contract better. Diuretics remove fluid. Nitrates open blood vessels so blood flows more easily. Angiotensin-converting enzyme (ACE) inhibitors help the ventricle contract. Beta-blockers help by slowing the heart rate. Other drugs reduce blood pressure. All may have side effects, including dehydration, cough, dizziness, fainting, and fatigue.

Pacemakers and implantable defibrillators may be used in some cases.

Heart transplantation is an option in some patients when other treatments fail.

DOs and DON'Ts in Managing CHF:

✓ **DO** take your medicines properly.

✓ **DO** maintain your ideal body weight.

✓ **DO** reduce salt and extra fluid in your diet.

✓ **DO** get your family involved in your care, especially the needed lifestyle changes.

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✓ **DO** call your doctor if you have side effects from your drugs or new or worsening symptoms, such as increasing shortness of breath, chest pain, or fainting.

⃠ **DON'T** forget to take all your medicines as directed.

⃠ **DON'T** smoke.

⃠ **DON'T** stop taking any medicines without telling your doctor.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website: http://www.americanheart.org**
- National Heart, Lung, and Blood Institute **Website: http://www.nhlbi.nih.gov**

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MANAGING YOUR

CONJUNCTIVITIS

What Is Conjunctivitis?

Conjunctivitis (also called pink eye) is the most common eye infection. It causes soreness and swelling (inflammation) of the skin that lines the eyelid and the white part of the eyeball. One or both eyes can have it. People of any age can get conjunctivitis. It occurs most often in the fall.

Serious complications that threaten sight are very rare.

What Causes Conjunctivitis?

The cause can be infection with bacteria or virus (very contagious) or an allergy to something such as pollen.

The virus is usually the one that causes a common cold. Different bacteria (such as *Staphylococcus* and *Streptococcus*) can cause the infection. Direct contact with tears or the infected area, which occurs by placing towels, fingers, or handkerchiefs near the eye, will pass these infections to others.

What Are the Symptoms of Conjunctivitis?

Conjunctivitis produces a red irritated eye with a watery discharge (allergic and viral) or a discharge of mucus and pus (bacterial). Bacterial conjunctivitis also causes soreness and swelling in one eye, slight pain and feeling dirt or grit in the eye, and a slimy discharge that causes lids to crust. It's most common in children.

Viral conjunctivitis usually causes inflammation and discharge that is more watery than that in bacterial conjunctivitis.

Allergic conjunctivitis produces red, irritated, itchy eyes; small watery discharge; and inflammation of both eyes. Itching is characteristic of allergic conjunctivitis. Allergies can be to

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pollen, pets, and house dust.

How Is Conjunctivitis Diagnosed?

The doctor makes a diagnosis from an examination.

How Is Conjunctivitis Treated?

For bacterial infection, the doctor will prescribe antibiotic eye drops or ointment. Warm compresses on the eye may also be used.

For viral conjunctivitis, the doctor may suggest eye drops that help increase moisture in the eye. Antibiotic eye drops or ointment won't work. Warm compresses on the eye may help.

For allergic conjunctivitis, the doctor will prescribe eye drops for inflammation. Cold, not hot, compresses may soothe the eye. Decongestant and antihistamines may also be used.

Bacterial conjunctivitis is usually much better within 48 hours of starting therapy. It's usually over in about 1 week.

Viral conjunctivitis usually improves in 1 to 2 weeks but may take longer.

Symptoms of allergic conjunctivitis may be seasonal.

DOs and DON'Ts in Managing Conjunctivitis:

✓ **DO** avoid direct contact with anyone who has conjunctivitis.

✓ **DO** wash your hands often.

✓ **DO** use separate towels, washcloths, and pillowcases from other family members if you have conjunctivitis.

✓ **DO** throw away old eye cosmetics and don't share eye cosmetics with others.

✓ **DO** avoid the cause of the allergy, if possible.

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✓ **DO** use medicines as directed. If using more than one eye drop, wait between use of each so that the second doesn't wash the first out.

✓ **DO** call your doctor if you have severe pain, fever, and blurred vision with conjunctivitis.

⃠ **DON'T** touch the infected area or rub your eye.

⃠ **DON'T** wear contact lenses until treatment is over. You may need to replace the contact lenses and the container normally used for storing them.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Academy of Ophthalmology Tel: (415) 561-8500 **Websites:** **http://www.aao.org** **http://www.eyenet.org**
- American Academy of Optometry Tel: (301) 984-1441 **Website:** **http://www.aaopt.org**

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MANAGING YOUR

CONSTIPATION

What Is Constipation?

Constipation is having bowel movements less frequently than usual. There is no normal number of bowel movements per week for everyone. Some people move their bowels three times daily and others do it once every 3 days. What is more important as far as colon cancer is if there is a change in bowel movement, frequency, and consistency of the stool.

What Causes Constipation?

Constipation is due to slow movement of stools (feces) through the colon. The many causes include benign conditions, such as not enough fluid and fiber intake, inactivity, pregnancy, recent travel, and stress, to more serious conditions, such as bowel obstruction because of colon cancer. Constipation is usually harmless and due to lifestyle changes. Medicines such as pain relievers containing narcotics, antihistamines, and some anti-depressants are other common causes.

What Are the Symptoms of Constipation?

Symptoms include straining to move bowels, dry or hard stools, bloating of the abdomen (belly), pain or bleeding from the rectum during or after a bowel movement, and feeling that the bowel movement wasn't enough, with a need to go again.

How Is Constipation Diagnosed?

The doctor makes a diagnosis from the medical history, including recent lifestyle changes (stress, travel, fluid intake) and medicines. The doctor will also do a physical examination, especially of the abdomen. The doctor may also do a digital rectal examination to check for problems such as hemorrhoids and rectal fissures, to look for stool in the rectum and its consistency, and to test for blood in the stool.

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If the stool contains blood, a colonoscopy and blood tests may be done. In a colonoscopy, a specialist uses a small tube attached to a lighted instrument to look at the colon. Blood tests will check for anemia (low blood).

If a lump or mass in the abdomen is found, additional tests such as computed tomography of the abdomen and pelvis may be needed.

How Is Constipation Treated?

Treatment of mild constipation involves lifestyle changes, with increased exercise and intake of fluids (six to eight glasses daily) and fiber. Laxatives are best avoided because people can become dependent on them. If needed, use natural laxatives such as prune juice. Set a regular time each day for bowel movements. Take enough time, and don't rush. Hot water or coffee a few minutes before may help stimulate the movement.

For moderate to severe constipation, stool softeners, over-the-counter laxatives, and enemas may be needed. Avoid harsh laxatives.

DOs and DON'Ts in Managing Constipation:

✓ **DO** tell your doctor about laxatives you use regularly.

✓ **DO** include lots of fiber in your diet, such as with fruits, vegetables, and whole grains.

✓ **DO** drink enough fluids, especially in warm weather.

✓ **DO** avoid over-the-counter products such as antihistamines that may cause constipation.

✓ **DO** call your doctor if constipation lasts even with lifestyle changes.

✓ **DO** call your doctor if you have rectal pain or bleeding with your bowel movements.

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✓ **DO** call your doctor if you have a fever or abdominal pain.

⃠ **DON'T** use laxatives daily.

⃠ **DON'T** rush your bowel movements.

⃠ **DON'T** ignore continuing constipation. It could be a sign of something serious.

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FOR MORE INFORMATION

Contact the following source:

- American College of Gastroenterology Tel: (703) 820-7400 **Website:** **http://www.acg.gi.org**

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CARING FOR YOUR CHILD WITH

CONSTIPATION

What Is Constipation?

Constipated children have fewer bowel movements than usual or hard, dry, painful-to-pass stools. There's no normal number of bowel movements for everyone. Constipation is usually temporary and not serious but can cause emotional problems and family stress. It's very common in children, slightly more boys than girls.

What Causes Constipation?

Causes include low-fiber diets, not drinking enough fluids, not enough exercise, and certain medicines such as over-the-counter cold medicines and antacids. Diseases including diabetes, cystic fibrosis, or Hirschsprung's disease can cause it. Some children don't want to have bowel movements (withhold stool) because they're stressed about potty training or worry about having painful or unpleasant bowel movements. They may not want to stop play or are embarrassed to use public bathrooms. Other causes are starting toilet training too soon, changes in children's routines, milk allergy, and family history.

What Are the Symptoms of Constipation?

Symptoms include no bowel movements for several days, pains and cramps in the belly (abdomen), and hard, dry, or large stools. Certain postures may mean children are withholding stool. Babies may extend their legs and squeeze anal and buttock muscles. Toddlers rise up on toes, rock back and forth, and hold legs and buttocks stiffly. Stool in underwear may mean constipation, not diarrhea. Other symptoms include poor appetite and crankiness. Sometimes children can have watery stools that look like diarrhea, as watery stool leaks past a hard stool mass in their colon. More serious symptoms that should mean a doctor's visit include fever, vomiting, bloody

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stool, and weight loss.

How Is Constipation Diagnosed?

The doctor uses the medical history, including lifestyle changes (stress, travel, fluid intake) and medicines. The doctor will do a physical examination, especially of the abdomen. The doctor may also do a rectal examination (putting a gloved finger in the anus) to check for more serious problems such as hemorrhoids. Stool may be tested for blood. Only severe cases need other tests.

How Is Constipation Treated?

Treatment depends on the child's age. If present, fecal impaction—a large, hard mass of stool in the lower abdomen—must be removed. Other measures can be simple diet changes, taking laxatives, and having healthy bowel habits. Eating more high-fiber foods, such as whole grains, beans, fruits, and vegetables should help. Water and other fluids, but not milk, will soften stool. Over-the-counter fiber supplements or stool softeners may be tried. However, laxatives or enemas shouldn't be given without a doctor's ok. Allow enough time and a regular routine for bowel movements. Sometimes relaxation, mental imagery, and gentle belly massage can promote bowel movements. Regular physical activity helps normal bowel function.

DOs and DON'Ts in Managing Constipation:

✓ **DO** include lots of fiber, such as fruits, vegetables, and whole grains, in your child's diet.

✓ **DO** have your child drink enough fluids, such as water and prune juice.

✓ **DO** encourage physical activity.

✓ **DO** call your child's doctor if constipation continues even with lifestyle changes.

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✓ **DO** call your child's doctor if your child has fever, severe abdominal pain, or if rectal pain or bleeding occurs with bowel movements.

⃠ **DON'T** give laxatives unless your doctor tells you to.

⃠ **DON'T** rush your child's bowel movements. Have a regular bathroom routine.

⃠ **DON'T** ignore continuing constipation. It could be a sign of something serious.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- The American Academy of Pediatrics Tel: (847) 434-4000 **Website: http://www.aap.org**
- American College of Gastroenterology Tel: (703) 820-7400 **Website: http://www.acg.gi.org**

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MANAGING YOUR

CONTACT DERMATITIS

What Is Contact Dermatitis?

Contact dermatitis is a common skin irritation due to exposure to a skin irritant. Contact dermatitis is not infectious.

More than 50% of adult Americans have had it at least once.

What Causes Contact Dermatitis?

Causes include substances that come into direct contact with the skin and irritate it or cause skin allergies. The resin urushiol, produced by poison ivy, poison oak, and poison sumac plants, is a common cause. Contact with the substance may occur not only by touching the plants but also clothing or pets carrying the substance.

Other causes include clothing (wool), household cleaners, fragrances (e.g., in soaps, shampoos), the metal nickel, dyes, medicines, pesticides, and other chemicals.

What Are the Symptoms of Contact Dermatitis?

Symptoms include dry, red, or blistered skin; itching; and mild discomfort. Intense itching and burning of the skin develop 24 to 36 hours after exposure, followed by weeping blisters and crusting and swelling of the skin. The liquid in the blisters is not infectious to others.

Breathing in or swallowing the substance can cause wheezing or nausea. Scratching the skin may lead to infection.

How Is Contact Dermatitis Diagnosed?

The doctor will diagnose dermatitis from the history of exposure and by looking at the skin.

How Is Contact Dermatitis Treated?

The best treatment is avoiding exposure. For example, avoid buying wool clothes and blankets if

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you are sensitive to wool products, and learn to recognize poison ivy. Wear gloves, long sleeves, and long pants to avoid contact with the plants and anything that has touched them.

Other treatments include topical or oral antiinflammatory drugs (steroids), antihistamines (for itching), and immunotherapy (desensitization) to minimize the reaction.

Steroids (such as prednisone) can be given in pill form, injection, or as creams and ointments.

Lotions, such as calamine, and oatmeal baths soothe oozing, blistery rashes and may be used as needed.

DOs and DON'Ts in Managing

Contact Dermatitis:

✓ **DO** use your oral steroids as directed. Oral antihistamines can be used as needed and stopped if itching improves.

✓ **DO** use anti-itch lotions as needed, but avoid using them during the first hour after applying steroids, creams, or ointments. (Give the steroid time to soak in first!)

✓ **DO** eat a good diet.

✓ **DO** exercise, but realize that hot, sweaty skin will itch more. Wash and cool the skin soon after exercise.

✓ **DO** use a mild soap or cleanser to clean skin. Avoid extra irritation that might be caused by deodorants or fragrances in soaps.

✓ **DO** wash your skin immediately with soap and water if you're exposed to a substance that caused previous contact dermatitis.

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✓ **DO** call your doctor if you have a fever, coughing, wheezing, vomiting, or diarrhea; if the rash worsens despite treatment; or if a new or different rash occurs.

⃠ **DON'T** skip doses of steroid medicines. Your dermatitis may worsen.

⃠ **DON'T** use antihistamine lotions or creams without your doctor's advice. These can cause rashes themselves!

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FOR MORE INFORMATION

Contact the following sources:

- Asthma and Allergy Foundation of American Tel: (800) 727-8462 **Website:** **http://www.aafa.org**
- American Academy of Dermatology Tel: (866) 503-SKIN (503-7546) **Website:** **http://www.aad.org**

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UNDERSTANDING YOUR OPTIONS

CONTRACEPTION

What Is Contraception?

Contraception is prevention of pregnancy by any method.

How Pregnancy Occurs

Each month, approximately 2 weeks after a woman bleeds (menstrual period), the ovary releases an egg (called ovulation). The egg travels to the fallopian tube, which connects to the uterus. If sex occurs near the time of ovulation and the man ejaculates (climaxes), sperm are released into the vagina. Sperm travel through the opening of the uterus (cervix) into the uterus and then into fallopian tubes. If a sperm fertilizes the egg, pregnancy occurs.

How Pregnancy Can Be Prevented

Pregnancy can be prevented in three ways: stop ovulation, stop sperm from getting to eggs in the fallopian tube, and change the uterine lining (endometrium) so it won't support pregnancy.

Pills

Birth control pills, the most common method, contain hormones similar to ovarian hormones and stop ovulation. Pills plus smoking, high blood pressure, obesity, or family history of clotting disorders may lead to increased chance of stroke, heart attack, or blood clots.

Implants

Implants are capsules containing a certain hormone that are surgically placed under the skin on the arm.

Progesterone Injections

A contraceptive containing only the hormone progesterone is injected every 3 months and stops ovulation.

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Barriers

Condoms, diaphragms, and cervical caps are barriers that stop sperm from getting to the egg. All should be used with a spermicide (chemical that kills sperm).

A condom is a thin rubber or animal membrane covering that is put on the penis. A rubber, dome-shaped diaphragm is put in the vagina over the cervix. A cervical cap (small rubber cap) fits right on the cervix. It works like the diaphragm but is smaller.

Intrauterine Devices (IUDs)

IUDs are small devices inserted into the uterus by a doctor. They change the uterus or fallopian tube so pregnancy cannot occur. The Copper T is a small T-shaped plastic IUD with a wrapping of copper. Another IUD produces progesterone.

Permanent Surgical Methods

The two methods are tubal ligation (tying the tubes) in a woman and vasectomy in a man. A tubal ligation is done by special (laparoscopic) surgery. Very small cuts are made and fallopian tubes are sealed or closed. In vasectomy, which is minor surgery, tubes called vas deferens in the scrotum are tied off.

Abstinence (Rhythm) Method

Not having sex around the time of ovulation prevents pregnancy. This method works only if the woman has regular cycles. It is not recommended for young women whose cycles are still changing.

How Do You Choose a Contraception?

Some couples may use more than one form of birth control. Things to think about when choosing a method include how each is used, age, health, frequency of sex, and partner's feelings about methods.

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DOs and DON'Ts in Deciding

About Contraception:

✓ **DO** think about protection from sexually transmitted diseases (STDs) when choosing a method. Certain methods prevent both pregnancy and STDs.

✓ **DO** try a new method if you don't like your current one.

✓ **DO** talk with your partner to figure out the best method.

✓ **DO** talk with your doctor about the benefits and risks of your chosen methods.

⃠ **DON'T** assume that your partner is taking care of it.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website:** **http://www.acog.org**
- National Women's Health Information Center Tel: (800) 994-9662

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MANAGING YOUR

CONVERSION DISORDER

What Is Conversion Disorder?

"Somatoform disorders" have physical symptoms suggesting that a medical condition exists. However, no medical condition, substance use, or mental disorder can explain them. These illnesses include conversion disorder. This disorder is defined as findings suggesting a neurological condition (such as paralysis, numbness, loss of sensation) but without a diagnosis of a real neurological problem.

Conversion disorders are rare, occurring in 11 of 100,000 people, more women than men. Children younger than 10 and people older than 35 rarely have them.

What Causes Conversion Disorder?

The cause is unknown. It's not contagious or passed from parents to children.

What Are the Symptoms of Conversion Disorder?

Most symptoms occur suddenly and usually last for a short time. They usually go away in 2 weeks. Complaints include one-sided muscle paralysis or weakness, numbness, loss of sensation, loss of voice, blindness, deafness, tremors, and pseudoseizures. Pseudoseizures aren't caused by electrical brain disturbances. Their cause is psychological.

How Is Conversion Disorder Diagnosed?

The doctor does a neurological examination and may refer you to a neurologist. A neurologist is a specialist in nervous system diseases. Imaging tests may include computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography. Electroencephalography (EEG) may also be done. For diagnosis, people must have one or more symptoms, not intentionally produced, that affect movement or senses. These symptoms suggest a neurological or other condi-

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tion. People must have psychological problems related to these symptoms. Symptoms cannot be explained by actual medical conditions, effects of substances, or behaviors. Symptoms cause distress or inadequacy in social situations or jobs. Symptoms aren't only pain or sexual dysfunction. They aren't explained by another mental disorder.

How Is Conversion Disorder Treated?

Treatment is hard because people have physical symptoms but test results are normal. A psychiatrist (a medical specialist) or psychologist (another kind of specialist, for psychological problems) may be involved in care. A psychiatrist can prescribe medicines; a psychologist can treat the patient but cannot prescribe medications.

Psychological treatment involves cognitive and behavioral therapy. Cognitive therapy teaches people how certain thinking patterns cause symptoms. Behavioral therapy breaks the connection between worry about stresses and usual reactions to them.

DOs and DON'Ts in Managing

Conversion Disorder:

✓ **DO** realize that a good prognosis is related to a sudden start of the disorder, stress (such as loss or life change) at that time, and a short time between diagnosis and treatment.

✓ **DO** call your doctor if you have paralysis, blindness, or loss of sensation.

✓ **DO** call your doctor if you need a referral to a psychiatrist or psychologist.

✓ **DO** call your doctor if you feel anxious or depressed. Call if you think that you will harm yourself or others.

⦸ **DON'T** forget that this disorder can recur.

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⦸ **DON'T** forget this disorder may be triggered by stress that makes the brain unconsciously turn off a body function.

⦸ **DON'T** doctor shop. Stay with one primary doctor. Going from one doctor to another can lead to unneeded blood tests, x-rays, and risky studies.

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FOR MORE INFORMATION

Contact the following sources:

- American Psychiatric Association Tel: (888) 357-7924 **Website: http://www.psych.org**
- American Psychological Association Tel: (800) 374-2721 **Website: http://www.apa.org**

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MANAGING YOUR

CORNEAL FOREIGN BODY AND CORNEAL ABRASION

What Are a Corneal Foreign Body and

Corneal Abrasion?

The cornea acts as a clear window on the front of the eye. A corneal foreign body is something that hits the eye and stays on the cornea. A corneal abrasion is a scratch on the surface of the cornea.

What Causes a Corneal Foreign Body and

Corneal Abrasion?

A foreign body scratching the cornea usually causes an abrasion. For example, wood slivers, pieces of mascara, or a damaged contact lens can scratch the cornea. Also, using power tools or hand tools can make something fly into the eye.

What Are the Symptoms of a Corneal Foreign

Body and Corneal Abrasion?

A foreign body makes the eye red, painful, and sensitive to light. Vision may be blurred.

Main symptoms of a corneal abrasion are redness, tearing, and severe eye pain. It may be hard to keep the eye open or look at light. It may feel as if something is in the eye. Blinking makes the pain worse.

How Are a Corneal Foreign Body and

Abrasion Diagnosed?

The doctor will diagnose the abrasion by looking in the eye with a special light. Eyedrops containing a dye may first be put into the eye so that the doctor can see the abrasion better. The doctor will also check to see whether the foreign body is still in the eye. If a blow to the eye caused

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the abrasion, a complete eye examination should be done to look for other injuries.

How Are a Corneal Foreign Body and Corneal

Abrasion Treated?

The doctor will remove the foreign body. A scratch may remain on the corneal surface for a few days. The eye will hurt until the scratch heals. Antibiotic ointment or eyedrops will be used to treat the scratch. The ointment prevents infection and keeps the corneal surface moist and smooth. It stops the eyelid from rubbing against the irritated area with each blink. Eyedrops are sometimes used instead of ointment to prevent infection.

Oral medicine and moist, cold compresses can help ease pain.

A foreign body that is deeply embedded may need surgery to remove it. Corneal abrasions usually heal in a few days. Larger abrasions may take longer.

DOs and DON'Ts in Managing a Corneal Foreign

Body and Corneal Abrasion:

✓ **DO** get treatment as soon as possible.

✓ **DO** use ointment or eyedrops exactly as your doctor tells you.

✓ **DO** rest your eye. Avoid prolonged eye strain.

✓ **DO** have your eye rechecked if doesn't heal after 24 hours or pain gets worse.

✓ **DO** wear safety glasses when working with hand tools, power tools, and machinery.

✓ **DO** call your doctor if you have increasing pain or redness or worsening vision.

⃠ **DON'T** touch or rub your eye, especially when you wake up.

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⦸ **DON'T** wear contact lenses until the eye heals and you have finished all ointments or eye-drops for at least 1 day.

⦸ **DON'T** look at bright light.

⦸ **DON'T** use topical anesthetic for pain relief. It may delay the eye from healing.

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FOR MORE INFORMATION

Contact the following sources:

- MedlinePlus **Website:** **http://medlineplus.gov**
- National Eye Institute, National Institutes of Health Tel: (301) 496-5248 **Website:** **http://www.nei.nih.gov/health/cornealdisease/**
- American Academy of Ophthalmology Tel: (415) 561-8500 **Website:** **http://www.aao.org**

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MANAGING YOUR

CORONARY ARTERY BYPASS SURGERY

What Is Coronary Artery Bypass Surgery?

Coronary artery bypass graft (CABG) surgery is one of the most common major operations. It's used for people with narrow or blocked heart arteries (coronary artery disease, or CAD). CAD occurs when atherosclerotic plaque builds up in artery walls (hardening of the arteries). CABG surgery makes a new route, or bypass, around these arteries, so blood can get to the heart to deliver oxygen and nutrients. Three (triple), four (quadruple), or five (quintuple) bypasses are now routine.

Who Needs CABG Surgery?

People with angina who haven't been helped by drugs or can't have angioplasty may have CABG surgery. Other reasons for CABG surgery include angina after a heart attack (myocardial infarction, or MI), heart valve disorders, and other kinds of heart damage. CABG surgery is best for people with severe narrowing in many coronary artery branches, such as in diabetics.

How Is CABG Surgery Done?

Bypass grafting involves sewing the graft vessels to the coronary arteries to go around the narrowing or blockage. CABG surgery usually means using a heart-lung bypass machine. The heart is stopped while people are connected to this machine, which does the work of the heart. The machine adds oxygen to blood and circulates blood through the body. The heart is cooled with iced salt water, and a preservative solution is injected into the heart arteries to minimize damage. CABG surgery takes about 4 hours, and the bypass machine is used for about 90 minutes.

Several newer, less invasive methods may be used instead of open-chest surgery. They include off-pump coronary artery bypass, or OPCABG. It doesn't use the bypass machine. The

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heart still beats during surgery. This method minimizes complications such as memory problems that may be seen after CABG. Other newer methods are minimally invasive surgery (uses a small incision) and robotic technology.

What Are the Risks of CABG Surgery?

Risks include needing another operation because blood clots cause grafts to be blocked. Grafts can get narrow after the first 5 years as scar tissue forms and atherosclerosis occurs. Internal mammary arteries remain open longer than do veins. Problems with anesthesia, heart attack, stroke, bleeding, infections, and abnormal heart rhythms also occur. Low-grade fever and chest pain could last up to 6 months. Some people have memory loss and problems thinking. During and shortly after CABG surgery, heart attacks occur in 5–10% of people and are the main cause of death.

DOs and DON'Ts in Managing CABG Surgery:

- ✓ **DO** understand the risks of surgery. Talk to your doctor about the operation and cardiovascular health.
- ✓ **DO** make sure that your doctors have experience with CABG surgery.
- ✓ **DO** use cholesterol-lowering medicines (such as statins) that your doctor prescribes. LDL levels below 70 help long graft survival and reduce heart attack risk.
- ✓ **DO** make lifestyle changes to be heart healthy: quit smoking, lower your cholesterol levels, keep to a healthy weight, control other conditions such as diabetes and high blood pressure, and exercise regularly.
- ✓ **DO** call your doctor after CABG if you develop shortness of breath, fever, unexplained

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bleeding or bruising, excessive weight gain or wound infection.

- ⃠ **DON'T** smoke or eat fatty foods.
- ⃠ **DON'T** forget: CABG surgery doesn't cure CAD. Reducing risk factors and slowing atherosclerosis with lifestyle changes and medications are important.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:**

  http://www.americanheart.org

- American College of Cardiology Tel: (800) 253-4636 **Website: http://www.acc.org**

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MANAGING YOUR

CORONARY ARTERY DISEASE

What Is Coronary Artery Disease (CAD)?

The heart pumps oxygen-rich blood through the extensive network of arteries throughout the body. The blood carries oxygen and other nutrients, needed by organs in the body. In coronary artery disease (CAD), or coronary heart disease, fatty deposits build up on inner layers of coronary arteries. These blood vessels are on the outside of the heart and take blood to the heart muscle itself. These fatty deposits, or plaque, also contain other substances that promote inflammation. They may form in teenage years and continue to thicken and enlarge throughout life. This thickening, called atherosclerosis, narrows the arteries and can reduce or block blood flow to the heart.

More than 12 million Americans have CAD, the number one killer of both men and women in the country.

What Are the Risk Factors for CAD?

Risk factors include high cholesterol levels in blood, high blood pressure (hypertension), inactivity, smoking, obesity, diabetes, and a family history of CAD.

What Are the Symptoms of CAD?

If too little oxygenated blood reaches the heart, chest pain called angina occurs. Angina is generally described as tightness or heaviness in the chest but symptoms vary from person to person. A complete block of the blood supply can cause a heart attack, with damage to the heart muscle. Symptoms of CAD depend on how severe the disease is. Some people with CAD have no symptoms, some have mild chest discomfort, and some have more severe angina. Other symptoms include feelings of heaviness, tightness, and pressure in the chest; pain in the arms, shoulders,

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jaw, neck, or back; shortness of breath; and nausea.

How Is CAD Diagnosed?

The doctor will take a complete medical history and do a physical examination and blood tests. Other tests include an electrocardiogram (ECG or EKG), which records the heart's electrical activity, and a stress test (also called treadmill or exercise ECG). The doctor may also order nuclear scanning, which uses a radioactive dye to show healthy and damaged parts of the heart. Coronary angiography (takes x-ray pictures of arteries by inserting a flexible tube called a catheter from a blood vessel in the groin area and guiding it into the heart) may be done if the stress test or nuclear scanning reveals a possible blocked coronary artery.

How Is Coronary Artery Disease Treated?

Controlling risk factors is crucial for preventing and treating CAD. Lifestyle changes include eating a low-fat diet and losing weight (if overweight), following a good exercise program, quitting smoking, controlling blood sugar (glucose) if diabetic, and reducing blood pressure.

Drugs are often prescribed to lower blood pressure, lower cholesterol, and increase coronary blood flow. More severe CAD may need coronary angioplasty, a procedure to widen arteries, which may include using a stent (special device to keep the artery open). In some cases the doctor may advise coronary artery bypass surgery, in which blood vessels from another part of the body (e.g., legs) are used to create a new route around blocked arteries.

DOs and DON'Ts in Managing Coronary

Artery Disease:

✓ **DO** eat a healthy diet, rich in fruits, vegetables, and low-fat dairy products with less saturated and total fats.

✓ **DO** take your prescribed medicines.

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✓ **DO** lower your dietary sodium (salt) intake to no more than 2400 mg per day.

✓ **DO** regular aerobic physical exercise, such as brisk walking (at least 30 minutes per day, most days of the week)only after consulting with your physician to determine what level of activity is appropriate for you.

✓ **DO** keep to a normal body weight.

⃠ **DON'T** smoke or use tobacco products.

⃠ **DON'T** over exert yourself, and avoid extreme cold and stress.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:** **http://www.americanheart.org**
- National Heart, Lung, and Blood Institute **Website:** **http://www.nhlbi.nih.gov**
- American College of Cardiology **Website:** **http://www.acc.org**

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MANAGING YOUR

COSTOCHONDRITIS

What Is Costochondritis?

The ribs connect to the sternum (breastbone) by cartilage, a thick elastic tissue. This connection is called the costochondral junction, a joining of bone and cartilage. Costochondritis is pain and tenderness in this part of the chest. Most people get better and are pain free in a few days. It may go away on its own. Costochondritis cannot be prevented.

One type of costochondritis caused by swelling of the cartilage is Tietze's syndrome. It can occur anywhere in the chest but is usually on the left side.

What Causes Costochondritis?

Exercise, injury, chronic cough, or viral infection can cause the cartilage connecting ribs and breastbone to become painful and swollen. The cause can also be unknown.

What Are the Symptoms of Costochondritis?

Symptoms include pain and tenderness in the chest. Pain may be mild or severe and may last for several days or longer. Coughing, sneezing, deep breaths, and certain movements can make the pain worse. Some people feel anxious and short of breath. The pain is often sharp, and can last from minutes to hours.

How Is Costochondritis Diagnosed?

The doctor makes a diagnosis from a medical history and physical examination, which often shows tenderness over the cartilage. No specific blood tests or x-rays are needed, but the doctor may order tests to be sure that no other condition is present.

How Is Costochondritis Treated?

Costochondritis may last several days or weeks. It first gets better and then goes away, with or

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without treatment. Nonsteroidal antiinflammatory drugs (NSAIDs) such as ibuprofen may be especially helpful. Other treatments include heat and stretching exercises. If these treatments don't work, cortisone injections might be tried but are rarely needed.

Using a heating pad also helps to take the pain away. If the condition persists, the doctor may suggest seeing a rheumatologist (a doctor who specializes in joint diseases) or an orthopedist (a doctor who specializes in bone diseases) if the disorder doesn't get better with treatment.

DOs and DON'Ts in Managing Costochondritis:

✓ **DO** follow your doctor's instructions. Take your medicine until the pain and swelling go away completely.

✓ **DO** tell your doctor if you take over-the-counter or prescription medicines.

✓ **DO** make sure your doctor says that it's OK before starting to exercise.

✓ **DO** tell your doctor if pain gets worse even with treatment. Another problem may be causing the pain.

✓ **DO** call your doctor if you have side effects from medicines.

✓ **DO** call your doctor if you have a new, unexplained symptom with your chest pain.

⃠ **DON'T** use a heating pad more than three times a day or for more than 20 minutes at a time. Don't use oils or creams with a heating pad. The pain could get worse or you could get burned.

⃠ **DON'T** exercise until your pain is completely gone and your doctor says that it's OK.

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⦸ **DON'T** continue an exercise program that causes pain most of the time.

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FOR MORE INFORMATION

Contact the following source:

• American College of Rheumatology Tel: (404) 633-3777 **Website:**

http://www.rheumatology.org

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MANAGING YOUR

CRANIOPHARYNGIOMA

What Are Craniopharyngiomas?

Craniopharyngiomas are tumors that develop near the pituitary gland at the base of the skull. They account for 2% to 4% of all brain tumors. Most grow slowly and are benign (not cancerous). They can spread (metastasize), however. They can occur at any age but most often affect children 5 to 10 years old, boys and girls equally, and adults 65 to 74 years old.

What Causes Craniopharyngiomas?

The cause is unknown. They are thought to grow from groups of special cells commonly found in the part of the brain called the suprasellar area surrounding the pituitary gland.

What Are the Symptoms of Craniopharyngiomas?

Tumors usually start slowly. People usually have no symptoms in early stages. They commonly have symptoms that progress slowly for 1 to 2 years. Symptoms are usually related to where the tumor is. Most people report headaches and have problems with vision. The usual problem is loss of side vision, called bitemporal hemianopsia. Other symptoms include mental changes, nausea, vomiting (especially in the morning), balance problems, and sleepiness. Damage to the pituitary can lead to lack of hormones. Adults often have sexual dysfunction. Men can be impotent. Women can stop having their periods. Urinating too often with large volumes of urine occurs in 25% of cases. It's due to not enough antidiuretic hormone (diabetes insipidus), as the tumor grows and destroys pituitary tissue. These tumors may cause children to be very short (dwarfism), because of loss of pituitary cells that make growth hormone. Other endocrine problems can be precocious puberty in children and obesity in adults. Large tumors in adults can cause neuropsychiatric symptoms, memory loss, apathy, incontinence, depression, and lethargy.

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How Are Craniopharyngiomas Diagnosed?

The location of the tumors can make them hard to diagnose. The health care provider makes a preliminary diagnosis from the medical history, physical examination, and laboratory tests that measure hormone levels. Magnetic resonance imaging (MRI) or computed tomography (CT) of the brain will be done if craniopharyngioma is suspected. Special tests will include measuring vision loss (visual field evaluation). The health care provider will recommend seeing specialists (endocrinologist, neurosurgeon).

How Are Craniopharyngiomas Treated?

The main treatment is surgery to remove the tumor. Transsphenoidal surgery is used for small intrasellar tumors. Most people have subfrontal craniotomy. The goal is total tumor removal but making sure that the vision and pituitary structures (stalk) are preserved. Radiation therapy usually follows surgery. MRI is used after surgery to determine if the entire tumor has been removed. External beam radiotherapy is used for treatment of any remaining tumor.

The 5-year survival after treatment is 55% to 85%. When the tumor isn't completely removed, the condition may recur, usually within the first year. People can have lasting hormonal, visual, and neurological problems after treatment and will need close follow-up and medications from an endocrinologist.

DOs and DON'Ts in Managing Craniopharyngiomas:

✓ **DO** keep all scheduled office visits with your primary care health care provider and all specialists.

⦸ **DON'T** stop taking any prescribed medicine or change the dosage because you feel better unless your health care provider tells you to.

⦸ **DON'T** ignore symptoms. Call your health care provider if your symptoms don't get better

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or they get worse with treatment. Call if you have new symptoms.

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Neurological Disorders and Stroke Tel: (800) 787-6537 **Website: http://www.ninds.nih.gov**
- American Academy of Ophthalmology Phone: 415-561-8500 **Website: www.aao.org**
- National Cancer Institute Tel: (1-800) 4-CANCER **Website: http://www.nci.nih.gov**

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MANAGING YOUR

CROHN'S DISEASE

What Is Crohn's Disease?

Crohn's disease is a disorder that causes inflammation (swelling, redness) of the wall of the bowel (intestines). Nutrients and vitamins in food may not be easily absorbed.

Most people have this disorder throughout life, but with treatment most people can often live a normal life. It affects women slightly more than men, usually between 15 and 25 years old. It is not contagious and cannot be prevented.

What Causes Crohn's Disease?

The cause is unknown. It's thought to be an autoimmune disease, which means that the body's immune system reacts against its own tissues. It seems to run in families.

What Are the Symptoms of Crohn's Disease?

Common symptoms include middle or lower abdominal (belly) pain (may be worse after eating), and diarrhea (sometimes bloody). Other possible symptoms are joint pain, eyelid redness and swelling, skin lesions, mouth sores, weight loss, tiredness, and fever.

Many complications, such as bowel blockages, can occur. Fistulas (abnormal passages) and fissures (cracks in the skin) in and around the anus and rectum can form and lead to infections.

How Is Crohn's Disease Diagnosed?

The doctor may suspect Crohn's disease based on your medical history and physical exam. He or she may order blood tests and abdominal CT to exclude other causes, but ultimately colonoscopy will be necessary. The doctor may suggest seeing a digestive disease specialist (gastroenterologist).

Colonoscopy is used to examine the inside of the large intestine (colon). In colonoscopy, the

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gastroenterologist inserts a flexible tube (which holds a scope and camera) into the rectum and then up into the intestine. During this test, the doctor takes a sample of tissue (biopsy) for study with a microscope.

How Is Crohn's Disease Treated?

The goals of treatment are to relieve symptoms, control inflammation, and prevent complications. People without symptoms need no treatment. Mild diarrhea is controlled with medicine and dietary fiber. Severe symptoms need antiinflammatory drugs. Antibiotics may help infections. Pain relievers are given for abdominal pain and cramping; vitamin and mineral supplements, for malnutrition. Diet changes such as adding some fiber also help. High-nutrition liquid formulas may be used during severe symptoms to rest the intestines.

About 70% of people need surgery for symptoms. During surgery, part of the intestine is removed. In some cases, intestines are temporarily connected to a pouch attached outside the body (ileostomy pouch), which allows going to the bathroom while allowing another part of the intestines to heal.

DOs and DON'Ts in Managing Crohn's Disease:

✓ **DO** stay active, except when you must rest because of symptoms.

✓ **DO** take medicines as advised by your doctor.

✓ **DO** follow the diet plan from your doctor and dietitian.

✓ **DO** see your doctor regularly.

✓ **DO** tell your doctor if you have medicine side effects.

✓ **DO** call your doctor if you have a fistula and leak stool through the skin or vagina, have in-

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creased number of bowel movements, start bleeding, or have tarry-looking stool.

✓ **DO** call your doctor if you get fever or chills or a swollen abdomen.

⃠ **DON'T** eat a fatty diet.

⃠ **DON'T** eat foods that irritate your bowels or drink coffee and alcohol.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- Crohn's and Colitis Foundation of America Tel: (800) 343-3637 **Website:** **http://www.ccfa.org**
- National Digestive Diseases Information Clearinghouse Tel: (800) 891-5389 **Website:** **http://www.niddk.nih.gov/health/digest/nddic.htm**

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CARING FOR YOUR child WITH

CROUP

What Is Croup?

Croup (or laryngotracheobronchitis) is a respiratory infection that mainly affects children. The larynx (voice box) and trachea (windpipe) going into the lungs become irritated and swollen. Children have a very hoarse voice and a cough that sounds like a seal barking. Children and parents may be frightened because it is hard for air to go in and out of the lungs and children find it hard to breathe.

Young children between 3 months and 5 years old are more prone to croup. Boys seem to get it more often than girls. Croup is also more likely in children who have at least one parent with asthma or allergies.

Most cases are not serious, and complications are rare. A few children can have pneumonia or serious bacterial infection in the lungs.

What Causes Croup?

An infection in the throat or lungs can lead to croup. The infection is usually due to a virus, such as the flu virus.

What Are the Symptoms of Croup?

Many children have a sore throat, runny nose, or fever before croup. Croup symptoms include a hoarse voice, cough that sounds like a barking seal, fast breathing, and a high-pitched, windy sound while trying to breathe air into the lungs.

Symptoms get worse when the child lies down. Often, symptoms are worse at night.

How Is Croup Diagnosed?

The doctor makes a diagnosis from a medical history and physical examination. X-rays of the

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child's neck and lungs may be done. X-rays may show swelling of the neck and whether something is stuck or pus or blood in the airway is causing symptoms.

Blood tests may be done if the doctor suspects that the infection could be due to bacteria.

How Is Croup Treated?

Antibiotics don't help because a virus causes croup. Cough medicines also don't help much. Acetaminophen may lower the fever.

Having the child breathe air that is very moist (humid) or very cold may help. Provide moist air by going into a steamy bathroom. For cold air, wrap the child in a warm blanket and stand outside in the cold air for a few minutes.

The doctor may prescribe medicine to reduce airway swelling. In severe cases, the doctor may refer a child who has trouble breathing to the emergency department for oxygen.

Children who don't respond to these treatments may need corticosteroids (injected, by mouth, by nebulizer). Sometimes, children need admission to a hospital.

DOs and DON'Ts in Managing Croup:

✓ **DO** wash hands often, which is the best way to stop the spread of infections.

✓ **DO** keep your children away from children with a sore throat or runny nose.

✓ **DO** get emergency care if your child has trouble breathing and is very pale or has blue lips, face, or fingers. Get emergency care if the child doesn't wake up when you talk to or gently shake the child.

✓ **DO** call your doctor if symptoms don't get better or are getting worse.

✓ **DO** call your doctor if think that your child has side effects from medicine.

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⦸ **DON'T** forget to give your child medicine as instructed by the doctor.

⦸ **DON'T** forget follow-up doctor appointments.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Family Physicians (AAFP) **Website: http://www.familydoctor.org**
- The American Academy of Pediatrics Tel: (847) 434-4000 **Website: http://www.aap.org**

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MANAGING YOUR

CRYPTOCOCCCOSIS

What Is Cryptococcosis?

Cryptococcosis is a disease caused by a fungus that usually starts in the lungs without symptoms and then spreads to the nervous system, kidneys, bone, or skin. It's more serious for people with disorders of the immune system. The fungus may spread through the air on dust particles contaminated by pigeon droppings. It isn't passed from person to person.

What Causes Cryptococcosis?

The fungus named *Cryptococcus* is the cause. People with human immunodeficiency virus (HIV) infection, organ transplants, cancer, or weakened immune systems from other diseases or people without a spleen (after it's removed) have an increased risk of infection. For these people, cryptococcosis may be life threatening.

What Are the Symptoms of Cryptococcosis?

Symptoms include dull chest pain, a cough that may produce bloody sputum, severe headache, fever, blurred vision, confusion, red facial rash, and skin ulcers.

How Is Cryptococcosis Diagnosed?

The doctor will do a physical examination and tests of blood and urine. A spinal tap may be done to look for infection in spinal fluid and membranes around the brain (meningitis). In a spinal tap, a sample of spinal fluid is taken by inserting a needle in the spine and removing fluid. Computed tomography or magnetic resonance imaging of the brain may also be done to check for brain infection.

How Is Cryptococcosis Treated?

Most people with a normal immune system will do well. Mild cases in healthy people may need

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no treatment. Those with a weakened immune system may need hospitalization and lifelong treatment.

The doctor will prescribe antifungal medicines. These may first be given intravenously and then given by mouth when the condition improves. Side effects of the medicine include nausea, vomiting, and headache. Acetaminophen can be used for minor pain and fever. No special diet is needed. Bed rest may be needed until fever and cough stop.

DOs and DON'Ts in Managing Cryptococcosis:

✓ **DO** avoid contact with areas with pigeon droppings, especially if you have a weak immune system.

✓ **DO** rest until fever and cough improve.

✓ **DO** take acetaminophen for minor pain and fever.

✓ **DO** drink enough and eat a good diet. Try small frequent meals if nausea is a problem.

✓ **DO** keep follow-up doctor appointments, to look for recurrence of the disease.

✓ **DO** call your doctor if you cannot take the medicine because of nausea and vomiting.

✓ **DO** call your doctor if you have unexplained weight loss, high fever, severe headache, neck stiffness, or blurred vision.

⃠ **DON'T** skip doses or stop taking the antifungal medicine.

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FOR MORE INFORMATION

Contact the following sources:

- National Heart, Lung, and Blood Institute Tel: (301) 592 8573 **Website:** **http://www.nhlbi.nih.gov**
- National Institute of Allergy and Infectious Disease Tel: (301) 496-5717 **Website:** **http://www3.niaid.nih.gov**

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MANAGING YOUR

CUBITAL TUNNEL SYNDROME

What Is Cubital Tunnel Syndrome?

Cubital tunnel syndrome refers to a group of symptoms related to pressure (compression) on the ulnar nerve behind the elbow (cubitus). At the spot that is called the funny bone, the ulnar nerve is right next to the bone and can be hurt if pressure on it is great enough.

What Causes Cubital Tunnel Syndrome?

Causes include direct pressure on the nerve from splints or repeated trauma. A deformity of the elbow called cubitus valgus, in which the elbows are turned in, can cause it. A loose ulnar nerve, repeated stretching during throwing, elbow inflammation (swelling) called synovitis, and local growth of muscles (hypertrophy) are others.

What Are the Symptoms of Cubital Tunnel Syndrome?

Symptoms include feelings of pins and needles and numbness along the path of the ulnar nerve on the forearm and hand. These feelings and pain can occur in the elbow, forearm, hand, and/or fingers. Numbness and tingling most often are felt in the ring and little fingers. Flexion of the elbow with wrist extended for 30 seconds may cause symptoms. Flexion is bending the elbow so that the angle between the two parts of the arm is smaller. This test is called the positive elbow flexion test.

How Is Cubital Tunnel Syndrome Diagnosed?

The health care provider makes a diagnosis from the medical history and physical examination. X-rays may also be done to rule out other conditions. No laboratory tests are needed. Special tests that may be needed, however, are electrodiagnostic studies. These are called nerve conduction tests and electromyography (EMG). These tests help in making a diagnosis and

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ruling out other disorders.

The health care provider may suggest seeing specialists (neurologist, orthopedic surgeon).

How Is Cubital Tunnel Syndrome Treated?

The main treatment is to protect the nerve from pressure. Change patterns of use. Prolonged elbow flexion should be avoided. This would include talking on the phone with the elbow bent. Elbow pads and splints worn at night during sleep may help. Medical management may include using anti-inflammatory medicines (NSAIDs) to relieve pain and inflammation. Treatment may continue as long as symptoms are controlled and no movement problems develop. Most people get better within days to a few weeks. If muscles have started to waste away (atrophy), people may not recover their full strength even with treatment. Surgery may be considered if these treatments don't work or if signs of loss of muscle control or movement occur.

DOs and DON'Ts in Managing Cubital Tunnel Syndrome:

✓ **DO** keep all scheduled visits with your primary care health care provider and specialists.

✓ **DO** protect your elbow. Don't put it on hard surfaces for long periods. Keep your elbow straight at night with a splint. Seeing a therapist to learn how to avoid pressure on the nerve may help.

⃠ **DON'T** ignore symptoms. Call your health care provider if your symptoms don't improve or they get worse with treatment. Call if you have new symptoms.

⃠ **DON'T** do daily physical activities that make symptoms worse.

⃠ **DON'T** stop taking your medicine or change the dosage because you feel better unless your health care provider tells you to.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopedic Surgeons Tel: (847) 823-7186 **Website:** **http://www.aaos.org**
- American Physical Therapy Association Tel: (800) 999-2782 **Website:** **http://www.apta.org**

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MANAGING YOUR

CUSHING'S SYNDROME

What Is Cushing's Syndrome?

Cushing's syndrome is a rare endocrine illness caused by exposure of body tissues to too much cortisol in the bloodstream. Produced by the adrenal glands, cortisol is a substance (hormone) that helps the body control blood pressure and respond to stress. Extra cortisol, however, produces abnormal body changes.

Cushing's syndrome affects both men and women of any age but occurs most often in women 25 to 45 years old. It may increase the risk of getting diabetes, hypertension, osteoporosis, and obesity.

What Causes Cushing's Syndrome?

Extra cortisol may come from medicines prescribed by doctors for other conditions (e.g., asthma, bronchitis, arthritis). Certain tumors may produce excess cortisol. These tumors may be in the pituitary gland, adrenal gland, or other places.

What Are the Symptoms of Cushing's Syndrome?

Symptoms are weight gain, rounded face, fat around the neck, and thin arms and legs. Children are obese and grow slowly. The stomach, legs, arms, and breasts may show purplish-pink stretch marks. Thin, delicate skin bruises easily and heals poorly. Bones are weak and brittle and may break. Hormonal changes in women mean that they usually have too much hair growth on the face, neck, chest, stomach, and thighs. Periods may be irregular or stop. Men may be impotent. Other symptoms are urinating often, severe tiredness, weak muscles, high blood pressure, personality changes, and feeling irritable, anxious, and depressed.

How Is Cushing's Syndrome Diagnosed?

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The doctor will make a diagnosis by doing a physical examination and testing blood and urine.

If cortisol levels are high, another doctor (an endocrinologist, a specialist who treats diseases of glands and hormones) will order other tests. These tests usually involve taking medicine and providing blood and urine samples. Computed tomography (CT) or magnetic resonance imaging (MRI) of the belly (abdomen) to look for tumors of adrenal glands (located above the kidneys) or of the brain to look for pituitary gland tumors may be done.

How Is Cushing's Syndrome Treated?

If medicine is the cause, the doctor can change the dose to lower the cortisol levels or give medicine that blocks effects of cortisol on the body.

For an abnormal growth (tumor), treatment may include surgery to remove the growth, radiation, and drugs (chemotherapy).

If no cause is found, rarely adrenal glands are removed to prevent extra cortisol from being made. Medicine to replace missing cortisol is then needed.

Recovery time depends on duration of the illness, cortisol levels, and basic health.

DOs and DON'Ts in Managing Cushing's Syndrome:

✓ **DO** minimize using corticosteroid hormones.

✓ **DO** see your doctor regularly. Have regular checkups for blood sugar level, blood pressure, and bone density.

✓ **DO** look for a nearby support group.

✓ **DO** tell your doctor if you have had depression or drink alcohol daily.

✓ **DO** find an experienced surgeon if you need surgery.

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✓ **DO** eat less fat and calories.

✓ **DO** call your doctor if you have a fever, infection, or increased bruising or you gain too much weight.

✓ **DO** call your doctor for weakness or dizziness after surgery.

⃠ **DON'T** become discouraged.

⃠ **DON'T** begin exercise until your doctor checks blood pressure, blood sugar, and bones.

⃠ **DON'T** overeat.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Association of Clinical Endocrinologists Tel: (904) 353-7878 **Website:** **http://www.aace.com**
- Cushing's Support and Research Foundation Tel: (617) 723-3824
- National Institute of Diabetes and Digestive and Kidney Diseases Tel: (301) 496-3583 **Website:** **http://www.endocrine.niddk.nih.gov/pubs/cushings/cushings.htm**

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CARING FOR YOUR CHILD WITH

CYSTIC FIBROSIS

What Is Cystic Fibrosis?

Cystic fibrosis (CF) is a lifelong illness affecting cells that make sweat and mucus. Mucus is a slippery, somewhat sticky fluid that lubricates and protects mucous membranes. CF mucus is abnormally thick and sticky; it clogs the lungs and causes frequent lung infections.

CF also affects the pancreas, which has trouble making special chemicals called enzymes to digest food. Without enzymes, nutrients can't be absorbed from food.

CF is the most common fatal genetic disease in Caucasians in the United States (1 of every 2000 births). People with CF have a shorter life span, but with modern treatments, more people with CF live to middle age or older.

What Causes CF?

CF results from abnormal movement of the chemicals sodium and chloride (salt) in certain cells in mucous and sweat glands.

CF is inherited. A child must inherit a CF gene from each parent (called an autosomal recessive disorder). Both parents can be healthy but are carriers of CF. More than 12 million Americans carry the CF gene but have no symptoms.

What Are the Symptoms of CF?

Children with CF have normal lungs at birth, and symptoms may not appear until later.

Common symptoms are chronic cough and diarrhea, frequent bronchitis and pneumonia, bulky foul-smelling bowel movements (stool), large appetite in spite of poor weight gain, salty skin, and shortness of breath.

The first sign of CF in newborns may be a block of the intestines caused by increased thick-

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ness of the first stool.

How Is CF Diagnosed?

The doctor will do a sweat test called pilocarpine iontophoresis. This painless test measures the amount of salt in the child's sweat. A high level can mean CF.

The doctor can do genetic blood tests to look for changes inside cells. The doctor can also do tests on bowel movements (stool) and blood to check effects on the pancreas, and get chest x-rays or do breathing tests to check the lungs.

CF can also be diagnosed with prenatal (before birth) testing.

How Is CF Treated?

Medicines help thin the mucus and prevent lungs from clogging. Antibiotics are also often given for infections. Enzyme supplements supply missing pancreatic enzymes. A special high-protein, low-fat diet may also improve nutrition.

Respiratory therapy is for the lungs. Thick mucus can be removed from lungs by tapping on the chest (chest percussion). Lying with the head lower than the feet can also help drain mucus. Lung transplantation is a treatment option in some cases and should be discussed with your doctor.

DOs and DON'Ts in Managing CF:

✓ **DO** follow your doctor's instructions and give medicines and treatments as directed. Take your child to the doctor at least three or four times yearly.

✓ **DO** avoid contact with people with respiratory infections.

✓ **DO** get your child a yearly flu shot.

✓ **DO** have your child drink plenty of fluids.

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✓ **DO** have your child avoid gas fumes and smoke. These things irritate lungs and make CF worse.

✓ **DO** reach out to support groups.

⃠ **DON'T** neglect respiratory therapy, if advised by your doctor.

⃠ **DON'T** give your child soy protein, which is hard to digest.

⃠ **DON'T** miss doctor appointments.

⃠ **DON'T** stop prescribed antibiotics early or forget to do chest physical therapy.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- Cystic Fibrosis Foundation Tel: (800) 344-4823 **Website: http://www.cff.org**
- American Lung Association **Website: http://www.lungusa.org**
- National Heart, Lung, and Blood Institute **Website: http://www.nhlbi.nih.gov**

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MANAGING YOUR

CYSTICERCOSIS

What Is Cysticercosis?

Cysticercosis is an infection caused by eating the pork tapeworm, named *Taenia solium*, in contaminated food or water, or eating tapeworm eggs passed on by an infected person.

This tapeworm occurs worldwide, and cysticercosis affects about 50 million people, usually in rural developing countries. About 1000 new cases are diagnosed each year in the United States. Cysticercosis of the brain can cause seizures in adults.

What Causes Cysticercosis?

People can have adult tapeworms living in the intestine or the young stage (larval cysts) living in muscle, liver, lung, brain, or other tissues. Pigs usually become infected by eating eggs in contaminated human bowel movements (stools). People eat raw or undercooked meat from an infected pig and thus eat the eggs too. With poor hygiene, these eggs can spread to food, water, or other items.

What Are the Symptoms of Cysticercosis?

Tapeworm eggs hatch in the stomach, go into the intestine, through the bloodstream, and may develop into cysticerci (small cysts) in muscles, brain, or eyes. Symptoms can occur months to years after infection and depend on where cysts are found. Cysts in eyes can cause blurred vision, loss of vision, swelling, and detachment of the retina. Cysts in the brain and spinal cord can cause seizures, headaches, confusion, lack of attention, difficulty with balance, brain swelling, and even death. Cysts in the heart can cause heart rhythm abnormalities and rarely heart failure. Cysts in muscles may cause no symptoms.

How Is Cysticercosis Diagnosed?

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The doctor makes a diagnosis by looking at samples of stool under a microscope for tapeworm eggs. The doctor may also order blood tests and x-rays. For brain symptoms, magnetic resonance imaging (MRI) or CT of the head may be needed. A biopsy is sometimes done for diagnosis. In a biopsy, a piece of tissue is taken with a needle from a part of the body for study with a microscope.

How Is Cysticercosis Treated?

Cysticercosis is treated with antiparasitic medicines, which are safe and work well.

DOs and DON'Ts in Managing Cysticercosis:

✓ **DO** avoid eating raw or undercooked pork and other meats.

✓ **DO** wash your hands with soap and water after using the toilet and before handling food, especially when traveling in developing countries.

✓ **DO** wash and peel all raw vegetables and fruits before eating. Avoid food that may be contaminated with stool.

✓ **DO** drink only bottled water and water boiled for 1 minute to prevent cysticercosis.

✓ **DO** remember that family members of infected people should also have stool tested.

✓ **DO** remember that some antiparasitic medicines shouldn't be used during pregnancy.

✓ **DO** call your doctor if you or a family member may have cysticercosis and want to be tested.

⦸ **DON'T** forget that the tapeworm infection can be difficult to diagnose, so your doctor may

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ask for several stool specimens over several days to study them for signs of a tapeworm.

⦸ **DON'T** eat meat of pigs that are likely to be infected.

⦸ **DON'T** drink fountain drinks or drinks with ice cubes.

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FOR MORE INFORMATION

Contact the following source:

- Centers for Disease Control and Prevention (CDC) **Website:**

  http://www.cdc.gov/ncidod/dpd/parasites/ cysticercosis/factsht_cysticercosis.htm

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MANAGING YOUR

CYSTITIS

What Is Cystitis?

Cystitis is a condition in which the bladder becomes inflamed (red and swollen). The top of the urethra (the tube that takes urine from the bladder to outside the body) also becomes inflamed. It's much more common in women, but men can also have it. Sometimes, cystitis can become chronic (occur over and over) and become hard to treat.

What Causes Cystitis?

The cause is most often an infection, usually with bacteria (named *Escherichia coli*). Other causes are friction during sex, wearing tight underwear, drugs, foreign bodies such as catheters, and irritants such as feminine hygiene spray and spermicidal jelly. Cystitis can be a complication of another illness, and pregnant women can have greater chances of having cystitis.

What Are the Symptoms of Cystitis?

Common symptoms include pain or burning when urinating, pain or pressure in the lower abdomen (belly), cloudy or fishy-smelling urine, blood in the urine, frequent and urgent need to urinate, and low-grade fever.

How Is Cystitis Diagnosed?

The doctor will take a sample of urine and send it to a laboratory to check for infection.

If infections occur often, the doctor may want a sonogram of the bladder and kidneys and may suggest seeing a urologist (doctor specializing in urinary disorders). The urologist may do more tests, such as cystoscopy. In cystoscopy, a small flexible tube is put into the urethra and then the bladder. The tube has a camera so the doctor can see inside the urethra and bladder.

How Is Cystitis Treated?

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Antibiotic medicine, usually as pills, will be prescribed to stop a bacterial infection. The pills are taken for 3 to 10 days. The doctor may want to do another examination after 1 to 2 weeks, or earlier, to make sure that the infection is gone. If infections occur often, medicine may be needed for up to 6 months.

Causes other than infections need other treatments, including avoiding certain products, such as bubble bath and spermicides, nerve stimulation, and other drugs.

DOs and DON'Ts in Managing Cystitis:

✓ **DO** take your medicine exactly as prescribed.

✓ **DO** drink plenty of fluids, especially water.

✓ **DO** empty your bladder completely when urinating.

✓ **DO** urinate right after having sex.

✓ **DO** wear cotton clothing. Women should wear cotton pantyhose. Avoid tight-fitting undergarments and clothing.

✓ **DO** keep your genital area clean. Take showers instead of tub baths.

✓ **DO** avoid perfumed or deodorant products in the genital area.

✓ **DO** keep other medical conditions under control. For example, if you have diabetes, keep your blood sugar under control.

✓ **DO** call your doctor if you develop a fever or if symptoms continue even with antibiotics.

✓ **DO** wipe from front to back after a bowel movement.

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⦸ **DON'T** wear tight-fitting undergarments and clothing.

⦸ **DON'T** ignore symptoms. Untreated infection can spread to the kidneys and cause serious illness.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following source:

- Interstitial Cystitis Association Tel: (301) 610-5300, (800) 435-7422 **Website:** **http://www.ichelp.org**

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MANAGING YOUR

DE QUERVAIN'S TENOSYNOVITIS

What Is De Quervain's Tenosynovitis?

Tendons are bands of tough fibrous connective tissue that usually connect muscles to bones. They transmit forces of muscle contraction to bones. Tendons in the hands are covered and protected by sheaths lined by a membrane called the synovium. When these sheaths are inflamed (swollen, red), they thicken and cause pain. De Quervain's tenosynovitis (or stenosing tenosynovitis) is inflammation of sheaths around tendons of certain muscles in the hand. These muscles work to extend the thumb at the wrist joint.

This disorder is 10 times more common in women than men. It usually occurs between the ages of 30 and 50 and can be associated with rheumatoid arthritis.

What Causes De Quervain's Tenosynovitis?

The cause is unknown. Repeated use or overuse of the hands can lead to this disorder. It's common in people with clerical, assembly, and manual jobs. Direct trauma is another cause. It isn't contagious.

What Are the Symptoms of De Quervain's Tenosynovitis?

A main symptom is pain over the base of the thumb, near the wrist. This pain occurs slowly and may spread to the thumb or into the forearm. It usually involves the dominant hand, which becomes tender when touched or when doing certain movements, such as pinching and grabbing.

How Is De Quervain's Tenosynovitis Diagnosed?

The doctor diagnoses this condition from the medical history and the simple "Finkelstein test." In this test, the doctor holds the thumb of the hand and pulls the thumb and wrist to stretch the tendon. Pain means de Quervain's tenosynovitis.

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The doctor may order blood tests and x-rays to rule out other causes, such as osteoarthritis, gout, and carpal tunnel syndrome.

How Is De Quervain's Tenosynovitis Treated?

Treatment includes resting, splinting (prevent friction on tendons), and medicines. Over-the-counter pain medicines include ibuprofen, aspirin, and naproxen. Side effects include upset stomach, heartburn, nausea, and gastrointestinal bleeding. Applying ice or a cold pack over the base of the thumb may also help swelling and pain.

If these treatments don't help, one or more injections of steroids helps pain.

When all these treatments don't work, surgery is needed. About 90% of people get relief of symptoms by surgery.

DOs and DON'Ts in Managing

De Quervain's Tenosynovitis:

✓ **DO** remember that repetitive movements are thought to lead to this disorder. Bricklayers, typists, computer keyboard operators, factory workers, concert pianists, and mothers of new-borns should be careful to avoid repetitive movements of the wrist and thumb.

✓ **DO** call your doctor if your pain doesn't get better with conservative therapy.

✓ **DO** call your doctor if you see redness or drainage from a surgical or injection site.

✓ **DO** call your doctor if you get heartburn, nausea, vomiting, or abdominal pain after starting antiinflammatory medicines.

✓ **DO** call your doctor if you're thinking about surgery. You can get a referral to an orthopedic surgeon (specialist in hand disorders).

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⦸ **DON'T** forget that conservative management (rest, drugs, or both) may be all that's needed to help symptoms.

⦸ **DON'T** miss follow-up doctor appointments.

⦸ **DON'T** be afraid to ask for a second opinion.

⦸ **DON'T** take more than the prescribed dose of anti-inflammatory medicine. You might get an upset stomach and other gastrointestinal or kidney or liver problems.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following source:

- National Institute of Arthritis and Musculoskeletal and Skin Diseases Tel: (877) 226-4267

  Website: http://www.niams.nih.gov/

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MANAGING YOUR

DEEP VEIN THROMBOSIS

What Is Deep Vein Thrombosis?

Deep vein thrombosis (DVT) is an illness that develops when the blood clots in a vein. Affected veins are usually deep in leg muscles but can also be in other areas. The clot (thrombus) causes blood flow to slow. The area becomes swollen and painful. If the clot moves to the lungs, a pulmonary embolism (blocked vein in the lungs) occurs and serious breathing problems or death can develop.

DVT most often affects people who are physically inactive, elderly, pregnant, or have blood disorders that increase the risk of blood clotting.

What Causes DVT?

Prolonged bed rest (more than 3 days), recent surgery (with anesthesia for more than 30 minutes), smoking, being overweight, air or car travel for prolonged periods, using certain oral contraceptives and estrogen replacement therapies, and family or personal history of blood clotting problems can increase the risk of DVT.

What Are the Symptoms of DVT?

Symptoms are pain, tenderness, and swelling in the area. Initially there may be no symptoms.

How Is DVT Diagnosed?

The doctor will ask about symptoms and do an examination. If DVT is suspected, the doctor may recommend a sonogram (ultrasound) of the swollen leg or other part to measure blood flow in the area. A blood test (D-dimer) may also be done. In rare cases when the diagnosis is suspected but sonogram and blood tests are inconclusive, the doctor may also order a special x-ray study (venography) in which a dye is injected into the vein to see whether a clot is blocking blood flow.

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How Is DVT Treated?

Treatment is immediate injection of a blood thinner (heparin) to thin the blood and prevent growth of blood clots. Heparin can be given intravenously or injected under the skin (subcutaneously). Your doctor will decide which option is best for you. The doctor will also prescribe blood thinning pills (usually warfarin) to prevent the clot from enlarging and stop new ones from forming. For a few days, both heparin and warfarin are given. When warfarin reaches the desired level in blood, heparin will be stopped and warfarin will be continued, usually for 3 months, at times longer, depending on the cause of the DVT. Lifetime treatment may sometimes be needed. Blood tests to make sure that the warfarin dose is correct must be done. Newer blood thinners which do not require periodic blood tests and dose adjustments are now available in place of warfarin.

The doctor may also recommend special stockings to control swelling in the legs. Overweight people should lose weight and become more active to prevent future clots.

DOs and DON'Ts in Managing DVT:

✓ **DO** take medicine and go for the blood tests (INR) as directed by your doctor to monitor the blood thinner level.

✓ **DO** follow your doctor's advice about losing weight and exercising more to lower your risk of recurrence of DVT.

✓ **DO** walk around and stretch your legs if you sit for long periods.

✓ **DO** call your doctor if your symptoms don't get better.

✓ **DO** call your doctor immediately if you have chest pain or cough up blood.

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✓ **DO** call your doctor before you go on a long trip and ask your doctor about taking aspirin if you are no longer taking warfarin.

✓ **DO** try to keep your legs elevated when sitting or lying down.

⃠ **DON'T** stand or sit in one spot for a long time.

⃠ **DON'T** wear clothing that restricts blood flow in your legs.

⃠ **DON'T** cross your ankles or legs when sitting or lying down.

⃠ **DON'T** smoke.

⃠ **DON'T** participate in contact sports when taking warfarin, because you're at risk of bleeding from trauma.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- The Center for Outcome Research and the Venous Education Institute of North America (VEIN) **Website: http://www.dvt.org**
- The American Heart Association Tel: (800) 242-8721 **Website: http://www.americanheart.org**

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MANAGING YOUR CHILD'S

DELAYED PUBERTY

What Is Delayed Puberty?

Puberty is the time when children's bodies start to mature. They make hormones, which are chemicals of the endocrine system. Certain hormones are made by the hypothalamus and pituitary gland. Some hormones cause ovaries in girls and testes in boys to develop. Girls make the hormone estrogen and boys make the hormone testosterone (sex steroids). These changes cause growth spurts and secondary sex characteristics. Boys grow hair on the face, girls develop breasts, and pregnancy can occur in sexually active females. Delayed puberty means that puberty doesn't start at the usual time. Normally, puberty usually starts between the ages of 7 and 13 for girls and between the ages of 9 and 15 for boys.

What Causes Delayed Puberty?

The many causes include abnormal chromosomes, chronic disease, and other factors. Eating problems, excessive exercise, tumors, and infections are others. The condition often runs in families. It also occurs with rare congenital syndromes and in people with defects in enzymes that make sex steroids. The usual cause of delayed puberty is a constitutional delay in growth and development. This delay affects the whole body. It's a variant and not a disorder.

What Are the Symptoms of Delayed Puberty?

Puberty is delayed for girls if breasts don't develop by age 13, periods don't start by age 16, or periods don't start within 5 years of the start of puberty. Puberty is delayed for boys if testes don't get bigger by age 14, or if the delay between the start and end of genital growth is more than 5 years.

How Is Delayed Puberty Diagnosed?

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The health care provider makes a diagnosis from the medical history, physical examination, and laboratory tests. The family and social history helps the health care provider find causes such as abnormal eating habits (bulimia, anorexia nervosa) and extreme exercise (marathon runners, gymnasts) that can delay puberty. The health care provider will also measure growth (height, weight) of the child and check the parents' height. Standard methods that compare normal growth and development such as Tanner staging will be used. This method gives usual physical changes at specific ages. Laboratory tests will be done to measure hormone levels in blood. In some cases with possible genetic abnormalities, special tests called chromosomal analysis are done to rule out rare disorders.

Children's bone age is closely related to growth and development. Tests, including X-rays, may be done to find the bone age. Computed tomography (CT) or magnetic resonance imaging (MRI) of the head may be done to look for brain tumors, which can affect normal development. The health care provider may suggest seeing a specialist (endocrinologist).

How Is Delayed Puberty Treated?

Treatment depends on the cause. Children with constitutional growth delay need no treatment. If the delay causes great stress, hormones to start puberty can be given for short periods. People with lack of hormones called gonadotropins or the condition called hypogonadism will need sex steroids for life. Psychological treatment may be needed.

DOs and DON'Ts in Managing Delayed Puberty:

✓ **DO** remember that delayed puberty is often related to a history of the condition in parents and/or siblings.

⦸ **DON'T** let children stop taking medicine or change the dosage because they feel better unless your health care provider tells you to.

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FOR MORE INFORMATION

Contact the following sources:

- American Association of Clinical Endocrinologists Tel: (904) 353-7878 **Website: http://www.aace.com**
- The American Academy of Family Physicians **Website: http://www.aafp.org**
- The American Academy of Pediatrics **Website: http://www.aap.org**

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MANAGING YOUR

DELIRIUM TREMENS

What Is Delirium Tremens?

Delirium is sudden confusion with disorientation, hallucinations, changing emotions, and unruly or violent behavior. Delirium tremens, or DTs, is a severe kind of alcohol withdrawal. Nearly 500,000 cases occur each year in the United States.

What Causes Delirium Tremens?

Problem drinking is drinking more than 7 drinks per week or more than 3 drinks per occasion for women, and more than 14 drinks per week or more than 4 drinks per occasion for men. Heavy drinking is drinking more than 3 or 4 drinks per day for women and more than 5 or 6 drinks per day for men. One standard drink is one 12-oz bottle of beer; one 5-oz glass of wine; or 1.5-oz glass of 80 proof spirits. People who regularly drink too much alcohol and then stop can get DTs. DTs usually occur within 1 week after drastically reducing or stopping heavy drinking, and last 1 to 3 days.

What Are the Symptoms of Delirium Tremens?

Symptoms include tremors, unsteadiness, nausea, stomach pains, diarrhea, and vomiting. Sweating, palpitations, tiredness, weakness, blackouts, seizures, mood swings, depression, anxiety, and forgetfulness are others.

How Is Delirium Tremens Diagnosed?

The health care provider makes a diagnosis from a history of alcohol withdrawal in people who abuse alcohol. A scale used to measure how severe the withdrawal is and to guide treatment is used. It includes the symptoms above plus agitation, headache, feeling disoriented, and touch, hearing, and vision problems.

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How Is Delirium Tremens Treated?

DTs can be life-threatening and are a medical emergency. Most people need treatment in a detox unit. Detoxification usually takes a few days to a week. People may need extra fluids during this time, usually given intravenously. Vitamins, electrolytes, and sedating medicines are given with the intravenous fluids to control agitation and prevent seizures. Other medical, surgical, or psychiatric conditions also need treatment. Long-term goals include getting social support for recovery. The 12-step programs, AA, and getting family members involved in support groups for families of alcohol abusers may help. People need to learn new coping skills to use instead of drinking. Old routines and habits, such as drinking with friends, should change.

DOs and DON'Ts in Managing Delirium Tremens:

✓ **DO** call your health care provider if you have effects of alcohol abuse. These are nausea; lasting vomiting; constant diarrhea; heartburn or tightness in your chest; blood in the stools, especially dark red blood; and vomiting blood. Tell your health care provider about these possibly life-threatening conditions.

✓ **DO** call your health care provider if you have thoughts of suicide or suicidal behavior.

✓ **DO** find a support group for alcoholics if you think that would help.

⦸ **DON'T** stop taking prescribed medicines or change the dosage because you feel better unless your health care provider tells you to.

⦸ **DON'T** lie to your health care provider about alcohol abuse. If the health care provider doesn't mention it, you should.

⦸ **DON'T** forget that DTs can be lethal if not carefully treated. The death rate is 15% in untreated people.

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FOR MORE INFORMATION

Contact the following sources:

- National Institute on Alcohol Abuse and Alcoholism (NIAAA) **Website:**

  http://www.niaaa.nih.gov/

- Alcoholics Anonymous (International Office) Tel: (212) 870-3400 **Website:**

  http://www.alcoholics-anonymous.org

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MANAGING YOUR

DEPRESSION

What Is Depression?

Depression is a very common mood disorder. It's not the same as feeling sad when bad things happen. If sadness lasts for days or weeks, makes it hard to work or do things with family or friends, or involves thoughts of suicide, depression is present.

Depression is treatable but often not preventable. Lifestyle changes such as lowering stress and increasing leisure time and exercise may lower the risk of having depression. It affects about 80% of people at some time in life and can occur at any age. It's more common in women than in men.

What Causes Depression?

The cause is unknown. Probably, many things contribute to it. These include chemicals being out of balance in the brain; genetic, environmental, or developmental events; and biological and psychological factors. Drugs such as alcohol or downers can worsen it. Some medical conditions, such as thyroid disease and stroke, are also often related to depression.

What Are the Symptoms of Depression?

Symptoms include trouble sleeping, such as trouble falling asleep but more likely waking up very early in the morning for no reason. Less often, depression can involve too much sleep (people sleep most of the day).

Some people have less appetite, which leads to weight loss, but some people eat more. Other symptoms include losing interest in things; being unable to concentrate; feeling sad; having crying spells, often for no reason; feeling as if the future won't be better; being agitated or restless; moving and speaking very slowly; and losing interest in sex.

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Severe depression involves suicidal or homicidal thoughts or thinking or dreaming about death.

How Is Depression Diagnosed?

No laboratory tests or x-rays can diagnose depression. The doctor makes a diagnosis from symptoms and past medical history.

How Is Depression Treated?

Treatment usually involves using medicines and talking to a therapist or psychiatrist. Medicines used are antidepressants. Some more common drugs are escitalopram, paroxetine, sertraline, fluoxetine, and citalopram. These are selective serotonin reuptake inhibitors (SSRIs). Others are venlafaxine, duloxetine, and bupropion. Some drugs increase sleep and appetite, but it usually takes 2 to 3 weeks before these drugs help the depression. They also have side effects, such as weight gain, sexual problems, and nausea.

DOs and DON'Ts in Managing Depression:

✓ **DO** lower your exposure to stress.

✓ **DO** make sure you eat a healthy diet.

✓ **DO** exercise regularly.

✓ **DO** call your doctor if your symptoms get worse.

✓ **DO** call your doctor if you have side effects from your medicines.

✓ **DO** call your doctor immediately if you have suicidal thoughts or thoughts about killing or hurting someone else.

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✓ **DO** call your doctor immediately if you have psychotic symptoms, such as hearing voices, seeing things that aren't there, or feeling paranoid.

⃠ **DON'T** use alcohol or drugs. These will increase your depression or interfere with certain drugs used to treat depression.

⃠ **DON'T** take any prescription or over-the-counter medicine without first checking with the doctor who prescribed your medicine for depression.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

• Mental Health America Tel: (800) 969-6642 **Website:**

http://www.mentalhealthamerica.net/

• American Psychiatric Association **Website: http://www.psych.org**

• National Mental Health Association **Website: http://www.depression-screening.org**

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MANAGING YOUR

DERMATITIS HERPETIFORMIS

What Is Dermatitis Herpetiformis?

Dermatitis herpetiformis is a chronic, recurrent skin disorder manifesting with clumps of small blisters (vesicles) and red bumps (papules). Outbreaks may last for days, weeks, months, or even years.

Dermatitis herpetiformis is uncommon. It usually affects adults between 20 and 60, but children may also have it. It occurs in males slightly more often.

Other family members may have a history of this condition. This disorder is not contagious and cannot be prevented.

What Causes Dermatitis Herpetiformis?

The cause is unknown, but the disorder is probably autoimmune (i.e., a condition in which the body's own immune system attacks itself, causing injury or disease).

Some people also have celiac disease (disorders in which people cannot digest gluten, a protein in grains such as wheat).

What Are the Symptoms of Dermatitis Herpetiformis?

Lesions are very itchy and may cause burning or stinging. The clumps of blisters are symmetric (i.e., similar on both halves of the body). Lesions usually involve the scalp, face, elbows, forearms, knees, shoulder blades, lower back, and buttocks.

Scratching may cause abrasions, crusting, and infections.

How Is Dermatitis Herpetiformis Diagnosed?

The doctor makes a diagnosis usually from the look of the skin. The doctor may also do a skin biopsy (i.e., removing a small piece of skin for study) or blood tests.

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How Is Dermatitis Herpetiformis Treated?

Treatment depends on its location and how severe it is, its impact on quality of life, and response to therapy. The condition can be controlled but cannot be cured. Treatment includes avoiding triggers, general measures, and medicines. General measures involve soaking the area in cool water to soothe irritation and reduce itching and avoiding gluten in the diet.

Medicines (such as steroids, calamine lotion, antihistamines, and dapsone or sulfapyridine) can reduce inflammation (swelling, redness), improve symptoms, and reduce the severity and duration of the outbreak.

DOs and DON'Ts in Managing Dermatitis Herpetiformis:

✓ **DO** take medicines prescribed by your doctor.

✓ **DO** tell your doctor about all medicines, including over-the-counter drugs, that you take.

✓ **DO** read medicine labels and follow instructions.

✓ **DO** avoid gluten in your diet, which may improve the condition.

✓ **DO** avoid activities that cause overheating and too much sweating. Shower and clean skin lesions immediately if you sweat too much.

✓ **DO** use good skin hygiene to reduce risks of bacterial infection.

✓ **DO** keep follow-up doctor appointments.

✓ **DO** watch your skin for healing and signs of infection, including redness around skin lesions, pus, increased pain or swelling of the lesions or lymph nodes, and fever.

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✓ **DO** wash clothing, towels, and linens often if skin lesions ooze, crust, or may be infected.

✓ **DO** call your doctor if lesions become worse or new lesions appear despite therapy.

⃠ **DON'T** stop taking your medicine or change the dose without asking your doctor.

⃠ **DON'T** do activities that can cause overheating or sweating.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Dermatology Tel: (866) 503-SKIN (503-7546) **Website:** **http://www.aad.org**

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MANAGING YOUR

DERMATOMYOSITIS AND POLYMYOSITIS

What Are Dermatomyositis and Polymyositis?

Dermatomyositis and polymyositis are rare diseases that cause inflammation and weakness of muscles and some skin tissues. They are also known as "idiopathic inflammatory myopathies." They affect both adults (ages 45 to 60) and children (ages 10 to 15), more females than males.

What Causes Dermatomyositis and Polymyositis?

The cause is unknown, but they are thought to be autoimmune disorders. In autoimmune disorders, the immune system attacks the body's own tissues. Small blood vessels in muscles and some skin tissues get damaged, which weakens muscle fibers and makes them break down. The disorders aren't contagious or passed from parents to children.

What Are the Symptoms of Dermatomyositis and Polymyositis?

Symptoms of dermatomyositis are a rash (on the face, chest, back, elbows, knees, and knuckles) and weakness of neck, shoulder, upper arm, hip, and thigh muscles. People may have trouble getting out of chairs, climbing stairs, lifting things, or reaching over their heads. Sometimes, trouble swallowing, sore muscles, tiredness, fever, hard bumps under the skin, and weight loss occur. The disease may also affect the lungs, heart, or gut. No rash occurs in polymyositis, but other symptoms are the same.

How Are Dermatomyositis and Polymyositis Diagnosed?

The doctor makes a diagnosis based on your history, physical examination, blood tests, electromyography, and muscle biopsy. Blood tests can show muscle breakdown, inflammation, or antibodies. Electromyography measures how muscles are working. In a biopsy, the doctor removes a small piece of muscle that is sent for study.

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How Are Dermatomyositis and Polymyositis Treated?

Treatments may help the rash and muscle strength improve, but some muscles may be permanently weak. However, treatment may last for months or even years. Sometimes, the disease goes away on its own.

Corticosteroid drugs, especially prednisone, are the main treatment for inflammation. If corticosteroids don't work, immunosuppressant drugs and immunoglobulins may be tried. Skin cream (such as prednisone and tacrolimus) may be used for the rash.

Muscle exercises are an important part of treatment. They're for flexibility and help strengthen muscles. A physical therapist can create the right exercise program.

DOs and DON'Ts in Managing Dermatomyositis and Polymyositis:

✓ **DO** get treatment as soon as possible. Early treatment gets better results.

✓ **DO** tell your doctor if you have medicine side effects.

✓ **DO** see your doctor right away if you have trouble swallowing or shortness of breath.

✓ **DO** keep active. This will help keep your muscles from getting weaker. Do your physical therapy exercises.

✓ **DO** cover your skin or wear strong sunscreen when you go out.

✓ **DO** remember that treatments may be needed for years. You may need frequent blood tests to monitor your disease and side-effects of the medications. About half of people have a remission and stop therapy within 5 years of diagnosis. The others will have active disease that needs ongoing treatment or inactive disease with permanent muscle weakness.

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✓ **DO** understand that the disease may be related to an increased risk of cancers of the colon, breast, and ovary.

✓ **DO** call your doctor if you have increasing muscle weakness.

⃠ **DON'T** push your body too hard. Learn to pace yourself. Rest when you're tired.

⃠ **DON'T** miss follow-up appointments.

⃠ **DON'T** stop taking medicines without talking to your doctor. Prednisone, if used for a long time, must be tapered off rather than stopped suddenly.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

• The Myositis Association Tel: (202) 887-0088, (800) 821-7356 **Website:** **http://www.myositis.org**

• National Organization for Rare Disorders Tel: (800) 999-6673, (203) 744-0100 **Website:** **http://www.rarediseases.org**

• National Institute of Arthritis and Musculoskeletal and Skin Diseases Tel: (301) 496-8188 **Website:** **http://www.niams.nih.gov**

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MANAGING

DIABETES INSIPIDUS

What Is Diabetes Insipidus?

Diabetes insipidus is a disorder resulting from a decreased amount or action of a hormone that helps regulate water balance. This hormone is antidiuretic hormone (ADH), also called vasopressin. The pituitary gland controls flow of ADH into the bloodstream. ADH helps kidneys keep the body's water balance normal.

The two main types of diabetes insipidus are central and nephrogenic. The central type is caused by lower ADH production. In nephrogenic diabetes insipidus, ADH production is normal or increased, but kidneys don't respond normally to the hormone.

What Causes Diabetes Insipidus?

Tumors of the hypothalamus or pituitary or infections may cause central diabetes insipidus. Head injuries or meningitis may also cause central diabetes insipidus. Nephrogenic diabetes insipidus may be hereditary or caused by medicines such as lithium.

What Are the Symptoms of Diabetes Insipidus?

Symptoms include frequent passing of a lot of very dilute, watery urine. Urinating at night, extreme thirst (especially wanting cold water), dehydration with dizziness on standing, and behavioral changes are others. Untreated diabetes insipidus may lead to very high blood sodium levels, confusion, seizures, and death.

How Is Diabetes Insipidus Diagnosed?

The doctor makes a diagnosis from symptoms, and blood and urine tests (such as specific gravity of urine and 24-hour urine collection). After diagnosis, the cause must be found. Magnetic resonance imaging (MRI) of the brain and additional tests may be done. You will be referred to a

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specialist (endocrinologist) who will be closely involved in the diagnosis and treatment of this rare disorder.

How Is Diabetes Insipidus Treated?

If the cause is pressure on the pituitary by a tumor, treatment is removal of the tumor. If it is due to a temporary condition after pituitary or brain surgery for other diseases, it may go away by itself without treatment. If the condition is caused by a medicine, the medicine should be stopped.

Stopping drugs that make nephrogenic diabetes insipidus worse and drinking enough water when thirsty should help the nephrogenic condition.

Central diabetes insipidus can be controlled with the drug DDAVP (desmopressin), given once or twice daily under the skin or as a nasal spray. Complications of using this medicine may include low sodium level from overtreatment.

DOs and DON'Ts in Managing Diabetes Insipidus:

- ✓ **DO** drink water whenever you're thirsty. You are the best person to regulate your blood sodium level based on your natural thirst.
- ✓ **DO** take your medicine as prescribed.
- ✓ **DO** find an experienced surgeon if you need surgery.
- ✓ **DO** call your doctor if you can't stop feeling thirsty or family members see a change in your thinking.
- ✓ **DO** call your doctor if you have high fever, diarrhea, sweating, or worsening frequency of urination even with treatment.

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✓ **DO** call your doctor if you're having elective surgery.

⃠ **DON'T** drink lots of high-sodium fluids such as soft drinks. Your symptoms can worsen. Instead, choose water.

⃠ **DON'T** confuse diabetes insipidus with diabetes mellitus. Both may cause frequent urination, but only diabetes mellitus is related to high blood sugar levels.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- Pituitary Tumor Network Association Tel: (800) 642-9211 or (805) 499-9973
- The Endocrine Society Tel: (888) ENDOCRINE

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CARING FOR YOUR CHILD WITH

DIABETES MELLITUS TYPE 1

What Is Diabetes Mellitus Type 1?

Diabetes mellitus type 1 (or just diabetes) is a lifelong disorder that prevents your child's body from getting energy from food. Most cases start in children 12 to 15 years old.

In type I diabetes, the body doesn't produce enough insulin, a hormone produced by special beta cells in the pancreas. Insulin is vital because it controls the amount of sugar (glucose) absorbed by body cells from the blood. The body needs sugar for energy. People with diabetes have too much sugar in the blood, and not enough glucose gets into body cells.

What Causes Diabetes?

Not enough insulin is the cause. In most diabetic people, the body's own defense, the immune system, destroys beta cells in the pancreas, but the reason for this isn't known.

Other causes are some diseases, such as cystic fibrosis, and surgical removal or severe inflammation (swelling, irritation) of the pancreas.

What Are the Symptoms of Diabetes?

Diabetes warning signs include urinating frequently, feeling very thirsty and hungry, getting infections, losing weight quickly, and feeling tired and weak. Symptoms of uncontrolled diabetes also include blurred vision or blindness, slow-healing skin sores, numbness in hands or feet, and kidney failure (needing dialysis).

In diabetic ketoacidosis, another complication of diabetes, substances (ketones) form when fats break down faster than kidneys can remove them. Ketones in blood make the blood dangerously acidic, which affects organs including the brain.

How Is Diabetes Diagnosed?

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For diagnosis, the doctor uses a medical history, physical examination, and different measures of blood sugar (fasting level, average levels during 2 to 3 months [hemoglobin A1c test], glucose tolerance test).

The doctor may test the kidney function (serum creatinine level test), and check the urine (urine microalbumin level).

How Is Diabetes Treated?

A special diet will help control blood sugar. A nutritionist can help manage this diet. A glucometer can be used to check blood sugar levels.

The doctor will explain how to give insulin injections at home. Children 7 to 10 years old can often check their own blood sugar levels. Children can also learn how to watch for signs of low blood sugar. Children 10 to 12 years old can often give themselves insulin.

The doctor will suggest exercises, because exercise affects blood sugar levels.

Regular foot care and eye checkups are needed to prevent complications.

Having your child under the care of a diabetes specialist (endocrinologist) in addition to the primary care doctor can also help prevent complications from diabetes.

DOs and DON'Ts in Managing Diabetes Mellitus:

✓ **DO** prepare the special diet and have your child eat snacks at the same time every day, as instructed by your doctor.

✓ **DO** make sure that your child gets enough exercise and sleep.

✓ **DO** check your sick child's blood sugar level. Call your doctor if your child has fever, nausea, or vomiting and can't keep down solids or liquids.

✓ **DO** call your doctor right away if your child's blood sugar level is too high.

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✓ **DO** take your child to the hospital right away if he or she has a seizure, can't wake up, or loses consciousness.

✓ **DO** follow your doctor's orders about insulin exactly.

✓ **DO** give your child a sugar snack or glass of orange juice if the sugar level is too low and call the doctor to adjust future insulin doses.

⃠ **DON'T** let your child eat too much sugar.

⃠ **DON'T** give your child too much insulin.

⃠ **DON'T** let your child become dehydrated.

⃠ **DON'T** serve foods that are not suggested by your doctor.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- National Diabetes Information Clearinghouse Tel: (800) 860-8747 **Website:** **http://www.niddk.nih.gov/health/diabetes/diabetes.htm**
- American Diabetes Association (ADA) Tel: (800) DIABETES (342-2383) **Website:** **http://www.diabetes.org**

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MANAGING YOUR

DIABETES MELLITUS TYPE 1: FOR ADOLESCENTS

What Is Diabetes Mellitus Type 1?

Diabetes mellitus type 1 (or called just diabetes) is a lifelong condition that stops the body from getting energy from food.

In diabetes, the body doesn't make enough insulin, a substance called a hormone that is made by special cells in the pancreas. Insulin is important because it controls the amount of sugar (glucose) absorbed by body cells from the blood. The body needs sugar for energy. People with diabetes have too much sugar in the blood, and not enough energy gets into body cells.

What Causes Diabetes?

Not enough insulin is the cause. In most diabetic people, the body's own defense, called the immune system, destroys the special cells in the pancreas that make insulin. The reason for this isn't known, but it is believed to be due to a combination of hereditary and environmental factors. Other diseases such as cystic fibrosis, removing the pancreas in an operation, and inflammation (swelling, irritation) of the pancreas can also cause diabetes by damaging the pancreas.

What Are the Symptoms of Diabetes?

Symptoms start slowly and include needing to urinate often, feeling very thirsty and hungry, getting frequent infections, losing weight quickly, and feeling tired and weak. Other problems related to uncontrolled diabetes include blurred vision, slow-healing skin sores, numbness in hands or feet, and kidney failure (leading to dialysis).

How Is Diabetes Diagnosed?

For diagnosis, the doctor uses a medical history, physical examination, and measurement of the

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level of sugar in the blood.

The doctor will also test the kidneys for signs of damage and measure blood fat (lipid) level.

How Is Diabetes Treated?

The doctor will explain how to check blood sugar levels at home by using a meter called a glucometer. The doctor will also explain how to watch for signs that the blood sugar level is too low and how to give insulin injections or use an insulin pump at home.

A special diet will help control blood sugar. A specialist in foods and diet (nutritionist) can help plan this diet.

The doctor will suggest exercises, because exercise improves blood sugar levels.

Regular foot care and eye checkups are needed to prevent future problems.

DOs and DON'Ts in Managing Diabetes Mellitus:

✓ **DO** follow your special diet and eat snacks at the same time every day, as instructed by your doctor.

✓ **DO** get enough exercise and sleep.

✓ **DO** check your blood sugar level if you're sick.

✓ **DO** ask your parents to call your doctor right away if your blood sugar level is too high, you often have low blood sugar levels, or your urine has sugar in it.

✓ **DO** follow your doctor's orders about insulin exactly. Using too much or too little insulin is dangerous.

✓ **DO** if you don't know anyone with diabetes, ask your doctor how you can meet people who

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take good care of their diabetes.

- ⃠ **DON'T** smoke or drink alcohol, because they can make diabetes worse.
- ⃠ **DON'T** eat foods with high sugar content.
- ⃠ **DON'T** become overly thirsty. Drink plenty of water or sugar-free beverages.
- ⃠ **DON'T** eat foods that aren't part of your doctor's meal plan.

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FOR MORE INFORMATION

Contact the following sources:

- National Diabetes Information Clearinghouse Tel: (800) 860-8747 **Website: http://diabetes.niddk.nih.gov**
- American Diabetes Association Tel: (800) DIABETES (342-2383) **Website: http://www.diabetes.org**

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MANAGING YOUR

DIABETES MELLITUS TYPE 1: FOR ADULTS

What Is Diabetes Mellitus Type 1?

Diabetes mellitus type 1 (or just diabetes) is a lifelong disorder that prevents the body from getting energy from food. The body doesn't make enough insulin, a hormone produced by special beta cells in the pancreas. Insulin is vital because it controls the amount of sugar (glucose) that body cells get from the blood. People with diabetes have too much sugar in the blood, and not enough sugar getting into body cells.

Slightly more men than women have diabetes. It often starts at ages 12 to 15 years, with most cases diagnosed before age 30. More than 300,000 people in the United States have type 1 diabetes.

What Causes Diabetes?

Not enough insulin is the cause. In most diabetic people, the body's own defense, the immune (infection-fighting) system, destroys beta cells in the pancreas, but the reason for this isn't fully known. Other rarer causes are certain diseases, such as cystic fibrosis, which affects the pancreas, and surgical removal or severe inflammation (swelling, irritation) of the pancreas.

What Are the Symptoms of Diabetes?

Diabetes warning signs include urinating often, feeling very thirsty, getting frequent infections, losing weight quickly, and feeling tired and weak. Symptoms of uncontrolled diabetes also include blurred vision or blindness, slow-healing skin sores, numbness in hands or feet, and kidney failure (needing dialysis).

In diabetic ketoacidosis, another complication of diabetes, substances (ketones) accumulate. Ketones in the blood make the blood dangerously acidic, which affects multiple organs including

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the brain and can be life-threatening, if not rapidly diagnosed and treated in the hospital.

How Is Diabetes Diagnosed?

For diagnosis, the doctor uses a medical history, physical examination, and different measures of blood sugar. These measures include fasting and nonfasting levels, average glucose levels during 2 to 3 months (hemoglobin A1c [HbA1c] test), and glucose tolerance test. The doctor may also do kidney tests and measure blood fat (lipid) level.

How Is Diabetes Treated?

A special diet will help control blood sugar. A nutritionist can help manage this diet. Blood sugar levels need checking often, which can be done with a glucometer. People must watch for signs that the blood sugar level is too high or too low. Insulin injections are given at home, usually two or three times daily. The doctor can explain how to give them.

The doctor will suggest exercises to help control blood sugar levels.

Regular foot care and eye checkups are needed to prevent complications.

DOs and DON'Ts in Managing Diabetes Mellitus:

✓ **DO** follow your special diet and eat snacks at the same time every day.

✓ **DO** get enough exercise and sleep.

✓ **DO** check your blood sugar level if you're sick. Call your doctor if you have fever, nausea, or vomiting and can't keep down solids or liquids.

✓ **DO** call your doctor if your blood sugar level is too high.

✓ **DO** go to the hospital right away if you have a seizure, can't wake up, or lose consciousness.

✓ **DO** follow your doctor's orders about insulin exactly.

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⦸ **DON'T** smoke or use alcohol. They can affect blood sugar levels and make diabetes worse.

⦸ **DON'T** eat food with high sugar content.

⦸ **DON'T** use more insulin than your doctor recommends, it can lower your sugar to a dangerous level.

⦸ **DON'T** get dehydrated.

⦸ **DON'T** eat foods that your doctor or dietitian doesn't suggest.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Diabetes Information Clearinghouse Tel: (800) 860-8747 **Website: http://diabetes.niddk.nih.gov**
- American Diabetes Association Tel: (800) DIABETES (342-2383) **Website: http://www.diabetes.org**

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MANAGING YOUR

DIABETES MELLITUS TYPE 2

What Is Diabetes Mellitus Type 2?

Diabetes mellitus type 2, or type 2 diabetes (abbreviated type 2 DM), is one type of diabetes. In type 2 DM, a problem with insulin prevents body cells from using sugar (glucose) in food. Insulin is a chemical made by the pancreas. Insulin helps sugar enter body cells, which use the sugar for energy. DM involves poor responses of cells to insulin (insulin resistance) in type 2 DM, lack of insulin in type 1 DM, and too much sugar in the blood (hyperglycemia) in both types of DM.

People of any age can have DM. Type 2 DM occurs more often in overweight adults, especially those with diabetic relatives. DM is a lifelong illness.

Another name for type 2 DM no longer commonly used is adult-onset diabetes.

What Causes Type 2 Diabetes?

In DM, when cells don't have or don't respond to insulin, they can't get the sugar. Sugar stays in the blood until some extra sugar goes into urine and is removed. Too much blood sugar damages blood vessels, which can cause serious diseases.

What Are the Symptoms of Type 2 Diabetes?

Symptoms start slowly but get worse, although some people have no symptoms. Some people complain of often being thirsty and hungry and may need to urinate often.

More symptoms are tiredness, blurred vision, chest pain or other heart trouble, weight gain or loss, foot ulcers, numbness or tingling in hands or feet, sores that don't heal, infections, and impotence (in men).

Serious complications of long-term DM include blindness, kidney failure, nerve damage, coronary heart disease, and peripheral vascular disease.

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How Is Type 2 Diabetes Diagnosed?

The doctor uses a medical history, physical examination, and blood sugar levels for diagnosis.

Other laboratory tests include average sugar levels during 2 to 3 months (hemoglobin A1c [HbA1c] test) and glucose tolerance test. The doctor will also test the kidneys with blood and urine tests and the blood fat (lipid) level.

How Is Type 2 Diabetes Treated?

Many people control DM through just diet and exercise. New diet rules allow many food choices, but avoiding high-sugar and high-fat foods is important. Exercise helps control weight and keep blood sugar level down, and the body uses insulin better.

Some people need medicine, however. Medicine for type 2 DM usually consists of pills to help the body use sugar. If the pills don't work, insulin is given by injection.

Blood sugar levels must be tested often (usually at least daily). Being under the care of specialists (endocrinologist, podiatrist, eye doctor) in addition to your primary care doctor can also help prevent complications from diabetes.

DOs and DON'Ts in Managing Diabetes Mellitus Type 2:

✓ **DO** keep your blood sugar level near normal.

✓ **DO** exercise regularly.

✓ **DO** keep to a normal body weight.

✓ **DO** eat regular meals.

✓ **DO** eat healthy: whole-grain foods, fruit, vegetables, and high-quality proteins. Avoid high-sugar, high-fat, and white flour foods.

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✓ **DO** keep alcohol intake low.

✓ **DO** have your eyes checked yearly and visit the dentist twice yearly.

✓ **DO** quit smoking.

✓ **DO** take good care of your feet. Visit your podiatrist at least twice per year.

✓ **DO** call your doctor if you have a fever or vomiting and cannot eat or drink.

✓ **DO** call your doctor if you have high or low blood sugar levels that you cannot explain.

⃠ **DON'T** smoke.

⃠ **DON'T** drink liquor or high-sugar liquids.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Diabetes Information Clearinghouse Tel: 1-800-860-8747 **Website:** **http://www.niddk.nih.gov/health/diabetes/diabetes.htm**
- American Diabetes Association Tel: 1-800-DIABETES (1-800-342-2383) **Website:** **http://www.diabetes.org**

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MANAGING YOUR

DIABETES MELLITUS TYPE 2: FOR ADOLESCENTS

What Is Diabetes Mellitus Type 2?

Diabetes mellitus type 2 (DM) , or type 2 diabetes, is one kind of diabetes. A problem with the action of insulin prevents body cells from using sugar (glucose) in food. Insulin helps sugar enter body cells, which use the sugar for energy. The pancreas makes the hormone insulin. DM involves poor responses of cells to insulin (insulin resistance), not enough insulin, and too much sugar in the blood (hyperglycemia).

More teens today are getting DM, probably because they eat in excess and don't exercise enough. These lead to more insulin resistance. The most important way to prevent DM in teens is to prevent obesity.

What Causes DM?

Obesity is the most important reason for developing DM in teens. In DM, when cells don't have or don't respond to insulin, they can't get sugar. Sugar stays in the blood until extra sugar can be removed in urine. High blood sugar can cause problems with eyes, heart, blood vessels, nerves, and kidneys. Other risk factors for developing type 2 diabetes are being Native American, African American, Hispanic, Asian, or Pacific Islander, and having a family history of DM.

What Are the Symptoms of DM?

Some people with mild DM have no symptoms. Others have symptoms that start slowly but get worse. Signs and symptoms include being thirsty and needing to urinate often. Others are tiredness, blurred vision, weight gain or loss, foot ulcers, numbness or tingling in hands or feet, sores that don't heal, and infections. In some cases, patches of thick, dark skin that feels like velvet (acanthosis nigricans) can form on the neck or under the arms.

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How Is DM Diagnosed?

The doctor uses a medical history, physical examination, and blood sugar levels for diagnosis. Weight loss, thirst, and polyuria (urinating too much) can suggest to the doctor that DM may be present. Other laboratory tests include average blood sugar levels over a 3-month period (hemoglobin A1c [HbA1c] test), glucose tolerance test, tests for kidney function, and measurement of blood fat (lipid) tests.

How Is DM Treated?

Many teens control DM by just diet and exercise. Avoiding high-sugar and high-fat foods is important. Exercise helps control weight and blood sugar level, so the body uses insulin better. Medicine, usually pills (such as metformin) to help the body use sugar. Insulin shots may be needed in resistant cases.

The treatment team often includes a primary care doctor, diabetes educator, dietitian, social worker, an endocrinologist, and an eye doctor.

DOs and DON'Ts in Managing DM:

✓ **DO** keep your blood sugar level near normal.

✓ **DO** exercise and get enough sleep.

✓ **DO** keep your body weight normal.

✓ **DO** eat regular meals. Eat healthy: whole-grain foods, fruit, vegetables, and high-quality proteins. Avoid high-sugar, high-fat, and white flour foods and alcohol.

✓ **DO** have your eyes checked yearly. Visit the dentist twice yearly. Take good care of your feet.

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✓ **DO** ask your parents to call your doctor if you have a fever or vomiting and can't eat or drink or you have blood sugar levels that you don't understand.

⦸ **DON'T** smoke.

⦸ **DON'T** drink alcoholic beverages.

⦸ **DON'T** eat sugar, rich foods, or foods that aren't in your doctor's meal plan.

⦸ **DON'T** get too thirsty. Drink plenty of fluids but avoid those containing sugar.

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FOR MORE INFORMATION

Contact the following sources:

- National Diabetes Information Clearinghouse Tel: (800) 860-8747 **Website:** **http://diabetes.niddk.nih.gov**
- American Diabetes Association Tel: (800) DIABETES (342-2383) **Website:** **http://www.diabetes.org**

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CARING FOR YOUR CHILD WITH

DIABETES MELLITUS TYPE 2

What Is Diabetes Mellitus Type 2?

Diabetes mellitus type 2 (DM), or type 2 diabetes, is one type of diabetes. In DM, a problem with the action of insulin prevents body cells from using sugar (glucose) in food. Insulin helps sugar enter body cells, which use the sugar for energy. The pancreas makes the hormone insulin. DM type 2 usually involves poor responses of cells to insulin (insulin resistance) resulting in too much sugar in the blood (hyperglycemia).

Usually children with diabetes have type 1. Type 2 diabetes in children is much rarer. Obesity is important in development of type 2 diabetes in children.

What Causes DM?

In DM, when cells don't have or don't respond to insulin, they can't get the sugar they need for energy. Sugar stays in the blood until extra sugar can be removed in urine. Too much blood sugar damages blood vessels and can cause serious problems with eyes, heart, nerves, and kidneys. In addition to obesity, other risk factors are family history of DM; being Native American, African American, Hispanic, Asian, or Pacific Islander; and a family history of diabetes.

What Are the Symptoms of DM?

Most obese children with DM don't have symptoms at first. Signs and symptoms, if they occur, include losing weight for no reason, having sugar in the urine, feeling more thirsty, and needing to urinate more.

How Is DM Diagnosed?

The doctor uses a medical history, physical examination, and blood sugar levels for diagnosis.

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Other laboratory tests include average blood sugar levels (hemoglobin A1c [HbA1c] test), glucose tolerance, and kidney and blood fat (lipid) levels.

How Is DM Treated?

Type 2 DM in children has been rare and linked to obesity and sedentary lifestyle. Blood sugar control is critical to prevent later complications. Blood sugar levels must be tested often. Pills (metformin, sulfonylureas, or meglitinides) are used initially when medications are needed. Insulin is used only when sugar control is inadequate with pills. Diet, such as avoiding high-sugar and high-fat foods, can help control DM. Eating about the same amount of carbohydrate at each meal helps keep blood sugar levels steady. Sugar, sweets, grains, fruit, starchy vegetables, milk, and yogurt contain carbohydrate. Exercise also works to control weight and blood sugar.

The treatment team often includes a primary care doctor, diabetes educator, dietitian, social worker, and psychologist. Children and family members should get self-care DM education.

DOs and DON'Ts in Managing DM:

✓ **DO** keep your child's blood sugar level near normal.

✓ **DO** have your child exercise and eat regularly.

✓ **DO** help your child have a normal body weight.

✓ **DO** provide a healthy diet: whole-grain foods, fruit, vegetables, and high-quality proteins, not high-sugar, high-fat, and white flour food.

✓ **DO** take your child to the eye doctor yearly and the dentist twice yearly.

✓ **DO** call your child's doctor if your child cannot eat or drink because of fever or vomiting.

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✓ **DO** call your child's doctor if unexplained abnormal blood sugar levels occur.

✓ **DO** look for support groups for help dealing with DM.

⃠ **DON'T** let your child drink high-sugar sodas or juices. Give water instead.

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FOR MORE INFORMATION

Contact the following sources:

- National Diabetes Information Clearinghouse Tel: (800) 860-8747 **Website: http://diabetes.niddk.nih.gov**
- American Diabetes Association Tel: (800) DIABETES (342-2383) **Website: http://www.diabetes.org**

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MANAGING YOUR

DIABETIC RETINOPATHY

What Is Diabetic Retinopathy?

Diabetic retinopathy is an eye disease caused by diabetes mellitus. It affects the retina, the part of the eye that lets us see. Diabetes hurts the retina's tiny blood vessels and can cause swelling and leaking of fluid into the eye. Extra retinal blood vessels can grow, which damages eyesight. Diabetic retinopathy is the leading cause of blindness in people 20 to 70 years old. All people with diabetes—type 1 or 2—are at risk. Almost half of Americans with diabetes have some stage of diabetic retinopathy. There are four stages of diabetic retinopathy. The first is early mild nonproliferative retinopathy, with small balloonlike swollen areas in tiny retinal blood vessels. Then moderate nonproliferative retinopathy occurs, with blocked blood vessels. Severe nonproliferative retinopathy follows (more blood vessels are blocked, and new vessels grow). In the advanced stage (proliferative retinopathy), new abnormal, fragile blood vessels grow along the retina and watery soft gel (vitreous gel) inside the eye.

What Causes Diabetic Retinopathy?

Damaged blood vessels can cause vision loss when fragile, abnormal blood vessels grow and leak blood into the center of the eye. This advanced stage is called proliferative retinopathy. Also, fluid can leak into the center of the macula of the eye, where sharp, straight-ahead vision occurs. The macula swells (macular edema) and vision becomes blurry.

What Are the Symptoms of Diabetic Retinopathy?

Symptoms include seeing a few specks of blood or floating spots. Bleeding (hemorrhages) in the vitreous can occur, without pain, and lead to blurred vision or blindness. Diabetic retinopathy often has no warning signs.

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How Is Diabetic Retinopathy Diagnosed?

The doctor makes a diagnosis by doing an examination to look for leaking blood vessels, retinal swelling, damaged nerve tissue, and pale fatty deposits on the retina. The doctor may order fluoresce in angiography (using a special dye to see leaking vessels).

How Is Diabetic Retinopathy Treated?

For early disease, no treatment may be needed.

Two treatments can help people with advanced disease: laser surgery and vitrectomy (another operation). In the first procedure, which is painless, a laser beam is used to destroy abnormal blood vessels. Focal laser surgery is used for macular edema; a small laser burns slow leakage from vessels. A similar scatter laser treatment helps shrink abnormal blood vessels in proliferative retinopathy. In vitrectomy, blood that leaked from vessels is removed.

Control of blood sugar (glucose) levels and other risk factors (blood pressure and cholesterol) is important to prevent worsening disease.

DOs and DON'Ts in Managing Diabetic Retinopathy:

✓ **DO** watch your diet to control blood sugar levels.

✓ **DO** exercise.

✓ **DO** remember that untreated diabetic retinopathy can cause severe vision loss and blindness.

✓ **DO** remember that macular edema may need focal laser treatment more than once.

✓ **DO** call your doctor if you have symptoms of uncontrolled diabetes (e.g., increased thirst, increased urination, increased appetite with weight loss).

✓ **DO** call your doctor if you notice vision changes.

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⦸ **DON'T** smoke or drink alcohol.

⦸ **DON'T** wait until you have symptoms. Get yearly eye examinations.

⦸ **DON'T** forget that proliferative retinopathy and macular edema can develop without symptoms.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Ophthalmology Tel: (415) 561-8500 **Website:** **http://www.aao.org**
- American Diabetes Association Tel: (800) DIABETES (342-2383) **Website:** **http://www.diabetes.org**
- National Eye Institute Tel: (301) 496-5248 **Website:** **http://www.nei.nih.gov**

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MANAGING YOUR

DIAGNOSTIC HEART CATHETERIZATION

What Is Heart Catheterization?

Heart catheterization involves putting a catheter into the right or left side of the heart to measure pressures. Right heart catheters are called pulmonary artery (PA) catheters. They're used to find out how well the heart and its blood vessels are working and to treat heart disease. PA catheters are mainly used in cardiac catheterization laboratories, intensive care units (ICUs), and operating rooms. Left heart catheterization is done by putting a catheter across the aortic valve into the left ventricle. Left and right heart catheterization can be done simultaneously.

Heart catheterization and coronary angiography, a different procedure, are often done together. In coronary angiography, a special dye (contrast material) is put into the catheter, and x-rays are taken to see how blood flows through the heart. Coronary angiography is also used to diagnose coronary artery disease.

Who Needs Heart Catheterization?

People have heart catheterization for diagnosis of different heart and valve disorders and coronary artery diseases.

People shouldn't have heart catheterization if they have severe uncontrolled high blood pressure, certain abnormal heart rhythms (arrhythmias), acute stroke, severe anemia or bleeding, heart failure, and infections.

How Is Heart Catheterization Done?

Avoiding eating or drinking for 6–8 hours before the test is needed. A mild sedative is given before the test to help people relax. The doctor puts a sheath into a blood vessel in the arm, leg, or groin, usually the femoral, internal jugular, or subclavian vein. A catheter and guide wire are

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then placed into the sheath. From there, it's threaded into the heart or coronary arteries. This takes a few seconds and there is no pain since blood vessels have no pain nerves. Once the catheter is in place, the guide wire is removed. Once the catheter is in place, dye is injected and pictures (angiograms) are taken to show narrowing of the arteries. In some cases, interventional procedures (angioplasty and stenting) may be done right away to improve blood flow.

People are awake and can follow instructions during the test. The test may last 1 to several hours. Some discomfort at the spot where the catheter is placed is possible. After the test, the catheter is removed. If it was put into the groin, lying flat on the back for a few hours after the test is needed to avoid bleeding.

What Are Risks of Heart Catheterization?

Heart catheterization is very safe when done by an experienced team. Risks include arrhythmias (abnormal heartbeat), heart attack, bleeding from the catheter insertion site, low blood pressure, allergic reactions to contrast dye, blood clots, stroke, injuries to blood vessels, chest pain, infections, kidney failure, and, rarely, death.

The rare complication with the highest death rate is bursting of a PA because the balloon at the catheter tip is inflated too much or because of trauma to the PA.

DOs and DON'Ts in Managing Heart Catheterization:

✓ **DO** understand the risks. Talk to your doctor about the test and about heart health. Take medication as instructed.

✓ **DO** tell your doctor if you're allergic to contrast material, iodine, or shellfish or if you might be pregnant.

✓ **DO** be heart healthy: have your blood pressure and cholesterol levels checked regularly. Eat

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low-fat foods (fruits and vegetables). Lose weight if you're overweight. Exercise, such as walking, if your doctor says it's OK.

- ⃠ **DON'T** forget to avoiding eating or drinking for 6–8 hours before the test.
- ⃠ **DON'T** forget to tell your doctor about any medications you take, including over-the-counter medications, herbs, and supplements.
- ⃠ **DON'T** forget to arrange for an adult to take you home after the procedure.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website: http://www.americanheart.org**
- American College of Cardiology Tel: (800) 253-4636 **Website: http://www.acc.org**

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CARING FOR YOUR BABY WITH

DIAPER RASH

What Is Diaper Rash?

Diaper rash, or diaper dermatitis, is a skin irritation underneath the area covered by a diaper. It affects most babies at least once.

What Causes Diaper Rash?

The cause can be irritating substances, yeast, or bacteria trapped against the baby's skin by the diaper. Materials such as synthetic absorbents in disposable diapers and germ-killing rinses can also cause irritation. Commercial diaper wipes are another source of irritation.

What Are the Symptoms of Diaper Rash?

Redness and irritation in the diaper area often begin with faint, raised, pink spots, which seem to get larger and soon cover the diaper area if untreated. In the worst cases, skin may look red and begin to peel. Skin folds may become raw. Babies are usually fretful and fussy and cry, especially after urinating or moving the bowels. Diaper rash doesn't usually cause a fever.

How Is Diaper Rash Diagnosed?

The doctor will make a diagnosis by examining the skin.

How Is Diaper Rash Treated?

Treatment includes use of creams and ointments on the skin (topical) and frequent diaper changes. If irritation from urine is the main problem, a simple ointment containing zinc oxide will often give relief. It should be applied at each diaper change, after the diaper area is gently cleaned with lukewarm water and patted dry.

If the rash lasts even with these treatments, changing the type of diaper may help. Some babies are sensitive to chemicals in cloth diaper rinses, and others are irritated by synthetic materi-

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als in disposable diapers. Switching disposable brands or rinsing cloth diapers twice may solve the problem.

If yeast (*Candida*) caused the rash, the doctor may prescribe an ointment containing nystatin or clotrimazole. This kind of rash, perhaps with yeast infection in the mouth (thrush), often occurs after antibiotic treatment for ear infections. The doctor may also prescribe nystatin drops for the thrush.

DOs and DON'Ts in Managing Diaper Rash:

✓ **DO** your best to prevent diaper rash by keeping your baby's diaper area as dry as possible.

✓ **DO** leave the skin open to fresh air as much as possible.

✓ **DO** diaper loosely, and change baby frequently.

✓ **DO** use lukewarm water with a soft washcloth for cleaning the diaper area after the baby urinates. A small amount of baby bath can be used on the washcloth for cleaning after bowel movements.

✓ **DO** apply zinc oxide or antiyeast ointment at each diaper change.

✓ **DO** call your doctor if the baby develops a fever.

✓ **DO** call your doctor if the rash worsens despite home treatment or if it goes beyond the diaper area.

✓ **DO** call your doctor if your baby refuses breast or bottle or if vomiting or diarrhea occurs.

⊘ **DON'T** wait for a doctor visit to begin treating diaper rash. If the diaper area looks red, be-

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gin frequent (hourly) diaper checks right away, and change the diaper if you note dampness.

⦸ **DON'T** use commercial diaper wipes because they'll worsen the rash.

⦸ **DON'T** use over-the-counter antibacterial ointments unless your doctor recommends them.

These can cause irritation and rash themselves and are rarely needed.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Dermatology Tel: (866) 503-SKIN (7546) **Website:**

  http://www.aad.org

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MANAGING YOUR

DIETARY FIBER

What Is Dietary Fiber?

Dietary fiber, also called roughage or bulk, is the part of plant foods that the body cannot digest or absorb. It passes unchanged through the stomach and small intestine and into the colon. The two kinds of fiber are those that don't dissolve in water (insoluble) and those that do (soluble).

What Does Dietary Fiber Do?

Insoluble fiber helps material move through the digestive system and increases the size of stools (bowel movements). It's good for people with constipation or irregular stools. Soluble fiber dissolves in water to become a gel-like material. It can help lower blood cholesterol and sugar (glucose) levels.

Which Foods Are High in Fiber?

High-fiber foods include nuts, brown rice, certain cereals, whole wheat bread, raspberries, blackberries, pears, figs, acorn squash, carrots, okra, corn, Brussels sprouts, asparagus, broccoli, and beans. Whole wheat flour, wheat bran, nuts, and many vegetables are good sources of insoluble fiber. Oats, peas, beans, apples, citrus fruits, carrots, barley, and psyllium have soluble fiber.

How Much Fiber Is Needed?

Fiber needs change with age. Women 50 years old and younger should aim for 25 grams (about 5 tablespoons) of fiber daily. Men of that age need 38 grams daily. Older women (51 years old and older) need 21 grams. Men of that age should have 30 grams daily. The American Academy of Family Physicians recommends eating at least nine servings (four ½ cups) of fiber-filled fruits and vegetables each day.

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How Does Dietary Fiber Affect Health and Disease?

Dietary fiber has many health benefits, including better digestive health and better glucose and insulin control. It lowers blood cholesterol levels and may reduce the risks of heart disease and cancer. It can help weight loss and leads to better weight control. It can prevent constipation, diarrhea, and diverticula (small pouches) in the colon. A high-fiber diet may lower the risk of certain disorders such as hemorrhoids and irritable bowel syndrome.

DOs and DON'Ts in Managing Dietary Fiber:

✓ **DO** drink lots of water. Fiber works best when it absorbs water and makes your stool soft and bulky. Without the added water, you could become constipated.

✓ **DO** get all the fiber from your fruits and vegetables by leaving peels on. If you worry about dirt and pesticides, rinse your produce in warm water before you eat it. Remember, whole foods have more fiber than juices do.

✓ **DO** eat more beans, peas, and lentils. Eat more whole grains and whole-grain products.

✓ **DO** eat fruit at every meal. Good examples are apples, bananas, oranges, pears, and berries.

✓ **DO** eat healthy snacks. Fresh and dried fruits, raw vegetables, low-fat popcorn, and whole-grain crackers are good choices.

⦸ **DON'T** eat refined or processed foods such as fruit juice, white bread, pasta, and non-whole-grain cereals. They don't have enough fiber. Also, don't peel the skin off of fruits and vegetables. Peeling takes away the fiber.

⦸ **DON'T** eat too much fiber. Adding too much fiber too quickly can cause gas, bloating, and cramping. Increase fiber in your diet slowly over a few weeks to let your body adjust.

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FOR MORE INFORMATION

Contact the following sources:

- National Digestive Diseases Information Clearing house E-mail: nddic@aerie.com

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- American College of Gastroenterology Tel: (703) 820-7400 **Website:**

  http://www.acg.gi.org

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MANAGING YOUR

DILATED CARDIOMYOPATHY

What Is Dilated Cardiomyopathy?

Dilated cardiomyopathy is a disease of the heart muscle that prevents the muscle from producing the normal force of contraction. Therefore the heart cannot pump enough blood to the organs in the body. The heart becomes weaker and the four heart chambers get larger (dilate). These chambers are the atria (upper chambers) and ventricles (lower chambers). The heart muscle may thicken so that it can produce more force to keep blood pumping normally. The heart valves may also be affected as the heart chambers get large, which may worsen the flow of blood. The impaired heart action can affect lungs, liver, and other organs.

More men (about three times as many) than women have cardiomyopathy, and more African Americans (about three times) than whites.

What Causes Dilated Cardiomyopathy?

The cause is usually unknown. Factors that damage the heart muscle and lead to heart failure can cause it. These factors include coronary artery disease, poorly controlled diabetes, anemia, and valvular heart disease. Harmful chemicals (such as alcohol), infections, medications, cocaine, heroin, and some connective tissue diseases may also cause it. Cardiomyopathy cannot be prevented, but avoiding harmful chemicals such as alcohol may reduce the risk of getting it.

What Are the Symptoms of Dilated Cardiomyopathy?

Most people feel tired (fatigue), less able to exercise, or short of breath. Swelling of the legs or feet, chest pain, fast heartbeat, and palpitations (feeling that the heart skips beats) may also occur.

How Is Dilated Cardiomyopathy Diagnosed?

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The doctor will ask about symptoms, do a complete physical examination, and order tests. Electrocardiography (ECG) and chest x-rays, which can show an enlarged heart, will be done. The doctor will suggest seeing a heart specialist (cardiologist) for additional tests. Echocardiography (ultrasound examination of the heart) or angiography (special x-ray examination to check blood flow through the heart) may be done to determine how much damage is present.

How Is Dilated Cardiomyopathy Treated?

Therapy is aimed at relieving symptoms and correcting abnormal heart rhythms (arrhythmias). Lowering salt intake and resting are important. A heart valve operation may be needed for damaged valves. If the cause of the cardiomyopathy is known, that condition is treated. The doctor may prescribe medicines to control the heart rhythm (antiarrhythmics) and dilate blood vessels (vasodilators), water pills (diuretics), and nutritional supplements. A cardioverter defibrillator may be inserted in the chest in people responding poorly to medications. If the heart's pumping action is seriously impaired and symptoms of heart failure get worse, heart transplantation can be considered for young people.

DOs and DON'Ts in Managing Dilated Cardiomyopathy:

✓ **DO** lower the amount of sodium (salt) and fluid in your diet.

✓ **DO** take all medicines as prescribed.

✓ **DO** call your doctor if you have new or worsening chest pain, shortness of breath, swelling in the legs, or fainting.

⃠ **DON'T** drink alcohol.

⃠ **DON'T** do strenuous exercise until your doctor says that you can.

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⦸ **DON'T** abuse drugs. Cocaine, heroin, and organic solvents such as glue can cause dilated cardiomyopathy.

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FOR MORE INFORMATION

Contact the following source:

- American Heart Association Tel: (800) 242-8721 **Website:** **http://www.americanheart.org**

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MANAGING YOUR

DISCOID LUPUS ERYTHEMATOSUS

What Is Discoid Lupus Erythematosus?

Discoid lupus erythematosus (DLE) is a chronic skin disorder with red, raised plaques (scales) having sharp edges. The lesions usually occur on sun-exposed areas, especially the face, scalp, and neck.

DLE can be more frequent and more severe in African Americans. It affects women more often than men, usually adults between ages 20 and 50. Remissions occur between episodes.

Other family members may have DLE, but it is not contagious.

Some people with DLE develop systemic lupus erythematosus (SLE), a more serious disease involving many body organs.

What Causes DLE?

The cause is unknown, but DLE is likely an autoimmune condition (i.e., one in which the body's immune system attacks itself, causing injury or disease). Exposure to sunlight may increase the risk of getting DLE.

What Are the Symptoms of DLE?

Lesions are red, raised bumps (papules; smaller than 1 centimeter) and scales (plaques; larger than 1 centimeter) with clear borders. Lesions may also have scaling and thinning (atrophy) of the skin. Scarring is common.

In African Americans, lesions may be darker than normal skin. Lesions tend to be round or oval with irregular borders. They involve the face, scalp, neck, nose, forearms, hands, fingers, and toes. Sometimes, the trunk and mucous membranes are involved. Scalp lesions are often related to hair loss.

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Later lesions tend to be flat and faint pink or white. They tend to show atrophy and depression in the center, with slightly raised borders.

How Is DLE Diagnosed?

The doctor makes a diagnosis from the look of the skin. The doctor may do blood tests and a skin biopsy (removing a small piece of skin for study).

How Is DLE Treated?

Treatment depends on its location and how severe, its impact on quality of life, and response to therapy. DLE can be controlled but cannot be cured. Treatment lessens the severity of the condition and reduces scarring. Treatment includes avoiding triggers (sunlight and fluorescent lights), general measures, and medicines. Use maximum protection sunscreens and wear protective clothing.

Sunscreens with a sun protection factor (SPF) of 30, steroids, and drugs to inhibit the immune system can reduce inflammation (redness, swelling), scarring, and lessen the severity of DLE.

DOs and DON'Ts in Managing DLE:

✓ **DO** take medicines as prescribed.

✓ **DO** tell your doctor about all medicines, including over-the-counter drugs, that you take.

✓ **DO** read medicine labels and follow instructions.

✓ **DO** avoid exposure to sunlight and fluorescent lights to reduce the severity of DLE.

✓ **DO** keep follow-up doctor appointments.

✓ **DO** call your doctor if lesions become worse or new lesions appear despite therapy.

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✓ **DO** call your doctor if you have new or unexplained symptoms.

⃠ **DON'T** stop taking your medicine or change the dose without asking your doctor.

⃠ **DON'T** suddenly stop using steroids or immunosuppressive therapy without asking your doctor.

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FOR MORE INFORMATION

Contact the following sources:

- Lupus Foundation of America Tel: (800) 558-0121 **Website:** **http://www.lupus.org/newsite/index.html**
- American Academy of Dermatology Tel: (847) 330-0230 **Website:** **http://www.aad.org**

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MANAGING YOUR

DISSEMINATED INTRAVASCULAR COAGULATION

What Is Disseminated Intravascular Coagulation (DIC)?

Coagulation (clotting) involves proteins, platelets, and cells lining the walls of blood vessels (endothelial cells). Platelets are blood components that help blood clot. Stimulation of the proteins involved in blood coagulation, such as by injury or illness, causes the protein prothrombin to be changed into another protein, an enzyme named thrombin. Thrombin is the key to clotting. Diseases can change the normal balance between blood clotting and thinning (anticoagulation).

DIC is a serious disorder in which proteins that help clotting are activated throughout the body. Small blood clots form in tiny blood vessels and can cut off the blood supply to organs. These organs stop working and in time, clotting proteins are used up, so bleeding can occur from even small injuries. Damage to red blood cells and low platelet counts may occur. DIC can lead to thrombosis (too much clotting) or, more likely, hemorrhage (bleeding). DIC isn't actually an illness but is instead a complication or effect of other illnesses.

What Causes DIC?

Causes include many different disorders, such as severe infections (e.g., sepsis), malignancies, trauma, liver failure, and some obstetric problems.

What Are the Symptoms of DIC?

Bleeding occurs at different places in the body, such as the digestive tract, lungs, and urinary tract. Other symptoms are low blood pressure, coughing, breathing problems, fever, bruising, and confusion. Oozing from places where blood is drawn may occur. Severe DIC causes very low blood pressure (shock). DIC-related bleeding after surgery or childbirth may be uncontrollable. DIC that starts slowly, as in some people with cancer, causes clotting more than

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bleeding.

How Is DIC Diagnosed?

The doctor makes a diagnosis from symptoms and laboratory blood tests. Broken, very small, and damaged red blood cells, and fewer platelets can be found on a blood smear. Coagulation tests include prothrombin time (PT), partial thromboplastin time (PTT), and thrombin time. Levels of coagulation proteins are checked.

How Is DIC Treated?

The underlying condition must be treated. People with DIC are quite ill and are usually admitted to the hospital. DIC that starts suddenly is life-threatening. Blood products such as packed red blood cells, platelets, and clotting factors are replaced. Plasma transfusions may provide clotting factors. Heparin (an anticoagulant drug that inhibits the coagulation factors) or other anticoagulants may be useful in some cases. Hematologists (specialists in blood diseases), transfusion specialists, or critical care doctors may be involved in your care.

DOs and DON'Ts in Managing DIC:

✓ **DO** follow any special diet if your underlying condition requires it.

✓ **DO** exercise if you can, once your general condition improves.

✓ **DO** call your doctor if you start bleeding from the nose or gums, see bloody urine, or find black-and-blue spots on your skin.

✓ **DO** go to the hospital emergency department or call 911 if your bleeding won't stop.

⃠ **DON'T** take medicines such as aspirin or nonsteroidal antiinflammatory drugs (NSAIDs) without your doctor's ok. They can increase the bleeding tendency.

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⦸ **DON'T** exercise until your condition improves.

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- National Heart, Lung, and Blood Institute Information Center Tel: (301) 592-8573

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MANAGING YOUR

DIVERTICULAR DISEASE

What Is Diverticular Disease?

Diverticular disease is a disorder of the large intestine (colon). The colon is the last part of the digestive tract. Food passes through it just before waste leaves the body as a bowel movement (stool).

In diverticular disease, parts of the colon wall are weak. These weak places can puff out like small sacs (diverticula). Each sac is called a diverticulum. These parts can become swollen (inflamed) and even infected. Diverticulosis refers to the presence of diverticula in many places. Diverticulitis is the name for the disorder when diverticula become inflamed or infected.

Diverticular disease can develop if food moves too slowly through the colon. Pressure in the colon from this food causes weak spots and sacs.

Food moves too slowly when there is not enough fiber in the diet or if muscle spasms occur in the colon. Fiber is found in fruits, vegetables, and whole grains. The colon is made of muscle, and during muscle spasms, the colon tightens. Food can't move easily through it, so a high pressure spot results.

Diverticular disease is common, especially among older people.

What Are the Symptoms of Diverticular Disease?

Many people have diverticular disease but feel fine. Diverticulosis usually causes no symptoms. Diverticulitis may cause one or more of these symptoms: pain in the lower left abdomen, fever, difficulty having a bowel movement, and gas and bloating.

How Is Diverticular Disease Diagnosed?

In people with abdominal pain, the doctor will want pictures of the colon. Computed tomography

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(CT) scan of the belly (abdomen) can show diverticulosis and diverticulitis.

The best test to diagnose diverticulosis is colonoscopy. A thin, bendable tube (endoscope, or scope) is inserted into the rectum and then the colon. The tube has a tiny camera that lets the doctor look for problem spots and take pictures. Before this test, a laxative must be taken to empty all food from the colon. Colonoscopy is not performed when diverticulitis is suspected because of the increased risk of perforation of the colon.

When just the lower colon is checked, the test is called sigmoidoscopy. When the whole colon is checked, it is called colonoscopy.

How Is Diverticular Disease Treated?

For diverticulosis, eating a high-fiber diet and avoiding nuts and seeds, which may become stuck in diverticula, are important.

For diverticulitis, not eating for a few days rests the colon. Only liquids are taken until the colon heals. Antibiotics will treat the infection. Hospitalization and intravenous fluids and antibiotics may be necessary for severe cases.

Pain medicine may help, but take only the type the doctor recommends. Some types of pain medicine may worsen the condition.

In severe cases, surgery may be needed to remove damaged colon.

DOs and DON'Ts in Managing Diverticular Disease:

✓ **DO** eat a high-fiber, low-salt, low-fat diet.

✓ **DO** drink enough fluids.

✓ **DO** proper physical activities.

✓ **DO** keep to the proper weight. Try to lose weight if you're overweight.

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✓ **DO** maintain proper bowel habits (try to have a bowel movement daily).

✓ **DO** watch for blood in the stool.

✓ **DO** watch for signs of diverticulitis, such as fever and pain, and other complications.

✓ **DO** call your physician if you have abdominal pain.

⃠ **DON'T** strain with bowel movements.

⃠ **DON'T** use laxatives.

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FOR MORE INFORMATION

Contact the following source:

- National Digestive Diseases Information Clearinghouse Tel: (800) 891-5389 **Website:**

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MANAGING YOUR

DIVERTICULITIS

What Is Diverticulitis?

The large intestine (colon) is the last part of the digestive tract. Food passes through it just before waste leaves the body as a bowel movement (stool). In diverticular disease, parts of the colon wall are weak. These weak places can puff out like small sacs (diverticula). Each sac is called a diverticulum. These parts can become red and swollen (inflamed) and infected. Diverticulitis is the disorder when diverticula become inflamed and infected. Diverticulitis can be a minor inflammation or a serious infection.

Diverticulitis occurs in about half of people who have diverticuli. About 3 cases per 100 people occur each year. With treatment the prognosis is good, but relapses do occur. Complications include hemorrhage (bleeding), perforation (rupture), bowel blockage, and abscesses.

What Causes Diverticulitis?

Diverticuli become inflamed and infected, and small abscesses form, which causes symptoms. This disorder can occur if breakdown products from food move too slowly through the colon. Pressure in the colon from feces and food by-products causes weak spots and sacs. Diverticulitis is not contagious or cancerous.

What Are the Symptoms of Diverticulitis?

Symptoms are cramping and pain in the abdomen (belly) that stops and starts but then becomes constant. The pain is usually in the left lower abdomen. It's usually severe and starts suddenly. Other symptoms are fever, chills, constipation or diarrhea, and loss of appetite and nausea.

How Is Diverticulitis Diagnosed?

The doctor will make a diagnosis from a medical history, physical examination, blood tests, x-

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rays, and computed tomography (CT). Blood tests will check for infection. CT will show the inflammation and infection. Certain tests such as colonoscopy and barium enema shouldn't be done during acute diverticulitis because they may cause the colon to burst at the place of diverticulitis.

How Is Diverticulitis Treated?

Outpatient treatment is usual, unless symptoms are severe and widespread infection or complications occur. Rest, stool softeners, liquid diet, and oral antibiotics are used. If a hospital stay is needed, treatment is similar, but intravenous fluids and antibiotics are given, together with pain medicine. At first, eating may not be allowed. Then, high-fiber, low-fat foods are slowly returned to the diet.

For severe or complicated cases, surgical removal of the affected part of the colon is possible. Surgery is also used for frequent diverticulitis to remove the affected area of the colon.

DOs and DON'Ts in Managing Diverticulitis:

✓ **DO** take medicines as prescribed.

✓ **DO** eat a high-fiber, low-salt, low-fat diet between attacks to avoid constipation. This will reduce your chances of getting diverticulitis.

✓ **DO** drink plenty of fluids between attacks.

✓ **DO** keep physically active between attacks.

✓ **DO** maintain your correct weight. Try to lose weight if you're overweight.

✓ **DO** maintain good bowel habits by trying to have a bowel movement daily.

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✓ **DO** call your doctor if you have blood in your stool or dark, tarry bowel movements or unexplained weight loss.

✓ **DO** call your doctor if abdominal pain develops or becomes worse.

✓ **DO** call your doctor if you get a fever.

⃠ **DON'T** strain with bowel movements.

⃠ **DON'T** use laxatives.

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FOR MORE INFORMATION

Contact the following sources:

- National Digestive Diseases Information Clearinghouse Tel: (800) 891-5389 **Website:** **http://www.niddk.nih.gov/health/digest/nddic.htm**
- American College of Gastroenterology Tel: (703) 820-7400 **Website:** **http://www.acg.gi.org**

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MANAGING YOUR

DIVERTICULOSIS

What Is Diverticulosis?

The large intestine (colon) is the last part of the digestive tract. Food passes through it just before waste leaves the body as a bowel movement (stool). In diverticular disease, parts of the colon wall are weak. These weak places can puff out like small sacs (diverticula). Each sac is called a diverticulum. These parts can become red and swollen (inflamed) and infected. Diverticulosis refers to the presence of diverticula in many places. Most often, diverticuli occur in the lower part of the colon (sigmoid and distal colon) near the rectum.

The condition is a lifelong problem. Up to 20% of the general population has diverticulosis. Older people tend to have diverticuli more often than younger people. Up to 50% of people at age 50 will have them. Complications include infection (diverticulitis) and bleeding.

What Causes Diverticulosis?

The cause is the bulging (herniation) of the colon wall (mucosa) through the muscular layer of the colon. The reason for the herniation is unknown. Diverticulosis can occur if food breakdown products and feces move too slowly through the colon. People who eat a low-fiber diet are much more likely to form diverticula. It's not contagious or cancerous.

What Are the Symptoms of Diverticulosis?

Most people don't have any symptoms. About 10% to 20% of people have mild cramping in the left side of the abdomen (belly). A bowel movement or passing gas often relieves the cramping. Constipation may be an occasional problem.

How Is Diverticulosis Diagnosed?

Diverticulosis is diagnosed with a colonoscopy. In a colonoscopy, the doctor looks at the whole

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colon using a lighted flexible tube put through the rectum. The tube has a tiny camera that lets the doctor look for problem spots and take pictures. Before this test, a laxative must be taken to empty all food from the colon. Rarely a barium enema may be done in place of colonoscopy. For the barium enema x-ray examination, a liquid containing the substance barium is placed in the rectum. The liquid makes it easier to see inside the colon. Diverticulosis is often found when tests are done for another disorder.

How Is Diverticulosis Treated?

No treatment is needed unless symptoms occur. For symptoms, a change in diet, with more fiber and fluids, and use of stool softeners will help. Avoid nuts and seeds, which can get stuck in diverticula.

DOs and DON'Ts in Managing Diverticulosis:

- ✓ **DO** eat a high-fiber, low-salt, low-fat diet. Avoiding constipation with a high-fiber diet will lower chances of getting diverticulosis.
- ✓ **DO** drink plenty of fluids.
- ✓ **DO** keep physically active.
- ✓ **DO** maintain your correct weight. Try to lose weight if you're overweight.
- ✓ **DO** maintain good bowel habits by trying to have a bowel movement daily.
- ✓ **DO** call your doctor if you have blood in your stool or dark, tarry bowel movements.
- ✓ **DO** watch for signs of diverticulitis and complications, such as abdominal pain and fever.
- ✓ **DO** call your doctor if you have a fever or abdominal pain or your pain becomes worse.

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⦸ **DON'T** strain with bowel movements.

⦸ **DON'T** use laxatives.

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CARING FOR YOUR CHILD WITH

DOWN SYNDROME

What Is Down Syndrome?

Down syndrome is a hereditary condition with moderate-to-severe mental deficiency. Children with Down syndrome are born with an extra chromosome 21. Other names for this condition are trisomy 21 and mongolism. Dr. John Down, a British doctor, first identified this condition in 1866. Down syndrome occurs in about 1 of 800 to 1000 live births.

The syndrome cannot be cured, but people can live long lives, into their 60s.

What Causes Down Syndrome?

Chromosomes hold all genetic information. Normally, each person has 46 chromosomes, 23 from each parent. People with Down syndrome have 47 chromosomes. The mother's age is important, because the older the mother, the greater the chance of having a child with this syndrome. At age 25 years, the risk is 1 in 1400. At age 40, it's 1 in 100. Down syndrome cannot be prevented. Future parents may want genetic counseling before having a child.

What Are the Symptoms of Down Syndrome?

Children differ mentally and physically from other children their age. They tend to be calm and rarely cry. Other features include a small head, mental retardation, delays in development, slanting eyes, short height, and small, low-set ears. The tongue seems too big for the mouth, and muscles seem floppy. Hands are short and broad with one crease in the palm.

Babies develop language and learning skills (crawling, walking) more slowly than other babies.

How Is Down Syndrome Diagnosed?

The diagnosis is usually made just after birth, from the physical look of the baby. A blood test to

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check chromosomes will confirm the diagnosis. Two tests done during pregnancy can tell whether the fetus has the syndrome. They are chorionic villus biopsy and amniocentesis. The doctor may also do tests for heart problems. A new genetic test may detect Down syndrome with a blood sample from the mom-to-be.

How Is Down Syndrome Treated?

Many medical and developmental conditions can be helped. For example, in some cases surgery may be used for heart and digestive problems. Physical therapy and special education can help children control their muscles and develop social skills. Many children can reach a very high level of functioning and be independent.

DOs and DON'Ts in Managing Down Syndrome:

✓ **DO** work with your health care team to plan a treatment program for your child.

✓ **DO** consider help from mental health workers, which may help you understand this condition. You may feel guilty, but it's not your fault for having a child with Down syndrome.

✓ **DO** enroll your child in an early intervention program. Look for educational, developmental, and vocational options as your child grows up.

✓ **DO** get help from local and national support groups.

✓ **DO** get genetic counseling.

✓ **DO** call your doctor if you have questions about your child's health or need information about services for your child.

✓ **DO** call your doctor if your child becomes ill or confused or has problems with medicines.

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⦸ **DON'T** underestimate your child's ability. Enroll your child in a special teaching program.

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Contact the following source:

- National Down Syndrome Society Tel: (800) 221-4602 **Website: http://www.ndss.org**

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MANAGING YOUR

DRUG ABUSE

What Is Drug Abuse?

Abuse of prescription and illicit drugs is a major problem in the United States. Three terms related to abuse need definitions: tolerance, physical addiction, and psychological addiction.

Tolerance means abusers need more drug to get the same effect as before or to avoid going through withdrawal.

Physical addiction exists with tolerance. People with physical addiction go through withdrawal when they stop using the drug. Symptoms of withdrawal include gooseflesh, nausea, vomiting, abdominal cramps, diarrhea, rapid heartbeat, sweating, insomnia, and severe anxiety. Withdrawal from benzodiazepines, barbiturates, and alcohol can be life-threatening.

Psychological addiction means having a severe drug craving and using drug-seeking behaviors, such as forging prescriptions, faking illnesses, and using violence to get drugs.

What Are the Types of Drug Abuse?

Anyone can be an abuser. Unlike in the past, more women than men today are admitted to drug abuse programs.

Five types of drugs are commonly abused. Depressants make people feel down. They're strongly physically addicting. They include alcohol, barbiturates, opiates, other painkillers, and drugs such as meprobamate. Stimulants produce a high and can cause severe insomnia, restless feelings, and inability to sit still. Stimulants include cocaine (crack), amphetamines (such as methamphetamine), caffeine, over-the-counter drugs with pseudoephedrine, and diet pills. Hallucinogens cause people to see, hear, or feel things that are not actually there, or they make people misinterpret things. They're very dangerous. Hallucinogens include LSD, mescaline, and psilo-

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cybin. Inhalants are huffed, snorted, or sniffed. Examples are gasoline, cleaning products, anesthetics (such as nitrous oxide), hair sprays, bug sprays, spray paints, solvents such as toluene, airplane glue, typewriter correction fluid, and kerosene. Teenagers often use these drugs, which are cheap and obtained easily. They can cause serious physical damage and strong drug craving and drug-seeking behaviors. PCP, or angel dust, can cause psychosis or depression, with flashbacks.

Other abused drugs include marijuana, designer drugs, and GHB (date rape drug).

How Is Drug Abuse Treated?

Treatment involves detoxification, education and keeping drug free, and peer support counseling. Support groups include Alcoholics Anonymous (AA), Cocaine Anonymous (CA), and Narcotics Anonymous (NA). The main point of treatment is to stop drug abuse. Sometimes, other drugs are used to help stop the abuse. Education is often done in peer support groups with other drug abusers. Abusers need a sponsor, a former abuser who has had years of being clean. People should call their sponsors when they feel that they could relapse.

Some people have both a psychiatric condition and drug abuse. Both need treatment.

DOs and DON'Ts in Managing Drug Abuse:

✓ **DO** tell your doctor or emergency room doctor that you're a recovering drug abuser.

✓ **DO** contact your doctor or support group if you have strong urges to use drugs again (relapse warning signs).

✓ **DO** eat well, drink plenty of fluids, get enough rest, exercise moderately, and reduce stress during recovery.

✓ **DO** call your doctor if you have seizures, psychosis, or suicidal thoughts.

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⦸ **DON'T** take other medicines, including over-the-counter drugs, before checking with your doctor.

⦸ **DON'T** see friends and relatives who abuse drugs or remind you of when you did. Socialize with your sponsor and AA or NA members.

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FOR MORE INFORMATION

Contact the following sources:

- National Clearinghouse for Alcohol and Drug Information Substance Abuse and Mental Health Services Administration Tel: (800) 729-6686 **Website:** **http://ncadi.samhsa.gov/**
- Habit Smart **Website:** **http://www.habitsmart.com**
- Cocaine Anonymous Tel: (310) 559-5833 **Website:** **http://www.ca.org**
- Narcotics Anonymous Tel: (818) 773-9999 **Website:** **http://www.na.org**

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MANAGING YOUR

DRY EYE

What Is Dry Eye?

Dry eye is a very common problem. Anyone can get it, but people are more likely to get it if they wear contact lenses, are over 65, or are female. Dry eyes don't make enough tears to keep the eyes moist. In time and if left untreated, dry eye can scar the eye's surface.

What Causes Dry Eye?

Usually, no serious medical problem exists. Natural aging, drugs (such as antihistamines, blood pressure medicines, and birth control pills), and living in a dry, dusty, or windy climate can cause dry eye. Other causes are air conditioning, dry heating systems, blinking problems (staring at a computer screen), and wearing contact lenses. Autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus, or Sjögren's syndrome, can rarely cause it. Autoimmune means that the immune system fights itself instead of disease or organisms. Some eye conditions, thyroid disease, and AIDS or HIV can also cause dry eye.

What Are the Symptoms of Dry Eye?

Symptoms include burning, itching, or stinging eyes; feeling as if grit or sand is in the eyes; and sensitivity to bright light. Stringy mucus in or around the eyes, eye fatigue, tearing, and blurred vision are other symptoms.

How Is Dry Eye Diagnosed?

The doctor makes a diagnosis from a description of symptoms. If the doctor thinks that an eye disorder or another illness is causing dry eye, the doctor may suggest seeing an ophthalmologist (specialist in eye diseases).

The specialist may do a Schirmer test. For this simple test, the doctor numbs the eye and puts

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little paper tabs in the lower lid. After a few minutes, the doctor removes the tabs and measures how damp they are. Tabs with too little moisture mean dry eye.

The eye doctor may also do a slit lamp examination. The slit lamp has a microscope that makes the eye appear larger, so the doctor can see more clearly if the surface of the eye has any damage.

How Is Dry Eye Treated?

Treatment includes using artificial tears, as eye drops, during the day. Ointments can add extra moisture to the eyes at night.

Other treatments include using hot compresses and eyelid scrubs or massages with baby shampoo (to give the eyes a thicker oily layer). Humidifiers, air filters, and slowing fans to stop too much air from moving can also help.

In severe cases, tiny plugs may be put into ducts that drain the tears of the eyes to provide more moisture.

DOs and DON'Ts in Managing Dry Eye:

✓ **DO** use artificial tears regularly and as often as needed to control symptoms.

✓ **DO** use a humidifier in your house and office to provide extra moisture in the air.

✓ **DO** ask your doctor how to put a hot compress on your eye and how to do eyelid massage.

✓ **DO** ***c***all your doctor if you have eye pain, problems with your vision, or drainage from your eyes.

⃠ **DON'T** use contact lenses. If you were using them, wear glasses instead.

⃠ **DON'T** use hot air vents to heat your house.

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⦸ **DON'T** go out in windy weather if you can help it.

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FOR MORE INFORMATION

Contact the following sources:

• American Academy of Ophthalmology Tel: (415) 561-8500 **Website: http://www.aao.org**

• National Eye Institute, National Institutes of Health Tel: (301) 496-5248 **Website:**

http://www.nih.gov/health/cornealdisease/

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MANAGING YOUR

DUPUYTREN'S CONTRACTURE

What Is Dupuytren's Contracture?

Dupuytren's contracture is a condition affecting the hands. Tissue inside the palm tightens so fingers curl down toward the palm (contract) and stay there. It may occur in one hand only, but often both hands have this problem. In time, the hands become hard to use. Dupuytren's contracture is most common between ages 40 and 65. The condition isn't life-threatening, but it doesn't go away and can lead to disability.

What Causes Dupuytren's Contracture?

The cause is unknown, but the disorder isn't contagious. It sometimes runs in families. It's slightly more common in people with a history of hand injury and certain conditions such as diabetes, epilepsy, and HIV infection.

What Are the Symptoms of Dupuytren's Contracture?

Curling of the fingers toward the palm and a small painless lump in the middle of the hand are the main symptoms. People often first notice it when it's hard to reach for something. The little finger and finger next to it (ring finger) are most often affected. Eventually, the hand can't be placed flat on a surface. Usually there's no pain, but people may have discomfort when trying to hold something. The skin on the palm may pucker.

How Is Dupuytren's Contracture Diagnosed?

The doctor makes a diagnosis by looking at the hand. The doctor may find a painless nodule (lump) on the palm. The nodule feels hard and ends in a band that goes from the finger to the palm. In time, it's very hard to straighten the finger. The skin over the finger has thin grooves and pits. Attempts to extend the finger lead to skin blanching (whitening).

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How Is Dupuytren's Contracture Treated?

Often no treatment is needed, but treatment may help problems with normal daily movements. Physical therapy (stretching and flexing exercises) is usually tried first. Occupational therapy can be used early and after an operation. Specially made tools, such as door handles and jar openers, may make daily activities easier. Splinting of the finger is generally ineffective. Medicines (collagenase or corticosteroids) can be injected into the hand to slow the disease progress. Surgery done by a hand surgeon (orthopedic or plastic surgeon) may help people with significant trouble using their hands. Tissue in the palm is divided or removed. This lets fingers to return to their normal position. The problem can recur, however.

DOs and DON'Ts in Managing

Dupuytren's Contracture:

✓ **DO** control contributing factors such as diabetes, epilepsy, and repetitive hand trauma.

✓ **DO** wear protective gloves when doing manual work.

⃠ **DON'T** stop using your hands in a normal everyday way, as much as possible.

⃠ **DON'T** put your hands in a position where they could get injured.

⃠ **DON'T** move your hands the same way over and over. Avoid putting your hands where they get a lot of vibration.

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Contact the following sources:

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- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website:**

http://www.aaos.org

- Curtis National Hand Center Tel: (410) 235-5405

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MANAGING YOUR

DYSFUNCTIONAL UTERINE BLEEDING

What Is Dysfunctional Uterine Bleeding?

Dysfunctional uterine bleeding (DUB) is abnormal bleeding unrelated to your normal period. This very common problem doesn't have any single cause.

What Causes DUB?

A common cause is hormonal irregularities, most often because an ovary did not produce an egg during that one cycle. This cycle is called anovulatory. Anovulation is very common. Many women have one or two anovulatory cycles each year.

Abnormal bleeding might have other causes, including uterine fibroids (benign tumors of the uterus), endometrial polyps, cervical abnormalities, miscarriage, and uterine cancer (mostly in women before or after menopause, or change of life).

What Are the Symptoms of DUB?

Bleeding sometimes continues from one period to the next; other times it may be a heavy flow or just spotting. DUB may occur as bleeding between periods—bleed for a few days, stop for a few days, then bleed again—until the next period.

How Is DUB Diagnosed?

The doctor will diagnose DUB on the basis of a medical history and physical examination. Blood tests and ultrasonography may be done to rule out other causes.

How Is DUB Treated?

Most DUB is self-limiting and needs no treatment. Abnormal bleeding will often stop after the next period. However, sometimes very heavy bleeding can cause significant blood loss and does need treatment. Heavy flow can usually be reduced by taking a progestin hormone, such as me-

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droxyprogesterone. Side effects include feeling bloated, breast tenderness, lower backache, increased irritability, and mild depression. However, usually progestin is taken for 7 to 10 days, so they last for only a short while. Birth control pills can be used temporarily to control heavy bleeding. They may cause mild nausea. A minor procedure called dilation and curettage (D&C) is rarely needed to control bleeding. During a D&C, the lining of the uterus (endometrium) is scraped out.

DOs and DON'Ts in Managing DUB:

✓ **DO** take your medicine as directed.

✓ **DO** call your doctor if your period lasts longer than 7 or 8 days, you bleed between periods, or bleeding doesn't slow or stop as expected.

✓ **DO** call your doctor if your period is much heavier than usual, such as soaking through maxi pads or super tampons every 2 hours, or passing large (walnut size or larger) clots.

✓ **DO** call your doctor if you bleed heavily and feel dizzy or weak. These feelings may be symptoms of severe anemia.

✓ **DO** call your doctor if you may be pregnant.

⊘ **DON'T** stop your medicine early (even if bleeding stops) unless your doctor tells you to do so.

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Contact the following source:

- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website:** **http://www.acog.org**

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MANAGING YOUR

DYSMENORRHEA

What Is Dysmenorrhea?

Dysmenorrhea is pain in the abdomen (belly) or back occurring during periods (menstruation).

Up to 50% of all women have menstrual pain. For about 15% of them, the pain is so severe that they cannot continue with normal activities. This kind of pain is dysmenorrhea. It can disappear by itself or become less bothersome as you age or after delivery of a baby. Women usually develop menstrual pain 1 to 2 years after periods start or in their early 20s. It usually improves with time, but some women can have it into their 40s.

What Causes Dysmenorrhea?

The cause is thought to be high levels of prostaglandin (a substance produced by the uterus). In other women, fibroids or endometriosis may cause it. Endometriosis is a condition in which tissue from the lining of the uterus (endometrium) occurs in places where it's not normally found, such as on the ovaries.

Women with mothers and sisters with menstrual pain are slightly more likely to develop dysmenorrhea.

What Are the Symptoms of Dysmenorrhea?

Symptoms are cramping, tenderness, and sharp or dull pain in the lower abdomen that may spread to the lower back and inner thighs. Nausea, vomiting, diarrhea or constipation, bloating, needing to urinate often, chills, sweating, and feeling irritable and depressed may occur.

These symptoms usually begin the day blood flow begins and last 1 to 3 days. Symptom severity can vary, with cramping sometimes being mild and other times, severe.

How Is Dysmenorrhea Diagnosed?

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The doctor will do a pelvic examination to make sure reproductive organs (uterus, ovaries, fallopian tubes) are normal. Blood tests and ultrasound of the uterus and ovaries may also be done. The doctor may suggest seeing a gynecologist, who will check for other problems. A gynecologist is a specialist in diseases of the female reproductive system.

How Is Dysmenorrhea Treated?

Over-the-counter or prescription pain relievers help with pain. If one doesn't work, another may. Over-the-counter drugs include ibuprofen and naproxen. Taking birth control pills works well and makes bleeding lighter. It can take up to 3 months to notice a decrease in symptoms.

Applying a heating pad or hot water bottle to the lower abdomen, taking hot baths, or massaging the area may help.

Other treatments may include transcutaneous electrical nerve stimulation (TENS) and acupuncture. For TENS, a gentle electric current is applied to the skin. Acupuncture uses needles inserted through the skin into muscles.

DOs and DON'Ts in Managing Dysmenorrhea:

✓ **DO** exercise regularly, especially activities to strengthen lower abdominal muscles.

✓ **DO** lose weight if you are overweight.

✓ **DO** limit drinking of alcohol.

✓ **DO** try using heat, such as a heating pad, hot water bottle, or soaking in a hot tub.

✓ **DO** call your doctor if medicine doesn't relieve symptoms or if you don't tolerate the medicine.

✓ **DO** call your doctor if your dysmenorrhea becomes worse, even with treatment.

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⦸ **DON'T** smoke.

⦸ **DON'T** take ibuprofen or similar medicines if you had stomach problems such as ulcers or gastritis.

⦸ **DON'T** use someone else's medicines.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website:** **http://www.acog.org**
- National Women's Health Resource Center Tel: (877) 986-9472 **Website:** **http://www.healthywomen.org**

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CARING FOR YOUR CHILD WITH AN

EARACHE

What Is an Earache?

An earache, called otitis media, is an infection in the middle ear (between the eardrum and auditory tube, which links the middle ear to the back of the nose). This area contains nerves and small bones for hearing. Earaches can affect people of any age but are most common in babies and children. Three fourths of children get earaches. Infection occurs when germs causing colds, sore throats, and flu spread and cause inflammation (swelling, redness) of the eardrum and area around it.

What Causes an Earache?

Causes include viruses, bacteria, allergies, and rupture of the eardrum. Allergies cause blockage of sinuses and Eustachian tubes.

What Are the Symptoms of an Earache?

Usual symptoms or behaviors include fever, sleeping problems, irritability, pulling on the ears, fluid coming out of ears, loss of hearing and balance, headache, waking in the middle of the night crying in severe pain, and dizziness.

How Is an Earache Diagnosed?

The doctor will look into the child's ear with a special tool called an otoscope. This tool lets the doctor see signs of inflammation in the middle ear. A hearing test may also be done to see if the hearing has been affected.

How Is an Earache Treated?

The doctor may prescribe an oral antibiotic that kills bacteria (such as amoxicilin) and pain relievers (such as acetaminophen). Eardrops containing an antibiotic and maybe steroids to reduce

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swelling may also be used. If a virus (such as the cold or flu virus) is the cause, antibiotics cannot help. Watchful waiting may be proper for some earaches.

Resting is suggested until fever and pain leave. No special diet is needed, but drinking more fluids is important to help thin secretions.

DOs and DON'Ts in Managing an Earache:

✓ **DO** follow your doctor's advice about pain relievers and antibiotics if prescribed.

✓ **DO** hold babies in the sitting position while feeding.

✓ **DO** keep a follow-up appointment for the doctor to recheck the ears.

✓ **DO** use nonaspirin medicines for fever and pain.

✓ **DO** use a heating pad or hot water bottle wrapped in a towel on the ear for pain.

✓ **DO** have your child drink more fluids.

✓ **DO** call your doctor if your child has the earache for more than 2 days after treatment starts.

✓ **DO** call your doctor if your child has a severe headache or fever after treatment starts.

✓ **DO** call your doctor if your child has redness or swelling behind the ear or dizziness.

⦸ **DON'T** let your child swim until the infection clears.

⦸ **DON'T** let your child be near cigarette smoke for long periods. In young children this can increase the chance of more infections.

⦸ **DON'T** put anything in the ear other than drops prescribed by your doctor.

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⦸ **DON'T** give aspirin to children, to avoid the dangerous Reye's syndrome.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Otolaryngology—Head and Neck Surgery Tel: (703) 836-4444 **Web-site: http://www.entnet.org/**
- American Academy of Pediatrics Tel: (847) 228-5005

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MANAGING YOUR

ECHINOCOCCOSIS

What Is Echinococcosis?

Echinococcosis is an infection caused by tiny tapeworms named *Echinococcus.* Tapeworms can infect the liver, lungs, kidneys, bone, or brain. They become cysts that can enlarge and damage these organs.

Echinococcosis is common in many parts of the world, especially the Middle East, in livestock-producing areas. It also occurs in similar areas in Africa, Australia, New Zealand, Europe, and the Americas, including the southwestern United States. In the United States, it's seen mostly in immigrants.

What Causes Echinococcosis?

Four species of the tapeworm cause the illness: *Echinococcus granulosus, Echinococcus multilocularis, Echinococcus oligarthrus,* and *Echinococcus vogeli.* People get the disease by close contact with infected livestock (sheep) and dogs or by bites of infected dogs, wolves, and foxes. Feces of infected animals contain tapeworm eggs. People get infected by eating eggs in contaminated drinking water or foods such as fruits and vegetables.

What Are the Symptoms of Echinococcosis?

People can have the disease for years without showing symptoms, which depend on where the lesions are. A growing mass caused by cysts in the liver, lungs, kidneys, bone, or brain causes symptoms. Cysts are sacs that form around tiny organisms that are going into a resting or spore stage. Cysts can burst and cause allergic reactions such as skin itching and irritation. Pain in the abdomen (belly) or chest, cough that won't go away, weight loss, and weakness can occur. Fever, jaundice (yellow skin), bloody stools, headache, and enlarged liver are other possible

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symptoms.

How Is Echinococcosis Diagnosed?

The health care provider makes a diagnosis from the medical history, physical examination, and laboratory tests. The health care provider must know about recent travel to places where echinococcosis is common. Laboratory tests include antibody assays (such as ELISA) and blood tests. X-ray studies such as computed tomography (CT) and ultrasonography can find cysts, especially in the liver. The health care provider may suggest seeing specialists such as an infectious disease doctor, surgeon, liver specialist, lung specialist, or neurologist.

How Is Echinococcosis Treated?

Treatment for cysts is surgery when possible depending on the size and location of the cysts. Medical treatment consists of high-dose benzimidazole medications (mebendazole, albendazole). If surgery can't be done, draining cysts by using a needle may be tried. Medicines such as 95% ethanol can also be put into the cysts to kill larvae (young worms) in liver cysts and prevent their spread to other parts of the body. Surgical removal or drainage of cysts is followed by treatment with medicines such as albendazole pills.

DOs and DON'Ts in Managing Echinococcosis:

✓ **DO** remember that long-term follow-up is needed because late relapses often occur. Also, medicine must sometimes be taken for the rest of life.

✓ **DO** try to avoid infection. Avoid contact with foxes or wild dogs. Don't eat uncooked fruits or vegetables collected from fields. Give your dogs routine worming treatments. Wash your hands after handling pets. Fence in your garden to keep out animals.

⦸ **DON'T** ignore symptoms. Call your health care provider if your symptoms don't improve or

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they get worse with treatment. Call if you get new symptoms.

⦸ **DON'T** stop taking your medicine or change the dosage because you feel better unless your health care provider tells you to.

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FOR MORE INFORMATION

Contact the following sources:

- Centers for Disease Control and Prevention Tel: (800) 311-3435
- National Institute of Environmental Health Sciences Tel: (919) 541-3345 **Website: http://www.niehs.nih.gov**
- National Heart, Lung, and Blood Institute Information Center Tel: (301) 592-8573 **Website: http://www.nhlbi.nih.gov**
- National Institute of Allergy and Infectious Disease Tel: (301) 496-5717 **Website: http://www.healthfinder.gov**

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MANAGING YOUR

ECLAMPSIA

What Is Eclampsia?

Preeclampsia and eclampsia are complications of pregnancy. Preeclampsia involves high blood pressure, loss of protein in the urine (which means kidney damage), and swelling of the feet that starts after the 20th week of pregnancy. Eclampsia is also called toxemia of pregnancy or seizures of pregnancy. It's the life-threatening occurrence of seizures (convulsions) or coma in a woman with preeclampsia. It can also occur when there's no preeclampsia. The seizures aren't related to a brain disorder. Eclampsia usually occurs after 20 weeks of pregnancy or less than 48 hours after delivery. Eclampsia that occurs before or after those times is called atypical eclampsia.

Eclampsia isn't common. It occurs in 1 in 2000 to 3000 pregnancies. It's much more common in women with preeclampsia. Of those women, 2% to 4% get eclampsia.

What Causes Eclampsia?

The exact cause is unknown. Higher risks are related to having multiple babies or a first-degree relative (sister or mother) who had eclampsia. The occurrence is 3.6% in women with twins. Hypertension (high blood pressure) that's not controlled or that existed before, kidney disease, being 35 or older, being African-American, diabetes, and first pregnancy are other risk factors.

What Are the Symptoms of Eclampsia?

The major symptom is seizures. Seizures usually start as facial twitching and then spread to a general seizure. After the seizure, amnesia, agitation, and confusion occur. Other symptoms are general fluid retention (edema) with rapid weight gain, muscle aches and pains, lasting headache in the back of the head, and stomach pain.

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How Is Eclampsia Diagnosed?

The health care provider makes a diagnosis from the medical history and physical examination. Laboratory tests of blood and urine are done to rule out similar disorders. For headaches, the health care provider may want X-rays including computed tomography (CT) or magnetic resonance imaging (MRI) of the brain to rule other causes of headaches.

How Is Eclampsia Treated?

Because serious permanent harm can come to mothers and babies, eclampsia is usually managed by a team of health care providers. Obstetricians and specialists in care of newborns and critically ill people are important members of the team. Treatment takes place in the hospital. In treating eclampsia, the mother must be stabilized. Oxygen is given, a stable blood pressure must be maintained, and laboratory abnormalities must be corrected. Magnesium is given for seizures. Intravenous fluids and medicines are given to make sure the mother and baby are hydrated and to keep blood pressure steady until delivery. The baby's heart rate will be monitored. The obstetrician will decide after checking the mother and baby when delivery can be performed.

DOs and DON'Ts in Managing Eclampsia:

- ✓ **DO** remember that eclampsia is a serious illness. The mortality rate for women with eclampsia averages 5%.
- ✓ **DO** get early and regular medical care so that there is an early diagnosis and treatment of conditions such as preeclampsia. Treating preeclampsia may prevent eclampsia.
- ⃠ **DON'T** ignore symptoms. Call your health care provider if your symptoms don't improve or they get worse with treatment. Call if you get new symptoms.

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⦸ **DON'T** use any medicines (including over-the-counter and herbal products) without first asking your health care provider.

⦸ **DON'T** smoke or use any tobacco products.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website: http://www.acog.org**

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MANAGING YOUR

ECTOPIC PREGNANCY

What Is an Ectopic Pregnancy?

An ectopic pregnancy is one that develops outside the uterus. The most common place for it is the fallopian tubes, so it's also called a tubal pregnancy. These narrow tubes connect the uterus and ovaries. In a normal pregnancy, the fertilized egg travels through fallopian tubes to the uterus.

Fallopian tubes aren't big enough for a growing embryo, and the pregnancy cannot continue normally. If the pregnancy continues, the tube will stretch and burst. This situation is an emergency. It's life-threatening for the mother.

Less often, an ectopic pregnancy develops in an ovary, the cervix, or the abdomen (belly).

What Causes an Ectopic Pregnancy?

Most often, fallopian tubes are blocked or too narrow, so the egg can't get to the uterus from the ovary. Usually, an infection called pelvic inflammatory disease (PID) causes the blocked or narrow tubes. Other risk factors are having an ectopic pregnancy before, surgery on the fallopian tubes or uterus, using an intrauterine device (IUD) for birth control, and endometriosis. Endometriosis is inflammation caused by the presence of the lining of the uterus outside the uterus.

What Are the Symptoms of an Ectopic Pregnancy?

Symptoms include abnormal bleeding from the vagina, often after a missed period; sharp pain or cramping in the lower abdomen; dizziness or fainting; and an abdomen that is tender to touch.

How Is an Ectopic Pregnancy Diagnosed?

An ectopic pregnancy can be hard to diagnose because symptoms are at first like those of a regular pregnancy. The doctor first does a pregnancy test. The best one is a blood test, so the doctor

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will take a blood sample from a vein.

The doctor may also order ultrasonography of the abdomen. Ultrasonography is similar to an x-ray, because it lets the doctor see the uterus and ovaries inside the body. The doctor may also want to do laparoscopy, done in the hospital with anesthesia. An instrument with a light attached is put into the abdomen for a very close look at the organs. An ectopic pregnancy can be removed at the same time.

How Is an Ectopic Pregnancy Treated?

If the embryo is very small, a drug (methotrexate) can be used to end the pregnancy. The embryo can sometimes be flushed out of the tube by salpingostomy. In this procedure, the tube is surgically opened, so high-pressure fluid can flush out the embryo.

Surgery is often needed and may be a laparoscopy. In a laparoscopy, a very small abdominal cut is made. The fallopian tube is opened, the embryo is removed, and the tube is stitched closed. If the tube cannot be fixed, it's also removed.

For a ruptured fallopian tube, emergency surgery is done, and the tube is almost always removed.

DOs and DON'Ts in Managing Ectopic Pregnancy:

✓ **DO** avoid using an IUD for birth control.

✓ **DO** treat vaginal or pelvic infections right away.

✓ **DO** remember that having one ectopic pregnancy puts you at risk for having others in the future.

⃠ **DON'T** have many sexual partners, have sex without condoms, or get sexually transmitted

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diseases—all risk factors for PID.

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FOR MORE INFORMATION

Contact the following sources:

- National Women's Health Information Center Tel: (800) 994-9662 **Website:** **http://womenshealth.gov/**
- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website:** **http://www.acog.org**

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MANAGING YOUR

ECZEMA

What Is Eczema?

Eczema, or atopic dermatitis, is a skin disease caused by increased sensitivity to the environment. It often runs in families and may occur with hay fever, asthma, and nasal allergies. It cannot be caught. Eczema is very common, affecting 1% of adults and 5% to 10% of children in the United States. In most people, eczema goes away completely by adulthood.

This sensitivity causes inflammation (redness), itching, and scratching. Scratching, however, often makes itching worse and can cause breaks in the skin, increasing risks of infection.

What Causes Eczema?

Causes of eczema or things that make it worse include stress; very hot or cold air; foods including wheat, milk, eggs, and pod vegetables such as beans, peas, and lentils; certain types of cloth; perfumes; dust mites; and animal hair.

What Are the Symptoms of Eczema?

Eczema produces a rash that is red, swollen, itchy, dry, flaky, hard, thick, oozing, and crusty.

How Is Eczema Diagnosed?

The doctor can usually diagnose eczema without doing tests but may order general blood tests and skin testing when the diagnosis is unclear or when trying to determine the cause of the eczema.

How Is Eczema Treated?

Four main ways of treating eczema involve avoiding triggers that cause or worsen it; keeping skin moist with special lotions, soaps, and bath products; treating redness and swelling with anti-inflammatory medicines (corticosteroid creams and pills), tar, and light therapy; and helping stop

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itching with antihistamines, creams, and pills.

Simple, nonmedicated moisturizing cream may be used daily. Steroid creams are for severe itching.

Medicines taken by mouth (pills) to relieve itching include antihistamines, which calm nerve endings in skin. Corticosteroids given as pills can stop inflammation and itching and reduce redness, but they do have side effects (e.g., stomach ulcers, weight gain) when taken long term.

Covering the rash with bandages helps by keeping creams and lotions on the skin and protecting skin from being scratched.

DOs and DON'Ts in Managing Eczema:

✓ **DO** avoid triggers of the rash, including stress.

✓ **DO** moisturize your skin daily, even when you have no symptoms. Use an odor-free oil-based cream or ointment (not lotion), best applied just after bathing while skin is still damp. Use hypoallergenic products when possible. For severe itching, also use a very mild over-the-counter steroid cream (1% hydrocortisone). Bathe with warm, not hot, water and mild soap.

✓ **DO** take all pills prescribed by your doctor. Don't stop taking the medicines unless your doctor approves.

✓ **DO** avoid foods that cause your eczema to worsen.

✓ **DO** exercise daily, but avoid excessive sunlight exposure and skin damage with a sunblock (SPF 15 or greater).

✓ **DO** wash clothing and linens in fragrance-free soap; double rinse when possible.

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✓ **DO** call your doctor if you have signs of infection (worsening redness, pus); wheezing or trouble breathing; or a severe stomachache or bone pain when taking steroid pills.

⃠ **DON'T** let your skin or home become too dry. A home humidifier may help.

⃠ **DON'T** forget your daily skin regimen even if you feel well. Plan ahead for trips by saving some of your usual products.

⃠ **DON'T** drive, cook, or operate machinery while using antihistamines if they make you sleepy.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Dermatology Tel: (866) 503-SKIN (7546) **Website:** **http://www.aad.org**
- Asthma and Allergy Foundation of America Tel: (800) 727-8462 **Website:** **http://www.aafa.org**

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MANAGING YOUR

EHLERS-DANLOS SYNDROME

What Is Ehlers-Danlos Syndrome?

Ehlers-Danlos syndrome is a rare disease that involves connective tissues of the body, which support and bind other tissues. The disorder mainly affects skin and joints but can also affect the eyes and blood vessels. This disorder is inherited—parents pass it to their children.

No cure exists. Most people have normal life spans, but the type that involves blood vessels could mean a shortened life.

What Causes Ehlers-Danlos Syndrome?

The cause is probably a mutation (change or defect) of a gene. At least 11 different types of the syndrome exist. Types I, II, and III make up almost 90% of the cases.

What Are the Symptoms of Ehlers-Danlos Syndrome?

Symptoms are fragile skin that bruises easily and rubbery elastic skin that's very stretchy. Joints are very movable so that a finger can extend back onto the wrist. Hips and other joints can dislocate easily. Arthritis can occur because of repeated joint dislocations. Other possible manifestations are mitral valve prolapse (leaking of the mitral heart valve), flat feet, and curved spine.

Complications include slow and poor healing of cuts or wounds. In type IV syndrome, muscular walls of the arteries, intestine, and bladder can weaken and burst. Bursting of blood vessels such as the aorta can cause sudden death. The disorder can cause aneurysms (dilations of arteries), so the abdominal aorta should be screened yearly, usually with an ultrasound (sonogram).

How Is Ehlers-Danlos Syndrome Diagnosed?

The doctor makes a diagnosis by a physical examination and a family history of the disorder. Genetic and biochemical tests are available for some syndrome types. Sometimes a skin biopsy

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is done. In a biopsy, the doctor gets a small piece of skin with a needle and checks it with a microscope.

How Is Ehlers-Danlos Syndrome Treated?

Treatment is supportive and symptomatic, so affected joints are braced, protected, and supported. No treatment can reverse the disorder. Surgery must be done carefully, because people heal poorly, and connective tissues that hold the stitches are defective. If an aneurysm is found, the doctor may suggest surgery or close monitoring, depending on its size.

DOs and DON'Ts in Managing

Ehlers-Danlos Syndrome:

✓ **DO** understand that in type IV syndrome, pregnancy should be discussed before you try to conceive. Bleeding, bursting of the uterus, and tearing of internal tissues can complicate the pregnancy.

✓ **DO** use sunscreen.

✓ **DO** get yearly eye examinations. Nearsightedness is common, and you may need prescription glasses.

✓ **DO** call your doctor if you have a family history of this syndrome.

✓ **DO** call your doctor if you need a referral to specialists in this syndrome.

✓ **DO** call your doctor if you have bleeding, sudden abdominal pain, visual problems, or joint pain, swelling, or deformity.

⊘ **DON'T** participate in competitive sports. Contact sports, weightlifting, and exerting yourself

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for long periods can cause joint injury, dislocations, and damage to body structures. Talk to a physical therapist about muscle-strengthening exercises.

⦸ **DON'T** miss appointments. Don't be afraid to ask your doctor for another opinion from a specialist in this syndrome.

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FOR MORE INFORMATION

Contact the following sources:

- Ehlers-Danlos National Foundation Tel: (213) 368-3800 **Website: http://www.ednf.org**
- National Organization for Rare Disorders Tel: (800) 999-6673 **Website: http://www.rarediseases.org**

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MANAGING YOUR

ELBOW DISLOCATION

What Is Elbow Dislocation?

The elbow is a complex joint that is really three joints in one. Dislocation happens when bones of these joints are pulled out of place and get stuck. Bones of the upper and lower arm no longer come together as they should, so normal elbow movements aren't possible.

What Causes Elbow Dislocation?

The cause is usually a fall on an outstretched arm. People may also break one or more of the elbow bones, hurt ligaments that hold the bones in place, or hurt nearby nerves or blood vessels.

Partial elbow dislocation (called nursemaid's elbow) sometimes happens in small children, usually younger than 4. An adult pulling the child up by the arm can cause it.

What Are the Symptoms of Elbow Dislocation?

Symptoms include swelling and pain. Moving it is hard or impossible. The elbow may have an unusual shape, or the lower arm may look longer or shorter than normal.

Nursemaid's elbow usually causes only mild pain and little or no swelling.

How Is Elbow Dislocation Diagnosed?

The doctor can usually tell from a physical examination whether the elbow is dislocated. The doctor may also use x-rays, computed tomography (CT), or magnetic resonance imaging (MRI) to look at the elbow.

How Is Elbow Dislocation Treated?

The joint needs to be put back into place. The doctor will do this by placing the arm in position and putting pressure in the right direction. A click can be heard or felt when the joint goes back into place. A complex injury may need surgery to repair it.

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After treatment, the elbow will be put in a splint to stop it from moving. Simple dislocations normally need splinting for 5 to 7 days; complicated dislocations may take longer. After this, it's important to get the elbow moving again. Exercises will help, as may sessions with a physical therapist. Playing sports can resume as before, but elbow pads may help protect the joint.

It may be 3 to 6 months before the elbow can move completely freely. Some people have a permanent small loss of movement, especially if the elbow was broken as well as dislocated. The elbow may not extend as far as before, but this shouldn't affect work or everyday tasks.

A partial elbow dislocation (nursemaid's elbow) usually goes back into place easily. X-rays and painkillers aren't usually needed. The child should be able to use the arm freely and painlessly as soon as it's back in place. Some doctors suggest keeping it in a sling for a week. Children can have partial dislocation repeatedly, but usually grow out of this condition. Don't pull hard on a child's arm. Rarely, surgery may be used to stop repeated dislocations.

DOs and DON'Ts in Managing Elbow Dislocation:

✓ **DO** exercises suggested by your doctor or physical therapist. This will help your chances of regaining full movement in your elbow.

⃠ **DON'T** remove the splint before your doctor tells you to.

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FOR MORE INFORMATION

Contact the following source:

- The American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website:** **http://www.aaos.org**

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IDENTIFYING AND UNDERSTANDING

ELDER ABUSE

What Is Elder Abuse?

Elder abuse can mean abuse of older people in the home, abuse in an institution, and self-neglect or self-abuse. It can involve physical abuse, physical neglect, psychological abuse, and material abuse. Physical abuse consists of assaults, rough handling, burns, sexual abuse, and confinement. Physical neglect includes dehydration, malnutrition, poor hygiene, letting people wear odd or soiled clothing, giving the wrong medicines, and not getting medical care when needed.

Psychological abuse involves verbal or emotional abuse, threats, and isolation or confinement. Material abuse means withholding, misuse, or theft of money, and withholding means of living.

Elder abuse has become more common in the last 20 years. In the United States, about 4% of people older than 65 (about 1 million people) are abused or neglected. These people are usually older than 75, women, white, and widowed. They have behavioral problems, are incontinent, are very noisy or shout (especially at night), have many physical complaints, and are socially isolated so that abuse is less likely to be noticed. Those more likely to be abused are totally dependent on a caregiver.

How Is Elder Abuse Identified?

Abusers of elderly people are usually married to them. In about 25% of cases, the abuser is an adult child, living in the home, who is dependent on the older person. Elder abuse occurs in all races and economic groups.

To find elder abuse, there should first be a suspicion that it's occurring. People who often have falls and injuries, have many problems with their medicines, and lose weight at home but

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gain weight in the hospital may be abused. Unexplained leakage of urine (incontinence) and body odor may be signs of elder neglect.

How Is Elder Abuse Treated?

Treatment involves fixing medical problems that may result from the abuse. Contacting Adult Protective Services (APS) or hospitalizing for urgent medical care may be needed. The abused should be supported and helped, and stress in the environment should be reduced. Sometimes, legal charges must be filed, and the elderly person must be removed from the home.

Elderly people are often vulnerable and dependent and can be abused easily. Abuse can be prevented by being aware that the problem exists, sharing responsibility for caring for an elderly parent, treating medical or psychiatric problems in the elderly person, and having more social contacts for elderly people. Everyone should check on elderly people in neighborhoods and families to prevent mistreatment.

DOs and DON'Ts in Managing Elder Abuse:

✓ **DO** realize that help is available. APS can check into reports of elder abuse and help victims and their families with treatment and protective services.

✓ **DO** call to report abuse. Calls are usually confidential.

⃠ **DON'T** forget that the APS, the Area Agency on Aging, or the county Department of Social Services can investigate elder abuse and neglect. If investigators find abuse or neglect, they can arrange for services to help protect the victims.

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Contact the following sources:

- Often people who want to help older relatives or friends don't live near them. Long-distance caregivers can call a nationwide toll-free Eldercare Locator number (800-677-1116) to locate services in the community in which the elder lives.
- National Center on Elder Abuse **Website:**

http://www.ncea.aoa.gov/NCEAroot/Main_Site/Index.aspx

- National Association of Area Agencies on Aging Tel: (202) 872-0888 **Website:**

http://www.n4a.org

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MANAGING YOUR

ELECTRICAL INJURY

What Is an Electrical Injury?

An electrical injury (also called electric shock) is an injury resulting from contact with an electric current. How bad the injury is depends on the strength of the current, its path through the body, and how long the contact with it was. Burns, problems with the heart and brain, and other injuries to the body can occur. People who survive an electric shock usually recover, but if the shock was severe, they may have lasting health problems.

What Causes an Electrical Injury?

Electrical injuries are usually caused by accidents with electrical appliances, wiring, or machinery. Sometimes a lightning strike can cause these injuries.

What Are the Symptoms of an Electrical Injury?

Symptoms depend on how bad the shock was. Immediate symptoms include numbness, tingling, or pain; burns; confusion or loss of memory; problems speaking; shortness of breath; and headache. Others are seizures, paralysis (inability to move), hearing loss, and loss of consciousness. Broken bones can result from a fall after the shock.

Long-term effects of more serious electrical injuries include burns, psychological problems, altered state of mind, and eye, heart, and internal injuries.

How Is an Electrical Injury Diagnosed?

The doctor makes a diagnosis from the medical history, as well as how the electrical injury occurred. The doctor will do a physical examination, blood tests, and maybe a urinalysis. Other tests may be done, depending on how severe the shock was, including chest X-ray, electrocardiography (ECG), and brain computed tomography (CT). The ECG records the heart's

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rhythm.

How Is an Electrical Injury Treated?

Treatment depends on the seriousness of the injury. Sometimes, a hospital visit is needed. Dressings are applied to burns. Oxygen is given for breathing difficulties. Broken bones will be treated. Fluid and medicines, either by mouth or through a vein, may be given.

DOs and DON'Ts in Managing Electrical Injury:

✓ **DO** follow your doctor's directions.

✓ **DO** tell your doctor about your other medical problems.

✓ **DO** tell your doctor about your medicines, including prescription and over-the-counter drugs.

✓ **DO** tell your doctor if you're pregnant or breastfeeding.

✓ **DO** exert caution around electrical equipment, in the home and at work.

✓ **DO** make sure your hands are dry before you use an electrical appliance or turn on a switch.

✓ **DO** disconnect electrical appliances before trying to repair or fix them.

✓ **DO** make sure that small children aren't exposed to electrical hazards. Use plastic safety covers in electrical sockets.

✓ **DO** unplug electrical appliances once you finish with them, especially hairdryers and electric shavers. Put them out of reach of children.

⦸ **DON'T** turn on an electrical appliance or a switch with wet hands.

⦸ **DON'T** give electric blankets to children younger than 2 years old or to those who wet the

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bed.

⦸ **DON'T** use a frayed or damaged electrical cord.

⦸ **DON'T** use extension cords or space heaters in the bathroom.

⦸ **DON'T** use electrical appliances such as hairdryers or radios near full bathtubs or sinks.

⦸ **DON'T** try to fix household wiring yourself. Get a qualified electrician for this.

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FOR MORE INFORMATION

Contact the following sources:

- U.S. Department of Labor, Occupational Safety & Health Administration **Website:** **http://www.osha.gov/SLTC/electrical/index.html**
- US Consumer Product Safety Commission **Website:** **http://www.cpsc.gov/cpscpub/pubs/elec_sfy.html**
- Lightning Injury Research Program Department of Emergency Medicine (M/C 724) University of Illinois at Chicago Tel: (312) 413-7489
- Centers for Disease Control and Prevention **Website:** **http://www.cdc.gov/niosh/topics/electrical/**

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MANAGING YOUR

EMPHYSEMA

What Is Emphysema?

Emphysema is a chronic disease of the lungs. It causes decreased lung function and swelling (inflammation) and irritation of airways. Emphysema often occurs with chronic bronchitis (together these two conditions are called *chronic obstructive pulmonary disease*, or COPD).

The lungs consist of two main parts: airways (bronchial tubes) and air sacs (alveoli). During a breath, air passes through airways and into air sacs, where oxygen enters the blood. In emphysema, air sacs become larger, their walls become stiff, and the sacs cannot hold enough air.

What Causes Emphysema?

The main cause is cigarette smoking or exposure to second- hand smoke. Cigarette smoke destroys lung tissue and irritates airways.

Other risk factors include asthma, air pollution, and family history of emphysema.

What Are the Symptoms of Emphysema?

The main symptom is shortness of breath. Others are persistent cough, wheezing, decreased ability to exercise or do usual daily activities, and weight loss.

How Is Emphysema Diagnosed?

The doctor will talk about your symptoms with you and do a physical examination, especially of the chest. He or she will listen to the lungs with a stethoscope to see whether breathing is normal.

A monitor (pulse oximeter) may be used to measure the blood's oxygen level.

Simple blood tests check general health. Some people may need blood tests for levels of oxygen and carbon dioxide in an artery or for alpha-1-antitrypsin enzyme deficiency, a risk factor for emphysema.

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A chest x-ray will be done to look at the lungs. Lung function testing (spirometry) may be done to tell whether the disease is emphysema or another lung disorder (e.g., asthma). The testing involves blowing into a tool to measure how much and how fast the lungs blow out air.

How Is Emphysema Treated?

Treatment depends on the severity of the emphysema. Severe disease may need treatment in the hospital.

The lifestyle change of stopping smoking is the most important step to slow the progress of the disease or even improve it.

Medicines that may help include bronchodilators and corticosteroids. Bronchodilators, usually given by inhalers, cause airways to open. Corticosteroids work by reducing inflammation. They may be given by inhalers or in pill form.

Oxygen may be given in a hospital emergency department. In severe cases, it may be provided in tanks for home use.

Antibiotics may be prescribed if a chest infection is suspected.

Surgery may become an option for advanced emphysema in rare cases.

DOs and DON'Ts in Managing Emphysema:

✓ **DO** quit smoking and avoid a smoky environment.

✓ **DO** ask your doctor and support groups for help with quitting smoking.

✓ **DO** visit your doctor regularly.

✓ **DO** take your medicines as prescribed.

✓ **DO** exercise regularly as tolerated.

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✓ **DO** get a flu shot every year and a pneumonia vaccination every 5 years.

✓ **DO** contact your doctor about new or worsening symptoms.

⃠ **DON'T** delay going to the emergency department if you become very short of breath or notice your tongue, fingernails, skin, or lips are turning blue.

⃠ **DON'T** stop taking your medicines without checking with your doctor.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Lung Association Tel: (800) LUNG-USA **Website: http://www.lungusa.org**
- National Lung Health Education Program Tel: (303) 839-6755 **Website:**

http://www.nlhep.org

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CARING FOR YOUR CHILD WITH

ENCOPRESIS

What Is Encopresis?

Encopresis is passage of stools (bowel movements) or feces on places other than the toilet by children past the toilet training age (4 years old). These places can be clothing or floors. More boys than girls are affected. It can be involuntary or voluntary. To make a diagnosis of encopresis, it must occur at the rate of at least one episode a month for 3 months or more. It cannot be due only to a substance (for example, a laxative) or other medical conditions. It most commonly occurs in children with constipation. "Primary encopresis" means that the child never mastered toilet training. In "secondary encopresis" the child was toilet trained for at least 1 year or more before the development of encopresis.

What Causes Encopresis?

The cause is unknown, but encopresis may occur after constipation, illness, or change in diet. Stressful events such as birth of a sibling, starting a new school, and moving can be involved. Too much stress during toilet training can lead to anxiety, so-called pot phobia, and encopresis.

The three types of encopresis (which can overlap) include voluntary control (children choose inappropriate places), true failure to control bowels, and soiling caused by liquid feces (from constipation and overflow or from anxiety). In the first type, encopresis tends to be temporary. Children may put feces in places (such as furniture or walls) to cause anger. In the second group, medical illness may stop children from learning to control their bowels. In the third group, children may have a medical condition that causes diarrhea.

How Is Encopresis Diagnosed?

The doctor will do a medical examination and laboratory and x-ray studies to rule out other dis-

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eases. Psychiatric, psychosocial, and family interviews will get information about the child's development, behaviors, and stressful events.

How Is Encopresis Treated?

Treatment involves four stages: the first (assessment) will find out whether encopresis is primary or secondary and rule out physical conditions.

The second involves advice, with education about diet, toileting, and parental punishment.

The third stage focuses on toilet training, eating a high-fiber diet, and toileting after meals for a maximum of 15 minutes. Laxatives and enemas (bisacodyl) may be used. The fourth stage consists of biofeedback, but only for children who relapse after training.

Other treatments include behavior therapy such as positive reinforcement and family therapy to shift the family's focus away from encopresis. Behavior therapy plus laxatives works well, in about 75% of cases, in reducing encopretic episodes. Biofeedback for control of the external sphincter muscle also works relatively well.

A healthy, high-fiber diet is often suggested, with bran added to cereals, fruit, and milkshakes.

DOs and DON'Ts in Managing Encopresis:

✓ **DO** avoid constipation by feeding a high-fiber diet and having your child drink plenty of water.

✓ **DO** understand that relapses are normal, so don't get discouraged and be patient.

✓ **DO** call your doctor if your child has a fever, begins to have nausea or vomiting, or has especially hard stools.

✓ **DO** call your doctor if your child has diarrhea and becomes really dehydrated.

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✓ **DO** call your doctor right away if you see blood in your child's stool or blood around the rectum.

⦸ **DON'T** start toilet training too early, and don't be too forceful. Use positive reinforcement (rewards) and encouragement.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Pediatrics Tel: (847) 434-4000 **Website: http://www.aap.org**
- American Psychiatric Association Tel: (888) 357-7924 **Website: http://www.psych.org**

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MANAGING YOUR

ENDOCARDITIS

What Is Endocarditis?

Endocarditis is inflammation, with or without infection, that affects the inside lining of the heart and heart valves.

What Causes Endocarditis?

Bacteria or fungi are the usual cause. Bacteria include *Staphylococcus* and *Streptococcus*. The bacteria or fungi can get to the heart by entering the bloodstream from infections somewhere else in the body (e.g., urinary or gastrointestinal tract or skin). Surgical or dental procedures can also let these organisms reach the heart.

What Are the Symptoms of Endocarditis?

Symptoms include fever, fatigue, weakness, chills and night sweats, muscle and joint pain, and heart murmur. Later symptoms are swelling of feet and legs and shortness of breath with an irregular heartbeat.

How Is Endocarditis Diagnosed?

The doctor can make a diagnosis by taking a medical history, doing a physical examination, and getting blood cultures and an echocardiogram (ultrasound of the heart). The doctor usually finds a new heart murmur due to the damaged heart valve at the physical.

How Is Endocarditis Treated?

Intravenous antibiotics, usually given for 4 to 6 weeks, are used to get rid of the infection. A home health nurse will help with intravenous antibiotic treatment at home. Nonaspirin medications such as acetaminophen can be used for fever and minor pain. A regular diet can be followed. Fluid intake should be increased for fever. Good dental hygiene is needed to prevent in-

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fection.

Another goal is to treat complications (e.g., congestive heart failure or blood clots). The doctor may suggest surgery in some cases. Surgery may be needed for congestive heart failure that doesn't respond to usual therapy, endocarditis caused by fungi, recurrent blood clots, abscesses leading to heart rhythm abnormalities, and lasting high fever or sepsis after 72 hours of antibiotics.

DOs and DON'Ts in Managing Endocarditis:

✓ **DO** take your antibiotics until they're gone. Endocarditis may be prevented by using antibiotics before dental procedures if you have a history of prior infectious endocarditis, heart transplant, certain congenital heart diseases, or prosthetic valves.

✓ **DO** use nonaspirin drugs for fever and minor pain.

✓ **DO** increase fluid intake, especially during fever.

✓ **DO** resume normal activity slowly as your strength allows.

✓ **DO** see your dentist regularly. Use a soft-bristled toothbrush.

✓ **DO** call your doctor if, after your treatment, you have fever, loss of appetite or weight gain without diet changes, blood in your urine, chest pain, shortness of breath, or sudden weakness in muscles of your face or limbs.

⊘ **DON'T** skip doses or stop taking antibiotics until you finish a complete treatment course, or until your doctor tells you to stop.

⊘ **DON'T** try to keep your normal schedule; you need rest for a full recovery.

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⦸ **DON'T** have dental work or surgical procedures without telling your doctor of your history of endocarditis.

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FOR MORE INFORMATION

Contact the following source:

- National Heart, Lung, and Blood Institute Tel: (301) 592-8573 **Website:** **http://www.nhlbi.nih.gov**

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MANAGING YOUR

ENDOMETRIAL CANCER

What Is Endometrial Cancer?

The uterus, or womb, lies between the bladder and rectum. The inner layer of the uterus is the endometrium. Endometrial cancer is cancer of this layer.

Untreated endometrial cancer spreads and causes problems in the pelvic area, including bowel and urinary disorders. If the spread continues, swollen glands (lymph nodes), an abdominal (belly) mass, and eventually liver, lung, and bone disease can result.

More than 30,000 new cases cancer are diagnosed each year in the United States.

What Causes Endometrial Cancer?

The cause is unknown. It most often occurs in women between 55 and 70 years old, but can occur in younger women before they go through menopause. Women at increased risk are overweight, have diabetes, have never been pregnant or given birth, or took estrogen for effects of menopause.

What Are the Symptoms of Endometrial Cancer?

Bleeding from the vagina after menopause is the main symptom. For women who haven't gone through menopause, abnormal vaginal bleeding—heavy bleeding, minimal bleeding, bleeding between menstrual cycles—is the main symptom.

How Is Endometrial Cancer Diagnosed?

The doctor will ask about symptoms and do a physical examination, including a pelvic examination. Vaginal ultrasonography may also be done.

To confirm the diagnosis, the doctor may take a biopsy specimen from the uterus by dilation and curettage (D&C). To do this, the cervix is dilated (widened) and a curette (a small spoon-

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shaped instrument) is inserted into the uterus to remove tissue.

The cancer is then classified into stages. Staging tells whether and how much the cancer spread. Stage I means tumor is only in the uterus; stage II, tumor invaded the cervix; stage III, tumor involved the vagina, ovary, or abdomen; and stage IV, tumor invaded the bladder and intestine. Blood tests, chest x-rays, and computed tomography (CT) of the abdomen and pelvis are studied to look for cancer spread.

How Is Endometrial Cancer Treated?

Surgery, radiation, hormones, and chemotherapy are used for treatment, which depends on the cancer's stage. Most endometrial cancers are diagnosed in early stages (I or II), and an operation to remove the uterus, fallopian tubes, and ovaries (hysterectomy and bilateral salpingo-oophorectomy) is usually suggested. Radiation may then be given if needed. Both surgery and radiation have side effects.

Hormones or chemotherapy may be recommended for cancer that has spread or returned after other treatment. Both these treatments also have side effects.

DOs and DON'Ts in Managing Endometrial Cancer:

✓ **DO** remember that hysterectomy doesn't affect sexual intercourse and desire.

✓ **DO** remember you won't have periods. You can have hot flashes, sweating, and other symptoms if your ovaries are surgically removed or hurt by radiation.

✓ **DO** keep follow-up doctor visits during and after treatment to watch for treatment responses or cancer recurrence.

✓ **DO** call your doctor if you have vaginal bleeding or abnormal vaginal discharge.

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✓ **DO** ask your doctor about services and support groups for emotional support.

✓ **DO** call your doctor if you have treatment side effects.

⃠ **DON'T** ignore vaginal bleeding after menopause.

⃠ **DON'T** ignore abnormal vaginal bleeding (excess, between periods) before menopause.

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FOR MORE INFORMATION

Contact the following sources:

- American Cancer Society Tel: (800) 227-2345 **Website: http://www.cancer.org**
- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website: http://www.acog.org**

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MANAGING YOUR

ENDOMETRIOSIS

What Is Endometriosis?

The uterus (womb) is between the bladder and rectum. The inner layer of the uterus is the endometrium. In the disorder endometriosis, the kind of tissue that usually lines the inside of the uterus is present in other places. The most common places are ovaries, fallopian tubes, and lining of the pelvis (peritoneum), especially behind the uterus.

Hormones that affect the uterine lining also affect the extra tissue. Each month, during a period, this extra lining also bleeds, which causes pain. This blood can't go anywhere, so cysts and scar tissue form.

About 5% to 15% of women of childbearing age get endometriosis. It can be managed but not prevented.

What Causes Endometriosis?

The cause is unknown. It may run in families. Scar tissue from endometriosis around pelvic organs can cause pain and infertility by blocking fallopian tubes. This scar tissue can sometimes block the intestines (bowel) or ureters (tubes that connect kidneys and bladder).

What Are the Symptoms of Endometriosis?

Endometriosis may cause no symptoms and be found only because of abdominal or pelvic surgery for something else. Symptoms include abdominal (belly) cramps during periods that are worse than normal, dull constant pain in the lower abdomen and back, pain during sex or bowel movements, a period more than once a month, heavier periods that last longer than usual, and trouble getting pregnant.

How Is Endometriosis Diagnosed?

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The doctor will do a pelvic examination and a pregnancy test. The doctor may also do blood and urine tests to see if infection may be causing symptoms. Ultrasound, CT, or MRI may also be done to show organs inside the body. However, laparoscopy is the only way to have a definite diagnosis. In this operation, a telescope-like tool is put through a small cut into the abdomen to see the extra tissue. Laparoscopy can also be used as treatment. Biopsy samples (small pieces of tissue) may be taken for the diagnosis.

How Is Endometriosis Treated?

The treatment chosen depends on symptoms, the woman's age, and if children are wanted.

Medicines work well. Pills for pain include nonsteroidal antiinflammatory drugs (NSAIDs) such as ibuprofen. Birth control pills or other hormones can help relieve symptoms.

In laparoscopic surgery, another treatment, the doctor can remove some endometriosis tissue by cauterizing (burning) or using a laser. Endometriosis can return, but this surgery may reduce pain and help chances of getting pregnant.

Surgery to remove the uterus and ovaries (total hysterectomy) is done only if the woman is older and doesn't want to have more children.

Problems can continue until menopause (change of life) and estrogen levels fall. At that time, lower levels of this hormone won't stimulate endometriosis.

DOs and DON'Ts in Managing Endometriosis:

✓ **DO** take pills as instructed by your doctor.

✓ **DO** see your doctor regularly.

✓ **DO** exercise and take ibuprofen or similar drugs to help relieve painful periods and cramps.

✓ **DO** call your doctor if treatment isn't helping symptoms.

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✓ **DO** call your doctor if you cannot take your medicine or birth control pills.

⃠ **DON'T** forget to keep follow-up doctor appointments.

⃠ **DON'T** take herbal therapies without checking with your doctor.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- National Women's Health Information Center Tel: (800) 994-9662
- American Society of Reproductive Medicine Tel: (205) 978-5000 **Website:** **http://www.asrm.org**
- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website:** **http://www.acog.org**

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MANAGING YOUR

ENLARGED PROSTATE

About the Prostate

The prostate is a walnut-sized reproductive gland in men. It produces a fluid that is a major part of the semen. It lies in front of the large intestine and below the urinary bladder (which stores urine). It surrounds the urethra, the tube that carries urine out of the body. The prostate often enlarges as a man ages.

What Is Benign Prostatic Hyperplasia (BPH)?

BPH is the common condition of enlargement of the prostate gland. Benign means that BPH is not cancer. It is also not contagious or sexually transmitted.

What Causes BPH?

The cause is unknown, but aging and male hormones are related to BPH.

What Are the Symptoms of BPH?

Symptoms are rare before age 40 but occur in more than half of men in their 60s and as many as 90% in their 70s and 80s. Symptoms are related to difficulty urinating, including weak urine stream, urgency (need to urinate quickly), leaking or dribbling urine, and more frequent urination, especially at night.

Severe BPH can cause serious problems, such as infections, bladder or kidney damage, and incontinence. If bladder damage is permanent, BPH treatment may not work. When BPH is found earlier, it is less likely to cause serious complications.

How Is BPH Diagnosed?

Diagnosis begins with a medical history and doctor's examination of the prostate with the finger (digital rectal examination). Blood and urine tests and a sonogram (ultrasound) may be done to

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evaluate for incomplete bladder emptying due to obstruction from an enlarged prostate and to exclude other causes of the symptoms. A blood test called prostate-specific antigen (PSA) may be used to help rule out prostate cancer. The doctor should review risks and benefits of this controversial test.

How Is BPH Treated?

Most people with symptoms require treatment at some point. Effective treatments range from conservative, which means simply drinking less fluid at night, to taking medicines or having surgery.

Medicines include alpha-blockers such as tamsulosin to help urine flow and reduce blockage in the bladder. Other medications, such as finasteride, inhibit production of the hormone testosterone, so the prostate shrinks or stops growing. Over-the-counter drugs include saw palmetto, but their effectiveness has not been proven.

If drugs don't work, surgery can be tried. These operations range from slightly invasive to very invasive. The operation called TURP (transurethral resection of the prostate) is used for most surgeries for BPH. Other operations include transurethral microwave therapy (uses microwave heat), transurethral needle ablation (radiofrequency therapy, uses radio waves), and laser surgery.

DOs and DON'Ts in Managing BPH:

✓ **DO** understand that common drug side effects include lightheadedness and dry mouth.

✓ **DO** tell your doctor about any over-the-counter medicines, herbs, or supplements you take. These may cause symptoms.

✓ **DO** realize that surgical complications may include urinary incontinence, erection problems,

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and bleeding.

✓ **DO** understand that 10% to 30% of men with BPH also have prostate cancer.

✓ **DO** call your doctor if you cannot urinate or have blood in your urine.

⃠ **DON'T** forget that caffeine and certain prescription drugs (e.g., for colds and allergy) may cause irritating prostate symptoms.

⃠ **DON'T** forget to discuss with your doctor the risks and benefits of operations and use of the PSA blood test for diagnosing prostate cancer.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Urological Association Tel: (401) 727-1100 **Website: http://www.auanet.org**
- National Kidney and Urologic Diseases Information Clearinghouse **Website:**

http://www.niddk.nih.gov

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MANAGING YOUR

EOSINOPHILIC ESOPHAGITIS

What Is Eosinophilic Esophagitis?

Eosinophilic esophagitis (EE) is an allergic inflammatory disease. In EE, the esophagus (tube connecting the mouth and stomach) has too many eosinophils. Inflammation (redness, swelling) of the esophagus results. Eosinophils, a kind of white blood cells, are an important part of the immune (infection-fighting) system. Foods, airborne allergens, and acid reflux can cause too many eosinophils.

Children and adults of any ethnic group can get EE. Almost three-fourths of people affected are white males, often young boys and men. It can run in families.

What Causes Eosinophilic Esophagitis?

The exact cause isn't known. EE is more common in people with other allergic conditions such as asthma, hay fever, food allergies, and dermatitis than in people without allergies. It's most often related to allergies to foods, usually milk, soy, eggs, wheat, corn, chicken, and beef.

What Are the Symptoms of Eosinophilic Esophagitis?

Symptoms depend on age. Adults usually have trouble swallowing solid food (dysphagia), or less often, have solid food stick in the esophagus (food impaction). Children may have pain in the abdomen (belly), nausea, vomiting, coughing, chest pain, diarrhea, or failure to thrive (poor growth, weight loss). Heartburn often occurs, especially in older children and adults. People can also have reflux that doesn't respond to usual medicines. About half of people have other allergic symptoms.

How Is Eosinophilic Esophagitis Diagnosed?

The doctor uses a medical history and upper endoscopy and biopsy for diagnosis. In endoscopy,

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the doctor puts a long, narrow tube (endoscope) with a light source and camera into the esophagus. The doctor checks for inflammation, horizontal rings, vertical furrows (narrow, long channels), and white spots. In a biopsy, a microscope is used to look at tissue samples. EE can be confused with gastroesophageal reflux disease (GERD).

How Is Eosinophilic Esophagitis Treated?

Food allergy testing (skin pricks) is often done to guide treatment. In elimination diets, problem foods are avoided. These foods are often dairy, eggs, wheat, soy, nuts, and fish. Foods are then slowly added back to the diet. A dietitian or nutritionist can help make sure that enough nutrients are eaten.

If special diets don't work, medicines such as steroids can help. Steroids can be given in pills, liquids, or sprays. They include oral prednisone tablets, topical swallowed fluticasone spray, and swallowed budesonide.

Children do better with dietary therapy. Drugs are more commonly used in adults.

Other treatments include asthma medicines, acid-blocking drugs, and dilating (stretching) the esophagus (for severe disease).

DOs and DON'Ts in Managing Eosinophilic Esophagitis:

✓ **DO** learn about EE. As with food allergies, education is a key to a full and productive life.

✓ **DO** follow your special diet carefully. Nutritionists and dietitians can help.

✓ **DO** manage your stress. Increased stress can worsen symptoms. Try deep breathing, taking regular walks, meditating, or going to therapists, counselors, or massage therapists.

⃠ **DON'T** be afraid to ask for help from your doctor, family, or friends. Consider joining a support group.

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⦸ **DON'T** eat foods that make your symptoms worse.

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FOR MORE INFORMATION

Contact the following sources:

- National Digestive Diseases Information Clearinghouse E-mail: nddic@aerie.com

  Website: http://www.niddk.nih.gov/health/digest/nddic.htm

- American College of Gastroenterology Tel: (703) 820-7400 **Website:**

  http://www.acg.gi.org

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MANAGING YOUR

EPIDIDYMITIS

What Is Epididymitis?

Epididymitis is an infection or inflammation (swelling) of the epididymis. The epididymis is a tube at the upper part of each testicle that carries sperm to the tube called the vas deferens, which takes the sperm out. Epididymitis is curable with treatment.

What Causes Epididymitis?

The cause is usually a bacterial infection or long-term pressure on the epididymis. Bacteria from a urinary tract or prostate infection can spread to the testicles. In sexually active men, a sexually transmitted disease (STD) is often the cause. Pressure epididymitis occurs after sitting too long, such as when driving a car or riding a bicycle for long periods. Injury and urinary tract blockage are other causes. The cause is often unknown.

What Are the Symptoms of Epididymitis?

Symptoms include pain, swelling, and tenderness in the scrotum; a burning feeling when urinating; discharge from the penis; fever; and pain during sex. Swelling may last for several days.

How Is Epididymitis Diagnosed?

The doctor will ask about symptoms and examine the penis and scrotum. The doctor may order a urinalysis and a blood test to look for infection. The doctor may also take a sample of discharge from the penis, to be checked with a microscope. A sonogram (ultrasound) of the painful testicle may be done to exclude other causes of the pain and swelling.

How Is Epididymitis Treated?

Antibiotics will be given for a bacterial infection. Over-the-counter drugs, such as ibuprofen, can help pain. Stronger medicine may be needed for moderate to severe pain. Scrotal rest is advised.

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This means getting pressure off this area by leaning back, as if sitting in a lawn chair. An ice pack on the area will help swelling and discomfort. A rolled towel under the scrotum helps support and elevate it and reduces swelling and pain. Pain usually begins to go away 1 to 3 days after starting antibiotics or scrotal rest.

Sex should be avoided for several days after symptoms go away.

In rare cases, surgery may be needed for complications of infection.

DOs and DON'Ts in Managing Epididymitis:

✓ **DO** rest until fever, swelling, and pain improve.

✓ **DO** put a soft, rolled towel under the scrotum while in bed.

✓ **DO** apply an ice pack to the scrotal area.

✓ **DO** wear an athletic supporter when your activity increases.

✓ **DO** take antibiotics until they are finished.

✓ **DO** take nonprescription pain medicine.

✓ **DO** use condoms to prevent STD infection.

✓ **DO** call your doctor if you get a high fever during treatment, if nonprescription drugs don't control your pain, or if you become severely constipated.

✓ **DO** call your doctor if your symptoms don't improve in 3 or 4 days after you start treatment.

⦸ **DON'T** skip doses or stop your antibiotics even if you feel better.

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⦸ **DON'T** have sex for several days after symptoms go away.

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FOR MORE INFORMATION

Contact the following source:

- American Urological Association Tel: (866) 746-4282 **Website: http://www.auanet.org**

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MANAGING YOUR

EPIGLOTTITIS

What Is Epiglottitis?

Epiglottitis is an inflammation (swelling, pain, redness) of the epiglottis. The epiglottis is a small flap of tissue over the opening of the windpipe (trachea). It covers the windpipe during swallowing. The windpipe connects the pharynx or larynx (voicebox) to the lungs. Epiglottitis causes the epiglottis to swell and block air from getting to the lungs. Children from 2 to 12 years old are usually affected, but adults who don't have immunity to the bacterium named *Haemophilus influenzae* can develop it. Prevention is available with the *H. influenzae* type B (Hib) vaccine.

Epiglottitis can be mistaken for croup, but it's much more dangerous. It's a life-threatening medical emergency.

What Causes Epiglottitis?

The usual cause in children is bacteria (*H. influenzae* or sometimes streptococcus). Rarer causes include burns from hot liquids, or direct injury to the throat.

What Are the Symptoms of Epiglottitis?

Epiglottitis starts suddenly. Symptoms in children include severe sore throat, difficult and painful swallowing, fever, and drooling caused by swallowing problems. Children often tilt their neck back and lean forward, as they try to breathe in more air. They also are anxious and restless. In adults, symptoms may develop more slowly. Adults also have a muffled voice with hoarseness and harsh, raspy breathing.

How Is Epiglottitis Diagnosed?

For diagnosis, the doctor will use the medical history and X-rays of the epiglottis. Detailed

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examination of an inflamed epiglottis can be dangerous because it can lead to an obstructed (blocked) airway. This examination should be done only in a hospital setting, usually in an operating suite with an anesthesiologist present in case there is respiratory arrest requiring an emergency airway.

How Is Epiglottitis Treated?

The first step is to provide enough air. A hospital stay is usually needed so that oxygen and intravenous antibiotics and fluids can be given. A mask can get oxygen to the lungs, or a breathing tube is put into the windpipe through the nose or mouth. Doctors observe the airway closely in case it becomes totally blocked and an emergency airway is needed. Antiinflammatory medicines (corticosteroids) may help throat swelling.

Death can occur if epiglottitis isn't treated. With treatment, symptoms usually improve in 24 hours, with complete relief of swelling in 72 hours.

Children with suspected epiglottitis should be kept upright to help breathing. They should be kept calm until they're in the hospital because breathing becomes more difficult during a panic. After hospitalization, antibiotics should be continued for at least 10 days. A cool-mist humidifier at night for several weeks will help. The water should be changed and the unit cleaned daily.

DOs and DON'Ts in Epiglottitis:

✓ **DO** have your child immunized with Hib vaccine.

✓ **DO** get emergency treatment for suspected epiglottitis.

✓ **DO** continue antibiotics as directed, usually at least 10 days.

✓ **DO** start activity again slowly after all symptoms are gone.

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✓ **DO** encourage drinking fluids and follow a normal diet as tolerated.

✓ **DO** continue using a cool-mist vaporizer at the bedside for several weeks. Change water and clean the unit daily.

✓ **DO** wash your hands often.

⃠ **DON'T** delay treatment. Death can occur without treatment.

⃠ **DON'T** skip doses or stop antibiotics before they're finished.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Otolaryngology Tel: (703) 836-4444
- National Institute of Allergy and Infectious Diseases of the NIH Office of Communications Tel: (301) 496-5717

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MANAGING YOUR

EPILEPSY

What Is Epilepsy?

Epilepsy is a brain disorder causing a temporary electrical problem in the brain. It's like a tiny lightning flash that causes the brain's function to start to skip, like a damaged CD. This problem causes seizures (convulsions), changes in consciousness, or odd movements or behavior.

Epilepsy is usually a lifelong condition, but some types, such as seizures caused by brain damage, infections, or tumors, may go away after treatment of the cause.

What Causes Epilepsy?

Causes include brain disorders present at birth, head injuries, infections (meningitis, encephalitis), tumors, poisoning, and drug and alcohol abuse. It isn't contagious but can run in families. Often, the cause is unknown.

What Are the Symptoms of Epilepsy?

Symptoms vary with the kind of epilepsy—partial (simple or complex) or generalized (absence, myoclonic, atonic, or tonic-clonic).

Some people stop what they're doing, stare blankly, and aren't aware of what's happening. Other people lose consciousness, stiffen, twitch, and have uncontrollable jerky movements. They lose bladder control, become violent or angry, laugh for no reason, or make odd body movements. Deep sleep or feelings of confusion follow.

Before a seizure, some people may have warnings such as a tense feeling, bad smell, hearing a strange noise, or not seeing right.

How Is Epilepsy Diagnosed?

The doctor will make a diagnosis from a medical history and physical examination. The doctor

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will check the brain's electrical activity with a test called electroencephalography (EEG). The electroencephalogram tracing shows the electrical activity. Magnetic resonance imaging (MRI) or computed tomography (CT) may be done. Positron emission tomography (PET) is a newer radiology test that shows brain activity in different areas of the brain. Blood tests will be done to check for other causes of seizures.

How Is Epilepsy Treated?

Antiepileptic drugs are the most common treatment to control seizures. Medicine is often changed or adjusted for better seizure control. Surgery may be used if drugs don't help. Other newer treatment options are vagus nerve stimulation and special diets. An electrical device is placed in the shoulder to stimulate a cranial nerve. A high-fat, low-carbohydrate diet may help reduce certain seizures if other treatments don't work.

Medicines can cause side effects, which the doctor will explain.

When someone has a seizure, prevent injuries by cushioning the head, turning the person on their side, and taking away items that could cause injuries. Don't hold the person down, force anything into the mouth, or shout or shake the person. Afterward, let the person rest or sleep if needed.

DOs and DON'Ts in Managing Epilepsy:

✓ **DO** wear a medical alert bracelet or pendant that shows you have epilepsy.

✓ **DO** check with your state about driving. Most states allow people with epilepsy to drive after being seizure-free for 1 year.

✓ **DO** tell your doctor if you have side effects from your medicine.

✓ **DO** tell your doctor if you have new symptoms.

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✓ **DO** try to reduce your stress and get adequate sleep.

✓ **DO** keep a record of your seizures. Call your doctor if the pattern or duration of seizures increases.

✓ **DO** have blood tests to make sure that your medicine levels are in the proper range.

⃠ **DON'T** drink alcohol.

⃠ **DON'T** expose yourself to anything that triggered a seizure before.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- Epilepsy Foundation of America Tel: (301) 459-3700 **Website:** **http://www.epilepsyfoundation.org**
- American Academy of Neurology **Website**: **http://www.neurology.org**

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MANAGING YOUR

EPISCLERITIS

What Is Episcleritis?

Episcleritis is an inflammatory disorder involving a thin layer of tissue that surrounds the eyeball. The white of the eye is the sclera. It's a tough, thick tissue that protects the eyeball. A thin membrane over the sclera and the inside of your eyelids is the conjunctiva. Between the conjunctiva and the sclera is another thin layer of tissue called the episclera. Infection or inflammation (swelling, redness) of the episclera is called episcleritis. It may be confused with a similar disorder called scleritis. Scleritis affects the sclera, not the episclera. Episcleritis is usually mild and often goes away on its own. It rarely causes lasting damage. Episcleritis is often seen in adults 40 to 50 years old.

What Causes Episcleritis?

The cause is usually unknown. Episcleritis may be linked to infections with bacteria, viruses, fungi, or parasites. Gout, allergies, and chemicals may also be related to the disorder. Episcleritis and scleritis are more common in people with collagen-vascular diseases including rheumatoid arthritis, scleroderma, psoriasis, ankylosing spondylitis, inflammatory bowel disease, Reiter syndrome, Wegener's granulomatosis, dermatomyositis, and systemic lupus erythematosus.

The disease isn't passed from parents to children.

What Are the Symptoms of Episcleritis?

Symptoms include sudden eye pain or discomfort, watery discharge, sensitivity to light, and redness. Episcleritis occurs in two forms: simple and nodular. Simple episcleritis is most common and lasts 1 to 3 weeks. It can recur. Nodular episcleritis causes similar symptoms and is

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more often related to the diseases just named in the section on causes of episcleritis.

How Is Episcleritis Diagnosed?

The health care provider makes a preliminary diagnosis from the medical history and physical examination. An eye specialist (ophthalmologist) will do a more detailed eye examination. After special drops are put into the eye, the specialist uses a special light to look at the eye. If the health care provider thinks that a disease may be related to the condition, blood tests may be done.

How Is Episcleritis Treated?

Episcleritis usually goes away without treatment. If it persists, laboratory tests may be done to rule out other causes (e.g., rheumatoid arthritis or gout). Simple episcleritis often requires no treatment, but if treatment is needed, it's often to relieve symptoms. Warm compresses over the eye may give relief. Medicines for eye pain include ibuprofen, naproxen, or acetaminophen. If other diseases are present, they will also need treatment. Nodular episcleritis usually produces more symptoms. Local corticosteroid drops or antiinflammatory agents may be prescribed by the ophthalmologist.

DOs and DON'Ts in Managing Episcleritis:

✓ **DO** ask your health care provider about wearing contact lenses during treatment.

✓ **DO** tell your health care provider if you don't feel well while using eye drops or pills.

✓ **DO** tell your health care provider about all your medicines.

✓ **DO** see your health care provider right away if your vision becomes affected or if you have severe eye pain.

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⦸ **DON'T**miss follow-up appointments.

⦸ **DON'T** use someone else's eye drops, especially if the drops contain corticosteroids.

⦸ **DON'T** stop using your medicine even if you feel better before your health care provider tells you to stop.

⦸ **DON'T** touch the applicator tip of your eye drops to any surface.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Ophthalmology Tel: (415) 561-8500 **Website:** **http://www.aao.org**

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MANAGING YOUR

EPSTEIN-BARR VIRUS INFECTION

What Is Epstein-Barr Virus (EBV) Infection?

EBV, a herpesvirus, occurs worldwide as one of the most common viruses affecting humans. Many children and young adults have EBV infection. In the United States, about half of children 5 years old and 95% of adults 35 to 40 years old have had EBV. In young people, EBV can cause infectious mononucleosis, which affects the respiratory system, liver, and lymphatic system. It spreads by close contact (kissing, sharing food or utensils) and coughing. A more severe infection can affect people with weak immune systems such as people infected with HIV, those receiving cancer chemotherapy, and people taking medicines to prevent organ rejection. EBV in such people can be associated with oral hairy leukoplakia. A lasting infection may cause chronic fatigue syndrome. EBV infection is also associated with a greater risk of having certain lymphomas (cancer of the lymphatic system) and other cancers (nose and throat, or nasopharyngeal).

EBV stays in some cells for life. The virus can reactivate, usually without symptoms, and people can then infect others.

What Are the Symptoms of EBV Infection?

EBV can cause different symptoms. Most children younger than 5 have no symptoms. Symptoms of mononucleosis can appear 10 to 30 days after exposure. They include sore throat (sometimes severe); fever, usually higher in the evening; loss of appetite; and fatigue. Others are swollen lymph glands in the neck, underarms, or groin; pain in the abdomen (belly) from an enlarged spleen or liver; headache; and general body aches. The liver and spleen enlarge. Sometimes jaundice occurs. A ruptured spleen is rare.

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How Is EBV Infection Diagnosed?

The doctor makes a diagnosis from the medical history, physical examination, and blood tests.

How Is EBV Infection Treated?

Rest and good nutrition are best for acute EBV infection causing mononucleosis. For muscle aches and minor discomfort, acetaminophen or ibuprofen are given. Aspirin shouldn't be given to children younger than 16 because of the risk of the dangerous Reye's syndrome in this age group. Severe throat inflammation (redness, pain, swelling) may need antiinflammatory steroids (corticosteroids such as prednisone). Recovery may take a few days to months. Fatigue usually lasts 3 to 6 weeks after other symptoms are gone. Complications (such as spleen rupture) need immediate treatment. Psychological and behavioral therapy may help chronic post-EBV fatigue in some patients.

DOs and DON'Ts in Managing Epstein-Barr Virus Infection:

✓ **DO** rest in bed until fever goes away.

✓ **DO** eat a good diet. Soups, juices, milkshakes, and bland foods may be best. Drink enough, at least 8 glasses a day.

✓ **DO** slowly return to normal activity.

✓ **DO** gargle with warm salt water to help sore throat.

✓ **DO** call your doctor if your temperature is higher than 102° F, you have swallowing or breathing problems, or constipation causes straining.

✓ **DO** call your doctor if you have sudden severe abdominal pain, especially in the left upper

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part, for more than 5 minutes. It could mean a ruptured spleen. Call if you have a severe headache, neck pain, or stiffness.

⦸ **DON'T** use aspirin for children younger than 16.

⦸ **DON'T** lift heavy objects.

⦸ **DON'T** do contact sports until after complete recovery or until your doctor says you can.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Allergy and Infectious Diseases of the NIH Tel: (301) 496-5717

  Website: http://www.healthfinder.gov (Choose "index" to search by topic.)

  http://www.healthanswers.com

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MANAGING YOUR

ERECTILE DYSFUNCTION

What Is Erectile Dysfunction?

Erectile dysfunction (ED), or male impotence, is a man's inability to get or keep an erection long enough to finish sexual activity. ED causes great distress and problems with relationships.

The percentage of men affected with ED increases with age. About 10% of men in their 60s and 30% in their 70s have ED.

What Causes Erectile Dysfunction?

Causes are both physical and psychological (psychogenic). Most older men with ED have heart and blood vessel disease. Other causes are medicines, nervous system problems, hormone deficiency, diabetes, hypertension, and smoking. Psychogenic ED, a result of emotional problems, is much more common and harder to diagnose.

What Are the Symptoms of Erectile Dysfunction?

The main symptom is inability to get or keep an erection until the end of sexual activity.

If the cause is psychological, men may have associated anxiety, mood swings, depression, insomnia, and concerns about sexual performance.

If the cause is physical, symptoms of medical illness may include poor circulation in the legs, chest pains, or shortness of breath with exercise (possible heart disease). Diabetes is frequently associated with ED.

How Is Erectile Dysfunction Diagnosed?

The doctor will ask about the firmness and duration of erections at different times (e.g., sex with partners, erections after sleep). Discussing sexual dysfunction with a doctor is very important because many conditions causing it can be successfully treated. If a man has no diseases that

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cause ED and can have an erection with masturbation or early morning awakening, he likely has ED due to psychological causes.

How Is Erectile Dysfunction Treated?

The basic treatment for performance anxiety is to ask the man to make love with his partner without trying intercourse, to show him and the partner how lovemaking can feel without a concern with failure. This method (called sensate focus) lets the man have a different focus: pleasing his partner and himself.

Men with physical causes of ED have options, including such medicines as sildenafil (Viagra®), vardenafil (Levitra®), or tadalafil (Cialis®). Men who use nitroglycerin products and those who should avoid sexual activity because of cardiovascular disease shouldn't take these drugs. Other treatment modalities include use of a vacuum pump or injection of a substance (papaverine) into the penis to increase blood flow to the penis. Men can also have surgery to put a prosthesis into the penis.

DOs and DON'Ts in Managing Erectile Dysfunction:

✓ **DO** discuss ED with your doctor.

✓ **DO** make sure that you tell your doctor all the medicines that you take because many, including high blood pressure medications and antidepressants, can cause ED.

✓ **DO** talk with your partner. Keep lines of communication open.

✓ **DO** exercise regularly, eat a healthy diet, and relax.

✓ **DO** call your doctor if you see blood or discharge from your penis, sexual intercourse becomes painful, your erection lasts long after intercourse, or you have severe depression or

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suicidal thoughts.

⦸ **DON'T** expect to have normal sex during times of stress, grieving, or depression.

⦸ **DON'T** take Viagra®, Levitra®, or Cialis® if you use nitroglycerin products. These medicines may also interfere with vision and shouldn't be used within several hours of operating an airplane.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- WebMD Erectile Dysfunction Health Center **Website:** **http://www.webmd.com/erectile-dysfunction/default.htm**
- American Academy of Family Physicians Tel: (800) 274-2237 **Website:** **http://www.aafp.org**

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MANAGING YOUR

ERYSIPELAS

What Is Erysipelas?

Erysipelas is an infection of the skin and tissue below it.

What Causes Erysipelas?

The cause is a type of bacteria called group A streptococci.

The infection may occur in people without medical problems but most often occurs in very young or elderly people and those who are immunocompromised such as those infected with human immunodeficiency virus (HIV) or who have acquired immunodeficiency syndrome (AIDS). Diabetics and alcoholics are also more prone to it. It may also occur in wounds after surgery.

What Are the Symptoms of Erysipelas?

The skin becomes painful and then gets red and swollen, with a very distinct edge. The area is tender and hot. Small or large blisters may develop in the red area.

This infection may develop on the face, but is more common on the legs, after heart bypass surgery, often near the vein that was used in coronary artery bypass surgery.

Other symptoms are fever, chills, headache, tiredness, loss of appetite, belly (abdominal) pain, and swollen glands (lymph nodes).

How Is Erysipelas Diagnosed?

The doctor will make the diagnosis by obtaining a medical history and doing a physical examination. Nose and throat cultures for the streptococcus bacteria and blood tests (e.g., white blood cell count) may also be done to see whether an infection is present.

How Is Erysipelas Treated?

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Antibiotics are the best treatment. For frequent or very severe infections, long-term treatment with low-dose antibiotics may be needed.

With proper treatment, most infections go away after few days. Without treatment, abscesses, infections in veins, and gangrene can develop. These problems are also more likely to occur in people with weakened immune systems, such as in diabetes, alcoholism, HIV infection, and those with previous blood clots in legs.

DOs and DON'Ts in Managing Erysipelas:

✓ **DO** elevate your leg to help with swelling.

✓ **DO** separate your towels, washcloths, and bedding from laundry of other household members. Use very hot water for washing.

✓ **DO** take all of your antibiotics, even after the skin clears.

✓ **DO** call your doctor if you have a reaction to your antibiotic, or if the rash and redness continue to spread.

✓ **DO** call your doctor if you have fever, chills, dizziness when you stand up, or rapid heart rate.

⦸ **DON'T** stop your antibiotic, even if the infection has greatly improved. Erysipelas is a serious infection. You must finish all the antibiotic that your doctor gave you.

⦸ **DON'T** put any salves, creams, or lotions on the infected part. If the area "weeps" a little, dress it with plain gauze.

⦸ **DON'T** let other family members use your towels. If the skin weeps, the substance may con-

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tain bacteria, and you can give the infection to others.

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FOR MORE INFORMATION

Contact the following source:

- American College of Dermatology Tel: (866) 503-SKIN (7546) **Website:** **http://www.aad.org**

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MANAGING YOUR

ERYTHEMA MULTIFORME

What Is Erythema Multiforme?

Erythema multiforme is a reddening, swelling, and sometimes blistering of the skin. A milder form, called erythema multiforme minor, usually doesn't cause complications and clears up on its own. The mild form usually affects children and young adults, lasts from 2 to 4 weeks, and can recur during the first few years. The more severe form, called Stevens-Johnson syndrome or erythema multiforme major, can cause serious symptoms that need prompt treatment and maybe hospitalization.

What Causes Erythema Multiforme?

The cause is unknown in half the cases. Most of these skin irritations result from infections, allergic reactions to drugs such as penicillin or vaccines, physical conditions such as pregnancy and other hormone changes, and illnesses such as cancer.

What Are the Symptoms of Erythema Multiforme?

Skin in the minor form has round red bumps and blisters on the face, lips, arms, and legs on both sides of the body. These bumps can look like red or pink targets; they can become large blisters. Fever and muscle and joint aches may be present.

In the serious form, people have high fever, large blisters, severe itching, and ulcers on membranes of the mouth, nose, eyes, genital area, arms, and skin. Without complications, symptoms go away in 4 weeks, but mouth sores can last for months. Untreated eye involvement can lead to blindness.

How Is Erythema Multiforme Diagnosed?

The doctor will examine the rash and take a medical history to make a diagnosis.

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Blood tests may be done to check for an infection. A skin biopsy may also be done to rule out another medical condition. In a biopsy, a small sample of skin with the rash will be removed and studied with a microscope.

How Is Erythema Multiforme Treated?

Treatment focuses on controlling the cause and symptoms. For a drug reaction, the drug needs to be stopped. If a bacterial infection is the cause, antibiotics are given. Symptoms are relieved by using moist compresses (for itching), soothing lukewarm or cool baths, drugs such as steroid (prednisone) creams (for itching and swelling), mouthwashes and rinses (for mouth blisters), and eyewash and other topical medicine (for a rash near the eyes). Eye involvement may mean a visit to an eye specialist.

The severe disorder can cause major skin damage. In that case, hospitalization in a burn unit may be needed.

DOs and DON'Ts in Managing Erythema Multiforme:

✓ **DO** promptly treat any illness or condition that may lead to erythema multiforme. Avoid suspected causes as much as possible, such as drugs you are allergic to.

✓ **DO** eat a soft or liquid diet if you have mouth sores.

✓ **DO** apply cool wet Burow's solution compresses or just a cool wet cloth to blisters.

✓ **DO** call your doctor immediately if you have vision changes, eye pain, vomiting, or diarrhea.

✓ **DO** take acetaminophen for pain unless otherwise directed by your doctor.

✓ **DO** call your doctor if new symptoms occur during treatment, or if symptoms get much

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worse.

⃠ **DON'T** apply skin creams or ointments to broken or bleeding skin.

⃠ **DON'T** take hot baths or hot showers (they may worsen skin irritation).

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Dermatology Tel: (866) 503-SKIN (7546) **Website:** **http://www.aad.org**

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MANAGING YOUR

ERYTHEMA NODOSUM

What Is Erythema Nodosum?

Erythema nodosum (EN) is a skin condition involving inflammation (swelling) of fat and other tissues under the skin. Red nodules (small round masses) form on the legs, thighs, lower arms, and other parts of the body. EN is more common in young women, but anyone can get it.

What Causes EN?

The most common causes are drugs (especially birth control pills, penicillin, and sulfa medicines) and infections. Sarcoidosis, ulcerative colitis, Crohn's disease, thyroid conditions, lupus, and pregnancy are other causes. Many times, the cause is unknown.

What Are the Symptoms of EN?

The main symptom is large red nodules on lower legs. The nodules are usually painful or tender, are warm to touch, and appear suddenly. Nodules look like bruises and slowly change from pink to red to bluish to brown over 7 to 10 days. The nodules usually go away within 8 weeks, but new ones may form, so recovery may take several weeks or months. Fever and swollen ankles and knees often occur.

How Is EN Diagnosed?

The doctor makes a diagnosis by the look of the nodules. Sometimes, a skin biopsy sample is needed. In a biopsy, a small piece of skin is removed and studied with a microscope. A medical history, physical examination, chest x-ray, and blood tests may help find out whether something specific is the cause.

How Is EN Treated?

Treatment depends on the cause. For example, if a drug is the cause, it may have to be stopped.

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If an infection is found, medicine will be used to treat it.

Some things can ease pain and discomfort. These include keeping the legs raised as much as possible and wearing support stockings (for swelling). Taking aspirin or other over-the-counter medicine and nonsteroidal antiinflammatory drugs (NSAIDs) may help reduce pain and inflammation. Use warm water soaks for pain and swelling, and cool water soaks for itching. Severe cases may need steroid drugs such as prednisone.

DOs and DON'Ts in Managing

Erythema Nodosum:

✔ **DO** take your medicines as prescribed.

✔ **DO** follow your doctor's treatment instructions.

✔ **DO** ask your doctor which over-the-counter medicines you may take with your prescription drugs.

✔ **DO** call your doctor if you have side effects from your medicines.

✔ **DO** call your doctor if treatment isn't improving your symptoms in a reasonable amount of time.

✔ **DO** call your doctor if you get new, unexplained symptoms.

⃠ **DON'T** use drugs and other substances that may have caused EN.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Dermatology Tel: (866) 503-7546 **Website: http://www.aad.org**
- Arthritis Foundation Tel: (800) 283-7800 **Website: http://www.arthritis.org.**

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MANAGING YOUR

ESOPHAGEAL CANCER

What Is Esophageal Cancer?

The esophagus is the part of the digestive tract that connects the mouth with the stomach. Esophageal cancer is a cancerous (malignant) tumor of this tube. Most of these cancers occur in the lower part of the esophagus. More than 10,000 new cases are diagnosed in the United States every year.

What Causes Esophageal Cancer?

The cause is unknown. Certain risk factors, such as heavy alcohol and tobacco use, increase the chances of getting this cancer. It isn't contagious. Acid reflux from the stomach that occurs for a long time can lead to changes in the lining of the esophagus (Barrett's esophagus), which can, in some cases, lead to esophageal cancer.

What Are the Symptoms of Esophageal Cancer?

Trouble swallowing solid foods is the usual symptom. As the tumor grows, liquids become hard to swallow, and pain with swallowing can occur. Cancer usually spreads nearby, to lungs, windpipe, lymph glands, and liver. Hoarseness, coughing, coughing up or vomiting blood, and chest pain can result.

How Is Esophageal Cancer Diagnosed?

The best way for the doctor to make a diagnosis is with an endoscope and biopsy. With this lighted tube, passed through the mouth into the esophagus, the doctor can get tissue to study with a microscope. X-ray studies, a barium swallow examination or esophagography, can also be done, but will need to be followed by endoscopy and biopsy to make the diagnosis.

After diagnosis, staging is needed to tell the extent of disease and whether it spread. A physi-

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cal examination, blood tests, and computed tomography (CT) of the chest and abdomen are used. Spread to the voice box (larynx) is checked with laryngoscopy. Spread to the lungs may also be checked with bronchoscopy. These examinations use lighted tubes passed into the larynx or lungs.

How Is Esophageal Cancer Treated?

Therapy depends on the stage of disease and its spread. It can include surgery, radiation, and chemotherapy (cancer-fighting drugs). In an operation called esophagectomy, the surgeon removes the cancerous part of the esophagus and lymph glands. Radiation is used instead of surgery when the tumor is too large to remove or the person cannot undergo an operation. Chemotherapy can be used with radiation and surgery.

DOs and DON'Ts in Managing Esophageal Cancer:

✓ **DO** treat chronic acid reflux to avoid precancerous conditions such as Barrett's esophagus.

✓ **DO** ask about your prognosis. This cancer is hard to cure.

✓ **DO** understand that nutrition is important before and after the operation. Eat high-calorie foods and nutritional supplements. A nutritionist (diet specialist) can help.

✓ **DO** ask for help from support groups.

✓ **DO** call your doctor if you have pain with swallowing, trouble swallowing, or food getting stuck when eating.

✓ **DO** call your doctor if you cough up or vomit blood.

✓ **DO** call your doctor if you have shortness of breath and fever.

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✓ **DO** call your doctor if you cannot eat and continue to lose weight.

⃠ **DON'T** smoke.

⃠ **DON'T** drink alcohol in excess.

⃠ **DON'T** miss follow-up appointments, such as with your primary care doctor, surgeon, and oncologist (cancer specialist).

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Cancer Institute Tel: (800) 422-6237 **Website: http://www.cancer.gov**
- American Cancer Society Tel: (800) 227-2345 **Website: http://www.cancer.org**

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MANAGING YOUR

ESSENTIAL TREMOR

What Is Essential Tremor?

A tremor is a rhythmic, involuntary muscle contraction. A part of the body moves back and forth. Tremor without a known cause is called essential tremor.

Tremors can be put into five categories: resting, postural, kinetic, task-specific, and psychogenic. Resting tremor occurs when a muscle is at rest, for example, when hands are lying in the lap. People with Parkinson's disease have this type. Postural tremor occurs when people try to hold a position, such as holding the hands out. These tremors include physiological, essential, posttraumatic, and alcoholic tremors. Kinetic tremor occurs during movement with purpose, for example, during finger-to-nose testing. Task-specific tremor appears when doing tasks such as handwriting, speaking, or standing. Psychogenic tremor occurs in older and younger people and can be lessened or can disappear when people get distracted.

Essential tremors affect men and women equally, usually after age 40. These tremors can cause disability and social embarrassment.

What Causes Essential Tremor?

Although the cause is unknown, abnormal communications between certain parts of the brain are thought to lead to tremors. They're not contagious but may run in families, with parents having a 50% chance of passing them to children.

What Are the Symptoms of Essential Tremor?

Essential tremor can affect hands, head, facial structures, vocal cords, trunk, and legs. Most occur in the hands and arms. Tremors usually affect both sides of the body, but may be more noticeable on one side. Tremors are worse when limbs are held out or in uncomfortable positions.

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They usually stop at rest.

How Is Essential Tremor Diagnosed?

The doctor makes a diagnosis from a detailed history and physical examination. Other causes (e.g., neurological disorders, thyroid conditions, caffeine use, and medicines) must be ruled out. No specific blood tests, genetic testing, or x-ray studies can diagnose essential tremors. However, the doctor might order blood and urine tests, computed tomography (CT), or magnetic resonance imaging (MRI) to find other possible causes of the tremors.

How Is Essential Tremor Treated?

Mild tremors may not be treated as long as they don't affect the ability to function. More severe tremors may first be treated with medicines called beta-blockers. such as propranolol, the one most often used.

Primidone, gabapentin, clonazepam, diazepam, and alprazolam may also be tried.

If medicines don't work, botulinum toxin injections and surgical options may help for tremor localized to one area of the body.

DOs and DON'Ts in Managing Essential Tremor:

✓ **DO** have an active lifestyle.

✓ **DO** understand that although Parkinson's disease causes a tremor at rest, there are many other signs and symptoms associated with this disease and having a resting tremor does not mean that one has Parkinson's disease.

✓ **DO** realize that although alcohol tends to reduce tremors, it shouldn't be used for treatment.

✓ **DO** call your doctor if you have medicine side effects.

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✓ **DO** call your doctor if you're worried that you have Parkinson's disease.

✓ **DO** call your doctor if you need a referral to a neurologist (specialist in movement disorders).

⃠ **DON'T** stop medicines without first asking your doctor.

⃠ **DON'T** use caffeine. It may worsen your symptoms.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- The National Institute of Neurological Disorders and Stroke **Website:**

  http://www.ninds.nih.gov

- International Essential Tremor Foundation Tel: (888) 387-3667 **Website:**

  http://www.essentialtremor.org

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MANAGING YOUR

EXERCISES AND CARDIOVASCULAR HEALTH

Why Is Exercise Good for Cardiovascular Health?

Coronary heart disease (CHD) is the main cause of death and disease in the United States. Although regular physical activity can reduce risks of cardiovascular (CV) diseases such as CHD and high blood pressure (hypertension), many people don't exercise. Fitness is important for CV health and survival. Changing behaviors leading to CV disease can limit or reverse heart disease. Such lifestyle changes include low-fat diets, aerobic exercise, controlling stress, stopping smoking, and support groups. Active people have a 45% lower risk of developing heart disease than do inactive people. Exercise helps men and women, young and old, and different races and ethnic groups.

Exercise also lowers risks of stroke, metabolic syndrome, and type 2 diabetes. Metabolic syndrome is a group of risk factors leading to atherosclerosis.

How Do Exercises Affect Cardiovascular Health?

Higher level exercise programs improve CV disease risk factors such as high blood pressure, being overweight, low bone calcium levels (osteoporosis), and insulin sensitivity (diabetes). Regular exercise lowers blood pressure. Exercise reduces the heart's need for oxygen, and the heart doesn't have to work as hard. Aerobic exercises increase breathing, heart rate, and endurance. The lungs and heart get stronger, as do muscles. Exercise boosts positive effects of low-fat, low-cholesterol diets on blood lipid (fat) levels, which helps atherosclerosis. It also improves carbohydrate metabolism, especially in overweight adults.

What Exercises Affect Cardiovascular Health?

Exercises that help CV health include sports, exercise conditioning or training, and gardening.

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Aerobic exercises are especially good for CV health. Walking, dancing, swimming, jogging, cycling, and playing tennis are examples. Yoga and tai chi may lower blood pressure almost as well as moderate-intensity aerobics.

How Should Exercises Be Done?

Exercises should be enjoyable, whether group or individual, and should fit into a regular schedule. Asking doctors which exercises to do is critical.

New guidelines for adults 18–64 years old suggest 2.5 hours a week of moderate-intensity activity, or 1.25 hours a week of vigorous aerobic activity, or some equal combination. Activity periods should last at least 10 minutes. The best way to exercise may be to use many short periods of intense exercise, which may help older people.

People with heart disease may do light to moderate exercise: gardening, walking, jogging, cycling, rowing, swimming, and treadmill exercises. They need longer warm-up and cool-down periods than healthy people. Exercises should first last 10–20 minutes, or even 2–6 minutes alternating with 1–2 minutes of rest. Then, exercise time may increase slowly to 20–40 minutes per session.

DOs and DON'Ts in Managing Exercises and Cardiovascular Health:

✓ **DO** check with your doctor before starting exercise programs.

✓ **DO** make exercising a habit. Exercise with friends. Choose exercises that are fun and that you enjoy.

✓ **DO** vary exercises so you don't get bored. For example, walk one day and swim the next.

⦸ **DON'T** do exercises that hurt or cause pain. For example, swimming is easier on joints if you have arthritis.

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⦸ **DON'T** get discouraged and give up. It may be a long time before you see benefits of exercise.

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:** **http://www.americanheart.org**
- American College of Cardiology Tel: (800) 253-4636 **Website: http://www.acc.org**

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MANAGING YOUR

FAMILIAL ADENOMATOUS POLYPOSIS AND POLYPOSIS SYNDROMES

What Are Familial Adenomatous Polyposis and Polyposis Syndromes?

Gastrointestinal polyposis is the presence of many growths (polyps) in the gastrointestinal tract. The rare familial adenomatous polyposis (FAP) is the most common of these syndromes. Hundreds to thousands of noncancerous (benign) polyps grow in the large intestine (colon or bowel) and rectum. Some people have a different type of the disorder called attenuated FAP, which is accompanied by delayed polyp growth.

People of all races can get it—males and females equally.

What Causes FAP and Polyposis Syndromes?

FAP is an inherited autosomal dominant disorder. Autosomal dominant means that having only one parent with the abnormal gene can give a child a 50% chance of having the disorder. A germline mutation of the *APC* tumor suppressor gene is the cause. A germline mutation is found in all body cells. The *APC* gene controls cell growth and cell death. People with a mutated (changed) gene have a higher risk of having polyps and cancer.

What Are the Signs and Symptoms of FAP and and Polyposis Syndromes?

People often have a family history of the syndrome or of colorectal cancer. Nonspecific symptoms, such as rectal bleeding, diarrhea, abdominal pain, or desmoid tumors, may suggest FAP in young people. Polyps usually start to grow at age 16. Most people don't have symptoms until they get colon cancer at an early age (usually before age 50).

How Are FAP and Polyposis Syndromes Diagnosed?

Cancer screening often begins in childhood. Colonoscopy is essential to rule out malignant changes in polyps. The doctor also uses genetic testing, upper endoscopy, and may also order

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computed tomography (CT scan).

A medical history (especially family history) and physical examination are also important for diagnosis. An eye examination with a slit lamp can find many flat pigmented lesions in the retinas. Masses that the doctor can feel in the abdomen (belly) and rectum in young people suggest FAP.

How Are FAP and Polyposis Syndromes Treated?

Hundreds to thousands of polyps form, so they cannot be removed separately. Surgery to remove the whole colon (colectomy) is the only effective treatment. It greatly improves life expectancy. Surgery can be done in adulthood. However, because of the high colon cancer risk, sometimes early ileal pouch-anal anastomosis (IPAA) is done instead of colostomy. Most people can eat normal diets and lead normal lives after surgery. Surgery doesn't cure the disease, however, and polyps continue to form. Certain medicines (sulindac, celecoxib) may make polyps shrink or prevent new growths. These drugs should be used only with regular check-ups and screening. Upper endoscopy to find polyps, genetic testing, and screening of family members are needed.

DOs and DON'Ts in Managing FAP and Polyposis Syndromes:

✓ **DO** go for regular doctor check-ups. Surveillance programs, especially after colectomy, are essential.

✓ **DO** remember that your life expectancy is much greater with colectomy treatment.

✓ **DO** look for gastroenterologists, surgeons, and geneticists familiar with FAP.

✓ **DO** go for genetic counseling. Your family should also have genetic testing.

✓ **DO** learn all you can about FAP.

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✓ **DO** join a support group if you think that would help.

⦸ **DON'T** forget to see your doctors regularly for cancer screening.

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FOR MORE INFORMATION

Contact the following sources:

- National Digestive Diseases Information Clearinghouse E-mail: nddic@aerie.com

  Website: http://www.niddk.nih.gov/health/digest/nddic.htm

- American College of Gastroenterology Tel: (703) 820-7400 **Website:**

  http://www.acg.gi.org

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MANAGING YOUR

FATTY LIVER

What Is Fatty Liver?

A fatty liver refers to a collection of too much fat in liver cells that often occurs in patients with diabetes or obesity or patients who drink too much alcohol. A fatty liver by itself is not harmful, but prolonged swelling (inflammation) of a fatty liver can lead to scarring (cirrhosis) and poor functioning of the liver.

Nonalcoholic fatty liver disease (nonalcoholic steatohepatitis, or NASH) is inflammation of a fatty liver that is not caused by alcohol or hepatitis. It is more common in overweight people, but the specific cause is unknown. NASH is not transmitted from person to person or from generation to generation. NASH is the most common liver disease in teenagers and the third leading cause of liver disease in adults.

What Are the Symptoms of Fatty Liver?

Most patients with fatty liver or NASH do not know they have it because they usually have no symptoms. Some patients may feel tired or have pain and discomfort in the abdomen (belly), if the liver is much larger than normal.

How Is Fatty Liver Diagnosed?

The doctor may make this diagnosis by accident when testing for another complaint. Often, liver function blood tests, done as part of annual or routine blood work, show results are not normal. In this case, the doctor will take a detailed history and do a physical examination and other studies to rule out common causes of these abnormal results (such as hepatitis, alcohol, or too much iron in the liver). At an examination, the doctor may feel for a liver or spleen that is too large but in most cases this will not be evident on physical examination.

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The doctor may also want special x-ray studies and scans of the liver: ultrasound scan, computed tomography (CT), or magnetic resonance imaging (MRI).

A diagnosis of NASH is proved by a liver biopsy. In a biopsy, a large needle is inserted into the liver. Then, a small piece of the liver is removed and examined under a microscope.

How Is Fatty Liver Treated?

Weight loss and avoiding alcohol are the best ways to treat fatty liver.

If you have NASH and are obese or diabetic or have high cholesterol, you should lose weight and control your blood sugar and lipid levels by eating a good diet and exercising.

Your doctor may try drugs to reduce the liver's fats and inflammation.

DOs and DON'Ts in Managing Fatty Liver:

✓ **DO** realize that often a liver biopsy is not done and fatty liver or NASH is diagnosed by ruling out other causes such as alcohol or virus (called a diagnosis of exclusion).

✓ **DO** ask your doctor about drugs that can hurt the liver, such as acetaminophen and some used for diabetes and high cholesterol.

✓ **DO** lose weight if you are obese.

⃠ **DON'T** drink alcohol. Avoiding alcohol may help get rid of the fat stored in liver cells.

⃠ **DON'T** forget that a few patients with NASH can get liver cirrhosis and have complications from liver failure, for example, yellow skin color (jaundice), fluid in and swelling of the belly (ascites), and swelling (edema) of the legs.

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FOR MORE INFORMATION

Contact the following sources:

- National Digestive Diseases Information Clearinghouse Tel: (800) 860-8747 **Website:** **http://www.niddk.nih.gov/health/diabetes/diabetes.htm**
- American College of Gastroenterology Tel: (703) 820-7400 **Website:** **http://www.acg.gi.org**

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MANAGING YOUR

FEMALE SEXUAL DYSFUNCTION

What Is Female Sexual Dysfunction?

Female sexual dysfunction refers to any disorder that interferes with sexuality and causes marked distress in that woman. These disorders can usually be divided into four types: disorders of desire, disorders of arousal, disorders of orgasm, and disorders related to sexual pain.

What Causes Female Sexual Dysfunction?

The more common of the many causes are chronic medical conditions, such as diabetes, heart disease, arthritis, and urinary disorders. Drugs such as antidepressants and blood pressure medicines can interfere with orgasm. Also, gynecologic and hormonal conditions, such as after pregnancy, after menopause, and cancer of the cervix, uterus, or breast, can lead to dysfunction. Possible psychological issues include religion, taboos, guilt, relationship problems, abuse or rape, depression, and stress.

What Are the Symptoms of Female Sexual Dysfunction?

Symptoms include loss of desire, painful sex, no orgasms, feeling guilt or shame, depression, anxiety, and insomnia.

How Is Female Sexual Dysfunction Diagnosed?

The doctor will make a diagnosis on the basis of a medical history and physical examination (including a pelvic exam).

Blood tests may be done to rule out factors such as diabetes and thyroid problems.

The doctor may suggest seeing a gynecologist for conditions that can be treated with surgery, a psychologist or psychiatrist if emotional issues are causing the dysfunction, and social services for issues of abuse.

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How Is Female Sexual Dysfunction Treated?

Treatment depends on the cause. If a medicine is the cause, a change in dose or to another drug may be suggested. Women who have gone through menopause (change of life) and have painful intercourse because of dryness of the vagina can use lubricants (not petroleum-based) and estrogen creams. Women with severe arthritis may change positions used during sex and try naproxen or ibuprofen before sex. Education, psychotherapy, and activities for better stimulation and changing routines also usually help.

Behavioral treatments such as couple's therapy can often get to the heart of relationship problems. Sometimes, a combination of treatment methods works best.

DOs and DON'Ts in Managing Female Sexual Dysfunction:

✓ **DO** talk and listen to your partner. Be open and honest.

✓ **DO** follow a healthy lifestyle. Start exercising. Take time for fun and relaxation.

✓ **DO** exercise your pelvic floor muscles (Kegel exercises) to strengthen them. This can help with some arousal and orgasm problems. To do these exercises, tighten your pelvic muscles as if you're stopping the stream of urine. Hold for a count of five, relax, and repeat.

✓ **DO** get counseling if needed. Your doctor can refer you to a sex therapist or counselor specializing in sexual and relationship problems.

✓ **DO** learn more about your body and how it works. Talk to your doctor about how many things can affect sex. These include medicines, illnesses, surgery, age, pregnancy, and menopause.

✓ **DO** remember that many things together make the sexual response work. These factors in-

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clude emotions, experiences, beliefs, lifestyle, and relationships. Problems with any one of these can affect sexual arousal or satisfaction.

⃠ **DON'T** abuse alcohol.

⃠ **DON'T** smoke.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website: http://www.acog.org**
- American Psychiatric Association Tel: (888) 357-7924 **Website: http://www.psych.org**

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MANAGING YOUR

FEMORAL HERNIA

What Are Femoral Hernias?

A femoral hernia is a bulge of intestine (bowel) or fatty tissue pushing through a weak muscle in the groin. It occurs near the thigh, usually on the right side. More women than men tend to have them. It can't be entirely prevented.

What Causes Femoral Hernias?

Contributing factors include being overweight, pregnancy, coughing a lot, constipation, straining to have a bowel movement (stool), and heavy lifting. Getting older, smoking, being born prematurely or having a low birth weight, illness, and using steroid medicines tend to increase chances of having a femoral hernia.

What Are the Symptoms of Femoral Hernias?

Very small hernias may cause no symptoms. The main symptom is a bulge in the groin. It gets bigger on standing and smaller when lying down. It may cause an aching pain that might be felt in the inner part of the thigh.

A bulge that gets bigger and starts to hurt more can mean an incarcerated or strangulated hernia. With an incarcerated hernia, bowel or fat became stuck in the hernia. With a strangulated hernia, blood flow is blocked. Other symptoms of incarcerated or strangulated hernias include nausea, vomiting, and severe constipation. Also, the hernia won't get smaller when lying down.

How Are Femoral Hernias Diagnosed?

The doctor will make a diagnosis by doing a physical examination. If surgery is suggested, blood and urine tests, electrocardiography (ECG) (a record of the heart's electrical activity), and chest x-ray may be done before the surgery.

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How Are Femoral Hernias Treated?

First, the doctor will try to push the hernia back, to prevent incarceration and strangulation.

However, femoral hernias can be fixed by outpatient surgery. The operation used depends on the hernia size and general health. The surgeon may fix it through a small cut in the skin (laparoscopy). The surgeon repairs the hernia by using a lighted tube that is put through a very small hole in the skin. A mesh material may be put over the hernia to add strength, so that the hernia won't occur again.

The doctor will prescribe pain pills and may suggest using a mild laxative to avoid straining when moving the bowels. After surgery, sudden and severe twisting and turning and driving a car should be avoided to prevent loosening the stitches or incision.

DOs and DON'Ts in Managing Femoral Hernias:

✓ **DO** follow your doctors instructions about taking pain pills, returning to work, and resuming sex after surgery.

✓ **DO** eat a high-fiber diet and drink eight glasses of water a day to prevent constipation and straining to have a bowel movement.

✓ **DO** call your surgeon if the incision gets red or swells or fluid seeps from it. Also call your surgeon if your temperature gets higher than 100° F.

✓ **DO** reduce your chance of getting femoral hernias by keeping your weight down, eating a high-fiber diet, drinking enough water, and following safety instructions about lifting heavy objects.

⊘ **DON'T** forget follow-up appointments.

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⦸ **DON'T** lift heavy objects or drive until your surgeon says you can.

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FOR MORE INFORMATION

Contact the following sources:

• American Gastroenterological Association Tel: (301) 654-2055 **Website:**

http://www.gastro.org

• Society for Surgery of the Alimentary Tract Tel: (978) 526-8330 **Website:**

http://www.ssat.com

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CARING FOR YOUR CHILD WITH

FEVER SEIZURES

What Are Fever Seizures?

Fever (or febrile) seizures are a type of convulsion that occurs when a child has a high temperature (usually more than 100° F). They almost always occur in children aged 6 months to 5 years and are rare in older children.

What Causes Fever Seizures?

The cause is unknown. The high temperature is believed to interfere with the normal function of the brain, which causes a brief short circuit in brain activity.

What Are the Symptoms of Fever Seizures?

Symptoms are similar to those of an epileptic attack. The most common symptoms are loss of consciousness that lasts from 30 seconds to 5 minutes or more, muscle contractions in the whole body that last 15 to 20 seconds, trouble breathing, loss of control of bladder or bowels (stool), biting the tongue or cheek, clenched jaw or teeth, and skin turning blue.

More symptoms after the seizure are headache, sleepy feeling, confusion and fear, and memory loss (forgetfulness) of things that happened during the seizure.

How Are Fever Seizures Diagnosed?

The doctor will make a diagnosis from the history the seizure (as described by parents or caretakers) during the fever. The doctor will ask about injections (shots) given during 2 weeks before the seizure to make sure that the shots didn't cause the seizure. The doctor will also ask about medicines (prescription or over-the-counter), vitamins, or supplements to rule out bad reactions to drugs.

Tests will find more serious causes. These tests include electroencephalography (for epilepsy) and others to rule out meningitis and encephalitis.

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How Are Fever Seizures Treated?

Almost all febrile seizures are harmless, so drugs aren't usually given to prevent more seizures. Avoiding fever and overheating may help, but this is very hard to do in children. Make sure that your child sleeps enough, drinks plenty of fluids, and eats healthy food.

It is very unusual for a febrile seizure to last more than 10 minutes. Some children may have another febrile seizure at some time. Children rarely need treatment.

DOs and DON'Ts in Managing Fever Seizures:

✓ **DO** put your child on his or her side during a seizure, to avoid choking on saliva.

✓ **DO** remain calm. It's normal to be scared during and after seeing a seizure, but you'll be better able to comfort your child if you stay in control.

✓ **DO** call your local emergency number if the seizure lasts more than 10 minutes.

✓ **DO** *c*all your doctor if your child has seizures often.

⃠ **DON'T** put anything in your child's mouth.

⃠ **DON'T** restrain your child's movements during the seizure.

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FOR MORE INFORMATION

Contact the following sources:

- Epilepsy Foundation Tel: (800) EFA-1000 (332-1000) **Website:** **http://www.epilepsyfoundation.org**

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- American Academy of Family Physicians Tel: (800) 274-2237 **Website: http://www.aafp.org**
- American Academy of Neurology **Website: http://www.neurology.org**

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MANAGING YOUR

FEVER OF UNKNOWN ORIGIN

What Is Fever of Unknown Origin?

Fever of unknown origin (FUO), as its name says, is a high temperature without any known cause after diagnostic tests have been done.

What Causes FUO?

Three major causes are infections, tumors, and collagen vascular diseases. Collagen-vascular diseases include systemic lupus, rheumatoid arthritis, and scleroderma. They're caused by the body's immune (infection-fighting) system attacking its own organs.

Infections, the most common cause, include endocarditis (infection of the heart's lining or valves), tuberculosis, abscesses, and viral infections such as cytomegalovirus infection. Tumors, the second most common cause, include Hodgkin's and non-Hodgkin's lymphomas. Other tumors are leukemia, multiple myeloma, and renal, liver, colon, and breast cancers. The most common collagen-vascular disease in young people is juvenile rheumatoid arthritis. In older people, it's inflammation of the temporal artery, found at the temple region of the head.

Other rare causes of FUO are drugs such as antibiotics, antihistamines, antiseizure drugs, anti-inflammatory drugs, and medicines used for acid reflux and peptic ulcers.

What Are the Symptoms of FUO?

The medical definition describes the symptom: a temperature of 101° F (38.3° C) for more than 3 weeks and no diagnosis after 1 week of evaluation.

How Is FUO Diagnosed?

As part of the evaluation, the doctor will take a detailed history, do a physical examination, and order blood tests.

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If the diagnosis remains unclear, the doctor may order imaging studies, such as x-rays and computed tomography (CT) of the chest, abdomen (belly), and pelvis.

If endocarditis may be the cause, echocardiography (an ultrasound test using sound waves to take pictures of the heart) will be done.

How Is FUO Treated?

The disease causing the fever must be treated. A doctor who specializes in infections will help with diagnosis, evaluation, and treatment of infectious diseases. Antibiotics will be given for infections. If a tumor is found, an oncologist (a doctor specializing in cancer treatment) will be involved. For a collagen-vascular disease, a rheumatologist (a doctor specializing in joint and collagen-vascular diseases) will help.

DOs and DON'Ts in Managing FUO:

✓ **DO** remember that your doctor won't usually start using medicines without making a diagnosis. If the FUO remains undiagnosed, your doctor may just watch for more symptoms.

✓ **DO** report any new symptoms if you are being evaluated for FUO.

✓ **DO** call your doctor if you have a long-lasting fever (101° F or higher).

✓ **DO** call your doctor if you have symptoms that may help make the diagnosis (e.g., cough, sputum production, shortness of breath, abdominal pain, diarrhea, bloody stools, muscle aches, joint aches, joint swelling, bone pain, or burning with urination).

⃠ **DON'T** get frustrated. FUO may be very hard to diagnose. About 5% to 15% of cases don't have a diagnosis.

⃠ **DON'T** self-medicate. Follow the instructions of your doctor and specialists.

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⦸ **DON'T** forget that infection is the main cause of FUO. Common infections include urinary tract infections, pneumonia, tuberculosis, endocarditis, osteomyelitis (infection of the bone), tick-borne diseases (e.g., Lyme disease), gonorrhea, syphilis, herpes, HIV, AIDS, and abdominal abscesses.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Family Physicians Tel: (800) 274-2237 **Website:** **http://www.aafp.org**
- American Medical Association Tel: (312) 464-5000, (800) 621-8335 **Website:** **http://www.ama-assn.org**

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MANAGING YOUR

FIBROCYSTIC BREAST CHANGES

What Are Fibrocystic Breast Changes?

The newer term fibrocystic breast changes refers to many different conditions and includes older names such as fibrocystic breast disease. It's the most common benign (noncancerous) breast condition. The breast tissue forms cysts (sacs filled with fluid), which feel like smooth, firm, movable lumps. These changes also lead to thickening throughout the breast, pain, and tenderness. The cysts may spread through the breast, be in one area, or appear as one or more large lumps.

About 60% to 75% of all women will have changes in fibrous tissue in their breasts. Fibrocystic changes occur most often in women 30 to 50 years old. Only 10% of women younger than 21 are affected.

What Causes Fibrocystic Breast Changes?

The cause isn't clear, but hormones made by the ovaries may be important. Also, fibrocystic breast changes usually decrease or stop after menopause (change of life).

What Are the Symptoms of

Fibrocystic Breast Changes?

Symptoms can be mild to severe. Almost half of women have no symptoms. Most common symptoms are cyclic general pain and swelling in both breasts, with the worst symptoms just before periods. Breasts feel full, with dull, heavy pain and tenderness to pressure or touch. Breast tissue is dense and feels lumpy, as if it contains pebbles. A ropy thickening, especially in the upper outer parts of the breast, may also be present.

How Are Fibrocystic Breast Changes Diagnosed?

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The doctor makes a diagnosis on the basis of symptoms and examination. The doctor will order mammography and ultrasound examinations. Rarely, a biopsy may be needed to make sure that no other conditions are present.

How Are Fibrocystic Breast Changes Treated?

Good support (a well-fitting bra worn day and night) and pain relievers such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are all that's needed by most women. Other things that may help include avoiding caffeine (coffee, tea, cola, chocolate), lowering fat in the diet, using heat (heating pad or hot water bottle), and taking vitamins and herbal preparations. Cold compresses or ice may also work. A monthly breast self-examination is important.

The doctor may prescribe stronger pain relievers, diuretics, or hormones (such as birth control pills) for severe symptoms. Sometimes, the doctor may treat cysts in the office by a method called aspiration, done with a needle. The needle removes the fluid, which will make the lump disappear. If it doesn't go away completely, a biopsy may be needed to rule out cancer.

DOs and DON'Ts in Managing

Fibrocystic Breast Changes:

✓ **DO** become familiar with the normal feel of your breasts by monthly breast self-examinations.

✓ **DO** contact your doctor if you have changes in symptoms or feel something different during your self-examination.

✓ **DO** wear a well-fitting support bra, especially during exercise or vigorous activity.

⃠ **DON'T** use too much caffeine.

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⦸ **DON'T** skip mammograms or other routine breast health care.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website: http://www.acog.org**
- WebMD **Website: http://www.webmd.com**
- American Cancer Society **Website: http://www.cancer.org**
- Susan G. Komen Breast Cancer Foundation **Website: http://www.komen.org**

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MANAGING YOUR

FIBROMYALGIA

What Is Fibromyalgia?

Fibromyalgia (FM) is a chronic condition causing pain in muscles, tendons, and ligaments. In FM, specific places in the body where pain is felt are called *tender points*.

What Causes Fibromyalgia?

The cause is unknown, but it is not thought to be an infection or a hereditary problem. Possibilities include poor sleep, certain chemicals called serotonin and substance P, muscle abnormalities, and stress hormones.

FM can occur in both men and women but is most common in women aged between 20 and 50 and is also common in women older than 60.

What Are the Symptoms of Fibromyalgia?

Pain and fatigue are the main symptoms and can affect activities at work and home.

Pain is usually worse in the upper back and neck and the lower back and hips. Pain can occur near any tender point, however.

Fatigue can be severe. Headaches, numbness or tingling in the hands or feet, and forgetfulness are other symptoms.

How Is Fibromyalgia Diagnosed?

A doctor uses a medical history and an examination of joints and muscles for diagnosis. For a diagnosis of FM, the doctor must find at least 11 of the 18 tender points.

Laboratory tests and x-rays may be done to rule out other diseases causing similar symptoms. Blood tests and x-rays are usually normal in fibromyalgia.

How Is Fibromyalgia Treated?

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No cure exists for FM, but people with FM can feel better with treatment. Medicines, exercise, reducing stress, and improving sleep to reduce fatigue can help people feel better.

Medications can improve the amount and quality of sleep. Interrupted sleep prevents people from reaching the deepest sleep, but medicines can help them reach this deeper stage of sleep. As a result, pain decreases. The most common medicines include antidepressants (e.g., milnacipran, amitriptyline, duloxetine). Common side effects include grogginess, dry mouth, constipation, and weight gain.

Exercises help reduce pain. Stretching and posture exercises should be done daily for good body alignment and to prevent pain. Endurance exercises should be done three or four times a week; these include walking, biking, and water therapy. It is important to begin to exercise slowly and to increase gradually. Often people with FM forget how to relax. A counselor can offer relaxation therapy as well as family counseling to see whether depression or family or financial problems are contributing to FM.

DOs and DON'Ts in Managing Fibromyalgia:

✓ **DO** call your doctor if you have drug side effects.

✓ **DO** ask your doctor what over-the-counter pain medications you may take.

✓ **DO** communicate and follow up with your health care workers.

⦸ **DON'T** expect medicines alone to reduce your pain and fatigue. Feeling better involves better sleep, exercise, and stress management.

⦸ **DON'T** take any diet supplement without discussing it first with your doctor.

⦸ **DON'T** stop exercising.

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FOR MORE INFORMATION

Contact the following sources:

- Arthritis Foundation Tel: (800) 283-7800 **Website: http://www.arthritis.org**
- American College of Rheumatology Tel: (404) 633-3777 **Website:**

http://www.rheumatology.org

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CARING FOR YOUR CHILD WITH

FIFTH DISEASE

What Is Fifth Disease?

Fifth disease is a mild, infectious viral illness that occurs in outbreaks, often during the winter and spring. The face has a characteristic rash. The name of the illness relates to its place in a list of childhood diseases developed in the early 1980s. It affects mostly children 5 to 14 years old.

Fifth disease can't be prevented, and children aren't contagious after the rash appears. People usually won't get fifth disease a second time, because immunity to the virus develops.

Healthy people rarely have complications, but children with sickle cell anemia have an increased risk of complications. A pregnant woman has a small risk of miscarriage if infection occurs during the first trimester.

What Causes Fifth Disease?

The cause is a virus called human parvovirus B19. It spreads by means of particles in the air.

What Are the Symptoms of Fifth Disease?

Symptoms usually appear 4 to 14 days after a child is exposed to someone with the disease. Symptoms, which usually last 5 to 10 days, include a fiery red rash on the cheeks that makes the cheek look like it was slapped. The rash then spreads to the rest of the body and has a lacy look to it. Slight tiredness, headache, and itching may occur. Some people have a fever. Adults may have mild pain and swelling in the joints. Many people have no symptoms.

How Is Fifth Disease Diagnosed?

The doctor will diagnose fifth disease on the basis of the physical examination and history. Blood tests aren't usually needed.

How Is Fifth Disease Treated?

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No specific treatment is needed, but symptoms can be controlled. Nonaspirin products (e.g., acetaminophen) can be given for fever and aches. Don't give aspirin to a child with fifth disease. Aspirin can lead to a serious complication called Reye's syndrome.

DOs and DON'Ts in Managing Fifth Disease:

✓ **DO** have your child rest during the early days of the illness.

✓ **DO** have your child drink plenty of liquids.

✓ **DO** use cool cloths or calamine lotion if the rash itches.

✓ **DO** call your doctor if symptoms get worse with normal treatment.

✓ **DO** call your doctor if your child gets symptoms of Reye's syndrome, such as vomiting, restlessness, irritability, and a decrease in the level of consciousness.

⃠ **DON'T** give aspirin to a child with fifth disease.

⃠ **DON'T** worry if the rash recurs after the illness is over, especially during exposure to the sun and temperature changes.

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Allergy and Infectious Diseases Tel: (301) 496-5717 **Website:** **http://www3.niaid.nih.gov**
- The American Academy of Pediatrics Tel: (847) 434-4000 **Website:** **http://www.aap.org**

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- National Institute of Child Health and Human Development Tel: (800) 370-2943 **Web-site: http://www.nichd.nih.gov**

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MANAGING YOUR

FINGER SPRAIN

What Are Finger Sprains?

Sprains are injuries in which ligaments are stretched or torn. Ligaments are tough, fibrous bands of tissue connecting bones. Fingers and thumbs can suffer sprains by being bent in an odd way, commonly during a fall on an outstretched hand. Sprains are common in ball games (such as football, basketball, and handball) and games involving sticks or rackets (such as hockey and lacrosse). Thumb sprains involving collateral (side) ligaments may be called skier's (or gamekeeper's) thumb.

What Causes Finger Sprains?

Accidents in sports can cause sprains, as when balls hit fingers in ball games, or sticks (as in hockey) forcefully bend fingers. Forceful falls can also cause sprains. People with previous finger injuries, poor strength and flexibility, and poorly fitting or inadequate protective equipment may have greater risk of sprained fingers.

What Are the Symptoms of Finger Sprains?

Symptoms include pain over the joint in the finger, pain when bending the finger, joint swelling, tenderness, and restricted finger movement. A popping or tearing feeling inside the finger may occur. Severe injuries or complete tears of the ligament can cause an unstable finger.

How Are Finger Sprains Diagnosed?

The doctor makes a diagnosis from an examination of the finger and sometimes x-rays to make sure that bones aren't broken (fractured). Magnetic resonance imaging (MRI) may help with diagnosis of certain injuries of collateral ligaments.

How Are Finger Sprains Treated?

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Treatment goals are to reduce pain and swelling and help people return to sports or activities as soon as safely possible. First treatments include RICE: rest, ice, compression, and elevating the hand. Ice packs can be put on the finger for 15 to 20 minutes, four times a day, until swelling and pain are gone. Putting the hand on a pillow to raise it for 2 days can also help swelling go away. Anti-inflammatory drugs (ibuprofen, aspirin) or other medicines (acetaminophen) can reduce pain and inflammation. To support sprained fingers, they can be taped to other fingers (buddy taped) or splints can be put on the finger. Splinting that prevents movement too long can make fingers stiffen, however. Thumb sprains (skier's thumb) may need longer immobilization, especially if a ligament may have been torn, and sometimes surgery to repair the damage. Sprained fingers can be swollen and have reduced movement and strength for weeks or even months, but without joint dislocation or broken bones, symptoms may go away in 1 to 3 weeks. Returning to activities too soon may worsen the injury and lead to permanent damage, but in some cases the finger may be protected for early return.

Exercises such as ball squeezing and finger extension can help fingers get stronger during healing. Physical therapy can help stiff joints move better.

DOs and DON'Ts in Managing Finger Sprains:

✓ **DO** use ice and elevation to keep swelling down.

✓ **DO** exercises (ball squeezing, finger extension, passive range of motion) to help your finger get stronger during healing.

✓ **DO** take medicines as directed.

✓ **DO** learn and use the right sports techniques and equipment.

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✓ **DO** use support, like buddy taping, to protect healing ligaments, especially with early return to activity.

⦸ **DON'T** return to activities too soon. Your injury can get worse.

⦸ **DON'T** wrap your finger too tightly, or it may cut off circulation.

⦸ **DON'T** put ice directly on skin. Wrap it in a towel.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website:** **http://www.aaos.org**
- The American Orthopaedic Society for Sports Medicine Tel: (847) 292-4900 **Website:** **http://www.sportsmed.org**

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MANAGING YOUR

FOLLICULITIS

What Is Folliculitis?

Folliculitis is a common skin infection of hair follicles or skin around the hair. When follicles become damaged, they get infected and small, white, pus-filled bumps (pustules) appear on the skin's surface. The skin usually looks inflamed (red). It can affect people of any age and race.

What Causes Folliculitis?

Bacteria, usually ones called *Staphylococcus* or *Pseudomonas*, cause folliculitis. Anyone can get the infection, but people who have poor hygiene, are diabetic, or have chronic illnesses have a higher chance of getting it. Using public hot tubs or saunas in hotels is a major risk factor.

What Are the Symptoms of Folliculitis?

The most common symptom is a small pustule or pimple around a hair follicle. Pustules can appear anywhere on the body. They may be painful to touch. Skin around them may be red and itchy. Pimples can crust over.

How Is Folliculitis Diagnosed?

The doctor usually diagnoses folliculitis by looking at the skin. Sometimes, the doctor may want to take a sample of a pustule for study in a laboratory when the diagnosis is unclear or when suspecting folliculitis due to a bacterium resistant to common antibiotics.

How Is Folliculitis Treated?

Mild cases may get better on their own, without treatment. They usually start to clear up in 2 to 3 days. The affected area should be washed with an antibacterial soap and kept very clean. Sometimes, prescription or over-the-counter antibiotic ointment can help healing. Folliculitis can come back, however.

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People with more severe cases may need to take antibiotics by mouth. The doctor will prescribe these. Antibiotics usually heal folliculitis in 1 to 2 weeks.

DOs and DON'Ts in Managing Folliculitis:

✓ **DO** bathe at least once daily to keep your skin clean. Your doctor may prescribe a special soap to use.

✓ **DO** follow your prescribed medical treatment and take good care of yourself if you have diabetes or another chronic condition. You are more likely to get folliculitis.

✓ **DO** avoid using public hot tubs or saunas.

✓ **DO** use cool compresses for itching and irritation.

✓ **DO** try to keep clothing from rubbing against the pustules.

✓ **DO** try to avoid shaving the area with pustules, such as your face and neck. If that's not possible, use a clean new razor or an electric razor each time you shave.

✓ **DO** call your doctor if you have folliculitis that recurs.

✓ **DO** call your doctor if you develop signs of spreading infection.

⃠ **DON'T** scratch the affected area. That can cause the infection to spread.

⃠ **DON'T** share towels, face cloths, and clothing. Using personal items of others can spread the infection.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Dermatology Tel: (866) 503-SKIN (503-7546) **Website:** **http://www.aad.org**

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MANAGING YOUR

FOOD ALLERGIES

What Are Food Allergies?

Food allergies are abnormal responses to foods. They're triggered by the body's immune (infection-fighting) system. They may be chronic (last a long time) or acute (sudden). Acute reactions can cause serious illness or even life-threatening reactions called anaphylaxis.

Food allergies are most common in children, especially babies and toddlers. Food allergies occur in 6% to 8% of young children and about 4% of adults. Children may outgrow allergies to milk, soy, wheat, and eggs.

What Causes Food Allergies?

The immune system mistakenly sees a food as harmful (an allergen). Cells make immunoglobulin E (IgE) antibodies to fight the food. Even a tiny amount of the food can trigger symptoms. Foods accounting for 90% of all such reactions are milk, eggs, peanuts, tree nuts (walnuts, cashews), fish, shellfish (shrimp, lobster, crab), soy, and wheat. Adults usually have reactions to fish, shellfish, peanuts, tree nuts, fruits, and eggs. Children react to eggs, milk, peanuts, and tree nuts. Tree nuts and peanuts are leading causes of anaphylaxis.

What Are the Symptoms of Food Allergies?

Symptoms usually start minutes to 2 hours after food is eaten. Symptoms include tingling in the mouth and swelling of lips, face, tongue, and throat. Others are wheezing, nasal congestion, hives, itching, and eczema. People can have nausea, vomiting, cramps or pain in the abdomen (belly), diarrhea, or low blood pressure. Severe reactions include trouble breathing, dizziness, lightheadedness, fainting, chest or throat tightness, rapid or abnormal heartbeat, losing consciousness, and even death.

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How Are Food Allergies Diagnosed?

The medical (and family) history is most important for diagnosis. The doctor also uses food diaries, elimination diets, skin tests, blood tests, and food challenges. In elimination diets, possible problem foods are avoided for a week or two and then are added back into the diet one at a time.

How Are Food Allergies Treated?

Avoiding problem foods is most important, as is learning how to do this. Reading ingredient labels for all foods is critical.

Over-the-counter antihistamines can help minor reactions. Doctors sometimes prescribe antihistamines and steroids. Severe reactions may need emergency epinephrine and a trip to the hospital. Many people carry an autoinjector (EpiPen, Twinject) that contains epinephrine.

DOs and DON'Ts in Managing Food Allergies:

✓ **DO** avoid eating problem foods.

✓ **DO** always read food labels.

✓ **DO** talk to your doctor about getting a prescription for an emergency epinephrine injector pen. Learn how to use the autoinjector and teach others around you to use it. Always carry it with you.

✓ **DO** wear a medical alert bracelet or necklace to let others know about your allergy.

✓ **DO** inform family, babysitters, and teachers if your child has food allergies. Make sure that they know what to do in an emergency (call 911).

✓ **DO** learn about food allergies. Join a support group if you think that would help.

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⦸ **DON'T** eat possible problem foods at restaurants and social gatherings.

⦸ **DON'T** give your baby foods other than breast milk for at least the first 4 months. It may protect your baby against food allergies.

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FOR MORE INFORMATION

Contact the following sources:

- National Digestive Diseases Information Clearinghouse E-mail: nddic@aerie.com **Website: http://www.niddk.nih.gov/health/digest/nddic.htm**
- American College of Gastroenterology Tel: (703) 820-7400 **Website: http://www.acg.gi.org**

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MANAGING YOUR

FORGETFULNESS

What Is Forgetfulness?

Many older people worry about becoming forgetful. They think that forgetfulness is the first sign of Alzheimer's disease. Memory loss and confusion can be a normal part of aging. However, most people stay alert and able as they age, even though it may take them longer to remember things.

How Does Forgetfulness Differ from Dementia?

Many people have memory lapses. Some are serious, and others aren't.

Many medical conditions cause confusion or Alzheimer-like symptoms. Some conditions can be reversed or treated; others cannot. Fever, dehydration, vitamin deficiency, and poor nutrition can be treated. Reactions to medicines, thyroid problems, or minor head injury can also be helped.

Emotional problems and depression can be mistaken for dementia. Older people who are retiring or coping with death can feel sad, lonely, worried, or bored. They can get confused or forgetful.

People who have serious changes in memory, personality, and behavior may have dementia. The two most common forms in older people are Alzheimer's disease and multi-infarct dementia. The last kind is also called vascular dementia. These types of dementia cannot be cured.

In Alzheimer's disease, symptoms start slowly and get worse. In multi-infarct dementia, small strokes or changes in the brain's blood supply may cause symptoms to start suddenly. High blood pressure can cause this dementia.

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Dementia symptoms include asking the same questions often and becoming lost in familiar places. People cannot follow directions and are disoriented about time, people, and places. They neglect personal safety, hygiene, and nutrition.

How Is Forgetfulness Diagnosed?

The doctor will do physical, neurological, and psychiatric examinations. The doctor will want a complete medical history.

The doctor may test blood, urine, memory, problem solving, counting, and language skills. In special cases, brain computed tomography (CT), magnetic resonance imaging (MRI), or positron emission topography (PET) scans may help the doctor rule out another disorder or changes of a normal aging brain.

How Is Forgetfulness Treated?

Aging-related forgetfulness needs no treatment. Exercising the mind, having new interests or hobbies, and being involved in activities sharpen the mind. Keeping physically fit stimulates the body. Limiting alcohol can prevent brain damage.

Many people find it useful to plan tasks, make to-do lists, and use notes, calendars, and other memory aids.

Stress, anxiety, or depression can make people forgetful. If these feelings last a long time, treatment may include counseling, medicine, or both.

Even for dementia, a neurologist, psychiatrist, family doctor, internist, and geriatrician can help people and families cope. A geriatrician specializes in care of elderly people. For people with early and middle-stage Alzheimer's disease, medicines may keep some symptoms from getting worse. People with multi-infarct dementia should prevent strokes. Controlling high blood pressure, high cholesterol, and diabetes and not smoking can do this.

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Many people with dementia do not need medicine for mild problem behaviors. Some people may take medicine for mild agitation, anxiety, depression, or sleeping problems.

No special diets or supplements prevent or reverse Alzheimer's disease or multi-infarct dementia. However, a balanced diet helps good health and prevent strokes.

Family and friends can help people continue their routines, activities, and social contacts. Big calendars, lists of plans, notes about things to do for safety, and written directions for using household items can help memory.

DOs and DON'Ts in Managing Forgetfulness:

✓ **DO** visit your doctor if you are experiencing forgetfulness.

✓ **DO** exercise your mind by developing new interests or hobbies.

✓ **DO** make to-do lists and use notes, calendars, and other memory aids.

⃠ **DON'T** drink alcohol excessively.

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FOR MORE INFORMATION

Contact the following sources:

- Alzheimer's Association Tel: (800) 272-3900 (24-hour helpline) **Website: http://www.alz.org**
- Alzheimer's Disease Education and Referral Center Tel: (800) 438-4380 **Website: http://www.alzheimers.org**

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MANAGING YOUR

FRIEDREICH'S ATAXIA

What Is Friedreich's Ataxia?

Ataxia refers to movement problems, such as being clumsy or awkward and unsteady. Friedreich's ataxia is a rare genetic disease that damages the nervous system. The result can range from muscle weakness and speech problems to heart disease and diabetes. The disease progression varies from person to person, but years after first symptoms, people may be confined to a wheelchair. Most people die in early adulthood if they have severe heart disease, a common cause of death in this condition. Some people with less severe symptoms live much longer. Males and females are equally affected.

What Causes Friedreich's Ataxia?

The disease is autosomal recessive, which means a person must inherit two genes with the mutation, one from each parent. Nerve tissue in the spinal cord and nerves controlling muscle movement in arms and legs degenerate and cause the movement problems.

What Are the Symptoms of Friedreich's Ataxia?

Symptoms usually start between ages 5 and 15. They rarely start as young as 18 months or as old as 30 years. The first one is usually walking problems (gait ataxia). It slowly worsens and spreads to the arms and then the trunk. Foot deformities (clubfoot, involuntary bending of toes, hammer toes, or foot turning in) may be early signs. Muscles (especially in feet, lower legs, and hands) weaken and waste away, and deformities develop. Other symptoms include loss of reflexes (in knees and ankles) and loss of feeling in extremities, which may spread to other parts of the body. People get tired easily, and speech gets slurred and slow. Rapid, rhythmic, involuntary movements of eyeballs are common. Most people get scoliosis (spine curves to one side), which

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can cause breathing problems.

Other symptoms (chest pain, shortness of breath, palpitations, fast heart rate) result from heart disease. As the disease progresses, some people get diabetes and some lose hearing or eyesight.

How Is Friedreich's Ataxia Diagnosed?

The doctor will make a diagnosis from the medical history and physical examination. A specialist (neurologist) should confirm the diagnosis.

Blood tests, MRI, and nerve conduction studies will be done.

How Is Friedreich's Ataxia Treated?

So far, no treatment can cure this condition. However, treatment of symptoms and complications can help people function as long as possible.

Drugs can treat diabetes and heart conditions. Braces or surgery can help foot deformities and scoliosis. Physical therapy is helpful to maintain function.

DOs and DON'Ts in Managing

Friedreich's Ataxia:

✓ **DO** realize that Friedreich's ataxia is rare. Find doctors with experience with this disease.

✓ **DO** understand that this progressive disease will need services of a health care team, such as physical therapist, occupational therapist, speech therapist, and social workers.

✓ **DO** call your doctor if you fall often or have trouble swallowing, shortness of breath, or chest pain.

✓ **DO** call your doctor if you have symptoms of diabetes (e.g., thirst, increased urination, weight loss).

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✓ **DO** call your doctor if you want genetic counseling.

⃠ **DON'T** be afraid to ask for a second opinion.

⃠ **DON'T** forget that Friedreich's ataxia is an inherited genetic disease, and genetic counseling for family members is helpful.

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FOR MORE INFORMATION

Contact the following sources:

- Brain Resources and Information Network National Institute of Neurological Disorders and Stroke Tel: (800) 352-9424 **Website: http://www.ninds.nih.gov**
- Friedreich's Ataxia Research Alliance Tel: (703) 413-4468
- National Ataxia Foundation Tel: (763) 553-0020 **Website: http://www.ataxia.org**
- Genetic Alliance Tel: (800) 336-GENE (336-4363) **Website: http://www.geneticalliance.org**

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MANAGING YOUR

FROSTBITE

What Is Frostbite?

Frostbite is the condition in which living human tissues freeze and are damaged because of exposure to low temperatures. Frostbite will most likely affect the hands, feet, nose, and ears.

Frostbite can be a very serious injury. Recovery of nearby tissues can take weeks. People can lose skin, fingers, and toes as well as have deformities and discoloration. People who have frostbite may also suffer from low body temperature (hypothermia).

Children and the elderly are at greater risk than adults.

What Causes Frostbite?

Exposure of bare or poorly protected skin, hands, and feet to freezing temperatures will cause frostbite. Increased wind speed, known as wind chill, is often a factor. Drinking alcohol, being dehydrated, taking beta-blockers (medicine for heart disease), smoking, and having diabetes, peripheral vascular disease (of arteries), peripheral neuropathy (nervous system disorder), and Raynaud's syndrome increase the risk of frostbite.

What Are the Symptoms of Frostbite?

Symptoms include a pins-and-needles feeling, numbness, pain, decreasing ability to sense touch, and red skin. If the problem is recognized and treated at this stage, mild swelling and peeling of the skin may be the only effects. As the process gets worse, the affected area becomes pale and firm. As the area is rewarmed, large blisters, blood blisters, and dead tissue that looks black, blue, or dark gray (from gangrene) can occur.

How Is Frostbite Diagnosed?

The doctor will diagnose frostbite on the basis of the history of exposure to freezing tempera-

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tures and a physical examination.

How Is Frostbite Treated?

The best treatment is prevention! Dress properly for the weather and make sure children are protected and watched closely.

Drink plenty of nonalcoholic and noncaffeinated liquids. Plan ahead and limit exposure to cold when possible.

If frostbite is possible, get to shelter and warmth immediately. Immersing the injured area in warm water (104° F) is best. Don't use hot water because it may cause more injury.

If possible, rewarm the entire body, encourage fluid intake, and raise the affected area after rewarming.

If blisters occur, don't burst them. Wrap the area in dry, clean bandages and get emergency care.

DOs and DON'Ts in Managing Frostbite:

✓ **DO** watch weather conditions and dress properly.

✓ **DO** drink plenty of nonalcoholic liquids.

✓ **DO** get indoors at the first sign of symptoms.

✓ **DO** protect and watch small children closely in freezing weather.

✓ **DO** raise the injured area after rewarming.

✓ **DO** warm the entire body if possible.

✓ **DO** remove all wet clothing as soon as possible.

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✓ **DO** get emergency care immediately if blisters or dead tissue appear.

✓ **DO** call your doctor if you think that you have frostbite.

⃠ **DON'T** rub the injured area with snow! This makes the injury worse.

⃠ **DON'T** drink alcohol before going out in freezing cold.

⃠ **DON'T** become dehydrated in freezing weather.

⃠ **DON'T** ignore frostbite's early symptoms: pain, numbness, and redness.

⃠ **DON'T** burst blisters that form.

⃠ **DON'T** let frostbitten parts freeze again.

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FOR MORE INFORMATION

Contact the following source:

- American Red Cross Tel: (800) REDCROSS (733-2767) **Website:** **http://www.redcross.org**

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MANAGING YOUR

FROZEN SHOULDER

What Is Frozen Shoulder?

A "frozen shoulder" is a medical term that describes a severe injury that affects the movement of the shoulder and the arm. A frozen shoulder becomes stiff and painful, with limited range of motion. The space inside the shoulder joint slowly gets smaller. Frozen shoulder may take months to years to improve.

A frozen shoulder develops in stages. In the first stage (freezing), people notice shoulder pain and that it's harder to move that arm. This stage usually lasts about 4 months. In the next 4 months, the shoulder stays very painful. It's possible to move the arm only a little. This is known as being frozen. In the last stage, thawing, pain slowly goes away, and the arm can be moved again. This phase also lasts about 4 months in most cases.

What Causes Frozen Shoulder?

Causes of spontaneous frozen shoulder are unknown. A long period of immobilization, such as with wearing a sling or a cast after an injury, can cause it. Things that can increase chances of getting a frozen shoulder include long-term bed rest, shoulder injury, diabetes, stroke, Parkinson's disease, and thyroid problems.

What Are the Symptoms of Frozen Shoulder?

Pain occurs throughout the shoulder area. The pain is in bones and the soft tissues of the shoulder joint. Other nearby bones, including the scapula (shoulder blade) and clavicle (collarbone), can also be painful. Pain can reach down into muscles of the upper arm. The pain occurs at the front and side of the shoulder. It's constant, even at rest and at night.

Besides the pain, movement becomes very limited. It becomes very hard to lift the arm.

How Is Frozen Shoulder Diagnosed?

The doctor makes a diagnosis from a physical examination. The doctor may order x-rays to rule

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out other illnesses that may cause symptoms. These conditions include degenerative arthritis, tumors, and shoulder dislocation.

How Is Frozen Shoulder Treated?

When frozen shoulder occurs without an injury or operation, conservative treatment with physical therapy is best. When it develops after shoulder surgery, more aggressive treatment, including more surgery, may be needed.

The doctor can prescribe different treatments, including nonsteroidal antiinflammatory drugs (NSAIDs) for pain. Sometimes, stronger pain pills are ordered if NSAIDs don't help.

The key to recovery is to keep moving. Physical therapy, home exercises, and occupational therapy can be prescribed to relieve pain and maintain arm movement. Occupational therapy helps continue normal activities.

The doctor may inject steroids into the joint itself. In some cases, surgery or manipulation of the shoulder may be needed.

After recovery, frozen shoulder usually won't occur in the same shoulder. Sometimes the other shoulder can become frozen.

DOs and DON'Ts in Managing Frozen Shoulder:

✓ **DO** take pills as your doctor directs.

✓ **DO** follow all instructions from the physical and occupational therapists.

✓ **DO** exercises as instructed.

✓ **DO** call your doctor if you have symptoms that worry you.

✓ **DO** call your doctor if you have shoulder pain that doesn't respond to rest and is related to

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decreased range of motion of the shoulder joint.

✓ **DO** use and move your shoulder normally. A frozen shoulder often follows periods of lack of use, or immobility, in a shoulder.

⃠ **DON'T** forget to do exercises.

⃠ **DON'T** stop your physical therapy without talking to your doctor.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopaedic Surgeons Tel: (800) 346-AAOS (346-2267) **Website: http://www.aaos.org**
- American Physical Therapy Association Tel: (800) 999-2782 **Website: http://www.apta.org**
- American College of Rheumatology Tel: (404) 633-3777 **Website: http://www.rheumatology.org**
- Arthritis Foundation Tel : (800) 568-4045 **Website: http://www.arthritis.org**

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MANAGING YOUR

GALACTORRHEA

What Is Galactorrhea?

Galactorrhea is a condition in which an abnormal discharge comes from the breast. A milky fluid seeps from the nipples of women who are not breast-feeding. It's fairly common in women who have had children and in women who were recently pregnant or stopped breast-feeding. It also occurs somewhat often in newborn infants (this used to be called witch's milk). In most women, it usually stops without treatment. It is a rare condition in men.

What Causes Galactorrhea?

The cause is usually irritation or stimulation of the breast, which can happen with an injury, surgery, or just squeezing the nipples. Soaps, creams, and scratchy clothing can also cause it.

In most women, galactorrhea is most likely when the level of female hormone (estrogen) changes, such as when starting or stopping birth control pills, after surgery to remove the ovaries, or after an abortion.

In women who never had a baby or in men, it can be due to a more serious problem. Such causes include medicines, kidney or liver disease, or a growth in the pituitary gland (an endocrine gland near the brain). This growth can be very serious because it may be cancerous, and this gland controls many body functions.

What Are the Symptoms of Galactorrhea?

The main symptom is a milky fluid seeping from the nipples. It may seep on its own or only if the nipples are squeezed.

How Is Galactorrhea Diagnosed?

The doctor will do a physical examination and blood tests to measure hormone levels, such as

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prolactin.

Your doctor may also order magnetic resonance imaging (MRI) or computed tomography (CT) of the head. These tests take pictures of the inside of the brain and may show whether there is a growth on the pituitary gland.

How Is Galactorrhea Treated?

If medicine is the cause, the doctor may recommend stopping it. If galactorrhea continues, the doctor may prescribe a medicine that will stop it.

Surgery, radiation therapy, or medications will be used to treat a growth on the pituitary gland. With surgery, the growth will be removed. With radiation therapy, a special x-ray machine is used and causes the growth to shrink. Radiation therapy works slowly, often taking several months to shrink the tumor. Medication will decrease the abnormal hormone levels produced by the pituitary.

DOs and DON'Ts in Managing Galactorrhea:

✓ **DO** wear a breast binder. A breast binder or firmly fitting bra can help prevent fabric from rubbing your nipples, which can cause stimulation or irritation and lead to galactorrhea.

✓ **DO** call your doctor about symptoms that worry you.

⦸ **DON'T** squeeze your breasts or nipples. This can stimulate your breasts and cause more milky fluid to seep from your nipples.

⦸ **DON'T** forget follow-up doctor appointments.

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FOR MORE INFORMATION

Contact the following sources:

- Pituitary Network Association Tel: (805) 499-9973 **Website: http://www.pituitary.org**
- American Academy of Family Physicians Tel: (800) 274-2237 **Website:**

  http://www.aafp.org

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MANAGING YOUR

GALLSTONES

What Are Gallstones?

Gallstones are solid deposits of cholesterol and other substances in bile that develop because the levels of these chemicals become unbalanced. The gallbladder is a small sack located underneath the liver. It stores bile that the liver makes and squirts the bile into the bowel (intestine) when a meal is eaten. Bile helps digest fats in the food. Under certain conditions, the gallbladder can form gallstones (cholelithiasis).

Gallstones are common: up to 20% of men and 40% of women get gallstones. More women get gallstones because of the effects of estrogen (a female hormone) on bile. Being overweight, aging, and fasting for a long time increase the risk of getting gallstones.

What Are the Symptoms of Gallstones?

Most gallstones produce no symptoms and may never lead to trouble, but they can cause intense pain if they obstruct bile flow. If a gallstone gets stuck in the tube (duct) that takes bile to the bowel, the gallbladder will squeeze harder, and the duct may tighten around the stone. Severe cramps in the belly (abdomen), or maybe between the shoulder blades, will result. Feeling sick to the stomach and vomiting are likely. Symptoms go away if the stone falls back into the gallbladder or moves through the bile duct into the bowel. A gallstone stuck at the end of the duct may cause swelling (inflammation) in the pancreas, and the skin and eyes may turn yellow (jaundice) if the bile ducts are blocked and there is a backup of bile.

How Are Gallstones Diagnosed?

Ultrasound (a special x-ray machine that uses sound waves to get pictures of body organs) can be used to find almost all gallstones and is usually the first test ordered. When ultrasound shows

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unclear results, the doctor can use a special x-ray test (HIDA scan).

How Are Gallstones Treated?

Gallstones can be cured by surgically removing the gallbladder and gallstones (cholecystectomy). This is usually done with a laparoscopic method using only tiny cuts, instead of one large cut, for the doctor to insert instruments into the belly to remove the gallbladder. This operation allows a shorter recovery time and can be an outpatient surgery.

Treatment of gallstones in people without symptoms (asymptomatic) remains unclear. Some doctors recommend avoiding surgery unless symptoms are present. Others suggest surgery because of possible complications and the risk of complications from surgery is generally small. You should discuss the situation with your doctor, because you may have a higher risk (e.g., if you have diabetes, heart disease, emphysema).

In rare cases when surgery is too dangerous, your doctor may suggest drugs to dissolve the gallstones, but medicines may not work and must be used for a long time.

DOs and DON'Ts in Managing Gallstones:

✓ **DO** maintain a normal weight. If you are overweight, ask your doctor to help you with slow, steady weight loss.

✓ **DO** notify your doctor if you have pain that you think may be related to gallstones. Call your doctor immediately if you have a fever with the pain.

⃠ **DON'T** eat meals high in fat, extra-large meals, and foods that cause stomach upset. Fatty foods make the gallbladder tighten and it may squeeze a stone into the duct. Even more important, avoid high-fat meals after following a low-fat diet.

⃠ **DON'T** fast for long periods or go on a crash diet.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Surgeons Tel: (312) 202-5000 **Website: http://www.facs.org**
- American College of Gastroenterology Tel: (703) 820-7400 **Website:**

http://www.acg.gi.org

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MANAGING YOUR

GANGLIA

What Are Ganglia?

Ganglia are fluid-filled sacs commonly found on hands or wrists.

What Causes Ganglia?

The exact cause is unknown, but trauma or degeneration of tissue lining joint covers (capsules) and sheaths (synovium) around tendons can be causes. Synovial tissue makes fluid that lubricates joints, and ganglia are protrusions or expansions of this tissue. Ganglia are three times more common in women than in men. They usually occur in people between 20 and 50 years old. Ganglia aren't contagious.

What Are the Symptoms of Ganglia?

Ganglia occur most often (50% to 70% of cases) on the back of the wrist. The next most common site is over the front of the wrist. Other sites are fingers. They occur on either hand, usually as single bumps that are firm, smooth, and round. When pushed, they may have a wave-like movement.

Ganglia usually develop for months but can arise suddenly. Some people may have pain, because of pressure on nearby structures. Hand numbness and muscle weakness are other symptoms.

How Are Ganglia Diagnosed?

The doctor usually makes a diagnosis from physical examination. The doctor may order x-rays to rule out other bone or joint abnormalities. Other possible causes of a mass on the hand or wrist include lipoma (fatty tumor), gout, rheumatoid arthritis, osteoarthritis, aneurysm of a radial artery, and infection. Ultrasonography sometimes helps by showing a smooth wall of a cyst rather than a

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solid mass.

How Are Ganglia Treated?

Treatment may not be needed unless pain or muscle weakness is present or cosmetic issues are a concern.

Aspiration with a large needle, followed by injection of cortisone, can be tried. Ganglia come back in 35% to 40% of cases.

If these treatments don't work or ganglia come back, surgery is the best treatment. The operation is called a total ganglionectomy and cures ganglia in 85% to 95% of cases.

Complications of ganglia include carpal tunnel syndrome (pressure on medial nerve) and also pain and muscle weakness and pressure on the radial nerve and radial artery. Complications of ganglion surgery include infection, scar formation, and recurrence.

DOs and DON'Ts in Managing Ganglia:

✓ **DO** understand that ganglia are usually not treated surgically unless certain symptoms appear or cosmetic concerns are an issue.

✓ **DO** go to follow-up appointments with your doctor, especially if the mass changes (e.g., size, redness, warmth, drainage).

✓ **DO** avoid repetitive movements of hands and wrists. It will lower the risk of having ganglia.

✓ **DO** call your doctor if you have pain with ganglia, muscle weakness, or numbness in the area of the ganglia.

✓ **DO** call your doctor if drainage, redness, fever, chills, or sweats occur after surgery.

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✓ **DO** call your doctor if the cyst returns after treatment.

⃠ **DON'T** be worried. Ganglia are not cancer or associated with cancer.

⃠ **DON'T** forget that, if surgery is indicated, the operation is usually done with local anesthesia, not general anesthesia. You can expect complete use of the arm and hand by 2 to 6 weeks after surgery, depending on the ganglia location.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Rheumatology Tel: (404) 633-3777 **Website:** **http://www.rheumatology.org**
- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website:** **http://www.aaos.org**

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MANAGING YOUR

GASTRINOMA (ZOLLINGER-ELLISON SYNDROME)

What Are Gastrinomas?

The pancreas is an organ in the abdomen (belly) next to the liver and stomach. As part of the digestive system, it makes substances (pancreatic enzymes) that help with digestion. As part of the endocrine system, pancreatic cells also make substances called hormones (such as insulin).

Gastrinomas are small tumors in the pancreas that make the hormone gastrin. This hormone causes the stomach to release acid. Too much acid because of high levels of gastrin leads to ulcers. Gastrinomas can cause Zollinger-Ellison syndrome.

People with the rare Zollinger-Ellison syndrome have three conditions: too much acid in the stomach, peptic ulcer disease, and gastrinomas. Usually, people have more than one gastrinoma, typically in the pancreas but they can also be found in the first part of the small intestine (duodenum). The syndrome usually occurs between the ages of 30 and 60.

What Causes Gastrinomas?

The cause is unknown, but it may be genetic, because many gastrinomas occur in people with an inherited disease called multiple endocrine neoplasia type I (MEN I).

What Are the Symptoms of Gastrinomas?

Abdominal pain, usually in the upper middle part, occurs with an empty stomach. This pain is like pain in peptic ulcer disease, but it's more severe and is more resistant to the usual doses of medications used for peptic ulcers. Nausea and vomiting can occur. Diarrhea is also common.

How Are Gastrinomas Diagnosed?

The doctor makes a diagnosis from symptoms, blood test measuring gastrin, and tests that stimulate gastrin release. Measuring the amount of stomach acid made per hour also helps

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diagnosis.

The doctor does upper endoscopy to look for stomach ulcers. Endoscopy involves putting a tube with a lighted tip into the stomach. Other tests used to find the gastrinoma are computed tomography (CT), magnetic resonance imaging (MRI), angiography, and ultrasonography. Gastrinomas are often cancerous and tend to spread to nearby lymph nodes (glands) and liver.

How Are Gastrinomas Treated?

Treatment goals are to control excess acid secretion and remove the gastrinoma. Medicines can reduce acid production, heal ulcers, and prevent ulcers from returning. They don't cure the gastrinoma. Only surgery and complete removal of the gastrinoma can cure it. Unfortunately, only 30% of cases are cured because the tumors are so small and hard to find.

DOs and DON'Ts in Managing Gastrinomas:

✓ **DO** get advice from centers with experience in this syndrome.

✓ **DO** get the advice of a gastroenterologist (specialist in GI disorders) and surgeon.

✓ **DO** call your doctor if you have abdominal pain or diarrhea.

✓ **DO** call your doctor if you have pain, drainage, or fever after surgery.

⃠ **DON'T** ignore abdominal pain, especially if it doesn't respond to usual treatment.

⃠ **DON'T** forget to tell your doctor about family history related to this disease.

⃠ **DON'T** miss follow-up appointments after surgery. Blood tests and acid-stimulating tests help rule out return of gastrinomas.

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FOR MORE INFORMATION

Contact the following sources:

- National Digestive Diseases Information Clearinghouse Tel: (800) 891-5389 **Website:** **http://digestive.niddk.nih.gov**
- American Gastroenterological Association Tel: (301) 654-2055 **Website:** **http://www.gastro.org**
- American College of Gastroenterology Tel: (703) 820-7400 **Website:** **http://www.acg.gi.org**
- American College of Surgeons Tel: (312) 202-5000, (800) 621-4111 **Website:** **http://www.facs.org**

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MANAGING YOUR

GASTRITIS

What Is Gastritis?

Gastritis is an inflammation (swelling, redness) of the lining of the stomach. This common condition affects almost everyone at some point in life. Most cases are short-term and have no lasting effects.

What Causes Gastritis?

The many causes include lifestyle excesses (e.g., smoking, alcohol, caffeine). Gastritis is also a side effect of many medicines, such as aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs). Other causes are bacterial and viral infections, stress from surgery, kidney failure, severe burns, and trauma. These things may increase acid production in the stomach or weaken the lining of the stomach. The bacterium named *Helicobacter pylori* is one of the more common causes of gastritis.

One type of gastritis that doesn't involve increased acid is atrophic gastritis. In this type, the stomach lining becomes damaged and shrunken.

What Are the Symptoms of Gastritis?

The main symptoms are discomfort in the upper abdomen (belly) and cramps. Eating often makes the pain worse. Many people have less appetite. Pain may radiate to the chest, so people think that it's related to the heart. Other symptoms may be bad breath, a burning acid taste in the mouth, and sometimes nausea, vomiting, and bleeding.

How Is Gastritis Diagnosed?

The doctor will diagnose gastritis from the medical history. A physical examination is usually normal or may show slight pain in the stomach area.

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The doctor may schedule upper endoscopy (looking at the stomach through a lighted, flexible tube) to rule out more serious conditions such as stomach ulcers or cancer. During endoscopy, the doctor can take a sample of stomach tissue (biopsy). This tissue can be checked for bacteria (*H. pylori*).

If endoscopy isn't done and symptoms continue, other tests may be done. These tests will also look for *H. pylori* by checking blood, stools (bowel movements), or breath.

How Is Gastritis Treated?

Treatment focuses on symptoms and avoiding the cause. For *H. pylori* infection, a combination of antibiotics and acid-reducing medicines will cure it. Medications such as ibuprofen, naproxen, or aspirin and alcoholic beverages should be avoided.

Mild symptoms are controlled with antacids, over-the-counter histamine-2 (H_2) blockers, or proton pump inhibitors (PPIs). H_2 blockers include famotidine and ranitidine. PPIs include omeprazole and pantoprazole. H_2 blockers and PPIs block stomach acid production. Antacids neutralize stomach acid. Some of these medicines are also available in prescription strength.

For severe gastritis with bleeding, a hospital stay may be needed. Intravenous fluids and medicines are given to control symptoms, reduce stomach acid, and protect the stomach lining.

DOs and DON'Ts in Managing Gastritis:

✓ **DO** eat regularly and not in excess.

✓ **DO** use antacids and over-the-counter H_2 blockers or PPIs for mild symptoms.

✓ **DO** call your doctor if abdominal pain becomes severe or you vomit blood.

✓ **DO** call your doctor if symptoms don't get better after 3 to 5 days of treatment.

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✓ **DO** call your doctor if you get severe chest pain that radiates to your neck, jaw, or arm and is associated with sweating or shortness of breath.

✓ **DO** call your doctor if you have blood with bowel movements or dark tarry stools.

⃠ **DON'T** smoke.

⃠ **DON'T** drink alcohol.

⃠ **DON'T** eat foods that are hard to digest.

⃠ **DON'T** use medicines that can irritate your stomach, such as aspirin and NSAIDs.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- National Digestive Diseases Information Clearinghouse Tel: (800) 891-5389 **Website:** **http://www.niddk.nih.gov/health/digest/nddic.htm**
- American Gastroenterological Association Tel: (301) 654-2055 **Website:** **http://www.gastro.org**
- American College of Gastroenterology Tel: (703) 820-7400 **Website:** **http://www.acg.gi.org**

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MANAGING YOUR

GASTROENTERITIS

What Is Gastroenteritis?

Gastroenteritis is inflammation (redness, swelling) of the stomach and intestines. Viral gastroenteritis, often called stomach flu, is an infection caused by a virus that affects the stomach and small intestine.

What Causes Gastroenteritis?

Many viruses can cause gastroenteritis. These viruses include rotaviruses and noroviruses. People get the virus by eating or drinking contaminated food or water, or by directly contacting someone infected by the virus, such as by shaking hands, kissing, or sharing a drink, food, or utensils. Often, someone with the virus handles food without washing hands after using the bathroom, so the virus is passed on by eating the food.

What Are the Symptoms of Gastroenteritis?

The most common symptoms are vomiting and diarrhea. Others include headache, fever, abdominal cramping, loss of appetite, feeling tired and weak, nausea, chills, and aching muscles.

How Is Gastroenteritis Diagnosed?

The doctor will do a physical examination and review the symptoms. The doctor may also order tests to rule out certain conditions, such as appendicitis, dehydration, or a serious infection.

How Is Gastroenteritis Treated?

Medicines such as antibiotics aren't used for viral gastroenteritis. Antibiotics don't work on viruses, and overusing them can result in growth of antibiotic-resistant bacteria.

The most important thing to do is avoid dehydration (loss of too much body fluid).

Drinking clear fluids allows the stomach and intestines to rest and get better. Fluids should be

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drunk slowly. Fluid loss from diarrhea and vomiting can affect babies and children more than adults, so they may need oral rehydration solutions (such as Pedialyte®). Drinking fluids should start slowly.

If the stomach can keep fluids down, soft, bland foods can be tried slowly. Such foods include toast, broth, apples, bananas, and rice. Avoid dairy products, caffeine, and alcohol.

Medicine may be used to treat symptoms such as nausea, vomiting, fever, and body aches.

People usually get better in a few days, but if not, another visit to the doctor may be needed.

DOs and DON'Ts in Managing Gastroenteritis:

✓ **DO** clean surfaces that have been touched by infected people.

✓ **DO** drink clear fluids, then add food gradually.

✓ **DO** wash your hands often, especially after using the bathroom.

✓ **DO** call your doctor if you have persistent vomiting or diarrhea.

⃠ **DON'T** have close contact (for example, by shaking hands) with others until symptoms have resolved.

⃠ **DON'T** give your child medicine without asking your doctor.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Gastroenterological Association Tel: (301) 654-2055 **Website:**

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http://www.gastro.org

- American College of Gastroenterology Tel: (301) 263-9000 **Website:**

  http://www.acg.gi.org

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MANAGING YOUR

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

What Is Gastroesophageal Reflux Disease (GERD)?

GERD (acid reflux disease) occurs when stomach acid flows up into the esophagus (the tube connecting the mouth with the stomach). The stomach can handle stomach acid, but the throat and esophagus can't. As a result, stomach acid in these areas may cause damage. To some extent, everyone has acid reflux. Normal reflux usually happens after meals, is brief and without symptoms, and rarely happens during sleep. Normal reflux becomes GERD when symptoms occur frequently (generally at least two or three times a week) or the esophagus becomes damaged.

What Are the Causes of GERD?

Abnormalities of the lower esophageal sphincter (LES), a muscle at the bottom of the esophagus, cause GERD. Other causes include hiatal hernias and other pressures on the stomach, such as pregnancy and being overweight. A hiatal hernia is the bulging of the upper part of the stomach into the chest through an enlarged opening in the diaphragm (the sheet of muscle separating the bottom of the ribcage from the abdomen).

What Are the Symptoms of GERD?

The most common symptom is heartburn, a burning feeling in the middle of the chest. It sometimes spreads to the throat. An acid taste may occur. Heartburn affects about 10 million adults in the United States daily. Other symptoms include chronic cough, hoarseness, upset stomach, stomach bloating, and wheezing. More serious symptoms are bleeding, weight loss, and difficulty swallowing.

How Is GERD Diagnosed?

The doctor relies on symptoms and the response to treatment for diagnosis. Life-threatening dis-

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eases, such as heart disease, that can cause symptoms similar to those of GERD must be ruled out. Specific tests are needed for an unclear diagnosis or more serious symptoms. These tests may include upper GI (gastrointestinal) x-ray series, endoscopy (using a scope to look at your esophagus and stomach directly), 24-hour esophageal pH study (measurement of acidity), and esophageal manometry (measures esophageal muscle pressure).

How Is GERD Treated?

First options for mild reflux include eating smaller portions and changing the diet. Certain foods, such as tomatoes and fatty foods, and medicines, such as aspirin, can make symptoms worse. Over-the-counter drugs, including antacids and acid-blocking medicines called H_2 blockers, may help. Antacids neutralize stomach acid. H_2 blockers (e.g., ranitidine or famotidine) prevent or block production of stomach acid. These drugs can be taken before eating to prevent heartburn. Omeprazole is another over-the-counter drug now available, which blocks the action of stomach cells responsible for making acid. It is generally more effective than antacids and H_2 blockers.

People with severe or frequent symptoms may need prescription drugs. In resistant cases, your doctor may refer you to a surgeon to perform an operation called fundoplication to strengthen the LES.

DOs and DON'Ts in Managing GERD:

✓ **DO** eat a healthy diet, rich in fruits, vegetables, and low-fat dairy products. Lower your intake of saturated and total fats.

✓ **DO** raise the head of your bed 6 to 8 inches with wooden blocks.

✓ **DO** maintain a healthy body weight.

✓ **DO** take medicines recommended by your doctor.

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⦸ **DON'T** eat reflux-inducing foods, such as citrus fruits and juices, coffee, peppermint, chocolate, and spicy foods.

⦸ **DON'T** eat large meals.

⦸ **DON'T** eat meals late in the day.

⦸ **DON'T** lie down just after eating.

⦸ **DON'T** wear tight-fitting clothing.

⦸ **DON'T** smoke or use tobacco products.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Gastroenterological Association Tel: (301) 654-2055 **Website:** **http://www.gastro.org**
- American College of Gastroenterology Tel: (703) 820-7400 **Website:** **http://www.acg.gi.org**

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CARING FOR YOUR CHILD WITH

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

What Is GERD?

The common gastroesophageal reflux (GER), or acid reflux, is normal, and babies usually outgrow it by 1 or 2 years old. GERD is the more serious form. It's the most common disorder of the esophagus in children of all ages, especially in premature children and in children with other disorders such as cerebral palsy. The esophagus is the tube that connects the mouth with the stomach. In GERD, the muscle that stops food from returning to the esophagus from the stomach doesn't work well and stomach contents may move in the wrong direction back into the esophagus ("reflux"). Reflux that occurs more than twice a week is GERD and can lead to serious health problems.

What Are the Causes of GERD?

GERD most often occurs in babies with immature digestive tracts. Other causes include anatomic problems of the esophagus and other structures such as hernias, certain medicines, and neurodevelopmental disabilities.

What Are the Symptoms of GERD?

Common symptoms in babies are regurgitation and vomiting. Regurgitation ("spitting up") is return of undigested food back up the esophagus into the mouth, without the force of vomiting. Other symptoms are crying and irritability, arching of the back, breathing problems, refusing food, and failure to thrive. Children may have pain in the abdomen (belly) or heartburn after meals, nausea, coughing, trouble swallowing, asthma, sore throat, ear pain, unhealthy teeth, bad breath, and hoarseness.

How Is GERD Diagnosed?

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The doctor uses a medical and dietary history and physical examination for diagnosis. Other studies are for more serious or unusual symptoms. These studies include X-rays (upper gastrointestinal, or GI, series), endoscopy, and esophageal pH monitoring.

How Is GERD Treated?

Treatment goals are to reduce symptoms, heal the esophagus, and prevent complications. Babies with GERD need lifestyle changes, including thickened formula or breast milk, smaller and more frequent feedings, frequent burping, and keeping upright for longer periods (30 minutes) after feedings. Older children should eat small, frequent meals. Foods to avoid are caffeine-containing sodas; chocolate; peppermint; spicy foods; acidic foods such as oranges, tomatoes, and pizza; and fried and fatty foods. Not eating for 2 to 3 hours before bed may help. Raising the head of the child's bed may work. Weight management of overweight or obese children is important. If these treatments don't work or if children develop serious illnesses, medicines or surgery can be tried. Medicines include antacids, H_2-receptor antagonists (such as ranitidine), and proton pump inhibitors (such as omeprazole).

Antireflux surgery is one of the most common procedures done for babies and young children, but it's generally the last resort because it includes risks.

DOs and DON'Ts in Managing GERD:

✓ **DO** burp your infant frequently, give smaller and more frequent feedings and keep them upright for 30 minutes after feedings.

✓ **DO** give your child a healthy diet, rich in fruits, vegetables, and low-fat dairy products.

✓ **DO** raise the head of your child's bed 6 to 8 inches.

✓ **DO** make sure that your child has a healthy body weight.

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✓ **DO** give medicines recommended by your child's doctor.

⦸ **DON'T** give your child reflux-inducing foods, such as citrus fruits and juices, coffee, peppermint, chocolate, and spicy foods.

⦸ **DON'T** let your child eat large meals.

⦸ **DON'T** feed your child too close to bedtime.

⦸ **DON'T** let your child lie down just after eating.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- The American Academy of Pediatrics Tel: (847) 434-4000 **Website: http://www.aap.org**
- American Gastroenterological Association Tel: (301) 654-2055 **Website: http://www.gastro.org**
- American College of Gastroenterology Tel: (703) 820-7400 **Website: http://www.acg.gi.org**

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MANAGING YOUR

GASTROPARESIS AND GASTRIC MOTILITY DISORDERS

What Are Gastroparesis and Gastric Motility Disorders?

The stomach grinds food into small pieces and sends them to the small intestine. Gastric motility disorders include delayed gastric emptying (gastroparesis, meaning stomach paralysis), rapid gastric emptying (dumping syndrome), functional dyspepsia (indigestion), and cyclic vomiting syndrome.

In gastroparesis, the stomach doesn't work well. It doesn't contract, crush food, or send food to the small intestine in a normal way. Food stays in the stomach too long. Digestion isn't normal. Food can harden into solid chunks (bezoars) that may cause nausea and vomiting and block the stomach.

Gastroparesis affects males and females of almost any age.

What Causes Gastroparesis and Gastric Motility Disorders?

The most common cause is diabetes, which damages nerves that control stomach muscles. Other causes include pregnancy, uremia (kidney failure), gastritis (stomach inflammation), and ulcers. Cancer, infections, and surgery on the stomach or vagus nerve are more causes. Connective tissue disorders, anorexia, bulimia, and gastroesophageal reflux disease (GERD) can lead to these disorders. Medicines causing the conditions include narcotics, calcium channel blockers, antidepressants, and chemotherapy drugs. Endocrine, autoimmune, metabolic, nervous system, and muscle disorders are additional causes. The cause can also be unknown.

What Are the Symptoms of Gastroparesis and Gastric Motility Disorders?

Symptoms include bloating, pain or swelling in the abdomen (belly), nausea, and vomiting. People feel full after eating just a few bites and may have no appetite. Anorexia, heartburn,

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gastroesophageal reflux, and abnormal blood sugar (glucose) levels may occur. People can lose weight because they don't get enough nutrients.

How Are Gastroparesis and Gastric Motility Disorders Diagnosed?

For diagnosis, the doctor may use a nuclear medicine test called a gastric emptying test (scintigraphy). The test involves eating foods or drinking liquids containing a radioactive substance. The dose isn't dangerous. A device similar to a Geiger counter tells how fast food leaves the stomach. The doctor will also perform a physical exam and obtain a detailed medical history to rule out other causes (drugs, diseases). The doctor may also order breath tests, ultrasonography, upper endoscopy, computed tomography, manometry, and X-rays.

How Are Gastroparesis and Gastric Motility Disorders Treated?

Treatment usually means drugs and nutritional support. Surgery or electrical pacing may also be used in resistant cases. Controlling diabetes or other diseases is critical. Weight loss must be watched, so added nutrition can be given if necessary. Eating smaller meals more often may help, as can low-fat, low-fiber foods and liquids (soups) or pureed foods.

Drugs help nausea and vomiting. Promotility drugs can get stomach muscles to contract. Medicines are also given for abdominal pain. Botulinum toxin (Botox) and electrical stimulation are being tried. Feeding tubes and surgery are last resort treatments.

DOs and DON'Ts in Managing Gastroparesis and Gastric Motility Disorders:

✓ **DO** control your glucose levels. You may need to change some of the diabetic medications, or the type of insulin or how you take it.

✓ **DO** avoid high-fiber and fatty foods. High-fat foods include vegetable shortenings, crackers, candies, cookies, snack foods, fried and processed foods, butter, and whole milk. Avoid

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legumes, lentils, and citrus.

✓ **DO** avoid drugs that cause symptoms.

✓ **DO** join a support group if you need one.

⃠ **DON'T** eat big meals. Instead, eat six small, low-fat, low-fiber meals daily.

⃠ **DON'T** drink caffeine or alcohol.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Digestive Diseases Information Clearinghouse E-mail: nddic@aerie.com

  Website: http://www.niddk.nih.gov/health/digest/nddic.htm

- American College of Gastroenterology Tel: (703) 820-7400 Website:

  http://www.acg.gi.org

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MANAGING YOUR

GENERALIZED TONIC-CLONIC SEIZURES

What Are Generalized Tonic-Clonic Seizures?

Generalized tonic-clonic seizures, or grand mal seizures, affect the whole body. They usually involve rigid muscles, severe muscle contractions, and loss of consciousness (fainting). People of any age can have them, as a single seizure or part of epilepsy.

What Causes Generalized Tonic-Clonic Seizures?

Abnormal activity of brain nerve cells occurring at the same time in many parts of the brain causes these seizures. Seizures may be brought on by head injuries, strokes, brain infections, very low blood sugar, and tumors. More than half the time, the cause is unknown.

What Are the Symptoms of Generalized Tonic-Clonic Seizures?

These seizures involve four phases. Often signs (auras) warn of a coming seizure. Auras include an odd feeling, strange taste or odor, and headache. Phase 2 (tonic phase) consists of rigid stiffening of the body for a minute or less, and fainting. The tonic-clonic phase (phase 3) appears as strong muscle contractions and relaxations and convulsions and can last several minutes. Loss of consciousness and loss of bladder and/or bowel control may occur. People may have trouble breathing or temporarily stop breathing. Just after a seizure is the postictal phase (phase 4). People slowly return to consciousness.

Lasting tonic-clonic seizures are an emergency called “status epilepticus.”

How Are Generalized Tonic-Clonic Seizures

Diagnosed?

The doctor will make a diagnosis from a medical history and physical examination. The doctor will do electroencephalography (EEG), a test to check the electrical activity in the brain. Mag-

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netic resonance imaging (MRI) or computed tomography (CT) will be done to get pictures of the brain. Blood tests will also be done to check for other causes of seizures.

How Are Generalized

Tonic-Clonic Seizures Treated?

The main treatment is medicine. Sometimes more than one anticonvulsant drug may be used. The doctor may get blood samples periodically to make sure that the correct dose is being used. Often, medicine will reduce the frequency and severity of seizures, but some people may continue to have them.

DOs and DON'Ts in Managing

Generalized Tonic-Clonic Seizures:

✓ **DO** take your medicine as prescribed to prevent seizures.

✓ **DO** wear a medical alert bracelet stating that you have a seizure disorder and listing your medicines.

✓ **DO** teach your family and friends about your disorder and what to do if you or someone else has a seizure. Prevent injuries by cushioning the head, turning the person on their side, and taking away items that could cause injuries. Don't hold the person down or force anything into the mouth.

✓ **DO** tell someone near you that you feel a seizure starting, and lie down.

✓ **DO** call for medical help if someone is injured during a seizure, has trouble breathing, or doesn't regain consciousness shortly after a seizure.

✓ **DO** call 911 if someone has continuous tonic-clonic seizures. Status epilepticus is a medical

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emergency.

✓ **DO** call your doctor if you have any problems with your medicines.

✓ **DO** call your doctor if your seizures become more frequent or severe.

⃠ **DON'T** operate dangerous machinery or drive unless your doctor approves.

⃠ **DON'T** swim alone.

⃠ **DON'T** climb on ladders or roofs in case you have a seizure.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- Epilepsy Foundation of America Tel: (301) 459-3700 **Website:** **http://www.epilepsyfoundation.org**
- American Academy of Neurology **Website:** **http://www.neurology.org**

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MANAGING YOUR

GENITAL HERPES

What Is Genital Herpes?

Genital herpes is a very contagious infection caused by the herpes simplex virus, or HSV. There are two types of HSV, type 1 and type 2. Type 1 usually causes mouth blisters or cold sores but can also infect the genital area. Type 2 causes most genital herpes cases.

How Is Genital Herpes Transmitted?

Most people get genital herpes from having sex with someone who is infected. The virus settles in a nerve in the body and remains there permanently. Condoms are not a complete barrier because the virus and lesions can also be on thighs and buttocks.

What Are the Symptoms of Genital Herpes?

Many people never have symptoms and don't know that they have herpes until the first outbreak. Symptoms of a first outbreak may include pain and itching in the lip or genital area. Sometimes, during a first outbreak, there may be a feeling of pressure in the abdomen, discharge from the penis or vagina, headache, fever, and difficulty urinating. The first outbreak is the longest and most painful. It may last several days.

HSV starts as small red bumps, which develop into blisters. These blisters become painful open sores. After several days, the sores crust and in time disappear completely. About 50% of people who have a first outbreak of herpes will have more blisters. These outbreaks are usually milder and shorter and usually end in 7 to 10 days. Symptoms vary, so some people may have only one or two outbreaks in a lifetime, but others may have several per year. The cause of repeated outbreaks is unclear. Emotional stress, fatigue, illness, and menstruation may trigger them. As time goes on, the number of outbreaks usually decreases.

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How Is Genital Herpes Diagnosed?

The doctor usually makes a diagnosis from a physical examination. The doctor will also ask questions about symptoms and sexual activity.

Sometimes a sample may be taken from the blisters and sent to a laboratory to confirm that HSV is in the blister or to rule out other illnesses. A blood test can be done to check for antibodies to HSV, which indicate a current or past infection.

How Is Genital Herpes Treated?

No cure exists at this time. Antiviral drugs including acyclovir, famciclovir, and valacyclovir can be prescribed to shorten and prevent outbreaks. The antiviral medicines may be taken at the beginning of symptoms or daily to help prevent frequent outbreaks.

Over-the-counter pain medicine, such as acetaminophen or topical preparations, can be used to relieve discomfort.

DOs and DON'Ts in Managing Genital Herpes:

✓ **DO** take medication as directed.

✓ **DO** keep the infected area clean and dry.

✓ **DO** avoid touching the sores. If you touch them, wash your hands immediately to avoid spreading the infection to another part of your body or to someone else.

✓ **DO** tell sexual partners if you have symptoms for the first time or if you have been diagnosed with herpes.

⦸ **DON'T** pick at the sores. This may cause them to become infected.

⦸ **DON'T** allow the sores to be in direct contact with another person.

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⦸ **DON'T** have sex during an outbreak to avoid infecting your partner.

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FOR MORE INFORMATION

Contact the following sources:

- National Herpes Resource Center Tel: (919) 361-8400 **Website: http://www.ashastd.org**
- American Academy of Dermatology Tel: (847) 330-0030 **Website: http://www.aad.org**

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MANAGING YOUR

GENITAL WARTS

What Are Genital Warts?

Condyloma acuminatum is the medical term for warts that occur in the genital area, including the urethra (the tube taking urine from the bladder to outside the body) and anus. Genital warts are thought to be one of the most common sexually transmitted disease (STD). People who are 17 to 33 years old are at greatest risk of getting genital warts.

What Causes Genital Warts?

The cause is the same human papillomavirus (HPV) that causes other warts. About 90% are caused by HPV-6 and HPV-11. These warts are much more contagious than other warts and are easily passed from skin of infected people. After exposure, warts appear in 1 to 6 months. Having multiple sex partners and prior history of STD are risk factors for getting these warts.

What Are the Symptoms of Genital Warts?

People usually have no symptoms, but itching, burning, and discharge can occur if the warts become irritated or infected. These warts appear on moist surfaces, such as the penis and the entrance to the vagina and rectum. They grow in clusters, as small pink or white nodules. The warts are small, but the clusters can quickly become very large, cauliflower-like masses. Complications of untreated warts can include cervical cancer in females and urinary blockage in males if they occur on the urethra.

How Are Genital Warts Diagnosed?

The doctor will make a diagnosis by the look of the warts at physical examination. The doctor may also do a culture or biopsy of the area. Testing may also be done for other STDs.

How Are Genital Warts Treated?

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A doctor should treat genital warts. Don't use over-the-counter wart removers. Topical medicines such as imiquimod, 5-fluorouracil, podofilox, and trichloroacetic acid cream can be applied to small warts. Larger warts may be treated with liquid nitrogen. Laser treatment or surgical removal may be needed. Warts commonly come back, so treatment may need to be repeated. The doctor may prescribe ointment to apply at home.

DOs and DON'Ts in Managing Genital Warts:

✓ **DO** apply medicine as instructed.

✓ **DO** keep follow-up doctor appointments until all warts are gone.

✓ **DO** tell sexual partners about your condition so that they can be examined and treated.

✓ **DO** avoid sex until warts are completely gone.

✓ **DO** use proper hygiene.

✓ **DO** get tested for other STDs.

✓ **DO** always use latex condoms during sex.

✓ **DO** get vaccinated with HPV recombinant vaccine if you are between ages 9 to 26. It will protect against genital warts caused by HPV types 6, 11, 16, and 18.

✓ **DO** call your doctor if warts come back.

✓ **DO** call your doctor if treated areas show signs of infection: redness, swelling, tenderness, or

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foul smell.

⦸ **DON'T** apply medicine to moles, birthmarks, or warts that are bleeding.

⦸ **DON'T** have sex until warts are gone and healing is complete.

⦸ **DON'T** skip follow-up appointments. Warts can come back, and you may need a different treatment.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- The American Social Health Association Tel: (800) 230-6039 **Website:** **http://www.ashastd.org**
- National Institute of Allergy and Infectious Diseases **Website:** **http://www3..niaid.nih.gov**

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MANAGING YOUR

GESTATIONAL DIABETES

What Is Gestational Diabetes?

Diabetes is a condition in which blood glucose (sugar) levels are too high. Gestational means during pregnancy, so gestational diabetes (GD) occurs when diabetes is first found during pregnancy. GD usually goes away after the birth of the child. However, some women develop diabetes or prediabetes (impaired glucose tolerance) after delivery.

GD is common. About 1 in 20 pregnant women have it. It can cause problems in babies such as a higher birth weight (leading to a cesarean, or C-section, delivery), damage during birth (e.g., to shoulders), breathing problems, low blood sugar levels after birth, and higher risk of obesity and diabetes in later life. For women, GD increases the chance of getting preeclampsia late in pregnancy.

What Causes GD?

GD develops when women cannot make enough insulin. Insulin is a hormone that helps the body to break down sugar for energy. Without enough insulin, blood sugar levels rise and diabetes occurs. Certain hormones produced by women during pregnancy block insulin's effect, so more insulin than normal is needed.

What Are the Symptoms of GD?

GD has no clear symptoms. Pregnant women without GD may also have symptoms such as greater thirst, need to urinate, and hunger.

Women at greatest risk include those with diabetic family members, who are overweight or older than 35, or who already gave birth to a large baby, a baby born with an abnormality, or a stillbirth (dead baby). Also, women who had GD in another pregnancy or are Hispanic, African

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American, Native American, or Pacific Islander have a greater risk.

How Is GD Diagnosed?

It's hard to rely on symptoms to diagnose GD, so blood sugar levels should be tested during pregnancy, especially in high-risk women. If tests show high levels, the doctor will do frequent blood sugar tests for the rest of the pregnancy. Also, testing blood sugar levels at home will help monitor the condition.

How Is GD Treated?

Treatment is aimed at keeping blood sugar in the normal range. Special meal plans, moderate exercise, regular (e.g., daily) blood sugar testing, and insulin injections will do this.

DOs and DON'Ts in Managing GD:

- ✓ **DO** follow your doctor's advice about when to test blood sugar. It's important to check it after delivery.
- ✓ **DO** take insulin as prescribed.
- ✓ **DO** avoid sugary foods such as cakes, biscuits, and soft drinks.
- ✓ **DO** limit bread, pasta, rice and potatoes to smaller portions, and eat plenty of fruit and vegetables.
- ✓ **DO** regular moderate exercise such as walking.
- ✓ **DO** keep a snack handy if you are taking insulin. Test your blood sugar if you start to feel dizzy, faint, or tired.
- ✓ **DO** understand that GD will probably go away after birth.

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⦸ **DON'T** eat high-fat foods such as butter, cream, fatty meat, burgers, and sausages.

⦸ **DON'T** cook your food with fat or oil. Try grilling, steaming, or microwaving.

⦸ **DON'T** skip meals when you're hungry.

⦸ **DON'T** get too tired when exercising. Stop if you feel tired, dizzy, faint, or very hungry.

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Child Health and Human Development Tel: (800) 370-2943 **Web-site: http://www.nichd.nih.gov**
- American Diabetes Association Tel: (800) 342-2383 **Website: http://www.diabetes.org**
- National Institute of Diabetes and Digestive and Kidney Diseases Tel: (800) 860-8747 **Website: http://www.niddk.nih.gov/health/diabetes/ndic.htm**
- American Dietetic Association Tel: (800) 877-1600 **Website: http://www.eatright.org**

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MANAGING YOUR

GIANT CELL ARTERITIS

What Is Giant Cell Arteritis?

Giant cell arteritis is a condition that causes arteries to become inflamed or swollen. It's also called "temporal arteritis" because the temporal arteries, which are at the temples on both sides of the head, are the ones usually affected. However, arteries in any part of the body can be inflamed. Inflammation can lead to narrowing of an artery, which sometimes becomes completely blocked. This then reduces the blood supply to nearby tissues and organs. Blindness can result if arteries taking blood to the eyes are involved.

What Causes Giant Cell Arteritis?

The cause is unknown. It almost always occurs in people older than 50, more women than men. Another disorder called polymyalgia rheumatica often occurs with giant cell arteritis. Polymyalgia rheumatica causes stiffness and aching in the back, shoulders, and hips.

What Are the Symptoms of Giant Cell Arteritis?

Most symptoms are related to the head and face. They include headaches; scalp tenderness, especially over the temples; pain in the jaw or tongue when chewing or talking; blurred or double vision; and flu-like symptoms (muscle aches, joint stiffness, fever, fatigue, and loss of appetite).

How Is Giant Cell Arteritis Diagnosed?

The doctor makes a diagnosis from symptoms and a complete physical examination. A special blood test (erythrocyte sedimentation rate), which measures inflammation, will be done. This rate is very high in this disorder. The doctor may also do a biopsy of the temporal artery. The doctor will remove a small piece of artery and check it with a microscope for signs of inflammation. A chest x-ray may also be done since giant cell arteritis carries an increased risk of aneu-

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rysm (abnormal enlargement) of the aorta, the main artery that brings blood to body parts.

How Is Giant Cell Arteritis Treated?

A corticosteroid such as prednisone is given, usually starting at 40 to 60 mg per day. The same dose is continued for the first month. If symptoms and sedimentation rate improve, the dose can slowly be reduced (tapered). The treatment will probably last 1 to 2 years.

People with vision loss or impairment at the time of diagnosis may be given intravenous methylprednisolone for the initial 3 to 5 days of treatment.

DOs and DON'Ts in Managing

Giant Cell Arteritis:

✓ **DO** take medicines as prescribed. Symptoms usually improve after a few days, but continuing your medicine as directed is important. Don't change your dosage or stop the medicine unless your doctor tells you to.

✓ **DO** report medicine side effects to your doctor.

✓ **DO** see your doctor if you don't see improvement in a week or so.

✓ **DO** understand the side effects from prednisone. Long-term use can cause cataracts, peptic ulcer disease, osteoporosis, diabetes, and hypertension.

✓ **DO** call your doctor for vision loss or changes in vision.

✓ **DO** call your doctor if you have new headaches with fever or pain when chewing food.

⦸ **DON'T** miss follow-up doctor visits. Your doctor must monitor your symptoms and do periodic blood tests (sedimentation rate).

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⦸ **DON'T** forget that prednisone therapy may be needed for 1 to 2 years to prevent the disease from coming back.

⦸ **DON'T** ignore visual problems. Blindness can occur in people with giant cell arteritis if diagnosis and treatment is delayed.

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FOR MORE INFORMATION

Contact the following sources:

• American College of Rheumatology Tel: (404) 633-3777 **Website:**

http://www.rheumatology.org

• National Institute of Arthritis and Musculoskeletal and Skin Diseases Tel: (301) 496-8188

Website: http://www.niams.nih.gov

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MANAGING YOUR

GIARDIASIS

What Is Giardiasis?

Giardiasis is an intestinal illness caused by a parasite. It's one of the main causes of diarrhea in the United States. Giardiasis isn't usually serious, but complications, such as poor absorption of foods, weight loss, and fluid loss, can occur.

What Causes Giardiasis?

The cause is a tiny parasite you can't see named *Giardia*. Drinking water or eating food that contains *Giardia* can result in giardiasis. It's very easy to get it when traveling to countries with infected water supplies.

Giardiasis also spreads easily in crowded or unclean places or in areas with a poor water supply or sanitation system. Children in day care centers and preschools are at risk. Drinking stream water while camping or hiking, or swimming in a pool contaminated with *Giardia* can lead to giardiasis.

People who had stomach surgery have a higher risk for infection because stomach acid usually protects against infection. The risk is also greater for oral-anal and oral-genital sexual practices.

What Are the Symptoms of Giardiasis?

Up to half of people with giardiasis have no symptoms.

When symptoms occur, they'll start in 1 to 3 weeks after entry of *Giardia* into the body. Diarrhea starts suddenly. Bowel movements (stools) will be very watery and foul smelling. Stomach cramping, indigestion, discomfort at the top of the stomach, belching, gas, slight fever, and weight loss are other symptoms. Sometimes, symptoms keep returning for several months.

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How Is Giardiasis Diagnosed?

The doctor may suspect giardiasis on the basis of travel history, symptoms, and physical examination. Diagnosis is made by studying samples of stool in the laboratory.

How Is Giardiasis Treated?

Oral antiparasitic medicines such as metronidazole are taken to get rid of the parasite.

A hospital stay and intravenous fluids may be needed for severe diarrhea and loss of too much body fluid.

Prevention is the best treatment. Be careful about drinking water or eating food that may not be safe. Don't drink from surface water (rivers and ponds) when hiking or camping. If in doubt, boil the water, drink bottled water, or treat water with chemical purifiers available in camping supply stores.

Also, frequent hand washing is important, especially before meals, for people who have diarrhea or are around others with diarrhea, and after handling soiled diapers. Keep children with giardiasis home from day care and away from other children until symptoms improve.

DOs and DON'Ts in Managing Giardiasis:

✓ **DO** drink only bottled water when traveling, and don't use ice cubes (they may be made with contaminated water).

✓ **DO** drink plenty of fluids (at least eight glasses of water or liquid daily) if you have giardiasis.

✓ **DO** wash your hands often, especially after handling soiled diapers, to prevent the infection from spreading.

✓ **DO** keep children with giardiasis home until symptoms are better, to prevent spread of infec-

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tion to others.

✓ **DO** call your doctor if you have new, unexplained symptoms. Sometimes the medicine causes side effects.

⃠ **DON'T** drink alcohol. It interacts with medicines and causes stomach cramps and nausea.

⃠ **DON'T** use nonprescription drugs for stomach problems. They can mask symptoms.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following source:

- Centers for Disease Control and Prevention Tel: (404) 639-3534, (800) 311-3435 **Website: http://www.cdc.gov**

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MANAGING YOUR

GINGIVITIS

What Is Gingivitis?

Gingivitis is inflammation (swelling, redness) of the gums around the teeth caused by poor oral hygiene and poor nutrition. Most cases of simple gingivitis clear up quickly with treatment. Good mouth care is important for prevention, treatment, and recovery. Recovery time can depend on medical conditions that may affect the mouth.

What Causes Gingivitis?

The usual cause is buildup of plaque around the teeth. Plaque is a sticky material made up of bacteria, food debris, and mucus. When plaque isn't removed, it hardens into a substance called calculus or tartar, which becomes trapped at the base of the teeth and irritates the gums. Certain medicines, such as birth control pills; pregnancy; and chronic diseases, such as diabetes, can increase the chance of getting gingivitis.

What Are the Symptoms of Gingivitis?

The most common symptoms are gums that bleed easily (especially when brushing the teeth), swollen and reddened gums, bad breath, and bad taste in the mouth.

How Is Gingivitis Diagnosed?

The dentist or doctor does an examination of the teeth and gums to diagnose gingivitis. X-rays may be taken to see whether infection has spread below the gum line.

How Is Gingivitis Treated?

Cleaning at the dentist's office every 6 months is important. Different tools are used to remove plaque. Then, a home mouth care routine must be continued. Careful brushing of teeth with a soft-bristled toothbrush and daily flossing are important. Fluoride mouthwash may be prescribed.

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Avoid high-sugar foods because they stimulate production of acid that attacks the teeth. Eat a well-balanced diet.

Severe infection may need prescription antibiotics and sometimes surgery to remove infected gum tissue.

DOs and DON'Ts in Managing Gingivitis:

✓ **DO** follow your dentist's advice for cleaning your teeth.

✓ **DO** use the right brushing method to get the area between the gums and teeth really clean. Brush and floss twice daily. Change your toothbrush often, even monthly. Use a fluoride toothpaste to reduce tooth decay.

✓ **DO** rinse your mouth after flossing with an antiseptic mouthwash.

✓ **DO** see your dentist regularly for examinations and cleanings.

✓ **DO** keep your appointments for follow-up visits.

✓ **DO** call your dentist if you have a high temperature, excessive bleeding from your gums, or pain in your gums or teeth.

⃠ **DON'T** brush with a hard-bristled brush that may irritate the gums.

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Dental and Craniofacial Research Tel: (301) 496-4261 **Website:**

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http://www.nidcr.nih.gov/OralHealth/

- American Dental Association Tel: (312) 440-2500 **Website: http://www.ada.org**
- American Academy of Periodontology Tel: (312) 787-5518 **Website:**

http://www.perio.org/consumer/gingivitis.htm

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MANAGING YOUR

GLAUCOMA

What Is Glaucoma?

Glaucoma is an illness caused by too much pressure in the eye (intraocular pressure, IOP). Normally, watery fluid (called aqueous humor) flows into and out of the eye. If this flow becomes blocked, pressure in the eye rises, causing glaucoma. Too much pressure can damage the eye nerve and cause vision loss. Glaucoma must be caught early to prevent this damage.

Average IOP is 16 millimeters of mercury (mm Hg). It's considered to be elevated if it is above 21 mm Hg. Glaucoma is rare before the age of 40 and becomes more common with aging. Women and people who are farsighted may have an increased risk of glaucoma.

The two types of glaucoma are open-angle and closed-angle (angle-closure). In open-angle glaucoma, flow of fluid is blocked slowly (chronic condition). In acute closed-angle glaucoma, fluid flow is blocked suddenly; this is a medical emergency. The causes of open-angle glaucoma, the most common type, are not clear.

What Are the Symptoms of Glaucoma?

Open-angle glaucoma usually produces no symptoms early on. Later, loss of side vision (or peripheral vision) may occur.

Closed-angle glaucoma can cause headache, halos around lights, loss of central vision, severe eye pain, sudden vision change, and vomiting.

How Is Glaucoma Diagnosed?

Glaucoma is easy to diagnose. An eye specialist (optometrist or ophthalmologist) measures eye pressure with a painless test called tonometry. The specialist also tests whether vision is good, especially side vision, and looks inside the eye with an instrument (ophthalmoscope).

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The test of side vision is the visual field test. It can show early damage to side vision, the first sign of glaucoma.

How Is Glaucoma Treated?

Treatment—eye drops and surgery—is aimed at lowering a high IOP to a more normal IOP.

Some people need only one or two different eye drops. These drops, however, can affect other parts of the body. For example, eye drops that are beta-blockers should be used carefully in people with asthma or breathing or cardiac problems.

Other people need laser surgery or other types of surgery. Laser surgery can be quite effective, but many people will need to continue using eye drops after surgery.

Other operations for glaucoma involve making a new drain to let aqueous fluid flow out faster, so IOP is lowered.

DOs and DON'Ts in Managing Glaucoma:

✓ **DO** take all the medicine prescribed by your doctor. Use it exactly as directed. Once you begin to use the medicine, you will probably use it indefinitely.

✓ **DO** tell your eye doctor if you have another medical illness (e.g., asthma, heart problems, or emphysema) or an allergy to drugs used for glaucoma.

✓ **DO** tell your eye doctor about all medicines you take, because these may interfere with glaucoma medicines.

✓ **DO** call your eye doctor immediately if your symptoms get worse.

⦸ **DON'T** stop taking your medicine or change your dose because you are feeling better.

⦸ **DON'T** use corticosteroids such as prednisone without checking with your eye doctor, be-

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cause these drugs can raise eye pressure.

⦸ **DON'T** do exercises, such as yoga, that involve standing on the head, but do exercise normally.

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FOR MORE INFORMATION

Contact the following source:

• American Academy of Ophthalmology Tel: (415) 561-8500 **Website:** **http://www.aao.org**

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MANAGING YOUR

GLOMERULONEPHRITIS

What Is Glomerulonephritis?

Glomerulonephritis is inflammation of the part of the kidney that filters blood; it is caused by several diseases. The kidney is damaged and cannot get rid of waste products and extra body fluid. Sometimes, kidneys may stop working completely. The two forms are acute and chronic. The acute form starts suddenly, but the chronic form may develop slowly, over many years, and produce no symptoms until severe damage has occurred.

Glomerulonephritis may occur in adults but is most common in children.

What Causes Glomerulonephritis?

Acute glomerulonephritis may start after a throat or skin infection. Other illnesses that may cause glomerulonephritis include lupus, erythematosus, Goodpasture's syndrome, Wegener's granulomatosis, Henoch-Schönlein purpura, polyarteritis nodosa, and immune system changes. Many times, the cause is unknown. Chronic disease can follow acute disease years later.

What Are the Symptoms of Glomerulonephritis?

Mild glomerulonephritis usually has no symptoms. More serious disease causes slightly red or bloody urine, drowsiness, nausea or vomiting, headaches, appetite loss, less urination, and sometimes fever. Face, eyelids, and hands swell in the morning, and ankles swell in the evening. Shortness of breath, cough, high blood pressure, and blistery, dry, or itchy skin are others. Nighttime muscle cramps may occur. Symptoms may last from weeks to several months.

How Is Glomerulonephritis Diagnosed?

The doctor makes a diagnosis from the medical history, urine tests showing protein and blood cells, blood tests, and imaging tests such as ultrasonography of the kidney. Sometimes, a kidney

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biopsy is needed to find the best treatment. In a biopsy, the doctor removes a tiny piece of kidney with a special needle.

How Is Glomerulonephritis Treated?

Children usually recover more quickly than adults. A doctor who specializes in kidney treatment (nephrologist) will be involved in the care.

Sometimes, glomerulonephritis goes away by itself. However, high doses of medicines that affect the immune system or special filtering of the blood (plasmapheresis) may be needed. Temporary treatment with an artificial kidney machine may be needed to remove extra fluid and poisons that build up in the body.

No specific treatment is available for chronic glomerulonephritis. Following a special diet with less protein, salt, and potassium may be needed. Blood pressure pills and calcium supplements may also be taken.

DOs and DON'Ts in Managing

Glomerulonephritis:

✓ **DO** follow dietary advice. It prevents complications.

✓ **DO** keep to your fluid restrictions. Fluid could build up in your lungs and could be dangerous.

✓ **DO** control your blood pressure if you have chronic glomerulonephritis. This is *the most important thing that may slow kidney damage.*

✓ **DO** exercise but limit strenuous activities.

⃠ **DON'T** stop taking your medicine or change your dosage because you feel better unless your

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doctor tells you to.

⦸ **DON'T** take any over-the-counter medicine or herbal supplements without checking with your doctor. Some herbal preparations at health food stores may cause kidney damage.

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FOR MORE INFORMATION

Contact the following source:

- National Kidney Foundation, Inc. Tel: (800) 622-9010 **Website: http://www.kidney.org**

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MANAGING YOUR

GLOSSITIS

What Is Glossitis?

Glossitis is inflammation (redness, swelling) of the tongue. This common condition may come and go quickly or last several weeks. It may appear alone or be part of another illness. It affects people of all ages and seems to occur more often in men than women.

What Causes Glossitis?

The many causes include bacterial and viral infections; trauma or mechanical irritation from hot beverages, teeth, and dental appliances; local irritants, such as tobacco, alcohol, and hot or spicy foods; aphthous ulcers; and allergic reactions to toothpaste, mouthwash, or other substances put in the mouth.

Other causes affecting the whole body include diet (e.g., lack of iron or B vitamins), skin diseases (e.g., lichen planus), and infections (e.g., most often viral infections, in rare cases, syphilis and human immunodeficiency virus [HIV]).

What Are the Symptoms of Glossitis?

Symptoms depend on the cause. The tongue usually changes color, gets swollen, and hurts. The color changes from a dark beefy red to fiery red to pale to white, and the tongue looks inflamed or irritated. Pain may be bad enough to make chewing, swallowing, or talking hard to do. Sometimes, the tongue gets white patches or little ulcers. Symptoms usually go away in about 2 weeks, depending on the cause.

How Is Glossitis Diagnosed?

Glossitis is diagnosed by your doctor with a physical examination. Blood tests may be done to help find the cause. The doctor may also test the tongue for infection.

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If glossitis doesn't go away, the doctor may do a biopsy. A very tiny piece of tongue tissue is removed and studied with a microscope.

How Is Glossitis Treated?

The treatment depends on the cause. The doctor may prescribe medicine, especially if an infection occurs. People with poor nutrition may need to take vitamins or iron pills. Other pills may help stop the swelling. Sometimes, medicines are placed on the tongue for swelling and pain. Medicated mouth rinses may also give relief.

DOs and DON'Ts in Managing Glossitis:

✓ **DO** eat a well-balanced diet, or follow a bland or liquid diet if your doctor tells you to.

✓ **DO** keep your mouth clean. Brush and floss your teeth and clean your tongue after each meal.

✓ **DO** see your dentist regularly. If you wear dentures, have your dentist check the fit.

✓ **DO** keep heartburn under control, as stomach acid can irritate your esophagus and mouth.

✓ **DO** rinse your mouth if you use inhaled steroids for a lung condition after each time you breathe in the steroids.

✓ **DO** avoid things that you know will trigger your condition. Triggers include hot or spicy foods, alcohol, smoking and tobacco in all forms, tartar-control toothpaste or toothpaste containing peroxide, and mouthwash.

✓ **DO** call your doctor if you have breathing, speaking, chewing, or swallowing problems. These may mean that a swollen tongue is blocking your airways. This emergency needs

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immediate medical care.

✓ **DO** call your doctor if symptoms of glossitis last for more than 10 days.

⃠ **DON'T** smoke, and avoid all forms of tobacco.

⃠ **DON'T** drink alcohol or use spicy foods.

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FOR MORE INFORMATION

Contact the following source:

- American Dental Association Tel: (312) 440-2500 **Website: http://www.ada.org**

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MANAGING YOUR

GOLFER'S ELBOW

What Is Golfer's Elbow?

Golfer's elbow is an inflammation of the elbow. Tendons attach muscles to bones. The elbow has an upper arm bone (humerus) and two bones in the forearm (ulna and radius). Bony bulges on the inside and outside of the elbow are the epicondyle part of the upper bone. Tendons of forearm muscles attach to these bulges.

Inflammation (swelling, redness) of the tendons on the inside of the elbow (with the palm facing forward) has the medical name medial epicondylitis. It's also called golfer's elbow, but people using their wrists repeatedly or clenching their fingers can have it.

What Causes Golfer's Elbow?

Causes include repeated stress or overuse of the wrist, especially forceful wrist and finger movements, as in golf and racket and throwing sports. Other causes include painting, raking, carpentry, chopping wood, using hand tools, and typing. An injury, such as from lifting something that's too heavy, can also cause it.

What Are the Symptoms of Golfer's Elbow?

The inner side of the elbow becomes tender and painful. The pain can go down the forearm from the elbow. Pain can start suddenly or slowly and can get worse when swinging a golf club or racket, shaking hands, or turning a doorknob. It may hurt to make a fist. Stiffness, weakness, and numbness and tingling in fingers can also occur.

How Is Golfer's Elbow Diagnosed?

The doctor makes a diagnosis by the medical history and physical examination, including putting pressure on the area or moving the elbow, wrist, and fingers. Occasionally, the doctor may order

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x-rays to rule out conditions such as arthritis or broken bones. The doctor may rarely order magnetic resonance imaging (MRI) to get pictures of inflamed tendons.

How Is Golfer's Elbow Treated?

Treatment includes RICE: rest, ice, compression, and elevation. Rest and avoiding activities that may have started the problem are critical. Returning to activities too soon may make the condition worse. Using ice packs 15 to 20 minutes, four times a day, and special stretching and strengthening exercises often help. A physical therapist may be involved in treatment. Put a pillow under the elbow or put the elbow on the back of a chair or couch for elevation.

Nonsteroidal anti-inflammatory drugs (NSAIDs) (ibuprofen, naproxen) may relieve pain. If pain continues, steroid injections can be tried. When symptoms last more than a year, even with treatment, surgery may be needed.

DOs and DON'Ts in Managing Golfer's Elbow:

✓ **DO** stop the activity causing the pain until your doctor says you can start again.

✓ **DO** lift things carefully. Make sure that you use the right sports equipment and technique.

✓ **DO** the exercises, such as using light weights or squeezing a tennis ball, that your physical therapist gives you.

✓ **DO** call your doctor if treatment doesn't help symptoms.

✓ **DO** take frequent breaks if your problem is work related. Get information about performing tasks safely.

⃠ **DON'T** do activities that need extending or rotating the wrist.

⃠ **DON'T** put ice or chemical cold packs directly on your skin.

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⦸ **DON'T** forget that muscles should stay warm during sports. Always do gentle stretching to loosen up before activities.

⦸ **DON'T** use sporting equipment that's too large or too small.

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FOR MORE INFORMATION

Contact the following sources:

- Arthritis Foundation Tel: (800) 283-7800 **Website: http://www.arthritis.org**
- Nicholas Institute of Sports Medicine and Athletic Trauma **Website: http://www.nismat.org**
- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website: http://www.aaos.org**

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MANAGING YOUR

GONOCOCCAL URETHRITIS

What Is Gonococcal Urethritis?

Urethritis is inflammation (swelling, redness) of the urethra, the tube that takes urine from the bladder to the outside of the body. Gonococcal urethritis results from infection with the bacteria causing gonorrhea.

What Causes Gonococcal Urethritis?

Infections with the bacteria named *Neisseria gonorrhoeae* (and *Chlamydia trachomatis*) cause most cases of urethritis. It occurs most often in people 15 to 24 years old. Gonococcal urethritis is caused by *Neisseria gonorrhoeae*. Some infections may be passed by sexual contact. Having had gonococcal urethritis does not protect against future infections.

What Are the Symptoms of Gonococcal Urethritis?

The most common symptom is pain with urination.

Some men don't have symptoms but others have pus or thick yellow discharge from the penis, frequent and painful urination, rash over the penis, and swollen lymph glands (nodes) in the pelvic area.

Some women also may not have symptoms. Symptoms, if they occur, may be frequent and painful urination; pain in the lower abdomen (belly); pain with sex; urgent urination; and thick, smelly, vaginal discharge.

How Is Gonococcal Urethritis Diagnosed?

The doctor makes a diagnosis from the medical history and examination, with attention to the urethra, anus, and genitals. The doctor will collect fluid from the urethra and test blood and urine samples for infection. Women will have a pelvic examination.

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If gonococcal urethritis is diagnosed, the doctor will recommend testing sexual partners for infection.

How Is Gonococcal Urethritis Treated?

Antibiotics will be used to treat the infection. Sitz baths several times a day may help ease pain. Over-the-counter drugs (acetaminophen, ibuprofen) can also help the pain.

No special diet is needed, but fluid intake should be increased to several glasses of water a day. Make the urine more acid by drinking cranberry juice. Acid urine may help with infection. Avoid alcohol and caffeine because they irritate the urethra.

Avoid sexual intercourse until the infection is gone.

DOs and DON'Ts in Managing Gonococcal Urethritis:

✓ **DO** tell your doctor about medicines you take, including prescription and over-the-counter drugs.

✓ **DO** tell your doctor if you're pregnant. The infection can be passed to babies during birth.

✓ **DO** increase your fluid intake to several glasses of water per day during treatment.

✓ **DO** avoid sex until the infection is gone.

✓ **DO** avoid bubble baths and bath oils that may irritate the urethra.

✓ **DO** keep the genital area clean, but use unscented plain soaps.

✓ **DO** call your doctor if you get a high temperature or see blood in your urine.

✓ **DO** call your doctor if symptoms don't improve in 1 week.

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✓ **DO** practice safe sex. Use condoms.

✓ **DO** make sure your partner is tested and treated so you don't get infected again.

⃠ **DON'T** stop taking your medicine or change your dosage because you feel better, unless your doctor tells you to.

⃠ **DON'T** have sex until you have been treated and your doctor tells you that you can. Be sure that you use condoms to protect against sexually transmitted diseases.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website:** **http://www.cdc.gov**
- American Social Health Association Tel: (800) 230-6039 **Website:** **http://www.ashatd.org**
- National Kidney and Urologic Diseases Information Clearinghouse Tel: (800) 891-5390 **Website:** **http://kidney.niddk.nih.gov**

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MANAGING YOUR

GONORRHEA

What Is Gonorrhea?

Gonorrhea is a sexually transmitted disease (STD) that is caused by bacteria. It usually affects the sex organs but may also occur in other parts of the body, such as the eyes, throat, and joints.

Untreated gonorrhea can lead to serious problems, including bloodstream infection. In women, it can cause pelvic inflammatory disease (PID) and can be passed from pregnant women to their babies during birth. In men, it can cause infections called urethritis and epididymitis. Urethritis is inflammation (swelling, redness) of the urethra, the tube that carries urine and semen through the penis. Epididymitis is inflammation or infection of the epididymis, a long tube above and behind each testicle.

More than half a million people in the United States get gonorrhea every year.

What Causes Gonorrhea?

The cause is a type of bacteria named *Neisseria gonorrhoeae*. It spreads very easily by having sex with an infected person.

What Are the Symptoms of Gonorrhea?

Most men have symptoms when first infected, but many women may have very mild or no symptoms. They often don't know that they have gonorrhea until they have other problems. Symptoms in men usually start within 2 weeks after exposure. They include creamy green-yellow discharge from the penis, pain when urinating, and painful and swollen testicles. Symptoms in women include pain or burning when urinating, yellow or green vaginal discharge that can be bloody, bleeding between periods, and pain during sex. Other symptoms may include sore throat, low-grade fever; tender lower abdomen (belly); pain in knees, ankles, or elbows; and a

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rash on the palms of the hands.

How Is Gonorrhea Diagnosed?

For diagnosis, the doctor asks about symptoms and sexual activity and examines the sexual organs, including the pelvic area for women. Blood and urine tests and tests for STDs will be done. A sample of discharge from the penis or cervix will be taken and sent to a laboratory for study. Throat, rectum, or eye discharges may also be tested.

How Is Gonorrhea Treated?

Treatment with antibiotics cures gonorrhea in 1 to 2 weeks. The antibiotic is either given by injection or taken by mouth.

DOs and DON'Ts in Managing Gonorrhea:

✓ **DO** practice safe sex. Use condoms if you think that there's any chance of catching an STD.

✓ **DO** get treatment as soon as possible.

✓ **DO** make sure your sexual partner visits a doctor to check for infection.

✓ **DO** realize that gonorrhea is often diagnosed with other STDs. Your doctor will also test you for other STDs.

✓ **DO** wash hands thoroughly and often after using the bathroom.

✓ **DO** use sitz baths for discomfort.

✓ **DO** remember that follow-up cultures should be done.

✓ **DO** call your doctor if you get fever, chills, and abdominal pain after treatment starts.

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✓ **DO** call your doctor if you get joint pain, genital sores, or swollen testicles.

✓ **DO** call your doctor if you were told that a sexual contact has gonorrhea.

⃠ **DON'T** have unprotected sex until you finish treatment, are tested again, and your doctor says that you can. This is important to avoid spreading the infection.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- Infectious Diseases Society of America Tel: (703) 299-0200 **Website:** **http://www.idsociety.org**
- Centers for Disease Control and Prevention Tel: (404) 639-3534 **Website:** **http://www.cdc.gov**

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PROVIDING YOUR CHILD

GOOD NUTRITION

What Is Good Nutrition?

Everyone needs the same kinds of nutrients for good nutrition. These nutrients include vitamins, minerals, carbohydrates, protein, fat, and fiber. Children have different requirements according to their ages.

Why Is Good Nutrition Important?

Proper nutrition is critical for good health. It's important for children to grow properly, learn, have energy, and feel good about themselves. It helps maintain a healthy weight and so avoids obesity-related diseases such as diabetes. Carbohydrates, for example, give the body fuel. Fiber helps avoid constipation and lowers risks of diabetes and heart disease. Calcium and vitamin D are important for bone health.

How Do Children Learn to Eat Healthy?

Parents play a big role in helping children develop eating habits. Parents who eat low-fat, low-sugar, high-fiber foods teach their children to like these foods. Child care providers, friends, and the media also shape eating habits. If parents help children be aware of these other pressures, children will more likely make healthy choices themselves.

What Are Good Diets?

Children older than 2 should eat various nutrient-dense foods: fruits, vegetables, fat-free or low-fat milk and milk products, lean meats, poultry, fish, beans, eggs, nuts, and whole grains. Diets should be low in saturated fats, trans fats, cholesterol, salt (sodium), and sugars. Low-carbohydrate diets are not usually best for children. Children also need the right amounts of fluids and electrolytes (special chemicals such as sodium and potassium). Children who eat healthy

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diets probably don't need vitamin supplements, but always discuss this with your child's doctor.

Ways to help children eat better include making sure children eat breakfast—the most important meal of the day. Offer a wide variety of foods. Give a snack or two in addition to three daily meals. Limit the amount of added sugar in the diet. Cook with less fat and salt. Bake or grill meat, and take skin off chicken. Involve children in planning and fixing meals.

Parents who follow alternative diets such as vegetarian and vegan may need to check with a nutrition counselor make sure that children get enough of the correct nutrients and vitamins.

What Are the Best Food Choices?

Food groups include grains; fruits; vegetables; milk, cheese, and yogurt; fats; and meat, poultry, fish, dried beans, and eggs. Five daily servings of fruits and vegetables are recommended. Eating whole-grain breads and cereals (high in fiber) and healthy proteins such as lean meat, nuts, and eggs is important. Broccoli, cooked greens, and canned salmon (with bones) provide calcium. Food sources of iron include meat, fish, poultry, iron-fortified cereals, spinach, greens, and dried beans and peas.

Babies and toddlers should snack because they need high energy and have small stomachs. Teens who grow and develop quickly also need snacks. Healthy snacks include fresh and dried fruits, nuts, low-fat yogurt, and air-popped popcorn.

Be careful about portion sizes: a clenched fist is about a cup, the amount for a serving of pasta, rice, cereal, vegetables, and fruit. A meat portion is about as big as the palm. Eating out can be a challenge. At fast-food restaurants, choose healthier foods such as grilled, not fried, sandwiches. Order side salads instead of fries. Most restaurant servings are three or four times the right size, so share meals or take doggie bags home. Drink water or low-fat milk instead of sodas. Eat meals on smaller plates. Instead of buying lunches, take favorite healthy foods to

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school.

Dos and DON'Ts in Providing Good Nutrition:

✓ **DO** limit fast food and junk food.

✓ **DO** offer water and milk instead of sugary drinks and sodas**.**

✓ **DO** broil, grill, or steam foods instead of frying them.

✓ **DO** read nutrition labels on foods before you buy them.

✓ **DO** provide at least 5 servings of fruits and vegetables**.**

⊘ **DON'T** tell children to clean their plates, which may make them overeat.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- The Endocrine Society Tel: (301) 941-0200, (888) 363-6274 **Website:** **http://www.endo- society.org**
- The National Institutes of Health Tel: (301) 496-4000 **Website: http://www.nih.gov**
- The Obesity Society Tel: (301) 563-6526 **Website: http://www.obesity.org**
- The American Academy of Pediatrics Tel: (847) 434-4000 **Website:** **http://www.aap.org**

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MANAGING YOUR

GOODPASTURE'S SYNDROME

What Is Goodpasture's Syndrome?

Goodpasture's syndrome is an autoimmune disease that can affect the lungs and kidneys. An autoimmune disease is one in which the immune (infection-fighting) system attacks the body's own tissues, structures, and organs. Goodpasture's syndrome is rare, affecting 1 in 2 million people per year. The disease affects mostly those 5 to 40 years old, more men than women. People 50 to 60 years old can also have it, but women and men equally in this group.

What Causes Goodpasture's Syndrome?

The cause is unknown, but the condition isn't contagious. A genetic trend may exist, because almost 80% of people have an antigen (protein) named HLA-DR2. Environmental factors including cigarette smoking and exposure to certain chemicals may in some cases also trigger the autoimmune response.

What Are the Symptoms of Goodpasture's Syndrome?

Lung symptoms include coughing, hemoptysis (coughing up bloody phlegm), and shortness of breath. Other symptoms aren't specific for the syndrome: fever, nausea, muscle aches, and pale skin. Lung symptoms usually occur before kidney problems. Urinary symptoms aren't common. Blood in the urine (hematuria) and abnormal kidney function blood tests suggest kidney trouble.

How Is Goodpasture's Syndrome Diagnosed?

The doctor makes a diagnosis from blood tests, including one for a protein called anti–glomerular basement membrane antibody, which is positive in almost all people. Low red blood cell counts (anemia), abnormally high kidney function tests, and red blood cells in the urine also occur. For lung symptoms, the doctor may order a chest x-ray. The best way to confirm the

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diagnosis is a kidney biopsy. In a biopsy, the doctor puts a needle through the back into the kidney and takes out a piece of tissue, which is then studied with a high-power electron microscope.

How Is Goodpasture's Syndrome Treated?

Treatment begins with immunosuppressive medicines, drugs that inhibit the immune system. Such drugs include prednisone and cyclophosphamide. Also, a procedure called plasmapheresis can be done on an emergency basis. In plasmapheresis, antibodies attacking the kidney and lungs are removed from the blood circulation.

DOs and DON'Ts in Managing Goodpasture's Syndrome:

✓ **DO** understand that the syndrome may last only a few weeks or as long as several years.

Bleeding in the lungs can be very serious and even life-threatening. However, most cases usually don't lead to permanent lung damage.

✓ **DO** call your doctor if you cough up blood, are short of breath, see blood in your urine, or have a fever.

⦸ **DON'T** forget that the earlier treatment starts, the better you respond to it.

⦸ **DON'T** forget if your kidneys fail, you may need dialysis, to remove waste products and extra fluid from the blood, or a kidney transplant.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following source:

- National Kidney and Urologic Diseases Information Clearinghouse Tel: (800) 891-5390

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Website: http://kidney.niddk.nih.gov

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MANAGING YOUR

GOUT

What Is Gout?

Gout is a kind of arthritis, an illness that causes pain and swelling in joints.

What Causes Gout?

Crystals released into a joint cause inflammation, pain, and swelling. These crystals are made of a substance called uric acid. Either too much uric acid is made, or not enough is removed from the blood by the kidneys. Alcohol, aspirin, medicines, and some foods (liver and other organ meats, sardines, anchovies) can cause high uric acid levels. Attacks may occur at any time, but injuries, surgery, acute illness, rich foods, and alcohol can trigger them.

What Are the Symptoms of Gout?

Sudden, intense joint pain and swelling are symptoms. Joints may feel hot and tender and turn red. Even lightly touching the joint can cause severe pain, which is usually continuous and worse if the joint is moved. A sudden attack usually lasts several days. Attacks can happen years apart or occur back to back. Some people can have long-lasting, constant pain. Everyday activities (walking, dressing, lifting) may be hard to do.

Gout can occur in any joint, but most often feet are affected, usually the big toe. Gout can also occur in hands, ankles, insteps, or knees.

How Is Gout Diagnosed?

The doctor will make a diagnosis from the medical history and physical examination. The doctor may do blood tests but they can be unreliable, since the uric acid level can be high or normal during a gout attack. The only sure way to diagnose gout is to use a needle to take fluid from the joint. The fluid is checked to see whether it contains uric acid crystals.

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How Is Gout Treated?

Attacks can be treated and prevented. Nonsteroidal anti-inflammatory drugs (NSAIDs), such as indomethacin and naproxen, are used for treatment. Other drugs include colchicine, another anti-inflammatory drug, and prednisone. Removal of fluid from the joint, followed by cortisone injection, is another treatment. Cortisone injections usually give the fastest and best relief of pain and swelling.

After attacks are treated, symptoms usually go away within hours to a few days. Untreated attacks may last several days. People with higher blood uric acid levels are more likely to have many attacks. High uric acid levels for many years can cause deposits of uric acid under the skin, called tophi.

Prevention is needed for people with tophi, kidney stones, and frequent attacks. Lowering uric acid levels prevents attacks. The medicines allopurinol, febuxostat, and probenecid can do this.

DOs and DON'Ts in Managing Gout:

✓ **DO** rest the affected joint until symptoms start to improve.

✓ **DO** take your medicines as prescribed.

✓ **DO** ask your doctor which over-the-counter medicines you're allowed to take.

✓ **DO** make lifestyle changes to prevent attacks. Lose weight if you're very overweight. Avoid liver and other organ meats, sardines, and anchovies, which may increase uric acid levels. Stop drinking alcohol.

✓ **DO** call your doctor if you have medicine side effects or medicine doesn't help symptoms.

✓ **DO** call your doctor if you begin to lose movement in the joint.

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✓ **DO** call your doctor if you have warmth, redness, or pain after a cortisone injection.

⃠ **DON'T**drink alcohol. Too much alcohol can bring about an attack of gout in someone with a high uric acid level.

⃠ **DON'T**start medications that lower uric acid, such as allopurinol or febuxostat, immediately after an attack subsides since this may prolong the attack or cause another gout attack. It's best to wait several days after an attack subsides before starting these medications.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American College of Rheumatology Tel: (404) 633-3777 **Website:** **http://www.rheumatology.org**
- Arthritis Foundation Tel: (800) 283-7800 **Website:** **http://www.arthritis.org**
- The Arthritis Society **Website:** **http://www.arthritis.ca**

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MANAGING YOUR

GRANULOMA ANNULARE

What Is Granuloma Annulare?

Granuloma annulare is a rather uncommon, harmless skin condition. Most often, children and young adults have it. It usually disappears on its own but often comes back. Treatment with medicine applied to the skin may help speed healing.

What Causes Granuloma Annulare?

The cause is unknown, but it cannot be caught and isn't passed from parents to children. Granuloma annulare does tend to return, but it isn't cancerous or life-threatening.

What Are the Symptoms of Granuloma Annulare?

Granuloma annulare may start as a small, red bump and develop into a ring of bumps or even many bumps. It appears evenly on both sides of the body. The bumps are red to tan, and the rings can grow up to a few inches but are usually smaller. The bumps are smooth and may have a shallow indented area in the center. Some bumps may go away in a few months, but others may last for years. The bumps may be tender or itchy. Granuloma annulare usually appears on the hands, feet, arms, and legs, and over joints (elbows and knees).

How Is Granuloma Annulare Diagnosed?

The doctor usually makes a diagnosis by looking at the skin. The doctor may do a minor skin biopsy to confirm the diagnosis. In a biopsy, a small piece of skin with the lesion is removed and studied under a microscope. A skin biopsy is generally not necessary and only done when the diagnosis is unclear.

How Is Granuloma Annulare Treated?

Treatment is usually not needed. Diet and exercise don't affect the condition. Most cases im-

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prove within months. People with this disorder have no restrictions.

The doctor may prescribe steroid creams to put on the skin. A small amount of cream or lotion is applied to the affected area. It is best to do this just before bedtime.

For severe or extensive cases of granuloma annulare, the doctor may prescribe medicine to be taken by mouth. The doctor may also inject steroids directly into the affected area. A special treatment combining a cream put on the skin and a special ultraviolet light therapy (called PUVA, for psoralen plus ultraviolet A) may also be used.

DOs and DON'Ts in Managing Granuloma Annulare:

✓ **DO** be patient. Granuloma annulare is not life-threatening.

✓ **DO** call your doctor if you have itching or scaling.

✓ **DO** call your doctor if you have signs of infection, such as fever, swelling, or pus drainage.

⃠ **DON'T** apply over-the-counter creams or ointments to the bumps without checking with your doctor first.

⃠ **DON'T** expect immediate improvement. It may take weeks or months for the skin lesions to resolve.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Dermatology Tel: (866) 503-SKIN (7546) **Website:** **http://www.aad.org**

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MANAGING YOUR

GRANULOMA INGUINALE

What Is Granuloma Inguinale?

Granuloma inguinale is a sexually transmitted disease (STD) that is common in tropical areas and developing countries. It does rarely occur in the United States, usually in the Southeast. It's a chronic infection affecting genital and groin areas. More than twice as many men have it as women. Most infections occur in people 20 to 40 years old.

What Causes Granuloma Inguinale?

The cause is the kind of bacteria named *Calymmatobacterium granulomatis*.

What Are the Symptoms of Granuloma Inguinale?

Symptoms can take 1 to 2 weeks to occur after exposure. Small, raised, red lumps appear on the penis, vulva, or vagina and maybe also in the groin area. These lumps are painless, but then the lumps grow bigger and break down (become ulcers). As this happens, the area becomes dark red and may have raised edges that heal with formation of large scars.

How Is Granuloma Inguinale Diagnosed?

The doctor makes a diagnosis on the basis of the history of exposure, physical examination, and finding bacteria in the ulcers. The doctor does a biopsy or takes scrapings of the area to find the bacteria.

Testing for other STDs will be done.

How Is Granuloma Inguinale Treated?

Antibiotics such as doxycycline, ciprofloxacin, or azithromycin must be taken for 3 weeks, until healing is complete. The areas should be kept clean and dry. Sexual activities should be restricted until treatment is completed. No special diet is needed.

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A follow-up examination with the doctor is important to make sure that no other treatment is necessary.

DOs and DON'Ts in Managing Granuloma Inguinale:

✓ **DO** take the antibiotics until they're finished.

✓ **DO** keep the lesions clean and dry.

✓ **DO** keep follow-up appointments with your doctor to make sure that the infection is over.

✓ **DO** tell your sexual contacts so that they can be examined and treated if needed.

✓ **DO** get tested for other STDs.

✓ **DO** avoid sexual partners whose health practices may be unknown.

✓ **DO** practice safe sex. Use a latex condom.

✓ **DO** call your doctor if ulcers become painful or have increased drainage.

✓ **DO** call your doctor if you get a fever during treatment.

✓ **DO** call your doctor if you cannot take the antibiotic medicine.

⃠ **DON'T** skip or stop the antibiotics until the treatment course is finished.

⃠ **DON'T** skip follow-up appointments with your doctor. If the infection isn't completely gone, it can come back.

⃠ **DON'T** apply creams or lotions to the lesions unless your doctor tells you to.

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⦸ **DON'T** have sex until your doctor says that it's OK.

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FOR MORE INFORMATION

Contact the following source:

- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website:** **http://www.cdc.gov**

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MANAGING YOUR

GRAVES' DISEASE

What Is Graves' Disease?

The thyroid is an important endocrine gland found in the front of the neck. It produces substances (hormones) that act on metabolism and control mood, weight, and energy. Graves' disease is an autoimmune disease that is the most common cause of too much thyroid hormone being produced (hyperthyroidism). It can affect both sexes but affects primarily women. An autoimmune disease is one in which the immune system of the body attacks itself and destroys healthy organs or tissues.

What Causes Graves' Disease?

The cause is substances called antibodies that stimulate the thyroid to enlarge (goiter) and make too much thyroid hormone. Eye disease can result. It may run in families but cannot be caught from someone else.

What Are the Symptoms of Graves' Disease?

Symptoms include problems with the thyroid, eyes, and rarely the skin. Eye problems include blurred vision, dryness, bulging of the eyeball (exophthalmos), or a staring look. Double vision and blindness can occur if Graves' disease isn't treated.

An overactive thyroid gland results in fast or irregular heartbeat, high blood pressure, diarrhea, weight loss, increased sweating, and nervousness. Long-term complications include heart failure, bone loss (osteoporosis), and stroke.

How Is Graves' Disease Diagnosed?

The doctor will make a diagnosis from the medical history, physical examination, and blood tests for thyroid function and antibody levels.

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X-rays (ultrasound of the gland and radioactive iodine study) may also be done.

How Is Graves' Disease Treated?

High thyroid hormone levels and eye problems can both be treated.

Medicine, surgery, and/or radioactive iodine are used for high hormone levels. Medicines such as propylthiouracil (PTU) and methimazole prevent the thyroid from producing hormone. Other medicines that may help are beta-blockers (such as propranolol), which lower the heart rate and reduce the hormone's damaging effect on the heart. These drugs have side effects and should be used with care.

Radioactive iodine usually has few side effects, gives permanent results, and is very effective, but it cannot be used during pregnancy. It can be done as an outpatient or with a short hospital stay. The long-term risk is an underactive thyroid (hypothyroidism), so thyroid supplements may be needed lifelong after radioactive iodine treatment.

People who cannot have radiation therapy or cannot use oral antithyroid medicines may have surgery. Surgery risks include damage to vocal cord nerves and glands that regulate calcium.

An eye doctor (ophthalmologist) should check for eye problems at least once yearly. Treatments for eye disease include laser therapy, surgery, eye drops, medications, and ointments.

DOs and DON'Ts in Managing Graves' Disease:

✓ **DO** take your medicines exactly as prescribed. Skipping doses makes medicines useless.

✓ **DO** exercise daily if your doctor says you can. Daily exercise can improve your well-being and health.

✓ **DO** visit your eye doctor at least once yearly or more, if needed.

✓ **DO** call your doctor if you have palpitations, shortness of breath, chest pain, or sudden wors-

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ening of nervousness or jitters.

✓ **DO** call your doctor if you have eye pain or vision changes, sore throat, fever, chills, nausea, or vomiting.

⃠ **DON'T** skip medicine doses.

⃠ **DON'T** miss your laboratory test appointments.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following source:

- Thyroid Foundation of America Tel: (800) 832-8321 **Website: http://www.allthyroid.org**

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MANAGING YOUR

GROIN STRAIN

What Are Groin Strains?

Groin strains are injuries in which adductor muscles are stretched or torn. These inner thigh muscles start in the groin and end at the inner side of the knee. They pull legs together and help move hip joints. They are important to sprinters, swimmers, and football players. Anyone can have a groin strain but they're common in ice hockey and soccer players.

What Causes Groin Strains?

Running, jumping, sudden changes of direction while running, and quick starts and stops can cause strains. Using adductor muscles too much, direct hits to these muscles, fatigue, tight groin muscles, cold weather, previous injuries, and poor conditioning can also lead to groin strains. Risks of getting groin strains increase in activities needing bursts of speed (hurdles, basketball, soccer, football, hockey, tennis, figure skating, baseball, horseback riding, karate).

What Are the Symptoms of Groin Strains?

Swelling, pain, and tenderness occur in the inner thigh. Lifting the knee, bringing the legs together, stretching legs out, and walking may cause pain. A popping or tearing feeling inside the thigh and stiffness and bruising in the groin may occur. Groin strains are graded on the basis of how severe they are: 1 (stretching with some microtearing of muscle fibers), 2 (partial tearing), and 3 (complete tearing).

How Are Groin Strains Diagnosed?

The doctor uses symptoms, physical examination, and medical history for a diagnosis. The doctor may want x-rays to make sure that bones aren't broken. Magnetic resonance imaging (MRI) may help when diagnosis is unclear.

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How Are Groin Strains Treated?

Treatment depends on how severe the strain is. First treatments include RICE: rest, ice, compression, and elevation. Resting is critical. Ice packs can be put on the thigh for 15 to 20 minutes, four times a day, until swelling and pain are gone. Swelling can be reduced by using an elastic compression bandage (thigh wrap) around the upper thigh. For the first day, raise the thigh on a pillow. Over-the-counter anti-inflammatory drugs (ibuprofen, aspirin) or other medicines (acetaminophen) can reduce pain and inflammation. Recovery time depends on many things, such as age, health, previous groin injury, and how severe the injury was. Returning to play after injury can be hard. Returning to activities too soon may worsen the injury and lead to permanent damage.

After swelling goes away, exercises to stretch and strengthen muscles are important. These include adductor stretching, hamstring stretch on wall, side-lying leg lift (cross over), and straight leg raise. Physical therapy can help. During recovery, change activities (swim, not run), to avoid making the strain worse.

DOs and DON'Ts in Managing Groin Strains:

✓ **DO** use ice and elevation to keep swelling down.

✓ **DO** exercises to help your adductor muscles get stronger. Always do warm-up exercises before stretching these muscles.

✓ **DO** take medicines as directed.

✓ **DO** learn and use the right sports techniques and equipment.

⦸ **DON'T** play sports until the pain is gone. Don't do activities that cause pain. Your injury can

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get worse.

- ⃠ **DON'T** wrap your thigh too tightly, or it may cut off circulation.
- ⃠ **DON'T** put ice directly on skin. Wrap it in a towel.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website:** **http://www.aaos.org**
- The American Orthopaedic Society for Sports Medicine Tel: (847) 292-4900 **Website:** **http://www.sportsmed.org**

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MANAGING YOUR

GUILLAIN-BARRÉ SYNDROME

What Is Guillain-Barré Syndrome?

Guillain-Barré syndrome is a rare disorder of the peripheral nerve system that results in muscle weakness. Peripheral nerves travel to and from the brain. About 3500 cases are diagnosed each year in the United States and Canada. Anyone can get it, at any age, and both sexes are equally affected. There's no cure, but about 85% of people recover completely. It cannot be prevented.

What Causes Guillain-Barré Syndrome?

The exact cause is unknown, but more than two thirds of people have an infection 1 to 3 weeks before the muscle weakness. It isn't contagious. Most experts believe that it's an autoimmune disease. Autoimmune means that the body's own immune (infection-fighting) system attacks the body.

What Are the Symptoms of Guillain-Barré Syndrome?

First symptoms include weakness and tingling in the legs that often spread to the arms and upper body.

These symptoms can get so bad that the muscles cannot be used at all and people are almost totally paralyzed. Then, the disorder can become life-threatening. It can interfere with breathing, blood pressure, or heart rate. Abnormal heartbeat, infections, and blood clots can also occur.

The disorder can progress rapidly over a few hours or days or more slowly over 3 to 4 weeks. Most people have the greatest weakness in the first 2 weeks after symptoms start, so by the third week, 90% are at their weakest.

How Is Guillain-Barré Syndrome Diagnosed?

The doctor will make a diagnosis from the medical history and physical examination. The doctor

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may want tests to rule out other diseases. These tests include electromyography (EMG) to measure electrical activity of nerves and muscles, lumbar puncture (spinal tap) and analysis of spinal fluid, and breathing and blood tests.

How Is Guillain-Barré Syndrome Treated?

The key to treatment is to prevent complications. Plasmapheresis and high-dose immunoglobulin therapy are also used to reduce the severity and duration of the illness. In plasmapheresis, whole blood is removed from the body, and red and white blood cells are separated from plasma (liquid portion of blood). Blood cells without plasma are then returned to the body. In high-dose immunoglobulin therapy, doctors give intravenous injections of proteins that, in small amounts, the immune system normally uses to attack organisms.

The most critical part of treatment is to keep the body working during recovery of the nervous system. Using a respirator, heart monitor, or another machine that helps the body work may be needed. Usually, people are treated in the hospital, often in the intensive care ward.

DOs and DON'Ts in Managing

Guillain-Barré Syndrome:

✓ **DO** understand that Guillain-Barré syndrome can be devastating because of its sudden and unexpected onset.

✓ **DO** realize that recovery isn't necessarily quick. Recovery may take a few weeks or as long as months or years.

✓ **DO** call your doctor if you notice muscle weakness.

✓ **DO** call your doctor if you develop numbness or tingling feelings, have trouble swallowing

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or breathing, feel depressed, or get a fever.

⦸ **DON'T** be afraid to ask for a second opinion.

⦸ **DON'T** be afraid to ask for social and emotional support.

⦸ **DON'T** miss follow-up appointments after you leave the hospital.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following source:

- GBS/CIDP Foundation International Tel: (610) 667-0131, (866) 224-3301 **Website: http://www.gbs-cidp.org/**
- American Academy of Neurology **Website: http://www.neurology.org**

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MANAGING YOUR

GYNECOMASTIA

What Is Gynecomastia?

Gynecomastia is a disorder in which one or both breasts become enlarged in males. It occurs most often in three age groups: newborn baby boys, boys 12 to 16 years old, and older men. In the boys, breasts may return to normal in 6 months to 3 years after puberty.

What Causes Gynecomastia?

The usual cause in boys is a change in hormone levels during puberty. Hormone changes can also occur in baby boys and older men.

Some medicines, illegal drugs, and drugs used for bodybuilding can cause gynecomastia, as can foods and drinks containing too much soy. Rare causes include tumors, birth defects, and liver disease.

What Are the Symptoms of Gynecomastia?

Breasts are larger than is typical for males. An area of firm tissue can be felt behind the nipples. Breasts may be tender but aren't usually painful.

How Is Gynecomastia Diagnosed?

The doctor can diagnose gynecomastia by physical examination of the chest and breasts. Blood tests may be done to check hormone levels and look for other causes. Sometimes other tests, such as mammography and a sonogram of the breast are needed to exclude breast tumors.

How Is Gynecomastia Treated?

Treatment includes lifestyle changes to promote weight loss, avoidance of medications associated with gynecomastia, or surgery. Many times, lifestyle changes alone are enough. Boys 12 to 16 years old and newborn babies aren't usually treated. If the condition has lasted less than 1

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year, it usually responds well to treatment. It may not go away in someone who has finished puberty and has gynecomastia lasting for more than 1 year.

For hormone level problems, medicine may balance the levels and may help breast tissue return to normal. The doctor may suggest seeing a specialist called an endocrinologist, a doctor who is an expert in the study of hormones.

When other treatments fail, an operation called breast reduction surgery can remove breast tissue. This operation is generally thought of as cosmetic and may not be covered by medical insurance.

DOs and DON'Ts in Managing Gynecomastia:

✓ **DO** tell your doctor about medicines you take.

✓ **DO** tell your doctor about cosmetic products you use.

✓ **DO** tell your doctor if you don't feel well while taking medicine for gynecomastia.

✓ **DO** talk to a counselor if you're distressed about your condition.

✓ **DO** lose weight if you're overweight.

✓ **DO** call your doctor if your breasts become sore or red, because you may have an infection.

⦸ **DON'T** drink alcohol in excess.

⦸ **DON'T** use bodybuilding drugs.

⦸ **DON'T** include large amounts of soy products in your diet.

⦸ **DON'T** use cosmetics that include the female hormone estrogen.

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FOR MORE INFORMATION

Contact the following sources:

- American Society of Plastic Surgeons Tel: (888) 475-2784 **Website:**

  http://www.plasticsurgery.org

- American Association of Clinical Endocrinologists Tel: (901) 353-7878 **Website:**

  http://www.aace.com

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MANAGING YOUR

HAIRY CELL LEUKEMIA

What Is Hairy Cell Leukemia?

Hairy cell leukemia is a rare kind of blood cancer (malignancy). It's a disease of B cells, or lymphocytes, a type of white blood cell. The name refers to the hairy look of the cells under a microscope. This kind of leukemia is more common among men than women, usually middle-aged. About 2% of all leukemia cases are hairy cell leukemia.

What Causes Hairy Cell Leukemia?

The cause is unknown. No chemical or radiation exposure has been linked to the disease. DNA mutations cause bone marrow stem cells to make too many malignant white blood cells. Why these mutations occur isn't known. The disease isn't contagious or inherited.

What Are the Symptoms of Hairy Cell Leukemia?

Abnormal cells get into the spleen and bone marrow, which leads to symptoms. These include fullness or discomfort in the abdomen (belly) because of the enlarged spleen. Low red blood cell counts (anemia) cause fatigue or shortness of breath. Very low white blood cell counts (neutropenia) mean people are more prone to infections. Low platelet counts (thrombocytopenia) cause easy bruising or bleeding. Weight loss can also occur.

How Is Hairy Cell Leukemia Diagnosed?

The health care provider makes a preliminary diagnosis from the medical history, blood tests, and physical examination. The final diagnosis depends on finding the special hairy white blood cells in the blood. A referral will be made to a blood specialist (hematologist). A biopsy of bone marrow is performed. In this biopsy, the hematologist takes a sample of bone marrow for study with a microscope and performs additional tests on the bone marrow sample.

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How Is Hairy Cell Leukemia Treated?

Not everyone needs treatment right away because this blood cancer usually progresses very slowly. Low blood counts and symptoms caused by an enlarged spleen mean treatment is needed. Treatment consists of chemotherapy. Chemotherapy often leads to lasting complete remission of hairy cell leukemia. New drugs include cladribine (2-CDA) and 2 deoxycoformycin (DCF, pentostatin). About three-fourths of people have a complete response. Side effects include a temporary decrease in blood counts and numbness and tingling in fingers and toes. Interferon or rituximab might be tried if chemotherapy doesn't work or isn't possible.

DOs and DON'Ts in Managing Hairy Cell Leukemia:

✓ **DO** participate in your chemotherapy regimen as prescribed by your health care provider.

✓ **DO** get a flu shot every fall. Consider pneumonia immunizations also.

✓ **DO** avoid contact sports, brush your teeth with a soft toothbrush, and shave with an electric razor if you have a low platelet count.

✓ **DO** call your health care provider if you have a fever or bleeding that doesn't stop after pressure is put on the area for 5 minutes.

✓ **DO** learn all you can about your illness.

✓ **DO** find a support group if you think that would help.

⃠ **DON'T** eat uncooked fruits, vegetables, and milk products if you have a very low white blood cell count.

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FOR MORE INFORMATION

Contact the following sources:

- American Cancer Society Tel: (1-800) ACS-2345 **Website: http://www.cancer.org**
- National Cancer Institute Tel: (1-800) 4-CANCER **Website: http://www.nci.nih.gov**
- Leukemia Society of America Tel: (1-800) 955-4LSA

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MANAGING YOUR

HALITOSIS

What Is Halitosis?

Halitosis is the medical word for bad breath. About one in ten Americans have persistent foul- or unpleasant-smelling breath.

What Causes Halitosis?

The most common cause is the breakdown of food in the mouth by bacteria that live there. Certain foods, such as garlic, may make it worse.

Medical conditions causing bad breath include infected teeth, gums, or oral tissues; cancer of the mouth; the common cold; lung and sinus infections; postnasal drip; infections such as tonsillitis, strep throat, and mononucleosis; untreated nasal polyps; diabetes; and other diseases of the stomach, lungs, liver, and kidneys.

Medicines such as antihistamines may cause halitosis because they dry the mouth. A dry mouth can also occur because of stress or nervous tension. Saliva is the mouth's natural mouthwash. It has antibiotic substances that get rid of mouth bacteria, so less saliva can mean bad breath. Tobacco and alcoholic beverages can also cause halitosis.

What Are the Symptoms of Halitosis?

People usually don't notice their own mouth odor, even after breathing out into their hand or licking the hand to smell the odor. They usually become aware of halitosis only when they see others avoiding them or when someone tells them. Bad breath tends to get worse and occur more often with aging. The odor intensity varies.

How Is Halitosis Diagnosed?

The doctor makes a diagnosis by taking a medical history and doing a physical examination, es-

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pecially of the mouth and nose. The doctor may also do a sniff test (the doctor smells air that the person breathes out through just the nose and then just the mouth) and a throat culture if a sore throat or mouth sores are present. More tests may be done if other medical conditions may be the cause.

How Is Halitosis Treated?

The key to treatment is good oral hygiene. Daily brushing and flossing are essential. Using an over-the-counter mouthwash helps remove food particles and odors. Regular dental checkups are a must to prevent, identify, and treat problems.

Avoiding certain foods and tobacco can also help. These foods include garlic, onions, cheese, spices, orange juice, and soda. If a medical condition is the cause, that condition should be treated.

DOs and DON'Ts in Managing Halitosis:

✓ **DO** brush with baking soda toothpaste, floss between the teeth, and clean the tongue after each meal.

✓ **DO** make sure that your mouth is moist by drinking adequate water. Hold water in the mouth for as long as possible, swishing it hard to remove food particles.

✓ **DO** increase saliva production by chewing sugarless gum or sugarless candy mints.

✓ **DO** snack on carrots, celery, or other vegetables to help prevent plaque.

✓ **DO** use an oral irrigation device to clean the teeth.

✓ **DO** avoid foods and beverages that can cause bad breath, such as garlic, raw onions, cab-

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bage, horseradish, eggs, broccoli, brussels sprouts, fish, red meat, peppers, alcohol, and coffee.

✓ **DO** call your doctor or dentist if bad breath becomes chronic and simple treatments don't work.

⃠ **DON'T** smoke cigarettes or use tobacco.

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FOR MORE INFORMATION

Contact the following source:

- American Dental Association Tel: (312) 440-2500 **Website: http://www.ada.org**

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MANAGING YOUR

HAMSTRING STRAIN

What Are Hamstring Strains?

Hamstring muscles include three muscles in the back of the thigh: semitendinosus, semimembranosus, and biceps femoris. They work to bend the knees, pull back the legs, and extend the hips.

Hamstring strains are often called "pulled muscles," meaning that muscles are stretched and torn. There are three grades of severity, which are based on the number of muscle fibers injured. Grade 1 means there are stretched muscles and minor, very tiny tears. Grade 2 means there are partial muscle tears. Grade 3 is severe and means muscles are completely torn and may need surgery. Hamstring strains are fairly common in activities that involve running, jumping, and kicking. They can also occur with stretching too much (as in yoga) and in other activities needing quick starts and stops.

What Causes Hamstring Strains?

It's unclear what the exact causes of hamstring strains are, but decreased flexibility, strength, and endurance of the muscles are often considered. Injury most often occurs when the muscles are contracted forcefully and at their longest. Other factors that increase risks of having a pulled hamstring include increasing age, previous injury, nerve pinches in the low-back area, fatigue, and poor fitness. High-risk activities for hamstring strains are soccer, football, baseball, basketball, water skiing, weightlifting, tae kwon do, ice skating, dancing, and track and field events.

What Are the Symptoms of Hamstring Strains?

Symptoms are pain in the back of the leg during exercise, muscle spasm, swelling, bruising, and

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tenderness. With a significant injury, an individual can feel the muscle “tighten” or “pop” and sometimes feel as if they have been struck in the back of the leg. Pain can occur when passively extending the knee with the hip flexed at 90 degrees and with resisted knee flexion. With severe injury, there may be a palpable defect, bruising can occur, and people may have trouble contracting the muscle.

How Are Hamstring Strains Diagnosed?

The doctor makes a diagnosis by the medical history and physical examination. Imaging studies, such as x-rays, may be helpful in the younger athlete, especially to make sure that the muscle hasn’t pulled off a small piece of bone where it connects. Other imaging studies, such as ultrasonography and magnetic resonance imaging (MRI), are rarely needed for simple muscle strains, but may be helpful in more severe injuries and/or if the diagnosis is unclear.

How Are Hamstring Strains Treated?

The goal of treatment is to return to activities as soon as it is safely possible. Returning too soon may worsen the injury and lead to permanent damage. The first 48 hours after injury are the most important. Use RICE (rest, ice, compression, and elevation). Rest and avoiding activities that may have started the problem are critical. Using ice packs and special stretching and strengthening exercises often help. Wrapping an elastic bandage around the leg for compression may keep swelling from getting worse. Put a pillow under the thigh for elevation. It is important to avoid rigorous excessive stretching early on, because this may increase the damage to the muscle and impair recovery. Rehabilitation often includes restoring range of motion, then advancing strengthening as well as running and sprinting activities as tolerated. Strengthening of the muscles and returning to sport-specific activities is the final goal of treatment.

Nonsteroidal anti-inflammatory drugs (NSAIDs) (ibuprofen) and acetaminophen, may be useful

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in relieving pain. Recovery time depends on the person, the extent of the injury, and also the sport that they participate in, and may take 6 to 18 weeks.

DOs and DON'Ts in Managing Hamstring Strains:

✓ **DO** stop the activity causing the pain until your doctor says you can start again.

✓ **DO** make sure that you use the right sports technique.

✓ **DO** warm-up exercises, such as light aerobic exercise, correctly.

✓ **DO** call your doctor if treatment doesn't help symptoms.

✓ **DO** stretch before and after sports or exercising.

✓ **DO** strengthen muscles in the thighs, pelvis, and lower back for correct muscle balance.

⦸ **DON'T** put ice or chemical cold packs directly on your skin.

⦸ **DON'T** forget to do gentle stretching to loosen up before activities.

⦸ **DON'T** use sporting equipment that's too large or too small.

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FOR MORE INFORMATION

Contact the following sources:

- American Trauma Society Tel: (800) 556-7890 **Website: http://www.amtrauma.org**
- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website: http://www.aaos.org**
- The American Orthopaedic Society for Sports Medicine Tel: (847) 292-4900 Fax: (847)

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292-4905 **Website: http://www.sportsmed.org**

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CARING FOR YOUR CHILD WITH

HAND, FOOT, AND MOUTH DISEASE

What Is Hand, Foot, and Mouth Disease?

Hand, foot, and mouth disease (HFMD) is a common viral illness that starts in the throat and affects mainly children younger than age 10. The disease isn't serious, needs no specific treatment, and usually goes away within 2 weeks.

What Causes HFMD?

The cause is coxsackievirus A16. This virus can be found in bowel movements (stool) and body fluids of the nose and throat. It spreads from person to person by touching the body fluids of someone who is infected.

What Are the Symptoms of HFMD?

Symptoms usually start within a week after an exposure and include feeling sick, low-grade fever, sore throat, loss of appetite, headache, and a rash on the palms of the hands, soles of the feet, and buttocks. Sores may begin in the mouth—on the tongue, gums, and insides of the cheeks—several days after fever starts. They start as small red spots that blister.

How Is HFMD Diagnosed?

The doctor makes a diagnosis by checking symptoms and looking at the rash and sores. The doctor may take samples of stool or of fluid from the throat for testing.

How Is HFMD Treated?

No specific treatment is needed. Medicine such as acetaminophen may reduce fever and help control pain. Rinsing the mouth or gargling with warm salt water, taking antacids, and using topical anesthetic gels can relieve pain from mouth sores.

Children should rest until the fever is gone. Encourage drinking fluids and offer ice cream,

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custard, and Jell-O, because solid foods may not be tolerated.

To avoid spreading the disease, use separate eating utensils and boil them, or use disposable utensils. Boil pacifiers and bottle nipples separately from bottles. Keep the child away from other children.

DOs and DON'Ts in Managing HFMD:

✓ **DO** wash your hands, especially after changing diapers.

✓ **DO** wash contaminated surfaces.

✓ **DO** wash dirty clothing.

✓ **DO** call your doctor if symptoms get worse and don't improve within 2 weeks.

✓ **DO** keep your child away from others.

✓ **DO** use acetaminophen or tepid sponge baths for fever. Don't give aspirin.

✓ **DO** boil bottle nipples, pacifiers, and eating utensils after use.

✓ **DO** have your child use a mild saltwater solution to rinse the mouth.

✓ **DO** have your child rest until the fever is gone.

✓ **DO** have your child drink liquids and eat soft foods.

✓ **DO** call your doctor if your child gets a high fever that doesn't respond to acetaminophen or sponge baths.

✓ **DO** call your doctor if your child has trouble swallowing and can't take fluids.

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⦸ **DON'T** let your child become dehydrated.

⦸ **DON'T** send your child to preschool or day care until the rash resolves and the child feels better.

⦸ **DON'T** share drinking cups or eating utensils.

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FOR MORE INFORMATION

Contact the following sources:

- Centers for Disease Control and Prevention Division of Viral and Rickettsial Diseases Tel: (800) 311-3435 **Website: http://www.cdc.gov**
- The American Academy of Pediatrics Tel: (847) 434-4000 **Website: http://www.aap.org**

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MANAGING YOUR

HEALTHY DIET AS A TEENAGER

What Is Good Nutrition?

Everyone needs the same kinds of nutrients for good nutrition. These nutrients include vitamins (such as vitamin C), minerals (such as calcium and potassium), carbohydrates, proteins, fats, fiber, and water. Eating healthy is better than taking vitamin pills.

Why Is Good Nutrition Important?

Good eating habits as teenagers can mean avoiding later health problems. Proteins are good for energy and make bones strong and muscles flex. Carbohydrates give the body fuel. Fiber helps avoid constipation and lowers risks of diabetes and heart disease. Calcium and vitamin D are important for bone health. Eating lots of bad fats (such as those in burgers and fries) can start to clog arteries and lead to heart disease. Other food-related health problems are high blood pressure (hypertension), obesity, diabetes, stroke, some cancers, and osteoporosis.

What Are Good Foods?

Healthy carbohydrates are found in natural sugars; starches that are in whole-grain foods, beans, peas, and corn; and fiber. Unhealthy carbohydrates include corn sweetener, corn syrup, fructose, honey, sugar, brown sugar, and molasses. Healthy proteins are from fish and shellfish, poultry, lean red meat, eggs, nuts, peanut butter, nut butters, seeds, beans, peas, lentils, soy products such as tofu, milk, and milk products. Good (unsaturated) fats are in oils (olive, peanut, canola), nuts, avocados, and fatty fish (such as salmon).

What Are Tips for Eating Healthy?

Eat three well-rounded meals from all food groups: whole grains, vegetables, fruits, oils, dairy (low-fat), and meat (lean) and beans. Try to eat at least five servings of fruit and vegetables a

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day, about 2½ cups. Eat a serving or two of fruit with breakfast daily. It's also ok to eat even more fruits and vegetables. For example, eat 1 cup of broccoli or tomatoes instead of the usual ½ cup. Remember, always eat breakfast—the most important meal of the day.

Be careful about portion sizes: a clenched fist is about a cup, the amount for a serving of pasta, rice, cereal, vegetables, and fruit. A meat portion is about as big as the palm. Eating out can be a challenge. At fast-food restaurants, choose healthier foods such as grilled, not fried, sandwiches. Order side salads instead of fries. Most restaurant servings are three or four times the right size, so share meals or take doggie bags home. Drink water or low-fat milk instead of sodas. Eat meals on smaller plates. Instead of buying lunches, take favorite healthy foods to school.

Teens who grow and develop quickly also need snacks. Fruits and vegetables provide extra energy. Healthy snacks include fresh and dried fruits, trail mix, nuts, low-fat yogurt, and air-popped popcorn. Try freezing grapes, pineapple, strawberries and bananas for a new taste.

DOs and DON'Ts in Managing Your Healthy Diet:

✓ **DO** drink water and milk instead of sugary drinks and sodas.

✓ **DO** limit fast food and junk food. Eat healthy snacks.

✓ **DO** help at home by making meals or favorite dishes.

✓ **DO** read nutrition labels on foods before you buy them.

⃠ **DON'T** eat the supersize servings. Watch your serving sizes!

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FOR MORE INFORMATION

Contact the following sources:

- The Endocrine Society Tel: (301) 941-0200, (888) 363-6274 **Website: http://www.endo-society.org**
- The National Institutes of Health Tel: (301) 496-4000 **Website: http://www.nih.gov**
- The Obesity Society Tel: (301) 563-6526 **Website: http://www.obesity.org**
- The American Academy of Pediatrics Tel: (847) 434-4000 **Website: http://www.aap.org**

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MANAGING YOUR

HEARING LOSS (DEAFNESS)

What Is Hearing Loss?

Deafness is a decreased ability or complete inability to hear. It may be partial or total and affect one or both ears. Approximately 40% of adults over age 65 have some degree of hearing loss.

What Causes Hearing Loss?

Hearing loss can occur for unknown reasons and at any age, including in infants. The cause can be a problem in the ear canal or middle ear that blocks sound. The inner ear or nerves that carry sound to the brain can also be damaged. Other causes are sudden loud noise or continued exposure to loud noise (as with earphones), viral or bacterial infection of the ear, certain drugs, and puncture of the eardrum.

Medical causes include high blood pressure, brain tumors, head injury, and Paget's disease. Most people older than 65 have some hearing loss.

Risk factors are a family history of deafness and having a job or hobby with exposure to high noise levels (such as rock musicians or jackhammer operators).

What Are the Symptoms of Hearing Loss?

Infants with hearing loss don't respond to sounds around them, especially startling sounds.

In adults, symptoms include trouble telling the difference among sounds, such as being unable to follow a conversation if there's background noise; turning up the radio or television volume; ringing in the ears; dizziness; and ear pain.

How Is Hearing Loss Diagnosed?

The doctor will examine the ears and test hearing. Audiometry (test of hearing) uses a device that makes tones of different loudness. Other tests involve using a tuning fork, checking the ability to

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hear differences between words that sound similar, and measuring how loudly words have to be spoken. If hearing loss seems to be related to the brain, magnetic resonance imaging (MRI) may be done.

How Is Hearing Loss Treated?

Treatment depends on the cause. Sometimes, simple earwax removal or eardrum puncture repair may solve the problem. The doctor will prescribe medicine for an infection. Drugs or exposure to loud noise causing hearing loss should be stopped.

Surgery may sometimes restore hearing. For profound hearing loss (deafness), a cochlear implant can sometimes help. This implant, placed inside the ear, is a type of hearing aid that can make sounds louder. Many people learn to rely on hearing aids.

Even if hearing loss is permanent, people can live normally. The important thing is not to become isolated. A local rehabilitation facility may teach sign language and lipreading. Speech therapy may be necessary.

DOs and DON'Ts in Managing Hearing Loss:

✓ **DO** avoid long-term use or overuse of drugs that cause hearing loss. Talk with your doctor about possible problem drugs.

✓ **DO** get treatment for ear infections, allergies, and respiratory problems that could affect the ear.

✓ **DO** avoid long-term exposure to loud noise. If you cannot, wear ear protection (earplugs or earmuffs).

✓ **DO** call your doctor for removal of earwax.

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✓ **DO** call your doctor if you have pain in or drainage from your ear or you develop dizziness, headaches, or fever.

⃠ **DON'T** put anything, such as cotton-tipped swabs, in your ears.

⃠ **DON'T** ignore worsening loss of hearing.

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FOR MORE INFORMATION

Contact the following sources:

- National Hearing Aid Helpline Tel: (800) 521-5247
- National Institute on Deafness and Other Communication Disorders Tel: (800) 241-1044

Website: http://www.nidcd.nih.gov/health/hearing

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MANAGING YOUR

HEART ATTACK

What Is a Heart Attack?

A heart attack, or myocardial infarction (MI), means that some heart muscles were injured or died because they didn't get enough oxygen. An MI occurs when arteries carrying blood to heart muscles (coronary arteries) are blocked.

What Causes a Heart Attack?

A heart attack occurs when a blood clot forms in a coronary artery and stops blood flow to the heart muscle, so the muscle is injured or dies. Smoking, high blood pressure, diabetes, high levels of cholesterol (a fatty substance), and a family history of heart disease and inflammation of the coronary arteries increase the risk of heart attacks.

What Are the Symptoms of a Heart Attack?

Chest pain, moderate to severe, is the most common symptom. Pain can also occur in the jaw, back, shoulders, or arms (especially the left arm). Pain is often described as crushing, heavy, or pressurelike. Some people have no pain. Sweating, shortness of breath, fast or irregular heartbeat, nausea, feeling of indigestion, and vomiting are other symptoms. Women and diabetics may have symptoms different from those in men, such as shortness of breath without chest pain.

How Is a Heart Attack Diagnosed?

The doctor will do an examination, take blood samples, and order electrocardiography (ECG) to see which areas of the heart may have been damaged.

How Is a Heart Attack Treated?

The treatment goal is to save as much heart muscle as possible. The choice of treatment depends on how much time has passed from the start of the heart attack and on the availability of special

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procedures at the hospital where you are treated. To salvage as much heart muscle as possible, medications to improve circulation and dissolve the clot blocking the artery are given, or a procedure called angioplasty may be done. Other medicine will control pain and blood pressure, and oxygen will help breathing. Other drugs, including aspirin and cholesterol-lowering drugs (statins), may be suggested.

If angioplasty is done, a catheter (long plastic tube) is placed into a leg artery and passed to the heart to take pictures of coronary arteries. The blocked artery is opened with a small balloon on the tip of a catheter. A small metal wire mesh (stent) put into the blocked coronary artery will help keep the artery from blocking again. Medicine can also stop new blockage.

DOs and DON'Ts in Managing a Heart Attack:

✓ **DO** call 911 emergency if you have heart attack symptoms.

✓ **DO** understand that time is critical. The longer the blockage, the more heart damage.

✓ **DO** understand risk factors.

✓ **DO** stop smoking.

✓ **DO** take medicine as prescribed.

✓ **DO** have your cholesterol level checked regularly. Eat low-fat foods.

✓ **DO** try to maintain your ideal body weight.

✓ **DO** regular exercise, such as walking, if your doctor says it's OK.

✓ **DO** see your doctor regularly and call your doctor about changes in your condition, such as if

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you had a heart attack and develop shortness of breath when walking, and leg swelling or difficulty breathing when lying down.

⦸ **DON'T** forget to see a cardiologist (doctor specializing in heart diseases) for advice, both during and after a heart attack.

⦸ **DON'T** try to treat yourself or delay getting medical care.

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:** **http://www.americanheart.org**
- National Heart, Lung, and Blood Institute Tel: (301) 592-8573 **Website:** **http://www.nhlbi.nih.gov**
- American College of Cardiology Tel: (800) 253-4636 **Website:** **http://www.acc.org**

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MANAGING YOUR

HEART ATTACK: FOR WOMEN

What Is a Heart Attack?

A myocardial infarction (MI), or heart attack, means that heart muscles were injured or died because they didn't get enough oxygen because of blocked arteries. Doctors often attribute symptoms of heart disease to other factors in female patients, and women often don't believe that they're having an MI and delay getting emergency treatment, so they account for almost half of all MI deaths. Women also tend to be about 10 years older than men when they have an MI and often have other chronic medical conditions.

What Causes an MI?

An MI occurs when a blood clot forms in a coronary artery and stops blood flow to heart muscle. Smoking, high blood pressure and diabetes commonly cause clots. Other major causes of MI include hardening or blocking of coronary arteries (coronary atherosclerosis), usually from cholesterol plaques.

What Are the Symptoms of an MI?

Like men, women have the most common symptom of chest pain that may include back pain and/or deep aching and throbbing in one or both arms. But women may also have no chest pain. They often have nausea, dizziness, anxiety, shortness of breath, and jaw pain. Clammy sweating, unusual or unexplained tiredness or weakness, and pain in the abdomen (belly) or heartburn may also occur. Palpitations (rapid heartbeats), and feelings of heaviness are also common.

How Is an MI Diagnosed?

The doctor will do an examination and take blood samples. The doctor will also order electrocardiography (ECG).

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How Is an MI Treated?

The treatment goal is to save as much heart muscle as possible. The blood clot blocking the artery is treated, usually first by clot-busting medicines. Other medicine will control pain and blood pressure and oxygen will help breathing. Other drugs, including aspirin and cholesterol-lowering drugs (statins), may be suggested.

A blocked artery can also be treated by coronary angioplasty. A catheter (long plastic tube) is placed into a leg artery and passed to the heart to take pictures of coronary arteries. Then, coronary angioplasty can open the blocked artery. A small metal wire mesh (stent) put into the blocked coronary artery will stop the artery from getting blocked again. Medicine can also stop new blockage from developing.

DOs and DON'Ts in Managing an MI:

✓ **DO** call 911 emergency if you have symptoms. Minutes matter! Don't wait to call. The longer the blockage, the more heart damage. Consider taking aspirin at the first symptoms.

✓ **DO** understand risk factors. Be proactive in talking to your doctor or gynecologist about heart health.

✓ **DO** stop smoking. Drink alcohol in moderation or not at all.

✓ **DO** take medicine as prescribed.

✓ **DO** have blood pressure and cholesterol levels checked regularly. Eat low-fat foods (fruits and vegetables).

✓ **DO** lose weight if you're overweight.

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✓ **DO** exercise, such as walking, if your doctor says it's OK.

✓ **DO** see your doctor and gynecologist regularly. Call your doctor about changes in your condition, such as shortness of breath when walking.

⃠ **DON'T** forget to see a cardiologist during and after an MI.

⃠ **DON'T** delay getting medical care.

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Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:** **http://www.americanheart.org**
- National Heart, Lung, and Blood Institute Tel: (301) 592-8573 **Website:** **http://www.nhlbi.nih.gov**
- American College of Cardiology Tel: (800) 253-4636 **Website: http://www.acc.org**

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MANAGING YOUR

HEAT EXHAUSTION AND HEATSTROKE

What Are Heat Exhaustion and Heatstroke?

Heat exhaustion refers to a group of symptoms caused by exposure of the body to excessive heat. The body loses fluids and salt (sodium) when exposed to high temperatures. Heat exhaustion can make people look and feel very sick, but it's a minor illness and there is usually rapid improvement with treatment. Heatstroke, however, is a rare but serious life-threatening illness. Heatstroke needs intensive medical care to prevent death.

What Causes Heat Exhaustion and Heatstroke?

Heat exhaustion is common during heat waves or during vigorous exercise in warm, humid environments. Getting dehydrated, overdressing, and drinking alcohol are contributing factors. Heatstroke can follow untreated heat exhaustion.

What Are the Symptoms of Heat Exhaustion and Heatstroke?

Symptoms of heat exhaustion are heavy sweating in a warm or hot place, feeling ill, and looking pale and sweaty. The skin feels cool and clammy or warm and moist. People's temperature may be normal or high. Other symptoms are fast pulse rate and feeling dizzy, lightheaded, achy, weak, tired. Headache, muscle cramps, and vomiting can occur.

People with heatstroke have very hot, dry, flushed skin but no sweating. They also have rapid breathing, racing heart rate, muscle cramps, weakness, and neurologic problems (seizures, coma, hallucinations).

How Are Heat Exhaustion and Heatstroke Diagnosed?

The health care provider makes a diagnosis from the medical history, physical examination, and laboratory tests.

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How Are Heat Exhaustion and Heatstroke Treated?

Treatment of heat exhaustion includes getting people to cooler places, with shade, fans, or air conditioning. Take off excessive or tight-fitting clothes. Cool water can be put on the skin. People should lie down. Fluids should be given slowly, at least 1 quart, by mouth if possible. Sports drinks are best, but any nonalcoholic beverage can be given. For severe illness or if people can't drink or are vomiting, fluids may be given intravenously.

Heatstroke needs emergency medical care by trained rescuers, nurses, and health care providers in the hospital. Intravenous fluids and medicines are used to control blood pressure and maintain steady urine flow. To cool the body, it can be immersed in a cold water or ice water bath, misted with cool water, or wrapped in a cooling blanket.

DOs and DON'Ts in Managing Heat Exhaustion and Heatstroke:

✓ **DO** treat heat exhaustion, to avoid heatstroke. Don't try to treat heatstroke at home. It's an emergency!

✓ **DO** drink plenty of nonalcoholic fluids when you sweat or are hot. Don't drink caffeinated beverages. Rehydrate as soon as possible.

✓ **DO** wear light-colored, lightweight, loose-fitting clothing when you're in hot places. Take sun protection such as an umbrella and wide-brimmed hat.

✓ **DO** avoid overexertion in the heat. Avoid hot environments if you feel sick.

✓ **DO** get to shade, fans, or air conditioning if you're hot and feel sick.

✓ **DO** watch elderly people for signs of heat exhaustion.

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✓ **DO** get emergency care if the person seems unconscious or drunk.

⃠ **DON'T**exercise during times of high heat and humidity.

⃠ **DON'T** plan activity without plenty of fluids in the heat, especially during the hottest part of the day.

⃠ **DON'T** overdo it. Plan for plenty of rest, cooling, and water breaks.

⃠ **DON'T** stop athletes from drinking fluids during heavy exercise.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Emergency Physicians Tel: (800) 798-1822 or (972) 550-0911 **Website: http://www.acep.org**
- National Institute of Environmental Health Sciences Tel: (919) 541-3345 **Website: http://www.niehs.nih.gov**

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MANAGING YOUR

HELICOBACTER PYLORI INFECTION

What Is a Helicobacter pylori Infection?

Gastritis is inflammation (swelling) of the lining of the stomach because of a stomach infection. The bacteria called *Helicobacter pylori* (also called *H. pylori*) causes this infection. It's the most common cause of gastritis worldwide. There is no known way to prevent it.

What Causes an H. pylori Infection?

How people get this infection is unclear. Possible sources of bacteria may be contaminated water or utensils. *H. pylori* can grow in the stomach lining covered by a layer of mucus that protects it from stomach acid.

What Are the Symptoms of an H. pylori Infection?

The main symptom is chronic stomach upset. Pain in the upper abdomen (belly) and cramps may be present and are often made worse by eating. Many people will have less appetite. Bad breath (halitosis) may also be present. A burning acid taste in the mouth, nausea, vomiting, and bleeding may occur.

Many people may have no symptoms, and the infection is found when a stomach biopsy is done during upper endoscopy.

How Is an H. pylori Infection Diagnosed?

The doctor makes a diagnosis from a history of stomach upset, pain, and cramps. Sometimes, upper endoscopy (looking at the stomach through a lighted, flexible tube) is done to confirm the diagnosis and rule out other causes. A stomach biopsy (removing a small piece of tissue) may be done to test for bacteria in the stomach and to exclude other stomach diseases.

A breath test (testing with a substance called urea) or stool test may also be used for diagno-

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sis. Blood tests can also measure antibodies to *H. pylori*, but these won't tell whether the infection is new or old because antibodies to the bacteria can last for several years after treatment.

How Is an H. pylori Infection Treated?

Three or four drugs may be taken for several days. These usually include the following types of medicines: (1) antibiotics (e.g., clarithromycin, amoxicillin, tetracycline, metronidazole, or some combination); (2) acid-suppressing drugs (e.g., omeprazole, lansoprazole, and pantoprazole); and (3) bismuth subsalicylate (Pepto-Bismol™).

Complications, such as stomach ulcers, bleeding, and increased risk of stomach cancer, can occur in people with long-lasting infection left untreated.

DOs and DON'Ts in Managing H. pylori Infection:

✓ **DO** eat regularly and in moderation.

✓ **DO** take medicines as directed by your doctor.

✓ **DO** call your doctor if abdominal pain becomes severe or if symptoms don't improve 2 to 3 days after treatment.

✓ **DO** call your doctor if you have side effects from the medicines.

✓ **DO** call your doctor if you vomit blood or you have blood with bowel movements or dark tarry stools.

⊘ **DON'T** smoke.

⊘ **DON'T** drink alcohol.

⊘ **DON'T** take medicines that can irritate your stomach, such as aspirin and nonsteroidal anti-

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inflammatory drugs (NSAIDs).

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FOR MORE INFORMATION

Contact the following sources:

- National Digestive Diseases Information Clearinghouse Tel: (800) 891-5389 **Website:** **http://www.niddk.nih.gov/health/digest/nddic.htm**
- American College of Gastroenterology Tel: (703) 820-7400 **Website:** **http://www.acg.gi.org**

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MANAGING YOUR

HEMOCHROMATOSIS

What Is Hemochromatosis?

Hemochromatosis is a condition in which the body stores too much iron. The excess iron builds up in different organs (mostly the liver, heart, and pancreas) and damages them. Hemochromatosis is more common in Caucasians.

Hemochromatosis is not contagious. It's not curable, but treatment can stop or slow down disease progression and sometimes reverse symptoms. Men have symptoms more often and at an earlier age than women, because women lose iron during menstrual periods.

What Causes Hemochromatosis?

The most common form in the United States is called primary, or hereditary (passed on from parents to children), hemochromatosis. People who inherit a copy of the gene from both parents (2 or 3 per 1000 people) are at risk.

What Are the Symptoms of Hemochromatosis?

The abnormal gene is present at birth, but symptoms usually don't show up until adulthood. The most common symptoms are fatigue, joint pain, darkening of the skin and other organs, arthritis, weakness, erectile dysfunction in men or loss of interest in sex, and pain in the abdomen (belly).

Diabetes, liver disease, heart disease, thyroid disease, or reproductive system problems can occur.

How Is Hemochromatosis Diagnosed?

The doctor makes a diagnosis from the medical history, physical examination, and additional tests. Blood tests called transferrin saturation and ferritin level that measure the amount of iron in blood are done. Computed tomography (CT) or magnetic resonance imaging (MRI) of the liver

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may also be done.

A biopsy of the liver is usually needed to confirm the diagnosis. In a biopsy, a long hollow needle is put into the liver, a piece of liver tissue is removed for study with a microscope. The iron level in the tissue will also be measured.

Special genetic tests can now check for the gene for hemochromatosis.

How Is Hemochromatosis Treated?

The best therapy is removal of iron by taking blood (phlebotomy) once or twice weekly until the iron level is at or near normal.

Regular blood tests to measure iron levels and liver function will also be needed.

When phlebotomy is not possible or is insufficient and the disease is advanced, a medication called deferoxamine may also be given. It is known as an iron chelating agent and helps to remove iron from the body.

DOs and DON'Ts in Managing Hemochromatosis:

✓ **DO** eat a balanced diet, but avoid red meat and eat more fruits and vegetables.

✓ **DO** restrict exercise if you have heart disease caused by hemochromatosis. Otherwise exercise as tolerated.

✓ **DO** ask other family members to be tested for hereditary hemochromatosis. If diagnosed, they should begin treatment before heart or liver disease develops.

✓ **DO** call your doctor if you have fever, chest pain, shortness of breath, or abdominal pain.

⦸ **DON'T** take iron pills or vitamin C. They can increase the harmful effects of iron.

⦸ **DON'T** drink alcohol. It increases your risk for liver disease.

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FOR MORE INFORMATION

Contact the following sources:

- National Heart, Lung, and Blood Institute Tel: (301) 592-8573 **Website:** **http://www.nhlbi.nih.gov**
- American College of Gastroenterology Tel: (703) 820-7400 **Website:** **http://www.acg.gi.org**

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MANAGING YOUR

HEMOLYTIC-UREMIC SYNDROME

What Is Hemolytic-uremic Syndrome?

Hemolytic-uremic syndrome (HUS) is a serious condition that may occur following severe bloody infectious diarrhea or a severe intestinal disorder for several days. HUS affects the blood clotting system, especially tiny blood vessels (capillaries) in and around the kidneys. Clots form in these vessels, so fewer blood cells are available for other clotting. As a result, internal bleeding may occur, especially in the kidneys. HUS is most common in children younger than 4 years old. It's the most common cause of kidney failure in children. In kidney failure, the kidneys stop working, so kidney dialysis may be needed for several weeks or longer.

What Causes HUS?

The usual cause is a type of bacteria called VTEC (verocytotoxin-producing *Escherichia coli*). Sometimes other bacteria cause it. Some people getting certain medical treatments or drugs can also have HUS. HUS at times follows a viral infection such as an upper respiratory tract infection. Unpasteurized milk and undercooked meat may also contain bacteria that cause HUS.

What Are the Symptoms of HUS

Symptoms include fever, nausea, vomiting, pain in the abdomen (belly), and high blood pressure. Less frequent or absent urination or reddish urine may occur.

Other symptoms are swelling of the hands, face, or body; pale or yellowish skin color (jaundice); small spots of bleeding under the skin (petechiae); and bruising. Stroke and seizures can also occur.

How Is HUS Diagnosed?

The health care provider makes a diagnosis from a careful examination and medical history.

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Blood and urine samples, and maybe stool, are tested. The health care provider may order ultrasonography to check for kidney damage. This painless test uses sound waves to look at organs. Other kidney tests may be done.

How Is HUS Treated?

Treatment takes place in the hospital. Intravenous fluids and medicines are given to control blood pressure, correct the body's salt and water balance, and keep the urine flow steady and prevent more kidney damage. Most children and adults recover after hospital treatment. People usually improve in 1 to 2 weeks. Most children recover completely. During treatment, some people need medicine to prevent seizures or treat complications involving the heart. Rarely, people may need kidney dialysis. In dialysis, the blood passes through small tubes in a machine that filters out harmful substances. Kidneys usually start to work normally after a few weeks of dialysis. About 20% to 30% of adults develop chronic renal failure. Adults are more likely than children to get HUS again.

DOs and DON'Ts in Managing HUS:

✓ **DO** pay attention to changes in urinary habits that could mean kidney disease.

✓ **DO** wash your hands thoroughly after contact with livestock and their food products.

✓ **DO** call your health care provider if you or your child has had any of the following: severe bloody diarrhea, high temperature, nausea, vomiting, inability to urinate or less frequent urination than normal, bloody or reddish urine, seizures, or extreme weakness and tiredness.

⊘ **DON'T** eat undercooked meat, especially ground beef. Meat should be cooked to an internal temperature of 155° F or higher.

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Contact the following sources:

- American Society of Pediatric Nephrology Tel: (312) 503-4000 **Website:** **http://www.aspneph.com**
- National Kidney Foundation Tel: (1-800) 622-9010 or (212) 889-2210 **Website:** **http://www.kidney.org**

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MANAGING YOUR

HEMOPHILIA

What Is Hemophilia?

Hemophilia is an inherited blood disorder that causes bleeding. Factor VIII or factor IX, which are important proteins in the blood for clotting, are too low. Hemophilia A (lack of factor VIII) is much more common than hemophilia B (lack of factor IX). About 80% of people have hemophilia A. Many hemophiliacs lead normal lives. Hemophilia is rather rare, occurring in 1 per 10,000 to 30,000 newborn boys.

What Causes Hemophilia?

Hemophilia is genetically passed to children, usually males, by their mothers. It's called a sex-linked disorder. Women usually have no symptoms because they have two X chromosomes, so one can be affected but the other one has normal genes. Men have only one X chromosome, so if that one is affected, hemophilia results.

What Are the Symptoms of Hemophilia?

Bleeding and easy bruising are the most common symptoms and can be mild to severe. Some people bleed after a minor injury, others rarely bleed, and sometimes bleeding starts without an injury. Bleeding can occur anywhere, but many bleeds start in a muscle or joint such as the knee and may cause pain or swelling. Bleeding gums and bloody urine are also common. Other symptoms include joint and muscle pain or stiffness and slow wound healing. Hemophilia can cause joints to tighten and lose the ability to move.

How Is Hemophilia Diagnosed?

Hemophilia is usually found in childhood, but sometimes people are diagnosed in early adulthood, such as after a tooth is pulled and bleeding can't be stopped.

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The doctor will take a medical history, do a physical examination, and test blood for levels of factor VIII and factor IX. The doctor may suggest seeing a hematologist (specialist in blood problems).

How Is Hemophilia Treated?

Treatment involves replacing blood factors or using medicine. When bleeding starts, treatment must start also, usually as self-infusion of factor VIII. If started at home, infusion can continue at the hospital. Serious bleeding needs hospital treatment. To prevent damage, bleeding into a muscle or joint must be stopped as soon as possible. Surgery is sometimes needed to fix damaged joints or muscles. Special physical therapy exercises may help heal joints. Pain medicine is given. People who suffer trauma should go to the hospital immediately.

People who need surgery get factor replacement before and after surgery. Medicine such as desmopressin or aminocaproic acid can be used in mild cases.

Contamination of blood factors has caused more than 50% of hemophiliacs to be HIV positive.

DOs and DON'Ts in Managing Hemophilia:

✓ **DO** follow your doctor's directions about what to do if you bleed or are injured.

✓ **DO** tell your doctor about medicines you take, prescription and nonprescription.

✓ **DO** see your dentist twice yearly.

✓ **DO** exercise but avoid contact sports such as football. Swimming is OK.

✓ **DO** tell your doctor if you're going to the dentist or having surgery.

✓ **DO** go to the emergency room if you bleed from your rectum, cough up blood, suddenly

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have a bad headache, or cannot stop bleeding.

✓ **DO** avoid intramuscular injections.

✓ **DO** accident-proof your home. Wear a seatbelt and drive safely.

⃠ **DON'T** take medicine unless your doctor tells you to.

⃠ **DON'T** use aspirin, ibuprofen (e.g., Motrin®, Advil®), naproxen (e.g., Aleve®), or other nonsteroidal antiinflammatory drugs. These medications will increase the risk of bleeding.

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FOR MORE INFORMATION

Contact the following sources:

- National Hemophilia Foundation Tel: (212) 328-3700 **Website:** **http://www.hemophilia.org**

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MANAGING YOUR

HEMORRHOIDS

What Are Hemorrhoids?

Hemorrhoids (also called piles) are inflamed, swollen blood vessels located in and around the anus and lower rectum. These vessels can stretch under pressure, like varicose veins in the legs. Hemorrhoids are either inside the anus (internal) or under the skin around the anus (external). About 50% of the adult population of the United States, both men and women, have hemorrhoids.

Hemorrhoids aren't usually dangerous or life-threatening. They aren't contagious.

What Causes Hemorrhoids?

Causes include increased pressure and swelling from straining to move the bowel and conditions such as pregnancy and chronic constipation or diarrhea. Heredity and aging are other factors.

What Are the Symptoms of Hemorrhoids?

Many people have hemorrhoids but not all have symptoms. Pain or tenderness can occur during bowel movements. The most common symptom of internal hemorrhoids is bright red blood covering stools (bowel movements), on toilet paper, or in the toilet. Internal hemorrhoids may poke through to outside the body and become irritated and painful. These are protruding hemorrhoids. Symptoms of external hemorrhoids include painful swelling or hard lump near the anus. Straining, rubbing, or cleaning around the anus may cause irritation with bleeding and itching. Draining mucus may cause itching.

How Are Hemorrhoids Diagnosed?

The doctor may suspect hemorrhoids from the symptoms and will make a diagnosis by doing a physical examination. Hemorrhoids can be painless, and the doctor may find them on routine

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physical examinations.

How Are Hemorrhoids Treated?

Soft bowel movements are important for preventing and treating hemorrhoids. Eating a high-fiber diet and drinking plenty of fluids are important. Measures to reduce symptoms include warm tub or sitz baths several times a day. Ice packs can help reduce swelling. Cream or suppositories can be applied to the affected area. If hemorrhoids are very inflamed, the doctor may prescribe cortisone cream. Daily use of stool softeners such as docusate during flare-ups helps. Most people get better in about 2 weeks if they follow the doctor's suggestions.

Some hemorrhoids are treated surgically to remove or reduce the size of hemorrhoids. These methods include rubber band ligation, sclerotherapy, electric or laser heat (laser coagulation) or infrared light (infrared photocoagulation), and hemorrhoidectomy. For ligation, a rubber band around the bottom of the hemorrhoid cuts off circulation, and the hemorrhoid goes away. Sclerotherapy uses a chemical to shrink hemorrhoids. For heat and light methods, special tools are used to burn hemorrhoids. Hemorrhoidectomy is surgery to remove hemorrhoids permanently.

DOs and DON'Ts in Managing Hemorrhoids:

✓ **DO** eat more grains, fruits, and vegetables.

✓ **DO** drink more liquid, especially water.

✓ **DO** remember that many problems in your rectal area have similar symptoms and are incorrectly said to be hemorrhoids. Call your doctor for an examination.

✓ **DO** avoid anything that will cause constipation.

✓ **DO** remember that straining can make hemorrhoids worse.

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✓ **DO** call your doctor if you see blood on your stool or toilet paper or in the toilet.

✓ **DO** call your doctor if you have anal pain, burning, or itching or if you have fever or drainage after surgery.

⃠ **DON'T** strain during bowel movements.

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FOR MORE INFORMATION

Contact the following sources:

- American Gastroenterological Association Tel: (301) 654-2055 **Website:** **http://www.gastro.org**
- National Digestive Diseases Information Clearinghouse Tel: (800) 891-5389 **Website:** **http://www.niddk.nih.gov/health/digest/nddic.htm**
- American College of Surgeons Tel: (312) 202-5000, (800) 621-4111 **Website:** **http://www.facs.org**

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CARING FOR YOUR CHILD WITH

HENOCH-SCHÖNLEIN PURPURA

What Is Henoch-Schönlein Purpura?

Henoch-Schönlein purpura is a disease in which small blood vessels throughout the body become inflamed (swollen). These blood vessels may be in the skin, joints, stomach, or kidneys.

This disease is also called allergic purpura or anaphylactoid purpura. It affects mostly younger children (usually boys), but older children and adults may also get it.

Most children recover completely, but recovery may take several months or years. Also, because of possible kidney problems, regular follow-up blood pressure checks and urine tests will be needed for several months.

What Causes Henoch-Schönlein Purpura?

The cause isn't fully known. It usually occurs a few weeks after a strep throat infection or a cold or other viral infections. Substances (antibodies) produced by the body's immune system to fight the initial infection may contribute to its development.

What Are the Symptoms of Henoch-Schönlein Purpura?

The first symptom may be small purplish spots (purpura), usually on the buttocks and legs. The ankles are usually affected. The rash may first look like hives but usually changes to purplish or brownish bruises in 1 to 2 days.

Joints, usually knees and ankles, are painfully swollen. The pain may be so severe that walking is hard.

Other symptoms may be pain in the belly (abdomen), nausea, vomiting, diarrhea, and blood in the urine. Adolescent girls and women may have painful periods.

How Is Henoch-Schönlein Purpura Diagnosed?

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The doctor will examine your child's skin and may take a sample of it for study with a microscope. Urine and blood samples may also be taken. The doctor may refer your child to a kidney specialist (nephrologist) and other specialists such as a rheumatologist.

If the doctor thinks that there may be a kidney problem, a kidney biopsy may be done. This biopsy involves using a hollow needle to remove a tiny bit of tissue from the kidney and sending it to a laboratory for study.

How Is Henoch-Schönlein Purpura Treated?

This disease often goes away by itself. Symptoms may flare up and disappear several times. The doctor may prescribe medicine for your child's pain. Over-the-counter medicine, such as ibuprofen, naproxen, or acetaminophen, may also be used to control pain and fever. Your doctor may prescribe a steroid (prednisone) for severe symptoms or kidney disease.

DOs and DON'Ts in Managing Henoch-Schönlein Purpura:

✓ **DO** encourage your child to drink plenty of fluids and eat a normal diet as much as possible.

✓ **DO** call the doctor immediately if your child's abdominal pain gets worse or the bowel movements (stool) or urine contain blood; if there is puffiness, especially around the face or eyes; or if your child hasn't urinated in more than 12 hours.

✓ **DO** call the doctor immediately if your child appears very sick.

⃠ **DON'T** give aspirin to children, because it may cause a serious illness called Reye's syndrome and may cause increased bleeding from the blood vessels.

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Contact the following sources:

- American College of Rheumatology Tel: (404) 633-3777 **Website:**

  http://www.rheumatology.org

- American Academy of Dermatology Tel: (866) 503-SKIN (7546) **Website:**

  http://www.aad.org

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MANAGING YOUR

HEPATIC ENCEPHALOPATHY

What Is Hepatic Encephalopathy?

Hepatic encephalopathy refers to changes in behavior, mental state, and nervous system in people with liver failure. It's not a disease but a group of symptoms seen in people whose livers don't work well. High levels of ammonia in the bloodstream and brain are thought to cause these changes. Bacteria in the stomach and intestines make ammonia. Usually, the liver normally metabolizes the ammonia (makes ammonia harmless). However, people with liver disease have more ammonia because their liver doesn't work. Ammonia enters the blood, gets to the brain, and causes symptoms by interfering with brain function.

This encephalopathy occurs in more than 50% of all people with liver cirrhosis. Untreated, it can lead to coma and death. It's not contagious and cannot be passed from parents to children.

What Causes Hepatic Encephalopathy?

Disorders that destroy the liver and cause liver failure can lead to hepatic encephalopathy. Some of these disorders are viral hepatitis (such as hepatitis B and hepatitis C), severe infections, autoimmune diseases, cancer, and Reye's syndrome. Medicines such as nonsteroidal antiinflammatory drugs and toxins such as alcohol are other causes. People with cirrhosis can get encephalopathy from using sedatives and analgesics. Gastrointestinal bleeding can also increase the risk of hepatic encephalopathy.

What Are the Symptoms of

Hepatic Encephalopathy?

Symptoms include being disoriented, forgetful, and confused. People feel sleepy and have mood changes, lethargy, and memory loss. Coma can occur. Others include jaundice, problems speak-

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ing, tremors, being agitated, and uncoordinated movements. People usually have signs of liver disease such as jaundice, enlarged breasts and small testicles (men), fluid in the abdomen (belly), and swelling in the legs.

Hepatic encephalopathy is divided into grades 1 to 4. Grade 1 involves mild confusion, poor attention, being irritable, and decreased ability to do mental tasks. In grade 2, people have lethargy, drowsiness, personality changes, and great trouble doing mental tasks. In grade 3, people are sleepy (but can be aroused), cannot do mental tasks, and are disoriented (place and time). In grade 4, coma occurs.

How Is Hepatic Encephalopathy Diagnosed?

The doctor will do a complete physical examination. The doctor may order blood tests and x-rays to rule out other problems, because hepatic encephalopathy mimics symptoms of other disorders. These disorders include alcohol withdrawal, sedative overdose, meningitis, low blood sugar, brain cancer, and blood clots in the brain.

How Is Hepatic Encephalopathy Treated?

Treatment goals are to find and treat causes, such as drugs, GI bleeding, and metabolic problems. Almost all people need hospitalization. Gastrointestinal bleeding must be stopped and other causes must be eliminated. A drug called lactulose acts as a laxative and helps empty the intestines, so bacteria cannot make ammonia. Sometimes, an antibiotic called neomycin is used. This drug kills bacteria in the intestine so that there is less ammonia.

DOs and DON'Ts in Managing

Hepatic Encephalopathy:

✓ **DO** remember that hepatic encephalopathy may be reversible. However, the chance of death is high if coma occurs.

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✓ **DO** call your doctor if a family member with liver disease has behavior, personality, or mental changes.

⦸ **DON'T** drink alcohol, especially if you have cirrhosis.

⦸ **DON'T** forget that common over-the-counter and prescription sleeping drugs can cause the disorder in people with liver disease.

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FOR MORE INFORMATION

Contact the following sources:

- American Gastroenterological Association Tel: (301) 654-2055 **Website:** **http://www.gastro.org**
- National Digestive Diseases Information Clearinghouse Tel: (800) 891-5389 **Website:** **http://www.niddk.nih.gov/health/digest/nddic.htm**

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MANAGING YOUR

HEPATITIS A

What Is Hepatitis A?

Hepatitis A is infection of the liver with the hepatitis A virus. About 150,000 people are infected every year in the United States. Most people recover in 2 to 6 months without serious health problems.

People with hepatitis A very rarely develop liver failure.

What Causes Hepatitis A?

The cause is the hepatitis A virus. Food (such as shellfish from polluted water) or water contaminated with infected stools (bowel movements) can spread the virus. The most common source of spread is infected food handlers who don't wash their hands well after using the bathroom. Direct contact with infected people will pass the infection to others. Outbreaks occur most often in day care centers, military bases, and institutions for disabled. In more than 40% of cases, it isn't known how people get infected.

What Are the Symptoms of Hepatitis A?

Not all people have symptoms. Symptoms may occur, usually during the first month following infection. The main symptom is jaundice (yellow skin and whites of the eyes), plus pale or clay-colored stools, dark urine, and itching all over the body. Flu-like symptoms of fatigue, loss of appetite, nausea and vomiting, low-grade fever, and pain in the abdomen (belly) in the liver area may occur before jaundice.

How Is Hepatitis A Diagnosed?

The doctor will do a physical examination and a blood test to show antibody to the virus. The antibody is a substance made by the immune, or infection-fighting, system. Liver function tests

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will also be much higher than normal.

How Is Hepatitis A Treated?

No specific treatment exists. Most people can be cared for at home. Proper rest for several days after diagnosis is important. During this time, intimate contact with other people should be avoided. The diet should be balanced and include high-calorie foods. People who come in close contact with the infected person and who have not been previously vaccinated should be given immune serum globulin within 2 weeks of exposure by their physician.

DOs and DON'Ts in Managing Hepatitis A:

✓ **DO** get plenty of rest and eat a well-balanced diet.

✓ **DO** make sure to wash your hands if you have hepatitis or care for someone who does, especially if you contact fecal material.

✓ **DO** use separate or disposable eating and drinking utensils.

✓ **DO** wash your hands properly after changing a diaper and before doing anything else if you work in a day care center. Restaurant workers should always wash their hands properly.

✓ **DO** use proper protection, such as gloves and eyeglasses, if you're exposed to fecal material and other body fluids on the job.

✓ **DO** call your doctor if you were exposed to someone with hepatitis A or you have symptoms of the disease.

✓ **DO** call your doctor if your hepatitis symptoms don't go away within 4 weeks.

⦸ **DON'T** drink alcohol. Avoid substances that may hurt the liver.

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Contact the following sources:

- Hepatitis Foundation International Tel: (800) 891-0707 **Website: http://www.hepfi.org/**
- American Gastroenterological Association Tel: (301) 654-2055 **Website: http://www.gastro.org**
- National Digestive Diseases Information Clearinghouse Tel: (800) 891-5389 **Website: http://www.niddk.nih.gov/health/digest/nddic.htm**

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MANAGING YOUR HEPATITIS B

What Is Hepatitis B?

Hepatitis B is infection of the liver with a virus. More than 1 million people in the United States are carriers of the virus. About 200,000 people get this disease each year. Certain racial and ethnic groups, including African Americans, Asians, Pacific Islanders, Hispanics, and Native Americans, have higher rates of infection.

About 90% of people recover completely in a few months. Others become carriers or chronically infected. Hepatitis B is a serious disease, and about 1% of people die during the acute stage.

What Causes Hepatitis B?

The cause is the hepatitis B virus. The virus is passed to others by sexual contact with infected people and using nonsterile needles. Infected blood and other body fluids (e.g., semen, vaginal secretions, breast milk, tears, saliva, and fluid in open sores) can spread the virus. Infected mothers can give it to babies.

What Are the Symptoms of Hepatitis B?

Not all people have symptoms. If they do occur they usually appear within 6 months from when the infection is acquired. First symptoms may be rashes, joint pains, fatigue, and other flu-like symptoms. Then, jaundice (yellow skin or whites of the eyes) may occur. Other symptoms are pale or clay-colored stools, dark urine, itching, loss of appetite, nausea, vomiting, low-grade fever, and pain in the abdomen (belly). Severe disease may lead to cirrhosis (liver scarring), fluid in the abdomen (ascites), and liver failure.

How Is Hepatitis B Diagnosed?

The doctor will do an examination and blood test to show the presence of the virus in the blood (hepatitis B antigens) and the body's response to the infection (hepatitis B antibodies). Liver function tests will also be abnormal.

How Is Hepatitis B Treated?

No treatment exists for acute disease. Most people can receive care at home. Activity is as tolerated. Proper rest for 1 to 4 weeks after diagnosis is beneficial. During this time, intimate contact with other people should be avoided. The diet should be high in calories. People who

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come in contact with infected people and newborns of infected mothers should be given immune globulin plus hepatitis B vaccine within 2 weeks of exposure.
Medicine is given to those with persistent infection (chronic hepatitis B) to prevent more liver damage.

DOs and DON'Ts in Managing Hepatitis B:

- DO get plenty of rest and eat a well-balanced diet.
- DO use condoms when having sex.
- DO avoid exposing others to your blood and other body fluids.
- DO call your doctor if symptoms don't go away in 4 or 6 weeks or new symptoms develop.
- DO ask your doctor about vaccines for family members and others close to you.
- DON'T drink alcohol or take medications such as acetaminophen that can further damage your liver.
- DON'T share needles, donate blood, or breast-feed your baby.
- DON'T have sex with an infected person or carrier.

FOR MORE INFORMATION

Contact the following sources:

- American Liver Foundation
  Tel: (800) 465-4837
  Website: http://www.liverfoundation.org/
- Hepatitis Foundation International
  Tel: (800) 891-0707
  Website: http://www.hepfi.org/

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MANAGING YOUR

HEPATITIS C

What Is Hepatitis C?

Hepatitis C is infection of the liver with a virus (hepatitis C virus).

Some people with hepatitis C never have serious health problems, but up to 20% get liver cirrhosis. Cirrhosis means liver scarring, so the liver cannot work well. At least 50% of the people infected with hepatitis C virus may have chronic liver disease, meaning liver inflammation (swelling) is long-lasting. About 1% to 5% of infected people die of liver disease.

What Causes Hepatitis C?

The cause is the hepatitis C virus.

The virus is passed to others by infected blood, as when people share needles to inject drugs. The next most common way is anal sex.

Other ways to get hepatitis C are by pricking a finger on a contaminated needle; tattooing, body piercing, or acupuncture with nonsterile equipment; mother-to-baby infection during birth; and blood transfusions or organ transplants done in the United States before July 1992 or in other countries with poor blood donor screening.

Hugging, kissing, toilet seats, or sharing cups or kitchen utensils cannot transmit hepatitis C.

What Are the Symptoms of Hepatitis C?

Most people have no symptoms, but symptoms can be mild to severe and sometimes life-threatening. Symptoms of acute disease include headache, aches and pains, fatigue, and upset stomach. These can last for several weeks. The most common symptom of chronic hepatitis C is fatigue. Others are nausea, vomiting, diarrhea, loss of appetite, and pain in the upper abdomen (belly), under the ribs.

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How Is Hepatitis C Diagnosed?

People often find out about having hepatitis C by a routine blood test showing high liver enzyme levels or when donating blood and hepatitis C antibody is found. If your doctor suspects hepatitis C, blood tests will be done to look for the presence of antibodies to the hepatitis C virus. The antibody is a substance made by the immune, or infection-fighting, system in response to an infection.

How Is Hepatitis C Treated?

Acute hepatitis C generally has no specific treatment. Most people can receive care at home. Rest and proper diet are important for severe symptoms. Avoid alcohol and substances that hurt the liver.

People with chronic disease are treated with medicines such as interferon for 24 to 48 weeks, but they don't work for everybody and not everyone wants to take the drugs because of potential side effects. Success depends on which type of hepatitis C virus caused the infection. With genotypes 2 and 3, about 80% of people get well. The cure rates are lower in those with genotypes 1 and 4.

DOs and DON'Ts in Managing Hepatitis C:

✓ **DO** get help for a drug problem if you have one.

✓ **DO** follow a healthy lifestyle. Avoid alcohol, which may further damage the liver. If possible, give it up completely.

✓ **DO** get regular medical checkups.

✓ **DO** see your doctor right away if you get jaundice (yellow skin and dark-colored urine), pain

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in your abdomen, nausea or vomiting lasting more than 1 to 2 days, or blood in your vomit.

✓ **DO** call your doctor if hepatitis C symptoms persist after completion of treatment.

⃠ **DON'T** take medicines that can hurt the liver, such as acetaminophen.

⃠ **DON'T** share needles.

⃠ **DON'T** breast-feed your baby.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- Hepatitis Foundation International Tel: (800) 891-0707 **Website: http://www.hepfi.org**
- American Gastroenterological Association Tel: (301) 654-2055 **Website: http://www.gastro.org**
- National Digestive Diseases Information Clearinghouse Tel: (800) 891-5389 **Website: http://www.niddk.nih.gov/health/digest/ nddic.htm**

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MANAGING YOUR

HEPATORENAL SYNDROME

What Is Hepatorenal Syndrome?

Hepatorenal syndrome is a group of symptoms due to kidney failure starting in people with advanced liver disease. It's a serious complication of liver cirrhosis and can be life-threatening. This syndrome occurs in up to 10% of people hospitalized with liver failure. It's not contagious and cannot be passed from person to person. It also isn't passed from parents to children. The syndrome occurs in people of all races who have chronic liver disease, equally men and women.

What Causes Hepatorenal Syndrome?

The cause isn't known. One possible cause is drastically lower blood flow to the kidneys caused by certain hormones. The result is blood vessels going to the kidneys being constricted, so kidney failure occurs. Main risk factors include liver cirrhosis, alcoholic hepatitis, acute liver failure, and bacterial peritonitis. Gastrointestinal bleeding and sudden drop in blood pressure caused by medicines, dehydration, or blood loss are contributing factors.

What Are the Symptoms of Hepatorenal Syndrome?

Symptoms include fatigue, feeling ill, nausea, and vomiting. Liver disease causes jaundice (yellow skin), abdominal swelling, leg swelling (edema), weight gain, and changes in mental status (delirium and confusion). Other symptoms are enlarged liver and spleen, muscle wasting, jerking muscle movements, tremors, red color of the palms, and small spider-like veins usually on the upper chest. Kidney failure causes less urine, dark-colored urine, and too much fluid retained in the body.

How Is Hepatorenal Syndrome Diagnosed?

The health care provider makes a diagnosis from the medical history, physical examination, and

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laboratory tests. Blood tests show low sodium, high blood urea nitrogen, and high creatinine levels. Low blood protein levels and abnormal clotting times may occur. People with mental changes may have a high blood ammonia level due to complications from liver failure.

How Is Hepatorenal Syndrome Treated?

Treatment is difficult and controversial. It aims to improve liver function and make sure that the body has enough blood volume for its organs. First, volume challenges are tried. Fluids are given intravenously to try to increase blood volume and flow to the kidneys. People with ascites may also need to have fluid removal (paracentesis). Ascites is extra fluid in the abdominal cavity. People with cirrhosis and ascites should be very careful about taking new medicines, especially those toxic to kidneys, such as nonsteroidal antiinflammatory drugs.

A medicine called vasopressin may be given to help kidney blood flow. Octreotide plus midodrine, albumin, or dopamine may be given to maintain adequate blood flow. Generally, these drugs are used temporarily to prevent kidney function from getting worse while a liver transplant can be arranged. The only effective treatment of this syndrome is liver transplantation.

DOs and DON'Ts in Managing Hepatorenal Syndrome:

✓ **DO** understand that the prognosis is grim. The mortality rate is higher than 80%.

✓ **DO** remember that as the liver works better, kidneys also improve.

⃠ **DON'T** lose hope. The 3-year survival of people who get a liver transplant is nearly 60%.

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FOR MORE INFORMATION

Contact the following sources:

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- American Liver Foundation Tel: 800-465-4837 **Website: www.liverfoundation.org**
- National Heart, Lung, and Blood Institute Information Center Phone: 301-592-8573

  Website: www.nhlbi.nih.gov
- National Kidney Foundation Phone: (800) 622-9010 **Website: http://www.kidney.org**

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CARING FOR YOUR CHILD WITH

HERNIA

What Are Hernias?

Parts of organs or tissues (such as a loop of intestine) can protrude into areas where they don't belong. They push through openings or weaknesses in a muscle wall, so a bulge or lump appears. These bulges are called hernias. Most common in babies and children are external hernias: inguinal (in the groin) and umbilical (near the belly button). Umbilical hernias are very common, especially in premature babies, females, African-Americans, and babies with certain diseases. Inguinal hernias occur more in males than females and premature babies. Congenital diaphragmatic hernia and hiatal hernia are the most common internal hernias (inside the body) in children.

If hernias bulge only during pressure or strain, they're called reducible and aren't very harmful. Tissues trapped in an opening or pouch that can't pull back are incarcerated hernias, which are serious problems. The most dangerous hernia is strangulated. In these, trapped tissue loses the blood supply and dies.

What Causes Hernias?

Indirect inguinal hernias, present at birth, are caused by mistakes during development. Direct inguinal hernias form after birth. Umbilical hernias occur when the umbilical ring doesn't close properly. In other hernias, membranes, wall muscles, or other structures don't form correctly or are hurt, so they slowly weaken.

What Are the Symptoms of Hernias?

Symptoms of inguinal and umbilical hernias are painless swellings, which may go away on their own. They're most obvious with crying, straining, coughing, or standing. Inguinal hernias in

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boys can make the scrotum (sac holding testicles) large. In girls, labia (tissue around the vagina) can swell. Internal hernias may have no symptoms or may cause vomiting and heartburn. Incarcerated hernias cause tender firm masses, pain, vomiting, constipation, and irritability. Strangulated hernias lead to fever and swollen, red, inflamed, and very painful areas.

How Are Hernias Diagnosed?

The doctor uses the medical history and physical examination with the child lying down and standing. Blood tests or laparoscopy may be needed. Imaging studies in certain cases include X-rays and ultrasonography.

How Are Hernias Treated?

Treatment is based on type of hernia. Umbilical hernias usually cause no discomfort, and most tend to close on their own by age 1 or 2. Doctors can often easily push them back in. Doctors usually suggest waiting and watching these hernias. Operations are needed only if hernias don't heal by age 4 or 5, or if they become trapped or block the intestines. Surgery, often outpatient, is used for inguinal hernias to prevent incarceration.

DOs and DON'Ts in Managing Hernias:

✓ **DO** watch your child's hernia to make sure that it gets smaller in the first 2 or 3 years of life.

✓ **DO** give your child pain medicine that your doctor prescribes after surgery.

✓ **DO** protect your child after surgery from respiratory infections that might cause coughing and sneezing. These could strain the stitches. Frequent hand washing is the best way to prevent these infections.

✓ **DO** learn the symptoms of inguinal hernia incarceration. Delayed treatment can cause serious

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problems.

✓ **DO** keep the incision clean and dry until it heals. You may need to limit your child's activity for a while.

⃠ **DON'T** forget follow-up doctor appointments.

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FOR MORE INFORMATION

Contact the following sources:

- The American Academy of Pediatrics Tel: (847) 434-4000 **Website: http://www.aap.org**
- American Gastroenterological Association Tel: (301) 654-2055 **Website: http://www.gastro.org**
- American College of Gastroenterology Tel: (703) 820-7400 **Website: http://www.acg.gi.org**

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MANAGING YOUR HERPANGINA

What Is Herpangina?

Herpangina is a self-limited viral disease in which ulcers and sores form inside the mouth. The throat and mouth become inflamed (swollen, red). It's a common childhood infection in children 1 to 10 years old. It may be confused with strep throat or canker sores. It often occurs during the summer and fall. Recovery takes a few days to a week. Little treatment is needed.

What Causes Herpangina?

The cause is a virus called coxsackievirus. It spreads from person to person by the respiratory route or by close contact, such as kissing or sharing food. It also spreads by contamination with feces (bowel movements), such as when people go to the bathroom, don't wash their hands, and then touch their mouth or food.

What Are the Symptoms of Herpangina?

Signs and symptoms usually appear 2 to 9 days after exposure. They include a temperature of 100° F to 104° F, a sudden sore throat that makes swallowing painful, grayish-white spots with red borders on the upper mouth, headache, loss of appetite, and fatigue. The feet, hands, and buttocks can have sores similar to those in the mouth.

How Is Herpangina Diagnosed?

The doctor will make a diagnosis on the basis of the medical history and physical examination. Blood tests are rarely needed.

How Is Herpangina Treated?

No specific treatment is needed. Fluid intake should be increased to prevent dehydration. Rest is needed until the fever is gone. A nonaspirin medicine, such as acetaminophen or ibuprofen, can be used for fever and pain. Tepid sponge baths can also be used to reduce fever.

A soft or liquid diet should be given until the throat is no longer painful. Ice pops, ice cream, gelatin, and ice chips may ease mouth and throat pain. Avoid acidic fruit juices that may irritate the throat. Sometimes a topical pain medicine such as lidocaine can help the sore throat or mouth.

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DOs and DON'Ts in Managing Herpangina:

- DO rest until the fever is gone.
- DO use nonaspirin drugs such as acetaminophen for pain and fever. Use tepid sponge baths to reduce the fever.
- DO use ice pops or ice chips to decrease discomfort.
- DO wash hands carefully, to prevent spreading the disease. Avoid kissing and sharing food.
- DO call your doctor if symptoms don't go away in 1 week or if fever becomes very high or doesn't go away.
- DO call your doctor if fluids cannot be tolerated.
- DO call your doctor if signs of dehydration appear, such as dry, wrinkled skin; dark urine; or less need to urinate.
- DO call your doctor if anyone else in the family shows symptoms of the disease.
- DON'T share food or kiss anyone until the infection has resolved.
- DON'T give aspirin to a child younger than 16 years (because of the risk of Reye's syndrome).
- DON'T give acidic fruit juices, which will irritate the mouth and throat.
- DON'T eat spicy foods that may irritate the mouth.

FOR MORE INFORMATION

Contact the following sources:

- National Institute of Allergy and Infectious Diseases
  Tel: (301) 496-5717, (866) 284-4107
  Website: http://www3.niaid.nih.gov
- American Academy of Otolaryngology—Head and Neck Surgery
  Tel: (703) 836-4444
  Website: http://www.entnet.org
- American Academy of Pediatrics
  Tel: (847) 434-4000
  Website: http://www.aap.org

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MANAGING YOUR

HERPES ENCEPHALITIS

What Is Herpes Encephalitis?

Encephalitis means "inflammation of the brain," usually virus-caused brain inflammation. Herpes simplex virus (HSV) causes several types of infections. One type, HSV-1, causes mouth sores (fever blisters). Another type, HSV-2, causes most genital herpes cases. The virus settles in a nerve in the body and stays there permanently. Rarely, HSV causes encephalitis (HSE). It's a medical emergency. Untreated HSE can be fatal. It also causes significant illness, including severe nervous system problems, in most survivors.

Herpes affects both sexes equally. One-third of cases occur in children.

What Causes Herpes Encephalitis?

HSV-1 causes HSE in older children and adults. The virus, maybe from a cold sore, can move through the nose up into the sinuses and then the brain, where it can cause HSE. HSV-2 causes HSE in newborn babies, who get it during delivery because of the mother's genital herpes infection.

What Are the Signs and Symptoms of Herpes Encephalitis?

Symptoms include sore throat, fever, headache, stiff neck, nausea, vomiting, runny nose, drowsiness, hyperactivity, and weakness. Then, lethargy, confusion, and delirium occur. Then, more serious symptoms including personality changes, paralysis, hallucinations, seizures, and even coma can occur. Severe HSE can lead to death if it's untreated or resistant to treatment.

How Is Herpes Encephalitis Diagnosed?

The doctor may suspect the diagnosis based on the medical history and physical examination. Laboratory tests, computed tomography (CT), magnetic resonance imaging (MRI), and electro-

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encephalography (EEG) may be done to help make the diagnosis and exclude other diseases. A lumbar puncture (spinal tap) will be done to test the cerebrospinal fluid. A brain biopsy may be needed for a final diagnosis.

How Is Herpes Encephalitis Treated?

HSE is a neurologic emergency and a neurologist should be involved in care. Hospital ICU care may be needed. Therapy aims to shorten the illness, prevent complications, and prevent later recurrences. Because this infection can be life-threatening, the doctor may start medicine right away, before knowing test results. Antiviral drugs include acyclovir and vidarabine. Acyclovir generally works better and is less toxic. Anticonvulsants may be used to stop and prevent seizures. Nutritional and fluid support is important. Brain swelling may need therapy, such as raising the head of the bed and using drugs such as corticosteroids to lower brain inflammation. Even with treatment, people often have complications and after effects, especially thinking and memory problems and seizures. Rehabilitation services, physical and speech therapy, and permanent assistance may be needed after HSE. Recovery can take a long time.

DOs and DON'Ts in Managing Herpes Encephalitis:

- ✓ **DO** try to prevent HSE by avoiding HSV. Take steps to prevent genital herpes. Kissing and having oral sex can spread the infection.
- ✓ **DO** call your doctor right away, or go to the emergency room, if you have flu-like symptoms such as fever, muscle aches, and especially a severe headache and stiff neck. You may have HSE.
- ✓ **DO** eat healthy foods. Get enough sleep and exercise. Wash your hands often.
- ✓ **DO** keep appointments with your doctors, physical therapist, and occupational therapist.

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✓ **DO** have a cesarean delivery if you're a woman with an active genital herpes infection at delivery.

✓ **DO** see a counselor if you feel discouraged or depressed.

⃠ **DON'T** expose newborn babies to people who have herpes infections.

⃠ **DON'T** delay getting help! Proper diagnosis and prompt treatment are critical.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Family Physicians Tel: (800) 274-2237 **Website:** **http://www.aafp.org**
- Centers for Disease Control and Prevention Tel: (800) 232-4636 **Website:** **http://www.cdc.gov**

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MANAGING YOUR

HIATAL HERNIA

What Are Hiatal Hernias?

A hiatal hernia is a weakness or stretching of the digestive tract where it passes through the diaphragm. The diaphragm is the muscle separating the chest from the abdomen (belly). Because of this stretching, acid from the stomach may flow back into the esophagus (the tube that connects the mouth and stomach). This acid causes irritation. Part of the stomach may also come up through the opening into the lower chest. Hiatal hernias can affect people of all ages, but they are more common in people older than 50.

What Causes Hiatal Hernias?

The cause is unknown. Obesity, pregnancy, straining or lifting with tightened abdominal muscles, coughing, abdominal trauma, and long-lasting constipation or straining with bowel movements may slightly increase the chance of having a hiatal hernia.

What Are the Symptoms of Hiatal Hernias?

People often have no symptoms, but when they do occur, they are usually about an hour after meals. They include heartburn, chest pain, belching, and rarely swallowing problems. Bending over or lying down can make heartburn worse. A complication is bleeding, caused by irritation of the esophagus.

How Are Hiatal Hernias Diagnosed?

The doctor uses endoscopy or barium swallow x-rays to diagnose hiatal hernias. In endoscopy, a small lighted tube with a tiny camera on the end is passed into the esophagus to see the hernia. Pressure measurements (manometry) may be done to prove that there is lower pressure where the esophagus and stomach meet.

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How Are Hiatal Hernias Treated?

The goals of treatment are to control symptoms and prevent complications. The main approach is changing lifestyle and diet. Raising the head of the bed 4 to 6 inches (with wooden blocks or bricks, not pillows) will keep stomach acid from backing up and reaching the esophagus during sleep. Avoid foods and drinks that make symptoms worse.

Medicines can be used when these changes aren't enough. Antacids neutralize stomach acid, and drugs to reduce stomach acid include ranitidine, famotidine, and proton pump inhibitors such as omeprazole.

If symptoms cannot be controlled or complications such as scarring, ulceration, or bleeding occur, surgery may be needed to correct the hernia.

DOs and DON'Ts in Managing Hiatal Hernias:

✓ **DO** lose weight if you're overweight.

✓ **DO** eat slowly. Eat four or five small daily meals instead of one or two large meals.

✓ **DO** call your doctor if you feel that food stops beneath the breastbone.

✓ **DO** call your doctor if you have pain with shortness of breath, sweating, or nausea.

✓ **DO** call your doctor if you vomit blood or vomit often.

✓ **DO** call your doctor if symptoms don't improve after 1 month of treatment.

⊘ **DON'T** drink alcohol and caffeine products (coffee, tea, cocoa, cola).

⊘ **DON'T** eat fried, spicy, and fatty foods; citrus juices; peppermint; and spices that may irri-

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tate the hernia.

⦸ **DON'T** eat large meals.

⦸ **DON'T** eat anything for at least 2 hours before bedtime.

⦸ **DON'T** bend over or lie down right after eating.

⦸ **DON'T** smoke.

⦸ **DON'T** wear tight-fitting pants, belts, and undergarments.

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FOR MORE INFORMATION

Contact the following source:

- American College of Gastroenterology Tel: (703) 820-7400 **Website:** **http://www.acg.gi.org**

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MANAGING YOUR

HIGH BLOOD PRESSURE (HYPERTENSION)

What Is Hypertension?

Blood pressure is the force of the blood pushing against artery walls from your heart pumping blood through your arteries. The increased blood pressure puts a strain on your circulatory system. Blood pressure is given as two numbers. The systolic pressure is the top number, and the diastolic pressure is the bottom number. Both are recorded as mm Hg (millimeters of mercury), which tells how high a column of mercury is raised by the pressure. The systolic pressure is the maximum pressure as the heart contracts, the diastolic pressure is the lowest pressure between contractions (heart at rest). Normal values are usually 120/80. The American Heart Association defines hypertension for adults as 140 mm Hg or higher systolic and/or 90 mm Hg or higher diastolic. These numbers should be used as a guide only.

What Causes Blood Pressure to Increase?

Being overweight, excessive salt (sodium) intake, some medications, and lack of physical activity contribute to hypertension.

What Are the Risk Factors for Hypertension?

More than half of all Americans age 65 and older have hypertension. People with obesity, diabetes, gout, or kidney disease; heavy drinkers of alcohol; and women taking birth control pills are at increased risk. African Americans (especially those living in southeastern United States) and people with parents or grandparents with hypertension have an increased risk.

What Are the Symptoms of Hypertension?

People usually have no or only mild vague symptoms. Severe hypertension can produce headaches, dizziness, blurred vision, nausea, ringing in the ears, confusion, and fatigue.

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How Is Hypertension Diagnosed?

Hypertension is diagnosed if blood pressure is high during at least two office visits. The doctor may check blood pressure in lying down and standing up positions, and in both arms.

What Are the Complications of Hypertension?

Untreated hypertension strains the heart and arteries and in time damages them. Hypertension is a key risk factor for heart failure, heart attack (myocardial infarction), stroke, and eye or kidney damage.

How Is Hypertension Treated?

Benefits of treatment for hypertension are well known. Deaths from heart disease and stroke are greatly reduced by treatment.

Many people can control hypertension by lifestyle changes, such as choosing foods that are low in salt, calories, and fat. Also, limiting serving sizes, maintaining a healthy weight, and increasing physical activity all help reduce blood pressure.

People must take medicine daily to control hypertension. These drugs usually include diuretics, beta-blockers, vasodilators, angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, and alpha-blockers.

People with hypertension should have blood pressure checked routinely and be under a doctor's care.

DOs and DON'Ts in Managing Hypertension:

✓ **DO** reduce daily sodium (salt) intake to 2400 milligrams (mg) or less.

✓ **DO** maintain a healthy diet, rich in fruits, vegetables, and low-fat dairy products with less saturated and total fats.

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✓ **DO** maintain a normal body weight.

✓ **DO** regular aerobic physical activity such as brisk walking (at least 30 minutes per day, most days of the week).

✓ **DO** take medicine as recommended.

✓ **DO** limit caffeine intake.

⃠ **DON'T** drink too much alcohol: for most men, no more than 2 drinks per day; for women and lighter-weight people, no more than 1 drink per day.

⃠ **DON'T** smoke or use tobacco products.

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:** **http://www.americanheart.org**
- American College of Cardiology Tel: (800) 253-4636 **Website:** **http://www.acc.org**

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CARING FOR YOUR CHILD WITH

HIGH BLOOD PRESSURE (HYPERTENSION)

What Is Hypertension?

Blood pressure is the force of the blood pushing against artery walls. Hypertension is blood pressure that's the same as or higher than 95% of children of the same sex, age, and height. What's normal for children changes as they grow, so there's no target blood pressure reading like that for adults. What may be high for a 4-year-old boy may be normal for a 10-year-old girl. Hypertension is either primary (essential, meaning occurring on its own) or secondary (caused by another medical condition).

What Causes Hypertension?

Causes differ according to a child's age. Children younger than 10 usually have secondary hypertension. Diabetes, adrenal disorders, and hyperthyroidism can cause it. Hypertension in babies can result from prematurity or problems with kidneys, lungs, heart, and blood vessels. Some children get hypertension for the same reasons as adults: being overweight, eating a poor diet (such as too much salt), and not getting enough exercise. Older children and teens usually have primary hypertension.

What Are the Symptoms of Hypertension?

Many children have no symptoms, but symptoms of secondary hypertension usually point to the underlying disease. Some children may have chest pain, fatigue, headaches, and trouble concentrating and sleeping.

How Is Hypertension Diagnosed?

Blood pressure readings can vary greatly, so an average of at least three separate measurements is used for diagnosis. The measured pressure is compared with values that are normal for children of

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the same sex, age, and height. Pressure in both arms and legs should be measured. Cuff size also affects measurement. Before diagnosis, other causes of high blood pressure such as pain, being nervous at the doctor's office, and drugs must be ruled out. Regular doctor checkups, starting when children are 3 years old, are important for screening. The doctor must check out medical conditions causing secondary hypertension.

How Is Hypertension Treated?

Therapy aims to reduce blood pressure and thereby risks of organ damage and problems later in life. These problems include stroke, heart attack, and kidney disease. Treatments include lifestyle changes such as losing weight, eating more vegetables and fruits, increasing physical activity, and reducing dietary salt (sodium). Children should never start smoking or should stop. If these changes don't work, drugs can be tried. Control of other medical conditions such as diabetes is essential.

DOs and DON'Ts in Managing Hypertension:

✓ **DO** provide a heart-healthy diet, rich in fruits, vegetables, whole-wheat breads and pasta, and low-fat foods. For example, breakfasts high in fiber and low in sugary cereals are best.

✓ **DO** encourage a normal body weight.

✓ **DO** have your child participate in regular exercise and aerobic physical activity such as brisk walking. Most children need at least 30 to 60 minutes of physical activity daily. Limit TV and computer time.

✓ **DO** give your child medicine as prescribed.

✓ **DO** involve the whole family in healthy lifestyle changes.

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⦸ **DON'T** let your child smoke.

⦸ **DON'T** give your child salty snacks, such as chips or pretzels. Pay attention to salt used in cooking and in canned and processed foods. Take the saltshaker off the table.

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FOR MORE INFORMATION

Contact the following sources:

- The National Institutes of Health Tel: (301) 496-4000 **Website: http://www.nih.gov**
- The American Academy of Pediatrics Tel: (847) 434-4000 **Website: http://www.aap.org**
- American Heart Association Tel: (800) 242-8721 **Website: http://www.americanheart.org**
- American College of Cardiology Tel: (800) 253-4636 **Website: http://www.acc.org**

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MANAGING YOUR

HIGH CHOLESTEROL

What Is High Cholesterol?

Cholesterol is a lipid, or type of fat. It helps the body perform many normal functions. Cholesterol is made in the liver and carries fats in the bloodstream.

In the body, cholesterol forms fat-protein chemicals called lipoproteins. Lipoproteins are grouped as very low-density lipoproteins (VLDLs), low-density lipoproteins (LDLs), also known as "bad cholesterol," and high-density lipoproteins (HDLs). HDLs, "good cholesterol," help remove lipids from the bloodstream, so higher HDL levels are better.

VLDLs and LDLs can clog arteries. High levels of cholesterol, LDLs, and triglycerides (fatty substances) increase the risk for hardening of the arteries (atherosclerosis) and heart disease.

What Are the Causes and Symptoms of High Cholesterol?

Causes of hyperlipidemia include a family history, high-fat diet, being overweight, certain illnesses including diabetes, and some drugs.

Most people have no symptoms until their blood vessels are nearly closed or become clogged. Some people may have small fat deposits under the skin when lipids are very high.

How Is High Cholesterol Diagnosed?

Blood levels of cholesterol, HDL, LDL, and triglycerides are measured. Preferred levels are less than 200 milligrams per deciliter (mg/dl) for cholesterol, less than 150 mg/dl for triglycerides, and over 40 mg/dl for HDLs. Recommended LDL levels are less than 130 mg/dl for most people but much lower (less than 70 mg/dl) for those with heart disease and diabetes.

How Is High Cholesterol Treated?

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Diet is the best way to reduce lipid levels. Lifestyle changes should reduce consumption of saturated fat to less than 7% of calories and cholesterol to less than 200 mg/day. Weight loss, exercise, and avoiding smoking are also important.

Lipid-lowering drugs are used when diet and exercise are not enough. The main classes of drugs include statins, fibrates, nicotinic acid, and omega-3 fatty acids.

Statins (e.g., atorvastatin) reduce cholesterol and LDL production. They are effective and preferred for treatment of high cholesterol and LDL levels. They are usually well tolerated but in some cases they can have side effects such as muscle aches and liver abnormalities. They may also slightly increase the blood sugar level.

Fibrates (e.g., fenofibrate, gemfibrozil) help removal of VLDLs but have a small effect on cholesterol and are not preferred for treatment of high cholesterol.

Nicotinic acid helps lower VLDL levels and increase HDL levels. Side effects (itching, facial flushing, liver problems) limit its use.

Omega-3 fatty acids (over-the-counter fish oil supplements) help patients with high triglyceride, and low HDL, but they are not effective or preferred for the treatment of high cholesterol.

DOs and DON'Ts in Managing High Cholesterol:

✓ **DO** exercise regularly.

✓ **DO** eat more fruits and vegetables and high-fiber foods such as oat bran. Cook with oils high in polyunsaturated fats such as safflower, sunflower, and corn oils (omega-6 fatty acids).

✓ **DO** eat fish (fish oils contain omega-3 fatty acids).

✓ **DO** stop smoking.

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✓ **DO** lose weight by changing your diet and doing aerobic exercise such as walking, jogging, bicycling, or swimming. Exercise at least 30 minutes a day, 3 or 4 days a week.

⃠ **DON'T** forget to treat other medical conditions.

⃠ **DON'T** forget to take your usual medicines.

⃠ **DON'T** change your diet or medicines without your doctor's approval.

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Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website: http://www.americanheart.org**
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MANAGING YOUR

HIGH TRIGLYCERIDES

What Are High Triglycerides?

Triglycerides are a kind of fat (lipid) found in blood, the most common type of fat in the body. Cholesterol is another kind. Stored in fat cells for later use, triglycerides are a major energy source. Normal amounts are important for good health. Eating more fat than the body burns can lead to high triglyceride levels (hypertriglyceridemia). High triglyceride levels may result in hardening of the arteries (atherosclerosis), which increases risks of stroke, heart attack, and heart disease. They can be part of metabolic syndrome, which also includes too much fat around the waist, high blood pressure, high blood sugar, and abnormal cholesterol levels.

Sometimes high triglyceride levels mean poorly controlled type 2 diabetes, low thyroid hormone levels (hypothyroidism), liver or kidney disease, or rare genetic conditions.

What Are the Causes and Symptoms of High Triglycerides?

Causes include obesity, eating too much unhealthy food, genetics, certain illnesses including poorly controlled diabetes, kidney disease, and underactive thyroid (hypothyroidism). Some drugs, such as steroids and birth control pills, and drinking a lot of alcohol can also cause it.

Most people have no symptoms. Very high levels can cause small fat deposits under the skin and a painful inflammation of the pancreas called pancreatitis.

How Are High Triglycerides Diagnosed?

Blood levels are measured. Normal levels are below 150 milligrams per deciliter (mg/dL). High levels are 200 to 499. Very high levels are 500 or above.

How Are High Triglycerides Treated?

The best ways to lower triglycerides include losing weight, eating fewer calories, and exercising

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regularly (30 minutes daily). Diet changes that may help include avoiding fats and sugar and *refined foods* (simple carbohydrates such as sugar and foods made with white flour). Also avoid alcohol and limit fats found in meats high in saturated fat, egg yolks, and whole milk products. Trans fats, found in fried foods and commercial baked products, are unhealthy. Eat healthy monounsaturated fats—olive, peanut, and canola oils. Eat fish high in omega-3 fatty acids (mackerel, salmon) instead of red meat.

If diet changes and exercise don't work, medicines such as nicotinic acid (niacin), fibrates (e.g., fenofibrate, gemfibrozil), and omega-3 fatty acids (over-the-counter fish oil supplements) can help lower triglycerides. Niacin side effects (itching, facial flushing, liver problems) limit its use. Cholesterol-lowering medications known as statins (e.g., simvastatin, atorvastatin, rosuvastatin) can also lower triglycerides, but their effect is limited.

It's also important to control diabetes since a high sugar level will also increase triglycerides.

DOs and DON'Ts in Managing High Triglycerides:

✓ **DO** exercise regularly.

✓ **DO** eat more fruits and vegetables and high-fiber foods such as oat bran. Cook with monounsaturated fats—olive, peanut, and canola oils.

✓ **DO** eat fish.

✓ **DO** stop smoking.

✓ **DO** lose weight by changing your diet and doing aerobic exercise, such as walking, jogging, bicycling, or swimming. Exercise at least 30 minutes daily.

⦸ **DON'T** forget to treat other medical conditions such as diabetes and underactive thyroid.

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⦸ **DON'T** drink more than two alcoholic drinks per day.

⦸ **DON'T** change your diet or medicines without your doctor's approval.

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Medicine Tel: (888) FIND-NLM (346-3656) **Website:**

  http://www.nlm.nih.gov/medlineplus/triglycerides.html

- American Heart Association Tel: (800) 242-8721**Website: http://www.americanheart.org**

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MANAGING YOUR

HIP FRACTURE

What Is a Hip Fracture?

A femoral neck fracture is a break of the thigh bone (femur) at the hip. The hip joint is a ball-and-socket joint. The break occurs at the neck, which is the part just below the ball. The hip fracture can also occur in other locations (extrascapular fracture, intertrochanteric fracture). The blood supply to the broken bone is often interrupted, so these fractures may have trouble healing. Most people do have a complete recovery after surgery.

What Causes a Hip Fracture?

The cause can be a severe fall or an auto accident. More often, older people, especially women, have these fractures. They result from osteoporosis (thinning of bone) related to aging. If the bone of the hip is thin enough, even twisting can break the bone. People may twist while standing, which breaks the bone, and then they fall. As many as one quarter of all women older than 75 may have severe enough osteoporosis to have a hip fracture.

What Are the Symptoms of a Hip Fracture?

Symptoms are pain in the hip, buttock, or pubic area, especially with movement of the hip or leg. The affected leg is shorter than the other leg, and the foot turns in. Later, bruising on the hip, especially in thin people, can be seen.

How Is a Hip Fracture Diagnosed?

The doctor makes a diagnosis from the physical examination and x-rays of the hip.

How Is a Hip Fracture Treated?

Treatment is nearly always surgical. Pins can be placed across the fracture, or metal plates and screws can be used to hold bone fragments together. Other choices include replacing the ball of the joint with a metal one, and replacing both the socket and the ball. Sometimes, surgery doesn't

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make the joint stable, usually because the bone that's left is too thin.

For people who are very sick, treatment may be bed rest to try to let the fracture heal.

The best ways to prevent hip fractures are to prevent and treat osteoporosis with diet, exercise, and medicine. Also, make sure that the home environment is safe.

DOs and DON'Ts in Managing a Hip Fracture:

✓ **DO** take medicines as prescribed and follow your doctor's instructions.

✓ **DO** use pain medicines to help recovery.

✓ **DO** eat a good diet to provide protein and calcium. This will help the bone to heal.

✓ **DO** your exercises in the form of physical therapy. They're important for recovery from surgery.

✓ **DO** call your doctor if you have increasing pain in your hip after surgery. This pain could mean infection, bleeding, or loosening of the hip replacement or screws.

✓ **DO** call your doctor if you have trouble walking. It can be a sign of loosening of the hip replacement.

✓ **DO** call your doctor if you have symptoms of infection, such as fever or swelling or redness of the incision line. Tell your doctor about shortness of breath and coughing, which could mean pneumonia or a blood clot to the lungs.

✓ **DO** reduce chances of falls in the home. Use good lighting and avoid tripping hazards such as loose rugs and poor- fitting shoes.

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⦸ **DON'T** use alcohol and tobacco. They increase the risk of osteoporosis, as does lack of weight-bearing exercise.

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Contact the following source:

• American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website:**

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MANAGING YOUR

HIP PAIN

What Is Hip Pain?

The hip is the ball-and-socket joint where the pelvis and leg (femur) meet. Tendons are fibrous tissues that connect muscles to bones. Ligaments join bones (or cartilages) together. Hip pain refers to pain affecting this whole area.

What Causes Hip Pain?

The many causes include injuries, fractures, tumors, or diseases, such as osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis, that affect the hip joint. Inflammation is another cause. It can affect tendons (tendinitis) and the thin, fluid-filled sac (bursa) that protects the joint (bursitis). Problems in sacroiliac joints or low back can also cause hip pain.

What Are the Symptoms of Hip Pain?

Symptoms depend on the cause. Osteoarthritis may cause mild pain only with activity. Sudden injuries, fractures, and tumors may cause severe pain when trying to walk, make the hip look deformed, and cause bruising in the hip area.

How Is Hip Pain Diagnosed?

The doctor makes a diagnosis by taking a medical history and doing a physical examination. X-rays of the joint may also be done. The doctor may also order blood tests to see whether the pain is caused by diseases with similar symptoms. Magnetic resonance imaging (MRI) may be done if the doctor needs a clearer picture of the bones and structures around them.

How Is Hip Pain Treated?

Treatment depends on the cause. If the cause is osteoarthritis, the doctor may prescribe acetaminophen or a nonsteroidal antiinflammatory drug (NSAID). If the cause is bursitis or tendinitis,

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the doctor may prescribe an NSAID, suggest physical therapy, or do both. Physical therapy usually consists of using deep heat, ultrasound, or both. For severe bursitis, the doctor may inject a steroid-containing medicine (a strong antiinflammatory drug) into the bursa.

More serious causes of hip pain such as a fracture or severe degenerative joint disease may need surgery.

DOs and DON'Ts in Managing Hip Pain:

✓ **DO** take your medicines as prescribed.

✓ **DO** call your doctor if you have side effects from medicines.

✓ **DO** ask your doctor which over-the-counter pain medicines you may take with your prescription drugs.

✓ **DO** your prescribed hip exercises daily.

✓ **DO** call your doctor if medicine and other treatments don't help the pain.

✓ **DO** call your doctor if you need a referral to a physical therapist for exercise.

⃠ **DON'T** wait for a medicine side effect to go away on its own.

⃠ **DON'T** continue an exercise program that causes persistent pain. Pain after exercise usually means that the exercise has to be changed.

⃠ **DON'T** cross your legs. This position can make your hip pain worse.

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FOR MORE INFORMATION

Contact the following sources:

- Arthritis Foundation Tel: (800) 283-7800 **Website: http://www.arthritis.org**
- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website: http://www.aaos.org**

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MANAGING YOUR

HIRSUTISM

What Is Hirsutism?

Hirsutism refers to the growth of too much hair on the face and body in women. Thick, dark hair grows in areas where men have hair: upper lip, chin, and sideburns. Hirsutism is very common, occurring in 5% to 10% of women, and it's usually not serious. Increased body hair is also normal in Caucasian women of Mediterranean origin. Most women do not need medical care. Therapy may improve hirsutism, but it may take months to work. Hirsutism cannot be prevented.

What Causes Hirsutism?

The cause is production of too much male sex hormones (called androgens). Women normally make small amounts of androgens in their ovaries and adrenal glands. Problems in these organs can lead to too much hormone being made. Certain endocrine disorders (e.g., Cushing's syndrome, acromegaly) may cause hair to grow. Tumors in adrenal glands or ovaries may also cause high hormone levels. Other less serious disorders of these organs, including polycystic ovary syndrome (PCOS) and congenital adrenal hyperplasia (CAH), can also lead to hirsutism.

Other sources of androgens are medicines, including steroids, phenytoin, diazoxide, progestins, cyclosporine, and minoxidil.

Some women have idiopathic hirsutism, meaning that the cause is unknown.

What Are the Symptoms of Hirsutism?

Hair develops on the face (as a beard or mustache) and body, specifically the upper lip, chin, sideburns, upper back, neck, chest, thighs, belly, and around the nipples. Hair becomes thick and dark. Women may also have problems with periods, with fertility, and have acne.

Serious causes can mean rapid growth of hairs, balding, deepening of the voice, muscle de-

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velopment, change in sexual desire, or infertility.

How Is Hirsutism Diagnosed?

The doctor will do a physical examination and take blood and urine samples to measure levels of the androgens called testosterone and dehydroepiandrosterone sulfate (DHEAS). The doctor may order computed tomography (CT) or magnetic resonance imaging (MRI) to check organs that may be the cause.

How Is Hirsutism Treated?

Treatment depends on the cause. No treatment may be needed for a mild case with no menstrual problems. Ways to remove unwanted hair include medicines, shaving, plucking, bleaching, waxing, using creams (depilatories), and electrolysis or laser light (for permanent removal).

For hirsutism related to menstrual problems, the doctor may prescribe medicine that contains female sex hormones. Other treatment may be needed to get pregnant.

Growths on ovaries or adrenal glands can be removed surgically.

DOs and DON'Ts in Managing Hirsutism:

✓ **DO** follow your doctor's advice. Contact your doctor if you had successful treatment and unwanted hair returns.

✓ **DO** lose weight if you're overweight. Weight loss reduces hirsutism.

✓ **DO** tell your doctor if you shaved, plucked, or bleached your hair or if you received electrolysis.

✓ **DO** tell your doctor if you want to become pregnant.

✓ **DO** consider bleaching, shaving, and electrolysis.

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✓ **DO** call your doctor if you notice male pattern hair growth.

✓ **DO** call your doctor if you have side effects from your medicine.

⃠ **DON'T** use medicine that contains male sex hormones unless your doctor prescribes it.

⃠ **DON'T** expect hirsutism to go away completely or immediately. Successful drug treatment may take 3 to 6 months.

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- The Endocrine Society Tel: (301) 941-0200 **Website: http://www.endo-society.org**

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MANAGING YOUR

HISTOPLASMOSIS

What Is Histoplasmosis?

Histoplasmosis (Ohio valley fever) is an infection caused by a fungus. The lung infection is usually mild, but it can be more severe in people with weak immune systems. Such people include those with HIV infection or cancer and those taking immunosuppressive drugs or steroids. Infections can sometimes spread to other parts of the body, including lymph glands, nervous system, and heart. Infants, very young children, and elderly people also have higher risk of severe infection.

What Causes Histoplasmosis?

The cause is the fungus *Histoplasma capsulatum*. It's found in soil, especially that with bird or bat droppings. Breathing air containing the fungus gets it into the lungs. Histoplasmosis isn't contagious.

What Are the Symptoms of Histoplasmosis?

Most people have few symptoms such as dry cough or low-grade fever. They may not know that they had histoplasmosis until years later. Symptoms are usually mild and flu-like. They include fever, chills, headache, and muscle aches. More severe symptoms from worse infections may last several weeks. Older people with lung disease (such as smokers with emphysema) can get a chronic infection. Symptoms include coughing up sputum, chest pain, weight loss, night sweats, and fatigue. People with weak immune systems may have widespread infections with severe and longer lasting symptoms of fever, headache, and weight loss.

How Is Histoplasmosis Diagnosed?

The health care provider makes a preliminary diagnosis from the medical history and physical

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examination, especially of the lungs and heart. Chest X-rays and tests of blood, urine, and sputum may also be done.

How Is Histoplasmosis Treated?

Mild infections in generally healthy people may go away without treatment. In most people, treatment with antifungal medicine is needed. This medicine can be given by mouth (orally) or intravenously. The intravenous amphotericin-B may be given for up to 3 weeks.

Antifungal medicine may be needed for a long time, often 1 year or more. People with weak immune systems may need lifelong treatment.

Antifungal medicines should always be finished. Stopping too soon may let the disease come back. Blood tests will make sure that the infection is gone.

A healthy lifestyle with regular exercise and good diet helps the body fight the infection. Smokers should stop smoking. Prevent more infections by avoiding places where contaminated dust can be breathed in. These include chicken houses, old buildings, and caves. Workers in dirty or dusty areas should wear facemasks and protective clothing.

DOs and DON'Ts in Managing Histoplasmosis:

✓ **DO** visit your health care provider regularly.

✓ **DO** take your medicines prescribed by your health care provider.

✓ **DO** ask your health care provider about side effects of your medicines.

✓ **DO** avoid exposures to contaminated areas such as farms.

✓ **DO** use preventive measures, such as facemasks, if exposure is likely.

✓ **DO** quit smoking.

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✓ **DO** have a flu shot yearly and a pneumonia immunization every 5 years.

✓ **DO** contact your health care provider if you cough up blood or have new symptoms or worsening shortness of breath.

⃠ **DON'T** delay getting medical care if your symptoms get worse.

⃠ **DON'T** stop taking your medicine without talking to your health care provider.

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FOR MORE INFORMATION

Contact the following sources:

- Centers for Disease Control and Prevention Tel: 404-639-3311 **Website: http://www.cdc.gov**
- National Institute of Environmental Health Sciences Tel: (919) 541-3345 **Website: www.niehs.nih.gov**
- National Institute of Allergy and Infectious Disease Phone: 301-496-5717 **Website: http://www.healthfinder.gov**

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MANAGING

HIVES

What Are Hives?

The medical term for hives is urticaria, also called wheals (bumps). Swollen, small, pale red bumps or larger patches suddenly appear on the skin. Severe itching usually follows. Each bump tends to go away in 24 hours without leaving marks, but then others appear. They can be very small to large. Scratching can cause the affected skin area to get larger, leading to big, fiery red patches. Hives usually don't last long. When they last more than 6 weeks, they're called chronic; when they last less than 6 weeks, they're called acute.

What Causes Hives?

Hives can be allergic or nonallergic, but often the cause remains unknown. Allergic hives, the least common, are triggered by an overreaction of the immune system to certain things, most commonly foods (nuts, shellfish), insect stings and bites, and drugs (e.g., penicillin).

Causes of nonallergic hives include cold (after exposure to cold weather) and heat (after exercise, hot shower, or stress).

What Are the Symptoms of Hives?

Symptoms include itching, or less often burning or stinging; raised, often red, swellings; and separate swellings that usually go away in 24 hours, but new ones often appear as the old ones disappear.

How Are Hives Diagnosed?

The doctor will ask about symptoms: when they appeared, how long they lasted, what things may have triggered them. If the doctor thinks that an allergy is the cause, seeing a specialist in allergies may be suggested. A diary of foods eaten, drugs taken, illnesses, work and home life,

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and when symptoms appear should be kept.

No specific tests are used for these conditions, so the choice of tests depends on answers to questions about symptoms and a full physical examination. Sometimes, blood and urine tests and skin testing may be done.

How Are Hives Treated?

Antihistamines (like those taken for hay fever) are the most common treatment. In complicated or severe cases, drugs called corticosteroids (prednisone) may be prescribed for a short time.

DOs and DON'Ts in Managing Hives:

✓ **DO** avoid anything your doctor says will trigger your condition.

✓ **DO** take your prescribed drugs and follow directions for their use.

✓ **DO** avoid stress. This can make your symptoms worse.

✓ **DO** call your doctor if you have shortness of breath or wheezing.

✓ **DO** call your doctor if you develop a swollen tongue, lips, or face.

⃠ **DON'T** wear tight-fitting clothes that can rub your skin.

⃠ **DON'T** towel yourself vigorously after a bath or shower, because this can increase the area of skin affected.

⃠ **DON'T** scratch, because this can make the hives worse.

⃠ **DON'T** drink alcohol or eat spicy foods. These can make your condition worse.

⃠ **DON'T** use harsh soaps or wash too much. Dry skin can cause more itching.

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Contact the following sources:

- American Academy of Allergy, Asthma & Immunology Tel: (800) 822-2762 **Website: http://www.aaaai.org/**
- American Academy of Dermatology Tel: (866) 503-7546 **Website: http://www.aad.org**

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MANAGING YOUR

HODGKIN'S LYMPHOMA

What Is Hodgkin's Lymphoma?

Hodgkin's lymphoma (or Hodgkin's disease) is a type of cancer of the lymph nodes (lymph glands). Lymph glands and lymph vessels are part of the immune system that filter infection and other diseases from the body. The disease usually affects lymph glands, white blood cells, and the spleen. People of any age can have it, but those between 15 and 30 and older than 50 years most often get it. It can range from mild to severe. About 80% of people can be cured, especially if the disease is found and treated early.

What Causes Hodgkin's Lymphoma?

The cause is unknown. People with impaired immune systems have greater risk.

What Are the Symptoms of Hodgkin's Lymphoma?

The most common symptom is swollen, painless, rubbery lymph glands, usually in the armpit, groin, and neck. Others include bleeding or easy bruising, fatigue, fever, itching, night sweats, pain in lymph glands after drinking alcohol, weakness, and weight loss. Certain symptoms relate to where the disease spreads.

How Is Hodgkin's Lymphoma Diagnosed?

The doctor will make a diagnosis from a medical history, physical examination, blood tests, and lymph gland and bone marrow biopsies. Biopsies involve getting bone marrow (with a needle) and/or small pieces of lymph node tissue for study with a microscope. Other tests may in some cases include laparotomy, which is surgery on the abdomen (belly) for disease staging. Staging shows how far the disease has spread. Chest x-ray, computed tomography (CT), and positron emission tomography (PET, a kind of x-ray) may also be done for staging. The doctor will sug-

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gest seeing an oncologist (cancer treatment specialist) and radiation oncologist (specialist in treating cancer with radiation).

How Is Hodgkin's Lymphoma Treated?

Treatment depends on how far the disease has spread. Chemotherapy (using drugs) and radiation therapy (or radiotherapy) are used to kill the cancer cells. Chemotherapy is usually first given intravenously (directly into vein), in the hospital. Pain medicine will also be given. Severe or recurrent disease may need a bone marrow transplant. Some treatments may affect the ability to have children.

Treatment is generally very effective and cures four out of five patients.

DOs and DON'Ts in Managing Hodgkin's Lymphoma:

✓ **DO** tell your doctor about your medicines, including prescription and over-the-counter ones.

✓ **DO** tell your doctor if you're pregnant or breastfeeding.

✓ **DO** talk to someone about the stress of having cancer. Call your doctor if you feel depressed. Find support groups.

✓ **DO** take care of your teeth and mouth to prevent mouth sores.

✓ **DO** consider placing sperm in a sperm bank or eggs in an egg bank if you are planning to have children.

✓ **DO** remember that treatment involves a team: primary care doctor, oncologist, radiation oncologist, surgeon, nutritionist, and social service workers.

✓ **DO** call your doctor if you have pain, fever, or drainage from the incision after surgery.

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✓ **DO** call your doctor if you have shortness of breath, chest pain, or coughing with a fever after radiation.

✓ **DO** call your doctor if you have bleeding, bruising, fever, nausea, or vomiting after chemotherapy.

⃠ **DON'T** ignore swollen lymph glands.

⃠ **DON'T** miss follow-up appointments during or after treatment.

⃠ **DON'T** be afraid to ask for medicine for pain, nausea, or vomiting.

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FOR MORE INFORMATION

Contact the following sources:

- Leukemia and Lymphoma Society Tel: (800) 955-4572 **Website: http://www.leukemia-lymphoma.org**
- National Cancer Institute Tel: (800) 422-6237 **Website: http://www.cancer.gov**

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MANAGING YOUR

HOOKWORM INFECTION

What Are Hookworm Infections?

Hookworms, also known as roundworms, are parasitic worms. They cause common infections in tropical and subtropical areas with poor sanitation. Hookworms affect more than 1 billion people worldwide. In the United States, hookworm infections are more common in southern states. Hookworms can cause serious problems, such as anemia and protein deficiency, for newborns, children, pregnant women, and malnourished people. Skin, lungs, and intestines are involved. Other complications include tiredness, breathing problems, enlarged heart, and irregular heartbeat.

What Causes Hookworm Infections?

Two kinds of roundworms infect people. Their names are *Ancylostoma duodenale* and *Necator americanus*. Infected people pass worm eggs in their stools (bowel movements). The eggs can hatch in moist soil and incubate for 2 days before they become larvae (young, immature forms). Then, larvae can get inside people through their skin (often bare feet) and travel through the bloodstream to the lungs and intestines. People can also get hookworms by eating contaminated food and drinking contaminated water.

What Are the Symptoms of Hookworm Infection?

Symptoms include itching and redness of the skin where larvae entered the body (commonly the feet). A skin infection caused by scratching may also be present.

When larvae travel through the lungs, a dry cough, bloody sputum, wheezing, and low-grade fever may occur. After 2 weeks, larvae make their way to the upper small intestine (bowel) where the adult worms attach to the intestinal lining and suck blood. At this point, loss of appe-

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tite, diarrhea, abdominal pain, and anemia can occur. Or people may have no symptoms.

How Are Hookworm Infections Diagnosed?

The doctor makes a diagnosis by taking a stool specimen and sending it to a laboratory to look for hookworm eggs and larvae in the stool. A chest x-ray may be done to look for infection in the lungs. Blood tests may also be done to check for low blood (anemia) and malnutrition.

How Are Hookworm Infections Treated?

Treatment goals are to cure the infection, prevent and treat complications, and improve nutrition. The doctor will prescribe medicine, such as albendazole or mebendazole, to kill the worms. These drugs cannot be taken during pregnancy because they may harm the fetus.

If anemia is present, the doctor will prescribe iron pills. After anemia is corrected, a high-protein diet and vitamin supplements may be needed for about 3 months.

DOs and DON'Ts in Managing Hookworm Infections:

- ✔ **DO** take medicines as prescribed.
- ✔ **DO** eat a high-protein diet for 3 months.
- ✔ **DO** take vitamin supplements and iron as directed by your doctor.
- ✔ **DO** tell your doctor if you're pregnant.
- ✔ **DO** wash your hands well after using the bathroom and before eating.
- ✔ **DO** call your doctor if skin at the point of worm entry appears infected, red, swollen, and warm.
- ✔ **DO** call your doctor if you get a fever, chest pain, or shortness of breath.

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✔ **DO** call your doctor if you cannot keep foods or fluids down.

⃠ **DON'T** skip doses or stop your medicine before you finish taking all of it.

⃠ **DON'T** walk barefoot in public areas, especially when visiting tropical regions.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- National Institute of Allergy and Infectious Diseases Tel: (866) 284-4107 **Website:** **http://www3.niaid.nih.gov/topics/hookworm/**
- American College of Gastroenterology Tel: (703) 820-7400 **Website:** **http://www.acg.gi.org**
- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website:** **http://www.cdc.gov**

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MANAGING YOUR

HORNER'S SYNDROME

What Is Horner's Syndrome?

The word syndrome means a group of symptoms that together are features of a disease or abnormal condition. Horner's syndrome is a rare condition affecting nerves to the eye and face. It involves a constricted (smaller) pupil, drooping eyelid, and problems with sweating on the affected side of the face.

Prognosis and effects depend on the underlying cause. For example, when it is due to herpes zoster (causing shingles), it is usually not life-threatening and has a good prognosis. However, when due to lung cancer, prognosis is much worse.

What Causes Horner's Syndrome?

Any disease that interrupts nerve fibers to the eye can cause this disorder. Nerve fibers can be damaged from strokes, brain hemorrhage, cerebral aneurysms, or brain tumors. Infections including syphilis, meningitis, and herpes zoster can lead to Horner's syndrome. The disorder can result from blunt trauma injury, motor vehicle accidents, or operations involving the neck, thyroid, lung, aorta, carotid artery, or coronary bypass surgery. Other causes are tumors involving the upper part of the lung or spinal cord in the neck, and drugs including local anesthetics (e.g., lidocaine, bupivacaine), antipsychotics (e.g., thioridazine, chlorpromazine), hypertension medicines (e.g., reserpine, guanethidine), and illicit drugs (e.g., heroin).

Horner's syndrome is not contagious or passed from generation to generation.

What Are the Symptoms of Horner's Syndrome?

Symptoms are a smaller (constricted) pupil (miosis), drooping eyelid (ptosis), and problems with sweating on the affected side of the face (anhidrosis).

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How Is Horner's Syndrome Diagnosed?

The doctor will make a diagnosis from the physical examination, as well as x-rays (ultrasonography, angiography, computed tomography [CT], magnetic resonance imaging [MRI], and magnetic resonance angiography [MRA]). X-rays help rule out lung cancer. CT of the neck and chest rule out head and neck disease, aortic aneurysm, and lung tumors. Ultrasonography rules out problems with the carotid artery (large artery in the neck taking blood from the heart to the brain).

Usually, an ophthalmologist (doctor specializing in eye diseases) or neurologist (doctor specializing in diseases of the brain, spinal cord, and nervous system) will be involved in diagnosis.

How Is Horner's Syndrome Treated?

No specific treatment exists for Horner's syndrome. Instead, the underlying cause must be treated (e.g., stopping use of a drug, treating any cancer).

DOs and DON'Ts in Managing

Horner's Syndrome:

✓ **DO** follow your doctor's recommendations. Be patient. Many tests may be needed before the cause of the disorder is found.

✓ **DO** call your doctor if you notice symptoms of Horner's syndrome.

✓ **DO** call your doctor if you are have new signs or symptoms such as coughing up blood, lump in the neck, swollen lymph glands in the neck, trouble swallowing, loss of appetite, and weight loss.

⃠ **DON'T** forget that Horner's syndrome is not a disease. The underlying disease must be

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treated to correct Horner's syndrome.

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FOR MORE INFORMATION

Contact the following sources:

- NIH/National Eye Institute Tel: (301) 496-5248 **Website: http://www.nei.nih.gov**
- American Cancer Society Tel: (800) 227-2345 **Website: http://www. cancer.org**

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MANAGING YOUR

HOT FLASHES

What Are Hot Flashes?

Hot flashes are sudden feelings of intense warmth that start in the neck, face, or chest and often occur with sweating and anxiety. Hot flashes occur most often in women at menopause (change of life, when periods stop). Most begin 1 to 2 years before menopause and stop after 2 years, but some women have hot flashes for more than 15 years! They affect 75% of women after menopause.

What Causes Hot Flashes?

Changes in the level of the female hormone estrogen at menopause usually cause hot flashes. Chemotherapy causing ovaries to stop working and use of tamoxifen, a drug treatment for breast cancer, are other causes.

Hormone therapy to block or inhibit the male hormone testosterone, used in men for prostate cancer, and the medication niacin can also cause flushing.

Hot flashes cannot be caught or passed on from parents to children (inherited).

What Are the Symptoms of Hot Flashes?

Symptoms include sudden feelings of heat in the upper or whole body. The face, neck, chest, back, and arms become red (flushed). Heavy sweating and cold shivering can follow. Flashes can be mild or bad enough to awaken people from sound sleep (called night sweats). Most flashes last between 30 seconds and 5 minutes and vary in frequency, with one third of women reporting more than 10 flashes per day.

Palpitations, brisk reflexes, and increases in temperature, heart rate, and blood flow to the hands and face also occur.

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How Are Hot Flashes Diagnosed?

The doctor may order blood tests (such as thyroid function tests) and special hormone studies (e.g., follicle stimulating hormone, luteinizing hormone, estrogen level) to find out whether another condition may be causing hot flashes. Such other conditions include hyperthyroidism (overactive thyroid gland), anxiety, lymphoma, and carcinoid syndrome (rare tumor in the gastrointestinal system).

How Are Hot Flashes Treated?

Estrogen therapy in postmenopausal women to replace missing hormone, called estrogen replacement therapy (ERT), reduces hot flashes by 80% to 90%. Estrogen therapy may increase the risk of uterine cancer, breast cancer, heart attacks, strokes, and blood clots and can have side effects of abdominal bloating and breast tenderness. Options such as herbal products have also been tried but are generally ineffective.

Other drugs, including antidepressants called selective serotonin reuptake inhibitors (e.g., fluoxetine, paroxetine), anti-seizure medications (e.g., gabapentin), vitamin E, and soy protein (estrogens from plants), are often used with limited success.

DOs and DON'Ts in Managing Hot Flashes:

✓ **DO** realize that nonmedical treatments (e.g., air conditioners, fans, cold water) have been tried with different degrees of success. Lifestyle changes with diet, exercise, and stopping smoking can provide some relief.

✓ **DO** call your doctor if you also have other symptoms, such as diarrhea, nausea, vomiting, fever, chills, palpitations, chest pains, or pains in the abdomen (belly). These may suggest other conditions (e.g., infections, hyperthyroidism, carcinoid syndrome, myocardial infarction).

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✓ **DO** call your doctor if you think that you're going through menopause and have concerns about using ERT.

⃠ **DON'T** use medicines for hot flashes unless hot flashes are severe and have a major impact on your life.

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FOR MORE INFORMATION

Contact the following source:

- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website:** **http://www.acog.org**

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MANAGING YOUR

HUMAN IMMUNODEFICIENCY VIRUS INFECTION

What Is Human Immunodeficiency Virus (HIV) Infection?

The human immunodeficiency virus (HIV) causes acquired immunodeficiency syndrome (AIDS). This virus attacks the immune (infection-fighting) system and destroys white blood cells called lymphocytes. People who are infected with HIV are HIV positive (HIV1). However, blood tests may be negative if done very early after being infected. After several months or years of being HIV1, AIDS may develop, when the immune system is very weak.

Over 30 million people are infected with HIV worldwide.

What Causes HIV Infection?

HIV is usually caught from sexual activity (opposite or same sex) partners, use of an infected needle, or from blood transfusion. It may also be passed from an infected mother to her unborn child. People cannot get infected by casual contact such as holding hands.

What Are the Symptoms of HIV Infection?

People may at first have no symptoms, but 1 to 6 weeks after infection, many have flu-like symptoms. These may include body aches, fatigue, fever, headache, nausea, and rash. After these symptoms, most people may not have any others for several months or years until the virus significantly weakens the immune system. Then they get infections that can involve lungs, eyes, or skin and can be life threatening. Other symptoms may be diarrhea, fatigue, fever, loss of appetite and weight, memory loss, mouth sores, night sweats, skin cancer, swollen glands, and trouble thinking.

How Is HIV Infection Diagnosed?

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The doctor makes a diagnosis from a medical history, physical examination, and blood tests.

How Is HIV Infection Treated?

Treatment depends on the stage of infection. An infectious disease specialist will prescribe medicine to strengthen the immune system and fight the virus. Blood tests must be done often to see how well the medicines work. Life-long medicine will be needed.

Other medicines may be needed for loss of appetite. A nutritionist will help plan a healthy diet.

Exposure to other infections should be avoided. Support groups can help people deal with HIV. Activities aren't restricted, but rest and eating well are important. To avoid exposing others to HIV infection, use condoms and don't donate blood or sperm.

DOs and DON'Ts in Managing HIV Infection:

✓ **DO** follow your doctor's directions.

✓ **DO** practice safe sex. Use latex condoms. Tell your partners about being HIV1 so that they can be tested.

✓ **DO** avoid people who have infections.

✓ **DO** eat a healthy diet and get enough sleep and exercise.

✓ **DO** get help for the emotional stress of being HIV1.

✓ **DO** tell your doctor if you're pregnant or planning a pregnancy.

✓ **DO** call your doctor if you have signs of infection (fever, rash, cough, diarrhea, skin lesions).

✓ **DO** call your doctor right away or go to the emergency room if you have a severe headache,

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fever, cough, severe diarrhea or vomiting, or bad stomach pain or if bright lights bother you.

⦸ **DON'T** donate blood, sperm, or organs.

⦸ **DON'T** stop taking your medicine or change your dosage because you feel better unless your doctor tells you to.

⦸ **DON'T** have unprotected sex.

⦸ **DON'T** abuse alcohol, use drugs, or share needles.

⦸ **DON'T** eat foods such as raw eggs, raw oysters, or unpasteurized milk that may contain harmful bacteria.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- World Health Organization **http://www.who.int/hiv/en**
- American Social Health Association Tel: (800) 227-8922 **http://www.ashastd.org**
- Centers for Disease Control and Prevention Tel: (800) 232-4636 **Website:** **http://www.cdc.gov/hiv/**

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MANAGING YOUR

HUMAN PAPILLOMAVIRUS INFECTION

What Is Human Papillomavirus Infection?

The human papillomavirus (HPV) is a virus that causes warts, which are unsightly growths on the skin. Warts are very common and aren't serious or dangerous, but they aren't pretty and can spread. Most warts disappear without treatment in 2 years, but they often return. Genital warts in females need treatment because they can lead to cervical cancer. A vaccine (Gardasil) against the genital wart virus is recommended for girls and women 9 to 26 years old. The vaccine to protect against HPV is also available for and recommended in boys and men from 9 to 26 years old.

What Causes Human Papillomavirus Infection?

Viruses called human papillomavirus (HPV) cause warts. Types 6, 11, 16, and 18 cause genital warts and cervical cancer.

Because warts are a viral infection, they can be passed from one person to another or spread to different parts of the body. Moist skin and open skin are more likely to become infected.

What Are the Symptoms of Human Papillomavirus Infection?

Warts look different on different parts of the body. Common warts look like little rough cauliflowers and often occur on hands, arms, and legs. Periungual warts occur around fingernails. Flat warts, slightly raised and flesh colored, occur on the face, knees, and elbows of children and young women. Genital warts occur on genital and rectal areas and are often transmitted sexually. Plantar warts occur on bottoms of feet. Filiform warts are small with hairlike bulges.

How Is Human Papillomavirus Infection Diagnosed?

The doctor will do a physical examination and may order a biopsy of the wart or skin abnormality and blood tests to confirm the diagnosis. In a biopsy, a small piece of skin with the lesion is removed and studied under a microscope.

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How Is Human Papillomavirus Infection Treated?

Treatment isn't always successful, and not all warts need treatment. Treatment itself can cause problems, such as pain, infection, and scarring.

Treatment depends on wart location. Common warts can first be treated by a solution of salicylic and lactic acids. The solution is put on the wart each night, and the next morning dead skin is peeled off. Plantar warts can be treated with 40% salicylic acid plasters that are placed on the warts and removed weekly so dead skin can be taken off. The doctor can prescribe stronger medicine if these treatments don't work.

Genital warts almost always need a doctor's care. The doctor will use a blistering agent. Sexual partners will also need to be examined.

Other treatments include freezing, cutting, and burning (using a laser or electricity).

DOs and DON'Ts in Managing Human Papillomavirus Infection:

- ✔ **DO** treat warts early.
- ✔ **DO** wash hands after touching your warts, but try not to touch them.
- ✔ **DO** use salicylic acid solution on common warts and salicylic acid plasters on plantar warts as directed.
- ✔ **DO** call your doctor if your warts aren't better after several weeks of treatment.
- ✔ **DO** call your doctor if you have genital warts.
- ⃠ **DON'T** bite fingernails, pick cuticles, or soak hands for long periods.
- ⃠ **DON'T** pick at, dig at, or pull on warts.
- ⃠ **DON'T** cut or scrape warts.
- ⃠ **DON'T** let other body parts come in contact with warts.

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⃠ **DON'T** shave or cut hair over warts.

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FOR MORE INFORMATION

Contact the following sources:

- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website:** **http://www.cdc.gov**
- American Academy of Dermatology Tel: (866) 503-SKIN (7546) **Website:** **http://www.aad.org**

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MANAGING YOUR

HUNTINGTON'S DISEASE

What Is Huntington's Disease?

Huntington's disease (or Huntington's chorea) involves degeneration of certain parts of the brain. These parts control movement, thinking, memory, perception, and intelligence. About 30,000 people have this disease in the US. At least 150,000 others have a 50% chance of getting the disease.

Today, genetic testing can confirm the diagnosis.

What Causes Huntington's Disease?

This inherited disorder is passed from parents to children. The specific cause is a mutation of a gene on chromosome 4. A mutation means that an error was made in building blocks that make up the DNA (deoxyribonucleic acid). DNA carries genetic information. The mutation leads to too much protein called huntingtin being made. This protein may cause a loss of brain cells and symptoms of the disease.

What Are the Symptoms of Huntington's Disease?

This disease can occur between the ages of 2 and 70 years but is usually diagnosed in early adulthood, at age 30 to 40. Uncontrolled movements called chorea, unsteadiness, clumsiness, loss of balance, slurred speech, and trouble swallowing and eating are symptoms. Chorea is a twisting dance-like motion, usually starting in the feet, fingers, face, or upper chest. Anger, mood swings, irritability, loss of memory, and poor judgment can also occur. Not all people have these exact symptoms. Some may appear rigid, with little movement, or have fine twitching with tremors.

The disease is progressive, meaning slow loss of motor and thinking skills continues. Death

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can result, most often from pneumonia or complications from injuries.

How Is Huntington's Disease Diagnosed?

The doctor will make a diagnosis from the medical history, physical examination, and laboratory tests. Other tests such as computed tomography (CT) and magnetic resonance imaging (MRI) will be done to exclude other illnesses that may cause similar symptoms.

A neurologist (specialist in nervous system diseases) and other specialists may help with diagnosis and treatment.

How Is Huntington's Disease Treated?

No treatment is available that will reverse Huntington's disease.

Antidepressant medicines can be used for depression. Antipsychotic drugs (haloperidol) or benzodiazepines (e.g., diazepam or clonazepam) may help the problems with movement.

DOs and DON'Ts in Managing

Huntington's Disease:

✓ **DO** understand that this disease is inherited. When a family member is diagnosed with Huntington's disease, you may have overwhelming anxiety about knowing or not knowing whether you have the Huntington's disease gene. Children of a person with the disease have a 50% chance of inheriting the disease gene.

✓ **DO** remember that genetic markers or tests can be done to find out whether you carry the Huntington's gene. The decision to have this test won't be easy. Refer to guidelines of the Huntington's Disease Society of America (HDSA).

✓ **DO** call your doctor if a family member has been diagnosed with Huntington's disease.

⊘ **DON'T** forget that people with this disease need a team of caregivers. The best person to see

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for advice is the neurologist. Physical therapists, occupational therapists, psychiatrists, and social workers can all help with treatment.

⦸ **DON'T** be afraid to ask for more information. If you are thinking of being tested for Huntington's disease, it is important to have pre- and post-test counseling.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- Huntington's Disease Society of America Tel: (800) 345-4372 **Website:** **http://www.hdsa.org**
- American Academy of Neurology **Website:** **http://www.neurology.org**

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HYDRATION FOR ATHLETES

Hydration and Dehydration

Water is the most important nutrient for athletes, who often don't pay enough attention to it. Drinking enough before, during, and after exercise is critical. Hydration means having enough fluid in body tissues, and dehydration is not having enough. Dehydration is the most common reason for poor sports performance, but it's also the most preventable. In addition to urination, water is lost by sweating and through the lungs by breathing. Losing as little as 1% to 2% of total body weight as water can make core body temperature start to increase during exercise. Dehydration of more than 3% of body weight can lead to heat-related illness.

Dehydration can be acute or chronic. Acute dehydration can occur in 2 to 3 hours (common in endurance athletes such as marathon runners and triathletes). Chronic dehydration (days of not enough fluids) can be more dangerous (seen during early preseason soccer or football training).

General Recommendations

Teens and adults should replace any body weight lost during exercise or sports with fluids. Cool water is best. Thirst isn't a good signal of fluid needs. Thirst means that dehydration already occurred. Clear urine means that hydration is good.

Maintaining and Checking Hydration

Check body weight before and after exercise, and drink enough fluid to replace weight. The amount needed depends on many things, including the kind and length of activity, weather, and the person. Athletes with large or lasting acute weight loss should be restricted from activity until rehydrated. Infrequent urination, dark yellow urine, headache, and weakness mean dehydration, a signal to stop and drink fluids. Drinking too much water without electrolyte replacement can also cause problems, however, such as a low sodium level in the blood (hyponatremia).

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The best way to have good fluid balance is to drink fluids before, during, and after training or exercise. Drink 15 to 20 ounces 2 to 3 hours before, and 8 to 16 ounces of cool or cold fluid 15 to 30 minutes before exercise. During exercise, drink 4 to 10 ounces every 10 to 15 minutes. Children should drink water often during sports (every 15 to 20 minutes). They don't respond to thirst as well as adults.

Fluid Type

Fluids from all foods and beverages add to overall hydration. Water can work well for some athletes, but others benefit from sports drinks that contain carbohydrate (6% to 8%), electrolytes, and maybe some protein. Don't drink sugary, carbonated drinks or caffeine-containing beverages. Caffeine is a diuretic and increases fluid loss.

Illnesses Related to Dehydration and Exercise

Minor disorders include cramps, weakness, or lightheadedness, often occurring at the end of an endurance event, usually running. Drinking fluids (such as electrolyte solutions) helps these disorders. More serious illnesses are heat exhaustion and heat stroke from exertion. Heat stroke is a medical emergency.

Hyponatremia in athletes is often related to endurance exercise. It may be due to a combination of too much intake of hypotonic (without enough sodium) fluids, inadequate fluid clearance, and loss of sodium in sweat, among other things.

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FOR MORE INFORMATION

Contact the following sources:

- American Medical Society for Sports Medicine Tel: (913) 327-1415 **Website:**

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http://www.newamssm.org

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MANAGING YOUR

HYDROCELE

What Is a Hydrocele?

A hydrocele is a sac of clear fluid that develops in the scrotum, the loose pouch of skin that holds the testicles. Hydroceles are most often found in newborn babies. They can be on one side or both sides of the scrotum. In babies, most hydroceles go away on their own. Also, men, usually older than 40, can have hydroceles. There is no known way to prevent hydrocele.

What Causes a Hydrocele?

In babies, hydroceles are usually caused during the baby's development. As babies develop, the testicles should move from the lower abdomen (belly) into the scrotum. Each testicle moves in a sac with fluid around it. Usually, the sac closes and the fluid moves back into the body. If fluid remains after the sac closes, one type of hydrocele forms. Sometimes, the sac may not close completely, and another type of hydrocele forms. Hydroceles can also be caused by infections, inflammation, radiation therapy, and injuries. Hydroceles aren't contagious or hereditary.

What Are the Symptoms of a Hydrocele?

Hydroceles generally don't cause much pain. They do cause the scrotum to get swollen on one or both sides. This swelling makes the scrotum feel like a balloon filled with water.

How Is a Hydrocele Diagnosed?

The doctor will make a diagnosis from a physical examination of the scrotal area. Sometimes, the doctor will order ultrasonography of the scrotum to diagnose a hydrocele. Ultrasonography is a test that uses sound waves to get pictures of inside the body. It's important to find out whether a hydrocele or another more serious problem (such as testicular torsion or a tumor) is present.

How Is a Hydrocele Treated?

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Some hydroceles clear up in a few months with no treatment. Those that don't go away in that time may be treated with surgery. Surgery can be done as an outpatient operation. Either spinal or local anesthesia may be needed. Another treatment possibility is aspiration. In this procedure, the doctor sticks a needle into the scrotum and takes out the excess fluid. A urologist (doctor specializing in the genital and urinary system) can do this. Some urologists use aspiration along with injection of scarring agents to prevent the hydrocele from returning. As with any operation, complications of bleeding and infection can occur.

DOs and DON'Ts in Managing a Hydrocele:

✓ **DO** call your doctor if you have swelling in the scrotal area.

✓ **DO** get the opinion of a urologist if you're thinking of surgery.

✓ **DO** remember there's 2% chance that the hydrocele will come back after surgery.

✓ **DO** call your doctor if you notice pain or swelling of a testicle or feel a lump on the testicle.

✓ **DO** call your doctor if you need a referral to a surgeon (urologist).

✓ **DO** call your doctor if you have pain, bleeding, or fever after surgery for a hydrocele.

⊘ **DON'T** forget that hydroceles don't affect how the testicles work and won't make you impotent or make you unable to have an erection.

⊘ **DON'T** forget to report lumps or swelling to your primary doctor. Other causes of lumps include spermatoceles, testicular torsion, and testicular cancers.

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Contact the following source:

- American Urological Association Tel: (866) 746-4282 **Website: http://www.auanet.org**

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MANAGING YOUR

HYDRONEPHROSIS

What Is Hydronephrosis?

Hydronephrosis is the dilation or swelling of kidneys because of a blockage that stops urine from flowing out of the body.

Hydronephrosis can be cured, depending on the cause. Complications include urinary infections, high blood pressure, kidney failure, and dehydration.

What Causes Hydronephrosis?

The cause is a blockage of any part of the urinary tract. In children, the blockage is often due to abnormalities such as narrowing or pinching of the urethra. The urethra is the tube taking urine from the bladder to outside the body. Also narrowing at the opening of the ureters, the tubes carrying urine from the kidneys to the bladder, can cause a blockage.

In adults, causes often include kidney stones, enlarged prostate gland, and prostate cancer. Other causes are cancers of the bladder, uterus, ovary, and colon.

What Are the Symptoms of Hydronephrosis?

Symptoms depend on the cause. For example, people with kidney stones may have blood in the urine and severe pain in the side (flank) that travels to the groin. Men with prostate cancer or an enlarged prostate may have problems urinating, need to urinate at night, and be unable to completely empty the bladder. People with colon cancer may see blood in the stools (bowel movements) or change in bowel movements.

How Is Hydronephrosis Diagnosed?

In addition to the physical exam, the doctor will make a diagnosis by using ultrasonography or computed tomography (CT).

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How Is Hydronephrosis Treated?

Treatment depends on the cause. The goal is to get rid of the blockage. For a sudden obstruction, as in men with enlarged prostate glands, a catheter is put through the urethra into the bladder. The catheter gives temporary and instant relief of symptoms until more complete therapy, such as medicine or surgery, can be given.

People with kidney stones are usually treated by a urologist (a surgeon specializing in diseases of the genital and urinary tract) with medications for pain control and increasing fluid intake. Shock wave treatment (lithotripsy) or surgery can be done to remove the stones if they are too large to pass on their own.

The kidney can return to normal, depending on how long the blockage has been there; whether problems such as infections, stones, or other causes of the blockage are also present; and how severe the blockage is.

DOs and DON'Ts in Managing Hydronephrosis:

✓ **DO** understand that hydronephrosis is not a disease but is the result of many different diseases.

✓ **DO** realize that the longer hydronephrosis remains untreated, the more kidney function is lost.

✓ **DO** get advice from a urologist if hydronephrosis is found.

✓ **DO** call your doctor if you have abdominal or flank pain or blood in the urine.

✓ **DO** call your doctor if you see a drop in your urine output or you cannot urinate.

⃠ **DON'T** forget that hydronephrosis can occur in both children and adults.

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⦸ **DON'T** miss follow-up doctor appointments. You may need more ultrasound scans to monitor the kidney size.

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FOR MORE INFORMATION

Contact the following source:

- National Kidney Foundation Tel: (800) 622-9010 **Website: http://www.kidney.org**

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MANAGING YOUR

HYPEREMESIS GRAVIDARUM

What Is Hyperemesis Gravidarum?

Hyperemesis gravidarum (HG) is an extreme form of morning sickness, with severe nausea and vomiting. It leads to dehydration, disturbances in metabolism (abnormal levels of chemicals called electrolytes and ketones), and rapid weight loss. These changes can mean a hospital stay. It's rare, so even though 70% to 85% of women have morning sickness, only about 1% to 2% will have HG. HG may mean you have a multiple pregnancy (twins or more). Complications of HG may be serious and related to kidney, nervous system, and liver damage.

What Causes HG?

The cause is unknown, but factors that may be involved include hormones called human chorionic gonadotropin and estrogen. Other possibilities are younger age of the mother, body weight (obesity), no previous completed pregnancies, first pregnancy, and history of HG in prior pregnancies. Biological, psychological, and social factors may all play a role.

What Are the Symptoms of HG?

Symptoms usually begin between the fourth and eighth week of pregnancy and last until 16 weeks or more. Most women vomit often throughout the day, with few if any symptom-free periods. Other symptoms include severe nausea, weight loss, reduced urination, headaches, confusion, fainting, and jaundice. Dehydration is indicated by ketones in urine, increased pulse rate, and lower blood pressure.

How Is HG Diagnosed?

The doctor makes a diagnosis when severe nausea and vomiting lead to weight loss, dehydration, or disturbances in the body's chemistry. To be sure that nothing else is causing these symptoms,

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the doctor may do blood and urine tests. Ultrasonography may also be done.

How Is HG Treated?

When symptoms aren't too bad, eating dry foods such as crackers and small, frequent meals may be enough. Drinking more fluids may help. (If you drink fizzy drinks such as seltzer or other sparkling water, pour it over ice and let it sit for a bit to let some of the fizz out.) Women with HG may need intravenous fluids and vitamins and hospitalization. Medicines to prevent nausea (antiemetics) are for women with severe and long-lasting vomiting. Once fluids can be taken, eating small bland meals and then more food may be possible. If these methods don't work, drugs or a method of feeding called total parenteral nutrition may be used.

DOs and DON'Ts in Managing HG:

✓ **DO** get treatment from a doctor experienced with HG.

✓ **DO** eat small, frequent meals.

✓ **DO** have high-protein snacks.

✓ **DO** have crackers, dry toast, or dry cereal when you first get up in the morning.

✓ **DO** call your doctor if your symptoms get worse or you're losing weight.

⃠ **DON'T** eat large or spicy meals or high-fat foods.

⃠ **DON'T** eat just before you go to bed or lie down.

⃠ **DON'T** take medicines (even over-the-counter) or try home remedies without asking your doctor.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website: http://www.acog.org**
- WebMD **Website: http://www.webmd.com**
- U.S. Department of Health and Human Services **Website: http://womenshealth.gov**

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MANAGING YOUR

HYPERHYDROSIS

What Is Hyperhydrosis?

Hyperhydrosis, or too much sweat, is a rather common problem. It can also be related to abnormal sweat odor (called bromhidrosis). Hyperhydrosis often affects the feet, but can also involve hands and armpits. It's usually not curable, but it can be treated.

What Causes Hyperhydrosis?

The cause is unknown but may be related to stress in some people. Other less common causes include certain kinds of arthritis, nervous system diseases and trauma to the spinal cord, disorders of the blood system, and certain medicines.

What Are the Symptoms of Hyperhydrosis?

Symptoms are excessive sweating of the feet, hands, or armpits, or all three. Sometimes other parts of the body are affected. The sweating can cause embarrassment and sometimes a foul odor. Shirt, socks, and shoes can become stained.

How Is Hyperhydrosis Diagnosed?

The doctor makes a diagnosis of hyperhydrosis from a medical history and physical examination. Blood tests may be done to rule out conditions, such as overactive thyroid, that may cause similar symptoms.

How Is Hyperhydrosis Treated?

Treatment may involve the use of a drying medication called Drysol® (20% aluminum chloride hexahydrate). Before bedtime, affected areas are washed and dried and a small amount of Drysol® is applied. It's washed off in the morning. This treatment is repeated for 1 to 2 weeks, then once per week or as needed. Sensitive skin should have treatments less often. After symptoms are controlled, Drysol® should be

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used as little as possible, especially in armpits. Other medicines may also be prescribed if Drysol® doesn't work. Sometimes, oral medicines called anticholinergics are prescribed, but these may cause side effects, such as dry mouth, blurred vision, and dizziness.

Iontophoresis—use of a mild electric current in tap water—can be tried in some cases for about 30 minutes a day. Botox® (botulinum toxin) injections to the armpit sweat glands also work and are often used by dermatologists (specialists in skin diseases) in severe cases.

DOs and DON'Ts in Managing Hyperhydrosis:

✓ **DO** avoid other deodorants and antiperspirants when you first use Drysol® for armpit sweating. Dry the armpit with a hairdryer first, apply Drysol®, then immediately dry with the hairdryer again. After you use Drysol® once or twice a week, you can use other antiperspirants and deodorants during the day.

✓ **DO** drink plenty of water to avoid dehydration. Drink more during hot summer months, 8 to 10 glasses (8 ounces per glass) of water per day. Drink more if you're in hot sun.

✓ **DO** wear cotton clothing that absorbs sweat. Change clothing and socks frequently.

✓ **DO** take a bath or shower every day, more often if needed.

✓ **DO** consider stress reduction counseling if stress is a major cause.

✓ **DO** call your doctor if you see redness, swelling, or pus drainage.

✓ **DO** call your doctor if symptoms don't get better in 3 to 4 weeks of treatment.

⃠ **DON'T** wear nylon or manufactured fabrics.

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⃠ **DON'T** use deodorants and antiperspirants on armpits during the first 1 to 2 weeks of Dry-sol® therapy. Use baking soda instead.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Dermatology Tel: (847) 330-0230, (866) 503-7546 **Website: http://www.aad.org**

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MANAGING YOUR

HYPERPARATHYROIDISM

What Is Hyperparathyroidism?

The parathyroids are four tiny glands usually found in the neck, next to the thyroid gland. They control calcium balance in the body. When blood calcium levels fall too low, these glands make a hormone to restore normal calcium levels. This hormone is named parathyroid hormone (PTH). Hyperparathyroidism means that the parathyroid glands are too active, and people have high blood calcium levels. Untreated hyperparathyroidism can lead to osteoporosis, kidney stones, high blood pressure, inflammation (swelling) of the pancreas, or stomach ulcers.

About 100,000 people per year are diagnosed with hyperparathyroidism, twice as many females as males.

What Causes Hyperparathyroidism?

Most people (85%) have a benign (not cancerous) parathyroid gland tumor (adenoma). Others may have enlarged parathyroid glands (hyperplasia). Rarely, the cause is cancer. Aging increases the risk. Some people have disorders related to other endocrine conditions.

What Are the Symptoms of Hyperparathyroidism?

People may have no symptoms. Some may feel weak, tired, and depressed or have muscle aches and joint pains. They may have less appetite, nausea, vomiting, constipation, confusion, or frequent urination and thirst.

How Is Hyperparathyroidism Diagnosed?

The doctor makes a diagnosis by measuring blood levels of calcium and PTH. High levels of both confirm the diagnosis.

How Is Hyperparathyroidism Treated?

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A parathyroid gland tumor is best removed surgically. Only people with high calcium levels, bothersome symptoms, or possible cancer need surgery. Surgery cures 95% of people. Complications of surgery include low calcium level, bleeding, and infection. The low calcium level that occurs may be temporary or permanent. Many doctors suggest taking calcium and vitamin D supplements.

The doctor may just watch people with enlarged parathyroids and monitor them with frequent measurement of blood calcium levels. In an emergency (a very high calcium level), intravenous fluids and medicines may be given to lower the levels.

DOs and DON'Ts in Managing Hyperparathyroidism:

✓ **DO** tell your doctor if you have a family history of parathyroid or other endocrine tumors. Make sure that your doctor has your old records of blood calcium measures.

✓ **DO** drink plenty of water to prevent high blood calcium levels.

✓ **DO** find an experienced surgeon for your operation.

✓ **DO** see your doctor regularly if no surgery is planned. Blood, urine, bone density, and kidney function tests should be done regularly.

✓ **DO** call your doctor if you become dehydrated or immobilized because of trauma or illness, as this may affect your calcium level.

✓ **DO** call your doctor if you have symptoms of a kidney stone, including severe pain on your side or back and blood in your urine.

✓ **DO** call your doctor if you notice muscle spasms, face twitching, or numbness around the

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lips after surgery on the parathyroid glands. These symptoms of a very low blood calcium level are due to a low level of parathyroid hormone and need attention right away.

⦸ **DON'T** let yourself become dehydrated. Dehydration will increase your calcium level.

⦸ **DON'T** take calcium supplements unless your doctor approves. They can lead to kidney stone formation and high blood calcium levels.

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FOR MORE INFORMATION

Contact the following sources:

- American Association of Clinical Endocrinologists Tel: (904) 353-7878 **Website:** **http://www.aace.com**
- National Health Information Center Tel: (800) 336-4797 **Website:** **http://www.health.gov/nhic/**

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MANAGING YOUR

HYPERSENSITIVITY PNEUMONITIS

What Is Hypersensitivity Pneumonitis?

Hypersensitivity pneumonitis (or extrinsic allergic alveolitis) is an inflammation or irritation of the lungs due to recurrent exposure to various environmental agents. It has many other names related to the specific cause, such as farmer's lung (the most common type), air-conditioner or humidifier lung, bird fancier's lung, bagassosis, cheese worker's lung, chemical worker's lung, grain handler's lung, wine grower's lung, and mushroom picker's disease.

What Causes Hypersensitivity Pneumonitis?

The cause is exposure to environmental agents in the air. Lungs of workers get irritated by long or repeated exposures to dust, mold, or fungus. For example, dust may come from moldy hay, straw, and grain (farmer's lung). Bird fanciers are exposed to proteins from feathers and droppings of pigeons, parakeets, and other birds. Particles may move easily through the air by air conditioners and heaters in a building.

What Are the Symptoms of Hypersensitivity Pneumonitis?

The most common symptoms are fever, chills, cough, shortness of breath, weakness, wheezing, headache, and loss of appetite. The acute illness may start 4 to 6 hours after exposure to the cause. Symptoms often go away on their own in 12 hours to several days after exposure stops. In time, with repeated exposure, the acute illness may turn into a long-lasting (chronic) lung disease.

How Is Hypersensitivity Pneumonitis Diagnosed?

Diagnosis is based on the physical examination and additional tests. The doctor may hear certain sounds (called crackles or rales) with the stethoscope while you are breathing. These sounds are

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faint, brief crackling noises. The doctor may also order blood tests, chest x-ray, and breathing test to find out how the lungs are working and to exclude other disorders that have similar symptoms.

How Is Hypersensitivity Pneumonitis Treated?

The main treatment is to find the cause of the irritation and try to avoid it, if possible. Usually, symptoms go away after the exposure stops. In serious cases, medicines called corticosteroids (prednisone) may be given.

DOs and DON'Ts in Managing Hypersensitivity Pneumonitis:

✓ **DO** avoid exposure to the irritant if you are diagnosed with hypersensitivity pneumonitis and the irritant is known. Remove or reduce the irritant, such as dust.

✓ **DO** call your doctor if your symptoms last after you are no longer exposed to the irritant.

✓ **DO** wear protective masks and use a good ventilation system. These may help prevent becoming sensitized to the irritant and recurrence of the illness.

⃠ **DON'T** ignore symptoms, especially if they last more than a few days.

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FOR MORE INFORMATION

Contact the following source:

• American Lung Association Tel: (212) 315-8700, (800) 586-4872 **Website:** **http://www.lungusa.org**

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MANAGING YOUR

HYPERSPLENISM

What Is Hypersplenism?

The spleen is an organ in the abdomen (belly), just under the left ribs. It's about the size of a fist. It fights infections and filters blood to get rid of cell debris. Different diseases can cause an enlarged spleen (splenomegaly). These include leukemia, lymphoma, metastatic tumors (cancers that spread), infections, liver cirrhosis, and congestive heart failure. Infections that may cause an enlarged spleen are viral hepatitis, mononucleosis, HIV, malaria, and endocarditis (a heart infection).

Hypersplenism is a syndrome that involves splenomegaly plus destruction of blood cells. Destruction of red blood cells causes anemia. Destruction of white blood cells causes leukopenia (low white blood cell count). Destruction of platelets causes thrombocytopenia (low platelet count).

What Causes Hypersplenism?

Hypersplenism is generally due to liver disease (cirrhosis), blood cancers, connective tissue and inflammatory diseases, and infections (tuberculosis, malaria).

What Are the Symptoms of Hypersplenism?

Symptoms include early satiety (feeling full after eating only very little), pain in the left upper part of the abdomen due to a large spleen, and feeling bloated. Easy bruising and bleeding and getting frequent and severe bacterial infections may be other manifestations of hypersplenism. Fever, weakness, heart palpitations, and ulcers of the mouth, legs, and feet can occur.

How Is Hypersplenism Diagnosed?

The health care provider makes a diagnosis from the medical history, physical examination, blood

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tests, and imaging studies. These studies may include ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI). If suspecting hypersplenism, the health care provider may in some cases refer you to a hematologist to do a bone marrow biopsy to help determine the cause of the hypersplenism. A hematologist is a specialist in blood diseases. In the biopsy, the doctor uses a needle to take a sample of bone marrow tissue to check with a microscope.

How Is Hypersplenism Treated?

Untreated hypersplenism can lead to serious complications. The cause must be identified and treated. For example, chemotherapy is used for cancers. Antibiotics are used for bacterial infections (e.g., Lyme disease and bacterial endocarditis). Antiparasitic drugs are used for parasitic infections (e.g., schistosomiasis and malaria). Surgery to remove the spleen (splenectomy) may be done for people whose diagnosis cannot be made or people who have lasting symptoms even with treatment. A splenectomy may fix the low blood cell counts commonly seen in people with hypersplenism.

DOs and DON'Ts in Managing Hypersplenism:

✓ **DO** realize that people can live without a spleen, even though it helps fight infections and removes cell debris.

✓ **DO** remember that people who have their spleens removed are more likely to get serious infections caused by bacteria such as pneumococci and *Haemophilus influenzae.* Vaccinations can help protect against these infections and should be administered before the spleen is removed.

✓ **DO** call your health care provider if you have abdominal pain, long-standing abdominal

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bloating, an alcohol problem, or a drug problem.

- ⃠ **DON'T** forget that the prognosis depends on the cause of hypersplenism. For example, parasitic infections such as malaria, toxoplasmosis, and leishmaniasis can be treated. Metastatic cancer, however, may not have a cure.
- ⃠ **DON'T** drink alcohol. Long-term use can damage your liver and lead to splenomegaly.
- ⃠ **DON'T** do drugs. Intravenous drug use places you at high risk for viral hepatitis and HIV. Both of these can lead to hypersplenism.

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FOR MORE INFORMATION

Contact the following sources:

- National Digestive Diseases Information Clearing house Phone:1-800-891-5389 or 1-301-654-3810 **Website: www.niddk.nih.gov/health/digest/nddic.htm**
- American Liver Foundation Tel: 800-465-4837 **Website: www.liverfoundation.org**

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MANAGING YOUR

HYPERTHYROIDISM

What Is Hyperthyroidism?

Hyperthyroidism is an illness caused by a thyroid gland that's too active. The thyroid gland is located in the neck and makes thyroid hormone. This hormone controls the rate at which the body works. Too much hormone causes symptoms of hyperthyroidism. Three times more women than men have an overactive thyroid.

What Causes Hyperthyroidism?

The most common cause is a condition called Graves' disease. This disease causes 80% to 90% of cases. This disease is thought to be autoimmune. Autoimmune means that the body's own immune system attacks certain organs in one's body. In Graves' disease, the thyroid gland is attacked. Other less common causes include thyroiditis, toxic adenoma, and using too much thyroid medicine. Thyroiditis is inflammation of the thyroid. An adenoma is a thyroid tumor that makes thyroid hormone. Sometimes the cause isn't known. This illness can run in families, but it's not contagious.

What Are the Symptoms of Hyperthyroidism?

Symptoms include nervousness, sweating, fatigue, and fast or skipped heartbeats or other heart rhythm abnormalities such as atrial fibrillation. Others are eye irritation, weight loss, sensitivity to heat, and frequent bowel movements or diarrhea. People with Graves' disease have an enlarged thyroid gland (goiter) and may have bulging eyeballs (exophthalmos).

How Is Hyperthyroidism Diagnosed?

The doctor makes a diagnosis from the medical history, physical examination, and blood tests to measure blood thyroid hormone levels. The doctor may also order a thyroid scan or ultrasono-

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graphy to get pictures of the thyroid gland.

The doctor may also suggest seeing a thyroid specialist (endocrinologist).

How Is Hyperthyroidism Treated?

Thyroid hormone levels are lowered with medicines, radiation therapy, or surgery. Medicines may be needed for a few months, a few years, or more. Ones that prevent thyroid hormone production include propylthiouracil (PTU) and methimazole. They can be used as the main therapy or to prepare for other treatments.

Radioactive iodine is used to destroy the thyroid. This therapy is best for people older than 21 and younger people who can't control their disease with medicines.

Surgery is for people with large thyroid glands that block or interfere with other structures in the neck. People who don't want to use radioactive iodine may have surgery. Pregnant women may also need surgery.

DOs and DON'Ts in Managing Hyperthyroidism:

✓ **DO** protect your eyes if you have eye complications of Graves' disease. Use sunglasses and artificial tears, and wear eye protection at night.

✓ **DO** remember that radioactive iodine shouldn't be used during pregnancy. It may cause an underactive thyroid condition in the baby.

✓ **DO** realize that successful treatment means that you need lifelong care. The doctor must check you for onset of an underactive thyroid gland (hypothyroidism) after treatment and for possible recurrence of hyperthyroidism.

✓ **DO** call your doctor if you have palpitations, serious weight loss, diarrhea, or tremors.

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✓ **DO** call your doctor if you have restlessness, anxiety, or mood swings.

⦸ **DON'T** do physical exercise until your illness is controlled.

⦸ **DON'T** smoke. Smoking may worsen eye problems.

⦸ **DON'T** forget that complications of surgery may include paralysis of vocal cords, underactive thyroid (hypothyroidism), and calcium problems. Calcium problems can result if parathyroid glands are accidentally removed.

⦸ **DON'T** forget that hyperthyroidism may recur after surgery in 10% to 15% of people.

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FOR MORE INFORMATION

Contact the following sources:

- American Association of Clinical Endocrinologists Tel: (904) 353-7878 **Website:** **http://www.aace.com**
- Thyroid Foundation of America Tel: (800) 832-8321 **Website:** **http://www.allthyroid.org**

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MANAGING YOUR

HYPERTROPHIC CARDIOMYOPATHY

What Is Hypertrophic Cardiomyopathy?

Hypertrophic cardiomyopathy (also known as HCM, IHSS, hypertrophic obstructive cardiomyopathy) is an illness affecting the heart muscle. It interferes with the heart's ability to pump blood. Sometimes it also changes the heart's natural rhythm, which leads to irregular heartbeats (arrhythmias).

Hypertrophic cardiomyopathy, occurs when the heart's muscle fibers grow abnormally. Heart walls thicken, especially in the left ventricle (the main pumping chamber). The left ventricle chamber becomes smaller inside, the heart cannot rest completely between beats, and the ventricle pumps less blood out of the heart. People are at risk for fainting (syncope), chest pain (angina), difficulty breathing (dyspnea), and sudden death.

Hypertrophic cardiomyopathy affects people of all ages, including children. It can cause sudden death even in children and young adults.

What Causes Hypertrophic Cardiomyopathy?

Hypertrophic cardiomyopathy is usually inherited (passed on from parents). Once someone is diagnosed, all immediate family members should be tested.

What Are the Symptoms of Hypertrophic Cardiomyopathy?

Symptoms include shortness of breath when walking, performing household tasks, or with any exertion; chest pain; fainting after exercising; and irregular or very rapid heartbeat. Some people have no symptoms, and sudden cardiac arrest may often be the first sign of this disorder.

How Is Hypertrophic Cardiomyopathy Diagnosed?

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The doctor will check the medical history and do a physical examination. Tests for diagnosis include chest x-rays, electrocardiogram (ECG), and echocardiography (ultrasound of the heart). Other tests, such as 24-hour recording of the heartbeat and blood tests may also be done. Genetic testing using a blood test and magnetic resonance imaging (MRI) of the heart may also be done.

How Is Hypertrophic Cardiomyopathy Treated?

Treatment is aimed at controlling symptoms and slowing the disease progress by reducing excessive contractions of the ventricle. Symptoms of heart failure and arrhythmias are also treated. Drugs are usually prescribed to regulate the heart rate and strength of contractions. These drugs include beta-blockers (e.g., propranolol) and calcium channel blockers (e.g., verapamil). A pacemaker/defibrillator/cardioverter is an option to control the heartbeat. It is a small device that is put into the body during surgery. Surgery may also be done to remove part of the abnormal muscle (septal myectomy) and reduce the blockage of blood flow. Destruction of a portion of the wall between ventricles (alcohol septal ablation) may also be done. Heart transplantation is possible for people who don't respond to other treatments.

DOs and DON'Ts in Managing Hypertrophic Cardiomyopathy:

✓ **DO** take medicine as prescribed by your doctor.

✓ **DO** tell your doctor if your symptoms get worse or don't improve with treatment.

✓ **DO** remember that family members should be checked for this disorder.

✓ **DO** call your doctor if you have new or worsening chest pain, shortness of breath, swelling in the legs, or fainting.

⦸ **DON'T** change your exercise program without telling your doctor first.

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⦸ **DON'T** take over-the-counter drugs, foods, or herbal supplements before checking with your doctor because they may react with your heart medicine.

⦸ **DON'T** smoke.

⦸ **DON'T** drink alcohol.

⦸ **DON'T** use diuretics (water pills).

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:** **http://www.americanheart.org**
- American College of Cardiology Tel: (800) 253-4636 **Website:** **http://www.acc.org**

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MANAGING YOUR

HYPOCHONDRIA

What Is Hypochondria?

Hypochondria is a kind of illness with physical symptoms suggesting a medical ailment. However, the symptoms are due to a psychiatric condition because they aren't explained by a medical condition or substance use. In hypochondria, or hypochondriasis, people fear having a serious disease. They misinterpret symptoms that are actually related to normal body sensations. Hypochondria is found in 1% to 5% of the general population, equally in men and women. It can begin at any age but usually starts in early adulthood.

What Causes Hypochondria?

The cause is unknown. It's not contagious or passed from parents to children.

What Are the Symptoms of Hypochondria?

Most people have a long-term (chronic) up-and-down course. Symptoms get better and then worse. Symptoms include fear or anxiety about having a certain condition, even with minor symptoms. People often check their bodies for problems, such as lumps or sores. They may focus on stomach gurgling or chest pains. People "doctor-shop," or switch doctors. They don't listen to their doctor's suggestion to see a psychiatrist. Marital or social problems, job loss, family tension, and emotional distress can occur.

How Is Hypochondria Diagnosed?

The doctor suspects hypochondria in people who complain of lasting symptoms despite many normal physical examinations and laboratory and imaging studies. The belief isn't a delusion or specific to worries about appearance. The preoccupation causes great distress at home, work, or

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social situations. It lasts for more than 6 months. It's not due to other psychiatric conditions. The doctor uses a medical history, physical examination, laboratory tests, and X-rays to rule out other causes of symptoms.

How Is Hypochondria Treated?

Treatment is difficult because most people are sure that something is seriously wrong. One doctor, preferably the primary care doctor, should coordinate all medical evaluations. A psychiatrist or a psychologist will probably be involved in care. Psychiatrists are specialists in mental and emotional disorders who can prescribe drugs. Psychologists are nonmedical specialists in diagnosis and treatment of mental and emotional problems who don't prescribe drugs.

The first kind of treatment is usually psychologic (cognitive behavioral therapy). This therapy teaches people how certain thinking patterns cause symptoms. It also helps break the connection between the preoccupation with symptoms and the usual reaction to (behavior or anxiety about) them. Sometimes, medicines help with anxieties or depression.

DOs and DON'Ts in Managing Hypochondria:

✓ **DO** realize that only 5% of people recover completely from their disorder.

✓ **DO** learn about hypochondria, but don't spend too much time on research about other medical conditions. Join a support group if you think that will help.

✓ **DO** keep physically active.

✓ **DO** call your doctor if you're worried about another symptom. Call if you need a referral to a psychiatrist or psychologist. Call if you feel depressed, anxious, or afraid that you'll hurt yourself or others.

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- ⃠ **DON'T** use too much caffeine. Caffeine can cause anxiety, which can make preoccupations worse. Don't use drugs or drink alcohol.
- ⃠ **DON'T** forget that seeing one primary care doctor is best. Seeing one doctor after another can mean tests, X-rays, and risky studies are duplicated.

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FOR MORE INFORMATION

Contact the following sources:

- Mental Health America Tel: (800) 969-6642 **Website: http://www.nmha.org**
- American Psychiatric Association Tel: (888) 357-7924 **Website: http://www.psych.org**
- American Psychological Association Tel: (800) 374-2721 **Website: http://www.apa.org**

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MANAGING YOUR

HYPOGLYCEMIA IN DIABETES

What Is Hypoglycemia?

Hypoglycemia means that a person's blood sugar (glucose) level is too low. In diabetes, the blood sugar level is usually too high (hyperglycemia), but sometimes blood sugar can be low after treatment. Because hypoglycemia can cause people to pass out (lose consciousness), symptoms must be recognized and treated right away.

What Causes Hypoglycemia?

Hypoglycemia occurs when insulin and glucose aren't in balance. This problem can occur after taking too much insulin or another diabetes medicine, not eating enough or waiting too long between meals (such as overnight), exercising without having eaten enough, or not eating enough carbohydrates. Foods rich in carbohydrates include pasta, rice, potatoes, bread, tortillas, cereal, milk, yogurt, fruit, and sweets.

What Are the Symptoms of Hypoglycemia?

Symptoms include shakiness; dizziness; sweating; hunger; headache; rapid heartbeats; pale skin color; sudden moodiness or behavior problems, such as crying for no reason; clumsy, jerky movements; confusion or trouble paying attention; tingling around the mouth; and seizures.

How Is Hypoglycemia Diagnosed?

Symptoms are the best way to tell whether hypoglycemia is occurring. People having any of the symptoms should immediately have a sugar snack and check their blood glucose level right away. Your doctor can order fasting blood sugar tests and other blood tests to determine if you have hypoglycemia.

How Is Hypoglycemia Treated?

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To return the balance between insulin and glucose to normal during an episode of hypoglycemia, sugar should be eaten quickly. Three glucose tablets (available at a drugstore), one-half cup of fruit juice, or five or six pieces of hard candy should help. This snack should help within 15 to 20 minutes, when the blood sugar level should be checked again. If the level isn't normal, another snack should be eaten and blood sugar level checked again 15 to 20 minutes later.

If these snacks don't help and loss of consciousness occurs, emergency treatment is needed. A doctor or someone trained to give shots (family members or co-workers) can give a shot of glucagon. If no one who knows about glucagon is available, someone should call 911 immediately.

DOs and DON'Ts in Managing Hypoglycemia:

✓ **DO** take steps to prevent an imbalance between insulin levels and glucose.

✓ **DO** eat regular, well-balanced meals with the amount of carbohydrates that your doctor or dietitian approved.

✓ **DO** take your insulin or other diabetic medicine as prescribed.

✓ **DO** check your blood sugar level according to the schedule that your doctor gave you.

✓ **DO** keep sugar pills, fruit juice, or hard candy handy.

✓ **DO** be aware of symptoms of hypoglycemia.

✓ **DO** eat enough carbohydrates before exercise and snack during exercise if needed.

✓ **DO** eat snacks as soon as your sugar level is too low or you get symptoms.

✓ **DO** explain to people with whom you live and work that you have diabetes and how to inject

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glucagon if you lose consciousness.

✓ **DO** call your doctor if you have hypoglycemic symptoms. Your medicine doses may need adjusting.

⃠ **DON'T** wait too long between meals.

⃠ **DON'T** exercise without eating enough carbohydrates.

⃠ **DON'T** ignore symptoms of hypoglycemia or put off treating hypoglycemia. Hypoglycemia can lead to coma and brain damage.

⃠ **DON'T** become discouraged if you have type 1 diabetes and it takes time to adjust your insulin dose to allow exercise.

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FOR MORE INFORMATION

Contact the following source:

- American Diabetes Association Tel: (800) 342-2383 **Website: http://www.diabetes.org**

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MANAGING YOUR

HYPOPITUITARISM

What Is Hypopituitarism?

Hypopituitarism, or underactive pituitary gland, occurs when the pituitary gland doesn't produce enough hormones. It's a rare medical disorder. The pituitary, located below the brain, is called the master gland because it helps control other glands that also produce hormones. These other glands include the thyroid, adrenals, and sex organs. This disorder can affect just one other gland, a number of others, or all others, with effects that may be gradual or sudden and dramatic. The pituitary is important for regulating water balance, blood pressure, sexual function, stress responses, and basic metabolism. In hypopituitarism, these hormone systems don't work as well as they should.

What Causes Hypopituitarism?

The many causes include pituitary tumors or other brain tumors, brain infections, pituitary bleeding, trauma, pituitary surgery, stroke, congenital malformations, rare hereditary conditions, and radiation to the brain for tumors.

What Are the Symptoms of Hypopituitarism?

Some people have no symptoms until a stressful situation occurs that requires higher than usual levels of hormones. Others have symptoms that start suddenly. These symptoms include headache, blurred vision, and increased sensitivity to light with neck stiffness.

Symptoms depend on the organ system that is affected. An affected thyroid gland may cause you to feel weak and tired, become constipated, feel bloated, and gain weight. Affected ovaries may cause changes in periods, vaginal dryness, and painful intercourse. Affected testicles may cause problems in getting an erection. Affected adrenal glands may cause weakness, dizziness

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when standing, feeling sick to the stomach, and pain in the belly (abdomen). Children with hypopituitarism grow slowly.

How Is Hypopituitarism Diagnosed?

The doctor will ask questions and do a physical examination. The doctor will take samples of blood and urine to measure hormone levels. The doctor may also prescribe medicine to see whether these hormone levels change after taking medicine. A special imaging test called magnetic resonance imaging (MRI) may be done of the pituitary to see if it has changed.

How Is Hypopituitarism Treated?

Treatment is based on the cause of the hypopituitarism. The doctor will prescribe medicine to replace each hormone that the body doesn't make. People with hypopituitarism may have to take medicine for the rest of their lives. Taking the medicine can stop the symptoms from happening again. Surgery may be necessary if abnormal growths in the pituitary gland or nearby tissues of the brain are causing hypopituitarism.

DOs and DON'Ts in Managing Hypopituitarism:

✓ **DO** take your medicine as prescribed.

✓ **DO** see your doctor regularly to make sure that your hormone levels are normal.

✓ **DO** make sure that you understand how to use the medicine.

✓ **DO** wear a medical alert bracelet showing that you have hypopituitarism.

✓ **DO** call your doctor if you have a fever, nausea, or vomiting or if you feel weak or dizzy.

✓ **DO** ask your doctor about purchasing a home emergency treatment kit.

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⦸ **DON'T** stop taking your medicine without informing your doctor.

⦸ **DON'T** leave home without your emergency treatment kit, if you have one.

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FOR MORE INFORMATION

Contact the following source:

- American Association of Clinical Endocrinologists Tel: (904) 353-7878 **Website:** **http://www.aace.com**

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CARING FOR YOUR CHILD WITH

HYPOSPADIAS

What Is Hypospadias?

The urethra is the tube that takes urine from the bladder out of the body through the penis. Hypospadias is a condition, present at birth, that occurs when a boy's urethra is too short. The urethra opens along the shaft of the penis (usually underneath) rather than at the tip (head) of the penis. Hypospadias can be mild to severe, depending on where the urethra opens.

It's fairly common, occurring in about 1 in 250 to 300 male babies in the United States.

What Causes Hypospadias?

The cause is unknown, but genetic, endocrine, and environmental factors may be involved.

What Are the Symptoms of Hypospadias?

The opening of the urethra isn't at the head of the penis. It's usually near the head but can be at the middle or bottom of the penis. Some males also have a curved penis when erect, have abnormal spraying of urine, and may need to sit down to urinate.

How Is Hypospadias Diagnosed?

The doctor makes a diagnosis from the physical examination. The doctor may suggest seeing a urologist (specialist in urinary problems).

How Is Hypospadias Treated?

Surgery is the usual treatment. The doctor makes a new opening for the urethra in the head of the penis. Surgery is best done early, between 6 and 12 months of age. However, surgery can also be done on adults.

Surgery isn't major. Most boys go home the day they have the surgery. They will have a

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catheter in the penis. A catheter is a plastic tube that drains urine. The urine normally has blood in it. The doctor may prescribe medicine for pain and antibiotic medicine to prevent infection.

Most catheters are removed in 10 days. Usually two checkups are needed after surgery. After surgery, a normal future sex life and the ability to father children are expected.

If hypospadias isn't treated, problems with toilet training, sex in adulthood, and urethral strictures and fistulas may occur.

DOs and DON'Ts in Managing Hypospadias:

✓ **DO** tell your doctor about your child's medical problems.

✓ **DO** use two diapers after surgery, one to collect stool and one to collect urine from the catheter.

✓ **DO** keep your child's penis clean. If stool gets on the wound, rinse the area with clear water.

✓ **DO** call your child's doctor right away if after surgery your child has fever, pus coming from the penis, no urine coming from the penis for more than 1 hour, or urine squirting from any part on the penis.

✓ **DO** call your doctor right away or go to the emergency room if after surgery your child has bleeding from his penis that doesn't stop.

⦸ **DON'T** have your child circumcised without your doctor's OK.

⦸ **DON'T** let your child straddle toys such as a tricycle or bouncer without your doctor's OK.

⦸ **DON'T** give your child a bath without your doctor's OK.

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⦸ **DON'T** try to move your child's catheter.

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FOR MORE INFORMATION

Contact the following sources:

- Hypospadias and Epispadias Association **Website: http://www.heainfo.org**
- American Society for Reproductive Medicine Tel: (205) 978-5000 **Website: http://www.asrm.org**

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MANAGING YOUR

HYPOTHERMIA

What Is Hypothermia?

Hypothermia is abnormally low body temperature. Normal human body temperature is about 98.6° F. People with hypothermia have temperatures below 95° F. It occurs when the body loses heat faster than it can produce it. The heart, nervous system, and other organs cannot work correctly. It's a medical emergency.

What Causes Hypothermia?

Of the many causes, the most common is exposure to cold weather or cold water without proper protection. Wet clothes or skin, windy conditions, and exposed skin contribute to temperature loss. Boating accidents can lead to immersion in cold water and hypothermia. Drinking alcohol is often involved. Certain medical conditions and drugs can contribute to hypothermia. Very small children and the elderly are especially at risk for hypothermia, from poor heating in the home during the winter.

What Are the Symptoms of Hypothermia?

Symptoms are feeling cold, constant shivering, goosebumps, blue lips, and the feeling of not being able to get warm. As the body temperature falls, shivering stops and people become confused, sleepy, and clumsy. They may have slurred speech, mumbling, and stumbling. People don't usually realize that they need help. Babies can have bright red, cold skin and very low energy. The heart rate slows and may become irregular. Complications include frostbite, gangrene, chilblains, and trench foot.

How Is Hypothermia Diagnosed?

The doctor suspects hypothermia when someone is found in a cold environment. A special

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thermometer that can measure low body temperatures, usually available in hospital emergency departments, can confirm the diagnosis. Other tests to rule out damage to vital organs include electrocardiography, laboratory tests, and X-rays.

How Is Hypothermia Treated?

Until medical care is available, people should be moved out of the cold and rewarmed. Wet clothes should be removed and replaced with dry clothes. Cut away clothing if needed to avoid too much movement and delay in treatment. Use layers of dry blankets or coats for warming. Warm, noncaffeinated beverages can be given. People should be placed near a safe heat source, and body heat can be shared. However, don't apply direct heat such as hot water or a heating pad. Avoid wind and draft exposure. The confused or unconscious person should receive emergency medical care. This includes blood rewarming, warm intravenous fluids, and airway rewarming.

DOs and DON'Ts in Managing Hypothermia:

✓ **DO** dress correctly for cold weather. Remember the wind chill effect for cold weather exposure.

✓ **DO** take extra care with the elderly and small children.

✓ **DO** have enough caloric and fluid intake.

✓ **DO** stay alert for dangerous weather situations and plan accordingly.

✓ **DO** replace wet clothing with dry clothing as soon as possible.

✓ **DO** get out of cold water immediately. A few minutes can be deadly!

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✓ **DO** call for medical assistance if a person seems hypothermic and confused or someone with a medical condition (such as diabetes) is hypothermic.

⃠ **DON'T** drink alcohol before or during cold exposure.

⃠ **DON'T** underestimate the effect of wind and weather conditions.

⃠ **DON'T** go boating alone on cold water.

⃠ **DON'T** ignore your body's signals that you're getting cold.

⃠ **DON'T** travel in remote areas during cold weather without telling someone.

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FOR MORE INFORMATION

Contact the following source:

- National Heart, Lung, and Blood Institute Information Center Tel: (301) 592-8573 **Website: http://www.nhlbi.nih.gov**

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MANAGING YOUR

HYPOTHYROIDISM

What Is Hypothyroidism?

Hypothyroidism is a disorder of the thyroid gland, which is an endocrine gland in your neck located just below the Adam's apple. The thyroid produces hormones (thyroxine [or T_4] and triiodothyronine [or T_3]). These hormones affect how the body works (e.g., control metabolism). In hypothyroidism, the gland doesn't make enough thyroid hormone. Hypothyroidism affects both sexes. It can occur at any age but is more common in adult women. Once a person has developed hypothyroidism, the condition is usually permanent.

What Causes Hypothyroidism?

Hypothyroidism is usually caused when the body makes antibodies (proteins that are part of the immune system) against its own thyroid gland. This form is called an autoimmune disease. It can also occur after treatment for hyperthyroidism (overactive thyroid) and as a side effect of some medicines.

What Are the Symptoms of Hypothyroidism?

Mild hypothyroidism may not cause symptoms. One person will probably not have all the symptoms but may have several of the following ones.

Poor appetite and difficulty with bowel movements (constipation) may lead to gaining or losing weight. Anemia may develop. Becoming pale, feeling cold and unable to sweat, and often feeling tired are possible.

Problems with mental abilities may include poor memory and feeling depressed. Trouble sleeping at night and numbness and tingling in hands and feet may occur.

Hair may become coarse, thin, or grow slowly. The voice may get deeper and hoarse. Some

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people may feel the effects in other parts of the body. They may have shortness of breath and changes in heart rate. Fluid may be retained, especially around the eyes. Women may have problems with periods. Both men and women may have less interest in sex. In severe hypothyroidism, the tongue may become enlarged (macroglossia) and the skin may look darkened and rough (hyperkeratosis).

How Is Hypothyroidism Diagnosed?

The doctor will do a complete physical examination and measure levels of thyroid hormones in the blood.

How Is Hypothyroidism Treated?

Medicine can replace hormones that your body doesn't make. It is inexpensive, very effective, and available in many doses to properly treat each patient. The goal is to provide the body with enough hormone so that it works normally.

The medicine, called synthetic thyroid hormone or levothyroxine, should be taken daily because the body needs a new supply each day. Regular blood tests will ensure the right dose. The right dose of the synthetic hormone has no side effects. Doses that are too high may cause palpitations, nervousness, shakiness, bone loss, and increased bowel movements. These symptoms should prompt blood tests to check whether the dose should be changed.

Patients should start feeling better within a few weeks after starting thyroid medicine.

DOs and DON'Ts in Managing Hypothyroidism:

✓ **DO** follow your doctor's advice.

✓ **DO** see your doctor regularly to check hormone levels.

✓ **DO** contact your doctor if your condition changes or new problems develop.

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✓ **DO** let your doctor know if you become pregnant or want to get pregnant.

✓ **DO** keep your weight within normal limits.

✓ **DO** stay as active as possible.

⃠ **DON'T** stop taking your medicine because you feel better, unless your doctor says it's ok.

Hypothyroidism usually needs lifelong treatment.

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FOR MORE INFORMATION

Contact the following sources:

- American Association of Clinical Endocrinologists Tel: (904) 353-7878 **Website:** **http://www.aace.com**
- Thyroid Foundation of America Tel: (800) 832-8321 **Website:** **http://www.allthyroid.org**

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MANAGING YOUR

IDIOPATHIC PULMONARY FIBROSIS

What Is Idiopathic Pulmonary Fibrosis?

Idiopathic pulmonary fibrosis (IPF) is a disease of the lungs that causes scarring (fibrosis). Fibrosis can build up so that lung function is impaired and not enough oxygen can get to body tissues. Men and women are affected equally. Most people are diagnosed at 50 to 60 years old. IPF is not contagious.

What Causes IPF?

The cause is unknown. In a few cases, heredity appears to play a part.

What Are the Symptoms of IPF?

Early symptoms include a dry cough and shortness of breath (dyspnea). Later, dyspnea becomes the major problem. Activities, such as climbing stairs, walking short distances, and dressing, become hard and sometimes almost impossible. Enlargement of the fingertips (clubbing) may develop. The body has difficulty fighting infections. In advanced stages, people may need oxygen constantly. Most people live an average of 4 to 6 years after diagnosis.

How Is IPF Diagnosed?

The doctor may suspect the diagnosis from your symptoms and the physical exam and medical history.

The doctor will order additional tests: chest x-ray, computed tomography (CT) of the chest, blood tests, and pulmonary (lung) function tests. Bronchoscopy and lung biopsy may also be done. In bronchoscopy, the doctor puts a long, narrow, flexible, lighted tube (bronchoscope) into the lungs.

In a biopsy, small pieces of lung are studied to see how much inflammation and fibrosis the

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lungs have.

How Is IPF Treated?

Most people need lifelong treatment, and a lung specialist is usually involved in care.

The goals of treatment are to reduce lung inflammation and stop fibrosis. Once scar tissue forms, the lung cannot return to normal. Drugs are used as treatment. Prednisone and cyclophosphamide, together or alone, are drugs commonly used. Oxygen improves breathing. Lung transplantation is an option in people who do not respond well to other treatments.

DOs and DON'Ts in Managing IPF:

✓ **DO** try to continue your normal activities, including work and exercise but avoid overexertion.

✓ **DO** get emotional and psychological support if you get depressed.

✓ **DO** call your doctor if you get short of breath or have symptoms of an infection (e.g., fever, chills, sweats, cough producing phlegm).

✓ **DO** call your doctor if you have side effects from medicines.

⊘ **DON'T** miss doctor appointments.

⊘ **DON'T** be afraid to ask for second opinions from lung doctors specializing in IPF.

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FOR MORE INFORMATION

Contact the following sources:

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• National Heart, Lung, and Blood Institute Tel: (800) 575-9355 **Website:**

http://www.nhlbi.nih.gov

• American Lung Association Tel: (212) 315-8700, (800) 586-4872 **Website:**

http://www.lungusa.org

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MANAGING YOUR

IMMUNE THROMBOCYTOPENIC PURPURA

What Is Immune Thrombocytopenic Purpura?

Immune thrombocytopenic purpura (ITP) is a blood-clotting disorder in which the immune system attacks and destroys platelets. It's also called idiopathic thrombocytopenic purpura. Platelets are tiny, irregularly shaped cell-like particles in blood. They are important in blood clotting. People of any age can have ITP, but it's most common in children 2 to 5 years old and adults 20 to 50 years old, more women than men.

What Causes ITP?

The exact cause is unknown. However, ITP is an autoimmune illness, which means that the body's own immune system causes the spleen to destroy platelets. The spleen is an organ that removes old platelets from the blood. Antibodies attach to the platelets, and the spleen destroys the platelets that have the antibodies. In children, a viral infection (such as mumps or flu) often causes ITP, which usually goes away by itself. In adults, ITP isn't generally related to a virus, but people with human immunodeficiency virus (HIV) infection can be more prone to getting it. ITP in adults ranges from mild to severe and tends to be chronic (longer-lasting).

What Are the Symptoms of ITP?

The most common symptoms are bleeding and easy or excessive bruising on the skin (purpura, ecchymoses). Others include bleeding gums, bloody stool (bowel movements), heavy periods, nosebleeds, and a rash of tiny red spots (petechial rash).

How Is ITP Diagnosed?

The doctor makes a diagnosis from the medical history and physical examination. Blood tests to measure the platelet count and to see if another illness is the cause are done. A hematologist

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(specialist in blood diseases) may in some cases take a sample of bone marrow from near the hip to check the cells under a microscope. The doctor may use computed tomography (CT) to look at the spleen and other organs.

How Is ITP Treated?

Treatment depends on how severe the symptoms are. Mild cases don't need treatment and get better on their own. Medicines called steroids are given if the platelet count is very low. If steroids don't work, another medicine (IVIG, or intravenous immune globulin) may be given into the vein. If these measures don't work, the spleen may need to be removed.

DOs and DON'Ts in Managing ITP:

✓ **DO** follow your doctor's directions, especially when taking pain medicine.

✓ **DO** tell your doctor about your other medical problems and your medicines, both prescription and over-the-counter.

✓ **DO** tell your doctor if you're pregnant.

✓ **DO** limit drinking of alcohol.

✓ **DO** shave with an electric razor and brush your teeth with a soft toothbrush to avoid trauma and bleeding.

✓ **DO** tell your dentist that you have ITP.

✓ **DO** call your doctor right away or go to the emergency room if you have severe bleeding or minor bleeding that doesn't stop in 5 minutes.

⦸ **DON'T** stop taking your medicine or change your dosage because you feel better unless your

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doctor tells you to.

⦸ **DON'T** take aspirin or medicines such as ibuprofen or naproxen. These can increase your risk of bleeding.

⦸ **DON'T** play contact sports such as football without your doctor's OK.

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FOR MORE INFORMATION

Contact the following sources:

- National Organization of Rare Diseases Tel: (800) 999-6673 or (203) 746-6518 **Website: http://www.rarediseases.org**
- National Heart, Lung, and Blood Institute Information Center Tel: (301) 592-8573 **Website: http://www.nhlbi.nih.gov**

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MANAGING

IMPETIGO

What Is Impetigo?

Impetigo is a very common skin infection. It occurs most often in babies and children. It spreads easily from one person to another, especially when they're crowded together. Brothers and sisters and people who play contact sports can often get it.

What Causes Impetigo?

Two kinds of bacteria called *Staphylococcus* (staph) and *Streptococcus* (strep) cause impetigo, separately or together. These bacteria normally live on the skin surface, but they can get into top layers of the skin and cause infection. Impetigo is more likely when skin is hurt, such as with scratches, scrapes, or insect bites.

Young children can spread it because hands carry bacteria and the children touch each other a lot and don't wash their hands.

What Are the Symptoms of Impetigo?

Impetigo starts with painless blisters, usually on the face, especially around the nose and mouth. Blisters fill with clear or yellow fluid, eventually burst open, and leave a gold crust. Blisters may itch or burn. They don't usually leave scars.

Rarely, impetigo can lead to kidney inflammation, with blood or protein in the urine.

How Is Impetigo Diagnosed?

The doctor will make a diagnosis from the look of the skin blisters and sores. Tests may be done to find out which bacteria are causing the infection. A swab may be used to take a sample of fluid inside a blister. Blood or urine tests may also be done to be sure that bacteria haven't caused a complication.

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How Is Impetigo Treated?

Impetigo should be treated quickly to keep it from spreading under the skin and preventing additional damage. If left untreated, impetigo can continue for weeks, and the bacteria may, in rare cases, damage the kidneys.

Impetigo responds rapidly to medicine plus soaking and washing. Most cases go away within 7 to 10 days. Antibiotics, given as skin creams or pills, will kill the bacteria. Crusts that remain after blisters burst should be removed. Blisters are first soaked with a wet cloth. Then the area is washed with anti-bacterial soap.

DOs and DON'Ts in Managing Impetigo:

✓ **DO** keep your skin clean by hand washing. Maintain good hygiene. Bathe or shower at least once daily. Wash your whole body with an antibacterial soap.

✓ **DO** thoroughly wash skin scrapes and cuts and insect bites.

✓ **DO** keep toys and other objects that children play with clean.

✓ **DO** tell your doctor if you don't feel well while taking medicine.

✓ **DO** trim children's nails if scratching is a problem.

✓ **DO** call your doctor if you're not better in 7 to 10 days, you have persistent fever even with treatment, family members become infected, or your urine has blood in it.

⦸ **DON'T** scrape or scratch blisters.

⦸ **DON'T** have close contact with other people while you still have blisters.

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⦸ **DON'T** shave infected areas or anywhere that is red and inflamed.

⦸ **DON'T** share washcloths, towels, or beds while you have impetigo.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Dermatology Tel: (866) 503-SKIN (503-7546) **Website:** **http://www.aad.org**

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CARING FOR YOUR CHILD WITH

IMPETIGO

What Is Impetigo?

Impetigo is a very common, mild skin infection. It occurs most often in babies and children. It spreads easily from one person to another, especially when they're crowded together. Brothers and sisters and people who play contact sports can often get it.

What Causes Impetigo?

Two kinds of bacteria called *Staphylococcus* (staph) and *Streptococcus* (strep) cause impetigo, separately or together. These bacteria normally live on the skin surface, but they can get into top layers of skin and cause infection. Impetigo is more likely when skin is injured such as with scratching, scrapes, or insect bites.

Young children can spread it easily because they don't wash their hands that can have bacteria on them.

What Are the Symptoms of Impetigo?

Impetigo starts with painless blisters, usually on the face, especially around the nose and mouth. Blisters fill with clear or yellow fluid, eventually burst open, and leave a gold-color crust. Blisters may itch or burn. They don't usually leave scars.

Rarely, impetigo can lead to kidney inflammation, with blood or protein in the urine.

How Is Impetigo Diagnosed?

The doctor will make a diagnosis from the look of the skin blisters and sores on your child. Tests may be done to find out which bacteria are causing the infection. A swab may be used to take a sample of fluid inside a blister. Blood or urine tests may also be done in severe cases to be sure that bacteria haven't caused a complication.

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How Is Impetigo Treated?

Impetigo should be treated quickly to keep it from spreading under the skin and preventing complications such as kidney damage. If left untreated, impetigo can persist for weeks.

Impetigo responds rapidly to medicine plus soaking and washing. Most cases go away within 7 to 10 days. Antibiotics, given as skin creams or pills, will kill the bacteria. Crusts that are left after blisters burst should be gently removed. The blisters are first soaked with a wet cloth. Then the area is washed with antibacterial soap.

DOs and DON'Ts in Managing Impetigo:

✓ **DO** have your child avoid close contact with others with impetigo.

✓ **DO** apply a prescription antibiotic cream inside your child's nose to help prevent impetigo from coming back if your child has frequent impetigo infections. Bacteria live inside the nose and can be carried on fingers.

✓ **DO** keep your skin clean and prevent passing on the infection by hand washing. Use an antibacterial soap.

✓ **DO** bathe your child at least once daily.

✓ **DO** thoroughly wash skin scrapes, cuts, and insect bites on your child.

✓ **DO** keep toys and other objects that your children play with clean.

✓ **DO** tell your doctor if your child doesn't feel well while taking the antibiotic medicine.

✓ **DO** trim your child's nails if scratching is a problem.

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✓ **DO** call your doctor if your child isn't better in 7 to 10 days, your child has a temperature of 101° F even with treatment, other family members become infected, or your child's urine has blood in it.

⦸ **DON'T** let your child scrape or scratch the blisters.

⦸ **DON'T** let your child with blisters have close contact with others.

⦸ **DON'T** let your child with impetigo share washcloths, towels, or beds.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Dermatology Tel: (847) 330-0230, (866) 503-7546 **Website: http://www.aad.org**

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UNDERSTANDING

INFERTILITY

What Is Infertility?

The inability to become pregnant and have children affects 8% to 18% of people in the United States. Usually, 80% to 90% of normal couples become pregnant during 1 year of attempting to do so. Infertility usually means being unable to get pregnant after 1 year of trying.

Infertility may be divided into primary and secondary on the basis of reproductive history. Women who were never pregnant are in the primary group. Women who were pregnant more than 1 year before are in the secondary group. Slightly more than half of people with infertility fall into the primary group. It's harder to become pregnant after the age of 30.

What Causes Infertility?

About 35% to 50% of infertility is due to a male factor such as low sperm count, abnormal sperm shape, or abnormal sperm motion (motility).

About 50% to 60% of infertility is related to female conditions. These conditions include fallopian tube disease, disorders related to ovaries (ovulation), and factors related to the uterus or cervix. The reason for infertility of the other 10% to 20% of couples isn't known (idiopathic).

What Are the Symptoms of Infertility?

The symptom is being unable to get pregnant after 1 year of regular intercourse without contraception.

How Is Infertility Diagnosed?

Testing to find a cause ranges from simple things, such as getting a sperm count, to much more complicated testing. This testing includes blood tests (to measure female hormones, such as estrogen, progesterone, and follicle-stimulating hormone), ultrasound of the uterus and ovaries, and

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even laparascopic surgery to look at the reproductive organs. Before testing, it is important to understand what's involved in an infertility evaluation, including the methods, how long it will take, the limits, and the cost.

How Is Infertility Treated?

Treatment is based on finding out the reasons for infertility and overcoming them so that it's possible to get pregnant. Ways to do this include lifestyle changes (such as losing or gaining weight), medicines (for medical conditions), hormones, and drugs, such as clomiphene citrate, to make the ovaries start to release eggs. Surgery (such as to unblock fallopian tubes) and other methods, such as intrauterine insemination and in vitro fertilization, may also be tried.

DOs and DON'Ts in Managing Infertility:

✓ **DO** talk to your doctor if you're worried about getting pregnant.

✓ **DO** continue to have intercourse according to your usual schedule.

✓ **DO** eat a healthy diet and exercise in moderation. Excessive exercise and weight loss may cause fertility problems by interfering with ovulation and menses.

⃠ **DON'T** give up: up to 85% of infertile couples may be helped.

⃠ **DON'T** let the process of trying to get pregnant get in the way of the rest of your relationship.

⃠ **DON'T** smoke or drink alcohol if you are trying to get pregnant.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website: http://www.acog.org**
- WebMD **Website: http://www.webmd.com**
- U.S. Department of Health and Human Services **Websites: http://womenshealth.gov http://www.4women.gov/faq/infertility.cfm**

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MANAGING YOUR

INFLUENZA

What Is Influenza?

Influenza, or the flu, is a respiratory viral infection. It begins suddenly, lasts for 7 to 10 days, and goes away. Most people recover completely. However, the elderly, the very young, and the immunocompromised can have a more severe course and even die from complications.

Influenza spreads quickly. People get it mostly in fall and winter.

In the USA, over 200,000 people are hospitalized yearly and more than 30,000 die from influenza.

What Causes Influenza?

Influenza is caused by viruses. These are classified as type A, B, or C. Type A is most common.

People get the virus that causes influenza by breathing in small droplets that an infected person has coughed or sneezed into the air, or from touching something that an infected person touched. It's similar to the common cold but worse.

What Are the Symptoms of Influenza?

Symptoms come on suddenly. They usually start 24 to 48 hours after exposure to the flu virus. The worst symptoms and fever usually last 3 to 5 days. They include high temperature (as high as 104° F), chills, muscle aches, feeling very weak or tired, headache, eye pain in bright light, coughing, sneezing, sore throat, runny nose, and upset stomach (more in children than adults). A cough and feeling very weak and tired can last for up to 6 weeks.

How Is Influenza Diagnosed?

The doctor will make a diagnosis from the symptoms, especially during fall and winter. At other times of the year, the doctor may do tests to confirm the diagnosis. Testing may involve taking a

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sample of liquid from a runny nose or using a blood sample. The doctor may also order a chest x-ray to check for pneumonia (a complication).

How Is Influenza Treated?

The best treatment is rest. Influenza cannot be cured with antibiotics, but other medicines can control symptoms, and others (antivirals) can shorten its duration. For discomfort, nonaspirin medicines, such as acetaminophen and ibuprofen, cough syrups, and decongestants are used. Don't give aspirin to a child younger than 16 because of the risk of the serious Reye's syndrome that can occur with aspirin in the young.

Warm baths or heating pads can help muscle aches. A cool mist vaporizer may thin secretions, and gargling with warm salt water or mouthwash may ease a sore throat. Drinking lots of fluids is important.

DOs and DON'Ts in Managing Influenza:

✓ **DO** get a flu shot every year.

✓ **DO** drink plenty of fluids (at least 8 glasses daily) to thin lung secretions. Small children should avoid milk (it can thicken secretions).

✓ **DO** stop smoking to reduce the risk of complications.

✓ **DO** rest as much as possible. Continue to rest for 2 or 3 days after the fever goes away.

✓ **DO** wash hands often and have those who care for you wash their hands also. Throw away all tissues quickly.

✓ **DO** call your doctor if your fever or cough worsens, you get shortness of breath or chest pain, you cough up bloody sputum, or you have neck pain or stiffness.

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✓ **DO** call your doctor if you have pain with a thick discharge from the ears or sinuses.

⃠ **DON'T** go to work or school if you think you have the flu. Avoid spreading the virus to others.

⃠ **DON'T** let anyone with a chronic illness or poor immune system (such as those with AIDS or getting chemotherapy) come near a person with the flu.

⃠ **DON'T** share glasses or eating utensils.

⃠ **DON'T** give aspirin to a child younger than 16.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- Infectious Disease Society of America Tel: (703) 299-0200 **Website:** **http://www.idsociety.org**
- National Institute for Allergy and Infectious Diseases Tel: (301) 496-5717, (866) 284-4107 **Website:** **http://www.niaid.nih.gov**
- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website:** **http://www.cdc.gov**
- WHO Collaborating Center for Influenza CDC Influenza Branch Tel: (800) 232-4636 **Website:** **www.cdc.gov/flu/**

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GETTING A

FLU VACCINATION

What Is Influenza?

Influenza (flu) is a very contagious respiratory viral infection. Each year in the United States, it causes an average of 36,000 deaths and 200,000 hospitalizations. The best way to protect against the flu is to get yearly vaccinations.

Why Vaccinate Against the Flu?

Flu symptoms are severe and cause people to miss days of work or school. Flu stresses the body. When serious bacterial infections occur with the flu, the body can be overwhelmed and death can result, especially in elderly and very young people. Because of these things, it's important to prevent the flu by vaccination. It reduces the chance of getting the flu by up to 80%.

What Is the Flu Vaccine?

Two kinds of vaccines are available. The flu shot contains an inactivated vaccine (killed virus) to protect against that specific kind of live virus. Each year, the virus can change, so a new vaccine must be made for the new virus strain.

The nasal mist vaccine contains live, weakened flu viruses. People with weakened immune systems or certain health conditions shouldn't get this vaccine.

Who Should Get Vaccinated?

Flu vaccine is generally beneficial in all age groups except those younger than 6 months. Certain people are especially at high risk and should get vaccinated each year. These people are adults 50 and older, pregnant women, children 6 months to 18 years old, and people with chronic medical conditions (such as diabetes, lung disorders such as asthma, heart disease, HIV/AIDS). They can have serious complications from flu, such as pneumonia. Others who need vaccination are

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people living in nursing homes or long-term care facilities, health care workers, people in contact with those high-risk groups, and household contacts and caregivers of babies younger than 6 months.

Who Should Not Get Vaccinated?

Some people should check with a doctor about vaccination. These include people who have a severe allergy to eggs, had a severe reaction to a flu vaccination, or had Guillain-Barré syndrome within 6 weeks of getting vaccinated. Babies younger than 6 months and people who are sick and feverish shouldn't get vaccinated.

What Are the Side Effects of Flu Vaccinations?

Side effects from the shot aren't common. Minor ones include soreness, redness, or swelling where the shot was given, low-grade fever, feeling sick, and muscle aches. Rarely, flu vaccination can cause serious problems, such as severe allergic reactions.

The nasal spray vaccine can cause runny nose, wheezing, headache, vomiting, muscle aches, sore throat, cough, and fever.

DOs and DON'Ts in Getting Flu Vaccinations:

✓ **DO** get a flu shot every year.

✓ **DO** remember that side effects of the shot may last for a day, but the flu can last 2 to 3 weeks and can cause serious complications (pneumonia, ear infections, sinus infections, other lung problems).

✓ **DO** put a warm compress on the injection site for soreness or swelling.

✓ **DO** give acetaminophen or ibuprofen for headache or low-grade fever after a flu shot.

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✓ **DO** remember that you cannot catch the flu from the shot. However, the nasal spray flu vaccine is made from live viruses, so it may cause mild flu-like symptoms (runny nose, headache, vomiting, muscle aches, fever).

⃠ **DON'T** give aspirin to children younger than 16, to avoid the dangerous Reye's syndrome.

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FOR MORE INFORMATION

Contact the following sources:

- Infectious Diseases Society of America Tel: (703) 299-0200 **Website: http://www.idsociety.org**
- National Institute of Allergy and Infectious Diseases Tel: (301) 996-5717 **Website: http://www3.niaid.nih.gov**
- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website: http://www.cdc.gov**
- National Influenza Center Tel: (510) 540-2815
- WHO Collaborating Centre for the Surveillance, Epidemiology and Control of Influenza CDC Influenza Branch Tel: (800) 232-4636 **Website: http://www.cdc.gov/flu/**

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MANAGING YOUR

INGROWN TOENAIL

What Is an Ingrown Toenail?

An ingrown nail occurs when a toenail (or fingernail) has a sharp end that grows down and burrows into the flesh of the finger or toe. Any finger or toe can have an ingrown nail, but usually the big toes are affected. Untreated, ingrown toenails can lead to serious skin and bone infections.

What Causes an Ingrown Toenail?

Causes include wearing shoes that are too small, using the wrong method to trim the nail, bone abnormalities, or a toe injury such as stubbing the toe. People who are elderly, who have diabetes, or who have problems with blood circulation in their legs have greater chances of having ingrown toenails. This is also true of children and teenagers who may outgrow their shoes. Nails tend to thicken with age, which leads to elderly people having ingrown toenails.

What Are the Symptoms of an Ingrown Toenail?

Symptoms include a hard, swollen, and tender toe around the nail. This area becomes red and very sore and feels warm. Skin grows over the ingrown nail. If the toe becomes infected, pus or fluid may drain from the toe.

How Is an Ingrown Toenail Diagnosed?

The doctor makes a diagnosis by looking at and examining the nail and toe. If the ingrown nail is infected, the doctor may take a sample of pus or fluid and send it for study to find out which bacteria is causing the infection.

How Is an Ingrown Toenail Treated?

If the problem isn't severe, soaking the foot or hand in warm, soapy water several times each day

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may solve the problem. Lifting the edge of the ingrown nail gently and putting some cotton under the nail to separate it from the toe may help. For a severely infected toe or ingrown toenails that keep coming back, the doctor may remove part of nail. The doctor will numb the toe and use scissors to cut away the ingrown part of the toenail. A podiatrist, a doctor who specializes in foot problems, can also remove the toenail.

The doctor will prescribe antibiotic medicine for an infected toe with an ingrown nail. People with diabetes can have serious complications from ingrown toenails, such as sores (foot ulcers), which could need surgery.

DOs and DON'Ts in Managing an

Ingrown Toenail:

✓ **DO** wear clean socks and open-toed shoes while your toe heals.

✓ **DO** clean and dry the areas around your nails after a bath or shower. Always keep your feet clean.

✓ **DO** call your doctor if you develop a fever or red streak going from your foot up your leg. You may have a serious infection such as thrombophlebitis or cellulitis.

✓ **DO** wear shoes that fit well (not too short or too tight).

✓ **DO** cut your toenails properly. Cut straight across with no rounded corners. Don't cut them too short. If you don't want to or can't cut your toenails yourself, go to a podiatrist.

⦸ **DON'T** cut into your nails on the side so that you have a sharp edge. The edge may grow into the toe around the nail.

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⦸ **DON'T** pick at your toenails or tear them off.

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FOR MORE INFORMATION

Contact the following sources:

• American Academy of Family Physicians Tel: (800) 274-2237 **Website:**

http://familydoctor.org

• American College of Foot and Ankle Surgeons Tel: (800) 421-2237 **Website:**

http://www.acfas.org

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MANAGING YOUR

INGUINAL HERNIA

What Is an Inguinal Hernia?

An inguinal hernia is a bulge in the groin area. Intestines and fat slip through the muscle wall into a sac formed by the hernia. Both men and women can have an inguinal hernia, and at any age. However, these hernias happen more often in males than females.

What Causes an Inguinal Hernia?

The cause is a weakness in the muscle wall or connective tissue.

What Are the Symptoms of an Inguinal Hernia?

Sometimes a bulge occurs without other symptoms. Sometimes, people feel an ache or sense of fullness in the groin. Usually, people can push the bulge back in. Bulges might go back in on their own when people lie down. Babies have a bulge that comes and goes with straining, crying, coughing, or standing. The bulge can be pushed back into the baby's stomach. Complications include a hernia becoming incarcerated or strangulated. Incarcerated hernias have part of the intestine, some fat, or an ovary stuck in the sac. Strangulated means that tissues in the hernia become twisted. It can lead to gangrene, which means that tissues in the hernia die because they have no blood supply.

If a hernia becomes incarcerated, it can't be pushed back. It's an emergency.

How Is an Inguinal Hernia Diagnosed?

The doctor makes a diagnosis from a medical history and physical examination done in sitting and standing positions and when coughing.

How Is an Inguinal Hernia Treated?

Surgery is the treatment of choice. It should be done as soon as possible, even in very young ba-

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bies, if the hernia is painful or cannot be pushed back in. The operation can be standard (with a regular incision) or laparoscopic. In laparoscopic surgery, the doctor uses a thin tube that goes through a small cut in the skin. The doctor can see through the tube, which has a light at its tip, to the inside of the body.

DOs and DON'Ts in Managing

an Inguinal Hernia:

✓ **DO** use pain medicine after surgery as directed by your doctor.

✓ **DO** walk around and even climb stairs if your doctor approves, but don't overdo it.

✓ **DO** be careful that you don't get constipated. Eat enough high-fiber foods and drink eight glasses of liquids daily. You may need a mild laxative (such as milk of magnesia).

✓ **DO** shower if you wish, with dressings on or off after your doctor says that it's OK. The strips of tape across the incision can get wet. After you dry yourself, replace dressings with clean, dry ones.

✓ **DO** have sex when your doctor says you can.

✓ **DO** call your doctor if you have unusual symptoms or if your scrotum swells.

✓ **DO** call your doctor if the incision becomes red, swollen, or has drainage. Call if you have a temperature higher than 100° F.

✓ **DO** keep your weight down.

✓ **DO** follow safety instructions when you do heavy lifting.

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✓ **DO** see your doctor if you have a long-lasting cough or allergies.

⃠ **DON'T** lift anything heavier than 5 pounds after surgery. Ask someone to do it for you.

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FOR MORE INFORMATION

Contact the following sources:

• American Gastroenterological Association Tel: (301) 654-2055 **Website:**

http://www.gastro.org

• American Pediatric Surgical Association Tel: (847) 480-9576 **Website:**

http://www.eapsa.org

• Society for Surgery of the Alimentary Tract Tel: (978) 526-8330 **Website:**

http://www.ssat.com

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MANAGING YOUR

INSOMNIA

What Is Insomnia?

Insomnia is trouble sleeping. It's very common. About 80 million American adults have sleep problems.

Primary insomnia can involve less sleep, less restful sleep, interrupted sleep, and delay in falling sleep. Secondary insomnia is usually related to a psychiatric disorder (depression, anxiety), medical condition, or using alcohol, caffeine, or illicit drugs (amphetamines, cocaine).

Nightmares often occur early in sleep and are usually remembered. Night terrors, which children often have, occur later and aren't remembered. Other conditions affecting sleep include enuresis (bedwetting) and sleepwalking.

What Causes Insomnia?

Insomnia is most common in elderly people. It may be related to a crisis, a medical condition, such as heart disease, or an emotional or psychiatric problem, such as depression, anxiety, and schizophrenia. Medicines, cigarette smoking, and poor sleep habits lead to insomnia.

What Are the Symptoms of Insomnia?

Symptoms include trouble falling asleep or staying asleep, waking early in the morning, and daytime tiredness.

How Is Insomnia Diagnosed?

The doctor can identify insomnia by hearing about symptoms. Sometimes a sleep study is done to look at brain waves and sleeping pattern and to rule out disorders such as sleep apnea and restless leg syndrome. Measuring the total amount of sleep is not enough to diagnose insomnia. The quality of sleep is also important.

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How Is Insomnia Treated?

Treatments include reducing stress, by learning and practicing relaxation. For example, a warm bath, soft music, relaxation tapes, earplugs, eyeshades, and electric blanket may help. The doctor may prescribe medicine, usually used for a short time or just on certain nights. Sometimes, long-term treatment is needed. Prescription medicines include sedative and hypnotic drugs. They include zolpidem and benzodiazepines such as temazepam. They should be used temporarily because of the chance of addiction.

Herbal (melatonin and valerian root) and over-the-counter medicines are also used. Several over-the-counter drugs are available. Over-the-counter sleep aids and some herbal agents may have serious interactions with other drugs. The most commonly used sleep inducer is alcohol, but alcohol makes sleeping problems worse.

Diet is important. Caffeine or other stimulants shouldn't be taken late in the evening.

DOs and DON'Ts in Managing Insomnia:

✓ **DO** have regular bedtime routines. Try to go to bed the same time every night.

✓ **DO** exercise regularly, but not within 2 hours of going to bed.

✓ **DO** get up and do something relaxing if you cannot sleep after 20 to 30 minutes.

✓ **DO** take medicine for severe pain. Pain interferes with sleep.

✓ **DO** call your doctor if you sleepwalk, have night terrors, or snore too much.

✓ **DO** call your doctor if you have side effects from medicines.

✓ **DO** call your doctor if you have depression, anxiety, or mania.

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⦸ **DON'T** use sleeping pills given to you by a friend.

⦸ **DON'T** eat within 3 hours or drink liquids within 1 hour of bedtime.

⦸ **DON'T** read or watch TV in bed. Use the bedroom only for sleep.

⦸ **DON'T** go to bed until you feel sleepy.

⦸ **DON'T** take naps after the early afternoon.

⦸ **DON'T** drink alcohol, smoke, or use caffeine. They can disrupt sleep.

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FOR MORE INFORMATION

Contact the following source:

• National Center on Sleep Disorders Research Tel: (301) 435-0199 **Website:**

http://www.nhlbi.nih.gov/about/ncsdr

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MANAGING YOUR

INTERSTITIAL NEPHRITIS

What Is Interstitial Nephritis?

Kidneys get rid of waste products and balance body fluids. Each kidney has 1 million tiny filters called nephrons. A nephron is a tiny coiled tube with a bulb at one end. Nephrons take urine to the tube (ureter) connecting kidneys to the bladder.

Nephritis is inflammation (swelling) of nephrons. Interstitial nephritis means a disorder affecting spaces around nephrons. It can be acute or chronic.

What Causes Interstitial Nephritis?

Interstitial nephritis is usually caused by medicines, including antibiotics, anti-inflammatory drugs, and diuretics. Other drugs, as well as infections with bacteria and viruses, can also cause it. Rarely, it's associated with immune system disorders such as lupus, sarcoidosis and Sjögren's syndrome. Sometimes, the cause is unknown.

What Are the Symptoms of Interstitial Nephritis?

Symptoms include fever and rash. The urine may contain abnormal cells. These cells are eosinophils, a kind of white blood cell. Often, people may not have symptoms until kidney function is very poor. By then, symptoms of renal failure (weakness, nausea, itchiness, vomiting, leg swelling, and a metal taste in the mouth) occur. When infection is causing nephritis, people have fever, chills, low back pain, and urinary symptoms (burning, frequency, hesitancy, and bloody urine). Blood pressure may be high and sometimes hard to control.

How Is Interstitial Nephritis Diagnosed?

The doctor makes a diagnosis from the medical history, physical examination, and blood and urine tests. The doctor may use ultrasonography, which uses sound waves to get pictures of the

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kidneys. For an unclear diagnosis, the doctor may want a kidney biopsy. In a biopsy a special needle is inserted in the kidney and a small piece of kidney tissue is removed and examined with a microscope.

How Is Interstitial Nephritis Treated?

Treatment aims to fix failing kidneys and metabolic problems associated with kidney failure (high potassium, low calcium, and high phosphorus levels; low blood counts). A nephrologist (specialist in kidney disease) may help with care.

Treatment also tries to correct the underlying cause. If a drug is causing the acute disorder, the problem drug is stopped. Bacterial infections are treated with an antibiotic. If people don't respond to initial treatment, corticosteroids such as prednisone may be given. If corticosteroids don't work, stronger medications such as cyclophosphamide may be tried.

DOs and DON'Ts in Managing Interstitial Nephritis:

- ✓ **DO** know that most acute disorders get better in a few days after the problem drug is stopped.
- ✓ **DO** take your medicines as prescribed.
- ✓ **DO** understand that about one-third of people with the acute illness will need temporary dialysis.
- ✓ **DO** realize that people with persistent (chronic) illness usually have kidney failure and may need permanent dialysis.
- ✓ **DO** call your doctor if you see blood in your urine or you have chills, a fever, and low back pain.
- ✓ **DO** call your doctor if you get a rash after starting new medicine, you're allergic to penicillin

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or other antibiotics, or you have drug side effects.

⦸ **DON'T** miss follow-up doctor appointments. Your doctor needs to watch your blood levels and your response to medicines.

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Diabetes & Digestive & Kidney Diseases National Institutes of Health **Website: http://www.niddk.nih.gov/health/kidney/kidney.htm**
- National Kidney Foundation Tel: (800) 622-9010 **Website: http://www.kidney.org**

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MANAGING YOUR

INTERSTITIAL PULMONARY DISEASE

What Is Interstitial Pulmonary Disease?

Diffuse interstitial pulmonary disease is the name of a group of many different lung diseases with different causes and symptoms. However, all these diseases cause inflammation of the area around air sacs in the lungs. Inflammation often leads to scarring (fibrosis), and thus the lungs don't work well. These conditions are hard to treat because no cures are usually available. They are not contagious, and no vaccines can prevent them.

What Causes Interstitial Pulmonary Disease?

Often the cause is unknown. Breathing in irritating substances in the environment or workplace, taking certain medicines, radiation exposure, and inflammatory diseases outside lungs may be contributing factors.

What Are the Symptoms of Interstitial Pulmonary Disease?

Symptoms vary, but almost all these diseases cause shortness of breath and a dry cough that usually start slowly and get worse. Fingertips may appear clubbed.

Other symptoms may include chest pain, fever, coughing up blood, fatigue, and weight loss.

How Is Interstitial Pulmonary Disease Diagnosed?

The doctor uses a medical and job history and physical examination for the preliminary diagnosis.

When severe lung scarring is present, the doctor may hear crackling breath sounds, like the two pieces of Velcro being pulled apart.

The chest x-rays may show lung changes, including a honeycomb-like appearance. Chest computed tomography (CT), lung biopsy, and breathing tests may also be done. The biopsy sam-

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ples can be obtained by bronchoscopy, a test in which the doctor uses a lighted tube to look into the lungs.

How Is Interstitial Pulmonary Disease Treated?

Treatment depends on the specific cause.

In all cases, smoking should stop.

Inhalers may help for smoking-related lung disease. If the cause is something in the environment, that substance should be avoided. For example, wear protective breathing masks.

Antiinflammatory drugs such as prednisone (a steroid) may be helpful in some cases.

Unfortunately, treatment is not always effective and no drugs reverse lung scarring. Oxygen may help reduce shortness of breath and improve stamina. Lung transplantation is an option in people with progressive disease.

DOs and DON'Ts in Managing Interstitial Pulmonary Disease:

✓ **DO** get a flu shot each fall.

✓ **DO** get a pneumococcal pneumonia vaccination every 5 years.

✓ **DO** help your cardiovascular fitness by exercising.

✓ **DO** call your doctor if you think that you have a lung infection, because of a sudden worse cough, yellow or green phlegm, fever, chills, or increased shortness of breath.

✓ **DO** call your doctor if you have bloody sputum, chest pain, new ankle swelling, problems with medicines, or dusky-colored skin, fingertips, or lips.

⊘ **DON'T** expose yourself to substances thought to be responsible for your lung disease or en-

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vironmental pollutants.

⦸ **DON'T** go near people with respiratory infections.

⦸ **DON'T** smoke.

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FOR MORE INFORMATION

Contact the following source:

• American Lung Association Tel: (800) 586-4872, (212) 315-8700 **Website:**

http://www.lungusa.org

• National Heart, Lung, and Blood Institute Tel: (800) 575-9355 **Website:**

http://www.nhlbi.nih.gov

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CARING FOR YOUR CHILD WITH

INTUSSUSCEPTION

What Is Intussusception?

Intussusception is a serious disorder that involves the bowel—either the small or large intestine. Part of the intestine collapses into itself, so one part slips inside the other, like a telescope. The intestine becomes blocked. Food and fluids can't pass through. The blood supply to the intestines may also be cut off, which causes injury or death of that part of the intestine. Intussusception most often occurs in babies and children between the ages of 3 months and 6 years. It's two to three times more common in boys than girls. It's rare in adults.

What Causes Intussusception?

The cause of most cases is unknown. It sometimes occurs after an infection of the intestines. A noncancerous growth inside the bowel or in rare cases, cancer in the intestine can trigger it.

What Are the Signs and Symptoms of Intussusception?

Early in the illness, children may complain of stomach cramping. Babies start sudden, loud crying caused by pain in the abdomen (belly) and bring their knees up to their chest. The severe abdominal pain comes and goes. Children may also vomit and become pale and sweaty. As the intestinal blockage gets worse, blood and mucus can appear in the stool and the stomach may get swollen. Children may become very listless and weak. Sometimes a lump can be felt in the stomach. Other signs and symptoms include diarrhea, fever, and dehydration.

How Is Intussusception Diagnosed?

The health care provider makes a preliminary diagnosis from the medical history and physical examination. If the child seems very ill, has a fever, or lost blood, or if symptoms have been going on for more than a few hours, immediate surgery may be done to fix the problem. For

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more stable children, the next step is usually a barium enema. In this test, a liquid containing a substance called barium is given. Special X-rays are taken as barium moves through the intestine. The barium helps in diagnosis and sometimes can force the intestine to straighten. It can therefore also act as a treatment.

How Is Intussusception Treated?

If the barium enema doesn't straighten the intestine and clear the blockage, surgery is needed. Antibiotics are given for infections. Children are given fluids intravenously (through a vein). Additional treatment may also include using a tube put through the nose and into the stomach (nasogastric tube) to help decrease pressure in the intestines. Untreated intussusception can lead to necrosis (death of tissue) and widespread infection (sepsis), which can be life-threatening. Sometimes intussusception is very mild and the problem is temporary and gets better on its own. As children get older the risk of recurrence decreases. Most recurrences take place within the first 24 hours after the condition is treated. Call the health care provider right away if symptoms seem to be returning.

DOs and DON'Ts in Managing Intussusception:

✓ **DO** remember that intussusception is an emergency. Call your health care provider immediately if you see symptoms. Then call 911 or take your child to the emergency room. Untreated intussusception is almost always fatal for babies and young children.

⃠ **DON'T** use home remedies, such as laxatives. These can be dangerous.

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- American Academy of Pediatrics Tel: (847) 434-4000 **Website: http://www.aap.org**
- American College of Gastroenterologists Tel: (703) 820-7400 **Website: http://www.acg.gi.org**
- National Digestive Diseases Information Clearinghouse Phone:1-800-891-5389 or 1-301-654-3810 **Website: www.niddk.nih.gov/health/digest/nddic.htm**
- American College of Emergency Physicians Tel: (800) 798-1822 or (972) 550-0911 **Website: http://www.acep.org**

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MANAGING YOUR

IRON DEFICIENCY ANEMIA

What Is Iron Deficiency Anemia?

Iron deficiency anemia occurs when the body doesn't have enough iron to make a normal supply of red blood cells.

What Causes Iron Deficiency Anemia?

The cause is usually loss of blood resulting in increased iron requirements to make more blood cells to replace the ones that are lost or having too little iron in the diet. Normally, the body saves iron. As old red blood cells break down, iron inside is reused to make new red blood cells.

Iron-rich foods are animal products such as meat, milk, and eggs. Vegetables such as spinach and broccoli are iron rich, but the intestine can't absorb them as well. In developing countries, poor nutrition is the main cause of anemia. In Europe and the United States, chronic blood loss is more often the cause of iron deficiency.

People who are vegetarians (don't eat animal products), have a poor diet, or need large amounts of iron (such as pregnant or nursing women) have greater chances of getting the disorder. Also at risk are people with celiac disease, gastric ulcers, or intestinal tumors.

What Are the Symptoms of Iron Deficiency Anemia?

Symptoms are feeling tired and dizzy and having trouble doing normal daily activities. Severe disease may cause shortness of breath and pale skin. Long-lasting disease causes sore mouth, trouble swallowing, and soft, curling fingernails.

Another symptom is craving crunchy foods or ice cubes or eating odd things such as dirt or clay (called pica).

How Is Iron Deficiency Anemia Diagnosed?

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The doctor makes a diagnosis by doing blood tests to measure the iron and hemoglobin content. Finding the reason for iron loss is important, especially for babies, teens, and pregnant women. Blood loss from the intestinal tract due to cancer or bleeding ulcers must be ruled out.

If the diagnosis remains unclear, the doctor may do a bone marrow test. A blood specialist will get a small sample of bone marrow from a spot near the hip and will study it with a microscope to determine the iron content and rule out other blood disorders that can cause anemia.

How Is Iron Deficiency Anemia Treated?

Treatment depends on how severe the anemia is. Usually, people need to take extra iron as pills or liquids. Iron is taken at least once daily for 3 to 6 months. Severe anemia may mean a blood transfusion. Recovery is slow. An iron supplement may be needed for several months or years, but people start feeling better in a few weeks.

DOs and DON'Ts in Managing Iron Deficiency Anemia:

- ✔ **DO** take your iron supplement as directed by your doctor.
- ✔ **DO** take prenatal vitamins if you're pregnant. Keep taking them if you breast-feed.
- ✔ **DO** eat a well-balanced diet with foods high in iron, such as meat, beans, and leafy green vegetables.
- ✔ **DO** watch for and report symptoms of worsening anemia. Call your doctor if you have severe tiredness, dizziness, chest pain, or shortness of breath.
- ✔ **DO** call your doctor if you have bleeding or chronic bleeding increases.
- ✔ **DO** call your doctor if you have abdominal pain from the iron supplement. A lower dose or changing the supplement may help.
- ⃠ **DON'T** overexert yourself.

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Contact the following sources:

- The American Society of Hematology Tel: (202) 776-0544 **Website:** **http://www.hematology.org**
- Centers for Disease Control and Prevention Tel : (800) 311-3435 **Website:** **http://www.cdc.gov**
- National Heart, Lung, and Blood Institute Health Information Center Tel: (301)592 8573 **Website: http://www.nhlbi.nih.gov/health/index.htm**

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MANAGING YOUR

IRRITABLE BOWEL SYNDROME (IBS)

What Is Irritable Bowel Syndrome (IBS)?

IBS is a common digestive disorder that affects about 20% of people in the United States, mostly women. It affects how the large intestine (colon) works.

Food moving through the digestive tract passes from the small intestine to the colon. The main function of the colon is to absorb water. Muscles in the colon usually contract in a way that pushes stool (waste products) through. In IBS, these muscle contractions may be abnormal. Too many contractions may cause diarrhea. Slowed or fewer contractions may cause constipation. Irregular or intermittent (spasmodic) muscle contractions may cause pain or a feeling of urgent need to move the bowels (go to the bathroom).

What Causes IBS?

The cause is unknown but appears to be related to the nervous system. People with IBS have a colon that reacts very strongly to signals from the brain. Many people find that stress, anxiety, and emotional upset trigger symptoms. Certain foods or eating too much or too little may also cause the colon to overreact.

What Are the Symptoms of IBS?

The most common symptoms are pain in the abdomen (belly), bloating, and constipation or diarrhea or both. Other symptoms include an urgent need to move the bowels and feeling of incomplete evacuation. These symptoms come and go over days, weeks, or months.

How Is IBS Diagnosed?

Not everyone who has gastrointestinal symptoms has IBS. The doctor diagnoses IBS by taking a careful medical history to detail the symptoms. No test can prove that someone has IBS. The

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doctor may use blood tests, x-rays, and looking at the colon through a thin, flexible tube (special instrument called an endoscope) to rule out other disorders.

How Is IBS Treated?

Lifestyle changes may help relieve IBS symptoms. These changes include eating a high-fiber diet, avoiding foods that make symptoms worse, eating regular meals that are not too big, drinking enough water, getting regular exercise, and reducing stress.

Several medicines are available for IBS. The doctor can help decide which are best. Over-the-counter laxatives should be taken only under a doctor's direction, because overuse of laxatives may be harmful. Tranquilizers and antidepressants may also help people with IBS.

DOs and DON'Ts in Managing IBS:

✓ **DO** learn what foods worsen your symptoms and avoid them.

✓ **DO** eat a good diet with high-fiber foods, including whole grains, fruits, and vegetables. Fiber supplements may help if your diet does not have enough fiber.

✓ **DO** eat regular, balanced meals.

✓ **DO** drink plenty of water to help the colon work correctly.

✓ **DO** take medicines as instructed by your doctor.

✓ **DO** exercise. Try to do 30 minutes of moderate physical activity daily.

✓ **DO** try to lower stress. Don't take on more work or obligations than you can handle.

⃠ **DON'T** take over-the-counter laxatives without a doctor telling you to do so.

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⦸ **DON'T** skip meals, and don't eat extra-large meals.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Family Physicians Tel: (913) 906-6000 **Website:** **http://www.aafp.org**
- American Gastroenterological Association Tel: (301) 654-2055 **Website:** **http://www.gastro.org**
- American College of Gastroenterologists Tel: (703) 820-7400 **Website:** **http://www.acg.gi.org**

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CARING FOR YOUR NEWBORN WITH

JAUNDICE

What Is Jaundice?

Jaundice, also called icterus, is yellowing of the skin and whites of the eyes. It's a very common condition in newborns. Jaundice usually gets better by itself and disappears in a few days.

What Causes Jaundice?

A substance called bilirubin can build up in the blood. Bilirubin forms when red blood cells break down. The body usually gets rid of bilirubin through the liver. Because the liver in newborns is immature, sometimes bilirubin builds up faster than the body can get rid of it. Jaundice is the result. Very high levels of bilirubin can hurt the baby's nervous system. This condition is called kernicterus. Premature babies are more likely to get jaundice than are full-term babies.

Other causes include infection, a blood type conflict between mother and baby, and breast milk. Sometimes, breast milk interferes with the ability of a baby's liver to process bilirubin. This type of jaundice develops later than the others and can last for several weeks.

What Are the Symptoms of Jaundice?

The most common symptom is yellowing of the skin and whites of the eyes. Other symptoms, with very high bilirubin levels, are being drowsy and not eating well.

How Is Jaundice Diagnosed?

The doctor will do a simple blood test to check the bilirubin level.

How Is Jaundice Treated?

Many babies don't need treatment.

When treatment is needed, the best is phototherapy. The baby lies naked under fluorescent lights. The baby has eye patches to protect the eyes during the treatment. The lights help break

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down excess bilirubin so it can be removed more easily. An "ultraviolet blanket" can also be used. Bilirubin blood levels are checked regularly. Phototherapy usually lowers bilirubin levels in 2 days. Sometimes, the bilirubin level goes up after phototherapy, but only temporarily. The yellow color may last for a few days or even a week or two, even with low bilirubin blood levels.

In rare cases of extremely high bilirubin levels that can't be lowered by phototherapy, exchange transfusion may be done. This treatment involves removing blood with high levels of bilirubin and replacing it with different blood.

DOs and DON'Ts in Managing Jaundice:

✓ **DO** feed your baby often. This helps the baby pass more stool, which reduces the amount of bilirubin that the intestines absorb.

✓ **DO** see your doctor right away if your baby seems to be getting jaundice again, because it can mean that there's a different problem. Once newborn jaundice clears up, it usually doesn't come back.

⃠ **DON'T** panic. Most babies recover completely without treatment.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Pediatrics Tel: (847) 434-4000 **Website:** http://www.aap.org

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MANAGING YOUR

JELLYFISH AND OTHER MARINE ANIMAL STINGS AND BITES

About Jellyfish and Marine Animal Stings and Bites

Venomous animals in oceans include corals, jellyfish and sea nettles, sea urchins and starfish, sting rays, and fish. Dangerous fish include lionfish, scorpionfish, and stonefish. Most inject venom by stinging or making puncture wounds from spines. People encounter these animals during skin or scuba diving and wading or swimming in shallow waters. Contact can also occur with animals washed up on beaches.

What Are the Symptoms of Jellyfish and Marine Animal Stings and Bites?

Fire coral, jellyfish, and sea anemones rapidly cause stinging, itching, or pain at contact sites. Blistering, welts, or swelling lasting 1 to 2 weeks may follow stings. More severe cases can cause allergic reactions, muscle cramps and spasms, and convulsions. Headache, paralysis, unconsciousness, heart and breathing problems, and nausea and vomiting can also occur. Puncture wounds from sea urchins, sting rays, and fish may contain spine pieces. Rapid, often burning, pain may spread to the whole limb. Long-lasting bleeding and discoloration around the wound can occur. Other symptoms are severe muscle spasms and cramps and limb paralysis. In severe cases, nausea and vomiting, fainting or unconsciousness, breathing problems, and delirium occur. Wounds can get infected.

How Are Jellyfish and Marine Animals Stings and Bites Treated?

For fire coral, anemones, and jellyfish, the first treatment is flushing the area with vinegar soaks or rubbing alcohol (but not fresh water alone). Treatment is for 10 to 30 minutes, 3 or 4 times/day. Jellyfish tentacles may remain attached to skin and must be removed by careful scraping with a knife or razor. Steroids (cream or pills) may help severe conditions. Sea nettle

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stings may get better with a baking powder solution used for the first flushing, but vinegar is best when unsure about the animal.

For punctures, the best first treatment is flushing the wound with seawater. Then, the wound is soaked in nonscalding hot water (about 110° F) for 30 to 90 minutes or until pain decreases. The doctor should examine a wound for spines. The doctor may want X-rays to find hidden spines. Antibiotics may help prevent infection.

DOs and DON'Ts in Managing Jellyfish and Marine Animals Stings and Bites:

✓ **DO** take medicines as prescribed.

✓ **DO** limit moving an injured limb until it's better, to reduce swelling and slow the venom's spread.

✓ **DO** avoid problem animals. Ask local experts such as lifeguards or dive shop personnel for advice about local venomous animals. Ask what to do about contact with them.

✓ **DO** call a doctor. You can have delayed effects, so get medical attention for any bite or sting. Call if you have symptoms of infection such as fever, increasing pain, and increasing swelling, or pus in the wound.

⦸ **DON'T** handle unknown animals, including sponges, corals, sea worms, jellyfish, sea urchins, and spiny starfish. Don't handle stingrays or venomous fish. These fish are popular in the underground tropical aquarium business, and many people get hurt by them.

⦸ **DON'T** wade in water in which you cannot see bottom. If you must, move by shuffling, to scare stingrays or fish away from your feet. Watch out for sea urchins when wading.

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Contact the following source:

- National Institute of Environmental Health Sciences Tel: (919) 541-3345 **Website:** **http://www.niehs.nih.gov**

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CARING FOR YOUR CHILD WITH

JUVENILE IDIOPATHIC ARTHRITIS

What Is Juvenile Idiopathic Arthritis?

Juvenile idiopathic arthritis (JIA) is a form of arthritis in children. It is also known as "juvenile rheumatoid arthritis" (JRA) and "Still's disease." JIA differs from adult rheumatoid arthritis. It is a chronic disease and last for months or years, but about 75% of children outgrow it. No cure exists, but earlier detection, better drugs, and good treatment greatly improve chances for a full, active life.

JIA can make it hard to do daily activities such as writing, dressing, and carrying things (hands, wrists); walking, playing, and standing (hips, knees, feet); and turning the head (neck).

What Causes JIA?

JIA is an autoimmune disorder but its cause is unknown. Autoimmune means that the body's infection-fighting (immune) system attacks its own tissues. Genetic and environmental factors may increase chances of getting JIA. JIA cannot be caught from another person.

What Are the Symptoms of JIA?

Symptoms include joint pain and stiffness that are usually worse in the morning but get better toward the end of the day. Children may hold painful joints close to the body or bent. The three JIA types are pauciarticular, polyarticular, and systemic.

Pauciarticular JIA affects only a few joints (normally less than four: knees, elbows, and ankles) and occurs in 50% of children with JIA, more often in girls. Eye disease (inflammation, or swelling) can develop.

Polyarticular JIA affects many joints and occurs in about 30% of children with JIA, more commonly in girls. Neck, knees, ankles, feet, wrists, and hands are affected. Children with this

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type may also have eye inflammation.

Systemic JIA occurs in about 20% of children with JIA, boys and girls equally. It often starts with fever, rash, changes in blood cells, and joint pain.

How Is JIA Diagnosed?

The doctor takes a medical history, examines the joints, and may order laboratory tests and x-rays. Testing for the specific blood proteins rheumatoid factor (RF) and antinuclear antibody (ANA) may help diagnosis. Systemic JIA may be hard to diagnose because inflammation may not start right away.

How Is JIA Treated?

A combination of medicines, therapies, exercise, education, and pacing activities to prevent tiredness is best. A doctor who treats arthritis should care for your child.

Medicines for inflammation include nonsteroidal antiinflammatory drugs (NSAIDs). Disease-modifying drugs (such as methotrexate) or medications that affect the immune system (such as etarnecept) can also be tried.

Exercise is important for joint movement and muscle strength. Splints can help rest painful, swollen joints.

DOs and DON'Ts in Managing JIA:

✓ **DO** have your child take prescribed medicines.

✓ **DO** call the doctor if your child has medicine side effects.

✓ **DO** encourage exercising.

✓ **DO** encourage your child to participate in many of the same activities as other children, but

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alternate activities with rest.

- ✔ **DO** speak to your child's teachers and school nurse. Ask about school services to help your child.
- ✔ **DO** call your child's doctor if medicines don't help or if you need referrals to physical or occupational therapists.
- ⃠ **DON'T** give up. If one drug doesn't work, talk with your child's doctor about changing to a different one.
- ⃠ **DON'T** have your child continue with exercises that make the symptoms worse. Speak with the doctor about alternate exercises.
- ⃠ **DON'T** forget to have your child get regular eye examinations. Some drugs can affect the eyes.

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FOR MORE INFORMATION

Contact the following sources:

• Arthritis Foundation Tel: (800) 283-7800 **Website:** **http://www.arthritis.org**

• American College of Rheumatology Tel: (404) 633-3777 **Website:**

http://www.rheumatology.org

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MANAGING YOUR

KAPOSI'S SARCOMA

What Is Kaposi's Sarcoma?

Kaposi's sarcoma (KS) is a rare cancer thought to start in tissue lining blood or lymph vessels under the skin or in mucous membranes (as in the mouth). Four types have been described: epidemic, immunosuppression-related, classic, and African. Epidemic KS is associated with acquired immunodeficiency syndrome (AIDS). Immunosuppression-related KS is usually found in people with kidney transplants. In transplantation, strong drugs are used to suppress the immune system and prevent it from rejecting the kidney. This type of KS can be slow and inactive or aggressive.

Classic KS is more common in Jewish and Mediterranean men. Most survive more than 10 years and die of some other condition. African KS is typically found among young black men in Africa.

What Causes Kaposi's Sarcoma?

The cause is thought to be a herpesvirus (HHV-8). The virus can be passed to others sexually and through nonsexual contact such as mothers to babies (common in African countries).

What Are the Symptoms of Kaposi's Sarcoma?

The usual symptom is a rash (lesion) of small reddish-purple spots, commonly seen on the lower legs. KS can also be found on the nose and rest of the face. It can spread into lymph glands (nodes), stomach, and lungs. If it's in the stomach, bleeding or abdominal pain can occur. If it's in the lungs, shortness of breath occurs.

How Is Kaposi's Sarcoma Diagnosed?

The doctor may suspect KS from the medical history and physical examination, but the only sure

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way to diagnose it is by doing a biopsy. In a biopsy the doctor takes a small piece of tissue to check with a microscope. Blood tests may be done to rule out HIV infection.

How Is Kaposi's Sarcoma Treated?

Treatment depends on how severe the disease is and how far it spread. Watching (monitoring without treatment), supportive therapy, radiation therapy, and chemotherapy may be used. The decision to undergo treatment must be made with a specialist who has experience with KS. Inactive forms of the classic, African, and immunosuppressive types of KS need only observation and follow-up visits to watch for symptoms or for surgery to fix skin problems. Radiation therapy is effective for single lesions that cause symptoms. Complications of radiation therapy include dry, red, itchy skin.

Chemotherapy can be given directly into the lesion when treating a single lesion or intravenously for multiple lesions, or advanced disease. Side effects of chemotherapy are nausea, vomiting, hair loss, easy bruising and bleeding, and infections.

DOs and DON'Ts in Managing Kaposi's Sarcoma:

✓ **DO** get an expert's opinion.

✓ **DO** remember that there are types of KS and that the way the disease acts changes for each type.

✓ **DO** call your doctor if you find a discolored lesion on your face, nose, or legs. Call if you're in pain, have shortness of breath, vomit blood, or have swollen lymph glands. Call if a skin lesion breaks down.

✓ **DO** practice safe sex!

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⦸ **DON'T** forget that among homosexuals, KS is thought to be transmitted through anal sex.

⦸ **DON'T** think that if you're not homosexual, you won't get KS. Women can get KS after having sex with bisexual men.

⦸ **DON'T** use illicit drugs. Intravenous drug abusers are at higher risk to get KS.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Cancer Institute (NCI) Tel: 800-4-CANCER
- American Cancer Society Tel: (800) ACS-2345

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CARING FOR YOUR CHILD WITH

KAWASAKI DISEASE

What Is Kawasaki Disease?

Kawasaki disease (KD) is a rare condition that causes inflammation of blood vessels (vasculitis) and several other manifestations noted below. KD usually occurs in children younger than 5, more often in boys than girls. In the United States, about 4000 new cases are diagnosed each year. It's the leading cause of acquired heart disease in children.

What Causes KD?

The cause is unknown, but an infectious agent may trigger the inflammation. KD isn't contagious, however. It is not a hereditary disorder.

What Are the Symptoms of KD?

Symptoms include fever that lasts for more than 5 days, and is associated with red swollen eyes (conjunctivitis); cracking lips; strawberry-colored tongue; red, swollen, sore throat; swollen lymph glands in the neck; and rash on the trunk and limbs. Complications that may mean heart involvement include shortness of breath; chest pain; and symptoms of congestive heart failure, such as leg swelling, being unable to lie flat in bed, suddenly waking up short of breath, and shortness of breath with exertion.

How Is KD Diagnosed?

The doctor makes a diagnosis from physical examination and symptoms: fever lasting more than 5 days plus four of five other features. These features include inflammation of the whites of the eyes (conjunctivitis) and swollen eyes; mucous membrane changes (red tongue and dry, cracked lips); swollen hands and feet; swollen neck lymph glands; and rash on the trunk of the body.

The doctor may order blood tests and x-rays, but no specific blood test can diagnose KD.

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For suspected heart involvement, echocardiography (a sonogram of the heart) and cardiac catheterization can be done. In catheterization, the doctor puts a tube into the leg artery and moves it up into heart arteries. Dye is then injected to show blockages in coronary (heart) arteries.

How Is KD Treated?

Aspirin is used for fever, rash, and pain and to prevent blood clots in coronary arteries. Intravenous immunoglobulin can significantly reduce coronary artery disease and improve the heart's pumping if given early. For coronary artery and heart involvement, the doctor may suggest percutaneous transluminal coronary angioplasty. In this procedure, a balloon-tipped tube is put into the coronary artery. The balloon is inflated to open the diseased artery. A child with many diseased vessels may have coronary artery bypass surgery. Heart transplant may sometimes be considered.

DOs and DON'Ts in Managing KD:

✓ **DO** remember that nearly 20% of children may have heart damage.

✓ **DO** understand that risk factors for coronary artery problems are fever of more than 10 days, age younger than 1 year, and male sex.

✓ **DO** call your child's doctor if your child has a fever, rash, or shortness of breath.

✓ **DO** call your child's doctor if you see swollen lymph glands in the neck.

✓ **DO** call your child's doctor if you need a second opinion.

⃠ **DON'T** forget that KD is a rare disease that requires care from a team of doctors who have

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experience with this condition.

⦸ **DON'T** be afraid to ask for a second opinion.

⦸ **DON'T** ignore symptoms.

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FOR MORE INFORMATION

Contact the following sources:

- Kawasaki Disease Foundation Tel: (978) 356-2070 **Website:** http://www.kdfoundation.org
- American Heart Association Tel: (800) 242-8721 **Website:** http://www.americanheart.org
- American College of Cardiology Tel: (800) 253-4636 **Website:** http://www.acc.org

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KEGEL EXERCISES

STRENGTHENING YOUR PELVIC FLOOR MUSCLES

What Are Kegel Exercises?

Kegel exercises can help strengthen pelvic muscles. The part of the body that includes the hip bones is the pelvic area. Pelvic muscles are at the bottom of this area (pelvic floor), between the legs, roughly the part covered by a panty liner. These muscles are important for supporting the bladder, uterus (womb), and rectum. They prevent urine and stool (bowel movements) from leaking out. These muscles also do important work during sex.

What Conditions Can Kegel Exercises Help?

When pelvic floor muscles are stretched or damaged, most often by childbirth, they may stop supporting the bladder, uterus, or rectum. These organs can drop downward and cause feelings of pressure, fullness, and heaviness. They can bulge (prolapse) into the vagina. Lost bladder support can cause problems holding urine during coughing, sneezing, or laughing hard. Urine leakage can happen during and after pregnancy. When support for the rectum fails, trouble having bowel movements can occur. Kegel exercises can help these conditions. They can also help women who have problems reaching orgasm during sex.

How Do You Do Kegel Exercises?

Kegel exercises consist of contracting (squeezing) and relaxing pelvic floor muscles. Learn to do this by thinking of the muscles used to stop the stream of urine once it has started. Contracting these muscles stops the urine. Relaxing these muscles lets the flow start again. Once the right muscles are found, they can be contracted and released without urinating. Kegel exercises are most often done in sets. Quickly contract and release the muscles 15, 20, or more times, and then rest for 30 seconds and repeat this process. Also, muscles can be contracted and held tight for 3

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seconds and then released for 3 seconds, with this process repeated 20 or more times. Longer times are used until muscles can be contracted for 10 seconds and relaxed for 10 seconds between contractions. With either method, repeat the process two or three times each day.

It's best to tighten only pelvic floor muscles, not muscles in the abdomen (belly), thighs, or buttocks. Don't start and stop the urine stream. Doing Kegel exercises with a full bladder or while urinating can actually weaken the muscles. Also, overexercising can make muscles tired and increase urine leakage.

These exercises can be done anywhere without anyone knowing about it. Some people use tricks to remember to exercise—getting ready for a break from work, when the evening news starts, checking e-mail, while waiting for a stop light.

Many doctors recommend the exercises to all people and to pregnant women to help them get ready for labor and delivery.

DOs and DON'Ts for Kegel Exercises:

✓ **DO** keep doing your exercises. As with other exercises, seeing results takes time.

✓ **DO** try to spread out your exercise sets. Do them at different times of the day, so muscles can rest between exercises.

✓ **DO** talk to your doctor about worries about your pelvic muscles or their function.

⃠ **DON'T** feel silly doing Kegel exercises. Nobody has to know that you're doing them.

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- The American College of Obstetricians and Gynecologists **Website: http://www.acog.org**
- WebMD **Website: http://www.webmd.com**
- National Women's Health Information Center U.S. Department of Health and Human Services **Website: http://womenshealth.gov**

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MANAGING YOUR

KELOIDS

What Are Keloids?

Keloids and scars that are hypertrophic (meaning growing abnormally large) are an overgrowth of scar tissue on the skin. They can appear anywhere, usually in a place that was injured, such as after a burn, severe acne, surgery, ear piercing, or a scratch.

What Causes Keloids?

Keloids result from too much scar tissue forming as a wound heals. No one knows why they form. They cannot be caught from someone else and aren't skin cancer, but the tendency to get keloids often runs in families. Keloids affect people of all skin types but are more common in people with dark skin.

What Are the Symptoms of Keloids?

Keloids are raised lumps of pink, red, or dark scar tissue that go beyond the original wound. They sometimes start after very small wounds, such as ear piercing. They may grow large and don't get smaller with time, but they may become paler. Keloids are different from hypertrophic scars. A hypertrophic scar is raised, red and lumpy, or uneven. It doesn't spread beyond the original wound. It often gets smaller and paler over time.

Both hypertrophic scars and keloids are usually painless but can itch. If they form over a joint they may make it harder to move.

How Are Keloids Diagnosed?

The doctor makes a diagnosis from the look of the scar. Tests are usually not needed.

How Are Keloids Treated?

No one treatment is effective. With keloids, prevention is better than cure. Avoid body piercing,

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tattoos, or any kind of unnecessary surgery. If possible, the best thing may be to leave them alone.

Different treatments have had success but don't work for everyone. Keloids may come back in the same areas despite treatment. The various treatments include surgery, steroid injections, dressings, freezing, and lasers.

Surgery usually doesn't work because keloids often come back, sometimes larger than before. Injecting a steroid drug into the keloid may make it smaller. Dressings include pressure bandages or special dressing sheets placed over the area for several weeks or months. Freezing (cryosurgery) can make keloids flatter, and lasers can make the color paler and make the scar flatter.

Certain newer treatments, including chemotherapy drugs, interferon, imiquimod cream, retinoic acid, and tacrolimus, are sometimes successful.

DOs and DON'Ts in Managing Keloids:

✓ **DO** use makeup to help cover your scar if it bothers you. Special products are available.

✓ **DO** continue to lead a normal, healthy lifestyle. There are no restrictions for keloids.

✓ **DO** call your doctor when you see signs of keloids forming.

⃠ **DON'T** have piercings, tattoos, or any unnecessary surgery if you have ever had keloids.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Dermatology Tel: (866) 503-SKIN (7546) **Website:** **http://www.aad.org**

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MANAGING YOUR

KIDNEY CANCER

What Is Kidney Cancer?

The kidneys are reddish-brown bean-shaped organs located just above the waist, one on each side of the spine. As part of the urinary system, their main jobs are filtering blood and making urine to get rid of body wastes. Renal cell carcinoma is a certain type of kidney cancer. It accounts for 90% to 95% of kidney cancers, but it's not very common (occurs in 1 of 10,000 people yearly). Twice as many men as women have it, usually between 50 and 70 years old.

What Causes Kidney Cancer?

The cause is unknown. However, risk factors include cigarette smoking, radiation, and on-the-job exposure to petroleum products, asbestos, or steel plant emissions. People with von Hippel-Lindau disease, tuberous sclerosis, and polycystic kidney disease have an increased risk for this cancer.

What Are the Symptoms of Kidney Cancer?

Early disease may cause no symptoms. As the tumor grows, symptoms may include blood in the urine, lump or mass in the kidney area, tiredness, loss of appetite, weight loss, fevers, and pain in the abdomen (belly).

How Is Kidney Cancer Diagnosed?

The doctor makes a diagnosis by special x-rays including computed tomography (CT), magnetic resonance imaging (MRI), and ultrasonography. The only way to confirm the diagnosis is with a biopsy. For a biopsy, the doctor removes a small piece of the kidney and checks it with a microscope. CT or MRI is also used to learn the stage or extent of disease, which helps plan treatment. Staging tells the doctor whether the cancer has spread and if so how far, such as to lymph nodes

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(glands) or lungs.

How Is Kidney Cancer Treated?

The most common treatment is an operation to remove the kidney (nephrectomy). The whole kidney, adrenal gland, tissue around the kidney, and lymph nodes may be removed. A procedure called arterial embolization may be used to shrink the tumor. It blocks the main blood vessel to the kidney so the tumor doesn't get the oxygen-carrying blood and other substances that it needs to grow.

Radiation therapy (or radiotherapy) uses high-energy radiation to kill cancer cells. It can also be used to relieve pain (as palliative therapy) when kidney cancer spread to bones.

Chemotherapy (drugs for killing cancer cells) is generally not very helpful against kidney cancer. Immunotherapy involves the use of biological agents such as interferon, sunitinib, and bevacizumab. It is a newer treatment modality that has shown some success in the treatment of advanced kidney cancer.

DOs and DON'Ts in Managing Kidney Cancer:

✓ **DO** understand that diagnosis and treatment of this cancer will need a team of doctors including your primary care doctor, surgeon, oncologist (specialist in cancer), and maybe radiation oncologist (specialist in use of radiation to treat cancer).

✓ **DO** call your doctor if you see blood in your urine or you have pain or a lump in your abdomen.

✓ **DO** call your doctor if you have fever after surgery.

✓ **DO** call your doctor if you see drainage from the surgical incision site.

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⦸ **DON'T** forget that all treatments have side effects. For example, surgery can cause pain and infection. Radiation can cause dry, red, itchy skin. Chemotherapy can cause nausea, vomiting, hair loss, easy bruising, easy bleeding, and infections.

⦸ **DON'T** be afraid to ask for a second opinion.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Cancer Institute Tel: (800) 422-6237 **Website: http://www.cancer.gov**
- American Cancer Society Tel: (800) 227-2345 **Website: http://www.cancer.org**

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MANAGING YOUR

KIDNEY STONES

What Are Kidney Stones?

Kidney stones are hard deposits that form in kidneys from substances in the urine. This process is called nephrolithiasis. Kidney stones can be tiny or up to several inches around. Very large stones that fill the tubes carrying urine from the kidneys to the bladder (ureters) are called stag-horn stones.

What Causes Kidney Stones?

Stones may form if urine contains too much of certain chemicals, such as calcium, uric acid, cystine, or struvite (a mixture of phosphate, magnesium, and ammonium). Having a diet that is very high in protein and drinking too little water increase the risk of getting stones. About 85% of kidney stones are made from calcium. Uric acid stones occur more often if gout is present. Struvite stones form more often in infected urine (infection stones).

What Are the Symptoms of Kidney Stones?

About one-third of people have kidney stones, but only half of these have symptoms. Even without symptoms, stones may cause problems, such as infections and blocking urine flow. Stones getting stuck in ureters cause the symptoms.

The most common symptom is severe pain (urinary colic) that comes and goes and usually moves from the side of the back (flank) to the lower belly (abdomen). Other common symptoms include pain in the back, thigh, groin, and sex organs (genitals); blood in the urine; nausea; and vomiting.

If a stone causes an infection, additional symptoms may be chills; fever; painful, frequent, and urgent urination; and sweating.

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How Are Kidney Stones Diagnosed?

The doctor takes a medical history, does a physical examination, and tests the urine. An x-ray or ultrasound study of your abdomen may be needed. These studies will uncover most stones (calcium, cystine, and struvite stones). X-rays cannot show uric acid stones and also may miss smaller stones. Computed tomography (CT) of the urinary tract is an excellent test to diagnose stones and look for other disorders that can cause symptoms similar to kidney stones. Very rarely, if the diagnosis is still unclear, a special x-ray study (intravenous pyelogram, or IVP) may be done. In this study, dye is used to outline the urinary tract and look for the stone.

How Are Kidney Stones Treated?

Treatment depends on several things, such as the size and number of stones, where they are, and whether an infection is present. Most stones pass out of the body without a doctor's help.

The simplest way to treat a small stone is to flush it out by drinking lots of fluid. Medicine may help relieve pain. Antibiotics are given for an infection.

Stones that do not pass by themselves may need removal by a urologist. A urologist is a doctor who specializes in diseases of the urinary system. The urologist may use a long, thin tool (ureteroscope) to do this.

Sometimes, shock waves are used to break the stone into smaller pieces that can be passed. This treatment is called extracorporeal shock wave lithotripsy (ESWL). Occasionally, surgery may be needed to remove the stones (percutaneous nephrolithotomy).

DOs and DON'Ts in Managing Kidney Stones:

✓ **DO** take all your prescribed medicines.

✓ **DO** follow your doctor's advice about diet.

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✓ **DO** drink plenty of fluids, at least 4 pints a day.

✓ **DO** call your doctor's office if you feel worse.

✓ **DO** call your doctor or go to the emergency room if you have severe vomiting, severe pain, or fever with severe back pain.

⃠ **DON'T** get dehydrated.

⃠ **DON'T** stop taking your medicine or change the dosage because you feel better unless your doctor tells you to.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Urological Association Tel: (866) 746-4282 **Website:** **http://www.urologyhealth.org**
- National Kidney Foundation Tel: (800) 622-9010 **Website:** **http://www.kidney.org**
- National Kidney & Urologic Diseases Information Clearinghouse Tel: (800) 891-5390 **Website:** **http://www.kidney.niddk.nih.gov**

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MANAGING YOUR

KLINEFELTER'S SYNDROME

What Is Klinefelter's Syndrome?

Klinefelter's syndrome is an inherited disorder of males. It can affect different stages of development—physical, language, and social. Normal male sexual characteristics of puberty don't develop.

Klinefelter's syndrome affects about 1 in 400 to 1 in 1000 males.

What Causes Klinefelter's Syndrome?

The cause is a defect in sex chromosomes. Normal females have a chromosome pattern of 46,XX. Normal males have a 46,XY pattern. In this syndrome, the pattern is 47,XXY. This extra X chromosome interferes with normal male sexual development in the womb and at puberty.

What Are the Symptoms of Klinefelter's Syndrome?

Most teenagers and men have long arms and legs compared with the body trunk. Teenagers may be less muscular than other boys, have problems expressing themselves, be shy, and have trouble being part of a social group. Men have a low sperm count or no sperm and therefore are infertile. The testicles are small and firm, and some men may have breasts (gynecomastia). Men may have problems with erections, small penis, poor beard growth, and little underarm or pubic hair. Symptoms vary greatly.

This syndrome leads to osteoporosis (low bone density), an increased risk for breast cancer, and sometimes personality disorders.

How Is Klinefelter's Syndrome Diagnosed?

The doctor makes a diagnosis by doing a physical examination of a boy who doesn't develop normally. Analysis of chromosomes (karyotype) done from obtaining a smear from cells inside

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your mouth (buccal smear) gives the number and type of chromosomes. Sometimes, a man sees a doctor because of impotence (cannot get an erection) or infertility (inability to father children). Blood tests show a low level of testosterone (male hormone) and high level of another hormone, follicle-stimulating hormone (FSH). Your primary care doctor may also refer you to a specialist who deals with hormone abnormalities (endocrinologist).

How Is Klinefelter's Syndrome Treated?

No treatment for infertility is possible, because testes cannot make sperm. Replacing testosterone will help the male secondary sexual characteristics. Testosterone, given as an injection or skin patch, leads to normal male muscle development and hair growth (beard, underarms, and genitals). Excess testosterone may cause mood changes, aggressive behavior, abnormal prostate growth, or high blood pressure. Use of the testosterone patch may cause a local skin reaction.

Gynecomastia can be treated surgically (breast reduction). Lumps in the breast should be checked for breast cancer.

Osteoporosis may be treated with testosterone plus enough calcium and vitamin D and regular weight-bearing exercises.

DOs and DON'Ts in Managing Klinefelter's Syndrome:

✓ **DO** see an endocrinologist if you have concerns about male sexual development or function.

✓ **DO** see a surgeon if gynecomastia is troubling or you note a breast lump.

✓ **DO** call the doctor if you have severe mood swings with testosterone replacement.

✓ **DO** call the doctor if you notice sudden bone pain in the back, hip, wrist, or rib.

✓ **DO** call the doctor if you have a rash while using a testosterone patch.

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✓ **DO** ask your doctor about support groups if you're interested in learning from others with Klinefelter's syndrome.

⦸ **DON'T** assume your child has Klinefelter's syndrome because he's behind his peers in pubertal development. See a pediatric endocrinologist.

⦸ **DON'T** forget that you can get help if you're having emotional problems with your diagnosis.

⦸ **DON'T** put the testosterone patch on the same spot of skin every time, to prevent skin irritation.

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FOR MORE INFORMATION

Contact the following source:

- American Association of Clinical Endocrinologists Tel: (904) 353-7878 **Website:** **http://www.aace.com**

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MANAGING YOUR

KNEE PAIN

What Is Knee Pain?

Knee pain is a rather vague diagnosis. It may be pain in the front part of the knee just under the kneecap or deep in the knee joint itself. The location of the pain is important because it will suggest the most likely cause.

Knee pain is very common and usually goes away by itself after the activity causing it is found and stopped.

What Causes Knee Pain?

The many causes include a sprained or torn ligament, torn cartilage, and arthritis of the kneecap or the whole joint. These inflammatory conditions affecting the knees include rheumatoid arthritis and osteoarthritis.

What Are the Symptoms of Knee Pain?

Pain, swelling, and sometimes a clicking or popping feeling are common symptoms. Sometimes, the knee can catch and lock. In that case, a piece of torn cartilage is trapped in the joint and stops the knee from bending or straightening.

How Is Knee Pain Diagnosed?

The doctor will make a diagnosis from the medical history and physical examination. X-rays of the knees and sometimes blood tests may be done. If fluid is present in the knee (knee effusion), the doctor may put a needle in the knee and take fluid out. The fluid will be sent to a laboratory for study.

How Is Knee Pain Treated?

The most important thing to do is find out the cause, especially if an activity such as aggressive

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walking or jogging was started recently. Many people who participate in sports on a court that involve sideways movement have knee symptoms. When these activities are stopped for 2 to 6 weeks, symptoms slowly go away.

Over-the-counter nonsteroidal antiinflammatory drugs (NSAIDs), such as ibuprofen or naproxen, help inflammation (swelling, redness) and pain. These drugs can cause stomach problems and should be taken with meals. People who have ulcers or bleeding ulcers should check with the doctor before using these drugs.

Kneecap pain can usually be managed with physical therapy to strengthen the quadriceps muscles (front of the thigh) and stretch hamstring muscles (back of the thigh) and calf muscles (lower leg). Sprained ligaments often heal with rest and time. Torn ligaments around the knee sometimes need immobilization and then aggressive physical therapy. If the knee pain persists or worsens despite treatment, a surgeon may suggest an operation (arthroscopy) to repair the damage. After symptoms have stopped, activities can be restarted slowly, beginning with activities such as walking or cycling.

DOs and DON'Ts in Managing Knee Pain:

✓ **DO** take your medicines as prescribed.

✓ **DO** stop the activity that causes pain.

✓ **DO** restart activities slowly. Resume very carefully the activity that caused the pain.

✓ **DO** call your doctor if you have tried conservative treatment on your own and you still have symptoms.

✓ **DO** call your doctor if you are doing physical therapy or rehabilitation and your symptoms

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worsen.

✓ **DO** call your doctor if you have side effects from medicines.

✓ **DO** ask your doctor about taking ranitidine or omeprazole to protect your stomach if you are using NSAIDs for a long period.

⃠ **DON'T** use NSAIDs if you had bleeding ulcers.

⃠ **DON'T** continue the offending activity, such as running. You can further injure the knee, which may worsen or damage the joint itself.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website:** **http://www.aaos.org**
- American College of Sports Medicine Tel: (317) 637-9200 **Website:** **http://www.acsm.org**
- National Athletic Trainers' Association Tel: (800) 879-6282 **Website:** **http://www.nata.org**

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MANAGING YOUR

KNEE SPRAIN

What Is Knee Sprain?

The knee joint is called a hinge joint because it moves forward and backward but doesn't turn in other directions. Ligaments are tough fibrous tissues that connect bones to other bones. Two strong ligaments make this hinge stable: the medial and lateral collateral ligaments (MCL and LCL). Deep in the joint, two more ligaments crisscross each other and attach to the thigh bone at one end and the shinbone at the other. These are the anterior and posterior cruciate ligaments (ACL and PCL).

A knee sprain involves damage to these ligaments. It can be mild, moderate, or severe.

What Causes Knee Sprain?

A sprain occurs when these ligaments stretch or tear. Damage to a collateral ligament can happen when the knee is hit on the opposite side. Damage to a cruciate ligament can occur when the knee joint is twisted or hit directly.

What Are the Symptoms of Knee Sprain?

Symptoms include knee pain and swelling, bruising around the knee, feeling of unsteadiness, knee giving way, and snapping feeling inside the knee.

How Is Knee Sprain Diagnosed?

The doctor will make a diagnosis by examining the knee, moving it in different directions and testing ligaments. The doctor will also order x-rays and magnetic resonance imaging (MRI) of the knee. For a very swollen knee, the doctor may take fluid from the knee with a needle. This may ease pain and helps make the diagnosis.

How Is Knee Sprain Treated?

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Treatment depends on the severity of the injury. Treatments include putting an ice pack, wrapped in cloth, on the swollen knee. Raising the leg (higher than the heart) and resting it on something like a soft pillow may help swelling go away. The doctor may prescribe antiinflammatory drugs to help pain and swelling. The knee can be wrapped in an elastic compression bandage. Crutches may help until walking is possible without pain. Exercises may reduce stiffness. The doctor may suggest a knee brace to control joint movement.

For a severe injury with a ligament that was completely torn, surgery may be needed to fix the ligament. Recovery may take 2 to 3 months or longer.

A mild sprain may take 2 to 3 weeks for full recovery. A severe sprain may take 6 weeks or longer. Recovery will be slower if sports or other activities that put pressure on the knee joint are restarted too soon.

DOs and DON'Ts in Managing Knee Sprain:

✓ **DO** follow the advice you get about whether to put weight on your leg.

✓ **DO** be patient. You may not be able to do sports for several weeks.

✓ **DO** report continued swelling or pain to your doctor.

✓ **DO** follow instructions for rehabilitation so that you develop good strength and stability and don't injure the knee again. This may prevent another sprain.

✓ **DO** use safe techniques and warm-up stretching exercises. They may reduce the risk of knee injury.

✓ **DO** ask your doctor about taking antiinflammatory medicines regularly.

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⦸ **DON'T** return to normal activities or sports if your knee still feels unstable.

⦸ **DON'T** forget to do your rehabilitation exercises.

⦸ **DON'T** try to do activities that cause you pain.

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Contact the following sources:

- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website:** **http://www.aaos.org/**
- American College of Sports Medicine Tel: (317) 637-9200 **Website:** **http://www.acsm.org/**
- National Athletic Trainers' Association Tel: (800) 879-6282 **Website:** **http://www.nata.org/**

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MANAGING YOUR

KNEE SWELLING

What Is Knee Swelling?

Knee swelling, sometimes called an "effusion," refers to swelling within the knee joint. An effusion can be caused by many different things, including injuries to the ligaments, cartilage, bones, or surrounding structures. Swelling can occur within the knee joint (effusion) or on the outside of the knee joint (bursitis), and can occur suddenly as a result of an injury or slowly as a result of overuse injuries.

What Causes Knee Swelling?

The many causes of effusions include injuries such as tears of the anterior cruciate (ACL), posterior cruciate (PCL), and medial and lateral collateral (MCL, LCL) ligaments. Tearing of the meniscus (knee cartilage), fractures of the bones of the knee joint, or injuries to the cartilage lining the inside of the bones (articular cartilage) can also cause knee effusions. Bursitis, tendinitis, strains, and sprains are causes of swelling outside the knee joint. Forceful injuries, such as blows during contact sports or falls, can cause fluid or blood to build up within the knee. Broken bones, arthritis, gout, cysts, dislocated kneecaps, infections, tumors, and aging-related degeneration are other causes. Sudden turning, stopping, moving from side to side, and awkward landings can lead to knee stress or overuse.

What Are the Symptoms of Knee Swelling?

Symptoms depend on the cause and they range from mild to severe swelling. Pain, tenderness, redness, fever, and chills can also occur. Knees can have bruises or become stiff so that walking is hard.

How Is Knee Swelling Diagnosed?

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The doctor makes a diagnosis from the medical history, physical examination, and additional tests as indicated. The doctor will ask questions about the nature of the swelling, how quickly it occurred, and if there was an injury, how it happened. In addition, answering questions about what kind of exercises and activities have been performed, as well as previous injuries may be important. X-rays are often useful in evaluating knee swelling, and additional tests such as computed tomography (CT), magnetic resonance imaging (MRI), and arthrocentesis may help determine the cause of knee swelling. In arthrocentesis, the doctor puts a needle into the knee joint using sterile technique and removes fluid. This fluid is sent to a laboratory for study to determine what is causing the fluid to accumulate.

How Is Knee Swelling Treated?

Treatment goals are to determine what is causing the swelling, decrease the swelling, and allow for return to activities as soon and safely as possible. Self-care often works well, but any underlying conditions (such as rheumatoid arthritis or gout) must be treated. After injuries, the first 48 hours are most important. Use PRICE: protection, rest, ice, compression, and elevation. Resting and avoiding activities that may have started the problem (such as high-impact running, skiing, or playing tennis) are critical. Using ice packs, an elastic bandage around the knee, pillows under the knee, cane or crutches, and special stretching and strengthening exercises often help. Rehabilitative exercises to restore range of motion and strength are useful once a diagnosis is determined.

Nonsteroidal anti-inflammatory drugs (NSAIDs) (ibuprofen, naproxen) and acetaminophen may relieve pain. Other treatments depend on the underlying condition and can include orthotics, braces, other medications, and surgery if indicated. Arthrocentesis is a short-term treatment for alleviating pain due to swelling, but the swelling can recur, and this procedure can cause infection

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in the joint if not performed properly.

DOs and DON'Ts in Managing Knee Swelling:

✓ **DO** stop the activity causing the swelling until your doctor says you can start again.

✓ **DO** make sure that you use the right sports technique and equipment, such as shoes and knee pads.

✓ **DO** warm-up exercises, such as light aerobic exercise, correctly.

✓ **DO** maintain a healthy weight.

✓ **DO** stretch before and after sports or exercising, especially quadriceps and hamstring muscles.

✓ **DO** call your doctor if you see signs of infection (fever, redness, warmth). Call if your knee, lower leg, or foot becomes pale, cool, or blue. Call if you don't get better with treatment. Call if you have severe pain or cannot put weight on your knee. Call if your leg gets numb, weak, or tingles.

⃠ **DON'T** put ice or cold packs directly on your skin.

⃠ **DON'T** forget to do gentle stretching to loosen up before activities.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website:**

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http://www.aaos.org

- The American Orthopaedic Society for Sports Medicine Tel: (847) 292-4900 Fax: (847) 292-4905 **Website: http://www.sportsmed.org**

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MANAGING YOUR

LABYRINTHITIS

What Is Labyrinthitis?

Labyrinthitis is an inflammation of the inner ear that causes dizziness. Deep inside each ear is a structure called a labyrinth that helps regulate balance. If the labyrinth is irritated, it sends the wrong signal to the brain. Labyrinthitis may be associated with hearing loss, vertigo (feeling of spinning), loss of balance, and nausea.

What Causes Labyrinthitis?

The cause is often a viral infection. Rarely, the cause is a bacterial infection. Many times the cause is unknown.

What Are the Symptoms of Labyrinthitis?

Symptoms may start suddenly, usually come and go, and last from less than a minute to several hours or days. People have vertigo, usually made worse by changing position quickly. Other symptoms include dizziness, feeling unsteady, loss of balance, nausea, ringing in the ears, tiredness, and feeling sick. Vomiting may occur. Hearing slowly returns to normal in most people, usually within 2 weeks.

How Is Labyrinthitis Diagnosed?

The doctor makes a diagnosis from symptoms and an examination (especially of the eyes, ears, nose, and throat). Mild redness of the nose or throat can occur with a viral infection. Sometimes, the doctor may do special tests for other symptoms such as hearing loss. The doctor may suggest seeing an ear, nose, and throat (ENT) specialist or neurologist (specialist in nervous system diseases). X-rays and laboratory tests are not usually needed.

How Is Labyrinthitis Treated?

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Labyrinthitis usually goes away by itself, in several days to 2 weeks. For severe dizziness the doctor may prescribe meclizine. Lying still with eyes closed in a dark room will help severe sickness or dizziness. Change positions, such as getting up from lying down, slowly.

Head movements, called Epley maneuvers, may be prescribed to help relieve the dizziness. Drinking plenty of water or other fluids is important. Dehydration can make symptoms worse.

Antibiotics are not helpful, since most cases are not due to bacterial infections. The doctor may prescribe an antibiotic only in rare cases when suspecting bacterial infection.

DOs and DON'Ts in Managing Labyrinthitis:

✓ **DO** sit or lie down if you're dizzy.

✓ **DO** tell your doctor if your symptoms suddenly worsen.

✓ **DO** drink plenty of fluids.

✓ **DO** tell your doctor about your medical problems and your medicines (including over-the-counter and herbal products).

✓ **DO** call your doctor immediately if you have a severe headache, fever, or a stiff, sore neck with your symptoms.

✓ **DO** call your doctor if you have problems with your medicines.

⃠ **DON'T** stick anything in your ear.

⃠ **DON'T** stop taking your medicine or change your dosage because you feel better unless your doctor tells you to.

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⦸ **DON'T** get up from a bed or chair too fast. This may make you more dizzy.

⦸ **DON'T** do activities that require good balance.

⦸ **DON'T** drive until you are symptom free without medicine.

⦸ **DON'T** use alcohol, tobacco, and caffeine. They may worsen symptoms.

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FOR MORE INFORMATION

Contact the following source:

- Vestibular Disorders Association Tel: (503) 229-7705 **Website: http://www.vestibular.org**

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MANAGING YOUR

LACTATIONAL MASTITIS

What Is Lactational Mastitis?

Mastitis is an infection of one or more ducts of the breast. It's usually related to breastfeeding and can cause serious illness if not found and treated aggressively. Some 2% to 3% of nursing women get mastitis.

What Causes Lactational Mastitis?

Mastitis is often caused by common bacteria found in the nose and mouth of the baby. Bacteria enter the breast through a crack in the skin (of the nipple) or through the milk duct openings of the nipple. Diabetes and cracked or bruised nipples can increase chances of getting this infection.

What Are the Symptoms of Lactational Mastitis?

Symptoms include a firm, sore, red, tender breast. The upper outer part of the breast is usually affected. Pain or burning in the breast all the time or only when breastfeeding can occur. The breast may show swelling. Some women may develop a high temperature, chills, headaches, and loss of appetite. Persistent high fever and pain in the breast may indicate that an abscess (collection of pus) has occurred in the breast.

How Is Lactational Mastitis Diagnosed?

The doctor makes a diagnosis from symptoms and an examination. Blood tests, breast milk analysis, or cultures of samples taken from the baby's mouth may also be done but aren't really needed to make the diagnosis or start treatment.

How Is Lactational Mastitis Treated?

Treatment involves pain relievers such as ibuprofen and acetaminophen, ice packs, rest, and support (a well-fitting bra). Women with mild mastitis don't need to stop nursing. The doctor

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will prescribe antibiotics for the infection and suggest nursing from the unaffected breast, pumping, or expressing the involved breast. Emptying the breast adequately may stop bacteria from collecting in the breast and may help shorten the infection.

If tenderness and fever don't get better quickly, an abscess (pocket of pus) may be present. The abscess may need prompt surgical drainage.

DOs and DON'Ts in Managing Lactational Mastitis:

✓ **DO** pay attention to good hygiene practices during nursing. Avoid using drying agents, always wash your hands, and keep your nipples and baby clean.

✓ **DO** breastfeed from the uninfected breast and empty both breasts completely using a pump on the infected breast.

✓ **DO** avoid getting dehydrated. Drink extra fluids.

✓ **DO** get enough rest and eat a balanced diet when you nurse. You have a greater chance of infection if you're run-down.

✓ **DO** prevent cracking or fissuring of nipples. Use a breast or nipple shield if you have cracked nipples.

✓ **DO** call your doctor if you have a high temperature, vomiting, or increasing redness, swelling, or pain in your breast.

✓ **DO** check with your doctor in 1 to 2 weeks to make sure that the infection is gone.

⃠ **DON'T** stop nursing unless your doctor says to.

⃠ **DON'T** ignore worsening symptoms. Untreated mastitis can lead to breast abscesses, a

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serious condition.

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Contact the following sources:

- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website: http://www.acog.org**
- WebMD **Website: http://www.webmd.com**
- U.S. Department of Health and Human Services **Website: http://womenshealth.gov**

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MANAGING YOUR

LACTOSE INTOLERANCE

What Is Lactose Intolerance?

Lactose is a sugar in dairy products such as cheese and milk. Lactase, an enzyme in the intestines, digests lactose. Without enough lactase, lactose intolerance can occur.

Lactose intolerance is common. It affects almost 50 million Americans. Almost half of all babies with persistent diarrhea have it. Anyone can have it, but it's more common in African Americans, Asians, and Mexican Americans.

What Causes Lactose Intolerance?

Cells that make lactase enzyme can be damaged by injury or diseases, and then don't make enough lactase. Rarely, children are born with a lactase enzyme deficiency and cannot make lactase.

What Are the Symptoms of Lactose Intolerance?

Most symptoms occur within 30 minutes to 2 hours after eating milk products. They include stomach pain and cramps, bloating, nausea, diarrhea, gas, feeling sick, and rumbling sounds in the abdomen (belly). Children have slightly different symptoms: foamy diarrhea, diaper rash, slowed growth and development, and sometimes vomiting.

How Is Lactose Intolerance Diagnosed?

The doctor will take a medical history and do a physical examination. Tests are done to measure absorption of lactose in the digestive tract. These tests are the lactose tolerance test, hydrogen lactose breath test (most accurate test), and stool acidity test (for children). Rarely, a small tissue sample (biopsy) may need to be taken from the intestine for study when the diagnosis is unclear.

How Is Lactose Intolerance Treated?

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Babies and young children shouldn't have foods containing lactose. Older children and adults usually don't have to avoid lactose completely but should figure out the amount that they can have, based on symptoms after ingestion of lactose. Calcium and vitamin D pills may be needed to replace what would normally be obtained from milk. Calcium is very important for children, teenagers, and pregnant, breastfeeding, and postmenopausal women. Instead of calcium pills, eating more calcium-rich foods, such as shrimp, broccoli, and leafy green vegetables, is possible. Over-the-counter lactase enzymes (drops or chewable) are available. Drops can be put into milk. Chewable tablets help people digest solid foods.

Symptoms take about 3 weeks to go away once eating dairy products stops.

DOs and DON'Ts in Managing Lactose Intolerance:

✓ **DO** get enough calcium and vitamin D, from diet or supplements. Read food labels to see whether food contains lactose or has too much vitamin D and calcium. High-calcium foods include broccoli, kale, greens, oysters, and fish with soft bones (salmon, sardines).

✓ **DO** tell your doctor about all your medicines. Some contain lactose.

✓ **DO** consider breastfeeding your baby if you have a family history of lactose intolerance.

✓ **DO** give babies soy-based formula, not milk.

✓ **DO** call your doctor if a milk-free diet doesn't help symptoms.

✓ **DO** call your doctor if your child doesn't gain weight or refuses food or formula.

⦸ **DON'T** eat foods that may contain hidden lactose. These foods include bread and baked goods, processed breakfast cereals, instant potatoes, soups, breakfast drinks, margarine, lunch

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meats, salad dressings, candies, and mixes for pancakes, biscuits, and cookies.

⦸ **DON'T** take medicines that contain lactose as a base.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Gastroenterology Tel: (703) 820-7400 **Website:** **http://www.acg.gi.org**
- National Digestive Diseases Information Clearinghouse Tel: (800) 891-5389 **Website:** **http://www.niddk.nih.gov/health/digest/nddic.htm**

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MANAGING YOUR

LARYNGEAL CANCER

What Is Laryngeal Cancer?

The larynx lies in front of the neck just above the windpipe (trachea). It's used to make voice sounds and is also called the voice box. It helps breathing and swallowing. During breathing, vocal cords relax and open. The vocal cords close when holding the breath. With swallowing, the larynx stops foods and liquids from going down the windpipe into the lungs. Laryngeal carcinoma is cancer of the larynx.

More than 10,000 new cases are diagnosed in the United States each year. More men than women get it, but in the past 30 years women have been getting it more often, maybe because of increasing tobacco and alcohol use.

What Causes Laryngeal Cancer?

The exact cause is unknown. Some things that increase chances of getting it include age (older than 55), sex (men more than women), smoking, drinking alcohol, gastroesophageal reflux disease (GERD), and work exposures to substances such as sulfuric acid and asbestos. Smoking with drinking means even higher risk. Laryngeal cancer is not contagious.

What Are the Symptoms of Laryngeal Cancer?

A common symptom is lasting hoarseness or change in the voice. Other symptoms are a cough that doesn't go away, trouble swallowing, pain with swallowing, loss of appetite and weight, swollen lymph glands in the neck, and shortness of breath.

How Is Laryngeal Cancer Diagnosed?

For diagnosis, the doctor may do indirect laryngoscopy. The doctor uses a long-handled mirror to look down the throat to see whether vocal cords move properly. The doctor may also do direct

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laryngoscopy and put a thin lighted tube (laryngoscope) through the nose or mouth to look down the throat. Biopsy may be done. In a biopsy, a small piece of tissue is removed to look for cancer cells with a microscope.

Laryngeal cancer must be staged to find out how far it has spread. Staging is usually done with computed tomography (CT) or magnetic resonance imaging (MRI).

How Is Laryngeal Cancer Treated?

Treatments includes surgery, radiation therapy, and chemotherapy. Surgery to remove the larynx is called laryngectomy, either total (removing the whole larynx) or partial (removing only part). Sometimes, lymph nodes are removed. After laryngectomy, a new airway through the front of the neck (tracheostomy) may be needed.

Radiation therapy uses high-energy x-rays to kill cancer cells. It may be used alone to kill small tumors, before surgery to shrink large tumors, or with chemotherapy.

Chemotherapy (drugs that kill cancer cells) may be used before or after surgery or radiation.

DOs and DON'Ts in Managing Laryngeal Cancer:

✓ **DO** ask about loss of voice after treatment and different approaches for learning to speak again.

✓ **DO** call your doctor if you have hoarseness or changes in your voice.

✓ **DO** call your doctor if you have neck or ear pain with hoarseness or swollen lymph glands in your neck.

✓ **DO** call your doctor if you have pain with swallowing or trouble swallowing.

⃠ **DON'T** smoke or drink alcohol.

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⦸ **DON'T** forget that you need a team of doctors, including an oncologist (specialist in diagnosing and treating cancer), radiation oncologist (specialist in radiation treatment), and surgeon.

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FOR MORE INFORMATION

Contact the following source:

- National Cancer Institute Tel: (800) 422-6237 **Website: http://www.cancer.gov**

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MANAGING YOUR

LARYNGITIS

What Is Laryngitis?

Laryngitis is an inflammation (swelling, redness) of the vocal cords that results in hoarseness. Vocal cords are folds of mucous membrane in the larynx (voice box). When they're swollen, sounds made by air passing over the cords are distorted, so the voice sounds hoarse. Laryngitis usually goes away in 2 to 3 weeks, but when it lasts longer, it is said to be a chronic, or long-lasting, illness. Chronic laryngitis may take much longer to go away, depending on the cause.

What Causes Laryngitis?

Most often, a cold, the flu, or using the voice too much (singing or shouting) causes laryngitis, but viral or bacterial infections can also do so. Causes of chronic laryngitis include allergies, chronic sinusitis (sinus infection), smoking, alcohol, and breathing in irritating chemicals. Less often, heartburn or a sore on the vocal cords is the cause. More rarely, a growth causes the condition.

What Are the Symptoms of Laryngitis?

Main symptoms are a low, raspy hoarse voice or the loss of voice. Others include a dry cough, scratchy throat, stuffed nose, or feeling that there's a lump in the throat.

How Is Laryngitis Diagnosed?

The doctor will do a physical examination (head and neck) and maybe a throat culture or a blood test. For chronic laryngitis, a test called a laryngoscopy may be done. In this test, the doctor examines the throat with a mirror or viewing tube.

How Is Laryngitis Treated?

For minor discomfort, a nonaspirin medicine such as acetaminophen can be used. Cough syrups

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and lozenges can also help. Resting the voice by whispering or writing notes instead of talking is usually all that is needed. If a bacterial infection is causing laryngitis, the doctor will prescribe antibiotics. This medicine should be taken until it's completely finished. No special diet is needed, but liquids may be easier going down the throat. No activity restrictions are needed.

If the cause is a growth, a doctor may need to remove it.

DOs and DON'Ts in Managing Laryngitis:

✓ **DO** use a humidifier or breathe in warm steam.

✓ **DO** drink more fluids. Warm liquids, such as chicken soup, are best.

✓ **DO** call your doctor if you get a high fever or have trouble breathing.

✓ **DO** call your doctor if your symptoms last longer than 2 weeks.

⃠ **DON'T** take decongestants.

⃠ **DON'T** drink alcohol, coffee, or tea.

⃠ **DON'T** smoke or breathe in cigarette smoke. Smoking can worsen laryngitis.

⃠ **DON'T** use your voice unless you absolutely have to.

⃠ **DON'T** skip doses or stop taking any prescribed antibiotic, even if you feel better. You must finish all the medicine for it to work well.

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FOR MORE INFORMATION

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Contact the following sources:

- American Academy of Family Physicians Tel: (800) 274-2237 **Website:**

  http://www.aafp.org

- National Institute of Allergy and Infectious Disease Tel: (301) 496-5717 **Website:**

  http://www.niaid.nih.gov

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MANAGING YOUR

LEAD POISONING

What Is Lead Poisoning?

Lead poisoning is a condition in which too much lead accumulates in the body. Lead can then prevent an important step in making blood cells. Severe anemia (low blood) and neurological problems can result, especially in children. Lead poisoning is most common in children 1 to 5 years old. It occurs most often in people with low incomes, and urban children. Children are more sensitive than adults to lead poisoning. It can cause long-term damage but if diagnosed early can be treated.

What Causes Lead Poisoning?

The cause is usually repeated exposure to lead-based paint, plumbing, storage of batteries, pottery, or lead soldering. Indoors, painted windows usually have the most lead. Lead-contaminated dust can occur in older buildings. Air, soil, and some toys and cosmetics can be contaminated with lead. Children in low-income families living in urban areas and adults whose jobs involve lead exposure, such as construction workers and painters, have highest risks.

What Are the Signs and Symptoms of Lead Poisoning?

Symptoms vary with the degree of toxicity and type of exposure (acute or long-term). Children can have subtle symptoms such as speech, language, and learning problems. Some people have muscle aches, irritability, headache, and general fatigue. Symptoms of severe toxicity are cramping in the abdomen (belly), constipation, weight loss, tremor, learning disorders, sensory abnormalities, seizures, and coma. Acute poisoning may lead to severe abdominal pain and neurologic symptoms such as confusion.

How Is Lead Poisoning Diagnosed?

A diagnosis is based on the history of exposure to lead-based paint, blood and urine tests, and

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physical examination. Lead blood levels are measured in micrograms per deciliter (µg/dL). A normal lead level is under 5 µg/dL. An unsafe level is 10 µg/dL or higher.

How Is Lead Poisoning Treated?

The first, most important step is finding and removing the lead source. Children's toys such as swings, including those in public areas, can contain lead. Children should be kept away from old house paint. Families need education about sources of lead exposure. Treatment varies with blood lead levels. Getting enough dietary calcium, iron, zinc, and protein is also important. Children with blood levels between 20 and 44 µg/dL benefit from case management by qualified social workers, environmental assessment, and lead hazard control. Children with high blood lead levels (over 45 µg/dL) will need medicines (chelation therapy). Commonly used medications are succimer (DMSA), edetate (EDTA), and dimercaprol (BAL).

DOs and DON'Ts in Managing Lead Poisoning:

✓ **DO** make sure that toys are lead-free and that children avoid old lead-based paints.

✓ **DO** let cold water run for a minute before using it for cooking or drinking. You may have water with lead from lead pipes. Boiling water doesn't remove lead.

✓ **DO** call your health care provider if you or your child has severe abdominal pain, shortness of breath, fatigue, or chest pain. Call if you think that you or your child has been exposed to lead.

⃠ **DON'T** let children eat paint chips. Don't let them put newspapers and magazines in their mouths.

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⦸ **DON'T** work around lead without using protective equipment and clothes.

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FOR MORE INFORMATION

Contact the following sources:

- National Heart, Lung, and Blood Institute Information Center Phone: 301-592-8573

  Website: www.nhlbi.nih.gov
- National Lead Information Center **Website: http://www.epa.gov/lead/pubs/nlic.htm**
- Housing and Urban Development Office of Lead Hazard Control **Website:**

  http://www.hud.gov/lea/leahome.html
- Environmental Protection Agency Office of Pollution Prevention and Toxics-Lead

  Program **Website: http://www.epa.gov/opptintr/lead/index.html**
- Centers for Disease Control and Protection **Website: http://www.cdc.gov/nceh/lead/**

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CARING FOR YOUR CHILD WITH

LEGG-CALVÉ-PERTHES DISEASE

What Is Legg-Calvé-Perthes Disease?

Legg-Calvé-Perthes disease involves a loss of the blood supply to the ball part of the ball and socket hip joint. The ball part is the top (head) of the femur (thigh bone). This loss of blood supply to the femoral head can lead to collapse of the hip joint and early arthritis and stiffness of that joint. This disease usually occurs in children 4–12 years old, with more boys affected than girls. The disease isn't very common. If it's found early enough, it can be treated. Usually one hip is affected, but sometimes symptoms can occur in both hips.

What Causes Legg-Calvé-Perthes Disease?

The cause of the loss of blood supply is unknown.

What Are the Symptoms of Legg-Calvé-Perthes Disease?

This disease usually starts with hip pain, but some children report pain in the thigh or groin or near the knee. Usually, the pain starts without a direct injury to the area. The child may limp or have more and more trouble walking because of the pain.

How Is Legg-Calvé-Perthes Disease Diagnosed?

The doctor makes a diagnosis from the medical history, age of the child, and a physical examination that shows pain when the hip is rotated. The child also will have a limp. X-rays are needed to confirm the diagnosis. Magnetic resonance imaging (MRI) will also show how much of the ball of the hip joint is involved.

How Is Legg-Calvé-Perthes Disease Treated?

The goals of treatment are to prevent severe arthritis, have good range of motion of the joint, take weight off the area, and keep the ball of the thigh bone inside the socket. An orthopedic sur-

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geon (specialist who treats bone and muscle disorders) who has treated children should be involved in care.

The best treatment is to find the disease early. After the orthopedic surgeon confirms the diagnosis, several treatment options are available. The surgeon will use the child's age and the look of the joint on x-rays to decide whether to use casts, braces, or sometimes surgery.

DOs and DON'Ts in Managing

Legg-Calvé-Perthes Disease:

✓ **DO** be careful with body casts and long leg braces. They are important for your child to wear but can be troublesome and uncomfortable. To relieve itching, use a hair dryer on a cool setting to blow air into the cast, or tap on the cast directly over the itch. Don't put something into the cast.

✓ **DO** call your doctor if your child constantly feels pain in one spot under the brace or cast. This spot may be a pressure sore.

✓ **DO** call your doctor if redness or swelling occurs, or a foul odor comes from the cast.

✓ **DO** call your doctor if after the treatment plan has been chosen, there are any changes from the program.

✓ **DO** ask your doctor for referrals to specialists who treat this condition.

⦸ **DON'T** put anything inside the cast to scratch. This can cause a skin sore, which can become infected.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186, (800) 346-2267 **Website:** **http://www.aaos.org**
- National Institute of Arthritis and Musculoskeletal and Skin Disease Tel: (877) 226-4267 **Website:** **http://www.niams.nih.gov**

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MANAGING YOUR

LEGIONNAIRES' DISEASE

What Is Legionnaires' Disease?

Legionnaires' disease is an uncommon type of pneumonia (lung infection). It may present as an isolated case, but sometimes the disease spreads through a group, such as passengers on a ship or people staying at a hotel.

Elderly people, people with diabetes mellitus or impaired immune systems, and those who have organ transplants are most likely to develop Legionnaires' disease.

What Causes Legionnaires' Disease?

The cause is a bacterium named *Legionella pneumophila*. The disease gets its name because it was first identified when it affected many people attending an American Legion convention in the 1970s. This bacteria can often be found in water containers. Places holding water such as parts of air conditioning cooling towers may be a source of contamination. That's why many people can be affected in one location. People are exposed when they breathe in droplets containing *Legionella* bacteria. The organism generally doesn't spread from person to person. No vaccine is available to prevent the disease.

What Are the Symptoms of

Legionnaires' Disease?

First symptoms are headache, muscle aches, tiredness, and weakness. A high temperature (more than 103˚ F, chills, shortness of breath, cough, and chest pain may develop. The fever usually goes down in 3 days, and other symptoms improve in 6 to 10 days. Coughing can bring up blood-streaked sputum or phlegm. People can also have diarrhea, stomach pain, loss of appetite, confusion, and inability to sleep.

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How Is Legionnaires' Disease Diagnosed?

The doctor does a physical examination and obtains laboratory tests (of urine and blood). A chest x-ray is also done. Diagnosis may be hard because symptoms aren't specific but are like those of many other forms of pneumonia and some viral infections.

How Is Legionnaires' Disease Treated?

People with Legionnaires' disease are often hospitalized. Antibiotics are given for 14 to 21 days. Intravenous antibiotics are given initially and then switched to oral antibiotics before discharge. Symptoms usually begin to improve within 48 to 72 hours of starting antibiotic therapy.

The disease can be very serious and potentially life threatening in immunocompromised people. Most healthy people usually recover from the disease.

After the first treatment or hospital discharge, people may still feel tired and weak for several weeks. People with heart and lung diseases, diabetes, or weakened immune system may take longer to recover.

DOs and DON'Ts in Managing

Legionnaires' Disease:

✓ **DO** take your antibiotics as prescribed. If you miss a dose, just start again with the next dose and continue to take pills as scheduled until they're gone.

✓ **DO** rest until you feel better. Some symptoms may last for several weeks, but all should eventually go away.

✓ **DO** take acetaminophen for fever and pain.

✓ **DO** drink plenty of fluids (six to eight glasses a day) and breathe moist air to help raise

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phlegm.

✓ **DO** call your doctor if you are being treated at home and don't improve or you become more ill after 48 hours of antibiotic therapy.

⃠ **DON'T** smoke. Smoking can increase your risk of getting Legionnaires' disease.

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FOR MORE INFORMATION

Contact the following sources:

- Infectious Diseases Society of America Tel: (703) 299-0200 **Website:** **http://www.idsociety.org**
- American Thoracic Society Tel: (212) 315-8600 **Website:** **http://www.thoracic.org**
- American Lung Association Tel: (212) 315-8700, (800) 586-4872 **Website:** **http://www.lungusa.org**

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MANAGING YOUR

LEPROSY

What Is Leprosy?

Also called Hansen's disease, leprosy is an infection that involves mainly the skin and nerves. The number of cases worldwide has fallen, so now approximately half a million new cases are diagnosed yearly. Nearly three fourths of leprosy cases occur in India, Brazil, Bangladesh, Indonesia, and Myanmar. About 150 new cases occur yearly in the United States, more than 85% in immigrants.

There are two types: paucibacillary and multibacillary. In paucibacillary leprosy, people have fewer than five skin lesions and skin smears show no bacteria. In multibacillary leprosy, people have six or more skin lesions and bacteria are found.

Leprosy is more common in women than men. People of any age can get it, but it usually occurs in young children. Leprosy can spread from person to person (through the respiratory tract or broken skin), but the risk of catching it is low. Found early, leprosy can be cured without major lasting effects.

What Causes Leprosy?

The cause is a kind of bacteria called *Mycobacterium leprae*.

What Are the Symptoms of Leprosy?

Skin and nerves that control muscle movement and feeling in the arms and legs are affected. A rash or lumps called nodules are usually noted first. Skin lesions may look darker or lighter than usual. Nodules have a clear center, with loss of feeling; the affected area can't sweat. Many people complain of feeling pins and needles in hands or feet and lumps along the nerve, especially on arms and legs.

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Nerve involvement can lead to muscle weakness and wasting (atrophy), especially in hands and feet. Hands and feet contract and can't be used well, and foot drop and clawed hands and toes result. Leprosy involving facial nerves may cause the bridge of the nose to collapse, trouble closing upper eyelids, and loss of eyebrows.

How Is Leprosy Diagnosed?

The doctor relies on a medical history and physical examination. The bacteria will be found on skin smears or biopsy. A smear involves scraping skin, smearing the sample on a slide, and looking at cells under a microscope. A biopsy involves removing a piece of skin (or nerve) for study under a microscope.

How Is Leprosy Treated?

Antibiotics (rifampin, dapsone) are usually given for paucibacillary leprosy. People with multibacillary leprosy take a combination of antibiotics. A doctor who specializes in infections should be involved in care.

DOs and DON'Ts in Managing Leprosy:

✓ **DO** take medicines as prescribed.

✓ **DO** get proper foot care and shoes if leprosy involves leg nerves, to prevent skin breakdown and ulcers.

✓ **DO** see an infectious disease expert. Call your doctor if you need a referral.

✓ **DO** call your doctor if you have a rash, tender lumps on your skin, muscle weakness, or a feeling of pins and needles going down your arms or legs.

✓ **DO** call your doctor if you have medicine side effects.

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⦸ **DON'T** miss follow-up appointments.

⦸ **DON'T** forget that, although the risk of giving leprosy to someone else is low, your family members and close contacts should be examined often.

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FOR MORE INFORMATION

Contact the following sources:

- American Leprosy Missions Tel: (800) 543-3135 **E-mail:** amlep@leprosy.org
- International Federation of Anti-Leprosy Associations **Website:** http://www.ilep.org.uk/

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MANAGING YOUR

ORAL HAIRY LEUKOPLAKIA

What Is Oral Hairy Leukoplakia?

Leukoplakia refers to white spots that occur on the inner lining (mucosa) of the mouth, lips, or tongue. Oral hairy leukoplakia is the mucosal disorder in the mouth. If untreated, up to 20% of cases can become cancer. Treatment can usually cure leukoplakia, but it often comes back and needs treatment again.

What Causes Oral Hairy Leukoplakia?

Smoking is the most common cause of oral leukoplakia. Chronic irritation, such as from poorly fitting dental appliances, is also related to leukoplakia. Some mouth infections such as syphilis, Epstein-Barr virus (EBV) infection, and candidiasis may also increase the risk of getting leukoplakia. It's one of the most common viral oral diseases of people with human immunodeficiency virus (HIV) infection. It's not contagious.

What Are the Symptoms of Oral Hairy Leukoplakia?

The most common symptom is a small white patch inside the mouth or on the tongue or lips. The patch is slightly raised and well defined. Many patches can occur. The area feels firm and may be more sensitive during eating.

How Is Oral Hairy Leukoplakia Diagnosed?

The doctor makes a diagnosis by examining the area. A biopsy is usually needed to find out whether cancer or precancerous lesions are present. In a biopsy, the doctor removes a small piece of the leukoplakia. The doctor first uses an anesthetic such as lidocaine to numb the area. A sharp sterile knife or biopsy tool is then used to get the sample, which is sent to a laboratory for

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study with a microscope to find out if cancer or precancerous cells are present.

How Is Oral Hairy Leukoplakia Treated?

All people should stop smoking. Small areas of leukoplakia sometimes go away after smoking stops. Sometimes the doctor removes a problem area completely instead of just taking a biopsy sample. Electrosurgery (using an electric needle) and cryosurgery (freezing) can be used to treat small areas. Beta-carotene (a form of vitamin A) and isotretinoin are two medicines taken by mouth that are sometimes used for treatment. These drugs usually should be taken daily for a few months. Isotretinoin can cause birth defects and shouldn't be taken by pregnant women. Leukoplakia of the lip (and outer vaginal area) can sometimes be treated with fluorouracil cream, applied two times per day for 2 to 3 weeks. This drug causes redness, soreness, and inflammation and actually destroys the involved area.

DOs and DON'Ts in Managing

Oral Hairy Leukoplakia:

✓ **DO** tell your doctor about suspicious-looking or unusual areas, including anything on the skin, inside the mouth, or on the tongue.

✓ **DO** call your doctor if leukoplakia doesn't go away after treatment.

✓ **DO** avoid chronic irritation caused by teeth, dentures, or sharp dental appliances.

✓ **DO** call your doctor if new white patches occur.

✓ **DO** call your doctor if fever or bleeding occurs after treatment.

⊘ **DON'T** smoke or use tobacco products. Smoking is the major risk factor for leukoplakia of

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the mouth and tongue.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Otolaryngology—Head and Neck Surgery Tel: (703) 836-4444 **Website: http://www.entnet.org**
- American Academy of Dermatology Tel: (847) 330-0230, (888) 462-3376 **Website: http://www.aad.org**

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MANAGING YOUR

LICE

What Are Lice?

Lice are tiny parasites that live on the body or in clothing and cause skin inflammation (redness, itching, swelling) called pediculosis. The three types are head lice, body lice, and pubic (crab) lice. Head lice are most common in children. About 6 to 12 million cases per year occur in the United States.

What Causes Lice?

Lice live on the head, eyebrows, eyelashes, facial hair, pubic hair, and the back of the neck. Lice eggs, called nits, are white and are easier to see than the small gray lice. Sharing a brush, comb, or hat with someone who is infected spreads lice. They can also spread by close person-to-person contact. Pubic lice spread by sexual contact.

What Are the Symptoms of Lice?

Symptoms usually go away within a few days of treatment. They include an itchy scalp (worse at night), a moving feeling in the hair, rash and sores on the scalp, and nits on the scalp and eyebrows.

How Are Lice Diagnosed?

The doctor will take a medical history and do an examination, with special attention to the scalp and using a magnifying glass. The doctor may also use a special light called a Wood's lamp to see nits.

How Are Lice Treated?

Lice are treated with medicated creams, lotions, or shampoos applied to affected body parts. Some of these include permethrin (Nix®, Elimite®), applied once; pyrethrins (Rid®, R and C®,

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A-200®), reapplied in 7 days; and lindane (Kwell®, by prescription), reapplied in 7 days.

Lice can also be removed with a special comb and by pulling out lice or nits that are left with fingers or tweezers. A magnifying glass helps show the nits and lice. Eyelashes should be checked for lice and nits.

Side effects of treatments include skin irritation or body absorption of the medicine. These usually occur when medicine is applied more often than recommended. Keep all preparations out of the eyes and out of the reach of children.

DOs and DON'Ts in Managing Lice:

✓ **DO** tell your doctor if you're pregnant.

✓ **DO** check the heads of all family members.

✓ **DO** call your doctor if symptoms don't get better after 1 week.

✓ **DO** protect your eyes from the anti-lice shampoo.

✓ **DO** keep your child out of school, day care, or camp until your doctor says that it's OK to go back.

✓ **DO** clean clothing, bedding, pillows, stuffed toys, and fabric furniture that was used during the infection. Wash all clothes in hot water at 130º F for 20 minutes. Dry them in a hot dryer. Clean the house. Put clothes that cannot be washed in a sealed plastic bag for 2 weeks before dry-cleaning them.

✓ **DO** soak combs and brushes for at least 1 hour in anti-lice shampoo, disinfectant, hot water, or rubbing alcohol.

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✓ **DO** call your doctor if family members or sexual partners have symptoms of lice or symptoms return after treatment.

⊘ **DON'T** use more anti-lice shampoo than recommended.

⊘ **DON'T** use anti-lice shampoo and medicine if you're pregnant unless your doctor says to.

⊘ **DON'T** use medicine around your eyes unless your doctor tells you to.

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FOR MORE INFORMATION

Contact the following source:

- National Pediculosis Association Tel: (781) 449-6487, (866) 323-5465 **Website:** **http://www.headlice.org**

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MANAGING YOUR

LICHEN PLANUS

What Is Lichen Planus?

Lichen planus (LP) is an illness that affects the skin and mouth. It occurs at any age but is more common in people older than 40. It develops slowly and can spread over several months. No cure exists, but LP usually tends to disappear or improve significantly after 6 to 18 months. Some people have it more than once.

What Causes LP?

The cause is unknown. LP cannot spread to others by contact or germs. It doesn't run in families and isn't passed on from parents to children. Some medicines, including antimalarial drugs, penicillamine, tetracycline, water pills (diuretics), quinine, propranolol, and captopril, tend to cause LP-like reactions. LP isn't skin cancer.

What Are the Symptoms of LP?

LP can occur anywhere but is most common on inner wrists, forearms, and ankles. Small, very itchy bumps that are reddish-purple with a whitish surface appear. The bumps are raised, with flat tops and maybe white scales or flakes.

An irregular whitish line inside the mouth or vagina may also occur. Mouth sores may hurt. Patches of hair on the head may be lost.

How Is LP Diagnosed?

The doctor can diagnose LP by looking at the skin and mouth. The doctor may suggest seeing a specialist who treats skin problems (dermatologist). This doctor may remove a small piece of tissue (biopsy sample) for study, to help with diagnosis.

How Is LP Treated?

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If LP isn't itchy or painful, no treatment is needed. After about 4 months, the rash doesn't get worse.

For symptoms, LP has many treatments. Some treatments control symptoms (in days to weeks), and some may reduce the number of lesions. Because the cause is unknown, no specific treatment is effective in all people. Treatment can make your skin look better. Creams and ointments help control itching, as do antihistamines. Medicines should be applied just after bathing. Cortisone-like medicines are used most often.

For severe LP, there are medicines that can be taken by mouth. The affected area can be soaked in cool water to relieve itching.

Reducing stress, by using relaxation techniques or getting counseling, can help LP.

The doctor may suggest stopping a medicine that is related to LP. A substitute drug may be needed for chronic conditions such as high blood pressure.

DOs and DON'Ts in Managing LP:

✓ **DO** see your doctor regularly for oral cancer screening. LP in your mouth means that you may have a greater risk of getting oral cancer.

✓ **DO** treat your skin gently, because LP is caused by inflammation, and trauma can cause further lesions. No specific diet, exercise, or other medicines will cure LP.

✓ **DO** see your doctor if the lesions are scratched and become infected and drain pus.

✓ **DO** see an eye doctor (ophthalmologist) if irritation of the eye develops when you have this condition.

✓ **DO** call your doctor if your mouth lesions become so painful that you cannot eat.

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⦸ **DON'T** scratch, to avoid starting new lesions.

⦸ **DON'T** use over-the-counter medicines, creams or lotions containing perfumes, or anything that can irritate the skin.

⦸ **DON'T** get too much sun, because sunburn is traumatic to the skin. Sun exposure itself doesn't make LP worse.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Dermatology Tel: (866) 503-SKIN (7546) **Website:** **http://www.aad.org/**

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MANAGING YOUR

LICHEN SCLEROSUS

What Is Lichen Sclerosus?

Lichen sclerosus is an uncommon skin disorder that most often affects women. It can also affect men and children. It's most common in women after menopause and in men 40 to 60 years old. It usually occurs on the vulva (the outer lip of the vagina) in women. Men can have it on the head of the penis. It can affect skin around the anus. It sometimes occurs on the upper body, breasts, and upper arms.

What Causes Lichen Sclerosus?

The cause is unknown. Some think that it's the result of an overactive immune system or a genetic problem. It's not contagious, however.

What Are the Symptoms of Lichen Sclerosus?

When the disease occurs outside the genital area, people usually have no symptoms.

Women with early disease of the vulva usually have an itchy, small, shiny, smooth, patchy white skin. The skin is thinner than normal. Rubbing or scratching can lead to painful sores, irritation, genital bleeding, and bruising. Burning or pain can occur during urination and especially during sex. When the disorder occurs around the anus, discomfort can interfere with bowel movements and in rare cases lead to constipation. This problem is more common in children. Most men with the genital disorder often haven't been circumcised. Sometimes, erections are painful, and urethra can become narrow or blocked. The urethra is the tube that takes urine out of the body.

How Is Lichen Sclerosus Diagnosed?

The health care provider diagnoses most advanced cases by a physical examination of the area. Early cases usually need a biopsy. In a biopsy, a piece of tissue is removed and checked with a

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microscope.

How Is Lichen Sclerosus Treated?

No treatment is needed for lichen sclerosus outside the genital area. Lichen sclerosus of genital skin should be treated, even if there aren't any symptoms. Untreated, scarring can occur that may narrow genital openings and interfere with urination or sex. In uncircumcised men, circumcision is the treatment. Circumcision removes the affected skin, and the disorder usually doesn't come back. Prescription medicines (topical corticosteroids) are the standard for people with the disorder and symptoms. Creams and ointments can stop the itching, but treatment can't reverse scarring that may have occurred.

DOs and DON'Ts in Managing Lichen Sclerosus:

✓ **DO** avoid activities that involve pressure or friction on the vulvar area. Pressure or friction can lead to pain, irritation, and bleeding.

✓ **DO** call your health care provider if you see new skin lesions on your body, see genital skin lesions, or cannot retract the foreskin over the head of your penis. Call if you have pain with sex or pain or burning with urination. Call if you need a referral to a dermatologist, gynecologist, or urologist.

⃠ **DON'T** forget that this condition doesn't cause skin cancer. However, skin that is scarred by lichen sclerosis is more likely to get skin cancer. About 1 in 20 woman with untreated vulvar lichen sclerosis develops skin cancer. People with the disease should see their health care provider every 6 to 12 months. The health care provider should watch for and treat changes that might mean skin cancer.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Dermatology Tel: (847) 330-0030 **Website: http://www.aad.org**
- National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Information Clearinghouse National Institutes of Health Phone: 301-495-4484 Toll free: 877-22-NIAMS TTY: 301-565-2966

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MANAGING YOUR

LIPOMA

What Is a Lipoma?

A lipoma is a deposit of fatty material that grows slowly under the skin, between the skin and muscle layer. They occur most often on the neck, back, shoulders, arms, and thighs; they may also grow in other parts of the body such as the intestine. Lipomas are harmless. They are not cancerous and are the most common benign tumors in adults. Lipomas can affect both sexes and all ages, but are more common in middle-aged women than other people.

What Causes a Lipoma?

The cause is unknown. Lipomas tend to be more common in certain families, so hereditary factors may be involved in their development.

What Are the Symptoms of a Lipoma?

A lipoma usually starts as a painless, round, soft bump under the skin. People may not know that they have a lipoma. Most feel a bit doughy or rubbery, but they range in firmness from soft to hard. They can usually be moved around easily. More than one may be present. They can be painful if they press on nerves or if they have many blood vessels inside them. They vary in size but are rarely larger than 3 inches across. They occur most often on the forearms, legs, torso, and neck area. Lipomas can occur in other parts of the body, such as the lungs, intestines, and breasts, and their symptoms depend on the location.

How Is a Lipoma Diagnosed?

The doctor will suspect the diagnosis from a physical examination. However, the diagnosis can be confirmed only by a biopsy. In a biopsy, the doctor removes a piece of the tissue and looks at it with a microscope.

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How Is a Lipoma Treated?

Lipomas are harmless lumps that usually don't need any treatment. Lipomas that bother people because of cosmetic reasons or because they are extremely large are usually removed by surgery. Lipomas don't usually recur after surgery. They can also be removed by liposuction, but liposuction often cannot remove the whole lipoma.

Lipomas are harmless, but the doctor should make sure that the lump isn't another kind of lump such as a cyst, abscess, or liposarcoma. Liposarcomas are cancers that grow in fatty tissues. However, they grow quickly (instead of slowly, like lipomas), don't easily move under the skin, and can be painful.

DOs and DON'Ts in Managing a Lipoma:

✓ **DO** have any lump that may appear on your body checked. Lipomas are harmless, but other lumps may be more serious and may need treatment.

✓ **DO** call your doctor if you see a significant increase in the size, such as doubling, of your lipoma in a 12-month period. Because lipomas grow slowly, the size increase could be a sign of another problem.

✓ **DO** call your doctor if you see redness or swelling and warmth at the site of surgery for the lipoma.

✓ **DO** call your doctor if the lipoma becomes painful.

⃠ **DON'T** ignore lumps that you find on your body. Have your doctor check them.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Dermatology Tel: (847) 330-9239, (866) 503-7546 **Website:** **http://www.aad.org**
- American College of Surgeons Tel: (312) 202-5000 **Website:** **http://www.facs.org**

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MANAGING YOUR

LISTERIOSIS

What Is Listeriosis?

Listeriosis is a serious infection caused by eating food contaminated with bacteria. These bacteria are found most often in undercooked meat and in dairy products. Listeriosis is a serious public health problem but it's an uncommon infection.

Anyone can get infected, but healthy adults and children rarely become seriously ill. However, certain people, such as pregnant women and unborn babies, have a higher risk. Listeriosis causes a premature birth, miscarriage, or stillbirth. A newborn can also become seriously ill if infected before birth. People with weak immune (infection-fighting) systems are also at high risk. These people include those with diseases such as cancer or AIDS, those who have organ transplants, and elderly people.

What Causes Listeriosis?

The cause is eating food contaminated with the kind of bacteria named *Listeria monocytogenes*. *Listeria* is found in soil and water and can get on raw vegetables from soil or from fertilizer (manure). *Listeria* can also get into raw meats and milk and processed foods (such as deli cheeses, cold cuts, and hot dogs).

What Are the Symptoms of Listeriosis?

Some people have a flulike illness, with symptoms such as fever, muscle aches, nausea, vomiting, diarrhea, and stomach pain. If bacteria enter the nervous system, symptoms may be worse. Headache, stiff neck, seizures, loss of balance, and feeling confused or disoriented can occur.

How Is Listeriosis Diagnosed?

The doctor will do a physical examination and take a medical history. Tests done for diagnosis

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may include a blood culture and spinal tap. A blood culture involves taking blood from a vein and sending it to a laboratory for study, to see whether bacteria are in the blood and can grow.

The spinal tap involves removing a small sample of fluid from around the spinal cord and having a laboratory test it for the presence of the *Listeria* bacterium.

How Is Listeriosis Treated?

Treatment is with antibiotics. People are often treated in the hospital. Antibiotics can then be given intravenously (injected directly into the vein). This method is the fastest and most effective way of giving an antibiotic.

Antibiotic treatment usually lasts for 2 weeks. People with weak immune systems may need longer treatment, because the illness often comes back.

DOs and DON'Ts in Managing Listeriosis:

✓ **DO** tell your doctor about all your medicines (including over-the-counter drugs and herbal products).

✓ **DO** call your doctor if you still have symptoms after you finish the antibiotics.

✓ **DO** thoroughly cook all animal products including eggs, meat, and poultry.

✓ **DO** wash all fruits and vegetables before eating them.

✓ **DO** wash your hands and cooking utensils with hot soapy water after handling food, especially after contact with raw and deli meats.

⊘ **DON'T** stop taking your antibiotics without asking your doctor first.

⊘ **DON'T** drink unpasteurized milk. Pasteurized milk has been heated to kill bacteria.

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FOR MORE INFORMATION

Contact the following source:

- Centers for Disease Control and Prevention Tel: (800) 232-4636 **Website:**

  http://www.cdc.gov

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MANAGING YOUR

LIVER ABSCESS

What Are Liver Abscesses?

The liver is an important organ with many functions: it stores energy, makes proteins, and removes harmful substances from the body. When infected by bacteria or parasites, the liver can form small holes that fill with pus. Any pus-filled hollow pockets or cavities in the liver are called liver abscesses.

What Causes Liver Abscesses?

Bacteria can cause abscesses that are called pyogenic abscesses (meaning forming pus). Infections spread from appendicitis, diverticulitis, and gallbladder cause most pyogenic abscesses. Parasites such as the ameba *Entamoeba histolytica* also cause abscesses (called amebic abscesses). Most of these occur because of poor sanitation. People get these parasites by eating food contaminated by stools (bowel movements) of infected people. Drinking and eating contaminated water and food can also transfer parasites to people. Worldwide, amebic abscesses are more common than pyogenic abscesses.

What Are the Symptoms of Liver Abscesses?

Symptoms may not appear right away. Symptoms include fever, chills, sweats, nausea, vomiting, and diarrhea. Pain over the right upper part of the abdomen (belly) usually occurs.

Other less common symptoms are chest pain, loss of appetite, and jaundice (yellow color of skin and eyes).

How Are Liver Abscesses Diagnosed?

The doctor usually finds liver abscesses by ultrasonography, which uses sound waves to make pictures of the liver. Computed tomography (CT) of the abdomen is better for finding abscesses.

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A needle biopsy of the abscess may be done when antibiotic treatment is not working well. With this procedure a needle is passed through the abdomen into the abscess. Tissue and fluid are taken out and are studied with a microscope. Cultures are done to grow and identify the specific cause of the abscess.

How Are Liver Abscesses Treated?

The best treatment is draining pus and using antibiotics. Most people need two or three different antibiotics. Usually, antibiotics are given intravenously until fever and infection are gone.

People with pyogenic abscesses may have pus drained from the abscesses. This is done by passing a needle through into the abscesses and draining the pus. Drainage of an amebic abscess isn't needed, unless antibiotic treatment doesn't work or a pyogenic cause is suspected.

DOs and DON'Ts in Managing a Liver Abscess:

✓ **DO** remember that most people with pyogenic liver abscesses improve within 2 weeks of antibiotic treatment and drainage. The fever usually resolves in most people with amebic abscesses in 4 to 5 days of treatment.

✓ **DO** take your antibiotics as instructed. Finish taking all the medicine, even if you feel better.

✓ **DO** wash your hands before eating.

✓ **DO** call your doctor if you have severe abdominal pain, vomiting, diarrhea, fever, chills, and sweats.

✓ **DO** call your doctor if your skin turns yellow.

⊘ **DON'T** drink alcohol when taking medicines prescribed for liver abscesses.

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⦸ **DON'T** drink tap water in countries where water may be contaminated.

⦸ **DON'T** ignore symptoms.

⦸ **DON'T** forget that untreated pyogenic liver abscess is fatal in nearly 100% of cases!

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FOR MORE INFORMATION

Contact the following source:

- Centers for Disease Control and Prevention Tel: (404) 639-3311 **Website:** **http://www.cdc.gov**

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MANAGING YOUR

LIVER TRANSPLANTATION

What Is Liver Transplantation?

The liver is an important organ in the upper abdomen (belly). It helps in digesting food, cleans the blood, and stores nutrients.

Liver transplantation is surgery to remove a diseased liver and replace it with a healthy one. It's used for end-stage liver disease (ESLD), acute fulminant liver failure, and unresectable hepatocellular carcinoma (liver cancer).

What Are the Reasons for Liver Transplantation?

The most common reason in adults is cirrhosis. Cirrhosis destroys healthy liver cells and scars the liver. Viruses (hepatitis B and C), alcohol, autoimmune liver diseases, buildup of fat in the liver, and hereditary liver diseases can cause cirrhosis. In children, the most common reason is missing or damaged bile ducts (tubes that take bile out of the liver). Blocked bile ducts cause cirrhosis. Other reasons are liver cancer and hereditary diseases.

What Are the Symptoms of Liver Disease?

People feel tired or weak. They have nausea, weight loss, no appetite, and easy bruising or bleeding. Fluid builds up in the abdomen and causes bloating (ascites). Jaundice (yellow skin and eyes) may occur.

How Are People Chosen for Liver Transplantation?

Many more people need a transplant than there are livers available. The nonprofit organization called United Network for Organ Sharing (UNOS) handles selection. The MELD scoring system is used for most people to decide who gets a transplant.

Liver transplantation generally isn't done for people with other cancer; serious heart, lung,

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or nerve disease; persistent alcohol or illegal drug abuse; or severe infection.

How Is Liver Transplantation Done?

Whole livers come from people who have died (cadaveric donor). Healthy living donors (usually family members) can also donate part of their liver. This can be done because the liver can regrow to near normal size.

All livers are tested before surgery. Tests make sure that the liver is healthy, the right size, and that blood types match. The surgeon disconnects the diseased liver from bile ducts and blood vessels. The surgeon then puts in the healthy liver and reconnects it.

What Are Complications of Liver Transplantation?

Return of the original disorder is the most common problem. Other complications include rejection, which can result in nausea, pain, fever, and jaundice. Rejection occurs when the immune (infection-fighting) system attacks the new liver. Medicines (steroids, cyclosporine, tacrolimus) can stop rejection. A liver biopsy is often needed to confirm rejection. For a biopsy, the doctor takes a piece of liver to study with a microscope.

Hepatitis C and other infections may also hurt a new liver.

DOs and DON'Ts in Managing Liver Transplantation:

✓ **DO** see your doctor often and have regular blood tests to be sure that your new liver works well.

✓ **DO** use medicines, including over-the-counter ones, only if your doctor says you can.

✓ **DO** avoid sick people.

✓ **DO** eat a balanced diet, get regular exercise, and take your prescribed medicines.

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✓ **DO** tell your transplantation team about sickness, fever, nausea, vomiting, or diarrhea.

⃠ **DON'T** drink alcohol, especially if it damaged your original liver.

⃠ **DON'T** get pregnant in the first year after transplantation. Talk to your transplant team about pregnancy after transplantation.

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FOR MORE INFORMATION

Contact the following sources:

- National Digestive Diseases Information Clearinghouse E-mail: nddic@aerie.com

  Website: http://www.niddk.nih.gov/health/digest/nddic.htm

- American College of Gastroenterology Tel: (703) 820-7400 **Website:**

  http://www.acg.gi.org

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MANAGING YOUR

LIVER CANCER

What Is Liver Cancer?

Hepatoma (also called hepatocellular carcinoma) is the most common cancer of the liver. It's a primary tumor, meaning the tumor started growing in the liver and did not spread from someplace else in the body.

In the United States, about 6000 new cases occur each year. Hepatomas are more common in men than women, usually occurring in people 50 to 70 years old. Unfortunately, many hepatomas are found late. Early diagnosis gives the best hope for cure.

What Causes Liver Cancer?

Hepatoma occurs most often in people with cirrhosis (liver scarring), chronic hepatitis B, or chronic hepatitis C or after severe liver damage from chronic alcohol abuse. Hepatomas aren't contagious or passed from parents to children.

What Are the Symptoms of Liver Cancer?

One third of people do not have any symptoms. Symptoms may include pain in the abdomen (belly), an abdominal mass, abdominal fluid (ascites), and jaundice (yellow skin color). Later, weakness, loss of appetite, weight loss, and fatigue can occur.

How Is Liver Cancer Diagnosed?

Diagnosis is difficult because hepatomas often don't have many early symptoms. To help diagnosis, the doctor may initially do blood tests called alpha-fetoprotein and liver function tests for people with cirrhosis or hepatitis B or C. However, these tests are not diagnostic because not everyone with a hepatoma has abnormal blood tests, so the doctor may want imaging studies called ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI). If these imaging studies show a probable tumor, a liver biopsy will be done. In a biopsy, liver tissue is taken with a needle and looked at with a microscope.

How Is Liver Cancer Treated?

Untreated people have a rapid downhill course. Surgery offers the best chance for cure, but most people cannot have surgery because of cirrhosis or tumor spread. Smaller tumors (less than 5 cm, or about 2 inches) that haven't spread and with remaining liver working well are less likely to recur after surgery.

People who cannot have surgery may have other treatments, including injecting chemother-

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apy drugs into the artery that feeds the tumor or injecting ethanol (alcohol) directly into the tumor to destroy it.

People with very large tumors or with too much liver damage may be candidates for liver transplantation. A team of doctors and other health care workers must work together to manage care.

DOs and DON'Ts in Managing Liver Cancer:

✓ **DO** call your doctor if you have abdominal pain or vomit blood.

✓ **DO** tell your doctor if you have a drinking problem.

✓ **DO** tell your doctor if you feel a mass or large lump in the right upper part of your abdomen (belly).

⃠ **DON'T** drink alcohol. Alcohol abuse can lead to cirrhosis and increase the risk of hepatoma.

⃠ **DON'T** miss follow-up doctor appointments.

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FOR MORE INFORMATION

Contact the following sources:

- American Liver Foundation Tel: (800) 223-0179 **Website:** **http://www.liverfoundation.org**
- American Cancer Society Tel: (800) 227-2345 **Website:** **http://www.cancer.org**
- National Cancer Institute Cancer Information Service Tel: (800) 422-6237 **Website:** **http://www.cancer.gov**

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MANAGING YOUR

LONG QT SYNDROME

What Is Long QT Syndrome?

Long QT syndrome is a heart disorder in which the heart's electrical system is abnormal. The name comes from the Q-T interval of the electrocardiogram. A tiny electrical current stimulates the heart to contract. As the heart muscle relaxes, its cells recharge (become repolarized). Long QT syndrome affects this phase and can lead to serious heart rhythm disturbances. The syndrome can cause fast, chaotic heartbeats. The syndrome usually affects children and young adults. It usually starts at 8 to 20 years old. It may account for more than 3000 deaths per year in the United States.

What Causes Long QT Syndrome?

The syndrome may be inherited, caused by mutations of genes controlling the heart's electrical system. When associated with congenital deafness, the syndrome is called Jervell and Lange-Nielsen syndrome. With normal hearing, it's called Romano-Ward syndrome. An acquired syndrome may be caused by drugs such as quinidine, procainamide, disopyramide, amiodarone, methadone, and sotalol. Antidepressants, antipsychotics, certain antihistamines, and use of the antibiotic erythromycin with the antifungal drug ketoconazole, have caused the syndrome.

What Are the Symptoms of Long QT Syndrome?

Symptoms include syncope (fainting), frequent palpitations (rapid heartbeats), and seizures. The syndrome can start without warning symptoms, and sudden death may be the first and last one. Heart rhythm problems may affect blood pressure, which can lead to loss of consciousness and death.

How Is Long QT Syndrome Diagnosed?

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Your health care provider may suspect long QT syndrome from your medical history. The diagnosis is made by measuring the QT interval on an electrocardiogram (ECG).

How Is Long QT Syndrome Treated?

People may not need therapy if they have no symptoms and no family history of sudden death. However, they should avoid competitive sports, strenuous exercise, and the drugs named previously. People with rhythm disturbances and a family history of sudden death need medications (beta-blockers) and should be evaluated for placement of a permanent pacemaker. Prescribed medicines won't cure the condition, but they offer some protection against serious abnormal heart rhythms. A beta-blocker may need to be taken indefinitely. People who continue with symptoms, even with medical and pacemaker insertion, should have an implantable defibrillator. This device is put into the body and attached to the heart with wires. It gives the heart an electrical shock to restore the normal rhythm when it starts to have an abnormal rhythm.

DOs and DON'Ts in Managing Long QT Syndrome:

✓ **DO** report palpitations, feeling lightheaded, and loss of consciousness to your health care provider.

✓ **DO** understand that this syndrome may be inherited. Your health care provider should be told if any family members have died suddenly.

✓ **DO** talk with specialists and other families with the condition for support. Cardiologists, genetics counselors, psychiatrists, or psychologists may help.

⃠ **DON'T** play competitive sports. Your health care provider should recommend this, especially if you have the inherited syndrome.

⃠ **DON'T** forget that commonly used drugs for allergies and infections, used together, can

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cause the acquired syndrome. Ask your health care provider or pharmacist about over-the-counter medicines and drug interactions.

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website: www.americanheart.org**
- American College of Cardiology Tel: (800) 253-4636 ext. 694 or (301) 897-5400

  Website: http://www.acc.org

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MANAGING YOUR

Low Back Pain

What Causes Low Back Pain?

The back is made up of bones (vertebrae) of the spinal column, discs between these bones, the spinal cord (which contains nerves), and muscles and ligaments. Muscles in the back and belly (abdomen) help support the spine. Injury in this area can cause pain. The term low back pain means pain in the lower parts of the spine.

An injury or accident such as a fall can cause *acute* low back pain lasting 1 to 7 days. *Chronic* low back pain lasts longer, for more than 3 months. Many such injuries result from twisting or sudden movement. Obesity, poor posture, and weak back and abdominal muscles may also cause this pain. Some people have pain after sitting for a long time or reaching for something too far away.

Low back pain may also occur with diseases such as arthritis or fibromyalgia and rarely, in more serious conditions such as tumors, kidney disease and blood disorders.

What Are Other Symptoms of Low Back Pain?

Bending at the waist, lifting, walking, and standing may be hard to do. Pain may disturb night-time sleep. Chronic pain may affect the ability to do a job. If the sciatic nerve is in the injured area, the pain, called *sciatica*, will travel down the leg.

How Is Low Back Pain Diagnosed?

Your doctor will make a diagnosis by taking a medical history and doing a physical. X-ray studies or magnetic resonance imaging (MRI) may be done if clearer pictures of bones, nerves, discs between the bones, or other areas are needed.

A study using electrical current, called an electromyogram (EMG), helps diagnose muscle

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and nerve problems and may be done if pressure on the nerves may be causing numbness or tingling in the legs.

The doctor may also order blood tests to see whether the pain is caused by another ailment that may have similar symptoms.

How Is Low Back Pain Treated?

Treatment depends on the cause of the pain and how long pain has lasted.

If the pain is due to an injury, the doctor may suggest use of cold compresses. Nonsteroidal anti-inflammatory drugs (NSAIDs) may relieve the pain. Severe pain may require stronger narcotic-containing medicines for a short time. For muscle spasms, a doctor may prescribe a muscle relaxant.

All medicines have side effects. NSAIDs may cause stomach upset, ulcers, rash, and kidney or liver problems. Muscle relaxants may bring about drowsiness, dizziness, or rash.

Physical therapy may help reduce pain. Chronic low back pain can improve with exercises for the lower back and abdomen.

DOs and DON'Ts in Managing Low Back Pain:

✓ **DO** take your medicine as prescribed.

✓ **DO** call your doctor if you have drug side effects.

✓ **DO** lose weight if you are overweight.

✓ **DO** back stretching and strengthening exercises daily.

✓ **DO** use good posture when sitting, standing, or lifting.

✓ **DO** call your doctor if you have difficulty urinating or lose control of your bowels or blad-

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der.

- ⃠ **DON'T** wait for a drug side effect to go away by itself.

- ⃠ **DON'T** give up. If you do not feel better, ask your doctor about starting in a special treatment program.

- ⃠ **DON'T** completely stop exercising.

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FOR MORE INFORMATION

Contact the following sources:

American Physical Therapy Association Tel: (800) 999-2782 **Website:** http://www.apta.org

American Academy of Orthopaedic Surgeons Tel: (800) 346-AAOS **Website:** http://www.aaos.org

American Chronic Pain Association Tel: (916) 632-0922 **Website:** http://www.theacpa.org

North American Spine Society Tel: (708) 588-8080 **Website:** http://www.spine.org

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MANAGING YOUR

LOW BACK STRAIN

What Is Low Back Strain?

The back is made up of bones (vertebrae) of the spinal column, disks between these bones, the spinal cord (which contains nerves), and muscles, tendons, and ligaments. Muscles in the back and belly (abdomen) help support the spine. The lower back (lumbar spine) supports most of the body weight and helps with moving, twisting, and bending. The most common low back injuries are strains, in which lower back muscles or tendons are stretched or torn. Tendons are tough bands of tissues connecting muscles and bones. Anyone can have a low back strain. Athletes, especially football players and gymnasts, are more likely to strain in practice than during competition.

What Causes Low Back Strain?

Causes include activities that stress the lower back, such as stretching, bending, improper lifting, too much pulling (weightlifting), or twisting (basketball, baseball, golf). Playing sports without stretching or warming up back muscles can lead to strains. Other causes are poor conditioning, obesity, smoking, coughing hard, emotional stress, falling, and trauma.

What Are Symptoms of Low Back Strain?

Symptoms include sudden lower back pain that becomes worse with activities (bending, stretching, coughing, sneezing). Painful and stiff back, painful buttocks and legs, and lower back spasms are others.

How Is Low Strain Pain Diagnosed?

Diagnosis is made from taking a medical history, doing a physical, and maybe doing x-ray studies. Computed tomography (CT) or magnetic resonance imaging (MRI) may be done in

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special cases if clearer pictures of bones, nerves, or disks between the bones are needed.

A study using electric current, called electromyography (EMG), helps diagnose muscle problems and may be done on rare occasions.

How Is Low Back Strain Treated?

Treatment involves rest, ice, heat, medicines, and exercises. People should rest for a day or two, but then light physical activity should be started. Apply heat to the back but only after 2 to 3 days of using ice first, after the swelling has gone. Hot water bottles or soaking in a hot bath is helpful. Medicines include muscle relaxants and nonsteroidal anti-inflammatory drugs (NSAIDs) for pain. Physical therapy and exercises can help strengthen muscles in the abdomen and can stretch and strengthen lower back muscles during and after healing.

All medicines have side effects. NSAIDs may cause stomach upset, diarrhea, ulcers, headache, dizziness, difficulty hearing, or rash. Muscle relaxants may bring about drowsiness, dizziness, or rash.

DOs and DON'Ts in Managing Low Back Strain:

✓ **DO** take your medicine as prescribed. Call your doctor if you have drug side effects.

✓ **DO** lose weight if you're overweight.

✓ **DO** back stretching and strengthening exercises daily.

✓ **DO** use good posture when sitting, standing, or lifting. When picking up something heavy, bend at the knees.

✓ **DO** call your doctor if you have trouble urinating or lose control of your bowels or bladder.

⃠ **DON'T** wait for a drug side effect to go away by itself.

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- ⦸ **DON'T** give up. If you don't feel better, ask your doctor about starting a special treatment program.
- ⦸ **DON'T** smoke.
- ⦸ **DON'T** sleep on your stomach.
- ⦸ **DON'T** completely stop exercising, but stop activities if you feel pain when you do them.

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FOR MORE INFORMATION

Contact the following sources:

- Spine Health **Website: http://www.spine-health.com**
- American College of Rheumatology Tel: (404) 633-3777 **Website: http://www.rheumatology.org**
- Arthritis Foundation Tel: (800) 283-7800**Website: http://www.arthritis.org**

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MANAGING YOUR

LUMBAR DISC SYNDROME

What Is Lumbar Disc Syndrome?

The lumbar spine (low back) is made of five vertebrae (bones) separated by cartilaginous discs. These discs are shock absorbers. They cushion the bones and increase flexibility of the lower back. Lumbar disc syndrome is a group of symptoms related to disorders of these lumbar discs. Degenerative changes or trauma may burst the annulus fibrosus. The annulus fibrosus is the tough band of cartilage around each disc. Disc material may bulge (herniate) into the spinal canal or nerve root canal and cause pain.

What Causes Lumbar Disc Syndrome?

Degenerative changes in discs are due to normal aging. Poor posture and strenuous work with poor lifting methods may make these changes worse. Discs slowly become worn, less plump, and flat. When disc spaces become so narrow that vertebrae rub together, vertebrae edges have wear-and-tear changes. Then bone spurs develop that may press on the spinal cord or nerve roots. As the nerve is irritated, back and leg pain, tingling, and numbness or weakness in the legs or feet can occur. Rarely, with very large, sudden disc bulges, bladder and bowel control may be lost.

What Are the Symptoms of Lumbar Disc Syndrome?

Pain in the back or tingling and numbness may reach the buttocks, hips, groin, or legs. Pain from a bulging disc is worse while moving, coughing, laughing, or straining when having a bowel movement. Some people also have weakness, clumsiness, foot-drop, or trouble walking.

How Is Lumbar Disc Syndrome Diagnosed?

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The doctor will obtain a medical history and do an examination. X-rays may also be done. One or more of the following tests: computed tomography (CT), magnetic resonance imaging (MRI), combined myelography/CT, and electromyography/nerve conduction velocity test (EMG/NCV), may also be done for persistent pain or if surgery is being considered.

How Is Lumbar Disc Syndrome Treated?

A trained physical therapist will use conservative treatments, such as physical therapy, ultrasound, localized heat, and special exercises. Injection of steroids and an anesthetic drug into the spinal canal may help pain. Surgery is usually the final option if other treatments don't work.

DOs and DON'Ts in Managing

Lumbar Disc Syndrome:

✓ **DO** use good sitting and walking postures.

✓ **DO** always wear a seat belt when traveling in a motor vehicle.

✓ **DO** make a lumbar support, if you sit for long periods. Put a small pillow or rolled towel between your low back and the seat. Stand and walk around often (about every hour).

✓ **DO** always lift heavy objects with the correct straight posture. Hold the object close to your body and use your thigh and leg muscles to lift.

✓ **DO** regular exercises approved by your doctor.

✓ **DO** call your doctor if you have problems with your medicines.

✓ **DO** call your doctor if you have trouble walking, develop weakness or cannot move your limbs, or lose control of your bowels or bladder.

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⦸ **DON'T** sit for long periods.

⦸ **DON'T** lift and twist, push, or pull heavy objects. Lift with leg muscles.

⦸ **DON'T** return to work without your doctor's OK.

⦸ **DON'T** do strenuous activities until your doctor says you can.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Physical Therapy Association Tel: (800) 999-2782 **Website:** http://www.apta.org
- American Academy of Orthopaedic Surgeons Tel: (800) 346-AAOS (346-2267) **Website:** http://www.aaos.org
- American Chronic Pain Association Tel: (800) 533-3231 **Website:** http://www.theacpa.org
- North American Spine Society Tel: (630) 230-3600 **Website:** http://www.spine.org
- Arthritis Foundation Tel: (800) 283-7800 **Website:** http://www.arthritis.org

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MANAGING YOUR

LUMBOSACRAL RADICULOPATHY

What Is Lumbosacral Radiculopathy?

Lumbosacral radiculopathy is a common condition involving spinal nerves and nerve roots in the low back (lumbar) and bottom of the spine (sacrum). It affects 3–5% of the population, men and women equally. Men in their 40s and women 50–60 years old have it most often. It's a major cause of disability and the primary reason for workers' compensation disability in the United States.

What Causes Lumbosacral Radiculopathy?

Pressure from herniated (ruptured, or slipped) disks lead to irritation and inflammation (swelling) of nerve roots. Disk degeneration is another cause. Disks are cartilage pads that separate bones (vertebrae) in the spine. These shock absorbers cushion moving vertebrae. With age, the tough disk covering can tear. The jelly-like substance in the disk center can seep out (herniate), press on nerve roots, and cause symptoms. Other causes are spinal stenosis (narrowing), tumors, infections, and trauma.

What Are the Signs and Symptoms of Lumbosacral Radiculopathy?

Symptoms include pain and numbness in the arms or legs and muscle weakness. The most common symptom is sciatica: pain that goes along the path of the sciatic nerve, the longest nerve in the body. This nerve runs from the back down the buttock and leg (back of the thigh and calf). Sciatica is a symptom of a problem such as a herniated disk. Other symptoms are numbness, tingling, and loss of bladder or bowel control.

How Is Lumbosacral Radiculopathy Diagnosed?

The doctor takes a medical history and does a physical examination, especially of the spine and

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legs, and checks muscle strength and reflexes. Because most people improve with rest, self-care, and medications, imaging tests are not always needed. For persistent pain, magnetic resonance imaging (MRI) is the main imaging test. X-rays, computed tomography (CT), myelography, and electrodiagnostic studies (e.g., nerve conduction) are also used.

How Is Lumbosacral Radiculopathy Treated?

Most people need no treatment, or pain goes away with self-care measures. These include hot or cold packs, stretching, exercises, and over-the-counter pain medicines. Physical therapy helps recovery; prolonged bed rest is not recommended. People need to get moving as soon as possible. Rehabilitation can help prevent new injuries. For more chronic, nondisabling pain, lifestyle changes with weight loss and health club membership are best. Exercises correct posture, strengthen back muscles, and improve flexibility. Nonsteroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, analgesics, and steroid injections may be given. If these treatments don't work, or for certain symptoms, surgery is needed.

DOs and DON'Ts in Managing Lumbosacral Radiculopathy:

✓ **DO** make a lifelong commitment to exercise. The most important risk factor for future back pain is a previous episode. Pay special attention to your core muscles—those in your abdomen (belly) and lower back that are essential for good posture and alignment.

✓ **DO** practice good body mechanics and posture when sitting, standing, and lifting. Take frequent breaks, even just walking around your office. Lift and carry heavy objects properly.

✓ **DO** learn all you can about your condition, to help manage your pain.

⃠ **DON'T** give up. If you don't feel better, ask your doctor about starting a special treatment program.

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⦸ **DON'T** rest in bed for more than 48 hours, to avoid blood clots and getting weaker.

⦸ **DON'T** lift or push any heavy objects unless you know how to do so safely.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopedic Surgeons Tel: (847) 823-7186 **Website: http://www.aaos.org**
- American Academy of Family Physicians Tel: (800) 274-2237 **Website: http://www.aafp.org**

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MANAGING YOUR

LUNG ABSCESS

What Is a Lung Abscess?

Lung abscess is an infection of the lung. Pus-containing cavities form that are made up of bacteria or other microorganisms, dead (necrotic) tissue, and fluid. People over age 60 have a greater risk of getting abscesses.

What Causes a Lung Abscess?

Aspiration is the most important reason for formation of lung abscesses. Aspiration means that foreign material (usually food, drink, vomit, or secretions from the mouth) is breathed into the lungs. Inflammation, pneumonia, and abscess formation can occur in 7 to 14 days. Stroke, seizure disorders, drug abuse, alcoholism, poor oral hygiene (gum disease), emphysema, lung cancer, and disorders of the esophagus (swallowing problems) can lead to aspiration.

Bacteria causing lung abscesses are usually anaerobes (don't need oxygen to grow) and originate from the mouth. Other microorganisms, such as parasites and fungi, can also infect lungs and cause abscesses.

What Are the Symptoms of a Lung Abscess?

Symptoms usually develop during weeks to months. Symptoms include fever, chills, sweats, and a cough with foul-smelling and bad-tasting sputum. People are often tired, are weak, lose their appetite, and lose weight. Sometimes, blood in the sputum and chest pain made worse by coughing or taking deep breaths occur. People may have rapid heart rate, rapid breathing, wheezing, and fluid in the lungs (pleural effusion).

How Is a Lung Abscess Diagnosed?

The doctor makes a diagnosis from symptoms and chest x-rays. The doctor may order computed

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tomography (CT) of the chest to see the abscess. Sputum and blood cultures may help confirm the bacteria or microorganism causing the abscess. The doctor may order bronchoscopy to rule out lung cancer if there are signs that something may be obstructing the airways. In this test, a lighted tube is passed through the mouth into the lungs to see in the lungs and get samples of lung tissue.

How Is a Lung Abscess Treated?

First, the microorganism causing the abscess is treated. Second, the condition leading to aspiration (e.g., seizures, alcoholism, poor oral hygiene, or stroke) is treated.

Most people usually need intravenous and oral antibiotics, given for 4 to 6 weeks. Up to 95% of people are cured, but the cure will depend on the infection's cause.

DOs and DON'Ts in Managing a Lung Abscess:

✓ **DO** finish all your antibiotics as prescribed by your doctor.

✓ **DO** tell your doctor about symptoms of relapse, such as chest pain, fever, or coughing up blood, or problems with medicines (e.g., rash, diarrhea, tongue swelling, wheezing, or shortness of breath).

✓ **DO** report pain with swallowing or food getting stuck when you swallow.

✓ **DO** call your doctor if you have a drinking or drug problem.

✓ **DO** call your doctor if you have a seizure.

✓ **DO** call your doctor if your fever lasts for more than 7 days after starting antibiotics.

⊘ **DON'T** stop your antibiotics unless your doctor tells you to.

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⦸ **DON'T** smoke. Smoking can lead to lung abscess, emphysema, and lung cancer.

⦸ **DON'T** use recreational drugs.

⦸ **DON'T**abuse sleeping pills, anxiety pills, and opiate narcotics. They can lead to aspiration.

⦸ **DON'T** drink alcohol in excess. Lung abscesses are common in alcoholics, who have greater chances of aspiration.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following source:

- American Lung Association Tel: (212) 315-8700, (800) 586-4872 **Website:** **http://www.lungusa.org**

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MANAGING YOUR

LUNG CANCER

What Is Lung Cancer?

Lung cancer is one of the most common cancers among men and women. More than 170,000 new cases are diagnosed yearly in the United States.

Almost 90% of lung cancers start in the lining of air passages or air sacs. Air passages are tubes called bronchi (main tubes) and bronchioles (smaller tubes). Air sacs (alveoli) are at the ends of the tubes.

Lung cancer is usually divided into two types: non–small cell and small cell, stages I, II, III, or IV. Therapy differs for each.

What Causes Lung Cancer?

Use of cigarettes, cigars, and pipes is the main cause. Others include exposure to asbestos radon, radiation, and second-hand smoke.

What Are the Symptoms of Lung Cancer?

Some people may have no symptoms until cancer is advanced. Others have long-lasting cough, coughing up bloody phlegm, shortness of breath, wheezing, recurrent pneumonia, loss of appetite, and weight loss. Swelling of the face and neck (superior vena cava syndrome) and pain in shoulders, arms, and hands (Pancoast tumor) can occur in some cases.

How Is Lung Cancer Diagnosed?

Early diagnosis can be hard because some people may have no symptoms until cancer is advanced. The only sure way to diagnose it is to take and study samples of lung fluid or tissue (biopsy). The doctor gets these by bronchoscopy (inserting a lighted, thin, flexible tube into the lungs), needle aspiration (passing a needle through the chest), or surgery.

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How Is Lung Cancer Treated?

After diagnosis, staging is done to find out whether the cancer spread. Early detection is important because only early lung cancers, before spread (metastasis) occurs, can be cured.

For non–small cell cancer, computed tomography (CT) of the chest and abdomen helps find spread of cancer to other body parts, such as lymph nodes (glands) and liver. A radiology test called positron emission tomography (PET) can also do this. If surgery is a treatment option, breathing tests (pulmonary function tests) are done before surgery to help find out whether removal of part of the lung will be tolerated. Surgery for localized cancer offers the best hope for cure. For more advanced disease or people who cannot have surgery, radiation therapy alone or radiation and chemotherapy (drugs) are tried.

For small cell cancer, CT of the chest, abdomen, and head; PET; and bone marrow biopsy are usually done to look for spread into the brain or bone marrow. Surgery usually cannot cure small cell lung cancer, so chemotherapy and chemotherapy with radiation therapy are options.

All treatments have complications, including pain and shortness of breath (surgery), tiredness and shortness of breath (radiation); and easy bruising and bleeding, nausea, vomiting, and hair loss (chemotherapy).

DOs and DON'Ts in Managing Lung Cancer:

✓ **DO** understand the effects of smoking and its major role in lung cancer.

✓ **DO** see an oncologist (cancer specialist) about therapy.

✓ **DO** understand the importance of nutrition before and after treatment. Eat a healthy diet, including fruits and vegetables.

⦸ **DON'T** smoke—the most important lifestyle change.

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⦸ **DON'T** be afraid to ask questions or ask for a second opinion. Therapy is complicated, and many decisions have to be made before you feel comfortable with the type of treatment you receive.

⦸ **DON'T** be afraid to ask about support groups.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Lung Association Tel: (212) 315-8700, (800) 586-4872 **Website: http://www.lungusa.org**
- American Cancer Society Tel: (800) ACS-2345 (227-2345) **Website: http://www.cancer.org**

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LUNG CANCER

SCREENING AND PREVENTION

What Is Lung Cancer?

Lung cancer occurs when cells in the lung grow out of control and form a mass. Nearly 90% of lung cancers start in the lining of air passages or air sacs. Air passages are tubes called bronchi (main tubes) and bronchioles (smaller tubes). Air sacs (alveoli) are at the ends of the tubes.

Lung cancer is usually divided into two types: non–small cell and small cell.

Lung cancer is one of the most common cancers among both men and women. Every year, more than 170,000 new cases are diagnosed in the United States.

What Causes Lung Cancer?

Almost 90% of lung cancers occur among smokers or former smokers. Therefore use of tobacco (cigarettes, cigars, pipes) is the main cause.

Other causes include exposure to asbestos (especially for smokers), radon and radiation, and secondhand smoke (other people's smoke).

What Are the Symptoms of Lung Cancer?

Some people may have no symptoms until the cancer is advanced.

In others, symptoms include a cough that doesn't go away, coughing up bloody phlegm, shortness of breath, wheezing, continuing problems with pneumonia, tiredness, difficulty swallowing, loss of appetite, and weight loss.

A tumor may press on a large blood vessel, which causes swelling of the face and neck (called superior vena cava syndrome).

A tumor pressing on nerves near the lung can lead to pain in the shoulder, arm, and hand (called Pancoast's tumor).

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Some types of lung cancer can produce certain chemicals (hormones) that lead to abnormal blood test results, such as a high calcium level; weakness; and other problems (e.g., Lambert-Eaton syndrome, clubbing of fingers or toes, and syndrome of inappropriate secretion of antidiuretic hormone [SIADH]).

How Is Lung Cancer Diagnosed?

Early diagnosis can be hard because people may have no symptoms until the cancer is advanced. In these people, a tumor may be found on a routine chest x-ray or computed tomography (CT) scan. Screening for lung cancer with low-dose computed tomography is now advocated by some medical organizations for current or former strokers aged 55 to 74.

The only sure way to diagnose lung cancer is by taking and studying a sample of lung tissue (biopsy) or fluid from the lungs that contains cancer cells.

The doctor gets these samples in different ways, depending on the location of the problem area. One technique is bronchoscopy, or examination with a lighted scope (a thin, flexible tube) that passes through the mouth into the air passages. If this method doesn't work, needle aspiration can be done. In this procedure, a needle is passed through the chest into the tumor to get the cells.

Sometimes, the space surrounding the lungs has fluid in it. This fluid can be removed with a needle (thoracentesis) to check for cancer cells.

If none of these techniques works, surgery (thoracotomy) can be done to open the chest and get tissue samples directly.

DOs and DON'Ts in Preventing Lung Cancer:

✓ **DO** understand the effects of smoking and its major role in causing lung cancer.

✓ **DO** eat a healthy diet, including fruits and vegetables.

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✓ **DO** avoid exposure to hazards such as radon and air pollution.

⃠ **DON'T** smoke—the most important lifestyle change.

⃠ **DON'T** ignore signs of lung cancer such as persistent cough or bloody phlegm. Early diagnosis is important.

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FOR MORE INFORMATION

Contact the following sources:

- American Lung Association Tel: (212) 315-8700 **Website: http://www.lungusa.org**
- American Cancer Society Tel: (800) 227-2345 **Website: http://www.cancer.org**

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MANAGING YOUR

LYME DISEASE

What Is Lyme Disease?

Lyme disease is an infection that affects many parts of the body, including the skin, joints, and nervous system. This illness was first recognized in 1975. More than 150,000 cases have been reported in the United States since 1980. It's named for the Connecticut town where the first case was found. Most cases occur in the Northeast US, but cases have also been reported in several other states including California, Wisconsin, and Minnesota.

What Causes Lyme Disease?

A bacterium named *Borrelia burgdorferi* causes it. A tick bite passes bacteria to people. Deer often carry these ticks.

What Are the Symptoms of Lyme Disease?

People may only have one or a few symptoms before the disease is diagnosed and treated. Early symptoms are flu-like ones: headache, joint and muscle pain, fever, chills, fatigue, and enlarged lymph glands. A rash may appear on the site of the tick bite, often on the armpit, groin, or thigh. It's raised or flat, and red with a white area in the middle. Tick bites usually leave a large, bull's-eye type of rash that lasts for a few days.

Untreated flu-like symptoms may get worse. Neck stiffness, shortness of breath, chest pain, and dizziness may occur. Then, without treatment, people may develop arthritis-like symptoms in joints, rash, continued fatigue and heart problems, and neurological symptoms, such as confusion, weakness in the face, arm, and legs; or even paralysis in the face.

How Is Lyme Disease Diagnosed?

The doctor will do a physical examination and take a medical history. Living or recent travel in

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areas of high prevalence, such as New England, makes the diagnosis more likely. The doctor must know about recent tick bites or outings to wooded areas or fields where deer ticks live. Deer ticks are so small, you may not even know you were bitten. Most people with Lyme disease do not remember getting bitten by a tick or having a bull's-eye type of rash. The doctor will do a blood test for bacteria that cause Lyme disease. The doctor may do other tests to rule out illnesses with similar symptoms.

How Is Lyme Disease Treated?

Early treatment with antibiotics is usually very effective. If the illness is very advanced, symptoms may not completely go away. The duration of therapy and type of antibiotic used depend on the stage of the disease. Different medicine is used for young children and pregnant women. During antibiotic treatment, acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs) can be used for pain. Other types of treatment may also be necessary, for example, for heart or neurological problems.

DOs and DON'Ts in Managing Lyme Disease:

✓ **DO** take antibiotics as directed.

✓ **DO** tell your doctor if your symptoms don't improve or you have side effects from medicine.

✓ **DO** avoid getting bitten by a tick. Avoid areas where ticks live, especially in spring and summer when they are most numerous. Wear protective clothing when you're out in the woods or other areas where deer ticks live. Use insect repellent containing the chemical called DEET.

✓ **DO** check your body for tick bites after any possible exposure to ticks.

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✓ **DO** call your doctor if treatment doesn't help your symptoms in a reasonable amount of time.

✓ **DO** call your doctor if you have new or unexplained symptoms.

⃠ **DON'T** wait to see whether side effects from medicines go away.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- Lyme Disease Foundation, Inc. Tel: 800-886-LYME (886-5963) **Website:** **http://www.lyme.org**
- Arthritis Foundation Tel: (800) 283-7800 **Website:** **http://www.arthritis.org**
- U.S. Department of Health and Human Services **Websites:** **http://womenshealth.gov**

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MANAGING YOUR

LYMPHANGITIS

What Is Lymphangitis?

The lymphatic system consists of organs, nodes (glands), ducts, and vessels (channels) throughout the body. It's part of the immune system. It makes and moves a fluid called lymph from tissues through vessels to the blood. Lymphangitis is an inflammation (swelling) of the lymphatic vessels. It's a common complication of bacterial infections. Lymphangitis may suggest that an infection is quickly getting worse. Life-threatening infections and septicemia (blood poisoning) can result.

What Causes Lymphangitis?

A wound that becomes infected with *Staphylococcus* (staph) or *Streptococcus* (strep) bacteria can cause lymphangitis, as can most other infections.

What Are the Symptoms of Lymphangitis?

Symptoms include red streaks near the wound that move toward the nearest lymph nodes. For example, if the arm is infected, nodes in the armpit are affected. If the leg is infected, nodes in the groin are affected. Nodes will get swollen and tender. Fatigue, throbbing pain at the wound site, loss of appetite, headache, muscle aches, chills, and fever may also occur.

How Is Lymphangitis Diagnosed?

The doctor will make a diagnosis from a medical history and physical examination, especially feeling the lymph nodes. The doctor will also order blood tests to find out the type of bacteria involved and how severe the illness is.

How Is Lymphangitis Treated?

Lymphangitis should be treated very quickly. Treatment of an uncomplicated disorder is usually

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successful. Treatment includes antibiotics and pain medicines. People with symptoms of a serious illness (fever, chills, muscle pains) may need anti-biotics given intravenously (directly into a vein). Hot moist compresses or a heating pad put on the wound site several times a day will help inflammation, as will anti-inflammatory drugs. The affected area should be elevated and immobilized if possible. Wound care, including drainage of the wound if needed, should be done only after antibiotics are started.

People with group A streptococcal infections should be treated aggressively. These illnesses can get worse very quickly and can have serious complications. Complications can be life-threatening.

DOs and DON'Ts in Managing Lymphangitis:

✓ **DO** take your antibiotics until you finish them.

✓ **DO** use over-the-counter medicines such as acetaminophen or ibuprofen for pain.

✓ **DO** tell your doctor if the medicines don't help the pain.

✓ **DO** drink more fluids and eat a good diet for better healing.

✓ **DO** immobilize and elevate the affected area.

✓ **DO** use hot moist compresses on the area for inflammation and to increase blood flow to the area.

✓ **DO** have any wound treated quickly if you see signs of infection.

✓ **DO** call your doctor if you continue to have a high temperature after you start antibiotics.

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✓ **DO** call your doctor if red streaks continue to occur near the wound and spread toward the closest lymph node area after treatment starts.

⃠ **DON'T** skip doses or stop your antibiotics until they're all gone.

⃠ **DON'T** use the affected limb. Keep it raised.

⃠ **DON'T** ignore a wound if it looks infected.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Heart, Lung, and Blood Institute Tel: (301) 592-8573 **Website:** **http://www.nhlbi.nih.gov**
- Centers for Disease Control and Prevention Tel: (800) 232-4636 **Website:** **http://www.cdc.gov**

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MANAGING YOUR

LYMPHEDEMA

What Is Lymphedema?

Lymph is light yellow, cloudy fluid from body tissues. Lymph flows in tiny vessels called lymphatic vessels up toward the heart. The body drains about 3 quarts of lymph per day. Lymphatic vessels lead to lymph nodes (glands). In these nodes, lymphocytes (infection-fighting cells) filter wastes, which are taken out of the body. Lymphedema is swelling of the arms, legs, or both. It results from poor lymph drainage caused by blockage, injury, or abnormal development of the lymph vessels. Extreme lymphedema is sometimes called elephantiasis because the swollen leg looks like an elephant's foot.

What Causes Lymphedema?

Lymphedema can be primary or secondary. The rare primary types are caused by developmental abnormalities. Primary lymphedema occurs in people younger than 20, more females than males. Secondary lymphedema is caused by another disease, such as infections (streptococcus bacteria, filarial worms). Injury from trauma or radiation therapy can also cause it, as can cancer. The most common cancers causing lymphedema are breast and prostate cancers and lymphoma.

What Are the Symptoms of Lymphedema?

The most common symptom is swelling or edema of the legs. Women who received radiation therapy for breast cancer can have arm swelling. Men whose blockage of lymph vessels is caused by prostate cancer that spread (metastasis) can have swollen legs. Swelling is painless but constant. Sometimes, other parts of the body such as the genitals and face can swell. An affected foot can look like a buffalo hump, and a leg can look like a tree trunk because of ankle swelling. A square foot can result from swollen toes.

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How Is Lymphedema Diagnosed?

The doctor makes a diagnosis from the medical history, physical examination, and X-ray studies called lymphoscintigraphy. The doctor may also want blood tests and computed tomography (CT) to rule out other diseases. Sometimes, the doctor orders lymphangiography. In this study, the doctor puts a dye into a lymph vessel and takes pictures to see where blockages are.

How Is Lymphedema Treated?

Treatment depends on the cause. Treatment of primary lymphedema involves leg elevation, leg massage, and elastic compression stockings. Stockings must be properly fitted and have the correct pressure. Stockings can be knee-high, thigh-high, and pantyhose.

Surgery for long-standing lymphedema is used for continuing increase in leg size even with treatment, legs that don't work well, recurring leg infections, and distress about the cosmetic appearance. A vascular surgeon with experience in surgical lymphedema treatment should be involved.

In secondary lymphedema, the underlying cause (e.g., prostate or breast cancer) needs treatment.

DOs and DON'Ts in Managing Lymphedema:

✓ **DO** encourage children to have a normal life and take part in school activities and sports.

✓ **DO** remember that infections of the legs, arms, and feet are complications and need treatment.

✓ **DO** understand that in some cases you may need diuretics (water pills) to reduce swelling.

✓ **DO** call your doctor if you have leg swelling or you had radiation therapy for breast cancer and see arm swelling. Call if you have redness, warmth, and pain over the arm or leg.

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⦸ **DON'T** forget that surgery isn't a cure. It tries to improve lymph flow.

⦸ **DON'T** miss follow-up appointments.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Cancer Institute (NCI) Tel: (800) 422-6237 (1-800-4-CANCER)
- American College of Surgeons Tel: (800) 621-4111 **Website: http://www.facts.org/**

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MANAGING YOUR

LYMPHOGRANULOMA VENEREUM

What Is Lymphogranuloma Venereum (LGV)?

Lymphogranuloma venereum (LGV) is an infectious disease spread through sexual contact—a sexually transmitted disease (STD). It usually involves lymph glands and genitals but may also affect the rectum and mouth. It's found mostly in subtropical and tropical areas and is rather rare in the United States. It generally affects men much more than women, 20 to 40 years old.

What Causes LGV?

The cause is the kind of bacteria named *Chlamydia trachomatis*. In addition to sexual spread, contact with items that carry the bacteria and nonsexual personal contact can spread the bacteria.

What Are the Symptoms of LGV?

Symptoms start 1 to 4 weeks after exposure and occur in the following order. A blister forms on the genitals and ulcerates but heals quickly. Then lymph glands in the groin area become large, red, and tender. Abscesses (pockets containing pus) form and drain thick pus and bloody fluid. Fever, muscle aches, headache, loss of appetite, nausea, vomiting, and joint pain also occur.

How Is LGV Diagnosed?

The doctor makes a diagnosis on the basis of a history of recent exposure, physical examination, and blood tests, including tests for other STDs. The doctor may also take a sample of the discharge from the lesion to see whether bacteria can be grown from it. Growth of the *Chlamydia* organisms proves the diagnosis. The presence of antibodies against the bacteria also means LGV. Antibodies are proteins that are part of the immune (infection-fighting) system.

How Is LGV Treated?

Antibiotics are needed to fight the infection and must be taken for 3 weeks. Nonprescription pain

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medicines, such as acetaminophen and ibuprofen, and local heat can be used for minor discomfort. No special diet is needed, but good nutrition is important to promote healing. In some cases, surgery may be necessary to drain the affected lymph glands or remove the abscesses. Complications include chronic infection, impotence, and bowel and bladder disorders.

DOs and DON'Ts in Managing LGV:

✓ **DO** take medicines as directed by your doctor. Take them until they are all gone.

✓ **DO** rest during the acute phase of the infection. Then slowly return to your normal activities.

✓ **DO** practice safe sex—use condoms with new partners.

✓ **DO** keep follow-up appointments with your doctor.

✓ **DO** tell your sexual contacts about your disease so that they can be examined for infection and treated if needed.

✓ **DO** call your doctor if you have a high temperature during treatment.

✓ **DO** call your doctor if you have severe pain that over-the-counter medicines don't help.

✓ **DO** call your doctor if you get diarrhea while taking the antibiotics.

✓ **DO** call your doctor if you cannot tolerate the medicine.

✓ **DO** remember that you can catch this infection more than once.

⦸ **DON'T** have unprotected sex.

⦸ **DON'T** touch your eyes without washing your hands first, to prevent spreading the infection

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to your eyes.

⦸ **DON'T** skip doses or stop taking the antibiotics, even if you feel better, unless your doctor tells you to.

⦸ **DON'T** resume sex until your doctor says you can.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- Sexually Transmitted Diseases Centers for Disease Control and Prevention Tel: (800) 232-4636 **Website: http://www.cdc.gov/std**
- American Social Health Association Hotline: (800) 227-8922 **Website: http://www.ashastd.org**

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MANAGING YOUR

MACULAR DEGENERATION

What Is Macular Degeneration?

The macula is in the center of the retina of the eye. It lets fine detail be seen. The retina is the light-sensitive part at the back of the eye. The retina changes light, or an image, into electrical impulses. These electrical impulses then go to the brain. Macular degeneration is an eye disease that involves loss of central vision and damage to the macula. It has two forms: wet and dry.

Macular degeneration is a main cause of blindness in the United States. It increases with age, with most cases occurring between ages 75 and 80.

What Causes Macular Degeneration?

Wet macular degeneration occurs when abnormal blood vessels behind the retina start to grow under the macula. These new vessels tend to be fragile and leak blood and fluid. The blood and fluid raise the macula from its normal place. Central vision loss tends to occur quickly.

Dry macular degeneration occurs when light-sensitive cells in the macula slowly break down. The loss of central vision is more gradual.

What Are the Symptoms of Macular Degeneration?

The most common symptom of dry macular degeneration is blurred vision that leads to central vision loss. As dry macular degeneration gets worse, a blurred spot is seen in the center of vision. An early symptom of wet macular degeneration is that straight lines look wavy.

The most common abnormality seen on physical exam is drusen, or yellowish deposits deep in the retina.

Unlike wet macular degeneration, dry macular degeneration has three stages, which may occur in one or both eyes. In stage I (early), several small drusen or a few medium-sized drusen are

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seen. People have no symptoms and no vision loss. In stage II (intermediate), many medium-sized drusen or one or more large drusen are seen. Some people see a blurred central spot. In stage III (advanced), people have drusen and blurred central vision. It's harder to read and recognize faces until they're very close.

How Is Macular Degeneration Diagnosed?

The doctor makes a diagnosis from symptoms and a full eye examination.

How Is Macular Degeneration Treated?

Early treatment from an ophthalmologist (specialist in eye diseases) is very important. If dry macular degeneration is advanced, no treatment can stop vision loss. Treatment can delay and maybe prevent intermediate disease from getting worse. Antioxidants and zinc may slow progression of ARMD.

Treatment of wet macular degeneration involves laser surgery or photodynamic therapy. Neither is a cure, but they may slow the rate of vision loss.

Newer treatment modalities include injections in the eye (intravenous) of substances known as monoclonal antibodies and antivascular endothelial growth factor. These injections tend to be very expensive.

DOs and DON'Ts in Managing

Macular Degeneration:

✓ **DO** realize that an antioxidant-zinc medicine isn't a cure. It won't restore lost vision, but it may delay the start of advanced disease.

✓ **DO** call your doctor if you have blurred vision, you notice wavy lines that should be straight, or you have changes in your vision.

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⦸ **DON'T** forget that age is the major risk factor for developing macular degeneration. Other risk factors include smoking, obesity, and family history.

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FOR MORE INFORMATION

Contact the following sources:

- National Eye Institute, National Institutes of Health Tel: (301) 496-5248 **Website:** **http://www.nei.nih.gov/health/maculardegen/armd_facts.asp**
- American Academy of Ophthalmology Tel: (415) 561-8500 **Website:** **http://www.aao.org**

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MANAGING

MALARIA

What Is Malaria?

Malaria is an infection caused by a parasite carried by a mosquito found in tropical and subtropical areas. It involves the blood cells, liver, and nervous system.

About 300 to 500 million cases of malaria occur worldwide every year, but only about 1200 in the United States. It occurs mainly in immigrants or travelers returning from areas with malaria.

What Causes Malaria?

The parasite named *Plasmodium* is the cause. Four types (species) infect humans: *P. falciparum, P. vivax, P. malariae,* and *P. ovale*. The parasite is passed along by bites of a female mosquito of the genus *Anopheles*. The parasite enters the human bloodstream during a bite. It travels to the liver, multiplies, and then reenters the bloodstream where it destroys red blood cells. Some parasites stay in the liver and are released later, which causes attacks off and on.

What Are the Symptoms of Malaria?

The main symptom is high fever. Symptoms can start 10 to 35 days after the mosquito bite. During the first 2 or 3 days, people have a low-grade fever, tiredness, headache, muscle aches, and chilly feeling. Then a cold stage (hard shaking chills for 1or 2 hours) is followed by a hot stage (high fever for 12 to 24 hours with rapid breathing and heavy sweating). These attacks come and go every 2 or 3 days. Untreated, they can continue for years.

How Is Malaria Diagnosed?

The doctor will do a physical examination, ask about symptoms, and examine blood with a microscope. The diagnosis is confirmed if parasites are seen inside red blood cells with the micro-

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scope on a specially stained blood smear. Newer blood tests such as polymerase chain reaction (PCR) can also be used for diagnosing malaria.

How Is Malaria Treated?

The treatment is medicine. The drug choice depends on the type of malaria. Most people with mild malaria start to feel better within 48 hours after treatment begins. However, parasites can be resistant to drugs. If symptoms don't get better, different treatment is needed. People with severe malaria take longer to recover.

DOs and DON'Ts in Managing Malaria:

- ✔ **DO** take preventive medicine when traveling in a country with malaria. To find out which countries have malaria, call the International Travelers' Hotline at (404) 332-4559.
- ✔ **DO** take your medicine exactly as directed by your doctor. Take it at the same time every day.
- ✔ **DO** finish all the medicine, to treat malaria effectively and prevent the parasite from becoming resistant to the drug.
- ✔ **DO** protect others by making your environment mosquito free.
- ✔ **DO** rest during fevers and chills. Begin normal activities slowly.
- ✔ **DO** drink more fluids during the attacks to avoid dehydration.
- ✔ **DO** call your doctor if you can't drink fluids.
- ✔ **DO** call your doctor if you still have symptoms, such as fever and chills, after treatment or if you get new symptoms.
- ✔ **DO** call your doctor if you have severe side effects from medicines.
- ⃠ **DON'T** skip doses of medicine or stop taking it because symptoms have gone.
- ⃠ **DON'T** donate blood until your doctor says you can.

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FOR MORE INFORMATION

Contact the following sources:

- National Center for Preparedness, Detection, and Control of Infectious Diseases Tel: (800) 311-3435
- CDC Travelers' Health webpage Tel: (800) 232-4636 **Website:** **http://wwwn.cdc.gov/travel/default.aspx**

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MANAGING YOUR

MALLORY-WEISS TEAR

What Is Mallory-Weiss Tear?

The esophagus is the tube that carries food from the mouth to the stomach. A Mallory-Weiss tear is a tear in the tissue lining the esophagus, called the mucous membrane. It often occurs near the place where the esophagus joins the stomach. Most people with this tear are men who are often heavy alcohol users. Women and children can also have it.

What Causes Mallory-Weiss Tear?

The usual cause is forceful or long-lasting vomiting in which the upper esophageal sphincter doesn't relax. This sphincter is a muscular valve at the upper esophagus that can make the diameter of the esophagus smaller. Coughing, vomiting from pregnancy, straining during bowel movements, trauma, and inflammation of the esophagus (esophagitis) and stomach (gastritis) can also cause it. It's not contagious or passed from parents to children.

What Are the Symptoms of Mallory-Weiss Tear?

Symptoms include vomiting blood or passing large amounts of blood from the rectum. Others are lasting heartburn, pain in the abdomen (belly) or back, dizziness, lightheadedness, and fainting.

How Is Mallory-Weiss Tear Diagnosed?

For diagnosis, the doctor uses upper endoscopy. The endoscope is a long flexible tube with a lighted end that the doctor puts into the mouth or rectum. The endoscope lets the doctor see into the esophagus, stomach, and duodenum (part of the small intestine). The doctor can collect samples of tissue (biopsy), take pictures, and stop bleeding.

How Is Mallory-Weiss Tear Treated?

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Mallory-Weiss tears usually heal on their own without any major treatment. However, the first treatment is to monitor vital signs (blood pressure and pulse). Fluids are given intravenously (into a vein) for low blood pressure. This low pressure can occur during periods of massive bleeding. The doctor may also suggest blood transfusions if blood is lost too quickly. Some people need medicines or surgery to stop the bleeding. For long-lasting bleeding, a gastroenterologist or surgeon may be involved in care. Gastroenterologists are specialists in diseases of the esophagus, stomach, and intestines. They use endoscopes to give drugs such as vasopressin or inject other medicines over the tear to stop bleeding.

DOs and DON'Ts in Managing Mallory-Weiss Tear:

✓ **DO** realize that Mallory-Weiss tears usually heal within 96 hours, so tears may not be found by upper endoscopy if endoscopy is delayed.

✓ **DO** understand that in the hospital, you may not have anything to eat until the cause of bleeding is found and bleeding stops. Then, you may change from drinking clear liquids (e.g., water, ginger ale, gelatin) to eating a regular diet, as tolerated.

✓ **DO** feel reassured that almost all Mallory-Weiss tears don't bleed again.

✓ **DO** call your doctor if you vomit blood or pass blood from your rectum or if you're pregnant and vomiting. Call if you have abdominal pain or lasting heartburn or feel dizzy or lightheaded.

✓ **DO** call your doctor if you have problems with alcohol.

⦸ **DON'T** forget that pregnancy and morning sickness with vomiting can lead to a Mallory-Weiss tear.

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⦸ **DON'T** forget that the prognosis for people with Mallory-Weiss tears is very good.

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FOR MORE INFORMATION

Contact the following sources:

- National Digestive Diseases Information Clearinghouse Tel: (800) 891-5389 **Website:** **http://www.niddk.nih.gov/health/digest/digest.htm**
- American College of Gastroenterology Tel: (703) 820-7400 **Website:** **http://www.acg.gi.org**

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MANAGING YOUR

MARFAN'S SYNDROME

What Is Marfan's Syndrome?

Marfan's syndrome is an inherited disorder involving the body's connective tissues. Connective tissues of the body support and bind other tissues. The syndrome mainly affects the eyes, heart, blood vessels, and skeleton.

This condition is rare. Only 4 to 6 people of 100,000 have it. It affects females and males equally, of all races.

What Causes Marfan's Syndrome?

This syndrome is caused by a genetic defect (gene mutation). In 70% of cases, the genetic defect is passed from parents to children. Each child has a 50% chance of inheriting the disorder from a parent with the syndrome. Approximately 30% of Marfan's cases are due to a new gene mutation.

What Are the Symptoms of Marfan's Syndrome?

No major symptoms are usually seen with Marfan's syndrome, so it can be hard to diagnose in children. Features include eye conditions such as dislocation of the lens and nearsightedness; skeletal conditions such as tall height with long spidery fingers, an arm span greater than height, and chest deformities; heart valve abnormalities; and a positive family history.

How Is Marfan's Syndrome Diagnosed?

The doctor may suspect that the syndrome is present from the family history and a physical examination that shows certain abnormalities. No special test can diagnose the syndrome. Diagnosis isn't usually made until early adulthood. Three of the four features mentioned must be present. An eye doctor (ophthalmologist) will also do a detailed eye examination. A cardiologist

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(specialist in heart diseases) will look for heart problems and do echocardiography. Echocardiography is a kind of ultrasound that can examine the heart valves. Blood tests may also be done for genetic testing.

How Is Marfan's Syndrome Treated?

The syndrome isn't curable, but diagnosis and proper treatments prolong life. A medical team—geneticist, cardiologist, ophthalmologist, surgeons, and psychologist—will likely be involved in care. Heart and eye examinations done every year are important to both find problems and follow the progress of the disorder. Medicines such as beta-blockers may be prescribed to help the heart problems. Heart and blood vessel complications can be life-threatening and may mean that surgery is needed. Valve surgery may be done for severe disease. With surgery, most patients can live a normal life span. Without treatment, people live an average of about 35 years. The major cause of death is enlargement (dilation) and bursting (rupture) of the aorta, the largest artery carrying blood from the heart to the body.

DOs and DON'Ts in Managing

Marfan's Syndrome:

✓ **DO** low and moderate impact activities, such as golf, bowling, billiards, walking, and fishing. Vigorous exercise may lead to serious complications.

✓ **DO** get genetic counseling if you have a family history of Marfan's syndrome.

✓ **DO** call your doctor if you think that you or your family members have symptoms of the syndrome.

⊘ **DON'T** participate in physically or aerobically demanding sports or activities (weightlifting,

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gymnastics, racket sports) without the OK from your doctor. Avoid contact sports.

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FOR MORE INFORMATION

Contact the following source:

- National Marfan Foundation Tel: (800) 862-7326 **Website: http://www.marfan.org**

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MANAGING YOUR

MASTOIDITIS

What Is Mastoiditis?

Mastoiditis is a relatively rare infection of a bulge in the skull behind the ear, a bony part called the mastoid process. The infection may cause destruction of this bony part followed by hearing loss. Mastoiditis most often affects young children, usually those 6 to 13 months old. Also, healthy teenagers and adults can get it; so can people with weakened immune (infection-fighting) systems.

What Causes Mastoiditis?

Bacteria, most commonly the kind named *Haemophilus influenzae*, *Staphylococcus*, or *Streptococcus*, are the cause. Mastoiditis can be a complication of an untreated middle ear infection.

What Are the Symptoms of Mastoiditis?

Symptoms can appear 2 weeks or more after the start of an untreated middle ear infection. They include pain, redness, tenderness, and swelling behind the ear; increased pain and redness in the ear; fever; headache; dizziness; nausea; drainage from the ear; and hearing problems in the ear.

How Is Mastoiditis Diagnosed?

The doctor will make a diagnosis on the basis of the medical history and physical examination. The doctor may get a sample of the ear drainage and send it to a laboratory for culture, to find out which bacteria will grow. The doctor may also want to order x-rays, CT, or MRI.

How Is Mastoiditis Treated?

Treatment may be difficult because it's hard for medicine to go deep enough into the mastoid bone. Repeated or long-term treatment may be needed. More severe infections need intravenous (injected directly into a vein) antibiotics. Antibiotics are first given intravenously and then orally

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(by mouth). The antibiotic treatment must continue for at least 2 weeks. Complications include hearing loss (partial or complete), abscesses, facial paralysis or palsy, and spread of infection to the brain (meningitis) or other parts of the body. If an abscess occurs, an operation to drain the abscess may be needed. An operation called mastoidectomy is done if treatment with antibiotics and myringotomy (surgical drainage of the ear) don't help. Simple mastoidectomy involves removing infected bone cells, cleaning the area, and draining the middle ear. Then antibiotics are put into the ear. Other operations, rarely needed, are radical mastoidectomy (for serious or chronic infection) and modified radical mastoidectomy.

DOs and DON'Ts in Managing Mastoiditis:

✓ **DO** take your antibiotics until they're all gone.

✓ **DO** use nonaspirin products such as acetaminophen for fever and pain.

✓ **DO** keep the ear clean and dry. A light cotton ball placed on the outer canal may help absorb drainage.

✓ **DO** drink more fluids during your fever.

✓ **DO** call your doctor if you continue to have a fever while you take antibiotics.

✓ **DO** call your doctor if you have a severe headache, dizziness, weakness, or increased pain.

✓ **DO** call your doctor if you have nausea, vomiting, or diarrhea.

✓ **DO** call your doctor if you get a rash.

⊘ **DON'T** skip doses or stop taking antibiotics until you have finished all your medicine.

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⦸ **DON'T** miss follow-up doctor appointments. It's important to make sure that the infection is gone.

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FOR MORE INFORMATION

Contact the following source:

American Academy of Otolaryngology—Head and Neck Surgery Tel: (703) 836-4444 **Web-site: http://www.entnet.org**

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MANAGING YOUR

MEASLES

What Is Measles?

Measles is a highly contagious infection caused by a virus. The disease usually starts 7 to 14 days after exposure and lasts 4 to 10 days.

What Causes Measles?

Measles is caused by a virus that easily spreads among people. People breathe in droplets in the air that contain the virus when they are near someone who has it, or they touch things that are contaminated with the virus, such as drinking glasses, and then put their fingers in their mouths.

People don't get measles more than once.

The best way to stop measles is to get vaccinated. Most cases occur in preschool children, adolescents, young adults, and people who haven't had vaccinations. Adults may get measles if they only had one vaccine dose many years ago and may need a booster shot for travel to countries where measles is still common.

Complications include ear infections, pneumonia, strep throat, and meningitis.

What Are the Symptoms of Measles?

The first symptom is fever, followed by feeling tired, loss of appetite, and later, a runny nose, sneezing, dry hacking cough, and light sensitivity. Then, tiny white-gray spots appear in the mouth and throat, followed by a red-brown rash that starts on the forehead and around the ears and spreads to the body. The fever starts to go down on the second or third day of the rash. When the rash reaches the feet, it starts to fade. The rash can leave a brownish color that disappears in 7 to 10 days.

How Is Measles Diagnosed?

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The doctor makes a diagnosis from the medical history and physical examination. No specific tests are needed, but a blood test may confirm the diagnosis.

How Is Measles Treated?

People should be isolated for 4 days after the rash starts and rest until the fever and rash are gone. Saline eye drops can help eye irritation, and sunglasses help severe light sensitivity. Non-aspirin products (e.g., acetaminophen) should be given for fever. Never give aspirin to a child younger than 16 with a viral infection because of the risk of Reye's syndrome. Antibiotics aren't needed because the infection is due to a virus. Fluid intake should be increased.

DOs and DON'Ts in Managing Measles:

✓ **DO** tell your doctor if you're pregnant. Measles during pregnancy can affect your baby.

✓ **DO** cover your mouth when coughing.

✓ **DO** wash hands regularly and encourage others to do so.

✓ **DO** use a cool-mist vaporizer to soothe coughing.

✓ **DO** use saline eye drops for irritation and sunglasses for light sensitivity.

✓ **DO** call your doctor if a sore throat and high temperature develop during the illness, or if you have a severe headache, trouble breathing, chest pain, earache, increased drowsiness or weakness, and a cough with thick yellow sputum.

⃠ **DON'T** send a child with measles to school for about 10 days. They can give measles to others from 5 days before the first spots appear until at least 5 days after the rash develops.

⃠ **DON'T** give aspirin to a child younger than 16 during a viral infection to avoid Reye's syn-

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drome.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Pediatrics Tel: (847) 434-4000 **Website: http://www.aap.org**
- Pediatric Infectious Disease Society Tel: (703) 299-6764 **Website: http://www.pids.org**

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MANAGING YOUR

MECKEL DIVERTICULUM

What Is Meckel Diverticulum?

A diverticulum is a small saclike swelling in the wall of the intestine, a part of the digestive system. A Meckel diverticulum is one that is in the lower part of the small intestine. It's found in the part of the small intestine called as the ileum, usually about 40 inches from the start of the large intestine. It's usually 1 to 2 inches long. Meckel diverticulum occurs in less than 5% of the population. It's the most common congenital abnormality of the gastrointestinal (GI) tract. Most of these diverticula also contain tissue that is normally found in the stomach or pancreas. This abnormal tissue makes chemicals that are usually made in the stomach and pancreas, so ulcers and bleeding of the lining of the small intestine may occur. Only a few people get symptoms from a Meckel diverticulum. Males are three to four times more likely than females to have complications.

What Causes Meckel Diverticulum?

Meckel diverticulum is present at birth (congenital). It's due to abnormal development of the GI tract in the fetus. Tissue left over from structures in the unborn baby's GI tract don't get fully absorbed before birth.

What Are the Signs and Symptoms of Meckel Diverticulum?

Most people (80% to 95%) have no symptoms. Only about 1 in 25 people born with it will have problems, which depend on age. Most people who have symptoms are children younger than 10 years old. They usually have bleeding from the rectum. Sometimes blood can be seen in the stool. Complications in adults include intestinal blockage and inflammation (swelling), with stomach pain and vomiting. Abdominal discomfort or pain ranges from mild to severe. Other

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symptoms may be fever, constipation, and swelling of the stomach. Inflammation called Meckel diverticulitis can seem like acute appendicitis. In rare cases, tumors (carcinoid, sarcoma, leiomyoma, or adenocarcinoma) can grow in the diverticulum.

How Is Meckel Diverticulum Diagnosed?

Meckel diverticulum is often diagnosed in the operating room when someone is taken to surgery for suspected appendicitis. In children with intestinal bleeding, a special imaging test called a technetium scan can be done to find the diverticulum. In people with possible blockage or diverticulitis, computed tomography (CT) of the abdomen and pelvis helps make the diagnosis. Blood tests may be done to help rule out appendicitis and similar disorders.

How Is Meckel Diverticulum Treated?

People who have this diverticulum but are asymptomatic don't need any treatment. People with symptoms need surgery. The part of the small intestine with the diverticulum is taken out. The intestine is then repaired. Heavy bleeding due to the diverticulum may necessitate a blood transfusion. Antibiotics may be given for complications involving intestinal blockage or infection. The need to take out a diverticulum that's found by accident on imaging tests isn't clear. Most surgeons believe that surgical removal is best to prevent future complications.

DOs and DON'Ts in Managing Meckel Diverticulum:

✓ **DO** remember that complicated Meckel diverticulum can lead to serious bleeding, infection and death, usually because of a delay in diagnosis.

⃠ **DON'T** ignore symptoms. Call your health care provider if you or your child has lower abdominal pain or dizziness or you see bleeding after bowel movements.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Surgeons Tel: (800) 621-4111 **Website: http://www.facs.org**
- American College of Gastroenterologists Tel: (703) 820-7400 **Website: http://www.acg.gi.org**
- National Digestive Diseases Information Clearinghouse Phone:1-800-891-5389 or 1-301-654-3810 **Website: www.niddk.nih.gov/health/digest/nddic.htm**

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MANAGING YOUR

MELANOMA

What Is Melanoma?

Melanoma is a skin cancer that begins in melanocytes. Melanocytes are skin cells that make pigment. Most melanomas appear as new moles; some start from a mole already present. Melanoma starts in the mole, spreads nearby and then deeper into the skin, into veins and lymph nodes, and finally into the liver, brain, lungs, and bones.

The number of new cases in the United States increased greatly in the last 25 years. If found early, about 85% of melanomas are curable.

What Causes Melanoma?

The cause is too much ultraviolet radiation from the sun, which hurts the skin. Higher risk is related to severe sunburns, light-colored skin, blue eyes, blond hair, getting freckles, using tanning salons, and having many abnormal moles or family members with melanoma. People with dark skin can also get melanoma.

What Are the Symptoms of Melanoma?

Initially there are no symptoms. When the melanoma spreads, symptoms include ABCD changes in a mole, swollen glands (lymph nodes), shortness of breath, bone pain (when melanoma spreads to bones), and headache, seizures, and visual problems (when melanoma spreads to brain). Skin signs of melanoma are *a*symmetry (the shape of one half doesn't match the other), irregular *b*order, uneven *c*olor, and increasing *d*iameter (change in size). These are known as ABCD changes.

How Is Melanoma Diagnosed?

The doctor makes a diagnosis by doing a biopsy (removing a piece of the mole and studying it

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with a microscope). The biopsy must be done for staging the cancer (how thick it is and how deep it goes in the skin). Also, to see whether the cancer spread (metastasized), the doctor looks for swollen lymph nodes during an examination and orders blood tests, chest x-rays, computed tomography (CT) of the head, and a bone scan.

How Is Melanoma Treated?

Treatment depends on the stage of the cancer and whether it spread to other organs. Early detection is critical for a cure, because advanced melanoma cannot be cured.

Surgery is done for all stages. For early stages, a surgeon cuts a wide margin of skin to make sure that all cancer is removed. If the melanoma has spread to other organs, surgery, radiation, chemotherapy, and immunotherapy help symptoms but usually don't cure it.

DOs and DON'Ts in Managing Melanoma:

✓ **DO** check your skin regularly for odd-looking new moles or changes in old moles. Call your doctor if you find any.

✓ **DO** have your doctor do a complete check of your skin at least yearly.

✓ **DO** avoid tanning booths.

✓ **DO** a skin self-examination at least once monthly. Look at all moles on your body or any new moles that have developed.

✓ **DO** use sunscreen with a sun protection factor (SPF) more than 30, which provides the best protection.

✓ **DO** remember that treating malignant melanoma requires a team effort, involving a primary

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care doctor, dermatologist (skin specialist), oncologist (cancer specialist), and surgeon.

✓ **DO** call your doctor if you feel swollen glands or you have pain, fever, or drainage after surgery.

⃠ **DON'T** stay out in the sun for long periods, especially if you burn easily.

⃠ **DON'T** delay calling your doctor if you see a mole that has changed or one that looks different.

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FOR MORE INFORMATION

Contact the following sources:

- National Cancer Institute Tel: (800) 422-6237 **Website: http://www.cancer.gov**
- American Academy of Dermatology Tel: (866) 503-SKIN (7546) **Website: http://www.aad.org**

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MANAGING YOUR

MÉNIÈRE'S DISEASE

What Is Ménière's Disease?

Ménière's disease is a disorder affecting the inner ear. One in every 1000 people has this disease. It's most common in people 20 to 50 years old, women and men equally. Children rarely get it. In half of all people, attacks usually go away after 2 years. In up to three fourths, attacks go away after 8 years. Some people may have lasting ringing in the ears, and some hearing loss may become permanent.

What Causes Ménière's Disease?

The cause is unknown. Viral infections and autoimmune causes have been suggested.

What Are the Symptoms of Ménière's Disease?

Symptoms include feelings of fullness or pressure in one ear, tinnitus (ringing, buzzing, roaring, or clicking in the ear), dizziness, vertigo (feeling of everything spinning), vomiting, sweating, jerky eye movements, loss of balance, and hearing loss. Some people have all these symptoms, but others have only some. Length and frequency of attacks vary among people. Vertigo is the worst symptom. Vertigo attacks start suddenly, last from a few hours to 24 hours, and go away slowly, leaving a dizzy or unsteady feeling for a few days. Dizziness may occur often and can be severe.

How Is Ménière's Disease Diagnosed?

The doctor will make a diagnosis from the medical history and physical examination. Blood tests, hearing and balance tests, and magnetic resonance imaging (MRI) may be done to exclude other conditions that may cause similar symptoms.

How Is Ménière's Disease Treated?

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Treatment goals are to reduce symptoms during an attack and prevent attacks with medications.

For many years, a low-salt diet and diuretics (water pills) have been used for treatment, but their value is unclear.

For frequent and disabling attacks, surgery involving the inner ear may bring permanent relief. However, most people recover without surgery in a few years.

DOs and DON'Ts in Managing

Ménière's Disease:

✓ **DO** rest quietly in bed until dizziness and nausea go away.

✓ **DO** exercise regularly when you can.

✓ **DO** ask your doctor about surgery as a treatment option if you have persistent disabling symptoms.

✓ **DO** call your doctor if your attacks become more frequent or last longer than usual.

✓ **DO** call your doctor if you have symptoms that are unlike your usual attack (such as fever or headache).

✓ **DO** call your doctor if your medicine doesn't work or causes other problems.

✓ **DO** cut down on caffeine, salt, and alcohol.

⊘ **DON'T** walk without help if you are dizzy.

⊘ **DON'T** smoke. Smoking can reduce blood flow to the inner ear.

⊘ **DON'T** make sudden changes in position.

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⦸ **DON'T** drive, climb ladders, or use heavy machinery if you have frequent attacks or take drugs that make you drowsy.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- Deafness Research Foundation Tel: (866) 454-3924 **Website:** **http://www.drf.org**
- Vestibular Disorders Association Tel: (800) 837-8428 **Website:** **http://www.vestibular.org**

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MANAGING YOUR

MENINGIOMA

What Is a Meningioma?

Meningiomas are slow-growing tumors in membranes (meninges) that cover the surface of the brain, spinal cord, or spinal nerve root. About one-fifth of all brain tumors are meningiomas. Almost all meningiomas are benign (not cancerous), but they still cause problems because they press on the brain or spinal cord. Meningiomas occur nearly twice as often in women as in men, the most common age at time of diagnosis being 45. They are rare in children and adolescents. About 80% of people are cured if the tumor can be completely removed. Rarely, meningiomas are cancerous (malignant) and may recur quickly and destroy normal tissues nearby.

What Causes a Meningioma?

Meningiomas are caused by abnormal growth of cells on surface coverings of the brain, spinal cord, or spinal nerve roots. The cause of the abnormal growth is unknown.

What Are the Symptoms of a Meningioma?

Symptoms include headaches, vision changes, hearing changes, nausea and vomiting, weakness (especially on one side of the body), numbness or tingling, and loss of memory and the ability to think clearly. Meningiomas may sometimes irritate the brain's surface and cause epilepsy (seizures).

How Is a Meningioma Diagnosed?

The doctor may suspect a meningioma on the basis of the medical history and physical examination. The doctor will order computed tomography (CT) or magnetic resonance imaging (MRI) of the brain. A special x-ray of the blood vessels in the brain called angiography may be done if surgery is necessary.

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How Is a Meningioma Treated?

Some people with small, slow-growing meningiomas and no symptoms need no treatment but will be checked regularly with CT or MRI to monitor the growth of the tumor. Otherwise, treatment is surgery. After the tumor is removed, it will be examined to see whether it's cancerous. If it is cancer, more treatment with radiation may be used. In some cases, non-invasive radiosurgery (focused radiation [gamma knife]) may be used to treat deep tumors that are hard to reach surgically. For seizures before or after surgery, antiseizure medicine may be taken to prevent more seizures.

DOs and DON'Ts in Managing a Meningioma:

✓ **DO** follow treatments as prescribed by your doctor.

✓ **DO** keep all follow-up appointments to monitor growth of your tumor.

✓ **DO** return to activity and take medicines as prescribed by your doctor. Exercise daily if your doctor says you can.

✓ **DO** eat a healthy diet.

✓ **DO** get enough sleep and reduce your stress.

✓ **DO** call your doctor if you have new or repeating symptoms, or if symptoms become much worse.

✓ **DO** call your doctor if you have problems with your medicines.

✓ **DO** look for a support group if you think that will help you cope.

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⦸ **DON'T** panic. In most cases, your illness can be cured with surgery.

⦸ **DON'T** drive if you've had a seizure, unless your doctor says that you can.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- • National Brain Tumor Foundation Tel: (800) 934-2873 **Website:** **http://www.braintumor.org**
- • Mayo Clinic **Website:** **http://www.mayoclinic.com/**

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MANAGING YOUR

MENINGITIS

What Is Meningitis?

Meningitis is inflammation of membranes around the brain and spinal cord. It can be bacterial, viral, or fungal. People of any age can get meningitis, but most adults are older than 60 and most children younger than 15, and half are younger than 4.

People who have greater chances of getting bacterial meningitis include those who had their spleen removed, have poor immune (infection-fighting) systems, have suffered a head injury, or have cancer or diabetes mellitus. Those living in crowded camps or dormitories and alcoholics also have a greater chance of getting meningitis.

What Causes Meningitis?

The many causes include bacteria, viruses, fungi, chemicals, drugs, and tumors. The most common bacteria include *Neisseria meningitidis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Listeria monocytogenes*, *Escherichia coli*, *Klebsiella* species, and group B *Streptococcus*. Bacteria spread through passing of respiratory and throat secretions (coughing, kissing).

What Are the Symptoms of Meningitis?

In adults common symptoms include high fever, severe headache, and stiff neck, which start over several hours. Others are nausea, vomiting, light sensitivity, feeling sick, muscle and joint aches, and seizure-like muscle jerks. Poor coordination, confusion, drowsiness, loss of consciousness, and rash also occur.

Children have fever, high-pitched moaning or crying, grunting, fretfulness, and tiredness. They don't eat, are sick, arch their back or neck, and have pale, blotchy skin and rash. Newborns and small babies may seem only slow or inactive, be irritable, vomit, or feed poorly. They may

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not have the common symptoms.

How Is Meningitis Diagnosed?

The doctor makes a diagnosis by looking for bacteria in a sample of spinal fluid. The doctor gets fluid by doing a spinal tap. A needle is put into a spot in the lower back where fluid in the spinal canal can be reached. The doctor may also order blood tests and x-ray imaging tests of the brain.

How Is Meningitis Treated?

People need a hospital stay for treatment with intravenous antibiotics, plenty of fluids, and rest. Bacterial meningitis is usually fatal if untreated. Other types of meningitis (viral) aren't as dangerous, and people don't usually need a hospital stay. Viral meningitis usually goes away on its own. Antibiotics can't help it.

A neurologist (specialist in brain diseases) or a doctor who treats infectious diseases may be involved in care.

Most people usually recover completely from meningitis. Recovery can take 2 to 3 weeks or longer.

A vaccine protects against four types of *N. meningitidis*. It's not routinely used in the United States, but is sometimes used for outbreaks. College students, especially those living in dormitories, have more chances of getting meningitis and should consider getting this vaccine.

DOs and DON'Ts in Managing Meningitis:

✓ **DO** understand the importance of bacterial meningitis. It's a medical emergency and needs immediate attention and treatment.

✓ **DO** call your doctor if you have symptoms of bacterial meningitis.

✓ **DO** call your doctor if you have questions about meningitis vaccines.

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⦸ **DON'T** forget that people who are close contacts of someone with meningitis caused by *N. meningitidis* should get antibiotics to prevent meningitis.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- Meningitis Foundation of America Tel: (800) 668-1129 **Website: http://www.musa.org**
- National Meningitis Association Tel: (866) 366-3662 **Website: http://www.nmaus.org**

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MANAGING YOUR

MENOPAUSE

What Is Menopause?

Menopause is the time in a woman's life when menstrual periods have stopped for at least 1 year. It is often called the change of life. Menopause is not an illness.

Periods become irregular and stop because ovaries stop producing hormones, and hormone levels change. Hormones are chemicals in the body that control certain body functions. The hormone estrogen in women helps control the menstrual cycle. As a woman ages, the amount of estrogen decreases.

Most women go through menopause at about age 50 or 51. Sometimes menopause happens earlier (early forties), and sometimes later (mid fifties).

What Are the Symptoms of Menopause?

The most common symptoms are hot flashes and end of periods. Hot flashes can be very mild (feeling a little warmth in the face) to very severe (becoming red in the face and sweating excessively). A hot flash only lasts a few minutes. Hot flashes can disturb sleep, so women may feel very tired during the day.

Other symptoms include vaginal dryness, vaginal sensitivity, pain during intercourse, bladder control problems, weight gain, loss of sex drive (libido), and mood swings.

How Is Menopause Diagnosed?

Hot flashes and the end of periods for about 6 months mean that menopause is occurring.

Blood tests for follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels can be done to find out whether ovaries are slowing down or no longer working.

How Is Menopause Treated?

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Treatment of mild symptoms with drugs is unnecessary.

The most effective treatment for severe symptoms is hormone replacement therapy (HRT). Women with a uterus need estrogen and progesterone. Estrogen relieves symptoms of menopause very well. Progesterone reduces the risk of developing uterine cancer while taking estrogen. Women without a uterus do not take progesterone. Because taking hormones may slightly increase the risk of developing breast cancer, HRT should be prescribed as needed for each woman and only at the lowest effective dose. Vaginal creams or lubricants may help dryness and pain during intercourse.

During menopause, metabolism slows down, muscle mass decreases, and body fat percentage tends to increase. It becomes more important to eat healthy, low-fat foods and to exercise. Exercise helps burn calories and keep up bone strength and muscle mass. Exercise also increases the body's metabolism, which helps weight loss.

DOs and DON'Ts in Managing Menopause:

✓ **DO** follow a healthy diet. Eating and drinking products that contain chemicals called plant estrogens may help. Such foods include fennel, soy, nuts, whole grains, and apples.

✓ **DO** take care of your health. Exercise. Women who have gone through menopause may be more likely to develop certain diseases, including heart disease and osteoporosis.

✓ **DO** get regular checkups.

✓ **DO** tell your doctor if you don't feel well while using HRT. Estrogen sometimes has side effects.

✓ **DO** use simple exercises called Kegel exercises to improve bladder control if you have prob-

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lems with it.

⦸ **DON'T** drink beverages containing caffeine.

⦸ **DON'T** drink alcohol in excess.

⦸ **DON'T** eat hot spicy foods. These may make hot flashes worse.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Women's Health Resource Center Tel: (877) 986-9472 **Website:** **http://www.healthywomen.org**
- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website:** **http://www.acog.org**

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MANAGING YOUR

MENORRHAGIA

What Is Menorrhagia?

Menorrhagia is the term for unusually heavy bleeding during otherwise normal menstruation (periods).

About 9% to 14% of all women have it, about 10% during childbearing years.

What Causes Menorrhagia?

Menorrhagia occurs more often in young women. It can also occur in older women who are close to menopause (change of life). Other causes are polyps, fibroids, certain drugs, cancer, and infection.

What Are the Symptoms of Menorrhagia?

Very heavy blood flow means soaking through at least one pad or tampon every hour for several hours, bleeding for more than 7 days or heavy periods regularly lasting 10 or more days, and unusually heavy bleeding for two periods in a row.

How Is Menorrhagia Diagnosed?

The doctor will make a diagnosis from the medical history, physical examination, and blood tests (to check for anemia). Anemia occurs when blood loss is so great that your blood count is too low. Anemia causes tiredness and feeling weak. Other special tests include a Pap test, biopsy of the lining of the uterus, ultrasound tests, hysteroscopy, laparoscopy, hysterosalpingography, and D&C (dilation and curettage). For the biopsy, a tissue sample is removed and looked at with a microscope. Ultrasound uses sound waves to take pictures of the uterus, ovaries, and pelvis. For hysteroscopy, a thin metal tube with a tiny camera in it is passed through the cervix into the uterus to look inside. Laparoscopy also lets the doctor look in the abdomen (belly) through a

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small cut. For hysterosalpingography, dye that is put into the uterus and fallopian tubes lets the doctor see the uterus on x-ray. The doctor uses a D&C to dilate the cervix and take samples of the lining of the uterus for study.

How Is Menorrhagia Treated?

Treatment choice depends on the cause, side effects, and the woman's preference. Different treatments such as medicine and surgery can reduce heavy bleeding. Medicines include birth control pills, hormones (e.g., progesterone), and iron supplements. If medicines don't work, outpatient surgery may be done, which includes D&C and operative hysteroscopy. Other operations can cause infertility and are usually for older women who are not planning to get pregnant. These operations include endometrial ablation (the lining of the uterus is destroyed permanently), endometrial resection (removing the lining), and hysterectomy (removing the uterus and usually the cervix). A hysterectomy involves a hospital stay.

DOs and DON'Ts in Managing Menorrhagia:

✓ **DO** tell your doctor about medicines you take, including over-the-counter drugs.

✓ **DO** return for follow-up care when needed.

✓ **DO** call your doctor if symptoms worsen after treatment starts.

✓ **DO** eat iron-rich foods.

⃠ **DON'T** delay getting care. Prolonged bleeding can result in severe anemia.

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Contact the following sources:

- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website:** **http://www.acog.org**
- National Women's Health Resource Center Tel: (877) 986-9472 **Website:** **http://www.healthywomen.org**

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MANAGING YOUR

MESOTHELIOMA

What Is Mesothelioma?

Mesothelioma is a rare cancer that affects the mesothelium. The mesothelium is a sac that covers and protects some internal organs. In most cases, the cancer begins in the pleura (membrane around the lungs and lining the wall inside the chest) or peritoneum (membrane lining the abdominal cavity). About 3000 new cases are diagnosed in the United States each year. More men than women get this illness, and risks increase with age.

What Causes Mesothelioma?

Working with asbestos is the major risk factor. However, it can occur in some people without any asbestos exposure. The combination of smoking and asbestos exposure increases the risk.

What Are the Symptoms of Mesothelioma?

Symptoms may not appear until 20 to 50 years after asbestos exposure. Symptoms of pleural mesothelioma include shortness of breath and chest pain. Signs and symptoms of peritoneal mesothelioma include weight loss, abdominal pain and swelling, bowel obstruction, blood clotting abnormalities, anemia, and fever.

If cancer spreads to other body parts, pain, trouble swallowing, or neck or face swelling may occur.

How Is Mesothelioma Diagnosed?

Diagnosing this illness is often difficult, because symptoms are similar to those of other conditions. The doctor will check the medical history (especially history of asbestos exposure), do a physical examination, and order x-rays, lung function tests, computed tomography (CT), or magnetic resonance imaging (MRI).

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A biopsy is needed to confirm the diagnosis. In a biopsy, a surgeon removes a sample of tissue for study with a microscope.

The doctor may do thoracoscopy for cancer in the chest. The doctor makes a small cut through the chest and puts in a thin, lighted tube (thoracoscope) to look inside.

The doctor may do peritoneoscopy for cancer in the abdomen (belly). In this case, a similar instrument, called a peritoneoscope, is used.

How Is Mesothelioma Treated?

The doctor will also want to learn the stage of the disease, or how far it has spread. Knowing the stage helps the doctor plan treatment. Mesothelioma can be localized (found only on the membrane) or advanced (spread to lymph nodes, lungs, chest wall, or abdominal organs).

Treatment depends on the cancer's location and stage and your age and general health.

Surgery, radiation therapy, and chemotherapy are sometimes combined. The doctor may remove part of the lining of the chest or abdomen and some tissue around it. Radiation therapy involves using high-energy x-rays to kill cancer. Radiation may come from a machine or from putting materials that produce radiation where cancer cells are found. Chemotherapy uses drugs to kill cancer cells. Most drugs are injected into a vein (intravenous, or IV).

DOs and DON'Ts in Managing Mesothelioma:

✓ **DO** report symptoms to your doctor.

✓ **DO** call your doctor if you have chest pain, shortness of breath, abdominal pain, trouble swallowing, or a fever.

⃠ **DON'T** smoke.

⃠ **DON'T** miss follow-up appointments.

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⦸ **DON'T** be afraid to ask for pain medicine, especially after surgery.

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FOR MORE INFORMATION

Contact the following source:

- National Cancer Institute Information Cancer Information Service Tel: (800) 422-6237

  Website: http://cis.nci.nih.gov/

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MANAGING YOUR

METABOLIC SYNDROME

What Is Metabolic Syndrome?

Metabolic syndrome refers to the presence of several factors that increase your risk of getting cardiovascular disease (such as heart disease and stroke), kidney disease, and diabetes.

Nearly 47 million adults in the United States have the syndrome. It's more common in middle-aged and elderly people.

What Causes Metabolic Syndrome?

The exact cause is unknown, but genetics and lifestyle choices (e.g., diet, food intake, physical inactivity) both play a role. Metabolic syndrome can't be caught or passed from person to person.

What Are the Symptoms of Metabolic Syndrome?

Metabolic syndrome has no specific symptoms. Many people don't know that they have it and find out only after blood tests, measurements of the waist, and blood pressure readings show its presence.

How Is Metabolic Syndrome Diagnosed?

The doctor makes a diagnosis if the combination of certain risk factors is present: too much fat around the waist (abdomen), so that the waist measures more than 40 inches in men and 35 inches in women. A second factor is high blood triglyceride levels (higher than 150 mg/dl). Triglycerides are a kind of fat in the blood. Another factor is a high-density lipoprotein (HDL) level lower than 40 mg/dl in men and 50 mg/dl in women. HDL is good cholesterol, because it carries cholesterol including low-density lipoprotein (LDL, or bad cholesterol) away from the arteries and back to the liver for removal from the body. Other factors are high blood pressure

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(130/85 mmHg or higher), and a high fasting blood sugar (glucose) level (100 mg/dl or higher).

How Is Metabolic Syndrome Treated?

First, changes in lifestyle, specifically diet, weight, and exercise, are important. A small weight loss can lead to a great decrease in blood pressure, blood fat levels, and blood glucose levels.

Diet changes to lower cholesterol include using unsaturated fats instead of saturated fats, reducing total fat intake to 30% of daily calories, and eating no more than 300 mg of cholesterol daily. Also, less salt should be used.

Moderate daily exercise, defined as 30 minutes of brisk walking or 15 minutes of running, can produce important health benefits.

Weight loss, exercise, and less salt can reduce blood pressure. If they don't, the doctor may prescribe medicines.

The doctor may prescribe cholesterol-lowering medicine, such as statins (e.g., lovastatin, pravastatin, simvastatin, atorvastatin, rosuvastatin), if lifestyle changes don't lower cholesterol levels.

DOs and DON'Ts in Managing Metabolic Syndrome:

✓ **DO** remember that fasting for at least 12 hours before testing is needed for accurate blood cholesterol, triglycerides, and glucose levels.

✓ **DO** call your doctor if you have high blood pressure, you need advice about diet or exercise, or you have symptoms of diabetes (increased thirst, increased urination, blurred vision, and overeating).

✓ **DO** call your doctor if you want to know your blood levels of total cholesterol, HDL (good) cholesterol, LDL (bad) cholesterol, and triglycerides.

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⦸ **DON'T** smoke. Cigarette smoking is a major risk factor for coronary artery disease.

⦸ **DON'T** forget that reasonable lifestyle changes can have big benefits in reducing chances of getting metabolic syndrome and cardiovascular disease.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American College of Cardiology Tel: (800) 253-4636 **Website: http://www.acc.org**
- American Heart Association Tel: (800) 242-8721 **Website: http://www.americanheart.org**

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MANAGING YOUR

METATARSALGIA

What Is Metatarsalgia?

Metatarsalgia is a term used for pain and inflammation (swelling) in the ball of the foot. Each foot has five metatarsal bones from the arch to the toe joints. The first metatarsal is shorter and thicker than the others, which are usually similar in size. During the push-off phase when walking, jumping, or running, body weight is transferred to the toes and metatarsals. Excess pressure on metatarsals can lead to metatarsalgia, especially in the metatarsal heads (rounded ends of metatarsals).

Metatarsalgia is a common overuse injury. It's important to have a correct diagnosis. This kind of pain can be confused with other causes of forefoot pain.

What Causes Metatarsalgia?

Pain is usually due to increased pressure on the forefoot, such as when wearing high heels or when the fat pad has shrunk. Causes also include intense training or activity, certain foot shapes such as a high arch, hammertoes, and bunions. Others are shoes that don't fit well, stress fractures, Morton's neuroma, excess weight, arthritis, sesamoiditis, and synovitis.

What Are the Symptoms of Metatarsalgia?

The symptom is pain in the ball of the foot, the sole just behind the toes, when walking. Pain can also occur in the area around the second, third, or fourth toes, or only near the big toe. Pain gets better with resting. The toes can have sharp or shooting pain, numbness, or tingling. Calluses can form under the metatarsal heads, usually one of the middle three toes. Other symptoms include tenderness, deformity, and joint stiffness. Problems usually develop slowly but can start suddenly.

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How Is Metatarsalgia Diagnosed?

The health care provider makes a diagnosis from a medical history, physical examination, and X-rays.

How Is Metatarsalgia Treated?

Treatment first includes RICE (rest, icing, compression, and elevation). Ice packs, wrapped in a thin towel, can be put on the area for 20 minutes at a time, several times a day. Over-the-counter pain relievers may help. Wearing proper shoes such as running shoes is important. Soft shoe inserts or pads made of cork, plastic, rubber or gels and sometimes custom soft orthotic devices may be needed. All lower friction and pressure through the forefoot. A metatarsal bar or rigid rocker can be put on shoe soles to reduce pressure. Regular trimming of calluses may provide dramatic relief. Medicines such as steroids and diet are not as effective as other measures and aren't a long-term solution. Physical therapy and recreational therapy such as swimming may help. Metatarsalgia may last for several months or even years. If all other treatments don't work, surgery may be an option.

DOs and DON'Ts in Managing Metatarsalgia:

✓ **DO** change the type and style of your shoes. A simple pad or soft shoe insert can make a big difference.

✓ **DO** call your health care provider if pain becomes constant or doesn't respond to therapy.

✓ **DO** eat a good diet, which is needed for healthy tissues. Keep your weight within a healthy range.

✓ **DO** warm-up and passive stretching before you exercise. They will help the blood supply and

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flexibility.

⦸ **DON'T** continue wearing shoes that don't fit or aren't practical.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopedic Surgeons Phone: 847-823-7186 **Website: www.aaos.org**
- American Physical Therapy Association Phone: 800-999-2782 **Website: www.apta.org**
- American College of Rheumatology Phone: 404-633-3777 **Website: www.rheumatology.org**

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MANAGING YOUR

MICROSCOPIC COLITIS (LYMPHOCYTIC OR COLLAGENOUS COLITIS)

What Is Microscopic Colitis?

Microscopic colitis got its name because a microscope must be used to look at tissue samples to make the diagnosis. This syndrome includes two disorders—collagenous colitis and lymphocytic colitis. These two kinds of bowel inflammation affect the colon (large intestine, or bowel). They aren't related to Crohn's disease or ulcerative colitis.

More women than men have collagenous colitis; lymphocytic colitis affects men and women equally. People are usually first diagnosed in their 50s or 60s.

What Causes Microscopic Colitis?

The cause is unknown. However, bacteria and their toxins, viruses, and nonsteroidal antiinflammatory drugs (NSAIDs) or other drugs may damage the bowel lining. NSAIDs include aspirin, ibuprofen, and naproxen. An autoimmune response may cause the colitis. This means that the body's own immune (infection-fighting) system does not recognize cells as belonging to one's body and destroys them. The disorder can run in families.

What Are the Symptoms of Microscopic Colitis?

The main symptom is chronic watery, nonbloody diarrhea. It often starts quite suddenly. The diarrhea may be constant or come and go. Other symptoms are pain, cramps, or bloating in the abdomen (belly); weight loss; nausea; fecal incontinence; and dehydration.

How Is Microscopic Colitis Diagnosed?

The doctor may suspect microscopic diarrhea based on the medical history and physical exam. A colonoscopy will be done. For a colonoscopy, the doctor puts a tube through the large bowel. The tube has a lighted end and camera so that the doctor can see inside the colon. Specific biopsy

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findings are needed to confirm the diagnosis. For a biopsy, the doctor takes small pieces of bowel tissue for study with a microscope. In collagenous colitis, the bowel lining has a thickened layer of connective tissue (collagen). In lymphocytic colitis, tissue pieces show inflammation with many white blood cells (lymphocytes) in the bowel lining, but with normal collagen.

How Is Microscopic Colitis Treated?

Lifestyle changes to stop diarrhea are usually tried first. The amount of fat in the diet is reduced, foods that contain caffeine or lactose are avoided, and NSAIDs are stopped. If these changes aren't enough, drugs are tried. Medicines such as bismuth subsalicylate (Pepto-Bismol), loperamide (Imodium), or the combination diphenoxylate and atropine (Lomotil) may help the diarrhea. Bulking agents (psyllium, methylcellulose) may also help. Antiinflammatory medicines, such as mesalamine, sulfasalazine, and steroids including budesonide, reduce inflammation.

DOs and DON'Ts in Managing Microscopic Colitis:

- ✓ **DO** avoid eating problem foods such as fat, caffeine, and lactose (milk sugar found in dairy products). Avoid spicy foods and alcohol. Stay away from foods that cause gas and diarrhea: carbonated beverages, raw fruits, and vegetables such as beans, cauliflower, broccoli, and cabbage.
- ✓ **DO** talk to your doctor about using pain relievers other than NSAIDs. NSAIDs can worsen diarrhea.
- ✓ **DO** ask your doctor whether you should drink an oral rehydration solution (ORS). Severe diarrhea can cause dehydration. An ORS has the right amounts of water, salts, and sugar to replace body fluids.

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✓ **DO** look into eating a gluten-free diet. Microscopic colitis may respond to this diet.

✓ **DO** learn all you can about microscopic colitis.

✓ **DO** join a support group if you think that would help.

⃠ **DON'T** eat possible problem foods at restaurants and social gatherings.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Digestive Diseases Information Clearinghouse E-mail: nddic@aerie.com

  Website: http://www.niddk.nih.gov/health/digest/nddic.htm

- American College of Gastroenterology Tel: (703) 820-7400**Website:**

  http://www.acg.gi.org

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MANAGING YOUR

MIGRAINE HEADACHE

What Are Migraine Headaches?

Migraine headaches are intense headaches that usually affect one side of the head and are often preceded by other symptoms. A migraine can last from 2 hours to 3 days.

What Causes Migraine Headaches?

The cause is unknown, but 60% to 80% of people inherit the tendency to have migraines. Migraines may be associated with alcohol (red wine), skipped meals, foods containing monosodium glutamate, nitrates (hot dogs, luncheon meats), tyramine (aged cheese, smoked fish), fatigue, and weather changes. Other triggers are stress, too little or too much sleep, medicines, menstrual periods, pregnancy, and birth control pills.

What Are the Symptoms of

Migraine Headaches?

In classic migraine, hours to days before a headache, people have a symptom (prodrome) that tells them that a headache is starting. These include mood changes, sensitivity to light (photosensitivity), sensitivity to sound (phonosensitivity), hyperactivity, feeling sluggish, fatigue, appetite changes, and nausea. Auras (temporary disturbance of the senses or muscles) then come before the headache. They usually last 10 to 30 minutes, then the headache starts and aura symptoms go away. Aura symptoms include hearing and vision problems (flashes of light, flickering lights, blind spots). Dull pain on one side of the head may become intense and throbbing. Nausea and vomiting may occur.

With a common migraine, people don't have an aura, and pain usually occurs on both sides of the head. People have nausea and sometimes numbness or weakness. Some people have vision or

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stomach problems without the headache.

How Are Migraine Headaches Diagnosed?

The doctor makes a diagnosis from the medical history and physical examination. Computed tomography (CT) or magnetic resonance imaging (MRI) may be done to exclude other disorders that may cause similar symptoms.

How Are Migraine Headaches Treated?

Many medicines are prescribed for migraine. Early treatment is best for faster relief. Nonsteroidal antiinflammatory drugs (NSAIDs) such as ibuprofen and naproxen, as well as ergotamine and sumatriptan and other triptans, may be given to stop migraines.

To prevent frequent migraines, people may use medicine daily. These drugs include beta-blockers, calcium channel blockers, antidepressants (amitriptyline, venlafaxine), anticonvulsants (topiramate, divalproex), NSAIDs, and hormones. Other medicine may be given for long and severe headaches.

Migraine triggers include chocolate, red wine, port wine, cheese, onions, fatty foods, and acidic foods (e.g., oranges and tomatoes) and should be avoided.

DOs and DON'Ts in Managing

Migraine Headaches:

✓ **DO** apply a cold cloth or ice pack to your head or splash your face with cold water when you feel a migraine starting.

✓ **DO** lie down in a quiet, dark room, with pillows under your head. Relax and sleep.

✓ **DO** minimize noise, light, and odors (especially cooking odors and tobacco smoke).

✓ **DO** avoid migraine triggers, such as foods, stress, not sleeping, and medicines. Keep a food

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diary.

✓ **DO** call your doctor if your headache is worse than usual, your usual medicine doesn't work, you have a fever and headache, or you have severe vomiting.

✓ **DO** exercise as much as possible, to be healthy.

⃠ **DON'T** drive or use heavy machinery during an attack.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Headache Foundation Tel: (888) 643-5552 **Website:** http://www.headaches.org
- American Headache Society Committee for Headache Education Tel: (800) 255-2243 **Website:** http://www.achenet.org
- MAGNUM: Migraine Awareness Group: A National Understanding for Migraine Tel: (703) 349-1929 **Website:** http://www.migraines.org

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UNDERSTANDING AND MANAGING YOUR MISCARRIAGE

What Is a Miscarriage?

A miscarriage, or spontaneous abortion, is the loss of a pregnancy before the embryo or fetus can survive. Miscarriage affects 10% to 15% or more of all pregnancies. A complete miscarriage occurs before 20 weeks of pregnancy (counting from the first day of the last normal period). Most miscarriages occur before 6 weeks or after 14 weeks of gestation. An incomplete miscarriage is the loss of some, but not all, of the elements of the pregnancy. When membranes (bag of waters) break or dilation (widening) of the cervix takes place during the first half of pregnancy, the term is inevitable miscarriage, and women lose the pregnancy. In a missed miscarriage, the uterus (womb) keeps the failed pregnancy for several weeks. A threatened miscarriage is a pregnancy in which symptoms such as bleeding or cramping indicate that a miscarriage is possible (but not automatic).

What Causes a Miscarriage?

Separation of the fetus and placenta from the wall of the uterus leads to a miscarriage. Almost all miscarriages during the first 3 months of pregnancy (first trimester) occur because of an abnormal fetus. More than half of these fetuses have problems in the genes, which would cause major birth defects. The risk of a miscarriage increases with mother's age above 35 years. Miscarriage during the second trimester (fourth through sixth months) is usually related to a problem in the woman. Such problems include chronic illness (such as diabetes, high blood pressure, or thyroid disease), infection, abnormal female organs (fibroids in the uterus), and drug use (such as tobacco and cocaine).

Exercising, working, and having sex don't normally cause miscarriages, unless a woman is

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already at high risk for this condition.

What Are the Symptoms of a Miscarriage?

Vaginal bleeding and cramping in the lower abdomen (belly) are the most common symptoms. Up to 40% of women may have mild symptoms but then have perfectly healthy pregnancies.

How Is a Miscarriage Diagnosed?

The doctor can check the possibility of a miscarriage by a vaginal or ultrasound examination. Levels of certain pregnancy-related hormones may be measured, but they don't always prove that a problem exists.

How Is a Miscarriage Treated?

When a complete loss of pregnancy occurs, you and your body may only need to get back to normal before you try to become pregnant again. For an incomplete loss of pregnancy, the doctor may prescribe medicines to complete the process or may remove tissues (by a simple surgical procedure called dilation and curettage, or D&C).

DOs and DON'Ts in Managing a Miscarriage:

✓ **DO** take time to grieve and heal emotionally and physically. A support group may help.

✓ **DO** begin to care for your pregnancy as soon as you know that you're pregnant again.

✓ **DO** tell your doctor about vaginal bleeding, loss of fluid, or abdominal cramping.

⃠ **DON'T** change your diet or activities unless your doctor tells you to do so.

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FOR MORE INFORMATION

Contact the following sources:

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- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website: http://www.acog.org**
- WebMD **Website: http://www.webmd.com**

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MANAGING YOUR

MITRAL REGURGITATION

What Is Mitral Regurgitation?

The mitral valve in the heart is between the left atrium (a chamber in the top part of the heart) and left ventricle (a chamber in the bottom part). It opens when the atrium pumps blood into the ventricle. It closes when the ventricle pumps blood out into the body. Closing prevents the blood from going back into the atrium. Blood leaking back into the atrium from the ventricle is called regurgitation (or insufficiency or incompetence). Blood isn't pumped out of the heart properly, and the atrium cannot fill during the next cycle. Blood may back up in the right-sided system (to the lungs) and cause lungs to fill with fluid. The left ventricle then has to do more work to move blood. This extra work may later cause heart failure.

What Causes Mitral Regurgitation?

The cause is damage to the mitral valve. Damage may result from a congenital abnormality (present at birth) or a heart attack (or myocardial infarction, in which parts of the heart die because they don't have enough blood). Other causes are infections such as rheumatic fever (from streptococcal infections such as strep throat), connective tissue disorders such as lupus, and inherited conditions such as Marfan syndrome. Mitral valve prolapse also can lead to mitral regurgitation.

What Are the Symptoms of Mitral Regurgitation?

People often live for years without knowing that they have this condition. People with a small defect have no symptoms. Symptoms developing after a few years usually include tiredness and difficulty breathing.

How Is Mitral Regurgitation Diagnosed?

The doctor diagnoses mitral regurgitation by listening to heart sounds. Abnormal blood move-

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ment makes a sound called a murmur. The doctor hears the murmur through a stethoscope. The doctor may also order sonography of the heart (echocardiography), chest x-rays, and electrocardiography (ECG) to confirm the diagnosis. The x-rays often show a large left atrium. Abnormal heart rhythms (arrhythmias such as atrial fibrillation) can occur and may cause palpitations, or irregular heartbeat.

How Is Mitral Regurgitation Treated?

For a mild condition, medicines are used to prevent complications. Surgery consisting of mitral valve replacement is done when regurgitation worsens and medicines don't work to control symptoms.

DOs and DON'Ts in Managing Mitral Regurgitation:

✓ **DO** take your medicines as directed.

✓ **DO** limit fluid and salt in your diet if you have symptoms of heart failure.

✓ **DO** exercise under the guidance of a physician.

✓ **DO** call your doctor if you have side effects from medicines or new or worsening symptoms, especially chest pain, shortness of breath, difficulty breathing at rest, lightheadedness, palpitations (rapid heartbeat), or new swelling in your feet or legs.

⦸ **DON'T** ignore worsening symptoms.

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Contact the following sources:

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- American Heart Association Tel: (800) 242-8721 **Website:**

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MANAGING YOUR

MITRAL STENOSIS

What Is Mitral Stenosis?

Mitral stenosis is abnormal narrowing or blocking of the mitral valve. The mitral valve lies between the left atrium (one of the upper chambers in the heart) and left ventricle (one of the lower chambers in the heart). A narrow valve means that the left atrium must pump harder to move blood into the left ventricle. If the left atrium cannot empty the blood properly, blood backs up into the right-sided heart system, and fluid leaks into the lungs. Mitral stenosis occurs two to four times more often in women than in men. It is a major cause of congestive heart failure.

What Causes Mitral Stenosis?

The cause may be scarring of the valve from rheumatic fever that occurred earlier in life, usually in childhood. Rheumatic fever comes from a bacterial (streptococcus, or strep) infection. Other causes are congenital heart disease, calcium deposits, and infection.

What Are the Symptoms of Mitral Stenosis?

Symptoms include difficulty breathing (especially when lying down), swelling (edema) in legs, and tiredness. Other symptoms may be irregular heartbeat, coughing up blood, and chest pain. If an abnormal heartbeat called atrial fibrillation develops, the atrium doesn't contract normally, so blood pools in the atrium. Clots may form and move out of the heart to the brain and cause a stroke.

How Is Mitral Stenosis Diagnosed?

The doctor can make a diagnosis by listening to heart sounds. Blood moves abnormally through the mitral valve and causes a sound called a murmur. The doctor hears the murmur with a stethoscope. The timing and location of the murmur help the doctor tell which valve is affected. A

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sonogram of the heart (echocardiogram) can confirm the diagnosis. Other tests ordered may include a chest x-ray and electrocardiography (ECG).

How Is Mitral Stenosis Treated?

For a mild condition, attempts are made to prevent complications with medicines. When medicines cannot control symptoms any longer, an operation to have the mitral valve widened or replaced is usually performed.

DOs and DON'Ts in Managing Mitral Stenosis:

✓ **DO** take your medicine as directed.

✓ **DO** change your diet. Use moderate salt restriction (don't add salt to your food).

✓ **DO** call your doctor if you have side effects from your medicines.

✓ **DO** call your doctor if you have new or worsening symptoms, such as chest pain, shortness of breath, or swelling in the legs.

✓ **DO** call your doctor if you take anticoagulants and have a cut that doesn't stop bleeding.

⃠ **DON'T** ignore worsening symptoms.

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Contact the following sources:

- American College of Cardiology Tel: (800) 253-4636 **Website: http://www.acc.org**
- American Heart Association Tel: (800) 242-8721 **Website:**

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MANAGING YOUR

MITRAL VALVE DISEASE

What Is Mitral Valve Disease?

Mitral valve disease includes mitral valve stenosis (MVS), mitral valve regurgitation (MVR), and mitral valve prolapse (MVP). In MVS, mitral valve leaflets become stiff, calcified, and unable to open fully. In MVR, leaflets cannot close tightly, so blood leaks back from the left ventricle into the left atrium. Ventricles are bottom heart chambers. Top heart chambers are the atria. MVP is the bulging (prolapse) of one or both leaflets into the left atrium. The most common congenital heart disease in adults, MVP is usually not serious. However, it can lead to complications including endocarditis and severe MVR. About two-thirds of MVS cases occur in women.

What Causes Mitral Valve Disease?

Age-related calcifications can damage the mitral valve. Rheumatic fever causes most cases of MVS in developing countries, much less in the U.S. Less common causes include endocarditis, systemic lupus erythematosus, rheumatoid arthritis, and carcinoid heart disease.

MVR has many causes: MVP, rheumatic fever, endocarditis, age-related wear-and-tear, and high blood pressure. Heart attack, coronary artery disease, cardiomyopathy, and congenital heart defects are others.

The cause of MVP is unknown.

What Are the Symptoms of Mitral Valve Disease?

Symptoms of MVS are shortness of breath, tiredness, abnormal heartbeat (arrhythmias), and chest pain.

Some people have no symptoms of MVR. When present, signs and symptoms include shortness of breath (especially with exercise), tiredness, and feeling lightheaded. Others are pal-

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pitations, swollen feet or ankles, and heart murmur.

Most people with MVP have no symptoms. The most common complaint is chest pain. Other symptoms include palpitations, dizziness, shortness of breath, anxiety, numbness, and tingling.

How Is Mitral Valve Disease Diagnosed?

To diagnose MVS and MVR, the doctor obtains a medical history, does a physical examination, and orders echocardiography, X-rays, and electrocardiography (ECG). Cardiac catheterization is used if surgery is being considered. MVP is usually found accidentally, during a routine physical examination when the doctor hears a heart murmur.

How Is Mitral Valve Disease Treated?

Monitoring for mild MVS and MVR involves regular doctor checkups. People with MVS symptoms may need diuretics, beta-blockers, or calcium channel blockers. Surgery is reserved for severe cases. Surgery includes percutaneous mitral balloon valvotomy, valvotomy, and mitral valve replacement. Mechanical valves, made of synthetic materials, may be used. Another option is biological valves, made from animal or human tissue. MVR is fixed by valve repair (the usual operation) or replacement. Surgery can often be delayed until dysfunction of the left ventricle.

Most people with MVP can be reassured about their disorder being not serious and can generally be controlled with medications. In people with MVP and severe MVR, mitral valve repair can be done.

DOs and DON'Ts in Managing Mitral Valve Disease:

✓ **DO** control high blood pressure and high cholesterol levels. Eat low-fat, low-salt, low-cholesterol foods. Lose weight if you're overweight.

✓ **DO** exercise regularly.

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✓ **DO** see your doctor for regular checkups.

✓ **DO** prevent rheumatic fever by seeing your doctor when you have fever and a sore throat.

Untreated strep throat can result in rheumatic fever.

⃠ **DON'T** smoke or drink alcohol or caffeine.

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:**

  http://www.americanheart.org

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MANAGING YOUR

MITRAL VALVE PROLAPSE

What Is Mitral Valve Prolapse?

The mitral valve of the heart lies between the left atrium (one of the upper chambers in the heart) and left ventricle (one of the lower chambers in the heart). The mitral valve normally opens when the left atrium pumps blood into the ventricle. It closes to prevent blood from going back into the atrium as the ventricle pumps blood out of the heart. Mitral valve prolapse (MVP) means that the valve, which is thickened, bulges back into the atrium. Blood leaking back into the atrium from the ventricle is called regurgitation.

Prolapse can cause some degree of regurgitation. This means that the left ventricle must do more work to move the blood. Severe regurgitation occurs in about 15% of people with prolapse.

MVP is rather common and affects about 5% of the population, women more than men.

What Causes MVP?

Any damage to the mitral valve may cause MVP. Damage may result from a congenital abnormality (one present at birth) or heart attack. Other causes are infections such as rheumatic fever (from streptococcal infections, e.g., strep throat) and connective tissue disorders such as Marfan syndrome.

What Are the Symptoms of MVP?

People often live for years without knowing that they have this condition. People with a small defect usually do well and never have symptoms.

Symptoms when present may include rapid or skipped heartbeat (palpitations), chest pain, and rarely, difficulty breathing. Abnormal heart rhythms (arrhythmias) such as atrial fibrillation may occur if changes in the atrium affect the heart's electrical system.

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How Is MVP Diagnosed?

The doctor diagnoses MVP on the basis of a physical examination. Blood moving against the valve in MVP produces a sound called a murmur. The doctor hears the murmur with a stethoscope. The timing and location of the murmur help the doctor tell which valve is affected.

The doctor may also order sonography of the heart (echocardiography) to confirm the diagnosis and estimate the degree of MVP.

How Is MVP Treated?

Treatment of MVP depends on how severe it is. People with no symptoms and no mitral regurgitation need no treatment.

If people have mitral regurgitation, attempts are made to prevent complications by using medicines and lifestyle changes.

DOs and DON'Ts in Managing Mitral Valve Prolapse:

✓ **DO** exercise on a regular basis.

✓ **DO** lose weight if you're overweight.

✓ **DO** call your doctor if you have new or worsening symptoms, especially chest pain, shortness of breath at rest, lightheadedness, palpitations, or new swelling in your feet or legs.

✓ **DO** call your doctor if you have side effects from your medicines.

⃠ **DON'T** use too much caffeine, because excess caffeine may worsen your symptoms.

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CARING FOR YOUR CHILD WITH

MOLLUSCUM CONTAGIOSUM

What Is Molluscum Contagiosum?

Molluscum contagiosum is an infection of the top layers of the skin caused by a virus. It spreads easily and so is fairly common in children (more often boys) and young adults. In adults and teenagers, when it affects the genital area, it's said to be a sexually transmitted disease (STD).

What Causes Molluscum Contagiosum?

The cause is a poxvirus (the same virus family that causes warts). The virus spreads by direct contact, touching either the infected skin of someone else or infected items such as clothes.

What Are the Symptoms of Molluscum Contagiosum?

Usually, children with molluscum contagiosum feel fine and don't have itching, pain, or tender spots. It takes from 2 to 7 weeks after exposure to see the rash. Small bumps occur on the skin in the affected part of the body, often in the face, eyelids, underarms, and thighs (groin). Usually, bumps don't appear on the palms of the hands, soles of the feet, and mouth.

The bumps are domed with a central pit and contain white curdlike (cheeselike) material. This material contains the virus.

The bumps may go away on their own over several weeks, but some may last for months. They don't usually leave scars.

How Is Molluscum Contagiosum Diagnosed?

Tests are usually not needed. The doctor will usually diagnose the infection just by looking at the bumps on the skin. In some cases, the doctor may want to take a scraping of the bumps and look at it under a microscope.

How Is Molluscum Contagiosum Treated?

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The bumps may go away on their own, but children often have treatment to keep the virus from infecting someone else or to keep the rash from spreading to other body parts. Treatments include removing the bumps by using lasers, freezing, or scraping. Sometimes these treatments leave scars. Special medicated skin creams can also help bumps go away.

Treatment may have to be repeated as new bumps appear. Also, children can get this infection more than once. Sharing contaminated hand towels or other personal items and having close contact with someone who has the infection should be avoided.

DOs and DON'Ts in Managing Molluscum Contagiosum:

✓ **DO** keep the affected area clean and covered with clothing or a bandage, to avoid spreading the virus.

✓ **DO** call your doctor if your child's bumps get worse.

⃠ **DON'T** let your child share hand towels with another person until the bumps are gone.

⃠ **DON'T** let your child scratch the bumps and then touch other parts of their body. The virus will spread this way and they may get another (bacterial) infection.

⃠ **DON'T** let your child use public swimming pools, saunas, and showers until the bumps are gone, to avoid passing the infection to others.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Dermatology Tel: (866) 503-SKIN (7546) **Website: http://www.aad.org**

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MANAGING YOUR

MONONUCLEOSIS

What Is Mononucleosis?

Mononucleosis, also called "mono" and "kissing disease," is an acute infection affecting the respiratory system, liver, and lymphatic system. It spreads by close contact. It's common in adolescents and young adults and rare in people older than 35. It's usually harmless and goes away by itself. Rarely, it becomes serious and causes major fatigue, so people miss weeks of school or work. The most serious complication is the spleen becoming swollen. It may burst if hit by direct contact, such as while playing contact sports.

What Causes Mononucleosis?

The cause is the Epstein-Barr virus (EBV). The virus spreads through saliva, such as by kissing, coughing, or sharing food or utensils with someone who's infected.

What Are the Symptoms of Mononucleosis?

Most important symptoms are fever, sore throat, and swollen and sore glands, especially in the neck. Headache, joint and muscle pain, general body aches, loss of appetite, feeling sick, puffy eyes, rash, stomach fullness or pain, severe tiredness (sleeping 12 to 16 hours daily), abdominal pain, and yellow skin may also occur.

Fever, body aches, and sore throat usually go away after 1 to 4 weeks. If the spleen got large, 6 weeks may be needed before it becomes normal and risk of bursting goes away. People may feel tired for several months after having mononucleosis. Sometimes tonsils get large and can cause breathing problems.

How Is Mononucleosis Diagnosed?

The doctor takes a medical history and does an examination, with special attention to the neck,

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throat, and abdomen. Blood tests and maybe throat cultures are done to be sure of the diagnosis and exclude other diseases.

How Is Mononucleosis Treated?

Most cases get better by themselves. Antibiotics don't work because a virus is the cause. Bed rest and good nutrition are the best treatment. No special diet is needed. For muscle aches and minor discomfort, ibuprofen or naproxen is used. Children younger than 16 years shouldn't take aspirin because of the risk of Reye's syndrome. For severe throat inflammation, anti-inflammatory steroids may be prescribed. Recovery takes 10 days to months.

DOs and DON'Ts in Managing Mononucleosis:

✓ **DO** get plenty of rest and drink lots of fluids.

✓ **DO** tell your doctor about all your medicines, including prescription and nonprescription.

✓ **DO** tell your doctor if your symptoms get worse or don't get better after 2 weeks.

✓ **DO** tell your doctor if you have stomach or shoulder pain.

✓ **DO** get your doctor's OK to lift heavy weights or play contact sports.

✓ **DO** arrange for schoolwork to be done at home, if needed.

✓ **DO** avoid kissing or sharing food or utensils with someone who's sick. Wash your hands often.

✓ **DO** call your doctor if your temperature is higher than 102° F.

✓ **DO** call your doctor if you have trouble swallowing or breathing, are constipated and strain

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during bowel movements, or get sudden severe abdominal pain.

✓ **DO** call your doctor if you have a severe headache, neck pain, or stiffness.

⃠ **DON'T** drink alcohol.

⃠ **DON'T** play contact sports.

⃠ **DON'T** give your child aspirin because of the chance of Reye's syndrome. Reye's syndrome causes organ failure, especially affecting the brain and liver. Its symptoms usually start with vomiting.

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FOR MORE INFORMATION

Contact the following sources:

- The Infectious Diseases Society of America Tel: (703) 299-0200 **Website:** **http://www.idsociety.org**
- Centers for Disease Control and Prevention Tel: (800) 232-4636 **Website:** **http://www.cdc.gov**

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MANAGING YOUR

MORNING SICKNESS

What Is Morning Sickness?

Morning sickness is nausea and vomiting that happens during early pregnancy (generally between 8 and 12 weeks), but it can occur at any time. Though 70% to 85% of women have morning sickness, only about 1% to 2% will have enough problems that it can threaten their health or the health of the pregnancy. This much more severe disorder is called hyperemesis gravidarum (HG). Morning sickness is more likely with a multiple pregnancy (twins or more).

What Causes Morning Sickness?

The cause is unknown, but factors that may be involved include hormones called human chorionic gonadotropin and estrogen. Other contributing factors are younger age of the mother, body weight (obesity), no previous completed pregnancies, first pregnancy, and history of morning sickness in prior pregnancies. Biological, psychological, and social factors may all play a role.

What Are the Symptoms of Morning Sickness?

Symptoms usually begin between the fourth and eighth week of pregnancy and last until 16 weeks or more. Most women vomit more often early in the day, but it can happen throughout the day. If this becomes severe, other symptoms can include severe nausea, weight loss, reduced urination, headaches, confusion, fainting, and jaundice. Dehydration is manifested by decreased need to urinate, increased pulse rate, and lower blood pressure.

How Is Morning Sickness Diagnosed?

The diagnosis of morning sickness is one that you can make yourself: If you don't have any other reason for being sick and you are pregnant, you have morning sickness. The severe form (hyperemesis gravidarum) is diagnosed by your doctor when severe nausea and vomiting lead to

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weight loss, dehydration, or disturbances in the body's chemistry. To be sure that nothing else is causing these symptoms, the doctor may do blood and urine tests. Ultrasonography may also be done.

How Is Morning Sickness Treated?

When symptoms aren't too bad, eating dry foods such as crackers and small, frequent meals may be enough. Drinking more fluids may help increase fluid intake. (If you drink fizzy drinks such as seltzer or other sparkling water, pour it over ice and let it sit for a bit to let some of the fizz out.) Women with the severest form may need intravenous fluids and vitamins and hospitalization. Medicines to prevent nausea (antiemetics) are for women with severe and long-lasting vomiting.

DOs and DON'Ts in Managing HG:

✓ **DO** get treatment if your symptoms cause you to lose weight or become dehydrated.

✓ **DO** eat small frequent meals.

✓ **DO** have high-protein snacks.

✓ **DO** have crackers, dry toast, or dry cereal when you first get up in the morning.

⃠ **DON'T** eat large or spicy meals or high-fat foods.

⃠ **DON'T** eat just before you go to bed or lie down.

⃠ **DON'T** take medicines (even over-the-counter) or try home remedies without asking your doctor.

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- WebMD **Website: http://www.webmd.com**
- U.S. Department of Health and Human Services **Website: http://womenshealth.gov**

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MANAGING YOUR

MORTON'S NEUROMA

What Is Morton's Neuroma?

Morton's neuroma is a thickening of a nerve that runs between the toes. It most often affects the nerve between the bones of the third and fourth toes of the forefoot. It can also affect the nerve between the second and third toes. Usually, only one foot is affected at a time. This common condition occurs more often in women than men.

What Causes Morton's Neuroma?

The cause is compression or irritation of the nerve. Wearing high-heeled shoes or shoes with narrow toes can lead to this condition. Walking or running or jogging too much may also contribute to it. People with certain foot deformities such as hammertoes or flat feet have greater risk of getting Morton's neuroma. The cause can also be unknown.

What Are the Symptoms of Morton's Neuroma?

Symptoms include a painful, numb forefoot, and pain shooting into the toes. Pain may be eased by removing the shoe and rubbing the foot. The affected area may feel tingling and burning. The ball of the foot may be tender. Usually, there's no outward sign of this condition, but sometimes a lump may be felt between the toes. Symptoms may first come and go but then become more persistent and severe.

How Is Morton's Neuroma Diagnosed?

The doctor makes a diagnosis by asking about symptoms and examining the foot. X-rays may be done to rule out other foot problems such as a fracture. The doctor will look for areas of tenderness, swelling, or numbness. The doctor will squeeze the sides of the foot, which may trigger typical pain. The doctor will apply pressure from the top to the bottom of the foot and feel

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for a painful click. This click is called Mulder's sign. Magnetic resonance imaging (MRI) of the foot may be needed for an unclear diagnosis.

How Is Morton's Neuroma Treated?

Treatment depends on how severe symptoms are. Treatment includes shoe modifications: wearing comfortable wide-fitting shoes with a low heel may help symptoms. Nonsteroidal antiinflammatory drugs (NSAIDs) such as ibuprofen, taken by mouth, can reduce pain, as can ice massages. Padding and orthotics may help. Wearing metatarsal pads or arch supports may reduce pressure and relieve pain. The doctor may inject steroids into the affected area. If symptoms don't get better after treatment, surgery may be used to remove or release the affected nerve.

Recovery time depends on how severe symptoms are. Changing shoes and usual activities speeds up recovery. Recovery after surgery may take several weeks. Crutches may be needed for a few days after surgery.

DOs and DON'Ts in Managing Morton's Neuroma:

✓ **DO** wear properly fitting shoes with wide toes and low heels.

✓ **DO** wear padding under the ball of the foot.

✓ **DO** use an icepack on the affected area.

✓ **DO** take your medicines as prescribed by your doctor.

✓ **DO** cut back on vigorous activities until symptoms have improved.

✓ **DO** avoid becoming overweight.

✓ **DO** call your doctor if the problem continues.

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⦸ **DON'T** wear narrow shoes or shoes with heels higher than 0.5 to 1 inch.

⦸ **DON'T** stand for long periods.

⦸ **DON'T** do activities that put repeated pressure on your foot.

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FOR MORE INFORMATION

Contact the following sources:

- The American College of Foot and Ankle Surgeons Tel: (773) 693-9300; (800) 421-2237

  Website: http://www.footphysicians.com

- American Podiatric Medical Association, Inc. Tel: (301) 571-9200; (800) FOOTCARE

  Website: http://www.apma.org

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MANAGING YOUR

MOTION SICKNESS

What Is Motion Sickness?

Motion sickness is a condition in which people become dizzy and feel sick when in a moving vehicle such as a car. This feeling usually goes away with or without treatment in a few hours.

Motion sickness is most common in children 2 to 12 years old, but anyone can have this problem. Pregnant women are also more likely to have motion sickness.

What Causes Motion Sickness?

The cause is inner ear organs, called semicircular canals, that are too sensitive. These canals deep in the ear control balance. This balance center is connected to the nausea and vomiting center in the brain. Repeated motion causes fluid changes in the inner ear that may affect balance and cause feelings of motion and nausea. Motion sickness isn't contagious.

What Are the Symptoms of Motion Sickness?

Symptoms include dizziness, nausea, vomiting, clammy skin, extra saliva, headache, feeling lightheaded, stomach pain, sweating, tiredness, and yawning. These symptoms usually get worse with longer trips. Motion sickness normally goes away after leaving the moving vehicle (car, plane, or boat). Sometimes, people feel better after throwing up.

How Is Motion Sickness Diagnosed?

The doctor makes a diagnosis from symptoms, a medical history, and examination, with special attention to ears and eyes. Other tests such as computed tomography (CT) and magnetic resonance imaging (MRI) of the brain may be needed if the cause of the symptoms is unclear.

How Is Motion Sickness Treated?

Medicine helps prevent motion sickness. A medicine patch (scopolamine patch) may be put be-

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hind the ear. Other things can help: getting plenty of rest before a trip, sitting in the car's front seat and looking out the front window, sitting back and moving as little as possible, sitting in the middle of a boat or plane where there's less movement, getting fresh air from an open window, trying to relax, avoiding reading books or magazines in a moving vehicle, and avoiding spinning amusement park rides.

Prevention is easier than treatment. Some over-the-counter and prescription medicines can prevent motion sickness or help symptoms.

DOs and DON'Ts in Managing Motion Sickness:

✓ **DO** tell your doctor about your medical problems, such as eye, stomach, or breathing problems.

✓ **DO** tell your doctor about your medicines, both prescription and over-the-counter.

✓ **DO** tell your doctor if you're pregnant.

✓ **DO** call your doctor if symptoms persist longer than 24 hours.

✓ **DO** call your doctor if you continue to throw up and become faint or dizzy when you change positions suddenly.

✓ **DO** take medicines prescribed to you by your doctor. Avoid rides that you know will make you sick.

⦸ **DON'T** sit in the back of a car or in a cramped area.

⦸ **DON'T** eat a big, high-fat meal before a trip.

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⦸ **DON'T** smoke or drink alcohol before or during a trip.

⦸ **DON'T** read or write during a trip.

⦸ **DON'T** drive if you take medicine for motion sickness, since these medicines can make you very drowsy.

⦸ **DON'T** sit in an area with odors of food or fuel.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- MedlinePlus **Website:** **http://www.nlm.nih.gov/medlineplus/ motionsickness.html**
- Vestibular Disorders Association Tel: (800) 837-8428 **Website:** **http://www.vestibular.org**

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MANAGING YOUR

MOUTH AND TOOTH CARE

Cleaning the Teeth and Gums

Good oral health involves knowing how to brush and floss correctly. Use a soft-bristled brush and fluoride toothpaste to remove plaque. Bacteria on teeth form the sticky, colorless film called plaque. Brush the tongue and along the gum line. Flossing removes plaque and leftover food that a toothbrush cannot reach. If brushing or flossing causes bleeding gums, pain, or irritation, see the dentist. Also, using an antibacterial mouth rinse helps control plaque and swollen gums. People with arthritis or other conditions who have trouble holding a toothbrush can use special devices or an electric toothbrush to help.

Tooth Decay (Cavities)

Bacteria that normally live in the mouth cause tooth decay and gum disease. Fluoride is important to prevent tooth decay for all people. Fluoride is in the water supply, toothpastes, and mouth rinses. The dentist or dental hygienist may give fluoride treatments in the office.

Gum (Periodontal) Disease

People often lose teeth after age 35 because of gum (periodontal) disease. Gums become inflamed (swollen, red) and bleed easily. Untreated gum disease gets worse and causes receding gums and bone loss. Teeth may become loose and fall out. Prevent gum disease by removing plaque by brushing and flossing daily. See the dentist every 6 to 12 months, or right away if these signs are present.

Dry Mouth (Xerostomia)

Dry mouth, common in many adults, may make it hard to eat, swallow, taste, and speak. Dry mouth occurs when salivary glands don’t work because of diseases, medical treatments (chemo-

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therapy, radiation), or medicines (for high blood pressure, depression, allergies). For dryness, drink extra water and avoid sugary snacks, caffeinated beverages, tobacco, and alcohol. Before starting cancer treatment, which can cause oral problems, see a dentist.

Oral Cancer (Mouth Cancer)

This cancer most often occurs in people older than 40. It often goes unnoticed in early, curable stages, partly because pain isn't usually an early symptom. People who use tobacco products or drink too much alcohol have increased risk for oral cancer. Red or white patches on the gums or tongue, sores that don't heal within 2 weeks, and trouble chewing or swallowing are signals to see a dentist.

Dentures

Keep false teeth (dentures) clean and free from food that can cause stains, bad breath, and gum irritation. Put dentures in water or a denture-cleansing liquid during sleep. Rinse the mouth with warm salt water in the morning, after meals, and at bedtime. When learning to eat with false teeth, choose soft nonsticky food, cut into small pieces, and chew slowly on both sides of the mouth. Don't fix dentures at home. The dentist should do this.

Dental Implants

Dental implants hold replacement teeth. The most popular types are metal screws surgically put into jawbones.

Professional Care

Everyone should use good oral hygiene and have regular checkups by the dentist. Get any special treatments to have good oral health. For example, if teeth are sensitive because of receding gums, the dentist may suggest using a special toothpaste for a few months. Taking good care of the teeth and gums can protect them for many years.

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FOR MORE INFORMATION

Contact the following sources:

• National Institute of Dental and Craniofacial Research Tel: (301) 402-7364 **Website:**

http://www.nidcr.nih.gov/OralHealth/

• American Dental Association Tel: (312) 440-2500 **Website: http://www.ada.org**

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MANAGING YOUR

MOUTH CANCER

What Is Mouth Cancer?

Mouth cancer is a malignant tumor growing inside the mouth. It usually grows on the tongue or floor of the mouth but may grow on the gums, lips, jaw, and roof of the mouth. Most often, this cancer occurs in older men who used tobacco and drank alcohol in excess.

When found early, mouth cancer is highly curable with surgery or radiation therapy. Treatment is much less effective if smoking and drinking alcohol continue.

What Causes Mouth Cancer?

Chances of getting mouth cancer are greater with use of any kind of tobacco—cigarettes, cigars, pipe tobacco, and chewing tobacco. Using alcohol with tobacco greatly increases chances of getting it. Other causes include anything that irritates the inside of the mouth, poor oral care, poorly fitting dentures, and sun exposure (lip cancer).

What Are the Symptoms of Mouth Cancer?

The first sign is usually a small sore in the mouth or on the lip. It may be a small red or white bump or patch or an open sore (or ulcer) that doesn't heal.

Symptoms include tongue pain, feeling that something is caught in the throat, trouble swallowing, swollen jaw, and voice changes.

How Is Mouth Cancer Diagnosed?

The doctor will examine your mouth. A small long-handled mirror to see the back of the tongue may be used. A small piece of tissue will be removed (biopsy) and sent to the laboratory for study. The doctor may also do a chest x-ray.

If the biopsy shows mouth cancer, other tests may include computed tomography (CT) and

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magnetic resonance imaging (MRI), to see the size of the cancer and how far it spread, which is called staging.

How Is Mouth Cancer Treated?

Treatment can involve surgery, radiotherapy, a combination of surgery and radiotherapy, and anticancer drugs (chemotherapy).

Surgery will depend on where the cancer is, its size, and how far it has spread. For very large tumors, the surgeon may remove part of the jaw bone. Mouth surgery may cause swelling that makes it hard to cough, spit, eat, and even breathe. Sometimes a temporary opening is made through the skin in the low part of the neck into the windpipe. This opening, a tracheostomy, makes it easier to breathe and cough and clear fluid from the lungs.

DOs and DON'Ts in Managing Mouth Cancer:

✓ **DO** follow all directions from your doctor.

✓ **DO** call your doctor if you have breathing problems, bleeding, or infection.

✓ **DO** avoid tobacco products and heavy alcohol drinking to prevent mouth cancer.

✓ **DO** have poorly fitting dentures repaired so that they don't irritate the inside of your mouth.

✓ **DO** see your doctor if you have a new sore in your mouth or on your lip that doesn't heal.

Mouth cancer is highly curable when it's very small and is found early.

⦸ **DON'T** use tobacco or drink alcohol.

⦸ **DON'T** drive a car after surgery until your doctor says you can.

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FOR MORE INFORMATION

Contact the following sources:

- National Cancer Institute Tel: (800) 422-6237 **Website: http://www.cancer.gov**
- American Academy of Otolaryngology—Head and Neck Surgery Tel: (703) 836-4444

  Website: http://www.entnet.org
- American Cancer Society Tel: (800) ACS-2345 (227-2345) **Website:**

  http://www.cancer.org

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MANAGING YOUR

MULTIPLE MYELOMA

What Is Multiple Myeloma?

Multiple myeloma is cancer of the plasma cells, which are special types of white blood cells (B lymphocytes). Lymphocytes are produced in bone marrow (the soft substance in the middle of bones). Plasma cells are involved in the immune system. They make antibodies that attack foreign substances (antigens such as viruses and bacteria) in the body. When plasma cells become abnormal and malignant, they multiply rapidly, interfere with normal blood cells, and make abnormal antibodies that can't fight disease. Overgrowth of these malignant cells can weaken bones and cause pain and fractures.

This disorder is uncommon, but more than 14,000 new cases are diagnosed yearly in the United States. Most cases occur after age 60.

What Causes Multiple Myeloma?

The cause is unknown. The disease isn't contagious.

What Are the Symptoms of Multiple Myeloma?

Bone pain is the most common symptom, with the back and ribs most often affected. Pain is worse with movement. Low blood count (anemia) and infections are common.

Myeloma cells destroy the bone and release calcium into blood, which leads to complications such as nerve compression, lower leg weakness, and kidney failure. High blood calcium levels can cause increased urination, weakness, and confusion.

How Is Multiple Myeloma Diagnosed?

The doctor will do a complete physical examination and order blood and urine tests, x-rays, and bone marrow biopsy for diagnosis. In a biopsy, marrow is removed from the bone and

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checked with a microscope. An abnormal protein in the blood, x-rays results, and abnormal plasma cells in the biopsy confirm the diagnosis.

How Is Multiple Myeloma Treated?

Staging of the cancer is done to give a prognosis. Staging involves finding out the extent of disease. Many people with very early stage disease live longer than 5 years, but people with advanced disease have a much shorter life expectancy.

An oncologist (doctor specializing in cancer) will be involved in treatment, which depends on the stage of disease. Stem cell transplantation, chemotherapy, biologic therapy, blood transfusions, radiation therapy, and surgery are used.

Radiation therapy is used for bone pain and medical emergencies (spinal cord compression).

Operations are needed for bone fractures. Supportive treatments, such as antibiotics (for infections), medications to lower the calcium level, and narcotic pain medicines, help well-being.

DOs and DON'Ts in Managing Multiple Myeloma:

✓ **DO** drink lots of fluids (for elevated calcium blood levels) and prevention of dehydration.

✓ **DO** take your medicines as prescribed.

✓ **DO** ask your doctor about counseling and support groups.

✓ **DO** call your doctor if you have fevers, back pain, leg numbness or weakness, and problems with bowel movements or urination. These can be caused by spinal cord compression.

✓ **DO** call your doctor if you see blood in stools, urine, phlegm, or vomit.

✓ **DO** call your doctor if you feel depressed.

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⦸ **DON'T** be sedentary. This can lead to higher calcium levels.

⦸ **DON'T** lift heavy items. It can increase the risk of bone fractures.

⦸ **DON'T** suffer. Ask for pain medicines if you are in pain.

⦸ **DON'T** miss follow-up appointments. Your doctor needs to repeat blood tests, x-rays, and urine collections to check responses to treatment or decide to start treatment.

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FOR MORE INFORMATION

Contact the following sources:

- International Myeloma Foundation Tel: (800) 452-2873 **Website:** **http://www.myeloma.org**
- National Cancer Institute Tel: (800) 422-6237 **Website:** **http://www.cancer.gov**
- American Cancer Society Tel: (800) 227-2345 **Website:** **http://www.cancer.org**

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MANAGING YOUR

MULTIPLE SCLEROSIS

What Is Multiple Sclerosis?

Multiple sclerosis (MS) is a progressive, lifelong illness that affects nerve cells in the brain and spinal cord. Normally, myelin protects nerve cells. Myelin is a fatty substance that acts like electrical wire insulation. Myelin helps signals move along nerves. In MS, myelin becomes damaged or inflamed, interrupts nerve signals, and causes symptoms. People can have only one mild symptom, very few symptoms, or many symptoms with severe disability.

MS is more common in women than men and in temperate climates more than the tropics.

What Causes MS?

The cause is unknown, but MS is thought to be an autoimmune illness. That is, the body's own immune system attacks itself. In MS, it attacks the myelin covering.

What Are the Symptoms of MS?

Symptoms improve (during remissions) and then can worsen. Symptoms depend on whether the brain or spinal cord is affected and which areas are involved. Symptoms of brain involvement may include sudden vision loss or blurry vision, clumsiness, slurred speech, tiredness, muscle weakness, and trouble walking. Loss of bladder control and numbness, tingling, weakness, or heavy feelings in arms or legs mean spinal cord involvement.

How Is MS Diagnosed?

The doctor may think of MS because of age, symptoms, and physical and neurological examinations. No specific test proves the diagnosis. The doctor will suggest seeing a neurologist (specialist in nervous system diseases). Magnetic resonance imaging (MRI), spinal tap, and visual-evoked response may be done. MRI shows areas where myelin is inflamed or destroyed. In a

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spinal tap, the doctor takes a sample of fluid from the spinal cord for study.

How Is MS Treated?

MS cannot be cured, but many treatments are available to control the symptoms and slow the progression of the disease. Both the disease and complications (e.g., spastic movements, fatigue, pain, thinking problems, and bladder and bowel problems) are treated.

Corticosteroid drugs are the main treatment to control symptoms. Medicines such as interferon beta-1a and -1b and glatiramer slow MS progress and reduce the number of relapses.

Medicines used for complications include amantadine, baclofen, gabapentin, oxybutynin, propantheline, stool softeners, psyllium, fiber, nonsteroidal antiinflammatory drugs (NSAIDs), and acetaminophen.

Maintaining a healthy lifestyle, getting enough rest and exercise, and keeping to a normal weight are important.

DOs and DON'Ts in Managing MS:

✓ **DO** start physical therapy. It may improve or maintain mobility. Exercises can give you more energy and keep your body fit. Do regular exercises approved by your doctor.

✓ **DO** get counseling. It may help you and your family adjust to MS. Contact support groups.

✓ **DO** call your doctor if you have facial weakness, weakness of a limb, partial blindness, or eye pain.

✓ **DO** use medicines to help prevent or reduce the number of relapses.

✓ **DO** get enough rest and eat a healthy diet for better overall health.

⃠ **DON'T** ignore worsening symptoms, especially visual changes. These can sometimes be

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stopped if medicine is started promptly.

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FOR MORE INFORMATION

Contact the following sources:

- National Multiple Sclerosis Society Tel: (800) 344-4867 **Website:**

  http://www.nationalmssociety.org

- Multiple Sclerosis Association of America Tel: (800) 833-4672 **Website:**

  http://www.msassociation.org

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MANAGING YOUR

MUMPS

What Is Mumps?

Mumps is a contagious viral infection that causes painful swelling of salivary glands. These glands, on both sides of the jaw, make saliva. Mumps is most often seen in children between 10 and 15 years old.

Before the mumps vaccine was developed, mumps was a common childhood illness. It's now much less common.

Complications can happen, usually in adults. Hearing can be lost temporarily. Organs can become swollen and irritated. These organs include testicles in boys who have gone through puberty and men (sometimes with infertility), ovaries or breasts in women and girls who have gone through puberty, pancreas, lining of the brain, heart, and joints.

What Causes Mumps?

A virus causes mumps. It spreads easily from person to person by airborne droplets or direct contact. It takes 14 to 18 days to come down with mumps. People with mumps are contagious 48 hours before and up to 6 days after swelling begins.

What Are the Symptoms of Mumps?

Earliest symptoms before the swelling are feeling sick, no appetite, and often a headache. Then, symptoms include pain and swelling on one or both sides of the neck, in front of the ears at the corner of the jaw; trouble swallowing or talking; fever; and rash. Fever is better in 3 or 4 days, and swelling and pain get better in about a week. About half the people don't have symptoms.

How Is Mumps Diagnosed?

The doctor will make a diagnosis from the medical history and physical examination. Tests may

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also done on a throat swab and blood samples.

How Is Mumps Treated?

Recovery usually takes 10 days and gives lifetime immunity to mumps. Acetaminophen or ibuprofen can help reduce fever and pain. Cool compresses to the jaw can also ease pain. Tepid sponge baths can bring high temperature down. Drink more fluids, but not acidic or sour liquids. Avoid spicy foods and foods that make more saliva or need a lot of chewing. Rest until fever disappears and strength returns. Children shouldn't go to school until they're no longer contagious (8 to 9 days after swelling resolves).

DOs and DON'Ts in Managing Mumps:

✓ **DO** drink plenty of fluids (not sour or acidic).

✓ **DO** stay home to avoid exposing other people. Rest while you have fever and until strength returns.

✓ **DO** use an ice pack near the testicles to help pain if the testicles are affected. Wear an athletic supporter.

✓ **DO** use cool compresses on the jaw for discomfort.

✓ **DO** eat a soft diet without spicy irritating foods that may make more saliva or need a lot of chewing.

✓ **DO** call your doctor if you have vomiting, diarrhea, temperature more than 101° F, or severe headache that acetaminophen doesn't help.

✓ **DO** call your doctor if pain or swelling develops in your testicles.

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✓ **DO** call your doctor if symptoms aren't better in about 7 days.

⊘ **DON'T** give aspirin to children younger than 16 because of the risk of Reye's syndrome, a dangerous illness.

⊘ **DON'T** send children to school until they're no longer contagious.

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FOR MORE INFORMATION

Contact the following sources:

- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website:** **http://www.cdc.gov**
- American Academy of Pediatrics Tel: (847) 434-4000 **Website:** **http://www.aap.org**

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MANAGING YOUR

MUSCULAR DYSTROPHY

What Is Muscular Dystrophy?

Muscular dystrophy (MD) is a group of more than 30 inherited muscle diseases. Muscles, mostly voluntary muscles, slowly become weaker. People have trouble walking or sitting up. The more severe forms tend to start in early childhood. Others start in adults. The most common type, Duchenne muscular dystrophy (DMD), the similar Becker muscular dystrophy (BMD), and Emery-Dreifuss MD (EDMD) mainly affect boys. Limb-girdle muscular dystrophies (LGMDs), facioscapulohumeral muscular dystrophy (FSHD), and congenital muscular dystrophy (CMD) affect boys and girls. Myotonic dystrophies (MMDs) are the most common adult forms. Some kinds of MD affect heart muscles, other involuntary muscles, and other organs. These disorders aren't contagious.

What Causes MD?

Incorrect or missing information in genes prevents people from making proteins (usually the protein named dystrophin). These proteins are needed for healthy muscles. The pattern of inheritance varies with the type of MD. DMD, BMD, and EDMD are sex-linked (mothers carry the gene and pass it to male children). FSHD, distal, ocular, and oculopharyngeal are autosomal dominantly inherited. LGMD is autosomal recessive.

What Are the Signs and Symptoms of MD?

Symptoms can start in babies, teenagers, or adults. They depend on the type of MD. All muscles or only certain groups of muscles, such as those around the pelvis, shoulder (LGMD), or face, may be affected. Symptoms include muscle weakness that slowly gets worse, trouble walking, and falling. Heart (cardiomyopathy), breathing, and swallowing problems occur. Mental retarda-

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tion occurs in some types of MD. Other symptoms may include drooling, eyelid drooping, loss of mobility, large calf muscles, fainting or dizziness, curved spine (scoliosis), and sleeping problems.

How Is MD Diagnosed?

The doctor does a physical examination and takes a medical history. The doctor also orders electromyography (EMG), ultrasonography, and electrocardiography (ECG). EMG helps measure how well nerves and muscles work. Other studies include genetic testing and blood tests for enzymes such as creatine kinase (CK). A muscle biopsy may be done. In a biopsy, a small piece of muscle is removed and sent to a laboratory for study.

How Is MD Treated?

Because no cure is available, treatment aims to control symptoms and keep people mobile as long as possible. Drugs, assistive devices, surgery, and physical, respiratory, and occupational therapy are used.

Drugs may slow muscle degeneration, control seizures, and fight infections. Physical therapy uses range-of-motion exercises to keep joints flexible, delay stiff muscles near joints (contractures), and reduce or delay spine curvature. Using hot baths (hydrotherapy) also can help joint range of motion. Braces, canes, walkers, and wheelchairs can help mobility and independence. A ventilator may be used for weak breathing muscles. Surgery can release tendons, which helps contractures, and correct scoliosis.

DOs and DON'Ts in Managing MD:

✓ **DO** become as active as possible. Complete inactivity (such as bed rest) can make the disease worse.

✓ **DO** join a self-help group for support.

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✓ **DO** get genetic counseling when there's a family history of MD. Get an accurate diagnosis. It's important for prognosis and counseling.

✓ **DO** learn as much as you can about MD and what to do about it.

⃠ **DON'T** lose hope. The prognosis varies. Some cases may be mild and progress very slowly over a normal life span.

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FOR MORE INFORMATION

Contact the following sources:

- Muscular Dystrophy Association (MDA) Tel: (800) 572-1717 **Website:** **http://www.mda.org**
- American Academy of Family Physicians Tel: (800) 274-2237**Website:** **http://www.aafp.org**

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MANAGING YOUR

MUSHROOM POISONING

What Is Mushroom Poisoning?

Mushrooms are the fruit of fungi. More than 10,000 different species are known. Poisonous mushrooms fall into eight groups. Almost 95% of all deaths caused by mushroom poisoning are due to substances called amatoxins. These toxins are poisons from mushrooms named *Amanita*, *Galerina*, and *Lepiota*. Most poisoning occurs from late July to early September. In the United States, more than 10,000 cases are reported each year. Of these, almost two thirds are in children.

What Causes Mushroom Poisoning?

Species of mushrooms that cause most deaths are *Amanita phalloides* (death cap) and *Amanita virosa* (destroying angel). They make toxins that affect the liver.

What Are the Symptoms of Mushroom Poisoning?

Nausea, vomiting, cramping pain in the abdomen (belly), and severe diarrhea usually start 6 to 12 hours after eating the mushrooms. Dehydration and a shock-like condition can result. Intestinal symptoms can last up to 24 hours. On days 1 to 3, abnormal blood tests suggest liver damage with signs of liver failure, such as jaundice (yellow skin), lethargy, seizures, coma, and pain over the liver. Kidney failure with less urine output also occurs.

How Is Mushroom Poisoning Diagnosed?

The doctor makes a diagnosis by a history of eating mushrooms, symptoms, and abnormal liver and kidney blood tests. It helps to identify the mushroom by checking the cap, stem, undersurface of the cap, base, and spores. Special tests can help identify *Amanita* species.

How Is Mushroom Poisoning Treated?

Treatment is similar to that for any poisoning. First treatment is supportive. Control the ABCs:

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Airway, Breathing, and Circulation. Hydration with intravenous fluids is critical to maintain blood pressure. Oxygen therapy and, in severe cases a breathing machine (mechanical ventilator) can be used. The stomach and intestines will also need to be decontaminated. Decontamination means that absorption of the toxin is prevented by putting a tube into the nose and down into the stomach to wash out the stomach. Activated charcoal can also prevent absorption of the toxins. The bowel (intestine) can be cleaned with bowel preparations that cause diarrhea.

Antidotes and increasing hydration to have more urine output can all help remove the toxin. Even with treatment, some people have liver failure and may need liver transplantation.

DOs and DON'Ts in Managing Mushroom Poisoning:

✓ **DO** realize that identification of the thousands of species of mushrooms can be hard. Telling the difference between a poisonous mushroom and one you can eat is even more difficult. Use only mushrooms that you buy at reputable markets.

✓ **DO** go to the closest emergency room if you think you have eaten a poisonous mushroom.

✓ **DO** call your doctor if you have abdominal pain with severe diarrhea.

✓ **DO** call your doctor if you get jaundice.

⦸ **DON'T** trust amateur mushroom pickers, a leading cause of accidental mushroom poisoning in children and adults.

⦸ **DON'T** believe that boiling, salting, or drying mushrooms can purify them.

⦸ **DON'T** drink alcohol. Some edible mushrooms can cause an abnormal reaction when eaten with alcohol.

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FOR MORE INFORMATION

Contact the following source:

- American College of Emergency Physicians Tel: (800) 798-1822 **Website: http://www.acep.org**

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MANAGING YOUR

MYASTHENIA GRAVIS

What Is Myasthenia Gravis (MG)?

Myasthenia gravis (MG) is an illness that causes muscles in the eyes, face, throat, arms, and legs to get weak and tired. Muscles that control breathing may also be affected. The worst weakness usually occurs during the first 3 years.

MG affects people of both sexes, all ages, and all ethnic groups. Women usually get MG in the late teens and 20s, and men usually get it after age 60. Progression of MG is extremely slow and most people lead full lives.

What Causes MG?

MG is an autoimmune disease. This means that the body's immune system attacks itself. MG isn't contagious or passed from parents to children. MG is more common in people with tumors of the thymus gland called thymoma. The thymus gland is located in the chest and is part of the immune system.

What Are the Symptoms of MG?

Symptoms may get better (remission) and then worsen (exacerbation). The time between remission and exacerbation varies. The major symptom is muscle weakness that gets worse when people are more active. Temperature, menstrual periods, illness, and stress can affect the weakness. Other symptoms are eye problems (double vision, droopy eyelids); problems chewing, speaking, or swallowing; drooling; and arm and leg weakness. One symptom, shortness of breath, can be very frightening.

How Is MG Diagnosed?

The doctor will make a diagnosis from a complete physical examination, with tests of lungs, re-

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flexes, and muscle weakness. A specialist may do more tests, including electromyography, Tensilon® test, blood test, and computed tomography (CT). Electromyography measures muscle electrical activity as they contract after nerve stimulation. In the Tensilon® test, medicine temporarily improves muscle strength in people with MG. CT will check for a tumor or enlargement of the thymus gland.

How Is MG Treated?

The treatment depends on how severe symptoms are, age, sex, and physical activity level. Medicines such as steroids and anticholinesterase drugs can help symptoms. Lifestyle changes such as eating a good diet and getting enough rest can also help. Rest briefly during the day (about 10 to 15 minutes), and avoid strenuous work that may make fatigue worse. Try to exercise daily, as advised by the doctor and physical therapist. For double or blurred vision, see an eye doctor, and don't drive or use heavy equipment. If swallowing is a problem, try foods of different consistency to find out which is best. Often thin liquids such as juice and water are harder to swallow than thick ones. Manage stress better. Regular exercise may help with stress management. Avoid smoke and dust.

DOs and DON'Ts in Managing MG:

✓ **DO** try to find a balance between rest and physical activity to prevent muscle weakness.

✓ **DO** get physical therapy to keep muscles strong.

✓ **DO** wear a medical alert bracelet or necklace that says you have myasthenia gravis.

✓ **DO** take medicines as prescribed. Call your doctor if you have problems with your medicines.

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✓ **DO** call your doctor if you have shortness of breath or your symptoms worsen to include double vision, blurred vision, or weakness.

⃠ **DON'T** gain weight and become inactive.

⃠ **DON'T** use tobacco. It may worsen shortness of breath.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- Myasthenia Gravis Foundation of America Tel: (651)917-6256, (800)541-5454 **Website:** **http://www.myasthenia.org**
- American Academy of Neurology **Website:** **http://www.neurology.org**

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MANAGING YOUR

MYCOPLASMA PNEUMONIA

What Is Mycoplasma Pneumonia?

Pneumonia is an infection of the lungs. People of all ages can get this kind of pneumonia, but it usually affects people younger than 40, most often those who are 5 to 20 years old. Some people may not be sick enough to stay in bed or go to the doctor, and they may never even know that they had pneumonia. It's often called "walking pneumonia". These infections occur throughout the year but are seen slightly more often during winter.

What Causes Mycoplasma Pneumonia?

Infection occurs after breathing in airborne droplets that someone who is infected coughs into the air. These droplets are contaminated with the kind of bacteria named *Mycoplasma pneumoniae*, the cause of this pneumonia. *Mycoplasma* infections often spread quickly when people live or work in close quarters, such as within families or schools.

What Are the Symptoms of Mycoplasma Pneumonia?

Symptoms are mild and usually start 2 to 3 weeks after exposure to the bacteria. A dry, persistent cough is the most common symptom. Fever, headaches, chills, sweating, chest pain, and sore throat also occur. Exposure to *Mycoplasma* may also cause ear and throat infections.

How Is Mycoplasma Pneumonia Diagnosed?

The doctor will make a diagnosis from the medical history and physical examination. The doctor will order tests to find out how severe the pneumonia is. These tests include chest x-rays and possibly blood and sputum tests. People who are in the emergency department of a hospital will have their blood oxygen level measured.

How Is Mycoplasma Pneumonia Treated?

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Oral antibiotics are given, usually for 5 to 14 days, to treat the infection. Improvement usually begins within 1 or 2 days of starting antibiotics, but the cough may last for weeks. Nasal sprays and oral decongestants are often used for nasal symptoms. Rest, a well-balanced diet, and drinking enough fluids are important for recovery.

DOs and DON'Ts in Managing

Mycoplasma Pneumonia:

✓ **DO** take your antibiotic medicine exactly as the doctor prescribed. Take the pills as scheduled until they are all gone.

✓ **DO** use acetaminophen or aspirin (except in children) for relief of fever and pain.

✓ **DO** drink plenty of fluids to avoid dehydration.

✓ **DO** breathe moist air (use a humidifier) to help get rid of phlegm.

✓ **DO** call your doctor if you suspect *Mycoplasma* pneumonia because of a sense of being sick, fever, shortness of breath, or phlegm.

✓ **DO** call your doctor if your symptoms fail to go away or they get worse after 48 hours of antibiotic therapy.

✓ **DO** call your doctor if nausea prevents you from taking your prescribed antibiotics.

✓ **DO** call your doctor if you see blood in your sputum.

⊘ **DON'T** spend time with people who have chronic medical conditions if you are sick. They can become very sick if they get *Mycoplasma* pneumonia.

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FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following source:

- American Lung Association Tel: (800) LUNG-USA (586-4872) **Website:**

  http://www.lungusa.org

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MANAGING YOUR

MYELODYSPLASTIC SYNDROME

What Is Myelodysplastic Syndrome?

Myelodysplastic syndrome (MDS) refers to uncommon conditions with abnormal bone marrow cells. It is often a precursor to acute leukemia. Bone marrow is the spongy material inside bones where blood cells are made. In myelodysplastic syndrome, these blood cells are poorly formed or don't work normally. The five subtypes of MDS include types I and II, with anemia that's hard to manage (refractory anemia). The other three types have too many blasts (immature blood cells in bone marrow). The higher the percentage of blasts, the faster leukemia can develop. With time, about 30% of people get acute leukemia. MDS occurs most often in people older than 60, more men than women.

What Causes Myelodysplastic Syndrome?

In most cases, the cause is unknown. Chemotherapy and radiation therapy can lead to increased risks of getting MDS. In some cases, it can run in families.

What Are the Symptoms of Myelodysplastic Syndrome?

About half of people have no symptoms. The most frequent one is fatigue due to anemia (low red blood cell count and hemoglobin). Two-thirds of people also have a low white blood cell count or platelet count. Easy or unusual bruising or bleeding and pinpoint-sized red spots just under the skin, caused by bleeding (petechiae), can occur. Other symptoms seen with severe anemia include pallor, and shortness of breath with exertion. Low platelet counts can lead to bleeding. The main risk of low white blood cell counts is serious infections.

How Is Myelodysplastic Syndrome Diagnosed?

The doctor may suspect MDS from the medical history, physical examination, and blood tests. The doctor will review a blood smear and do a biopsy and examine the bone marrow. In a

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biopsy, the doctor removes a small sample of marrow from a bone and checks it with a microscope. Special genetic analysis of bone marrow cells helps diagnose those who have a poor prognosis.

How Is Myelodysplastic Syndrome Treated?

Bone marrow transplantation can cure some younger people (age 60 and younger) with a good prognosis. Combinations of chemotherapy and medicines (including growth factors) can cause remissions and help symptoms in others who are not candidates for bone marrow transplantation.

Supportive care is best for most people. This involves regular transfusions and antibiotics for infections. Transfusions with red blood cell and platelet concentrates support people with low blood cell counts. Chemotherapy can lead to remissions, but remissions are temporary. Using erythropoietin can reduce the number of transfusions needed.

DOs and DON'Ts in Managing Myelodysplastic Syndrome:

✓ **DO** consider transplantation of bone marrow, from a close relative or suitable unrelated donor.

✓ **DO** get hepatitis vaccinations if you're undergoing transfusions, and after transplantation.

✓ **DO** use medical alert identification.

✓ **DO** avoid large crowds and people who have signs of infections if you have a low white blood cell count.

✓ **DO** call your doctor if you have fever, bleeding, chest pain, or dizziness.

⃠ **DON'T** use aspirin and aspirin-like medicines. They can make bleeding worse. Some other medicines can lower blood counts. Check with your doctor.

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⦸ **DON'T** eat fresh vegetables and fruit, cheese, and yogurt if you have a low white blood cell count.

⦸ **DON'T** do moderate and strenuous exercise if you have severe anemia.

⦸ **DON'T** do activities that may involve trauma (such as football) if you have a low platelet count.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Cancer Society Tel: (800) 227-2345 **Website: http://www.cancer.org**
- National Cancer Institute Tel: (800) 422-6237 **Website: http://www.cancer.gov**

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MANAGING YOUR

MYOCARDITIS

What Is Myocarditis?

Myocarditis is inflammation of heart muscle.

What Causes Myocarditis?

The many causes of the inflammatory response include injury, infections, radiation, and medicines. Most often, it is a virus, that causes myocarditis. Myocarditis is not contagious or hereditary.

What Are the Symptoms of Myocarditis?

Some people do not have any symptoms.

People who have early symptoms note chest pain, skipped heartbeats (palpitations), trouble breathing, fever or chills, inability to exercise, or feeling tired and run down much of the time. Irritation of the heart muscle may lead to abnormal heart rhythms (arrhythmias) and heart failure (when the heart doesn't pump blood well).

How Is Myocarditis Diagnosed?

Myocarditis is hard to diagnose because of the many causes and frequent lack of specific symptoms. The doctor diagnoses myocarditis by doing a physical examination, electrocardiography (ECG), and laboratory tests to look for damage to heart muscle. A biopsy of the heart muscle may also be done to confirm the diagnosis and help find the cause.

How Is Myocarditis Treated?

Treatment of chest pain and arrhythmias is most important. Heart failure must also be treated.

The doctor may prescribe nonsteroidal antiinflammatory drugs (NSAIDs) for inflammation and chest pain.

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For more severe disease, steroid-containing medicines or immunosuppressive drugs may be used.

Medications may be given to control irregular heartbeat and improve heart function.

DOs and DON'Ts in Managing Myocarditis:

✓ **DO** take your medicines as prescribed for your symptoms.

✓ **DO** rest.

✓ **DO** call your doctor if you cannot tolerate your medicines or have a reaction to them.

✓ **DO** call your doctor if you have new or worsening chest pain, palpitations, shortness of breath, or fainting.

✓ **DO** call your doctor if you notice blood in your vomit or stools.

⃠ **DON'T** exercise until your doctor says that you can. Avoid strenuous exercise. Exercise increases the work of the heart, which may cause rapidly worsening inflammation and dangerous heart rhythm problems.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following source:

- American Heart Association Tel: (800) 242-8721 **Website:** **http://www.americanheart.org**

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MANAGING YOUR

NAIL FUNGUS

What Is Nail Fungus?

Nail fungus, or onychomycosis, is an infection of nails with fungal organisms. More toenails than fingernails are affected. It's more common in elderly people with poor circulation and diabetics. People often have a fungal foot infection (athlete's foot), along with toenail fungus.

What Causes Nail Fungus?

The most frequent causes are fungi called dermatophytes. People often pick up and spread the infection at public swimming pools and locker rooms, where they walk around barefoot. Conditions there are warm and damp, which are best for fungi to grow.

Fungal infections can also spread in families by sharing towels and footwear. Damage to nails can make it easier to get infected.

What Are the Symptoms of Nail Fungus?

Symptoms include change in nail color to yellow, brown, or white; thicker nails with shape changes; brittle and flaky nails, with splits and chips; accumulation of fungus and dirt under nails, leading to a bad smell; separation of nails from toes or fingers; and, rarely, pain.

How Is Nail Fungus Diagnosed?

The doctor makes a diagnosis from an examination of the nails. A scraping of the nail or nail clippings may be taken and sent to a laboratory for study.

How Is Nail Fungus Treated?

Early treatment is best, but getting rid of the fungus may be hard. Untreated, nails may have permanent damage and deformity, leading to problems wearing shoes or walking.

Oral antifungal drugs, such as terbinafine, taken for 3 months for toenail fungus and 6 weeks

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for fingernail fungus are the usual treatment. Some people cannot take these drugs because of their other drugs or medical problems.

Antifungal drugs can also be put directly on infected nails (topical treatment) for up to 12 months. These topical drugs don't usually work very well.

Other treatments, not usually done, include removing the infected nail and scraping the nail to make it less thick. Usually, a foot doctor (podiatrist) does these. Newer treatment options include laser therapy. This can be very effective but also expensive, since it's not generally covered by most insurances.

DOs and DON'Ts in Managing Nail Fungus:

✓ **DO** follow directions for using your antifungal medications.

✓ **DO** tell your doctor about your other medical problems and drugs.

✓ **DO** wear shoes that fit well and let air circulate.

✓ **DO** wear clean socks that absorb moisture. Wash used socks, towels, and bathmats at 150˚ F or more.

✓ **DO** go to a podiatrist for nail trimming.

✓ **DO** wash and check your feet daily. Keep your feet dry. Report signs of infection (swelling, drainage) to your doctor.

✓ **DO** call your doctor if your toes or fingers crack around the nails or become red and tender.

✓ **DO** call your doctor if pus drainage, swelling, or redness occurs near nails.

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✓ **DO** call your doctor if nails become painful to touch.

✓ **DO** avoid going barefoot in public places, especially gyms, showers, and locker rooms.

⃠ **DON'T** wear shoes for too long if they make your feet sweat a lot.

⃠ **DON'T** use nail polish all the time. It prevents moisture from escaping from your nails.

⃠ **DON'T** share shoes, towels, or nail-trimming instruments.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following source:

- American Academy of Dermatology Tel: (847) 330-0230, (866) 503-7546 **Website:** **http://www.aad.org**

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MANAGING YOUR

NARCISSISTIC PERSONALITY DISORDER

What Is Narcissistic Personality Disorder?

Personality refers to the special characteristics and behaviors that make up a person's identity. Personality disorders are mental disorders. They lead to many problems in relations with family, friends, and coworkers. In narcissistic personality disorder, people have an inflated feeling of their own importance. They're self-absorbed and need admiration from others but don't have good understanding of others' feelings. Half to three-fourths of people with this disorder are male.

What Causes Narcissistic Personality Disorder?

The cause isn't known. Parental behaviors may be related to the disorder. These behaviors include abuse, neglect, being overindulgent, and giving too much praise. Genetics or psychobiology may also be involved. Psychobiology studies the relation between the brain and behavior and thinking.

What Are the Symptoms of Narcissistic Personality Disorder?

People depend on others to help control their self-esteem. They have an exaggerated sense of their own importance. They believe that they're superior, special, and gifted. However, they need constant praise and admiration from others to feel deserving. They seek constant attention. They have fantasies of great success and are oversensitive to failure. They have extreme mood swings between self-admiration and insecurity. They're often inflexible and don't respond to feelings and needs of others. They also tend to take advantage of personal relationships.

How Is Narcissistic Personality Disorder Diagnosed?

Your doctor may suspect narcissistic personality disorder from your medical history and may

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refer you to a psychiatrist to confirm the diagnosis. This disorder isn't contagious or passed from parents to children.

How Is Narcissistic Personality Disorder Treated?

Individual psychotherapy is the best treatment. Psychiatrists and psychologists use it. Psychiatrists are medical specialists in mental and emotional disorders who prescribe medicines. Psychologists are specialists in diagnosing and treating mental and emotional problems. They use testing, counseling, or psychotherapy but don't prescribe drugs. The goal is to relieve symptoms and change behavior. One method to do this is cognitive behavioral therapy. It helps discover unhealthy, negative beliefs and behaviors and replace them with healthy, positive ones. Group therapy and family therapy can also be tried.

Antidepressants and antianxiety medicines may sometimes be used in people who are also depressed or anxious.

DOs and DON'Ts in Managing Narcissistic Personality Disorder:

- ✓ **DO** realize that this personality disorder can lead to trouble with interpersonal and family relations.
- ✓ **DO** go to the emergency department if you think of hurting yourself or others.
- ✓ **DO** learn as much as you can about this disorder.
- ✓ **DO** try to reduce stress, such as with meditation, yoga, or tai chi.
- ✓ **DO** understand that many people may avoid going to doctors.
- ✓ **DO** call your doctor if you think that a family member may have this disorder.

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✓ **DO** call your doctor if you need a referral to a psychiatrist.

✓ **DO** call your doctor if you feel depressed or are going to hurt yourself or others.

⃠ **DON'T** forget that people with this disorder may also have other psychiatric problems, such as depression, anxiety, or bipolar disease.

⃠ **DON'T** forget that treatment can be hard work and take a long time. Keep focused, take your medicines, and stick to your treatment plan.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- National Mental Health Association Tel: (800) 969-6642 or (703) 684-7722 **Website: http://www.nmha.org**
- Center for Mental Health Services National Mental Health Information Center Tel: (800) 789-2647

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MANAGING YOUR

NARCOLEPSY

What Is Narcolepsy?

Narcolepsy is a rare condition in which people fall asleep anytime or anywhere without control, regardless of the amount of sleep that they had. People may feel rested after sleeping for 10 or 15 minutes during an attack, but then this rested feeling goes away, and they get sleepy again. These attacks can occur, in men and women equally, when driving, working, or talking. Symptoms are first noticed in teenagers and young adults but may be undiagnosed for years. Narcolepsy is a lifelong condition.

What Causes Narcolepsy?

The cause is unknown. Narcolepsy rarely follows brain trauma but it may occur with nervous system diseases. It tends to run in families.

What Are the Symptoms of Narcolepsy?

Symptoms include daytime sleep attacks lasting from a few seconds to 30 minutes and occurring up to 10 times daily, vivid dreams during attacks, and temporary inability to move before or after the attack.

A common symptom of narcolepsy is partial or complete weakness of muscles (cataplexy) that is caused by intense emotions such as excitement or anger. Other symptoms include doing normal activities without being aware of it and waking often or tossing and turning at night.

Poor nighttime sleeping can lead to tiredness during the day, depression, trouble concentrating or memorizing, vision problems, eating binges, and trouble handling alcohol.

How Is Narcolepsy Diagnosed?

The doctor will do an examination and ask about sleep patterns. The doctor may suggest seeing a

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doctor who specializes in sleep disorders. Diagnosis may involve spending a night in a sleep laboratory so equipment can be used to find out about sleep patterns.

How Is Narcolepsy Treated?

No cure is known, and no one therapy will control all symptoms. The doctor will probably prescribe medicines to reduce daytime sleepiness and help get a good night's sleep. Regular naps during the day may also help.

Stimulant medicines combined with 15- to 20-minute naps may improve disabling effects of narcolepsy.

DOs and DON'Ts in Managing Narcolepsy:

✓ **DO** take your medicines as directed.

✓ **DO** take regular naps during the day, if you can.

✓ **DO** go to sleep and wake up according to a regular routine. Try to sleep at least 8 hours a night.

✓ **DO** find a safe, well-lit place to stop and nap if you get sleepy while driving.

✓ **DO** wear a medical alert bracelet that notes your condition.

✓ **DO** educate your friends and family about your disorder.

✓ **DO** call your doctor if you have problems with your medicines or if the number of attacks or their severity increases.

⊘ **DON'T** drive until you control your narcolepsy.

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⦸ **DON'T** drive or commute long distances.

⦸ **DON'T** smoke or drink beverages with caffeine or alcohol in the late afternoon or evening.

⦸ **DON'T** use the bed for nonrelaxing activities.

⦸ **DON'T** climb ladders. Don't do things that may be dangerous should you fall asleep or lose muscle control.

⦸ **DON'T** work around dangerous machinery.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Narcolepsy Foundation Tel: (831) 646-2055 **Website:** **http://www.narcolepsy.com**
- Narcolepsy Network, Inc. Tel: (888) 292-6522, (401) 667-2523 **Website:** **http://www.narcolepsynetwork.org**
- National Sleep Foundation Tel: (202) 347-3471 **Website:** **http://www.sleepfoundation.org**

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MANAGING YOUR

NECK PAIN

What Is Neck Pain?

The neck is made up of the vertebrae (bones), spinal cord (which contains nerves), discs between vertebrae, and tissues such as muscles and ligaments. Vertebrae protect the spinal cord. Discs are like shock absorbers for the head and neck. They cushion the bones and allow the head and neck to bend. Ligaments are fibrous bands of tissue connecting bones (or cartilages) together. Neck pain may be caused by an injury or disease affecting this area.

What Causes Neck Pain?

Being in an uncomfortable position for a long time and poor posture can cause neck pain. It may occur with diseases such as osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and fibromyalgia. It may also result from a neck injury. Stress that causes muscle tension may worsen neck pain.

What Are the Symptoms of Neck Pain?

Symptoms include problems looking from side to side, driving, and reading. Sometimes, pain may prevent sleeping. Neck pain can cause headaches. Neck pain that lasts for months may affect a person's ability to work.

How Is Neck Pain Diagnosed?

The doctor makes a diagnosis from a medical history, physical examination. X-rays may also be done. The doctor may order blood tests to see whether neck pain is due to diseases with similar symptoms.

Magnetic resonance imaging (MRI) may be done if the doctor needs a clearer picture of bones, nerves, discs, and other soft tissues. Sometimes, electromyography (EMG), which helps

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find muscle and nerve problems, may be done if the neck problem may be causing numbness or tingling in the arms because of pressure on nerves.

How Is Neck Pain Treated?

Treatment depends on the cause of the pain. If an injury is the cause, the doctor may suggest using ice on the area. Nonsteroidal antiinflammatory drugs (NSAIDs) may help reduce the pain. For especially severe pain, stronger narcotic medicines may be needed for a short time. Muscle spasms may be helped with a muscle relaxant. Physical therapy may reduce pain with deep heat treatments, traction, and exercise. All medicines have side effects. NSAIDs may cause upset stomach, diarrhea, ulcers, headache, dizziness, trouble hearing, or rash. Some side effects of muscle relaxants are drowsiness, dizziness, and rash.

DOs and DON'Ts in Managing Neck Pain:

✓ **DO** take your medicines as prescribed.

✓ **DO** call your doctor if you have side effects from medicines.

✓ **DO** use good posture when sitting and standing.

✓ **DO** ask your doctor about using a cervical pillow for severe pain.

✓ **DO** neck exercises every day.

✓ **DO** call your doctor if you continue to have neck pain or headaches.

✓ **DO** call your doctor if you have numbness or tingling in your arms.

✓ **DO** call your doctor if you need a referral to a physical therapist.

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⦸ **DON'T** wait to see whether a side effect of medicine goes away on its own.

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FOR MORE INFORMATION

Contact the following sources:

- National Arthritis Foundation Tel: (800) 283-7800 **Website: http://www.arthritis.org**
- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website: http://www.aaos.org**

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MANAGING YOUR

NECK STRAIN

What Are Neck Strains?

The neck is made up of vertebrae (bones), spinal cord (a continuation of the central nervous system from the brain), discs between vertebrae, and tissues such as muscles, tendons, and ligaments. Vertebrae protect the spinal cord. Discs are like shock absorbers and cushion the bone and provide nutrition to the joint. They let the head and neck bend. Neck strains are injuries in which muscles and tendons are stretched or torn. Tendons are tough bands of tissues connecting muscles and bones. Neck strains are common injuries and occur often in sports as well as accidents (whiplash).

What Causes Neck Strains?

Common causes include falls, auto accidents (whiplash), poor sitting posture (such as at a computer), trauma to the head and face, and overuse of neck muscles. Contact in sports such as in football can lead to neck strains or even more serious injuries (fractures). It's critical to use the right tackling and blocking techniques in football, because "spearing," or straightening the spine and using the head as a point of initial contact is associated with a high risk of cervical spine fracture. Fitness, neck muscle strengthening, proper coaching and well-fitting equipment can decrease the risk for neck injury.

What Are the Symptoms of Neck Strains?

Symptoms include dull, aching pain, or cramping in the back or sides of the neck. Pain is often worse with movement, and range of motion is often decreased. The back and shoulders can have muscle spasms and pain. Other symptoms are headaches, stiffness, trouble sleeping, and problems looking side to side or up and down. Nerve and blood vessel injuries and broken bones

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cause different symptoms, which are often more severe and associated with different physical findings.

How Are Neck Strains Diagnosed?

The doctor makes a diagnosis from a medical history, physical examination, and additional imaging tests as indicated. These often include x-rays, though additional studies such as magnetic resonance imaging (MRI), computerized tomography (CT), myelography (spinal cord imaging), and radionuclide scanning may be necessary in some cases.

MRI may be done if the doctor needs a clearer picture of the soft tissue structures of the neck, such as discs, nerves, and surrounding muscles or ligaments. CT scanning is useful if fractures are considered. Electromyography (EMG) may be done if pressure on nerves causes weakness, pain, and/or numbness or tingling in the arms.

How Are Neck Strains Treated?

Treatment depends on the cause. For an injury, the doctor may suggest using ice on the area for 2 to 3 days and then heat (heating pads or warm showers). Nonsteroidal anti-inflammatory drugs (NSAIDs) may help reduce pain. For severe pain unresponsive to anti-inflammatories and acetaminophen, stronger pain medications or muscle relaxants may be useful. Short-term rest, gentle stretching, injections of steroids or lidocaine, and short-term immobilization (with a soft collar) are also used. Physical therapy may reduce pain with deep heat treatments, traction, and exercise. All medicines have side effects. NSAIDs may cause stomach upset, diarrhea, ulcers, headache, dizziness, trouble hearing, or rash. Some side effects of muscle relaxants are drowsiness, dizziness, and rash.

DOs and DON'Ts in Managing Neck Strains:

✓ **DO** take your medicines as prescribed.

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✓ **DO** call your doctor if you have side effects from medicines.

✓ **DO** use the right sports equipment and techniques.

✓ **DO** use good posture when sitting and standing. Take frequent breaks and stretch.

✓ **DO** ask your doctor about using a cervical pillow.

✓ **DO** neck exercises every day.

✓ **DO** call your doctor if you have numbness or tingling in your arms or significant weakness.

⃠ **DON'T** sleep on your stomach.

⃠ **DON'T** wait to see whether a side effect of medicine goes away on its own.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Arthritis Foundation Tel: (800) 283-7800 **Website: http://www.arthritis.org**
- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website: http://www.aaos.org**

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MANAGING YOUR

NEPHROTIC SYNDROME

What Is Nephrotic Syndrome?

Nephrotic syndrome, also called nephrosis, is a condition in which kidneys don't work well. It's most common in children, but adults can also have it.

Each kidney consists of 1 million fine filters to clean the blood of poisons. Healthy kidneys also keep important chemicals called proteins in the blood. The body needs proteins to grow and repair itself. With nephrotic syndrome, kidneys get rid of needed proteins with other wastes that leave the body during urination. This causes swelling, weakness, and other problems throughout the body.

What Causes Nephrotic Syndrome?

Various kidney problems can lead to nephrotic syndrome. The most common are primary inflammatory conditions of kidneys called glomerulonephritis. Others include diabetes. Sometimes, the cause is unknown. The condition isn't contagious.

What Are the Symptoms of Nephrotic Syndrome?

Nephrotic syndrome is usually painless. People gain excessive amounts of water weight, which causes distress and discomfort. Initial symptoms from this gain are puffy eyes and ankles. Skin then becomes puffy. The abdomen (belly) swells. Much less urine is made. Urine can look frothy. Other symptoms include weakness, loss of appetite, and a sense of feeling sick. High cholesterol levels result from kidney damage.

How Is Nephrotic Syndrome Diagnosed?

Most people go to the doctor because of swollen ankles or legs, or even a swollen face. The doctor will find high levels of protein in urine tests. Blood tests will be done to evaluate kidney

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function. A kidney specialist (nephrologist) will be consulted. In some cases, a kidney biopsy may be done to determine the cause of your nephrotic syndrome. In a biopsy, a small piece of tissue is removed from the kidney with a special needle and studied in a laboratory.

How Is Nephrotic Syndrome Treated?

Symptoms usually start to improve in 2 to 3 weeks after starting treatment with diet and medicines. Different medicines may be needed. Immunosuppressive drugs, such as prednisone and cyclophosphamide, may be needed to help kidney inflammation. Diuretics ("water pills" such as furosemide) reduce swelling. Medicine often must be taken for 3 months or more.

Because people with nephrotic syndrome tend to develop blood clots in the legs, keeping active is important. Anticoagulant medicines help prevent blood clots.

Other drugs such as angiotensin-converting enzyme (ACE) inhibitors lower protein loss and blood pressure. Cholesterol-lowering drugs such as statins are often used to lower very high cholesterol levels that occur with nephrotic syndrome.

DOs and DON'Ts in Managing

Nephrotic Syndrome:

✓ **DO** eat a low-fat, low-salt diet.

✓ **DO** ask your doctor how much protein you should eat and about a recommended fluid intake.

✓ **DO** stay out of bed and keep active to help fluid loss and prevent clots.

✓ **DO** take medicines as prescribed.

✓ **DO** call your doctor if you have fever, chills, shortness of breath, or pain in the chest, abdo-

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men, or legs.

⦸ **DON'T** eat prepared foods that contain excessive salt.

⦸ **DON'T** eat a high-protein, high-fat diet.

⦸ **DON'T** become a "couch potato."

⦸ **DON'T** smoke.

⦸ **DON'T** take over-the-counter pills (especially drugs such as ibuprofen or naproxen) that will complicate your treatment.

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FOR MORE INFORMATION

Contact the following sources:

- National Kidney and Urologic Diseases Information Clearinghouse Tel: (800) 891-5390 **Website:** http://www.niddk.nih.gov
- National Kidney Foundation Tel: (800) 622-9010 **Website:** http://www.kidney.org
- American Association of Kidney Patients Tel: (800) 749-2257 **Website:** http://www.aakp.org

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Caring for your child with

NEUROBLASTOMA

What Are Neuroblastomas?

Neuroblastomas are tumors of special nervous system cells called postganglionic sympathetic neurons. These cells grow in the adrenal medulla, at the center of the adrenal gland. They also grow in special peripheral nervous system cells. Children often have tumors at birth, but they're not diagnosed until later. Neuroblastomas are the third most common childhood cancer, after leukemia and brain tumors. They account for 10% of all solid tumors of childhood.

What Causes Neuroblastomas?

Most neuroblastomas are due to abnormalities of chromosomes called deletions. Neuroblastomas can sometimes be hereditary (passed from parents to children) nongonococcal urethritis.

What Are the Signs and Symptoms of Neuroblastomas?

Symptoms vary with the tumor location. About two-thirds start in the abdomen (belly). Of these, two-thirds are in the adrenals. Tumors may cause fatigue, weakness, weight loss, and low red blood cell count (anemia). Children may have a mass in abdomen, neck, or chest. Pressure on the spinal cord may cause back pain and urination or bowel movement problems. Tumors in the chest may mean breathing and swallowing problems, infections, and chronic cough. Symptoms from disease spread (metastasis) include fatigue, pain (usually bone pain), bruising, loss of appetite, and weight loss. Fever, bluish lumps under the skin, and irritability may also occur. Tumors may also cause jerky movements and uncontrolled eye movements called dancing eyes, dancing feet.

How Are Neuroblastomas Diagnosed?

The health care provider makes a preliminary diagnosis from the medical history and physical

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examination. Laboratory tests, computed tomography (CT), magnetic resonance imaging (MRI), and bone and other body scans and bone marrow biopsy may be needed for diagnosis. The health care provider will refer you to specialists in cancer treatment (oncologists and hematologists), radiation oncologists, and surgical oncologists.

How Are Neuroblastomas Treated?

Treatment depends on age at diagnosis, stage of disease, location of the tumor and metastases, and how aggressive the tumor is. Medicines (chemotherapy) may be given to kill cancer cells. Radiation therapy may be used to shrink tumors and ease pain. Surgery may be done to remove a tumor if it hasn't spread or to ease symptoms (palliative surgery) of incurable cancer. Pain management, nutritional support, and spiritual and family support are needed. Children with advanced disease can have bone marrow transplantation after chemotherapy. Children at the highest risk can also have this treatment. New therapies include immunotherapy. Substances called monoclonal antibodies and vaccines try to make the body have an immune reaction to the disease. This reaction helps the body fight the disease. Overall survival is higher than 40%. Children younger than 1 year have a cure rate as high as 90%.

DOs and DON'Ts in Managing Neuroblastomas:

- ✓ **DO** remember to keep follow-up appointments with all health care providers. Children may be at risk for additional cancers, including renal cell cancer.
- ⃠ **DON'T** ignore symptoms. Call your health care provider if your child's symptoms don't get better or get worse with treatment. Call if your child has new symptoms.
- ⃠ **DON'T** let your child stop taking medicine unless your health care provider tells you to.
- ⃠ **DON'T** use any medicines (including over-the-counter and herbal products) without first asking your health care provider.

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FOR MORE INFORMATION

Contact the following sources:

- National Cancer Institute Tel: (1-800) 4-CANCER **Website: http://www.nci.nih.gov**
- American Cancer Society Tel: (1-800) ACS-2345 **Website: http://www.cancer.org**
- American Society of Clinical Oncology Tel: (703) 299-0150 **Website: http://www.asco.org**
- American College of Surgeons Tel: (800) 621-4111 **Website: http://www.facs.org**

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MANAGING

NEUROFIBROMATOSIS TYPE 1

What Is Neurofibromatosis Type 1?

Neurofibromatosis (NF) is a genetic disorder that primarily affects growth of nerve cell tissue. It causes nerve tumors and skin and bone changes. Two types occur, type 1 (NF1) and type 2 (NF2). NF1 is also called von Recklinghausen's disease. NF1 isn't common, occurring in 1 of every 4000 people. It affects men and women equally and has been related to tumors of the brain, eye, and spinal cord and certain types of leukemia. There is no cure for it yet.

What Causes NF1?

NF1 is inherited, but more than half of people have no family history of NF1. It happens because of genetic mutations on chromosome 17. Each child born to a parent with NF1 has a 50% chance of getting it.

What Are the Symptoms of NF1?

Symptoms include small brown patches (café-au-lait spots), mostly on the chest, back, and tummy. Present from birth, they vary in size.

Several types of growths develop in and under the skin. They often appear in late childhood or early adolescence. They also vary from smaller than 1 inch to many inches. Larger ones can be disfiguring.

Other symptoms are freckling in body parts that normally don't get sun (such as armpits and groin), learning problems (e.g., learning disabilities and low IQ, in about half of children), curved spine, bones that break easily, and high blood pressure.

Growths in different places in the body cause symptoms. Growths inside the head or on the spine can lead to seizures, loss of vision, and leg weakness (paralysis).

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How Is NF1 Diagnosed?

The doctor will ask about family medical history and will do physical and eye examinations. Electroencephalography (EEG), which records brain waves, is done for seizures. Children have their IQ tested.

A biopsy is done if cancer is possible. In a biopsy, a sample of the growth is removed and studied.

How Is NF1 Treated?

No general treatment is available, but specific treatments may control symptoms. The doctor will watch for and treat complications. Children with learning disabilities need special schooling. Physical and occupational therapy can help. Physical therapy benefits people with a curved spine and broken bones. Occupational therapy teaches people how to manage normal activities.

Surgery can help with bone abnormalities. Scoliosis may need surgery plus back braces. Painful or disfiguring tumors can be removed but may grow back. For rare cancerous tumors, surgery, radiation, or chemotherapy (anticancer drugs) can be used.

DOs and DON'Ts in Managing NF1:

✓ **DO** find doctors and hospitals that have experience with NF1.

✓ **DO** realize that NF1 diagnosis before birth is possible with methods called amniocentesis and chorionic villus sampling.

✓ **DO** call your doctor if you see café-au-lait spots or freckles in your groin or armpit.

✓ **DO** call your doctor if you have new nervous system problems (hearing loss, muscle weakness, or difficulty with walking or balance).

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⦸ **DON'T** be afraid to ask for a second opinion.

⦸ **DON'T** forget that NF1 is rare and will need a team approach for management.

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FOR MORE INFORMATION

FOR MORE INFORMATION

Contact the following sources:

- Neurofibromatosis, Inc. Tel: (800) 942-6825 **Website: http://www.nfinc.org**
- National Neurofibromatosis Foundation, Inc. Tel: (800) 323-7938 **Website: http://www.neurofibromatosis.org**

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MANAGING YOUR

NEUROFIBROMATOSIS TYPE 2

What Is Neurofibromatosis Type 2?

Neurofibromatosis (NF) is a genetic disorder that primarily affects growth of nerve cell tissue. It causes nerve tumors and other abnormalities, such as skin changes and bone deformities. Two types occur, type 1 (NF1) and type 2 (NF2). NF2 is called bilateral acoustic neurofibromatosis. NF2 isn't common, occurring in 1 of every 33,000 people. It affects men and women equally and has been related to tumors of the brain, eye, and spinal cord and certain types of leukemia. No cure exists as yet.

What Causes NF2?

NF2 is inherited, but more than half of people have no family history of it. Genetic mutations occur on chromosome 22. Each child born to a parent with NF2 has a 50% chance of getting it.

What Are the Symptoms of NF2?

People with NF2 don't tend to get the skin swellings and growths and bone problems that people with NF1 get. The main symptom is hearing loss.

With NF2, other symptoms may occur because of growths in different places in the body. A growth inside the head or on the spine can lead to seizures, loss of vision, and leg weakness (paralysis).

How Is NF2 Diagnosed?

The doctor will ask about family medical history and will do physical and eye examinations. Magnetic resonance imaging (MRI) of the brain and spine is done to look for growths. They usually develop in the ear, but they can also grow inside the head or on the spinal cord.

Electroencephalography (EEG), which records brain waves, is done if seizures are present.

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A biopsy is done if cancer is suspected. In a biopsy, a sample of the growth is removed and studied.

How Is NF2 Treated?

Treatments try to control symptoms. The doctor will watch for and treat complications. Children with learning disabilities need special schooling. Physical and occupational therapy can help. Physical therapy benefits people with a curved spine and broken bones. Occupational therapy teaches people how to manage normal activities.

Better diagnostic methods such as MRI can show tumors as small as a few millimeters in diameter, so treatment can begin earlier. Surgery to remove tumors completely is one option, but it may cause hearing loss. Other possibilities include partial removal of tumors, radiation, and, if tumors aren't growing rapidly, the approach called watchful waiting.

DOs and DON'Ts in Managing NF2:

✓ **DO** find doctors and hospitals that have experience with NF2.

✓ **DO** remember that genetic testing is possible, but it can't predict how severe the disease will be.

✓ **DO** understand that genetic counseling is good for coping with, diagnosing, and understanding NF2.

✓ **DO** realize that NF2 diagnosis before birth is possible with methods called amniocentesis and chorionic villus sampling.

✓ **DO** call your doctor if you have new nervous system problems (hearing loss, muscle weakness, walking and balance difficulties).

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⦸ **DON'T** be afraid to ask for a second opinion.

⦸ **DON'T** forget that NF2 is rare and patients will benefit from having a team approach for management.

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FOR MORE INFORMATION

Contact the following sources:

- Neurofibromatosis, Inc. Tel: (800) 942-6825 **Website: http://www.nfinc.org**
- National Neurofibromatosis Foundation, Inc. Tel: (800) 323-7938 **Website: http://www.neurofibromatosis.org**

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MANAGING YOUR

NIGHT TERRORS

What Are Night Terrors?

Night terrors happen during deep sleep, not the lighter, rapid eye movement (REM) sleep. They usually occur during the first half of the night, a few hours after people fall asleep. They last 5 to 20 minutes. People seem to wake up and start screaming, panicking, and sweating. However, they aren't awake, even though their eyes may be open. After people do wake up, they may remember only frightening images, or nothing. Night terrors are most common in children, especially boys 4 to 12 years old, but adults sometimes have them. Most children outgrow night terrors. Night terrors cause no lasting damage.

Night terrors aren't nightmares. Nightmares occur in early morning, during REM sleep, and include unpleasant or frightening dreams.

What Causes Night Terrors?

The cause is unknown. They're often related to emotional tension, stress, fatigue, or conflict. They can occur when people are taking a new medicine or sleeping away from home.

What Are the Symptoms of Night Terrors?

Symptoms include screaming, sweating, confusion, seeing frightening things, rapid heart rate, inability to wake up properly, moving arms or legs, and sometimes sleepwalking. Some people may not be aware of their surroundings or other people, so they may be hard to comfort. After an episode, they often cannot explain what happened or remember it.

How Are Night Terrors Diagnosed?

Children usually need no tests for diagnosis. Tests to rule out other illnesses are done only when severe night terrors last for more than a month with many episodes each night. People with

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extreme night terrors may need examination by a doctor or observation in a sleep laboratory.

How Are Night Terrors Treated?

Waking children about 30 minutes before night terrors usually start might prevent night terrors. Get children out of bed and keep them awake for about 5 minutes by talking to them. Then let them go back to sleep. After a week of this treatment, night terrors usually stop. Sleep medicines are rarely used for this problem, and only in extreme cases.

Night terrors in adults are sometimes a symptom of psychological trauma. The doctor may prescribe medicines and may suggest psychotherapy, which helps deal with emotional problems.

DOs and DON'Ts in Managing Night Terrors:

✓ **DO** gently restrain people having night terrors to help them avoid hurting themselves.

✓ **DO** make sure babysitters and other family members know what to expect.

✓ **DO** call your doctor if night terrors last for a month or more, with many episodes each night.

✓ **DO** call your doctor if other symptoms occur with the night terror or if night terrors cause an injury.

✓ **DO** relax and comfort children at bedtime.

✓ **DO** remember that in adults, night terrors are usually a sign of a psychological problem.

✓ **DO** limit stress.

⦸ **DON'T** shake or shout at someone having night terrors. If you manage to wake up people who are having night terrors, they'll only be more confused.

⦸ **DON'T** let a child who has night terrors sleep in a top bunk bed.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Family Physicians Tel: (800) 274-2237 **Website:**

  http://www.aafp.org

- National Institute of Child Health and Human Development Tel: (800) 370-2943 **Website:**

  http://www.nichd.nih.gov

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MANAGING YOUR

NOCARDIOSIS

What Is Nocardiosis?

Nocardiosis is an infection with soil bacteria. The lungs, soft tissues, and central nervous system (brain and spinal cord) are usually affected. It's serious and can be fatal in people with weak immune (infection-fighting) systems. This disease is found worldwide. In the United States, 500 to 1000 new cases are diagnosed yearly. This infection occurs more in men than women and more often in adults than children.

What Causes Nocardiosis?

The cause is the type of bacteria named *Nocardia*. People get infected when a break in the skin lets bacteria into the body or when the immune system is weakened by medicines (cortico-steroids) or illness (leukemia, lymphoma, or lung cancer). Having liver cirrhosis, ulcerative colitis, rheumatoid arthritis, Cushing's disease, or pemphigus vulgaris can increase risks of getting infected. Nocardiosis isn't contagious.

What Are the Symptoms of Nocardiosis?

Pneumonia occurs in 75% of cases, with fever, chills, breathing problems, and a cough with phlegm. Lung infections can spread into the heart and major blood vessels. Skin and soft tissue infections can follow a puncture of the skin by a thorn or splinter. Swelling, redness, and increased warmth of infected skin occur. Sometimes, large lumps called mycetomas form, usually on the hands and feet. These can lead to skin breakdown and spread of the infection deeper into other tissues, including muscles and bones. Almost one-third of cases have central nervous system infection. A brain abscess causes fever, nausea, headache, vomiting, seizures, neurologic problems, and mental changes.

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How Is Nocardiosis Diagnosed?

Your health care provider may suspect the diagnosis based on the medical history and physical examination. However, the only sure way to make the diagnosis is by isolating the bacteria. Samples of sputum, skin, or pus (from an abscess) are sent to a laboratory where bacteria are cultured. A chest X-ray or computed tomography (CT) may also be done.

How Is Nocardiosis Treated?

Antibiotics, given for a long time, are the standard treatment. People with infections of the skin or soft tissues are usually treated for 2 to 4 months. Mycetomas are best treated for 6 to 12 months, but a surgeon may have to drain and remove the infection. Pneumonia is also treated for 6 to 12 months. People with central nervous system infections or weak immune systems have 12 months of antibiotics.

DOs and DON'Ts in Managing Nocardiosis:

✓ **DO** take your medicines as prescribed. The infection can come back if treatment isn't long enough.

✓ **DO** realize that nocardiosis can be fatal.

✓ **DO** understand that other infections can mimic nocardiosis.

✓ **DO** call your health care provider if you have a fever, chills, and sweats. Call if you have breathing problems, headaches, nausea, stiff neck, and vomiting. Call if you have a skin infection or notice large lumps on your hands and feet.

⃠ **DON'T** miss follow-up appointments with your health care provider who must check your response to antibiotics.

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⦸ **DON'T** forget that people who are sick or take medicines that weaken the immune system are at risk for this infection.

⦸ **DON'T** forget that up to 5% of people with pneumonia caused by nocardiosis die of the infection. The percentage is higher for people with central nervous system infections.

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FOR MORE INFORMATION

Contact the following sources:

- Centers for Disease Control and Prevention Phone: 800-311-3435
- National Institute of Allergy and Infectious Disease Phone: 301-496-5717 **Website: http://www.healthfinder.gov**

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MANAGING YOUR

NONGONOCOCCAL URETHRITIS

What Is Nongonococcal Urethritis (NGU)?

Urethritis is inflammation (swelling, redness) of the urethra, the tube that takes urine from the bladder to outside the body. Nongonococcal urethritis (NGU) is most often due to infection with *Chlamydia*. It's one of the most common sexually transmitted infection (STI) or disease (STD) in the United States and can be prevented by having safe sex. Males 15 to 30 years old with multiple sex partners have the greatest chance of getting NGU.

What Causes NGU?

The most common cause (more than 50% of cases) is infection with a bacteria named *Chlamydia trachomatis*. The infection spreads almost always by sexual contact. Other causes are another bacterium named *Ureaplasma urealyticum* (15% to 30% of cases), a one-celled parasite named *Trichomonas vaginalis*, and herpes simplex virus. In up to 20% of cases, the cause isn't known.

What Are the Symptoms of NGU?

Symptoms appear 1 to 5 weeks after infection, but some men and women may not have them. The most common symptom is pain with urination. Other symptoms are whitish to clear discharge, frequent urination, urgent urination, itching or burning during urination, and pain with sex. People can get NGU more than once; having the infection doesn't provide immunity.

How Is NGU Diagnosed?

After taking a medical history, the doctor will do an examination. The doctor may collect fluid coming from the urethra to test for infection. Blood tests and urine tests can confirm the diagnosis. Many people

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have both NGU and syphilis at the same time, so tests for syphilis should be done before treatment for NGU begins.

How Is NGU Treated?

Antibiotics such as doxycycline or azithromycin are needed to cure the infection. Both sexual partners should be treated at the same time.

Sitz baths several times a day may help ease the pain.

Over-the-counter medicines (such as acetaminophen and ibuprofen) can be taken for pain.

People should avoid sex until the infection is gone. Men should use a condom during treatment if having sex.

In men, if blood and urine tests show that the infection is gone but symptoms continue, the doctor may check for prostate inflammation.

DOs and DON'Ts in Managing NGU:

✓ **DO** tell your doctor if you're pregnant. The infection can be passed to babies during birth. Pregnancy may also affect treatment since some antibiotics cannot be used in pregnant women.

✓ **DO** take antibiotics as prescribed until they are all gone.

✓ **DO** call your doctor if you have a high temperature.

✓ **DO** call your doctor if you see blood in your urine.

✓ **DO** call your doctor if symptoms don't get better in 1 week.

⊘ **DON'T** ever have unprotected sex. Either you or your partner should wear a condom to pro-

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tect against STDs.

⦸ **DON'T** have sex until the infection is gone.

⦸ **DON'T** stop taking your medicine or change your dosage because you feel better unless your doctor tells you to.

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FOR MORE INFORMATION

Contact the following source:

- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website:** **http://www.cdc.gov**

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MANAGING YOUR

NON-HODGKIN'S LYMPHOMA

What Is Non-Hodgkin's Lymphoma NHL?

Non-Hodgkin's lymphoma (NHL) is cancer of the lymphatic system, which is part of the body's immune (infection-fighting) system. It affects white blood cells called lymphocytes. Lymphocytes are made in bone marrow, lymph nodes (lymph glands), and spleen. NHL is more common than Hodgkin's lymphoma.

Most cases occur in men and women, usually older than 60.

What Causes NHL?

The cause is unknown. Weakening of the immune system by viruses such as human immunodeficiency virus (HIV) and Epstein-Barr virus (EBV), organ transplantation medicines, and too much radiation may increase risks.

What Are the Symptoms of NHL?

The most common symptoms are swollen, painless lymph glands in the neck, armpits, and groin. Others include fever, chills, soaking night sweats, coughing, trouble breathing, chest pain, weakness, tiredness, weight loss, swollen legs and face, and abdominal pain and swelling. Nausea, vomiting, loss of appetite, headache, and itching can occur.

How Is NHL Diagnosed?

The doctor will make a diagnosis from a medical history, physical examination, blood tests, and lymph gland and bone marrow biopsy. In a biopsy, tissue taken from a gland or bone marrow is studied with a microscope. Other tests may include laparotomy, which is surgery on the abdomen (belly). X-rays, computed tomography (CT), and positron emission tomography (PET) may be done for staging.

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An oncologist (specialist in cancer treatment) will be involved in the care.

How Is NHL Treated?

Low-grade lymphomas have a longer life expectancy but cannot be cured, whereas with aggressive treatment, some intermediate and high-grade lymphomas can be cured. About 60% of NHLs can be cured.

Some NHLs grow so slowly that treatments are given only if symptoms occur. This is called watching and waiting.

Medicines, radiation, and maybe bone marrow transplantation are used for treatment. Chemotherapy may be given by mouth or through a vein in the hospital, or at home or the doctor's office. Biological treatment uses medicines made from substances produced by the body's immune system. Radiation therapy uses high-energy x-rays from machines or injections.

DOs and DON'Ts in Managing NHL:

✓ **DO** tell your doctor about your medicines, including prescription and over-the-counter ones.

✓ **DO** tell your doctor if you're pregnant or breastfeeding.

✓ **DO** talk to someone about the stress of having cancer. Call your doctor if you feel depressed. Find support groups.

✓ **DO** take care of your teeth and mouth to prevent mouth sores.

✓ **DO** consider placing sperm in a sperm bank or eggs in an egg bank if you plan to have children.

✓ **DO** remember that treatment is complex and involves a team: primary care doctor, oncolo-

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gist, radiation oncologist, surgeon, nutritionist, and social worker.

✓ **DO** call your doctor if you have swollen lymph glands or low back pain with numbness or pain down your legs.

✓ **DO** call your doctor if you have cough, nausea, vomiting, shortness of breath, diarrhea, bloody stools, fever, or bruising after radiation.

✓ **DO** call your doctor if you have fever after chemotherapy.

⃠ **DON'T** ignore swollen lymph glands.

⃠ **DON'T** miss follow-up appointments during and after treatments.

⃠ **DON'T** be afraid to ask questions about infertility, stress, fear, life insurance, and job discrimination.

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FOR MORE INFORMATION

Contact the following sources:

- Leukemia and Lymphoma Society Tel: (800) 955-4572 **Website:** **http://www.leukemia-lymphoma.org**
- Lymphoma Research Association Tel: (212) 349-2910, (800) 235-6848 **Website:** **http://www.lymphoma.org**
- National Cancer Institute, Cancer Information Service Tel: (800) 4-CANCER **Website:** **http://www.cancer.gov**

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- American Cancer Society Tel: (800) ACS-2345 (227-2345) **Website:**

  http://www.cancer.org

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MANAGING YOUR

NORMAL PRESSURE HYDROCEPHALUS

What Is Normal Pressure Hydrocephalus (NPH)?

Normal pressure hydrocephalus (NPH) is a condition with an abnormally high amount of cerebrospinal fluid in the brain's ventricles (cavities). NPH is rare, occurring in 1 of 100,000 people. People of any age can have it, but it occurs most often in elderly people.

What Causes NPH?

In almost 50% of NPH cases, the cause is unknown. It's called idiopathic. The rest of the cases result from trauma, brain surgery, meningitis, infection, or bleeding into the subarachnoid space, the part between the brain and thin tissues that cover it.

NPH isn't contagious or passed from parents to children.

What Are the Symptoms of NPH?

Symptoms often start slowly and progress. Symptoms include walking problems, mental impairment (dementia), and problems holding urine in the bladder (incontinence).

Most people have a slow, shuffling, and wide-based walk. Many complain of problems starting to walk, with the feeling that the feet are stuck to the floor (called magnet gait).

Dementia involves slowed thinking, memory loss, forgetfulness, problems focusing, and lack of attention.

In early stages of NPH, people need to urinate often and have sudden urges to urinate. Later, incontinence occurs. Incontinence is usually urinary, but people may also have problems with bowel movement (stool) incontinence.

How Is NPH Diagnosed?

The diagnosis may be hard to make, because many symptoms aren't specific and may be seen

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with other diseases (e.g., Parkinson's, Alzheimer's, and other types of dementia). Imaging studies, including computed tomography (CT) or magnetic resonance imaging (MRI), can help with diagnosis. CT uses special computer x-ray machines to develop pictures of the body. MRI uses radio waves and strong magnetic fields to develop pictures.

Sometimes, lumbar puncture is performed. The doctor puts a needle through the lower back into the space containing cerebrospinal fluid around the spinal cord, and the fluid is removed and sent for study.

How Is NPH Treated?

No medicines are available for treatment. Treatment involves surgery. A shunt is put into the brain to drain excess cerebrospinal fluid through the shunt. The fluid drains into the abdomen, where it can be absorbed. This draining allows the brain ventricles to return to normal size.

DOs and DON'Ts in Managing NPH:

✓ **DO** realize that about 30% of people with idiopathic NPH have significant improvement after shunts are used. If a cause of NPH is known, 60% will have significant improvement after this operation.

✓ **DO** understand that people with a history of prior strokes have a poor prognosis after treatment compared with those without such a history.

✓ **DO** call your doctor if you have trouble walking.

✓ **DO** call your doctor if you or family members have problems with memory.

✓ **DO** call your doctor if you have urinary incontinence.

⃠ **DON'T** forget that NPH symptoms usually get worse over time if the condition isn't treated,

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even though some people may show temporary improvements. Some people recover almost completely after treatment and have a good quality of life. Early diagnosis and treatment improve the chance of good recovery.

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FOR MORE INFORMATION

Contact the following sources:

- Hydrocephalus Foundation, Inc. Tel: (781) 942-1161 **Website:** **http://www.hydrocephalus.org/**
- Hydrocephalus Association Tel: (888) 598-3789 **Website:** **http://hydroassoc.org/**

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MANAGING YOUR

NOSEBLEEDS

What Are Nosebleeds?

Epistaxis, or a nosebleed, is the common event of blood draining from the nose. Most people have at least one nosebleed during their lifetime. They are twice as common in children compared with adults. Most stop with direct pressure on the nose, but some may need medical care.

What Causes Nosebleeds?

A break in blood vessels in the nose, such as from an injury (blow to the nose) causes a nosebleed. Other causes include chemicals, infections, abnormal blood vessels in the nose, and diseases such as high blood pressure or bleeding disorders. The most common cause is dry nasal passages from dry air, especially in winter.

What Are the Symptoms of Nosebleeds?

Symptoms include bleeding from one or both nostrils and bleeding down the back of the throat with spitting, coughing, or vomiting of blood.

Prolonged or recurrent nosebleeds may cause anemia.

After a big nosebleed, dark or tarry bowel movements mean that a large amount of blood was swallowed.

How Are Nosebleeds Diagnosed?

The doctor will diagnose the nosebleed from a physical examination. Blood work may be done if a large amount of blood was lost or a blood disorder may be causing the nosebleed.

How Are Nosebleeds Treated?

The first treatment is direct pressure. Grasp the nose firmly between the thumb and forefinger and squeeze it for 10 to 30 minutes without stopping.

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Putting an ice pack on the neck or bridge of the nose may help slow blood flow. Leaning forward to spit out blood instead of letting it run down the throat and be swallowed may help prevent vomiting. Using salt water nasal sprays and humidifying the air may help dryness.

Sometimes, packing the nose with absorbent gauze may be needed. The doctor may also cauterize the bleeding site. Some elderly people can have a slowed pulse rate or blood pressure abnormalities from packing and may in some cases need hospitalization.

DOs and DON'Ts in Managing Nosebleeds:

✓ **DO** control your blood pressure. High blood pressure may contribute to nosebleeds.

✓ **DO** avoid aspirin products if you get many nosebleeds. They may slow clotting.

✓ **DO** humidify air in your home and if possible at work, put a little petroleum jelly inside the nostrils, and use a scarf or cloth mask in cold, dry air. Salt water nasal sprays may also help stop nosebleeds caused by dryness.

✓ **DO** avoid chemicals or dusts or wear a filter mask. Your doctor may prescribe a steroid nasal spray if you have infections or allergies.

✓ **DO** call your doctor if blood gushes from your nose or you vomit repeatedly from swallowed blood.

✓ **DO** call your doctor if you cannot control the bleeding or you have repeated nosebleeds in one day.

✓ **DO** call your doctor if you know that high blood pressure or bleeding problems (hemophilia, leukemia) are causing nosebleeds.

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✓ **DO** call your doctor if you take blood thinners (warfarin).

✓ **DO** call your doctor if you have a temperature higher than 102° F, especially if your nose was packed or cauterized.

⃠ **DON'T** blow your nose hard or pick at any clots, which may restart the nosebleed.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

• American College of Emergency Physicians Tel: (800) 798-1822 **Website:** **http://www.acep.org**

• American Academy of Otolaryngology—Head and Neck Surgery Tel: (703) 836-4444 **Website: http://www.entnet.org**

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NUTRITION FOR ATHLETES

Definition

Athletes should know how nutrition affects growth, health, and physical and mental performance. The best sports performance comes from good nutrition. Balanced diets should include energy foods, which are fats, proteins, and carbohydrates such as starches and sugars. They should also include vitamins, minerals, and enough fluids.

Function

Good nutrition means eating daily grains, fruits, vegetables, beans, lean meat, and low-fat dairy products. Drinking fluids prevents dehydration, which causes poor athletic performance.

Young athletes may think that a poor diet is not harmful, but bad eating habits may be hard to stop later and can cause disease. Some athletes also overexercise or use dangerous purging, diuretics, or laxatives to lose weight.

General Recommendations

Many things—age, sex, genetics, body size and weight, and training frequency, duration, and intensity—affect energy intake. The food guide pyramid is an excellent starting place for planning a balanced diet. Refueling with carbohydrates and small amounts of protein immediately after exercise can help in replacing energy stores (muscle glycogen) more effectively and thus improve performance.

Carbohydrates

The body changes carbohydrates into glucose (sugar) for energy. Carbohydrates include starches (in vegetables, grains, pasta, cereals), sucrose (table sugar), fructose (fruits, juices), and lactose (milk sugar). Usually, two thirds of an athlete's plate should be carbohydrate-rich foods, not processed or convenience foods (e.g., chips, candy, pizza).

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Protein

About one third of an athlete's plate should be protein-rich foods (meat, beans, eggs). Eat from different plant and animal sources to get all essential amino acids (proteins), vitamins, minerals, and antioxidants. Well-planned vegetarian diets can also provide enough energy and nutrients.

Fat

Some dietary fat is important. Meats, cheeses, nuts, and oils (olive, canola, fish) provide fat. Avoid high-fat foods (whole milk, fatty beef, fried foods), which can lead to heart disease, diabetes, and obesity. Also avoid very low fat diets because some vitamins are fat soluble vitamins and can only be obtained by ingesting dietary fat.

Micronutrients (Iron, Calcium)

A balanced diet can meet vitamin and mineral needs, but supplements (calcium, vitamin D) may sometimes be needed.

Water and Fluids

Dehydration is the most common reason for poor performance, but it's also the most preventable. Drink water as well as fluids that have electrolytes in them, because they can help the body hold on to water. Drinking large quantities of water, without electrolytes, can be very dangerous. Don't rely on thirst to signal fluid needs; when you're thirsty you're already dehydrated. Acute dehydration can occur in 2 to 3 hours (marathon runners, triathletes). Chronic dehydration (days of not enough fluids) may be even more dangerous. It's often seen during preseason soccer or football training. Infrequent urination, dark yellow urine, headache, and weakness may mean dehydration.

Fuel for Training

Follow eating guidelines for before, during, and after exercise. Always drink enough fluids. Eat a

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high-carbohydrate, low-fat meal (grains, pasta, potatoes, fruits, and vegetables), with lean protein, 3 to 4 hours before an event. Shortly before an event, eat easy-to-digest high-carbohydrate foods (bananas, bagels) and drink cool water. These prevent cramping, diarrhea, and hunger pains during an event. During exercise, drink ½ cup of water every 20 minutes. For long exercise (more than 90 minutes), sports or sugary drinks can fuel muscles. More fuel (high-carbohydrate foods) may be needed right after exercise, and then a balanced meal within 2 hours. For repeated bouts of prolonged exercise, it is helpful to increase the salt intake during meals to help the body maintain fluid balance.

Weight Issues

Athletes who need to lose body fat should do so in the off-season. Don't lose too much too fast: 0.5 to 1.0 pound/week (lean and normal weight), up to 2 pounds/week (excess body fat). Athletes who need to gain weight can use resistance training and increased calorie intake.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Medical Society for Sports Medicine Tel: (913) 327-1415 **Website: http://www.newamssm.org**

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helping YOUR CHILD treat

OBESITY

What Is Obesity?

Childhood obesity means that a child's weight is above the healthy weight range of other children of the same age.

Overweight means that the child's weight is in the upper 15% of that range, and obese means only 5% of children weigh more. This excess weight may cause serious health problems, such as diabetes, orthopedic issues, and emotional problems.

Being overweight as a child often leads to being overweight as an adult. Adults who weigh too much can have serious health problems, such as heart disease, high blood pressure, joint problems, and some cancers.

About 18% to 20% of children in the United States are obese, and an additional 34% to 36% are overweight.

What Causes Obesity?

Eating more than the amount of food needed will cause weight gain. Why certain children gain too much weight isn't known. Genetics (parents passing on a tendency to gain weight), eating too much junk food or fast food, being inactive, and living in a society that promotes watching TV and playing video games more than sports and other physical activities contribute to obesity.

What Are the Symptoms of Obesity?

There may not be any symptoms. Some children may have a sleep disorder, such as snoring or irregular breathing; feeling tired; being unable to exercise enough; having trouble making friends; and feeling depressed.

How Is Obesity Diagnosed?

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The doctor will do a physical examination and will measure height and weigh the child. These results will be compared with those for other children of the same age. The doctor will also take a family medical history and may use other tests (such as of blood and urine) to find out about other health problems and to rule out other causes for weight gain.

How Is Obesity Treated?

The doctor will set a weight-loss goal and suggest a weight-loss diet and an exercise plan. The doctor may suggest counseling to control impulse eating from stress and depression and help the child reach and maintain the goals. Children need help meeting these goals by having their families eat healthy foods, exercise as a family, and encourage sports activities. Family exercise could be walking and bike riding. It's best to lose weight slowly to keep it off. The earlier a child is treated for obesity, the better the chance for success.

DOs and DON'Ts in Managing Obesity:

✓ **DO** encourage your child to follow the recommended weight-loss diet.

✓ **DO** encourage sports or other physical activities.

✓ **DO** serve healthy foods and snacks, in correct portion sizes.

✓ **DO** eat dinner together, with the TV set off.

✓ **DO** serve lots of fruits and vegetables.

✓ **DO** follow your doctor's suggestions about counseling.

✓ **DO** call your doctor if your child complains of shortness of breath or daytime fatigue.

✓ **DO** call your doctor if your child is following the diet and exercise plans and hasn't lost

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weight.

⦸ **DON'T** let your child spend too much time watching TV.

⦸ **DON'T** let your child eat after dinner.

⦸ **DON'T** let your child drink soda or eat fast food.

⦸ **DON'T** drive your child everywhere. Walking or bike riding is good.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- The Endocrine Society Tel: (301) 941-0200, (888) 363-6274 **Website: http://www.endo-society.org**
- The National Institutes of Health Tel: (301) 496-4000 **Website: http://www.nih.gov**
- The Obesity Society Tel: (301) 563-6526 **Website: http://www.obesity.org**
- The American Academy of Pediatrics Tel: (847) 434-4000 **Website: http://www.aap.org**

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WEIGHT CONTROL FOR WOMEN

TAKING CHARGE OF YOUR OBESITY

What Is Obesity?

Obesity is an increased percentage of total body fat compared with normal. Overweight is increased body weight relative to height. Both have important effects on health.

Body mass index (BMI) is one way to see whether someone is overweight. The formula for BMI is weight (kg)/height^2 (m^2). Women 19 to 35 years old should have a BMI of 19 to 25, and women older than 35, of 21 to 27.

Skinfold measurements are used to determine relative obesity. Waist and hip size are used to determine body fat distribution. Females with a body fat content higher than 33% are obese. An increased waist-to-hip ratio is a risk factor for diabetes and heart disease.

What Causes Obesity?

Obesity is caused by eating too many calories for the physical activities performed. Why certain people gain too much weight isn't known. Genetics (parents passing on a tendency to gain weight to children), psychological reasons (eating when stressed), culture, and society (people are encouraged to eat too much) may play a role.

What Are the Symptoms of Obesity?

A women with a BMI higher than 25 is overweight; a woman with a BMI of 30 or higher is obese; and a woman with a BMI of 40 or more is severely obese. Being overweight increases the chances of having serious health problems, such as high blood pressure, diabetes, and coronary artery disease. It strains arthritic joints and causes shortness of breath and tiredness.

How Is Obesity Diagnosed?

The doctor will do a physical examination (weight, BMI, blood pressure) and take a medical his-

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tory. The doctor may use calipers (a tool that measures thickness) to find the amount of body fat. Blood and urine tests may also be done as part of the medical evaluation.

How Is Obesity Treated?

Diet, exercise, medicines, and surgery are all used. A registered dietitian and doctors can help plan a good low-fat, low-calorie diet. Exercise is very effective, and an individualized supervised program helps prevent complications. Few drugs (such as amphetamines) are available for weight loss, and they cause side effects. They should be tried only after diet and exercise and only under direct supervison of the doctor.

Morbidly obese women (more than 100% above ideal body weight or with a BMI higher than 40) who had no success with other methods may consider surgery, such as gastric bypass, lap band, or vertical band gastroplasty (stomach stapling).

DOs and DON'Ts in Managing Obesity:

✓ **DO** tell your doctor about other medical problems.

✓ **DO** tell your doctor about all your drugs. Call your doctor if you have side effects from medicines.

✓ **DO** tell your doctor if you're pregnant or nursing.

✓ **DO** consider joining a support group.

✓ **DO** some daily exercise activity.

✓ **DO** learn your current weight, body mass index, and body fat content.

✓ **DO** call your doctor if you gain weight even with diet and exercise.

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✓ **DO** call your doctor if you have severe diarrhea or low blood sugar (glucose) after surgery.

⃠ **DON'T** try fad diets.

⃠ **DON'T** try to lose weight too quickly.

⃠ **DON'T** drink a lot of alcohol and soft drinks or eat fast food.

⃠ **DON'T** smoke to control body weight.

⃠ **DON'T** become discouraged if weight loss stops for a while.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- The Endocrine Society Tel: (301) 941-0200 **Website:** **http://www.endo-society.org**
- National Institutes of Health Tel: (301) 496-4000 **Website:** **http://www.nih.gov**

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WEIGHT CONTROL FOR MEN TAKING CHARGE OF YOUR OBESITY

What Is Obesity?

Obesity is an increased percentage of total body fat compared with normal. Overweight is increased body weight relative to height. Both have important effects on health.

Body mass index (BMI) is one way to see whether someone is overweight. The formula for BMI is: Men 19 to 35 years old should have a BMI of 19 to 25, and men older than 35, a BMI of 21 to 27.

Skinfold measurements are used to determine relative obesity. Waist and hip size are used to determine body fat distribution. Males with a body fat content higher than 25% are obese. An increased waist-to-hip ratio is a risk factor for diabetes and heart disease.

What Causes Obesity?

Obesity is caused by eating too many calories for the physical activities performed. Why certain people gain too much weight isn't known. Genetics (parents passing on a tendency to gain weight to children), psychological reasons (eating when stressed), culture, and society (people are encouraged to eat too much) may play a role.

What Are the Symptoms of Obesity?

A man with a BMI higher than 25 is overweight; a man with a BMI of 30 or more is obese; and a man with a BMI of 40 or more is severely obese. Being overweight increases the chances of having serious health problems, such as high blood pressure, diabetes, and coronary artery disease. It also strains arthritic joints and causes shortness of breath with exertion, sleep apnea, and tiredness.

How Is Obesity Diagnosed?

The doctor will do a physical examination (weight, BMI, blood pressure). The doctor will also

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take a medical history. The doctor may use calipers (a tool that measures thickness) to find the amount of body fat. Blood and urine tests may also be done as part of the medical evaluation.

How Is Obesity Treated?

Diet, exercise, medicines, and surgery are all used. A registered dietitian and doctors can help plan a good low-fat, low-calorie diet. Exercise is very effective, and an individualized supervised program helps prevent complications. Few drugs (such as amphetamines) are available for weight loss, and they cause side effects. They should be tried only after diet and exercise and only under direct supervision of the doctor.

Morbidly obese men (more than 100% above ideal body weight or with a BMI higher than 40) who had no success with other methods may consider surgery, such as gastric bypass, lap band, or vertical band gastroplasty (stomach stapling).

DOs and DON'Ts in Managing Obesity:

✓ **DO** tell your doctor about other medical problems.

✓ **DO** tell your doctor about all your drugs. Call your doctor if you have side effects from medicines.

✓ **DO** consider joining a weight loss support group.

✓ **DO** some daily activity.

✓ **DO** learn your current weight, body mass index, and body fat content.

✓ **DO** call your doctor if you gain weight even with diet and exercise.

✓ **DO** call your doctor if you have severe diarrhea or low blood sugar (glucose) after surgery.

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⦸ **DON'T** try fad diets.

⦸ **DON'T** try to lose weight too quickly.

⦸ **DON'T** spend spare time watching television or playing video games.

⦸ **DON'T** drink a lot of alcohol and soft drinks or eat fast food.

⦸ **DON'T** smoke to control body weight.

⦸ **DON'T** become discouraged if weight loss stops for a while.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- The Endocrine Society Tel: (301) 941-0200 **Website:** http://www.endo-society.org
- National Institutes of Health (NIH) Tel: (301) 496-4000 **Website:** http://www.nih.gov

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MANAGING YOUR

OBSESSIVE-COMPULSIVE DISORDER

What Is Obsessive-Compulsive Disorder?

Obsessive-compulsive disorder (OCD) is a psychiatric condition affecting the way people think and behave. Troublesome thoughts called obsessions come constantly. The thoughts may be about violence, fear of something bad happening, or worry about forgetting something. People may feel the need to repeat something. These behaviors, called compulsions, are done because of the thoughts. For example, wondering whether the door is locked may lead to checking the lock several times.

OCD usually begins in the late teens to early 20s. Symptoms may sometimes improve but never really go away.

What Causes OCD?

The cause is unknown.

What Are the Symptoms of OCD?

Common obsessions include aggressive thoughts, such as seeing violent images or having fears of harming others or oneself, of doing something embarrassing, of acting on impulses, of feeling responsible for things going wrong, and of something terrible happening. People with contamination obsessions are excessively focused on body waste, dirt, or germs; are overly concerned with contaminants; and are worried about becoming sick to a degree beyond reasonable expectations. Other obsessions are sexual, hoarding or collecting, and religious. Obsessions involve socially unacceptable behaviors, so people feel guilty and anxious.

The many compulsions include repeating rituals and cleaning or hand washing, counting, checking, and ordering or arranging compulsions. For example, people may get up several times

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during the night to make sure that appliances were turned off, doors were locked, and windows were closed. Or people must have clothes, shoes, or dishes in a certain order or pointing in a certain direction to get relief from anxiety. People may not want to do these behaviors but often cannot control them. These compulsive behaviors can take up a large part the day and make it hard to complete other more productive activities.

How Is OCD Diagnosed?

The doctor usually bases the diagnosis of OCD on symptoms: feelings of distress plus the problem behaviors. Symptoms usually get worse during stress. People who feel that obsessions and compulsions take up most of their time and are disturbed by this need treatment. Family members or co-workers may point out the symptoms.

How Is OCD Treated?

Treatment goals are to reduce the symptoms and minimize their interference in life. Behavior therapy reduces the compulsions, such as frequent hand washing. People may need a combination of medicines and behavioral treatment. Medicines called selective serotonin reuptake inhibitors (SSRIs), such as fluvoxamine, sertraline, and fluoxetine, are often used.

DOs and DON'Ts in Managing OCD:

✓ **DO** tell your doctor if your symptoms persist or worsen after having treatment for some time.

✓ **DO** tell your doctor if you have new symptoms or you don't feel well from your medicine.

✓ **DO** exercise in moderation.

✓ **DO** call your doctor if you have physical symptoms such as chest pains or palpitations or you have suicidal or homicidal thoughts.

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✓ **DO** call your doctor if your obsessions become bizarre. Psychosis may occur with OCD.

⃠ **DON'T** take drugs that stimulate you or make you nervous. These drugs include such illicit drugs as phencyclidine (PCP) and cocaine.

⃠ **DON'T** eat or drink foods and beverages with caffeine.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Psychiatric Association Tel: (888) 357-7924 **Website: http://www.psych.org**
- American Psychological Association Tel: (800) 374-2721 **Website: http://www.apa.org**

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MANAGING YOUR

ORAL HERPES

What Is Oral Herpes?

Oral herpes (also called herpes labialis, herpes simplex-1, or HSV-1) leads to blisters around the mouth and gums. This virus is in the family of viruses that causes chickenpox, shingles, cold sores, and mononucleosis. Most infections spread by contact during childhood, so 80% of adults have been exposed to HSV-1. The other HSV, HSV-2, spreads by sexual contact.

These infections cannot be cured.

What Causes Oral Herpes?

The cause, HSV-1, spreads mainly by nonsexual intimate contact with saliva of an infected person, for example, a child kissed by an adult who's shedding the virus but has no symptoms. The virus may enter the body through a break in the skin or through tender skin of the mouth.

What Are the Symptoms of Oral Herpes?

Most people never have symptoms. Blisters, if they appear, occur days or weeks after exposure to the virus. Blisters can return months or years after the initial infection. Some people have blisters once; others get them many times. Itching, pain, burning, or tingling can occur before blisters form. Then small blisters start and form ulcers and crusts. Other symptoms include eye pain (especially to bright light), red eyes, fatigue, fever, headache, itching, muscle aches, tearing from eyes, and tingling.

How Is Oral Herpes Diagnosed?

The doctor will make a diagnosis by examining the area. Blood tests for antibodies against HSV may also be done. The doctor may take fluid from a blister for study if the diagnosis is unclear.

How Is Oral Herpes Treated?

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Drugs (acyclovir, valacyclovir, and famciclovir) can help shorten or prevent an attack.

Penciclovir and acyclovir are topical creams useful for herpes outbreaks. Popular remedies (such as moisturizing or anesthetic lip balms) may not work at all.

Aspirin, acetaminophen, or ibuprofen can help pain.

DOs and DON'Ts in Managing Oral Herpes:

✓ **DO** wash your hands with soap and warm water often, especially after using the bathroom.

✓ **DO** keep blistered skin clean and dry. Avoid shaving the affected area.

✓ **DO** understand that kissing or having oral sex will spread the infection.

✓ **DO** learn to recognize early symptoms (tingling, itching). Starting antiviral drugs early may abort or shorten the duration of an attack.

✓ **DO** avoid sharing personal hygiene items.

✓ **DO** call your doctor if your symptoms get worse, you have a fever, or pus drains from a blister.

✓ **DO** call your doctor right away, or go to the emergency room, if you have a severe headache, shortness of breath, or eye pain, or if bright lights bother you.

✓ **DO** call your doctor for infections that return more than four to six times a year. You may benefit from daily prophylactic therapy.

✓ **DO** avoid and learn how to deal with physical and emotional stress. Stress can weaken your immune system and make blisters return.

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✓ **DO** eat healthy foods. Get enough sleep and exercise.

✓ **DO** avoid spending too much time in the sun or getting sunburned. Sun can make blisters return. Always apply sunscreen.

⃠ **DON'T** kiss anyone or share eating utensils or personal care items with others while you have symptoms.

⃠ **DON'T** have oral sex until you and your partner have no symptoms and your blisters are gone.

⃠ **DON'T** touch, rub, or scratch blisters. You can get a bacterial infection.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Herpes Resource Center American Social Health Association Tel: (800) 227-8922
- American Academy of Dermatology Tel: (866) 503-7546 **Website:** **http://www.aad.org**

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MANAGING YOUR

ORCHITIS

What Is Orchitis?

Orchitis is inflammation (swelling) of one or both testes in the scrotum.

Most cases go away without complications. Very rarely, sterility can result.

What Causes Orchitis?

Different factors, including viruses and bacteria, cause orchitis. One common cause is mumps, the childhood disease that involves swelling of glands that make saliva. However, when teenage boys get the mumps, they can also get orchitis. About 15% to 25% of adults and teenagers who get the mumps also get orchitis.

Urinary tract infections, multiple sexual partners, and sexually transmitted diseases (STDs) such as gonorrhea and chlamydia can also lead to orchitis. Being older than 45 also increases chances of having orchitis.

What Are the Symptoms of Orchitis?

Common symptoms include pain and swelling in the scrotum, nausea, fever, pain when urinating, a heavy feeling on the affected side, scrotum that is tender to touch, and pain with sex. Swelling may last for several weeks after the infection is gone.

How Is Orchitis Diagnosed?

The doctor will do a complete physical examination, take a medical history, and may do tests to check for infection. These tests may include urinalysis, urine culture, and blood tests.

If a discharge is coming from the penis, the doctor may take a sample of the discharge and send it to a laboratory for study. This test may also help find out if an STD is present.

How Is Orchitis Treated?

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Treatment depends on the cause. A bacterial infection usually responds to antibiotics within 2 to 3 days. If the cause is a virus, such as the mumps virus, orchitis will just have to run its course. Antibiotics don't work against viruses. The worst pain should lessen within a few days, but the doctor may prescribe pain medicine for severe symptoms. Using an athletic supporter and applying cool compresses or ice packs to the affected area may also help with pain.

DOs and DON'Ts in Managing Orchitis:

✓ **DO** apply ice packs to the scrotum to help relieve swelling and pain.

✓ **DO** wear an athletic supporter, which may help with the pain.

✓ **DO** drink plenty of fluids and take over-the-counter medicine for pain relief. If pain is severe, your doctor may prescribe something stronger.

✓ **DO** call your doctor if you have severe pain, high temperature, or trouble urinating.

✓ **DO** use latex condoms to prevent being infected with an STD.

✓ **DO** talk to your doctor if you are prone to getting urinary tract infections.

✓ **DO** get vaccinated and have your child vaccinated against mumps to prevent orchitis from mumps. It's given as part of the measles-mumps-rubella (MMR) vaccine during childhood.

⃠ **DON'T** put pressure on your scrotum while it's swollen.

⃠ **DON'T** have unprotected sex if an STD is suspected. Use a condom if you think there's any chance of catching an STD.

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FOR MORE INFORMATION

Contact the following sources:

- American Urological Association Tel: (866) 746-4282 **Website: http://www.auanet.org**
- American Academy of Pediatrics Tel: (847) 434-4000 **Website: http://www.aap.org**

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CARING FOR YOUR CHILD WITH

OSGOOD-SCHLATTER DISEASE

What Is Osgood-Schlatter Disease?

Osgood-Schlatter disease is a painful condition that usually affects the rapidly growing knee. The bony knob just below the kneecap, where the tendon attaches to the leg bone (shinbone, or tibia), becomes painful.

This overuse disorder occurs more often in boys, usually 11 to 18 years old, at the time of the growth spurt. Girls, usually 8 to 16 years old, can also have it. This problem occurs after they take part in athletics or after a sports-related injury.

This condition usually causes no permanent damage. Most children recover completely.

What Causes Osgood-Schlatter Disease?

The cause is vigorous exercise that may put too much stress on bones and muscles of the knee and lower leg, which are still growing.

Some doctors believe that the bony attachment tries to pull away from the leg bone, which causes inflammation (swelling) and tenderness.

What Are the Symptoms of Osgood-Schlatter Disease?

Pain, tenderness, and swelling below the knee and on the shin are symptoms. They can occur in one or both legs. Pain gets worse when the knee is moved or the bony knob is pressed.

In mild cases, symptoms start to disappear in 6 weeks. After the area is rested, all symptoms should be gone in 1 year. Kneeling may be uncomfortable for 2 to 3 years. Pain usually disappears when the attachment site fuses to the leg bone.

How Is Osgood-Schlatter Disease Diagnosed?

The doctor will examine the area and may order an x-ray of the knee.

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How Is Osgood-Schlatter Disease Treated?

Treatment involves RICE: ***R***est, ***I***ce, ***C***ompressing the area with an elastic bandage or splint, and ***E***levating the area. Most children respond to a fairly brief period of rest during the most painful time. If an injury just occurred, the leg should be rested in a raised position for the first day. Ice should be used for the first few days. Not taking part in the sport that caused the injury for a few weeks may help.

Your doctor may suggest seeing a physical therapist for exercises to stretch and strengthen muscles, speed recovery, and increase flexibility. These exercises can prevent the condition from returning.

Your doctor may prescribe pain relievers and antiinflammatory medicines. If treatment doesn't help, a doctor who specializes in bone and muscle disorders (orthopedist) may be seen. Severe cases may need surgery, but this is rare.

DOs and DON'Ts in Managing Osgood-Schlatter Disease:

✓ **DO** encourage your child lose weight if needed.

✓ **DO** have your child do less strenuous activities.

✓ **DO** have your child do exercises prescribed by the physical therapist.

✓ **DO** have your child rest and immobilize the area as needed.

✓ **DO** have your child take medicines as prescribed.

✓ **DO** call your child's doctor if the pain begins to limit activities or returns after treatment.

✓ **DO** have your child warm up and stretch for 15 to 30 minutes before and after activities.

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⦸ **DON'T** let your child participate in the sport or activity that caused the injury for 6 weeks.

⦸ **DON'T** let your child do other activities in which the leg is stressed for 6 weeks.

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NOTES

FOR MORE INFORMATION

Contact the following source:

• American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website:**

http://www.aaos.org

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MANAGING YOUR

OSTEOMYELITIS

What Is Osteomyelitis?

Osteomyelitis is a bacterial infection of the bone, bone marrow, and soft tissue around the bone. Bacteria get into bone from the bloodstream after a broken bone or other trauma, boil or break in the skin, middle ear infection, pneumonia, or other infections.

Osteomyelitis can start quickly and be very painful, or it can build slowly and cause less pain. People are more likely to get osteomyelitis if they have diabetes, are having dialysis, or inject drugs into the body.

What Causes Osteomyelitis?

Microorganisms such as bacteria and fungi can cause the infection. The infection usually starts somewhere else in the body and moves through the blood to end up in bone.

What Are the Symptoms of Osteomyelitis?

Symptoms include high temperature and pain in the bone. The area around the bone and nearby joint can be swollen, red, and warm. Other symptoms are feeling sick, nausea, sweating, and chills. Complications include an abscess that won't heal until the bone heals and permanent joint stiffness.

How Is Osteomyelitis Diagnosed?

The doctor will do blood tests to check white blood cells for infection and look for bacteria or fungi causing the infection.

Other tests are x-rays of the bone, magnetic resonance imaging (MRI) or bone scan to find infected bone, and bone biopsy. In a biopsy, a needle is used to get a sample of bone for study.

How Is Osteomyelitis Treated?

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Osteomyelitis can be cured with medicine. Antibiotics are given, maybe for several weeks, to get rid of infection.

A hospital stay may be needed to drain an abscess or give high doses of intravenous antibiotics. Pain relievers may be needed.

The affected limb should be rested, kept slightly raised, and immobilized with pillows. A lower limb shouldn't bear weight. If long bed rest is needed, other limbs should be exercised, with frequent changes of position.

In people with long-term infection, the bone may die. A surgeon will remove dead bone.

DOs and DON'Ts in Managing Osteomyelitis:

✓ **DO** take the full course of antibiotics.

✓ **DO** change position in bed often to prevent pressure sores. Check skin for redness at pressure points.

✓ **DO** isometric exercises often to prevent muscle weakness and maintain joint flexibility.

✓ **DO** increase normal activities slowly after symptoms go away.

✓ **DO** use sterile dressings if you have an open wound. Wash hands before and after changing dressings.

✓ **DO** call your doctor if fever increases during treatment.

✓ **DO** call your doctor if pain becomes intolerable.

✓ **DO** call your doctor if a new abscess forms or drainage increases from an old abscess.

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✓ **DO** see your doctor if you have symptoms of an infection anywhere in your body. This is very important if you had a recent injury, have diabetes, are having dialysis, or inject drugs.

⃠ **DON'T** stop taking antibiotics or change your dosage because you feel better. If you stop too soon, infection can return.

⃠ **DON'T** dangle the affected limb. Keep it slightly raised.

⃠ **DON'T** put weight on an affected leg. Crutches may help for trips to the bathroom.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Arthritis and Musculoskeletal and Skin Diseases Tel: (877) 226-4267 **Website: http://www.niams.nih.gov**
- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website: http://www.cdc.gov**

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MANAGING YOUR

OSTEOARTHRITIS OF THE HIP

What Is Osteoarthritis?

Osteoarthritis (degenerative joint disease) is an illness in which joints become painful and stiff. Most often, the knees, hips, and spine are involved, but other joints, such as those in the hands, can also show signs. These joints contain cartilage, the substance that cushions bones that touch. During osteoarthritis, cartilage breaks down and loses the ability to cushion the joints. In the hips, the protective barrier between the thigh bone (femur) and the hip bone is lost. The bones rub together, so pain and limited movement result. In advanced osteoarthritis, cartilage in the joints is completely worn away.

What Causes Osteoarthritis of the Hip?

Osteoarthritis is caused by aging, injury, trauma, and other factors. Osteoarthritis is very common when people reach their 70s. It can occur at a younger age in overweight people. It affects both men and women.

What Are the Symptoms of Osteoarthritis of the Hip?

Osteoarthritis develops gradually. The first symptom may be pain, usually in the front part of the thigh or groin. Pain gets worse with exercise and stops during rest. Sometimes, pain travels to the buttocks or lower part of the thigh. Morning stiffness may occur but goes away during the day.

As osteoarthritis gets worse, joints become less flexible. The hips become tender, and a grating sensation may be felt during movement.

How Is Osteoarthritis of the Hip Diagnosed?

The doctor's diagnosis is based on symptoms and a physical examination. The most important sign of early disease is an inability to turn (rotate) the leg toward the center of the body.

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The doctor may also take an x-ray of the hip joints or do more tests to rule out other illnesses that can affect joints. Magnetic resonance imaging (MRI) of the hip may be done if surgery is being considered.

How Is Osteoarthritis of the Hip Treated?

Treatment goals are to control pain and preserve mobility. The type of treatment depends on lifestyle and the degree of osteoarthritis. Keeping to a healthy weight is very important. Mild osteoarthritis may need only exercises to protect the hip joints and sometimes medicine for pain.

The doctor may prescribe nonsteroidal antiinflammatory drugs. They reduce pain but can have side effects (e.g., stomach pain and bleeding, or kidney, liver, and heart problems). Over-the-counter products, such as glucosamine and chondroitin, are popular but have not been proven effective.

Heating pads, warm soaks, and cold packs may help relieve symptoms.

The doctor may prescribe a physical therapy program and medicines (pain relievers and anti-inflammatory drugs) for more severe disease. Low-impact exercises, especially swimming, may improve muscle strength.

Devices such as canes or walkers may minimize stress on the hips. Correcting leg length differences with a heel lift may help.

If these approaches don't work, hip replacement surgery may be offered as a last resort.

DOs and DON'Ts in Managing Osteoarthritis of the Hip:

✓ **DO** take your medicines as prescribed.

✓ **DO** use physical therapy to maintain muscle strength and joint flexibility.

✓ **DO** make lifestyle changes to reduce discomfort and stress on affected hip joints.

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✓ **DO** lose weight if you are overweight.

⃠ **DON'T** take part in work or sport activities that stress your hips.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopaedic Surgeons Tel: (800) 346-AAOS **Website: http://www.aaos.org**
- Arthritis Foundation Tel: (800) 283-7800 **Website: http://www.arthritis.org**

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MANAGING YOUR

OSTEOARTHRITIS OF THE KNEE

What Is Osteoarthritis?

Osteoarthritis (degenerative joint disease) is an illness in which joints become painful and stiff. Most often, the knees, hips, and spine are involved, but other joints, such as those in the hands, can also show signs. These joints contain cartilage, the substance that provides a cushion where two bones touch. During osteoarthritis, cartilage breaks down and loses the ability to cushion the joints. In the knee, the protective barrier between the thigh bone (femur) and the knee is lost. Bones rub together, and joints swell and become sore and painful. Movement becomes limited. In advanced osteoarthritis, cartilage in the joints is completely worn away.

What Causes Osteoarthritis of the Knee?

Osteoarthritis is caused by aging, injury, trauma, and other factors. Osteoarthritis is very common when people reach their 70s. It can occur at a younger age in overweight patients. It affects both men and women.

What Are the Symptoms of Osteoarthritis of the Knee?

Osteoarthritis develops gradually. The first symptom may be pain. Pain gets worse with exercise and stops during rest. Over time there is limited movement and less flexibility. Morning stiffness may occur but goes away during the day, as the knee warms up.

As osteoarthritis gets worse, the knees lose their ability to bend. They become tender, and a grating sensation may be felt during movement.

How Is Osteoarthritis of the Knee Diagnosed?

The doctor's diagnosis is based on symptoms and a physical examination. An x-ray can confirm the diagnosis.

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More tests may be done to rule out other illnesses that can affect joints, such as gout and infections. These tests include blood tests and removing a sample of knee joint fluid. Magnetic resonance imaging (MRI) of the knee may be done if surgery is being considered or if other disorders such as a torn knee ligament are suspected.

How Is Osteoarthritis of the Knee Treated?

Treatment goals are to control pain and prevent joint destruction. The type of treatment depends on lifestyle and the degree of osteoarthritis.

Keeping to a healthy weight is very important. In people with mild osteoarthritis, occasional pain medicine and exercises to protect the knees may be all that is needed. The doctor may prescribe nonsteroidal antiinflammatory drugs. They reduce pain but can have side effects (e.g., stomach pain and bleeding, or kidney, liver, and heart problems). Over-the-counter products, such as glucosamine and chondroitin, are popular but their effectiveness has not been proven.

Heating pads, warm soaks, and cold packs may help relieve symptoms.

The doctor may prescribe physical therapy and medicines (pain relievers, antiinflammatory drugs, or cortisone injections of the knee) for more severe disease. Low-impact exercises, such as swimming or cycling, may improve muscle strength and flexibility.

Devices such as canes or braces may minimize stress on the knees.

If these approaches don't work, surgery may be offered. Knee replacement surgery is a last resort.

DOs and DON'Ts in Managing Osteoarthritis of the Knee:

✓ **DO** take your medicines as prescribed.

✓ **DO** physical therapy to maintain muscle strength and knee flexibility.

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✓ **DO** make lifestyle changes to reduce discomfort and stress on the knees. Try swimming, walking, or riding a bicycle rather than running or jogging.

✓ **DO** lose weight if you are overweight.

⃠ **DON'T** take part in work or sport activities that stress your knees.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopaedic Surgeons Tel: (800) 346-AAOS **Website: http://www.aaos.org**
- Arthritis Foundation Tel: (800) 283-7800 **Website: http://www.arthritis.org**

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MANAGING YOUR

OSTEOCHONDRITIS DISSECANS

What Is Osteochondritis Dissecans?

Osteochondritis dissecans is a condition in which a portion of cartilage and underlying bone separates from a joint surface and may even become detached. It occurs most often in the hip and knee joints, followed by the ankle and elbow. Young (ages 10 to 20) and middle-aged (ages 30 to 60) people most often have it, more men than women.

Osteochondritis dissecans may cause symptoms only off and on and may not need treatment other than observation. Early diagnosis and treatment are important for the best chances for recovery and return to usual activities, including sports.

What Causes Osteochondritis Dissecans?

The cause remains unclear, but osteochondritis dissecans appears to be related to loss of blood supply in the bone. This loss causes a small part of the bone to die. The affected part of bone may collapse, which makes a notch in the joint surface. Cartilage over this dead bone may become damaged. The dead bone may break off and form a loose body that floats around inside the joint. The disorder can occur in people after an injury or after repetitive trauma to the affected area. Other risk factors are sickle cell anemia and radiation therapy.

What Are the Symptoms of Osteochondritis Dissecans?

Pain may occur, but not always. When pain does occur, it may be vague, mild, and aching and stop and start, which makes diagnosis hard. The symptoms, common in athletes, are similar to those of other knee problems. If a part of the joint loosens, the affected joint may lock and swell and become sore. Poor range of motion may be the most important symptom. In time, an affected knee can’t hold the body’s full weight.

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How Is Osteochondritis Dissecans Diagnosed?

The x-ray shows an area in the joint that is either darker or lighter than the bone around it. Sometimes, MRI is needed to show the extent of the lesion.

Hip, knee, ankle, or elbow pain may occur for different reasons. The x-ray finding of an osteochondritis dissecans lesion doesn't always explain the source of the pain. More tests are often done to confirm the osteochondritis dissecans diagnosis. These may include MRI and nuclear bone scans.

How Is Osteochondritis Dissecans Treated?

Rest, immobilization, and antiinflammatory drugs usually produce excellent results. No diets or exercise programs speed healing. Surgery is rarely needed, especially for young people. Protecting the joint with a cast or brace can let the lesion heal without problems. If pain worsens and becomes constant or the joint locks and doesn't bend or straighten, surgery, sometimes arthroscopic, may be done.

DOs and DON'Ts in Managing

Osteochondritis Dissecans:

✓ **DO** rest and immobilize the area as needed.

✓ **DO** take your medicines as prescribed.

✓ **DO** call your doctor if pain becomes constant or suddenly changes.

✓ **DO** call your doctor if the joint locks and doesn't bend or straighten. Your doctor may be able to gently manipulate it or may recommend surgery.

⃠ **DON'T** participate or compete in an activity that causes symptoms of osteochondritis disse-

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cans. You may harm the affected joint.

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Arthritis and Musculoskeletal and Skin Diseases Tel: (877) 226-4267, (301) 496-8190 **Website:** **http://www.niams.nih.gov**
- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website:** **http://www.aaos.org**
- American College of Rheumatology Tel: (404) 633-3777 **Website:** **http://www.rheumatology.org**

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MANAGING YOUR

OSTEOPOROSIS

What Is Osteoporosis?

Osteoporosis is the continuing thinning and loss of density in bones (bone mass), which makes bones more brittle, fragile, and likely to break after minor trauma. Loss of height and back pain are common. Women are at special risk for osteoporosis after their menstrual periods end (menopause), because quicker bone loss occurs after reduced production of the hormone estrogen. Estrogen blocks a protein that weakens bones.

Osteoporosis is a silent disease, and it may not be evident until a bone breaks.

What Causes Osteoporosis?

Normal bone formation needs the minerals calcium and phosphate. If the body does not get enough calcium from the diet, bone production and bone tissues may suffer.

The main causes of osteoporosis include aging, which leads to a drop in estrogen in women at menopause and a drop in testosterone (a male hormone) in men. Other causes are being underweight, lifestyle habits (being sedentary or inactive), alcohol use, cigarette smoking, eating disorders, taking certain drugs, some chronic diseases, and long-term bed rest or immobilization.

What Are the Symptoms of Osteoporosis?

No symptoms may be obvious early in the disease, but in time, low back and neck pain, stooped posture, and gradual loss of height may be seen. In other cases the first sign is a fracture (ribs, wrists, or hips). Bones (vertebrae) in the spine may collapse (become flattened or compressed) and break, which is the most common fracture. Hip fractures can cause the greatest disability.

How Is Osteoporosis Diagnosed?

The physician will take a medical history and do a physical examination to look for age-related

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signs of a deformed spine. Laboratory tests can measure calcium and vitamin D levels. An x-ray examination called DEXA can measure bone density at important places, such as the spine and the hip. Screening for osteoporosis may be recommended for all women after menopause and for men with risk factors such as long-term use of corticosteroids such as prednisone, which predisposes to osteoporosis.

How Is Osteoporosis Treated?

Lifestyle changes may help reduce fracture risk. Such changes include doing regular weight-bearing and muscle-strengthening exercises, stopping smoking, limiting alcohol intake, and getting enough calcium (at least 1,200 mg/day) and vitamin D (at least 800 IU/day) in the diet. Calcium supplements may increase calcium intake, with vitamin D used to help the body absorb calcium. Treatments focus on slowing down or stopping bone loss and on preventing bone fractures by minimizing the risk of falls.

Different drugs, including bisphosphonates such as alendronate, and adequate supplementation of calcium and vitamin D are used as well.

DOs and DON'Ts in Managing Osteoporosis:

✓ **DO** regular weight-bearing and muscle-strengthening exercises as suggested by your doctor.

✓ **DO** make sure you get enough calcium and vitamin D. Eat a healthy diet that is rich in calcium-containing foods, such as dairy products, fish, beans, and green leafy vegetables.

✓ **DO** take your medicines as prescribed.

✓ **DO** discuss screening for osteoporosis with your doctor.

⃠ **DON'T** smoke.

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⦸ **DON'T** drink alcohol in excess.

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FOR MORE INFORMATION

Contact the following sources:

- NIH Osteoporosis and Related Bone Diseases Tel: (800) 624-BONE **Website:** **http://www.osteo.org**
- National Osteoporosis Foundation Tel: (800) 223-9994 **Website:** **http://www.nof.org**

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MANAGING YOUR

OTITIS EXTERNA

What Is Otitis Externa?

Otitis externa, or swimmer's ear, is an infection of the skin lining the ear canal. The ear canal goes from the eardrum to the outside of the ear.

People with diabetes mellitus or skin allergies and those whose ears don't make enough wax are also more prone to get this infection.

It usually lasts 7 to 10 days with treatment.

What Causes Otitis Externa?

The cause is bacteria or fungi that infect the lining of the ear canal. The infection can start after swimming in dirty water or in pools treated with insufficient chlorine or after having too much water in the ear for any reason. Inflammation (swelling) caused by an allergy to hair spray can also cause otitis externa, as can regular use of earphones, which can trap moisture in the ear canal. Sometimes injury to the ear canal, as from cleaning the ear too hard with a bobby pin, cotton swab, or other object, will cause the disorder. Such cleaning can push earwax and dirt back toward the eardrum. This material can trap water and lead to infection.

What Are the Symptoms of Otitis Externa?

Symptoms include ear pain that gets worse when pulling on the earlobe or outer ear or pushing on the little bump (tragus) in front of the ear, itching in the ear, slight fever (sometimes), pus coming from the ear, temporary loss of hearing in the ear, and sometimes a small painful lump or boil in the ear canal. These boils may cause severe pain. If they burst, a small amount of blood or pus may leak from the ear.

How Is Otitis Externa Diagnosed?

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The doctor will examine the ear and in cases of severe or recurrent infection may take a sample of the fluid from inside the ear for study. The doctor may also suggest seeing an otolaryngologist, a doctor who specializes in diseases of the ears, nose, and throat.

How Is Otitis Externa Treated?

Treatment involves medicine as pills, eardrops, cream, or ointment for the infection. Over-the-counter medicine, such as aspirin or acetaminophen, and warm compresses may help with minor pain.

The ear canal shouldn't get wet for 7 to 10 days after all symptoms go away.

DOs and DON'Ts in Managing Otitis Externa:

✓ **DO** keep water out of your ear. Wear earplugs or a shower cap when showering.

✓ **DO** call your doctor if pain continues in spite of treatment or if your ears feel clogged, as if they need cleaning.

✓ **DO** use eardrops as directed.

✓ **DO** call your doctor if pain becomes severe and isn't helped by nonprescription drugs.

✓ **DO** call your doctor if you get a high temperature after treatment starts.

⊘ **DON'T** clean your ears with any object or chemical.

⊘ **DON'T** leave earplugs in too long.

⊘ **DON'T** use hairspray or hair dye near your ears.

⊘ **DON'T** go swimming or get any water in your ear for 7 to 10 days after symptoms go away.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Otolaryngology Tel: (703) 836-4444 **Website:** **http://www.entnet.org**
- American Academy of Pediatrics Tel: (847) 434-4000 **Website:** **http://www.aap.org**

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MANAGING YOUR

OVARIAN CANCER

What Is Ovarian Cancer?

Ovarian cancer is a malignant tumor in the ovary, the woman's reproductive organ that releases eggs and female hormones, such as estrogen. It's the second most common women's cancer (after cancer of the uterus). About half of women with this cancer are older (average age of 59) and have gone through menopause (change of life), so their ovaries no longer work.

What Causes Ovarian Cancer?

The cause isn't clear, but certain things can increase chances of getting it. The most important are age and having relatives who had it. Others are obesity, having breast cancer, starting periods early, and going through menopause late. Some other factors, such as having children, breast feeding, and using birth control pills, can lower the chances.

What Are the Symptoms of Ovarian Cancer?

The most common symptoms are vague or mild and include discomfort or a heavy feeling in the lower abdomen (belly), loss of appetite, and weight loss or gain. Others are abnormal periods, back pain, nausea, and loss of appetite.

How Is Ovarian Cancer Diagnosed?

The doctor may suspect cancer because of symptoms and physical examination. Imaging tests (such as ultrasonography) can suggest the possibility of cancer. Biopsy is the only way to tell whether a mass in the ovary is cancer. In a biopsy, a small piece of tissue is surgically removed and studied with a microscope. The doctor also uses the surgery to find out the stage (extent) of a cancer. The stage relates to how far the cancer spread. Sometimes, tumor markers (CA-125, a substance found in blood) may help diagnosis.

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How Is Ovarian Cancer Treated?

Treatment depends on the location and stage of disease, type of cancer, and age and general health. The main treatment is surgery, usually to remove ovaries, fallopian tubes, lymph glands (nodes), and uterus. Special doctors called gynecologic oncologists are the best doctors for treatment.

Drugs (chemotherapy) and radiation therapy are other choices.

DOs and DON'Ts in Managing Ovarian Cancer:

✓ **DO** tell your doctor about relatives with ovarian cancer.

✓ **DO** remember, if you have not yet gone through menopause, that removing your ovaries and uterus means that you cannot become pregnant. You'll also go through menopause.

✓ **DO** ask your doctor about emotional and social support groups in your community.

✓ **DO** tell your doctor about medicine side effects.

✓ **DO** live a healthy lifestyle. Eat more fruits, vegetables, and whole grains and less fat. Keep to your ideal weight. Exercise.

⃠ **DON'T** miss follow-up doctor appointments.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Obstetricians and Gynecologists **Website: http://www.acog.org**

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- WebMD **Website: http://www.webmd.com**
- U.S. Department of Health and Human Services **Website: http://womenshealth.gov**

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MANAGING YOUR

OVARIAN CYSTS

What Are Ovarian Cysts?

Ovarian cysts are fluid-filled growths on or in the ovary, the woman's reproductive organ that releases eggs and female hormones such as estrogen. They may occur during normal ovulation. Most are harmless, benign growths, and are rarely cancer. Types of cysts include functional (normal, not disease related), dermoid, endometrioma, cystadenoma, or part of a disorder called polycystic ovarian syndrome (PCOS). Cysts occur more often in younger women than in women who have gone through menopause (change of life). Complications include twisting (torsion), bursting (rupture), and bleeding.

What Causes Ovarian Cysts?

Chances of having ovarian cysts increase with certain risk factors, including previous cysts, irregular periods (menstruation), increased upper body fat, and family history.

What Are the Symptoms of Ovarian Cysts?

Most ovarian cysts, especially those found during a regular pelvic examination, cause no symptoms or problems. When symptoms do occur, they can start suddenly, such as severe stabbing pain after a cyst bleeds or bursts. They can also start slowly and be nonspecific, such as a vague sense of pressure or fullness in the abdomen (belly). Abnormal bleeding, pain with intercourse or bowel movements, nausea, and fever may also occur.

How Are Ovarian Cysts Diagnosed?

The doctor may find a cyst during a routine pelvic examination. Ultrasonography, CT, or MRI may help diagnosis. For some special cysts, blood tests may also be done. Large or long-lasting cysts, or cysts that may be cancerous may need a biopsy. In a biopsy, a small piece of tissue is

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surgically removed and studied with a microscope.

How Are Ovarian Cysts Treated?

Treatment depends on the type of cyst and why it started. About 90% of ovarian cysts in younger women are noncancerous and need little or no therapy. Functional cysts need no therapy. They'll go away on their own. The doctor may prescribe birth control pills so that normal periods start and functional cysts don't develop as often. The doctor may also prescribe medicine for pain. Other cysts that don't go away or could be cancerous may need surgery to remove all or part of the ovary. Surgery can sometimes be done by using methods such as laparoscopy that use only small incisions (cuts into the abdomen).

DOs and DON'Ts in Managing Ovarian Cysts:

✔ **DO** tell your doctor about any relatives with ovarian cancer.

✔ **DO** get regular gynecologic care, including a pelvic examination, even if you're older.

✔ **DO** be aware of any changes in your periods.

⃠ **DON'T** panic if you have an ovarian cyst. Most aren't cancer, but all need to be checked by a doctor.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Obstetricians and Gynecologists **Website:** **http://www.acog.org**
- WebMD **Website:** **http://www.webmd.com**
- U.S. Department of Health and Human Services **Website:** **http://womenshealth.gov**

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MANAGING YOUR

PAGET'S DISEASE OF BONE

What Is Paget's Disease of Bone?

Paget's disease is a disorder with abnormal bone formation. Bone cells (osteoblasts) normally form new bone in smooth even layers, like a bricklayer building a brick wall. At the same time, other bone cells (osteoclasts) knock down older parts of this bony structure and take pieces away in the process called resorption. Formation and resorption are balanced, so bones grow straight and strong. In Paget's disease, the process is unbalanced, as if the wall had bricks facing in all directions, weakened by gaps and holes. These bones break easily.

Any bone can be affected, but the skull, spine, leg, pelvis, and collar bone are usually involved.

Up to 4% of Caucasians of Northern European descent older than 40, more males than females, have Paget's disease. It's much less common in other ethnic groups. Paget's disease can be mild to severe. Most people have the mild form that doesn't need treatment.

What Causes Paget's Disease of Bone?

The cause is unknown.

What Are the Symptoms of Paget's Disease of Bone?

Many people have no symptoms. The most common symptom is mild to severe bone pain that is worse at night. Other symptoms include warmth and swelling over the bone (especially skull or long leg bones), large skull, bone breaks, curved spine, deformed bones, headache, hearing loss, joint pain and stiffness, loose teeth, trouble moving, numbness and tingling in hands or feet, shortness of breath, and nerve problems.

How Is Paget's Disease of Bone Diagnosed?

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The doctor will take a medical history, do a physical examination, and order bone x-rays. Blood and urine may be tested. Bone scan and hearing and vision tests may also be done.

How Is Paget's Disease of Bone Treated?

Treatment depends on the severity of symptoms. Mild pain relievers such as acetaminophen or ibuprofen may be enough. Moderate to severe disease is treated with other medicines (bisphosphonates) for pain and to slow new bone growth.

A cane may be helpful for balance and weight-bearing pain.

Exercising is important, because not moving may cause high calcium levels in blood and urine and lead to kidney stones. Surgery may be needed to fix a bone or when weight-bearing bones break.

DOs and DON'Ts in Managing Paget's Disease of Bone:

✓ **DO** tell your doctor about your other medical problems (especially kidney or liver).

✓ **DO** tell your doctor if you're pregnant or plan to get pregnant.

✓ **DO** sleep on a firm bed to support your back.

✓ **DO** exercise and stay slim. Ask your doctor which exercises are right for you.

✓ **DO** try to avoid injury. Accident-proof your home. For example, put hand rails next to your tub and toilet and don't use throw rugs.

✓ **DO** call your doctor if your bone pain or hearing worsens, your ankles swell, or you have shortness of breath on exertion.

⦸ **DON'T** stop taking your medicine or change your dosage because you feel better unless your

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doctor says to.

⦸ **DON'T** exercise, do heavy work, or play sports without your doctor's OK.

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FOR MORE INFORMATION

Contact the following sources:

- The Paget Foundation Tel: (800) 23-PAGET (237-2438), (212) 509-5335 **Website: http://www.paget.org**
- The Endocrine Society Tel: (888) 363-6274 **Website: http://www.endo-society.org**

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MANAGING YOUR

PAGET'S DISEASE OF THE BREAST

What Is Paget's Disease of the Breast?

Paget's disease of the breast is a rare breast cancer. It usually affects the nipple and the area below. This disease, like other breast cancer, spreads to lymph glands (nodes) nearby and then through the blood stream to other parts of the body, such as bones, lungs, and liver. The cancer is curable if found early, before it spreads.

What Causes Paget's Disease of the Breast?

The cause isn't known, but Paget's disease isn't contagious.

What Are the Symptoms of Paget's Disease of the Breast?

Redness, scaling, and crusting of the nipple that itches and burns may occur. Nipple drainage may also occur. A lump under the nipple may be felt.

How Is Paget's Disease of the Breast Diagnosed?

The doctor may suspect Paget's disease from the physical examination. A mammogram and sonogram may be done, but the only sure way to diagnose Paget's disease is by biopsy. In a biopsy, a small piece of tissue from the area is removed and studied with a microscope.

After diagnosis, the cancer must be staged, to find out the extent of disease. Blood tests; computed tomography (CT) of the head, chest, and abdomen; and bone scans may be used for this. The surgeon needs to determine the tumor size, whether it has spread to lymph nodes, and whether the cancer has certain hormone receptors. This information is critical for treatment.

How Is Paget's Disease of the Breast Treated?

Therapy is similar to that for other breast cancers, except that the nipple and tissue just under it are removed. Surgery, radiation therapy, chemotherapy, hormonal therapy, or a combination of

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all these are used. Treatment often involves a team of many specialists, including an oncologist (doctor specializing in cancer), surgeon, radiation oncologist (doctor specializing in radiation treatments), nutritionist, and social worker.

Side effects of surgery depend on the type of operation and how much breast tissue is removed (mastectomy or breast conserving operation). Removal of lymph nodes under the armpit may cause the arm to swell. Radiation side effects include red, dry, itchy skin over the radiation site; shortness of breath; coughing; and arm swelling.

Chemotherapy can cause nausea, vomiting, hair loss, easy bruising, bleeding, and infections.

Hormonal treatment can cause hot flashes, nausea, vomiting, irregular periods, vaginal bleeding, and rash.

DOs and DON'Ts in Managing Paget's Disease of the Breast:

✓ **DO** keep your doctor appointments during and after treatment so your doctor can check your response to treatment and look for cancer that may recur.

✓ **DO** remember the importance of exercise and good nutrition during and after treatment.

✓ **DO** call your doctor if you feel a lump, see nipple drainage, or feel swollen lymph glands under your armpits.

✓ **DO** call your doctor if you have fever, nausea, and vomiting after chemotherapy.

✓ **DO** call your doctor if you have back pain, leg weakness, stool or urine incontinence (leaking), or bone pain.

✓ **DO** find a support group if you think that would help you handle your disease.

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⦸ **DON'T** ignore lumps, nipple discharge, or changes in nipple skin.

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FOR MORE INFORMATION

Contact the following sources:

- American Cancer Society Tel: (800) 227-2345 **Website: http://www.cancer.org**
- American College of Surgeons Tel: (312) 202-5000, (800) 621-4111 **Website: http://www.facs.org**

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MANAGING YOUR

PAINFUL INTERCOURSE

What Is Painful Intercourse?

Painful intercourse is also called dyspareunia or coital pain. Some women have pain during or after sexual intercourse. It can be primary or secondary. Primary means that sex is always painful. Secondary means that sex is only sometimes painful. It can be superficial (pain in or around the vaginal opening) or deep (pain from strong thrusting). Up to 60% of women have pain with intercourse but don't tell their doctor.

What Causes Painful Intercourse?

The many causes include spasms at the vaginal opening, infection, scars or adhesions after giving birth or surgery, growths (fibroids) in the womb (uterus), dry vagina (from medicines or too little sexual arousal), menopause (change of life), and first time having sex (with torn hymen). Also, an allergy to birth control foam or jelly, diaphragms, or condoms can cause pain.

Other causes are endometriosis, radiation, trauma, sexually transmitted diseases (STDs), pelvic inflammatory diseases, urinary tract infections (UTIs), depression, and sexual injury.

What Are the Symptoms of Painful Intercourse?

The symptom is mild or severe pain during foreplay, sex, or attempted sex. Superficial pain occurs on entry into the vagina. Pain can be stinging, burning, itchy, and constant. Deep pain occurs over the lower abdomen (belly) or deep in the vagina. This pain feels like cramping, muscle spasms, or tight feeling before, during, or after sex.

How Is Painful Intercourse Diagnosed?

The doctor will take a medical history, do a physical examination, and maybe order blood tests and take a sample with a swab to check for infection.

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Other tests include ultrasonography (uses harmless sound waves to look for tumors in the pelvis), cystoscopy, and colonoscopy. Cystoscopy uses a lighted tube put into the urinary bladder to look for cancer and infections. Colonoscopy uses a lighted tube that is put into the rectum and large intestine (colon), to check for inflammation (swelling), obstruction, and tumors.

How Is Painful Intercourse Treated?

Treatment depends on the cause and includes using more foreplay or store-bought lubricants for a dry vagina to antibiotics for UTIs or STDs. Adhesions from surgery, radiation, or endometriosis may need surgery. Deep pain can be prevented by simply changing position (woman on top) or stopping forceful thrusting.

DOs and DON'Ts in Managing

Painful Intercourse:

✓ **DO** use sitz baths to help pain. Sit in a tub of hot water for 10 to 15 minutes.

✓ **DO** use a proper lubricant.

✓ **DO** get information about foreplay and exercises that help relax your vagina.

✓ **DO** try different sexual positions. Talk to your partner.

✓ **DO** avoid perfumed soaps.

✓ **DO** stop using foam or jelly for birth control if you may have an allergy.

✓ **DO** talk to a counselor about fears from past sexual trauma.

✓ **DO** call your doctor if you have a fever, vaginal bleeding or discharge, worsening vaginal

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pain, symptoms that don't go away after 3 months of treatment, or abdominal pain with nausea or vomiting.

⃠ **DON'T** use vaginal perfumes and avoid douching.

⃠ **DON'T** put up with the pain. Tell your doctor about it.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- Office on Women's Health, U.S. Department of Health and Human Services Tel: (800) 994-9662
- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website: http://www.acog.org**

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MANAGING YOUR

PANCREATIC CANCER

What Is Pancreatic Cancer?

Cancer of the pancreas refers to growth of cancer cells in the pancreas. The pancreas is in the abdomen (belly), with the stomach, intestines, and other organs around it. It makes juices used in digestion and several hormones, including insulin, which controls blood sugar (glucose) level. It releases these substances into ducts (tubes). Pancreatic cancer starts from cells lining these ducts.

Almost 30,000 people in the United States are diagnosed with this cancer each year. Early detection is best for a cure, but this cancer is hard to find early because most symptoms do not occur until the cancer has spread.

What Causes Pancreatic Cancer?

Causes are unclear, but smoking, alcoholism, and chronic inflammation (swelling) of the pancreas (pancreatitis) are related to this disease. Pancreatic cancer isn't contagious or hereditary.

What Are the Symptoms of Pancreatic Cancer?

Symptoms depend on the cancer's location and size. If the bile duct is blocked so that bile cannot pass into the intestines, jaundice may occur. The skin and whites of the eyes become yellow and urine may become dark.

Growing cancer causes pain in the upper abdomen and sometimes the back. Pain becomes worse after eating or lying down. Other symptoms are nausea, reduced appetite, weight loss, and weakness.

How Is Pancreatic Cancer Diagnosed?

The doctor makes a preliminary diagnosis from symptoms and special imaging tests called com-

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puted tomography (CT), magnetic resonance imaging (MRI), and ultrasound. They help decide the stage (extent) of disease by showing whether cancer affects other organs.

The doctor may, in some cases, also order a test called endoscopic retrograde cholangiopancreatography (ERCP). This test uses dye and a flexible tube passed down the throat and into the intestine to get x-rays. The best way to diagnose cancer is with a biopsy. A piece of pancreas is taken and checked with a microscope to detect cancer cells.

How Is Pancreatic Cancer Treated?

Surgery may be done to remove all (total pancreatectomy) or part of the pancreas and other tissues. In the Whipple procedure, the surgeon removes the head of the pancreas, parts of the small intestine and stomach, and other tissues. Sometimes cancer cannot be completely removed, but surgery can help relieve some symptoms.

Radiotherapy and chemotherapy are also used. Radiotherapy uses high-energy rays to kill cancer cells. Chemotherapy (drugs to kill cancer cells) may be given alone or with radiotherapy if cancer cannot be removed. Doctors sometimes give chemotherapy after surgery to control cancer cell growth.

DOs and DON'Ts in Managing Pancreatic Cancer:

✓ **DO** understand that you'll need a team of doctors for care. The team will include a primary care doctor, surgeon, oncologist (a doctor specializing in cancer), and maybe a radiation oncologist (a doctor specializing in using radiotherapy for cancer).

✓ **DO** call your doctor if you have jaundice, abdominal pain, weight loss, or no appetite.

✓ **DO** call your doctor if you have fever or see drainage from the incision site after surgery.

⦸ **DON'T** forget that treatments have side effects, such as pain and infection (surgery) and

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nausea, vomiting, and hair loss (chemotherapy).

⦸ **DON'T** be afraid to ask for a second opinion.

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FOR MORE INFORMATION

Contact the following sources:

- National Cancer Institute Phone: (800) 4-CANCER (422-6237) **Website:** **http://www.cancer.gov**
- American Cancer Society Tel: (800) ACS-2345 (227-2345) **Website:** **http://www.cancer.org**

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MANAGING YOUR

PANIC DISORDER

What Is Panic Disorder?

Severe stress occurs when people have too many demands and pressures. They find it impossible to cope and can feel very anxious. Some people have generalized anxiety disorder (GAD), one of many anxiety disorders. Other people can have different anxiety disorders, such as panic disorder or panic attacks. A panic attack is a relatively brief, sudden episode of intense fear or apprehension, often associated with a sense of impending doom. Symptoms occur for no reason, last briefly, and then go away. People may be calm between attacks.

What Causes Panic Disorder?

The cause isn't known. Certain brain chemicals called neurotransmitters (serotonin and epinephrine) may play a role. The disorder tends to occur in some families. Caffeine, nicotine, and other stimulants can increase panic attacks. Drugs causing anxiety include steroids, inhalers used for breathing problems, thyroid medicine, diet pills, medicines containing caffeine, and some antihistamines and cough and cold medicines.

What Are the Signs and Symptoms of Panic Disorder?

Symptoms include increased heart rate and blood pressure, faster breathing, cold sweats, and feelings of doom. People can have stomach aches, shortness of breath, diarrhea, and feel very anxious or helpless. During an attack, people often have rapid speech. They may be very restless and move about in a chair, tap their fingers or toes, wring their hands, and get up and walk across a room. People may say, "I feel as if I'm going to jump out of my skin."

How Is Panic Disorder Diagnosed?

The health care provider makes a diagnosis from the medical history and physical examination.

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Panic attacks may occur out of the blue (uncued) or be triggered by an object or situation (cued). Panic disorder is diagnosed after two uncued panic attacks followed by at least 1 month of serious worry about having more attacks and what they mean, or a major change in behavior related to these attacks. Laboratory tests may be done to rule out similar disorders.

How Is Panic Disorder Treated?

All people with anxiety disorders should reduce stress levels, have enjoyable activities such as reading or writing, exercise regularly, and eat healthy. There are several treatment options for panic disorders. Many of these are combined to get the best results. Treatment often involves behavioral methods such as biofeedback. People learn to change their muscle tone or brain waves by controlling breathing. Other methods are progressive muscle relaxation, imagery, meditation, and hypnosis. Many people will need treatment with benzodiazepine tranquilizer medicines. These drugs include alprazolam, lorazepam, clonazepam, and diazepam. They have side effects (such as making people drowsy) and can be habit forming. People with a history of substance abuse shouldn't usually take these drugs. Other effective drugs for anxiety and panic disorder are selective serotonin reuptake inhibitors (SSRIs), antidepressants, and combination serotonin and norepinephrine reuptake inhibitors (SNRIs).

DOs and DON'Ts in Managing Panic Disorder:

- ✓ **DO** get lots of sleep, exercise daily, and eat a well-balanced diet.
- ✓ **DO** reduce stress in your life. Learn about meditation, massage, yoga, tai chi, and stress-reducing exercise.
- ✓ **DO** call your health care provider if you are experiencing frequent panic attacks. Call if you have side effects from medicines. Call if you have depression or suicidal thoughts.

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⦸ **DON'T** use products containing caffeine. Don't drink alcohol if you are taking medications for panic disorder.

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FOR MORE INFORMATION

Contact the following sources:

- American Psychiatric Association Tel: (888) 357-7924 **Website: www.psych.org**
- American Psychological Association Tel: (800) 374-2721 **Website: www.apa.org**
- National Institute of Mental Health **Website: www.nimh.nih.gov** Type 'stress' into the search box AGORAPHOBIA AND PANIC

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UNDERSTANDING YOUR

PAP SMEAR ABNORMALITIES

What Are Pap Smear Abnormalities?

The Pap smear is a test done during a pelvic examination. Cells from the cervix, which is the opening of the uterus, are removed and checked at a laboratory. To do this test, the doctor places a small tool called a speculum into the vagina. This tool holds open the vaginal walls and lets the doctor see the cervix and vagina. The doctor gently rubs a swab or spatula around and inside the cervix to get a sample. The sample is smeared onto a glass slide and sent for testing. The Pap smear test shows how the female hormone estrogen affects the cervix and vagina. It also shows whether the cervix has an infection or abnormal cells.

What Causes Pap Smear Abnormalities?

An abnormal Pap smear may be caused by inflammation, infection, or cancer of the cervix.

What Are the Symptoms of Pap Smear Abnormalities?

An abnormal Pap smear doesn't cause symptoms, but some discomfort may be felt during the pelvic examination.

How Are Pap Smear Abnormalities Diagnosed?

After one abnormal Pap smear, the doctor will probably do another in a few weeks. Other tests such as colposcopy may also be done. In a colposcopy, the doctor uses a colposcope (an instrument with a magnifying lens) to look closely at the cervix through the opening of the vagina. Small samples of tissue that looks abnormal may be removed and sent for testing.

How Are Pap Smear Abnormalities Treated?

A few women need treatment, which depends on the cause of the abnormalities. To destroy abnormal tissue, the doctor may use freezing, burning, a laser, or the loop electrosurgical excisional

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procedure (LEEP). LEEP uses a thin wire loop attached to an electrical unit.

For more serious abnormalities, the doctor may do a cone biopsy. A cone-shaped piece of the cervix, with all abnormal cells, is removed and checked for causes of the abnormality. The doctor cuts the tissue out with a surgical knife, cautery (burning tool), laser, or wire loop.

DOs and DON'Ts in Managing Pap Smear Abnormalities:

✓ **DO** have a regular Pap smear. If you're sexually active or are 18 years old or older, you should have a Pap smear yearly, or more often if you're at high risk for getting cervical cancer, at least until age 65. This way, you can find abnormalities very early, when treatment is most effective.

✓ **DO** get vaccinated against human papilloma virus (HPV) if you are between the ages of 9-26. It will lower your risk of cervical cancer.

✓ **DO** call your doctor if you have severe pain or bleeding after the Pap smear.

✓ **DO** schedule your Pap smear between your periods. Menstrual blood can make the Pap smear less accurate. Also, don't douche before you have a Pap smear. Douching can change Pap smear results.

✓ **DO** use a condom during sex to avoid infection. A diaphragm doesn't protect you as well.

⃠ **DON'T** douche before having your Pap smear.

⃠ **DON'T** smoke. Smoking may increase your risk of getting cervical cancer.

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Contact the following sources:

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- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website:**

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- National Cancer Institute Tel: (800) 4-CANCER (422-6237) **Website:**

  http://www.cancer.gov

- National Women's Health Network Tel: (202) 628-7814 **Website:**

  http://www.nwhn.org

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MANAGING

PARANOID PERSONALITY DISORDER

What Is a Paranoid Personality Disorder?

Personality refers to the characteristics and behaviors that make people individuals. A personality disorder is a pattern of behavior that differs from the normal of the culture. It leads to many problems in forming relationships with family, friends, and co-workers. People with a paranoid personality disorder distrust and are suspicious of others. It makes them think that others have evil, ill will, and wicked motives. More men than women have this disorder.

What Causes a Paranoid Personality Disorder?

The cause is unknown. The disorder isn't contagious or passed from parents to children. However, it's found more often in families with members having schizophrenia and delusional disorders.

What Are the Symptoms of a Paranoid

Personality Disorder?

People may have social anxiety and overly sensitive, peculiar thoughts, language, and fantasies. They don't perform well in school. As children they may have seemed odd. Their suspiciousness often caused arguments and complaints. They misinterpreted actions of others and were often rigid and critical. They were standoffish and seemed cold to others.

How Is a Paranoid Personality

Disorder Diagnosed?

A psychiatrist or psychologist usually makes the diagnosis, most often in people in early adulthood. People must have four or more of the following. They falsely think that others are harming or deceiving them. They have unjustified doubts about loyalty or trustworthiness of friends or

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associates. They don't confide in others because they fear that information will be used against them. They think that innocent remarks or events have hidden threats. They hold grudges. They see attacks on their reputation that others don't see and are quick to get angry. They're suspicious of spouses or sexual partners.

How Is a Paranoid Personality Disorder Treated?

Treatment involves individual psychotherapy with cognitive behavioral therapy. Psychiatrists and psychologists use psychotherapy. Psychiatrists are specialists in mental and emotional disorders and can prescribe medicines. Psychologists are nonmedical specialists in these problems but don't prescribe drugs. The goal is to help symptoms and change behavior, so relationships with family, friends, colleagues, and co-workers get better.

Cognitive therapy teaches people how certain thinking patterns cause symptoms. Behavioral therapy breaks the connection between worry about stresses and usual reactions to them.

Drugs for psychosis, depression, and anxiety may sometimes help people who also have other mental disorders.

DOs and DON'Ts in Managing a Paranoid

Personality Disorder:

✓ **DO** realize that this disorder can lead to problems in relationships.

✓ **DO** realize that people may challenge their doctors, which makes treatment hard.

✓ **DO** call your doctor if you think that a family member may have this disorder.

✓ **DO** call your doctor if you need a referral to a psychiatrist or psychologist.

✓ **DO** call your doctor if you feel depressed.

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✓ **DO** call your doctor if you feel that you're going to harm yourself or others.

⦸ **DON'T** forget that people with this disorder may have other psychiatric problems. These include depression, anxiety, obsessive-compulsive disorder, and agoraphobia (fear of crowds).

⦸ **DON'T** forget that this disorder is chronic with lifelong problems with relationships.

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FOR MORE INFORMATION

Contact the following sources:

- Mental Health America Tel: (800) 969-6642 **Website:** http://www.nmha.org
- American Psychiatric Association Tel: (888) 357-7924 **Website:** http://www.psych.org

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MANAGING YOUR

PARKINSON'S DISEASE

What Is Parkinson's Disease?

Parkinson's disease is a progressive neurological disorder. It gradually worsens over a period of years with loss of control of muscle movements.

Older people usually get Parkinson's disease more frequently, but people younger than 40 can develop early-onset disease.

What Causes Parkinson's Disease?

Brain cells that make the chemical dopamine start to die, which causes symptoms due to low dopamine levels. It's unclear why this happens, but risk factors include medicines, head injury or repeated trauma (from sports such as boxing), blood vessel problems, infection, toxins such as pesticides and carbon monoxide, tumors, water on the brain (hydrocephalus), and thyroid and parathyroid gland problems. Parkinson's disease is generally not hereditary, but in rare cases it seems to run in families.

What Are the Symptoms of Parkinson's Disease?

An early symptom is a slight tremor of the hand or fingers. It's often first noticed when handwriting changes or when people have trouble with fine motor movements (such as buttoning clothes). Tremor (called pill rolling) or shaking occurs in one or both hands, especially at rest. Other symptoms are muscle stiffness and freezing, gradual slowing and loss of movement, trouble with walking (especially starting up), swallowing problems, drooling, loss of facial expression, and trouble speaking.

How Is Parkinson's Disease Diagnosed?

The doctor makes a diagnosis from a medical history and physical examination. Laboratory tests,

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magnetic resonance imaging (MRI), and computed tomography (CT) may be done to rule out other disorders. The doctor will suggest seeing a neurologist (specialist in nervous system diseases).

How Is Parkinson's Disease Treated?

No cure exists, but symptoms can be treated and complications can be prevented. Medicines, taken lifelong, are used to treat symptoms or slow disease progress. Surgery is rarely done and doesn't always help, but may be suggested when symptoms get very bad and medicines don't work. Stereotaxic surgery can carefully destroy brain cells causing movement problems. This stops or reduces tremors. Another operation involves transplanting cells from an embryo into the brain. The cells take over the work of the diseased cells in making dopamine. The third operation involves putting small electrodes in the brain to stimulate diseased parts to provide more dopamine.

People later need help with activities of daily living. An occupational therapist can assist with these.

DOs and DON'Ts in Managing

Parkinson's Disease:

- ✓ **DO** take medicines as your doctor prescribes.
- ✓ **DO** join a support group. These groups can help your sense of well-being and help reduce stress.
- ✓ **DO** get legal and financial counseling.
- ✓ **DO** get occupational therapy and counseling.
- ✓ **DO** exercise. Daily exercise, such as walking, helps keep muscles limber and strong.

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✓ **DO** try to drink thick liquids (nectars, milk shakes) instead of thin ones (apple juice, tea) if swallowing becomes hard.

✓ **DO** call your doctor if you see a change in the severity of your symptoms.

✓ **DO** call your doctor if you fall or become injured.

⃠ **DON'T** forget to take your medicines or change your dosage because you feel better unless your doctor tells you to.

⃠ **DON'T** walk on unfamiliar ground without assistance if you have trouble walking.

⃠ **DON'T** drive or operate dangerous equipment unless your doctor says that you can.

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FOR MORE INFORMATION

Contact the following sources:

- American Parkinson Disease Association Tel: (800) 223-2732 **Website:** **http://www.apdaparkinson.org**
- Parkinson's Disease Foundation (PDF) Tel: (800) 457-6676 **Website:** **http://www.pdf.org**

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MANAGING YOUR

PARONYCHIA

What Is Paronychia?

Paronychia is a common infection under the skin around the fingernails. It can be acute (come on suddenly) or chronic (last a long time). It occurs more in females than males. An abscess, or pus, can form if the infection is not treated.

What Causes Paronychia?

Bacteria (usually the ones called *Staphylococcus* and *Streptococcus*) or fungi cause paronychia by getting into the skin through a wound. These wounds can come from biting nails or hangnails; thumb sucking; penetrating injuries; foreign bodies such as splinters; and exposure to harsh chemicals, acrylic nails, or nail glue. People who often have wet hands that aren't dried well (such as dishwashers, bartenders, and housekeepers) and people who have diabetes have a higher risk of getting paronychia.

What Are the Symptoms of Paronychia?

Redness and swelling of the skin near the fingernail occur first. Then, fluid or pus may be seen under the nail. The area is usually very tender and feels puffy or fluid filled. As paronychia continues, throbbing pain often occurs.

How Is Paronychia Diagnosed?

The doctor will diagnose paronychia by doing an examination of the fingernails.

How Is Paronychia Treated?

Antibiotics are used if paronychia is due to a bacterial infection, or antifungal medications are used if it is due to a fungus. The doctor may also drain the area of pus. Draining the pus usually provides a complete cure. Draining may involve making a small cut over the area or separating a

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small part of the nail from the skin. In advanced cases, a small piece of nail may be removed, but the nail almost always grows back.

DOs and DON'Ts in Managing Paronychia:

- ✓ **DO** protect your hands from water. Keep them clean and dry. Wash with soap and water after doing dirty work.
- ✓ **DO** wear vinyl gloves to prevent contact with irritating substances, such as water, soap, detergent, metal scrubbing pads, scouring pads, and chemicals, such as paint, paint thinner, turpentine, and polishes for cars, floors, shoes, metal, and furniture. Also wear gloves when you peel or squeeze lemons, oranges, sour fruits, tomatoes, or potatoes.
- ✓ **DO** wear leather or heavy-duty fabric gloves for housework or gardening.
- ✓ **DO** keep your bandage clean and dry. Change it at least twice daily.
- ✓ **DO** leave hangnails alone and avoid injuring your fingertips.
- ✓ **DO** take prescribed antibiotics as directed.
- ✓ **DO** call your doctor if the pad of your finger becomes swollen or painful, or your finger or knuckle becomes swollen or hurts to bend.
- ✓ **DO** call your doctor if you have red streaks from the infected area, fever, or chills.
- ✓ **DO** call your doctor if your pain lasts for more than 24 hours after treatment.
- ✓ **DO** call your doctor if you have a reaction to your medicine.

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⦸ **DON'T** try to drain paronychia yourself with pins or knives.

⦸ **DON'T** bite your nails.

⦸ **DON'T** allow the wound to become dirty.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Dermatology Tel: (866) 503-SKIN (7546) **Website:** **http://www.aad.org**

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MANAGING YOUR

PARTIAL MOTOR SEIZURES

What Are Partial Motor Seizures?

A seizure is caused by abnormal electrical signals in the brain. This kind of seizure often starts in the arm or leg and then moves upward to other areas on that side of the body. These seizures don't last long.

What Causes Partial Motor Seizures?

Simple partial seizures may be brought on by a head injury, stroke, brain infection, or tumor, but more than half the time the cause is unknown.

What Are the Symptoms of

Partial Motor Seizures?

Simple partial seizures usually don't make people unconscious or unaware of what's going on around them. They will be aware of the seizure as it occurs. Abnormal movements start in one part of the body and then spread to another. A hand or foot may be affected first and then spread up the limb. These seizures may involve movements that seem to have a purpose. The movements might be turning the head, mouth and eye movements, lip smacking, drooling, and rhythmic muscle contractions in a part of the body. Abnormal numbness, tingling, and a crawling feeling on the skin may occur.

How Are Partial Motor Seizures Diagnosed?

The doctor will make a diagnosis on the basis of the medical history. The doctor may also want to order computed tomography (CT) of the brain or MRI, and a brain wave study called electroencephalography, or EEG. These tests may tell the doctor whether the seizures have a known cause.

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How Are Partial Motor Seizures Treated?

The main treatment for seizures is medicine. Sometimes more than one antiseizure or anticonvulsant drug may be used. The doctor may have to get regular blood samples to make sure that the correct dose of medicine is given. The dose schedule may be adjusted to achieve the blood level of medicine that protects against more seizures. Several different medicines may be used, and the doctor will describe the side effects related to each one prescribed. Often, the medicine will reduce the frequency and severity of the seizure. Some people, even though they're taking drugs, continue to have seizures.

People newly diagnosed with epilepsy should take precautions until they are sure that the disorder is controlled. When living alone, they should arrange for someone to stay with them until the doctor believes that it's safe to live alone again.

DOs and DON'Ts in Managing

Partial Motor Seizures:

✓ **DO** take your medicine as your doctor prescribed to prevent seizures.

✓ **DO** wear an ID bracelet saying that you have a seizure disorder and listing the drugs that you take.

✓ **DO** teach your family and friends about your disorder and what to do if you have a seizure.

✓ **DO** call your doctor if you have problems with your medicines.

✓ **DO** call your doctor if your seizures become more frequent or severe.

⃠ **DON'T** operate dangerous machinery or drive unless your doctor has approved.

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⦸ **DON'T** swim alone.

⦸ **DON'T** climb on ladders or roofs or anything that may be dangerous if you have a seizure.

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FOR MORE INFORMATION

Contact the following sources:

- Epilepsy Foundation of America Tel: (800) EFA-1000 (332-1000) **Website:** **http://www.epilepsyfoundation.org**
- American Academy of Neurology **Website:** **http://www.neurology.org**

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MANAGING YOUR

PATELLAR TENDINITIS

What Is Patellar Tendinitis?

The kneecap (patella) moves up and down, tilts, and rotates. The patellar tendon connects the kneecap to the shinbone. This tendon, made of tough string-like bands, is very strong. It helps the quadriceps muscles straighten the leg when kicking a ball, pushing bicycle pedals, and jumping up.

Patellar tendinitis is an injury of this tendon. It's often called jumper's knee because it's most common in athletes in sports with a lot of jumping, running, and stopping and starting (basketball, soccer, volleyball). Anyone can have it, however.

What Causes Patellar Tendinitis?

The causes include overuse of the knee during activities involving intense running, jumping, frequent stops and starts, and frequent knee impacts. Such sports include basketball, soccer, and volleyball. Repeated stress causes tiny tears in the tendon, possibly with inflammation (swelling, redness). Other causes are tight quadriceps muscles, being overweight, raised kneecap, muscle imbalance, and problems in alignment of hips, legs, knees, or feet.

What Are the Symptoms of Patellar Tendinitis?

Pain (sharp or dull) may usually be felt in the patellar tendon before, during, or after physical activity. It can make going up and down stairs painful or make it hard to sleep. Swelling, tenderness, aching and stiffness after activities, and calf weakness may occur.

How Is Patellar Tendinitis Diagnosed?

The doctor will make a diagnosis from the medical history and physical examination. Ultrasonography and maybe x-rays, magnetic resonance imaging (MRI), and other tests may be

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done if the diagnosis is unclear.

How Is Patellar Tendinitis Treated?

First treatments are conservative: rest, strengthening the tendon and nearby muscles, and stretching exercises for muscles (quadriceps, hamstrings). Ice wrapped in a towel can be put on the knee. Extracorporeal shock wave therapy, bracing with a patellar tendon strap, and sports massage can help but may not heal the tendon. Physical therapists can work on the body's mechanics and alignment. Prevent injury by exercising to maintain leg muscle strength, flexibility, and endurance and by using good training methods. Surgery is used as the last resort.

Over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen or naproxen, help inflammation and pain. These drugs can cause stomach problems and should be taken with meals. People who have ulcers or bleeding ulcers should check with the doctor before using these drugs.

DOs and DON'Ts in Managing Patellar Tendinitis:

✓ **DO** take your medicines as prescribed.

✓ **DO** stop the activity that causes pain. Restart the activity that caused the pain very carefully.

✓ **DO** put ice on your knee after workouts or games.

✓ **DO** continue exercises that you learn in physical therapy to make quadriceps and hamstrings stronger and more flexible.

✓ **DO** call your doctor if you tried self-care conservative treatment and still have symptoms.

✓ **DO** call your doctor if you are doing physical therapy or rehabilitation and your symptoms

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worsen.

✓ **DO** call your doctor if you have side effects from medicines.

⃠ **DON'T** use NSAIDs if you had bleeding ulcers.

⃠ **DON'T** continue the offending activity, such as running. You can worsen the injury or damage the joint itself.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website: http://www.aaos.org**
- American College of Sports Medicine Tel: (317) 637-9200 **Website: http://www.acsm.org**
- National Athletic Trainers' Association Tel: (800) 879-6282 **Website: http://www.nata.org**

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MANAGING YOUR

PATELLOFEMORAL PAIN SYNDROME

What Is Patellofemoral Pain Syndrome?

The kneecap (patella) moves up and down, tilts, and rotates. Patellofemoral pain syndrome is pain under and around the kneecap from changes in the patellofemoral joint. One or both knees can have it. High-impact sports such as football, basketball, soccer, tennis, and running can worsen kneecap problems. Running on uneven surfaces (hills or trails) or playing on different surfaces (grass and hard tennis courts) may also lead to this syndrome. Even sitting for long periods can hurt (movie-goer's knee).

What Causes Patellofemoral Pain Syndrome?

The causes include weak quadriceps muscles (front of the thigh), tight hamstrings (back of the thigh) or calf muscles, and weak or tight hip muscles. It's an overuse syndrome and can affect active people such as runners. It's also an overload syndrome because it affects inactive people (who are overweight).

What Are the Symptoms of Patellofemoral Pain Syndrome?

Dull, aching kneecap pain occurs with activity and often worsens when going down steps or hills or when sitting. The knee can catch when bending. A painful grating or creaking feeling can occur.

How Is Patellofemoral Pain Syndrome Diagnosed?

The doctor will make a diagnosis from the medical history and physical examination. X-rays of the knees, magnetic resonance imaging (MRI), and arthroscopy may be done when diagnosis is unclear. In arthroscopy, the doctor puts a tiny camera into the knee to see inside.

How Is Patellofemoral Pain Syndrome Treated?

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First treatments are rest, quadriceps strengthening exercises, and icing (especially after exercise, used for 10 to 20 minutes). If possible, change to nonimpact aerobic activities, such as swimming or elliptical exercise machines. Hip, hamstring, calf, and iliotibial band stretching exercises may also help. It's important to wear the right footwear, such as running shoes with extra cushioning and arch supports. Most runners, for example, change shoes every 300 to 500 miles. Orthotics, knee sleeves, and braces may be of benefit. Surgery is the last resort. Recovery can take up to 6 weeks.

Over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen or naproxen, help inflammation (swelling, redness) and pain. These drugs can cause stomach problems and should be taken with meals. People who have ulcers or bleeding ulcers should check with the doctor before using these drugs.

Kneecap pain can often be managed with physical therapy to strengthen quadriceps muscles and stretch hamstring and calf muscles.

DOs and DON'Ts in Managing Patellofemoral Pain Syndrome:

✓ **DO** take your medicines as prescribed.

✓ **DO** stop the activity that causes pain. Restart the activity that caused the pain very carefully.

✓ **DO** continue for life the exercises to strengthen knee, hamstring, and calf muscles that you learn in physical therapy.

✓ **DO** call your doctor if you tried conservative treatment on your own and still have symptoms.

✓ **DO** call your doctor if you are doing physical therapy or rehabilitation and your symptoms

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worsen.

✓ **DO** call your doctor if you have side effects from medicines.

⃠ **DON'T** use NSAIDs if you had bleeding ulcers.

⃠ **DON'T** do bent-knee exercises, such as squats, deep knee bends, or 90-degree leg extensions.

⃠ **DON'T** continue the offending activity, such as running. You can worsen the injury or damage the joint itself.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website: http://www.aaos.org**
- American College of Sports Medicine Tel: (317) 637-9200 **Website: http://www.acsm.org**
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MAKING YOURSELF AWARE OF AND UNDERSTANDING

PEDOPHILIA

What Is Pedophilia?

Pedophilia is a sexual disorder that involves repeated, intense, distressing sexual urges and/or fantasies about children. A person must be at least 16 years old and at least 5 years older than the child affected. Behaviors include looking, fondling, masturbation, and forcing sex. In the United States, 2% of men and 17% of women report being touched in a sexual way during childhood by an older person. Most pedophiles are men, with 75% being attracted to only girls and 25% attracted to only boys. Girls are sexually abused three times more often than boys. Children from families with the lowest income are 18 times more likely to be sexually abused. One of every seven sexual assaults of youngsters occurs in children younger than 6. One-third are younger than 12.

What Causes Pedophilia?

The cause is unknown. Most experts think that psychosocial, not biological factors, are involved. Some say personality factors influence pedophiles. Such factors include problems with attachment that may depend on having a dysfunctional family. Being molested at a young age may be important. However, only certain molested children develop pedophilia.

What Are the Signs and Symptoms of Pedophilia?

Pedophiles are often attractive to their victims, have good interpersonal skills with children, and easily gain their trust. They may volunteer with athletic teams, Scout troops, or community organizations. They may offer to baby-sit for relatives. Some pedophiles blame children for being too attractive. They may say that they're "teaching" a child about love. They may have other mental disorders such as anxiety, major depression, mood disorders, and substance abuse

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disorders.

Sexually abused children may be depressed, aggressive, and anxious. They may have problems with the right sex roles for their age.

How Is Pedophilia Diagnosed?

Diagnosis is difficult because most pedophiles don't talk about their feelings, even with health care providers who ask direct questions. A good personal history is critical for diagnosis. Other information should be collected from family members, possible victims, or legal and social organizations. Even experienced interviewers may be unable to diagnose pedophilia all the time.

How Is Pedophilia Treated?

Pedophilia is a chronic disorder. Treatment should focus on making long-term behavioral changes. Behavioral therapy includes aversion conditioning, in which something unpleasant is paired with the fantasy. Outpatient group therapy and medicines that lower sexual desire are sometimes combined. Chemical castration with medicines works for most people. These drugs include medroxyprogesterone acetate. Testosterone-lowering medicines and serotonin reuptake inhibitors can also be used. Other conditions, such as alcoholism or substance abuse, must be treated.

In treating child abuse, the most important goal is protection of the child. Medical consequences of abuse must be treated, and children should have therapy for the abuse. Brief periods of hospitalization may sometimes be needed for great stress from the abuse.

DOs and DON'Ts in Managing Pedophilia:

✓ **DO** remember that if untreated, pedophiles are highly likely to be repeat offenders.

✓ **DO** remember that episodes of abuse should be reported to the police and your health care

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provider. They should be investigated.

⦸ **DON'T** ignore problems in your family. Even family members should be reported.

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FOR MORE INFORMATION

Contact the following sources:

- American Psychiatric Association Tel: (888) 357-7924 **Website: www.psych.org**
- American Psychological Association Tel: (800) 374-2721 **Website: www.apa.org**
- There are several commercial videos available through your local library or children's hospital. The book entitled *How to Raise a Street Smart Child* is particularly helpful.
- Local Child Protective Hotline Phone: 800-422-4453
- Childhelp USA Phone: 480-922-8212 **Website: www.childhelpusa.org**

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MANAGING YOUR

PELVIC ABSCESS

What is a Pelvic Abscess?

An abscess is a walled-off collection of pus caused by an infection that can occur in any part of the body. Pelvic abscesses occur in the pelvis. They can be a complication of a hysterectomy or childbirth. They are seen in about one third of women admitted to the hospital with pelvic inflammatory disease (PID). It occurs most frequently in women between 30 and 40 years old.

What Causes Pelvic Abscesses?

Bacteria (aerobic and anaerobic) are most often the cause. Aerobic bacteria grow only when oxygen is present. Anaerobic bacteria grow without oxygen. Common bacteria include *Escherichia coli, Bacillus fragilis, Prevotella* species, streptococci, *Peptococcus*, and *Peptostreptococcus*. Sometimes, sexually transmitted bacteria causing PID, including *Neisseria gonorrhoeae* (gonorrhea) and nongonorrhea *Chlamydia* cervicitis (infection of the cervix), can also lead to pelvic abscess formation.

In elderly women, a common cause is diverticular disease (a condition affecting the intestine).

Infections can spread from one organ in the pelvic cavity to a nearby organ. Infections such as appendicitis or diverticulitis, can also cause pelvic abscesses.

Risk factors include multiple sexual partners, vaginal douching, use of an intrauterine device, and previous gonorrhea.

What Are the Symptoms of Pelvic Abscess?

Almost all people complain of pain in the abdomen (belly). Other symptoms may include fever, chills, nausea, vomiting, abdominal bleeding, discharge from the vagina, and pain during examination.

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How is a Pelvic Abscess Diagnosed?

The doctor will make a diagnosis from the medical history and physical examination. Blood tests, cultures, and x-ray studies will be done to confirm the diagnosis. The doctor may also order pelvic ultrasonography and computed tomography.

How Are Pelvic Abscesses Treated?

Treatment can be medical or surgical. Medical management includes using antibiotics, which may be given in the hospital. Antibiotic treatment alone may not be effective in people with large pelvic masses (larger than 3 inches) or severe infections, high fever, high white blood cell count, and larger abscesses. If medical treatment doesn't help, a surgeon can drain the abscess. Drainage can often be done with a long needle put into the abscess with the help of CT scan to position it in the correct spot. In some cases, surgery is needed to drain or remove the abscess and infected organs. Rupture of a pelvic abscess is life-threatening and needs immediate surgery.

DOs and DON'Ts in Managing Pelvic Abscesses:

✓ **DO** remember that about three quarters of people treated with antibiotics get better with antibiotics alone. Those who don't are usually treated with drainage or surgery.

✓ **DO** call your doctor if you have abdominal pain, vaginal bleeding or discharge, or fever and chills.

✓ **DO** call your doctor if you think you have a sexually transmitted disease.

⃠ **DON'T** forget that a pelvic abscess may be hard to diagnose because it may act like other diseases, such as tumors (e.g., ovarian tumors) and blood clots in the pelvic cavity.

⃠ **DON'T** forget that the people with pelvic abscesses have greater chances of abscess rupture

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that can lead to sepsis (major infection), peritonitis (inflammation of abdominal and pelvic lining), shock, and death. Another complication in young women with PID is problems getting pregnant, because of scarring of fallopian tubes.

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FOR MORE INFORMATION

Contact the following source:

- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website:** **http://www.acog.org**

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MANAGING YOUR

PELVIC INFLAMMATORY DISEASE

What Is Pelvic Inflammatory Disease?

Pelvic inflammatory disease (PID) is an infection of a woman's reproductive organs. The infection spreads up through the cervix (opening of the uterus), into the uterus, fallopian tubes, ovaries, and lowest part of the abdomen (belly, pelvic area). Infection tends to spread most easily during a period.

PID diagnosed and treated early usually has no long-term complications. However, PID can scar fallopian tubes and ovaries, making it hard to get pregnant or causing an ectopic pregnancy (fetus grows in a fallopian tube).

What Causes PID?

The cause is usually having sex with a person infected with gonorrhea or chlamydia, or other sexually transmitted diseases (STDs). Chances of getting PID increase with a new sexual partner, or more than one partner, and using an intrauterine device (IUD) for birth control.

What Are the Symptoms of PID?

The most common symptoms are pelvic pain, with or without fever and increased vaginal discharge.

How Is PID Diagnosed?

The doctor makes a diagnosis from symptoms plus a physical and pelvic examination and laboratory tests. Blood tests will show if an infection is present. In premenopausal women, a pregnancy test should be done before starting treatment. Sometimes, symptoms of an ectopic pregnancy are the same as PID symptoms, and the doctor needs to know which is causing symptoms. Other tests to check for infection include a culture from the cervix. For a culture, the cervix is swabbed,

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as for a Pap smear, and tested.

Imaging tests may also be done to get pictures of inside the body and exclude other medical disorders causing similar symptoms. These tests include ultrasonography (uses sound waves), magnetic resonance imaging (MRI), and computed tomography (CT).

How Is PID Treated?

Early treatment is best, before the infection spreads.

The doctor may prescribe a combination of antibiotics given by injection and taken by mouth (oral), or just oral antibiotic. Severe infections may first need a hospital stay and antibiotics given intravenously.

For a pocket of pus around a fallopian tube or an ovary that doesn't get better with antibiotics, the doctor may operate (usually laparoscopic surgery) to drain the pus. Laparoscopic surgery is done through a special lighted tube put into a small cut in the belly.

DOs and DON'Ts in Managing PID:

✓ **DO** take all antibiotics as directed.

✓ **DO** have your sexual partner get treatment so you don't infect each other.

✓ **DO** call your doctor if your symptoms aren't better in 48 hours or symptoms worsen even with treatment, for example, if fever is higher or pelvic pain is worse.

✓ **DO** call your doctor if you cannot tolerate the antibiotic (e.g., you throw up afterward).

✓ **DO** call your doctor if you think that you're allergic to the medicine.

⃠ **DON'T** have unprotected sex. Use condoms for protection against STDs.

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⦸ **DON'T** have sex until symptoms are gone completely or until your doctor says you can.

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Contact the following sources:

- National Institute of Allergy and Infectious Diseases Tel: (866) 284-4107 **Website:** **http://www3.niaid.nih.gov**
- American Academy of Family Physicians Tel: (800) 274-2237 **Website:** **http://www.aafp.org**
- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website:** **http://www.acog.org**

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MANAGING YOUR

PELVIC ORGAN PROLAPSE

What Is Pelvic Organ Prolapse?

The uterus, bladder, and rectum near the vaginal canal can push through (prolapse) into this canal. A bulging uterus is called uterine prolapse. A bladder prolapse is a cystocele. A prolapsed rectum is a rectocele. The prolapsed organ can cause tissue to bulge out of the vagina. Women may first notice something like a ball of tissue coming out of the vagina. Most rectoceles occur in women. Rarely, men may have rectoceles.

What Causes Pelvic Organ Prolapse?

The most common cause is childbirth because it stretches muscles that support pelvic organs. Normal aging and menopause (change of life) contribute to prolapse. Levels of estrogen, which strengthen muscles near the bladder, rectum, and vagina, decrease with menopause. Being overweight, lifting heavy objects, having long-lasting cough, straining during bowel movements (from constipation), and cancers also cause prolapses.

What Are the Symptoms of Pelvic Organ Prolapse?

Mild or moderate prolapses may cause pelvic pressure, low backache, pain, or feeling that something is falling out. Urine may leak, especially with coughing, sneezing, or laughing. Rectoceles can cause bowel movement problems.

Severe prolapses also cause a feeling of fullness in the abdomen (belly) or a bulge that may go away when lying down. Other symptoms are problems emptying the bladder or having bowel movements, pelvic pain, abdominal discomfort, urgent or painful urination, and problems during sex.

How Is Pelvic Organ Prolapse Diagnosed?

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The doctor will make a diagnosis from a physical examination, including a pelvic exam. Urine and blood tests may be done. Ultrasonography and voiding cystogram (cystourethrogram) may also be done. The cystogram is an x-ray taken during urination to show bladder shape.

How Is Pelvic Organ Prolapse Treated?

More severe prolapses with pelvic organ bulges need treatment. Mild to moderate prolapses (no organ bulges) and no symptoms need no treatment, just watching. Straining during bowel movements, heavy lifting, coughing, and constipation should be avoided. Eating high-fiber foods can help constipation. Kegel exercises involve tightening pelvic floor muscles and can help symptoms. These exercises strengthen muscles supporting the bladder and vagina. If Kegel exercises don't help, physical therapy (biofeedback, electrical stimulation) may. If all these treatments don't work, a pessary (plastic or rubber ring fitted into the vagina) can hold the bladder in place. Women after menopause may take hormone replacement therapy to help strengthen muscles. Surgery can be done when the pessary doesn't fit properly or if there is more than one prolapsed organ. Surgery may hold the bladder in the correct position.

DOs and DON'Ts in Managing Pelvic Organ Prolapse:

✓ **DO** Kegel exercises as directed. Do them when you lift anything heavy (books, luggage, groceries, baby) or when you cough, sneeze, or laugh.

✓ **DO** call your doctor if you have trouble emptying your bladder, you see vaginal bleeding, or your pessary falls out or isn't comfortable.

✓ **DO** eat a healthy diet with lots of fiber, fruits, and vegetables and drink plenty of liquids to prevent constipation.

✓ **DO** treat chronic cough. Don't smoke. Smoking can cause chronic cough.

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✓ **DO** keep to a healthy body weight.

⃠ **DON'T** lift heavy objects (more than 20 to 25 pounds).

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MANAGING

PEMPHIGUS VULGARIS

What Is Pemphigus Vulgaris?

Pemphigus vulgaris is a serious blistering disease of the skin and mucous membranes. It has large blisters (bullae) that break down and form crusts.

Pemphigus vulgaris is rare. It affects men and women equally, usually adults 40 to 60 years old.

What Causes Pemphigus Vulgaris?

Pemphigus vulgaris is likely an autoimmune illness. Autoimmune means that the body's own immune system attacks the body and causes disease. Certain drugs can trigger it. It's not an infection or cancer.

What Are the Symptoms of Pemphigus Vulgaris?

Painful ulcers of the mucous linings of the mouth, nose, throat, vagina, and anus are the first symptoms. Many people cannot eat because of the mouth blisters, become weak and tired, and lose weight. Dehydration and malnutrition can result.

The skin may not be affected for months. Skin lesions are usually small blisters (vesicles) and larger ones (bullae) that are flabby, easily broken, and weeping. As bullae burst, they weep fluid, bleed easily, and crust. These lesions can get bacterial infections. Scarring can also occur. Irritated mucous membranes can cause trouble swallowing, painful swallowing, and bleeding.

How Is Pemphigus Vulgaris Diagnosed?

The doctor makes a diagnosis from the look of the lesions and blood and skin tests. The doctor may do a skin biopsy (remove a small piece of skin) for study in the laboratory.

How Is Pemphigus Vulgaris Treated?

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Pemphigus vulgaris can be fatal in rare cases if not treated aggressively. Immunosuppressive medicines lessen effects of the immune attack; reduce blisters, inflammation, and pain; and promote healing. These medicines include corticosteroids, intravenous immune globulins, and immunosuppressants such as methotrexate and cyclophosphamide. Talc or powder for wounds and bed linens (plus antibiotic ointments put on the skin) can reduce symptoms.

Severe illness needs other measures, including intravenous fluids, surgical removal of dead tissue (débridement), antibiotics for serious bacterial infections, and intensive wound care. Plasmapheresis is also used with medicines. In plasmapheresis, blood is taken from the body and put into a machine to remove antibodies causing pemphigus vulgaris. Healthier blood is then put back into the body. These measures often mean hospitalization.

Eating a healthy diet is important. Cleaning and watching wounds can prevent infections.

DOs and DON'Ts in Managing Pemphigus Vulgaris:

✓ **DO** take medicines as prescribed. Follow all instructions. Tell your doctor about all your medicines (including over-the-counter).

✓ **DO** eat a well-balanced diet. Follow a liquid or soft diet if needed.

✓ **DO** keep follow-up doctor appointments.

✓ **DO** use cleaning baths, wound care, and dressings as directed.

✓ **DO** check your lesions carefully. Call your doctor if you have signs of bacterial infection, such as redness, pus, pain or swelling, and fever.

✓ **DO** clean towels, linens, and clothing often.

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✓ **DO** call your doctor if you have symptoms of another illness (fever, confusion, weakness).

⃠ **DON'T** stop your medicines or change the dose unless your doctor says you can.

⃠ **DON'T** stop taking steroids or immunosuppressants suddenly, to avoid a rebound worsening of your condition.

⃠ **DON'T** share towels, linens, or clothing with other people.

⃠ **DON'T** swim or use a Jacuzzi until your doctor says you can.

⃠ **DON'T** do activities that may contaminate skin wounds.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Dermatology Tel: (866) 503-SKIN (503-7546) **Website:** **http://www.aad.org**

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MANAGING YOUR

PEPTIC ULCER

What Are Peptic Ulcers?

Peptic ulcers are small open sores in the stomach or upper intestine. Sores occur when the lining of the stomach or intestine breaks down and exposes tissue underneath. Ulcers may be gastric (stomach) or duodenal (first 12 inches of the small intestine). Duodenal ulcers occur four times more often than gastric ulcers. Peptic ulcer disease (PUD) is common.

What Causes Peptic Ulcers?

Three things cause most peptic ulcers: infection with a bacterium named *Helicobacter pylori* (*H. pylori*), taking aspirin or similar medicines (nonsteroidal antiinflammatory drugs, or NSAIDs, such as ibuprofen), and too much acid secretion. Ulcers aren't contagious but may run in families. Smoking increases the risk of stomach ulcers.

What Are the Symptoms of Peptic Ulcers?

The main symptom is stomach pain that feels like heartburn, indigestion, or hunger. A burning, boring, or gnawing feeling can last from 30 minutes to 3 hours. It's usually felt in the upper stomach area, but it sometimes occurs below the breastbone. Pain usually happens when the stomach is empty. It can also occur right after eating or hours later, depending on the location of the ulcer.

Complications include bleeding and perforation (hole in the stomach or duodenum). Black, tarry stools and vomiting with blood or with what looks like "coffee grounds" material (blood mixed with stomach acid) indicate bleeding ulcers.

How Are Peptic Ulcers Diagnosed?

The doctor will suspect PUD from the medical history and physical examination. The doctor

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may order blood and stool tests. Endoscopy or barium x-rays may be done. For endoscopy, the better test, the doctor uses a lighted tube to see into the stomach and take a tissue sample for study. Tests will be done to see whether the stomach or duodenum has *H. pylori* infection.

How Are Peptic Ulcers Treated?

Treatment heals the ulcer, helps symptoms, stops relapses, and avoids complications. With treatment, people usually start to feel better in about 2 weeks. Relapses can occur if the risk factors persist.

Two treatment options are drugs and surgery. Medicines to reduce stomach acid include antacids, histamine-2 blockers such as ranitidine or famotidine, and proton pump inhibitors such as omeprazole. Sucralfate is another medication that can form a protective coating on the ulcer to help it heal. Antibiotics, proton pump inhibitors, and bismuth can be used for *H. pylori* infection.

Surgery is used when drugs don't work or serious complications occur. Today, surgery is rarely needed.

DOs and DON'Ts in Managing Peptic Ulcers:

✓ **DO** avoid things that increase the risk of PUD: aspirin, NSAIDs, smoking, and drinking alcohol.

✓ **DO** call your doctor if you have diarrhea.

✓ **DO** call your doctor if your vomit is bloody or looks like coffee grounds.

✓ **DO** call your doctor if blood is in your stools or stools are dark and tarry.

✓ **DO** call your doctor if you are unusually weak or pale.

✓ **DO** call your doctor if pain doesn't get better with treatment.

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⦸ **DON'T** change your medicine or dosage because you feel better unless your doctor tells you to.

⦸ **DON'T** smoke. Get help finding a smoking cessation program.

⦸ **DON'T** drink caffeine and eat foods that make symptoms worse.

⦸ **DON'T** drink alcohol.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Gastroenterology Tel: (703) 820-7400 **Website:** **http://www.acog.org**
- National Digestive Diseases Information Clearinghouse Tel: (800) 891-5389 **Website:** **http://www.niddk.nih.gov/health/digest/nddic.htm**

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MANAGING YOUR

PERCUTANEOUS CORONARY INTERVENTION

What Is Percutaneous Coronary Intervention?

Percutaneous coronary intervention (PCI) is also called coronary angioplasty, percutaneous transluminal coronary angioplasty, and balloon angioplasty. It's used to open clogged heart arteries (atherosclerosis), and it's successful in almost all people. Atherosclerosis refers to a slow buildup of fatty plaques in the heart's blood vessels. In PCI, a tiny balloon is temporarily put into an artery to widen it. PCI is often combined with use of a stent, which is a small tube of wire mesh that props open the artery and stop it from narrowing again (restenosis). Some stents are coated with medicine to help keep the artery open (drug-eluting stents); others are not (bare-metal stents).

Who Needs PCI?

People with chest pain (angina), shortness of breath, or heart attack (acute myocardial infarction, or MI) caused by a blood clot, and others with blocked coronary arteries with or without symptoms that can benefit from PCI.

How Is PCI Done?

The procedure, without general anesthesia, can take 30 minutes to hours. First, an imaging test (coronary angiography) is done to make sure that the main arteries to the heart are narrowed or blocked and can be treated with PCI. In angiography, a very small cut is made in a blood vessel, usually in the groin (femoral artery). A catheter (long, thin tube) is pushed through that artery to heart arteries. Dye is put into the arteries through the catheter.

Then, a small balloon at the catheter end is inflated, widening the blocked artery. The balloon stays inflated to stretch the artery before it's deflated and removed. Most people also have a stent

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put in the blocked artery during PCI. The balloon at the tip of a special catheter helps place the stent.

PCI with stenting can reduce angina or other symptoms of coronary artery disease by keeping the artery open.

What Are the Risks of PCI?

Risks include renarrowing of the artery (restenosis), blood clots, bleeding, MI, coronary artery damage, kidney problems, stroke, and abnormal heart rhythms.

The most frequent complications relate to the spot where the catheter is put into the artery, where bleeding may occur. Heart and blood vessel complications (such as blockage or puncture) are rare.

DOs and DON'Ts in Managing PCI:

✓ **DO** understand the risks. Talk to your doctor about the test and about cardiovascular health.

✓ **DO** make sure that your doctors have experience with PCI.

✓ **DO** call your doctor or hospital staff immediately if you have bleeding, swelling, or pain at the catheter insertion spot. Call if you have signs of infection, such as redness, swelling, drainage, or fever. Call if you feel faint or weak or you have chest pain or shortness of breath.

✓ **DO** make lifestyle changes to be heart healthy: quit smoking, lower your cholesterol levels, keep to a healthy weight, control other conditions such as diabetes and high blood pressure, and exercise regularly.

⦸ **DON'T** smoke or eat fatty foods.

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⦸ **DON'T** forget to take medication prescribed daily by your doctor to keep the artery open.

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:**

  http://www.americanheart.org

- American College of Cardiology Tel: (800) 253-4636 **Website: http://www.acc.org**

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MANAGING YOUR

PERICARDITIS

What Is Pericarditis?

The pericardium is the thin fibrous sac that covers the heart. This sac-like membrane helps hold the heart in position in the chest and lubricate the heart. Pericarditis is inflammation of the pericardium. It can be acute (sudden) or chronic (long-lasting). This inflammation may injure the membrane and cause complications. The pericardium can become scarred and thickened and the heart can be constricted (squeezed) (constrictive pericarditis). It may also cause another complication, reduced blood flow from the heart (cardiac tamponade). This occurs when too much fluid collects in the pericardium, so excess pressure on the heart doesn't let it fill correctly. Blood pressure and heart output can fall to dangerous levels. Untreated, cardiac tamponade can cause death.

More men than women are affected, often 20 to 50 years old. Most people recover in 2 weeks to 3 months. Early diagnosis and treatment may prevent complications.

What Causes Pericarditis?

The cause is often a viral infection. Other causes include myocardial infarctions (heart attacks), cancer, radiation, other infections (such as tuberculosis, fungal, and parasitic), trauma, medicines, and allergic reactions. It may have no known cause (idiopathic pericarditis).

What Are the Symptoms of Pericarditis?

Symptoms include sharp chest pain behind the sternum (breast bone) that may go to the shoulder and neck. Some people have dull, achy pain or pressure. Pain worsens with changes in position or with deep breathing. The pain is lessened by sitting forward. A fever may occur if infection is causing the pericarditis. Sometimes people feel palpitations (irregular or rapid heartbeats). Con-

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strictive pericarditis can lead to severe swelling (edema) of the legs and abdomen (belly) and shortness of breath. Reduced blood flow from the heart causes symptoms of heart failure, including problems breathing and swelling in tissues of the legs, feet, or abdomen. The neck veins may also appear distended or very prominent.

How Is Pericarditis Diagnosed?

The doctor makes a diagnosis from symptoms, a physical examination, and tests. Electrocardiography (ECG) may show signs of the inflammation. A chest x-ray may show an enlarged heart if fluid collects around the heart. Echocardiography may show fluid in the pericardial sac. Echocardiography is a type of ultrasound examination that uses sound waves to see the heart. The doctor may also order computed tomography (CT) or magnetic resonance imaging (MRI) if complications from pericarditis are suspected. Blood tests may be done to measure inflammation and look for infection.

How Is Pericarditis Treated?

Treatment focuses on the cause of the inflammation and pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen are given for pain. In more severe cases, steroidal antiinflammatory drugs such as prednisone may be used. If fluid in the pericardium affects how the heart works, an operation may be done to release the pressure. A window is cut in the membrane to let fluid drain out. For severe complications such as cardiac tamponade, the doctor must drain fluid from the sac (pericardiocentesis).

DOs and DON'Ts in Managing Pericarditis:

✓ **DO** take your medicines as prescribed.

✓ **DO** call your doctor if you have new or worsening chest pain or pain with deep breaths or

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changes in position.

⦸ **DON'T** exert yourself until after your symptoms have gone away.

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MANAGING YOUR

PERIPHERAL ARTERIAL DISEASE

What Is Peripheral Arterial Disease (PAD)?

Peripheral arterial disease (PAD) refers to blockage of leg arteries by atherosclerosis (hardening of the arteries), so legs have poor blood flow. In atherosclerosis, cholesterol plaques block arteries. PAD occurs in men and women equally. It likely affects 8 to 10 million people in the United States.

What Causes PAD?

Fatty deposits build up inside arteries and make them narrower. Tobacco, diabetes, cholesterol, and high blood pressure make PAD likely. PAD isn't contagious or passed from parents to children.

What Are the Symptoms of PAD?

About half of people don't have symptoms. The most common symptoms are pain, cramping, aching, and numbness in the affected area. Others are heavy or tight feeling, cold skin, pale or bluish skin, pulse that's hard to feel, and sores or ulcers that don't heal. Aching or cramping leg pain often occurs during exercise and goes away during rest (intermittent claudication). If blood flow is completely blocked, the leg gets very painful and hard to move. In men, impotence can occur if vessels leading to the penis are affected.

How Is PAD Diagnosed?

The doctor makes a preliminary diagnosis from your symptoms, a physical examination, fasting blood tests, and by measuring the ankle-brachial index (ABI). The doctor gets the ABI by dividing the highest ankle blood pressure by the highest arm blood pressure. ABI values less than 1 are abnormal.

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A treadmill test, Doppler ultrasound, angiography (a kind of x-ray with dye), and magnetic resonance angiography (MRA) may also be done to evaluate the extent of the disorder and areas of blockage.

How Is PAD Treated?

Treatment goals are to reduce pain and prevent damage to the affected area. Measures include avoiding tobacco, eating a healthy diet, and restricting salt. Diabetics should follow the American Diabetes Association (ADA) diet. Exercise such as walking 30 to 60 minutes per day helps walking distance and quality of life.

Medicines can help blood flow, thin blood, dissolve clots, lower blood pressure, and lower cholesterol levels.

The doctor may suggest angioplasty for a severely narrowed vessel. The doctor puts a wire (catheter) into the artery and inflates a tiny balloon to open the blocked artery. The doctor may put a small metal or mesh tube (stent) into the vessel to keep it open.

People sometimes need bypass surgery to get around the blockage. A procedure called percutaneous atherectomy can also be performed to remove the blockage by inserting a "plaque-eating" device in the blocked artery and shaving off the plaque. In the most advanced stages, PAD may lead to amputation.

DOs and DON'Ts in Managing PAD:

✓ **DO** understand that lifestyle changes for cholesterol, diabetes, hypertension, and tobacco are critical.

✓ **DO** eat a healthy diet, with less fat, especially saturated fat, and less salt. Eat plenty of fruits, vegetables, and whole-grain cereals.

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✓ **DO** lose weight.

✓ **DO** get active. Walk for 20 to 30 minutes daily.

✓ **DO** take extra care with controlling your blood sugar if you have diabetes.

✓ **DO** take care of your feet. Examine them regularly, and avoid getting cuts or blisters. Call your doctor if you have a foot ulcer that doesn't heal.

⊘ **DON'T** smoke. Smoking is the biggest single risk factor for PAD and a major risk factor for heart attack and stroke.

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FOR MORE INFORMATION

Contact the following sources:

- The National Heart, Lung, and Blood Institute Tel: (301) 592-8573 **Website:** **http://www.nhlbi.nih.gov**
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MANAGING YOUR

PERIPHERAL NEUROPATHY

What Is Peripheral Neuropathy?

Neuropathy, also called neuralgia, means nerve disease or damage. Nerves are made of fibers that affect pain sensation, movement, and balance. Peripheral nerves take messages from the brain and spinal cord to muscles, organs, and other body tissues. Damage may mean being more sensitive to things that are painful (such as pinpricks) or not painful (such as light touch). The first is called hyperalgesia; the second, hyperesthesia. Allodynia is pain caused by something that's not normally painful. From 1.6% to 8.2% of the general population have neuropathy.

What Causes Peripheral Neuropathy?

Many causes exist, including direct injury and pressure on nerves. Metabolic causes include diabetes mellitus, malnutrition, and porphyria. Others are vitamin B deficiencies. Inflammatory causes are lupus, Sjögren's syndrome, polyarteritis nodosa, acute and chronic inflammatory demyelinating polyneuropathy, sarcoid, and multiple sclerosis. Infectious causes are HIV/AIDS, herpesvirus, varicella-zoster virus (postherpetic neuralgia), Lyme disease, leprosy, and syphilis. Rare cancer of nerves can also cause neuropathy. Alcohol, chemotherapeutic drugs, isoniazid, metronidazole, and heavy metals (arsenic) are other causes of neuropathy.

What Are the Signs and Symptoms of Peripheral Neuropathy?

Symptoms depend on the nerves and fibers affected. Numbness and tingling in feet and hands may start slowly and spread to legs and arms. People may have burning, hot or cold, "icy hot," pins and needles, stinging, shooting (lancinating), or sharp feelings. Extreme sensitivity to even light touch can occur. Affected limbs may be numb and weak. Muscle tissue may be lost (muscle atrophy) if the neuropathy has been present for a prolonged period. Spinal cord involvement may

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mean the urinary bladder and bowel problems.

How Is Peripheral Neuropathy Diagnosed?

The health care provider makes a preliminary diagnosis from the medical history and physical examination. Laboratory tests, magnetic resonance imaging (MRI) of the brain and spinal cord and special tests including nerve conduction studies and electromyography (EMG), nerve biopsy, and lumbar puncture may be done to confirm the diagnosis and determine the cause. The health care provider may suggest seeing specialists (neurologist, physical therapist, pain management specialist) for additional evaluation and treatment.

How Is Peripheral Neuropathy Treated?

Symptoms often improve with time, especially if causes can be treated. For example, better control of blood sugar (glucose) can lower the risk of diabetic neuropathy. Vitamin B_{12} supplements can help with vitamin B_{12} deficiency. Medicines used for treatment of painful neuropathy include antidepressants, antiepileptics, and analgesics. Counseling may help deal with psychologic issues that make pain worse. Physical therapy helps, especially for chronic neck and low back pain. Acupuncture and biofeedback can also be tried. Surgery and nerve blocks are options mostly for people having pain from spinal cord injury. Surgery is usually used when other treatments don't work.

DOs and DON'Ts in Managing Peripheral Neuropathy:

✓ **DO** take care of your feet, especially if you have diabetes.

✓ **DO** keep healthy. Exercise, eat healthy meals, lose weight, and quit smoking.

✓ **DO** avoid repetitive movements, cramped positions, toxic chemicals, and too much alcohol—things that cause nerve damage.

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- ⃠ **DON'T** ignore symptoms. Call your health care provider if your symptoms don't get better or they get worse with treatment. Call if you have new symptoms.
- ⃠ **DON'T** stop taking your medicine or change the dosage because you feel better unless your health care provider tells you to.
- ⃠ **DON'T** use any medicines (including over-the-counter and herbal products) without asking your health care provider.

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FOR MORE INFORMATION

Contact the following sources:

- Neuropathy Association **Website: www.neuropathy.org**
- American Academy of Orthopedic Surgeons Phone:847-823-7186 **Website: www.aaos.org**
- North American Spine Society Phone 708-588-8080 **Website: www.spine.org**
- American Physical Therapy Association Phone 800-999-2782 **Website: www.apta.org**
- National Institute of Neurological Disorders and Stroke Phone: (800) 787-6537 **Website: www.ninds.nih.gov**

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MANAGING YOUR

PERIRECTAL ABSCESS

What Is a Perirectal Abscess?

The rectum is the last part of the large intestine, where stools (bowel movements) are stored before leaving the body through the anal canal and anus. When the rectal space (the perirectal space) and glands in the rectum that make mucus are infected by bacteria, small hollow cavities or holes that fill with pus form. These collections of pus-filled cavities in this area are called perirectal abscesses. Abscesses can also form around the anus and are called perianal abscesses.

Anyone can have a perirectal abscess, but men get them more often than women.

What Causes a Perirectal Abscess?

The most common cause is a bacterial infection from the anal canal into one of the perirectal spaces. All these bacteria are normally found in the bowel (large intestine) and on skin outside the anal canal.

What Are the Symptoms of a Perirectal Abscess?

Symptoms include rectal pain that is lasting, throbbing, and often made worse with movement or straining. Others are fever, constipation, and trouble urinating. Sometimes, a rectal mass can be felt that is red, hot, tender, and swollen.

How Is a Perirectal Abscess Diagnosed?

The doctor makes a diagnosis from symptoms and doing a physical examination. Blood tests and urine tests may also be done.

How Is a Perirectal Abscess Treated?

The main treatment is surgery. People with surface abscesses can be treated as an outpatient with local anesthesia. Deeper abscesses usually need hospitalization. A general surgeon or surgeon

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who specializes in diseases of the colon and rectum does the operation.

Antibiotics are often given but don't substitute for prompt surgery and draining the abscess. Pain after surgery is usually treated by sitting in warm water (called sitz baths) three or four times daily. Medicines can also help relieve pain.

Stool softeners are used to prevent getting constipated and stop straining with bowel movements.

Complications that can occur after surgery include incomplete healing, having the abscess come back, and formation of a fistula. A fistula is a tunnel connecting the skin with the anal gland that the abscess started from. A fistula usually occurs 4 to 6 weeks after abscess drainage and needs surgery to fix it.

DOs and DON'Ts in Managing a Perirectal Abscess:

✓ **DO** get treatment. Untreated perirectal abscesses can spread into other tissues and make the problem worse.

✓ **DO** call your doctor if you have rectal pain and high temperature.

✓ **DO** call your doctor if you notice a mass in your rectum or drainage of pus from your anus.

✓ **DO** call your doctor if you have lasting drainage from your incision, fever, or pain after surgery.

⊘ **DON'T** ignore symptoms. The earlier surgery is done, the less the chances for complications (such as the abscess spreading to nearby tissues).

⊘ **DON'T** miss follow-up doctor appointments. The surgical wound should be checked fre-

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quently to make sure that it heals properly.

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MANAGING YOUR

PERNICIOUS ANEMIA

What Is Pernicious Anemia?

Pernicious anemia is a lack of sufficient red blood cells and hemoglobin because the body doesn't have enough cobalamin (vitamin B12). This vitamin is essential for normal growth and development of red blood cells, other blood cells, and cells in the nervous system. Absorption of vitamin B12 occurs in the part of the small intestine called the ileum. Absorption needs a specific protein (intrinsic factor) made in the stomach.

Pernicious anemia is uncommon. Both sexes are affected equally, most often after age 30. It's more common among people of northern European descent.

What Causes Pernicious Anemia?

Most often, absence of intrinsic factor is the cause, not poor intake of the vitamin. The immune system attacks cells lining the stomach and prevents them from making intrinsic factor. Other ways that people may not have intrinsic factor include absence of part of the stomach after surgery for ulcers or cancer, and certain stomach diseases that interfere with how vitamin B12 is made. Diseases of the small intestine (where vitamin B12 is absorbed), such as tapeworm infestation, Crohn's disease, or tropical sprue, can also cause lack of vitamin B12.

What Are the Symptoms of Pernicious Anemia?

Symptoms of anemia include fatigue and neurological problems. In severe cases, memory impairment, sensory impairment, shortness of breath, and rapid heartbeat occur. Lack of vitamin B12 can also cause problems with feeling and numbness in feet and hands. Severe deficiency can result in severe neurological problems, such as confusion and being disoriented.

How Is Pernicious Anemia Diagnosed?

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The doctor makes a diagnosis with blood tests. Special tests (such as the Schilling test) may be needed to check for abnormal absorption of the vitamin and the presence of specific antibodies.

How Is Pernicious Anemia Treated?

Therapy is injection of vitamin B12 under the skin or into a muscle. Treatment of severe deficiency first involves daily injections followed by weekly and then monthly injections. It takes 4 to 8 weeks to see increased hemoglobin concentration. Treatment is lifelong.

People with poor intake due to special diets can take oral vitamin B12 supplements.

A gel solution of vitamin B12 can also be given by the nose via a metered dose nasal inhaler, once weekly instead of monthly injections. This method is much more expensive and should be used only after first giving vitamin B12 injections until levels are normal.

Vitamin B12 replacement leads to full correction of anemia. People who cannot absorb the vitamin need long-term treatment.

DOs and DON'Ts in Managing Pernicious Anemia:

✓ **DO** continue monthly injections, even if anemia is corrected.

✓ **DO** talk with your doctor if you're pregnant.

✓ **DO** eat a well-balanced diet, rich in folic acid (another vitamin important for the blood cells) and other essential nutrients.

✓ **DO** supplement your diet with oral vitamins if you eat a special diet, such as a vegetarian (especially vegan) diet.

✓ **DO** call your doctor if you have signs of severe anemia, such as chest pain, palpitations, or shortness of breath.

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⦸ **DON'T** stop treatment. This lets anemia and all symptoms return.

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MANAGING YOUR

PERTUSSIS

What Is Pertussis?

Pertussis is also called whooping cough because the cough can sound like a whoop or bark. People of any age can get pertussis but it most often infects children younger than 2. It can be very serious in babies younger than 1 year old.

People with pertussis can cough for a long time, to the point of getting exhausted. The infection starts with flu-like symptoms that turn into a severe cough, which can last up to a few weeks.

What Causes Pertussis?

Pertussis is caused by a bacterium named *Bordetella pertussis*.

What Are the Symptoms of Pertussis?

Symptoms first seem like those of a cold, with a mild cough, but then, in 1 week, the cough becomes a dry, severe whooping cough that lasts more than 2 weeks. Long coughing spells occur, and coughing bursts often happening at night, with an average of 15 spells in 24 hours. The whoop isn't always heard. Most children don't have fever during the coughing. Other common symptoms include slight fever, flushing (red face), loss of appetite, feeling sick, pink eyes, runny nose, and sweating.

How Is Pertussis Diagnosed?

The doctor will ask about the medical history and do an examination, paying attention to the lungs, ears, nose, and throat. The doctor may use a swab on the throat and nose to take a sample and make sure that another infection isn't causing symptoms. Blood tests and chest x-ray may also be done.

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How Is Pertussis Treated?

Children and adults can usually be treated at home. The doctor will prescribe antibiotics. Warm fluids such as apple juice can help the cough. It's important to keep the nose and throat clear of thick mucus to make it easier to breathe. The doctor can show you how to do this with salt water and a bulb syringe. Putting a humidifier in a bedroom can also help breathing.

Pertussis spreads easily, so people who have it should stay away from others. Frequent hand washing is important to avoid spreading the infection. Also, family members and other contacts will need treatment to protect them from infection.

DOs and DON'Ts in Managing Pertussis:

- ✔ **DO** make sure that your children get vaccinations for pertussis and that you are up to date on your pertussis vaccination.
- ✔ **DO** make sure that you or your child drinks plenty of fluids.
- ✔ **DO** make sure that you or your child stays away from smells or smoke that can make the cough worse.
- ✔ **DO** use good hand-washing practices, especially after being with someone who's sick. Hand washing is important to avoid spreading infection.
- ✔ **DO** call your doctor right away or go to the emergency room if you or your child has breathing problems, stops breathing, or is breathing fast; cannot drink; has a high fever; has a seizure; has blue hands, face, or feet; or is very tired or sluggish.
- ⃠ **DON'T** stop taking medicine or change the dosage because you feel better unless the doctor says to do so.
- ⃠ **DON'T** try to treat pertussis with cough or allergy medicines. These can at times make symptoms worse.

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MANAGING YOUR

PEUTZ-JEGHERS SYNDROME

What Is Peutz-Jeghers Syndrome?

Peutz-Jeghers syndrome is a condition in which the intestine (bowel) contains many polyps, the skin has dark (pigmented) spots, and there is an increased risk of certain types of cancer. A polyp is a benign (not cancerous) growth in the intestinal lining. Polyps may be flat (sessile) or can sit on a stalk (pedunculated). It's thought that most intestinal cancers start from polyps. This syndrome is rare and affects men and women equally. The average age of people at diagnosis is about 25 years.

What Causes Peutz-Jeghers Syndrome?

This syndrome is inherited. People have a 50% chance of inheriting this disease from a parent with it.

What Are the Signs and Symptoms of Peutz-Jeghers Syndrome?

Symptoms vary according to where the polyps are. Many small polyps (hamartomas) occur throughout the gastrointestinal (GI) tract but mostly in the small intestine. Symptoms include pain in the abdomen (belly), intestinal bleeding, and signs of intestinal obstruction. Those signs are fever, abdominal pain, nausea, and vomiting. Almost all people have spots on the skin, most often on the lining of the mouth, gums, and lips, around the mouth and eyes, and on fingers, toes, or genitals.

How Is Peutz-Jeghers Syndrome Diagnosed?

The health care provider makes a preliminary diagnosis from the medical history and physical examination. If there's a family history of the syndrome, screening studies including upper endoscopy and lower colonoscopy will be done. In endoscopy, a tube (endoscope) with a lighted end is put into the mouth down into the stomach and the first parts of the small intestine. The

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intestine can be seen through the tube. In colonoscopy, a similar tube (colonoscope) is put into the rectum to see the large intestine. Other imaging studies may include upper GI series and small bowel follow-through to follow the path of barium in the small intestine after barium is swallowed.

How Is Peutz-Jeghers Syndrome Treated?

Continuing detection and observation with endoscopy and colonoscopy are important. Polyps can be removed with endoscopes or colonoscopes, in others, surgery may be necessary.

People with this syndrome have increased risks of cancers of the breast, ovaries, pancreas, uterus, and testicles. Screening for these cancers should also be done. Screening tests include abdominal ultrasonography to look at the pancreas. Mammography should be performed on a regular basis. Women should have yearly Pap smears and pelvic ultrasonography or endometrial biopsy. Boys 10 years old and older should have testicular examination and ultrasonography.

DOs and DON'Ts in Managing Peutz-Jeghers Syndrome:

✓ **DO** realize that this syndrome is inherited. Tell your health care provider about family members who have this syndrome, were diagnosed with colon cancer, or died young from colon cancer.

✓ **DO** call your health care provider if you have changes in bowel habits (e.g., diarrhea, constipation). Call if you see blood in your stools. Call if you have abdominal pain, nausea, or vomiting and cannot keep food down.

⃠ **DON'T** forget that most people with Peutz-Jeghers syndrome develop some kind of cancer before they're 65, so early detection and screening are critical.

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- American Gastroenterological Association Phone: (301) 654-2055 **Website: http://www.gastro.org**
- National Cancer Institute Phone: (1-800) 4-CANCER **Website: http://www.nci.nih.gov**
- National Digestive Diseases Information Clearinghouse Phone:1-800-891-5389 or 1-301-654-3810 **Website: www.niddk.nih.gov/health/digest/nddic.htm**
- American Society of Clinical Oncology Phone: (703) 299-0150 **Website: http://www.asco.org**

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MANAGING YOUR

PEYRONIE'S DISEASE

What Is Peyronie's Disease?

Peyronie's disease is a disorder involving the penis. The penis is made of spongy tissues called the corpus cavernosum and corpus spongiosum. With sexual arousal, these tissues fill with blood, so an erection occurs. The penis is normally straight in an erection. In Peyronie's disease, the penis curves abnormally during an erection.

This disease is seen in about 1% of men, usually 45 to 60 years old. It's not serious but can be embarrassing and uncomfortable and can lead to erectile dysfunction.

What Causes Peyronie's Disease?

The exact cause is unknown. However, scar tissue may make a hard lump or plaque on one side of the penis. The scar tissue pulls that side of the penis so it cannot expand properly during arousal. This makes the penis curve. Trauma caused by vigorous sex, accidents, medicines, or previous surgery on the penis may cause the scar tissue to form. The disease isn't contagious or hereditary.

What Are the Symptoms of Peyronie's Disease?

The most common symptoms are painful erections and curvature (bending) of an erect penis. The penis curves up if scar tissue is on top, and it curves down if the plaque is under the penis. These symptoms can occur slowly, usually during 2 years. Other symptoms include impotence (cannot get an erection), no pleasure with sex, pain without an erection, problems with sex (penetration), and penis shortening. One side or more of the penis may have a thick band of hard tissue.

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How Is Peyronie's Disease Diagnosed?

The doctor makes a diagnosis from a physical examination, especially of the penis, and medical history. The doctor may order blood tests to rule out other causes and ultrasonography to look for scar tissue. Ultrasonography uses sound waves to make pictures of inside the body and is painless and harmless.

How Is Peyronie's Disease Treated?

Very mild symptoms may not need treatment. Peyronie's disease often goes away on its own. For mild to moderate symptoms, medicine or a vacuum device may be used to help get erections. A vacuum device stops blood from leaving the penis too early, so the penis stays erect. Medicine may be taken by mouth, put on the penis, or given as a shot in the penis. For severe symptoms, surgery may be needed to remove scar tissue, remove tissue from the side opposite the plaque (cancels the bend), or implant a device to help rigidity. Surgery often offers the best results, and sex can be resumed 6 weeks after surgery. Many men have a tender midline scar, which often goes away without treatment in 6 to 15 months.

DOs and DON'Ts in Managing

Peyronie's Disease:

✓ **DO** tell your doctor about your other medical problems.

✓ **DO** tell your doctor about your medicines, both prescription and over-the-counter.

✓ **DO** call your doctor if pain or curvature of the penis is getting worse.

✓ **DO** call your doctor after surgery if you have a fever or foul-smelling drainage.

⃠ **DON'T** stop taking your medicine or change your dosage because you feel better unless your

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doctor tells you to.

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MANAGING YOUR

PHEOCHROMOCYTOMA

What Is Pheochromocytoma?

Humans have two adrenal glands located above the kidneys. They make substances called hormones that regulate blood pressure, fluid metabolism, and other body functions. A pheochromocytoma is an uncommon tumor of the adrenal gland. Rarely, this type of tumor develops outside the adrenal glands.

Pheochromocytomas secrete a hormone called epinephrine or related compounds. High blood pressure, heart palpitations, headaches, and sweating are the result. Pheochromocytomas account for a very small number of hypertension cases.

What Causes Pheochromocytoma?

The cause is unknown. Most tumors aren't related to family history, but about 10% are part of familial endocrine tumor disorders.

What Are the Symptoms of Pheochromocytoma?

Common symptoms are headaches that come and go, anxiety, palpitations (abnormal, rapid heartbeats), sweating, high blood pressure, heat intolerance, and dizziness when standing. Some people have none.

Uncontrolled hypertension can cause vision loss, heart disease, kidney disease, and stroke.

How Is Pheochromocytoma Diagnosed?

Your doctor may suspect a pheochromocytoma because of your medical history and physical examination. Urine and blood tests will be done to measure hormone levels. One urine test, a 24-hour collection, measures substances called catecholamines. You shouldn't drink alcohol or caffeine or take amphetamines, benzodiazepines, certain antidepressants, or lithium when doing the

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test. These substances may lead to false high levels.

Magnetic resonance imaging (MRI), CT, and other scans may be done to look for the tumor. Tumors outside the adrenals may need whole-body imaging with special nuclear medicine tests.

How Is Pheochromocytoma Treated?

More than 90% of pheochromocytomas are in the adrenal glands and can be cured with surgery. Medicines to control blood pressure should be given before surgery.

Complications from surgery include bleeding and infection. Temporary low and high blood pressure readings can occur while the tumor is being removed.

Pheochromocytomas that are malignant and have spread cannot be cured with surgery. A combination of chemotherapy, radiation therapy, and other treatments is used to help control the disease.

DOs and DON'Ts in Managing

Pheochromocytoma:

✓ **DO** tell your doctor if you had pheochromocytomas before or family members have endocrine tumors. Your family may need screening blood or urine tests.

✓ **DO** call your doctor if you have vision changes, severe headache, weakness on one side of the body, chest pains, or increasing palpitations.

✓ **DO** call your doctor if you have ankle swelling, shortness of breath, or weakness or dizziness when standing.

✓ **DO** call your doctor if symptoms return after surgery.

⊘ **DON'T** do strenuous exercise until your pheochromocytoma has been removed.

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⦸ **DON'T** expect that your high blood pressure will be completely normal after the operation.

Some permanent changes may have already occurred in the kidneys and blood vessels.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Adrenal Diseases Foundation Tel: (516) 487-4992 **Website:** **http://www.nadf.us/**
- The Endocrine Society Tel: (888) 363-6274 **Website:** **http://www.endo-society.org**

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MANAGING YOUR

PHOBIAS

What Are Phobias?

Phobias are overwhelming, unreasonable fears of objects or situations that aren't really very dangerous. The most common phobias are specific: fear of flying, heights (acrophobia), spiders (arachnophobia), strangers (xenophobia), having injections, seeing blood, and enclosed spaces (claustrophobia). Social phobias are serious, long-lasting fears of social situations with exposure to unfamiliar people or inspection by others.

Most phobias begin in teenage years, but phobias of animals, blood, storms, and water often start in early childhood. More women than men have specific phobias. About equal numbers of males and females have social phobias.

What Causes Phobias?

No specific cause is known. However, phobias tend to run in families and some begin after a traumatic event. Phobias can start suddenly or slowly.

What Are the Symptoms of Phobias?

Phobias often produce rapid heartbeat, shortness of breath, feeling a lump in the throat, chest tightness, and diarrhea. Exposure to phobia-related situations almost always causes severe anxiety, which may lead to panic attacks. Sometimes it's easy to avoid these situations. Other situations, such as riding in an elevator, are hard to avoid. People cannot control their fears and cannot function normally. They may have problems at work because of social phobia.

How Are Phobias Diagnosed?

The doctor makes a diagnosis from a medical history. Blood tests may be done to rule out medical disorders such as overactive thyroid that can mimic phobias.

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How Are Phobias Treated?

Treatment aims to reduce fear to a level that doesn't cause major distress and to minimize the need to avoid the object or situation. Treatment for social phobia usually lasts several months, but treatment of specific phobias is shorter. Most people with phobias of animals, blood, or injections can overcome phobias in one session of behavioral treatment.

Both medicines and behavioral methods are used. Drugs are better for social phobias than for specific phobias. Medicines can help panic disorders that result from specific phobias, however. These drugs reduce some signs of anxiety, especially rapid heartbeat and a pounding heart. Exposure-based treatments are best for specific phobias, including fear of blood, injections, dentists, animals, enclosed places, flying, heights, and choking. Exposure seems to work best when sessions are spaced close together. Long exposures seem better than short exposures. Gradual exposure to feared objects (animals) or situations (driving cars) is the most common behavioral treatment and is very helpful. Biofeedback, hypnosis, or other methods help people reduce anxiety and control heart rates.

DOs and DON'Ts in Managing Phobias:

✓ **DO** tell your doctor about your condition. Don't be embarrassed to admit fears.

✓ **DO** remember that specific phobias can be treated, often in few sessions.

✓ **DO** avoid stressful situations when possible.

✓ **DO** exercise, to reduce anxiety.

✓ **DO** avoid the object (such as snakes) of your specific phobia, if possible.

✓ **DO** call your doctor if you have phobic attacks more often. Call if you have physical

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complications from increased anxiety or depression and suicidal thoughts.

- ⃠ **DON'T** use too many stimulants, including caffeine and sugar.
- ⃠ **DON'T** take medicines without checking with your doctor. Over-the-counter drugs are stimulants and can increase anxiety.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Mental Health Association Tel: (800) 969-6642 or (703) 684-7722 **Website: http://www.nmha.org**
- Center for Mental Health Services National Mental Health Information Center Tel: (800) 789-2647

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MANAGING YOUR

PHIMOSIS AND PARAPHIMOSIS

What Are Phimosis and Paraphimosis?

When a baby boy is born, the foreskin over the penis is usually too tight to show the head (tip) of the penis. During the first year or two of life, the foreskin slowly loosens. Phimosis is an inflammation (swelling, redness) of the foreskin. It occurs when the foreskin doesn't loosen but stays too tight. Phimosis can also develop in babies and teenagers because of infections (including diaper rash) or irritation. Phimosis can occur in males with diabetes if they use catheters.

Paraphimosis occurs when the foreskin is so tight that, after it's pulled back, it becomes stuck behind the head of the penis. It cannot be pulled forward again. This condition can occur after pulling the foreskin back when cleaning the penis. It can also happen after an erection or after sex.

These disorders can occur at any age, but a higher occurrence is seen in babies and teenagers.

What Causes Phimosis and Paraphimosis?

Phimosis and paraphimosis are usually due to irritation that is present for a long time, chronic inflammation, or repeated infections of the head of the penis.

What Are the Symptoms of Phimosis and Paraphimosis?

Symptoms of phimosis are trouble urinating, problems pulling the foreskin back, repeated infections, and problems having sex. Symptoms of paraphimosis are being unable to pull the foreskin forward, severe pain in the penis, and swelling of the penis.

How Are Phimosis and Paraphimosis Diagnosed?

The doctor will make a diagnosis by examining the penis. No tests are needed, but the doctor may suggest seeing a urologist. A urologist is a doctor who specializes in treating the urinary

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system and male reproductive organs.

How Are Phimosis and Paraphimosis Treated?

Phimosis is not usually a medical emergency. It can get better without treatment. It can often be treated with gentle stretching of the foreskin by using the hands. A special medicated cream can also be applied. This procedure is repeated at regular times for 2 to 4 weeks. If this treatment doesn't work, the foreskin can be surgically loosened or removed (circumcision).

Paraphimosis is a serious medical emergency. It must be treated quickly because this condition can hurt the penis. The procedure involves making small cuts into the foreskin to loosen it and release the penis. Circumcision will cure paraphimosis.

DOs and DON'Ts in Managing

Phimosis and Paraphimosis:

✓ **DO** learn to keep your foreskin clean if you have phimosis. Phimosis can be caused by infection.

✓ **DO** ask your doctor for advice if you are diabetic and use a catheter. A catheter that is causing irritation or infections can lead to phimosis.

✓ **DO** make sure that if you use a catheter you remember to pull your foreskin forward again after using it. If you don't, you may get paraphimosis.

✓ **DO** get to a doctor right away for treatment if you have paraphimosis.

⃠ **DON'T** try to loosen the foreskin yourself if it gets stuck. You can make your symptoms worse.

⃠ **DON'T** use creams or lotions on your penis unless your doctor has prescribed them.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Family Physicians Tel: (800) 274-2237 **Website:**

http://www.aafp.org

- American Urological Association Tel: (866) 746-4282 **Website: http://www.auanet.org**

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MANAGING YOUR

PILONIDAL CYST

What Are Pilonidal Cysts?

A pilonidal cyst is a small sac that forms along the tailbone (coccyx), at the top of the cleft between the buttocks. These cysts usually contain hair and skin debris. They form when a hair on the buttocks grows inward, becomes trapped under the skin, and forms a cyst. One cyst or a row of them can occur. A pilonidal cyst may be harmless. If it becomes infected, it causes symptoms. These cysts affect more men than women, most often young pilonidal adults, usually before the age of 40.

What Causes Pilonidal Cysts?

The reason cysts form is unknown. Friction and pressure may force hairs down into skin. The body treats the hair as a foreign substance and makes a cyst around it. Friction can occur from tight clothing, bicycling, or long periods of sitting. These cysts occur more often in people with a family history of them. People who have a lot of hair in the buttock area, are overweight, or are inactive have higher risks of getting these cysts. People who have poor hygiene, sweat a lot, or sit a lot are also more likely to have them.

What Are the Signs and Symptoms of Pilonidal Cysts?

Pilonidal cysts are often harmless but can become infected and painful. Symptoms of infection are pain, tenderness, warmth, redness, and swelling. Pus or an oily discharge can occur.

How Are Pilonidal Cysts Diagnosed?

The health care provider makes a diagnosis from the medical history and physical examination.

How Are Pilonidal Cysts Treated?

The two main treatments are drainage and surgical removal of the cyst. Draining the pus is simple and is done if the cyst flares up. Because cysts tend to come back, after the flare-up has

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quieted down, surgery is often suggested.

Surgery involves removing the cyst while people are awake and the area is numbed. The surgeon cuts out the cyst and some tissue around it. The cut is usually left open to heal and close itself. Most people go home from the hospital that day. Recovery takes several days. Surgical treatment usually means a complete cure. A small scar will remain.

DOs and DON'Ts in Managing Pilonidal Cysts:

✓ **DO** follow your health care provider's instructions about taking care of the area.

✓ **DO** use good hygiene. Clean the area with glycerin soap. Keep the area clean and dry. Using a washcloth briskly, shaving, or using depilatory creams helps keep the area free of hair. Don't use oils or herbal products.

✓ **DO** contact your health care provider if your incision isn't healing, if it bleeds, or if you develop a fever.

✓ **DO** lose weight if you're overweight.

⃠ **DON'T** ignore symptoms. Call your health care provider if your symptoms don't get better, if they worsen with treatment, or if you have new symptoms.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Surgeons Tel: (800) 621-4111 **Website: http://www.facs.org**

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CARING FOR YOUR CHILD WITH

PINWORMS

What Are Pinworms?

Pinworms are tiny worms that cause a common intestinal infection. It's often found in children 5 to 14 years old. Crowded living conditions increase chances of spread to family members. It is usually more a nuisance than a major health problem.

People get the worms by eating contaminated food or drinking contaminated beverages. Eggs hatch and baby worms grow in the intestine. Female worms travel to the anal area to lay more eggs. Eggs get to other people by direct contact.

What Causes Pinworms?

Worms named *Enterobius vermicularis*, about the length of a staple, usually spread when children touch their hands and anus and then touch something else.

What Are the Symptoms of Pinworms?

Itching around the anus or buttocks (especially at night) is the most common symptom. Others include irritated skin around the anus, restlessness in infants, trouble sleeping, and itching in the area of the vagina.

How Are Pinworms Diagnosed?

The doctor will take a medical history and do an examination. Because worms usually move around at night, the best time to check for worms is a couple of hours after children go to sleep and right after children wake in the morning. Parents can use a flashlight to better see the worms. A piece of transparent adhesive tape placed on the anus can get some worms that are then looked at with a microscope.

How Are Pinworms Treated?

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All family members will take an antiworm medicine. Creams or lotions may help with itching and irritation. Worms are killed in a couple of days, and itching should stop in 1 week.

All eggs must be destroyed. To do this, family members should wash hands and clean fingernails often. They should shower daily and wash the anal area carefully. Hands should be kept away from mouths. Hot water should be used to wash dishes, eating utensils, clothing, bedding, and towels. The house (especially toilet bowls, bathrooms, and bedrooms) and children's toys should be cleaned with a disinfectant.

DOs and DON'Ts in Managing Pinworms:

✓ **DO** tell your children's doctor about other medical problems and medicines.

✓ **DO** call your children's doctor if itching doesn't get better after 1 week.

✓ **DO** have your children take medicine as directed.

✓ **DO** teach children good hand-washing methods with soap after toileting and before eating.

✓ **DO** tell the school nurse or day care about the pinworms.

✓ **DO** keep your children's fingernails clean and short.

✓ **DO** bathe your children and change underwear and bed linens daily.

✓ **DO** use very hot water to wash dishes, scrub all washable toys with a bleach solution, and scrub toilets thoroughly.

✓ **DO** follow-up with your children's doctor after treatment to make sure all worms were killed.

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✓ **DO** call your children's doctor if anyone has symptoms again after treatment or side effects from medicines that don't go away quickly.

⃠ **DON'T** let your children scratch their anal area, suck their fingers, or bite their nails.

⃠ **DON'T** let other children play or sleep over until treatment is over.

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FOR MORE INFORMATION

Contact the following sources:

- National Center for Preparedness, Detection, and Control of Infectious Diseases Tel: (800) 311-3435 **Website: http://www.cdc.gov/ncpdcid/**
- National Institute of Allergy and Infectious Diseases Tel: (301) 496-5717, (866) 284-4107 **Website: http://www3.niaid.nih.gov/**

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MANAGING YOUR

PITUITARY ADENOMA

What Are Pituitary Adenomas?

A pituitary adenoma is a growth in the pituitary gland. The pituitary gland, or master gland, lies at the base of the brain and controls growth, metabolism, and reproduction. This gland makes a number of hormones including corticotropin (ACTH), which causes the adrenal gland to produce corticosteroids, and thyroid-stimulating hormone (TSH), which causes the thyroid gland to make thyroid hormone. The pituitary also makes growth hormone (GH), which controls body growth; prolactin, which is needed for breast development and milk production; follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which work in sexual development and reproduction; antidiuretic hormone, which is needed for water balance and blood pressure; and oxytocin, which helps the uterus contract during childbirth.

Adenomas can cause the pituitary to make too much or too little of a hormone. A very large adenoma can press on the brain itself and cause headaches and other symptoms.

What Causes Pituitary Adenomas?

The cause is unknown.

What Are the Symptoms of Pituitary Adenomas?

Symptoms depend on the size of the growth and its effects in the body. The most common symptoms are headache and vision changes. Depending on which pituitary hormones are affected, there are many other possible symptoms, including acne, loss of menstrual periods, inability to get pregnant (women), nipple discharge, inability to have an erection, easy bruising, too much body hair, large jaw, joint pain, oily skin, round face, thin skin, and vaginal dryness.

How Are Pituitary Adenomas Diagnosed?

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The doctor will take a medical history, do a physical examination, and test blood and urine to measure hormone levels. Magnetic resonance imaging (MRI) of the brain will be done to find the tumor and measure its size. Vision tests will be done to rule out damage to the visual areas near the pituitary.

The doctor may suggest seeing an endocrinologist and a neurosurgeon. An endocrinologist is a doctor who specializes in disorders of the endocrine system. A neurosurgeon is a doctor who specializes in brain surgery.

How Are Pituitary Adenomas Treated?

Treatment depends on the adenoma size and its effects. Treatment may involve surgery, radiation, and medicines.

People with very small growths and no symptoms usually don't need treatment. Every few months, blood tests and MRI will be done to make sure that it's not growing.

If an adenoma is making too much hormone, drugs will be given to prevent more hormone from being made and to control symptoms.

If an adenoma is causing a lack of a hormone, the missing hormone will be prescribed (hormone replacement therapy).

Surgery and radiation, if needed, will depend on the adenoma size and location.

DOs and DON'Ts in Managing Pituitary Adenomas:

✓ **DO** tell your doctor about your other medical problems.

✓ **DO** tell your doctor about medicines you take, including prescription and over-the-counter drugs.

✓ **DO** tell your doctor if you're pregnant or plan to get pregnant.

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✓ **DO** call your doctor right away or go to the emergency room if you have a fever, stiff neck, sudden headache, or change in vision.

⃠ **DON'T** stop taking your medicine or change your dose, even if you feel better, unless your doctor says you can.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Brain Tumor Society Tel: (800) 934-2873 **Website:** **http://www.braintumor.org**
- The Endocrine Society Tel: (888) 363-6274 **Website:** **http://www.endo-society.org**

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MANAGING YOUR

PITYRIASIS ROSEA

What Is Pityriasis Rosea?

Pityriasis rosea is a rash that is usually on the trunk. The rash starts as a single, small, round or oval spot that measures 1 to 2 inches across. This first spot is called a herald patch. Then, more spots start to form, from a few spots to over 100, following the lines of the trunk, in a Christmas tree pattern over the back, trunk, and chest. The neck, arms, legs, and face may also be involved. These oval spots are smaller than the first, usually less than ¼ inch across. They are pink, red, or tan (or lighter) and may have a scale around their borders. The rash should heal in 2 to 8 weeks without scars. Sometimes, the rash can last longer. Dark-skinned people may have some long-lasting lighter brown spots.

The rash most often affects men and women, 10 to 35 years old.

What Causes Pityriasis Rosea?

The cause isn't known, but it's believed that a viral infection is the most likely cause. It's more common in the spring and fall than other seasons. It's not contagious.

What Are the Symptoms of Pityriasis Rosea?

Most people don't have symptoms. Some have mild itching with the rash. Other symptoms may include fatigue, fever, headache, and sore throat. Symptoms are usually gone by the time the rash appears.

How Is Pityriasis Rosea Diagnosed?

The doctor will make a diagnosis from a medical history and physical examination. Other tests are generally not necessary, but in some cases the doctor may order blood tests to make sure that another condition isn't causing the rash. Rarely, the doctor may also scrape the rash to collect

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some skin or cut out (biopsy) a small piece of skin that will be checked with a microscope.

How Is Pityriasis Rosea Treated?

Treatment is aimed at reducing itching. It doesn't shorten the course of the disorder. Over-the-counter medicines such as calamine lotion, Benadryl, and Aveeno oatmeal baths can help itching. Ultraviolet light treatments may also be prescribed in some cases. Exposure to sunlight may help, but sunburns should be avoided. Prednisone may be prescribed by your physician if the itching is severe.

The doctor may want to make sure that the rash is going away during an office visit in 2 to 3 weeks.

DOs and DON'Ts in Managing Pityriasis Rosea:

✓ **DO** tell your doctor about your medicines, including prescription and over-the-counter ones.

✓ **DO** tell your doctor if you're pregnant.

✓ **DO** call your doctor if your symptoms get worse, you have a fever, or the rash has pus coming from it.

✓ **DO** call your doctor if medicines don't help the itching after a few days of using them.

✓ **DO** call your doctor if you're not better in 6 to 8 weeks.

✓ **DO** call your doctor if you have symptoms of another infection, such as high temperature, pus drainage, or swelling.

⃠ **DON'T** take a hot bath or sauna. Heat will worsen the itching.

⃠ **DON'T** use lotion too often, maybe once per day or every other day, if your skin gets too

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dry.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Dermatology Tel: (847) 330-0230, (866) 503-7546 **Website:** **http://www.aad.org**

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MANAGING YOUR

PLACENTA PREVIA

What Is Placenta Previa?

The placenta is an organ that connects the developing fetus to the wall of the uterus. It gets nutrients to the fetus, gets rid of waste, and allows oxygen exchange by means of the mother's blood supply. The placenta usually moves up and away from the cervix (opening at the bottom of the uterus) during growth of the fetus. If it doesn't, the cervix may be blocked. Placenta previa occurs when the placenta attaches to the uterine wall in the wrong spot, close to or covering the cervix. Placenta previa affects about 1 in 200 pregnancies. It's a major cause of bleeding during pregnancy. It can be total, partial, marginal, or low-lying. In total placenta previa, the opening is fully covered. In partial placenta previa, the opening is partly covered. In marginal placenta previa, the edge of the placenta is at the edge of the opening. In low-lying placenta previa, the placenta attaches in the lower part of the uterus and its edge is close to the edge of the opening.

What Causes Placenta Previa?

The cause is unknown. Risk factors include previous cesarean delivery, having been pregnant before, carrying twins or triplets, having had placenta previa or uterine surgery, age 35 or older, being Asian, and smoking.

What Are the Signs and Symptoms of Placenta Previa?

Most often, painless vaginal bleeding, usually in the second or third trimester, occurs. Uterine contractions may or may not be present. The uterus is soft and without pain. Fetal distress doesn't usually occur.

How Is Placenta Previa Diagnosed?

The health care provider makes a diagnosis from the medical history and physical examination.

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Vaginal bleeding after 24 weeks of gestation is key. The best, safest way to find the place of attachment is by using ultrasonography. This test, using sound waves, can also tell whether delivery is needed. Magnetic resonance imaging (MRI) can also help detect the condition.

How Is Placenta Previa Treated?

Treatment depends on the status of the fetus and of the mother. Fetal status and gestational age are checked by using the sonogram and continuous fetal heart rate monitoring. Outpatient treatment is possible for a fetus at less than 30 weeks of gestation, and if mother and fetus aren't in distress. Placenta previa with a mature fetus or distress of the mother or fetus means immediate delivery. Cesarean delivery is done in almost all cases, especially for heavy bleeding. Vaginal delivery can be tried if the cervix is partly covered. Blood volume may need to be replaced to keep blood pressure normal. Blood transfusion may be done to replace lost blood. Levels of fibrinogen must be kept normal. Fibrinogen is a protein that's important in clotting.

DOs and DON'Ts in Managing Placenta Previa:

✓ **DO** get plenty of rest. Avoid overexertion.

⃠ **DON'T** ignore symptoms. Call your health care provider if you're pregnant and see vaginal bleeding.

⃠ **DON'T** use medicines (including over-the-counter drugs and herbal products) without first asking your health care provider.

⃠ **DON'T** smoke or use tobacco products.

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- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website: http://www.acog.org**

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MANAGING YOUR

PLANTAR FASCIITIS

What Is Plantar Fasciitis?

The plantar fascia is a strong band of tissue, like an elastic band, that runs underneath the bones of the foot. It attaches at one end to the heel bone and at the other near the toes. Plantar fasciitis is an inflammation (swelling) of plantar fascia. It causes foot pain.

What Causes Plantar Fasciitis?

The cause is damage to the plantar fascia. The stress of walking around, running, and being on the feet for long periods can strain and injure the fascia. Pain results. About half of people with this condition also have a bone spur attached to the heel bone, but the spur itself doesn't cause pain.

What Are the Symptoms of Plantar Fasciitis?

Symptoms include sharp or dull, achy pain in the bottom of the heel. This pain is usually worse during first steps after getting up in the morning or getting up after a rest. Pain usually gets better with walking. In the more severe condition, pain may occur all the time during walking. Sometimes pain spreads from the heel toward the toes, and the heel becomes swollen or bruised.

How Is Plantar Fasciitis Diagnosed?

The doctor makes a diagnosis from the symptoms and a foot examination. Other tests, including x-rays of the foot, bone scan, and magnetic resonance imaging (MRI) may also be done if the diagnosis is unclear and other diseases are suspected.

How Is Plantar Fasciitis Treated?

Stress on the heel may be reduced by not standing for long periods and by resting the foot. Losing weight will also decrease stress on the heel and lessen pain. Painkillers such as acetamino-

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phen and antiinflammatory medicine may help milder symptoms.

If these measures don't work, referral to an orthopedic physician, physiotherapist or podiatrist may be needed. A physiotherapist can teach simple stretching exercises or massage, which are good for a tight Achilles tendon. The physiotherapist may also tape the heel and arch of the foot. A podiatrist can measure the feet for insoles. Insoles can improve problems caused by high arches or flat feet or may just be shock absorbers for the heel.

A night splint can help continuing pain by resting the foot and stopping the Achilles tendon from tightening overnight. Steroid injections into the painful heel may also help. Lasting pain may need other treatments such as a plaster cast over the foot and ankle, transcutaneous nerve stimulation (TENS), and acupuncture.

Surgery is for severe pain that remains. Surgery involves relieving tension of the plantar fascia by detaching it from the heel bone.

DOs and DON'Ts in Managing Plantar Fasciitis:

✓ **DO** rest your foot more, lose weight, and wear the right footwear, such as soft-soled shoes and insoles.

✓ **DO** reduce your exercise for a while. Stop running or run for shorter distances.

✓ **DO** call your doctor if symptoms don't get better with treatment.

✓ **DO** stretching regularly, especially before other exercise. You may be able to help prevent pain from coming back.

⃠ **DON'T** expect an immediate result. This condition often takes several weeks or months to improve.

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⦸ **DON'T** do things that you know will make the pain worse.

⦸ **DON'T** walk barefoot on hard surfaces or wear hard-soled shoes.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Foot and Ankle Surgeons Tel: (800) 421-2237 **Website:** **http://www.acfas.org**
- American College of Sports Medicine Tel: (317) 637-9200 **Website:** **http://www.acsm.org**

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MANAGING YOUR

PNEUMOCYSTIS PNEUMONIA

What Is Pneumocystis Pneumonia?

Pneumonia is an infection of the lungs. Pneumocystis pneumonia is a serious, possibly life-threatening illness. Most people survive if treated, but survival is lower for people with severe immune (infection-fighting) system problems. Pneumocystis pneumonia can reoccur back after treatment if preventive drugs aren't used.

What Causes Pneumocystis Pneumonia?

Pneumocystis jiroveci (formerly called *Pneumocystis carinii*) is a fungus that usually causes pneumonia in people with weak immune systems. Such people include those with human immunodeficiency virus (HIV) infection and those getting cancer chemotherapy, long-term prednisone therapy, or drugs to stop transplant rejection. It's unclear how this pneumonia develops. The fungus may spread person to person. It may also be inactive for years and then become active when the immune system is weak.

What Are the Symptoms of Pneumocystis Pneumonia?

Symptoms usually start slowly and become worse over time. The most common symptoms are shortness of breath, dry cough, and fever. Others are weight loss, chest discomfort, and chills.

How Is Pneumocystis Pneumonia Diagnosed?

The doctor uses chest x-rays and blood tests to decide the severity of the illness. Special tests may be needed, including sputum tests for *Pneumocystis* and bronchoscopy. For bronchoscopy, the doctor looks at the lungs with a lighted tube passed through the nose or mouth. Lung fluids are collected and biopsy samples may be taken.

How Is Pneumocystis Pneumonia Treated?

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The combination trimethoprim/sulfamethoxazole (TMP/SMX) is usually the first drug tried. It's given orally or intravenously. Other drugs include pentamidine, for those allergic to sulfa or who don't get better with TMP/SMX. Therapy is usually given for up to 21 days. Steroids are used in severe cases to help reduce lung inflammation.

Severely ill patients are hospitalized for supportive treatments such as supplemental oxygen and mechanical ventilation in an intensive care unit. The most common side effects include rash, nausea, fever, and low white blood cell counts.

Oral TMP/SMX is effective for preventing this pneumonia. It can be given as one tablet three times per week or daily. People who are HIV-positive, have low CD4 counts, had previous pneumocystis pneumonia, or are using steroids or other immunosuppressant drugs should receive this preventive therapy.

Prognosis is worse for people with lung disease, with pneumothorax, needing mechanical ventilation, and when diagnosis and treatment are delayed.

DOs and DON'Ts in Managing

Pneumocystis Pneumonia:

✓ **DO** take your prescription medicines exactly as prescribed. Finish all the antibiotics.

✓ **DO** use nonprescription cough suppressants as needed.

✓ **DO** use acetaminophen or aspirin (except in children) for fever and pain.

✓ **DO** see your doctor regularly to check your immune system if you're HIV-positive.

✓ **DO** call your doctor if you think that you have pneumonia because of a fever, cough, or shortness of breath.

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✓ **DO** call your doctor if your symptoms get worse even with therapy.

✓ **DO** call your doctor if you get a rash (may mean a drug allergy).

✓ **DO** call your doctor if you cannot take your prescribed medicines because of nausea.

⃠ **DON'T** smoke!

⃠ **DON'T** stop taking your antibiotics just because you feel better, unless your doctor tells you to.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Lung Association Tel: (800) LUNG-USA (586-4872) **Website:** **http://www.lungusa.org**
- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website:** **http://www.cdc.gov**

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MANAGING YOUR

PNEUMOCONIOSIS (COAL WORKERS' PNEUMOCONIOSIS)

What Is Pneumoconiosis?

Pneumoconiosis, or black lung, is a lung disease caused by breathing in coal dust. Small round nodules (bumps) develop inside the lungs when coal dust first gets into the lung. The disease is called simple pneumoconiosis if these nodules are smaller than about 2.5 inches in diameter. Later, with continued exposure, their number and size may grow (complicated pneumoconiosis). The nodules can join together to form large fibrous tissue masses in the lung and lung scarring. The lungs are permanently damaged and can't work properly. This condition is called progressive massive fibrosis.

The risk of getting pneumoconiosis depends on how long and how intense the exposure was. Risk also increases for exposure to harder coals. Long-term exposure (usually at least 15 years) is usually needed for the illness to develop, but symptoms may occur sooner with shorter but more intense exposures. Most people with this disease are older than 50.

What Causes Pneumoconiosis?

Exposures occur in the workplace. Industries in which workers can be at risk include mining, excavating, quarrying, sandblasting, and stoneworking. Coal refers to materials that have a different hardness, or rank. They range from peat (the softest) to anthracite (the hardest). Silica in coal dust may contribute to development of this disorder.

What Are the Signs and Symptoms of Pneumoconiosis?

Symptoms may vary. Early in the disease, people may have no symptoms other than a mild cough and sputum production. Lungs don't show major effects. The disease may stay at this point and never affect life span. In some people, the disease gets worse, even after dust exposures stop.

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Shortness of breath and dry cough are the most common symptoms of progressive, massive fibrosis. Severe respiratory disability may lead to early death.

How Is Pneumoconiosis Diagnosed?

Diagnosis is usually made by work history, physical examination, and chest X-ray. A lung biopsy is sometimes needed to make the diagnosis or rule out other disorders when the diagnosis is unclear. Breathing tests can help find out how lungs are working. These tests often show airflow blockage and lung restriction.

How Is Pneumoconiosis Treated?

No treatments can successfully reduce the number of nodules in the lung or stop progressive fibrosis from developing. Symptoms such as shortness of breath due to low oxygen level may be treated with oxygen; flu and pneumococcal vaccinations are given. Workers with this disorder should avoid coal dust exposures. Smoking has an additive effect on the disorder, so people shouldn't smoke. Lung transplantation is a treatment option in some cases.

DOs and DON'Ts in Managing Pneumoconiosis:

✓ **DO** stop smoking.

✓ **DO** obtain a flu vaccination each fall and pneumococcal vaccination as needed.

✓ **DO** exercise to keep your heart healthy but avoid strenuous activities.

✓ **DO** call your health care provider if you have increased coughing, yellow or green sputum, bloody sputum, increased shortness of breath, fever, or chills.

✓ **DO** call your health care provider if you have dusky skin, fingertips, or lips. Call if you have chest pain, new ankle swelling, or unexplained weight loss.

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✓ **DO** stay away from people with acute respiratory infections.

⃠ **DON'T** expose yourself to other known lung irritants: smoke, strong fumes, and very cold or very humid air.

⃠ **DON'T** forget that this disease is preventable by limiting exposure to dust (keeping dust down; masks). Having chest X-rays when hired and during work (every 5 years) can help with monitoring.

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FOR MORE INFORMATION

Contact the following sources:

- American Lung Association Phone:800-LUNG-USA **Website: www.lungusa.org**
- National Lung Health Education Program Tel: (303) 839-6755 **Website: http://www.nlhep.org**
- National Institute of Environmental Health Sciences Tel: (919) 541-3345 **Website: www.niehs.nih.gov**

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MANAGING YOUR

PNEUMOTHORAX

What Is Pneumothorax?

Pneumothorax is a condition in which air leaks from a hole in a lung and gets trapped between the lung and the chest wall (the pleural space). A small amount of fluid in this space normally keeps the outside of the lung from getting stuck against the inside of the chest. This keeps the lung expanded. When air gets into the pleural space, the lung partly or completely collapses.

What Causes Pneumothorax?

Air leaking into the pleural space through a hole in the chest wall or a leak in the lung that lets air escape causes pneumothorax. Traumatic pneumothorax results from an injury such as a puncture of the chest wall or a broken rib that punctures the lung.

Spontaneous pneumothorax can occur in people with emphysema and in tall, very thin people. A hard cough makes part of the lung burst and air leak from the lung. Spontaneous pneumothorax may run in families. About 9 of 100,000 people in the United States have this condition each year.

What Are the Symptoms of Pneumothorax?

The most common symptoms are shortness of breath and sharp chest pain, especially when inhaling and exhaling. Others are fainting and fatigue.

How Is Pneumothorax Diagnosed?

The doctor will take a medical history and do a physical examination. The doctor will hear decreased loudness of breath sounds on one side of the chest with a stethoscope. A chest x-ray can confirm pneumothorax. The doctor will check the oxygen level in the blood and check the heart with electrocardiography (ECG). The ECG measures the heart's electrical activity.

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How Is Pneumothorax Treated?

Treatment depends on the degree of pneumothorax and the cause. A small pneumothorax can be treated by letting the body absorb the air by itself. For a larger pneumothorax, a needle can be put into the chest to remove the air so the lung expands. A large pneumothorax may need to have a chest tube put into the chest to remove the air. A suction machine connected to the tube draws out the air so the lung expands. If the leak is large, the tube may need to stay in for a few days to keep the lung expanded until the leak heals.

DOs and DON'Ts in Managing Pneumothorax:

✓ **DO** tell your doctor about your other medical problems.

✓ **DO** tell your doctor about your medicines, both prescription and over-the-counter.

✓ **DO** tell your doctor if you're pregnant.

✓ **DO** call your doctor if your symptoms get worse.

✓ **DO** call your doctor if you have a fever (temperature higher than 101.0° F) or see pus coming from your chest tube. You could have an infection or pneumonia.

✓ **DO** call your doctor if your symptoms come back, if you had pneumothorax before. Up to 50% of people with spontaneous pneumothorax have another pneumothorax.

✓ **DO** call your doctor right away if you have sudden onset of shortness of breath. Your lung could be collapsing.

⃠ **DON'T** try to remove the chest tube by yourself.

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⦸ **DON'T** exert yourself or cough too much, which can lead to air leaks.

⦸ **DON'T** smoke. Smoking increases your risk of pneumothorax and may cause coughing.

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FOR MORE INFORMATION

Contact the following sources:

• American Lung Association Tel: (800) LUNG-USA (586-4872) **Website:**

http://www.lungusa.org

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MANAGING YOUR

POISON IVY

What Is Poison Ivy?

Poison ivy is a common plant that can cause a severe skin reaction (contact dermatitis) in sensitive people. Affected skin may be dry and red and can blister. This dermatitis isn't contagious, but contact with resin on the skin of affected people can cause a reaction.

What Causes Poison Ivy?

Contact with any part of the plant or with the oily substance (resin) that the plant makes can cause the reaction. Contact can occur directly, by touching the plant, or indirectly, by touching something carrying the oils, such as pets. Oils on clothing, pet fur, and tools may stay active for a long time and can be the source of the rash.

What Are the Symptoms of Poison Ivy?

The main symptom is skin that looks dry, red, or blistered, usually within few hours of contact. Blisters on the skin usually follow the line where the plant brushed the skin. Other symptoms include itching and mild pain, but not fever. Because the skin is fragile, scratching may in some cases lead to infection, which may need antibiotic treatment.

How Is Poison Ivy Diagnosed?

The doctor will diagnose poison ivy dermatitis by a skin examination.

How Is Poison Ivy Treated?

The best treatment is avoidance. Learn how to recognize the plant, and avoid contact as much as possible. Wearing gloves, long sleeves, and long pants when outdoors or gardening will prevent exposure.

Other treatments include oral (by mouth) or topical (put on the skin) antiinflammatory drugs

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(steroids). Also, antihistamines can reduce itching, and immunotherapy (desensitization) can minimize reactions. Steroids are powerful drugs and quickly reduce swelling and irritation but also may have serious side effects. For these reasons, steroids are usually prescribed for short periods. Antihistamines can cause sleepiness, so being careful is important when driving, cooking, or using machinery when taking them. Anti-itch lotions, such as calamine, and oatmeal baths are soothing for oozing, blistery rashes and may be used as needed.

DOs and DON'Ts in Managing Poison Ivy:

✓ **DO** use oral steroids each day as prescribed. Oral antihistamines can be used as needed and may be skipped if itching improves.

✓ **DO** use steroid ointments and creams on clean, dry skin. Repeat two or three times per day as directed.

✓ **DO** use anti-itch lotions as needed, but avoid using them during the first hour after applying steroid creams or ointments. Give the steroid time to soak in first!

✓ **DO** call your doctor if you have a fever, vomiting, or diarrhea.

✓ **DO** call your doctor if your rash worsens despite treatment, or you get a new or different rash.

⃠ **DON'T** skip doses of steroid medicines. Your dermatitis may worsen.

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Contact the following sources:

- Asthma and Allergy Foundation of America Tel: (800) 727-8462 **Website:** **http://www.aafa.org**
- American Academy of Dermatology Tel: (866) 503-SKIN (503-7546) **Website:** **http://www.aad.org**

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MANAGING YOUR

POLIOMYELITIS

What Is Poliomyelitis?

Poliomyelitis (also called polio) is an infection caused by poliovirus. This virus attacks the central nervous system and hurts or destroys nerves that control muscles. This can lead to paralysis, that is, being unable to move a limb or another part of the body. The paralysis in serious cases most often affects the legs, but in the worst cases it can also affect breathing and swallowing. Now, thanks to a vaccine that works very well, this infection is rare in most parts of the world but does occur in developing countries.

Most infections last only a few days or weeks. The paralytic kind most often causes serious symptoms for 2 to 6 months, but people usually get somewhat better after that.

What Causes Poliomyelitis?

The poliovirus is the cause. The disease is very contagious and can spread by contact with water and food contaminated with infected stool (bowel movements). This can happen in areas with poor sanitation systems. It can also spread by direct contact with someone who has the virus or who got oral polio vaccine, which is made of live virus.

What Are the Symptoms of Poliomyelitis?

Three different types of infections occur: abortive, nonparalytic, and paralytic. Polio can range from a mild disease, as in the abortive kind, to a very serious disease, as in the paralytic type. Most infected people don't have symptoms. The most common symptoms of the abortive form are the same mild, flulike symptoms of other viral infections: headache, fever, sore throat, nausea, vomiting, and constipation or diarrhea. The most common symptoms of the nonparalytic form are headache, stiff neck, and change in mental function. The most common symptoms of

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the paralytic form are fever and then headache, neck and back stiffness, constipation, and being sensitive to touch. People lose feeling and movement in the lower part of the body, with some recovery from paralysis after 2 to 6 months.

How Is Poliomyelitis Diagnosed?

The doctor makes a diagnosis from symptoms including neck and back stiffness, trouble swallowing and breathing, and abnormal reflexes. The doctor will get a sample of fluid from the spine by doing a lumbar puncture (spinal tap) and will test the fluid to look for infection. The doctor can also test stool, fluids from the throat, and blood to look for the virus.

How Is Poliomyelitis Treated?

No drugs can cure polio. Ibuprofen or similar drugs can treat pain. Physical and occupational therapy and a good nutritious diet can help improve strength and stamina. The doctor will also suggest other things that will help people feel more comfortable during the active infection.

DOs and DON'Ts in Managing Poliomyelitis:

✓ **DO** physical therapy to keep your muscles from wasting.

✓ **DO** call your doctor if you think that you were exposed to or have polio.

✓ **DO** call your doctor if you were diagnosed with polio and your symptoms are getting worse.

✓ **DO** make sure that you have been vaccinated against polio with inactivated polio vaccine (IPV) before you travel to places where the infection occurs.

⦸ **DON'T** ignore symptoms of polio.

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FOR MORE INFORMATION

Contact the following source:

- Post-Polio Health International Tel: (314) 361-0475 **Website: http://www.post-polio.org**

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MANAGING YOUR

POLYCYSTIC KIDNEY DISEASE

What Is Polycystic Kidney Disease?

Polycystic kidney disease (PKD) is a genetic disorder. In PKD, many fluid-filled cysts grow in the kidneys. These cysts can slowly replace much of the kidney tissue, so kidneys don't work well. After many years, kidney failure can result. About half of people with the major type of PKD have kidney failure (also called end-stage renal disease, ESRD).

In the United States, about 500,000 people have PKD. It's the fourth leading cause of kidney failure. No cure is known.

What Causes PKD?

The two major inherited forms are autosomal dominant PKD and autosomal recessive PKD. The first is most common (about 90% of all cases) and initially manifests in people 30 to 40 years old. Autosomal recessive PKD is rare and usually affects young children.

What Are the Symptoms of PKD?

Most people have no symptoms until adulthood. Then symptoms appear and slowly worsen. Early manifestations are frequent kidney infections and high blood pressure. Symptoms when cysts get larger are dull pain in the back and sides (between ribs and hips); fatigue; weakness; swelling (especially around ankles or eyes); shortness of breath; and itching skin.

Autosomal dominant PKD can also cause hematuria (blood in urine) and kidney stones. Cysts in the liver and pancreas, abnormal heart valves, kidney stones, brain aneurysms (bulges in blood vessel walls), and diverticulosis (small sacs on the colon) occur more frequently in people with PKD.

How Is PKD Diagnosed?

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The doctor diagnoses PKD by checking the family history for PKD and finding three or more kidney cysts with ultrasonography. Ultrasonography uses harmless sound waves to get pictures of the cysts.

The doctor may suggest consultation with a nephrologist, a doctor who specializes in kidney diseases, because of increased risk of kidney failure with PKD.

How Is PKD Treated?

Treatment focuses on treating high blood pressure and preventing complications such as kidney stones, urinary tract infections (UTIs), and renal failure.

Over-the-counter medicines such as aspirin and acetaminophen help pain. Surgery to shrink cysts can relieve severe back and side pain. Antibiotics treat UTIs. Lifestyle changes (diet and exercise) and medicines help high blood pressure.

For ESRD, dialysis or transplantation may be used. In hemodialysis, blood goes through a machine that cleans it and is returned to the body. In peritoneal dialysis, fluid is put into the abdomen where it picks up wastes and is then removed. New kidneys (transplants) don't develop cysts.

DOs and DON'Ts in Managing PKD:

- ✔ **DO** call your doctor if you get a fever or other signs of infection.
- ✔ **DO** call your doctor if you pass less urine, have blood in your urine, feel burning during urination, need to urinate more often, or feel greater urgency to urinate.
- ✔ **DO** call your doctor if you have abdominal pain.
- ✔ **DO** understand that severe or unusual headaches may be caused by brain aneurysms or high blood pressure.
- ✔ **DO** get counseling with a genetics expert if you're thinking of becoming pregnant.

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⦸ **DON'T** forget that PKD will need a team approach involving several doctors.

⦸ **DON'T** be afraid to ask for a referral to a doctor or institution experienced with kidney transplantation or dialysis.

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FOR MORE INFORMATION

Contact the following sources:

- PKD Foundation Tel: (800) 753-2873 **Website:** http://www.pkdcure.org
- National Kidney Foundation Tel: (800) 622-9010 **Website:** http://www.kidney.org
- National Kidney and Urologic Diseases Information Clearinghouse Tel: (800) 891-5390

Website: http://www.kidney.niddk.nih.gov/

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MANAGING YOUR

POLYCYSTIC OVARIAN SYNDROME

What Is Polycystic Ovarian Syndrome?

Polycystic ovarian syndrome (PCOS) is a condition in which ovaries have many cysts (fluid-filled sacs). It's also called Stein-Leventhal syndrome. PCOS is a disorder related to the body's hormones. For example, the pituitary gland, which is at the base of the brain, makes hormones that tell the body how to work. One of these hormones tells the ovary when to release an egg. When the pituitary gland is overactive and makes too much hormone, ovaries get cysts.

PCOS usually starts in women younger than 30.

What Causes Polycystic Ovarian Syndrome?

The cause of changes in hormone levels isn't clear. One possibility is genetic reasons that cause PCOS in overweight or obese women. Also, it's related to type 2 diabetes.

What Are the Symptoms of Polycystic Ovarian Syndrome?

The most common symptom is irregular periods. They occur a few times a year, sometimes only once a year, and sometimes not at all. Bleeding can be very light or very heavy. Other symptoms include acne; hair loss on the head; too much hair on the face (can be thick and dark), chest, or stomach; high cholesterol levels; high blood pressure; deep voice; oily skin; dark rash on the neck, underarm, or groin; trouble getting pregnant (infertility); depression; and weight gain.

How Is Polycystic Ovarian Syndrome Diagnosed?

The doctor will take a medical history, do a physical and pelvic examination, and order blood tests to measure hormone levels and rule out other illnesses. Blood pressure and blood glucose and cholesterol levels will be measured. The doctor will also order ultrasonography of the ovaries to see how many cysts they have. The doctor may suggest a visit to a gynecologist (a doctor

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who specializes in female reproductive health) and to an endocrinologist (a specialist in hormone disorders).

How Is Polycystic Ovarian Syndrome Treated?

Treatment depends on how severe symptoms are and if pregnancy is wanted. Overweight women will need to diet and exercise. Weight loss can help many women with PCOS.

Medicine can be given to make periods more regular, control other symptoms, and help in becoming pregnant. Surgery (laparoscopic ovarian wedge resection) is sometimes performed to decrease hormone release from the ovaries.

High blood pressure, diabetes, and high cholesterol should also be treated.

DOs and DON'Ts in Managing Polycystic Ovarian Syndrome:

✓ **DO** follow your doctor's directions and take your medicine.

✓ **DO** tell your doctor about your other medical problems.

✓ **DO** tell your doctor about your medicines, including prescription and nonprescription drugs.

✓ **DO** tell your doctor if you're pregnant or trying to have a baby.

✓ **DO** see your doctor regularly. Get a pelvic examination every year.

✓ **DO** try to lose weight by eating a healthy diet and exercising.

✓ **DO** call your doctor right away or go to the emergency room if you have very heavy vaginal bleeding or severe stomach pain.

⃠ **DON'T** stop taking your medicine just because you feel better.

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⦸ **DON'T** abuse alcohol.

⦸ **DON'T** use any other medicines, including herbal supplements, without asking your doctor first.

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FOR MORE INFORMATION

Contact the following sources:

- Polycystic Ovarian Syndrome Association Tel: (877) 755-7276 **Website:** **http://www.pcosupport.org**
- The Endocrine Society Tel: (888) 363-6274 **Website:** **http://www.endo-society.org**

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MANAGING YOUR

POLYCYTHEMIA VERA

What Is Polycythemia Vera?

Polycythemia vera is an uncommon blood disorder involving stem cells. Stem cells make blood cells and platelets in bone marrow, the soft, pink pulp inside bones. Polycythemia vera leads to too many red and white blood cells and platelets and an enlarged spleen. Total blood volume and blood thickness are also increased. Most people with the disorder are diagnosed around 60 years of age. Men are affected more often than women.

What Causes Polycythemia Vera?

The cause is unknown. The disorder rarely runs in families.

What Are the Signs and Symptoms of Polycythemia Vera?

Symptoms may include fatigue, headache, drowsiness, and dizziness. Itching after bathing, nosebleeds or gastrointestinal bleeding, and breathing problems may also occur. The eyes and face look red due to increased blood. People with this disorder can also develop peptic ulcer disease and an enlarged liver. Three-fourths of people have an enlarged spleen. It gives a feeling of fullness and discomfort in the right upper portion of the abdomen (belly). Vision problems, such as temporary blindness, double vision, specks, and bright points in front of the field of vision, are common. Fingers and toes may feel tingling and numb. Blood clots can form in the veins of the lungs and legs and cause strokes.

How Is Polycythemia Vera Diagnosed?

The health care provider makes a diagnosis from the medical history, physical examination, blood tests, and laboratory tests. You will be referred to a blood specialist (hematologist) for more studies. Special tests that may be done include bone marrow biopsy. In this test, a long

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hollow needle is put into bone marrow to remove a sample for study with a microscope.

How Is Polycythemia Vera Treated?

Phlebotomy (removing blood through a vein) is the safest therapy. It can control symptoms for most people. One pint of blood is removed at regular times to keep the hemoglobin and hematocrit in normal ranges. If phlebotomy can't control symptoms, chemotherapy (hydroxyurea, interferon, or busulfan) may help. Splenectomy (removing the spleen) can be considered in people with persistent pains from an enlarged spleen.

Antihistamines (diphenhydramine and hydroxyzine) can be used for itching. H_2 blockers such as famotidine may be used for peptic ulcer disease.

Cure is possible only by bone marrow transplantation.

DOs and DON'Ts in Managing Polycythemia Vera:

✓ **DO** have regular phlebotomy to keep blood counts at levels recommended by your health care provider.

✓ **DO** call your health care provider if you have fatigue, shortness of breath, severe headaches, bleeding, severe abdominal pain, or sudden swelling of an arm or leg.

✓ **DO** avoid strenuous activity if your blood counts are low during chemotherapy or you have an enlarged spleen or anemia.

⃠ **DON'T** smoke.

⃠ **DON'T** stop taking your medicine or change the dosage because you feel better unless your health care provider tells you to.

⃠ **DON'T** use any medicines (including over-the-counter drugs and herbal products) without asking your health care provider. Some medicines such as aspirin and ibuprofen can increase

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bleeding risks.

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FOR MORE INFORMATION

Contact the following sources:

- National Cancer Institute Tel: (1-800) 4-CANCER **Website: http://www.nci.nih.gov**
- American Cancer Society Tel: (1-800) ACS-2345 **Website: http://www.cancer.org**

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MANAGING YOUR

POLYMYALGIA RHEUMATICA

What Is Polymyalgia Rheumatica (PMR)?

Polymyalgia rheumatica (PMR) is an inflammation of the muscles. Muscles around the neck, shoulders, buttocks, hips, and thighs get painful and stiff. Many people have trouble rolling over in bed or getting out of bed. It usually affects people older than 50.

What Causes PMR?

The cause is unknown, but it may be an autoimmune condition. In an autoimmune disorder, the body's immune system attacks the body itself. PMR isn't contagious or hereditary.

What Are the Symptoms of PMR?

Muscle stiffness and pain most commonly affect the hips, neck, arms, shoulders, back, and thighs. Symptoms are worse in the morning and tend to get better during the day. Other symptoms include poor appetite, sadness and depression, tiredness, weight loss, fever, sweats, and restless and disturbed sleep. Joint pain, stiffness, and swelling may occur. Some people also have a condition called giant cell arteritis (temporal arteritis), which may cause headaches and sudden vision changes.

How Is PMR Diagnosed?

The doctor makes a diagnosis from the physical examination, symptoms, and blood tests that measure inflammation. Two blood tests commonly performed are erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level. Other blood tests may be done to be sure that another problem isn't present. The doctor may suggest seeing a rheumatologist (specialist in joint and muscle disorders).

How Is PMR Treated?

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Treatment leads to improvement in almost all symptoms in a few days. Treatment may be necessary for several months or often up to 2 to 3 years. The most common treatment is corticosteroids (such as prednisone), taken with food. Nonsteroidal antiinflammatory drugs (NSAIDs) such as ibuprofen are sometimes also used. Corticosteroids can cause increased appetite, weight gain, trouble sleeping, easy bruising, and stomach upset. Longer term use can lower resistance to infection and cause stomach ulcers and bone thinning (osteoporosis). Regular blood tests are needed to see how the treatment is working. People should receive enough calcium and vitamin D to prevent osteoporosis.

A regular exercise program can help ease the pain.

DOs and DON'Ts in Managing PMR:

- ✔ **DO** tell your doctor about your other medical problems (diabetes, high blood pressure, stomach problems).
- ✔ **DO** tell your doctor about your medicines, including prescription and over-the-counter drugs.
- ✔ **DO** take your steroid medicine with food.
- ✔ **DO** ask your doctor about how to keep your bones strong.
- ✔ **DO** have your blood pressure checked and blood tested for diabetes while you take prednisone.
- ✔ **DO** see your eye doctor yearly.
- ✔ **DO** exercise, at least 30 minutes daily. Ask your doctor which exercise is best for you.
- ✔ **DO** try to control your weight.
- ✔ **DO** stop smoking.
- ✔ **DO** call your doctor if you have medicine side effects.
- ✔ **DO** call your doctor if your pain or stiffness returns during treatment.

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✔ **DO** call your doctor if you have new headaches, cramping in your tongue or jaw, or sudden changes in vision.

⃠ **DON'T** stop taking your medicine or change your dosage because you feel better unless your doctor tells you to.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Rheumatology Tel: (404) 633-3777 **Website:** **http://www.rheumatology.org**
- Arthritis Foundation Tel: (800) 283-7800 **Website:** **http://www.arthritis.org**

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MANAGING YOUR

PORPHYRIA

What Is Porphyria?

Porphyria refers to a group of different illnesses. All cause the body to produce an excess of chemicals known as porphyrins. Porphyrins are chemicals that make an important part of blood called hemoglobin that carries oxygen. The excess chemicals in the blood are excreted in the urine. Porphyria can affect the skin or nervous system (brain, spinal cord) or both. Acute porphyrias cause mainly nervous system symptoms. Cutaneous porphyrias cause skin symptoms. Porphyria is rare. It can affect anyone.

What Causes Porphyria?

Most kinds of porphyria are inherited, passed from parents to children. Sometimes it can occur without having a family history. Hepatitis C or exposure to some chemicals or certain medicines has been associated with development of porphyria. Liver disease, fasting, emotional and physical stress, major surgery, and prostate cancer treatment can trigger attacks in people with a history of porphyria.

What Are the Signs and Symptoms of Porphyria?

People may not know that they have the illness until they're exposed to something that triggers the first attack. Symptoms depend on the kind of porphyria. Porphyria affecting the nervous system may cause chest pain, stomach pain, muscle cramps, weakness, tingling, paralysis, hallucinations, and seizures. Vomiting, diarrhea, and constipation are other symptoms. Depression, anxiety, insomnia, and paranoia can also occur. Urine color may range from pink to purple-red. Porphyria affecting the skin causes blisters, itching, swelling, redness, and sensitivity to light. Attacks can involve painful urination or leaking urine.

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Triggers include medicines, smoking, drinking alcohol, infections, stress, and sun exposure. Attacks develop over hours or days and can last for days or weeks.

How Is Porphyria Diagnosed?

The health care provider makes a diagnosis from the medical history, physical examination, and urine, blood, and stool tests. Special attention is paid to the skin, teeth, and nails. The health care provider may suggest seeing other specialists such as a skin specialist (dermatologist) to help with treatment of this rare disorder.

How Is Porphyria Treated?

Treatment of porphyrias affecting skin aims to reduce the amount of porphyrins in the body to relieve symptoms. These treatments may include phlebotomy and medication such as activated charcoal. Phlebotomy involves taking some blood from a vein, which reduces the iron and porphyrins in the body. A hospital stay may be necessary for severe attacks. Blood transfusions, intravenous fluids, and medications are given. Medicines may also be prescribed to prevent future attacks. Triggers of attacks, drinking, and smoking should be avoided to prevent attacks.

DOs and DON'Ts in Managing Porphyria:

✓ **DO** avoid the sun if you have the skin-type porphyria. Remember that you're sensitive to light. Wear protective clothing and use a strong sunscreen outdoors.

✓ **DO** avoid known triggers of attacks.

✓ **DO** talk to your health care provider about genetic testing for the disease. Porphyria is usually inherited, so your siblings and other family members should consider having genetic tests to see if they have the disease.

✓ **DO** wear a medical identification bracelet or necklace.

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- ⃠ **DON'T** drink alcohol or smoke. Don't fast or follow a diet involving severe calorie restriction.
- ⃠ **DON'T** use prescription or over-the-counter drugs or supplements without asking your health care provider.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Porphyria Foundation Tel: (713) 266-9617**Website:**

  http://www.porphyriafoundation.com

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MANAGING YOUR

POST-CONCUSSION SYNDROME

What Is Post-Concussion Syndrome?

A concussion is a very brief and temporary loss of consciousness after a head injury. It usually doesn't cause any problems that might be found during a physical examination or tests such as computed tomography (CT) or magnetic resonance imaging (MRI).

Post-concussion syndrome is a complicated disorder that may follow a concussion. It's a collection of different specific symptoms. Up to 80% of people who have a concussion will have post-concussion syndrome, usually more women than men.

What Causes Post-Concussion Syndrome?

The cause is a jarring injury to the brain. The syndrome may also be related to psychological factors.

What Are the Symptoms of

Post-Concussion Syndrome?

Symptoms include a headache, poor concentration, mild memory loss, irritability, trouble sleeping, bad dreams, dizziness, tiredness, and sensitivity to noise and light. Sometimes mild personality changes occur. These symptoms go away during weeks to months, but they may last for a year or more. People usually improve slowly during this period.

How Is Post-Concussion Syndrome Diagnosed?

The doctor makes a diagnosis by noting the presence of symptoms in someone who has had a concussion.

How Is Post-Concussion Syndrome Treated?

Treatment consists of watchful waiting until the symptoms go away. Most people recover to their

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normal pre-injury state, usually without permanent effects.

No medicines will shorten the recovery time. Mild analgesics such as acetaminophen, aspirin, and ibuprofen usually help the headache. Medicines may also be needed for depression or anxiety.

Strenuous exercise may make the headache worse. Moderate exercise, however, may make relaxation easier. Exercise may also help with sleep problems by causing just enough fatigue. Some people find biofeedback and relaxation techniques helpful.

Changing work or school areas to minimize the effects of memory loss or trouble concentrating may also be useful.

Support from friends and family to remind people that the condition is temporary may help in dealing with the symptoms.

DOs and DON'Ts in Managing

Post-Concussion Syndrome:

✓ **DO** avoid medicines such as stimulants or decongestants. They may make the irritability worse. This condition will take some time to go away, so avoid medicines that might be habit forming. These drugs include narcotics, sleeping pills, and tranquilizers.

✓ **DO** avoid making life-changing decisions such as quitting school or changing jobs because of your symptoms.

✓ **DO** call your doctor if your symptoms increase over time or if they have not improved in several months.

✓ **DO** call your doctor if you start to have symptoms such as increasing dizziness, blurred or

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double vision, loss of strength or coordination, vomiting, or severe headaches. These symptoms would be especially worrisome.

⦸ **DON'T** do strenuous exercises. Strenuous activity may make the headache more intense. Even though this condition may last for several months, remember that it will go away.

⦸ **DON'T** take part in activities that could lead to another concussion while you have this syndrome. It may be that having many concussions may lead to permanent brain injury or even death.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- Brain Injury Association Tel: (800) 444-6443 **Website: http://www.biausa.org**
- American Academy of Neurology **Website: http://www.neurology.org**

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MANAGING YOUR

POSTTRAUMATIC STRESS DISORDER

What Is Posttraumatic Stress Disorder?

Posttraumatic stress disorder (PTSD) refers to an anxiety disorder that stems from repeated memories after a stressful event. People can get PTSD after living through or merely seeing a traumatic event that involves actual or threatened death or serious injury, to themselves or others. About half of people with PTSD will recover, and about half have a chronic form that's long-lasting.

What Causes PTSD?

Living through or seeing things that cause fear, horror, or feeling helpless can lead to PTSD. Events that are most often the cause include child abuse, rape, mugging, serious accidents, military combat, earthquakes, plane crashes, and terrorism.

PTSD can occur with other psychiatric disorders, such as phobias, anxiety disorders, and depression.

Lack of family, cultural, or social supports that make it easy to adapt to trauma can also increase the chance of PTSD, such as for Iraq, Afghanistan, and Vietnam era veterans.

What Are the Symptoms of PTSD?

Symptoms can begin right after an event but may not start for many years. People can have traumatic flashbacks and nightmares, with the same memories over and over and thoughts that they can't seem to shake. People may relive the event through images or thoughts that can occur at any time.

Physical symptoms, such as sweating, rapid heartbeat, and rapid breathing, can make people avoid thoughts, feelings, and conversations that are related to the trauma. Many people stay away

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from activities and places that make them remember the event.

People may have hyperarousal and are always waiting to respond to another similar event. They startle easily, cannot sleep or concentrate, become irritable, and have angry outbursts.

People can become numb to emotions. They don't feel connections to others and isolate themselves from friends and family. They lose interest in activities. They can lose contact with reality and their sense of self. They may remember little of the actual event or certain parts of the trauma.

How Is PTSD Diagnosed?

Tests aren't needed. The doctor will diagnose PSTD from the medical history.

How Is PTSD Treated?

Treatment is aimed at helping people control their impulses. Peer support groups composed of others who lived through the same kind of trauma can help. Certain drugs are used for treatment.

Cognitive therapy tries to change the way people think so that they feel better. Usually, it's better to talk about the event (debriefing). Other methods such as meditation, muscle relaxation, imagery, and biofeedback also help.

Anger control training may also help.

DOs and DON'Ts in Managing PTSD:

✓ **DO** take prescribed medicine as directed.

✓ **DO** minimize stress. Exercise is very important, as is avoiding drugs such as caffeine and other stimulants.

✓ **DO** avoid situations that might produce flashbacks.

✓ **DO** call your doctor if you have worse symptoms, feelings of homicide or suicide, uncon-

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trolled rage, or psychotic feelings, especially paranoia.

✓ **DO** call your doctor if you develop physical symptoms, such as asthma or ulcers.

⃠ **DON'T** stop taking medicine or change your dosage because you feel better unless your doctor says to.

⃠ **DON'T** use alcohol or other drugs.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- National Institute of Mental Health Tel: (800) 647-2642 **Website:** **http://www.nimh.nih.gov**
- American Psychiatric Association Tel: (888) 357-7924 **Website:** **http://www.psych.org**
- American Psychological Association Tel: (800) 374-2721 **Website:** **http://www.apa.org**

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CARING FOR YOUR CHILD WITH

PRECOCIOUS PUBERTY

What Is Precocious Puberty?

Puberty is the time of physical changes when girls and boys begin physical transformation into adults. Hormones made by glands in the endocrine system start puberty. The main physical manifestation in girls is developing breasts. Later, estrogen made by ovaries causes periods (menstruation) to start. In boys, the first sign is growth of testicles (testes), which make more testosterone. Hormones in girls and boys cause hair growth under the arms and in pubic areas (on and around genitals), armpit sweating, and body odor. Hormones can also cause acne (pimples). Boys get deeper voices. Everyone is different, but changes usually start for girls 7 to 13 years old and for boys, 10 to 15. Precocious puberty means that these changes start too young, before 8 years old in girls and 9 years old in boys. About 1 in 5000 to 10,000 children have this condition, more girls than boys.

What Causes Precocious Puberty?

Many causes include normal variation, abnormal chromosomes, and chronic diseases. It also runs in families. Main causes include central nervous system (CNS) diseases such as tumors, hydrocephalus, and cysts. Others are thyroid gland abnormalities, head injury from trauma, and genetic disorders such as neurofibromatosis and congenital adrenal hyperplasia. Exposure to sex hormones from outside the body is another.

What Are the Signs and Symptoms of Precocious Puberty?

Symptoms depend on the sex of the child. Girls have development of breasts and pubic hair, growth spurts, and the start of periods. Boys show larger testicles and penis, pubic hair development, growth spurts, development of muscles, acne, voice changes, and erections.

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How Is Precocious Puberty Diagnosed?

The health care provider makes a diagnosis from the medical history (including family and social history) and physical examination. Measurements of growth, height, and weight are compared with normal growth values. Tanner staging, which shows standard development, is checked. Also checked are secondary sex characteristics, medicines, and neurologic symptoms which may reveal a cause of the precocious puberty.

The health care provider may suggest seeing an endocrinologist (specialist in endocrine disorders). This specialist may test for hormone abnormalities. This referral is important because most children need long-term monitoring and treatment.

X-rays may be done to find out an accurate bone age. Computed tomography (CT) or magnetic resonance imaging (MRI) of the head may also be done. They can check for pituitary or hypothalamus tumors, which can affect development.

How Is Precocious Puberty Treated?

Therapy depends on the cause. Medicines called GnRH agonists (such as leuprolide or goserelin) work for certain types. For a sluggish thyroid (hypothyroidism), thyroid hormone is given. Children may need psychologic support to help their self-image and problems with peer acceptance. For true precocious puberty and some CNS lesions, the long-term outcome is usually very good. Drug therapy continues for a certain period. It's then stopped, so children can go through puberty.

DOs and DON'Ts in Managing Precocious Puberty:

✓ **DO** remember that precocious puberty is often associated with a history of the disorder in parents and/or siblings.

✓ **DO** remember that attention to children's emotional needs is important.

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⦸ **DON'T** have children stop taking medicine or change the dosage because they feel better unless your health care provider tells you to.

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FOR MORE INFORMATION

Contact the following sources:

- American Association of Clinical Endocrinologists Tel: (904) 353-7878 **Website: http://www.aace.com**
- The American Academy of Family Physicians **Website: http://www.aafp.org**
- American Academy of Pediatrics **Website: http://www.aap.org**

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MANAGING YOUR

PREDIABETES (IMPAIRED GLUCOSE TOLERANCE, IMPAIRED FASTING GLUCOSE)

What Is Prediabetes?

Prediabetes, also called impaired fasting glucose (IFG) or impaired glucose tolerance, occurs when blood glucose (sugar) levels are higher than normal but not high enough to be called diabetes. Many people with prediabetes develop diabetes mellitus type 2 (DM) within 10 years. People with prediabetes have a greater risk of heart disease or stroke.

What Causes Prediabetes?

Sugar builds up in the blood instead of moving into cells, so blood levels are too high (hyperglycemia). This occurs when the pancreas doesn't make enough of the hormone insulin, when the body's cells become resistant to insulin (insulin resistance), or both. Insulin helps sugar enter body cells, which use sugar for energy. Exactly why prediabetes occurs isn't clear, but too much fat—especially fat in the abdomen (belly)—and inactivity seem to be important. Other risk factors include age and family history. African Americans, Hispanics, American Indians, and Asian Americans have higher risks of developing prediabetes. Gestational diabetes and polycystic ovary syndrome can also lead to an increased risk of developing prediabetes.

What Are the Symptoms of Prediabetes?

Many people have prediabetes but don't know it because they don't have symptoms or because symptoms start so slowly that people don't notice them. Diabetes warning signs include urinating often, feeling very thirsty, losing weight quickly, getting frequent infections, and feeling tired and weak. Symptoms of uncontrolled diabetes include blurred vision and slow-healing skin sores.

How Is Prediabetes Diagnosed?

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The doctor will test by measuring blood glucose levels. These tests include fasting plasma glucose (FPG) and/or oral glucose tolerance test (OGTT). The normal FPG value is below 100 mg/dL. The prediabetes level is between 100 and 125 mg/dL. A level of 126 mg/dL or above means diabetes. For the OGTT, blood glucose is measured after fasting and 2 hours after drinking a glucose-rich beverage. The normal level is below 140 mg/dL. The prediabetes level is 140 to 199 mg/dL. A level of 200 mg/dL or above means diabetes.

How Is Prediabetes Treated?

People with prediabetes can delay or prevent type 2 DM by changing lifestyle, including losing weight and exercising. Reducing weight by 5% to 10% and exercising regularly for 30 minutes a day, 5 days a week, will help. Making these changes early may actually turn back the clock, so high blood glucose levels return to normal.

People who are at high risk of diabetes may try medicines, such as metformin and acarbose. High risk means that prediabetes is getting worse or that cardiovascular disease, fatty liver disease, or polycystic ovary syndrome is present. Other people may need medicines such as statins for high cholesterol and drugs for high blood pressure.

DOs and DON'Ts in Managing Prediabetes:

✓ **DO** lose weight if you are overweight (BMI over 25).

✓ **DO** eat healthy foods.

✓ **DO** get more physical activity.

⦸ **DON'T** smoke or use alcohol. Smoking is dangerous to your health, and alcohol can affect (increase) blood sugar levels.

⦸ **DON'T** eat foods rich in sugar.

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⦸ **DON'T** get dehydrated. Drink plenty of water or sugar-free beverages.

⦸ **DON'T** eat foods that your doctor or dietitian doesn't suggest.

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FOR MORE INFORMATION

Contact the following sources:

- National Diabetes Information Clearinghouse Tel: (800) 860-8747 **Website: http://diabetes.niddk.nih.gov**
- American Diabetes Association Tel: (800) DIABETES (342-2383) **Website: http://www.diabetes.org**

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MANAGING YOUR

PREECLAMPSIA

What Is Preeclampsia?

Preeclampsia is also called toxemia and pregnancy-induced hypertension (high blood pressure). It can cause swelling, sudden weight gain, and kidney problems. It may develop around the 20th week of pregnancy and last until the baby is born.

Preeclampsia affects about 6% to 8% of all pregnancies. It's more common with the first baby. Preeclampsia is a serious condition that needs immediate treatment because it can become a serious problem called eclampsia. Eclampsia is life-threatening and may lead to convulsions or coma. In rare cases, the mother or baby can die.

What Causes Preeclampsia?

The cause is unknown. Some believe that a problem with the placenta may be the trigger. Women who are carrying twins, have chronic high blood pressure, diabetes, kidney disease, or poor nutrition have greater chances of getting it. It seems to run in families.

What Are the Symptoms of Preeclampsia?

Symptoms are a major increase in blood pressure, sudden weight gain of more than a pound a week, and swelling of hands, face, and feet.

Severe preeclampsia causes these symptoms to get worse, along with abdominal pain, blurred vision, and headache. If it isn't treated and becomes eclampsia, symptoms will continue to get worse.

How Is Preeclampsia Diagnosed?

No specific test is done for preeclampsia. The doctor will make a diagnosis from the symptoms, such as increased blood pressure and large weight gain. Blood tests are done and urine is

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checked for protein, which indicates preeclampsia. Key signs are increased blood pressure and protein in urine.

How Is Preeclampsia Treated?

Treatment depends on the age of the fetus and how severe symptoms are. Home treatment is enough for mild symptoms. Daily activities are cut back. Resting in bed, preferably on the left side, is recommended. Measuring body weight frequently and keeping a record of these weights are important. A home kit is used to test urine for protein.

Women with more severe symptoms need a hospital stay, maybe even until the baby is born. Medicines may be given intravenously to prevent convulsions.

The baby may need to be delivered early by cesarean section if symptoms continue to get worse, if the preeclampsia becomes eclampsia.

Preeclampsia usually starts to go away 4 to 6 hours after the baby is born. Most women don't have high blood pressure after pregnancy.

DOs and DON'Ts in Managing Preeclampsia:

- ✔ **DO** get plenty of rest.
- ✔ **DO** lie on your left side.
- ✔ **DO** follow any special diet that your doctor advises.
- ✔ **DO** check your urine as instructed.
- ✔ **DO** tell your doctor if your hands, legs, or face swells, or if you have vision changes, headaches, or pain in your abdomen (belly).
- ✔ **DO** call your doctor if you have a weight gain of more than 3 pounds in 24 hours.
- ⃠ **DON'T** use medicines of any kind during pregnancy without first asking your doctor.

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FOR MORE INFORMATION

Contact the following sources:

- Preeclampsia Foundation Tel: (800) 665-9341 **Website: http://www.preeclampsia.org**
- National Women's Health Information Center Tel: (800) 994-9662
- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website: http://www.acog.org**

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MANAGING YOUR

PREMATURE EJACULATION

What Is Premature Ejaculation?

About 25% to 40% of men have premature ejaculation. A man with premature ejaculation cannot hold an erection long enough during sex. The result is both the man and partner aren't satisfied. It leads to distress and social isolation. The disorder is grouped according to when it starts, i.e., whether it's lifelong or started later in life. It's also important to know whether it happens all the time or just in certain situations. In the lifelong condition, men usually ejaculate in less than a minute after entry into the vagina. Men can't delay ejaculation all the time or almost all the time. Rarely, ejaculation can occur just before entry. In the condition that starts later, men had good sexual relationships before without problems. However, they ejaculate before, on, or shortly after entry, before they want it. Premature ejaculation can also occur during masturbation.

What Causes Premature Ejaculation?

The exact cause isn't known. A psychological condition or a combination of things can cause the disorder. Hormones, stress, medical conditions such as thyroid problems, and inflammation (swelling) are causes. The lifelong condition starts with the first sexual experience and continues throughout life until treatment. Sexual activity that happens less often or severe performance anxiety can lead to the condition. Some men who used to use alcohol to delay orgasm and then stop drinking may have the condition.

How Is Premature Ejaculation Diagnosed?

To make a diagnosis, the doctor asks questions about sexual history: experience, emotions, fears, and sexual disorders. For the diagnosis, premature ejaculation must cause distress or problems with a relationship. It can't be related to drugs, such as narcotics.

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How Is Premature Ejaculation Treated?

Medicines, psychological counseling, and techniques that delay ejaculation can improve sex. For many men, a combination of treatments works best. Sometimes, just reassuring the man will help, as will giving him realistic expectations about sex. Medicines include selective serotonin reuptake inhibitors (SSRIs) and clomipramine. Some doctors suggest stopping sex for a short time. Instead, other kinds of physical pleasure and affection can be shared.

Another method is the so-called squeeze technique. In this method, the man and his partner try to interrupt ejaculation by squeezing the penis. This method needs excellent communication between both people. The main concern isn't "normal" sexual behavior but what's preventing the pleasure of both partners.

DOs and DON'Ts in Managing Premature Ejaculation:

✓ **DO** have the best atmosphere for sex. Fear of interruption and secret sex increase chances of premature ejaculation.

✓ **DO** talk with your partner, so you both can express feelings and expectations about sex. Together you may work out methods to prolong erections.

✓ **DO** try to relax. Anxiety (especially performance anxiety) makes the condition worse.

✓ **DO** call your doctor if you cannot have an erection. Call if you're depressed about premature ejaculation.

✓ **DO** call your doctor if you have a bloody or bad-smelling discharge or pain during sex.

⦸ **DON'T** use risky birth control methods such as withdrawal before ejaculation.

⦸ **DON'T** feel embarrassed to discuss this condition with your doctor.

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FOR MORE INFORMATION

Contact the following sources:

- National Mental Health Association Tel: (800) 969-6642 or (703) 684-7722 **Website: http://www.nmha.org**
- Center for Mental Health Services National Mental Health Information Center Tel: (800) 789-2647

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MANAGING YOUR

PREMATURE VENTRICULAR CONTRACTIONS

What Are Premature Ventricular Contractions (PVCs)?

The heart has four pumping chambers, two upper ones (atria) and two lower ones (ventricles). Cells in the right atrium normally control heartbeats. Electrical impulses go from the atria to the ventricles and make them contract and pump blood from the heart to the body. Premature ventricular contractions (PVCs) are extra, abnormal heartbeats in the ventricles that occur too early in the rhythm sequence. These heartbeats don't work well in pumping blood through the body. This condition is known as an arrhythmia, a disorder of the heart's regular beating rhythm. The abnormal heartbeats will result in an irregular pulse.

PVCs are very common and occur in most people at some point. They can happen in otherwise healthy people and are usually harmless. Most people with PVCs don't need treatment.

What Causes PVCs?

The most common causes among healthy people are caffeine, nicotine, alcohol, and stress. Heart disease such as ischemia (reduced blood flow to the heart muscle), high blood pressure, congestive heart failure (reduced pumping of the heart), medicines, and illegal drugs are other causes.

What Are the Symptoms of PVCs?

Most people don't have symptoms. Some have a feeling of the heart missing a beat followed by a stronger beat. Other symptoms are fluttering, palpitations (irregular or rapid heartbeat), a sensation of heart pounding, and jumping.

How Are PVCs Diagnosed?

The doctor may find an irregular pulse during a physical examination. The doctor will diagnose PVCs by doing electrocardiography (ECG). The ECG records the heart's electrical activity. The

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test is best done while symptoms are occurring. Other tests include Holter monitoring. The Holter monitor records an ECG for 24 hours. Exercise stress testing may also be done. This test lets the doctor see effects of exercise on the heart's rhythms. Other tests are echocardiography (a type of ultrasound test that uses sound waves) and an electrophysiology study (checks the heart's electrical system). This test is done by a heart specialist (cardiologist).

How Are PVCs Treated?

Healthy people with no symptoms need no treatment. The condition may go away on its own. Limiting or avoiding caffeine, alcohol, nicotine, and stress can make PVCs become less frequent. Medicines can control PVCs if symptoms become severe. These drugs include antiarrhythmic medicines, beta-blockers, and calcium channel blockers. Exercise can help people who are inactive.

DOs and DON'Ts in Managing PVCs:

✓ **DO** reduce exposure to PVC triggers, such caffeine, alcohol, nicotine, drugs, and stress.

✓ **DO** try stress reduction methods, such as biofeedback, meditation, or yoga.

✓ **DO** exercise. People with PVCs can usually exercise safely. PVCs may even stop during exercise. If PVCs increase in frequency with exercise, you may have heart disease. An exercise stress test can be used to make sure that you can exercise safely.

✓ **DO** call your doctor if you have palpitations, chest pain, shortness of breath, or fainting.

⃠ **DON'T** forget to take your prescribed medicines.

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:**

  http://www.americanheart.org

- American College of Cardiology Tel: (800) 253-4636 **Website: http://www.acc.org**

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MANAGING YOUR

PREMENSTRUAL SYNDROME

What Is Premenstrual Syndrome?

Premenstrual syndrome (PMS) is a common group of symptoms that may occur during the second half of a woman's period (after the ovary releases the egg). About 50% of women have PMS, sometimes during their 20s and 30s, or not until their 40s. Emotional, mental, and physical symptoms vary from very mild to very severe. Most women cope with mild symptoms. Severe symptoms can affect family life, relationships, and work.

What Causes PMS?

The cause isn't known. PMS may be due to an imbalance of female hormones, estrogen and progesterone, which the ovaries produce. Other body chemicals, such as prostaglandin, may also cause PMS.

What Are the Symptoms of PMS?

The most common symptoms are being nervous and irritable; dizziness or fainting; wide mood swings; having less sex drive; headache; tender swollen breasts; feeling bloated; constipation or diarrhea; swelling of ankles, hands, and face; and acne.

Other behavioral symptoms are being depressed, crying easily, tension, anxiety, and trouble concentrating. Other physical symptoms are swelling in the lower abdomen (belly), and fatigue.

Sometimes, PMS may be mild and barely noticeable, but other times PMS may be more severe.

How Is PMS Diagnosed?

PMS can be diagnosed by keeping a calendar of periods and when symptoms occur. If symptoms always occur within 2 weeks before the period and always stop during or after the period, PMS is

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likely. No blood or x-ray tests are useful for diagnosis.

How Is PMS Treated?

Helpful treatments include eating a healthy, well-balanced diet and getting plenty of exercise and rest. A diet especially high in complex carbohydrates (whole-grain foods such as pasta, breads, and rice) may help. Other lifestyle changes may be reducing or not drinking caffeinated beverages and not scheduling too many activities during PMS. Medicines that may help include drugs for depression; water pills (for fluid retention); pain medicine; antianxiety drugs, tranquilizers, or sedatives; medicines to change the balance of female hormones or control their effect; and birth control pills.

Try to reduce stress by using relaxation techniques such as yoga or meditation. Stop smoking if you smoke.

Join a support group or get counseling if you think that would help.

DOs and DON'Ts in Managing PMS:

✓ **DO** eat less salt just before your period.

✓ **DO** stop smoking and using alcohol.

✓ **DO** eat frequent, small meals. Eat a healthy, well-balanced diet, especially whole-grain breads and pastas. Eat less sugar and fewer carbohydrates.

✓ **DO** limit your intake of chocolate and caffeine (coffee, soft drinks, tea).

✓ **DO** call your doctor if symptoms don't get better with treatment, or if new, unexplained symptoms develop.

✓ **DO** exercise on a regular basis.

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✓ **DO** call your doctor if your symptoms interfere with daily activities or your ability to work or do things at home.

⃠ **DON'T** drink alcohol.

⃠ **DON'T** smoke. Smoking may be related to heavier, more painful periods.

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NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Academy of Family Physicians Tel: (800) 274-2237 **Website:** **http://www.aafp.org**
- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website:** **http://www.acog.org**

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SQUAMOUS CELL CARCINOMA

PREVENTION AND SCREENING

What Is Squamous Cell Carcinoma?

Squamous cells form the part of the skin called the epidermis. Cutaneous squamous cell carcinoma is a common kind of skin cancer that involves these cells. It occurs most often in people older than age 50.

What Causes Cutaneous Squamous Cell Carcinoma?

The major cause is longtime sun exposure. Exposure to many x-rays or chemicals, and having light-colored skin, blue or green eyes, and blond or red hair can also give people greater risks of having this cancer.

What Are the Symptoms of Squamous Cell Carcinoma?

This cancer usually starts as a reddish skin patch with a crusty surface. It may grow and look like a wart or sore. It can grow anywhere, including hands, scalp, ears, and lips. It can form a sore that bleeds on and off. A sore that doesn't heal may mean squamous cell carcinoma. If you develop any of these symptoms, you should contact your doctor immediately.

How Is Squamous Cell Carcinoma Diagnosed?

The doctor will examine the skin, but a skin biopsy is needed for diagnosis. For a biopsy, a tiny piece of skin is shaved off and sent to a laboratory for study. A dermatologist (specialist in skin diseases) or a surgeon may do this.

How Is Squamous Cell Carcinoma Treated?

Squamous cell carcinoma can most often be cured by removing the cancer. The way to do this depends on the size of the tumor growing below the skin surface.

Small tumors can be burned with an electric needle and scraped out. Some can be removed by

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freezing. These procedures are usually done in the doctor's office.

Larger tumors need to be cut out. The doctor may use a special type of surgery called Mohs micrographic surgery. This operation involves slowly removing layers of skin until the whole cancer is gone. The wound may take up to 6 weeks to heal. The doctor must be told about any signs of infection during this time.

Rarely, the tumor spreads. If this occurs, a doctor specializing in treating cancer can treat this tumor with radiation or cancer drugs.

Squamous cell carcinoma can recur, so regular follow-up appointments are a must to detect new squamous cell carcinomas early.

DOs and DON'Ts in Preventing Squamous Cell Carcinoma:

✓ **DO** avoid too much sun, especially the strongest sun during the middle of the day (between 10 AM and 2 PM).

✓ **DO** wear sunscreens with high sun protection factors and protective clothing when you're in the sun.

✓ **DO** use a lot of sunscreen. Don't forget your face, the backs of your hands, and your ears.

✓ **DO** stay out of tanning parlors.

✓ **DO** watch for changes in the look, color, size, or texture of any lesions on your skin. Call your doctor if you see these changes. Also call if you have pain, inflammation, bleeding, or itching of a skin lesion.

⦸ **DON'T** smoke. Cigarette, cigar, and pipe smoking can increase the risk for squamous cell carcinoma of the lips and mouth.

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⦸ **DON'T** miss follow-up doctor appointments for early detection of possible cancers.

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FOR MORE INFORMATION

Contact the following source:

- American Cancer Society Tel: (800) ACS-2345 (227-2345) **Website:**

  http://www.cancer.org

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MANAGING YOUR

PRIAPISM

What Is Priapism?

Priapism is an unwanted erection of the penis that lasts several hours. The two major kinds are low-flow priapism and high-flow priapism. In the first kind, blood has difficulty leaving the penis. In the second, too much blood flows into the penis. Priapism isn't very common. It occurs most often in boys 5 to 10 years old with sickle cell anemia and men 20 to 50 years old, usually due to medications. Immediate medical care may be needed.

What Causes Priapism?

The cause is unknown. In the younger group, priapism is often related to sickle cell disease or cancers. Abnormal red blood cells in sickle cell disease can block blood flow out of the penis. Acute attacks often begin during sleep, and a full bladder due to impaired urination is usually associated with them. In men, medicines used to manage erectile dysfunction can increase risks. Antianxiety drugs, blood thinners, alcohol, and illicit drugs may be associated with the disorder. Other causes include trauma, spinal cord injury, metabolic and nervous system diseases, and blood clots.

What Are the Signs and Symptoms of Priapism?

Priapism can be recurrent (stuttering), prolonged, or persistent. In the recurrent type, repeated erections come and go, last less than 3 hours, are painful, and cause no problem with sex after treatment. This kind is very common and occurs in 10 to 40% of sexually active men. Acute, prolonged priapism can last several hours or a few days. Erections are painful, and impotence may occur. Persistent priapism can last weeks to years and usually starts after an acute attack. It's usually painless. The penis gets erect but not rigid. It may also lead to impotence.

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How Is Priapism Diagnosed?

The health care provider makes a diagnosis from the medical history, and physical examination. Blood tests, Doppler ultrasonography, and arteriography are usually performed. Seeing a specialist in urogenital diseases (urologist) may be suggested by your health care provider. A blood specialist (hematologist) will also be involved in your care if you have sickle cell anemia.

How Is Priapism Treated?

Recurrent priapism is often managed at home. Drinking plenty of fluids and emptying the bladder often are important once an attack starts. Warm baths and exercise help. If the attack doesn't get better in 3 hours, medical care is needed. Prolonged priapism usually requires hospitalization. Intravenous fluids and narcotics usually are given for pain. Blood transfusions or exchange transfusions may be started. Exchange transfusions involve being connected to a machine that exchanges fresh blood with the man's old blood. If these methods don't work, blood may be drained from the penis. If all these treatments don't work, a surgeon may put a shunt in the penis to reroute blood so that it moves through the penis normally. No standard treatment exists for persistent priapism. Inflatable or fixed prostheses can be used to treat erectile dysfunction.

DOs and DON'Ts in Managing Priapism:

✓ **DO** empty your bladder as often as possible to prevent urinary retention.

✓ **DO** avoid dehydration and long-lasting sex.

⃠ **DON'T** ignore symptoms. Call your health care provider if your symptoms don't improve or get worse with treatment. Call if you get new symptoms.

⃠ **DON'T** use medicines (including over-the-counter and herbal products) without first asking your health care provider.

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FOR MORE INFORMATION

Contact the following sources:

- National Heart, Lung, and Blood Institute Information Center Phone: 301-592-8573

  Website: www.nhlbi.nih.gov

- Sickle Cell Disease Association of America Phone: 800-421-8453 **Website:**

  www.sicklecelldisease.org

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MANAGING YOUR

PRIMARY BILIARY CIRRHOSIS

What Is Primary Biliary Cirrhosis?

Primary biliary cirrhosis refers to scarring of the liver caused by blockage of the tiny bile tubules (ducts) inside and outside the liver. This disorder accounts for 10% of all cases of liver cirrhosis. About 90% of all cases occur in women 30 to 60 years old.

What Causes Primary Biliary Cirrhosis?

The exact cause is unknown, but it's thought to be an autoimmune disorder. Autoimmune means that the body's immune system attacks the body's own tissues.

What Are the Symptoms of Primary

Biliary Cirrhosis?

An early symptom is itchiness of the whole body or just palms and feet. Jaundice (yellow skin) follows. Fatigue and easy bruising are other symptoms. As the liver becomes more scarred, it fails, so fluid in the belly (ascites), leg swelling, confusion, and lethargy occur. Other complications are bleeding from the esophagus from enlarged veins known as varices that develop in people with cirrhosis and vitamin deficiencies, osteoporosis, and joint pains.

How Is Primary Biliary Cirrhosis Diagnosed?

The doctor makes a preliminary diagnosis from symptoms, physical examination, and blood tests. The blood tests are liver function tests and a specific test for antimitochondrial antibody. Almost 90% of people have this antibody. A liver biopsy is the best way to confirm the diagnosis. In a biopsy, the doctor puts a needle into the liver to get a small sample for study with a microscope.

How Is Primary Biliary Cirrhosis Treated?

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No specific treatment is available. Treatment is for relief of symptoms. Treatment includes the drugs ursodiol and colchicine to help symptoms and decrease liver damage. Cholestyramine helps itchiness.

For confusion or lethargy from advanced liver failure, a medicine called lactulose can be used. The lactulose syrup acts as a laxative and may cause diarrhea. By causing diarrhea, lactulose gets rid of metabolic wastes such as ammonia. High ammonia levels cause confusion and lethargy. Confusion and thought processes get better after the lactulose syrup lowers the ammonia levels.

In the most advanced cases, liver transplantation is an option for better survival. A team made up of the primary doctor, gastroenterologist (specialist in digestive system diseases), surgeon, and transplant surgical team will help make the decision about transplantation.

DOs and DON'Ts in Managing

Primary Biliary Cirrhosis:

✓ **DO** get the opinion of a gastroenterologist if you may have this disorder.

✓ **DO** call your doctor if you have yellow skin or persistent itchiness.

✓ **DO** call your doctor if you have easy bruising, leg swelling, or bleeding.

⊘ **DON'T** ignore jaundice, especially with itchiness.

⊘ **DON'T** be afraid to ask for second opinions about diagnosis or treatment.

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FOR MORE INFORMATION

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Contact the following sources:

- National Digestive Diseases Information Clearinghouse Tel: (800) 891-5389 **Website:** **http://digestive.niddk.nih.gov**
- American College of Gastroenterology Tel: (703) 820-7400 **Website:** **http://www.acg.gi.org**

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MANAGING YOUR

PROBIOTICS

What Are Probiotics?

Probiotics are live microorganisms that are similar to helpful microorganisms that people normally have in their gastrointestinal system (stomach, intestine). Microorganisms are tiny living creatures—bacteria, viruses, and yeasts—that are seen only with a microscope. Probiotics are also called friendly or good bacteria.

These bacteria usually come from two groups—*Lactobacillus* and *Bifidobacterium.* Others include *Bacillus, Enterococcus,* and *Escherichia.* In each group are different species (such as *Lactobacillus acidophilus* and *Bifidobacterium bifidus*). Each species has different strains (varieties). Certain probiotics such as *Saccharomyces boulardii* are yeasts (one-celled plants called fungi).

What Do Probiotics Do?

Disease-causing bacteria, yeasts, fungi, and parasites can upset the body's microbial balance. Probiotics help the balance return to normal. People use probiotics to prevent and treat illnesses and for general good health.

Probiotics can help treat diarrhea and some infections. They may improve the immune (infection-fighting) system. They may benefit people with irritable bowel syndrome, gas, ulcerative colitis, Crohn's disease, and *Helicobacter pylori* infections. They may also shorten intestinal *Clostridium difficile* infections. Probiotics reduce milk allergy symptoms and may lower cholesterol levels.

How Are Probiotics Used and How Much Is Needed?

This natural remedy can be found in foods such as yogurt, fermented and unfermented milk,

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miso, tempeh, and some juices and soy drinks. Probiotics are also given as powders, tablets, capsules, and liquids. The amount needed varies among strains. Probiotics don't work the same in everyone. They appear to help older people more than younger ones.

What Are Side Effects and Problems with Probiotics?

Natural remedies aren't always safe. They affect the body and may interact with prescription drugs. Natural remedies also aren't standardized and may be contaminated. They may have different strengths and effects.

People with allergies to *Lactobacillus,* lactose, or milk products should be careful about using probiotics. Also, people with weakened immune systems from diseases such as HIV and AIDS or from taking medicines to prevent organ transplant rejection should be careful. Pregnant or breastfeeding women, infants, children, and older adults should get their doctor's approval prior to using probiotics.

Side effects can occur; they are usually mild and most often affect the digestive tract. The most common one is gas. Some may be serious. Probiotics may cause infections, unhealthy metabolic activities, or too much stimulation of the immune system. Probiotics can change the way other medicines work. These medicines include antibiotics, cancer drugs (cyclophosphamide, cisplatin), steroids, and medicines that suppress the immune system (cyclosporine, tacrolimus, azathioprine). Vitamins and certain foods may also interact.

DOs and DON'Ts in Managing Probiotics:

✓ **DO** remember that the effects of one strain of probiotics aren't necessarily the same as the effects of other strains or even different preparations of the same strain.

✓ **DO** tell your doctor about all your probiotics and drugs.

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✓ **DO** call your doctor if you use a probiotic and have an effect that worries you.

✓ **DO** remember to eat a probiotic food daily. A week or two may be needed to see results.

⃠ **DON'T** forget to be careful of some products claiming to be filled with probiotics.

Remember, chocolate bars with added probiotics are still candy.

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FOR MORE INFORMATION

Contact the following sources:

- National Digestive Diseases Information Clearinghouse E-mail: nddic@aerie.com

  Website: http://www.niddk.nih.gov/health/digest/nddic.htm

- American College of Gastroenterology Tel: (703) 820-7400**Website:**

  http://www.acg.gi.org

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MANAGING

PROLACTINOMA

What Are Prolactinomas?

A prolactinoma is a tumor of the prolactin-producing cells of the pituitary gland. The pituitary gland, or master gland, lies at the bottom of the brain and controls growth, metabolism, and reproduction. One of the many hormones secreted by the pituitary is prolactin. Prolactin causes a woman's breasts to secrete milk after pregnancy. Tumors in prolactin-secreting cells of the pituitary cause too much prolactin to get into the bloodstream.

Prolactinomas are rare and occur in 1 or 2 people in 10,000. Most are curable.

What Causes Prolactinomas?

The cause is unknown.

What Are the Symptoms of Prolactinomas?

Women may have changes in menstruation (periods) or produce milk when they aren't pregnant. High prolactin levels may lower estrogen levels, which lead to vaginal dryness and painful intercourse.

Males may notice impotence or lower sex drive.

Untreated prolactinomas may lead to reduced amounts of mineral in bones (osteoporosis). Tumors may also press on nerves near the pituitary, such as optic nerves, which are important for vision. The result may be decreased peripheral vision.

How Are Prolactinomas Diagnosed?

The doctor diagnoses a prolactinoma by finding high blood prolactin levels. Breast stimulation will also increase prolactin levels, as will many drugs, especially antidepressants. People with hypothyroidism (low thyroid gland function) or advanced liver or kidney disease can also have

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high prolactin levels. The doctor will take into account medicines you are taking and other medical disorders when making the diagnosis.

Magnetic resonance imaging (MRI) of the brain will show a tumor in the pituitary gland.

How Are Prolactinomas Treated?

The best treatment depends on symptoms and tumor size. The treatment goal is to have normal reproductive and pituitary function and minimize symptoms, such as production of breast milk and changes in periods.

Some people with very small tumors (called microadenomas), who have no symptoms may be followed up with annual MRI and prolactin level tests. Many of these small prolactinomas don't get larger.

People with symptoms need medicine (e.g., bromocriptine and cabergoline) to shrink the tumor and reduce prolactin levels.

If medicine isn't tolerated or doesn't control tumor growth, surgery is used and can be very successful. But tumors may come back after surgery. Larger tumors (macroadenomas) can be treated with surgery, irradiation of the pituitary, and medications. The tumor may also be destroyed with radiation delivered through multiple ports (stereotactic surgery, also called gamma knife surgery).

DOs and DON'Ts in Managing Prolactinomas:

✓ **DO** make sure that your prolactin level was measured after an 8-hour fast, and that there was no recent breast stimulation, to get an accurate prolactin level.

✓ **DO** find an experienced surgeon if you need surgery. A neurosurgeon (doctor who specializes in surgery for the nervous system) should do the operation. Success depends on the neu-

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rosurgeon's experience and skill.

✓ **DO** call your doctor if you have vision changes or an unusual increase in headaches.

✓ **DO** call your doctor if you have nausea or dizziness from the medicine.

✓ **DO** call your doctor if you feel extremely weak and tired or urinate often after surgery.

⃠ **DON'T** forget to use birth control if you're sexually active after starting treatment. With successful treatment, women will again have normal periods and men will have normal testosterone levels.

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FOR MORE INFORMATION

Contact the following sources:

- National Brain Tumor Society Tel: (800) 934-2873 **Website:** **http://www.braintumor.org**
- Pituitary Tumor Network Association Tel: (805) 499-9973

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MANAGING YOUR

PROSTATE CANCER

What Is Prostate Cancer?

Prostate cancer is an abnormal growth in the prostate gland. This walnut-shaped gland in the male reproductive tract makes seminal fluid, which mixes with sperm. The prostate is around the urethra, near its connection to the bladder. The urethra is the tube that takes urine from the bladder to outside the body. Cancer develops when cells divide out of control. Early detection and treatment have led to better survival for all stages of prostate cancer in the past 20 years.

What Are the Symptoms of Prostate Cancer?

Early prostate cancer generally does not cause symptoms. Depending on its location within the prostate and how far it has spread, it may cause pain, problems urinating, erectile dysfunction, and other symptoms.

A weak or interrupted flow of urine, having to urinate often (especially at night), trouble holding back urine, being unable to urinate, pain or burning when urinating, blood in urine or semen, and nagging pain in the back, hips, or pelvis may occur as the cancer spreads.

These symptoms are not always due to prostate cancer and may have other less serious causes, including benign prostatic hypertrophy (BPH) and infections. Always see your doctor for a diagnosis.

How Is Prostate Cancer Diagnosed?

The doctor may suspect prostate cancer from a complete medical history and physical examination. The doctor will do a digital rectal examination (DRE) and a blood test known as prostate-specific antigen test (PSA test).

The doctor will usually recommend that men older than 50 have yearly DREs and PSA tests until age 70-75.

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Men in high-risk groups, such as African Americans, or those with a family history of prostate cancer may need testing at a younger age (usually at age 40).

The diagnosis can be proved only by a biopsy, in which the doctor takes a sample of prostate tissue for study.

What Are the Complications of Prostate Cancer?

Many prostate cancers are slow-growing and don't lead to death because older patients will die from other causes, but prostate cancer can spread (metastasize) through blood and lymph nodes (glands) to bones and major organs. This is called extracapsular spread.

How Is Prostate Cancer Treated?

The choice of treatment depends on a man's age and health, how far the cancer spread (stage of disease), what the cancer looks like under the microscope, and response to first treatment. Standard treatments include watchful waiting, surgery, radiation therapy, and hormone therapy. Radiation therapy can be external beam radiation (x-rays to kill cancer cells) or proton beam therapy (special high-dose treatment). Also, tiny radioactive implant (seeds) can be put directly into the prostate. Hormone therapy affects testosterone production, so cancer cells shrink or grow more slowly.

Surgery is called radical prostatectomy. It's used for localized cancer (one that hasn't spread). Sometimes, chemotherapy (drugs), cryosurgery (freezing), or some treatment combination may be tried.

Prostate cancer usually occurs in older men, who often die of other causes before slowly growing prostate cancer spreads or causes symptoms. When occurring in younger men, it tends to much more aggressive. Also, treatments generally have side effects, such as incontinence and erectile dysfunction, that may decrease quality of life. Choosing a treatment is therefore hard. The decision whether to try to cure localized prostate cancer is a trade-off between survival and

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quality of life.

DOs and DON'Ts in Managing Prostate Cancer:

✓ **DO** have yearly DRE and PSA tests as your doctor suggests.

⃠ **DON'T** eat too much saturated fat.

⃠ **DON'T** smoke.

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FOR MORE INFORMATION

Contact the following sources:

- American Cancer Society Tel: (800) 227-2345 **Website: http://www.cancer.org**
- National Cancer Institute Tel: (800) 422-6237 **Website: http://www.cancer.gov**
- American Urological Association Tel: (866) RING-AUA (746-4282) **Website: http://www.auanet.org**

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PROSTATE CANCER

SCREENING AND PREVENTION

What Is Prostate Cancer?

Prostate cancer is a growth of abnormal cells in the prostate gland. The prostate is a walnut-shaped gland in the male reproductive tract that makes seminal fluid, which mixes with sperm and other fluids. This gland surrounds the urethra, near its connection to the bladder. The urethra is the tube that carries urine from the bladder, through the penis, to outside the body. Cancer develops when cells mutate and begin to multiply out of control. These cells may spread (metastasize) from the prostate to other parts of the body, especially bones and lymph nodes. In the past 20 years, the survival rate for all stages of prostate cancer has improved because of early detection and treatment.

A higher risk of developing prostate cancer may be related to age (especially older than 65), race (African American), and family history (father, brother).

What Are the Symptoms of Prostate Cancer?

Early prostate cancer may not cause symptoms. Some men, however, may have pain, difficulty urinating, and rarely problems with erections (erectile dysfunction).

Other symptoms include a weak or interrupted flow of urine, need to urinate often (especially at night), difficulty holding back urine, inability to urinate, pain or burning when urinating, blood in the urine or semen, and nagging pain in the back, hips, or pelvis.

It is important to realize that these symptoms may have other less serious causes, such as benign prostatic hypertrophy (BPH) or infection. Always see your doctor for a diagnosis.

How Is Prostate Cancer Diagnosed?

The doctor will take a complete medical history and do a physical examination including a digital

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rectal examination (DRE). A blood test called prostate-specific antigen test (PSA test) will also be done.

The doctor will usually recommend that a DRE and a PSA be done every year for men older than 50 until at least age 70. Men in high-risk groups, such as African Americans or those with a strong family history of prostate cancer, should ask about being tested at a younger age. The diagnosis of cancer can be confirmed only with a biopsy (a tissue sample of the prostate).

What Are the Complications of Prostate Cancer?

Many prostate cancers don't cause death, but some can spread outside the prostate gland and metastasize through the blood and lymph nodes to bones and major organs. This is known as extracapsular spread.**{5**

DOs and DON'Ts in Preventing Prostate Cancer:

✓ **DO** have a yearly DRE as recommended by your doctor.

✓ **DO** have a yearly PSA test as recommended by your doctor.

✓ **DO** remember that the majority of men who reach age 80 are found to have prostate cancer but generally die from other causes unrelated to their prostate cancer.

⃠ **DON'T** ignore possible symptoms of prostate cancer such as pain or difficulty urinating.

⃠ **DON'T** smoke.

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MANAGING YOUR

PROSTATITIS

What Is Prostatitis?

The prostate is a walnut-sized gland in the male reproductive tract. It lies in front of the rectum, just below the bladder, which stores urine. The prostate surrounds the urethra (tube that takes urine out of the body). Prostatitis refers to inflammation of the prostate gland. The swollen, painful gland can make it hard to urinate. About 50% of men may have prostatitis sometime in life.

Prostatitis can be subdivided into four disorders. Acute bacterial prostatitis is least common, usually seen in young or middle-aged men. Chronic bacterial prostatitis is rather uncommon, usually found in men with a problem in the prostate. The most common is chronic pelvic pain syndrome (CPPS), or prostatodynia. Men have prostatitis symptoms but without inflammation or bacterial infection (few or no infection-fighting white blood cells in prostate secretions).

Nonbacterial prostatitis refers to inflammation with infection-fighting white blood cells but no bacterial infection.

What Causes Prostatitis?

Bacteria causing acute and chronic prostatitis get into the prostate from the urethra by backward flow of infected urine.

Prostatitis may also result from sexual contact, infection with chlamydia or mycoplasma, or chemical or immune reaction to urine.

Muscle spasm may cause CPPS.

What Are the Symptoms of Prostatitis?

Common symptoms are fever, chills, pain when urinating, urinating more often than usual, pain in the lower back or penis, and slow urine stream. Sometimes, symptoms are severe and start

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suddenly. Other times, symptoms are milder and start slowly. Chronic bacterial prostatitis may cause no symptoms, but bloody urine, incontinence, or bladder infection may occur. Additional symptoms of nonbacterial prostatitis or CPPS are pelvic pain and urgent, burning, or nighttime urination.

How Is Prostatitis Diagnosed?

The doctor may examine the prostate by doing a rectal exam (inserting a gloved finger into the rectum). The gland may feel warm, tender, and swollen. A tender prostate suggests acute bacterial prostatitis. An enlarged prostate is common in chronic bacterial prostatitis. Men with nonbacterial prostatitis or CPPS may have a normal prostate.

The doctor may check samples of urine, prostate gland fluid, and blood for infection.

How Is Prostatitis Treated?

Antibiotics are usually given for acute bacterial prostatitis for 14 days to 4 weeks. More serious infections may need intravenous antibiotics. Men with chronic bacterial prostatitis usually take antibiotics for 4 weeks. Relapses or infections that don't clear up may need long-term antibiotics. Nonbacterial prostatitis and CPPS may need no specific treatment other than ibuprofen or similar pain-relieving medications.

DOs and DON'Ts in Managing Prostatitis:

✓ **DO** finish all the antibiotic medicine when prescribed by your doctor.

✓ **DO** tell your doctor about medicines you take for other illnesses.

✓ **DO** call your doctor if you have burning or pain with urination or you see blood in the urine.

✓ **DO** call your doctor if you have symptoms plus fever, chills, and sweats.

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✓ **DO** call your doctor if you have urinary frequency, urgency, or nighttime urination or if you leak urine.

⃠ **DON'T** ride a bicycle. This puts pressure on the prostate gland.

⃠ **DON'T** eat foods or drink alcohol if they make symptoms worse.

⃠ **DON'T** stop taking your medicine even if you start to feel better.

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FOR MORE INFORMATION

Contact the following source:

- The Prostatitis Foundation Tel: (888) 891-4200 **Website:** **http://www.prostatitis.org**

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MANAGING YOUR

PSEUDOGOUT

What Is Pseudogout?

Pseudogout is a very painful form of joint inflammation and arthritis that may occur at any age but usually affects people older than 60. Normally only one joint at a time, usually knees, is involved. Other joints affected are ankles, wrists, elbows, and shoulders. Because it's similar to gout but has a different cause, it's called pseudogout, meaning false gout.

About 5% of people over age 60 get pseudogout.

What Causes Pseudogout?

Release and accumulation of chemical crystals into a joint causes the attacks. These crystals, made of calcium pyrophosphate dehydrate (CPPD), cause joint inflammation (redness, swelling). Why some people get pseudogout and others don't isn't clear. It's not caused by an infection and is not contagious.

What Are the Symptoms of Pseudogout?

Symptoms are joint pain, swelling, warmth, and redness that start quickly. Pain is often constant and gets worse if the joint is moved. Activities such as walking, dressing, and lifting may be hard. Sometimes, more than one joint is involved.

Attacks may occur at any time, but certain events such as surgery or an illness can trigger them. Symptoms usually go away within days after treatment; untreated they may last for several weeks or more. Between attacks, most people have no symptoms.

How Is Pseudogout Diagnosed?

The only way to be certain of the diagnosis is to put a needle into the affected joint, remove joint fluid, and look for pseudogout crystals under a microscope.

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How Is Pseudogout Treated?

There's no way to get rid of the crystals, but medicine can help symptoms. Nonsteroidal antiinflammatory drugs (NSAIDs), such as ibuprofen, naproxen, or indomethacin, are used for treatment.

Sometimes, stronger antiinflammatory medicines, such as prednisone or colchicine, are needed.

Removal of joint fluid followed by cortisone injection into the joint is another common treatment. Cortisone injections usually give the fastest and most complete relief of pain and swelling.

Regardless of the treatment, it is important to rest the affected joint until symptoms start to go away.

DOs and DON'Ts in Managing Pseudogout:

✔ **DO** rest the affected joint until you start to get better.

✔ **DO** take your medicines as prescribed.

✔ **DO** call your doctor if treatment isn't improving symptoms, you start to lose full motion in the affected joint, or you have worsening warmth, redness, or pain after a cortisone injection.

⃠ **DON'T** wait to see whether side effects of medicine will go away. Call your doctor.

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FOR MORE INFORMATION

Contact the following sources:

• The Arthritis Foundation Tel: (800) 283-7800 **Website:** http://www.arthritis.org

• American College of Rheumatology Tel: (404) 633-3777 **Website:** http://www.rheumatology.org

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MANAGING YOUR

PSEUDOMEMBRANOUS COLITIS

What Is Pseudomembranous Colitis?

Pseudomembranous colitis, also known as *Clostridium difficile* infection (CDI), is a disorder involving inflammation (swelling, redness) of the large intestine (colon, or large bowel). It's related to use of antibiotics. Antibiotics given to treat an infection can destroy bacteria that normally lives in the colon. This makes it easier for other more harmful bacteria to grow in its place, such as the one named *Clostridium difficile*. It grows excessively and the colon becomes inflamed, and severe diarrhea occurs.

This disorder affects nearly 3 million people each year in the U.S. It occurs more often in adults than in children and in people in hospitals and nursing homes. Patients who had recent surgery or are having cancer treatments have a slightly greater chance of getting it.

Most people respond to treatment and have no lasting effects, but recurrences are not uncommon. Untreated, the condition can lead to severe dehydration from the diarrhea, and in rare cases can be fatal.

What Causes Pseudomembranous Colitis?

The antibiotics most frequently responsible for this colitis are penicillins, cephalosporins, clindamycin, and sulfa drugs. However, any antibiotic may cause the disease.

What Are the Symptoms of Pseudomembranous Colitis?

Symptoms are diarrhea that is watery and yellow-green, smells foul, and may be bloody. Cramps and pain in the abdomen (belly) and fever also occur.

Symptoms usually start 4 to 10 days after beginning antibiotics. However, some people may not have symptoms until after stopping the antibiotics.

Severe colitis may have symptoms of shock, low blood pressure, weak pulse, and increased heart rate.

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How Is Pseudomembranous Colitis Diagnosed?

The doctor diagnoses the condition by doing cultures of stools (bowel movements) that grow the bacteria. Blood tests may also be done to check for signs of infection and dehydration. If the diagnosis isn't clear or therapy isn't helping, sigmoidoscopy can be done. In this procedure, a lighted flexible tube is inserted into the rectum to look at the bowel and to get tissue samples for study with a microscope. Abdominal x-rays or CT scanning may be done if complications are suspected.

How Is Pseudomembranous Colitis Treated?

The key to treatment is to stop taking the antibiotics. People with severe symptoms may need hospitalization and rehydration with intravenous fluid. The diet is then slowly returned to normal. The antibiotic metronidazole is prescribed to destroy the *Clostridium difficile* bacteria. When this antibiotic is ineffective, the antibiotic vancomycin can be used.

DOs and DON'Ts in Managing Pseudomembranous Colitis:

✓ **DO** increase drinking fluids to avoid dehydration.

✓ **DO** avoid dairy products, which may make diarrhea worse.

✓ **DO** call your doctor if you have symptoms of pseudomembranous colitis, such as diarrhea, bloody stool, and abdominal pain, especially when taking or just finishing antibiotics.

✓ **DO** call your doctor if your symptoms don't get better with treatment.

✓ **DO** call your doctor if new symptoms appear during treatment.

✓ **DO** call your doctor if you see signs of dehydration, such as dry skin and mouth, rapid pulse,

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confusion, and tiredness.

⦸ **DON'T** use antidiarrheal agents unless your doctor says that you should.

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FOR MORE INFORMATION

Contact the following sources:

- National Digestive Diseases Information Clearinghouse Tel: (800) 891-5389 **Website:** **http://www.niddk.nih.gov/health/digest/nddic.htm**
- American College of Gastroenterology Tel: (703) 820-7400 **Website:** **http://www.acg.gi.org**

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MANAGING YOUR

PSORIASIS

What Is Psoriasis?

Psoriasis is a chronic skin disorder. Skin cells reproduce too rapidly and accumulate and form silvery patches on the surface of the skin. It can be mild to severe. Psoriasis is common but occurs less in African, Asian, and Native American people. It affects men and women equally. It is a lifelong disorder that usually starts in adolescence or early adulthood.

Outbreaks can start with minor injury, stress, infections, exposure to cold and dry climates, obesity, and other autoimmune conditions. They can also occur without an obvious reason.

What Causes Psoriasis?

The cause is unknown but psoriasis is likely autoimmune. Autoimmune means that the body's immune system attacks normal parts of the body and causes injury or disease. Psoriasis is not infectious or cancerous.

What Are the Symptoms of Psoriasis?

Skin lesions are slightly raised, silvery white scales with red or pink margins. Painful cracks can appear. Lesions may be single, in certain body parts, or all over the body.

Skin of the scalp, face, elbows, hands, knees, feet, chest, lower back, and folds between buttocks is usually affected. Fingernails and toenails are often involved.

Itching may be present, and joint pain sometimes occurs. Scratching can cause bacterial infections. The skin's appearance can lead to feeling embarrassed.

Up to a quarter of people with psoriasis have symptoms of arthritis that worsen when the psoriasis becomes more severe.

How Is Psoriasis Diagnosed?

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The doctor makes a diagnosis from the look of the skin, nails, and scalp. The doctor may do a skin biopsy (i.e., remove a small piece of skin) for study when the diagnosis is unclear.

How Is Psoriasis Treated?

Psoriasis is treatable but not curable. The goal of treatment is to decrease inflammation and control skin shedding. A doctor who treats skin problems (dermatologist) may be involved in care. Avoiding things that trigger psoriasis and using prescribed medications can control and lessen symptoms. General measures include good skin hygiene, avoiding skin injury and dryness, exposing skin to moderate sunlight, and oatmeal baths. Treatment of mild to moderate psoriasis includes topical creams, lotions, shampoos, and ointments containing coal tar. These will reduce inflammation (redness), scaling, and itching. Steroids and other antiinflammatory drugs applied to skin (topical) are for mild to moderate cases and as combination therapy for more severe cases. Other treatments include salicylic acid in mineral oil (removes plaques), PUVA (psoralen and exposure to ultraviolet light A [UVA]), immunosuppressant drugs (e.g., methotrexate, isotretinoin), antihistamines (for itching), and antibiotics (for secondary bacterial infections).

DOs and DON'Ts in Managing Psoriasis:

✓ **DO** take medicines as prescribed by your doctor.

✓ **DO** tell your doctor about all of your medicines, including over-the-counter.

✓ **DO** expose your skin to some sunlight.

✓ **DO** maintain good skin hygiene.

✓ **DO** keep follow-up doctor appointments.

✓ **DO** watch your skin for healing and for bacterial infections. Redness around skin lesions,

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pus, pain or swelling of lesions or lymph glands, and fever are signs.

✓ **DO** avoid skin injuries and dry skin. These can trigger outbreaks.

✓ **DO** call your doctor if signs of infection appear, lesions become worse, or new lesions start even with therapy.

✓ **DO** call your doctor if you see pustules on the skin, especially with fever, fatigue, muscle aches, or joint pain or swelling.

⃠ **DON'T** stop your medicine or change the dose without asking your doctor.

⃠ **DON'T** exceed recommended medicine doses.

⃠ **DON'T** use over-the-counter topical steroids on the face or genitals without checking with your doctor.

⃠ **DON'T** stop steroids or immunosuppressants suddenly, to avoid rebound worsening of psoriasis.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Dermatology Tel: (866) 503-SKIN (503-7546) **Website:** **http://www.aad.org**
- National Psoriasis Foundation Tel: (503) 244-7404, (800) 723-9166 **Website:** **http://www.psoriasis.org**

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MANAGING YOUR

PSORIATIC ARTHRITIS

What Is Psoriatic Arthritis?

Psoriatic arthritis is a type of arthritis affecting people with the serious skin condition psoriasis. It causes inflammation of certain joints and a rash. Areas most often affected are fingers, neck, and lower back. Less often, eyes, nails, and heart are inflamed. The rash usually starts before the joint pain, but some people aren't aware of the rash until after pain develops. Psoriasis may affect the nails, scalp, umbilicus (belly button), and genital area. Psoriatic arthritis occurs most often between the ages of 30 and 50 years, equally in men and women.

What Causes Psoriatic Arthritis?

The cause isn't known, but certain hereditary and environmental factors may increase the risk of getting psoriatic arthritis. The condition can run in families but isn't infectious and can't be caught from others.

What Are the Symptoms of Psoriatic Arthritis?

Symptoms are pain, swelling, and warmth of certain joints plus a rash. Psoriatic arthritis of the fingers can make it hard to write, open jars, and lift and carry items. An affected back can cause problems bending or standing. Psoriatic arthritis of the neck may make it hard to move the head. The rash from psoriasis can cause embarrassment in social situations.

How Is Psoriatic Arthritis Diagnosed?

For diagnosis, the doctor uses a medical history; examines the joints, skin, and nails; and orders laboratory tests. X-rays of the joints, neck, and lower back may also be done. Laboratory tests may include the erythrocyte sedimentation rate (ESR), which measures inflammation, and a complete blood cell count (CBC).

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How Is Psoriatic Arthritis Treated?

No cure exists. However, with earlier detection, better medicines, and good treatment most people can lead a full life. The best way to manage the illness is to use a combination of medicines, physical therapy, exercise, and education. Medications such as nonsteroidal antiinflammatory drugs (NSAIDs) help reduce inflammation causing pain and swelling. If these medicines don't work well, disease-modifying drugs may slow down the disease process. These drugs tend to have serious side effects and need close watching. A dermatologist (skin doctor) may prescribe medicines for psoriasis.

Learning about arthritis is critical because it's a lifelong disease. Exercise is important for proper joint movement and muscle strength. Alternating periods of rest and activity helps manage fatigue.

DOs and DON'Ts in Psoriatic Arthritis:

✓ **DO** take your medicines as prescribed.

✓ **DO** call your doctor if you have side effects from the drugs or if the drugs don't help joint pain, stiffness, or swelling or the psoriasis.

✓ **DO** ask your doctor what over-the-counter pain drugs and skin products you may use with the prescription medicines.

✓ **DO** exercise, to help maintain joint range of motion and muscle strength.

✓ **DO** call your doctor if you need a referral to a physical or occupational therapist for exercise or joint protection.

⃠ **DON'T** wait and see if a drug's side effect will go away. Call your doctor.

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- ⦸ **DON'T** give up. If one drug doesn't help, work with your doctor until you find one that does.
- ⦸ **DON'T** follow a specific diet without the ok of your doctor.
- ⦸ **DON'T** continue an exercise program that causes pain. Pain usually means that the exercise must be modified for you.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- The Arthritis Foundation Tel: (800) 283-7800; or (503) 297-1545 **Website:** **http://www.arthritis.org**
- The American College of Rheumatology Tel: (404) 633-3777 **Website:** **http://www.vascularweb.com**

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MANAGING

PSYCHOSIS

What Is Psychosis?

Psychosis is a medical term used for an impaired or abnormal mental state with delusions or hallucinations. Delusions are false beliefs. Hallucinations are things that are seen or heard but aren't really there.

What Causes Psychosis?

The cause is unknown. Psychosis is thought to result from a combination of social, genetic, environmental, psychological, and physical factors. It's not contagious. Psychosis is a key symptom of many mental illnesses including schizophrenia, depression, schizoaffective disorder, and bipolar disorder. Psychosis may also be one of the symptoms in many conditions, such as human immunodeficiency virus (HIV) infection, Parkinson's disease, malaria, strokes, brain tumors, and seizure disorders. Medicines, including those for Parkinson's disease and seizures, steroids, and chemotherapy, can cause a psychotic episode. Illicit drugs (e.g., LSD, cocaine, alcohol, amphetamines, marijuana, PCP) can also lead to a psychotic change.

What Are the Symptoms of Psychosis?

Psychosis means that people lose contact with reality. A disorganized thought pattern usually results in odd speech (e.g., jumbling words, making no sense with words, thought blocking, and rhyming) and lack of insight. Behavior is bizarre, odd, and unpredictable. People may say that they hear voices telling them to do things (auditory hallucinations). Others may see signs or images telling them to do something (visual hallucinations).

How Is Psychosis Diagnosed?

The doctor makes a diagnosis from a medical history and physical examination. The doctor will

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do tests to rule out medical illnesses. These include blood tests and imaging studies, such as computed tomography (CT) and magnetic resonance imaging (MRI) of the brain. A spinal tap may also be done. In this procedure, the doctor puts a needle into the spine to collect fluid. This fluid is checked for infection, cancer, and other causes of psychosis.

How Is Psychosis Treated?

Medicines called neuroleptics are used for acute treatment of people with bizarre, unpredictable behavior. The aim is to prevent people from hurting themselves or others. These medicines include haloperidol and drugs called benzodiazepines, which are medicines for anxiety (e.g., lorazepam, alprazolam).

Treatment then depends on the underlying cause. For example, for a mental illness such as depression or schizophrenia, a psychiatrist (specialist in mental and emotional disorders) will be involved in treatment with antidepressant or antipsychotic medicines. People with conditions such as Parkinson's disease and seizure disorders will take medicines for those disorders. For substance abuse (e.g., alcohol, narcotics), counseling is offered.

Psychosis often means that a severe mental illness is present. Cognitive behavioral therapy may help. Cognitive therapy teaches people how certain thinking patterns cause symptoms. Behavioral therapy breaks the connection between worry about symptoms and reactions to those symptoms.

DOs and DON'Ts in Managing Psychosis:

✓ **DO** remember that psychosis is a symptom, not a diagnosis.

✓ **DO** call your doctor if you need a referral to a psychiatrist or psychologist.

✓ **DO** call your doctor if you feel depressed or anxious.

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✓ **DO** call your doctor if you think that you will harm yourself or others.

✓ **DO** call your doctor if you hear voices or see things that aren't really there.

⃠ **DON'T** do drugs. Alcohol, amphetamines, cocaine, sleeping agents (e.g., barbiturates), and antianxiety medicines (e.g., benzodiazepines) can all cause psychosis.

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FOR MORE INFORMATION

Contact the following sources:

- Mental Health America Tel: (800) 969-6642 **Website:** http://www.nmha.org
- American Psychiatric Association Tel: (888) 357-7924 **Website:** http://www.psych.org

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UNDERSTANDING

PUBERTY: FEMALE

What Is Puberty?

Puberty is the time when girls change into adults. All girls (and boys) go through puberty. Everyone is different, but changes usually start between ages 7 and 13. Hormones bring about puberty.

What Changes Occur?

The main sign of puberty is developing breasts, first with little swellings under nipples. Usually about 2 years after breasts start developing, estrogen causes periods (menstruation) to begin. Ovaries make estrogen and other female hormones. Each month, an ovary releases an egg. Pregnancy occurs if an egg is fertilized. If eggs aren't fertilized, the lining of the uterus (womb) falls off and becomes blood flowing out of the body through the vagina. Periods last 2 to 7 days. Periods may not be regular (occur at same time every month) for a year or two after periods first appear, but should become regular/monthly after that time. Many girls feel better using pads, but tampons are also fine to use right away.

Sometimes girls have PMS (premenstrual syndrome): cramps in the lower abdomen (belly), moody or emotional feelings, and puffy or swollen (bloated) body.

Before periods begin, girls start to grow taller really fast. Other hormones cause hair growth under the arms and in pubic areas (on and around genitals), armpit sweating, and body odor. The new hormones can cause acne (pimples) on the face, back, or chest. Many girls have a thin, white vaginal discharge (oozing) about a year before periods start.

Girls may feel confused or have strong new emotions, especially feelings about sex. Getting upset easily or angry with friends or families (particularly parents) and feeling anxious about body changes are common.

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What Risks Are Possible During Puberty?

Sexually transmitted diseases (STDs) can be serious problems for sexually active girls. Because some STDs have no symptoms, regular doctor checkups are important. HPV (human papillomavirus) infection is the most common STD, especially in teen girls. Vaginitis, with bad-smelling vaginal discharge and swelling, is also a common problem. Chemical or physical irritation and infections can cause it.

How Do Girls Avoid Pregnancy?

Girls can get pregnant even the first time having sex or during periods. It's possible without having orgasms. The only way to avoid pregnancy is abstinence (not have sex). Sexually active girls should learn about contraception, such as barrier methods (diaphragms, condoms) and hormones (birth control pills). Girls should rely on doctors and parents, not friends, for birth control information.

DOs and DON'Ts in Managing Puberty:

- ✓ **DO** talk to parents, teachers or doctors if you are feeling exceedingly sad, depressed, anxious or hopeless.
- ✓ **DO** remember that everyone changes at her own pace: how long periods last, how often periods come, heavy or light bleeding, and PMS symptoms.
- ✓ **DO** use mild soap to wash your face. Don't squeeze or pick pimples. Your doctor can suggest medicines for acne.
- ✓ **DO** experiment until you find the pad or tampon that's best for you. Remember, pads and tampons don't show through clothing. Nobody will know that you have your period. Change

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tampons frequently—don't leave in for more than one day.

✓ **DO** exercise or use a heating pad or over-the-counter pain medicine for PMS symptoms. Exercise is also important for a healthy body.

✓ **DO** keep clean with showers, especially after sports, to control body odor. Deodorant can help.

✓ **DO** learn about birth control and safe sex methods from doctors and/or parents. Use condoms every time you have sex. Practice safe sex!

⦸ **DON'T** follow fad diets. Maintain a healthy weight.

⦸ **DON'T** feel pressure to have sex because "everyone is doing it."

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Women's Health Information Center Tel: (800) 994-9662
- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website: http://www.acog.org**

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UNDERSTANDING

PUBERTY: MALE

What Is Puberty?

Puberty is the time when boys change into adults. All boys (and girls) go through puberty. Everyone is different, but changes usually start between ages 10 and 15. Hormones cause puberty to happen.

What Changes Occur?

In boys, the first sign of puberty is the growth of testicles (testes), which make more testosterone. The penis and scrotum also grow bigger. Testes produce sperm, which can be released at night during sleep (nighttime ejaculations, or wet dreams). These emissions are normal in puberty.

Boys then start to grow taller really fast (a growth spurt) and get larger muscles and wider shoulders. The voice cracks and gets deeper. Hair grows under the arms, on the face and chest, and in pubic areas (on and around genitals). Other hormones cause armpit sweating and body odor. The new hormones can cause acne (pimples) on the face, back, or chest. During early puberty, some boys may have a slight swelling of the breasts, but this will go away.

Boys may feel clumsy or awkward, but these feelings are normal. Boys may also feel confused and have strong new emotions, especially feelings about sex. Getting upset easily or angry with friends or families (especially parents) and feeling anxious about body changes are common. Boys can struggle with abstract, logical thought, such as algebra.

What Risks Do Boys Face During Puberty?

Sexually active boys can get sexually transmitted diseases (STDs), which can be serious problems. Compared with girls, boys more often have no symptoms and give their partners STDs without knowing that they do. Regular doctor checkups are thus important. Using condoms (rub-

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bers) will help prevent both STDs and pregnancy.

How Do Boys Avoid Getting Girls Pregnant?

As a result of changes during puberty, boys can get girls pregnant. Be sure to get the truth about getting girls pregnant. Don't be misinformed. For example, pregnancy can occur even the first time a boy has sex. Pregnancy can result even if a boy has no full orgasm or removes the penis from the girl's vagina before completing ejaculation. Sex during a girl's period in some cases can also lead to pregnancy if it's not a normal menstrual period.

The only way to completely avoid getting girls pregnant is abstinence (not have sex). Sexually active boys should learn about contraception such as barrier methods (condoms). Boys should rely on doctors and parents, not friends, for birth control information.

DOs and DON'Ts in Managing Puberty:

✓ **DO** remember that everyone changes at his own pace, such as how much hair you grow on your face and when your voice gets deeper.

✓ **DO** use a mild soap to wash your face. Don't squeeze or pick pimples. Your doctor can suggest medicines to clear up acne.

✓ **DO** keep clean with showers, especially after sports, to control body odor. Deodorant can also help.

✓ **DO** learn about how to avoid getting girls pregnant or passing STDs to others. Practice safe sex!

⃠ **DON'T** worry about wet dreams, which are normal in puberty.

⃠ **DON'T** feel pressure to have sex because "everyone is doing it."

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FOR MORE INFORMATION

Contact the following sources:

- American Urological Association Tel: (866) 746-4282 **Website: http://www.urologyhealth.org/**
- National Institutes of Health Tel: (301) 496-4000 **Website: http://www.nih.gov**
- American Academy of Family Physicians Tel: (800) 274-2237 **Website: http://www.familydoctor.org/**

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MANAGING YOUR

PULMONARY EMBOLISM

What Is a Pulmonary Embolism (PE)?

A pulmonary embolism (PE) is an emergency medical condition that occurs in the lungs as a result of a blocked blood vessel. The blockage occurs when a blood clot dislodges from a vein (venous thrombus) in another part of the body (usually the legs) and reaches the lungs. It can be life-threatening and needs immediate treatment.

What Causes a PE?

A blood clot is a clump of platelets with red blood cells and the protein fibrin. Platelets are cells that help stop injured blood vessels from bleeding. Clots usually form to help stop bleeding, but sometimes they occur due to blood clotting abnormalities. A clot that stays in a vein is called a thrombus. One that moves to another part of the body is called an embolus. Clots can also form during long periods of inactivity if blood moves too slowly through the veins. The clot formed in another part of the body moves to the lungs through the bloodstream. Veins deep in the legs are the most common source of clots.

What Are the Symptoms of PE?

The most common symptoms are shortness of breath, chest pain, coughing up blood, and fast heartbeat. Nausea, fainting, sweating, wheezing, and clammy or bluish skin are others. The chest pain may last from minutes to hours. PE can be fatal.

How Is a PE Diagnosed?

The doctor makes a diagnosis from an examination and symptoms. Tests include electrocardiography (ECG), chest x-ray, blood tests, computed tomography (CT) of the chest, or lung scan. Blood tests check for clotting problems (D-dimer) and lung gases such as oxygen level in the

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blood. In rare cases when the tests are inconclusive and pulmonary embolus is still suspected, a special x-ray known as angiography may be done. Angiography requires injecting a dye in the veins before x-rays can be taken.

How Is a PE Treated?

Treatment involves hospitalization and intravenous medicines (heparin) to dissolve the clot and stop new ones from forming. Anticoagulant drugs (warfarin or newer anticoagulants) will also be given by mouth and continued for at least 3 months. Special compression stockings may help control swelling in the legs. The doctor will suggest that people who are overweight lose weight since obesity and sedentary lifestyle are major risk factors for pulmonary embolism.

In rare cases, a special (Greenfield) filter can be put in the main vein (vena cava) going from the legs and pelvis to the heart to stop clots from getting into the lungs.

DOs and DON'Ts in Managing PE:

✓ **DO** report bleeding or bruising easily to your doctor if you take medicine to prevent clots from forming.

✓ **DO** avoid activities that may cause injury.

✓ **DO** move around when you're at work or traveling. If you can't get up, move your legs and bend your ankles and toes. Avoid long periods of bed rest or sitting or standing in one place.

✓ **DO** call your doctor if you develop pain or swelling of your legs, have chest pain or are short of breath, or cough up blood.

✓ **DO** try to keep your feet higher than your hips when you're lying down or sitting.

⦸ **DON'T** smoke. Smoking may increase your risk of forming blood clots.

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⦸ **DON'T** wear clothing that restricts blood flow in your legs.

⦸ **DON'T** forget that blood thinners such as warfarin require frequent monitoring with blood tests to ensure that you are receiving the correct dose.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Chest Physicians Tel: (847) 498-1400, (800) 343-2227 **Website:** **http://www.chestnet.org**
- American Thoracic Society Tel: (212) 315-8600 **Website:** **http://www.thoracic.org/**

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MANAGING YOUR

PULMONARY HYPERTENSION

What Is Pulmonary Hypertension?

Pulmonary hypertension is high blood pressure in the pulmonary artery. The pulmonary artery is the blood vessel that takes oxygen-poor blood from the right side of the heart into the lungs. Blood in the lungs picks up oxygen and flows back to the left side of the heart and the rest of the body. The average pulmonary artery pressure is about 14 mmHg at rest. Hypertension is pressure higher than 25 mmHg at rest or 30 mmHg during exercise. Pulmonary hypertension is primary or secondary. Primary pulmonary hypertension (PPH) is a very rare and serious condition. More women than men have it, usually by age 30 to 40. Secondary pulmonary hypertension occurs in people with other diseases. It's more common than PPH.

What Causes Pulmonary Hypertension?

The cause of PPH isn't known. People with secondary pulmonary hypertension often have severe pulmonary disease, COPD (emphysema or chronic bronchitis), or blood clots (pulmonary emboli) in the lungs.

What Are the Signs and Symptoms of Pulmonary Hypertension?

The first symptom is often tiredness. Breathing problems (dyspnea), dizziness, and fainting are also seen early. Ankle or leg swelling (edema), bluish lips and skin, and chest pain (angina) are other possible manifestations of pulmonary hypertension. People with PPH may also have a racing pulse or feel that they can't get enough air. Palpitations (unusually strong or odd heartbeats) can also occur.

How Is Pulmonary Hypertension Diagnosed?

The health care provider first rules out other causes of pulmonary hypertension. These causes

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include emphysema, pulmonary emboli, heart valve disease, neurologic muscle disorders, and obstructive sleep disorder. Blood tests, X-rays, echocardiography, pulmonary function tests, and imaging studies of the lungs are usually done. Imaging may include nuclear scans, computed tomography (CT), and magnetic resonance imaging (MRI). Cardiac catheterization may also be done if the diagnosis remains unclear. In this test, a tube (catheter) is put into a leg or neck artery and passed into the heart to measure pulmonary artery pressures.

How Is Pulmonary Hypertension Treated?

The main goal is to lower pulmonary artery pressures and increase oxygen levels. Oxygen is given to improve the oxygen level. Strenuous exertion or exercises, which lead to lower oxygen levels in the blood and symptoms, should be avoided. Medicines used in the treatment of pulmonary hypertension include prostanoids (epoprostenol, treprostinil, iloprost, and beraprost). Other effective medicines are endothelin receptor antagonists, phosphodiesterase inhibitors, blood thinners, and calcium-channel blockers. Diuretics (water pills) can be given for ankle and leg swelling. If these treatments don't help shortness of breath at rest, lung and heart-lung transplantation may be an option.

DOs and DON'Ts in Managing Pulmonary Hypertension:

✓ **DO** understand that PPH has no known cure. However, treatments can improve quality of life.

✓ **DO** see lung and heart specialists who are experienced in the treatment of pulmonary hypertension.

✓ **DO** call your health care provider if your shortness of breath is worse. Call if you have leg swelling, chest pain, or palpitations. Call if you're thinking of becoming pregnant. Getting

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pregnant may not be advisable if you have pulmonary hypertension.

- ⃠ **DON'T** be afraid to ask for a second opinion.
- ⃠ **DON'T** smoke!
- ⃠ **DON'T** use birth control pills. They may increase your risk of blood clots.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Heart, Lung, and Blood Institute Information Center Phone: 301-592-8573

  Website: www.nhlbi.nih.gov
- Pulmonary Hypertension Association (PHA) Phone: 1(800) 748-7274
- American Lung Association Phone: 800-LUNG-USA **Website: www.lungusa.org**
- Centers for Disease Control and Prevention

  Website:

  http://www.cdc.gov/DHDSP/data_statistics/fact_sheets/fs_pulmonary_hypertension.htm

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MANAGING YOUR

PULMONARY HYPERTENSION AND THROMBOEMBOLIC DISEASE

What Are Pulmonary Hypertension and Thromboembolic Disease?

Pulmonary hypertension (PH) is high pressure in the blood vessels in the lungs and right side of the heart. PH starts because tiny blood vessels (arteries and capillaries) in the lungs get hard, narrow, blocked, or destroyed. The heart works harder to pump blood through the lungs. The heart weakens, and heart failure can result. It's a serious condition with treatments but no cure. One reason for PH is thromboembolic disease (TED), or blockage because of pulmonary thromboembolism (PE). Thrombi (blood clots) move from deep leg veins through the heart into pulmonary arteries.

What Causes PH and TED?

Idiopathic pulmonary hypertension (IPH) is the name of the condition when no cause is known. IPH may be inherited. Secondary PH, resulting from another disease, is much more common than IPH. These diseases include PE, lung diseases (emphysema, fibrosis), and heart diseases. Others are connective tissue disorders, apnea, sickle cell anemia, liver disease (cirrhosis), AIDS, and lupus.

PE is a complication of venous thrombosis, when clots break loose and travel to block lung blood vessels.

What Are the Symptoms of PH and TED?

Most people with mild or moderate PH don't have symptoms. When they occur, they include shortness of breath with exertion, tiredness, chest pain, and fainting.

PE symptoms are shortness of breath, tiredness, dizziness, fainting, and swelling (edema) in the ankles, legs, abdomen (belly). People may have palpitations, abnormal heartbeats, wheez-

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ing, and bluish lips and skin. They may cough up blood. Many people have no symptoms in the early stages of this disease.

How Are PH and TED Diagnosed?

The doctor may use echocardiography, lung function testing, perfusion lung scans, X-rays, computed tomography (CT) scan, genetic tests, right-sided heart catheterization, and open-lung biopsy.

How Are PH and TED Treated?

Treatment is complicated and needs a team approach. Drugs such as warfarin, an anticoagulant, help PH due to blood clots. Vasodilators open narrowed blood vessels. High-dose calcium channel blockers, diuretics, and oxygen are often used. If other treatments don't work, lung or heart-lung transplantation may be possible.

In people with pulmonary embolism, treatment goals are to stabilize the person's condition and then prevent emboli. Warfarin is used to prevent further clots. Inferior vena cava filter devices can be used in people who cannot have anticoagulants.

DOs and DON'Ts in Managing PH and TED:

✓ **DO** get plenty of rest, but stay as active as possible. Ask your doctor which exercises are best for you.

✓ **DO** avoid traveling to or living at high altitudes.

✓ **DO** eat a low-salt, low-fat diet. Keep to a healthy weight.

✓ **DO** reduce stress with yoga, meditation, and biofeedback. Relax with warm baths, music, or good books.

⦸ **DON'T** smoke.

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⦸ **DON'T** stop taking your medicines or take over-the-counter drugs without your doctor's approval.

⦸ **DON'T** get pregnant. Don't use oral contraceptives. They may cause clots.

⦸ **DON'T** do things that cause prolonged straining, such as lifting heavy objects or weights.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:** **http://www.americanheart.org**
- American College of Cardiology Tel: (800) 253-4636 **Website: http://www.acc.org**

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MANAGING YOUR

PYELONEPHRITIS

What Is Pyelonephritis?

Pyelonephritis is a kidney infection. It usually starts as a urinary tract infection (UTI), which is an infection of the bladder with bacteria. The bladder stores urine before it leaves the body. These bacteria usually get into the bladder from the urethra (tube that takes urine from the bladder to outside the body). When bacteria get to the kidney, pyelonephritis results.

Kidney infections are less common than UTIs, but they're more serious. Repeated infections may lead to scarring. Infection that keeps damaging the kidneys can cause chronic pyelonephritis, which can cause kidney failure.

What Causes Pyelonephritis?

Bacteria first infect the urine and then reach the kidneys by traveling up the ureter or from the bloodstream.

People who have greater chances of getting pyelonephritis include women, older people, and people with catheters, diabetes, or urinary tract blocked because of stones or enlarged prostate gland.

What Are the Symptoms of Pyelonephritis?

Some people have no symptoms. The most common symptoms are fever and back pain. Other symptoms include chills, frequent urination, nausea, painful urination, rib or flank pain, sudden urge to urinate, and vomiting.

How Is Pyelonephritis Diagnosed?

The doctor makes a diagnosis from the medical history, physical examination, and tests of urine and blood for infection. Ultrasonography or CT of the kidneys may help find an infection. Ultra-

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sonography uses sound waves to see kidneys and is painless and harmless.

The doctor may suggest seeing a urologist (doctor who specializes in urinary problems).

How Is Pyelonephritis Treated?

Most people are admitted to the hospital and treated with antibiotics put directly into a vein. After symptoms improve, antibiotics given by mouth may be needed for 3 to 4 weeks.

Pain medicine and fluids are also given through a vein if dehydration is present. For repeated UTIs, low doses of antibiotic may be given daily for several weeks to prevent infections.

If a kidney stone caused the infection, a urologist may take the stone out.

DOs and DON'Ts in Managing Pyelonephritis:

✓ **DO** tell your doctor about your other medical problems, especially kidney problems.

✓ **DO** tell your doctor about your medicines, including prescription and over-the-counter medicines.

✓ **DO** tell your doctor if you're pregnant.

✓ **DO** drink plenty of water and cranberry juice.

✓ **DO** urinate when you need to. Don't hold your urine for prolonged periods.

✓ **DO** call your doctor if your symptoms get worse or don't get better with treatment.

✓ **DO** call your doctor right away or go to the emergency room if you have a temperature higher than 101˚ F or are vomiting.

✓ **DO** have kidney stones removed.

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✓ **DO** urinate before and after sex.

✓ **DO** wipe away from the vagina, toward the back, after using the bathroom to prevent UTIs.

✓ **DO** have your prostate checked and get treated if you have an enlarged prostate.

⃠ **DON'T** stop taking your medicine or change your dosage because you feel better unless your doctor tells you to.

⃠ **DON'T** become dehydrated. Drink plenty of fluids, but don't drink alcohol.

⃠ **DON'T** take any herbal preparations that you may find at health food stores. Some may cause kidney disease.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Kidney Foundation Tel: (800) 622-9010 **Website:** **http://www.kidney.org**
- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website:** **http://www.cdc.gov**

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MANAGING YOUR

PYLORIC STENOSIS

What Is Pyloric Stenosis?

In pyloric stenosis, the part of the stomach that leads to the small intestine (called the pylorus) is thickened, leading to blockage. It usually happens in newborn babies and is rare in children older than 6 months. It can sometimes happen in adults.

What Causes Pyloric Stenosis?

Pyloric stenosis in infants is fairly common but the cause isn't known. The muscle of the pylorus gets too large and thick and blocks the tube leading out of the stomach (the stomach outlet). Liquids and solid foods can't go from the stomach to the small intestine. Stenosis happens most often to firstborn boys when they are about 3 to 6 weeks old and can also occur at 4 or 5 months.

Adults may get a form of pyloric stenosis because of a stomach ulcer, scarring after stomach surgery, or a tumor near the pylorus.

What Are the Symptoms of Pyloric Stenosis?

Babies vomit after feeding because milk can't drain from the stomach into the small intestine. This vomiting is much worse than normal spitting up and becomes more forceful as time passes. Babies may not get enough fluids because of the vomiting and become dehydrated and thirsty. They may be constipated. They may have trouble gaining weight and may even lose weight. Babies also have a lump in the stomach, about the size of an olive. This lump is the muscle that got too large.

Adults have only mild vomiting, upset stomach, feelings of being very full after eating, or stomach pain.

How Is Pyloric Stenosis Diagnosed?

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The doctor makes a diagnosis from the medical history and physical examination. During the examination, the doctor may feel the lump in the stomach. The doctor may order barium x-rays or ultrasonography. These tests take pictures of inside the body.

How Is Pyloric Stenosis Treated?

Babies need surgery. During surgery (called pyloromyotomy), the large, thick muscle is cut. Babies are given intravenous fluids until after surgery. They can usually feed again in about 6 to 8 hours. A mild aspirin-like medicine may be given for pain.

Adults also need surgery and treatment for the condition that caused the stenosis. Sometimes, the pylorus can be opened without surgery (called endoscopic balloon dilation). In this procedure, the doctor puts a tube with a balloon on its tip through the mouth and into the stomach. The balloon is inflated and stretches the pylorus open.

Both babies and adults usually do well after surgery.

DOs and DON'Ts in Managing Pyloric Stenosis:

✓ **DO** apply warm compresses to the incision site if your baby seems uncomfortable.

✓ **DO** call your doctor if your baby keeps vomiting, has weight loss or poor weight gain, seems too tired, or has few or no stools for 1 or 2 days.

✓ **DO** call your doctor if your baby has pain, swelling, redness, bleeding, or drainage at the incision site. Also call your doctor if your baby develops a fever after surgery.

⃠ **DON'T** forget follow-up doctor appointments.

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FOR MORE INFORMATION

Contact the following sources:

- American Pediatric Surgical Association Tel: (847) 480-9576 **Website:**

  http://www.eapsa.org

- American Academy of Family Physicians Tel: (913) 906-6000, (800) 274-2237 **Website:**

  http://www.aafp.org

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MANAGING YOUR

RABIES

What Is Rabies?

Rabies is an infection caused by the rabies virus. People get the virus after being bitten by an infected animal. Rabies exists mainly in wildlife, most frequently in skunks, raccoons, bats, and foxes. Pets including cats and dogs can also get it.

Only about two cases occur yearly in the United States, most caused by wild animal bites. Rabies is more common in developing countries.

What Causes Rabies?

The cause is the virus named rhabdovirus in saliva of infected animals.

What Are the Symptoms of Rabies?

The time from infection with the virus to first symptoms averages 35 to 65 days. First symptoms may be general, such as fever, headache, and feeling down. Also, loss of appetite, nausea, and pain or numbness at the bite site may last for the first 3 to 4 days.

Later, nervous system symptoms occur, including being agitated and restless with extreme hyperactivity, with bizarre behavior and calm periods. Hallucinations, muscle spasms, and paralysis may also occur. The fear of water (hydrophobia) occurs during this stage.

Unfortunately, if rabies isn't treated soon after exposure, it almost always leads to coma, convulsions, and death, usually by the 4th to 7th day after onset of symptoms.

How Is Rabies Diagnosed?

A doctor will examine the wound and do blood tests. The animal may be captured and killed so that its brain can be checked for the presence of rabies virus.

How Is Rabies Treated?

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All bite wounds should be cleaned immediately with soap and water and in the emergency room with povidone-iodine or something similar. Then, treatment depends on the risk of rabies. For simple dog or cat bites, the animal is observed for 10 days and, if it's healthy and not showing rabid behaviors, no treatment is needed. For an animal with rabid behavior, the doctor will start treatment with human rabies immune globulin (HRIG) and human diploid cell rabies vaccine (HDCV).

HRIG is given once with half the dose usually injected near the wound and the other half given as a shot into a muscle. HDCV is given in five doses on days 0, 3, 7, 14, and 28. Treatment should continue even if local reactions to the vaccine occur.

A tetanus booster may also be given.

DOs and DON'Ts in Managing Rabies:

✓ **DO** ask your doctor or emergency room staff to tell state and local health department and animal control agencies about your animal bite.

✓ **DO** realize that the animal that bit you should be isolated. Cats and dogs are usually watched for 10 days for signs of rabies.

✓ **DO** remember that animal bites occurring outside the United States should be considered high risk for rabies. Get prompt medical care.

✓ **DO** realize that most rabid animals are weak, agitated, and dangerous.

✓ **DO** go to the closest emergency department if you have an animal bite.

✓ **DO** call your doctor if you have a reaction (e.g., pain, swelling) to rabies vaccine.

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⦸ **DON'T** forget that most rabid animals have odd behavior. They may approach people, drool from the mouth, and seem weak. They may attack anything that moves.

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FOR MORE INFORMATION

Contact the following source:

- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website:** **http://www.cdc.gov**

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MANAGING YOUR

RADIAL NEUROPATHY

What Is Radial Neuropathy?

The radial nerve in the arm helps muscles of the arm, forearm, wrist, and fingers extend the arm and fingers and flex the arm. It also provides sensation to the hand and certain fingers. Radial neuropathy refers to inflammation (swelling) of the nerve because the nerve is pinched (entrapped), usually at the front of the lower elbow or upper forearm.

Radial neuropathy is the fourth most common mononeuropathy. All ages, both sexes, and all races can have it. It's also called Saturday night palsy and honeymooner's palsy.

What Causes Radial Neuropathy?

Causes include impaired consciousness during anesthesia or drug or alcohol intoxication (Saturday night palsy). Sitting for a long time with the arm draped over a seat back or improper use of crutches would also put pressure on the nerve. Other causes are fractures, repeated movements, puncture wounds, cysts, and surgery.

What Are the Signs and Symptoms of Radial Neuropathy?

Symptoms depend on how severe the lesion is and its location. The most common symptom is wrist drop, or being unable to extend the wrist upward when the hand is palm down. Others are numbness and muscle weakness. People may be unable to straighten the fingers but may have little or no pain.

How Is Radial Neuropathy Diagnosed?

The doctor examines the arm, hand, and fingers and may order ultrasonography. Other tests include X-rays, magnetic resonance imaging (MRI), nerve conduction studies, and electromyography (EMG). EMG tests the electrical activity of muscles. Nerve conduction studies can tell how

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well the nerve is working and help find the point of compression.

How Is Radial Neuropathy Treated?

Treatment depends on the site and cause of the lesion. The usual treatments are conservative and successful. The nerve usually recovers over several weeks. In more severe injuries, the nerve fibers at the injury die, and their surviving stumps need to send out sprouts to replace the missing parts. Nerve regeneration is slow, and full recovery may never occur. The source of compression must be removed. Physical therapy and wrist splinting help use of the hand return. Until damaged nerve fibers reconnect with muscle fibers, the most useful exercises are passive range-of-motion exercises. If other treatments don't work, or for certain kinds of problems, surgery may be considered. Surgery can release the nerve from tethered points in the forearm or can reattach nerve endings.

DOs and DON'Ts in Managing Radial Neuropathy:

✓ **DO** eat healthy. Daily multiple vitamins can help the nerve recover.

✓ **DO** avoid alcohol. Alcohol can lead to injuries and has a toxic effect on nerves.

✓ **DO** consider electrical stimulation of your muscles with probes applied to the skin.

✓ **DO** follow your doctor's and physical therapist's instructions.

✓ **DO** try a splint in a neutral position with a device that leaves your fingers free to move.

⦸ **DON'T** repeatedly rotate your forearm and hand so that your palm faces forward or upward.

⦸ **DON'T** rest your arm for long periods on seat backs.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopedic Surgeons Tel: (847) 823-7186 **Website: http://www.aaos.org**
- American Academy of Family Physicians Tel: (800) 274-2237 **Website: http://www.aafp.org**

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RAMSAY HUNT SYNDROME

What Is Ramsay Hunt Syndrome?

Ramsay Hunt syndrome is a group of symptoms complicating the viral infection called shingles. Shingles is a painful, blistering rash. In Ramsay Hunt, the shingles virus attacks the ear, tongue, and facial nerve.

The syndrome is rare in children but is often seen in elderly people, both men and women equally.

Other names for the syndrome are geniculate zoster, herpes zoster oticus, and herpetic geniculate ganglionitis.

What Causes Ramsay Hunt Syndrome?

The cause is the same virus that causes chickenpox (varicella-zoster). The virus was reactivates when the body's immune system weakens and causes shingles. If the infection involves the area near the ear, it can cause the Ramsay Hunt syndrome.

What Are the Symptoms of Ramsay Hunt Syndrome?

Small blisters occur in and around the ear, in the tympanic membrane of the ear, and along the side of the mouth.

Other symptoms are pain, loss of hearing, loss of taste over the front part of the tongue, dizziness, ringing in the ear (tinnitus), and possibly facial paralysis. The facial paralysis is on the same side as the skin lesions. People have difficulty smiling and frowning, and they may have puffy cheeks and trouble closing the eye. The result is drooling, food getting stuck on the affected side, and dry eye. Sometimes, hearing loss and facial paralysis can be permanent.

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How Is Ramsay Hunt Syndrome Diagnosed?

The doctor makes a diagnosis from the medical history and physical examination. Sometimes, the doctor will peel off the top of the blister and scrape the bottom. This scraping (called Tzanck smear) will be sent for study. Viral cultures may also be done. A culture involves isolating the virus by growing it on a special culture plate.

Rarely, magnetic resonance imaging (MRI) may be needed to exclude other disorders.

How Is Ramsay Hunt Syndrome Treated?

Treatment is with antiviral medicines (such as acyclovir, famciclovir, and valacyclovir). These may help skin lesions heal more quickly and reduce pain related to shingles. The doctor will prescribe pain medicines for the acute flare of the rash and for persistent pain after the rash is gone, known as postherpetic neuralgia.

Postherpetic neuralgia is a bothersome effect in some people with shingles and Ramsay Hunt syndrome. After the rash has gone, pain can last for 6 months and maybe longer. Gabapentin or pregabalin may help people with postherpetic neuralgia. Prednisone given early in the course of shingles can in some cases prevent postherpetic neuralgia.

Antiinflammatory drugs such as ibuprofen and naproxen can also help the pain. Sometimes, the doctor may prescribe a short course of narcotic pain medicine for severe pain not controlled by the other medications.

DOs and DON'Ts in Managing Ramsay Hunt Syndrome:

✓ **DO** remember that it takes 2 to 3 weeks for skin lesions to clear up. All symptoms usually go away, but hearing loss or paralysis can sometimes be permanent.

✓ **DO** call your doctor if you have a rash around your ear, loss of hearing, one-sided facial pa-

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ralysis, or facial pain with headaches.

⦸ **DON'T** miss follow-up doctor appointments. If facial paralysis continues, a visit to an ear, nose, and throat (ENT) specialist and a specialist of the nervous system (neurologist) may be needed to treat the facial nerve.

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FOR MORE INFORMATION

Contact the following sources:

- Herpes Resource Center American Social Health Association Tel: (919) 361-8400
- American Academy of Neurology **Website: http://www.neurology.org**

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MANAGING YOUR

RAYNAUD'S PHENOMENON

What Is Raynaud's Phenomenon?

Raynaud's phenomenon is a condition causing decreased blood flow to the fingers, toes, ears, and tip of the nose. It usually occurs with exposure to cold temperatures. Skin in the area first turns white, then blue, and then purple or red. These attacks may last from a few minutes to several hours. Without treatment, sores or ulcers may develop. With low blood flow for a long time, skin in affected areas could be permanently damaged.

Raynaud's phenomenon may occur at any age, but usually people 20 to 40 years old have it, more women than men.

What Causes Raynaud's Phenomenon?

The cause is unknown. Cold and emotional stress are the main triggers. It's not contagious. Raynaud's phenomenon may be associated with more severe diseases such as scleroderma.

What Are the Symptoms of

Raynaud's Phenomenon?

Fingers lose color (turn white) when exposed to cold. Pain, tingling, and numbness can occur when the areas turn white. Areas later turn bluish and then red. Some people have swelling, warmth, or throbbing when the areas turn purple or red. Toes, nose, and ears can also be affected.

How Is Raynaud's Phenomenon Diagnosed?

The doctor makes a diagnosis from a medical history and physical examination. Blood tests may be done to find out whether other conditions are present. The doctor may put a person's hands in cold water to test the body's reaction to cold.

How Is Raynaud's Phenomenon Treated?

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The best way to manage the phenomenon is by a combination of therapies and prevention. To keep the body warm, dress in layers, wear lined mittens rather than gloves, wear a hat and scarf, and always carry a sweater. To avoid exposure to cold, have someone warm the car in the winter, use an oven mitt to get items out of the refrigerator and freezer, and warm the bathroom by letting warm water run before taking a shower or bath.

Smoking impairs circulation so less blood flows to affected areas. Sores or infections have a greater chance of developing in those areas. People with this condition must stop smoking.

If emotional stress seems to cause an attack, relaxation and biofeedback may help.

For a severe condition, the doctor may prescribe calcium channel blockers (such as amlodipine) that can improve blood flow by decreasing spasm. If these medicines don't help and symptoms are severe, surgery called sympathectomy may be suggested. This surgery involves cutting nerves that cause blood vessels to contract and decrease blood flow.

Most people lead fairly normal lives by following the doctor's advice. People who work outside or have jobs exposing the body to cold temperatures should try to modify the job or look for another job.

DOs and DON'Ts in Managing

Raynaud's Phenomenon:

✔ **DO** wear gloves if you're exposed to cold.

✔ **DO** stop smoking. Smoking further impairs circulation.

✔ **DO** check your fingers, toes, nose, and ears daily for new sores or infections.

✔ **DO** call your doctor if treatments don't help your symptoms.

✔ **DO** call your doctor if you need a referral to a smoking cessation program.

⃠ **DON'T** get too nervous; emotional stress may trigger attacks.

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FOR MORE INFORMATION

Contact the following sources:

- National Heart, Lung, and Blood Institute Tel: (301) 592-8573 **Website:** **http://www.nhlbi.nih.gov**
- Arthritis Foundation Tel: (800) 283-7800 **Website:** **http://www.arthritis.org**

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MANAGING YOUR

RECTAL CANCER

What Is Rectal Cancer?

The rectum is part of the colon (large intestine) in the digestive tract. It's the last 10 inches or so of the colon and ends at the anus, which is the opening to the outside. Rectal cancer is cancer that grows in the rectum. It tends to happen more with older age, especially in men, and usually grows slowly. Most of the time, it starts as a small growth called a polyp.

What Causes Rectal Cancer?

The cause is unknown.

What Are the Symptoms of Rectal Cancer?

People may not have symptoms for a long time, especially if the growth is small. Sometimes, people have blood in the stools (bowel movements). The stool may be thinner than usual, because it squeezes past the cancer. People may also feel urges to have bowel movements, but nothing comes out.

How Is Rectal Cancer Diagnosed?

The doctor makes a preliminary diagnosis from a medical history, physical examination, and laboratory tests. The doctor will do a colonoscopy. The doctor puts a small flexible tube into the anus. The tube has a light at the tip, so the doctor can see inside the rectum and colon. It's long enough to go into the whole colon. It also has a tool at the tip so the doctor can take a small sample of tissue (biopsy) to be checked with a microscope to see if it has cancer cells.

If cancer is found, the doctor will do other tests to see if the cancer has spread. This is called staging. These tests include computed tomography (CT) of the abdomen (belly) and pelvis, x-rays, and blood tests.

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How Is Rectal Cancer Treated?

Small polyps and very small rectal cancers may be removed during colonoscopy. Larger cancers will be removed by surgery. The type depends on the size and location of the cancer and how far it has spread. Anticancer medicines (chemotherapy) and radiotherapy may also be used to shrink the cancer. If the cancer is large, the doctor may have to remove the whole rectum and anus. If this happens, the doctor will do a colostomy. In this procedure, a pouch is made from the colon and comes out through the skin. Stool will come out into a small bag.

DOs and DON'Ts in Managing Rectal Cancer:

✓ **DO** understand the importance of colon screening for everyone starting at age 50, and earlier for family members of people with colon cancer.

✓ **DO** make sure that you have a colonoscopy generally 1 year after surgery and regularly after that, or as recommended by your doctor, to screen for return of cancer.

✓ **DO** call your doctor if you have trouble moving your bowels, abdominal pain, or blood in the stool.

⦸ **DON'T** miss follow-up appointments with your primary doctor and specialists who treated you for rectal cancer.

⦸ **DON'T** be afraid to ask your primary doctor about support groups. In these groups, you can share your concerns with others who have also been diagnosed and treated for rectal cancer.

⦸ **DON'T** forget the importance of good nutrition after surgical treatment.

⦸ **DON'T** delay telling your doctor about new symptoms or concerns.

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Contact the following sources:

- American Cancer Society Tel: (800) 227-2345 **Website: http://www.cancer.org**
- American College of Surgeons Tel: (312) 202-5000, (800) 621-4111 **Website:**

http://www.facs.org

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MANAGING YOUR

REITER'S SYNDROME

What Is Reiter's Syndrome?

Reiter's syndrome is an illness that causes three seemingly unrelated symptoms: a type of arthritis, eye inflammation called uveitis or conjunctivitis, and a urinary tract condition called urethritis. Another name for the illness is reactive arthritis. This term means that arthritis usually occurs as a reaction to something else that's happening in the body, usually an infection.

Reiter's syndrome is most often found in men 20 to 40 years old.

What Causes Reiter's Syndrome?

The cause is unknown, but symptoms often follow a bacterial infection. Most cases tend to occur after a sexually transmitted disease (STD), such as chlamydia; a stomach illness, such as food poisoning; or an intestinal infection. People may also inherit a tendency to get it.

What Are the Symptoms of Reiter's Syndrome?

The first symptoms usually involve the urinary tract and start a few days after an infection. Arthritis and eye symptoms (pinkeye or blurry vision) then develop in the next several weeks. Common symptoms are burning or stinging when urinating; discharge from the penis; red, itchy, burning eyes; joint pain and swelling, usually in large joints, such as knees, hips, and ankles; painless ulcers on the mouth and tongue; and rashes on the tip of the penis and soles of the feet. Other symptoms are low-grade fevers, fatigue, muscle aches, stiff joints, heel pain, and low back pain.

How Is Reiter's Syndrome Diagnosed?

The doctor makes a diagnosis from symptoms and a physical examination. No specific tests exist for this syndrome, but the doctor may order blood tests. One test is an erythrocyte sedimentation

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rate (ESR). People with arthritis usually have a high rate. Another test looks for specific substances in the blood known as antigens. About 80% to 90% of people with the syndrome have one substance, HLA-B27 antigen. The doctor may also order an x-ray of joints that may be affected. Your doctor may refer you to an eye specialist (ophthalmologist) for treatment of the eye inflammation.

How Is Reiter's Syndrome Treated?

Treatment involves medicines, exercises, and physical therapy. Antibiotics can treat an infection. Nonsteroidal antiinflammatory drugs (NSAIDs) such as ibuprofen or naproxen help pain, stiffness, and swelling. People with long-lasting arthritis may need other medicines for the immune system. Sometimes cortisone injections into joints help. Steroid eye drops may be needed for eye inflammation.

Physical therapy and exercises are very important. Physical therapists can teach simple stretching and strengthening exercises. Good posture reduces pain and keeps normal motion in the joints and spine.

Some people may recover fully, in 3 to 4 months. Even with treatment, however, many people have many bouts of arthritis, back pain, rashes, eye inflammation and urinary symptoms.

DOs and DON'Ts in Managing

Reiter's Syndrome:

✓ **DO** take medicine to help pain and swelling.

✓ **DO** daily stretching exercises to keep your joints from getting stiff.

✓ **DO** use a heating pad or hot shower to help stiffness and aches. Applying ice or cold packs can reduce swelling.

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✓ **DO** learn and maintain good sitting, standing, and sleeping postures.

✓ **DO** call your doctor if you have medicine side effects.

✓ **DO** call your doctor if medicines and other treatments don't help the pain.

✓ **DO** call your doctor if you need a referral to a physical or occupational therapist.

⃠ **DON'T** engage in unsafe sexual practices. Use latex condoms to help avoid spreading STDs.

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Arthritis and Musculoskeletal and Skin Diseases Tel: (301) 495-4484, (877) 226-4267 **Website:** **http://www.niams.nih.gov**
- Arthritis Foundation Tel: (800) 283-7800 **Website:** **http://www.arthritis.org**

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MANAGING YOUR

RENAL ARTERY STENOSIS

What Is Renal Artery Stenosis?

Each kidney gets blood through an artery that comes from the aorta, the major blood vessel from the heart. Renal artery stenosis (RAS) is the narrowing or complete blocking of arteries bringing blood to the kidneys. Narrow arteries can lead to high blood pressure (hypertension). When both arteries are blocked, serious problems, including kidney failure, can result. One or both kidneys can be blocked.

What Causes Renal Artery Stenosis?

In older people, the usual cause is atherosclerosis (hardening of the arteries). In atherosclerosis, fat, cholesterol, and other substances collect in artery walls. In younger adults, a condition known as fibromuscular dysplasia is the most common cause. In this illness, tissue grows in walls of renal arteries and narrows or blocks them.

What Are the Symptoms of Renal Artery Stenosis?

People usually have no symptoms. They don't know that they have it until they begin to have high blood pressure or kidney failure.

How Is Renal Artery Stenosis Diagnosed?

The doctor makes a diagnosis from a medical history and physical examination. Blood and urine tests and magnetic resonance angiography (MRA) of renal arteries may be done. MRA is a special x-ray of blood vessels bringing blood to kidneys.

How Is Renal Artery Stenosis Treated?

Treatment depends on the severity and cause of the stenosis and personal preference. Mild or moderate symptoms can sometimes be treated with medicine to control high blood pressure. A

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more severe condition may need the artery to be widened or reopened by surgery.

A treatment called angioplasty may be used instead of surgery. This treatment is more frequently performed when the cause is fibromuscular dysplasia but not atherosclerosis. A plastic balloon is used to open the narrowed artery. A metal or mesh tube called a stent may be put in to keep the artery open. The procedure may have to be repeated because narrowing may return. High blood pressure medicine may still be needed.

DOs and DON'Ts in Managing Renal Artery Stenosis:

✓ **DO** take your medicine regularly and as directed. This is the most important thing you can do to delay or prevent worsening of kidney function.

✓ **DO** exercise regularly. Exercise will reduce the risk of complications, such as heart disease, caused by high blood pressure.

✓ **DO** eat healthy food. Follow your dietitian's advice to lower your blood cholesterol levels. High levels increase the risk of heart disease. A low-salt diet also helps lower blood pressure.

✓ **DO** call your doctor if your blood pressure stays high.

✓ **DO** call your doctor if you have side effects from medicines.

✓ **DO** make regular appointments with your doctor to check your kidneys and blood pressure.

⊘ **DON'T** smoke. Smoking can damage your arteries.

⊘ **DON'T** miss appointments to have your blood pressure checked. Do this at least every 6 months.

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⦸ **DON'T** stop taking your medicine without asking your doctor.

⦸ **DON'T** take over-the-counter drugs, especially drugs similar to ibuprofen, unless your doctor says you can. Some may not be safe to take with your kidney condition and may make it worse.

⦸ **DON'T** take herbal preparations. Some may cause kidney disease.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- National Kidney Foundation Tel: (800) 622-9010 **Website: http://www.kidney.org**
- National Kidney and Urologic Diseases Information Clearinghouse Tel: (800) 891-5390

  Website: http://kidney.niddk.nih.gov

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MANAGING YOUR

RESTLESS LEG SYNDROME

What Is Restless Leg Syndrome (RLS)?

Restless leg syndrome (RLS) is a neurological condition that causes people to have an almost uncontrollable urge to move their legs. It usually occurs in bed at night, or when people lie down and try to relax. These feelings can also occur in the arms.

This common condition affects up to 10% of the population at some time in their lives. Symptoms can vary from mild to severe, with severe RLS occurring most frequently in people middle-aged or older.

What Causes RLS?

The cause is unknown. It tends to run in families. Middle-aged people and pregnant women are most likely to get it.

Certain medicines such as some antidepressants can cause RLS. People with iron deficiency, anemia, kidney disease, diabetes, Parkinson's disease, nerve damage, muscle problems, or lung disease have greater chances of developing RLS. It has also been related to tobacco, caffeine, and alcohol.

What Are the Symptoms of RLS?

Itching, burning, or crawling feelings deep in the legs make it hard to sleep. Moving the legs temporarily relieves the symptoms. Usually, both sides of the body are affected. Because these feelings can interrupt sleep, people often feel very tired during the day.

Some people also have restless fidgeting in their toes, legs, or feet while they sit.

How Is RLS Diagnosed?

The doctor can usually make a diagnosis from just a description of symptoms. The doctor may

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order a blood test to rule out other causes, such as iron deficiency. If RLS is severe, the doctor may suggest spending a night in a sleep laboratory where sleeping and symptoms can be monitored.

How Is RLS Treated?

Treatment is aimed at reducing symptoms and enabling sound sleep. The doctor may recommend self-help treatment and medicines. Often, a combination of self-help and medicines works well. Some drugs work better than others, so trying different ones to find the best treatment may be needed. Avoiding caffeine, cigarettes, and alcohol may be helpful.

If symptoms are severe and treatment does not work, a visit to a specialist in sleep disorders or a neurologist may be needed. A neurologist is a doctor who specializes in treating disorders of the nervous system.

DOs and DON'Ts in Managing RLS:

✓ **DO** practice good sleep habits. Go to sleep around the same time every night, get up at the same time every morning, and sleep long enough to feel well rested.

✓ **DO** exercise regularly.

✓ **DO** learn relaxation techniques, such as meditation, yoga, and biofeedback. Biofeedback is a method that trains you to control unconscious responses.

✓ **DO** try these methods to relieve the restless feelings in your legs temporarily: walk or stretch, take a hot or cold bath, massage your legs, or apply hot or cold packs.

✓ **DO** call your doctor if your symptoms continue even with medical treatment.

⃠ **DON'T** take herbal products without your doctor's approval. Some of these my affect your

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sleep cycle.

⦸ **DON'T** use caffeine, tobacco products, or alcohol. These may worsen symptoms.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- Restless Legs Syndrome Foundation, Inc. Tel: (507) 287-6465 **Website: http://www.rls.org**
- American Academy of Sleep Medicine Tel: (708) 492-0930 **Website:**

  http://www.aasmnet.org

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MANAGING YOUR

RESTRICTIVE CARDIOMYOPATHY

What Is Restrictive Cardiomyopathy?

Restrictive cardiomyopathy is a disease of heart muscle that prevents the muscle from contracting (squeezing) with normal force. The result is that the heart doesn't pump blood well. Restrictive cardiomyopathy means that the heart has a restricted ability to contract because the inner lining of the heart becomes stiff. The heart does not expand properly when it fills. The heart muscle thickens to make more muscle so it can increase its strength of contraction, but due to the abnormal filling of the heart is unable to function normally.

This type of heart disease is much less common than heart disease from coronary artery disease or heart valve problems.

What Causes Restrictive Cardiomyopathy?

Most of the time the cause is unknown. Amyloidosis, a condition in which abnormal deposits of protein in some body tissues occur, may be a cause. Sarcoidosis, a condition involving abnormal inflammation of lymph nodes and other tissues, may be another cause. It may also be caused by inflammatory or autoimmune conditions. Drinking alcohol in excess can make it worse.

What Are the Symptoms of Restrictive Cardiomyopathy?

Most people have tiredness, less ability to exercise, and shortness of breath. Swelling in the legs or feet, chest pain, or palpitations (feeling that the heart is skipping or beating too fast) may also occur. Cardiomyopathy can cause heart failure.

How Is Restrictive Cardiomyopathy Diagnosed?

The doctor may suspect the disorder on the basis of the medical history and physical examination. The doctor may also order electrocardiography (ECG) and chest x-rays. These tests usually

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show an enlarged heart. ECG may also show an irregular heartbeat (arrhythmia). Echocardiography (ultrasound examination of the heart) may be done to check the heart's pumping action. Blood tests may also be done to look for other causes.

In some cases, cardiac catheterization and biopsy of heart tissue may be done to confirm the diagnosis.

How Is Restrictive Cardiomyopathy Treated?

Therapy is aimed at relieving symptoms of heart failure and correcting abnormal heart rhythms (arrhythmias).

Medications known as diuretics reduce fluid in the blood to decrease the work of the heart.

The doctor may prescribe drugs that regulate the heartbeat or drugs that suppress immune function (corticosteroids) to fight conditions causing the cardiomyopathy.

If the heart's pumping is very poor and symptoms of heart failure worsen, heart transplantation may be needed.

DOs and DON'Ts in Managing Restrictive Cardiomyopathy:

✓ **DO** eat a low-salt diet to reduce fluid accumulation.

✓ **DO** take all your prescribed medicines as directed.

✓ **DO** exercise when your doctor says that you can.

✓ **DO** call your doctor if you have new or worsening chest pain, shortness of breath, swelling in the legs, or fainting.

⦸ **DON'T** drink alcohol.

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:**

  http://www.americanheart.org

- American College of Cardiology Tel: (800) 253-4636 **Website: http://www.acc.org**

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MANAGING YOUR

RETINITIS PIGMENTOSA

What Is Retinitis Pigmentosa?

The eye is a globe with three separate outer layers. The outer layer is the sclera, or the white of the eye. The second layer is the choroid. It's made up of a delicate network of blood vessels and connective tissue. The inner layer is the retina, which has two special kinds of cells that send images to the brain. These light-sensitive cells are rods and cones. Retinitis pigmentosa is a group of diseases affecting the retina. Retinitis pigmentosa destroys rods in the retina, which causes a slow loss of vision and can ultimately result in blindness. About 1 in 4000 people have this disorder.

What Causes Retinitis Pigmentosa?

The cause is unknown. A mutation in the gene that controls rod cells may lead to the disorder. Sometimes, cone cells are also damaged. This disorder is inherited and usually passed from parents to children. It's not contagious.

What Are the Signs and Symptoms of Retinitis Pigmentosa?

Progressive night blindness and the loss of side (peripheral) vision occur. These usually start during the teen years or young adulthood. As side vision worsens, people are left with tunnel vision. They may often have accidents such as tripping and falling. As side vision continues to get worse, many times people can see only what is directly in front. The presence of dark deposits in the retina is the main sign of the disorder.

How Is Retinitis Pigmentosa Diagnosed?

The health care provider makes a diagnosis from the medical history and physical examination. An examination of the back of the eye with an ophthalmoscope shows pigmented (dark) spots on

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the retina. An ophthalmoscope is a small scope, with a light at the end, that's used to see the retina.

How Is Retinitis Pigmentosa Treated?

There is no proven effective therapy for retinitis pigmentosa. In some rare forms of the disorder, vitamin E and vitamin A supplements have some benefit. Aids including magnifying glasses and infrared night vision scopes can help people with night blindness and tunnel vision. Wearing sunglasses can protect the retina from ultraviolet light and may help preserve some vision.

DOs and DON'Ts in Managing Retinitis Pigmentosa:

✓ **DO** see an ophthalmologist (specialist in eye diseases).

✓ **DO** understand that no cure exists for this disorder.

✓ **DO** remember that retinitis pigmentosa is inherited. Knowing your family history may give you valuable information about the type of your disorder. Genetic counseling and testing may find out whether your children are at risk for the disease.

✓ **DO** call your health care provider if you have vision problems, have trouble seeing at night, or notice a loss of your side vision. Call if you need a referral to an ophthalmologist. Call if you feel depressed or discouraged.

✓ **DO** see an eye care specialist regularly. A low-vision specialist can help you adapt to vision loss.

⃠ **DON'T** lose hope. People with this disorder can lead normal, productive lives.

⃠ **DON'T** forget that many services can help with your vision loss and vocational rehabilitation. Counseling is available.

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⦸ **DON'T** be afraid to ask for a second opinion from a retinitis pigmentosa specialist.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Ophthalmology Phone: 415-561-8500 **Website: www.aao.org**
- The Foundation Fighting Blindness **Website: http://www.blindness.org/**

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MANAGING YOUR

RETINOBLASTOMA

What Is Retinoblastoma?

Retinoblastoma is a malignant tumor of the eye. It affects the retina, the thin nerve tissue at the back of the eye. The retina senses light and makes images. Retinoblastoma mainly occurs in very young children, with 90% of cases diagnosed before the age of 4 years. It's the most common eye cancer in children. Adults can rarely have it.

What Causes Retinoblastoma?

The cause is thought to be mutations in a gene called retinoblastoma-1 (RB1). These mutations can be passed from parents to children and result in hereditary retinoblastoma. New mutations lead to sporadic retinoblastoma. Hereditary retinoblastomas may form in one or both eyes and usually occur in younger children. Most that form in only one eye are not hereditary and more often occur in older children. Tumors in both eyes mean that the disease is almost always hereditary.

What Are the Signs and Symptoms of Retinoblastoma?

A white pupil that doesn't reflect light is a major sign. Others are eyes that seem to look in different directions and eye redness and swelling.

How Is Retinoblastoma Diagnosed?

The ophthalmologist makes a diagnosis from the eye examination. An ophthalmologist is a specialist in diagnosing and treating eye diseases. Other tests are done to stage the tumor. Staging means finding out whether the tumor spread from the eye to nearby tissues or other parts of the body. Ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) are used for this. Tumors may be intraocular or extraocular. Intraocular retinoblastoma

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means cancer in one or both eyes but not outside the eye. Extraocular retinoblastoma means cancer outside the eye.

How Is Retinoblastoma Treated?

Treatment depends on whether one or both eyes are affected and whether the disease has spread outside the eye. Enucleation, which is surgery to remove the whole eye, can be done. Radiation therapy uses high-energy X-rays to kill cancer cells and shrink tumors. Cryotherapy uses extreme cold to kill cancer cells. Photocoagulation uses laser light to destroy blood vessels taking nutrients to the tumor. Thermotherapy uses heat to kill cancer cells. Chemotherapy uses drugs to kill cancer cells. For intraocular retinoblastoma, if only one eye has large tumors, the eye is removed when vision cannot be preserved. Radiation, photocoagulation, cryotherapy, or thermotherapy may be used for smaller tumors when sight might be preserved. If both eyes have cancer, the eye with the most cancer may be removed and/or radiation therapy is given to the other eye. If both eyes could have sight, both may have radiation therapy. Chemotherapy can also be used. Extraocular retinoblastoma needs radiation therapy and/or chemotherapy.

DOs and DON'Ts in Managing Retinitis Pigmentosa:

✓ **DO** remember that retinoblastomas in both eyes means the inherited disorder. Family members should be examined and counseled and genetic testing done to find out their risk for the disease.

✓ **DO** realize that the untreated cancer is almost always fatal. Early diagnosis is critical.

⦸ **DON'T** forget that a child who has hereditary retinoblastoma may also be at risk for a brain tumor during treatment of the eye tumor. This is called trilateral retinoblastoma.

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FOR MORE INFORMATION

Contact the following sources:

- National Cancer Institute Cancer Information Service Phone: 1-800-4-CANCER (1-800-422-6237)
- American Academy of Ophthalmology Phone: 415-561-8500 **Website: www.aao.org**

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MANAGING YOUR

RHABDOMYOLYSIS

What Is Rhabdomyolysis?

Rhabdomyolysis is a condition that occurs when muscle is damaged. This damage releases the pigment myoglobin from muscle into the blood. Kidneys normally filter the pigment out of the blood. Substances from the muscle breakdown may harm the kidneys by blocking their filtering structures. The kidneys fail and release toxic waste products into the blood.

What Causes Rhabdomyolysis?

Causes include crushing injuries to muscle, seizures, and exercise-related heatstroke. Other causes are severe frostbite, severe burns, drug overdose, cocaine use and side effects of medicines such as statins (used to treat high cholesterol). Sometimes, too much high endurance exercise by someone who isn't trained enough can cause excessive muscle breakdown and rhabdomyolysis. People with alcohol abuse have a much higher risk of rhabdomyolysis due to the effects of alcohol and frequent falls in alcoholics.

What Are the Symptoms of Rhabdomyolysis?

The main symptoms are muscle pains and red or brown urine that may then turn into less urine or no urine being produced. This serious sign of being unable to urinate, a symptom of kidney failure, means that immediate medical care is needed. Other symptoms are fatigue, lethargy, joint pain, extreme thirst, and fast or irregular heartbeat.

How Is Rhabdomyolysis Diagnosed?

The doctor will make a diagnosis from the medical history, physical examination, and laboratory tests. Blood studies will show poor kidney function, high potassium levels, and other abnormalities of body fluids. Urine may be red or brown because of pigments and dehydration.

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How Is Rhabdomyolysis Treated?

Treatment takes place in the hospital. Intravenous fluids are first given to keep a steady urine flow. This treatment is helpful to flush pigments through the kidneys. Medicines may be given to change the acidity of the urine, to make the urine alkaline, and to increase urination. This also flushes pigments out of the kidneys.

The main adverse effect of this treatment is fluid overload if kidneys already started to fail before treatment. In this case, dialysis (kidney machine) may be needed to remove fluid and wastes and to rest the kidneys until they can recover. Weeks to months may be needed, depending on how severe the problem is.

DOs and DON'Ts in Managing Rhabdomyolysis:

✓ **DO** get medical care right away if you see red or brown urine or have general muscle aches, if you had one of the causes of rhabdomyolysis, especially a crushing muscle injury or exercise-related heatstroke.

✓ **DO** also get medical care if after you had treatment for rhabdomyolysis you see colored urine or decrease in urine output. Get immediate medical care if you cannot urinate.

✓ **DO** stay well hydrated and drink plenty of fluids.

✓ **DO** stop using alcohol or drugs that may have contributed to your condition. Find a program that can help you with your alcohol problem.

⃠ **DON'T** let yourself become dehydrated if you are at risk of having rhabdomyolysis. Being dehydrated may let pigments build up in the kidney. This is especially important if you had exercise-induced heatstroke, because you're already dehydrated.

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⦸ **DON'T** take part in high endurance sports without having had the proper training.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Emergency Physicians Tel: (800) 798-1822 **Website:** **http://www.acep.org**
- American Association of Kidney Patients Tel: (800) 749-2257 **Website:** **www.aakp.org**

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CARING FOR YOUR CHILD WITH

RHEUMATIC FEVER

What Is Rheumatic Fever?

Rheumatic fever is an inflammation of the heart, nervous system, skin, and joints after a recent bacterial infection. Rheumatic fever usually occurs in children younger than 18. It cannot be caught, but the infection that causes it can.

What Causes Rheumatic Fever?

Rheumatic fever is an autoimmune disorder, which means that the body reacts against its own cells or tissues. A recent strep throat infection triggers it. The infection with the bacteria named *Streptococcus* may have been mild or untreated. Substances called antibodies produced during the infection also attack and can destroy cells in the joints, the heart, and other body parts.

What Are the Symptoms of Rheumatic Fever?

Symptoms include fever, loss of appetite, mild rash, tiredness, paleness, small bumps under the skin over bony areas (such as hands, wrists, elbows, and knuckles), and joint inflammation with pain, swelling, and warmth.

If the heart is affected, shortness of breath, swelling of the ankles and around the eyes, and rapid heartbeat may occur. If the brain is affected, uncontrolled jerky movements may occur.

The most common complication is damage to heart valves that causes a heart murmur. Sometimes the damaged valves may need to be replaced.

How Is Rheumatic Fever Diagnosed?

The doctor will suspect a diagnosis from the medical history, physical examination, and laboratory tests. A chest x-ray, electrocardiography (ECG), and throat culture will be done. The doctor will order another test called echocardiography to look for heart valve damage.

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If heart damage is present, you will be referred to a cardiologist (a doctor who specializes in heart treatment).

How Is Rheumatic Fever Treated?

Children must limit their activity until symptoms are gone, which could take 2 to 5 weeks.

Antibiotics for the bacteria will be given for several days. Tell your doctor if your child is allergic to penicillin.

In the early stages a liquid or soft diet may be better. Later a normal diet that is high in calories, protein, and vitamins is followed.

Aspirin or other antiinflammatory drugs are given for muscle and joint pain.

DOs and DON'Ts in Managing Rheumatic Fever:

✓ **DO** have your child take antibiotics until the prescription is all gone.

✓ **DO** have your child with a fever drink enough fluids.

✓ **DO** have your child rest and then start activity gradually. Rest periods and naps should be scheduled.

✓ **DO** get prompt evaluation for future sore throats.

✓ **DO** tell doctors and dentists about your child's rheumatic fever.

✓ **DO** call your doctor if during treatment your child has swollen legs or ankles, shortness of breath, vomiting, diarrhea, dry hacking cough, severe pain in the abdomen (belly), or a temperature of 101˚F or higher.

⦸ **DON'T** let your child resume activity until the fever and other symptoms are gone.

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FOR MORE INFORMATION

Contact the following sources:

- National Heart, Lung, and Blood Institute Information Center Tel: (301) 592-8573 **Website: http://www.nhlbi.nih.gov**
- American Heart Association Tel: (800) 242-8721 **Website: http://www.americanheart.org**

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MANAGING YOUR

RHEUMATOID ARTHRITIS

What Is Rheumatoid Arthritis?

Rheumatoid arthritis (RA) is a disease that causes inflammation (swelling, redness) leading to pain, stiffness, and swelling in joints. Affected most often are hands, wrists, feet, and knees. Less common are affects in other body parts, including lungs, eyes, heart, blood vessels, skin, and nerves. RA can affect the ability to do daily activities. RA of hands can affect writing, opening jars, dressing, and carrying items. Arthritis affecting hips, knees, or feet can make it hard to walk, bend, or stand.

RA affects 1% to 5% of adults worldwide. Two to three times more women than men have RA. It's more common during a woman's childbearing years.

There is no cure for RA, but with treatment people with RA can lead full lives.

What Causes RA?

RA is an autoimmune disorder. Autoimmune means that the body's own immune (disease-fighting) system attacks healthy cells. Some inherited and environmental factors may increase a person's chance of getting RA, but the exact cause is unknown. RA is not contagious.

What Are the Symptoms of RA?

The most common symptoms are joint pain and stiffness that is worse in the morning after waking up and after sitting still for a long time. Stiffness usually gets better after movement. Symptoms tend to come and go and can be mild to severe. Other symptoms may include burning or itching eyes, tiredness, leg ulcers, reduced appetite, numbness and tingling, shortness of breath, skin nodules, weakness, and fever. Joints can be red, swollen, tender, deformed, and warm.

How Is RA Diagnosed?

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The doctor takes a medical history, examines the joints, and orders tests and x-rays. Tests may include erythrocyte sedimentation rate (ESR), which measures inflammation; complete blood cell count (CBC); and a test called rheumatoid factor (RF). Sometimes, fluid from a joint is tested.

How Is RA Treated?

The best way to manage RA is to use medicines, different therapies, exercise, education, and pacing of activities to prevent fatigue. Medicines called nonsteroidal antiinflammatory drugs (NSAIDs), such as naproxen and ibuprofen, reduce pain and swelling. Disease-modifying drugs may slow the RA process and should be started early.

Learning about RA is essential. Exercise is important for joint movement and muscle strength. Being active plus resting helps fatigue. Physical therapy and special exercises can help symptoms, as can hot soaks, heat lamps, heating pads, and whirlpool treatments. Splints may protect joints. Sometimes surgery is needed to fix a joint.

DOs and DON'Ts in Managing RA:

- ✔ **DO** tell your doctor about your other medical problems.
- ✔ **DO** take your medicines as prescribed.
- ✔ **DO** tell your doctor if you're pregnant or plan to get pregnant.
- ✔ **DO** lose weight if overweight.
- ✔ **DO** talk to someone to help with stress.
- ✔ **DO** exercise.
- ✔ **DO** call your doctor if you have side effects from medicines or if treatments aren't helping pain, swelling, or fatigue.
- ✔ **DO** call your doctor right away or go to the emergency room if you have fever with a red,

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warm joint.

⦸ **DON'T** stop taking your medicine or change your dosage because you feel better unless your doctor says to.

⦸ **DON'T** let yourself get run-down.

⦸ **DON'T** drink alcohol in excess while being treated.

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FOR MORE INFORMATION

Contact the following sources:

- Arthritis Foundation Tel: (800) 283-7800 **Website: http://www.arthritis.org**
- American College of Rheumatology Tel: (404) 633-3777 **Website:**

http://www.rheumatology.org

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MANAGING YOUR

RINGWORM

What Is Ringworm?

Ringworm is a general name for a very common skin infection. The name ringworm comes from the appearance (ring-shaped or oval patches), not the cause, of the infection. The cause is not a worm at all but is actually a fungus. These fungal infections are named according to where they occur, such as ringworm of the body (tinea corporis), ringworm of the scalp (tinea capitis), athlete's foot (tinea pedis, ringworm of the feet), and jock itch (tinea cruris, ringworm of the groin).

People of all ages can get ringworm, but it's seen more often in children, diabetics and, athletes. Ringworm commonly occurs during hot, humid weather.

What Causes Ringworm?

Fungi that cause ringworm are very small and can be seen only with a microscope. They are passed among other people or animals. They can also be found in towels, carpet, bedding, showers, and baths.

What Are the Symptoms of Ringworm?

The most common symptom is itching. Ringworm on the body or face starts as slightly raised, ring-shaped or oval, red-to-brown, round, itchy patches on the skin. Sometimes, scaling or flaking of the skin occurs.

How Is Ringworm Diagnosed?

The doctor makes a diagnosis by doing a physical examination and seeing the typical appearance of patches on the skin. Sometimes, a small scraping of an affected area can be studied under a microscope to confirm the diagnosis.

How Is Ringworm Treated?

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Over-the-counter medicines can treat mild cases. A small amount of antifungal cream, ointment, or powder is applied to affected areas twice daily, for 7 days after areas have healed. Calamine lotion twice daily can help reduce severe itching. Diphenhydramine (Benadryl®) and other anti-histamines can also help itching.

The doctor can prescribe a stronger skin cream if over-the-counter medicines don't work. Treatment continues for 7 days after the infection seems to be over to prevent another infection.

For severe cases, when medicines applied to the skin don't work, medicine taken by mouth can be used.

DOs and DON'Ts in Managing Ringworm:

✓ **DO** use good general hygiene and keep the skin clean and dry.

✓ **DO** apply medicines as directed.

✓ **DO** bathe or shower daily. Gently wash affected areas with a cloth, dry off, then apply cream or ointment.

✓ **DO** wear clean, dry clothes. Cotton or other absorbent cloth is best. Avoid nylon.

✓ **DO** wear loose-fitting underwear and clothes.

✓ **DO** wash your hands after touching soil, plants, and animals, including pets (such as cats).

✓ **DO** avoid touching ringworm patches on other people or contaminated items, such as clothes, combs, showers, and pools.

✓ **DO** call your doctor if you get symptoms of another infection, such as fever, pus drainage,

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oozing, crusting, or swelling.

✓ **DO** call your doctor if you see skin changes, such as scarring or bleeding.

⃠ **DON'T** scratch or rub infected areas to avoid spreading the infection or causing another infection.

⃠ **DON'T** let anyone else come into contact with your clothing or other items (such as a hairbrush) that may have touched the infection.

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Allergic and Infectious Diseases Tel: (301) 496-5717 **Website:** **http://www.niaid.nih.gov**
- American Academy of Dermatology Tel: (866) 503-SKIN (7546) **Website:** **http://www.aad.org**

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MANAGING YOUR

ROCKY MOUNTAIN SPOTTED FEVER

What Is Rocky Mountain Spotted Fever?

Rocky Mountain spotted fever is an acute illness caused by a bacterium named *Rickettsia rickettsii.* Infected ticks carry the bacteria. These ticks live in wooded areas, in low bushes and tall grasses. The illness is common during warm weather—spring and summer. The illness can occur at any age but is most common in adults 60 to 69 years old and children 5 to 9 years old, more males than females.

What Causes Rocky Mountain Spotted Fever?

People get infected after a bite by a tick that has the bacteria. Ticks carrying the bacteria are American dog ticks (*Dermacentor variabilis*) in the eastern United States, where the illness is most common. In the western United States, wood ticks (*Dermacentor andersoni*) carry the bacteria. Dogs and rodents carry these ticks, so the illness occurs in cities and rural areas. The infection doesn't spread from person to person.

What Are the Symptoms of Rocky Mountain Spotted Fever?

Symptoms usually start within 2 to 5 days after the tick bite. They include a high temperature with chills, headaches, nausea, vomiting, and shortness of breath with a cough. A red rash starts on the wrists and ankles and spreads to the palms of the hands and soles of the feet and finally to the legs and trunk of the body. Other later symptoms are weakness with muscle aches and confusion.

How Is Rocky Mountain Spotted Fever Diagnosed?

The doctor makes a diagnosis from the medical history, physical examination, and blood tests.

How Is Rocky Mountain Spotted Fever Treated?

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In severe cases, a hospital stay may be needed during the worst part of the illness. Antibiotics such as doxycycline or tetracycline are prescribed in males and in nonpregnant women. Aspirin products should be avoided to prevent possible bleeding complications. People should rest until the fever is gone. A regular diet can be eaten as tolerated. Drinking extra fluids should be encouraged. Milk and antacids shouldn't be given with the antibiotics.

DOs and DON'Ts in Managing Rocky Mountain Spotted Fever:

✓ **DO** take all your antibiotics.

✓ **DO** drink more, especially during the fever. Also, rest as much as possible.

✓ **DO** try a heating pad for muscle aches.

✓ **DO** try to avoid exposure to ticks. Wear light-colored clothing with long sleeves and legs. Use insect repellent that works against ticks.

✓ **DO** check your body often for ticks during outdoor activities.

✓ **DO** remove a tick by using tweezers to gently hold it and pull it off. Don't crush the tick. You can also put oil on the tick body before pulling with tweezers.

✓ **DO** report a rash or fever that starts after a tick bite.

✓ **DO** call your doctor if you have chest pain or increased shortness of breath. Call if you cannot drink fluids and are dehydrated. Call if the rash looks infected. Call if you get a severe headache or seizures, severe abdominal pain, or bleeding.

⃠ **DON'T** use aspirin or aspirin-containing medicines. Use only nonaspirin products (such as

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acetaminophen) for fever and minor pains.

⦸ **DON'T** drink milk or take antacids within 2 hours of taking antibiotics.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Heart, Lung, and Blood Institute Information Line Tel: (800) 575-WELL
- National Institute of Allergy and Infectious Disease Tel: (301) 496-5717
- Centers for Disease Control and Prevention **Website:**

  http://www.cdc.gov/rmsf/index.html

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MANAGING YOUR

ROSACEA

What Is Rosacea?

Rosacea, which is also called acne rosacea or adult acne, is a skin disease that usually affects the face. Women are more likely to show symptoms on the chin and cheeks, whereas in men the nose is commonly involved. Rosacea is most common during or after middle age and is often called adult acne. People of northern European descent and those with fair complexions are more likely to have rosacea. It's treatable but usually not curable.

What Causes Rosacea?

The cause is unknown. Alcohol, hot beverages, and certain foods do not cause it but can make it worse. Rosacea may run in families.

What Are the Symptoms of Rosacea?

The skin of the nose, cheeks, chin, and forehead is affected. Redness, swelling, and pimples or pustules appear on the skin. Small blood vessels under the skin can get bigger and noticeable. They look like thin red lines on the face or nose. Skin can become oily. In more severe cases, larger bumps on the nose occur. Rarely, eyes and eyelids are affected, with swelling, redness, dry eyes, and burning.

Rosacea has three stages, each with different symptoms. Early symptoms include flushing or redness that comes and goes. Spicy food, sunlight, or alcohol can trigger these. Middle stage symptoms are the same but last longer. Skin may burn or sting, and eyes feel itchy or gritty. In the advanced stage, redness becomes permanent, small and sometimes painful pimples may appear, skin may burn or sting, eyes may be watery and irritated, and the nose can become red and swollen.

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Because their skin looks similar to that of chronic alcohol abusers, people with rosacea are often thought of as being closet alcoholics. This isn't true.

How Is Rosacea Diagnosed?

The doctor makes a diagnosis from the physical examination.

How Is Rosacea Treated?

Mild cases can sometimes be treated with a topical antibiotic cream (metronidazole, clindamycin, erythromycin) or antibiotics taken by mouth. Rosacea often returns and may need a smaller dose of medicine taken regularly to control symptoms. Early treatment may slow disease progress. In more severe cases, a combination of medicines may be needed. Severe nose swelling in rare cases needs surgery, but laser treatment may help. A laser is sometimes used for large veins and redness. The doctor will usually suggest seeing a dermatologist (specialist in skin diseases).

DOs and DON'Ts in Managing Rosacea:

✓ **DO** wash your face twice a day with a washcloth and mild soap.

✓ **DO** follow your doctor's instructions about soaps, sunscreens, and medicines. Early treatment may prevent some long-term effects.

✓ **DO** keep a diary of activities performed, kinds of foods eaten, and personal care items used when a flare-up occurs to see whether you can find a pattern. For example, if your skin becomes irritated and red when you eat chili peppers, they probably trigger symptoms.

✓ **DO** change to milder soap or skin creams that don't contain perfumes, alcohol, or harsh additives, to minimize skin irritation.

✓ **DO** call your doctor if you have symptoms involving your eyes or eyelids.

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✓ **DO** call your doctor if treatment isn't helping after 3 or 4 weeks.

⃠ **DON'T** eat foods that make rosacea worse. These may include hot liquids and spicy foods, chocolates, cheeses, nuts, iodized salt, and seafood.

⃠ **DON'T** drink alcohol.

⃠ **DON'T** get exposed to sun without sunscreen and avoid extreme heat and cold.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Rosacea Society Tel: (888) NO-BLUSH (662-5874) **Website:** **http://www.rosacea.org**
- American Academy of Dermatology Tel: (847) 330-0230, (866) 503-7546 **Website:** **http://aad.org**

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CARING FOR YOUR CHILD WITH

ROSEOLA

What Is Roseola?

Roseola is an infection caused by a virus. Other names for this common illness of small children are exanthem subitum and sixth disease. Roseola is generally not serious and isn't any special risk for pregnant women. The infection occurs most often in children from 6 months to 3 years old. It's rare after the age of 5 years.

What Causes Roseola?

Roseola is caused by a herpesvirus. This virus is from the same family of viruses that cause cold sores, shingles, and genital herpes, but it's not the same one. The illness spreads when droplets from an infected person's mouth get into the air by talking, sneezing, or coughing. Then, someone breathes in the droplets. Someone without symptoms often spreads the illness.

What Are the Symptoms of Roseola?

The illness begins with a sudden fever. The child may have a very high temperature, up to 105° F. Even with the high temperature, however, the child usually doesn't look or act very sick. The fever will last from 2 to 5 days, but most often it lasts for 3 or 4 days. Other symptoms are being fussy, having less appetite, and swelling of the neck glands. Suddenly, the child will break out in a rash, and the fever will go away. The rash is rose pink and blotchy. It starts first on the chest and upper back, and then spreads to the arms and neck. At this point, with the fever gone, the child acts completely well.

How Is Roseola Diagnosed?

A doctor will diagnose roseola on the basis of a medical history and physical examination. Blood tests are not usually needed.

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How Is Roseola Treated?

Because this common childhood illness is caused by a virus, no specific treatment is needed. Make the child more comfortable by lowering the fever with acetaminophen or children's ibuprofen. Other things that can be done for fever are to give the child lukewarm baths, have the child wear lightweight clothing, keep the child quiet, and give the child cool drinks. Don't use ice, cold water, or alcohol rubs. Because of the rapid start of the fever, sometimes a child may have what is called a febrile convulsion (or seizure). In a seizure, the child may be unconscious or have twitching of the arms, legs, or face. If a seizure occurs, contact the doctor immediately.

DOs and DON'Ts in Managing Roseola:

✓ **DO** treat your child as normally as possible, because this illness is generally mild. Nothing can be done to make the illness go away faster. The child doesn't need a special diet.

✓ **DO** call your doctor if the illness doesn't follow the usual course.

✓ **DO** call your doctor if your child becomes more ill, acts as if there's pain, or doesn't eat or drink fairly normally. Your child may have another virus or very rare complication.

⃠ **DON'T** put cortisone creams, calamine lotion, or petroleum jelly (Vaseline®) on the rash. Acetaminophen or children's ibuprofen can help your child feel more comfortable.

⃠ **DON'T** give aspirin to children with viral infections because of the dangerous Reye's syndrome that occurs with aspirin use in children.

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FOR MORE INFORMATION

Contact the following source:

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MANAGING YOUR

ROTATOR CUFF PAIN

About the Shoulder

The shoulder area, or girdle, includes bones and joints. The bones are the scapula, clavicle, and humerus. The joints are the glenohumeral, acromioclavicular, and sternoclavicular joints. The shoulder has the greatest range of motion of all joints in the body but is more prone to injury. The large deltoid muscle provides most of the power in shoulder motion. Underneath the deltoid muscle, four rotator cuff muscles fine-tune shoulder movement. Tendons attach these muscles to bones. The rotator cuff is made up of muscles and tendons that hold the upper arm in the shoulder joint.

What Are Common Rotator Cuff Disorders?

Disorders include swelling (inflammation), called tendonitis, and tears of tendons or muscles. Other names for rotator cuff tendonitis include shoulder impingement syndrome, tennis shoulder, and swimmer's shoulder.

What Causes Rotator Cuff Disorders?

Trauma throughout one's lifetime leads to rotator cuff problems. Activities in which the arms are repeatedly moved over the head, such as baseball, swimming, and tennis, cause such trauma. Certain jobs, such as house painting, use similar motions, which stress the shoulders and cause inflammation and pain.

What Are the Symptoms of

Rotator Cuff Disorders?

The main symptom is shoulder pain, especially when the arm is moved to the side, up over the head. The arm and shoulder may also feel weak. Other symptoms include pain that worsens with

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activities, such as brushing hair and lying down to sleep. Pushing objects away from the body with the arm can be painful, but pulling objects is usually not.

Tendonitis can also lead to a tear in the rotator cuff tendon. Then the shoulder becomes weak, and it becomes very hard to do anything with the arm overhead.

How Are Rotator Cuff Disorders Diagnosed?

The doctor uses a medical history and physical examination for diagnosis. The shoulder and arm are moved in specific ways. Magnetic resonance imaging (MRI) helps when a tear is suspected.

How Are Rotator Cuff Disorders Treated?

Rotator cuff tendonitis can usually be treated without surgery.

The doctor may prescribe medicines such as nonsteroidal anti-inflammatory drugs (NSAIDs) for inflammation and pain. These drugs, however, can cause stomach pain and bleeding and other problems.

Exercise can help reduce pain. This exercise may include physical therapy to strengthen rotator shoulder tendons. Ice packs applied to the shoulder also help reduce pain and inflammation.

Surgery can repair a torn tendon or can be done when physical therapy does not help. Surgery might be a less invasive arthroscopic operation (inserting a small tool to see the rotator cuff directly and repair any damage).

DOs and DON'Ts in Managing Rotator Cuff Pain:

✓ **DO** take your medicines and perform your exercises as directed.

✓ **DO** rest your arm. Sometimes rest is all that is needed.

✓ **DO** try to do tasks with your unaffected arm.

✓ **DO** call your doctor if pain is bad enough to interrupt sleep at night and can't be controlled

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with over-the-counter drugs.

⦸ **DON'T** use pain medicine that may be addictive for long-term therapy.

⦸ **DON'T** do activities in which you put your hands above your head. Don't do push-ups, and don't do strenuous sports while healing.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopaedic Surgeons Tel: (800) 346-AAOS **Website:** **http://www.aaos.org**
- American Physical Therapy Association Tel: (800) 999-2782 **Website:** **http://www.apta.org**
- Arthritis Foundation Tel: (800) 283-7800 **Website:** **http://www.arthritis.org**

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MANAGING YOUR

ROTATOR CUFF TEAR

What Is a Rotator Cuff Tear?

The shoulder girdle includes three bones (scapula, clavicle, and humerus) and three joints (glenohumeral, acromioclavicular, and sternoclavicular). The shoulder has a greater range of motion than any other joint. It's also more likely to get injured.

The large, powerful deltoid muscle gives shoulder motion most of the power. Underneath this muscle are four rotator cuff muscles (subscapularis, supraspinatus, infraspinatus, and teres minor). They fine-tune shoulder movement and make the shoulder more stable. These muscles attach to bones by tendons. The rotator cuff is made up of muscles and tendons that hold the upper arm in the shoulder joint. A rotator cuff tear is a partial- or full-thickness tear of one or more rotator cuff tendons. It's fairly common.

What Causes a Rotator Cuff Tear?

The cause is trauma throughout one's lifetime. The tendon touches a bone spur in the shoulder. Tears usually occur during activities or jobs in which the arm is often moved over the head or raised and lowered. Playing baseball, swimming, and tennis are such activities. House painting and carpentry are such jobs.

What Are the Symptoms of a Rotator Cuff Tear?

The main symptom is shoulder pain, especially when moving the arm sideways up over the head. Pain gets worse with overhead activities such as hair brushing. The arm and shoulder may feel weak. Other symptoms include shoulder pain that worsens when lying down. Pushing objects away from the body can hurt, but pulling them does not. A tear in the rotator cuff tendon itself makes the shoulder much weaker, and it's hard to do any overhead activities.

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How Is a Rotator Cuff Tear Diagnosed?

The doctor will make a diagnosis from a history and physical examination, especially of the shoulder and back. The doctor puts the shoulder through ranges of motion that cause pain. The doctor will want the arm moved in specific ways. Magnetic resonance imaging (MRI) can help confirm the diagnosis.

How Is a Rotator Cuff Tear Treated?

A partial rotator cuff tear can usually be helped with nonsurgical methods. The doctor may prescribe medicines such as nonsteroidal antiinflammatory drugs (NSAIDs) to help inflammation and pain.

Exercise, specifically physical therapy, can help rotator cuff tendons of the shoulder get stronger and reduce pain. Ice packs put on the shoulder after exercise reduce pain and inflammation.

When physical therapy doesn't work or a full tear is present, surgical decompression may be used. The torn tendon may be fixed with an open or arthroscopic procedure. Surgery involves removing the undersurface of the acromion, fixing other inflamed parts, and repairing the rotator cuff tear.

DOs and DON'Ts in Managing Rotator Cuff Tear:

✓ **DO** take your medications as prescribed.

✓ **DO** try to do tasks with your unaffected arm.

✓ **DO** your exercises as directed.

✓ **DO** call your doctor if pain is bad enough to stop you from sleeping at night and isn't helped

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with over-the-counter medicines.

⦸ **DON'T** use addictive pain medicines as long-term therapy.

⦸ **DON'T** do activities in which you must use your hands above your head. Don't do pushups.

Don't do strenuous sports while your shoulder heals.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186, (800) 346-2267 **Website:** **http://www.aaos.org**

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MANAGING YOUR

ROTATOR CUFF TENDONITIS

What Is Rotator Cuff Tendonitis?

The shoulder has a greater range of motion than any other joint in the body. It's also more likely to get injured.

The large, powerful deltoid muscle gives shoulder motion most of the power. Underneath this muscle are four rotator cuff muscles (subscapularis, supraspinatus, infraspinatus, and teres minor). They attach to bone by tendons. The rotator cuff is made up of these muscles and tendons that attach the arm to the shoulder joint and allow arm movement. Rotator cuff tendonitis is inflammation of the tendons of the shoulder. Long-lasting inflammation or injury can cause rotator cuff tendons to tear. Common names for rotator cuff tendonitis include shoulder impingement syndrome, tennis shoulder, pitcher's shoulder, and swimmer's shoulder.

What Causes Rotator Cuff Tendonitis?

The cause is often participation in sports that involve repeated overhead activities, such as basketball, swimming, lifting weights, and tennis. In some jobs, such as house painting and carpentry, the arm must be raised and lowered often. This motion puts stress on the shoulder that then causes the inflammation of those muscles and tendons. Being older than 40 years is also related to higher risk of having rotator cuff tendonitis.

What Are the Symptoms of Rotator Cuff Tendonitis?

The main symptom is shoulder pain, especially when moving the arm sideways up over the head. The pain gets worse with overhead activities such as hair brushing. The affected arm and shoulder may also feel weak.

How Is Rotator Cuff Tendonitis Diagnosed?

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The doctor can diagnose the rotator cuff tendonitis by means of a medical history and physical examination. The doctor usually finds the problem by putting the shoulder through ranges of motion that reproduce the pain. The doctor will examine the shoulder and back and want the arm moved in specific ways.

Magnetic resonance imaging (MRI) of the shoulder can help when the doctor thinks that a rotator cuff tear is present.

How Is Rotator Cuff Tendonitis Treated?

The first treatments to try are rest, using nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, and limiting activities that cause pain. If these treatments don't work, physical therapy may be needed to maintain flexibility in the shoulder.

If all these options fail to relieve pain, surgery may be done. Surgery is usually needed only for severe pain that doesn't go away with other treatments or for people who have had a serious injury.

DOs and DON'Ts in Managing

Rotator Cuff Tendonitis:

✓ **DO** rest your arm. Sometimes resting the arm and shoulder is all that is needed for healing.

✓ **DO** try to do tasks with your unaffected arm.

✓ **DO** take over-the-counter pain medicine as needed.

✓ **DO** call your doctor if pain is severe enough to stop you from sleeping well at night and isn't helped with over-the-counter medicines.

⦸ **DON'T** participate in strenuous sports while your shoulder is healing.

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⦸ **DON'T** involve the affected shoulder in repeated overhead arm movements.

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MANAGING YOUR

ROTATOR CUFF TENDINOSIS

What Is Rotator Cuff Tendinosis?

The shoulder has a greater range of motion than any other joint in the body. It's also more likely to get injured. The large, powerful deltoid muscle gives shoulder motion most of the power. Underneath this muscle are four rotator cuff muscles (subscapularis, supraspinatus, infraspinatus, and teres minor). They attach to bone by tendons. The rotator cuff is made up of these muscles and tendons that attach the arm to the shoulder joint and allow arm movement. Rotator cuff tendinosis is an overuse injury of the muscles/tendons of the rotator cuff. RC tendinosis is a form of shoulder impingement, and other common names include tennis shoulder, pitchers shoulder, or swimmers shoulder.

What Causes Rotator Cuff Tendinosis?

Rotator cuff tendinosis is characterized by decreased tendon strength, tendon degeneration, and can also be caused by compression of the rotator cuff tendons by other structures. Sports that involve repeated overhead activities, especially when leaning forward, such as basketball, swimming, lifting weights, and tennis can be difficult. In some jobs, such as house painting and carpentry, the arm must be raised and lowered often. This motion puts stress on the shoulder that can also cause overuse of those muscles and tendons. Being older than 40 years is also related to higher risk of having rotator cuff tendinosis.

What Are the Symptoms of Rotator Cuff Tendinosis?

The main symptoms are shoulder pain, weakness, or fatigue, or any combination of these. The pain is often worse when moving the arm sideways up over the head and with overhead activities, such as hair brushing. The pain can also be worse at night.

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How Is Rotator Cuff Tendinosis Diagnosed?

The doctor can diagnose the rotator cuff tendinosis by means of a medical history and physical examination. A history of a fall on an outstretched hand, pain or weakness with overhead activities, or pain at night are common. On physical examination, the doctor can often find the problem by putting the shoulder through ranges of motion that reproduce the pain, testing the muscles that form the rotator cuff and the other muscles that surround the shoulder, and doing special tests to look at the other parts of the shoulder. Magnetic resonance imaging (MRI) of the shoulder can help when the doctor thinks that a rotator cuff tear is present.

How Is Rotator Cuff Tendinosis Treated?

The first treatments to try are ice, using nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or acetaminophen for pain, and relative rest (limiting the activities that cause pain). Physical therapy to maintain normal range of motion, strengthen the rotator cuff muscles and the other muscles that provide support to the shoulder (scapular stabilizers) can be useful if the pain persists. Surgery is rarely needed, unless a significant rotator cuff tear or other shoulder problem that doesn't go away with other treatments is present.

DOs and DON'Ts in Managing Rotator Cuff Tendinitis:

✓ **DO** rest your arm. Sometimes resting the arm and shoulder is all that is needed for healing.

✓ **DO** try to do tasks with your unaffected arm.

✓ **DO** take over-the-counter pain medicine as needed.

✓ **DO** call your doctor if pain is severe enough to stop you from sleeping well at night and isn't helped with over-the-counter medicines.

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⦸ **DON'T** participate in strenuous sports while your shoulder is healing.

⦸ **DON'T** involve the affected shoulder in repeated overhead arm movements.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopaedic Surgeons (847) 823-7186, (800) 346-2267 **Website:**

  http://www.aaos.org

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MANAGING YOUR

RUBELLA

What Is Rubella?

Rubella, also called German measles, is a viral illness. It was once common in childhood before widespread vaccination for measles, mumps, and rubella (MMR) in the United States.

In both children and adults, rubella tends to be brief and mild. Complications are rare. The real danger of rubella is for pregnant women. If a pregnant woman becomes infected with the virus during the first 4 months of pregnancy, very serious birth defects and even death of the unborn baby can occur.

What Causes Rubella?

Rubella virus is the cause. The virus is passed from person to person through contact with droplets and secretions from the nose and throat of infected people. It's highly contagious and spreads very easily. A person can pass the virus to others starting 1 week before the rash appears until 1 week after the rash goes away. A pregnant woman can pass the virus to her unborn baby through the bloodstream.

What Are the Symptoms of Rubella?

Some people have no symptoms at all. It usually takes 2 to 3 weeks after exposure before symptoms start. If symptoms do appear, they may include a rash on the head and body that usually lasts 2 to 3 days, headache, low-grade fever, stuffy or runny nose, and swollen glands in the neck or behind the ears. Adults and teenagers usually have more symptoms than children do. These other symptoms include loss of appetite, mild conjunctivitis (inflammation of the lining of the eyelids and eyeballs), and swelling and pain in joints (especially in young women). Symptoms are usually gone in several days. Sometimes, it may take a few days longer for the rash and

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symptoms to go away.

How Is Rubella Diagnosed?

Rubella can be difficult to diagnose because its symptoms are very vague. The doctor will take a medical history and do a physical examination. To make the diagnosis, the doctor may take a swab of throat secretions or get a sample of blood or urine. These are sent to a laboratory for study. These tests are usually done only if a woman thinks that she may be pregnant. Also, testing is advisable if someone with rubella has been in close contact with a pregnant woman and may have infected her.

How Is Rubella Treated?

No treatment exists for rubella. Discomfort is generally minimal, and in most cases it can be relieved with over-the-counter medicines. Once people have rubella, they become immune to it. Children 12 to 15 months old should receive the MMR vaccine.

DOs and DON'Ts in Managing Rubella:

- ✓ **DO** take over-the-counter medicine (acetaminophen) for fever, headache, and joint pain as directed by your doctor.
- ✓ **DO** adjust your activity to how you feel.
- ✓ **DO** call your doctor if you or your child has a high temperature, severe headaches, or shortness of breath.
- ✓ **DO** call your doctor immediately if you are pregnant, were exposed to rubella, and have not been vaccinated against it.
- ✓ **DO** vaccinate your child with MMR to prevent rubella.

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⦸ **DON'T** give aspirin to children with rubella, because of the dangerous Reye's syndrome. Use acetaminophen for body aches or fever.

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FOR MORE INFORMATION

Contact the following source:

- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website:** **http://www.cdc.gov**

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MANAGING YOUR

SALIVARY GLAND INFLAMMATION

What Is Salivary Gland Inflammation?

Salivary glands make saliva to keep the mouth moist and to lubricate food being chewed. These glands are divided into major and minor glands. Major glands are the parotid gland in front of the ear and under the cheek, submandibular glands under the jaw bone, and sublingual glands under the tongue. Most of the more than 500 minor salivary glands are in the roof of the mouth. Inflammation (swelling) of the salivary glands is called sialadenitis. Most often the parotid gland is affected. People in their 50s and 60s, chronically ill people with dry mouth, people who had radiation therapy to the mouth, and teenagers and young adults with anorexia have greater chances of getting it.

What Causes Salivary Gland Inflammation?

The cause is usually infection with bacteria, mainly the ones called *Staphylococcus aureus, Pseudomonas, Klebsiella, Enterobacter, Enterococcus,* and *Proteus*. Often, the duct going from the gland under the tongue becomes blocked with mucus or a stone and then becomes infected. Salivary gland inflammation is often related to a chronic illness or dehydration.

What Are the Symptoms of Salivary Gland Inflammation?

Symptoms are pain and swelling in the back of the mouth; pain while eating; redness, irritation, and tenderness where saliva enters the throat from the gland, and the presence of sticky liquid near the salivary gland.

How Is Salivary Gland Inflammation Diagnosed?

The doctor will diagnose this condition from the medical history and physical examination. Usu-

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ally no tests are needed.

For serious cases that don't get better with medicine, computed tomography (CT) or a special x-ray test called a sialogram may be done.

How Is Salivary Gland Inflammation Treated?

Massaging the salivary gland to relieve pressure from swelling, rinsing out the mouth, applying heat such as warm compresses to the swollen area, and drinking more water are treatments for less serious cases.

Most cases need antibiotics and measures to make more saliva flow, to clear the salivary duct. In addition to the measures noted above, sucking on hard candies and lemon drops helps stimulate saliva production. A liquid or soft diet may help reduce pain during eating. Dilation of the duct may be needed if other things don't work. Your doctor may refer you to a specialist known as an otorhinolaryngologist.

DOs and DON'Ts in Managing

Salivary Gland Inflammation:

✓ **DO** take acetaminophen, ibuprofen, or naproxen for minor pain.

✓ **DO** try a liquid or soft diet until the duct is clear.

✓ **DO** drink more (8 to 10 glasses of water daily).

✓ **DO** apply warm compresses to the swollen gland.

✓ **DO** suck on hard candies or lemon drops to help make saliva.

✓ **DO** call your doctor if you get a fever, pain becomes severe and isn't helped by medicine, or

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your symptoms don't get better after 3 days of taking antibiotics.

⦸ **DON'T** skip doses or stop taking prescribed medication until all medicine is gone.

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FOR MORE INFORMATION

Contact the following sources:

• American Academy of Otolaryngology—Head and Neck Surgery Tel: (703) 836-4444 **Website: http://www.entnet.org**

• American Dental Association Tel: (312) 440-2500 **Website: http://www.ada.org**

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MANAGING YOUR

Salivary gland stones

What Are Salivary Gland Stones?

The major salivary glands are the parotid (on both sides of the face), submandibular (under the jaw), and sublingual (under the tongue). These glands mainly make saliva to help digestion of food. Saliva drains into the bottom of the mouth, next to the upper teeth, and under the tongue through salivary ducts. Blockage of these ducts from calcified stones (calculi) is called sialolithiasis. Most stones are made of chemicals called calcium phosphate and calcium carbonate mixed with cell debris and mucus. Sialolithiasis usually affects people between 50 and 80 years old.

Salivary gland stones affect ducts to the submandibular gland in nearly 80% of cases, the parotid gland in 14%, and the sublingual gland in 6%. Stones in submandibular glands are large and usually occur as one stone when compared with stones in the parotid gland.

What Causes Salivary Gland Stones?

The cause is unknown. It's not contagious or passed from parents to children.

What Are the Symptoms of Salivary

Gland Stones?

The main symptoms are pain and swelling in the cheek and under the tongue. Pain becomes worse during and after eating. Other symptoms include salivary gland swelling and tenderness. If the gland becomes infected, fever and increased pain may occur.

How Are Salivary Gland Stones Diagnosed?

The doctor usually makes a diagnosis from symptoms and a physical examination. Symptoms tend to come and go. These periodic painful attacks may be called salivary colic. The stone can sometimes be felt by an examining hand. If the doctor feels a swollen mass, computed tomogra-

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phy (CT) may be done to see the mass and rule out other causes, such as tumors, dental abscesses, swollen lymph glands, lymphoma, sarcoidosis, and sialadenitis (salivary gland infection). Rarely, x-rays may be taken of the gland (sialography), after a dye is injected into the duct to confirm the diagnosis. The doctor may also order blood tests.

How Are Salivary Gland Stones Treated?

The goal of treatment is to reduce pain and swelling. Therapy at first may be conservative, with heat (warm soaks) applied to the area, massage, and increased fluid intake. The doctor may prescribe an antibiotic for infected glands.

A stone can sometimes be removed by squeezing them out by hand or by making a small cut in the opening to the duct. Stones that are hard to remove may need surgery, usually done by a surgical ear, nose, and throat specialist or a head and neck specialist.

DOs and DON'Ts in Managing Salivary Gland Stones:

✓ **DO** drink plenty of fluids and take care of your mouth. Dehydration puts you at risk for having salivary gland stones.

✓ **DO** call your doctor if you have mouth pain, especially when eating citrus or spicy foods.

✓ **DO** call your doctor if you have a fever or you see a lump on the side of your mouth or in your neck.

⦸ **DON'T** eat citrus and spicy foods if you think that you have salivary gland stones. Both types of foods increase secretion of saliva and can make pain of a blocked gland worse.

⦸ **DON'T** forget that salivary gland stones most often affect the gland under the jaw.

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FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Otolaryngology—Head and Neck Surgery Tel: (703) 836-4444 **Website: http://www.entnet.org**
- American Dental Association Tel: (312) 440-2500 **Website: http://www.ada.org**

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MANAGING YOUR

SALIVARY GLAND TUMORS

What Are Salivary Gland Tumors?

Salivary glands are in the back of the mouth and make saliva that helps the body digest food. The major glands are parotid glands (along both sides of the face), submandibular glands (below the jaw bone), and sublingual glands (under the tongue).

Salivary gland tumors are rare abnormal growths in these glands. They may be benign or malignant (cancerous). In the parotid gland, 80% of tumors are benign; in the minor salivary glands, 80% of tumors are malignant.

What Causes Salivary Gland Tumors?

The cause is unknown. They aren't contagious or passed on from one generation to the next.

What Are the Symptoms of Salivary Gland Tumors?

A lump or mass is the usual first sign. Salivary gland cancers tend to spread by invading nearby tissue. Local spread of parotid tumors may involve the facial nerve. This tumor can lead to paralysis in the face, with facial droop and inability to close the eye on the affected side. Other salivary gland cancers spread into muscles at the floor of the mouth and base of the skull, and to local lymph glands (nodes). Facial pain, ear pain, headache, and swollen lymph glands result.

Advanced cancer can spread by blood to lungs and bones.

How Are Salivary Gland Tumors Diagnosed?

The doctor uses computed tomography (CT) or magnetic resonance imaging (MRI) and physical examination to diagnose the tumor. The only sure way to confirm the diagnosis is to biopsy the mass and check the tissue for cancer cells with a microscope.

How Are Salivary Gland Tumors Treated?

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Salivary gland tumors can be cured if found and removed before they spread. Treatment is removal of the entire gland and nearby structures and lymph glands, if these are involved. Complications of surgery include cutting important nerves, such as the facial nerve and the nerve that goes to the tongue.

Radiation therapy can be used for advanced inoperable tumors or tumors that return. Complications may be dry, red, itchy skin; loss of ability to produce saliva, which causes dry mouth, sore throat, and trouble swallowing; loss of facial hair growth; and loss of taste.

DOs and DON'Ts in Managing Salivary Gland Tumors:

✓ **DO** look for an experienced surgeon who specializes in tumors of the head and neck.

✓ **DO** understand that good nutrition is important. Pain, loss of saliva, and loss of taste can make you lose weight. You may need nutritional supplements and lots of fluids.

✓ **DO** remember to keep all doctor appointments to watch for side effects or cancer that may return.

✓ **DO** remember that the earlier the cancer is found, the better the prognosis. The 10-year survival rate is 90% for very small tumors with no spread, but only 25% for larger tumors with spread to a lymph gland.

✓ **DO** call your doctor if you find a lump in your head or neck or have facial or ear pain.

✓ **DO** call your doctor if you suddenly have facial droop and can't close your eye on the same side.

✓ **DO** call your doctor if you need emotional support.

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⦸ **DON'T** ignore lumps in your mouth, cheek, or neck.

⦸ **DON'T** ignore swollen lymph glands.

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FOR MORE INFORMATION

Contact the following sources:

- National Cancer Institute Tel: (800) 422-6237 (800-4-CANCER) **Website:** **http://www.cancer.gov**
- American Academy of Otolaryngology—Head and Neck Surgery Tel: (703) 836-4444 **Website: http://www.entnet.org**

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MANAGING

SALMONELLOSIS

What Is Salmonellosis?

Salmonella is the name of a kind of bacteria. Salmonellosis is an infection of the stomach and intestines that's caused by *Salmonella*. It's similar to stomach flu. Most people with mild infection get better in 4 to 7 days without treatment. An epidemic can occur when many people eat the same contaminated foods, such as at a restaurant. Some people have such severe diarrhea that they may need a hospital stay for intravenous fluids and antibiotics.

What Causes Salmonellosis?

People get *Salmonella* infection by eating contaminated foods, especially eggs, beef, poultry, or fruit, or by drinking contaminated water or milk. Cooking helps reduce but does not eliminate chances of getting infected. *Salmonella* can spread among people when they don't wash their hands after going to the bathroom. *Salmonella* can also spread from pets, such as turtles and iguanas, to people.

What Are the Symptoms of Salmonellosis?

Diarrhea is the main symptom. It may be mild, with two or three loose bowel movements (stools) daily. It may be severe, with watery diarrhea every 10 or 15 minutes. Other symptoms are blood in stool, stomach cramps, vomiting, fever, and headaches.

How Is Salmonellosis Diagnosed?

The doctor makes a diagnosis by testing stool, blood, and urine samples. Blood tests are also done to rule out other diseases.

How Is Salmonellosis Treated?

Mild infections (gastroenteritis) don't usually need medicine. Most go away in 24 to 48 hours.

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If possible, infected people should be isolated or at least use a separate bathroom. Good hand washing is essential to avoid spreading the infection.

People who have fever and more severe infection (typhoid fever) will need antibiotics. Drinking more fluids helps prevent dehydration. A liquid diet including Gatorade® or Pedialyte® should be followed until diarrhea stops. Then, eating regular foods can slowly begin again. Dairy products can make the diarrhea worse and should be avoided for several days.

People with severe diarrhea may need intravenous fluids.

DOs and DON'Ts in Managing Salmonellosis:

- ✔ **DO** thoroughly cook food such as meat and poultry.
- ✔ **DO** handle and store food correctly. For example, don't let a salad with mayonnaise sit for hours at room temperature.
- ✔ **DO** drink only pasteurized milk.
- ✔ **DO** use only bottled water when traveling. Ask your doctor about how to prepare if you're traveling to a developing country.
- ✔ **DO** avoid contact with anyone who has a *Salmonella* infection.
- ✔ **DO** avoid animals, such as pet turtles, that could be infected.
- ✔ **DO** wash your hands well after using the bathroom to avoid spreading the infection.
- ✔ **DO** drink watered-down electrolyte solutions, such as sports drinks, until diarrhea stops.
- ✔ **DO** eat a bland, high-calorie, well-balanced diet after diarrhea stops.
- ✔ **DO** call your doctor if you're dehydrated (have dry wrinkled skin and dark or less urine).
- ✔ **DO** call your doctor if you have symptoms longer than 48 hours, high fever, worse diarrhea, or yellow skin or eyes.
- ⃠ **DON'T** let others use the same bathroom unless it was thoroughly cleaned.

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⦸ **DON'T** eat raw or undercooked poultry or eggs or drink unpasteurized milk.

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FOR MORE INFORMATION

Contact the following sources:

- • Centers for Disease Control and Prevention Tel: (800) 232-4636 **Website:** **http://www.cdc.gov/salmonella**
- • Intestinal Disease Foundation Tel: (412) 261-5888 **Website:** **http://www.intestinalfoundation.org**
- • National Institute of Allergy and Infectious Diseases Tel: (866) 284-4107

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MANAGING YOUR

SARCOIDOSIS

What Is Sarcoidosis?

Sarcoidosis is an illness that causes inflammation of many organs. It most often starts in the lungs or lymph nodes (glands). The illness affects both sexes, usually people 15 to 65 years old.

What Causes Sarcoidosis?

The cause isn't known. It is a granulomatous disease. Granuloma means a special kind of tissue inflammation seen with a microscope, and granulomatous means related to granuloma. Sarcoidosis isn't contagious or hereditary.

What Are the Symptoms of Sarcoidosis?

Some people have only one or two symptoms, but others have many. These may include shortness of breath, dry cough, joint aches and pain, chest pain, dry eyes, dry mouth, fever, large lymph glands, loss of appetite and weight, palpitations, chronic runny or stuffy nose, rash, and stiff or swollen joints. Other signs and symptoms are tiredness, vision changes, and tender red areas over the legs known as "erythema nodosum." In complicated cases, eye inflammation, high blood calcium levels, liver and kidney problems, heart rhythm problems, and skin lesions may occur.

How Is Sarcoidosis Diagnosed?

The diagnosis is difficult, because people may not have symptoms, and other disorders can cause similar problems. The doctor will do a physical examination and order a chest x-ray. The x-ray is often abnormal and the physical examination may be normal. The doctor may want blood tests, breathing tests, computed tomography (CT), tissue biopsy, tuberculosis (TB) tests, and electrocardiography (ECG). If the doctor needs a lung sample for diagnosis, a procedure called bron-

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choscopy will be done by a lung specialist (pulmonologist). The doctor puts a flexible tube through the nose into the lungs. If results are unclear, surgery to open the lungs and get a more extensive piece of tissue (open lung biopsy) may be done.

How Is Sarcoidosis Treated?

Many people get better without treatment, especially in earlier stages and people without symptoms. However, in people with severe symptoms, treatment may be needed for several weeks to years. Oral corticosteroids (prednisone) usually help in 1 to 3 months, but close follow-up and dose changes are necessary. Prednisone is usually given for at least 6 to 12 months. Usually, the lowest dose to control sarcoidosis is used. Response to treatment is checked by watching for changes in symptoms, chest x-rays, breathing tests, and other abnormalities. Relapses may occur. For severe progressive disease not responding to prednisone, more powerful medications, such as methotrexate, azathioprine, or hydroxychloroquine, may be used.

DOs and DON'Ts in Managing Sarcoidosis:

✓ **DO** tell your doctor about your medicines (prescription and over-the-counter).

✓ **DO** tell your doctor if you're pregnant.

✓ **DO** eat a low-salt diet if you take steroids, to prevent fluid gain.

✓ **DO** have your blood pressure checked and blood tested for diabetes while taking steroids.

✓ **DO** get a flu shot each fall.

✓ **DO** get vaccinated for pneumococcal pneumonia.

✓ **DO** call your doctor if you're very thirsty, urinate a lot, or have weight changes. It could in-

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dicate a very high sugar level from prednisone.

✓ **DO** call your doctor if you cough discolored sputum or blood.

✓ **DO** call your doctor if you have fever, chills, vision changes, chest pain, or palpitations.

✓ **DO** call your doctor if your symptoms don't get better or get worse.

⃠ **DON'T** stop taking your medicine or change your dosage because you feel better, unless your doctor tells you to.

⃠ **DON'T** smoke. Smoking makes symptoms worse.

⃠ **DON'T** get too much direct sun exposure. It will make any skin rash from sarcoidosis worse.

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FOR MORE INFORMATION

Contact the following sources:

• National Sarcoidosis Resources Center Tel: (732) 699-0733 **Website:** **http://www.nsrc-global.net**

• American Lung Association Tel: (800) LUNG-USA (586-4872) **Website:** **http://www.lungusa.org**

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MANAGING

SCABIES

What Is Scabies?

Scabies is a very common skin infection that causes an extremely itchy rash. It's not dangerous and doesn't usually lead to lasting damage, but excessive scratching can result in a skin bacterial infection. Anyone can catch scabies, but it occurs much more in young children. Children often get scabies from their classmates and bring the infection home and spread it to their family. It's also common in people who live together, such as those in nursing homes.

What Causes Scabies?

The cause is a tiny mite that burrows into the skin. The mite is only slightly larger than the head of a pin and doesn't burrow very far. The infection spreads easily from person to person by skin-to-skin contact, such as sharing a bed with an infected person. It doesn't depend on personal cleanliness.

What Are the Symptoms of Scabies?

Severe itching, especially at night, is common. Tiny pimples, tiny blisters, or bumps that break easily when scratched and tiny, very itchy burrows on the skin are manifestations of scabies. Blisters usually form a thin line between fingers and on skin folds of the wrist, elbows, knees, breasts, shoulder blades, or penis. Children and babies often have the rash on the head, neck, face, palms (hands), and soles (feet).

Scratching can cause hives, skin scaling, sores, blisters, and small blisters around the nose and mouth.

How Is Scabies Diagnosed?

The doctor makes the diagnosis by looking closely at the skin. No other tests are generally

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needed. The doctor may painlessly scrape the skin to get a sample containing mites and put it on a slide for study with a microscope.

How Is Scabies Treated?

The standard treatment is a topical prescription lotion, such as permethrin, which kills the mites. The lotion is put on the whole body, left on for a specific time, and then washed off. These medicines are usually safe, but caution is especially important with infants younger than 2 years and with pregnant women. All close family contacts should be treated at the same time.

All clothes, bedding, and toys must be washed with hot, soapy water.

Severe itching may need antihistamines or topical salves and corticosteroids. Elderly people and those with weak immune (infection-fighting) systems can get more serious infections and need stronger treatment. In resistant cases an oral medication (ivermectin) can be prescribed by your doctor.

DOs and DON'Ts in Managing Scabies:

✓ **DO** use medications or lotions as instructed by your doctor.

✓ **DO** wash all clothing, bedding, and towels that you've used in the past 2 days in hot water. Keep your bedding and clothing separate.

✓ **DO** put items that can't be washed into plastic bags, and keep them there for 14 days to kill the mites.

✓ **DO** clean chairs, mattresses, and other items with a special solution (called antiseptic scabicide) that kills mites.

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✓ **DO** use good personal hygiene.

✓ **DO** wash your hands often.

✓ **DO** call your doctor if you show redness, pus, swelling, or pain after treatment.

✓ **DO** call your doctor if itching or pain lasts for 1 to 2 weeks after treatment.

⃠ **DON'T** share bedding.

⃠ **DON'T** wash off prescribed cream before 8 to 12 hours.

⃠ **DON'T** use home remedies such as detergents, scrubbing, or kerosene.

⃠ **DON'T** use steroid creams unless your doctor prescribes them.

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FOR MORE INFORMATION

Contact the following sources:

- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website:** **http://www.cdc.gov**
- American Academy of Dermatology Tel: (866) 503-7546 **Website:** **http://www.aad.org**

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CARING FOR YOUR CHILD WITH

SCARLET FEVER

What Is Scarlet Fever?

Scarlet fever is a common illness in children. It starts as a bacterial infection in the throat. A reaction to a toxin (poison) produced by a specific kind of bacteria causes a bright red rash. Not everyone who has this type of infection will have scarlet fever.

What Causes Scarlet Fever?

The bacteria named *Streptococcus* (strep) is the cause. The infection is contagious and spreads by direct contact, from the day the sore throat starts until 24 to 48 hours after starting antibiotics.

What Are the Symptoms of Scarlet Fever?

First symptoms are usually a bad sore throat, fever (higher than 101˚ F), swollen glands in the neck, cough, headaches, and loss of appetite. Tonsils and the back of the throat may have a whitish coating or look red and swollen. The tongue may be coated.

A bright red rash is the most striking symptom. It usually starts several days after the sore throat, first on the neck and face and then the chest and back. The tongue becomes red (strawberry or raspberry tongue). Areas with the rash turn white when they're pressed on. By the sixth day, the rash starts to fade and the skin begins to peel. The skin peeling may last 1 to 2 weeks before returning to normal.

How Is Scarlet Fever Diagnosed?

The doctor will make a diagnosis from the medical history and physical examination. A small scraping from the child's throat will be taken and sent for culture, to show which bacteria are in the throat.

How Is Scarlet Fever Treated?

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Treatment includes antibiotics, such as penicillin or erythromycin, and bed rest. Children should be kept away from others to prevent disease spread. No special diet is needed, but fluid intake should be increased. Using a cool mist vaporizer and gargling with warm salt water can help the sore throat.

DOs and DON'Ts in Managing Scarlet Fever:

- ✓ **DO** give the medicine on schedule and for as many days as your doctor directs.
- ✓ **DO** make your child comfortable. Give soft foods and liquids and make sure your child drinks plenty of fluids. Use a humidifier to add moisture to the air.
- ✓ **DO** keep your child away from other family members from the day he or she develops a sore throat until 2 days after antibiotics are started. Your child can usually return to school within 2 weeks.
- ✓ **DO** keep drinking glasses and eating utensils separate, and wash them in very hot soapy water.
- ✓ **DO** wash your own hands often.
- ✓ **DO** trim your child's fingernails to prevent scratches if the rash itches.
- ✓ **DO** call your child's doctor if fever (temperature higher than 101° F) returns after it went away for a few days.
- ✓ **DO** call your child's doctor if nausea or vomiting, severe headache or earache, or chest pain and a cough that produces thick sputum develop.

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✓ **DO** call your child's doctor if areas of peeling skin show signs of infection.

⃠ **DON'T** let your sick child play with other children.

⃠ **DON'T** let your sick child skip doses or stop antibiotics before they are finished.

⃠ **DON'T** send your child to school until the infection is over.

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Allergy and Infectious Diseases Tel: (301) 496-5717 **Website:** **http://www3.niaid.nih.gov**
- The American Academy of Pediatrics Tel: (847) 434-4000 **Website:** **http://www.aap.org**
- National Institute of Child Health and Human Development Tel: (800) 370-2943, (301) 496-5133 **Website:** **http://www.nichd.nih.gov**

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MANAGING YOUR

SCHIZOPHRENIA

What Is Schizophrenia?

Schizophrenia is a mental illness causing a disturbance in the way people think. It affects about 1% of the population. It usually starts in late teenage years to early adulthood. It equally affects males and females; however, males usually have a more severe illness with earlier onset.

Thoughts become disordered and out of touch with the real world. Thoughts may race, slow down, or stop, so people talk fast, slowly, or halting. It may be hard for people to think, remember, or understand.

Schizophrenia also causes strange behaviors because of hearing voices inside the head and seeing things that aren't really there. People can have delusions, feel that others are out to get them (paranoia), or act angry or want to fight.

Schizophrenia may also cause people to lose interest in other people and activities and in staying clean, neat, or healthy. People can lose mental abilities and become socially isolated.

What Causes Schizophrenia?

The cause is unknown. It may run in families. First-degree relatives of schizophrenics are 10 times more likely to become schizophrenic than the general population.

What Are the Symptoms of Schizophrenia?

Schizophrenia's main features include ambivalence (e.g., trouble making decisions), problems displaying and expressing emotions, inability to function in social situations, and abnormal thinking.

Abnormal thinking can mean having hallucinations, especially hearing voices of people not actually there. Voices may tell people to do something that they may feel uncomfortable about,

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such as killing themselves or others. People can also feel paranoid or believe that they have special powers or some medical condition.

How Is Schizophrenia Diagnosed?

No diagnostic tests (blood or genetic testing) exist. A doctor—usually a mental health specialist (psychologist or psychiatrist)—makes the diagnosis from the medical history and physical examination. Blood and urine tests, imaging scans, or x-rays are not needed for diagnosis but may be done to check for other conditions that may cause similar symptoms.

How Is Schizophrenia Treated?

Schizophrenia isn't curable, but many symptoms can be treated with medicines and counseling (cognitive behavioral therapy). A significant social support system is required by most schizophrenics.

Drugs called antipsychotics can stop hallucinations and paranoia if taken daily. Psychosocial treatment involves having a counselor help with different aspects of daily living, including getting to appointments and helping with medicines. A support group can help teach social skills.

DOs and DON'Ts in Managing Schizophrenia:

✓ **DO** take your medicines every day as prescribed.

✓ **DO** attend programs or participate in activities recommended by your doctor. Consider joining a support group.

✓ **DO** tell your doctor about side effects from medicine.

✓ **DO** avoid alcohol because it may interfere with your medicines.

✓ **DO** avoid stress. Stress, lack of sleep, poor diet, and using caffeine may make psychotic be-

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haviors more likely.

✓ **DO** call your doctor if you hear voices, feel paranoid, or have other odd thoughts.

✓ **DO** call your doctor if you sleep less or if depression or suicidal thoughts occur.

⃠ **DON'T** drive unless your doctor says you can.

⃠ **DON'T** take any recreational drugs.

⃠ **DON'T** use medicines, including over-the-counter drugs, without first checking with your doctor.

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FOR MORE INFORMATION

Contact the following sources:

• National Alliance for the Mentally Ill Tel: (800) 950-NAMI (950-6264) **Website:** **http://www.nami.org**

• National Institute of Mental Health Tel: (866) 615-6464 **Website:** **http://www.nimh.nih.gov**

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MANAGING YOUR

SCIATICA

What Is Sciatica?

The back is made up of the bones (vertebrae) of the spinal column, disks between the bones, the spinal cord (which contains nerves), muscles, and ligaments. The sciatic nerve is the longest nerve in the body. It goes from the spinal cord to the hips and down the back of the legs. Sciatica refers to pain that this nerve causes in these areas. Instead of a disorder, it's a symptom of a problem with the nerve. The pain usually goes away on its own in 4 to 8 weeks.

What Causes Sciatica?

The usual cause is a herniation (bulge) of a disk that presses directly on the sciatic nerve. Disks are pads of a jelly-like substance with a tough, fibrous outer covering. They separate vertebrae and cushion them like shock absorbers, but they can herniate and press on the nerve. Other causes include irritation or inflammation (swelling) of this nerve from degenerative arthritis and rarer causes, such as tumors, muscles, bleeding, infections, and injuries such as pelvic bone fractures (breaks). Spinal stenosis, or narrowing of the spinal canal that puts pressure on the nerve, can cause sciatica. It is often due to degenerative arthritis. *R*isk factors include age, occupation, prolonged sitting, and obesity.

What Are the Symptoms of Sciatica?

Symptoms include pain, burning, numbness, *muscle weakness,* or tingling going from the lower (lumbar) back to the buttock and down the back of the leg. Usually only one leg is involved. The toes or part of the foot can be affected. Walking, bending at the waist, sitting for long periods, coughing, or sneezing may make symptoms worse. Lying down may make them better. The pain can be mild and achy, sharp and burning, or extreme. Severe sciatica can make walking hard or

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even impossible.

How Is Sciatica Diagnosed?

Diagnosis results from taking a medical history and doing a physical. X-ray studies are not usually needed. Computed tomography (CT), magnetic resonance imaging (MRI), and other tests may be done if treatment has not resulted in symptom relief and surgery is being considered.

How Is Sciatica Treated?

Treatment depends on the cause and pain severity. Medicines such as nonsteroidal anti-inflammatory drugs (NSAIDs) may relieve pain and inflammation. Muscle relaxants, oral steroids, *or epidural steroid injections* may be given. Severe pain may need stronger narcotic-containing medicines for a short time. Alternating heat and ice massage *may soothe muscles* and relieve acute pain.

All medicines have side effects. NSAIDs may cause stomach upset, diarrhea, ulcers, headache, dizziness, difficulty hearing, or rash. Muscle relaxants may cause drowsiness, dizziness, or rash.

Physical therapy and exercises may also help reduce the pain.

Surgery may be an option if other treatments don't work.

DOs and DON'Ts in Managing Sciatica:

✓ **DO** take your medicine as prescribed.

✓ **DO** call your doctor if you have drug side effects.

✓ **DO** lose weight if you're overweight.

✓ **DO** back stretching and strengthening exercises daily.

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✓ **DO** use good posture when sitting or standing. Use good body mechanics and lifting techniques.

✓ **DO** call your doctor if you have trouble urinating or lose control of your bowels or bladder.

⦸ **DON'T** wait for a drug side effect to go away by itself.

⦸ **DON'T** give up. If you don't feel better, ask your doctor about starting in a special treatment program.

⦸ **DON'T** stop exercising completely.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopaedic Surgeons Tel: (800) 346-AAOS **Website: http://www.aaos.org**
- North American Spine Society Tel: (708) 588-8080 **Website: http://www.spine.org**
- American Association of Neurosurgeons **Website: http://www.neurosurgerytoday.org/what/patient_e/herniated.asp**

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MANAGING YOUR

SCLERODERMA

What Is Scleroderma?

Scleroderma is a disorder that causes the body to make too much collagen, the result being inflammation (swelling) and stiffness. Collagen is the main protein in connective tissue, which supports the organs and skin. Too much collagen causes skin and organs to get thick and stiff. Scleroderma can affect the heart, esophagus (tube connecting the mouth and stomach), kidneys, lungs, blood vessels, and skin.

Scleroderma affects women four times more often than men, usually starting at age 30 to 50.

What Causes Scleroderma?

The cause is unknown, but scleroderma is an autoimmune disorder. In autoimmune disorders, the body's own immune system mistakenly attacks normal parts of the body and causes disease.

What Are the Symptoms of Scleroderma?

People can have many symptoms. Mild to severe symptoms depend on the organs affected. Most common symptoms are dry eyes and mouth, joint stiffness and pain, heartburn, muscle pain, numbness, poor circulation, poor wound healing, swallowing problems, weakness, and weight loss. Skin becomes thick, hard, and tight and loses flexibility. The face looks masklike, with thin lips and furrowing around the mouth. Fingers become thick, stiff, painful, and less moveable.

Complications include kidney failure (most common cause of death), heart failure, abnormal heart rhythms, high blood pressure, poor lung function, heartburn, and constipation.

How Is Scleroderma Diagnosed?

The doctor will take a medical history, do an examination, order blood and urine tests, do electrocardiography (ECG), and x-rays. The ECG measures the heart's electrical activity. A small

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piece of skin may be taken and looked at with a microscope. Since scleroderma affects many organs, your primary care doctor may refer you to a rheumatologist (specialist of muscle joint diseases), a nephrologist (kidney specialist), a dermatologist (skin specialist), a cardiologist (heart specialist), a pulmonologist (lung specialist), and a gastroenterologist (specialist of digestive tract).

How Is Scleroderma Treated?

Scleroderma isn't curable. Treatment is aimed at controlling symptoms, relieving symptoms, and treating or preventing complications. Treatment consists of general measures and medicines. General measures include medications for heartburn or gastroesophageal reflux; avoiding smoking, alcohol, and caffeine; and not eating close to bedtime or lying down. For joint pain and stiffness, use mild heat. Avoid very cold temperatures and skin injuries and burns such as from hot water. Psychological counseling and biofeedback may help depression. Physical therapy and occupational therapy improve joint mobility.

Helpful medicines include steroids, over-the-counter antacids or prescription drugs (gastroesophageal reflux), blood pressure drugs, aspirin or anti-inflammatory drugs (arthritis), and immunomodulators (which help the immune system). Lotions, moisturizers, and bath oils soften the skin.

DOs and DON'Ts in Managing Scleroderma:

✓ **DO** raise the head of your bed with blocks to prevent acid reflux and heartburn while sleeping. Eat small meals. Avoid alcohol, tobacco, caffeine, and fatty and spicy foods.

✓ **DO** wear warm clothing. Avoid cold weather.

✓ **DO** use sunscreen, and avoid skin-drying hot baths or showers and harsh soaps.

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✓ **DO** exercise regularly.

✓ **DO** stop smoking.

✓ **DO** call your doctor if you have worse or new symptoms.

⃠ **DON'T** stop taking your medicine or change your dosage because you feel better unless your doctor says to.

⃠ **DON'T** smoke.

⃠ **DON'T** stop steroids suddenly.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- Scleroderma Foundation Tel: (877) 722-4673 **Website:** **http://www.scleroderma.org**
- American Academy of Dermatology Phone: (866) 503-7546 **Website:** **http://www.aad.org**
-

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UNDERSTANDING AND MANAGING YOUR CHILD'S

SCOLIOSIS

What Is Scoliosis?

Scoliosis is a lateral, or sideways, curving of the spine. It usually begins in childhood or adolescence and may slowly worsen. The younger the age when scoliosis starts, the worse it's likely to become. The degree of curving is measured by angles. The larger the angle, the greater is the chance that scoliosis will worsen. Curves less than 30 degrees at the end of childhood growth rarely get worse and don't usually need close watching. Curves larger than 50 to 75 degrees may need aggressive therapy. More girls than boys have the severe disorder.

What Causes Scoliosis?

The cause is usually unknown. Some cases are due to uneven leg length, congenital (present at birth) spine disorders, or rare neurological disorders. The risk increases with a family history of scoliosis. Backpacks, poor diet, exercising, and bad posture don't cause it.

What Are the Symptoms of Scoliosis?

Most children don't have symptoms such as pain, but may have a hump, with one side of the back or one shoulder blade higher than the other, when they bend forward. Children may have uneven hips and tend to lean to one side.

Emotional aspects of scoliosis may be severe, especially for teenagers. Breathing problems may develop with large curves.

How Is Scoliosis Diagnosed?

Scoliosis is often found when children 10 to 14 years old have examinations with their primary care doctor or at school. The doctor makes a diagnosis from a physical examination (with the forward bending test) and x-ray of the spine. The doctor can use a scoliometer, a tool to measure

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spine curvature.

How Is Scoliosis Treated?

A slowly progressive curve may not be painful and not need treatment. Only about 10% of teenagers with scoliosis need treatment, other than x-rays to make sure that it isn't getting worse. A curve that causes pain and deformity may need aggressive treatment.

Analgesics and antiinflammatory drugs may reduce pain. No medicines, injections, diets, or exercises can fix the curve itself.

The doctor will use regular x-rays to watch for progression of the curve. Braces can help prevent a curve from getting worse but don't fix an already developed curve. Braces can prevent the need for surgery approximately 70% of the time. When the curve progresses or causes severe pain, surgery may be an option. The operation involves fusing, or joining, the bones (vertebrae) of the back together.

DOs and DON'Ts in Managing Scoliosis:

✓ **DO** have your child wear a brace as the doctor says.

✓ **DO** encourage your child to exercise. No activities make scoliosis worse. If surgery is needed, talk to your child's doctor about what your child can do safely.

✓ **DO** call your child's doctor if you see a change in the deformity, such as ribs sticking out more, change in leg length, or new pain.

✓ **DO** talk to your doctor about getting emotional support for your child. Look for support groups to help.

⃠ **DON'T** let your child stop wearing the brace unless the doctor tells you to do so.

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FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Scoliosis Foundation Tel: (800) 673-6922 **Website: http://www.scoliosis.org**
- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website: http://www.aaos.org**

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MANAGING YOUR

SCOLIOSIS AS AN ADULT

What Is Scoliosis?

Scoliosis is a lateral, or sideways, curving of the spine. The degree of curving is measured by angles. The larger the angle, the greater is the chance that the disorder will get worse. Curves less than 30 degrees at the end of childhood growth rarely get worse and don't usually need close watching. Curves larger than 50 to 75 degrees may need aggressive therapy.

Scoliosis usually begins in childhood or adolescence and may slowly worsen into adulthood. The younger the age when scoliosis starts, the worse it's likely to become. More girls than boys have the severe disorder.

What Causes Scoliosis?

The cause is usually unknown. Some cases are due to uneven leg length, congenital (present at birth) spine disorders, or rare neurological disorders. The risk increases with a family history of scoliosis. It's not caused by backpacks, poor diet, exercise, or bad posture.

What Are the Symptoms of Scoliosis?

Pain is the most common reason that adults go to doctors for treatment. The true source of pain isn't clear.

Some people may have a loss of height, increase in prominence of a rib, or changes in waistline, which can mean progression of the curve.

The emotional aspects of scoliosis may be severe, especially for teenagers. Breathing problems may develop with large curves, but usually pain and fatigue are felt before the breathing trouble.

How Is Scoliosis Diagnosed?

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The doctor makes a diagnosis from a physical examination and x-ray of the spine. Deformities can range from mild to painful and severe. X-rays taken for several years is the best way to watch the curving.

How Is Scoliosis Treated?

A slowly progressive curve may not be painful and not need treatment. A curve that causes pain and deformity may need aggressive treatment.

Analgesics and anti-inflammatory drugs may reduce pain. No medicines, injections, diets, or exercises can fix the curve itself.

The doctor will take routine x-rays at regular times to watch for progression of the curve. Braces can help prevent a curve from getting worse but don't correct an already developed curve. Exercises and electrical stimulation of muscles don't help people with scoliosis.

When the curve progresses or causes severe pain, surgery may be used. If the curve is not getting worse, people must decide whether the pain is bad enough that a complex operation should be done. The operation involves fusing, or joining, the bones (vertebrae) of the back. The surgeon must be sure that something else unrelated to scoliosis is causing the back pain.

DOs and DON'Ts in Managing Scoliosis:

✓ **DO** take your medicines as prescribed.

✓ **DO** wear your brace as directed, but be aware that many curves can get worse even with braces.

✓ **DO** call your doctor if you see a change in the deformity, such as ribs sticking out more, change in leg length, or new pain.

⦸ **DON'T** stop wearing your brace unless your doctor tells you to.

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Contact the following sources:

- National Scoliosis Foundation Tel: (800) 673-6922 **Website: http://www.scoliosis.org**
- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website: http://www.aaos.org**

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COLON CANCER

SCREENING AND PREVENTION

What Is the Colon?

The colon is part of the digestive system. Food moves from the mouth to the stomach. Several hours later, it moves into the intestines, first the small intestine and then the large intestine. After digestion of food is finished, what's left leaves the body as waste (stool) through the rectum. The colon is the last part of the large intestine, just before the rectum.

What Is Colon Cancer?

Colon cancer is a tumor in the colon. It is the most common cancer of the digestive tract. Other names are adenocarcinoma of the colon and colorectal cancer (often the lower rectum and sigmoid part of the colon are involved). The cancer can also be found in the first part of the colon (cecum). Colon cancer can also spread (metastasize) to other parts of the body.

Colon cancer usually starts as a small growth (polyp) on the surface of the colon. Some polyps are harmless, but some can turn into cancer.

Colon cancer tends to run in families. If you have a strong family history of colon cancer, you should discuss with your doctor genetic testing done with blood tests to look for genetic changes that predispose to rare hereditary colon cancers known as familial adenomatous polyposis (FAP) and Lynch syndrome.

What Are Symptoms of Colon Cancer?

Symptoms to be aware of are a change in bowel habits, such as constipation or diarrhea, a change in stool size (e.g., pencil-thin) or stool appearance (e.g., black and tarry), rectal bleeding, and abdominal pain.

Sometimes no symptoms are present, but iron deficiency anemia from long-term blood loss

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may occur.

Early diagnosis is critical because undetected or untreated cancer usually spreads through the intestine wall into neighboring areas and into the liver. Sometimes it can also spread to lungs and bones.

How Is Colon Cancer Diagnosed?

The doctor will do a complete physical examination, including a digital rectal examination (DRE), and take one or more stool samples. These samples are analyzed for any occult (hidden) blood. This testing can find bleeding in the intestine, but results can be inaccurate because certain medicines or red meat may produce positive results that are really normal (false-positive results).

The doctor also looks inside the colon with a flexible tube called a colonoscope. This scope is passed through the rectum to see the whole colon. The doctor can see problem areas and biopsy (take samples of) these areas and remove any polyps. The samples are studied under a microscope to look for cancerous cells. Other tests, such as computed tomography (CT), of the abdomen and pelvis may be done to see whether cancer has moved to other parts of the body.

A newer screening test involves using CT only for the intestine (CT colonography). This test is also called virtual colonoscopy. For this test, compressed air is pumped into your rectum through a tube and then a picture is taken of your colon. For this test you will also have to take laxatives the day before to clean out the colon. Any possible problem areas found by CT colonography will need a follow-up colonoscopy and biopsy to see whether they are cancerous.

DOs and DON'Ts in Diagnosing and Preventing Colon Cancer:

✓ **DO** realize the importance of colon screening for everyone, starting at age 50 or earlier for people who have family members with colon cancer.

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✓ **DO** follow your doctor's advice.

✓ **DO** eat a high-fiber diet.

✓ **DO** watch your weight.

✓ **DO** exercise. Exercising can improve your overall health.

⃠ **DON'T** forget the importance of screening.

⃠ **DON'T** smoke.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- Colon Cancer Alliance Tel: (877) 422-2030 **Website:** **http://www.ccalliance.org**
- American Cancer Society Tel: (800) ACS-2345 **Website:** **http://www.cancer.org**
- American College of Gastroenterology Tel: (703) 820-7400 **Website:**

  http://www.acg.gi.org

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MANAGING YOUR

SEASONAL AFFECTIVE DISORDER

What Is Seasonal Affective Disorder?

Seasonal affective disorder (SAD) is depression that occurs each year in fall and winter. Symptoms are not present during spring and summer. SAD can be disabling and can stop people from functioning normally.

SAD affects between 4% and 6% of the U.S. population. It usually occurs between ages 20 and 40, in women more than men at a ratio of 4 to 1. SAD also affects children and adolescents but is less likely to affect elderly people. SAD occurs more often in people living in higher latitudes (such as Alaska) where seasonal changes are more extreme.

What Causes SAD?

The exact cause of SAD is unknown. However, it's thought to be related to a biochemical abnormality in the part of the brain that keeps body functions working properly. This part is called the hypothalamus. It controls such functions as blood pressure, body temperature, fluid and electrolyte balance, and body weight. The biochemical problem is thought to be triggered by less sunlight during winter.

What Are the Symptoms of SAD?

Symptoms are similar to those of major depression, including sadness, low energy, trouble concentrating, lack of interest, more appetite leading to weight gain, fatigue, and always wanting to sleep.

How Is SAD Diagnosed?

The doctor diagnoses SAD by taking a medical history. Blood tests to rule out conditions that mimic SAD may also be done when the diagnosis is unclear. These other conditions include hy-

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pothyroidism (underactive thyroid gland), abnormal blood calcium levels, conditions caused by medicines, substance abuse (alcohol or recreational drugs), and other psychiatric conditions (e.g., bipolar disorder, major depression).

How Is SAD Treated?

Light therapy is the best treatment. Bright white fluorescent lights can reverse symptoms. Up to 80% of people treated with light therapy have fewer symptoms, sometimes after only 2 to 3 days of treatment. Light therapy is suggested for 30 minutes every day and is used until spring. Tanning booths shouldn't be used to treat SAD.

Different treatments may be combined. Sometimes, medicines are added to light therapy. Antidepressants called selective serotonin reuptake inhibitors (SSRIs) may be used. These drugs include fluoxetine, sertraline, and paroxetine. People can start SSRIs before symptoms begin in the fall and taper them off after symptoms leave in early spring.

Counseling can also help people get through this period. Light therapy can be combined with counseling. All three methods (light therapy, medicines, and counseling) can be used together.

DOs and DON'Ts in Managing SAD:

✓ **DO** tell your doctor about medicines and herbal remedies you take.

✓ **DO** reduce your stress.

✓ **DO** spend some time outdoors every day, if possible, even in winter.

✓ **DO** call your doctor if you feel down or depressed for a long period or if you feel suicidal.

⃠ **DON'T** use tanning beds to get extra light.

⃠ **DON'T** isolate yourself socially. Stay active with exercise, diet, and spending time outdoors

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during winter.

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NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Psychiatric Association Tel: (888) 357-7924 **Website: http://www.psych.org**
- Society for Light Treatment and Biological Rhythms **Website: http://www.sltbr.org**
- National Organization for Seasonal Affective Disorder **Website: http://www.nosad.org**

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MANAGING YOUR

SEBORRHEIC DERMATITIS

What Is Seborrheic Dermatitis?

Seborrheic dermatitis is a skin disorder that causes dry flaking skin. Seborrhea is oiliness of the skin without redness or scaling. Seborrheic dermatitis has both redness and scaling. The condition usually affects skin that has hair, most often the face, ears, and scalp. It can also cause thick areas of dry skin to form. Symptoms range from mild to severe. Babies, children, and adults can have it. In babies, the condition is called cradle cap. The condition isn't contagious. It doesn't cause any hair damage or hair loss but can be unsightly. In adults, the dermatitis can come and go for several years, with flare-ups in early winter.

What Causes Seborrheic Dermatitis?

The cause is unknown. A yeast-like organism may play a role in causing seborrheic dermatitis. In infants, cradle cap may be due to the gradual disappearance of hormones passed from the mother before childbirth.

What Are the Symptoms of Seborrheic Dermatitis?

Almost any part of the body can have the dermatitis, but most often the scalp, eyelashes, eyebrows, and sides of the nose are involved. The upper chest, back, and oily parts of the body, such as groin and armpits, can also have it. Symptoms include dandruff, diaper rash, dry flaking skin, greasy scales, mild itching, rash, waxy skin (especially behind the ears), and red skin (especially next to the nose and in the middle of the forehead).

How Is Seborrheic Dermatitis Diagnosed?

The doctor makes a diagnosis from a medical history and examination, with special attention to the face and scalp. The doctor may do blood tests and take a skin sample when the diagnosis is

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unclear and the patient is not responding to treatment.

How Is Seborrheic Dermatitis Treated?

Treatment depends on where the dermatitis is and how bad the symptoms are. Shampoo is usually used for both babies and adults with scalp dermatitis. Mild baby shampoo can be used, with scales loosened with a soft brush before rinsing. If scales aren't loosened easily, a few drops of mineral oil can be rubbed onto the scalp before brushing and shampooing. Sometimes, a medicated cream is used, especially if dermatitis is severe. For mild symptoms, the doctor may suggest a nonmedicated cream to keep the skin moist.

The doctor may also suggest seeing a dermatologist (specialist in skin conditions). The dermatologist may take a small sample of skin to look at with a microscope. If skin around the eyes is severely affected, the doctor may suggest seeing an ophthalmologist (specialist in eye disorders).

DOs and DON'Ts in Managing Seborrheic Dermatitis:

✓ **DO** tell your doctor about other medical problems you may have.

✓ **DO** tell your doctor about all your medicines, both prescription and over-the-counter.

✓ **DO** use a skin cream to keep your skin moist.

✓ **DO** shampoo your hair every day or according to your doctor's directions.

✓ **DO** go outside every day. Sunlight may help your symptoms. Ask your doctor how much sunlight you should get. Don't forget to use sunscreen.

✓ **DO** call your doctor if you have a fever or see fluid coming from your rash.

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✓ **DO** tell your doctor if your symptoms don't get better or get worse.

⃠ **DON'T** stop using your medicine or change your dosage because you feel better unless your doctor tells you to.

⃠ **DON'T** use any acne medicine without your doctor's permission. These drugs can make the dermatitis worse.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Skin Association Tel: (212) 889-4858 **Website: http://www.americanskin.org**
- American Academy of Dermatology Tel: (847) 330-0230, (866) 503-7546 **Website: http://www.aad.org**

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MANAGING YOUR

SECOND-DEGREE HEART BLOCK

What Is Second-Degree Heart Block?

The heart is a muscular pump with four chambers, two upper (left and right atria) and two lower (left and right ventricles). These contract and pump blood. Special tissue in the heart produces and sends electrical impulses to make the muscle contract. Normal electrical signals start from the sinoatrial (SA) node in the wall of the right atrium. From there the signal goes to the left atrium and reaches the atrioventricular (AV) node between the atria and ventricles. The signal then goes to the left and right bundle branches and finally the ventricles. There it stimulates ventricles to contract.

Heart block refers to a delay of electrical signals from the atria through the AV node. Second-degree heart block is one of three types of heart block; the others are first-degree and third-degree (or complete). It affects the AV node (type I block) or conduction below the node (type II block). The atria contract normally, but the ventricles may not contract as often as they should because of the delayed impulses.

People with type II block are at risk for complete heart block, cardiomyopathy (disease of heart muscle), or death from asystole (the heart stops beating).

What Causes Second-Degree Heart Block?

About half the time, the cause of the type I heart block is unknown. Most other times, some type of heart disease exists, perhaps damage from a heart attack (myocardial infarction) or myocarditis (inflammation, or swelling, of heart muscle). Drugs, such as digoxin, or a congenital heart abnormality (present at birth) are other causes. Type II block usually results from heart disease.

What Are the Symptoms

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of Second-Degree Heart Block?

People may have no symptoms. When present, symptoms relate to not enough blood being pumped by the heart: feeling very tired, light-headed, or faint (syncope). Severe heart block can cause chest pain (angina) or stroke (not enough blood flow to the brain).

How Is Second-Degree Heart Block Diagnosed?

The doctor uses electrocardiography (ECG) for diagnosis. ECG measures the heart's electrical activity and will usually show some impulses from the atrium not reaching the ventricles.

How Is Second-Degree Heart Block Treated?

People without symptoms and no heart disease may not need any treatment.

Those with symptoms may need a pacemaker. Pacemakers are small electrical devices with a wire to the heart muscle that tells the ventricles to contract regularly (fixed-rate pacers) or to beat faster because of need for more activity (demand pacers). Pacemakers may be attached outside the body or implanted inside. New pacemakers are safer and better than old ones, but people should still be careful around strong magnetic or ultrasonic forces, such as those used in airport security screening.

DOs and DON'Ts in Managing

Second-Degree Heart Block:

✓ **DO** eat a heart-healthy diet, low in fat and cholesterol.

✓ **DO** lose weight.

✓ **DO** stop smoking.

✓ **DO** call your doctor if you have dizziness, fainting, chest pain, or shortness of breath.

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⦸ **DON'T** exercise until your doctor says that you can.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- The American Heart Association

  Tel: (800) 242-8721

  Website: http://www.americanheart.org

- American College of Cardiology

  Website: http://www.acc.org

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MANAGING YOUR

SEPTIC ARTHRITIS

What Is Septic Arthritis?

Septic arthritis (or infectious arthritis) is a bacterial infection inside a joint. Joints are usually germfree (sterile). When bacteria get into a joint, they cause inflammation (swelling, redness) and pain. Infection usually affects only one joint at a time: knee, hip, wrist, shoulder, elbow, or ankle.

Anyone can have a joint infection, but it's most common in children younger than 3 and adults older than 80.

Untreated septic arthritis can damage and destroy the joint and lead to joint replacement surgery.

What Causes Septic Arthritis?

Usual causes are abnormal changes in a joint from other forms of arthritis, a poorly working immune (infection-fighting) system, and an artificial joint (joint replacement). The immune system problem may be caused by medicines and other conditions, such as diabetes, kidney disease, or cancer.

What Are the Symptoms of Septic Arthritis?

Infected joints swell quickly and are very painful and hard to bend. High temperature, chills, shakes, muscle aches, and fatigue occur. Depending on the joint, people may be unable to walk or use their arms.

How Is Septic Arthritis Diagnosed?

The doctor may suspect a joint infection on the basis of the medical history and physical examination. The doctor will diagnose a joint infection by removing fluid from the joint with a needle

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and testing it in the laboratory for evidence of infection.

Magnetic resonance imaging (MRI), nuclear scans and computed tomography (CT) are also commonly used when your doctor suspects an infection in a joint.

How Is Septic Arthritis Treated?

Three stages of therapy are needed: antibiotics, joint drainage, and restoring normal motion to the joint.

Antibiotics are usually given through a vein for the first 2 weeks and then by mouth for 2 to 4 weeks or more.

Joint fluid should generally be drained to help resolve the infection. Most joints can be drained by sticking a needle into the joint and taking fluid out. This procedure is called arthrocentesis. Other joints are harder to drain this way and instead need drainage by an operation.

After the first few days of treatment, people with joint infections should start therapy to restore normal joint motion. Physical therapists help with restoring normal movement. Therapy should continue until after the pain leaves and the joint works normally.

DOs and DON'Ts in Managing Septic Arthritis:

✓ **DO** take your medicines as prescribed.

✓ **DO** ask your doctor which over-the-counter drugs you may take with your prescription medicines.

✓ **DO** exercises to maintain joint motion and preserve strength.

✓ **DO** call your doctor if you have drug side effects or if medicines and treatments don't help the pain.

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✓ **DO** call your doctor if you have new fever, chills, and worsening pain or swelling.

✓ **DO** call your doctor if you need a referral for physical or occupational therapy.

⃠ **DON'T** wait to see whether medicine side effects will go away.

⃠ **DON'T** continue an exercise program that causes pain. If you have pain after exercise, the exercise program usually needs to be modified specifically for you.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- Arthritis Foundation Tel: (800) 283-7800 **Website:** **http://www.arthritis.org**
- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website:** **http://www.cdc.gov**
- Infectious Disease Society of America Tel: (703) 299-0200 **Website:** **http://www.idsociety.org**

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MANAGING YOUR

SHIGELLOSIS

What Is Shigellosis?

Shigellosis is an infection of the intestines with a bacterium named *Shigella*. More than 15,000 cases per year occur in the United States. Shigellosis commonly affects children and can rapidly spread in daycare centers.

What Causes Shigellosis?

Shigellosis is a bacterial infection caused by bacteria of the *Shigella* species. *Shigella sonnei* is the species most often isolated in the United States. *Shigella* is the most common cause of bacillary dysentery in the United States. Spread is from person to person with close contact. It's usually passed along by contaminated food or water. Male homosexuals have a higher risk of getting the infection because of oral-anal contact.

What Are the Signs and Symptoms of Shigellosis?

The incubation time can be 1 to 7 days, with an average of 3 days. Symptoms include fever, which can be high in children, and cramps in the abdomen (belly). Watery diarrhea, nausea or vomiting, muscle aches and pains, and mucus or blood in the stools may occur. Severe disease is more common in children and elderly people, and in countries with poor sanitation.

How Is Shigellosis Diagnosed?

The health care provider may suspect shigellosis because of the medical history and physical examination. Obtaining a stool sample for culture is needed for diagnosis. Other laboratory tests may be done to rule out similar diseases.

How Is Shigellosis Treated?

The main treatment is drinking enough fluids and replacing electrolytes lost with the diarrhea.

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Antibiotics may be given to shorten the illness and prevent passing it to others. If possible, infected people should use a separate bathroom. If that's not possible, gloves should be worn and the toilet scrubbed with a bleach solution after each use. Good hand washing with soap and water is a must after using the bathroom and before eating. To lessen the diarrhea, a liquid diet (gelatin, soups) is preferred initially. Then, the diet should be added to slowly, but without raw fruits and vegetables. Antidiarrheal medicines shouldn't be used because they can prevent bacteria from being eliminated and make the illness last longer. Bedrest is helpful, except for trips to the bathroom, until fever and diarrhea are gone. Soiled bed linens and clothes should be washed in soap and the hottest water possible.

DOs and DON'Ts in Managing Shigellosis:

✓ **DO** take any prescribed antibiotics until they're finished.

✓ **DO** wash your hands well after using the bathroom and before eating.

✓ **DO** increase fluid intake to prevent dehydration. Use preparations containing electrolytes such as Gatorade® or Pedialyte®.

✓ **DO** call your health care provider if your abdominal pain persists or your abdomen swells. Call if your temperature is higher than 102° F during treatment. Call if you have blood in your stools. Call if you're dehydrated (weight loss, dry skin, sunken eyes, or less need to urinate). Call if you get shortness of breath or swollen joints.

⃠ **DON'T** use over-the-counter medicines to stop diarrhea. They may make the illness last longer.

⃠ **DON'T** eat solid foods until the diarrhea slows.

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⦸ **DON'T** eat raw fruits and vegetables until the infection is completely gone.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- Centers for Disease Control and Prevention Phone: 800-311-3435
- National Institute of Allergy and Infectious Disease Phone: 301-496-5717 **Website:**

  www.healthfinder.gov (Choose SEARCH to search by topic.)

  http://www.healthanswers.com
- National Institute of Environmental Health Sciences Tel: (919) 541-3345 **Website:**

  www.niehs.nih.gov

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MANAGING YOUR

SHIN SPLINTS

What Are Shin Splints?

The term shin splints refers to a group of problems causing pain in the shinbone (tibia), the big bone in the front of the lower leg. These problems include medial tibial stress syndrome (the most common cause of shin splints), stress fractures, and flat or high-arched feet. Dancers and athletes such as runners or power walkers can have this common exercise-related pain. People who play soccer, jog, or train for a race are at risk of having shin splints. The two types are anterolateral (front, outside) and posteromedial (back, inside).

What Causes Shin Splints and Exertional Leg Pains?

Pain is caused by inflammation (irritated tissue) from injury to muscles, tendons, and the outside of bones. Causes include overuse, tight Achilles tendon, weak ankle muscles, flat arches, high arches, and sudden increase in intensity, frequency, or duration of activity. Running downhill or on slanted surfaces, playing sports with frequent starts and stops (basketball, tennis), training too hard or too long, and wearing worn-out shoes can also cause it.

What Are the Symptoms of Shin Splints?

Symptoms are dull, aching pain along the shinbone or in lower leg muscles. Pushing the foot down against resistance can cause the pain. Tenderness, soreness, or mild swelling can occur.

How Are Shin Splints Diagnosed?

The doctor makes a diagnosis from the medical history and physical examination. Imaging studies, such as x-rays, bone scans, or magnetic resonance imaging (MRI), may help find other problems such as broken bones (stress fractures).

How Are Shin Splints Treated?

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Treatment goals are to return to activities as soon as is safely possible. Returning too soon may worsen the injury. Use RICE (rest, ice, compression, and elevation). Resting and avoiding activities that may have started the problem are critical. Apply ice packs or do ice massages for up to 20 minutes, three times a day, for 2 to 3 days or until the pain is gone. Special stretching and strengthening exercises such as toe raises often help. Raise the leg with pillows. A physical therapist may be involved in treatment. Other measures include wearing proper shoes with arch supports (orthotics), cross-training (stationary bicycling or pool running), doing range-of-motion exercises, and slowly increasing running activities.

Nonsteroidal anti-inflammatory drugs (NSAIDs) (ibuprofen, acetaminophen, aspirin) may relieve pain but can cause stomach problems and should be taken with meals.

DOs and DON'Ts in Managing Shin Splints and Exertional Leg Pains:

✓ **DO** stop the activity causing the pain until your doctor says you can start again.

✓ **DO** make sure that you use the right sports technique.

✓ **DO** warm-up exercises, such as light aerobic exercise, correctly. Do gentle stretching before and after sports or exercising.

✓ **DO** call your doctor if treatment doesn't help symptoms.

✓ **DO** strengthen leg muscles for correct muscle balance.

⃠ **DON'T** put ice or chemical cold packs directly on your skin.

⃠ **DON'T** run or play on hard surfaces such as concrete when you are having symptoms.

⃠ **DON'T** use sporting equipment that's too large or too small. Wear the right footwear.

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FOR MORE INFORMATION

Contact the following sources:

- The American Orthopaedic Society for Sports Medicine Tel: (847) 292-4900 Fax: (847) 292-4905 **Website: http://www.sportsmed.org**
- American Occupational Therapy Association Tel: (301) 652-2682 **Website: http://www.aota.org**

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MANAGING YOUR

SHINGLES

What Is Shingles?

Herpes zoster, also called shingles, is an uncomfortable and often very painful outbreak of skin blisters and sores. It affects nearly one million individuals per year in the United States. Most individuals are over age 50 or have a weakened immune system.

Some medicines can help relieve symptoms and prevent complications. Also, a vaccine (Zostavax) is now available for prevention in people 60 years and older.

What Causes Shingles?

The cause is varicella-zoster virus, the same virus that causes chickenpox. After people have chickenpox, the virus usually stays inactive. But if antibodies to this virus get low decades later, the virus can become active and cause shingles.

People who have not been vaccinated for chickenpox can catch it from someone with active shingles.

What Are the Symptoms of Shingles?

The virus lives in nerves near the spine. Activated virus travels along the nerves to the skin. It then causes a rash on the skin in groups or bands at the nerve endings. The rash usually stays as a band going across part of the body on one side. The rash can occur anywhere.

Early vague symptoms are mild itching, tingling, pain, headache, fever, or flulike syndrome. The rash that follows consists of many small, fluid-filled blisters in groups that dry, scab over, and heal (like chickenpox) in a few weeks. Healing is usually complete. Scars may persist in the area of the blisters.

The amount of pain and discomfort of shingles varies from person to person.

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A significant number of people, especially those older than 50, can have pain (called postherpetic neuralgia) for more than 30 days. It can be very severe and interfere with daily activity.

People who scratch the rash can also get a bacterial infection.

Shingles on the face can involve the eyes, which is serious and can cause scarring and blindness.

How Is Shingles Diagnosed?

The doctor will diagnose shingles by examining the skin. Blood tests are rarely needed. Blister fluid may be studied if the diagnosis is unclear.

How Is Shingles Treated?

The main goals are to shorten the infection, reduce discomfort, and prevent complications. Antiviral medicine, started early (within 2 or 3 days), can help the rash and pain. These drugs include acyclovir, valacyclovir, and famciclovir. Other drugs and lotions can help with pain and itching.

DOs and DON'Ts in Managing Shingles:

✓ **DO** tell your doctor about your medical problems and prescriptions and over-the-counter medicines.

✓ **DO** tell your doctor if you're pregnant or breast-feeding.

✓ **DO** keep blisters clean. Don't bandage the blisters.

✓ **DO** avoid anyone who never had chickenpox or didn't get immunized, pregnant women, or people with cancer.

✓ **DO** get medical care as soon as you think that you may have shingles.

✓ **DO** call your doctor if the rash is on your face or nose, the pain doesn't get better after the

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rash heals, or the rash looks infected.

⦸ **DON'T** stop taking your medicine or change your dose because you feel better unless your doctor tells you.

⦸ **DON'T** shave the area with the rash.

⦸ **DON'T** scratch, contaminate, or break the blisters.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Dermatology Tel: (866) 503-SKIN (7546) **Website: http://www.aad.org**
- Centers for Disease Control and Prevention **Website: http://www.cdc.gov**

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MANAGING YOUR

SHORT BOWEL SYNDROME

What Is Short Bowel Syndrome?

Short bowel syndrome occurs as a complication of major surgery of the small bowel (intestine). After surgery, not enough bowel is left to get nutrients from food. The result is that people can become malnourished.

What Causes Short Bowel Syndrome?

If more than half of the bowel is taken out during surgery, the risk of small bowel syndrome is great. Disorders of the small bowel that may need surgical treatment include congenital abnormalities and necrotizing enterocolitis in infants and Crohn's disease in adults.

What Are the Symptoms of Short Bowel Syndrome?

The key symptoms are diarrhea, seen as large amounts of foul-smelling stools, and weight loss. Painful cramps in the abdomen (belly), bloating, heartburn, tiredness, and weakness also occur. Symptoms usually begin a few days after abdominal surgery.

How Is Short Bowel Syndrome Diagnosed?

The doctor makes a diagnosis by taking a medical history and doing blood tests and an upper gastrointestinal (GI) barium x-ray study. For this x-ray, a chalky substance, barium, is swallowed and moves quickly through the stomach and small bowel. X-rays are then taken to show what the small bowel looks like.

How Is Short Bowel Syndrome Treated?

Treatment involves nutritional support. The treatment at first is usually intravenous hyperalimentation (TPN, or total parenteral nutrition). Liquid mixtures with all required nutrients are given through a vein. This type of feeding allows the bowel to rest and somewhat recover. Hospitaliza-

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tion may be needed.

Medicines may be given to help prevent secretion of acid and excessive fluids by the stomach.

Usually after 1 to 4 weeks, the diarrhea will go away and the appetite will return. At this time, enteral feedings are started. For these feedings, mixtures are put through a tube directly into the stomach. This is a slow process while the intestine learns to work again. After weeks to months of this, feedings by mouth are slowly given.

Close monitoring of the diet is key to successful treatment. A high-calorie, low-fat, low-residue diet is needed. In some cases, people use TPN for the rest of their life. Fat-soluble vitamins and mineral supplements are also taken.

Symptoms may get better over time but will always mean close attention to diet.

DOs and DON'Ts in Managing Short Bowel Syndrome:

✓ **DO** be patient. This condition takes months to slowly get better and may need lifelong treatment.

✓ **DO** take vitamin and mineral supplements as prescribed.

✓ **DO** call your doctor if you have diarrhea after bowel surgery.

✓ **DO** call your doctor if you're being treated for short bowel syndrome and your symptoms worsen or return.

⃠ **DON'T** eat high-fat foods.

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FOR MORE INFORMATION

Contact the following sources:

- Gastro-Intestinal Research Foundation Tel: (312) 332-1350 **Website: http://www.girf.org**
- American College of Surgeons Tel: (800) 621-4111 **Website: http://www.facs.org**

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MANAGING YOUR

SHOULDER DISLOCATION

What Is Shoulder Dislocation?

A joint is a point where two or more of bones come together. The shoulder joint is the body's most movable joint. Because of this, it's the most likely one to become dislocated. Dislocation occurs when the ball of the joint (the top rounded part of the upper arm bone) is pulled out of its socket. The two types of shoulder dislocation are atraumatic and traumatic. The atraumatic one often occurs in a teenager who has a loose joint. The traumatic one often results from sporting injuries or using the joint excessively with manual labor.

What Causes Shoulder Dislocation?

Shoulder dislocation happens most often to people in their 30s when they play sports. It frequently occurs in manual laborers who get injured. People who are 60 to 80 years old commonly dislocate their shoulders in a fall. People with generalized seizures may also develop shoulder dislocation during seizures. After the first dislocation of a shoulder, the shoulder will be more likely to dislocate again, but this likelihood may decrease with time as the shoulder heals.

What Are the Symptoms of Shoulder Dislocation?

Signs and symptoms include the arm of the affected shoulder looking dislocated or out of place, swelling, bruising or discoloration, holding the shoulder or arm in a fixed position, being unable to move the shoulder, numbness, weakness, and pain in the shoulder. This pain may travel down the arm and into the hand.

How Is Shoulder Dislocation Diagnosed?

The doctor will make a diagnosis from the medical history, and physical examination. You will be asked questions about events leading up to the injury or overuse of the arm. The doctor will

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do a physical examination and order x-rays. Other imaging tests, such as a magnetic resonance imaging (MRI), may be done.

How Is Shoulder Dislocation Treated?

The doctor may move the joint back into place. The arm may be put into a sling or splint to minimize movement of the joint. The doctor may prescribe medicines for pain and inflammation (swelling, redness).

The doctor may suggest seeing a physical therapist. This health care professional can teach how to reduce the risk of injuring the shoulder again. The therapist may also teach exercises to strengthen the shoulder joint.

Care from another specialist, such as an orthopedist, may be needed. An orthopedist specializes in treating joints and bones. This referral is especially likely if the shoulder was dislocated before or if it becomes increasingly harder to use the shoulder and arm. Surgery may be needed if the shoulder is weak and dislocates often.

DOs and DON'Ts in Managing

Shoulder Dislocation:

✓ **DO** tell your doctor about the medicines you take, including prescription and over-the-counter medicines.

✓ **DO** exercises that your doctor, physical therapist, or other health care professional recommends.

✓ **DO** return to your doctor for follow-up care when suggested.

✓ **DO** wear protective clothing and equipment when playing sports.

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✓ **DO** call your doctor if your shoulder pain persists after treatment.

✓ **DO** call your doctor if you develop weakness in your arm or hand.

⃠ **DON'T** do strenuous activities or lift heavy objects without your doctor's permission.

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Arthritis and Musculoskeletal and Skin Diseases Tel: (877) 226-4267

  Website: **http://www.niams.nih.gov**

- American Academy of Orthopaedic Surgeons Tel: (800) 346-AAOS (346-2267) **Website:**

  http://www.aaos.org

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MANAGING YOUR

SICKLE CELL ANEMIA

What Is Sickle Cell Anemia?

Sickle cell anemia is a hereditary blood disease that's passed from parents to children. It affects red blood cells. Normal red blood cells are soft and round and contain hemoglobin. Hemoglobin helps carry oxygen to parts of the body. People with sickle cell anemia have red blood cells with abnormal hemoglobin-S (Hb-S). Red blood cells become crescent or sickle shaped and cannot pass through small blood vessels. Vessels get blocked, tissues and organs may become damaged because they cannot get enough blood, and acute illness (crisis) results. Problems can affect every organ.

People may have sickle cell trait. Sickle cell trait means having one sickle cell gene and one normal gene, so both abnormal and normal hemoglobin are made. People with the trait are healthy but can have children with sickle cell anemia if their sexual partner also has sickle cell trait.

More than 50,000 people in the United States have the disease.

What Causes Sickle Cell Anemia?

The cause is a mutation in DNA for beta-globin, a protein that makes up hemoglobin. The disease is most common among African Americans but people of Mediterranean, Caribbean, South and Central American, Arabian, and East Indian descent can have it.

What Are the Symptoms of Sickle Cell Anemia?

Common symptoms include chronic anemia (low blood cell count), fast heartbeat, yellow skin (jaundice), tiredness, and severe bone pain during a sickle cell crisis. Symptoms get worse during a crisis. Pregnancy, surgery, infection, and high altitudes make symptoms worse. Complications

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include kidney and eye disease, heart disease, leg ulcers, and strokes. Infections such as osteomyelitis (bone infection) and pneumonia (acute chest syndrome with cough and shortness of breath) can occur. In aplastic crisis, bone marrow stops making red blood cells.

How Is Sickle Cell Anemia Diagnosed?

The doctor makes a diagnosis from a family history of the disease and blood tests. Blood tests look for sickle-shaped red blood cells and abnormal hemoglobin. A simple screening test in early pregnancy or after birth can check for the disease in a baby.

How Is Sickle Cell Anemia Treated?

Treatment involves controlling pain. Oral medicine can help mild crises. Severe pain may need intramuscular or intravenous narcotics. Hydroxyurea is a medication that can reduce the number of crises. Fluids are given to prevent dehydration. Sometimes, blood transfusion is needed. Abnormal blood cells are replaced with normal cells.

Children usually receive penicillin to prevent bacterial infection.

Bone marrow transplantation from a brother or sister may cure the disease, but this treatment is experimental.

DOs and DON'Ts in Managing Sickle Cell Anemia:

✓ **DO** drink fluids to avoid dehydration.

✓ **DO** eat a healthy diet with plenty of green, leafy vegetables (high in folate). Take a daily folate supplement.

✓ **DO** mild to moderate exercise. Rest if you feel tired and drink enough fluids.

✓ **DO** consider genetic counseling to check your risk for having an affected child.

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✓ **DO** get prenatal care from your obstetrician and primary care doctor.

✓ **DO** call your doctor if you have fever, shortness of breath, severe abdominal pain, or neurological symptoms (such as trouble speaking).

✓ **DO** get appropriate vaccinations as recommended by your physician.

⃠ **DON'T** fly on airplanes without pressurized cabins.

⃠ **DON'T** overuse pain drugs.

⃠ **DON'T** drink alcohol in excess.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- Sickle Cell Disease Association of America, Inc. Tel: (800) 421-8453 **Website:** **http://www.sicklecelldisease.org**
- National Heart, Lung, and Blood Institute Information Center Tel: (301) 592-8573 **Website: http://www.nhlbi.nih.gov**

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MANAGING YOUR

SILICOSIS

What Is Silicosis?

Silicosis is a lung disease caused by breathing in silica (quartz) dust. Silica is a crystal that occurs naturally, in sand and in rock beds. It becomes dust during mining and working with metal ores. In silicosis, first, small rounded nodules (lumps) develop when the silica collects in the lung. Then, the number and size of the nodules may increase. The nodules later join together to make large masses and scar the lungs, which can make the lungs work poorly. This condition is called progressive fibrosis.

The risk of having silicosis depends mainly on how much and how long people are exposed to silica dust. Years of exposure are usually needed for the illness to develop. However, symptoms may occur in months with shorter but more intense periods of breathing in the silica.

What Causes Silicosis?

Silica exposures usually occur on the job. Industries in which workers are at risk include metal working (in factories), mining, road and building construction, quarrying, sandblasting, stone cutting, and ceramics and abrasives manufacturing.

What Are the Symptoms of Silicosis?

Symptoms may vary. Early in the disease, silicosis doesn't cause symptoms or hurt lung function. With chronic, repeated exposure, the disease progresses and may decrease life span. Some people may have the disease progress, even after silica exposures stop. Shortness of breath and dry cough are the most common symptoms, with progressive, massive fibrosis. Fever and weight loss are others. Severe respiratory disability may lead to early death.

How Is Silicosis Diagnosed?

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The doctor makes a diagnosis from the job history, physical examination, and chest x-ray. Breathing tests may be needed to determine the extent of damage. In some cases a lung biopsy may be done. In a biopsy, the doctor removes a small piece of lung for study with a microscope. Having silicosis increases the risk of developing tuberculosis, a serious lung infection. If silicosis is diagnosed, a tuberculin skin test should be done to check for tuberculosis.

How Is Silicosis Treated?

No treatments are known to reduce the number of silica nodules in the lung or to prevent development of progressive fibrosis. Workers whose chest x-rays show silicosis changes should avoid more exposure to silica. Some people with severe progressive lung disease may need lung transplantation.

DOs and DON'Ts in Managing Silicosis:

✓ **DO** get a flu shot each fall.

✓ **DO** get vaccinated for pneumococcal pneumonia every 5 years.

✓ **DO** maintain good cardiovascular fitness by exercising.

✓ **DO** call your doctor if you think that you have a lung infection as suggested by symptoms. Such symptoms include a sudden worsening of cough, yellow or green sputum, increased shortness of breath, and fever or chills.

✓ **DO** call your doctor if you have weight loss, chest pain, or blood in your sputum.

✓ **DO** call your doctor if you develop dusky skin, fingertips, or lips, your oxygen level may be low.

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✓ **DO** call your doctor if you have new ankle swelling.

⃠ **DON'T** expose yourself to inhaled silica. Use special industrial protection measures, such as wearing dust masks and respirators.

⃠ **DON'T** expose yourself to smoke, fumes, and very cold or very humid air. These conditions may irritate the lungs.

⃠ **DON'T** smoke.

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FOR MORE INFORMATION

Contact the following source:

• American Lung Association Tel: (800) LUNG-USA (586-4872) **Website:**

http://www.lungusa.org

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MANAGING YOUR

SINUSITIS

What Is Sinusitis?

Four hollow spaces in bones of the face are known as sinuses. Each sinus has an opening to allow air and mucus in the nose to move in and out. If sinuses become blocked, sinusitis, or sinus infection, results. Sinusitis is inflammation and swelling of one or more sinuses. Blocked sinuses can also lead to infection caused by bacteria.

Sinusitis is very common. Sinusitis can be sudden and short (acute) or long-lasting (chronic).

What Causes Sinusitis?

The cause can be viruses, bacteria, allergies, pollution, or nasal polyps. It often starts after a cold or allergic reaction.

What Are the Symptoms of Sinusitis?

Main symptoms are headache and pressure or pain in the forehead or face. The nose may be stuffed and runny, with a green or yellow-green discharge. Swollen eyes, with pain behind them and dark circles underneath, may occur. The throat may become sore. Children may be irritable, and have a long-lasting cough, in addition to sinus congestion. Symptoms usually go away in 7 to 21 days.

How Is Sinusitis Diagnosed?

The doctor will examine the face, nose, and ears, and listen to the chest. X-rays or maybe other imaging tests of the sinuses may be done on rare occasions. If sinusitis is due to an allergy or sinusitis occurs three times a year or more, the doctor may suggest seeing an allergist (specialist in allergies).

How Is Sinusitis Treated?

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The doctor may prescribe antihistamines for sinusitis caused by allergies. Nasal sprays and decongestants help congestion. Increasing fluid intake helps thin secretions. Resting with the head slightly raised will let secretions drain easier. For minor pain, acetaminophen or ibuprofen can be used.

For sinusitis caused by bacterial infection, the doctor will prescribe an antibiotic. Most sinus infections are caused by viruses, and antibiotics don't work and shouldn't be taken.

Acute sinusitis usually goes away in 2 to 3 weeks with treatment.

DOs and DON'Ts in Managing Sinusitis:

✓ **DO** drink plenty of fluids, especially water.

✓ **DO** use a saline nasal spray for nasal congestion.

✓ **DO** quit smoking. Smoking can worsen sinusitis.

✓ **DO** use a vaporizer or inhale steam from a shower to relieve congestion.

✓ **DO** use warm compresses over the sinus area four times a day, for 1 or 2 hours.

✓ **DO** use a humidifier in the winter and an air conditioner in the summer.

✓ **DO** call your doctor if you have lasting fever and chills.

✓ **DO** call your doctor if your face swells over the sinuses.

✓ **DO** call your doctor if you have blurred vision or a severe headache that medicines don't help.

✓ **DO** avoid allergy triggers.

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⦸ **DON'T** use over-the-counter nose sprays. They can make symptoms worse.

⦸ **DON'T** travel in an airplane during an acute attack. Pressure changes can make symptoms much worse. Check with your doctor first if you must fly.

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FOR MORE INFORMATION

Contact the following source:

- American Academy of Otolaryngology—Head and Neck Surgery Tel: (703) 836-4444 **Web-site: http://www.entnet.org**

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MANAGING YOUR

SJÖGREN'S SYNDROME

What Is Sjögren's Syndrome?

Sjögren's syndrome is an illness caused by inflammation of glands that make tears, saliva, and other substances. Inflammation of joints, lungs, kidneys, blood vessels, nerves, and muscles can also occur.

This syndrome affects one in every 250 adults in the United States. It occurs nine times more often in women than in men. It is also more common in people with other autoimmune diseases such as lupus or rheumatoid arthritis. It rarely develops before age 20.

What Causes Sjögren's Syndrome?

The syndrome occurs when the body's own immune system attacks glands that make saliva and tears and makes them stop working. The cause is unknown, but some hereditary and environmental factors may increase chances having it. The syndrome isn't contagious.

What Are the Symptoms of Sjögren's Syndrome?

The most common symptoms are dry eyes and dry mouth. Dry eyes may cause a sandy feeling under the eyelids, burning eyes, increased sensitivity to light, reduced tears, and eye ulcers. A dry mouth may cause problems chewing and swallowing dry foods and an increased tooth decay, gum disease, and mouth infections. Other symptoms include blurred vision, dry lips and throat, fever, itchy eyes, joint pain, mouth sores, red eyes, rash, shortness of breath, stomach pain, swollen cheek glands, swollen lymph nodes (glands), thirst, tiredness, and dry vagina. Vaginal dryness can cause pain with sex.

How Is Sjögren's Syndrome Diagnosed?

The doctor will make a diagnosis from a medical history, physical examination, and laboratory

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tests. These tests may include an erythrocyte sedimentation rate (ESR) (to measure inflammation), a complete blood cell count (CBC), and tests for Sjögren's antibodies. The doctor may do a Schirmer test to find out the amount of tears in the eyes and a lip biopsy.

An ophthalmologist (eye doctor) and a rheumatologist (specialist in joint problems) may help with care.

How Is Sjögren's Syndrome Treated?

There's no cure, but medicines and other therapies can manage the syndrome. Over-the-counter moisturizers for dry eyes, mouth, and vagina may help. Nonsteroidal antiinflammatory drugs (NSAIDs) may help joint pain and swelling. Prednisone and other medicines may be used for severe joint pain or lung, kidney, and blood vessel problems.

DOs and DON'Ts in Managing

Sjögren's Syndrome:

✓ **DO** tell your doctor about your medicines, both prescription and over-the-counter.

✓ **DO** tell your doctor if you're pregnant or breastfeeding.

✓ **DO** see your dentist regularly. Brush and floss your teeth after meals.

✓ **DO** ask your doctor what over-the-counter products are available for dryness. If an artificial tear medicine burns your eyes, switch to another one or one without a preservative. If your eyes get dry at night, an eye ointment may help. Vaginal lubricants used during the day or before sex can also help.

✓ **DO** use a cream or ointment for dry skin. These help seal in moisture.

✓ **DO** use a humidifier at night to prevent dry eyes, mouth, and nose.

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✓ **DO** call your doctor if you have severe stomach pain, eye pain, or sudden vision change.

⦸ **DON'T** stop taking your medicine or change your dosage because you feel better unless your doctor says to.

⦸ **DON'T** smoke. Smoking can make symptoms worse.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- Sjögren's Syndrome Foundation Tel: (800) 475-6473 **Website:** **http://www.sjogrens.org**
- American College of Rheumatology Tel: (404) 633-3777 **Website:** **http://www.rheumatology.org**
- The Arthritis Foundation Tel: (800) 283-7800 **Website:** **http://www.arthritis.org**

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MANAGING YOUR

SLEEP APNEA

What Is Sleep Apnea?

Sleep apnea is the condition in which breathing temporarily stops during sleep. Apnea episodes are usually brief, from 10 to 30 seconds. In severe cases, they occur hundreds of times a night.

When breathing stops, the oxygen level in the body drops. This tells the brain to signal the body to wake up and take a breath. Most people don't remember waking up, but they have troubled sleep cycles.

Apnea can lead to heart problems and daytime sleepiness.

About 4% of middle-aged men and 2% of women have apnea.

What Causes Sleep Apnea?

The most common cause is obesity (for men, a collar size larger than 17 inches increases the risk of sleep apnea). Very narrow windpipes or very large tonsils can block the throat and cause apnea. Using sleeping pills or alcohol before sleep may increase the chance of having apnea. Other reasons are nasal congestion, sleeping on the back, and sleep deprivation.

What Are the Symptoms of Sleep Apnea?

The most common symptom is loud snoring. Another symptom is breathing pauses during sleep with loud snorts or gasps as breathing starts. Others are daytime sleepiness, irritability, or problems concentrating; headache, dry mouth, or sore throat when awakening; and shortness of breath during the night.

How Is Sleep Apnea Diagnosed?

The doctor will check the medical history and examine the nose and throat for abnormalities. The diagnosis is made by doing an overnight sleep study in a sleep disorders clinic or at home. Dur-

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ing this test, called polysomnography, brain activity, breathing patterns, oxygen levels, and heart rate are recorded.

How Is Sleep Apnea Treated?

Treatment and recovery time depend on the severity of apnea. Many people need lifelong treatment. Losing weight, avoiding alcohol and sleeping pills, using nasal decongestants, and not sleeping on the back are usually suggested for mild apnea. Sleeping on the back can be prevented by old-fashioned treatments such as wearing a T-shirt with a pouch in the back filled with tennis balls. Fill a large sock with three or four tennis balls and attach it with a safety pin to the back of the shirt.

Many people use the system of continuous positive airway pressure (CPAP). CPAP has a mask for the nose connected to a bedside fan with a hose. Air from the fan goes under pressure through the hose and mask and into the throat, to keep lung passages open.

Other methods include using an oral appliance that make the jaw move forward during sleep. This helps keep the throat open. Operations to keep airways open are possible but may not work.

DOs and DON'Ts in Managing Sleep Apnea:

✓ **DO** lose weight if you're overweight.

✓ **DO** avoid sleeping pills or alcohol before sleep.

✓ **DO** use CPAP or an oral appliance every night if your doctor prescribes it. Call your doctor if you have problems with CPAP, such as dry nose, congestion, or sneezing.

✓ **DO** talk to your doctor if you still feel sleepy even if you use CPAP. You may have another sleep disorder.

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⦸ **DON'T** get sleep deprived. You should sleep 7 to 8 hours each night.

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FOR MORE INFORMATION

Contact the following sources:

• American Sleep Apnea Association Tel: (202) 293-3650 **Website:**

http://www.sleepapnea.org

• American Lung Association Tel: (800) LUNG-USA (586-4872) **Website:**

http://www.lungusa.org

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MANAGING YOUR

SLEEP DISORDER AND HEART DISEASE

What Are Sleep Disorders?

More than 90 sleep disorders exist. Common ones are obstructive sleep apnea (OSA), central sleep apnea, and obesity hypoventilation. In apnea, breathing stops or gets shallow for brief periods, usually 10–30 seconds. These breathing pauses can occur many times during sleep. About 4% of middle-aged men and 2% of women have apnea.

OSA, the more common kind, can seriously affect one's health. It can be bad for the heart and blood vessels (cardiovascular system).

How Are Sleep Disorders and Heart Disease Related?

Apnea may have serious health effects, such as increasing risks of high blood pressure (hypertension), heart failure, and stroke. Apnea causes very high levels of a stress hormone (epinephrine) to be released hundreds of times each night. It also causes sudden drops in blood oxygen levels. Both these events strain the cardiovascular system.

Apnea may also be related to abnormal heartbeats (atrial fibrillation), myocardial ischemia, heart attacks (myocardial infarction), and pulmonary hypertension. Long-lasting sleep deprivation is related to weight gain. People who sleep less than 5 hours or more than 9 hours a night have greater risks of getting coronary artery disease (CAD) and cardiovascular disorders.

What Are the Symptoms of Sleep Disorders and Heart Disease?

Symptoms of apnea include snoring, tiredness, morning headaches, falling asleep during the day, and depression.

How Are Sleep Disorders and Heart Disease Diagnosed?

The doctor uses a medical history and checks the lungs, heart, nose, and throat for abnormalities.

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The best way to diagnose OSA is an overnight sleep study done in a sleep disorders clinic. During this test, brain activity, breathing patterns, oxygen levels, and heart rate are recorded.

How Are Sleep Disorders and Heart Disease Treated?

Treating OSA may lower blood pressure, reduce heart disease risk, and help heart function. Treatment includes using continuous positive airway pressure (CPAP). A special mask worn at night increases pressure to keep the airway open. Other treatments involve lifestyle changes including weight loss, sleeping on the side, stopping smoking, and avoiding alcohol and medicines that cause sleepiness. Mouthpieces, breathing devices, and surgery to widen breathing passages are also used. Usually, excess tissue in the mouth and throat is taken out, shrunk, or stiffened. The lower jaw may be reset. No medicines are available to treat apnea.

DOs and DON'Ts in Managing Sleep Disorders and Heart Disease:

✓ **DO** visit your doctor for regular checkups.

✓ **DO** tell your doctor if you aren't comfortable with your CPAP device or it doesn't work. You may need a different device or mask or need treatment for CPAP side effects.

✓ **DO** make lifestyle changes to be heart healthy: stop smoking, lower your cholesterol levels, and lose weight if you're overweight. Control other conditions such as diabetes and high blood pressure. Exercise regularly.

✓ **DO** know the dangers of driving or operating heavy machinery while sleepy.

⦸ **DON'T** smoke.

⦸ **DON'T** drink alcohol, especially before bed.

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:**

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- American College of Cardiology Tel: (800) 253-4636 **Website: http://www.acc.org**

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MANAGING YOUR

SLIPPED DISC

What Is a Slipped Disc?

In the spine, bones (vertebrae) protect the spinal cord. Between the vertebrae are soft discs that act like shock absorbers. With aging, these discs weaken and can bulge. A bulge may press on nerves coming from the spinal cord and cause symptoms. A bulging disc is called a slipped disc (or a prolapsed intervertebral disc or herniated disc). These bulging discs can occur anywhere along the spine, from the neck to the lower back.

Slipped discs affect men and women and are most common in people between 30 and 50 years old. Most people get better after treatment.

What Causes a Slipped Disc?

Most slipped discs result from normal wear and tear, but an injury such as a fall can also cause them.

What Are the Symptoms of a Slipped Disc?

Most slipped discs don't cause symptoms. Symptoms depend on where in the spine the disc slips. They may include back pain, bowel and urinary changes, headache, neck pain, numbness, tingling, and weakness.

How Is a Slipped Disc Diagnosed?

The doctor will suspect a slipped disc on the basis of the medical history and physical examination. The doctor may order x-rays of the spine to be done. In severe cases, magnetic resonance imaging (MRI) of the spine will be done to confirm the diagnosis and find out the severity of the condition.

How Is a Slipped Disc Treated?

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Treatment depends on how severe the symptoms are. Ninety-five percent of people with a lower back slipped disc get better without surgery and return to a normal life within few weeks.

The doctor may prescribe medicine to treat the pain and relax the back muscles. The doctor will also advise to limit days of physical activity. Physical therapy will include special exercises that make the back strong and reduce pain. When a slipped disc doesn't respond to medicines and physical therapy, shots of pain medicine to the affected area may be tried. Surgery is sometimes needed if symptoms don't get better after several weeks of treatment.

DOs and DON'Ts in Managing a Slipped Disc:

✓ **DO** ask your doctor when you can return to work and normal activity.

✓ **DO** call your doctor if your symptoms get worse.

✓ **DO** call your doctor if you have trouble urinating or having a bowel movement or you cannot hold your urine or stool.

✓ **DO** call your doctor if you have numbness in your legs, have rectal pain, or have sudden weakness in any part of your body, especially your legs.

⃠ **DON'T** stop taking your medicine or change your dosage because you feel better unless your doctor says to do so.

⃠ **DON'T** return to work, play sports, or bend forward to pick up your children without your doctor's permission.

⃠ **DON'T** bend or twist when you lift something. Ask your doctor about the best way to lift things without hurting your spine.

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Contact the following source:

- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186, (800) 346-2267 **Website:**

  http://www.aaos.org

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CARING FOR YOUR CHILD WITH

SLIPPED FEMORAL EPIPHYSIS

What Is Slipped Femoral Epiphysis?

Slipped femoral epiphysis is a hip problem that occurs mainly in older children and teenagers. Average age is 12 years old. The femoral epiphysis is the ball part (top, or head) of the hip joint, which is a ball and socket joint. The growing end of the thigh bone (femur) is called the growth plate. This problem occurs when the growth plate slides off the thigh bone. Most often, the left hip is affected. Twice as many boys as girls have it.

Children who develop slipped femoral epiphysis in one hip have a 25% to 40% chance of also having it in the other hip.

What Causes Slipped Femoral Epiphysis?

The cause is often unknown, but the condition occurs more often in overweight children. Most of the time, it starts slowly. However, about 10% of the time it can happen suddenly, such as after a fall or injury playing sports.

What Are the Symptoms of Slipped Femoral Epiphysis?

The child's hip may first become stiff. After a while, this stiffness can turn into a limp. Pain can occur in the hip, but it sometimes may be felt in the groin, thigh, or knee. The pain worsens if the child runs, jumps, or turns. As the problem continues, the child may lose some ability to move the hip. The affected leg twists out and looks shorter than the other leg.

If slipped femoral epiphysis occurs after a fall or injury, the pain is sudden and severe, similar to the pain of a broken leg.

How Is Slipped Femoral Epiphysis Diagnosed?

The doctor will take a medical history and do a physical examination. The doctor will rotate the

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child's hip and check for tenderness. The doctor will also take x-rays of the pelvis and thigh area from several different angles. Other imaging tests may also be done.

How Is Slipped Femoral Epiphysis Treated?

Weight should be kept off the hip, but this problem must be fixed by surgery. The thigh bone must be moved back into the proper position and kept in place with a screw or pin. This operation is called *"in-situ fixation."* An orthopedic surgeon does this surgery. An orthopedic surgeon is a doctor specially trained to fix bone problems.

The child will usually need to use crutches or a wheelchair for 5 to 6 weeks after surgery. After that recovery time, the child can slowly resume normal activities, including sports.

The most serious complication is avascular necrosis (osteonecrosis). This disease is caused by loss of blood supply to the bone, so the bone dies and may collapse. Children may need surgery such as hip fusion or total hip replacement earlier as adults or even as teenagers.

DOs and DON'Ts in Managing

Slipped Femoral Epiphysis:

✓ **DO** make sure that your child is trained to use crutches.

✓ **DO** watch for symptoms of the disorder starting in the other hip.

✓ **DO** call your doctor if your child complains of hip or knee pains.

✓ **DO** encourage your child to have a healthy weight. Overweight children have more risk for the condition.

⃠ **DON'T** use therapy, such as manipulation or massage, that requires movement of the hip.

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MANAGING YOUR

SMALL INTESTINAL BACTERIAL OVERGROWTH

What Is Small Intestinal Bacterial Overgrowth (SIBO)?

The small intestine, part of the gastrointestinal (GI) tract, connects the stomach and colon (large intestine). It's 21 feet long and has three parts: duodenum, jejunum, and ileum. It digests and absorbs food for the body. The GI tract normally contains bacteria. The small intestine usually has 10,000 bacteria per milliliter (mL) of fluid (less than the colon). In SIBO, too many bacteria (at least 100,000 per mL) are present. Also, the type of bacteria is different than the one normally found in the small intestine. They're more like colon bacteria than small intestinal bacteria.

Newborn and young babies and elderly people are especially at risk for SIBO.

What Causes SIBO?

The cause may be any condition that interferes with small intestinal muscle movements. Bacteria stay longer and grow in the small intestine. These conditions include metabolic disorders (diabetes), scleroderma, blockage (related to scars from surgery and Crohn's disease), and small intestinal diverticula (pouches). Abnormal anatomy of the intestine (blind loops), reduced stomach acid secretion, and medicines are more causes.

What Are the Symptoms of SIBO?

Symptoms depend on the cause. GI symptoms may occur from one to several hours after eating. They include gas; diarrhea; and bloating, distention, and pain in the abdomen (belly). Some people may have chronic constipation. SIBO usually causes malnutrition and weight loss from malabsorption.

How Is SIBO Diagnosed?

Breath tests that measure bacteria by-products are used for diagnosis. These include the lactulose

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hydrogen, glucose hydrogen, fasting hydrogen, bile acid, and xylose breath tests. Imaging tests (x-rays) may also be done to show dilated loops of small intestine, diverticula, and strictures.

How Is SIBO Treated?

Underlying conditions that can be treated include diarrhea, malnutrition, malabsorption, hypothyroidism, inflammatory bowel disease, and immune deficiency. Other diseases are harder to treat. These include diabetic neuropathy, scleroderma, and amyloidosis. Some disorders (such as diverticula) may need surgery.

Treatment also aims to reduce damage caused by poor absorption and to help bacteria return to normal. Antibiotics are given and alternated with times of no treatment. People may need antibiotics repeatedly or for prolonged periods. Supplements can help vitamin or mineral deficiencies. Treatment can prevent malnutrition.

Probiotics can also be used. Probiotics are live bacteria that are similar to helpful microorganisms that are found in the intestines. The most common are lactobacilli (found in yogurt) and bifidobacteria.

DOs and DON'Ts in Managing SIBO:

✓ **DO** keep your doctor follow-up appointments. SIBO can come back even after symptoms go away.

✓ **DO** take your prescription medicines according to schedule.

✓ **DO** take all your antibiotic medicine. You must take all of the doses for it to work.

✓ **DO** eat a good diet. Take supplements if needed to prevent malnutrition.

⦸ **DON'T** miss doses of your antibiotic medicine. Don't stop taking it just because you feel

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better.

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FOR MORE INFORMATION

Contact the following sources:

- National Digestive Diseases Information Clearinghouse E-mail: nddic@aerie.com

  Website: http://www.niddk.nih.gov/health/digest/nddic.htm

- American College of Gastroenterology Tel: (703) 820-7400 **Website:**

  http://www.acg.gi.org

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MANAGING YOUR

SMOKE INHALATION

What Is Smoke Inhalation?

Smoke inhalation occurs when people breathe in soot and toxic fumes, often during a fire. Some fumes given off by substances when they melt or burn are poisonous. They damage the lungs and tubes leading to them, called the trachea (windpipe) and bronchi.

Smoke can cause the trachea and bronchi to swell, so it's hard to breathe. Toxins (such as cyanide and carbon monoxide) can also hurt the lungs by preventing them from absorbing enough oxygen. Without enough oxygen getting to the brain, people can have trouble thinking and can faint. Steam that is breathed in can burn the throat and lungs.

What Causes Smoke Inhalation?

The cause is exposure to fumes during a fire.

What Are the Symptoms of Smoke Inhalation?

Symptoms usually include coughing, wheezing, or sounding hoarse. Eyes may be red and teary. Soot in and around the mouth, singed nose hairs, and facial burns can be seen.

Poisoning by carbon monoxide can cause headaches, nausea, vomiting, confusion, vision problems, or loss of consciousness.

How Is Smoke Inhalation Diagnosed?

The doctor makes a diagnosis from a medical history and physical examination, especially of the throat and lungs. A chest x-ray may be done to check for fluid accumulations in the lungs and lung damage. A blood test (arterial blood gases) measures levels of oxygen and other gases in the blood. Other tests measure carbon monoxide levels.

How Is Smoke Inhalation Treated?

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Oxygen treatment may be given at the site of the fire or in an ambulance on the way to the hospital. Oxygen is critical. In the hospital emergency room, more treatment is given to make sure that people can breathe well and get enough oxygen. People are usually observed for 4 to 12 hours. If the smoke inhalation is not severe and they do well, they may be able to leave the hospital after a few hours. Some people may need to see their doctor in 12 to 24 hours for a follow-up visit.

For breathing problems, more oxygen may be given at the hospital. A mask or nose tube is used. Sometimes, oxygen under high pressure (hyperbaric oxygen) is given. A special oxygen chamber can take out carbon monoxide from the body faster than regular oxygen can. Sometimes inhalers with bronchodilators are given for easier breathing.

Some people with a swollen windpipe can have a tube placed in the windpipe to help breathing. Other treatments include suction to remove debris from lungs, extra fluids (for burn victims), antidotes for poisons such as cyanide, and antibiotics for infections such as pneumonia.

Recovery occurs in stages. Total recovery time depends on how much smoke and poison were inhaled. People with minor smoke damage recover in 2 to 3 days with no lasting effects. People with severe injuries may need several weeks in the hospital and may have long-lasting breathing problems.

DOs and DON'Ts in Managing Smoke Inhalation:

✓ **DO** call 911 and go to the closest emergency department if you suffer smoke inhalation.

✓ **DO** call your doctor if you have a lasting cough, shortness of breath, or fatigue.

⃠ **DON'T** forget to follow up with your doctor after your discharge from the hospital.

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FOR MORE INFORMATION

Contact the following sources:

- World Burn Foundation Tel: (310) 858-1717
- American Lung Association Tel: (212) 315-8700, (800) 586-4872 **Website:**

http://www.lungusa.org

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MANAGING YOUR

SMOKING

What Is Smoking and What Does It Do?

Smoking harms almost every organ in the body. It leads to many kinds of cancer: lung, mouth, esophageal, stomach, pancreas, kidney, and bladder. Smoking damages cells lining the heart and blood vessels and makes blood clots form easily. These effects increase chances of having a heart attack or stroke. Smokers are four times more likely than nonsmokers to die of heart disease. Smoking increases the risk of aortic aneurysm (swelling of a main artery) and circulation problems.

Cigarette smoke damages the lungs and causes chronic obstructive pulmonary disease (COPD, or emphysema and chronic bronchitis). Smokers get colds and chest infections (pneumonia) more often.

Smoking during pregnancy increases the risk of premature birth, low birth weight, stillbirth, and sudden infant death syndrome (SIDS).

Other smoking-related health problems include mouth problems, sexual problems (men), thinning of bones after menopause (women), and stomach ulcers.

Benefits of Quitting

After quitting smoking, the levels of the poisonous gas carbon dioxide in the blood decrease to normal. Between 2 and 12 weeks, lungs start to work better and the risk of heart attack decreases. Coughing and shortness of breath may take 1 to 9 months to improve. After 1 year, heart disease risk falls by half. After 15 years, risks of heart disease and stroke will be normal. After 10 years, the risk of getting lung cancer is half that of a continuing smoker.

How Do I Quit?

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Quitting isn't easy. Nicotine is addictive. People can have withdrawal symptoms (irritability, restlessness, sleep problems), but these go away after a few days.

Certain methods double the chances of success. Counseling can be individual, group, or telephone-based. The doctor, local hospital, or health center can advise about free support programs. Nicotine replacement therapy involves approved gums, patches, sprays, inhalers, and lozenges that have specific amounts of nicotine. Both over-the-counter and prescription preparations are available. Drugs include bupropion, which is a prescription antidepressant, and varenicline, which is an effective prescription pill that can reduce the urge to smoke. It works for 44% of people who take it for the full 12 weeks.

DOs and DON'Ts in Managing Smoking:

- ✔ **DO** set a date for quitting.
- ✔ **DO** prepare yourself mentally. Think about how you will deal with cravings and temptation. Focus on why you want to give up.
- ✔ **DO** throw out all your cigarettes.
- ✔ **DO** ask friends and family for support.
- ✔ **DO** change your routine for a while to avoid situations that tempt you to smoke.
- ✔ **DO** chew gum or eat fruit or vegetables to distract yourself from the urge to smoke.
- ✔ **DO** think about getting counseling or joining a support program.
- ✔ **DO** call your doctor if you need a prescription for a smoking cessation product.
- ✔ **DO** call your doctor if you have medicine side effects.
- ⃠ **DON'T** let yourself smoke at all once you've quit, not even just one.
- ⃠ **DON'T** be discouraged if you fail. Most people try several times before they quit success-

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fully.

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Contact the following sources:

• American Lung Association Tel: (212) 315-8700, (800) 586-4872 **Website:** **http://www.lungusa.org**

• The American Cancer Society Tel: (800) 227-2345 **Website:** **http://www.cancer.org**

• Centers for Disease Control and Prevention Tobacco Information and Prevention Source (TIPS) Telephone counseling: (800) QUIT-NOW (784-8669) **Website:** **http://www.cdc.gov/tobacco/**

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MANAGING YOUR

SNAKE BITES

About Snake Bites

In North America, snake bites can be one of four types. The first is bites of nonvenomous snakes such as rat snakes. The second is bites of coral snakes. These snakes have a special type of venom that affects the nervous system. The third is bites of pit vipers: rattlesnakes, copperheads, and water moccasins. These snakes usually inject venom when they bite. The fourth includes rare bites of snakes imported from other areas.

What Are the Symptoms of Snake Bites?

The doctor can usually tell from the look of the bite or the snake (if captured) whether the snake was venomous. Luckily, pit vipers don't inject venom (envenomate) in about 25% of bites. Symptoms are intense pain, swelling, and discoloration at the place of the bite. Swelling and pain that move away from the bite and toward the body usually mean more severe bites. Bites from the coral snake and some exotic snakes may cause no symptoms for the first few hours, but then sudden and rapid paralysis may occur.

How Are Snake Bites Treated?

Bites of nonvenomous snakes need only simple medical attention. Bites of coral snakes need a hospital stay. Bites of pit vipers and imported snakes need emergency attention.

After 911 is called, emergency care should include keeping calm and limiting movements and activity. The bitten area should be below the level of the heart. Don't try to cut the bite or suck poison from the bite with the mouth. These methods don't work! Don't use ice or heat. Don't try to capture the snake. If treatment is delayed, a constriction band (such as a shoestring) put near the bite, between the bite and the body, may help. It should be loose enough to let a finger fit in

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snugly, under the band.

Treatment after discharge concentrates on wound care. The wound should be inspected and cleaned with soap and water at least once daily. Old dressings that stick to the wound can be removed by soaking with water for several minutes. Hydrogen peroxide can be used to take off clotted blood and dirt. After cleansing, the wound should dry. An antibiotic ointment can then be put on, as suggested by the doctor. Wounds should be covered with a dry, clean dressing. Change the dressing with each cleansing. Change it more often if it becomes wet or if fluid soaks through.

DOs and DON'Ts in Managing Snake Bites:

✓ **DO** make sure you have an up-to-date tetanus toxoid vaccination (tetanus shot).

✓ **DO** clean and check the wound daily.

✓ **DO** take your antibiotics as directed (if prescribed).

✓ **DO** keep follow-up appointments.

✓ **DO** call your doctor if you have increasing pain, swelling, discoloration, or bleeding at or near the wound. Call if you have fever, shortness of breath, bleeding from the nose or gums, or easy bruising. Call if you become sweaty or feel bad or if the wound looks infected (redness, swelling, pain, streaking, pus, bad smell).

⦸ **DON'T** try to find the snake. More bites are likely.

⦸ **DON'T** ignore your symptoms.

⦸ **DON'T** put your wound in dirty water.

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MANAGING

SOMATIZATION DISORDER

What Is Somatization Disorder?

Somatoform disorders are illnesses with the physical symptoms suggesting a medical disorder. However, they cannot be explained by any general medical condition, substance use, or mental disorder. Included in these disorders is somatization disorder. This disorder has a combination of pain, gastrointestinal (stomach or bowel), sexual, and neurological symptoms. Young people who complain of persistent symptoms that cannot be explained by any known medical condition may have it. The disorder occurs 10 times more often in women than in men.

What Causes Somatization Disorder?

The cause is unknown. It's not contagious or passed from parents to children. Male relatives of women with the disorder have an increased risk of antisocial personality and substance abuse.

What Are the Symptoms of Somatization Disorder and How Is It Diagnosed?

Symptoms usually start before age 30 and rarely if ever go away completely. Diagnosis is based on the following symptoms, not intentionally produced. People have years of a history of many physical complaints for which they try to get treatment. They have impaired social, occupational, and family functioning. They may also have a history of pain related to at least four different places in the body or functions (e.g., head, back, joints, extremities, or chest; during menstrual periods, sex, or urination). They may have two gastrointestinal symptoms (e.g., nausea, bloating, vomiting, diarrhea, or intolerance to foods) and one sexual symptom (erectile dysfunction, irregular periods). One pseudoneurological symptom (e.g., weakness, trouble swallowing, double vision, deafness, seizures, amnesia) is often present. Symptoms cannot be explained by a known medical condition or substance abuse, or, if there is a condition, physical complaints result in

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more social or occupational problems than expected.

Most people have a long-term (chronic) course with times of improvement and times of worse symptoms.

People often doctor shop, which can lead to frustration and disappointment. They often won't see a psychiatrist because they believe that they have a serious medical condition.

How Is Somatization Disorder Treated?

Treatment is difficult. It's always important for one doctor, preferably a primary care doctor, to coordinate care. Often, the primary care doctor will suggest seeing a psychiatrist (who can prescribe drugs) or psychologist (who can also provide counseling but cannot prescribe drugs).

For people who also have anxiety or depression, the primary care doctor or psychiatrist may prescribe medicines to help these problems.

DOs and DON'Ts in Managing

Somatization Disorder:

✓ **DO** understand that people with a somatization disorder rarely recognize that their illness is psychological.

✓ **DO** call your doctor if you're worried about a symptom that hasn't been checked.

✓ **DO** call your doctor if you would like a referral to a psychiatrist or psychologist.

✓ **DO** call your doctor if you feel depressed.

✓ **DO** call your doctor if you think that you're going to harm yourself or others.

⦸ **DON'T** forget that it's best to stay with one primary care doctor you feel comfortable with,

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even though he or she may not find any medical conditions causing symptoms. Going from one doctor to another can lead to duplication of blood tests, x-rays, and ordering of unneeded and risky studies.

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- American Psychiatric Association Tel: (888) 357-7924 **Website: http://www.psych.org**

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MANAGING YOUR

SORE THROAT

What Is a Sore Throat?

Pharyngitis, the medical term for sore throat, is an infection with throat pain. It usually goes away by itself in a week without causing damage.

What Causes a Sore Throat?

The cause is usually a virus, but air pollution, alcohol, allergies, bacteria, chemicals, and smoking can also cause a sore throat.

What Are the Symptoms of a Sore Throat?

Throat discomfort is the most common symptom. Others, depending on the cause of the sore throat, may be earache, fever, large tonsils, neck pain, pain when talking or swallowing, red throat, runny nose, snoring and trouble breathing, drooling, general aches, and swollen, painful glands in the neck.

How Is a Sore Throat Diagnosed?

The doctor will make a diagnosis from the medical history and examination, especially of the ears and throat. Usually, no other tests are needed. A swab of the throat may also be done if a streptococcal (strep) bacterial infection is suspected to be the cause. Blood tests may be done for other diseases, such as mononucleosis, if these are suspected.

How Is a Sore Throat Treated?

Most cases go away by themselves. Antibiotics are not helpful for viral infections. The doctor will prescribe antibiotics only for a suspected bacterial infection. Drinking warm liquids, eating soft cold food, and gargling with warm saltwater solution may help the pain. Acetaminophen or ibuprofen can also be taken for fever and pain. A cool mist vaporizer may relieve a dry, tight

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feeling in the throat.

DOs and DON'Ts in Managing a Sore Throat:

✓ **DO** tell your doctor about your medicines, both prescription and over-the-counter.

✓ **DO** call your doctor if your symptoms get worse or you have a temperature higher than 101° F.

✓ **DO** call your doctor right away or go to the emergency room for breathing or swallowing problems.

✓ **DO** call your doctor if you have joint pain, body swelling, or dark urine.

✓ **DO** call your doctor if you have severe throat pain that stops you from swallowing.

✓ **DO** gargle with a warm saltwater solution.

✓ **DO** use a vaporizer for a dry, tight feeling in the throat. Clean the vaporizer and change the water daily.

✓ **DO** replace your toothbrush after treatment starts, to prevent reinfection.

✓ **DO** limit activities until symptoms go away.

✓ **DO** increase fluid intake.

✓ **DO** follow a liquid diet (soups, gelatin, ice cream, and juices) if swallowing is hard.

✓ **DO** call your doctor you get a severe headache, rash, or cough with thick, yellow-green or

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bloody sputum.

✓ **DO** eat a healthy diet and get plenty of sleep to improve your recovery time.

✓ **DO** wash your hands often, especially before you eat and after being with someone who's sick.

✓ **DO** stop smoking and drinking alcohol.

✓ **DO** stay away from cigarette smoke and air pollution.

✓ **DO** get a humidifier if air in your home is very dry.

⃠ **DON'T** give aspirin to a child with fever or sore throat, to avoid the dangerous Reye's syndrome.

⃠ **DON'T** stop taking your medicine or change your dosage because you feel better unless your doctor tells you to.

⃠ **DON'T** share food, utensils, or drinking glasses. Avoid kissing someone who's sick.

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FOR MORE INFORMATION

Contact the following sources:

• Infectious Diseases Society of America Tel: (703) 299-0200 **Website:**

http://www.idsociety.org

• American Academy of Otolaryngology—Head and Neck Surgery Tel: (703) 836-4444 **Web-**

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site: http://www.ent.net

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MANAGING YOUR

SPINAL CORD TRAUMA

What Is Spinal Cord Trauma?

Spinal cord trauma involves damage to the spinal cord. The spinal cord lies inside the spinal vertebrae (bones) of the neck, chest, and lower back. It's a dangerous injury and a medical emergency. Spinal cord injury causes permanent disability or loss of movement (paralysis) and sensation below the injury. Paralysis of both arms and legs is called quadriplegia. These injuries may affect only the lower body (paraplegia).

Traumatic injuries are most common in people 15–25 years old, usually males.

What Causes Spinal Cord Trauma?

Causes include sudden blows to the spine that fracture, crush, or compress vertebrae. Gunshot or knife wounds, motor vehicle accidents, falls, sports, and recreational activities (e.g., diving) are other causes.

Arthritis, cancer, blood vessel problems, bleeding, inflammation, infections, and spinal disk degeneration are nontraumatic causes. Older people with weakened spines (from osteoporosis) may have injuries from rather simple falls.

What Are the Signs and Symptoms of Spinal Cord Trauma?

Symptoms depend on where the injury is and how severe it is (partial or complete). Injuries that are higher in the spinal cord usually cause more paralysis. Symptoms include weakness, paralysis, and loss of feeling at and below the injury. Breathing and balance problems, loss of bowel and bladder control, spasms, and pain can occur.

How Is Spinal Cord Trauma Diagnosed?

The doctor does a physical examination, including a neurologic examination. The doctor tests

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pinprick, light touch, and vibration senses. Additional testing usually includes computed tomography (CT), magnetic resonance imaging (MRI), and x-rays.

How Is Spinal Cord Trauma Treated?

Treatment begins at accident scenes, including using a back board with the neck in a collar and checking the ABCs (airway, breathing, circulation). The spine must be stabilized and immobilized. Traction helps align the spine. The steroid methylprednisolone is an option for acute injury if given within 8 hours. Emergency surgery may be done to take out pieces of bones, foreign objects, ruptured (herniated) disks, or broken vertebrae. Surgery may be done to stabilize the spine. Bed rest is important, but early mobilization is critical. Medicines help spasms and pain.

Later, muscle contractions, bed sores, urinary infections, blood clots, and other complications must be prevented and promptly treated when they occur. Treatments include range-of-motion exercises, skin lotions, soft bed coverings or flotation mattresses, and changing positions often. Management of many possible complications and early rehabilitation are long-term goals. A medical team helps with these goals. This team can include physical and occupational therapists.

People's living environments may need changing. New devices help independence and mobility. These include modern wheelchairs, computer-controlled tools and gadgets, and electrical stimulation devices.

DOs and DON'Ts in Managing Spinal Cord Trauma:

✓ **DO** get emergency help (call 911) for people who aren't fully conscious, and get emergency help (call 911) for people with back or neck injuries.

✓ **DO** wear safety equipment and use proper techniques when participating in sports (e.g.,

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diving, playing contact sports). Use safety practices during work. Wear seat belts.

✓ **DO** learn everything you can about your injury. Join a support group if you think that would help.

✓ **DO** follow all your doctor's instructions.

⃠ **DON'T** dive into shallow water.

⃠ **DON'T** miss your follow-up doctor visits.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Trauma Society Tel: (800) 556-7890 **Website: http://www.amtrauma.org**
- American Academy of Family Physicians Tel: (800) 274-2237 **Website: http://www.aafp.org**

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MANAGING YOUR

SPINAL STENOSIS

About the Spine

The spine, also called the backbone or spinal column, is made up of 33 bones (vertebrae) from the bottom of the skull to the buttocks. Ligaments connect these bones. Between most vertebrae are flattened, round structures (intervertebral disks) composed of a soft substance in the middle and stronger outer covering. The spinal cord, which holds the nerves, runs through and is protected by vertebrae. Muscles in the back and abdomen support the spine.

What Is Spinal Stenosis?

Spinal stenosis is a narrowing in a part of the spine.

What Causes Spinal Stenosis?

The cause is usually wear and tear, past injury, disk rupture (herniation), or osteoarthritis related to aging. As disks between vertebrae wear out, spaces between vertebrae narrow. Vertebrae become deformed and may develop spurs (bony outgrowths or bulges) that can compress spinal nerves.

What Are the Symptoms of Spinal Stenosis?

Symptoms depend on which area of the spine is narrowed. Narrowing of the lower part produces pain in the lower back, buttocks, and thighs. In severe cases, legs or arms may become numb and weak.

Pinching (compression) of a spinal nerve root may cause intense pain in the buttocks or down the leg. *Sciatica* means pain in the leg caused by pinching, swelling (inflammation), or injury of the sciatic nerve. This nerve runs from the lower spine, down the buttock and back of the knee to the foot. Numbness and pins and needles may also be felt.

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Spinal stenosis pain is worse during walking (especially downhill) or standing and gets better by bending forward.

How Is Spinal Stenosis Diagnosed?

A medical history and physical examination are used for diagnosis. The doctor may order blood and urine tests to see whether another disorder may be causing symptoms. X-rays of the spine will be done. Magnetic resonance imaging (MRI) of the spine may be done if a better picture is needed of bones, nerves, disks between vertebrae, and other tissues, or if surgery is being considered. A nerve conduction test may tell whether pressure on nerves is causing numbness or tingling in the legs.

How Is Spinal Stenosis Treated?

Physical therapy may help reduce pain and improve mobility.

Over-the-counter pain relievers, such as acetaminophen, or nonsteroidal antiinflammatory drugs (NSAIDs), such as ibuprofen, can help. For really severe pain, stronger narcotic medicines may be used for a short time. All drugs have side effects. NSAIDs may cause stomach upset, rash, and internal bleeding. Narcotic drugs may also cause drowsiness and constipation.

Surgery is used only for pain that doesn't go away. The operation may remove the disk (discectomy) to relieve pressure on a nerve, or remove part of the bony arch, or lamina, of a vertebra (laminectomy) for a herniated disk. Removal of the vertebral body and surrounding soft tissue is called decompressive laminectomy. In people with spinal stenosis and instability of the spine, bone graft to maintain the structural support of the spinal column (spinal fusion) may be done following decompressive laminectomy.

DOs and DON'Ts in Spinal Stenosis:

✓ **DO** take medicines as prescribed.

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✓ **DO** call your doctor if you have drug side effects.

✓ **DO** call your doctor if you have new numbness or tingling in your legs.

✓ **DO** call your doctor if you have trouble urinating or lose control of your bowels or bladder.

⃠ **DON'T** wait for a drug side effect to go away on its own.

⃠ **DON'T** stop exercising completely.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopaedic Surgeons Tel: (800) 346-AAOS **Website:** **http://www.aaos.org**
- North American Spine Society Tel: (708) 588-8080 **Website:** **http://www.spine.org**

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MANAGING YOUR

SQUAMOUS CELL CARCINOMA

What Is Squamous Cell Carcinoma?

Squamous cells form the part of the skin called the epidermis. Cutaneous squamous cell carcinoma is a common kind of skin cancer that involves these cells. It occurs most often in people older than age 50.

What Causes Squamous Cell Carcinoma?

The cause is usually longtime sun exposure. Exposure to many x-rays and having light-colored skin, blue or green eyes, and blond or red hair can also give people greater risks of having this cancer.

What Are the Symptoms of Squamous Cell Carcinoma?

This cancer usually starts as a reddish skin patch with a crusty surface. It may grow and look like a wart or sore. It can grow anywhere, including hands, scalp, ears, and lips. It can form a sore that bleeds on and off. A sore that doesn't heal may mean squamous cell carcinoma.

How Is Squamous Cell Carcinoma Diagnosed?

The doctor will examine the skin, but a skin biopsy is needed for diagnosis. For a biopsy, a tiny piece of skin is shaved off and sent to a laboratory for study. A dermatologist (specialist in skin diseases) may do this.

How Is Squamous Cell Carcinoma Treated?

Squamous cell carcinoma can most often be cured by taking off the cancer. The way to do this depends on the size of the tumor growing below the skin surface.

Small tumors can be burned with an electric needle and scraped out. Some can be removed by freezing. These procedures are usually done in the doctor's office.

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Larger tumors need to be cut out. The doctor may use a special type of surgery called Mohs micrographic surgery. This operation involves slowly removing layers of skin until the whole cancer is gone. The wound may take up to 6 weeks to heal. The doctor must be told about any signs of infection during this time.

Rarely, the tumor spreads. If it has spread to other areas, a doctor specializing in treating cancer can treat this tumor with radiation or cancer drugs.

Squamous cell carcinoma can come back, so regular follow-up appointments are a must to find new squamous cell carcinomas early.

DOs and DON'Ts in Managing Squamous Cell Carcinoma:

✓ **DO** avoid too much sun, especially the strongest sun during the middle of the day (between 10 AM and 2 PM).

✓ **DO** wear sunscreens with high sun protection factors and protective clothing when you're in the sun.

✓ **DO** use a lot of sunscreen. Don't forget your face, the backs of your hands, and your ears.

✓ **DO** stay out of tanning parlors.

✓ **DO** watch for changes in the look, color, size, or texture of a lesion on your skin. Call your doctor if you see these changes. Also call if you have pain, inflammation, bleeding, or itching of a skin lesion.

✓ **DO** call your doctor if you see new growth in the area of the skin where the cancer was removed.

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⦸ **DON'T** smoke. Cigarette, cigar, and pipe smoking can cause squamous cell carcinoma of the lips and mouth.

⦸ **DON'T** miss follow-up doctor appointments for early detection of possible cancers.

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FOR MORE INFORMATION

Contact the following sources:

- American Cancer Society Tel: (800) ACS-2345 (227-2345) **Website:** **http://www.cancer.org**
- American Academy of Dermatology Tel: (866) 503-7546 **Website:** **http://www.aad.org**

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MANAGING YOUR

STASIS DERMATITIS

What Is Stasis Dermatitis?

Stasis dermatitis is chronic inflammation (redness, swelling) and irritation of the skin, usually in the lower legs. It's related to poor circulation of blood and lymphatic fluids, with fluids moving slowly up from the feet to the heart. It's very common, affecting 50% of Americans with certain risk factors. It usually occurs in middle-aged and elderly people.

What Causes Stasis Dermatitis?

Contributing factors include prolonged standing, varicose veins, inactivity, obesity, and congestive heart failure. These factors lead to leg swelling (edema).

What Are the Symptoms of Stasis Dermatitis?

Symptoms include reddened, swollen feet and lower legs and often shiny skin and painful feet. Small sores or ulcers may appear on feet or lower legs and may not heal well. Swelling and skin breakdown lead to infection, which may cause a skin ulcer or become severe and involve deeper tissues (muscle or bone). Severe pain and swelling limit activity, as walking becomes more painful. This decreased movement makes the condition even worse.

How Is Stasis Dermatitis Diagnosed?

The doctor will make a diagnosis by examining the feet and legs. If the doctor suspects heart failure or other disorders, more tests will be done.

How Is Stasis Dermatitis Treated?

Fluid trapped in feet and lower legs must be reduced. If the leg swelling is severe, mechanical devices such as hospital-grade support hose or leg compression pumps move fluid from legs if used correctly. Diuretics (water pills) may also help some, but not all, people, and can cause de-

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hydration and low potassium levels.

Steroid and zinc oxide creams and paste may be used for small ulcers. Antibiotics may be prescribed for skin infection. In severe cases, a special wrap filled with gelatin and containing zinc (called Unna's boot) may protect and heal skin and stop more swelling.

DOs and DON'Ts in Managing Stasis Dermatitis:

✓ **DO** take diuretics exactly as prescribed.

✓ **DO** use prescribed mechanical devices such as support hose or compression pumps every day. The hose should be ordered specifically for you, with your exact leg measurements. Put the hose on in the morning after bandaging ulcers or sores. Remove them at night for sleeping.

✓ **DO** learn to use your compression pump properly, for several sessions each day.

✓ **DO** eat a low-fat, low-cholesterol diet and avoid too much salt. Ask your doctor about the amount of salt you may have. Usually, more than 4 grams of sodium will increase foot swelling.

✓ **DO** ask your doctor about drinking water. You may need less than the usual 8 glasses daily.

✓ **DO** exercise daily. Mild to moderate exercise (walking) can improve circulation. If walking is too hard for you, physical therapy may improve strength and range of motion. Raising your legs when you sit or lie down may help.

✓ **DO** call your doctor if you notice new sores, ulcers, or redness in your feet or legs.

✓ **DO** call your doctor if you have more leg swelling even after using support hose or com-

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pression pumps.

✓ **DO** call your doctor if you have fever, chills, or shortness of breath.

⃠ **DON'T** exercise without your doctor's OK.

⃠ **DON'T** sit for long periods with your legs crossed or your feet hanging down.

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:**

  http://www.americanheart.org

- American Academy of Dermatology Tel: (866) 503-SKIN (503-7546) **Website:**

  http://www.aad.org

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MANAGING YOUR

STEVENS-JOHNSON SYNDROME

What Is Stevens-Johnson Syndrome?

Stevens-Johnson syndrome is an acute (sudden) allergic inflammatory skin disease. It's rare and is not contagious. More men than women get it. Most cases have a strong relation to exposure to specific medicines, starting 1 to 3 weeks after the first drug exposure. The disease can cause serious symptoms that need prompt treatment and maybe treatment in the intensive care unit of a hospital.

What Causes Stevens-Johnson Syndrome?

Stevens-Johnson syndrome is usually due to a reaction to a medicine. Most drugs can cause Stevens-Johnson syndrome, but the more common ones are sulfa antibiotics, nonsteroidal antiinflammatory drugs (NSAIDs), anticonvulsants, and allopurinol (used for gout). In rare cases, an infection (e.g., with bacteria or virus) or cancer may cause Stevens-Johnson syndrome. Sometimes the cause is unknown.

What Are the Symptoms of Stevens-Johnson Syndrome?

The syndrome begins with a high fever and flulike symptoms. After 1 to 3 days, skin lesions appear. The rash consists of raised target-type lesions, which look like blisters. The lesions will peel off and leave red, oozing skin. Mild to moderate skin tenderness and burning or itching of the eyes occur. People may have painful mouth lesions that make it hard to swallow and ulcers on membranes of the nose, eyes, and genital area. Mouth sores can last for months.

Other possible symptoms are sensitivity to light, anxiety, and painful urination. Fingernails may also be shed.

How Is Stevens-Johnson Syndrome Diagnosed?

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A doctor will diagnose Stevens-Johnson syndrome on the basis of a medical history of exposure to medicines and the physical examination.

How Is Stevens-Johnson Syndrome Treated?

Any medicine that may be the cause must be stopped immediately. If blistering and peeling are severe, a hospital stay may be needed. People are often placed in special burn units where damaged skin can get the best care. Topical ointments will be applied to the rash, and intravenous fluids will be given to prevent dehydration. Prevention of infection is the main concern. Medicated rinses can treat mouth lesions.

DOs and DON'Ts in Managing Stevens-Johnson Syndrome:

✓ **DO** wash hands carefully. Anyone caring for the lesions should do this to prevent infection.

✓ **DO** maintain good nutrition. A liquid diet may help if pain occurs with swallowing.

✓ **DO** drink enough fluids to prevent dehydration.

✓ **DO** wear a medical ID bracelet naming the medicine suspected of causing the syndrome.

✓ **DO** call your doctor if you get a high fever.

✓ **DO** call your doctor if you cannot drink enough fluids or have good nutrition because of mouth lesions.

✓ **DO** call your doctor if symptoms worsen.

⦸ **DON'T** scratch the lesions or peel the loose skin.

⦸ **DON'T** use the medicine suspected of causing the syndrome.

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Arthritis and Musculoskeletal and Skin Diseases of the NIH Tel: (877) 226-4267 **Website: http://www.niams.nih.gov**
- American Academy of Allergy, Asthma & Immunology Tel: (800) 822-2762 **Website: http://www.aaaai.org**
- American Academy of Dermatology Tel: (866) 503-SKIN (7546) **Website: http://www.aad.org**

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MANAGING YOUR

STOMACH CANCER

What Is Stomach Cancer?

Stomach (gastric) cancer refers to a cancerous (malignant) growth in the stomach.

These cancers occur in about 7 people per 100,000 in the United States. They are more common in Japan (more than 80 people per 100,000). Most cases are diagnosed in people older than 65.

What Causes Stomach Cancer?

The cause is unknown, but certain things increase chances of getting this disease. Diets high in nitrates may make this cancer more likely. Nitrates (found in smoked and salted foods) are converted to nitrites by bacteria, and nitrites are cancer-causing substances. Also, people whose stomach is infected with bacteria called *Helicobacter pylori* may have greater chances of getting stomach cancer. There is also a slight increase in risk if there is a family history of stomach cancer.

What Are the Symptoms of Stomach Cancer?

People with early stomach cancers may not have symptoms. As the tumor grows, people have abdominal (belly) pain, nausea, and loss of appetite. Other complaints are abdominal bloating after eating, trouble swallowing, heartburn, weight loss, blood in stools, a mass that can be felt, fullness in the stomach after meals, and fluid in the abdomen (ascites).

How Is Stomach Cancer Diagnosed?

The only sure way to diagnose stomach cancer is with a biopsy. The doctor uses a small lighted tube (scope) passed through the mouth, down the esophagus, and into the stomach (upper endoscopy). If the doctor finds abnormal areas, a sample is taken and studied with a microscope.

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How Is Stomach Cancer Treated?

Treatment depends on how far the cancer spread (its stage). Surgery is the only chance for cure. Surgery includes complete removal of the cancer by taking out part of the stomach (subtotal gastrectomy) or near-total removal of the stomach with nearby lymph glands.

People with advanced cancer may have chemotherapy, usually a combination of different drugs. The doctor will recommend other doctors including an oncologist (specialist in cancer) be involved in care.

Radiation therapy doesn't work well for stomach cancer and may be used only to help reduce pain.

DOs and DON'Ts in Managing Stomach Cancer:

✓ **DO** tell your doctor about a family history of stomach cancer and recurrent *H. pylori* infection, which may be linked to stomach cancer.

✓ **DO** keep your follow-up doctor appointments. A team of doctors including your primary care doctor, surgeon and oncologist, will care for you.

✓ **DO** call your doctor if you have abdominal pain or blood in your stool.

✓ **DO** call your doctor if you have a fever during chemotherapy.

✓ **DO** call your doctor if you have pain or abnormal drainage around the incision after surgery.

⦸ **DON'T** ignore stomach pain or blood in the stool. These may be signs of serious problems.

⦸ **DON'T** be afraid to ask for second opinions.

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FOR MORE INFORMATION

Contact the following sources:

- National Cancer Institute Tel: (800) 422-6237 **Website: http://www.cancer.gov**
- American College of Surgeons Tel: (800) 621-4111 **Website: http://www.facs.org**

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MANAGING YOUR

STOMATITIS

What Is Stomatitis?

Stomatitis is a general inflammation (swelling, redness) of the mouth. It involves the soft mucous membranes lining the mouth (mucosa), lips, tongue, and palate. It's called herpetic stomatitis when caused by herpesvirus, and aphthous stomatitis (canker sores) when causes are unknown. Stomatitis is common in all ages.

What Causes Stomatitis?

Herpesvirus is one of the most common causes. Others include allergic reactions, smoking, dental disease, vitamin deficiencies, systemic diseases, medicines, and other viral and bacterial infections.

What Are the Symptoms of Stomatitis?

Inflammation of the mouth may cause pain, fever, tiredness, headache, and loss of appetite. Usually, people have one or more small sores on their lips, gums, tongue, roof of the mouth, or inside the cheeks. Sores are often red and may hurt, burn, or tingle. Eating and swallowing hurt. Sometimes, people have bad breath (halitosis).

How Is Stomatitis Diagnosed?

The doctor makes a diagnosis by examining the mouth. The doctor may gently scrape a sample from the mouth to check with a microscope. This sample will show if a yeast infection caused the stomatitis. If the cause isn't clear or treatment doesn't help, a biopsy is done. A biopsy involves taking a small sample of the sore for study with a microscope. Blood tests are not usually necessary but may be done in recurrent or persistent cases.

How Is Stomatitis Treated?

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Stomatitis caused by irritation from foods, mouthwashes, or cigarettes usually heals after use of the product stops. Antibiotics are given for bacterial infections. Often, medicines for infections are liquids that are swished around in the mouth. Some need to be swallowed after swishing. Vitamin supplements are given for rare nutritional problems. For severe symptoms, oral corticosteroids may be needed. Canker sores and herpes sores usually heal in 1 or 2 weeks. Thrush heals quickly with medicine. Other types of stomatitis may take several weeks to heal.

Sometimes, complications such as bleeding and infection occur. Because of mouth pain, many people, especially babies, don't eat or drink enough. They lose weight and become dehydrated. This is especially dangerous for babies. Intravenous fluids may be needed for severe dehydration.

The key is to relieve symptoms. Pain medicine such as acetaminophen and topical anesthetic agents can do this. Mouth rinses with baking soda and warm water can help.

DOs and DON'Ts in Managing Stomatitis:

✓ **DO** see a dentist regularly.

✓ **DO** use good oral hygiene. Brush and floss teeth and clean the tongue after each meal. Use a soft-bristled toothbrush.

✓ **DO** avoid sharp-surfaced foods, such as peanuts, popcorn, and potato chips.

✓ **DO** take your dentures out at night. Have them adjusted so that they fit better.

✓ **DO** avoid strong mouthwashes, but rinse your mouth well, especially before going to bed.

✓ **DO** call your doctor if your symptoms don't go away after 7 to 14 days of treatment.

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⦸ **DON'T** smoke.

⦸ **DON'T** eat citrus foods or foods that are spicy or acidic.

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Dental and Craniofacial Research Tel: (301) 402-7364 **Website:** **http://www.nidcr.nih.gov/OralHealth/**
- American Academy of Periodontology Tel: (312) 787-5518 **Website:** **http://www.perio.org**
- American Dental Association Tel: (312) 440-2500 **Website:** **http://www.ada.org**

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MANAGING YOUR

STRABISMUS

What Is Strabismus?

Strabismus is a condition in which the eyes don't move in the same direction. They appear to point in different directions. One or both eyes may turn either in or out. Over time, the weaker eye becomes "lazier," or less used, as the brain uses signals from the stronger eye.

Strabismus runs in some families. Treatment can correct this condition, but without early treatment, some vision may be lost.

What Causes Strabismus?

Strabismus has two causes. The first is a difference in strength of muscles around each eye. The second is a difference in each eye's ability to focus. If either the muscle strength or focus of one eye is weaker, that eye may start to drift. Strabismus usually appears in early to middle childhood. It can also occur as early as at birth, but it's hard to diagnose strabismus until 3 months of age, because at birth the eyes cannot focus well. Adults can also develop strabismus. In adults, a disease such as diabetes or stroke or injury to the eye can cause it.

What Are the Symptoms of Strabismus?

The main symptom is that the eyes seem to look in two different directions. Squinting, frequent eye rubbing, and tilting of the head are common. Double vision and vision in only one eye are other symptoms.

How Is Strabismus Diagnosed?

The doctor will make a diagnosis by doing an eye examination. The examination may include looking through a set of prisms to find the differences between the eyes. The eye exam may also include a visual acuity test, examination of the retina, and a neurological examination. Your doc-

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tor may suggest seeing an ophthalmologist (specialist in eye disorders). The specialist will also check nerves and muscles around the eyes. Then, decisions about whether surgery might fix the problem can be made.

Children should usually have their eyes examined every 1 to 4 months until the eyes are stable. After that, they may need examinations every 6 months until the age of 6 years. Annual examinations should follow until age 9 to 11.

How Is Strabismus Treated?

The goal of treatment is to make the weaker eye stronger. To do this, glasses or an eye patch over the stronger eye may be used. This forces the weaker eye to become stronger. The doctor may suggest doing eye muscle exercises. Sometimes, surgery is needed to balance the muscle strength between the two eyes.

DOs and DON'Ts in Managing Strabismus:

✓ **DO** wear the patch or eyeglasses, or both, given to you by your doctor.

✓ **DO** call your doctor if you get a fever or pain and redness in the eye after surgery.

⃠ **DON'T** run when you're adjusting to wearing an eye patch. This will help prevent falls and injury.

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Contact the following source:

• American Academy of Ophthalmology Tel: (415) 561-8500 **Website:** **http://www.aao.org**

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STRESS TEST USED TO PREDICT HEART ATTACK RISK

Who Is at Risk of Having a Heart Attack?

People who smoke or have high blood pressure, diabetes, or high cholesterol levels are more likely to have heart attacks, or myocardial infarctions (MIs). In MIs, heart muscles are injured or die when they don't get enough oxygenated blood because of blocked arteries.

What Are Stress Tests and Nuclear Imaging?

Stress tests and nuclear imaging can help find out about past heart disease or MIs and predict future cardiac problems. Exercise stress testing, using treadmills or bicycles, is one of the best tests for cardiac function. People who can't exercise may be given medicines (adenosine or dipyridamole) to stress the heart. Nuclear imaging includes myocardial perfusion imaging such as SPECT (single-photon emission computed tomography). SPECT can see blood flow to the heart walls. PET (positron emission tomography) and MUGA (multiple gated acquisition) scanning, also called radionuclide angiography (RNA), are other such tests.

What Preparation Is Needed for Stress Tests?

To make the nuclear stress test more accurate and comfortable, solid food, nicotine, caffeine, alcohol, and some medicines may be restricted before the test. Comfortable clothing and shoes should be worn.

How Are Stress Tests Done?

During treadmill exercises, the speed and incline angle are slowly increased until the heart is stressed enough as determined by the cardiologist in attendance during the test. Pictures made after exercise show blood flow to the heart during the "stress" of exercise. Pictures are also taken to show blood flow during rest. These pictures are compared to see how well the heart works.

In nuclear imaging tests, small amounts of radioactive substances called tracers (such as

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thallium or sestamibi) are put into the body. These are safe and have no side effects. Special cameras find the tracer and take pictures during exercise and rest. With these pictures, computers measure blood flow through the heart, find abnormal heart muscle, and tell whether parts of the heart aren't getting enough blood.

What Are Risks of Stress Tests?

Risks of exercise on treadmills or bicycles are small. Complications include chest pain, fainting, muscle cramps, and blood pressure that's too high. Risks related to exposure to radiation from tracers are rare. Thallium stress tests can cause abnormal heart rhythms, problems breathing, and rashes. Exercise stress tests are not as accurate in young or middle-aged women who don't have usual heart disease symptoms. These tests are also not 100% accurate in detecting or ruling out heart disease.

DOs and DON'Ts in Managing Stress Testing for Heart Disease:

✓ **DO** understand risk factors about heart disease. Be proactive in talking to your doctor or gynecologist about heart health.

✓ **DO** stop smoking. Drink in moderation or not at all.

✓ **DO** be heart healthy: have your blood pressure and cholesterol levels checked regularly. Eat low-fat foods (fruits and vegetables). Lose weight if you're overweight. Exercise, such as walking, if your doctor says it's OK.

✓ **DO** see your doctor regularly. Call your doctor about changes in your condition, such as shortness of breath when walking.

⦸ **DON'T** forget to see a cardiologist (specialist in heart diseases), in follow-up after an MI.

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Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website:**

  http://www.americanheart.org

- American College of Cardiology Tel: (800) 253-4636 **Website: http://www.acc.org**

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MANAGING YOUR

STROKE

What Is Stroke?

A stroke, or cerebrovascular accident (CVA), is an event in which blood flow to an area of the brain stops and results in injury to that area of the brain.

What Causes Stroke?

Most strokes are caused by artery disease and/or high blood pressure. Most often, a blood vessel (artery) taking blood to the brain becomes blocked. This blockage is usually due to a blood clot (thrombus). This type of blockage is an ischemic stroke. A torn or burst blood vessel may also cause bleeding in the brain. This type is called a hemorrhagic stroke.

Plaques or clots in large arteries of the neck may cause warning signs called mini-strokes, or transient ischemic attacks (TIAs), and strokes, when they break away and block a blood vessel in the brain, stopping blood flow to an area of the brain. Plaque is made of fatty material that sticks to blood vessel walls.

What Are the Symptoms of Stroke?

Symptoms tend to occur suddenly and almost always affect only one side of the body. They are usually worst in the first 24 to 72 hours. Common symptoms include weakness or numbness of face, arm, and leg muscles and difficulty speaking or swallowing. Others are confusion, vision changes, dizziness, and loss of balance. TIA symptoms usually disappear in a few hours. Most last less than 10 minutes. Those lasting longer than 24 hours are called strokes.

The type of symptoms from a stroke depend on the area of the brain that is damaged. Serious strokes can cause extensive paralysis and loss of speech. Less serious strokes may not become apparent for several days.

How Is a Stroke Diagnosed?

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The doctor will suspect stroke, based on the medical history and physical examination. Computed tomography (CT) or magnetic resonance imaging (MRI) of the brain will be done to further evaluate the area of the brain involved in the stroke and to determine if the stroke is due to a blood clot or a burst blood vessel. A study of the heart's electrical activity (electrocardiogram, or ECG) will be done to rule out irregular heartbeat (atrial fibrillation), which may cause a stroke by promoting the development of blood clots in the heart that can travel to the brain and cause a stroke.

An ultrasound of the carotid arteries in the neck may be done to look for a blockage of the arteries supplying blood to the brain.

How Is a Stroke Treated?

The type of stroke determines the treatment. However, survival may depend on an immediate visit to the hospital emergency department. There, a potent blood thinner may be given to people with ischemic strokes. This drug, tPA, can dissolve a clot, although certain risks (e.g., bleeding in the brain) are related to it. The emergency room doctor, in consultation with a specialist of the nervous system (neurologist), will determine if this medication is appropriate depending on the type of stroke, elapsed time from beginning of the symptoms, and other criteria.

A stroke may have mild to severely disabling effects. How much ability one can recover may not be known for several months. Many people need rehabilitation, such as speech therapy, physical therapy, and occupational therapy.

Treatment must also target conditions such as high blood pressure, diabetes, tobacco use, lifestyle, and high cholesterol levels. Also, other strokes must be prevented by reducing or eliminating the cause(s) of the initial stroke. Many people can do this by using drugs to prevent blood clots from forming. Often, taking a small amount of aspirin each day will do this. Other people

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must control high blood pressure and reduce other risk factors for stroke, such as diabetes, high cholesterol levels, smoking, and being overweight.

DOs and DON'Ts in Managing and

Preventing Stroke:

✓ **DO** stop smoking.

✓ **DO** take your medicines as recommended by your doctor.

✓ **DO** exercise according to your doctor's instructions.

✓ **DO** eat a low-fat diet and drink no more than one alcoholic drink a day.

✓ **DO** control your blood pressure, cholesterol level, and diabetes.

⃠ **DON'T** ignore symptoms of stroke. It can be a matter of life or death.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- American Stroke Association Tel: (888) 478-7653 **Website:** **http://www.strokeassociation.org**
- National Stroke Association Tel: (800) 787-6537 **Website:** **http://www.stroke.org**

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MANAGING YOUR

STYE

What Is a Stye?

A stye, which is also known by the medical term hordeolum, looks like a pimple next to an eyelash. It starts quickly, when the opening in the eyelid for the eyelash (or root of the eyelash) becomes blocked. It can form on the inside or outside of the eyelid. People of any age can have a stye.

What Causes a Stye?

The opening for the eyelash becoming blocked with oil or dirt will lead to a stye. After the hole is blocked, bacteria grow inside and cause an infection. The kind of bacteria called *Staphylococcus aureus* causes the infection in almost all cases.

What Are the Symptoms of a Stye?

Symptoms are redness, tenderness, and swelling on the eyelid. The eye may water and may be sensitive to light. Sometimes the whole eyelid swells.

How Is a Stye Diagnosed?

The doctor will make this diagnosis by looking at the eye and eyelid.

How Is a Stye Treated?

A warm, wet compress placed on the eye helps open blocked eyelash holes and oil glands. It also helps reduce redness and swelling. The cloth should remain in place for up to 10 minutes. The compress should be applied four times a day.

The doctor may prescribe an antibiotic if an infection is present. Usually, the antibiotic is given in an ointment or eye drops. Rarely, a pill is also given. Other types of eye drops are sometimes used to help take away swelling. Sometimes, over-the-counter pain medicines can help

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discomfort.

In some cases, the doctor may make a small cut in the swollen area to let the pus drain, or send you to an ophthalmologist to have it lanced.

A stye usually goes away in 5 to 7 days. After that time, the swollen area opens and pus drains out.

DOs and DON'Ts in Managing a Stye:

✓ **DO** keep your face, scalp, eyebrows, and hands clean.

✓ **DO** use little or no eye make-up.

✓ **DO** call your doctor if your eyelid isn't getting better or if it's getting worse.

✓ **DO** call your doctor if the stye hasn't improved in 2 weeks.

✓ **DO** call your doctor if you develop a fever.

✓ **DO** call your doctor if you have trouble with your vision.

✓ **DO** call your doctor if the stye bleeds, the bump becomes very large or painful, a blister forms on your eyelid, or your whole eyelid or eye is red.

⊘ **DON'T** squeeze or try to break open the stye.

⊘ **DON'T** use eye drops or ointments not given to you by your doctor.

⊘ **DON'T** touch the eye drop applicator tip to any surface.

⊘ **DON'T** drive, operate machinery, or do any task that could be dangerous if your vision is

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blurry. Eye drops and ointment can cause blurry vision.

⃠ **DON'T** wear contact lenses until the stye goes away.

⃠ **DON'T** rub your eyes.

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FOR MORE INFORMATION

Contact the following source:

• American Academy of Ophthalmology Tel: (415) 561-8500 **Website: http://www.aao.org**

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MANAGING YOUR

SUBARACHNOID HEMORRHAGE

What Is a Subarachnoid Hemorrhage?

Subarachnoid hemorrhage (SAH) is sudden bleeding into the space that's between the brain and the middle membrane covering the brain. It's potentially life-threatening. Up to 10-15% of people die before reaching the hospital. As many as 40% die in the first week. About half die in the first 6 months. Also, more than one-third of survivors have major neurologic problems.

People older than 50 and women have higher risks of SAH. Because finding aneurysms that haven't burst in people without symptoms is hard, most SAHs cannot be prevented.

What Causes an SAH?

Causes include bleeding from a burst aneurysm or arteriovenous malformation (AVM), congenital conditions, and head injuries. Injuries result from falls in elderly people and motor vehicle crashes in younger people. Smoking, cocaine use, alcohol, using painkillers for a long time, and birth control pills have been related to aneurysmal SAH. High blood pressure (hypertension), blood vessel disorders, multiple aneurysms, fatty liver, cancer, and infections are also linked to these hemorrhages. A strong family history of aneurysms may increase SAH risk.

What Are the Signs and Symptoms of an SAH?

The classic symptom is a sudden, severe headache—the "worst headache ever." Other symptoms include decreased consciousness, loss of movement or feeling, and mood and personality changes including confusion and irritability. Muscle aches, nausea, vomiting, eye pain, light bothering the eyes, seizures, stiff neck, and vision problems may occur.

How Is an SAH Diagnosed?

The doctor makes a preliminary diagnosis based on the medical history and physical examina-

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tion, especially of the nervous system and eyes. Imaging studies and laboratory tests will be immediately done. The first is usually urgent cerebral (head) computed tomography (CT) without contrast. Cerebral angiography, magnetic resonance imaging (MRI), electrocardiography (ECG), and spinal tap may be done if the diagnosis is unclear. People with SAH have blood in their spinal fluid.

Several scales for grading SAHs are available; the most widely used is the Hunt-Hess scale.

How Is an SAH Treated?

Treatment aims to reduce pain, swelling, and severity of cerebral vasospasm; relieve nausea and vomiting; prevent seizures and rebleeding; and save lives. Treatment also tries to relieve symptoms and prevent complications such as permanent brain damage (stroke). A medical team is needed. People are usually in an intensive care unit (ICU) in the hospital. Surgery will fix aneurysms, remove large collections of blood, or relieve pressure on the brain. Strict bed rest is critical. Activities that can increase pressure inside the head (bending over, straining) must be avoided. Drugs include stool softeners or laxatives to prevent straining during bowel movements, blood pressure medicines, pain killers, and drugs for anxiety and seizures. Oxygen and fluids are given.

DOs and DON'Ts in Managing an SAH:

- ✓ **DO** go to the emergency room or call the emergency number (911) if you have SAH symptoms.
- ✓ **DO** learn everything you can about your injury. Join a support group if you think that would help.
- ✓ **DO** continue to have follow-up doctor examinations. Follow all your doctor's instructions.

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You may also need physical, occupational, and speech therapy.

⦸ **DON'T** smoke. People who smoke have a worse prognosis.

⦸ **DON'T** miss your follow-up doctor visits.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Family Physicians Tel: (800) 274-2237 **Website:** **http://www.aafp.org**
- American Stroke Association Tel: (888) 478-7653 **Website:** **http://www.strokeassociation.org**

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MANAGING YOUR

SUBDURAL HEMATOMA

What Are Subdural Hematomas?

The human brain and spinal cord are covered by layers of protective membranes called meninges. A hematoma is a collection of blood in an organ or tissue. In subdural hematomas, or subdural hemorrhages, blood or blood products collect between two of these layers: the arachnoidal (superficial) layer and the dura or meningeal layer. They're common among people with head trauma. They may be acute (start quickly) or chronic (develop slowly). Acute or very large hematomas may cause high pressure inside the skull (intracranial pressure). The result can be compression of and damage to brain tissue. This may be life-threatening.

What Causes Subdural Hematomas?

The usual cause is a shearing injury that tears the vein crossing the subdural space. The tear lets blood into the space. Contusions, other kinds of hemorrhage, and rarely abnormalities of blood vessels such as arteriovenous malformations or aneurysms can cause bleeding. These hematomas are common in elderly and alcoholic people because of brain wasting (atrophy) and frequent falls. Babies can also have them (e.g., shaken baby syndrome). Risk factors are things that make bleeding likely: medicines (e.g., anticoagulants); brain atrophy (e.g., dementia, alcoholism); and falls and trauma (e.g., movement disorders, stroke).

What Are the Signs and Symptoms of Subdural Hematomas?

Symptoms depend on how serious the injury is and the hematoma's size and location. Symptoms can start right away or weeks or more after injury. Some people seem fine at first (called the lucid interval) after the injury. Pressure on the brain can then cause loss of consciousness or changing levels of consciousness, vomiting, headache, dizziness, disorientation, slurred speech,

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amnesia, and seizures. Personality changes and abnormal breathing are possible. Blurred vision, abnormal eye movements, and different sized pupils can occur. People can have walking problems and limb weakness on one side of the body. Chronic and subacute hematomas often cause headache, mild weakness, slow thinking, speech abnormalities, mobility problems, and confusion.

How Are Subdural Hematomas Diagnosed?

The preliminary diagnosis is based on a medical history and physical examination. Computed tomography (CT) of the head without contrast will show hematomas.

How Are Subdural Hematomas Treated?

Treatment depends on the examination results, symptoms, hematoma size and location, and whether the hematoma is acute or chronic. Immediate surgery may be done. Other options are observation in an intensive care unit and outpatient treatment. For certain acute subdural hematomas and symptoms (e.g., coma, weakness), surgery is needed to remove the hematoma. People with chronic hematomas in stable condition can be watched until they need treatment.

People who have bleeding disorders or take drugs such as warfarin or aspirin need to treat the bleeding problem.

Recovery may be slow, even up to 2 years. Children generally recover faster than adults.

DOs and DON'Ts in Managing Subdural Hematomas:

✓ **DO** protect yourself and your children. Use seat belts, car seats, and safety sports equipment.

⃠ **DON'T** participate in contact and recreational sports until you have permission to.

⃠ **DON'T** ignore symptoms. Call your health care provider if symptoms don't improve or they get worse with treatment. Call if you have new symptoms.

⃠ **DON'T** use any medicines (including over-the-counter and herbal products) without first

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asking your health care provider.

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Neurological Disorders and Stroke Tel: (800) 787-6537 **Website: www.ninds.nih.gov**
- American College of Emergency Physicians Tel: (800) 798-1822 or (972) 550-0911 **Website: http://www.acep.org**
- American Stroke Association Phone: 88478-7653 **Website: www.strokeassociation.org**

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PREVENTING

SUDDEN INFANT DEATH SYNDROME

What Is SIDS (Sudden Infant Death Syndrome)?

SIDS, or crib death, is the sudden death of seemingly healthy babies during sleep. Most deaths occur in babies 2 to 4 months old, rarely before 1 month or after 6 months. SIDS affects more boys than girls, and more African-Americans and Native Americans than whites. It occurs more often in winter and sometimes runs in families. It can't be predicted or prevented.

What Causes SIDS?

The cause isn't known. Higher risks are related to sleeping on the stomach, especially for babies who are overdressed or covered with too many blankets or whose rooms are too warm. Premature, low-birth-weight, and multiple birth babies (being twins or triplets) have greater risk. It's also related to poor prenatal care, poverty, teen mothers, cigarette smoking, and drinking and drug use during pregnancy.

More is known about things that don't cause it: suffocation, vomiting, choking, birth defects, infections, immunizations, and kind of parenting.

What Are the Symptoms of SIDS?

SIDS has no symptoms or warning signs. Babies don't seem to suffer or struggle. They don't cry. Minor breathing or stomach problems might occur in the weeks before SIDS occurs.

How Is SIDS Diagnosed?

No tests can say for certain that SIDS caused death. When no other reason is found after reviewing medical histories, studying where the baby was found, and doing an autopsy, SIDS may be named as the cause.

How Is SIDS Risk Reduced?

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No home care is possible, but infant CPR can be tried. The emergency 911 number should be called.

Eliminating or preventing risk factors can lower SIDS risk. Everyone who cares for babies, including babysitters, day-care providers, and grandparents, should learn about SIDS. Preventing SIDS involves always placing babies on their back to sleep, not their stomachs or sides. Avoid too many fluffy, loose blankets and hot rooms. Having a fan in the room may reduce risk. Use firm mattresses. For the first 6 months, babies should sleep in cribs in parents' rooms, but not in parents' beds. A smoke-free environment is critical during pregnancy and for the first year of a baby's life. Breastfeeding may help. Pacifiers may reduce risk, offered after a baby is 1 month old.

Parents, who may suffer guilt feelings, need emotional support for their devastating loss. Allowing time to grieve and heal is critical.

DOs and DON'Ts in Preventing SIDS:

✓ **DO** put babies to sleep on their back.

✓ **DO** put babies to sleep in a crib, never in bed with other children or adults. Let babies sleep in the same room as parents.

✓ **DO** offer babies pacifiers at nap time and bedtime, but don't force babies to use them.

✓ **DO** keep babies in smoke-free environments.

✓ **DO** breastfeed, if possible.

✓ **DO** visit the doctor for prenatal care and take your baby for regular well-baby checkups.

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✓ **DO** look for help from a SIDS support group.

⃠ **DON'T** put babies to sleep on their stomachs or sides.

⃠ **DON'T** put babies to sleep on surfaces other than cribs, such as sofas.

⃠ **DON'T** use soft bedding, pillows, comforters, or quilts.

⃠ **DON'T** make the baby's room too hot.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Pediatrics Tel: (847) 434-4000 **Website: http://www.aap.org**
- American Psychiatric Association Tel: (888) 357-7924 **Website: http://www.psych.org**
- American Academy of Family Physicians Tel: (800) 274-2237 **Website: http://www.aafp.org**

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MANAGING

SUN POISONING

What Is Sun Poisoning?

Sun poisoning, also known medically as photodermatitis, is an itchy, scaly, blistery reddening of the skin. The skin is abnormally sensitive to effects of sunlight or ultraviolet rays A (UVA) or B (UVB). It can begin suddenly (acute) or be ongoing (chronic). How much exposure to sunlight or ultraviolet light (e.g., from a tanning bed) will cause problems is different for each person.

More than 10% of people in the United States have had sun poisoning.

What Causes Sun Poisoning?

Sensitivity to sun exposure can run in families (be genetic). Often, the cause can be traced to chemicals in medicines, cosmetics, and foods. Certain diseases, such as lupus and eczema, can also make skin sensitive to light.

What Are the Symptoms of Sun Poisoning?

Symptoms include skin that is red and dry. It may have blisters and a bumpy rash. The rash may feel painful or itchy. It's sometimes hard to tell from mild sunburn.

Long-term effects include skin thickening and scarring and an increased risk of skin cancer.

How Is Sun Poisoning Diagnosed?

The doctor will make a diagnosis from the history of exposure and a skin examination. The doctor will review the medicines you are taking and ask about new or different foods you have eaten.

How Is Sun Poisoning Treated?

Prevention is the best treatment for this disorder. However, if that's impossible, therapy is aimed at minimizing inflammation (swelling, redness) of damaged skin and relieving pain. Steroid

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creams or tablets may be prescribed. Antibacterial creams may be prescribed for burn-like reactions and suspected infection.

Avoiding the sun and the substance causing attacks are critical. If being outside in the sun cannot be avoided, a sunblock for both UVA and UVB light with an SPF of 15 or greater should be applied. Be sure to ask the doctor and pharmacist about avoiding sun exposure while taking any drugs.

DOs and DON'Ts in Managing Sun Poisoning:

✓ **DO** take medicines only as prescribed. Avoid ultraviolet light exposure as much as possible while taking drugs such as tetracycline antibiotics, sulfa drugs, and thiazide diuretics. These drugs cause greater sensitivity to light.

✓ **DO** use sunscreen, hats, and long sleeves to minimize effects of unavoidable exposure.

✓ **DO** avoid "natural" fruit-based skin lotions and cosmetics, because they may contain sensitizers as well.

✓ **DO** check with your doctor before using any tanning device.

✓ **DO** call your doctor if you develop fever or if your symptoms don't improve with treatment.

⊘ **DON'T** take sun exposure for granted. Once you've had sun poisoning, your skin will always be sensitive to the combination of the sun and the chemical you're sensitized to.

⊘ **DON'T** rely on sun lotions and lightweight clothing to provide protection for long periods.

⊘ **DON'T** rely on clouds for sunblock. They don't block ultraviolet light.

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Contact the following source:

- American Academy of Dermatology Tel: (866) 503-SKIN (503-7546) **Website:**

  http://www.aad.org

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MANAGING YOUR

SUPRAVENTRICULAR TACHYCARDIA

What Is Supraventricular Tachycardia?

In supraventricular tachycardia (SVT), the heart beats too fast, so it can't fill completely with blood. It usually beats 150–250 beats per minute (bpm), instead of the normal 60–100 bpm. The abnormal rhythm (arrhythmia) starts in the top heart chambers (atria). SVT includes arrhythmias from chronic atrial fibrillation (AFIB) to paroxysmal sinus tachycardia. AFIB is the most common type of SVT. Others are known as atrioventricular (AV) nodal reentry tachycardia (AVNRT) and atrioventricular reciprocating tachycardia (AVRT), including Wolff-Parkinson-White syndrome. SVT starts and ends suddenly and often occurs in people without heart disease.

Both men and women can have SVT, but it appears to be most common in women. It's the most common arrhythmia in children.

What Causes SVT?

Normally, the electrical signal that starts in the heart's sinoatrial (SA) node starts the contraction of the atria. Then, ventricles contract. SVT occurs when an extra electrical pathway triggers fast heartbeats. Causes include medicines (such as digoxin, theophylline) and lung conditions (such as chronic obstructive pulmonary disease, pneumonia). Alcohol, caffeine, illicit drugs, and smoking increase the risk of SVT. One type of SVT known as Wolff-Parkinson-White (WPW) syndrome may be inherited.

What Are the Symptoms of SVT?

The most common symptom is palpitation (feeling a racing or pounding heart). Others include dizziness, shortness of breath, fainting, chest pain, tiredness, sweating, and nausea. Symptoms may start and stop suddenly and last for a few minutes to hours.

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How Is SVT Diagnosed?

The doctor uses a physical examination, medical history, electrocardiography (ECG), laboratory tests, and chest X-ray for the initial diagnosis. The doctor may order a Holter monitor, a portable 24-hour ECG, to determine how often SVT occurs during a 24-hour period. The doctor may also want an electrophysiology study (EPS). In this test, flexible wires are put into a vein and threaded into the heart. Electrodes at the wire tips get information about the electrical activity of the heart.

How Is SVT Treated?

People without symptoms may not need treatment. For symptoms, treatment includes vagal maneuvers, such as the Valsalva maneuver or coughing, and splashing ice water on the face. Drugs include adenosine and verapamil. Electrical cardioversion may be used for emergency treatment or if other treatments don't work. In electrical cardioversion, a brief electric shock is given to reset the heart's rhythm. For recurring SVT, drugs (such as beta-blockers), pacemakers, catheter ablation, and surgery may be used.

DOs and DON'Ts in Managing SVT:

✓ **DO** control stress and other conditions such as diabetes and high blood pressure.

✓ **DO** eat low-fat, low-salt, low-cholesterol foods. Lose weight if you're overweight.

✓ **DO** exercise regularly.

✓ **DO** learn how to count your pulse. It should be 50–100 per minute and regular.

✓ **DO** take your prescribed medicine. Check with your doctor before taking over-the-counter cough, cold, or pain medicines.

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✓ **DO** call your doctor if you get chest pain, palpitations, fainting, or new, unexplained symptoms. Call if SVT doesn't go away on its own or with a Valsalva maneuver, or if symptoms return often.

⦸ **DON'T** take over-the-counter decongestants, herbal remedies, diet pills, and illegal drugs.

⦸ **DON'T** smoke or drink alcohol or caffeine.

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website: http://www.americanheart.org**
- American College of Cardiology Tel: (800) 253-4636 **Website: http://www.acc.org**

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MANAGING YOUR

SYNCOPE

What Is Syncope?

Syncope means fainting.

What Causes Syncope?

People faint most often because of a sudden drop in blood pressure from standing up too fast.

The usual cause is related to not enough blood flow to the brain, so not enough oxygen gets to the brain. Blood collecting in veins in the lower body because of gravity (venous pooling) or straining (Valsalva's maneuver) may prevent blood from reaching the brain. Damaged or stiff blood vessels and abnormal heart rhythms (arrhythmias) may also reduce blood flow.

Low blood pressure, ineffective pumping by the heart because of heart disease (heart failure), or heart valve abnormalities may cause fainting, as can anemia (low red blood cell count), drugs (especially those for high blood pressure), lung diseases, and too much water loss from the body (dehydration).

One type of fainting called vasovagal syncope refers to overstimulation of the vagus nerve, which lowers blood pressure and causes fainting. This type may occur with anxiety, pain, urination, or coughing.

What Are the Symptoms of Syncope?

Symptoms are sudden brief loss of consciousness, and heart rate may be too fast or irregular (palpitations) or too slow.

How Is Syncope Diagnosed?

The doctor will diagnose syncope on the basis of a history of fainting or feeling faint.

The doctor will obtain a medical history, do a physical examination and electrocardiography

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(ECG), and take blood pressure with the person in different positions (lying, sitting, standing, after exercise). Tilt table testing is a test done by specialists when the cause of syncope is unclear. It can check for symptoms with the body in different positions.

Blood sugar (glucose) level and blood count (hematocrit) may be checked.

If an irregular heartbeat is suspected, the doctor may use a Holter monitor, a device worn at home and work to monitor the heart rhythm.

How Is Syncope Treated?

If not enough blood is pumped by the heart, the heart's condition must be checked. The doctor may suggest seeing a heart specialist (cardiologist) for additional tests.

For people with low blood pressure (hypotension) or heart disease, drugs that may be causing fainting are stopped on a trial basis.

DOs and DON'Ts in Managing Syncope:

✓ **DO** keep a record of fainting, for example, it happens when you suddenly stand from being seated.

✓ **DO** eat a proper diet and drink enough fluids. These are needed for avoiding fainting caused by low blood sugar and dehydration.

✓ **DO** sit or lie down if you feel faint, to help improve blood flow to the brain. Drink plenty of fluids once you are able to drink. If you are a diabetic and have low blood sugar, eat something.

✓ **DO** call your doctor if you have fainting with chest pain, shortness of breath, or history of heart disease.

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⦸ **DON'T** ignore any fainting episodes. Call your doctor.

⦸ **DON'T** put yourself in situations such as driving that make your fainting worse.

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- American Heart Association

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MANAGING YOUR

SYNDROME OF INAPPROPRIATE SECRETION OF DIURETIC HORMONE

What Is Syndrome of Inappropriate Secretion of Diuretic Hormone?

Antidiuretic hormone (ADH) is important for normal water balance in the body. Too much ADH leads to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The body can't get rid of water (water retention) and has lower blood sodium levels.

What Causes SIADH?

Causes include many different conditions and drugs. Certain tumors, such as lung cancer, and chronic lung diseases may produce ADH. Common drugs causing SIADH are antidepressants, antianxiety agents, antipsychotic agents, diuretics, and seizure medicines. More advanced cases with very low serum (blood) sodium levels usually occur in hospitalized people who are having surgery or are being treated for brain tumors, seizure disorders, lung cancers, or other chronic conditions.

What Are the Symptoms of SIADH?

Early SIADH has no symptoms. Untreated SIADH may cause lethargy, weakness, seizures, coma, and even death. People with quickly falling serum sodium levels have worse symptoms and possible seizures.

How Is SIADH Diagnosed?

The doctor makes a diagnosis with blood and urine tests that show that the body has too much water in relation to the amount of sodium. Other causes of low sodium levels, such as an underactive thyroid (hypothyroidism) or adrenal insufficiency (Addison's disease), must be ruled out before SIADH can be diagnosed.

How Is SIADH Treated?

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SIADH can be cured by removing the cause (drug or tumor) and by treating the underlying condition. Water restriction is the key to treatment. Less water intake allows serum sodium levels to rise normally. The maximum amount of water that people are allowed to drink is just slightly more than the amount of urine that they produce.

People need regular serum sodium measurements to make sure that water restriction has worked. Some people may need a medicine called demeclocycline. In emergency situations your doctor may prescribe a strong diuretic such as furosemide to help get rid of excess fluids.

DOs and DON'Ts in Managing SIADH:

✓ **DO** restrict the amount of water you drink. This may be the only treatment you need.

✓ **DO** understand the reason for your SIADH. If you treat the underlying cause, SIADH will go away.

✓ **DO** have regular follow-up serum sodium measurements.

✓ **DO** call your doctor if you feel weak or extremely tired, or if you have an illness with a fever.

✓ **DO** call your doctor if you are to have elective surgery.

⃠ **DON'T** assume that you have SIADH just because you have a low blood sodium level. Other disorders must be excluded.

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FOR MORE INFORMATION

Contact the following source:

- American Association of Clinical Endocrinologists Tel: (904) 353-7878 **Website:** **http://www.aace.com**

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MANAGING YOUR

SYPHILIS

What Is Syphilis?

Syphilis is a sexually transmitted infection (STI)/disease (STD) caused by bacteria that can infect the skin, mouth, sex organs, and nervous system.

If found early, syphilis is easy to cure and doesn't cause any lasting damage. Untreated syphilis can cause serious damage to the brain or nervous system and other organs, including the heart.

What Causes Syphilis?

The cause is a bacterium called *Treponema pallidum*. The infection is usually passed by sexual contact. Very rarely, bacteria can be passed through a break or cut in the skin, after a sore on an infected person is touched. If bacteria get near any moist areas or on any cuts or breaks in the skin, syphilis may occur.

Individuals infected with HIV appear to be more prone to contracting and spreading syphilis. Having syphilis once does not make people immune to the infection. They can get it again.

Transmission of syphilis can also occur from a pregnant women to her fetus (congenital syphilis).

What Are the Symptoms of Syphilis?

Syphilis has three stages. Stage one symptoms occur 2 to 4 weeks after infection and include a painless sore (chancre) where bacteria entered the body. This sore often occurs on genitals but can also be seen in the mouth or rectum if these parts were involved in sexual activity with the infected person. It usually heals on its own in 1 to 5 weeks. If the infection is not treated, stage two symptoms begin 6 to 12 weeks later. They include fever, headache, joint pain, loss of appetite, rash (small, red scaly bumps on the penis, vagina, or mouth, and especially on palms and

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soles), sore throat, swollen lymph glands (armpit, groin, neck), and tiredness. This latent stage may last for years with no symptoms.

Stage three symptoms appear 10 to 40 years after the initial infection. They include brain and heart damage, memory problems, paralysis, and balance problems.

Some people with stage two or three syphilis may not have symptoms.

How Is Syphilis Diagnosed?

The doctor makes a diagnosis from the medical history and examination, with attention to sex organs, mouth, and anus. If a syphilitic sore is present, a very small piece of the sore or fluid from the sore will be removed to look for bacteria using a special microscope known as a dark-field microscope. A blood test (known as VDRL) will be done to determine if antibodies (substances produced by the immune system to fight infection against the *Treponema pallidum* bacteria) are present. The doctor will also want to test recent sexual partners.

How Is Syphilis Treated?

Stage one is easy to cure with antibiotics, given as a shot or taken by mouth. People with stage two and stage three disease are given antibiotics for a longer time. Blood is tested after treatment to make sure that the infection is gone.

DOs and DON'Ts in Managing Syphilis:

✓ **DO** tell your doctor if you're pregnant. Transmission of syphilis to the fetus is very dangerous.

✓ **DO** tell your doctor if you have a drug allergy, especially to penicillin.

✓ **DO** wash your hands often to avoid spreading the infection.

✓ **DO** practice safe sex. Use condoms.

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✓ **DO** tell your sexual contacts that you have been treated for syphilis so that they can get tested.

✓ **DO** avoid sex for at least 2 weeks after treatment or until cleared by your doctor.

✓ **DO** get tested for other STDs.

✓ **DO** call your doctor if you have a rash, fever, sore throat, or joint swelling after treatment.

⃠ **DON'T** stop taking your medicine or change the dosage because you feel better unless your doctor says to.

⃠ **DON'T** have sex with anyone until your doctor tells you that you can.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- Infectious Diseases Society of America Tel: (703) 299-0200 **Website:** **http://www.idsociety.org**
- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website:** **http://www.cdc.gov**

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MANAGING YOUR

SYRINGOMYELIA

What Is Syringomyelia?

A watery substance called cerebrospinal fluid flows around the spinal cord and brain. It protects and cushions those areas. It takes nutrients to them and removes wastes. Syringomyelia is a disease of the spine. This cerebrospinal fluid fills a cavity, or cyst (syrinx), in the spinal cord. The cavity grows and can destroy the center of the spinal cord. Sometimes it reaches the brain stem. About 21,000 men and women in the United States have syringomyelia.

What Causes Syringomyelia?

The cause is unclear, but blockage of normal cerebrospinal fluid movement can lead to the disorder. This abnormal flow can result in the abnormal cavity being filled with cerebrospinal fluid. Conditions such as meningitis and bleeding (hemorrhage) can block the fluid. A congenital abnormality called Chiari malformation and birth injuries are risks for syringomyelia. Congenital means present at birth. Cavities forming later in life may result from trauma or brain and spinal cord tumors. Rarely, syringomyelia is inherited.

What Are the Signs and Symptoms of Syringomyelia?

The disorder usually starts slowly, over several months. Symptoms may show up months or years after an injury. Early symptoms affect the back of the neck, shoulders, arms, and hands. They include muscle weakness and wasting (atrophy) and loss of reflexes. The ability to feel pain or extremes of hot or cold, especially in the hands, is lost. This loss may lead to unnoticed burns or other injuries. Other symptoms are pain and stiffness in the back, shoulders, neck, arms, and legs. Bowel and bladder problems may occur. Tingling can go from the trunk into the legs.

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How Is Syringomyelia Diagnosed?

The diagnosis is made from the symptoms, physical examination, and magnetic resonance imaging (MRI). MRI uses a magnetic field to form images of inside the body.

How Is Syringomyelia Treated?

Treatment depends on the cause of the disorder and the person's condition, age, and symptoms. Surgery is usual. Without surgery, syringomyelia often leads to progressive weakness of the arms and legs, loss of hand sensations, and chronic weakness and pain. Surgery often stops worsening of the disorder but doesn't help existing neurologic problems get better. If syringomyelia occurs again after surgery, more operations may be needed. These may not be completely successful.

People without symptoms may not need any treatment. Older people, who could not tolerate surgery, or those without worsening of the condition may be closely monitored rather than treated surgically.

DOs and DON'Ts in Managing Syringomyelia:

✓ **DO** remember that symptoms may not start for several months or years.

✓ **DO** avoid heavy lifting, straining (such as excessive coughing), or putting too much force on your spine (such as playing high-impact sports such as football).

✓ **DO** consider physical therapy to help symptoms.

✓ **DO** manage chronic pain.

✓ **DO** keep your scheduled appointments with your health care provider and specialists. People usually see a neurosurgeon (specialist in diseases of the nervous system).

✓ **DO** call your health care provider if you have muscle weakness, numbness, or loss of feeling

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(touch or temperature). Call if you have headaches or pain or new symptoms after surgery.

⦸ **DON'T** ignore symptoms.

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FOR MORE INFORMATION

Contact the following sources:

- The National Institute of Neurological Disorders and Stroke National Institutes of Health **Website:** **http://www.ninds.nih.gov/health_and_medical/disorders/syringomyelia_short.htm**
- American Syringomyelia & Chiari Alliance Project (ASAP) Phone: 800-ASAP-282 (272-7282) **Website: http://www.asap.org**
- North American Spine Society Phone 708-588-8080 **Website: www.spine.org**

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MANAGING YOUR

SYSTEMIC LUPUS ERYTHEMATOSUS

What Is Systemic Lupus Erythematosus (SLE)?

Systemic lupus erythematosus (SLE) is a disease that causes inflammation in connective tissue and can damage several organs. It can affect joints, skin, lungs, heart, blood vessels, kidneys, nervous system, and blood cells. Some people also have Raynaud's phenomenon, which causes spasms in blood vessels, and pain and discoloration in the fingers, toes, ears, and nose.

SLE affects about 1 in 2000 people, five times more women than men; it is most often diagnosed in people 15 to 40 years old. African Americans and people of Asian and Hispanic ancestry get SLE more often than Caucasians.

No cure exists.

What Causes SLE?

The cause is unknown, but hereditary and environmental factors may increase the risk of having SLE. SLE isn't contagious or transmitted from parent to offspring.

What Are the Symptoms of SLE?

Symptoms depend on which organ is involved. The first ones may be fatigue and joint pain, and swelling or stiffness, usually in hands, wrists, and knees. Joint pain can be severe and interfere with activities and work. People may have a rash on sun exposed parts of the body, often the face (cheeks and nose). This is called a butterfly rash. Raynaud's phenomenon makes fingers change color and become painful when exposed to cold. Some people have pleurisy (inflammation of the lining of lungs), which can make breathing painful, with shortness of breath. Affected kidneys may lead to high blood pressure and kidney failure. SLE may affect memory and mood and cause stress or confusion.

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How Is SLE Diagnosed?

The doctor makes a diagnosis from a medical history, physical examination, and laboratory tests. X-rays may be done. Laboratory tests include an erythrocyte sedimentation rate (ESR), complete blood cell count (CBC), antinuclear antibody (ANA), and urinalysis. The ESR measures inflammation. The CBC counts blood cells and platelets. The doctor may order an anti-DNA test, which is more specific for SLE. The doctor may suggest seeing a rheumatologist (specialist in joint problems).

How Is SLE Treated?

Treatment depends on symptoms and which organs are involved. Medicines help reduce inflammation. Nonsteroidal anti-inflammatory drugs (NSAIDs) are often given first. The doctor may also prescribe prednisone, which works quickly. If they don't help enough, disease-modifying medicines can slow the disease. These include hydroxychloroquine, methotrexate, azathioprine, and cyclophosphamide.

Exercise is important for joint movement and muscle strength.

DOs and DON'Ts in Managing SLE:

- ✔ **DO** tell your doctor if you're pregnant or plan to get pregnant.
- ✔ **DO** have your blood pressure checked and blood tested for diabetes while you're taking prednisone.
- ✔ **DO** see your eye doctor yearly.
- ✔ **DO** get sleep and exercise. Alternating rest and activity helps manage fatigue.
- ✔ **DO** take your medicines as prescribed. Call your doctor if you have medicine side effects.
- ✔ **DO** call your doctor if you have a temperature higher than 101° F, blood in urine or stool, shortness of breath, chest pain, or severe stomach pain.

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⦸ **DON'T** stop taking your medicine or change your dosage because you feel better unless your doctor tells you to.

⦸ **DON'T** give up. If one medicine doesn't work, talk to your doctor about others.

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FOR MORE INFORMATION

Contact the following sources:

- The Arthritis Foundation Tel: (800) 283-7800 **Website:** http://www.arthritis.org.
- Lupus Foundation of America Tel: (301) 670-9292, (800) 558-0121 **Website:** http://www.lupus.org

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MANAGING YOUR

TAPEWORM INFECTION

What Is Tapeworm Infection?

Tapeworms are flatworm parasites that live in different animals such as pigs, cattle, sheep, and fish. Tapeworms can also infect people and live in the intestines. People can eat eggs or baby worms (larvae) in contaminated food or water. Eggs and larvae can pass out of the body with bowel movements (stools). Eggs can also hatch into larvae that move out of the intestines, form cysts in other organs (lungs and liver), and cause serious illness.

People usually get it when traveling to developing countries such as those in Asia, Latin America, or Africa. It isn't common in the United States.

What Causes Tapeworm Infection?

The tapeworm named *Taenia saginata* is found in beef, *Diphyllobothrium* occurs in fish, and *Taenia solium* is found in pork. Eating undercooked meat or fish or drinking contaminated water can lead to infection.

What Are the Symptoms of Tapeworm Infection?

Many times people don't have symptoms. Parts of worms might appear in stools. Symptoms of intestinal infection, when present, include diarrhea, nausea, pain in the upper abdomen (belly), unexplained weight loss, loss of appetite, weakness, and anemia (low blood count).

Symptoms of damage from cysts in other organs include fever and nervous system symptoms (such as seizures if larvae get to the brain).

How Is Tapeworm Infection Diagnosed?

The doctor can find a tapeworm infection through a stool sample. The sample is checked in a laboratory for worm eggs and body parts.

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How Is Tapeworm Infection Treated?

Drugs can kill the tapeworm. One dose is usually all that's needed. When more than just intestines are affected, treatment is more difficult.

After treatment, another stool specimen should be checked in 3 to 6 weeks to make sure that the infection is gone. Activities and diet can remain normal.

DOs and DON'Ts in Managing Tapeworm Infection:

✓ **DO** take your medicine as directed.

✓ **DO** have a follow-up doctor's examination in 3 to 6 weeks.

✓ **DO** have all family members checked for the infection.

✓ **DO** buy only meats that have been inspected.

✓ **DO** cook your beef, pork, and fish so that it's well done (to at least 150° F).

✓ **DO** call your doctor if you have symptoms after treatment.

✓ **DO** use good hygiene. Washing your hands after going to the bathroom will prevent infections.

⊘ **DON'T** miss your follow-up examination.

⊘ **DON'T** eat raw or undercooked meats or fish, especially when traveling in a foreign country.

When traveling, don't eat fruits and vegetables until they're washed and cooked with safe water.

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FOR MORE INFORMATION

Contact the following source:

- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website:**

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MANAGING YOUR

TARDIVE DYSKINESIA

What Is Tardive Dyskinesia?

Tardive dyskinesia is a neurological condition caused by use of medicines called neuroleptics (antipsychotics). Neuroleptic drugs are usually given for psychiatric disorders. They are used to make psychotic symptoms, such as delusions, hallucinations, and bizarre behaviors, less intense and occur less often.

In the United States, tardive dyskinesia is seen most often in people treated for schizophrenia and bipolar disorder. People who have taken neuroleptics can develop movement disorders while taking the medicine or after stopping the medicine. Older people, especially women, have a greater risk of getting tardive dyskinesia.

What Causes Tardive Dyskinesia?

The cause is unknown. Almost half of all people who take neuroleptics for longer than 6 months will get it. The occurrence increases with the age of the person and the longer the medicine is taken. Tardive dyskinesia isn't contagious or passed from parents to children.

What Are the Symptoms of Tardive Dyskinesia?

Symptoms include repeated, involuntary, purposeless movements. These include making grimaces; pushing the tongue out; smacking, puckering, and pursing the lips; and rapidly blinking the eyes. People may also have rapid movements of the arms, legs, fingers, and trunk. Movements usually get worse with emotional stress and when people move with purpose. They decrease with sedation (calming) and during sleep.

How Is Tardive Dyskinesia Diagnosed?

The doctor makes a diagnosis from a detailed medical history and physical examination. No spe-

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cific blood tests are used for diagnosis, but the doctor may order blood tests to rule out other causes of the symptoms. The doctor may also order computed tomography (CT) or magnetic resonance imaging (MRI) to make sure that other medical conditions that have symptoms similar to those of tardive dyskinesia aren't causing the symptoms.

How Is Tardive Dyskinesia Treated?

Treatment is mainly directed at prevention by using the lowest possible dose for the shortest time. If tardive dyskinesia does occur, treatment then focuses on reducing the dosage of the medicine or stopping the medicine completely. Some drugs, such as levodopa, benzodiazepines, and botulinum toxin, have been used to relieve symptoms of tardive dyskinesia, but with limited success.

DOs and DON'Ts in Managing

Tardive Dyskinesia:

- ✓ **DO** realize if you're being treated with neuroleptics and develop tardive dyskinesia, you and your doctor must decide whether you should stop taking the drugs and maybe avoid getting a permanent movement disorder. However, you could then have worse psychotic symptoms.
- ✓ **DO** ask your doctor about the newer atypical neuroleptics such as clozapine, olanzapine, quetiapine, and risperidone. All these drugs can be related to tardive dyskinesia, but tardive dyskinesia may occur less often with these atypical neuroleptics than with the traditional neuroleptics.
- ✓ **DO** call your doctor if you develop involuntary repeated movements and are taking a neuroleptic drug.
- ✓ **DO** call your doctor if you've reduced your medicine and you notice worsening psychotic

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symptoms (e.g., delusions and hallucinations).

⦸ **DON'T** forget that tardive dyskinesia can also show up after stopping the use of neuroleptic medicines.

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FOR MORE INFORMATION

Contact the following sources:

National Institute of Mental Health Tel: (866) 615-6464 **Website:** **http://www.nimh.nih.gov**

National Alliance on Mental Illness Tel: (800) 950-6264 **Website:** **http://www.nami.org/**

American Psychiatric Association Tel: (888) 357-7924 **Website:** **http://www.psych.org**

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MANAGING YOUR

TARSAL TUNNEL SYNDROME

What Is Tarsal Tunnel Syndrome?

Tarsal tunnel syndrome is an uncommon condition that causes burning pain along the inside of the ankle and down into the bottom of the foot. It's a type of nervous system disorder called compression neuropathy. The name is similar to carpal tunnel syndrome which affects the upper extremities, but it's much less common.

What Causes Tarsal Tunnel Syndrome?

The cause is usually pressure (compression) on the tibial nerve or its branches that travel down the inside of the ankle and into the bottom of the foot. This compression can result from trauma from crushing injuries, fractures, and severe ankle sprains. Other reasons for the syndrome are local tumors and foot abnormalities.

What Are the Signs and Symptoms of Tarsal Tunnel Syndrome?

Symptoms include sharp pain, numbness, or tingling inside the ankle that goes into the bottom of the foot. Loss of feeling can occur. Pain is worse at night, during movement, and while standing, walking, or wearing certain shoes. It gets better after resting. Symptoms usually come and go. Sometimes the nerve loses function, but paralysis of the foot usually doesn't occur. Walking can become abnormal. This painful condition begins to limit the ability to walk or stand for long periods.

How Is Tarsal Tunnel Syndrome Diagnosed?

The health care provider makes a diagnosis from the medical history, physical examination, and sometimes electrical nerve testing, such as electromyography (EMG). As part of the physical examination, the health care provider taps or feels (palpates) the tibial nerve, which can cause

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tingling. X-rays may be done to rule out similar disorders. The health care provider may suggest seeing a specialist (orthopedic surgeon or podiatrist) for additional evaluation and treatment.

How Is Tarsal Tunnel Syndrome Treated?

Treatment includes rest, elevating the extremity, and injections of corticosteroids to reduce inflammation (swelling) around the nerve. Antiinflammatory drugs can sometimes help. No vitamins, diets, or exercises can effectively reduce pressure on the nerve once it occurs. Shoes and activities should be checked and changes made if needed. Shoe inserts called orthotics can help pain because they help redistribute weight and take pressure off the nerve. If these treatments don't work, surgery to release the nerve can be done. If the syndrome is caused by known conditions such as local tumors, it may respond better to surgery than when the syndrome has no clear cause. Surgery involves risks, including failure to relieve pain and recurrence of pain after surgery. Scarring around the nerve after an operation is common and can lead to long-term problems. Also, nerve damage that can't be reversed can occur. Recovery can take months.

DOs and DON'Ts in Managing Tarsal Tunnel Syndrome:

✓ **DO** call your health care provider if your symptoms change from intermittent to constant.

✓ **DO** take your medicines as prescribed.

✓ **DO** rest and elevate your leg.

✓ **DO** clean and check your feet regularly.

✓ **DO** wear shoes that fit properly, and don't wear the same pair every day. Wear the right shoes for the specific activity (such as running shoes for running).

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⦸ **DON'T** do activities or exercise that makes the condition worse.

⦸ **DON'T** ignore foot pain.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopedic Surgeons Phone: 847-823-7186 **Web www.aaos.org**
- American College of Rheumatology Phone: 404-633-3777 **Website:**

  www.rheumatology.org
- American Physical Therapy Association Phone: 800-999-2782 **Website: www.apta.org**

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MANAGING YOUR

TEMPORAL ARTERITIS (GIANT CELL ARTERITIS)

What Is Temporal Arteritis?

Temporal arteritis (TA) is inflammation and damage to arteries supplying blood to the temples. Arteries are blood vessels taking oxygen-rich blood from the heart to the body. Usually arteries in the head, at the temples, are inflamed. Inflammation affecting medium-sized and large vessels in the neck, upper body, and arms is known as giant cell arteritis (GCA). Inflammation can lead to narrowing and sometimes complete blockage of arteries. Almost all cases occur in people older than 50. Serious complications include permanent blindness. Women have it two to three times more than men.

What Causes TA?

The cause isn't known but may be an abnormal immune (infection-fighting) system response. TA may run in families. Another disorder called polymyalgia rheumatica often occurs with TA. Polymyalgia rheumatica causes stiffness and aching in the back, shoulders, and hips. These disorders are much more common is the elderly.

What Are the Signs and Symptoms of TA?

Symptoms include headaches on the sides or back of the head and scalp tenderness (hurts to comb hair). Others are sudden, painless vision loss; blurred or double vision; jaw pain; and in some cases, malaise and weight loss. Throbbing or continuous pain can be mild and overlooked. Flu-like symptoms (fever, tiredness, muscle aches, sweating, loss of appetite) can occur. Blindness and stroke are the most serious complications.

How Is TA Diagnosed?

The doctor does a complete physical examination, especially of the head, musculoskeletal and

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nervous systems, and a special blood test (erythrocyte sedimentation rate, or ESR) that measures inflammation. The only way to confirm the diagnosis is to take a sample (biopsy) of the temporal artery. The doctor removes a small piece of artery and checks it with a microscope. More than one sample may be needed.

How Is TA Treated?

TA is a chronic, self-limiting condition often lasting up to 2 years. Corticosteroids such as prednisone are given, usually on an outpatient basis, for inflammation. Because immediate treatment is needed to prevent optic neuropathy with vision loss, the doctor may prescribe medicine before the biopsy confirms the diagnosis. For visual or neurologic symptoms, higher steroid doses may be given at first. Symptoms usually improve in 1-3 days. This therapy may last for 1-2 years. People with vision loss or impairment can receive intravenous corticosteroids. The long treatment can lead to corticosteroid-induced complications.

DOs and DON'Ts in Managing TA:

- ✓ **DO** take medicines as prescribed. Don't change your dosage or stop the medicine unless your doctor tells you to.
- ✓ **DO** eat a healthy diet and exercise regularly, 30 minutes on most days. Walking and jogging have many benefits.
- ✓ **DO** learn everything you can about TA and its treatment. You can feel more in control of your condition.
- ✓ **DO** understand prednisone's side effects. Long-term use can cause cataracts, peptic ulcer disease, osteoporosis, diabetes, and hypertension.

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⦸ **DON'T** miss follow-up doctor visits. Your doctor must monitor your symptoms and do blood tests (ESR).

⦸ **DON'T** ignore vision problems. Blindness can occur in people with TA.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Family Physicians Tel: (800) 274-2237 **Website: http://www.aafp.org**
- American College of Rheumatology Tel: (800) 633-3777 **Website: http://rheumatology.org**

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MANAGING YOUR

TEMPOROMANDIBULAR JOINT SYNDROME

What Is Temporomandibular Joint Syndrome?

The temporomandibular joints (TMJs) are the two joints near the ears that let the jaw open and close. TMJ syndrome is a common condition with pain around the TMJ and muscles that control chewing. It affects 40 to 70 people of every 1000, women more often than men.

What Causes TMJ Syndrome?

Causes include clenching the jaw or grinding the teeth, especially under stress; poorly aligned teeth; and badly fitting dentures. TMJ syndrome can also be caused by arthritis and injury to the jaw, head, or neck.

What Are the Symptoms of TMJ Syndrome?

The most common symptom is a dull, aching pain that affects the side of the head and along the jawline. Also, tenderness in muscles used to chew, clicking or popping sounds when opening the mouth, and being unable to open the jaw fully may occur. More symptoms include headache, earache, mouth and facial pain, and ringing or buzzing in the ear.

How Is TMJ Syndrome Diagnosed?

The doctor will make a diagnosis from symptoms and an examination of the face and jaw. Tests may include checking the range of motion of the jaw and sometimes x-rays. Other types of imaging such as magnetic resonance imaging (MRI) and arthroscopy may be done. In arthroscopy, the doctor examines the jaw with a lighted tube.

How Is TMJ Syndrome Treated?

In some people, symptoms of TMJ disappear on their own. In others, conservative medical treatment and medications may be effective. Different medicines, both over-the-counter and pre-

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scription, can provide pain relief. Antiinflammatory medicine and applying heat or ice will lessen the pain. A soft diet that requires less vigorous chewing will reduce strain and fatigue in jaw muscles.

Teeth and jaw problems can be corrected by braces or wearing a splint or a bite plate to prevent teeth grinding. The dentist can provide a mouthpiece to prevent jaw clenching, especially at night. Some people need a dental examination to see whether alignment of the teeth or jaw is correct. Jaw exercises can help relax the jaw. If stress is part of jaw clenching and teeth grinding, counseling or special therapy may help.

Sometimes pain management methods such as acupuncture and transcutaneous electrical nerve stimulation (TENS) are useful. In TENS, a gentle electrical current is applied to the skin's surface. Acupuncture involves putting tiny needles into special points in the body.

Rarely, for severe pain and treatment failure, jaw surgery may be needed.

DOs and DON'Ts in Managing TMJ Syndrome:

✓ **DO** eat a soft diet if necessary.

✓ **DO** use heating pads or ice packs for discomfort.

✓ **DO** massage the area under your jaw.

✓ **DO** take your medicines as prescribed.

✓ **DO** use your prescribed mouthpiece.

✓ **DO** call your doctor if you have medicine side effects.

✓ **DO** call your doctor if the treatment doesn't help symptoms in a reasonable amount of time.

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✓ **DO** call your doctor if your jaw locks open or closed.

⃠ **DON'T** do too much chewing, such as with chewing gum.

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FOR MORE INFORMATION

Contact the following sources:

- The TMJ Association Tel: (262) 432-0350 **Website:** **http://www.tmj.org**
- National Institute of Dental and Craniofacial Research Tel: (301) 496-4261 **Website:** **http://www.nidr.nih.gov**
- American Chronic Pain Association Tel: (916) 632-0922, (800) 533-3231 **Website:** **http://www.theacpa.org**
- American Dental Association Tel: (312) 440-2500 **Website:** **http://www.ada.org**

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MANAGING YOUR

TENDINITIS

What Is Tendinitis?

Tendinitis is irritation, inflammation, pain, and swelling of a tendon. Tendons connect muscles to bones at joints. Injury, trauma, or stress to parts of the body with muscles and tendons can cause tendinitis. It's a common cause of pain in shoulders, elbows, wrists, and ankles in active people. Tendinitis is certain places has specific names, such as tennis elbow, golfer's elbow, rotator cuff tendinitis (shoulder), and Achilles tendinitis (ankle).

What Causes Tendinitis?

Tendinitis usually results from overuse or abnormal use of a tendon or muscle. Overworking the tendon in a job or injuring it during sports can lead to tendinitis. Other causes include aging-related wear and tear, injury, and inflammatory diseases such as arthritis. Most often, tendinitis occurs in the shoulder, but it can occur in any joint, in any tendon.

What Are the Symptoms of Tendinitis?

Symptoms include pain, discomfort, trouble using the involved joint, and tenderness. The area may be red, swollen, and hot to the touch. The area may feel stiff in the morning for a short time. In more severe cases, movement of the joint can be restricted. Pain is worse during activities, and gets better with resting the area. Depending on its location, tendinitis may make it hard to do everyday activities, such as dressing, grooming, reaching, lifting, writing, and walking.

How Is Tendinitis Diagnosed?

The doctor makes a diagnosis by taking a medical history and doing a physical examination of the painful area. X-rays and blood tests are generally not useful.

How Is Tendinitis Treated?

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Treatment includes using rest, ice, heat, strengthening and stretching exercises, splints, acetaminophen or nonsteroidal antiinflammatory drugs (NSAIDs), ultrasonography, and cortisone injections. Treatments are often used in combination.

If tendinitis occurred suddenly, within a few hours or days, an ice pack can be used for 15 to 20 minutes at a time, but is usually helpful only during the first few days. The affected area is kept raised, and pressure bandages are applied. The ice pack should not be put directly on the skin. For tendinitis that has lasted for a while, applying heat may help.

The doctor may suggest seeing a physical therapist or an occupational therapist. The physical therapist will provide an exercise program to make the tendon stronger and more flexible. If the problem is work related, an occupational therapist can advise how to prevent injuring the area again.

In very rare cases, surgery may be needed when all other treatments don't work.

DOs and DON'Ts in Managing Tendinitis:

✓ **DO** stop the activity that caused the tendinitis right away.

✓ **DO** rest the affected area.

✓ **DO** take your medicines as prescribed.

✓ **DO** your exercises as prescribed.

✓ **DO** call your doctor if you have side effects from your medicine.

✓ **DO** call your doctor if the treatments don't help the pain.

⃠ **DON'T** put ice or heat directly on the skin.

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⦸ **DON'T** stop the treatment prescribed because you feel better unless your doctor tells you to.

⦸ **DON'T** continue an exercise program that causes excessive or prolonged pain. If you get more pain, the program needs to be changed specifically for you.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American College of Rheumatology Tel: (404) 633-3777 **Website:** **http://www.rheumatology.org**
- Arthritis Foundation Tel: (800) 283-7800 **Website:** **http://www.arthritis.org**
- National Institute of Arthritis and Musculoskeletal and Skin Diseases Tel: (877) 226-4267 **Website:** **http://www.niams.nih.gov**

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MANAGING YOUR

TENNIS ELBOW

What Is Tennis Elbow?

Tendons attach muscles to bones. The elbow has an upper arm bone (humerus) and two bones in the forearm (ulna and radius). Bony bulges on the inside and outside of the elbow are the epicondyle part of the upper bone. Tendons of forearm muscles, responsible mainly for flexing and extending the wrist, attach to these bulges.

Inflammation of the outer tendons (for extending the wrist) has the medical name lateral epicondylitis. The common name "tennis elbow" is used because the problem often results from playing tennis or similar repetitive motion. Inflammation of inner tendons (for flexing the wrist) is medial epicondylitis, or "golfer's elbow."

What Causes Tennis Elbow?

The usual cause is overusing the arm, often related to work or sports. Carpenters, factory workers, musicians, and cashiers, who use their hands repeatedly, can have this problem. An injury, such as from lifting something that's too heavy, can also cause it.

What Are the Symptoms of Tennis Elbow?

The forearm becomes tender and painful. Burning feelings going down the arm from the elbow also occur. Pain may first be felt only when using the arm, but later pain may be constant, even at rest. The hand grip may be weak, and it may be hard to lift or grasp objects, or to do simple tasks (writing, brushing teeth).

How Is Tennis Elbow Diagnosed?

The doctor makes a diagnosis by the medical history and physical examination (shoulder, arm, and wrist). Resistance against extending the wrist or flexing it can bring on pain.

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The doctor may order other tests or x-rays to rule out other conditions with similar symptoms. These conditions include arthritis, cervical spine disease, neuropathy, and pinched nerve. The doctor may also order magnetic resonance imaging (MRI) to get pictures of inflamed tendons and to rule out a ruptured tendon.

How Is Tennis Elbow Treated?

Treatment involves rest and restricting activities that may have started the problem. Using ice after exercise and rest and special stretching and strengthening exercises often help. People should also lift objects with their palms facing upward to decrease stress on the elbow.

Wrapping the elbow with an elastic sleeve keeps the arm warm and helps flexibility. A physical therapist may oversee treatment and prescribe ultrasound treatment.

The doctor may prescribe antiinflammatory medicines (ibuprofen, naproxen).

If the pain continues, cortisone injections can be tried.

DOs and DON'Ts in Managing Tennis Elbow:

✓ **DO** stop the activity causing the pain for 1-2 weeks, or maybe longer, depending on your doctor's advice.

✓ **DO** massage your arm as your doctor tells you.

✓ **DO** follow the program that your physical therapist gives you.

✓ **DO** call your doctor if treatment doesn't help symptoms.

✓ **DO** call your doctor if you need a referral to an orthopedic surgeon (a specialist in musculoskeletal diseases).

✓ **DO** call your doctor if you have side effects from medicines.

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✓ **DO** take frequent breaks if your problem is work related. Get information about performing tasks safely.

⃠ **DON'T** perform any activity that involves extending or rotating the wrist.

⃠ **DON'T** apply chemical cold packs directly to your skin.

⃠ **DON'T** forget that muscles need to stay warm during sporting events. Always loosen up before activities.

⃠ **DON'T** use sporting equipment that is too large or too small.

⃠ **DON'T** overdo sports or activities.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- Arthritis Foundation Tel: (800) 283-7800 **Website:** http://www.arthritis.org
- Nicholas Institute of Sports Medicine and Athletic Trauma **Website:** http://www.nismat.org
- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website:** http://www.aaos.org

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MANAGING YOUR

TENSION HEADACHE

What Is Tension Headache?

Tension headaches are dull, aching, or throbbing headaches, often with feelings of fullness, tightness, or pressure. A feeling that the head will burst or is bound or clamped in a vise can occur. Both sides of the head and neck are usually affected, especially where neck muscles attach to the skull. These headaches also involve the forehead and temples.

What Causes Tension Headache?

The exact cause of tension headaches is unknown. Possible triggers can be stress, not enough or too much sleep, eating or drinking too much, work, anxiety, depression, eye strain (including sun glare), drugs, alcohol, allergies, food additives, fumes, and chemicals. Women can also get headaches more frequently because of hormone changes.

What Are the Symptoms of Tension Headache?

Symptoms include moderate pain in front or back of the head, neck or scalp tightness, constant pain over sides of the head (like a clamp), throbbing pain all over the face, head pain on awakening, and head pain that interrupts sleep.

How Is Tension Headache Diagnosed?

Tests aren't usually needed. The doctor will ask about headaches and other symptoms and will do a physical examination, especially a neurological examination. More tests such as MRI of the brain may be done to check for other possible problems or when the diagnosis is unclear.

How Is Tension Headache Treated?

The best way to stop these headaches is to avoid the cause if it's known.

Over-the-counter medications (aspirin or acetaminophen) can usually relieve pain.

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If headaches are due to stress, self-help activities such as yoga, exercise, tai chi, relaxation, and biofeedback may help control the stress. Counseling may be suggested for emotional problems, anxiety, or depression.

Tension headaches may respond to massage, relaxation, and antianxiety medicines. Some people may need prescription medicine.

DOs and DON'Ts in Managing Tension Headache:

✓ **DO** stop what you're doing and try to relax when a headache occurs.

✓ **DO** massage your shoulders, neck, jaw, or scalp.

✓ **DO** take a hot bath or shower.

✓ **DO** place a warm or cold cloth over your forehead.

✓ **DO** keep a diary of your headaches.

✓ **DO** follow a healthy lifestyle. Eat regular meals. Get enough sleep. Exercise regularly.

✓ **DO** call your doctor if your symptoms are worse or last longer than usual, your usual medicine doesn't work, or you have a fever, vomiting, or change in vision.

✓ **DO** call your doctor if you have problems with your medicine.

⃠ **DON'T** skip breakfast.

⃠ **DON'T** smoke or be in a smoky environment.

⃠ **DON'T** expose yourself to chemicals.

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⦸ **DON'T** drink alcohol in excess. Avoid stimulants such as caffeine.

⦸ **DON'T** take drugs not prescribed by your doctor.

⦸ **DON'T** eat foods containing nitrates (such as hot dogs) or other additives that may cause sensitivity.

⦸ **DON'T** overuse prescription or over-the-counter pain pills, which can cause a rebound headache.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- National Headache Foundation Tel: (888) 643-5552 **Website:** http://www.headaches.org
- American Council for Headache Education Tel: (800) 255-ACHE (255-2243) **Website:** http://www.achenet.org

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MANAGING YOUR

TESTICULAR CANCER

What Is Testicular Cancer?

Testicles (testes) are male sex glands that make and store sperm. Testicular malignancies are cancers that start in one of the testicles. About 7500 new cases are diagnosed each year in the United States. Most occur in men between 15 and 40 years old.

What Causes Testicular Cancer?

The cause is unknown. Men with a greater chance of getting it include those born with an undescended testicle and those who have fathers or brothers with testicular cancer. Testicular cancer isn't contagious.

What Are the Symptoms of Testicular Cancer?

The most common first symptom is a painless lump or swelling on or around the testicle. Other symptoms are a feeling of fullness or heaviness in the scrotum (the sac or pouch that holds the testicles), swollen lymph glands (nodes) in the groin or thigh, back pain, and testicular or scrotal pain.

How Is Testicular Cancer Diagnosed?

The best way to find testicular cancer is by doing self-examination of the testicles. A doctor will diagnose testicular cancer by doing a physical examination (including testicles) and ordering an ultrasound scan to find the mass. Ultrasound uses sound waves to see inside testicles; it's painless and harmless. If ultrasound shows a mass (lump), a urologist will operate to remove the testicle.

Then, staging is done to find out how far the disease has spread. Staging involves blood tests, computed tomography (CT), and possibly surgery to remove lymph nodes (called retroperitoneal

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lymph node dissection, or RPLND).

Stage I disease means the cancer is only in the testicle. Stage II disease has spread to nearby lymph nodes. Stage III disease has spread far from the testicles.

How Is Testicular Cancer Treated?

Treatment depends on the type of cancer (seminomatous or nonseminomatous) and its stage. Seminomatous tumors without spread are treated with radiation. With distant spread, chemotherapy is used.

Surgery (RPLND) is used for early-stage nonseminomatous tumors. For more advanced disease, chemotherapy is added.

Having one testicle removed shouldn't affect having sex or children.

Almost 90% of newly diagnosed testicular cancers are curable. Even cancers that spread have very good cure rates of 70% to 80%.

DOs and DON'Ts in Managing Testicular Cancer:

✓ **DO** ask your doctor if you need to save sperm for the future.

✓ **DO** learn and perform testicular self-examinations twice monthly.

✓ **DO** ask about emotional support groups.

✓ **DO** call your doctor if you feel a lump on your testicle.

✓ **DO** call your doctor if you have swelling or pain in your testicle.

✓ **DO** call your doctor if you have a fever after chemotherapy.

✓ **DO** call your doctor if you have excess drainage from the surgical area.

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⦸ **DON'T** stop taking medicine or change dosage because you feel better unless your doctor says to.

⦸ **DON'T** have sex until your doctor says you can.

⦸ **DON'T** miss follow-up doctor appointments. These are important to monitor for recurrence of the cancer.

⦸ **DON'T** forget to do self-examinations on the remaining testicle; it may also get cancer.

⦸ **DON'T** be afraid to ask about sex.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Cancer Society Tel: (800) ACS-2345 (227-2345) **Website:** **http://www.cancer.org**
- National Cancer Institute Tel: (800) 422-6237 **Website:** **http://www.cancer.gov**

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MANAGING YOUR

TESTICULAR TORSION

What Is Testicular Torsion?

Testicular torsion is a painful condition that occurs when the testicle twists on the end of the spermatic cord. This cord holds blood vessels that supply the testicle with blood. This corkscrew-like twisting cuts off the testicle's blood supply. If the testicle stays tightly twisted, it will be damaged and could die.

Testicular torsion occurs most often in young men between 12 and 20 years old and it's also common in newborn babies, but it can happen at any age. It's rare, occurring in 1 in 5000 males. It can occur suddenly, for no reason, or following trauma, and is a medical emergency.

What Causes Testicular Torsion?

Before birth, testicles start to develop inside the abdomen (belly). As the fetus grows, testicles move down until they are inside the scrotum. Testicles stay attached to the abdomen by the spermatic cord and are fixed to tissues around them. Sometimes, the attachment is too loose and the testicle hangs too freely on the spermatic cord. Testicular torsion is more common in men with this problem, but it can occur without any abnormality.

What Are the Symptoms of Testicular Torsion?

Symptoms are sudden severe pain in the testicle and sometimes lower abdominal pain with nausea. The testicle can be swollen, tender to touch, and drawn up toward the abdomen.

How Is Testicular Torsion Diagnosed?

The doctor will take a medical history and do a physical examination. Ultrasonography or a nuclear scan will be done to confirm the diagnosis and rule out other disorders. The scan shows low blood flow to the testicle if torsion exists.

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How Is Testicular Torsion Treated?

Immediate surgery must be done to prevent permanent damage to or loss of the testicle. Surgery untwists the testicle and the spermatic cord and puts them back in their normal positions. If surgery is delayed longer than 4 to 6 hours after the pain started, the testicle may not survive. The other testicle is often fixed to prevent similar torsion. If the testicle hasn't survived, it's removed (called orchiectomy). If the other testicle is healthy and not removed, sex life and the ability to father children won't be affected.

After surgery, bed rest and wearing scrotal support or a jock strap (for swelling or discomfort) may be needed. Lifting heavy items or playing contact sports should be avoided. Sex can be resumed when it's comfortable.

DOs and DON'Ts in Managing Testicular Torsion:

✓ **DO** get medical help right away if you have sudden severe pain or swelling in the testicles or if your symptoms come back after surgery. The testicle can twist again.

✓ **DO** call your doctor if you feel a lump on your testicle.

✓ **DO** call your doctor if you have fever, bleeding, or pain after surgery.

⃠ **DON'T** ignore a painful testicle, delay getting medical advice, or be embarrassed! This condition is a medical emergency and needs surgery quickly, within several hours, or the testicle may die. The surgeon will take your condition seriously.

⃠ **DON'T** miss follow-up appointments with the urologist (specialist in urinary problems) after surgery.

⃠ **DON'T** be misled. The loss of one testicle does not mean loss of erections, orgasms, or abil-

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ity to father children.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- American Urological Association Tel: (866) 746-4282 **Website:**

http://www.urologyhealth.org/

- National Institutes of Health Tel: (301) 496-4000 **Website: http://www.nih.gov**

- American Academy of Family Physicians Tel: (800) 274-2237 **Website:**

http://www.familydoctor.org/

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MANAGING YOUR

TETANUS

What Is Tetanus?

Tetanus is a disease caused by a type of bacteria named *Clostridium tetani*. These bacteria occur worldwide and are found primarily in the soil. The bacteria produce poison that damages nerves. Muscles controlled by these nerves become stiff or locked in place. Locked muscles in the face is why tetanus is also called lockjaw. If not treated quickly, the disease can be fatal, such as when muscles used for breathing stop working. Types of tetanus include generalized, localized, and neonatal (in newborns).

Tetanus isn't contagious, and vaccination can prevent it.

What Causes Tetanus?

Contamination of a wound, usually following a puncture wound, with bacterial spores causes the disease. Spores enter the wound, multiply, and make a toxin (poison) that binds to nerve endings. The toxin reaches the spinal cord and base of the brain. The toxin blocks chemical signals from the brain and spinal cord to muscles. Muscles have severe spasms, breathing can stop, and death can occur. Neonatal tetanus usually results from infection of the umbilical cord stump.

What Are the Symptoms of Tetanus?

Generalized tetanus is most common. Muscles get rigid and painful spasms occur about 7 days after the injury. Affected muscles are most often in the jaw, neck, shoulder, back, abdomen (belly), arm, and thigh. Muscles of the face contract, so the face has a grimace. Some people get violent, painful, generalized muscle spasms. The illness may be mild (rigid muscles with few spasms), moderate (lockjaw and trouble swallowing), or severe (violent spasms and breathing cessation).

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Localized tetanus is not common. Symptoms occur in muscles near the wound.

How Is Tetanus Diagnosed?

The doctor diagnoses tetanus by doing a physical examination, especially of muscles and nerves. The doctor may rub a swab on the wound and send it to a laboratory. It will be checked for tetanus bacteria. Blood tests may also be done.

Diagnosis of neonatal tetanus is based on symptoms in a newborn.

How Is Tetanus Treated?

The doctor treats tetanus by removing the toxin source, making toxin harmless, preventing and treating muscle spasms, and providing support.

All wounds must be cleaned and dead tissue removed. Antibiotics will be given to kill bacteria.

Antitoxin called human tetanus immunoglobulin is injected, to make the toxin harmless.

Drugs such as diazepam and lorazepam will control spasms.

A breathing machine may be needed by people with lockjaw, those who have trouble swallowing, and those with muscle spasms.

Tetanus may last for a 2 to 3 months. Complete recovery can take up to 4 months. Physical therapy will help make muscles strong again.

DOs and DON'Ts in Managing Tetanus:

✓ **DO** clean wounds with soap and water right away.

✓ **DO** call your doctor if you have a wound and don't know if you need tetanus vaccine.

✓ **DO** call your doctor if you have muscle spasms, trouble swallowing, or trouble breathing.

✓ **DO** vaccinate your children; start vaccination in babies at 2 months. Stay up-to-date with

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tetanus vaccines. Adults should have booster shots every 10 years.

✓ **DO** call your doctor if you need a tetanus booster.

⃠ **DON'T** ignore any wounds.

⃠ **DON'T** forget that the best treatment is prevention by vaccination.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following source:

- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website:** **http://www.cdc.gov**

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CARING FOR YOUR CHILD WITH

TETRALOGY OF FALLOT

What Is Tetralogy of Fallot?

Tetralogy of Fallot is a heart abnormality that is present at birth (congenital). The heart is a muscular pump with four chambers, two upper (left and right atria) and two lower (left and right ventricles). These contract and pump blood. A muscular wall (septum) separates the ventricles.

Tetralogy of Fallot has four features: (1) a hole between the ventricles called ventricular septal defect (VSD); (2) blocked flow of blood leaving the right ventricle (infundibular pulmonary stenosis); (3) an enlarged, thickened right ventricle; and (4) an aorta that gets mixed blood from both ventricles because it sits directly over the VSD (overriding aorta). The aorta is the main artery bringing oxygen-rich blood from the heart to the body. The hole lets blood mix between ventricles, and pressure building in the right ventricle makes that ventricle larger. Blood without enough oxygen reaches body cells, causing a bluish tinge (cyanosis) of the lips, nails, and other body tissues.

What Causes Tetralogy of Fallot?

The cause is unknown.

What Are the Symptoms of Tetralogy of Fallot?

As a result of the blocking of blood flow from the right ventricle to the lungs, oxygen-poor blood is shunted (switched) from the right ventricle through the VSD to the left ventricle. The most common symptom is cyanosis, when lips, nail beds, ears, and cheeks turn blue. Some children squat after exercise, which reduces the amount of oxygen-poor blood shunting from the right ventricle to the left. Other symptoms include shortness of breath with exertion, weakness, fainting (syncope), clubbing of fingers, and heart murmurs. A heart murmur is a sound that the doctor

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hears with a stethoscope.

How Is Tetralogy of Fallot Diagnosed?

The doctor may suspect the diagnosis in any infant or child who has cyanosis and a heart murmur. The initial test is echocardiography, which uses sound waves to get pictures of the heart and its blood flow. The doctor will also order blood tests, electrocardiography (ECG), and chest x-rays. After the doctor makes the diagnosis, a heart catheterization may be done. In this test, a thin tube is put into a leg vein and passed up to the heart to measure pressure, oxygen levels, and degree of blood shunting among heart chambers.

How Is Tetralogy of Fallot Treated?

Surgery is the treatment of choice for almost all children with the abnormality. Surgery involves closing the VSD with a patch and relieving the blockage of blood flow from the right ventricle to the lungs.

DOs and DON'Ts in Managing Tetralogy of Fallot:

✓ **DO** realize that tetralogy of Fallot isn't very common.

✓ **DO** consult with a doctor specializing in heart diseases of children (pediatric cardiology).

✓ **DO** understand that children with tetralogy of Fallot need antibiotics before any dental work or surgery on the bowel or bladder to prevent heart infections.

✓ **DO** remember that fewer than 3% of people with this disorder reach age 40 without having surgery.

✓ **DO** call your doctor if your child has cyanosis or trouble breathing.

⦸ **DON'T** forget that nearly 40% of people with this tetralogy will have other heart abnormali-

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ties, such as atrial septal defect (a hole between the right and left atria) and lack of a pulmonary artery.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Cardiology Tel: (800) 575-9355 **Website: http://www.acc.org**
- American Heart Association Tel: (800) 242-8721 **Website: http://www.americanheart.org**

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MANAGING YOUR

THORACIC OUTLET SYNDROME

What Is Thoracic Outlet Syndrome?

Thoracic outlet syndrome consists of symptoms caused when nerves or blood vessels in the brachial plexus are compressed (squeezed). The brachial plexus is the space between the collarbone and first rib, where nerves and blood vessels pass into the arms from the neck. Symptoms depend on whether the nerves, artery, or vein is compressed. The artery takes blood away from the heart. The vein takes blood back to the heart. The nerve is affected most, 95% of the time. The syndrome is more common in women 20 to 50 years old. It's rare in people younger than 20.

What Causes Thoracic Outlet Syndrome?

Causes include an abnormal muscle position, an abnormal congenital rib in the neck, blood clots, and abnormalities of the first rib. Shoulder and collarbone problems from injuries, trauma, or carrying heavy backpacks for long periods can cause it. The syndrome isn't passed from parents to children and isn't contagious.

What Are the Symptoms of Thoracic Outlet Syndrome?

Symptoms include pain in the shoulder, arm, or hand, or in all three. Hand pain is often worst in the fourth and fifth fingers. Fingers can get numb and tingle, and the grip can get weak. Pain gets worse with use of the arm, and the arm often gets tired.

The artery or vein is rarely affected alone. Artery compression causes a pale skin color, coolness, and numbness of the arm. Vein compression causes swelling and pain of the arm.

How Is Thoracic Outlet Syndrome Diagnosed?

The doctor makes a diagnosis with the medical history, physical examination, blood tests, X-

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rays, and special imaging scans. Scans may include chest computed tomography (CT), mainly to rule out other disorders. Arteriography or venography may be done. In arteriography, dye is injected into the artery. In venography, dye is injected into the vein.

How Is Thoracic Outlet Syndrome Treated?

Treatment aims to fix abnormalities in posture that may contribute to compression and to develop an exercise program to strengthen shoulder muscles. Treatment of nerve compression is usually conservative. Surgery may be done for vascular or major nerve difficulties, but it's used for only a few people. In certain cases (e.g., compression of the vein with a blood clot), the doctor may suggest using a blood thinner called warfarin to prevent more clots.

DOs and DON'Ts in Managing Thoracic Outlet Syndrome:

✓ **DO** realize that thoracic outlet syndrome isn't very common.

✓ **DO** understand that in the most cases, recommended treatment will involve a conservative approach with special exercises to strengthen your shoulder and posture.

✓ **DO** call your doctor if you have arm pain; a cold, pale extremity; or numbness and swelling of your arm.

✓ **DO** call your doctor if you need a referral to a specialist.

⃠ **DON'T** put heavy objects (e.g., backpacks) on your shoulders for long periods.

⃠ **DON'T** miss follow-up doctor appointments. You may see a vascular surgeon, physical therapist, and neurologist. A vascular surgeon specializes in diseases of the circulatory system. A physical therapist specializes in exercise treatment of musculoskeletal and neurologic disorders. A neurologist specializes in diseases of the nervous system.

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FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- The National Institute of Neurological Disorders and Stroke National Institutes of Health

  Website: http://www.ninds.nih.gov/health_and_medical/disorders/thoracic_doc.htm

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MANAGING YOUR

THROMBOANGIITIS OBLITERANS (BUERGER'S DISEASE)

What Is Thromboangiitis Obliterans?

Thromboangiitis obliterans, also known as TAO or Buerger's disease, is a disease of small and medium-sized blood vessels of the arms and legs. Inflammation leads to scarring and blockage of blood vessels, eventually by clots. Affected areas have poor blood flow. This disease is most common in men younger than 50 who abuse tobacco products. It's a rare cause of poor circulation.

What Causes Thromboangiitis Obliterans?

The cause is unknown. However, the disease is found only in tobacco smokers. If smoking continues, the disease gets worse; if smoking stops, the disease often improves. It's not contagious and doesn't seem to be inherited. It is most common in the Middle East, the Far East, and Asia. In the U.S., it occurs in about 10 to 20 people for every 100,000.

What Are the Signs and Symptoms of Thromboangiitis Obliterans?

Symptoms usually start in hands and feet. Arms and legs feel numb and cold. Calf pain may occur with walking (claudication). Skin ulcers can form and are due to low blood flow. Ulcers occur at tips of fingers and toes. Tissue there can become necrotic (dead), which leads to gangrene and maybe amputation.

How Is Thromboangiitis Obliterans Diagnosed?

The health care provider makes a preliminary diagnosis from the medical history and physical examination. Migratory thrombophlebitis is common. This thrombophlebitis is the presence of small blood clots that move from one spot to another. Angiography can help confirm the diagnosis. In this test, a catheter (tube) is put into the blood vessel of the affected limb, dye is

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injected into it, and a picture of the blood vessel is taken. Echocardiography may be done to make sure that clots aren't forming inside the heart and traveling to blood vessels in the legs.

How Is Thromboangiitis Obliterans Treated?

The best treatment is to stop smoking. If smoking continues, the disease becomes worse. Skin ulcers, necrotic fingers and toes, and gangrene can occur. Amputation may be needed. Treatment may also include bypass operations for better circulation and surgery to cut nerves that may cause blood vessel constriction. Medicines may be used to dilate blood vessels, improve blood flow, or dissolve clots. Compression devices may improve calf blood flow. Hyperbaric chambers and surgical ulcer removal may also be used.

DOs and DON'Ts in Managing Thromboangiitis Obliterans:

- ✓ **DO** understand that treatments aim to provide relief of pain from poor circulation. They also try to heal ulcers. However, these treatments won't work if smoking continues.
- ✓ **DO** realize that surgery to bypass blocked blood flow can lead to faster healing of ulcers.
- ✓ **DO** protect your fingers and toes from cold and injury.
- ✓ **DO** look for a vascular surgeon who has experience with this disorder.
- ✓ **DO** call your health care provider if you get pain in the legs with walking or at rest. Call if you have skin breakdown or ulcers, cold feet or fingers, or color changes of your fingers or toes.
- ✓ **DO** call your health care provider if you're interested in smoking cessation programs or if you need a referral to a vascular surgeon.

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⦸ **DON'T** SMOKE!

⦸ **DON'T** miss follow-up appointments. Ulcer healing must be checked. Antibiotics can be used for infections, and surgery to remove dead tissue around the ulcers helps healing.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- Vascular Disease Foundation **Website: http://www.vdf.org**
- Mayo Foundation for Medical Education and Research **Website: http://www.mayoclinic.com**
- National Heart, Lung, and Blood Institute Information Center Phone: 301-592-8573 **Website: www.nhlbi.nih.gov**
- National Organization for Rare Disorders, Inc. (NORD) Phone: 800-999-6673
- American Heart Association Tel: (800) 242-8721 **Website: www.americanheart.org**

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MANAGING YOUR

THROMBOPHILIA

What Is Thrombophilia?

Thrombophilia, or a hypercoagulable state, is a condition related to the increased tendency of blood to clot (thrombosis). People can inherit it or have it because of another illness (an acquired disorder). Sometimes, serious and life-threatening complications result.

What Causes Thrombophilia?

Inherited causes involve mutations in certain genes. People get these genes from their parents. The most common is factor V Leiden mutation. Others are a prothrombin mutation, hyperhomocysteinemia, and increased factor VIII activity. Prothrombin is a clotting protein in blood. Hyperhomocysteinemia means that there is too much of the amino acid homocysteine in the blood, which is related to not having enough of certain vitamins. Other rare inherited disorders include deficiency (not enough) of protein C, protein S, and antithrombin III (another protein that helps blood clotting). These disorders are often related to complications in pregnancy.

Antiphospholipid antibody syndrome is the most common cause of acquired thrombophilia. Antiphospholipid antibody is thought to be an abnormal blood protein. The cause of this syndrome is unknown, but it's not contagious or passed from parents to children.

What Are the Symptoms of Thrombophilia?

People can get blood clots in veins (venous thrombosis) or arteries (arterial thrombosis). Venous clots occur most often in deep veins of the legs and cause swelling, pain, redness, and warmth in the leg. Arterial thrombosis occurs most often in vessels in the head. They cause symptoms of stroke (e.g., slurred speech, paralysis, numbness, weakness, loss of vision, swallowing problems). People with antiphospholipid antibody syndrome have too much blood clotting. The clot-

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ting is usually related to problems with pregnancy (e.g., miscarriage, premature birth) and having antiphospholipid antibodies in the blood.

How Is Thrombophilia Diagnosed?

For diagnosis, the doctor looks for clotting disorders, especially clots occurring in people younger than 50, repeated clots without an obvious cause, clots in unusual places, clots during or after pregnancy, and loss of a baby during pregnancy. The doctor will order tests to rule out the inherited and acquired disorders. Usually, these are blood tests (e.g., Factor V Leiden, protein C, protein S, lupus anticoagulant). Imaging studies can be used to locate clots. For example, ultrasonography will show clots in deep veins of the leg.

How Is Thrombophilia Treated?

Medicine will be prescribed to thin the blood. Common drugs include heparin (given intravenously), low-molecular-weight heparin (given by injections under the skin), and warfarin (taken orally). If thrombophilia is caused by another disease, such as systemic lupus erythematosus or rheumatoid arthritis, that condition will be treated. For hyperhomocysteinemia, vitamins such as folic acid, vitamin B6, and vitamin B12 may be given.

DOs and DON'Ts in Managing Thrombophilia:

✓ **DO** remember that oral birth control pills can cause a clotting event. You may have to avoid taking these pills. Check with your doctor.

✓ **DO** consider screening family members for thrombophilia.

✓ **DO** call your doctor immediately if you have swelling of one of your arms or legs, shortness of breath, or symptoms of a stroke.

⃠ **DON'T** smoke. Tobacco can increase your chances of having a clotting disorder.

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⦸ **DON'T** forget that lifelong blood-thinning medicine may be needed.

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MANAGING YOUR

THROMBOPHLEBITIS

What Is Thrombophlebitis?

Thrombophlebitis (or phlebitis) is inflammation of a vein. When this happens, the blood circulation in that area becomes slow and small blood clots (thrombi) can form in the vein. It happens most often in veins just under the skin after blood is taken for a blood test or intravenous medicine is injected. Inflammation of the vein and these small clots can cause pain, redness, and swelling of the affected arm or leg. Leg veins are affected more often than arm or neck veins.

Thrombophlebitis near the surface of the skin is called superficial thrombophlebitis. It's not life-threatening. The major danger from thrombophlebitis is that clots can travel to veins deeper in the body. These can cause larger clots to form (thrombosis) in the deep veins (called deep vein thrombosis, or DVT). DVT is a very serious condition because blood clots from the deep veins are likely to break off and go to the lungs. They can cause a life-threatening condition called pulmonary embolism.

What Causes Thrombophlebitis?

The usual cause is infection or injury to a vein from trauma. Other risk factors include having varicose veins in the legs, being inactive for a long time (such as sitting in a car or an airplane), smoking, being pregnant, using birth control pills, and being overweight. People with blood clotting abnormalities and those with cancer are also at increased risk for thrombophlebitis.

What Are the Symptoms of Thrombophlebitis?

The most common symptoms are redness, swelling, or warmth in the area; a feeling of hardness in the superficial veins of the leg or arms; tenderness and pain in the affected area; and fever.

How Is Thrombophlebitis Diagnosed?

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The doctor will make a diagnosis by doing a physical examination that finds swelling and redness in the area and by noting the symptoms. If the doctor thinks that clots in the deep veins may be present, the doctor will order ultrasonography to find them. Ultrasonography uses sound waves to see inside the vein and is painless and harmless. A blood test called D-dimer may also be done to check for DVT. This test isn't specific for thrombophlebitis.

How Is Thrombophlebitis Treated?

Treatment of superficial thrombophlebitis involves rest and raising the affected limb. A warm compress may also be used. Prescription support stockings may be used to prevent DVT. The doctor may also prescribe antiinflammatory medicine to help control the pain and reduce the inflammation. Antibiotics will be prescribed for an infection.

People with thrombophlebitis usually feel better with treatment in 7 to 10 days.

DOs and DON'Ts in Managing Thrombophlebitis:

✓ **DO** stop smoking.

✓ **DO** lose weight if you are overweight or obese.

✓ **DO** call your doctor right away if you have redness, swelling, and pain in your leg.

✓ **DO** get up to walk around or stretch your legs if you take long car or plane trips.

⃠ **DON'T** wear garters or knee-high stockings that might squeeze your veins and slow the blood flow in them.

⃠ **DON'T** sit or stand for long periods without moving your legs.

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MANAGING YOUR

THYROID CANCER

What Is Thyroid Cancer?

The thyroid gland in the neck makes hormones that control metabolism. Cells in the thyroid gland are called follicular and parafollicular cells. Thyroid cancers are abnormal growths of these cells. These cancers start from either follicular cells (papillary, follicular, and anaplastic cancers) or parafollicular cells (medullary carcinoma). The papillary type is the most common. It occurs among young people. The follicular type occurs in older people. The medullary type can occur as isolated cancers or in families, as a hereditary form. The anaplastic type is aggressive and hard to treat.

About 10,000 new thyroid cancers are diagnosed each year in the United States.

What Causes Thyroid Cancer?

The cause is unknown. Radiation exposure is a risk for this cancer, especially in children who have radiation therapy to the head, neck, or upper chest during infancy or childhood. Thyroid cancer isn't contagious.

What Are the Symptoms of Thyroid Cancer?

Usually, a thyroid nodule (lump) is the first symptom. As the cancers grow, they usually spread to nearby areas and cause hoarseness, trouble swallowing, swollen lymph glands, and neck pain.

How Is Thyroid Cancer Diagnosed?

The doctor may suspect thyroid cancer by finding a lump on the thyroid during a physical examination. For proof of cancer, cells are taken from the lump by fine-needle aspiration biopsy (FNAB) and studied with a microscope. In this type of biopsy, the doctor uses a needle to get a sample.

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How Is Thyroid Cancer Treated?

Treatment can be surgery, radiation therapy, or chemotherapy. Type of treatment depends on whether the cancer has spread.

Removal of the thyroid, either part or the whole gland, is called thyroidectomy. Complications of surgery include injury to vocal cords.

If the whole thyroid is removed, thyroid replacement medicine is taken for the rest of life. If only part is removed, hormone may also be given to stop growth of remaining thyroid tissue.

Radioactive iodine can be used after surgery or to treat spread of cancer. Radioactive iodine kills normal and cancer cells.

Chemotherapy is used if other treatments don't work.

DOs and DON'Ts in Managing Thyroid Cancer:

✓ **DO** take your prescribed medicines.

✓ **DO** find a surgeon with experience in thyroid operations.

✓ **DO** remember that the earlier the cancer is found, the better the chances of cure.

✓ **DO** call your doctor if you find a lump in your neck or are hoarse.

✓ **DO** call your doctor if you have hand tremors (shaking), diarrhea, sweats, and palpitations. You may be taking too much thyroid medicine after surgery.

✓ **DO** call your doctor if you cannot tolerate cold, have a raspy voice, are constipated, lose eyebrow hair, or gain weight. You may be taking too little thyroid medicine.

✓ **DO** call your doctor if after surgery you have numbness around your mouth, tips of your fin-

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gers, and feet, with muscle spasms of your hands, legs, or face. You can have a low calcium level.

⦸ **DON'T** miss follow-up doctor appointments. Careful neck examinations, blood tests, and thyroid scans are done to make sure the cancer hasn't returned.

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FOR MORE INFORMATION

Contact the following sources:

- National Cancer Institute Tel: (800) 4-CANCER (422-6237) **Website:** **http://www.cancer.gov**
- American Cancer Society Tel: (800) 227-2345 **Website:** **http://www.cancer.org**

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MANAGING YOUR

THYROID NODULE

What Is a Thyroid Nodule?

The thyroid gland lies in the neck. It is part of the endocrine system and produces a substance (thyroid hormone) that helps control metabolism. A thyroid nodule is a lump of tissue on this gland. Nodules may be caused by an infection, cyst, benign tumor, or malignant tumor of the thyroid. Most nodules are benign tumors or cysts filled with fluid. Because some thyroid nodules are cancerous, all nodules should be examined.

What Are the Symptoms of a Thyroid Nodule?

Most people don't know that they have a nodule. Some people may have no symptoms. Others may feel or see a soft, painless swelling near the thyroid in the neck. Most nodules are benign, cold (inactive) nodules, with no effect on health. Hot (overactive) nodules cause anxiety, sweating, weight loss, hunger, and tremor by producing excess thyroid hormone (hyperthyroidism).

A rock-hard nodule that grows rapidly and causes a voice change (hoarseness) or swallowing difficulty suggests cancer and should be removed quickly.

How Is a Thyroid Nodule Diagnosed?

A sonogram (which uses sound waves to make pictures of body parts) can tell whether nodules are present and whether a nodule is solid. Solid nodules may be cancerous.

Specialists may also discover nodules on x-ray films of the chest or neck done for other reasons. After nodules are found, two important questions need answers:

- Is the thyroid working normally?
- Is the nodule benign or malignant?

Thyroid function blood tests answer the first question. Most people have normal thyroid func-

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tion.

A special test (radioactive iodine scan) can tell whether an overactive nodule is producing too much hormone and must be treated.

A doctor will check a tissue sample (biopsy) of the nodule to see whether the nodule is benign. A fine-needle aspiration biopsy (FNAB) is used to get this sample. Using a needle passed into the nodule, the doctor will collect cells from the thyroid gland and examine them under a microscope.

How Is a Thyroid Nodule Treated?

Most nodules are benign. Benign solid nodules are easily treated with thyroid supplements (levothyroxine) that help prevent nodule growth. Nodules that contain only fluid are drained during the FNAB.

Surgery may be needed to remove large nodules if they could be cancerous or if they crush blood vessels or other tissues in the neck. If the whole tumor cannot be removed, radioactive iodine can destroy remaining cancer cells. This treatment also destroys normal thyroid cells, so after treatment most people develop an underactive thyroid (hypothyroidism) and need medicine to replace thyroid hormone.

Complications after surgery include bleeding, infection, low calcium levels from damage to the parathyroid glands near the thyroid during surgery, or damage to vocal cords. An experienced surgeon usually causes few complications, however. Hormone therapy for benign nodules can lead to an overactive thyroid (hyperthyroidism). Radioactive iodine therapy may cause other glands to swell and dry out.

DOs and DON'Ts in Managing a Thyroid Nodule:

✓ **DO** have an FNAB of any suspicious nodule.

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✓ **DO** find an experienced thyroid specialist.

✓ **DO** examine your neck to find new nodules.

✓ **DO** tell your doctor if you had radiation therapy to the neck or a family history of thyroid cancer.

✓ **DO** call your doctor if you develop symptoms after treatment or surgery.

⃠ **DON'T** stop taking or change your medicine because you feel better unless your doctor tells you to.

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MANAGING YOUR

THYROIDITIS

What Is Thyroiditis?

The thyroid is a small gland in the middle of the neck and is important for controlling metabolism. Thyroiditis is inflammation (swelling) of this gland. Inflammation may result in an overactive gland (called hyperthyroidism) or underactive gland (called hypothyroidism).

The most common type of thyroiditis is Hashimoto's thyroiditis. About 10 times more women than men get it, up to 2% of women in the United States. Other types called subacute and silent thyroiditis can also result in an overactive thyroid. Postpartum thyroiditis occurs in women who were recently pregnant. Thyroiditis can lead to both overactive and underactive thyroid symptoms depending on its stage.

What Causes Thyroiditis?

Many things can cause thyroiditis. In the most common type, the body's own immune (infection-fighting) system attacks thyroid cells. The result may be high hormone levels (hyperthyroidism) followed by low hormone levels (hypothyroidism).

What Are the Symptoms of Thyroiditis?

Symptoms depend on the type of thyroiditis and how severe it is. The most common symptoms of acute disease in early stages are enlarged thyroid, sometimes pain and tenderness in the thyroid, and sometimes dry eyes and dry mouth. One type, painless thyroiditis, causes no pain. Symptoms of hyperthyroidism occur in silent, subacute, or early postpartum thyroiditis. They include weight loss, greater appetite, diarrhea, irregular periods, racing heartbeat, anxiety, heat sensitivity, and shaking. Hypothyroidism may cause weight gain, less appetite, constipation, tiredness, depression, cold sensitivity, and weakness. In subacute thyroiditis, which occurs after a

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viral infection, an enlarged thyroid may cause neck pain and swelling. Postpartum thyroiditis may cause anxiety (hyperthyroid) and depression and fatigue (hypothyroid).

How Is Thyroiditis Diagnosed?

The doctor takes a medical history, does a physical examination, and orders blood tests. These tests measure thyroid-stimulating hormone (TSH) and antithyroid antibodies. A special x-ray called radioactive iodine uptake (RAIU) may also be done.

How Is Thyroiditis Treated?

People treated with thyroid hormone will likely need lifelong therapy. People with Hashimoto's disease take levothyroxine (thyroid hormone) to replace missing hormone.

Silent and subacute thyroiditis may go away without treatment or may need antiinflammatory medicines. These drugs include a nonsteroidal antiinflammatory drug (NSAID) or prednisone for pain. A beta-blocker such as propranolol or atenolol may be given for rapid heartbeats.

DOs and DON'Ts in Managing Thyroiditis:

✓ **DO** follow-up with your doctor. Thyroiditis changes over time and you usually change from being hyperthyroid to hypothyroid.

✓ **DO** learn about your type of thyroiditis. Find out whether you have an overactive or underactive gland.

✓ **DO** take your medicine as prescribed.

✓ **DO** tell your doctor if you're pregnant or breastfeeding or want to become pregnant.

✓ **DO** call your doctor if you have chest pain, chest pressure, or palpitations after starting thyroid hormone therapy.

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✓ **DO** call your doctor if you have a high fever or severe illness.

✓ **DO** call your doctor if you have a reaction to medicine.

✓ **DO** call your doctor if you feel sick even with treatment for several weeks.

⃠ **DON'T** expect an overnight response to treatment. You'll need 4 to 6 weeks before you begin to feel better.

⃠ **DON'T** exercise too hard if you have symptoms.

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Contact the following sources:

- American Association of Clinical Endocrinologists Tel: (904) 353-7878 **Website:** **http://www.aace.com**
- American Thyroid Association Tel: (718) 882-6047

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MANAGING YOUR

TINEA CAPITIS

What Is Tinea Capitis?

Tinea capitis (ringworm) is an infection of the scalp (and sometimes eyebrows and eyelashes) with mold-like fungi called dermatophytes. It's widely known as ringworm because of its round lesions. It is a common childhood disease that is often confused with other scalp conditions, and is the most common fungal infection in children. Ages usually affected are 2 to 10 years. Tinea capitis is slightly more common in African American children. In adults, more women than men are infected. Because symptoms are often mild, it can go untreated for long periods. Tinea capitis is easily cured but usually requires weeks to months of treatment. If left untreated, it can cause hair loss.

What Causes Tinea Capitis?

The cause is a very common fungus named *Trichophyton*. People get it by direct contact with infected people or infected animals, especially cats and dogs.

What Are the Symptoms of Tinea Capitis?

Symptoms may be mild and first include redness and swelling (inflammation) of the scalp, followed by hair loss. Infected hairs become brittle and broken. Pustules called kerions, or small, pus-filled, blister-like lesions, may be present. Some people may have a tender, swollen area with drainage. Severe ringworm can also cause fever and enlarged lymph nodes (glands).

How Is Tinea Capitis Diagnosed?

The doctor makes a diagnosis by a skin examination. The doctor may take small samples of hair or infected skin with fungi for culture, to see whether fungi grow. A microscope is used to study them. Culture results are usually available after several days.

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How Is Tinea Capitis Treated?

Medicines taken by mouth (such as griseofulvin or terbinafine) can cure tinea capitis, but treatment usually takes weeks to months. Rarely, these drugs cause changes in liver function tests, and the doctor may order laboratory tests to make sure that the liver is working properly. It's very important to finish the full course of treatment and follow the doctor's instructions. Otherwise, the disorder can return.

The doctor may also prescribe special creams or shampoos (such as selenium sulfide) if needed.

DOs and DON'Ts in Managing Tinea Capitis:

✓ **DO** avoid contact with infected people.

✓ **DO** wash your hair after every haircut.

✓ **DO** continue treatment until your doctor tells you to stop.

✓ **DO** check pets (such as cats, dogs, hamsters, and guinea pigs) for skin infections or irritations, and if they're present, have your veterinarian treat your pets.

✓ **DO** check brothers and sisters for ringworm of the scalp.

✓ **DO** call your doctor if you have fever, pus drainage, or swelling.

✓ **DO** call your doctor if other areas of the scalp or body become infected even with treatment.

✓ **DO** call your doctor if tinea capitis comes back after you have finished the treatment.

⊘ **DON'T** share combs, brushes, or hats with other people.

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⦸ **DON'T** get close haircuts, shave your head, or wear caps as long as you're taking your medicine.

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MANAGING YOUR

TINEA CRURIS

What Is Tinea Cruris?

Tinea cruris is a very common fungal infection of the skin in the groin and upper thighs. It occurs most often in men and adolescent boys. Tinea cruris can be cured in 2 to 3 weeks with the right treatment.

Tinea cruris is also called ringworm of the groin and is related to other similar fungal infections that are named according to where they occur, such as ringworm of the body (tinea corporis), ringworm of the scalp (tinea capitis), and athlete's foot (tinea pedis, ringworm of the feet).

What Causes Tinea Cruris?

The cause is a very common fungus that can be seen only with a microscope. Factors that increase the risk for infection include excessive sweating, athlete's foot, obesity, hot humid weather, and use of public baths or showers.

What Are the Symptoms of Tinea Cruris?

Symptoms include usually slightly raised, red-to-brown skin that itches. The skin may show patches, scaling with sharp edges, or small blisters. Both sides of the groin are usually affected, and pain in the groin may occur.

As long as redness and scaling are present, the infection can be passed to other people.

Scratching can cause oozing, swelling, and infections caused by other organisms.

How Is Tinea Cruris Diagnosed?

The doctor makes a diagnosis by doing an examination of the skin. The doctor may take small samples of infected skin if the diagnosis is unclear. These samples are cultured and studied under

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a microscope. Culture results are usually available after several days.

How Is Tinea Cruris Treated?

In very mild cases, topical antifungal cream or ointment available without a prescription may be used. Treatment with the cream continues for 7 days after the area has cleared.

Most people, however, may need prescription antifungal creams ordered by the doctor.

The doctor may also prescribe medicines to be taken by mouth for severe or resistant infections. When such medicine is prescribed, the full course of therapy must be finished as prescribed.

DOs and DON'Ts in Managing Tinea Cruris:

✓ **DO** dry the groin with a separate towel after bathing or showering to prevent the infection from spreading to other areas.

✓ **DO** wear loose-fitting, clean cotton underwear. Boxer shorts are preferred. Change underwear daily or more often to keep the groin dry.

✓ **DO** call your doctor if the rash doesn't improve after 2 weeks of treatment.

✓ **DO** call your doctor if you have signs of another infection, such as fever, pus drainage, oozing, crusting, or swelling.

✓ **DO** call your doctor if you have scarring or bleeding.

⃠ **DON'T** share towels.

⃠ **DON'T** touch or scratch your feet and then touch your groin area.

⃠ **DON'T** wear nylon or other synthetic underwear that keeps moisture in the groin area.

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⦸ **DON'T** wear clothes that rub or irritate the skin.

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MANAGING YOUR

TINEA INFECTIONS

What Are Tinea Infections?

Tinea infections (or ringworm) are caused by different fungi. The name ringworm comes from the appearance (ring-shaped or oval patches), not the cause, of the infection. Different fungi affect different parts of the body. These infections are named according to where they occur, such as ringworm of the body (tinea corporis), ringworm of the scalp (tinea capitis), athlete's foot (tinea pedis, ringworm of the feet), jock itch (tinea cruris, ringworm of the groin), and nail ringworm (tinea unguium).

What Causes Tinea Infections?

These infections aren't caused by worms but by fungi (microscopic plants) called dermatophytes. The more common ones are named *Trichophyton, Microsporum,* and *Epidermophyton.* Fungi that cause ringworm are very small, can be seen only with a microscope, and thrive in warm, moist areas.

What Are the Symptoms of Tinea Infections?

The most common symptom is itching. Sometimes scaling or flaking of the skin occurs.

On the body, ringworm starts as slightly raised, ring-shaped or oval, red-to-brown patches on the skin that itch. It usually develops on the legs or on the trunk of the body.

Jock itch is a tinea infection on the inner thighs. It causes pain and severe itching and usually produces a rash of red, ringlike patches that grow outward in the crease of the thighs. The rash usually has bumps and a different color than the skin around it.

Athlete's foot is another tinea infection affecting areas between the toes and bottoms of the feet. It causes severe itching, a rash, scaling, dead skin, burning, small blisters, and a musty or

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unpleasant odor. Dry skin may flake, peel, or crack. Itching is often worst between the toes.

How Are Tinea Infections Diagnosed?

The doctor makes a diagnosis by doing a physical examination and seeing the typical appearance of patches on the skin. The doctor may also take a sample of the skin for study under a microscope to confirm the diagnosis.

How Are Tinea Infections Treated?

Over-the-counter medicines (antifungal cream, ointment, or powder) can treat mild cases.

The doctor can prescribe antifungal cream to rub on the infected area or antifungal medicines to be taken by mouth for worse cases.

Jock itch usually improves in 2 to 8 weeks. Body ringworm usually gets better in 4 weeks, and athlete's foot may take longer.

DOs and DON'Ts in Managing Tinea Infections:

✓ **DO** use good general hygiene. Bathe or shower daily.

✓ **DO** keep infected skin clean and dry.

✓ **DO** wear loose-fitting underwear (for prevention of jock itch).

✓ **DO** wear cotton socks and well-ventilated sneakers with small holes to keep your feet dry (for prevention of athlete's foot).

✓ **DO** apply medicines exactly as directed.

✓ **DO** wear clean, dry clothes. Cotton or other absorbent cloth is best. Avoid nylon.

⃠ **DON'T** scratch or rub the infected area.

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⦸ **DON'T** let anyone come in contact with your clothing or other items (such as a hairbrush) that may touch the infection. Don't touch ringworm patches on other people or contaminated items, such as clothes or combs.

⦸ **DON'T** shower in public places.

⦸ **DON'T** scratch or rub infected areas to avoid spreading the infection or causing another infection.

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MANAGING YOUR

TINEA VERSICOLOR

What Is Tinea Versicolor?

Tinea versicolor is a rash caused by a fungus that normally lives on the skin. The infection affects the top layer of the skin and causes many irregular spots that are pale brown, pink, or white. Sometimes scales are seen on the rash. The rash usually appears on the upper body of both dark- and light-skinned people.

The rash is more common in the summer. It usually affects teenagers and young adults and rarely affects elderly people and children, except in tropical areas where people of any age can have it.

What Causes Tinea Versicolor?

Tinea versicolor is caused by the fungus *Malassezia furfur*, which is a kind of yeast. Heat and humidity increase the risk of having tinea versicolor, as can too much sweating, oily skin, hormone changes, and a weak immune system. It cannot be caught from someone else.

What Are the Symptoms of Tinea Versicolor?

Most people who have this rash don't have symptoms, but some have mild itching and increased sweating. The rash can be various colors and has small, white to pink or tan to dark spots with sharp edges and scales. It occurs on the upper arms, chest, back, and neck and sometimes the face. Light skin may show faint or tan to pink spots, but dark skin may show light or dark spots. The affected skin doesn't tan normally.

How Is Tinea Versicolor Diagnosed?

The doctor can usually make a diagnosis by the look of the skin. Ultraviolet light may be used to see the rash more clearly. Also, the doctor may gently scrape the rash to get some skin to look at

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under a microscope if is the diagnosis is unclear.

How Is Tinea Versicolor Treated?

The usual treatment is medicated skin cream, lotion, or gel. If the rash is severe or doesn't get better with over-the-counter products, the doctor can prescribe stronger medicine, either topical (applied to the skin) or given by mouth as pills. Sunlight may help the skin get better. Medicine is also given for itching.

Treatment usually lasts 1 to 2 weeks, but may take up to 1 month. The skin should return to normal after several months, without scars.

The rash can come back and will need treatment again.

DOs and DON'Ts in Managing Tinea Versicolor:

✓ **DO** tell your doctor about medicines you take, including prescription drugs and ones you buy over the counter.

✓ **DO** tell your doctor if you're pregnant.

✓ **DO** call your doctor if your symptoms get worse or you have a fever.

⃠ **DON'T** stop taking your medicine or change your dosage because you feel better.

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MANAGING YOUR

TINNITUS

What Is Tinnitus?

Tinnitus is a condition that affects hearing. A ringing or buzzing sound is heard in the ears. It causes people to hear noise even when everything around them is silent. The noise may be soft or loud. It could also be a rushing sound that matches the heartbeat. The sounds may be constant or on and off.

Tinnitus may develop in one or both ears. For some people, it's a minor problem. For others, it becomes a serious handicap. Hearing may be lost in the affected ears.

What Causes Tinnitus?

The cause may be an illness or condition, for example, ear infections or very high blood pressure. An injury to the hearing system from loud noise exposure can also cause tinnitus. In most cases, the cause is unknown.

What Are the Symptoms of Tinnitus?

Symptoms include buzzing, ringing, clicking, roaring, and hissing sounds. Other symptoms may include hearing loss, dizziness, and vertigo.

How Is Tinnitus Diagnosed?

The doctor will do an examination, take a medical history, and maybe order tests. Blood tests may be done to check for other illnesses that may cause tinnitus. Special hearing tests may also be done. The doctor will pay extra attention to your emotional state of mind. Many people with chronic tinnitus are depressed or very anxious and frustrated about their problem. You may be referred to an ear, nose, and throat (ENT) specialist for additional evaluation.

How Is Tinnitus Treated?

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The doctor may prescribe a treatment to reduce the annoying noise. The doctor will also treat any illness or injury causing the tinnitus. For example, medicine may be prescribed to lower high blood pressure.

Several treatments can help reduce the annoying noise. More than one treatment may be used at the same time. Masking uses a device that makes calm, soothing background noise (called white noise). This background noise helps cover up the more annoying noise. Sometimes, soothing background music helps mask the noise. Another treatment is called tinnitus retraining therapy. People work with hearing experts who help retrain the ear not to hear the annoying noise. Biofeedback also teaches people how to change the way their bodies respond to stress. Biofeedback has helped many people with tinnitus. Some medicines may also help. A hearing aid may be needed if hearing loss has occurred.

People with mild tinnitus may not need treatment.

DOs and DON'Ts in Managing Tinnitus:

✓ **DO** try another treatment if one treatment doesn't help. Different people are helped by different treatments.

✓ **DO** try to listen to soothing background music or to the static between stations on a radio if you have trouble sleeping. The static will help mask the noise.

✓ **DO** keep your ears clear of wax.

✓ **DO** limit your use of caffeine, tobacco, and alcohol.

✓ **DO** call your doctor if you feel anxious or depressed.

⃠ **DON'T** listen to loud noises. Wear earplugs whenever you can.

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⦸ **DON'T** take medicines that can harm your ears. These medicines include a certain type of antibiotics called aminoglycoside antibiotics and medicines containing salicylates, such as high-dose aspirin.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following source:

- American Tinnitus Association Tel: (800) 634-8978 **Website: http://www.ata.org**

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CARING FOR YOUR CHILD WITH

TONSILLITIS

What Is Tonsillitis?

Tonsillitis is infection that causes inflammation (swelling and redness) of the tonsils. Tonsils are clumps of tissue, one on each side of the throat, that trap bacteria and viruses.

Tonsillitis is very common in children 6 to 12 years old. Most children recover quickly. The disease usually lasts 4 to 6 days. Tonsillitis is contagious and spreads by direct contact with infected secretions, such as saliva, mucus, and tears.

What Causes Tonsillitis?

The cause is often a virus, but bacteria can also cause tonsillitis. Tonsillitis caused by bacteria is called strep throat when it is caused by *Streptococcus* bacteria.

What Are the Symptoms of Tonsillitis?

Symptoms include a sore throat, pain and trouble swallowing, drooling, fever, earache, tender swollen glands in the neck, and tonsils that look swollen and red. Tonsils may have a yellow or thin white coating or small white patches. Some children have a hard time breathing because of very large tonsils.

How Is Tonsillitis Diagnosed?

The doctor will diagnose tonsillitis by examining the throat. The doctor may use a swab to get a sample from the throat to test for strep bacteria. The doctor may also do blood tests if other infections such as mononucleosis are suspected.

How Is Tonsillitis Treated?

Rest and good fluid intake are the best treatment. If bacteria are the cause, the doctor will prescribe antibiotics. Acetaminophen or ibuprofen can be used for pain and fever. Gargling with a

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saltwater solution or other soothing liquid may help pain and irritation. A cool mist vaporizer may also help the cough and irritation.

For some children, the doctor may suggest removing the tonsils (tonsillectomy). This surgery is usually done for frequent or long-lasting tonsillitis that causes breathing problems.

DOs and DON'Ts in Managing Tonsillitis:

✓ **DO** make sure that your child drinks plenty of fluids, especially warm liquids.

✓ **DO** have your child gargle with warm saltwater.

✓ **DO** give your child over-the-counter pills or liquids, such as acetaminophen, for pain and fever.

✓ **DO** make sure that your child takes all the antibiotics.

✓ **DO** practice good hygiene to avoid spreading the infection to other family members. Don't let your child eat or drink from the same utensils as other family members.

✓ **DO** let your child increase activity slowly after fever has been gone for 2 to 3 days.

✓ **DO** call your doctor if your child has severe swelling of the tonsils and has trouble breathing.

✓ **DO** call your doctor if your child's fever is gone for a few days and suddenly returns.

✓ **DO** call your doctor if your child gets new symptoms, such as a rash, nausea, vomiting, chest pain, shortness of breath, or cough with thick or discolored sputum.

⦸ **DON'T** give aspirin to children younger than 16. They can get a serious illness called Reye's

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syndrome.

⦸ **DON'T** smoke or let people smoke around your child. Smoking can worsen the infection and delay recovery.

⦸ **DON'T** let your child stop taking antibiotics until they're all gone.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

• Infectious Diseases Society of America Tel: (703) 299-0200 **Website:** **http://www.idsociety.org/**

• The American Academy of Pediatrics Tel: (847) 434-4000 **Website:** **http://www.aap.org**

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MANAGING YOUR

TORTICOLLIS

What Is Torticollis?

Torticollis is a movement disorder (dystonia) with involuntary muscle contractions. These contractions lead to abnormal movements of neck muscles and can cause the head to tilt to one side. Other names for torticollis are twisted neck and wry neck. Torticollis is a focal dystonia. Spasmodic torticollis is the most common focal dystonia.

It can be idiopathic (the cause isn't known) or posttraumatic, after a head injury. Torticollis isn't life-threatening and doesn't shorten life expectancy. Complications of chronic pain and abnormalities of the spine in the neck can occur, however.

What Causes Torticollis?

The exact cause is unknown, but torticollis is thought by some to result from a defect in the brain's ability to process chemicals called neurotransmitters. The part of the brain called the basal ganglia is affected. This part takes care of processing messages that start muscle contractions. Torticollis may be present at birth (congenital torticollis). Posttraumatic torticollis can start suddenly, a few days after head and neck trauma. It can also start months after such trauma.

What Are the Symptoms of Torticollis?

Early symptoms include involuntary contraction of neck muscles causing abnormal head and neck movements and positions. The movements may be long lasting and jerky. The movements are described by direction. Anterocollis means forward movement and posture of the head. Retrocollis means backward movement and posture of the head. Laterocollis means sideways head movement.

Muscle spasms lead to pain and a feeling of a tightly contracted neck muscle.

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Problems swallowing may occur with pain moving down the arms. The neck position leads to nerves coming from the cervical (neck) spine being pinched. People also have tension-type headaches, because of spastic neck muscles.

Many people suffer from depression, often from social embarrassment because of body movements and position.

How Is Torticollis Diagnosed?

The doctor makes a diagnosis from the medical history and physical examination. X-rays and studies of muscle movements may be done.

The doctor may suggest seeing a specialist who treats the nervous system (neurologist) and a specialist who treats the musculoskeletal system (orthopedist or rheumatologist).

How Is Torticollis Treated?

Various therapies are aimed at reducing or eliminating muscle spasms and pain. Physical therapy, splinting, stress management, and biofeedback may help. Medicines may reduce muscle spasms and fix the abnormal amounts of neurotransmitters. The preferred and best treatment involves injecting very small amounts of botulinum toxin (Botox®) into affected muscles. The toxin stops muscle spasms by stopping the neurotransmitter acetylcholine from being made. The effect lasts several months before more injections are needed.

Surgery may be considered when other treatments don't work.

DOs and DON'Ts in Managing Torticollis:

✓ **DO** take medicines as directed. Don't stop taking medicines even if you feel better without asking your doctor first.

✓ **DO** call your doctor if you have increasing neck pain or spasms.

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✓ **DO** call your doctor if you're depressed.

⃠ **DON'T** forget that torticollis can cause wear and tear to the neck and limit the range of motion. Your joints may then be more likely to have arthritis.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following source:

- National Spasmodic Torticollis Association Tel: (800) 487-8385 **Website:** **http://www.torticollis.org**

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MANAGING YOUR

TOURETTE'S SYNDROME

What Is Tourette's Syndrome?

Tourette's syndrome is an illness of the nervous system in which parts of the body move or twitch without control. In these movements, called tics, a part of the body moves repeatedly, quickly, suddenly, and uncontrollably. Tics can occur in any body part (face, hands, or legs). People can voluntarily stop them for brief periods. Some people also make abnormal sounds called vocal tics. Rarely, they will curse or say bad things to other people. As with body tics, people cannot control what they say. Sometimes, tics occur often, are severe, and can affect a person's life.

Children and adults can have the syndrome, but it usually starts between the ages of 5 and 15. Many tics may go away as a child gets older.

What Causes Tourette's Syndrome?

The cause is unknown, but it may be inherited with other nervous system problems.

What Are the Symptoms of Tourette's Syndrome?

Symptoms are usually mild and hardly noticeable but can be severe. Symptoms often come and go and may go away for a long time. Sometimes old tics go away and new tics appear. Symptoms include barking, behavior problems, blinking, cursing, grunting, head nodding or bobbing, imitating actions or words of others, licking or smacking the lips, shoulder shrugging, sniffing, snorting, spitting, and yelping.

How Is Tourette's Syndrome Diagnosed?

The doctor makes a diagnosis from the medical history and physical examination. The doctor will ask a child to sit very still to see whether a tic appears. A pediatric neurologist may confirm

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the illness. A neurologist is a doctor who specializes in nervous system problems. The neurologist may want electroencephalography (EEG), a test that measures brain waves. Magnetic resonance imaging (MRI) of the head may also be done. MRI is like an x-ray but uses magnets without x-rays to see inside the body.

Children may be disruptive in school and have behavior problems. They may see a psychiatrist or psychologist (specialists in behavior problems). Tourette's syndrome is associated with a variety of behavioral symptoms, most often attention deficit hyperactivity disorder and obsessive compulsive disorder.

How Is Tourette's Syndrome Treated?

Medicines called neuroleptics can help control tics. Medicine is usually not needed for mild tics. They may be prescribed separately or with other medicines to prevent their side effects.

The whole family may also go for counseling to help a child and family cope with the disorder.

DOs and DON'Ts in Managing

Tourette's Syndrome:

✓ **DO** tell your doctor about your medical problems and medicines, including prescription and over-the-counter drugs.

✓ **DO** tell your doctor if you're pregnant or breastfeeding and have Tourette's syndrome.

✓ **DO** become informed about support groups and other resources.

✓ **DO** call your doctor if you have trouble with your medicines.

✓ **DO** call your doctor if your symptoms get much worse.

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✓ **DO** call your doctor if you need help or resources to teach others about the syndrome.

✓ **DO** call your child's doctor if your child has fever, stiffness, or behavior change while taking medicine for Tourette's syndrome.

⃠ **DON'T** stop your medicine or change the dosage because you feel better unless your doctor says to.

⃠ **DON'T** punish your child for saying bad words. Remember, tics cannot be controlled.

⃠ **DON'T** drink alcohol if you take medicine for Tourette's syndrome.

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FOR MORE INFORMATION

Contact the following source:

- Tourette Syndrome Association Tel: (718) 224-2999 **Website: http://www.tsa-usa.org**

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MANAGING YOUR

TOXIC SHOCK SYNDROME

What Is Toxic Shock Syndrome?

Toxic shock syndrome is a severe, life-threatening form of blood poisoning caused by bacterial toxins. The best known type is related to tampon use during menstrual periods. However, both sexes can get it from wounds or infections of the skin, lungs, throat, or bones.

What Causes Toxic Shock Syndrome?

The cause is toxins made by *Staphylococcus aureus* bacteria. The syndrome is related to use of contraceptive sponge and diaphragm birth control methods as well as tampon use. The second type is caused by *Streptococcus pyogenes* bacteria after they enter the body through injured skin from wounds caused by surgery or minor trauma, such as cuts, scrapes, and chickenpox blisters infected with bacteria.

What Are the Symptoms

of Toxic Shock Syndrome?

Symptoms include sudden shaking and a fever (temperature often higher than 102˚ F), severe muscle pain or aches, vomiting, diarrhea, thirst, rapid pulse, deep red rash that looks like sunburn, severe weakness, headache, confusion, and low blood pressure. Symptoms of the streptococcal syndrome also include trouble breathing, dizziness, and weak and rapid pulse. The infected wound can look swollen and red, and liver and kidneys may stop working.

How Is Toxic Shock Syndrome Diagnosed?

The doctor makes a diagnosis from the medical history, symptoms, physical examination, and blood tests. The doctor may want samples from infected areas, such as wounds and vagina, to check for bacterial growth.

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How Is Toxic Shock Syndrome Treated?

Early diagnosis and hospital treatment are essential. Complications often include peeling of skin on the hands and feet, loss of hair and nails, kidney failure, congestive heart failure, and respiratory distress.

Intravenous fluids and antibiotics will be given in the hospital. Breathing problems may need oxygen and mechanical ventilation. Dialysis will be used for kidney failure.

After symptoms are controlled and initial dangers are over, care can be given at home. Antibiotics may still be needed. Rest is important, with activities increased slowly. Drink more fluids, and follow a well-balanced diet.

DOs and DON'Ts in Managing

Toxic Shock Syndrome:

✓ **DO** get treatment immediately for symptoms of toxic shock. It progresses rapidly and may be fatal if not treated.

✓ **DO** change tampons frequently.

✓ **DO** get medical treatment for wounds that look infected.

✓ **DO** finish all antibiotics.

✓ **DO** wash your hands carefully before you insert tampons. Bacteria are found on the skin, especially the hands.

✓ **DO** get immediate care if you have a fever or rash, especially during your period and when using tampons, or if you had recent surgery.

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✓ **DO** realize that toxic shock syndrome can come back. People who have it once can get it again.

⃠ **DON'T** skip doses or stop antibiotics unless your doctor tells you.

⃠ **DON'T** ignore a wound if it looks red and swollen or has pus.

⃠ **DON'T** use superabsorbent tampons, especially overnight. Alternate tampons with sanitary napkins.

⃠ **DON'T** use tampons if you have a skin infection, especially in the genital area.

⃠ **DON'T** use tampons at all if you ever had toxic shock syndrome.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

Centers for Disease Control and Prevention Tel: (404) 639-2215, (800) 232-4636 **Website:** **http://www.cdc.gov**

National Institute of Allergy and Infectious Disease Tel: (301) 496-5717 **Website:** **http://www3.niaid.nih.gov**

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MANAGING YOUR

TOXOPLASMOSIS

What Is Toxoplasmosis?

Toxoplasmosis is an infection caused by a microscopic organism (protozoa) that lives in birds, animals, and humans. It affects the gastrointestinal tract (which includes the mouth, esophagus, stomach, intestines, and anus), heart, nerves, and skin. The disease is most dangerous for pregnant women and people with weak immune systems. This includes people who are receiving chemotherapy, have AIDS, and have an organ transplant.

Children younger than 5 need treatment to prevent eye complications. Other complications include inflammation (swelling) of the brain and heart and lung damage. If a pregnant woman has the infection early in pregnancy, she may miscarry or have a stillbirth, or the baby may be born with birth defects.

Over 30% of healthy people in the United States may have toxoplasmosis. Many don't know it because they don't have symptoms.

What Causes Toxoplasmosis?

The cause is a microscopic parasite named *Toxoplasma gondii*. The disease can spread by eating undercooked meat from an infected animal (especially lamb and pork) or by handling cat litter or feces if the cat has the infection. People who eat contaminated, uncooked, or unwashed fruits or vegetables that had contact with manure can also get it. Mothers can pass the parasite to unborn babies through the blood.

What Are the Symptoms of Toxoplasmosis?

Most healthy people have no symptoms. Others may have fever, fatigue, muscle aches, headache, and swollen lymph glands.

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How Is Toxoplasmosis Diagnosed?

The doctor makes a diagnosis from a medical history, physical examination, and blood tests.

How Is Toxoplasmosis Treated?

Most people don't need treatment. Others may need prescription drugs such as the antibiotic sulfadiazine or antiparasitic pyrimethamine for 4 to 6 weeks or longer. These drugs can cause upset stomach, sun sensitivity, bleeding, or bruising. The doctor will do blood tests to watch for side effects.

Activity levels depend on the symptoms.

Acetaminophen or tepid sponge baths can be used to reduce fever. No special diet is needed, but fluid intake should be increased.

DOs and DON'Ts in Managing Toxoplasmosis:

✓ **DO** use acetaminophen for aches and fever.

✓ **DO** use tepid sponge baths to help reduce fever.

✓ **DO** rest until symptoms go away. Slowly increase your activity.

✓ **DO** keep doctor appointments for follow-up blood tests.

✓ **DO** use sunscreen when outdoors because the medicine may make you more sensitive to the sun.

✓ **DO** wash your hands often with soap and water, especially when you handle meats, vegetables, and fruits.

✓ **DO** cook meats well. Wash vegetables and fruits before eating them.

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✓ **DO** call your doctor if your symptoms don't get better with treatment.

✓ **DO** call your doctor if you have bleeding, bruising, visual changes, or increased weakness.

⃠ **DON'T** eat undercooked meats, especially lamb and pork, uncooked eggs, or unpasteurized milk.

⃠ **DON'T** change the cat litter box if you're pregnant, had an organ transplant, are receiving chemotherapy, or have AIDS. If you must change the box, use gloves and wash your hands afterward.

⃠ **DON'T** stop taking your medicine before it's all gone unless your doctor tells you to.

⃠ **DON'T** stay in the sun for long periods or forget to use sunscreen.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following sources:

- National Heart, Lung and Blood Institute Tel: (301) 592-8573 **Website:** **http://www.nhlbi.nih.gov**
- National Institute of Allergy and Infectious Diseases Tel: (301) 496-5717 **Website:** **http://www3.niaid.nih.gov**

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MANAGING YOUR

TRANSIENT ISCHEMIC ATTACK

What Is a Transient Ischemic Attack (TIA)?

A transient ischemic attack (TIA) is a neurologic deficit that lasts less than 24 hours, usually just a few minutes. It's also called a mini-stroke. It occurs when part of the brain isn't getting enough blood.

TIAs can occur at any age but tend to be more common in men older than 60. People have a higher risk of stroke if they had a TIA before.

What Causes a TIA?

Plaques or blood clots in arteries can block blood flow. Most of the time, the body breaks down these plaques, so blood flow begins again and symptoms go away. A TIA is caused by a blood clot that gets trapped in one of the brain's blood vessels. This clot usually comes from the heart or carotid arteries in the neck and is made of blood products or fat. The trapped clot stops blood from going to part of the brain, so the brain cannot get the oxygen from the blood.

What Are the Symptoms of a TIA?

The most common symptom is weakness in any part of the body. Other symptoms include confusion, dizziness, double vision, memory loss, numbness, speech and swallowing problems, tingling, vision changes, and trouble walking.

In 70% of cases, symptoms go away in less than 10 minutes, and in 90% they go away in less than 4 hours.

How Is a TIA Diagnosed?

The doctor will make a diagnosis from the medical history and physical examination. Computed tomography (CT) or magnetic resonance imaging (MRI) will be done to look for abnormalities in

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the brain. Other tests may include sonogram of the carotid arteries (blood vessels in the neck that bring blood to the brain) to look for blockages and ultrasound of the heart (echocardiogram) to look for the presence of blood clots in the heart that may travel to the brain.

How Is a TIA Treated?

Treatment depends on the cause. The doctor will be most concerned about preventing a stroke.

Conditions such as high blood pressure, diabetes, tobacco abuse, inactive lifestyle, and high cholesterol level are treated. Aspirin, clopidogrel, and warfarin may be given to thin the blood and prevent clots.

Surgery (carotid endarterectomy) may be needed to open severely blocked carotid arteries (over 70% blockage).

DOs and DON'Ts in Managing a TIA:

✓ **DO** note the conditions and symptoms when you have a TIA. What were you doing when it occurred? What symptoms did you have? How long did they last? When did they occur? This information is important for your physician to help determine what caused the TIA and which blood vessels may be involved.

✓ **DO** take only medicines prescribed by your doctor. Some may mean that you must get regular blood tests.

✓ **DO** make sure that your doctor knows about your other medical problems, such as diabetes, high cholesterol level, and high blood pressure.

✓ **DO** keep follow-up doctor appointments.

✓ **DO** call your doctor if you have another TIA after starting to take medicine.

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✓ **DO** call your doctor if you have an unusually severe headache.

✓ **DO** call your doctor if you have problems with your medicines.

⃠ **DON'T** stop taking your medicine or change your dosage because you feel better unless your doctor tells you to.

⃠ **DON'T** use tobacco products. They cause blood vessel disease and increase your risk of having a stroke.

⃠ **DON'T** eat a high-fat diet.

⃠ **DON'T** drive or do any activity that might be dangerous if you have a TIA.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Neurological Disorders and Stroke Tel: (800) 352-9424 **Website:** **http://www.ninds.nih.gov**
- National Stroke Association Tel: (800) 787-6537 **Website:** **http://www.stroke.org**

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MANAGING YOUR

TRAVELER'S DIARRHEA

What Is Traveler's Diarrhea (TD)?

Travelers' diarrhea (TD) is diarrhea in people who are or recently returned from traveling. It's the most common illness in travelers. Each year between 20% and 50% of international travelers develop TD. Three or more unformed (meaning no separate pieces) stools (bowel movements) in 24 hours are indicative of TD. In most cases, TD runs its course without complications, with 90% of cases going away within 1 week, and 98% within 1 month.

What Causes TD?

The usual cause is bacteria, but viruses and parasites can also cause TD. It's usually related to travel in developing countries with a contaminated water supply.

What Are the Symptoms of TD?

Most symptoms start suddenly. Symptoms include diarrhea (unformed bowel movements), cramps and tenderness in the abdomen (belly), and sometimes nausea or vomiting and fever. Stools are often large and watery, and may contain mucus or blood. Babies (who usually have frequent bowel movements) may have TD if they have stools twice as often or more often than normal over 2 to 3 days.

How Is TD Diagnosed?

The doctor will suspect TD on the basis of the medical history, recent travel, and physical examination.

For severe TD or for bloody stool the doctor may order a stool culture. In this test, a small amount of stool is checked to find the cause. Additional tests may also be done.

How Is TD Treated?

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Prevention is best. Drink bottled water. Avoid ice cubes when traveling. TD usually stops after 5 to 7 days without lasting effects. Drinking enough clear fluids is important, because diarrhea can lead to dehydration. Fluids are especially important for infants and young children, who can easily become dehydrated. A liquid that contains added substances such as electrolytes in water may be suggested. Pregnant women, older people, and people who are ill with another disease need to be careful about replacing fluids.

For severe or worsening symptoms, the doctor may prescribe an antibiotic or other drug. Knowing the area of travel helps the doctor pick the best medicine.

Sometimes, the doctor may suggest seeing a gastroenterologist (specialist in bowel diseases) if the diarrhea persists.

DOs and DON'Ts in Managing TD:

✓ **DO** drink enough fluids.

✓ **DO** be careful about fluid intake in children, elderly people, pregnant women, and people with other illnesses.

✓ **DO** wash your hands every time you use the toilet.

✓ **DO** call your doctor if you get a high temperature, have blood in your bowel movement, or get severe abdominal pain.

✓ **DO** make sure that the water you drink isn't contaminated. In certain parts of the world, use only bottled water that is well sealed when you get it. Be careful of tap water, ice, unpasteurized milk, and dairy products.

✓ **DO** wash all fruits and vegetables carefully in uncontaminated water. Avoid undercooked

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meat and seafood.

⦸ **DON'T** wait to talk to your doctor if you have blood or mucus in your stools or have a high temperature.

⦸ **DON'T** swim in contaminated water.

⦸ **DON'T** take medicine that may be offered to you as a cure unless a doctor ordered it. Some of these drugs may make TD worse.

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FOR MORE INFORMATION

Contact the following source:

- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website:** **http://www.cdc.gov**

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MANAGING YOUR

TRICHINOSIS

What Is Trichinosis?

Trichinosis is an infection caused by a parasitic roundworm that lives in intestines of pigs and other animals. Today, pigs aren't as common a source of infection as they were. Bear meat is now the most common source of infection.

People get trichinosis by eating the meat of an infected animal when the meat hasn't been cooked enough to kill the worm cysts. Within 2 days of eating the infected meat, the worms mature and lay eggs, which become larvae (young immature worms). By the seventh day, larvae are carried in the blood to muscles. In muscles, the worms curl into balls and become covered by a capsule (cyst).

Complications of trichinosis can include congestive heart failure; respiratory failure; pneumonia; and kidney, heart, and brain damage.

What Causes Trichinosis?

The cause is the worm *Trichinella spiralis.*

What Are the Symptoms of Trichinosis?

Early symptoms are diarrhea, a low-grade fever, nausea, vomiting, fatigue, and discomfort in the abdomen (belly). Seven to 10 days later, the eyelids and face may become puffy. Muscle pain, aching joints, headache, weakness, shortness of breath, high temperature, chills, sensitivity to light, and itching and burning of the skin also occur. Fatigue, weakness, and diarrhea can last for months. Severe infections can lead to death.

How Is Trichinosis Diagnosed?

The doctor may suspect trichinosis from the medical history and physical examination. To con-

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firm the diagnosis, the doctor will order blood tests and get a small piece of muscle tissue (muscle biopsy) for study. This tissue is checked with a microscope to identify the parasite.

How Is Trichinosis Treated?

The doctor will prescribe medicines (anthelmintic, or antiworm, drugs) to kill the worms, if the parasites are in the intestines. Acetaminophen and tepid sponge baths can be used to reduce fever. Corticosteroid drugs such as prednisone may be prescribed if the infection is severe or if it involves the brain and nervous system.

Maintaining proper nutrition is important. Appetite loss occurs, so it may help to eat small frequent meals.

DOs and DON'Ts in Managing Trichinosis:

✓ **DO** take your medicine as directed.

✓ **DO** rest. Rest is important until your symptoms are gone. Resume your normal activities slowly after you have no more symptoms.

✓ **DO** use acetaminophen or ibuprofen for fever and pain.

✓ **DO** eat small, frequent meals for proper nutrition.

✓ **DO** increase your fluid intake to prevent dehydration.

✓ **DO** call your doctor if you have side effects from the medicine and cannot tolerate them.

✓ **DO** call your doctor if you have a high fever, shortness of breath, or an irregular heartbeat.

✓ **DO** cook pork and meat products well, to kill worms.

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⦸ **DON'T** drive or operate heavy machinery while you're taking antiparasitic drugs. Most can cause drowsiness, dizziness, nausea, or diarrhea.

⦸ **DON'T** skip doses of medicine. Usually the course of treatment is short, but if you cannot tolerate the medicine, tell your doctor.

⦸ **DON'T** eat undercooked meat, to prevent future infections.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- National Institute of Allergy and Infectious Diseases Tel: (301) 496-5717 **Website:** **http://www3.niaid.nih.gov**
- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website:** **http://www.cdc.gov**

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MANAGING YOUR

TRICHOMONIASIS

What Is Trichomoniasis?

Trichomoniasis is an infection of the sex organs that spreads by sexual contact. It's one of the most common sexually transmitted infections (STIs) or diseases (STDs). It affects both sexes, but mainly women aged 16 to 35 years. In the United States, about 2 million women become infected each year. Infection isn't fatal but can lead to complications, such as infertility; infection of the vaginal skin tissue (cellulitis); and, in men, blockage of the urethra (the tube in the penis that carries urine out of the body). Infection during pregnancy may lead to premature labor and low birth weight.

What Causes Trichomoniasis?

The cause is the single-celled, microscopic parasite named *Trichomonas vaginalis*, found worldwide.

What Are the Symptoms of Trichomoniasis?

Women can have no symptoms (asymptomatic) or many symptoms. Typical symptoms include foul-smelling or frothy green discharge from the vagina, vaginal itching, and vaginal redness. Other symptoms are pain during sex, lower abdominal discomfort, and need to urinate.

Most men don't have symptoms. When symptoms occur, they most often are discharge from the urethra, need to urinate, and a burning feeling during urination.

How Is Trichomoniasis Diagnosed?

The doctor will do a pelvic examination to collect samples from the vagina for study. Diagnosis is confirmed by finding the parasite in the sample with a microscope. Growing the parasite in a culture is another way to diagnose infection. Culture results may take 3 to 7 days. Blood tests can

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also be done to diagnose the parasite.

In men, the doctor collects samples from the urethra and looks for the parasite with a microscope. The parasite is harder to find in men.

How Is Trichomoniasis Treated?

The doctor will prescribe antibiotics for treatment. Metronidazole is the best one and can be taken for 7 days. Both partners should be treated at the same time. Metronidazole can cross the placenta, so it isn't usually used during pregnancy. Side effects include nausea, vomiting, diarrhea, abdominal cramping, metallic taste in the mouth, seizures, and peripheral neuropathy. People should not drink alcohol while taking metronidazole, because flushing, headache, abdominal pain, nausea, and vomiting may occur.

DOs and DON'Ts in Managing Trichomoniasis:

✓ **DO** follow your doctor's instructions.

✓ **DO** avoid sex during treatment.

✓ **DO** practice safe sex. Use latex condoms if you think there's a chance of catching an STD. You could catch this infection from your partner.

✓ **DO** limit your sex partners. The more you have, the greater your chance of having sex with someone with an STD.

✓ **DO** call your doctor if you have burning with urination, vaginal discharge, pain with sex, or side effects from your medicines.

⃠ **DON'T** forget, if you have trichomoniasis, your sex partner should also be treated.

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⦸ **DON'T** forget that even though you were infected with *Trichomonas* once, you're not immune. You can get infected again. Take all precautions to prevent another infection.

⦸ **DON'T** forget that babies born to infected mothers may get the infection during delivery, although this is rare.

FROM THE DESK OF

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FOR MORE INFORMATION

Contact the following sources:

- Centers for Disease Control and Prevention Tel: (800) 311-3435 **Website:** **http://www.cdc.gov**
- Infectious Diseases Society of America Tel: (703) 299-0200 **Website:** **http://www.idsociety.org**
- National Institute of Allergy and Infectious Diseases Tel: (301) 496-5717 **Website:** **http://www.niaid.nih.gov**

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MANAGING YOUR

TRICUSPID REGURGITATION

What Is Tricuspid Regurgitation?

The tricuspid valve is between the right atrium (a top chamber) and right ventricle (a bottom chamber) in the heart. The valve opens when the atrium contracts to let blood into the ventricle. It closes when the ventricle contracts to stop blood flow back (regurgitation) into the atrium. In regurgitation, some blood flows back, so the atrium works harder and gets bigger (enlarged).

What Causes Tricuspid Regurgitation?

Tricuspid valve abnormalities are uncommon and often occur with abnormalities of other valves. Tricuspid valve damage may be congenital (present at birth). The most common cause is enlargement of the right ventricle secondary to pulmonary hypertension (increased pressure in the lung blood vessels). Heart infections such as rheumatic fever (from streptococcal infection) or bacterial endocarditis can cause it. Most teens and young adults with tricuspid regurgitation have congenital abnormalities.

What Are the Signs and Symptoms of Tricuspid Regurgitation?

People with mild tricuspid regurgitation may have no symptoms. Symptoms that do occur usually start after several years. They include swelling in the feet, legs, or abdomen (belly) and breathing problems, especially when lying down. Other symptoms are uneven heartbeat, coughing up blood, and chest pain. Weakness, tiredness, and low urine volume may occur. People may develop an irregular heartbeat called atrial fibrillation. When this occurs, the atrium doesn't contract normally, blood pools in the atrium, and clots may form. These clots may travel to the brain and cause strokes.

How Is Tricuspid Regurgitation Diagnosed?

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The health care provider makes a preliminary diagnosis from the medical history and physical examination. Blood moving abnormally through valves makes a sound called a murmur. Its timing in the heart's cycle and location help tell which valve is affected. Tests to help diagnose tricuspid regurgitation may include echocardiography, chest X-rays, and electrocardiography (ECG). Echocardiography is an ultrasound examination of the heart. ECG shows changes in the electrical system of the heart such as abnormal rhythms (arrhythmias).

How Is Tricuspid Regurgitation Treated?

Treatment depends on severity, age, and overall health. For mild conditions, no treatment is needed. Some people with atrial fibrillation take anticoagulant medicine to prevent blood clots. For heart failure, diuretics lower blood fluid volume so the heart doesn't have to work as hard. Vasodilator medicines may be used when heart failure becomes worse. Severe tricuspid regurgitation may require valve replacement or repair (valvuloplasty).

DOs and DON'Ts in Managing Tricuspid Regurgitation:

✓ **DO** take your medicines as prescribed.

✓ **DO** limit fluid and salt in your diet.

✓ **DO** exercise as much as recommended by your physician.

✓ **DO** call your health care provider if you have side effects from your medicines. Call if you have new or worsening symptoms such as chest pain, shortness of breath, palpitations, rapid heartbeat, or swelling in the legs or abdomen. Call if you're taking anticoagulants and have a cut that doesn't stop bleeding or have a head injury.

⃠ **DON'T** overexert yourself. If easy exercise is getting harder, rest until you see your health

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care

provider.

⦸ **DON'T** stop taking your medicine or change the dosage because you feel better unless your health care provider tells you to.

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website: www.americanheart.org**
- American College of Cardiology Tel: (800) 253-4636 **Website: http://www.acc.org**

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MANAGING YOUR

TRICUSPID STENOSIS

What Is Tricuspid Stenosis?

The tricuspid valve is between the right atrium (a top chamber) and right ventricle (a bottom chamber) in the heart. Stenosis is a narrowing of the valve opening. The valve opens when the atrium contracts to let blood into the ventricle. It closes when the ventricle contracts to stop blood flow back to the atrium. A narrow opening means that blood doesn't flow easily. The atrium works harder, so it gets bigger, and becomes less effective in moving blood to the right ventricle.

What Causes Tricuspid Stenosis?

Tricuspid stenosis is almost always related to rheumatic heart disease (from infection with streptococcal bacteria). It's usually found with mitral and aortic valve problems. Tricuspid valve damage may rarely be congenital (present at birth).

What Are the Signs and Symptoms of Tricuspid Stenosis?

People with mild tricuspid stenosis may have no symptoms. Symptoms usually start after several years. They include swelling in the feet, legs, or abdomen (belly) and breathing problems, especially when lying down. Other symptoms are uneven heartbeat, coughing up blood, chest pain, and fatigue.

How Is Tricuspid Stenosis Diagnosed?

The health care provider makes a preliminary diagnosis from the medical history and physical examination. Blood moving abnormally through valves makes an abnormal sound called a murmur. Its timing in the heart's cycle and location help tell which valve is affected. Additional tests to diagnose tricuspid stenosis may include an echocardiography, chest X-rays, and

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electrocardiography (ECG). Echocardiography is an ultrasound examination of the heart. ECG shows changes in the electrical system of the heart such as abnormal heart rhythms (arrhythmias).

How Is Tricuspid Stenosis Treated?

Treatment varies depending on severity, age, and overall health. Treatment of mild conditions tries to prevent complications. Salt and fluid restriction is important to prevent swelling (edema) of the arms and legs. Some people with irregular heartbeat known as atrial fibrillation take anticoagulant medicine to prevent blood clots. For heart failure, diuretics lower blood fluid volume so the heart doesn't work as hard. Vasodilator medicines may be used when heart failure gets worse. Treatment options in some people may include having the valve stretched with a catheter (tube). The catheter has an attached balloon that is inflated in the valve and stretches it (balloon valvuloplasty). Severe tricuspid stenosis may require valve replacement.

DOs and DON'Ts in Managing Tricuspid Stenosis:

✓ **DO** take your medicines as prescribed.

✓ **DO** limit your intake of fluids and salt.

✓ **DO** exercise as much as you can under the guidance of your physician.

✓ **DO** call your health care provider if you have side effects from your medicines. Call if you have new or worsening symptoms such as chest pain, shortness of breath, palpitations, rapid heartbeat, or swelling in the legs or abdomen. Call if you're taking anticoagulants and have a cut that doesn't stop bleeding or have a head injury.

⦸ **DON'T** overexert yourself. If easy exercise is getting hard, rest until you see your health care

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provider.

⦸ **DON'T** stop taking your medicine or change the dosage because you feel better unless your health care provider tells you to.

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FOR MORE INFORMATION

Contact the following sources:

- American Heart Association Tel: (800) 242-8721 **Website: www.americanheart.org**
- American College of Cardiology Tel: (800) 253-4636 Fax: (301) 897-9745 **Website: http://www.acc.org**

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MANAGING YOUR

TRIGEMINAL NEURALGIA

What Is Trigeminal Neuralgia?

Trigeminal neuralgia is a rare, painful disorder of the trigeminal nerve, a main nerve in the face. Another name for it is tic douloureux. It's a chronic condition with intense pain that can be very debilitating. Episodes can last for days, weeks, or months and then go away for months or years.

Trigeminal neuralgia rarely occurs in people younger than 50, and it's more common in women than in men.

What Causes Trigeminal Neuralgia?

The cause is usually unknown. Sometimes the disorder starts after a tooth extraction, facial nerve injury, herpesvirus infection, or pressing (compression) on the nerve from a blood vessel or tumor.

What Are the Symptoms of Trigeminal Neuralgia?

The most common symptom is intense, stabbing, electric shock–like pain in parts of the face affected by the nerve and its branches. The brief but severe facial pain tends to come and go in the jaw, lips, eyes, nose, scalp, forehead, and face. Pain can start without warning or may be triggered by talking, chewing, putting on makeup, washing the face, or brushing the teeth. Sometimes, even touching a certain part of the face (trigger point) can cause an attack.

How Is Trigeminal Neuralgia Diagnosed?

The doctor makes a diagnosis from symptoms, medical history, and physical examination. Computed tomography (CT) or magnetic resonance imaging (MRI) may be needed to see whether another medical condition is causing pain.

How Is Trigeminal Neuralgia Treated?

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Treatment depends on symptoms. The most important thing is to avoid doing things that will trigger the pain. Many people learn what the trigger points are and ways to not stimulate these areas.

Medicines are also given for the pain.

Surgery is for tumors or blood vessels that press on the nerve or for people who aren't helped by other treatments. These operations include noninvasive radiosurgery (focused radiation therapy), injection or electrical stimulation, and open operation to remove pressure on the nerve.

DOs and DON'Ts in Managing

Trigeminal Neuralgia:

✓ **DO** eat foods that don't involve much chewing.

✓ **DO** tell your doctor about your medicines, including prescription and over-the-counter drugs.

✓ **DO** tell your doctor if you're pregnant or plan to get pregnant.

✓ **DO** call your doctor if your symptoms don't get better with the drug that you were prescribed.

✓ **DO** call your doctor if you have side effects with your medicine.

✓ **DO** call your doctor if you have new symptoms, such as double vision, facial weakness, or changes in hearing or balance. These may indicate the presence of other medical disorders.

⦸ **DON'T** stop taking your medicine or change your dosage because you feel better unless your doctor tells you to.

⦸ **DON'T** despair. Many new treatments and support groups are available.

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FOR MORE INFORMATION

Contact the following sources:

- Trigeminal Neuralgia Association Tel: (800) 923-3608, (352) 331-7009 **Website: http://www.fpa-support.org**
- American Academy of Neurology **Website: http://www.neurology.org**

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MANAGING YOUR

TRIGGER FINGER

What Is Trigger Finger?

Trigger finger refers to a condition that causes a finger to lock in position. It mainly affects the layer of tissue around the tendons of the fingers called the tendon sheath. Tendons are thick fibrous tissues that connect muscles to bones. Inflammation of this sheath prevents the tendon from sliding smoothly through the sheath, so the finger locks in place.

People of all ages get trigger finger, but it's usually seen in those older than 45, and in more women than men. It's thought to be an occupational risk for dentists, tailors, seamstresses, and meat cutters.

What Causes Trigger Finger?

The cause is usually unknown, but some conditions have been related to it. These conditions include gout, diabetes, rheumatoid arthritis, and hypothyroidism (underactive thyroid gland). It's not contagious.

What Are the Symptoms of Trigger Finger?

The finger usually becomes fixed, trapped, or locked in a flexed position when it's flexed or extended. It needs someone to help straighten or move it back into its normal spot. Pain can occur over the tendon area and usually gets worse with movement. Swelling can also be present. In adults, the middle finger is often involved; in children, the thumb is usually affected.

How Is Trigger Finger Diagnosed?

The doctor usually makes the diagnosis from physical examination and symptoms. Sometimes blood tests and x-rays may be done to rule out other causes. These causes include gout, diabetes, fracture, thyroid abnormalities, and carpal tunnel syndrome.

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How Is Trigger Finger Treated?

The best treatment is to reduce inflammation and bring back the normal sliding movement of the tendon in the sheath. In more minor cases, symptoms may improve by avoiding certain tasks. Resting the finger in a special splint may help.

Otherwise, steroid medicine (cortisone) can be injected into the tendon through the palm. The doctor can do this in the office. Injections may be needed more than once, because the problem may come back. Cortisone injection relieves symptoms in 65% of people. Symptoms usually go away in 3 to 5 days, and the locking goes away in 2 to 3 weeks.

If the problem continues, the doctor may suggest surgery. This outpatient operation is done with local anesthetic. A surgeon will make a small cut in the palm and open up the tight band of tissue around the tendon. Sometimes, surgery can be done with the tip of a needle, without making an incision.

DOs and DON'Ts in Managing Trigger Finger:

✓ **DO** follow the instructions given by your doctor.

✓ **DO** see an orthopedic surgeon (a doctor who specializes in bone and tendon diseases) or rheumatologist (a doctor who specializes in joint and soft tissue diseases) if symptoms continue.

✓ **DO** understand that trigger finger can affect any finger. If it occurs in more than one finger, your doctor should rule out other conditions (e.g., diabetes) before you start treatment.

✓ **DO** call your doctor if you have a fever after surgery or you have drainage from the incision.

⃠ **DON'T** be discouraged if your first cortisone injection doesn't work. Repeated cortisone

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shots improve symptoms in more than 80% of people.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186, (800) 346-2267 **Website:** **http://www.aaos.org**
- American Society for Surgery of the Hand Tel: (847) 384-8300 **Website:** **http://www.assh.org**

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MANAGING YOUR

TROCHANTERIC BURSITIS

What Is Trochanteric Bursitis?

A bursa is a sac that is usually in places that can have friction, such as bones against soft tissues, tendons, or muscles. Bursitis means inflammation (swelling) of a bursa. The trochanter is a part of the bone called the femur (thigh bone) that forms the hip joint. Trochanteric bursitis is an inflamed bursa over the hip joint. More women than men, usually 40 to 60 years old, have it, but it can occur at any age. It's not a serious problem but can be uncomfortable and limiting.

What Causes Trochanteric Bursitis?

The cause is unknown. Gout, trauma, infection, and repeated high-intensity use of the hip joint can trigger it. Other conditions related to it are rheumatoid arthritis and arthritis of the hip and lower back. It's not contagious or passed from parents to children.

What Are the Symptoms of Trochanteric Bursitis?

The most common complaint is hip pain over the hip surface. Pain is worse when lying down or standing with weight on the affected side for long periods. Walking, climbing, and running make pain worse. Numbness may occur with the pain, and pressing on the area with a finger or hand may reproduce the numbness.

How Is Trochanteric Bursitis Diagnosed?

The doctor makes a diagnosis from symptoms. Sometimes, the doctor may order blood tests and x-rays to rule out other causes such as gout, neuropathy, osteoarthritis, or hip stress fracture.

How Is Trochanteric Bursitis Treated?

Treatment is usually conservative. Plenty of rest and heat applied to the area for 15 to 20 minutes, four to six times per day, are important.

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Physical therapy exercises can strengthen the hip, knee, and back muscles. The doctor may also use ultrasonography for treatment.

If these measures don't work, the doctor may prescribe antiinflammatory pain medicines. Commonly used medicines include ibuprofen (800 mg taken orally three times per day) and naproxen (500 mg taken orally twice per day). Acetaminophen can also be used.

If medicines don't help the pain, the doctor may suggest seeing a rheumatologist or orthopedist for cortisone injections. A rheumatologist is a doctor specializing in diseases of joints and soft tissues. An orthopedist is a doctor specializing in bone diseases.

Surgery is rarely done, but people who still have problems after these measures may have surgery to remove the bursa.

DOs and DON'Ts in Managing

Trochanteric Bursitis:

✓ **DO** take your medicines as prescribed. Most people get help from antiinflammatory drugs. If cortisone injections are needed, 70% of people respond after the first injection and 90% respond after two injections.

✓ **DO** call your doctor if you have pain and fever after a cortisone injection.

✓ **DO** call your doctor if you have medicine side effects.

✓ **DO** call your doctor if you need a referral to an orthopedist or rheumatologist.

✓ **DO** call your doctor if pain doesn't go away.

⊘ **DON'T** put too much weight on your leg when you have symptoms. Avoid high-intensity

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exercises such as jumping, running, and climbing.

⦸ **DON'T** ignore symptoms of hip pain, especially if you have a fever. You may have a more serious condition.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website:** **http://www.aaos.org**
- National Institute of Arthritis and Musculoskeletal and Skin Diseases Tel: (877) 226-4267 **Website:** **http://www.niams.nih.gov**

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MANAGING YOUR

TUBERCULOSIS

What Is Tuberculosis?

Tuberculosis (TB) is an infection caused by a type of bacteria that attacks and destroys body tissues. It usually affects lungs but can also spread (disseminate) to bones, lymph glands (nodes), nervous system, heart, and other organs.

Many people first have inactive TB, called a latent infection. Later TB becomes active, especially if the immune (infection-fighting) system is weakened, such as by HIV, cancer, or chemotherapy.

What Causes TB?

The cause is a type of bacteria named *Mycobacterium tuberculosis*. People catch TB by close contact, such as breathing in bacteria in the air that someone spread by coughing.

What Are the Symptoms of TB?

People in early stages often feel normal. Symptoms vary depending on which organs are affected and may include a cough lasting at least 3 weeks, coughing up sputum (phlegm) or blood, chest pain, fever, night sweats, losing weight and appetite, tiredness, and weakness.

How Is TB Diagnosed?

The doctor will suspect TB in people with an unexplained cough, weight loss, or fever. The doctor will ask about contact with places and people, history of TB or skin test results, risk factors (especially HIV), foreign travel, and job exposure. A tuberculin skin test (PPD) may be done. For this test, a tiny amount of fluid containing protein derived from TB bacteria is injected under the skin on the arm and swelling that appears is measured 48 to 72 hours later. The size of swelling (induration) where the fluid was injected determines if the tuberculin test is positive. A posi-

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tive test usually means that the person has been exposed to TB. A blood test (quantaferon [QFT-G]) is also available for testing exposure to TB.

The doctor may also want to take chest x-rays and samples of sputum, blood, or urine to look for the presence of mycobaceria. A test for HIV may also be done.

How Is TB Treated?

Active TB can nearly always be cured, usually by taking medicines for 6 months or longer. Appropriate treatment usually requires a regimen of 3 to 4 antibiotics taken daily. People should feel better after a few weeks. It's very important to finish the treatment, even if symptoms disappear. If medicines are stopped too soon, bacteria may stay in the body, and TB may return and spread to other parts of the body and to others. Family members and close contacts will need TB screening.

DOs and DON'Ts in Managing TB:

✓ **DO** take your medicines exactly as your doctor tells you.

✓ **DO** use a routine, such as a pill dispenser, that helps you remember to take your medicines.

✓ **DO** ask your doctor about medicine side effects.

✓ **DO** keep follow-up doctor appointments.

✓ **DO** be careful not to infect others. Follow your doctor's advice on hygiene.

✓ **DO** call your doctor if you have fever or chills, concerns about effects of medicines, or lasting or worsening symptoms despite taking medicines, or if you cough up discolored sputum or blood.

⦸ **DON'T** stop treatment early.

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⦸ **DON'T** smoke.

⦸ **DON'T** assume you're not infective unless your doctor says so.

⦸ **DON'T** drink alcohol or take other medicine unless you talk with your doctor first. Alcohol is toxic to the liver and may interfere with medications you are taking for TB.

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FOR MORE INFORMATION

Contact the following sources:

- Centers for Disease Control and Prevention Tel: (800) 232-4636 **Website:** **http://www.cdc.gov/tb/default.htm**
- The American Lung Association Tel: (800) 548-8252 **Website:** **http://www.lungusa.org**

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MANAGING YOUR

TUBEROUS SCLEROSIS

What Is Tuberous Sclerosis?

In tuberous sclerosis, small tumors grow in many parts of the body, such as the skin, kidneys, brain, heart, eyes, and lungs. The tumors aren't malignant (cancerous) but can cause other problems. The disorder affects about 1 in 10,000 people.

What Causes Tuberous Sclerosis?

Tuberous sclerosis is a genetic disease. It runs in families and is passed from parents to children. Two genes pass on this disorder. They are on chromosomes 9 (*TSC1* gene) and 16 (*TSC2* gene). However, only one-third of cases are familial. The others can result from new mutations. Mutations are changes in DNA, the chemical that carries genetic instructions.

What Are the Signs and Symptoms of Tuberous Sclerosis?

The disease is present at birth, but signs and symptoms may not start right away. Diagnosis is usually made by age 10. Most people have tumors only in one part of the body, such as the skin. Symptoms vary among people and can range from mild to severe. Severe symptoms can include learning problems, but many people have normal or above-normal IQs. In addition to small tumors, common symptoms are white patches on the skin (often on legs) and red bumps on the face (often in a butterfly pattern). Others are areas of rough pebbly skin (usually on the lower back) and fleshy tumors around the nails (especially toenails). Tooth enamel can be pitted, and spasms or seizures can occur. Mental or physical development can be delayed. This depends on where tumors are in the brain.

How Is Tuberous Sclerosis Diagnosed?

This disease is hard to diagnose. The health care provider uses the medical history and physical

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examination for a preliminary diagnosis. Seizures, spasms, or red bumps on the face may raise suspicion of this disease. Many tests may be done. They include electroencephalography (EEG), to check brain activity. Magnetic resonance imaging (MRI) is used to look for tumors. Echocardiography and electrocardiography (ECG) determine if the heart is affected. Eyes are examined for the presence of abnormalities. Urine tests are done to look for kidney problems. Different specialists may be involved in the care of this complex disorder.

How Is Tuberous Sclerosis Treated?

Many kinds of treatment may be needed, depending on how severe the disease is. Some people with mild disease may be undiagnosed and need no treatment. Skin tumors can be removed by lasers or surgery. Medicines treat seizures and tumors in the lungs. Surgery may get rid of tumors inside the body, such as those in the kidneys or brain. Children may need screening for psychiatric, behavioral, and developmental problems. Early intervention can help children do their best in the classroom. This disease has lifelong effects. Even after treatment, people need regular checkups. Treatment can be repeated if tumors grow back.

DOs and DON'Ts in Managing Tuberous Sclerosis:

✓ **DO** join a support group for families with this disease or other genetic diseases.

✓ **DO** talk to a genetic counselor about the effect of this disease on other or future children.

⃠ **DON'T** ignore symptoms. Call your health care provider if your child's symptoms don't get better or they worsen with treatment. Call if you see new symptoms.

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Contact the following sources:

- National Institute of Neurological Disorder and Stroke **Website:**

  www.ninds.nih.gov/health_and_medical/disorders/tuberous_sclerosis.htm

- Tuberous Sclerosis Alliance Tel: 800-225-6872 **Website: www.tsalliance.org**

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CARING FOR YOUR CHILD WITH

TURNER'S SYNDROME

What Is Turner's Syndrome?

Turner's syndrome is a genetic disorder related to a defect in chromosomes. Chromosomes consist of genes that are made up of DNA. Chromosomes inside cells contain a unique blueprint for each person's development. Turner's syndrome affects only girls, who are missing a chromosome that females normally have. This defect leads to physical symptoms that vary and can be mild or severe.

What Causes Turner's Syndrome?

The cause is one of the X chromosomes in females being partly or completely missing. The reason why this chromosome is missing is unknown.

What Are the Symptoms of Turner's Syndrome?

Babies with Turner's syndrome grow slowly and often have feeding problems.

Common physical features include a short webbed neck, short height, wide chest, large or low-set ears, and low hairline at the back of the neck.

Ovaries often don't develop, so neither do breasts. Older girls will be late having their first period or may not have periods. Almost all girls are unable to become pregnant.

Heart and kidney problems, hearing loss, and clumsiness may be present. Usually, girls and women have normal intelligence but rarely may have slight learning problems.

How Is Turner's Syndrome Diagnosed?

A doctor may suspect Turner's syndrome because of a baby's appearance. A chromosome test is done to see whether an X chromosome is missing and confirm the diagnosis. For this test, a small sample of blood is collected. Chromosomes from blood cells are counted, and their size

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and shape are studied. This arrangement of chromosomes is called a karyotype.

Other tests may be needed to check for other problems, such as heart or kidney disorders, caused by Turner's syndrome.

How Is Turner's Syndrome Treated?

Treatment with hormones can help correct some abnormalities. Hormones are chemicals in the body that control growth and other body functions.

Growth can improve by giving growth hormones. This treatment can increase height by several inches.

In early teen years, female hormones may be given. They will help physical development, such as breast growth and starting periods.

Other medicines are used as needed, such as for heart or kidney problems.

Specialists will help the doctor choose the best treatment. These specialists include a geneticist for chromosome problems and an endocrinologist for hormone treatment.

DOs and DON'Ts in Managing

Turner's Syndrome:

✓ **DO** use medicines as directed.

✓ **DO** follow up with an endocrinologist in addition to your primary care doctor.

✓ **DO** help your daughter exercise, eat healthy, and keep to a normal body weight.

✓ **DO** call the doctor if she needs special help with school.

✓ **DO** call the doctor if she feels depressed.

✓ **DO** look for and join a support group. Ask your doctor for help finding one or for more in-

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formation.

⦸ **DON'T** stop using medicines without asking your doctor first.

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FOR MORE INFORMATION

Contact the following sources:

- Turner Syndrome Society Tel: (800) 365-9944 **Website:** **http://www.turnersyndrome.org**
- The Endocrine Society Tel: (888) 363-6274 **Website:** **http://www.endo-society.org**

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MANAGING YOUR

TYPHOID FEVER

What Is Typhoid Fever?

Typhoid fever, also known as enteric fever, is a bacterial infection affecting mainly the intestines. People can get it from contaminated food, water, ice, eggs, and undercooked meat. Also, people who have or carry the bacteria can spread them to others when they handle food without properly washing their hands after using the bathroom.

Typhoid fever is more common in countries without purified water systems. There are about 20 million cases of typhoid fever worldwide yearly, but only about 300 in the United States. Treated, the infection is usually curable in 2 to 3 weeks. Untreated, it can be fatal, especially in children.

What Causes Typhoid Fever?

The kind of bacteria named *Salmonella typhi* cause the disease. Eating or drinking something contaminated with *Salmonella* spreads the illness. Sources include raw shellfish, especially oysters, raw fruits and vegetables, water, and milk. People with weakened immune (infection-fighting) systems have increased risk for typhoid fever.

What Are the Symptoms of Typhoid Fever?

Symptoms can begin 5 to 21 days after exposure to bacteria. The most common symptoms are fever, bellyache, rose-colored rash, chills, headache, loss of appetite, exhaustion, vomiting, and constipation (more common than diarrhea at the start).

How Is Typhoid Fever Diagnosed?

The doctor makes a diagnosis from a medical history (including travel abroad) and physical examination. Tests of blood, stools (bowel movements), and urine are done to look for bacteria.

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Other tests, including x-rays, may be needed to exclude other diseases causing similar symptoms.

How Is Typhoid Fever Treated?

People should rest until symptoms go away. Then activity can slowly increase. For diarrhea, increase fluid intake and don't eat solid foods. As symptoms go away, a well-balanced, high-calorie diet can be started. The doctor will prescribe antibiotics. Hospitalization and intravenous fluids may be needed in severe infection. If possible, use a separate bathroom. Otherwise, scrub the toilet with gloves and a bleach solution after each use. Hand washing is critical to prevent disease spread.

Don't use aspirin or aspirin products for fever. They can irritate the intestines. Instead, use acetaminophen and tepid sponge baths.

It can take 3 to 6 months for the infection to completely go away. Stool tests are done weekly. Negative tests 3 weeks in a row mean that the infection is gone.

DOs and DON'Ts in Managing Typhoid Fever:

✓ **DO** follow a clear liquid diet until you feel better. Drink electrolyte sports drinks.

✓ **DO** wash your hands well after using the bathroom.

✓ **DO** stay away from other people while you have a fever.

✓ **DO** take antibiotics as ordered and until they're all gone.

✓ **DO** increase fluid intake and stay on a liquid diet until diarrhea stops, then slowly start a high-calorie diet.

✓ **DO** call your doctor if during treatment you have shortness of breath, temperature higher

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than 102° F, severe abdominal pain, or severe headache or earache.

✓ **DO** get vaccinated for typhoid fever if you travel to an underdeveloped country.

✓ **DO** be careful in an underdeveloped country. Avoid tap water, ice, and raw fruits and vegetables. Make sure that water for hot drinks is properly boiled.

⃠ **DON'T** make food for anyone until your infection is gone.

⃠ **DON'T** eat raw fruits or vegetables unless you peel them yourself if the water supply may not be safe.

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FOR MORE INFORMATION

Contact the following sources:

- Travelers' Health Centers for Disease Control and Prevention Tel: (800) 311-3435

  Website: http://www.cdc.gov/travel/

- National Institute of Allergy and Infectious Diseases Tel: (301) 496-5717, (866) 284-4107

  Website: http://www3.niaid.nih.gov

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MANAGING YOUR

ULCERATIVE COLITIS

What Is Ulcerative Colitis?

Ulcerative colitis (UC) is a disease that causes sores in the lining of the digestive tract. Irritation is found in the lower part of the tract, the colon (large intestine), and can result in open sores or wounds called ulcers. These ulcers sometimes bleed and make pus and mucus. The colon also empties often, which causes diarrhea.

UC affects men and women equally and seems to run in families. About 250,000 Americans have UC. People between 15 and 35 years old are affected most often. Most people have UC for their whole lives. About half have mild symptoms. Others have more frequent, severe attacks.

What Causes UC?

The cause is unknown.

What Are the Symptoms of UC?

Most common symptoms are pain in the abdomen (belly) and bloody diarrhea with mucus. Bowel movements may relieve the pain, which is usually on the left side. As UC worsens, diarrhea increases, and several bowel movements daily is common. Periods of remission occur, but more than 75% of people have relapses.

Other symptoms include fatigue, weight loss, loss of appetite, and fever. Symptoms outside the colon include joint pains, usually in knees, ankles, and wrists. Eye problems may also occur. Complications include severe bleeding, perforation of the bowel, megacolon (dilation of the colon), and peritonitis (infection in the abdomen). People with UC also have greater chances of having colon cancer.

How Is UC Diagnosed?

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The doctor will review the medical history and do a complete physical examination. The doctor will take blood and stool samples to check for bleeding and infection. UC is confirmed by colonoscopy. In this procedure, a lighted flexible tube is put into the rectum to look at the rectum and lower part of the colon. Colon tissue samples are taken and sent for study with a microscope.

How Is UC Treated?

The goal is to relieve symptoms, control inflammation, and prevent complications.

The main medicines are antiinflammatory drugs, including mesalamine, sulfasalazine, olsalazine, and steroids. Mesalamine is used to maintain remissions and control minor to moderate symptom flare-ups. Steroids are for major flare-ups and to maintain remissions. Severe symptoms may mean hospitalization so the bowel can rest (no food by mouth), and intravenous food is given.

About one quarter of people need surgery, when medicines don't work or disease is severe. Surgery involves removing part of the colon.

DOs and DON'Ts in Managing UC:

✓ **DO** take medicine as prescribed.

✓ **DO** ask your doctor if you should take vitamins, minerals, or iron replacement.

✓ **DO** try to keep to normal physical activity.

✓ **DO** see your doctor regularly. Periodic colonoscopy is important to watch for cancerous changes.

✓ **DO** call your doctor if you get fever or chills, increased number of bowel movements, or increased bleeding.

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✓ **DO** call your doctor if your abdomen becomes swollen, pain increases, or vomiting starts.

⃠ **DON'T** use aspirin. It increases the risk of bleeding.

⃠ **DON'T** drink coffee and alcohol in excess. Limit roughage (raw fruits and vegetables). These can make diarrhea worse.

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FOR MORE INFORMATION

Contact the following sources:

- Crohn's and Colitis Foundation of America Tel: (800) 343-3637 **Website:** **http://www.ccfa.org**
- National Digestive Diseases Information Clearinghouse Tel: (800) 891-5389 **Website:** **http://www.niddk.nih.gov/health/digest/ digest.htm**

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MANAGING YOUR

ULNAR NEUROPATHY

What Is Ulnar Neuropathy?

The ulnar nerve is one of three main nerves in the arm and hand. It provides sensation to parts of the hand and fingers (ring and little fingers). It can become trapped or pinched, especially at or near the elbow and wrist. Ulnar neuropathy refers to inflammation (swelling) of this nerve.

What Causes Ulnar Neuropathy?

Causes include repeated stress on the nerve such as in cyclists, typists, and people who use certain tools (e.g., jackhammers) or play instruments (violin). Pressure on the nerve can result from injuries or blows to the elbow or leaning on the elbow for long periods. Fractures, bone spurs, cysts, tumors, and compression during surgery are other causes.

What Are the Signs and Symptoms of Ulnar Neuropathy?

Symptoms include weakness, numbness, and pain. Feelings of pins-and-needles in parts of the lower arm (especially the ring finger and little finger) can occur. It can be hard to straighten those fingers, so the hand looks odd (called a clawed hand). Symptoms happen more often when the elbow is bent, such as when driving or holding the phone. Some people wake up at night with numb fingers. If the nerve is very pinched or has been pinched for a long time, the hand can have muscle wasting, which cannot be reversed.

How Is Ulnar Neuropathy Diagnosed?

The doctor examines the arm, hand, and fingers and may order electromyography (EMG) to confirm the diagnosis. EMG tests the electrical activity of muscles. Other tests include ultrasonography, magnetic resonance imaging (MRI), nerve conduction studies, needle electrode examination, X-rays, and computed tomography (CT). Nerve conduction studies can tell how well the nerve is

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working and help find the point of compression.

How Is Ulnar Neuropathy Treated?

Nonsurgical conservative treatment will probably be used first. Treatments include drugs for pain, nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants, and anticonvulsants. Occupational therapy, exercises, splints, or cushions may help. Changing how exercises are done or wearing special equipment (gloves) may also prevent more direct nerve pressure. When other treatments don't help, surgery is used to take pressure off the nerve. It's usually done around the elbow but can be done at the wrist. Often, the nerve is moved from behind the elbow to a new place in front of the elbow.

DOs and DON'Ts in Managing Ulnar Neuropathy:

✓ **DO** avoid using your arm with your elbow bent.

✓ **DO** make sure that your chair isn't too low if you use a computer often.

✓ **DO** avoid leaning on your elbow or putting pressure on the inside of your arm.

✓ **DO** keep your elbow straight at night when you're sleeping. You can wrap a towel around your straight elbow, wear an elbow pad backward, or use a special brace.

✓ **DO** change your hand position on the handlebars frequently when you cycle.

⃠ **DON'T** rest your elbow on an armrest.

⃠ **DON'T** drive with your arm resting on an open window.

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Contact the following sources:

- American Academy of Orthopedic Surgeons Tel: (847) 823-7186 **Website: http://www.aaos.org**
- American Academy of Family Physicians Tel: (800) 274-2237 **Website: http://www.aafp.org**

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CARING FOR YOUR CHILD BORN WITH AN

UNDESCENDED TESTICLE

What Is an Undescended Testicle?

Undescended testicle or testis (also called cryptorchidism) is a disorder in which one or both testicles don't move into the scrotum before birth. Shortly before birth, the testicles usually move through a space from the abdomen (belly) down into the scrotum. When a testicle doesn't drop down, it's undescended.

This condition occurs in about 3% of male babies who are born at term and about 30% of premature babies. In fact, more than 90% of all boys who weigh less than 2 pounds at birth will have undescended testis.

What Causes an Undescended Testicle?

The reasons for undescended testicles aren't clear. Perhaps not enough hormones from the mother or from developing testicles were present to cause normal growth. Some blockage may have prevented descent. Hormones taken during pregnancy may also have affected the testicles.

What Are the Symptoms of an Undescended Testicle?

The testicle cannot be seen or felt in its normal location of the scrotum. Usually the baby has no other symptoms.

How Is an Undescended Testicle Diagnosed?

The doctor usually finds undescended testicles during a newborn's first physical examination. In about 80% of cases, the doctor can feel them further up in the inguinal canal (a passage in the lower abdominal wall).

If the doctor cannot feel them in the inguinal canal, an ultrasound examination may be done.

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This test uses sound waves to look inside the body.

The doctor may order other tests if the ultrasound doesn't show the testicles. Computed tomography (CT) can make images of the inside of the body more clearly. Sometimes an operation called laparoscopy needs to be done. In laparoscopy, the doctor uses a small, flexible, lighted tube (laparoscope) to see into the abdomen.

How Is Undescended Testicle Treated?

If the testicles can be felt up in the inguinal canal, they often descend on their own, without any treatment, usually by the baby's first birthday. If they haven't moved down on their own by that time, some treatment will be needed. Surgery, called orchiopexy, will be done to move the testicles into the scrotum.

Undescended testicles that aren't corrected may cause fertility problems, such as low sperm counts, later in life. Men who had an undescended testicle, either fixed by surgery or not, have a greater risk of getting testicular cancer.

DOs and DON'Ts in Managing an

Undescended Testicle:

✓ **DO** keep your baby's doctor appointments. Regular examinations are important.

✓ **DO** call your baby's doctor if your baby seems to be in pain.

⃠ **DON'T** panic. In most cases, the testicles will descend on their own without treatment.

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FOR MORE INFORMATION

Contact the following source:

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- American Urological Association Tel: (866) 746-4282 **Website: http://www.auanet.org**

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MANAGING YOUR

URINARY INCONTINENCE

What Is Urinary Incontinence?

Urinary incontinence is the uncontrollable loss of urine. It is very common, especially in women. Up to 60% of women have some degree of incontinence.

What Are the Causes of Urinary Incontinence?

The two most common types are stress incontinence and urge incontinence. Stress incontinence is losing urine in a spurt or gush with certain activities (e.g., coughing, sneezing, lifting, exercising). It can be caused by childbirth or growing older. Urge incontinence is losing urine on the way to the bathroom. It can be caused by drugs, caffeine, alcohol, or growing older. Many bladder problems worsen during menopause.

What Are the Symptoms of

Urinary Incontinence?

In very mild incontinence, a small amount of urine sometimes leaks (dribbles) during a cough or sneeze, or on the way to the bathroom. In mild to moderate incontinence, urine leaks daily and/or a pad is needed for protection. In severe incontinence, urine soaks a pad several times each day. Incontinence may limit daily activities.

How Is Urinary Incontinence Diagnosed?

Diagnosis involves taking a medical history, x-rays, blood tests, urinalysis, and other tests to see how the bladder works. These tests, called urodynamic tests, measure pressure in the bladder, urine flow, and the amount of urine left in the bladder after urination.

How Is Urinary Incontinence Treated?

Strengthening pelvic floor muscles is usually the first step in managing stress incontinence.

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Tightening these muscles is called a Kegel exercise. If Kegel exercises do not help, special physical therapy may improve bladder control. This therapy includes biofeedback and electrical stimulation.

Special devices, called pessaries, are also available to treat stress incontinence. These devices can be used to support organs such as the bladder. Sometimes pessaries are useful when urine is lost only during certain activities, such as jogging, aerobics, and horseback riding.

The first step in treating urge incontinence is usually training the bladder to empty (void) at certain times. The goal is for 3 hours to pass before the need to void during the daytime without any leaking. Sometimes medicines can help with bladder training. These drugs may cause dry mouth or eyes but are generally well tolerated. Various operations can also be used for stress incontinence. Specialists such as gynecologists or urologists do these operations.

DOs and DON'Ts in Managing Urinary

Incontinence:

✓ **DO** your Kegel exercises as directed.

✓ **DO** take your medicine as directed.

⃠ **DON'T** drink lots of liquids containing caffeine (e.g., coffee, black tea, sodas). Caffeine can make the kidneys produce more urine faster than normal. Both stress and urge incontinence will get worse, and you will void more often.

⃠ **DON'T** drink excessive amounts of alcohol. Alcohol is also a diuretic.

⃠ **DON'T** drink large amounts of fluids during the day or at one time.

⃠ **DON'T** drink liquids after 7 to 8 pm if you get up more than twice during the night to uri-

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nate.

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Contact the following sources:

- National Association for Continence Tel: (800) 252-3337 **Website: http://www.nafc.org**
- American Urological Association Tel: (866) 746-4282 **Website:**

http://www.urologyhealth.org

- Simon Foundation for Continence Tel: (800) 237-4666 **Website:**

http://www.simonfoundation.org

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MANAGING YOUR

URINARY TRACT INFECTION

What Are Urinary Tract Infections?

The urinary tract consists of organs that make, store, and get rid of urine: kidneys, ureters, bladder, and urethra.

Kidneys make urine. Urine then flows in tubes called ureters to the bladder. From the bladder, urine leaves the body through the urethra. Urinary tract infections (UTIs) are bacterial infections in any part of this tract.

What Causes UTIs?

The most common cause is a kind of bacteria named *Escherichia coli*, which is found in the intestines. Bacteria on the skin or near the anus can get into the urinary tract and move up. Women have a shorter urethra than men, so they get UTIs more often.

Bacteria also get into the tract through catheters (tubes) used during medical treatment, when stones or congenital abnormalities block the tract, or after vigorous sex. UTIs can also occur when another infection travels to the kidneys.

UTIs aren't usually contagious, but sex can be painful during an infection and should be avoided.

What Are the Symptoms of UTIs?

Symptoms include feeling the need to urinate often, painful urination, urinating only small amounts of urine, no control of the urine flow, cloudy or foul-smelling urine, and blood or pus in urine.

If the kidneys are infected, fever and back pain may occur.

How Are UTIs Diagnosed?

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The doctor may want to test the urine (urinalysis). A clean-catch urine sample is needed. To get this sample, special cleaning methods are used and urination is started, stopped, and started again.

How Are UTIs Treated?

Antibiotics are usually needed for 3 to 10 days. Fluid intake should be increased to help flush the urinary tract. Caffeine and alcohol should be avoided. The doctor may prescribe medicine such as phenazopyridine to relieve pain when urinating. This drug will turn urine orange. Over-the-counter pain relievers (acetaminophen, ibuprofen) may also help. Sitz baths may ease discomfort. Rest until fever and pain are gone.

No special diet is needed, but drinking juices (cranberry or prune juice) to make urine more acid can occasionally help, as can taking vitamin C.

DOs and DON'Ts in Managing UTIs:

✓ **DO** drink 6 to 8 glasses of water daily. Drinking water and cranberry juice may in some cases help the treatment of UTIs.

✓ **DO** use good hygiene. Women should wipe from front to back after using the toilet. Avoid douches and sprays (increase chances of getting UTIs). Showers may be better than baths. Wear cotton underwear and avoid tight pants.

✓ **DO** lower the risk of UTIs. Women can urinate just before and just after sex. Avoid using a diaphragm or spermicide.

✓ **DO** try to urinate often and empty your bladder completely.

✓ **DO** tell your doctor if you take birth control pills. Some antibiotics interfere with birth con-

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trol pills.

✓ **DO** take antibiotics until they're gone. If you get UTIs often, your doctor may give you antibiotics to prevent them.

✓ **DO** call your doctor if your fever continues after 48 hours of antibiotic therapy or symptoms return after you finish your antibiotics.

⃠ **DON'T** skip doses or stop taking antibiotics before they're gone.

⃠ **DON'T** have sex until fever and symptoms stop.

⃠ **DON'T** hold your urine for long periods.

⃠ **DON'T** drink caffeinated beverages or alcohol.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Family Physicians Tel: (800) 274-2237 **Website:** **http://www.familydoctor.org**
- American Urological Association Tel: (866) 746-4282 **Website:** **http://www.urologyhealth.org**
- National Kidney and Urologic Diseases Information Clearinghouse Tel: (800) 891-5390 **Website:** **http://kidney.niddk.nih.gov**

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CARING FOR YOUR CHILD WITH

URINARY TRACT INFECTIONS

What Are Urinary Tract Infections?

Urinary tract organs make, store, and get rid of urine. Kidneys make urine. Urine then flows in tubes called ureters to the bladder. From the bladder, urine leaves the body through the urethra. Urinary tract infections (UTIs), the most frequent bacterial infections in childhood, affect any part of this tract. Cystitis is infection of the lower part (bladder). Pyelonephritis is infection of the upper part.

In very young babies, more boys (uncircumcised) have UTIs. In older children, more girls than boys get them. Children who get UTIs may have abnormal urinary tracts.

What Causes UTIs?

The most common cause is bacteria, one named *Escherichia coli*, which lives in the stomach and intestines. *Staphylococcus* bacteria are common causes in teen girls. Bacteria on the skin or near the anus can get into the urinary tract. Bacteria can also get in from catheters (tubes) used during medical treatment.

Children who delay bathroom visits are more likely to get UTIs. Higher risks also involve not emptying the bladder completely, constipation, improper wiping methods, and sexual activity. Certain antibiotics and abnormalities such as vesicoureteral reflux (reflux of urine from the bladder back into the ureters) can cause UTIs.

What Are the Symptoms of UTIs?

Symptoms include fever (especially in babies and children younger than 2), irritability, poor feeding, and failure to thrive. Older children have symptoms similar to those of adults. These include fever, pain and tenderness in the abdomen (belly), need to urinate often, painful urination,

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no control of urine flow (incontinence), producing only a few drops of urine at a time, bloody urine, and vomiting. Some children have few or no symptoms. Fever and low-back pain may mean infected kidneys, a serious concern.

How Are UTIs Diagnosed?

The doctor uses a physical examination and urine tests. Urinalysis is the quick test done first, and then urine is cultured. By cultures, doctors see which bacteria grow in the laboratory and can pick the best treatment. Doctors get urine samples by using different methods, depending on the child's age. Imaging tests, done in special cases, look for abnormalities.

How Are UTIs Treated?

Certain children, such as very young babies and seriously ill children, get treatment in hospitals. Others are given oral antibiotics as outpatients. Medicine and sitz baths may be offered for pain. Drinking more fluids (especially cranberry and prune juice) may occasionally help flush out the urinary tract. Surgery may be needed for abnormalities. Exercises to strengthen and train the bladder may help prevention.

DOs and DON'Ts in Managing UTIs:

✓ **DO** encourage regular trips to the bathroom.

✓ **DO** encourage drinking lots of water to help prevent and get rid of UTIs.

✓ **DO** teach good hygiene. Girls should wipe from front to back after using the toilet. Showers may be better than baths. Wearing cotton underwear and avoiding tight clothing may also help.

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✓ **DO** make sure that your child takes antibiotics until all the pills or liquid are gone. Stopping sooner because symptoms are gone can make antibiotics less effective later.

⃠ **DON'T** offer your child caffeinated beverages.

⃠ **DON'T** use too many antibiotics, such as for colds, which can make it harder to treat UTIs.

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FOR MORE INFORMATION

Contact the following sources:

- The American Academy of Pediatrics Tel: (847) 434-4000 **Website: http://www.aap.org**
- American Academy of Family Physicians Tel: (800) 274-2237 **Website: http://www.familydoctor.org**
- American Urological Association Tel: (866) 746-4282 **Website: http://www.urologyhealth.org**
- National Kidney and Urologic Diseases Information Clearinghouse Tel: (800) 891-5390 **Website: http://kidney.niddk.nih.gov**

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MANAGING YOUR

UTERINE CANCER

What Is Uterine Cancer?

A woman's uterus (womb) is located between the bladder and rectum and includes the cervix and the body. The cervix connects the uterus and vagina, and the body is connected to the fallopian tubes. Uterine cancer is cancer that grows in the lining of the uterus. Cancer can start from the cervix or the inner layer of the uterus (endometrium). It can also start from the body of the uterus; these rare tumors are uterine sarcomas.

Uterine cancer occurs most often in women who went through menopause (change of life).

What Causes Uterine Cancer?

The cause isn't known, but many things can increase the risk. Diabetes, high blood pressure, taking the hormone estrogen without also using progesterone, and being very overweight may lead to higher risk.

Other conditions that increase risk are family history of breast or ovarian cancer, uterine polyps, hormone imbalance, and going through menopause later than usual.

What Are the Symptoms of Uterine Cancer?

Early symptoms include bleeding and spotting, especially after sex. Watery or blood-streaked vaginal discharge can happen just before bleeding or spotting. Often bleeding occurs after periods have stopped for 12 months or more. The uterus may get larger, large enough to feel low in the abdomen (belly).

Later symptoms, after cancer spreads to other organs, include pain in the abdomen and chest and weight loss.

How Is Uterine Cancer Diagnosed?

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The doctor will make a diagnosis from the medical history, physical examination, and endometrial biopsy. In this biopsy, the doctor will take a tissue sample from the uterus and test it for cancer. Uterine cancer can spread to the bladder, rectum, and other organs. Other tests will be done to stage the cancer—find out whether it has spread and how far. Tests include Pap smears, mammography, blood tests, computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography, and scraping the uterine wall.

How Is Uterine Cancer Treated?

Treatment depends on the cancer's spread. Usually the uterus and tumor, ovaries, and fallopian tubes will be removed in surgery.

Then radiotherapy, hormonal therapy, cortisone drugs, and chemotherapy may be used to shrink remaining cancer and prevent spread of cancer. An oncologist (doctor specializing in cancer) will help in your care.

DOs and DON'Ts in Managing Uterine Cancer:

✓ **DO** find a surgeon and oncologist with experience in uterine cancer treatment.

✓ **DO** keep doctor appointments during and after treatment to watch for side effects and return of cancer.

✓ **DO** resume sex and normal activities 4 to 8 weeks after surgery.

✓ **DO** realize that if you haven't gone through menopause, you won't have periods after your operation. You may have symptoms such as hot flashes if both of your ovaries were removed during surgery.

✓ **DO** call your doctor if you have abnormal vaginal discharge (smell, amount, color).

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✓ **DO** call your doctor if you need emotional support.

✓ **DO** call your doctor if you have side effects of treatment, signs of infection (fever, muscle aches, headache), or new, unexplained symptoms.

⃠ **DON'T** ignore vaginal bleeding before or after menopause.

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FOR MORE INFORMATION

Contact the following source:

- American Cancer Society Tel: (800) 227-2345 **Website: http://www.cancer.org**

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MANAGING YOUR

UTERINE FIBROIDS

What Are Fibroids?

Fibroids, or leiomyomata (myomas), are common noncancerous growths that usually occur in or on the muscle walls of the uterus. One cell divides repeatedly and grows into a firm, rubbery mass separate from the rest of the uterine wall. Almost half of women older than 50 have these growths. They're more common in African American women than in Caucasian women. They can grow as a single mass or more often as a number of masses of different sizes.

What Causes Fibroids?

The cause isn't clear. Several factors probably work together to produce fibroids. These factors may be hormones such as estrogen, genetics (runs in families), and environmental. Being overweight, never having had a child, and getting periods before age 10 also may have an effect. The fibroids usually, but not always, shrink after menopause (change of life).

What Are the Symptoms of Fibroids?

Most fibroids (30% to 50%) cause no symptoms. Problems, when they occur, are related to the size and location of the fibroids. Fibroids may grow to be quite large so that a woman may look pregnant and have symptoms of pregnancy: pressure in the pelvic area (lower belly), heaviness, and need to go to the bathroom often to urinate. Fibroids in the uterine wall or in the cavity of the uterus may cause bleeding between periods or heavier and more painful periods. Constipation, backache, pain during sex, and lower belly pains may occur. Rarely, fibroids cause sudden pain or bleeding.

How Are Fibroids Diagnosed?

The doctor will do an examination of the pelvic area. Ultrasound or x-rays may be used but

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aren't always needed for diagnosis. The doctor may do a special procedure (hysteroscopy) for women with bleeding symptoms. This simple procedure lets the doctor look into the uterus to find the cause of the bleeding or to plan or carry out therapy.

How Are Fibroids Treated?

Most fibroids need no treatment and only regular checks to be sure that they're not growing too large or causing problems. Medicines including hormones and drugs that act against hormones can be tried. If fibroids continue to be a problem, hysterectomy (surgery to remove the uterus) is an option. Sometimes, fibroids alone may be surgically removed (myomectomy), which saves the uterus if children are wanted. Another newer method is uterine artery embolization. In this method, arteries to the uterus are blocked so they don't feed the fibroids. Myolysis (electric current destroys fibroids and shrinks blood vessels feeding them) and cryomyolysis (liquid nitrogen is used instead of electric current) are other methods. However, fibroids can return and mean more surgery later. Newer medicines may shrink fibroids, but this change is only temporary.

DOs and DON'Ts in Managing Fibroids:

✔ **DO** get regular doctor checkups.

✔ **DO** tell your doctor your concerns and describe your symptoms.

⃠ **DON'T** delay having children just because you have fibroids. They usually won't get in the way of pregnancy. If you do need treatment for fibroids, some treatments can temporarily or permanently prevent you from becoming pregnant.

⃠ **DON'T** worry about getting cancer from fibroids. Typical fibroids are not cancerous.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Obstetricians and Gynecologists **Website: http://www.acog.org**
- WebMD **Website: http://www.webmd.com**
- U.S. Department of Health and Human Services **Websites: http://womenshealth.gov**

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MANAGING YOUR

UTERINE PROLAPSE

What Is Uterine Prolapse?

Uterine prolapse , also known as "pelvic organ prolapse," is a bulging of the uterus (womb) into the vagina.

Normally, the uterus is held just above the vagina by muscles and ligaments. With uterine prolapse, these muscles and ligaments stretch and get too weak to hold the uterus. The uterus slowly sags and moves out of its normal position, so that it bulges into the vagina. In severe cases, the uterus bulges so much that it protrudes outside the vagina, in between the legs. The bladder (which stores urine), urethra (which carries urine to outside the body), and rectum (muscle that controls bowel movements) may bulge out with the uterus.

An untreated prolapse can cause sores on the cervix (opening to the uterus) and increase chances of infection or injury to other pelvic organs.

What Causes Uterine Prolapse?

The cause is often pregnancy and childbirth. The more pregnancies, the more likely it will happen. Large babies, long labors, and use of forceps during delivery can make it even more likely.

Other causes include older age, being overweight or not physically fit, and heavy lifting. It can also happen if a condition puts extra pressure in the belly. Such conditions include a growth, a lot of coughing (such as from smoking), and constipation.

What Are the Symptoms of Uterine Prolapse?

Symptoms include feelings of pressure, fullness, or heaviness; pelvic pain (low in the belly); a backache that worsens during heavy lifting; and pain with sex. Other symptoms are a lump in the front or back of the vagina; bulging outside of the vagina, between the legs; pain when urinating; leaking urine during laughing, sneezing, or coughing; and problems with bowel movements.

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How Is Uterine Prolapse Diagnosed?

The doctor makes a diagnosis by a physical examination (including a pelvic examination and Pap smear). The doctor may do other tests, including pelvic ultrasonography, computed tomography (CT), and biopsy (to check for growths inside the uterus).

How Is Uterine Prolapse Treated?

Treatment depends on how bad the prolapse is, age, sexual activity, if other pelvic problems exist, and if pregnancy is desired.

Mild symptoms may mean using exercises (Kegel), hormone therapy, or a device called a pessary. Kegel exercises strengthen muscles and ligaments holding the uterus and vagina in place. Hormone creams also make these muscles and ligaments stronger. A pessary is a small ring-shaped device put into the vagina to hold the uterus in place.

More severe prolapse may mean surgery. Sometimes the uterus must be removed (hysterectomy).

DOs and DON'Ts in Managing Uterine Prolapse:

✓ **DO** Kegel exercises daily. Do general exercises regularly for good overall muscle tone.

✓ **DO** lose weight if you're overweight.

✓ **DO** eat a well-balanced, high-fiber diet to avoid getting constipated.

✓ **DO** call your doctor if you have unusual vaginal bleeding, discomfort, or trouble urinating.

✓ **DO** call your doctor if symptoms don't get better after 3 months of treatment or exercise.

✓ **DO** avoid heavy lifting.

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⦸ **DON'T** ignore pain or bleeding from your vagina.

⦸ **DON'T** smoke.

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MANAGING YOUR

BACTERIAL VAGINAL INFECTION

What Is Bacterial Vaginal Infection (Bacterial Vaginosis)?

Overgrowth of normal or abnormal bacteria in the vagina can result in irritation, inflammation (swelling), odor (especially after sex), and other symptoms. The balance of bacteria normally found in the vagina is upset and there is overgrowth of other types of bacteria. This common disorder accounts for about half of all vaginal infections. The urethra (opening of the bladder), the bladder, and skin in the genital area may also be affected.

Bacterial vaginal infection occurs most during years when women can have children. However, women of all ages can get it.

What Causes Bacterial Vaginal Infection?

The cause of the upset in the balance of bacteria isn't clear. Factors that may be related to bacterial vaginal infection include a new or many sex partners, douching, hot weather, poor health, and poor hygiene. However, women who never had sex can get it too. The risk of getting it can increase if you have diabetes or a weakened immune (infection-fighting) system.

It can't be caught from toilet seats, linens, or swimming pools.

What Are the Symptoms of Bacterial Vaginal Infection?

A strong fishy odor (often worse after sex) or increased vaginal secretions may be the first or only symptoms. The secretions may be clear, white, or gray and may be thin or heavy. Burning during urination and itching around the vagina may occur. Irritation, swelling, redness, and pain with sex are all common. Many women have no symptoms.

How Is Bacterial Vaginal Infection Diagnosed?

The doctor will examine the pelvic area, especially the vagina. The doctor will also take samples

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of the secretions with a swab to study with a microscope and perform additional tests.

How Is Bacterial Vaginal Infection Treated?

Antibiotics (metronidazole, clindamycin) are given either by mouth or as a vaginal cream or suppository.

Untreated bacterial vaginal infection may lead to complications, such as pelvic inflammatory disease (PID), endometritis, cervicitis, pregnancy problems, and postoperative infections.

DOs and DON'Ts in Managing Bacterial Vaginal Infection:

✓ **DO** see a doctor if you think that you have an infection.

✓ **DO** follow your doctor's instructions.

✓ **DO** finish all your antibiotic medicine even though you may feel better.

✓ **DO** limit your number of sexual partners, to prevent future infections.

⦸ **DON'T** use over-the-counter medicines, leftover drugs, or medicines that you get from friends to treat your infection.

⦸ **DON'T** douche or rinse away your vaginal secretions before your doctor's appointment. Your doctor will want to see the secretions to make a correct diagnosis. For that matter, don't douche at all.

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MANAGING YOUR

VAGINAL CANCER

What Is Vaginal Cancer?

Cancer refers to uncontrolled growth of abnormal cells in the body. Vaginal cancer means cancer cell growth in the vagina. The vagina is the tube connecting the uterus with genitals outside. This cancer often occurs in cells lining the vagina (or birth canal). This rare cancer affects 1 per 200,000 women. It mainly occurs after menopause (change of life). The mean age at diagnosis is 60 years. The cancer can spread (metastasize) to nearby organs or other parts of the body through the bloodstream or lymph system.

What Causes Vaginal Cancer?

The cause is unknown. Women whose mothers took a drug called DES (diethylstilbestrol) during pregnancy have a higher risk of getting it, and at a younger age. Anything that causes long-term inflammation of the vagina may increase the risk of this cancer. This includes overuse of a pessary (a device that is put into the vagina to keep it from dropping). Pelvic radiation therapy, infection with human papillomavirus (HPV), and a family history of cancer of reproductive organs may also increase the risk.

What Are the Signs and Symptoms of Vaginal Cancer?

Common symptoms include bleeding that isn't related to normal periods, pelvic pain or pressure, pain and problems when urinating, and pain or bleeding during sex. Constipation and a lump in the vagina can also occur.

How Is Vaginal Cancer Diagnosed?

The health care provider may suspect the diagnosis from symptoms and will perform a pelvic examination to look and feel for inflammation, ulcers, lumps, or tumors. A Pap smear is done.

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This involves gently scraping the vagina and cervix to collect cells. These are then checked with a microscope. Other tests may include a biopsy, chest X-ray, and computed tomography (CT) of the pelvis and abdomen (belly). A biopsy involves taking a small tissue sample to study with a microscope.

How Is Vaginal Cancer Treated?

Surgery, chemotherapy, and radiation are used. Which treatment or combination of treatments depends on where and how severe the cancer is and the woman's age and physical condition. The more the disease spread, the longer and more complicated the treatment. The health care team may include specialists in cancer treatment (oncologists and hematologists), radiation oncologists (specialists who use X-ray therapy to shrink tumors), and surgical oncologists (specialists who use surgery to treat cancer).

Surgery is the most common treatment. Small cancers may have surgery with a laser, a narrow beam of light that can destroy the tumor. Radiation therapy may be used alone or with surgery. Chemotherapy drugs can be used to kill cancer cells. They're usually given with surgery or radiation.

DOs and DON'Ts in Managing Vaginal Cancer:

✓ **DO** keep all appointments with specialists.

✓ **DO** follow a good diet to help stamina and coping with treatment's side effects.

✓ **DO** learn about your illness. Find a support group if you think that will help.

⃠ **DON'T** ignore symptoms. Call your health care provider if your symptoms don't get better or they worsen with treatment. Call if you get new symptoms.

⃠ **DON'T** stop taking your medicine or change the dosage because you feel better unless your

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health care provider tells you to.

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- American Cancer Society Tel: (800) 227-2345 **Website: www.cancer.org**
- National Cancer Institute Tel: (1-800) 4-CANCER **Website: http://www.nci.nih.gov**
- American College of Obstetricians and Gynecologists Tel: (202) 638-5577 **Website: http://www.acog.org**

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MANAGING YOUR

VAGINAL DRYNESS

What Is Vaginal Dryness?

Vaginal dryness is the loss of normal moisture (or lubrication) in the vagina. The result can be feelings of discomfort and pain. It can also make sexual activity uncomfortable. It's a common problem. Any woman can have it, but it's more common in women close to or after menopause (change of life). It affects about one in five women near that time and more than half of women after they don't make the female hormone estrogen for 5 years.

What Causes Vaginal Dryness?

Vaginal dryness may be due to changes in the vagina caused by infection or low estrogen levels. Low estrogen levels can occur after menopause (atrophic change), childbirth and breast-feeding, cancer treatment, smoking, and surgery (removal of ovaries). Vaginal dryness may also occur because of medicines, douching (cleaning the vagina with special liquids), skin conditions in the genital area, and not enough or improper sexual stimulation. Sometimes, the cause is unknown.

What Are the Symptoms of Vaginal Dryness?

Irritation, itching, burning, and pain with sex are the most common symptoms. Because the vaginal tissues are less elastic, small tears or slight bleeding after wiping or sex may also occur.

How Is Vaginal Dryness Diagnosed?

The doctor makes a diagnosis from symptoms and an examination of vaginal tissues. The doctor may in some cases also get a sample of cells or secretions from the vagina for study with a microscope or other tests.

How Is Vaginal Dryness Treated?

The doctor will discuss the best way to manage symptoms. Some women may use estrogen

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supplements, which may be taken by mouth as a pill, absorbed from a patch placed on the skin, applied as a cream directly on the vagina and its opening, or absorbed from a pill placed in the vagina. Many women sometimes use water-soluble lubricants during sex. Some long-acting moisturizers can give some relief. Other treatments include self-care measures, such as increasing water intake to avoid getting dehydrated.

DOs and DON'Ts in Managing Vaginal Dryness:

✓ **DO** let your doctor know if you have symptoms of vaginal dryness.

✓ **DO** practice good vaginal hygiene.

✓ **DO** drink more water.

✓ **DO** try over-the-counter moisturizers or water-based lubricants.

✓ **DO** give yourself time to become aroused and lubricated.

⃠ **DON'T** use oil-based substances, such as petroleum jelly, without getting your doctor's okay. They can result in a gummy mess that can do more harm than good.

⃠ **DON'T** use products that can irritate the vagina. These products include soaps, lotions, bubble bath, douches (vinegar or yogurt), feminine sprays, and perfumes.

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MANAGING YOUR

VAGINAL YEAST INFECTION

What Are Vaginal Yeast Infections?

A yeast called *Candida albicans* usually lives in the vagina, rectum, and mouth as well as in the air. Normally, bacteria that also live in the vagina make it hard for this yeast to grow. Being sick, taking antibiotics, and other factors can change the acid balance of the vagina, so the yeast can grow and cause problems. These yeast infections are very common, and about 75% of women have such infections during their lives. Some women have two or more infections.

What Causes Vaginal Yeast Infections?

Many things can increase the chance of getting an infection. These include pregnancy, stress, antibiotics, birth control pills, diabetes, being overweight, poor diet (eating too much sugar), lack of sleep, and sickness.

What Are the Symptoms of Vaginal Yeast Infections?

Women can have only a few symptoms, which may be mild or severe. The most frequent symptom is severe itching in and near the vagina. Sometimes, a thick lumpy discharge that looks like cottage cheese but doesn't smell bad also occurs. Burning, swelling, and redness of the vagina and pain with sex are also possible, but these are also symptoms of other diseases, not just a yeast infection.

How Are Vaginal Yeast Infections Diagnosed?

The doctor will examine the pelvic area, especially the vagina, to check for swelling and a discharge. The doctor will also take samples of the vaginal secretions with a swab to study with a microscope.

How Are Vaginal Yeast Infections Treated?

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The treatment goal is to get the vaginal bacteria and yeast back in a healthy balance, by stopping the excessive growth of the yeast. The doctor may prescribe a tablet of the antifungal drug fluconazole to be taken by mouth. Antifungal medicines can also be given as creams, tablets, ointments, or suppositories that are put into the vagina. These over-the-counter medicines include butoconazole, clotrimazole, miconazole, nystatin, tioconazole, and terconazole.

DOs and DON'Ts in Managing Vaginal Yeast Infections:

✓ **DO** call your doctor if you think that you have an infection.

✓ **DO** follow your doctor's instructions. Finish your medicine even though your symptoms may be gone.

✓ **DO** limit your number of sexual partners, to prevent future infections.

✓ **DO** wear cotton underwear and pantyhose with a cotton crotch.

✓ **DO** change tampons and pads often during your period.

✓ **DO** eat a good diet and drink enough water daily.

✓ **DO** follow proper hygiene. Wipe from front to back after going to the bathroom.

✓ **DO** use condoms during sex, but don't have sex while you're being treated for a yeast infec-

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tion.

⦸ **DON'T** douche or rinse away your vaginal secretions before your doctor's appointment.

Your doctor will want to see the secretions to make a correct diagnosis. For that matter, don't douche at all.

⦸ **DON'T** use perfumed products such as bubble bath, sprays, pads, and tampons.

⦸ **DON'T** wear tight underwear or clothes made of synthetic fibers.

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MANAGING YOUR

VARICOCELE

What Is a Varicocele?

A varicocele is an enlargement of veins inside the scrotum, similar to a varicose vein that can appear in the leg. The scrotum is the pouch that hangs below the penis and holds the testicles. Veins carry blood from tissues and cells back to the heart, where the blood cells get oxygen. The scrotum has two sides, the right and the left. A varicocele can form in either side or both sides. It often forms on the left because these veins are normally under more pressure than the ones on the right. A varicocele may result in an enlarged scrotum.

Varicoceles are common. About 15% of all men get them. They can develop in childhood, but most often they occur in teenage boys and young men. Varicoceles are usually harmless, but they can affect fertility (the ability to make a woman pregnant). About 40% of infertile men have a varicocele.

What Causes a Varicocele?

Veins contain one-way valves that push blood in one direction, toward larger veins. When valves inside the veins in the testicles and scrotum don't work properly, blood backs up and causes these veins to swell. A varicocele is the result.

What Are the Symptoms of a Varicocele?

A varicocele usually causes no symptoms. People don't know that it exists until a doctor examines the scrotum. Sometimes a man or boy becomes aware of a larger scrotum, but this is painless. There may be a dull pain or a heavy, dragging feeling in the scrotum. A varicocele may also cause the testicle on the affected side to shrink because of the pressure. People may notice a painless swelling in the scrotum that feels like a bag of worms. The enlarged veins make the

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scrotum feel like this.

How Is a Varicocele Diagnosed?

The doctor will diagnose a varicocele by examining the scrotum. If the diagnosis is unclear, the doctor may order an imaging test called ultrasonography. This test can get pictures of the veins with the scrotum. Other causes of swelling of the scrotum can be ruled out.

How Is a Varicocele Treated?

No treatment is needed unless pain or other symptoms occur, the testicle shrinks, or fertility problems appear. Treatment, if needed, involves an operation called a varicocelectomy. In this operation, veins may be taken out or tied so that the blood supply is stopped and the veins collapse. A doctor called a urologist will do this surgery. A urologist specializes in treating the male and female urinary system and male reproductive system. This procedure may help fertility. Surgical removal of the veins is a minor operation, and 1 to 7 days off work will be needed. Discomfort or bruising may occur. There's about a 15% chance that the problem will return. If it does, the surgery can be done again.

DOs and DON'Ts in Managing a Varicocele:

✓ **DO** wear an athletic supporter if you have a large varicocele.

✓ **DO** call your doctor if you have symptoms.

✓ **DO** call your doctor if you have fertility problems.

⃠ **DON'T** ignore pain or swelling in your scrotum.

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MANAGING YOUR

VARICOSE VEINS

What Are Varicose Veins?

Blood travels in vessels called arteries and veins. Arteries take blood with oxygen and nutrients away from the heart to body cells. Veins carry blood back to the heart after cells get the oxygen and nutrients. Varicose veins are enlarged, twisted-looking veins that lie close to the skin's surface. They occur most often in the legs. Leg muscles help support veins and push blood up toward the heart. Valves in veins help stop blood from falling down or pooling in the legs.

For many people, varicose veins are mostly a cosmetic problem. For others, they cause symptoms and more serious problems, such as blood clots, skin ulcers, or blood circulation disorders.

What Causes Varicose Veins?

The cause is weakening or failure of valves in veins to stop blood from pooling in the legs. They aren't contagious or inherited but do run in families. They're more common in older people, women, overweight people, and people who stand in one place for long periods.

What Are the Symptoms of Varicose Veins?

Symptoms include legs that ache or feel heavy, especially after standing or sitting for long periods. Others are bulging, bluish veins along the thigh or ankles or across the knees; swelling; and dry, itchy skin. Skin color changes, thin skin, ulcers, and infection of soft tissue (cellulitis) can occur near the ankles.

How Are Varicose Veins Diagnosed?

The doctor makes a diagnosis from a leg examination and symptoms. If a blood clot is suspected, the doctor may order ultrasonography to look for the clot.

How Are Varicose Veins Treated?

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Treatment includes staying off your feet as much as possible, wearing elastic support stockings, having sclerotherapy, and having surgery. For people without symptoms and no ulcers or skin breakdown, observation, exercise, losing weight, raising the legs, and elastic stockings are used. Stockings can be knee-high, thigh-high, or pantyhose length and should cover the veins.

In sclerotherapy, the doctor injects sclerosing solutions or a sclerosing foam into a small dilated vein that's causing symptoms. The solutions make the veins collapse and scar.

Surgery is usually used if other treatments don't help symptoms; if ulcers, leg swelling, skin breakdown, and leg clots occur; and if people have cosmetic concerns. The most common surgery is called ligation (tying) and stripping. A certain large vein is tied and pulled out of the leg. Many smaller varicose veins are branches of this large vein. The smaller veins are injected with sclerosing solution. The leg is then wrapped with elastic bandages.

Endovenous laser ablation involves targeting the vein walls internally with a laser beam to shrink them.

DOs and DON'Ts in Managing Varicose Veins:

✓ **DO** exercise (walk) regularly and lose weight.

✓ **DO** raise your legs, and avoid standing in one place for long periods.

✓ **DO** wear compression stockings daily for them to work properly.

✓ **DO** call your doctor if your varicose veins cause pain, you have skin breakdown or ulcers, or you're bleeding from a varicose vein.

✓ **DO** call your doctor if you have a tender, hot lump near a varicose vein. It can be a dangerous blood clot (thrombophlebitis).

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⦸ **DON'T** stand or sit for long periods; this helps prevent blood from pooling in the legs.

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- The American Society for Dermatologic Surgery (ASDS) Tel: (800) 441-2737

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MANAGING YOUR

VENTRICULAR SEPTAL DEFECT

What Is Ventricular Septal Defect?

The two ventricles are lower chambers of the heart and are divided by a wall (septum). Ventricular septal defect (VSD) is a hole in this septum. The left side of the heart normally pumps under higher pressure than the right side. The VSD produces a left-to-right switch (shunt) that allows blood from both sides of the heart to mix. The heart has trouble getting oxygen to the rest of the body because it pumps blood with less oxygen to the body. Circulation on the right side of the system can be overloaded, so increased pressure occurs in the lungs (pulmonary hypertension).

VSDs are the most common type of heart abnormality developing before birth (congenital). Defects usually close by themselves or are surgically closed in childhood, but they may last into adulthood. More girls than boys have VSDs.

A small defect may not cause a problem. Large defects can cause heart failure (the heart can't pump enough blood). The result is feeling tired, trouble breathing (especially with exertion), or chest pain. Sometimes the skin turns blue (cyanosis) because blood with less oxygen reaches the skin. Abnormal heart rhythms (arrhythmias) may develop. If a defect is near the aortic valve, damage to that valve may occur as children grow.

What Causes Ventricular Septal Defect?

The cause is unknown.

What Are the Symptoms of Ventricular Septal Defect?

The most common symptoms are a feeling of weakness, trouble breathing, chest pain, bluish color of the skin, and irregular heartbeat.

How Is Ventricular Septal Defect Diagnosed?

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The doctor uses symptoms and a physical examination to make a diagnosis. Electrocardiography (ECG) may show abnormalities. A chest x-ray may also be abnormal and show enlargement of the heart and of lung vessels. Echocardiography (a test using sound waves to get pictures of the heart) can be used to study the heart's structure and pumping and measure how well the ventricles work, and examine blood flow.

How Is Ventricular Septal Defect Treated?

People with a small defect or a defect that has closed may never have symptoms and usually need no treatment. If the defect lasts, treatment to correct the defect would likely be needed.

People with VSDs usually see a heart specialist (cardiologist). Treatment may involve surgery to correct the defect. Heart failure, if it occurs, can be treated with drugs to reduce the excess blood volume and help the heart contract better. Sometimes the aortic valve is replaced. If no other heart disease exists, correcting the defect usually allows a normal life span and lifestyle.

People with an open VSD must take antibiotics before and after dental work or surgery. Antibiotics help prevent infection of the lining of the heart (bacterial endocarditis). Antibiotics are generally no longer needed 6 months after surgery is performed to close the VSD.

DOs and DON'Ts in Managing Ventricular Septal Defect:

✓ **DO** take your medicines as prescribed.

✓ **DO** call your doctor if you have VSD symptoms.

⃠ **DON'T** neglect worsening symptoms. See your doctor.

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MANAGING YOUR

VERTIGO

What Is Vertigo?

The word vertigo means the feeling of spinning or whirling. Dizziness means feeling out of balance, lightheaded, or faint.

What Causes Vertigo?

Most cases are mild and brief and are due to changes in the inner ear (the vestibular system). Structures in this system sense the position and movement of the head. In a condition called benign paroxysmal positional vertigo (BPPV), very tiny crystals in semicircular canals of the fluid-filled chamber in the inner ear (labyrinth) can loosen and irritate nerve endings. The feeling of spinning results. Viral infections, aging, and head trauma are the most common causes. Another common cause is labyrinthitis, or inflammation (swelling) of the labyrinth from an inner ear infection. Middle ear infections can also cause vertigo. Medicines, such as high blood pressure pills and high doses of aspirin, can also lead to vertigo.

More serious causes include stroke, Ménière's disease, epilepsy, infections, multiple sclerosis, vascular disease, and tumors (acoustic neuroma). In Ménière's disease, there's too much pressure on membranes in the labyrinth. An acoustic neuroma is a benign tumor (not cancer) of a nerve from the brain.

What Are the Symptoms of Vertigo?

People usually have spinning with nausea and sometimes vomiting and nystagmus. Nystagmus is slow movement of the eyes to one side followed by quick movement back to their original position. Ménière's disease involves decreased hearing and ringing or buzzing in the ear (tinnitus). Acoustic neuromas cause hearing loss, usually subtle and occurring slowly. Sudden

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hearing loss can also occur. A growing tumor may press on nerves and cause facial numbness and tingling (trigeminal nerve), or facial muscle paralysis and loss of facial expression (facial nerve).

Stroke often involves weakness on one side of the body, trouble speaking, and vision problems.

How Is Vertigo Diagnosed?

The doctor will make a diagnosis from the medical history and physical examination. The doctor may do other tests, such as magnetic resonance imaging (MRI), depending on the possible cause.

How Is Vertigo Treated?

Treatment depends on the cause. Medicines that may be causing vertigo will be stopped. Other drugs such as meclizine may be given to help vertigo go away. For BPPV, the doctor may move the head to put crystals in their proper place. This treatment is called canalith repositioning (or the Epley maneuver). For more serious causes (such as an acoustic neuroma), surgery or radiation therapy may be needed. The best treatment depends on the specific person and doctor.

DOs and DON'Ts in Managing Vertigo:

✓ **DO** take medicines as prescribed.

✓ **DO** call your doctor if you have hearing loss or one-sided facial numbness and tingling, especially if it's with a headache.

⦸ **DON'T** ignore vertigo, especially when you have other symptoms.

⦸ **DON'T** use very high doses of aspirin. Aspirin may cause vertigo.

⦸ **DON'T** forget to tell your doctor about any drugs you take, including over-the-counter and herbal products. Many can cause vertigo.

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- American Academy of Otolaryngology—Head and Neck Surgery Tel: (703) 836-4444

  Website: http://www.entnet.org

- Acoustic Neuroma Association Tel: (770) 205-8211, (877) 200-8211 **Website:**

  http://www.anausa.org

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MANAGING YOUR

VIRAL PNEUMONIA

What Is Viral Pneumonia?

Pneumonia is an infection of the lungs. In viral pneumonia, infection is caused by viruses. People of any age can be affected. Smokers, elderly people, and people with chronic lung diseases may be most likely to get it. People with weak immune (infection-fighting) systems because of chemotherapy or drug treatment after organ transplantation are especially at risk of getting cytomegalovirus pneumonia.

Bacterial pneumonias can follow viral pneumonias, especially those caused by influenza virus, because viruses can weaken lung defenses.

What Causes Viral Pneumonia?

Viral infections start after contaminated droplets from someone with an infection are breathed in. Virus can also be directly transferred to the nose, mouth, or eyes by hands that touched something contaminated with virus. The usual causes include influenza virus, respiratory syncytial virus, adenovirus, parainfluenza virus, and varicella virus.

What Are the Symptoms of Viral Pneumonia?

Usual symptoms include fever, chills, cough, shortness of breath, chest discomfort, muscle aches, tiredness, and poor appetite. Runny nose, irritated eyes, sore throat, and symptoms outside the respiratory tract (such as rashes) may occur.

How Is Viral Pneumonia Diagnosed?

It's hard to tell whether a virus, and which virus, is causing pneumonia. Many viruses produce similar symptoms, and few specific diagnostic tests exist. The doctor usually diagnoses pneumonia by using chest examinations, x-rays, and maybe tests of blood and respiratory secretions.

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Studies of blood and sputum are usually done to make sure a bacterial infection isn't also present.

How Is Viral Pneumonia Treated?

Antiviral drugs may be prescribed, depending on the virus and how severe symptoms are.

Viral pneumonia in healthy people goes away in 1 to 2 weeks, but cough and fatigue may last for many weeks. Viral pneumonia can be serious and life-threatening in people with other medical illnesses.

DOs and DON'Ts in Managing Viral Pneumonia:

✓ **DO** tell your doctor about all your medical problems.

✓ **DO** tell your doctor about medicines you take, prescription and over-the-counter.

✓ **DO** call your doctor if you're getting worse or don't feel better after 2 to 3 days.

✓ **DO** tell your doctor if you're pregnant.

✓ **DO** call your doctor right away or go to the emergency room if shortness of breath gets worse.

✓ **DO** try to cough up as much phlegm as possible.

✓ **DO** put an air humidifier in your room so you can breathe moist air, which helps get rid of phlegm.

✓ **DO** drink plenty of fluids so you don't get dehydrated.

✓ **DO** use acetaminophen or aspirin (except in children) for fever and pain.

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✓ **DO** call your doctor if you think that you have pneumonia because you have fever, too much sputum, increased shortness of breath, or chest pain.

✓ **DO** call your doctor if you have dusky-colored skin, lips, or fingernails.

✓ **DO** call your doctor if nausea or vomiting stops you from taking your medicines.

✓ **DO** call your doctor if you get dehydrated because of vomiting or diarrhea.

⃠ **DON'T** stop taking your medicine just because you feel better, unless your doctor tells you to.

⃠ **DON'T** smoke.

⃠ **DON'T** drink alcohol in excess.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following source:

- American Lung Association Tel: (800) LUNG-USA (586-4872) **Website:** **http://www.lungusa.org**

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MANAGING YOUR

VITAMIN D DEFICIENCY

What Is Vitamin D Deficiency?

Rickets is a disease affecting children's bones. Osteomalacia is the same bone disease in adults. In children, bones don't grow as well as they should and become soft and weak. In adults, bones weaken and may break. These disorders start when people don't have enough vitamin D in their diet.

The disorder occurs most often in elderly, institutionalized, or hospitalized people, such as those in nursing homes, but it can also occur in otherwise healthy adults. In the United States, rickets is rare. It occurs most during fast growth periods, when the body needs a lot of calcium and phosphorus (such as children 6 to 24 months old).

What Causes Vitamin D Deficiency?

The cause is a lack (deficiency) of vitamin D. Bones need vitamin D to form properly and be healthy. The vitamin helps the intestines absorb calcium and phosphorus, which are needed to make healthy bones. Vitamin D deficiency can occur because of a poor diet (lack of dairy products, cereals, fish liver oils) or a vegetarian diet. Poor vitamin D absorption can occur because of some seizure medicines, kidney or liver disease affecting metabolism of the vitamin, and not enough sunshine. Vitamin D forms in the skin when it's exposed to the sun. Adults with darker skin have a greater risk of having the deficiency. Also, because breast milk has low amounts of vitamin D, babies fed only breast milk can have the disorder.

What Are the Symptoms of Vitamin D Deficiency?

Adults may have chronic bone pain and muscle aches and tend to break bones easily. Children can grow slower than other children, their bones tend to break more easily, and they can have

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tenderness or pain in arm, leg, back, or hip bones. Their bones can have an unusual shape. They may have bowlegs, and the spine may have an abnormal curve. They can have problems with teeth, which may appear later and have more cavities. Other symptoms include fever, restlessness (especially at night), poorly developed muscles, and muscle cramps.

How Is Vitamin D Deficiency Diagnosed?

The doctor may suspect the diagnosis from a medical history and physical examination. Blood and urine samples will be tested. X-rays may be done to check bone structure. Rarely, the doctor may take a sample of bone to look at with a microscope.

How Is Vitamin D Deficiency Treated?

Treatment consists of daily supplements of calcium, phosphorous, and vitamin D and eating foods rich in these substances. Good food sources of vitamin D are fish (salmon, mackerel, bluefish), liver, and fortified milk and orange juice.

Both children and adults should go outside as often as possible. Sunshine helps vitamin D work well. Children should try to use good posture to correct bone deformities. Some deformities may need an operation.

DOs and DON'Ts in Managing

Vitamin D Deficiency:

✓ **DO** eat a good diet including milk. If you're allergic to milk, find other sources of calcium and vitamin D.

✓ **DO** ask your doctor about vitamin supplements.

✓ **DO** call your doctor if you have bone pain.

⃠ **DON'T** forget to go outdoors as much as possible, but remember to use sunscreen.

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FOR MORE INFORMATION

Contact the following source:

• American Association of Clinical Endocrinologists Tel: (904) 353-7878 **Website:**

http://www.aace.com

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MANAGING YOUR

VITILIGO

What Is Vitiligo?

Vitiligo is a fairly common skin condition involving loss of pigmentation (color) in the skin. Color is lost in patches, often on the back of the hands, face, and armpits. Vitiligo affects people of all races and ethnic groups. It is more obvious in people with darker skin. It can occur at any age, but half of the cases occur in people younger than 20. Vitiligo can cause serious cosmetic changes in the skin. It's not life threatening or curable, but some skin pigment may return on the face and neck. It's sometimes related to other illnesses such as thyroid diseases.

What Causes Vitiligo?

The cause is unknown. Vitiligo is the result of disappearance of cells in the skin called melanocytes that produce melanin, the pigment that determines the color of hair. Vitiligo isn't cancerous and is not contagious. It can run in families.

What Are the Symptoms of Vitiligo?

Small areas of skin lose pigment and color and become flat and white. Patches can't be felt with the fingers. They don't hurt or itch. They vary in size and may be up to an inch across. Patches spread to form larger areas with irregular shapes. They often occur on both sides of the body in about the same place. Sometimes hair in the area also loses pigment.

How Is Vitiligo Diagnosed?

The doctor will examine the skin to make a diagnosis and may suggest seeing a doctor who specializes in skin diseases (dermatologist). The doctor may take a small sample of skin (biopsy sample) for closer study with a microscope.

How Is Vitiligo Treated?

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Treatment involves a combination of cosmetics, prescription creams, and specialized light therapy.

Mild vitiligo may not need treatment. People with small patches can do well with cosmetic stains and makeup. Fair-skinned people may benefit from avoiding tanning by using sunscreens with an SPF of 15 or higher and keeping away from direct sunlight.

For limited patches, a steroid cream applied to the skin can help. Best results may take 3 or 4 months. Steroid creams should not be put on eyelids, armpits, or groin areas.

Specialized light therapy, or PUVA, consists of applying a solution of medicines called psoralens, followed by ultraviolet light. Psoralens can also be taken as pills. This treatment is best for the face, neck, trunk, upper arms, and upper legs. Results begin after 25 to 50 treatments depending on areas involved. Major side effects are severe sunburn and blistering.

DOs and DON'Ts in Managing Vitiligo:

✓ **DO** use sunscreen in areas with vitiligo.

✓ **DO** contact your doctor if new symptoms develop. Drugs for vitiligo may have side effects.

✓ **DO** use a sunscreen with an SPF of 15 or higher and wear a hat, long-sleeved shirt, and long pants.

✓ **DO** call your doctor if you get severe reddening or blistering during treatment.

✓ **DO** remember that none of the repigmentation methods can give total, permanent cures.

⃠ **DON'T** expose yourself to direct sunlight, especially between 11 AM and 3 PM during summer.

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⦸ **DON'T** get sunburns or tan. When skin not affected by vitiligo tans, affected areas will become more obvious.

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FOR MORE INFORMATION

Contact the following sources:

- National Vitiligo Foundation Tel: (614) 261-8145 **Website: http://www.nvfi.org**
- American Academy of Dermatology Tel: (866) 503-SKIN (503-7546) **Website: http://www.aad.org**

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MANAGING YOUR

VOMITING

What Is Vomiting?

Vomiting is forcing the stomach contents up through the esophagus and out of the mouth. It may be involuntary or done on purpose.

What Causes Vomiting?

There are numerous diseases and disorders that can cause vomiting. Most causes are viral infections called gastroenteritis. Gastritis is an inflammation (redness, swelling) of the stomach lining that can also cause vomiting. Bowel diseases such as intestinal obstruction, gallbladder attack, stomach ulcers, and appendicitis are more serious causes.

Medicines such as chemotherapy, codeine, morphine, and antibiotics commonly cause nausea and vomiting.

Stress-related psychological problems and bulimia nervosa are other common causes, as are pain, vertigo, surgery, severe burns, trauma, and motion sickness (getting sick on airplanes, cars, boats, and trains). Vomiting is also common during pregnancy, especially in the first trimester.

What Are the Symptoms of Vomiting?

Most people have nausea before vomiting. People with gastroenteritis also have cramps in the abdomen (belly), diarrhea, chills, and low-grade fever. Main gastritis symptoms are upper abdominal pain and cramps with vomiting. Intestinal obstruction, appendicitis, and gallbladder attack usually also cause abdominal pain and fever.

How Is Vomiting Diagnosed?

The doctor will make a diagnosis by a physical examination and maybe blood and urine tests and x-rays.

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How Is Vomiting Treated?

Treatment depends on the cause. The key is to replace fluids and electrolytes (special substances that control fluid balance in the body). Clear broth or special oral glucose-electrolyte solutions are used. Severe symptoms may mean hospitalization and intravenous fluids. Antibiotics may help bacterial, but not viral, infections. Antacids, over-the-counter histamine-2 (H_2) blockers, and proton pump inhibitors (PPIs) such as omeprazole control mild gastritis symptoms. Antiemetic medicines can help nausea and vomiting of gastroenteritis.

Gallbladder attack, appendicitis, and intestinal obstruction usually need hospitalization and surgery.

People with bulimia need cognitive and behavioral therapy.

DOs and DON'Ts in Managing Vomiting:

✓ **DO** consume only liquids if you vomit repeatedly. Start a soft, bland diet if you can. Then slowly return to a normal diet.

✓ **DO** take your medicine as instructed.

✓ **DO** lie back in the seat and take slow deep breaths when you're in a car, boat, or plane. Try to sit where there's least motion.

✓ **DO** rest in bed near the bathroom or with the bedpan handy.

✓ **DO** contact the local health department if many people are sick after eating at the same event to help find the infection's source.

✓ **DO** cook and store foods properly.

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✓ **DO** wash your hands after using the bathroom and when preparing foods. Keep cooking areas and utensils clean.

✓ **DO** call your doctor if symptoms don't get better after 48 hours or worsen after treatment starts.

✓ **DO** call your doctor if you vomit and become faint or dizzy when changing positions suddenly.

✓ **DO** call your doctor if vomiting is so bad that you cannot keep liquids down.

⦸ **DON'T** use alcoholic and caffeinated beverages.

⦸ **DON'T** read or watch the horizon while in a moving vehicle.

⦸ **DON'T** eat anything for at least 2 hours before bedtime.

⦸ **DON'T** bend over or lie down right after eating.

⦸ **DON'T** eat raw seafood or meat.

⦸ **DON'T** eat fresh unwashed vegetables or unpasteurized foods.

⦸ **DON'T** drink tap water or eat raw foods when traveling abroad. Fruits that you peel before eating are usually safe.

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FOR MORE INFORMATION

Contact the following sources:

- National Digestive Diseases Information Clearinghouse Tel: (800) 891-5389 **Website: http://digestive.niddk.nih.gov**

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- American College of Gastroenterology Tel: (703) 820-7400 **Website:**

  http://www.acg.gi.org

- Gastro-Intestinal Research Foundation Tel: (312) 332-1350 **Website:**

  http://www.girf.org

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MANAGING YOUR

VON WILLEBRAND'S DISEASE

What Is von Willebrand's Disease?

von Willebrand's disease is an inherited bleeding disorder that may not be diagnosed until after major trauma or surgery. Most cases are mild. The severe type is rare. About 1% to 3% of the population has the gene for von Willebrand's disease. The disease affects different ethnic groups, men and women equally.

What Causes von Willebrand's Disease?

The cause is a lack or abnormality in the protein named von Willebrand factor. This factor helps platelets clump together and stick to the blood vessel wall during normal blood clotting. Parents pass it to children.

What Are the Symptoms of von Willebrand's Disease?

Three types of the disease occur. Type I involves reduced von Willebrand factor. People may not know that they have the disease. Type II involves production of von Willebrand factor that doesn't work normally. People with this type have mild symptoms. Symptoms include bleeding during operations, dental extractions, or trauma. Abnormal periods, bruising, nosebleeds, and rash can occur. Only people with the rare type III have almost no von Willebrand factor. Bleeding can start for no reason, from the gums, mouth, nose, and even into muscles or joints.

How Is von Willebrand's Disease Diagnosed?

The doctor may suspect the disease from the history of easy bruising, bleeding from the mouth or nose, or excessive bleeding after surgery or dental procedures. Special tests measure bleeding time and the amount and quality of von Willebrand factor in the blood. First-degree relatives of people with the disease may need to have these tests. Early diagnosis is important.

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How Is von Willebrand's Disease Treated?

The disease cannot be cured, but treatment and preventive measures usually prevent excessive bleeding. Most people with types I and II disease don't need treatment. People with mild or moderate disease also have no limits on regular exercise. Most need treatment only for an operation or after serious trauma. A very small number need constant treatment. People with type III disease need regular treatment. Desmopressin (DDAVP) is a synthetic hormone that helps get more von Willebrand factor into the blood.

DDAVP is most often given intravenously in a hospital or surgical center. It can also be used at home as a nasal spray to control minor bleeding and before activities that cause bleeding or minor operations.

If DDAVP doesn't work, von Willebrand factor from human plasma can be used.

DDAVP can cause high blood pressure, headaches, nasal congestion, and nausea. Risks of using von Willebrand factor from human plasma are infection, especially viral infections, and allergic reactions.

DOs and DON'Ts in Managing von Willebrand's Disease:

✓ **DO** have your doctor prescribe and check your DDAVP treatment.

✓ **DO** use medical alert identification.

✓ **DO** call your doctor if you're having surgery or dental procedures or will play sports that can lead to trauma and bleeding.

✓ **DO** report bleeding that cannot be controlled with your regular medicine to your doctor immediately.

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⦸ **DON'T** use antiinflammatory medicines, such as aspirin or ibuprofen, without asking your doctor. They can worsen bleeding.

⦸ **DON'T** play sports and games that can lead to trauma.

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FOR MORE INFORMATION

Contact the following sources:

- National Heart, Lung, and Blood Institute Information Center Tel: (301) 251-1222
- World Federation of Hemophilia **Website: http://www.wfh.org**

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MANAGING YOUR

VULVAR CANCER

What Is Vulvar Cancer?

Cancer of the vulva affects the outer part of a woman's reproductive system. This area includes the opening of the vagina, labia (vaginal lips), clitoris, and skin and tissue covering the pubic bone. Most often, the cancer occurs on inner edges of vaginal lips.

This cancer is rather rare. Less than 1% of all cancers in women are vulvar cancers, usually in women older than 50 years.

What Causes Vulvar Cancer?

The cause is unknown, but some things can give women greater chances of getting this cancer. These things are long-term inflammation (swelling, redness) of the vulva, human papillomavirus (HPV) infection, and prior cervical or vaginal cancer. HPV causes genital warts, a sexually transmitted disease (STD).

What Are the Symptoms of Vulvar Cancer?

Common symptoms may include pain during sex or with urination, long-lasting itching in the vulva region, thickening or lump on the labia, rough white area on the vulva, and blood or discharge that isn't related to normal menstrual periods.

How Is Vulvar Cancer Diagnosed?

The doctor can often see early changes in the vulva during a routine pelvic examination. Because of the examination and symptoms, the doctor may order a biopsy to confirm the diagnosis. A biopsy involves taking a small piece of tissue for study with a microscope. An instrument called a colposcope may be used to do the biopsy. This tool has magnifying lenses for looking at the vagina and lets the doctor pick the best spot for a biopsy.

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If biopsy results show cancer cells, other tests may be done to see if the cancer spread and how far.

How Is Vulvar Cancer Treated?

Treatment depends on the type and size of cancer and its spread.

For very small cancers that are in only one spot, a laser beam can be used to burn off the top layer of skin that contains the cancer cells.

Surgery called excision or simple partial vulvectomy is often used to remove abnormal cells and some healthy tissue nearby. For large cancers, an operation called a vulvectomy may be needed. In this operation, all or part of the vulva is removed.

DOs and DON'Ts in Managing Vulvar Cancer:

✓ **DO** have regular check-ups, to catch problems early.

✓ **DO** reduce your risk factors as much as possible. A large percentage of women with vulvar cancer have HPV infection. Practice safe sex. Use condoms if you think that there's any chance of catching an STD.

✓ **DO** talk to your doctor about getting vaccinated for HPV (Gardasil®) if you are between ages 13 and 26.

✓ **DO** call your doctor if you notice skin changes on your labia.

✓ **DO** call your doctor if you have vaginal bleeding that's not related to your period.

⃠ **DON'T** ignore thickening of the skin or sores on your labia.

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FOR MORE INFORMATION

Contact the following source:

- American Cancer Society Tel: (800) 227-2345 **Website: http://www.cancer.org**

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MANAGING YOUR

WARFARIN THERAPY

What Is Warfarin and What Does It Do?

People who form blood clots may be at risk for heart attacks, strokes, and other serious medical problems. The drug warfarin (Coumadin®) helps prevent blood clots and is also used to treat blood clots. It's an anticoagulant (blood thinner).

How Should Warfarin Be Taken?

Pills are usually taken daily at the same time. The doctor bases the dose on a blood test called the INR (International Normalized Ratio). Never skip doses or take double doses unless instructed to do so by your doctor.

How Is the Dose Decided?

The doctor decides the dose by testing how fast the blood clots. If the INR result is too high, bleeding may occur. If it's too low, clots may form. Certain foods and illness such as a fever or flu can affect the INR test and warfarin dose, as can diarrhea and vomiting lasting more than 1 day.

What Are the Side Effects?

Side effects include bleeding. A little bleeding may occur even with correct doses. Such bleeding includes easy bruising, slight gum bleeding when brushing teeth, nosebleeds, and menstrual periods that are a little heavier than normal. Major bleeding requires immediate care. This bleeding includes red or tarry bowel movements, gum bleeding or nosebleeds that don't stop quickly, coffee-colored or bright red vomit, or red, coffee-colored, or cola-colored urine. Other problems may include severe headaches or stomach aches, bruises for no reason, much heavier periods, cuts that don't stop bleeding in 10 minutes, dizziness, and weakness.

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DOs and DON'Ts in Managing Warfarin Therapy:

✓ **DO** be careful using sharp objects, such as knives and scissors. Wear gloves when doing yard work. Use an electric razor, soft toothbrush, and waxed dental floss. Don't use toothpicks. Trim nails carefully. Avoid activities and risky sports that could cause injury. Safe activities are swimming and walking.

✓ **DO** remember that you can bleed but not see blood. For example, a fall could cause bleeding under the skin, so you see only a bruise. Call your doctor or go to the hospital immediately if you have a severe fall or head trauma, even if you don't see blood.

✓ **DO** talk to your doctor about wearing a medical alert bracelet or necklace.

✓ **DO** talk with your doctor about all your other medicines. Warfarin can change the way they work, and other medicines can affect warfarin.

✓ **DO** talk with your doctor before using aspirin. Aspirin interferes with warfarin and the blood's ability to clot. Because over-the-counter medicines may contain aspirin, your doctor must approve all drugs.

✓ **DO** talk to your doctor about diet and foods with high amounts of vitamin K. This vitamin may affect warfarin. Such foods include kiwi, blueberries, broccoli, cabbage, Brussels sprouts, green onions, asparagus, cauliflower, peas, lettuce, spinach, parsley, kale, endive, and turnip, collard, and mustard greens. Beef and pork liver, mayonnaise, margarine, canola and soybean oil, vitamins, soybeans, and cashews also have vitamin K.

✓ **DO** call your doctor if you cannot eat for several days or have vomiting or diarrhea for more

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than 1 day. These problems could affect warfarin dosage.

✓ **DO** limit alcohol. Drinking more than two drinks a day or changing your usual drinking pattern can affect warfarin dosage. Avoid binge drinking.

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FOR MORE INFORMATION

Contact the following source:

- Agency for Healthcare Research and Quality Tel: (301) 427-1364 **Website:** **http://www.ahrq.gov/coumadin.htm**

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MANAGING YOUR

WARTS

What Are Warts?

Warts are skin growths. They are classified by how they look and where they occur. Common warts occur on hands, arms, and legs. These warts often look like little rough cauliflowers. Periungual warts occur around fingernails. Flat warts, on the face, knees, and elbows of children and young women, are slightly raised and flesh colored. Genital warts on genital and rectal areas are often sexually transmitted. Plantar warts on bottoms of feet are often passed along by bare feet. Filiform warts are small with hairlike pieces.

Warts are very common, especially in people 10 to 20 years old. Most warts (up to 65%) disappear on their own without treatment in 2 years. They often come back, even when treated.

What Causes Warts?

The viruses of the human papillomavirus (HPV) group cause warts. Different types of viruses tend to infect different body parts. Warts can be passed from one person to another. Scratching and picking warts also spreads the infection. Skin that is moist from soaking or that has cuts or scratches is more likely to become infected by virus and form warts.

What Are the Symptoms of Warts?

Most warts are little more than unpleasant growths on skin. They sometimes catch and bleed if they're on the face and head. Plantar warts may cause pain and tenderness when stepping on the foot.

How Are Warts Diagnosed?

The doctor will diagnose warts by examining the skin. If the diagnosis is unclear, the doctor may remove a small piece of wart (biopsy) for study with a microscope.

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How Are Warts Treated?

Treatment is usually but not always successful, and not all warts need treatment. Treatment itself can often cause problems, such as pain, infection, and scarring.

Warts causing no pain may need no treatment. Spreading the virus should be avoided, for example, by making sure the wart is covered when using community swimming pools, locker rooms, or showers.

Treatment depends somewhat on the wart location. Common warts on arms, hands, and legs can be treated with salicylic acid in solution. The solution is put on warts each night and each morning dead skin is peeled off.

Plantar warts can be treated with 40% salicylic acid plasters. Flat warts are often treated by skin peeling using tretinoin cream or 5-fluorouracil. Genital warts almost always need a doctor's visit for both partners. Treatment is usually with a blistering agent. If these treatments don't work, your doctor may prescribe stronger medicine, such as imiquimod cream or trichloroacetic acid.

Other treatments include freezing, injecting warts with drugs that stimulate the immune (infection-fighting) system, surgically cutting them, and burning them with a laser or electricity.

DOs and DON'Ts in Managing Warts:

✓ **DO** wash your hands well after touching warts to avoid spreading them.

✓ **DO** call your doctor if you have warts that cannot be treated by over-the-counter salicylic acid solutions.

✓ **DO** call your doctor if your warts aren't better after several weeks of treatment.

⃠ **DON'T** scratch, pick, or cut warts.

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⦸ **DON'T** shave or cut hair over warts.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Dermatology Tel: (888) 462-3376 **Website: http://www.aad.org**
- American Podiatric Medical Association Tel: (800) 366-8227 **Website:**

  http://www.apma.org

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MANAGING YOUR

WEGENER'S GRANULOMATOSIS

What Is Wegener's Granulomatosis?

Wegener's granulomatosis , also known as "granulomatosis with polyangiitis," is a rare condition causing inflammation of blood vessels, which affects many body tissues. The main organs involved are the lungs, kidneys, eyes, nose, and muscles. The disease ranges from mild to severe, with kidney failure, shortness of breath with damage to the respiratory system, or eye pain.

People are usually older than 40 when they get it, women more than men.

What Causes Wegener's Granulomatosis?

The cause isn't known. Wegener's is an autoimmune disease, which means that the body's own immune system makes proteins (antibodies) that attack cells and cause damage. It's not inherited or contagious.

What Are the Symptoms of Wegener's Granulomatosis?

Signs and symptoms may include shortness of breath, cough, fevers, weight loss, nosebleeds, redness and roughness of the lining of the nose, chest pain, eye inflammation, weakness, neurological symptoms similar to strokes, and kidney disease (puffy face, swollen legs).

How Is Wegener's Granulomatosis Diagnosed?

The doctor will make a diagnosis from a medical history, physical examination, blood tests, x-rays, and biopsy of one or more affected organs.

An antibody (ANCA antibody) can be found in the blood of most affected people and has been linked to Wegener's granulomatosis.

How Is Wegener's Granulomatosis Treated?

Treatment seems to help most symptoms.

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The two main treatments are steroid medicine, such as prednisone, and other medicines called cyclophosphamide or azathioprine that suppress the immune system. The antibiotic trimethoprim-sulfamethoxazole taken daily may reduce the number of relapses.

For severe disease, the doctor may give intravenous medicine in the hospital and may order a special type of blood treatment (plasmapheresis). In this treatment, antibodies in the blood are removed quickly, and fresh proteins are given.

DOs and DON'Ts in Managing

Wegener's Granulomatosis:

- ✓ **DO** take prednisone with food to avoid irritating the stomach. Take the full course of medicine because stopping suddenly can be harmful.
- ✓ **DO** eat well and use supplements as needed, to avoid getting debilitated. Your dietitian can help.
- ✓ **DO** follow the diet used by diabetic patients, if your blood sugar goes up with daily use of prednisone.
- ✓ **DO** exercise. Stay as active as possible to minimize the time spent recovering. People who are bed bound have a slower recovery.
- ✓ **DO** keep your doctor appointments. People taking these drugs need close supervision and frequent blood tests.
- ✓ **DO** call your doctor if you have symptoms related to treatment, get a fever or chills during treatment, or have any concerns.

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✓ **DO** call your doctor if you have new symptoms (cough, shortness of breath, ulcer pains, trouble swallowing, and sore throat).

⃠ **DON'T** take over-the-counter medicines unless your doctor says you can.

⃠ **DON'T** skip doses of prednisone. To do so can be harmful.

⃠ **DON'T** cheat on dietary advice. People with high blood glucose levels (mild diabetes) and kidney problems need to restrict food intake to avoid serious illness.

⃠ **DON'T** overdo work or exercise.

FROM THE DESK OF

NOTES

FOR MORE INFORMATION

Contact the following source:

• National Kidney and Urologic Diseases Information Clearinghouse Tel: (800) 891-5390

Website: **http://kidney.niddk.nih.gov/**

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MANAGING YOUR

WEST NILE VIRUS INFECTION

What Is West Nile Virus Infection?

West Nile virus infection is an infection passed by infected mosquitoes. Most infections don't cause symptoms. Rarely, West Nile virus can cause serious illnesses of the brain (encephalitis) and the membranes covering the brain (meningitis). Adults older than 50 have a higher risk of serious infection.

What Causes West Nile Virus Infection?

Mosquitoes carrying the virus pass the virus to humans by bites. The virus is in the flavivirus family. It's found in many places in nature, and it infects many birds and certain mammals. The infection isn't contagious from person to person.

What Are the Symptoms of West Nile Virus Infection?

Most people have no symptoms. Others have the most common symptoms, which are like those of the flu. They include cough, diarrhea, fever, loss of appetite, and painful joints and muscles. Other signs and symptoms are rash, tiredness, nausea, and vomiting. Symptoms of more serious illness are eye pain, headache, stiff neck, trouble walking, weakness, seizures, paralysis, and coma.

How Is West Nile Virus Infection Diagnosed?

The doctor makes a diagnosis from the medical history, physical examination, and blood tests. For symptoms related to the nervous system, the doctor may take a small amount of cerebrospinal fluid (spinal tap) to look for infection. The doctor may want computed tomography (CT) or magnetic resonance imaging (MRI) of the head if the diagnosis is unclear.

How Is West Nile Virus Infection Treated?

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Treatment isn't usually needed, but the doctor may prescribe medicine for symptoms. Over-the-counter medicines can help mild headaches and muscle aches. For more serious infections, a hospital stay is needed. Most people get better in 3 to 6 days, but those with brain infections may need several weeks. Some people with serious infections may have long-lasting symptoms.

Prevention of another infection is important. To do this, insect repellent with DEET should be used on uncovered skin, clothes, and window, door, and tent screens. Repellents containing more than 10% DEET shouldn't be used for children. Carriers and strollers for babies younger than 2 months should have mosquito netting used instead of DEET. Prevent mosquitoes from breeding by getting rid of small pools of standing water, such as in clogged drains, rain gutters, flowerpots, old tires, and swimming pool covers. Avoid areas with mosquitoes. Stay indoors during when mosquitoes are most active, or wear long-sleeved shirts and long pants when outdoors. Use screens at home or in tents.

DOs and DON'Ts in Managing West Nile Virus Infection:

✓ **DO** follow your doctor's advice.

✓ **DO** tell your doctor about your medical problems.

✓ **DO** tell your doctor if you're pregnant or breastfeeding.

✓ **DO** call your doctor right away or go to the emergency room if your symptoms get worse; if you have a headache, neck pain, or eye pain; or if bright lights bother your eyes.

⦸ **DON'T** stop taking your medicine because you feel better.

⦸ **DON'T** donate blood or organs if you've been infected with West Nile virus even after you're all better. People who get organs from donors who were infected with West Nile virus

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are at risk of developing encephalitis, meningitis, and other serious infections.

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Contact the following sources:

- The Centers for Disease Control and Prevention Tel: (404) 639-3534 or (800) 311-3435

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MANAGING YOUR

WHIPLASH

What Is Whiplash?

The part of the spinal column in the neck (cervical spine) has seven bones called cervical vertebrae. Thick fibrous bands called ligaments hold these bones together. Disks between the bones are cushions and act like shock absorbers during normal daily activities. Neck muscles support and move the neck. Whiplash is a neck injury in which the neck is forced to extend too far back and then quickly go forward. Ligaments, muscles, bone, and disks are injured. Whiplash can be uncomfortable and make people miss work. It occurs at any age, more often in women than in men. More than 1 million people a year have whiplash.

What Causes Whiplash?

The cause is usually a motor vehicle accident, trauma from falling, contact sport injury, or physical abuse. Rear-end vehicle collisions account for more than 40% of cases.

What Are the Symptoms of Whiplash?

Neck pain is the most common complaint. Pain usually starts hours to days after the accident. Neck tightness, stiffness, and headaches over the back of the head occur. Pain over the shoulder and arms, numbness, reduced range of motion, ringing in the ears, and trouble swallowing can also be noted in severe cases with extensive injury.

How Is Whiplash Diagnosed?

The doctor makes a diagnosis from the medical history and physical exam. Sometimes blood tests, x-rays, and magnetic resonance imaging (MRI) may be done to check for nerve injury and to rule out other causes. Your doctor may suggest seeing a neurologist (specialist in nervous system diseases) or orthopedic surgeon (specialist in bone diseases).

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How Is Whiplash Treated?

The goals of treatment are to reduce pain and allow time for the injury to heal. Conservative treatment is usual. Ice packs are applied to the area first, and then heat (heating pad, hot shower) or cold. A soft cervical collar is usually suggested.

For sleeping, a small rolled towel that is 2 inches in diameter or cervical pillow (neck support pillow) should be used. Ultrasound may also help symptoms.

Medicines for pain include antiinflammatory drugs and acetaminophen (alone or with antiinflammatory drugs). Muscle relaxants can also be tried for muscle spasms.

DOs and DON'Ts in Managing Whiplash:

✓ **DO** take muscle relaxants before bedtime. Take medicines as prescribed by your doctor.

✓ **DO** sit in a firm chair and sit against the chair's back.

✓ **DO** remember that most people recover within weeks. However, 20% to 40% of people may develop a chronic syndrome, with headache, neck pain, and anxiety and depression related to the accident.

✓ **DO** wear a seat belt, and drive safely. Raise the padded headrest on the seat so it will protect you.

✓ **DO** wear safety gear if you play contact sports such as football.

✓ **DO** call your doctor if you have numbness or tingling down your arms, muscle weakness, or headaches or if your symptoms get worse.

⦸ **DON'T**stop taking your medicine or change your dosage because you feel better, unless your

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doctor tells you to.

⦸ **DON'T**lift heavy objects without your doctor's OK.

⦸ **DON'T**miss follow-up doctor appointments.

⦸ **DON'T**ignore your symptoms. Many serious conditions can mimic whiplash.

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FOR MORE INFORMATION

Contact the following sources:

- American Academy of Orthopaedic Surgeons Tel: (847) 823-7186 **Website:** **http://www.aaos.org**
- North American Spine Society Tel: (708) 588-8080 **Website:** **http://www.spine.org**

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MANAGING YOUR

WILSON'S DISEASE

What Is Wilson's Disease?

Wilson's disease is a rare inherited disorder of copper metabolism. Copper is a metal found in small amounts in the blood. Copper plays an essential role in production of hemoglobin. Hemoglobin is a large protein molecule in red blood cells that attaches to oxygen and takes it to body tissues. Copper is also important for bone development and connective tissues.

Wilson's disease causes too much copper to collect in the body due to insufficient or defective copper excretion in the liver. The excess copper accumulates in vital organs, mainly the liver and brain. Untreated Wilson's disease is usually fatal. The disease affects 1 in 30,000 people.

What Causes Wilson's Disease?

A mutation of a gene that passes from parents to children causes the disease. The disease is autosomal recessive, which means that both parents must have the mutation and give it to a child for the child to have the disease. It's not contagious.

What Are the Symptoms of Wilson's Disease?

Symptoms don't usually start until after a child is 3 years old and may not start until the teenage years or later. Usually, the liver is affected first. Liver inflammation (hepatitis) develops and can be mistaken for hepatitis caused by a virus. Other possible symptoms are jaundice (yellow skin), fluid in the belly (ascites), mental confusion, and lethargy. Liver cirrhosis may also develop. Effects on the brain lead to spastic muscle movements, tremors, and trouble swallowing and speaking.

How Is Wilson's Disease Diagnosed?

The doctor makes a diagnosis from a medical history, physical examination, blood tests, and

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liver biopsy. High blood ceruloplasmin and liver copper levels confirm the diagnosis. Ceruloplasmin is an oxygen-carrying protein in the blood. A key effect in the eye is a brownish color where the cornea and sclera (white part of the eye) meet, called a Kayser-Fleischer ring. Psychiatric problems may occur, including neurosis and psychosis.

How Is Wilson's Disease Treated?

The doctor may suspect the disease in anyone younger than 40 with abnormal liver blood tests, abnormal behavior, and unexplained liver cirrhosis and nervous system symptoms. Treatment goals are to remove excess copper and prevent it from reaccumulating by using medications. Penicillamine is a chelating agent, which means a drug that binds to copper, so it can remove it. It's usually given for life. Drug side effects may include rash, fever, swollen lymph glands, kidney problems, and lower red and white blood cell counts. If penicillamine cannot be tolerated, another chelating drug called trientine can be used. Zinc acetate also helps, by preventing absorption of copper from the gut. This drug shouldn't be used with penicillamine or trientine.

DOs and DON'Ts in Managing Wilson's Disease:

✓ **DO** keep follow-up doctor appointments. Once treatment begins, your doctor needs to monitor your condition and blood tests (blood counts, liver function tests, and copper levels).

✓ **DO** call your doctor if you have side effects from your medicine.

⃠ **DON'T** stop taking the medicine. Treatment must continue for life. If you must stop taking it, your doctor should supervise this and can change the drug to another medicine.

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FOR MORE INFORMATION

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Contact the following source:

- Wilson's Disease Association International Tel: (888) 264-1450 **Website:** **http://www.wilsonsdisease.org**

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MANAGING YOUR

WOLFF-PARKINSON-WHITE SYNDROME

What IS Wolff-Parkinson-White Syndrome?

Wolff-Parkinson-White (WPW) syndrome is a heart condition in which the heart has an extra electrical pathway. The heartbeat is abnormally fast (tachycardia) and irregular. WPW often manifests initially in people in their teens or early 20s. It's also one of the most common causes of fast heart rate disorders in babies and children.

What Causes Wolff-Parkinson-White Syndrome?

WPW syndrome is present at birth. The extra electrical pathway is between the atria, which are the heart's upper chambers, and the ventricles, which are the lower chambers. The result is irregular and very rapid heart rhythms called supraventricular tachycardia.

What Are the Symptoms of Wolff-Parkinson-White Syndrome?

Symptoms occur only when the heart beats abnormally fast, so most of the time people have no symptoms. Episodes can start suddenly and last for a few seconds or several hours. They often happen during exercise. When symptoms do occur, they include rapid heartbeat, heart palpitations or heart fluttering, lightheadedness, chest pain, fatigue, fainting, dizziness, anxiety, loss of consciousness, and breathing problems. Sudden death can occur.

How Is Wolff-Parkinson-White Syndrome Diagnosed?

The doctor may suspect WPW syndrome because of the medical history. The doctor uses electrocardiography (ECG), which records the heart's electrical activity. Several small electrodes are put on the chest, arms, and legs, and then the heart's electrical pattern is recorded. The pattern shows an abnormal delta wave. The test is best done while symptoms are present. The doctor may want other tests such as Holter monitoring. This test is a 24-hour ECG. Exercise stress testing and

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electrophysiology may also be done.

How Is Wolff-Parkinson-White Syndrome Treated?

Treatment depends on how severe symptoms are. For very mild symptoms or those that don't happen often, no treatment may be needed. Some people can slow the heart rate by using simple physical movements called vagal maneuvers. These include coughing, bearing down as if having a bowel movement, and putting an icepack on the face. Treatment is needed for fainting, dizziness or chest pains. A very rapid heartbeat can be life-threatening.

Treatments include drugs called antiarrhythmics. Medicines may need to be taken indefinitely. The preferred treatment is radiofrequency catheter ablation. For this treatment, a tube (catheter) is threaded through a blood vessel in the leg until it reaches the heart. Then the catheter tip provides a special kind of energy called radiofrequency waves to damage the abnormal pathways. This treatment usually stops the abnormal signals and symptoms completely. Other treatments include cardioversion and surgery. In cardioversion, the heart is shocked through paddles or patches on the chest. These methods are used when other treatments don't work.

DOs and DON'Ts in Managing Wolff-Parkinson-White Syndrome:

✓ **DO** avoid tobacco, smoking, caffeine, alcohol, pseudoephedrine (a nasal decongestant) and similar antihistamines, amphetamines, and cocaine.

✓ **DO** tell your doctor about unusually fast heartbeats or near fainting.

✓ **DO** keep your doctor's appointments.

⃠ **DON'T** stop taking your medicines or change the dosage because you feel better unless your doctor tells you to.

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- American Heart Association Tel: (800) 242-8721 **Website:**

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MANAGING YOUR

WRIST FRACTURE

What Are Wrist Fractures?

The area where the lower arm and hand connect is called the wrist. A fracture is a break in bones in this area. Healing time ranges from 6 weeks for a simple fracture to 24 weeks for a more severe break. It may take 6 to 12 months to get back normal flexibility and strength in the wrist.

What Causes Wrist Fractures?

Falls usually cause these fractures. People almost always put out their hand to break a fall. The impact when hitting the ground with the body's weight on the extended hand can cause breaks.

Several things make wrist fractures more likely. Elderly people may have fragile bones (osteoporosis) that are more likely to break in a fall, even a low-impact fall. Children can break their wrists because they often play sports and their bones are soft. Playing contact sports such as football and soccer and other activities such as skating, skateboarding, and biking can lead to fractures. Breaks can also result from trauma in motor vehicle accidents.

What Are the Symptoms of Wrist Fractures?

Fractured wrists are painful, bruised, and sore. The wrist often swells and may be bent at a strange angle. People may have trouble holding things and may have numbness in the wrist and hand.

How Are Wrist Fractures Diagnosed?

The doctor will ask about any trauma and will examine the wrist, and maybe other parts of the body if a car accident or severe fall occurred. The doctor will order x-rays to check the bones for breaks. Magnetic resonance imaging (MRI) may be done if the initial x-rays are negative and pain persists or increases after several days of treatment.

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How Are Wrist Fractures Treated?

A splint or cast is used for treatment. The first splint or cast may cover the elbow and fingers. As the bone heals, another one that allows more movement is put on. Weekly x-rays for the first 2 or 3 weeks may be taken to see how the bone heals. A cast is usually worn for 6 to 8 weeks.

For a severe break, surgery may be needed. The surgeon will put pins, screws, and a metal plate into each end of the broken bone to hold pieces together. Metal frames that go outside the body instead of inside are sometimes used.

The doctor may prescribe pain medicine for a few days to control symptoms.

Recovery will depend on how bad the fracture was and which bone or bones were broken. For simple breaks, people recover fully. A serious break may mean that full strength and flexibility in the wrist won't return. Physical therapy can help regain movement in the wrist.

DOs and DON'Ts in Managing Wrist Fractures:

✓ **DO** wear a wrist support device while playing sports.

✓ **DO** call your doctor if you notice loss of feeling or a color change in your hand.

✓ **DO** call your doctor if you develop a fever or pain lasts or gets worse.

⃠ **DON'T** skip follow-up visits with your doctor. They are important so the doctor can watch your progress.

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MANAGING YOUR

ZENKER'S DIVERTICULUM

What Is Zenker's Diverticulum?

A diverticulum is a pouch or sac that opens from a hollow organ such as the esophagus. The esophagus is the tube connecting the mouth with the stomach. Zenker's diverticulum can occur anywhere in the esophagus but is usually found in the upper part. The lining of the esophagus pushes backward, so some food stays in the pouch rather than moving down into the stomach.

Zenker's diverticulum is rare, occurring in less than 0.01% of the population. It's found more often in women than in men, usually those 60 years old or more.

This disorder can be associated with hiatal hernias, esophageal spasm, gastroesophageal reflux disease, and, rarely, cancer of the esophagus.

What Causes Zenker's Diverticulum?

The cause is unknown, but it may result from increased pressure in the esophagus. This pressure may occur if the esophagus doesn't relax completely when food is swallowed. The pressure leads to a tear or break (herniation) in muscle tissues lining the esophagus. The result is a diverticulum. Zenker's diverticulum isn't passed from parents to children and isn't contagious.

What Are the Symptoms of Zenker's Diverticulum?

The most common complaint is trouble swallowing (called dysphagia) solids and liquids. Coughing, bad breath (halitosis), weight loss, fullness in the neck, and spitting up undigested food are others.

An untreated diverticulum becomes larger and can lead to complications. These include food getting into lungs (aspiration), shortness of breath, fever, and pneumonia.

How Is Zenker's Diverticulum Diagnosed?

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The doctor makes a diagnosis by taking a medical history and ordering a barium swallow. In this test, barium contrast material is swallowed and x-rays are taken to get pictures of the esophagus.

The doctor may suggest seeing a gastroenterologist (doctor specializing in disorders of the esophagus, stomach, and intestines). The gastroenterologist may want to do a test called endoscopy. In this test, a scope with a lighted end is inserted into the mouth and passed through the esophagus into the stomach. Endoscopy will confirm the diagnosis and can also look for other disorders such as ulcers, abnormal tissue, and cancer in the esophagus.

How Is Zenker's Diverticulum Treated?

Surgery is the recommended treatment for people with symptoms. For people without symptoms and with a small diverticulum (less than ¼ inch), treatment may be conservative. This means that the doctor will wait for symptoms to occur before doing surgery.

Surgery helps dysphagia, cough, and aspiration in almost all people.

DOs and DON'Ts in Managing Zenker's Diverticulum:

✓ **DO** realize that Zenker's diverticulum can sometimes return after surgery (less than 4% of cases).

✓ **DO** understand that if treatment is conservative, you should eat soft foods (e.g., mashed potatoes) that can be easily chewed and swallowed.

✓ **DO** call your doctor if you have problems swallowing, develop a fever, or food gets stuck after swallowing.

✓ **DO** call your doctor if you have shortness of breath.

✓ **DO** call your doctor if you need a referral to a gastroenterologist or surgeon.

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⦸ **DON'T** eat seeds, skins, or nuts. These foods can lead to retaining food in the esophagus and maybe aspirating it.

⦸ **DON'T** forget that drugs cannot get rid of the diverticulum. However, medicines may be prescribed for heartburn, acid indigestion, or pneumonia from aspiration.

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FOR MORE INFORMATION

Contact the following sources:

- American College of Gastroenterology Tel: (703) 820-7400 **Website:** **http://www.acg.gi.org**
- American College of Surgeons Tel: (800) 621-4111 **Website:** **http://www.facs.org**

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conditions misperceived as contraindications to, 1716t–1717t
contraindication and precautions, 1714t–1715t
indicated for adults based on medical and other indications, 1723t–1724t
recommended immunization schedule, 1723t–1724t
Zygomycetes fungi, 822

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Migraine headache	I
Mild cognitive impairment	I
Mononeuropathies, isolated	II
Motion sickness	I
Multiple sclerosis	I
Muscle disease	II
Muscle weakness, algorithm	III
Muscular dystrophy	I
Myasthenia gravis	I
Myelin disorders	II
Myoclonus	I
Myopathies, idiopathic inflammatory	I
Myotonia	I
Narcolepsy	I
Neuroblastoma	I
Neuromuscular junction dysfunction	II
Neuronopathies, sensory (ganglionopathies)	II
Neuropathic bladder	II
Neuropathic pain	I
Neuropathies, peripheral, asymmetrical proximal/distal	II
Neuropathies with facial nerve involvement	II
Nystagmus, monocular	II
Opsoclonus	II
Optic atrophy	II
Optic neuritis	I
Osteosclerosis, diffuse	II
Otosclerosis (otospongiosis)	I
Paraneoplastic neurologic syndromes	II
Paraparesis, acute or subacute	II
Paraparesis, chronic progressive	II
Paraphilic disorders	I
Parkinsonism-plus syndromes	II
Parkinson's disease	I
Partial seizures	I
Poliomyelitis	I
Polyneuropathies, demyelinating	II
Polyneuropathies, distal, sensorimotor	II
Postconcussive syndrome	I
Postpoliomyelitis syndrome	I
Progressive multifocal leukoencephalopathy	I
Progressive supranuclear palsy	I
Ramsay Hunt syndrome	I
Restless legs syndrome	I
Seizures, mimics	II
Shaken baby syndrome	I
Smell disturbance	II
Spasticity	I
Spina bifida	I
Spinal cord compression	I
Spinal cord compression, epidural	II
Spinal cord dysfunction, non-traumatic	II
Spinal cord ischemic syndromes	II
Spinal stenosis	I
Spinocerebellar ataxia	I
Status epilepticus	I
Stroke, acute ischemic	I
Stroke, hemorrhagic	I
Stroke, secondary prevention	I
Subarachnoid hemorrhage	I
Subclavian steal syndrome	I
Subdural hematoma	I
Syncope	I
Syringomyelia	I
Tabes dorsalis	I
Tardive dyskinesia	I
Tension-type headache	I
Tics	II
Tinnitus	I
Transient ischemic attack	I
Transverse myelitis	I
Traumatic brain injury (TBI)	I
Tremors	II
Trigeminal neuralgia	I
Tuberous sclerosis	I
Unconscious patient	III
Vegetative state, persistent	II
Vertigo, algorithm	III
Vestibular neuronitis	I
Weakness, neuromuscular	III
Wernicke's encephalopathy	I
Whiplash	I
Wilson's disease	I

OPHTHALMOLOGY

Amaurosis fugax	I
Amblyopia	I
Anisocoria	III
Blepharitis	I
Blindness, monocular, transient	II
Cataracts	I
Conjunctival neoplasm	II
Conjunctivitis	I
Corneal abrasion	I
Corneal disorders	III
Corneal sensation, decreased	II
Corneal ulceration	I
Cytomegalovirus infection	I
Diabetic retinopathy	I
Dilated pupil	III
Diplopia, monocular	II
Diplopia, vertical	II
Episcleritis	I
Esotropia	II
Eyelid neoplasm	II
Eyelid retraction	II
Glaucoma, open-angle	I
Glaucoma, primary angle-closure	I
Hordeolum (stye)	I
Horner's syndrome	I
Intraocular neoplasm	II
Keratitis, noninfectious	II
Macular degeneration	I
Nystagmus, diagnosis	III
Nystagmus, monocular	II
Ocular foreign body	I
Opsoclonus	II
Optic atrophy	I, II
Optic neuritis	I
Orbital lesions, calcified	II
Orbital lesions, cystic	II
Pupillary dilatation, poor response to darkness	II
Ramsay Hunt syndrome	I
Red eye, acute	III
Reiter's syndrome (reactive arthritis)	I
Retinal detachment	I
Retinal hemorrhage	I
Retinitis pigmentosa	I
Retinoblastoma	I
Retinopathy, hypertensive	II
Scleritis	I
Sjögren's syndrome	I
Strabismus	I
Tuberous sclerosis	I
Uveitis	I
Von Hippel-Lindau disease	I
Wilson's disease	I

ORTHOPEDICS

Achilles tendon rupture	I
Ankle fracture	I
Ankle sprain	I
Ankylosing spondylitis	I
Arthralgia limited to one or few joints	III
Aseptic necrosis	I
Back pain, algorithm	III
Back pain, low, acute	II
Back pain, viscerogenic origin	II
Baker's cyst	I
Biceps tendonitis	I
Bone tumor, primary malignant	I
Bursitis	I
Calcium pyrophosphate dihydrate crystal deposition disease	I
Carpal tunnel syndrome	I
Cervical disk syndromes	I
Charcot's joint	I
Compartment syndrome	I
Complex regional pain syndrome	I
Concussion	I
Costochondritis	I
Cubital tunnel syndrome	I
De Quervain's tenosynovitis	I
Diffuse idiopathic skeletal hyperostosis (DISH)	I
Dupuytren's contracture	I
Elbow pain	II
Epicondylitis	I
Fibromyalgia	I
Foot and ankle pain, in different age groups	II
Footdrop	II
Foot lesion, ulcerating	II
Fracture, bone	III
Frozen shoulder	I
Ganglia	I
Glenohumeral dislocation	I
Gout	I
Granulomatous arthritis	I
Heel pain	II
Hip fracture	I
Hip pain, in different age groups	II
Hip pain without obvious fracture	II
Hypertrophic osteoarthropathy	I
Inflammatory arthritis	III
Juvenile idiopathic arthritis	I
Knee pain, anterior	III
Knee pain, in different age groups	II
Legg-Calvé-Perthes disease	I
Lumbar disk syndrome	I
Metatarsalgia	I
Morton's neuroma	I
Muscle cramps and aches	III
Muscle weakness, algorithm	III
Myofascial pain syndrome	I
Osgood-Schlatter disease	I
Osteoarthritis	I
Osteochondritis dissecans	I
Osteomyelitis	I
Osteoporosis	I
Osteoporosis, secondary causes	II
Paget's disease of the bone	I
Patellofemoral pain syndrome	I
Piriformis syndrome	I
Plantar fasciitis	I
Pronator syndrome	I
Psoriatic arthritis	I
Rheumatoid arthritis	I
Rib defects on x-ray	II
Rib notching on x-ray	II
Rotator cuff syndrome	I
Scoliosis	I
Septic arthritis	I
Shin splints	III
Shoulder pain	III
Shoulder pain, in different age groups	II
Slipped capital femoral epiphysis	I
Spinal cord compression	I
Spinal cord compression, epidural	II
Spinal stenosis, lumbar	I
Spine tumor	III
Spondyloarthropathy, diagnosis	III
Spondyloarthropathy, treatment	III
Spondylosis, cervical	III
Tarsal tunnel syndrome	I
Temporomandibular joint syndrome	I
Thoracic outlet syndrome	I
Torticollis	I
Trigger finger	I
Trochanteric bursitis	I
Vertebral compression fractures	I
Whiplash	I
Wrist and hand pain, in different age groups	II
Wrist pain	II

OTORHINOLARYNGOLOGY (ENT)

Abscess, peritonsillar	I
Acoustic neuroma	I
Allergic rhinitis	I
Behçet's disease	I
Bruxism	I
Burning mouth syndrome	I
Cogan's syndrome	I
Epiglottitis	I
Epistaxis	I
Gingivitis	I
Glossitis	I
Goiter evaluation and management	III
Head and neck, soft tissue masses	II
Hearing loss	III
Hemoptysis, algorithm	III
Herpangina	I
Labyrinthitis	I
Laryngeal carcinoma	I
Laryngitis	I
Mastoiditis	I
Meneire's disease	I
Mononucleosis	I
Motion sickness	I
Mucormycosis	I
Mumps	I
Oral cancer	I
Otitis externa	I
Otitis media	I
Otosclerosis (otospongiosis)	I
Pharyngitis/tonsillitis	I
Rhinorrhea	III
Salivary gland neoplasms	I
Sialadenitis	I
Sialolithiasis	I
Sinusitis	I
Sleep apnea, obstructive	I
Smell disturbance	II
Stomatitis	I
Temporomandibular joint syndrome	I
Thyroid carcinoma	I
Thyroid nodule	I
Thyroid, painful	III
Thyroiditis	I
Tinnitus	I
Torticollis	I
Tracheitis	I
Vertigo, algorithm	III

PEDIATRICS

Abscess, retropharyngeal	I
Absence seizures	I
Abuse, child	I
Anemia in newborn	III
Appendicitis, acute	I
Asthma	I
Ataxia, cerebellar, children	II
Attention deficit hyperactivity disorder	I
Autistic spectrum disorders	I
Bleeding neonate	III
Bone marrow failure syndromes, inherited	II

Breastfeeding difficulties III
Bruxism I
Childhood and adolescent immunizations V
Colic, acute abdominal II
Convulsive disorder, pediatric age III
Craniopharyngioma I
Cryptorchidism I
Cystic fibrosis I
Dehydration correction, pediatric patient III
Developmental delay III
Down syndrome I
Ear pain III
Encopresis I
Enuresis I
Epiglottitis I
Failure to thrive I
Febrile seizures I
Fetal alcohol syndrome I
Fever and neutropenia, pediatric patient III
Fifth disease (parvovirus infection) I
Food allergies I
Friedreich's ataxia I
Generalized tonic-clonic seizures I
Genitalia, ambiguous III
Glomerulonephritis, acute I
Hand-foot-mouth disease I
Hematuria, pediatric patient II, III
Hemophilia I
Histiocytosis X I
HIV: Recommended immunization schedule for HIV-infected children V
Hypertension, in children II
Hypogonadism, algorithm III
Hypogonadism, differential diagnosis II
Hypospadias I
Immunizations, childhood, accelerated schedule V
Immunizations, childhood and adolescent schedule V
Immunizations, contraindications and precautions V
Immunizations, immunocompromised infants and children V
Impetigo I
Infantile hypotonia I
Intubation, pediatric patient III
Jaundice, neonatal, algorithm III
Juvenile rheumatoid arthritis I
Kawasaki disease I
Laryngotracheobronchitis I
Marfan's syndrome I
Measles (rubeola) I
Meckel diverticulum I
Mononucleosis I
Mumps I
Murmur, diastolic III
Murmur, systolic III
Muscular dystrophy I
Nephroblastoma I
Nephrotic syndrome I
Neuroblastoma I
Osgood-Schlatter disease I
Otitis media I
Papulosquamous disorders, pediatric patient III
Patent ductus arteriosus I
Partial seizures I
Pediatric medication errors I
Pediculosis I
Pertussis I
Pharyngitis/tonsillitis I
Pinworms I
Poliomyelitis I
Precocious puberty I
Pseudohermaphroditism, female II
Pseudohermaphroditism, male II
Puberty, delayed, differential diagnosis II
Puberty, precocious II
Reactive erythema, pediatric patient III
Reye's syndrome I
Rh incompatibility I
Rheumatic fever I
Rickets I
Roseola I
Rubella (German measles) I
Scabies I
Scarlet fever I
Sexual precocity, female breast development III
Sexual precocity, female pubic hair development III
Sexual precocity, male III
Shaken baby syndrome I
Short stature III
Spina bifida I
Splenomegaly, children II
Status epilepticus I
Stevens-Johnson syndrome I
Strabismus I
Sturge-Weber syndrome I
Tetralogy of Fallot I
Thrombocytopenia, inherited disorders II
Torticollis I
Tourette's syndrome I
Tuberous sclerosis I
Turner's syndrome I
Urethral obstruction, children II
Vaginitis, prepubescent I
Varicella I
Varicocele I
Ventricular septal defect I
Vision loss, children II
Wilson's disease I

PSYCHIATRY

Abuse, child I
Abuse, drug I
Abuse, elder I
Acute stress disorder I
Alcoholism I
Amnestic disorders I
Anorexia nervosa I
Anxiety (generalized anxiety disorder) I
Autistic spectrum disorders I
Bipolar disorder I
Body dysmorphic disorder I
Borderline personality disorder I
Bruxism I
Bulimia nervosa I
Conduct disorder I
Conversion disorder I
Delirium I
Delirium tremens I
Delusions of parasitosis I
Dementia III
Dependent personality disorder I
Depression, major I
Dyspareunia I
Encopresis I
Enuresis I
Erectile dysfunction I
Fatigue, algorithm III
Factitious disorder (including Munchausen's syndrome) I
Gender dysphoria I
Histrionic personality disorder I
Illness anxiety disorder (hypochondriasis) I
Insomnia I
Intermittent explosive disorder I
Korsakoff's psychosis I
Memory loss symptoms, elderly patients II
Narcissistic personality disorder I
Neuroleptic malignant syndrome I
Obsessive-compulsive disorder (OCD) I
Opioid dependence I
Oppositional defiant disorder I
Panic disorder, with or without agoraphobia I
Paranoid personality disorder I
Patient with ill-defined physical complaints, algorithm III
Pedophilia I
Phobias I
Posttraumatic stress disorder I
Premenstrual syndrome I
Schizophrenia I
Seasonal affective disorder I
Serotonin syndrome I
Sexual assault I
Sexual dysfunction III
Sexual dysfunction, female II
Sleep disorders III
Social anxiety disorder I
Somatization disorder I
Stuttering I
Suicide I
Tardive dyskinesia I
Tourette's syndrome I
Tricyclic antidepressant overdose I

PULMONARY DISEASE

Abscess, lung I
Acid-base homeostasis III
Acidosis, respiratory, acute III
Acidosis, respiratory, chronic III
Acute bronchitis I
Acute respiratory distress syndrome I
Air-space opacification on x-ray II
Alkalosis, respiratory, treatment III
Alpha-1-antitrypsin deficiency I
Asbestosis I
Aspergillosis I
Aspiration, gastric contents III
Aspiration, oral contents III
Aspiration pneumonia I
Asthma I
Atelectasis I
Bacterial pneumonia I
Bronchial obstruction II
Bronchiectasis I
Bronchopleural fistula II
Chronic obstructive pulmonary disease I
Churg-Strauss syndrome I
Chylothorax II
Cor pulmonale I
Cough, chronic, algorithm III
Cyanosis II
Cyanosis, algorithm III
Cystic fibrosis I
Deep vein thrombosis I
Diaphragm elevation, bilateral, symmetrical II
Diaphragm elevation, unilateral II
Dyspnea, diagnosis III
Empyema I
Eosinophilic lung disease II
Eosinophilic pneumonias I
Goodpasture's syndrome I
Granulomatosis with polyangiitis (Wegener granulomatosis) I
Hemoptysis I
Hemoptysis, algorithm III
Hepatopulmonary syndrome I
High-altitude sickness I
Hypersensitivity pneumonitis I
Idiopathic pulmonary fibrosis I
Interstitial lung disease I
Lung cancer, occupational causes II
Lung neoplasms, primary I
Mesothelioma, malignant I
Mycoplasma pneumonia I
Necrotizing pneumonias II
Neurofibromatosis I
Opacification of hemidiaphragm on x-ray II
Pertussis I
Pleural effusion, malignant III
Pleural effusions, malignancy-associated II
Pleural space fluid III
Pleurisy I
Pneumocystis jiroveci (*carinii*) pneumonia I
Psittacosis I
Pulmonary cysts on x-ray II
Pulmonary edema, non-cardiogenic II
Pulmonary embolism I
Pulmonary hemorrhagic syndromes, diffuse II
Pulmonary arterial hypertension I
Pulmonary mass, solitary, causes II
Pulmonary mass, solitary, mimics II
Pulmonary nodule, algorithm III
Pulmonary nodule, solitary, differential diagnosis II
Sarcoidosis I
Severe acute respiratory syndrome I
Silicosis I
Sleep apnea, obstructive I
Tracheobronchial narrowing on x-ray II
Tuberculosis, pulmonary I
Ventilation-perfusion mismatch on lung scan II
Viral pneumonia I

RHEUMATOLOGY

Adult onset Still's disease I
Ankylosing spondylitis I
Antinuclear antibody (ANA) IV
Antiphospholipid antibody syndrome I
Arthralgia limited to one or few joints III
Arthritis and abdominal pain II
Arthritis and diarrhea II
Aseptic necrosis I
Back pain, algorithm III
Back pain, low, acute II
Baker's cyst I
Biceps tendonitis I
Bisphosphonate-related osteonecrosis of jaw I
Bursitis I
Calcium pyrophosphate dihydrate crystal deposition disease I
Carpal tunnel syndrome I
Cerebral vasculitis I
Cervical disk syndromes I
Charcot's joint I
Cogan's syndrome I
Compartment syndrome I
Complex regional pain syndrome I
Costochondritis I
Cryoglobulinemia I
Cubital tunnel syndrome I
De Quervain's tenosynovitis I
Discoid lupus I
Dupuytren's contracture I
Ehlers-Danlos syndrome I
Elbow pain II
Epicondylitis I
Erythema nodosum I
Felty's syndrome I
Fibromyalgia I
Finger lesions, inflammatory II
Foot and ankle pain, in different age groups II
Frozen shoulder I
Ganglia I
Giant cell arteritis I

Glenohumeral dislocation I
Gout I
Granulomatous arthritis I
Hip pain, in different age groups II
Hip pain without obvious fracture II
Hypertrophic osteoarthropathy I
Hyperuricemia I
Inclusion body myositis I
Inflammatory arthritis III
Joint pain, polyarticular II
Juvenile idiopathic arthritis I
Knee pain, anterior, algorithm III
Knee pain, in different age groups II
Lyme disease I
Metatarsalgia I
Microscopic polyangiitis I
Mixed connective tissue disease I
Monoarthritis, acute II
Morton's neuroma I
Muscle cramps and aches III
Myofacial pain syndrome I
Myositis III
Nodules, painful II
Osgood-Schlatter disease I
Osteoarthritis I
Osteoarthritis dissecans I
Osteoporosis I
Osteoporosis, secondary causes II
Paget's disease of the bone I
Panniculitis I
Patellofemoral pain syndrome I
Piriformis syndrome I
Plantar fasciitis I
Polyarteritis nodosa I
Polymyalgia rheumatica I
Psoriatic arthritis I
Raynaud's phenomenon I
Red hot joint II
Reiter's syndrome (reactive arthritis) I
Rotator cuff syndrome I
Scleroderma (systemic sclerosis) I
Scleroderma-like symptoms II
Scoliosis I
Septic arthritis I
Shin splints, algorithm III
Shoulder pain III
Shoulder pain, in different age groups II
Sjögren's syndrome I
Spinal cord compression I
Spinal stenosis, lumbar I
Spondyloarthropathy, diagnosis, algorithm III
Spondyloarthropathy, treatment, algorithm III
Spondylosis, cervical III
Synovial fluid analysis IV
Systemic lupus erythematosus I
Takayasu's arteritis I
Tarsal tunnel syndrome I
Temporomandibular joint syndrome I
Torticollis I
Trigger finger I
Trochanteric bursitis I
Vasculitis, systemic I
Whiplash I
Wrist and hand pain, in different age groups II

SURGERY, GENERAL

Abscess, breast I
Abscess, liver I
Abscess, lung I
Abscess, pelvic I
Abscess, perirectal I
Acute pancreatitis I
Adrenal incidentaloma III
Adrenal mass, algorithm III
Anal fissure I
Anorectal fistula I
Appendicitis, acute I
AV malformations, cerebral I
Bite wounds I
Bleeding, gastrointestinal, algorithm III
Bleeding, variceal, algorithm III
Brain neoplasm, glioblastoma I
Breast cancer I
Breast, nipple discharge evaluation III
Breast, radiologic evaluation III
Breast, routine screen or palpable mass evaluation III
Burns I
Carcinoid syndrome I
Cholecystitis I
Cholelithiasis I
Chronic pancreatitis I
Colorectal cancer I
Compartment syndrome I
Constipation, algorithm III
Diabetic foot I
Diverticular disease (diverticulosis, diverticulitis) I
Dumping syndrome I
Electrical injury I
Epistaxis I
Esophageal tumors I
Esophageal varices I
Fibrocystic breast disease I
Frostbite I
Gastric cancer I
Gastric dilatation II
Gastric emptying, delayed II
Gastrinoma I
Goiter evaluation and management III
Hemorrhoids I
Hepatocellular carcinoma I
Hepatomegaly, algorithm III
Hepatomegaly, differential diagnosis II
Hiatal hernia I
Hypospadias I
Intra-abdominal mass lesion, neonatal II
Large bowel stricture II
Leg ulcer, algorithm III
Mesenteric adenitis I
Mesenteric arterial embolism, associated factors II
Mesenteric venous thrombosis I
Nasal and paranasal sinus tumors II
Nasal masses, congenital II
Neck mass, algorithm III
Oral cancer I
Paget's disease of the breast I
Pancreatic cancer, exocrine I
Pancreatic islet cell tumors III
Paronychia I
Parotid swelling II
Pelvic mass, algorithm III
Pelvic pain, causes in women II
Pelvic pain, reproductive-age woman III
Peripheral arterial disease I
Peritonitis I
Pilonidal disease I
Pituitary region tumors II
Pneumatosis intestinalis in neonate and older child II
Pneumoperitoneum, neonatal II
Pneumothorax, spontaneous I
Portal vein thrombosis I
Preoperative evaluation I
Scrotal mass, algorithm III
Short bowel syndrome I
Splenomegaly, algorithm III
Testicular cancer I
Testicular torsion I
Thyroid carcinoma I
Thyroid nodule I
Ureteric obstruction, congenital II
Urethral obstruction, children II
Urolithiasis I
Varicose veins I
Ventricular septal defect I
Zenker's (pharyngoesophageal) diverticulum I

UROLOGY

Acute urinary retention (AUR) I
Benign prostatic hyperplasia I
Bladder cancer I
Calcifications, genital tract, female on x-ray II
Cryptorchidism I
Cystitis, acute III
Ejaculation disorders I
Epididymitis I
Erectile dysfunction I
Erosions, genitalia II
Groin masses II
Hematuria, differential diagnosis II
Hematuria, pediatric patient II, III
Hydrocele I
Hypospadias I
Incontinence (urinary) I
Infertility I
Interstitial cystitis I
Kidney enlargement, unilateral II
Nephroblastoma I
Neuropathic bladder II
Oliguria III
Orchitis I
Pelvic mass, algorithm III
Pelvic pain, reproductive-age woman III
Penile rash II
Peyronie's disease I
Pigmenturia II
Polycystic kidney disease I
Priapism I
Prostate cancer I
Prostatitis I
Renal mass, algorithm III
Scrotal mass, algorithm III
Sexual dysfunction III
Sexual dysfunction in women I, II
Testicular cancer I
Testicular torsion I
Ureteral colic II
Ureteric obstruction, congenital II
Urethral obstruction, children II
Urinary retention II
Urinary tract infection I
Urine color abnormalities II
Urolithiasis I
Varicocele I

INTERDISCIPLINARY MEDICINE

Acetaminophen poisoning I
Acid-base homeostasis III
Acidosis, metabolic, algorithm III
Acidosis, metabolic, differential diagnosis II
Acute respiratory distress syndrome I
Alkalosis, metabolic, algorithm III
Alkalosis, metabolic, differential diagnosis II
Amyloidosis I
Aneurysm, abdominal aorta I
Angioedema I
Aortic dissection I
Aseptic necrosis I
Behçet's disease I
Bisphosphonate-related osteonecrosis of jaw I
Carbon monoxide poisoning I
Cardiorenal syndrome I
Chronic fatigue syndrome I
Chronic pain management I
Churg-Strauss syndrome I
Claudication I
Cocaine overdose I
Constipation, algorithm III
Creatine kinase (CK, CPK) IV
Cyanosis, algorithm III
Deep venous thrombosis I
Diarrhea, acute III
Diarrhea, chronic III
Digoxin overdose I
Dilated pupil III
Dyspepsia III
Dyspnea, evaluation, algorithm III
Dyspnea, differential diagnosis II
Edema, generalized III
Edema, regional, algorithm III
Electrical injury I
Failure to thrive I
Falls in the elderly I
Fatigue, algorithm III
Fever of undetermined origin I
HELLP syndrome I
Hemolytic-uremic syndrome I
Hepatomegaly III
High-altitude sickness I
Histiocytosis X I
Hot flashes I
Hypotension III
Insomnia I
Lymphadenopathy, generalized, algorithm III
Lymphedema I
Malabsorption III
Mallory-Weiss tear I
Mediastinitis I
Mediastinitis, acute II
Mesenteric venous thrombosis I
Milk-alkali syndrome I
Muscle cramps and aches III
Muscle weakness, algorithm III
Neck pain III
Neurofibromatosis I
Neuroleptic malignant syndrome I
Obesity I
Oliguria III
Patient with ill-defined physical complaints III
Peripheral arterial disease I
Polypharmacy I
Portal vein thrombosis I
Postural hypotension, nonneurologic causes II
Pressure ulcers I
Priapism I
Pruritus, generalized III
Psychosis II
Radiation exposure I
Reye's syndrome I
Rh incompatibility I
Rhabdomyolysis I
Sexual dysfunction III
Shock, clinical algorithm III
Subclavian steal syndrome I
Superior vena cava syndrome I
Thoracic outlet syndrome I
Thromboangiitis obliterans I
Thrombophlebitis, superficial I
Tricyclic antidepressant overdose I
Tumor lysis syndrome I
Unconscious patient III
Weakness, nonneuromuscular causes II
Weight gain, algorithm III
Weight loss, unintentional, algorithm III